

APPROACHES TO THE SYNTHESIS OF d,l-ALNUSENONE VIA NON-
ENZYMIC, BIOGENETIC-LIKE POLYOLEFIN CYCLIZATIONS

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To my lovely wife, Arlene, and my darling daughter,
Phyllis Michelle...

...and to Libavius, whose spirit turned
the tide.

ABSTRACT

Several 4-methyl-4-polyalkenyl-2-cyclohexenols were synthesized in the hope that their acid-promoted cyclizations would yield polycyclic compounds in which the first two ring junctures formed would have a cis,anti,trans backbone, a procedure which is well precedented in the literature. Compounds of this stereochemistry bear a structural relationship to the pentacyclic triterpenes alnusenone and friedelin, thus offering a possible route to these and other triterpenoid compounds. Consequently, the model compounds 58 and 82 were synthesized. Their cyclizations in formic acid yielded complex mixtures of products with varying degrees of cyclization. Using stannic chloride as cation initiator in dichloromethane, these two alcohols cyclized to afford good yields of tricyclic products with high degrees of stereoselectivity. The structure of the tricyclic olefin 68, formed in 32% yield from alcohol 58, is believed to be that shown based on fact that the first three centers formed must be in a cis,anti relationship in order for cyclization to occur, and that the fourth center is trans to the third by previous analogies and by spectral data. Absolute confirmation of the structure is pending the results of an x-ray analysis. The structures of the olefins 109 and 110, formed in 62% yield from the alcohol 82, were confirmed by alternate synthesis of their hydrogenation product. Based on the results of these model studies, alcohol 51 was

synthesized, and its cyclization was studied, in hopes of obtaining the pentacyclic olefin 50. A compound with spectroscopic data consistent with the structure of 50 was isolated on brief treatment with stannic chloride in dichloromethane. Unfortunately, the yield was only 12%. In order to establish the structure of the pentacyclic olefin as 50, a sequence of reactions was devised to transform the olefin into the pentacyclic ether D-6. The required two carbon atoms were introduced via an eight-step sequence, affording the pentacyclic aldehyde 191 in 6.5% yield from olefin 50. Attempts to deoxygenate the carbonyl oxygen were unsuccessful. The structure of the olefin is believed to be 50 on the basis of its nmr spectrum, which shows an angular methyl group at 1.05 ppm, assigned to the methyl at C-6b, since it would lie in plane of the C-11,12 double bond. The other stereochemically possible product is the trans,anti,cis,anti,cis olefin 204. In addition to being an unlikely product on mechanistic grounds, the structure of this olefin would place the C-6b α out of the plane of the double bond, thereby placing its chemical shift at higher field.

The yield and selectivity in the cyclization reaction appears to decrease as the number of alkyl substituents on the internal double bonds is increased. This is explained on the basis of the stronger interactions that would develop in the transition states in the substituted cases, as opposed to those with a lesser degree of olefin substitution.

In a related study, the cyclopentenol 194 was cyclized with stannic chloride to afford a 37% yield of the pentacyclic olefin 195, which was successfully transformed into a known compound, the enone D-4. Like the ether D-6, D-4 was used previously as an intermediate in the first total synthesis of alnusenone (Ireland and Welch, 1970). Successful transformation of olefin 195 into enone D-4 served to confirm the structure of 195 and also constituted another formal total synthesis of alnusenone.

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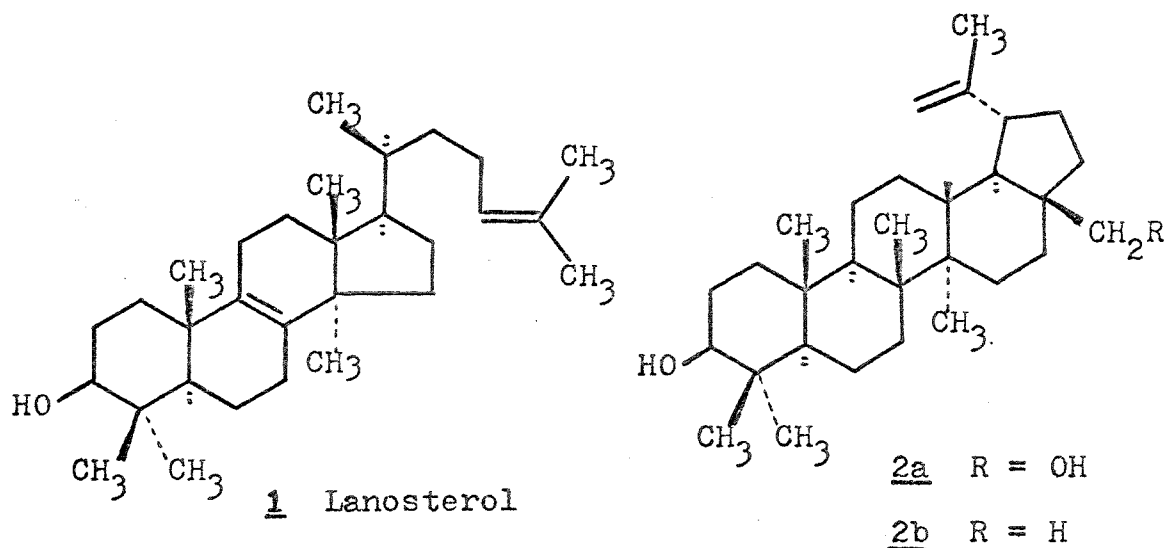
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Historical Introduction

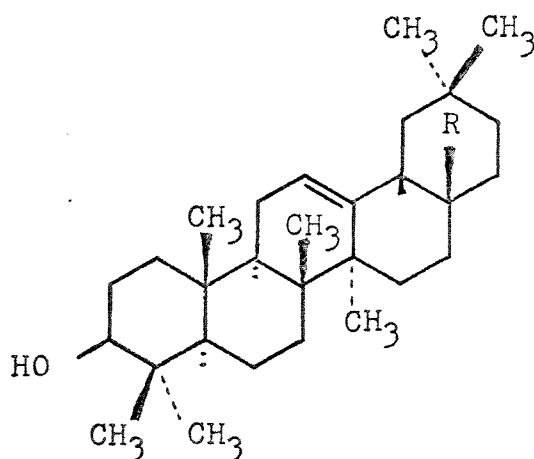
I. Triterpene Chemistry

The triterpenes are a large, diverse class of C_{30} isoprene compounds which are widely found in nature. While most of the triterpenes are restricted to the plant kingdom, a few, such as lanosterol (1) have been isolated from animal sources (1).



Betulin (2a) was the first triterpene isolated, in 1788 (2). However, their size, multiple centers of asymmetry, and meager functionality hampered the structural elucidation of the triterpenes until 1949, when Ruzicka and co-workers (3) postulated that the gross structure of oleanolic acid was 3a. Prior to this, oleanolic acid had been chemically correlated to β -amyrin (3b), as well as betulin (2a) to lupeol (2b) (4).

Thus, with the knowledge of structure 3a for oleanolic



3a R = COOH, Oleanolic acid

3b R = CH₃, β -Amyrin

acid, the basic structural types of the common triterpenes were rapidly determined. The elucidation of the relative structure and stereochemistry of the triterpenes has been reviewed by several authors (1,4-9). In addition, two excellent volumes, which catalogue the triterpenes known through 1972, have recently appeared (10,11).

Once the interest in the chemistry of the triterpenes had been evoked, chemists turned their attention toward the biogenetic aspects of triterpene synthesis. In 1953, Woodward and Bloch (12) and Dauben and coworkers (13) postulated that the acyclic polyene squalene (4) was the precursor of lanosterol (1) and ultimately, cholesterol (5) (Fig. 1) via a series of olefin cyclizations, Wagner-Meerwein rearrangements, and losses of methyl groups. It was then experimentally confirmed by Bloch (14,15) that squalene (4) was converted to cholesterol in vivo. The details of this work have been reviewed (16).

In 1955, Stork (17) and Eschenmoser (18) independent-

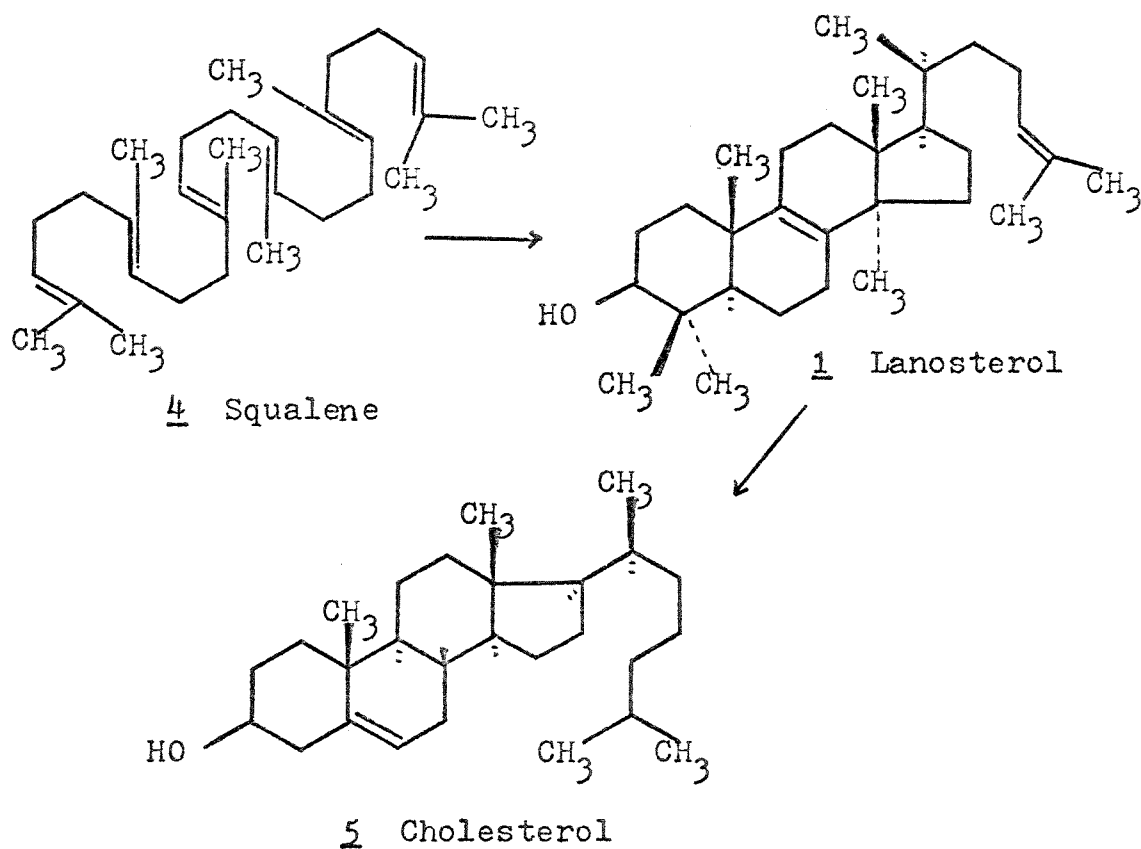


Fig. 1

ly proposed a theory which postulates that not only lanosterol (1), but all the triterpenes are ultimately derived from squalene(4) via cyclization - rearrangement sequences. The implications of their theory, commonly known as the Stork-Eschenmoser hypothesis, will be discussed in Part II of the introduction (vide infra).

More recently, 2,3-oxidosqualene (6) has been implicated

as the precursor of lanosterol (1) (19,20), β -amyrin (3b) (21), and the mold metabolite, fusidic acid (7) (22) (Fig. 2).

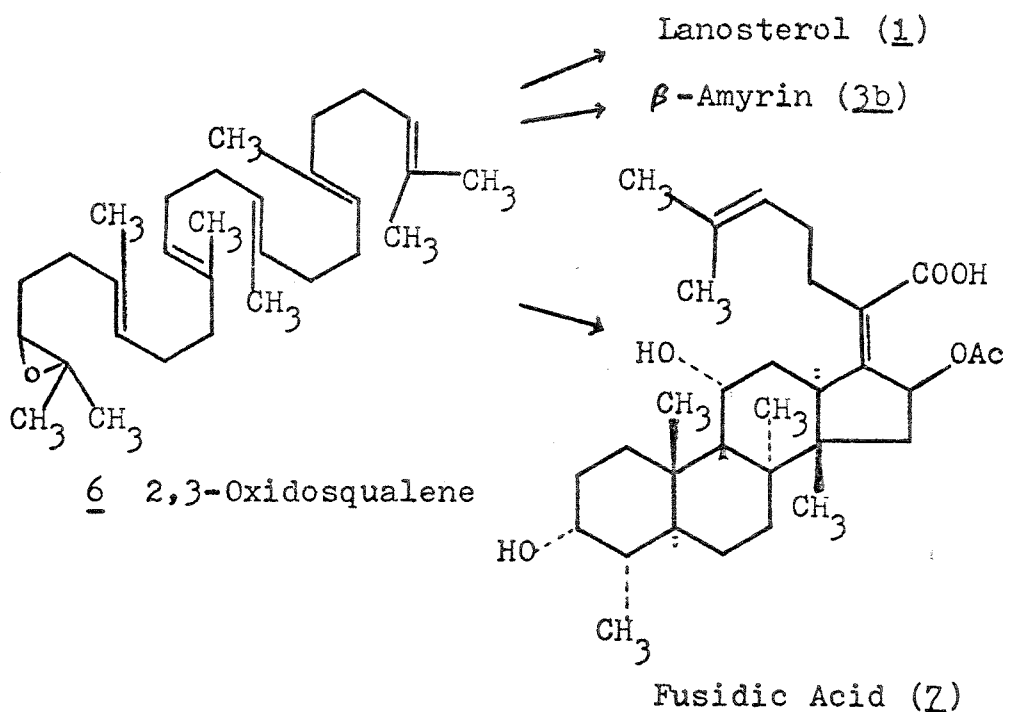


Fig. 2

Chart A illustrates squalene oxide (6) in a chair-chair-chair-boat form, which is believed to cyclize (23) according to the above hypothesis with the aid of a protonic enzyme, EnzH^+ , to the tetracyclic carbonium ion A-1. Stereospecific attack by water at C-18* of A-1 would produce dam-

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

Bicyclic compounds are described as derivatives of naphthalene. Tricyclic compounds are described as derivatives of phenanthrene. Tetracyclic and pentacyclic compounds of the

Chart A

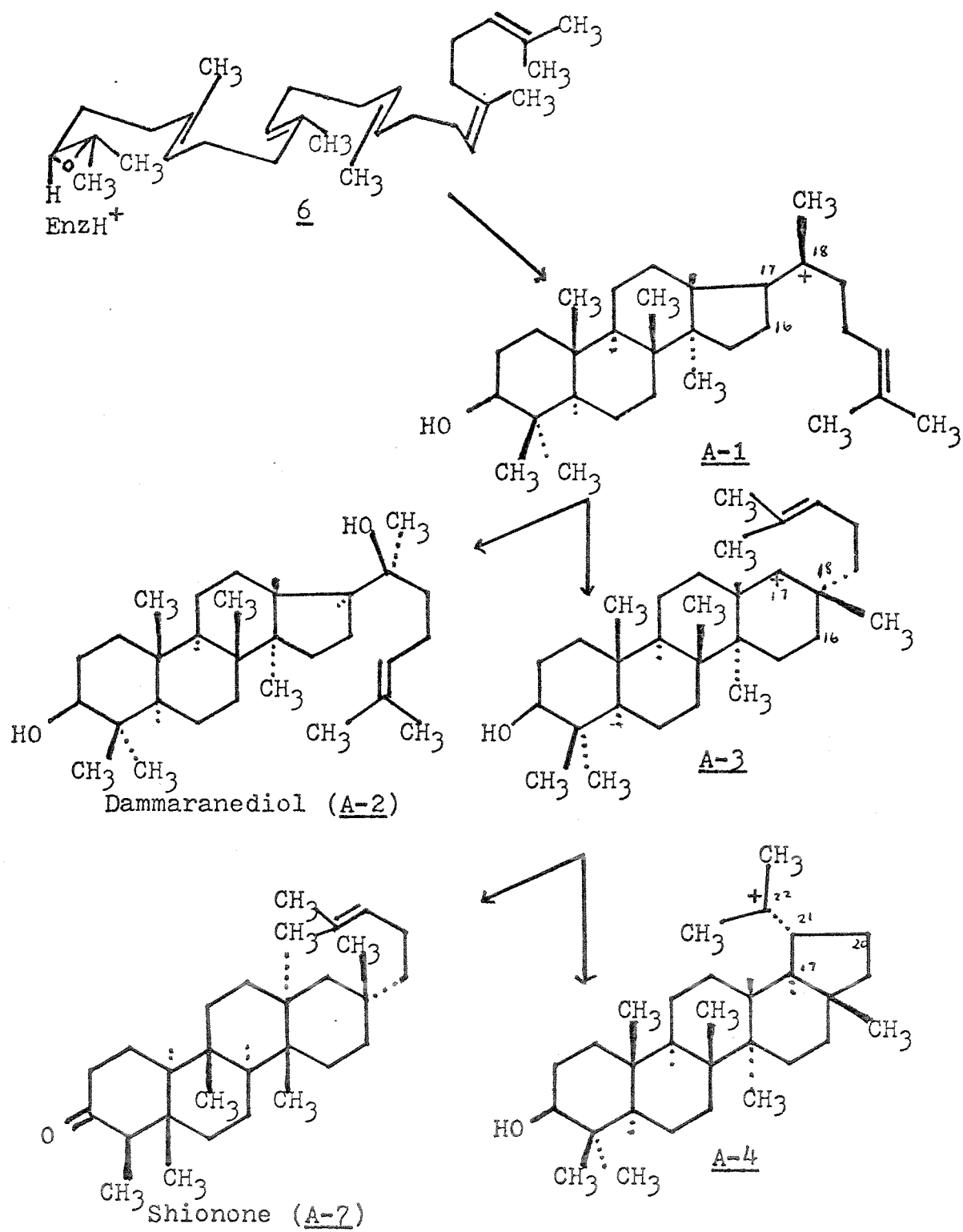


Chart A (continued)

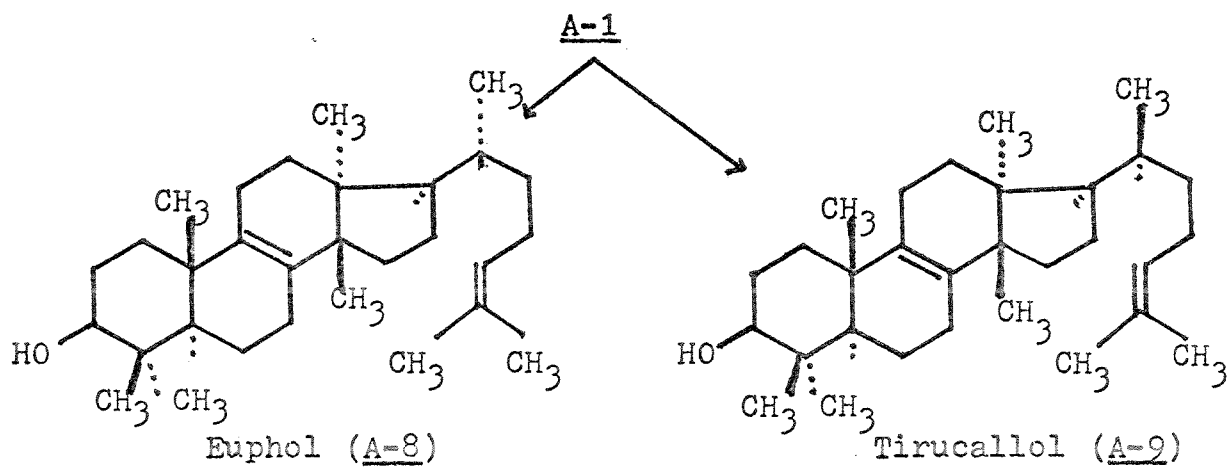
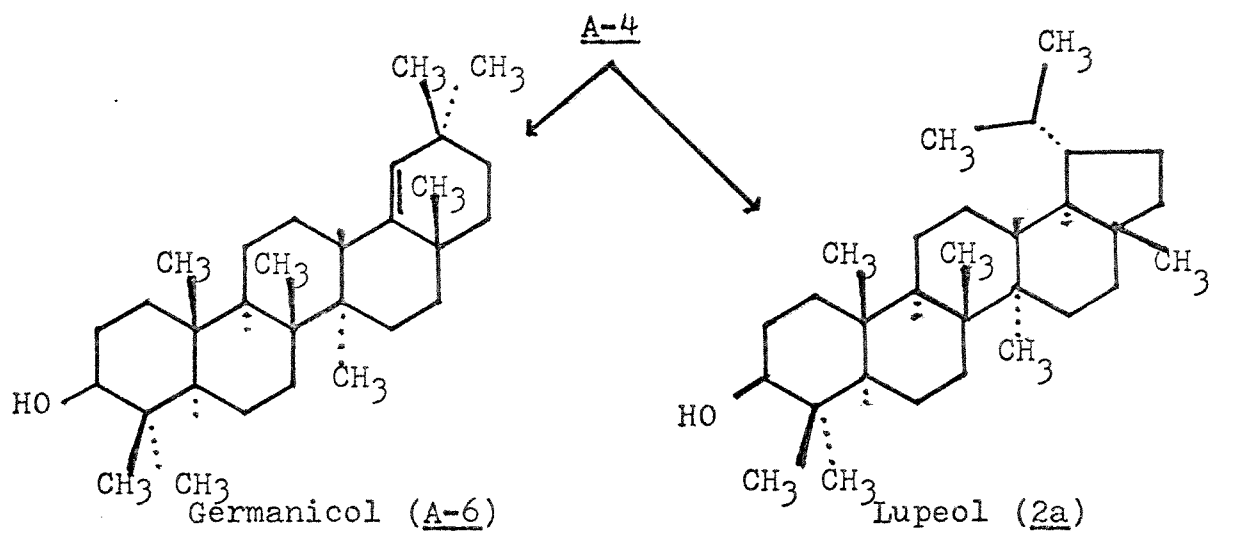
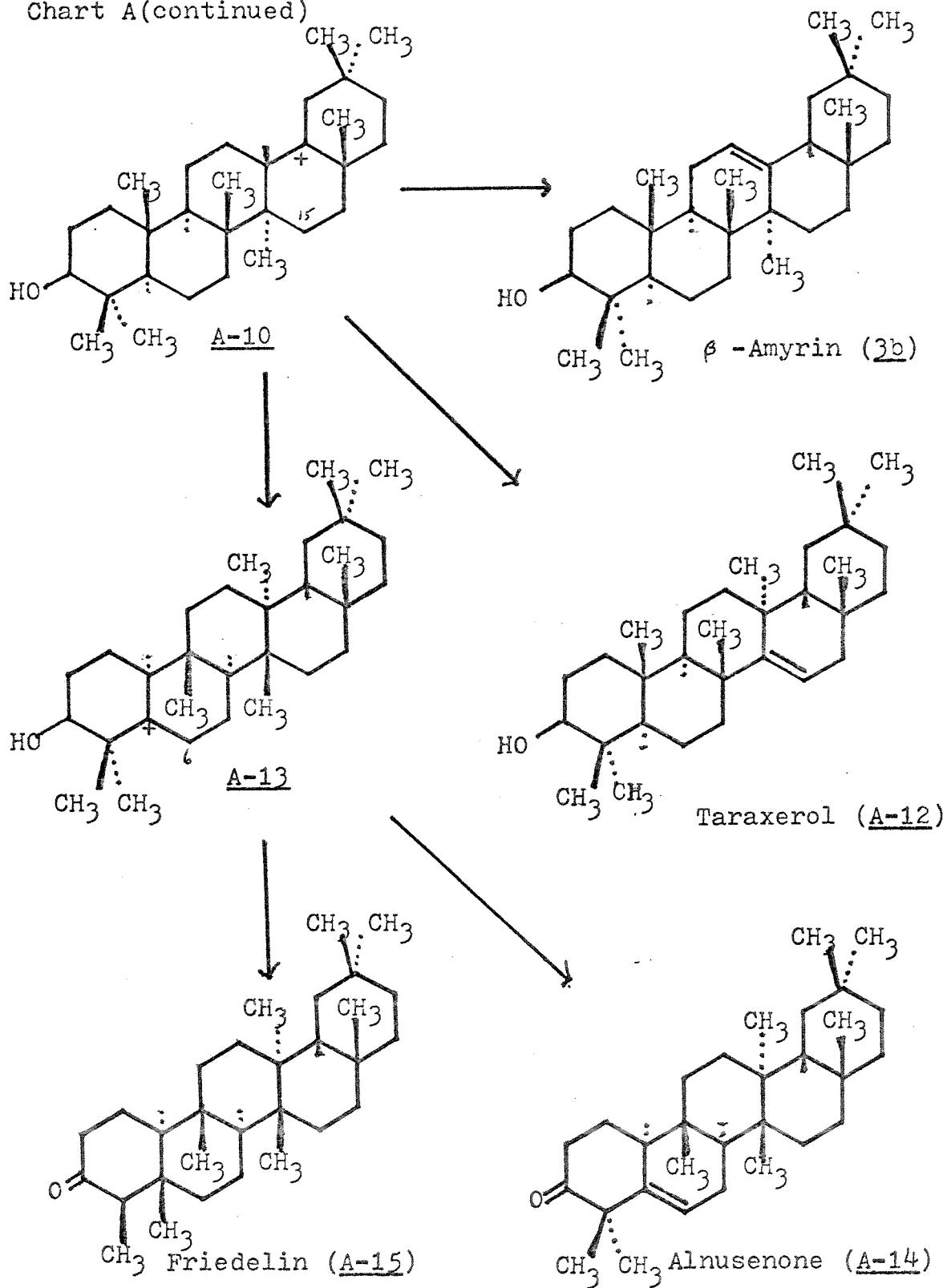


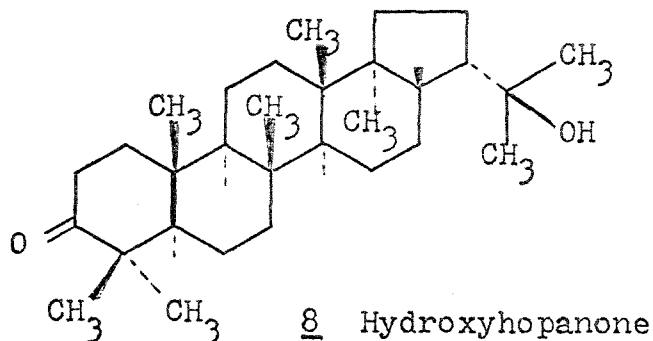
Chart A(continued)



maranediol (A-2). Alternatively, the C-16,17 bond could migrate to C-18 to produce the tetracyclic ion A-3, with the charge at C-17. Markownikov addition to the C-21,22 double bond would produce the pentacyclic ion A-4, which, on loss of a proton from either terminal methyl group would yield lupeol (2a). Migration of the C-20,21 bond to C-22 in A-4 would produce a cation which, on loss of the C-17 proton, would yield germanicol (A-6). Alternatively, seven sequential 1,2-hydrogen and methyl shifts in cation A-3, followed by loss of the C-3 hydroxyl proton, would afford the tetracyclic triterpene, shionone (A-7). Cation A-1 could also undergo sequential hydride and methyl shifts, and loss of a proton at C-8 to give either euphol (A-8) or tirucalol (A-9). Cation A-10, the probable precursor of germanicol (A-6), could also undergo a single hydride shift from C-13 and subsequent loss of a proton from C-12 to yield β -amyrin (3b). Two consecutive shifts and loss of the C-15 proton from A-10 would produce taraxerol (A-12). Alternatively, sequential hydride and methyl shifts to the rearranged cation A-13, would yield alnusenone (A-14) on deprotonation and oxidation. Further rearrangement of cation A-13 would produce friedelin (A-15).

[6,6,6,6,6] type are described as derivatives of chrysene and picene, respectively. Pentacyclic compounds of the type [6,6,6,6,5] are described as derivatives of cyclopenta[a]-chrysene, as indicated in "The Ring Index" (24).

Other conformations of squalene oxide (6) will yield triterpenes upon enzymatic cyclization (23). Lanosterol (1), for example, is formed via a chair-boat-chair-boat cyclization of squalene oxide, whereas hydroxyhopanone (8) is a



product of squalene oxide in the all-chair conformation.

The combination of methyl and hydrogen migrations, commonly referred to as backbone rearrangements, are common to a number of triterpene biosyntheses (25), and several such processes have also been observed in vitro. Examples of special interest to the present work are the rearrangements of friedelene (9) (26a-d) and alnusene (10) (27) to the same mixture of 18 β -olean-12-ene (11) and olean-13(18)-ene (12) (fig. 3). The identical mixture is also obtained from olean-12-ene (13) or germanicane (14) under the same conditions (28). This establishes the structural relationship between alnusenone (A-14), friedelin (A-15), and β -amyrin (3b). What is especially interesting about these backbone rearrangements is that they constitute a complete reversal of the

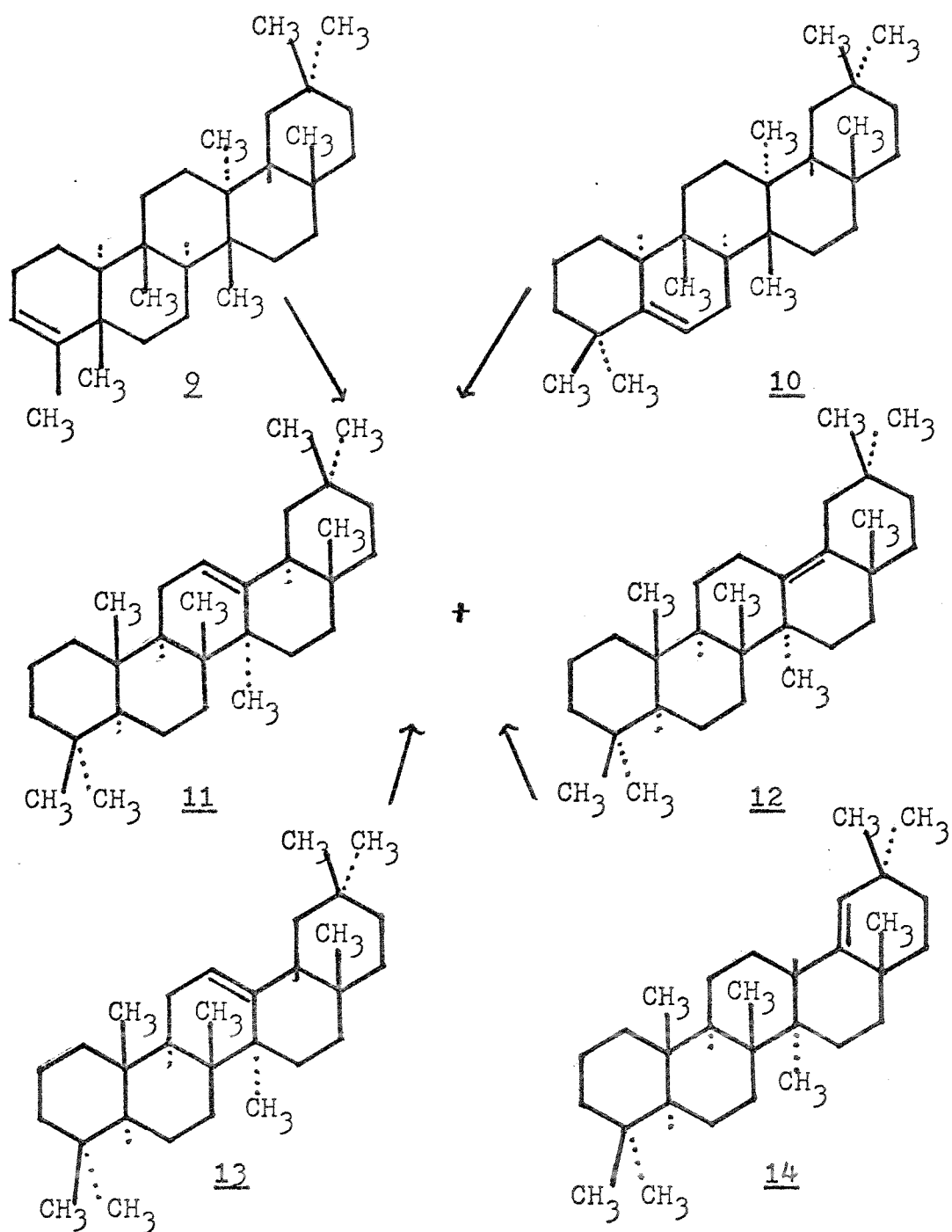
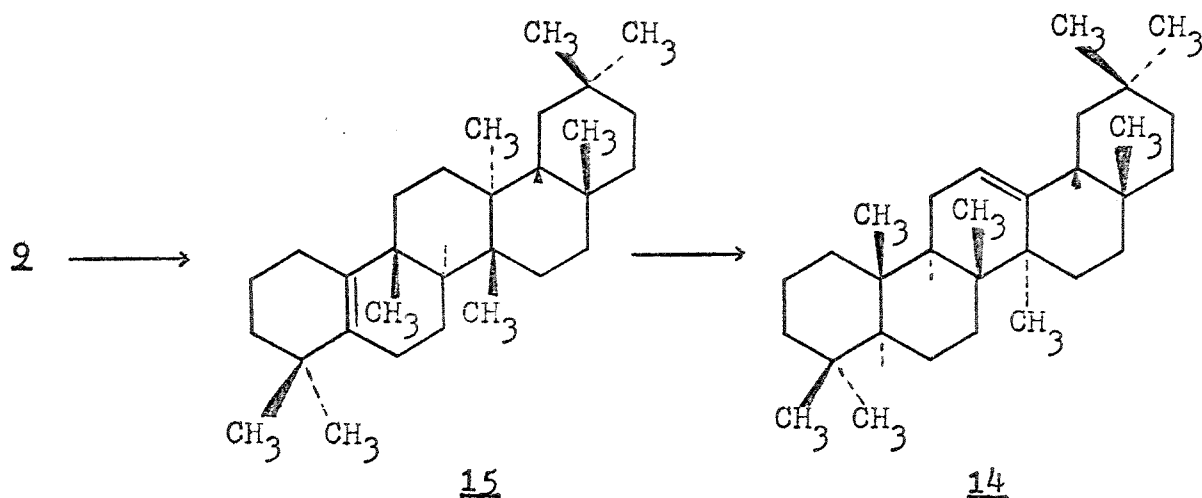
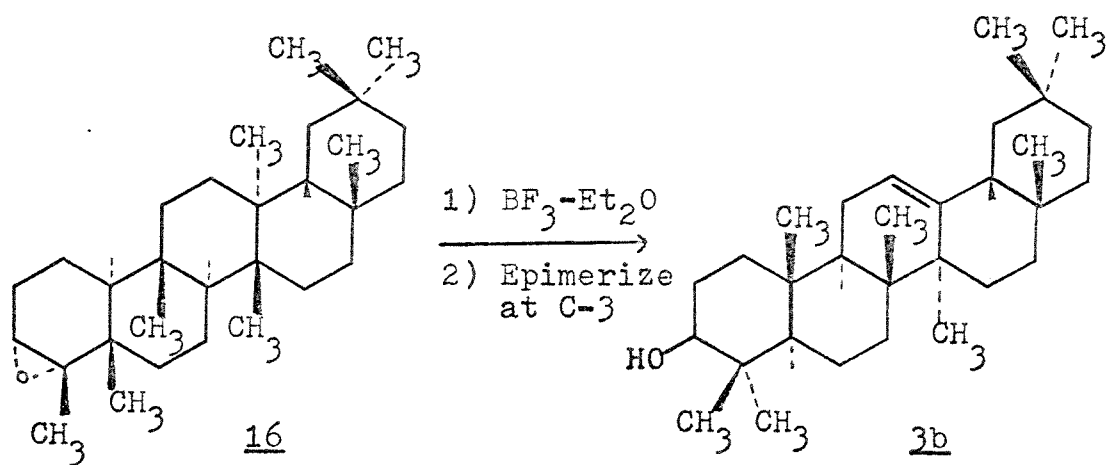


Fig. 3

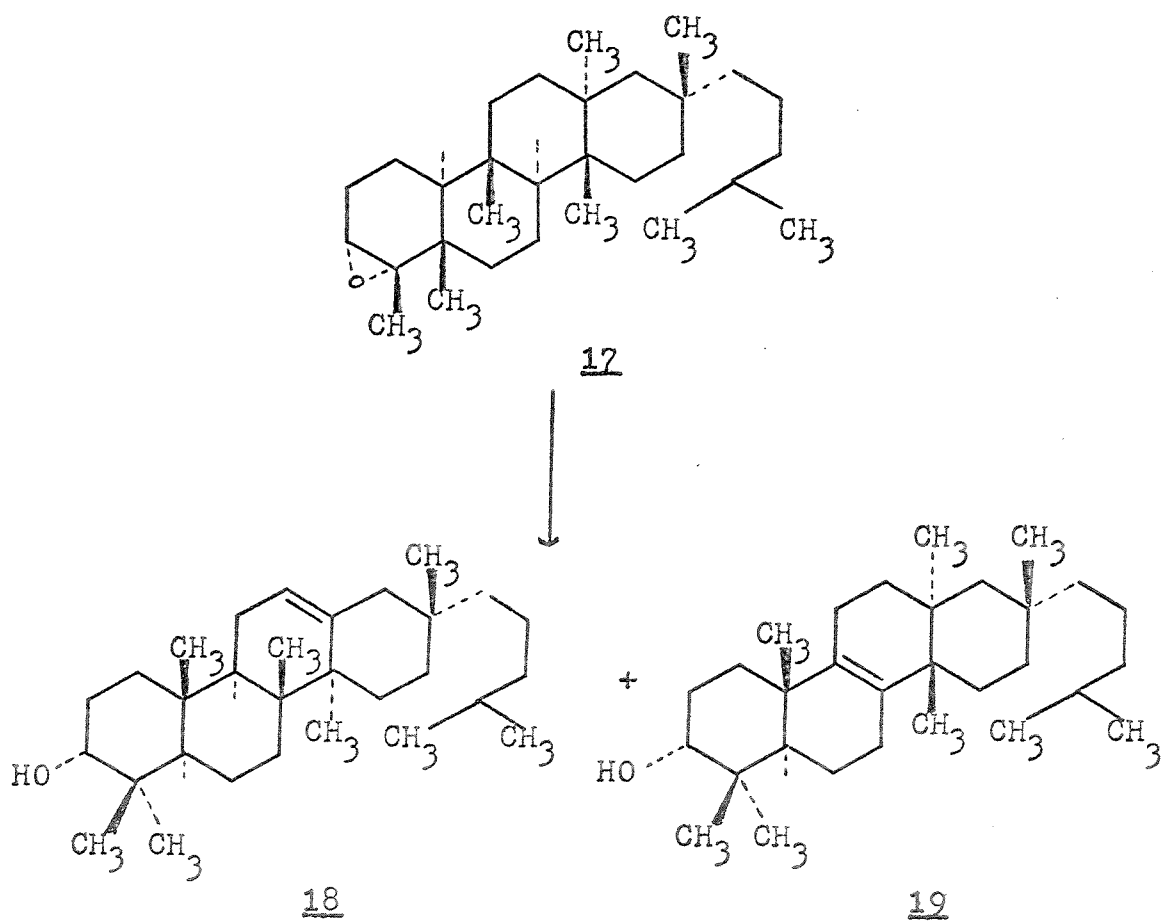
proposed biogenetic process (17,18). In a study of the friedelene-oleanene rearrangement, Coates (29) suggested that in the enzyme process, a compensation mechanism must occur which lowers the energy barrier for the β -amyrin-friedelin conversion, since the reverse process is energetically more favorable. Prior to Coates's work (29), Courtney and co-workers (26d) were able to isolate glutin-5(10)-ene (15) and



hypothesized that it was an intermediate in the rearrangement to olean-13(18)-ene (14). Furthermore, it was found (26d,29) that olean-12-ene (11) could be isolated without further rearrangement, provided the conditions were mild enough (ie, zinc chloride-acetic acid or chloroform-hydrochloric acid). This suggests that conditions might be found in which an appropriately substituted friedelin derivative, ie, 3 α ,4 α -epoxyfriedelene (16) could be made to undergo rearrangement, so as to yield 3-epi- β -amyrin, which should be readily converted to β -amyrin (3b). A rearrangement of this

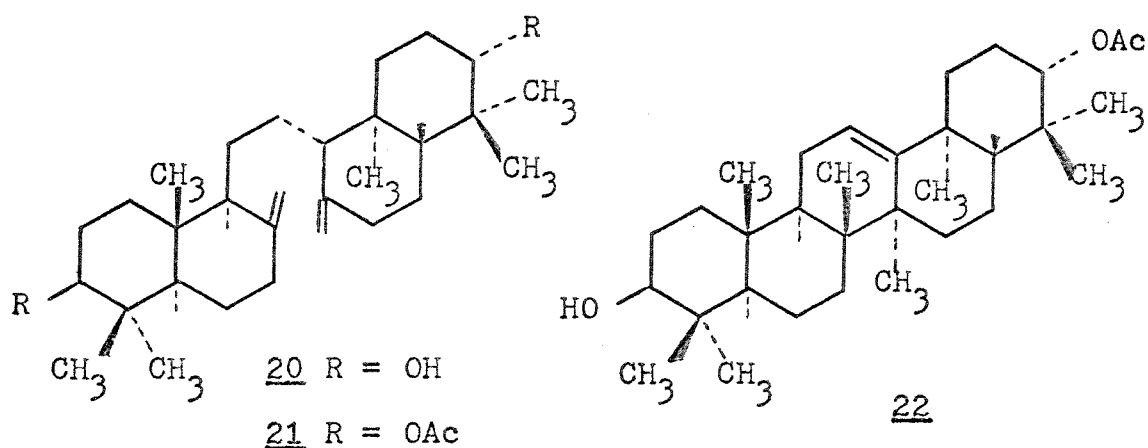


type has been recently effected by Yamada and coworkers (30) for 3 α ,4 α -epoxyshionane (17). Treatment of the oxide 17



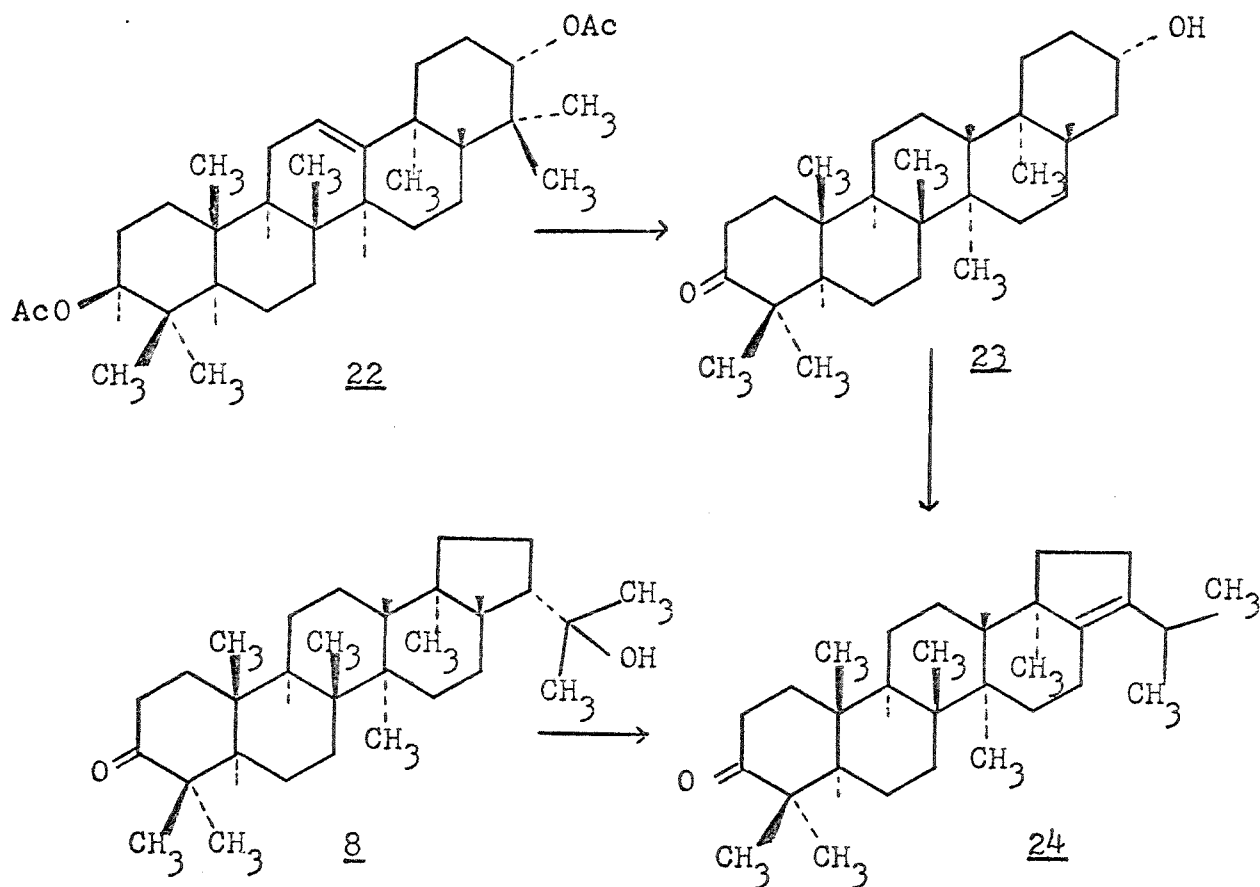
with boron trifluoride etherate afforded, among other products, the hydroxy olefins 18 and 19. Olefin 18 bears a structural relationship to β -amyrin (3b).

Total syntheses of polycyclic triterpenes began a decade ago with the synthesis of the symmetrical triterpene α -onocerin (20) by Stork (31). Logically, the symmetry



of the product suggested that the skeleton be constructed through the coupling of two identical units. Previously, while elucidating the structure of α -onocerin (20), Barton and Overton (32) had discovered that treatment of α -onocerin diacetate (21) with acid afforded the cyclized compound 22, which was named γ -onocerin diacetate. This transformation, coupled with the findings of Schaffner and coworkers (33) signified that Stork's α -onocerin synthesis (31) also constituted the first synthesis of a pentacyclic triterpene. Their work (33) involved the conversion of γ -onocerin diacetate (22) to the keto alcohol 23, and then to hopenone-I

(24), which is derived from hydroxyhopanone (8).



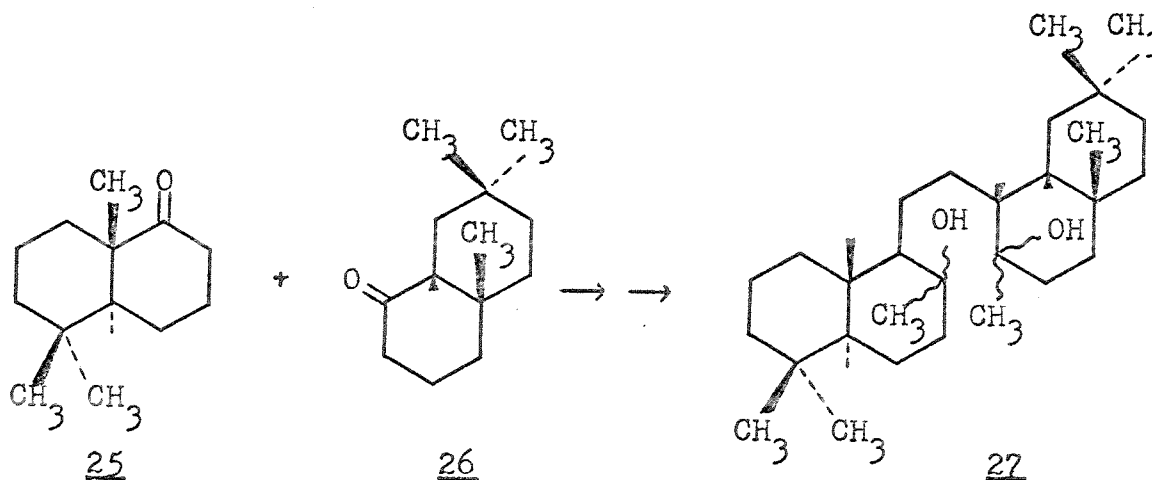
The details of these and other triterpene syntheses have been reviewed by Evans (34) and Tilley (35). The early syntheses had the disadvantage of limiting the scope to symmetrical compounds, or those which are readily converted to unsymmetrical ones, i.e., 22 → 23. In addition, the yields in the ring closure step were too low (2-20%) to provide efficient entry into the unsymmetrical triterpenes.

In 1956, Halsall and Thomas (36) first suggested the

idea of constructing the pentacyclic skeleton by joining the AB and DE portions, followed by cyclization. This approach was used by Corey and coworkers (37) in the synthesis of olean-11,13(18)-diene (B-6) by joining the olefinic bromide B-1 to the enol lactone B-2, according to the procedure outlined in Chart B. Although the scheme was fairly straightforward up to the dienol B-5, the cyclization to the diene B-6 proceeded in only 2-8% yield.

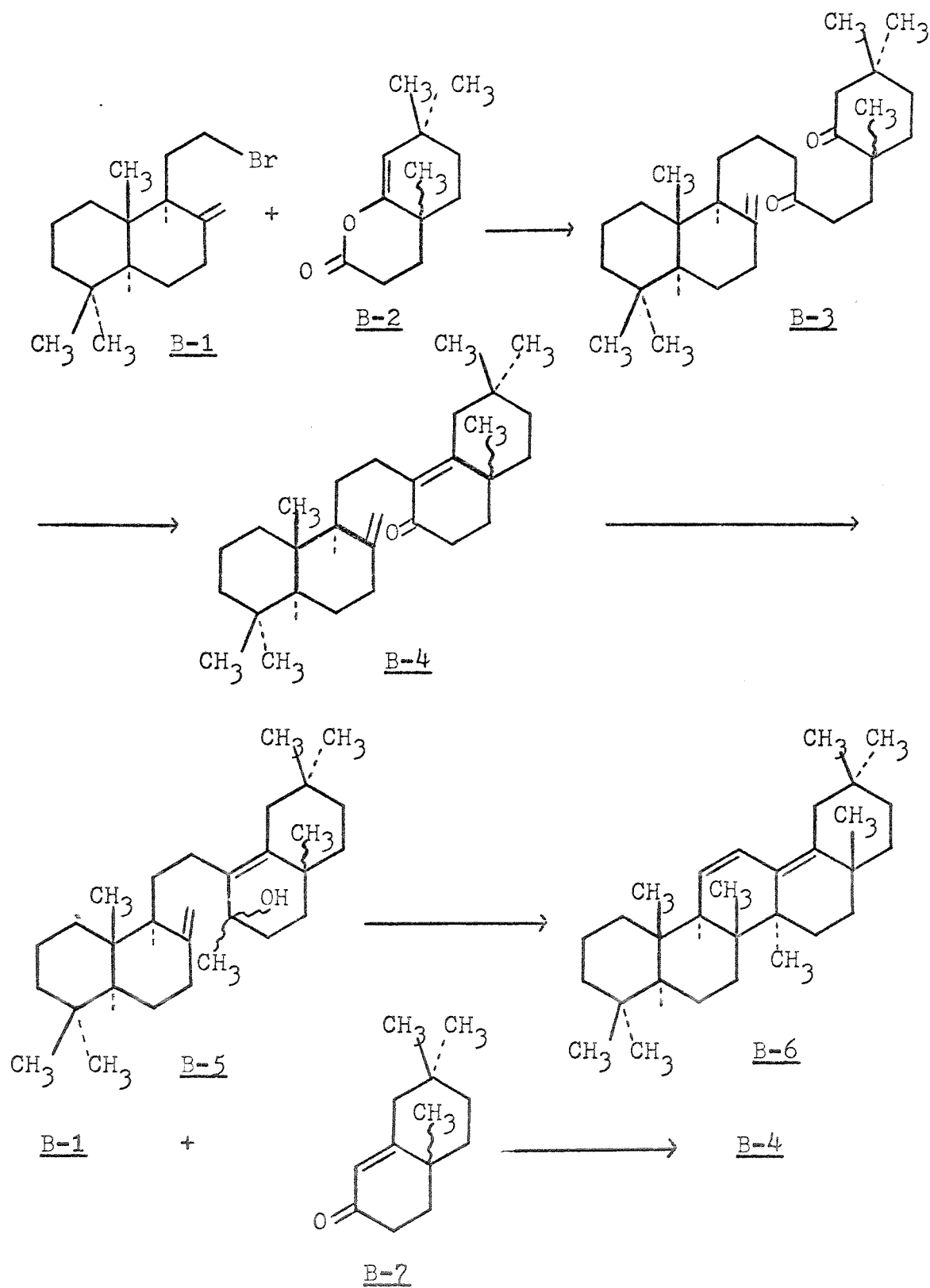
A similar approach was followed by Barltrop and coworkers (38) who synthesized enone B-4 via the bromide B-1, and the enone B-7 by treatment with base. Again, great difficulties in the cyclization step were encountered.

In a different synthesis, Ghera and Sondheimer (39) joined the trans and cis decalones, 25 and 26, via a two-



step coupling with acetylene, to ultimately form the tetracyclic diol 27. Cyclization in acid (yield not reported) yielded the equilibrium mixture of 18 α -olean-12-ene (11) and

Chart B



olean-13(18)-ene (12).

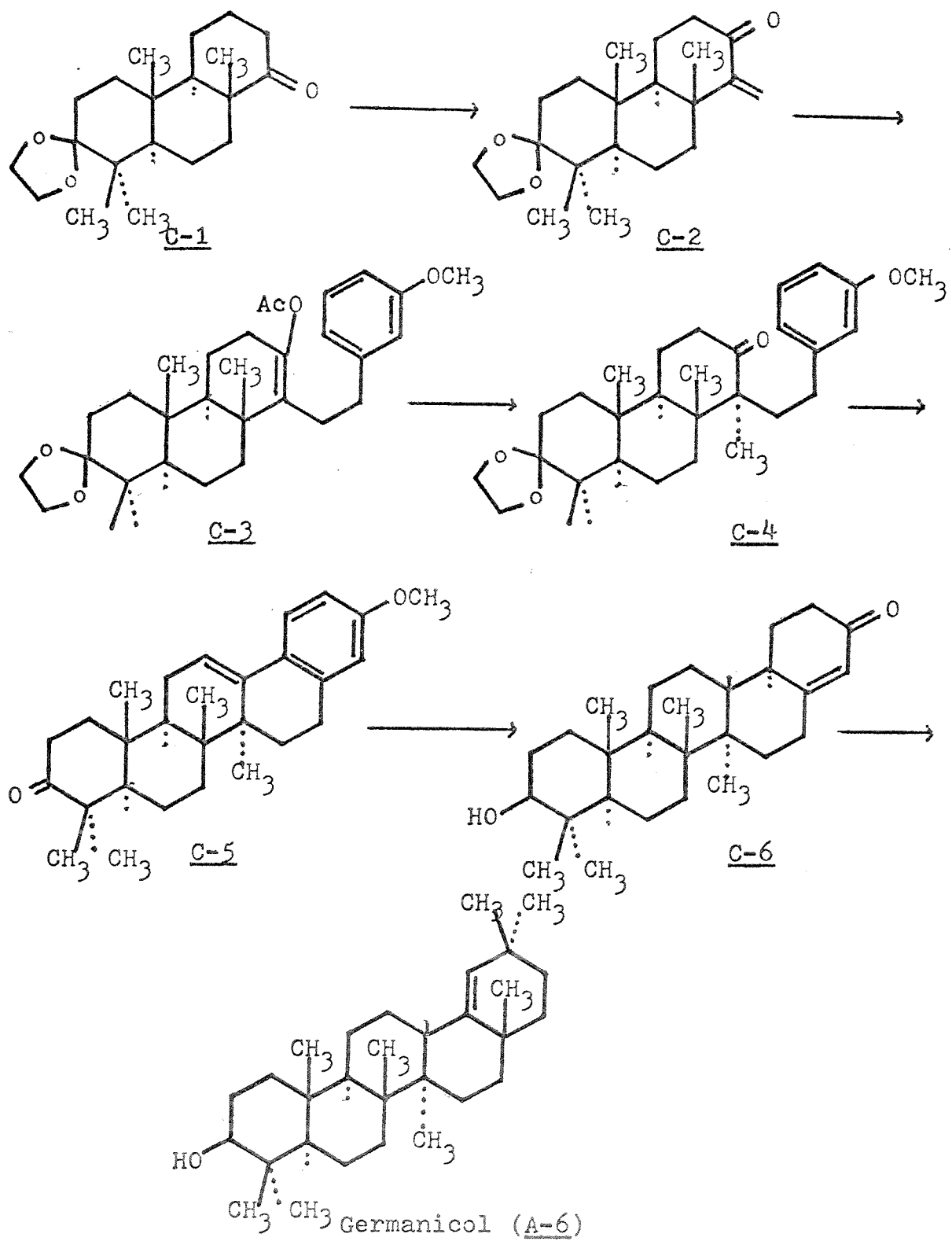
A synthesis of β -amyrin (3b) from olean-13(18)-ene (12) was reported by Barton (40) in 1968. However, its length and complexity made this route to the unsymmetrical triterpenes unattractive.

Alternatively, the ability of triterpenes of the friedelin type to rearrange to compounds having the β -amyrin skeleton does offer some attractive possibilities for the synthesis of a wide variety of triterpenes. Thus, a large part of the research efforts in the Ireland laboratory has focused on the synthesis of triterpenes of both the friedelin and β -amyrin types. This work has been highlighted by the stereoselective total syntheses of d,l-alnusenone (A-14) (41) and d,l-germanicol (A-6) (42).

The key steps in both of these syntheses lay in the stereoselective introduction of two angular methyl groups oriented trans to each other on adjacent quaternary centers.* In the case of germanicol (A-6), the problem was solved (42-44) by the steps outlined in Chart C. The ketone ketal C-1 was transformed in three steps to the unsaturated ketone C-2. Treatment of C-2 with excess m-methoxybenzylmagnesium chloride afforded an enolate which was acetylated. The resulting enol acetate C-3 could be isolated, and the enolate be regenerated in an appropriate solvent. Methyla-

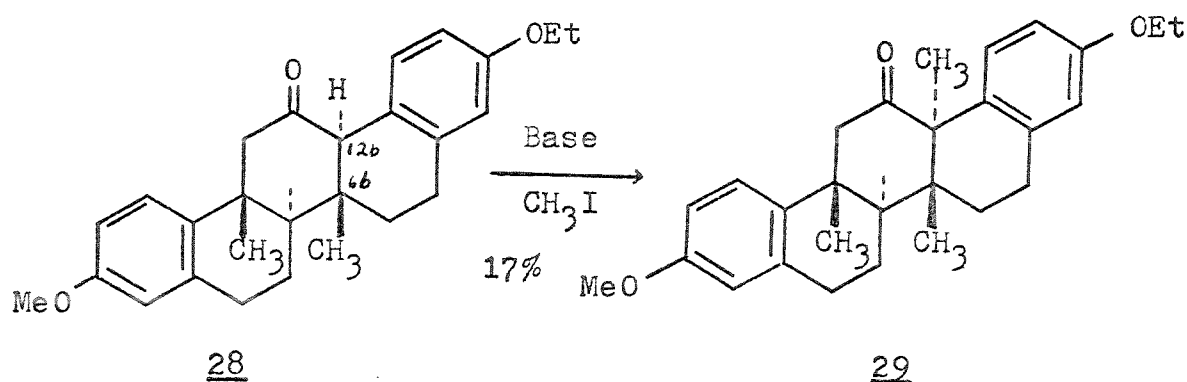
* This structure occurs widely in the triterpene family. For an extensive tabulation of the compounds, see ref. 10.

Chart C



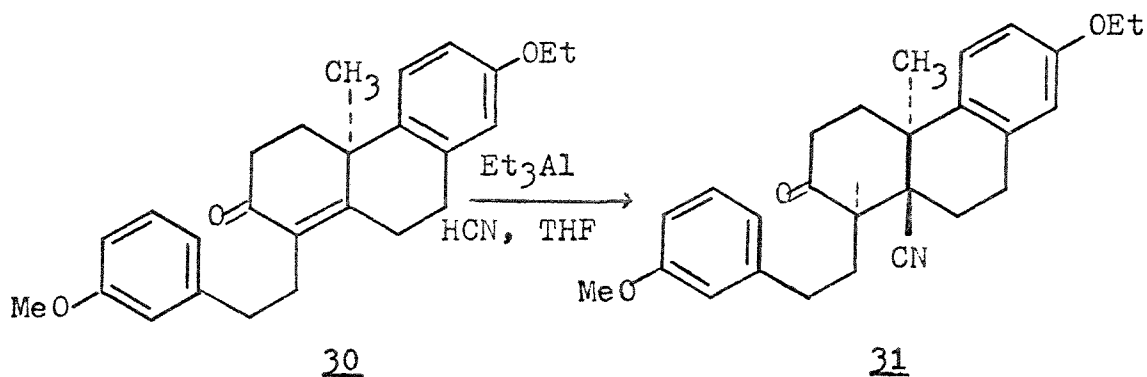
tion produced the ketone ketal C-4. Hydrolysis of the ketal and cyclization with polyphosphoric acid proceeded smoothly, yielding the unsaturated ketone C-5. Reduction of the carbonyl group and a two-step lithium-ammonia reduction afforded the hydroxy enone C-6. The methyl group at C-4a was introduced via a conjugate addition of cyanide (45). Formation of unsaturation next to the C-3 carbonyl group, followed by geminal methylation and removal of the carbonyl and C-4a functionality afforded d,l-germanicol (A-6). The conversion of ketone C-4 to enone C-6 played an important part in a related phase of the present work (see discussion section).

In an early attempt at the synthesis (34,46) of alnusone (A-14), the introduction of a methyl group at C-12b oriented trans to the one at C-6b in ketone 28 to produce



ketone 29 met with poor success. Only 17% of ketone 29 was formed, along with 60% of O-methylated product and 13% of starting material, ketone 28. This problem was circumvented

in the final synthesis (41) via a conjugate addition of cyanide (45) to enone 30 to afford the trans cyano ketone



31 in high yield. The subsequent features of the synthesis are outlined in Chart D. From the cyano ketone 31, a four-step sequence produced the olefinic mixture D-1, in which the cyano group at C-6b had been reduced to the required β -methyl group. Cyclization of the mixture D-1 afforded a 1:3 mixture of the B/C cis compound D-2, and the desired B/C trans isomer D-3. Elaboration of ring E was effected through a four-step sequence to enone D-4. The C-8a methyl group was introduced via a cyclopropane in two steps, followed by oxidation to afford the cyclopropyl ketone D-5. The methano group served not only as a precursor to the C-8a methyl, but also as a protective group against methylation at C-9. Base-catalyzed methylation occurred exclusively at C-11, and removal of the carbonyl group afforded the pentacyclic ether D-6. Birch reduction, followed by methylation afforded d,l-alnusenone (A-14).

Chart D

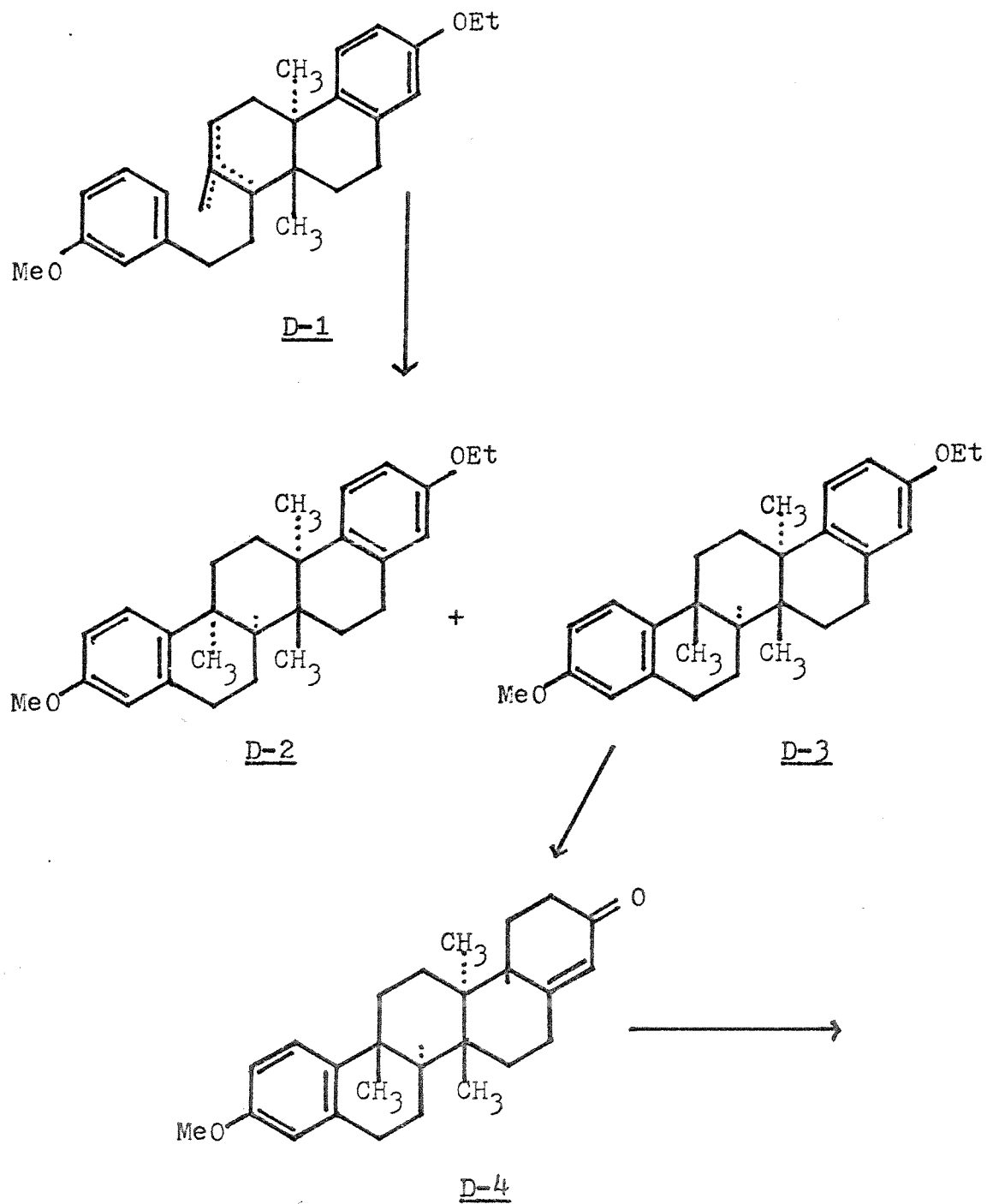
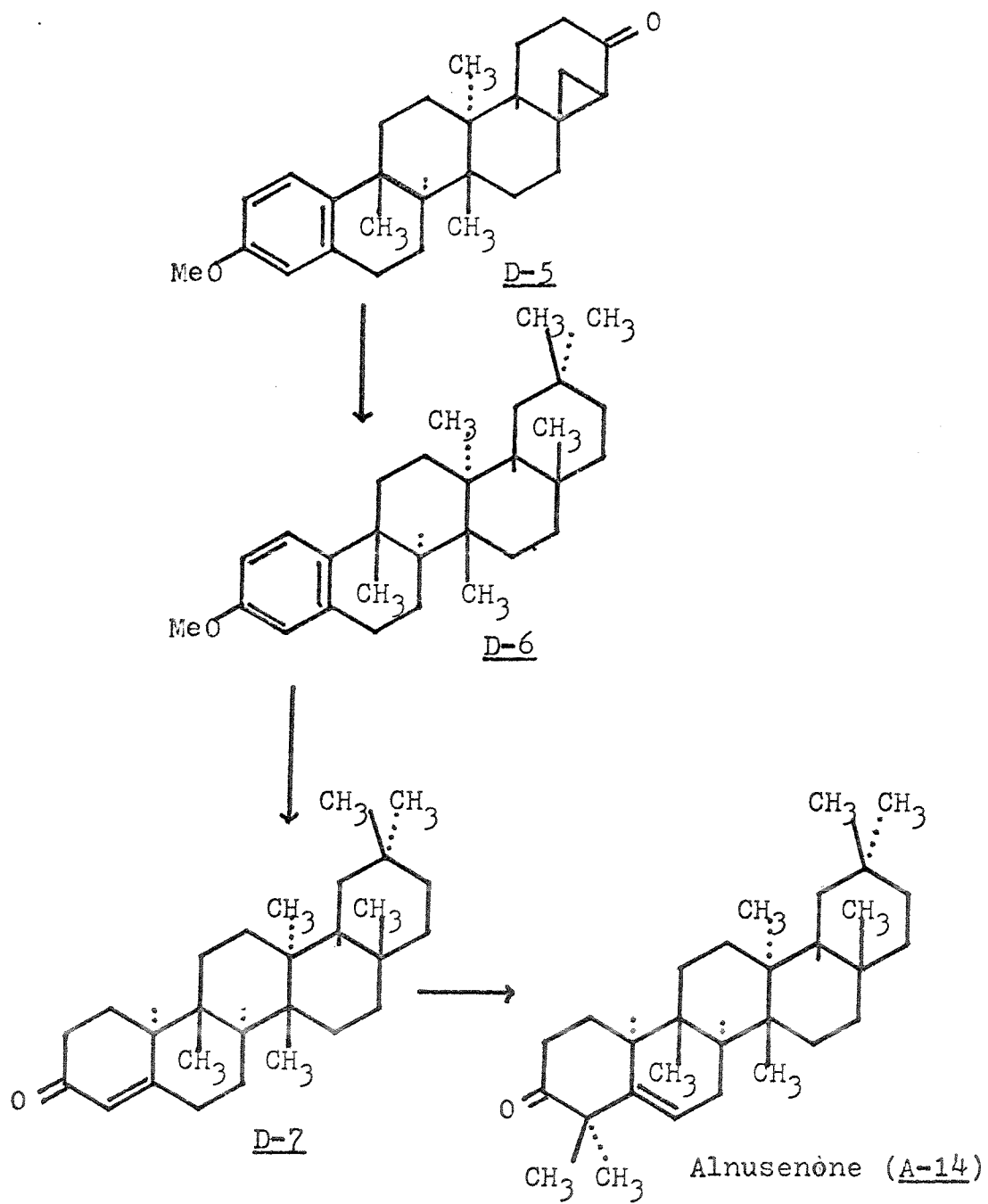


Chart D (continued)



The use of aromatic rings as precursors to cyclohexane rings has found wide application in the steroid field (47a,b). The pentacyclic enone D-7 might also serve as a suitable precursor for friedelin (A-15). Recently, Tilley (35) synthesized the tetracyclic keto olefin 32 in five steps from the dienone 33, as a possible approach to the synthesis of shionone A-7, as a possible approach to the synthesis of shionone 34,

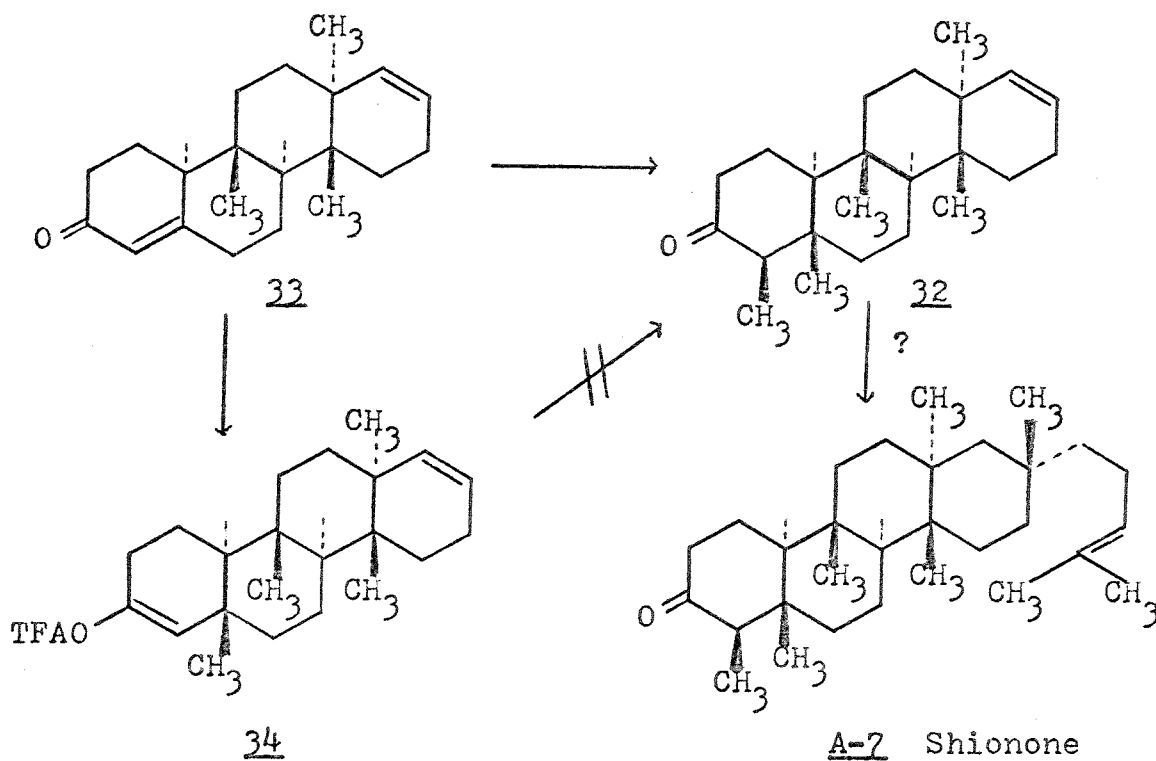
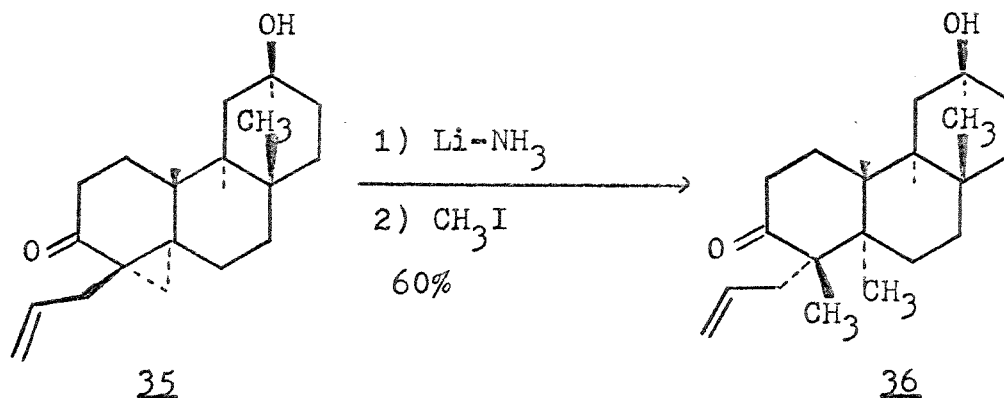


Fig. 4

onone (A-7) (Fig. 4). Thus, a plausible route was available for the synthesis of friedelin (A-15) from enone D-7. The synthesis described in Figure 4 was complicated by stereochemical problems and some low yields. This was partially

overcome by Kowalski (48) who prepared the dienol-trifluoroacetate 34 from dienone 33, but could not convert it into ketone 32. Hence, the elaboration of ring A for shionone and friedelin has not yet been accomplished with good efficiency.

Recently, Stork and coworkers (49) have completed a synthesis of lupeol (2b). One aspect of the synthesis is especially important in relation to the present work. That is the reductive cleavage-methylation of the cyclopropyl ketone 35, to afford the keto olefin 36. This provides another example of trans vicinal methylation, as well as providing a precedent for a reaction to be discussed later.



Finally, the biogenetic-like approach (50) to natural product synthesis has resulted in the ingenious syntheses of a number of triterpenoids (Chart E), such as β -onocerin (E-1) (51a), malabricanediol (E-2) (51b), hexanor-isoeuphenol (E-3, R = H) (51c), 24,25-dihydrolanosterol (E-4) (51d,e), 24,25-dihydroprotosterol (E-5) (51e), parkeol (E-7) (51e), tetrahymanol (E-8) (51f), α -amyrin (E-9) (51g), β -amyrin (3b) (51g), and germanicol (A-6) (51g), isoeuphenol

Chart E

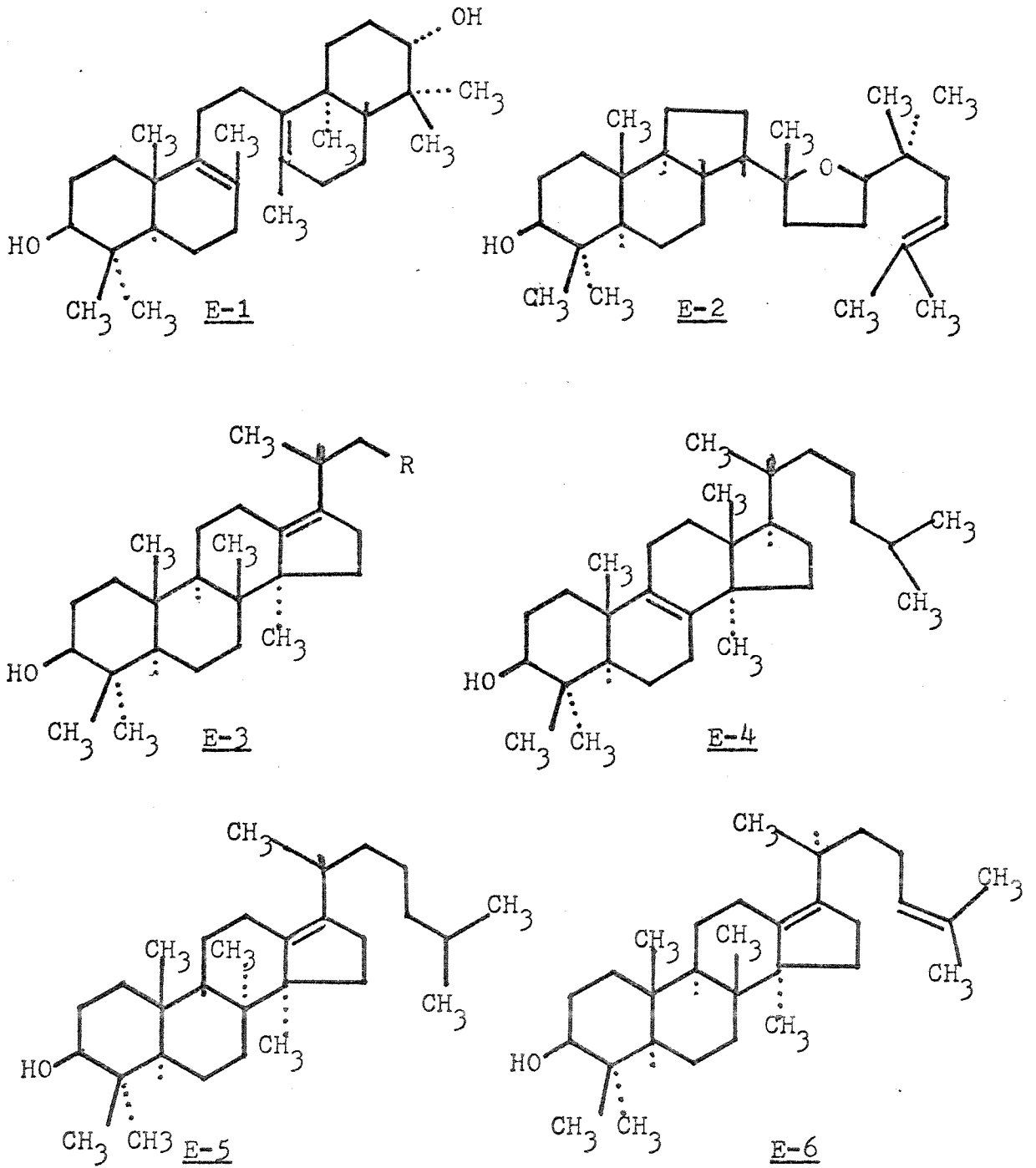
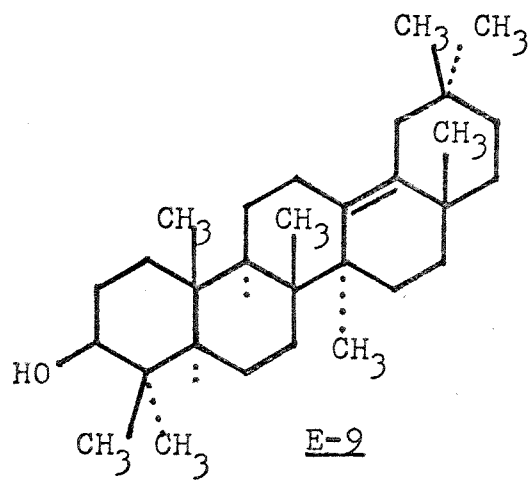
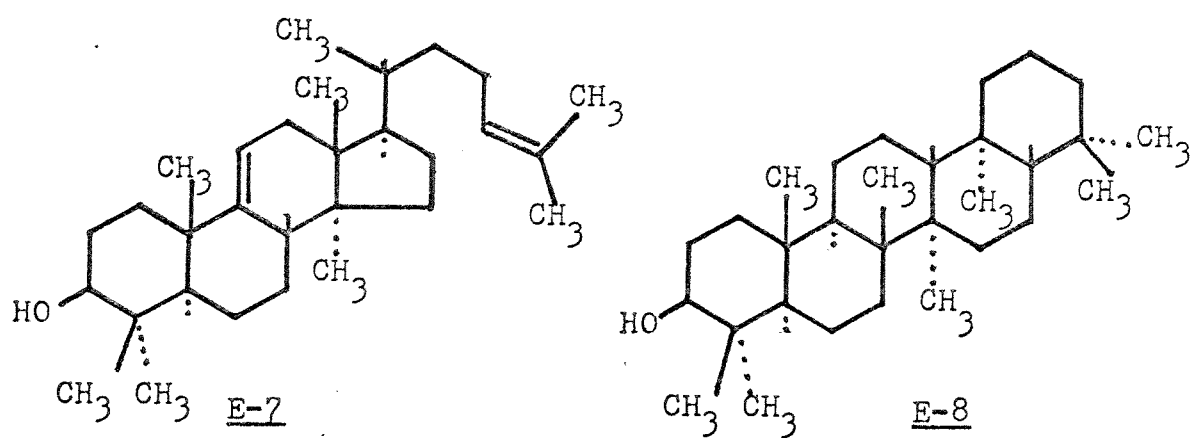


Chart E (continued)



(E-3, R = CH₂CH=C(CH₃)₂) (51e), and isotirucallol (E-6) (51e).

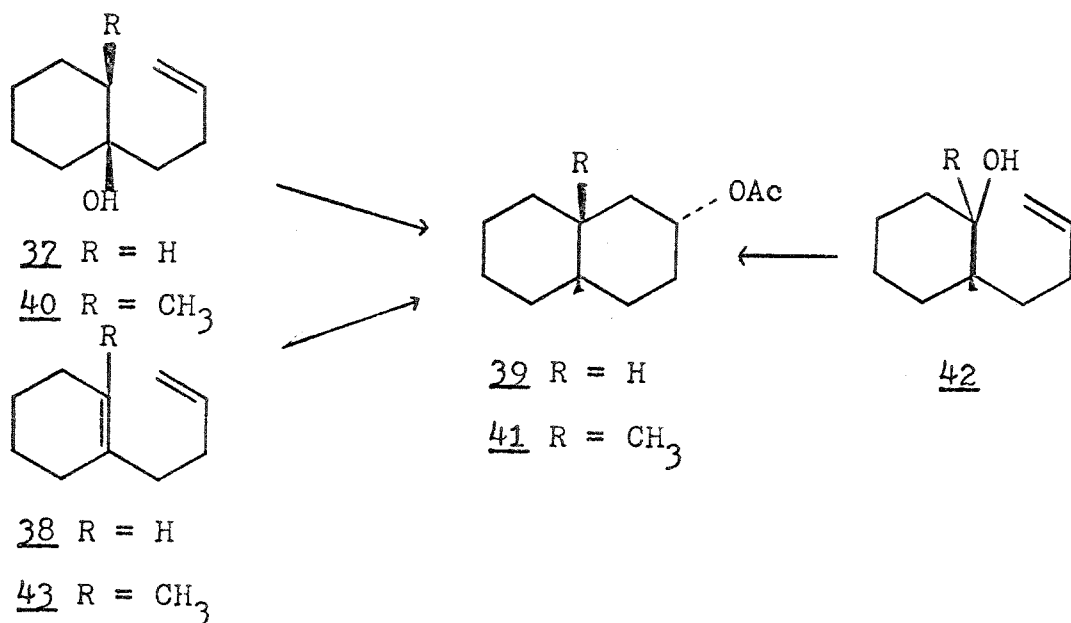
II. Polyolefin Cyclizations

The process of forming alicyclic compounds by the acid treatment of acyclic, polyolefinic substrates has been known for some time, largely from work in the terpene field (52). In 1936, Hibbit and Linstead (53) studied the cyclizations of a number of monoolefinic alcohols and established the most favorable structural relationships for cyclization. The two basic rules are: 1) the cationic center should be separated from the double bond by three tetrahedral carbons (cyclohexyl cation formation), and 2) that the attacking double bond have a substituent on the first olefinic carbon to stabilize the newly formed cation.* There are some exceptions to these rules. If the electronic factors are such that a five-membered ring would be more stable electronically than a six-membered one, then its formation will be preferred or at least competitive (54). Secondly, five-membered rings can also be formed if the attacking double bond is of low nucleophilicity (or an aromatic ring) (55), so as to allow a non-concerted cyclization.

The stereochemical aspects of polyene cyclization began to take shape with some later work of Linstead (56). Treatment of 1-(3-butenyl)-cyclohexanol (37) or 1-(3-butenyl)-

* For a recent study on this subject, see ref. 65b.

cyclohexene (38) with mixtures of acetic and sulfuric acids and acetic anhydride gave a 25% yield of cis- α -decalyl acetate (39) (56a). Similarly, cyclization of the 2-methyl alcohol 40 yielded mostly the cis acetate 41 (56b). Acetate 41 was also produced from the isomeric alcohol 42 (56c).



Stork's first interpretation of these results (57) postulated the intermediacy of the monocyclic diene 43 (Fig. 5).

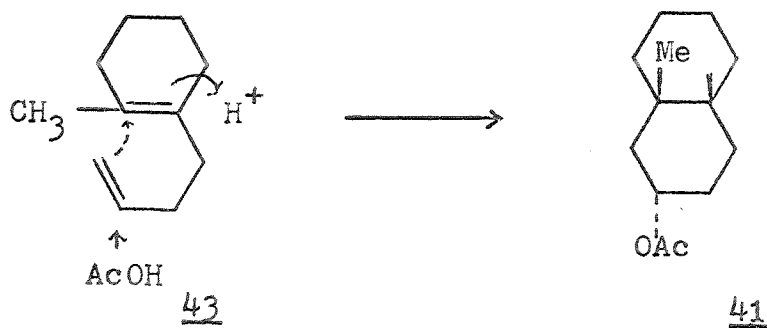


Fig. 5

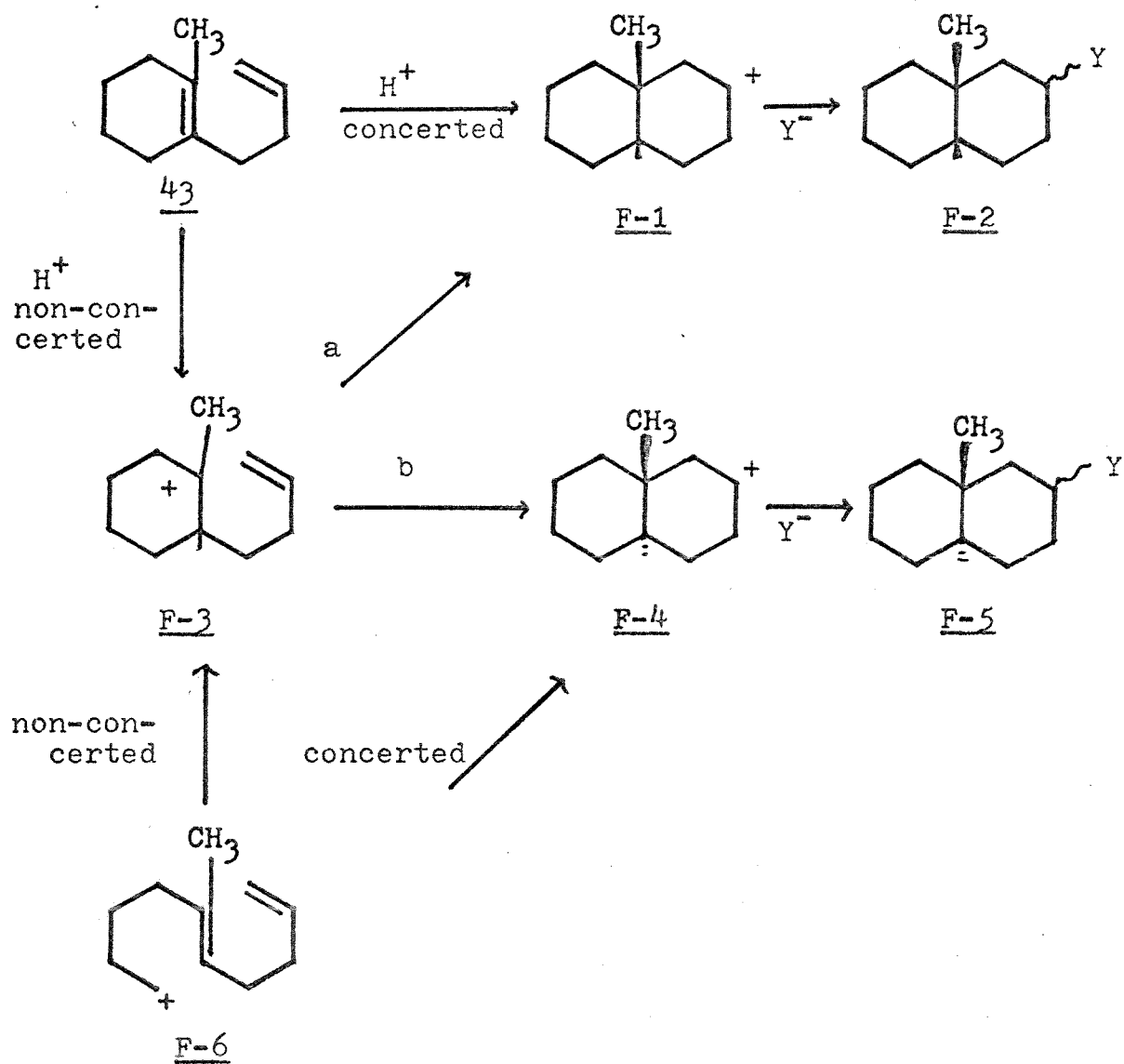
Concerted protonation is believed to occur at the endocyclic double bond with concomitant migration of the butenyl double bond in a trans, antiparallel fashion, followed by attack by acetate on position 3 of the side chain.

The finding that lanosterol (1) was biogenetically derived from squalene (4) (12,13) set the stage for intensified study of the polyene cyclization process. Thus, in 1955, Stork (17) and Eschenmoser (18) independently formulated their hypothesis which launched the ever-growing field of research on non-enzymic polyolefin cyclization.

The essential features of their hypothesis is outlined in Chart F. If a polyolefin, such as the monocyclic diene 43 is protonated by acid in a concerted fashion (Fig. 5), then cyclization will lead to the formation of the bicyclic cation F-1, which can undergo attack by a nucleophile Y^- , to give the bicyclic product F-2, possessing a cis ring fusion. On the other hand, if the protonation is non-concerted, then the monocyclic cation F-3 is produced, and the cyclization could then proceed through two alternate pathways, a and b, leading to the bicyclic cations F-1 and F-4, respectively. Attack by Y^- on F-1 would again produce cis-fused F-2, whereas attack on the trans cation F-4 would give rise to the trans-fused decalin F-5.

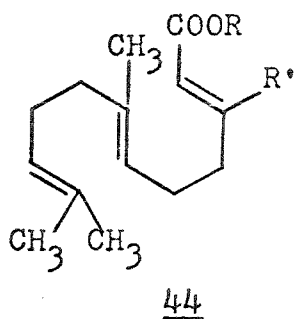
Extending this one step further, if an acyclic dienyl cation, such as F-6 could be produced, then concerted cyclization would produce the trans-fused cation F-4, leading to

Chart F



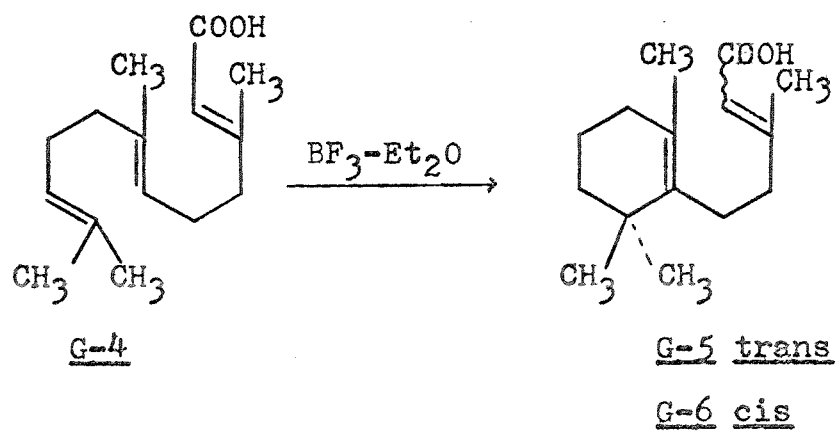
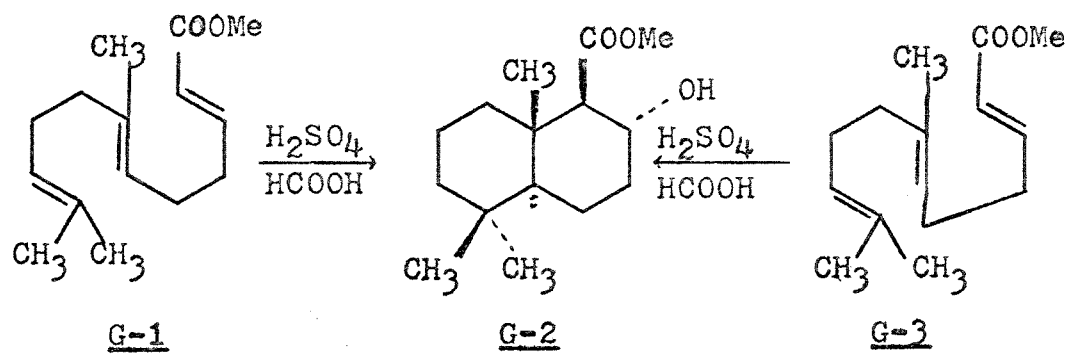
trans decalin F-5. Non-concerted cyclization would then produce the monocyclic cation F-3, which would then react as previously described. In summary, concerted cyclization of a polyene containing a trans double bond yields a product with trans fused rings. Similarly, cis fused rings are formed if the internal double bond in the substrate is cis.

Eager to test their hypothesis, Stork (17) and Eschenmoser (18) made compounds of general formula 44 and tested their cyclization under acidic conditions. A summary of



their work is described in Chart G. Eschenmoser subjected trans-desmethyl farnesic ester (G-1) to acid and obtained the bicyclic hydroxy ester G-2 in 60-70% yield. However, on cyclization of the cis ester G-3, the trans product G-2 was also obtained (59). The results are explained on the basis of Stork's findings (17) from the cyclization of farnesic acid (G-4) with boron trifluoride etherate in benzene, in which the monocyclic acids, G-5 and G-6, were isolated. Thus, the isomeric esters G-1 and G-3 were probably cyclizing to the monocyclic ester 45, which was then protonated in a

Chart G



non-concerted fashion to give the cation 46 (see F-3 in

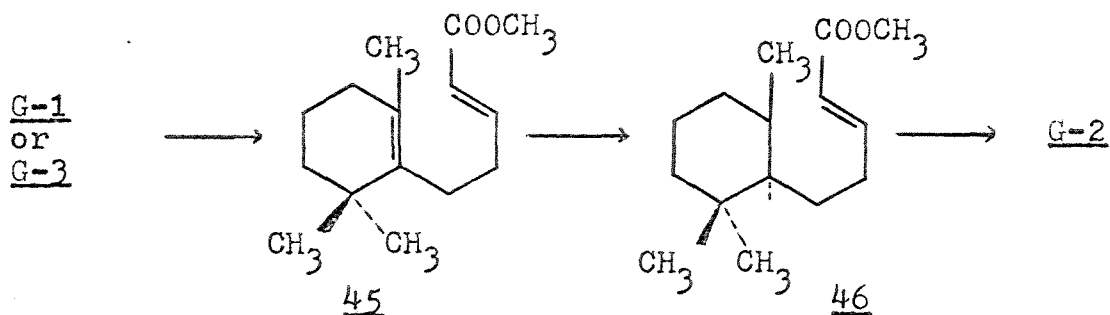


Chart F) which then cyclized to give the trans bicyclic ester G-2. The feasibility of alicyclic cations as intermediates in certain cyclizations has been discussed (59-62).

When attempts were made to extend these cyclizations to larger systems containing more double bonds, the yields were drastically lowered. This was explained by Johnson (63) on the premise that a molecule containing a number of highly substituted double bonds would probably suffer indiscriminate protonation, resulting in a myriad of cyclization products. Consequently, the answer to the dilemma lay in the construction of a substrate, which under the appropriate conditions, would lead to the selective formation of a single cation.* The results of some of the efforts in the laboratories of Johnson (63) and van Tamelen (64) have been reviewed.

* The term "cation" is used here and throughout this thesis in a rather loose interpretation. It is used for the purpose of clarity, with no attempt being made to distinguish between actual cations, transitory cations, bridged cations, or solvated cations.

The key feature of all these and related studies (51,61, 62,65-71) is the selective formation of a cation in the presence of properly juxtaposed double bonds of known stereochemistry, via the acidic protonation or complexation of an appropriate oxygen-containing functional group. Those groups which have been successfully utilized for selective cation generation include alcohol esters (63,65), epoxides (51,66), acetals (67), aldehydes (68), and allylic alcohols (69,70). Of related interest are cyclizations in which the initiating functionality is a cyclopropyl ketone (71), and in which acetylenic bonds, as well as olefins, participate in the cyclization (70,72).

The yields of fully-cyclized material in those cases studied depended on a number of factors. These variables included reaction conditions, type of oxygen functionality, number of double bonds, and the degree of substitution about them. However, one phenomenon was common to all these studies: the stereochemistry about the ring fusions in the products were obtained stereospecifically, and were determined solely by the stereochemistry of the double bond from which it was formed. Some possible exceptions to this were those cases in which there was the possibility of a deprotonation-reprotonation sequence during the cyclization (72,73). Cyclizations of this type have been observed frequently in the Ireland laboratories (35,72-75).

The complete preservation of stereochemistry during the

cyclization is consistent with either the concerted mechanism of Stork (17) and Eschenmoser (18), or one which involves intermediate bridged ions (Fig. 6). These bridged intermedi-

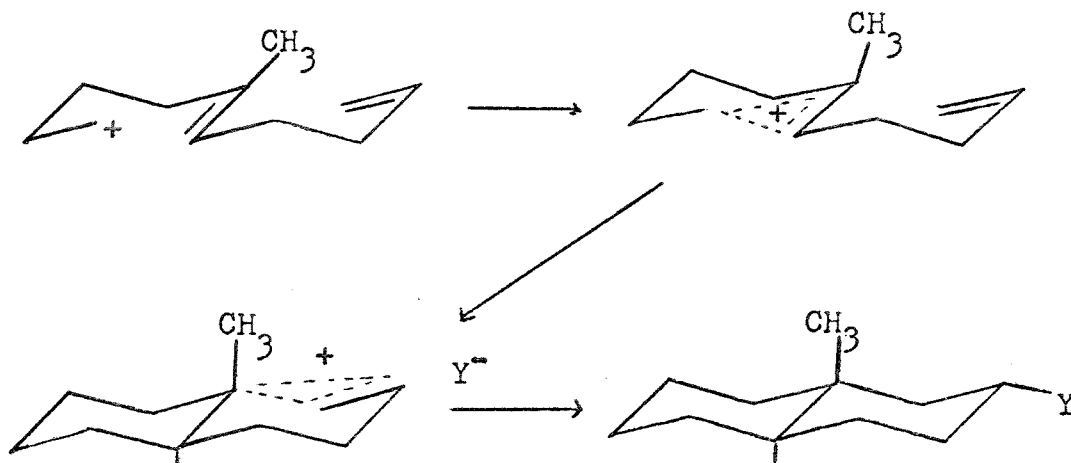


Fig. 6

ates have been suggested by Johnson and Crandall (76) as a possible explanation for the observations in their sulfonate ester solvolyses.

