PART I

EFFORTS DIRECTED TOWARDS THE TOTAL SYNTHESIS OF SHIONONE

PART II

CONVERSION OF ESTRONE TO ANDROST-4-EN-3-ONE: A NEW METHOD FOR ACTIVATING THE C-9 AND C-10 POSITIONS OF ESTROGENIC STEROIDS FOR SUBSTITUTION

Thesis by

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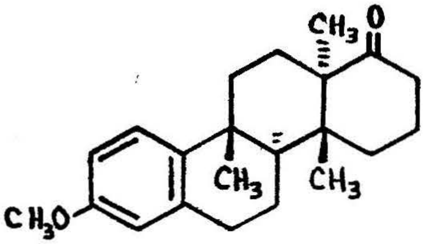
To Marcia, with love

Acknowledgements

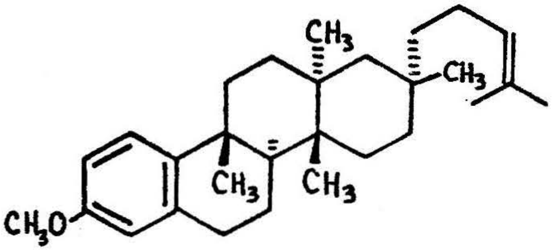
I would like to sincerely thank Professor Robert E. Ireland for his guidance, patience, teaching, and friendship. I would also like to extend my appreciation to my colleagues for many stimulating discussions and useful suggestions, and especially to Dr. Steven C. Welch who taught me so many of the laboratory techniques which have been important to this research. I offer a special thanks to my wife, Marcia, for her patience, support, and sacrifice during the course of this work, and for typing this entire thesis. Finally, I would like to thank the National Institutes of Health and the California Institute of Technology for financial support.

Abstract

Part I: An approach to the total synthesis of the triterpene shionone is described, which proceeds through the tetracyclic ketone 1. The shionone side chain has been attached to this key intermediate in 5 steps, affording the olefin 2 in 29% yield. A method for the stereospecific introduction of the angular methyl group at C-5 of shionone has been developed on a model system. The attempted utilization of this method to convert olefin 2 into shionone is described.



1



2

Part II: A method has been developed for activating the C-9 and C-10 positions of estrogenic steroids for substitution. Estrone has been converted to $4\beta,5\beta$-epoxy-10β-hydroxyestr-3-one; cleavage of this epoxyketone using an Eschenmoser procedure, and subsequent modification of the product afforded 4-seco-9-estren-3,5-dione 3-ethylene acetal. This versatile intermediate, suitable for substitution at the 9 and/or 10 position, was converted to androst-4-ene-3-one by known procedures.

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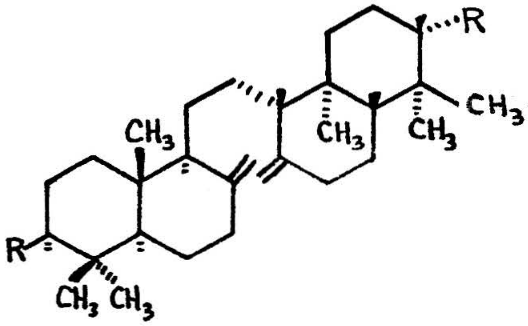
PART I

EFFORTS DIRECTED TOWARDS THE TOTAL SYNTHESIS OF SHIONONE

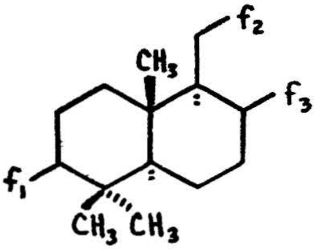
Introduction

While it seems unlikely that steroids (1) and triterpenes (2) have been produced by nature primarily for the edification of organic chemists, it remains true that these molecules provide conformationally well-defined substrates upon which the chemist may test and develop many of his ideas (3). For the synthetic chemist, they provide as goals a variety of molecular structures which are complex enough to tax available methods and also to require new ones; yet which are simple enough to allow progress and understanding to grow from the attempted syntheses. Due to their biological activity and somewhat uniform structure, the steroids have received a great deal of attention from synthesists over the past few decades (4), but the rather more complex and diversified triterpenes have only begun to yield to total synthesis within the past ten years.

The first triterpenoid structures totally synthesized were those of the α-onocerin skeleton **1**. Most characteristic of this structure is the symmetrical nature of the molecules, which are composed of two identical halves joined by the C-11, C-12 bond. Such symmetry greatly simplified the synthesis of these molecules, for every recorded approach has proceeded through the dimerization of an intermediate such as **2**. By means of this technique, both Corey (5) and Eschenmoser (6) have formally achieved total synthesis of the onoceradiene structure **1** (R=H), while Stork (7) has accomplished the first total synthesis of a natural triterpene, α-onocerin (**1**, R=OH) (8). Construction of the



1



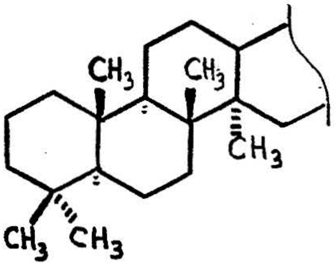
2

small molecules to be dimerized involves only relatively minor stereochemical problems, but a price must be paid before these can be joined since enantiomeric mixtures will couple to give both the desired and undesired diastereomers. Thus enantiomeric purity must either be purchased in some natural starting material or achieved by resolution of dl products prior to dimerization; the stereochemical serpent must be appeased.

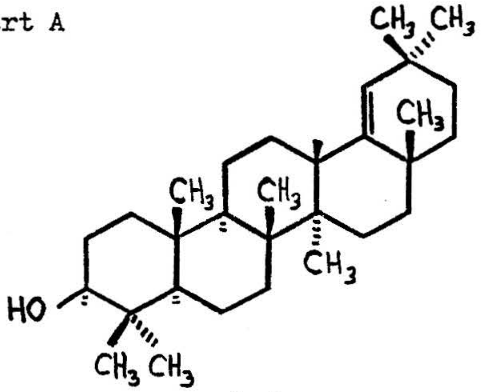
Another structure common to many natural triterpenes is the polycyclic carbon framework A-1, which is shared for example by germanicol (A-2), lupeol (A-3) and oleanoic acid (A-4, R=CO_2H, Δ12 olefin). This atomic array is characterized by a *trans-anti-trans-anti* backbone (C-5, C-10, C-9, C-8 and C-14), by 1,3-diaxial angular methyls (on C-10 and C-8), and by two adjacent quaternary carbons (C-8 and C-14) bearing methyl groups in the *anti* orientation.

Early syntheses of this structure were all based upon the discovery by Barton and Overton (9) that α-onoceradienedione (A-6) cyclizes

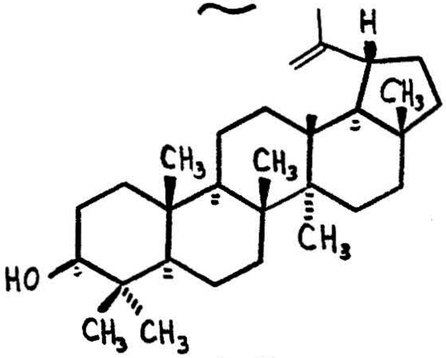
Chart A



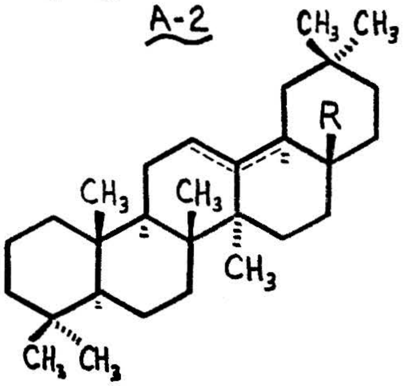
A-1



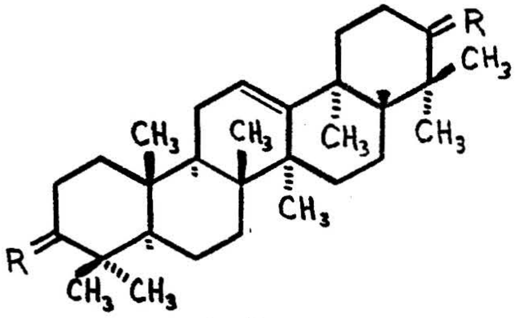
A-2



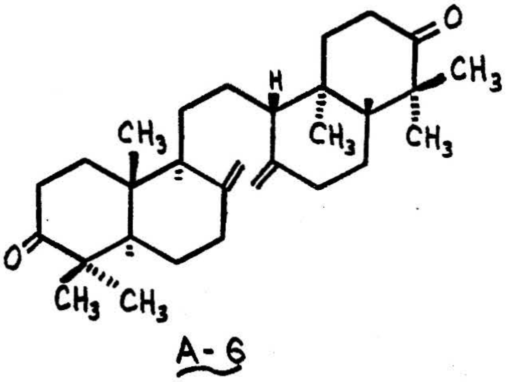
A-3



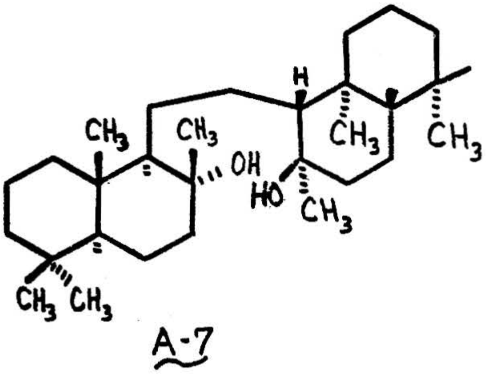
A-4



A-5



A-6



A-7

under strongly acidic conditions in 18% yield to the unnatural pentacyclic triterpene γ-onocerenedione (A-5, R=O). This molecule bears the desired carbon framework A-1, and thus all of the previously mentioned syntheses of the α-onocerin series might in principle provide entry into this system as well. Corey demonstrated this transformation on his α-onoceradiene intermediate A-7, which he converted to γ-onocerene (A-5, $R=H_2$) in 10% yield (5).

When this approach was directed towards nonsymmetrical pentacyclic triterpenes of the oleanene structure [A-4, $R=CH_3$, Δ12 or Δ13 (18) olefin] (10, 11, 12) its shortcomings became clear. Joining of two nonidentical fragments to form the C-11, C-12 bond was always performed in a totally nonstereospecific manner, since resolution of two sets of enantiomers and matching of the proper pairs was never attempted. Given the mixture of diastereomers produced from this coupling, workers reported obtaining oleanenes after cyclization in yields of from 2% (10) to "low" or "small" (12, 11). It is apparent from these results that syntheses which do not provide specifically for the introduction of properly oriented backbone substituents cannot succeed to any appreciable degree.

Recently, elegant and highly stereospecific syntheses have been reported of molecules containing the A-1 structure, specifically of germanicol (A-2) by Ireland and co-workers (13) and of lupeol (A-3) by Stork and co-workers (14). Each asymmetric center in these molecules was introduced with careful regard for achieving proper stereochemistry. While each center presented a challenge, the stereospecific orientation of the *anti*-methyl groups on adjacent quaternary carbons probably proved the most demanding aspect in each of these syntheses.

Ireland discusses two attempts at introducing this configuration of atoms. Methylation of the aldehyde **B-1**, although it does afford the desired *anti*-methyl groups in **B-2**, was found to proceed with difficulty and in only 50% yield. This approach was therefore abandoned and the enone **B-3** was synthesized. Conjugate addition of the appropriate Grignard reagent to this enone, followed by enolate trapping and subsequent regeneration, afforded the crucial enolate anion **B-4**. Treatment of this with iodomethane stereospecifically produced the desired intermediate **B-5**, from axial attack on the enolate anion.

Stork reports only a single approach to "... the critical introduction of the two vicinal *trans*-methyl groups at C-8 and C-14 ...". Reductive opening of the cyclopropyl ketone **B-7** affords the enolate anion **B-6** (drawn in a different orientation), which on alkylation with iodomethane stereospecifically produces the desired *anti*-methyl groups in **B-8**. The striking similarity of the enolate anions **B-4** and **B-6** is indicative of the fact that the actual carbon-carbon bond forming reaction which produces the difficult to achieve *anti*-methyl groups is the same in both syntheses. The ingenious methods by which these enolates are generated, however, are vastly different and suit other purposes of the schemes into which they fit.

Total synthesis has recently approached yet a third triterpenoid carbon framework **C-1**, which is shared by the natural products alnusenone (**C-2**), friedelin (**C-3**), and shinone (**C-4**). Characteristic of this

Chart B

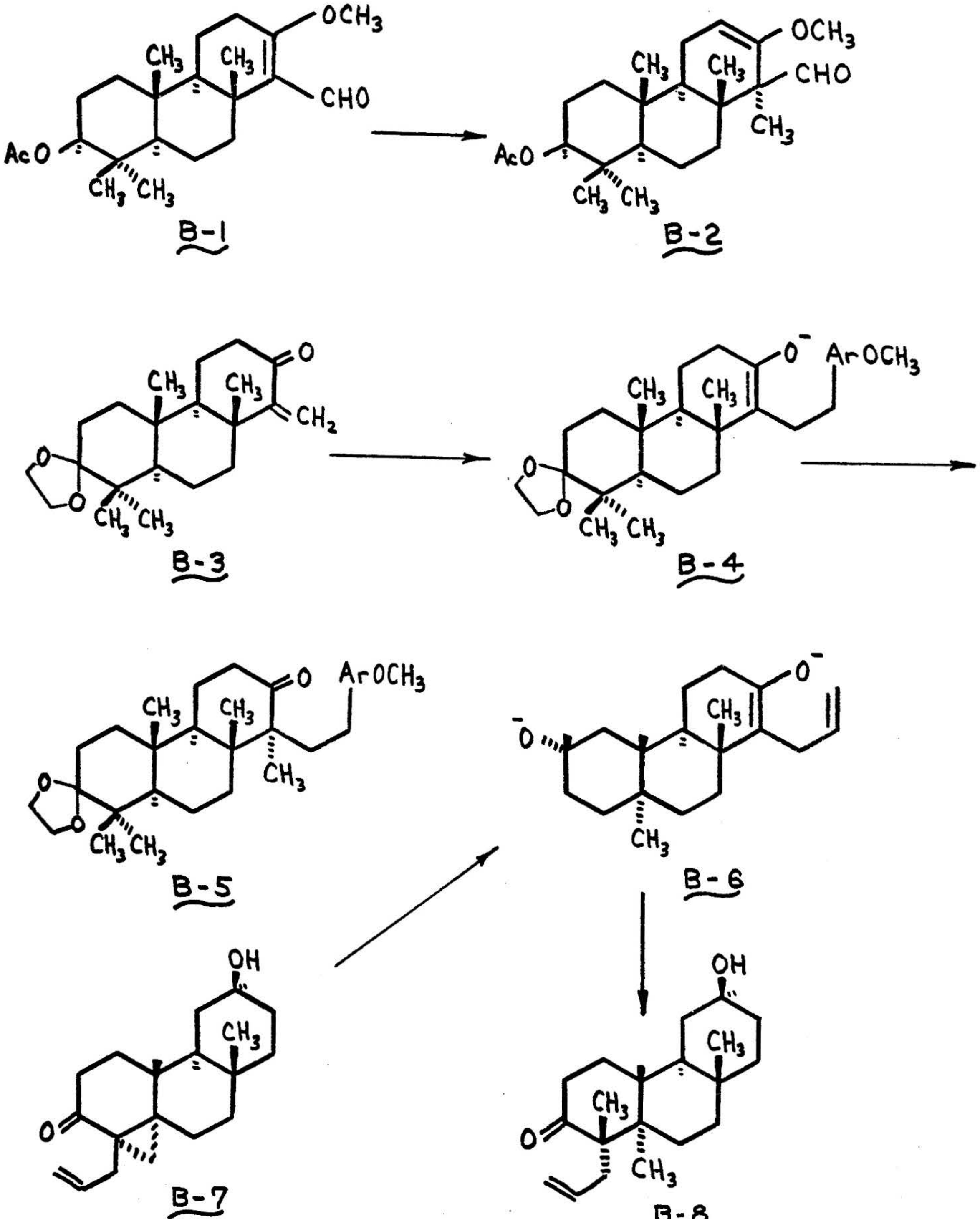
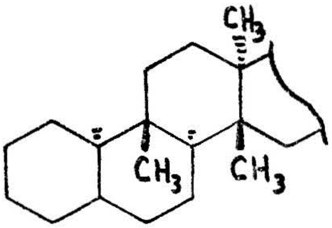
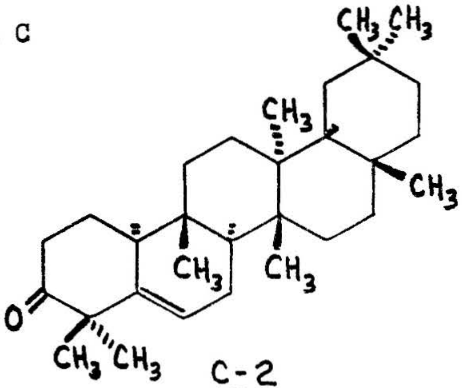

OCH3
CH3
CH3
CHO
AcO
CH3
CH3
B-1
OCH3
CH3
CH3
CHO
CH3
AcO
CH3
CH3
B-2
O
CH3
CH3
CH2
O
O
CH3
CH3
B-3
O⁻
ArOCH3
CH3
CH3
O
O
CH3
CH3
B-4
O
ArOCH3
CH3
CH3
CH3
O
O
CH3
CH3
B-5
O⁻
CH3
⁻O
CH3
B-6
OH
CH3
O
B-7
OH
CH3
CH3
O
CH3
B-8

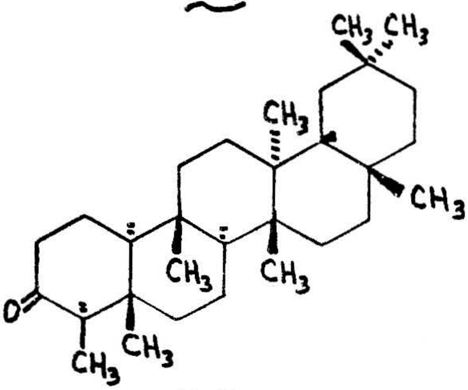
Chart C



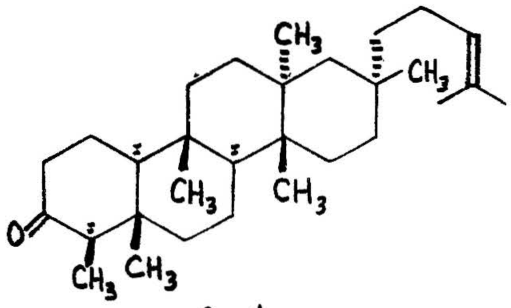
C-1



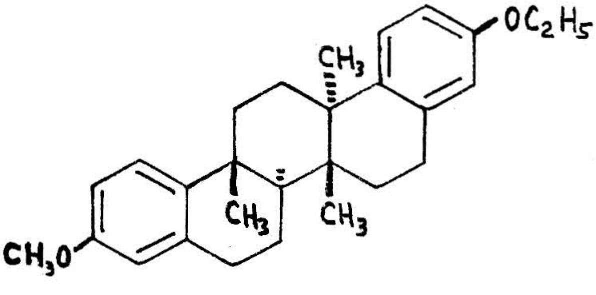
C-2



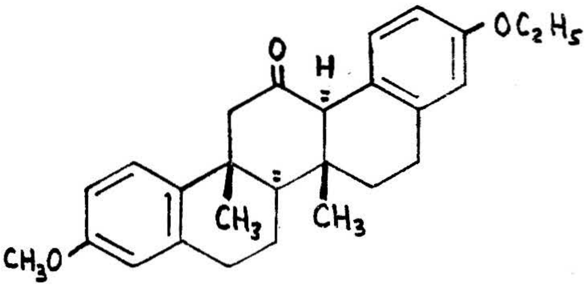
C-3



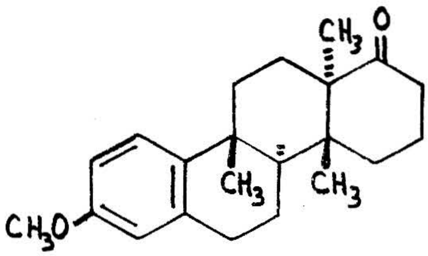
C-4



C-5



C-6



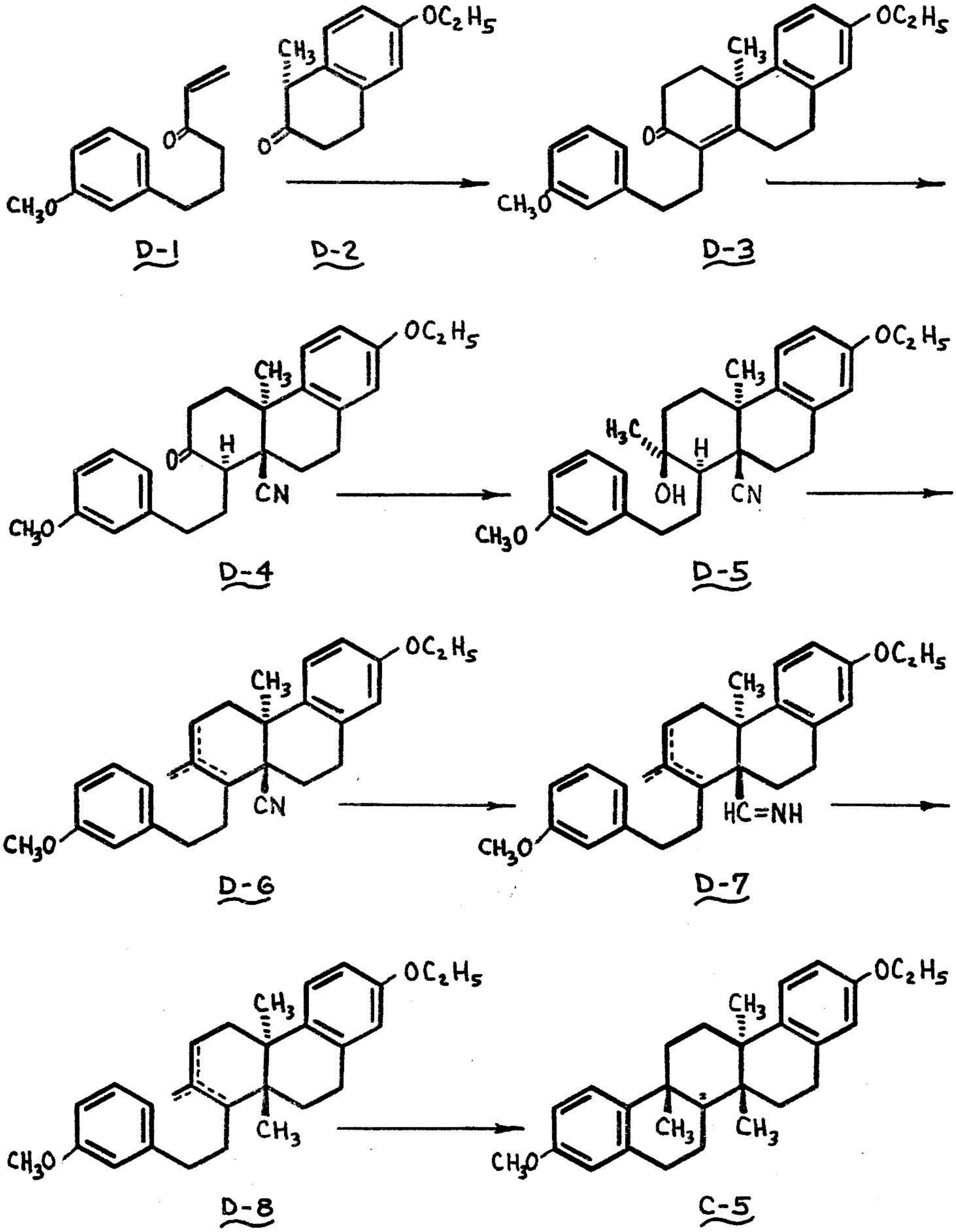
C-7

structure are the *anti*-*trans*-*anti*-*trans* backbone (C-10, C-9, C-8, C-14, C-13), the two 1,3-diaxial angular methyls (at C-9 and C-14), and the two adjacent quaternary carbons (C-13 and C-14) bearing *trans*-oriented methyl groups at the C-D ring juncture. Ireland selected the molecule C-5 as a key intermediate for the synthesis of the pentacyclic molecules alnusenone (**C-2**) and friedelin (**C-3**) (15a), and found that once again construction of the substituted adjacent quaternary centers was a difficult problem (15b). An initial approach to intermediate **C-5** was finally abandoned when all attempts to introduce the α-methyl group at the C-D ring juncture of ketone **C-6** proceeded in low yield.

It became clear at this point that logistically it would be wise to introduce the *trans* vicinal methyl grouping at an early stage in the synthesis. Thus a new approach to the pentacyclic **C-5** was attempted, and at the same time the synthesis of a new intermediate **C-7** was embarked upon. This second intermediate was primarily aimed at the triterpene shionone (C-4), but potentially could have served as a precursor for alnusenone or friedelin should the pentacyclic **C-5** have proven unattainable. For this tetracyclic intermediate as well, the emphasis of the synthetic planning was heavily placed upon the proper introduction of the *trans* vicinal methyl groups.

Ireland and Welch were able to synthesize the intermediate **C-5** by the method shown in Chart D, and finally converted this to dl-alnusenone (16). The key step in introducing the *trans* diaxial substituents relied upon Nagata's hydrocyanation reaction (17) to transform the enone **D-3** to the *trans*-fused cyano ketone **D-4**. Subsequent

Chart D



reduction of the nitrile to a methyl group followed by a Friedel-Crafts type cyclialkylation (18) of the olefin mixture D-8, afforded the required intermediate C-5 in high overall yield.

While this work was in progress, three independent routes towards the tetracyclic intermediate C-7 were being explored, all with different methods for the introduction of the trans vicinal methyl groups. J. W. Tilley arrived at the tetracyclic ketone C-7 in ca. 3% overall yield by the route outlined in Chart E (19a). Crucial to this synthesis was the directive effect of the alcohol function of E-4 on cyclopropylation of the enol ether (20), which resulted in the required trans-substituted C-D ring fusion of E-5.

C. Lipinski developed a biogenetically patterned synthesis outlined in Chart F based upon acid catalized cyclization of the polyolefinic aldehyde F-7 (21). Previous work on a model system (22) indicated that cyclization should proceed to give the trans-fused C-D ring juncture, and this was realized in practice. The overall yield of ketone C-7 from dibromide F-1 was ca. 3%.

The third synthesis of key intermediate C-7 was the cyanide addition approach developed by C. J. Kowalski; the details surrounding its elucidation have already been discussed (23). This approach parallels that outlined in Chart D for the pentacyclic intermediate C-5, and in fact these routes were developed at the same time. Since the overall yield of ketone C-7 is greatest (10%) by this method, and since the reactions employed are amenable to large scale production, this route was used in practice for the actual preparation of tetracyclic C-7.

Chart E

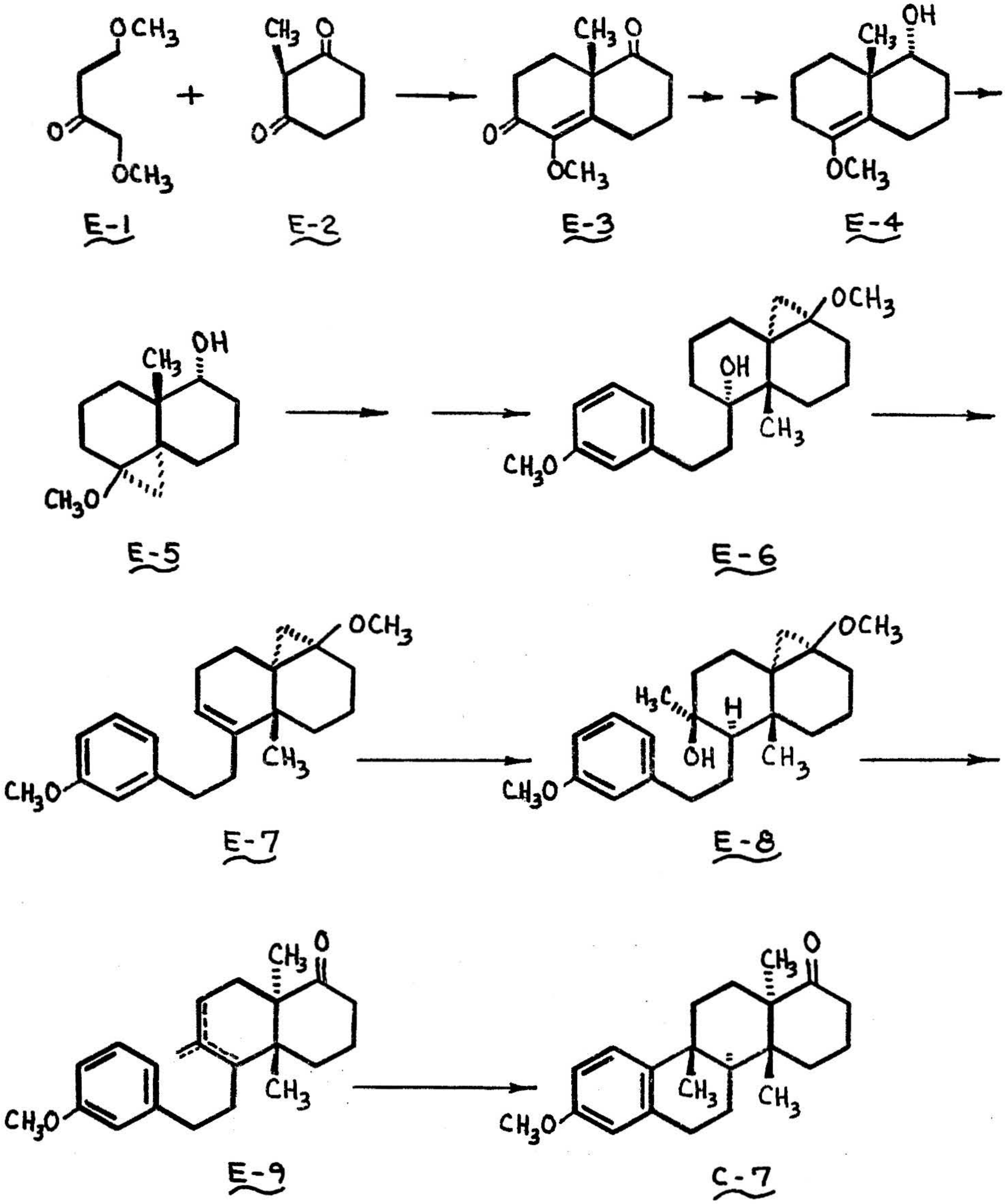
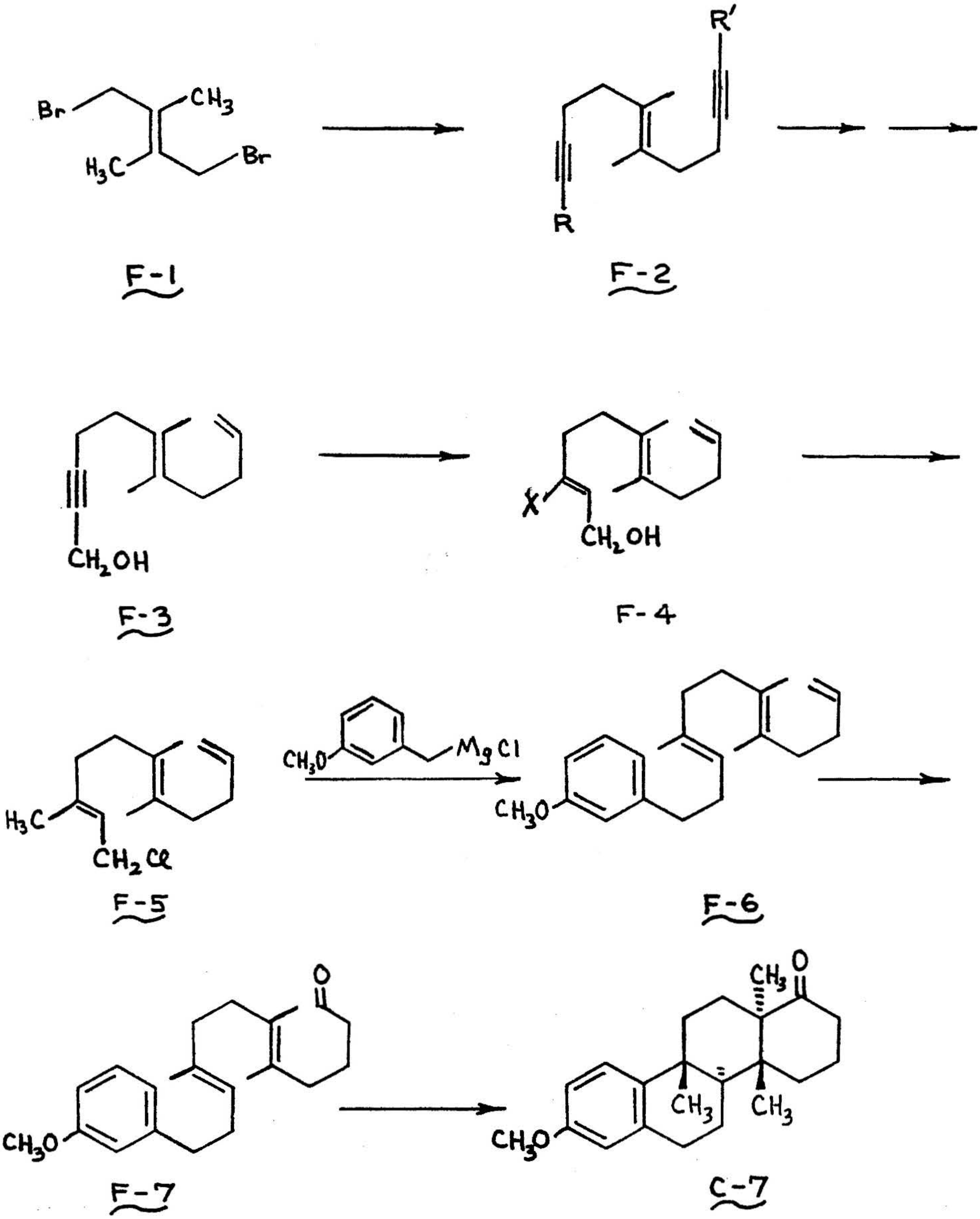

OCH3
OCH3
O
CH3
O
O
E-1
E-2
E-3
E-4
E-5
E-6
E-7
E-8
E-9
C-7
OH
OCH3
CH3O
CH3
H3C
H

Chart F


Br
CH3
H3C
Br
F-1
R'
R
F-2
CH2OH
F-3
X
CH2OH
F-4
H3C
CH2Cl
F-5
CH3O
MgCl
CH3O
F-6
O
CH3O
F-7
CH3
O
CH3
CH3
CH3O
C-7

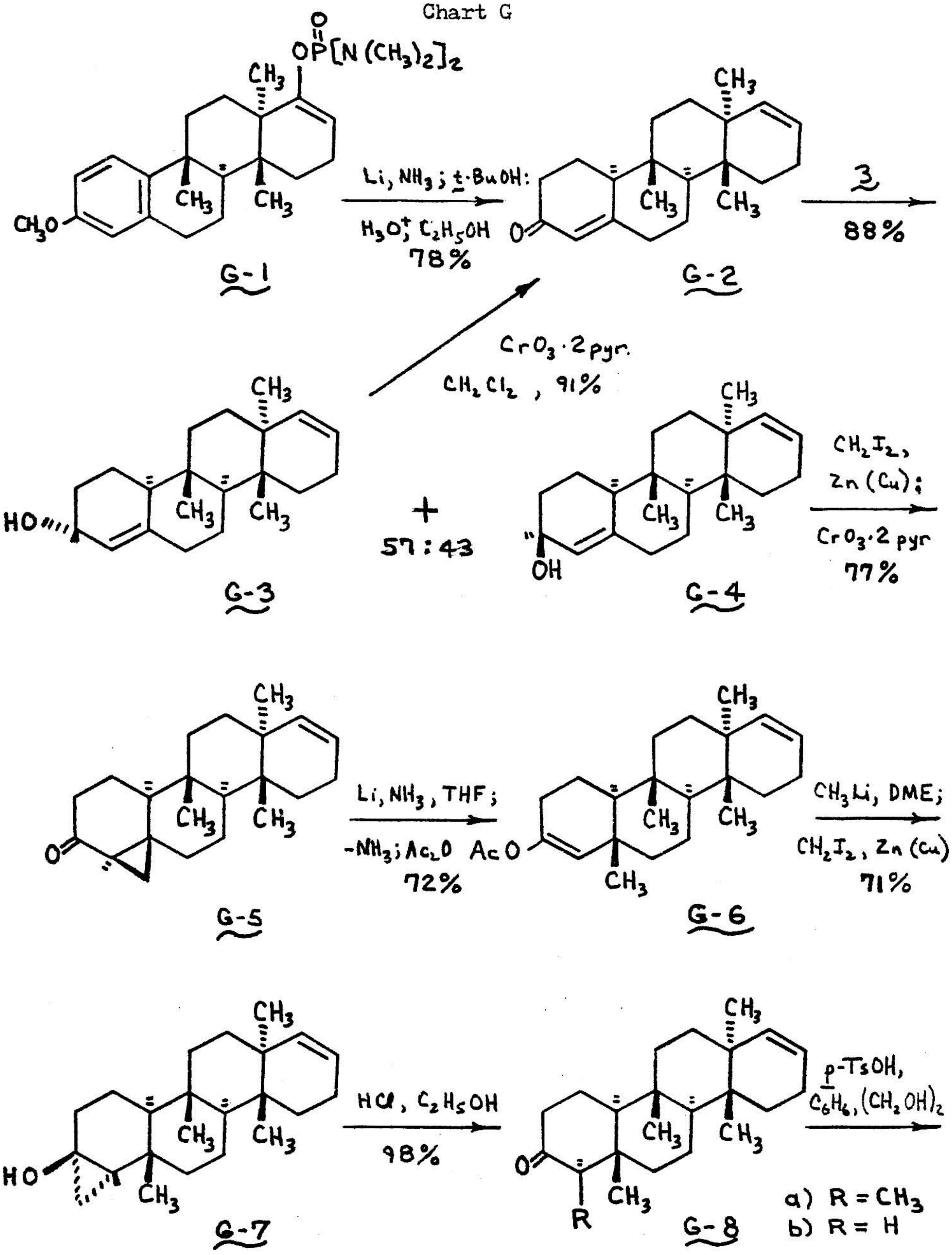
The improvements and modifications which have been made in this scheme after repeated utilization have not as yet been described in any one work; so the complete and updated version of this key route to intermediate C-7 has been included in the discussion and experimental sections of this thesis (Charts H and I).

All three syntheses of the tetracyclic intermediate C-7 reached their goal at about the same time. The products from these routes were shown to be identical in all respects (mp, mmp, ir, nmr), and a single-crystal X-ray structure analysis indicated that this material did indeed have structure C-7 (19b).

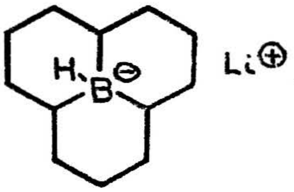
Efforts then turned to elaboration of this intermediate into one of the desired triterpenes, and when the synthesis of alnusenone from pentacyclic C-5 became fact, shionone (C-4) (24) was singled out as the logical choice. J. Tilley attempted to convert the ketone C-7 into shionone (C-4) by the route outlined in Chart G (19d, 25). Construction of the A ring was the first goal, but this could be accomplished only after masking the D ring functionality in some suitable form. A simple olefin was chosen for the mask, and to this end the enol phosphorodiamidate G-1 was prepared from intermediate C-7. Lithium/ammonia reduction of both the phosphorodiamidate and the aromatic ring in the same reaction vessel gave the dienone G-2 in good yield.

A problem arose at this point, however, for the scheme required β-alcohol G-4 in order to direct cyclopropylation of the A ring olefin from the β side. Upon reduction of the enone G-2, even using Brown's tricycloborohydride reagent 3, the ratio of G-3 to G-4 could not be

Chart G


G-1
Li, NH₃; t-BuOH:
H₃O⁺, C₂H₅OH
78%
G-2
3
88%
CrO₃·2pyr.
CH₂Cl₂, 91%
G-3
+
57:43
G-4
CH₂I₂,
Zn(Cu);
CrO₃·2pyr
77%
G-5
Li, NH₃, THF;
-NH₃; Ac₂O
72%
G-6
CH₃Li, DME;
CH₂I₂, Zn(Cu)
71%
G-7
HCl, C₂H₅OH
98%
G-8
p-TsOH,
C₆H₆, (CH₂OH)₂
a) R = CH₃
b) R = H

lowered below 57 to 43. Thus, in order to make this scheme reasonable, the predominant α-alcohol had to be separated from the sensitive β-isomer by chromatography, reoxidized to enone G-2, and then recycled in this manner two more times to obtain a 63% yield of the desired alcohol G-4.



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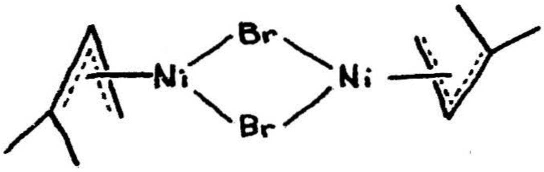

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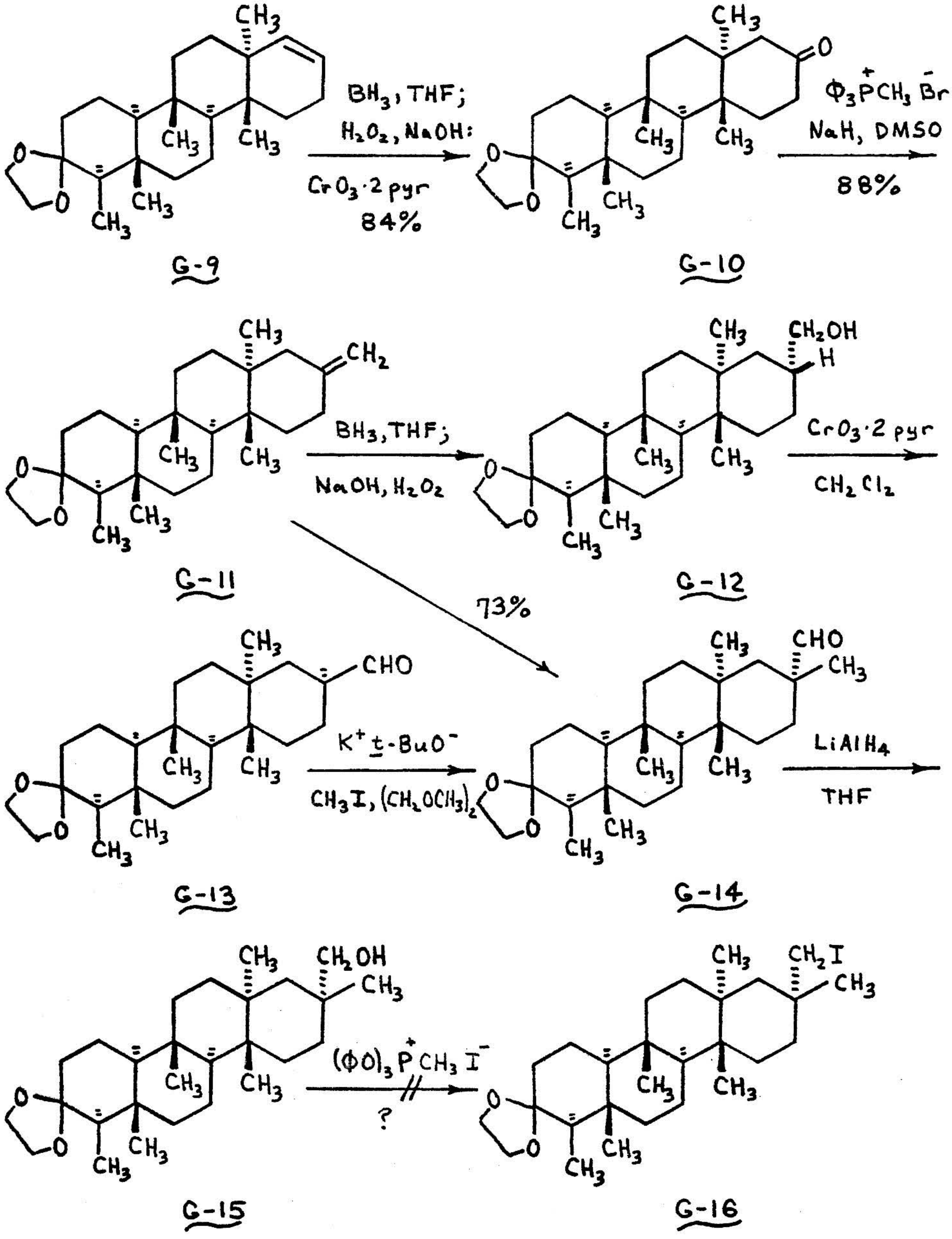
Once this alcohol had been obtained, however, it was readily cyclopropylated and oxidized to ketone G-5. Lithium/ammonia reductive cleavage of this cyclopropyl ketone, followed by acetic anhydride trapping of the enolate anion, produced enol acetate G-6 in 72% yield. A certain amount of the ketone G-8b was almost always isolated from this reaction as well. Direct alkylation of the enolate anion generated from enol acetate G-6 was never attempted, due to some difficulties encountered on a model system. Instead the enolate anion was treated with Simmons-Smith reagent to generate the sensitive cyclopropyl alcohol G-7, which was cleaved in acid to the desired methylated A ring intermediate G-8a.

Tilley then protected the A ring ketone as the ethylene ketal, and functionalized the D ring by hydroboration and oxidation to obtain ketone G-10. Of several varied attempts to convert the ketone G-10 to

Chart G continued



the aldehyde **G-13**, only the simple methylene Wittig reaction, followed by hydroboration and oxidation proved successful. Aldehyde **G-13** was methylated and the product reduced to afford the neopentyl alcohol **G-15**. Iodide **G-16** was required for coupling with π-(1,1-dimethylallyl)-nickel bromide (**4**) (26) to afford the completed side chain; but material limitations allowed only two attempts at preparation of the iodide from alcohol **G-15**. Both of these attempts failed, and the only material remaining then was a small amount of enone **G-2**, from which completion of the synthesis would not have been possible.

While the goal of shionone had been so closely approached, it had not been reached. The work of J. Tilley had generated the shionone A ring, but at the same time had demonstrated the shortcoming of the cyclopropylation approach, i.e. generation of the required axial allylic alcohol **G-4**. His work had nearly resulted in completion of the side chain, but in its failure pointed to a second possible trouble spot in the scheme, preparation of the neopentyl iodide **G-16**. In light of the knowledge Tilley had shed on the problems of constructing the shionone molecule, we set about to attempt the conversion of intermediate **C-7** to shionone. The results of these attempts are set forth in the body of this thesis.

Discussion

Elucidation of the cyanide addition approach to key intermediate **C-7** has already been described in detail elsewhere (23). In order to assemble in one work, however, a complete and updated version of this synthesis, we have decided to present once again the preparative route to shionone intermediate **C-7**. An outline of this approach is contained in Charts H and I.

Reduction of the starting material, m-methoxycinnamic acid (**H-1**), affords alcohol **H-2** in only moderate (61%) yield after purification. The crude alcohol **H-2** may be used directly in the second step, however, and when this is done the chloride **H-3** is obtained following vacuum distillation in an excellent 79% overall yield from the starting acid **H-1**. Preparation of the allylic alcohol **H-4** is quite straightforward, as is its oxidation to enone **H-5** using Collins reagent; Jones oxidation in this instance proved quite unpredictable and at times produced only intractable products. Under very mild conditions 2-methyldihydroresorcinol underwent Michael addition with enone **H-5**, and the resulting trione **H-6** underwent the known transformation to enone **H-8** according to the procedure of H. Smith and co-workers (27).

Diethylaluminum cyanide (17a, c, f) was used to convert enone **H-8** to the *trans*-cyanoketone **H-9** in 82% yield, and only small amounts of the *cis*-fused isomer **5** were ever produced. It is interesting to note that when Ireland and Welch used this same reagent on the enone **D-3** (16), they obtained principally the *cis*-fused cyanide **6** and only minor

Chart H

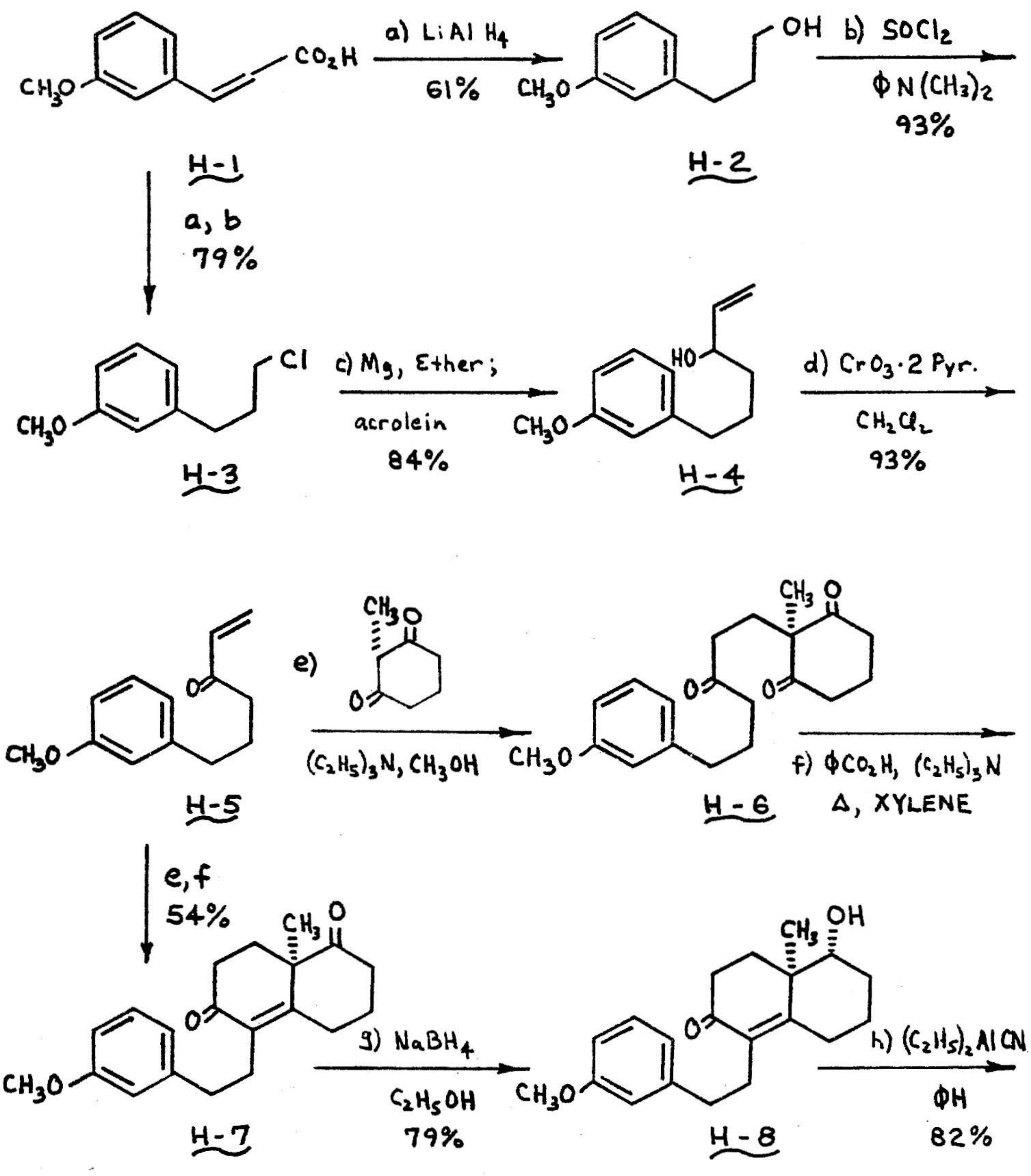
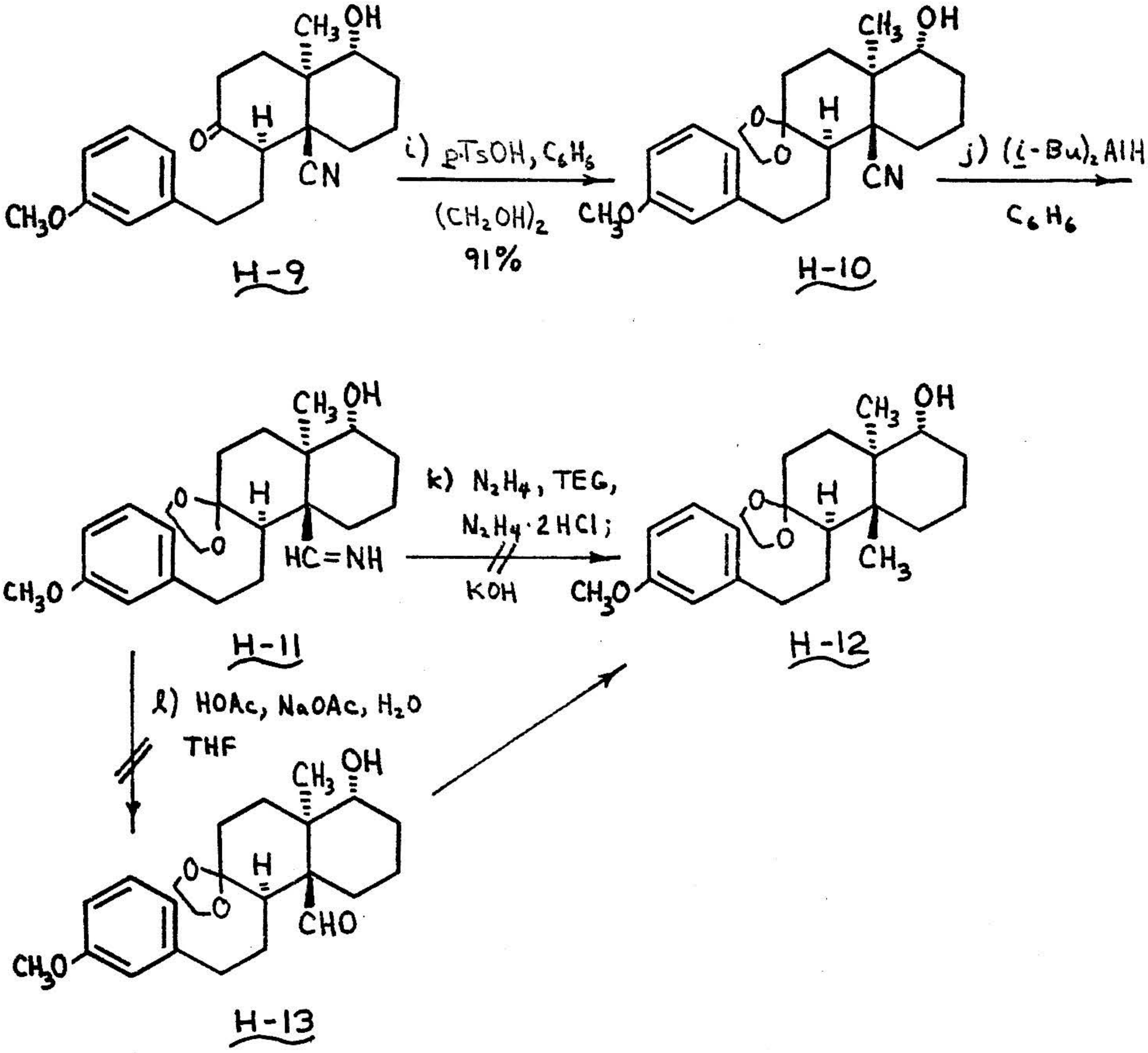
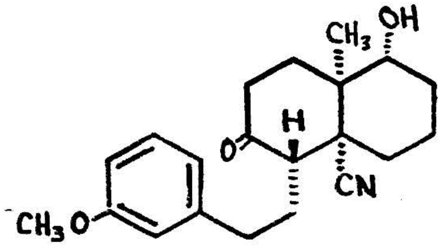

CH3O
CO2H
H-1
a) LiAlH4
61%
CH3O
OH
H-2
b) SOCl2
ΦN(CH3)2
93%
a, b
79%
CH3O
Cl
H-3
c) Mg, Ether;
acrolein
84%
HO
CH3O
H-4
d) CrO3·2 Pyr.
CH2Cl2
93%
CH3O
O
H-5
e)
CH3
O
O
(C2H5)3N, CH3OH
CH3
O
O
O
CH3O
H-6
f) ΦCO2H, (C2H5)3N
Δ, XYLENE
e, f
54%
CH3
O
O
CH3O
H-7
g) NaBH4
C2H5OH
79%
CH3
OH
O
CH3O
H-8
h) (C2H5)2AlCN
ΦH
82%

Chart H continued



amounts of the *trans*-isomer D-4. In order to obtain the desired *trans*-



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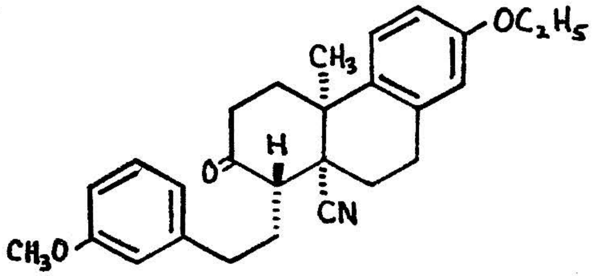

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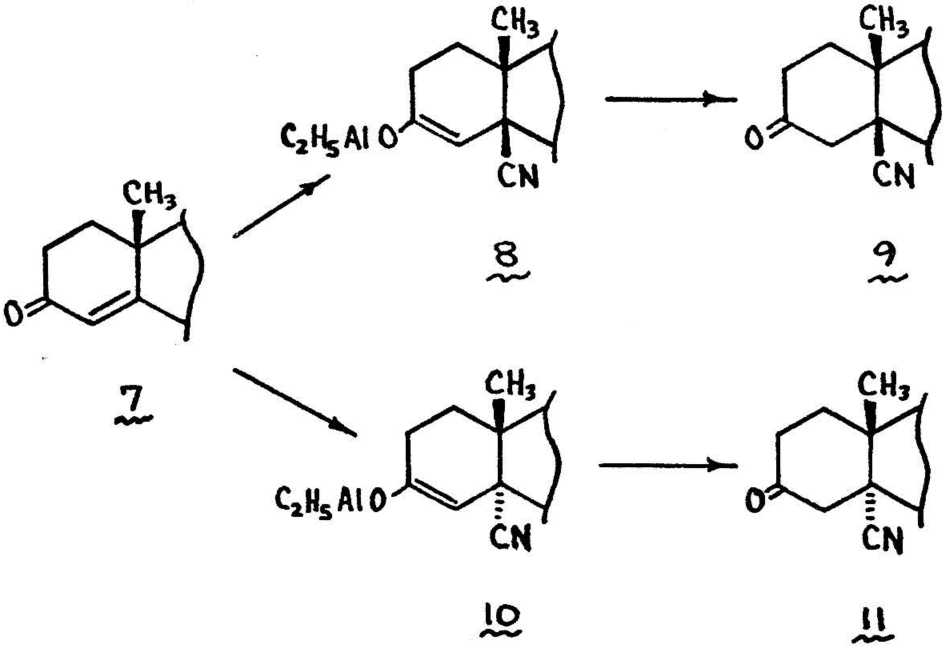
isomer D-4, they had to use a mixed reagent (17a, c, e) of triethylaluminum and hydrogen cyanide in tetrahydrofuran.

