

A STEREOSPECIFIC APPROACH TOWARDS THE SYNTHESIS
OF SOME PENTACYCLIC TRITERPENES

Thesis by
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To my wife, Selena

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ABSTRACT

An approach to the synthesis of pentacyclic triterpenes of the friedelin type has been outlined, and the synthesis of pentacyclic intermediates related to this approach has been accomplished.

TABLE OF CONTENTS

	Page
Title Page.....	i
Acknowledgements.....	ii
Abstract.....	iii
Table of Contents.....	iv
Historical Introduction.....	1
Synthesis of the Onocerin Skeleton.....	6
Synthesis of Symmetrical Triterpenes.....	8
Synthesis of Unsymmetrical Triterpenes.....	12
Discussion.....	18
Experimental.....	74
1-Methyl-6-methoxy-3,4-dihydronaphthalene (<u>H-2</u>)....	75
1-Methyl-6-methoxy-3,4-dihydro-2(1H)-naphthalenone (<u>H-3</u>).....	75
4,4a,9,10-Tetrahydro-7-methoxy-1,4a-dimethyl-2(3H)- phenanthrone (<u>H-4</u>).....	76
<u>m</u> -Methoxyphenyl- α -methylstyrene (<u>I-2</u>).....	78
2-(<u>m</u> -Methoxyphenyl)-1-bromopropene (<u>I-3</u>).....	79
2-Keto-1 β ,4a β -dimethyl-1-(2- <u>m</u> -methoxyphenyl-2-propenyl)- 7-methoxy-1,2,3,4,4a,9-hexahydrophenan- threne (<u>I-5</u>).....	80
Attempted Oxidations of Ketone <u>I-5</u>	82
2-Keto-1,4a-dimethyl-1-(2- <u>m</u> -methoxyphenyl-2-propenyl)- 1-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenan- threne (<u>I-7</u>).....	83
2-Keto-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9-hexa- hydro-1-phenanthreneacetic Acid (<u>XIVc</u>).....	84
Methyl 2-Keto-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a- 9-hexahydro-1-phenanthreneacetate (<u>XIVb</u>).....	86

Ethyl 2-Keto-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a-9,10,10a β -octahydro-1-phenanthreneacetate (<u>K-1a</u>).....	88
Methyl 2-Keto-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9-10,10a β -octahydro-1-phenanthreneacetate (<u>K-1b</u>).....	89
2 β -Hydroxy-1,4a-dimethyl-7-methoxy-1,2,3,4,4a,9-hexahydro-1-phenanthreneacetic Acid (<u>K-3</u>).....	92
Lactonization of Unsaturated Hydroxy Acid (<u>K-3</u>).....	93
2 β -Hydroxy-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9-10,10a α -octahydro-1-phenanthreneacetic Acid (<u>K-4</u>).....	94
Ethyl 2-Ethylenedioxo-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10a β -octahydro-1-phenanthreneacetate (<u>L-1</u>).....	95
2-Ethylenedioxo-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a-9,10,10a β -octahydro-1-phenanthreneacetic Acid (<u>L-2</u>).....	96
2-Ethylenedioxo-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a-9,10,10a β -octahydro-2-phenanthreneacetophenone (<u>L-3a</u>).....	97
3,4,4a,9,10,10a β -Hexahydro-7-methoxy-1 α -(2 phenylethyl)-1 β ,4a β -dimethyl-2(1H)-phenanthrone (<u>L-4</u>).....	98
Attempted Acid-Catalyzed Cyclizations of Ketone <u>L-4</u>	99
2 α -Hydroxy-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10-10a β -octahydro-1-phenanthreneacetic Acid Lactone (<u>M-1</u>).....	100
Standard Diborane Solution.....	101
2 α -Hydroxy-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10-10a β -octahydro-1-phenanthreneacetaldehyde Hemiacetal (<u>M-2</u>).....	102
3,4,4a,9,10,10a β -Hexahydro-1 β ,4a β -dimethyl-7-methoxy-1-(2- <u>m</u> -methoxyphenyl)-2(3H)-phenanthrone (<u>M-4</u>).....	103
3,21-Dimethoxy-9 β ,14 β -dimethyl-6,7,8 β ,9,11,14,15,16-octahydronicene (<u>M-5</u>).....	105

12-Keto-3,21-dimethoxy-9 β ,14 β -dimethyl-6,7,8 β ,9,11- 12,13 α ,14,15,16-decahydropicene (<u>N-2</u>).....	107
Base Equilibration of Ketone (<u>N-2</u>).....	108
12-Keto-3,21-dimethoxy-9 β ,13 β ,14 β -trimethyl-6,7,8 β - 9,11,12,13,14,15,16-decahydropicene (<u>N-3</u>).....	109
12-Keto-11 β -bromo-3,21-dimethoxy-9 β ,13 β ,14 β -trime- thyl-6,7,8 β ,9,11,12,13,14,15,16-decahydropi- cene (<u>N-4</u>).....	111
Catalytic Hydrogenation of Pentacyclic Olefin (<u>M-5</u>)	112
Birch Reduction of Pentacyclic Olefin (<u>M-5</u>).....	113
2 β -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10- 10 $\alpha\alpha$ -octahydro-1-phenanthreneacetic Acid Lac- tone (<u>O-1a</u>).....	114
Attempted Hydroboration of the Lactone <u>O-1a</u>	115
2 β -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10- 10 $\alpha\alpha$ -octahydro-1-phenanthrene-N-methyl-acetamide (<u>O-2a</u>).....	116
2 α -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10- 10 $\alpha\alpha$ -octahydro-1-phenanthreneacetic Acid Lactone (<u>O-5</u>).....	118
2 α -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10- 10 $\alpha\alpha$ -octahydro-1-phenanthreneacetaldehyde Hemi- acetal (<u>O-6</u>).....	119
3,4,4 α ,9,10,10 $\alpha\alpha$ -Hexahydro-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy- 1-(2- <u>m</u> -methoxyphenyl)-2(3H)-phenanthrone (<u>P-2</u>)	120
3,21-Dimethoxy-9 β ,14 β -dimethyl-6,7,8 α ,9,11,14,15,16- octahydropicene (<u>P-3</u>).....	122
Attempted Hydroboration of Olefin (<u>P-3</u>).....	123
Epoxidation of Pentacyclic Olefin (<u>P-3</u>).....	124
Base Equilibration of Epimeric Ketones (<u>P-4</u>) and (<u>P-5a</u>).....	125
Methylation of Pentacyclic Ketone (<u>P-4</u>).....	127
The Effect of Solvent on the Alkylation of Pentacyclic Ketone (<u>P-4</u>).....	129

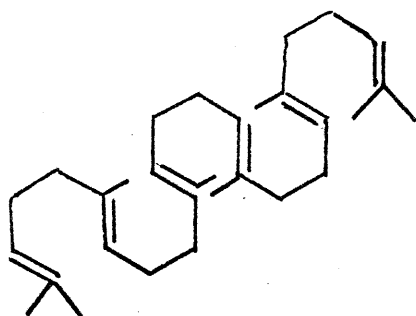
3,21-Dimethoxy-9 β ,14 β -dimethyl-6,7,8 α ,9,11,12,13 β , 14,15,16-decahydropicene (<u>XXXIV</u>).....	130
Hydrogenation of Pentacyclic Olefin (<u>P-3</u>).....	132
2 β -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10- 10 $\alpha\alpha$ -octahydro-1-phenanthreneacetophenone (<u>Q-1</u>)	132
3,4,4 α ,9,10,10 $\alpha\alpha$ -Hexahydro-7-methoxy-1 α -(2-phenyl- ethyl)-1 β ,4 $\alpha\beta$ -dimethyl-2(1H)-phenanthrone (<u>Q-3</u>)	134
References.....	136
Appendix.....	142
Proposition I.....	148
Proposition II.....	155
Proposition III.....	164
Proposition IV.....	175
Proposition V.....	184

HISTORICAL INTRODUCTION

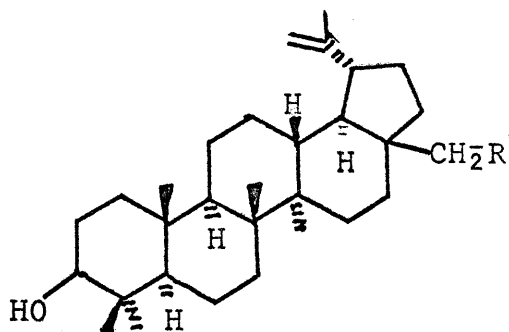
As a class, triterpenes constitute a diverse group of C_{30} isoprenoid compounds which may be derived biologically from squalene (i)(1). This class represents the largest group of terpenes found in plants, where they are most frequently found as pentacyclic compounds bearing few functional groups (2). In addition to their presence in plants, several triterpenes have recently been isolated from oil shale (3,4) as well as from protozoa (5,6).

Due to the lack of functionality present in triterpenes coupled with their stereochemical complexity, the structural elucidation of members of this class of naturally occurring compounds proceeded quite slowly. Although the first triterpene, betulin (ia), was isolated from the outer bark of the white birch (*Betula alba*) in 1788 (7), it was not until 161 years later that the first complete triterpene structure had been established.

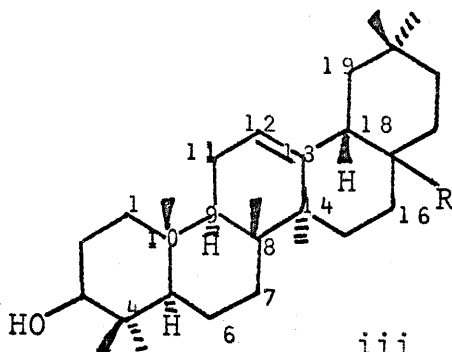
In 1949 Ruzicka and Jeger (8) proposed the gross structure ia for oleanoic acid. However, the relative as well as absolute stereochemistry of this compound was still unknown. Prior to 1949 the main endeavor in this area had been to relate the various triterpenes to a limited number of widely occurring members. For example, oleanoic acid (ia) had been related to β -amyrin (ib), and betulin (ia) to lupeol (ib)(9).



i
squalene



ii
a: R=OH
b: R=H



iii
a: R=COOH
b: R=CH₃

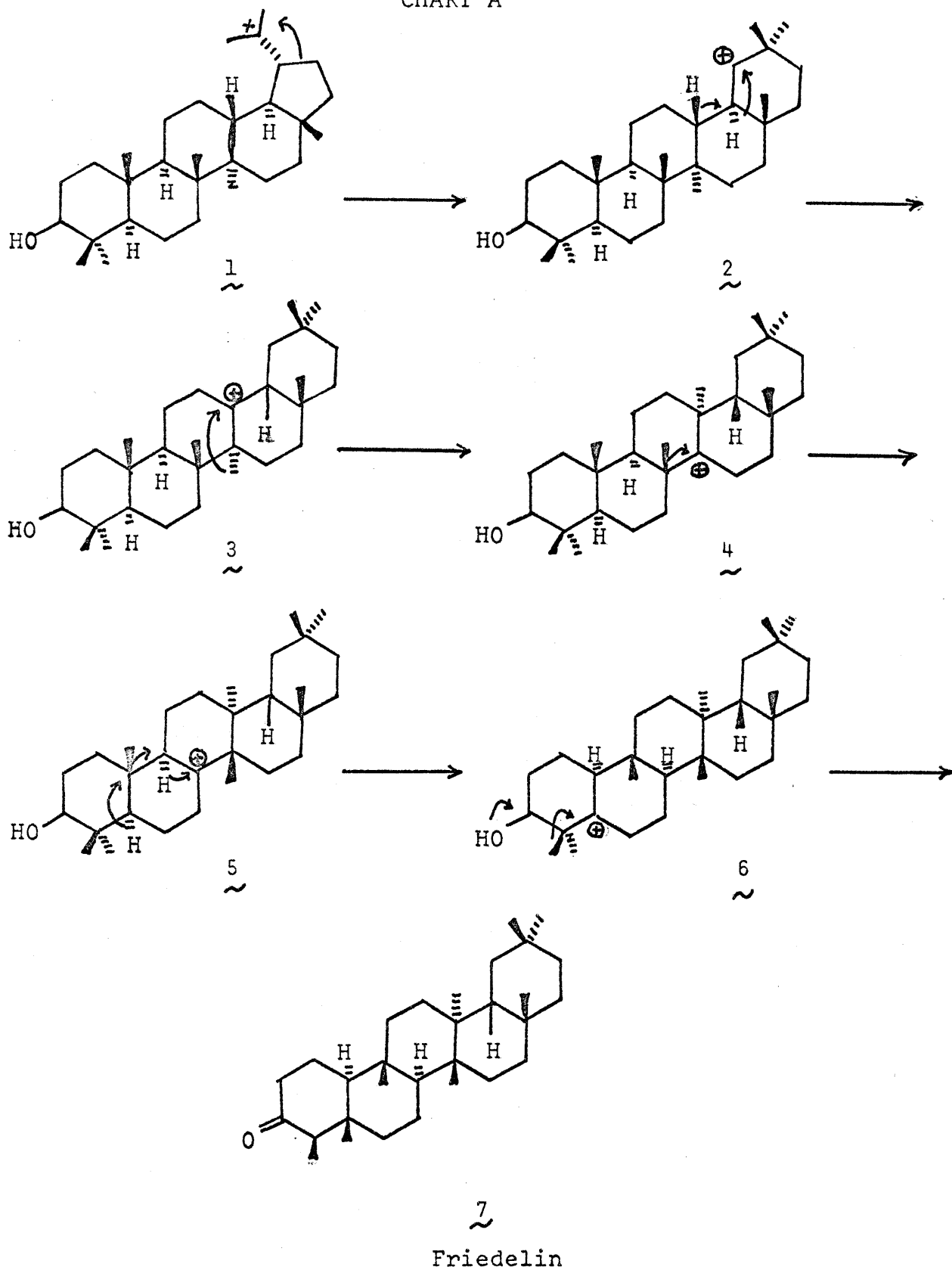
With the establishment of the basic triterpene skeletal types, there arose the attractive postulate that squalene was the probable acyclic precursor of the various classes of triterpenes. In 1955, G. Stork (10) and A. Eschenmoser (11) proposed a theoretical model for triterpene biogenesis in which the various triterpene skeletal types could be derived from *trans*-squalene by a series of concerted cyclizations followed by Wagner-Meerwein migrations (12).

During the last 10 years, with the advent of the modern tools of structural analysis, the relative stereochemistry of a large number of triterpenes has been determined. This work has been reviewed by several authors (1, 9, 13-15).

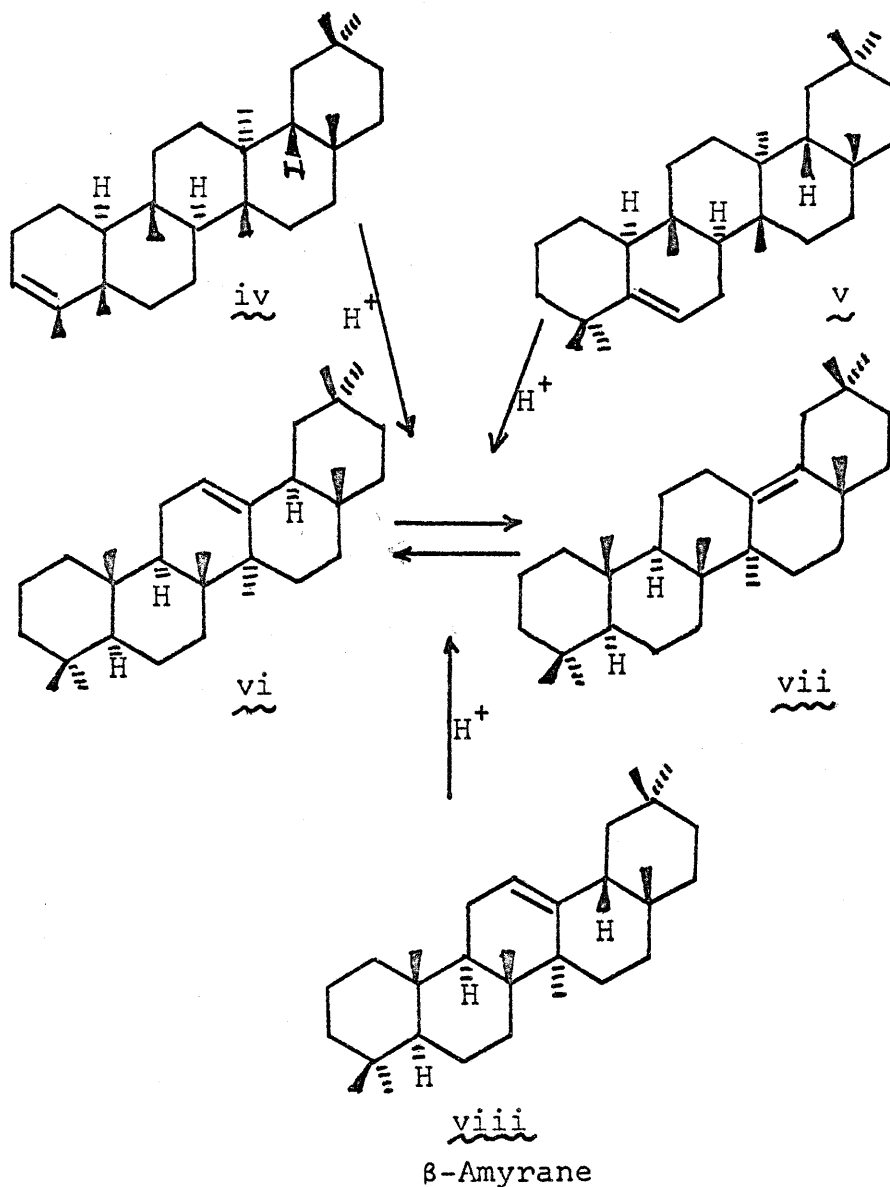
Quite recently, the existence of 2,3-oxidosqualene as a precursor to both lanosterol and β -amyrin (iiib) has been established by Corey (16-18) and van Tamelen (19). Furthermore, the enzyme which transforms 2,3-oxidosqualene into β -amyrin in germinating peas (*Pisum sativum*) has been obtained in water-soluble form, and the *in vitro* enzymic synthesis of β -amyrin from 2,3-oxidosqualene has been accomplished (19).

Since the theoretical model for triterpene biogenesis was postulated (10,11), a large number of the hypothetical carbonium ion intermediates appear to be precursors of the various classes of triterpenes having modified pentacyclic skeletons. As an illustration, Chart A depicts some of the proposed cationic intermediates which may intervene in the biogenesis of friedelin (A-7) from the prelupeol cation A-1. In fact, triterpenes which are derivable from each of the illustrated intermediates by loss of an appropriate proton have been isolated from various sources.

CHART A

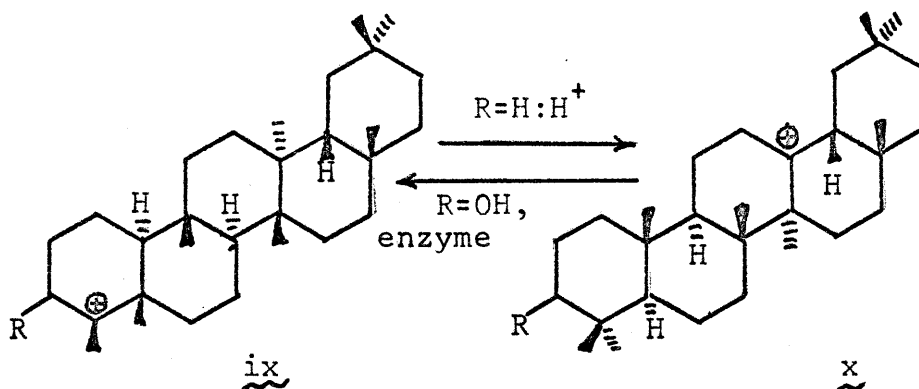


A similar series of extended methyl-hydrogen migrations of this type has been found to take place *in vitro* when friedelene (iv)(20) or alnusene (v)(21) is treated with hydrochloric acid.



These two olefins rearrange in good yields to the same olefinic mixture vi and vii that is obtained when β -amyrane (viii) is subjected to similar acid treatment. This

nonenzymic transformation essentially reverses the biogenetic sequence in proceeding from the pre-friedelin cation ix to the pre- β -amyrin cation x.

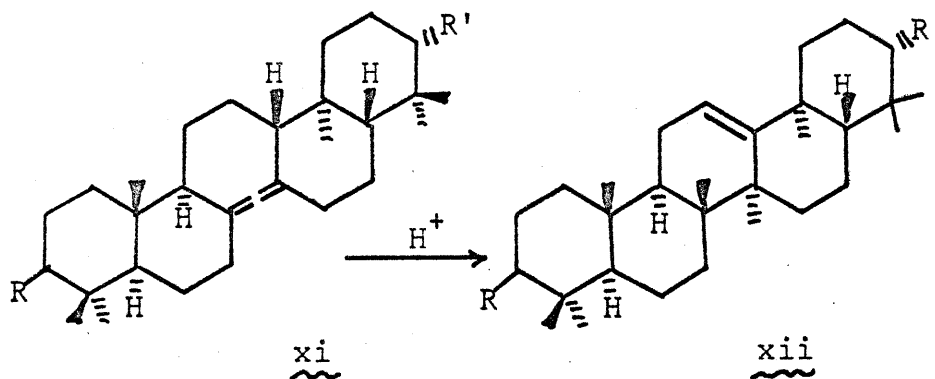


It has been suggested by Spring and co-workers (21) that these acid-catalyzed Wagner-Meerwein rearrangements are promoted by the rather severe nonbonded interactions that the *cis*-D/E ring fusion imposes on the pentacyclic structure ix. In the biogenesis of friedelin, the enzyme must play a significant role in lowering the energy of the friedelin cation ix relative to the β -amyrin cation x, enabling the reverse process to take place. In recent years, these extended *in vitro* methyl-hydrogen rearrangements have become commonplace in triterpene chemistry, and they have been reviewed by de Mayo (22).

Synthesis of the Onocerin Skeleton

α -Onocerin (xi:R=R'=OH) is a naturally occurring triterpene, first isolated by Hlasiwetz (23) in 1855 from

the roots of *Ononis spinosa* L. Considerable interest has been focused on this compound for various reasons. In contrast to the other triterpenes whose biosynthesis may be explained in terms of a unidirectional acid-catalyzed cyclization, the cyclization of squalene to form the onocerin skeleton proceeds from either end of the polyene chain.

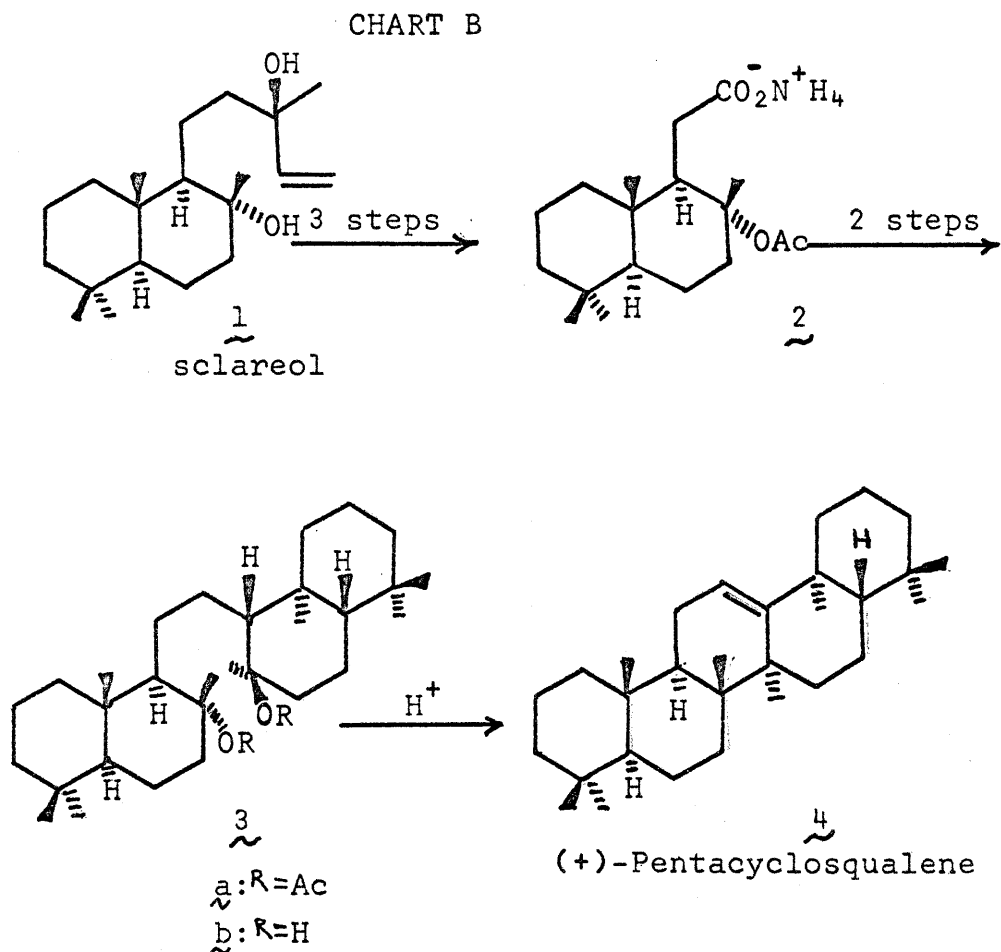


During the course of their work on the structural elucidation of α -onocerin, Barton and Overton (24) found that on treatment with acid, α -onocerin diacetate (xi: $R=R'=OAc$) could be isomerized to xii: $R=R'=OAc$ whose structure they designated as γ -onocerin (xii: $R=R'+OH$). The fact that a pentacyclic structure could be generated in this way in addition to the observation that α -onocerin possesses a two-fold axis of symmetry has influenced most of the synthetic endeavors in the area of triterpene synthesis. To date, all successful synthetic approaches to

the synthesis of pentacyclic triterpenes have invoked this type of acid-catalyzed ring closure (27).

Synthesis of Symmetrical Triterpenes.

α -Onoceradiene (xi:R=R'=H) and its cyclization product, γ -onocerene (pentacyclosqualene) (xii:R=R'=H), have been synthesized by Corey and Sauers (25) from sclareol (B-1) by the general route illustrated in Chart B.



The ingenious step in this synthesis involved the Kolbe electrolytic dimerization of the acid salt B-2 to the diacetate B-3a in 34% yield. Treatment of this diacetate

The diol B-3 has also been synthesized independently by A. Eschenmoser and co-workers (26). Their synthesis (Chart C) invoked the Diels-Alder reaction to effect dimerization of the (\pm)- α,β -unsaturated ketones C-4.

The reaction scheme illustrates the synthesis of (+)-6 from compound 1:

- Compound 1 (a bicyclic ketone with a methyl ester group) reacts with LiAlH_4 to form compound 2 (the corresponding diol).
- Compound 2 is converted to compound 3 (a bicyclic ketone with a tosylate group) via two steps: 1) TsCl , 2) CrO_3 .
- Compound 3 undergoes intramolecular condensation to form compound 4 (a bicyclic ketone with an exocyclic methylene group), labeled as (\pm)-4.
- Compound 4 is treated with RONa to form compound 5 (a tricyclic ether-ketone), which is noted to have a meso isomer.
- Compound 5 is reduced with Na/ROH to form compound 6 (a complex polycyclic alcohol), labeled as (\pm)-6.
- Compound 6 is oxidized with CrO_3 and then treated with CH_3MgI to yield the final product, B-3 (a complex polycyclic alcohol).