A third mechanism which may explain some of the observations reported (17,18,63,64,66d,f) involves the intermediacy of short-lived alicyclic cations. Strong arguments in favor of this mechanism have been presented by Harding (61, 62,77). While this mechanism cannot explain reactions in which a cis double bond is cyclized with complete stereochemical retention, the possibility of its occurrence in the formation of trans fused rings cannot be ruled out.

Thus, polyene cyclization studies have provided the opportunity for chemists to employ a series of highly predictable theoretical concepts to gain high achievements in synthetic endeavors, none the least of which are the synthesis of steroids (69g,j,70) and triterpenoids (51). In addition, the study of polyene cyclizations have led to the discovery of efficient methods for the stereoselective synthesis of trisubstituted olefins. These methods developed through 1971 have been reviewed (78).

Of special interest to the present work are the early studies of Johnson (61,69a,c,e-i) and Marshall (69b,d,k) in which an allylic alcohol was used as a substrate for cyclization. These studies are summarized in Table I. Allylic alcohols have the advantage of being capable of easily generating stable allylic cations, which can readily undergo cyclization with an appropriately situated double bond (60, 79). In addition, attack on the allylic cation by an ionizing solvent, such as formic acid, would not hamper the cyclization, since this process is potentially reversible. From those studies outlined in Table I, of special note are those in which a cis octalin system is generated in the first two rings of the product (reactions 2,5-8). The rationale behind the formation of the cis product has been discussed previously (61,69a,f) and is shown in Fig. 7. The generalized allylic cation 48, which could be formed from allylic alcohol 47, can exist in either of two possible ground state

Table I

<u>Rxn.</u>	<u>Substrate</u>	<u>Major product</u>	<u>% Yield</u>	<u>Ref.</u>
1			80-92	69a
2			50	61, 69a, f
3			80	69b, d
4			30	69c
5			90	61, 69c, f
6				69k

Table I (continued)

<u>Rxn.</u>	<u>Substrate</u>	<u>Major Product</u>	<u>% Yield</u>	<u>Ref.</u>
7			55	61
8			22	61
9			30, 70	69g, j
10			34	69e, h
			60	
11			52	69i

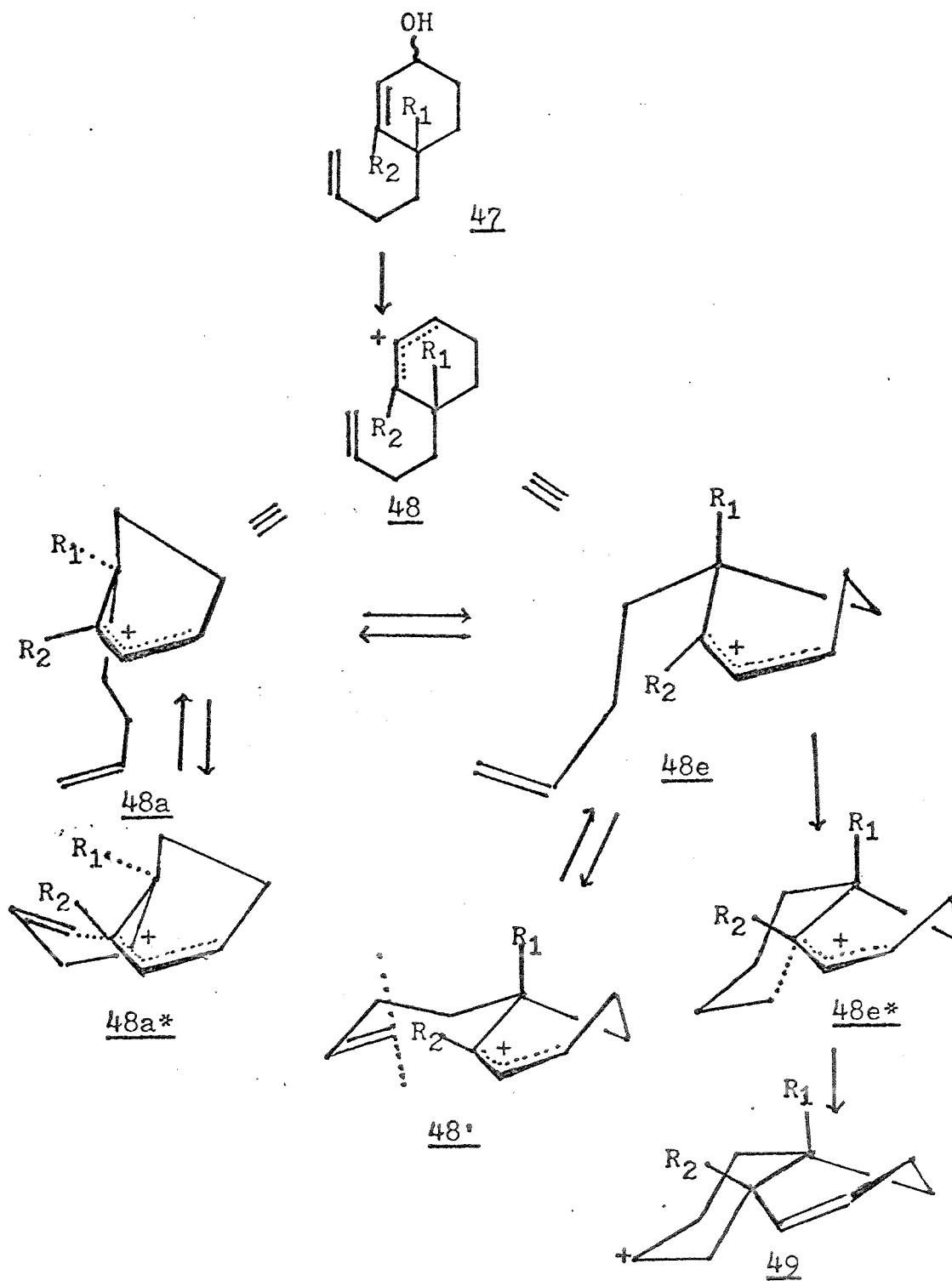
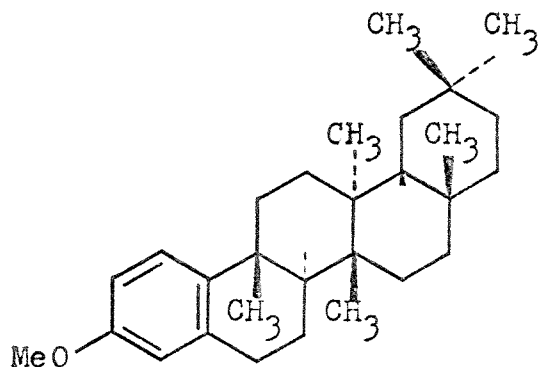


Fig. 7

conformations, 48a and 48e, depending on whether the side is axial or equatorial, respectively. For cyclization to occur, the attacking double bond must be oriented parallel to the plane of the allylic system, so as to allow maximum π -orbital overlap in the transition state (80). While this is theoretically possible for transition states 48a* and 48e*, the conformation of the side chain in 48a* is in the form of a highly distorted boat, the energy of which would be high enough to prevent cyclization and allow ring inversion to produce the other conformer, 48e, and finally, 48e*. The other possible transition state conformation of cation 48 is 48*, in which the side chain is above the plane of the ring. Cyclization in this conformation would lead to trans fused products. Examination of a model of cation 48* indicates that the side chain is not long enough to allow overlap between the π -orbitals of the allylic system and the side chain double bond without serious distortion of the latter. Hence, it is reasonable to assume that only transition state 48e* is of sufficiently low energy to permit cyclization, leading to the cis fused octalyl cation 49. Once the first cyclization step has occurred, or if the cyclization is concerted, the stereochemistry of the remaining double bonds will determine ring fusion geometry, as was discussed above.

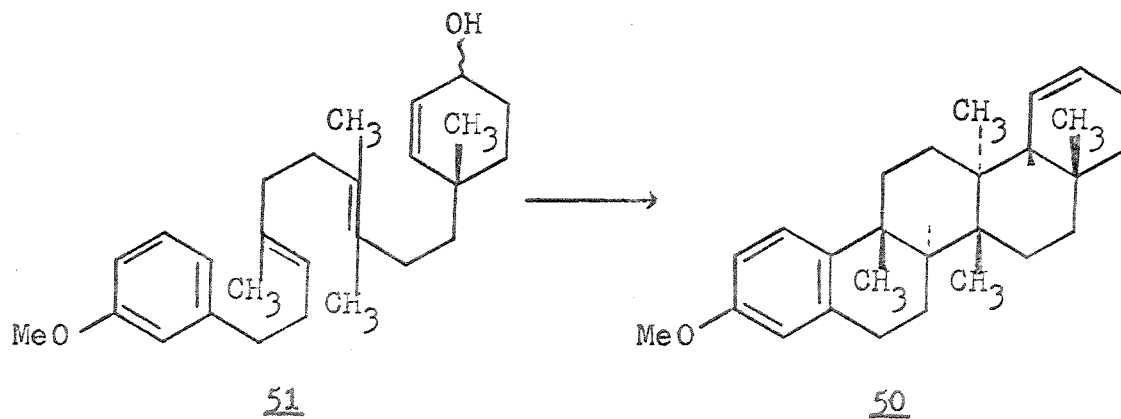
Referring again to Table I, it is noteworthy that the polycyclic products from reactions 7 and 8 have cis,anti,trans geometries about their first three rings. This is exactly

the proper stereochemistry for the C/D and D/E ring junctions of the pentacyclic ether D-6, an intermediate in the



D-6

alnusenone synthesis (41). Hence, it was hoped that the olefinic ether 50 could be synthesized via a cationic cyclization of allylic alcohol 51, and that D-6 could be made via elaboration of olefin 50, thus constituting a formal total synthesis of alnusenone (A-14). The studies leading toward this ultimate goal comprise the essential features of the research described in this thesis.

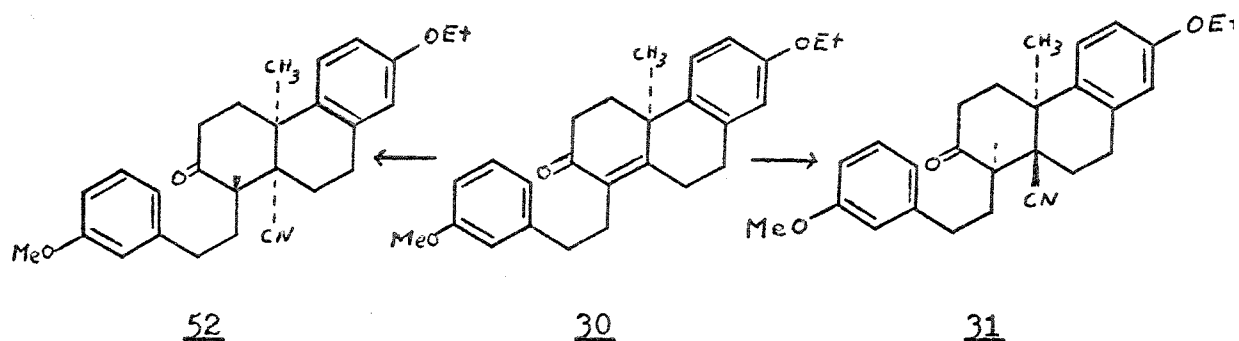


51

50

Discussion

Early in the work leading to the synthesis of alnusenone (A-14) (41), progress was hampered to some extent by the finding that the product resulting from the addition of diethylaluminum cyanide in benzene (45b) to enone 30 was al-

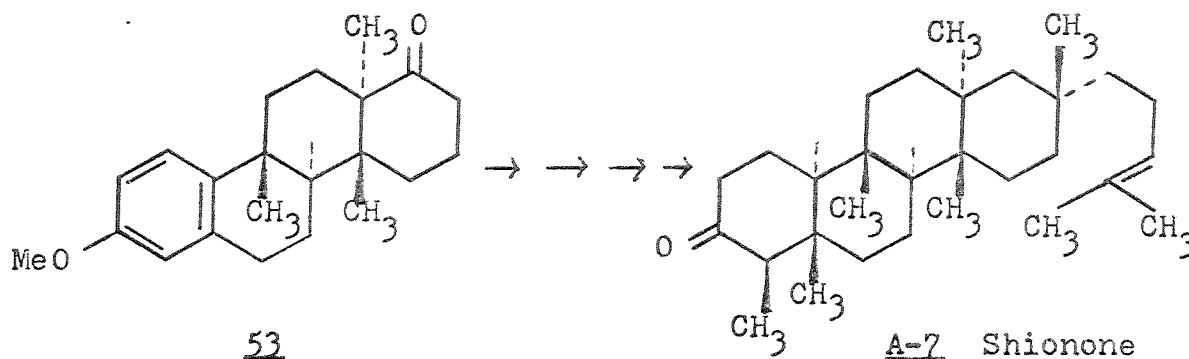


most exclusively the cis cyano ketone 52. This difficulty was soon overcome by employing the protonic conditions of triethylaluminum and hydrogen cyanide in tetrahydrofuran (45a), thus affording the desired trans cyano ketone 31 in high yield.

While this work was in progress, other methods of selective generation of trans 1,2-diaxial methyl groups in cyclic systems became the subject of extensive investigation in the Ireland laboratory. Other previous approaches from this laboratory (34,46) and others (81,82) gave predominately cis products.

One synthetic goal to which several investigators directed

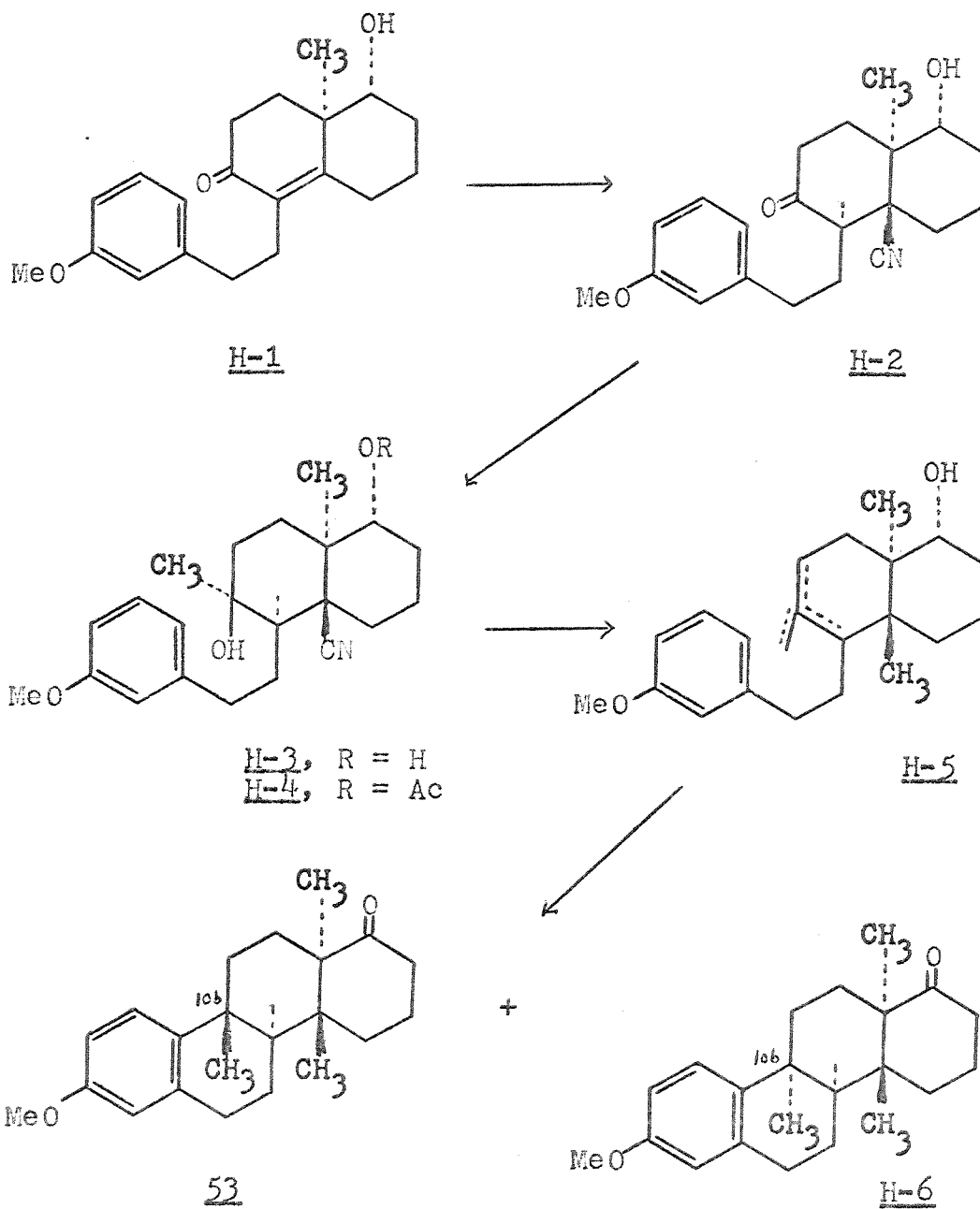
their efforts was the tetracyclic ketone 53, a potentially



useful intermediate for the synthesis of shionone (A-7). In one approach, ketone 53 was synthesized by procedures similar to those described for alnusenone (A-14) (41). The details of this route are described in Chart H (74). Addition of either cyanide reagent to the hydroxy enone H-1, afforded the trans cyano ketone H-2 as the major product in 80% yield. Addition of methyl Grignard to ketone H-2 yielded the cyano diol H-3, which was monoacetylated to the hydroxy cyano acetate H-4. Dehydration, followed by nitrile reduction proceeded with hydrolysis of the acetate, affording the mixture of hydroxy olefins H-5. Oxidation of the hydroxyl and acid-catalyzed cyclization with *p*-toluenesulfonic acid in boiling toluene afforded an 82:18 ratio of the desired ketone 53, and the cis,anti,trans isomer, H-6. The overall yield was 10% from commercial materials.

In another approach the cyclopropyl methyl ether J-1 (35,83) was caused to react with lithium *m*-methoxyphenyl

Chart H



acetylide, followed by triple bond reduction, to afford alcohol J-2 and its C-1 epimer in roughly equal amounts (Chart J). Dehydration of alcohol J-2, followed by hydroboration, yielded the secondary alcohol J-3. Oxidation of the hydroxyl group and treatment of the resulting ketone with methyl lithium afforded the tertiary alcohol J-4, which underwent dehydration and cyclopropane cleavage to afford the olefinic ketone H-5. Treatment with trifluoroacetic acid* produced the tetracyclic ketones 53 and H-6. The overall yield was 3.3% from commercial materials.

Prior to these studies, Ireland and Dawson (68c) had successfully effected a concerted cyclization (see introduction, part II) of aldehyde 54 (Fig. 8) with stannic chloride in

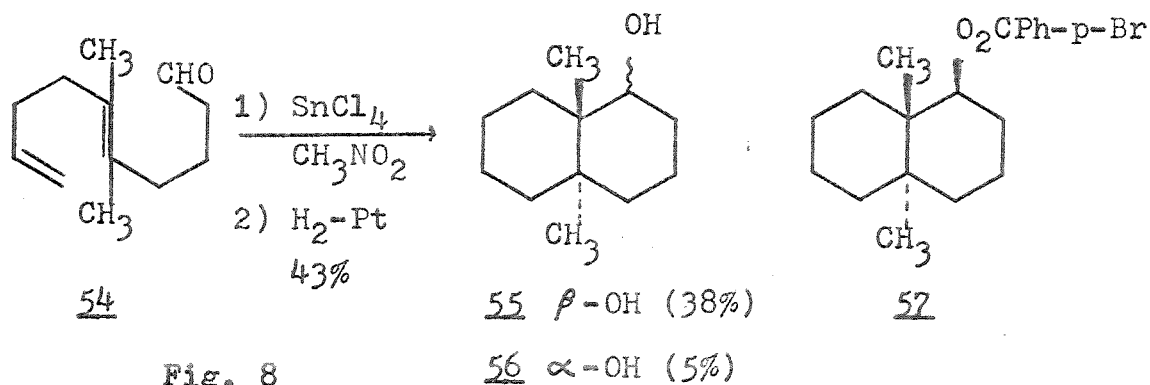


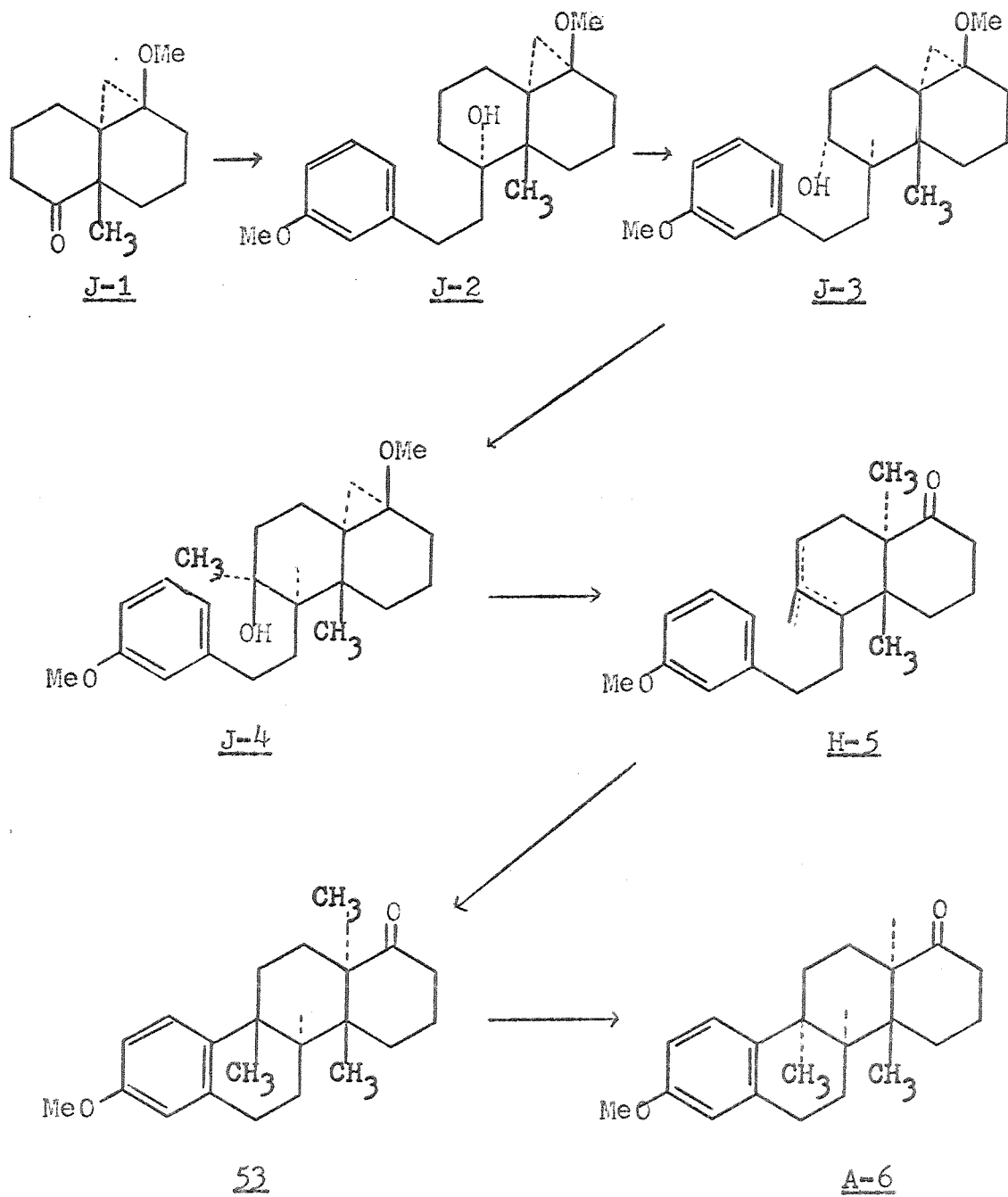
Fig. 8

nitromethane to produce the epimeric alcohols 55 and 56.

Proof of the trans stereochemistry of the methyl groups was shown by an x-ray crystallography study of the p-bromoben-

* These conditions produced an 85:15 ratio of the tetracyclic ketones 53 and H-6 in contrast to the 82:18 ratio using p-toluenesulfonic acid in toluene.

Chart J



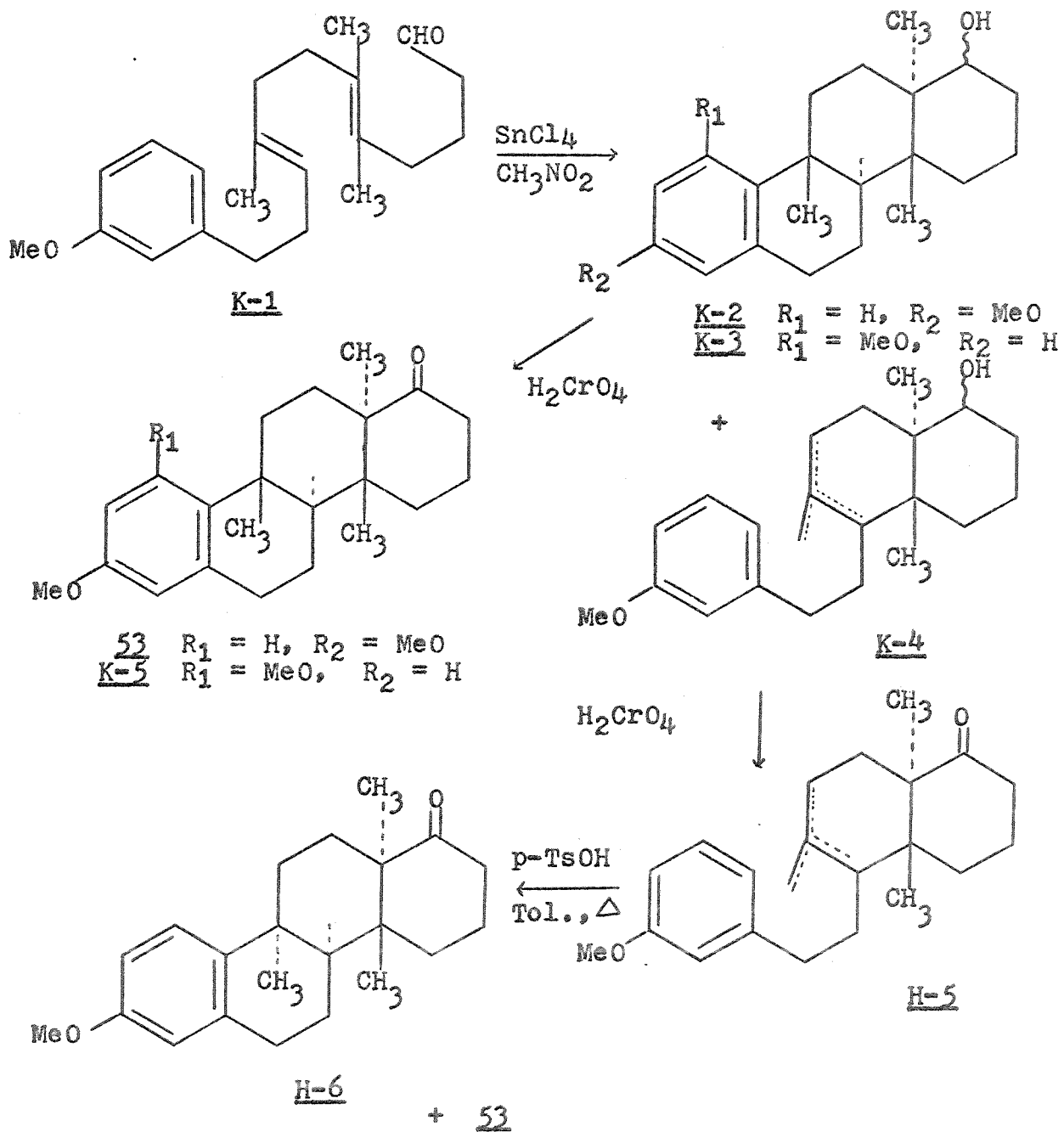
zoate 52, which was derived from the β -alcohol 55.

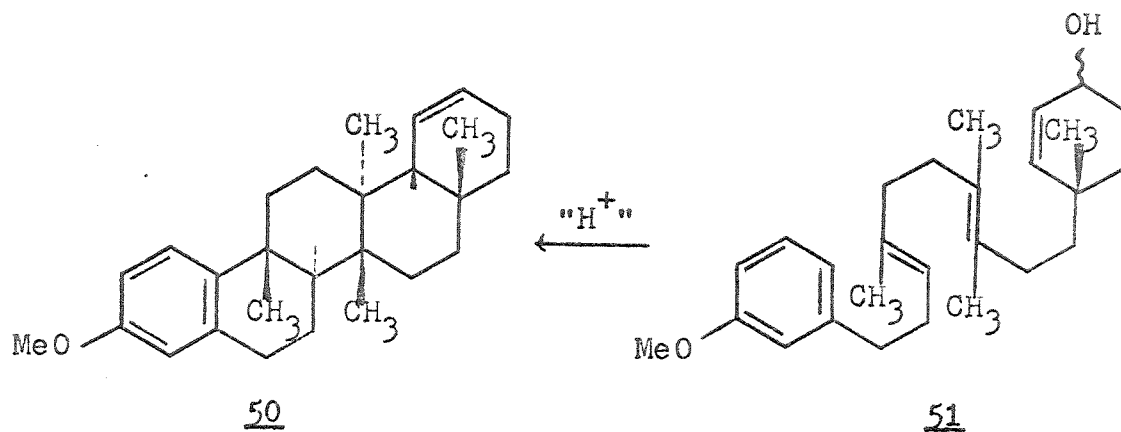
The success of this work prompted an extension of the cyclization studies, in order to utilize aldehyde K-1* (75) to furnish the tetracyclic ketone 53 (Chart K). Thus, treatment of aldehyde K-1 with stannic chloride in nitromethane afforded a mixture of products, from which three could be identified as the tetracyclic alcohols K-2 and K-3, and the partially cyclized alcohols K-4. Although the partially cyclized products could be separated from the tetracyclic ones, this was not necessary, for oxidation of the mixture afforded the tetracyclic ketones K-5 and 53, as well as the bicyclic ketones H-5. Treatment of the entire mixture with *p*-toluenesulfonic acid in boiling toluene yielded more of the desired ketone 53, and some isomeric ketone H-6. The overall yield of ketone 53 from this sequence was 2%.

The successful formation of the desired 9,10-dimethyl-trans-decalol systems via a polyolefin cyclization, coupled with the studies of Johnson and Harding (61), in which a cis,anti,trans-perhydrophenanthrene system was formed (see reactions 7 and 8 in Table I), suggested the possibility of utilizing this approach to synthesize the pentacyclic compound 50, via the cyclization of the alcohol 51.

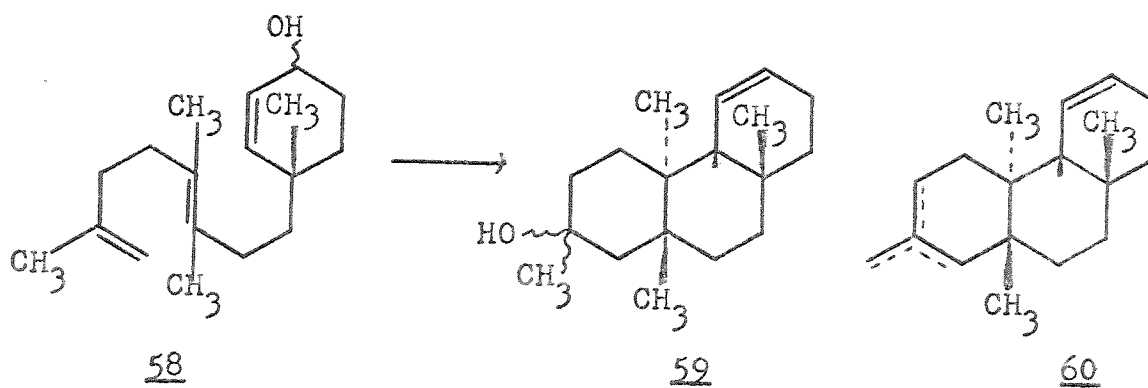
* Aldehyde K-1 has been utilized twice as a key intermediate in the present work. A modified synthesis of this compound will be described later on.

Chart K





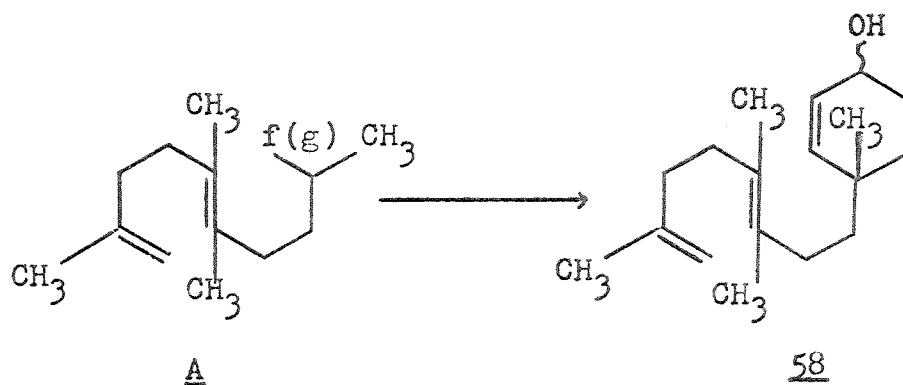
Rather than plunge directly into a problem of this complexity, it was decided to study the cyclization reaction on a simpler model compound, with the hope of eventually extending the work to alcohol 51 if the results from the model study were encouraging. A suitable model polyene to study was alcohol 58. It was felt that cyclization of this alcohol



in formic acid would yield, after cleavage of the formate products, a mixture of the tricyclic alcohols 59, and olefins 60.

In devising a synthetic route to alcohol 58, it was advantageous to note the structural symmetry elements present

in the molecule. Besides the obvious symmetry of the trans tetrasubstituted double bond, it is apparent that both carbon chains extending from the double bond possess a 4-methylbutyl residue. Therefore, it was anticipated that a symmetrically structured intermediate, A, could be made and subsequently elaborated into alcohol 58. The compound ideally



suited for this purpose was the aldehyde 61 (A, $f(g) = \text{CHO}$). This compound had been synthesized previously in this laboratory (84) in the course of another study. Aldehyde 61 should be readily elaborated via a Stork enamine synthesis (85) with methyl vinyl ketone (MVK) into the trienone 62 (fig. 9). Reduction of enone 62 would yield the desired al-

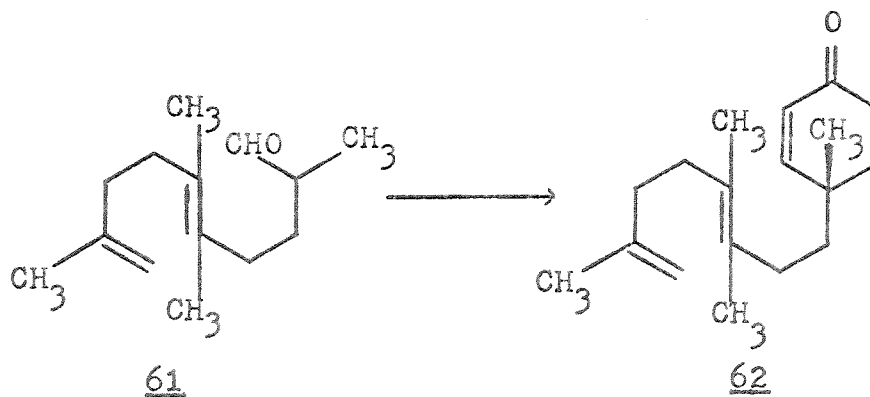
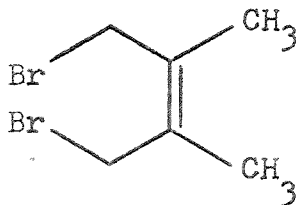


Fig. 9

cohol 58.

The synthesis of aldehyde 61 and its conversion to alcohol 58 is described in Chart L. The reactions leading to aldehyde 61 have been modified from the previous study (84). The trans dibromide L-2 was prepared by the known procedure (86) of treating 2,3-dimethyl-1,3-butadiene (L-1) with bromine. The product obtained after crystallization was isomerically pure, uncontaminated by any of the cis isomer 63 (86). Coupling (87) of the dibromide L-2 with methallylmagnesium chloride afforded the triene L-3 in 93% yield.*

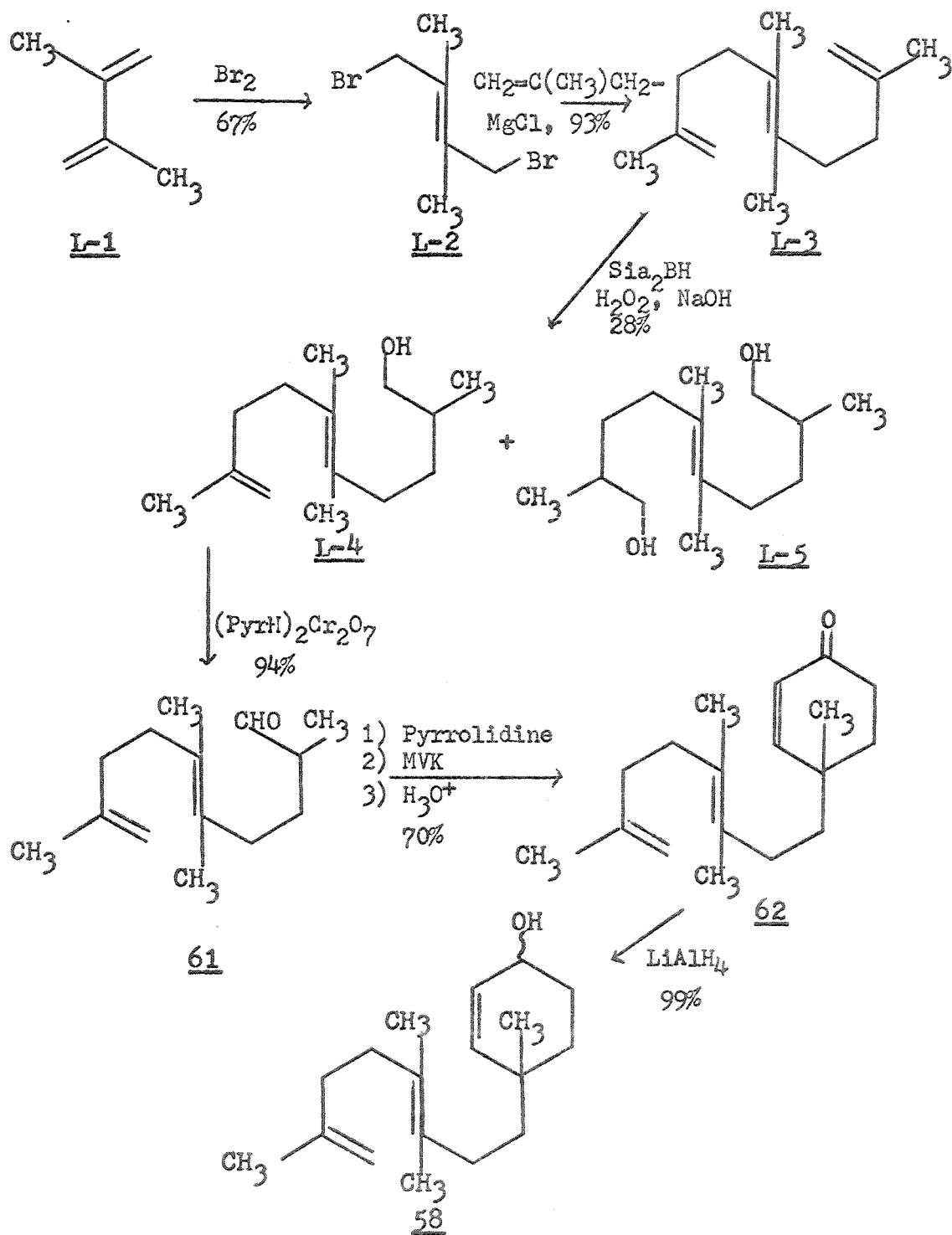


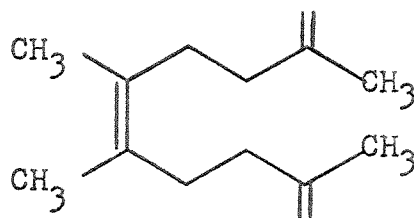
63

Actually, the product obtained was contaminated with 10-15% (vpc) of an impurity, which could be almost completely removed by spinning band distillation. The structure of the contaminant was not determined, but the cis triene 64 is a reasonable postulate. The propensity for the trans dibromide L-2 to undergo isomerization to the cis isomer 63 under a

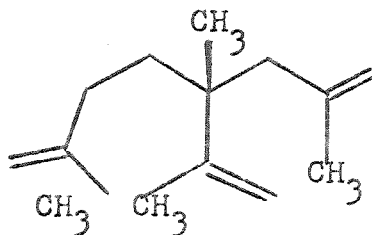
* The coupling of dibromide L-2 with a variety of unsaturated Grignard reagents has been utilized for the synthesis of other unsaturated compounds bearing the trans tetrasubstituted double bond (68c,88).

Chart L

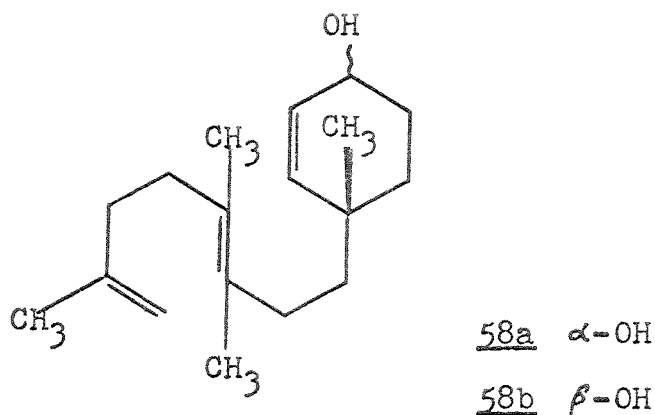


64

variety of conditions is known (86). This may be occurring during the coupling reaction. The fact that this was not discovered by Muchmore or in an earlier run during the present work may have been due to the quality of the vpc column used in the analysis. Even on a new 4% SE-30 column, the impurity appears as a small shoulder that is barely discernible. Although rearrangement during the coupling of allylic units may also be a problem (89), this did not appear to be the case here, as the nmr spectrum of the product was relatively simple, which would not be the case for a compound such as the triene 65, in which rearrangement had occurred.

65

The next step in the synthesis called for the differentiation of the two ends of the triene 1-3. This was accomplished by hydroboration (90) with the hindered reagent, disiamyl-

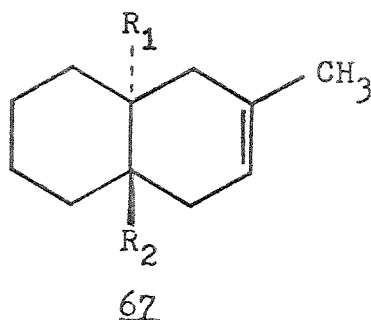


of triene 1-3.

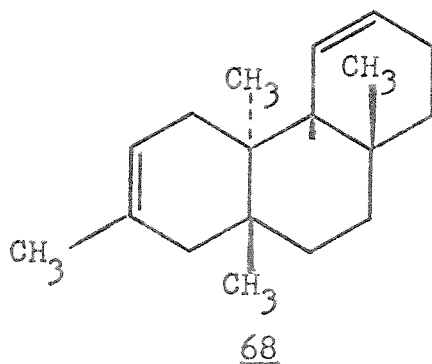
The initial cyclization studies of alcohol 58 were conducted using formic acid as both solvent and cation initiator. The use of formic acid has been reported in other studies (61,63,69a-f,h,i,k) (see Table I) with gratifying results. Treatment of alcohol 58 with anhydrous formic acid for five minutes, followed by brief treatment of the crude product with lithium aluminum hydride, afforded a colorless oil which appeared to consist of at least thirteen volatile components by vpc. These components were subdivided into three groups, A, B, and C, based on their retention times (180°, 4% SE-30 on Chromosorb WAW-DMCS, 6° x 1/8"). Group A consisted of six components accounting for about 80% of the volatile material. All had retention times under two minutes. Group B consisted of four unresolved peaks, ranging from 2.4-3.5 minutes, and accounted for 10% of the volatile material. Group C had only one component at 4 minutes, and this accounted for the remaining 10% of the material.

An initial preparative tlc separated the mixture into a

hydrocarbon fraction (14.6%) and an alcohol fraction (85.3%). The former consisted of components A₁-A₄, with A₄ comprising 80% of the total hydrocarbon mixture. The nmr spectrum showed a cluster of peaks at 0.91 ppm, corresponding to angular methyl groups, and a broad peak at 5.30 ppm, which is indicative of the olefinic hydrogen at position 2 of a 3-methyl-trans-octalin, such as 67 (67b,c,f,69e,g,h), and a signal indicating two olefinic hydrogens on adjacent carbons

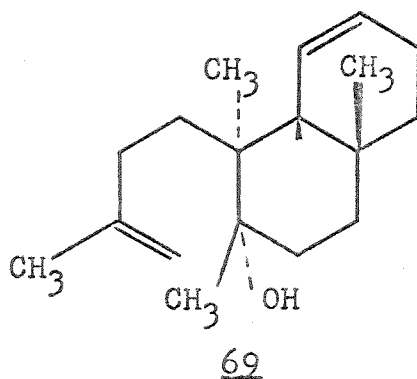


at 5.71 ppm. The spectrum was virtually superimposable with that of the major product isolated from the cyclization of alcohol 58 with stannic chloride (vide infra), which is tentatively assigned the tricyclic diene 68. The alcohol



fraction isolated from the chromatography displayed eight volatile components in the vpc trace. Three had retention times of 1.35, 1.55, and 1.85 minutes. These were part of the group A components and were designated $A_{4'}$, A_5 , and A_6 , respectively. The $A_{4'}$ peak had identical retention time to A_4 of the hydrocarbon fraction. The three components comprised about 50% of the alcohol fraction. The four components of group B made up 25% of the volatile material, and peak C accounted for the remaining 25%. Preparative tlc of the alcohol fraction (40% ether in pet. ether) yielded at least six separate bands. The bulk of the material was found in two groups of two unresolved bands each, designated D ($R_f = 0.5$ to 0.7) and E ($R_f = 0.0$ to 0.25). The product in bands D and E accounted for 31% and 34% of the total product, respectively. Band D contained the components $A_{4'}$, A_5 , and A_6 in a ratio of ca. 2:1:1. The ir spectrum displayed a strong hydroxyl frequency at 3600 cm^{-1} and strong bands at 1650 - 1700 and 900 cm^{-1} , which are characteristic of a terminal methylene. The nmr spectrum also displayed the signals of a terminal methylene, but integration of this region indicated that the signal accounted for less than one hydrogen. Bands D and E contained the four components of group B and component C. This band displayed a very strong hydroxyl group in the ir spectrum. Preparative tlc afforded band F, which accounted for 18% of the product and consisted of ca. 80% of component C. The chief nmr spectral characteristic of this

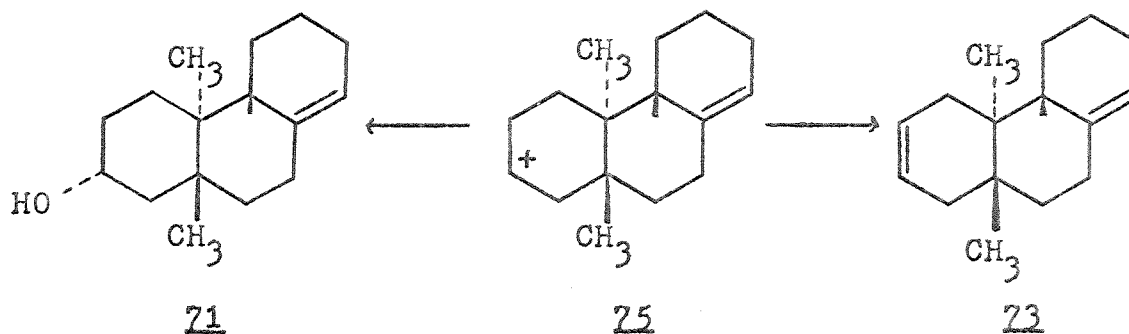
band was the presence of a signal at 4.13 ppm, which is characteristic of a methine hydrogen on a carbon bearing a hydroxyl group. On the basis of the above chromatographic and spectral data, the following deductions are made concerning the structures of the cyclization products. Components A_1 - A_4 were hydrocarbons, of which A_4 , the major component, appeared to be tricyclic and had the spectral characteristics of the tricyclic diene 68, which was also isolated from a subsequent cyclization using stannic chloride. The three components A_4 , A_5 , and A_6 were alcohols, and at least one of them was non-tricyclic. A possible structure with these characteristics is the alcohol 69, which could result from



nucleophilic attack by formate on an intermediate cation. The major portion of the product consisted of highly polar components, which are probably diols, resulting from the attack of formic acid on the double bonds of the intermediate cyclization products (69c,95).

The complexity of the product mixtures resulting from the cyclization of alcohol 58 in formic acid were discour-

aging, especially in light of other studies being conducted at the same time. P. Bey had studied the cyclization of alcohol 70 (Fig. 10) (96). Treatment of alcohol 70 with formic acid at 9° , followed by hydride reduction afforded a mixture of products from which the two major alcohols, 71 and 72, were isolated in 20% and 8% yields, respectively. In addition, two tricyclic hydrocarbons, tentatively assigned structures 73 and 74 were isolated in respective yields of 7.5% and 2%.* The isolation of alcohol 71 and hydrocarbon 73 suggested that the tricyclic carbonium ion 75 had to have been formed in at least 27.5% yield, which was much greater



than any possible formation of cation 76, as suggested by the cyclization of alcohol 58. In another study by Bey (96), alcohol 77 was treated with formic acid at 9° for five minutes to yield, after reduction, the tricyclic hydrocarbon 78, and the epimeric alcohols 79 and 80 (Fig. 11). The stereochemical identity of the cyclization products of both alco-

* The yield of hydrocarbon 74 was not representative, since it appeared to react with oxygen on standing.

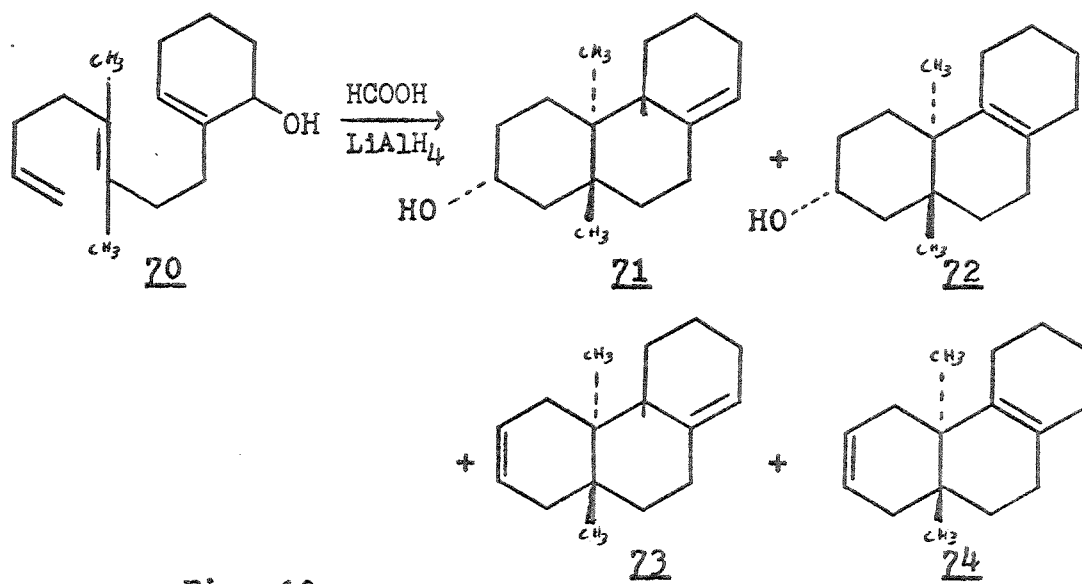


Fig. 10

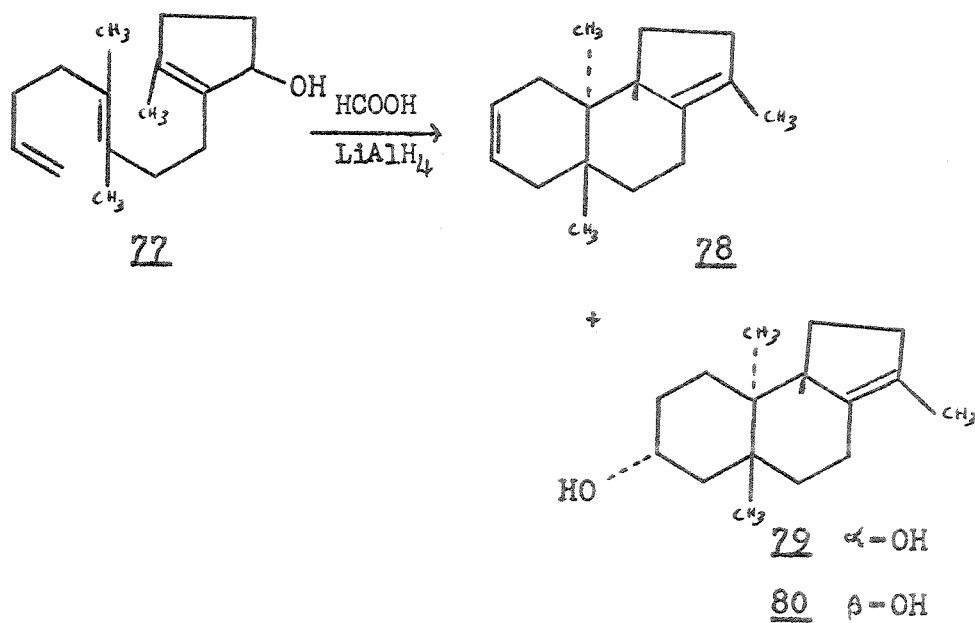
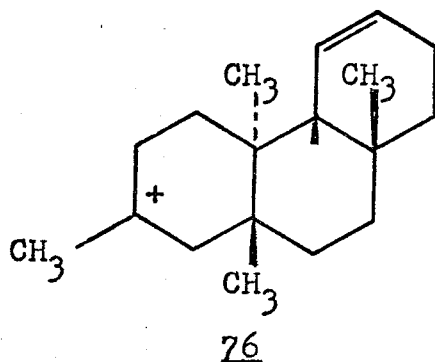


Fig. 11



hols, 70 and 77, was established by chemical correlation with each other and with compounds of known stereochemistry (97).

A priori, it is not possible to predict that the cyclizations of alcohols 70 and 77 should proceed with a high degree of selectivity, while that of alcohol 58 should not. In fact, since the terminal double bond of alcohol 58 is disubstituted, it is not unreasonable to anticipate that its cyclization would proceed even better than alcohols 70 and 77 on the basis of electronic factors. On steric grounds, however, examination of models of the major products predicted* for the three compounds suggest a possible explanation for alcohol 58's non-selectivity (Fig. 12). Alcohols 71 and 79 are free of 1,3-diaxial interactions between positions 3 and 5, since there is no methyl group at position 3. On the other hand, alcohol 81 would possess a severe inter-

* The major products are expected to be equatorial alcohols, since attack on the terminal carbonium ion is expected to occur in an equatorial fashion, avoiding a 1,3 interaction with the C-5 methyl group (98).

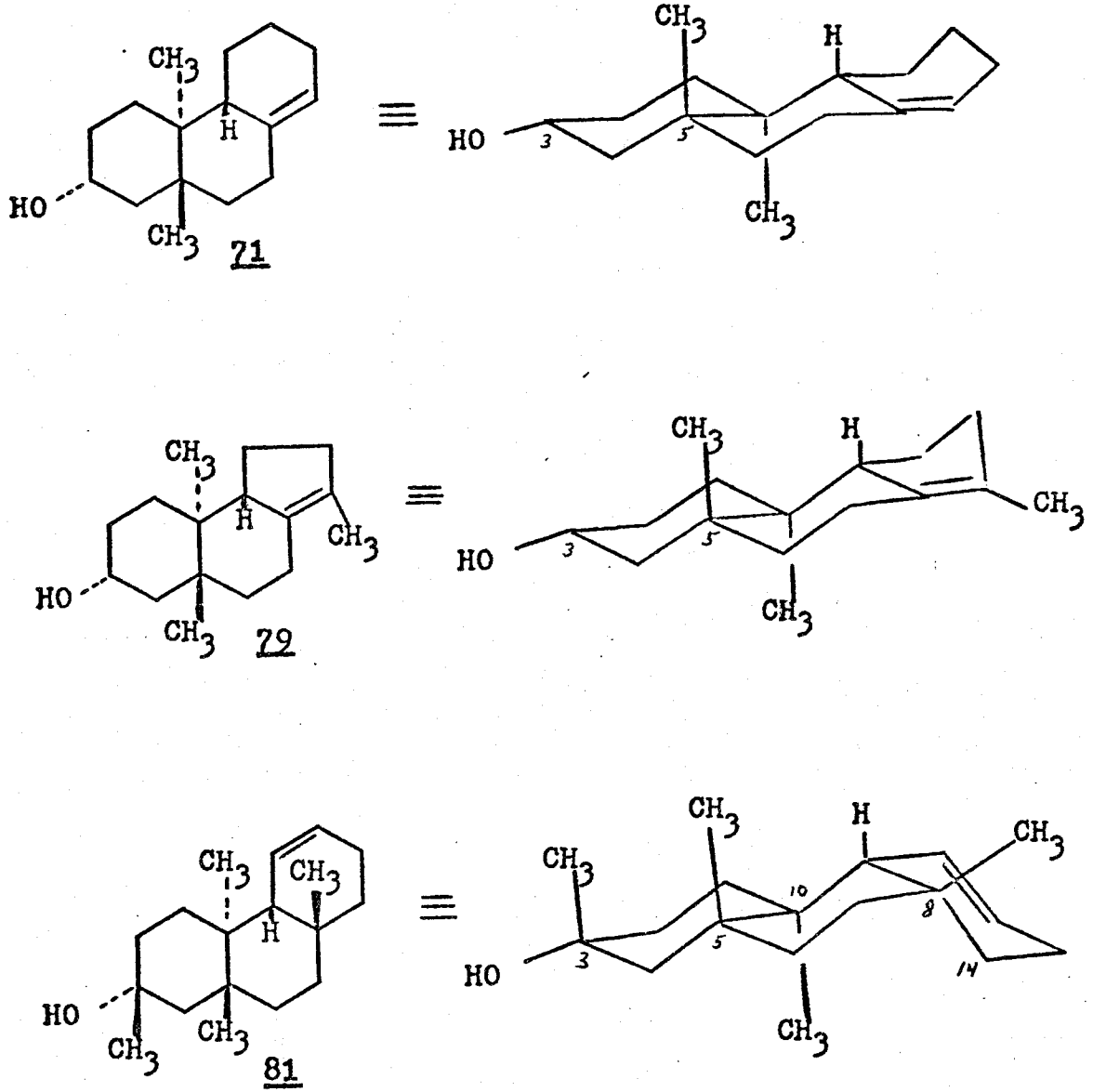
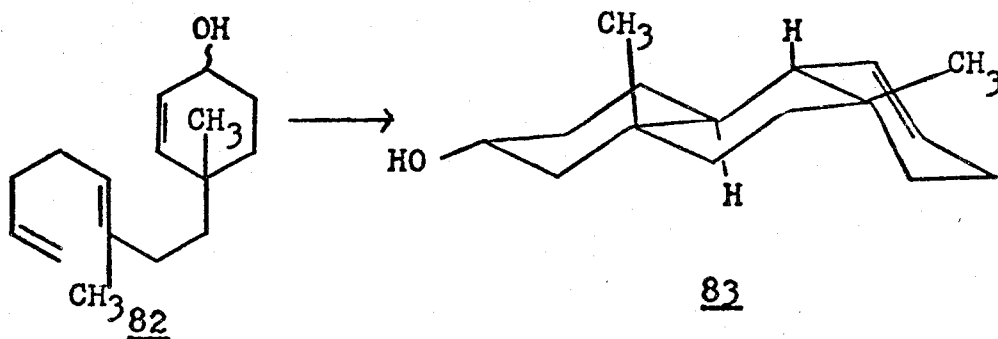


Fig. 12

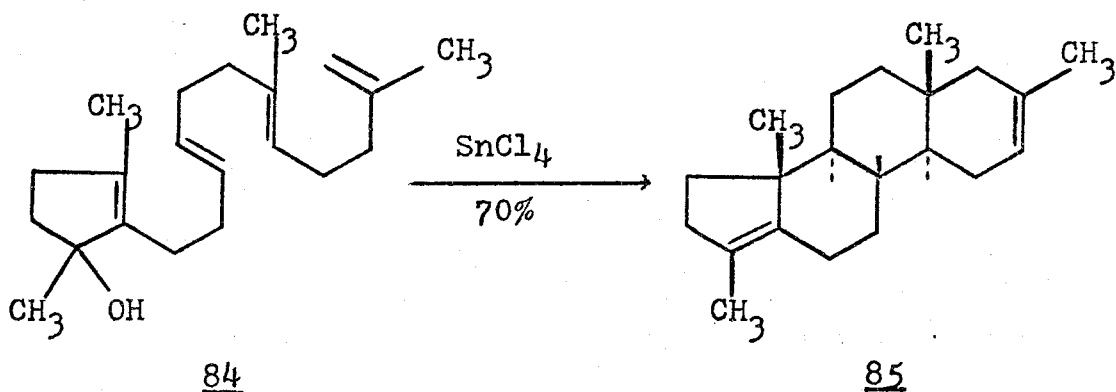
action at these positions, which would tend to destabilize the molecule. In addition, alcohols 71 and 79 contain double bonds at the B/C ring junctures, which would flatten out the C ring, thus avoiding any strong interactions there. However, because of the cis fused B/C ring juncture in alcohol 81, an additional 1,3-diaxial interaction exists between the C-10 methyl group and the C-8(14) single bond. Harding (77) predicts that 1,3 interactions present in a final cyclization product would also be present in the transition state leading to its formation, especially if the cyclization is stepwise. Therefore, it is reasonable to assume that the transition state leading to the cyclization of alcohol 58 would have an additional energy of roughly 7.4 kcal/mole (99) as compared to the transition states in the cyclization of alcohols 70 and 72. Hence, there may be a greater possibility for side reactions with alcohol 58.

In order to test this hypothesis, the cyclization of a modified alcohol 82 was studied, since the major product



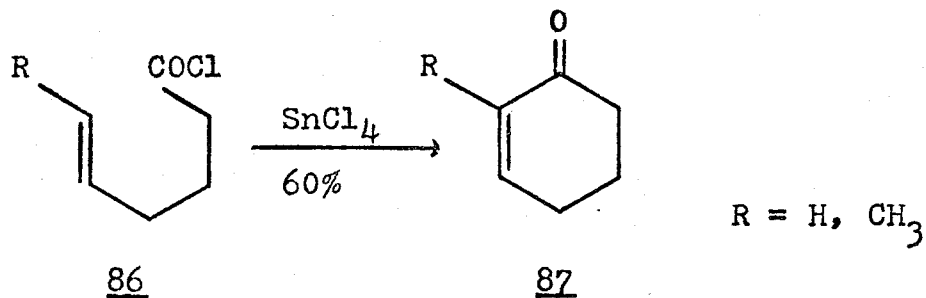
predicted, alcohol 83, would be devoid of the interactions expected in alcohol 81. During the course of this study (vide infra), it was determined that formic acid was a poor cyclization medium for this type of substrate, and that stannic chloride in dichloromethane gave high yields of tri-cyclic products. Based on these findings, the cyclization of alcohol 58 using stannic chloride was investigated.

The use of Lewis acids to promote cationic reactions in oxygen-containing substrates is well known. Epoxides have been made to undergo rearrangements to allylic alcohols by the action of triisobutylaluminum (100), diisobutylaluminum hydride (100,101), activated alumina (102), and aluminum isopropoxide (103). Boron trifluoride etherate has been used to produce polycyclic alcohols from polyolefinic epoxides (51a,c-g,66). Stannic chloride reacts with polyolefinic aldehydes (68) and acetals (67) to afford polycyclic alcohols also. Stannic chloride has also been employed successfully in the cyclization of allylic alcohol 84 (69j) to pro-



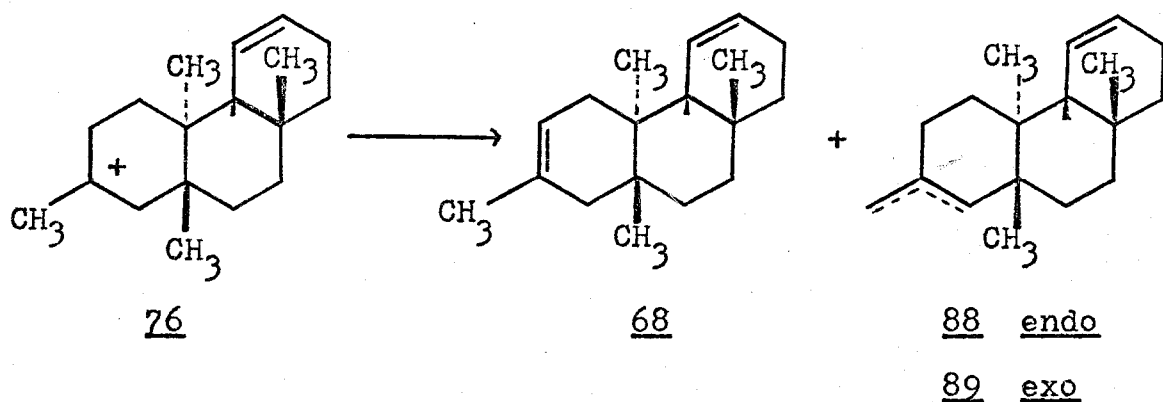
duce the tetracyclic diene 85 in ca. 70% yield.

Less known are the cyclizations of δ,ϵ -unsaturated acid chlorides, such as 86 (104), with stannic chloride to produce the 2-cyclohexenones 87.



The cyclization of alcohol 58 proceeded readily with stannic chloride in dichloromethane to yield a mixture of seven hydrocarbons. There was always a preponderance of one component under a variety of conditions. This major component could be optimized if the reaction was carried out at low temperature. Thus, treatment of alcohol 58 with excess stannic chloride in dichloromethane at -78° produced a 41% yield of hydrocarbons, in which the major component comprised 76% of the mixture, and three others accounted for about 6% each. No other material was recovered after column chromatography, suggesting that polymerization had occurred to a large extent. Use of more solvent did not alter the results significantly, nor did the addition of dialkyl carbonates (70a,b). The major product was estimated by vpc to have formed in 31.5% yield (18.6% isolated pure). Purification was effected by either preparative vpc (6' x 1/8" col., 10%

carbowax on Chromosorb WAW-DMCS, 200^o), or more conveniently, by repeated column chromatography on either silica gel or alumina. The major product isolated displayed an nmr spectrum characteristic of the tricyclic diene 68, which is believed to be the major hydrocarbon from the formic acid cyclization. The formation of the double bond at C-2,3 (steroid numbering) instead of C-3,4 from the tertiary carbonium ion 76 is based on the studies of Barton and coworkers (105),



and is explained on the basis of steric (106) and hyperconjugative (107) effects. The utility of this selective bond formation has been utilized by Johnson (69j) in a dihydroprogesterone synthesis and by Soffer (108) for a sesquiterpene synthesis. It is reasonable to assume that the other double bond isomers of diene 68, the $\Delta^{3,4}$ isomer 88 and the exocyclic olefin 89 are also formed. If this is the case, then cyclization actually proceeded with greater selectivity than the 31.5% yield represented by the isolation of diene 68.

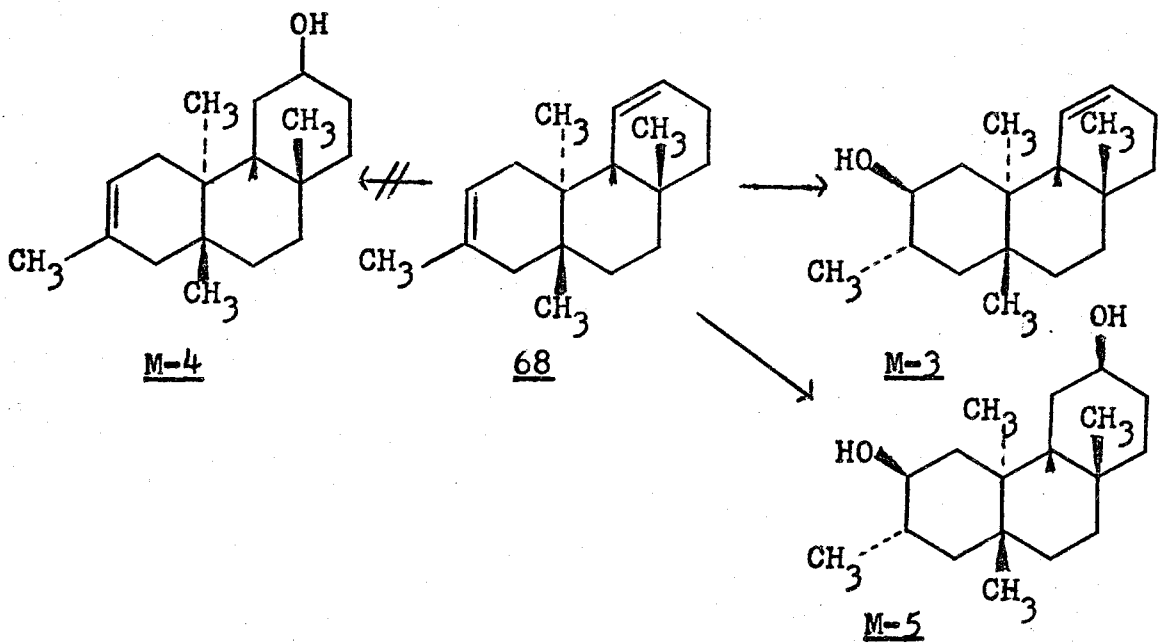
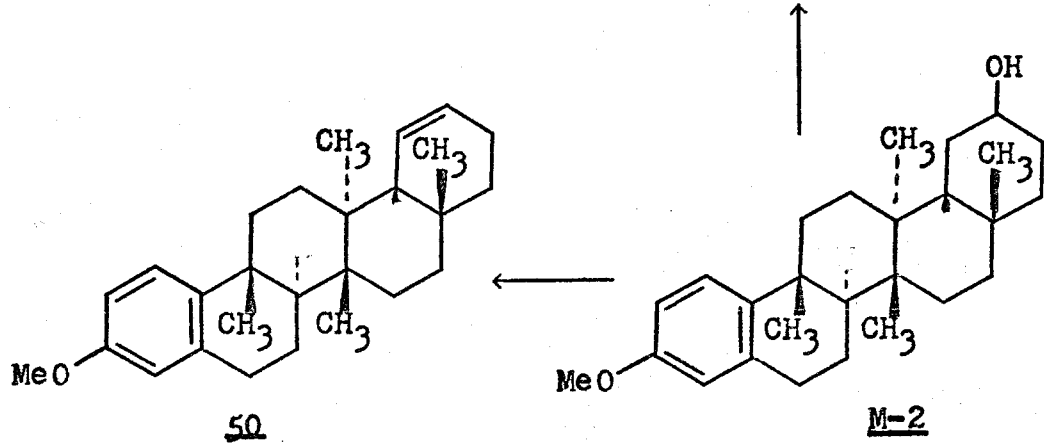
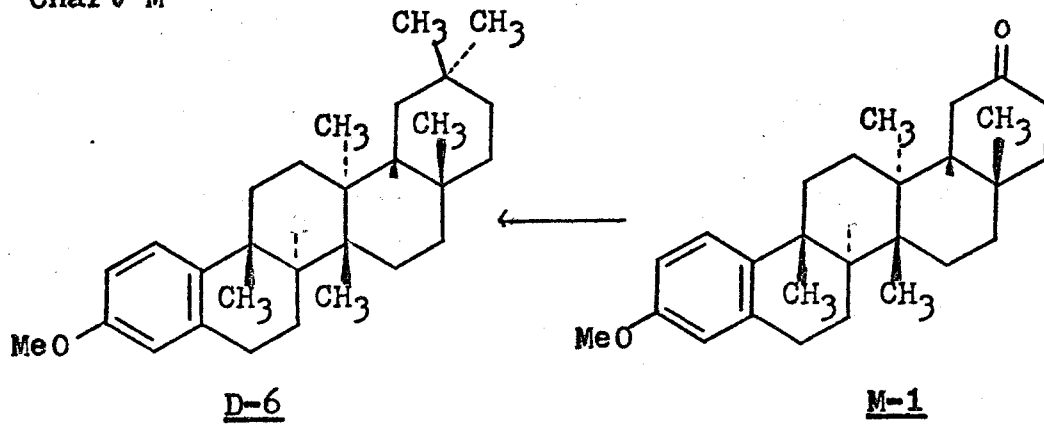
The higher yields of tricyclic products in the stannic

chloride study are probably due to the lower acidity and lower nucleophilicity of the medium. In formic acid, the products were susceptible to attack by protonation of the double bonds, leading to diols after reduction. Also, the nucleophilicity of formic acid is probably high enough to attack the intermediate non-tricyclic cations. In stannic chloride-dichloromethane, the double bonds of the substrate would be able to attack the intermediate cations without competition from an external nucleophile.

With the tricyclic diene 68 now readily available, an attempt was made to study the reactivities of the two double bonds toward a number of reagents. Since the ultimate goal of this work would be the synthesis of the pentacyclic ether D-6 from olefin 50 (Chart M), then diene 68 might serve as an excellent model to study this conversion. It was envisioned that the most straightforward approach would be through the ketone M-1. This ketone should be readily available from olefin 50 via hydroboration (90) with a hindered reagent to produce the alcohol M-2. The selective oxidation at C-2 is expected (35,109) on the premise that attack at C-1 would be more sterically hindered, since the reagent would encounter a 1,3 interaction with the methyl group at C-4a. A striking example of regioselective hydroboration in a cis-decalin has been reported recently by Hochstetler (110).

Returning to diene 68, it was felt that hydroboration would proceed faster at the disubstituted double bond than

Chart M



at the trisubstituted one (90). Surprisingly, treatment of diene 68 with either disiamylborane (91), hexylborane (111), or 9-borabicyclononane (9-BBN) (112) resulted only in the recovery of starting material. Finally, treatment with a slight excess of diborane, followed by basic peroxide oxidation afforded the alcohol M-3 as the sole hydroboration product in 69% yield, based on recovered starting material. No trace of the desired alcohol M-4 was detected. When diene 68 was treated with a large excess of diborane, the diol M-5 was isolated in 67% yield. Evidence that the product was indeed the diequatorial alcohol M-5 lay in the nmr spectrum, in which the signals of the two methine protons on the carbons bearing hydroxyl groups appeared as broad multiplets with half-band widths of 19 and 22 Hz (113).

In addition to hydroboration, an attempt was made to selectively epoxidize one double bond in diene 68. Treatment with a 50% excess of 99% m-chloroperbenzoic acid (114) afforded a 75% yield (based on recovered starting material) of a single epoxide, in which only the trisubstituted double bond was oxidized (Fig. 13). The product was tentatively assigned the structure 92, since examination of a model of diene 68 indicated that attack from the α -face would encounter less hindrance. Epoxide 92 rearranged quantitatively to a single ketone, tentatively assigned structure 93 on the premise that migration of the C-2 hydrogen is stereospecific (115). A crystal of this ketone was submitted for x-ray analysis.

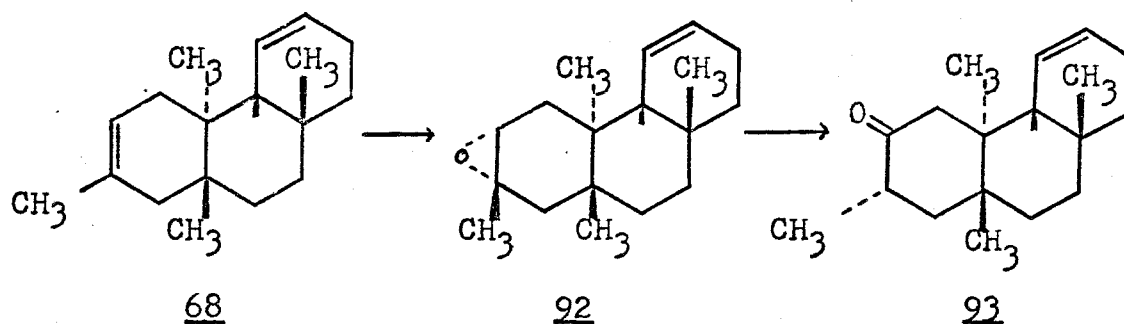
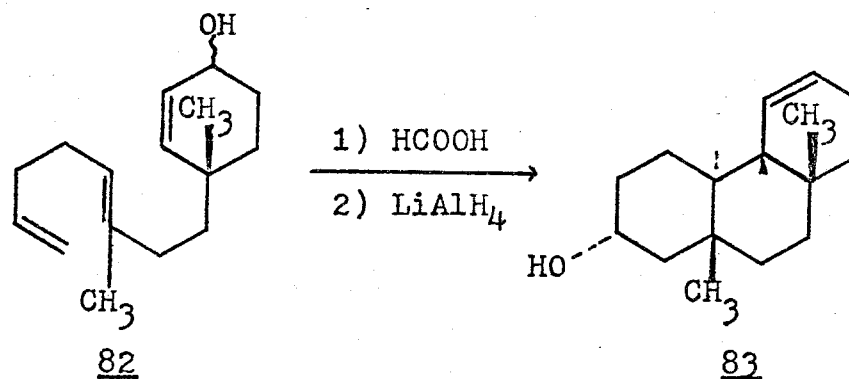


Fig. 13

In addition, an attempt was made to reduce epoxide 92 with lithium in ethylenediamine (116), but a complex mixture of products was obtained, and this was not investigated further.

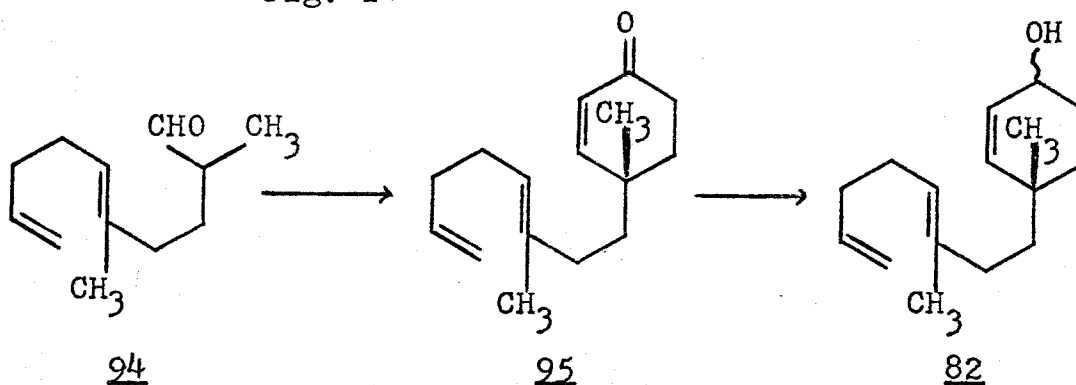
The study described above in which stannic chloride was used as a cyclization catalyst for alcohol 58 was a result of the success achieved in the next study, the cyclization of alcohol 82. The selection of this alcohol as a substrate



for cyclization was made in order to determine if the lack of two 1,3-diaxial interactions in product 83 would render the cyclization more selective than that of alcohol 58 (vide supra).

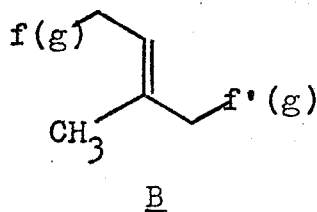
In planning the synthesis of alcohol 82, it was determined that the latter step should be analogous to those in the synthesis of alcohol 58 (Chart L). Specifically, enamine homoannulation (85) of aldehyde 94 to form the enone 95 and

Fig. 14



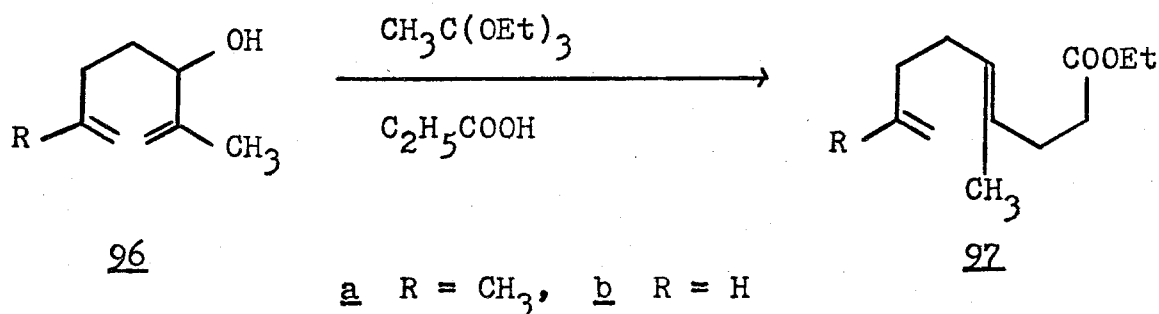
reduction to alcohol 82 (Fig. 14).

Consequently, the problem was reduced to the synthesis of aldehyde 94. The general key intermediate, B, in this synthesis must possess a trans trisubstituted double bond with functional groups $f(g)$ and $f'(g)$, which would be ca-

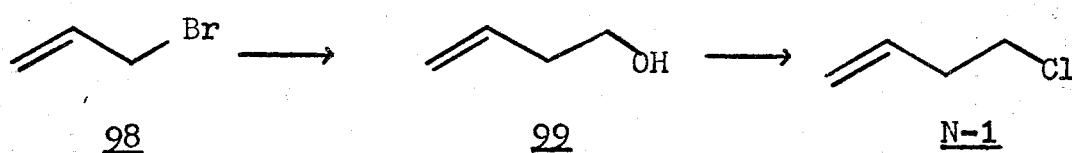


pable of being elaborated into an allyl and 2-formyl-group, respectively. Of the many syntheses of trisubstituted double bonds (78), the one that appeared most attractive for this study was the orthoester Claisen rearrangement developed by Johnson and coworkers (117), in which the allylic alcohol

96a was converted into ester 97a in over 90% yield with >97% stereoselectivity. Therefore, the synthesis of the



lower homolog, alcohol 96b, and its elaboration into aldehyde 94 was envisioned. The synthetic route to aldehyde 94 is outlined in Chart N. Conversion of 4-chloro-1-butene (N-1) (118) to its Grignard reagent and reaction with methacrolein produced alcohol 96b in 69% yield. Although commercially available, chloride N-1 is rather expensive. Consequently, it was prepared from the readily available and inexpensive allyl bromide (98) via conversion to the Grignard (119) and condensation with paraformaldehyde to give 3-buten-1-ol (99)



(118) in 56% yield. Reaction of alcohol 99 with thionyl chloride and a catalytic amount of pyridine (120) yielded 69% of the chloride N-1. On heating alcohol 96b with excess triethylorthoacetate and a catalytic amount of propionic acid

Chart N

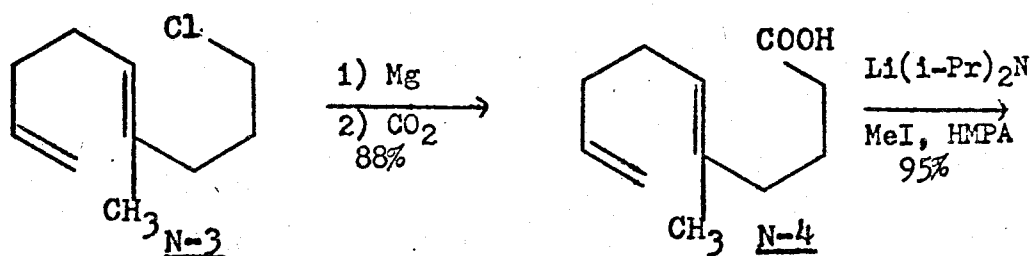
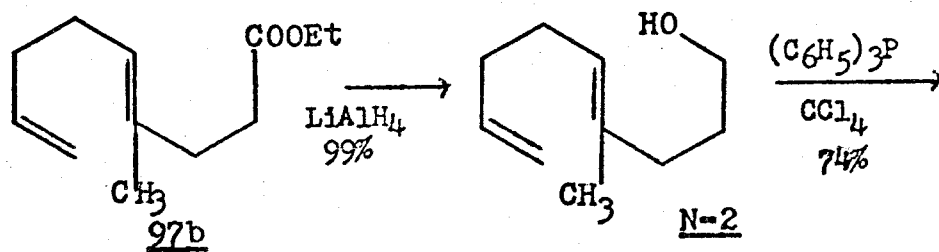
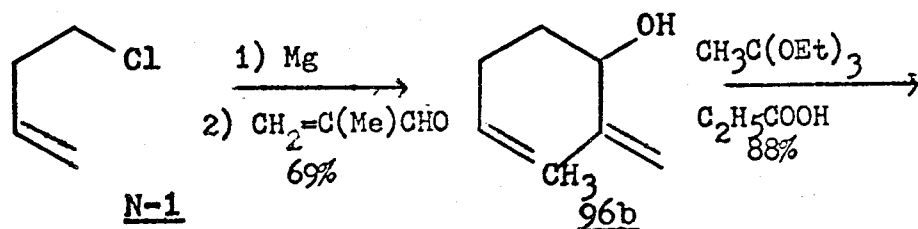
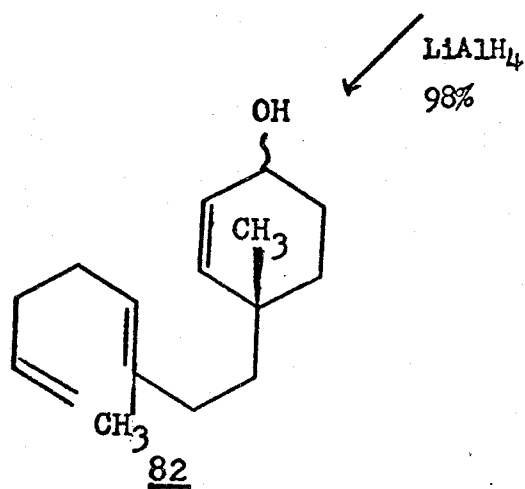
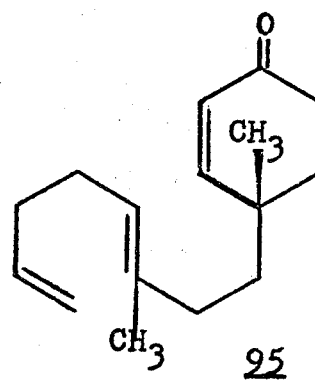
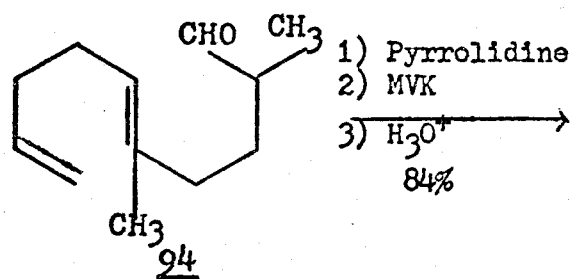
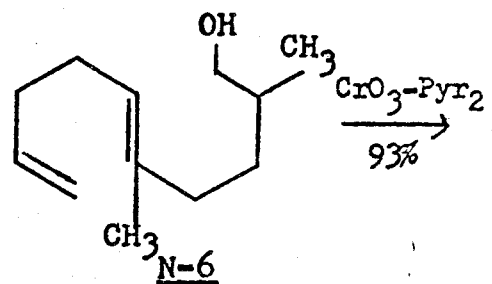
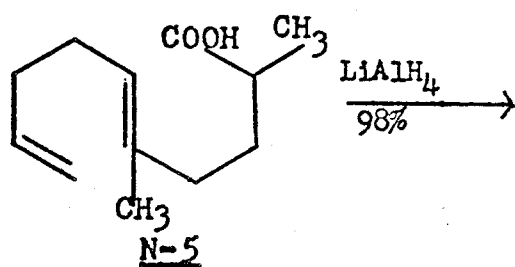


Chart N (continued)



at 140°, the desired diene ester 97b was formed in 88% yield (121). From the nmr spectrum, the ratio of trans to cis esters was determined to be 97:3, based on the integration of the signals at 1.60 and 1.67 ppm, which were assigned to the methyl group on the trans and cis double bonds, respectively (78a).* Reduction of ester 97b with lithium aluminum hydride proceeded readily, yielding 99% of alcohol N-2. This alcohol was converted to the corresponding chloride N-3, by reaction with triphenylphosphine and carbon tetrachloride (122) in 74% yield. The Grignard reagent of chloride N-3 was treated with excess carbon dioxide and afforded the homologated acid N-4 in 88% yield. Methylation of acid N-4 was effected by the excellent procedure of Pfeffer and Silbert (123). Conversion of acid N-4 to its dilithium salt with lithium diisopropylamide, and reaction with methyl iodide in the presence of hexamethylphosphoramide (HMPA) afforded the methylated acid N-5 in 95% yield, uncontaminated by either the unmethylated acid N-4 or dimethylated acid. Lithium aluminum hydride reduction of acid N-5 yielded alcohol N-6 (98%), which was oxidized using Collins reagent (94) to the desired aldehyde 94 in 93% yield. The conversion of the aldehyde into alcohol 82 was effected as described previously. Condensation of the pyrrolidine enamine of the aldehyde 94 with methyl vinyl ketone, followed by acid hydrolysis afforded

* Subsequent structures in this series are depicted as being trans, although the cis isomer was present throughout.

an 84% yield of enone 95. Reduction to the allylic alcohol 82 proceeded in 98% yield.

The cyclization of alcohol 82 in formic acid was studied. The alcohol was mixed with anhydrous formic acid at 9°, and the mixture was poured onto aqueous base and cracked ice after eight minutes. The resulting crude product was then treated with lithium aluminum hydride. The vpc trace of the resulting mixture consisted of at least fourteen components, in which six peaks, designated A-F, having retention times (205°, 10' x $\frac{1}{4}$ " 10% carbowax) of 1.65, 4.3, 5.15, 5.55, 6.3, and 8.0 minutes, respectively. These six peaks comprised ca. 75% of the total peak area. In addition, three unresolved peaks, ranging from 6.6-7.7 minutes, comprised 20% of the peak area, and five minor peaks at 1.15, 1.75, 2.3, 2.55, and 2.8 minutes accounted for the remaining 5% of the volatile material. The ir spectrum indicated the presence of a hydroxyl group (3550 cm^{-1}) and the terminal vinyl moiety ($1635, 995, 915\text{ cm}^{-1}$). The nmr spectrum also showed chemical shifts characteristic of the terminal vinyl group (see experimental section). The mixture was subjected to preparative vpc (same column as above), and components A-F were isolated. Each component displayed the spectral characteristics of the terminal vinyl group, indicating that each was non-tricyclic. Components A, C, D, and E contained only two proton signals in the 4.76-5.23 ppm range of the nmr spectrum, indicating that they were probably bicyclic. Components B and F dis-

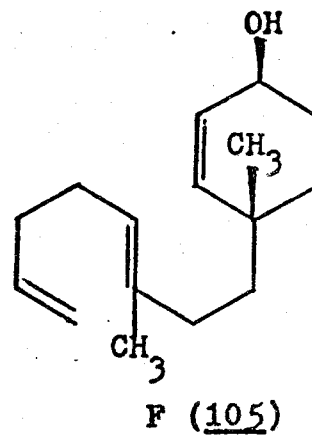
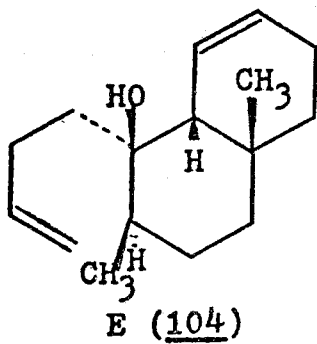
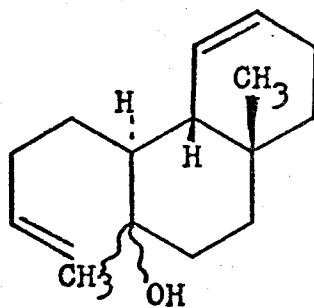
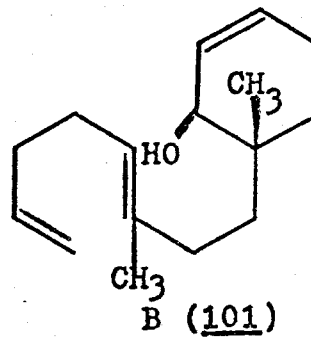
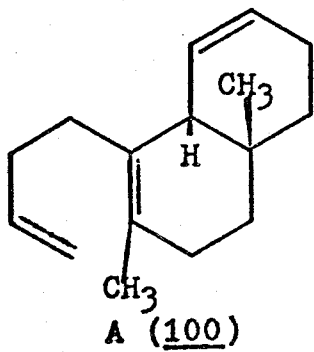
played three protons in this range, indicating that they were probably monocyclic. The isolated yields and functionality assignments for components A-F are summarized in Table II.

Table II

<u>Component</u>	<u>% Yield Isolated</u>	<u>Type</u>
A	6.7	Olefin
B	4.4	Alcohol
C	3.2	Alcohol
D	2.5	Alcohol
E	6.4	Alcohol
F	3.8	Alcohol

The structural assignments for components A-F are illustrated in Chart O. These assignments were made largely on the basis of spectral data. Rigorous confirmation of the structures was not possible, since only 3-6 mg of each component was isolated. It was apparent from the spectral data that all six were non-tricyclic, and hence, the experiments were not repeated. The structure of all the components except the bicyclic alcohol 104 are consistent with a stepwise cyclization mechanism, as is described in Fig. 15. Ionization of alcohol 82 would produce the allylic cation 106. This cation could undergo attack by the trisubstituted double bond to produce the bicyclic cation 107, or by formic acid to yield, upon reduction, the allylic alcohols 101 and 105. The fact that these alcohols are single epimers strongly suggests that they are formed by attack on the allylic cation 106, while it is in the conformation 106a, with the side

Chart 0



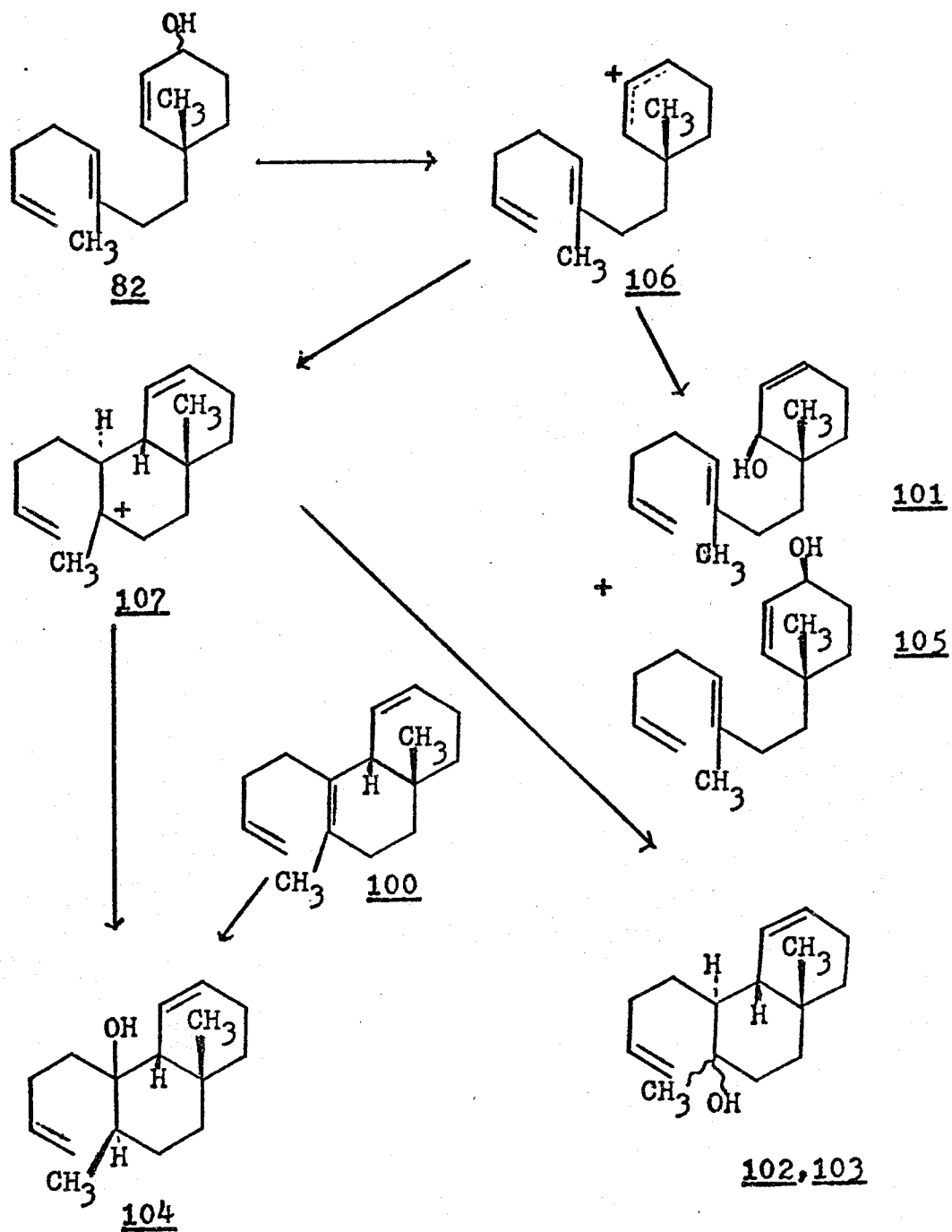


Fig. 15

chain oriented axially (Fig. 16). Attack by formic acid

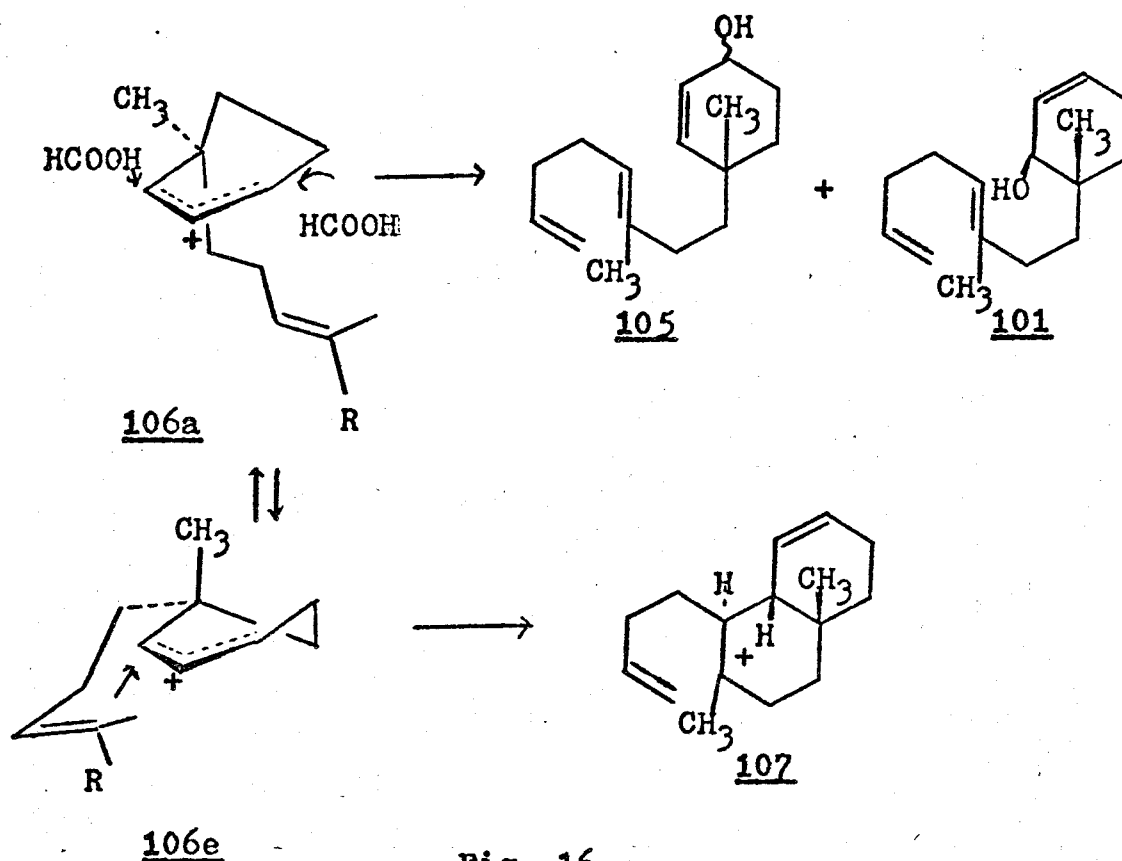


Fig. 16

should proceed preferentially from the top, yielding alcohols **101** and **105**, after hydride reduction. It has already been implicated (61) (see introduction) that the conformation **106e** with the equatorial side chain should lead to cyclization. Attack by formic acid on cation **107** would yield the epimeric alcohols **102** and **103** after reduction. Loss of a proton from cation **107** would produce the bicyclic triene **100**. The formation of the rearranged alcohol **104** could occur either by reprotonation of triene **100**, followed by formate attack. Al-

ternatively, a 1,2 hydride shift in cation 107 could occur (Fig. 17) to yield the rearranged cation 108. Attack by formic acid and reduction would afford alcohol 104.