The results of Ireland and Welch are consistent with studies by Nagata (17b, d) which indicate that with diethylaluminum cyanide, enones such as 7 undergo reversible 1,4-addition of cyanide; the thermodynamically more stable *cis*-fused enolate 8 is produced, which generates the *cis*-fused product 9 on work-up. The kinetic cyanide adduct, however, is the *trans*-fused enolate 10, and in the presence of HCN in the mixed reagent this gets trapped by protonation to give 11. The observed *trans* product from diethylaluminum cyanide and enone H-8 seems inconsistent with these results, until one considers the alcohol function present in this molecule. This alcohol may well be acting as a proton source to trap out the kinetic *trans*-enolate, thus accounting for formation of the *trans*-fused product H-9.

In our previous work (23), the failure of attempts at reducing the nitrile in ketal H-10 to the angular methyl group of H-12 have been



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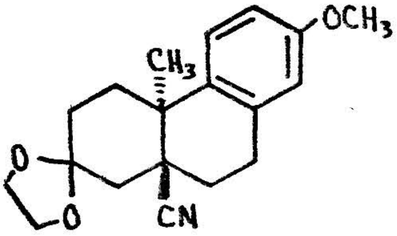
9

10

11

described. These attempts employed diisobutylaluminum hydride reduction of H-10 to imine H-11, and treatment of this crude imine under the conditions of the Nagata modification of the Wolff-Kishner reduction (28). This second reduction involves prolonged formation of the hydrazone from the imine in a hydrazine/hydrazine hydrochloride buffered medium prior to the addition of strong base. R. Czarny has subsequently had difficulty in reducing nitrile 12 using this same method (29), and found indications that the ketal function was hydrolyzing during hydrazone formation. Employing another of Nagata's techniques (30), Czarny subjected the crude imine from diisobutylaluminum hydride reduction of nitrile 12 to buffered hydrolysis conditions. He was able to obtain a quantitative crude yield of aldehyde 13, which on Wolff-Kishner reduction using the normal basic conditions afforded an 86% yield of ketal 14



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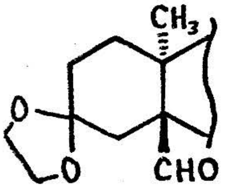

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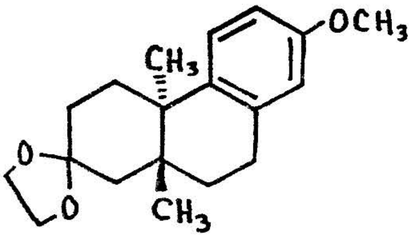


14

after purification.

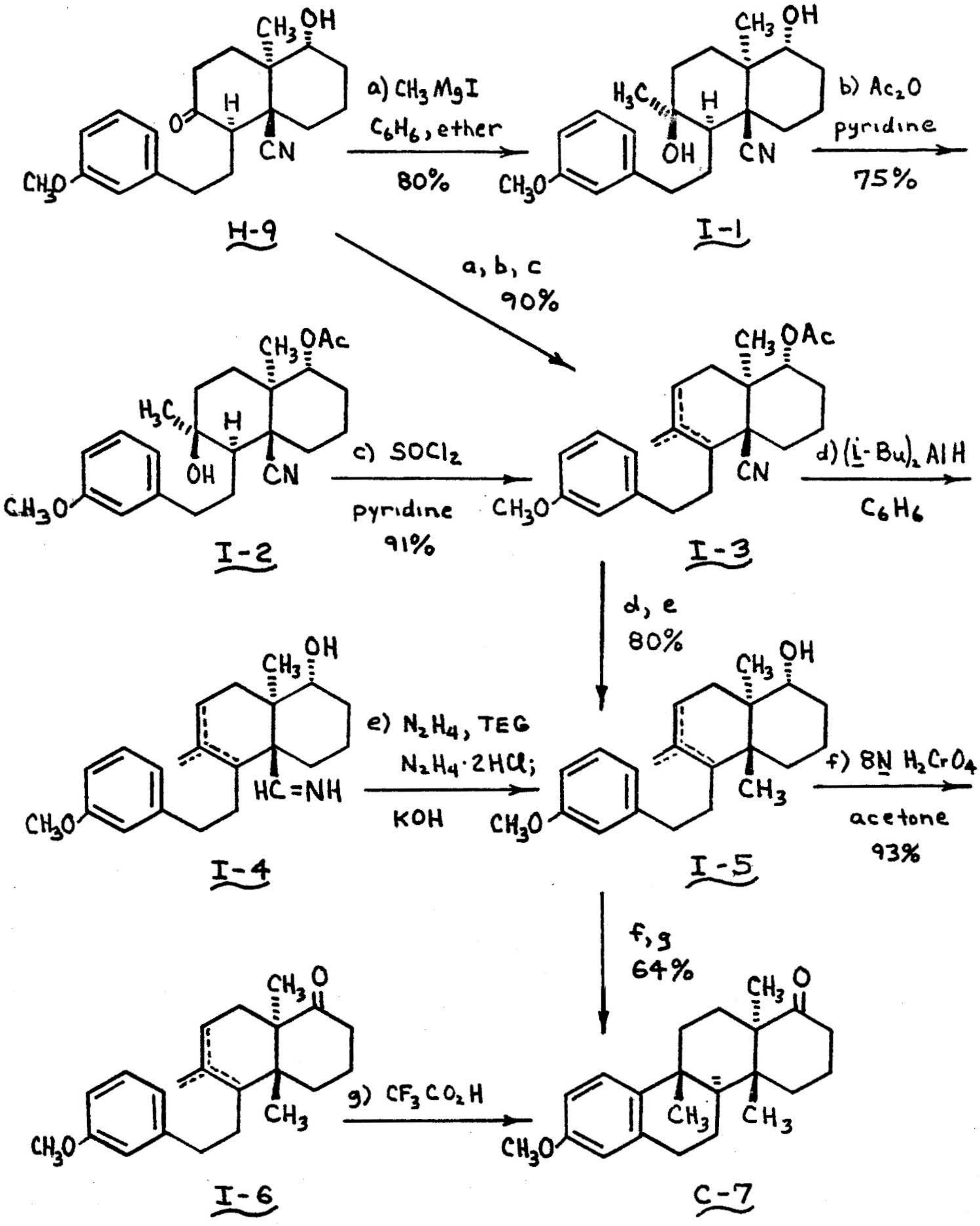
In light of these results, the nitrile H-10 was submitted to the exact procedure described by Czarny. The product from reduction of H-10 with excess diisobutylaluminum hydride, still exhibited some nitrile absorption in its ir spectra. Attempted hydrolysis of the crude imine H-11 under Czarny's conditions produced none of the aldehyde H-13, but returned only unchanged imine. When a longer time was employed for hydrolysis, the product which resulted showed only a weak carbonyl band in its ir spectrum, and some loss of the ethylene ketal signal in its nmr spectrum. Since the reduction and hydrolysis were clearly not proceeding as they had on the tricyclic 12, and since the pathway to key intermediate C-7 had already been completed at this point, Czarny's approach was pursued no longer.

As outlined in Chart I, addition of methylmagnesium iodide to cyanoketone H-9 results in diol I-1. This reaction can be performed either by adding the Grignard reagent to a solution of the ketone, or by using the reverse addition process. The former procedure was used initially and results in significant amounts of starting ketone in the product (from enolization), while the latter modification by J. Tilley eliminates this problem. Grignard addition to H-9, selective acetylation of I-1 and hydration of I-2 all proceeded in good yield; when these reactions were performed in sequence with purification of only the final product, then olefinic acetate mixture I-3 was obtained in 90% yield from the cyanoketone H-9.

Treatment of cyanide I-3 with diisobutylaluminum hydride afforded the crude imine I-4 which was reduced using the Nagata modification of the Wolff-Kishner reduction (28). Hydroxy olefin mixture I-5 thus obtained in 80% yield was then oxidized to the keto olefin mixture I-6. J. Tilley's improved cyclization procedure for the olefin I-6 (19e) using refluxing trifluoroacetic acid afforded an ~85:15 mixture of the *trans*-*anti*-*trans* ketone C-7 and the *cis*-*anti*-*trans* isomer 15. The structure determination of this first isomer has already been mentioned in the Introduction; the purification and characterization of this latter isomer have been performed by Tilley (19e). From this mixture a 64% yield (from alcohol I-5) of the desired tetracyclic ketone C-7 was obtained by crystallization. When the mother liquors from this crystallization, containing nearly a 1:1 ratio of the two isomers (determined by vpc), were treated with refluxing trifluoroacetic acid for 48 hr, no change in the ratio of isomers was observed.

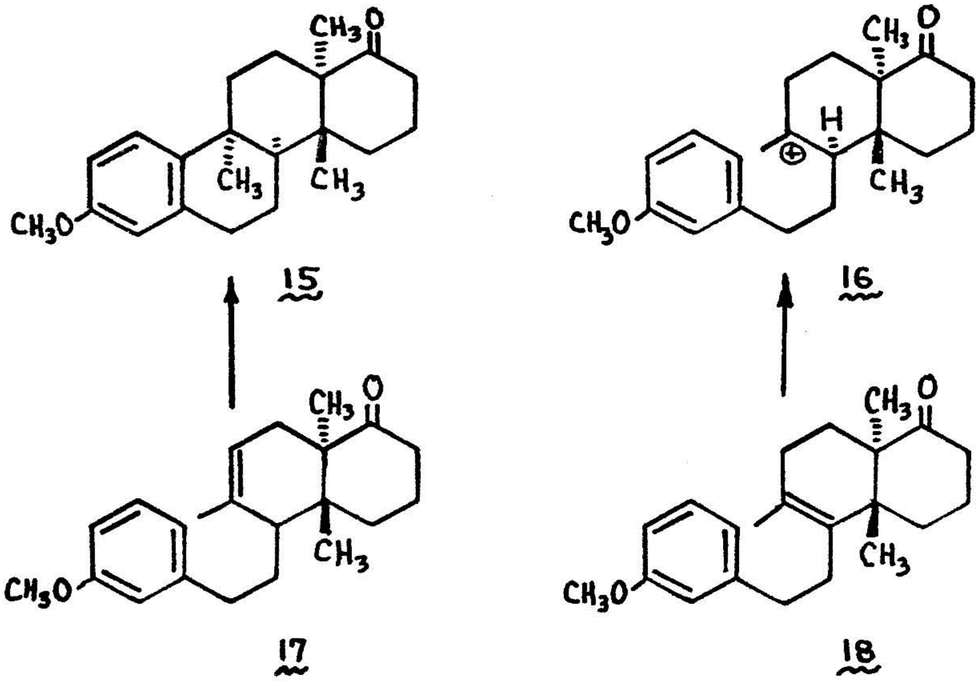
In an effort to possibly raise the proportion of the *trans*-*anti*-*trans* isomer produced, the cyclization of ketone I-6 was run in trifluoroacetic acid at room temperature. Under these conditions, the

Chart I


H-9
a) CH3MgI
C6H6, ether
80%
I-1
b) Ac2O
pyridine
75%
a, b, c
90%
I-2
c) SOCl2
pyridine
91%
I-3
d) (i-Bu)2AlH
C6H6
d, e
80%
I-4
e) N2H4, TEG
N2H4·2HCl;
KOH
I-5
f) 8N H2CrO4
acetone
93%
f, g
64%
I-6
g) CF3CO2H
C-7

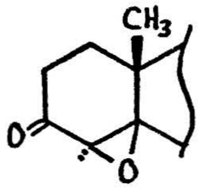
reaction required 10 days to reach completion, whereupon the product it afforded had essentially the same composition as that from refluxing acid. Analysis by vpc of quenched aliquots from this reaction indicated that during the first two days both the *trans*-*anti*-*trans* and the *cis*-*anti*-*trans* isomers were formed in nearly equal amounts. Following this the former isomer continued to increase with respect to the latter, until the final 85:15 ratio was achieved. This result seems to indicate that a minor olefin isomer in the ketone mixture **I-6** cyclizes at a faster rate than most of the sample and affords a higher proportion of the *cis*-fused B-C ring juncture.

The exact reason why this might be occurring is not clear but the results can be rationalized by assuming the operation of two cyclization mechanisms, as recently discussed by K. E. Harding (31). He has suggested that *cis*-fused cyclization products in such systems result mainly from the concerted *trans* addition of a proton and the intramolecular nucleophile (in our case an aromatic ring) across the substrate's double bond. *Trans* products he maintains are the principal result of cyclization of the nucleophile into a discrete cationic intermediate in a nonconcerted process. These mechanisms can account for our results, if for some subtle conformational or electronic reasons our principal minor isomer **17** readily cyclizes by a concerted pathway while the major isomer **18** does not. The exocyclic olefin isomer is present in such small amounts in olefin mixture **I-6** that it is unimportant to this discussion. Then early in the cyclization, olefin **17** would lead mainly to *cis*-fused ketone **15** by the concerted mechanism, while isomer **18** would generate principally *trans*-fused ketone **C-7** via the discrete cationic intermediate **16**. Nearly equal rates of these two cyclizations would produce both products in about the same amount. Once all of the minor isomer **17** had been consumed, however, continued cyclization mainly through cation **16** would increase the amount of the *trans*-fused ketone **C-7** but produce little additional *cis*-fused isomer **15**. This rationalization explains both the initially observed 1:1 formation of isomers, and the finally obtained preponderance of ketone **C-7**.

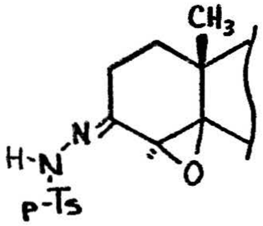


This cyclization completes the synthesis of tetracyclic ketone **C-7**. The overall yield of this key intermediate originally reported for the cyanide addition route was 3% (23). As a result of the modifications and step combinations which have been discussed above, the yield for the fourteen steps from m-methoxycinnamic acid has been raised to 10%. The collected procedures describing this synthesis are included in the Experimental section.

During the period when J. Tilley was attempting the conversion of intermediate C-7 to shionone as described in the Introduction, the work comprising Part II of this thesis was being performed. Experience with the Eschenmoser cleavage reaction of α-keto epoxides (32) was gained in that work, and we were impressed by the ease with which epoxy-ketones such as 19 could be converted to ring opened acetylenic ketones (21), by means of p-toluenesulfonylhydrazone intermediates (20). In light of our experience and a series of publications at that time, a possible new use for this cleavage reaction began to become apparent.



19



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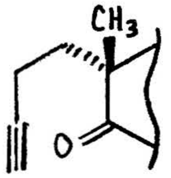
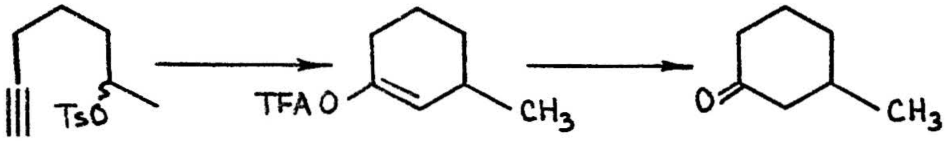


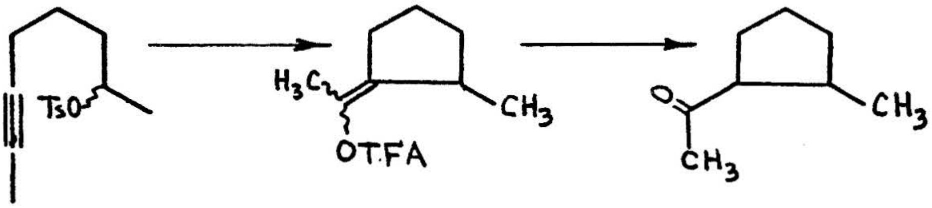
21

Peterson and Kamat (33) had shown that trifluoroacetolysis of acetylenic tosylate J-1 proceeded to give mainly ketone J-3 after hydrolysis of the intermediate enol trifluoroacetate J-2; while the methylated acetylene J-4 following this sequence afforded predominantly the five-membered ring ketone J-6. Johnson and co-workers (34) applied these findings to polyolefin cyclization reactions, and found that formolysis of allylic alcohol J-7, followed by hydrolysis of the re-

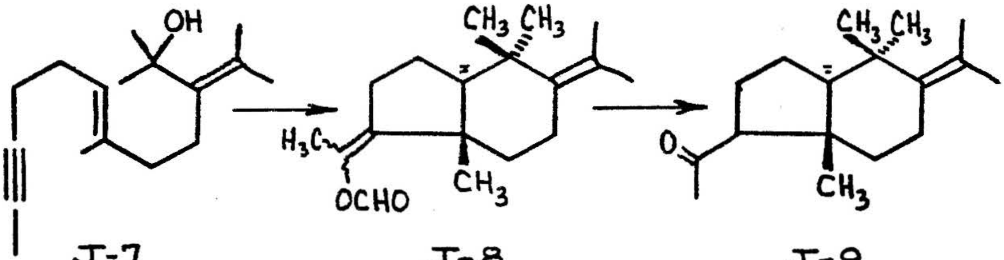
Chart J



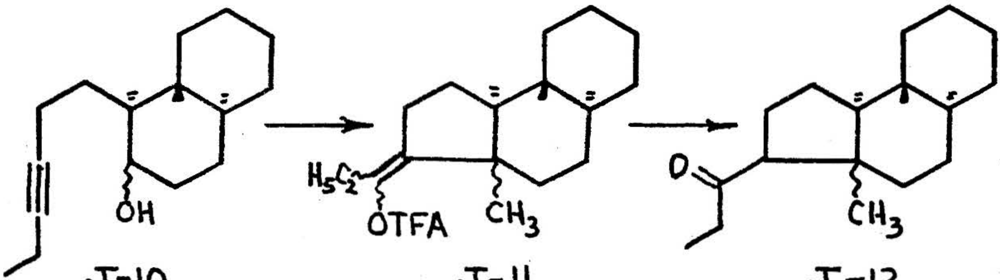
J-1 J-2 J-3



J-4 J-5 J-6



J-7 J-8 J-9



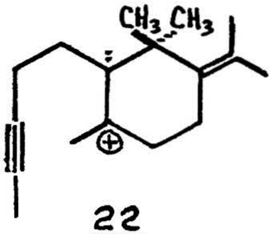
J-10 J-11 J-12

sulting enol formates **J-8**, gave an excellent yield of the *trans*-fused hydrindane **J-9**. Later, Lansbury and DuBois (35) showed that such cyclization could be initiated from the tertiary alcohol **J-10** using cold trifluoroacetic acid; they obtained good yields of ketone **J-12** (4:1 ratio β:α-methyl) from hydrolysis of the enol trifluoroacetate **J-11**.

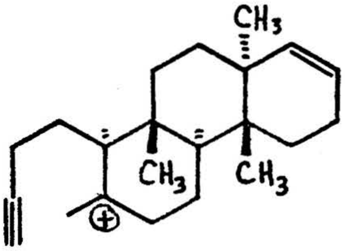
Thus it appeared that cationic cyclization of acetylenic alcohols offered promise as an annelation reaction. At the same time it was clear from our experience that the Eschenmoser cleavage of α,β-epoxyketones provided an easy route to acetylenic ketones, and so ultimately to the alcohols. The possibility of combining these reactions into some useful scheme became a question of more than idle interest when the problem of converting intermediate **C-7** into shionone arose once again. In light of the difficulties J. Tilley had encountered trying to obtain β-allylic alcohol **G-4**, we sought another method of introducing the β-methyl at **C-5** of shionone. This prompted our investigation of the pathway outlined in Chart K for construction of the A ring.

As a model for this study, a small amount of intermediate **G-2** still remained from the work of Tilley. If this could be converted to acetylenic alcohol **K-3**, then it seemed trifluoroacetic acid cyclization of the alcohol should afford principally the enol trifluoroacetate **K-4**. The correct ring size could be expected since Peterson had obtained only six-membered ring cyclized products from acetylene **J-1**. It seemed that the desired stereochemistry of the newly formed angular methyl group should predominate since on cyclization alcohol **J-10** afforded 80% *trans*-fused product and alcohol **J-7** gave exclusively *trans*-fused product.

This latter cyclization may proceed through cationic intermediate 22 and may owe its high degree of stereospecificity to the axial methyl group 1,3 to the cationic center (31, 18). This group should hinder approach by the acetylene nucleophile from the β face of the cation,



22



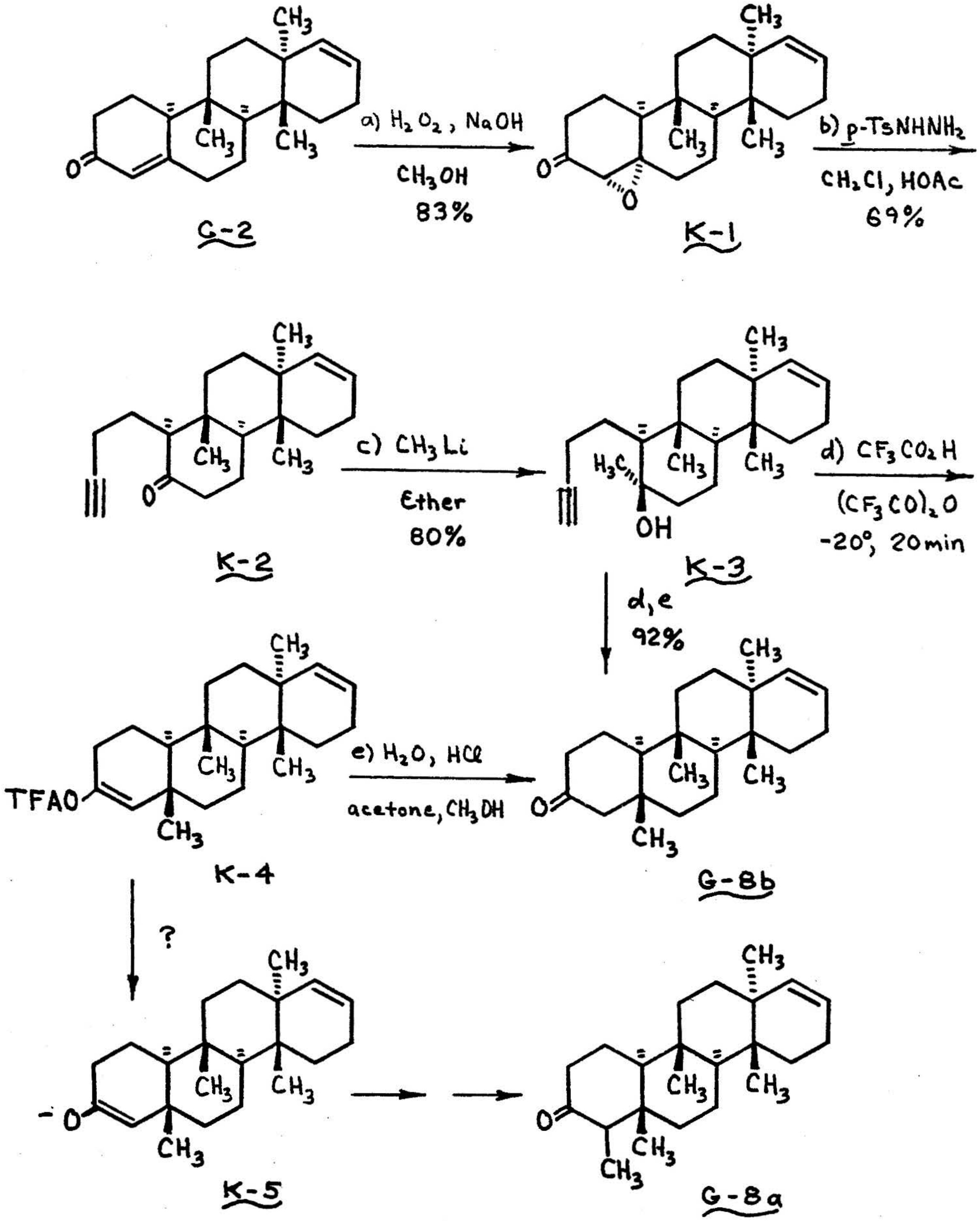
23

and thus lead to a *trans* ring juncture as observed. It was hoped that alcohol K-3 would cyclize principally through cationic intermediate 23; in this case the axial methyl group held rigid at the B-C ring juncture should similarly affect the cyclization and cause *trans*-fused product K-4 to predominate.

In order to prepare alcohol K-3, the enone G-2 was treated with base and hydrogen peroxide and afforded α,β-epoxyketone K-1 in excellent yield. The *p*-toluenesulfonylhydrazone of the ketone was formed in situ at -18° in a 1:1 mixture of acetic acid and methylene chloride (32b, c); this intermediate decomposed as the mixture was then stirred at room temperature, and acetylenic ketone K-2 was obtained in 69% yield after chromatography. Methyllithium addition to the ketone proceeded smoothly to afford acetylenic alcohol K-3 for the cyclization study.

When alcohol K-3 was treated with a mixture of trifluoroacetic

Chart K

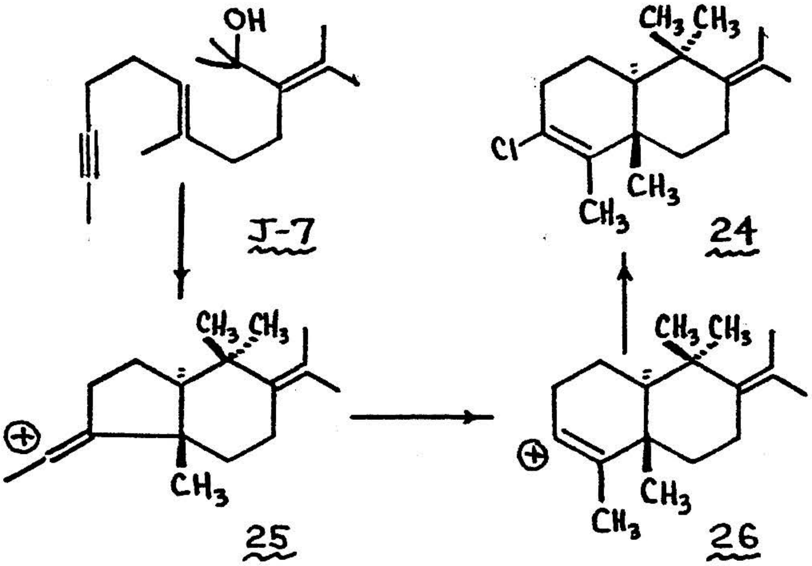

G-2
a) H_2O_2, NaOH
CH_3OH
83%
K-1
b) p-TsNHNH$_2$
CH_2Cl_2, HOAc
69%
K-2
c) CH_3Li
Ether
80%
K-3
d) CF_3CO_2H
$(CF_3CO)_2O$
-20°, 20min
d, e
92%
K-4
TFAO
e) H_2O, HCl
acetone, CH_3OH
G-8b
?
K-5
G-8a
CH_3
OH

acid and trifluoroacetic anhydride at -18° (35), the ensuing reaction required 20 min to reach completion as determined by vpc. After evaporation of the solvents from this mixture under reduced pressure, the single product obtained was an enol trifluoroacetate. This was deduced to have structure K-4 when upon hydrolysis it afforded G-8b as the only product, having the same mp, mmp, ir, and nmr as the material previously prepared by J. Tilley. The yield of G-8b from the acetylenic alcohol was 92% after chromatography; apparently the cyclization proceeds under these conditions with a remarkable degree of stereospecificity.

This result is consistent with cyclization through a discrete cationic intermediate such as 23 as discussed above. It casts some doubts, however, on Harding's proposal (31) that cyclizations of such tertiary alcohols (for instance Lansbury's alcohol J-10) proceed through initial dehydration to intermediate olefins, even under these conditions. He has used this argument to account for cis-fused cyclization products (about 20% in Lansbury's case) which he maintains are due to concerted protonation/cyclization of the intermediate olefins. Our alcohol K-3 should be as prone (or more so) to dehydration as is alcohol J-10, and should therefore yield cis-fused product from concerted protonation/cyclization as does J-10. Yet no cis-fused products are observed. Either the intermediate olefins in our case do not participate in such concerted reactions, or the alcohol K-3 does not dehydrate to olefins prior to cyclization. This latter possibility seems most reasonable, and casts doubts on whether Lansbury's alcohol J-10 is dehydrating under these conditions either. If both alcohols J-10 and K-3 are cyclizing through discrete cationic intermediates, then the 20% *cis*-fused product in Lansbury's case could be due to the lack of any bulky axial substituents 1,3 to the cationic center (18).

Regardless of the detailed mechanism of cyclization, the Eschenmoser cleavage/cyclialkylation procedure provided an extremely stereospecific way of introducing the required axial methyl group at the A-B ring juncture. In addition, it had been possible to trap the enol trifluoroacetate **K-4**. The great similarity between this compound and Tilley's enol acetate **G-6**, made us confident we could generate enolate anion **K-5** as he had done, only from enol trifluoroacetate **K-4**. The anion could then be cyclopropylated, or possibly methylated, to ultimately yield the desired A ring of **G-8a**. Unfortunately our confidence was so great and the amount of enone **G-2** was so small that this reaction was never attempted. Instead, the remainder of **G-2** was used in a second study.

Subsequent to Johnson's published conversion of **J-7** to **J-9**, he reported an unusual cyclization of this same molecule under different conditions (36). On treatment of **J-7** in methylene chloride at -78° with trifluoroacetic acid (which is only very slightly soluble at this temperature), he obtained the olefinic chloride **24** in 60% yield after purification. He offers a possible explanation for this unusual transformation, based upon the very low concentration of trifluoroacetic acid present in the cyclization mixture. He proposes that the kinetic intermediate from cyclization resembles the linear vinyl cation **25**, which is quickly trapped by normal concentrations of good nucleophiles



to afford 5-membered ring products such as J-8. When no good nucleophile is present in any appreciable concentration, however, this cation rearranges to the thermodynamically more stable (due to the trans ring juncture) system 26. Eventually, this abstracts a chloride from methylene chloride to afford the observed product 24.

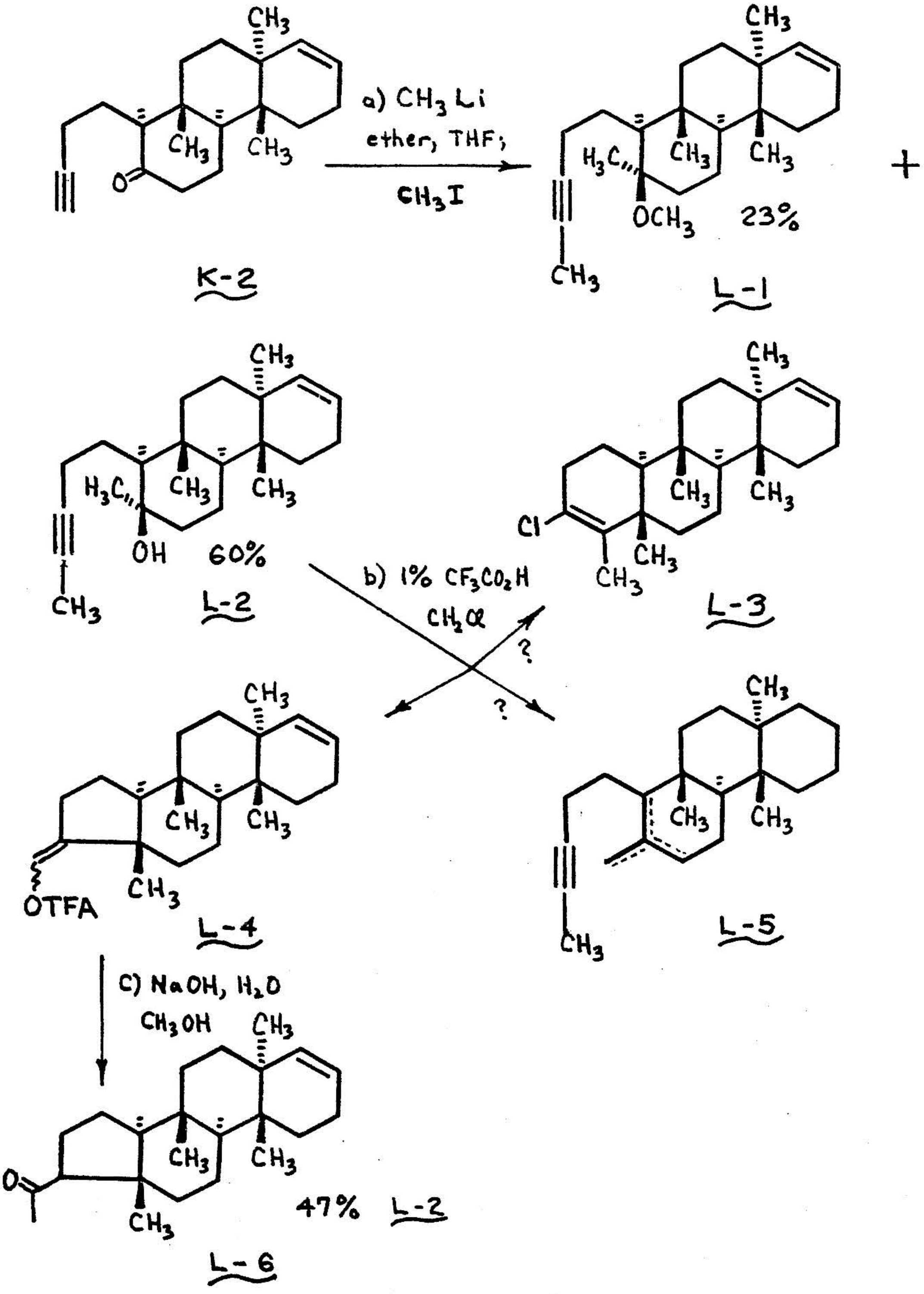
This cyclization of a methylated acetylene to a cylohexane derivative looked very attractive for generation of the shionone A ring since it introduced the C-4 methyl group of shionone without resorting to experimentally difficult procedures involving an enolate anion. In order to determine the applicability of Johnson's finding to our system, the methylated acetylene L-2 was prepared. This was accomplished by treating acetylenic ketone K-2 in ether and tetrahydrofuran with an excess of methyllithium and then methyl iodide. The product mixture obtained in 83% yield contained alcohol L-2 and ether L-1 in a 2.6:1 ratio. When this reaction was performed using 20% HMPA-tetrahydrofuran as solvent, only ether L-1 was obtained.

When alcohol L-2 was treated with 1% trifluoroacetic acid in methylene chloride at -20°, no reaction seemed to occur within 25 min as determined by vpc. The mixture was then allowed to warm to room temperature for 75 min, and afforded after work-up a crude product containing a moderately strong enol trifluoroacetate band in the ir. After hydrolysis of the enol trifluoroacetate and purification of the product, a 47% yield of pregnenone L-6 was obtained (the small scale of the reaction may account for a somewhat low yield). The stereochemistry of this product was assigned by analogy with Johnson's results from acetylene J-7 and our experience with alcohol K-3. Some nonpolar material was also obtained from chromatography of the hydrolyzed product, but it was obtained in such a small amount that it could not be determined whether it was the desired chloride L-3 or dehydration product L-5.

This rather disappointing result suggested that under conditions vigorous enough to solvolyze our tertiary alcohol at an appreciable rate, enough trifluoroacetic acid had to be present that it trapped out the undesirable 5-membered ring product. In view of our success with the cyclization of terminal acetylene K-3, and of our confidence that enolate anion K-5 could be generated from enol trifluoroacetate K-4, the cyclization of methylated acetylenes was temporarily abandoned.

Although the new A ring sequence seemed essentially worked out,

Chart L

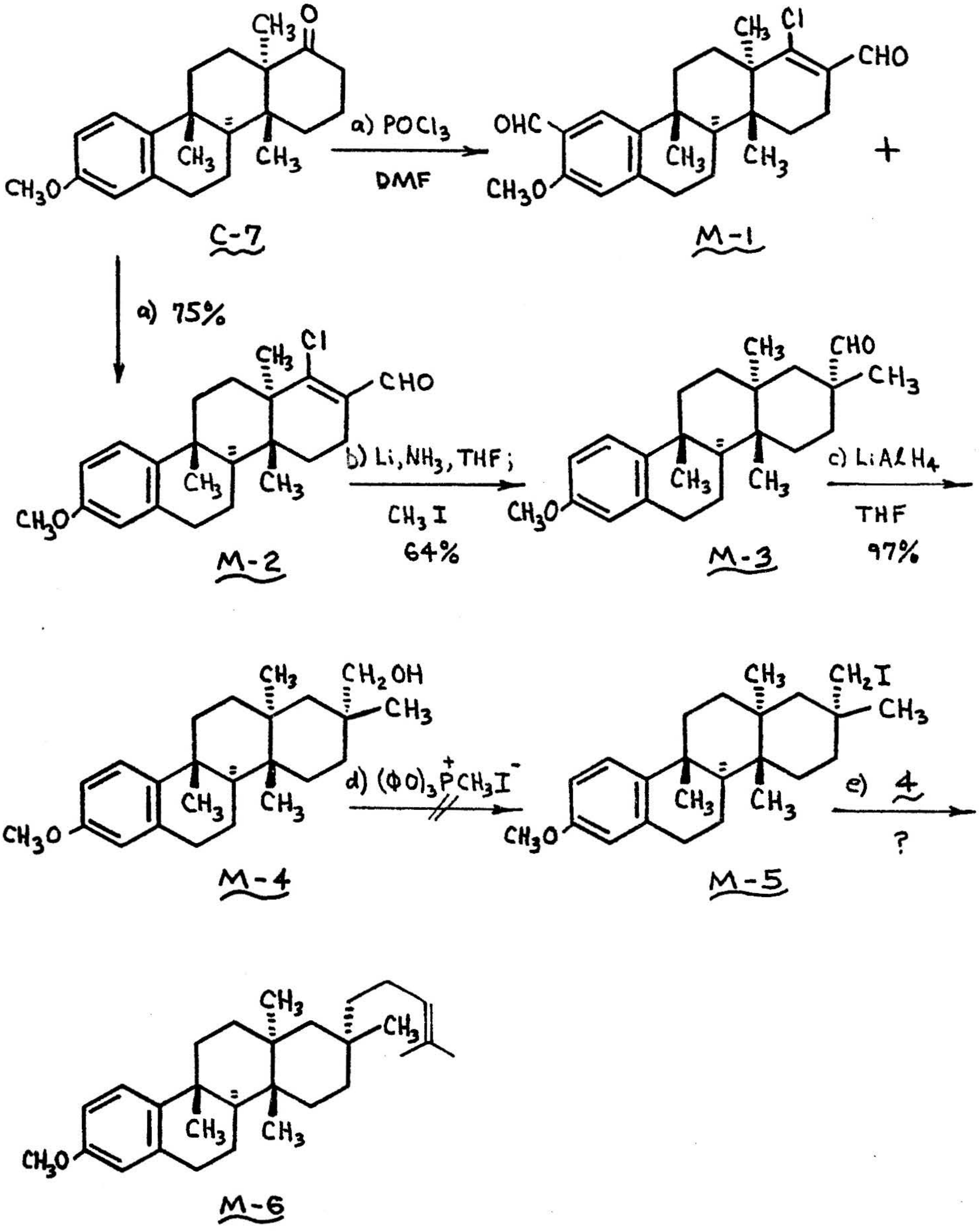

K-2
a) CH_3Li
ether, THF;
CH_3I
OCH_3
23%
L-1
+
OH
60%
L-2
b) 1% CF_3CO_2H
CH_2Cl_2
?
?
Cl
L-3
OTFA
L-4
L-5
c) NaOH, H_2O
CH_3OH
47% L-2
L-6

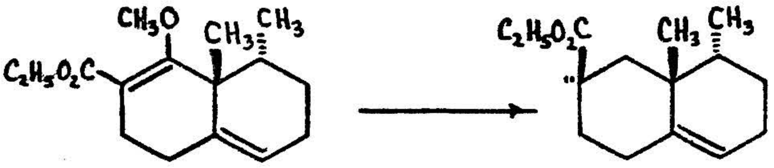
it appeared unwise at this point to preparatively apply this sequence to the generation of Tilley's intermediate alcohol G-15, via the olefin G-8a. Tilley had already encountered problems in trying to complete the side chain from alcohol G-15, raising the possibility that this transformation might require considerable study. Since a great many steps were involved in reaching the alcohol, it could only be prepared in relatively small amounts which might again prove insufficient to achieve the final transformation. Thus a more reasonable alternative was pursued, that of elucidating a pathway for the completion of the side chain on more readily available material.

As a substrate for this work, the simplest model from key intermediate C-7 would still possess the aromatic A ring intact. For construction of such a model the D ring ketone of C-7 does not have to be masked or protected for operations in the A ring, and thus can be utilized directly as an aid for introduction of the side chain as outlined in Chart M. When the tetracyclic ketone C-7 was treated with Vilsmeir reagent ($POCl_3$-DMF) (37a) and the reaction was carried to 87% conversion, a 75% yield (based on recovered starting material) of chloro aldehyde M-2 was obtained (37b). If the reaction was carried to complete conversion, this yield dropped to 71%. A second principal product isolated from the reaction mixture was found to be the chloro dialdehyde M-1. Formation of this species accounts for the lower yield of the desired mono-aldehyde M-2 when the reaction was carried to higher conversion.

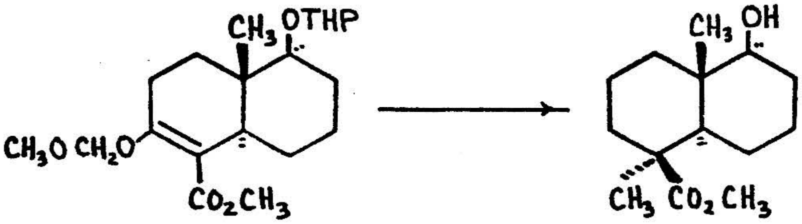
Chloro aldehyde M-2 was sought partly as a result of work by Coates and Shaw (38); they demonstrated that α,β-unsaturated ester 27,

Chart M


C-7
a) POCl3
DMF
M-1
+
a) 75%
M-2
b) Li, NH3, THF;
CH3I
64%
M-3
c) LiAlH4
THF
97%
M-4
d) (ΦO)3P+CH3I−
M-5
e) 4
?
M-6



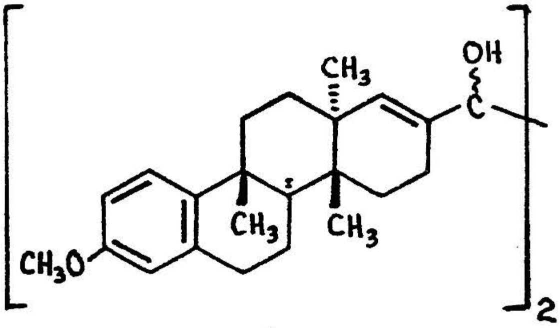
27 28



29 30

substituted with a methoxy leaving group at the β-position, could be reduced with lithium in ammonia to the demethoxy saturated ester 28. Welch and Hagan (39a) subsequently showed that such reductions could be coupled with methylation of the intermediate ester enolate anion to afford α-methylated esters (e.g. 29→30). In both of these cases, the initially formed product bears the ester group in an axial orientation, 1,3 to an axial methyl group. The relationship of this work to chloro aldehyde M-2 is clear; such a reductive alkylation of this intermediate should afford principally the methylated aldehyde M-3 with the aldehyde oriented in the α configuration as desired for elaboration into the side chain.

Dissolving metal reductions of α,β-unsaturated aldehydes are almost unmentioned as preparative reactions in the literature (40); the proposed reduction in our system promised to accomplish so much in one step, however, that its investigation was deemed worthwhile. Chloro aldehyde M-2 was therefore treated with lithium in ammonia followed by iodomethane quenching under a variety of conditions. Initial attempts afforded low yields of the desired aldehyde M-3. From these reactions varying amounts of acid soluble compounds were obtained from the 10% hydrochloric acid wash of work-up, while considerable amounts of polar material were obtained after chromatography. The polar chromatography products appear by ir and nmr to be a mixture of diastereomeric alcohols of structure 31, probably formed by dimerization of the intermediate radical anion 32. Formation of dimers in the reduction



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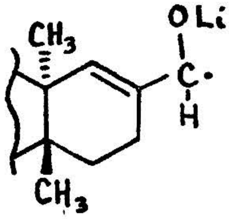


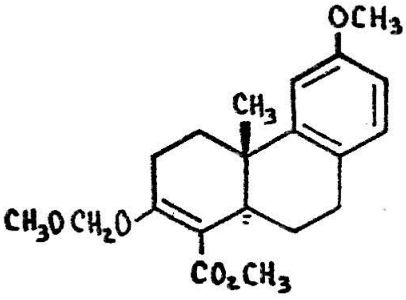
32

of α,β-unsaturated carbonyl compounds is not uncommon in the absence of a proton source (41a,b). The acid soluble products are probably amines of some sort formed by various possible reactions between ammonia and the starting aldehyde or product (41c).

Conditions were modified in order to minimize these side reactions.

Chloro aldehyde M-2 was kept isolated from the ammonia atmosphere of the reaction vessel during addition by the use of a non pressure-equalized dropping funnel. A high concentration of dissolved lithium was employed, and most of the ammonia was removed from the reaction mixture prior to quenching of the enolate anion with iodomethane. These steps were taken in order to limit undesired reactions of ammonia with the starting material or product. A high dilution of the chloro aldehyde, a slow addition rate of chloro aldehyde to the reducing solution and vigorous stirring of the reaction mixture during addition were also employed; in this case the purpose was to minimize coupling of the radical anions. When all these modifications were finally arrived at and applied in a single reaction, a 64% yield of the desired aldehyde M-3 was realized after chromatography. No epimeric methylated aldehydes were observed.

There is little doubt that aldehyde M-3 has the proper stereochemistry about the newly formed asymmetric center. House and co-workers have examined the stereochemical course of alkylation of enolate anions exocyclic to simple cyclohexane rings, and have observed a marked preference for equatorial alkylation (42). Welch has commented on the stereospecificity of this process in relation to his experience with the reductive alkylation of unsaturated ester 33; on methyl iodide alkylation of the presumed ester enolate anion 34, he obtained greater than 95% stereoselective equatorial alkylation, resulting in podocarpic acid derivative 35 (39b). This is completely analogous to his result discussed earlier from the reductive alkylation of ester 29, which also



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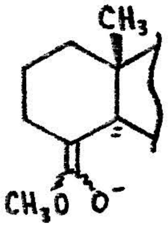

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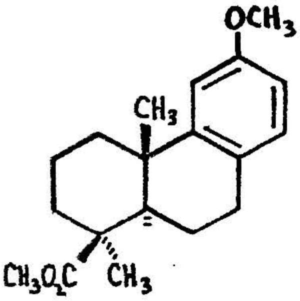
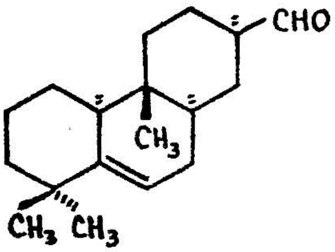


35

gave equatorially methylated product. Ireland and Mander have examined the alkylation of a system very similar to ours, that of an aldehyde enolate anion exocyclic to a fused cyclohexane ring. They observed that methylation of aldehyde 36 with potassium *t*-butoxide and iodomethane affords only the equatorial alkylation product 37 (43). All of these examples exhibit predominant or exclusive equatorial alkylation of enolate anions exocyclic to saturated six-membered rings; there is no reason to suppose that the alkylation which generated aldehyde M-3 would have behaved any differently.



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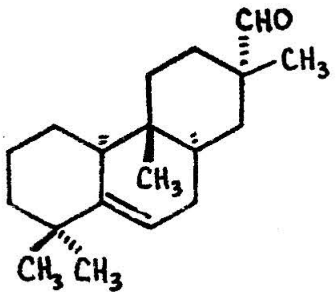
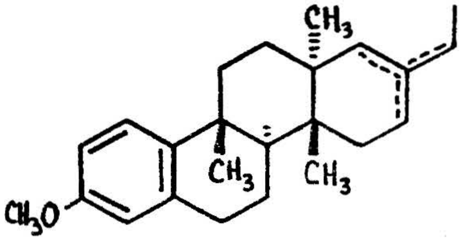


37

In two steps from the D ring ketone of key intermediate C-7 the methylated aldehyde M-3 had been synthesized. This conversion argued strongly against use of olefin G-2 in our synthetic planning since six steps are required to achieve the parallel transformation by way of that intermediate. In order to make either route worthwhile, however, the remainder of the side chain still had to be attached to an aldehyde such as M-3.

Aldehyde M-3 was smoothly reduced to the alcohol M-4 with lithium aluminum hydride, and we hoped to convert this to the iodide M-5 for coupling with π-(1,1-dimethylallyl)-nickel bromide (4) (26). A number of attempts at preparing this iodide failed however. With the reagent methyltriphenoxyphosphonium iodide, under conditions which afford good yields of iodide from other sensitive primary alcohols (44), only mixtures of nonpolar olefinic compounds (probably 38 and 39) were produced;



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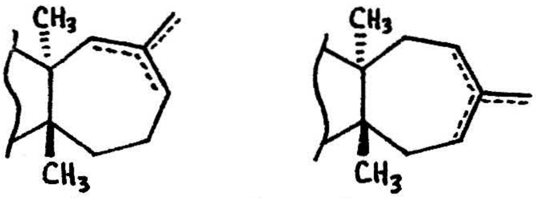
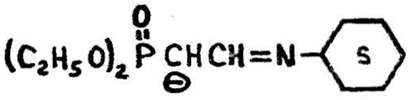


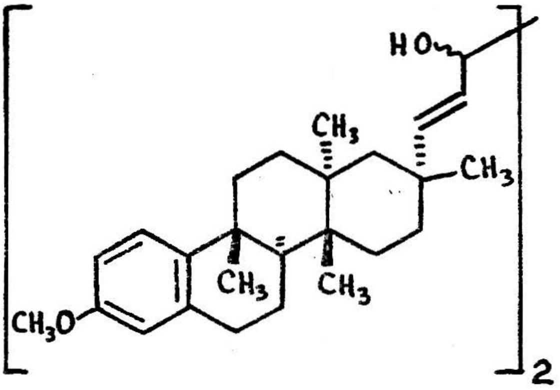
39

under milder conditions, little or no reaction occurred. The reagent itself was shown to be good when it smoothly converted dodecyl alcohol to the corresponding iodide. These results are not unreasonable since the alcohol function of M-4 not only has neopentyl character, but is attached to a carbon 1,3-diaxially disposed to a methyl group held rigid at the ring juncture. Steric hindrance should tend to prevent intermolecular reactions of this alcohol. Once such a reaction occurs, however, such as formation of a phosphonium ester, then steric crowding probably accelerates elimination of any bulky leaving group which may have formed. This steric acceleration and the neopentyl nature of the alcohol might well be expected to produce rearranged olefinic products through cationic intermediates. A different route to the side chain intermediate M-6 was devised to avoid this problem, and is presented in Chart N.

Nagata's formylolefination reaction of carbonyl compounds which has been used on hindered aldehydes (30) was applied to aldehyde M-3. Treatment of this aldehyde with a sevenfold excess of the phosphonate anion 40 and hydrolysis of the intermediate aldimine N-1, afforded an



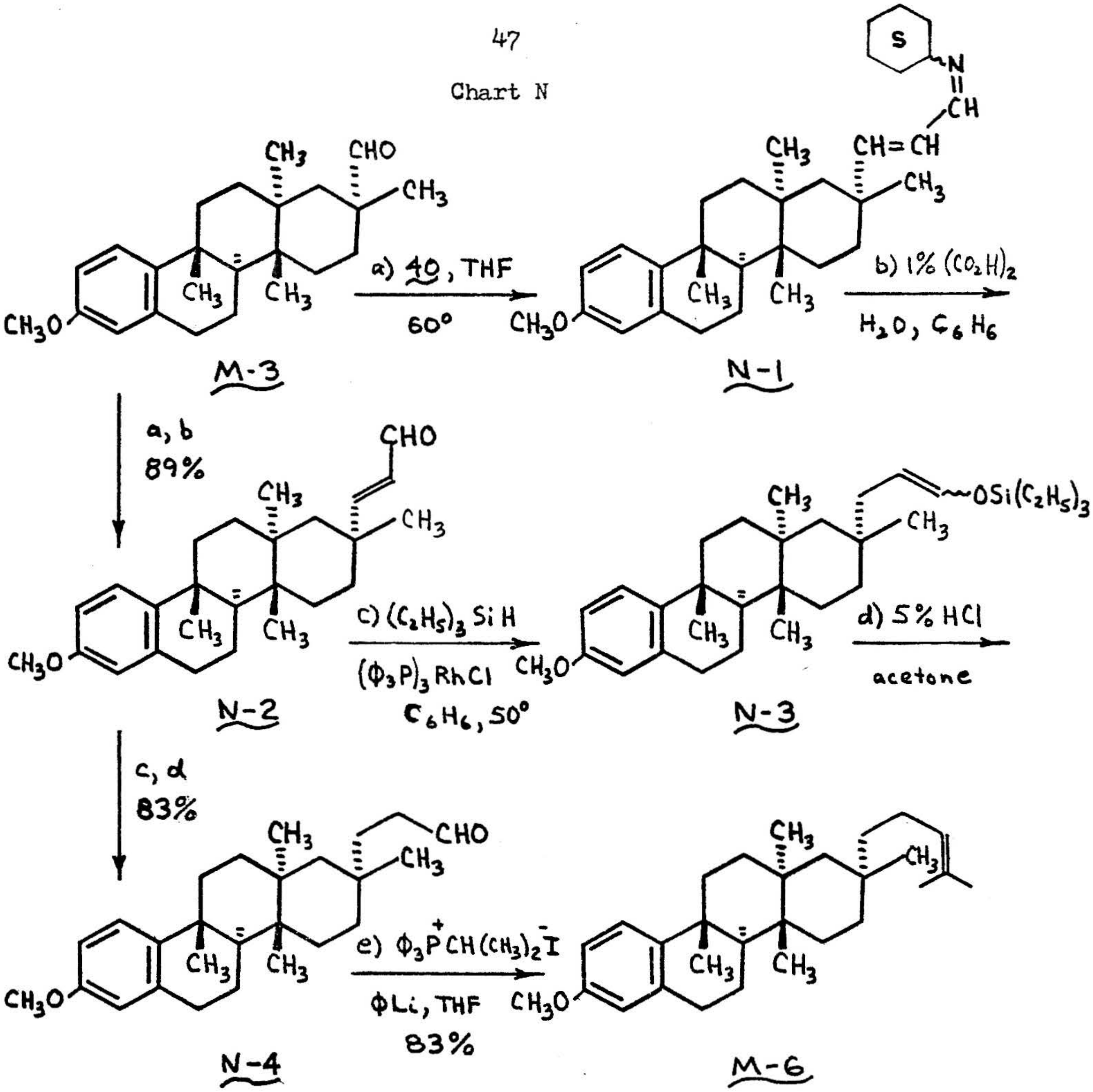
40



41

89% yield of the α,β-unsaturated aldehyde N-2 after purification. Reduction of this aldehyde was initially attempted using lithium in ammonia, but only a 34% yield of the saturated product N-4 could be obtained; the principal product appeared to be the dimeric alcohols 41.

Chart N


M-3
a) 40, THF
60°
N-1
b) 1% (CO2H)2
H2O, C6H6
a, b
89%
N-2
c) (C2H5)3SiH
(Φ3P)3RhCl
C6H6, 50°
N-3
d) 5% HCl
acetone
c, d
83%
N-4
e) Φ3P+CH(CH3)2 I−
ΦLi, THF
83%
M-6
S
N
CH
CH=CH
CHO
CH3
CH3O
OSi(C2H5)3

Such large amounts of coupling may be due to the very unhindered nature of the aldehydic carbon; no attempts were made to increase the yield of this reaction.

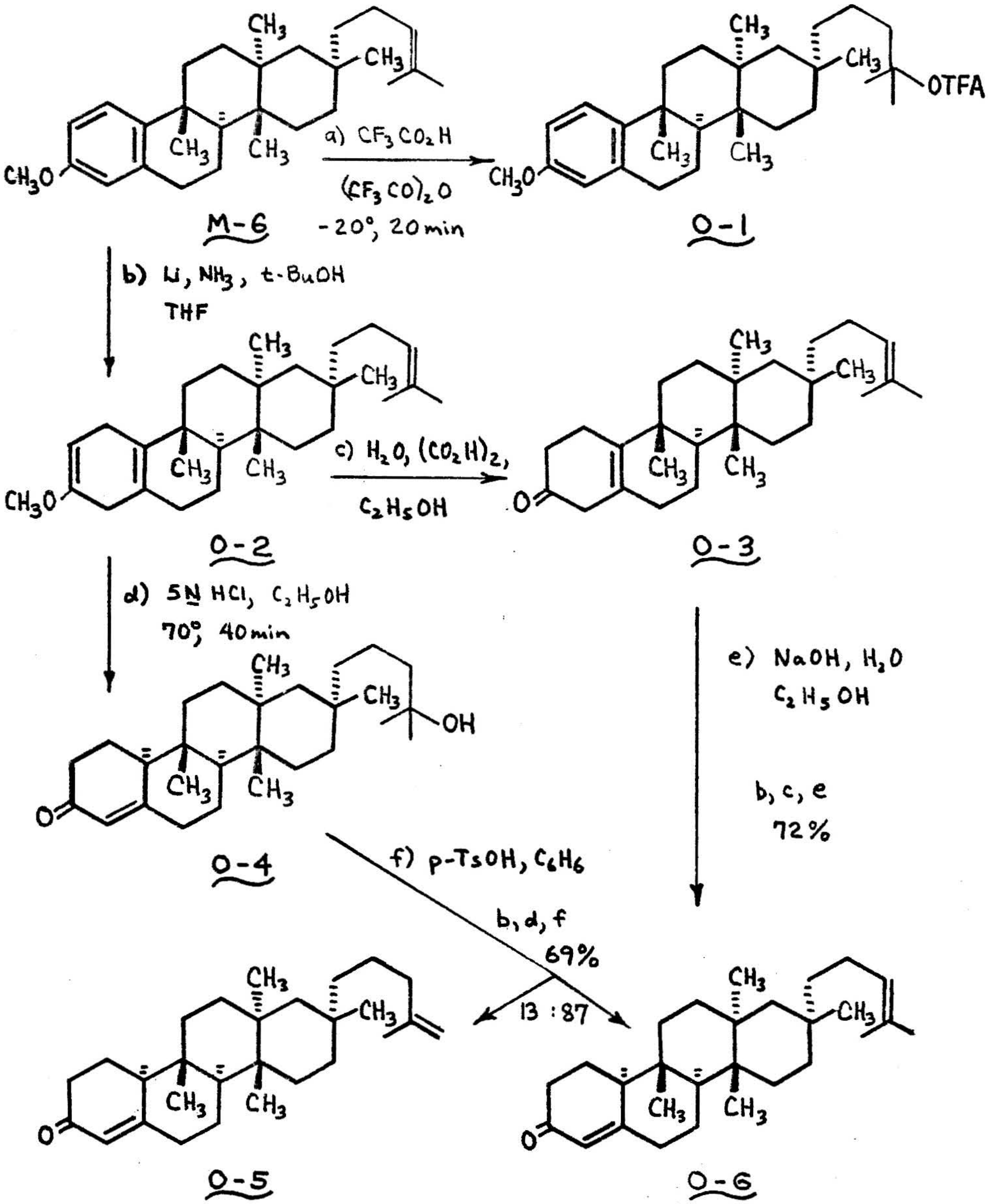
Another method pursued to effect this reduction was based upon the recent procedure of Nagai and co-workers (45) for reducing α,β-unsaturated carbonyl compounds to silyl enol ethers. Treatment of the aldehyde **N-2** with excess triethylsilane in a small amount of benzene, with the periodic addition of catalytic amounts of tris-(triphenylphosphine)-rhodium chloride, produced the crude silyl enol ether **N-3**. This was hydrolyzed under mildly acidic conditions and an 83% yield of the desired saturated aldehyde **N-4** was obtained after chromatography.