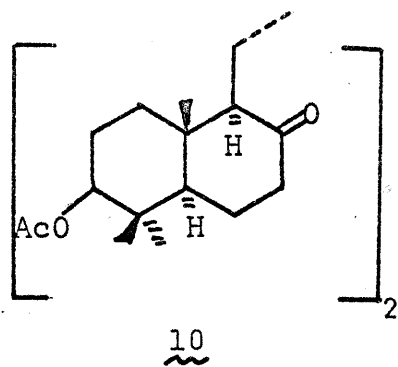
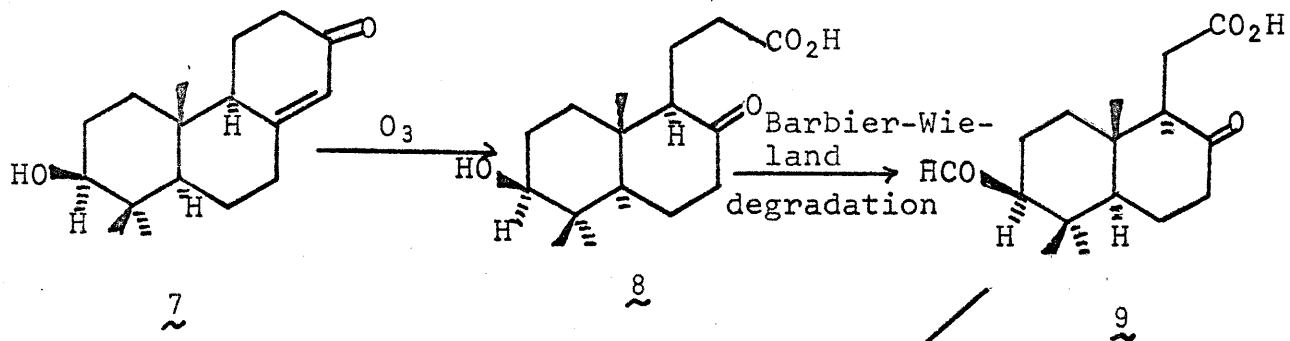
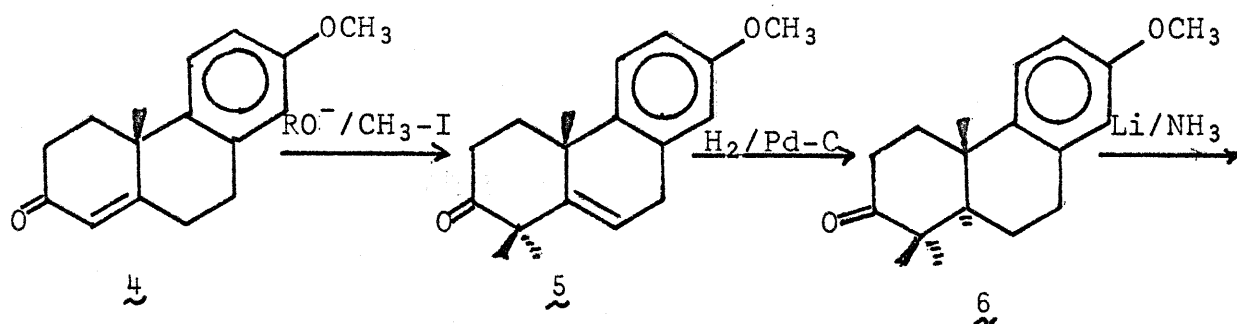
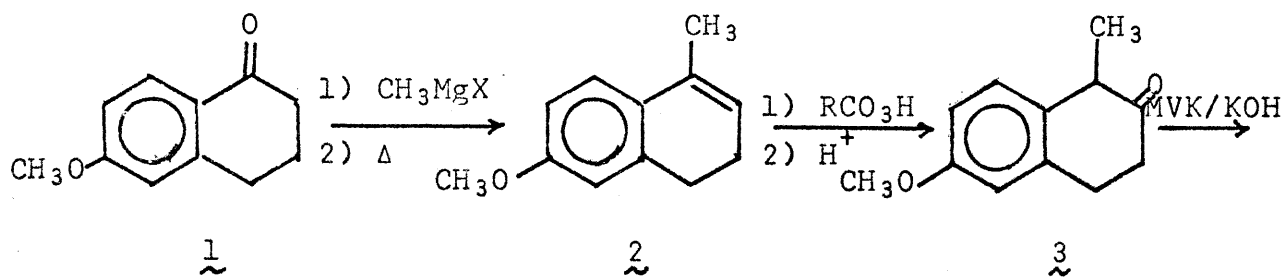
Of the four possible Diels-Alder dimers, only two appear to have been formed, one of which led to racemic bisnoroceranediol (B-6), and the other of which produced the *meso*-compound (27).

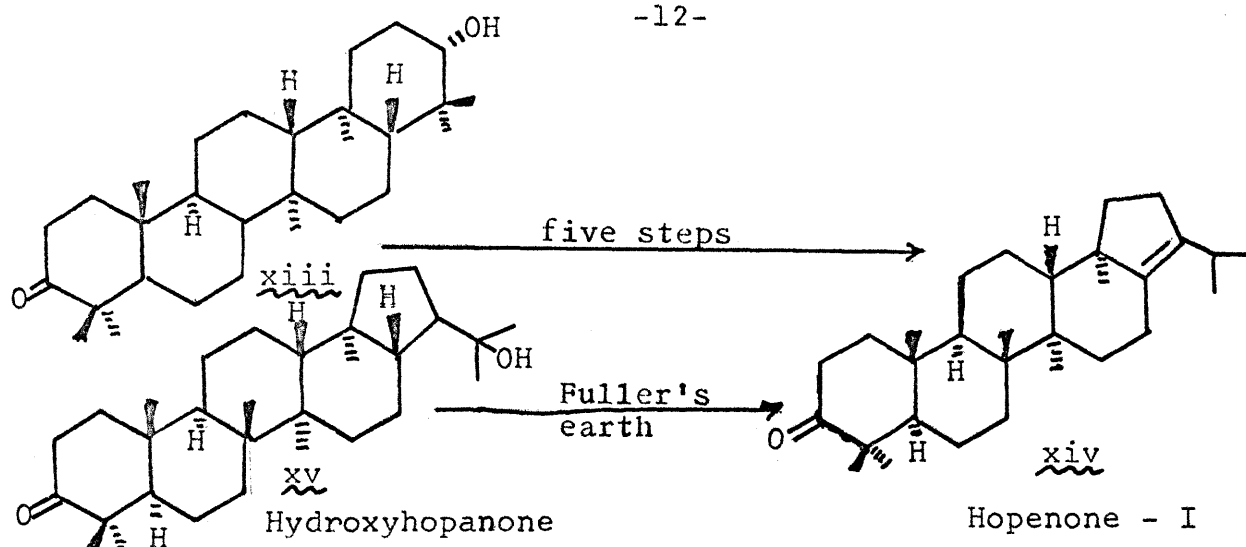
The first total synthesis of a naturally occurring onocerin derivative, α -onocerin (xi:R=R'=OH), was accomplished by G. Stork and co-workers (Chart D)(28). The basic coupling process of the appropriate bicyclic moieties used to construct the onocerin skeleton was similar to that used by Corey (25) in his pentacyclosqualene synthesis (Chart B). The major contribution of this work involved the construction of the (+)-acid D-9 from 6-methoxy- α -tetralone (D-1). Electrolytic coupling of the (-)-acid D-9 afforded the symmetrical diketone D-10 which was transformed *via* a three step sequence into (-)- α -onocerin (xi:R=R'=OH). Subsequent to this work, several other successful approaches to the synthesis of the keto acid D-9 have been published (29,30).

Since hopenone-I (xiv), a dehydration product of hydroxyhopanone (xv), has been obtained in a five-step sequence from α -onocerin proceeding *via* the hydroxy ketone xiii (31), the Stork synthesis represents the first total synthesis of this series of triterpenes.

In addition to the preceeding syntheses of the onocerin skeleton, other contributions have been made by E. E. van Tamelen (32) and F. Sondheimer (33).

CHART D



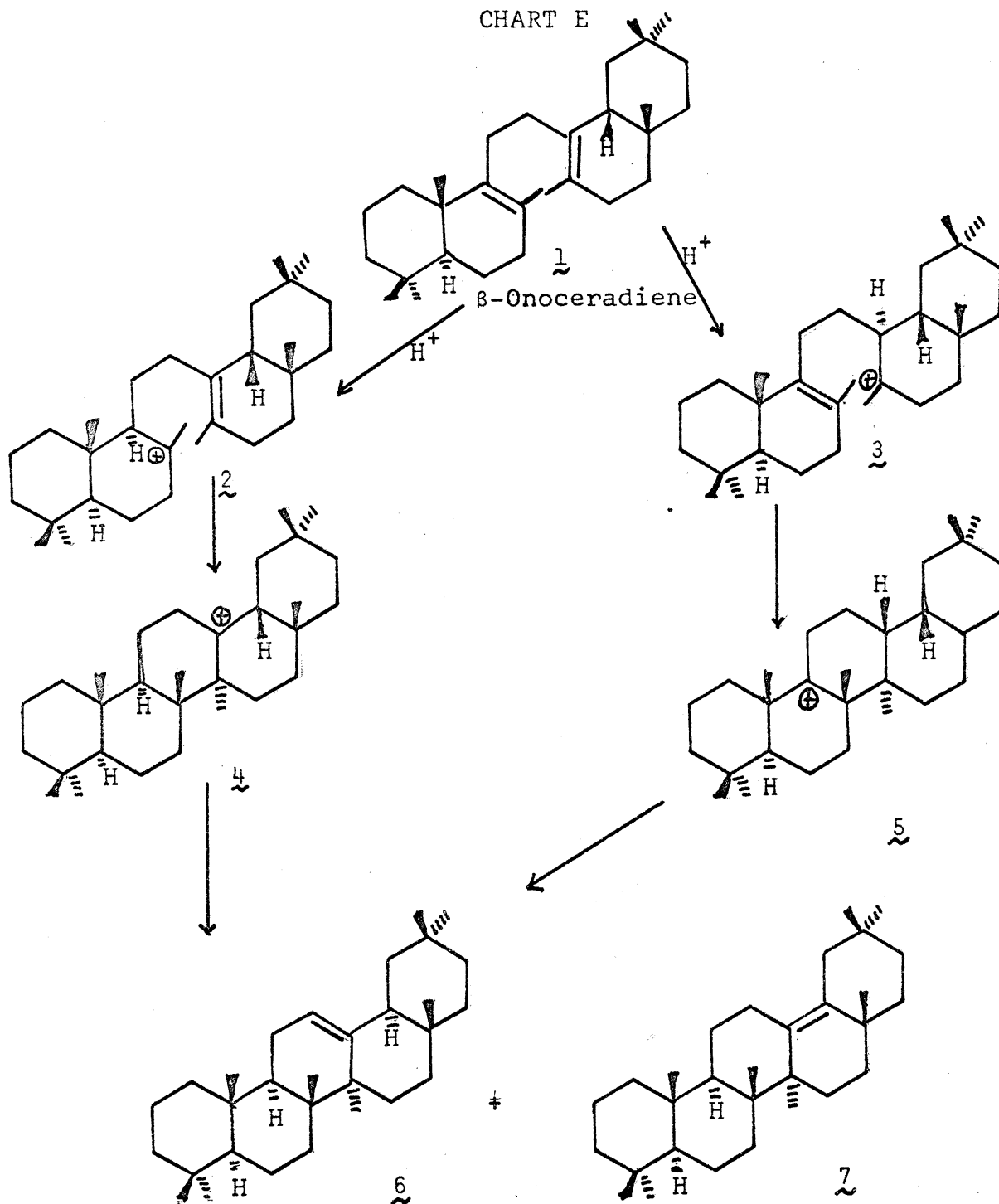


Synthesis of Unsymmetrical Triterpenes.

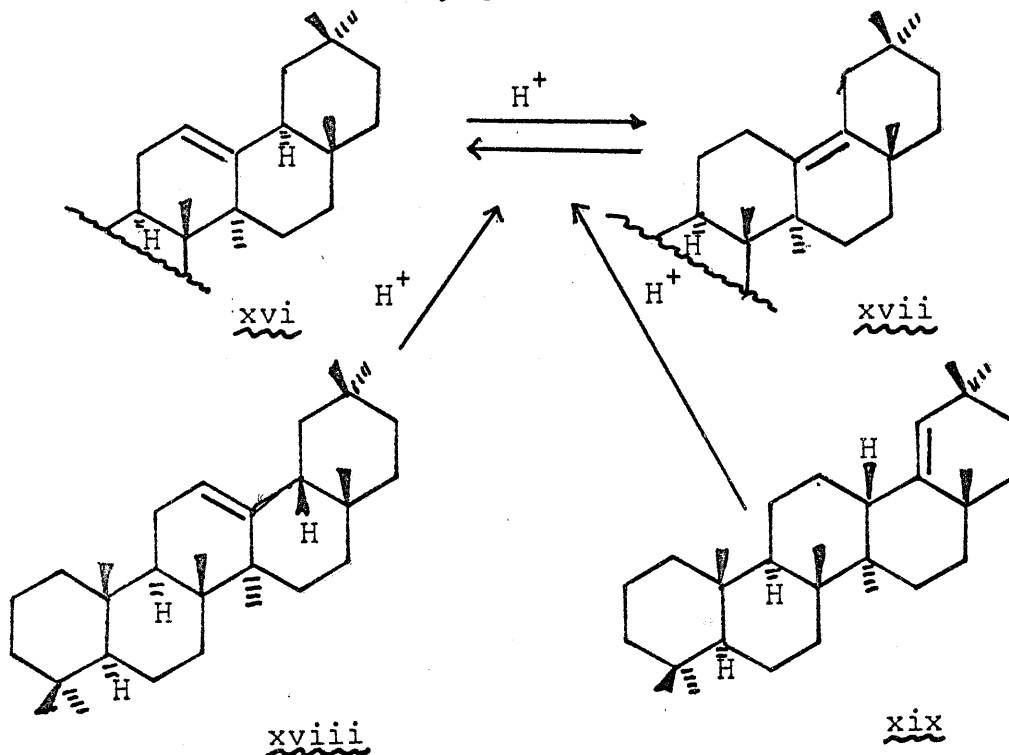
In the syntheses which have been discussed so far in the onocerin series, the general method of synthesis has involved the coupling of identical bicyclic intermediates. This approach is thus limited to the synthesis of symmetrical triterpenes such as the onocerins or those triterpenes which are readily derivable from symmetrical intermediates such as hydroxyhopanone (xv). Furthermore, all successful synthetic approaches have thus far employed an acid-catalyzed ring closure to form the C-8, C-14 carbon-carbon bond of the pentacyclic structure. It has been well documented from the work which will be discussed presently that this approach suffers from several drawbacks, not the least of which is the low yield (2-20%) with which this type of transformation may be accomplished. The main problem in such an approach is the lack of control that this system affords in the *direction* of the acid-catalyzed ring closure. This problem is illustrated in Chart E. When

β -onoceradiene (E-1) is treated with acid, either carbonium ions E-2 or E-3 may be generated. Their subsequent closure to the pentacyclics E-4 and E-5 will thus be nonselective with respect to placement of the electrophilic center.

CHART E



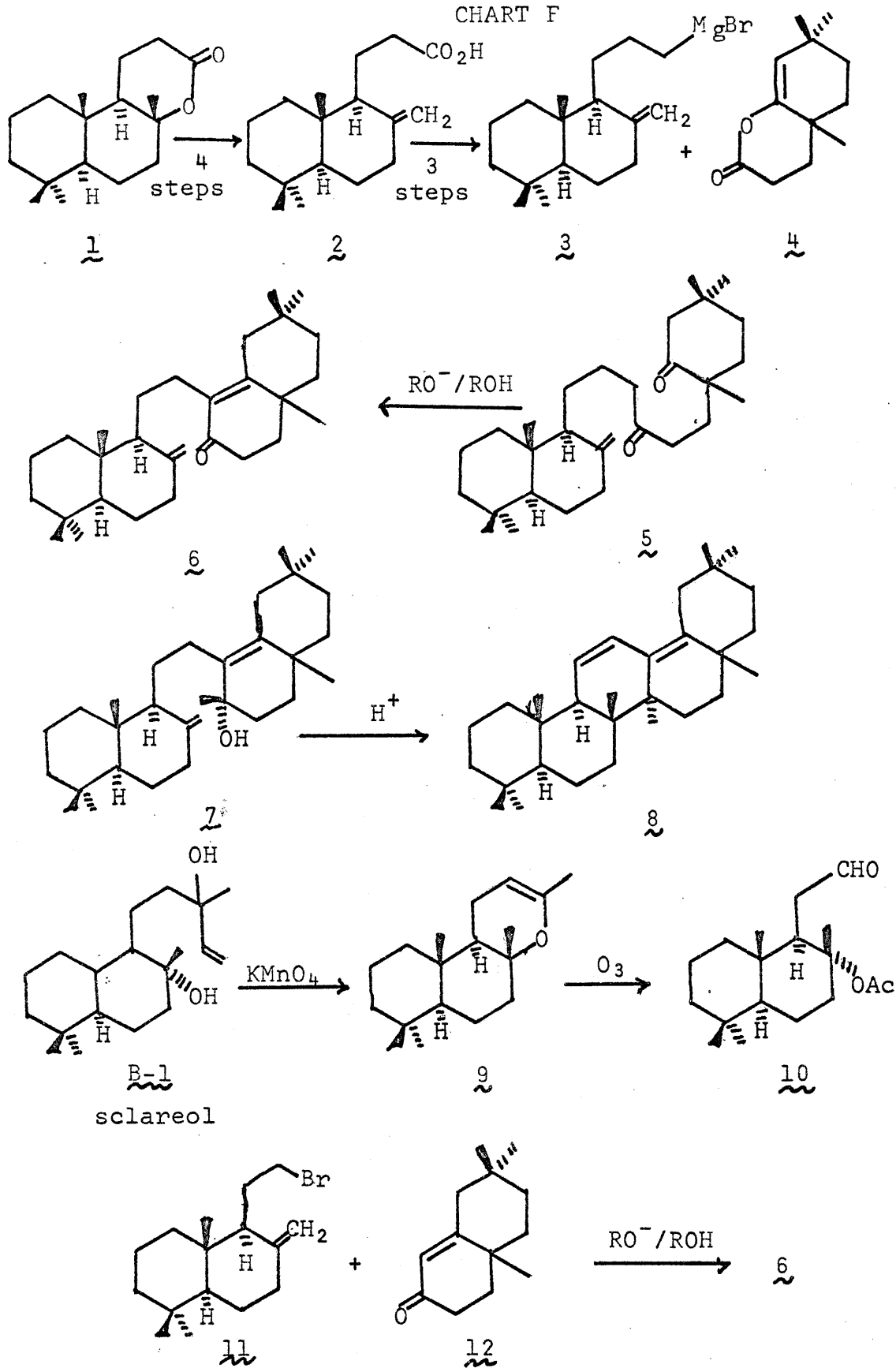
Assuming that even if one *could* generate carbonium ion E-4 in a selective fashion from an intermediate such as E-2, the stereochemical integrity of the *cis*-D/E ring fusion would be destroyed in proceeding to olefin E-7. This point has been demonstrated by Brownlie and co-workers in a study of the effect of acid on the β -amyrin (xviii) and germanicol (xix) hydrocarbons (34). Both of these olefins are isomerized irreversibly with mineral acid to an equilibrium mixture of 18 α -olean-12-ene (xvi) and olean-13(18)-ene (xvii) under conditions which are required for cyclization of β -onoceradiene (E-1). Hence, any synthetic approach that embodies the scheme outlined in Chart E will not generate the amyrin structure (xviii).



$$\underline{xvi/xvii} = 1.25$$

The synthetic approaches to unsymmetrical triterpenes which have been published to date have all more or less followed the same scheme which was previously discussed. The basic concept of independently constructing two dissimilar bicyclic moieties, which would ultimately become integrated into the A/B and D/E portions of the oleanane skeleton, was first suggested by Halsall and Thomas (35). Using this approach, Corey and co-workers synthesized amrya-11,13(18)-diene (F-8) from (+)-ambreinolide (F-1) using the route outlined in Chart F (36). The Grignard reagent F-3, which had been synthesized from (+)-ambreinolide, was caused to react with an excess of the enol lactone F-4 and gave the mixture of diones F-5. On treatment with alkoxide, the dione was transformed into the isomeric unsaturated ketones F-6. Treatment of F-6 with methyllithium produced the mixture of allylic alcohols F-7 which was subjected to acid-catalyzed cyclization. After extensive chromatography, a 2% yield of (-)-amyra-11,13(18)-diene (F-8) was obtained. Working independently, Barltrop and Rogers developed an alternate synthesis of the epimeric unsaturated ketones F-6 from sclareol (B-1) (37). Treatment of B-1 with potassium permanganate under carefully controlled conditions afforded the enol ether F-9 which, on ozonolysis, gave the aldehyde F-10. Reduction of this aldehyde with lithium aluminum hydride and treatment of the resulting diol with phosphorus tribromide gave a good yield

CHART F



of the olefinic bromide F-11. Alkylation of the hetero-annular enolate of the ketone F-12 with this bromide afforded a 68% yield of the epimeric mixture of ketones F-6. Efforts by these workers to improve the yields of the desired diene F-8 were fruitless.

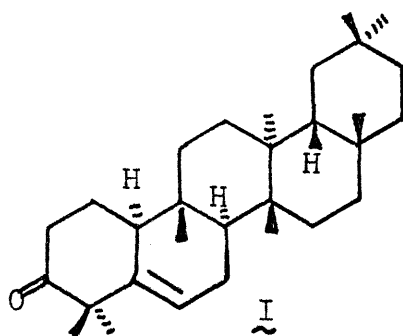
Recently, Ghera and Sondheimer (38) have published still another approach to the synthesis of unsymmetrical tetracyclic systems such as F-7; however, the basic problem of constructing the pentacyclic skeleton from such intermediates has been largely left unsolved.

DISCUSSION

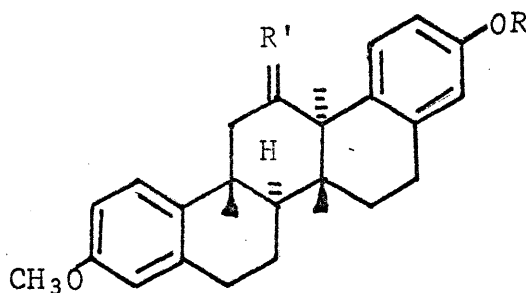
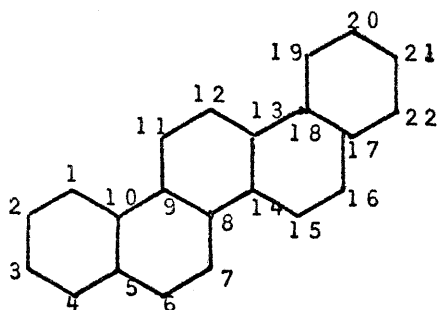
The existing synthetic approaches directed towards the construction of pentacyclic triterpenes of the oleanane type have suffered mainly from a lack of stereochemical control. Furthermore, their versatility has been limited to such an extent that only a single triterpene skeletal type could be achieved by such a synthetic scheme. The inability to modify the reaction sequence to include a wide variety of potential carbocyclic systems encountered in this area led us to a potentially versatile synthetic approach to this problem.

Since the friedelin system may be transformed by acid catalysis into the oleanane skeletal type by a series of methyl-hydrogen migrations along the triterpene backbone, and since during the course of these extended migrations virtually all of the potential triterpene carbocyclic systems containing five 6-membered rings are generated, it was felt that the primary emphasis should be placed on the construction of the friedelin-carbocyclic system. The second phase of the problem would then concern itself with the question of controlling the acid-catalyzed methyl-hydrogen migrations along the backbone of the triterpene framework.

For reasons which will be presently discussed, alnuse-none (I)(39), also commonly referred to as glutinone, was chosen as the primary goal of this project.



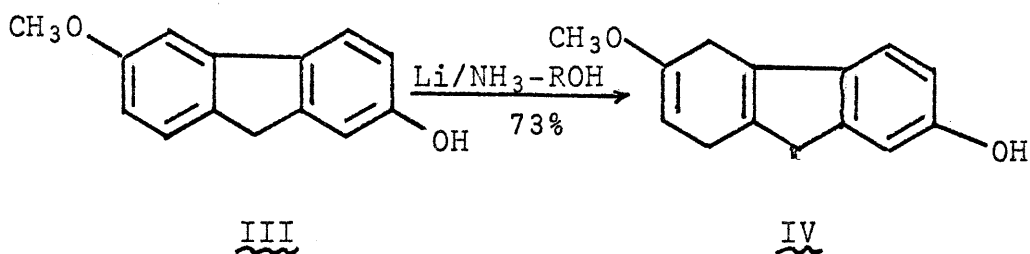
I
Alnusenone



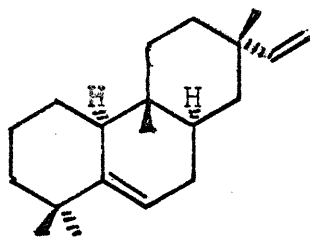
II a: R=CH₃; R'=O
b: R=H; R'=H₂

The carbocyclic framework of alnusenone (I) is arranged in such a fashion that there are seven contiguous asymmetric centers present in the molecule. It was envisaged that six of the seven points of asymmetry could be established from an intermediate such as II. It has been well established that the Birch reduction of *trans*-fused octahydrophenanthrene systems proceeds to give reduced phenanthrenes having a *trans-anti* backbone (28). This fact has been similarly established in the synthesis of 19-nor-steroids from their phenolic precursors (40). In this way the appropriate stereochemistry at C-10 and C-18 of the carbocyclic structure could be introduced by a step-wise reduction of the

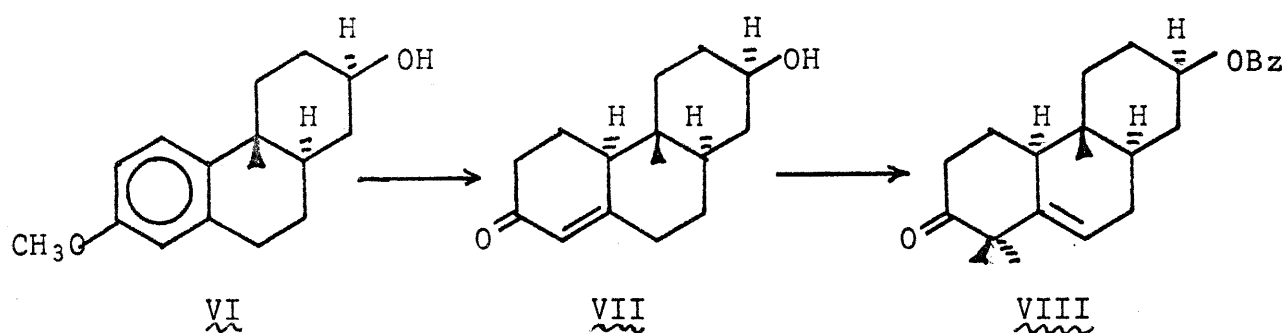
decahydropicene derivative II using the Birch procedure (41). The problem of distinguishing chemically between the two aromatic rings during the step-wise elaboration of the decahydropicene intermediate II may be circumvented by constructing a derivative such as IIb. It has been demonstrated that anisole rings are more prone to Birch reduction than are phenolic systems. This point is illustrated by the partial reduction of 2-hydroxy-7-methoxyfluorene III (42).



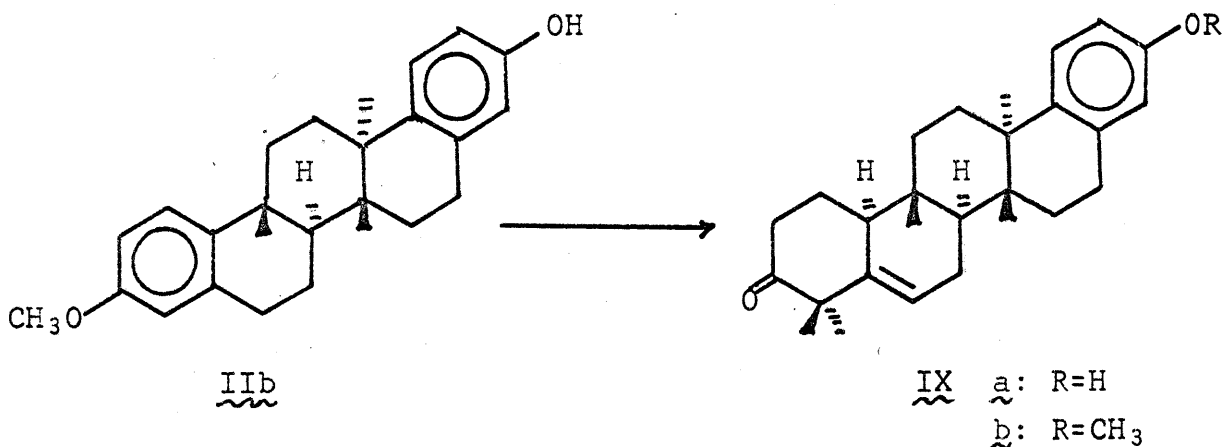
A method which may be used for the modification of ring A of the decahydropicene IIb has already been published by Ireland and Mander in their synthesis of (\pm)-rimuene V (43).