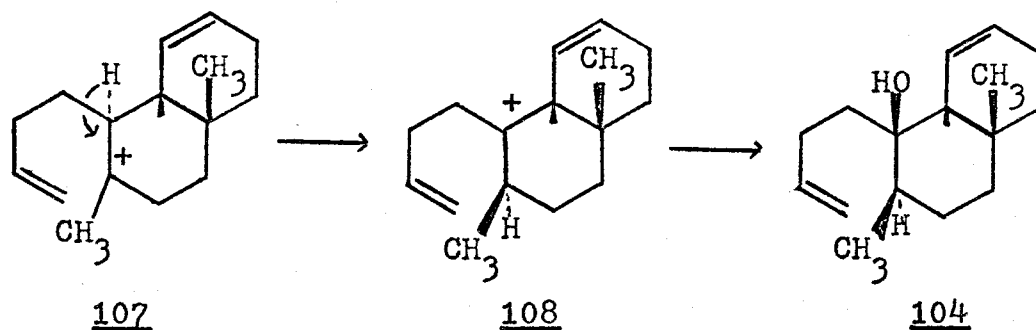
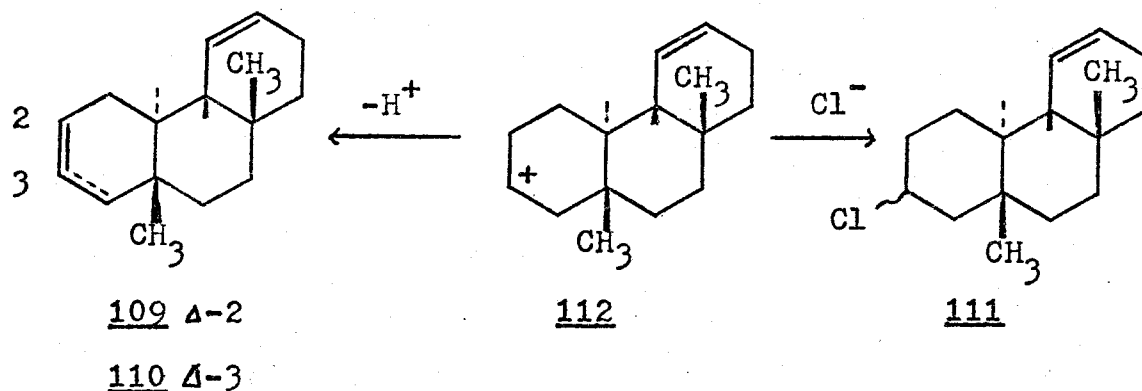


Fig. 17

The failure to isolate any products having a tricyclic structure in the cyclization of alcohol 82 with formic acid indicated that complete cyclization could have only occurred to the extent of about 20%, if at all. The isolation of bicyclic alcohols suggested that formic acid was competing for the positive site on cation 107 with the terminal vinyl group. To make double bond attack the more favorable process, it would be necessary to use conditions in which a strong external nucleophile was absent from the medium.

The success of stannic chloride in nitromethane as a cyclization medium for allylic alcohols (69j) prompted its implementation in the present study. Treatment of alcohol 82 with stannic chloride in nitromethane for 1½ minutes at -28° afforded an oil, from which a mixture of two hydrocarbons were isolated in 24.7% yield, (4% SE-30, 6' x 1/8 ", 170°, 0.95 and 1.0 min). In addition, a 12.3% yield of a mixture

of compounds with retention times of 1.8-2.2 minutes was isolated. The hydrocarbon fraction displayed an nmr spectrum characteristic of completely cyclized material, i.e., no terminal vinyl group. The two signals for angular methyl groups were observed at 0.81 and 0.91 ppm. The region for allylic hydrogens integrated to between six and seven hydrogens, indicating that the mixture consisted of the two hydrocarbons 109 and 110, with 109 predominating. The higher boiling components were not characterized at the time, but were identified from the dichloromethane study (*vide infra*) as containing the chlorocarbon mixture 111. These compounds are believed to originate by abstraction of a chlorine atom from stannic chloride by the tricyclic cation 112.



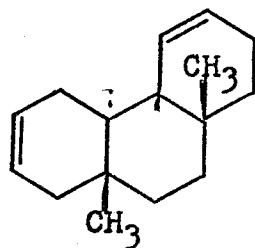
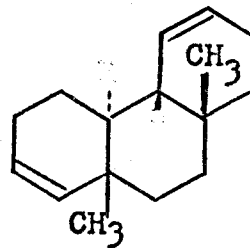
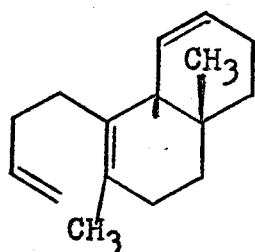
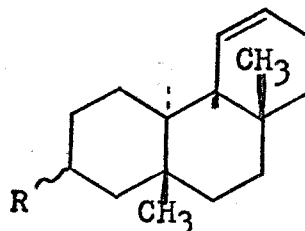
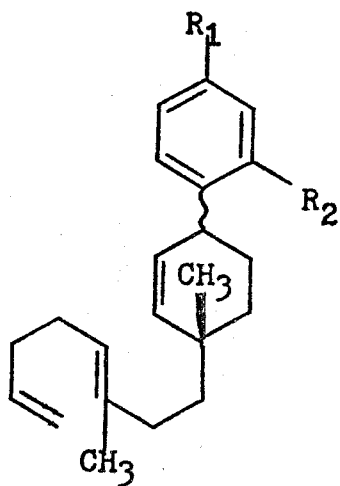
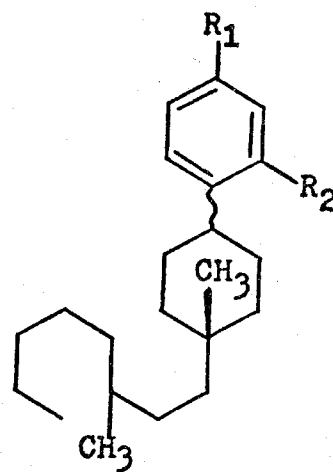
An extensive study was undertaken in hopes of increasing the yield of the tricyclic dienes 109 and 110. The variation of cyclization conditions is summarized in Table III. The products isolated from the various reactions are illustrated in Chart P. The best yield of tricyclic dienes 109

Table III

Run	Solvent	SnCl ₄ /82	Temp.	Rxn. Time	% 109 and 110	Other Products (%)
1	CH ₃ NO ₂	3:2	-28°	1.5 min.	24.7	
2	CH ₂ Cl ₂ /CH ₂ CH ₂ O CO	6:1	25°	1 hr.	56.4 ^a 61.4 ^b	111(3.9)
3	C ₆ H ₆	6:1	5°	1.5 hr.	22.2	100(12), P-1(28)
4	CH ₂ Cl ₂	3:2	25°	4 min.	14.4	111(34.9)
5	F ₃ CCH ₂ OH	3:1	0°	3 hr.	20.2	P-2(16)
6	CH ₃ OC ₆ H ₅	3:1	-10°	15 min.	12.2	100(6.4), 111(24.6) P-4, P-5(28), P-6, P-7(20)
7	MeO ₂ CC ₆ H ₅	3:1	0° then 25°	1 hr. 5 hours	35.4	100(7.8) 111(3.0)

a, isolated yield; b, yield estimated by vpc

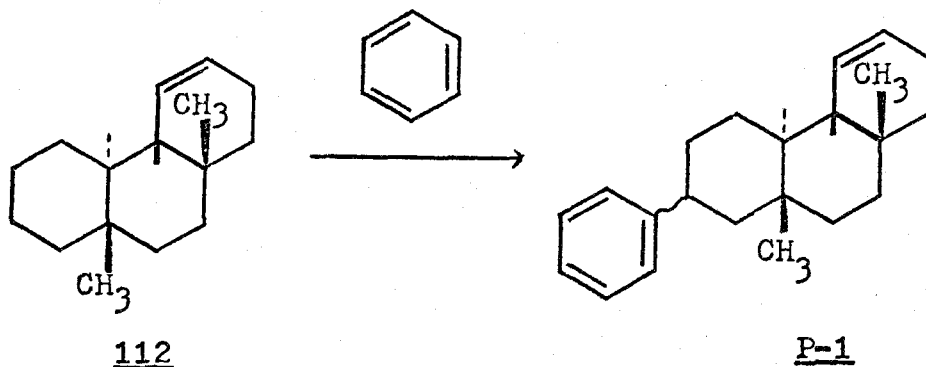
Chart P

109110100P-1 R=C₆H₅111 R= ClP-2 R=CF₃CH₂OP-6 R=o-CH₃O-C₆H₄P-7 R=p-CH₃O-C₆H₄P-4 R₁=H, R₂=CH₃OP-5 R₁=CH₃O, R₂=HP-8 R₁=H, R₂=CH₃OP-9 R₁=CH₃O, R₂=H

and 110 was obtained in the dichloromethane-ethylene carbonate reaction (run 2). The reversal of the distribution of hydrocarbons (109 and 110) and chlorocarbons 111, as compared to dichloromethane only (run 4) is noteworthy. Apparently, the abstraction of chlorine by the tricyclic cation 112 to produce chlorocarbons 111 is competitive with the loss of a proton to form hydrocarbons 109 and 110. It is possible that the ethylene carbonate may be acting as a mild base to enhance the rate of proton removal at the expense of chlorine abstraction. The high proportion of chlorocarbons 111 in the dichloromethane study (run 4) does not rule out the possibility that chlorine abstraction from the solvent is also occurring. The abstraction of chlorine from dichloromethane by reactive vinyl cations has been observed by White (124). Another side reaction which appears to be competitive with the formation of tricyclic dienes 109 and 110 is the interruption of the cyclization at the bicyclic stage, i.e., removal of a proton from the bicyclic cation 107 to yield the triene 100 (Fig. 15). The results in Table III indicate that there is a relationship between the proportion of triene 100 produced and the polarity of the solvent used in the cyclization. While the exact nature of this effect is difficult to ascertain, it is possible that the solvent polarity may have an effect on the conformation or "coiling" of the side chain in alcohol 82. The effects of solvent on the conformation and reactivity of polyolefinic compounds has been discussed

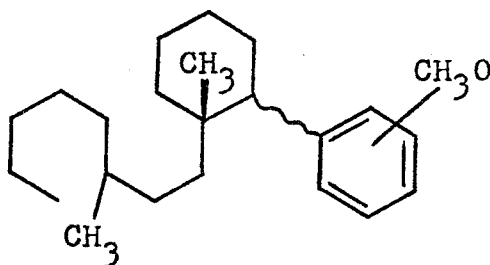
by van Tamelen (125). It is postulated that in a solvent of low polarity, the conformation of the side chain may be oriented in a number of random positions, including those in which the internal double bonds are exposed to the surrounding medium and are probably solvated by it. In solvents of high polarity, the molecule is believed to exist in a more compact, coiled conformation, in which the double bonds are internally solvated. Such a conformation for alcohol 82 would increase the probability that the terminal vinyl group is oriented in a position favorable for cyclization from the bicyclic cation 107. On the contrary, if the chain is unfolded, as in a non-polar solvent, cyclization would be hampered by the necessity of an additional chain-folding step, and hence, proton loss would probably become competitive.

Another phenomenon worthy of comment is the formation of the phenylated hydrocarbon mixture P-1 in the benzene study (run 3). It is, of course, readily deduced that these products originated from the attack of the tricyclic cation 112 on benzene.



It seems odd that these types of products resulting from the trapping of a terminal cation by aromatic solvents have not been observed in other cyclizations using these conditions (67). While not exactly a preparative experiment, the proportion of tricyclic products indicate that the tricyclic cation 112 had to have been formed in at least 50% yield.

From the results of the benzene study, it was of interest to test the Friedel-Crafts nature of the intermediate cations formed during the cyclization of alcohol 82. Thus, anisole and methyl benzoate were selected as solvents because of their propensities to respectively activate and deactivate the aromatic ring toward electrophilic substitution (126). As expected, cyclization of alcohol 82 in anisole (run 6) yielded a high proportion (48%) of arylated material. On examination of these products, it became apparent that partially cyclized products were present in addition to the tricyclic products P-6 and P-7. The fully cyclized material was readily separated from the rest by silver nitrated silica gel chromatography. The remainder of the arylated material was identified as the substituted cyclohexenes P-4 and P-5 by their spectral characteristics and by their conversion to the hexahydro derivatives P-8 and P-9 via catalytic hydrogenation. Products P-8 and P-9 appeared to each consist of two products by vpc, suggesting that they are either epimeric about C-4, or they contain the isomeric components 113.

113

The cyclization in methyl benzoate (run 7) proceeded without any observation of solvent trapping. The tricyclic diens 109 and 110 were isolated in relatively good yield (35%). In addition, the occurrence of the bicyclic triene 100 or chlorocarbons 111 was minimal. This solvent system is closely related to the run in dichloromethane-ethylene carbonate, and probably exerts the same effect.

The success of Clarke and Bergman (127) with cyclizations of vinyl cations in trifluoroethanol prompted its utilization in the present study. This system should possess the two features of high polarity and low nucleophilicity necessary to effect selective cyclization. However, the results obtained with alcohol 82 in trifluoroethanol (run 5) offered no advantage over other solvents. Besides the other products isolated from the other runs, the tricyclic trifluoroethyl ethers P-2 were isolated in 16% yield.

With the efficacy of obtaining tricyclic products with alcohol 82 successfully demonstrated, attention was directed toward unequivocally establishing the structures of the tri-

cyclic hydrocarbons 109 and 110. The fact that these compounds were virtually inseparable, and that they each had two electronically equivalent double bonds, suggested that conversion to a derivative suitable for structural analysis would be impractical. This left the possibility that proof of the structures of hydrocarbons 109 and 110 might lie in the alternative synthesis of a derivative common to both. A suitable candidate for this was the tricyclic saturated hydrocarbon 114, which could be obtained by catalytic hydrogenation of the tricyclic dienes 109 and 110 (Fig. 18).

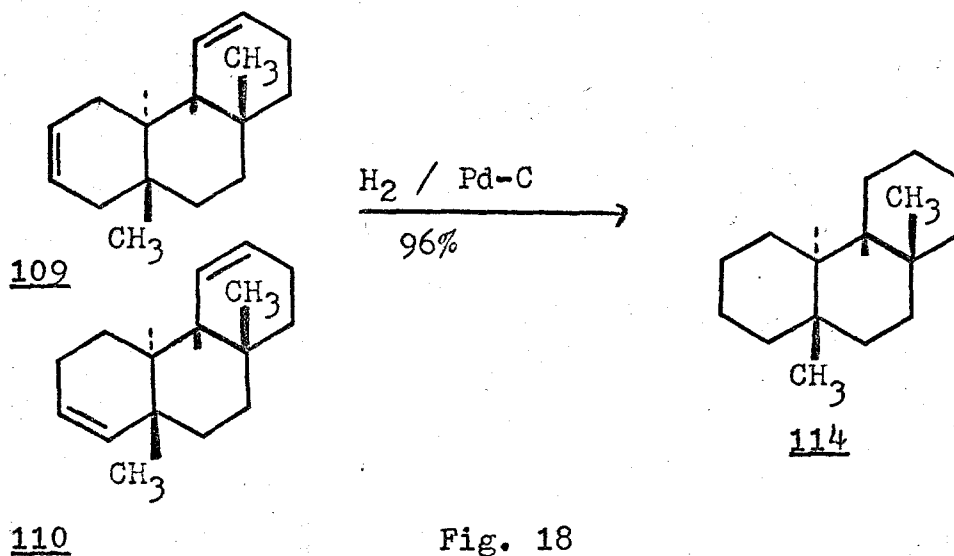
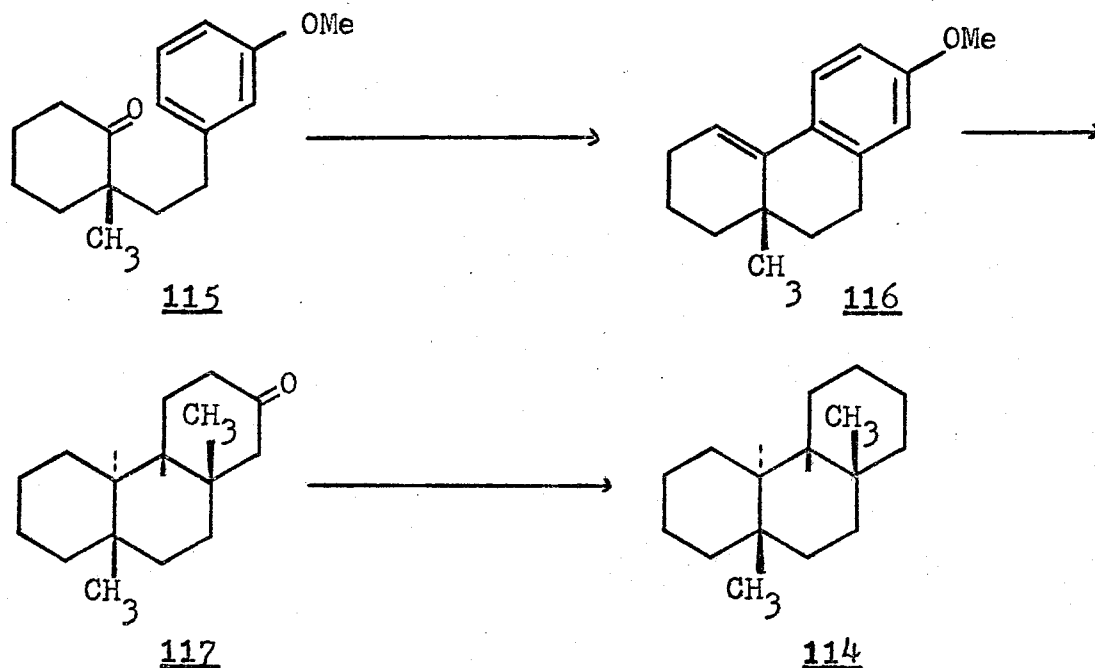


Fig. 18

Treatment of the hydrocarbon mixture with palladium on carbon in hexane under a hydrogen atmosphere afforded a 96% yield of a single saturated hydrocarbon, tentatively assigned the structure 114.

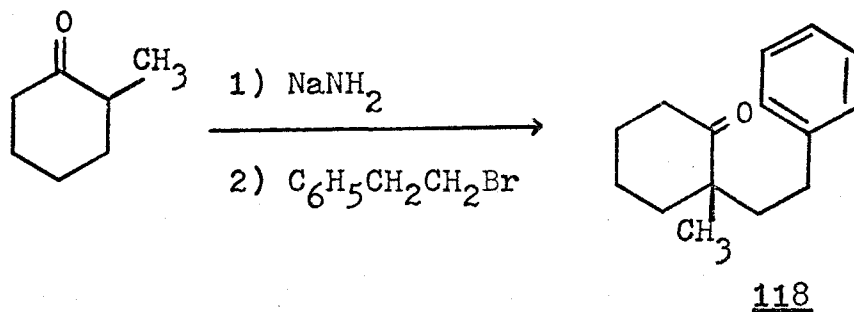
In planning an alternate route to hydrocarbon 114, care must be taken to assure that each asymmetric center is intro-

duced in a stereoselective manner that would allow for the isolation of a single stereoisomer at or near the final step. The route envisioned utilized 2-(2-m-methoxyphenyl)ethyl-2-methylcyclohexanone (115) as the key intermediate. Using



transformations patterned after the germanicol synthesis (42), ketone 115 should readily undergo cyclization in polyphosphoric acid (128) to the tricyclic olefin 116. This compound possesses the basic carbon skeleton necessary for conversion to hydrocarbon 114, and has only one asymmetric center. The remaining chirality should be readily introduced by a variety of possible reactions until a suitable intermediate, i.e. 117, would be obtained which possesses all the required asymmetric centers in 114, and hence, conversion to hydrocarbon 114 would complete the synthesis.

The initial planning was reduced to the synthesis of the ketone 115. The parent compound, 2-methyl-2-(2-phenyl)ethylcyclohexanone (118) was first prepared by Kon (129) by the



alkylation of 2-methylcyclohexanone with β -phenylethyl bromide. The yield was not reported, but the procedure described that mostly starting material was recovered. This inefficient reaction is typical of attempts to alkylate strongly basic enolates with β -phenylethyl halides and tosylates. These types of compounds were first shown by Ingold (130) to yield styrenes in essentially quantitative yield on treatment with strong bases. Alkylation is readily achieved, however, if the enolate substrate has less basic character, i.e., additional electron withdrawing groups. Much of the early work in this area has been reviewed by Gillham (131), who attempted to alkylate the highly basic enolates through the use of the 3-bromomethyl-1,2-benzisothiazoles 119 (Fig. 19). While the reagents readily alkylated a variety of ketone enolates, i.e., cyclohexanone enolate (120), the general application of this method was thwarted by the poor conversion to the phenyl-

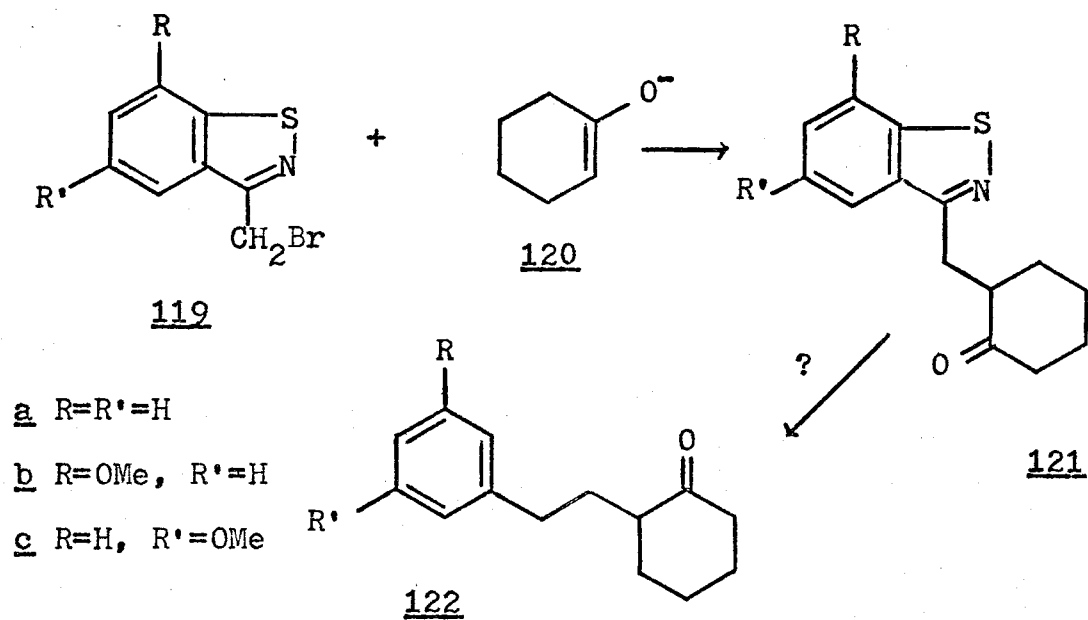
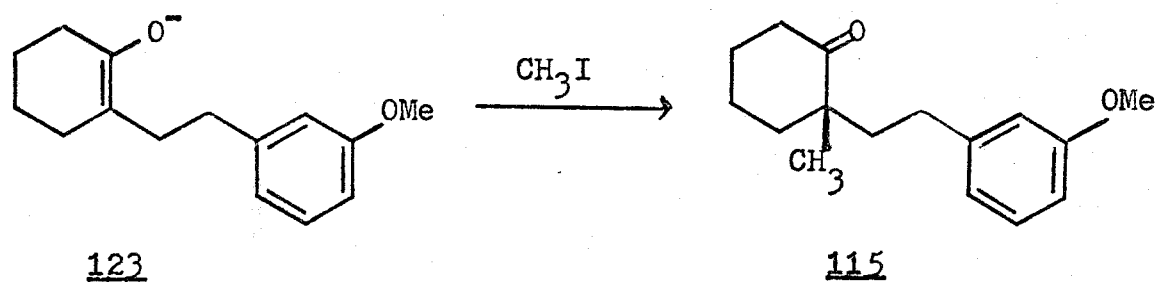


Fig. 19

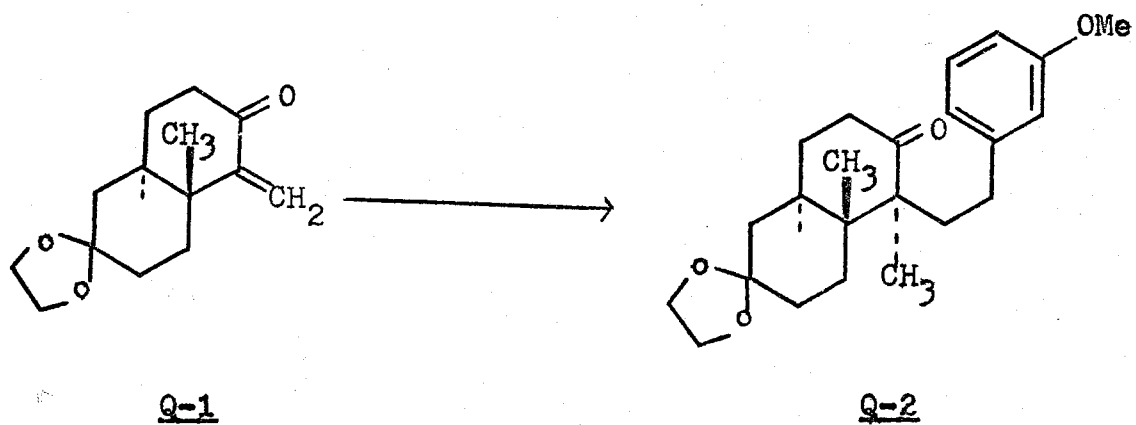
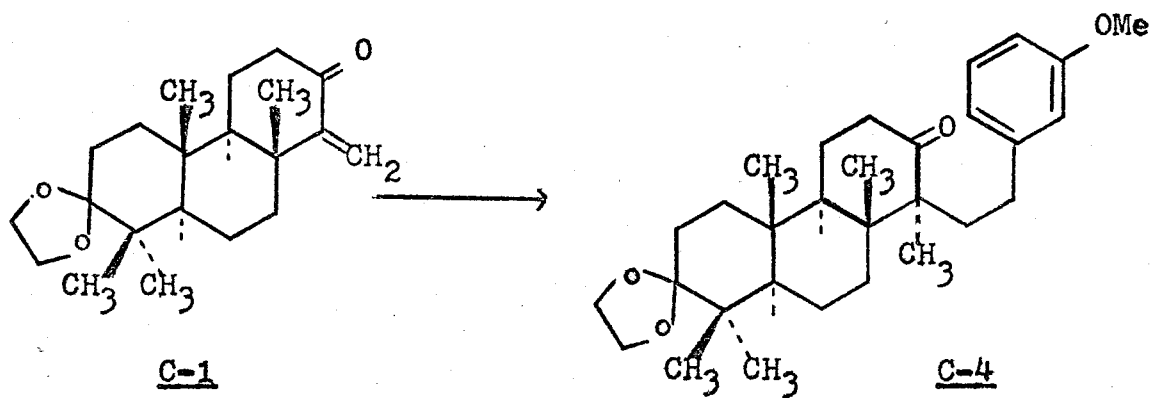
ethylated ketones 122.

Clearly, the approach that would circumvent all these problems would be to have the β -phenylethyl moiety already incorporated into the enolate 123. Methylation would yield

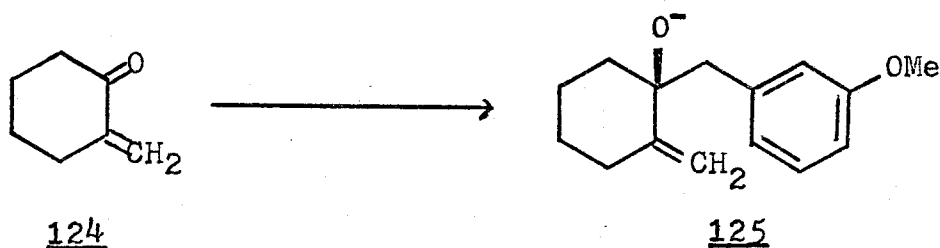


the desired ketone 115. The successful implementation of this of this procedure has been achieved in the Ireland laboratory and is illustrated in Chart Q. In the germanicol synthesis (42), the required ketone C-4 was generated via a conjugate addition of *m*-methoxybenzyl Grignard to enone C-2. Methyla-

Chart Q

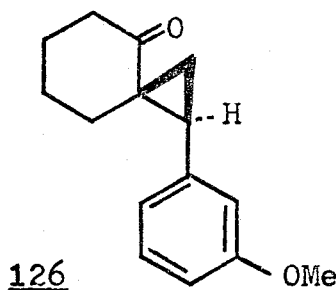


tion was accomplished via acetylation, followed by cleavage of the acetate with methyllithium, and treatment with methyl iodide. A similar sequence was utilized by Ireland and Baldwin (43) for the synthesis of the model compound Q-2, via conjugate addition-methylation of enone Q-1. When Ham (132) attempted to extend this to the parent enone, 2-methylenecyclohexanone (124), the products isolated appeared to stem from

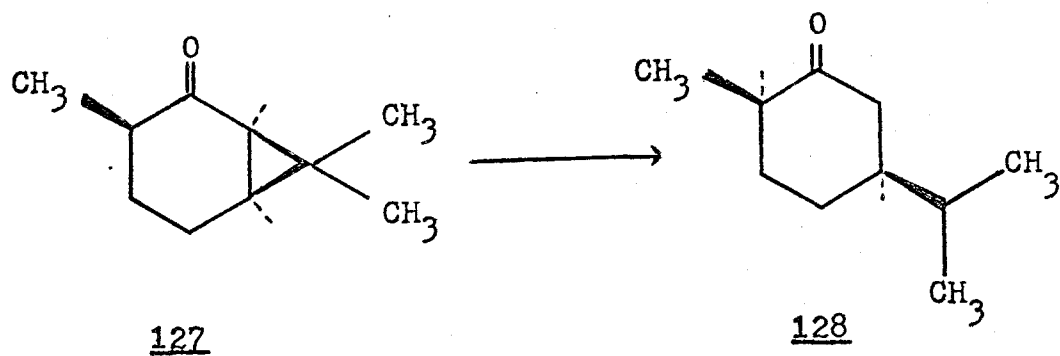


1,2 addition of the Grignard, forming the allylic alkoxide 125.

The approach that was ultimately selected was the reductive cleavage of the spirocyclohexanone 126. The cleavage of



the cyclopropyl ketone carone (127) to carvomenthone (128) was first reported by Bayer (133) and later confirmed by Norin (134a) and Dauben (134b). Several examples of regio-specific cleavage of cyclopropyl ketones appear in the liter-



ature, and many of these have been discussed by Staley in his comprehensive review (135).

The basic rationale for the selective cleavage of a particular bond of a cyclopropyl ketone is that the bond that is cleaved usually possesses the greatest amount of overlap with the π -orbital of the carbonyl group (134). This is illustrated in Figure 20 for carone (127). If the bond cleavage

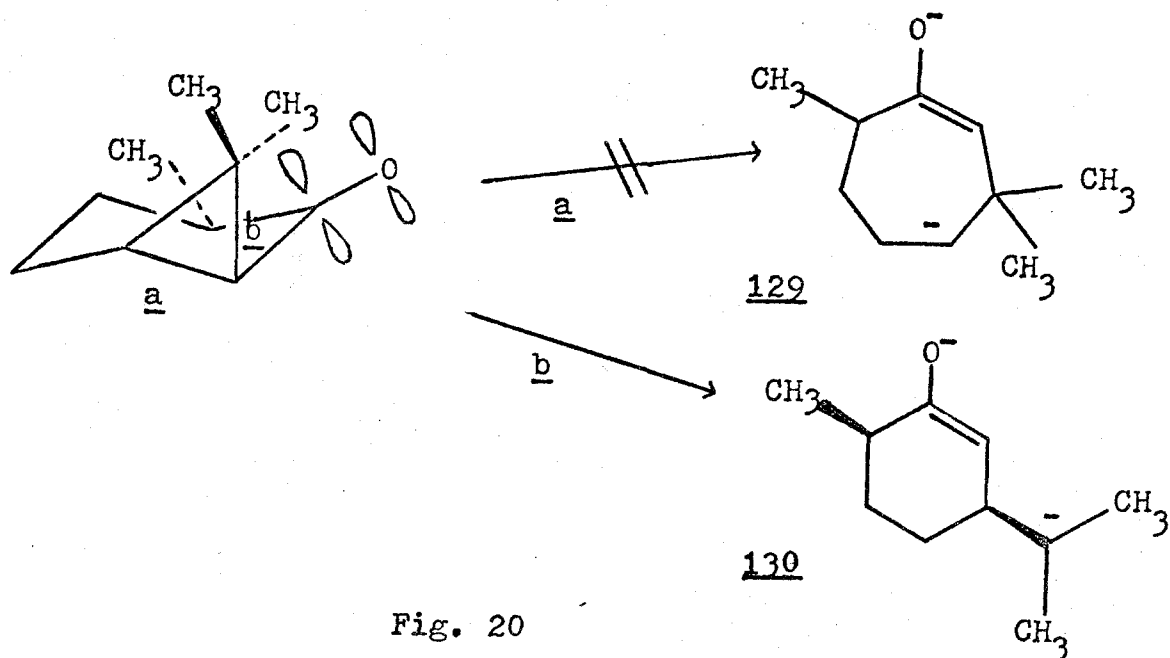
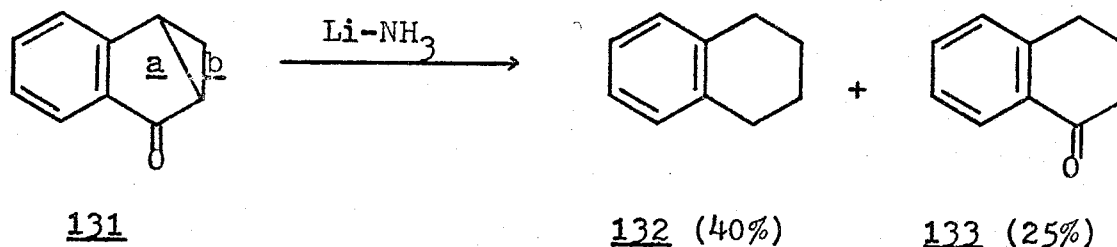
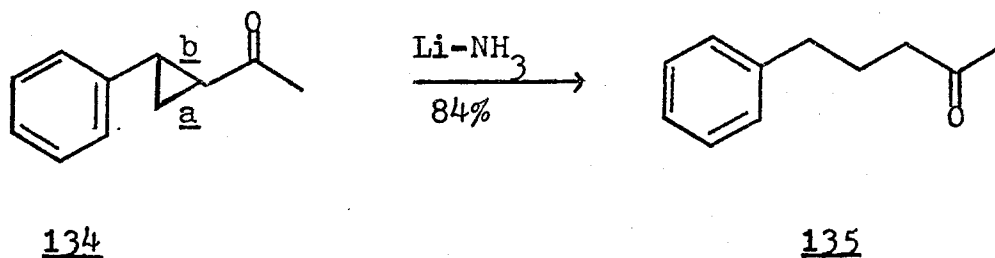


Fig. 20

were thermodynamically controlled, then bond a should be cleaved preferentially, since it would produce the dianion 129, in which both ionic sites are secondary. Cleavage of bond b would yield the less stable dianion 130, with the negative charge focused on a tertiary carbon. The observation that only bond b is cleaved to ultimately produce carvomenthone (128) lends support to the overlap hypothesis. There are several examples, however, in which orbital overlap considerations lead to an incorrect prediction of bond cleavage. This phenomenon is especially pronounced when a substituent on the cyclopropane is capable of stabilizing a negative charge. For example, Fraisse-Jullien and Frejaville (136) observed that reduction of the cyclopropyl ketone 131

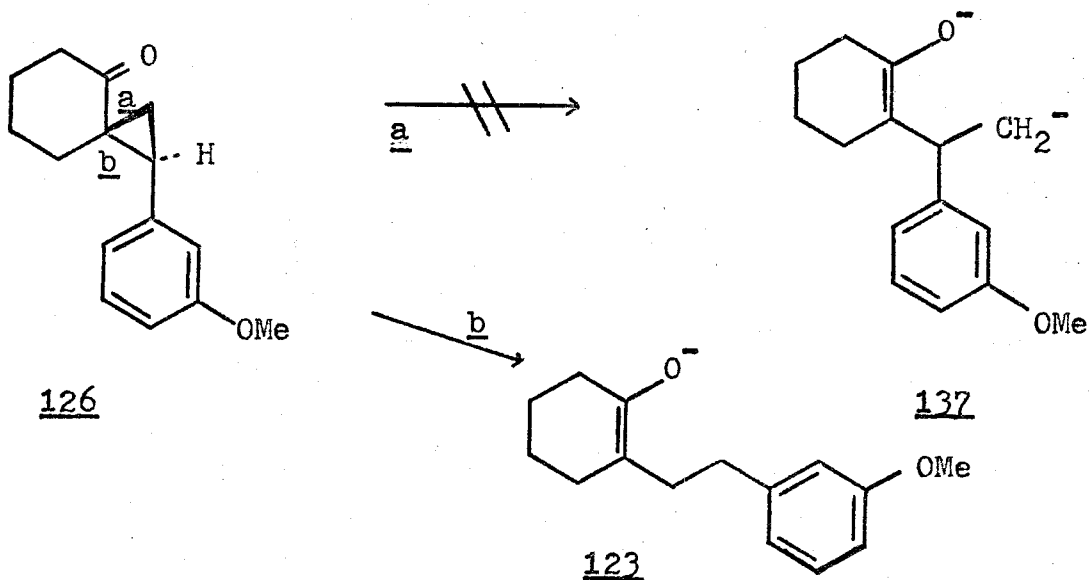


yields products exclusively from cleavage of bond a. Overlap considerations would predict that bond b is more susceptible to cleavage. A more striking example of the effect of an aryl substituent on ring cleavage was also demonstrated by the French authors (136) in the study of the reductive cleavage of trans-2-phenylcyclopropyl methyl ketone (134).



In this case, orbital considerations are meaningless, due to the non-rigidity of the molecule. Nevertheless, reductive cleavage occurred exclusively at bond b. Staley (135) attributes the selectivity in these cases to the ability of the aromatic ring to stabilize a negative charge in the transition state.

Extending this concept to the present study, reduction of the spiroketone 126 would be expected to undergo cleavage



of bond b to yield the enolate 123, as opposed to cleavage of bond a, which is favored on the basis of overlap considerations. The conformation of ketone 126 is expected to be that shown in Figure 21, in which the less substituted methy-



Fig. 21

lene is oriented axially. This is largely based on steric grounds, and by analogy to the observation made by Arbuzov (137) for the conformation of 2-benzylidene-cyclohexanone oxide (138) in which the oxirane oxygen preferentially occupies the axial position.

With the above considerations in mind, the synthesis of the saturated compound 114 was undertaken and is outlined in Chart R. The initial intermediate was the known (138) 2-(m-methoxy)benzylidene-cyclohexanone (R-2), which was readily available by the condensation of m-methoxybenzaldehyde (R-1) with excess cyclohexanone (57% yield). Aldehyde R-1 is, in turn, obtained from m-hydroxybenzaldehyde via methylation with methyl sulfate (139). The enone R-2 was reduced with sodium borohydride to afford the allylic alcohol R-3 in 90% yield. Methylenation of alcohol R-3 was accomplished in 98%

Chart R

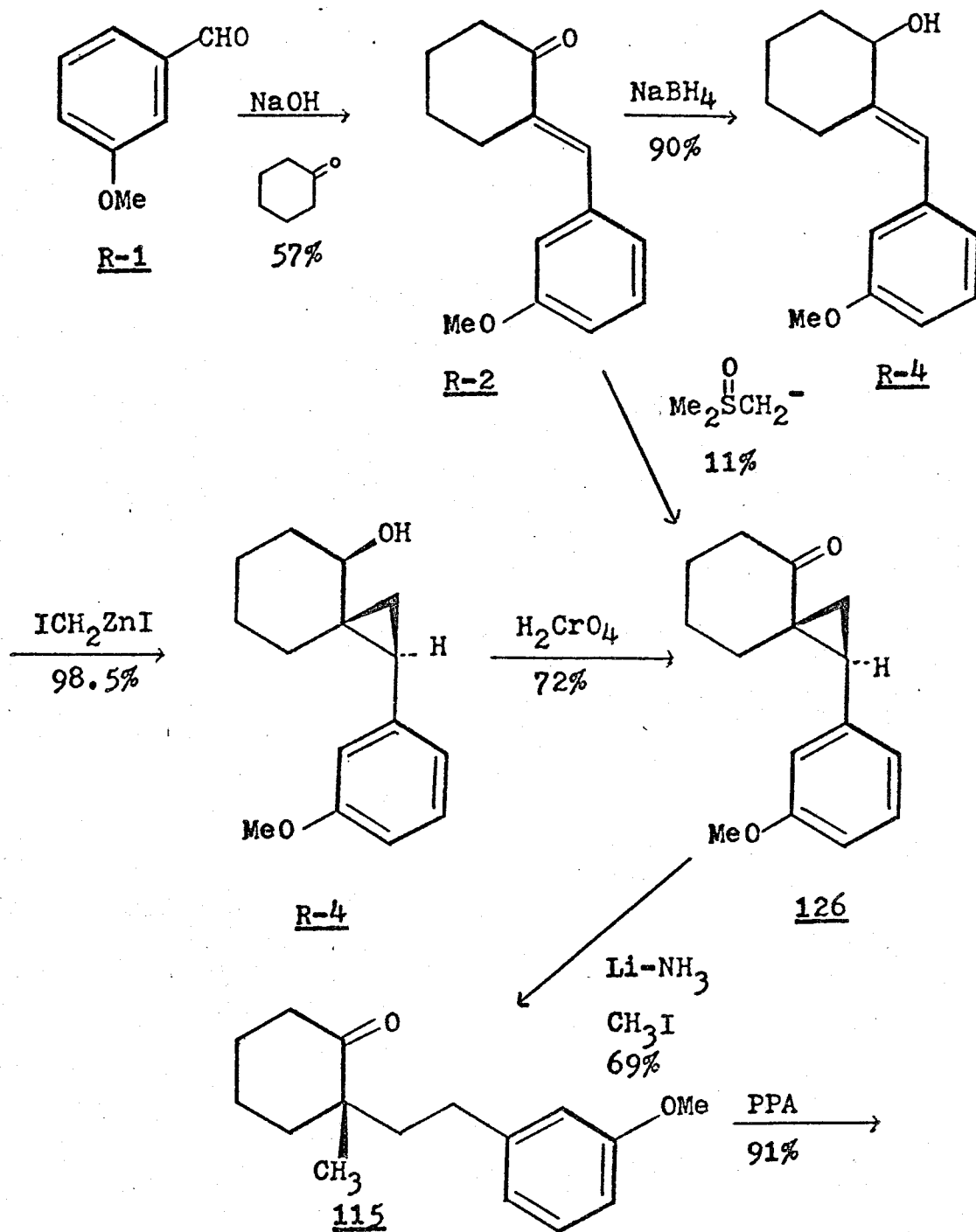
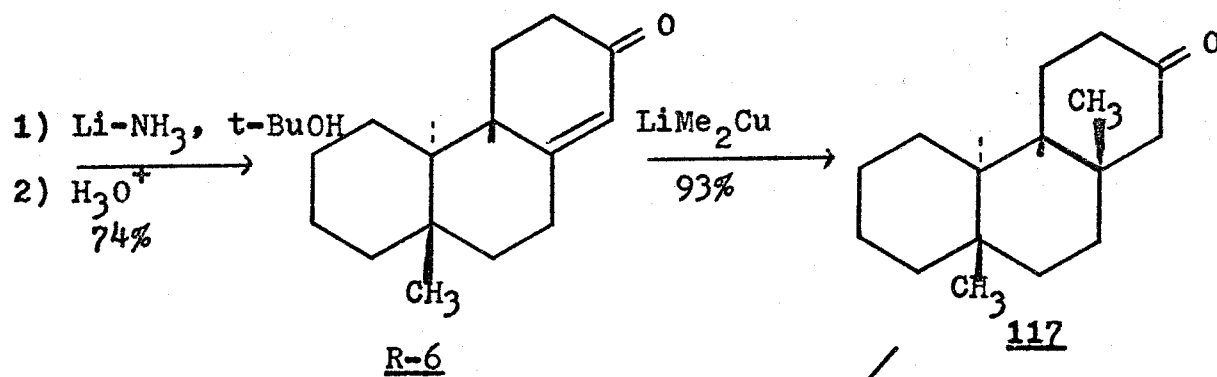
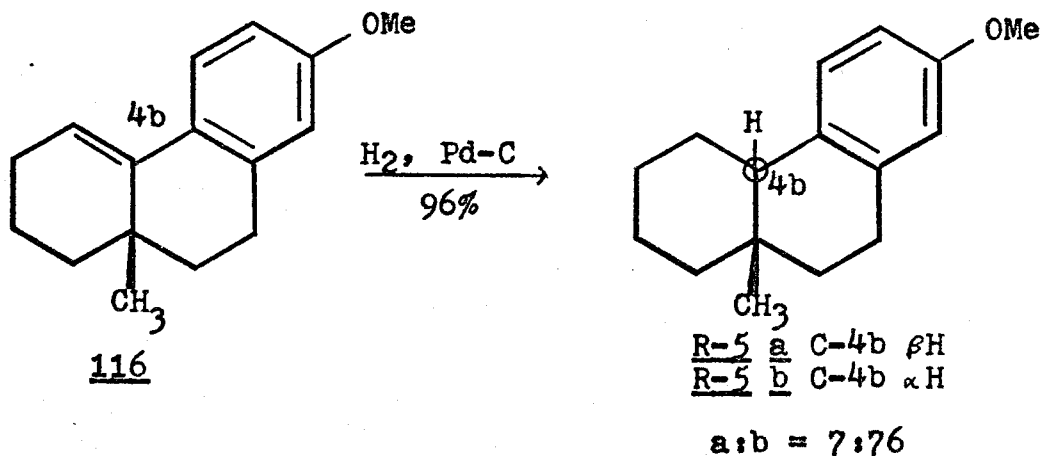
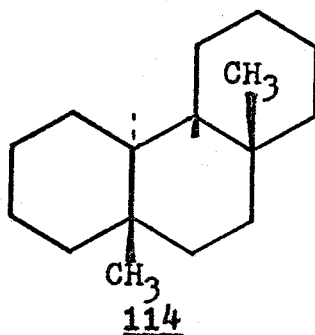


Chart R (continued)



W-K or
 TsNHNH₂, NaBH₄

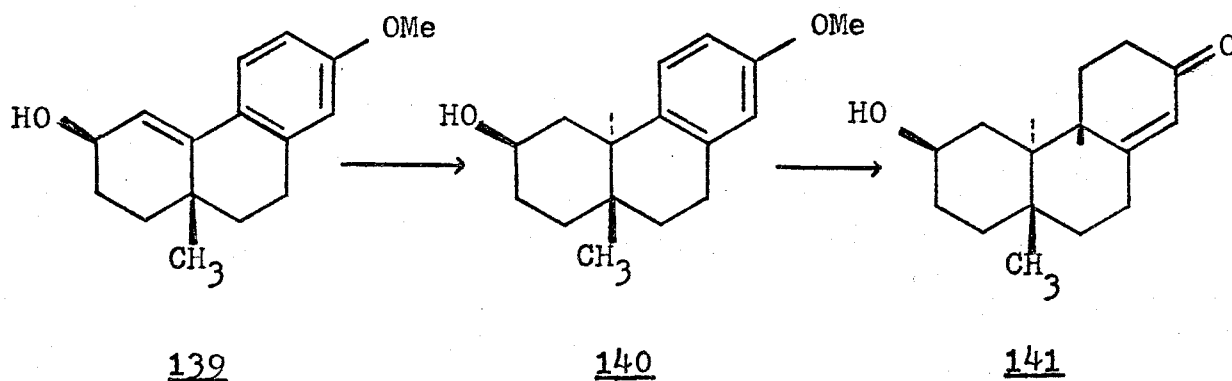
trace



yield by Simmons-Smith reaction (140), which utilizes iodo-methylzinc iodide, ICH_2ZnI , prepared from diiodomethane and a zinc-copper couple (141). The desired cyclopropyl alcohol R-4 was tentatively assigned as the cis structure, based on the directive effect of an allylic hydroxyl group (142). Presumably, the zinc reagent coordinates with the oxygen, thereby delivering the methylene exclusively from the same side as the alcohol. Oxidation of alcohol R-4 with Jones reagent (143) afforded the cyclopropyl ketone 126 in 72% yield. An attempt to convert enone R-2 directly into cyclopropyl ketone 126 with dimethyloxosulfonium methylide (144) was only partially successful, the desired ketone being isolated in a scant 11% yield.

Simultaneously with the synthesis of cyclopropyl ketone 126, Stork published his synthesis of lupeol (49). This appeared to contain the first example of a reductive cleavage-alkylation of a cyclopropyl ketone. Prior to this, the only attempts at trapping the enolate from a cyclopropane cleavage were acetylation (145). Reductive cleavage of ketone 126, followed by methylation was effected using Stork's conditions (49). The desired ketone 115 was formed in 69% yield. The product contained some impurities which were not characterized, but were assumed to be compounds resulting from unselective methylation, rather than non-regiospecific bond cleavage of the cyclopropane. This hypothesis was later confirmed by Gerrans (146), who was able to isolate ketone 115 in 82%

yield under modified conditions. Ketone 115 was readily cyclodehydrated with polyphosphoric acid to afford the tricyclic olefin 116 in 91% yield. To introduce a hydrogen stereoselectively at C-4b, which would be trans to the C-8a methyl group, catalytic hydrogenation was selected, based on the work of Stork (147), who was able to obtain the trans product 140 by catalytic hydrogenation of alcohol 139 with palladium



on strontium carbonate. Examination of a model of either olefin 116 or alcohol 139 indicated that the molecule was almost planar because of the large number of sp^2 carbons (Fig. 22).

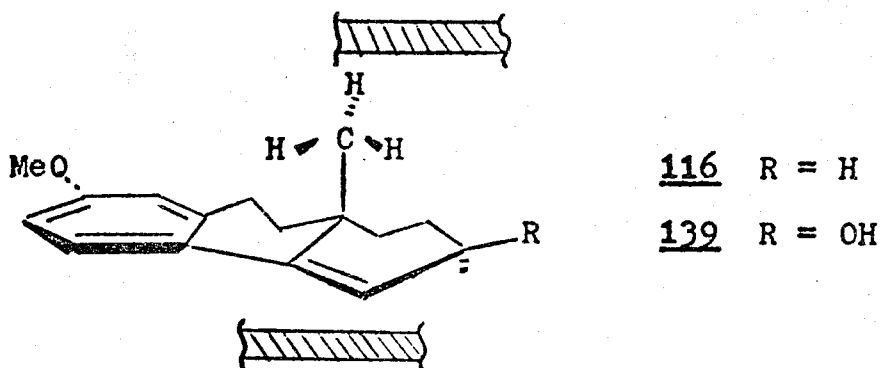
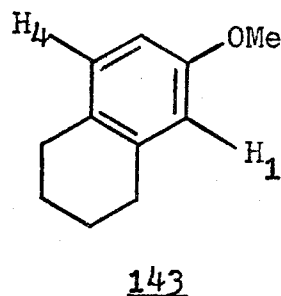
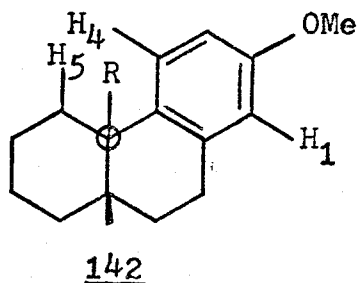


Fig. 22

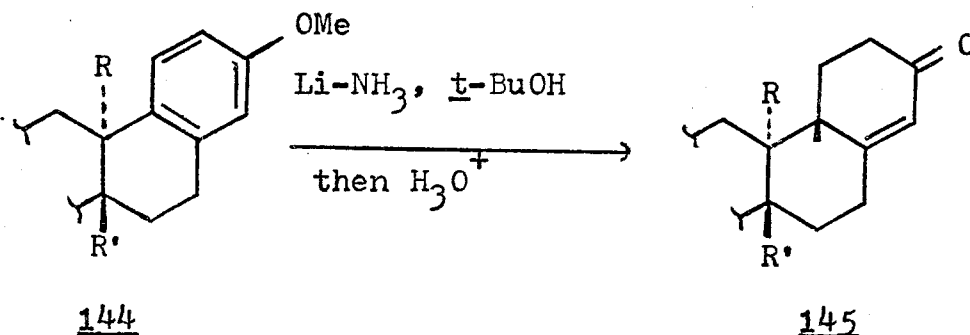
With a near-planar structure, the angular methyl group at C-8a should hinder catalyst binding from the top to a greater degree than from the bottom. The presence of a hydroxyl group in Stork's compound (139) may exert a little effect, but Augustine (148) suggests that an equatorial hydroxyl has a less-pronounced effect on hydrogenation stereochemistry than an axial one.

When olefin 116 was subjected to catalytic hydrogenation with palladium on carbon in hexane for 22 hours, a 96% yield of reduced material was obtained. The product consisted of two components in a ratio of 7:76 by vpc. The major product was isolated by preparative vpc (5% SE-30 on Chromosorb WAW-DMCS, 200°), affording >99% pure material. It was possible to prove unequivocally that the stereochemistry of the major component was trans using an nmr technique developed by Nagata and coworkers (149). He has shown that it is possible to determine the stereochemistry and conformations of compounds of the 2-methoxyoctahydrophenanthrene skeleton (142).



Nagata suggests (149) that magnetic deshielding of the C-4 proton is related to its steric environment. In the case where the B/C ring fusion is trans, there is a strong interaction between the C-4 and C-5 equatorial hydrogens, which tends to deshield the C-4 proton by about 0.21 ppm, relative to 2-methoxytetrahydronaphthalene (143). Taking the C-1 proton as an internal reference, then the difference in chemical shifts between the C-1 and C-4 hydrogens ($\Delta_{1,4}$) would give an indication of the stereochemistry of the ring fusion. For the octahydrophenanthrenes related to this study, the $\Delta_{1,4}$ values were shown (149) to be 0.60 and 0.39 ppm for the trans and cis compounds, respectively. The nmr spectrum of the major product from the hydrogenation of olefin 116 displayed a signal for the C-1 hydrogen at 6.58 ppm and for the C-4 proton at 7.12 ppm. The $\Delta_{1,4}$ for this product is therefore equal to 0.54 ppm, which is quite close to the 0.60 that is indicative of the trans isomer R-5b.

The next step was to reduce the aromatic ring to provide functionality for the introduction of the C-10a methyl group, and at the same time, introduce a hydrogen at C-4a anti to the one at C-4b. This should be readily accomplished via Birch reduction (150), followed by acid hydrolysis. The conversion of a 2-methoxyoctahydrophenanthrene structure 144, in which the B/C ring fusion is trans, into an enone of type 145 is well known in synthetic chemistry (31,147,151). Since the separation of isomers R-5a and R-5b by vpc was tedious,



it was felt that the Birch reduction should be carried out on the mixture, in hopes that the major product could be separated from the others. Reduction of the mixture of octahydrophenanthrenes R-5a and R-5b with lithium in ammonia and tert-butyl alcohol yielded, after hydrolysis, a semi-crystalline product. From this mixture, the major product could be isolated in 100% purity by recrystallization from methanol. The yield of the desired enone R-6, corrected for the isomer purity of the starting material, was 74%.

For the introduction of the C-10a methyl group, lithium dimethylcuprate (152) was selected for its efficacy in forming cis-decalones via conjugate addition to α, β -unsaturated ketones (153). Treatment of enone R-6 with excess lithium dimethylcuprate at 0° afforded a 93% yield of ketone 117. The crude product consisted of one volatile product in >96% abundance by vpc, indicating the high degree of stereoselectivity in the organocopper addition.

Progress in this scheme was temporarily halted at this

point when difficulties were encountered in reducing the carbonyl of ketone 117. Using the modified Wolff-Kishner reduction developed by Nagata (154), less than a 10% yield of hydrocarbon 114 was formed, which was not enough for an ir spectrum at the scale employed. Reduction of the tosylhydrazone of ketone 117 with sodium borohydride (155) gave a similar yield. Sufficient material was obtained for peak enhancement, by comparison with the hydrocarbon 114, derived from the hydrogenation of the tricyclic olefins 109 and 110, obtained from the cyclization of alcohol 82. This was encouraging and prompted the search for an alternative route to hydrocarbon 114.

The reduction of enol phosphates has been used for the selective synthesis of olefins (156). The use of enol phosphorodiamidates has been recently reported from this laboratory (157). Basically, the procedure (Fig. 23) requires the generation of an enolate (146) or alkoxide (147), and subsequent phosphorylation with N,N,N',N'-tetramethyldiaminophosphorochloridate (148) (158) to yield the enol or alkyl phosphorodiamidates 149 and 150, respectively. Reduction with lithium in ammonia or amine solvents affords the corresponding olefin 151 or alkane 152.

The route which ultimately led to the synthesis of hydrocarbon 114 is outlined in Chart S. Treatment of the enone R-6 with excess lithium dimethylcuprate, followed by the addition of HMPA and finally, the phosphorochloridate 148, afford-

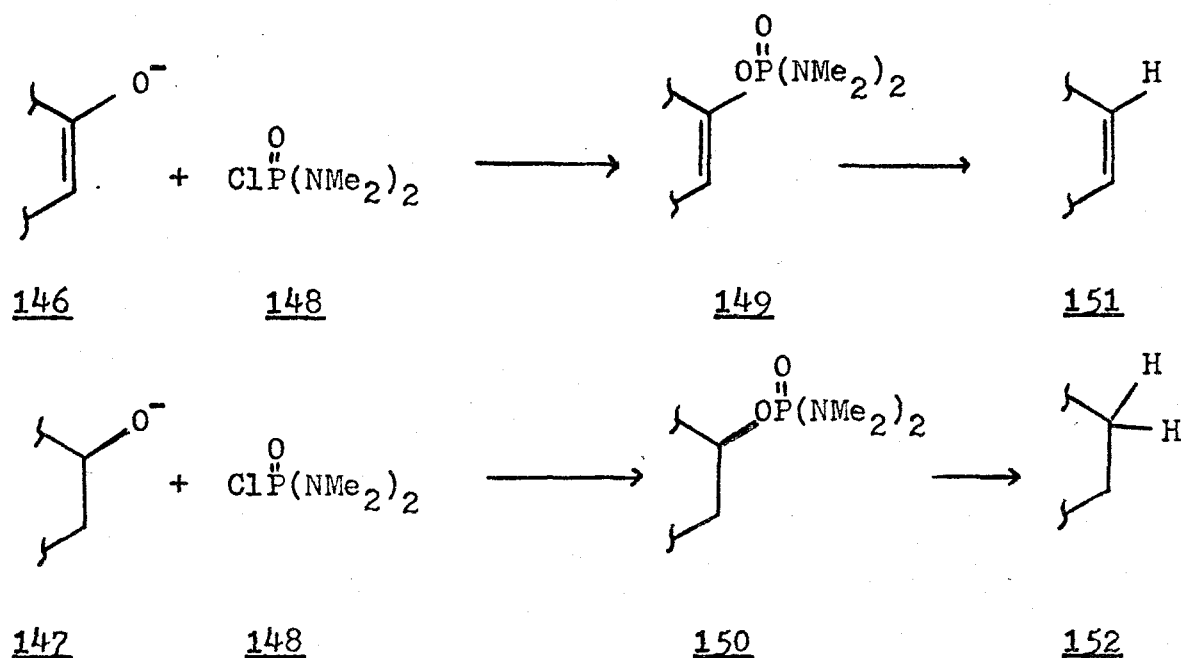
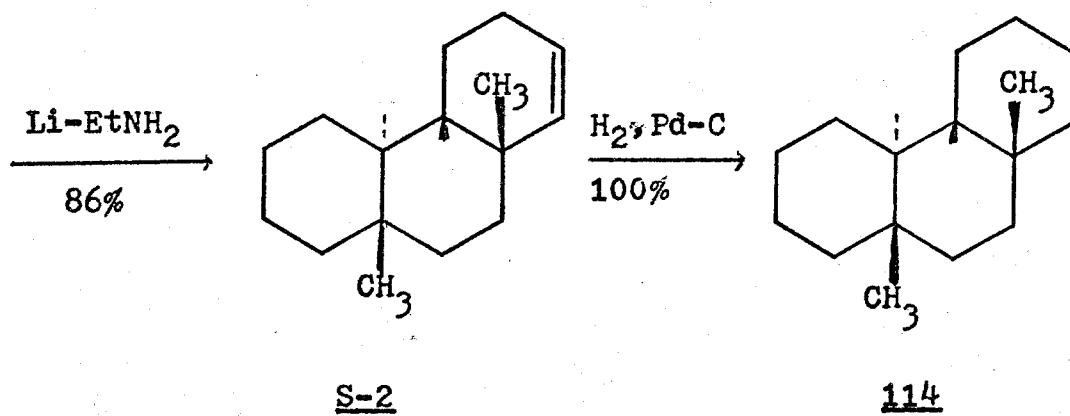
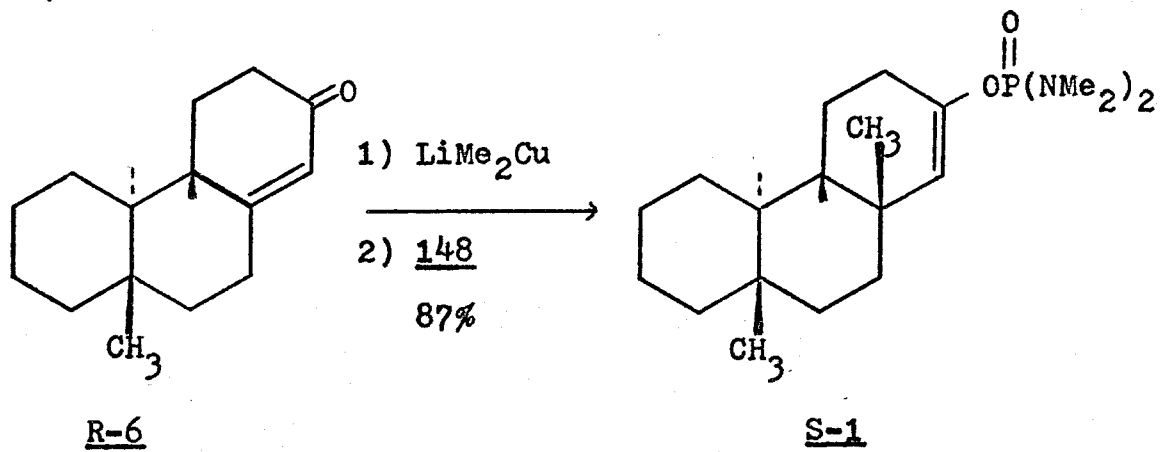


Fig. 23

ed an 87% yield of the phosphorodiamidate S-1. The reduction of S-1 proceeded readily with lithium in ethylamine and tert-butyl alcohol to yield 86% of olefin S-2. Catalytic hydrogenation of S-2 to the saturated tricyclic hydrocarbon 114 proceeded quantitatively. The ir spectra of the saturated hydrocarbons prepared by the two independent pathways were compared (Fig. 24) and were shown to be identical, as were their nmr spectra (Fig. 25). The vpc traces of the two products each showed one volatile component, which were completely superimposable when injected together.

Having established the identity of the two products from the two synthetic routes, the remaining task was to establish that the structure was indeed that of hydrocarbon 114. To accomplish this, ketone 117 was reduced with lithium tri(t-

Chart S



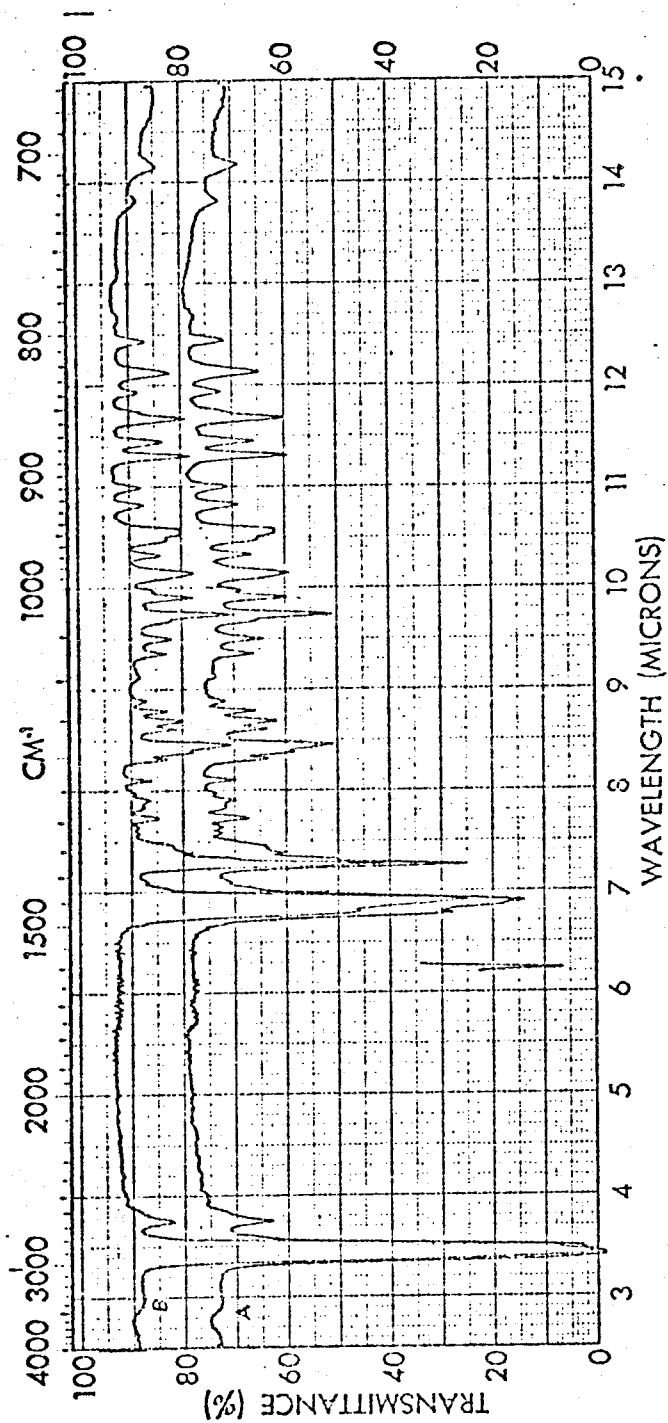


Fig. 24 Infra red spectra (neat) of hydrocarbon 114
(A) From tricyclic diene mixture, 109 and 110.
(B) From tricyclic olefin S-2.

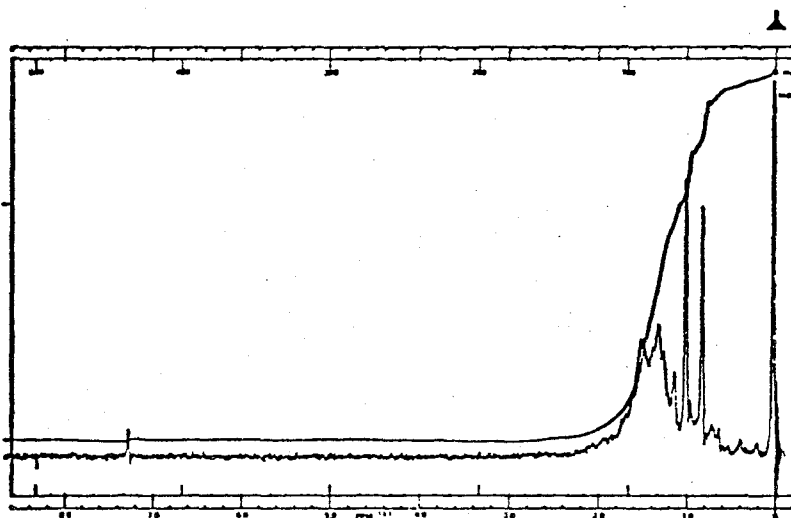


Fig. 25 A. Nmr spectrum of saturated hydrocarbon 114 from tricyclic diene mixture, 109 and 110. (CDCl_3)

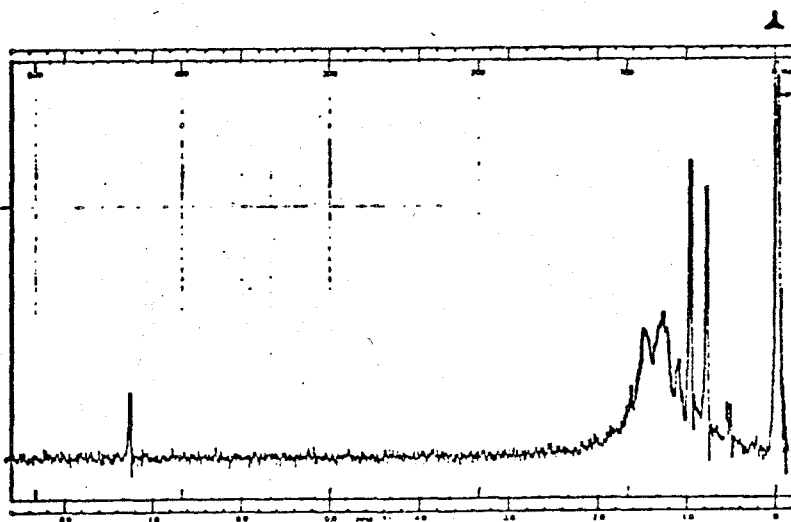
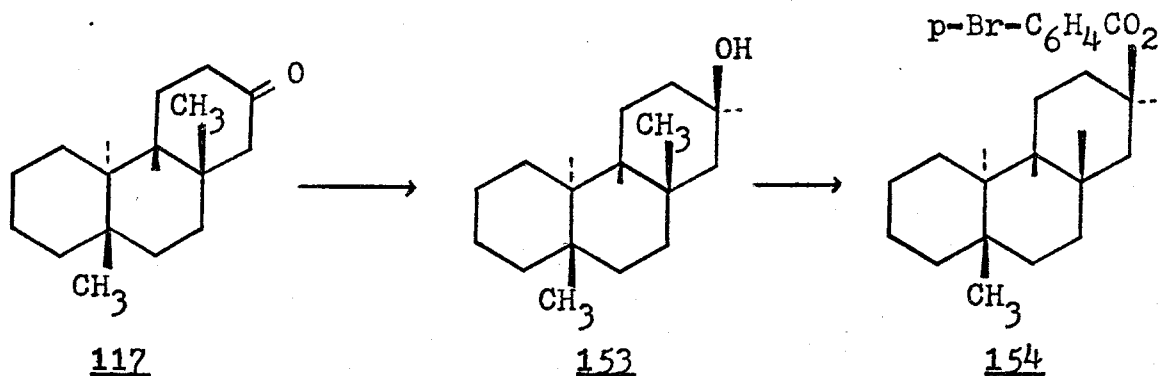


Fig. 25 B. Nmr spectrum of saturated hydrocarbon 114 from tricyclic olefin S-2. (CDCl_3)

butoxy)aluminum hydride to give a quantitative yield of alcohol 153. The conclusion that the product was the axial alco-



hol was based on the half-band width of the C-2 methine proton (9 Hz) and the fact that hydride attack would be unfavorable from the β -face, due to interaction with the C-10a methyl group (98). Treatment of alcohol 153 with p-bromobenzoic acid in pyridine afforded a 75% yield of the p-bromobenzoate 154, which was analyzed by x-ray crystallography by Dr. R. Marsh and Mr. J. Sherfinski (159).

These men obtained the following data. Ester 154 (MW = 418.4) crystallizes in the triclinic space group $P\bar{1}$ with the following cell dimensions: $a = 11.83 \pm 0.003 \text{ \AA}$, $b = 11.025 \pm 0.008 \text{ \AA}$, $c = 11.549 \pm 0.008 \text{ \AA}$, $\alpha = 130.05 \pm 0.04^\circ$, $\beta = 113.63 \pm 0.03^\circ$, $\gamma = 86.09 \pm 0.04^\circ$; $Z = 2$, $D_c = 1.36 \text{ g/cc}$. X-ray intensity data were collected on a modified General Electric XRD-5 quarter-circle diffractometer with nickel-filtered $\text{CuK}\alpha$ ($\lambda = 1.5418 \text{ \AA}$) radiation. Solution was by Patterson-Fourier techniques. Full matrix least squares refinement of heavy atom positional parameters and isotropic temperature

factors for carbon and oxygen, and anisotropic temperature factors for bromine converged at an R value of 0.138 for 3,018 independent reflections. Computations were done under the CRYM crystallographic computing system (160). The computer-drawn perspective structure of ester 154 is shown in Figure 26. The structure, as drawn, is the enantiomer of the one shown above. The hydrogen atoms have been omitted.

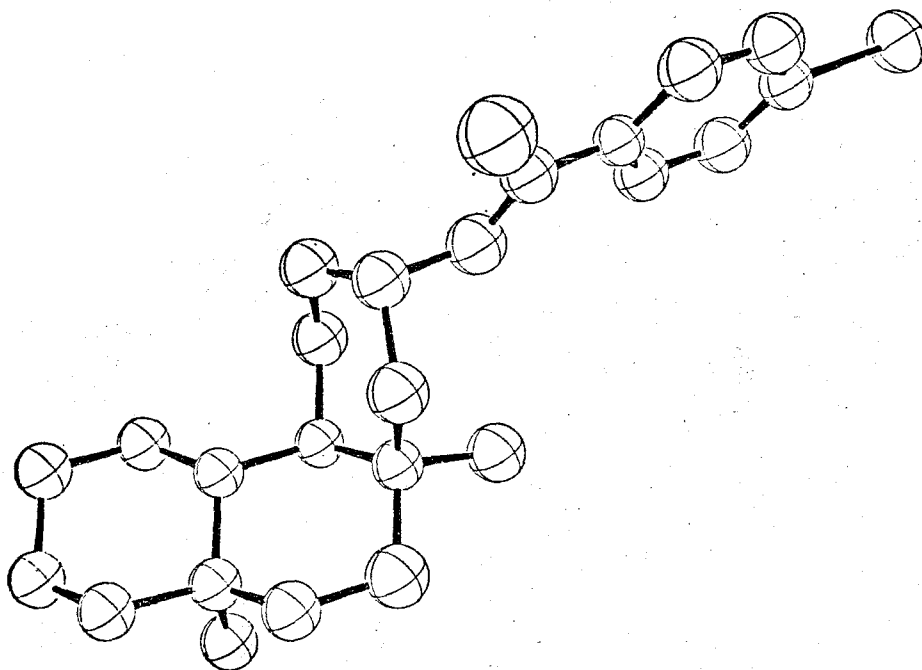
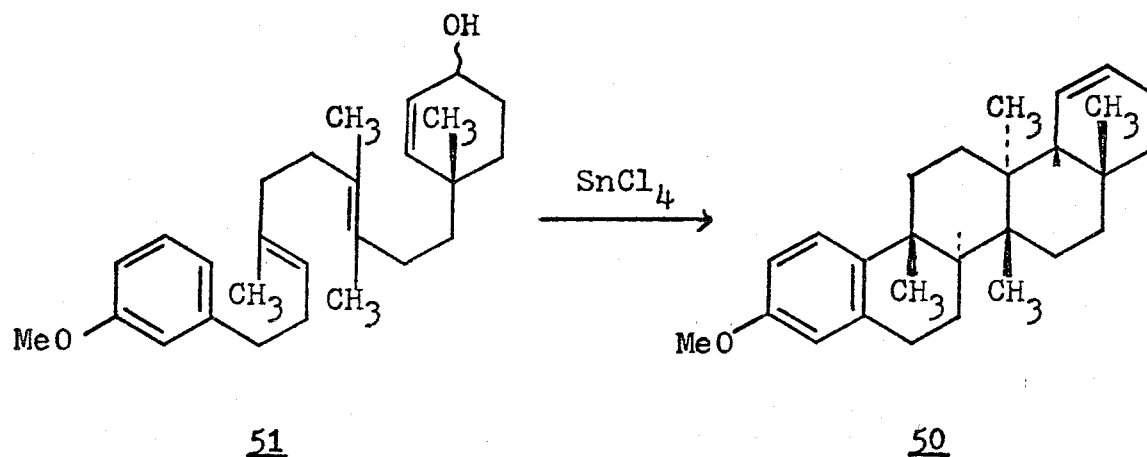


Fig. 26

The geometry of ester 154

The encouraging results obtained from the cyclizations of the two model alcohols 58 and 82 prompted the next study, namely, the synthesis and cyclization of alcohol 51, in hopes of obtaining the pentacyclic olefin 50. For the synthesis



of alcohol 51, advantage was taken of the previous synthesis of aldehyde K-1 by Lipinski (75) and later modified by Moser (162). It was necessary to repeat this synthesis in toto for elaboration into the alcohol 51. During the course of this reinvestigation, several improvements on the individual steps were made, and this greatly increased the overall yield of aldehyde K-1.

The improved synthetic scheme is outlined in Chart T. The first two steps have been described elsewhere (88). Coupling of the trans dibromide L-2 (86) with propargylmagnesium bromide (163), followed by bis-trimethylsilylation afforded an 82% yield of the disilyl enediyne T-1. The yield of 51%

Chart T

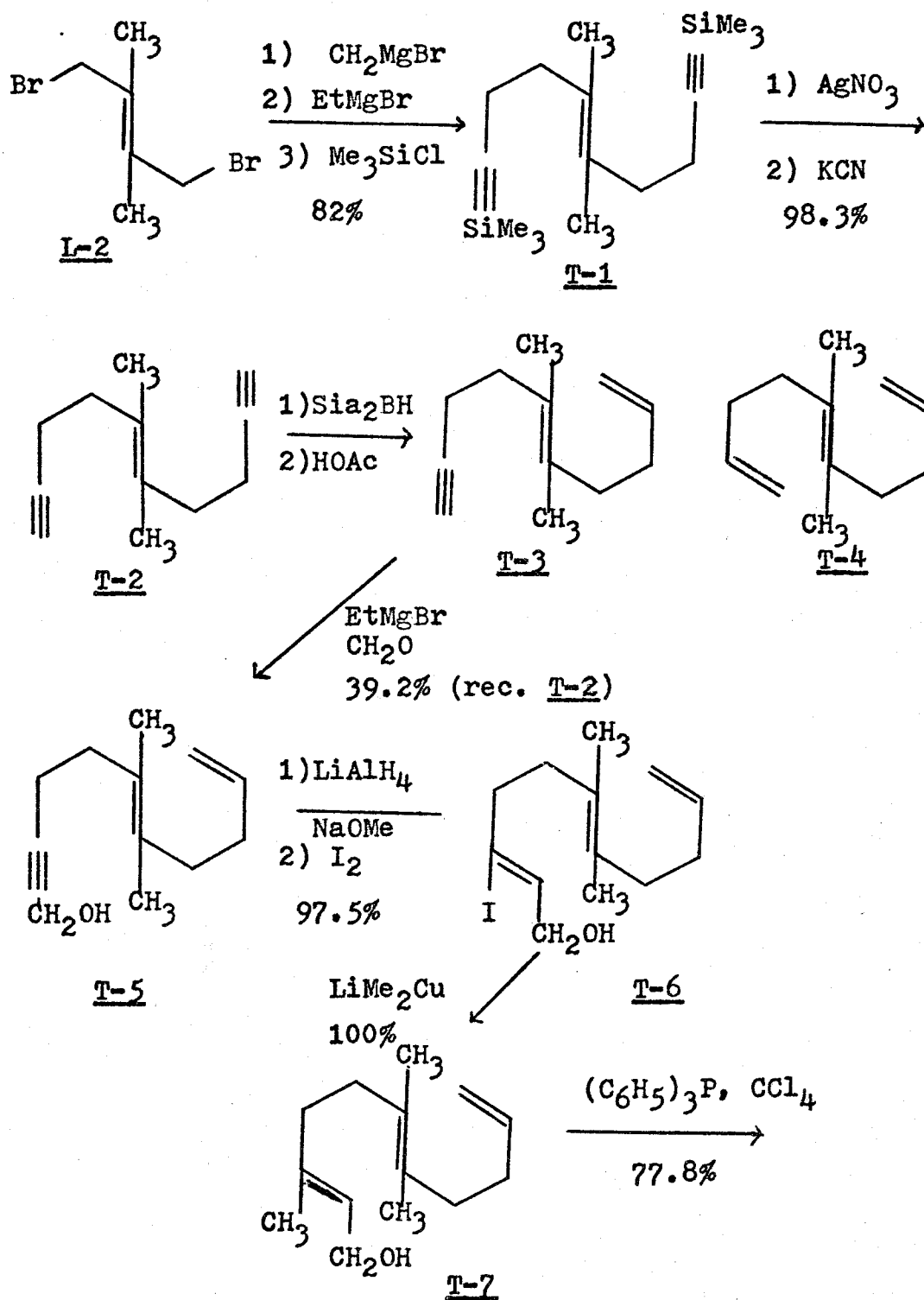
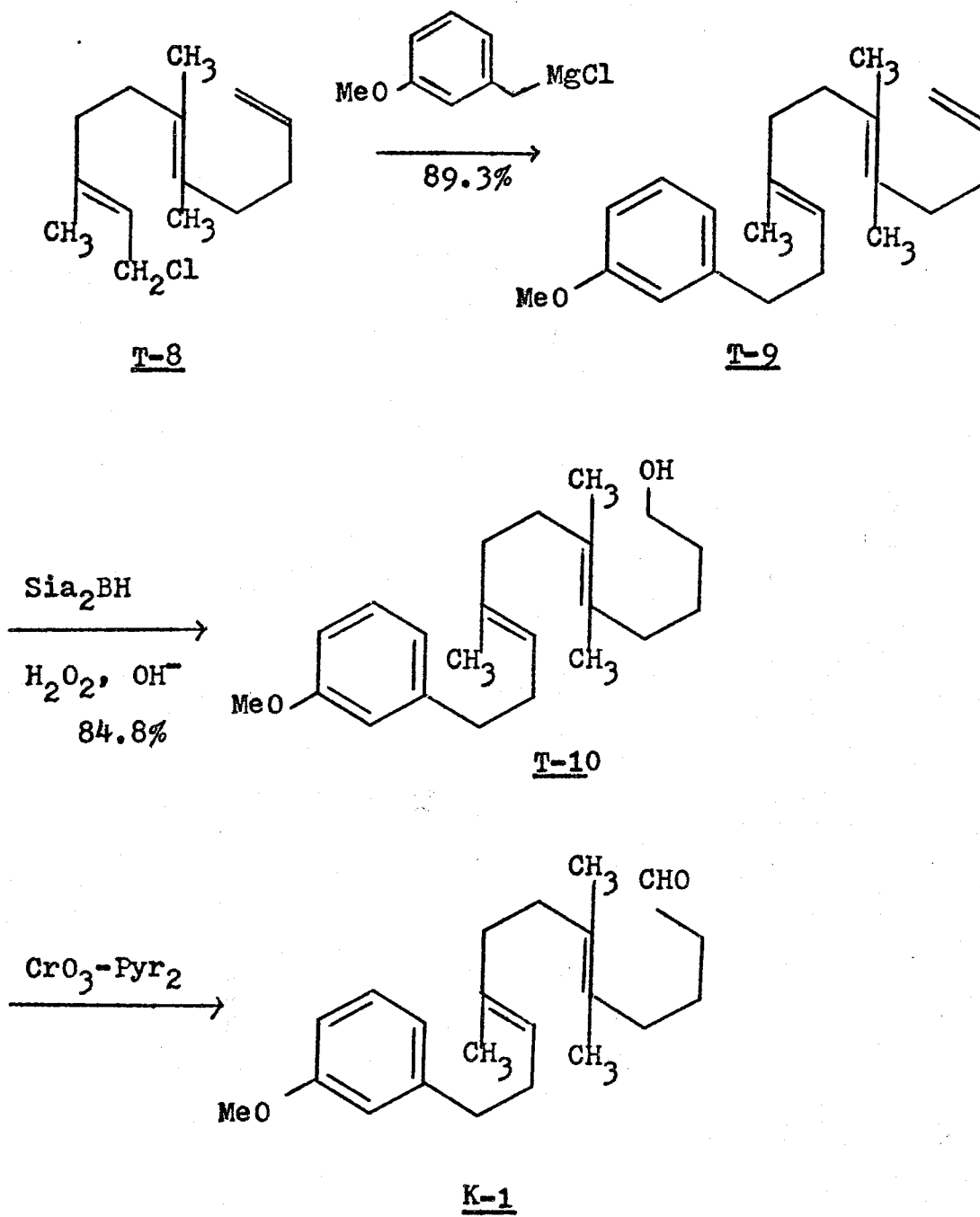
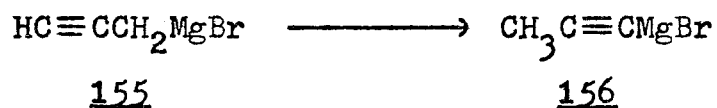


Chart T (continued)



previously reported (88) was undoubtedly due to rearrangement during the formation of the propargyl Grignard reagent (155) to 1-propynylmagnesium bromide (156) (163a). Apparently, the

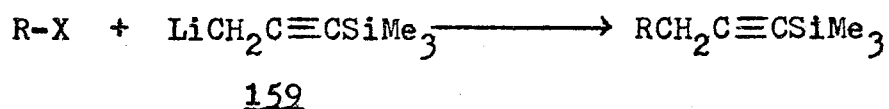


rearrangement is significant if the Grignard formation is carried out at temperatures above 25°. This was later confirmed by Sondheimer (164) who formed the reagent in boiling ether and allowed the mixture to reflux for several hours. Addition of this reagent to propargaldehyde afforded a 35% yield of only the rearranged carbinol 157, as opposed to the normal product 158. Unfortunately, this problem was not easily



overcome in the present study, since the formation of the reagent was rather capricious. The Grignard could not be formed below 20°, and even then, only after a large amount of propargyl bromide had been added. Once the reaction began, its own exothermicity forced the temperature up quite high, leading to rearrangement. While the temperature could be controlled rather well on a 1.2 mole scale of propargyl bromide, extensive rearrangement occurred with 1.95 moles, since the yield dropped from 82% to 54%, which is in the range previously reported (88).

The trimethylsilylation of acetylenes is a well known (165) reaction and is widely used due to its ability to protect the acetylene bond from a number of reactions, such as catalytic hydrogenation (166). Corey and Kirst (167) used lithio-1-trimethylsilylpropyne (159) for alkylation, since



it circumvents the problem of acetylene to allene isomerizations frequently observed upon treatment with strong bases (168). Ireland and coworkers (88) found this reagent ineffective in coupling with the dibromide L-2, thus resorting to the two-step procedure of coupling of propargyl bromide, followed by bis-trimethylsilylation. The disilyl compound T-1 is a highly crystalline solid, which allowed for its facile removal from any rearranged acetylenic or allenic material, which at best could only be monosilylated.

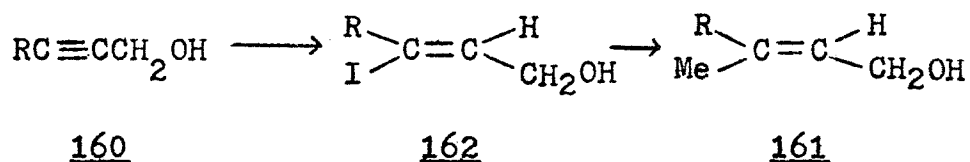
For the removal of the trimethylsilyl groups, the excellent procedure of Schmidt and Arens (169) was employed. As in the published procedure (88), a 98% yield of the enediyne T-2 was realized by treatment of the disilyl compound T-1 with silver nitrate, followed by potassium cyanide.

The next step required the differentiation of the two terminal acetylenic groups in such a way that one end of the molecule was rendered relatively inert, while the other end remained reactive for further manipulation. This was accomp-

lished via the hydroboration-protonation sequence developed by Brown (170). Treatment of the enediyne T-2 with one equivalent of disiamylborane, followed by protolysis with acetic acid, afforded a mixture of hydrocarbons which were approximately a 1:2:1 mixture of unreacted enediyne T-2, the desired dienyne T-3, and the triene T-4. While Lipinski (75) and Moser (162) both carried out the next reaction on the distillate from the crude mixture, it was felt that a recovery of unreacted enediyne T-2 would be desirable, as well as practical. This was accomplished by first distilling the crude product, followed by simple chromatographic filtration through silica gel with petroleum ether to remove most of the boronic impurities (75,162). Next, the mixture was subjected to high-pressure column chromatography with petroleum ether eluent, which readily separated any unreacted enediyne T-2 from a mixture of the dienyne T-3 and triene T-4.

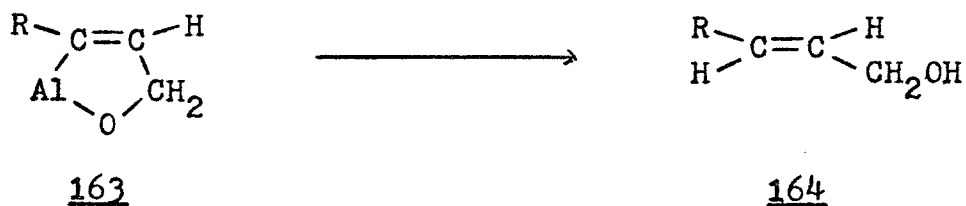
The latter mixture was subjected to hydroxymethylation (171) with ethylmagnesium bromide and formaldehyde to afford the propargylic alcohol T-5 in 39% yield, based on recovered enediyne. The triene was inert to these conditions and could be separated from alcohol T-5 by chromatography.

The triple bond in alcohol T-5 provided the rudiments of the trans trisubstituted 9,10-double bond in aldehyde K-1. The conversion was readily effected using the procedure developed by Corey (172). The transformation of a propargylic alcohol, such as 160, into a trans trisubstituted allylic



alcohol, such as 161, is accomplished by first reduction of the alcohol with lithium aluminum hydride in the presence of sodium methoxide. Subsequent treatment with iodine affords the 3-iodo alcohol 162 almost exclusively. A ratio of roughly 93:7 of 3-iodo alcohol 162 and the 2-iodo isomer has been postulated by Katzenellenbogen (172b). Reaction of the iodo alcohol 162 with lithium dimethyl cuprate results in the displacement of the vinyl halide (173) by methyl, yielding the methylated alcohol 161.

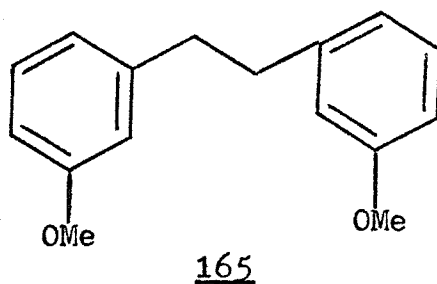
Utilizing this procedure, alcohol T-5 was treated with lithium aluminum hydride and sodium methoxide, followed by iodine to afford the desired iodo alcohol T-6 in 97% yield. This product contained ca. 7% of the 2-iodo isomer, which was carried throughout the remainder of the synthesis. During this reaction, it was imperative that the excess hydride be decomposed with ethyl acetate prior to the iodination step. Otherwise, formation of hydrogen iodide occurs, which results in protonation of the intermediate aluminum complex 163, re-



sulting in the formation of the disubstituted alcohol 164 (172b). Also, the reaction must be allowed to warm up completely to room temperature after iodination, or else the alcohol 164 will again be produced, presumably due to incomplete iodination (172b).

Treatment of the iodo alcohol T-6 with excess lithium dimethylcuprate, followed by methyl iodide, afforded the 3-methyl alcohol T-7 in quantitative yield.

To elaborate alcohol T-7 for the introduction of the aromatic ring, the procedure of Lee and coworkers (122) was used. Treatment of alcohol T-7 with triphenylphosphine in carbon tetrachloride gave the chloride T-8 in 78% yield. The resulting chloride T-8 was treated with excess m-methoxybenzylmagnesium chloride in 1:1 tetrahydrofuran-HMPA (174) to afford the triene T-9 in 89% yield. The major change from Lipinski's procedure (75) is the use of a four-fold excess of magnesium, along with more solvent during the preparation of the Grignard reagent. This reduces the amount of self-coupling product, 1,2-bis-(m-methoxyphenyl)-ethane (165) produced during the Grignard formation.



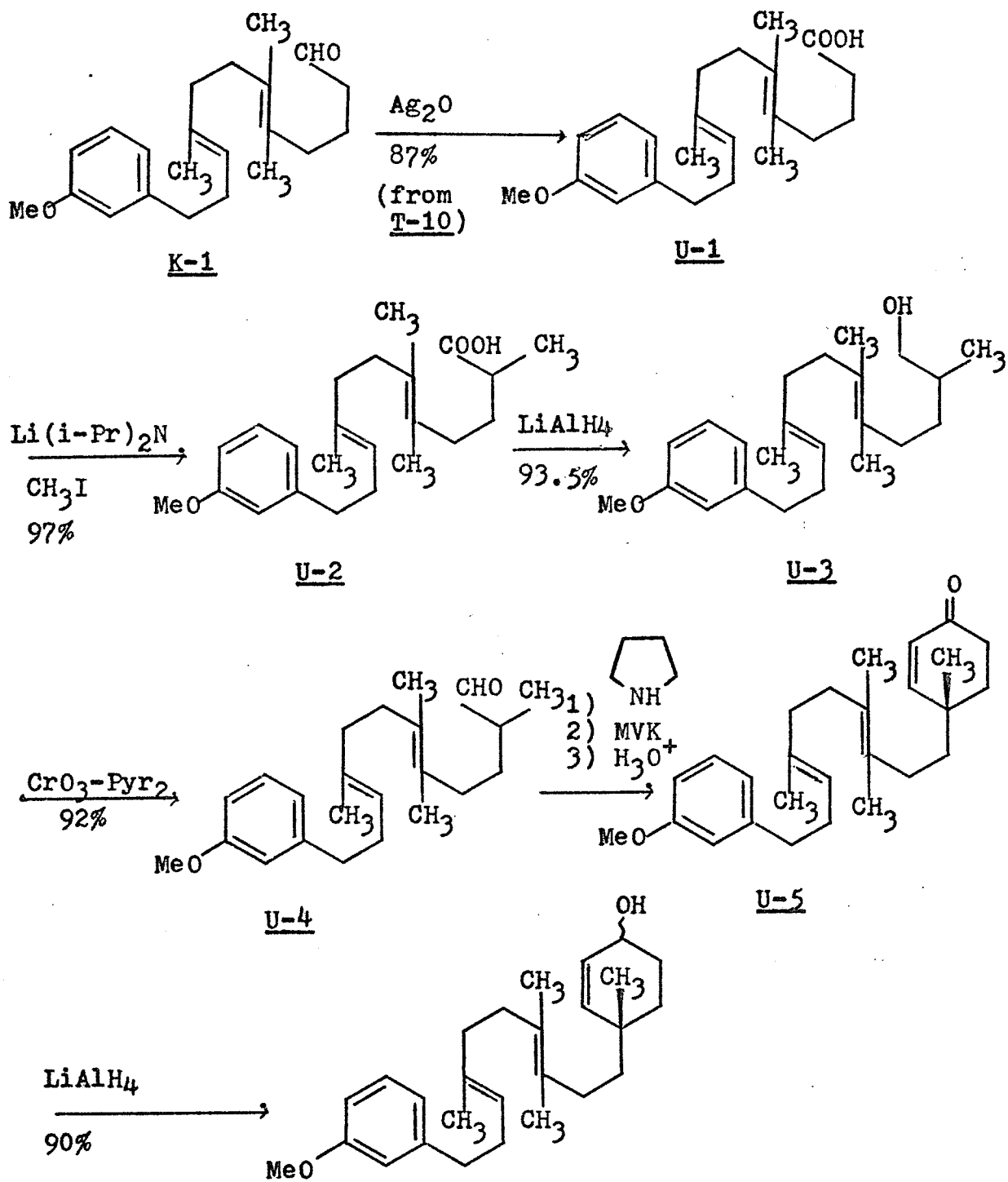
It was found that this by-product, 165, served as an excellent internal standard for the next reaction. Hydroboration of triene T-9 with disiamylborane, followed by basic peroxidation afforded the alcohol T-10 in 85% yield. Lipinski (75) described the use of a three to five-fold excess of disiamylborane, and his yields were 60-70%. This was found to be unnecessary. The use of 1.05 equivalents of the reagent completely consumed the starting triene T-9 in ten minutes.

Collins oxidation of the alcohol T-10 afforded the desired aldehyde K-1. The product was always used without further purification in the next reaction. The yield of alcohol T-10 from the dibromide L-2 was 18%, as compared to 4% obtained by both Lipinski (75) and Moser (162).

The remainder of the synthesis of alcohol 51 from aldehyde K-1 is outlined in Chart U. Treatment of aldehyde K-1 with a two-fold excess (175) of silver oxide yielded the acid U-1 in 88% yield from alcohol T-10.