Completion of the side chain was accomplished using the Wittig reaction. The crude salt obtained from triphenylphosphine and methyl iodide (still containing small amounts of unreacted phosphine) was treated with phenyllithium to generate isopropylidine Wittig reagent (46). Treatment of the aldehyde **N-4** with a fivefold excess of this reagent afforded the desired side chain intermediate **M-6** in 83% yield after chromatography. A viable side chain synthesis had thus been arrived at, which in five steps converted the tetracyclic ketone **C-7** into the side chain intermediate **M-6** in 29% overall yield.

With the side chain synthesis complete, the question then arose of how to couple this scheme with that for the A ring. In order to utilize the Vilsmeir/chloro aldehyde reduction sequence, it was almost necessary to perform these manipulations before reducing the A ring. Our experience with the extremely slow cyclization of olefin mixture **I-6** in trifluoroacetic acid at room temperature, and the stability of the D ring olefin of alcohol K-3 to the trifluoroacetic acid cyclization conditions for acetylenes, led us to believe that the side chain double bond would be stable to the -20° trifluoroacetic acid cyclization conditions. At the same time we felt confident that an enolate anion such as K-5 could be generated from an enol trifluoroacetate and alkylated using an HMPA co-solvent. These considerations, coupled with the fact that we had already completed a route to olefin M-6, prompted us to invest our time and material in the preparation of this intermediate for conversion to shionone.

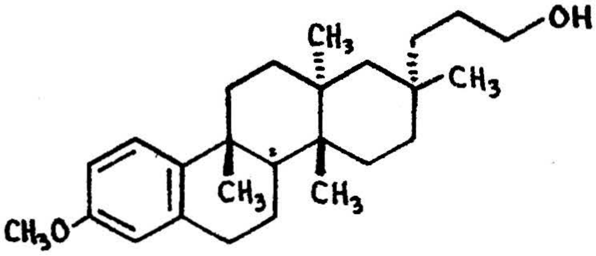
At this point it appeared that the most difficult portion of the work was over. After Birch reduction of the A ring in olefin M-6 and subsequent acid hydrolysis of the product, the α,β-unsaturated ketone formed should have been subject to the same procedures shown in Chart K for the D ring olefin G-2. Birch reduction of the aromatic ring of olefin M-6 using the procedure of Tilley (19f) afforded the crude enol ether O-2 as shown in Chart O. Tilley's hydrolysis procedure used to obtain enone G-2 was then employed. Enol ether O-2 was heated at 70° in a mixture of ethanol and 5*N* hydrochloric acid for 40 min. After work-up the desired enone O-6 was not obtained, but instead the hydroxyenone O-4 had been afforded, possessing none of the nmr signals characteristic of the side chain olefin. Crude alcohol O-4 was then treated with *p*-toluenesulfonic acid in refluxing benzene for 19 hr, in an attempt to regenerate the side chain double bond. The product from this reaction, obtained in 69% yield after chromatography, consisted of a

Chart O


M-6
a) CF3CO2H
(CF3CO)2O
-20°, 20 min
O-1
OTFA
b) Li, NH3, t-BuOH
THF
O-2
c) H2O, (CO2H)2,
C2H5OH
O-3
d) 5N HCl, C2H5OH
70°, 40 min
O-4
e) NaOH, H2O
C2H5OH
b, c, e
72%
f) p-TsOH, C6H6
b, d, f
69%
13 : 87
O-5
O-6
CH3O
CH3
OH
O

13:87 mixture (as determined by nmr) of olefins O-5 and O-6.

The observed hydration of the side chain olefin of O-6 under the relatively mild acidic hydrolysis conditions described above raised some serious questions about the stability of the side chain double bond throughout the rest of our synthesis. As a test, the aromatic olefin M-6 was subjected to the exact same trifluoroacetic acid/anhydride conditions used to effect cyclization of alcohol K-3. To our dismay no starting material was recovered, but instead the crude tertiary trifluoroacetate O-1 was obtained. It was clear that the side chain double bond was not compatible with our proposed cationic acetylene cyclization. Had a good deal of time and material not been invested in the olefin M-6 that was on hand, the synthetic plan would have been modified at this point to proceed through some intermediate such as alcohol 42. The A ring could then have been completed, and the side chain olefin



42

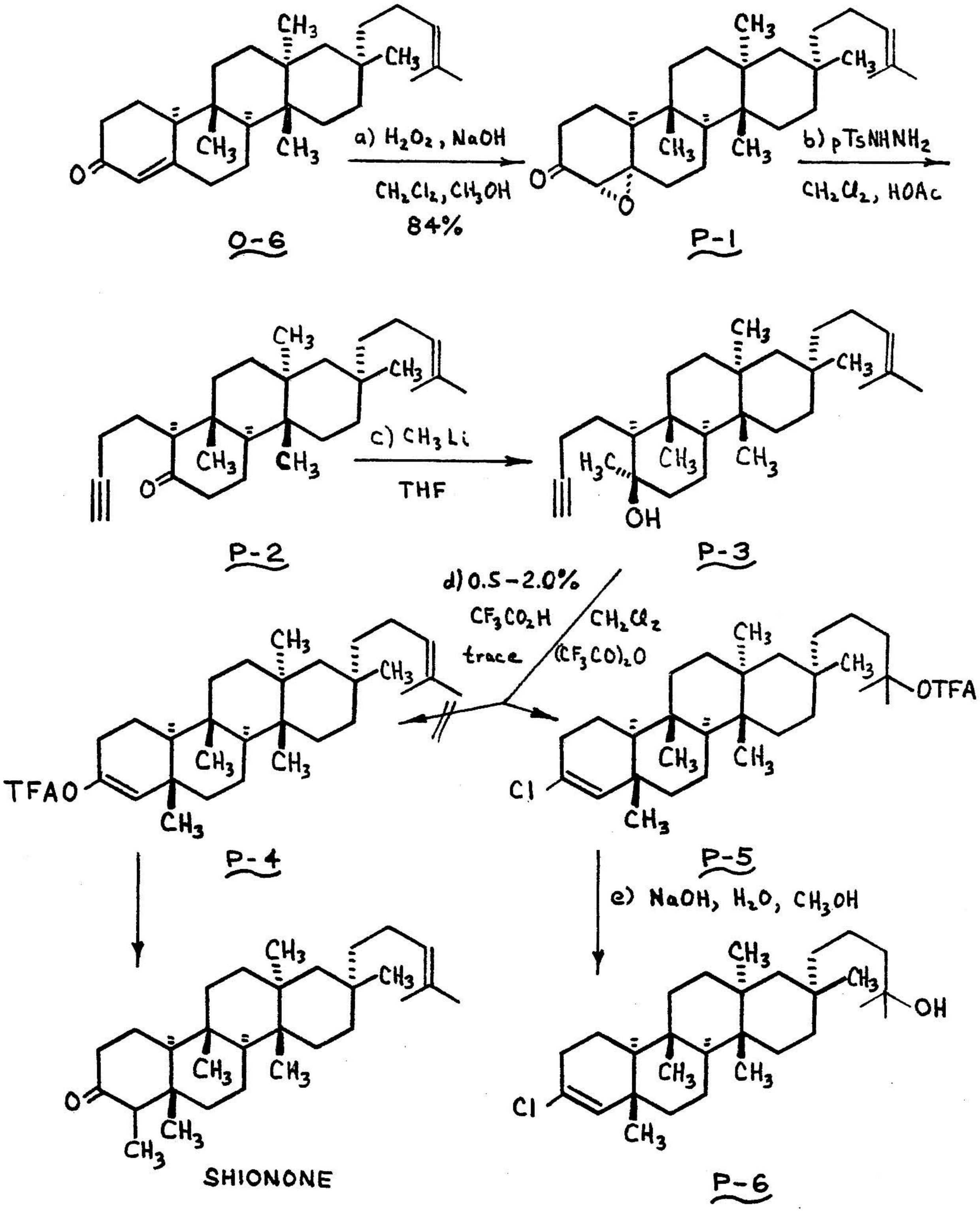
introduced by the Wittig reaction as nearly the last step. In view of our investment of time and material in the intermediate M-6, however, it was decided to proceed from this compound and later attempt finding milder cyclization conditions to form the A ring.

Another Birch reduction of olefin M-6 afforded crude enol ether O-2, which was hydrolyzed with oxalic acid to the β,γ-unsaturated ketone O-3 without affecting the side chain. This enone was then conjugated under mild basic conditions and a 72% yield (from M-6) of the desired α,β-unsaturated ketone O-6 was obtained after purification. We hoped to complete the synthesis from this enone by the route outlined in Chart P.

Epoxidation of the enone O-6 with basic hydrogen peroxide proceeded in excellent yield to afford the epoxyketone P-1. When the Eschenmoser cleavage reaction was attempted on this molecule using the same conditions employed for epoxide K-1, a low yield of the desired acetylene P-2 was obtained; this was possibly due to acid reacting with the side chain. When the reaction conditions were modified so that 2:1 methylene chloride acetic acid was used as solvent instead of a 1:1 mixture, a longer reaction time was necessary. The acetylenic ketone P-2 was obtained in 63% yield after chromatography, however, with the side chain still intact. Addition of methyllithium to this ketone was straightforward, and afforded the tertiary alcohol P-3 for cyclization.

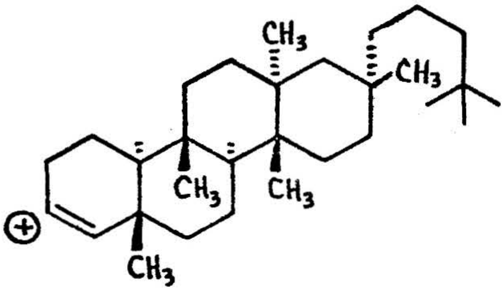
Our earlier experiment had shown that alcohol L-2 in 1% trifluoroacetic acid methylene chloride cyclizes principally to give enol trifluoroacetate L-4 (not vinyl chloride). Based on this observation, it was expected that cyclization of alcohol P-3 under similar conditions would give the desired six-membered ring enol trifluoroacetate in the A ring. It was hoped that these conditions would be mild enough to preserve the side chain as well, in which case enol trifluoroacetate

Chart P

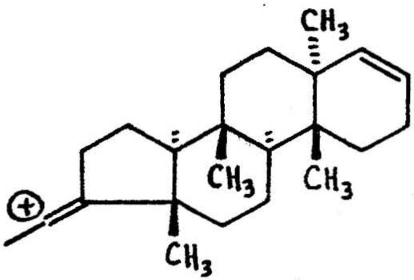

O-6
a) H_2O_2, NaOH
CH_2Cl_2, CH_3OH
84%
P-1
b) pTsNHNH$_2$
CH_2Cl_2, HOAc
P-2
c) CH_3Li
THF
P-3
d) 0.5-2.0%
CF_3CO_2H
trace
CH_2Cl_2
$(CF_3CO)_2O$
P-4
TFAO
P-5
Cl
OTFA
e) NaOH, H_2O, CH_3OH
SHIONONE
P-6
OH
CH_3
H_3C

P-4 would be obtained for conversion into shionone. When alcohol P-3 was treated for a short while with 0.5% trifluoroacetic acid (to about 50% reaction) and then with 2.0% trifluoroacetic acid in methylene chloride, essentially none of the desired enol trifluoroacetate P-4 was obtained. Surprisingly enough, the principal product from this reaction appears to have been the chloro olefin P-5, with trifluoroacetate in the side chain but not in the A ring. Upon hydrolysis of this crude product, an alcohol (not a ketone) was obtained with a single olefinic proton in the nmr, consistent with structure P-6. None of the nmr signals characteristic of the side chain double bond were present.

This cyclization result is quite interesting when compared to our previously discussed results obtained on acetylene L-2. Even with a higher concentration of trifluoroacetic acid present in the cyclization of alcohol P-3 as compared to that of alcohol L-2, the principal product obtained appears to be the chloride P-5 as opposed to the enol trifluoroacetate L-4. Since the substrates in these reactions differ by more than just the acetylenic methyl group, and since the reaction conditions were not exactly parallel, one can only speculate as to the meaning of these results. They seem to indicate that six-membered ring vinyl cation 43 from alcohol P-3 is more reactive towards methylene chloride than the five-membered ring cation 44 from alcohol L-2. Thus cation 43 reacts quickly with the solvent to afford principally chloro olefin P-5, while cation 44 does not react with solvent, but eventually reacts with the 1% trifluoroacetic acid present to afford enol trifluoroacetate L-4. Johnson's results with cyclization of acetylene J-7 to



43



44

chloride 24 (36) (page 36) can be rationalized along similar lines. One might argue that since the initially formed linear vinyl cation 25 reacts only slowly with methylene chloride, then when no appreciable concentration of trifluoroacetic acid is present, this cation reversibly rearranges to the bent vinyl cation 26. If this bent cation does react rapidly with methylene chloride, then even if it is not the more stable cation this rapid reaction would still account for formation of the six-membered ring chloride 24. Such a postulated difference in reactivity towards methylene chloride for the linear and bent vinyl cations in this series of compounds neatly explains the observed results.

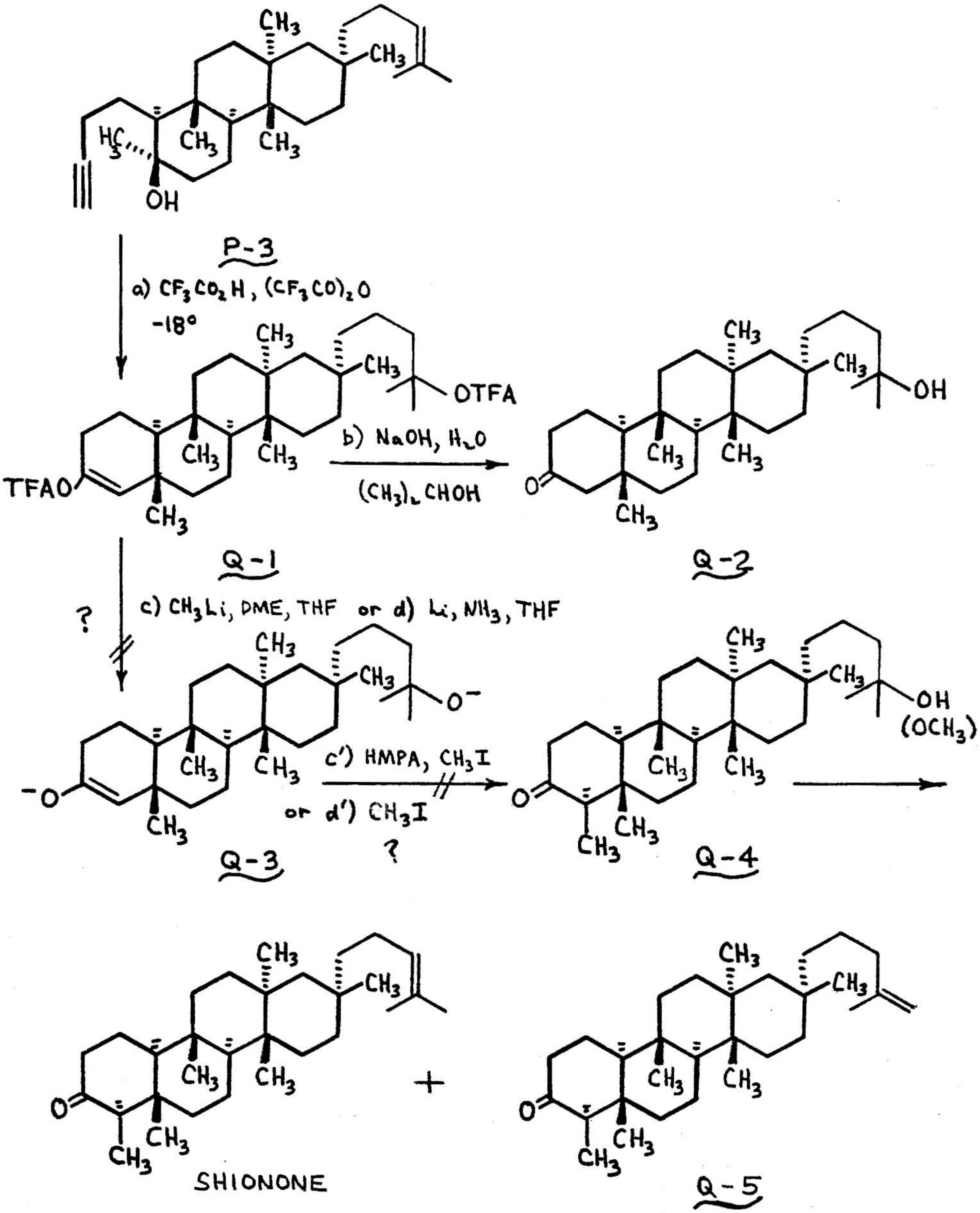
Although cyclization of alcohol P-3 to the chloride P-5 has inspired some interesting mechanistic speculation, it was rather a disaster for our synthetic purposes. Not only was the desired enol trifluoroacetate not produced, but even under these dilute acid conditions the side chain olefin had added acid. Since our results with the side chain alcohol O-4 indicated that *ca.* 85% of the desired olefin could be regenerated from such hydrated species, it seemed reasonable at this point to perform the originally intended trifluoroacetic acid cyclization at the expense of the side chain. As shown in Chart Q, shionone hydrate Q-4 might then be prepared and the olefin regenerated as the last step.

Toward this end, alcohol P-3 was treated with trifluoroacetic acid and trifluoroacetic anhydride at -18° to afford the crude bistrifluoroacetate Q-1. It was clear from spectra of this material that both an enol trifluoroacetate and the side chain trifluoroacetate had been formed. Hydrolysis of this material afforded a hydroxyketone consistent with the structure Q-2. Conversion of the bistrifluoroacetate Q-1 to the hydrated shionone species Q-4 was then attempted.

Bistrifluoroacetate Q-1 was added to methyllithium in 1,2-dimethoxyethane and tetrahydrofuran to generate the enolate dianion Q-3. This mixture was then treated with HMPA followed by methyl iodide, and the resulting product after work-up was stirred with ethanolic potassium hydroxide to epimerize any axial methyls α to the carbonyl of Q-4 (24e). The nmr spectrum of the crude product from this reaction exhibited no δ 0.73 singlet. This singlet is characteristic of the C-5 methyl group of shionone (24d), and is also present in friedelin and in Tilley's ketone G-8a; this singlet is not present, however, in ketones G-8b or Q-2 which lack a methyl group α to the carbonyl. Thus it appears doubtful that any of the methylated ketone Q-4 was present in the crude product. On silica gel tlc this material showed at least six spots, but no meaningful products could be isolated due to the small scale of the reaction.

Generation of the enolate dianion Q-3 was then attempted using excess lithium in ammonia to cleave the bistrifluoroacetate Q-1. The re-

Chart Q

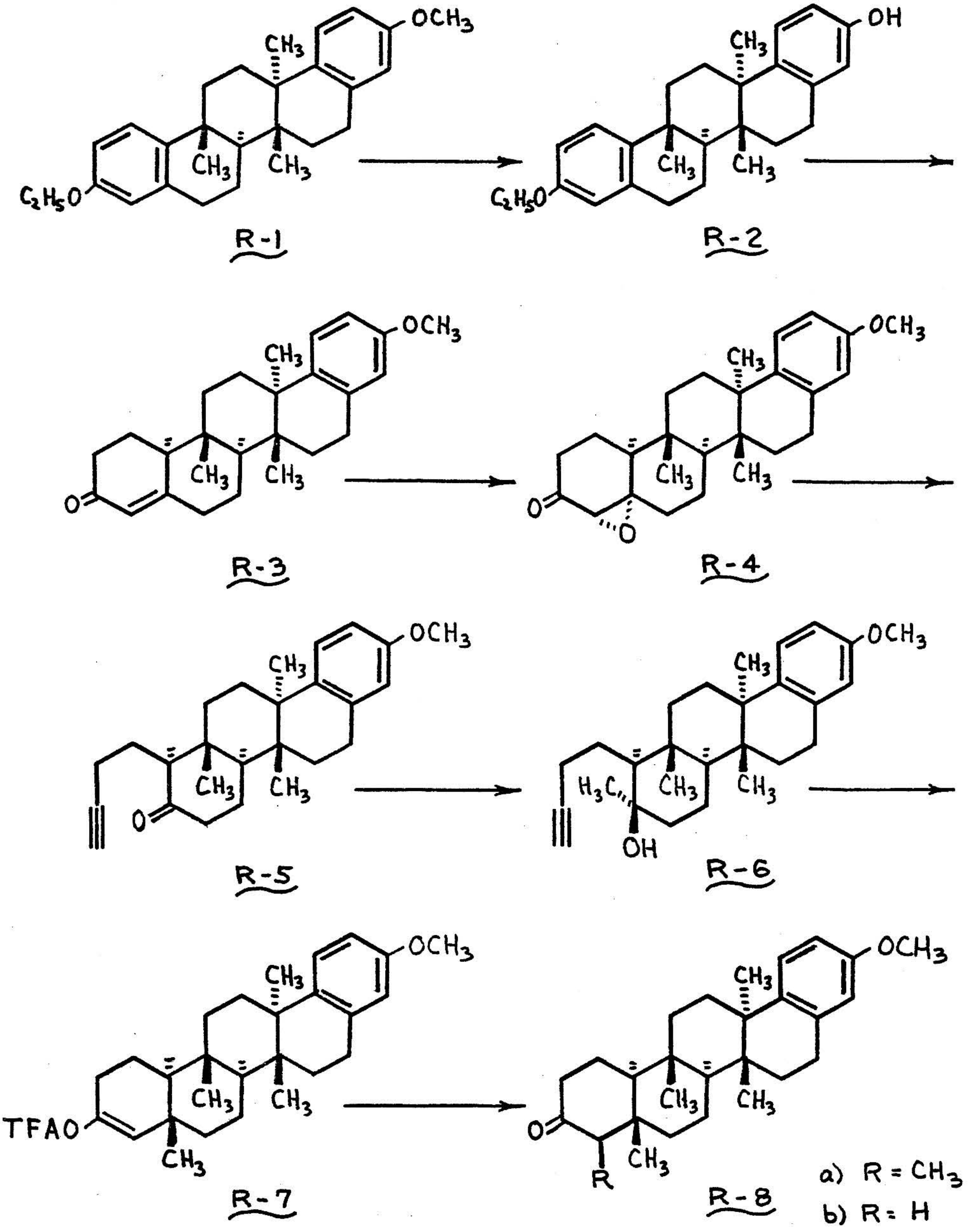

P-3
a) CF_3CO_2H, $(CF_3CO)_2O$ -18°
TFAO
OTFA
Q-1
b) NaOH, H_2O $(CH_3)_2CHOH$
OH
Q-2
?
c) CH_3Li, DME, THF or d) Li, NH_3, THF
^-O
O^-
Q-3
c') HMPA, CH_3I or d') CH_3I
?
OH (OCH_3)
Q-4
SHIONONE
+
Q-5

sulting blue solution from this reaction was quenched directly with iodomethane, and once again a complex product mixture was obtained. After treatment with ethanolic potassium hydroxide, this crude product had an nmr spectrum lacking any δ 0.73 singlet, and this experiment was pursued no further. Additional attempts at the conversion of Q-1 to Q-4 almost certainly would have been made at this point, had it not been for the results of D. Walba from some concurrent work in this laboratory (47).

Pentacyclic diether R-1 had been prepared in large quantity by A. Hagenbach in these laboratories (48) using a route which parallels that outlined in Chart D for the preparation of Welch's intermediate C-5. Walba converted a portion of this material to the enone R-3, and was able to transform this into acetylenic alcohol R-6 by the same sequence which had generated acetylenic alcohols K-3 and P-3. He then cyclized alcohol R-6 to the enol trifluoroacetate R-7, and attempted to generate and methylate the enolate anion from this intermediate. With methyllithium used to cleave the enol trifluoroacetate and methyl iodide used as alkylating agent, several attempts were unsuccessful at generating the desired methylated ketone R-8a; the only identifiable product from these reactions was the unalkylated ketone R-8b. Acetic anhydride was then employed to trap the enolate anions, but only low yields of enol acetates were achieved; the ketone R-8b was again the other major product. Additional studies on the enol trifluoroacetates from cholestanone, with methyllithium cleavage and acetic anhydride trapping, produced low yields of enol acetates as well.

It is well known that enol acetates are readily cleaved by methyl-

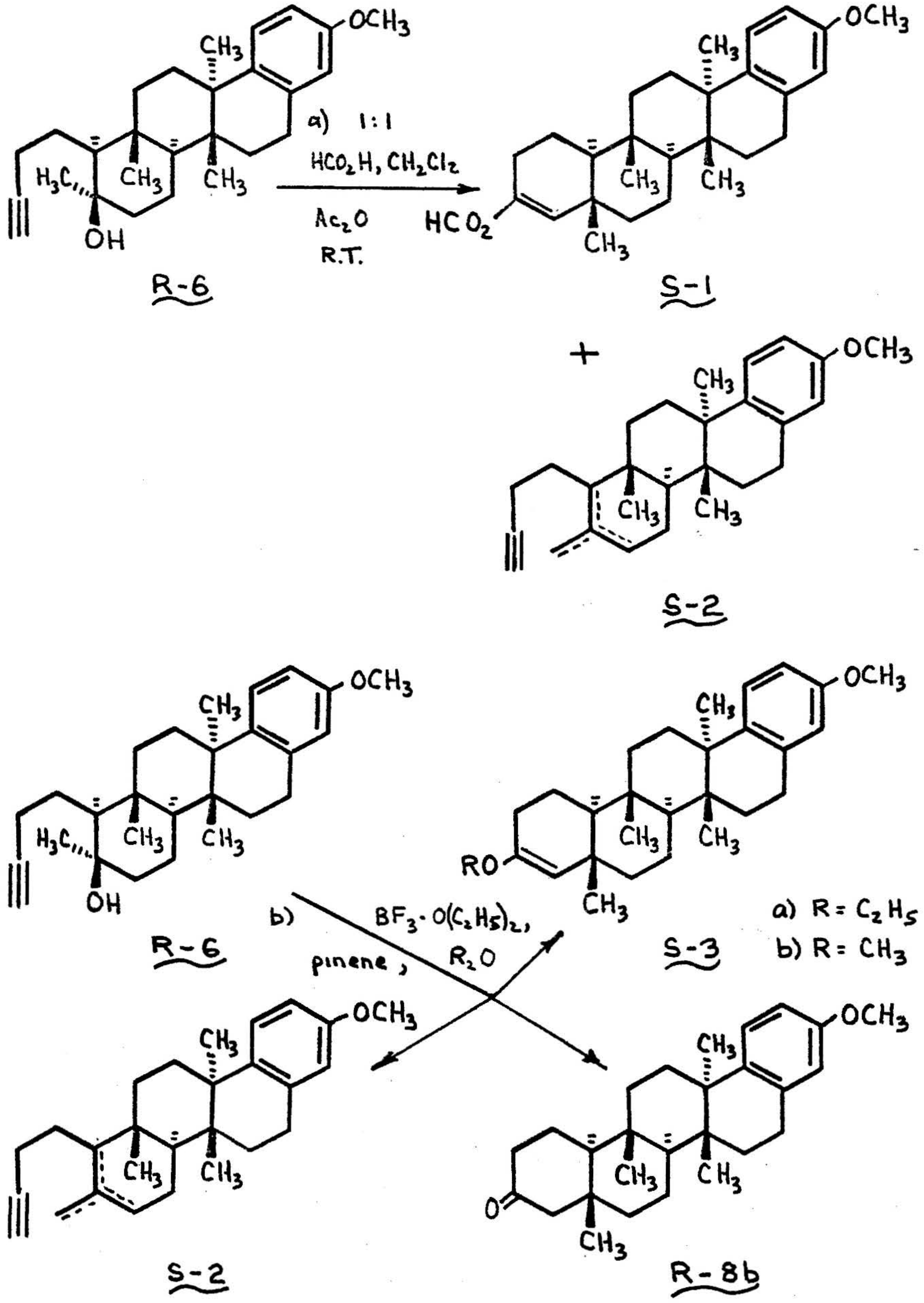
Chart R


OCH3
CH3
CH3
CH3
C2H5O
R-1
OH
CH3
CH3
CH3
C2H5O
R-2
OCH3
CH3
CH3
CH3
O
R-3
OCH3
CH3
CH3
CH3
O
O
R-4
OCH3
CH3
CH3
CH3
O
R-5
OCH3
CH3
H3C
CH3
CH3
OH
R-6
OCH3
CH3
CH3
CH3
TFAO
CH3
R-7
OCH3
CH3
CH3
CH3
O
CH3
R
R-8
a) R = CH3
b) R = H

lithium to the corresponding enolate anions (49); however, it would appear that our earlier assumption that enol trifluoroacetates would behave similarly is incorrect. No examples of this reaction of enol trifluoroacetates could be found in the literature, and the reason for their problematic behavior remains unclear. It would have been interesting to study this reaction in a simple system on a large enough scale to determine exactly what was occurring, but the problem of completing the A ring still remained unsolved.

Since the problems of the friedelin and shionone A rings were essentially the same, and since Walba's acetylene R-6 was in more plentiful supply than the alcohol P-3, he kindly afforded me a portion of his material for some experiments. Cyclization of acetylenic alcohol R-6 was attempted using formic acid (34) as shown in Chart S, in an effort to generate an enol ester more "normal" than the trifluoroacetate. When a 1:1 mixture of formic acid and methylene chloride, containing a trace of acetic anhydride to remove any water, was used to effect cyclization at *ca.* 0°, only starting material R-6 was recovered after 2 hr. When performed at room temperature, this reaction required 4.5 hr to reach completion as determined by vpc analysis. The crude product appeared to be a 1:1 mixture of the desired enol formate S-1 and the dehydration product S-2. When this mixture was resubmitted to the same reaction conditions for 5 hr longer it remained unchanged, indicating that olefin S-2 did not cyclize to enol formate S-1 under these conditions. Other experiments in the shionone series showed that the side chain olefin added formic acid under similar conditions, so no

Chart S


OCH₃
CH₃
H₃C
OH
R-6
a) 1:1
HCO₂H, CH₂Cl₂
Ac₂O
R.T.
HCO₂
S-1
+
S-2
RO
S-3
a) R = C₂H₅
b) R = CH₃
b)
BF₃·O(C₂H₅)₂,
R₂O
pinene,
R-8b

attempts were made to increase the ratio of S-1 to S-2.

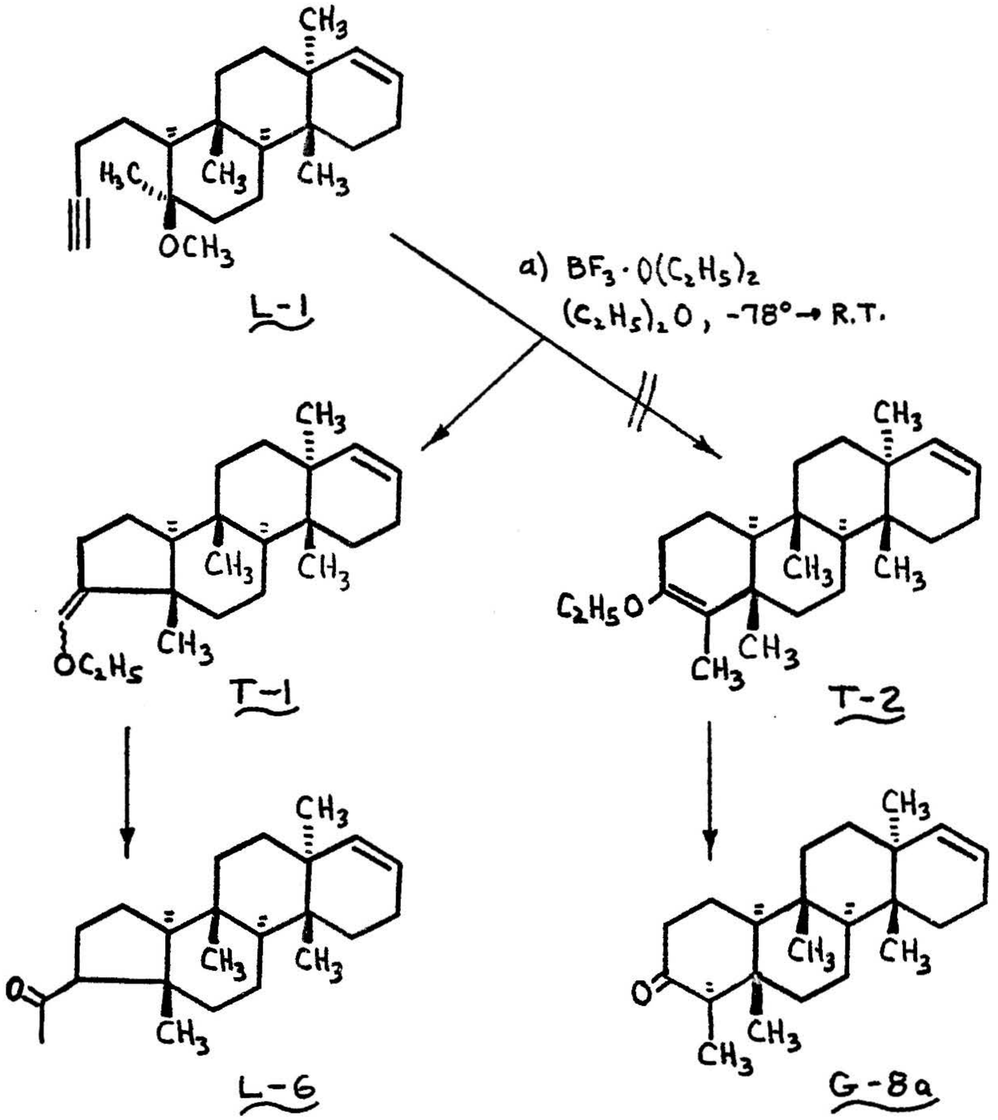
Another approach to the problem was prompted by our isolation of the olefinic chloride P-5. It seemed that if the six-membered ring vinyl cations such as 43 readily abstracted chloride from methylene chloride then they might also react with ethers to afford enol ethers such as S-3. These products would be desirable since they could be cyclopropylated (50) for introduction of the required methyl group upon acid hydrolysis (20). Thus acetylenic alcohol R-6 was treated with borontrifluoride etherate complex in ether, with some pinene added to scavenge protonic acids. These were mixed at -78° and warmed slowly to room temperature for a period. The crude product obtained after work-up appeared to be a mixture of the uncyclized olefin S-4 and the known ketone R-8b previously prepared by D. Walba, in a ratio of *ca.* 2:1. No enol ether S-3a was observed. It remains uncertain whether ketone R-8b was formed by quenching of the vinyl cation by hydroxyl from the alcohol substrate or by hydrolysis of the enol ether S-3 on work-up. Whatever the case, it would appear that the ether solvent is too basic and affords too much elimination product to be useful. A similar reaction was attempted under somewhat milder conditions in dimethyl ether (bp -24°) for 4 hr, but no reaction occurred to any significant extent.

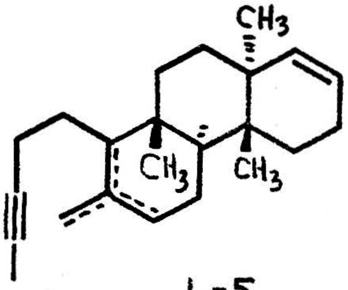
Peterson's work had shown that methylated acetylene J-4 cyclizes faster than the corresponding terminal acetylene J-1 (33). If the methylated acetylene in our A ring system would also cyclize faster, then perhaps less elimination would occur in using the borontrifluoride etherate/ethyl ether conditions on such a system. We decided to try the experiment shown in Chart T on the methylated acetylenic ether L-1, in hopes of getting principally cyclized product. A most important question to be answered, however, was whether ethyl ether would act analogously to trifluoroacetic acid and give five-membered ring enol ether T-1, or analogously to methylene chloride to give the six-membered ring enol ether T-2. The latter possibility would allow direct formation of the shionone A ring by hydrolysis.

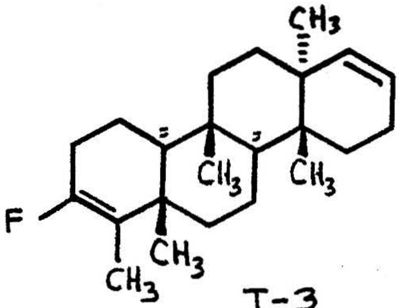
Acetylenic ether L-1 was treated with borontrifluoride etherate complex in ethyl ether; under mild conditions at -78° no reaction occurred, but under more vigorous conditions at room temperature all of the starting ether was consumed. Instead of the desired enol ether T-2 or ketone G-8a, the main product from this reaction appears to have been the previously isolated ketone L-6. The crude product seems to contain about half this ketone, with the remainder of the material consisting of two very nonpolar compounds by tlc. Not enough material was present to separate these, but one was probably olefin mixture L-5 analogous to the uncyclized material S-4. The other might have been vinyl fluoride T-3, as vinyl cations have been shown to trap fluoride from borontrifluoride etherate (51).

Whether the oxygen function in ketone L-6 came from the ethereal solvent or from the ether oxygen present in starting material L-1 remained unclear. Acetylenic ether L-1 was then treated with borontrifluoride etherate complex in methylene chloride for 30 min at -18°. This reaction afforded no enol ether or ketonic products, nor any start-

Chart T




L-5

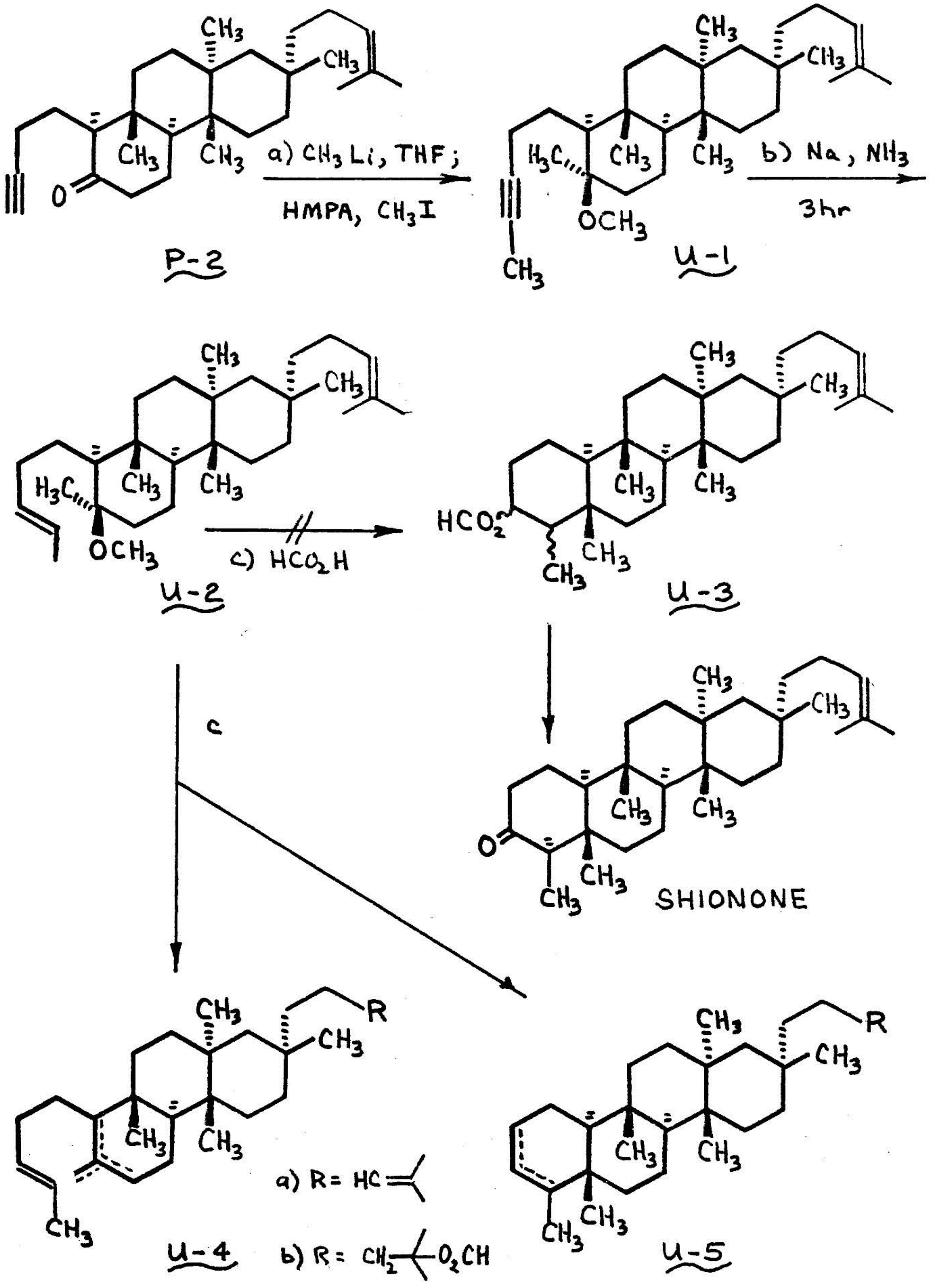

T-3

ing material; thus at least in methylene chloride the ether function from starting material is not quenching any vinyl cations produced. Only two nonpolar products were obtained having the same R_f on tlc as those from the ether reaction; again too little material was present to allow separation and identification of the products.

Our results at this point indicated that while the A ring enol trifluoroacetate could be made from P-3 (at the expense of the side chain), its conversion to the alkylated species was not the trivial matter we had expected. The use of other cyclization conditions on non-methylated acetylenes to generate enol formates or enol ethers gave considerable elimination products; thus we could not generate appropriate species to allow introduction of the C-4 methyl group. When methylated acetylenes were cyclized, five-membered ring products occurred. As a logical modification of this last scheme, cyclization of a methylated olefin was attempted next as outlined in Chart U. Since the intermediate cyclized cation should not have the preference for linearity exhibited by vinyl cations, we hoped to obtain six-membered ring products such as formate ester U-3.

Acetylenic ketone P-2 in tetrahydrofuran was treated with excess methyllithium, and then HMPA and excess methyl iodide were added sequentially. The single clean product from the reaction was methylated acetylenic ether U-1. Reduction of the acetylene with sodium in ammonia afforded the diolefinic ether U-2, which it was hoped would cyclize in formic acid to formate ester U-3. If the side chain could be maintained intact, hydrolysis and then oxidation of ester U-3 would afford shionone;

Chart U



P-2
a) CH3Li, THF;
HMPA, CH3I
U-1
b) Na, NH3
3hr
U-2
c) HCO2H
U-3
c
SHIONONE
U-4
a) R= HC=
b) R= CH2—O2CH
U-5

if the side chain did add acid, then a final dehydration step would be necessary as well. Under a variety of cyclization conditions employing formic acid or trifluoroacetic acid, the desired ester U-3 could not be formed. The products at low temperature appeared to be principally olefins, probably either U-4a or U-5a, with only small amounts of any ester products. At room temperature and with prolonged reaction times, significant addition of acid to the side chain olefin occurred (e.g. U-4b and U-5b), but hydrolysis of the esters afforded no secondary alcohols (A ring hydroxyl) for oxidation to shionone hydrate.

While it has not been possible through the efforts described above to effect the total synthesis of shionone, much has been accomplished towards the final realization of that goal. Most importantly a high yield, stereospecific method has been developed for introduction of the side chain. By means of the Vilsmeir reaction/reductive alkylation procedure, the methylated aldehyde M-3 has been arrived at in two steps from key intermediate C-7; six steps are required for the parallel transformation to aldehyde G-14 using previously established procedures. Such a reductive alkylation of a Vilsmeir reaction product has never before been performed; these efforts provide the first demonstration of the feasibility and utility of this useful and interesting process.

Completion of the shionone side chain from aldehyde M-3 has been accomplished in three high-yield steps. This compares most favorably with recorded syntheses of similar side chains in other systems which generally proceed in more steps and in lower yield (52). Such is the case even though intermediate M-3 possesses an unfavorable 1,3-diaxial steric interaction between the C-12a methyl group and the axial aldehyde function. An important feature of this sequence for the shionone problem is that it can be readily interrupted once the saturated aldehyde **N-4** has been reached. Protection of this aldehyde or the corresponding alcohol **42** would allow delay in introducing the side chain olefin until after completion of manipulations elsewhere in the molecule. Such flexibility is quite valuable in view of the extreme acid sensitivity of the double bond which has become apparent during these efforts.

Another significant accomplishment of this work, one which may still prove applicable to the synthesis of shionone, was elucidation of the cyclization route to enol trifluoroacetate **K-4**. Essentially what this route demonstrates is a new and highly stereospecific procedure for methylation of enones such as **G-2**; the new methyl group is introduced at the A-B ring juncture, β to the carbonyl, such that it becomes 1,3-diaxially disposed to the angular methyl group already present at the B-C ring juncture. This method could prove generally valuable for the synthesis of certain polycyclic ring systems, and complements nicely the efforts described in the second part of this thesis. In this latter work, a method has been developed for substituting similar A-B ring junctures at the position γ to the carbonyl; both methods employ the Eschenmoser cleavage reaction of epoxyketones, in parallel yet different schemes.

The acid cyclization sequence described above potentially could accomplish still more than the stereospecific introduction of a methyl group to such A-B ring junctures. The enol trifluoroacetate **K-4** can be isolated from the cyclization, and the enol trifluoroacetate function preserves what is the thermodynamically and kinetically less favored direction of enolization of the A ring ketone. It remains for future study to determine whether such a trapped enolate can be effectively utilized to introduce substitution at the otherwise difficultly accessible position α to the ring juncture. For the shionone synthesis, this could provide for introduction of the C-4 methyl group; regardless of the feasibility of this scheme, however, the cyclization procedure has been shown to introduce the required axial methyl group at the C-5 position of the shionone and friedelin type A rings.

A number of alternative cyclization procedures have also been examined for forming the shionone A ring from acetylenic or olefinic intermediates such as **P-3** or **U-2**. These studies have excluded certain possible cyclization conditions, and in doing so have uncovered some interesting results concerning the cationic cyclization of the acetylenic intermediates.

The efforts described above have served to overcome several difficult problems in the total synthesis of shionone, through the novel application and adaptation of certain reactions in new synthetic sequences. Knowledge has been gained in attempting to apply these sequences in an actual shionone synthesis, and what has thus been learned should serve to guide future attempts at the construction of this molecule.

Experimental Section

All reactions were run under an argon atmosphere unless otherwise noted. Melting points labeled (vac) were taken in evacuated capillaries on a Hoover capillary melting point apparatus, while all others were determined on a Kofler micro hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared spectra (ir) were taken on a Perkin Elmer 237B grating infrared spectrometer. Nuclear magnetic resonance spectra (nmr) were taken on a Varian Associates Model T-60. Ultraviolet spectra (uv) were taken on a Cary recording spectrometer, Model 11M.

Alumina refers to grade I, neutral alumina supplied by M. Woelm, Eschwege, Germany, made up to grade II or III as indicated by addition of 3% or 6% water with shaking and equilibration prior to use. Ordinary silica gel columns used the 0.05-0.2 mm silica gel "for column chromatography" manufactured by E. Merck, Darmstadt, Germany. High pressure silica gel chromatography used the Silica Gel H "For TLC Acc. To Stahl" manufactured by E. Merck, Darmstadt, Germany.

Anhydrous solvents were dried immediately prior to use. Ether, tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from lithium aluminum hydride; *tert*-butyl alcohol and pyridine were distilled from calcium hydride; hexamethylphosphoramide (HMPA) was distilled at reduced pressure from calcium hydride; ammonia was distilled from a blue lithium or sodium solution; and methylene chloride and methylene iodide were distilled from phosphorous pentoxide. Petroleum ether refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30-60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J. and was not further purified. When anhydrous solvents were required in amounts less than *ca.* 200 ml, especially in small volumes at different intervals throughout a reaction, it was found most convenient and time saving to distill them through the specially designed solvent drier described in the Appendix.

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

3-(m-Methoxyphenyl)-1-propanol (H-2).

To a rapidly stirred suspension of 52 g (1.38 moles) of lithium aluminum hydride in 640 ml of dry ether, a solution of 100 g (0.56 mole) of m-methoxycinnamic acid (H-1) in 400 ml of dry THF was added over a 2-hr period so as to maintain gentle reflux. The stirred mixture was heated at reflux for an additional 2 hr, cooled in an ice bath, and carefully treated with 50 ml of 95% ethyl alcohol to destroy excess lithium aluminum hydride. This suspension was poured onto 100 ml of concentrated sulfuric acid and 1.5 kg of ice, and the aqueous phase was separated and extracted with ether (six 500-ml portions). The combined organic phases were washed with 5% aqueous sodium hydroxide solution (two 150-ml portions) and saturated brine (150 ml), and then dried (Na_2SO_4). Upon removal of the drying agent and concentration at reduced pressure there was obtained 85 g of a yellow oil, which on distillation afforded 56.8 g (61%) of the alcohol H-2 as a nearly colorless liquid, bp 98-106° (0.1 mm); ir (neat) 3330 (OH), 1600, 1585, 1490 (aromatic), and 1260, 1150, 1035 cm^{-1} ($ArOCH_3$).

1-Chloro-3-(m-methoxyphenyl)-propane (H-3).

A. From the alcohol H-2.

The procedure of A. Cohen was employed (53). To a stirred and ice cooled solution of 56.8 g (0.342 mole) of the alcohol H-2 in 40 ml of N,N-dimethylaniline was added dropwise over a period of 20 min 26.5 ml (0.37 mole) of freshly distilled thionyl chloride. After stirring for an additional 30 min with ice cooling, the mixture was heated at 100°

for 15 min, and then cooled and treated with 200 ml of 10% hydrochloric acid and 100 ml of saturated brine. This mixture was extracted with five 150-ml portions of ether, and the combined organic phases were washed with 5% aqueous sodium hydroxide solution (two 100-ml portions) and water (two 100-ml portions), and then dried ($MgSO_4$). After removal of the drying agent, concentration of the solution at reduced pressure left 63.8 g of a brown liquid, which on distillation afforded 58.6 g (93%) of the chloride **H-3** as a yellow liquid; bp 82-87° (0.15 mm); ir (neat) 1600, 1585, 1490 (aromatic), and 1265, 1150, 1040 cm^{-1} (ArOMe).

B. From m-Methoxycinnamic acid (H-1).

To a rapidly stirred suspension of 200 g (5.27 moles) of lithium aluminum hydride in 2 l. of dry ether was added over a 4-hr period a solution of 400 g (2.25 moles) of m-methoxycinnamic acid (**H-1**) in 1.2 l. of dry THF at a rate such that moderately vigorous reflux was maintained. With continued stirring, the mixture was heated at reflux for another 6 hr, cooled with an ice bath, and cautiously treated with 500 ml of ethyl acetate followed by 500 ml of water. The resulting suspension was poured onto a mixture of 500 ml of concentrated sulfuric acid and 3 kg of ice, and the aqueous phase separated and extracted with 25% ether-methylene chloride (three 1-l. portions). The combined organic phases were washed with 5% aqueous sodium hydroxide solution (1 l.), water (1 l.), and saturated brine (two 1-l. portions), and then dried (Na_2SO_4). Removal of the drying agent and evaporation of solvent at reduced pressure left crude alcohol **H-2** as a pale yellow oil.

To a stirred solution of the entire crude alcohol **H-2** in 300 ml of ice cooled N,N-dimethylaniline was added over a 1-hr period 300 ml (480 g, 4.04 moles) of thionyl chloride. After stirring with cooling for an additional 3 hr, the red solution was heated on a steam bath at gentle reflux for 25 min until evolution of sulfur dioxide ceased. The reaction mixture was cooled, treated with 2 l. of 10% hydrochloric acid and 1 l. of water, and then extracted with ether (two 1-l. portions) and 25% ether-methylene chloride (two 1-l. portions). The combined organic extracts were washed with 5% hydrochloric acid (1 l.), 5% aqueous sodium hydroxide solution (two 1-l. portions), and saturated brine (two 1-l. portions), and then dried (Na_2SO_4). After removal of the drying agent and distillation of the solvent through a Vigreaux column, a dark oil was obtained which on distillation afforded 377.4 g (79%) of the chloride **H-3** as a yellow liquid, bp 83-118° (0.5-0.75 mm); ir (neat) identical to that of product from part A.

6-(m-Methoxyphenyl)-1-hexen-3-ol (H-4).

In an oven dried apparatus was placed 6.36 g (0.262 mole) of magnesium turnings and 15 ml of dry ether. This mixture was stirred and treated with about 6 ml of a solution of 43.8 g (0.237 mole) of the chloride **H-3** in 35 ml of dry ether. A drop of iodomethane was added to initiate the reaction, and once vigorous reflux had begun, 150 ml of dry ether was added over a 5-min period so as to maintain a moderate rate of reflux. The remainder of the chloride solution was then added over a 15-min period to maintain reflux, which was continued for an additional 2 hr by external heating. This mixture was chilled in an ice bath, and a solution of 17.4 ml (0.262 mole) of freshly distilled acrolein in 30 ml of dry ether was added with rapid stirring over a 30-min period. After continued stirring for 30 min without cooling, the mixture was poured onto 500 ml of ice and water, and 200 ml of saturated aqueous ammonium chloride solution was added. The aqueous layer was separated and extracted with ether (four 300-ml portions), and the combined organic phases were washed with water (300 ml), saturated aqueous sodium bicarbonate solution (two 300-ml portions), and saturated brine (300 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent under reduced pressure, the green liquid residue was distilled from a trace of barium oxide. After a forerun of 0.92 g, bp 39-40° (0.15 mm) there was obtained 41.0 g (84%) of the alcohol H-4 as a greenish liquid, bp 111-115° (0.07 mm); ir (neat) 3360 (OH), 1640 (C=C), 1600, 1585, 1490 (aromatic), and 1260, 1150, 1040 cm^{-1} (ArOMe). This alcohol, if protected from traces of acid, is stable for months when stored at -25°.

6-(m-Methoxyphenyl)-1-hexen-3-one (H-5).

A solution of 5.40 g (26.2 mmoles) of the allylic alcohol H-4 in 50 ml of dry methylene chloride was added all at once to a vigorously stirred solution of 44.4 g (170 mmoles) of chromium trioxide dipyridine complex (54) in 600 ml of dry methylene chloride. After stirring for 15 min, the dark solution was filtered with the aid of suction through 250 g of grade II alumina on a Buchner funnel; 300 ml of methylene chloride was used to rinse well the dark residue in the reaction flask and was then filtered through the alumina as well. The combined filtrates were concentrated under reduced pressure and dried at 0.05 mm pressure for one hour. In this manner 4.98 g (93%) of enone H-5 was obtained as a clear oil that smelled faintly of pyridine: ir (neat) 1675 (C=O), 1610 (C=C), 1600, 1580, 1485 (aromatic), and 1260, 1150, 1040 cm^{-1} ($ArOCH_3$).

5-(2′-m-Methoxyphenyl)-8aα-methyl-3,4,8,8a-tetrahydronaphthalene-1,6 (2H,7H)-dione (H-7).

A solution of 4.98 g (24.2 mmoles) of freshly prepared, crude vinyl ketone H-5 and 2.86 g (22.7 mmoles) of 2-methyldihydroresorcinol in 125 ml of methanol was treated with 1.4 ml of triethylamine and stirred at room temperature for 23 hr. Concentration of this solution at reduced pressure afforded crude trione H-6 as a brownish oil; ir (neat) 1725, 1715, 1695 (C=O), 1600, 1580, 1485 (aromatic), and 1260, 1150 cm^{-1} ($ArOCH_3$).

According to the procedure of H. Smith and co-workers (27), the above trione H-6 was combined with 3.3 g of benzoic acid and 2.75 ml of triethylamine in 51 ml of xylene. After 10 ml of the xylene was distilled from this mixture into an empty Dean Stark water separator, the solution was heated at reflux through the separator for 24 hr. Upon cooling, the solution was diluted with 500 ml ether, washed with saturated aqueous sodium bicarbonate solution (five 100-ml portions), 2% hydrochloric acid (three 100-ml portions), and saturated brine (two 100-ml portions), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, the resulting brown oil (6.52 g) was distilled in vacuum. After removal of 150 mg of a forerun that boiled at 114-116° (0.01 mm), 4.30 g of the enedione H-7 bp 175-205° (0.01 mm) was collected. A small amount of sublimed 2-methyldihydroresorcinol which contaminated the product was removed by washing the distillate with acetone; removal of the acetone at reduced pressure then afforded 4.11 g (54%) of enedione H-7; ir (neat) 1710, 1665 (C=O), 1600, 1580, 1485 (aromatic), and 1260, 1150 cm^{-1} (ArOMe).