V
Rimuene

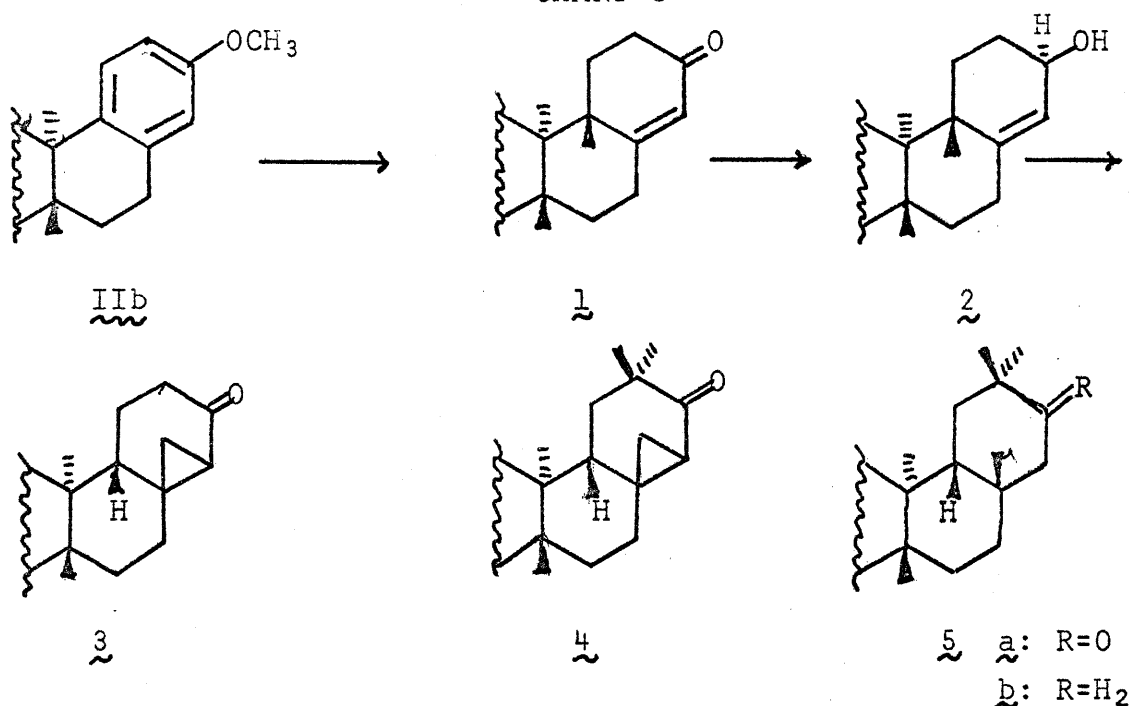


Thus, in a four step sequence which proceeded in an overall yield of 62.5%, the phenanthrene alcohol VI was transformed into the keto benzoate VIII (43). Based on this precedent, it was anticipated that the transformation of IIb to IXa should offer no serious problems.



A plausible synthetic scheme for the elaboration of ring E is illustrated in Chart G. By a series of routine transformations the allylic alcohol G-2 could be prepared from IIb. From this intermediate, the β -cyclopropyl ketone G-4 may be synthesized *via* the cyclopropylation-oxidation sequence developed by Dauben and Deviny (45).

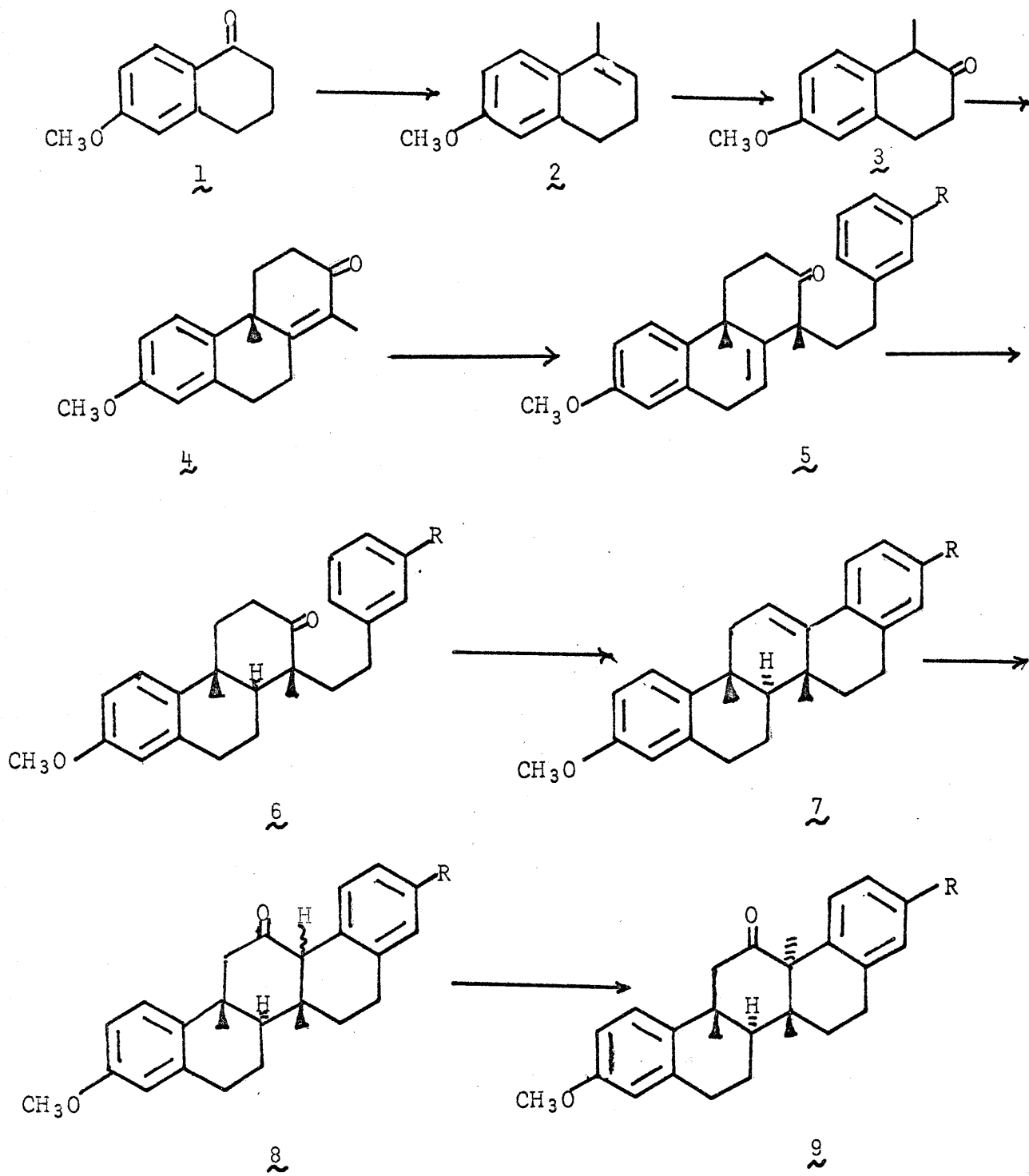
CHART G



Gem-dimethylation of the cyclopropyl ketone G-3 should occur exclusively at C-20 and afford the ketone G-4. The reductive cleavage of the cyclopropyl ketone G-4 with lithium and ammonia may be expected to proceed in the illustrated manner based on the work of Dauben and Deviny (45). This general sequence enables the stereochemistry of the C-17 methyl group to be controlled by the stereochemistry of the C-21 hydroxyl function.

Having devised a plausible synthetic scheme for the modification of the decahydronicotinic acid skeleton IIb, we turned our attention to possible ways in which such a carbocyclic system could be constructed in an efficient manner. The basic route which was conceived to accomplish this task is shown in Chart H.

CHART H*



* All compounds prepared during the course of this work were racemic mixtures.

The starting point for the synthesis was chosen as the commercially available 6-methoxy- α -tetralone (H-1) which was readily transformed, according to the procedure outlined by Stork (28) into the dihydronaphthalene H-2 by its reaction with methylmagnesium iodide followed by dehydration of the resulting tertiary benzylic alcohol. The conversion of the dihydronaphthalene H-2 to 1-methyl-6-methoxy- β -tetralone (H-3) *via* the epoxide procedure developed by Stork (28) proceeded in high yield and requires no further comment. Base-catalyzed condensation of the β -tetralone with ethyl vinyl ketone in the presence of aqueous methanolic potassium hydroxide afforded the crystalline tricyclic ketone H-4 in 82% yield(44).

Based on the work of Stork and Schulenberg (46) in their synthesis of (+)-dehydroabietic acid, it was anticipated that alkylation of the heteroannular enolate of the ketone H-4 with 2-(m-methoxyphenyl)-ethyl bromide (47) should afford the ketone H-5:R=OCH₃. This desired transformation, although attempted under a wide variety of conditions, was never successful. The source of the difficulty lay in the fact that under the conditions which were required for C-alkylation of the heteroannular enolate of H-4, the alkylating agent suffered dehydrohalogenation. The same result was experienced when the corresponding iodide was prepared.

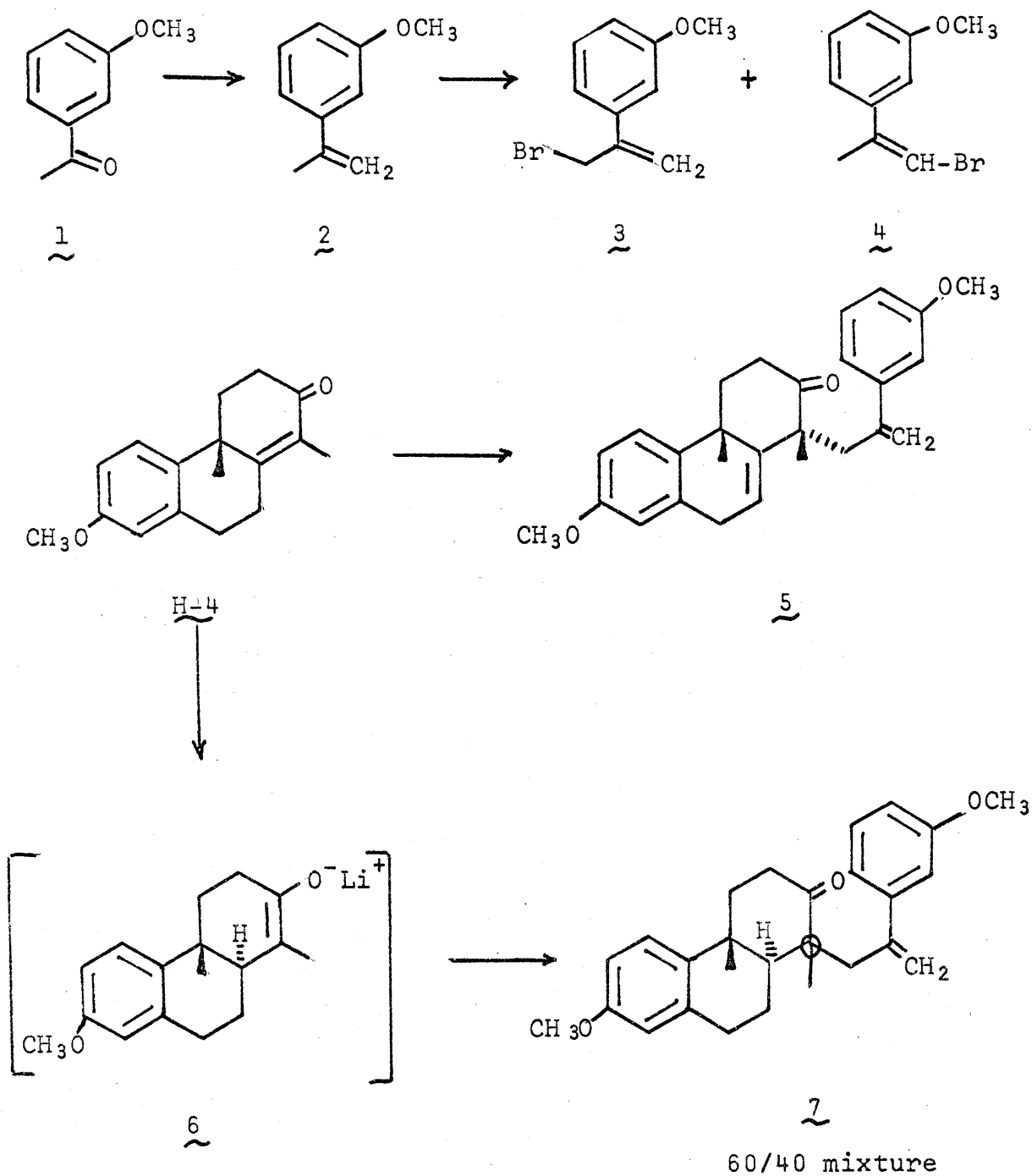
The inability to transform ketone H-4 into the phenylethyl ketone H-5 by a direct method prompted an investigation of various less direct routes which would achieve this goal.

An alternative alkylating agent, 2-bromo-3'-methoxyacetophenone, appeared to be a suitable choice. The great reactivity of such bromo ketones as well as the inability of these compounds to undergo dehydrohalogenation rendered this alkylating agent quite attractive. However, at the time it was not realized that the bromo ketone was a weaker conjugate base than the heteroannular enolate of ketone H-4. As a consequence, when this halide was used to alkylate the ketone the products derived from the reaction were recovered ketone H-4 and condensation products derived from the alkylating agent.

An alternative scheme (Chart I) was then investigated in an effort to achieve the introduction of the β -phenylethyl moiety into the ketone H-4. The styrene derivative I-2 was synthesized in a routine fashion by the reaction of m-methoxyacetophenone with methylenetriphenylphosphorane. The α -methyl styrene I-2 was then brominated with N-bromosuccinimide and gave a 75% yield of a mixture of allylic bromide I-3 and vinyl bromide I-4 in a 2:1 ratio. The formation of vinyl bromides of this type during the bromination of α -methyl styrene has been previously observed by several other groups of workers (48,49). No effort was made to separate this mixture since the allylic bromide proved to be rather unstable. Alkylation of the tricyclic ketone H-4 with this mixture of bromides according to Stork's general procedure (46) afforded a 48% yield of the ketone I-5 whose stereochemistry was assigned

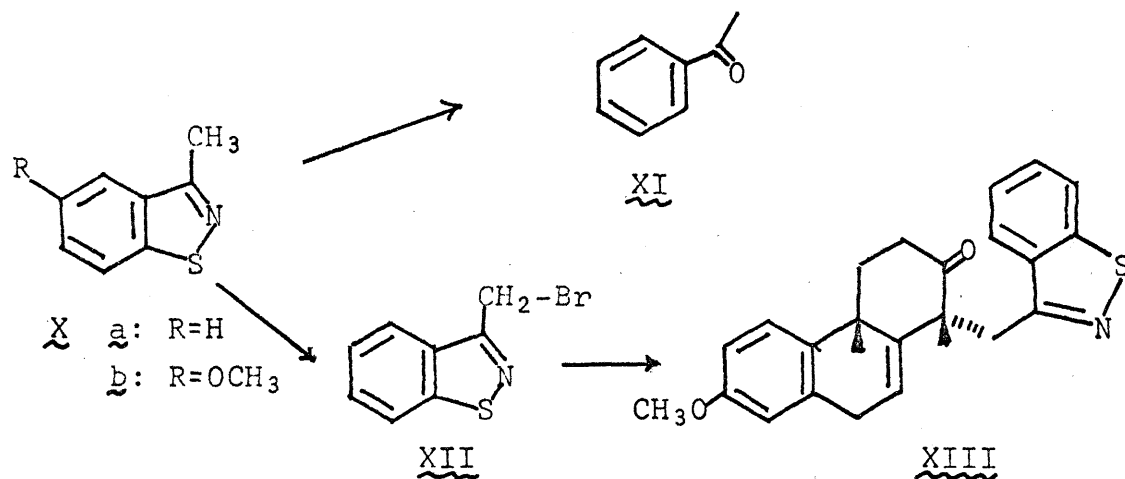
by analogy with the generally observed orientations in such alkylations (46).

CHART I



Efforts were then directed towards degrading ketone I-5 back to the desired phenylethyl ketone H-5:R=OCH₃. However, difficulty was experienced in attempting to accomplish this task. Although reasonably good selectivity between the two double bonds was achieved with osmium tetroxide, the cleavage of the resulting diol with paraperiodic acid afforded a variety of ill-defined ketonic products which were not characterized. Similar results were obtained with the above reagent on the alcohol obtained by lithium aluminum hydride reduction of ketone I-5. To circumvent the difficulty of having to distinguish between two apparently similar double bonds, the unsaturated ketone H-4 was reduced with lithium in ammonia, and the enolate I-6, which was formed *in situ* (50), was quenched with the allylic bromide mixture and gave a 91.5% yield of an isomeric mixture of alkylated ketones I-7. This mixture, consisting of nearly equal amounts of the two C-1 isomers, could not be resolved by column chromatography. As a result of the low degree of selectivity that the enolate I-6 exhibited with this alkylating agent as opposed to the high degree of selectivity exhibited by the heteroannular enolate of H-4, the former route was abandoned.

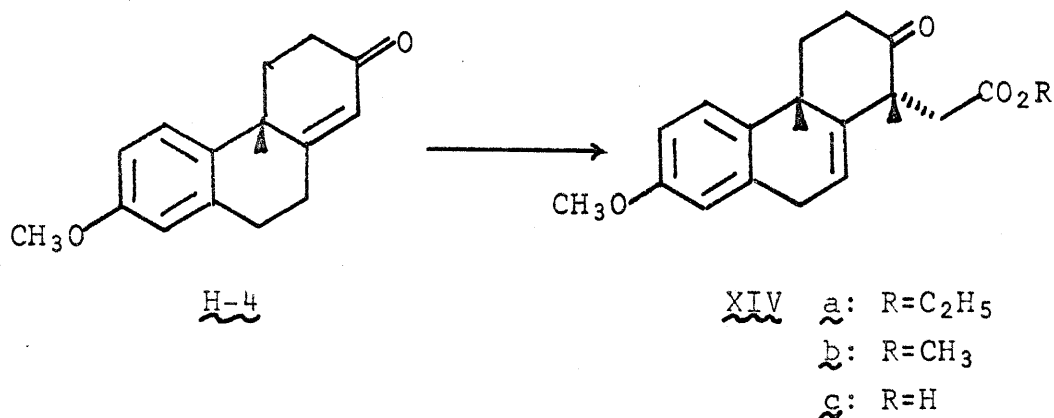
In view of the rather discouraging results which were obtained in the aforementioned experiments, a new approach to the problem of introducing the phenylethyl moiety was envisaged. This approach is illustrated below.



2-Methylbenzisothiazole (Xa) may be conveniently brominated in good yield with N-bromosuccinimide, and this bromide appears to be a suitable alkylating agent for highly basic systems. Thus, unsaturated ketone H-4 was alkylated in a 72% yield with this reagent and gave what appears* to be the ketone XIII. Exploratory work has been done on converting the benzisothiazole to acetophenone. This was accomplished by the use of W-2 Raney nickel in ethanol. However, an attempted desulfurization of the alkylated ketone XIII under similar conditions led to a variety of products which were not characterized. It was surmised that the C-2 ketone function was becoming involved in the nickel-catalyzed disruption of the isothiazole ring. For various reasons this approach was temporarily abandoned in favor of other more versatile approaches. The utility of bromobenzisothiazole derivatives such as XII for the ultimate use in this problem as well as for the synthesis of some steroid hormones is being currently investigated in this laboratory.

*Structure identified by n.m.r. analysis only.

In view of the general difficulties which were encountered in attempting to introduce the phenylethyl moiety into the unsaturated ketone H-4 as a single fragment, it was finally decided to break the process into two steps. The first step would involve the incorporation of a functionalized two-carbon fragment, and the second step would involve the introduction of the phenyl nucleus at the terminus of the newly introduced side chain. This general approach offered a wide variety of alternatives to the basic problem. The stereospecific introduction of the two-carbon fragment was accomplished according to the general scheme outlined below.



The heteroannular enolate of tricyclic ketone H-4 was caused to react with ethyl bromoacetate according to a modified procedure in which sodium hydride was used as a base rather than the normally used alcoholic bases. It was found that if alkylations of this type were carried out in protic solvents the yields of alkylated material were quite low. Apparently alkoxide reacts with ethyl bromoacetate at a faster

rate than does the enolate of the ketone H-4. In the original procedure published by Stork (46) on the alkylation of these types of ketones, the reaction system consisted of benzene as a solvent and potassium t-butoxide as a base. This choice of reagents required the removal of t-butanol from the reaction mixture prior to the addition of alkyl halide to the enolate. In this procedure, the alcohol was distilled from the reaction mixture along with benzene. It was discovered that the use of sodium hydride as a base and dimethoxyethane as a solvent was far simpler than the more laborious procedure described above. Alkylations carried out in this fashion resulted in 80-90% yields of C-alkylated material. The product mixture, containing predominately the unsaturated keto ester XIVa, also afforded small amounts (ca. 2-4%) of two other components which were deduced to be the C-1 and C-3 isomeric keto esters by their similar retention times on gas chromatographic analysis. In addition to these two contaminants, there was usually 5-10% of the unalkylated ketone H-4 present in the product mixture. This mixture, which was obtained as an oil, was saponified without purification with aqueous methanolic potassium hydroxide to a crystalline solid mixture of keto acids from which the desired keto acid XIVc was crystallized in 60-75% yields based on the unsaturated ketone H-4. No direct comparison may be made between these results and the results of Stork (46) on similar systems. Stork reports "crude" yields of 80-88% for his alkylation step with ethyl bromoacetate. These reported

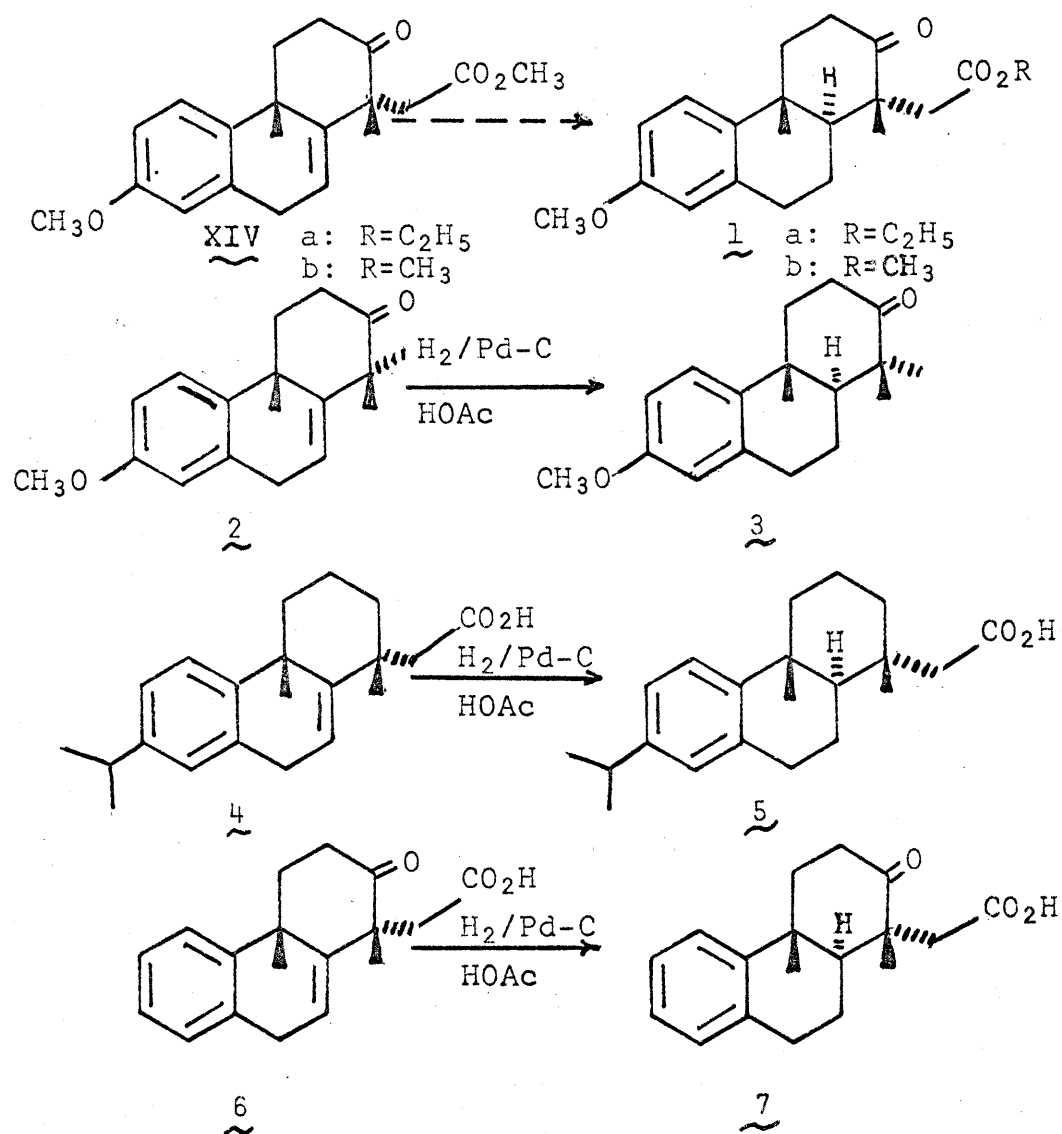
yields of unsaturated keto ethyl esters were based on total weight of crude product without any indication as to the purity or isomeric composition of the material.

Due to the highly crystalline nature of the unsaturated keto acid XIVc which rendered the compound virtually insoluble in most organic solvents, the more soluble methyl ester was prepared. This transformation was best accomplished by refluxing an acetone solution of the acid in the presence of methyl iodide and anhydrous potassium carbonate. In this manner, a 93% yield of the crystalline unsaturated keto methyl ester XIVb was obtained. Acid-catalyzed esterification of the keto acid XIVc proved to be somewhat less desirable than the above method.

With the ample number of available examples (Chart J) acting as a precedent, it was anticipated that catalytic hydrogenation of the unsaturated keto ester XIVb would occur from the *alpha* face of the molecule to afford the desired *trans*-fused keto ester J-1b.