Subsequent reactions in the scheme were carried out exactly like the synthesis of alcohol 82 and require no further comment. The carboxylic acid U-1 was methylated with lithium diisopropylamide to afford acid U-2 in 97% yield. Reduction of the acid with lithium aluminum hydride afforded a 94% yield of the alcohol U-3. This alcohol was oxidized to aldehyde U-4 by Collins oxidation in 92% yield. Enamine annelation with methyl vinyl ketone afforded a 92% yield of

Chart U



enone U-5. Reduction with lithium aluminum hydride yielded 99% of the desired alcohol 51. The overall yield of alcohol 51 from the dibromide L-2 was 12%.

The cyclization of alcohol 51 appeared to take on a much higher degree of complexity than the previous model studies would have indicated. The best conditions for cyclization again proved to be low temperature. However, at least two equivalents of stannic chloride were necessary for reaction to occur. The addition of dimethyl carbonate led to a decrease in the reaction rate, but did not offer any improvement in the product distribution.

A typical vpc analysis of the products is shown in Figure 27. In contrast to the rather simple traces observed in the model studies, the major product D from the cyclization of alcohol 51 accounted for only about 25% of the volatile material. The chief problem, however, appeared to be polymerization. Chromatography of the crude mixture resulted in the recovery of only about 45% of the material. Since this recovered material displayed identical vpc behavior as in Figure 27, it is assumed that the material which could not be recovered was involatile, and hence, polymeric. From the chromatographed material, component D could be isolated virtually pure by either trituration with cold hexane or a second chromatography on silica gel impregnated with 10% silver nitrate. The yield, as estimated by vpc, was 12% (8% isolated). Component D was assigned the structure of the desired penta-

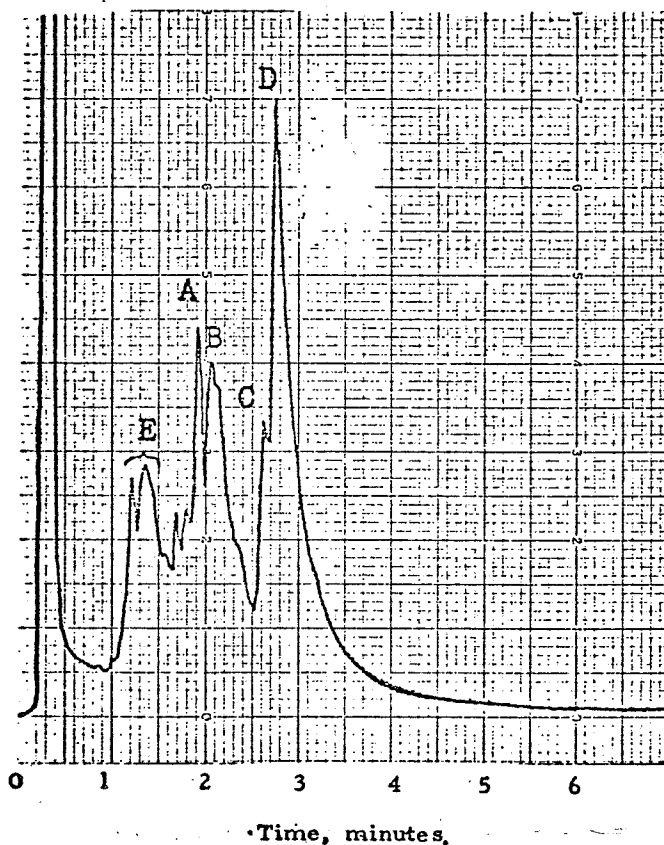
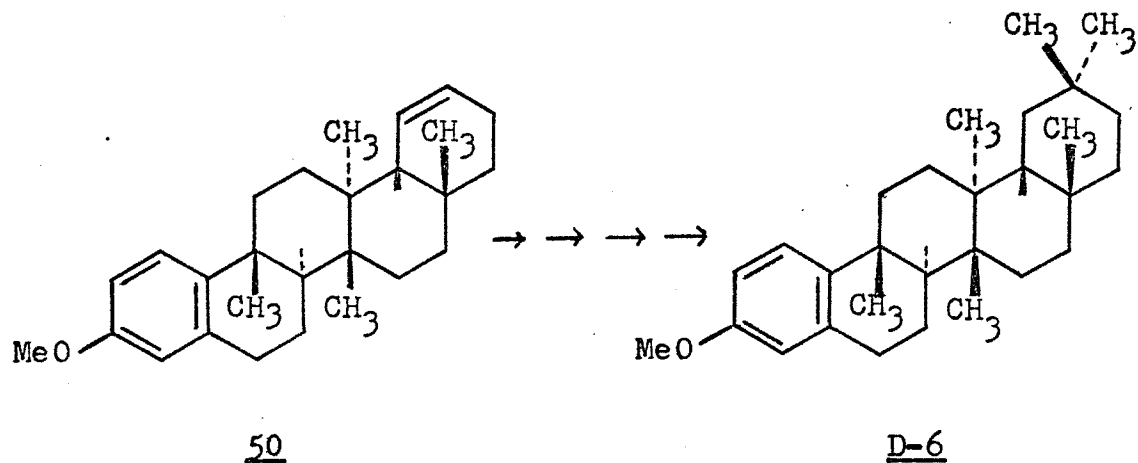


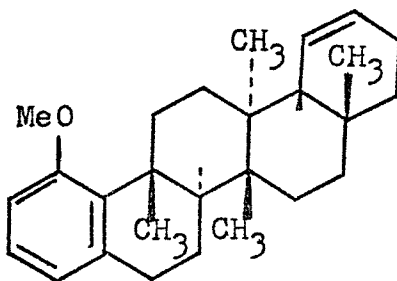
Fig. 27 The cyclization products from alcohol 51 (4% SE-30 on Chromosorb WAW-DMCS, 300^o)

cyclic olefin 50 on the basis of spectral data (see experimental section). The confirmation of this structure will be attained on conversion into the gem-dimethylated intermediate D-6 from the alnusenone synthesis (41).

None of the other components from the cyclization could be isolated in pure form. However, the ir spectra of chromatographic fractions rich in components A, B, and C all dis-



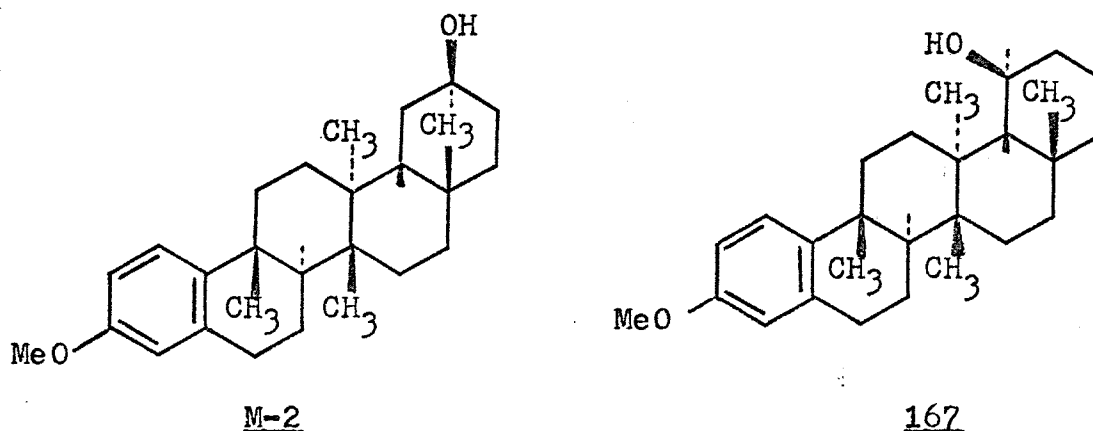
played a large band at 1602 cm^{-1} , and a weaker band at 1575 cm^{-1} , which are characteristic of a 1,2,4-trisubstituted benzene (176). No product was found with the methoxy group at the 1 position, i.e., the pentacyclic olefin 166.

166

The inability to characterize the other cyclization products fully renders an explanation of the mechanism of the

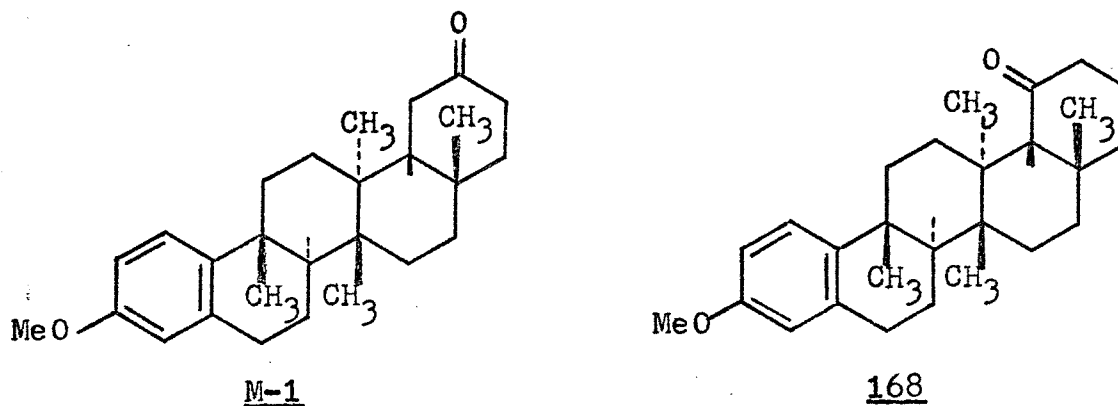
cyclization of alcohol 51 somewhat difficult. More work is needed in order to ascertain either the nature of the cyclization process, or to discover more suitable conditions for increasing the yield of the pentacyclic olefin 50.

The next task undertaken was that of converting olefin 50 into the pentacyclic intermediate D-6 from the alnusenone synthesis (41). Hydroboration of olefin 50 with diborane and basic peroxide oxidation afforded a mixture of two alcohols in quantitative yield. Preparative tlc readily separated the two products, which were assigned the structures of the equatorial alcohol M-2, and the axial alcohol 167. These



assigned structures were based largely on their half-band widths of the methine protons on the hydroxyl-bearing carbons, and on their mobility on tlc. The ratio of alcohols M-2 and 167 was 77:22. Proof that these alcohols were not simply epimeric about the same carbon was demonstrated by their oxi-

dation to the two different ketones, tentatively assigned the structures M-1 and 168. The lack of regioselectivity in the hydroboration of olefin 50 was resolved by the finding that



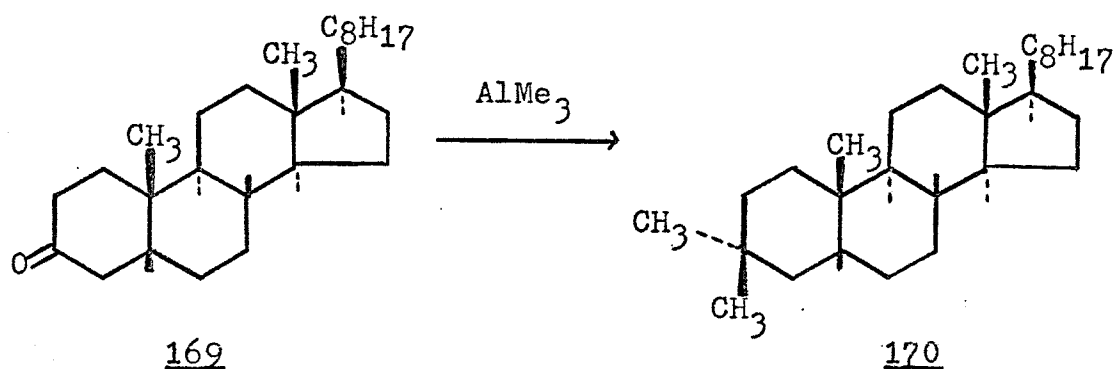
the undesired alcohol 167 readily underwent dehydration with phosphorous oxychloride in pyridine (177) to regenerate olefin 50 as the sole product in 93% yield. Hence, the actual yield of alcohol M-2 was increased to over 95%. The yield of ketone M-1 from the alcohol M-2 was 93%.

The elaboration of ring E of the ketone M-1 proved to be an exceedingly difficult task, for the carbonyl group was very unreactive, probably due to steric hindrance.

The first attempt at conversion of the carbonyl to the required gem-dimethyl grouping was the use of exhaustive methylation with trimethylaluminum. Meisters and Mole (178) were successful in converting several ketones, tertiary alcohols, and carboxylic acids to compounds with completely

methylated quaternary carbon sites.

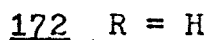
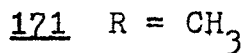
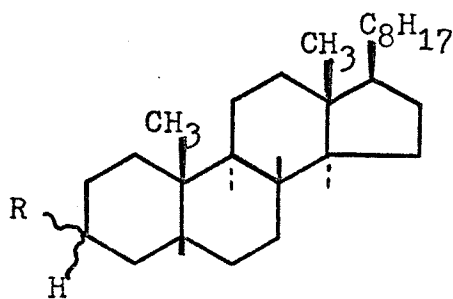
Since most of the examples described (178) utilized ketones in which one or more phenyl rings were adjacent to the carbonyl, it was deemed necessary to test the reaction on a model compound before subjecting the ketone M-1 to the reaction. For this, coprostanone (169) was chosen, since it



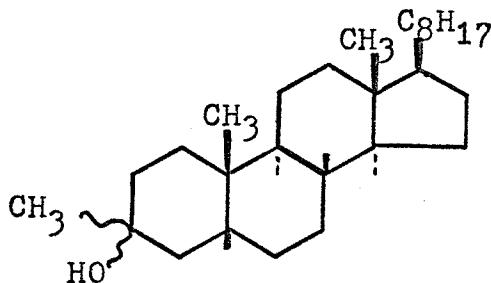
possessed an A/B cis ring fusion with a carbonyl at C-3, which is exactly the structure present in ketone M-1. When coprostanone was heated in a sealed tube at 200° in a 1:1 solution of trimethylaluminum in benzene for 64 hours, a 65% yield of the desired 3,3-dimethyl-5 β -cholestane (170) was isolated in ca. 85% purity after chromatography.

Proof that the reaction had indeed inserted two methyl groups in place of the carbonyl lay in the fact that the product was a saturated hydrocarbon, which possessed a doublet in the ir spectrum at 1385 and 1365 cm^{-1} , characteristic of the gem-dimethyl group. In addition, the methyl region of

the nmr spectrum integrated to twenty-one hydrogens (seven methyl groups). Interestingly, the minor product was also a saturated hydrocarbon, but it did not contain the gem-dimethyl group. This leaves the possibilities of the product being either the monomethylated hydrocarbon 171, or 5β -cholestane (172). How either of these products could be produced in the reaction is not clear.

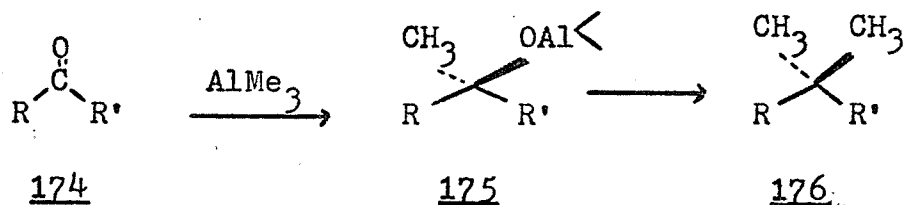


It was found that exposure of coprostanone (169) to neat trimethylaluminum for short periods at atmospheric pressure led to the formation of the tertiary alcohol 173. When this



173

alcohol was exposed to the trimethylaluminum-benzene conditions under pressure, the same hydrocarbon mixture was produced in essentially the same yield and distribution. This suggests that the first step in the methylation of the general ketone 174 is the addition of one methyl group, forming the



tertiary aluminum alkoxide 175, which undergoes C-O bond scission, followed by a second methylation via a tertiary carbonium ion.

When the pentacyclic ketone M-1 was subjected to trimethylaluminum at 200° under pressure, the product mixture obtained was mostly starting ketone, along with some alcoholic and hydrocarbon products as well. This implied that in the case of ketone M-1, the addition of the first methyl group was the slow step. This is quite reasonable, since it is readily seen from Figure 28 that the addition of a methyl

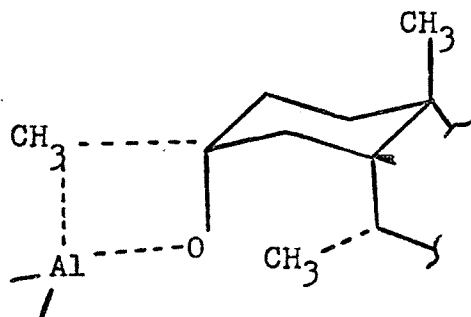


Fig. 28

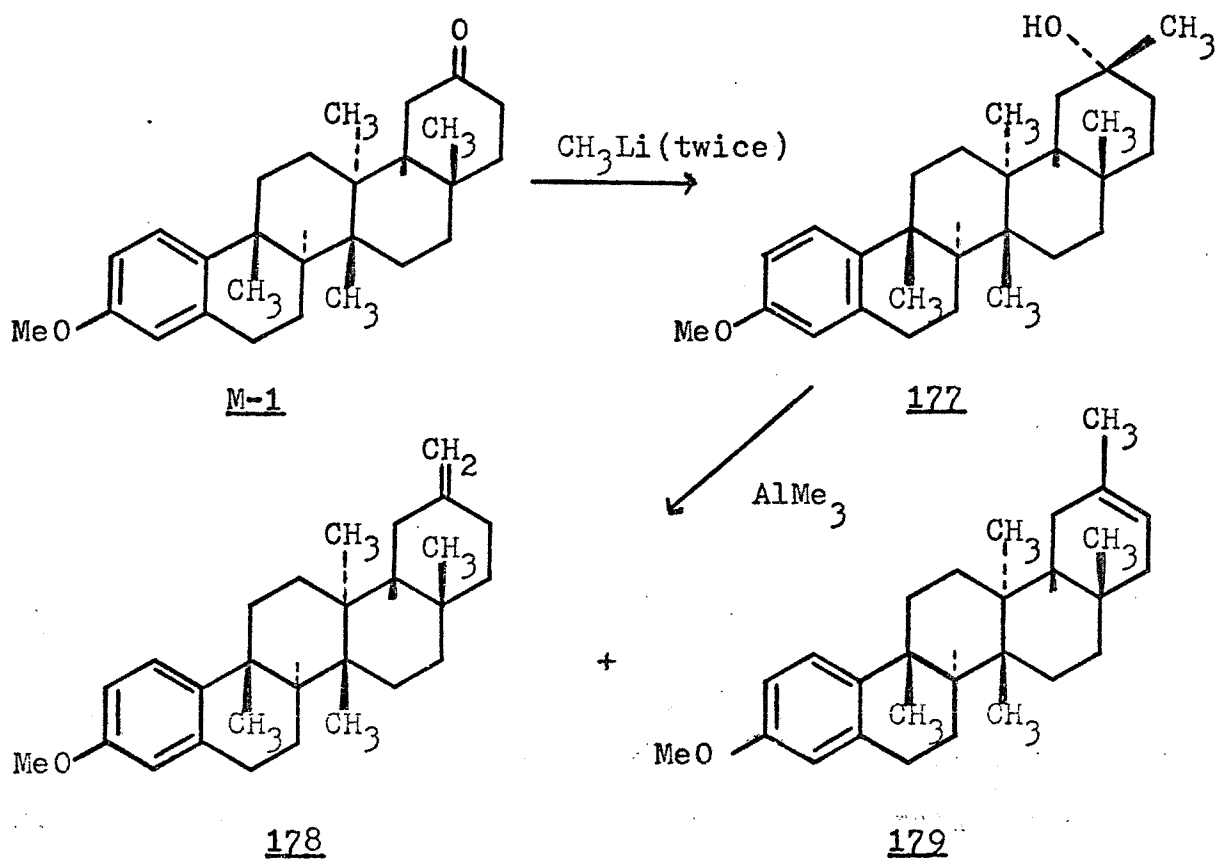
group from the top necessitates that the C-11 carbon attain sp^3 character, thus causing the oxygen to assume an axial position having severe interactions with the C-12b methyl group.

The hydrocarbon products isolated from the methylation attempt exhibited identical tlc and vpc behavior as the desired compound D-6, but not enough material was available for spectral determinations. Hence, a scaled-up repetition of the methylation reaction was called for.

It was felt, however, that since a tertiary aluminum alkoxide was a likely intermediate in the first step of the reaction, then one should be able to achieve the same overall effect by adding a methyl group, via a Grignard or methyllithium, followed by subjecting the resulting tertiary alcohol to trimethylaluminum.

The reaction of ketone M-1 with either organometallic reagent was exceedingly sluggish, serving as further indication of the steric hindrance in the vicinity of the carbonyl. The alcohol 177 could be formed in quantitative yield, but only by repeated treatments with methyllithium in tetrahydrofuran. In all probability, the addition of TMEDA would enhance the methyl addition (179).

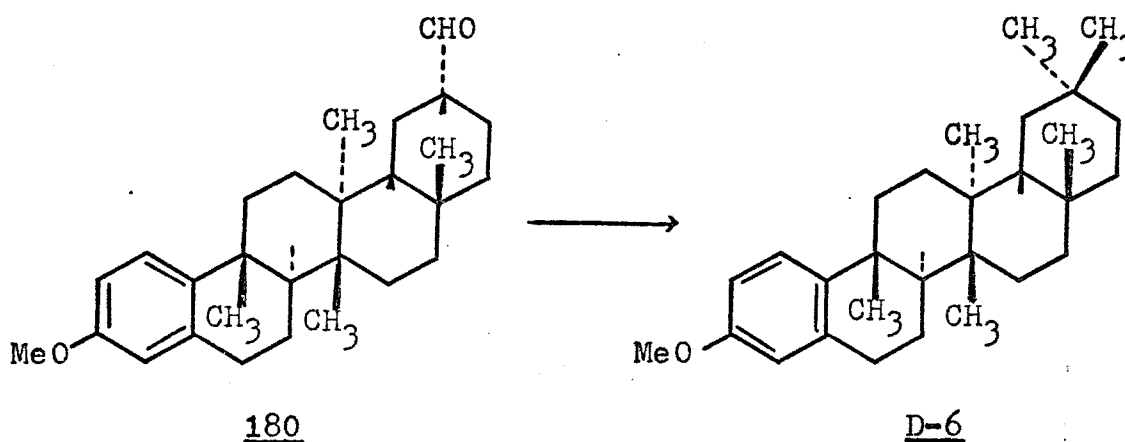
When the alcohol 177 was treated with trimethylaluminum in benzene at 200° , a 56% yield of hydrocarbon products was obtained. Unfortunately, the nmr spectrum indicated that the products were the two olefins 178 and 179 in a ratio of



roughly 45:55.

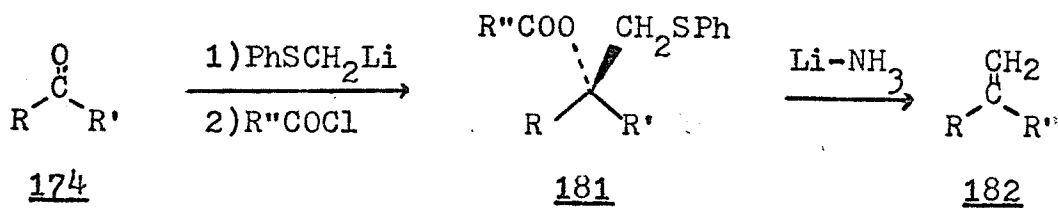
Thus, while the exhaustive methylation procedure had been successful on the steroid model, the method failed with the ketone M-1, probably due to the steric compression on the α -face of ring E, making dehydration the favored process.

The inability to gem-dimethylate the ketone M-1 directly necessitated an alternate scheme. It was felt that if the aldehyde 180 could be obtained, then methylation, followed by reduction would yield the desired compound D-6 (41).



The first attempt at the synthesis of the aldehyde 180 was via the exocyclic olefin 178. Although it was the minor product from the dehydration of the tertiary alcohol 177, it should be readily accessible via a Wittig reaction on the ketone M-1. Treatment of the ketone with excess methylene-triphenylphosphorane in dimethyl sulfoxide (180) resulted in the complete recovery of starting material.

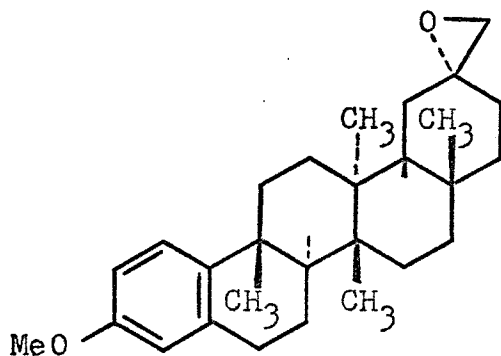
A less direct approach to the olefin 178 was prompted by a recent report of Coates and Sowerby (181) of a three-step procedure illustrated below. The ketone 174 is treated



with phenylthiomethyl lithium (182), and the resulting adduct is acylated. Reduction of the ester 181 with lithium in ammonia affords the methylene derivative 182.

The reaction of the ketone M-1 with phenylthiomethyl-lithium yielded a very complex mixture, as evidenced by its ir spectrum (C=O and OH) and tlc (7 spots, including starting material). As a result, this reaction was not investigated further.

Another approach to the aldehyde 180 would be via the epoxide 183, which should yield the desired aldehyde upon

183

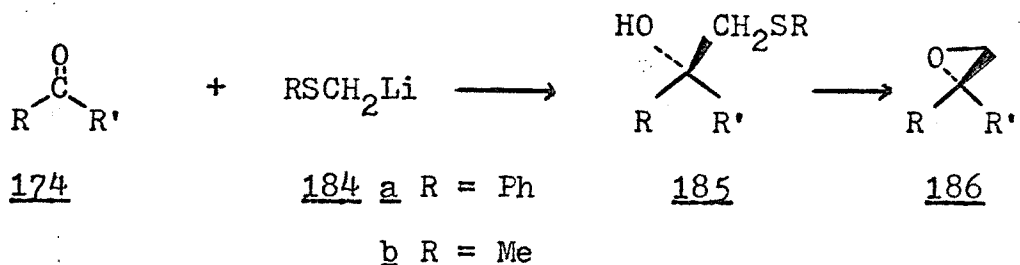
rearrangement with boron trifluoride etherate (183). Reaction of ketone M-1 with dimethylsulfonium methylide (144) yielded only recovered ketone (39%) and an unidentified olefin (48%). No trace of epoxide 183 was found.

At this point, it became apparent that the carbonyl group of ketone M-1 was simply too hindered to react with a good number of standard reagents which normally react with ketones. Thus, the use of ylides of phosphorous and sulfur were ruled out, since the partial negative charge on the reactive carbon would be too stabilized by the adjacent hetero-

atom (184).

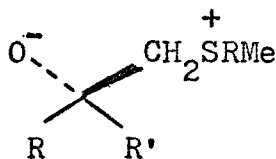
What was required, therefore, was a reagent possessing high nucleophilic reactivity, which was also not susceptible to either steric hindrance or proton abstraction (enolization), and yet capable of producing a product with suitable functionality for the elaboration into the aldehyde 180. The reagents that belong to this category are those in which a carbanion is adjacent to, but not in resonance with, a heteroatom. These include the modified Wittig reagents of Emmons (185) and Corey (186), in which a phosphonic acid derivative is the stabilizing moiety. Also in this category, but of more limited applicability, are the trimethylsilyl Grignard (187), dimethyl sodium (188), and 9-borabicyclo[3.3.1]nonane-9-carbanion (189). All these reagents would produce the methylene derivative 178, if successful.

Fortunately, a more attractive procedure appeared in a recent report of Johnson, Coates, and coworkers (190). Their procedure involved the reaction of ketone 174 with a substi-



tuted 1-lithiomethyl sulfide (184) to afford a β -hydroxy sulfide 185. Alkylation, followed by base treatment afforded the epoxide 186. The advantage of this three-step procedure

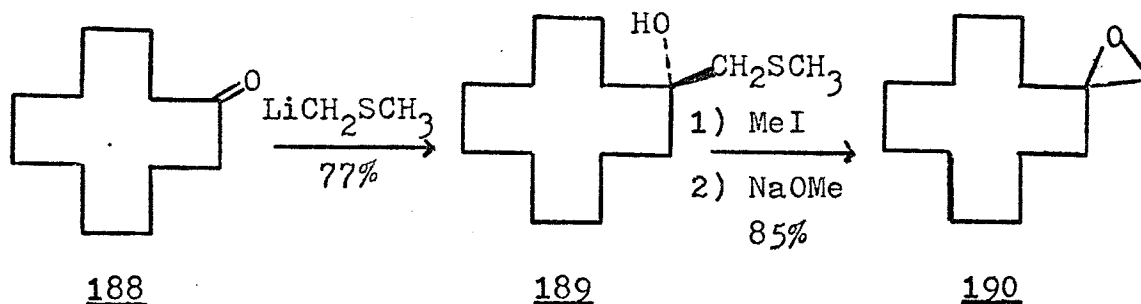
over that using a sulfur ylide is that one utilizes a highly reactive carbanion in the initial carbon-carbon bond-forming step, while still being capable of generating an intermediate betaine 187, as in the ylide reaction. This alternate for-

187

mation of a betaine in an epoxide synthesis has been utilized previously (191), although the present procedure eliminates the use of intermediate β -hydroxy sulfoxides, which require an additional reduction step, as well as their existence as diastereomers.

The specific sulfur reagents employed by Johnson and Coates (190) were phenylthiomethylithium (184a) (182) and methylthiomethylithium (184b) (192), with the latter possessing high reactivity, even with very hindered ketones. Since phenylthiomethylithium had already been used with ketone M-1 without success, the reaction with the aliphatic reagent appeared to be the most logical experiment to try next.

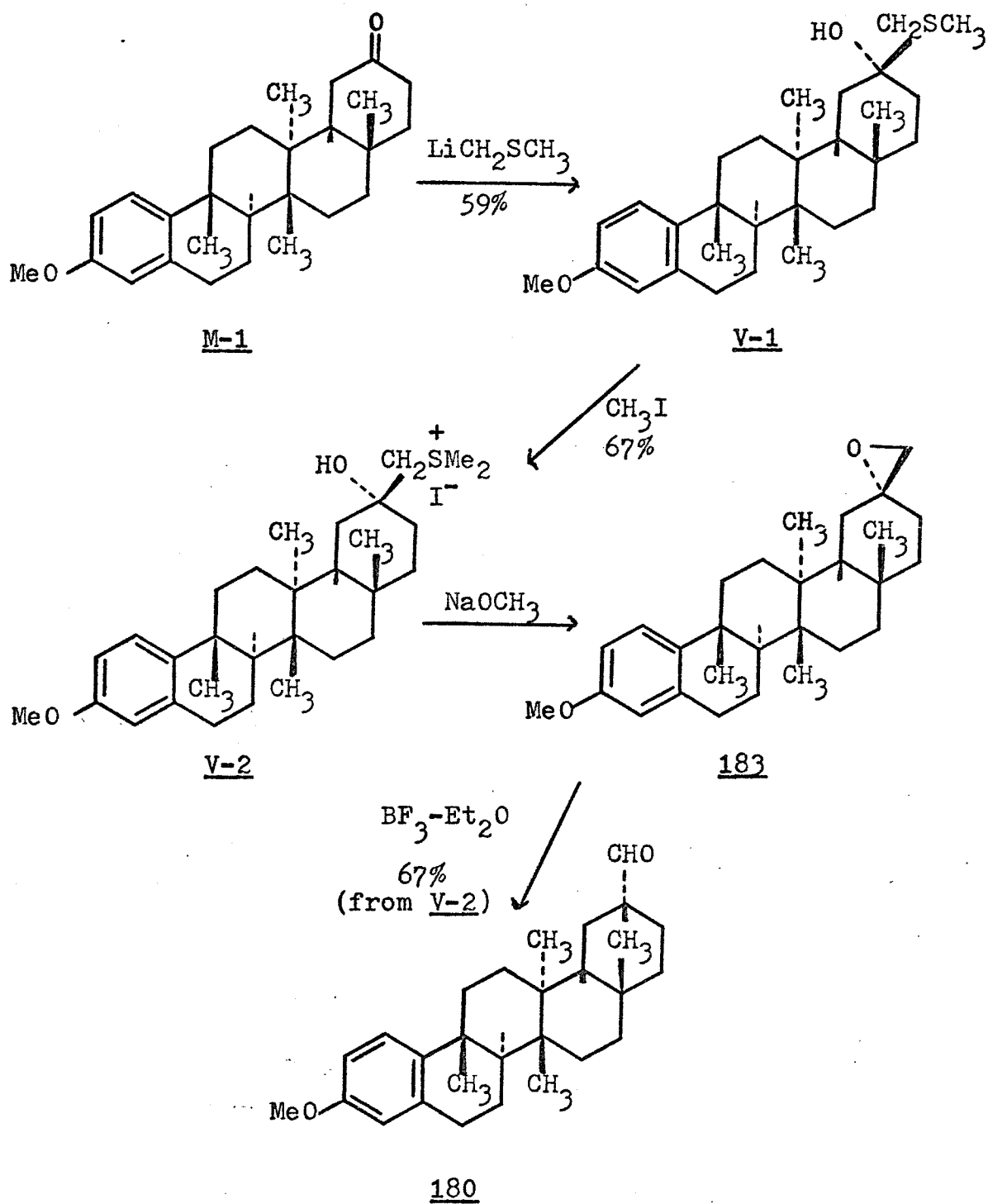
Unfortunately, the description of the procedure for methylation and base treatment was omitted from the paper. It was decided to experiment with cyclododecanone (188), since a study of that substrate was described in the article.



Treatment of cyclododecanone (188) with methylthiomethyl lithium afforded, after chromatography, the hydroxysulfide 189 in 77% yield. After brief experimentation, it was found that methylation with methyl iodide (191b,c), followed by treatment of the resulting sulfonium salt with methanolic sodium methoxide afforded the epoxide 190 in 85% yield. Other reagents that have been used in the ring closure step include aqueous hydroxide (191a,c), dimethyl sodium (191b), and sodium hydride (191d).

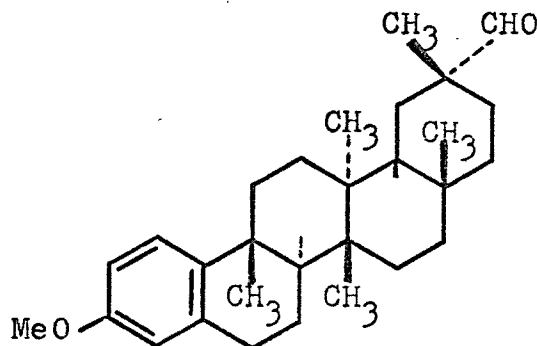
Having successfully effected the transformation of a ketone to an epoxide via a non-stabilized sulfur-containing carbanion, the stage was now set for its application to the pentacyclic ketone M-1. The outline of reactions for its conversion to the aldehyde 180 is outlined in Chart V. Treatment of ketone M-1 with methylthiomethyl lithium afforded the β -hydroxy sulfide V-1 in 59% yield. Methylation was effected with excess methyl iodide in acetone (193), yielding 67% of the β -hydroxy sulfonium salt V-2. Treatment of the salt with methanolic sodium methoxide afforded the epoxide 183, which

Chart V



rearranged to the desired aldehyde 180, as well as its C-11 epimer, in 67% yield, based on the sulfonium salt V-2.

Methylation of the aldehyde mixture was effected with methyl iodide and potassium tert-butoxide in glyme (194). A 57% yield of product was obtained, but examination of the nmr spectrum indicated that some unmethylated aldehyde was present (probably the one with the axial hydrogen, which could not be abstracted during the methylation). In addition to the desired aldehyde 191, there appeared to be some non-aldehydic material,

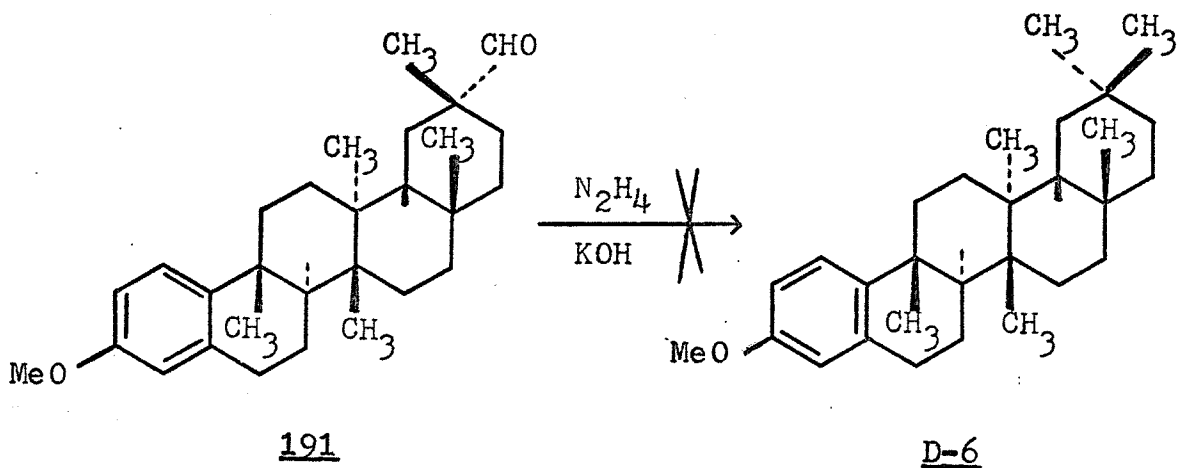


191

as evidenced by the weakness of the aldehyde chemical shift in the nmr spectrum and the low intensity of the carbonyl frequency in the ir.

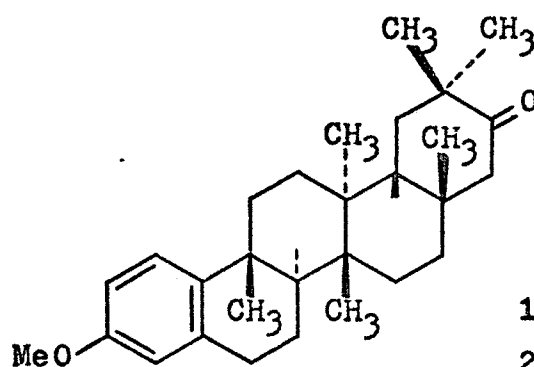
An attempt to reduce the carbonyl of the aldehyde, thereby yielding the desired ether D-6 (41) was not successful. This was not totally surprising in light of the fact that the carbonyl group would be subjected to intense steric hindrance, since it lay below the plane of the molecule and in close

proximity to the C-12b methyl group. The product displayed residual carbonyl absorption in the infrared and was largely resinous in nature. No product corresponding to the ether D-6 could be detected by vpc or tlc.



Alternatively, the reductive cleavage of a phosphorodi-
amidate ester of the alcohol 192 should be less susceptible
to steric interactions. Under aprotic conditions, the same
overall transformation would be effected, and the ether D-6
should be the product. However, with the aid of a proton
source during the reduction, the aromatic A ring should also
be reduced, thereby yielding the enone D-7 on acid hydrolysis
of the reduction product. A similar transformation was uti-
lized (157b) to circumvent the low yields previously obtained
(41) in the two-step sequence of Wolff-Kishner reduction,
followed by Birch reduction, beginning with the ketone 193.
The overall yield from ketone 193 to enone D-7 was 47%.

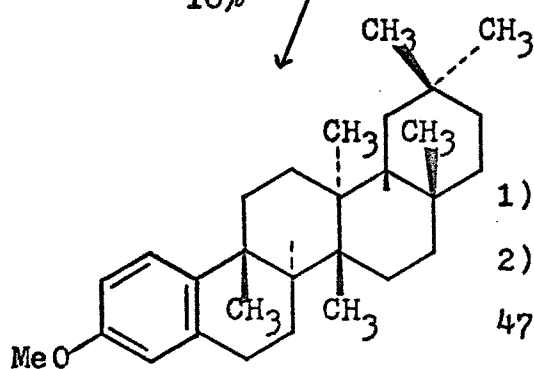
141



- 1) LiAlH_4
 - 2) $n\text{-BuLi}$, 148
 - 3) Li-NH_3
 - 4) H_3O^+
- 47%

193

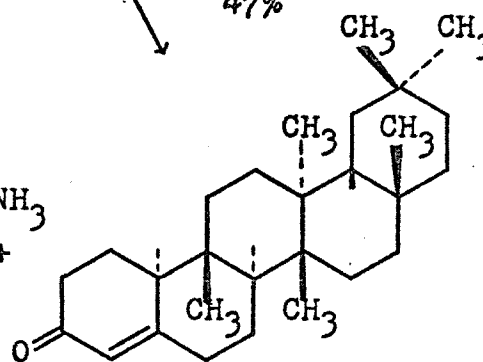
W-K
16%



- 1) Li-NH_3
 - 2) H_3O^+
- 47%

D-6

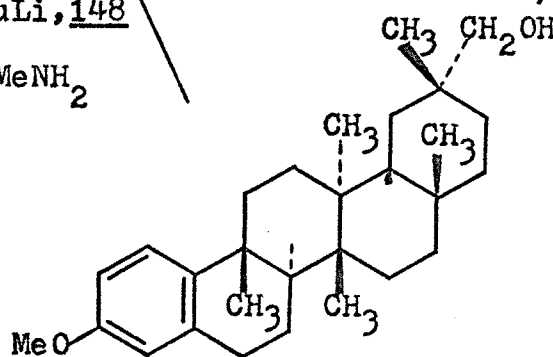
- 1) $n\text{-BuLi}$, 148
- 2) Li-MeNH_2



D-7

- 1) $n\text{-BuLi}$, 148
- 2) Li-NH_3
- 3) H_3O^+

None or trace



192

The alcohol 192 was readily produced via reduction of the aldehyde 191 with lithium aluminum hydride. Purification was possible at this stage, affording alcohol 192 in 60% yield. The alcohol underwent phosphorodiamidation upon treatment with n-butyllithium and the phosphorochloridate 148. The resulting phosphorodiamidate was used without purification in the remaining reactions.

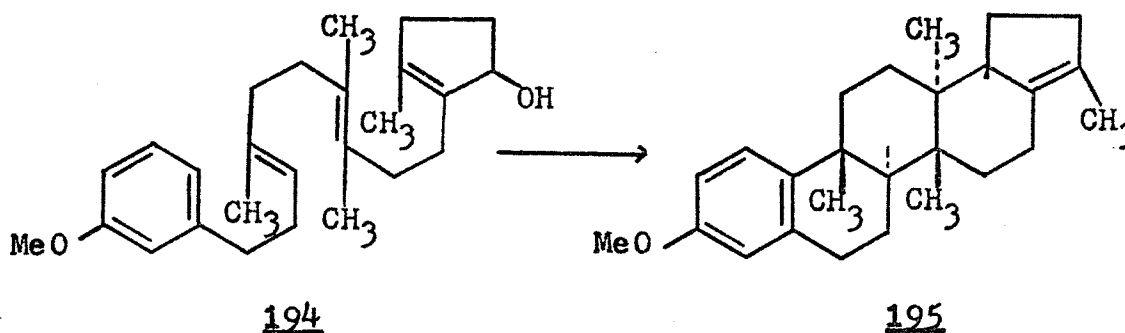
An attempt to effect an aprotic reduction to produce the ether D-6 was again unsuccessful. The product isolated (3 mg) exhibited vpc and tlc behavior different from that of an authentic sample of ether D-6. In addition, the compound was virtually insoluble in most common organic solvents, which is unusual for compounds of this type.

In a final attempt to produce a product which could be compared to a known compound, the phosphorodiamidate was subjected to normal Birch reduction conditions, following the previous procedure outlined for the ketone 193 (204). Working on a scale of 36 mg of alcohol 192, the phosphorodiamidate was reduced, yielding only 3.5 mg of product exhibiting the properties of an unsaturated ketone. This material appeared to consist of two components by vpc in a ratio of 1:3. The major component did appear to be the desired enone D-7, as demonstrated by peak enhancement experiments. The material also exhibited identical tlc behavior as an authentic sample of the enone D-7. Unfortunately, the small amount of material and the fact that it was a mixture pre-

vented conclusive spectral comparisons. The infrared spectra were quite similar, but the nmr spectrum contained some extraneous signals, when compared to the authentic sample. Whether these signals were due to the impurity or to the fact that the two products were different compounds cannot be ascertained.

The low yield in the reduction step can best be attributed to the instability of the reactive site. Since the carbon atom to be reduced is both primary and neopentyl in nature, it would be exceedingly unstable, especially in view of the intense steric compression that is present. There are basically two possibilities for side reactions. First, reduction of the phosphorodiamidate group may be slow. In this case, the aromatic ring may be reduced while the molecule is still phosphorylated. Under the conditions of acid hydrolysis, the oxygen of the ester could be protonated, allowing formation of a primary cation, which would certainly rearrange to a more stable species. Secondly, if reduction does occur, then there exists the possibility that a primary free radical is formed, and this could also lead to rearrangement or fragmentation.

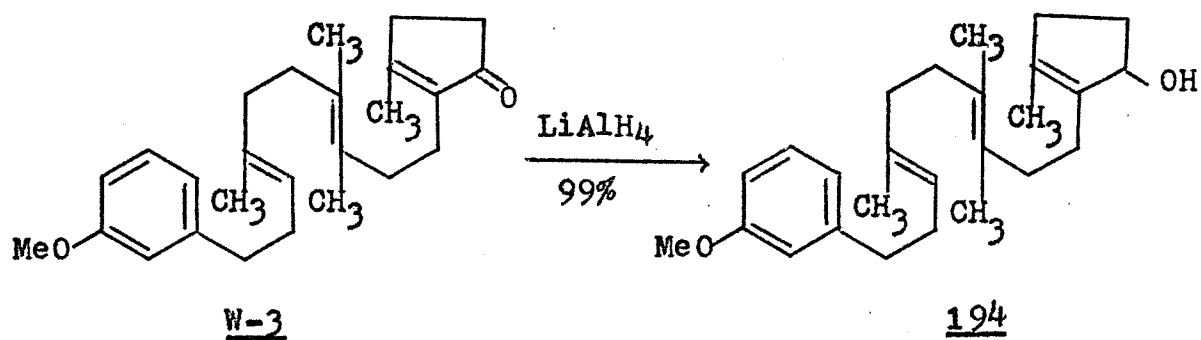
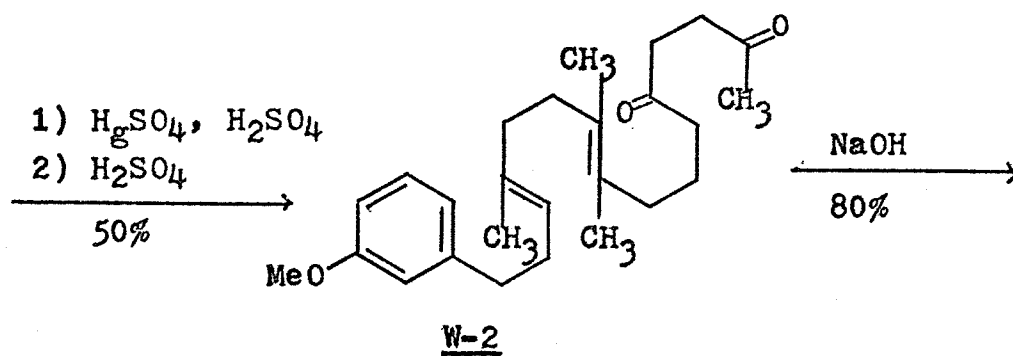
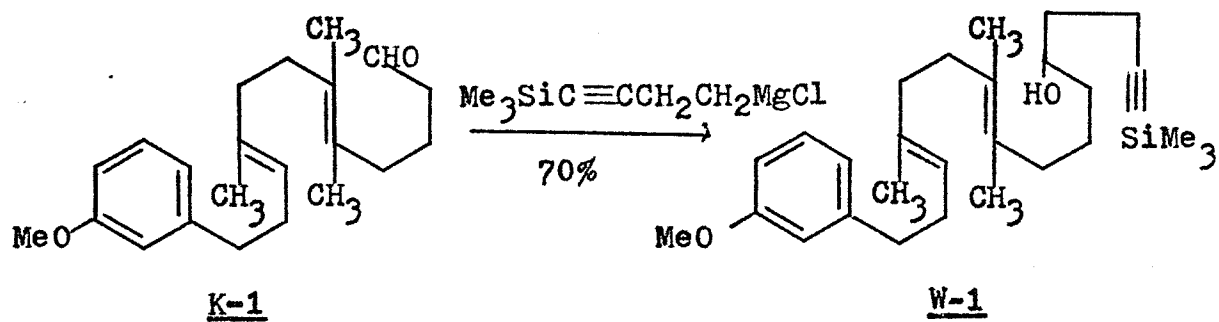
In hopes of extending the successful cyclizations of the cyclopentenol 77 (96) to larger systems capable of generating a pentacyclic skeleton, Moser (162) synthesized the cyclopentenol 194 from the aldehyde K-1 (75). Cyclization of this alcohol should yield the pentacyclic olefin 195. Elaboration



of this compound into an intermediate in the alnusenone synthesis (41) would constitute a formal total synthesis of the natural product (A-14).

The synthesis of the cyclopentenol 194 by Moser (162) is described in Chart W, and is patterned after the synthesis of alcohol 77 (96). Reaction of the aldehyde K-1 (75) with the Grignard reagent derived from 1-chloro-4-trimethylsilylbutyne afforded the alcohol W-1 in 70% yield. Hydrolysis of the trimethylsilyl group and hydration of the triple bond was accomplished in one step by reaction of the alcohol W-1 with acidic mercuric sulfate. The crude keto alcohol was oxidized

Chart W



with Jones reagent to yield the diketone W-2 in 50% yield from W-1. Base-catalyzed cyclization of the diketone W-2 produced the expected (195) cyclopentenone W-3 in 80% yield. Reduction of enone W-3 with lithium aluminum hydride afforded a 99% yield of the desired cyclopentenol 194.

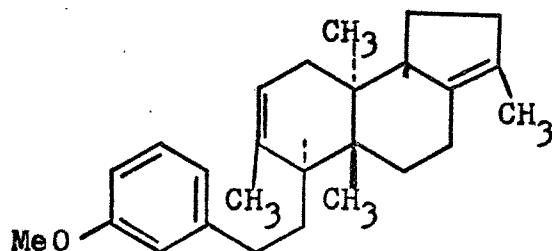
Moser found (162) that treatment of alcohol 194 with formic acid, followed by hydride reduction yielded a mixture consisting of six products, designated A-F. The distribution of these products is shown in Table IV. Component D was sep-

Table IV

Component(s)	Ret. time @ 290° (column A), min	Estimated portion of volatile mater.
A-C	2.1 - 3.0	25%
D	3.3	50%
E	4.15	12%
F	4.95	12%

arated from the rest of the mixture by chromatography on silica gel impregnated with 10% silver nitrate. Its structure was tentatively assigned as the tricyclic diene 196, on the basis of its nmr spectrum. A broad multiplet at 5.36 ppm was indicative of an olefinic hydrogen on a trisubstituted double bond, and the aromatic region integrated to four protons. Components E and F were not separated, but gave spectral data characteristic of fully-cyclized material.

With an unfavorable product distribution from the formic acid study, Moser (162) investigated the use of stannic chlo-

196

ride in dichloromethane. He found that not only was the product distribution altered in favor of the pentacyclic components, E and F, but that component F was made the predominant product over E by four to one, provided the reaction was run at -78° . Under these conditions, the product distribution was that shown in Table V.

Table V

Components	Ret. time @ 290° (column A), min	Estimated portion of volatile material
A-C	2.1-2.9	10%
D	3.05	5%
E	4.05	15%
F	4.7	55%

This concluded Moser's findings, and the remainder of the study was incorporated into this research. Treatment of the cyclopentenol 194 with excess stannic chloride in dichloromethane at -78° afforded a mixture of products, as described

in Table V. After chromatography and recrystallization, a 33% yield of the major component F was isolated. The total yield of F, as estimated by vpc, was 37%.

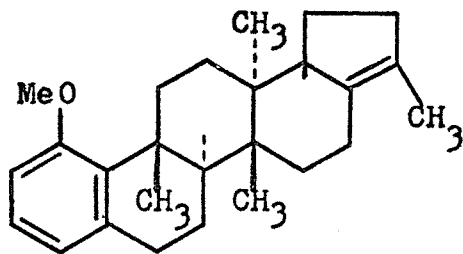
The structure of F was tentatively assigned as the pentacyclic olefin 195, on the basis of spectral data. This assignment was later confirmed by conversion to a compound of known structure. Since the proportions of components D and E were rather small, they were not isolated and characterized at this time. In fact, their ultimate isolation was somewhat serendipitous.

Alcohol 194 proved to be a very reactive compound, as was shown by its rapid consumption in dichloromethane with only a slight excess of stannic chloride. In contrast, cyclization of the cyclohexenol 51 (vide supra) required a larger excess of stannic chloride and longer reaction times. In addition, the cyclopentenol 194 was relatively clean, whereas that of cyclohexenol 51 was rather complex, even under optimum conditions.

Further proof of the greater reactivity of the cyclopentenol 194 was demonstrated in an attempted column chromatography on silica gel, in which the alcohol was completely destroyed. From this chromatography, a 65% yield of volatile material (the remainder being polymeric) was obtained, whose vpc trace was virtually superimposable with that from the formic acid cyclization (162). In addition to components A, B, and C, components D, E, and F were produced in a ratio

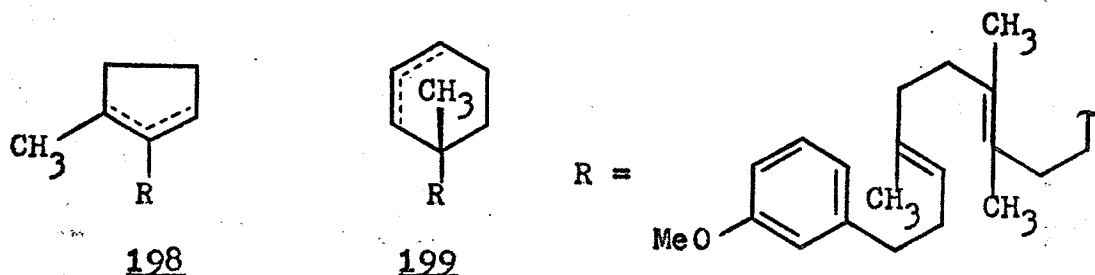
of 13:3:4. By repeated chromatography on silica gel-silver nitrate, component D (vide supra) was isolated virtually pure in 9.3% yield (13.3% estimated by vpc). Components E and F were isolated by preparative tlc, with E being slightly more mobile, using petroleum ether as eluent.

Component E (2.6% isolated, 3.2% estimated) displayed three methyl singlets in the nmr at 0.72, 1.01, and 1.33 ppm. The aromatic region contained three signals at 6.67, 6.73, and 7.05, whose coupling patterns were characteristic of a 1,2,3-trisubstituted benzene (66f). The structure of component E was tentatively assigned as the 1-methoxy olefin 197. Thus, with the isolation of the 3-methoxy pentacyclic olefin 195 in 37% yield, and of the 1-methoxy olefin 197 in

197

3.2% yield, it may be stated that the cyclization of the cyclopentenol 194 proceeded stereoselectively with the simultaneous formation of five consecutive asymmetric centers in at least 40% yield.

The higher reactivity of the cyclopentenol 194, in comparison to the cyclohexenol 51, is probably best explained on the basis of the stabilities of their respective intermediate allylic cations, 198 and 199. As a general rule,



cyclopentenyl cations are believed to be more stable than cyclohexenyl cations, and those cations possessing alkyl substituents on the terminal carbons of the allylic system are more stable than those without substituents at these positions (196). Therefore, it is expected that the cyclopentenyl cation 198 would be more stable than the cyclohexenyl cation 199 on both arguments. Consequently, it is reasonable to assume that the cyclopentenol 194 has a higher propensity to ionize, which would make selective cyclization a much more favored process than in the cyclohexenol 51, where ionization is more sluggish. In addition, the allyl cation 198 can only assume a planar structure, whereas 199 may have two different conformations, thus introducing the possibility of conformational equilibria and competitive side reactions.

The final task remaining in the cyclization study of the cyclopentenol 194 was to confirm the assigned structures for the pentacyclic olefins 195 and 197. To accomplish this, the 3-methoxy isomer 195 was transformed into a compound of known structure by the procedures outlined in Figure 29.

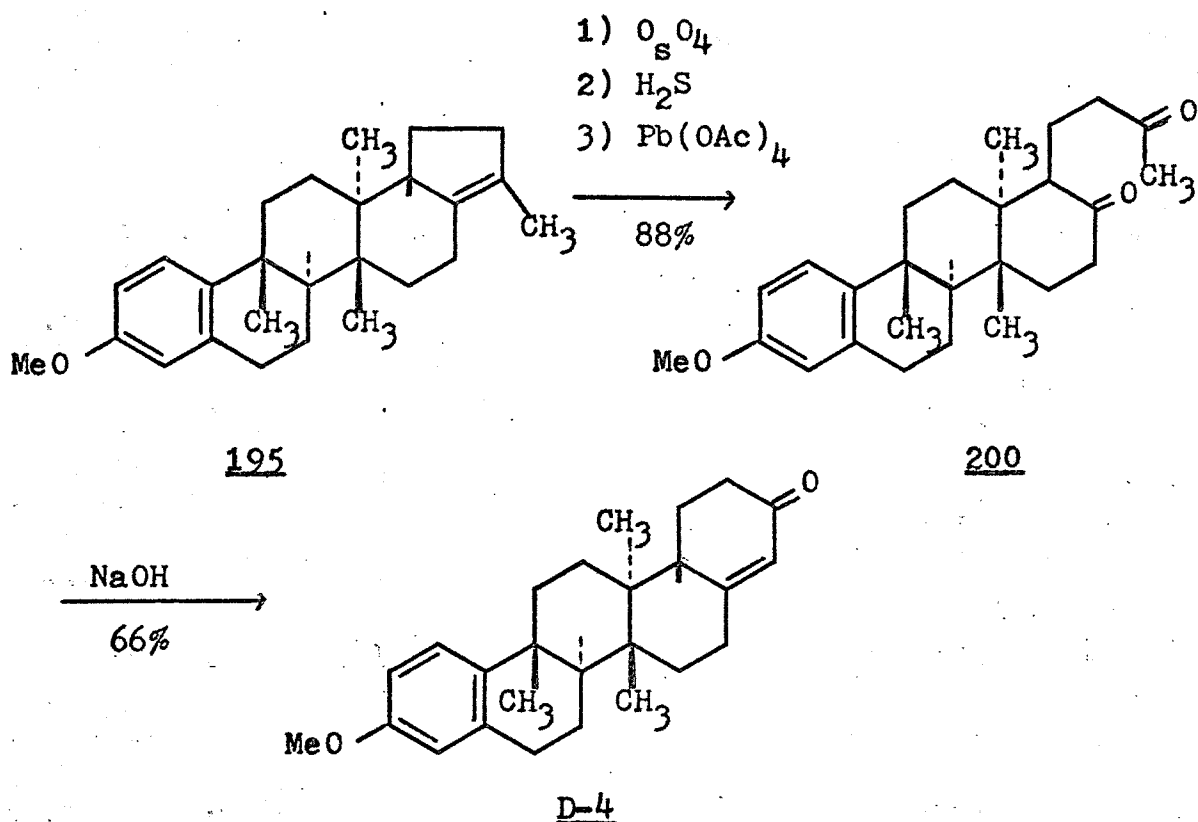


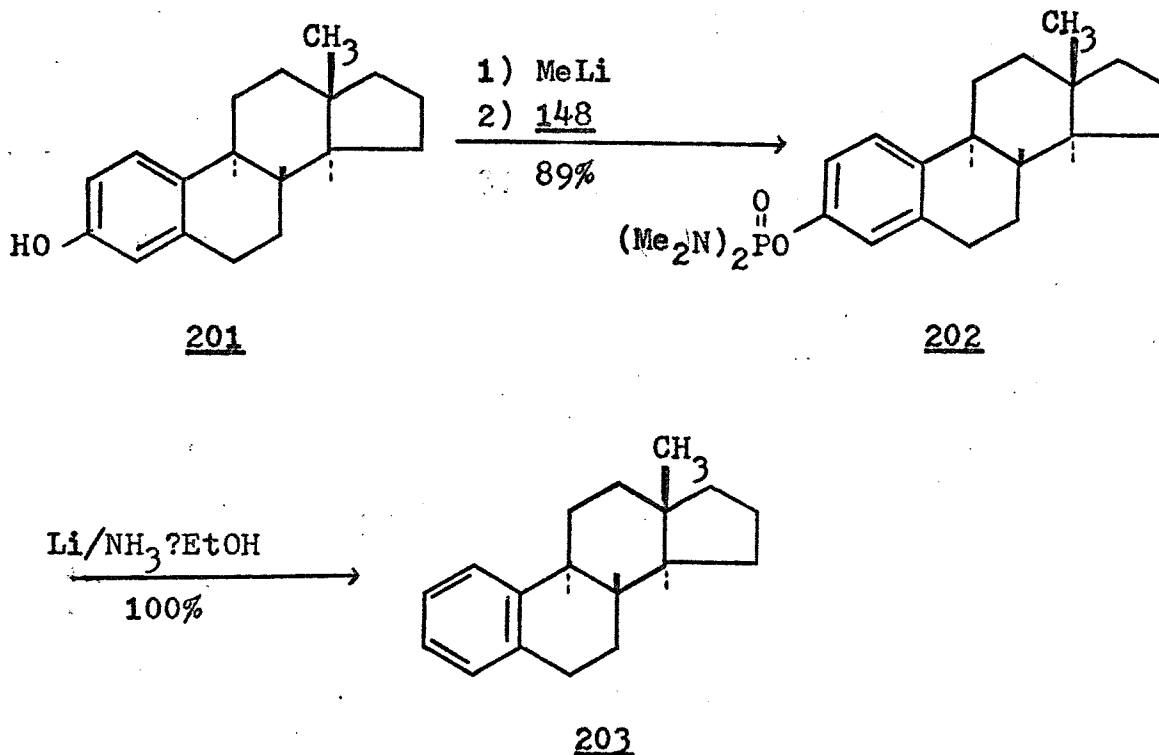
Fig. 29

The olefin 195 was osmylated with osmium tetroxide and pyridine (197). The resulting osmate ester was cleaved with hydrogen sulfide (198), and the glycol thus formed was oxidative-cleaved with lead tetraacetate (199) to yield the diketone 200 in 88% yield. Base-catalyzed cyclization afforded a 66% yield of the enone D-4, a known compound from the alnusenone

synthesis (41). The identity of the enones D-4 was established by comparison of their ir, nmr, vpc, and tlc behavior, as well as their melting points and the melting point of a 1:1 mixture.

In order to establish that the 1-methoxy pentacyclic olefin 197 was indeed stereochemically identical to the 3-methoxy isomer 195, both compounds needed to be demethoxylated. The phosphorodiamidate procedure (157) was selected for the deoxygenation of a phenol in order to effect the transformation, as well as to extend the scope of the method.

A model study was first performed on 3-hydroxy-1,3,5(10)-estratriene (201). Phosphorylation of the phenol 201 proceeded in 89% yield, and reduction of the phosphorodiamidate

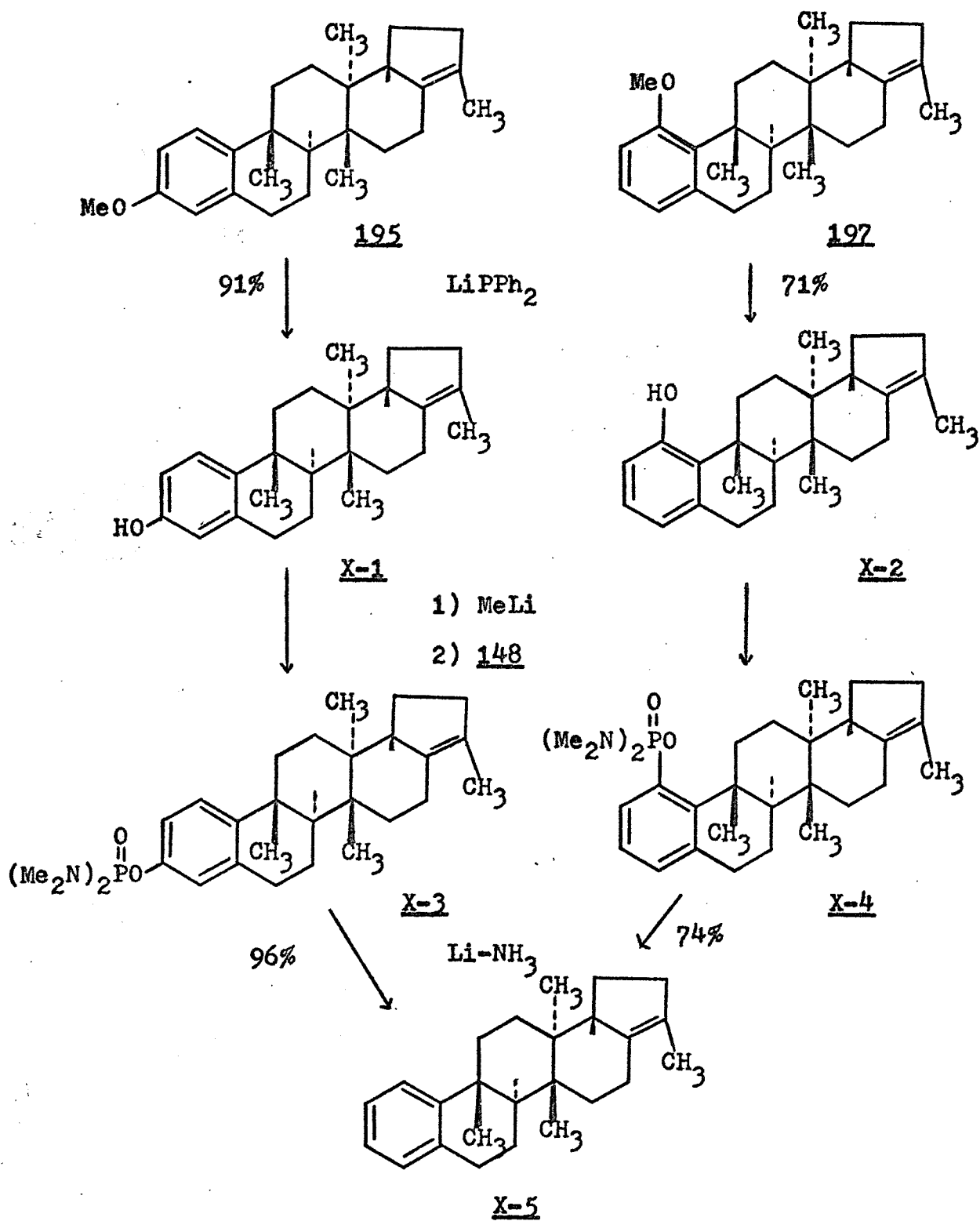


202 afforde 1,3,5(10)-estratriene (203) (200) in quantitative yield.

The sequence for the degradation of the pentacyclic olefins 195 and 197 is outlined in Chart X. The methyl groups on the oxygen atoms were cleaved off by the reaction of the olefinic ethers with lithium diphenylphosphide (201). The resulting phenols, X-1 and X-2, were produced in 91% and 71% yields respectively. Conversion of the phenols to their respective phosphorodiamidates, X-3 and X-4, was accomplished by treating the phenols in the same fashion as in the steroid model. The phenols X-1 and X-2 were treated with methyllithium and the phosphorochloridate 148 (158). Reduction of the phosphorodiamidates X-3 and X-4 proceeded smoothly with lithium in liquid ammonia. The same hydrocarbon, assigned structure X-5, was produced in 96% and 74% yield from the 3- and 1- isomers, respectively. This conversion of a phenol to a hydrocarbon is an adaptation of the method of Kenner and Williams (202) which describes the metal-ammonia reduction of phenolic phosphates.

Comparison of the ir, nmr, vpc, tlc, and melting point data confirmed the identity of the two hydrocarbon products as X-5. Thus, the cyclization of the cyclopentenol 194 to pentacyclic products proceeded stereospecifically, with the only variation being in the position of the final cyclization into the aromatic ring. A distribution of products resulting from attack at the positions ortho and para to the methoxyl

Chart X



group have been observed in this laboratory (75) and others (66f,71c).

The isolation of the enone D-4 as a transformation product of the pentacyclic olefin 195 constitutes another formal total synthesis of dl-alnusenone (A-14) (41).

CONCLUSION

From the studies undertaken in this research, it has been shown that certain 4-methyl-4-polyalkenyl-2-cyclohexenols can be made to undergo cationic cyclization upon treatment with the Lewis acid stannic chloride.

The yields, and therefore, the selectivity of the reactions vary greatly with the substrate. The general trend appears to be that the selectivity of the reaction varies inversely with the number of substituents on the internal double bonds of the polyene side chain. This is in direct contradiction to what is predicted on stereoelectronic grounds, based on the fact that increasing the substitution of a double bond should enhance its nucleophilicity by producing a more stable carbonium ion. This implies that the added substituents tend to cause increased steric interactions in the transition state, thereby allowing for possible side reactions either by conformational inversion, deprotonation, polymerization, or a combination of these, while in the cationic intermediate stages of cyclization.

It also becomes apparent from these studies that the ability for the initial cation to form in lieu of all other possible reactions is an important factor in the substrates propensity to yield cyclized products. A cyclopentenol, particularly one substituted in either the 1 or 3 position, such as in the alcohol 194, is much more reactive than a

cyclohexenol toward cation formation, besides producing intermediates with far less steric interactions.

As was shown from the extensive solvent studies of the alcohol 82, the nature of the solvent may also play an important role in the yield, as well as the product distribution, of the cyclization study. This effect of solvent is attributed to the capability of the double bonds in the side chain to be repelled by polar solvents, thereby becoming internally solvated, with the net effect being to increase the proximity of the double bond to a developing cationic site, making the cyclization more favorable.

The determination of the structures of the products obtained in the cyclizations is the most crucial aspect of the investigation. In the case of the alcohol 82 which contained an internal trans-trisubstituted double bond in the side chain, the products were formed in high yield and were identified through alternate synthesis of a derivative. The other model alcohol studied, alcohol 58, with a tetrasubstituted double bond, a comparatively lower, but still acceptable yield of a single product was realized, whose structure is virtually guaranteed by spectral data, while confirmation is pending the results of an x-ray analysis.

Turning attention to substrates which would produce a pentacyclic product for ultimate conversion into synthetic triterpenes, one finds that the cyclopentenol 194 gave fair yields of pentacyclic products, of which the major one was

identified by conversion to a known triterpene intermediate, and the minor one was correlated to the major one by parallel degradations to the same compound.

Although the overall yield of the synthesis of the alcohol 51 was excellent, the remainder of the study was hampered by a very low yield of cyclization product, coupled with a long reaction sequence required to convert it to another triterpene intermediate to establish its structure. The steric environment of the cis D/E ring juncture is undoubtedly responsible for both of the problems encountered, which combined to thwart the final confirmation steps by reducing the material available to a few milligrams of a product contaminated to the extent that valid comparisons could not be made, although the possibility of their identity can not be ruled out. To draw a viable conclusion from this cyclization study, further theoretical considerations are necessary, in addition to attempts to interpret whatever physical and chemical data are available. The aspects of these interpretations are presented in the following discussion.

The inability to confirm the structure of the pentacyclic olefin by chemical means necessitates that alternative procedures be sought to confirm the structure.

The pentacyclic olefin and its subsequent transformation products possess no less than six asymmetric centers as part of their structure. It would be advantageous to try to eliminate some of the $2^6 \times \frac{1}{2} = 32$ possible stereoisomers. Fortunately, this task is greatly simplified if the assumption is made that the first cyclization step yields a cis fused decalin ring system. This is a valid assumption, not only from the many precedented examples, but also from the fact that stereoelectronic factors require quasi-axial bond formation so as to assure maximum orbital overlap between the attacking double bond and the allylic system.

Once this is established, one can ascertain that the third asymmetric center formed in the reaction, that of C-12b, must be formed in such a way that the methyl group is oriented anti to the second center, C-12a, (Fig. 30). Attack in a cis

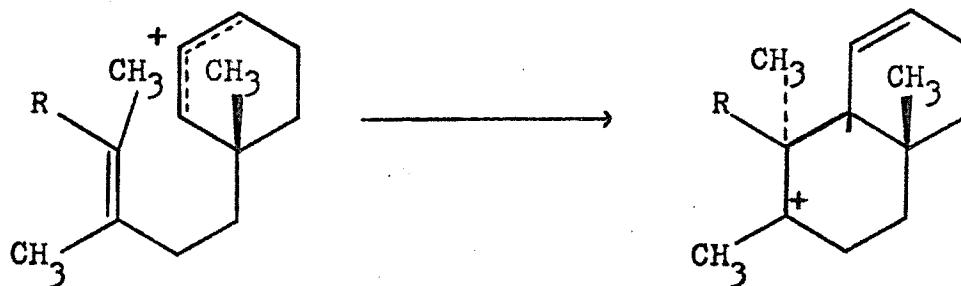


Fig. 30

fashion will push the methyl group and the R group back into the plane of the rings, establishing the stereochemistry as that shown. The poor reactivity observed during the E ring transformations subsequent to cyclization also serves as good evidence for the proposed stereochemistry.

Focusing attention on the B/C ring fusion, one may utilize the nmr spectrum of the aromatic region and the arguments developed by Nagata and coworkers (149) to establish that the ring juncture is trans (Fig. 31). The C-4 hydrogen at 6.60 ppm is taken as the reference. The C-1 hydrogen appears as a doublet centered at 7.16 ppm. This renders the $\Delta_{1,4}$ equal to 0.56 ppm, which is in close agreement with the value of 0.60 ppm for trans octahydrophenanthrenes of type A (149).

Using similar arguments described for the first cyclization step, it is easily demonstrated that the second cyclization step will place the hydrogen at C-6a anti to the methyl group at C-6b (Fig. 32). Therefore, with the information that the B/C ring fusion is trans, it is established that the 14a, 6a, and 6b carbons are oriented trans,anti. The pieces may now be fitted together, yielding the following information. The only structures possible are the desired trans,anti,trans,-anti,cis compound 50 and the trans,anti,cis,anti,cis compound 204. Therefore, the entire structure will be determined by the stereochemistry of the second cyclization step.

With this information in mind, one may examine the mechanistic aspects of this step to determine if one mode may

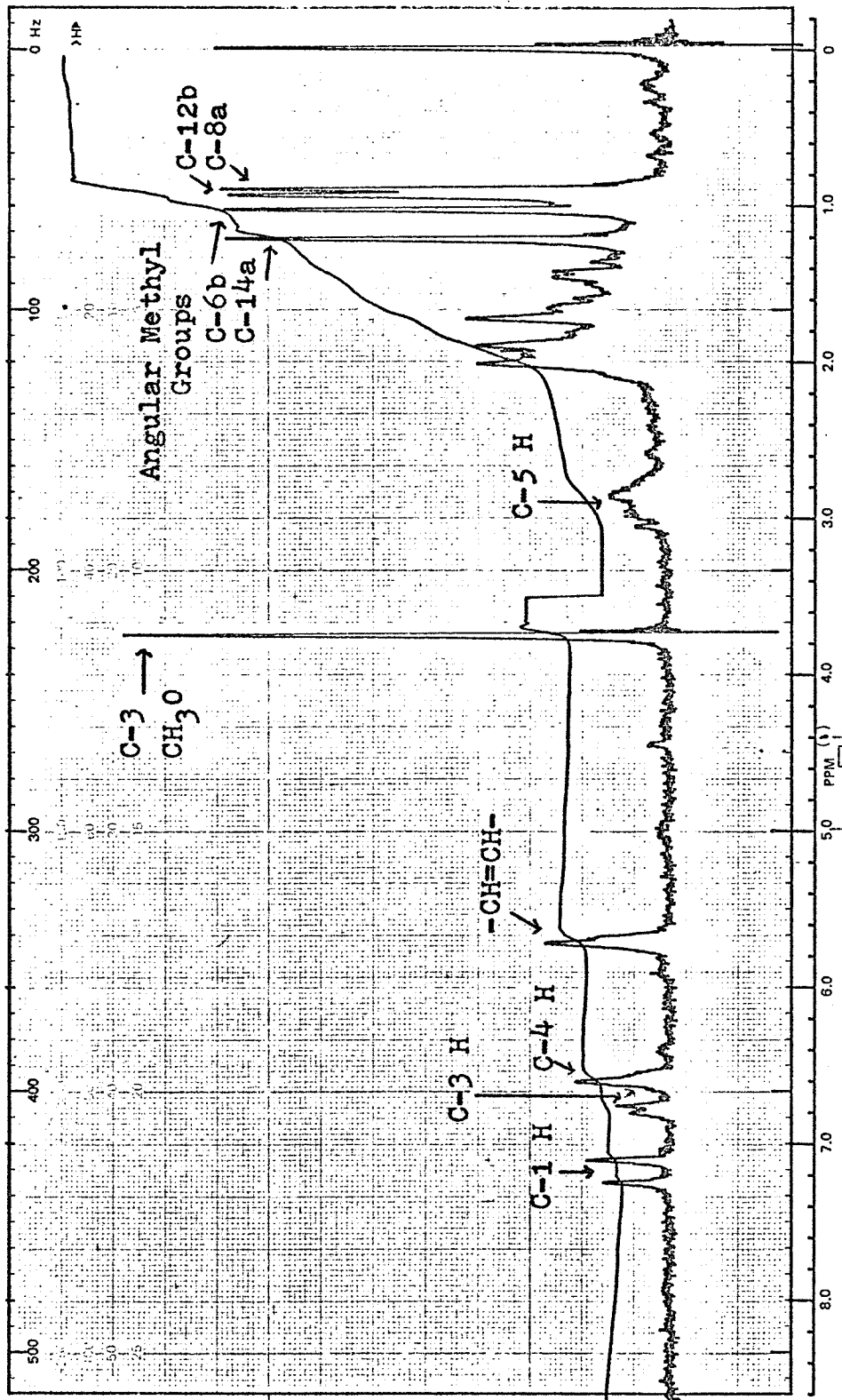


Figure 31 The nmr spectrum (CDCl_3) of the pentacyclic olefin from the cyclization of alcohol 51

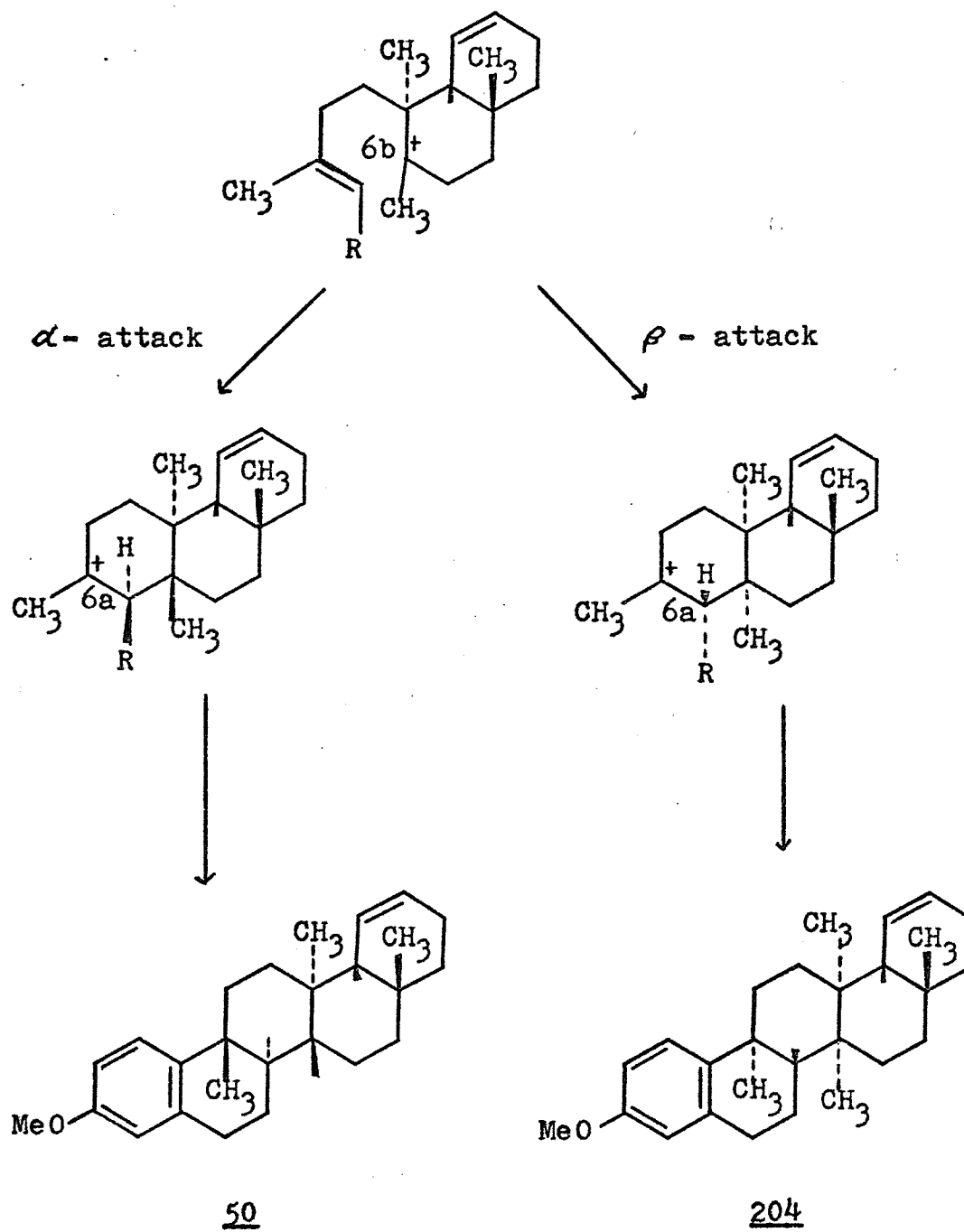
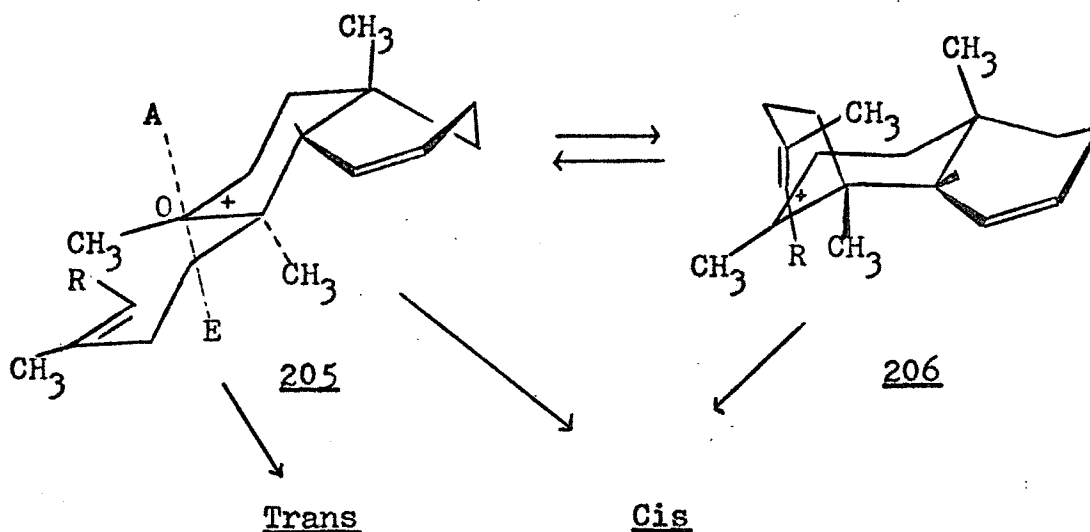


Fig. 32

be ruled out or at least be rendered improbable. The bicyclic cation intermediate that is formed initially must exist in the conformation depicted in structure 205, with the side

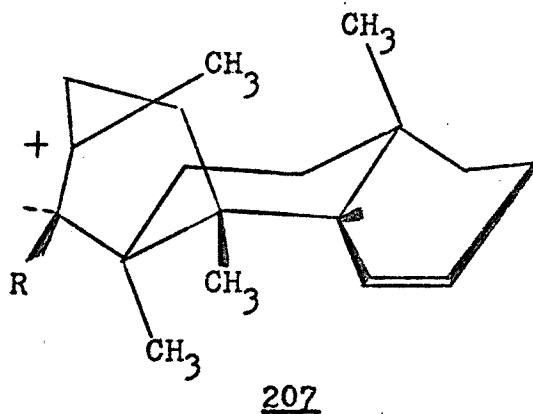


chain oriented equatorially. There are three possible phenomena that can occur at this point. First, the molecule can undergo ring inversion to give the form 206, with the side chain now oriented axially. In their ground states, the two are probably of almost equal energy, since each possesses one 1,3 diaxial carbon-carbon interaction. Cyclization in this conformation should be relatively strain free, with the major energy barrier being that of torsional strain (98) due to the eclipsing of the C-12b methyl by the one at C-6b.

Several arguments have been presented (67e,77) with the contention that ring inversion is slow relative to cyclization. This argument becomes especially important when the

cationic intermediates are polycyclic and cis fused. For the present case, one may envision the bicyclic intermediate 206 as a substituted 9-methyl-cis-decalin. A conformational study by Gerig and Roberts (205) of 2,2-difluoro-9-methyl-cis-decalin has shown that the barrier to inversion from one chair,chair form to the other is about 9 kcal/mole. The argument against ring inversion applies well in most cases, and may apply equally well here, but it is still possible that the barrier to cyclization is just as high as the barrier to ring inversion, and hence, may make the two processes competitive.

The argument which virtually eliminates this possibility is the fact that if cyclization were to occur in conformation 206, the tricyclic cation 207 would be formed, which is not



in the proper conformation for the last cyclization step. For that to occur, a second ring-inversion is necessary, only this time, it requires the inversion of two cis-decalin rings. The energy for this inversion would be rather high, and since the cyclization is carried out at -63.5° , it probably does not occur to any great extent. Therefore, it may be concluded that any product formed from the cyclization of cation 206 will not give pentacyclic products.

The remaining possibilities are the two which involve the bicyclic cation 205, with the equatorial side chain. The transition states for both of the possible modes of reaction are illustrated in Figure 33. The terminal carbon of the

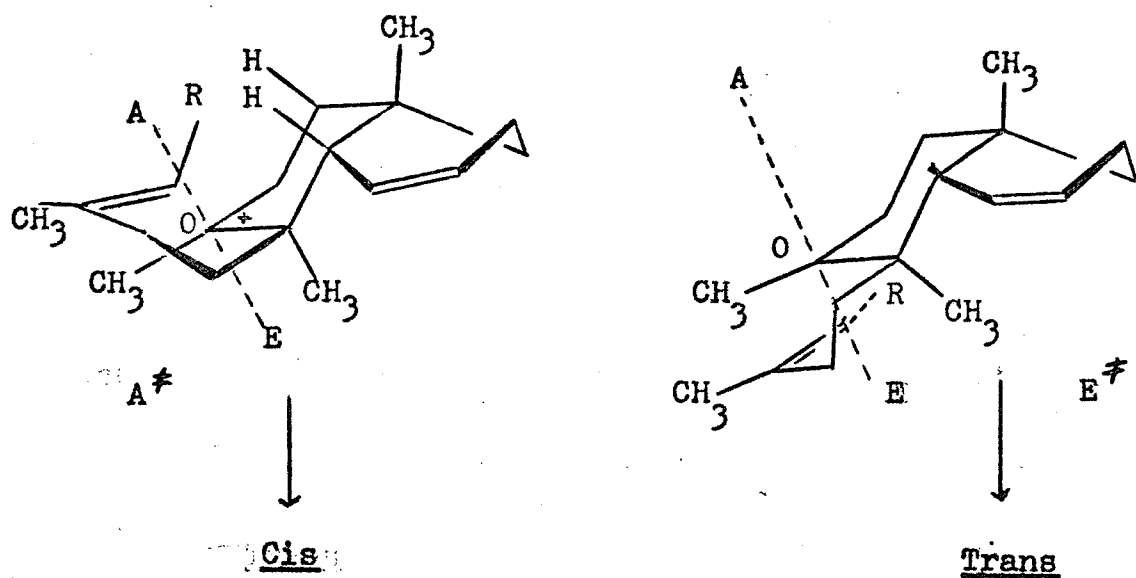


Fig. 33

double bond in the side chain must be oriented along a line AOE, which is perpendicular to the three bonds on the trigonal carbon, again to allow maximum orbital overlap. To

determine which stereochemistry will predominate, one must attempt to estimate the energy differences between the two transition states A^\ddagger and E^\ddagger .

According to the Felkin Principle (98), attack is favored from an axial direction, provided there are no severe steric interactions from that direction. These interactions may manifest themselves in two ways: (1) a bulky axial substituent which would be 1,3 to the attacking nucleophile, or (2) a bulky nucleophile. With only axial hydrogens at positions C-8 and C-12a, the former possibility may be ruled out. On the other hand, the attacking carbon atom has a β -phenylethyl group attached to it, which should render it bulkier than an atom with $R = H$, as in alcohol 58. Since it is almost certain that the tricyclic olefin 68, which is formed from alcohol 58 has the trans,anti,cis structure, then the steric interactions in the transition state A^\ddagger from alcohol 51 should be even greater.

In discussing the possibilities of axial vs. equatorial attack on a cyclohexyl cation, Harding (77) points out that the AO portion of the line AOE is inclined at an angle of 60° toward the syn axial hydrogens at positions 3 and 5 (Fig. 34). With the distance from point O to each hydrogen nucleus taken to be about 2.55 \AA (206), any point along line AO between 3.6 \AA and about 0.25 \AA from point O is less than 2.4 \AA from the hydrogens. The value of 2.4 \AA is the minimum combined van der Waals radii of two hydrogen atoms (207).

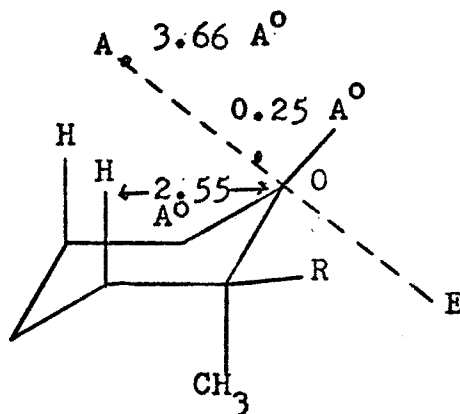


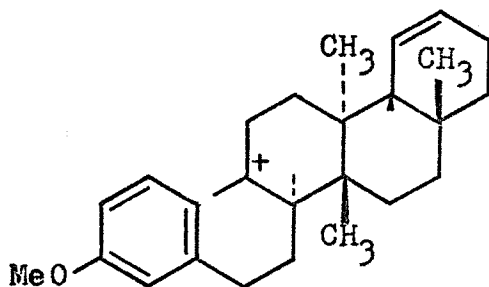
Fig. 34

Therefore, at a distance of 1.54 \AA , the normal carbon-carbon bond length, the distance between the hydrogens and the approaching carbon atom is less than the combined van der Waals radii of two hydrogen atoms. When one takes into account the hydrogens on the entering carbon, as in alcohol 58, the strain must necessarily increase. When a larger R group, such as in alcohol 51, is present, the effect would become exceedingly worse.

On the other hand, no such interactions would be present if the attacking carbon were to approach equatorially along line EO. In fact, due to the 60° angle of the axis, the distance between a point along the EO portion and the axial substituents in the 2 or 6 positions (which is the C-12b methyl in this case) should be virtually the same as in the product, which would be no more than the distance between

methyl groups in a gauche-butane situation, or about 3.25 \AA° . Fortunately, the R group is pointed away from the C-12b methyl group, thereby rendering the steric interactions for this example no greater than that when $R = H$.

If the Curtin-Hammett Principle is operating, the above theoretical considerations would predict that the major product should be the one resulting from equatorial attack to produce the cis,anti,trans cation 208. Since the B/C ring

208

fusion has already been shown to be trans, then the pentacyclic product which should be formed preferentially is indeed the desired olefin 50.

With the possibilities narrowed down to the C/D trans olefin 50 and the C/D cis olefin 204, the task of assigning the correct structure has been greatly simplified and virtually becomes apparent upon examination of the chemical shifts of the angular methyl groups (Fig. 31). These signals occur at 0.90, 0.95, 1.05, and 1.25 ppm. The lowest field shift

is easily assigned as the C-14a methyl group, since it is adjacent to the phenyl ring (66f,77). The signals at 0.90 and 0.95 are assigned to the methyl groups at C-8a and C-12b. Although the actual assignments cannot be made with absolute certainty, the signal at 0.90 is virtually catholic to all the cyclization products derived from the model alcohol 82, as well as the tricyclic olefins 109, 110, and 68. The consistency of this signal can only be ascribed to that methyl group which remains unchanged in all the products, namely, the one at the D/E ring juncture. There is no methyl peak at 0.95 ppm in the tricyclic olefin mixture 109 and 110, in which the methyl group corresponding to the one at C-12b is absent.

The peak at 1.05 ppm is assigned as the C-6b methyl group. Its low field resonance is attributed to the fact that it is in the plane of the 11,12 double bond (Fig. 35), which would

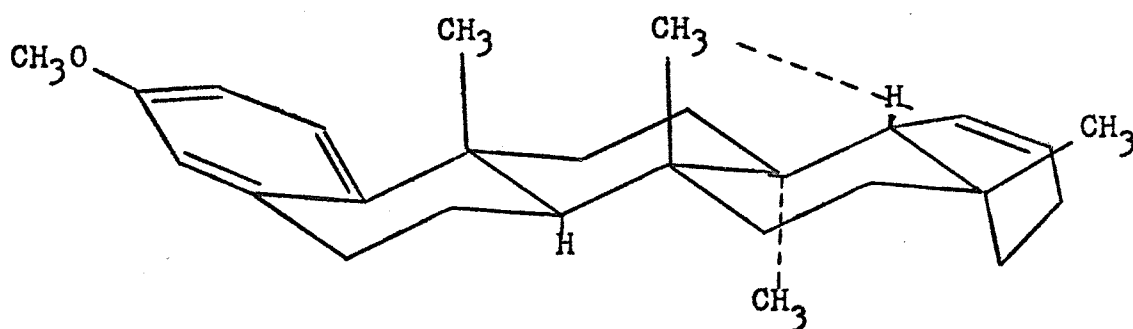
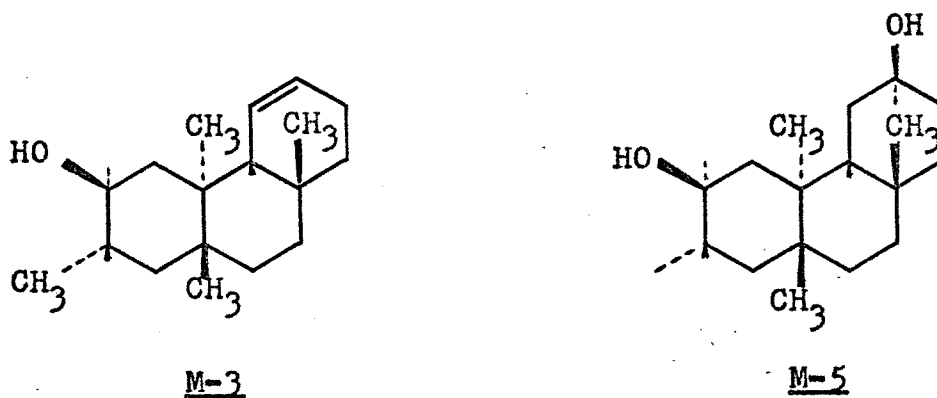
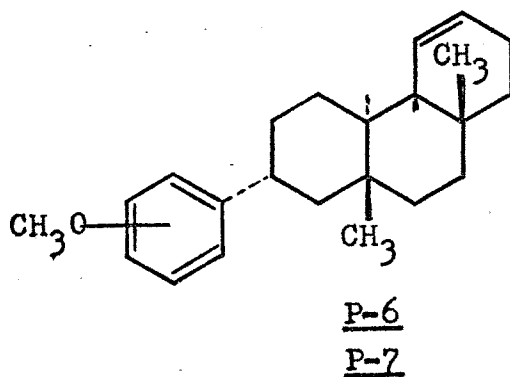


Fig. 35

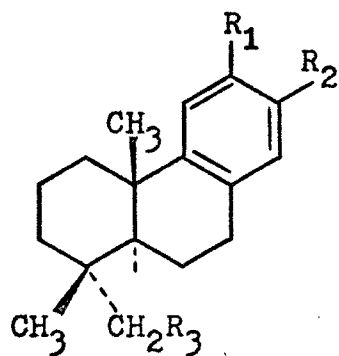
cause a deshielding effect, similar to the one observed for the same methyl group in the pentacyclic olefin 195 (vide supra). Several other examples of this downfield shift are observable in the model series related to this study. In the alcohol M-3, the chemical shift of the methyl group in ques-



tion is found at 1.1 ppm, whereas it is shifted to 1.0 ppm in the dihydroxy compound M-5. Similarly, the tricyclic anisole derivatives P-6 and P-7 show methyl resonances at 1.03 and 1.06 ppm.



The normal chemical shift for a methyl group in the same relative position in some tricyclic aromatic systems such as 209 (66f,208,209) occurs in the region of 0.88-0.94 ppm.

209

	R ₁	R ₂	R ₃
<u>a</u>	H	MeO	H
<u>b</u>	H	CHMe ₂	OH
<u>c</u>	MeO	H	H

Even in derivatives of olefin 50, such as the hydroboration products M-2 and 167, this resonance is shifted up to 0.90-0.95 ppm. If the cis isomer 204 was the correct one, then the C-6b methyl group would be out of the plane of the double bond (Fig. 36), and hence, its signal should appear in the

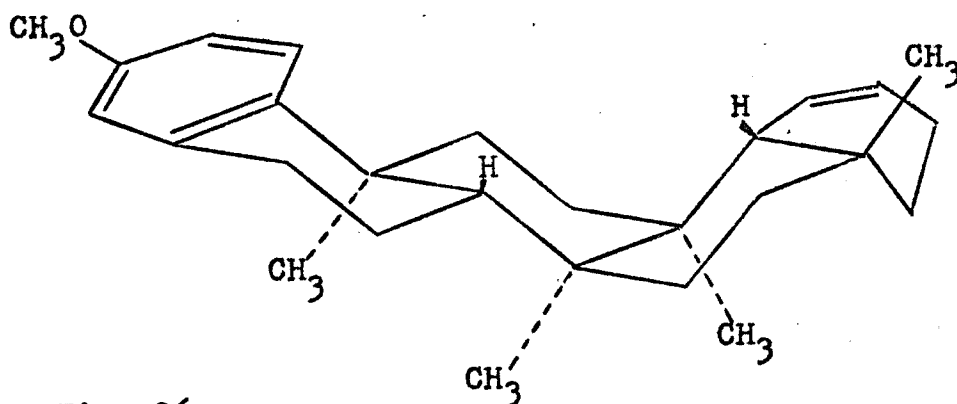


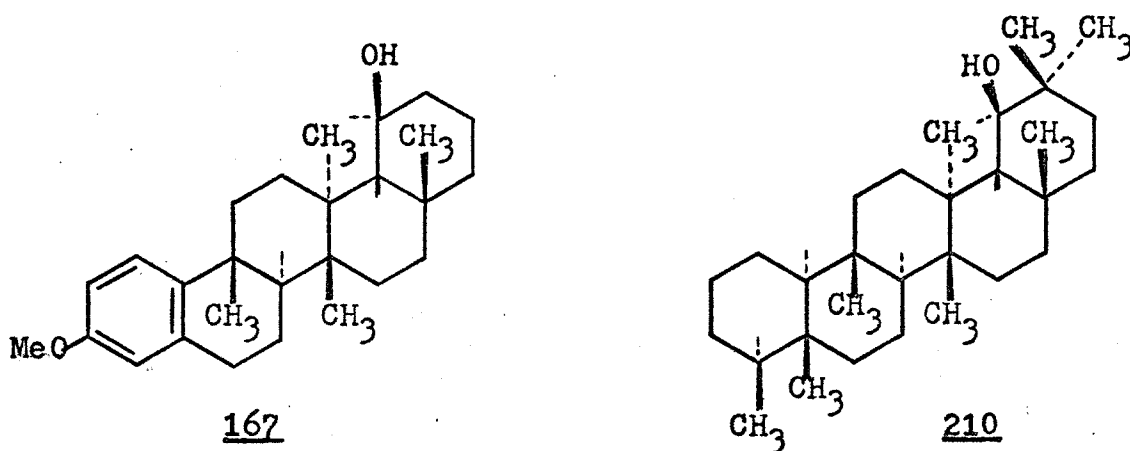
Fig. 36

normal region of about 0.96 ppm or less, which is the standard chemical shift for the C-9 methyl group on a cis-decalin (210).