1α-Hydroxy-5-(2′-m-methoxyphenylethyl)-8aα-methyl-1,2,3,4,8,8a-hexahydronaphthalen-6(7H)-one (H-8).

Selective reduction of the enedione H-7 was accomplished using the procedure of H. Smith and co-workers (27). A rapidly stirred solution of 11.0 g (35.2 mmoles) of dione H-7 in 290 ml of absolute ethanol was chilled between zero and five degrees and treated dropwise with a solution of 2.0 g (53 mmoles) of sodium borohydride in 390 ml of absolute ethanol. The addition was done over a 20-min period at such a rate that the internal temperature remained below 5°. After stirring at the low temperature for an additional 10 min, the reaction was quenched by the cautious addition of 14 ml of acetic acid followed by 50 ml of water. This mixture was extracted with five 150-ml portions of ether, and the combined extracts were washed with 2% aqueous sodium hydroxide solution (three 150-ml portions) and water (two 150-ml portions), and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, a yellow oil was obtained which on crystallization from ether-hexane afforded in two crops 8.74 g (79%) of hydroxy enone H-8 as white crystals; ir ($CHCl_3$) 3605 (OH), 1655 (C=O), and 1600, 1580, 1485 cm^{-1} (aromatic).

1α-Hydroxy-5β-(2′-m-methoxyphenylethyl)-8aα-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-4aβ-carbonitrile (H-9) and 1α-Hydroxy-5α-(2′-m-methoxyphenylethyl)-8aα-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-4aα-carbonitrile (5).

According to the general procedure of Nagata and co-workers (17a, c, e), 140 ml (210 mmoles) of a 1.5 M solution of diethylaluminum cyanide in benzene was added in a slow stream over several minutes to a stirred, ice cooled solution of 21.9 g (69.8 mmoles) of the enone H-8 in 230 ml of dry benzene. After stirring for 2.5 hr without cooling, the mixture was poured with vigorous stirring onto 1 l. of 10% aqueous sodium hydroxide solution and 1 kg of ice. The solution was extracted with four 800-ml portions of methylene chloride, and the combined organic extracts were washed with 10% aqueous sodium hydroxide solution (500 ml) and water (two 500-ml portions), and then dried (Na_2SO_4). After removal of the drying agent and concentration of the solution under reduced pressure, the resulting gum was crystallized from ether-hexane and afforded 19.04 g (80%) of trans fused cyanide H-9 as white crystals, mp 115-121°. The analytical sample, obtained after two further crystallizations of a portion of this material from ether-hexane, melted at 122-125°; ir ($CHCl_3$) 3615, 3480 (OH), 2225 (C≡N), 1720 (C=O), 1600, 1585, 1490 (aromatic), and 1260, 1150, 1050 cm^{-1} (ArOMe); nmr

($CDCl_3$) δ 1.12 (s, 3, C-8a CH_3), 3.70 (m, 1, C-1 H), 3.80 (s, 3, Ar OCH_3), and 6.6-7.3 (m, 4, Ar H).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.96; H, 7.96; N, 4.06.

The mother liquors from the first crystallization were chromatographed on 1 kg of silica gel; elution with ether gave none of the desired compound in the first 4.5 l., but afforded 0.610 g of an oil in the next 1.5 l.. Crystallization of this oil from ether-hexane afforded 0.361 g of crystalline cyanide **H-9**, mp 119-122°; nmr ($CDCl_3$) identical with that of pure material. The total yield of the *trans* fused cyanoketone was thus 19.4 g (81.5%). Continued elution of the column with 1.75 l. of ether produced mixtures of the cyanide **H-9** and two other compounds, one of which finally eluted with an additional 2 l. of ether and amounted to 0.947 g of a yellowish oil. Attempted crystallization of this oil from ethanol-hexane afforded the *cis* fused cyanoketone **5** as an amorphous white precipitate which turned into a sticky gum on drying; ir ($CHCl_3$) 3620, 3500 (OH), 2250 (C≡N), 1720 (C=O), 1600, 1585, 1490 (aromatic), and 1260, 1150 cm^{-1} ($ArOCH_3$): nmr ($CDCl_3$) δ 1.18 (s, 3, C-8a CH_3), 3.80 (s, 3, Ar OCH_3), 4.0 (m, 1, C-1 H), and 6.6-7.3 (m, 4, Ar H).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.73; H, 7.97; N, 4.07.

1α-Hydroxy-5β-(2′-m-methoxyphenylethyl)-8aα-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-4aβ-carbonitrile ethylene acetal (H-10).

A stirred mixture of 423 mg (1.24 mmoles) of the cyanoketone H-9, 1 ml of ethylene glycol and 6 mg of p-toluenesulfonic acid in 20 ml of benzene was heated at reflux through a Dean Stark water separator. After 2.6 hr at reflux the mixture was cooled, washed with saturated aqueous sodium bicarbonate solution (three 50-ml portions) and water (five 50-ml portions), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 482 mg of a white gum was obtained. Purification of this material on ptlc (55) (80% ether-petroleum ether, double development) afforded 436 mg (91%) of the ketal H-10 as a clear glass (R_f 0.26); ir ($CHCl_3$) 3605, 3460 (OH), 2230 (C≡N), 1600, 1585, 1485 (aromatic), and 1150, 1100, 1050, 1040 cm^{-1} ($ArOCH_3$ and ketal); nmr ($CDCl_3$) δ 0.98 (s, 3, C-8a CH_3), 3.79, 3.7-4.2 [s and m, 8, Ar OCH_3, $-O-CHR_2$ and $-O-(CH_2)_2-O-$] and 6.6-7.5 (Ar H). This material was used directly in the next step without further purification.

Attempted reduction of the cyano ketal H-10 and hydrolysis of the intermediate immine to the aldehyde H-13.

The exact procedure of R. Czarny (29) was applied to cyano ketal H-10. To a stirred solution of 24.0 mg (0.0624 mmole) of the cyano ketal H-10 in 1.5 ml of dry benzene was added 0.146 ml (0.144 mmole) of a 0.98 M solution of diisobutylaluminum hydride in benzene. After stirring at room temperature for 2 hr this solution was poured onto 50 ml of ice-cold 5% aqueous sodium hydroxide solution. The resulting mixture was extracted with three 30 ml portions of methylene chloride, and the combined organic phases were washed with 25 ml of water and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 21 mg of crude imine H-11 as a white gum. The ir spectrum of this material showed a new peak at 1625 cm^{-1} (-C=NH), but still showed about 30-40% of the original nitrile absorption (2230 cm^{-1}).

To a stirred solution of this oil in 1.5 ml of THF and 1.5 ml of methanol was added 23.6 mg of sodium acetate, 0.19 ml of water and 0.06 ml of acetic acid. This solution was heated at reflux with stirring for 10 min, and then was poured onto 50 ml of ice-cold saturated sodium carbonate solution. The resulting mixture was stirred for ca. 5 min, and then extracted with three 30-ml portions of methylene chloride. The combined organic phases were washed with 25 ml of water and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 21 mg of a cloudy oil was obtained. The ir spectrum of this material was almost the same as that of the imine H-11 before hydrolysis, and showed only a very small peak at 1715 cm^{-1} (ca. 15% of full scale); since this result does not agree with that obtained by Czarny, his procedure was modified at this point.

The crude product was resubmitted to the same hydrolysis and work-up conditions described above, except that reflux was maintained for 1 hr. The ir spectrum of the 20 mg of resulting oil showed a greatly diminished band at 1625 cm^{-1} (-C=NH, ca. 25% original intensity) yet still only a small carbonyl absorption at 1715 cm^{-1} (ca. 30% of a full scale peak). In the nmr spectrum, the integral of that portion of the

3.7-4.2 multiplet downfield of 3.86 $(-O-(CH_2)_2-O-)$ had dropped with respect to the integral of the total multiplet, as compared with the corresponding integrals for starting cyano ketal H-10. These data are most consistent with a product resulting from little hydrolysis of the imine but some hydrolysis of the ketal function.

$1\alpha,6\beta$-Dihydroxy-5β-(2′-m-methoxyphenylethyl)-$6\alpha,8a\alpha$-dimethyl-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-$4a\beta$-carbonitrile (I-1).

Methylmagnesium iodide solution was prepared by adding 8.78 ml (20 g, 140 mmoles) of iodomethane in 80 ml of dry ether to a stirred suspension of 3.75 g (0.154 mole) of magnesium turnings in 10 ml of dry ether. The addition was performed over the course of 30 min so as to maintain vigorous reflux, and the solution was then cooled. A 50 ml portion of this mixture was added dropwise with ice cooling to a stirred solution of 4.80 g (14.05 mmoles) of ketonitrile H-9 in 30 ml of dry benzene and 70 ml of dry ether. The white suspension which formed was stirred for 1 hr at room temperature, poured onto a mixture of 150 ml of saturated aqueous ammonium chloride solution and 100 g of ice, and extracted with six 100 ml portions of chloroform. The combined extracts were washed with water (200 ml) and saturated brine (two 200-ml portions), and then dried ($MgSO_4$); after removal of the dessicant and evaporation of the solvent under reduced pressure, 5.0 g of a white solid was obtained which showed significant ir absorption at 1720 cm^{-1} (C=O). This material was treated with the remaining 50 ml of the methylmagnesium iodide solution discussed above, under exactly the same reaction and work-up conditions described above and gave 4.75 g of a white solid. One recrystallization from ether-acetone afforded 4.02 g (80%) of crystalline diol I-1, mp 170-173°. The analytical sample obtained after two further crystallizations of a sample of this material from the same solvent system, melted at 175-178°; ir ($CHCl_3$) 3610, 3460 (OH), 2220 (-C≡N), 1600, 1585, 1485 (aromatic), and 1150, 1040 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.93 (s, 3, C-8a CH_3), 1.13 (s, 3, C-6 CH_3), 3.80 (s, 3, Ar OCH_3), 3.82 (m, 1, C-1 H), and 6.6-7.3 (m, 4, Ar H).

Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.82; H, 8.69; N, 3.81.

This product is sensitive to strong or prolonged acidic conditions, which should be avoided during work-up and handling.

1α-Acetoxy-6β-hydroxy-5β-(2′-m-methoxyphenyl)-6α,8aα-dimethyl-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-4aβ-carbonitrile (I-2).

To a stirred solution of 200 mg (0.56 mmole) of cyano diol I-1 in 4 ml of pyridine at room temperature was added 0.8 ml (86 mg, 8.4 mmoles) of acetic anhydride. After stirring for 22 hr, the reaction mixture was diluted with 250 ml of ether and 100 ml of ethyl acetate. This solution was washed with water (100 ml), saturated aqueous sodium bicarbonate solution (100 ml), and saturated brine (two 75-ml portions), and then dried (Na_2SO_4). Following removal of the drying agent and evaporation of the solvent at reduced pressure, there remained 249 mg of a sticky white solid which was crystallized from ethyl acetate-chloroform and afforded 167 mg (75%) of the acetate I-2 as fine white crystals, mp 159-164°. Two additional crystallizations of a portion of this material from the same solvent system provided the analytical sample which melted at 163-165°; ir ($CHCl_3$) 3600 (OH), 2225 (C≡N), 1725 (acetate C=O), 1600, 1585, 1485 (aromatic), and 1150, 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 1.02 (s, 3, C-8a CH_3), 1.12 (s, 3, C-6 CH_3), 2.03 (s, 3, $COCH_3$), 3.80 (s, 3, Ar OCH_3), 5.1 (m, 1, C-1 H), and 6.7-7.4 (m, 4, aromatic).

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.22; H, 8.22; N, 3.48.

1α-Acetoxy-5β-(2′-m-methoxyphenylethyl)-6,8aα-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4aβ-carbonitrile (I-3).

A. From pure cyano alcohol I-2.

To a stirred solution of 167 mg (0.418 mmole) of the cyano alcohol I-2 in 3.5 ml of dry pyridine at -10° was added dropwise over a 2-min period 0.15 ml (2.1 mmoles) of thionyl chloride. The solution was then stirred for 75 min with the temperature maintained between 0° and -10°, and then for 30 min without cooling. The mixture was diluted with 100 ml of ether and 100 ml of ethyl acetate, and the resulting solution was washed with water (two 50-ml portions) and saturated brine (two 50-ml portions), and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 157 mg of an oil which on purification by ptlc (55) (50% ether-petroleum ether, single development) afforded 145 mg (91%) of the mixture of olefins I-3 as a gum (R_f 0.34); ir ($CHCl_3$) 2220 (C≡N), 1735 (acetate C=O), 1600, 1585, 1490 (aromatic), and 1150, 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.95, 1.08 (two singlets, 3, C-8a CH_3, ratio ca. 4:1), 1.62 (s, 3, C-6 CH_3), 2.04 (s, 3, $COCH_3$), 3.80 (s, 3, Ar OCH_3), 5.0 (m, 1, C-1 H), 5.41 (m, ca. 0.2, C-7 H of Δ^6 olefin component), and 6.7-7.4 (m, 4, Ar H). A portion of this gum was crystallized once from ethanol to afford the analytical sample which melted at 89-108°; ir and nmr were the same as those of chromatographed material.

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.64; H, 8.21; N, 3.66.

B. From the cyano ketone H-9 without purification of intermediates.

A solution of 88 ml (200 g, 1.41 moles) of iodomethane in 800 ml of dry ether was added over the course of 90 min to a stirred mixture of 40.5 g (1.67 moles) of magnesium turnings in 130 ml of dry ether so as to initiate and maintain vigorous reflux. This mixture was cooled with an ice bath, and a solution of 51 g (0.15 mole) of the cyano ketone H-9 (dissolved with mild heating) in 900 ml of benzene was added over a 50-min period. Stirring and cooling were continued for an additional 45 min, and the solution was then carefully treated with 40 ml of saturated aqueous ammonium chloride solution. This mixture was poured onto 2.0 l. of ice and saturated aqueous ammonium chloride solution, and the resulting aqueous solution was extracted first with one liter of methylene chloride, and then with four 600-ml portions. The combined organic phases were washed with 500 ml of water and dried (Na_2SO_4). After removal of the drying agent, the solvents were evaporated at reduced pressure and 51.6 g of solid cyano diol I-1 remained.

A solution of 51.6 g of this crude diol I-1 in one liter of dry pyridine was treated with 385 ml of acetic anhydride and stirred at room temperature for 22 hr. The mixture was diluted with 2.0 l. of ethyl acetate and 1.5 l. of ether and the resulting solution was washed with water (two 750-ml portions), saturated aqueous sodium bicarbonate solution (four 500-ml portions), water (750 ml), and saturated brine (500 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 57 g of solid hydroxy acetate I-2.

This crude alcohol I-2 (57 g) was then dissolved in 1.1 l. of dry pyridine, and the solution was chilled with an ice bath. To this solution 61 ml (102 g, 0.856 mole) of thionyl chloride was then added dropwise with stirring over a 30-min period. The solution was stirred at 0° for an additional 75 min, and then without cooling for 45 min. This mixture was then diluted with 1 l. of benzene, 1 l. of ethyl acetate and 1.5 l. of ether, and poured onto 500 ml of ice and water. The organic layer was separated, washed with ice-cold 10% hydrochloric acid (four 1-l. portions), 5% aqueous sodium hydroxide solution (1 l.), and water (two 1-l. portions) and then dried ($MgSO_4$). After removal of the drying agent and concentration of the solution at reduced pressure, 55.6 g of brown oil was obtained which on crystallization from ethanol afforded 42.2 g (74%) of olefin mixture I-3 as slightly brown crystals; ir and nmr spectra are identical with those of pure material. The mother liquors were chromatographed on 2 kg of silica gel. Elution with 4 l. of 70% ether-petroleum ether gave 700 mg of material that lacked the 2220 cm^{-1} ($C\equiv N$) absorption in the ir. Continued elution with 3 l. of the same solvent system afforded 8.83 g (16.2%) of the desired cyano acetate I-3 as an oil. The ir spectrum of this material was almost identical with the spectrum of the crystalline cyano acetate except for a slightly diminished nitrile absorption (2220 cm^{-1}).

The combined yield of the olefin mixture I-3 from crystallization and chromatography was 51.03 g (89.6% from cyano ketone H-9).

5β-(2′-m-Methoxyphenylethyl)-4aβ,6,8aα-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphth-1α-ol (I-5).

To a stirred solution of 14.0 g (36.7 mmoles) of crystalline cyano acetate I-3 in 560 ml of dry benzene at room temperature was added 92 ml (0.147 mole) of a 1.6 M benzene solution of diisobutylaluminum hydride. After stirring for 2.5 hr, the mixture was poured onto 1 l. of 10% aqueous potassium hydroxide solution and ice and extracted with four 700-ml portions of ether. The combined ethereal phases were washed with 10% aqueous potassium hydroxide solution (two 600-ml portions), water (two 600-ml portions), and saturated brine (600 ml), and then dried ($MgSO_4$). After removal of the dessicant and concentration of the solution under reduced pressure, there remained 12.9 g of crude hydroxy imine I-4 as a white foam; ir ($CHCl_3$) 3620 (OH), 1612 ($\overset{H}{\diagup}C{=}NH$), 1600, 1585, 1485 (aromatic), and 1260, 1150, 1040 cm^{-1} ($ArOCH_3$).

The entire crude product from above was combined in a 2 l., three-neck flask with 60 ml of 99% hydrazine hydrate and 17.6 g of hydrazine dihydrochloride in 540 ml of triethylene glycol. This mixture was heated with stirring for 5 hr at an internal temperature of 135°. A brisk argon stream was then passed into the flask and out through a distillation head for a period of 1.75 hr to remove the moisture and excess hydrazine. During the first 15 min, 116 g of 85% potassium hydroxide pellets was added portionwise, and during the last 1.5 hr the internal temperature was raised to 155°. The argon flow was then stopped (although an argon atmosphere was maintained), and stirring was continued for 5 hr with the internal temperature at 155°. The heating bath was then turned off but not removed, and the mixture was allowed to cool to room temperature over a 7-hr period. The resulting solid white mass was dissolved in 1.4 l. of water and extracted with four 800-ml portions of ether. The combined organic layers were washed with nine 800-ml portions of water, one 800-ml portion of brine, and dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 10.2 g of a white solid which on crystallization from ether-hexane gave 9.57 g (80%) of crystalline olefin mixture **I-5**; mp 92-103°. Two subsequent recrystallizations of olefin mixture **I-5** from ether-hexane afforded the analytical sample, mp 98-105°; ir ($CHCl_3$) 3610, 3450 (OH), 1600, 1585, 1485 (aromatic), 1370 (CH_3), and 1150 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.75, 0.90 (two singlets, 3, C-8a CH_3, ratio *ca.* 1:3), 0.82, 1.00 (two singlets, 3, C-4a CH_3, ratio *ca.* 1:3), 1.61 (s, C-6 CH_3), 3.7 (m, 1, C-1 H), 3.76 (s, 3, Ar OCH_3), 5.38 (m, *ca.* 0.25, C-7 H of Δ^6 olefin component), and 6.6-7.3 (m, 4, Ar H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.82.

When this same experiment was performed on the cyano olefin mixture **I-3** obtained as an oil from chromatography, the crude olefin mixture **I-5** was afforded as an oil in 81% yield; the ir spectrum of this material was the same as that of crude olefin mixture **I-5** obtained from crystalline starting material. No attempts at purification of this oil were made, but it was subsequently oxidized and cyclized with acceptable results (c.f. preparation of tetracyclic ketone **C-7**).

5β-(2′-m-Methoxyphenylethyl)-4aβ,6,8aα-trimethyl-3,4,4a,7,8,8a-hexahydronaphalen-1(2H)-one (I-6).

To a stirred and ice cooled solution of 269 mg (0.82 mmole) of the crystalline olefin mixture **I-5** in 30 ml of acetone was added dropwise over a 1-min period 2.5 ml of 8 N Jones reagent (56). After stirring at 0° for 10 min, the reaction mixture was quenched with 10 ml of 2-propanol and diluted with 100 ml of water. Most of the acetone was evaporated from the solution at reduced pressure, and the remaining liquid was extracted with four 80-ml portions of ether. The combined ethereal extracts were washed with water (two 100-ml portions) and saturated brine (two 200-ml portions), and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 277 mg of a yellow oil. A 254 mg portion of this oil, on purification on ptlc (55) (30% ether-petroleum ether, single development), afforded 237 mg (93%) of ketone **I-6** as a semicrystalline oil (R_f 0.40); ir ($CHCl_3$) 1700 (C=O), 1600, 1585, 1485 (aromatic), and 1260, 1150, 1040 cm^{-1} ($ArOCH_3$). The analytical sample, prepared by crystallization of a portion of this material from ether, melted at 68-93°; ir ($CHCl_3$) same as above; nmr ($CDCl_3$) δ 0.70, 0.98 (two singlets, 3, C-8a CH_3, ratio ca. 1:3), 1.65 (s, 3, C-6 CH_3), 3.82 (s, 3, Ar OCH_3), and 6.6-7.3 (m, 4, Ar H).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.02; H, 9.38.

8-Methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysen-1(2H)-one (C-7).

A. From crystalline olefinic alcohol mixture I-5.

A stirred and ice cooled solution of 12.49 g (38 mmoles) of crystalline olefinic alcohol I-5 in 850 ml of acetone was treated portionwise over a 5-min period with 19.0 ml (152 meq wts) of 8 N Jones reagent (56). After stirring for 10 min with cooling the solution was treated with 12 ml of 2-propanol and poured onto 1.8 l. of water. This mixture was extracted with four 1-l. portions of ether, and the combined organic phases were washed with saturated aqueous sodium bicarbonate solution (two 800-ml portions) and saturated brine (700 ml), and then dried ($MgSO_4$). After removal of the dessicant and concentration of the solution at reduced pressure, there was obtained 12.0 g of ketone I-6 as a light brown solid.

1. Using refluxing trifluoroacetic acid.

The cyclization was performed using a slight modification of the procedure of J. Tilley (19g). An 11.5 g portion of crude keto-olefin I-6 was dissolved in 115 ml of trifluoroacetic acid, and the solution was heated at reflux with stirring for 3.5 hr. Analysis by vpc (57) of quenched aliquots from the reaction mixture showed that the peak corresponding to starting material (oven temperature 300°, ret. time 1.3 min) did not completely disappear until near the end of this period. The black mixture was cooled with an ice bath and diluted with 1 l. of ether and 1 l. of benzene. This solution was washed with water (two 500-ml portions), 10% aqueous sodium hydroxide solution (two 400-ml portions) and saturated brine (500 ml), and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent under reduced pressure there was obtained 12 g of a brownish foam which after two crystallizations from ethanol afforded 7.6 g (64% from alcohol I-5) of tetracyclic ketone C-7 as light tan crystals, mp 149-151° (vac). The analytical sample, prepared by three crystallizations of this solid from ether, melted at 150-152° (vac); ir ($CHCl_3$) 1700 (C=O), 1605, 1575, 1500 (3,4-disubstituted anisole), and 1030 cm^{-1} (ArOMe); nmr ($CDCl_3$) δ 0.90 (s, 3, C-4a CH_3), 1.19, 1.22 (two singlets, 6, C-12a and C-10b CH_3's respectively), 3.77 (s, 3, Ar OCH_3), and 6.6-7.3 (m, 3, Ar H).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.89; H, 9.34.

The mother liquors from the ethanol crystallization, on analysis by vpc (57) (oven temperature 300°), exhibited two peaks with ret. times of 1.7 and 2.0 min, in a ratio of nearly 1:1. These peaks correspond in retention time to the *cis*-*anti*-*trans* fused tetracyclic ketone **15**, and the *trans*-*anti*-*trans* fused product **C-7** respectively (19e). When a portion of this mixture was dissolved in trifluoroacetic acid and heated at reflux for 48 hr, quenched aliquots from the dark solution showed the same peaks in unvaried ratio on analysis by vpc (same conditions as above).

2. Using trifluoroacetic acid at room temperature.

A solution of 34 mg (0.103 mmole) of the crude keto-olefin mixture **I-6** in 0.5 ml of trifluoroacetic acid was stirred at room temperature in a closed flask under air. Small aliquots were periodically removed, quenched with potassium carbonate in ether, and analyzed by vpc (57) (oven temperature 300°). That peak corresponding to pure starting material (ret. time 1.3 min) gradually decreased with time until it was no longer present after 10 days. Two new peaks appeared (ret. time 1.7 min and 2.0 min), corresponding to the *cis*-*anti*-*trans* fused isomer **15** and the desired *trans*-*anti*-*trans* product **C-7** respectively. After 2 days, both peaks had formed to an equal extent, but then the latter peak started increasing with respect to the former so that at the end of 10 days they were present in a ratio of *ca.* 85:15; this ratio remained unchanged after four more days of stirring, at which time the solution was diluted with 50 ml of ether. This mixture was washed with water (50 ml) and saturated aqueous sodium bicarbonate (two 20-ml portions), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 34 mg of a brown oil, the analysis of which by vpc (same conditions as above) was unchanged from that of the last aliquot before work-up; this also provided the same analysis by vpc (same conditions as above) as the crude product obtained from refluxing trifluoroacetic acid (part 1). After crystallization of this oil from ethanol, 21 mg (60% from the hydroxy olefin mixture **I-5**) of the ketone **C-7** was obtained as brown crystals, melting at 146-149° (vac).

B. From the crude noncrystalline olefin mixture I-5.

When crude, noncrystalline olefin mixture **I-5** was employed in this reaction sequence, and refluxing trifluoroacetic acid was used to effect cyclization, tetracyclic ketone **C-7**, mp 144-148° (vac), was obtained in 54% yield (from crude alcohol **I-5**).

6a,7-Epoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,6a,7,10,10aα,10b,11,12,12a-tetradecahydrochrysen-8(9H)-one (K-1).

To a stirred solution of 125 mg (0.419 mmole) of enone **G-2** (19f) in 10 ml of methanol at room temperature was added 1 ml (*ca.* 300 mg, 16 mmoles) of 30% aqueous hydrogen peroxide solution and 0.5 ml of 10% aqueous sodium hydroxide solution. After stirring under air for 1 hr, this cloudy mixture was diluted with 75 ml of ether and the resulting solution was shaken with 25 ml of saturated brine in 100 ml of water. The aqueous phase was separated and extracted with two 30-ml portions of ether, and the combined organic phases were washed with two 30-ml portions of saturated brine and dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, there was obtained 126.4 mg of semi-crystalline material. Purification of this material on ptlc (55) (30% ether-petroleum ether, single development) afforded 108.4 mg (82.5%) of the epoxyketone **K-1** as a white solid (R_f 0.45); mp 98-100° (vac). The analytical sample obtained from two crystallizations of this solid from methanol-methylene chloride melted at 102.5-103.5° (vac); ir ($CHCl_3$) 1700 (C=O), 1450 ($-CH_2-$), and 1385 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.82, 0.87, 1.05 (3 singlets, 9, C-4a, C-10b, and C-12a CH_3's), 3.16 (s, 1, C-7 H), and 5.49 (s, 2, $H\text{-}C{=}C\text{-}H$).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.44; H, 9.69.

1α-(3′-Butynyl)-4bα,8aβ,10aα-trimethyl-3,4,4aβ,4b,5,6,8a,9,10,10a-decahydrophenanthren-2(1H)-one (K-2).

A slight modification of the general procedure of Eschenmoser and co-workers (32b, c) was employed in this reaction. To a dry mixture of 77.0 mg (0.244 mmole) of the epoxyketone **K-1** and 48.8 mg (0.261 mmole) of *p*-toluenesulfonylhydrazine at -20° was added with stirring and swirling 1.5 ml of -20° acetic acid-methylene chloride (1:1). After stirring for 5 min at -20°, the solution was stored in a -20° freezer for 15 hr. The mixture was then stirred at room temperature for an additional 4 hr (during which time it turned red) and was then diluted with 150 ml of ether. The resulting solution was washed with 5% aqueous sodium hydroxide solution (two 30-ml portions), water (30 ml), and saturated brine (two 30-ml portions), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, 81 mg of a yellow gum was obtained. Purification of this material on ptlc (55)

(30% ether-petroleum ether, single development) afforded 50.5 mg (69.2%) of the acetylenic ketone K-2 as a yellow oil (R_f 0.48) which was suitable for analysis; ir ($CHCl_3$) 3300 (acetylenic C-H), 2120 ($-C{\equiv}C-$), 1700 (C=O) and 1390 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.77, 0.85, 1.13 (3 singlets, 3 each, C-4b, C-8a and C-10a CH_3's) and 5.49 (s, 2, H-C=C-H).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.25; H, 10.02.

1α-(3′-Butynyl)-2β,4bα,8aβ,10aα-tetramethyl-1,2,3,4,4aβ,4b,5,6,8a,9,10,10a-tetradecahydro-2α-phenanthrol (K-3).

To a stirred and ice cooled mixture of 0.36 ml (0.685 mmole) of 1.9 M ethereal methyllithium solution (Ventron Corp.) and 2.0 ml of dry ether was added over a 2-min period a solution of 19.0 mg, (0.0636 mmole) of the acetylenic ketone K-2 in 0.4 ml of dry ether. Two additional 0.4-ml portions of dry ether were used to help effect complete addition. After stirring for 10 min longer at 0°, and for 5 min without cooling, the reaction mixture was cautiously quenched with 0.5 ml of water and was then diluted with 100 ml of ether. This solution was washed with water (20 ml) and saturated brine (two 20-ml portions), and then dried ($MgSO_4$ and a trace of K_2CO_3). After removal of the drying agents and evaporation of the solvent at reduced pressure, 18.8 mg of a clear oil was obtained. Purification of this material on ptlc (55) (50% ether-petroleum ether) afforded 16.0 mg (80%) of the alcohol K-3 as a white solid, mp 84-88° (vac). The analytical sample obtained from two crystallizations of a portion of this material from ether-hexane melted at 91.0-92.5°(vac); ir ($CHCl_3$) 3600 (OH), 3300 (acetylenic C-H), 2115 (-C≡C-), and 1385, 1370 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.81 (s, 3), 1.00, 1.03 (2 singlets, 6), 1.17 (s, 3, C-2, C-4b, C-8a and C-10a CH_3's) and 5.45 (s, 2, HC=CH).

Anal. Calcd for $C_{22}H_{30}O$: C, 84.02; H, 10.90. Found: C, 84.01; H, 11.04.

4aβ,6aβ,10bβ,12aα-Tetramethyl-3,4,4a,4bα,5,6,6a,7,10,10aα,10b,11,12,12a-tetradecahydrochrysen-8(9H)-one (G-8b).

A modification of the procedure of Lansbury and DuBois (35) was developed to allow isolation of the intermediate enol trifluoroacetate. A mixture of 2.0 ml of trifluoroacetic acid and 0.6 ml of trifluoroacetic anhydride was cooled in a -18° bath; 1.6 ml of this cold solution was then added to 16.0 mg (0.508 mmole) of the acetylenic alcohol K-3 at -18°, and the mixture was stirred at this temperature for 20 min. Analysis by vpc (57) of a base quenched aliquot of this mixture withdrawn 15 min into this period showed almost no remaining starting material (oven temperature 250°, ret. time 1.2 min). At the end of 20 min, the pressure in the system was reduced with a vacuum pump, and the cooling bath was then removed to facilitate evaporation of the solvents. Most of the liquid was gone within 5 min, but the residual oil was dried at room temperature for 20 min at *ca.* 0.05 mm pressure. This oil was handled so as to avoid prolonged contact with moist air and appeared to be the desired enol trifluoroacetate K-4: ir ($CHCl_3$) 1790 (enol trifluoroacetate C=O), 1695 (enol trifluoroacetate C=C), 1385 (CH_3)

and 1220, 1170, 1140 cm^{-1} (R-O-C and CF_3); no remaining 3300 cm^{-1} (acetylenic C-H): nmr ($CDCl_3$) δ 0.81, 0.90, 1.04 (3 singlets, 3, 3 and 6, C-4a, C-6a, C-10b, and C-12a CH_3's), 5.28 (m, 1, CF_3CO_2-C=C-H) and 5.44 (s, 2, H-C=C-H); analysis by vpc (57) showed only one peak (oven temperature 250°, ret. time 1.2 min).

A solution of the crude enol trifluoroacetate K-4 described above in 1 ml of acetone and 1 ml of methanol was treated with 3 drops of water and stirred at room temperature for 50 min. Analysis of an aliquot from the reaction mixture at this point by vpc (57) showed two peaks (oven temperature 250°, ret. times 1.2 and 1.8 min) in a ratio of 3:2, the first having the same ret. time as the enol trifluoroacetate. To the stirred solution were then added 5 drops of 10% hydrochloric acid and 2 drops of water. An aliquot from the reaction mixture 25 min after this addition showed only the ret. time 1.8 min peak on vpc (250°). After neutralization of this solution with sodium bicarbonate and removal of most of the solvent under reduced pressure, the resulting residue was treated with 100 ml of ether. This mixture was washed with 20 ml of water and two 20 ml portions of saturated brine, and then dried ($MgSO_4$). Following removal of the dessicant and evaporation of the solvent at reduced pressure, 17.5 mg of a yellow solid was obtained. Purification of this material by ptlc (55) (6X20 cm plate, 40% ether-petroleum ether, single elution) afforded 14.7 mg (92%) of the known tetracyclic ketone G-8b as a white solid, mp 166-172° (vac); the ir and nmr spectra of this material were superimposable on those of purified ketone G-8b prepared by J. Tilley (19h). Crystallization of this solid from methylene chloride-hexane afforded white crystals, mp 170-174° (vac) [lit. (19h) mp 172-176° (vac)]; a mixture of these crystals with a sample of ketone **G-8b** from J. Tilley [mp 172-176° (vac)], melted at 170-174° (vac).

2β,4bα,8aβ,10aα-Tetramethyl-1α-(3′-pentynyl)-1,2,3,4,4aβ,4b,5,6,8a,9,10,10b-dodecahydro-2α-phenanthrol (L-2) and 2α-Methoxy-2β,4bα,8aβ,10aα-tetramethyl-1α-(3′-pentynyl)-1,2,3,4,4aβ,4b,5,6,8a,9,10,10b-dodecahydrophenanthrene (L-1).

A quantity of 0.101 *M* ethereal methyllithium solution was prepared by dilution of 0.56 ml (1.01 mmole) of a 1.8 *M* ethereal methyllithium solution (Ventron Corp.) to 10 ml with dry ether. To a stirred and ice cooled 2 ml portion of this solution was added a solution of 24.0 mg (0.0805 mmole) of the acetylenic ketone **K-2** in 0.4 ml of dry ether; two additional 0.4-ml portions of ether were used to help effect complete addition. After stirring at 0° for 10 min, the reaction mixture was allowed to stir without cooling for 20 hr. During this period the following additions were made to the reaction mixture: 7.6 μl (0.121 mmole) of dry iodomethane after 15 min; 1.5 ml of dry THF after 35 min; 15 μl (0.242 mmole) of dry iodomethane after 1 hr; 0.5 ml of 0.101 *M* ethereal methyllithium solution and then 0.1 ml of dry iodomethane after 2.5 hr; 0.5 ml of 0.101 *M* ethereal methyllithium solution after 7.5 hr; 1.0 ml of dry iodomethane and then 0.1 ml of 1.8 *M* ethereal methyllithium (Ventron Corp.) after 17.5 hr. It was not until the end of the 20 hr period that the peak corresponding to unmethylated acetylenic alcohol K-3 on analysis by vpc (57) (oven temperature 280°, ret. time 1.5 min) had completely disappeared. Following this prolonged course of events, the above mixture was diluted with 100 ml of ether, and the resulting solution was washed with two 25-ml portions of water and two 25-ml portions of brine and then dried (Na_2SO_4 with a trace of K_2CO_3). After removal of the drying agents and evaporation of the solvents at reduced pressure, 27.5 mg of a yellow oil was obtained which after purification on ptlc (55) (10X20 cm plate, 25% ether-petroleum ether, single development) afforded two compounds. There was obtained 16.0 mg (60%) of the desired alcohol L-2 (R_f 0.30) as a white solid; ir ($CHCl_3$) 3605 (OH) and 1390, 1375 cm^{-1} (CH_3); nmr ($CDCl_3$) 0.80, 0.97, 1.01, 1.14 (4 singlets, 3, 6 and 3), 1.77 (m, 3, $C\equiv C-CH_3$), 5.44 (s, 2, $H-C=C-H$). Also obtained was 6.0 mg (23%) of the methyl ether L-1 (R_f 0.70) as a yellow oil; ir ($CHCl_3$) 1390, 1375 (CH_3) and 1075 cm^{-1} ($R-O-CH_3$); nmr ($CDCl_3$) δ 0.79, 0.92, 1.01, 1.06 (4 singlets, 12, C-2, C-4b, C-8a and C-10a CH_3's), 1.74 (m, 3, $C\equiv C-CH_3$), 3.06 (s, 3, $ROCH_3$) and 5.41 (s, 2, $H-C=C-H$). These compounds were not purified further but were used directly in subsequent experiments.

In another experiment performed on very crude acetylenic ketone K-2, the reaction mixture was treated with about 20% its volume of HMPA just prior to addition of excess iodomethane. None of the alcohol L-2 was formed in this instance, and only the ether L-1 could be isolated. For a detailed description of this procedure used on the closely analogous acetylenic ketone P-2, see the preparation of acetylenic ether U-1.

5α,8β-Dimethylpregn-3-en-20-one (L-6).

A modification of the cyclization procedure of W. S. Johnson and co-workers (36) was employed in this reaction. A stirred solution of 16.0 mg (0.0485 mmole) of acetylenic alcohol L-2 in 10 ml of methylene chloride was cooled with a -18° bath and treated with 0.1 ml of trifluoroacetic acid. Stirring was continued at -18° for 25 min, during which time analysis by vpc (57) of sodium bicarbonate-water quenched aliquots showed only one peak (oven temperature 280°, ret. time 1.8 min); this peak has the same ret. time as the starting material and as the cyclized enol trifluoroacetate L-4. The above mixture was then stirred without cooling for 1.25 hr and subsequently diluted with 100 ml of ether. The resulting solution was washed with 5% aqueous sodium hydroxide solution (two 30-ml portions), water (30 ml) and saturated brine (30 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, there was obtained 20.3 mg of crude enol trifluoroacetate L-4 as a yellow oil; ir ($CHCl_3$) 1790 (enol trifluoroacetate C=O), 1700 (enol trifluoroacetate C=C), 1385, 1370 (CH_3), 1220, 1175, 1050 (trifluoroacetate R-O- and CF_3), and no 3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.81 (s, 3), 0.89, 0.93 (2 singlets, 3), 1.04 (s, 6, C-5, C-8, C-10 and C-13 CH_3's), 1.96 (m, $CH_3\text{-}\overset{//}{C}\text{-}O_2CCF_3$), and 5.46 (s, 2, H-C=C-H); analysis by vpc (57) showed four peaks (oven temperature 280°, ret. times 1.4, 1.8, 2.3 and 2.6 min) in a ratio of ca. 6:12:1:1, which was unchanged from that of a quenched aliquot from the reaction after 30 min at room temperature.

To a stirred solution of 20.3 mg of the crude trifluoroacetate

L-4 in 1 ml of methanol and 0.5 ml of ether was added 1 ml of 10% aqueous sodium hydroxide solution. After stirring at room temperature for 1 hr this mixture was diluted with 100 ml of ether, and the resulting solution was washed with water (100 ml) and saturated brine (two 100-ml portions), and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, there was obtained 18.2 mg of a yellow oil. Purification of this material on ptlc (55) (10X20 cm plate, 15% ether-petroleum ether, single elution) afforded 8 mg (47%) of the pregnenone L-6 as a white solid; ir ($CHCl_3$) 1695 (C=O) and 1387, 1360 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.71, 0.81, 0.89, 1.03 (4 singlets, 3 each, C-5, C-8, C-10, C-13 CH_3's), 2.08 [s, *ca.* 3, $CH_3(C{=}O)R$], and 5.45 (s, 2, HC=CH); analysis by vpc (57) showed only one peak (oven temperature 280°, ret. time 2.2 min).

From the ptlc described above, a very nonpolar fraction (R_f 0.70) containing 4.2 mg of an oil was obtained; analysis by vpc (57) showed one peak (oven temperature 280°, ret. time 1.4 min); ir ($CHCl_3$) 1387 (CH_3) with no 3400-3650 (OH) or 1790-1650 cm^{-1} (C=O); nmr ($CDCl_3$, noisy) δ 0.80, 0.88, 1.02, 1.26 (4 singlets, $R_3C{-}CH_3$'s) 1.69 [s (broad), ⫽—CH_3], 1.78 [m (obscure), $C{\equiv}C{-}CH_3$], 5.45 (s, HC=CH). These spectra are consistent with either olefinic chloride L-3 or acetylenic dehydration product L-5.

1-Chloro-8-methoxy-4aβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysene-2-carbaldehyde (M-2) and 1-Chloro-8-methoxy-4aβ,10bβ, 12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysene-2,9-

dicarbaldehyde (M-1).

A modification of the procedure of Moersch and Neuklis (37a) was employed in this experiment. Ice cooled phosphoryl chloride (12 ml, 20.1 g, 0.131 mole) was stirred and treated over a 1-min period with 13.6 ml (12.8 g, 0.176 mole) of dimethylformamide. After stirring for 30 min without cooling, the viscous solution of Vilsmeir reagent was added at room temperature to a stirred solution of 1.158 g (3.54 mmoles) of tetracyclic ketone C-7 in 24 ml of dimethylformamide. The stirred reaction mixture was then heated with a preheated, 60° oil bath for 6 hr so that the internal temperature rose to a constant 55-56°. After cooling with an ice bath, the solution was poured onto 350 g of ice and 40 ml of 40% aqueous sodium hydroxide solution, and the resulting mixture was extracted with four 50-ml portions of methylene chloride. The combined organic phases were washed with water (six 50-ml portions) and saturated brine (two 50-ml portions), and then dried ($MgSO_4$). After removal of the drying agent and concentration of the solution at reduced pressure, there was obtained 1.310 g of a yellow solid which was chromatographed on 200 g of silica gel in a high-pressure column. After elution with 400 ml of methylene chloride, concentration of the next 600 ml of eluent from the column at reduced pressure provided 854 mg (64.5%) of the chloro aldehyde M-2 as a white solid, mp 196-198° (vac). The analytical sample, obtained after crystallization of a portion of this material from acetone-methylene chloride-water, melted at 198.5-199° (vac); ir ($CHCl_3$) 2750 (weak, aldehyde C-H), 1665 (unsaturated aldehyde C=O), 1605, 1575, 1500 (aromatic), 1385 (CH_3), and 1150, 1040 cm^{-1} (ArOCH$_3$); nmr (CDCl$_3$) δ 0.92, 1.21 (2 singlets, 3 and 6, C-4a, C-10b and C-12a CH's), 3.77 (s, 3, Ar OCH$_3$), 6.6-7.3 (m, 3, Ar H), and 10.30 (s, 1, CHO).

Anal. Calcd for $C_{23}H_{29}O_2Cl$: C, 74.08; H, 7.84; Cl, 9.51. Found: C, 74.12; H, 7.96; Cl, 9.49.

No material was eluted from the column by an additional 350 ml of methylene chloride, but concentration at reduced pressure of the following 600 ml afforded 154 mg (13.3%) of starting ketone as a white solid; ir and nmr spectra are the same as those of a purified sample of ketone **C-7**. Further elution with 500 ml of 5% methanol ether gave 147 mg of a white solid, which on crystallization from acetone methylene chloride water afforded the dialdehyde **M-1**, mp 265-266° (vac, dec); ir (CHCl$_3$) 2770 (aldehyde C-H), 1670 (aldehyde C=O's), 1605, 1570, 1495 (aromatic), and 1150, 1055 cm^{-1} (ArOCH$_3$); nmr (CDCl$_3$) δ 0.92, 1.21 (2 singlets, 3 and 6, C-4a, C-10b and C-12a CH$_3$'s), 3.90 (s, 3, Ar OCH$_3$), 6.70 (s, 1, C-7 H), 7.80 (s, 1, C-10 H), 10.30 (s, 1, C-2 CHO), and 10.50 (s, 1, C-9 CHO).

Anal. Calcd for $C_{24}H_{29}O_3Cl$: C, 71.90; H, 7.29; Cl, 8.84. Found: C, 71.82; H, 7.24; Cl, 8.90.

The yield of the desired chloro aldehyde **M-2** based upon recovered starting material was 74.5%. In a similar experiment, in which the reaction mixture was heated with a 69° bath for 4.5 hr, the yield of purified aldehyde **M-2** (without recovery of starting material) was 71%.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-1,2,3,4,4a,4bα,5,6,10b,11,

12,12a-dodecahydrochrysene-2α-carbaldehyde (M-3).

A three-neck flask was fitted with a Dry Ice condenser, a reflux condenser, a non pressure-equalized dropping funnel, and a magnetic football stirring bar. The system was flushed with argon, and 7 cm (259 mg, 37.6 mg atms) of lithium wire was added in pieces ca. 1 cm long. After the Dry Ice condenser was charged, ca. 120 ml of dry ammonia was distilled in from a reservoir of blue lithium/ammonia solution and then 50 ml of dry THF was added. A solution of (253 mg, 0.678 mmole) of the chloro aldehyde M-2 and 128 μl (100 mg, 1.356 mmoles) of dry t-butyl alcohol in 60 ml of dry THF was placed in the dropping funnel which was then externally pressurized with ca. 2 psi of argon. This mixture was added dropwise over a 50-min period to the vigorously stirred lithium/ammonia solution. After an additional 15 min, portions of dry powdered sodium benzoate were added until the blue color faded. A hot air gun was used to heat the yellow-orange suspension as most of the ammonia was evaporated over a 30-min period through a mercury bubbler. A gentle argon stream was then passed in through the Dry Ice condenser and out through the reflux condenser (fitted with the mercury bubbler), and the mixture was heated to reflux with hot air over a 30-min period. The argon flow was halted (although an argon atmosphere was maintained) and 40 ml of dry THF was added. The reaction mixture was stirred with ice cooling, and was treated after 10 min with 5 ml (11.4 g, 80 mmoles) of iodomethane. The suspension turned white, and after stirring without cooling for 2 hr, the mixture was diluted to 200 ml with ether. This mixture was washed with water (two 50-ml portions), 10% hydrochloric acid (50 ml), saturated aqueous sodium bicarbonate solution (50 ml) and saturated brine (50 ml), and then dried ($MgSO_4$). Following removal of the drying agent and concentration of the solution under reduced pressure, 281 mg of a gummy solid was obtained. Purification of this material on ptlc (55) (15% ether-petroleum ether, developed twice) afforded 154.4 mg (64.4%) of the aldehyde M-3 as a slightly yellow solid (R_f 0.45); ir ($CHCl_3$) 2805, 2705 (aldehyde C-H), 1720 (C=O), 1605, 1575, 1500 (aromatic), 1385 (CH_3), and 1245, 1040 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.76 (s, 3, C-12a CH_3), 0.93, 1.00 (2 singlets, 3 each, C-2 and C-4a CH_3's), 1.21 (s, 3, C-10b CH_3), 3.76 (s, 3, Ar OCH_3), 6.6-7.3 (m, 3, Ar H) and 9.45 (s, 1, CHO). Crystallization of a portion of this material from ether-hexane provided the analytical sample which melted at 111-116° (vac, dec w/bubbling); ir and nmr were the same as those of chromatographed material.

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.43; H, 9.67.

While this reaction has been performed on a 600 mg portion of chloro aldehyde in 57% yield, some difficulty was encountered with the alkylation in reactions of more than one gram. The nmr spectra of these reaction products showed both the δ 9.31 aldehyde singlet of methylated product, and a δ 9.50 doublet corresponding to the aldehyde signal split by a C-2 H. Although the reason for this incomplete alkylation has not yet been uncovered, it may well be due to incomplete removal of ammonia. Upon addition of iodomethane this could lead to formation of methyl ammonium iodide, a proton source.

Another reduction was performed in a manner similar to that detailed above; however, one third of the above lithium concentration was used, twice the aldehyde concentration, and twice the addition rate of aldehyde. Chromatography of the product from this reaction afforded a polar solid material in 16% yield, believed to be the dimer mixture **31**; ir ($CHCl_3$) 3610, 3550 (OH), 1605, 1575, 1500 (aromatic), 1380 (CH_3), and 1150, 1040 cm^{-1} ($ArOCH_3$); no 1665 or 1720 cm^{-1} (C=O): nmr ($CDCl_3$) δ 0.76-0.96 (broad overlapping singlets, 6, C-4a and C-12a CH_3's of various diastereomers), 1.20 (s, 3, C-10b CH_3), 3.76 (s, 3, Ar OCH_3), 4.00 [s (broad), 1, $-O\overset{R}{\underset{R'}{-}}CH$], 5.66 [s (broad), 1, C-1 H], and 6.6-7.3 (m, 3, Ar H). No further attempts were made at purification or characterization of this material.

2α-Hydroxymethyl-8-methoxy-2β,4aβ,10bβ,12aα-tetramethyl-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (**M-4**).

To a stirred suspension of 110 mg (2.9 mmoles) of lithium aluminum hydride in 5 ml of dry THF was added over a 5-min period a solution of 143 mg (0.403 mmole) of the aldehyde **M-3** in 4 ml of dry THF. Three additional 1-ml wash portions of dry THF were used to effect complete transfer. After stirring for 2 hr at room temperature, the reaction mixture was cooled with an ice bath and cautiously quenched by the sequential addition of 0.11 ml of water, 0.11 ml of 10% aqueous sodium hydroxide solution, and 0.33 ml of water. The resulting suspension was filtered, with the aid of 100 ml of ether, and after concentration of the filtrate under reduced pressure, there was obtained 139.3 mg (97%)

of the alcohol M-4 as a white foam; ir ($CHCl_3$) 3625, 3470 (OH), 1608, 1575, 1495 (aromatic), and 1385 cm^{-1} (CH_3); no 1720 cm^{-1} (C=O): nmr ($CDCl_3$) δ 0.97, 1.00 (two singlets, 9, C-2, C-4a, and C-12a CH_3's; ca. ratio of peaks 2:1); 1.21 (s, 3, C-10b CH_3), 3.43, 3.55 (two singlets, 1 each, $-OCH_aH_b-$), 3.67 (s, 3, Ar OCH_3), and 6.6-7.3 (m, 3, Ar H). Crystallization from methanol of a portion of this material afforded the analytical sample, mp 123.5-125.5° (vac); ir and nmr were the same as those of the crude material above.

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.73; H, 10.25.

Methyltriphenoxyphosphonium iodide.

The procedure of Landauer and Rydon (58) was employed. A stirred solution of 12.4 g (39.6 mmoles) of triphenylphosphite was treated with 3.70 ml (8.4 g, 59.3 mmoles) of iodomethane, and heated at reflux with a 75° bath for 18 hr. The bath temperature was then raised to 88° for 5 hr and 95° for 13 hr. The heating bath was then turned off but not removed, and the entire system allowed to cool over the course of five hours. At this time 20 ml of dry ether was added (the product was protected from air and moisture at all times), and the heavy red oil induced to crystallize with some scratching. Following removal of the ether layer, the product was washed with five 20-ml portions of dry ether, and any remaining solvent was then evaporated at reduced pressure. In this manner 14.8 g (83%) of the iodide was obtained as a yellow solid. This dry material was stored under argon and was stable over a period of weeks; it was not purified further, but was used as such in all experiments.

Attempted conversion of alcohol M-4 to iodide M-5.

A. Using methyltriphenoxyphosphonium iodide in dimethylformamide.

A modification of the procedure of Verheyden and Moffatt (44) was employed. To a stirred dry mixture of 45 mg (0.126 mole) of crystalline alcohol M-4 and 114 mg (0.252 mole) of powdered methyltriphenoxyphosphonium iodide at room temperature was added 1.0 ml of dimethylformamide. After stirring for 90 min, this mixture was diluted with 70 ml of ether, and the resulting solution was washed with 5% aqueous sodium thiosulfate solution (two 25-ml portions), water (four 25-ml portions) and saturated brine (25 ml), and then dried ($MgSO_4$) for 5 min. Following removal of the dessicant and evaporation of the solvent at reduced pressure, 110 mg of an oil remained. Purification of this material on ptlc (55) (12X20 cm plate, 30% ether-petroleum ether, single development) afforded 35.5 mg (83%) of an oil (R_f 0.58), which showed four peaks on analysis by vpc (57) (oven temperature 300°; ret. times 1.3, 1.5, 1.6 and 1.7 min; peak ratios, 1:1:3:3); nmr ($CDCl_3$) showed about 20% of the δ 3.43 and 3.55 singlets characteristic of starting material and about 80% of one proton contained in multiplets between δ 4.6-5.6, but no significant peaks in the region around δ 3.2 ($-CH_2-I$).

In a repetition of this experiment, dimethylformamide which was freshly distilled from 4Å molecular sieves was used and the reaction mixture was stirred for only 1 hr. The results obtained in this case were the same as those described above, and consistent with a product mixture resulting from rearrangement and dehydration of the starting alcohol.

Dodecyl alcohol was submitted to the same conditions described above as a check on the reagents. The crude product obtained exhibited in its nmr spectrum none of the δ 3.62, J = 6 Hz triplet characteristic of starting material, but instead showed a prominent new triplet, δ 3.19, J = 6 Hz, indicative of the iodide.

B. Using methyltriphenoxyphosphonium iodide and sodium iodide in dimethylformamide.

A dry mixture of 14.7 mg (0.412 mmole) of the alcohol M-4, 40 mg (0.885 mmole) of methyltriphenoxyphosphonium iodide, and 50 mg (0.33 mmole) of sodium iodide was cooled in a -22° bath and treated with 0.5 ml of chilled dimethylformamide at -22°. The resultant suspension was stirred for 1 hr at -22°, 80 min at 0°, and 16 hr at room temperature. During these periods, aliquots were removed from the reaction mixture and analyzed by tlc (55) (40% ether-petroleum ether, single development) and vpc (57) (oven temperature 300°); both tests indicated no change from starting material (tlc R_f 0.20; ret. time on vpc 2.7 min) during the entire time. The reaction mixture was diluted with 70 ml of ether and the resulting solution washed with 5% aqueous sodium thiosulfate solution (25 ml), water (25 ml), and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the drying agent and concentration of the solution at reduced pressure, there was obtained 37 mg of a clear oil; nmr ($CDCl_3$) clearly shows the δ 3.43 and 3.55 singlets of starting alcohol, which only integrate to *ca.* 75% of one proton each; and a small amount of two new singlets, δ 3.17 and 3.25, which integrate to less than 20% of one proton each: tlc (55) (40% ether-petroleum ether, one development) shows only one significant spot which corresponds to starting material (R_f 0.20).

The reaction was repeated using twice as much methyltriphenoxyphosphonium iodide and half as much solvent, with stirring at room temperature for 24 hr. A clear oil was obtained after work-up which was the same as the crude product above, mostly starting material.

C. Using methyltriphenoxyphosphonium iodide in methylene chloride.

In a modification of the procedure of Landor and co-workers (59), a dry mixture of 19.7 mg (0.0552 mmole) of the alcohol **M-4** and 125 mg (0.276 mmole) of methyltriphenoxyphosphonium iodide was treated with 0.5 ml of methylene chloride. After stirring for 45 hr at room temperature, this mixture was diluted with 75 ml of ether and the resulting solution was washed with saturated aqueous sodium bicarbonate solution (25 ml), water (three 25-ml portions) and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 97 mg of an oil; nmr ($CDCl_3$) still showed the δ 3.43 and 3.55 singlets of starting material, with a one proton integral each. Purification of the oil by ptlc (55) (10X20 cm plate, 20% ether-petroleum ether, one development) afforded 11.5 mg (59%) of starting alcohol **M-4** (R_f 0.09); ir ($CHCl_3$)

identical with that of pure starting material.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(3′-oxo-1′-propenyl)-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (N-2).

The general procedure of Nagata and Hayase (30) was adapted for this work. A stirred suspension of 880 mg (21 mmoles) of 57% sodium hydride oil dispersion in 13.5 ml of dry THF was cooled with an ice bath and treated over a 5-min period with a solution of 5.46 g (21 mmoles) of diethyl-2-(cyclohexylimino)-ethylphosphonate in 25 ml of dry THF. The ice bath was removed for 10 min and then replaced for 5 min; a solution of 1.100 g (3.10 mmoles) of the aldehyde M-3 in 18 ml of dry THF was then added over a 1-min period, with the aid of two 2-ml portions of dry THF to effect complete addition. This stirred mixture was heated with a preheated 60° oil bath for 80 min, cooled with an ice bath, and then poured onto 150 ml of ice and water. The resulting mixture was extracted with three 200 ml portions of ether, and the combined ethereal phases were washed with 200 ml of saturated brine and dried ($MgSO_4$). After removal of the drying agent and concentration of the solution at reduced pressure, 6.3 g of a yellow-brown oil containing the aldimine N-1 was obtained.

Hydrolysis of the aldimine N-1 was accomplished by treatment of the 6.3 g of crude product from above in 150 ml of benzene with 500 ml of 1% aqueous oxalic acid solution. This two phase system was stirred at room temperature for 19 hr. The organic layer was separated and the aqueous layer was then extracted with three 200-ml portions of ether.

The combined organic phases were washed with 2% hydrochloric acid (200 ml), 2% aqueous sodium hydroxide solution (two 200-ml portions) and saturated brine (200 ml), and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, 1.64 g of a yellow oil was obtained. Purification of this oil on 200 g of silica gel in a high pressure column was accomplished by elution with 40% ether-petroleum ether. The second 200 ml of eluent from the column was concentrated at reduced pressure, and there was obtained 1.066 g (89%) of unsaturated aldehyde N-2 as a white solid; ir ($CHCl_3$) 2735 (aldehyde C-H), 1675 (C=O), 1625 (C=C), 1605, 1575, 1495 (aromatic), 1385 (CH_3), and 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.87, 1.04 (2 singlets, 3 and 6, C-2, C-4a and C-12a CH_3's), 1.21 (s, 3, C-10b CH_3), 3.76 (s, 3, Ar OCH_3), 6.05 (dd, 1, J = 16 and 7.5 Hz, C-2′ ⫽H), 6.6-7.3 (m, 4, Ar H and C-1′ ⫽H), and 9.52 (d, 1, J = 8 Hz CHO). This material was not purified further but was used directly in subsequent reactions.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(3′-oxopropyl)-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (N-4).