In Stork's onocerin synthesis, hydrogenation of the unsaturated ketone J-2 gave a single saturated ketone J-3 which was shown to be the *trans* isomer (28). Similarly, the hydrogenation of unsaturated acid J-4 proceeded in a stereospecific manner to afford the saturated *trans*-fused acid J-5 (46). The proof of the stereochemistry of J-5 was established by its transformation into dehydroabietic acid whose stereochemistry had been previously determined (51). The hydrogenation

CHART J



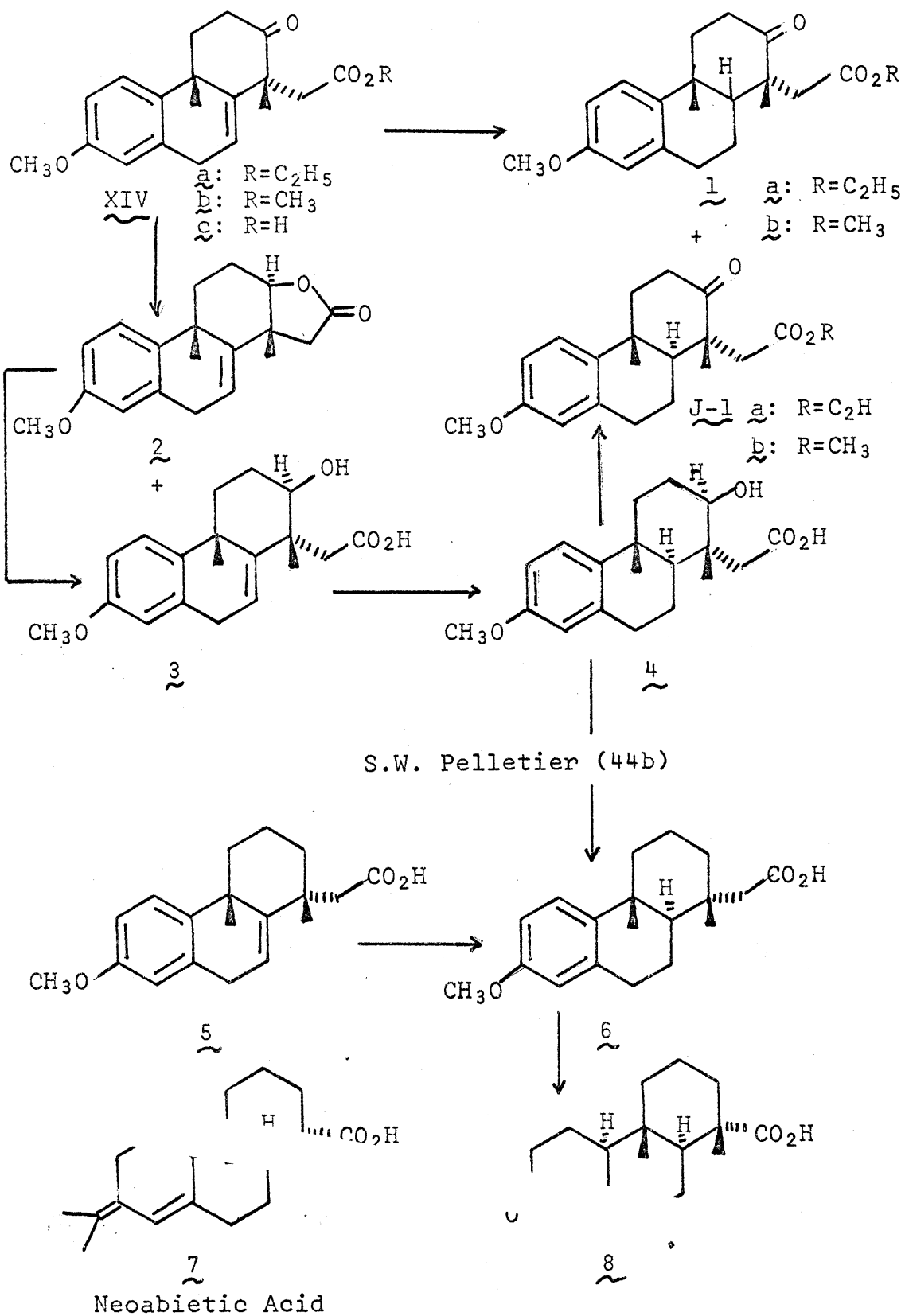
of the unsaturated keto ester J-6 using platinum metal as a catalyst has been accomplished by Ghatak and co-workers (52). They reported to have obtained a single isomeric saturated keto ester J-7 in high yield which they claimed to be the *trans*-fused isomer. However, their stereochemical proof is

somewhat tenuous in that no direct comparison was made between this material and material of known stereochemistry.

Based on these precedents, the unsaturated keto ester XIVb was hydrogenated under the conditions reported by Ghatak (52). Gas chromatographic analysis of the product mixture indicated the presence of two isomeric hydrogenation products in a 3:1 ratio. At the time it was assumed, based on the previously discussed precedents, that the major isomer was the desired *trans*-fused keto ester J-1b. An investigation of other conditions which would produce better relative yields of this keto ester was undertaken. It was discovered that the use of 10% palladium-on-charcoal rather than platinum oxide increased the product ratio from 3:1 to 8:1. However, from the work which was subsequently done, it was unequivocally established by X-ray crystallography that the major isomer from this hydrogenation was actually the isomeric *cis*-fused saturated keto ester K-1b. These results tend to cast some doubt on the validity of the stereochemical assignment made by Ghatak (52). After it was discovered that the major hydrogenation product was the *cis*-fused isomer, the problem of obtaining the other isomeric ketone presented itself. The successful solution to this problem is illustrated in Chart K.

Reduction of the unsaturated keto acid XIVc with sodium borohydride in tetrahydrofuran afforded a mixture of the hydroxy acid K-3 and *trans*-lactone K-2. Saponification of this lactone

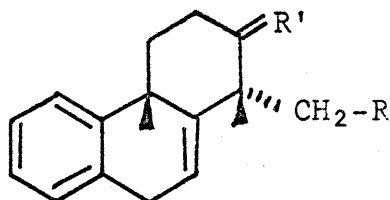
-34-
CHART K



with aqueous methanolic potassium hydroxide converted the lactone to the hydroxy acid. After it was discovered that some lactonization did occur on reduction of the unsaturated keto acid XIVc, the hydride reduction procedure was modified by saponifying the lactone *in situ* after the addition of sodium borohydride. In this manner, yields of greater than 95% of a single, isomerically pure hydroxy acid were produced. The configuration of the C-2 hydroxyl group was determined by relactonization of the hydroxy acid K-3 under conditions which were known to avoid isomerization about the C-2 carbon (53). The n.m.r. spectrum of the lactone K-2 formed in this manner exhibited a broad multiplet centered at 3.77 p.p.m. This signal was assigned to the C-2 hydrogen. Since the half-band width of this signal was approximately 15 c.p.s., the hydrogen was presumed to possess an axial orientation (54), and the hydroxyl, therefore, the *beta* orientation.

The hydrogenation of the unsaturated hydroxy acid K-3 in the presence of 10% palladium-on-charcoal in acetic acid proceeded in high yield (95%) to the *trans*-fused hydroxy acid K-4, the stereochemistry of which was rigidly established in the following manner. Transformation of this compound into the acid K-6 afforded a crystalline solid, m.p. 145.5-147.5° (55). This material had been previously prepared by R. E. Ireland and R. Kierstead (56a) by a different route in which the stereochemistry of the C-10a hydrogen

had been firmly established (56b). Pelletier and Ogiso (44b) have also prepared the saturated acid K-6 (m.p. 145-146°) by hydrogenation of the unsaturated acid K-5 following the precedent established by Stork and Schulenberg (46). The stereochemistry of the acid K-6 has also been firmly established by its transformation into the unsaturated keto acid K-8 which is a degradation product of neoabietic acid (K-7) (45). Furthermore, oxidation and esterification of the hydroxy acid K-4 to give the *trans*-fused keto ester J-1b was accomplished.* This material was shown to be identical (by v.p.c.) to the minor isomer which was obtained when the unsaturated keto ester XIVb was hydrogenated under the conditions reported by Ghatak (52).

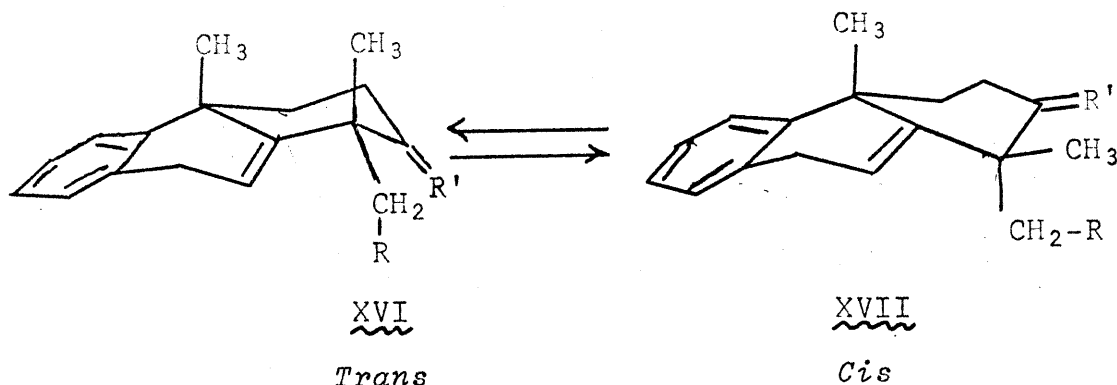


XV Hydrogenation Product

- | | |
|--|--------------------|
| <u>a</u> : R=H, R'=H ₂ | <i>trans</i> |
| <u>b</u> : R=CO ₂ CH ₃ , R'=H ₂ | <i>trans</i> |
| <u>c</u> : R=H, R'=O | <i>trans</i> |
| <u>d</u> : R=-CO ₂ CH ₃ , R'=O | <i>cis + trans</i> |

A reasonable rationalization for the hydrogenation products obtained from the phenanthrene derivatives XVa-d may be made using the following argument.

*An analytical sample of this material has been prepared by G. Rubottom and R. E. Ireland, unpublished results.

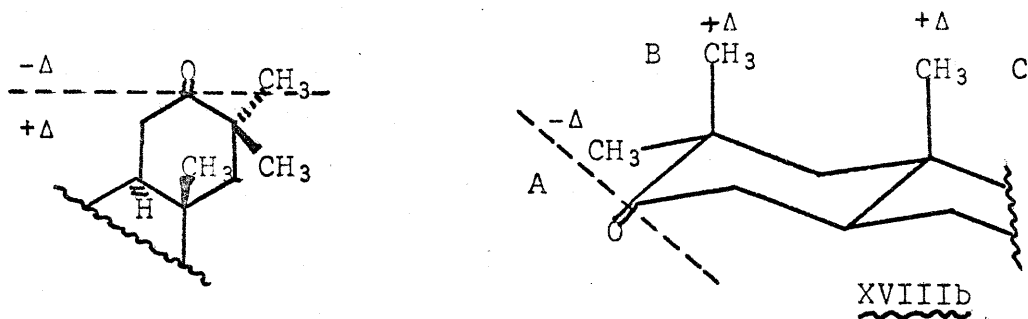


The first assumption which must be made is that the *trans*-fused phenanthrenes are generated by preferential hydrogenation through the quasi-chair conformation XVI while the *cis*-fused isomers are produced by preferential hydrogenation through the quasi-boat conformation XVII. Neglecting the intimate kinetic details of both the rates of adsorption and hydrogenation which cannot be evaluated in this case, it appears from the examples in Chart J (see general formula XVa-d) that the course of the hydrogenation is diverted from *trans* to *cis* in that case in which the relative energy barrier between the chair and boat conformations has been substantially lowered. It has been established qualitatively that this barrier is at least 4 kcal./mole lower in cyclohexanone than it is in cyclohexane (57,58). Therefore, the chair-boat inversion barriers of the phenanthrene derivatives XVc and XVd should be less than XVa and XVb. Also, as a result of the trigonal geometry of the carbonyl group, equatorial substituents which are situated in the *alpha* position are nearly eclipsed with the carbonyl oxygen. It has

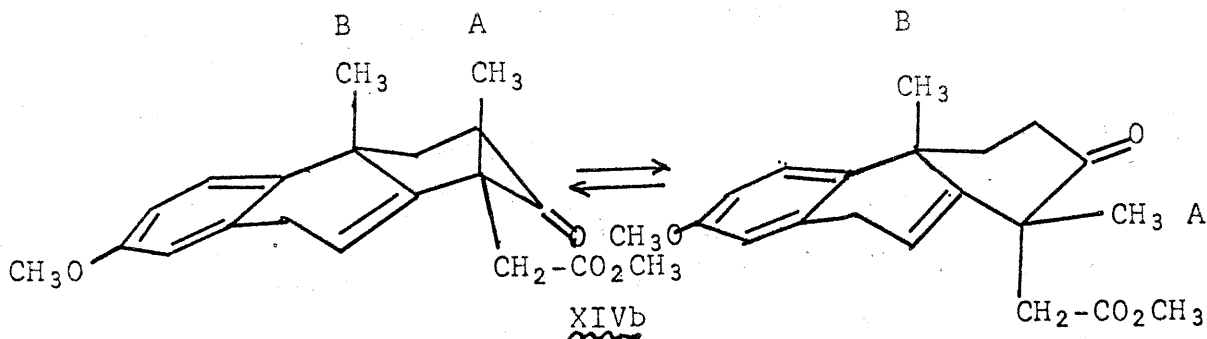
been demonstrated that for substituents which are *larger* than methyl, nonbonded interactions exist between the equatorial group and the oxygen which raise the ground state energy of the eclipsed conformation (59). This situation is found in the quasi-chair conformation of the unsaturated keto ester XVd. Conversely, this "2-alkyl ketone" effect should be absent in the ketone XVc. It is therefore concluded that *cis*-fused phenanthrene derivatives will be produced in those cases when both of the previously discussed conditions occur together, *e.g.* when $R'=O$ and R is larger than hydrogen as in XVd. The net result of the substituent changes in progressing from XVa to XVd is to lower the boat-chair inversion barrier by raising the ground state energy of the chair conformation XVI. This line of reasoning predicts that by reducing the keto acid XIVc to the hydroxy acid K-3, the course of the hydrogenation should be diverted from the *beta* face to the *alpha* face of the molecule. This prediction was adequately borne out by experiment.

In conjunction with this problem, it was of interest to determine which of the conformations, XVI or XVII, of the hexahydrophenanthrene derivative XVd was of lower energy. One explanation for the observed change in the course of the hydrogenation when proceeding from XVa to XVd was that in the keto ester XVd, the preferred conformation was actually the quasi-boat conformation XVII. This hypothesis was tested by the use of n.m.r. spectroscopy. It has been shown that aromatic solvents such as benzene appear to form collision complexes with molecules containing electron deficient centers (61). Large

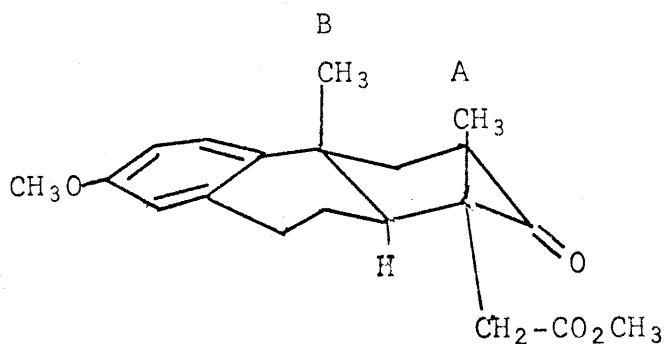
proton resonance shifts relative to tetramethylsilane have been observed for proton-containing substituents on comparison of the spectra of ketones in nonpolar solvents such as chloroform and in aromatic solvents such as benzene. Recently, the magnitude and direction of these solvent-induced shifts for quaternary methyl substituents have been determined for substituted cyclohexanones and keto-steroids (62,63,64). This work has established that methyl groups lying in or in front of a plane which is perpendicular to the carbonyl group passing through the carbonyl carbon exhibit downfield (negative) benzene-induced solvent shifts, while protons situated behind this plane experience upfield (positive) proton resonance shifts.



$$\Delta = \delta_{\text{CDCl}_3} - \delta_{\text{C}_6\text{H}_6} \text{ c.p.s.}$$



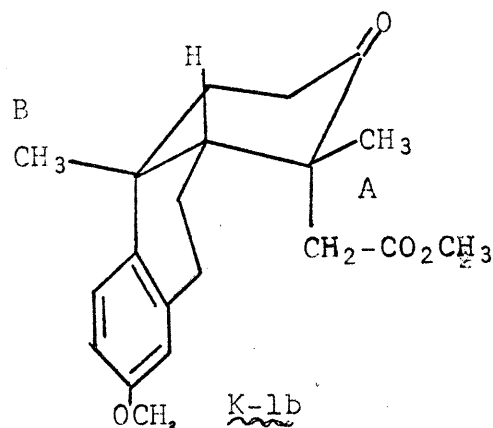
$$A = +5.7 \text{ c.p.s.} \quad B = +15.2 \text{ c.p.s.}$$



J-1b

A = +15.2 c.p.s.

B = +14.7 c.p.s.



K-1b

A = -4.0 c.p.s.

B = +13.0 c.p.s.

The utility of this concept is illustrated by the partial structures XVIIIa-b. Methyl groups B and C situated *alpha* to the ketone in the fused cyclohexanone ring exhibit benzene-induced solvent shifts (Δ) of opposite sign. Therefore, the orientation of a methyl substituent *alpha* to a ketone may be determined by observing the direction of the shift in the methyl resonance.

Using this technique, the preferred conformation of the unsaturated keto ester XIVb was deduced. The positive Δ -value of methyl A establishes that there is a preference for the quasi-chair conformation. The general magnitudes of the Δ -values for equatorial and axial methyl groups are illustrated by the values obtained for the isomeric keto esters J-1b and K-1b.

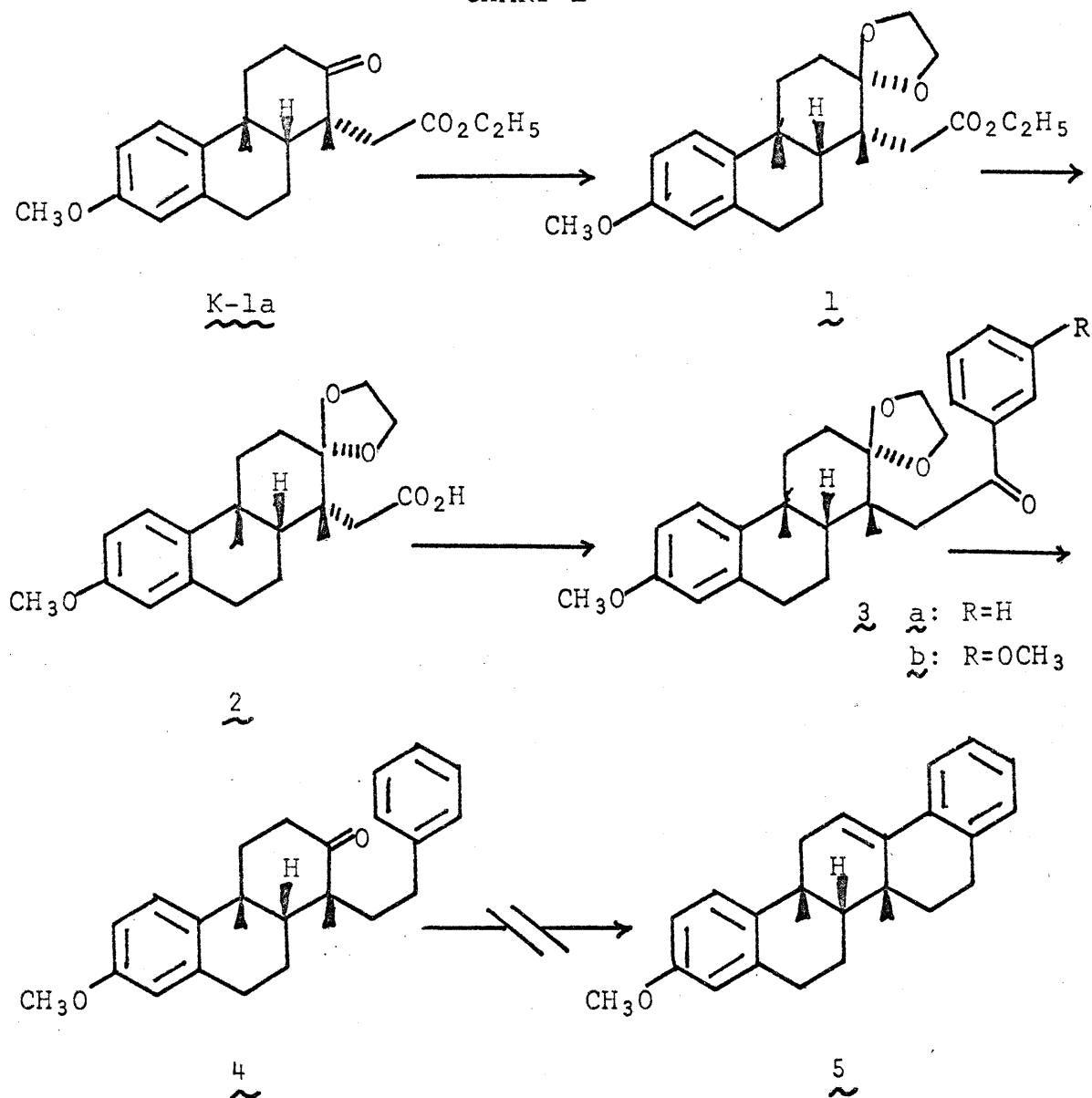
As was mentioned earlier, when the catalytic hydrogenation of unsaturated keto ester XIVb was initially studied, it was assumed that the *trans*-fused keto ester J-1b was the major product. From the work which will now be discussed, the correct

stereochemistry of the two isomeric saturated keto esters J-1 and K-1 was determined, and a successful synthetic route to the desired decahydropicene ring system IIa was developed.

The Synthesis of 8β-Decahydropicene Derivatives.

The first route which was investigated in an attempt to elaborate the *cis*-fused keto ester K-1a to the β-phenylethyl ketone L-4 is shown in Chart L.

CHART L



This keto ester was converted into the ethyleneketal ester L-1 by conventional methods in a 60% yield, and the ester was saponified with aqueous alcoholic potassium hydroxide to the highly crystalline acid L-2 in a 62% yield. Efforts to transform this phenanthreneacetic acid into the phenanthreneacetophenones L-3a and L-3b were only partially successful. The reaction of the acid L-2 with phenyllithium in dimethoxyethane afforded an 82% yield of the desired ketone L-3a. Removal of the ethylene ketal and benzylic ketone was then accomplished in a single step by stirring a solution of the ketone L-3a in ethyl acetate under a hydrogen atmosphere in the presence of 10% palladium-on-charcoal and a trace of hydrochloric acid. In this fashion a 55% yield of the phenylethyl ketone L-4 was obtained from the acid L-2. All attempts to effect acid-catalyzed ring closure of L-4 to the octahdropicene L-5 failed to produce a single well-defined product. From work which was later done in this series of compounds, it appeared that under conditions sufficiently vigorous to effect ring closure, the octahdropicene L-5 underwent further acid-catalyzed rearrangements.

Efforts to synthesize the oxygenated phenanthreneacetophenone derivative L-3b by the use of m-methoxyphenyllithium on the acid L-2 were not attempted because of the difficulty in preparing such lithium reagents (65). Likewise, the use of bis-m-methoxyphenylcadmium was rejected because of the anomalous results that this reagent has been reported to give with acid chlorides (66). It appeared that the only way to

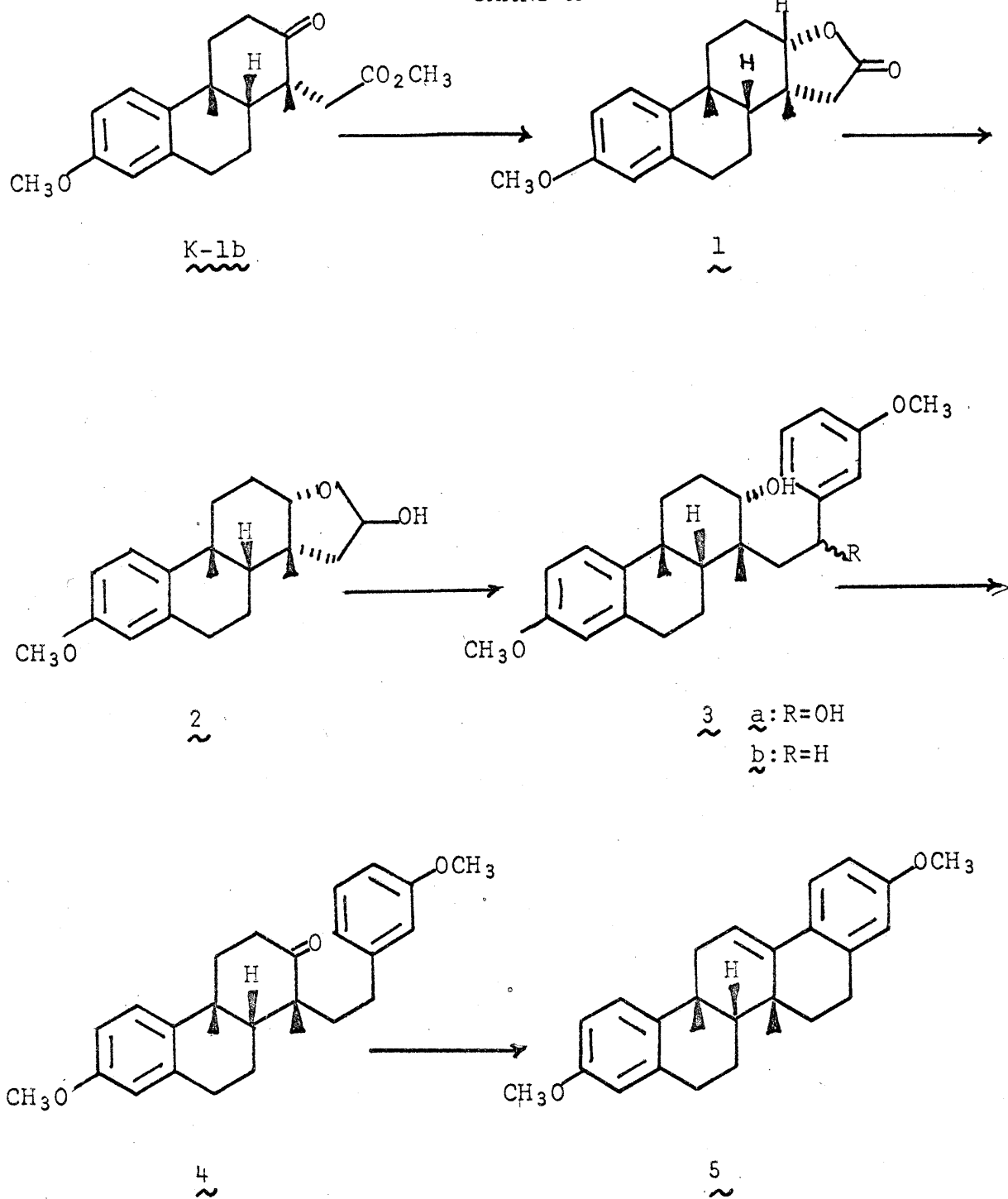
synthesize the desired oxygenated acetophenone was by the use of a *meta*-oxygenated phenyl Grignard reagent. Since the transformation of an acid to a ketone by the use of any Grignard reagent is generally a low-yield process, it seemed expedient to approach the synthesis of the ketone L-3b by a different process.

By the requirements set forth from the preceeding work, it was necessary to block the keto group of the ester K-1b and to modify the ester function so that the m-methoxyphenyl moiety could be attached onto the side chain of the phenanthrene skeleton. The series of reactions which accomplished this end in an efficient manner is shown in Chart M.

The reduction of the *cis*-fused keto ester K-1b with sodium borohydride proceeded in 79% yield to the crystalline *cis-cis*-lactone M-1. This lactone was then reduced with diisiamylborane (67a) according to the general procedure described by Brown and Moerikofer (67b). By this method, virtually quantitative yields of the crystalline hemiacetal M-2 were obtained from the *cis*-lactone M-1. The fact that this compound existed entirely in the hemiacetal form, as evidenced by its infrared spectrum, was convenient in that it rendered the normally labile aldehyde function inert to air oxidation. The addition of m-methoxyphenylmagnesium bromide to the hemiacetal proceeded without any complications and gave the diol M-3a as an oil. The benzylic alcohol was removed by stirring a methanolic solution of the diol and perchloric acid in the

presence of 10% palladium-on-charcoal under a hydrogen atmosphere.