Besides the inference of the correct structure of the pentacyclic olefin as 50 on the basis of spectral data, it would be advantageous to confirm the structure by other means. As was stated previously, the formation of the C/D cis olefin 204 is not likely on the basis of mechanistic considerations. In addition, there are the ample precedented examples which demonstrate that a cis ring fusion has never been formed from a trans double bond, unless there exists the possibility of deprotonation and reprotonation (see introduction), which makes possible a concerted protonation-cyclization sequence which would lead solely to cis fused products. The possibility of deprotonation-reprotonation has been suggested only once during the course of this work, when formic acid was used as the cyclization initiator. The use of stannic chloride renders the cyclization medium aprotic, thereby ruling out this possibility.

In order to possibly rule out any further doubt of the structure of the pentacyclic olefin, other non-chemical means may be employed. Of course, the most definitive determination would be x-ray analysis of a suitable derivative, such as the pentacyclic ketone M-1. Preliminary inspection of this compound (211) indicates that the crystals are monoclinic and may be suitable for crystallographic study.

Alternatively, one could employ the technique of nmr shift reagents on a suitable derivative, such as the alcohol 167. A preliminary study has been done (212) on a related compound, 19-hydroxyfriedelane (210) (213), and the results indicate



that one could make assignments of the methyl signals in this compound. Because of their similar structures, it may be possible to correlate the magnitude of the shifts in the alcohol 167. If the correct structure is the cis olefin 204, then the C-6b methyl group of its alcohol derivative should be further from the hydroxyl group and should therefore migrate to a lesser degree.

While other shift studies may be possible on other derivatives, the close correlation of the two pentacyclic alcohols 167 and 210 make this study most attractive.

Experimental

General

Melting point determinations were made on a Köfler hot stage or Thomas-Hoover melting point apparatus. Melting points and boiling points are uncorrected.

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

Vapor phase chromatograms (vpc) were determined on either a Hewlett-Packard 5750 or F&M 810 research chromatograph using helium carrier gas at a flow rate of 60 ml/min. The following liquid phases were used on Chromosorb WAW-DMCS solid support:

<u>Column</u>	<u>Liquid Phase</u>	<u>Length x O.D.</u>
A	4% SE-30	6' x 1/8"
B	5% SE-30	6' x 1/8"
C	10% Carbowax 20M	6' x 1/8"
D	20% Carbowax 20M	6' x 1/8"
E	10% Carbowax 20M	10' x 1/4"
F	20% Carbowax 20M	10' x 1/4"

Nuclear magnetic resonance spectra (nmr) were determined on a Varian Model T-60 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane internal standard. The abbreviation "br" preceding the multiplicity of a signal signifies that the signal was broad. Infra red spectra (ir) were determined on a Perkin-Elmer 237B spectrophotometer.

Mass spectra were determined on a CEC Model 21-103 mass spectrometer by Mr. Ronald Klefbeck. Ultraviolet spectra (uv) were determined on a Cary Model 14 spectrophotometer.

Solvents, unless otherwise specified, were obtained from commercial sources and used without purification. Solvents referred to as dry were distilled from their respective drying agents as follows:

Formic acid	Boric anhydride
Ether, tetrahydrofuran, 1,2-dimethoxyethane	Lithium aluminum hydride
Benzene, pyridine, <u>t</u> -butyl alcohol, pyrrolidine, HMPA	Calcium hydride
2,2,2-trifluoroethanol	Linde 4x molecular sieves
Dichloromethane, carbon tetrachloride, methyl iodide	Phosphorous pentoxide

Pet. ether refers to Baker Analyzed reagent grade petroleum ether (bp 30-60°).

Evaporative (bulb-to-bulb) distillations were done in a modified Büchi kugelrohrfen.

Supports used for column chromatography were either 70-325 mesh silica gel, Woelm neutral alumina, or Florisil. Preparative tlc was carried out on plates coated with a 2 mm layer of silica gel 254 + 366 (acc. to Stahl). Analytical tlc plates were coated with a 0.5 mm layer of silica gel G. High-pressure column chromatography was performed using a 2" x 20" glass column and fittings supplied by Chromatronix,

1,4-Dibromo-2,3-dimethyl-trans-2-butene (L-2)

The trans dibromide L-2 was prepared according to the procedure of Sweeting and Johnson (86) from 189.7 g (2.31 mole) of 2,3-dimethyl-1,3-butadiene (L-1) (Columbia Organic, distilled from hydroquinone) and 375.6 g (2.31 mole) of bromine. The total yield of dibromide L-2 was 378.6 g (68%). Crystallization from pet. ether yielded colorless needles, mp 46-47.5° (lit., (86) mp 47-47.4°).

2,5,6,9-Tetramethyl-trans-1,5,9-decatriene (L-3)

A. Preparation of methallylmagnesium chloride. To a mixture of 38.4 g (1.6 mole) of magnesium turnings and 300 ml of dry tetrahydrofuran was added a little methyllmagnesium iodide in ether, followed by the dropwise addition of a solution of 39 ml (36.2 g, 0.4 mole) of methallyl chloride (MC&B, distilled) in 38 ml of tetrahydrofuran over 7 hours. The temperature was maintained at 30-35° with external heating during the addition, and for an additional 6 hours after the addition was complete. The gray mixture was then allowed to cool to room temperature. Titration (as total base) indicated a concentration of 1.1 M.

B. Coupling. The freshly prepared Grignard solution was transferred to a clean, dry flask by means of a syringe, and a solution of 24.2 g (0.1 mole) of the dibromide L-2 in 75 ml of tetrahydrofuran was added over 5 hours. The temperature was kept at 30-35° during the addition and for an addi-

tional 4 hours after the dibromide was added. The excess Grignard reagent was then decomposed by the slow addition of 125 ml of saturated ammonium chloride (exothermic), followed by 125 ml of saturated brine. After stirring for 1 hour at room temperature, the layers were separated, and the aqueous layer was extracted with 2 x 150 ml of ether. The combined organic layers were washed with 2 x 200 ml of saturated brine and dried (MgSO_4). Evaporation of the solvent afforded a light yellow liquid which appeared to be a 15:85 mixture of two components by vpc (column A, 100°). Distillation of the mixture through a 6" Vigreux column at 0.15 mm afforded the following fractions:

<u>Fraction</u>	<u>Bp</u>	<u>Weight</u>	<u>% Trans</u>
1	39-40 $^\circ$	3.66 g	80%
2	40-46 $^\circ$	14.2 g	91%

The total yield of coupling product, based on the two fractions, was 17.86 g (93%). Spinning band distillation of fraction 2 at 0.85 mm yielded the following fractions:

<u>Fraction</u>	<u>Bp</u>	<u>Weight</u>	<u>% Trans</u>
2-1	61-63 $^\circ$	0.766 g	60%
2-2	63-64 $^\circ$	1.363 g	82%
2-3	64 $^\circ$	2.488 g	86%
2-4	64 $^\circ$	3.370 g	91%
2-5	64 $^\circ$	5.786 g	97%

The fractions composed of >90% trans product were combined: ir (CHCl_3) 1645 and 885 cm^{-1} ($>\text{C}=\text{CH}_2$); nmr (CDCl_3) δ 1.67

(s, 6, $(\text{CH}_3)\text{C}=\text{C}(\text{CH}_3)$), 1.77 (s, 3, $(\text{CH}_3)\text{C}=\text{CH}_2$), 2.10 (s, 8, $>\text{C}=\text{CCH}_2-$), and 4.72 (br s, 4, $>\text{C}=\text{CH}_2$).

2,5,6,9-Tetramethyl-trans-5,9-decadienol (L-4)

A solution of 35 g (0.183 mole) of the triene L-3 (>90% pure by vpc) in 100 ml of dry tetrahydrofuran was cooled to 0° , and 0.09 mole of a solution of disiamylborane (66) (91,92) was added dropwise over $1\frac{1}{2}$ hours. The mixture was then allowed to warm to room temperature and stir overnight. After cooling to 0° , a solution of 12 g of sodium hydroxide in 40 ml of water was added, followed by the slow addition of 35 ml of 30% hydrogen peroxide. The external ice bath was raised and lowered to keep the mixture below the reflux temperature. Water was then added, and the mixture was extracted with 3 x 200 ml of ether. The combined extracts were washed with 3 x 200 ml of water, 200 ml of saturated brine, and dried (MgSO_4). The solvent was evaporated, and the residual oil was subjected to column chromatography on 1200 g of Florisil with pet. ether as initial eluent. The recovered triene L-3 amounted to 20 g (57%). The desired alcohol L-4 was isolated by elution with 40% ether-pet. ether. Distillation afforded 10.83 g (28%, 65% based on recovered triene) of alcohol L-4 (bp $111-115^\circ$ @ 1.5 mm). The product was composed of >95% of one volatile component by vpc (column A, 140°): ir (CHCl_3) 3620, 3450 (OH), 1649, and 890 cm^{-1} ($\text{C}=\text{CH}_2$); nmr (CDCl_3) δ 0.93 (d, 3, $J = 6\text{ Hz}$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$),

1.43 (s, 1, OH), 1.67 (s, 6, (CH₃)C=C(CH₃)), 1.75 (br s, 3, (CH₃)C=CH₂), 3.48 (d, 2, J = 5.5 Hz, CH₂OH), and 4.72 (br s, 2, >C=CH₂).

2,5,6,9-Tetramethyl-trans-5,9-decadienal (61)

To a suspension of 15.04 g (40 mmole) of pyridinium dichromate (93) in 200 ml of dry dichloromethane was added 1.05 g (5 mmole) of alcohol L-4 in 20 ml of dichloromethane. The mixture was stirred for 40 hours at room temperature, and then filtered through a bed of Florisil, which was washed with 3 x 200 ml of dichloromethane. The filtrate and washings were concentrated through a Vigreux column on a steam bath. Bulb-to-bulb distillation of the pale yellow residue (72-76° @ 0.25 mm) afforded 0.98 g (94%) of aldehyde 61, containing 90% one volatile component by vpc (column A, 140°): ir (CHCl₃) 2720 (aldehyde C-H), 1720 (C=O), 1650, and 890 cm⁻¹ (>C=CH₂); nmr (CDCl₃) δ 1.11 (d, 3, J = 6.5 Hz, CH(CH₃)CHO), 1.67 (s, 6, (CH₃)C=C(CH₃)), 1.75 (s, 3, (CH₃)C=CH₂), 4.72 (s, 2, >C=CH₂), and 9.67 (d, 1, J = 2 Hz, CHO).

4-Methyl-4-(3,4,7-trimethyl-trans-3,7-octadienyl)-2-cyclohexenone (62)

To a solution of 1.40 g (6.7 mmole) of aldehyde 61 (90% pure by vpc) in 50 ml of benzene was added 0.72 g (10 mmole) of pyrrolidine in 5 ml of benzene. The mixture was maintained at reflux for 1½ hours under a Dean-Stark water sep-

arator and 6" Vigreux column. Most of the solvent was then distilled off, and the residue was allowed to cool. A solution of 0.91 g (13 mmole) of freshly distilled methyl vinyl ketone in 40 ml of dry benzene was added, and the yellow solution was stirred at room temperature for 1 hour and at reflux for 17 hours. The reaction was hydrolyzed by the rapid addition of a solution of 0.78 g of glacial acetic acid and 0.37 g of sodium acetate in 0.75 ml of water. After stirring at reflux for 5 hours, the mixture was allowed to cool, and then washed with 50 ml each of water, 5% hydrochloric acid, saturated sodium bicarbonate, water, and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow oil which consisted of three volatile components by vpc (column A, 180°). Two minor components accounted for 5% each of the volatile products, and the major product comprised the remaining 90%. Chromatography on 100 g of silica gel (benzene) afforded, after 1 l. of forefractions, 1.364 g of a pale yellow liquid, consisting of >95% one volatile component by vpc (column A, 180°). Bulb-to-bulb distillation ($116-124^\circ$ @ 0.1 mm) yielded 1.158 g (70%) of 96% pure enone 62 as a colorless liquid: ir (CHCl_3) 1665 (C=O), 1610, and 885 cm^{-1} ($>\text{C}=\text{CH}_2$); nmr (CDCl_3) δ 1.20 (s, 3, angular CH_3), 1.68 (s, 6, $(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_3)$), 1.77 (s, 3, $(\text{CH}_3)\text{C}=\text{CH}_2$), 4.73 (br s, 2, $>\text{C}=\text{CH}_2$), 5.91 (d, 1, $J = 10\text{ Hz}$, C-2H), and 6.75 (d, 1, $J = 10\text{ Hz}$, C-3H); uv (CH_3OH) 224 nm ($\epsilon = 10,900$).

Anal. Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}$: C, 83.02; H, 10.84. Found:

C, 82.95; H, 10.94.

Semicarbazone, mp 136.5-138.0°.

Anal. Calcd. for $C_{19}H_{31}N_3O$: C, 71.88; H, 9.84; N, 13.24. Found: C, 71.85; H, 9.65; N, 13.26.

4-Methyl-4-(3,4,7-trimethyl-trans-3,7-octadienyl)-2-cyclohexenol (58)

A mixture of 190 mg (5 mmole) of lithium aluminum hydride in 35 ml of dry ether was cooled to 0°, and 2.555 g (9.82 mmole) of enone 62 (98% pure by vpc) was added in 20 ml of ether over 35 minutes. After the mixture had stirred at 0° for 1½ hours, 0.7 ml of water was added (frothing), and the mixture was stirred for an additional 2 hours, during which time it formed a white suspension. Magnesium sulfate was added, and the slurry was stirred for an additional 1½ hours. The white solid was removed by filtration and washed several times with ether. The filtrate and washings were concentrated, and the residue was evaporatively distilled to yield 2.551 g (99%) of alcohol 58 as a colorless liquid. The mixture consisted of two volatile components by vpc (column A, 180°): ir ($CHCl_3$) 3600 (OH), 1648, and 885 cm^{-1} ($>C=CH_2$); nmr ($CDCl_3$) δ 0.96 (s, 1, angular CH_3 , α -alcohol), 1.01 (s, 2, angular CH_3 , β -alcohol), 1.63 (s, 6, $(CH_3)C=C(CH_3)$), 1.75 (s, 3, $(CH_3)C=CH_2$), 4.10 (m, 1, $W_{h/2} = 12$ Hz, $>CHOH$), 4.70 (s, 2, $>C=CH_2$), and 5.63 (m, 2, $CH=CH$).

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

C, 83.20; H, 11.48.

Cyclization of alcohol 58 in formic acid.

A mixture of 109 mg (0.416 mmole) of alcohol 58 and 20 ml of anhydrous formic acid was shaken at room temperature for 5 minutes (61,69f), during which time it became cloudy and slightly pink. The reaction mixture was then poured onto 200 g of cracked ice with rapid stirring. Sodium chloride and sodium bicarbonate were added, and the solution was extracted with ether. The combined extracts were washed with water and saturated sodium bicarbonate until the aqueous layer attained pH 8. After washing with saturated brine and drying over sodium sulfate, the solvent was evaporated. The resulting yellow oil (115 mg) was added in 5 ml of dry ether to a mixture of 70 mg (1.84 mmole) of lithium aluminum hydride and 5 ml of ether. After stirring for 11 hours at room temperature, 5 ml of 10% sodium hydroxide was added, and the stirring was continued for an additional hour. The mixture was extracted with ether, and the combined extracts were washed with water, saturated ammonium chloride, saturated brine, and dried (MgSO_4). Evaporation of the solvent afforded 103 mg of a colorless oil.

A vpc trace (column A, 180°) showed at least 13 components, which were divided into 3 groups:

<u>Group</u>	<u>Retention Time, min</u>	<u>% of Volatile Mater.</u>
A (A ₁ -A ₆)	less than 2 min	80%
B (B ₁ -B ₄)	2.4-3.25 min	10%
C	4 min	10%

Preparative tlc (pet. ether) separated the mixture into a hydrocarbon fraction (16 mg, 14.6%) and an alcohol fraction (93 mg, 85.3%). The hydrocarbon fraction consisted of the components A₁-A₄, with A₄ comprising ca. 80% of the mixture: nmr (CDCl₃) δ 0.91 (m, 9, angular CH₃), 5.30 (m, 1, $W_{h/2} = 8$ Hz, C=CH), and 5.71 (m, 2, CH=CH).

The alcohol fraction consisted of 8 peaks belonging to the three groups described above:

<u>Group</u>	<u>% of Volatile Material</u>
A (A ₄ ', A ₅ , A ₆)	50%
B (B ₁ -B ₄)	25%
C	25%

Preparative tlc of the alcohol fraction (40% ether-pet. ether) yielded two broad bands: D (34 mg, R_F = 0.5-0.7), and E (37 mg, R_F = 0.0-0.25). Band D consisted of a 2:1:1 ratio of A₄', A₅, and A₆: ir (CHCl₃) 3600 (OH), 1650-1700 (C=C), and 900 cm⁻¹ (>C=CH₂); nmr (CDCl₃) δ 4.70 (br s, 1, >C=CH₂), and 5.30-5.93 (m, 2, olefinic H).

Band E contained the components in groups B and C: ir (CHCl₃) 3600 cm⁻¹ (OH). Preparative tlc (50% ether-pet. ether) of Band E afforded 20 mg of material consisting of ca.

80% of component C by vpc (column A, 180°): nmr (CDCl₃) δ 0.73-1.05 (m, 3, angular CH₃), 1.21 (s, 3, angular CH₃) 1.63 (s, 3, C=C(CH₃)), 4.13 (m, 1, W_{h/2} = 8 Hz, >CHOH), and 5.50-5.80 (m, 1, olefinic H).

Cyclization of alcohol 58 with stannic chloride in dichloromethane. Isolation and purification of 2,4aα,8aβ,10aβ,-tetramethyl-1,4,4a,4bβ,7,8,9,10,10a-decahydrophenanthrene (68)

A solution of 198 mg (0.755 mmole) of alcohol 58 in 85 ml of dry dichloromethane was cooled to -78°, and 150 μl of stannic chloride was added. After stirring at -78° for 1 hour, the mixture was warmed to -6° in an ice-salt bath. The stirring was continued for ½ hour, during which time the solution turned orange. The mixture was then poured into a solution of 50 ml of water and 15 g of potassium carbonate, maintained at 0°. After stirring for ½ hour, the layers were separated, and the aqueous layer was extracted with 2 x 30 ml of dichloromethane. The combined organic layers were washed with 50 ml of water and dried (MgSO₄). Evaporation of the solvent afforded 199 mg of a colorless oil.

A vpc trace (column A, 180°) indicated the mixture to consist of seven volatile components, one of which predominated in >76% abundance. The mixture was subjected to column chromatography on 55 g of silica gel (pet. ether). After 70 ml, 41 mg of impure product containing ca. 75% of the major product was isolated in five 10 ml fractions, and 35 mg

(19%) of material in which the major product comprised >98% of the volatile material was isolated after 155 ml of additional eluent was collected. The total yield of the major product was estimated to be 58 mg (31.5%).

Alternatively, the product could be isolated in >99% purity by chromatography on neutral alumina (act. I) or preparative vpc (column E, 200°, ret. time = 17.6 min).

On standing at -20°, the pure product solidified to a waxy solid, mp 44-47°. An analytical sample was prepared by bulb-to-bulb distillation (102° @ 0.6 mm): ir (CHCl₃) 1670-1650 cm⁻¹ (w, C=C); nmr (CDCl₃) δ 0.83 (s, 3, angular CH₃), 0.91 (s, 6, angular CH₃), 1.67 (br d, 3, J = 3 Hz, (CH₃)C=CH), 5.28 (m, 1, W_{H/2} = 7.5 Hz, C=CH), and 5.56-5.96 (m, 2, CH=CH).

Anal. Calcd. for C₁₈H₂₈: C, 88.45; H, 11.55. Found: C, 88.60, 88.55; H, 11.44, 11.42.

2α,4α,8α,10α-Tetramethyl-1,2β,3α,4,4a,4bβ,7,8,8a,9,10,10a-dodecahydro-3β-phenanthrenol (M-3)

A solution of 25 mg (0.102 mmole) of diene 68 and 1.2 mg of hexadecane (Aldrich) in 1 ml of dry tetrahydrofuran was cooled to 0°, and 80 μl of a 0.93 M solution of diborane (0.148 mmole) was added. The reaction was stirred at 0° for 5 hours, and 1½ ml of 20% sodium hydroxide was added, followed by 2 ml of 30% hydrogen peroxide. After stirring at room temperature overnight, a little potassium carbonate

was added, and the mixture was poured into 30 ml of water and extracted with 3 x 20 ml of ether. The combined extracts were washed with 30 ml of water, 30 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent afforded 33 mg of a colorless oil. Chromatography on 8 g of silica gel afforded 9 mg of recovered diene 68 with 50 ml of 1-2% ether-pet. ether. On gradually increasing the ether-pet. ether ratio to 1:1, 11 mg (69%, based on recovered starting material) of a single alcohol M-3 was isolated after 150 ml of the solvent was eluted. A portion was rechromatographed on 15 g of neutral alumina (act. II) to yield alcohol M-3 as an oil, >99% of one volatile component by vpc (column A, 220°).

An analytical sample was prepared by bulb-to-bulb distillation (104° @ 0.55 mm). The colorless distillate solidified on standing in the microanalysis tube: ir (CHCl_3) 3620 cm^{-1} (OH); nmr (CDCl_3) δ 3.43 (br m, 1, $W_{h/2} = 20$ Hz, >CHOH), and 5.60-5.80 (m, 2, CH=CH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{30}\text{O}$: C, 83.20; H, 11.48. Found: C, 83.01; H, 11.42.

2 α ,4 α ,8 α ,10 α -Tetramethyl-1,2 β ,3 α ,4,4 α ,4 β ,5,6 α ,7,8,9,10,10 α -tetradecahydro-3 β ,-6 β -phenanthrenediol (M-5)

A solution of 26.2 mg (0.107 mmole) of diene 68 in 2 ml of dry tetrahydrofuran was cooled to 0°, and 215 μl of a 0.93 M solution of diborane (0.4 mmole) was added. After

14 hours at 0°, the mixture still contained starting material after vpc analysis (column A, 220°). An additional 500 μ l of the diborane solution was added (0.465 mmole). A second vpc trace showed complete depletion of starting material. An additional 250 μ l of the diborane solution was added after 6 hours, and the solution was stirred for 3 hours more. The excess diborane was decomposed by the addition of 3 ml of 20% sodium hydroxide (frothing), followed by 2 ml of 30% hydrogen peroxide. After stirring at room temperature for $\frac{1}{2}$ hour, a little potassium carbonate and 30 ml of water were added, and the mixture was extracted with 3 x 15 ml of ether. The combined extracts were washed with 2 x 20 ml of water and dried (MgSO_4). Evaporation of the solvent afforded 33 mg of a foam, which separated 17 mg of a white solid on trituration with hexane. The product consisted of one high boiling component by vpc (column A, 300°). An additional 3 mg of product was obtained on concentration of the mother liquor (total yield, 20 mg, 67%).

Crystallization from acetone and then chloroform-acetone afforded small, colorless needles, mp 193-194°: ir (CHCl_3) 3600 cm^{-1} (OH); nmr (CDCl_3) δ 3.40 (br m, 1, $W_{h/2} = 20$ Hz, $>\text{CHOH}$), and 3.93 (br m, 1, $W_{h/2} = 19$ Hz, $>\text{CHOH}$).

Anal. Calcd for $\text{C}_{18}\text{H}_{32}\text{O}_2$: C, 77.09; H, 11.50. Found: C, 77.11; H, 11.53.

2 α ,3 α -Epoxy-2,4 α ,8 $\alpha\beta$,10 $\alpha\beta$ -tetramethyl-1,2,3,4,4 α ,4 β ,5,8,-
8 α ,9,10,10 α -dodecahydrophenanthrene (92)

A mixture of 48.8 mg (0.2 mmole) of diene 68, 5 mg of sodium bicarbonate, and 1 ml of dry dichloromethane was cooled to 5°, and 51 mg (0.3 mmole) of 99% m-chloroperbenzoic acid (114) in 200 μ l of dichloromethane was added. After 1 hour, analysis by vpc (column A, 180°) showed roughly 84% reaction. An additional 5 mg of the peracid was added, and the reaction was quenched after 45 minutes by the addition of 2 ml of 10% sodium sulfite. A vpc trace (column A, 200°) of the crude product solution showed a mixture of 3 volatile components in a ratio of 10:85:5. The mixture was diluted with 30 ml of ether and washed with 20 ml each of 10% sodium sulfite, saturated sodium bicarbonate, saturated brine, and dried (Na₂SO₄). Chromatography on 8 g of silica gel afforded 6 mg of recovered diene 68 after elution with 25 ml each of pet. ether and 1% ether-pet. ether. After 25 ml each of 2% and 4% ether-pet. ether had eluted, 34 mg (75%) of epoxide 92 was obtained which was >99% one volatile component by vpc (column A, 200°) in 25 ml of 8% ether-pet. ether.

An analytical sample was prepared by bulb-to-bulb distillation (110° @ 0.5 mm): ir (CHCl₃) 1650 cm⁻¹ (w, C=C); nmr (CDCl₃) δ 0.88 (s, 6, angular CH₃), 0.98 (s, 3, angular CH₃), 1.08 (s, 3, CH₃C^O-CH), 2.80-3.03 (m, 1, >C^O-CH), and 5.36-5.96 (m, 2, CH=CH).

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.98; H, 10.83.

2,4 α ,8 α ,10 α -Tetramethyl-1,2 β ,4 α ,4 β ,7,8,8 α ,9,10,10 α -decahydro-3(4H)-phenanthrenone (93)

To a solution of 6 mg (0.023 mmole) of epoxide 92 in 1 ml of dry dichloromethane was added 8.5 μ l (9.95 mg, 0.7 mmole) of boron trifluoride etherate (Eastman, doubly distilled from calcium hydride). The solution immediately turned dark pink. After 1 hour, the mixture was poured into 10 ml of saturated sodium carbonate and extracted with 2 x 20 ml of ether. The combined extracts were washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent afforded 6 mg (100%) of white crystals whose vpc trace (column A, 200 $^{\circ}$) showed one volatile component, not identical with the starting material. Crystallization from ether-hexane afforded colorless crystals, mp 108.0-112.0 $^{\circ}$.

An analytical sample was prepared by recrystallization from methanol, mp 109.5-113.5 $^{\circ}$: ir ($CHCl_3$) 1690 (C=O), and 1655 cm^{-1} (w, C=C); nmr ($CDCl_3$) δ 0.78, 0.95, 1.28 (3 s, 9, angular CH_3), and 5.30-5.96 (m, 2, $\underline{CH=CH}$).

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.03; H, 10.72.

3-Buten-1-ol (99)

Allylmagnesium bromide was prepared according to the known procedure (119) from 73.5 g (3 mole) of magnesium turnings and 86.5 ml (121 g, 1 mole) of allyl bromide (98) (MC&B, distilled) in 970 ml of dry ether. The temperature was maintained at 0° throughout the addition (23 hours) and for an additional $\frac{1}{2}$ hour after the addition was complete. The Grignard solution was then heated to reflux, and 60 g (2 mole) of dry paraformaldehyde (dried in vacuo over phosphorous pentoxide) was added in one portion (118). The milky white suspension was maintained at reflux for 6 hours. After cooling to 0°, 500 ml of 5% hydrochloric acid was added dropwise. After the addition, the mixture was allowed to warm to room temperature, and the stirring was continued overnight. The two-layer mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with 500 ml of saturated brine and dried (Na₂SO₄). Evaporation of the solvent and distillation of the residue at atmospheric pressure yielded, after a small forerun, 40.5 g (56.2%) of the alcohol 99, as a colorless liquid, bp 108-111°, (lit. (118), bp 112.5-113.5°): ir (CHCl₃) 3620 (OH), 1640, 995, and 920 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 2.11-2.51 (m, 3, CH₂=CHCH₂, OH), 3.48-3.88 (m, 2, CH₂OH), 4.90-5.08, 5.11-5.31 (2 m, 2, CH=CH₂), and 5.50-5.68 (m, 1, CH=CH₂).

4-Chloro-1-butene (N-1)

The procedure of Roberts and Mazur (120) was modified. To a mixture of 49.8 g (0.691 mole) of the alcohol 99 and 1.57 ml of dry pyridine (maintained at 0°) was added 49 ml (82.23 g, 0.691 mole) of thionyl chloride over 3½ hours, during which time the solution turned pink. When the addition was complete, the mixture was heated to reflux. After 1 hour at reflux, the mixture was distilled. The opaque distillate (bp ca. 70°) was washed with 2 x 20 ml of saturated sodium bicarbonate, 20 ml of saturated brine, and dried (MgSO₄). Distillation of the filtered liquid afforded 43.44 g (69.4%) of the chloride N-1, as a colorless liquid, bp 68-70° (lit. (118), bp 75°): ir (CHCl₃) 1645, 1000, and 925 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 2.51 (q, 2, J_{1,2} = 6.5 Hz, J_{2,3} = 2 Hz, CH₂CH=CH₂), 3.56 (t, 2, J_{1,2} = 6.5 Hz, CH₂Cl), 4.93-5.13, 5.13-5.35 (2 m, 2, CH=CH₂), and 5.43-6.26 (m, 1, CH=CH₂).

2-Methyl-1,6-heptadien-3-ol (96b)

A 1 l. flask containing 15.7 g (0.654 mole) of magnesium turnings was flame dried under a stream of dry nitrogen. After cooling, 450 ml of dry ether and a crystal of iodine were added. The flask was heated slightly to maintain a temperature of ca. 30°, while a solution of 49.4 g (0.545 mole) of 4-chloro-1-butene (N-1) in 50 ml of dry ether was added dropwise. After about 30 ml of the chloride solution was

added, the yellow iodine color disappeared, and the mixture began to reflux spontaneously. The remainder of the chloride solution was added at a rate so as to maintain gentle reflux (2 hours). After the addition was complete, a solution of 40.07 g (0.572 mole) of methacrolein (Aldrich technical, redistilled) in 50 ml of dry ether was added dropwise, while the mixture was maintained at reflux. After 1½ hours at reflux, the mixture became slightly cloudy. The mixture was cooled to 0°, and 250 ml of 5% hydrochloric acid was added slowly, causing the mixture to separate into two layers. The coagulant aqueous layer was treated with additional 5% hydrochloric acid until the mixture became homogeneous. The aqueous layer was then extracted with 4 x 200 ml each of saturated sodium bicarbonate, saturated brine, and dried (Na₂SO₄). Evaporation of the solvent and distillation of the residue at 33 mm afforded 47.3 g (68.8%) of alcohol 96b, as a colorless liquid, bp 85-88°. A vpc trace (column A, 70°) of the distillate showed one volatile component in 99% purity.

An analytical sample was prepared by distillation through a 6" Vigreux column: ir (CHCl₃) 3605 (OH), 1640, 995, and 910 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 1.71 (d, 3, J = 1½ Hz, (CH₃)C=CH₂), 1.83 (s, 1, OH), 2.06 (t, 2, J_{4,5} = 5½ Hz, CH₂CH=CH₂), 4.08 (t, 1, J_{3,4} = 6 Hz, >CHOH), 4.76-5.30 (m, 4, (CH₃)C=CH₂, CH=CH₂), and 5.43-6.25 (m, 1, CH=CH₂).

Anal. Calcd. for C₈H₁₄O: C, 76.14; H, 11.18. Found: C, 75.98; H, 11.20.

Ethyl 4-methyl-trans-4,8-nonadienoate (97b)

The general procedure of Johnson, et al, (117) was followed (121). A mixture of 6.48 g (0.0513 mole) of the alcohol 96b, 44.5 g (0.274 mole) of triethyl orthoacetate (Aldrich, distilled, bp 138-142°), and 0.235 g of propionic acid was heated in a flask equipped with a Claisen adapter and receiver for the collection of ethanol. One thermometer was placed just above the liquid level, and another in the distilling head. With stirring, the mixture was slowly heated, while the ethanol distilled out, and the temperature above the liquid rose to 138°. When liquid ceased to distill, the reaction mixture was kept at 138-141° for 1 hour. The flask was allowed to cool to room temperature, and then heated slowly under reduced pressure (0.60-0.65 mm). The excess triethyl orthoacetate and propionic acid distilled out at 30°. Distillation of the residue afforded two fractions: (1) 0.55 g, bp 71-72°, 98% one volatile component (column A, 100°); (2) 8.29 g, bp 74.5-75.5°, 100% one component by vpc. The total yield of the desired ester 97b, based on the two fractions, was 88%: ir (CHCl₃) 1725 (C=O), 1640, 1000, and 920 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 1.25 (t, 3, J = 7 Hz, OCH₂CH₃), 1.60 (s, 2.91, trans CH=C(CH₃)), 1.67 (s, 0.09, cis CH=C(CH₃)), 4.14 (q, 2, J = 7 Hz, OCH₂CH₃), 4.76-5.35 (m, 3, CH=CH₂, CH=C(CH₃)), and 5.48-6.15 (m, 1, CH=CH₂).

Anal. Calcd. for C₁₂H₂₀O₂: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.40.

4-Methyl-trans-4,8-nonadienol (N-2)

A solution of 4.63 g (23.6 mmole) of the ester 97b in 30 ml of dry ether was added over 1 hour to a mixture of 0.90 g (23.6 mmole) of lithium aluminum hydride and 30 ml of dry ether. The gray suspension was stirred at room temperature for 12 hours. The excess hydride was decomposed by the dropwise addition of 1 ml of water, 2 ml of 10% sodium hydroxide, and 10 ml of water. The emulsion was stirred for 4 hours and then extracted with 3 x 20 ml of ether. The combined extracts were washed with 20 ml each of water, saturated brine, and dried (MgSO_4). Evaporation of the solvent and distillation of the residue yielded 3.58 g (98.6%) of alcohol N-2, as a colorless liquid. Bulb-to-bulb distillation (72° @ 0.5 mm) afforded analytically pure material: ir (CHCl_3) 3630 (OH), 1673 ($\text{CH}=\text{C}(\text{CH}_3)$), 1645, 1010, and 920 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.56 (s, 1, OH), 1.63 (s, 3, $\text{CH}=\text{C}(\text{CH}_3)$), 3.63 (t, 2, $J = 6\text{ Hz}$, CH_2O), 4.78-5.36 (m, 3, $\text{CH}=\text{C}(\text{CH}_3)$), and 5.50-6.20 (m, 1, $\text{CH}=\text{CH}_2$).

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}$: C, 77.87; H, 11.76. Found: C, 77.96; H, 11.79.

1-Chloro-4-methyl-trans-4,8-nonadiene (N-3)

The procedure of Lee, et al. (122) was modified. To a flask equipped as the one used to prepare ester 97b (vide supra) was added 2.038 g (13.2 mmole) of the alcohol N-2, 10 ml of dry carbon tetrachloride, and 3.80 g (14.5 mmole)

of triphenylphosphine (MC&B). The mixture was slowly heated to boiling. After 10 min at reflux, a colorless liquid (presumably chloroform) began to distill from the mixture (bp 60-63°), and a white solid precipitated from the reaction mixture. After ca. 5 ml of distillate was collected, the temperature in the distilling head began to decrease. The reaction was maintained at reflux for 33 hours, during which time additional liquid distilled (bp 70°). The reaction was allowed to cool, and 20 ml of pet. ether was added. Filtration of the precipitate, washing of the solid with pet. ether, and evaporation of the solvent yielded a yellow liquid (2.7 g). The product was isolated by column chromatography on 75 g of silica gel with 5 x 80 ml pet. ether after 180 ml of fore-fractions. Bulb-to-bulb distillation (75° @ 1.75 mm) afforded 1.688 g (74.1%) of the chloride N-3, as a colorless liquid. A vpc trace (column A, 100°) showed one volatile component: ir (CHCl₃) 1670 (CH=C(CH₃)), 1640, 995, and 920 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 1.61 (s, 3, CH=C(CH₃), CH=CH₂), and 5.46-6.13 (m, 1, CH=CH₂).

Anal. Calcd. for C₁₀H₁₇Cl: C, 69.55; H, 9.92; Cl, 20.52. Found: C, 69.63; H, 9.94; Cl, 20.47.

5-Methyl-trans-5,9-decadienoic acid (N-4)

To a dry flask containing 4.2 g (0.175 mole) of magnesium turnings was added 10 ml of dry tetrahydrofuran and a crystal of iodine. With rapid stirring, about 2 g out of a total of

7.55 g (43.7 mmole) of the chloride N-3 and a few drops of methyl iodide were added. The mixture was heated to reflux, while the remainder of the chloride N-3 in 50 ml of dry tetrahydrofuran was added over 2½ hours. The reaction was maintained at reflux for 4 hours after the addition was complete. Examination of a quenched aliquot indicated some unreacted chloride was still present. An additional 3 g of magnesium turnings and 0.1 ml of methyl iodide were added. The reaction proceeded spontaneously, as evidenced by rapid refluxing, and the external heating was discontinued. After the boiling had subsided, the flask was maintained at reflux for 2 hours. A vpc analysis (column A, 100°) of an aliquot indicated almost complete reaction. After cooling to room temperature, the reaction mixture was added to a swirled slurry of dry ice (1 lb) in 100 ml of ether. After the solid had disappeared, the mixture was acidified to pH 2, causing a light yellow liquid to separate. The mixture was extracted with 3 x 100 ml of ether. The combined extracts were washed with 3 x 100 ml of 10% sodium hydroxide. The combined washings were extracted with 50 ml of ether and acidified to pH 2. This mixture was extracted with 4 x 100 ml of ether, and the combined extracts were washed with 2 x 100 ml of saturated brine and dried (MgSO₄). Evaporation of the solvent and bulb-to-bulb distillation of the pale yellow residue (98-101° @ 0.15 mm) afforded 6.959 g (87.5%) of acid N-4, as a colorless liquid, consisting of one volatile component by

vpc (column A, 160°): ir (CHCl₃) 3400-2750 (OH), 1702 (C=O), 1635, 990, and 910 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 1.60 (s, 3, CH=C(CH₃)), 4.73-5.36 (m, 3, CH=C(CH₃), CH=CH₂), 5.50-6.26 (m, 1, CH=CH₂), and 10.81 (br s, 1, COOH).

Anal. Calcd. for C₁₁H₁₈O₂: C, 72.49; H, 9.95. Found: C, 72.57; H, 10.00.

2,5-Dimethyl-trans-5,9-decadienoic acid (N-5)

The procedure of Pfeffer and Silbert (123) was followed. A solution of 13.4 ml (9.64 g, 0.955 mole) of diisopropylamine (MC&B, distilled from calcium hydride) in 63 ml of dry tetrahydrofuran was cooled to 0°, and 28 ml of a 3.13 M solution of n-butyllithium in hexane (Alfa, 8.8 mmole) was added dropwise, keeping the temperature at 0-5°. A solution of 6.942 g (38.1 mmole) of acid N-4 in 30 ml of dry tetrahydrofuran was added dropwise, again keeping the temperature at 0-5°. The reaction was stirred at 0° for 15 min, and 17.2 ml (17.09 g, 95.5 mmole) of HMPA was added. After 15 min at 0°, 3.57 ml (8.16 g, 57.3 mmole) of dry methyl iodide was added in one portion to the amber solution. The color immediately lightened to yellow, and the temperature rose to 30°. The reaction was cooled to room temperature and stirred for 2 hours. Acidification to pH 2 caused the mixture to separate into 2 layers. The organic layer was washed with 5 x 75 ml of 10% hydrochloric acid, followed by 4 x 50 ml of 1:1 10% sodium hydroxide-saturated brine. The basic wash-

ings were reacidified and extracted with 4 x 75 ml of pet. ether. The extracts were washed with saturated brine and dried (MgSO_4). Evaporation of the solvent yielded a pale yellow liquid, which on bulb-to-bulb distillation, afforded 7.062 g (94.6%) of the methylated acid N-5, bp 106-111° @ 0.175 mm. The colorless distillate consisted of one volatile component by vpc (column A, 160°): ir (CHCl_3) 3400-2750 (OH), 1700 (C=O), 1640, 990, and 915 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.18 (d, 3, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)\text{COOH}$), 1.61 (s, 3, $\text{CH}=\text{C}(\text{CH}_3)$), 4.71-5.36 (m, 3, $\text{CH}=\text{C}(\text{CH}_3)$, $\text{CH}=\text{CH}_2$), 5.46-6.23 (m, 1, $\text{CH}=\text{CH}_2$), and 11.30 (br s, 1, COOH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.26.

2,5-Dimethyl-trans-5,9-decadienol (N-6)

A solution of 11.677 g (59.5 mmole) of the acid N-5 in 70 ml of dry ether was added dropwise over 1 hour to a mixture of 3.42 g (90.2 mmole) of lithium aluminum hydride in 120 ml of dry ether, maintained at 0°. The gray suspension was stirred at 0° for $\frac{1}{2}$ hour and at room temperature for 10 hours. The excess hydride was decomposed with 8.5 ml of water (frothing). After 14 hours of stirring, a white suspension formed, and ca. 5 g of magnesium sulfate and 25 ml of ether were added. The mixture was stirred for 6 hours and filtered. The white solid was washed several times with ether. Evaporation of the solvent yielded a colorless liquid,

which on bulb-to-bulb distillation afforded 10.624 g (98.1%) of alcohol N-6 (bp 84° @ 0.30 mm): ir (CHCl_3) 3620 (OH), 1665 (C=C), 1635, 995, 910 ($\text{CH}=\text{CH}_2$), and 1025 cm^{-1} (C-O); nmr (CDCl_3) δ 0.92 (d, 3, $J = 7$ Hz, $\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$), 1.60 (s, 3, $\text{CH}=\text{C}(\text{CH}_3)$), 3.48 (br d, 2, $J = 5$ Hz, CH_2OH), 4.76-5.33 (m, 3, $\text{CH}=\text{C}(\text{CH}_3)$, $\text{CH}=\text{CH}_2$), and 5.46-6.23 (m, 1, $\text{CH}=\text{CH}_2$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}$: C, 79.06; H, 12.16. Found: C, 79.15; H, 12.26.

2,5-Dimethyl-trans-5,9-decadienal (94)

To a suspension of 6.00 g (60 mmole) of chromium trioxide in 50 ml of dry dichloromethane was added 9.49 g (120 mmole) of dry pyridine. A slightly exothermic reaction ensued, accompanied by the immediate formation of a dark brown solution. After 15 min, 1.828 g (10.14 mmole) of the alcohol N-6 was added in one portion with a little dichloromethane. A tarry, black residue formed almost immediately. After stirring for 20 min at room temperature, the mixture was filtered through a bed of Florisil, which was washed several times with ether. The light yellow filtrate was concentrated under a 12" Vigreux column on a steam bath. After dilution with 125 ml of ether, the solution was washed with 2 x 100 ml of 5% sodium hydroxide, 2 x 50 ml of 5% hydrochloric acid, 50 ml of saturated sodium bicarbonate, 50 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent yielded aldehyde 94, as a pale yellow liquid, con-

sisting of one volatile component by vpc (column A, 120°). Bulb-to-bulb distillation afforded 1.678 g (92.8%) of colorless aldehyde 94, bp 80° @ 0.75 mm: ir (CHCl₃) 2720 (CHO), 1722 (C=O), 1655 (C=C), 1640, 995, and 915 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 1.09 (d, 3, J = 7 Hz, CH(CH₃)CHO), 1.61 (s, 3, CH=C(CH₃)), 4.80-5.35 (m, 3, CH=C(CH₃), CH=CH₂), 5.50-6.28 (m, 1, CH=CH₂), and 9.63 (d, 1, J = 2 Hz, CHO).

Anal. Calcd. for C₁₂H₂₀O: C, 79.94; H, 11.18. Found: C, 79.93; H, 11.04.

Aldehyde 94 was characterized further as the 2,4-dinitrophenylhydrazone, yellow crystals, mp 64.0-65.5° (from ethanol).

Anal. Calcd. for C₁₈H₂₄N₄O₄: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.98; H, 6.70; N, 15.62.

4-Methyl-4-(3-methyl-trans-3,7-octadienyl)-2-cyclohexenone (95)

To a solution of 4.594 g (25.5 mmole) of the aldehyde 94 in 250 ml of dry benzene under a Dean-Stark water separator was added 2.417 g (34 mmole) of dry pyrrolidine in 50 ml of dry benzene over 10 min. The mixture was slowly heated to reflux. After 2 hours at reflux, a vpc trace (column A, 120°) indicated only 20% of the aldehyde had reacted. The mixture was concentrated to half its volume, and 2 ml of pyrrolidine was added. After 2½ hours at reflux, the aldehyde was virtually depleted. After an additional ½ hour at reflux, the reaction mixture was allowed to cool to room temperature.

The benzene and excess pyrrolidine were removed at reduced pressure (aspirator), and the residue was dried in vacuo. The residue was then dissolved in 200 ml of dry benzene, and a solution of 3.57 g (51 mmole) of freshly distilled methyl vinyl ketone (containing 0.5% hydroquinone) in 50 ml of dry benzene was added over 15 min. After stirring at room temperature for 2 hours, the mixture was heated to reflux and maintained at reflux for 17 hours, during which time the reaction mixture was protected from light by wrapping the flask in glass wool and aluminum foil. A mixture of 1.55 g of sodium acetate, 5 ml of water, and 4.2 ml of glacial acetic acid was then added in one portion. After 4 hours at reflux, the reaction was allowed to cool to room temperature. The mixture was diluted with 200 ml of pet. ether, washed with 4 x 200 ml of 2% hydrochloric acid, 2 x 200 ml of saturated sodium bicarbonate, 200 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a pale yellow, viscous oil, which consisted of essentially one volatile component by vpc (column A, 160°). Fractional vacuum distillation yielded, after a small forerun, a fraction boiling at $98-101^\circ$ (0.1 mm), which contained one volatile component in 97% purity by vpc (column A, 160°). The residue was subjected to bulb-to-bulb distillation ($112-115^\circ$ @ 0.15 mm). A colorless distillate (3.912 g) was obtained consisting of one volatile component in 98% purity. The total yield of distilled enone 95 was 4.971 g (84%):

ir (CHCl_3) 1665 ($\text{CH}=\text{CH}$), 995, and 910 cm^{-1} ($\text{CH}=\text{CH}_2$); uv (95% ethanol) 226 nm ($\epsilon = 11,200$); nmr (CDCl_3) δ 1.15 (s, 3, angular CH_3), 1.61 (s, 3, $\text{CH}=\text{C}(\text{CH}_3)$), 2.46 (t, 2, $J = 6.5$ Hz, COCH_2), 4.80-5.33 (m, 3, $\text{CH}=\text{C}(\text{CH}_3)$, $\text{CH}=\text{CH}_2$), 5.46-6.16 (m, 1, $\text{CH}=\text{CH}_2$), 5.86 (d, 1, $J = 10$ Hz, C-2 H), and 6.68 (d, 1, $J = 10$ Hz, C-3 H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}$: C, 82.68; H, 10.43. Found: C, 82.59; H, 10.19.

4-Methyl-4-(3-methyl-trans-3,7-octadienyl)-2-cyclohexenol (82)

To a mixture of 0.314 g (8.2 mmole) of lithium aluminum hydride in 40 ml of dry ether, maintained at 0° , was added a solution of 3.87 g (16.5 mmole) of the enone 95 in 20 ml of dry ether over 35 min. After the addition was complete, the gray suspension was stirred for an additional $1\frac{1}{2}$ hours, and 1.5 ml of water was carefully added (frothing). The mixture turned from gray to white. After 15 min of additional stirring, magnesium sulfate was added. The white slurry was filtered, and the filtrate was concentrated to a viscous liquid. Bulb-to-bulb distillation ($110-112^\circ$ @ 0.1 mm) afforded 3.821 g (98.1%) of colorless alcohol 82. The vpc trace (column A, 160°) showed two broad, overlapping peaks in a ratio of 2:1 (epimeric alcohols): ir (CHCl_3) 3600 (OH), 1640, 990, 915 ($\text{CH}=\text{CH}_2$), and 1040 cm^{-1} (C-O); nmr (CDCl_3) δ 0.96 (s, 1, angular CH_3 , α -alcohol), 1.01 (s, 2, angular CH_3 , β -alcohol), 4.18 (br m, 1, >CHOH), and 4.76-5.33 (m,

3, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}$: C, 81.99; H, 11.18. Found: C, 81.82; H, 11.20.

Cyclization of alcohol 82 in formic acid

To a flask containing 78 mg (0.333 mmole) of the alcohol mixture 82 was added 6.5 ml of anhydrous formic acid at 9° . After 8 min, the cloudy mixture was poured onto a slurry of 25 g of cracked ice and 26 g of 50% sodium hydroxide. The mixture was stirred for $1\frac{1}{2}$ hours, and then worked up with ether to yield 83 mg of an oil, which was subsequently treated with excess lithium aluminum hydride. After hydrolysis and drying (MgSO_4), 76 mg of an oil was obtained. The vpc trace (column E, 205°) indicated the presence of 14 components, in which 6, designated A-F, accounted for ca. 75% of the volatile material. The retention times of components A-F were 1.65, 4.3, 5.15, 5.55, 6.3, and 8 min, respectively. There were 5 minor peaks at 1.15-2.8 min accounting for 5% of the volatile products, and 3 unresolved peaks ranging from 6.6-7.7 min, accounting for the remaining 20% of the volatile material: ir (CHCl_3) 3550 (OH), 1635, 995, and 915 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 3.66-4.33 (m, 1, $>\text{CHOH}$), 4.76-5.23 m, 2, $\text{CH}=\text{CH}_2$), and 5.50-5.68 (m, 3, $\text{CH}=\text{CH}$, $\text{CH}=\text{CH}_2$)

Preparative vpc (column E, 205°) yielded the components A-F in high purity:

Component A (100), 5.2 mg: ir (CHCl_3) 1635, 1000, and

915 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 4.91-5.28 (m, 2, $\text{CH}=\text{CH}_2$), and 5.30-5.86 (m, 3, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}$).

Component B (101), 3.5 mg: ir (CHCl_3) 3550 (OH), 1635, 995, and 910 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.00 (s, 3, angular CH_3), 1.15 (s, 1, OH), 1.71 (d, 3, $J = 2$ Hz, $\text{CH}=\text{C}(\text{CH}_3)$), 4.51-5.36 (m, 3, $\text{CH}=\text{C}$, $\text{CH}=\text{CH}_2$), and 5.36-6.16 (m, 3, $\text{CH}=\text{CH}$, $\text{CH}=\text{CH}_2$).

Component C (102) 2.5 mg: ir (CHCl_3) 3620 (OH), 1640, 995, and 915 ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 0.91 (s, 3, angular CH_3), 1.18 (s, 3, $\text{>}(\text{CH}_3)\text{OH}$), 4.73-5.23 (m, 2, $\text{CH}=\text{CH}_2$), and 5.36-6.16 (m, 3, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}$).

Component D (103), 2.0 mg: ir (CHCl_3) 3600 (OH), 1640, 1000, and 920 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 0.93 (s, 3, angular CH_3), 1.18 (s, 3, $\text{>}(\text{CH}_3)\text{OH}$), 4.75-5.28 (m, 2, $\text{CH}=\text{CH}_2$), and 5.41-6.11 (m, 3, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}$).

Component E (104), 5.0 mg: ir (CHCl_3) 3600 (OH), 1640, 995, and 915 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.05 (s, 6, angular CH_3), 4.76-5.30 (m, 2, $\text{CH}=\text{CH}_2$), and 5.30-6.00 (m, 3, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}$).

Component F (105), 3.0 mg: ir (CHCl_3) and nmr (CDCl_3) were identical with starting alcohol 82, except the only angular methyl signal in the nmr occurred at 1.01 ppm.

Cyclization of alcohol 82 in nitromethane with stannic chloride. Isolation of the tricyclic hydrocarbon mixture, $8a\beta$, - $10a\beta$ -dimethyl-1,2,4a β ,4b α ,5,8,8a,9,10,10a-decahydrophenan-

threne (109) and 8a β ,10a β -dimethyl-1,2,4a β ,4b α ,5,6,8a,9,10,10a-
decahydrophenanthrene (110).

A solution of 118 mg (0.504 mmole) of the alcohol 82 in 10 ml of nitromethane (MC&B, distilled from Drierite) was cooled to -23° , and 88 μ l (195 mg, 0.75 mmole) of stannic chloride was added. The cloudy, pale yellow mixture was stirred at -23° for $1\frac{1}{2}$ min, and then poured into 60 ml of saturated ammonium chloride, maintained at 0° . The mixture was extracted with 3 x 50 ml of ether. The combined extracts were washed with 3 x 50 ml of 10% sodium hydroxide, 50 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent afforded 114 mg of a pale yellow oil. A vpc trace (column A, 150°) of the crude mixture indicated one major component (1.25 min) with ca. 20% of a minor component (1.1 min). These two components comprised ca. 60% of the volatile material. In addition, a small peak at 1.0 min accounted for about 7% of the total peak area, and a cluster from 2.1-3.0 min accounted for the remaining 30%. Chromatography on 20 g of silica gel (pet. ether) afforded, after 60 ml of forefractions, 28 mg (24.7%) of the major components in 20 ml of the eluent. Bulb-to-bulb distillation ($60-64^{\circ}$ @ 0.3 mm) yielded an oil. The products were tentatively assigned the structures of the tricyclic diene 109 and 110: ir (CHCl_3) 1655 cm^{-1} (C=C); nmr (CDCl_3) δ 0.81 (s, 3, angular CH_3), 0.91 (s, 3, angular CH_3), 1.66-2.21 (m, >6,<7, C=CCH), 5.33-5.95 (m, 4, $\text{CH}=\text{CH}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}$: C, 88.82; H, 11.18. Found:

C, 88.76; H, 11.17.

Further elution (120 ml) afforded 31 mg (24.6%) of the higher boiling components, later assigned structure 111.

Cyclization of alcohol 82 with stannic chloride in dichloromethane-ethylene carbonate

To a solution of 117 mg (0.5 mmole) of the alcohol 82 and 6 ml of ethylene carbonate (Aldrich, distilled) in 2 ml of dry dichloromethane was added 350 μ l of stannic chloride. A mildly exothermic reaction ensued, and the solution became deep red. After 1 hour, the mixture was poured into a solution of 25 g of potassium carbonate and 50 ml of methanol. After the color disappeared, sufficient methanol was added to form a one-phase mixture. After 10 hours of stirring at room temperature, the mixture was extracted with 3 x 60 ml of ether. The combined organic layers were washed with 3 x 60 ml of water, 60 ml of saturated brine, and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure yielded 117 mg of a yellow oil. A vpc trace (column A, 150 $^{\circ}$) showed two overlapping peaks, corresponding to the tricyclic dienes 109 and 110 in roughly equal amounts, comprising ca. 75% of the volatile material. There were traces of lower boiling components, and some higher boiling material, later found to be the chlorocarbons 111, accounting for 15% of the total peak area. In addition, two minor peaks at 1.2 and 1.5 min amounted to 5% each. Column chromatography on 25 g of silica

gel (pet. ether) afforded, after 30 ml of forefractions, 7 mg of the tricyclic dienes 109 and 110 in 20 ml of eluent in about 75% purity (4.9%), followed by 61 mg of material in 40 ml of eluent, which consisted of dienes 109 and 110 in >99% purity (56.4%).

Finally, 5 mg (3.9%) of the chlorocarbon mixture 111 was isolated in 10 ml of eluent.

Cyclization of alcohol 82 in benzene. Isolation of 8a β ,10a β -dimethyl-7-phenyl-1,2,4a β ,4b α ,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene (P-1)

The reaction described above was repeated, except dry benzene (10 ml, maintained at 5^o) was used as solvent. After 1½ hour of stirring, the color changed from pale yellow to dark red brown. The mixture was poured into 50 ml of water at 0^o and extracted with 2 x 20 ml of ether. The combined extracts were washed with 20 ml of 10% sodium hydroxide, 20 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure yielded an oil which was dissolved in 7 ml of ether and stirred with 3 g of silica gel impregnated with 10% silver nitrate at room temperature for 10 hours. Filtration of the mixture and concentration of the filtrate at reduced pressure afforded 119 mg of an oil. The vpc trace (column A, 150-300^o @ 10^o/min) showed 3 groups of components. Group A (ca. 45% of the volatile mixture) consisted of 2 major peaks, A₁ and A₂, having retention times

of 1.25 and 1.55 min, respectively. Component A₂ had a retention time identical to the tricyclic dienes 109 and 110. Group B (ca. 20% of the mixture) was an unresolved cluster of peaks ranging from 2.8-3.6 min. Group C (ca. 30% of the mixture) consisted of 2 components, C₁ and C₂, with retention times of 7.25 and 7.7 min, respectively, in a 1:8 ratio.

The mixture was subjected to column chromatography on 23 g of silica gel (pet. ether), and samples were collected in 10 ml fractions. Component A₂ (24 mg, 22.2%) was eluted first (fractions 6 and 7). The ir and nmr spectra were identical to that of the tricyclic dienes 109 and 110.

In addition, 13 mg (12%) of component A₁ was isolated (fraction 9): ir (CHCl₃) 1640, 1000, and 915 cm⁻¹ (CH=CH₂); nmr (CDCl₃) δ 0.86 (s, 3, angular CH₃), 1.61 (s, 3, C=C(CH₃)), 5.30-6.23 (m, 3, CH=CH₂, CH=CH), and 4.80-5.21 (m, 2, CH=CH₂). Component A₁ rapidly reacted with oxygen, and a satisfactory combustion analysis could not be obtained. The structure of A₁ was assigned as the bicyclic triene 100.

The group B components were isolated in 8.5% yield (fractions 11-13) and were characterized as the chlorocarbons 111.

Components C₁ and C₂ were isolated in 27.8% yield (41 mg) from fractions 14-17): ir (CHCl₃) 1601 and 1495 cm⁻¹ (C₆H₅); nmr (CCl₄) δ 0.90 (s, 3, angular CH₃), 0.96 (s, 3, angular CH₃), 2.46-2.93 (m, 1, CHAr), 5.16-5.83 (m, 2, CH=CH), and 7.08 (s, 5, ArH); ms (70 eV) m/e 294 (M⁺).

Anal. Calcd. for $C_{22}H_{30}$: C, 89.73; H, 10.27. Found: C, 89.97; H, 10.20.

Cyclization of alcohol 82 with stannic chloride in dichloromethane. Isolation of 7-chloro-8 α ,10 α -dimethyl-1,2,4,4 α ,-4b α ,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene (111)

To a solution of 117 mg (0.5 mmole) of the alcohol 82 in 10 ml of dry dichloromethane was added 88 μ l (0.75 mmole) of stannic chloride. The solution immediately turned yellow-brown. After 4 min, the mixture was poured into 60 ml of ammonium chloride solution (saturated), maintained at 0°. The layers were separated, and the aqueous layer was extracted with 2 x 50 ml of dichloromethane. The combined organic layers were washed with 50 ml of 10% sodium hydroxide and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure yielded 144 mg of a yellow oil. A vpc trace (column A, 150°) showed a small amount of hydrocarbon peaks, which corresponded to the tricyclic dienes 109 and 110. The major products had retention times between 2 and 3 min.

The mixture was subjected to column chromatography on 20 g of silica gel (pet. ether), and 10 ml fractions were collected. The tricyclic dienes 109 and 110 were isolated in fractions 8 and 9, but were contaminated with other hydrocarbons (14.4% estimated by vpc).

Material consisting of two components with retention times of 2.45 and 2.8 min were isolated (fractions 13-16),

which yielded 44 mg of the chlorocarbons 111 on bulb-to-bulb distillation (75° @ 0.075 mm): ir (CHCl₃) 1650 cm⁻¹ (C=C); nmr (CDCl₃) δ 3.76-4.73 (m, 1, CHCl), and 5.33-6.00 (m, 2, CH=CH); ms (70 eV) m/e 254 (M⁺) and 256 (30% of M⁺, M+2⁺).

Anal. Calcd. for C₁₆H₂₅Cl: C, 76.00; H, 9.96; Cl, 14.02. Found: C, 75.84; H, 9.74; Cl, 13.96.

Cyclization of alcohol 82 in 2,2,2-trifluoroethanol. Isolation of 8a_β,10a_β-dimethyl-7-(2,2,2-trifluoroethoxy)-1,2,4a_β,-4b_α,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene (P-2)

The procedure described above was repeated using 176 μl (1.5 mmole) of stannic chloride and 117 mg (0.5 mmole) of the alcohol 82 in 10 ml of dry 2,2,2-trifluoroethanol, maintained at 0°. The solution immediately turned bright orange. After 3 hours at 0°, the mixture was allowed to warm up to 12°, and was poured into 50 ml of water maintained at 0°. After the color disappeared, sodium chloride was added, and the mixture was extracted with 3 x 30 ml of ether. The combined extracts were washed with 30 ml each of 10% sodium hydroxide, saturated brine, and dried (MgSO₄). Evaporation of the solvent afforded 138 mg of a yellow oil. The vpc trace (column A, 150°) indicated that the crude product consisted of two volatile components with retention times of 1.15 and 1.9 min, comprising 30% and 50% of the volatile material, respectively. The former corresponded to the tricyclic dienes 109 and 110.

Chromatography on 20 g of silica gel (pet. ether) afforded 22 mg (20.2%) of the tricyclic dienes 109 and 110 in 40 ml of eluent, after 30 ml of forefractions had been collected. After 50 ml each of 1%, 2%, and 4% ether-pet. ether had eluted through the column, an additional 50 ml of 4% ether-pet. ether yielded 49 mg (16%) of the major product P-2 (bulb-to-bulb distillation, 107° @ 0.075 mm): ir (CHCl_3) 1650 cm^{-1} ($\text{CH}=\text{CH}$); nmr (CDCl_3) δ 0.83 (s, 3, angular CH_3), 1.01 (s, 3, angular CH_3), 3.83 (q, 2, $J = 9\text{ Hz}$, CH_2CF_3), 3.83 (br s, 1, $>\text{CHO}-$), and 5.36-5.80 (m, 2, $\text{CH}=\text{CH}$).

Anal. Calcd. for $\text{C}_{18}\text{H}_{27}\text{F}_3\text{O}$: C, 68.32; H, 8.60; F, 18.01. Found: C, 68.45; H, 8.70; F, 18.09.

Cyclization in anisole. Isolation of 8a β ,10a β -dimethyl-(o-and p-methoxyphenyl)-1,2,4a β ,4b α ,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene (P-6 and P-7)

To a solution of 243 mg (1.04 mmole) of the alcohol 82 in 10 ml of anisole, maintained at -10° was added 176 μl (1.5 mmole) of stannic chloride. After 15 min at -10° , no starting material was detected by vpc (column A, 160°). The mixture was poured into a solution of 25 g of potassium carbonate in 50 ml of water, maintained at 0° . After 2 hours, the mixture was extracted with 20 ml of ether. The extract was washed with 20 ml each of water, 5% hydrochloric acid, saturated sodium bicarbonate, saturated brine, and dried (MgSO_4). The solvent was evaporated at reduced pressure,

and the excess anisole was removed in vacuo. The residue consisted of 303 mg of a yellow oil. A vpc trace (column A, 180°) indicated two peaks at 0.45 and 0.6 min comprising ca. 20% of the product (Group A), a peak at 1.2 min (ca. 10%, Group B), and a cluster of 5 peaks (Group C) comprising ca. 20% of the volatile material in a ratio of 1:3:2:3:2½, with retention times of 5.2, 5.7, 6.3, 6.6, and 7.5 min, respectively. Chromatography on 50 g of silica gel (pet. ether) in 100 ml fractions separated the mixture into the tricyclic dienes 109 and 110 (27.6 mg, 12.2%) (fractions 2 and 3), and 14.4 mg (6.4%) of the bicyclic triene 100 (fraction 4), and 32 mg (24.6%) of the chlorocarbons 111 (fractions 5 and 6). After 50 ml of 1%, 2%, and 250 ml of 4% ether-pet. ether had eluted from the column, 169 mg (49.5%) of aromatic products (Group C) were isolated in 250 ml of 4% ether-pet. ether.

The aromatic products were subjected to 3 successive column chromatographies on 60 g each of silica gel impregnated with 10% silver nitrate. Elution with pet. ether-benzene (7:1) separated the components into 3 monocyclic products (96 mg, 28%) in a ratio of 1:3:2 (50 ml): ir (CHCl₃) 1640, 1000, 910 (CH=CH₂), and 1670 (aromatic C=C); nmr (CDCl₃) δ 1.03, 1.06 (2 s, 3, C-1 angular CH₃), 1.65 (d, 3, J = 2 Hz, CH=C(CH₃)), 3.78 (s, 2, p-CH₃O), 3.85 (s, 1, o-CH₃O), 4.80-5.40 (m, 3, CH=C(CH₃), CH=CH₂), 5.40-6.16 (m, 3, CH=CH₂, CH=CH), and 6.63-7.36 (m, 4, ArH); ms (70 eV) m/e 324 (M⁺). The monocyclic products were used directly in the next reaction.

On further elution (100 ml), 68 mg (20%) of tricyclic products were isolated in a ratio of 3:2.5 and are assigned the structure P-6 and P-7: ir (CHCl_3) $1580\text{-}1610\text{ cm}^{-1}$ (aromatic C=C); nmr (CDCl_3) δ 0.80-1.13 (m, 6, angular CH_3), 3.76, 3.80 (2 s, 3, CH_3O), 5.36-6.03 (m, 2, $\text{CH}=\text{CH}$), and 6.73-7.36 (m, 4, ArH); ms (70 eV) m/e 324 (M^+). Bulb-to-bulb distillation afforded a colorless oil, bp 145° @ 0.05 mm.

Anal. Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}$: C, 85.13; H, 9.94. Found: C, 85.11; H, 9.97.

4-(o- and p-Methoxy)phenyl-1-methyl-1-(3-methyloctyl)-cyclohexane (P-8 and P-9)

To a solution of 60 mg (0.185 mmole) of the monocyclic aromatic trienes P-4 and P-5 in 7 ml of hexane was added 14 mg of 10% palladium on carbon. The black mixture was stirred under 1 atmosphere of hydrogen for 10 hours. Filtration through a bed of silica gel, washing the bed with ether, and concentration of the filtrate afforded 57 mg of a colorless oil. The vpc trace (column A, 220°) indicated 3 peaks at 1.4, 1.85, and 2.4 min in a relative ratio of 1:3:2. Preparative tlc (1:1 pet. ether-benzene) yielded two bands, A and B, with R_f values of 0.7 and 0.6, respectively.

Band A (17 mg, 27.8%) showed two peaks by vpc (column A, 220°) in essentially equal amounts: ir (CHCl_3) 1585 and 1600 cm^{-1} (C=C, o-substituted benzene); nmr (CDCl_3) δ 3.83 (s, 3, CH_3O) and 6.73-7.06 (m, 4, ArH). The components of

band A were assigned the epimeric ortho compounds P-8. An analytical sample was prepared by bulb-to-bulb distillation (155° @ 0.06 mm).

Anal. Calcd. for $C_{23}H_{38}O$: C, 83.59; H, 11.59. Found: C, 83.56; H, 11.70.

Band B (32 mg, 52.4%) also contained two components in equal amounts by vpc (column A, 220°): ir ($CHCl_3$) 1585, 1612 (C=C, para-substituted benzene), and 830 cm^{-1} (C-H out-of-plane bending); nmr ($CDCl_3$) δ 3.80 (s, 3, CH_3O), 7.12 (d, 2, $J = 8\text{ Hz}$, C-3',3" H), and 7.33 (d, 2, $J = 8\text{ Hz}$, C-2',2" H). The components in this band were assigned the structures of the epimeric para compounds P-9. An analytical sample was prepared by bulb-to-bulb distillation (160° @ 0.06 mm).

Anal. Calcd. for $C_{23}H_{38}O$: C, 83.57; H, 11.59. Found: C, 83.59; H, 11.62.

m-Methoxybenzaldehyde (R-1)

The Organic Synthesis procedure (139) was followed using 88.8 g (0.727 mole) of m-hydroxybenzaldehyde (Aldrich, mp $102-104^{\circ}$). The methylated aldehyde R-1 was obtained, bp $58-59$ @ 0.55 mm (lit. (139) bp $88-90^{\circ}$ @ 3 mm). The yield was 88.45 g (89.3%).

2-(m-Methoxy)benzylidinecyclohexanone (R-2)

The procedure of Baltzly, et al, (138) was modified. A two-phase mixture of 14.7 g (0.15 mole) of cyclohexanone (MC&B, distilled), 6.8 g (0.05 mole) of m-methoxybenzaldehyde (R-1), and 2.5 g of potassium hydroxide in 35 ml of water was heated to reflux with vigorous mechanical stirring. The mixture was maintained at reflux for 3 hours, during which time it formed a milky, yellow emulsion. After cooling to room temperature, the mixture again separated into two layers. The lower aqueous layer was extracted with 3 x 25 ml of ether. The combined organic layers were washed with 3 x 20 ml of water (last wash pH 7), 20 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a yellow oil which consisted of one major peak by vpc (column A, 150°), along with traces of a high boiling impurity. The mixture was dried in vacuo to remove most of the cyclohexanone. Distillation of the residue at 0.1 mm afforded a small forerun (bp $126-131^\circ$) and a major fraction weighing 6.16 g (57%), bp $135-140^\circ$ (lit. (138) bp $160-162^\circ$ @ 1.0 mm). A vpc trace (column A, 150°) showed only one volatile component.

On standing, the product solidified to a low-melting solid, mp $<24^\circ$: ir (CCl_4) 1680 cm^{-1} (C=O); nmr (CCl_4) δ 1.61-2.11 (m, 4, CH_2), 2.25-2.58 (m, 2, $\text{CH}_2\text{C}=\text{C}$), 2.61-3.05 m, 2, $\text{CH}_2\text{C}=\text{O}$), 3.76 (s, 3, CH_3O), and 6.63 (m, 5, C=CH, ArH).

2-(m-Methoxy)benzylidene-cyclohexanol (R-3)

A solution of 4.028 g (18.6 mmole) of the unsaturated ketone R-2 in 25 ml of methanol was added dropwise over 10 min to a solution of 7.07 g (0.186 mmole) of sodium borohydride (Ventron) in 150 ml of methanol. The cloudy mixture was stirred at room temperature for 12 hours, and 10% hydrochloric acid was added portionwise until the solution reached pH 8. The mixture was diluted with 65 ml of water and stirred for 10 hours, during which time a fluffy white solid precipitated. A little saturated brine was added, and the mixture was extracted with 3 x 75 ml of ether. The combined extracts were washed with saturated sodium bicarbonate, saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a colorless oil, which was unstable to vpc (column A, 150°), but was homogeneous by tlc (CHCl_3 , $R_f = 0.08$).

Bulb-to-bulb distillation (123° @ 0.1 mm) yielded 3.648 g (89.9%) of alcohol R-3 as a colorless oil: ir (CCl_4) 3620 (OH) and 1665 cm^{-1} (C=C); nmr (CCl_4) δ 3.71 (s, 3, CH_3O), 4.10 (br m, 1, >CHOH), and 6.31-7.43 (m, 5, >C=CH , ArH).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2$: C, 77.03; H, 8.31. Found: C, 76.99; H, 8.22.

1-m-Methoxyphenyl-trans-spiro[2.5]octan-4-ol (R-4)

A. Preparation of the zinc-copper couple. The procedure of LeGoff (141) was followed. To a solution of 2.5 g (12.5

mmole) of cupric acetate monohydrate (B&A, reagent) in 50 ml of glacial acetic acid at 80-90° was added 16.25 g (250 mmole) of zinc dust in one portion. After stirring for 2 min, the mixture was filtered, and the gray solid was washed with 4 x 50 ml of glacial acetic acid and 7 x 50 ml of dry ether and dried in vacuo.

B. Preparation of iodomethylzinc iodide (Simmons-Smith reagent (140)). The freshly prepared zinc-copper couple was covered with 250 ml of dry ether, and 22.3 ml (73.7 g, 0.275 mole) of diiodomethane (MC&B) was added in one portion. A small crystal of iodine was added, and the reaction was started by external heating. After 15 min, the reaction began to reflux spontaneously, which continued for an additional 15 min. After the reaction had subsided, external heat was again applied for an additional 25 min. The mixture was then allowed to cool to room temperature.

C. Cyclopropylation of the alcohol R-3. A solution of 3.75 g (17.2 mmole) of the allylic alcohol R-3 in 25 ml of dry ether was added to the freshly prepared Simmons-Smith reagent. A slightly exothermic reaction ensued, which was stirred for 4 hours at room temperature. The reaction was quenched by cooling the flask to 0° and slowly adding 25 ml of saturated ammonium chloride (frothing). The organic layer was washed with 400 ml each of 2% hydrochloric acid, water, 10% sodium bicarbonate, water, saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pres-

sure and rapid chromatography on 300 g of neutral alumina (act. III) separated the unreacted diiodomethane on elution with 1 l. of pet. ether. After 100 ml each of 2%, 5%, 10%, 25%, and 50% ether-pet. ether had eluted, 4.194 g of material was collected in 500 ml of ether. The product contained one volatile component by vpc (column A, 200°). The material was dried in vacuo to constant weight (3.92 g, 98.5%). An analytical sample of the desired cyclopropyl alcohol R-4 was prepared by bulb-to-bulb distillation (110-114° @ 0.1 mm):
 ir (CHCl₃) 3600 (OH) and 3050 cm⁻¹ (cyclopropyl C-H);
 nmr (CCl₄) δ 0.53-0.95 (m, 2, cyclopropyl CH₂), 1.91-2.25 (m, 1, cyclopropyl CH), 3.21-3.48 (m, 1, >CHOH), 3.75 (s, 3, CH₃O), and 6.45-7.31 (m, 4, ArH).

Anal. Calcd. for C₁₅H₂₀O₂: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.80.

1-m-methoxyphenyl-trans-spiro[2.5]octan-4-one (126)

To a solution of 261 mg (1.12 mmole) of the cyclopropyl alcohol R-4 in 15 ml of acetone, maintained at 0° was added excess Jones reagent (143) dropwise until a yellow color persisted. After 15 min, isopropanol was added until the mixture turned green. The mixture was then diluted with 50 ml of water and extracted with 3 x 20 ml of ether. The combined extracts were washed with 20 ml of saturated brine, 20 ml of saturated sodium bicarbonate, 20 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced

pressure yielded 235 mg of a pale yellow liquid, consisting of one volatile component by vpc (column A, 200°). Bulb-to-bulb distillation (104-108° @ 0.1 mm) afforded the cyclopropyl ketone 126, as a colorless liquid (186 mg, 72%): ir (CCl₄) δ 3050 (cyclopropyl C-H) and 1685 cm⁻¹ (C=O); nmr (CCl₄) δ 0.72-1.06 (m, 2, cyclopropyl CH₂), 2.16-2.76 (m, 3, cyclopropyl CH, CH₂C=O), 3.76 (s, 3, CH₃O), and 6.51-7.35 (m, 4, ArH).

Anal. Calcd. for C₁₅H₁₈O₂: C, 78.23; H, 7.88. Found: C, 78.37; H, 7.94.

Attempted direct cyclopropylation of enone R-2

To a mixture of 4.62 g (0.21 mole) of trimethyloxosulfonium iodide (144) and 0.504 g (0.021 mole) of dry sodium hydride was added 25 ml of dry dimethyl sulfoxide (frothing). When the gas evolution ceased, the flask was cooled to 0°, and 4.34 g (20 mmole) of the enone R-2 in 50 ml DMSO was added. The light brown suspension turned deep yellow. The mixture was stirred at 0° for 5 min and at room temperature for 2 hours, during which time the color changed to light green. The reaction was then heated to 55° and maintained at that temperature for 1.5 hours. The mixture was then poured into 100 ml of cold water. Extraction with 3 x 50 ml of water, saturated brine, drying over magnesium sulfate, and evaporation of the solvent afforded 4.25 g of a yellow oil. The vpc trace (column A, 200°) showed a complex mixture.

Column chromatography (CHCl_3) yielded, after 3.6 l. of fore-fractions, 1.7 g of material which had an ir spectrum resembling that of ketone 126. Bulb-to-bulb distillation of these combined fractions afforded 496 mg (10.8%) of ketone 126 which consisted of 95% of one volatile component by vpc (column A, 200°). The ir and nmr spectra were identical to those of the product obtained from the Simmons-Smith reaction on alcohol R-3, followed by Jones oxidation.

2-(2-m-Methoxyphenyl)ethyl-2-methylcyclohexanone (115)

A solution of 178 mg (7.74 mmole) of the cyclopropyl ketone 126 and 94 μl (74 mg, 1 mmole) of t-butyl alcohol in 5 ml of glyme was added to a solution of 40 mg (5.7 mmole) of lithium in 15 ml of ammonia. After 45 min at reflux, 180 μl (179 mg, 1 mmole) of HMPA was added. The ammonia was then evaporated in a nitrogen stream, and the mixture was warmed to 0° . With vigorous stirring, 18 ml of glyme and 1 ml of methyl iodide were added in one portion. A milky, white suspension formed almost immediately. After stirring for 1 hour, 80 ml of water was added, and the mixture was extracted with 3 x 40 ml of ether. The combined extracts were washed with 75 ml of 5% hydrochloric acid, 3 x 60 ml of water, 60 ml of saturated sodium bicarbonate, 60 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent afforded 179 mg of a pale yellow oil. The vpc trace (column A, 190°) indicated 2 components in a ratio of 9:1.

Chromatography on 20 g of silica gel afforded, after 200 ml of forefractions (1:1 pet. ether-benzene), 32 mg of material containing the major product in 80% purity (100 ml) and 109 mg of pure ketone 115 (550 ml). The total yield of the ketone 115, as estimated by vpc of the two fractions, was 69% (57% isolated). Bulb-to-bulb distillation (115-116° @ 0.1 mm) of the pure fractions yielded ketone 115 as a colorless oil: ir (CCl₄) 1700 cm⁻¹ (C=O); nmr (CCl₄) δ 1.08 (s, 3, angular CH₃), 3.73 (s, 3, CH₃O), and 6.46-7.26 (m, 4, ArH).

Anal. Calcd. for C₁₆H₂₂O₂: C, 78.01; H, 9.00. Found: C, 78.11; H, 9.00.

2-Methoxy-8a-methyl-6,7,8,8a,9,10-hexahydrophenanthrene (116)

To a solution of 246 mg (1 mmole) of the ketone 115 in 2.5 ml of dry benzene was added 75 ml of freshly prepared polyphosphoric acid (161). A cloudy, bright orange mixture formed immediately. After heating to 50°, the mixture was maintained at that temperature for 1 hour, and then poured into 450 g of an ice-water mixture with stirring. After the yellow color disappeared, the mixture was extracted with 3 x 100 ml of benzene. The combined extracts were washed with 200 ml each of water, saturated sodium bicarbonate, saturated brine, and dried (MgSO₄). The solvent was evaporated at reduced pressure, and the residue was subjected to chromatography on 25 g of silica gel. After 350 ml of pet.

ether and 50 ml each of 1%, 2% and 3% ether-pet. ether had eluted, 208 mg (91%) of a pale yellow solid was isolated in 200 ml of 4% ether-pet. ether. The solid product (mp 63-65°) consisted of one volatile component in 98.5% purity by vpc (column A, 200°).

Recrystallization from methanol afforded pure tricyclic olefin 116, mp 69-69.5°: ir (CHCl₃) 1635 cm⁻¹ (C=C); nmr (CCl₄) 1.00 (s, 3, angular CH₃), 3.75 (s, 3, CH₃O), 5.91 (br t, 1, J = 3.5 Hz, CH=C<), 6.16 (d, 2, J_{1,3} = 2 Hz, C-1 H), 6.70 (d of d, 1, J₃₄ = 7 Hz, J_{1,3} = 2 Hz, C-3 H), and 7.43 (d, 1, J₃₄ = 7 Hz, C-4 H).

Anal. Calcd. for C₁₆H₂₈O: C, 84.16; H, 8.83. Found: C, 84.01; H, 8.80.

2-Methoxy-8αβ-methyl-4bα,5,6,7,8,8a,9,10-octahydrophenanthrene (R-5b)

To a solution of 173 mg (0.754 mmole) of the tricyclic olefin 116 in 32 ml of hexane was added 50 mg of 10% palladium on carbon. The black suspension was stirred under 1 atmosphere of hydrogen for 22 hours. The mixture was then filtered through a bed of alumina (act III), which was washed several times with ether. Concentration of the filtrate and washing and bulb-to-bulb distillation of the residue (98° @ 0.08 mm) afforded 167 mg (96.3%) of a colorless liquid. The vpc trace (column A, 200°) indicated two volatile components in a ratio of 7:76: nmr (CDCl₃) δ 6.58 (s, 1, C-1 H), 7.12

(d, 1, $J = 10$ Hz, C-4 H); $\Delta_{1,4} = 0.54$ ppm (trans, 149).

The material was subjected to preparative vpc (column B, 200°), and the major product, the trans compound R-5b was isolated in >99% purity: ir (CCl_4) 1610 and 1575 cm^{-1} (C=C, 1,2,4-trisubst. benzene); nmr (CCl_4) δ 0.71 (s, 3, angular CH_3), 3.70 (s, 3, CH_3O), 6.50 (d, 1, $J_{1,3} = 2$ Hz, C-1 H), 6.55 (d of d, 1, $J_{1,3} = 2$ Hz, $J_{3,4} = 9$ Hz, C-3 H), and 6.98 (d, 1, $J_{3,4} = 9$ Hz, C-4 H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}$: C, 83.43; H, 9.63. Found: C, 83.35; H, 9.52.

8 α -Methyl-4,4 α ,5,6,7,8,8a,9,10-decahydrophenanthren-2(3H)-one (R-6)

A solution of 167 mg (0.726 mmole) of a 92:8 mixture of the trans tricyclic compound R-5b and its cis isomer R-5a in 20 ml of tetrahydrofuran was added over 10 min to a solution of 240 mg (34 mmole) of lithium in 62 ml of ammonia (distilled from sodium). After stirring for 15 min, a solution of 20 ml of dry t-butyl alcohol in 5 ml of tetrahydrofuran was added over 10 min. The blue solution was then stirred at reflux for $3\frac{1}{2}$ hours, and 25 ml of methanol was added, causing the blue color to disappear. The ammonia was allowed to evaporate overnight under a stream of dry nitrogen.

The residue was taken up in 100 ml of benzene and washed with 200 ml of water, 200 ml of saturated brine, and dried (MgSO_4). The solvent was evaporated, and the residue was

dissolved in 130 ml of methanol. The mixture was heated to reflux under nitrogen, and 55 ml of 5 M hydrochloric acid was added. The mixture was maintained at reflux for 2 hours. After cooling to room temperature, the reaction mixture was poured into 200 ml of saturated brine and extracted with 3 x 80 ml of benzene. The combined extracts were washed with 2 x 100 ml of water, 100 ml of saturated sodium bicarbonate, 100 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent yielded a yellow, partially crystalline solid.

The vpc trace (column A, 200°) showed a large peak comprising ca. 80% of the volatile material (ret. time, 2.0 min). After drying in vacuo overnight to remove any volatile impurities, the crude product was recrystallized from ether-hexane. The first crop of white crystals of enone R-6 weighed 91 mg (mp $125-128^\circ$). A second crop of 14 mg had mp $120-123^\circ$. Both crops showed only one volatile component by vpc (column A, 200°). The total yield, corrected for the purity of the starting material, was 74%.

An analytical sample was recrystallized from ether-hexane, mp $126-128^\circ$: ir (CHCl_3) 1660 (s, C=O) and 1615 cm^{-1} (C=C); nmr (CDCl_3) δ 0.98 (s, 3, angular CH_3), and 5.86 (br s, 1, $>\text{C}=\text{CH}$); uv (CH_3OH) 243 nm ($\epsilon = 14,400$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$: C, 82.52; H, 10.16. Found: C, 82.58; H, 10.07.

8a β ,10a β -Dimethyl-3,4,4a β ,4b α ,5,6,7,8,8a,9,10,10a-dodeca-
hydro-2(1H)-phenanthrenone (117)

A solution of lithium dimethylcuprate was prepared (152) from 347 mg (1.875 mmole) of cuprous iodide and 3.75 mmole of ethereal methyllithium in 18 ml of dry ether. After stirring for 10 min at 0°, 162 mg (0.743 mmole) of the unsaturated ketone R-6 in 12 ml of dry ether was added dropwise over $\frac{1}{2}$ hour, forming a bright yellow suspension. After 2 $\frac{1}{2}$ hours at 0°, the mixture was poured into 50 ml of a rapidly stirred solution of 2% hydrochloric acid, and extracted with 3 x 70 ml of ether. The combined extracts were washed with 50 ml each of water, dilute ammonia, saturated sodium bicarbonate, saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure yielded 187 mg of a white crystalline solid, consisting of 96% of one volatile component by vpc (column A, 200°)

Recrystallization from ether-hexane afforded 110 mg of white plates, mp 93-96°, which was >99% one volatile component by vpc. A second crop of crystals (19 mg, mp 85-87°) was >96% of the major product by vpc. The combined mother liquors were subjected to preparative tlc (1:1 benzene-chloroform), which afforded two crops of crystals, each containing the major volatile product in 97% purity by vpc. From the mother liquors of these second sets of crystals, an additional 6 mg of product, 96.6% of the major volatile product was isolated.

The total yield of the saturated ketone 117 was 161 mg

(92.6%). An analytical sample was recrystallized from ether-pentane, mp 96-98°: ir (CHCl₃) 1702 cm⁻¹ (C=O); nmr (CDCl₃) δ 0.90 (s, 3, angular CH₃) and 0.96 (s, 3, angular CH₃)

Anal. Calcd. for C₁₆H₂₆O: C, 81.99; H, 11.18. Found: C, 81.90; H, 11.17.

Attempted deoxygenation of the ketone 117

A. By Nagata's modified Wolff-Kishner reduction (154).

A mixture of 8.5 mg (0.0376 mmole) of the ketone 117, 58 mg (0.55 mmole) of hydrazine dihydrochloride (MC&B), 0.5 ml of hydrazine hydrate, and 15 ml of diethylene glycol was heated to 145° (internal temperature) in a flask equipped for the distillation of water. After 6½ hours, the mixture was cooled to 110°, and 2 g of potassium hydroxide was added. The mixture was heated under a stream of nitrogen until the temperature reached 175° (3 hours), and maintained at that temperature for 8 hours. After cooling to room temperature, the distillate and reaction mixture were combined and diluted with 100 ml of water. The mixture was extracted with 3 x 40 ml of ether, and the combined extracts were washed with 3 x 50 ml of water, 50 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent afforded 6 mg of an oil which showed strong carbonyl frequencies in the infrared spectrum. Filtration through 1.5 g of silica gel (pet. ether) afforded less than 1 mg of an oil whose vpc trace was identical to that of hydrocarbon 114 obtained from catalytic hyd-

rogenation of the dienes 109 and 110.

B. By reduction of the tosylhydrazone (155). A solution of 8 mg (0.0341 mmole) of the ketone 117, 25.3 mg (0.136 mmole) of p-toluenesulfonylhydrazide (Aldrich), and 3 ml of methanol was maintained at reflux for 3 hours, after which time no starting ketone could be detected by vpc (column A, 200°). To this mixture was added 11.34 mg (0.3 mmole) of sodium borohydride, and the mixture was maintained at reflux for an additional 6 hours. The solvent was evaporated, and the residue was subjected to chromatography of 1.5 g of silica gel impregnated with 10% silver nitrate. With pet. ether as eluent, less than 1 mg of material was isolated whose vpc trace (column A, 150°) was identical with the saturated hydrocarbon 114.

8a β , 10a β -Dimethyl-3,4,4a β ,4b α ,5,6,7,8,8a,9,10,10a-dodeca-
hydro-2-phenanthryl-N,N,N',N'-tetramethyldiaminophospho-
rodiamidate (S-1)

A solution of 54.5 mg (0.25 mmole) of the unsaturated ketone R-6 in 4 ml of dry ether was added dropwise over 15 minutes to a solution of lithium dimethylcuprate, prepared from 119 mg (0.625 mmole) of cuprous iodide and 1.250 mmole of ethereal methyllithium, with 6 ml of dry ether. After 2 hours at 0°, a vpc analysis (column A, 200°) of a quenched aliquot indicated complete disappearance of starting enone and formation of the saturated ketone 117 as the sole pro-

duct. To this mixture was added 0.2 ml of HMPA. The bright, yellow color that had formed disappeared, and a greenish, oily solid collected on the sides of the flask. To this was added 0.4 ml of the phosphorochloridate 148 (158) dropwise over 5 min. The oily solid coating the flask turned to a fine powder. After $2\frac{1}{2}$ hours, the mixture was added to 50 ml of dilute ammonia to dissolve the copper salts. The blue aqueous layer that formed was extracted with 3 x 30 ml of ether. The combined organic layers were washed with 3 x 30 ml of 5% hydrochloric acid, 30 ml of water, 30 ml of saturated sodium bicarbonate, 30 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 87 mg of a colorless oil, which consisted of one major high-boiling component in 95% abundance (column A, 230°).

Chromatography on 10 g of silica gel (ether, 100 ml, followed by 3:2 ether-ethyl acetate) yielded a colorless liquid, which was evaporatively distilled ($117^\circ @ 0.06 \text{ mm}$) to give 76 mg (86.8%) of the phosphorodiamidate S-1, as a colorless oil 97% one component by vpc (column A, 230°): ir (CHCl_3) 1675 cm^{-1} (C=C); nmr (CDCl_3) δ 0.81 (s, 3, angular CH_3), 1.06 (s, 3, angular CH_3), 2.68 (d, 12, $J = 10 \text{ Hz}$, CH_3N), and 5.03 (br s, 1, $>\text{C}=\text{CH}$).

Anal. Calcd. for $\text{C}_{20}\text{H}_{37}\text{N}_2\text{O}_2\text{P}$: C, 65.18; H, 10.12; N, 7.60; P, 8.40. Found: C, 65.05; H, 10.06; N, 7.52; P, 8.31.

8a β ,10a β -Dimethyl-3,4,4a β ,4b α ,5,6,7,8,8a,9,10,10a-dodecahyd-
rophenanthrene (S-2)

A solution of 69 mg (0.187 mmole) of the phosphorodiamide S-1 and 0.1 ml of t-butyl alcohol in 6 ml of dry tetrahydrofuran was added dropwise over 15 min to a blue solution of 25 mg (3.6 mmole) of lithium wire in 40 ml of ethylamine (distilled from sodium and lithium). After 2½ hours at reflux, the blue color faded, and 10 ml of ethanol was added. The mixture was then stirred under a slow stream of nitrogen to remove the amine. A vpc trace (column A, 170°) indicated one component which accounted for 95% of the volatile material.

The residue was poured into 50 ml of water and extracted with 3 x 50 ml of pet. ether. The combined extracts were washed with 2 x 50 ml of 10% hydrochloric acid, 50 ml of saturated sodium bicarbonate, 50 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure yielded 41 mg of a colorless liquid. Chromatography on 2 g of silica gel (pet ether) yielded an oil, which on bulb-to-bulb distillation (74° @ 0.55 mm) yielded 35 mg of the olefin S-2 in >99% purity by vpc (column A, 170°): ir (CHCl₃) 1645 cm⁻¹ (w, C=C); nmr (CDCl₃) δ 0.83 (s, 3, angular CH₃), 1.05 (s, 3, angular CH₃), 5.26 (d, 1, J_{1,2} = 7 Hz, C-1 H), and 5.63 (d of m, 1, J_{1,2} = 7 Hz, C-2 H).

Anal. Calcd. for C₁₆H₂₆: C, 88.00; H, 12.00. Found: C, 87.96; H, 11.90.

8a β ,10a β -Dimethyl-1,2,3,4,4a β ,4b α ,5,6,7,8,8a,9,10,10a-tetra-decahydrophenanthrene (114)

A. From the tricyclic dienes 109 and 110. To a solution of 49 mg (0.226 mmole) of the diene mixture in 5 ml of ethanol was added 10 mg of 10% palladium on carbon in 1 ml of ethanol. The black suspension was stirred under an atmosphere of hydrogen for 1 hour. Filtration through a bed of silica gel and evaporation of the solvent yielded 48 mg (96%) of a colorless oil, which contained minute traces of unsaturated material by nmr. Filtration through 1.5 g of silica gel impregnated with 10% silver nitrate (pet. ether) afforded the pure hydrocarbon 114 (evap. dist., 73-75° @ 0.35 mm); ir (neat) 2950, 1450 (C-H), and 1375 cm⁻¹ (CH₃); nmr (CDCl₃) δ 0.73 (s, 3, angular CH₃) and 1.00 (s, 3, angular CH₃).

Anal. Calcd. for C₁₆H₂₈: C, 87.19; H, 12.81. Found: C, 87.22; H, 13.00.

B. From the tricyclic olefin S-2. To a solution of 30 mg of the tricyclic olefin S-2 in 8 ml of hexane was added 10 mg of 10% palladium on carbon. The black suspension was stirred under an atmosphere of hydrogen for 5 hours. Filtration of the mixture through neutral alumina (act III) and evaporation of the solvent yielded 30 mg (100%) of the saturated hydrocarbon 114 as a colorless oil, consisting of >98% of one volatile component by vpc (column A, 170°). The ir and nmr spectra were superimposable with the product prepared in part A, above. Peak enhancement of the product from the

two route indicated one volatile component (column A, 170°).

8a β ,10a β -Dimethyl-1,2 α ,3,4,4a β ,4b α ,5,6,7,8,8a,9,10,10a-tetradecahydro-2 β -phenanthrenol (153)

A solution of 49 mg (0.209 mmole) of the tricyclic ketone 117 in 3 ml of dry tetrahydrofuran was added over 10 min to a suspension of 166 mg (0.653 mmole) of lithium tri(t-butoxy)-aluminum hydride (Ventron) in 7 ml of dry tetrahydrofuran, maintained at 0°. After 5 hours, an additional 150 mg of hydride was added, and the mixture was stirred at room temperature for 4 hours. The mixture was then poured into 50 ml of water and extracted with 3 x 30 ml of ether. The combined extracts were washed with 40 ml of saturated sodium bicarbonate, 40 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent afforded 49 mg (100%) of the alcohol 153, as a white solid consisting of a single component by vpc (column A, 220°): ir (CHCl₃) 3600 cm⁻¹ (OH); nmr (CDCl₃) δ 0.80 (s, 3, angular CH₃), 1.21 (s, 3, angular CH₃), and 4.16 (m, 1, W_{h/2} = 9 Hz, C-2 α H).

The product was recrystallized twice from ether-hexane to afford colorless microneedles, mp 133-135°.

Anal. Calcd. for C₁₆H₂₈O: C, 81.29; H, 11.94. Found: C, 81.32; H, 11.79.

2 β -p-Bromobenzoxy-8a β ,10a β -dimethyl-1,2 α ,3,4,4a β ,4b α ,5,6,7,-
8,8a,9,10,10a-tetradecahydrophenanthrene (154)

A mixture of 38 mg (0.161 mmole) of the alcohol 153, 43.8 mg (0.2 mmole) of p-bromobenzoyl chloride, and 3 ml of dry benzene containing 0.2 ml of dry pyridine was stirred at room temperature for 3 hours and then heated to 65°. After 1 hour at 65°, an additional 45 mg of the acid chloride was added. After 15 hours at 65-69°, the mixture was concentrated to a solid. On recrystallization of the crude product from acetone, 5 mg of a solid was isolated which appeared to be mostly unreacted acid chloride by ir.

Preparative tlc (1:1 benzene-chloroform) afforded 53 mg of white crystals (78% yield), which consisted of 95% of one volatile component by vpc (column A, 250°): ir (CHCl₃) 1710 (C=O) and 1590 cm⁻¹ (aromatic C=C); nmr (CCl₄) δ 0.83 (s, 3, angular CH₃), 1.18 (s, 3, angular CH₃), 5.30 (m, 1, W_{h/2} = 8 Hz, C-2 α H), 7.55 (d, 2, J = 8 Hz, C-3',5' H), and 7.88 (d, 2, J = 8 Hz, C-2',6' H).

The ester 154 was purified by two recrystallizations from acetone to yield colorless prisms, mp 149.5-151.5°, consisting of one volatile component by vpc (column A, 250°). In addition some material crystallized in clusters, mp 163-166°, which were ca. 90% of the major product by vpc.

The prisms were separated and submitted for combustion analysis and x-ray structure determination.

Anal. Calcd. for C₂₃H₃₁BrO₂: C, 65.87; H, 7.45;

Br, 19.05. Found: C, 65.94; H, 7.39; Br, 18.88.

5,6-Dimethyl-1,10-bis-(trimethylsilyl)-trans-5-en-1,9-diyne
(T-1) (75,88)

A. Preparation of propargylmagnesium bromide. The Grignard reagent was prepared by the method of Gaudemar (163). To a mixture of 28.8 g (1.2 mole) of magnesium turnings and 20 mg of mercuric chloride covered with 150 ml of dry ether, maintained at 15°, was added 2 ml of neat propargyl bromide (Aldrich, redistilled). After about 5 min, a vigorous, exothermic reaction ensued, and an ice bath was used to keep the temperature below 30°. The remainder of the propargyl bromide (total 143 g, 1.2 mole) was added in 300 ml of ether over 3½ hours, keeping the temperature at 10-20°. When the addition was complete, the mixture was filtered through a glass wool plug and stored at -20° overnight.

B. Coupling of the Grignard with the dibromide L-2. To the above Grignard solution was added a solution of 72.6 g (0.3 mole) of the dibromide L-2 in 100 ml of dry tetrahydrofuran over 10 min. After about half of the solution was added, a white precipitate formed, and the temperature rose to 20°. The addition was discontinued momentarily until the exothermic reaction had subsided. The addition was then continued, keeping the temperature at 10-15°. When the addition was complete, the mixture was allowed to warm to room temperature and stir for an additional 1 ¾ hours, after which

120 ml of saturated ammonium chloride was added. The aqueous layer was extracted several times with ether, and the combined organic layers were washed with saturated brine and dried (MgSO_4). Evaporation of the solvent afforded ca. 60 g of a light yellow liquid. As an additional precaution against moisture, the product was redissolved in benzene, and the solvent was evaporated at reduced pressure.

A vpc trace (column A, 80°) showed one major volatile component in ca. 80% abundance, along with two minor peaks of about 10% each: ir (neat) 3300 (s, $\text{C}\equiv\text{C}-\text{H}$), 2120 ($\text{C}\equiv\text{C}$), and 1960 cm^{-1} (w, $\text{>C}=\text{C}=\text{CH}_2$).

C. Silylation. The crude coupling product was dissolved in 50 ml of dry tetrahydrofuran and added dropwise over 45 min to a solution of ethylmagnesium bromide (prepared from 87.2 g, 0.8 mole, of ethyl bromide and 19.2 g, 0.8 mole, of magnesium turnings in 400 ml of dry tetrahydrofuran). During the addition, the mixture was kept at $40-45^\circ$ with a cooling bath. In addition to a great deal of heat, vigorous evolution of ethane and the formation of a gelatinous gray precipitate were observed during the addition. The mixture was heated at reflux for 1 hour, then cooled to 40° , and 94 g (0.863 mole) of neat trimethylchlorosilane (Aldrich, distilled from phosphorous pentoxide) was added dropwise over 45 min. A thick white solid precipitated making the stirring very difficult. This was partially alleviated by the addition of 100 ml of tetrahydrofuran. The mixture was then heated to

reflux and maintained at reflux for 1 hour. After cooling to room temperature, a mixture of 100 ml of saturated ammonium chloride and 10 ml of concentrated ammonium hydroxide was added with cooling. The aqueous layer was extracted with ether, and the combined organic layers were washed with water, saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a yellow, semi-crystalline solid.