A. Using triethylsilane and tris-(triphenylphosphine)-rhodium chloride.

A modification of the procedure of Nagai and co-workers (45) was developed for reduction of the unsaturated aldehyde N-2. In 1.25 ml of stirred triethylsilane, 135 mg (0.355 mmole) of the aldehyde N-2 did not dissolve over a period of 5 min at room temperature. This mixture was treated with 0.67 ml of benzene to effect solution, and then 4.5 mg

(4.9 μmoles) of tris-(triphenylphosphine)-rhodium chloride was added. The stirred solution was heated with a 50° bath for 2.75 hr; during this time, two 2-mg (2.2 μmoles) portions of the rhodium catalyst were added after 1.25 and 2.0 hr of heating. After transfer of this solution to a larger flask using ca. 25 ml of ether, evaporation of the solvent at reduced pressure afforded a yellow oil which contained the silyl enol ether N-3. A solution of this oil in 5 ml of acetone was treated with 0.5 ml of 5% hydrochloric acid and stirred for 20 min at room temperature. Ether (100 ml) was added and the resulting solution was washed with water (two 25-ml portions), saturated aqueous sodium bicarbonate solution (25 ml), and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 200 mg of a semicrystalline yellow product was obtained. Purification of this material on ptlc (55) (35% ether-petroleum ether, single development) afforded 113 mg (83.3%) of the aldehyde N-4 as a white solid (R_f 0.42); ir ($CHCl_3$) 2735 (aldehyde C-H), 1720 (C=O), 1605, 1575, 1495 (aromatic), 1380 (CH_3) and 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.90, 1.00, 1.05 (3 singlets, 9, C-2, C-4a and C-12a CH_3's), 1.22 (s, 3, C-10b CH_3), 3.77 (s, 3, Ar OCH_3), 6.6-7.3 (m, 3, Ar H) and 9.80 (m, 1, CHO). This material was not purified further but was used directly in subsequent reactions.

B. Using lithium in ammonia.

A solution of 1.35 cm (50 mg, 7.25 mmoles) of lithium wire in ca. 25 ml of dry ammonia and 10 ml of dry THF was prepared in a flask fitted with a non pressure-equalized dropping funnel. In this funnel was placed a solution of 52 mg (0.136 mmole) of the unsaturated aldehyde **N-2** and 12.8 μl (10.1 mg, 0.136 mmole) of *t*-butyl alcohol in 25 ml of dry THF. The funnel was externally pressurized with argon, and the aldehyde solution was added dropwise over a 35-min period to the stirred blue solution. After stirring for 10 min longer, the reaction mixture was treated with small portions of powdered sodium benzoate until the blue color faded. The ammonia was then evaporated through a mercury bubbler over a 20-min period, and the resulting suspension was poured onto 50 ml of 10% hydrochloric acid and ice. This mixture was extracted with three 50-ml portions of ether, and the combined extracts were washed with water (50 ml), 5% aqueous sodium hydroxide solution (two 50-ml portions), water (three 50-ml portions), and saturated brine (50 ml), and then dried ($MgSO_4$). After removal of the drying agent and concentration of the solution at reduced pressure, 67 mg of a yellow solid was obtained. Purification of this material by ptlc (55) (30% ether-petroleum ether, single development) afforded 24 mg (46%) of a white semicrystalline material (R_f 0.04); ir ($CHCl_3$) 3605, 3570 (OH), 1605, 1575, 1495 (aromatic), 1385 (CH_3) and 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.95, 0.98 (broad overlapping singlets, 9, C-2, C-4a and C-12a CH_3's), 1.22 (s, 3, C-10b CH_3), 3.76 (s, 3, Ar OCH_3), 3.91 (m, 1, ⫽⌒CH-O-), 5.1-6.0 (m, 2, H-C=C-H), and 6.6-7.3 (m, 3, Ar H). These spectra are consistent with those expected for the mixture of alcohol dimers **41**. Another 34 mg of solid (R_f 0.34) obtained from the above ptlc was submitted to a second purification on ptlc (55) (15% ether-petroleum ether, double development), and 17.6 mg (34%) of the desired aldehyde **N-4** (R_f 0.34) was obtained. The ir and nmr spectra of this material are the same as those obtained in part A above.

Preparation of isopropyltriphenylphosphonium iodide.

According to the procedure of Wittig and Wittenberg (60), 7.25 g (27.6 mmoles) of triphenylphosphine and 3.4 ml (5.78 g, 34 mmoles) of iodomethane were combined in a flask. This mixture was heated under a reflux condenser with a 98-102° bath for 24 hr and then cooled. The white solid mass which had formed in the flask was broken up and crushed (under an argon atmosphere) and the resulting coarse powder was washed with 10 ml of dry ether, and dried of any remaining solvent at reduced pressure. This crude iodide weighed 11.89 g and was not purified further; it was stored as a solid under argon for use in subsequent experiments, and remained intact for at least several weeks. Some of the triphenylphosphine starting material must have been present as an impurity in the iodide, as it was later identified in all reaction mixtures in which the iodide was employed.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(4′-methyl-3′-pentenyl)-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (**M-6**).

The Wittig reaction was performed using a modified procedure of Bothner-By and co-workers (46). A stirred suspension of 4.62 (10.7 mmoles) of crude isopropyltriphenylphosphonium iodide in 30 ml of dry THF at room temperature was treated dropwise over a 3-min period with

4.03 ml (8.55 mmoles) of a 2.12 M solution of phenyllithium in 30% ether-benzene (Alfa Inorganics, Inc.). The red suspension was stirred for 2.25 hr, and then a solution of 819 mg (2.14 mmoles) of the aldehyde N-4 in 9 ml of dry THF was added over a 5-min period; two 2-ml portions of dry THF were used to effect complete addition. After stirring at room temperature for 50 min longer, the red mixture was diluted with 500 ml of ether, and the resulting solution was washed with water (three 200-ml portions), 10% aqueous hydrogen peroxide solution (200 ml) and water (200 ml). The solution was then shaken with 200 ml of 10% aqueous hydrogen peroxide solution for 5 min to convert any remaining triphenylphosphine impurity to the oxide. The organic phase was separated, washed with 10% aqueous sodium thiosulfate solution (200 ml) and saturated brine (150 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, a semi-solid mixture was obtained. This material was filtered through a glass wool plug with the aid of 100 ml of petroleum ether to remove most of the relatively insoluble triphenylphosphine oxide. Concentration of the filtrate at reduced pressure afforded 1.2 g of a yellow oil which was purified by chromatography on 120 g of silica gel. The first 150 ml of eluent showed four spots on tlc (55) (4% ether-petroleum ether, single development) and was discarded; the next 25 ml was put aside, and concentration of the following 250 ml at reduced pressure afforded 651 mg (74.5%) of the olefin M-6 as a white solid; ir ($CHCl_3$) 1605, 1575, 1495 (aromatic), 1385 (CH_3), and 1035 cm^{-1} (ArOMe); nmr ($CDCl_3$) δ 0.92, 0.98, 1.05 (3 singlets, 3 each, C-2, C-4a and C-12a CH_3's), 1.21 (s, 3, C-10b CH_3), 1.59, 1.66 [2 singlets, $C=C(CH_3)_2$], 3.76 (s, 3, Ar OCH_3), 4.85-5.35 (m, 1, C=C-H) and 6.6-7.3 (m, 3, Ar H).

Evaporation of the solvent from the 25 ml fraction that was put aside afforded 101 mg of an oil. Purification of this material on ptlc (55) (13X20 cm plate, 4% ether-petroleum ether, single development) afforded an additional 69 mg (7.9%) of olefin M-6. This material had the same nmr spectrum as olefin M-6 described above; the combined yield was thus 720 mg (82.5%). Crystallization of a portion of this material from methanol with a trace methylene chloride afforded the analytical sample as fluffy white crystals, mp 78-80° (vac); ir and nmr of this sample were the same as those of chromatographed material above.

Anal. Calcd for $C_{29}H_{44}O$: C, 85.23; H, 10.85. Found: C, 85.06; H, 10.66.

Treatment of the aromatic olefin M-6 with trifluoroacetic acid/anhydride mixture at -20°.

The aromatic olefin M-6 was subjected to the same conditions used to cyclize the acetylenic alcohol K-3. A mixture of 2.0 ml of trifluoroacetic acid and 0.6 ml of trifluoroacetic anhydride was chilled in a -20° bath and a portion of this cold mixture was added to 20 mg (0.049 mmole) of the olefin M-6 at -20°. The resulting mixture was stirred at -20° for 20 min, and then the pressure over the solution was reduced with the aid of a vacuum pump. Following this the cooling bath was removed to facilitate evaporation of the solvents (which took about 5 min) and the remaining residue was dried at room temperature at ca.

0.05 mm pressure for 1 hr. This oil appears to be the crude trifluoroacetate O-1; ir ($CHCl_3$) 1775 (trifluoroacetate C=O), 1605, 1495 (aromatic), 1380, 1370 (CH_3), 1165 (CF_3), and 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.89, 0.97, 1.20 (3 singlets, C-2, C-4a, C-10b and C-12a CH_3's), 1.54 [s, $CF_3CO_2\text{-}\overset{R}{C}(CH_3)_2$], 3.74 (s, Ar OCH_3), 6.5-7.3 (m, Ar H) and almost no remaining 5.05 (m, $R_2C{=}CHR'$) or 1.61 [s, $C{=}C(CH_3)_2$]. The side chain olefin signals are clearly lacking in the nmr spectrum.

2β,4aβ,10bβ,12aα-Tetramethyl-2α-(4′-methyl-3′-pentenyl)-1,2,3,4,4a,4bα,5,6,10,10aα,10b,11,12,12a-tetradecahydrochrysen-8(9H)-one (O-6).

A. Attempted preparation using hydrochloric acid-ethanol treatment of Birch reduction product O-2.

1. Reduction

Both the Birch reduction and the acid catalyzed hydrolysis were performed using the procedure of J. Tilley (19f). A solution of 100 mg (0.254 mmole) of the aromatic olefin M-6 and 4.2 ml (3.32 g, 45 mmoles) of t-butyl alcohol in 8.0 ml of dry THF was added to ca. 25 ml of dry, stirred ammonia. Two 1-ml portions of dry THF were used to help effect complete addition. With continued stirring, this solution was treated with 1.3 cm (48 mg, 6.97 mmoles) of lithium wire, refluxed for 2 hr and then cautiously quenched with 1.25 ml of methanol. With the aid of gentle hot air heating the ammonia was evaporated under a stream of argon over a 1-hr period. The remaining mixture was partitioned between 100 ml of ether and 70 ml of water and the aqueous layer was separated and extracted with 25 ml of ether. The combined organic phases were washed with 50 ml of water and 50 ml of saturated brine, and then dried ($MgSO_4$) for 5 min. After removal of the dessicant and evaporation of the solvent at reduced pressure, 114 mg of the crude 1,4-dihydro compound **0-2** was obtained; nmr ($CDCl_3$) δ 0.92, 1.04, 1.10 (3 singlets, C-2, C-4a, C-10b and C-12a CH_3's), 1.62, 1.68 [2 broad singlets, $C{=}C(CH_3)_2$], 3.53 (s,  OCH_3), 4.63 (m, -O-C=C-H), 5.10 (s, $R_2C{=}CH{-}R'$), and no peaks between 6.6-7.4 (Ar H).

2. Hydrolysis and conjugation

The crude 1,4-dihydrocompound **0-2** was dissolved in 12 ml of ethanol and treated with 8 ml of 5 *N* hydrochloric acid. This solution was stirred and heated in a 65-70° bath for 40 min, and then cooled and poured onto 50 ml of water. The resulting mixture was extracted with three 50-ml portions of ether, and the combined extracts were washed with saturated aqueous sodium bicarbonate solution (two 50-ml portions) and saturated brine (50 ml), and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, 106 mg of a yellow oil was obtained; ir 3600, 3430 (OH), 1660 (C=O), 1615 (C=C), and 1390, 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.92, 0.95, 1.15 (3 singlets, *ca.* 6, 3 and 3, C-2, C-4a, C-10b and C-12a CH_3's), 1.24 [s, *ca.* 6, $^{-O}_{R}\!\!>\!C(CH_3)_2$], 5.86 (broad s, *ca.* 1, O=C-CH=C), and only traces of any peaks at 5.1 ($R_2C{=}CH{-}R'$) or 1.61 and 1.68 [$C{=}C(CH_3)_2$]. These spectral data are consistent with those of desired enone **0-6** with a hydrated side chain, i.e., the alcohol **0-4**. This material was not characterized further but was dehydrated in an effort to obtain enone **0-6**.

A stirred solution of 106 mg of the crude alcohol **0-4** described above and 6 mg of *p*-toluenesulfonic acid monohydrate in 10 ml of benzene was heated at reflux through a Dean Stark water separator. The side arm of the separator had been filled with Drierite before heating was begun. After 4 hr at reflux, the stirred solution was treated with an additional 6 mg of *p*-toluenesulfonic acid monohydrate, and then reflux was continued for 15 hr longer. The reaction mixture was then cooled and diluted with 100 ml of ether, and the resulting solution was washed with 5% aqueous sodium hydroxide solution (two 30-ml portions), water (30 ml) and saturated brine (30 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, 110 mg of a semicrystalline product was obtained. Purification of this material on ptlc (55) (40% ether-petroleum ether, single development) afforded 66.6 mg (68.8% based on the aromatic olefin M-6) of a mixture of olefins O-5 and O-6 as a pale yellow solid (R_f 0.29): nmr ($CDCl_3$) was the same as that of purified enone O-6 except that the δ 5.07 multiplet ($R_2C{=}CHR'$) integrated to only 87% of one proton, while a new multiplet was present at δ 4.63 ($RR'C{=}CH_2$) and integrated to 13% of two protons; the broad singlets at δ 1.62, 1.69 were also somewhat smaller than for the single isomer O-6: analysis by vpc (57) showed only one peak (oven temperature 300°, ret. time 3.9 min), having the same ret. time as the enone O-6.

B. Preparation employing mild acid hydrolysis of the enol ether O-2 and base catalyzed conjugation of the enone O-3.

1. Reduction

Birch reduction of the A ring was performed on 50 mg of the aromatic olefin M-6 exactly as described in part A above, except that all material quantities employed were reduced to half the stated amounts. In this manner 56 mg of crude enol ether O-2 was obtained.

2. Hydrolysis of the enol ether O-2

To a stirred solution of 56 mg of crude enol ether O-2 in 1 ml of methylene chloride at room temperature was added sequentially 2 ml of ethanol, 0.5 ml of water and 50 mg of oxalic acid. After stirring for 2 hr, the reaction mixture was diluted with 100 ml of ether, and the resulting solution was washed with 5% aqueous sodium hydroxide solution (two 25-ml portions), water (25 ml) and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, there was obtained 50 mg of crude β, γ-unsaturated ketone O-3 as an oil; ir ($CHCl_3$) 1710 (C=O), 1385 (CH_3) and no peak at around 3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.93, 1.06, 1.08 (3 singlets, ca. 2:1:1, C-2, C-4a, C-10b and C-12a CH_3's), 1.61, 1.68 [2 broad singlets, $C=C(CH_3)_2$], 2.39, 2.69 [2 broad singlets, ca. 2:1, allylic C-6, C-10 and C-7 H's] and 5.10 (m, $R_2C=CH-R'$).

3. Conjugation of the enone O-3

To a stirred solution of 50 mg of the crude nonconjugated enone O-3 in methylene chloride at room temperature was added sequentially 1 ml of ethanol, 0.15 ml of water and 0.10 ml of 10% aqueous sodium hydroxide solution. After stirring for 30 min, the solution was treated with 0.05 ml of 40% aqueous sodium hydroxide solution, and 1 hr later a white precipitate began forming in the reaction mixture.

This suspension was diluted with 100 ml of ether after stirring for a total of 2.3 hr, and the resulting mixture was washed with water (two 25-ml portions) and saturated brine (25 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 50 mg of a yellow solid was obtained. Purification of this material on ptlc (55) (40% ether-petroleum ether, single development) afforded 35 mg (72.2%) of the enone 0-6 as a pale yellow solid; ir ($CHCl_3$) 1655 (C=O), 1615 (C=C) and 1390, 1375 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.88, 0.90, 0.93 (3 singlets, 9), 1.15 (s, 3, C-2, C-4a, C-10b, C-12a CH_3's), 1.61, 1.67 [rather obscure singlets, $C{=}C(CH_3)_2$], 5.08 (m, 1, $R_2C{=}CHR'$) and 5.87 (broad s, 1, O=C-CH=C); analysis by vpc (57) indicated 99% one component (oven temperature 300°, ret. time 3.8 min). This material was utilized directly in subsequent experiments without further purification.

6a,7-Epoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(4′-methyl-3′-pentenyl)-1,2,3,4,4a,4bα,5,6,6a,7,10,10aα,10b,11,12,12a-hexadecahydrochrysen-8(9H)-one (P-1).

To a stirred solution of 392 mg (0.988 mmole) of enone 0-6 in 9 ml of methylene chloride at room temperature was added sequentially 20 ml of methanol, 5.3 ml of 30% aqueous hydrogen peroxide solution, and 1.2 ml of 10% aqueous sodium hydroxide solution. After stirring under air in a closed flask for 21 hr, this mixture was diluted with 300 ml of ether. The resulting solution was shaken with 100 ml of water, and the aqueous phase was separated and extracted with 100 ml of ether. The combined organic phases were washed with 100 ml of water and 100 ml of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, 429 mg of a white gum was obtained which on crystallization from methanol-methylene chloride afforded 310 mg (76.2%) of the epoxyketone P-1 as white crystals, mp 103.5-105.5° (vac, dec); ir ($CHCl_3$) 1700 (C=O), 1450 ($-CH_2-$) and 1375 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.90, 1.12 (2 singlets, 9and 3, C-2, C-4a, C-10b, C-12a CH_3's), 1.59, 1.67 [2 broad singlets, $C=C(CH_3)_2$], 3.11 (s, 1, $\overset{O}{C-CH}$), and 5.07 (m, 1, C=CH-). The analytical sample obtained from a second crystallization of a portion of this material from methanol-methylene chloride melted at 107-108.5° (vac); ir and nmr spectra of this sample were the same as those of the crystalline material described above.

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.49; H, 10.73.

Purification of the mother liquors from the first crystallization on ptlc (55) (10X20 cm plate, 40% ether-petroleum ether, single development) afforded an additional 30 mg (7.4%) of the desired epoxide P-1 as a solid (R_f 0.40); nmr spectrum of this material was the same as that of the crystalline product described above. The total yield of epoxyketone P-1 from crystallization and ptlc was 340 mg (83.6%).

1α-(3′-Butynyl)-4bα,7α,8aβ,10aα-tetramethyl-7β-(4′-methyl-3′-pentenyl)-3,4,4aβ,4b,5,6,7,8,8a,9,10,10a-dodecahydrophenanthren-2(1H)-one (P-2).

A slight modification of the general procedure of Eschenmoser and co-workers (32b, c) was employed in this reaction. To a dry mixture of 51.0 mg (0.124 mmole) of the epoxyketone P-1 and 24.5 mg (0.131 mmole) of *p*-toluenesulfonylhydrazine at -20° was added with stirring and swirling 2.5 ml of -20° acetic acid-methylene chloride (1:2). After stirring for 5 min at -20°, the solution was placed in a -15° to -25° freezer for 30 hr. The mixture was then stirred at room temperature for 13 hr (during which time it turned a bright red) and was then diluted with 100 ml of ether. The resulting solution was washed with water (two 25-ml portions), saturated aqueous sodium bicarbonate solution (two 25-ml portions), and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, 57 mg of a yellow oil was obtained. Purification of this material on ptlc (55) (6.5X20 cm plate, 15% ether-petroleum ether, single development) afforded 31 mg (63.3%) of the acetylenic ketone P-2 as a white solid (R_f 0.32); ir ($CHCl_3$) 3300 (acetylenic C-H), 2120 ($-C{\equiv}C-$), 1700 (C=O) and 1390, 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.76 (s, 3), 0.91 (s, 6), 1.21 (s, 3, C-4b, C-7, C-8a and C-10a CH_3's), 1.62 and 1.68 [2 broad singlets, $C{=}C(CH_3)_2$], and 5.1 (m, 1, RCH=C). The analytical sample obtained from two crystallizations of this material from methanol melted at 90.5-91.5° (vac); ir and nmr spectra of this sample were the same as those of chromatographed material described above.

Anal. Calcd for $C_{28}H_{44}O$: C, 84.79; H, 11.18. Found: C, 84.72; H, 11.21.

1α-(3′-Butynyl)-2β,4bα,7α,8aβ,10aα-pentamethyl-7β-(4′-methyl-3′-pentenyl)-1,2,3,4,4aβ,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-2α-phenanthrol (P-3).

To a stirred and ice cooled mixture of 1.1 ml (1.81 mmole) of 1.65 M ethereal methyllithium solution (Ventron Corp.) and 2.2 ml of dry THF was added over a 7-min period a solution of 55.0 mg (0.139 mmole) of the acetylenic ketone P-2 in 2.5 ml of dry THF. Two additional 1-ml portions of dry THF were used to help effect complete addition. After stirring for 25 min without cooling, the reaction mixture was cautiously quenched with 1 ml of water and was then diluted with 100 ml of ether. This solution was washed with 25 ml of water and 25 ml of saturated brine, and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvents at reduced pressure, there was obtained 56.7 mg (99%) of crude alcohol P-3; ir ($CHCl_3$) 3600 (OH) 3300 (acetylenic C-H), 2115 (-C≡C-) and 1385, 1375 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.89 (s, 6), 0.97, 1.06, 1.13 (3 singlets, 9, C-2, C-4b, C-7, C-8a and C-10a CH_3's); tlc (55) (50% ether-petroleum ether, single development) showed one dark spot (R_f 0.50) and several barely visible minor spots. This material was used directly without further purification in subsequent experiments.

Cyclization of the acetylenic alcohol P-3 with trifluoroacetic acid in methylene chloride to give the chloro olefin P-5.

A stock solution of ca. 2% trifluoroacetic acid and ca. 0.5% trifluoroacetic anhydride in methylene chloride was prepared by mixing 0.4

ml of trifluoroacetic acid, 0.1 ml of trifluoroacetic anhydride and 19.5 ml of dry methylene chloride. To a stirred solution at 0° of 12 mg (0.0291 mmole) of the alcohol P-3 in 0.4 ml CH_2Cl_2 was added 0.1 ml of the 2% acid solution. After stirring at 0° for 35 min and without cooling for 1.25 hr, this mixture was treated with 2 ml of dry methylene chloride and 0.5 ml of the 2% acid solution. The mixture was stirred at room temperature for another 1.5 hr and then diluted with 75 ml of ether. The resulting solution was washed with 20 ml of ice-cold, saturated aqueous sodium bicarbonate solution, 20 ml of water and 20 ml of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, there was obtained 17 mg of a yellow oil; ir ($CHCl_3$) 3600 (OH, ca. 50% normal intensity), 3300 (acetylenic C-H, ca. 50% normal intensity), and 1775 (trifluoroacetic C=O, ca. 30% of full scale). As cyclization appeared incomplete, this oil was treated with 2 ml of the 2% acid solution and stirred at room temperature for 30 min. The mixture was then diluted with 70 ml of ether, and the resulting solution was washed with ice-cold saturated aqueous sodium bicarbonate solution (25 ml), water (20 ml) and saturated brine (20 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 17 mg of the crude chloro olefin trifluoroacetate P-5 as an oil; ir ($CHCl_3$) 3300 (acetylenic C-H, ca. 10% normal intensity), 1775 (trifluoroacetate C=O), 1375 (CH_3) and 1170 cm^{-1} (CF_3); nmr ($CDCl_3$) δ 0.87, 0.98, 1.04 (3 singlets, R_3C-CH_3's), 1.56 [s, $(CH_3)_2\overset{R}{C}O_2CCF_3$], 5.43 (m, Cl-C=C-H), and no 5.05 (m, $R_2C{=}CHR'$) or 1.61 [$C{=}C(CH_3)_2$].

A mixture of 14 mg of the crude trifluoroacetate P-5 and 0.5 ml of 5% aqueous sodium hydroxide solution in 2 ml of methanol was stirred at room temperature for 20 hr. This mixture was then diluted with 70 ml of ether and the resulting solution washed with 25 ml of water and 25 ml of brine, and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, there was obtained 14 mg of crude chloro alcohol P-6 as a yellow oil; ir ($CHCl_3$) 3600 (OH), 3300 (acetylenic C-H, *ca.* 10% normal intensity), 1705 (C=O, *ca.* 10% normal intensity), and 1385 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.89, 0.96, 1.05 (3 singlets, R_3C-CH_3's), 1.22 [s, $(CH_3)_2\ C{<}^{R}_{O-}$], and 5.42 (ClC=CH).

Conversion of the acetylenic alcohol P-3 to the crude enol bis-trifluoroacetate Q-1.

A mixture of 2.0 ml of trifluoroacetic acid and 0.6 ml of trifluoroacetic anhydride was cooled at -18° and 2.0 ml of this cold solution was added to 26.2 mg (0.0635 mmole) of alcohol P-3 at -18°. The resulting brown solution was stirred at -18° for 30 min, and then the pressure in the system was reduced with a vacuum pump. Removal of the cooling bath facilitated evaporation of the solvents which took about 10 min, and the brown residue was then dried for 30 min at room temperature at *ca.* 0.05 mm pressure. In this manner 29 mg of crude enol trifluoroacetate Q-1 was obtained as a brownish gum; ir ($CHCl_3$) 1790 (enol trifluoroacetate C=O), 1775 (trifluoroacetate C=O), 1695 (enol trifluoroacetate C=C), 1370 (CH_3), 1165, 1140 (CF_3) and essentially no

(1-2%) 3300 cm^{-1} (acetylenic C-H); nmr ($CDCl_3$) δ 0.89 (s, 9), 1.02, 1.04 (2 singlets, 6, C-2, C-4a, C-6a, C-10b and C-12a CH_3's), 1.54 [s, 2, $(CH_3)_2C^{R}_{OTFA}$], and 5.23 [s (broad), 1, TFA-O-C=CH]. Due to the sensitive nature of this intermediate it was not purified further but was used directly in subsequent experiments.

Hydrolysis of the crude enol bis-trifluoroacetate Q-1 to the hydroxy ketone Q-2.

To a stirred solution of *ca.* 12 mg of trifluoroacetate **Q-1** in 1 ml of 2-propanol was added 0.1 ml of 5% aqueous sodium hydroxide solution. After stirring for 14.5 hr, this mixture was diluted with 70 ml of ether, and the resulting solution was washed with 20 ml of water, and 25 ml of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 11.4 mg of crude ketone **Q-2** as a yellow solid; ir ($CHCl_3$) 3600, 3450 (OH), 1700 (C=O), 1470 ($-CH_2-$) and 1385, 1375 cm^{-1} (CH_3); nmr ($CHCl_3$) δ 0.90, 1.10 (2 singlets, C-2, C-4a, C-6a, C-10b, C-12a CH_3's) and 1.22 [s, $(CH_3)_2C^{\diagup R}_{\diagdown O-}$]; tlc (55) (75% ether-petroleum ether, single elution) shows one large spot (R_f 0.30).

Attempted generation and alkylation of an enolate anion from the crude enol bis-trifluoroacetate Q-1.

A. Using methyllithium.

A stirred mixture of 0.14 ml (0.238 mmole) of 1.71 *M* ethereal methyllithium (Ventron Corp.) and 0.3 ml of dry DME was cooled in an ice bath (a white precipitate formed) and treated with a solution of ca. 16 mg (0.04 mmole) of the crude enol trifluoroacetate Q-1 in 0.32 ml of dry DME. After 10 min at 0°, the suspension was treated with 0.6 ml of dry THF to effect solution of the precipitate. This solution was stirred for 10 min at room temperature and then for 15 min at 0°, after which 0.25 ml of dry HMPA was added, followed by 0.25 ml of dry iodomethane. After stirring without cooling for an additional 23 min, this mixture was diluted with 75 ml of ether. The resulting solution was washed with 5% hydrochloric acid (seven 20-ml portions) and brine (20 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained ca. 25 mg of a yellow gum; ir and nmr spectra looked much like those of unalkylated ketone Q-2, with no δ 0.71 C-6a CH_3 singlet characteristic of the shionone A ring (24d). A solution of this gum in 3 ml of ethanol was treated with 36 mg of 85% potassium hydroxide and stirred at room temperature for 12.5 hr. The mixture was diluted with 75 ml of ether, and the resulting solution was washed with 20 ml of water and 20 ml of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 18 mg of a yellow oil; nmr ($CDCl_3$) was rather undescriptive, but still did not exhibit any δ 0.71 singlet; tlc (55) (75% ether-petroleum ether, single elution) showed at least 6 spots, one of which (R_f 0.30) had the same R_f as unalkylated ketone Q-2.

B. Using lithium/ammonia.

To a stirred solution of ca. 1 mm (4 mg, 0.6 mg atm) of lithium wire in ca. 5 ml of dry ammonia, was added a solution of 0.046 mmole of crude enol trifluoroacetate Q-1 in 1.5 ml of dry THF. Two additional 0.25-ml portions of dry THF were used to effect complete addition. The blue color faded after 10 min, so another 1 mm (4 mg, 0.6 mg atm) piece of lithium wire was added. The resulting blue solution was stirred at reflux for 55 min longer, and was then quenched by the rapid addition of 0.25 ml (595 mg, 2.5 mmoles) of dry iodomethane. After another 65 min the ammonia was evaporated from the solution with the aid of a hot air gun, and 75 ml of ether was added to the residue. This mixture was washed with two 20-ml portions of water and 20 ml of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 20 mg of a yellow oil. This material was submitted to the same hydrolysis conditions as described in part A, and afforded the same sort of complex mixture as in part A (possibly even worse); no δ 0.71 singlet was apparent in the nmr spectrum of this crude material.

Attempted cyclization of acetylenic alcohol R-6 to enol formate S-1 with formic acid.

A. At -5°-0°.

A cold (-5°) mixture of 1 ml of dry methylene chloride, 1 ml of formic acid (distilled from B_2O_3) and 0.1 ml of acetic anhydride was added to 15.5 mg of the alcohol R-6 at -5°. This mixture was stirred at -5° for 20 min and at 0° for 2.2 hr, and then the solvents were removed under reduced pressure (vacuum pump). After drying for 1 hr at *ca.* 0.05 mm pressure, the residue amounted to 15.5 mg of a white solid; ir (CHCl$_3$) was the same as that of starting material; analysis by vpc (57) showed one peak (oven temperature 300°, ret. time 2.9 min) with the same ret. time as starting material.

B. At room temperature.

The reaction was repeated using exactly the same amounts of materials as described above, but at room temperature. This mixture was stirred for 4.5 hr, during which time tlc (55) (50% ether-petroleum ether, single elution) of aliquots showed gradual disappearance of the R$_f$ 0.43 spot (starting material) and clean appearance of two new spots (R$_f$ 0.54 and 0.63) of about equal intensity. The solvents were then removed at reduced pressure (vacuum pump) and after drying for 12 hr at 0.05 mm pressure, the residue amounted to 16 mg of a yellow oil; ir (CHCl$_3$) 3300 (acetylenic C-H, *ca.* 50% normal intensity), 1730 (enol formate C=O, *ca.* 50% normal intensity) and no remaining 3600 cm^{-1} (OH); nmr (CDCl$_3$) δ 3.76 (s, 3, Ar OCH$_3$), 5.14 (m, *ca.* $\frac{1}{2}$, -O-C=CH), 5.50 (m, *ca.* $\frac{1}{2}$, R$_2$C=CH-R$'$), 6.6-7.3 (m, 3, Ar H) and 8.06 (s, *ca.* $\frac{1}{2}$, HCO$_2$C=C). These spectra are most consistent with a product that consisted of a 1:1 mixture of the desired enol formate **S-1** and the acetylenic olefin **S-2**.

Attempted cyclization of alcohol R-6 to enol ether S-3 with borontri-

fluoride etherate complex.

A. In diethyl ether.

To a stirred solution at -78° of 15.4 mg of acetylenic alcohol **R-6** and 0.1 ml of pinene in 1.5 ml of ether, was added over a 1-min period 0.5 ml of borontrifluoride etherate complex (distilled from calcium hydride). This mixture was stirred at -78° for 3 hr, at which time tlc (55) (50% ether-petroleum ether) was unchanged from that at the beginning of the reaction and still showed the R_f 0.40 spot corresponding to starting material. The temperature of the stirred solution was then raised slowly as the 250 ml Dry Ice/acetone cooling bath was allowed to warm to room temperature. After stirring for a total of 21 hr this solution was poured onto 50 ml of 10% aqueous sodium hydroxide solution and ice. The resulting mixture was extracted with two 50-ml portions of ether, and the combined organic layers were washed with 25 ml of water and 25 ml of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 53 mg of a thick gum was obtained; ir ($CHCl_3$) showed no 3600 cm^{-1} (OH), about 60% of the 3300 cm^{-1} (acetylenic C-H) band of starting material, and about 30% of a full scale peak at 1700 (C=O); nmr ($CDCl_3$) showed no quartets in the region *ca.* δ 3.0-3.7 (ethyl ether or ethyl enol ether); analysis by vpc (57) showed three significant peaks (oven temperature 300°, ret. time 2.7, 3.2 and 5.1 min) in a ratio of *ca.* 6:2:3, with the last peak having the same ret. time as the known ketone **R-8b** (47). These data are consistent with a mixture of dehydrated acetylene **S-4** and cyclic ketone **R-8b**.

B. In dimethyl ether.

This experiment was attempted on 16 mg of the acetylenic alcohol R-6 with 0.5 ml of pinene and 0.5 ml of borontrifluoride etherate complex in *ca.* 5 ml of refluxing dimethyl ether (distilled from sodium hydride). The reaction was allowed to proceed for 4 hr, but the ir spectrum of the product after work-up showed both 3600 (OH) and 3300 cm^{-1} (acetylenic C-H) bands, with the same intensities as in the spectrum of starting alcohol, and no 1700 cm^{-1} (C=O); nmr showed no new singlets or quartets δ 3.0-3.7 (ethyl or methyl ethers). These spectra are consistent with little or no reaction of the starting alcohol R-6 under the conditions of this reaction.

Cyclization of the acetylenic ether L-1 with borontrifluoride etherate complex in ether.

To a stirred solution at -78° of 9 mg of the ether L-1 in 0.5 ml of dry ether was added dropwise over a 5-min period 0.5 ml of borontrifluoride etherate complex. After stirring for 30 min at -78° the solution froze, so an additional 0.5 ml of dry ether was added. The resulting solution was then stirred at -78° for *ca.* 3 hr, after which the temperature was slowly raised as the Dry Ice/acetone bath was allowed to warm to room temperature. Stirring was continued at room temperature, and 17 hr after being mixed the solution was diluted with 70 ml of ether. The resulting solution was washed with two 25-ml portions of saturated aqueous sodium bicarbonate solution and 25 ml of brine, and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 10 mg of a yellow oil. The ir and nmr spectra of this material were the same as those of crude pregnenone **L-6** obtained from 1% trifluoroacetic acid cyclization of ether **L-1**; no starting ether or enol ether peaks (δ 3.1-3.7) were evident in the nmr. Analytical tlc (55) (15% ether-petroleum ether) showed about half the material in a spot (R_f 0.30) having the same R_f as pregnenone **L-6**, and the remainder in two overlapping spots (R_f 0.65). These data are most consistent with a product mixture containing *ca.* 50% of the pregnenone **L-6**, and *ca.* 50% of elimination and/or fluorinated products (**L-5**/**T-3**).

A similar experiment was performed on 9 mg of the ether **L-1** with 0.1 ml of borontrifluoride etherate in 1.0 ml of dry ether. After stirring at -78° for 3 hr, this mixture was worked up and a quantitative recovery of starting material was obtained. In another experiment, a solution at -18° of 9 mg of the ether **L-1** in 0.5 ml of methylene chloride was treated with 0.05 ml of borontrifluoride etherate. After stirring at -18° for 30 min, this mixture was worked up and the product obtained was found to contain no starting ether or enol ethers (nmr), nor any ketone (ir); tlc (55) (15% ether-petroleum ether, single elution) showed only the two overlapping spots (R_f 0.65) which were present on tlc (same conditions as above) of the crude pregnenone product described above.

2α-Methoxy-2β,4bα,7α,8aβ,10aα-pentamethyl-7β-(4′-methyl-3′-pentenyl)-1α-(3′-pentynyl)-1,2,3,4,4aβ,4b,5,6,7,8,8a,9,10,10a-tetradeca-

hydrophenanthrene (U-1).

To a stirred and ice cooled mixture of 1.0 ml (1.71 mmoles) of 1.71 *M* ethereal methyllithium solution (Ventron Corp.) and 1.0 ml of dry THF was added over a 10-min period a solution of 47 mg (0.118 mmole) of the acetylenic ketone **P-2** in 1.0 ml of dry THF. Two additional 0.5-ml portions of dry THF were used to help effect complete addition. After stirring for 25 min without cooling and then for 7 min with ice cooling, this solution was treated sequentially with 1.0 ml of dry HMPA and 0.5 ml of dry iodomethane. The ice bath was then removed and the solution was stirred at room temperature for 20 hr; tlc (50% ether-petroleum ether, single development) of an aliquot after 19 hr was the same as that of an aliquot after 1 hr; both showed two large spots (R_f 0.00 and 0.74) . The mixture was then diluted with 100 ml of ether, and the resulting solution was washed with water (eight 25-ml portions) and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 52 mg (quantitative) of the crude ether **U-1** as a clear oil; ir ($CHCl_3$) 1390, 1375 (CH_3), 1075 (R-OCH_3) and no 3600 (OH), 3300 (acetylenic C-H) or 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.89, 0.93 (2 singlets, 9, *ca.* 2:1), 1.05, 1.07 (2 singlets, 6, C-2, C-4b, C-7, C-8a and C-10a CH_3's), 1.61, 1.67 [2 broad singlets, $C{=}C(CH_3)_2$], 1.75 (m, $C{\equiv}C{-}CH_3$), 3.04 (s, 3, R OCH_3), and 5.06 (m, 1, $R_2C{=}CH{-}R'$); tlc (55) (5% ether-petroleum ether) shows one dark spot (R_f 0.56) and only faint traces of any other material. This oil was not purified or characterized further, but was used directly in subsequent reactions.

2α-Methoxy-2β,4bα,7α,8aβ,10aα-pentamethyl-7β-(4′-methyl-3′-pentenyl)-1α-(3′-pentenyl)-1,2,3,4,4aβ,4b,5,6,7,8,8a,9,10,10a-tetradecahydrophenanthrene (**U-2**).

To a stirred and refluxing blue solution of 15 mg (0.65 mg atm) of sodium in *ca.* 10 ml of dry ammonia and 2 ml of dry THF were added over a 5-min period a solution of 52 mg (*ca.* 0.118 mmole) of the crude acetylenic ether **U-1** in 2 ml of dry THF. Two additional 0.5-ml portions of dry THF were used to help effect complete addition. The blue color of this stirred mixture faded after 1 hr at reflux, so an additional 12 mg (0.52 mg atm) of sodium was added. After additional 2 hr the blue solution was quenched by the careful addition of 1 ml of water, and then the ammonia was allowed to evaporate through a mercury bubbler over an 18 hr period. This suspension was diluted with 100 ml of ether, and the resulting mixture was washed with water (two 25-ml portions) and saturated brine (25 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvents at reduced pressure, there was obtained 51 mg (98%) of the crude diene **U-2** as a cloudy gum; ir ($CHCl_3$) 1390, 1375 (CH_3) and 1075 cm^{-1} (R-OCH_3); nmr ($CDCl_3$) δ 0.05 (s, trace of silicon grease), 0.90, 0.93, 1.04, 1.09 (4 singlets, *ca.* 2:1:1:1, C-2, C-4b, C-7, C-8a and C-10a CH_3's), 1.62, 1.67 [2 broad singlets, $C{=}C(CH_3)_2$], 3.07 (s, 3, R OCH_3), 5.10 (m, 1, $R_2C{=}CH{-}R'$) and 5.40 (m, 2, H-C=C-H); tlc (55) (2% ether-petroleum ether) showed only one major spot (R_f 0.73) with only slight traces of impurities visible. This gum was not purified or characterized further, but was used directly in subsequent experiments.

Attempted cyclization of the olefinic ether U-2 with formic acid or trifluoroacetic acid.

A stirred and ice cooled solution of 6.9 mg of the ether U-2 in 0.5 ml of methylene chloride was treated with 2.0 ml of cold formic acid (distilled from B_2O_3). This cloudy solution was stirred with ice cooling for 5 min, and then poured onto 25 ml of 10% aqueous sodium hydroxide solution and 35 ml of crushed ice. The resulting mixture was extracted with two 40-ml portions of ether, and the combined organic phases were washed with 25 ml of water and 25 ml of saturated brine, and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, there was obtained 8.0 mg of a cloudy gum: ir ($CHCl_3$) showed no 3600 cm^{-1} (OH) peak but does show ca. 30% of a normal intensity C=O peak at 1715 cm^{-1} (formate): nmr ($CDCl_3$) has a rather obscure angular CH_3 region; all but ca. 10% of the δ 3.08 singlet (R OCH_3) is gone; the disubstituted olefin δ 5.4 appears unchanged; the trisubstituted olefin δ 5.05 (m) and 1.61, 1.67 (2 singlets) appears mostly intact; only a small amount of formate (δ 8.1) was present (ca. 10-20% of a proton). These spectra are most consistent with a product mixture resulting from elimination of the tertiary ether of starting material or elimination of the secondary formate from any cyclization product.

When this reaction was attempted using neat formic acid, the substrate was found to be insoluble. Formic acid and chloroform at room temperature for 12 min gave similar results to those described in detail above. Prolonged formic acid-methylene chloride treatment at room temperature for 7 hr completely destroyed the trisubstituted olefin, and yet did not afford any secondary alcohol on hydrolysis of the esters. Trifluoroacetic acid (10%) in methylene chloride at -40° for 6 min did not seriously affect the side chain, but destroyed *ca.* 60% of the starting ether functionality and afforded almost no trifluoroacetate ester products.

Appendix

For many of the reactions employed in this work, small amounts (less than ~100 ml) of anhydrous solvents were needed at several different times during a procedure. A special apparatus, which allows for the easy distillation and collection of such solvents immediately prior to use, was therefore designed. Shown in Fig. 1, this "solvent drier" eliminates the need for maintaining and handling a large number of dry collecting flasks by combining the collector and distilling head in one piece.

The apparatus as set up for use is shown in Fig. 2. With stopcock "B" closed (protecting the septum), and "A" open, the solvent is heated to reflux for a period of about 30 minutes or longer to thoroughly dry the solvent and interior walls of the apparatus. When solvent is about to be needed, stopcock "A" is closed and collecting begins. (If the system is accidentally forgotten while in this mode, solvent will fill the apparatus to the overflow tube and then begin returning to the distilling flask; the possibility of the pot going dry is greatly diminished). When enough solvent has collected, stopcock "B" is opened and dry solvent is removed through a septum protecting "B", using a dry syringe with a slightly curved six-inch needle. Stopcock "B" is then immediately closed. When enough solvent has been removed, stopcock "A" is opened until need for more dry solvent is anticipated; at that time the above processes are once again repeated.

This apparatus has proved most convenient in actual operation;

and since the solvent is always freshly distilled and never transferred to and stored in intermediate vessels, there is never any doubt as to its absolute dryness.

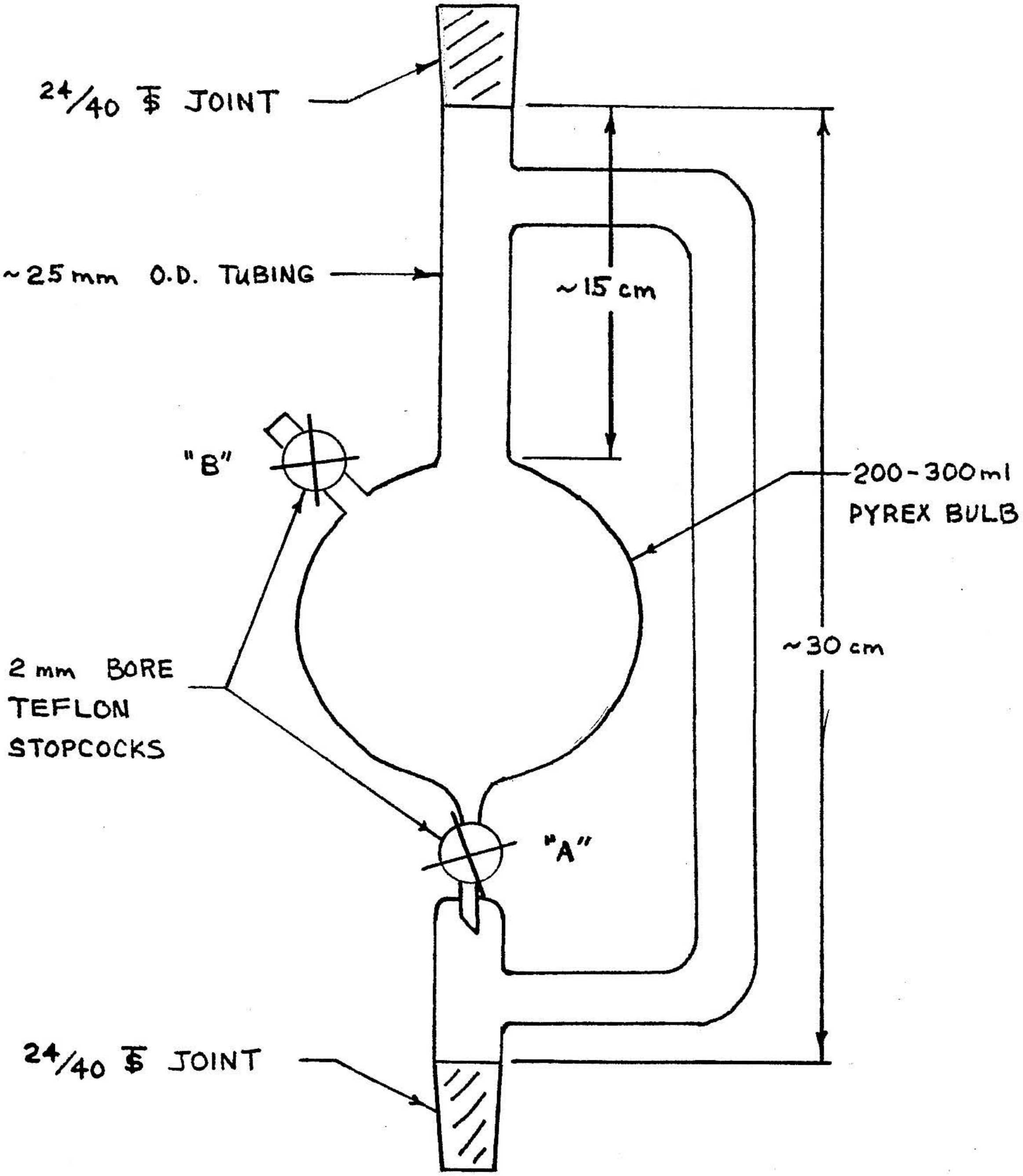


FIGURE 1

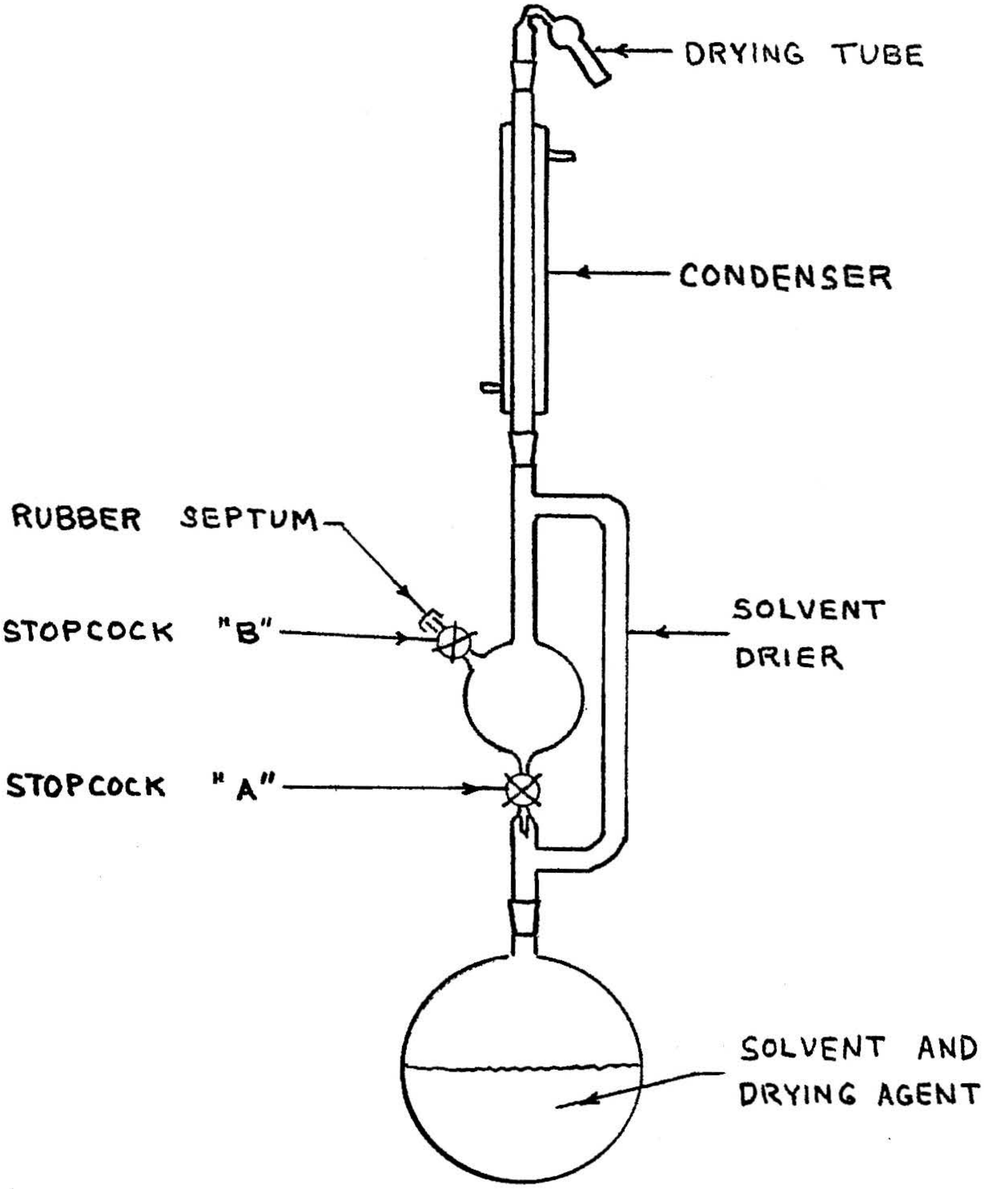

DRYING TUBE
CONDENSER
RUBBER SEPTUM
STOPCOCK "B"
SOLVENT DRIER
STOPCOCK "A"
SOLVENT AND DRYING AGENT

FIGURE 2

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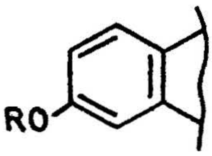
PART II

CONVERSION OF ESTRONE TO ANDROST-4-EN-3-ONE: A NEW METHOD FOR ACTIVATING THE C-9 AND C-10 POSITIONS OF ESTROGENIC STEROIDS FOR SUBSTITUTION

Introduction

One of the greatest difficulties in synthesizing complex organic molecules such as steroids and triterpenes is efficiently constructing the basic carbon skeleton (1). Logistically this task is best approached by joining large fragments which contain as many essential carbons as possible. These pieces must be suitably functionalized to allow later elaboration into final product, but must also be stable to a variety of reaction conditions. Readily available aromatic compounds often prove ideal for such purposes, and have therefore seen frequent use as an excellent source of annular carbons in synthesis (2).

Much of the value of these aromatic fragments is due to their susceptibility to partial reduction by metal-ammonia systems (3). The most useful and frequently encountered aromatic intermediates are of the same type as the O-alkylated A ring (1) of estrogen. These can be reduced in good yield to dihydro compounds (2), which can be hydrolyzed in mild acid to give β,γ-unsaturated ketones (3), or in strong acid to give conjugated enones (4, R=H) (4, 5a, 6a). The α,β-unsaturated products have been by far the most frequently used intermediates in such schemes, for many good synthetic methods are known which employ



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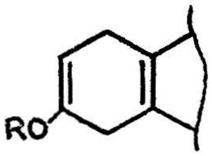

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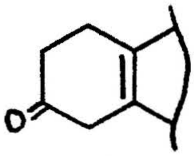

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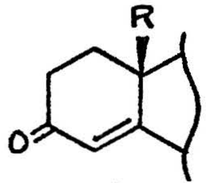

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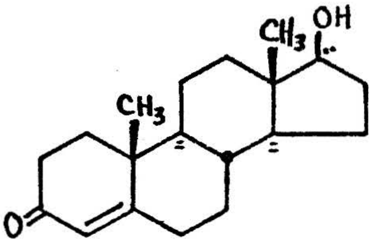
this grouping (7).

In many instances, however, it would be desirable to arrive at an unsaturated intermediate in which the ring fusion γ to the carbonyl group had been stereospecifically substituted with an appropriate alkyl group (e.g. 4, R=alkyl). For example, the androgenic steroid testosterone (5), the triterpene cycloartenol (6) and the antibiotic fusidic acid (7) all possess alkyl substitution at the ten position. In order to



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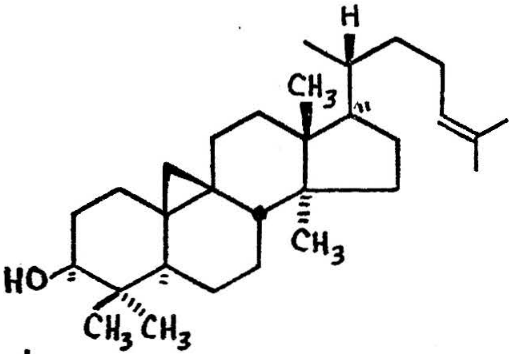

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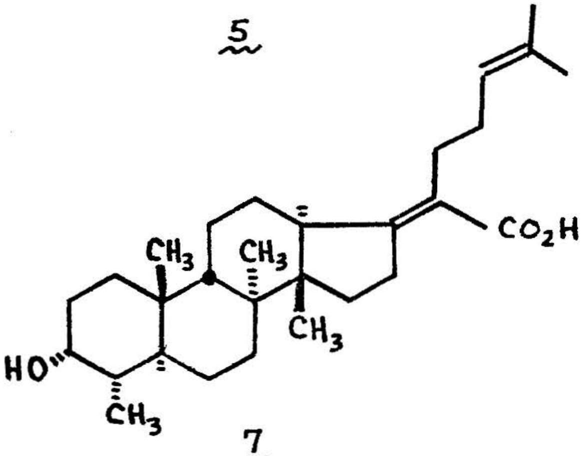

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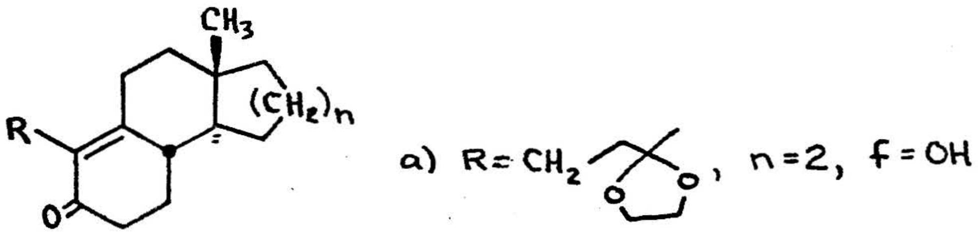
benefit from the possible utility of employing aromatic A ring precursors for the synthesis of those molecules, it must be shown that substitution at C-10 can effectively be introduced starting from the aromatic ring.

That no general method exists for accomplishing this transformation becomes evident in considering the highly explored field of steroid total synthesis. The highest yield, most straightforward synthetic routes are those to estrogenic compounds which utilize aromatic precursors for the aromatic A ring (8). These same routes modified by Birch reductions are used as well to generate 19-norsteroids in good yields (8). When 10-alkyl steroids are synthesized, however, intermediates bearing the aromatic A ring are seldom employed; and instead entirely different approaches are devised to provide for introduction of the C-10 substituent (8). Those few routes which do alkylate C-10 starting from an aromatic A ring (9) are very specific and hardly applicable as general solutions to the problem.

Thus it has been the purpose of this research to develop a somewhat general method for substituting the C-10 position of aromatic A ring type precursors for steroid and triterpene synthesis.

Discussion

In seeking a method of substituting the C-10 position of aromatic A ring type steroid and triterpene precursors, it was most helpful to consider the best methods by which the C-10 position has already been substituted from non aromatic intermediates. Many syntheses of 19-methyl steroids proceed through intermediates such as enone 8, with R=methyl or R= some protected 3-oxybutyl side chain (8). In developing one of the best of these synthesis, Stork and McMurry (10) have transformed enone 8a stereospecifically into the methylated ketone 9, via lithium/ammonia reduction of 8a, followed by methyl iodide alkylation of the



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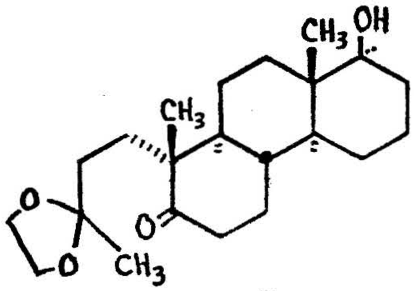

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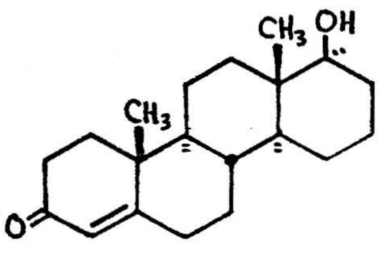

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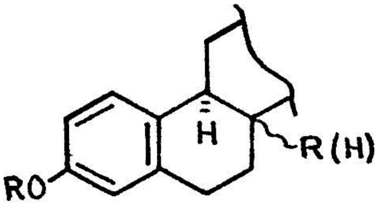
intermediate enolate anion. Hydrolysis of the ketal function of ketone 9 and subsequent cyclization then led to D-homotestosterone (10).

Since α,β-unsaturated ketones are subject to 1,4-additions, dissolving metal reductions, alkylations, and combinations of these reactions (7), then either the α or β or both positions of Stork's intermediate 8a could in principle be substituted before closing the A ring. If such an intermediate could readily be arrived at from an aromatic A ring, then the overall transformation from aromatic to C-10 (and possibly C-9) substituted enone would encompass exactly the conversion we seek to effect (e.g. 1 to 4, R=alkyl).

From the Birch reduction products of aromatic intermediates such as 11, one can envisage several ways to effect suitable cleavage to enone intermediates of type 12. An interest in the Eschenmoser cleavage reaction of α,β-epoxyketones (11), as possibly being synthetically useful in this as well as other applications, prompted the design of a scheme specifically incorporating this reaction; thus, we hoped to learn something of the generality of the cleavage reaction, as well as to effect the desired change in an aromatic system.