CHART M



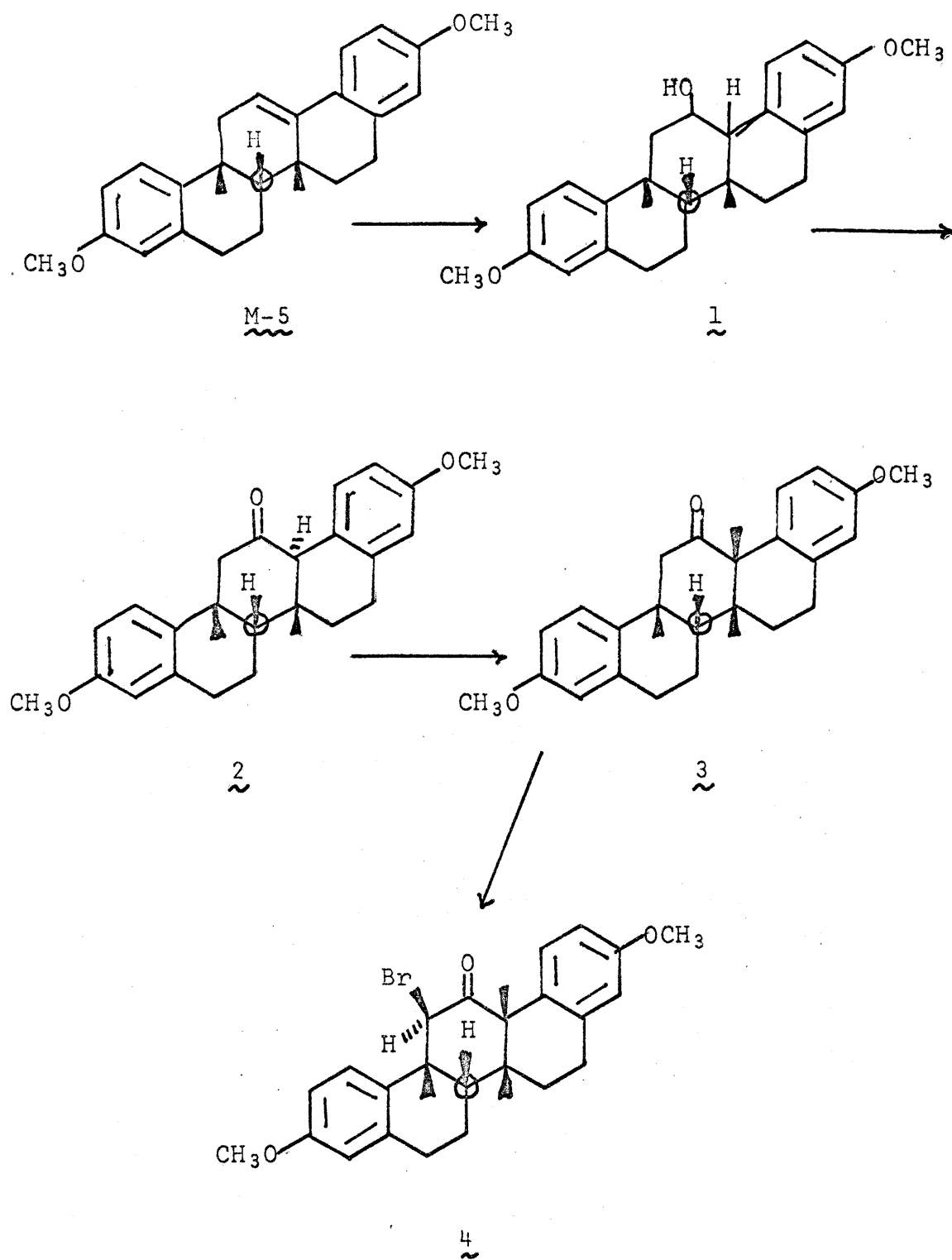
The alcohol M-3b was oxidized without purification to the crystalline ketone M-4 with Jones reagent. The series of four reactions which accomplished the transformation of the *cis-cis*-lactone M-1 to the ketone M-4 could be carried out in yields of greater than 75%. Cyclodehydration of the m-methoxyphenyl ketone M-4 was accomplished in an 82% yield by refluxing a benzene solution of the ketone in the presence of a catalytic amount of p-toluenesulfonic acid. In addition to the desired octahdropicene M-5, there was formed a second hydrocarbon in minor amounts. If the reaction was not terminated as soon as all of the ketone M-4 had been consumed, the percentage of this hydrocarbon gradually increased at the expense of the desired product. If the course of the reaction was followed by gas chromatography, it was observed that the minor constituent did not start to appear until about 90% of the ketone M-4 had been consumed. Apparently under the conditions of the cyclization, the ketone, which is more basic than the olefin M-5, effectively competed for the catalytic amount of acid present in the solution. If the cyclodehydration was run under conditions where more than a catalytic amount of acid was present, none of the desired olefin M-5 could be isolated. Thus, the use of polyphosphoric acid or liquid hydrogen fluoride for the cyclodehydration resulted in no fewer than ten products. These observations are also consistent with the results which were obtained when the acid-catalyzed cyclodehydration of the phenylethyl ketone L-4 was

attempted. It thus appeared necessary to have an activated phenyl ring present to facilitate ring closure under conditions mild enough to avoid secondary transformations in the product.

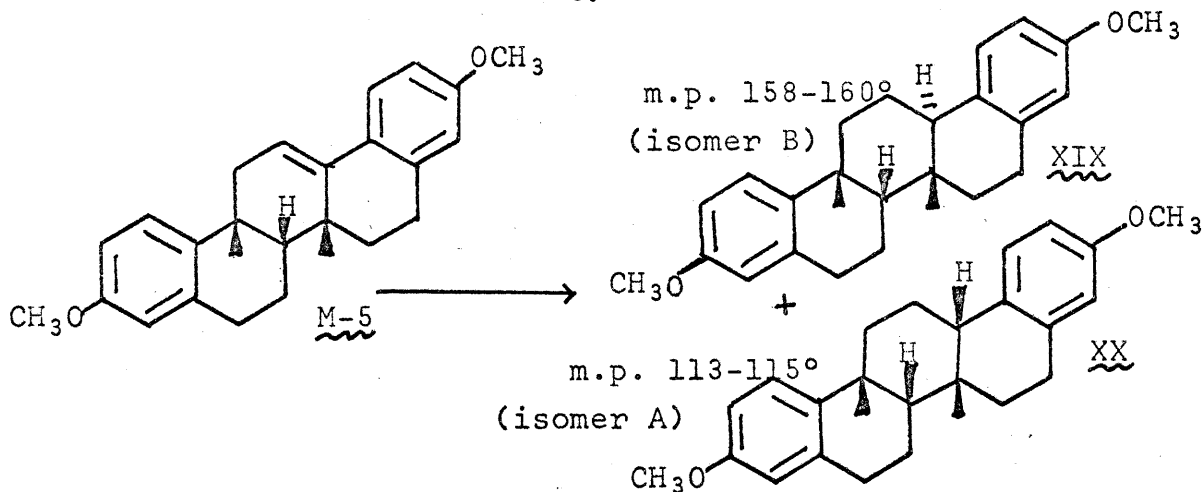
Having successfully devised a procedure for the construction of the elusive hexahydronicene structure M-5, we turned our attention to the problem of introducing the required angular methyl group into this system at the C-13 position. The decision as to how this task would be accomplished was influenced by the required *alpha* orientation of the methyl substituent and was based on the premise that the C-8 hydrogen possessed the *alpha* configuration. From both steric and electronic considerations, it was postulated that angular methylation of the ketone N-2 would occur from the *alpha* face of the molecule. With the C-8 hydrogen in the *alpha* configuration, the angular methyl groups at C-9 and C-14 render the *beta* face of the molecule quite congested. Likewise, methylation from the *alpha* face would involve the preferential axial approach to the carbanionic center at C-13. Based on this reasoning, the C-13 angular methyl group was introduced in the manner illustrated in Chart N.

The synthesis of ketone N-2 proceeded in a routine fashion. The olefin M-5 was treated with an excess of diborane, and the resulting organoborane was oxidized with basic hydrogen peroxide to an isomeric mixture of the alcohols N-1 in high yield. This mixture of alcohols was oxidized with

CHART N



Jones reagent, and the crude isomeric mixture of ketones, after chromatography on alumina, gave the ketone N-2 in an overall yield of 91% from the olefin. The stereochemistry of the hydrogen at C-13 was deduced from the following evidence. It was assumed that the method of purification of the ketone afforded the more stable of the two possible epimeric ketones. This fact was confirmed by treating a methanolic solution of the ketone N-2 with a catalytic amount of sodium methoxide for a 40-hour period. After this time period the ketone N-2 was recovered, contaminated by not more than 10% of a new compound as evidenced by the appearance of two new angular methyl resonances at 1.27 and 1.47 p.p.m. However, no evidence is available at this time as to whether this component is the isomeric ketone. From a consideration of the nonbonded interactions of the two possible epimeric ketones, it was concluded that the *cis-syn-trans*-ketone N-2 is the more stable of the two epimers. Verification of this conclusion was obtained by synthesizing the hydrocarbons XIX and XX illustrated below.



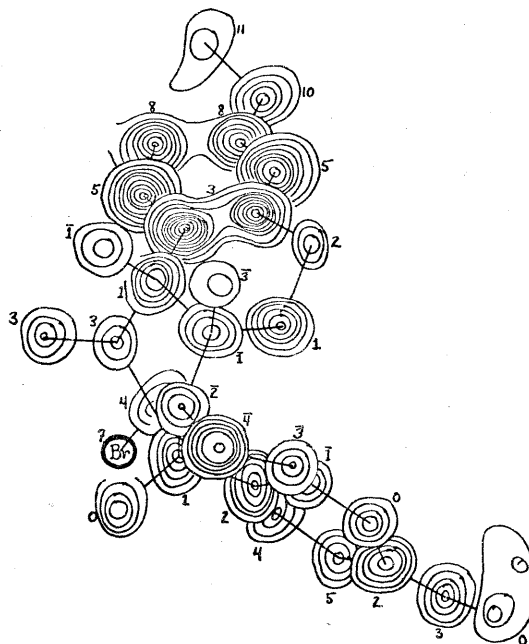
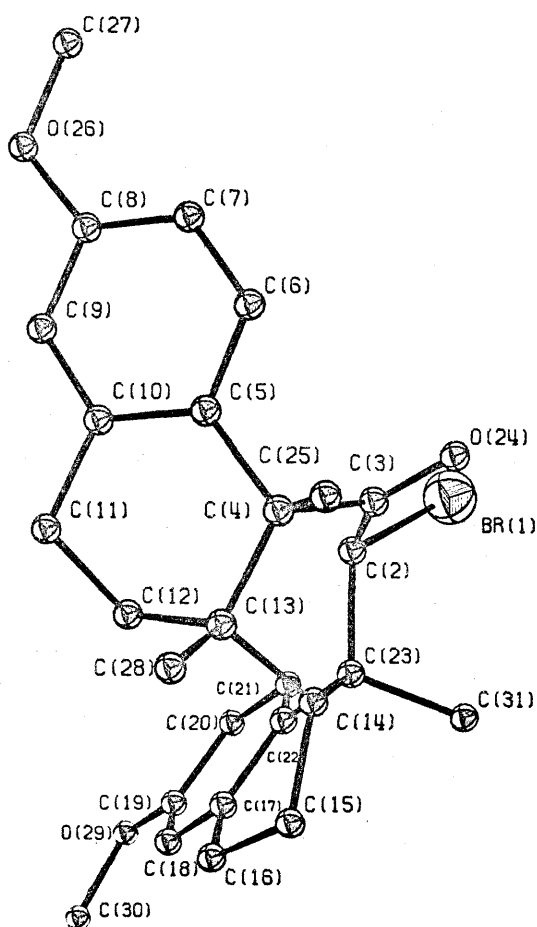
It is generally accepted that carbanion reductions of styrenoid systems are thermodynamically controlled and usually give the stereochemically favored product when the creation of a new asymmetric center is involved(70,71). When the olefin M-5 was reduced with potassium in liquid ammonia two isomeric hydrocarbons were produced in 82% and 18% yields. The major isomer, m.p. 158-160°, was easily isolated by fractional crystallization. When the same olefin was hydrogenated in the presence of 10% palladium-on-charcoal a mixture of the same two hydrocarbons was produced. The minor isomer (26%), m.p. 158-160°, was again readily separated by fractional crystallization from the major isomer (74%), m.p. 113-115°. Because of the geometry of olefin M-5, it was anticipated that hydrogenation would occur from the *beta* face of the molecule to produce mainly the *cis-syn-cis* decahydropicene XX. Also, from the predicted course of the metal-ammonia reduction it was assumed that the *cis-syn-trans* compound XIX would be produced by this method. Examination of the n.m.r. spectra of these two compounds lent firm support to the deduction that the higher-melting isomer was XIX and that the lower-melting isomer was XX. The lower-melting isomer contained two magnetically nonequivalent methoxyl resonances separated by 3.0 c.p.s. while the higher-melting isomer showed equivalent methoxyl resonances. The methylated *cis-syn-cis*-ketone N-3, whose synthesis and stereochemical proof will be discussed presently, also exhibited magnetically nonequivalent aromatic methoxyl

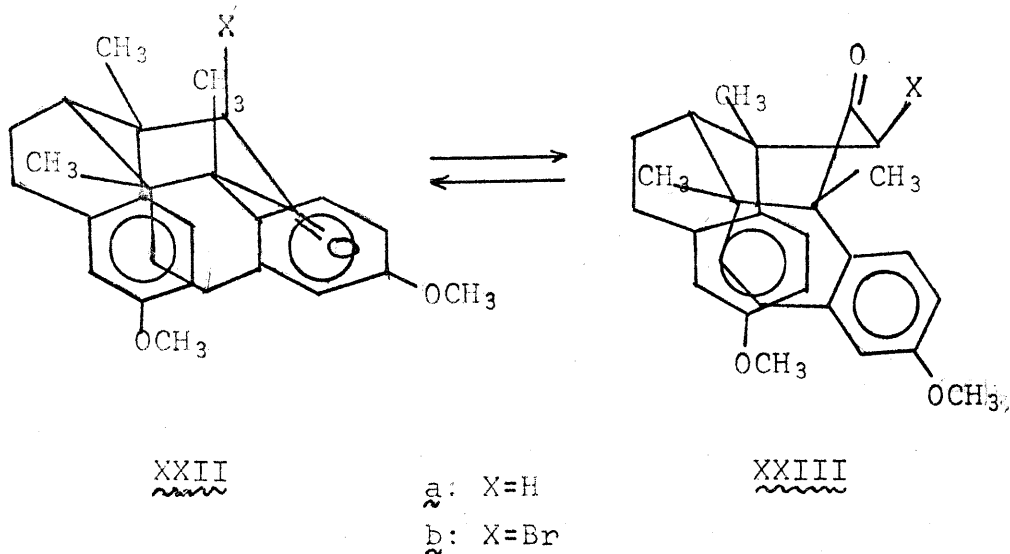
groups as evidenced by n.m.r. It appears that this nonequivalence is caused by the close proximity of the two anisole rings in the *cis-syn-cis*-decahydropicene derivatives, and thus, is a useful tool for distinguishing between the *cis-syn-cis* and *cis-syn-trans* isomers in this series.

With the desired ketone N-2 now in hand, the course of the angular methylation at C-13 was investigated. Treatment of this ketone with potassium t-butoxide in a solution of t-butanol and benzene (1:1) afforded the C-13 carbanion which was then quenched with methyl iodide. In this manner, a 52% yield of the C-alkylated ketone N-3 was obtained. The *beta* orientation of the newly introduced methyl group was firmly established by X-ray analysis (72).

In order to render the methylated ketone N-3 amenable to X-ray crystallographic analysis (72), the presence of a heavy atom in the molecule was required. Towards this end the bromoketone N-4 was prepared. Treatment of the ketone N-3 with phenyltrimethylammonium tribromide (73) in tetrahydrofuran afforded a 78.5% yield of the highly crystalline bromo ketone N-4. The infrared spectrum of this material exhibited a carbonyl frequency at 1718 cm^{-1} as compared to a carbonyl frequency of 1705 cm^{-1} for the unbrominated ketone N-3. The increased carbonyl frequency caused by the introduction of the bromine atom indicated that the halogen was in an equatorial or nearly eclipsed conformation with respect to the ketone (74). These observations were

verified by the X-ray analysis (see XXI) which demonstrated that in the crystalline state the bromo ketone N-4 adopts the conformation in which ring C is in a boat. Due to the bond restrictions imposed upon this decahydropicene system, the two most probable conformations of this skeleton are the ring-C chair and boat conformations (e.g. XXII and XXIII). In this particular case it appears that the boat conformation exists both in the crystal and in solution as observed by both the crystallographic study and the solution infrared spectrum.

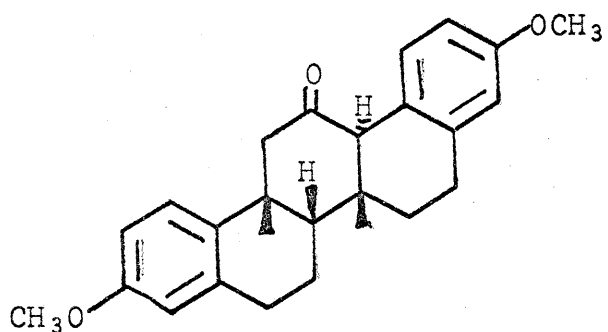




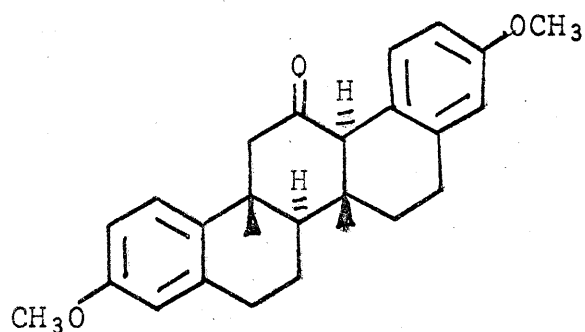
Since it was known that the bromo ketone N-4 existed in the ring-C boat conformation XXIIIb, it was of interest to determine the preferred conformation of the methylated ketone N-3. This was accomplished by observing the direction of the benzene-induced solvent shift (Δ) of the C-13 angular methyl group. If the chair conformation XXIIa were preferred, the C-13 methyl would experience a positive Δ -value, and if the boat conformation XXIIIa were preferred, a negative Δ -value would be observed. A positive Δ -value of +6.0 c.p.s. indicates that for the methylated ketone N-3, the chair conformation XXIIa is preferred. These results indicate that stereoelectronic control is operative during the bromination of the ketone N-3, and that the bromine atom is introduced axially

into the chair conformation XXIIa. The 1-3 diaxial interaction between the C-13 methyl group and the C-11 bromine atom is then severe enough to force the molecule to adopt the boat conformation XXIIb.

Having firmly established the stereochemical interrelationships between all of the asymmetric centers in the decahydropicene system, we were now in a position to evaluate the stereochemical course of each of the reactions which were used to introduce the points of asymmetry at C-8, C-9, C-13, and C-14. The assumption, based on the previously discussed precedents listed in Chart J, that the C-8 hydrogen possessed the *alpha* orientation was shown to be in error. Since the stereochemistry at this point strongly influences the shape of the decahydropicene skeleton, it is not surprising that the angular methylation of the ketone M-2 at C-13 occurs from the *beta* rather than the *alpha* face of the molecule.



N-2



P-5a

Since the main interest of this project was aimed at the construction of the *trans-anti-trans*-decahydropicene skeleton

(e.g. P-5a), and not the *cis-syn-trans* isomer N-2, the hydrogenation step which introduced the asymmetric center at C-8 was reinvestigated. As has already been discussed (Chart K), the stereo-relationship between the C-8 hydrogen and the C-9 and C-14 methyls was altered to give the *trans* tricyclic intermediate K-4 which was necessary for the construction of the desired *trans-anti-trans*-decahydropicene ketone P-5a.

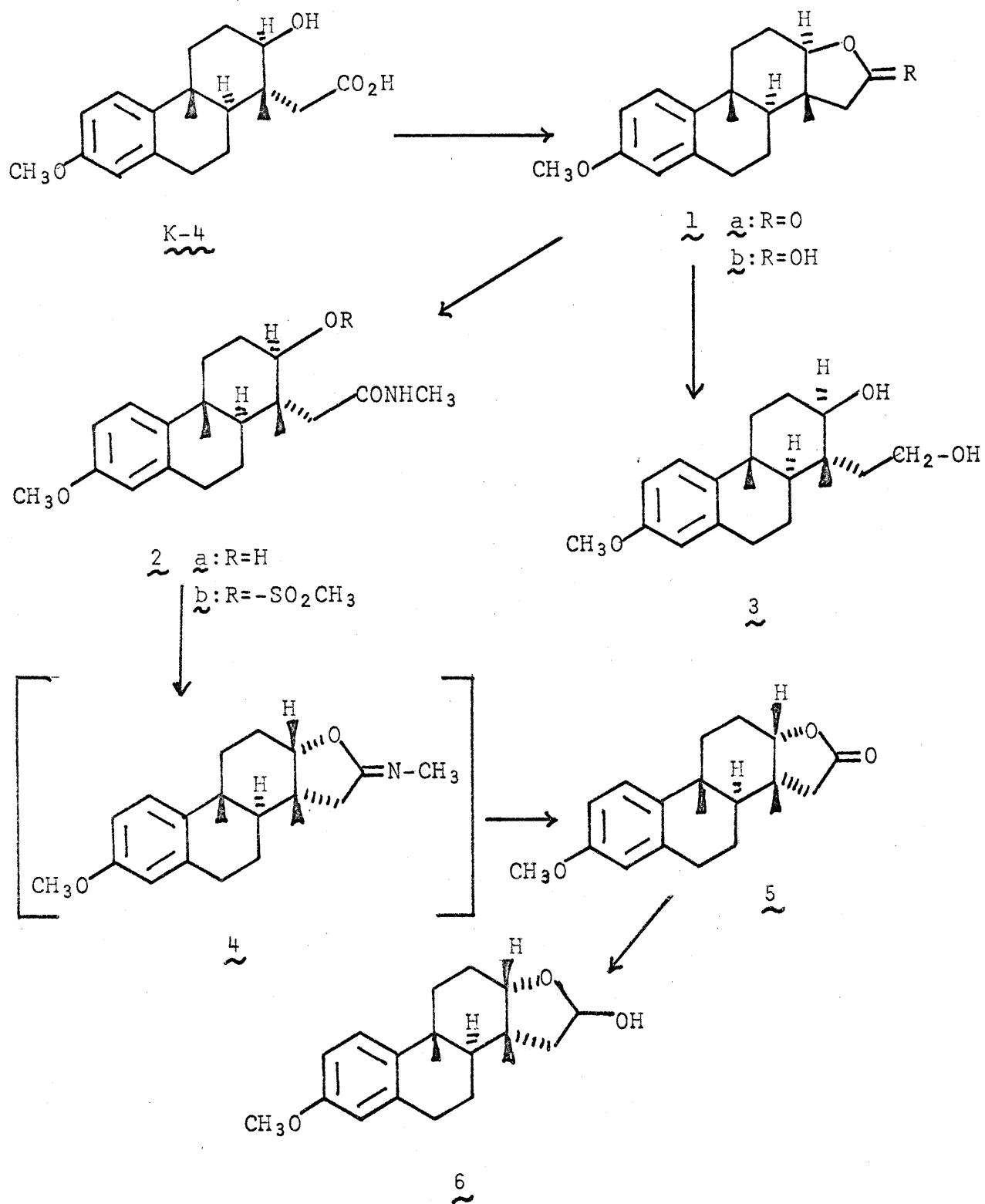
The Synthesis of 8 α -Decahydropicene Derivatives.

Although certain new problems were encountered in the synthesis of the *trans-anti-trans* decahydropicene skeleton II, the basic approach to this system remained the same as the two schemes which were developed earlier in the isomeric 8-*beta* series.

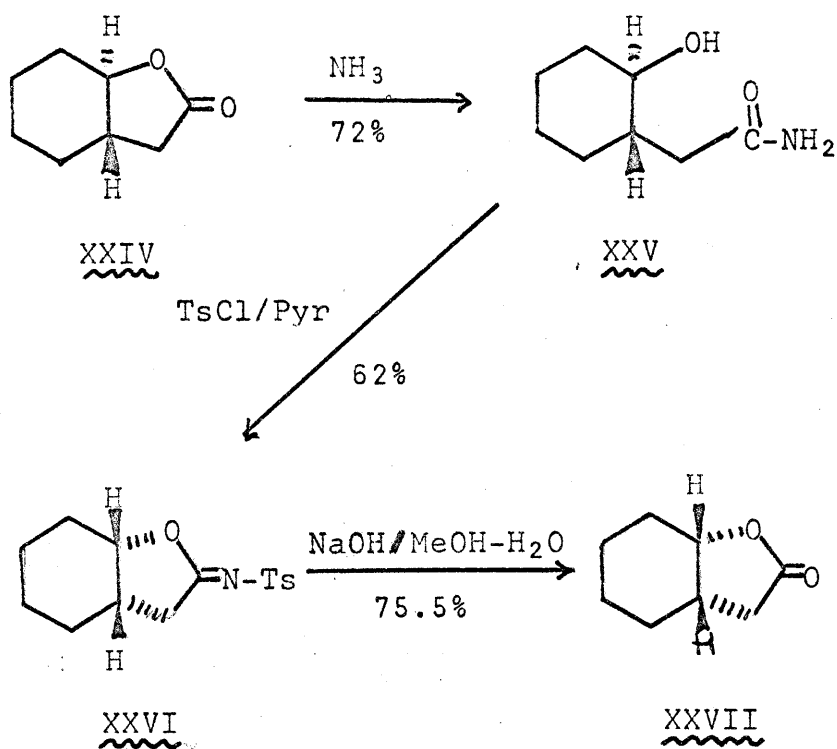
The lactonization of the hydroxy acid K-4 (see Chart O) to the crystalline *trans*-lactone O-1a was readily accomplished in 95% yield. From the earlier work on the reduction of the *cis*-lactone M-1, it was assumed that the *trans*-lactone O-1a would likewise be reduced with disiamylborane to the hemiacetal O-1b. However, this assumption proved to be false. Reduction of the lactone under the same conditions did not stop at the hemiacetal O-1b, and the exclusive product was the crystalline diol O-3. Apparently the added ring strain present in the *trans*-lactone was the cause for the observed over-reduction.

A remedy to the situation was suggested by the work of Brewster and Kucera (75). They were able to convert *trans*-2-hydroxycyclohexaneacetic acid lactone (XXIV) to the isomeric

CHART 0



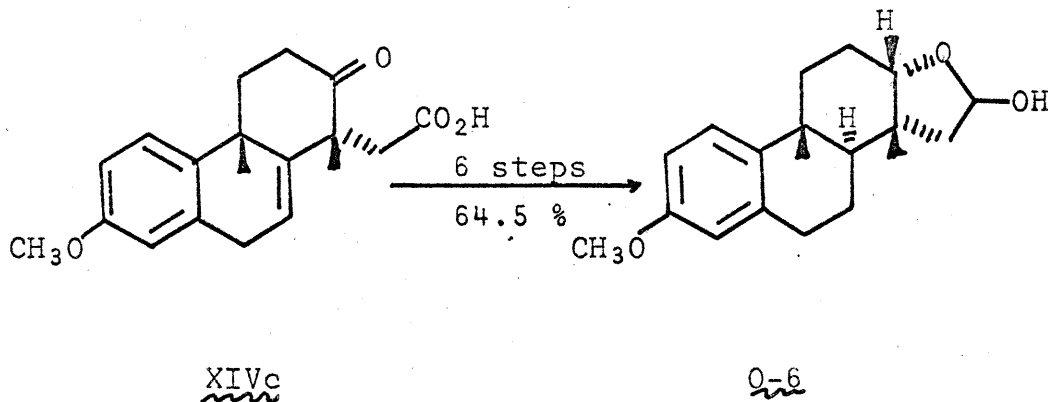
cis-lactone XXVII in 33.8% overall yield by the series of reactions shown below. Using the general ideas embodied in this transformation, we attempted to use this concept for the transformation of the *trans*-lactone 0-1a into the *cis*-lactone 0-5.