The crude product was dissolved in 75 ml of warm ethanol and kept at -20° overnight, during which time the product crystallized. Filtration of the mixture (cold ethanol wash) yielded 71.5 g of the disilyl compound T-1, white plates, mp $65-67^\circ$ (lit. (88), mp $65-67^\circ$). Concentration of the filtrate and washings at reduced pressure yielded 3.6 g of a second crop of white crystals, mp $61.5-65^\circ$. Both crops were >99% of one volatile component by vpc (column A, 150°). The total yield, based on the two crops, was 75.1 g (82%): ir (neat) 2170 (c C), 1250, and $835-875\text{ cm}^{-1}$ (CH_2Si); nmr (CDCl_3) δ 0.11 (s, 18, $(\text{CH}_3)_3\text{Si}$), 1.68 (s, 6, $\text{CH}_2\text{C}=\text{CCH}_2$), and 2.26 (s, 8, CH_2).

5,6-Dimethyl-trans-5-decen-1,9-diyne (T-2) (75,88).

The procedure of Schmidt and Arens (169) was followed. To a solution of 58.7 g (0.192 mole) of the disilyl compound T-1 in 600 ml of absolute ethanol, maintained at 30° , was added a solution of 81.5 g (0.480 mole) of silver nitrate

in 180 ml of water and 180 ml of 95% ethanol dropwise over $\frac{1}{2}$ hour. A thick, white precipitate formed. After stirring for 2 hours, a solution of 62.5 g (0.960 mole) of potassium cyanide in 500 ml of water was added over 20 min. When the addition was complete, the mixture clarified somewhat. The reaction was stirred until it had cooled to room temperature, after which it was poured into 1 l. of water and extracted with 4 x 300 ml of pet. ether. The combined extracts were washed with 3 x 500 ml of water, 500 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure and distillation of the residue afforded 30.2 g (98.3%) of the enediyne T-2, as a colorless liquid, bp 85.5-86.0° @ 4.3 mm. The distilled product consisted of one volatile component by vpc (column A, 100°): ir (neat) 3290 ($\text{C}\equiv\text{C}-\text{H}$) and 2120 cm^{-1} ($\text{C}\equiv\text{C}$); nmr (CDCl_3) δ 1.70 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 1.93 (m, 2, $\text{C}\equiv\text{C}-\text{H}$), and 2.26 (br s, 8, CH_2).

6,7-Dimethyl-trans-6,10-undecadien-2-ynol (T-5) (75)

A solution of 30.2 g (0.189 mole) of the enediyne T-2 in 300 ml of dry tetrahydrofuran was cooled to 0°, and a solution of disiamylborane (prepared from 0.19 mole of a solution of diborane and excess 2-methyl-2-butene) was added dropwise over 2 hours. The mixture was then stirred at room temperature for 4 hours, and 45 ml of glacial acetic acid was added dropwise over $\frac{1}{2}$ hour. The mixture was stirred for an additional 2 hours, and then poured into $1\frac{1}{2}$ l. of cold

water. The layers were separated, and the aqueous layer was extracted with 3 x 200 ml of ether. The combined organic layers were washed with 2 x 500 ml of saturated sodium bicarbonate, 500 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent under a 12" Vigreux column afforded an opaque liquid. The vpc trace (column A, 90°) indicated a mixture of three components in a ratio of 15:45:40.

Comparison with previous experiments (75) indicated that these three components were the doubly-reduced triene T-4, the desired dienyne T-3, and the unreacted enediyne T-2, respectively. Distillation of the crude product mixture through a 6" Vigreux column at 3 mm afforded the following fractions:

<u>Fraction</u>	<u>Bp (3 mm)</u>	<u>Weight</u>	<u>Composition (vpc)</u>
A	65-69 $^\circ$	12.4 g	<u>T-4</u> : <u>T-3</u> : <u>T-2</u> (1:1:0)
B	69-73	19.0 g	<u>T-4</u> : <u>T-3</u> : <u>T-2</u> (1:5:2)
residue	-	22.6 g	<u>T-3</u> : <u>T-2</u> (1:8)

In addition to the expected components, each fraction contained a substantial amount of boronic impurities (75,162). Each fraction was subjected to filtration through silica gel (10 g/ g product) with pet. ether eluent. The products thus obtained were subjected to high pressure chromatography (pet. ether). From these purifications, 7.4 g of pure enediyne T-2 was recovered, and 13.2 g of a 1:8 mixture of triene T-4 and dienyne T-3 were obtained.

The latter mixture was dissolved in 50 ml of dry tetrahydrofuran and added dropwise over $\frac{1}{2}$ hour to a solution of 0.163 mole of ethylmagnesium bromide in tetrahydrofuran. Considerable heat and gas were evolved during the addition. After the mixture was added, the reaction was maintained at reflux for 1 hour, (solution made red with 1,10-phenanthroline). The reaction mixture was then cooled to about 20° , and dry paraformaldehyde was depolymerized at $160-180^{\circ}$ and bubbled through the Grignard solution with a stream of dry nitrogen. A cooling bath was used to keep the temperature below 25° during the formaldehyde addition. After about 20 min, the red color faded to light gray, and the temperature began to drop. The addition was continued for an additional 10 min. The vpc trace (column A, 150°) of a hydrolyzed aliquot indicated complete disappearance of the enediyne T-3 and the presence of a new, high-boiling peak (T-5), as well as the triene T-4, which was inert to the reaction conditions. The mixture was cooled to 0° , and 75 ml of saturated ammonium chloride was added slowly. The two-phase mixture was then poured into 200 ml of water. The aqueous layer was extracted with 3 x 75 ml of ether. The combined organic layers were washed with 2 x 100 ml of water, 100 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 16.3 g of a yellow liquid.

The crude product was subjected to column chromatography on 140 g of silica gel. The triene T-4 was obtained (1.3 g)

with 500 ml of pet. ether eluent. On gradually increasing the ether content of the eluent to 40%, 10.7 g (39.2%, based on recovered T-2) of the propargylic alcohol T-5 was obtained with 1 l. of 40% ether-pet. ether.

Bulb-to-bulb distillation (89° @ 0.15 mm) yielded alcohol T-5, as a colorless liquid: ir (neat) 3700 (OH), 2290, 2230 (C=C), 1640, 1000, and 910 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.66 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 1.73 (s, 1, OH), 4.23 (br s, 2, CH_2OH), 4.80-5.20 (m, 2, $\text{CH}=\text{CH}_2$), and 5.73 (br m, 1, $\text{CH}=\text{CH}_2$).

6,7-Dimethyl-3-iodo-trans,trans-2,6,10-undecatrienol (T-6) (75)

The procedure of Katzenellenbogen (172b) was followed. To a suspension of 30.45 g (0.564 mole) of sodium methoxide in 625 ml of dry tetrahydrofuran was added 125 ml of a 2.06 M solution and 13.3 ml of a 1.86 M solution of lithium aluminum hydride in tetrahydrofuran* (0.282 mole) over 10 min. The mixture was stirred at room temperature for 30 min, and a solution of 27.1 g (0.141 mole) of the propargylic alcohol T-5 was added over 20 min. An exothermic reaction ensued, accompanied by vigorous gas evolution. The mixture was heated at reflux for $1\frac{1}{2}$ hours, after which it was cooled to -5° , and

* Standard solutions of lithium aluminum hydride were prepared (172b) by dissolving n grams of commercial lithium aluminum hydride in $10n$ ml of dry tetrahydrofuran, stirring for 2 hours, and filtration through a pad of Celite and glass wool under nitrogen in a Schlenk tube. The concentration was determined by hydrogen evolution from 10% hydrochloric acid.

26.3 ml (23.6 g, 0.282 mole) of dry ethyl acetate was added to destroy the excess hydride. The mixture was cooled to -78° , and 178 g (0.701 mole) of iodine in 310 ml of dry tetrahydrofuran was added dropwise over 40 min. The reaction mixture turned a deep red-brown. The flask was quickly warmed to 0° in an ice bath and allowed to stir until the temperature reached 25° . The reaction was quenched by the addition of 18 ml of water, followed by 600 ml of ether. After 2 hours of stirring at room temperature, the mixture was poured into 1 l. of ether. Magnesium sulfate was added, the mixture was filtered, and the solid was washed several times with ether. The combined filtrate and washings were washed with 2 x 150 ml of 10% sodium hydroxide, saturated with sodium thiosulfate until the iodine color disappeared. The washings were combined with an emulsion made from dissolving the filtered solid into 2 l. of water and extraction with ether, washed with saturated brine, and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure yielded 43.85 g (97.1%) of the 3-iodo alcohol T-6: ir (neat) 3700-3650 (OH), 1640, 1000, and 910 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.61 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 4.18 (br d, 2, $J = 5.5\text{ Hz}$, CH_2OH), 4.80-5.21 (m, 2, $\text{CH}=\text{CH}_2$), 5.73 (br m, 1, $\text{CH}=\text{CH}_2$), and 5.83 (d, 1, $J = 5.5\text{ Hz}$, $-\text{IC}=\text{CHCH}_2$).

3,6,7-Trimethyl-trans,trans-2,6,10-undecadienol (T-7) (75)

The procedure of Corey and Posner (173) was followed.

The crude 3-iodo alcohol T-6 (0.137 mole) in 100 ml of dry

hexane was added over $\frac{1}{2}$ hour to a solution of lithium dimethylcuprate, prepared from 134.1 g (0.705 mole) of cuprous iodide and 1.41 mole of ethereal methyllithium in ether, maintained at 0° . The gray suspension turned bright yellow, and the mixture was stirred at 0° overnight. To the mixture was added 190 ml of dry methyl iodide over $\frac{1}{2}$ hour, followed by 300 ml of saturated ammonium chloride over 1 hour (frothing). A gray precipitate formed during the aqueous addition. The mixture was poured into a solution containing 500 ml each of concentrated ammonium hydroxide and water. The aqueous layer was extracted with 2 x 100 ml of the ammonia-water solution, 100 ml of 5% hydrochloric acid, 100 ml of saturated sodium bicarbonate, and dried (MgSO_4). Evaporation of the solvent at reduced pressure yielded 28.9 g (100% crude) of an amber oil, which was combined with 24.25 g of product from a previous run.

The vpc trace (column A, 190°) indicated $<1\%$ of the 3-des-methyl alcohol and a mixture of ca. 95:5 of the desired 3-methyl alcohol T-7 and the 2-methyl isomer: ir (neat) 3650-3100 (OH), 1670 ($>\text{C}=\text{CH}$), 1645, 995, and 910 cm^{-1} ($\text{CH}=\text{CH}_2$); nmr (CDCl_3) δ 1.65 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 1.70 (d, 3, $\text{J} = 1.5$ Hz, $\text{CH}_3\text{C}=\text{CH}$), 6.16 (d, 2, $\text{J} = 6.5$ Hz, CH_2OH), 4.80-5.21 (m, 2, $\text{CH}=\text{CH}_2$), 5.45 (br t, 1, $\text{J} = 6.5$ Hz, $>\text{C}=\text{CH}$), and 5.66 (br m, 1, $\text{CH}=\text{CH}_2$).

1-Chloro-3,6,7-trimethyl-trans,trans-2,6,10-undecatriene
(T-8) (75)

The method of Lee, *et al.*, (122) was employed. A solution of 0.254 mole of the crude allylic alcohol T-7 and 79.7 g (0.304 mole) of triphenylphosphine were dissolved in 300 ml of dry carbon tetrachloride and heated to reflux. The mixture was maintained at reflux for 3 hours, during which time white triphenylphosphine oxide precipitated. The reaction was quenched by the addition of 2.5 ml of methanol, and the mixture was heated at reflux for an additional 10 min. After cooling to 0°, 500 ml of pre-cooled pet. ether was added, causing a heavy, white solid to precipitate. The mixture was filtered, and the solid was washed several times with cold pet. ether. The filtrate and washings were concentrated at reduced pressure, and an additional 500 ml of cold pet. ether was added, precipitating more triphenylphosphine oxide. Evaporation of the solvent at reduced pressure afforded an amber oil, which was distilled to give the chloride T-8, bp 85-92 @ 0.2 mm, as a pale yellow oil (43.5 g, 75.6% from the propargylic alcohol T-5).

The distilled product was stored at -20° for 1 day and then used immediately in the next reaction: ir (neat) 1665 ($>C=CH$), 1640, 995, and 913 cm^{-1} ($CH=CH_2$); nmr ($CDCl_3$) δ 1.65 (s, 6, $CH_3C=CCH_3$), 1.76 (d, 3, $J = 1.5$ Hz, $CH_3C=CH$), 4.11 (d, 2, $J = 8$ Hz, CH_2Cl), 4.80-5.21 (m, 2, $CH=CH_2$), 5.48 (br t, 1, $J = 8$ Hz, $>C=CH$), and 5.66 (br m, 1, $CH=CH_2$).

1-m-Methoxyphenyl-4,7,8-trimethyl-trans,trans-3,7,11-dodeca-
triene (T-9) (75)

The chloride T-8 was coupled with m-methoxybenzylmagnesium chloride according to the procedure of Stork, et al (174). To a solution of 43.5 g (0.192 mole) of the chloride T-8 in 200 ml of dry tetrahydrofuran and 200 ml of dry HMPA was slowly added a solution of m-methoxybenzylmagnesium chloride (prepared from 134.9 g (0.862 mole) of m-methoxybenzyl chloride and 82.8 g (3.448 mole) of magnesium turnings and a few crystals of 1,10-phenanthroline in 800 ml of dry tetrahydrofuran). During the initial stages of the addition, the red color that formed as the Grignard was added quickly lightened to yellow, and a large amount of heat evolved. After about 25% of the Grignard solution was added (1 hour), the red color persisted, and the temperature began to drop. The remainder of the Grignard was added over an additional 3 hours, and the mixture was stirred at room temperature overnight. The reaction mixture was then cooled to 0°, and 100 ml of saturated ammonium chloride was carefully added. The aqueous layer was extracted with 3 x 300 ml of ether. The combined organic layers were washed with 6 x 300 ml of water, 300 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a light yellow oil, which consisted of one high-boiling product (column A, 210°) with about 3% of contaminants. In addition, the bis-1,2-m-methoxyphenylethane (165) was present in about 16% of

the mixture. Also, there was a great deal of low-boiling m-methyl anisole, which was removed by distillation (bp 38° @ 1.0 mm) (55.7 g).

The amber residue (80.5 g) was distilled at 0.001 mm to give, after a small forerun, the following fractions:

<u>Fraction</u>	<u>Bp (0.001 mm)</u>	<u>Weight</u>	<u>Composition (165:T-9)</u>
1	124-131 $^{\circ}$	1.80 g	1:1
2	131-136 $^{\circ}$	1.18 g	1:1
3	136-140 $^{\circ}$	34.12 g	1:3
4	140-152 $^{\circ}$	27.9 g	0:1 (98.3% pure)

Fraction 3 was redistilled to give the following:

3-1	75-102 $^{\circ}$	0.675 g	mixture
3-2	122-136 $^{\circ}$	4.35 g	3:7
3-3	136-144 $^{\circ}$	6.67 g	3:7
3-4	144-148 $^{\circ}$	11.90 g	2:8
3-5	148 $^{\circ}$	10.10 g	2:98

Fractions 3-2, 3-3, and 3-4 were combined with fractions 1 and 2. Chromatography on 600 g of silica gel afforded, after 500 ml each of 1% and 2% ether-pet. ether, and 2 l. of 4% ether-pet. ether, 15.8 g of triene T-9, consisting of 98% of one volatile component by vpc (column A, 210 $^{\circ}$). The total yield of triene T-9 was 53.6 g (89.3%): ir (neat) 1640, 995, 910 ($\text{CH}=\text{CH}_2$), and 1615-1585 cm^{-1} (q, aromatic $\text{C}=\text{C}$); nmr (CDCl_3) δ 1.60 (d, 3, $J = 1.5$ Hz, $\text{CH}_3\text{C}=\text{CH}$), 1.63

(s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 3.80 (s, 3, CH_3O), 4.80-5.40 (m, 3, $\text{CH}=\text{CH}_2$, $\text{>C}=\text{CH}$), 5.66 (br m, 1, $\text{CH}=\text{CH}_2$), and 6.63-7.50 (m, 4, ArH).

12-m-Methoxyphenyl-5,6,9-trimethyl-trans,trans-5,9-dodeca-
dienol (T-10) (75)

A solution of 10.1 g (32.3 mmole) of the triene T-9 (98% one volatile component, containing 2% of the diphenylethane 165 as internal standard) in 10 ml of dry tetrahydrofuran was cooled to 0° , and 47.9 ml of a 6.76 M solution of disiamylborane (32.3 mmole) was added in one portion. After $\frac{1}{2}$ hour, a vpc trace (column A, 210°) showed ca. 98% reaction. After 5 ml of additional disiamylborane was added (3.38 mmole), a second vpc trace indicated complete consumption of starting material. After $2\frac{1}{2}$ hours of stirring at 0° , 1 ml of water was added (mild frothing), followed by 40 ml of 3N sodium hydroxide and 15 ml of 30% hydrogen peroxide (added dropwise over $\frac{1}{2}$ hour). The temperature rose to 30° during the peroxide addition. After the addition was complete, the mixture was heated to $40-45^\circ$ and maintained at that temperature for 2 hours. The mixture was then poured into 200 ml of water and extracted with 4 x 60 ml of ether. The combined extracts were washed with 100 ml of water, 100 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a colorless liquid, which was dried in vacuo to remove the 3-methyl-2-butanol by-product.

The residue (10.8 g) was chromatographed on 176 g of Florisil (20% ether-pet. ether) to afford, after 400 ml of forefractions, 9.05 g (84.8%) of alcohol T-10 in 2.15 l. of eluent. The product consisted of >98% of one volatile component by vpc (column A, 280°): ir (CHCl₃) 3620 (OH), 1665 (w, >C=CH), and 1615-1585 cm⁻¹ (q, aromatic C=C); nmr (CDCl₃) δ 1.40 (s, 1, OH), 1.60 (d, 3, J = 1.5 Hz, CH₃C=CH), 1.63 (s, 6, CH₃C=CCH₃), 3.66 (t, 2, J = 6.5 Hz, CH₂OH), 3.80 (s, 3, CH₃O), 5.21 (br t, 1, J = 5 Hz, >C=CH), and 6.61-7.40 (m, 4, ArH).

12-m-Methoxyphenyl-5,6,9-trimethyl-trans,trans-5,9-dodeca-
dienal (K-1) (75)

The chromium trioxide-dipyridine complex was prepared (94b) from 6 g (60 mmole) of chromium trioxide and 9.62 ml (9.48 g, 120 mmole) of dry pyridine in 150 ml of dry dichloromethane. After 20 min, a solution of 3.3 g (10 mmole) of the dienol T-10 in 5 ml of dichloromethane was added. After an additional 20 min, the mixture was filtered through a bed of Florisil, which was washed several times with ether. The filtrate and washings were concentrated at reduced pressure to a yellow oil, which was dissolved in 200 ml of ether and washed with 100 ml each of 5% sodium hydroxide, 5% hydrochloric acid (twice), saturated sodium bicarbonate, saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure afforded a pale yellow oil, which was ca. 95%

of one volatile component by vpc (column A, 280°): ir (CHCl₃) 2730 (CHO), 1720 (C=O), and 1615-1585 cm⁻¹ (aromatic C=C); nmr (CDCl₃) δ 1.60 (masked d, 3, CH₃C=CH), 1.63 (s, 6, CH₃C=CCH₃), 3.80 (s, 3, CH₃O), 5.20 (br t, 1, J = 7 Hz, >C=CH), 6.61-7.41 (m, 4, ArH), and 9.75 (t, 1, J = 2 Hz, CHO).

12-m-Methoxyphenyl-5,6,9-trimethyl-trans,trans-5,9-dodeca-
dienoic acid (U-1)

To a well-stirred solution of 10 mmole of the aldehyde K-1 (crude), 3.94 g (23.2 mmole) of silver nitrate, 5 ml of water, and 50 ml of absolute ethanol was slowly added 50 ml of a potassium hydroxide stock solution (made from 21 g of potassium hydroxide in 350 ml of water). There was an immediate formation of a heavy, black precipitate. After two hours of stirring at room temperature, the mixture was filtered, and the gray-black solid was washed with 100 ml of water. The combined filtrate and washings were extracted with 3 x 100 ml of ether. The aqueous layer was acidified to pH 2 and extracted with 3 x 75 ml of ether. The combined acid extracts were washed with 50 ml each of water, saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure afforded 3.00 g (87.5% from alcohol T-10) of the acid U-1, as a pale yellow oil.

An analytical sample was prepared by bulb-to-bulb distillation (184° @ 0.0005 mm): ir (CHCl₃) 3400-2800 (OH), and 1710 cm⁻¹ (C=O); nmr (CDCl₃) δ 1.60 (d, 3, CH₃C=CH),

1.63 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 3.80 (s, 3, CH_3O), 5.21 (br t, 1, $\text{J} = 6 \text{ Hz}$, $\text{>C}=\text{CH}$), and 6.61-7.41 (m, 4, ArH).

Anal. Calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_3$: C, 76.70; H, 9.36. Found: C, 76.79; H, 9.38.

12-m-Methoxyphenyl-2,5,6,9-tetramethyl-trans,trans-5,9-dodecadienoic acid (U-2)

A solution of 1.44 ml (1.045 g, 10.35 mmole) of dry diisopropylamine in 6 ml of dry tetrahydrofuran was cooled to -20° , and 4.31 ml of a 2.13 M solution of n-butyllithium in hexane (9.28 mmole) was added at a rate so as to keep the temperature below -5° . When the addition was complete, a solution of 1.424 g (4.14 mmole) of the carboxylic acid U-1 in 1.5 ml of dry tetrahydrofuran was added at a rate so as to keep the temperature below 2° . After 15 min of stirring, 1.04 ml of HMPA was added, causing the amber solution to turn deep red. After 15 min, 0.374 ml (0.852 g, 6 mmole) of dry methyl iodide was added. The color immediately turned light yellow, and the temperature rose to 23° . After stirring at room temperature for $1\frac{1}{2}$ hours, the mixture was poured into 50 ml of 5% sodium hydroxide and extracted with 3 x 30 ml of ether. The combined extracts were washed with 2 x 20 ml of 5% sodium hydroxide. The combined aqueous solutions were acidified to pH 2 and extracted with 3 x 75 ml of ether. The combined acid extracts were washed with 2 x 50 ml of 10% hydrochloric acid, 2 x 50 ml of saturated brine, and dried

(MgSO₄). Evaporation of the solvent at reduced pressure afforded 1.430 g (97%) of a yellow oil.

An analytical sample was prepared by bulb-to-bulb distillation (178° @ 0.0005 mm): ir (CHCl₃) 3450-2620 (OH) and 1705 cm⁻¹ (C=O); nmr (CDCl₃) δ 1.21 (d, 3, J = 7 Hz, CH(CH₃)COOH), 1.60 (masked d, 3, CH₃C=CH), 1.63 (s, 6, CH₃C=CCH₃), 3.80 (s, 3, CH₃O), 5.20 (br t, 1, J = 6.5 Hz, >C=CH), and 6.61-7.41 (m, 4, ArH).

Anal. Calcd. for C₂₃H₃₄O₃: C, 77.05; H, 9.56. Found: C, 77.16; H, 9.61.

12-m-Methoxyphenyl-2,5,6,9-tetramethyl-trans,trans-5,9,-dodecadienol (U-3)

A solution of 228 mg (6 mmole) of lithium aluminum hydride in 20 ml of dry ether was cooled to 0°, and 1.41 g (3.96 mmole) of the carboxylic acid U-2 in 5 ml of ether was added over 10 min. Hydrogen gas evolved during the addition. The mixture was allowed to warm to room temperature and stir overnight. The excess hydride was decomposed by the dropwise addition of 1 ml of water. When the gray suspension turned white (½ hour), magnesium sulfate was added. The mixture was stirred for 1 hour, filtered, and the white solid was washed several times with ether. Evaporation of the solvent afforded a colorless oil, containing 93% of one volatile component by vpc (column A, 280°). Chromatography on 100 g of Florisil afforded, after 100 ml each of 1%, 2%, 4%, and 7%

ether-pet. ether, and 800 ml of 10% ether-pet. ether, 1.274 g (93.5%) of the alcohol U-3, in 1.1 l. of 20% ether-pet. ether.

A chromatographic fraction containing the major product in 93% purity was used for combustion analysis and spectra (bulb-to-bulb distillation, 160° @ 0.0008 mm): ir (CHCl_3) 3620 (OH) and 1670 cm^{-1} ($>\text{C}=\text{CH}$); nmr (CDCl_3) δ 0.95 (d, 3, $J = 6$ Hz, $\text{CH}(\text{CH}_3)-$), 1.38 (s, 1, OH), 1.60 (d, 3, $J = 1.5$ Hz, $\text{CH}_3\text{C}=\text{CH}$), 1.65 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 3.52 (d, 2, $J = 5$ Hz, CH_2OH), 3.83 (s, 3, CH_3O), 5.23 (t, 1, $J = 6$ Hz, $>\text{C}=\text{CH}$), and 6.61-7.41 (m, 4, ArH).

Anal. Calcd. for $\text{C}_{23}\text{H}_{36}\text{O}_2$: C, 80.18; H, 10.53. Found: C, 80.05; H, 10.62.

12-m-Methoxyphenyl-2,5,6,9-tetramethyl-trans,trans-5,9-dodecadienal (U-4)

The chromium trioxide-dipyridine complex was prepared (94) from 500 mg (5 mmole) of chromium trioxide and $796\ \mu\text{l}$ (791 mg, 10 mmole) of dry pyridine in 12.5 ml of dry dichloromethane. After 20 min, 251 mg (0.729 mmole) of the alcohol U-3 in 2 ml of dry dichloromethane was added. After $\frac{1}{2}$ hour of stirring at room temperature, the mixture was decanted through a bed of Florisil, which was washed several times with ether. Evaporation of the solvent at reduced pressure afforded a yellow oil, which was dissolved in 50 ml of ether and washed with 20 ml each of 5% sodium hydroxide, 5% hydro-

chloric acid (twice), saturated sodium bicarbonate, saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 237 mg of a colorless liquid, consisting of >95% of one volatile component by vpc (column A, 280°).

Bulb-to-bulb distillation (153° @ 0.001 mm) yielded 227 mg (92.2%) of the aldehyde U-4, as a colorless liquid: ir (CHCl_3) 2720 (CHO), 1725 (C=O), and 1670 cm^{-1} (C=CH); nmr (CDCl_3) δ 1.11 (d, 3, $J = 6$ Hz, $\text{CH}(\text{CH}_3)\text{CHO}$), 1.60 (d, 3, $J = 1.5$ Hz, $\text{CH}_3\text{C}=\text{CH}$), 1.63 (s, 6, $\text{CH}_3\text{C}=\text{CCH}_3$), 3.80 (s, 3, CH_3O), 5.20 (t, 1, $J = 5.5$ Hz, $\text{>C}=\text{CH}$), 6.61-7.41 (m, 4, ArH), and 9.65 (d, 1, $J = 2$ Hz, CHO).

Anal. Calcd. for $\text{C}_{23}\text{H}_{34}\text{O}_2$: C, 80.65; H, 10.01. Found: C, 80.67; H, 10.10.

4-Methyl-4-(10-m-methoxyphenyl-3,4,7-trimethyl-trans,trans-3,7-decadienyl)-2-cyclohexenone (U-5)

To a solution of 1.401 g (4.09 mmole) of the aldehyde U-4 in 40 ml of dry benzene was added $453\ \mu\text{l}$ (386 mg, 5.44 mmole) of dry pyrrolidine in 8 ml of dry benzene. The mixture was heated at reflux under a Dean-Stark water separator and 6" Vigreux column for $2\frac{1}{2}$ hours, at which time a vpc trace (column A, 280°) indicated complete depletion of the starting aldehyde. The mixture was concentrated to ca. 15 ml in volume, and the remainder of the solvent was removed at reduced pressure, first under aspirator, and then in vacuo for 1 hour.

The residue was redissolved in 40 ml of freshly distilled benzene, and a solution of 622 μ l (538 mg, 7.68 mmole) of freshly distilled methyl vinyl ketone (0.5% hydroquinone) in 8 ml of dry benzene was added. The mixture was stirred at room temperature for 2 hours and then heated at reflux for 17 hours (flask wrapped in Al foil to protect from light). The solution turned a light yellow color during the reflux period. A hydrolysis mixture of 0.25 g of sodium acetate, 0.5 ml of water, and 0.5 ml of glacial acetic acid was added, and the mixture was maintained at reflux for an additional 4 hours.

After the reaction had cooled to room temperature, 50 ml of pet. ether was added, and the mixture was washed with 50 ml of water. The aqueous wash was extracted with 50 ml of pet. ether. The combined organic layers were washed with 3 x 50 ml of 5% hydrochloric acid, 50 ml of saturated sodium bicarbonate, 50 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a light yellow oil.

A vpc trace (column A, 290°) indicated one major volatile component (3.6 min) with ca. 10% of another component existing as a shoulder, and a trace of more volatile components (aldehyde). The ir spectrum showed a strong peak at 1675 cm^{-1} (unsaturated ketone) and a small peak at 1725 cm^{-1} (aldehyde).

Chromatography on 160 g of silica gel afforded, after

100 ml each of 1%, 2%, and 4% ether-pet. ether, 1.8 l. of 8% ether, 750 ml of 12% ether, and 250 ml of 16% ether as forefractions, 1.48 g (91.9%) of the enone U-5 in 750 ml of 16% ether-pet. ether. The product contained one volatile component in 94% purity by vpc(column A, 290°).

An analytical sample was prepared by bulb-to-bulb distillation (194° @ 0.0025 mm): ir (CHCl₃) 1675 cm⁻¹ (C=O); nmr (CDCl₃) δ 1.16 (s, 3, C-4 angular CH₃), 1.60 (d, 3, J = 1.5 Hz, CH₃C=CH), 1.63 (s, 6, CH₃C=CCH₃), 3.80 (s, 3, CH₃O), 5.21 (t, 1, J = 6 Hz, >C=CH), 5.90 (d, 1, J = 10 Hz, C-2 H), 6.73 (d, 1, J = 10 Hz, C-3 H), and 6.63-7.50 (m, 4. ArH).

Anal. Calcd. for C₂₇H₃₈O₂: C, 82.18; H, 9.71. Found: C, 82.25; H, 9.69.

4-Methyl-4-(10-m-methoxyphenyl-3,4,7-trimethyl-trans,trans-3,7-decadienyl)-2-cyclohexenol (51)

A solution of 103 mg (2.7 mmole) of lithium aluminum hydride in 25 ml of dry ether was cooled to 0°, and 2.102 g (5.33 mmole) of the enone U-5 was added in 20 ml of dry ether over 35 min. The mixture was stirred at 0° for 1½ hours, and 1 ml of water was carefully added (frothing). After the gray mixture had turned white, stirring was continued for 1½ hours. Magnesium sulfate was added, and the mixture was stirred for an additional ½ hour. The white slurry was then filtered, and the filtrate was concentrated at reduced pres-

sure to yield 2.092 g (99.1%) of the allylic alcohol 51, as a colorless oil: ir (CHCl₃) 3590 (OH), 1670 (>C=CH), and 1650 cm⁻¹ (CH=CH); nmr (CDCl₃) δ 0.96 (s, 0.4 x 3, angular CH₃, α-alcohol), 1.01 (s, 0.6 x 3, angular CH₃, β-alcohol), 1.61 (s, 6, CH₃C=CCH₃), 3.80 (s, 3, CH₃O), 4.16 (m, 1, >CHOH), 5.20 (t, 1, J = 5 Hz, >C=CH), 5.60 (m, 2, CH=CH), and 6.61-7.40 (m, 4, ArH).

Anal. Calcd. for C₂₂H₄₀O₂: C, 81.77; H, 10.17. Found: C, 81.68; H, 10.16.

Cyclization of the alcohol 51. Isolation of 3-methoxy-6bβ, -8aβ, 12bα, 14aβ-tetramethyl-5,6,6aα,7,8,8a,12aβ,12b,13,14,14a-tetradecahydropicene (50)

A solution of 240 mg (0.606 mmole) of the alcohol 51 in 24 ml of dry dichloromethane was cooled to -63.5° (cryostatic chloroform bath), and 13.5 ml of a solution of stannic chloride (0.1 M in dichloromethane, pre-cooled to -63.5°) was added. After 30 seconds, 40 μl of dimethyl carbonate was added. After stirring for 15 min, the yellow solution was poured into 75 ml of 20% potassium carbonate, maintained at 0°. The mixture was extracted with 3 x 20 ml of ether, and the combined extracts were washed with 20 ml of water, 20 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent afforded 240 mg of a foam.

A vpc trace (column A, 300°) indicated 4 major peaks, designated A-D, with retention times of 1.9, 2.1, 2.6, and

2.75 min, respectively. In addition, a cluster of peaks (E) at 1.2-1.4 min was also observed.

Column chromatography on 20 g of silica gel afforded, after 50 ml each of 2% and 4% ether-pet. ether, 112 mg of a mixture whose vpc trace (column A, 300°) was virtually identical to the crude mixture (150 ml of 10% ether). The estimated ratios of the components A-D were 2:1:2:6.

Chromatography on 14 g of silica gel impregnated with 10% silver nitrate (3:1 pet. ether-benzene, 10 ml fractions) afforded 32 mg of a fraction containing component D in ca. 85% abundance (fraction 4). Fraction 3 (6 mg) contained component D to the extent of about 15%. The yield of component D, based on these two fractions, was 28.1 mg (12%).

An analytical sample was obtained by recrystallization of the purer fraction from ether-hexane, mp 186-190°: ir (CHCl₃) 1555 (w, C=C), 1602, and 1575 cm⁻¹ (C=C, 1,2,4-tri-subst benzene); nmr (CDCl₃) δ 0.90, 0.93, 1.05, 1.21 (4 s, 12, angular CH₃), 2.66-3.13 (m, 2, ArCH₂), 3.75 (s, 3, CH₃O), 5.60-5.80 (m, 2, CH=CH), and 6.50-7.30 (m, 3, ArH).

Anal. Calcd for C₂₇H₃₈O: C, 85.66; H, 10.12. Found: C, 85.66; H, 10.25.

Hydroboration of the pentacyclic olefin 50. Isolation of 3-methoxy-6b β ,8a β ,12b α ,14a β -tetramethyl-5,6,6a α ,7,8,8a,9,-10,11 α ,12,12b,13,14,14b-hexadecahydro-11 β -picenol (M-2) and the 12 β -hydroxy isomer 167.

A solution of 59 mg (0.158 mmole) of the pentacyclic olefin 50 and 20 mg of 2,6,10,14-tetramethylpentadecane (Aldrich) in 1.5 ml of dry tetrahydrofuran was cooled to 0°, and 1.5 ml of a 0.85 M solution of diborane in tetrahydrofuran was added. After stirring at 0° for 9 hours, the excess hydride was decomposed by the careful addition of 0.75 ml of water (frothing). The organoborane was oxidized by the addition of 3 ml of 20% sodium hydroxide and 3 ml of 30% hydrogen peroxide. The cooling bath was removed, and the mixture was allowed to stir for an hour, during which time the temperature rose to about 40° and then cooled again. The two-phase reaction mixture was extracted with 3 x 25 ml of ether. The combined extracts were washed with 20 ml of water, 20 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent afforded 75 mg of a foam.

Preparative tlc (40% ether-pet. ether) separated the mixture into two bands: A (R_f = 0.3, 18 mg, 22.4%), and B (R_f = 0.0-0.2, 48 mg, 76.9%). Neither component was stable to vpc (column A, 300°).

The structure of the component of Band A was assigned as the 12-hydroxy axial alcohol 167: ir (CHCl₃) 3600 (OH).

1602, and 1575 cm^{-1} (C=C, 1,2,4-trisubst. benzene); nmr (CDCl_3) δ 0.98, 1.00, 1.20, 1.25 (4 s, 12, angular CH_3), 2.66-3.16 (m, 2, ArCH_2), 3.76 (s, 3, CH_3O), 4.23 (m, 1, $\text{W}_{h/2} = 7$ Hz, C-12 H), and 6.46-7.44 (m, 3, ArH).

The alcohol in Band B was assigned as the 11-hydroxy isomer M-2: ir (CHCl_3) 3600 (OH), 1602, and 1575 cm^{-1} (C=C, 1,2,4-trisubst. benzene); nmr (CDCl_3) δ 0.96, 1.00, 1.11, 1.20 (4 s, 12, angular CH_3), 2.66-3.16 (m, 2, ArCH_2), 3.75 (s, 3, CH_3O), 3.93 (m, 1, $\text{W}_{h/2} = 22$ Hz, C-11 H), and 6.46-7.30 (m, 3, ArH). Recrystallization (acetone) afforded colorless needles, mp 190-192.5 $^\circ$.

Anal. Calcd. for $\text{C}_{27}\text{H}_{40}\text{O}_2$: C, 81.77, H, 10.17. Found: C, . . ; H, . . .

3-Methoxy-6b β ,8a β ,12b α ,14a β -tetramethyl-5,6,6a α ,6b,7,8,9,-10,12b,13,14,14a-tetradecahydro-11(12H)-picenone (M-1)

A solution of 75 mg (0.189 mmole) of the alcohol M-2 in 8 ml of acetone was cooled to 0 $^\circ$, and excess Jones reagent was added dropwise until a yellow color persisted. After 15 min, isopropanol was added until a green suspension formed. The mixture was diluted with 50 ml of water and extracted with 3 x 50 ml of chloroform. The combined extracts were washed with 50 ml each of water, saturated sodium bicarbonate, saturated brine, and dried (MgSO_4). Evaporation of the solvent afforded 69 mg (92.6%) of white crystals which showed a single spot on tlc(20% ether-pet. ether, $R_f = 0.2$): ir (CHCl_3) 1700 cm^{-1} (C=O); nmr (CDCl_3) δ

0.83, 1.00, 1.20, 1.26 (4 s, 12, angular CH_3), 2.20-2.56 (m, 4, CH_2COCH_2), 2.66-3.20 (m, 2, ArCH_2), 3.73 (3, 3, CH_3O), and 6.46-7.26 (m, 3, ArH). Recrystallization from acetone afforded white crystals, mp 200.5-204.5°.

Anal. Calcd. for $\text{C}_{27}\text{H}_{38}\text{O}_2$: C, 82.18; H, 9.71. Found: C, . . . ; H, . . .

3-Methoxy-6b β ,8a β ,12b α ,14a β -tetramethyl-5,6,6a α ,6b,7,8,8a,-9,10,12b,13,14,14a-tetradecahydro-12(11H)-picenone (168)

A solution of 19 mg (0.047 mmole) of the axial alcohol 167 in 2 ml of acetone was cooled to 0°, and sufficient Jones reagent was added to impart a yellow color to the mixture. After 25 min, excess isopropanol was added, producing a green suspension. The mixture was diluted with 25 ml of water and extracted with 3 x 15 ml of chloroform. The combined extracts were washed with 10 ml of saturated sodium bicarbonate and dried (MgSO_4). Evaporation of the solvent afforded 15 mg (78.9%) of white crystals, consisting of one volatile component by vpc (column A, 300°): ir (CHCl_3) 1675 cm^{-1} (C=O); nmr (CDCl_3) δ 1.00, 1.20 (2 s, 12, angular CH_3), 2.70-3.26 (m, 2, ArCH_2), 3.76 (s, 3, CH_3O), and 6.53-7.22 (m, 3, ArH).

Regeneration of the olefin 50 from the axial alcohol 167

The general procedure of Koechlin and Reichstein (177) was followed. A solution of 43 mg (0.108 mmole) of the

12-hydroxy alcohol 167 in 1 ml of dry pyridine was cooled to 0°, and 0.1 ml of phosphorous oxychloride was added. The mixture was stirred at room temperature for 24 hours, during which time the solution turned yellow. After cooling to 0°, 0.5 ml of water was added dropwise. The mixture was diluted with 50 ml of water and extracted with 3 x 30 ml of chloroform. The combined extracts were washed with 2 x 20 ml of 10% hydrochloric acid, 20 ml of saturated sodium bicarbonate, and dried (MgSO₄). Evaporation of the solvent afforded 38 mg (93.1%) of the pentacyclic olefin 50, consisting of 90% one volatile component by vpc (column A, 300°). The ir, nmr, and vpc data indicated that the product was identical to the olefin isolated from the cyclization of alcohol 51.

3,3-Dimethyl-5 β -cholestane (170)

To a mixture of 31 mg (0.0803 mmole) of coprostanone (169) and 5 mg of valeric acid in a thick-walled glass tube was added 1 ml of a 1:1 mixture of trimethylaluminum in benzene (178). The tube was sealed in vacuo and placed in a stainless steel bomb, which was heated at 200° for 65 hours. After cooling to room temperature, the tube was opened, and 4 ml of dry benzene was quickly added through a serum stopper. The mixture was slowly pipetted into 40 ml of 5% hydrochloric acid covered with 30 ml of ether, maintained at 0°. After the methane gas had ceased to evolve, the layers were separated, and the aqueous layer was ex-

tracted with 2 x 30 ml of ether. The combined organic layers were washed with 30 ml of water, 30 ml of saturated sodium bicarbonate, 30 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded a colorless oil, whose vpc trace (column A, 260°) indicated the presence of two volatile components in a ratio of ca. 1:2 with retention times of 3.5 and 3.65 min, respectively. The ir spectrum showed only a small residual carbonyl band at 1710 cm^{-1} . The nmr spectrum showed an increase in the methyl region and no signals for either olefinic hydrogens of those adjacent to a carbonyl group.

The crude product was subjected to chromatography on 12 g of silica gel (pet. ether). After 17 ml of forefractions, 21 mg (65%) of a fraction was isolated in 5 ml of eluent, which contained the major product in about 85% purity. A second fraction was isolated in 5 ml of eluent consisting of 5 mg of material containing the minor component in ca. 75% purity. This product did not contain the gem-dimethyl group (ir) and was not investigated further.

The major product from a similar run was purified further by two successive chromatographies on 7 and 10 g of silica gel impregnated with 10% silver nitrate. The major product thus isolated contained 95% of one volatile component by vpc (column A, 260°): ir (CHCl_3) 1385 and 1365 cm^{-1} ($>\text{CMe}_2$); nmr (CDCl_3) δ 0.63-1.00 (m, 21, CH_3) and 1.00-2.16 (m, 31, CH_2 , CH).

Attempted formation of the gem-dimethyl compound D-6 by exhaustive methylation of the ketone M-1.

A. From the ketone directly. To a mixture of 14 mg (0.035 mmole) of the ketone M-1 and 2.5 mg of valeric acid was added 300 μ l of a solution of 1:1 trimethylaluminum and benzene, all in a tube as described above. The tube was sealed and heated at 200^o for 64 hours. Workup as described above afforded 12 mg of a yellow oil. The nmr and ir spectra indicated that the crude product was mainly starting material, although an analytical tlc (15% ether-pet. ether) indicated a spot with $R_f = 0.7$, identical with an authentic sample of the desired pentacyclic ether D-6 (41).

Preparative tlc (15% ether-pet. ether) afforded 3 mg of a non-polar material whose tlc and vpc behavior (column A, 300^o) were identical to those of the authentic sample. There was not sufficient material for spectral characterization.

B. From the methyl carbinol 177. A solution of 16 mg (0.04 mmole) of the ketone M-1 in 15 ml of tetrahydrofuran was added to 8 ml of a 1 M solution of methylmagnesium bromide in ether. After 4 hours, the excess Grignard was decomposed with 0.5 ml of saturated ammonium chloride. The mixture was then diluted with 30 ml of water and worked up with ether, affording 21 mg of an oily solid, whose ir spectrum was virtually identical to the starting ketone. No trace of OH absorption was observed.

The recovered ketone was then subjected to two consecu-

tive treatments of 0.5 ml of a 1.5 M solution of ethereal methyllithium in 3 ml of tetrahydrofuran for 8 hours. After the final workup, the ir spectrum showed no residual carbonyl absorption. The crude product was filtered through 2 g of neutral alumina (act. II) to yield 18 mg of an oil which slowly crystallized: ir (CHCl_3) 3600 cm^{-1} (OH).

The crude alcohol, 2 mg of valeric acid, and 1 ml of a 1:1 mixture of trimethylaluminum in benzene was placed in a glass tube, which was sealed and heated in a steel bomb for 48 hours at 200° . The mixture was worked up as described in the previous two experiments to yield 17 mg of an oil. The mixture appeared to consist of one major product whose retention time on vpc (column A, 300°) and R_f on tlc (12% ether-pet. ether) were identical to those of an authentic sample of the pentacyclic ether D-6 (41).

The crude product was subjected to column chromatography on 10 mg of silica gel (2% ether-pet. ether). After 55 ml of forefractions, 9 mg (56%) of material was isolated containing the major product in ca. 80% purity: ir (CHCl_3) 1640 cm^{-1} (w, C=C); nmr (CDCl_3) δ 2.85 (t, 2, ArCH_2), 3.75 (s, 3, CH_3O), 4.60 (s, 0.56 x 2, >C=CH_2), 5.25 (m, 0.45 x 1, $W_{h/2} = 16 \text{ Hz, >C=CH}$), and 6.45-7.35 (m, 3, ArH).

On the basis of these data, the non-polar products are assigned the structures of the pentacyclic olefins 178 and 179.

Attempted reaction of the ketone M-1 with methylenetriphenylphosphorane in DMSO (180a)

A solution of 0.5 mmole of methylsulfinylcarbanion (180b) was cooled to 0°, and a solution of 223 mg (0.625 mmole) of methyltriphenylphosphonium bromide in 0.5 ml of dry DMSO was added. After 10 min, 4 mg (0.01 mmole) of the ketone M-1 was added in 0.5 ml of dry tetrahydrofuran. The mixture was heated to 80° and maintained at that temperature for 24 hours. The excess Wittig reagent was decomposed by the addition of 1 ml of water. The mixture was then diluted with 20 ml of water and extracted with 3 x 20 ml of benzene. The combined extracts were washed with 3 x 20 ml of water, 20 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure afforded 38 mg of an orange, crystalline solid.

Chromatography on 2 g of silica gel (20% ether-pet. ether) afforded 4 mg of material which was indistinguishable from the starting ketone by ir or tlc.

Attempted reaction of the ketone M-1 with phenylthiomethyl-lithium (181)

A solution of 3.9 mg (0.01 mmole) of the ketone M-1 in 200 μ l of dry tetrahydrofuran was added to a solution of 0.426 mmole of phenylthiomethyl-lithium (182). The mixture was stirred for 24 hours at room temperature, and 5 ml of water was then added. The mixture was diluted with 20 ml

of water and extracted with 3 x 20 ml of ether. The combined extracts were washed with 10 ml of water, 10 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 5 mg of an oil: ir (CHCl_3) 3600 (OH) and 1700 cm^{-1} (C=O). A tlc of the mixture (30% ether-pet. ether) showed at least 7 spots, including one corresponding to starting ketone.

Attempted reaction of the ketone M-1 with dimethylsulfonium methylide (144).

A solution of 15.5 mg (0.04 mmole) of the ketone M-1 in 0.6 ml of dry tetrahydrofuran was added to a solution of 0.08 mmole of dimethylsulfonium methylide, prepared by the procedure of Corey and Chaykovsky (144), maintained at -3° . The reaction mixture was stirred at -3° for 5 min, at 0° for 2 hours, and at 25° for $\frac{1}{2}$ hour. The mixture was then poured into 50 ml of water and extracted with 3 x 30 ml of ether. The combined extracts were washed with 2 x 50 ml of water, 50 ml of saturated brine, and dried (K_2CO_3). Evaporation of the solvent at reduced pressure afforded 10 mg of an oil. A second workup of the aqueous layer yielded an additional 5 mg of product. The ir spectrum indicated a strong carbonyl band corresponding to starting ketone.

Preparative tlc (30% ether-pet. ether) yielded two bands: Band A ($R_f = 0.30$, 7.5 mg, 48.3%) displayed the following spectral data: ir (CHCl_3) 1685 and 1645 cm^{-1} (s, C=C);

nmr (CDCl_3) δ 1.03 (s, 6, angular CH_3), 1.10 (s, 3, angular CH_3), 1.20 (s, 3, angular CH_3), 2.86 (m, 2, ArCH_2), 3.75 (s, 3, CH_3O), 6.08 (m, 1, >C=CH), and 6.45-7.35 (m, 3, ArH). Band B ($R_f = 0.25$, 6 mg, 38.7%) had an ir spectrum identical with the starting ketone, contaminated with a little material from Band A.

1-(Methylthiomethyl)cyclododecanol (189)

The general procedure of Johnson, Coates, and coworkers (190) was followed. A solution of 182 mg (1 mmole) of cyclododecanone (188) in 0.5 ml of dry tetrahydrofuran was cooled to -78° , and 1 ml of a 1.35 M solution of methylthiomethyl lithium (192) was added. After 1 hour at -78° , the mixture was allowed to warm up to room temperature and stir for 1 hour. The reaction was quenched by the addition of 1 ml of dilute ammonium chloride (exothermic). Workup with ether afforded a yellow oil, which was subjected to preparative tlc (30% ether-pet. ether) to afford 188 mg (77%) of a colorless oil: ir (CHCl_3) 3600 and 3510 cm^{-1} (OH); nmr (CDCl_3) δ 1.38 (s, 22, OH, CH_2), 2.18 (s, 3, CH_2S), and 2.61 (s, 2, CH_2S).

1-Oxaspiro[2,11]tetradecane (190)

A. Preparation of the sulfonium salt. To a solution of 122 mg (0.5 mmole) of the β -hydroxy sulfide 189 in 0.2 ml of acetone was added 62 μl (142 mg, 1.0 mmole) of methyl

iodide. A white precipitate formed after 10 minutes. After 40 hours of stirring, the solvent was evaporated, and the cream-colored solid was dried in vacuo (173 mg, 89.6%).

B. Epoxide formation. A mixture of 45 mg (0.116 mmole) of the sulfonium salt and 11 mg of sodium methoxide was dissolved in 1 ml of methanol and stirred overnight. The mixture was worked up with ether to yield 25 mg of an oil. Preparative tlc (20% ether-pet. ether) afforded 21.5 mg (95%) of an oil, which consisted of one volatile component in 95% purity by vpc (column A, 70°): ir (CHCl₃) 3000 cm⁻¹ (CH); nmr (CDCl₃) δ 1.20-1.66 (m, 22, CH₂) and 2.56 (s, 2, >C^O-CH₂).

3-Methoxy-11β-(methylthiomethyl)-6bβ,8aβ,12bα,14aβ-tetramethyl-5,6,6aα,6b,7,8,8a,9,10,11,12,12aβ,12b,13,14,14a-hexadecahydro-picen-11α-ol (V-1)

To a solution of 76 mg (0.193 mmole) of the ketone M-1 in 5 ml of tetrahydrofuran at -78° was added 600 μl of methylthiomethyl lithium solution (prepared as above). The mixture was allowed to warm to room temperature and stir overnight. Dilute ammonium chloride solution was added, and the mixture was worked up with ether to afford 121 mg of an oil.

Preparative tlc (30% ether-pet. ether) afforded 52 mg (58.7%) of the β-hydroxy sulfide V-1, as a white, crystalline solid: ir (CHCl₃) 3500 cm⁻¹ (w, OH); nmr (CDCl₃) δ 0.96 (s, 3, angular CH₃), 1.05 (s, 3, angular CH₃), 1.20 (s, 6, angular CH₃), 2.18 (s, 3, CH₃S), 2.60 (s, 2, CH₂S), 2.85

(t, 2, $J = 5.5$ Hz, ArCH_2), 3.51 (s, 1, OH), 3.75 (s, 3, CH_3O), and 6.46-7.28 (m, 3, ArH).

An analytical sample was prepared by recrystallization from hexane-dichloromethane, mp 165.5-168.5°.

Anal. Calcd. for $\text{C}_{29}\text{H}_{44}\text{O}_2\text{S}$: C, 76.26; H, 9.71; S, 7.02.
Found: C, . ; H, . ; S, . .

Spiro[α -oxirane-2,11'-(3'-methoxy-6b' β ,8a' β ,12b' α ,14a' β -tetramethyl-5',6',6a' α ,6b',7',8',8a',9',10',11',12',12a' β ,12b',13',14',14a'-hexadecahydro)picene] (183)

A. Preparation of the β -hydroxy sulfonium salt V-2. To a solution of 52 mg (0.114 mmole) of the β -hydroxy sulfide V-1 in 5 ml of acetone was added 2 ml of methyl iodide. The mixture was stirred for 24 hours, during which time a cream-colored solid precipitated. An additional 1 ml of methyl iodide was added, and the mixture was allowed to stir for an additional 18 hours. Filtration and drying in vacuo afforded 46 mg of a white solid which was used directly in the next reaction.

B. Formation of the epoxide. To a suspension of 85 mg (0.142 mmole) of the sulfonium salt V-2 in 12 ml of methanol was added 40 mg of sodium methoxide. After a few minutes, the mixture became clear, but turbidity reappeared within an hour. The strong odor of methyl sulfide was detected. After 8 hours, the mixture was poured into 60 ml of water and ex-

tracted with 3 x 60 ml of chloroform. The combined extracts were washed with 60 ml of saturated brine and dried (K_2CO_3). Evaporation of the solvent afforded 63 mg of an oil which solidified in vacuo overnight: nmr ($CDCl_3$) δ 1.00, 1.10, 1.18, 1.21 (4 s, 12, angular CH_3), 2.51 (s, 2, $>C-CH_2$), 2.86 (t, 2, $J = 5.5$ Hz, $ArCH_2$), 3.75 (s, 3, CH_3O), and 6.46-7.28 (m, 3, ArH).

3-Methoxy-6b β , 8a β , 12b α , 14a β -tetramethyl-5, 6, 6a α , 6b, 7, 8, 8a, 9, 10, 11 β , 12, 12a β , 12b, 13, 14, 14a-hexadecahydricene-11 α -carboxaldehyde (180) and its epimer

A solution of the crude epoxide 183 (prepared above) in 8 ml of dry dichloromethane was cooled to -15° , and 53 μ l (60.5 mg, 0.426 mmole) of boron trifluoride etherate was added. The solution was kept at -15 to -10° for $\frac{1}{2}$ hour, during which time it took on a pale yellow cast. The reaction was quenched by the addition of 1 ml of saturated sodium bicarbonate. The mixture was then poured into 30 ml of water and extracted with 3 x 40 ml of chloroform. The combined extracts were washed with 20 ml of saturated brine and dried (K_2CO_3). Evaporation of the solvent afforded a foam.

Preparative tlc (25% ether-pet. ether) afforded 39 mg (67.3% from the sulfonium salt V-2) of the aldehyde 180, which consisted of ca. 50% of the C-11 epimeric aldehyde: ir ($CHCl_3$) 1360 (CHO) and 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.96 (s, 3, angular CH_3), 1.06 (s, 6, angular CH_3), 1.18

(s, 3, angular CH₃), 2.43 (m, 1, CHCHO), 2.85 (m, 2, ArCH₂), 3.75 (s, 3, CH₃O), 6.46-7.28 (m, 3, ArH), 9.55, and 9.63 (2 d, 0.5, J = 2 Hz each, CHO).

3-Methoxy-6b β ,8a β ,11 β ,12b α ,14a β -pentamethyl-5,6,6a α ,6b,7,8,-8a,9,10,11,12,12a β ,12b,13,14,14a-hexadecahydricene-11 α -carboxaldehyde (191)

A suspension of 112 mg (1 mmole) of potassium tert-butoxide in 3 ml of glyme was cooled to 0°, and a solution of 39 mg (0.0956 mmole) of the aldehyde 180 and 623 μ l (1.42 g, 10 mmole) of dry methyl iodide in 2 ml of dry glyme was added over 10 min. The mixture was allowed to warm to room temperature and stir for 6 hours. On the slow addition of 5 ml of water, an exothermic reaction ensued. The mixture was dissolved in an additional 10 ml of water and extracted with 3 x 20 ml of chloroform. The combined extracts were washed with 10 ml of saturated brine and dried (K₂CO₃). Evaporation of the solvent at reduced pressure afforded 38 mg of a foam.

Preparative tlc (25% ether-pet. ether) afforded 23 mg (57%) of the methylated aldehyde 191 (R_f = 0.30): ir (CHCl₃) 2700 (CHO) and 1720 cm⁻¹ (C=O); nmr (CDCl₃) δ 0.80 (s, 3, angular CH₃), 0.98 (3, 6, angular CH₃), 1.11 (s, 3, angular CH₃), 1.16 (s, 3, angular CH₃), 2.86 (m, 2, ArCH₂), 3.75 (s, 3, CH₃O), 6.46-7.28 (m, 3, ArH), and 9.41 (s, 0.5, CHO).

A band with R_f = 0.35 was also isolated whose ir and nmr were identical with the starting aldehyde 180 or its epimer (5 mg, 12%).

Attempted modified Wolff-Kishner reduction of the aldehyde 191 (154)

A mixture of 8.5 mg (0.02 mmole) of the crude methylated aldehyde 191, 1 ml of triethylene glycol, 0.1 ml (300 mg, 2 mmole) of hydrazine hydrate, and 30 mg (0.3 mmole) of hydrazine dihydrochloride was heated at 150° (bath temperature) for 5 hours under nitrogen, during which time the mixture became cloudy. The mixture was then cooled to 110°, and 120 mg of 85% potassium hydroxide was added. The mixture was then heated at 150-155° (bath temperature) for 5 hours and allowed to cool by discontinuation of the heating, but maintaining contact with the bath overnight.

The reaction mixture was poured into 25 ml of water and extracted with 3 x 20 ml of chloroform. The combined extracts were washed with 10 ml of water, 10 ml of saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure afforded 11.5 mg of a yellow, semi-crystalline solid, which was only slightly soluble in chloroform. The insoluble material appeared to be resinous.

The ir spectrum (CHCl₃) showed weak carbonyl and olefinic absorption at 1725 and 1650 cm⁻¹ respectively. A broad OH band (solvent) also appeared at 3450 cm⁻¹.

Preparative tlc (25% ether-pet. ether) yielded two 3 mg bands: Band A (R_f = 0.45) displayed the following spectral data: ir (CHCl₃) 1725 (m, C=O) and 1650 cm⁻¹ (w, C=C); nmr (CDCl₃) δ 3.75 (s, 3, CH₃O). No aldehyde frequencies

were detected in either spectrum.

Band B ($R_f = 0.0$) was virtually insoluble in chloroform: ir (CHCl_3) 1725 cm^{-1} (w, C=O).

In addition a band with $R_f = 0.55$ was isolated which may have contained the desired gem-dimethyl product D-6, but the fraction amounted to less than 0.5 mg.

11 α -Hydroxymethyl-3-methoxy-6b β ,8a β ,11 β ,12b α ,14a β -pentamethyl-5,6,6a α ,6b,7,8,8a,9,10,11,12,12a β ,12b,13,14,14a-hexadecahydro-picene (192)

A solution of 120 mg of lithium aluminum hydride in 20 ml of dry ether was cooled to 0° , and 58 mg of the partially-purified aldehyde 192 in 10 ml of ether was added dropwise. The mixture was stirred at 0° for 1 hour, and 1 ml of water was added dropwise (frothing) until the mixture turned white. Anhydrous potassium carbonate was added, and the mixture was stirred for 1 hour and filtered. Evaporation of the solvent afforded 60 mg of a foam. A vpc trace (column A, 300°) indicated one major volatile component in ca. 90% purity.

Chromatography on 10 g of Florisil (50% ether-pet. ether) resolved the mixture into three fractions, isolated in 25 ml each of eluent. Fraction A (7 mg) consisted of a complex mixture by vpc and was not characterized further. Fraction B (52 mg) appeared to contain the major component in 95% purity by vpc (column A, 300°). Fraction C (7 mg) consisted of essentially one volatile component with the same retention

time (7.3 min) as the major component, but was assigned the structure of an alcohol lacking the methyl group at C-11: nmr (CDCl_3) δ 3.33 (m, 2, CHCH_2OH).

Fraction B was induced to crystallize through trituration with ether-hexane. Two crops of crystals were isolated (35 mg, 60%) which consisted of >98% of one volatile component by vpc: ir (CHCl_3) 3620 (OH) and 1030 cm^{-1} (C-O); nmr (CDCl_3) δ 0.98, 1.03, 1.11, 1.15, 1.23 (5 s, 3 each, angular CH_3), 2.83 (m, 2, ArCH_2), 3.25 (s, 2, CH_2OH), 3.73 (s, 3, CH_3O), and 6.46-7.28 (m, 3, ArH).

Phosphorodiamidation of the alcohol 192 (157)

To a solution of 36 mg (0.0849 mmole) of the alcohol 192 and a few crystals of 1,10-phenanthroline in 3 ml of dry glyme was added 0.189 ml of a 2.12 M solution of n-butyllithium in hexane (0.4 mmole). After the solution turned red, the mixture was stirred for 5 min, and 0.4 ml of dry triethylamine, 0.2 ml of dry HMPA, and 0.4 ml of the phosphorochloridate 148 (158) were added in succession. On the addition of the last component, the red color faded to a pale yellow. The solution was stirred at room temperature for $\frac{1}{2}$ hour, diluted with 75 ml of ether, washed with 2 x 25 ml of water, 25 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 150 mg of an oil. The material was dried in vacuo overnight, affording 57 mg of a yellow semisolid: ir (CHCl_3) no OH; nmr (CDCl_3) δ 1.00, 1.10,

1.15, 1.17, 1.26 (5 s, 3 each, angular CH_3), 2.66 (d, 12, $J = 10$ Hz, P-N- CH_3), 3.56 (d, 2, $J = 4$ Hz, CH_2O), 3.75 (s, 3, CH_3O), and 6.46-7.33 (m, 3, ArH).

Note: two extraneous signals were also present, 2.73 (d, 6, $J = 14$ Hz, P-N- CH_3 , n-butylphosphonodiamidate).

Attempted deoxygenations of the phosphorodiamidate of 192

A. Aprotic reduction. A few small pieces of lithium wire were added to 5 ml of dry methylamine (distilled from sodium and lithium). After the mixture turned deep blue, the mixture was stirred at reflux for 2 minutes, and 6 mg of the phosphorodiamidate of alcohol 192 was added in 0.3 ml of dry tetrahydrofuran. The mixture was stirred for 5 min, and sufficient sodium benzoate was added to cause the blue color to disappear. The methylamine was allowed to evaporate under a stream of dry nitrogen, and the residue was diluted with 20 ml of water and extracted with 3 x 20 ml of chloroform. The combined extracts were washed with 2 x 10 ml of 5% sodium hydroxide and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 6 mg of a yellow oil. A vpc trace (column A, 300°) indicated the complete disappearance of starting material, but the major peak did not correspond to the desired pentacyclic ether D-6. The ir spectrum indicated a strong band at 1660 and a distorted aromatic region, suggesting possible reduction of the aromatic ring.

Chromatography on 2 g of silica gel afforded, after 25 ml

each of pet. ether and 5% ether-pet. ether, a 3 mg fraction in 25 ml of 10% ether-pet. ether. This material was virtually insoluble in most solvents, thereby making spectral analysis impossible. The vpc trace indicated that it consisted of two overlapping peaks at 2 min (column A, 300°). The retention time of an authentic sample of D-6 at this temperature was 1.6 min.

B. Protic reduction. The procedure of Hagenbach was followed (204). To a solution of the crude phosphorodiamidate (prepared from 0.0849 mmole of alcohol 192) in 16 ml of dry tetrahydrofuran was added 35 ml of dry ammonia (distilled from sodium). To this solution was added 37 mg of finely-cut lithium wire. After stirring for 25 min at reflux, 0.3 ml of absolute ethanol (dried over molecular sieves) was added. After 35 min, the blue color faded, and an additional 37 mg of lithium was added. After two hours following the ethanol addition, 2.5 ml of absolute ethanol was added. The blue color faded after 10 min, and the solvent was allowed to evaporate under a stream of dry nitrogen.

The residue was poured into 30 ml of 20% ammonium sulfate and extracted with 75 ml and 2 x 50 ml of ether. The combined extracts were washed with 50 ml of water, 50 ml of saturated brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow-green oil.

The crude reduction product was dissolved in 1 ml of benzene and 6 ml of 95% ethanol. To this solution was added

4 ml of 5 N hydrochloric acid. The mixture was heated at reflux for 1 hour and then allowed to cool to room temperature. The reaction mixture was poured into 50 ml of water and extracted with 4 x 50 ml of ether. The combined extracts were washed with 50 ml of saturated sodium bicarbonate, 50 ml of saturated brine, and dried (MgSO_4). Evaporation of the solvent afforded 15 mg of a yellow oil. The ir spectrum indicated the presence of an unsaturated ketone, along with some saturated carbonyl. The nmr spectrum showed traces of unreduced phosphorodiamidate and a single olefinic hydrogen at 5.88 ppm (adjacent to a ketone).

A vpc trace (column A, 300°) indicated two major components at 4.2 and 5.0 min in a ratio of ca. 1:3. The major component had the same retention time as an authentic sample of the enone D-7. There was also a component corresponding to the authentic sample by analytical tlc (50% ether-pet. ether, $R_f = 0.6$).

Chromatography on 2 g of silica gel (25% ether-pet. ether) afforded, after 24 ml of forefractions, 3.5 mg of material in 12 ml of 50% ether-pet. ether). This product (10% yield from alcohol 192) exhibited the spectral characteristics of an unsaturated ketone: ir (CHCl_3) 1660 (C=O) and 1615 cm^{-1} (C=C); nmr (CDCl_3) δ 5.88 (s, 1, C=CHCO). While the ir spectrum was essentially identical to the authentic sample of enone D-7, the nmr contained some extraneous methyl signals in the 1.2-1.4 ppm region. The vpc trace (column A, 300°) and tlc (50% ether-pet. ether) indicated that the

major component behaved identically to authentic enone D-2, but their identity cannot be established for certain, due to the differences in their nmr spectra.

Cyclization of the cyclopentenol 194. Isolation of 9-methoxy-3,5a β ,11a β ,13a α -tetramethyl-1,2,4,5,5a,5b α ,6,7,11a,12,-13a,13b β -tridecahydrocyclopenta[a]chrysene (195)

A solution of 38.2 mg (0.1 mmole) of the cyclopentenol 194 (90% one component by vpc) in 3 ml of dry dichloromethane was cooled to -78° , and 1.2 ml of a 0.1 M solution of stannic chloride in dichloromethane (pre-cooled to -78°) was added. The solution immediately turned yellow-brown, and then light yellow. After 5 min, 3 ml of 20% potassium carbonate solution was added, followed by 5 ml of ether. The mixture was then warmed to 0° in an ice bath. The mixture was then poured into 50 ml of water and extracted with 3 x 20 ml of ether. The combined extracts were washed with 20 ml each of water, saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 40 mg of a colorless oil.

The vpc trace (column A, 280°) indicated three major peaks, designated D, E, and F at 4.0, 5.05, and 6.1 min, respectively, in a ratio of 1:3:12. In addition, there were several unresolvable peaks from 2.8 to 4.4 min.

The crude product was combined with that of an identical run from 264 mg of the alcohol (0.69 mmole) to give 309 mg of the crude product mixture. This mixture was subjected to column chromatography on 45 g of silica gel impregnated with 10% silver nitrate (1:1 pet. ether-benzene). Fractions were collected in 10 ml quantities:

<u>Fraction</u>	<u>Weight, mg</u>	<u>Composition</u>
14,15	18	E 90%
16	3	E:F 1:3
17-22	157	D:E:F 5:4:90
23	3	D: F 1:1
24-28	23	D: 50% + others
29-45	17	eleven side products

The fractions rich in F crystallized on cooling. Trituration with pet. ether afforded 79 mg of a white solid, whose vpc (column A, 280°) contained component F in >96% purity. Recrystallization from ether-hexane afforded 66 mg of cubic crystals, mp 150-151.5°, containing only component F by vpc. The total yield of F was 96 mg (33% isolated) or 108 mg (37% estimated).

From those fractions containing component E, there was estimated to be 17 mg (5.9% yield).

The structure of component F is assigned the pentacyclic olefin 195: ir (CHCl₃) 1610 cm⁻¹ (1,2,4-trisubst. benzene); nmr (CDCl₃) 0.72, 1.03, 1.21 (3 s, 9, angular CH₃), 3.76 (s, 3, CH₃O), 6.60 (d, 1, J_{8,10} = 2 Hz, C-8 H), 6.70 (d of d, 1, J_{8,10} = 2 Hz, J_{10,11} = 8 Hz, C-10 H), and 7.20 (d, 1, J = 8 Hz, C-11 H).

Anal: Calcd. for C₂₆H₃₆O: C, 85.66; H, 9.95. Found: C, 85.65; H, 9.99.

Attempted column chromatography of the cyclopentenol 194.

Isolation of 11-methoxy-3,5a β ,11a β ,13a α -tetramethyl-1,2,4,5,-5a,5b α ,6,7,11a,12,13,13a,13b β -tridecahydrocyclopenta[a]chry-

sene (197) and 6 β -(2-m-methoxyphenylethyl)-3,5a β ,7,9a α -tetramethyl-1,2,4,5,5a,6 α ,9,9a,9b-nonahydrocyclopenta[a]naphthalene (196)

A 1.36 g portion of the cyclopentenol 194 was subjected to column chromatography on 95 g of silica gel (30% ether-pet. ether). After 100 ml of forefractions, 890 mg (65.2%) of cyclized material was isolated which contained the three components D, E, and F, isolated previously (vide supra) in a ratio of 13:3:4.

Chromatography on 40 g of silica gel impregnated with 10% silver nitrate (2% ether-pet. ether) afforded a 9 mg fraction in the first 250 ml of eluent, which contained components E and F in a ratio of 5:1. In the next 100 ml, a 127 mg fraction was isolated containing components D, E, and F in a ratio of 1 $\frac{1}{2}$:2:3. After an additional 1 l. of eluent, 184 mg of almost pure D was isolated (9.3%).

The fraction containing components D, E, and F was subjected to preparative tlc (pet. ether). A fraction containing component E was isolated consisting of 98.5% of E by vpc (column A, 280 $^{\circ}$). Also, a fraction containing roughly equal amounts of components D and F amounting to 83 mg was obtained. From the total solid products and mother liquors, the following yield summary is tabulated:

<u>Product</u>	<u>Isolated Yield</u>	<u>Estimated Yield (vpc)</u>
D	9.3%	13.3%
E	2.6%	3.2%
F	2.8%	4.2%

Component E was recrystallized from ether-hexane to give colorless, needle-like crystals, mp 157.5-161°.

A vpc trace (column A, 300°) consisted of only one volatile component: ir (CHCl₃) 1575 cm⁻¹ (C=C, 1,2,3-trisubstituted benzene); nmr (CDCl₃) δ 0.72, 1.01, 1.33 (3 s, 9, angular CH₃), 3.75 (s, 3, CH₃O), 6.67 (d of d, 1, J_{9,10} = 8 Hz, J_{8,10} = 1.5 Hz, C-10 H), 6.73 (s, 1, C-8 H), and 7.05 (d of d, 1, J_{8,9} = 7 Hz, J_{9,10} = 8 Hz, C-9 H).

Anal. Calcd. for C₂₆H₃₆O: C, 85.66; H, 9.95. Found: C, 85.57; H, 9.97.

Component D was evaporatively distilled (110° @ 0.075 mm) to give a colorless oil: nmr (CDCl₃) δ 0.62, 0.85 (2 s, 6, angular CH₃), 1.60 (br s, 3, >C=CCH₃), 3.75 (s, 3, CH₃O), 5.36 (m, 1, >C=CH), and 6.48-7.35 (m, 4, ArH).

Anal. Calcd. for C₂₆H₃₆O: C, 85.66; H, 9.95. Found: C, 85.76; H, 10.01.

On the basis of these data, the structures E and D are assigned the 1-methoxypentacyclic olefin 197 and the tricyclic diene 196, respectively.

1-(3-Oxobutyl)-8-methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,-5,6,10β,11,12,12a-decahydro-2(1H)-chrysenone (200)

The 3-methoxypentacyclic olefin 195 was osmylated with osmium tetroxide and pyridine (197), the resulting osmate ester was cleaved with hydrogen sulfide (198), and the re-

sulting glycol was oxidatively cleaved with lead tetraacetate (199), according to the following procedure. A solution containing 52.5 mg (0.144 mmole) of the 3-methoxy olefin 195, 119.7 mg (0.432 mmole) of osmium tetroxide, and 0.75 ml of dry pyridine in 12 ml of dry dioxane was stirred at room temperature for 62 hours, during which time a dark brown, opaque mixture resulted. The solvent was evaporated at reduced pressure, and the tan residue was dissolved in 12 ml of dichloromethane while hydrogen sulfide gas was bubbled through the solution for 40 min, causing a heavy black precipitate to form.

The mixture was filtered through a fine glass funnel, and the black solid was washed with 2 x 15 ml each of dichloromethane, methanol, and tetrahydrofuran. Evaporation of the solvent at reduced pressure afforded 58 mg of a cream-colored, crystalline solid, which was dissolved in 12 ml of dry tetrahydrofuran.

The solution was cooled to 0°, and 1.0 g of dry lead tetraacetate was added, causing the mixture to immediately turn yellow. After stirring at 0° for 20 min, 2.5 ml of ethylene glycol was added, causing the solution to lose its yellow color. The mixture was poured into 50 ml of water and extracted with 3 x 20 ml of ether. The combined extracts were washed with 30 ml each of water, saturated sodium bicarbonate, saturated brine, and dried (MgSO₄). Evaporation of the solvent at reduced pressure afforded 60 mg of a white,

crystalline solid, which consisted of two volatile components by vpc (column A, 300°) having retention times of 1.05 and 4.7 min in a ratio of 1:4.

Preparative tlc (7:5 chloroform-ether) afforded 49.2 mg (88.2%) of the major component, the diketone 200, as a white, crystalline solid, mp 148-150.5°.* The minor component was not isolated.

An analytical sample of the diketone 200 was prepared by recrystallization from ether-hexane, mp 134-135°*: ir (CHCl₃) 1710 (C=O) and 1610 cm⁻¹ (C=C, 1,2,4-trisubst. benzene); nmr (CDCl₃) 0.80 (s, 3, angular CH₃), 1.25 (s, 6, angular CH₃), 2.15 (s, 3, CH₃CO), 3.80 (s, 3, CH₃O), and 6.53-7.38 (m, 3, ArH).

Anal. Calcd. for C₂₆H₃₆O₃: C, 78.75; H, 9.15. Found: C, 78.68; H, 9.14.

10-Methoxy-6a β ,12b β ,14a α -trimethyl-1,5,6,6a,6b α ,7,8,12b,13,-14,14a,14b β -dodecahydro-3(2H)-picenone (D-4)

The diketone 200 was cyclized according to the procedure of Woodward, et al (203). A solution of 19 mg (0.048 mmole) of the diketone 200 in 1 ml of 10% sodium hydroxide and 10 ml of methanol was maintained at reflux for 10 hours. The mixture was then cooled, causing a fluffy, white precipitate

* Samples melting at either temperature exhibited identical ir and nmr spectra and chromatographic behavior. Both could be converted to the same enone D-4.

to form. The mixture was poured into 50 ml of water and extracted with 3 x 20 ml of benzene. The extracts were washed with 30 ml each of saturated sodium bicarbonate, saturated brine, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 22 mg of an orange oil.

Preparative tlc (9:2 chloroform-ether) afforded 12 mg (66%) of the enone D-4, as a cream-colored solid, having identical vpc, ir, and nmr behavior with an authentic sample prepared by M.I. Dawson.

Recrystallization from hexane-dichloromethane afforded light yellow crystals, mp $197-199^\circ$. An authentic sample melted at $197-200.5^\circ$, and a mixture had mp $195.5-198.5^\circ$. All three samples had identical retention times on vpc (column A, 300°) and showed only one spot on tlc (5.5:4.5 chloroform-ether): ir (CHCl_3) 1660 ($\text{C}=\text{O}$) and 1610 cm^{-1} ($\text{C}=\text{C}$); nmr (CDCl_3) δ 0.83, 1.10, 1.21 (3 s, 9, angular CH_3), 3.76 (s, 3, CH_3O), 5.95 (br s, 1, $>\text{C}=\text{CH}$), and 6.48-7.36 (m, 3, ArH).

1,3,5(10)-Estratrienyl-3-(N,N,N',N'-tetramethyldiaminophosphorodiamidate) (202)

To a solution of 128 mg (0.5 mmole) of 1,3,5(10)-estratrien-3-ol (201), mp $136.5-137^\circ$, and a few crystals of 1,10-phenanthroline in 8 ml of dry tetrahydrofuran was added 300 μl of a 1.6 M solution of ethereal methyllithium (0.48 mmole) until a brown-colored solution formed. To this was successively added 300 μl of triethylamine, 300 μl of HMPA, and

400 μ l of N,N,N',N'-tetramethyldiaminophosphorochloridate (148) (158). After 1 hour at room temperature, the mixture was poured into 50 ml of cold water and extracted with 3 x 30 ml of ether. The combined extracts were washed 2 x 10 ml of water, 2 x 10 ml of 5% hydrochloric acid, 10 ml of water, 10 ml of saturated sodium bicarbonate, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 201 mg of a yellow, crystalline solid.

A single recrystallization from hexane yielded 174 mg (89.2%) of white crystals, mp 129-133 $^\circ$, consisting of one volatile component by vpc (column A, 300 $^\circ$).

An analytical sample was prepared by recrystallization from hexane, mp 127-130.5 $^\circ$: ir (CHCl_3) 1610 cm^{-1} (C=C, 1,2,4-trisubst. benzene); nmr (CDCl_3) δ 0.73 (s, 3, angular CH_3), 2.71 (d, 12, J = 10 Hz, N- CH_3), and 6.75-7.35 (m, 3, ArH).

Anal. Calcd. for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_2\text{P}$: C, 67.67; H, 9.03; N, 7.17; P, 7.93. Found: C, 67.80; H, 8.91; N, 7.10; P, 8.01.

1,3,5(10)-Estratriene (203)

To a solution of 40.5 mg (0.103 mmole) of the phosphorodiamidate 202 in 5 ml of dry tetrahydrofuran and 50 ml of ammonia was added ca. 10 mg of lithium wire. After stirring for 15 min at reflux, sufficient ethanol was added dropwise to dissipate the blue color (about 0.5 ml). The ammonia was

allowed to evaporate under a slow stream of nitrogen. The mixture was then diluted with 50 ml of water, and the aqueous mixture was extracted with 3 x 25 ml of ether. The combined extracts were washed with 20 ml of water, 2 x 20 ml of 5% hydrochloric acid, 20 ml of saturated sodium bicarbonate, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 28 mg of a yellow oil, consisting of one volatile component by vpc (column A, 300°).

Filtration through 2 g of silica gel with benzene yielded 25 mg (100%) of pure hydrocarbon 203. Recrystallization from methanol gave colorless crystals, mp $80.5-81^\circ$ (lit. (200), mp 76°): nmr (CDCl_3) δ 0.75 (s, 3, angular CH_3), and 7.01-7.50 (m, 4, ArH).

3,5a β ,11a β ,13a α -Tetramethyl-1,2,4,5,5a,5b α ,6,7,11a,12,13,13a,-13b β -tridecahydrocyclopenta[a]chrysene (X-5)

A. From the 3-methoxy olefin 195. The general procedure of Mann and Pragnell (201) was followed for the cleavage of the phenolic methyl group. To a solution of 0.6 mmole of lithium diphenylphosphide (prepared from 111.6 mg, 0.6 mmole of diphenylphosphine and 0.66 mmole of *n*-butyllithium in hexane) was added 80 μl of TMEDA. To the deep orange solution was added 36.4 mg (0.1 mmole) of the 3-methoxy olefin 195. After the olefin dissolved, the mixture was heated at reflux for 19 hours, during which time the solvent had to be replenished. The reaction was quenched by the addition of 1 ml of

water. After the orange color had disappeared, the mixture was diluted with 30 ml of ether, washed with 10 ml of 5% hydrochloric acid, 10 ml of water, 10 ml of saturated sodium bicarbonate, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 110 mg of an oil, which contained one major peak by vpc (column A, 300°).

Preparative tlc (2:9 ether-pet. ether) afforded 32 mg (91.4%) of the major product, the phenol X-1 ($R_f = 0.25$). Recrystallization from ether-hexane yielded white crystals, mp $188-191^\circ$ (decomp): ir (CHCl_3) 3600 cm^{-1} (OH); nmr (CDCl_3) δ 0.70, 1.01, 1.20 (3 s, 9, angular CH_3), 4.58 (br s, 1, OH), and 6.43-7.43 (m, 3, ArH).

Anal. Calcd. for $\text{C}_{25}\text{H}_{34}\text{O}$: C, 85.66; H, 9.78. Found: C, 85.57; H, 9.74.

To a solution of 17.5 mg (0.05 mmole) of the 3-hydroxy olefin X-1 and a few crystals of 1,10-phenanthroline in 1 ml of dry tetrahydrofuran was added enough ethereal methyl-lithium to impart a brown color to the solution, followed by 35 μl of triethylamine, 35 μl of HMPA, and 50 μl of the phosphorochloridate 148. After stirring at room temperature for 17 hours, the mixture was poured into 15 ml of water and extracted with 4 x 15 ml of ether. The combined extracts were washed with 10 ml of 5% hydrochloric acid, 10 ml of water, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 24 mg (99%) of white crystals, containing

the phosphorodiamidate X-3 as the only volatile component by vpc (column A, 300°); ir (CHCl₃) 1610 cm⁻¹ (C=C, 1,2,4-trisubst. benzene); nmr (CDCl₃) δ 0.70, 1.03, 1.20 (3 s, 9, angular CH₃), 2.58 (d, 12, J = 12 Hz, N-CH₃), and 6.80-7.33 (m, 3, ArH).

The crude phosphorodiamidate X-3 was dissolved in 15 ml of ammonia and 2 ml of dry tetrahydrofuran, and ca. 3 mg of lithium wire was added. The blue solution was stirred for 15 min at reflux, and 0.5 ml of ethanol was added, causing the blue color to disappear. The ammonia was evaporated under a stream of dry nitrogen, and the residue was dissolved in 20 ml of water and extracted with 3 x 15 ml of ether. The combined extracts were washed with 2 x 15 ml of water and dried (MgSO₄). Evaporation of the solvent at reduced pressure afforded 21 mg of an oil, containing one volatile component by vpc (column A, 300°).

Preparative tlc (benzene) afforded 16 mg (96%) of pure pentacyclic hydrocarbon X-5. Recrystallization from methanol and bulb-to-bulb distillation (167° @ 0.0015 mm) yielded analytically pure material, mp 99-101.5°; nmr (CDCl₃) δ 0.70, 1.03, 1.23 (3 s, 9, angular CH₃) and 7.01-7.45 (m, 4, ArH).

Anal. Calcd. for C₂₅H₃₄: C, 89.76; H, 10.24. Found: C, 89.85; H, 10.19.

B. From the 1-methoxy olefin 197. The olefin 197 was demethoxylated in a manner similar to the 3-methoxy isomer 195. A solution of 36.4 mg (0.1 mmole) of the pentacyclic olefin 197 in 200 μ l of tetrahydrofuran was added to a solution of lithium diphenylphosphide (prepared from 56 mg, 0.30 mmole, of diphenylphosphine, 150 μ l of a 2.2 M solution of *n*-butyllithium (0.33 mmole) in hexane, and 40 μ l of TMEDA). The orange solution was heated at reflux for 18 hours, and then 2 ml of water was added, causing the orange color to disappear. The mixture was diluted with 30 ml of ether and washed with 3 x 15 ml of 10% sodium hydroxide.* The combined washings were extracted with 3 x 20 ml of ether and acidified with concentrated hydrochloric acid. The aqueous solution was then extracted with 3 x 20 ml of ether. The combined extracts were washed with water and dried (MgSO_4). Evaporation of the solvent at reduced pressure yielded 7 mg of an oil which showed no aromatic stretching frequencies in the ir and no aromatic hydrogens in the nmr.

Evaporation of the basic extracts at reduced pressure afforded 98 mg of a colorless oil which contained some starting material and a new peak (column A, 300°) in a ratio of 1:3.

The major product was isolated by preparative tlc (benzene) ($R_f = 0.6$) and is assigned the 1-hydroxy compound X-2: ir (CHCl_3) 3590 (OH) and 1580 cm^{-1} (C=C, 1,2,3-trisubst.

* The phenolic product did not dissolve in the basic medium.

benzene); nmr (CDCl_3) δ 0.71, 1.01, 1.36 (3 s, 9, angular CH_3), and 6.35-7.33 (m, 3, ArH).

The phosphorodiamidation of the phenol X-2 and subsequent reduction was carried out without further purification of intermediates.

To a solution of 14 mg (0.04 mmole) of the phenol X-2 and a few crystals of 1,10-phenanthroline in 800 μl of dry tetrahydrofuran was added enough ethereal methyllithium to impart a brown color to the solution. To this mixture was added, in succession, 30 μl of triethylamine, 30 μl of HMPA, and 40 μl of the phosphorochloridate 148. After 4 hours of stirring at room temperature, the mixture was poured into 10 ml of water and extracted with 3 x 15 ml of ether. The combined extracts were washed with 10 ml of water, 10 ml of saturated sodium bicarbonate, and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 26 mg of a pale yellow oil, consisting of one volatile component in >99% purity (column A, 300°). The product was assigned as the 1-phosphorodiamidate X-4: ir (CHCl_3) 3150 cm^{-1} (C=C, 1,2,3-trisubst. benzene); nmr (CDCl_3) δ 0.73, 1.03, 1.40 (3 s, 9, angular CH_3), 2.73 (d, 12, $J = 13\text{ Hz}$, N- CH_3), and 6.70-7.36 (m, 3, ArH).

To a solution of the crude phosphorodiamidate X-4 in 15 ml of ammonia and 2 ml of dry tetrahydrofuran was added ca. 3 mg of lithium wire, and the blue solution was stirred at reflux for 15 min. The excess lithium was destroyed by the

slow addition of 0.5 ml of ethanol. The ammonia was then allowed to evaporate under a stream of dry nitrogen.

The residue was dissolved in 20 ml of water and extracted with 3 x 15 ml of ether. The combined extracts were washed with 2 x 20 ml of water and dried (MgSO_4). Evaporation of the solvent at reduced pressure afforded 16 mg of an oily solid.

Preparative tlc (benzene) afforded 10 mg (74%) of white crystals, which were identical to the hydrocarbon X-5, which was prepared from the 3-methoxy olefin 195. Recrystallization from methanol afforded colorless microneedles, mp 97.5-99.5°. A mixed sample of the products from the two sources had mp 98.5-101.5°. Quantitative peak enhancement (column A, 300°) indicated only one volatile component.

References

1. G. Ourisson, P. Crabbé, and O.R. Rodig, "Tetracyclic Triterpenes," Holden-Day, Inc., San Francisco, 1964.
2. J. Siminsen and W.C.J. Ross, "The Terpenes," Vol. IV, Cambridge University Press, Cambridge, 1957, p 287.
3. B. Bischoff, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 32, 1911 (1949).
4. T.G. Halsall and R. Alpin, Fortschr. Chem. Org. Naturstoffe, 22, 153 (1964).
5. D.E. White, Rev. Pure Appl. Chem., 6, 191 (1956).
6. P. de Mayo, "The Higher Terpenoids," Interscience, New York, 1959.
7. J.A. Barltrop and N.A.J. Rogers, Prog. in Org. Chem., 5, 96 (1961).
8. A.R. Pinder, "Chemistry of the Terpenes," John Wiley and Sons, New York, 1960.
9. W. Templeton, "An Introduction to the Chemistry of the Terpenoids and Steroids," Butterworths, London, 1969.
10. T.K. Devon and A.I. Scott, "Handbook of Naturally Occurring Compounds," Vol. II, Terpenes, Academic Press, New York and London, 1972.
11. J.D. Connolly and K.H. Overton in A.A. Newman, ed., "Chemistry of Terpenes and Terpenoids," Chap. 5, Academic Press, New York and London, 1972.
12. R.B. Woodward and K. Bloch, J. Am. Chem. Soc., 75, 2023 (1953).
13. W.G. Dauben, S. Abraham, S. Hotta, I.L. Charkoff, H.L. Bradlow, and A.H. Soloway, ibid., 3038 (1953).
14. T.T. Tchen and K. Bloch, ibid., 77, 6065 (1955).
15. R.B. Clayton and K. Bloch, J. Biol. Chem., 218, 319 (1956).
16. R.B. Clayton, Quart. Rev. (London), 19, 168 (1965).

17. G. Stork and A.W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955).
18. A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, Helv. Chim. Acta, 38, 1890 (1955).
19. E.J. Corey, W.E. Russey, and P.R. Ortiz de Montellano, J. Am. Chem. Soc., 88, 4750 (1966).
20. E.E. van Tamelen, J.D. Willett, R.B. Clayton, and K.E. Lord, ibid., 88, 4752 (1966).
21. E. Capstack, Jr., N. Rosin, G.A. Blondin, and W.R. Nes, J. Biol. Chem., 240, 3258 (1965).
22. W.O. Godfredsen, H. Lorck, E.E. van Tamelen, J.D. Willett, and R.B. Clayton, J. Am. Chem. Soc., 90, 208 (1968).
23. For a comprehensive description of the possible modes of squalene cyclization and backbone rearrangements, see J.H. Richards and J.B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W.A. Benjamin, Inc., New York, 1964.
24. A.M. Patterson, L.T. Capell, and D.F. Walker, "The Ring Index," American Chemical Society, Washington, D.C., 1960.
25. J.F. King and P. de Mayo in P. de Mayo, ed., "Molecular Rearrangements," Interscience, New York, 1964, Chap. 13.
26. a. H. Dutler, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 38, 1268 (1955).
b. G. Brownlie, F.S. Spring, R. Stevenson, and W.S. Strachan, Chem. and Ind., 656 (1955).
c. E.J. Corey and J.J. Ursprung, J. Am. Chem. Soc., 77, 3667 (1955).
d. J.L. Courtney, R.M. Gascoigne, and A.Z. Szumer, J. Chem. Soc., 881 (1958).
27. a. F.S. Spring, J.M. Beaton, R. Stevenson, and J.L. Stewart, Chem. and Ind., 1954 (1956).
b. J.M. Beaton, F.S. Spring, R. Stevenson, and J.L. Stewart, Tetrahedron, 2, 246 (1958).
28. G. Brownlie, M.B.E. Fayez, F.S. Spring, R. Stevenson, and W.S. Strachan, J. Chem. Soc., 1372 (1952).

29. R.M. Coates, Tetrahedron Letters, 4143 (1967).
30. S. Yamada, S. Yamada, Y. Muriyama, Y. Tanahashi, and T. Takahashi, ibid., 5043 (1972).
31. G. Stork, J.E. Davies, and A. Meisels, J. Am. Chem. Soc., 85, 3419 (1967).
32. D.H.R. Barton and K.H. Overton, J. Chem. Soc., 2639 (1955).
33. K. Schaffner, L. Caglioti, D. Arigoni, and O. Jeger, Helv. Chim. Acta, 41, 152 (1958).
34. D.A. Evans, Ph. D. Thesis, California Institute of Technology, 1968.
35. J.W. Tilley, Ph. D. Thesis, California Institute of Technology, 1972.
36. T.G. Halsall and D.B. Thomas, J. Chem. Soc., 2431 (1956).
37. E.J. Corey, H.-J. Hess, and S. Proskow, J. Am. Chem. Soc., 81, 5258 (1959); ibid., 85, 3979 (1963).
38. J.A. Barltrop, J.D. Littlehailes, J.D. Rushton, and N.A.J. Rogers, Tetrahedron Letters, 429 (1962).
39. E. Ghera and F. Sondheimer, ibid., 3887 (1964).
40. D.H.R. Barton, E.F. Lier, and J.F. McGhie, J. Chem. Soc., 1031 (1968).
41. R.E. Ireland and S.C. Welch, J. Am. Chem. Soc., 92, 7232 (1970).
42. R.E. Ireland, S.W. Baldwin, D.J. Dawson, M.I. Dawson, J.E. Dolfini, J. Newbould, W.S. Johnson, M. Brown, R.J. Crawford, P.F. Hudrlik, G.H. Rasmussen, and K.K. Schmiegel, ibid., 92, 5743 (1970).
43. S.W. Baldwin, Ph. D. Thesis, California Institute of Technology, 1968.
44. D.J. Dawson, Ph. D. Thesis, California Institute of Technology, 1971.
45. a. W. Nagata, M. Yoshioka, and S. Hirai, Tetrahedron Letters, 461 (1962).
b. W. Nagata and M. Yoshioka, ibid., 1913 (1966).

For a complete description of the scope, limitations, kinetics, mechanism, and stereochemistry of this versatile reaction, see:

- c. W. Nagata, M. Yoshioka, and S. Hirai, J. Am. Chem. Soc., 94, 4635 (1972).
 - d. W. Nagata, M. Yoshioka, and M. Murakami, ibid., 4644, 4654 (1972).
 - e. W. Nagata, M. Yoshioka, and T. Terasawa, ibid., 4672 (1972).
46. R.E. Ireland, D.A. Evans, D. Glover, G.M. Rubottom, and H. Young, J. Org. Chem., 34, 3717 (1969).
 47. a. A.A. Akhrem and Y.-A. Titov, "Total Steroid Synthesis," Plenum Press, New York, 1970.
b. For a related approach to triterpenoid synthesis, see J.W. ApSimon, P. Baker, J. Buccini, J.W. Hooper, and S. Macaulay, Can. J. Chem., 50, 1945 (1972).
 48. Unpublished results of C.J. Kowalski in this laboratory.
 49. G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, J. Am. Chem. Soc., 93, 4945 (1971).
 50. E.E. van Tamelen, Fortschr. Chem. Org. Naturstoffe, 19, 245 (1961); Acc. Chem. Res., 1, 111 (1968).
 51. a. E.E. van Tamelen, M.A. Schwartz, E.J. Hessler, and H. Storni, Chem. Commun., 409 (1966).
b. K.B. Sharpless, J. Am. Chem. Soc., 92, 6999 (1970).
c. E.E. van Tamelen, G.M. Milne, M.I. Suffness, M.C.R. Chauvin, R.J. Anderson, and R.S. Achini, ibid., 7202 (1970).
d. E.E. van Tamelen and J.W. Murphy, ibid., 7204 (1970).
e. E.E. van Tamelen and R.J. Anderson, ibid., 94, 8225 (1972).
f. E.E. van Tamelen, R.A. Holton, R.E. Hopla, and W.E. Konz, ibid., 8228 (1972).
g. E.E. van Tamelen, M.P. Seiler, and W. Wierenga, ibid., 8229 (1972).

52. J.L. Simonsen and L.N. Owen, "The Terpenes," Vol. I, Cambridge University Press, Cambridge, 1947.
53. D.C. Hibbit and R.P. Linstead, J. Chem. Soc., 470 (1936).
54. P.G. Stevens and S.C. Spalding, J. Am. Chem. Soc., 71, 1687 (1949). See also: W.S. Johnson and J.K. Crandall, J. Org. Chem., 30, 1785 (1965).
55. J.W. Cook and C.L. Hewett, J. Chem. Soc., 365 (1934).
56. a. R.P. Linstead, A.B.L. Wang, J.H. Williams, and K.D. Errington, ibid., 1136 (1937).
b. R.P. Linstead, A.F. Millidge, and A.L. Walpole, ibid., 1140 (1937).
c. V.C.E. Burnop and R.P. Linstead, ibid., 720 (1940).
57. G. Stork and H. Conroy, J. Am. Chem. Soc., 73, 4758 (1951).
58. P.A. Stadler, A. Nechvatal, A.J. Frey, and A. Eschenmoser, Helv. Chim. Acta, 40, 1373 (1957).
59. A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Staevin, "Ciba Foundation Symposium of the Biosynthesis of Terpenes and Sterols," G.E.W. Wolsterholme and M. O'Connor, eds., J. and A. Churchill, Ltd., London, 1959.
60. W.S. Johnson, Pure Appl. Chem., 7, 317 (1963).
61. K.E. Harding, Ph. D. Thesis, Stanford University, 1968.
62. K.E. Harding, R.C. Ligon, T.-C. Wu, and L. Rode, J. Am. Chem. Soc., 94, 6425 (1972).
63. W.S. Johnson, Acc. Chem. Res., 1, 1 (1968).
64. E.E. van Tamelen, ibid., 111 (1968).
65. a. W.D. Closson and D. Gray, J. Org. Chem., 35, 3737 (1970).
b. H. Felkin and C. Lion, Tetrahedron, 27, 1375, 1387 (1971)
- See also: P.T. Lansbury and E.J. Nienhouse, J. Am. Chem. Soc., 88, 4290 (1966).
66. a. D.J. Goldsmith, ibid., 84, 3913 (1962).

- b. D.J. Goldsmith and C.J. Cheer, J. Org. Chem., 30, 2264 (1965).
- c. D.J. Goldsmith and B.C. Clark, Jr., Tetrahedron Letters, 1215 (1967).
- d. E.E. van Tamelen and J.P. McCormick, J. Am. Chem. Soc., 91, 1847 (1969).
- e. K.B. Sharpless and E.E. van Tamelen, ibid., 91, 1848 (1969).
- f. D.J. Goldsmith and C.F. Phillips, ibid., 5862 (1969).
- g. M.A. McKervey and J.R. Wright, Chem. Commun., 117 (1970).
- h. S.K. Talapatra, A. Patra, and B. Talapatra, ibid., 1534 (1970).
67. a. W.S. Johnson and R.B. Kinnel, J. Am. Chem. Soc., 88, 3861 (1966).
- b. W.S. Johnson, A. van der Gen, and J.J. Svoboda, ibid., 89, 170 (1967).
- c. W.S. Johnson, K. Wiedhaup, S.F. Brady, and G.L. Olson, ibid., 90, 5277 (1968).
- d. W.S. Johnson, C.A. Harbert, and R.D. Stipanovic, ibid., 5279 (1968).
- e. W.S. Johnson, Trans. N.Y. Acad. Sci., Vol. 2, 29, 1001, (1967).
- f. G.D. Abrams, W.R. Bartlett, V.A. Fung, and W.S. Johnson, Bioorg. Chem., 1, 243 (1971).
- g. A. van der Gen, K. Wiedhaup, J.J. Svoboda, H.C. Dunathan, and W.S. Johnson, J. Am. Chem. Soc., 95, 2656 (1973).
68. a. J.A. Marshall, N.H. Andersen, and R.C. Johnson, ibid., 89, 2748 (1967).
- b. J.A. Marshall and N.H. Andersen, Tetrahedron Letters, 1219 (1967).
- c. R.E. Ireland, M.I. Dawson, J. Bordner, and R.E. Dickerson, J. Am. Chem. Soc., 92, 2568 (1970).