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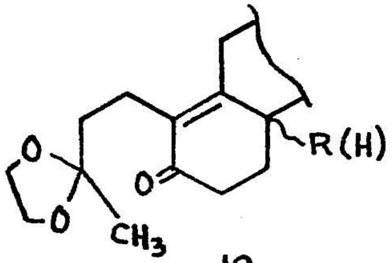

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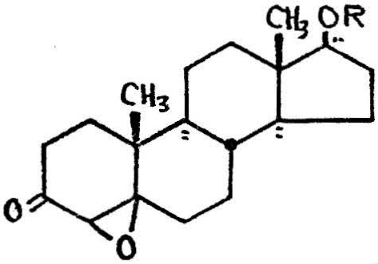
The Eschenmoser cleavage reaction is performed on α,β-epoxyketones by either of two principal methods. Epoxyketone 13 for example can be converted to the *p*-toluenesulfonylhydrazone 14 or the strained aziridine hydrazone 15. The former compound undergoes mild acid catalyzed cleavage



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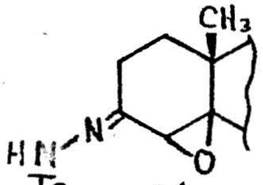

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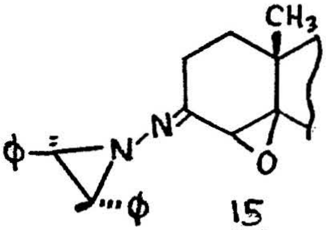

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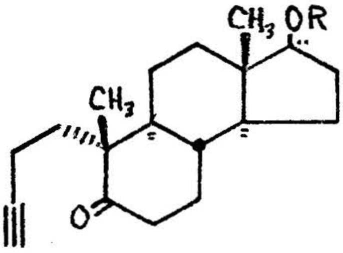

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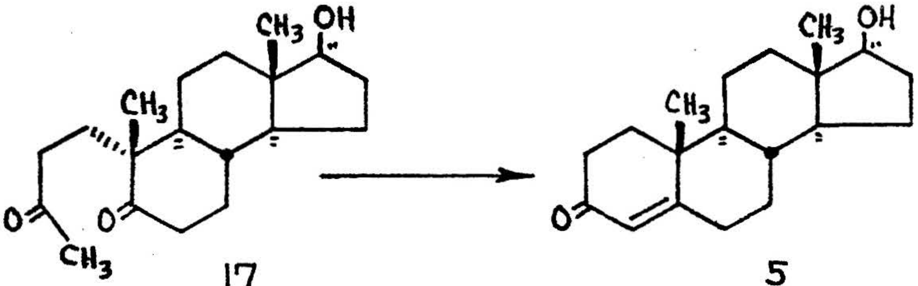
to the acetylenic ketone 16 (R=Ac) in 83% yield (from epoxyketone 13) (11b), while the latter affords the same product in 87% yield on heating (11a). Acetylenic ketones such as 16 are thus available in good yields by means of this reaction, which has been applied to a variety of other systems as well (11c). It has also been demonstrated that acetylene 16 (R=H) can be hydrated using mercuric ion catalysis to the 3-ketoseco-steroid 17, and this can be cyclized to testosterone (5) (11d).



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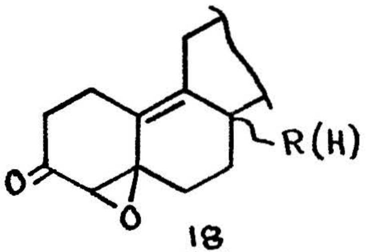
The transformation of epoxyketone 13 to the 3-ketosecosteroid 17 would have great bearing on the problem at hand if the Eschenmoser cleavage reaction could be induced to occur in a compound such as 18. If it could, then the acetylenic product 19 could be hydrated and selectively ketalized to give the desired unsaturated ketone 12, which corresponds directly to Stork's intermediate 8a. Thus it was decided to attempt the synthesis of an epoxyketone such as 18 from an aromatic intermediate such as 11; and determine if it could indeed be cleaved to an acetylenic ketone (19) and then converted to the desired enone ketal 12.



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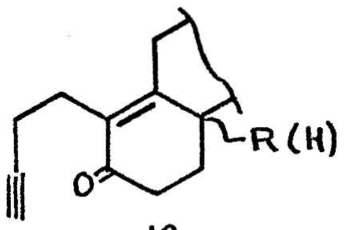

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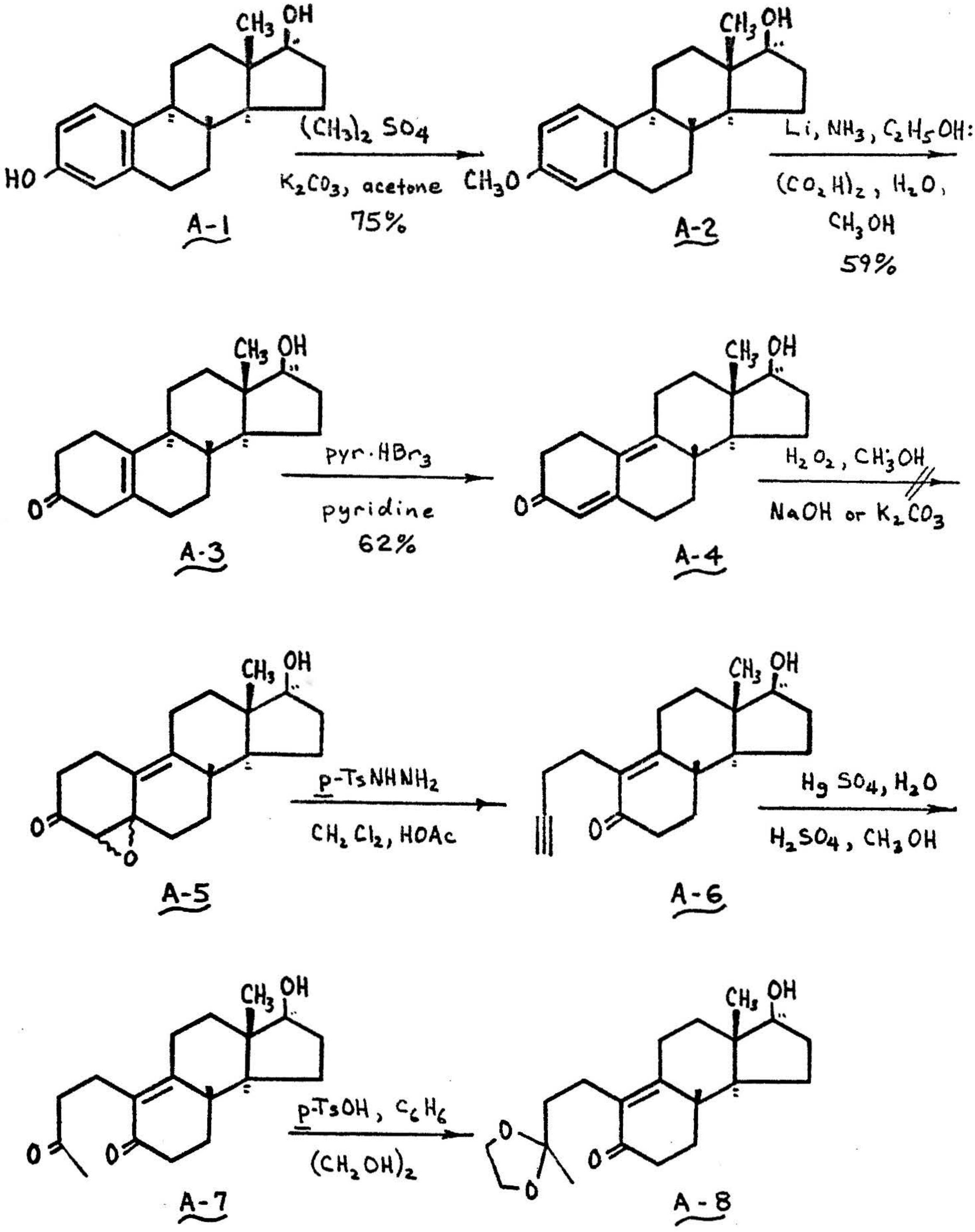
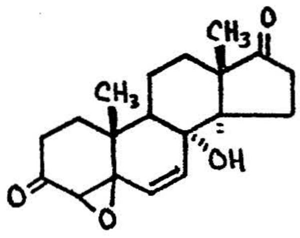
The actual system chosen for initial study of this transformation was estradiol, and the proposed route for its conversion to an intermediate such as enone 12 is outlined in Chart A. Estradiol (A-1) was selectively methylated on the phenolic oxygen to afford ether A-2. The aromatic ring was then reduced with lithium in ammonia and the resulting enol ether was hydrolyzed under mildly acidic conditions, all according to a modification of the procedure of Wilds and Nelson (4). The β,γ-unsaturated ketone A-3 thus obtained was converted to the dienone A-4 by treatment with pyridinium hydrobromide perbromide (12), and it was planned to effect epoxidation of this dienone with basic peroxide to

Chart A


A-1
$(CH_3)_2SO_4$
K_2CO_3, acetone
75%
A-2
Li, NH_3, C_2H_5OH:
$(CO_2H)_2$, H_2O,
CH_3OH
59%
A-3
pyr·HBr_3
pyridine
62%
A-4
H_2O_2, CH_3OH
NaOH or K_2CO_3
A-5
p-$TsNHNH_2$
CH_2Cl_2, HOAc
A-6
$HgSO_4$, H_2O
H_2SO_4, CH_3OH
A-7
p-TsOH, C_6H_6
$(CH_2OH)_2$
A-8

give the Eschenmoser reaction substrate A-5.

Unfortunately this last step could not be made to yield the desired product. Epoxidation was performed using either sodium hydroxide or potassium carbonate as base, and the disappearance of starting material was followed by the decrease in the ultraviolet absorption maximum at 304 $m\mu$ of diluted aliquots from the reaction mixture. Under conditions which effect complete epoxidation of α,β-unsaturated ketones within a few hours (13), the dienone A-4 was not completely consumed until nearly twenty-four hours; this is understandable as the second double bond should render the β position less electrophilic. Unfortunately, α,β-epoxyketones are known to be unstable to prolonged treatment with base or basic peroxide (14), and to yield a variety of cleavage/oxidation products. Apparently the rate of epoxidation of A-4 was slower than the rate of these secondary reactions; none of the epoxide A-5 could be isolated from the reaction mixture which yielded mostly complex mixtures of base soluble products. This is in accord with a recent observation in the literature (15) about the similar epoxide 20, which yields the diosphenol 21 and cleavage product 22 on treatment with base.



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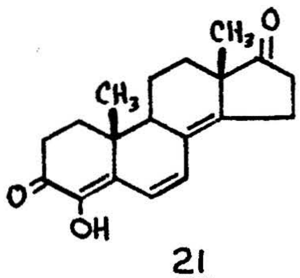

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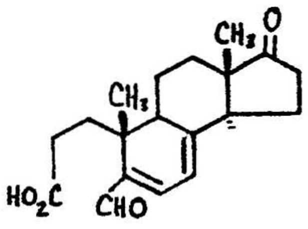

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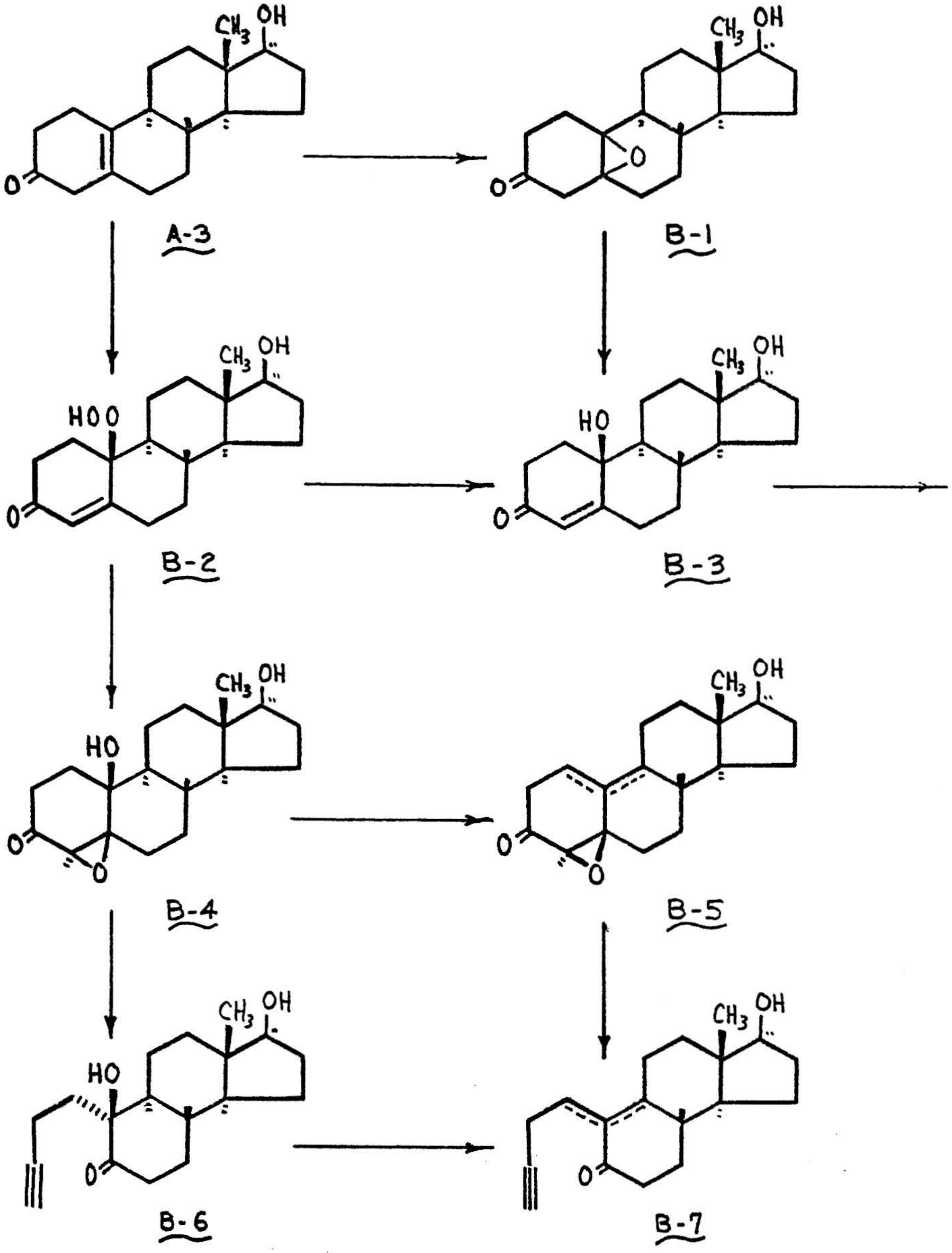
Considering the retarding effect of the 9(10) double bond on epoxidation of the A ring enone, it was decided to mask this olefin during epoxidation; but in such a way that it could be easily regenerated after the epoxide was formed (or even after the Eschenmoser cleavage reaction). A C-10 alcohol function appeared suitable for this purpose, and it had been shown that this group could be easily introduced to the enone A-3 by either of two methods. As outlined in Chart B, Djerassi and co-workers (16) had demonstrated that peracid epoxidation of the 5(10) double bond of enone A-3 proceeded to give epoxyketone B-1. Base induced opening of this epoxide then afforded the enone B-3, bearing the desired C-10 alcohol. Shapiro and co-workers (17) had also synthesized the alcohol B-3; they did so by reduction of the intermediate hydroperoxide B-2, which they had obtained as the principal product from photosensitized oxidation of the enone A-3. Presumably enone B-3 should be subject to epoxidation in basic hydrogen peroxide since the Δ^4 olefin is no longer part of an extended dienone system; thus epoxy-alcohol B-4 seemed easily attainable.

An interesting patent report by Legatt and Shapiro (18) had even described the conversion of hydroperoxide B-2 directly to the desired epoxide B-4 by treatment with dilute methanolic sodium hydroxide solution. This ingenious procedure presumably utilizes the hydroperoxide function present in the molecule B-2 itself to effect epoxidation (possibly intramolecularly) of the double bond. Although no yield was reported, this sequence seemed most intriguing, and it was decided to employ a photoöxygenation route to introduce the C-10 alcohol function. Rather than deal with the problems of protecting the C-17 alcohol for

Chart B

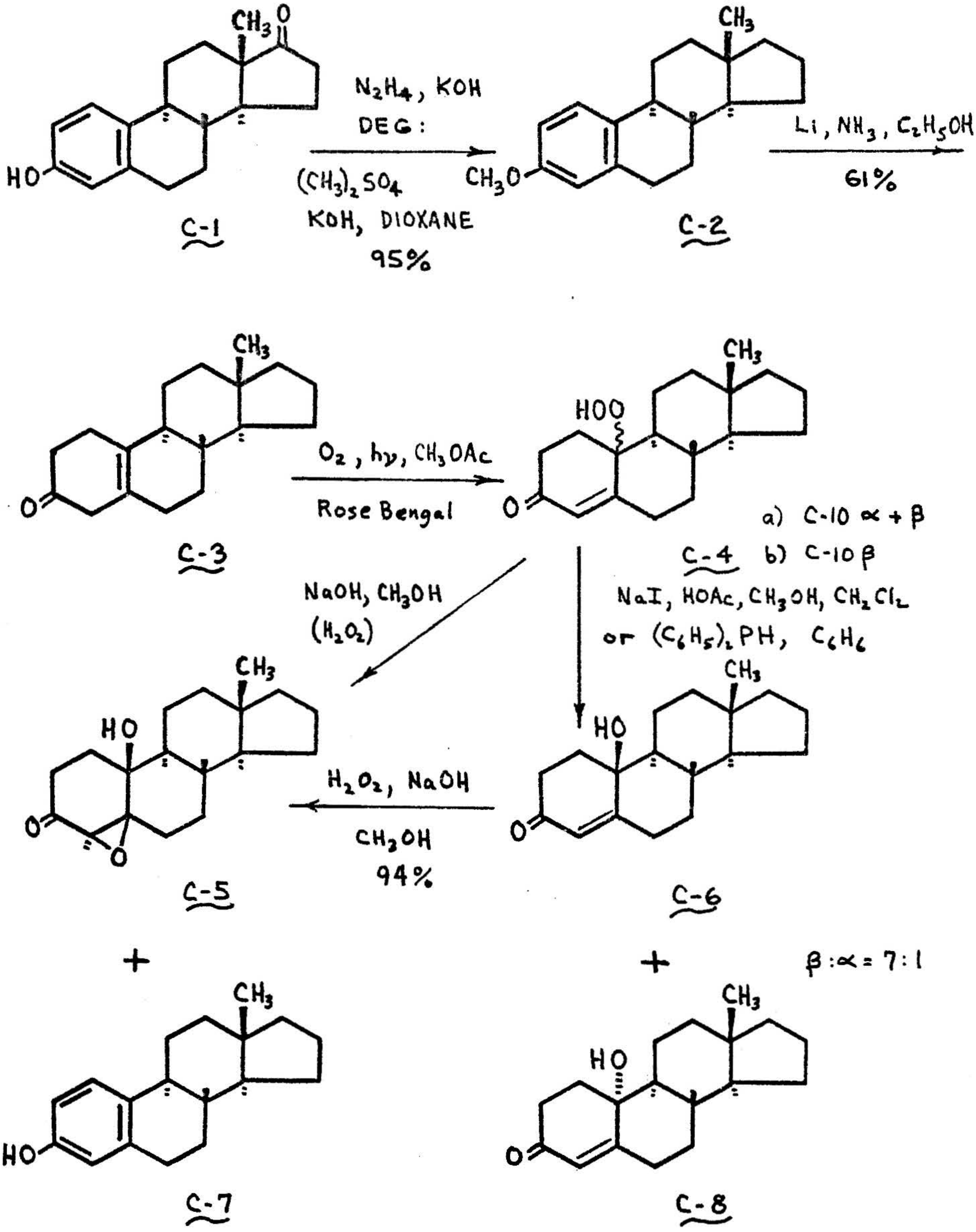


the subsequent dehydration step (i.e. B-4→B-5 or B-6→B-7), we chose to employ the 17-deoxy series for this study.

Estrone (C-1) was thus subjected to Wolff-Kishner reduction followed by methylation of the phenolic oxygen to give ether C-2 in 95% yield after crystallization. Reduction of the aromatic ring with lithium in ammonia, and mild acid hydrolysis of the resulting enol ether afforded the β,γ-unsaturated ketone C-3. Rose Bengal sensitized photoöxygenation (19) of this enone proceeded quite rapidly and there was obtained a 44% yield of the 10β-hydroperoxide C-4b after crystallization. The stereochemical assignment is made by analogy with the previously discussed photoöxygenation of enone A-3. This material proved extremely insoluble, however, and was difficult to work with and purify; for this reason it was not usually isolated, but instead the crude hydroperoxide mixture C-4a was employed directly for most reactions.

Sodium iodide reduction (20) of the crude hydroperoxide mixture C-4a afforded a 7:1 mixture of the β-alcohol C-6 and the α-alcohol C-8 in 63% overall yield from enone C-3. Better results were obtained reducing the hydroperoxide mixture with diphenylphosphine, in which case the desired alcohol C-6 was obtained itself in 64% yield. Also obtained from this second reduction was 9% of what appears to be the A ring phenol C-7. This material does not seem to be present to such an extent in the crude hydroperoxide mixture C-4a, and thus probably forms by elimination in some of the hydroperoxide during the reduction step.

Chart C


C-1
N₂H₄, KOH
DEG:
(CH₃)₂SO₄
KOH, DIOXANE
95%
C-2
Li, NH₃, C₂H₅OH
61%
C-3
O₂, hν, CH₃OAc
Rose Bengal
C-4
a) C-10 α + β
b) C-10 β
NaOH, CH₃OH
(H₂O₂)
NaI, HOAc, CH₃OH, CH₂Cl₂
or (C₆H₅)₂PH, C₆H₆
H₂O₂, NaOH
CH₃OH
94%
C-5
C-6
+
+
β:α = 7:1
C-7
C-8

Treatment of the enone C-6 with basic hydrogen peroxide afforded a 94% yield of the desired epoxyketone C-5; the overall yield of the epoxide C-5 from enone C-3 was thus 60% via the alcohol C-6.

Direct conversion of crude hydroperoxide mixture C-4a to epoxide C-5 was attempted next using the basic conditions of Legatt and Shapiro (18). Simply stirring the hydroperoxide mixture C-4a in methanolic sodium hydroxide did indeed afford epoxyketone C-5, but the yield after purification was a rather disappointing 32% (from enone C-3). The cause of this low yield was investigated by performing the same rearrangement on crystalline hydroperoxide C-4b. In this case a 64% yield (from hydroperoxide C-4b) of epoxyketone C-5 was obtained, and the major side product was found to be the alcohol C-6. Since this alcohol is subject to epoxidation by basic hydrogen peroxide, it seemed wise to treat the crude base rearrangement product from hydroperoxide C-4 with basic hydrogen peroxide prior to isolation of the epoxyketone C-5. This was done by treating crude hydroperoxide mixture C-4a with methanolic sodium hydroxide for 30 min, and then by adding hydrogen peroxide to this mixture and stirring for another 30 min. The yield of epoxyketone C-5 was 49% (from enone C-3) in this case, considerably improved from the 32% yield obtained without hydrogen peroxide treatment. Phenol C-7 was also isolated as a side product (12% yield) in this reaction; it has probably been present to some extent in all of the reactions involving hydroperoxide C-4, but has not always been isolated.

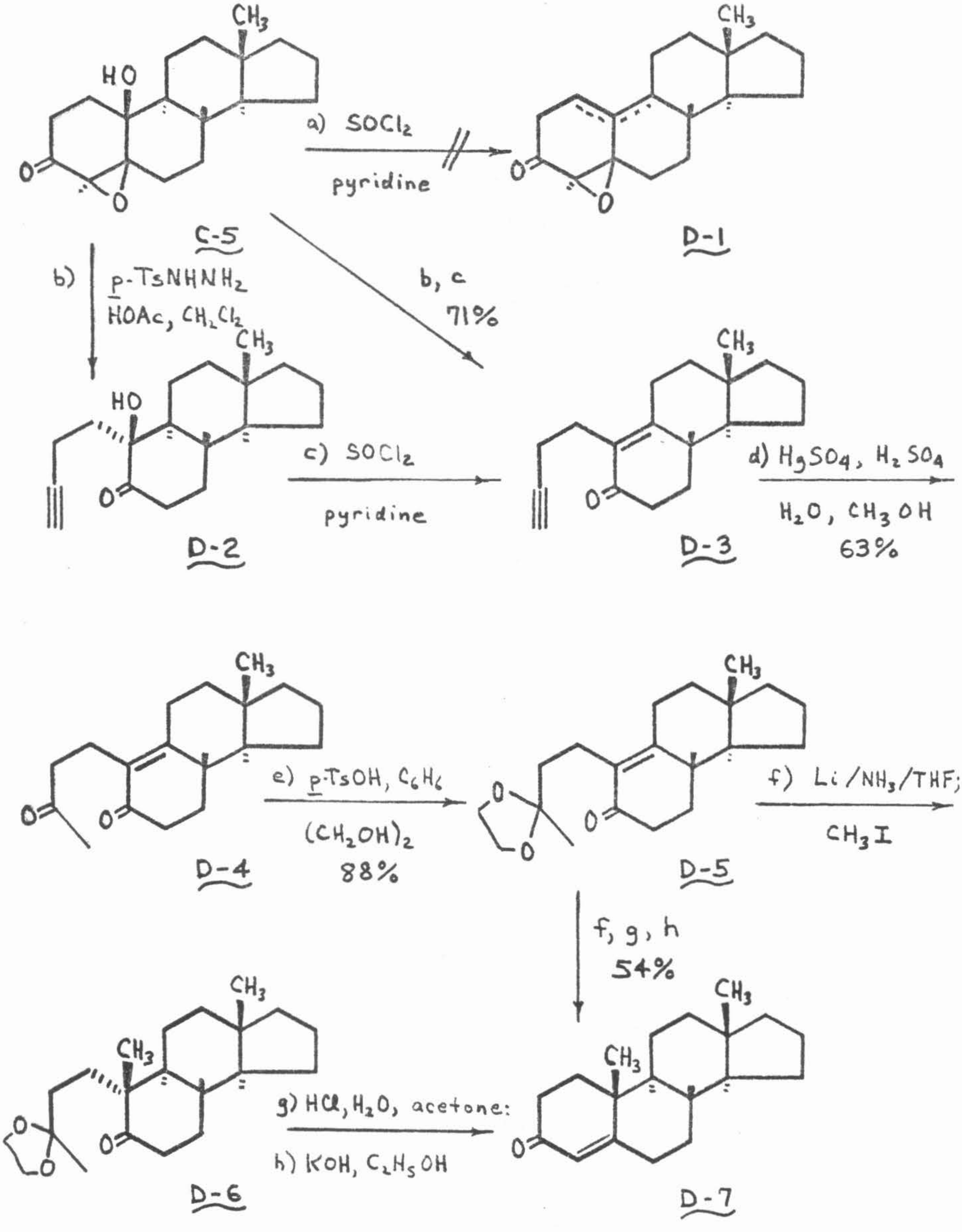
Several brief attempts at dehydration of the alcohol C-5, in an effort to generate the olefin D-1, resulted in complex product mixtures; this olefinic epoxide seemed a most difficult species to obtain. Since it appeared reasonable that the alcohol function might not interfere with the Eschenmoser reaction, it was decided to attempt cleavage with the 10β-hydroxy group in place. Thus epoxyketone C-5 was treated with p-toluenesulfonylhydrazine in 1:1 acetic acid-methylene chloride at -18° and later warmed to room temperature (11b, c). Spectra of the crude product, taken immediately after the reaction work-up, indicated nearly pure acetylenic hydroxyketone D-2; on standing overnight, however, this product underwent significant decomposition.

Since generation of the Δ^9-olefin was called for anyway, immediate dehydration of the crude cleavage product was attempted. Epoxyketone C-5 was cleaved and the resulting crude alcohol D-2 was treated within an hour of its isolation with thionyl chloride in pyridine. Enone D-3, obtained from this reaction in 71% yield (from epoxyketone C-5) after chromatography, contained a small amount of the phenol C-7 (~5%); none of the exocyclic olefin isomer was observable in the nmr.

The enone D-3 had only to be converted to the ketal D-5 and this transformation proceeded quite smoothly. Hydration of the acetylenic side chain of enone D-3 with mercuric sulfate in acidic aqueous methanol (21) afforded the diketone D-4 in 64% yield after purification (free of the slight phenolic impurity present in the starting enone). Selective ketalization of the saturated ketone proceeded quite well and an 88% yield of the desired ketal D-5 was obtained.

In converting the aromatic ether C-2 to the enone ketal D-5 we had effected the desired transformation of an aromatic A ring compound into an intermediate of the versatile type 12. Certain establishment

Chart D


C-5
D-1
D-2
D-3
D-4
D-5
D-6
D-7
a) SOCl₂
pyridine
b) p-TsNHNH₂
HOAc, CH₂Cl₂
b, c
71%
c) SOCl₂
pyridine
d) HgSO₄, H₂SO₄
H₂O, CH₃OH
63%
e) p-TsOH, C₆H₆
(CH₂OH)₂
88%
f) Li/NH₃/THF;
CH₃I
f, g, h
54%
g) HCl, H₂O, acetone;
h) KOH, C₂H₅OH
CH₃
HO
O

of the identity of enone D-5 was sought, however, and this was provided by elaborating this intermediate into the known androstenone D-7. The enone D-5 was treated with lithium in ammonia followed by iodomethane according to the reductive alkylation procedure of Stork and McMurry (10). Without purification the methylated ketone D-6 thus obtained was hydrolyzed to remove the ketal, and the resulting crude product was cyclized to afford androst-4-en-3-one (D-7) in 54% overall yield (from enone D-5). The melting point and nmr spectrum of this material are in agreement with those reported for enone D-7 in the literature (22). In addition to the desired product a small amount (5%) of a mixture was obtained which contained ~60% of what appears to be the 10α-isomer of enone D-7 (from nmr analysis). Not enough material was obtained to clearly establish this, however.

Synthesis of the α,β-unsaturated secosteroid D-5, from aromatic A ring ether C-2, demonstrates a transformation which expands the potential usefulness of aromatic intermediates in polycyclic systems. It may now be possible to substitute the 9 and/or 10 positions (steroid numbering) of such compounds in a variety of ways previously impossible starting from aromatic precursors. Modifications of this scheme are currently being investigated within the Ireland group on compounds related to fusidic acid.

Experimental Section

All reactions were run under an argon atmosphere unless otherwise noted. Melting points labeled (vac) were taken in evacuated capillaries on a Hoover capillary melting point apparatus while all others were determined on a Kofler micro hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared spectra (ir) were taken on a Perkin Elmer 237B grating infrared spectrometer. Nuclear magnetic resonance spectra (nmr) were taken on a Varian Associates Model T-60. Ultraviolet spectra (uv) were taken on a Cary recording spectrometer, Model 11M.

Alumina refers to grade I, neutral alumina supplied by M. Woelm, Eschwege, Germany, made up to grade II or III as indicated by addition of 3% or 6% water with shaking and equilibration prior to use. Ordinary silica gel columns used the 0.05-0.2 mm silica gel "for column chromatography" manufactured by E. Merck, Darmstadt, Germany. High pressure silica gel chromatography used the Silica Gel H "For TLC Acc. To Stahl" manufactured by E. Merck, Darmstadt, Germany.

Anhydrous solvents were dried immediately prior to use. Ether, tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from lithium aluminum hydride; *tert*-butyl alcohol and pyridine were distilled from calcium hydride; hexamethylphosphoramide (HMPA) was distilled at reduced pressure from calcium hydride; ammonia was distilled from a blue lithium or sodium solution; and methylene chloride and methylene iodide were distilled from phosphorous pentoxide. Petroleum ether refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30-60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J. and was not further purified.

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

3-Methoxy-1,3,5(10)-estratrien-17β-ol (**A-2**).

A stirred mixture of 3.99 g (14.6 mmoles) of estradiol (**A-1**), 28.0 g (0.20 mole) of potassium carbonate and 13.5 ml (18.2 g, 0.143 mole) of dimethylsulfate in 135 ml of acetone was heated at reflux for 75 min. After cooling, the mixture was treated with 100 ml of water and most of the acetone was evaporated under reduced pressure. This material was extracted with three 100-ml portions of ether, and the combined organic phases were washed with water (two 100-ml portions) and saturated brine (100 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the ether under reduced pressure, there was obtained 20 g of a liquid. This material was dissolved in 100 ml benzene and filtered through 600 g of grade III alumina with the aid of 2.5 l. of benzene. Evaporation of the filtrate at reduced pressure afforded 288 mg of crude 3,17β-dimethoxy-1,3,5(10)-estratriene as a white powder; nmr ($CDCl_3$) δ 0.78 (s, C-18 H), 3.36 (s, C-17 OCH_3), 3.74 (s, C-3 OCH_3), and 6.6-7.3 (m, Ar H); lit. (23) nmr ($CDCl_3$) δ 0.80 (s, C-18 H), 3.39 (s, C-17 OCH_3), and 3.76 (s, C-3 OCH_3).

Following elution of the alumina after 15 hr with 2 l. of acetone and concentration of the eluent at reduced pressure, there was obtained 4.9 g of a thick oil which on crystallization from n-hexane afforded in two crops 3.11 g (75%) of the alcohol **A-2** as fine white crystals mp 119-120° [lit. (4) 120.5-121.5°]; ir ($CHCl_3$) 3620 (OH), 1610, 1575, 1500 (aromatic), and 1260 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.76 (s, 3, C-18 H), 3.69 (m, 1, C-17 H), 3.76 (s, 3, Ar OCH_3), and 6.6-7.3 (m, 3, Ar H).

17β-Hydroxy-5(10)-estren-3-one (A-3).

A modification of the procedure of Wilds and Nelson (4) was employed for the reduction of the A ring and hydrolysis of the resulting enol ether. A solution of 2.96 g (10.3 mmoles) of the aromatic alcohol A-2 in 200 ml of THF was added dropwise over a 15-min period to a stirred blue solution of 3.5 g (0.5 g atm) of lithium wire in ca. 460 ml of ammonia (distilled from the cylinder through potassium hydroxide drying towers). After stirring for an additional 20 min, the solution was treated with 120 ml of ethanol over a 40-min period. The ammonia was then allowed to evaporate from the white suspension over the course of 16 hr, during which time the reaction mixture was protected from oxygen. Following evaporation of about half the solvent at reduced pressure, the remaining material was diluted with 1 l. of ether and the resulting mixture was washed with 250 ml of water and three 250-ml portions of saturated brine, and then dried ($MgSO_4$). After removal of the dessicant and concentration of the solution under reduced pressure, there was obtained 3.1 g (quantitative) of 3-methoxy-2,5(10)-estradien-17β-ol as a white solid; nmr ($CDCl_3$) δ 0.75 (s, C-18 H), 2.66 [s (broad), C-1 and C-4 H], 3.55 (s, $=\!\!\diagdown OCH_3$), 3.66 (m, C-17 H), and 4.65 [s (broad), C-2 H]; no δ 6.6-7.3 (Ar H).

To a solution 3.1 g of the crude 1,4-dihydro compound described above in 250 ml of methanol was added a solution of 3.8 g of oxalic acid dihydrate in 50 ml of water. The solution was stirred for 40 min at room temperature, and then poured onto 500 ml of saturated aqueous sodium bicarbonate solution. This mixture was extracted with three 300-ml portions of ether, and the combined organic phases were washed with saturated aqueous sodium bicarbonate solution (three 250-ml portions) and saturated brine (250 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent under reduced pressure, there was obtained 2.87 g of a white solid which upon two crystallizations from ethyl acetate afforded 1.65 g (59%) of enone A-3 as white plates; mp 197-198° (vac, dec) [lit. (4) 199.8-201° (vac, inserted at 180°)]; ir ($CHCl_3$) 3610, 3470 (OH), and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.76 (s, 3, C-18 H), 2.44 (s, 4, C-1 and C-6 H), 2.73 (s, 2, C-4 H), and 3.70 [t (broad), 1, J = 2 Hz C-17 H]. The mother liquors were chromatographed on 120 g of silica gel, eluted with 1:1 ethyl acetate-benzene. Following the first 280 ml, 120 ml of eluent was collected; concentration of this solution at reduced pressure afforded 570 mg of material which after crystallization from ethyl acetate gave 280 mg of enone A-3, mp 196-198° (vac, dec); the total yield of β,γ-unsaturated ketone A-3 was 1.93 g (68%).

17β-Hydroxy-4,9-estradien-3-one (A-4).

A stirred solution of 1.463 g (5.34 mmoles) of the enone A-3 in 75 ml of pyridine was chilled with an ice bath and treated with 2.06 g (6.4 mmoles) of pyridinium hydrobromide perbromide prepared according to the procedure of Fieser (24) . After stirring with ice bath cooling for 4 hr, the reaction mixture was kept in a 4° refrigerator for 16 hr. The solution was then diluted with 650 ml of ether and the resulting solution was washed with 10% aqueous sodium thiosulfate solution (250 ml), 10% hydrochloric acid (200 ml), saturated aqueous sodium bicarbonate solution (259 ml), water (250 ml) and saturated brine (250 ml), and then dried ($MgSO_4$). After removal of the dessicant and concentration of the solution at reduced pressure, there was obtained 1.4 g of yellowish solid which on crystallization from acetone and then from acetone-methylene chloride afforded 902 mg (62%) of the dienone A-4 as white crystals, mp 168.5-170.5° [lit. (25a) 187-188°, and (25b, c, d) 168.5-169.5]; ir ($CHCl_3$) 3615, 3440 (OH), 1655 (C=O), and 1605 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.90 (s, 3, C-18 H), 2.11 (s, 2), 2.44 (s, ca. 2), 3.67 [t (broad), 1, J = 8 Hz C-17 H], and 5.68 (s, 1, C-4 H); uv (EtOH) 304 mμ (ϵ=23,900).

Attempted epoxidation of the dienone A-4 to A-5.

Epoxidation was attempted using a modification of the procedure of Mancera and Reingold (13). To a stirred and ice cooled solution of 97.5 mg (0.357 mmole) of the dienone A-4 in 2.5 ml of methanol was added 0.5 ml of 30% aqueous hydrogen peroxide solution and 0.15 ml of 10% aqueous sodium hydroxide solution. Stirring and cooling of this mixture were continued, and at various times measured aliquots were withdrawn and diluted to an exact volume with ethanol. The 304 mμ uv absorbance of these diluted aliquots was measured to determine the remaining concentration of dienone A-4 in the reaction mixture. After 9 hr the absorbance had only decreased to half of its initial value, so additional 30% aqueous hydrogen peroxide solution (0.25 ml) and 10% aqueous sodium hydroxide solution (75 μl) were added. The reaction mixture was then stored in a 4° refrigerator for 15 hr, after which the 304 mμ absorbance of the diluted aliquot measured 23% of the initial value. At this point the reaction mixture was diluted with 200 ml of ethyl acetate and the resulting solution was washed with two 500-ml portions of water and 500 ml of saturated brine, and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, there was obtained 37 mg of a yellow solid which had the same principal peaks in its ir and nmr spectra that characterize the starting dienone A-4. After acidification with 10% hydrochloric acid, the aqueous phases were extracted with two 100-ml portions of methylene chloride, and these extracts were combined and dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, 21 mg of a yellow oil was obtained. This oil streaked badly on tlc (26) (acetone, single development); vpc (27) (oven temperature 300°) showed one principal peak (ret. time 2.9 min) comprising ca. 60% of the eluted material; ir ($CHCl_3$) 3610, 3550-3000 (acid OH), 1710 (C=O), 1655 (C=O), and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) showed nothing between δ 6.6-7.4 (no A ring Ar H).

A similar experiment was performed on 81 mg of dienone A-4 in 1.0 ml of methanol at room temperature, but 25 mg of potassium carbonate was used as base and five 0.1 ml portions of 30% aqueous hydrogen peroxide were added to the solution during the 69 hr it stirred. As in the experiment described above, this reaction afforded after work-up a small return of starting material from the neutral extracts and a mixture of base soluble components (no phenols) from the aqueous washes.

3-Methoxyestra-1,3,5(10)-triene (C-2).

A modification of the procedure of K. J. Sax and co-workers was employed (28). A stirred mixture of 5.0 g (18.4 mmoles) of estrone (C-1), 35 g of 85% potassium hydroxide pellets and 25 ml of 85% hydrazine hydrate in 250 ml of diethylene glycol was heated at reflux for 1 hr with an internal temperature of ca. 142°. With the aid of an argon stream passing through the reaction vessel, moisture and excess hydrazine were then distilled from this mixture over ca. a 45-min period until the internal temperature reached 200°. After continued gentle reflux at 200° for 3 hr the solution was cooled, diluted with 500 ml of water and then poured onto a mixture of 400 ml of concentrated hydrochloric acid and 600 ml of ice and water. The resulting mixture was extracted with ether (four 800-ml portions) and the combined organic phases were washed with water (six 800-ml portions) and brine (800 ml) and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure there was obtained 4.79 g (quantitative) of crude 3-hydroxyestra-1,3,5(10)-triene (C-7) as a white solid; ir ($CHCl_3$) 3595, 3420 (OH), 1610, 1585, 1500 (aromatic), 1380 (CH_3) and 1175 cm^{-1} (ArOH); nmr ($CDCl_3$) δ 0.72 (s, 3, C-18 H), 5.3 [s (broad), 1, ArO H], and 6.5-7.3 (m, 3, Ar H).

To a stirred solution of 4.79 g (18.4 mmoles) of the crude 3-hydroxyestra-1,3,5(10)-triene (C-7) described above in 95 ml of dioxane were added 65 ml of water, a solution of 1.9 g (29 mmoles) of 85% potassium hydroxide in 9 ml of water, and 2.5 ml (3.3 g, 26 mmoles) of dimethyl sulfate. This stirred mixture was heated with a 110° bath at gentle reflux for 4 hr, with the addition of another 1.9 g (29 mmoles) of 85% potassium hydroxide and 2.5 ml (26 mmoles) of dimethyl sulfate halfway into this period. After cooling, this mixture was then poured onto 100 g of ice and the resulting suspension was filtered; the white solid remaining in the filter was dissolved in ca. 500 ml of ether and this solution was dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure, 4.96 g of a light yellow solid was obtained which on crystallization from methanol-methylene chloride afforded 4.73 g (95%) of aromatic ether C-2 as white crystals, mp 77.0-78.5° [lit. (28) mp 78-79°]; ir ($CHCl_3$) 1608, 1575, 1500 (aromatic), 1377 (CH_3) and 1255, 1152, 1040 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) 0.72 (s, 3, C-18 H), 3.76 (s, 3, ArO CH_3) and 6.5-7.3 (m, 3, Ar H).

Estr-5(10)-en-3-one (C-3).

Reduction was accomplished according to a modified procedure of Wilds and Nelson (4). Into a flask containing a stirred solution of 4.73 g (17.45 mmoles) of the aromatic ether C-2 in 400 ml of dry ether was distilled ca. 500 ml of ammonia from the tank (through potassium hydroxide drying towers). To this stirred solution was added over a 10-min period 140 cm (5.1 g, 730 mg atms) of lithium wire in small pieces, followed by the dropwise addition over the course of 1 hr of 130 ml of absolute ethanol. The reaction mixture was protected from oxygen while most of the ammonia was allowed to evaporate over ca. 16 hr, and the remaining suspension was cautiously treated with 1 l. of water. This mixture was extracted with ether (three 900-ml portions) and the combined organic phases were washed with 300 ml of Claisen alkali, two 800-ml portions of water and 800 ml of saturated brine and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure, 7 g of a damp solid was obtained.

A modification of the procedure of F. Colton and co-workers (29), was employed for hydrolysis of the reduction product described above. A mixture of 7 g of the crude reduction product, 20 ml of water and 10 ml of acetic acid in 75 ml of methanol and 25 ml of chloroform was heated at reflux for 1 hr. After cooling the solution was diluted with 2.4 l. of ether and the resulting solution was washed with water (800 ml), saturated aqueous sodium bicarbonate solution (two 800-ml portions), water (800 ml) and saturated brine (800 ml), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 4.5 g of a damp product which on three crystallizations from methanol-methylene chloride afforded 2.78 g (61%) of enone **C-3** as white crystals, mp 117-119°. The analytical sample obtained from crystallization of a portion of this material again from methanol-methylene chloride melted at 118-119.5°; ir ($CHCl_3$) 1710 (C=O), 1450 ($-CH_2-$) and 1378 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.72 (s, 3, C-18 H), 2.44 [s (broad), 4] and 2.72 [s (broad), 2]; lit. (30) nmr ($CDCl_3$) δ 0.72, 2.43 and 2.72 (3 singlets).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.77; H, 10.15.

10β-Hydroperoxyestr-4-en-3-one (C-4b).

The photoöxygenation apparatus described in the Appendix was flushed with oxygen and a very gentle oxygen stream was circulated through the system to prevent liquid from passing through the fritted discs. A solution of 200 mg (0.774 mmole) of enone C-3 in 9 ml of methyl acetate was placed in the apparatus followed by a partial solution of 45 mg of Rose Bengal in 1 ml of pyridine; an additional 6 ml of methyl acetate was used to effect complete addition of the enone and sensitizer. The system was sealed and tap water was run through the cooling jacket at ca. 100 ml/min. The Dry Ice trap was filled and then the circulated oxygen stream was increased to a brisk flow. With a General Electric 650 watt DWY bulb positioned in the lamp cavity at the uppermost level of the solution, irradiation was begun by applying 75 volts to the lamp. Oxygen uptake ceased at the theoretical amount (17 ml) after about 2 min and illumination was stopped after 3.5 min. The oxygen stream was slowed and the mixture was rinsed from the apparatus with the aid of 90 ml of ether. The resulting solution was swirled with 30 ml of silica gel and this mixture was filtered with the aid of 50 ml of ether through a short column containing an additional 30 ml of silica gel. After evaporation of the solvent at reduced pressure the residue was dried for 1.5 hr at ~0.05 mm pressure and 229 mg (quantitative) of crude hydroperoxide C-4a was obtained as a pink oil; ir ($CHCl_3$) 3525, 3260 (-O-O-H), 1665 (C=O), 1595 (C=C) and 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.77 (s, C-18 H) and 5.98 [s (broad), C-4 H]. Crystallization of this material from ether-hexane afforded 100 mg (43.7%) of the hydroperoxide C-4b as slightly pink crystals, mp 170-172° (vac, dec). A second crystallization of a portion of this material afforded the analytical sample as white crystals, mp 170-172° (vac, dec); nmr $(CD_3)_2SO$ δ 0.74 (s, 3, C-18 H) and 5.88 [s (broad), 1, C-4 H]. This crystalline material was exceedingly insoluble in chloroform, carbon tetrachloride, benzene and acetone. No ir was obtained for this solid due to its insolubility.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.55; H, 9.02.

10β-Hydroxyestr-4-en-3-one (C-6) and 10α-Hydroxyestr-4-en-3-one (C-8).

A. Photoöxygenation of the enone C-3.

The photooxygenation apparatus described in the Appendix was flushed with oxygen and a very gentle oxygen stream was circulated through the system to prevent liquid from passing through the fritted discs. A solution of 200 mg (0.774 mmole) of enone C-3 in 9 ml of methyl acetate was placed in the apparatus followed by a partial solution of 45 mg of Rose Bengal in 1 ml of pyridine; an additional 7 ml of methyl acetate was used to effect complete addition of the enone and sensitizer. The system was sealed and tap water was run through the cooling jacket at ca. 100 ml/min. The Dry Ice trap was filled and then the circulated oxygen stream was increased to a brisk flow. With a General Electric 650 watt DWY bulb positioned in the lamp cavity at the uppermost level of the solution, irradiation was begun by applying 75 volts to the lamp. Oxygen uptake ceased after ca. 2.5 min and illumination was stopped after 3.0 min. The oxygen stream was slowed and the mixture was rinsed from the apparatus with the aid of 90 ml of ether. The resulting solution was washed with 5% aqueous sodium hydroxide solution (three 25-ml portions), 2% hydrochloric acid (25 ml), 5% aqueous sodium hydroxide solution (25 ml) and saturated brine (two 25-ml portions), and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 228 mg of the crude hydroperoxide mixture **C-4a** as a pink solid.

B. Reduction of the hydroperoxide mixture C-4.

1. Using sodium iodide

A modification of the procedure of Bailey and Erickson (20) was employed for the reduction. A stirred solution of -25° of 225 mg (*ca.* 0.774 mmole) of the crude hydroperoxide **C-4a** described above in 1.5 ml of methanol and 1 ml of methylene chloride was treated with a solution of 232 mg (1.55 mmoles) of sodium iodide in 1 ml of methanol, 0.5 ml of methylene chloride and 0.4 ml of acetic acid. The cooling bath was removed and after stirring at room temperature for 2.3 hr the mixture was diluted with 100 ml of ether. The resulting solution was washed with water (25 ml), 5% aqueous sodium hydroxide solution (25 ml), 10% aqueous sodium thiosulfate solution (2X25 ml), water (25 ml) and saturated brine (25 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 225 mg of a tan foam was obtained. Two crystallizations of this material from ether-hexane afforded 50 mg (24%) of β-alcohol **C-6** as faintly yellow crystals, mp 139-141° (vac); ir ($CHCl_3$) 3600, 3440 (OH), 1662 (C=O), 1625 (C=C), 1455 ($-CH_2-$) and 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.77 (s, 3, C-18 H) and 5.74 [d (broad), 2, J = 2 Hz, C-4 H]; uv (CH_3OH) 237 mμ (ϵ=1.3X10^4). Purification of the 175 mg of nonvolatile material remaining in the mother liquors from the above crystallizations was accomplished by ptlc (26) (ether, single development). The major fraction contained an additional 66 mg (31%) of β-alcohol C-6 as a white foam (R_f 0.39); nmr ($CDCl_3$) same as that from crystalline material above. This raised the total yield of β-alcohol C-6 to 116 mg (55% from enone C-3). The analytical sample was obtained as white crystals from crystallization of a portion of the chromatographed material above from methylene-chloride-hexane, and melted at 140.5-141.5° (vac); ir and nmr were the same as those of crystalline material described above.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.75; H, 9.58.

A second fraction obtained from the above ptlc (R_f 0.21) contained 17 mg (8% from enone C-3) of the α-alcohol C-8 as a white solid; ir ($CHCl_3$) 3590, 3420 (OH), 1665 (C=O), 1455 (CH_2) and 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.67 (s, 3, C-18 H) and 5.80 s (broad), 1, C-4 H . Crystallization of this material from ether and a trace of methylene chloride afforded the analytical sample which melted at 177-180° (vac, dec; inserted at 170°); ir and nmr were the same as those of chromatographed material above.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.74; H, 9.44.

2. Using diphenylphosphine

In the manner described in part A above, 205 mg of crude hydroperoxide **C-4a** was prepared from 176 mg (0.682 mmole) of enone **C-3**; irradiation in this case, however, was continued for only 2.5 min. A stirred suspension at $10-15^\circ$ of 205 mg of this crude hydroperoxide in 5 ml of benzene was treated with 177 μl (190 mg, 1.02 mmoles) of diphenylphosphine. The suspended solid dissolved at once, and after stirring at $10-15^\circ$ for 35 min the resulting solution was treated with 50 μl ($\sim$ 0.77 mmole) of 30% aqueous hydrogen peroxide solution. After 5 min, 90 ml of ether was added and the resulting solution was washed with saturated aqueous sodium bicarbonate solution (six 30-ml portions), 10% aqueous sodium bisulfite solution (30 ml) and saturated brine (30 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 363 mg of an oil was obtained. Purification of this material on ptlc (26) (ether, single development) afforded 120 mg (64% from enone **C-3**) of the β-alcohol **C-6** as a white foam (R_f 0.42); nmr ($CDCl_3$) was the same as that of β-alcohol **C-6** described in part B-1 above. A second fraction from ptlc (R_f 0.76) contained 17 mg (9%) of phenol **C-7**; nmr ($CDCl_3$) was the same as that of the Wolff-Kischner reduction product obtained in the preparation of aromatic ether **C-2**.

4β,5β-Epoxy-10β-hydroxyestr-3-one (**C-5**).

A. From crude hydroperoxide C-4a with methanolic sodium hydroxide.

Photooxygenation of 400 mg (1.54 mmoles) of enone **C-3** was performed using the same procedure described for obtaining **C-4b**, except that all material amounts were doubled, and illumination was continued for 5 min.

The entire 522 mg of crude hydroperoxide C-4a obtained as an oil from this reaction was dissolved in 10 ml of methanol, stirred at 0° and treated with 1 ml of 5% aqueous sodium hydroxide solution. After stirring with ice cooling for 6 hr this solution was diluted with 100 ml of water and the resulting mixture was saturated with sodium chloride and then extracted with ether (four 125-ml portions). The combined organic extracts were washed with water (three 100-ml portions) and saturated brine (two 100-ml portions) and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure, 421 mg of a yellow foam was obtained. This material was purified by column chromatography on 30 g of grade III alumina. The column was eluted with 125 ml of 50% ether-petroleum ether and then with 25 ml of 75% ether-petroleum ether; continued elution by this latter solvent mixture afforded in the next 100 ml, 144 mg (32% from enone C-3) of the epoxyketone C-5 as white crystals, mp 124-129°. Crystallization of a portion of this material from ether-hexane afforded the analytical sample as fine white needles, mp 128-129.5°; ir ($CHCl_3$) 3590, 3480 (OH), 1710 (C=O), 1450 (CH_2), 1380 (CH_3) and 1040, 1015, 995, 975, 950 cm^{-1} ($C\overset{O}{-}C$); nmr ($CDCl_3$) δ 0.76 (s, 3, C-18 H) and 3.10 (s, 1, C-4 H).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.34; H, 9.07.

Another experiment was performed using the same procedure and material amounts described above, except that the base catalyzed epoxidation was performed at room temperature for 1 hr. The yield of epoxyketone C-5 from this reaction was 31% after chromatography.

B. From pure hydroperoxide C-4b with methanolic sodium hydroxide.

A stirred solution of 140 mg (0.476 mmole) of crystalline hydroperoxide C-4b in 10 ml of 1:1 methanol-methylene chloride was treated at room temperature with 1 ml of 5% aqueous sodium hydroxide solution. After stirring for 1.6 hr this mixture was diluted with 150 ml of ether and 20 ml of methylene chloride and the resulting solution was washed with water (two 50-ml portions) and saturated brine (50 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure 141 mg of a yellow oil was obtained. Purification of this material on ptlc (26) (30% ether-petroleum ether, single development) afforded 90 mg (64%) of the epoxyketone C-5 as a slightly yellow solid, R_f 0.21; nmr ($CDCl_3$) was the same as that from material described in part A. Only one volatile component was present in this material as determined by vpc (27) (oven temperature 220°, ret. time 2.2 min), and it has the same ret. time as epoxyketone C-5 described in part A above. A second fraction obtained from ptlc (R_f 0.15) contained 36 mg of crude alcohol C-6 as a yellow oil; ir and nmr of this material show major peaks corresponding to those present in the spectra of purified alcohol C-6 described above. Analysis by vpc (27) reveals one major component (oven temperature 220°, ret. time 2.7 min) comprising about 90% of the volatile material; this component has the same ret. time as alcohol C-6.

C. From crude hydroperoxide C-4a with methanolic sodium hydroxide and hydrogen peroxide.

The same photooxygenation procedure described in part A of the experimental discussion of alcohols C-6 and C-8 was applied to 200 mg (0.774 mmole) of enone C-3; all material amounts and the work-up were the same, but irradiation of the solution was continued for 3.5 min. The entire 219 mg of pink-solid hydroperoxide C-4a thus obtained was dissolved in 3.5 ml of methanol and 1.5 ml of methylene chloride. This stirred solution was treated with 0.5 ml of 5% aqueous sodium hydroxide solution and after 30 min with 0.6 ml of 30% hydrogen peroxide solution. After stirring for an additional 30 min this mixture was diluted with 100 ml of ether and the resulting solution was washed with water (25 ml), 10% aqueous sodium thiosulfate solution (two 25-ml portions), water (25 ml) and saturated brine (two 25-ml portions) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 162 mg of a yellow oil was obtained. Purification of this material on ptlc (26) (30% ether-petroleum ether, single elution) afforded 111 mg (49% from enone C-3) of epoxyketone C-5 as a white solid, R_f 0.21; nmr ($CDCl_3$) was the same as that from material described in part A; analysis by vpc (27) showed only one major component (~90% of the volatile material) having the same ret. time as epoxyketone C-5 described in part A (oven temperature 220°, ret. time 2.2 min).

A second fraction from the above ptlc (R_f 0.29) consisted of 23 mg (11.5%) of phenol C-7 as a pale yellow solid; nmr ($CDCl_3$) was the same as that of the Wolff-Kischner reduction product C-7 obtained in making aromatic ether C-2; analysis by vpc (27) showed one volatile component having the same ret. time (oven temperature 220°, ret. time 2.7 min) as phenol C-7.

D. From hydroxy enone C-6 using basic hydrogen peroxide.

To a stirred solution of 50 mg (0.182 mmole) of the hydroxy enone C-6 in 1.5 ml of methanol was added at room temperature 0.3 ml (ca. 2 mmoles) of 30% aqueous hydrogen peroxide solution and then 0.1 ml of 10% aqueous sodium hydroxide solution. After stirring for 45 min this mixture was diluted with 100 ml of ether and the resulting solution was washed with water (two 25-ml portions) and saturated brine (two 50-ml portions) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure there was obtained 50 mg (94%) of epoxyketone C-5 as white crystals, mp 126-129°; nmr ($CDCl_3$) was the same as that from purified material from part A; on tlc (26) (50% ether-petroleum ether, single development) only one spot (R_f 0.36) was visible; analysis by vpc (27) showed only a single volatile component (oven temperature 220°, ret. time 2.2 min).

Attempted dehydration of alcohol C-5.

To a stirred solution at -10° of 47 mg (0.16 mmole) of alcohol C-5 in 1.7 ml of dry pyridine was added 75 μl (117 mg, 1 mmole) of thionyl chloride. After stirring at -10° for 15 min longer, the solution was diluted with 30 ml of saturated brine and 10 ml of water. This mixture was then extracted with ether (three 35-ml portions) and the combined organic phases were washed with water (three 35-ml portions) and saturated brine (two 35-ml portions) and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 13 mg of a brown oil; ir ($CHCl_3$) showed two weak bands at 1725 and 1665 cm^{-1} (saturated and unsaturated C=O), as well as bands at 3595, 3250-3540 cm^{-1} (OH, acid?); otherwise peaks were broad and ill-defined: nmr ($CDCl_3$) showed no singlet at ca. δ 3.1 (C-4 H of 4,5-epoxide). The combined aqueous phases described above were extracted with methylene chloride (three 50-ml portions) and the combined organic extracts were washed with 50 ml of water and two 50-ml portions of brine and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 28 mg of a brown oil; ir ($CHCl_3$) showed only a small peak at 1725 cm^{-1} (saturated C=O) with almost none at 1665 cm^{-1} (unsaturated C=O), and otherwise was comprised of broad, ill-defined absorptions; nmr ($CDCl_3$) showed no singlet at ca. δ 3.1 (C-4 H of 4,5-epoxide) and consisted mostly of broad unintelligible peaks. On tlc (26) the products from both the ethereal and the methylene chloride extracts streaked badly from the origin to R_f .42 (50% ether-petroleum ether, single development).