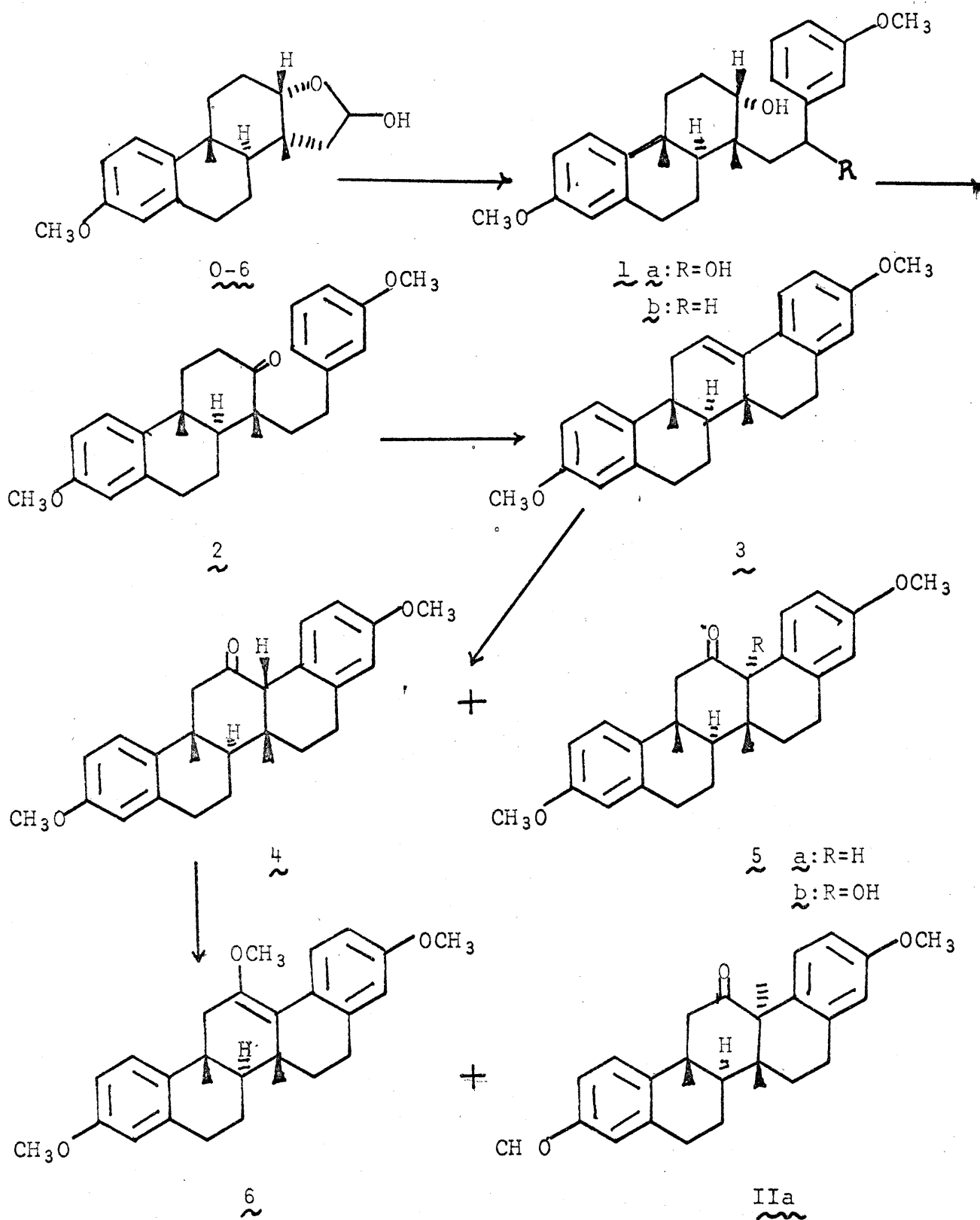
The N-methylhydroxy amide 0-2a was prepared in 97% yield from the *trans*-lactone 0-1a by the use of a reagent prepared from lithium aluminum hydride and excess monomethylamine in tetrahydrofuran. The hydroxy amide 0-2a was then caused to react with methanesulfonyl chloride in pyridine at room temperature. The mesylate 0-2b was transformed *in situ*

into the imino-lactone Q-4 which was not isolated. The imino-lactone was then readily hydrolyzed without isolation to the *cis*-lactone Q-5 by the addition of water followed by gentle warming of the reaction mixture. In this manner an 85.5% yield of the *cis*-lactone Q-5 was obtained from the *trans*-lactone Q-1a by this modified procedure.

In contrast to the *trans*-lactone Q-1a, the *cis*-lactone Q-5 was reduced by disiamylborane in nearly a quantitative yield to the hemiacetal Q-6. The utility of the synthetic route which was devised for the synthesis of this hemiacetal is illustrated by the efficiency with which this intermediate could be prepared. Thus, in a six-step reaction sequence the keto acid XIVc could be transformed into the hemiacetal Q-6 in an overall yield of 64.5%.



With the desired hemiacetal Q-6 now in hand, the elaboration of the side chain proceeded in a routine fashion as illustrated in Chart P. The hemiacetal was caused to react with *m*-methoxyphenylmagnesium bromide, and the resulting diol P-1a was transformed into the alcohol P-1b by the previously

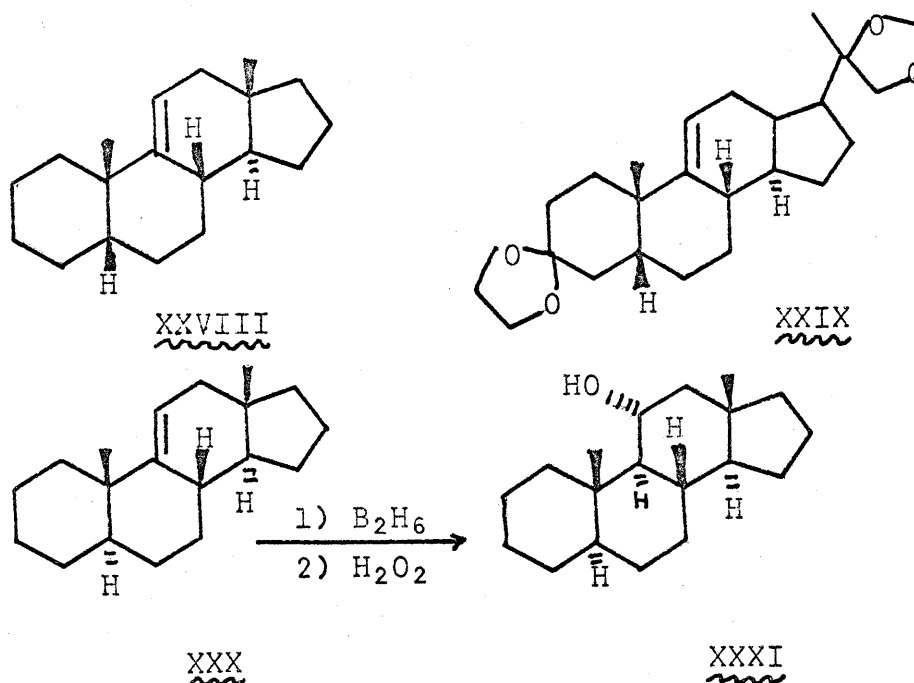


discussed hydrogenolysis procedure. Jones oxidation of the unpurified alcohol P-1b and chromatography of the product afforded the crystalline ketone P-2 in an 88% yield from the hemiacetal O-6. A comparison of this ketone with the isomeric m-methoxyphenylethyl ketone M-4 established that they were different compounds. Furthermore, since both ketones were synthesized from the same unsaturated keto acid XIVc, the only new asymmetric center in question was that of the C-10a hydrogen. Since the C-10a stereochemistry of the ketone M-4 had been unequivocally established by X-ray analysis, there was little doubt about the proposed C-10a-*alpha* stereochemistry of the ketone P-2.

Cyclodehydration of ketone P-2 to the octahydronicene P-3 was executed in 95% yield by refluxing a solution of the ketone and toluenesulfonic acid in toluene for 30 hours. Under these conditions the olefin was stable and, in contrast to the isomeric octahydronicene M-5, did not undergo any secondary acid-catalyzed transformations. However, an attempted cyclodehydration in liquid hydrogen fluoride did produce a hydrocarbon mixture containing, in addition to about 40% of olefin P-3, at least seven other products.

Unexpectedly, the conversion of the octahydronicene P-3 to either of the isomeric ketones P-4 or P-5a proved to be quite difficult. The hydroboration-oxidation sequence, which had proceeded readily in the isomeric 8-*beta* series (Chart M),

failed to effect the desired transformation in this particular case. The olefin P-3 demonstrated little reactivity towards diborane in either tetrahydrofuran or diglyme. Even after reaction periods on one week, only about 5% hydroboration had occurred. Since the steric requirements of this reaction appear to be minimal this result was quite unusual. There appears to have been only two reported cases in which a molecule containing a double bond has resisted hydroboration (76a).



Nussim and Sondheimer (76b) have reported that both test-9(11)-ene (XXVIII) and 3,20-biscycloethylenedioxy-5β-pregn-9(11)-ene (XXIX) failed to undergo hydroboration under the usual conditions. On the other hand, androst-9(11)-ene (XXX) may be hydroborated and oxidized in excellent yields to the 11α-alcohol XXXI.

These workers attribute the lack of reactivity of XXVIII and XXIX to the A/B-*cis* junction which, along with the C-18 and C-19 methyl groups, congests both the *alpha* and *beta* face of the molecule. In contrast to the above examples, an examination of a Dreiding model of the olefin P-3 indicates that, although the *beta* face of the molecule is quite congested, the *alpha* face appears to be relatively accessible. No obvious explanation can be made at this time for the apparent unreactivity of the Δ -12 double bond in this material.

In an effort to find an alternate procedure to functionalize the olefin P-3, the oxidation of this material with peracids was investigated. It was found that on treatment with m-chloroperbenzoic acid in methylene chloride at 0° the olefinic bond was readily oxidized to a variety of ketonic products. From this mixture there was isolated a 44% yield of the isomeric ketones O-4 and O-5a in relative yields of 63% and 37%. An additional product, which was produced in 37% yield, was identified as the hydroxy ketone P-5b. Attempts to suppress the formation of this product were fruitless. In addition to these three major products, there was also formed minor amounts of an isomeric hydroxy ketone and some unidentifiable diols which were not characterized. The isomeric ketones P-4 and P-5a could not be separated by fractional crystallization. On treatment with a trace of sodium methoxide in methanol, this isomeric mixture was equilibrated to an equilibrium mixture of the *trans-anti-cis* ketone P-4.

(95%), and the *trans-anti-trans* ketone P-5a (5%). This result indicated that these two ketones differed only in the orientation of the hydrogen at C-13. Assuming that complete equilibrium had been established, the *cis*-ketone P-4 is at least 1.7 kcal/mole more stable than the *trans*-ketone P-5a. Since the stereochemical assignments of these two isomeric ketones as well as the hydroxy ketone P-5b hinge upon the stereochemical proof of the methylated ketone IIa (Chart P), the discussion of this point will be deferred until later. The unfortunate occurrence of the undesired hydroxy ketone P-5b in this oxidation could not be avoided. It appears that this material is formed by the further oxidation of the ketonic mixture P-4 and P-5a and that the rate of this reaction is comparable to the rate of peracid oxidation of the olefin P-3 to the epoxide. Efforts to suppress the acid-catalyzed rearrangement of the epoxide mixture to the isomeric ketones and thus to prevent the formation of the hydroxy ketone, were fruitless.

Having found an acceptable method for functionalizing the olefin P-3 to the desired ketone P-4, we turned our attention to the problem of introducing the C-13 methyl group into the decahydropicene skeleton in a stereoselective manner. As was previously discussed, it was anticipated that the angular methylation of ketone P-4 should afford mainly the desired 13- α isomer. Accordingly, the methylation of the *cis-trans* mixture of ketones P-4 and P-5a was investigated

in detail to determine the optimal conditions for alkylation and the degree of selectivity observed in the reaction. In the alkylation of any relatively hindered enolate, there are several variables associated with the choice of a solvent which are important in determining the extent of C-alkylation. The enolate may either be alkylated on carbon or on oxygen, and in systems which are heavily congested about the carbanion, O-alkylation may be a significant or even predominant mode of reaction. In these cases, the nature of the solvent plays a significant part in determining the ratio of C- to O-alkylation. In addition to the solvent dependence on the O/C product ratio, the extent of alkylation of either type may be a function of the type of solvent. If a hydroxylic solvent is employed the alkylation of the hindered enolate may not be competitive with alkylation of the solvent itself, and both the base and the alkyl halide may be consumed by reaction with the solvent rather than with the substrate. This situation is illustrated by the data in Table I.

Table I

Products Derived from the Methylation of Ketones ~~P-4~~ & ~~P-5a~~

<u>Solvent</u>	<u>C-Alkylation (II-a)</u>	<u>O-Alkylation (P-6)</u>	<u>Starting ketone(P-4)</u>	<u>O/C Ratio</u>
<u>t</u> -BuOH/KO <u>t</u> -Bu ^a	22%	36%	42%	1.63
C ₆ H ₆ /KO <u>t</u> -Bu ^b	17.8%	60%	21%	3.37

a. 23 equivalents of base used.

b. 13 equivalents of base used.

It may be seen that methylation of the enolate of ketone O-4 occurs to a significant degree on oxygen both in benzene and to a lesser extent in t-butanol. Hence, from the standpoint of a favorable O/C ratio, the hydroxylic solvent is more advantageous. On the other hand, the extent of alkylation in this solvent is somewhat less than that which is observed when benzene is employed. In this particular case the two solvent effects nearly cancel each other, and changes in the solvent system will not greatly alter the absolute yield of C-alkylated material. In the previously encountered alkylation of the unsaturated ketone H-4 in glyme, O-alkylation did not effectively compete with C-alkylation, but if the reaction was carried out in a protic system, the alkylating agent (ethyl bromoacetate) was largely consumed by the conjugate base of the solvent.

In an effort to ascertain the degree of stereoselectivity exhibited during the course of the methylation of the ketone P-4, the n.m.r. spectra of the two reaction mixtures tabulated in Table I were examined closely for traces of isomeric C-methylated ketones other than the desired ketone IIa. Since the C-14 methyl resonance is strongly dependent upon the orientation about C-13, any C-methylated isomer in a quantity greater than 3-5% would have been detectable by this method. However, only a single ketone IIa was detectable. Thus, our initial prediction that the methylation would afford the 13- α methyl ketone IIa was verified.

The stereochemistry at C-13 of the methylated ketone IIa was deduced by observing the direction of the benzene-induced solvent shift of the C-13 methyl group (Table II).

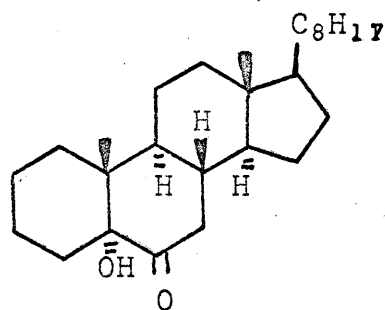
Table II

Solvent Effects on Angular Methyl Resonances in Decahydri-
cene Derivatives

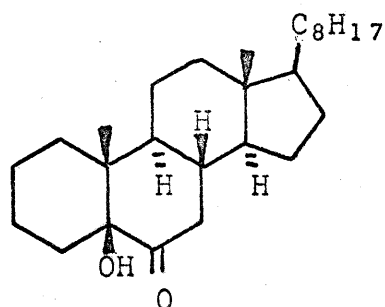
Compound	Angular Methyl	δ c.p.s.CDCl ₃	δ c.p.s.C ₆ H ₆	Δ (c.p.s.)
<u>IIa</u>	C-14	49.5	47.0	+2.5
	C-9	74.0	67.5	+6.5
	C-13	86.5	82.0	+4.5
<u>P-4</u>	C-14	66.5	58.0	+8.5
	C-9	77.0	74.0	+3.0
<u>P-5a</u>	C-14	48.5	TMS was used as an internal standard. Sample concentrations were ~ 10% w/v.	
	C-9	=77		
<u>P-5b</u>	C-14	48.0	$\Delta = \delta_{\text{CDCl}_3} - \delta_{\text{C}_6\text{H}_6}$ c.p.s.	
	C-9	74.0		

An observed positive solvent shift, Δ , of +4.5 c.p.s. implies that the C-13 methyl is in an axial configuration with respect to the carbonyl in ring C. This configuration may only be accommodated by the *trans-anti-trans* backbone in which the C-13 methyl is in the *alpha* axial orientation. By using the established stereostructure of this *trans-anti-trans* ketone IIa as a reference compound, the stereochemistry of the isomeric ketones P-4 and P-5a as well as the stereochemistry of hydroxy ketone P-5b may be deduced. An examination of the C-14 and C-9 methyl resonances of ketone P-5a and hydroxy ketone P-5b indicates that they are very similar (within 2.0 c.p.s.) to the corresponding methyl resonances of the *trans-anti-trans* ketone IIa. On this basis compounds P-5a and P-5b

were also assigned the *trans-anti-trans* configuration. Independent evidence for the validity of this assignment was obtained for the hydroxy ketone P-5b on examination of its infrared spectrum in chloroform. If the hydroxyl group possessed the *beta* equatorial orientation it would be in a favorable geometry to form an intramolecular hydrogen bond with the ketone. The result of this interaction would be to lower the carbonyl as well as the hydroxyl stretching frequencies. On the other hand, if the hydroxyl group possessed *alpha* axial orientation no such interaction could exist. The fact that a normal hydroxyl frequency of 3595 cm.^{-1} and carbonyl frequency of 1710 cm.^{-1} was observed strongly suggests that the hydroxyl group is in the axial orientation.



$$\gamma\text{-OH} = 3612\text{ cm.}^{-1}$$

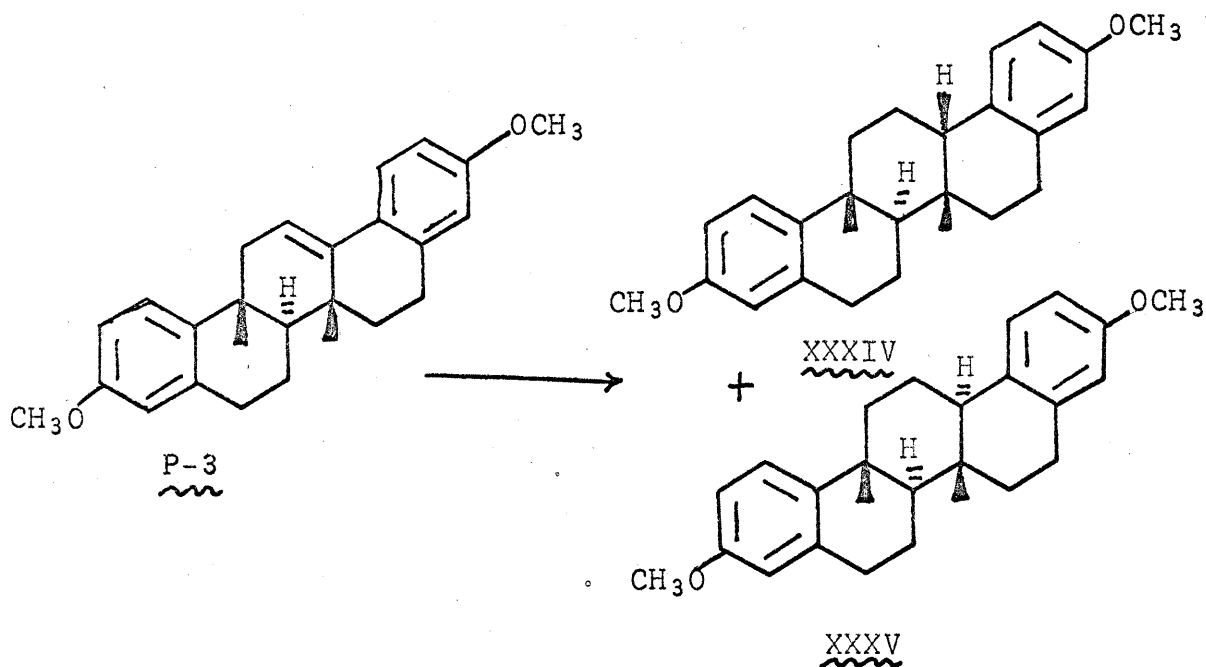


$$\gamma\text{-OH} = 3500\text{ cm.}^{-1}$$

These results were verified by the observed hydroxyl stretching frequencies for the isomeric hydroxy ketones XXXII and XXXIII (77).

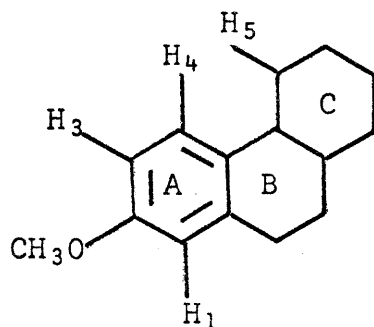
Once the stereochemistry of the ketone P-5a was established as the C-13 *alpha* isomer, it follows that the more stable isomeric ketone P-4 must possess the C-13 *beta* orientation. *A priori* this result was not anticipated. Due to the fact that

the *trans-anti-trans* perhydrophenanthrene is more stable by 2.4 kcal/mole than the *trans-anti-cis* isomer (69), it was anticipated that the *trans-anti-trans* decahydropicene skeleton would be of lower energy than the *trans-anti-cis* decahydropicene ring system. However, the fact that the *trans-anti-cis* ketone P-4 was approximately 1.7 kcal/mole more stable than the *trans-anti-trans* ketone P-5a indicated that the analogy between the perhydrophenanthrene and the decahydropicene systems was of little value in this case.



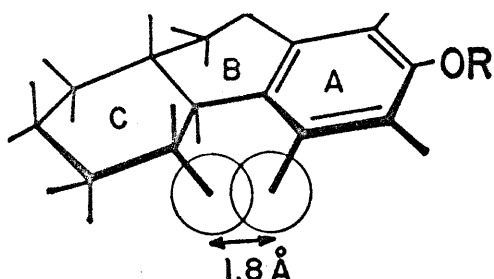
To determine which of the decahydropicenes, XXXIV or XXXV, possessed the more stable skeletal arrangement, the olefin P-3 was reduced with potassium in liquid ammonia. From the work referred to earlier on the general course of carbanion reductions (70,71), the major product of this reduction should be the more stable of the two possible C-13 epimeric decahydropicenes. Reduction of the olefin in this manner afforded the

two isomeric hydrocarbons in 76.5% and 21.2% yields. The major isomer XXXIV was readily isolated by fractional crystallization, and its configuration was determined by an n.m.r. technique developed by Nagata and co-workers (78).

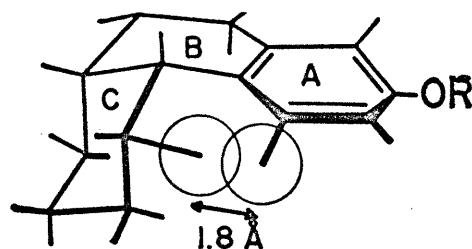


XXXVI

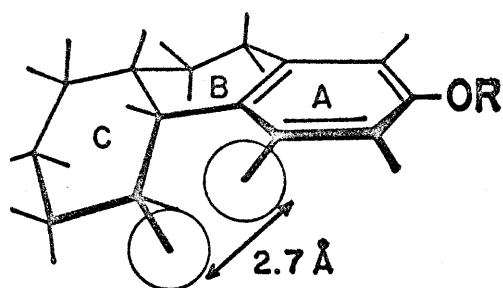
These workers have correlated the deshielding of the C-4 aromatic hydrogen by the C-5 equatorial hydrogen for a number of derivatives of the octahydrophenanthrene XXXVI. Inspection of Dreiding models indicates that the distance between the C-4 and C-5 protons varies considerably with both the nature of the B/C ring fusion and the various conformations of XXXVI. Using the C-1 aromatic proton as an internal reference, these workers have measured the difference in chemical shifts ($\Delta_{1,4}$) of the C-1 and C-4 hydrogens for a wide variety of octahydrophenanthrenes. Table III shows the average magnitude of the $\Delta_{1,4}$ -values as a function of conformation and B/C ring fusion.



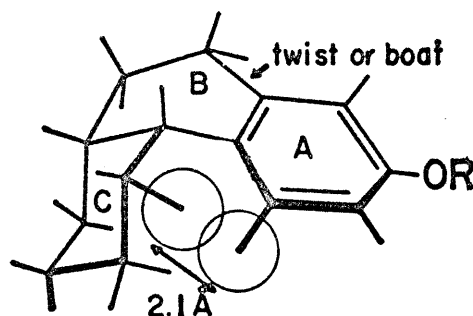
Type A (B/C trans)



Type B (B/C cis)



Type C (B/C cis)



Type D (B/C cis)

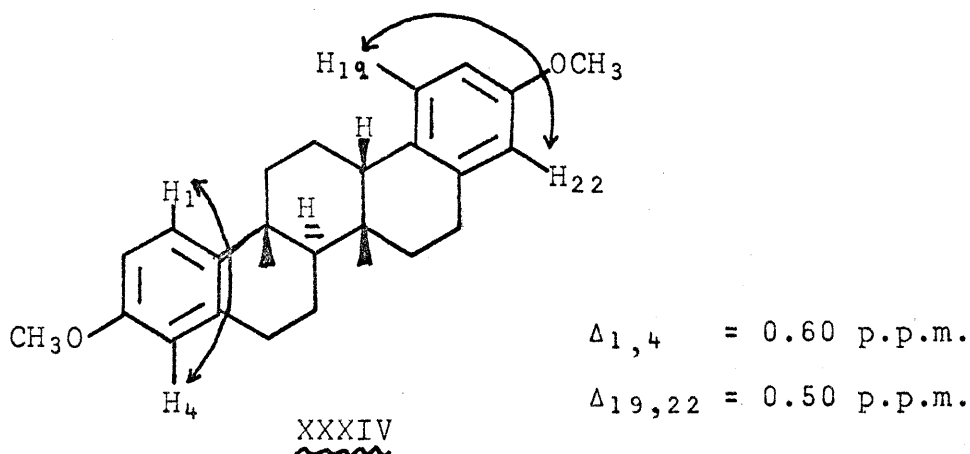
Table III

Type	B/C Ring Fusion	Ring B Conformation	Ring C Conformation	$\Delta_{1,4}^b$ p.p.m.
A(C=.6) ^a	<i>trans</i>	chair	chair	.58-.60
B(C=.6) ^a	<i>cis</i>	chair	chair	.58
C(C=-.3) ^a	<i>cis</i>	chair	chair	.39
D(C=.3-.4) ^a	<i>cis</i>	chair	boat	.47-.50

a. The compression factor "C" is the difference in Å between the sum of the van der Waals radii (2.4 Å) and the measured interatomic distance of the relevant C-4 and C-5 hydrogen atoms.