- d. M.A. Schwartz, J.D. Crowell, and J.H. Musser, ibid., 94, 4361 (1972).
- e. K. Sakai and O. Oda, Tetrahedron Letters, 4375 (1972).
- f. K. Salai, J. Ide, O. Oda, and N. Nakamura, ibid., 1287 (1972).
- g. N.H. Andersen, H. Uh, S.E. Smith, and P.G.M. Wuts, Chem. Commun., 956 (1972).
69. a. W.S. Johnson, W.H. Lunn, and K. Fitzzi, J. Am. Chem. Soc., 86, 1972 (1964).
- b. J.A. Marshall and N. Cohen, ibid., 87, 2773 (1965).
- c. W.S. Johnson, P.J. Neustaedler, and K.K. Schmiegel, ibid., 5148 (1965).
- d. J.A. Marshall, N. Cohen, and A.K. Hochstettler, ibid., 88, 3408 (1966).
- e. W.S. Johnson, N.P. Jensen, and J. Hooz, ibid., 88, 3859 (1966).
- f. W.S. Johnson and K.E. Harding, J. Org. Chem., 32, 478 (1967).
- g. W.S. Johnson, M.F. Semmelhack, M.U.S. Sultanbawa, and L.A. Dolak, J. Am. Chem. Soc., 90, 2994 (1968).
- h. W.S. N.P. Jensen, J. Hooz, and E.J. Leopold, ibid., 5879 (1968).
- i. W.S. Johnson and T.K. Schaaf, Chem. Commun., 611 (1969).
- j. W.S. Johnson, T. Li, C.A. Harbert, W.R. Bartlett, T.R. Herrin, B. Staskin, and D.H. Rich, J. Am. Chem. Soc., 92, 4461 (1970).
- k. J.A. Marshall and G.M. Cohen, J. Org. Chem., 36, 877 (1971).
- l. K.E. Harding and W.D. Nash, Tetrahedron Letters, 4972 (1972).
- m. J.A. Marshall, W.F. Huffman, and J.A. Ruth, J. Am. Chem. Soc., 94, 4691 (1972).
- n. P. Naegli and R. Kaiser, Tetrahedron Letters, 2013 (1972).

- o. N.H. Andersen and D.D. Syrdal, ibid., 2455 (1972).
- p. M. Yamasaki, Chem. Commun., 606 (1972).
70. a. W.S. Johnson, M.B. Gravestock, R.J. Parry, R.F. Myers, T.A. Bryson, and D.H. Miles, J. Am. Chem. Soc., 93, 4330 (1971).
- b. W.S. Johnson, M.B. Gravestock, and B.E. McCarry, ibid., 93, 4332 (1971).
- c. W.S. Johnson, M.B. Gravestock, R.J. Parry, and D.A. Okorie, ibid., 94, 8604 (1972).
71. a. G. Stork and M. Marx, ibid., 91, 2371 (1969).
- b. G. Stork and M. Gregson, ibid., 2373 (1969).
- c. G. Stork and P.A. Grieco, ibid., 2407 (1969); Tetrahedron Letters, 1809 (1971).
72. P.T. Lansbury and G.E. Dubois, Chem. Commun., 1107 (1971).
73. R.E. Ireland, S.W. Baldwin, and S.C. Welch, J. Am. Chem. Soc., 94, 2056 (1972).
74. C.J. Kowalski, M.S. Thesis, California Institute of Technology, 1971.
75. C.A. Lipinski, unpublished results in this laboratory.
76. W.S. Johnson and J.K. Crandall, J. Am. Chem. Soc., 86, 1784 (1964).
77. K.E. Harding, Bioorg. Chem., 2, 248 (1973).
78. a. D.J. Faulkner, Synthesis, 175 (1971).
- b. J. Reucroft and P.G. Sammes, Quart. Rev. (London), 25, 135 (1971).
79. a. K. Stephan, J. Prakt. Chem., 58, 109 (1898).
- b. V. Prelog and E. Watanabe, Ann., 603, 1 (1957).
80. a. H.L. Goering and R.R. Josephson, J. Am. Chem. Soc., 84, 2779 (1962).
- b. H.L. Goering and D.L. Towns, ibid., 85, 2295 (1963).
- c. H.L. Goering and V. Mayer, ibid., 86, 3753 (1964).

81. J.A. Marshall, G.L. Bundy, and W.I. Fanta, J. Org. Chem., 33, 3913 (1968).
82. H.W. Whitlock, Jr. and L.E. Overman, ibid., 34, 1962 (1969).
83. R.E. Ireland, D.R. Marshall, and J.W. Tilley, J. Am. Chem. Soc., 92, 4754 (1970).
- See also: E. Wenkert and D.A. Berges, ibid., 89, 2507 (1967).
84. D.C. Muchmore, unpublished results in this laboratory.
85. G. Stork, A. Brizzolara, H. Landesmann, J. Szmuszkovicz, and R. Terrel, J. Am. Chem. Soc., 85, 207 (1963).
86. O.J. Sweeting and J.R. Johnson, ibid., 68, 1057 (1946).
87. M.S. Kharash and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice Hall, New York, 1954.
88. R.E. Ireland, M.I. Dawson, and C.A. Lipinski, Tetrahedron Letters, 2247 (1970).
89. J.A. Katzenellenbogen and R.S. Lenox, ibid., 1471 (1972), and references cited therein.
90. a. G. Zweifel and H.C. Brown, Org. React., 13, 1 (1963).
b. H.C. Brown, "Hydroboration," W.A. Benjamin, Inc., 1962.
c. H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca (1972).
91. H.C. Brown and G. Zweifel, J. Am. Chem. Soc., 82, 3222, 3223 (1960).
92. H.C. Brown and A.W. Moerikofer, ibid., 85, 2063 (1963).
93. W.M. Coates and J.R. Corrigan, Chem. and Ind., 1594 (1969).
94. a. J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Letters, 3363 (1968).
b. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
95. W.S. Johnson, D.M. Bailey, R. Owyang, R.A. Bell, B. Jacques, and J.K. Crandall, J. Am. Chem. Soc., 86, 1959 (1964).

96. P. Bey, Unpublished results in this laboratory.
97. R. Czarny, M.S. Thesis, California Institute of Technology, 1972.
98. M. Cherest and H. Felkin, Tetrahedron Letters, 2205 (1968).
99. N.L. Allinger and M.A. Miler, J. Am. Chem. Soc., 83, 2145 (1961).
100. P. Teisseire, A. Galfre, M. Platter, and B. Corbier, Recherches, No. 15, 52 (1966); C.A. 65, 15430a (1966).
101. W. Kirchoff, Chem. Ber., 93, 2712 (1960).
102. V.S. Jorhi, N.P. Damodaran, and S. Dev, Tetrahedron, 24, 5817 (1968).
103. E.H. Eschinasi, Israel J. Chem., 6, 713 (1968); J. Org. Chem., 35, 1598 (1970).
104. O. Riobe, Compt. Rend. 248, 2774 (1959).
105. D.H.R. Barton, A. da S. Campos-Neves, and R.C. Cookson, J. Chem. Soc., 3500 (1956).
106. R.B. Turner, W.R. Meador, and R.B. Winkler, J. Am. Chem. Soc., 79, 4122 (1957).
107. D.A.H. Taylor, Chem. and Ind., 250 (1954).
108. L.A. Burk and M.D. Soffer, Tetrahedron Letters, 4367 (1971).
109. F. Sondheimer and M. Nussim, J. Org. Chem., 26, 630 (1961).
110. A.R. Hochstettler, ibid., 37, 1883 (1972).
111. G. Zweifel and H.C. Brown, J. Am. Chem. Soc., 85, 2066 (1963).
112. E.F. Knights and H.C. Brown, ibid., 90, 5280, 5281 (1968).
113. N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, pp 77-85.
114. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, John Wiley and Sons, New York, 1967, p 135.

115. H.B. Henbest and T.I. Wrigley, J. Chem. Soc., 4596 (1957).
116. H.C. Brown, S.I. Ikegami, and S.H. Kawakami, J. Org. Chem., 35, 3243 (1970).
117. W.S. Johnson, L. Werthemann, W.R. Bartlett, T.J. Brockson, T. Li, D.J. Faulkner, and M.R. Petersen, J. Am. Chem. Soc., 92, 741 (1970).
118. A. Juvala, Chem. Ber., 63B, 1989 (1930).
119. O. Grummit, E.P. Budewitz, and C.C. Chudd, Org. Syn., Coll. Vol. IV, 749 (1963).
120. J.D. Roberts and R.H. Mazur, J. Am. Chem. Soc., 73, 2509 (1951).
121. R.I. Trust and R.E. Ireland, Org. Syn., 53, in press.
- Added note: The synthesis of the allylic alcohol 96b and its conversion to ester 97b by the same method as described herein has been recently reported; M.P. Cooke, Jr., Tetrahedron Letters, 1281 (1973).
122. a. I.M. Downie, J.B. Holmes, and J.B. Lee, Chem. and Ind., 900 (1966).
- b. J.B. Lee, J. Am. Chem. Soc., 88, 3440 (1966).
- c. J.B. Lee and T.J. Nolan, Tetrahedron, 23, 2789 (1967); Can. J. Chem., 44, 1331 (1966).
123. a. P.E. Pfeffer and L.S. Silbert, J. Org. Chem., 35, 262 (1970).
- b. P.E. Pfeffer, L.S. Silbert, and J.M. Chirinko, Jr., ibid., 37, 451 (1972).
124. E.H. White, H.P. Tiwari, and M.J. Todd, J. Am. Chem. Soc., 90, 4734 (1968).
125. a. E.E. van Tamelen and T.J. Curphey, Tetrahedron Letters, 121 (1962).
- b. E.E. van Tamelen and K.B. Sharpless, ibid., 2655 (1967).
126. J.D. Roberts and M.C. Caserio, "Basic Principles of Organic Chemistry," W.A. Benjamin, Inc., New York, 1964, Cap. 22.

127. T.C. Clarke and R.G. Bergman, J. Am. Chem. Soc., 94, 3627 (1972).
128. For a review, see F.D. Popp and W.E. McEwen, Chem. Rev., 58, 321 (1958).
129. G.A.R. Kon, J. Chem. Soc., 1031 (1933).
130. E.D. Hughes, G. . Ingold, S. Masterman, and B.J. McNulty, ibid., 899 (1940).
131. R.A. Gillham, Jr., Ph.D. Thesis, California Institute of Technology, 1969.
132. J.H. Ham, IV, unpublished results in this laboratory.
133. A. Bayer, Chem. Ber., 28, 1586 (1895).
134. a. T. Norin, Acta Chem. Scand., 19, 1289 (1965).
b. W.G. Dauben and E. Deviny, J. Org. Chem., 31, 3794 (1966)
135. S.W. Staley in B.J. Thyagarajan, ed., "Selective Organic Transformation," Vol. 2, Wiley-Interscience, New York, 1972, p. 309.
136. R. Fraisse-Jullien and C. Frejaville, Bull. Soc. Chim. Fr., 4449 (1968).
137. B.A. Arbuzov, L.K. Yuldasheva, and R.P. Arshinova, Bull. Acad. Sci. USSR, 923 (1969).
138. R. Baltzly, E. Lorz, P.B. Russel, and F.M. Smith, J. Am. Chem. Soc., 77, 624 (1955).
139. R.N. Icke, C.E. Rademann, B.B. Wisegarver, and G.A. Alles, Org. Syn., Coll. Vol. III, 564 (1955).
140. H.E. Simmons and R.D. Smith, J. Am. Chem. Soc., 80, 5324 (1963).
141. E. LeGoff, J. Org. Chem., 29, 2048 (1964).
142. W.G. Dauben and G.H. Berezin, J. Am. Chem. Soc., 85, 468 (1963).
143. K. Bowden, I.M. Heilbron, E.R.H. Jones, and B.C.L. Weedon, J. Chem. Soc., 39 (1946).
144. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 87, 1353 (1965).

145. W.G. Dauben and R.E. Wolf, J. Org. Chem., 35, 2361 (1970).
146. G.C. Gerrans, unpublished results in this laboratory.
147. G. Stork, H.J.K. Lowenthal, and P.C. Mukharji, J. Am. Chem. Soc., 78, 501 (1956).
148. R.L. Augustine in J. Fried and J.A. Edwards, "Organic Reactions in Steroid Chemistry," Van Nostrand Reinhold, New York, 1972, Chap. 3.
149. W. Nagata, T. Terasawa and K. Tori, J. Am. Chem. Soc., 86, 3746 (1964).
150. A.J. Birch and H. Smith, Quart. Rev. (London), 12, 17 (1958).
151. J.A. Barltrop and N.A.J. Rogers, Chem. and Ind., 20 (1957).
152. H.O. House, W.L. Respess, and G.M. Whitesides, J. Org. Chem., 31, 3128 (1966).
153. For reviews on the synthetic uses of organocopper reagents, see J.F. Normant, Synthesis, 63 (1972); and G.H. Posner, Org. React., 19, 1 (1972).
154. W. Nagata and H. Itazaki, Chem. and Ind., 1194 (1964).
155. L. Cagliotti, Tetrahedron, 22, 487 (1966).
156. a. R.E. Ireland and G. Pfister, Tetrahedron Letters, 2145 (1969).
- b. M. Fetizon, M. Jurion, and N.T. Anh, Chem. Commun., 112 (1969).
- c. D.C. Muchmore, Org. Syn., 52, 109 (1972).
157. a. D.C. Muchmore, Ph. D. Thesis, California Institute of Technology, 1971.
- b. R.E. Ireland, D.C. Muchmore, and U. Hengartner, J. Am. Chem. Soc., 94, 5098 (1972).
158. a. E. Crunden and F. Hudson, J. Chem. Soc., 3591 (1962).
- b. H.G. Cook, J.D. Ilett, B.C. Saunders, G.J. Stacey, H.G. Watson, I.G. Wilding, and S.J. Woodcock, ibid., 2921 (1949).

159. We are grateful to Dr. Marsh and Mr. Sherfinski for performing the X-ray structure determination.
160. D.J. Duchamp, Program and Abstracts, Am. Cryst. Assoc. Mtg., Bozeman, Montana, Paper B-14 (1964).
161. Ref. 114, p. 894.
162. J.-F. Moser, unpublished results in this laboratory.
163. a. M. Gaudemar, Ann. Chim. (Paris), 190 (1956).
b. C. Prevost, M. Gaudemar, L. Miginiac, F. Bardone-Gaudemar, and M. Andrac, Bull. Soc. Chim. Fr., 679, (1959).
164. F. Sondheimer, Y. Amiel, and Y. Gaoni, J. Am. Chem. Soc., 84, 270 (1962).
165. K.C. Frisch and R.B. Young, ibid., 74, 4853 (1952).
166. B.G. Shakhovskoi, M.D. Stadnichuk, and A.A. Petrov, J. Gen. Chem. USSR, 34, 2646 (1964).
167. E.J. Corey and H.A. Kirst, Tetrahedron Letters, 5041 (1968).
168. J.F. Rutledge, "Acetylenes and Allenes," Reinhold, New York, 1969, p 35.
169. H.M. Schmidt and J.F. Arens, Rec. Trav. Chim., 86, 1138, (1967).
170. H.C. Brown and G. Zweifel, J. Am. Chem. Soc., 81, 1512 (1959); 83, 3834 (1961).
171. F. Sondheimer, ibid., 74, 4040 (1952).
172. a. E.J. Corey, J.A. Katzenellenbogen, and G.H. Posner, ibid., 89, 4245 (1967).
b. J.A. Katzenellenbogen, Ph. D. Thesis, Harvard University, 1969.
173. E.J. Corey and G.H. Posner, J. Am. Chem. Soc., 89, 3911 (1967).
174. G. Stork, P.A. Grieco, and M. Gregson, Tetrahedron Letters, 1393 (1969).
175. M. Shamma and H.R. Rodriguez, Tetrahedron, 24, 6583 (1968).

176. R.M. Silverstein and G.C. Bassler, "Spectrometric Identification of Organic Compounds," Second ed., John Wiley and Sons, New York, 1963.
177. B. Koechlin and T. Reichstein, Helv. Chim. Acta, 37, 549 (1944).
178. M. Meisters and T. Mole, Chem. Commun., 595 (1972).
179. F.A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Third ed., Interscience, New York, 1972, p. 203.
180. a. R. Greenwald, M. Chaykovsky, and E.J. Corey, J. Org. Chem., 28, 1128 (1963).
b. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 84, 866 (1962).
181. R.M. Coates and R.L. Sowerby, ibid., 94, 4758, 5386 (1972).
182. E.J. Corey and D. Seebach, J. Org. Chem., 31, 4097 (1966).
183. H.B. Henbest and T.I. Wrigley, J. Chem. Soc., 4596 (1957).
184. For a general discussion on the structure and reactions of ylides, see A.W. Johnson, "Ylid Chemistry," Academic Press, New York and London, 1966.
185. W.S. Wadsworth, Jr. and W.D. Emmons, J. Am. Chem. Soc., 83, 1733 (1961).
186. E.J. Corey and G.T. Kwiatkowski, ibid., 90, 6816 (1968); ibid., 88, 5654 (1966).
187. T.H. Chan, E. Chang, and E. Vinokur, Tetrahedron Letters, 1137 (1970).
188. I. Kuwajima and M. Uchida, ibid., 649 (1972).
189. M.W. Rathke and R. Kow, J. Am. Chem. Soc., 94, 6854 (1972).
190. J.R. Shanklin, C.R. Johnson, J. Ollinger, and R.M. Coates, ibid., 95, 3429 (1973).
191. a. M. Yoshimine and M.J. Hatch, ibid., 89, 5831 (1967).
b. C.R. Johnson and C.W. Schroeck, ibid., 93, 5303 (1971).
c. T. Durst, R. Viau, R. Van Den Elzen, and C.H. Nguyen, Chem. Commun., 1334 (1967).

- d. J.M. Townsend and K.B. Sharpless, Tetrahedron Letters, 3313 (1972).
192. D.J. Peterson, J. Org. Chem., 32, 1717 (1967).
193. V. Prelog, S. Juhasz, A. Rezek, and P. Stern, Helv. Chim. Acta, 25, 907 (1942).
194. Cf. R.E. Ireland and L.N. Mander, J. Org. Chem., 32, 689 (1967).
195. H. Hunsdiecker, Chem. Ber., 75, 455 (1942).
196. N.C. Deno in G.A. Olah and P. v. R. Schleyer, eds., "Carbonium Ions," Vol. II, Wiley-Interscience, New York, 1970, Chap. 18.
197. R. Criegee, B. Marchand, and H. Wannowius, Ann., 550, 99 (1942).
198. D.H.R. Barton and D. Elad, J. Chem. Soc., 2085 (1956).
199. R. Criegee, Chem. Ber., 64, 260 (1931).
200. H. Dannenberg and T. Kohler, Naturwiss., 49, 397 (1962).
201. F.G. Mann and M.J. Pragnell, Chem. and Ind., 1386 (1964); J. Chem. Soc., 4120 (1965).
202. G.W. Kenner and N.R. Williams, ibid., 522 (1955).
203. R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W.M. McLamore, J. Am. Chem. Soc., 74, 4223 (1952).
204. A. Hagenbach, unpublished results in this laboratory.
205. J.T. Gerig and J.D. Roberts, J. Am. Chem. Soc., 88, 2791 (1966).
206. E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Interscience, New York, 1965.
207. E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 206.
208. C.R. Narayanan, N.R. Bhadane, and M.P. Sarma, Tetrahedron Letters, 1561 (1968).
209. M. Fetizon and G. Moreau, Bull. Soc. Chim. Fr., 3479 (1965).
210. M.J.T. Robinson, Tetrahedron Letters, 1685 (1965).

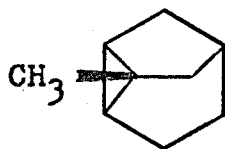
211. T. McKenzie, work in progress in this laboratory.
212. D. Walba, unpublished results in this laboratory.
213. T. Takahashi, T. Tsuyuki, T. Hoshino, and M. Ito, Tetra-
hedron Letters, 2997 (1967).

PROPOSITIONS

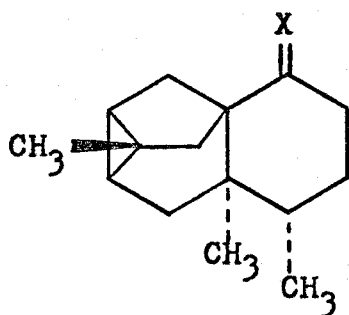
Proposition I

It is proposed to synthesize some terpenoid hydrocarbons which contain the 1-methyltricyclo[3.2.1.0^{2,7}]octane ring, as exemplified by ishwarane and trachylobane.

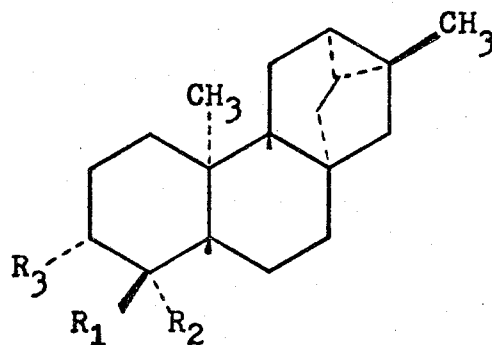
A number of terpenoid compounds have been isolated which contain the unusual 1-methyltricyclo[3.2.1.0^{2,7}]octane moiety (1) as part of their ring system. In the sesquiterpene

1

family, these compounds are represented by structure 2 (1a), while those in the diterpene family possess structure 3 (1b).



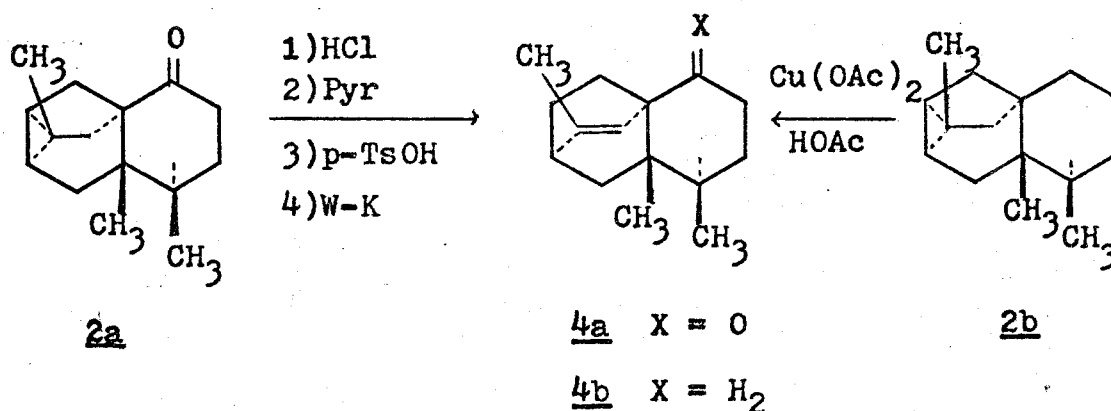
- 2a X = O
2b X = H₂
2c X = -OH, -H



- | | R ₁ | R ₂ | R ₃ |
|-----------|--------------------|-------------------|----------------|
| <u>3a</u> | CH ₂ OH | Me | H |
| <u>3b</u> | CO ₂ H | Me | OH |
| <u>3c</u> | CO ₂ H | Me | OAc |
| <u>3d</u> | CO ₂ H | Me | H |
| <u>3e</u> | Me | Me | H |
| <u>3f</u> | Me | CO ₂ H | H |

The first sesquiterpenes possessing structure 2 were named ishwarene, ishwarone, and ishwarol, all isolated in 1935 from the roots of the Indian vine Aristolochia indica, Linn. (2). These roots have been used for many years in the treatment of snake and poisonous insect bites (3). Structural elucidation of these compounds was achieved by Govindachari and coworkers for ishwarone (2a) (4-6), ishwarane (2b) (7), and ishwarol (2c) (8). Ishwarane (2b) is probably the hydrocarbon originally designated as ishwarene (2). This tetracyclic hydrocarbon has also been isolated from the essential oils of the flower petals of Cymbopetalum penduliflorum, Bail. (9), a source of beverage flavorings.

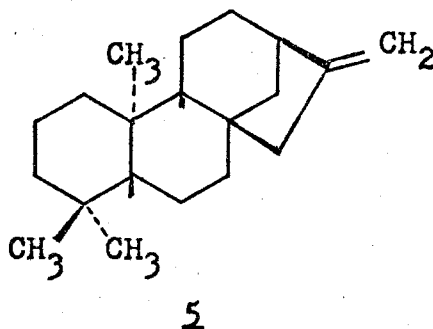
In the structural elucidation of ishwarone (2a), it was found that treatment with acid (5,6) afforded a ring-opened olefinic ketone, designated as isoishwarone (4a). Wolff-



Kishner reduction yielded the tricyclic olefin isoishwarane (4b), which was also formed (9) by treatment of ishwarane (2b) with cupric acetate in boiling acetic acid. The structure of 4b was confirmed by independent synthesis by Kelly

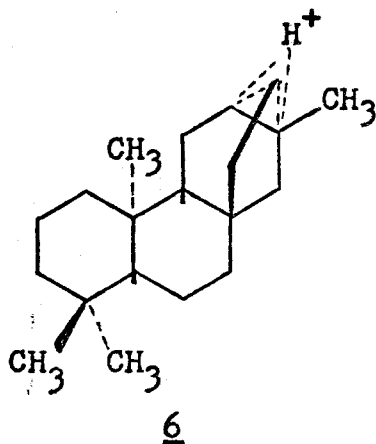
and coworkers (10), who later also synthesized ishwarane (2b) (11).

The isolation and characterization of the diterpenes possessing structure 3 is largely due to the work of Ourisson and coworkers (12). From the species Trachylobium verrucosum, Oliv., the following constituents were isolated: Trachylobanol (3a), 3 α -hydroxytrachylobanoic acid (3b), 3-acetoxytrachylobanoic acid (3c) and trachylobanoic acid (3d). Structural assignments of these pentacyclic compounds were readily made on the basis of spectral data and by chemical correlation with compounds possessing the kaurene skeleton (5) (13).

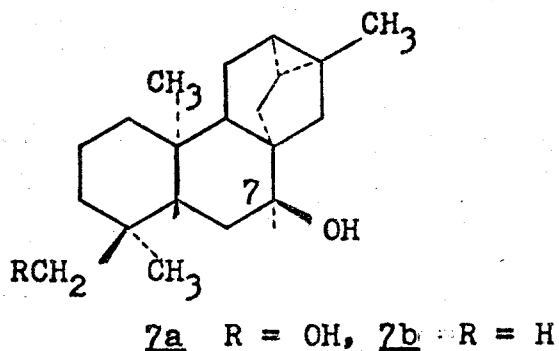


The isolation of compound possessing the structure of trachylobane (3e) completed the scheme of all possible diterpenoids derivable from the bridged cation 6, as proposed by Wenkert (14) as an intermediate in the biosynthetic pathway leading to the tetracyclic diterpenes.

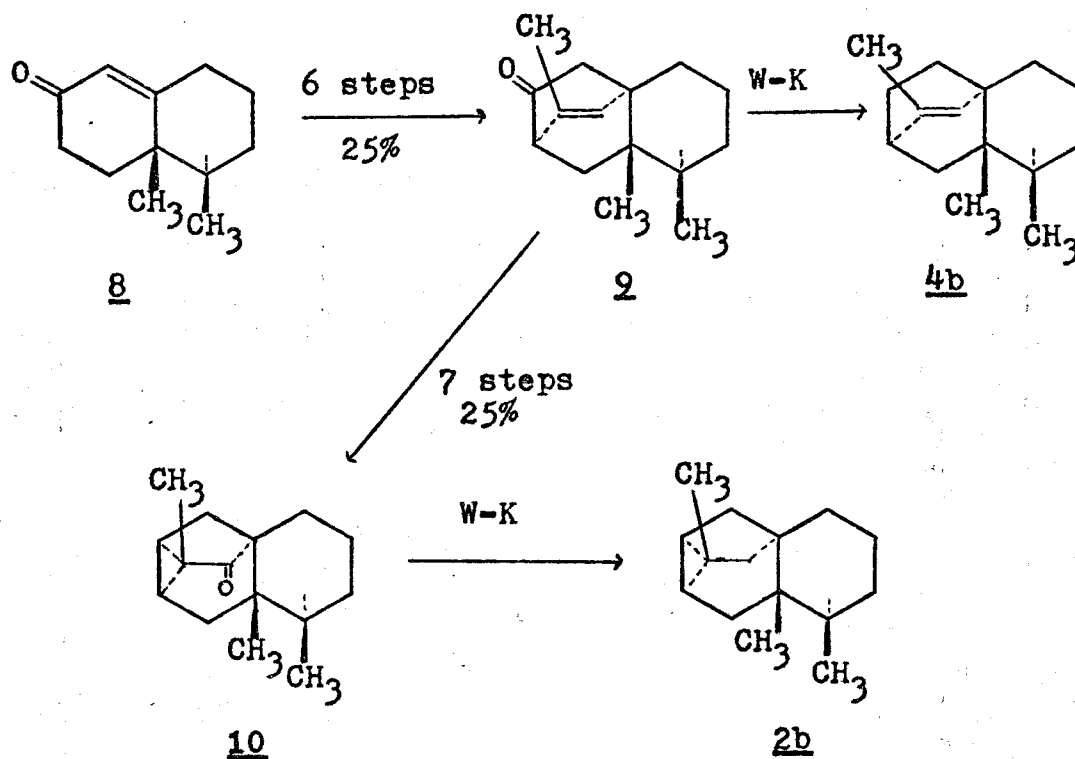
Recently, trachyloban-19-oic acid (3f) has been isolated from sunflowers (15) and its structure determined (16). In



addition, two new 7-hydroxy trachylobanes 7a and 7b have been isolated from Sideritis canariensis, Ait. (17), and have been named trachinodiol and trachinol, respectively.

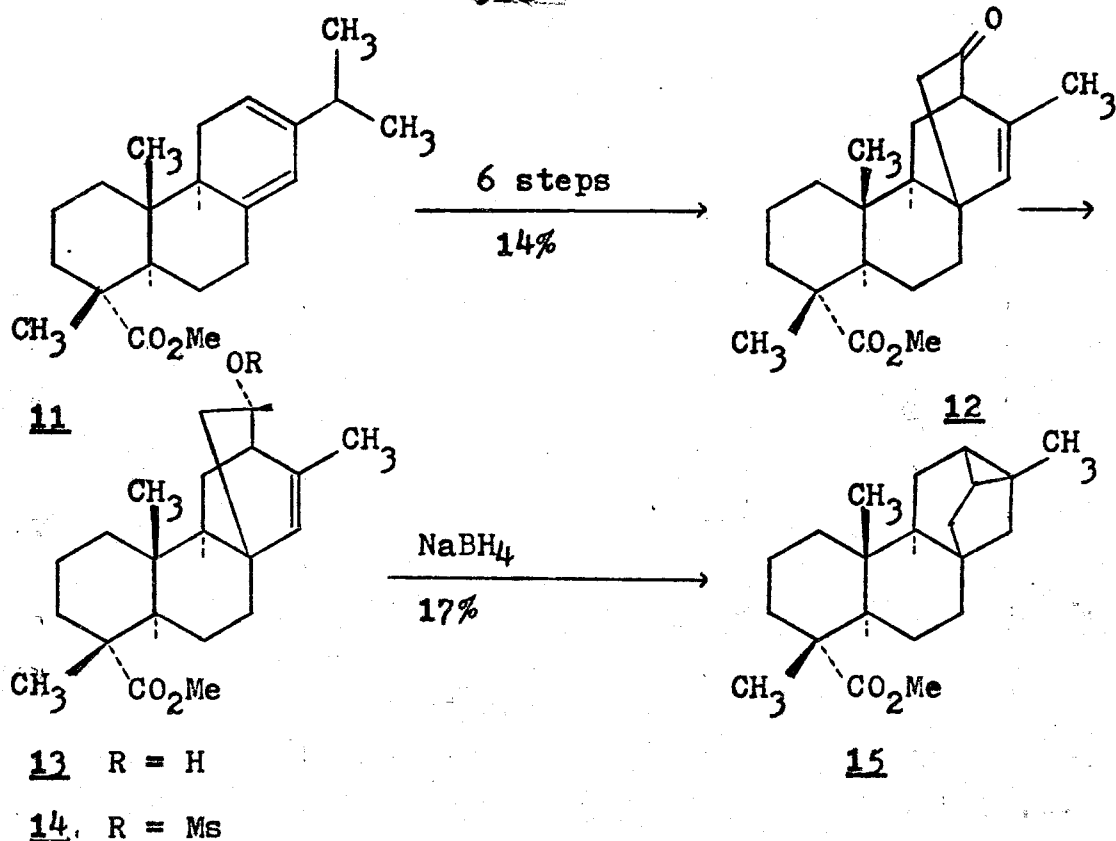


Synthetic endeavors towards these compounds have been scant, probably due to their structural complexity and lability of the cyclopropane group. In their synthesis of isoishwarane (4b), Kelly and Zamecnik (10) utilized the tricyclic enone 9 as a key intermediate. This enone was prepared in six steps from the octalone 8 (18-20) in about 25% yield. Transformation of the enone 9 into the tetracyclic ketone 10 (11) required seven additional steps, again in about 25% yield.

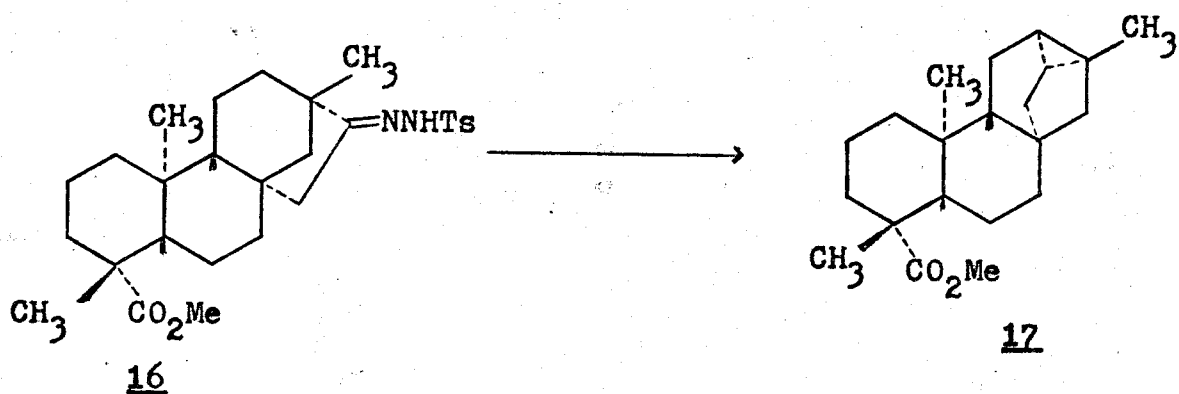


Entry into the trachylobane (2) field was achieved by Herz and coworkers (21) in a partial synthesis, beginning with levopimaric acid methyl ester (11). A six-step sequence afforded a 14% yield of the enone 12. In an attempt to effect a base-catalyzed cyclization, the carbonyl of enone 12 was reduced, and the major alcohol 13 was mesylated. An attempted hydroboration of the mesylate 14 led to spontaneous cyclization, and the desired ester 15 was obtained, albeit in only 17% yield.

In another partial synthesis, Coates and Bertram (22) decomposed the tosylhydrazone 16 derived from isosteviol methyl ester and obtained a four-component mixture in



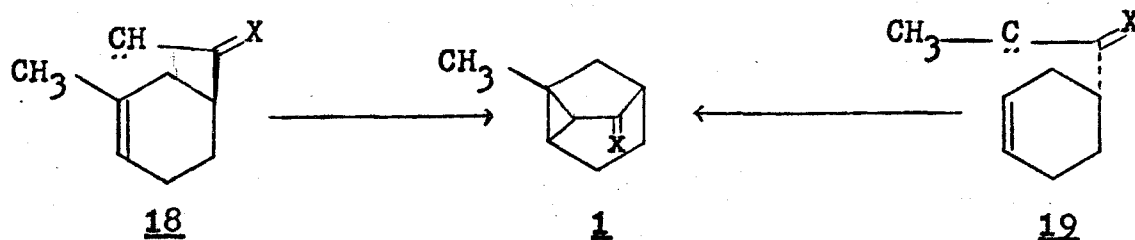
40-60% yield, of which ca. 25% consisted of methyl trachylo-
ban-19-oate (17).



Clearly, the above syntheses all suffer from low yields and the numerosity of steps necessary to construct the tri-cyclooctane ring system. Each of the above routes forms the three bonds of the cyclopropane individually.

It is suggested that a more efficient approach be sought

in which two bonds of the cyclopropane ring are formed at one time. This may be achieved via the intramolecular addition of a carbenoid substituent to a cyclic olefin, depicted below for the tricyclic system 1. Since the exact



nature of the carbenoid precursor is subject to variation, the synthetic studies will be divided into two separate phases: 1) synthesis of the polycyclic skeleton, and 2) synthesis of a suitable carbenoid precursor and its subsequent cyclization.

1. Construction of the polycyclic skeleton

a. Ishwarane (2b)

In order to decide exactly which two cyclopropane bonds should be formed in the final ring closure step, it is necessary to "hypothetically cleave" each of the three sets of two bonds in the cyclopropane ring, whose bonds are labelled a, b, and c (Figure 1). Of the three possibilities, structure 22, which results from "cleavage" of bonds b and c can be ruled out from a practical standpoint, since it possesses the spiro[4,5]decane system, whose complex structure and asymmetry would be difficult to synthesize stereoselect-

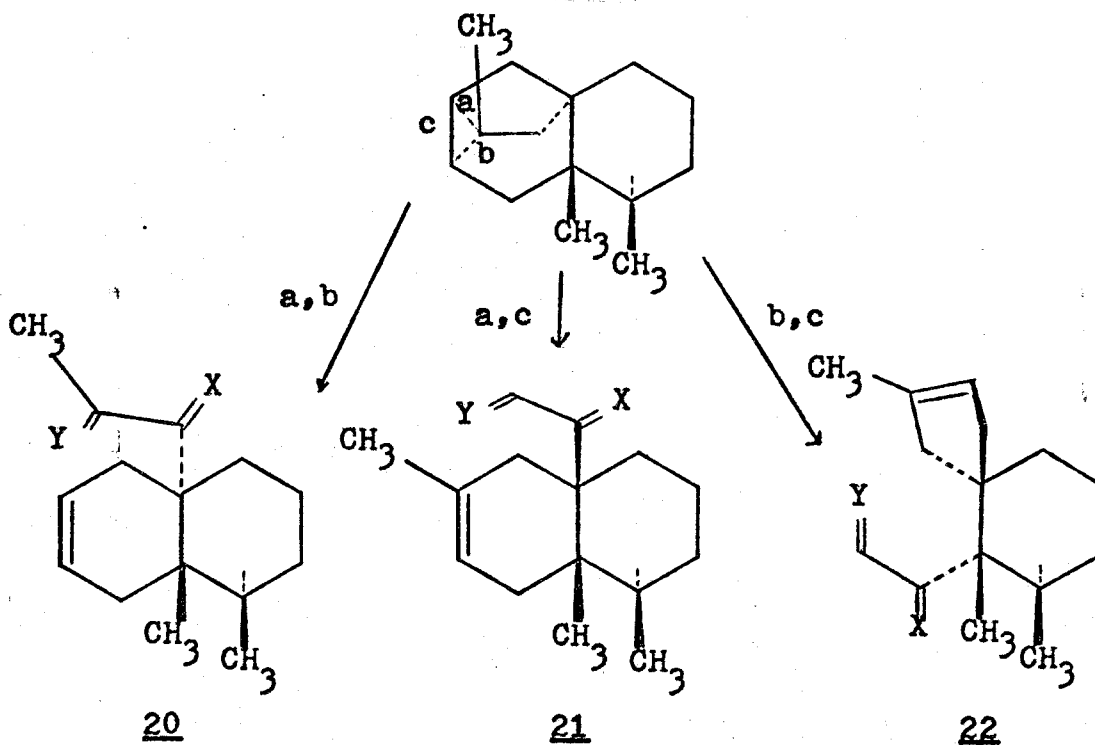


Fig. 1

ively. Intermediates 20 and 21, however, offer the possibility of starting from a decalin intermediate, thus reducing the problem to the stereoselective introduction of the pre-carbene side chain and Δ^2 double bond.

A priori, it is not possible to predict whether octalin 20 or 21 would be more suitable. However, it stands to reason that structure 20 may offer a slight advantage, since its trans stereochemistry insures that the side chain would be rigidly held in the axial position, thus restricting its movement during the cyclization. This is in contrast to structure 21, in which conformational inversion is possible (Figure 2), and hence, the increased chance of side reactions. In the study of the decomposition of some diazoketones, Fawzi and Gutsche (23) determined that the proximity of the

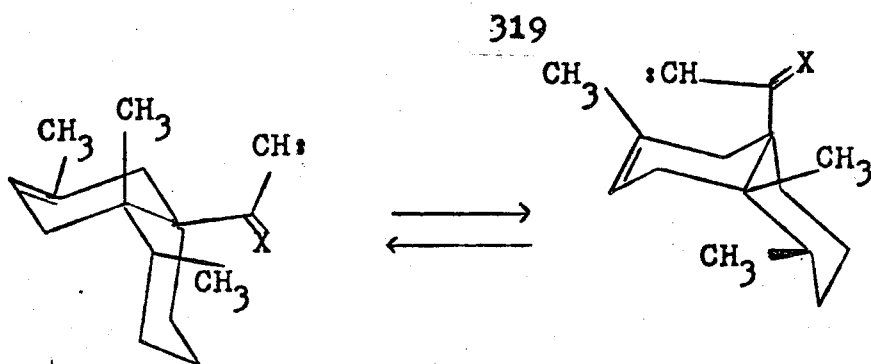
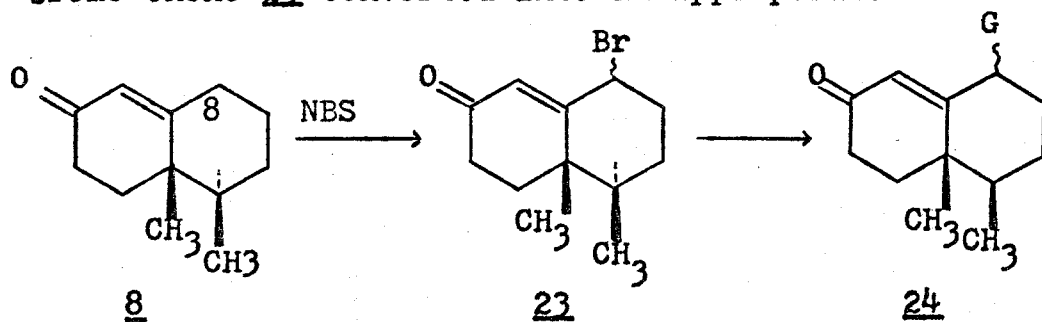


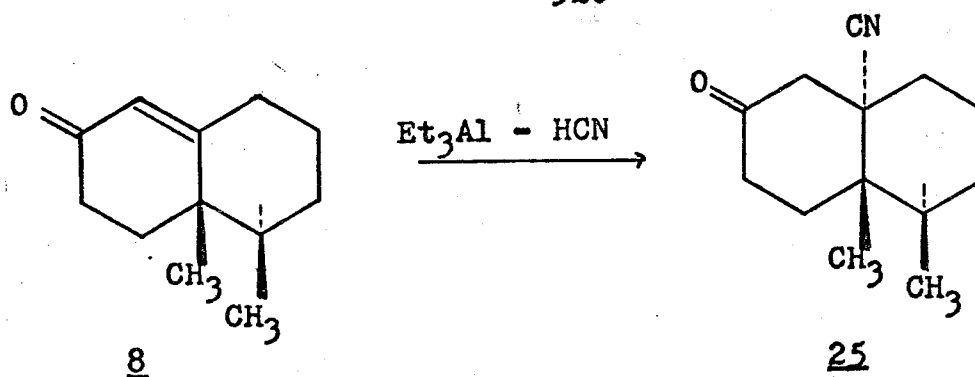
Fig. 2

olefinic bond to the incipient carbenoid center is an important factor in determining the extent of cycloaddition.

With the selection of an octalin with the structure of 20, a suitable starting material would be the octalone 8 (18-20), which was also used by Kelley and coworkers (10,11). Another reason for choosing the octalone 8 as a key intermediate is that it should be suitable for bromination at position 8 with N-bromosuccinimide (24), and the resulting bromo enone 23 converted into an appropriate functional

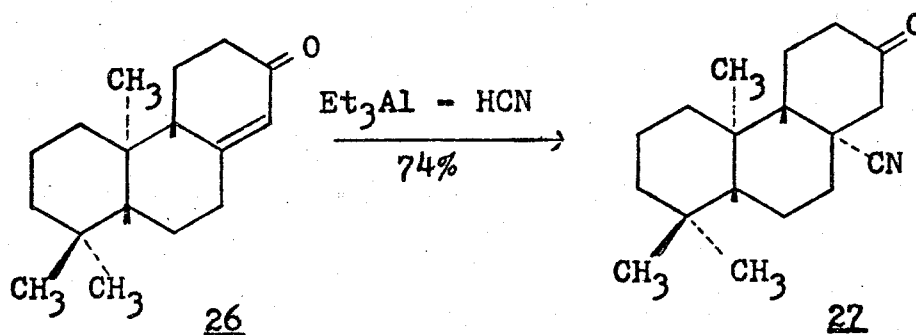


group, G (i.e., OAc), which could later be manipulated into a carbonyl group to afford ishwarone (2a), the synthesis of which has not yet been achieved. The problem of the introduction of the trans pre-carbenoid side chain should be most readily solved by the conjugate addition of cyanide, developed by Nagata and coworkers (25).



b. Trachylobane (3e)

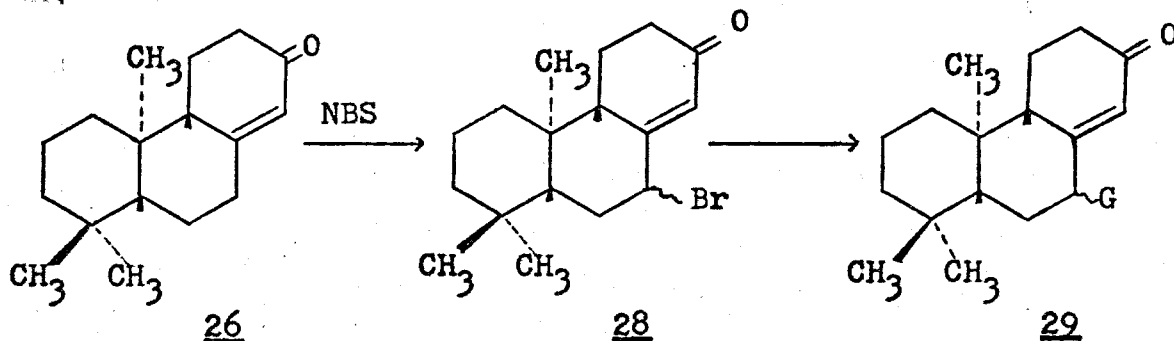
Using arguments similar to those presented above, the most suitable precursor for the synthesis of trachylobane (3e) is the tricyclic enone 26. Hydrocyanation of enone 26 has already been accomplished (27).



Enone 26 has been a vital intermediate in diterpene chemistry (26). Its optically active form (enantiomeric with 26, as drawn) was first isolated by Hosking (27) during the degradation of manöol, and later by Grant and Hodges (28) while degrading phyllocladene. The synthetic racemate of 26 has been employed as a key intermediate for a number of diterpenoid syntheses (29).

As with the bicyclic enone 8, bromination of enone 26

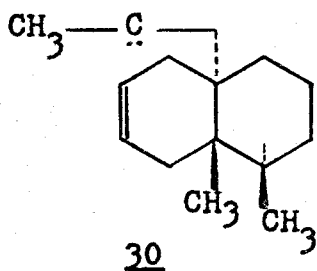
should allow entry into the 7-hydroxy trachylobanes 7a and 7b (17).



2. Construction of the side chain

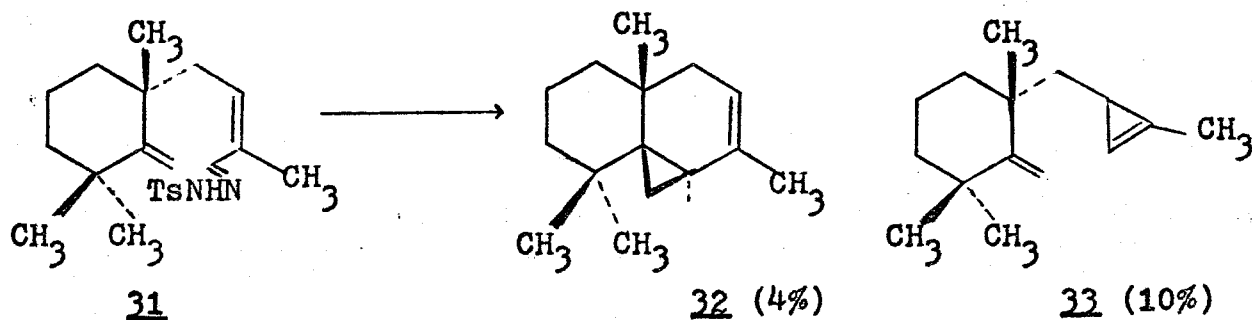
a. Ishwarane (2b)

The remainder of the problem involves the synthesis of a side chain capable of generating a carbenoid center to effect cyclopropane formation. Ideally, of course, one might utilize a simple alkyl carbene, as in the bicyclic carbene 30. The attractiveness of this procedure is that cyclization



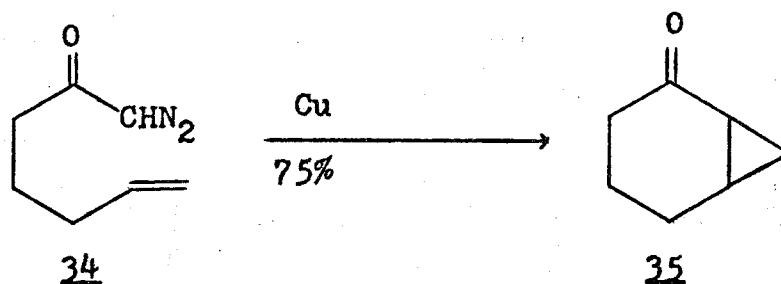
would yield ishwarane directly. The use of alkyl carbenes to form cyclopropanes is well documented (30), but their synthetic utility is somewhat limited. The chief problems result from their propensity to undergo single bond inser-

tions or olefin formation (31). An example of how a carbene side reaction detracted from an otherwise elegant synthesis is that of thujopsene (32), in which Büchi and White (32) decomposed the tosylhydrazone 31 with base. The desired



product, thujopsene (32), was obtained in only 4% yield, along with a 10% yield of the cyclopropene 33.

Considerable improvement in cyclopropane formation is realized if the carbenoid center is adjacent to a carbonyl group. This was first demonstrated by Stork and Ficini (33) in the decomposition of the diazoketone 34 with copper-bronze.



Subsequently, this reaction has become the reaction of choice for the synthesis of polycyclic cyclopropyl ketones, although the yield seldom exceeds 50%. Several natural products have been synthesized using this method (35).

The application of the diazoketone procedure for the

synthesis of ishwarane (2b) is illustrated in Chart A. Reduction of the cyano ketone 25 with lithium tri-(tert-butoxy)-aluminum hydride should proceed with the formation of the alcohol A-1, resulting from the equatorial attack of the hydride (36). Dehydration should proceed to yield the Δ^2 olefin A-2 as the major product (37). Hydrolysis of the cyano olefin A-2, followed by treatment of the acid A-3 with oxalyl chloride should yield the acid chloride A-4. Transformation of this chloride into the diazoketone A-5 should be readily effected with diazoethane (38). Decomposition of the diazoketone A-5 should yield the cyclopropyl ketone 10 (11).

Although Wolff-Kishner reduction was used to convert the ketone 10 into ishwarane (2b), it should be possible to increase the yield by employing the three-step sequence used by Welch (35s) in his recent synthesis of longicyclene. Hence, reduction of the cyclopropyl ketone 10 with lithium aluminum hydride should afford the alcohol A-6. Mesylation and reduction of the mesylate A-7 would yield ishwarane (2b).

b. Trachylobane (3e)

Using slightly modified procedures, the tricyclic cyano ketone 27 (25) should be readily transformed into trachylobane (3e), as illustrated in Chart B. In this case, the trisubstituted olefin B-1 is required. Addition of methyl Grignard, followed by acid dehydration should afford B-1 as the major product. Hydrolysis of the nitrile, chlorination of the resulting acid, and diazomethylation should yield the

Chart A

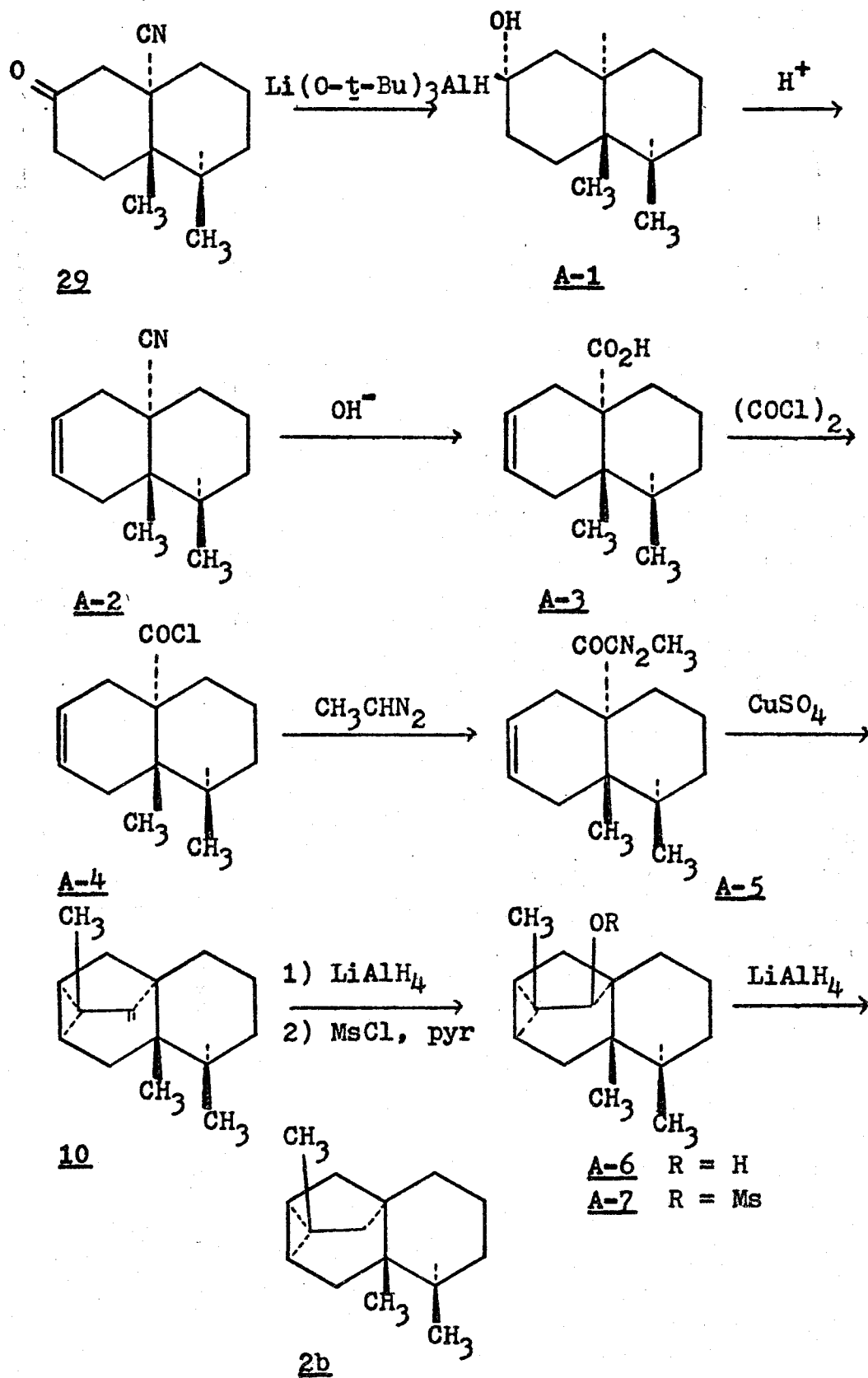
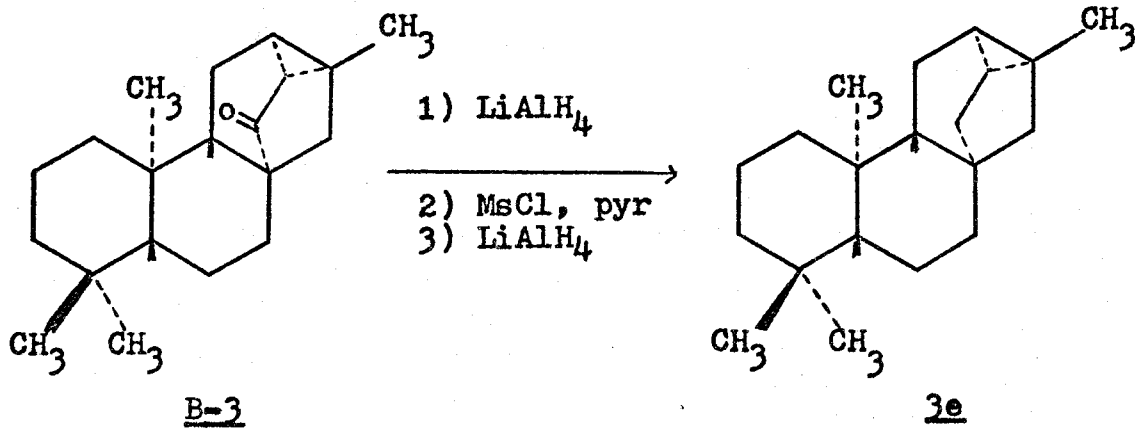
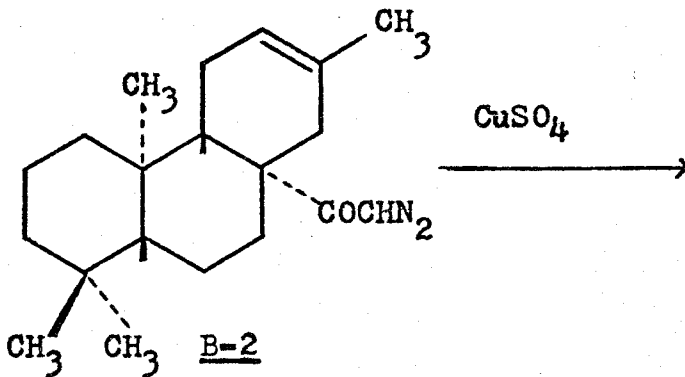
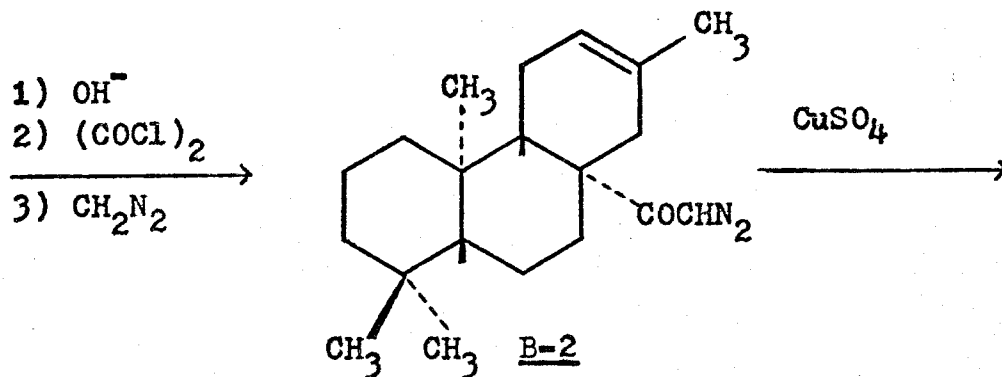
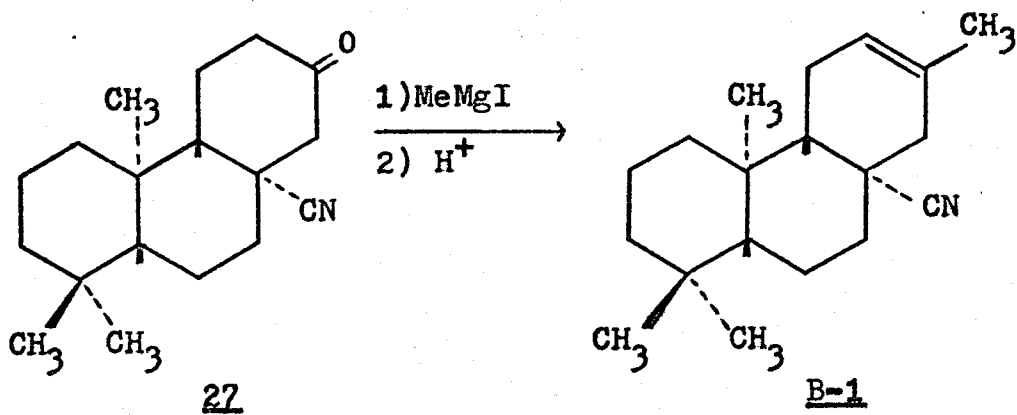


Chart B



diazoketone B-2. Copper-catalyzed decomposition would yield the cyclopropyl ketone B-3, which should be converted into trachyobane (3e) by the three-step sequence described above (35s).

With modifications in the starting materials, the other terpenoids related to the parent hydrocarbons should be obtained via routes similar to those described.

References

1. a. T.K. Devon and A.I. Scott, "Handbook of Naturally Occurring compounds," Vol. II, Terpenes, Academic Press, New York and London, 1972, p 181.
b. ibid., p 240.
2. U.S.K. Rao, B.L. Manjunath, and K.N. Menon, J. Ind. Chem. Soc., 12, 494 (1935).
3. P.R. Krishnaswamy, B.L. Manjunath, and S.V. Rao, ibid., 476 (1935).
4. A.K. Ganguly, K.W. Gopinath, T.R. Govindachari, K. Nagarajan, B.R. Pai, and P.C. Parthasarathy, Tetrahedron Letters, 133 (1969).
5. T.R. Govindachari, K. Nagarajan, and P.C. Parthasarathy, Chem. Commun., 823 (1969).
6. H. Fuhrer, A.K. Ganguly, K.W. Gopinath, T.R. Govindachari, K. Nagarajan, B.R. Pai, and P.C. Parthasarathy, Tetrahedron Letters, 2371 (1970).
7. T.R. Govindachari, P.A. Mohamed, and P.C. Parthasarathy, Tetrahedron, 26, 615 (1970).
8. a. H.K. Desai, D.H. Gawad, T.R. Govindachari, B.S. Joshi, U.N. Kamat, J.D. Modi, P.A. Mohamed, P.C. Parthasarathy, S.I. Pantankar, A.R. Sidhaye, and N. Viswanathan, Ind. J. Chem., 8, 851 (1970).
b. T.R. Govindachari and P.C. Parthasarathy, ibid., 9 1310 (1971).
9. L.C. Teng and J.F. DeBardleben, Experientia, 27, 14 (1971).
10. R.B. Kelly and J. Zamecnik, Chem. Commun., 1102 (1970).
11. R.B. Kelly, J. Zamecnik, and B.A. Beckett, ibid., 479 (1971); Can. J. Chem., 50, 3455 (1972).
12. a. G. Hugel, L. Lods, J.M. Mellor, D.W. Theobald, and G. Ourisson, Bull. Soc. Chim. Fr., 1974 (1963).
b. ibid., 2882, 2888 (1965).
c. G. Hugel, L. Lods, J.M. Mellor, and G. Ourisson, ibid., 2894 (1965).

13. For a recent review of the chemical interconversions of the pentacyclic and tetracyclic diterpenoids, see T. Money in W. Carruthers and J.K. Sutherland, eds., "Progress in Organic Chemistry," Vol. 8, John Wiley and Sons, New York, 1973, p 29.
14. E. Wenkert, Chem. and Ind., 282 (1955).
15. J. Pyrek, Tetrahedron, 26, 5029 (1970).
16. O. Achmatowicz, Jun., A. Ejchart, J. Jurczak, L. Kozerski, and J. Pyrek, Chem. Comm., 98 (1971).
17. G.G. González, J.L. Bretón, B.M. Fraga, and J.G. Luis, Tetrahedron Letters, 3097 (1971).
18. H.E. Ulery and J.H. Richards, J. Am. Chem. Soc., 86, 3113 (1964).
19. E. Piers, R.W. Britton, and W. de Waal, Can. J. Chem., 47, 4307 (1969).
20. C. Berger, M. Frank-Newmann, and G. Ourisson, Tetrahedron Letters, 3451 (1968).
21. a. W. Herz, R.N. Mirrington, and H. Young, ibid., 405 (1968).
b. W. Herz, R.N. Mirrington, H. Young, and Y.Y. Lun, J. Org. Chem., 33, 4210 (1968).
22. R.M. Coates and E.F. Bertram, Tetrahedron Letters, 5145 (1968); J. Org. Chem., 36, 3722 (1971).
23. M.M. Fawzi and C.D. Gutsche, ibid., 31, 1390 (1966).
24. a. C. Meystre and A. Wettstein, Experientia, 2, 408 (1946).
b. H.H. Inhoffen, G. Stoeck, and H. Martens, Ann., 563, 131 (1949).
25. W. Nagata, M. Yoshioka, and T. Terasawa, J. Am. Chem. Soc., 94, 4672 (1972), and earlier papers in this series.
26. J.R. Hanson and A.A. Newman, eds., "Chemistry of Terpenes and Terpenoids," Academic Press, New York and London, 1972, pp 155-199.
27. J.R. Hosking, Chem. Ber., 69B, 780 (1936).
28. a. P.K. Grant and R. Hodges, J. Chem. Soc., 5274 (1960).

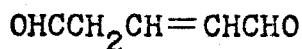
- b. R.C. Cambie and R.C. Hayward, Aust. J. Chem., 25, 959 (1972).
29. Ref. 28b, footnote 1.
30. a. J. Hine, "Divalent Carbon," The Ronald Press Company, New York, 1964, pp 20-25, 122-130.
- b. W. Kirmse, "Carbene Chemistry," Academic Press, New York and London, 1964, pp 26-33, 61-64.
- c. *ibid.*, Second ed., 1971, pp 267-362.
- d. W. Kirmse, "Carbene, Carbenoide, und Carbenanaloge," Verlag Chemie, Weinheim/Bergstr., 1969, pp45-48.
- e. T.L. Gilchrist and C.W. Rees, "Carbenes, Nitrenes, and Arynes," Appelton-Century-Crofts, New York, 1969, pp 57-60.
31. a. Ref. 30a, pp 15-20, 110-116.
- b. Ref. 30b, pp 21-24, 52-57.
- c. Ref. 30c, pp 209-266.
- d. Ref. 30d, pp 45-48.
- e. Ref. 30e, pp 72-75.
32. G. Büchi and J.D. White, J. Am. Chem. Soc., 86, 2884 (1964).
33. G. Stork and J. Ficini, ibid., 83, 4678 (1961).
34. Ref. 30c, pp 338-342.
35. a. F. Medina and A. Manjarrez, Tetrahedron, 20, 1807 (1968).
- b. E. Piers, W. de Waal, and R.W. Britton, Chem. Commun., 188 (1968).
- c. E. Piers, R.W. Britton, and W. de Waal, Tetrahedron Letters, 1251 (1969).
- d. E.J. Corey and K. Achiwa, ibid., 1837 (1969).
- e. E.J. Corey, K. Achiwa, and J.A. Katzenellenbogen, J. Am. Chem. Soc., 91, 4318 (1969).

- f. J.J. Plattner, U.T. Bhalerao, and H. Rapoport, ibid., 91, 4933 (1961).
- g. P.A. Grieco, ibid., 5660 (1969).
- h. K. Mori and M. Matsui, Tetrahedron Letters, 2729, 4435 (1969).
- i. E. Piers, R.W. Britton, and W. de Waal, Can. J. Chem., 47, 831, 4307 (1969).
- j. R.M. Coates and M. Freidinger, Chem. Commun., 871 (1969).
- k. K. Mori and M. Matsui, Tetrahedron, 25, 5013 (1969); 26, 2801, 2815 (1970).
- l. A.S. Sarma and S. Banerjee, Ind. J. Chem., 8, 665 (1970).
- m. O.P. Vig, M.S. Bhatia, A.K. Varma, and K.L. Matta, J. Ind. Chem. Soc., 47, 277 (1970).
- n. O.P. Vig, O.P. Chugh, R.C. Anand, and M.S. Bhatia, ibid., 5066 (1970).
- o. U.T. Bhalerao, J.J. Plattner, and H. Rapoport, J. Am. Chem. Soc., 92, 3429 (1970).
- p. K. Mori, M. Ohki, and M. Matsui, Tetrahedron, 26, 2821 (1970).
- q. K. Mori, M. Ohki, A. Kabayashi, and M. Matsui, ibid., 2815 (1970).
- r. M. Mongrain, J. Lafontaine, A. Belanger, and P. Deslongchamps, Can. J. Chem., 48, 3273 (1970).
- s. S.C. Welch and R.L. Walters, Syn. Commun., 3, 15 (1973).
36. M. Cherest and H. Felkin, Tetrahedron Letters, 2205 (1968).
37. D.H.R. Barton, A. da S. Campos-Neves, and R.C. Cookson, J. Chem. Soc., 3500 (1956).
38. C.J.V. Scanio and D.L. Lickel, Tetrahedron Letters, 1363 (1972).

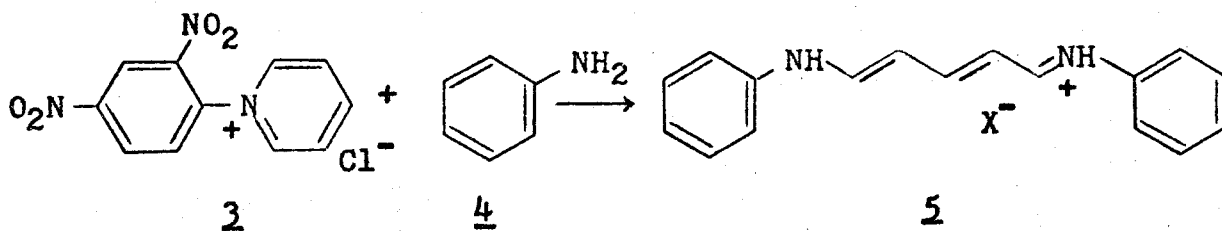
Proposition II

It is proposed to study the effects of certain substituents and their position on the rate of cyclization of glutacondialdehyde dianils to arylpyridinium salts. It is hoped that certain 1-(2,6-disubstituted)phenyl-2,6-disubstituted pyridinium salts will serve as interesting compounds for structural and stereochemical studies.

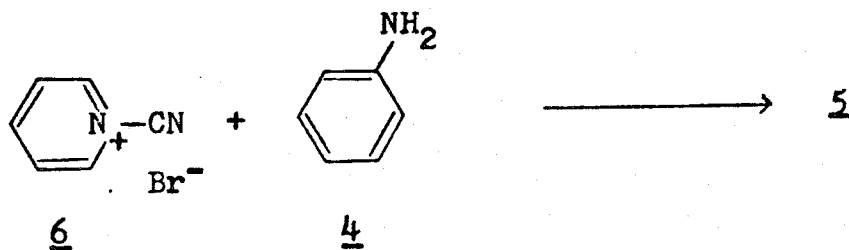
Glutacondialdehyde, $C_5H_6O_2$, may be represented as the dialdehyde 1 or the monoenol form 2 (1). Glutacondialdehyde

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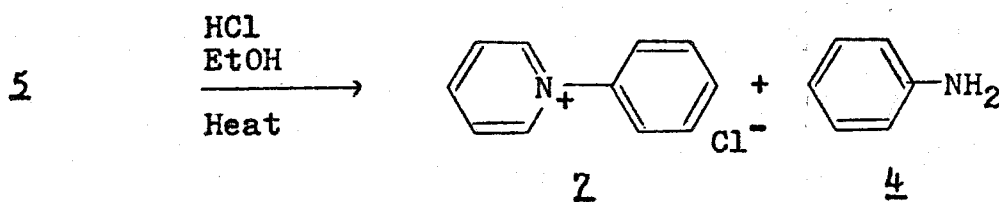
dianil hydrochlorides (5, $X = Cl$) were first isolated by Zincke (2) by the reaction of 2,4-dinitrophenylpyridinium chloride (3) (3) with aniline (4). Independently, König



showed (4) that the hydrobromide 5 ($X = Br$) was formed by the reaction of 1-cyanopyridinium bromide (6) with aniline. Furthermore, Zincke demonstrated (2,5) that the dianil dihydrochlorides 5 ($X = Cl$), on heating with ethanolic hydrogen chloride, lost a molecule of aniline and cyclized to afford

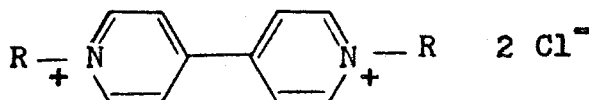


phenypyridinium chloride (7). Thus, a route was discovered



to N-arylpseudopyridinium salts which could not be formed by direct quaternization of pyridine with unactivated (6) aryl halides (7) or sulfonates (8).

Compounds similar to the dianil 5 have been used for the synthesis of azulene derivatives (9) and cyanine dyes (10). The facile cyanide-catalyzed dimerization of 1-phenylpyridinium chloride (2) to 1,1'-diphenyl-4,4'-bipyridinium dichloride (8, R = Ph) (11) offers an attractive, economical



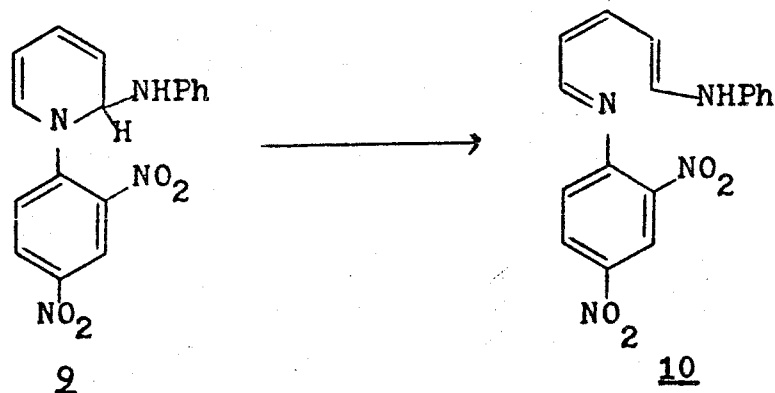
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entry into compounds of potential agricultural interest.*

* "Paraquat," 1,1'-dimethyl-4,4'-bipyridinium dichloride (8, R = Me) is a leading herbicide sold by Imperial Chemical Industries.

Despite the wide utility of the dianil 5 and its analogs, relatively little work has been published of the mechanisms of its formation or subsequent cyclization.

Van den Dungen and coworkers (12) studied the formation of the dianil 5 from 2,4-dinitrophenylpyridinium chloride (3). The rate-determining step was depicted as the electrocyclic ring cleavage of the dihydropyridine 9 to the unsymmetrically-arylated dianil 10. Transiminization, followed by cycliza-



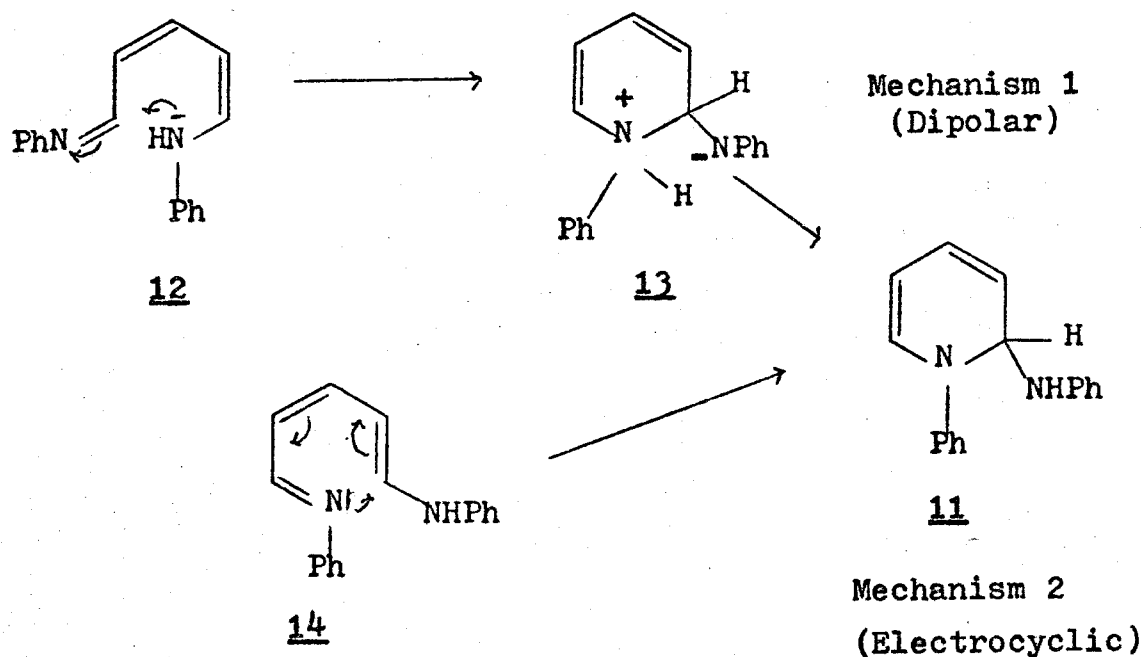
tion afforded 1-phenylpyridinium chloride (7).

In other studies, it was determined that two electron-withdrawing groups on the phenyl ring are required for aniline to attack the pyridinium salt (13). The reaction is also facilitated by electron-withdrawing groups on the pyridine ring (14).

The only studies reported thus far on the cyclization of the dianil 5 are those of Marvell and coworkers (15). Their initial studies (15a) indicated that the strongly acidic conditions employed by Zincke (2,5) were unnecessary. In fact, the addition of one equivalent or less of base

(i.e., sodium methoxide) caused a slight increase in the rate (15b). Added salts had no effect, but solvents of high ionizing power caused a slight increase. The rate-determining step was postulated to be the cyclization of the dianil 5 to the dihydropyridine 11 by one of two possible mechanisms.

The first is the nucleophilic addition of the phenylamino function to the imine with the dianil in the cis,cis form 12



(15b), yielding the zwitterionic species 13. The second mechanism proposed is an electrocyclization with dianil 5 in the cis,trans form 14, yielding the dihydropyridine 11.

On the basis of salt and solvent effects, mechanism 2 was chosen as the most likely candidate. However, on testing the reaction on dianils having para substituents on the

benzene ring (15c), it was found that electron-withdrawing groups increased the rate somewhat. This observation is more consistent with the dipolar mechanism 1, since the negatively charged nitrogen on species 15 could distribute its electrons via resonance or inductive effects (Figure 1).

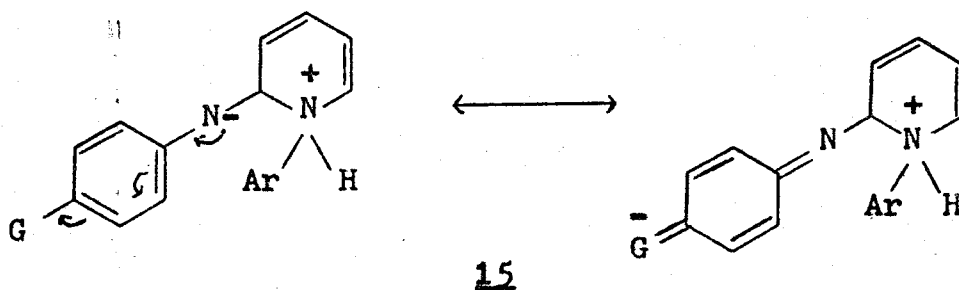
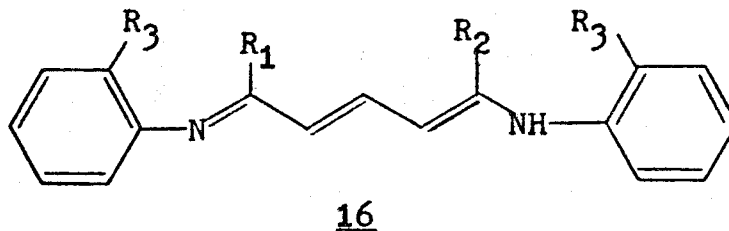


Fig. 1

Inconsistencies in the above results warrant further investigation into the reaction mechanism. The proposed study would involve the synthesis and cyclization of dianils which were substituted a) on the 1 and 5 carbons of the penta-adiene chain, and b) on the ortho positions of the phenyl ring. These dianils are represented by the trans,trans formula 16, although for cyclization to occur, the dianil must



undergo double bond isomerization to cis,trans for the dipolar mechanism 1, and cis,cis for the electrocyclic mechanism 2 (16).

In a dianil 16 in which only the imino carbon is substituted ($R_2 = R_3 = H$) (13), one would expect a rate decrease relative to a dianil having no substituents if R_1 was an electron-donating substituent and the dipolar mechanism were operating. The reason for this is twofold and is shown in Figure 2. Polarization of the imine bond would be partially

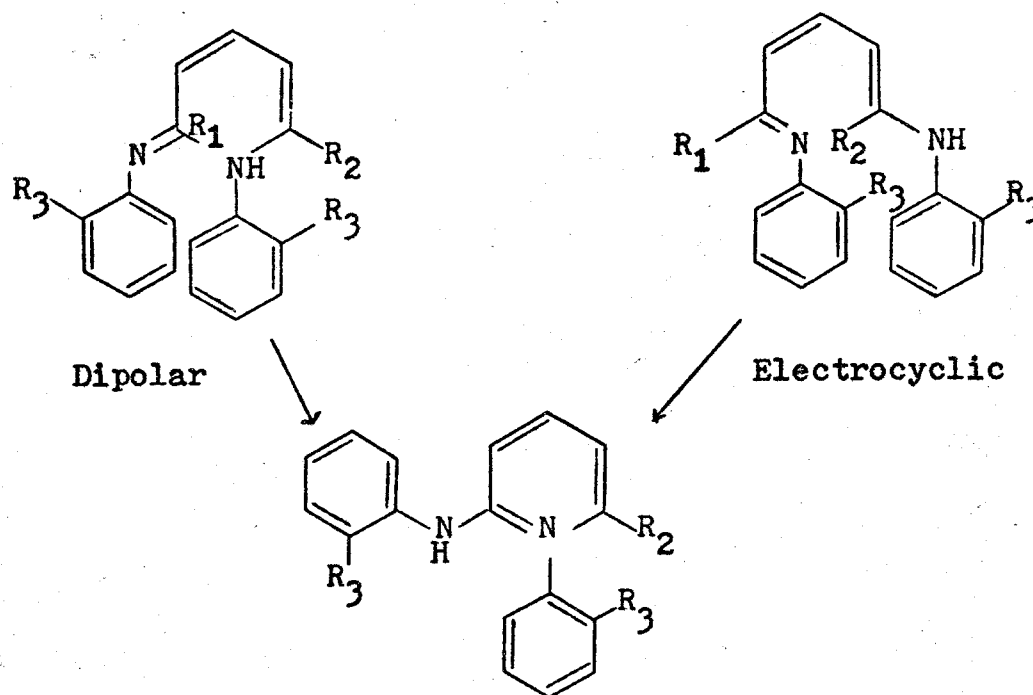
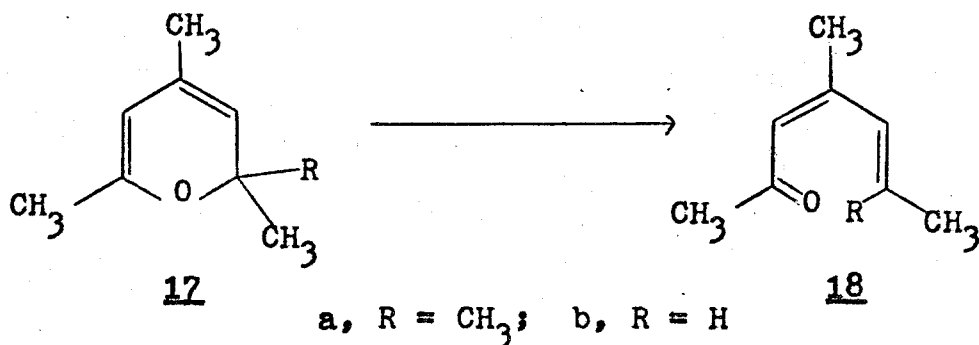


Fig. 2

neutralized by the electron-donating properties of R_1 . Hence, the amino nitrogen is less likely to attack the bond. In addition, the presence of R_1 in the internal region of the reaction site would probably cause a strong interaction, similar to nucleophilic addition to a hindered ketone.

In the electrocyclic mechanism, the R_1 substituent is located on the outside of the ring system (Figure 2). Since it is doubtful that an electron-donating substituent would exert an appreciable effect during a concerted cyclization, no significant rate change should be observed.

If one now studies a disubstituted dianil with $R_1 = R_2$, one should see no rate change over one substituent in the dipolar mechanism, since R_2 is fairly remote from the reaction site. On the other hand, a bulky R_2 group in an electrocyclic reaction would be expected to decrease the rate, relative to one substituent. This is analogous to a related study (17) in which the opening of 2,2,4,6-tetramethyl- α -pyran (17a) to give the acyclic dienone 18a proceeds about one-twentieth as fast as the des-methyl- α -pyran 17b (18).



For the next phase of the study, attention would be focused on dianils with substituents in the ortho positions on the phenyl ring (16, $R_1 = R_2 = \text{H}$, $R_3 = \text{substituent}$). As in the study of the para substituted dianils (15c), electron-withdrawing groups should aid in the polarization of the C=N bond, thus increasing the rate in the dipolar mechanism.

They should have a negligible effect in the electrocyclic mechanism. Sterically, ortho substituents would be expected to play an important role in the dipolar mechanism (Figure 3), since the R_3 groups would probably have to be in close

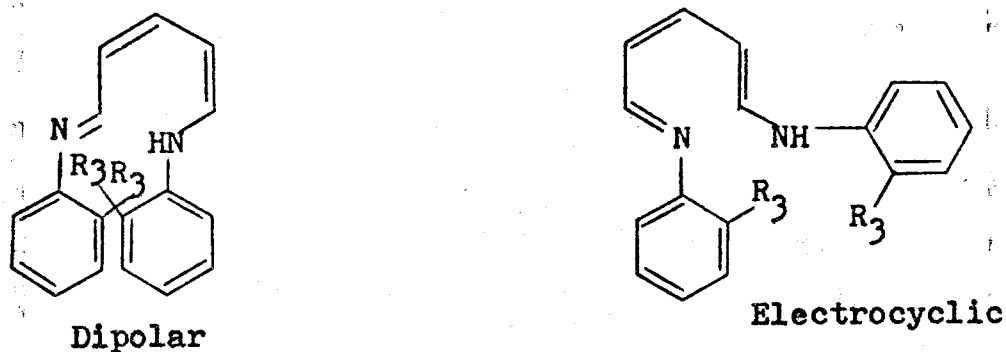


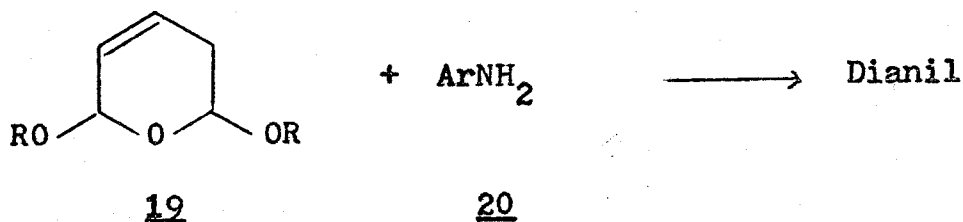
Fig. 3

proximity with each other at some time during the reaction pathway. On the other hand, the electrocyclic process should not incur any problems from bulky ortho groups. In light of the kinetic data already available from the para studies (15c), it is doubtful that variation in the electronic nature of the ortho substituents would provide all-conclusive results. Hence, any significant data would probably have to be obtained by variation of the size of R_3 , while keeping the electronic nature of the substituents somewhat constant (i.e., methyl, ethyl, etc.).

The experimental aspects of this study should be relatively straightforward. For the dianils in which R_1 and/or R_2 is substituted, it would be necessary to functionalize a suitable pyridine derivative, for example, α -picoline. The methods of Zincke (2,5) and König (4) would be satisfactory

for the quaternization of the pyridines and for the ring opening with aniline. Grochowski, Okon, and coworkers (19) have determined that not only 2-substituted pyridines, but also 2,6-disubstituted pyridines can be quaternized with 2,4-dinitrochlorobenzene.

The synthesis of many substituted pyridines has been reviewed (20). Besides the classical methods of dianil formation, a newer procedure has been introduced (21) which involves the reaction of a 2,6-dialkoxy- Δ^3 -dihydropyran 19 (22) with an aniline derivative 20.

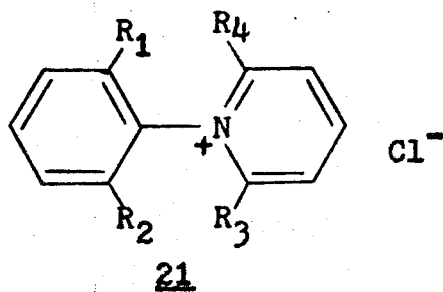


Commercial sources should provide an adequate supply of substituted anilines for the study. Most anilines would be expected to react with the dinitrophenyl salt 3 or cyano salt 6. Even phenylenediamines react cleanly (23) to yield diamino dianils.

The kinetic studies should probably be carried out in methanol solution in the presence of excess triethylamine (15c). The disappearance of the dianils would be followed spectrophotometrically. They should all show an absorption maximum at about 500 nm (16,24,25). A graphic plot of absorption vs. time should show first order kinetics, from

which rate constants could be calculated (26).

Another feature of this study is the possibility of producing pyridinium salts substituted in all four α positions (structure 21). These compounds could be used in stereochem-



ical studies (measurement of rotational barriers and rate of racemization), which are directly analogous to the studies done on substituted biphenyls (27).

References

1. I.M. Heilbron, "Dictionary of Organic Compounds," Vol 4, Oxford University Press, New York, 1965, p 2634.
2. T. Zincke, Ann., 330, 361 (1904).
3. E. Vongerichten, Chem. Ber., 32, 2571 (1899).
4. W. König, J. Prakt. Chem., (2), 69, 105 (1904); ibid., 70, 19 (1904).
5. T. Zincke, G. Heuser, and W. Möller, Ann., 333, 296 (1904).
6. In general, at least two electron-withdrawing groups on the phenyl ring in positions 2 and 4 or 2 and 6 are required, although they need not both be nitro. Recently, a method of direct quaternization with a single nitro group on a chlorobenzene has been reported: B. Lipke, Z. Chem., 10, 463 (1970).
7. Cf. a. J.A. McRae, R.Y. Moir, J.J. Ursprung, and H.H. Bibbs, J. Org. Chem., 19, 1500 (1954).
b. M. Allen and R.Y. Moir, Can. J. Chem., 37, 1799 (1959).
c. G.A. Neville and R.Y. Moir, ibid., 47, 2787 (1969).
d. S.S. Joshi, J. Chem. Soc., 313 (1933).
e. W. Borshe and D. Rantsheff, Ann., 379, 152 (1911).
f. F.T.O. Bankole, C.W.L. Bevon, and J. Hirst, Chem. and Ind., 119 (1963).
8. a. W. Borshe and E. Feske, Chem. Ber., 60B, 157 (1927).
b. F. Bell, J. Chem. Soc., 2343 (1931).
c. R.S. Tipson, J. Org. Chem., 9, 235 (1944).
d. E.T. Borrowes, J.C. Clayton, B.A. Hems, and A.G. Long, J. Chem. Soc., Supply House Issue, S190 (1949).
e. D. Klamann, Monatsch., 84, 54 (1953).
f. K.L. Sharma, V.N. Sharma, and R.C. Mital, Can. J. Chem., 44, 1327 (1966).

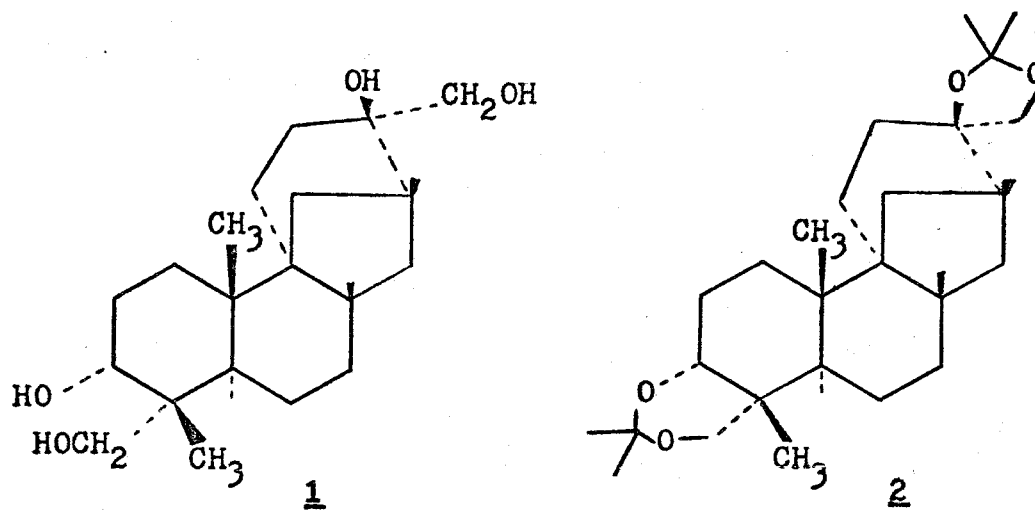
- g. A. Kirkien-Konasiewicz, G.M. Sammy, and A. Maccodl, J. Chem. Soc., B, 1364 (1968).
- h. S.E. Larrea and J.L. Fernández, Anales veal. Soc. españ. fis. yquinn., C.A. 55, 19119h (1961).
- i. J. Schwartz, Acta Chem. Acad. Sci. Hung, 20, 415 (1959).
9. a. K. Hafner, Ann., 606, 79 (1957); Angew. Chem., 70, 419 (1958).
- b. K. Hafner and H. Kaiser, Ann., 618, 140 (1958).
- c. K. Hafner and K. Asmus, ibid., 671, 31 (1964).
10. F. Hamer, "Cyanine Dyes and Related Compounds," Interscience, New York, 1964, pp 244-269.
11. L.J. Winters, N.G. Smith, and M.I. Cohen, Chem. Commun., 642 (1970).
12. E. Van den Dungen, J. Nasielski, and P. van Laer, Bull. Soc. Chim. Belges, 66, 661 (1957).
13. J.W. Grochowski and K. Okon, Bull. Acad. Polon. Sci., Ser. Sci. Chim., 10, 520 (1962).
14. A.F. Vompe and N.F. Turitsyna, Zh. Obshch. Khim., 28, 2864 (1958).
15. a. E.N. Marvell, G. Caple, and I. Shahidi, Tetrahedron Letters, 277 (1967).
- b. E.N. Marvell, G. Caple, and I. Shahidi, J. Am. Chem. Soc., 92, 5641 (1970).
- c. E.N. Marvell and I. Shahidi, ibid., 5646 (1970).
16. a. F. Dorn, J. Kotschy, and H. Kausen, Ber. Besenges Phys. Chem., 69, 11 (1965).
- b. F. Baumgartner, E. Gunther, and G. Scheibe, Z. Electrochem., 60, 570 (1956).
17. E.N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, J. Org. Chem., 37, 2992 (1972).
18. E.N. Marvell and T. Gosink, ibid., 3036 (1972).
19. a. J.W. Grochowski and K. Okon, Biul. Wojskowej Akad., Tech., 10, No. 111, 68 (1961), C.A. 58, 11156 d (1962).

- b. J.W. Grochowski and K. Okon, Bull. Acad. Polon Sci., Ser. Sci. Chim., 10, 527 (1962).
- c. J.W. Grochowski and K. Okon, Roczniki Chem., 37, 1429 (1963), C.A., 60, 9242f (1964).
- d. J.W. Grochowski and K. Okon, Roczniki Chem., 37, 1437 (1964), C.A., 60, 9242h (1964).
- e. K. Okon, J.W. Grochowski, W. Waclawek, and J. Zieba, Biul. Wojskowej Akad. Tech., 12, 25 (1963), C.A., 60, 495a (1964).
- f. J.W. Grochowski and K. Okon, ibid., 11, 45 (1962), C.A., 60, 570h (1964).
20. a. L.E. Tenenbaum in E. Klingsberg, ed., "Pyridine and Its Derivatives," Interscience, New York, 1961, pp 155-298.
- b. H.E. Martel, ibid., pp 299-419.
21. S.M. Makin and V.M. Likhosherstov, USSR, 161,721, C.A., 61, 4221f (1964); Zh. Org. Khim., 6, 640 (1965).
22. S.M. Makin, V.M. Likhosherstov, and M.I. Seleming, Zh. Obshch. Khim., 34, 1809 (1964).
23. N.E. Grigor'eva and I.K. Gintse, ibid., 26, 249 (1956).
24. A. Van Dormel and J. Nys, Bull. Soc. Chim. Belg., 61, 614 (1952).
25. N.E. Grigor'eva, I.K. Gintse, and A.P. Severina, Zh. Obshch. Khim., 26, 3447 (1956).
26. A.A. Frost and R.G. Pearson, "Kinetics and Mechanism," Second ed., John Wiley and Sons, New York, 1961, pp 8-26.
27. cf. a. F.H. Westheimer in M.S. Newman, ed., "Steric Effects in Organic Chemistry," John Wiley and Sons, New York, 1956, Chap. 12.
- b. E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw Hill, New York, 1962, pp 156-178.

Proposition III

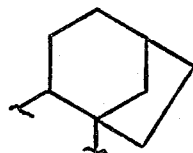
Studies leading toward a stereoselective synthesis of the antibiotic aphidicolin are proposed.

Aphidicolin (1) is a tetracyclic diterpenoid tetraol

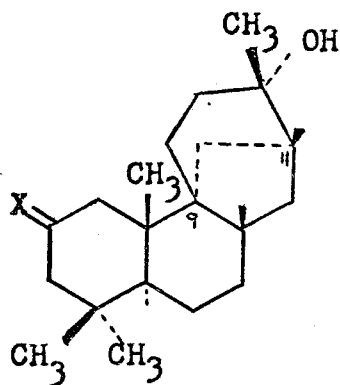


isolated from a culture of Cephalosporium aphidicola, Petch (1). It has been shown to possess antiviral activity against a range of DNA-containing viruses, eg., Herpes simplex, by inhibiting DNA synthesis (2). The structure of aphidicolin was confirmed as 1 by x-ray analysis of the bis-acetonide 2.

The isolation of aphidicolin (1) marks the first example of a diterpene possessing a bicyclo[3.2.1]octane ring system of its type, although several diterpenes contain the partial structure 3 (3). Recently, two new diterpenes,



stemodin (4) and stemodinone (5) have been isolated from



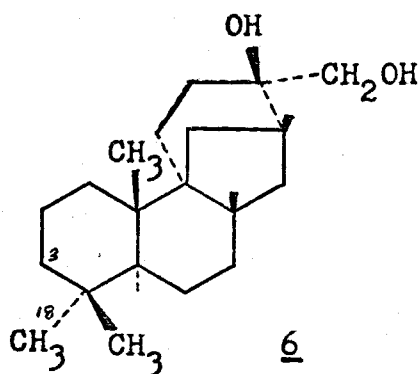
4 X = β -OH, α -H

5 X = O

Stemodina maritima L. (4). The stereochemistry about C-9 and C-11 (steroid numbering) is inverted in these latter compounds, relative to aphidicolin.

The potential medicinal value of aphidicolin, as well as its novel chemical structure prompt a study of its synthesis. The key reactions in any projected synthesis of the antibiotic would be the elaboration of the C and D rings which make up the bicyclo[3.2.1]octane ring system. It is therefore reasonable to undertake a model study in which full attention could be paid to the construction of the C and D rings, while still maintaining the gross structure of the desired product. A model compound with these characteristics is the tetracyclic diol 6, which differs from aphidicolin by the lack of hydroxyl groups at C-3 and C-18 (aphidicolane numbering) (1).