10β-Hydroxy-4,5-seco-3-estryn-5-one (D-2).

The general procedure of Eschenmoser and co-workers (11b, c) was adapted to epoxyketone C-5. A dry mixture at -20° of 54.3 mg (0.187 mmole) of epoxyketone C-5 and 37.3 mg (0.200 mmole) of p-toluenesulfonylhydrazine was treated with 1 ml of a -20° mixture of 1:1 acetic acid-methylene chloride. This mixture was stirred between -20° and -10° for 30 min, at 0° for 30 min, and at room temperature for 6 hr; a yellow color developed in the solution during the first hour at room temperature and remained throughout the remainder of the reaction. The solution was then poured onto 35 ml of water and the resulting mixture was extracted with ether (three 35-ml portions). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (two 35-ml portions) and saturated brine (two 35-ml portions) and then dried (Na_2SO_4). After removal of the dessicant and evaporation of the solvent at reduced pressure, 57 mg of a yellow oil was obtained. Purification of this oil the following day on ptlc (26) (10X20 cm plate, 50% ether-petroleum ether, single development) afforded 25 mg (49%) of acetylenic ketone D-2 as a yellow oil; ir ($CHCl_3$, within 1 hr of isolation) 3590, 3410 (OH), 3300 (acetylenic C-H), 2120 (C≡C), 1710 (C=O), 1455 (CH_2) and 1380 cm^{-1} (CH_3); nmr ($CDCl_3$, within 1 hr of isolation) δ 0.76 (s, C-18 H). On the following day examination of this material on tlc (26) (50% ether-petroleum ether, single development) revealed a large spot with R_f 0.40, and an equally large streak from the origin to R_f 0.20. Attempts to crystallize this oil from ether-hexane met with no success; reexamination of the product on tlc (same conditions described above) six days after isolation by ptlc revealed only a small spot at R_f 0.40 but a very large streak from the origin to R_f 0.22. Spectra were taken of the six day old material; ir ($CHCl_3$) 3510, 3400-3000 (acid OH?), 3300 (acetylenic C-H), 2120 (C≡C), 1710 (broad, C=O), and rather broad peaks below 1400 cm^{-1}; nmr ($CDCl_3$) still showed 0.76 (s, C-18 H), but numerous peaks in the methylene region δ 1.0-3.0 were different than in the nmr of this material within 1 hr after isolation. Since the initially obtained alcohol D-2 appears to be unstable on standing at room temperature, no combustion analysis was obtained.

4,5-Seco-9-estren-3-yn-5-one (D-3).

A. Eschenmoser cleavage of epoxyketone C-5.

The general procedure of Eschenmoser and co-workers (11b, c) was adapted to epoxyketone C-5. A dry mixture at -15° of 144 mg (0.495 mmole) of epoxyketone C-5 and 98 mg (0.525 mmole) of p-toluenesulfonylhydrazine was treated with stirring with 3.1 ml of a -15° mixture of 1:1 acetic acid-methylene chloride. The mixture was stirred between -15° and -10° for 1 hr, at 0° for 30 min, and at room temperature for 5 hr, and was then diluted with 150 ml of ether. The resulting solution was washed with water (50 ml), saturated aqueous sodium bicarbonate solution (three 50-ml portions) and saturated brine (two 50-ml portions) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 146 mg of crude acetylenic hydroxyketone D-2 as a yellow oil. Due to the unstable nature of this material it was used within ca. 1 hr in the next step.

B. Dehydration of acetylenic hydroxyketone D-2.

To a stirred -10° solution of 146 mg of freshly prepared crude hydroxyketone D-2 in 5.3 ml of pyridine was added 0.32 ml (540 mg, 4.5 mmoles) of thionyl chloride (distilled from triethylphosphite). After stirring for 15 min longer between -10° and -5°, this mixture was diluted with 150 ml of ether. The resulting solution was washed with 5% hydrochloric acid (two 50-ml portions), water (50 ml), saturated aqueous sodium bicarbonate solution (50 ml) and saturated brine (two 50-ml portions) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure 136 mg of a brown oil was obtained. Purification of this material on ptlc (26) (40% ether-petroleum ether, single development) afforded 90 mg (71% from epoxyketone C-5) of the acetylenic enone D-3 as a slightly brown oil; ir ($CHCl_3$) 3300 (acetylenic C-H), 2120 (C≡C), 1660 (C=O), 1600 (C=C), 1455 ($-CH_2-$), and 1385 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.89 (s, C-18 H), no peaks between 5.0-6.5 [C-1 H of Δ 1(10) olefin], with very small peaks at 0.73 and 6.6-8.0 (possibly a trace of phenol C-7). This slightly impure material was used in future experiments. The analytical sample was obtained by evaporative distillation of a portion of this material at 140-150° (0.3 mm); ir and nmr were the same as those described above except for the absence of the small impurity peaks in the nmr.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.27; H, 9.44.

4,5-Seco-9-estren-3,5-dione (D-4).

To a stirred solution of 100 mg (0.364 mmole) of acetylenic enone D-3 in 5 ml of methanol was added 0.5 ml of a 10% aqueous sulfuric acid solution saturated with mercuric sulfate. A yellow white precipitate formed immediately after this addition and remained as the mixture was stirred at room temperature for 1.25 hr. This suspension was then diluted with 150 ml of ether and the resulting mixture was washed with saturated brine (50 ml), saturated aqueous sodium bicarbonate solution (two 50-ml portions) and saturated brine (50 ml) and then dried ($MgSO_4$); some difficulty was had with emulsions during these washes. After removal of the dessicant and evaporation of the solvent at reduced pressure, 89 mg of a slightly yellow oil was obtained. Purification of this material on ptlc (26) (60% ether-petroleum ether, single development) afforded 67 mg (63%) of the enedione C-4 as a slightly yellow oil suitable for analysis; ir ($CHCl_3$) 1710 (saturated C=O), 1660 (unsaturated C=O), 1600 (C=C), and 1455 cm^{-1} ($-CH_2-$); nmr ($CDCl_3$) δ 0.88 (s, 3, C-18 H) and 2.14 [s, 3, $-C(O)\ CH_3$].

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.74; H, 9.66.

4,5-Seco-9-estren-3,5-dione 3-ethylene acetal (D-5).

A stirred mixture of 59 mg (0.215 mmole) of enedione D-4, 5 mg of p-toluenesulfonic acid and 1 ml of ethylene glycol in 12 ml of benzene was heated at reflux through a Dean Stark water separator with Drierite in the collecting tube. After stirring at reflux for 50 min the mixture was cooled and diluted with 60 ml of ether. The resulting solution was washed with saturated aqueous sodium bicarbonate solution (two 30-ml portions) and water (five 50-ml portions) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 68 mg of a yellow oil was obtained. Purification of this material on ptlc (26) (10X20 cm plate, 60% ether-petroleum ether, single elution) afforded 60 mg (88%) of the enone ketal D-5 as a clear oil suitable for analysis; ir ($CHCl_3$) 1655 (C=O), 1600 (C=C), 1380 (CH_3) and 1055 cm^{-1} (acetal C-O); nmr ($CDCl_3$) δ 0.88 (s, 3, C-18 H), 1.36 (s, 3, C-4 H) and 3.97 [s, 4, $-O(CH_2)_2O-$].

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.53; H, 9.32.

Androst-4-en-3-one (D-7).

A. Reductive methylation of enone D-5.

A modification of the procedure of Stork and McMurry (10) was employed in this step. A solution of 2 mm (7 mg, 1 mmole) of lithium wire in ~12 ml of dry ammonia and 2 ml of dry ether was prepared. To this stirred blue solution at reflux was added dropwise over a 2-min period a solution of 66.6 mg (0.209 mmole) of enone D-5 and 3.76 μl (0.209 mmole) of water in 4 ml of dry ether. After stirring for 20 min longer, the blue solution was quenched with a solution of 0.15 ml (0.34 g, 2.4 mmoles) of iodomethane in 1 ml of dry ether. The blue color faded immediately and stirring was continued for 1 hr longer. Most of the ammonia was then evaporated over a 10-min period with the aid of a hot air gun. This suspension was diluted with 100 ml of ether and the resulting mixture was washed with water (three 30-ml portions) and saturated brine (two 30-ml portions) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, there was obtained 72 mg of crude methylated ketone D-6 as a cloudy oil; ir ($CHCl_3$) 1700 (C=O), 1455 ($-CH_2-$) and 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.76 (s, ~3, C-18 H), 1.10 (s, ~3, C-19 H), 1.35 (s, ~3, C-4 H) and 3.89 [s, ~4, $-O(CH_2)_2O-$], as well as a large singlet at 0.07 (silicon grease impurity). This material was used directly in the next step without purification.

B. Hydrolysis of the ketal D-6 and subsequent cyclization to androstenone D-7.

A solution of 72 mg of crude ketal D-6 and 0.56 ml of 10% hydrochloric acid in 1.4 ml of acetone was stirred for 20 min at room temperature. The mixture was diluted with 100 ml of ether and the resulting solution was washed with water (25 ml), saturated aqueous sodium bicarbonate solution (25 ml) and saturated brine (25 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent there was obtained 63 mg of a cloudy oil. This material was dissolved in 1.9 ml of ethanol, treated with 13 mg of 85% potassium hydroxide pellets and the resulting mixture was heated to reflux. After refluxing for 90 min, the mixture was cooled and diluted with 75 ml of ether. This solution was washed with water (25 ml), saturated aqueous ammonium chloride (25 ml) and saturated brine (25 ml) and then dried ($MgSO_4$). After removal of the dessicant and evaporation of the solvent at reduced pressure, 52 mg of crude androstenone D-7 was obtained as a yellow oil. Purification of this material by ptlc (26) (25% ether-petroleum ether, double development) afforded one large uv active band which was removed from the plate in three equal parts. From the center portion of this band (R_f 0.33) there was obtained 30.5 mg (54% from enone D-5) of androstenone D-7 as white crystals, mp 101-104° [lit. (22a) mp 104-105°].

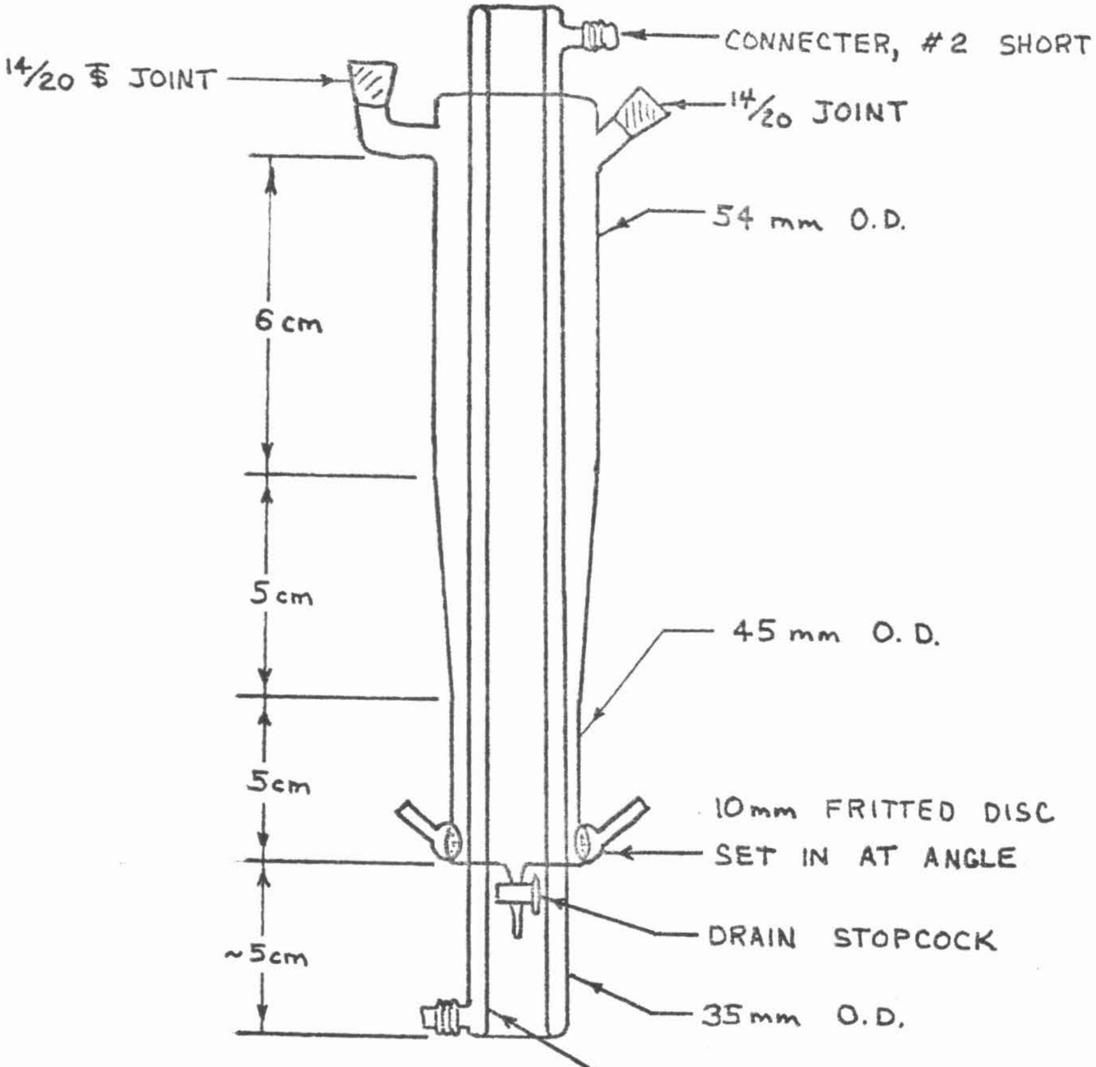
After one crystallization of this material from methanol, a sample was obtained which melted at 104-105°; ir ($CHCl_3$) 1665 (C=O), 1615 (C=C), 1455, 1435 ($-CH_2-$) and 1380 cm^{-1} (CH_3); nmr ($CDCl_3$) δ 0.76 (s, 3, C-18 H), 1.20 (s, 3, C-19 H) and 5.74 [s (broad), 1, C-4 H]: lit. (22b) nmr ($CDCl_3$) δ 0.76 (s, 3), 1.19 (s, 3) and 5.73 (s, 1). The lower portion (R_f 0.25) of the uv active chromatography band afforded 3.0 mg (5%) of an oil consisting of 2 volatile components by vpc (27) (oven temperature 230°); the minor component (~40%) had a ret. time of 2.3 min, the same as that of recrystallized androstenone D-7, while the major isomer (~60%) had a 2.0 min ret. time. The nmr ($CDCl_3$) of this mixture showed singlets at δ 0.79, 1.20 and 1.25, as well as two broad singlets at δ 5.83 and 5.74 (ca. 3:2 ratio); the lit. (31) nmr ($CDCl_3$) for 17β-acetoxy-10α-androst-4-en-3-one is reported as δ 0.77, 1.24 and 5.78 (singlets). The second component in this fraction may well be 10α-androst-4-en-3-one.

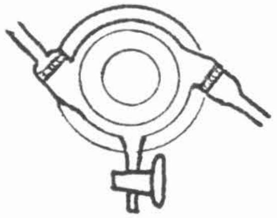
Appendix

A need to efficiently photoöxygenate small to moderate amounts ($\sim$1-20 mmoles) of material prompted the design of the photoöxygenation apparatus shown in Fig. 1 (32). A solution of compound and sensitizer is placed in the outside well (the tapered construction allows small amounts of material to be efficiently cooled and irradiated in the bottom of the well, while still maintaining an appreciable total volume for the apparatus). Oxygen is bubbled in through the fritted discs (a gentle flow must always be maintained when liquid is in the well to prevent seepage through the frits). Cooling water is circulated through the cooling jacket, and the lamp (usually a G.E. DWY bulb powered by a Variac) is suspended in the central cavity so that the filament is just below the liquid level in the well. A condenser (water or Dry Ice) is fitted atop the apparatus to limit solvent loss.

If desired, oxygen uptake can be measured to determine the extent of reaction. In this case a pump is used to circulate oxygen through the apparatus as part of a closed system (Fig. 2). The system is fitted with the same sort of manometer, burette gas reservoir and mercury filled leveling bulb commonly used to measure gas uptake during low-pressure hydrogenation. It is sometimes difficult to obtain exact readings, however, especially when volatile solvents are employed, as temperature variations on irradiation can cause significant vapor pressure changes of the solvent.

FIGURE 1




ATTACHMENT OF
FRITTED DISCS AND
DRAIN STOPCOCK

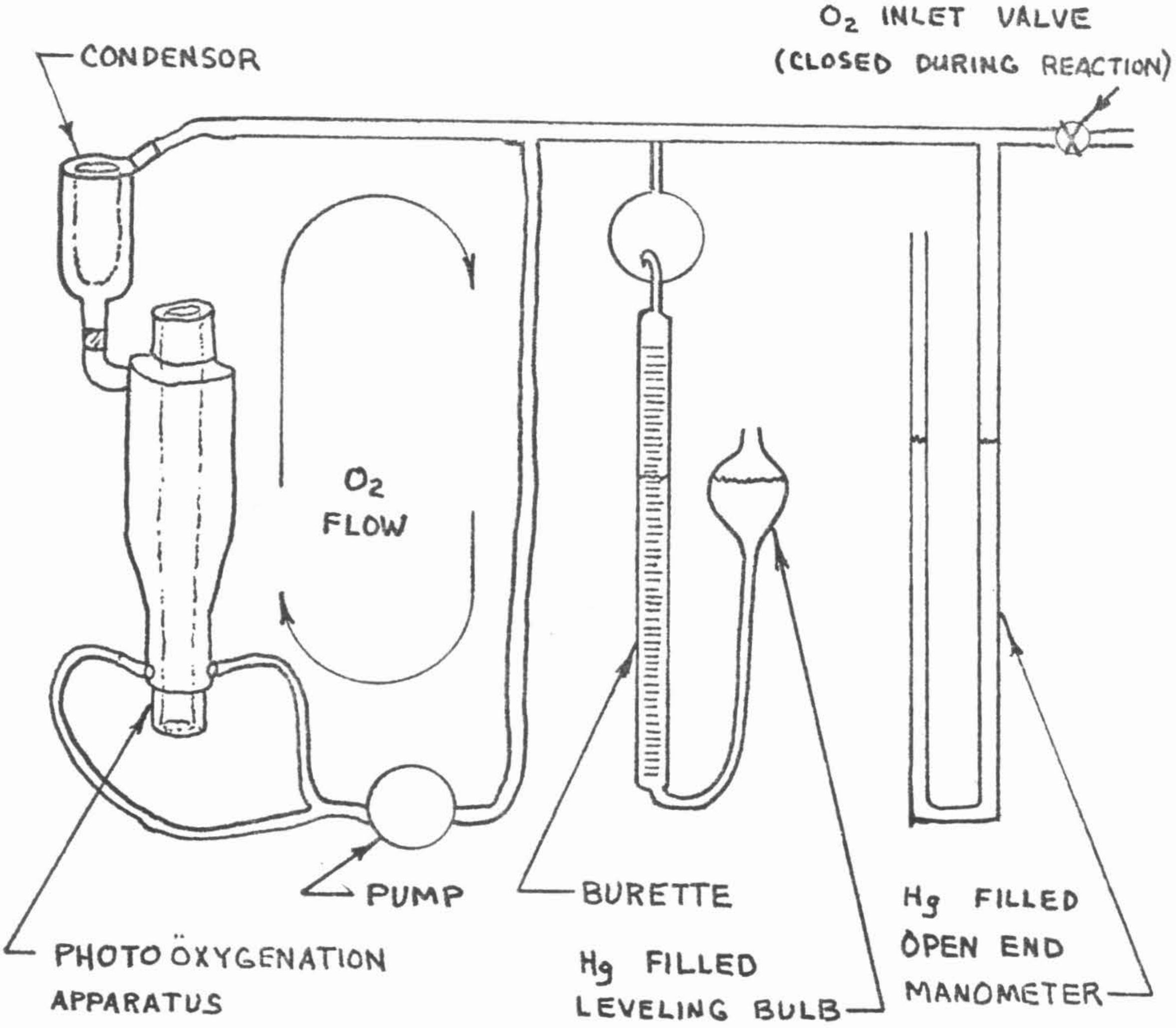

CONDENSOR
O2 INLET VALVE
(CLOSED DURING REACTION)
O2 FLOW
PUMP
BURETTE
PHOTO ÖXYGENATION APPARATUS
Hg FILLED LEVELING BULB
Hg FILLED OPEN END MANOMETER

FIGURE 2

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26. Preparative thin layer chromatography (ptlc) was performed commercially on 20cm X 20cm plates (unless other dimensions are specified) coated with a 2 mm layer of silica gel F-254, as manufactured by E. Merck, Darmstadt, Germany. Analytical thin layer chromatography (tlc) was performed on commercial 5 X 10cm plates coated with a thin layer of silica gel F-254, supplied by Brinkman Instruments Inc, Westburg, N.Y.

27. Analyses by vapor phase chromatography (vpc) were carried out on an F & M Model 810 gas chromatograph or on a Hewlett Packard Model 5750 gas chromatograph. Both machines were equipped with 6ft X 1/8in columns packed with 3% silicon gum rubber (SE 30) on Chromosorb Q (NAW), 60-80 mesh, and the carrier gas (helium) was maintained at 60 ml/min through each column.

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32. We wish to thank Dr. C. A. Foote for allowing us to examine a number of photooxygenation systems used in his lab. Several features of these systems were incorporated into our design.

Proposition 1

The synthesis of a detergent, specifically designed to solubilize membrane bound proteins in their active form; and its use in some test systems is proposed.

Among the earliest triumphs of biochemistry lies the elucidation of the Embden-Meyerhof glycolytic pathway and the Krebs' tricarboxylic acid cycle. Considering the complexity of these systems, it seems remarkable at first glance that their unraveling should have come so early in the history of biochemistry; however, an examination of the experimental methods used to attack these systems, reveals the important key which made understanding possible. Virtually all of the enzymes involved in these two pathways are water soluble proteins which can be readily purified in an active form. Thus, each pure enzyme can be combined with various substrates and co-factors in in vitro experiments, which allow direct determination of the enzymatic requirements and reaction products. Each reaction can be studied independently, and the pieces of the pathway systematically put into place.

Other systems have not been so easily studied. Electron transport, for example, long remained a poorly understood process until it was finally worked out in some detail by B. Chance (1), using transport inhibitors and spectroscopic techniques on essentially in vivo enzyme systems. The same powerful techniques used to unravel the glycolytic pathway could not be applied here since most of the electron transport enzymes are tightly bound to membrane surfaces and cannot be isolated in pure, active form for in vitro experiments. Thus, there is no easy way to do separate experiments with individual enzymes in order to determine which interact with which, which with NADH, and how these interactions occur. The problem of untangling the biochemistry in such a system is extremely difficult.

Unfortunately, there are a large number of important membrane bound proteins which, like the electron transport enzymes, cannot be isolated for study in any sort of pure, active, soluble form. If such isolation were possible, understanding of their exact functioning might progress at the fast rate associated with soluble proteins, and thus would greatly accelerate work in many areas of biochemistry. Much effort has gone into solving this very problem for specific enzymes, with varying degrees of success (2), but no good general technique has yet been developed. In order to approach a general solution, one must first consider the nature of membranes and membrane bound proteins.

Hardly understood themselves with any great certainty, membranes and their properties (3) seem reasonably well explained by the fluid mosaic model (4); in essence, this model views the basic membrane as a lipid bilayer, with hydrophobic groups abutting on the interior, and hydrophilic groups forming the two boundary surfaces which interact with the aqueous media (Fig. 1-a). Stabilizing this structure is the thermodynamic decrease in free energy associated with isolating the hydrophobic side chains essentially outside of the surrounding water structure. The actual membrane bound proteins are imbedded in this bilayer as shown in Fig. 1-b, with major hydrophilic regions exposed to the aqueous solution, and with an intensely hydrophobic middle section favorably interacting with the hydrocarbon region of the membrane. It is this hydrophobic belt which holds the protein in the bilayer (exactly as the lipids themselves are held in).

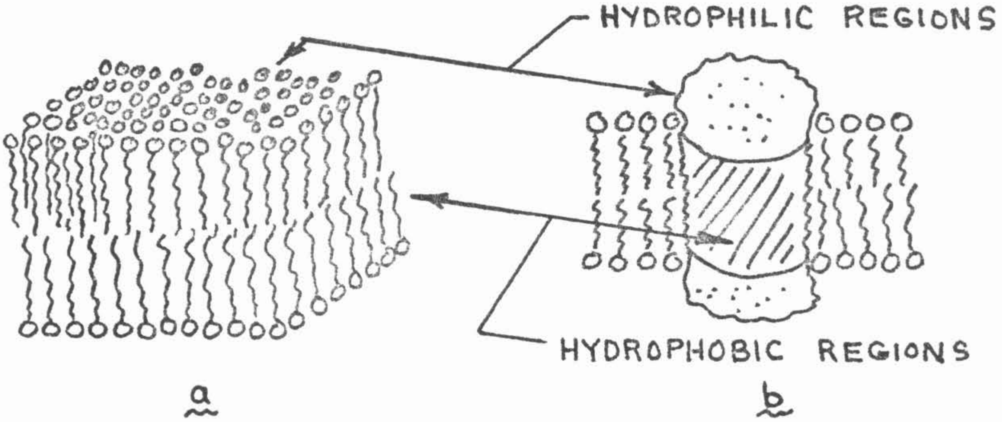


FIGURE 1

If this model is correct, then in order to remove an intact protein from the lipid bilayer, one would have to provide a suitable substitute nonpolar interaction for this middle section of the protein; in essence, what is called for is a less polar solvent than water, or a surface active agent (detergent) which can effectively solubilize this hydrocarbon region. Both approaches have been tried (2), but when proteins have indeed been solubilized two main problems have arisen. Most frequently, the protein is denatured, and no enzymatic activity can be observed [although in this state the various inactive components can be separated reasonably well (5)]. When it is possible to obtain active solubilized enzymes, they are difficult to purify as they tend to form large aggregates.

These results are understandable, for with a short chain, very nonspecific detergent such as SDS, the detergent is small and flexible enough to easily slip into the protein and destroy its tertiary structure (and hence its activity). The inactive polypeptide chains are completely dissolved, however, and thus become separable into distinct units. With large, polymeric, nonionic detergents (such as Triton X-100), penetration into the enzyme is less likely and thus denaturing is less of a problem. Since a molecule of the detergent is quite large and coiled, however, it probably interacts with itself, other molecules of detergent, and possibly even other protein molecules, as much as it interacts with any one specific molecule of protein. Thus, the solubilized detergent-protein-lipid mass may not contain any discrete species which are soluble and isolable, but more likely is an equilibrium mixture of everchanging aggregates of the various components. Removal of the detergent therefore, often leads to aggregation of the protein molecules, since protein-protein interaction (about their hydrophobic regions) should be quite strong, while the protein-detergent interaction should be no stronger than the weak detergent-detergent interaction.

What seems to be called for as a solution to this problem, is a detergent which interacts more strongly with the protein than with itself; such a detergent must not readily interact with several species at once to form solution aggregates, and yet must be large enough to remain outside of the protein and not destroy its tertiary structure.

In order to design such a detergent, one should begin by considering an interaction with membrane bound proteins which must be quite favorable, i.e. that between the protein and lipid in an actual membrane (Fig. 2-a). While a monolayer of these lipids should be most compatible with the protein, the hydrocarbon portion of the lipids offer no more favorable an interaction with water than the protein itself; hence such a monolayer would not solubilize the protein.

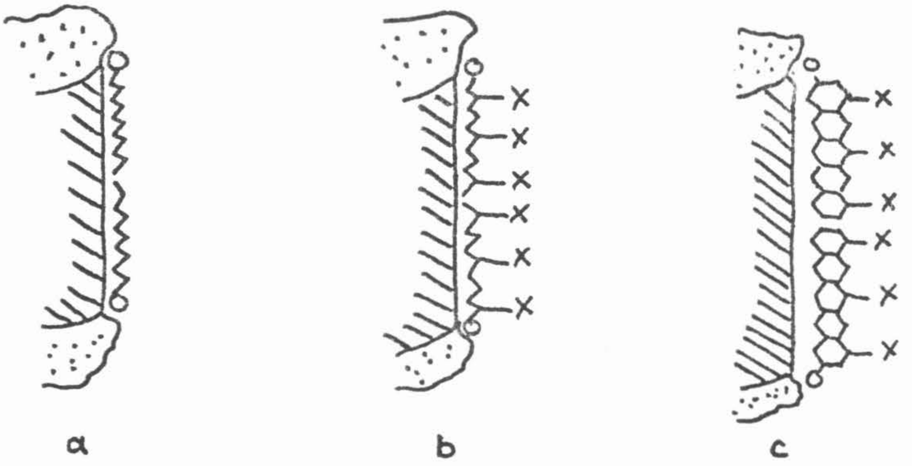
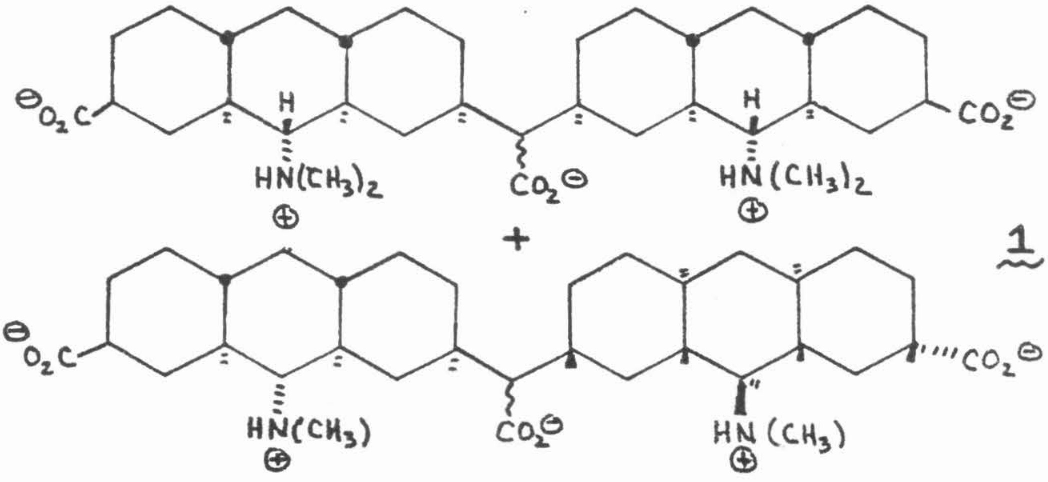


FIGURE 2

A suitably substituted hydrocarbon chain could be constructed, however, in order to provide a favorable interaction with both the protein and the water. Such a chain, when fully extended along the hydrophobic belt of the protein, would have polar groups (X) directed into the aqueous medium as shown in Fig. 2-b. As drawn, this species should be soluble; unfortunately, the hydrocarbon chains would probably coil on themselves (entropically more favorable) and cause the proteins to aggregate. If the hydrocarbon could be made rigid, however, this problem would be eliminated; the required rigidity could be suitably achieved by incorporating the proper ring structure in the molecule, as shown in Fig. 2-c. This type of molecule should meet all the criteria set forth above for a detergent, except possibly the first; in view of its large, totally rigid structure such a compound may be extremely crystalline and difficult to get into solution. The synthetic problems associated with such a molecule are formidable as well.

Fortunately, the solution to either of these problems may be the solution to both. Total rigidity may not be necessary (or even desired) as long as the detergent has enough structure to prevent coiling on itself. The detergent need not be a single compound, either, as certain diasteriomeric mixtures would do equally well in solvating the protein. Both of these modifications should tend to decrease the detergent's affinity for itself, while greatly simplifying the synthesis of the molecule.

In view of these considerations, the mixture of diastereomers 1 is proposed as meeting the criteria set forth for a membrane-protein detergent. Each tricyclic subunit is rigid, so any given molecule can-



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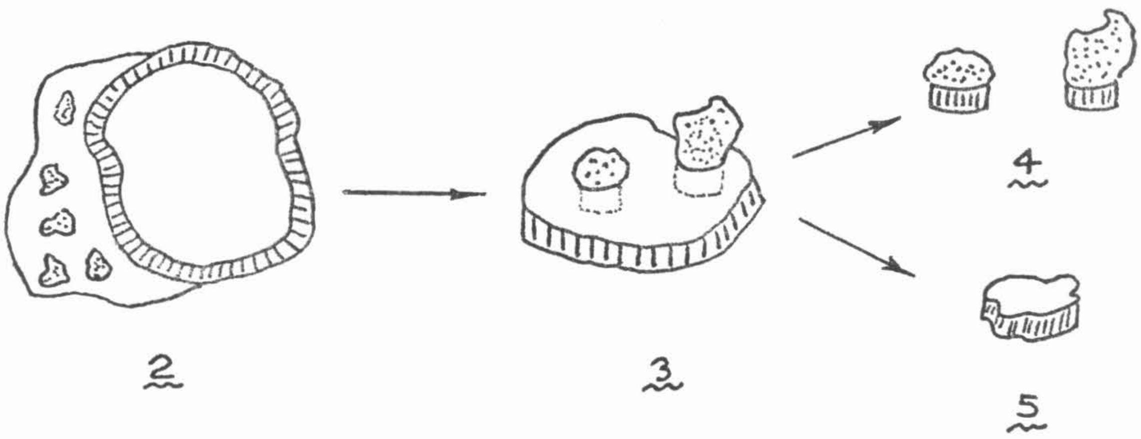
not coil upon itself. When laid flat, these molecules have a hydrophobic edge corresponding in length to a fully extended 15 carbon chain. Since the most prevalent fatty acids in membranes number 16 or 18 carbons, one of the detergent molecules should span halfway across the hydrophobic belt of a protein. Thus, two monolayer belts of these molecules around a membrane protein, with their hydrocarbon edges inward, should closely simulate for the protein the membrane itself. The outside functionalized edge, being quite polar, should interact very well with an aqueous media; hence the entire protein-detergent complex should be water soluble exactly as desired.

The actual process of solubilizing proteins held in membranes might best be accomplished by sonicating a mixture of the membranes and detergent. When closed membranes are sonicated themselves, they are torn apart and reform into smaller closed bilayer structures (vesicles). These vesicles have a minimum size which is a function of surface tension effects, and which is still large with respect to the membrane proteins.

Presumably such vesicles form since the exposed edge of a torn membrane is an unfavorable, high-energy species in aqueous solution. In the presence of a detergent such as **1**, however, the torn edge of the membrane should be able to favorably interact with the nonpolar edge of the detergent molecules. This interaction should lead to species such as **2**, which on further sonication with detergent should give smaller pieces **3**. Since a closed membrane surface no longer needs to be maintained, the ultimate products of this continued process should be



detergent solubilized proteins **4** and small detergent coated pieces of lipid bilayer **5**. Each detergent molecule **1** will bear a net charge at biological pH, and thus the solubilized species should be charged and repel one another. Having the charged detergent molecules dispersed over the large surface of the enzyme "belt" should be more favorable than having them in small charge-concentrated micelles of their own. Both of these effects should tend to stabilize the sonication fragments as discrete entities, separable from each other and from any excess detergent without aggregation.

In order to test the validity of the above reasoning, the detergent **1** should be synthesized. This can be approached most efficiently (6) by the construction of a suitable tricyclic fragment and the subsequent dimerization of this to give the large detergent molecules. One such possible synthesis is outlined in Chart A.

The starting material, 4,4 -dimethoxybenzophenone (**A-1**) is commercially available (7). Hall and co-workers have shown that the carbonyl function in such molecules can be completely reduced to the hydrocarbon using lithium-ammonia and ammonium chloride (8). Subsequent addition of more lithium and *t*-butyl alcohol to the reaction mixture should effect normal Birch reduction of the aromatic rings, to afford after mild acid hydrolysis the symetrical unsaturated diketone **A-2** (9). H. C. Brown's annelation reaction involving carbonylation of cyclic organoboranes (10) could then be employed. Treatment of diketone **A-2** with 3 equivalents of thexylborane should yield only the trans, trans fused intermediate **A-3**; after carbonylation of borane **A-3**, the keto dialcohol **A-4** should be obtained with the trans, trans ring fusions retained (10). The rigid tricyclic nucleus could thus be formed in essentially two steps.

Formation of the ketal **A-5** and protection of one alcohol function as a benzyl ether would afford alcohol **A-6**. This could be converted to the bromide **A-7** suitable for coupling to a dimeric species. A number of procedures might be envisaged for this coupling; among the simplest would be carbonation of the derived organolithium **A-8**, followed by subsequent addition of a second mole of organolithium **A-8** to the initially formed lithium carboxylate. This procedure should yield the ketone **A-9** (11) (note: all compounds after coupling are diastereomeric mixtures of coupled products).

Hydrogenation of both the ketone and benzyl ether would afford triol **A-10**, the ketal functions of which could then be hydrolyzed. Conversion of the resultant diketone **A-11** into the bis-dimethylamine **A-12** could be accomplished using the reductive amination procedure of Borch and Durst (12). Oxidation of the triol **A-12** would afford triketone **A-13**. Treatment of **A-13** with 2-lithio-2-trimethylsilyl-1,3-dithiane (13) should afford the tris-ketenethioacetal **A-14**, hydrolysis

CHART A

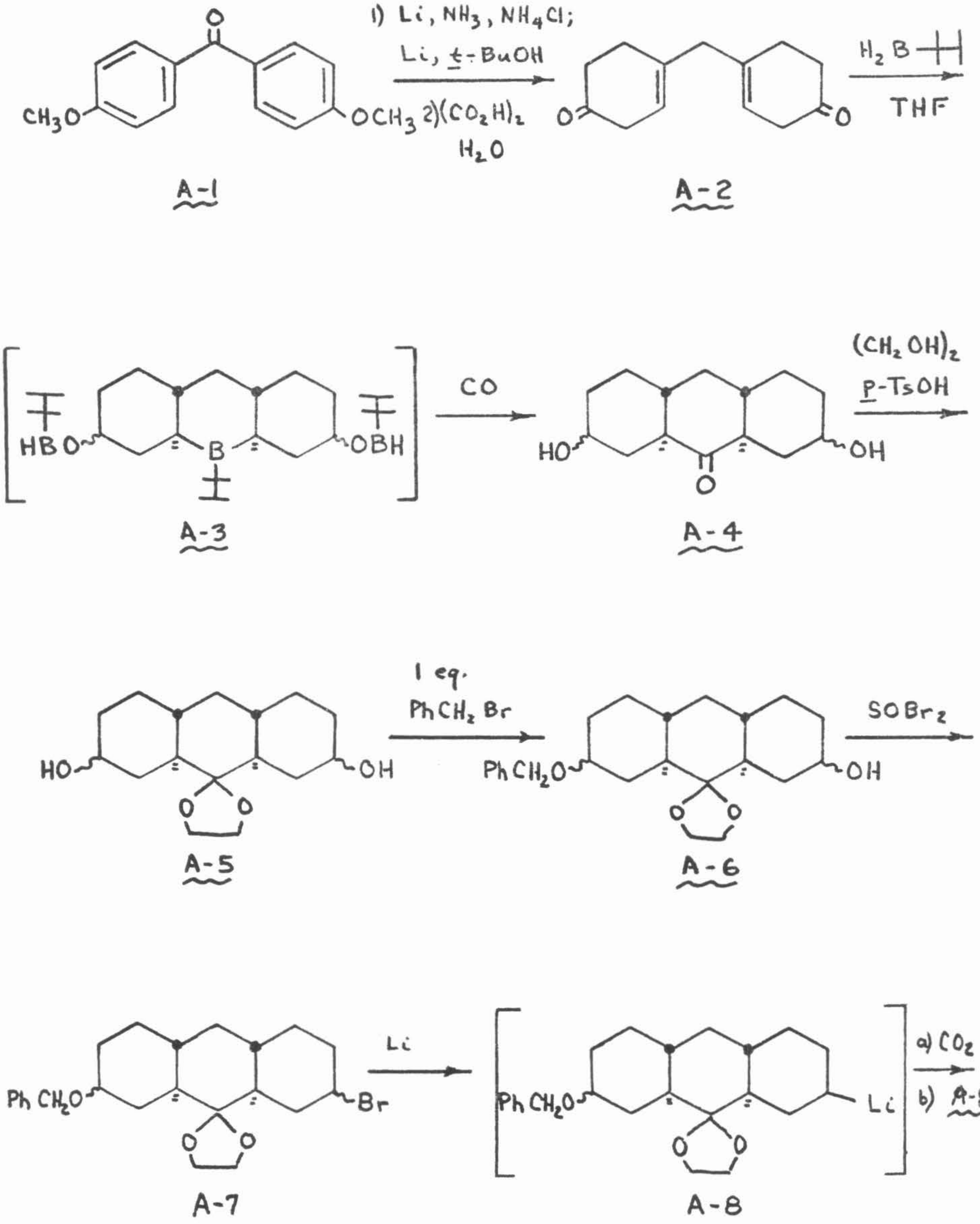
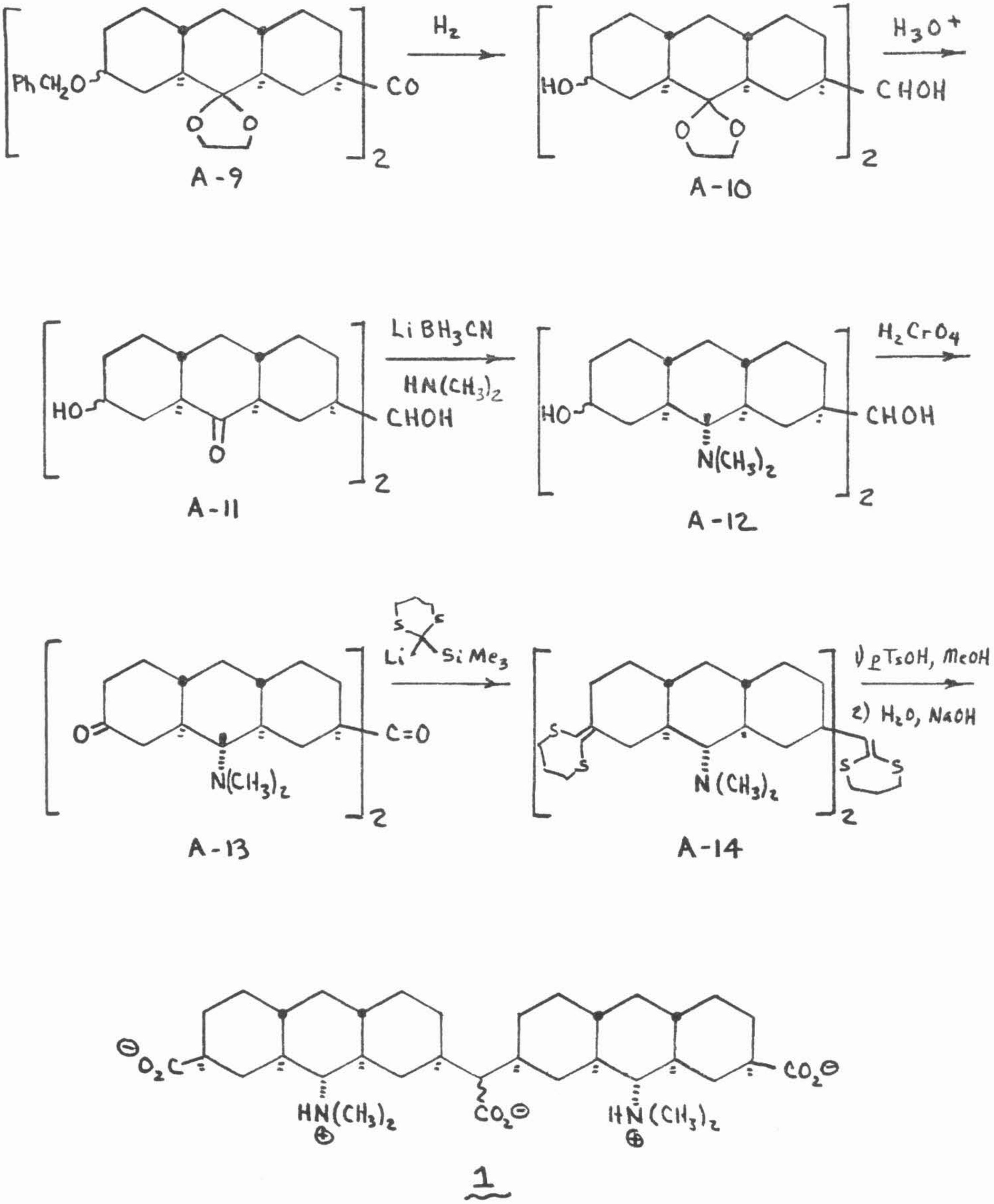

CH3O
OCH3
1) Li, NH3, NH4Cl; Li, t-BuOH
2) (CO2H)2 H2O
A-1
A-2
H2B
THF
HBO
B
OBH
A-3
CO
HO
OH
A-4
(CH2OH)2
p-TsOH
HO
OH
A-5
1 eq. PhCH2Br
PhCH2O
OH
A-6
SOBr2
PhCH2O
Br
A-7
Li
PhCH2O
Li
A-8
a) CO2
b) A-8

CHART A CONTINUED



of which (14) should result in the desired detergent **1**.

The synthesis of the mixture **1** would allow studies of its solubility and micellar behavior in aqueous solution at biological pH's (12). Assuming reasonable water solubility, its function as a membrane-protein detergent could then be tested. Several recent attempts to isolate active, solubilized (Na^+-K^+) ATPase (2b, c, d, e,f), NADH oxidase (2e, f), and glycerol-3-P acyltransferase (2g), have met with only partial, or no success; as assays have been established for all of these enzymes, they all represent good candidates for this study.

Membranes containing one or more of the desired enzymes (see above references), could first be combined with a solution of **1** and tested for activity to determine if the mere presence of detergent inactivates the protein. If not, this mixture would then be sonicated, centrifuged to separate undissolved material, and both phases would be tested for activity; if all the activity remained in the solid phase, conditions would have to be modified until activity could be obtained in the solution. Separation of the excess detergent from this solution would then be attempted by either dialysis or chromatography. If the excess detergent could be removed, leaving an active, soluble fraction behind, then detergent **1** would be performing as expected.

The next step would be to effect separation of the enzyme being sought, in a pure active form. Since the detergent should form a relatively stable species with the protein (preventing aggregation), it might well be possible to treat the solubilized proteins exactly as naturally soluble proteins; the standard techniques normally used to separate these could then be relied upon. If these techniques proved ineffective, then some of the more specialized techniques which have already been applied to solubilized systems (2b, 5) might be utilized. If the desired proteins could indeed be separated by these means, in a pure, active form, then the detergent could be considered a success.

Since this detergent would perform by mimicking the normal membrane, then success with one protein might well mean success for a great many proteins. Modifications of the polar groupings could be made, to determine which side chains allow enzyme solubilization under the mildest conditions; and perhaps if the results seemed promising, other stuctural modifications might be tried. If such a detergent could indeed be perfected, which would be generally applicable for solubilizing membrane proteins, its use would have a great accelerating effect upon the progress of modern biochemistry.

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Proposition 2

It is proposed that a study be made of the directive effects of the ether function on the course of hydroboration, for olefinic ethers in nonethereal solvents.

Since H. C. Brown's initial observation that the rate of addition of diborane to olefins is greatly enhanced in ethereal solvents (1), a great deal of work has been done in studying the reaction and developing its synthetic potential (2, 3). Hydroboration involves a stereospecifically-cis addition to double bonds, and the boron function in in the resulting product is open to replacement by a number of groups with complete retention of stereochemistry. Thus, effective control during hydroboration over which face and which end of an olefin boron attaches to, can be an important synthetic tool for stereospecifically introducing a great many groups into a molecule.

Two major factors have thus far been uncovered which clearly direct the addition of diborane. The first of these is the polarity (or polarizability) of the double bond, which is the principal determinant of which end boron attahes to. It is well-known that hydroboration proceeds in an anti-Markownikoff sense (2), and it seems generally true that the boron attaches itself to the more electron rich end of the pi bond. Substituents attached to the double bond (4), to allylic (5) and even to homoallylic (6) positions affect addition in keeping with this principle, as governed by their inductive and mesomeric interaction with the olefinic bond.

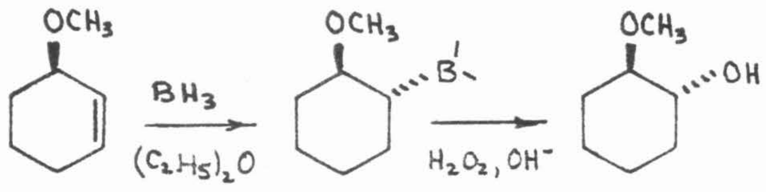
The second major factor, steric environment about the double bond, directs addition to that face of the olefin which is least hindered (2); and for electronically similarly substituted bonds, to that end which is less sterically demanding (2). This steric effect, coupled with the anti-Markownikoff nature of hydroboration, frequently leads in practice to the generation of principally one of the four possible cis adducts (2), and thus accounts for the value of the technique in stereospecific synthesis.

If another control over the direction of hydroboration could be devised, one which would reverse one (or both) of the normal directive effects, then all the many procedures developed for utilizing normal hydroboration adducts could be applied for synthetic purposes in previously unrealizable adducts. It would be especially valuable synthetically if one could induce borane to add to the more hindered face of certain olefins, since most reagents tend to avoid approaching from the hindered side. A possible key to such a control may be related to the strong catalysis of hydroboration by ethers.

Early workers found diborane to be rather unreactive in nonethereal surroundings. It was observed that for a gas phase mixture of ethylene and diborane, "Reaction at room temperature was slight, if at all" (7); while neat mixtures of diborane with acrylonitrile or methyl methacrylate, after twenty hours at room temperature, had only undergone 62% and 34% reaction respectively (8). Such sluggishness is in great contrast to the ether catalized reaction, the speed of which makes conventional kinetic studies most difficult (2).

It is well-known that borane forms complexes with the oxygen of ethereal solvents (9). As borane by itself is so unreactive, it is likely that the ether complexed species is actually the reactive agent. This suggests the possibility that olefinic compounds with ether functions incorporated in the same molecule might well undergo rapid hydroboration in nonethereal solvents; more importantly, when the ether function and olefin are stereospecifically held in close proximity, activation of the borane as an ether function complex might well lead to intramolecular addition (stereospecifically) at a much higher rate than the intermolecular process. Such a process could provide the sought after directive effect discussed above and thus warrants investigation.

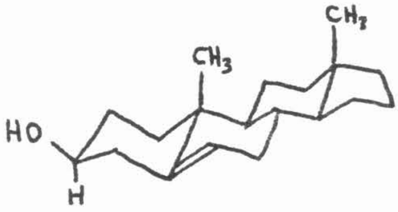
Studies already in the literature of the directive effects of substituents on hydroboration, have all been done in ethereal solvents (ether, diglyme, THF); thus, although the presence of directive effects can be looked for, the lack of any such effects can always be attributed to a very fast solvent catalyzed addition. In simple cyclic ethereal olefins such as 1, the principal products (e.g. 3) always result from intermediates (2) in which boron is bound α to the carbon bearing the



1 2 3

substituent (5b, c). This might suggest some sort of intramolecular complex addition, but the completely trans relationship between the adduct and ether function in such cases precludes this possibility. The study then, really gives little indication of whether an intramolecular complex would affect addition in the absence of competitive solvent catalized addition.

There are a few observations which may bear more directly on the problem. Cholest-5-ene adds borane to give 6α-cholestanol as the only alcoholic product following peroxide oxidation, this being the sterically less demanding adduct; cholest-5-ene-3β-ol (4), however, also yields 15-20% of a minor product, the 3β, 6β-diol (10).



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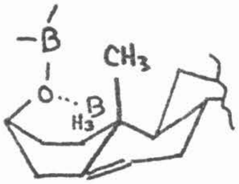

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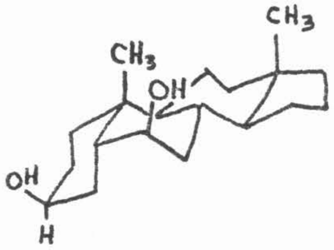

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A complex such as 5 could explain this difference in products, although the unfavorable methyl-oxygen interaction with the A ring in the required boat configuration strongly suggests that it may not be an important factor.

In a case where complex formation has definitely been observed (11), the molecule 7 was heated with one equivalent of borane in THF, and the adduct on nitrogen (8) was isolated with no addition to the double bond.

Such a result is reasonable as nitrogen forms very strong complexes with borane, which are much less reactive than ether complexed borane. Treatment of this adduct with excess ethereal borane at room temperature,

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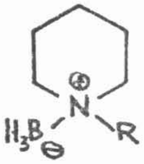

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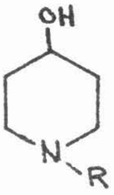

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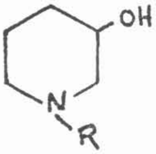

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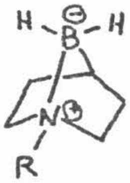

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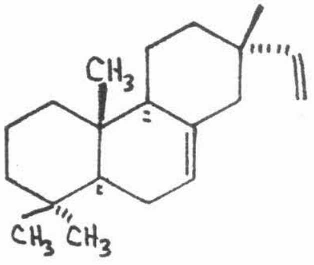
followed by oxidation, gave 9, and 10 in a ratio of 1:3. Heating the complex 8, however, with no excess borane at 150° for ten hours, gave 9 and 10 upon oxidation as a 1:1 mixture. It is tempting to attribute this difference in products to an intramolecular hydroboration intermediate such as 11, but other explanations could account for this observation just as well.

One literature case appears to involve an intramolecular hydroboration directed in an unfavorable Markownikoff sense, although not by a complexed borane. When the molecule 12 was treated with diborane in THF (12), the principal products upon oxidation were the diols 13.



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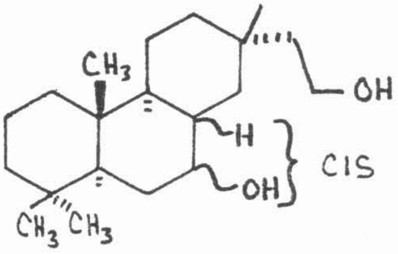

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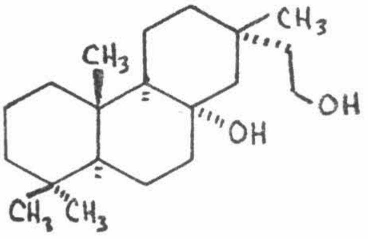
Under certain conditions, however, a third diol assigned the structure 14 was obtained. Presumably, this unexpected product arises from an



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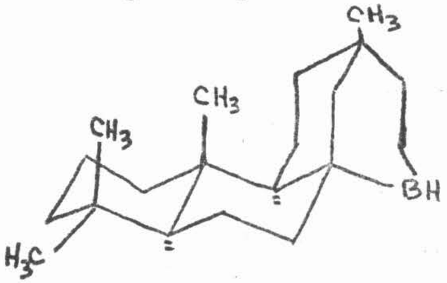

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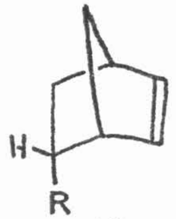
intramolecular hydroboration of the 7,8 double bond by the borane adduct to the vinyl group; for steric reasons, this can occur only at the ring juncture and only from the α face, probably through an intermediate such as 15. Thus some evidence exists that intramolecular addition can lead to reversal of the normal course of the hydroboration reaction.

Experiments reported to date contain little clear data bearing on the question of intramolecular complex-directed hydroboration; thus a study should be undertaken to determine the stereochemical course of diborane addition to ether-bearing olefinic molecules in nonethereal solvents. Any number of molecular frameworks could be constructed which would provide good systems for this study, but certain molecules already known to give single, well-defined hydroboration products in the hydrocarbon case should suffice for this study.

The norbornene system 16 (R=H), has been shown to give on hydroboration/oxidation, 99.5% of the exo-alcohol 17 (R=H), this result being attributed to steric hindrance about the endo face of the double bond (13). The carbomethoxy compound 18 ($R=CO_2Me$) has also been hydro-



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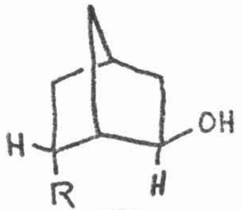

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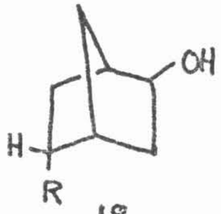

18

borated in THF to give a 1:1 mixture of the two exo alcohols 17 and 18 ($R=CO_2Me$), with no observed endo product (14). Exo approach is sterically much preferred in this system.