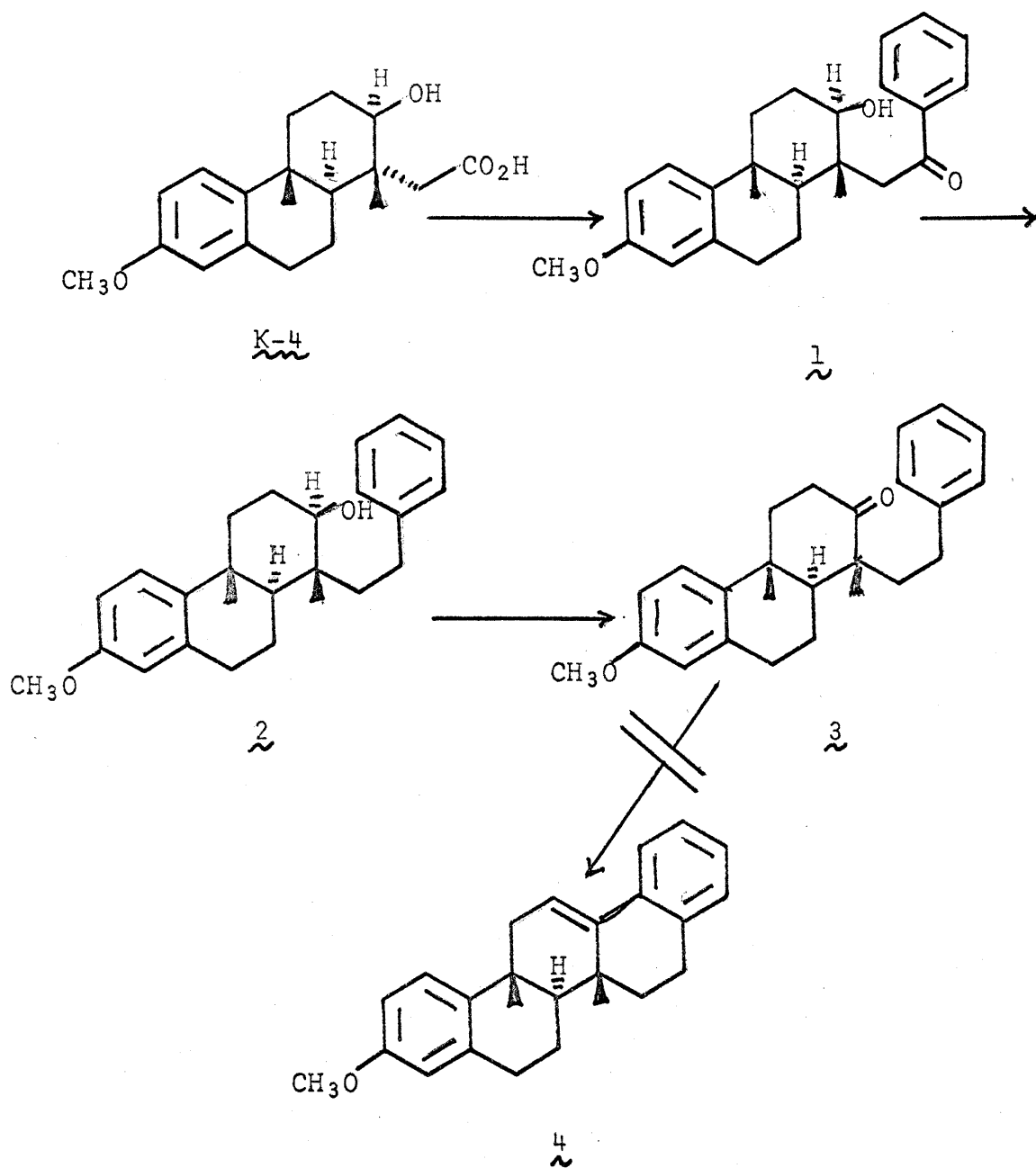
b. The difference in chemical shift between C-1 and C-4 hydrogens.

The utility of this technique as a tool to elucidate both stereochemistry and conformation has been verified in a number of octahydrophenanthrene derivatives prepared during the course of this work. Furthermore, this concept appears to be applicable to the decahydropicene ring systems as well.



Returning to the stereochemical assignment of the decahydropicene XXXIV obtained by the metal-ammonia reduction of the olefin P-3, it was observed that the $\Delta_{1,4}$ -value of 0.60 p.p.m. corresponded exactly to the $\Delta_{1,4}$ -value predicted for the type A *trans*-fused octahydrophenanthrene skeleton. The observed value of 0.5 p.p.m. for $\Delta_{19,22}$ also correlated nicely for Nagata's type D *cis*-fused phenanthrene. Using this technique we may assign the *trans-anti-cis* decahydropicene XXXIV as the major product of the metal-ammonia reduction. Furthermore, it appears that ring D of this compound exists in a quasi-boat conformation. These results, as well as the results obtained from the basic equilibration of the epimeric ketones P-4 and P-5a, demonstrate that the *trans-anti-cis* decahydropicene system contains fewer nonbonded interactions than the

CHART Q

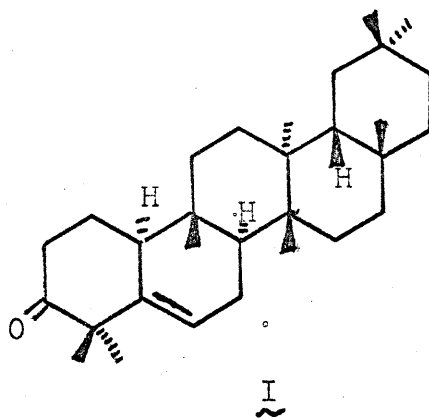
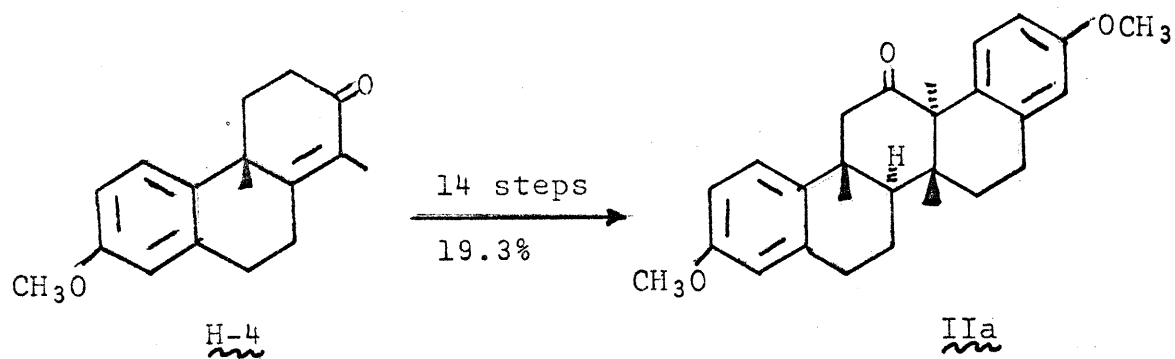


isomeric *trans-anti-trans* system.

As a sidelight to the developed synthetic route to the 3,21-dimethoxydecahydropicene ring system, an alternate route to the unsymmetrical 3-methoxydecahydropicene skeleton was also investigated. This route, as outlined in Chart Q, appeared attractive from a standpoint of brevity.

The saturated hydroxy acid K-4, on treatment with an excess of phenyllithium in dimethoxyethane, afforded a 63% yield of the hydroxy ketone Q-1. The benzylic ketone was then removed by catalytic hydrogenolysis, and the alcohol Q-2 was oxidized with Jones reagent to the phenylethyl ketone Q-3 in a 91.5% yield. Attempts to induce this ketone to cyclize to the octahydropicene Q-4 were fruitless. As was found with the isomeric 8-*beta* ketone L-4 (see Chart L), under conditions which were vigorous enough to effect ring closure the olefinic product appeared to be unstable. It now seems fairly evident that an activated phenyl ring is a requirement for successful cyclization to the octahydropicene skeleton.

Although the ultimate goal of synthesizing the triterpene alnusenone (I) was not achieved, the stereospecific synthesis of the important triterpene intermediate IIa was accomplished by a 14-step stereospecific reaction sequence in an overall yield of 19.3% from the unsaturated ketone H-4.



EXPERIMENTAL

All melting points were taken on a Kofler Hot Stage and are uncorrected. Boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infrared Spectrometer Model 237B. Ultraviolet spectra were taken on a Cary Recording Spectrometer Model 11M. Nuclear magnetic resonance spectra were taken on a Varian Associates Model A-60A Nuclear Magnetic Resonance Spectrometer. Ligroin, unless otherwise noted, refers to the fraction boiling at 30-60°. All gas chromatographic analyses were run on an F and M Model 810 Gas Chromatograph using a silicon gum rubber (SE-30) column. The term "dry tetrahydrofuran" refers to tetrahydrofuran which has been distilled from lithium aluminum hydride under anhydrous conditions. The term "dry benzene" refers to benzene which has been distilled from calcium hydride under anhydrous conditions.

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

Mass Spectra were run by Dr. D. A. Lightner at the University of California, Los Angeles.

1-Methyl-6-methoxy-3,4-dihydronaphthalene (H-2)..- This material was prepared according to the general procedure of Stork and co-workers (28). To a solution of methylmagnesium iodide prepared in the classical manner from 24.3 g. (1.0 mole) of magnesium turnings and 142 g. (1.0 mole) of methyl iodide in 1.0 l. of ether was added dropwise with stirring a solution of 100 g. (0.568 mole) of 6-methoxy- α -tetralone in 500 ml. of dry benzene. The rate of addition was regulated so that a gentle reflux was maintained throughout. After the addition was completed, the solution was refluxed for 2 hrs. and decomposed by pouring the solution into a solid ammonium chloride-ice mixture. The organic layer was separated, and the aqueous solution was extracted with 300 ml. of ether. The combined organic layers were washed with a 5% sodium bicarbonate solution, then with a brine solution, and dried over sodium sulfate. Evaporation of the solvent at reduced pressure yielded a colorless oil which was distilled *in vacuo* under nitrogen to give 85.5 g. (86.4%) of H-2, b.p. 85-93° (0.4 mm.). This material was used immediately for the next reaction since it appeared to be quite sensitive to oxygen.

1-Methyl-6-methoxy-3,4-dihydro-2(1H)-naphthalenone (H-3)..-

The β -tetralone was prepared according to the general procedure of Stork (28). To a stirred solution of 85.5 g. (0.491 mole) of 1-methyl-6-methoxy-3,4-dihydronaphthalene

(H-2) in 600 ml. of methylene chloride was slowly added 115 g. of m-chloroperbenzoic acid* over a 45-min. period while maintaining the temperature at -20°. After the addition was completed, the solution was allowed to warm to room temperature over a 2-hr. period, extracted with 600 ml. of 5% sodium hydroxide, and washed with water until neutral. The solvent was removed *in vacuo*, and the pale yellow oil was dissolved in 1.0 l. of ether. The organic layer was shaken with 200 ml. of 10% hydrochloric acid and allowed to stand for 2 hrs. The acid treatment was repeated, and the pink ethereal solution was washed once more with 200 ml. of 10% hydrochloric acid and allowed to stand for 12 hrs. The organic layer was washed once with water followed by one wash with a 10% sodium bicarbonate solution. Removal of the solvent after drying over magnesium sulfate yielded an oil which was distilled *in vacuo* through an 18 cm. Vigreux column to give 53.2 g. (57%) of the desired ketone as a pale yellow oil, b.p. 116-122° (0.4 mm.). On standing, the oil solidified to a low-melting solid.

Infrared: $\bar{\nu}_{\text{max}}^{\text{film}}$ 1720 cm.⁻¹ (carbonyl).

4,4a,9,10-Tetrahydro-7-methoxy-1,4a-dimethyl-2(3H)-phenanthrone (H-4)..- This compound was prepared by a modified procedure of N. Rigassi (44c). To a stirred, ice-cooled

* Obtained from F.M.C. Corporation; minimum activity 85%.

solution of 43.9 g. (0.226 mole) of 6-methoxy-1-methyl- β -tetralone in 700 ml. of methanol under nitrogen was added 16.9 g. (0.300 mole) of potassium hydroxide dissolved in 25 ml. of water and 50 ml. of methanol. After the addition was completed, the solution was cooled to -15° , and 19.1 g. (0.226 mole) of ethyl vinyl ketone in 50 ml. of methanol was added dropwise over a 1-hr. period. The reaction was stirred for 4 hrs. at -15° and allowed to stand overnight at room temperature. The solution was refluxed for 4 hrs., cooled, and acidified with concentrated hydrochloric acid. The majority of the methanol was removed at reduced pressure. The orange residue was dissolved in 700 ml. of a 1:1 ether-benzene solution and washed with water until neutral. The organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The solid residue was recrystallized from methanol to give 42.6 g. (73.5%) of unsaturated ketone as a pale yellow solid, m.p. $91-93^{\circ}$. An additional recrystallization from methanol afforded nearly colorless crystals, m.p. $92.5-93^{\circ}$. This melting point agrees with that reported by N. Rigassi (44c).

Fétizon and Delobelle (44a) have reported synthesizing this compound although they give no method of preparation. They report the compound as an oil, b.p. $159-161^{\circ}$ (0.06 mm.). They also report a 2,4-DNP, m.p. 236° . Pelletier and Ogiso (44b) also have reported synthesizing this compound, m.p. 95° .

Infrared: $\bar{\nu}$ _{max} ^{nujol} 1655 cm.⁻¹, 1615 cm.⁻¹.

n.m.r.: δ ^{CDCl₃}
 _{TMS}
1.88 p.p.m. (s), (C-1 methyl);
1.54 p.p.m. (s), (C-4a methyl);
3.86 p.p.m. (s), (C-7 methoxyl);
7.40 p.p.m. (d), (C-6 hydrogen)
 J=8.0 c.p.s.;
6.82 p.p.m., 6.94 p.p.m. (C-6 and
 C-8 hydrogens).

m-Methoxyphenyl- α -methylstyrene (I-2).

A. Wittig Procedure:- To a slurry of 500 ml. of anhydrous ether and 89.3 g. (0.25 mole) of methyltriphenylphosphonium bromide (Aldrich Chemical Co.) was added 28.0 g. (0.25 mole) of potassium tertiarybutoxide (M.S.A. Research Corp.) with stirring under nitrogen. A solution of 25 g. (0.167 mole) of m-methoxyacetophenone in 25 ml. of ether was added dropwise over a 1.5-hr. period. The reaction was allowed to stir for 12 hrs. at room temperature under nitrogen; the reaction was filtered, and the ether was removed at water pump pressure. The residue was dissolved in 800 ml. of ligroin and extracted twice with a solution of 50% methanol-water followed by an aqueous wash. The organic layer was dried over magnesium sulfate, and the solvent was removed at water pump pressure. The residue was distilled at reduced pressure and gave 20.8 g. (79%) of I-2 as a colorless liquid, b.p. 86-87° (5.0 mm.).

B. Grignard Procedure:- To 11.5 g. (0.474 mole) of magnesium turnings in a 1-l. three-necked flask equipped with a

mechanical stirrer and dry ice condenser was added 250 ml. of anhydrous ether. Methyl bromide was distilled into the reaction vessel at a rate which maintained a gentle reflux. When all of the magnesium had been consumed, the dry ice condenser was replaced with a water-cooled condenser, and the reaction was heated at reflux for 0.5 hr. A solution of 56.1 g. (0.375 mole) of m-methoxyacetophenone in 50 ml. of ether was added dropwise maintaining a gentle reflux. After the addition was completed, the reaction was refluxed for 3 hrs., cooled to 0°, and poured on to ice and solid ammonium chloride. The organic layer was diluted with 500 ml. of ether, washed with water, and dried over sodium sulfate. Removal of the solvent at reduced pressure yielded a colorless oil. The crude alcohol was distilled at reduced pressure in the presence of 0.5 g. of hydroquinone and 0.4 g. of p-toluenesulfonic acid monohydrate and gave 40.3 g. (72.6%) of olefin I-2, b.p. 82-90° (2.5 mm.).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16.

Found : C, 80.94; H, 8.13.

n.m.r.: δ $CDCl_3$ 2.08 p.p.m. (s), (vinyl methyl);
TMS 3.63 p.p.m. (s), (methoxy methyl);
4.98 and 5.28 p.p.m., (vinyl hydrogens).

2-(m-Methoxyphenyl)-1-bromopropene (I-3).— A solution of 7.0 g. (0.047 mole) of α -methylstyrene and 16 ml. of chloroform were refluxed in the presence of 8.33 g. (0.047 mole) of N-bromosuccinimide and 250 mg. of benzoyl peroxide for 6 hrs.

The reaction was cooled, diluted with 150 ml. of ligroin, and the solid succinimide was filtered. The filtrate was extracted twice with 50 ml. of 5% potassium hydroxide and then with water until neutral. The dried solution was concentrated and distilled through a short-path distillation apparatus at oil pump pressure. There was obtained 7.95 g. (74.5%) of a yellow oil, b.p. 77-102° (0.2 mm.), which was highly irritating to the skin. Gas chromatographic analysis of this oil on a silicon gum rubber column (SE-30) indicated its purity to be greater than 95% of a single component; however, an n.m.r. spectrum of this material showed the presence of two isomeric compounds, one of which was the desired allylic bromide I-3 and the other of which was the isomeric vinyl bromide I-4. The ratio of allylic to vinyl bromide was approximately 2:1. This ratio could not be altered significantly by changing the reaction conditions. Due to the lability of the allylic bromide, this mixture was used in subsequent reactions.

2-Keto-1 β ,4 α -dimethyl-1-(2-m-methoxyphenyl-2-propenyl)-7-methoxy-1,2,3,4,4a,9-hexahydrophenanthrene (I-5).- To a solution of 517 mg. (2.02 mmoles) of unsaturated ketone H-4 in 35 ml. of dimethoxyethane which had been freshly distilled from lithium aluminum hydride was added under a nitrogen atmosphere 257 mg. (2.3 mmoles) of commercial potassium t-butoxide (M.S.A. Research Corp.). The solution was brought to reflux, and, with frequent additions of dimethoxyethane, the

solvent was continuously removed until the distillate contained no further t-butanol as evidenced by v.p.c. analysis. The resulting solution of the anion of H-4 was deep red. It had been found from earlier experiments that if the t-butanol was not removed from the alkylation mixture incomplete alkylation resulted. In later work, it was discovered that the use of sodium hydride as a base obviated the necessity of distilling alcohol from the reaction mixture. The reaction was cooled to 0°, and 0.93 g. of the allylic bromide mixture I-3 and I-4 in 2 ml. of dimethoxyethane was added under nitrogen. The red color of the enolate was rapidly quenched. The reaction was allowed to stir at room temperature for 12 hrs., refluxed for 0.75 hr., cooled, and taken up in 200 ml. of benzene. The organic layer was washed with three 75-ml. portions of water, dried over sodium sulfate, and concentrated *in vacuo*. Chromatography of the pale yellow residue on 100 g. of alumina (Merck) yielded, on elution with 2% ether-hexane, 430 mg. (48%) of white crystalline solid, m.p. 97-101°. Several recrystallizations from ethanol yielded constant-melting material, m.p. 101.5-102.5°.

Anal. Calcd. for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51.

Found : C, 80.48; H, 7.45.

Infrared: $\bar{\nu}_{\text{max}}$ CHCl_3 1702 cm^{-1} (carbonyl);
1610 and 1500 cm^{-1} (aromatics);
1035 cm^{-1} (methoxy phenyl);
910 cm^{-1} (styrene double bond).

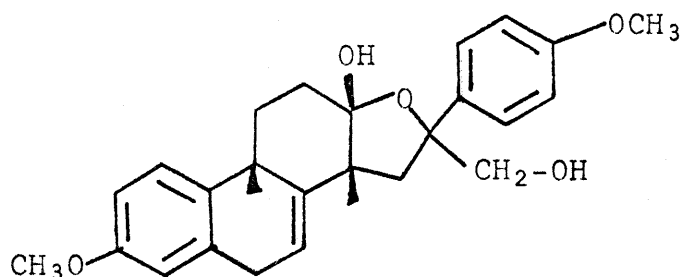
n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$ 1.02 p.p.m. (s), (C-1 methyl);
1.27 p.p.m. (s), (C-4a methyl);

3.68 and 3.77 p.p.m. (s), (methoxy
methyls);
5.04 p.p.m. (d), J=14 c.p.s.,
(styrene vinyl hydrogens);
5.78 p.p.m. (t), J=4.0 c.p.s.,
(C-10 vinyl hydrogen).

Attempted Oxidations of Ketone I-5.-

A. Peracid Oxidation.- One equivalent each, of the ketone I-5 and m-chloroperbenzoic acid, was dissolved in methylene chloride and allowed to stand for 12 hrs. at -5°. The reaction was worked up in the normal manner, and the product was isolated as an oil which could not be crystallized. Analytical thin layer chromatography indicated the presence of at least three products. An n.m.r. spectrum of this material indicated that the styrenoid bond showed a slight preference for oxidation.

B. Osmium Tetroxide Oxidation.- To a solution of 0.5 mmole of the ketone I-5 in 3.0 ml. of dioxane was added 0.6 mmole of osmium tetroxide. After 10 min., the characteristic black color of the osmate ester started to appear. The reaction was stirred at room temperature for 24 hrs., and the osmate ester was decomposed by bubbling hydrogen sulfide into the reaction mixture for 0.5 hr. The solution was filtered, and the filtrate was concentrated *in vacuo* to give an oily residue whose infrared spectrum exhibited a strong hydroxyl absorption and no carbonyl absorption. The lack of a carbonyl band was attributed to the presence of the possible hemketal structure XXXVII.



XXXVII

An n.m.r. spectrum of this material indicated that the styrenoid bond was preferentially, but not exclusively, oxidized. However, more selectivity was observed with this reagent than with the peracid. Attempted cleavage of this mixture of alcohols with paraperiodic acid afforded a gross mixture of ketonic and alcoholic products.

2-Keto-1,4a-dimethyl-1-(2-m-methoxyphenyl-2-propenyl)-1-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (I-7).-

A 300-ml. three-necked flask, fitted with a dry-ice condenser and soda lime drying tube, was charged with 25 ml. of dimethoxyethane (freshly distilled from lithium ammonium hydride) and 125 ml. of anhydrous liquid ammonia (distilled from lithium wire). To this solution was added 139 mg. (10.9 mmoles) of lithium wire. A solution of 2.43 g. (9.5 mmoles) of the ketone H-4 and 1.07 g. of t-butanol in 20 ml. of dimethoxyethane was added dropwise over a 5-min. period, and the reaction was stirred for 20 min. At the end of this period the blue color of the excess lithium metal still persisted. The enolate I-6 was then quenched with a solution

of 7.45 g. (20 mmoles) of the allylic bromide mixture I-3 and I-4 in 10 ml. of dimethoxyethane. The ammonia was allowed to evaporate over a 12-hr. period, and the excess solvent was removed *in vacuo*. The residue was dissolved in 200 ml. of benzene, and the organic layer was extracted once with a 5% solution of sulfuric acid followed by water until neutral. The benzene solution was dried over sodium sulfate and concentrated at reduced pressure to give a colorless oil which was chromatographed on 200 g. of alumina (Merck). The isomeric product mixture was eluted from the column initially with 80% benzene-ligroin and finally with 10% ether-benzene. In this manner, 3.2 g. (91.5%) of the isomeric mixture of ketones I-7 was obtained. Although these isomers could not be separated by gas chromatography, examination of the n.m.r. spectrum of this mixture showed the presence of two sets of vinyl hydrogens centered at 5.2 p.p.m. in a 3:2 ratio. All attempts to separate this epimeric mixture of ketones were fruitless.

2-Keto-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4a,9-hexahydro-1-phenanthreneacetic Acid (XIVc)..- Dimethoxyethane, 350 ml., was distilled from lithium aluminum hydride directly into a reaction flask which had been purged with nitrogen. Sodium hydride, 6.9 g. (0.17 mole), as a 59.4% dispersion in mineral oil, and 35.9 g. (0.14 mole) of unsaturated ketone H-4 were added to the reaction flask. The solution was refluxed under

nitrogen for 6 hrs. The deep red reaction mixture was cooled to 0°, and 50.0 g. (0.3 mole) of ethyl bromoacetate was added dropwise to the stirred solution at a rate which maintained the temperature at +5°. It was observed from other experiments that at temperatures below -5° the alkylation proceeded to give additional C-alkylated products other than the desired compound. As the heteroannular enolate was quenched, the color of the reaction turned from red to pale yellow. After the addition was completed, the reaction was stirred at 0° for 2 hrs., allowed to warm slowly to room temperature and to stand overnight. Water, 1.5 l. was then added, and the aqueous layer was extracted with two 600-ml. portions of benzene. The organic layer was washed with four 200-ml. portions of water, then with brine, and dried over sodium sulfate. Removal of the solvent under reduced pressure yielded an orange residue. The excess bromoacetate was removed by heating the residue gently with a heat lamp under vacuum (0.10 mm.) with stirring for 1.5 hrs. Gas chromatographic analysis of the crude reaction mixture indicated that 99% alkylation had taken place. The keto ester XIVa was saponified without purification.

The crude keto ester XIVa was dissolved in 325 ml. of methanol and refluxed in the presence of 23.5 g. (0.42 mole) of potassium hydroxide and 30 ml. of water under a nitrogen atmosphere for 3 hrs. The cooled reaction mixture was diluted with 400 ml. of water, and the aqueous layer was extracted

with two 150-ml. portions of 50% benzene-ligroin. The red, aqueous layer was poured onto ice and 10% hydrochloric acid. The crude acid was dissolved in 600 ml. of chloroform, and the organic layer was washed with water until neutral and dried over sodium sulfate. Removal of the solvent *in vacuo* yielded a yellow solid which was recrystallized from ethanol. There was obtained 29.7 g. (79%) of the desired keto acid XIVc, m.p. 176-180°, as a pale yellow solid. Several additional recrystallizations from ethanol afforded material of analytical purity, m.p. 179-180°.

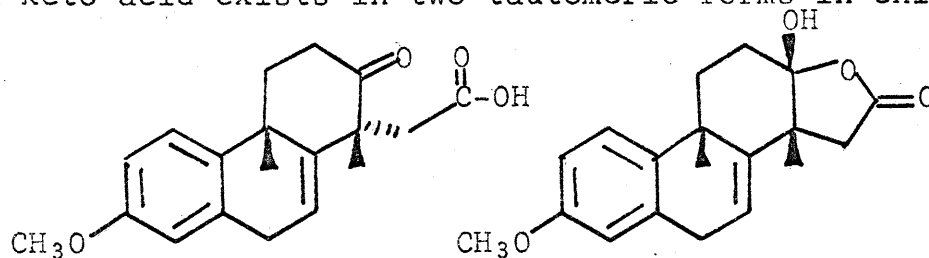
Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05.

Found : C, 72.52; H, 7.12.

Infrared: $\bar{\nu}$ $CHCl_3$
max

3500 and 3575 $cm.^{-1}$ (hydroxyl);
1775 $cm.^{-1}$ (γ -lactol carbonyl);
1705 $cm.^{-1}$ (both carbonyls of
keto acid).

It is apparent from the above infrared data that the unsaturated keto acid exists in two tautomeric forms in chloroform.



Methyl 2-Keto-1,3,4a,8,9-hexamethoxy-1,2,3,4,4a,9-hexahydro-1-phenanthreneacetate (XIVb)..- To a solution of 1.0 g. (3.19 mmoles) of unsaturated keto acid XIVc in 20 ml. of acetone under a nitrogen atmosphere was added 0.665 g. (4.8 mmoles) of anhydrous potassium carbonate and 3.0 ml. of

of methyl iodide. The reaction was heated at reflux for 5 hrs. Every 1.5 hrs. an additional 3.0 ml. of methyl iodide was added to the refluxing solution. The excess solvent was removed *in vacuo*. The residue was dissolved in ether and extracted with 10% potassium carbonate, then with water until neutral. The organic layer was washed with brine and dried over sodium sulfate. Removal of the solvent at reduced pressure yielded a pale orange oil which crystallized on cooling. Recrystallization from a hexane-ethanol mixture gave 961 mg. (93.3%) of pale orange crystals, m.p. 83-87°. A small sample was purified by preparative thin layer chromatography on silica gel (1:1 ether-hexane), and recrystallized twice from ethanol to give colorless prisms, m.p. 87-88°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37.

Found : C, 73.20; H, 7.27

Infrared: $\bar{\nu}$ $\begin{matrix} CHCl \\ max \end{matrix}$

1735 $cm.^{-1}$ (methyl ester);
1710 $cm.^{-1}$ (ketone);
1610, 1500 $cm.^{-1}$ (aromatics).

n.m.r.: δ $\begin{matrix} CDCl_3 \\ TMS \end{matrix}$

1.32 p.p.m., 1.375 p.p.m. (s),
(C-1 and C-4a methyls);
3.42 p.p.m. (s), (O-methyl ester);
3.79 p.p.m. (s), (C-7 methoxy methyl);
5.89 p.p.m. (t), (C-10 vinyl hydrogen), $J=4$ c.p.s.;
6.67 p.p.m. (s), (C-8 aromatic hydrogen);
6.76 p.p.m. doublet of doublets,
(C-6 aromatic hydrogen), J ortho=8 c.p.s., J meta=3 c.p.s.;
7.27 p.p.m. (d), (C-5 aromatic hydrogen).