The proposed synthetic scheme to the diol 6 is outlined in Chart A. A key intermediate is the tricyclic ether A-2, available in eight steps from 5-methoxy-1-tetralone (A-1)



(5,6). Birch reduction and acid hydrolysis of ether A-2 should yield the bicyclic enone A-3 (7), which should undergo stereoselective hydrocyanation with triethylaluminum-hydrogen cyanide (8) to afford the trans cyano ketone A-4.

It is now necessary to contract ring C to become the five-membered C ring in the diol 6. The α -cyano group will serve as a rudiment for the D ring. The approach envisioned for the final ring closure step involves the formation of the C-12,17 bond. To effect this, treatment of the keto aldehyde 7 with base should yield the hydroxy ketone 8.

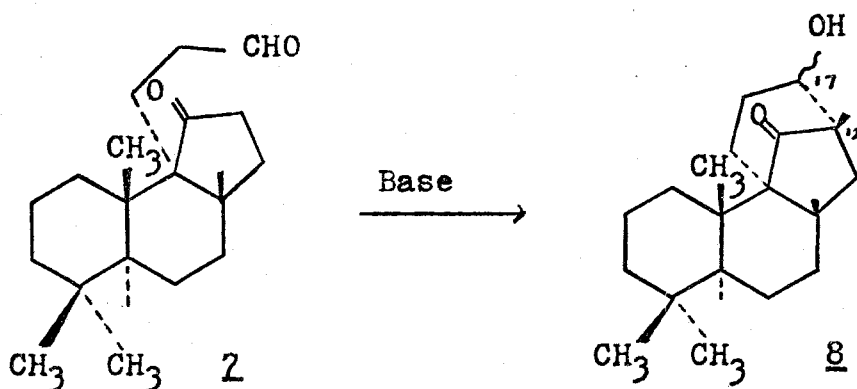


Chart A

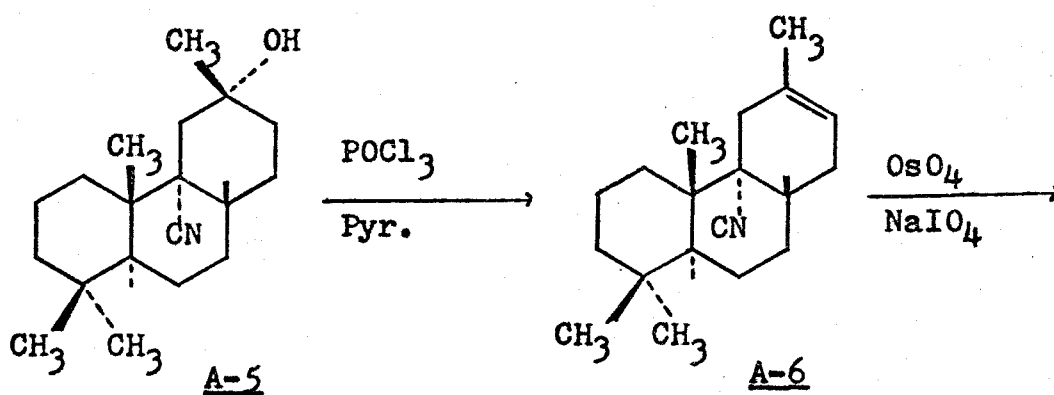
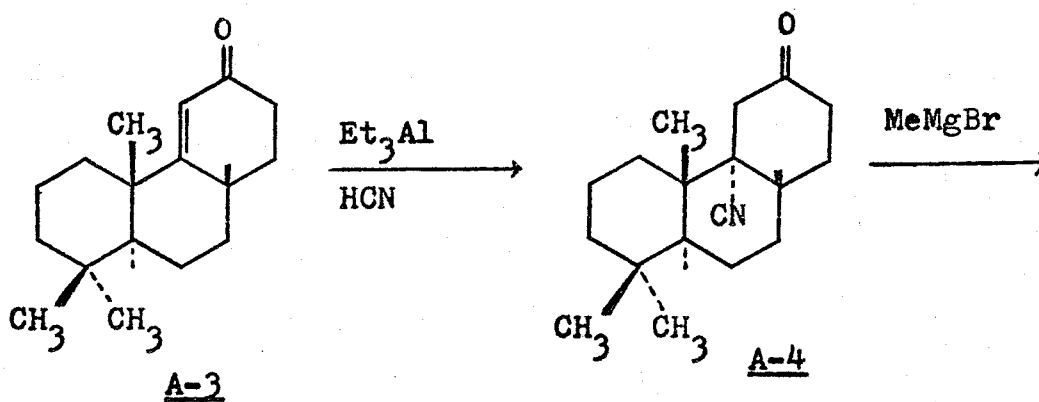
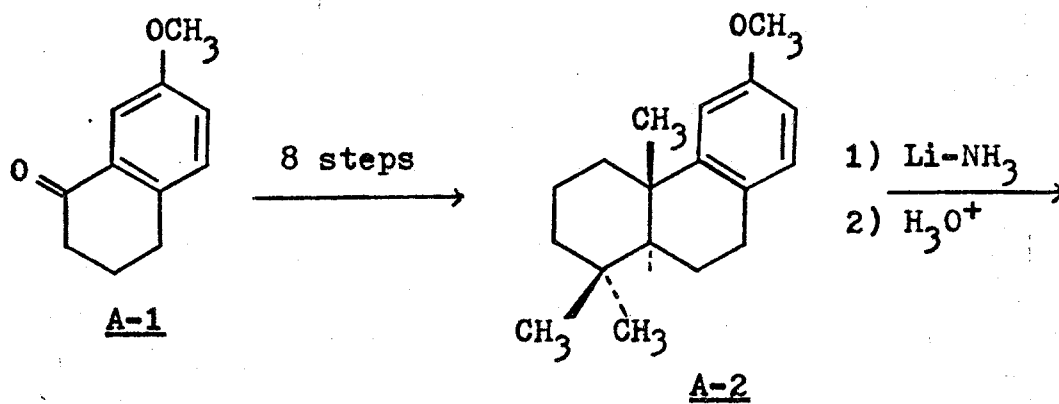


Chart A (cont'd)

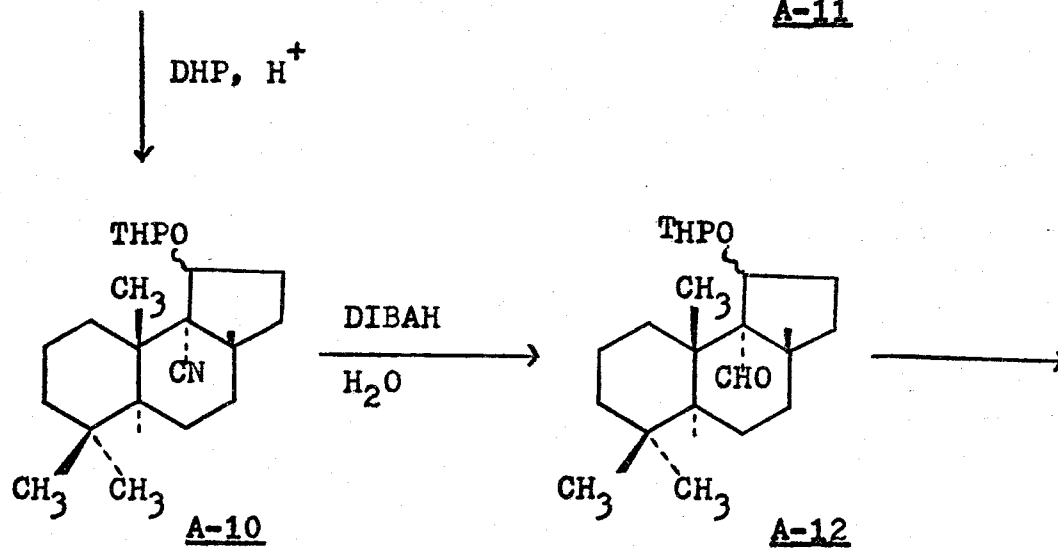
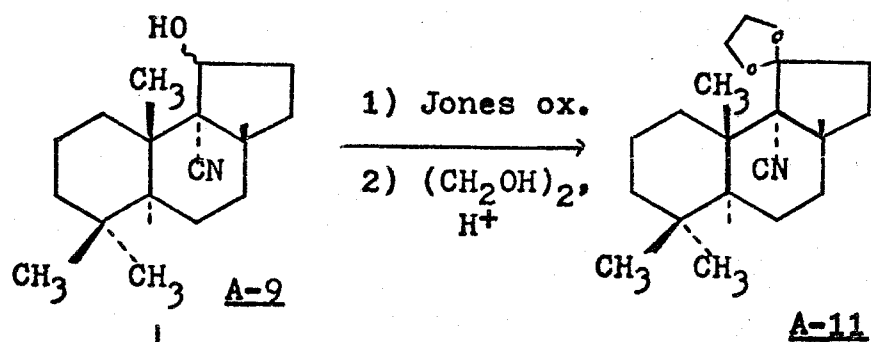
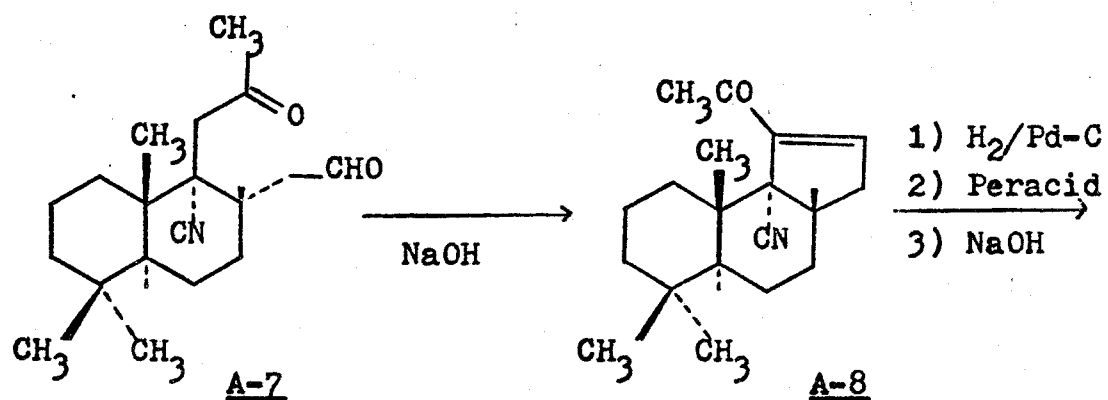
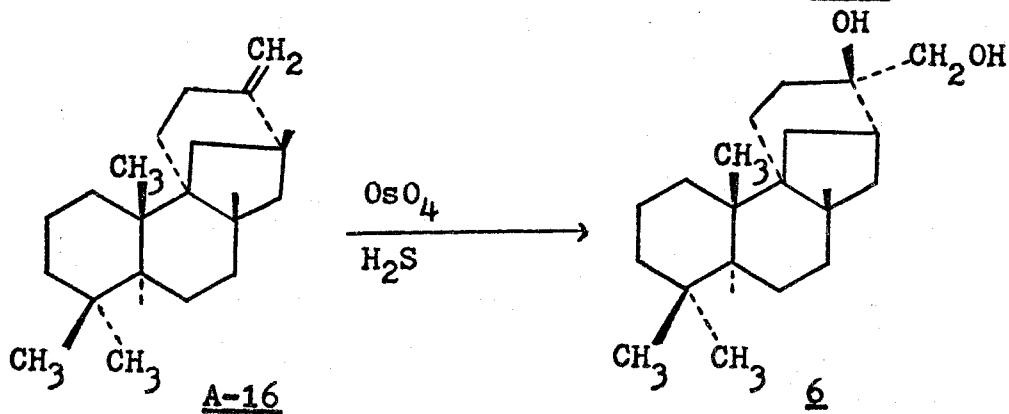
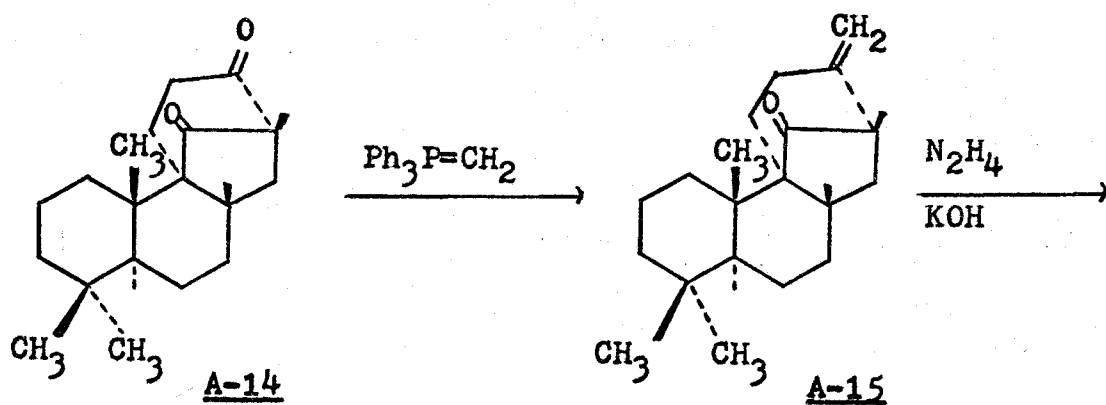
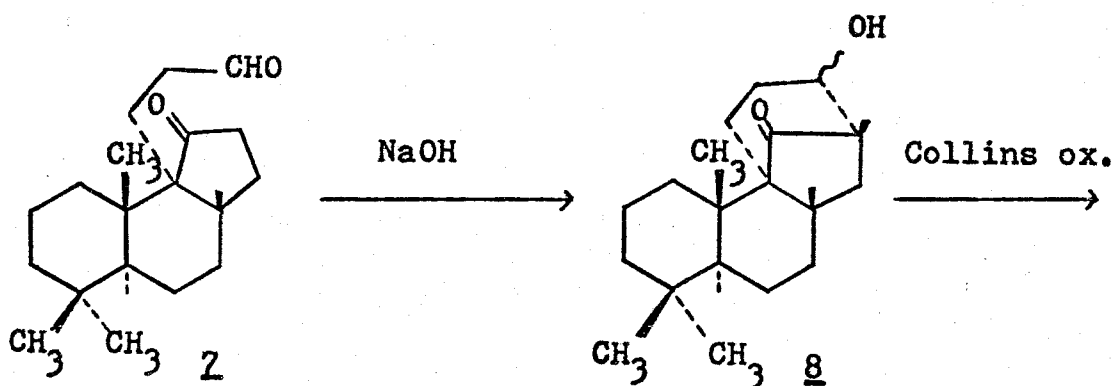
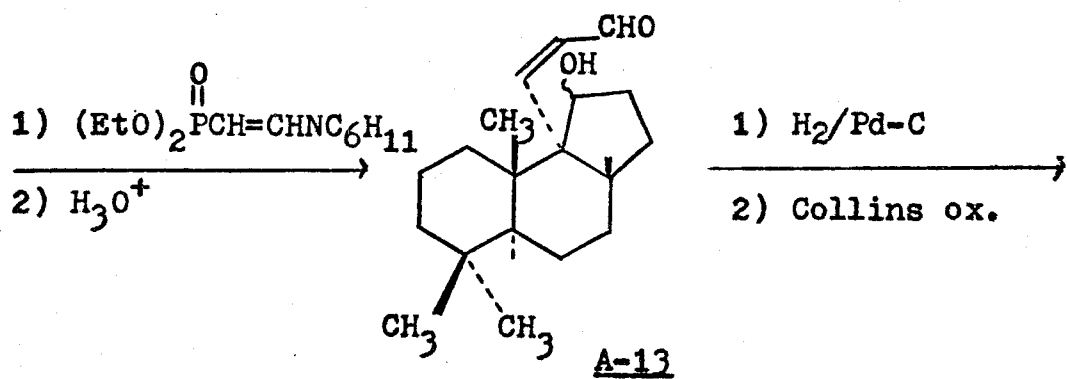


Chart A (cont'd)



Returning to Chart A, treatment of the cyano ketone A-4 with one equivalent of methyl Grignard should selectively attack the carbonyl (9), affording the hydroxy nitrile A-5. Dehydration with phosphorous oxychloride should give the $\Delta^{12,13}$ olefin A-6 (steroid numbering) as the major product (10). Oxidative cleavage of the olefin with osmium tetroxide-sodium periodate (11) should yield the keto aldehyde A-7, which on base catalysis should cyclize to the acetyl cyclopentene A-8. Catalytic hydrogenation, followed by Bayer-Villiger oxidation and saponification should afford the epimeric hydroxy nitriles A-9.

It would be advisable at this point to protect the hydroxyl group, either as the tetrahydropyranyl ether A-10, or as the acetal of the corresponding ketone A-11. The THP ether is arbitrarily chosen to complete the synthesis.

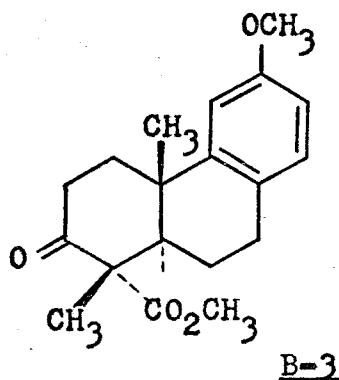
Treatment of A-10 with diisobutylaluminum hydride and hydrolysis should produce the aldehyde A-12, which could be made to undergo a two-carbon extension using diethyl β -(cyclohexylimino)-ethyl phosphonate and base (12a). Hydrolytic workup should cleave the tetrahydropyranyl group, yielding the unsaturated hydroxy aldehyde A-13. Catalytic hydrogenation, followed by Collins oxidation (13) should produce the keto aldehyde 7. Base or acid catalyzed cyclization and oxidation of the resulting keto alcohol 8 should yield the diketone A-14.

It is hoped that treatment of this diketone with methyl-

enetriphenylphosphorane (14) will react selectively with the C-17 carbonyl, since it is probably less hindered (15).

Wolff-Kishner reduction of the keto olefin A-15 should yield the olefin A-16, which on osmylation and reduction, should afford 3,18-dideoxyaphidicolin (6).

For the synthesis of aphidicolin itself, it is necessary to have suitable functionality at C-3 and C-18 for the ultimate conversion to hydroxyl groups. This may be readily accomplished via the keto ester B-3, which should be readily



available from the scheme outlined in Chart B. Reductive carbomethoxylation (16,17) of the enone B-1 (5) affords the known (18) keto ester B-2. Methylation of B-2 using sodium hydride in benzene, followed by methyl iodide should produce the keto ester B-3, with the desired stereochemistry at C-4 (19,20). Reduction of the C-3 carbonyl with lithium tri-sec-butylborohydride (21) should yield the hydroxy ester B-4, with the axial hydroxyl group. Reduction of the ester with lithium aluminum hydride should yield the diol B-5, and Birch reduction should afford the dihydroxy enone B-6.

Chart B

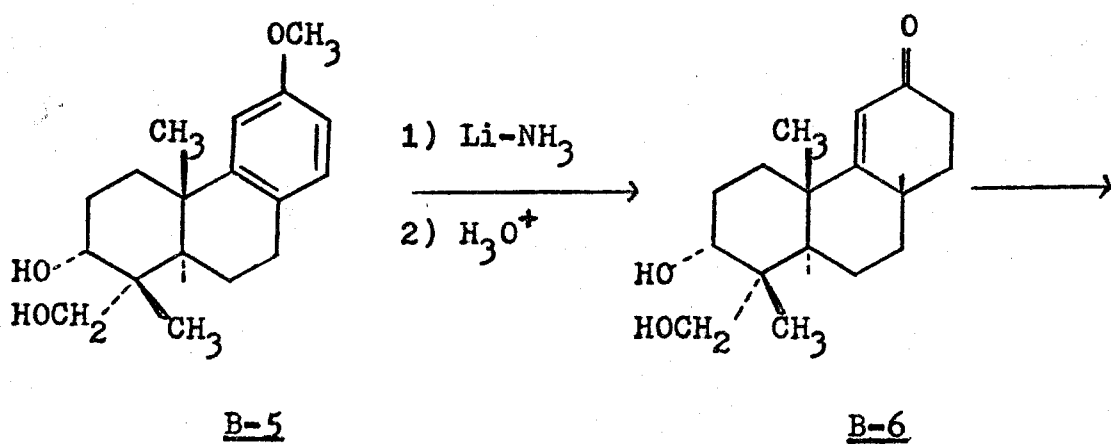
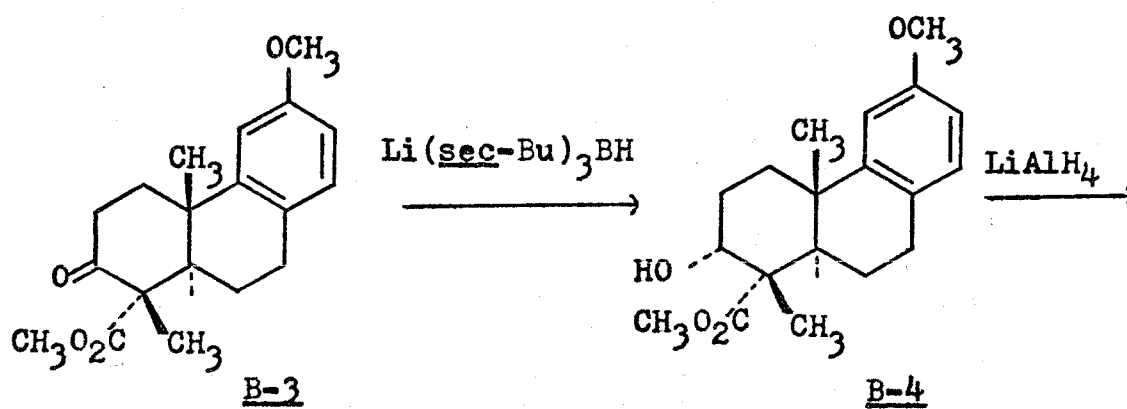
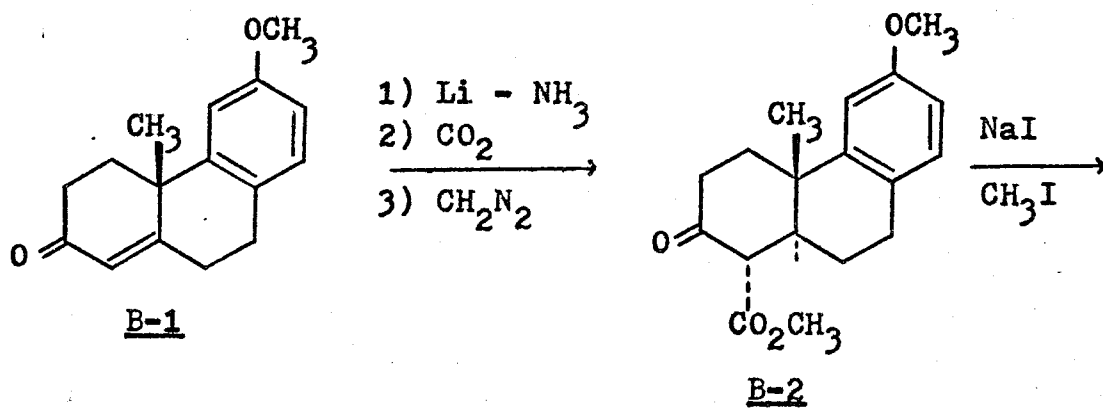
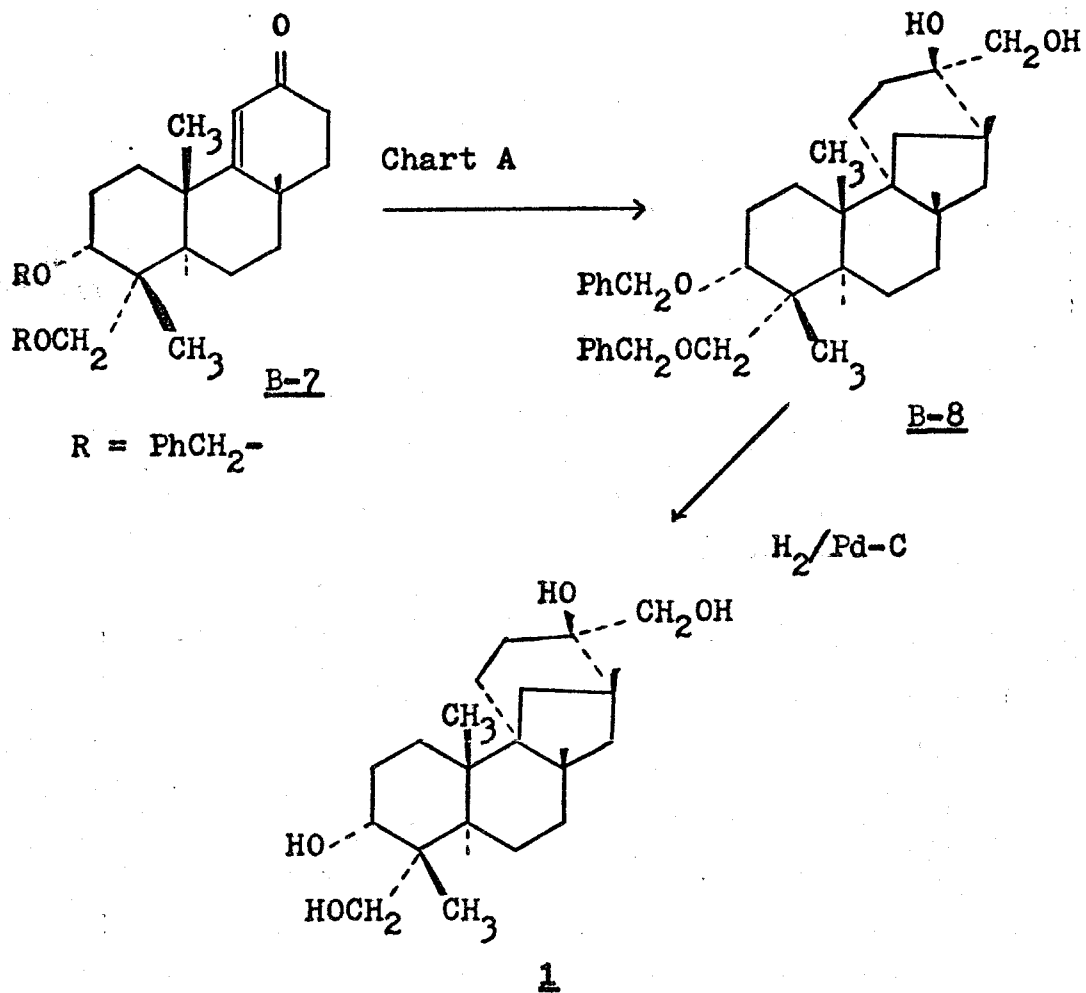


Chart B (cont'd)



Before elaborating the C and D rings, it is necessary to protect the hydroxyl groups. The dibenzyl ether B-7 should be suitable for this purpose. Through similar procedures to those outlined in Chart A, one should readily obtain the dihydroxy dibenzyl ether B-8. It is necessary to substitute a non-reductive hydrogenation of the α,β -unsaturated carbonyl groups in compounds analogous to A-8 and A-13. The triethylsilane procedure of Nagai and coworkers (22) should be suitable for this purpose.

Catalytic hydrogenation of the dihydroxy dibenzyl ether B-8 should yield aphidicolin (1)

References

1. K.M. Brundret, W. Dalziel, B. Hesp, J.A.J. Jarvis, and S. Neidle, Chem. Commun., 1027 (1972).
2. R.B. Bucknall, unpublished results; see ref. 1.
3. T.K. Devon and A.I. Scott, "Handbook of Naturally Occurring Compounds," Vol II, Terpenes, Academic Press, New York and London, 1972, pp 185-274.
4. R.S. Manchand, J.D. White, H. Wright, and J. Clardy, J. Am. Chem. Soc., 95, 2705 (1973).
5. a. K. Raman and P.N. Rao, Experientia, 2, 472 (1956).
b. P.N. Rao and K. Raman, Tetrahedron, 4, 294 (1958).
6. For other syntheses and uses of this versatile intermediate, see:
 - a. F.E. King, T.J. King, and J.G. Topliss, Chem. and Ind., 108 (1954); J. Chem. Soc., 573 (1957).
 - b. J. Delobelle and M. Fetizon, Bull. Soc. Chim. Fr., 1894 (1961).
 - c. M. Fetizon and G. Moreau, ibid., 3479 (1965).
7. R.H. Bible and R.R. Burtner, J. Org. Chem., 26, 1174 (1961).
8. W. Nagata, M. Yoshioka, and T. Terasawa, J. Am. Chem. Soc., 94, 4672 (1972).
9. R.E. Ireland and S.C. Welch, ibid., 92, 7232 (1970).
10. D.H.R. Barton, A. da S. Campos-Neves, and R.C. Cookson, J. Chem. Soc., 3500 (1956).
11. R. Pappo, D.S. Allen, Jr., R.U. Lemieux, and W.S. Johnson, J. Org. Chem., 21, 478 (1956).
12. a. W. Nagata and Y. Hayase, Tetrahedron Letters, 4359 (1968); J. Chem. Soc., C, 460 (1969).

For other methods of effecting this transformation, see:

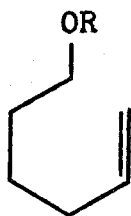
- b. G. Wittig and H. Reiff, Angew. Chem. Int. Ed. Eng., 7, 7 (1968).

- c. A.I. Meyers, A. Nabeya, H.W. Adickes, J.M. Fitzpatrick, G.R. Malone, and I.R. Politzer, J. Am. Chem. Soc., 91, 764 (1969).
- d. G. Stork and E. Colvin, ibid., 93, 2080 (1971).
13. a. J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Letters, 3363 (1968).
- b. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
14. G. Wittig and V. Schöllkopf, Chem. Ber., 87, 1318 (1954).
15. R.A. Bell, R.E. Ireland, and R.A. Partyka, J. Org. Chem., 31, 2530 (1966).
16. G. Stork, P. Rosen, N. Goldman, R.V. Coombs, and J. Tsuji, J. Am. Chem. Soc., 87, 275 (1965).
17. T.A. Spencer, T.D. Weaver, R.M. Villarica, R.J. Friary, J. Posler, and M.A. Schwartz, J. Org. Chem., 33, 712 (1968).
18. S.C. Welch and C.P. Hagan, Syn. Commun., 3, 29 (1973).
19. a. A. Afonso, J. Am. Chem. Soc., 90, 7375 (1968).
- b. A. Afonso, J. Org. Chem., 35, 1949 (1970).
20. An alternative procedure affords exclusively β -methylation, but requires more steps. E. Wenkert, A. Afonso, J.B. Bredenburg, C. Kaneko, and A. Tahara, J. Am. Chem. Soc., 86, 2038 (1964).
21. H.C. Brown and S. Krishnamurthy, ibid., 94, 7159 (1972).
22. I. Ojima, T. Kogure, and Y. Nagai, Chem. Commun., 938 (1972); Tetrahedron Letters, 5035 (1972).

Proposition IV

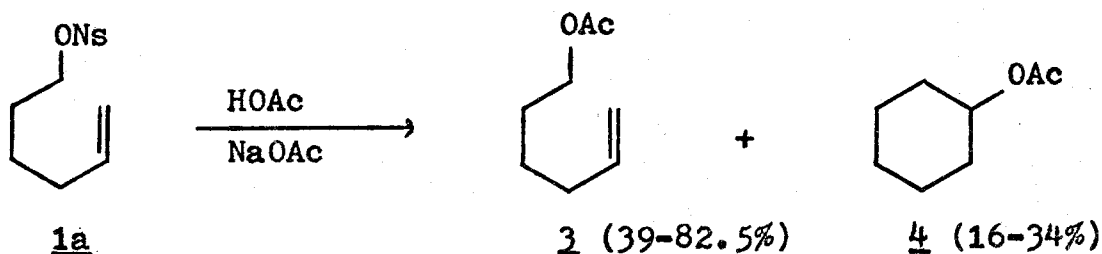
It is proposed to construct some polymeric sulfonic acids and to study the solvolyses of the sulfonate esters of some simple unsaturated alcohols on this solid matrix. The ultimate aim is to increase the degree of sophistication of the polymeric structures, so as to approach enzyme selectivity in the solvolytic reaction.

The solvolytic reactions of the sulfonate esters of δ,ϵ -unsaturated alcohols have been studied extensively in recent years. Initial studies on the esters 1 of the parent compound, 5-hexen-1-ol (2) were made by Bartlett (1) with 5-



- 1a R = Ns
1b R = Ts
2 R = H
3 R = Ac

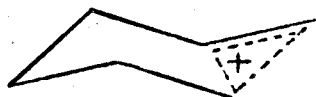
hexenyl-*p*-nitrobenzenesulfonate (1a). By subjecting this ester to acetolysis, the uncyclized 5-hexenyl acetate (3) and cyclohexyl acetate (4) were isolated as chief products.



The ratios of the two products varied, depending on the amount of sodium acetate added. In each case, however, the

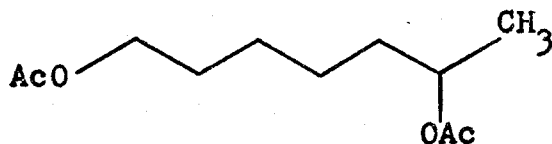
uncyclized acetate 3 was always the major product.

The solvolysis rates were found to vary from 1.5 to 1.7 times greater than that of the corresponding saturated n-hexyl ester. Bartlett (1) attributed the rate increase to anchimeric assistance (2,3) of the Δ^5 double bond, in forming the non-classical ion intermediate 5.



5

This work launched an increasing effort to study this reaction and to modify the conditions so as to increase the proportion of cyclized products, formed by what is commonly referred to as the " π route" (4). In a later study, Bartlett and coworkers (5) studied the acetolysis of the nosylate 1a again under more precise conditions. At 80.8° and with 1.6 equivalents of sodium acetate added, the reaction yielded 83.7% of 5-hexenyl acetate (3), 11.6% of cyclohexyl acetate (4), and 4.7% of cyclohexene (9). The amount of cyclohexyl acetate could be increased to 42% if the sodium acetate was omitted, but the major product was the diacetate 6, formed

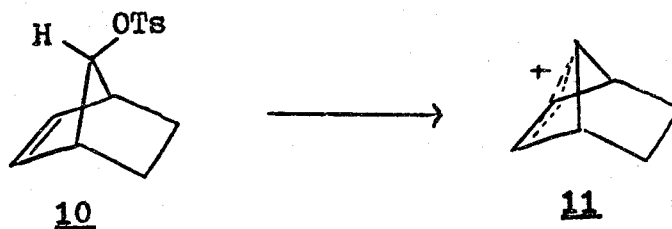


6

by protonation of the terminal double bond of the uncyclized acetate 3.

To account for the products isolated, these workers postulated that three independent mechanisms were in operation. These are described in Figure 1. First, the nosylate 1a can suffer direct S_N2 displacement by acetate to yield 5-hexenyl acetate (3). The marked decrease in the formation of 3 when sodium acetate is omitted supports this argument. Secondly, the ester could ionize to the acyclic classical cation 7, which could be attacked by acetate, again forming the acetate 3. Alternatively, intramolecular nucleophilic attack by the double bond would yield the cyclohexyl cation 8, which would yield cyclohexyl acetate (4) on attack by acetate, or cyclohexene (9) on deprotonation. Thirdly, assistance by the double bond would produce the non-classical ion 5, which on attack by acetate would also yield cyclohexyl acetate.

The fact that the overall rate is increased by only 72% over n-hexyl nosylate indicates that the last mechanism probably make a relatively small contribution to the total reaction process. This is in striking contrast to the acetylation of anti-7-norbornyl tosylate (10) which reacts 10^{11} times as fast as the saturated counterpart (6), presumably



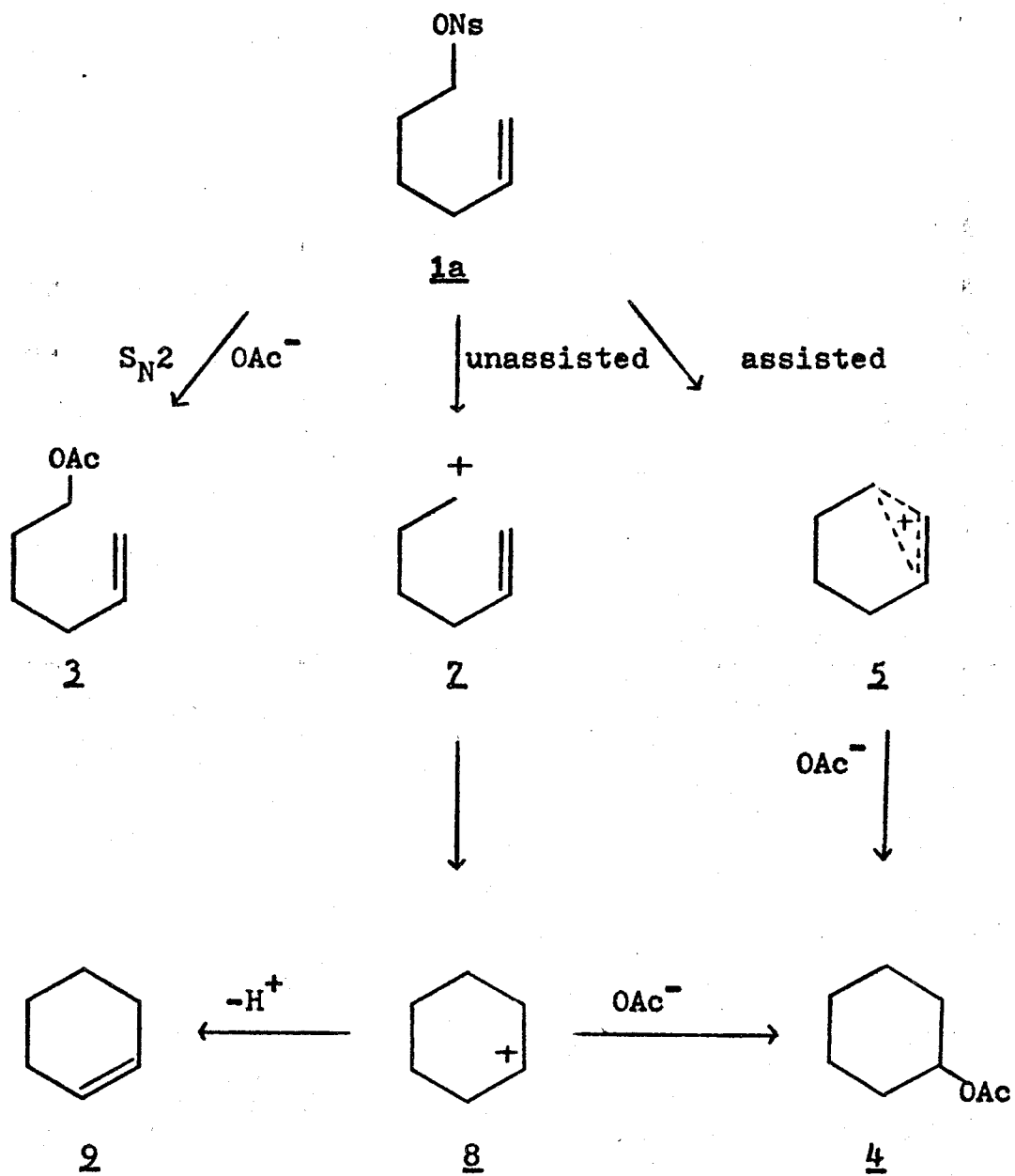


Fig. 1

due to the facile formation of the non-classical ion 11, by virtue of the proximity of the double bond to the incipient cationic site.

Clearly the way to increase the proportion of cyclized products is to somehow vary the conditions to favor the formation of either the classical ion 7 or the non-classical ion 8, the latter being preferred.

Substitution of urea for sodium acetate essentially doubles the yield of cyclized products (7), presumably by eliminating displacement by acetate. The use of formic acid-sodium formate as a medium also increases the yield of cyclized products, as well as enhancing the reaction rate (8). The effect of varying the leaving group has been studied (9) with the observation that arenesulfonates yield more cyclized products than halides. The use of cosolvents has also been studied (10), and the extent of cyclization has been shown to increase with increasing solvent polarity, although the yields are often variable. The best results have been obtained when the solvolysis was conducted in 2,2,2-trifluoroethanol (11).

It has been shown (12) that restricting the movement of the olefinic bond and/or the initial cationic site has a profound effect on the rate of solvolysis and the degree of cyclization. Of course, this requires structural modification of the substrate.

In the study on solvent variation (10), the reason given for increased cyclization with increased solvent polarity was the solvation of the leaving group by the polar solvent, which lowered the activation energy of the transition state leading to cation formation. It is quite possible, however, that the effect of the polar solvent was to cause the olefinic side chain to fold, or coil up, due to the repulsion of the double bond by the solvent. The result is an increase in the proximity of the double bond to the developing cationic site. The effect of olefinic chain folding vs. solvent polarity has been discussed for selective double bond reactivities (13) and with regard to the product distribution in some polyolefin cyclizations (14).

Unfortunately, those solvents which produced the highest ratio of cyclized to uncyclized products also gave the lowest yields, presumably due to reaction of the solvent with a cation intermediate.

One possible way of circumventing these problems would be to bind the substrate to a solid matrix. By doing this, one may be able to imitate the conditions that are present in an enzymic system. The use of polymeric reagents and micelles as models for enzymic reactions is well known (15).

In the proposed mechanism of triterpene biosynthesis, Stork (16) and Eschenmoser (17) proposed that the acyclic polyene squalene (12) is enzymatically hydroxylated at C-3 (Figure 2), causing a cationic cyclization to occur, producing

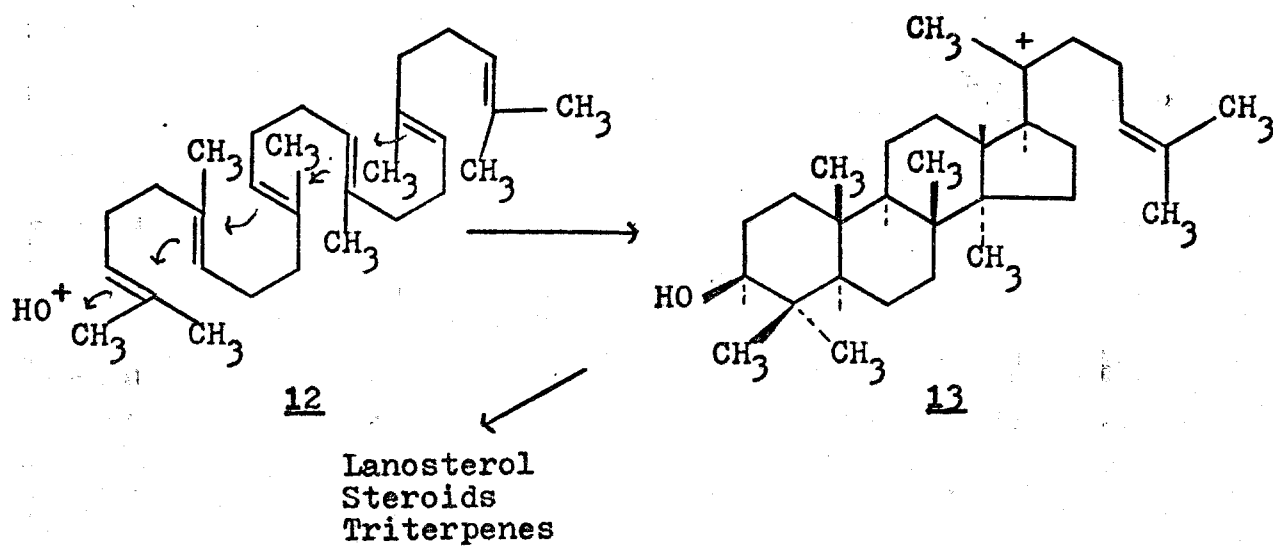


Fig. 2

the tetracyclic cation 13. Through a series of rearrangements, all the triterpenes may be produced. More recently, 2,3-oxidosqualene (14) has been shown (18) to be the actual precursor of the triterpenes, with the initiator depicted as the protonic enzyme EnzH^+ (Fig. 3).

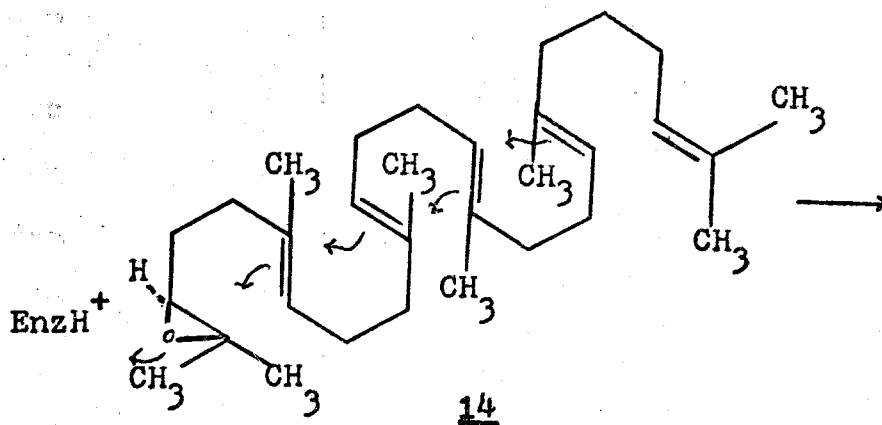


Fig. 3

It would be naive to believe that the cation initiation was the only interaction between the enzyme and the substrate. If this were the case, then one should be able to effect the cyclization of squalene oxide (14) and obtain products derivable from cation 13 in vitro. Attempts to do this have been unsuccessful (19). What is more likely, is that the substrate is held in a more or less restricted conformation prior to cation initiation. This would insure that the double bonds are in a favorable position for cyclization, once an appropriate positive site is generated.

Therefore, the polymer matrix to be constructed for the solvolyses must not only possess a suitable site for cation initiation, but also be capable of aiding the olefinic side chain in assuming a favorable conformation for cyclization, rather than relying on a statistical variation of ground state conformations.

The gross general structure of the polymeric arenesulfonate ester is depicted in Figure 4. The basic unit is a sul-

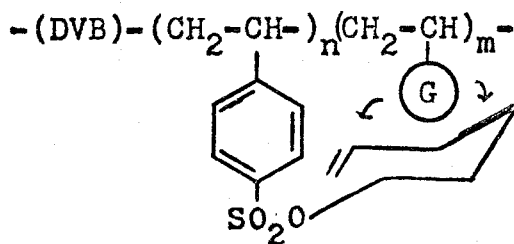


Fig. 4

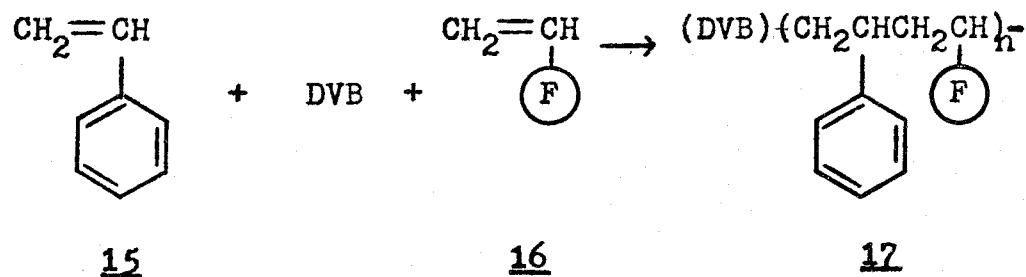
fonated polystyrene, crosslinked with divinylbenzene (DVB), which has been copolymerized with a vinylic monomer, ultimately to contain the polar group (G). It is not necessary that (G) actually be present in the monomer, for it could be introduced after polymerization. It is hoped that the polarity of (G) will cause the olefinic side chain to "see" a polar medium, and consequently assume a coiled conformation, so as to be closer in proximity to the incipient cationic site than in ordinary solution. This effect should be even more pronounced if the chain is extended (vide infra). On the other hand, the primary carbon atom attached to the sulfonate group should be sufficiently remote from the polar groups so as to "see" only the ionizing solvent used in the solvolysis. The phenomenon of causing a particular group to be near another, which wouldn't be in proximity ordinarily, is quite common in enzyme catalysis, and is known as the proximity effect (20).

The use of polymer-based substrates in chemical synthesis gained wide popularity when Merrifield introduced the technique for the synthesis of peptides (21). Its elegance and efficiency is exemplified by the solid phase total synthesis of the nonapeptide bradykin in ca. 40% isolated yield (22). Several modifications of the original procedure have been made in recent years, and these have been reviewed (23). The chief advantage of the method is the rapidity of the reaction sequences (4-6 residues/day). The ease of workup is

also important. The peptide is fixed to the insoluble support, and hence, never enters the solution. Consequently, purification is accomplished by simply washing the resin. Also, it is possible to use a large excess of reagents to insure complete reaction at each step, producing a homogeneous peptide.

Besides peptide synthesis, the solid phase technique has been expanded to include the synthesis of oligosaccharides (24) and adrenocorticotropins (25), as well as many novel organic reagents, including those for effecting Wittig reactions (26), monoacylation of ester enolates (27), unidirectional Dieckmann cyclizations (28), acylation of alcohols and amines (29), oxidation of primary alcohols (30), peracid oxidations (31), and methylene transfer reactions (32). A slight modification of this technique is the encapsulation of a reagent in a polystyrene-DVB resin (33).

The synthesis of the polymers described in Figure 4 should be relatively straightforward. Styrene (15), divinyl benzene, and the vinylic monomer 16 is suspension polymerized (34),

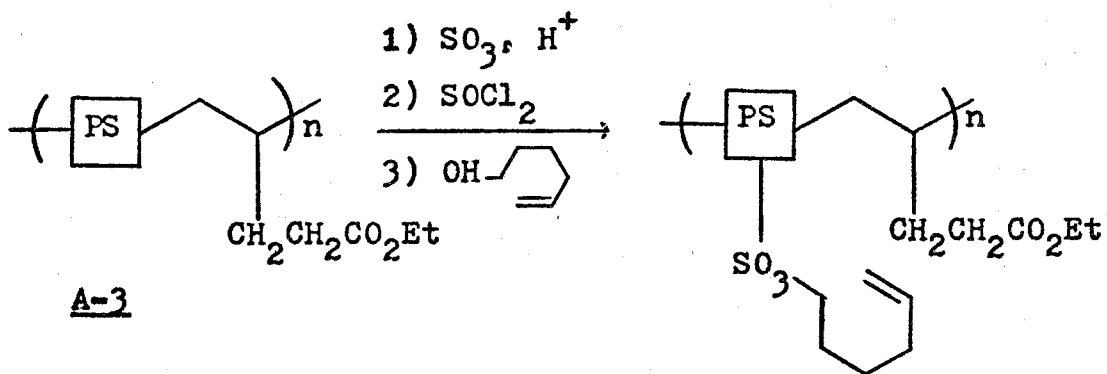
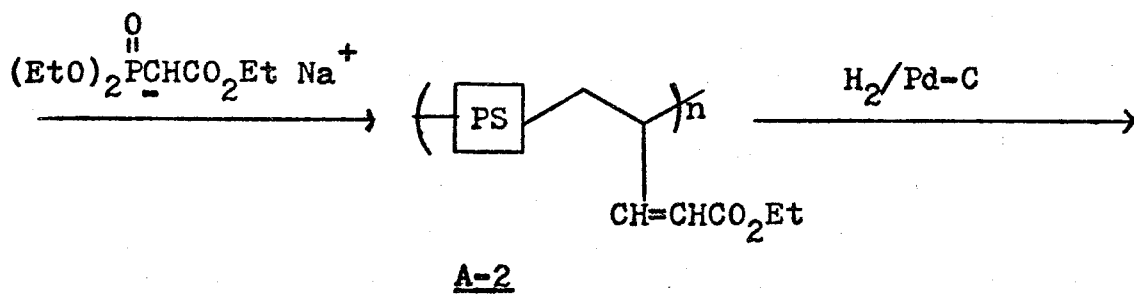
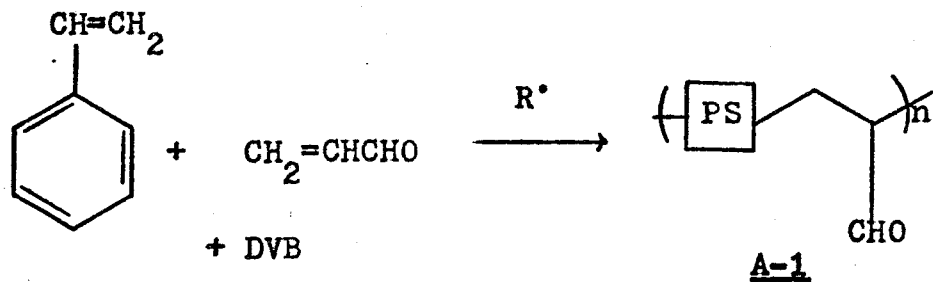


forming spheres of the polymer 17. In order to insure that each phenyl residue is surrounded by functionalized groups, a two to three-fold excess of the monomer 16 should be used. As was stated previously, the functional group (F) may or may not be equal to the polar group (G), the functional group ultimately desired in the polymeric support. In fact, their identity may not be practical at all, since the position of group (F) in the polymer structure would probably be too far from the olefin side chain in the polyester described in Figure 4.

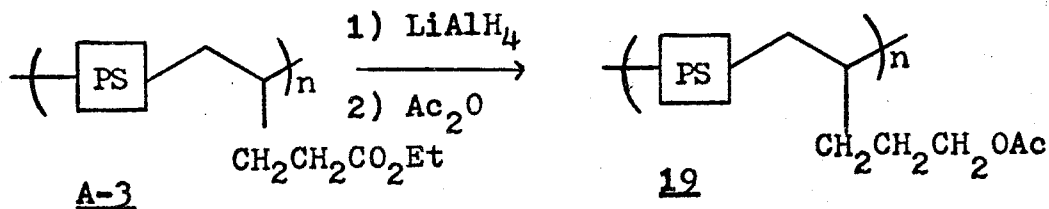
Therefore, some chain-extending transformations would be necessary. Exactly what monomers 16 are used in the synthesis of the polymer are, of course, dependent on the functional group desired at the end. For example, if a terminal ester function is desired, i.e., 18, then the polymerization could be conducted using styrene and acrolein (16, (F) = CHO) (Chart A). The resulting polymer, A-1, on reaction with sodium triethylphosphonoacetate (35) would yield the unsaturated ester A-2. Hydrogenation should afford the saturated polyester A-3. Sulfonation, followed by conversion to the sulfonyl chloride, and reaction with 5-hexen-1-ol (2) would yield the desired polymer 18.

Alternatively, a "reversed ester" function could be employed. Reduction of ester A-3 with lithium aluminum hydride and acetylation would yield the polyacetate 19.

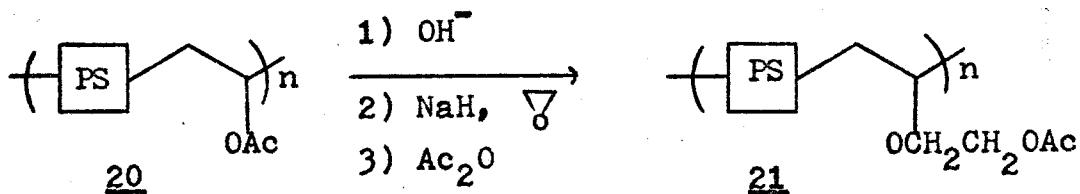
Chart A



PS = Polystyrene - DVB

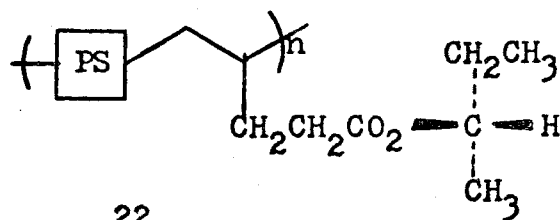


The use of vinyl acetate has some interesting possibilities. The polymer 20 that would be obtained could be hydrolyzed and alkylated with ethylene oxide. Acetylation should yield the acetate 21, an oxygenated analog of the ester 19.



In addition to increased polarity over ester 19, there may be some different conformational effects imposed on the hexenyl chain of the substrate that could alter the solvolysis.

A full description of all the possible polymers which could be made and used in this study is obviously beyond the scope of this discussion. It is clear, however, that tremendous freedom is possible, allowing the researcher to design and synthesize novel polymeric structures utilizing relatively simple reactions. For example, two different functional monomers could be used, yielding a polymer with different polar conditions. Another interesting possibility is the use of an ester with an optically active alcohol, i.e., 22. The aim would be to effect asymmetric induction in the



solvolysis product. The success of this aspect of the study is a matter of speculation.

For the solvolysis conditions, the use of 2,2,2-trifluoroethanol as a solvent is probably a reasonable first choice, because of the remarkable results obtained with its use as a solvolysis medium (11,36-39).

The fixed nature of the reaction should minimize intermolecular reaction, while still maintaining a high effective concentration of substrate (25). From an economical standpoint, once a polymer structure has shown promise as a support for selective solvolytic cyclization, its utility could be increased through regeneration by simply washing to remove the products and rechlorination of the sulfonic acid group.

Of course, it is doubtful that one could actually hope to achieve true enzyme selectivity using the solid phase reagents described above. However, for synthetic purposes, this is not entirely necessary. This point has recently been presented by Breslow (40), while discussing the merits of his remarkable steroidal remote oxidation reaction (40,41):

"Only when model systems achieve catalysis by factors on the order of 10^{10} do they begin to be interesting as models for enzymatic hydrolysis, but no such factors are required for enzymatic selectivity. If a random chemical reaction could simply be accelerated at a particular atom by a factor of 10^2 , the resulting selective attack at that atom would be highly practical. Accelerations by factors as large as 10^{10} seem to be difficult to achieve in model systems, but modest accelerations of 10^2 or greater are commonly obtainable by simple proximity effects."

For the present discussion, a rate enhancement of even 10^1 would be perfectly acceptable.

One could extend these studies to compounds containing multiple double bonds, in hopes of achieving polycyclic compounds by this method (42).

References

1. P.D. Bartlett, Ann., 653, 45 (1962).
2. S. Winstein, C.R. Lindgren, H. Marshall, and L.L. Ingraham, J. Am. Chem. Soc., 75, 147 (1953).
3. For discussions of several types of anchimeric assistance during solvolyses, see:
 - a. A. Streitweiser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, 1962, pp 103-156.
 - b. E.R. Thornton, "Solvolysis Mechanisms," The Ronald Press, New York, 1964, pp 127-130.
 - c. P.D. Bartlett, "Non-Classical Ions," W.A. Benjamin, New York, 1965.
4. S. Winstein and P. Carter, J. Am. Chem. Soc., 83, 4485 (1961).
5. P.D. Bartlett, W.D. Closson, and T.J. Cogdell, ibid., 87, 1308 (1965).
6. a. S. Winstein and M. Shatavsky, ibid., 78, 592 (1956).
b. S. Winstein, M. Shatavsky, C. Norton, and R.B. Woodward, ibid., 77, 4183 (1955).
7. W.S. Trahanovsky, M.P. Doyle, and P.D. Bartlett, J. Org. Chem., 32, 150 (1967).
8. W.S. Johnson, D.H. Bailey, R. Owyang, R.A. Bell, B. Jacques, and J.K. Crandall, J. Am. Chem. Soc., 86, 1959 (1964).
9. W.S. Trahanovsky and M.P. Doyle, Chem. Commun., 1021 (1967).
10. W.S. Trahanovsky and M.P. Doyle, J. Am. Chem. Soc., 89, 4867 (1967).
11. W.S. Trahanovsky and M.P. Doyle, Tetrahedron Letters, 2155 (1968).
12. P.D. Bartlett, E.M. Nicholson, and R. Owyang, Tetrahedron Supplement, 8, 399 (1966).

13. a. E.E. van Tamelen and T.J. Curphey, Tetrahedron Letters, 121 (1962).
b. E.E. van Tamelen and K.B. Sharpless, ibid., 2655 (1967).
14. This Thesis, p 85.
15. For reviews, see:
 - a. H. Morawetz, Adv. Catal. Rel. Subj., 20, 369 (1969).
 - b. E.H. Cordes and R.B. Dunlap, Acc. Chem. Res., 2, 329 (1969).
 - c. T.C. Bruice, "The Enzymes," Third ed., 217 (1970).
16. G. Stork and A.W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955).
17. A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, Helv. Chim. Acta, 38, 1890 (1955).
18. a. E.J. Corey, W.E. Russey, and P.R. Ortiz de Montellano, J. Am. Chem. Soc., 88, 4750 (1966).
b. E.E. van Tamelen, J.D. Willett, R.B. Clayton, and K.E. Lord, ibid., 4752 (1966).
c. E. Capstack, Jr., N. Rosin, G.A. Blondin, and W.R. Nes, J. Biol. Chem., 240, 3258 (1965).
d. W.O. Godfredsen, H. Lorck, E.E. van Tamelen, J.D. Willett, and R.B. Clayton, J. Am. Chem. Soc., 90, 208 (1968).
19. E.E. van Tamelen, J.D. Willett, M. Schwartz, and R. Nadeau, ibid., 88, 5937 (1966).
20. R. Lumry, "The Enzymes," Second ed., Vol. 1, 157 (1959).
21. a. R.B. Merrifield, Federation Proc., 21, 412 (1962).
b. R.B. Merrifield, J. Am. Chem. Soc., 85, 2149 (1963).
22. R.B. Merrifield, ibid., 86, 304 (1964).
23. a. R.B. Merrifield, Adv. in Enzym., 32, 221 (1969).
b. J.M. Stewart and J.D. Young, "Solid Phase Peptide Synthesis," W.H. Freeman, New York, 1969.

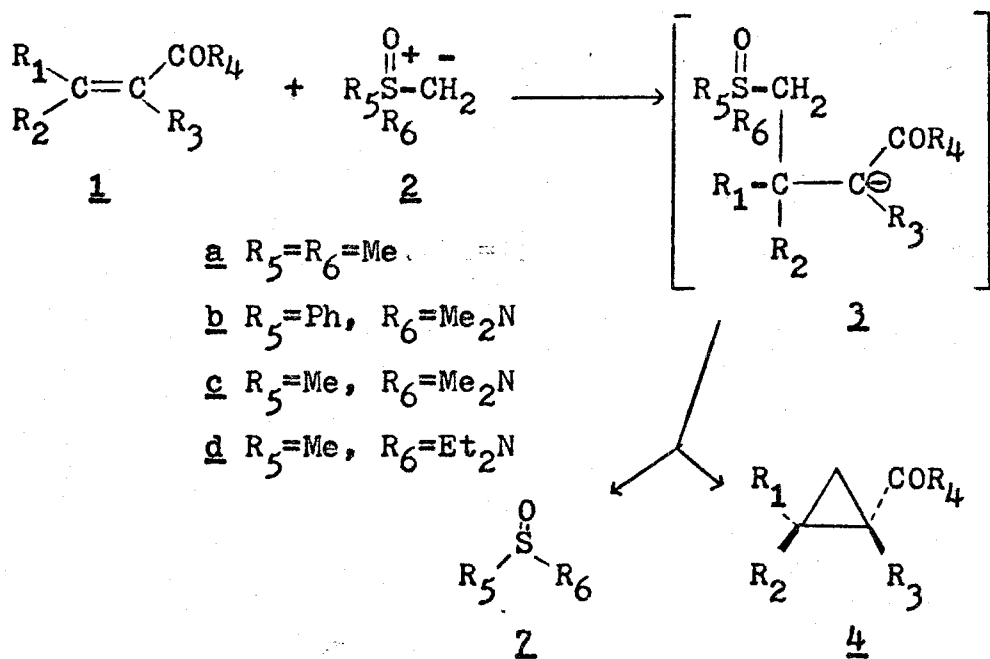
- c. E. Wüncch, Angew. Chem. Int. Ed. Eng., 10, 786 (1971).
- d. G.R. Marshall, Biochem. Aspects React. Solid Supp., 111 (1971).
- e. G. Lusse, Acta Phys. Chem., 18, 63 (1972).
- f. S.-S. Wang and R.B. Merrifield, Int. J. Peptide Protein Res., 4, 309 (1971).
- g. R.B. Merrifield, Beckman Rep., 1, 3, (1972).
24. a. J.M.J. Frechet, Ph. D. Thesis, Syracuse University, 1972.
- b. G. Excoffier, D. Gagnaire, J.P. Utille, and M. Vignou, Tetrahedron Letters, 5065 (1972).
25. D. Yamashiro and C.H. Li, J. Am. Chem. Soc., 95, 1310 (1973).
26. a. F. Camps, J. Castells, J. Font, and F. Vela, Tetrahedron Letters, 1715 (1971).
- b. S.V. McKinley and J.W. Rakshys, Jr., Chem. Commun., 134 (1972).
27. A. Patchornik and M.A. Kraus, J. Am. Chem. Soc., 92, 7587 (1970).
28. J.I. Crowley and H. Rapoport, ibid., 6363 (1970).
29. a. F. Camps, J. Castells, M.S. Ferrando, and J. Font, Tetrahedron Letters, 1713 (1971).
- b. M.B. Shambhu and G.A. Digenis, ibid., 1627 (1973).
30. N.M. Weinschenker and C.M. Shen, ibid., 3285 (1972).
31. T. Takagi, Polymer Letters, 5, 1031 (1967).
32. S. Tanimoto, J. Horikawa, and R. Oda, Kogyo Kagaku Zasshi, 70, 1269 (1967); C.A., 68, 69406h (1968).
33. D.C. Neckers, D.A. Kooistra, and G.W. Green, J. Am. Chem. Soc., 94, 9284 (1972).
34. H. Logemann in Houben-Weyl, "Methoden der Organischen Chemie," Fourth ed., Vol. 14/1, Georg Thieme Verlag, Stuttgart, 1961, pp 406-429.

35. W.S. Wadsworth, Jr., and W.D. Emmons, J. Am. Chem. Soc., 83, 1733 (1961).
36. F.L. Scott, Chem. and Ind., 224 (1959).
37. V.J. Shiner, Jr., W. Dowd, R.D. Fisher, S.R. Hartshorn, M.A. Kessick, L. Milakosky, and M.W. Rapp, J. Am. Chem. Soc., 91, 4838 (1969).
38. T.C. Clarke and R.G. Bergman, ibid., 94, 3627 (1972).
39. D.S. Noyce, R.L. Castenson, and D.A. Meyers, J. Org. Chem., 37, 4222 (1972).
40. R. Breslow, S.W. Baldwin, T. Flechter, P. Kalicky, S. Liu, and W. Washburn, J. Am. Chem. Soc., 95, 3251 (1973).
41. a. R. Breslow and S.W. Baldwin, ibid., 92, 732 (1970).
b. R. Breslow and P. Kalicky, ibid., 93, 3540 (1971).
42. a. W.S. Johnson, S.L. Gray, J.K. Crandall, and D.M. Bailey, ibid., 86, 1966 (1964).
b. W.S. Johnson and J.K. Crandall, ibid., 2085 (1964).
c. W.S. Johnson and R. Owyang, ibid., 5593 (1964).
d. W.S. Johnson and J.K. Crandall, ibid., 87, 1785 (1965).

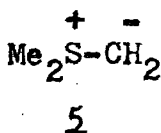
Proposition V

It is proposed that the preparation of lithium di(methylthiomethyl)cuprate and lithium di(phenylthiomethyl)cuprate be attempted and their reactions with a variety of electrophilic compounds be studied. It is hoped that these compounds will provide novel methylene transfer reagents for the preparation of α,β -cyclopropyl carbonyl compounds. If the above studies are successful, then an attempt to effect transannular methylene transfer is proposed, in order to provide a synthesis of bicyclo[2.2.1] heptan-2-one (2-norbornyl ketones). This is exemplified by a convergent, stereoselective, five-step synthesis of the sesquiterpene β -santalene from 2-methyl-2-cyclohexenone.

The transfer of a methylene group in a conjugated sense to α,β -unsaturated ketones (1) is limited to the use of oxygenated sulfur ylides of type 2 (1).

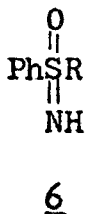


The first methylene transfer ylide to be studied extensively was dimethyloxosulfonium methylide (2a) (2). This ylide was found to react exclusively in a 1,4 sense with α,β -unsaturated ketones, which led to cyclopropanes, and in a 1,2 fashion with saturated ketones, yielding epoxides. In contrast, dimethylsulfonium methylide (5) (2) adds to all ke-



tones in a 1,2 fashion.

Johnson and coworkers (3) have developed another ylide, (dimethylamino)phenyloxosulfonium methylide (2b), which is prepared from the phenyl methyl sulfoximine (6, R = CH₃).

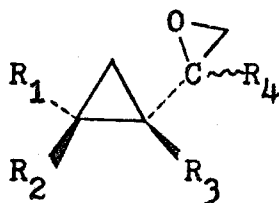


While the reactivity of this latter ylide parallels that of the dimethyl species 2a, it appears to have a much broader scope of usefulness. For example, using the optically active form of ylide 2b, Johnson and coworkers (3c,8b) could achieve an asymmetric synthesis of a number of cyclopropyl ketones with optical purities as high as 35%. Recently, Johnson and Rogers (3d,e) have reported the preparation of the (dialkylamino)methyloxosulfonium methylides 2c and 2d,

which are also effective reagents for cyclopropane or oxirane formation.

The ylide reaction, as depicted above, involves the formation of the unstable betaine 3 (1) which collapses to form the cyclopropyl ketone 4 and a sulfoxide 7. Because of the instability of the betaine intermediate, it is impossible to stop the reaction at this stage, therefore rendering cyclopropane formation the only possible mode of reaction.

Several disadvantages have been noted in the use of these ylides, especially 2a. First, the reactivity of the ylide is strongly dependent on the structure of the enone substrate, being only moderately reactive in some cases (4a-c), and unreactive in others, such as vinyl ketones and trans-2-penten-4-one (5,6). Second, the cyclopropyl ketone formed is probably capable of further reaction, which would lead to the epoxide 8, thereby necessitating the use of only

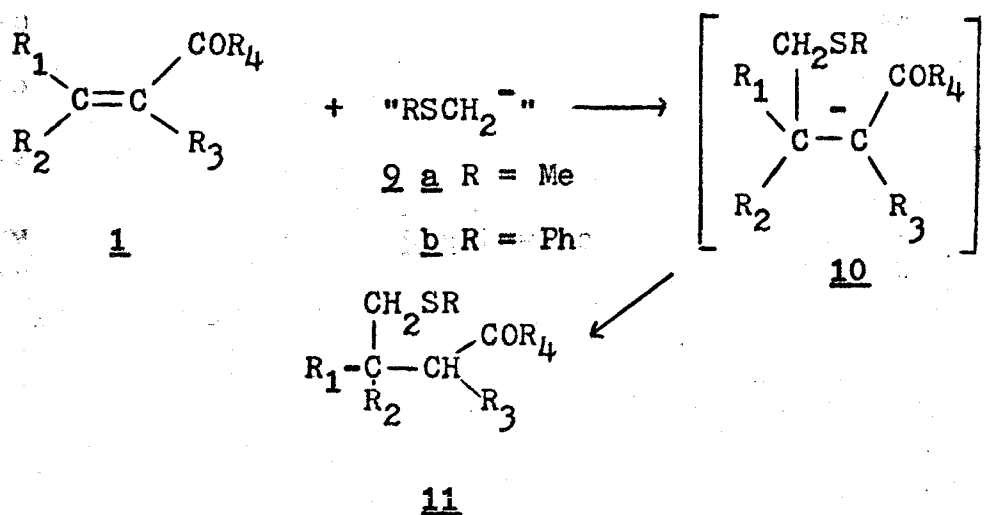


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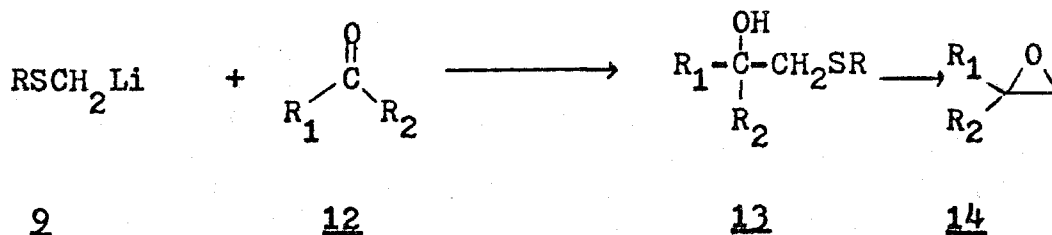
one equivalent of the ylide reagent, which may severely limit its use with hindered ketones. Third, the reagent also reacts with ester functional groups (4a). Finally, it is probably not possible to carry out the cyclopropylation in the presence of a saturated carbonyl, since the two

functional groups would undoubtedly compete for the reagent.

One possible way of circumventing most of these difficulties would be to add either the group methylthiomethide (9a) or phenylthiomethide (9b) in a 1,4 manner to an enone 1.



A procedure for the 1,2 addition of a substituted thio-methyl lithium compound to ketones has been reported recently (7). The metalated sulfide 9 is added to a ketone 12, forming the β -hydroxy sulfide 13. Methylation of 13 at sulfur,



followed by base treatment yields the corresponding epoxides 14 (8). Although this procedure requires three steps, as opposed to one with an ylide, one takes advantage of the

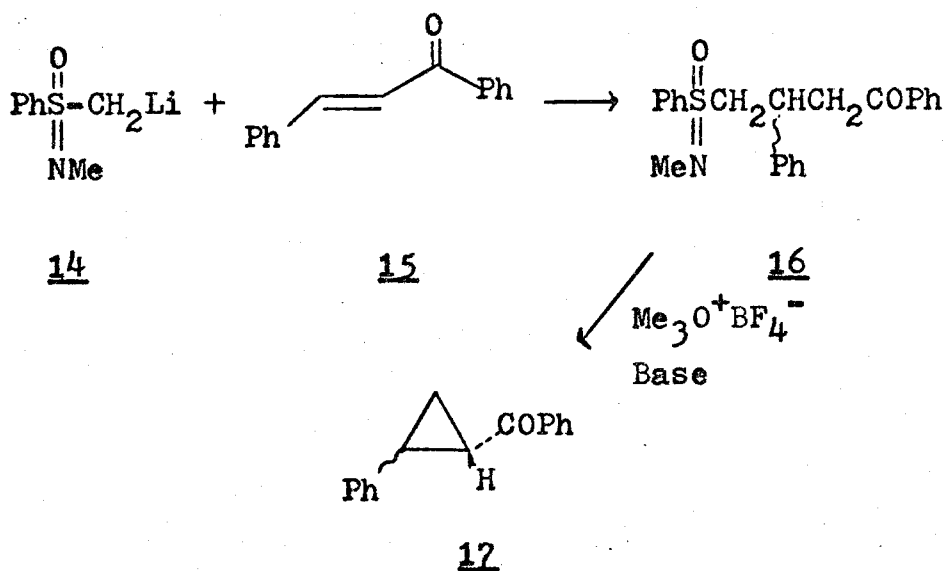
greater reactivity of the thiomethylithium species, as well as its lower susceptibility to steric hindrance and enolization.

Other thioalkyllithium reagents have been used for the synthesis of olefins from hindered ketones (9) and the formation of spiroannelated cyclobutanones (10).

If the conjugate addition of a thiocarbanion 9 could be effected, it should provide a versatile synthetic tool, while overcoming some of the disadvantages of the ylide reaction. First, the initial product formed is the enolate 10, which would not react with another molecule of reagent, thereby allowing the use of an excess of the reagent. Second, the protonated intermediate 11 would not form a cyclopropane until the molecule has been S-alkylated and treated with base. Therefore, the keto sulfide 11 could act as a compound containing a "masked" cyclopropane, which might allow further transformations to be performed on the molecule, while delaying cyclopropane formation until an appropriate stage of the scheme. Third, the increased reactivity of the reagent may permit reaction with enones that were inert to dimethyl-oxosulfonium methylide (2a) (5). Fourth, if the reagent could be made to react selectively with unsaturated carbonyls only, then it should be possible to use the reagent in the presence of other sensitive functional groups (i.e., ketones, aldehydes, esters, nitriles). Finally, if cyclopropane formation is blocked, it may be possible to utilize the sub-

stituent as a bridge for a transannular bond-forming reaction via intramolecular alkylation (vide infra).

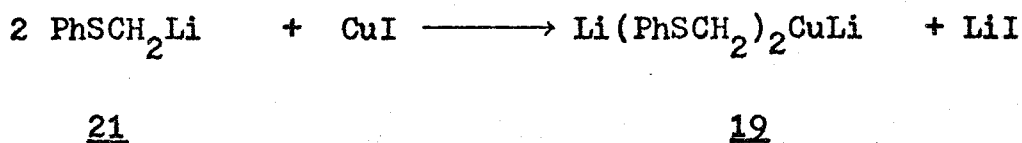
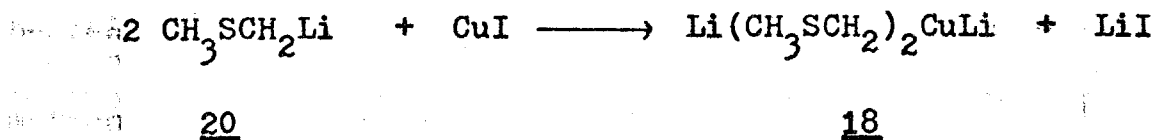
At the present time, no general method exists for the 1,4 addition of a substituted thiomethyl carbanion 9. In an isolated example, Johnson and Schroeck (8b) added lithium (S)-N-methylbenzenesulfonimidoylmethide (14) (11) to trans-benzalacetophenone (15) and obtained the diastereomeric adducts 16. Methylation and treatment with base afforded the



cyclopropyl ketones 17. While this example serves to effect the conjugate addition of a thiomethylene group, it is not clear that it possesses the desired qualities of the reagent under discussion. For one thing, it would certainly add in a 1,2 fashion to saturated ketones.

It is therefore suggested to explore the preparation of lithium di(methylthiomethyl)cuprate (18) and lithium di(phenylthiomethyl)cuprate (19), which should be readily

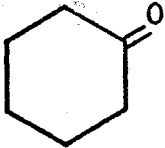
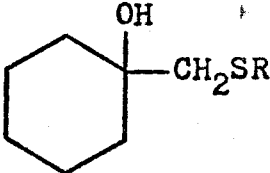
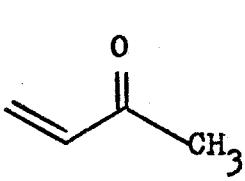
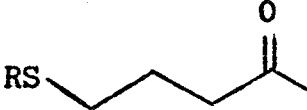
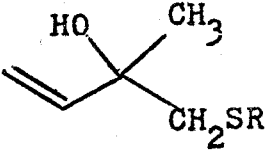
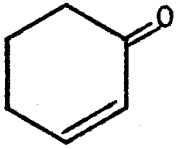
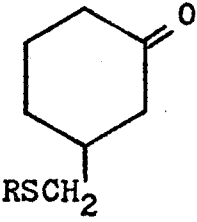
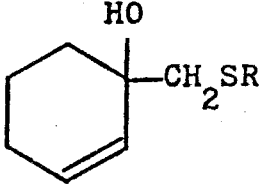
formed by the addition of cuprous iodide to methylthiomethyl-
lithium (20) (12) and phenylthiomethyl lithium (21) (13),
respectively.



The ability of lithium dialkyl cuprates to add to enones in a 1,4 fashion, while being unreactive toward saturated ketones, esters, and aldehydes is well known (14). It is hoped that the substituted thiomethyl lithium reagents 18 and 19 will behave in a similar manner. The initial studies to be undertaken would be to first attempt to form the reagents, and then to test their reactivity toward a number of substrates, such as saturated and unsaturated ketones, aldehydes, esters, and nitriles. Some typical reaction studies are outlined in Table I.

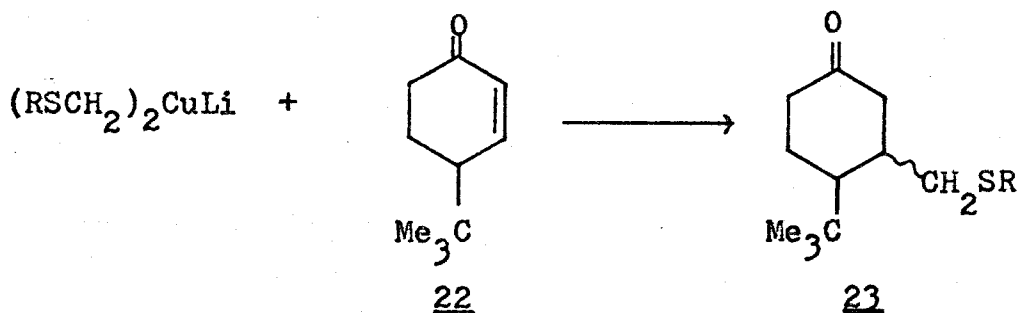
If these reactions proceed as desired, then the next set of experiments would be straightforward. If one encounters the problem of 1,2 addition to saturated ketones, it would still be possible to do competitive rate experiments to see if there is a substantial difference in the rates, so as to

Table I

<u>Substrate</u>	$(\text{RSCH}_2)_2\text{CuLi}$ →	<u>Desired Product</u>	<u>Possible Side Products</u>
$\text{CH}_3(\text{CH}_2)_3\text{CHO}$		N.R.	$\text{CH}_3(\text{CH}_2)_3\text{CHOHCH}_2\text{SR}$
$\text{CH}_3\text{CH}_2\text{COCH}_3$		N.R.	$\text{CH}_3\text{CH}_2\underset{\text{CH}_3}{\text{CHOHCH}_2}\text{SR}$
		N.R.	
			
			
CH_3CN		N.R.	$\text{CH}_3\text{COCH}_2\text{SR}$
$\text{CH}_3\text{CO}_2\text{Et}$		N.R.	$\text{CH}_3\text{COH}(\text{CH}_2\text{SR})_2$

afford selectivity. Typical examples of these studies are outlined in Table II for ketones. Similar experiments with compounds possessing other functional groups are possible, should the reagents prove to be reactive toward them.

If reasonable selectivity toward enones is demonstrated, then one could investigate the stereochemistry of the addition, such as with 4-tert-butyl-2-cyclohexenone (22), and



determine the stereochemistry of the product(s) 23.

Next, it is important to demonstrate the ability to convert the resulting keto sulfides into cyclopropyl ketones. This is illustrated below for trans-benzalacetophenone (15).

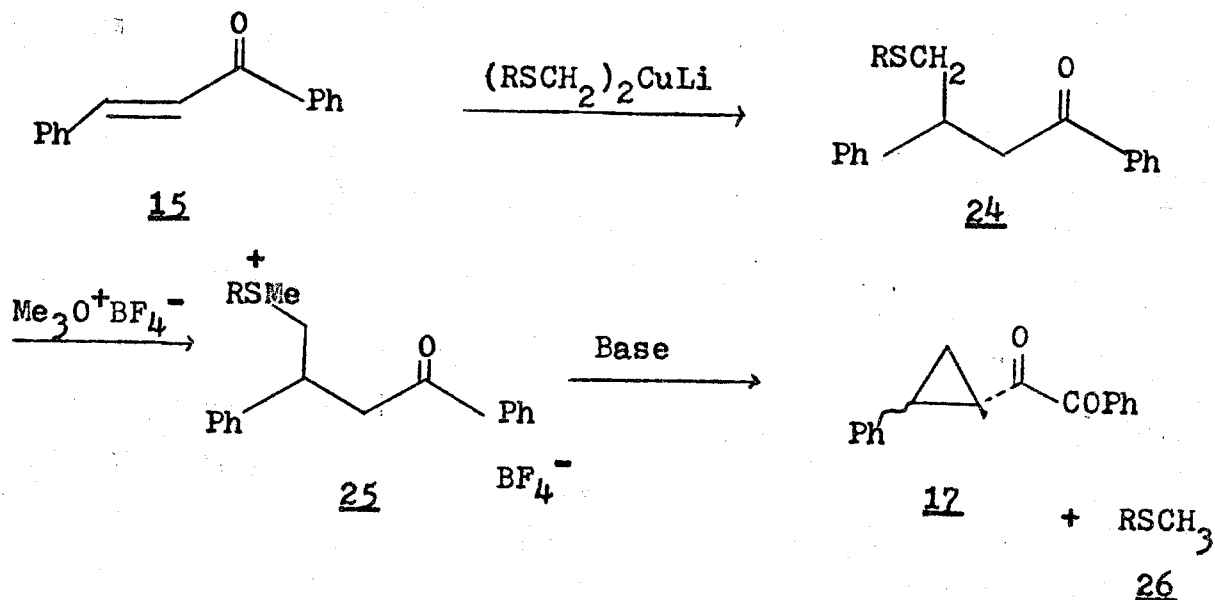
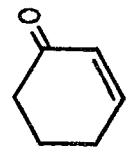
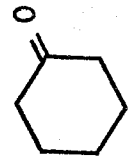
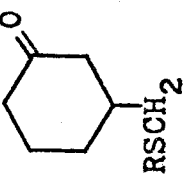
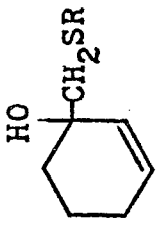
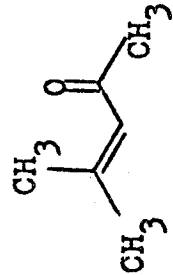
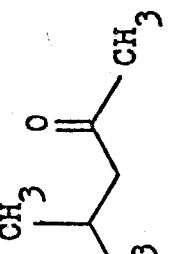
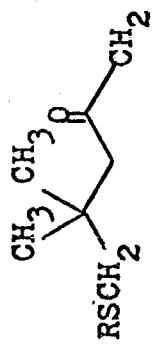
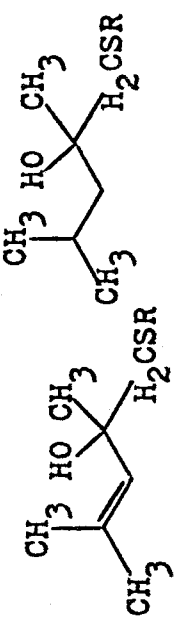
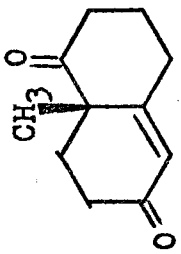
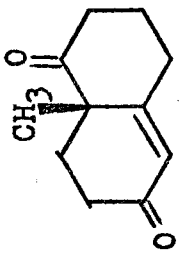
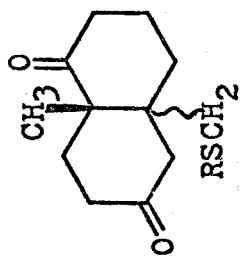
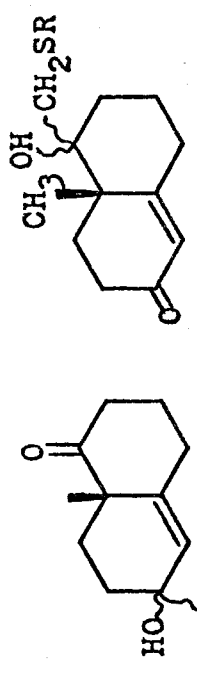
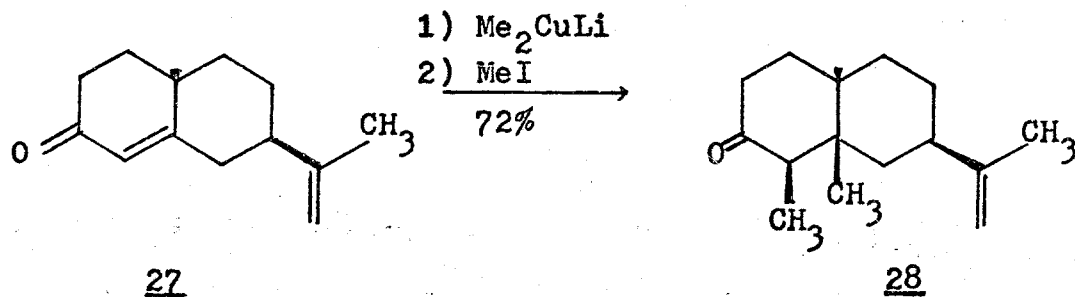


Table II

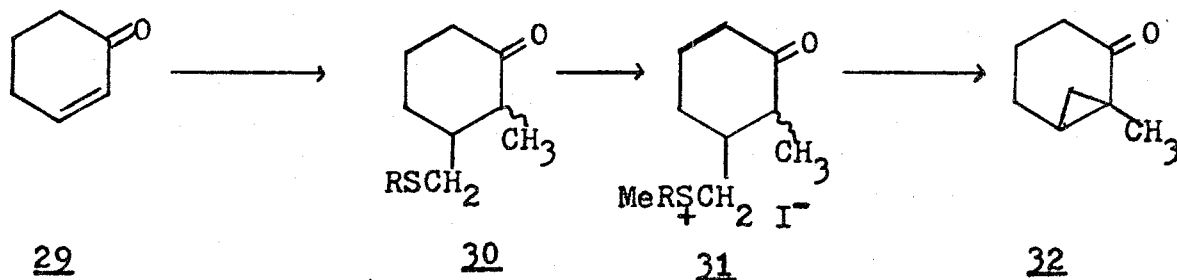
<u>Substrate(s)</u>	$(\text{RSCH}_2)_2\text{CuLi}$ (1 equiv.)	<u>Desired Product</u>	<u>Possible Side Products</u>
			
			
			

The keto sulfide 24 is alkylated, and the resulting keto sulfonium salt 25 is treated with base. This should form a betaine, identical with that formed from an ylide 2 and an enone. This betaine should collapse to the cyclopropyl ketones 17 and the methyl sulfide 26.

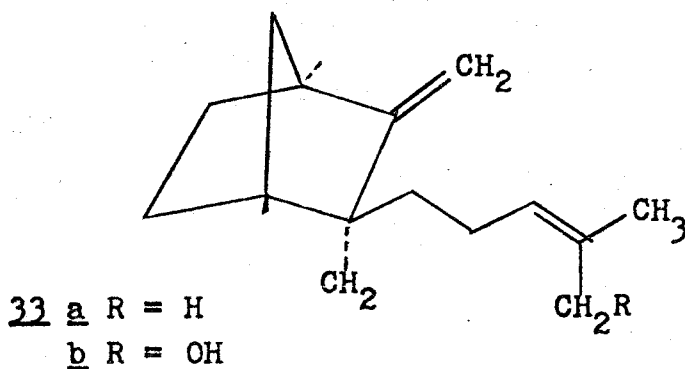
Another interesting experiment would be to see if the initially-formed enolate could be alkylated at the α -carbon. A similar procedure using lithium dimethylcuprate was used by Roebke (15) for the synthesis of the decalone 28 from the octalone 27. In the case of the sulfur reagent, this is



illustrated for 2-cyclohexenone (29). The methylation of the enolate would probably be rapid, relative to methylation on sulfur, although prolonged reaction times would effect this also. Subjecting the keto sulfonium salt 31 to basic conditions should yield the cyclopropyl ketone 32.



If this last study is successful, then one other experiment is suggested. If the α -carbon has no hydrogens to abstract (i.e., is disubstituted), could displacement of the sulfonium group be effected by the α' -carbon? The experiments to illustrate this point is shown in Chart A for a short, convergent synthesis of the sesquiterpene β -santalene (33a) (16).



Treatment of 2-methyl-2-cyclohexenone (A-1) with the copper reagent should afford an enolate 34, which should exist preferentially in the conformation shown with the thiomethyl substituent equatorial. Attack of an alkylating

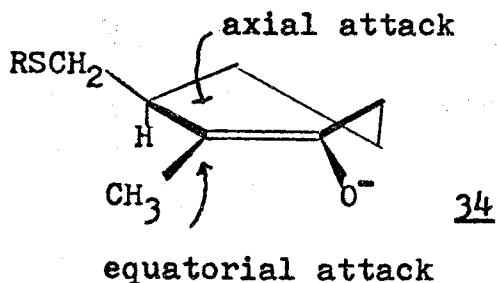
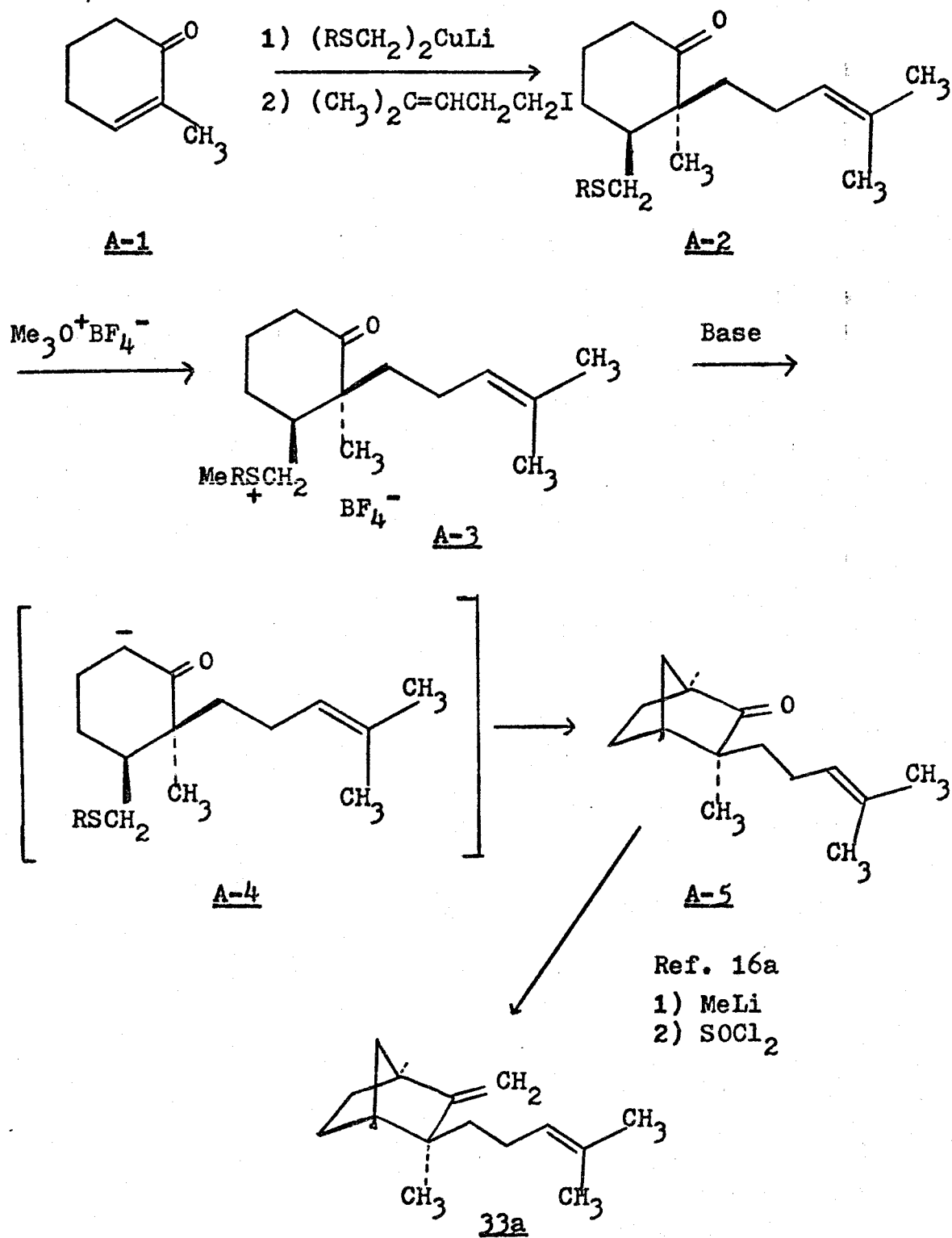


Chart A



agent at position 2 is expected (17) to occur so as to yield the species in which the entering group is axial. Hence, with 5-iodo-2-methyl-2-pentene, the desired (Z)-ketone A-2 should be the major product. Methylation with trimethyloxonium flouoroborate should produce the keto sulfonium salt A-3. With no α -hydrogens at C-2, treatment with base should abstract a proton from C-6, affording the enolate A-4. It is hoped that this will undergo transannular displacement of the sulfonium group to give the ketone A-5.

Thus, in the first step of the sequence, a carbon atom is introduced at C-3, which produces a negative charge on C-2 for the introduction of a side chain at that position. In addition, the C-3 carbon is properly functionalized for direct cyclization to form a bridged species between C-3 and C-6.

The intermediate ketone A-5 has already been converted (16a) to β -santalene by the two-step sequence shown, rendering the synthesis by the above method, if successful a formal total synthesis of β -santalene. Using a different alkylating agent for step 1, one could also envision a synthesis of β -santalol (33b).

References

1. For a general review of sulfur ylides, see A.E. Johnson, "Ylid Chemistry," Academic Press, New York and London, 1966.
2. a. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 84, 867 (1962).
b. ibid., 3782 (1962).
c. ibid., 86, 1640 (1964).
d. ibid., 87, 1353 (1965).
3. a. C.R. Johnson, E.R. Janiga, and M. Haake, ibid., 90, 3890 (1968).
b. C.R. Johnson, M. Haake, and C.W. Schroeck, ibid., 92, 6594 (1970).
c. C.R. Johnson and C.W. Schroeck, ibid., 90, 6852 (1968).
d. C.R. Johnson and P.E. Rogers, J. Org. Chem., 38, 1793 (1973).
e. ibid., 1798 (1973).
4. a. E.J. Corey and M. Chaykovsky, Tetrahedron Letters, 169 (1963).
b. H. Koenig, H. Metzger, and C. Seelert, Chem. Ber., 98, 3712 (1965).
c. This Thesis, p 101.
5. C. Agami, C. Prevost, and J. Aubouet, Bull. Soc. Chim. Fr., 2299 (1967).
6. C. Agami and J. Aubouet, ibid., 1391 (1967).
7. J.R. Shanklin, C.R. Johnson, J. Ollinger, and R.M. Coates, J. Am. Chem. Soc., 95, 3429 (1973).
8. a. M. Yoshimine and H.J. Hatch, ibid., 89, 5831 (1967).
b. C.R. Johnson and C.W. Schroeck, ibid., 93, 5303 (1971).
c. T. Durst, R. Viau, R. Van Den Elzen, and C.H. Nguyen, Chem. Commun., 1334 (1971).

- d. J.M. Townsend and K.B. Sharpless, Tetrahedron Letters, 3313 (1972).
9. R.M. Coates and R.L. Sowerby, J. Am. Chem. Soc., 94, 4758, 5386 (1972).
10. B.M. Trost, D. Keeley, and M.J. Bogdanowicz, ibid., 95, 3068 (1973).
11. C.W. Schroeck and C.R. Johnson, ibid., 93, 5305 (1971).
12. D.J. Peterson, J. Org. Chem., 32, 1717 (1967).
13. E.J. Corey and D. Seebach, ibid., 31, 4097 (1966).
14. a. H.O. House, W.L. Respass, and G.M. Whitesides, ibid., 3128 (1966).

For a comprehensive review of this reaction, as well as other uses of organocopper reagents, see:

- b. J.F. Normant, Synthesis, 63 (1972).
- c. G.H. Posner, Org. React., 19, 1 (1972).
15. H. Roebke, Ph. D. Thesis, Northwestern University, 1969.
16. For previous syntheses of β -santalene and β -santalol, see:
- a. E.J. Corey, R. Hartmann, and P.H. Vatakencherry, J. Am. Chem. Soc., 84, 2611 (1962).
- b. G. Brieger, Tetrahedron Letters, 1949 (1963).
- c. E.J. Corey and M.F. Semmelhack, J. Am. Chem. Soc., 89, 2755 (1967).
- d. W.I. Fanta and W.F. Erman, Tetrahedron Letters, 4155 (1969).
- e. H.C. Kretschman and W.F. Erman, ibid., 41 (1970).
- f. G.L. Hodgson, D.F. MacSweeney, and T. Money, ibid., 3683 (1972).
- See also:
- g. J. Wolinsky, D.R. Dimmel, and T.W. Gibson, J. Org. Chem., 32, 2087 (1967).

- h. W.I. Fanta and W.F. Erman, ibid., 37, 1124 (1972).
- i. T. Gibson and Z.J. Berneus, Tetrahedron Letters, 2207 (1972).