For the purpose of this study, the endo ether A-1 would be an ideal starting compound. A dilute solution of these molecules in a nonpolar, nonethereal solvent (benzene), could be treated with externally generated diborane, and the resulting adduct(s) oxidized with basic peroxide. As all four possible alcohols can be otherwise synthesized, the product(s) could easily be identified. Formation of principally or exclusively alcohol A-3 would strongly indicate addition via an intermolecular complex, as in A-2; formation of the other endo-alcohol would be very unlikely except for a very loose, active complex. Formation of endo-exo mixtures could indicate the occurrence of simple intramolecular versus intermolecular competition, or the possibility that the A-2 adduct is a more active hydroborating agent than intramolecularly ether complexed BH_3; such a result would call for solvent and temperature variation, or changes in the hydroborating agent (RBH_2 or R_2BH). Finally, complete exo addition might indicate that a five-membered transition state complex such as A-2 is just very unfavorable,

CHART A

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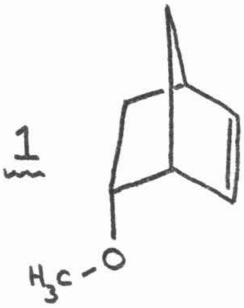

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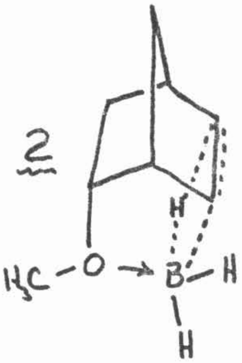

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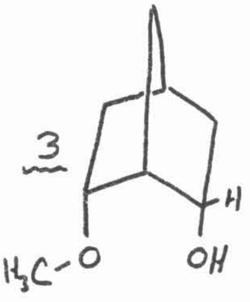

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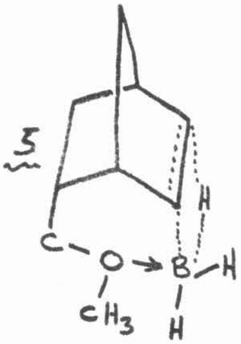

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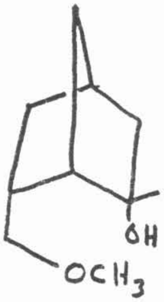

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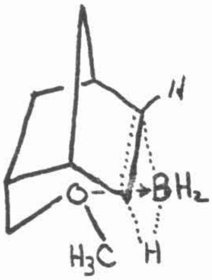

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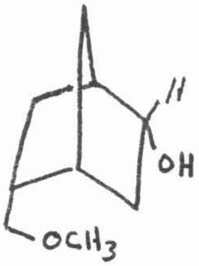

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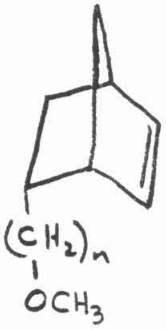

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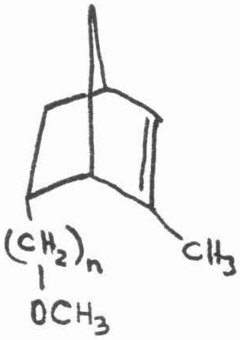

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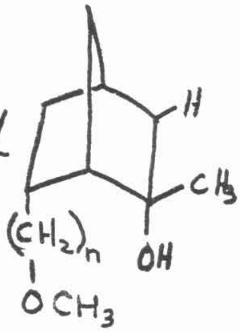
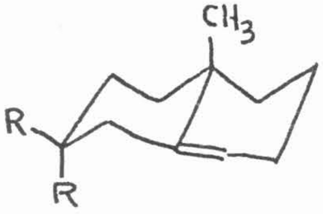


and the next homologous methyl ether A-4 would then be tried.

Depending upon the results obtained above, the compound A-4 should be studied to determine whether endo addition would occur at all, and whether only one, or both of the endo-alcohols A-6 and A-8 would form (reflecting on the possible transition states A-5 and A-7). Positive results at this stage might indicate investigation of further homologs A-9 (n=2,3,etc.), to determine the effects of chain lengthening on the regio- and stereospecificity of the reaction. If ether A-1 does indeed lead to alcohol A-3, then the C-6 methyl compound A-10 (n=0, or 1) should be studied to see whether the intramolecular complex can reverse the normal position of hydroboration to give tertiary alcohol A-11. At this stage, other ether functions (especially the readily cleaved benzyl ether) might be investigated, and possibly the unprotected alcohols as well. Although more convenient than the ether, the alcohol function introduces complicating features by virtue of its reactivity towards borane, which is why ether functions were selected for the initial proposed study. Finally those compounds studied should be hydroborated in ethereal solvents as well, to ascertain the significance of any observed directive effect.

Whether intramolecular complex addition is observed for the norbornene ethers or not, at least one other system might be studied to insure that the results are not unique to the somewhat strained bicyclo (2.2.1) heptene structure. Sondheimer and Wolfe (15) have observed that the octalene system 19 (R=H) on hydroboration/oxidation affords a mixture of both alcohols 20 and 21 (R=H). However, when R=CH_3, only the β-addition product 21 occurs, presumably since the axial α-methyl sterically hinders this face of the double bond. Compounds 23 and 24 (n=1 and 2) are both readily synthesized from the easily made α,β-unsaturated ketone 22. In accord with the results from 19 (R=CH_3), hydroboration/oxidation of these molecules in the absence of intramolecular complex addition, would be expected to give only the secondary β-alcohol, analogous to 21. Addition via an intramolecular complex, however, would be expected to give α-adducts instead. It should be possible by simple chemical manipulation and by nmr techniques to determine the position and stereochemistry of the alcohol function in the products. The results from this study would shed additional light on the question of intramolecular complex addition; and taken along with those from the norbornene system should allow some conclusions to be drawn as to the nature and generality of this process.



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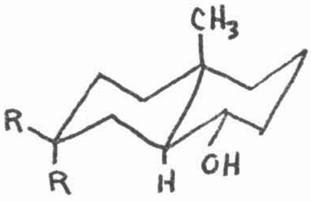

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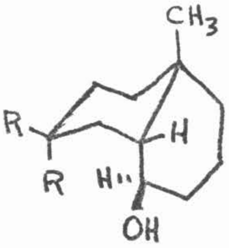

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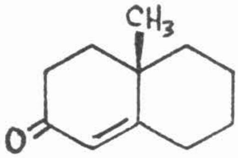

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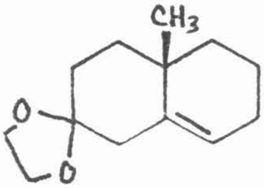

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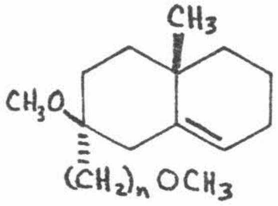

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The experiments suggested above could provide some interesting insights into the nature of the ether catalized hydroboration reaction, and might also afford a valuable new tool for stereospecific synthesis.

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Proposition 3

It is proposed that a molecular system be constructed that may promote and will unambiguously show the presence of intramolecular ($\pi 2_s + \pi 2_a$) cycloaddition between a pair of olefins.

Orbital symmetry considerations for the concerted (2 + 2) cycloaddition process for olefins indicate that for the thermal reaction only the ($\pi 2_s + \pi 2_a$) process should be allowed (1). The geometry of such a reaction is at first somewhat difficult to envisage, but one can see that the mode of addition shown in Fig. 1-a is indeed that required.

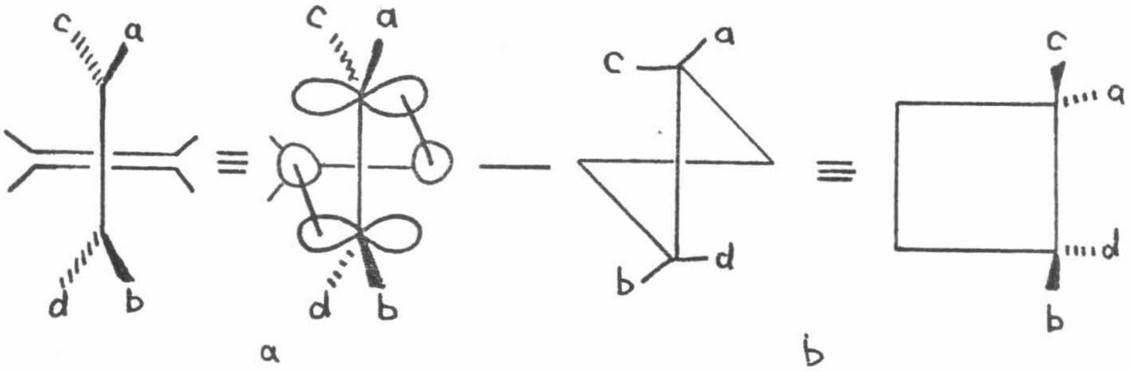
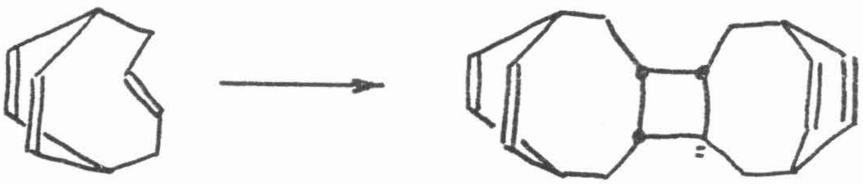


FIGURE 1

The lower olefin forms both new sigma bonds to the same side of the old pi bond (2_s), while the upper olefin forms one new sigma bond to each side of the old pi bond (2_a). It should be noticed that the two olefins are not equivalent in this process; and that groups which are cis in the 2_s component will remain cis in the product, while groups which are cis in the 2_a component will become trans in the product (Fig. 1-b).

One may validly argue that overlap between the orbitals involved in such a transition is poor at best, and that the activation energy for such a process may thus be quite high (even though it is symmetry "allowed"). In addition, the rigid geometric requirements are entropically quite unfavorable, and so the frequency factor for the reaction should tend to be rather low. One might therefore expect to observe little cyclization via this pathway.

It would appear that this is actually so, for the $(\pi 2_s + \pi 2_a)$ cycloaddition has been shown to occur definitely only in cases of rather unusual olefins, such as ketenes, allenes, and isocyanates (2). Only one case has been reported in the literature in which evidence indicates a thermal $(2_s + 2_a)$ process for a noncumulated double bond; this involving the very strained trans olefin **1**, dimerizing at room temperature



1 **2**

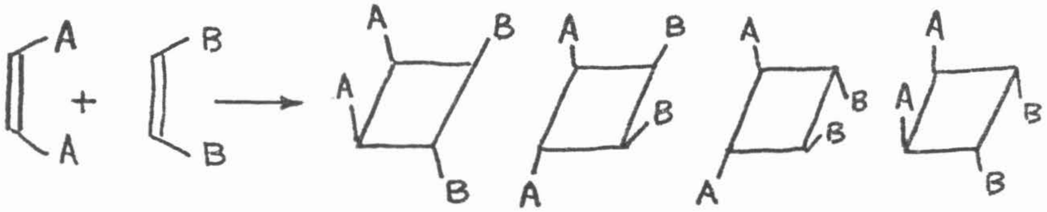
to give **2** (3). While this certainly seems to be an example of the concerted thermal reaction, it is rather discomforting that no other such additions have been found for noncumulated olefins.

Simple olefins will not undergo thermal (2 + 2) additions, but various gem difluoroolefins and especially tetrafluoroethylene, readily undergo reaction with themselves and other olefins to give substituted cyclobutanes (5). Several such reactions have been investigated, and at least for some tetrahalo olefins, addition appears to proceed via a diradical mechanism (6). In other cases, where radical stabilization should not be as great, the answer seems less clear. In a recent study of the cycloaddition of tetrafluoroethylene to pure cis and pure trans dideuteroethylene, it was found that both isomers give the same product mixture (7); it was argued that this result indicates a biradical mechanism must be operative, to account for this scrambling. Such may not be the case.

Earlier in this discussion, it was noted that the stereochemistry of the 2_a component is reversed in a concerted thermal process, while that of the 2_s component is retained; but no prediction is made as to which olefin will be which. For example, with cis dideuteroethylene and tetrafluoroethylene, one would get trans-1,2-dideuterocyclobutane from each addition in which the dideuteroethylene were 2_a, and cis-1,2-dideuterocyclobutane from each addition in which the dideuteroethylene were 2_s. If there were no preferred mode of addition, then a 1:1 mixture of products would result; a similar argument leads to the same conclusion for the trans starting olefin. Thus a $(2_s + 2_a)$ process could be consistent with the observed results.

The authors who performed this study, contend that since a CF_2 group has a larger moment than a CHD group, then tetrafluoroethylene should be much less prone to 2_a addition. Making such assumptions about a reaction pathway that has never been observed in such a system (much less well characterized) seems unwarranted. Unless systems are employed in which the mode of addition of both components can be clearly determined, then such studies cannot be used to rule out the $(2_s + 2_a)$ process; nor can they hope to reveal it, unless some preference for one addition mode does indeed exist. Hence it is possible that the concerted reaction is occurring in these simple cases.

The obvious experiment to be performed is the thermal cycloaddition of two compounds such as 3 and 4. Formation of principally isomers 5 and 6 would strongly indicate a $(2_s + 2_a)$ process, while the occurrence of large amounts of 7 and 8 as well, would be inconsistent with a concerted mechanism. Unfortunately, as mentioned above, only gem difluoroolefins readily undergo such cycloadditions; this makes the desired experiment impossible in simple systems, as there is no way in which to determine the addition mode of the fluoroolefin component. A possible solution to this problem would be to design a system in which steric contraints would allow only a single geometry for the $(2_s + 2_a)$ addition. In such a system, a gem-difluoroolefin could be employed for the 2_s component, and a cis or trans substituted (deuterated) olefin for the 2_a component. The relative stereochemistries in the product of the substituents from the 2_a component would allow determination of whether the concerted process had occurred.



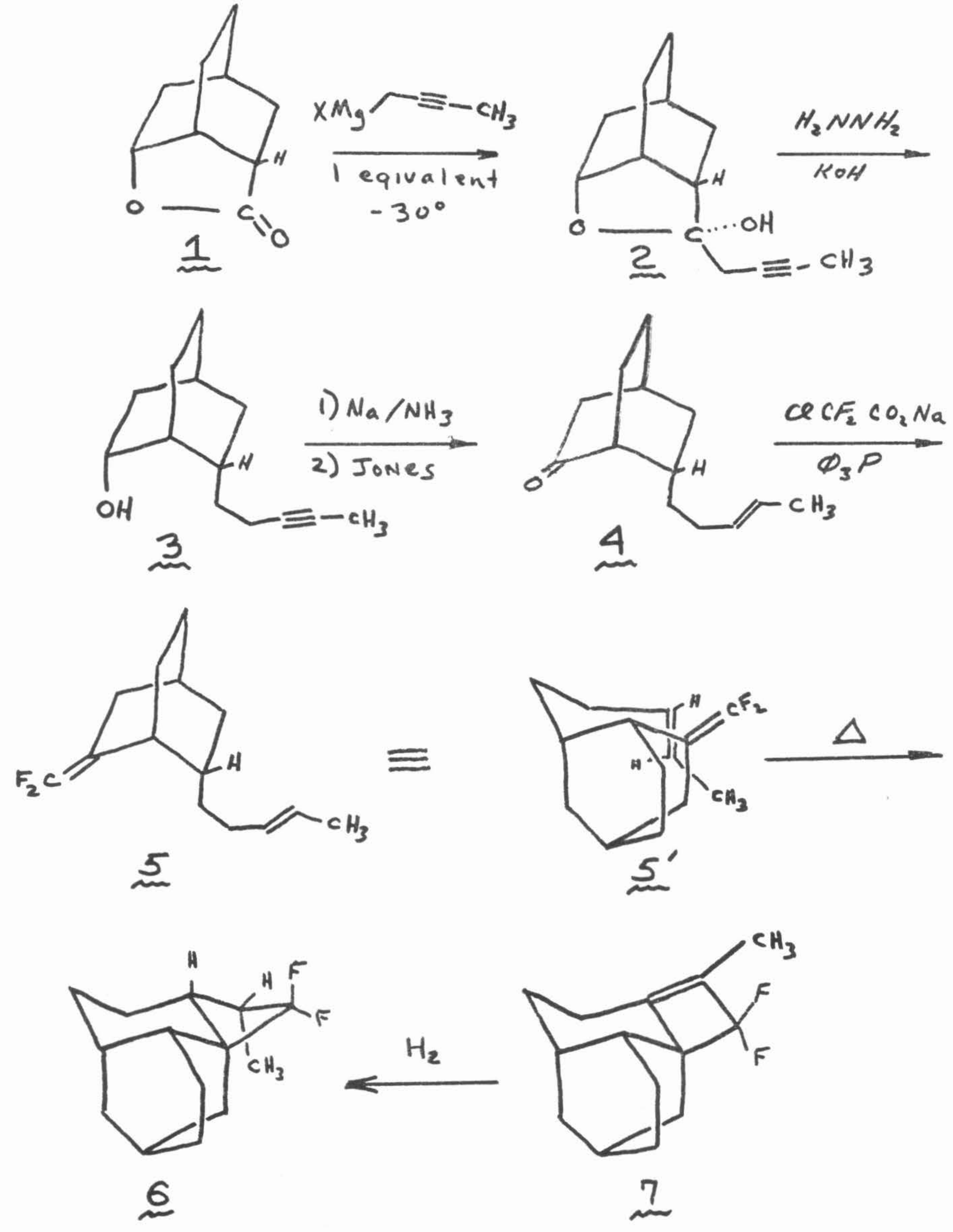
3 4 5 6 7 8

Constraining the olefins such that each can assume only one of the two possible addition modes can best be achieved by attaching them both to the same molecule. In doing so, it might also be possible to structure the system so that the $(2_s + 2_a)$ geometry of approach would be more favored than for free olefins approaching totally randomly. The unfavorable entropic effects associated with concerted addition might thus be somewhat countered, and the likelihood of observing this process increased.

One such system which could easily be synthesized is the molecule A-5. Treatment of the known bicyclolactone A-1 (8) with one equivalent of 2-butynyl Grignard at -30° should result in the lactol A-2 (9). Wolff-Kishner reduction of this would produce the alcohol A-3 (10), which upon metal ammonia reduction of the triple bond and Jones oxidation of the alcohol should result in the trans olefinic ketone A-4. Conversion of the ketone to a difluoromethylene can be accomplished via a Wittig reaction (11), which should give the desired diolefin in only five steps from A-1.

Examination of molecular models of A-5 shows that there is only one possible way in which the two olefinic fragments can interact with the $(2_s + 2_a)$ geometry; that mode is shown as A-5′. Only one product, A-6, can result from such a concerted process, and thus upon heating A-5 in dilute solution one should obtain principally one product (A-6) if the $(2_s + 2_a)$ addition predominates. Fortunately, the product A-6 should be available from the alcohol A-3; Jones oxidation, difluoromethylene Wittig treatment, and cyclization would produce the cyclo-

CHART A


XMg—CH2—≡—CH3
1 equivalent
-30°
H2NNH2
KOH
1) Na/NH3
2) Jones
ClCF2CO2Na
Φ3P
≡
Δ
H2
H
O
C=O
C····OH
≡—CH3
OH
CH3
CF2
F2C
F
1
2
3
4
5
5′
6
7

butene A-7, which after hydrogenation from the least hindered side should afford the desired A-6. This could then be compared to any product(s) formed on heating A-5, and also tested under the reaction conditions to determine its stability.

The cis olefin corresponding to A-5 should be cyclized as well. This product should be available from hydrogenation of the acetylene A-3 followed by a difluoromethylene Wittig reaction. Assuming A-6 is found to be stable to the cyclization conditions, then if on cyclization the cis olefin produces the same product mixture as the trans, then one of the cyclizations (and probably both) cannot be occurring via a concerted pathway. If, however, the trans olefin A-5 does yield principally A-6, while the corresponding cis olefin does not, then this would be strong evidence for the occurrence of the $(2_s + 2_a)$ cycloaddition among these nonstrained, noncumulated olefins.

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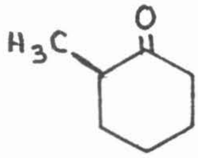
Proposition 4

It is proposed that the thermal rearrangements of methyl and allyl carbonates and sulfites derived from enolate anions be investigated, as a possible means of regiospecifically monoalkylating enolate anions.

The alkylation of enolate anions is an important synthetic tool which has received a great deal of study (1a, 2). For many unsymmetrical ketones, methods have been developed which allow selective formation of either of the two possible enolate anions. Treating a ketone (e.g. 1) with acetic anhydride under acid catalyzed, equilibrating conditions generally affords the more high substituted enol acetate (2) (3);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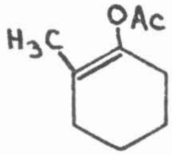
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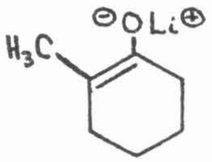
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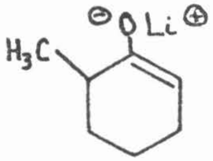
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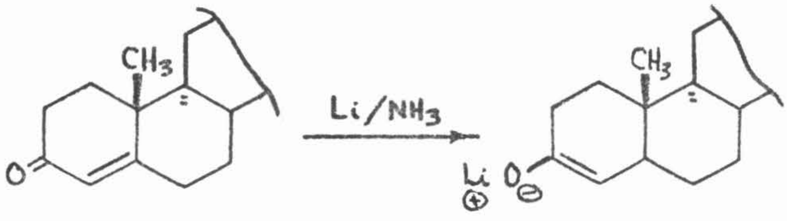
from this, the more highly substituted enolate anion (3) can be generated under conditions which preclude any equilibration to the isomeric enolate (4) (4). Treating ketones with an excess of strong base under nonequilibrating conditions produces the kinetic enolate, which usually consists of the less substituted isomer (4) (5).

These methods, along with dissolving metal reductions of α,β-unsaturated ketones (e.g. 5→6) (6) provide an excellent source of specific enolate anions. In view of the excellence of these procedures,



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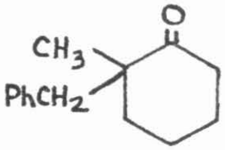
it seems unfortunate that regiospecific monoalkylation of such enolates frequently occurs in only poor to moderate yield. The principal reason for this problem seems to be equilibration of the enolates during alkylation, and reenolization of already alkylated material which leads to polyalkylation (1b).

For example, a 1:99 mixture of anions 3 and 4 on treatment with benzyl bromide only affords between 54 and 61% yields of the monoalkylated ketone mixture 7 + 8; although only 1% of the enolate mixture was represented by 3, between 10 and 14% of the product mixture consisted of the corresponding alkyl ketone 7 (7). A similar although more extreme case is exemplified by alkylation of enolates 9 and 10 (7). The former anion affords an acceptable 70% yield of monobenzylated ketone 11; while alkylation of a mixture of a 16:84 mixture of enolates 9 and 10 affords at best only a 27% yield of ketone 12. Longer reaction times



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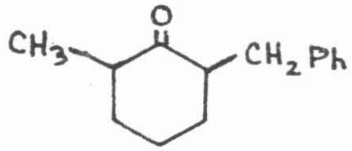

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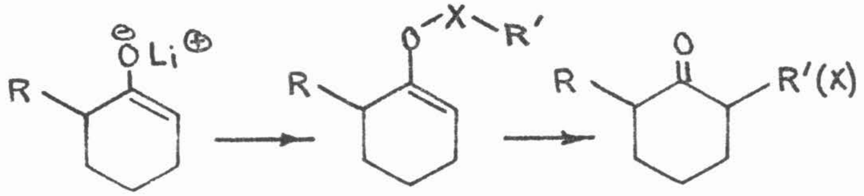
$$\underline{n}\text{-BuCH=}\overset{\text{OLi}}{\text{C}}\text{CH}_3 + \underline{n}\text{-BuCH}_2\overset{\text{OLi}}{\text{C}}\text{=CH}_2 \xrightarrow[\text{DME}]{\text{PhCH}_2\text{Br}} \underline{n}\text{-Bu}\underset{\text{PhCH}_2}{\text{CH}}\overset{\text{O}}{\text{C}}\text{CH}_3 + \underline{n}\text{-BuCH}_2\overset{\text{O}}{\text{C}}\text{CH}_2\text{CH}_2\text{Ph}$$

9	10	11	12
100%	0%	70%	-
16%	84%	19%	27%

in this instance lead to increased amounts of ketone 11 and polyalkylated material.

Numerous other situations have been found in which a specific enolate anion could be generated but not regiospecifically monoalkylated in acceptable yield. As a result of this, a number of procedures involving activating or protecting groups (1c), enamines (1d), metalo enamines (1e, 8) and cyclopropylation (9) have been employed to circumvent the problem. While all of these methods have merit, they often involve extra steps, sensitive intermediates, and reaction conditions incompatible with functional groups which are stable to normal enolate alkylation conditions. Enolate anions are the most readily obtained and most frequently encountered group for such alkylation reactions, and thus it would be valuable to find a good direct method of regiospecifically alkylating specific enolate anions.

Both the polyalkylation and enolate equilibration problems encountered during these alkylation reactions can occur as a result of ketone (product) formation in the presence of unalkylated enolate anion (a strong base). The product ketone acts as an acid promoting enolate anion equilibration, and at the same time generates a new enolate which leads to polyalkylation. In view of this inherent problem with alkylation on carbon, it might be better to attack the enolate anion (e.g. 13) on oxygen to provide an enol intermediate (14) capable of rearrangement

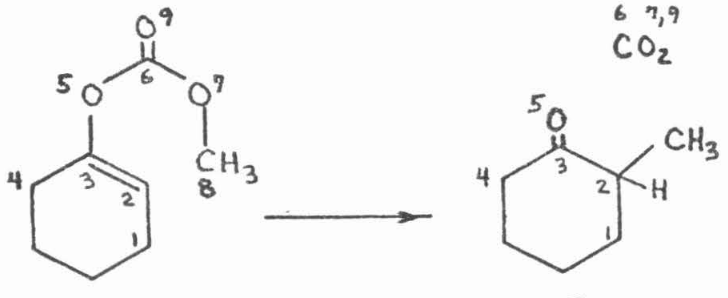


13 14 15

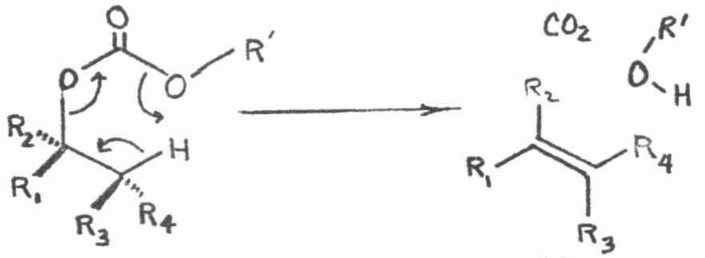
under neutral conditions to the alkylated ketone (15) or its equivalent. Since no ketone would ever be formed in the presence of enolate anion, the problems normally associated with alkylation reactions would be precluded.

A possible choice for an intermediate such as 14 would be enol carbonate 16. Enolate anions do indeed react with alkyl chloroformates on oxygen, to afford enol carbonates (10). Many pyrolytic studies have been performed on the analogous saturated carbonates 18, which have been shown to undergo thermal decarboxylation when one of the alkyl substituents bears hydrogens on the carbon β to oxygen (11). Such reactions appear to be concerted processes, probably occurring through a symmetry allowed, six electron transition state ($\sigma 2_s + \sigma 2_s + \sigma 2_s$). In an enol methyl carbonate such as 16, however, abstraction of a hydrogen from a β carbon would require formation of an allene or acetylene in a six-membered ring; such a process should be most unfavorable.

Another rearrangement pathway might exist for the enol carbonate



16 17



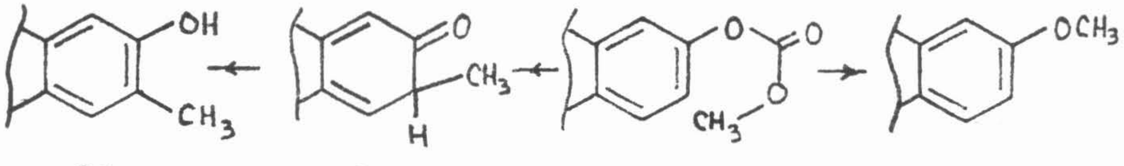
18 19

16, proceeding through an allowed six electron, six center transition state ($\pi 2_s + \sigma 2_s + \sigma 2_s$) and resulting in the methylated ketone 17. A rough calculation of the enthalpy change for this process is shown in Table 1. Using values from S. W. Benson's tables (12), this calculation indicates that ΔH^{o}_{298} for transforming carbonate 16 into ketone 17 should be ~-24 kcal/mol. Since carbon dioxide is released as part of the reaction, the entropy change for the reaction should be favorable as well. Thus, both mechanistic and thermodynamic considerations indicate that rearrangements of methyl enol carbonates such as 16 to methylated ketones such as 17 might indeed be realizable. Should this prove true, then in effect it would represent a means of regiospecifically methylating enolate anions.

TABLE 1

Enol Carbonate 16				Methyl Ketone 17 + CO_2			
Atom or Group		Substituents	ΔH_f°	Atom or Group		Substituents	ΔH_f°
1	C	$(C)(C_d)(H)_2$	- 4.76	1	C	$(C)_2(H)_2$	- 4.95
2	C_d	$(C)(H)$	+ 8.59	2	C	$(C)_2(CO)(H)$	- 1.8
3	C_d	$(O)(C)$	+10.34	3,5	CO	$(C)_2$	-31.5
4	C	$(C_d)(C_d)(H)_2$	- 4.76	4	C	$(CO)(C)(H)_2$	- 5.0
5	O	$(C_d)(CO)$	-44.1	6,7,9	CO_2		-94.1
6,9	CO	$(O)_2$	-34.9	8	C	$(C)(H)_3$	-10.8
7	O	$(C)(CO)$	-44.1				
8	C	$(O)(H)_3$	-10.8				
for pertinent atoms ΔH_f°			-124.5	for pertinent atoms ΔH_f°			-148.2
$\Delta H^\circ_{298^\circ}$ = [-148.2 - (-124.5)] kcal/mole = -23.7 kcal/mole							

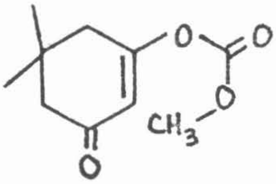
A survey of the past literature has revealed no attempts at such rearrangements. Most recorded carbonate pyrolyses were done on systems in which an alkyl group bearing hydrogens on the β-carbon was present (11). As discussed above, such systems on thermal rearrangement afford olefin and alcohol products. Several aromatic methyl carbonates such as 22 have been pyrolyzed, but were found to yield aromatic ethers (23)



20 21 22 23

and carbon dioxide as products (11, 13). Such a result is not entirely surprising, as rearrangement to the α-methyl phenol (20) would involve a nonaromatic intermediate (21) from a concerted six center cyclic process. The loss of aromaticity in such cases might cause other pathways to predominate.

The only enol methyl carbonate which could be found in the literature which might have served as a good model for this rearrangement is carbonate 24 (10a). Unfortunately, aside from its preparation, the



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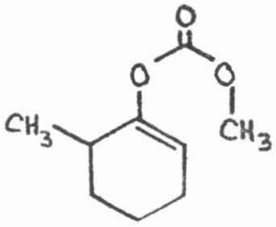
only significant data reported for this compound which relates to our discussion is its boiling point. At this temperature, 120° (14 mm), apparently no thermal rearrangements are observed; higher temperatures may thus be anticipated for the proposed transformation.

In view of the scarcity of information concerning the rearrangements of such enol methyl carbonates, and the possible synthetic utility of the proposed six center process, the thermal rearrangements of these species should be investigated. The initial study should be attempted on some simple enol carbonates such as 25 and 26, and the pyrolysis products should be carefully identified. If the major reaction pathway does indeed lead to the desired methylated ketones, then a number of other carbonates (such as 27, 28 and 29) could be studied as well. All



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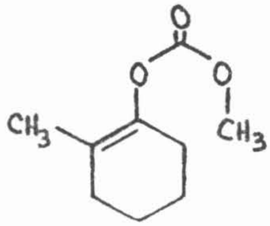

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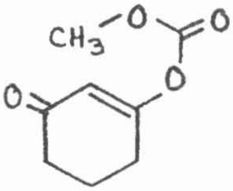

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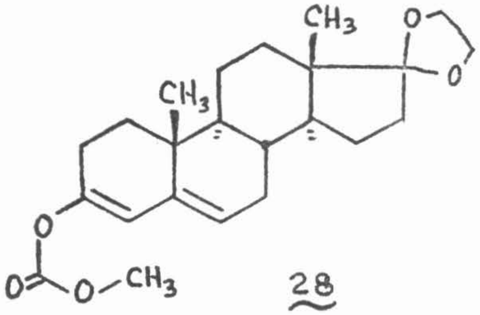

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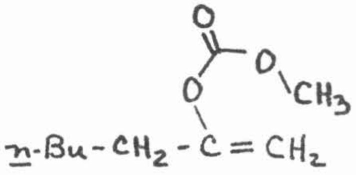

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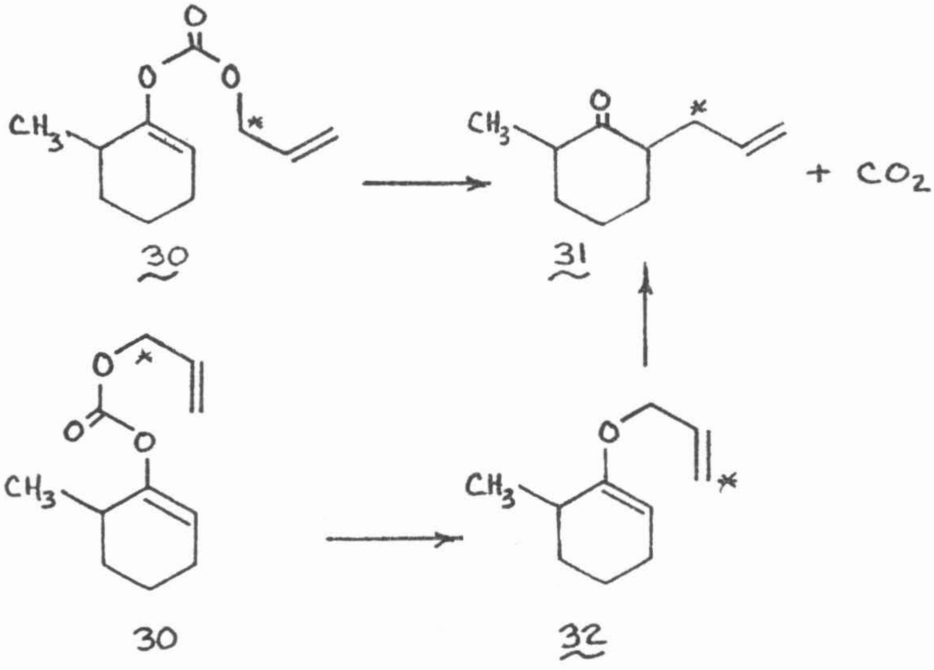
of these compounds correspond to enolate anions which are normally very difficult to regiospecifically monomethylate; demonstration of a good yield carbonate rearrangement procedure would be most significant in these cases.

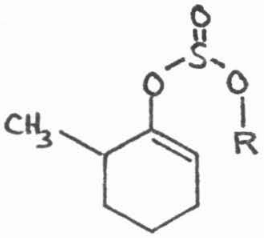
Regardless of the outcome of the above experiments, one or more of the allyl carbonates corresponding to methyl carbonates 25-29 should be studied as well. Enol carbonate 30, for example, could conceivably pyrolyze by three pathways. A simple ene elimination reaction would generate allene and ketone 1. A rearrangement pathway corresponding to that proposed for the methyl carbonates above would lead directly



to allyl ketone 31. Finally a third six center, six electron process might lead to the allyl enol ether 32, which could then rearrange itself to the ketone 31 in a normal Claisen reaction (1f).

If allyl rearrangements such as 30→31 could be effected in good yield for the "difficult to alkylate" species discussed above, this too would be significant. The terminal olefin of this group essentially functionalizes it for further transformations (or degradation). If the methyl carbonate rearrangements proceed as desired, they cannot be generalized to higher saturated homologues (ethyl, propyl...) as such groups would undergo the ene elimination reaction. The allyl rearrangement would thus provide entry into these homologous and functionalized alkylated species.

It should also be noted that the ideas and experiments discussed above apply just as well to the closely analogous but little studied enol sulfites (e.g. 33) (14). Depending upon the outcome of the proposed carbonate studies, the generally more labile sulfites might be similarly investigated, in hopes of improving yields or observing the desired rearrangements at all. If the proposed rearrangements can indeed be shown to occur smoothly in any of the above systems, then they should provide a synthetically useful means for regiospecifically monoalkylating enolate anions.



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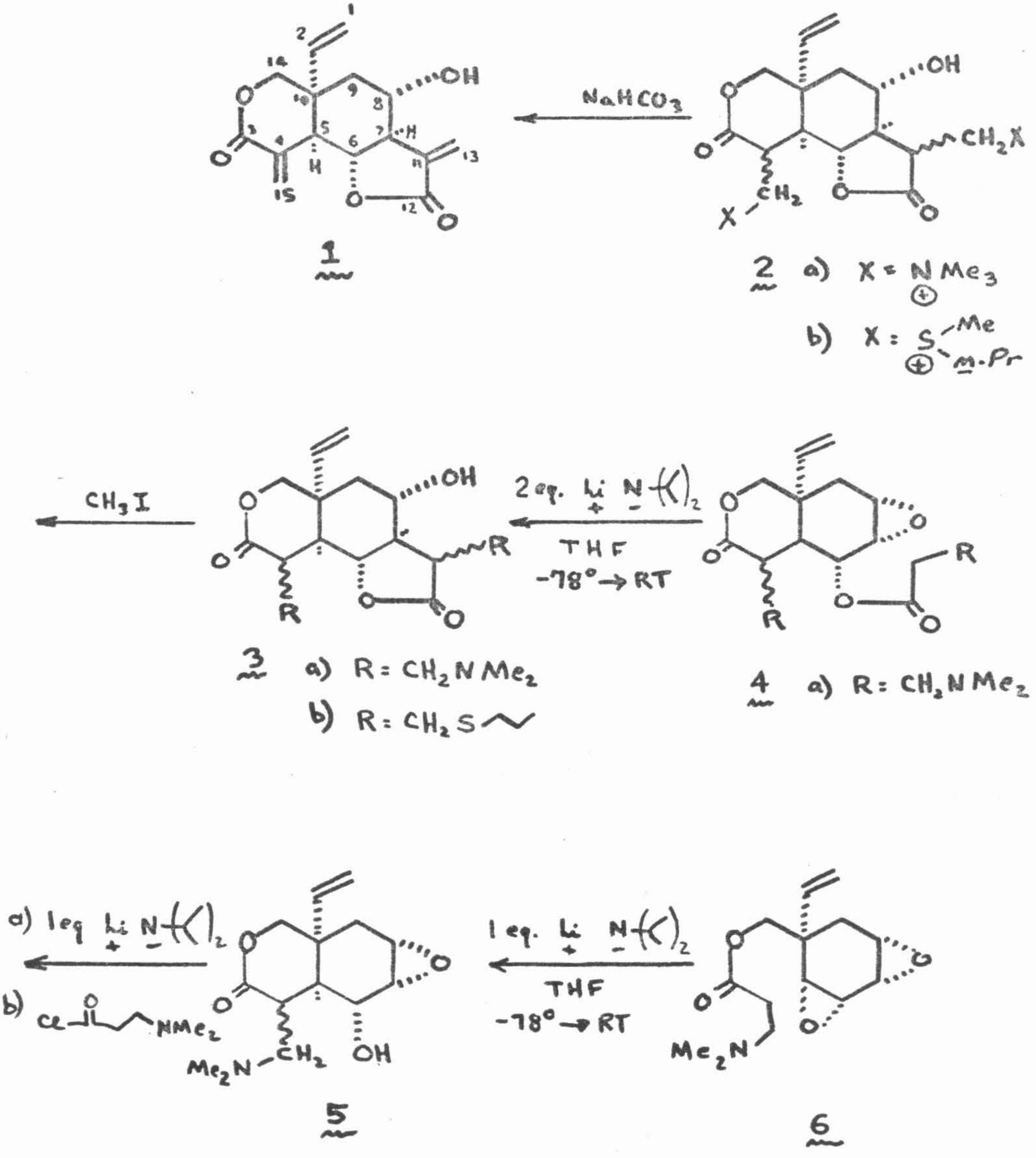
Proposition 5

A total synthesis of the sesquiterpene dilactone dl-vernolepin is proposed.

Several naturally occurring sesquiterpene lactones have recently been isolated and shown to possess significant in vivo tumor-inhibitory activity against carcinoma in rats (1a). Such compounds, if available in greater quantities and possibly in modified forms (i.e. synthetically), could be investigated further in the search for clinically valuable anti-cancer agents. Unfortunately, these molecules combine abundant, sensitive functionality with complex stereochemistry, resulting in quite challenging and as yet unrealized synthetic goals. The object of this proposed research is the total synthesis of one of these tumor-inhibitory lactones, vernolepin (1, 17) (A-1).

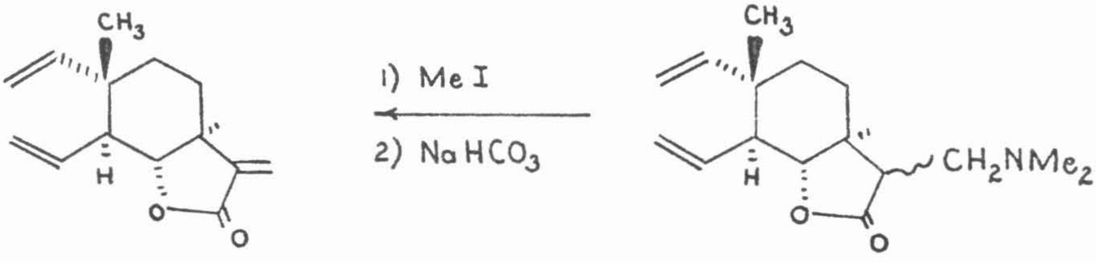
In considering synthetic approaches to vernolepin, it is important to recognize the high reactivity of both exocyclic methylene groups (1b, c). Such sensitive functionality should be introduced (or unmasked) at a very late stage in the synthesis to avoid problems during other transformations. Grieco and Hiroi have recently developed a method for introducing such α-methylene groups on α-unsubstituted lactones (2a). While this method should indeed be applicable to the vernolepin lactones, it proceeds in a rather disappointing 50% yield when applied to a model for the vernolepin δ-lactone (2b). Other previously developed methods for introducing such α-methylene groups,

Chart A


NaHCO$_3$
1
2 a) X = $\overset{\oplus}{N}Me_3$
b) X = $\overset{\oplus}{S}$-Me, n-Pr
CH$_3$I
2 eq. Li N(iPr)$_2$
THF
-78° → RT
3 a) R = CH$_2$NMe$_2$
b) R = CH$_2$S-nPr
4 a) R = CH$_2$NMe$_2$
a) 1 eq Li N(iPr)$_2$
b) Cl-C(=O)-CH$_2$CH$_2$NMe$_2$
1 eq. Li N(iPr)$_2$
THF
-78° → RT
5
6

or for forming α-methylene lactones in general (2c-j), appear even less promising for use on vernolepin.

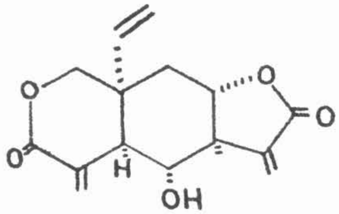
Two methods have been demonstrated, however, which do an excellent job of regenerating protected α-methylene groups in natural α-methylene lactones. Kupchan has shown (1c) that the di-*n*-propyl thiol adduct of vernolepin (**A-3b**) can be methylated to the sulfonium salt **A-2b**, and converted to vernolepin in high yield by treatment with saturated sodium bicarbonate solution. McCloskey has utilized the dimethylamino group for the same purpose in his dehydrosaussurea lactone (**1**) partial synthesis (3). Quaternization of the amine **2**, followed by bicarbonate promoted elimination according to the method of van Tamelen (2j), pro-



1 **2**

duced an almost quantitative yield of exocyclic methylene lactone **1**. In view of the simplicity of these procedures and their proven high yields in generating sensitive α-methylene lactones in actual sesquiterpenes, these methods make compounds **A-3a** and **A-3b** appear most attractive as intermediates for vernolepin. For these reasons and others to be discussed shortly, the bis-dimethylamine **A-3a** has been selected as an intermediate for this synthesis. Its transformation to vernolepin via the quaternized species **A-2a** would be expected to proceed well according to the method of McCloskey.

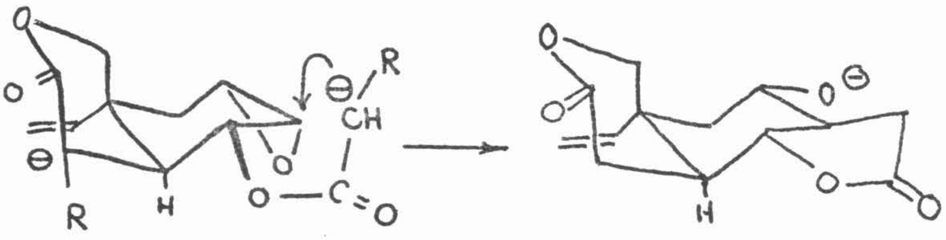
Since the *trans*-γ-lactone in vernolepin appears more sensitive than the δ-lactone (1b), formation of the γ-lactone of A-3a would probably best be performed late in the sequence. The possibility of lactone formation between the C-8 alcohol function and C-12 also supports this reasoning. The isomeric lactone vernomenin (1a, b) (3) actually does occur naturally along with vernolepin; the formation of such isomer mixtures should be avoided in a directed synthesis, however.



3

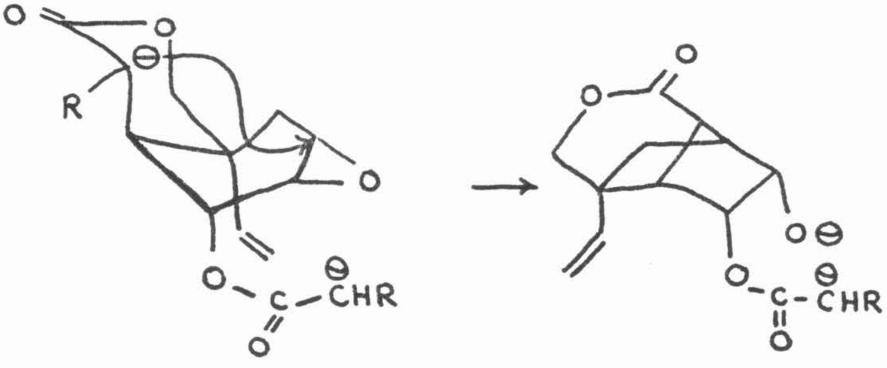
A possible method of introducing the desired γ-lactone in intermediate A-3a represents the principal key to this entire approach to vernolepin. It is proposed that this lactone be constructed by the intramolecularly directed attack of an ester enolate anion upon an epoxide, to insure both stereo- and regiospecific formation of the γ-lactone and C-8 alcohol function. Ester A-4a is the required intermediate for this step. The attack of enolate anions upon epoxides is well-known (2i, 4), and it seems likely that the conversion of A-4a to A-3a will work, provided the bis-ester-enolate anion of A-4a (4) can be formed and is stable long enough for the reaction to occur.

A number of factors having a bearing on this situation appear favorable. Comparison of the conditions necessary for non-nucleophilic base catalyzed opening of epoxides (5) (two hours in refluxing ether/hexane using lithium N-isopropylcyclohexylamide as base) with those needed for the formation of ester enolate anions (6a) (ten minutes at -78° in THF, using lithium N-isopropylcyclohexylamide as base), almost insure enolate formation in our system before epoxide cleavage. Once the enolate dianion 4 does form, it could conceivably undergo intramolecular attack of the 4 position upon the epoxide at the 8 position (4b) to give intermediate 5 (7). Such an attack is highly unlikely,



4a

3a′

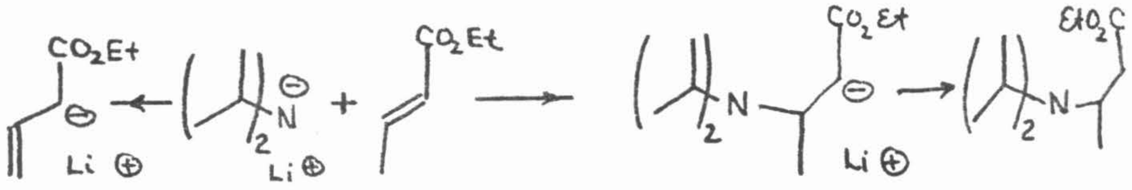


4b

5

however, since conformation 4b, necessary for this reaction to take place, requires a 1,3-diaxial interaction between the vinyl and ester groupings, as well as a boat like conformation of the cyclohexane ring. At the low temperatures which would be utilized for this reaction, conformation 4a (which leads to the desired product A-3) should be greatly preferred.

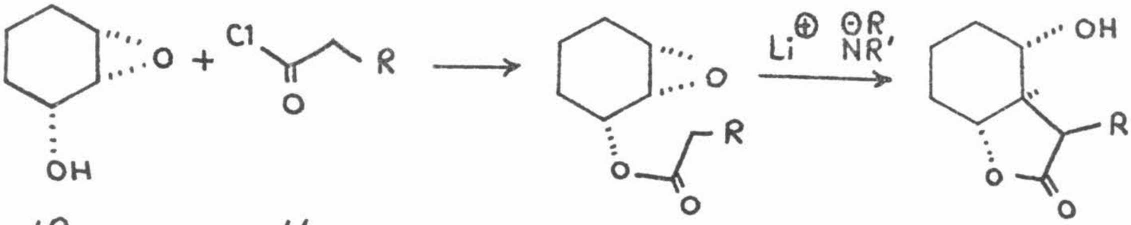
Another possible difficulty concerns the nature of the R groups in dianion 4. Ideally, one would desire R=CH_2S-*n*-Pr or R=CH_2NMe_2 for reasons already considered; forming an anion β to sulfur or nitrogen, however, might lead to direct elimination. While there is certainly evidence for elimination of sulfur anions (8), it would appear that lithium enolate anions of β amino esters are stable in THF at low temperatures. This stability has recently been demonstrated by Schlessinger and co-workers (9) who treated ethyl 2-butenoate (7) with lithium diisopropylamide in an effort to generate the ester enolate anion 6.



6 7 8 9

When they carried this reaction out in THF under a variety of temperature conditions (-40° to -100°), they obtained after quenching, nearly quantitative yields of the Michael adduct 9. This implies not only that the Michael addition is faster than proton removal from ester 7, but also that the intermediate anion 8 is stable under these conditions and is not in rapid equilibrium with the starting ester 7 and diisopropylamide anion. If such an equilibrium existed, eventually only the anion **6** would be present since its formation is certainly not reversible under these conditions.

While the above considerations indicate the transformation of **A-4a** to **A-3a** should be possible, this intramolecular epoxide opening is such a crucial part of the proposed synthesis that it should first be established on a model. Esterification of the readily prepared epoxy alcohol **10** (10) with 3-(N,N-dimethylamino)-propionyl chloride (**11a**) [also easily prepared (11)] would produce an ideal model compound **12a**. The first



10 **11** **12** **13**

a = CH_2NMe_2

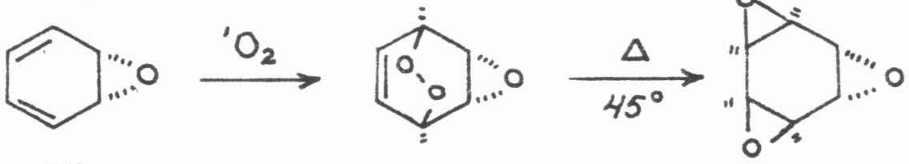
step in the realization of this proposal would be preparation of this model and study of the formation and reaction of its enolate anion. If the lactone alcohol **13a** can indeed be formed from epoxy ester **12a**, this would provide strong indication that the transformation of ester **A-4a** to lactone **A-3a** should be realizable.

If the β-amino anion proves unsuitable in the above study, then a parallel study should be performed using the simple acetate ester of **12** (R=H). If the anion of ester **12** (R=H) can be formed and cyclized to lactone 13 (R=H), then the overall synthetic plan could easily be directed towards producing lactone **A-3** (R=H) via cyclization of ester

A-4 (R=H). The method of Grieco and Hiroi could then be employed to convert A-3 (R=H) to vernolepin (A-1). It should be noted throughout the remainder of this discussion that merely by changing the acid chlorides employed in this scheme, one should be able to produce lactone A-3 with a variety of R groups.

Assuming the model study justifies our use of the β-amino ester, then the problem at hand becomes one of synthesizing the alcohol A-5 for esterification (as per model) to give A-4a. While one might approach A-5 by more conventional means, it might be of great advantage to utilize the methodology established in the model sequence at this point as well. The ester A-6, if subjected to the conditions used for the model, should generate the enolate anion; this would be expected to close, giving the six-membered ring *cis*-lactone (stereospecifically) rather than the less favorable seven or eight-membered ring bicyclo-compounds (the possible result of attack at the 6, 7, or 8 position). Again an intramolecular reaction would be employed to establish necessary stereochemistry.

The key intermediate A-6, which by this route essentially defines all the asymmetric centers in vernolepin, may be approached analogously to Berchtold's *trans*-benzene trioxide synthesis (12a). Singlet oxygen addition to 14 yields the epoxy epidioxide 15, which rearranges in



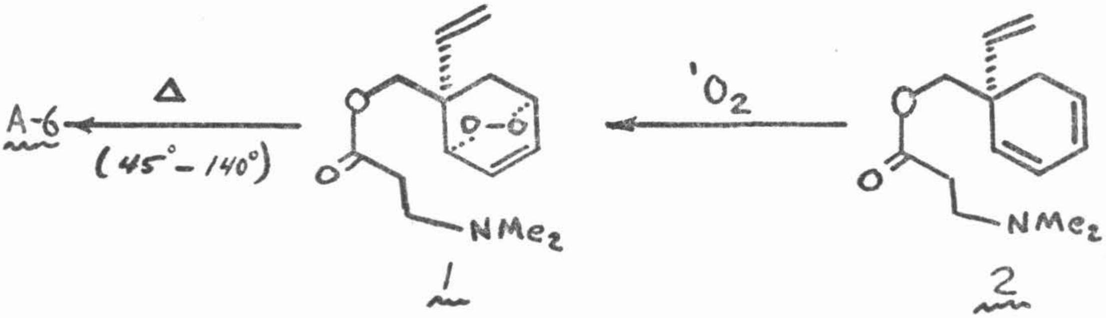
14 15 16

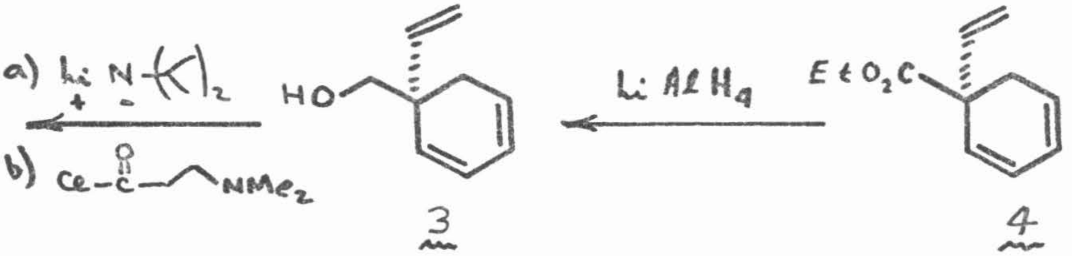
quantitative yield upon heating to give trans-benzene trioxide, 16. This thermal rearrangement of epidioxides has been performed in other systems as well (12b, c), and it seems likely that the diepoxide A-6 should result on heating epidioxide B-1.

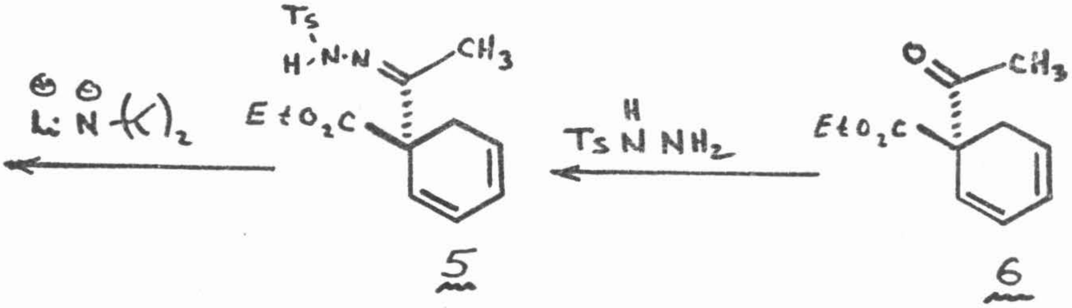
Although lack of stereospecificity may be a problem, epidioxide B-1 should be produced on sensitized photoöxygenation of diene B-2. Singlet oxygen participation in 4 + 2 cycloaddition reactions is well-known to be a fascile process (13a), quite subject to the directing effects of steric hinderance (13b). In the case of diene B-2, since there are only trigonal centers β to the quaternary carbon, one would expect no pseudo-axial or equatorial preference for either the ester or vinyl side chain. Any steric shielding then, of the sort which would accompany a rigid axial group, will not be present here; in this case, the length and bulk of each side chain must directly determine the amount of shielding on each face of the molecule. How significant this effect will be in the outcome of singlet oxygen addition is uncertain, yet for ester B-2 the effect must be at least operative in the proper sense; and one might thus hope to obtain a preponderance of addition from the side bearing the vinyl grouping.

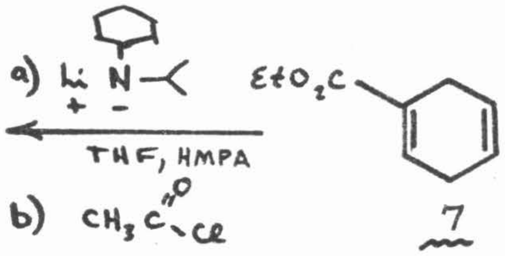
For initial experiments, even a 1:1 mixture of isomers (if separable) would be acceptable. If subsequent steps should prove workable, then other ester chains might be examined on B-3 to better direct the stereochemistry of photoöxygenation. Recent efforts of Corey (14) have demonstrated that intramolecular π-π interactions of conjugated systems with aromatic ester side chains can be used to effectively

Chart B


A-6
Δ
(45° - 140°)
O-O
NMe₂
1
¹O₂
NMe₂
2


a) Li N-(⟨)₂
+ -
b) Cl-C(=O)-CH₂CH₂-NMe₂
HO
3
Li Al H₄
EtO₂C
4


⊕ ⊖
Li N-(⟨)₂
Ts
H·N·N
CH₃
EtO₂C
5
H
Ts N NH₂
O
CH₃
EtO₂C
6


a) Li N-⟨
+ -
THF, HMPA
b) CH₃C(=O)Cl
EtO₂C
7

shield one side of a molecule and thus induce stereospecificity in reactions of the conjugated system. If the alcohol B-3 were esterified with the appropriate aromatic grouping, then shielding of the type observed by Corey should result in photoöxygenation predominantly from the side bearing the vinyl group, as desired. After rearrangement of the epidioxide to the diepoxide, the aromatic ester could then be replaced by the aminopropionate to afford A-6.

The synthesis then reduces to the preparation of the alcohol B-3, devoid of stereochemical problems, which may then be esterified to give B-2. Simple lithium aluminum hydride reduction of the ester B-4 would be expected to yield the desired alcohol, and this unsaturated ester should be the result of non-nucleophilic base induced cleavage (15) of the tosyl hydrazone B-5. The hydrazone would be prepared under mild conditions from the keto ester B-6, which would itself result from acetylation, by the method of Rathke and Dietch (6, 9), of the enolate anion of ethyl-2,5-dihydrobenzoate (B-7) (16).

In twelve steps it may thus be possible to synthesize *dl*-vernolepin from trivial starting material.

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