Ethyl 2-Keto-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10,10 $\alpha\beta$ -octahydro-1-phenanthreneacetate (K-1a).- To a solution of 1.02 g. (3.24 mmoles) of the unsaturated keto acid XIVc in 40 ml. of absolute ethanol was added 0.392 g. (3.5 mmoles) of potassium t-butoxide (M.S.A. Research Corp.) followed by 1.2 g. (6.3 mmoles) of triethyloxonium fluoroborate (79). The reaction was allowed to stir at room temperature for 2.5 hrs. and diluted with 200 ml. of an ether-benzene solution (1:1). The organic layer was washed with brine and dried over sodium sulfate. Removal of the solvent at reduced pressure afforded 1.22 g. of the unsaturated ethyl ester XIVa as a yellow oil which exhibited infrared bands at 1710 cm^{-1} and 1735 cm^{-1} . This material was hydrogenated without further purification.

The hydrogenation of the above material was carried out according to the procedure of Ghatak and co-workers (52). This material was dissolved in 5.0 ml. of glacial acetic acid and added to a slurry of 78 mg. of platinum oxide and 5.0 ml. of glacial acetic acid which had been prereduced with hydrogen. The contents were stirred under one atmosphere of hydrogen, and after 1 hr. the theoretical amount of hydrogen had been consumed. The catalyst was filtered, and the acetic acid was removed *in vacuo*. Gas chromatographic analysis of this material indicated the presence of 30-40% unreduced olefin. This material was recycled under the above conditions, and hydrogenation was continued for

12 hrs. The catalyst was filtered, and the acetic acid was removed *in vacuo*. Gas chromatographic analysis of this material showed the absence of the starting olefin and the presence of the *cis*-fused keto ester K-1a and what was presumed to be the *trans*-fused keto ester J-1a in a 3:1 ratio. Attempts to reproduce this experiment on a larger scale were only partially successful. In several of these reactions which were run with a different batch of catalyst, difficulty was encountered with reduction of the carbonyl group. If the reaction was allowed to proceed until all of the olefin was consumed, significant quantities of the lactone M-1 were produced by reduction of the ester K-1a. From one of these reactions, a 44% yield of the crystalline K-1a was isolated. Recrystallization of a small quantity of this material from 20% ether-hexane afforded an analytical sample of ester, m.p. 99-100°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19.

Found : C, 73.37; H, 8.18.

Infrared: $\bar{\nu}$ $CHCl_3$ max 1735 cm^{-1} , 1715 cm^{-1} .

n.m.r.: δ $CDCl_3$ TMS 1.21 p.p.m. (s), (C-1 and C-4a methyls);
3.78 p.p.m. (s), (C-7 methoxyl).

Methyl 2-Keto-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,-10a β -octahydro-1-phenanthreneacetate (K-1b).- A solution of 30.3 g. (0.092 mole) of unsaturated methyl ester XIVb in 130 ml. of acetic acid was hydrogenated in the presence of 7.0 g. of 10% palladium-on-charcoal in a Paar shaker under

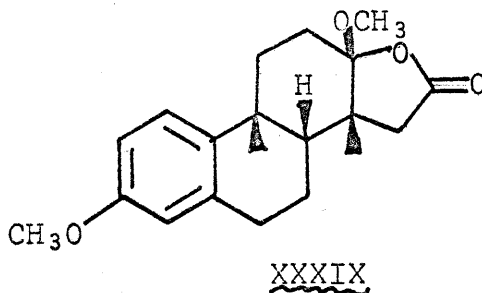
an initial pressure of 53 p.s.i. of hydrogen. A reaction time of 24 hrs. was required for complete hydrogenation. The catalyst was filtered, and the reaction mixture was diluted with 1.0 l. of chloroform. The solution was extracted with two 600-ml. portions of water, two 600-ml. portions of 10% sodium bicarbonate, then water until neutral. The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the solvent at reduced pressure yielded 31.1 g. of a colorless oil. Gas chromatographic analysis of this material indicated the presence of the *cis* and *trans*-fused saturated keto esters K-1b and J-1b in an 8:1 ratio. The crude product was dissolved in a 1:1 ether-hexane solution and allowed to stand at +5° in the refrigerator for 2 weeks. During this period a white solid slowly crystallized from the solution. The solid was filtered and air dried to give 20.0 g. (66%) of a crystalline substance. A v.p.c. analysis as well as an n.m.r. spectrum of this material indicated that it was the isomerically pure saturated keto ester K-1b. A small sample of this material was further purified for analysis by preparative thin layer chromatography on silica gel (eluted with 1:1 ether-hexane). Recrystallization of the chromatographed material once from ether-hexane afforded colorless prisms, m.p. 69-71°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93.

Found : C, 72.78; H, 7.90.

Infrared: $\bar{\nu}$	CHCl_3 max	1730 cm^{-1} (ester carbonyl); 1705 cm^{-1} (ketone); 1610, 1500 cm^{-1} (aromatics).
<u>n.m.r.:</u>	δ CDCl_3 TMS	1.20 p.p.m. (s), (C-1, C-4 methyls); 3.50 p.p.m. (s), (O-methyl ester); 3.77 p.p.m. (s), (C-7 methoxy methyl); 6.67 p.p.m. multiplet, (C-8, C-6 aromatic hydrogens); 6.75 p.p.m. doublet of doublets, J ortho=9.0 c.p.s., J meta=3.0 c.p.s., (C-6 aromatic hydrogen).
	δ C_6H_6 TMS	0.984 p.p.m. (s), (C-1 methyl); 1.265 p.p.m. (s), (C-4a methyl).

An n.m.r. spectrum of the mother liquors of the first crystallization indicated the presence of an additional quantity of the *cis*-fused ester K-lb, the *trans*-fused ester J-lb, and a new compound. An infrared spectrum of the mother liquors showed the expected bands at 1730 cm^{-1} and 1705 cm^{-1} for the isomeric keto esters and a new band at 1775 cm^{-1} which was not present in the crude product mixture. Apparently, this compound was formed during the period when the crude hydrogenation mixture was crystallizing. It was deduced that this material probably contained the γ -lactone structure XXXIX, and this material was derived from an acid-catalyzed isomerization of the keto ester K-lb.



2 β -Hydroxy-1,4a-dimethyl-7-methoxy-1,2,3,4,4a,9-hexahydro-1-phenanthreneacetic Acid (K-3).- A solution of 20.1 g. (0.064 mole) of unsaturated keto acid XIVc in 300 ml. of dry tetrahydrofuran was prepared by heating a slurry of the acid in the solvent until solution was effected. Sodium borohydride, 1.32 g. (0.035 mole), was added in portions to the stirred reaction mixture at 25° over a 5-min. period. The reduction was allowed to proceed for 10 hrs. at room temperature. The system was then purged with nitrogen, and 60 ml. of 10% potassium hydroxide solution and 60 ml. of methanol were added to the reaction. Stirring was continued for an additional 8 hrs. at room temperature. The hydroxy acid K-3 was isolated by pouring the reaction mixture into a slurry of 1.5 l. of ice and 1.0 N hydrochloric acid. This aqueous solution was acidified to Congo Red with concentrated hydrochloric acid, and the crystalline product was collected by filtration. The crystals were washed with water until the filtrate was neutral and then rinsed with 30 ml. of cold ethanol. After air drying for 24 hrs., there was obtained 19.3 g. (95.5%) of the desired hydroxy acid, which was sufficiently pure (>99%) for use in subsequent reactions. Recrystallization of a small sample of this material from ethanol yielded colorless crystals, m.p. 188-190°. The melting point of this material appeared to be somewhat variable. Apparently the compound lactonizes on melting.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65.

Found : C, 72.28; H, 7.55.

Infrared: $\bar{\nu}$ max ν max 3660, 1700, 1675 cm^{-1} (carboxylic acid and alcohol);
1610, 1575, 1500 cm^{-1} (aromatics).

A small sample of the crude unsaturated hydroxy acid was esterified with diazomethane. Both v.p.c. analysis and the n.m.r. spectrum of this ester indicated that the borohydride reduction had been stereoselective.

Hydroxy Methyl Ester

n.m.r.: δ CDCl_3 TMS

1.27	p.p.m. (s), (C-1 and C-4a methyls);
3.32	p.p.m. (d), $J=5.0$ c.p.s., (C-9 methylene);
3.52	p.p.m. (s), (methyl ester);
3.77	p.p.m. (s), (methoxy methyl);
5.97	p.p.m. (t), $J=5.0$ c.p.s., (C-10 vinyl hydrogen);
6.65	p.p.m. doublet of doublets, J ortho=8.0 c.p.s., J meta=3.0 c.p.s., (C-6 aromatic hydrogen);
7.23	p.p.m. (d), $J=8.0$ c.p.s., (C-5 aromatic hydrogen).

Lactonization of Unsaturated Hydroxy Acid (K-3).— A solution of 201 mg. (0.636 mmole) of hydroxy acid K-3 and 25 mg. of p-toluenesulfonic acid monohydrate in 25 ml. of benzene was refluxed for 1 hr., cooled, and diluted to 200 ml. with ether. The organic layer was extracted with 10% potassium carbonate, then with water until neutral. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Trituration of the crystalline residue with ether afforded

170 mg. (89%) of *trans*-lactone K-2 as colorless crystals, m.p. 134-136°. A small sample, recrystallized 4 times from acetone-hexane, gave constant-melting material, m.p. 137-139°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43.

Found : C, 76.46; H, 7.40.

Infrared: $\bar{\nu}_{\text{max}}$ ^{nujol} 1787 cm^{-1} (δ -lactone);
1615, 1575, 1500 cm^{-1} (aromatics).

n.m.r.: δ ^{CDCl₃} _{TMS} 1.325 p.p.m. (s), 1.40 p.p.m. (s),
(C-1 and C-4a methyls);
2.5 p.p.m. (s), (-CH₂-CO-);
3.34 p.p.m. (d), J=4.0 c.p.s., (C-9
methylene);
3.78 p.p.m. (s), (methoxy methyl);
3.86 p.p.m. multiplet, halfband
width \approx 15 c.p.s. (axial C-2
hydrogen);
4.02 p.p.m. (t), J=4.0 c.p.s.,
(C-10 vinyl hydrogen).

2 β -Hydroxy-1 β ,4 α β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10a-
octahydro-1-phenanthreneacetic Acid (K-4).- The unsaturated
hydroxy acid K-3, 3.16 g. (10.0 mmoles), was dissolved in
250 ml. of glacial acetic acid. Heating to 45-50° was re-
quired for complete solution to take place. The reaction was
stirred at 25° under one atmosphere of hydrogen in the pre-
sence of 0.5 g. of 10% palladium-on-charcoal until the theo-
retical amount of hydrogen had been consumed. The catalyst
was filtered, and the filtrate was diluted with 1.0 l. of
chloroform. The organic layer was extracted with four 500-
ml. portions of water and dried over sodium sulfate. Evapo-
ration of the solvent at reduced pressure yielded 3.12 g.

(98.8%) of a colorless crystalline solid, m.p. 184-186°. A small portion of the crude product was esterified with diazomethane. Gas chromatographic analysis of this hydroxy methyl ester indicated the presence of a single component. The n.m.r. spectrum likewise indicated the presence of a single, isomerically pure substance. A small sample of hydroxy acid recrystallized twice from ethanol for analysis melted 186-188°.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23.

Found : C, 71.70; H, 8.28.

Infrared: $\bar{\nu}_{\text{max}}$ ^{nujol} 3330 cm^{-1} broad, 1685 cm^{-1} ; (hydroxyl, carboxylic acid).

Hydroxy Methyl Ester

n.m.r.: δ ^{CDCl₃} TMS

- 0.967 p.p.m. (s), (C-1 methyl);
- 1.18 p.p.m. (s), (C-4a methyl);
- 3.61 p.p.m. (s), (methyl ester);
- 3.74 p.p.m. (s), (methoxy methyl);
- 6.58 p.p.m. (s), (C-8 aromatic hydrogen);
- 7.14 p.p.m. (d), J ortho=8.5 c.p.s., (C-5 aromatic hydrogen).

Ethyl 2-Ethylenedioxo-18,4a β -dimethyl-7-methoxy-1,2,3,4,4a,-9,10,10a β -octahydro-1-phenanthreneacetate (L-1).- A solution of 3.0 g. (8.7 mmoles) of keto ester K-1a, 5.0 g. of ethylene glycol and 200 mg. of p-toluenesulfonic acid monohydrate in 70 ml. of dry benzene were refluxed for 8 hrs. The cooled solution was extracted with 10% sodium bicarbonate followed by water until neutral. The organic layer, dried over sodium sulfate and concentrated *in vacuo*, yielded a

light yellow oil. Chromatography on alumina (Merck) afforded 2.0 g. (59%) of crystalline ethyleneketal, m.p. 68-69.5°, on elution with benzene. An additional 1.4 g. of ethyleneketal hydroxyethyl ester was obtained as a light yellow oil on elution with 10% ethanol-ether. Recrystallization of the ethyleneketal ethyl ester from hexane yielded colorless crystals, m.p. 68-70°, of analytical purity.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30.

Found : C, 71.02; H, 8.30.

Infrared: $\bar{\nu}$ nujol max 1730 cm^{-1} (ester carbonyl).

n.m.r.: δ $CDCl_3$ TMS

1.18	p.p.m. (t)	}J=7.5 c.p.s., (ethyl ester);
3.90	p.p.m. (q)	
1.32	p.p.m. (s), (C-1 and C-4 methyls);	
3.74	p.p.m. (s), (ethyleneketal);	
3.86	p.p.m. (s), (C-7 methoxy methyl);	
6.55	p.p.m. multiplet, (C-8 aromatic hydrogen);	
6.67	p.p.m. doublet of doublets, (C-6 aromatic hydrogen);	
7.14	p.p.m. (d), J=7.5 c.p.s., (C-5 aromatic hydrogen).	

2-Ethylenedioxo-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,-10a β -octahydro-1-phenanthreneacetic Acid (L-2)..- The ethyleneketal ester L-1, 2.6 g. (6.7 mmoles), was refluxed under nitrogen with 40 ml. of ethanol and 15 ml. of 0.66 N sodium hydroxide solution for 72 hrs. The solution was diluted with water, cooled to 0°, and carefully neutralized with dilute hydrochloric acid. The aqueous solution was extracted twice with 40 ml. of chloroform; the organic layer was washed with water and dried over sodium sulfate. Removal of the

solvent *in vacuo* yielded 3.1 g. of light yellow oil which crystallized on scratching. Recrystallization from ethanol yielded 1.5 g. (62.3%) of ethyleneketal acid, m.p. 174.5-176°.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83.

Found : C, 69.87; H, 7.73.

Infrared: $\bar{\nu}$ ^{nujol}_{max} 1715 cm^{-1} (carboxylic acid).

n.m.r.: δ ^{CDCl₃}_{TMS} 1.28 p.p.m. (s), (C-1 and C4a methyls);
3.75 p.p.m. (s) } (ethyleneketal and
3.92 p.p.m. (s) } C-7 methoxy methyl);
6.57 p.p.m. multiplet, (C-7 aromatic hydrogen);
6.65 p.p.m. doublet of doublets, (C-6 aromatic hydrogen);
7.17 p.p.m. (d), J=8.0 c.p.s., (C-5 aromatic hydrogen).

2-Ethylenedioxo-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,-10a β -octahydro-2-phenanthreneacetophenone (L-3a).- The ketal acid L-2, 1.4 g. (3.89 mmoles), was dissolved in 25 ml. of dimethoxyethane which had been freshly distilled from lithium aluminum hydride. The reaction was purged with nitrogen and cooled to 0°. A solution of 7.0 ml. (13.7 mmoles) of 1.96 M phenyllithium reagent (Alpha Inorganics, Inc.) was slowly added over a 15-min. period. After addition was completed, the reaction was allowed to stir at room temperature for 5 hrs. In a similar experiment a reaction time of 2.5 hrs. gave an equally good yield of desired phenyl ketone. The reaction was quenched by pouring into ice water, and the aqueous solution was extracted twice with 50 ml. portions of

a 3:1 benzene-ether solution. The organic layer was washed with water, then brine, and dried over sodium sulfate. Evaporation of the solvent yielded 1.9 g. of a yellow oil which deposited crystals on cooling. This material was chromatographed on 30 g. of alumina. On elution with benzene, there was obtained 1.34 g. (82%) of the desired product as colorless prisms, m.p. 162.5-164°. Recrystallization once from ethanol yielded material of analytical purity, m.p. 164.5-166°, which exhibited an infrared peak at 1685 cm.⁻¹ (mull).

Anal. Calcd. for C₂₇H₃₂O₄: C, 77.17; H, 7.67.

Found : C, 77.08; H, 7.72.

n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$

1.365 p.p.m. (s)	}(C-1 and C-4a methyls);
1.42 p.p.m. (s)	
3.68 p.p.m. (s),	(C-7 methoxy methyl);
3.89 p.p.m. (s),	(ethyleneketal).

3,4,4a,9,10,10a β -Hexahydro-7-methoxy-1 α -(2 phenylethyl)-1 β ,4a β -dimethyl-2(1H)-phenanthrone (L-4).- A solution of 0.720 g. (1.71 mmoles) of ethyleneketal phenyl ketone K-3a in 80 ml. of ethyl acetate and 2.25 ml. of concentrated hydrochloric acid was stirred in the presence of 225 mg. of 10% palladium-on-charcoal under one atmosphere of hydrogen. After 4 hrs. the theoretical amount of hydrogen had been consumed. The catalyst was filtered, and the reaction mixture was diluted with 50 ml. of ether. The organic layer was extracted twice with 20 ml. of saturated sodium bicarbonate solution and washed with water until neutral. The solution was then

dried over sodium sulfate and concentrated *in vacuo*. The semicrystalline residue was chromatographed on 40 g. of alumina (Merck). The desired ketone was eluted from the column with 80% benzene-ligroin. All of the crystalline column fractions were combined and triturated with ether. In this manner there was obtained 420 mg. (67%) of colorless prisms, m.p. 92-94°. Recrystallization from ethanol afforded material of analytical purity, m.p. 94-95°, which exhibited a strong infrared carbonyl frequency at 1700 cm^{-1} (nujol).

Anal. Calcd. for $\text{C}_{25}\text{H}_{30}\text{O}_2$: C, 82.83; H, 8.34.

Found : C, 82.73; H, 8.29.

n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$ 1.20 p.p.m. (s), (C-1 and C-4a methyls);
3.71 p.p.m. (s), (C-7 methoxy methyl).

Attempted Acid-Catalyzed Cyclizations of Ketone L-4.- A mixture of 26 mg. of the ketone L-4 and 2 g. of polyphosphoric acid (prepared from 11.3 g. of phosphorus pentoxide and 10.0 ml. of 85% phosphoric acid) was heated at 90° for 1.5 hrs. The acid mixture was poured onto ice, and the aqueous solution was extracted with 100 ml. of benzene. The organic layer was washed with water until neutral, dried over sodium sulfate, and concentrated *in vacuo*. Gas chromatographic analysis of this oily residue showed the presence of a variety of products. Additional experiments run under the above conditions, but for 0.5 hr., gave much the same results. In both cases, no ketone was present in the

product mixture. When a similar experiment was run at 55° for 15 min., in addition to a large amount of recovered starting material, at least five other hydrocarbons were produced.

A solution of 20 mg. of the ketone L-4 and 6 mg. of toluenesulfonic acid monohydrate in benzene was refluxed for 24 hrs. After workup, a quantitative yield of the ketone was recovered.

To 20 ml. of liquid hydrogen fluoride in a platinum crucible was added 20 mg. of the ketone L-4. The hydrogen fluoride was allowed to evaporate over a 3-hr. period. The residue was isolated as described above and analyzed by v.p.c. All of the ketone had been consumed, and at least five major hydrocarbon products were produced.

2 α -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10 $\alpha\beta$ -octahydro-1-phenanthreneacetic Acid Lactone (M-1).- To a solution of 10.3 g. (0.031 mole) of saturated keto ester K-1b in 500 ml. of methanol cooled to -5° was added 1.26 g. of sodium borohydride in small portions so that the temperature was maintained between -5° and 0°. After the addition was completed, the solution was stirred at -5° for 2.5 hrs.; Water, 1.5 l., was added, and the aqueous solution was extracted with ether. The organic layer was washed twice with water, then with brine, and dried over sodium sulfate. Removal of the solvent at reduced pressure yielded 9.1 g. of

the crystalline lactone. Recrystallization from acetone-hexane yielded 7.35 g. (78.5%) of colorless crystals, m.p. 142-145°. Three additional recrystallizations from ethanol yielded pure substance, m.p. 144-147°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05.

Found : C, 75.93; H, 7.98.

Infrared: $\bar{\nu}$ $CHCl_3$ max 1774 cm^{-1} (δ -lactone);
1613, 1500 cm^{-1} (aromatics);

n.m.r.: δ $CDCl_3$ TMS 1.20 p.p.m. (s), (C-1 and C-4a methyls);
3.74 p.p.m. (s), (C-7 methoxy methyl);
4.16 p.p.m. multiplet, half-band width 14 c.p.s., (axial C-2 hydrogen);
6.59 p.p.m. (s), (C-8 aromatic hydrogen);
7.14 p.p.m. (d), $J=8.0$ c.p.s., (C-5 aromatic hydrogen).

Standard Diborane Solution (82,83).- Tetrahydrofuran, 225 ml., which had been freshly distilled from lithium aluminum hydride, and 6.45 g. (0.17 mole) of sodium borohydride were introduced into a 500-ml. 3-necked flask under nitrogen. Boron trifluoride etherate, 28.4 g. (0.20 mole), which had been distilled from calcium hydride, b.p. 65-67°/50 mm., in 25 ml. of tetrahydrofuran was slowly added dropwise with stirring to the ice-cooled reaction vessel over a 1-hr. period. Stirring was continued for 1 hr. At this time stirring was stopped, and the solid sodium fluoroborate was allowed to settle out of the reaction mixture over a 12-hr. period.

The supernatant liquid was separated from the precipitate and standardized gasometrically by decomposing an aliquot of the diborane solution with ethylene glycol. It was found that the standardized diborane solutions prepared in this manner could be stored at +5° for up to six months without any noticeable change in the titer value.

2 α -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10 $\alpha\beta$ -octahydro-1-phenanthreneacetaldehyde Hemiacetal (M-2).-

The lactone was reduced according to the procedure of Brown and Moerikofer (67b). To an ice-cooled solution of 0.132 mole of disiamylborane in 285 ml. of dry tetrahydrofuran under nitrogen was added 10.1 g. (0.034 mole) of lactone M-1 in 75 ml. of dry tetrahydrofuran dropwise over a 15-min. period. The reaction was stirred at 0° for 2 hrs., at room temperature for 15 hrs., and then cooled to 0°. The excess borane was decomposed cautiously with 25 ml. of water which was added slowly to the reaction mixture. A solution of 60 ml. of 30% hydrogen peroxide adjusted to pH 8 was added, and the reaction was allowed to stir at room temperature for 1 hr. The reaction mixture was then concentrated on a rotary evaporator at reduced pressure. The semi-crystalline solid was dissolved in 500 ml. of benzene and washed with 5% potassium hydroxide solution then with water until neutral. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The white crystalline residue

was placed under high vacuum (0.05 mm.) for 8 hrs. to remove the *iso*-amyl alcohol. Gas chromatographic analysis of the crude product indicated that the reduction had proceeded to give a single compound in greater than 90% yield. Recrystallization of the crude product from acetone-hexane yielded 8.0 g. (77%) of colorless crystals, m.p. 175-180°. A small sample was recrystallized twice more giving a solid, m.p. 178-181°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67.

Found : C, 75.59; H, 8.57.

Infrared: $\bar{\nu}$ $\begin{matrix} CHCl_3 \\ \text{max} \end{matrix}$ 3590 and 3360 $cm.^{-1}$ (hydroxyl);
1650 and 1500 $cm.^{-1}$ (aromatics).

3,4,4a,9,10,10a β -Hexahydro-1 β ,4a β -dimethyl-7-methoxy-1-(2-m-methoxyphenyl)-2(3H)-phenanthrone (M-4).- To a refluxing solution of 63.5 mmoles m-methoxyphenylmagnesium bromide in 70 ml. of 1:1 ether-tetrahydrofuran prepared in the classical manner was added 6.4 g. (21.2 mmoles) of hemiacetal M-2 in 50 ml. of dry tetrahydrofuran slowly over a 0.5-hr. period. The deep red solution was refluxed for 5 hrs., cooled, and poured onto ice and solid ammonium chloride. The aqueous solution was extracted twice with 250 ml. of 1:1 ether-benzene, and the organic layer was extracted with 5 N hydrochloric acid, then water until neutral. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on 300 g. of alumina (Merck). The desired diol M-3a, 7.8 g. (87.5%),

was eluted with 10% methanol-ether as an oil. This material was carried on to the next reaction without further characterization.

Hydrogenation.- A solution of 7.8 g. diol M-3a in 125 ml. of methanol and 0.5 ml. of 60% perchloric acid was stirred under one atmosphere of hydrogen in the presence of 0.90 g. of 10% palladium-on-charcoal. After 7 hrs. the theoretical amount of hydrogen had been consumed. The catalyst was filtered, 1.0 g. of anhydrous potassium carbonate was added to the filtrate, and the reaction mixture was concentrated at reduced pressure. The residue was taken up in 200 ml. of ether, washed with water, and dried in the usual manner. Removal of the solvent *in vacuo* yielded a colorless oil, 7.5 g., which was oxidized without further purification.

Oxidation.- The alcohol M-3b was oxidized according to the procedure of Jones (68). To a stirred, ice-cooled solution of 7.5 g. of alcohol M-3b in 125 ml. of acetone was added dropwise 7 ml. of 8 N chromium trioxide in sulfuric acid over a 15-min. period. The reaction was stirred at 0° for 0.5 hr. and poured onto 500 ml. of ice water. The aqueous solution was extracted with two 200-ml. portions of 1:1 benzene-ether; the organic layer was washed with water 3 times and dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was chromatographed on 200 g. of alumina (Merck). On eluting the column with 75% benzene-ligroin, 6.22 g. (75% based on hemiacetal) of colorless

crystalline solid was obtained, m.p. 76-77°. Recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22

Found : C, 79.43; H, 8.15.

<u>Infrared:</u>	$\bar{\nu}$ max	1705 cm^{-1} (carbonyl); 1610, 1580, 1500 cm^{-1} (aromatics); 1035, 1048 cm^{-1} (methoxyls).
<u>n.m.r.:</u>	δ $CDCl_3$ TMS	1.22 p.p.m. (s), (C-1 and C-4a methyls); 3.71, 3.75 p.p.m. (s), (2 methoxy methyls).

3,21-Dimethoxy-9 β ,14 β -dimethyl-6,7,8 β ,9,11,14,15,16-octahydropicene (M-5)..- A solution of 2.39 g. (6.1 mmoles) of ketone M-4 in 400 ml. of benzene was refluxed in the presence of 116 mg. of p-toluenesulfonic acid monohydrate under a nitrogen atmosphere for 12 hrs. The water which was formed during the course of the reaction was removed by means of a Dean-Stark water separator. The course of the reaction was followed by thin layer chromatography, and the reaction was stopped as soon as all of the starting ketone had been consumed. If the reaction was allowed to proceed beyond this point a second hydrocarbon A was gradually produced at the expense of the desired product. The benzene solution was cooled, extracted with 5% potassium hydroxide, and washed with water until neutral. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Crystallization of the solid residue from ether-hexane afforded 1.96 g. (83%) of colorless prisms, m.p. 113-115°. Two additional

crystallizations from the same solvent yielded analytical material with no change in melting point.

Anal. Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07.

Found : C, 83.40; H, 8.22.

Infrared: $\bar{\nu}_{\text{max}}^{CHCl_3}$ 1610 (s), 1500 (s), 1260 (s),
1035 cm^{-1} (m).

u.v.: $\lambda_{\text{max}}^{CH_2Cl_2}$ 250 m μ , $\epsilon = 18,900$.

n.m.r.: $\delta_{\text{TMS}}^{CDCl_3}$

- 1.15 p.p.m. (s), (C-14 methyl);
- 1.44 p.p.m. (s), (C-9 methyl);
- 3.73 p.p.m. (s), (2 methoxyls);
- 5.87 p.p.m. (t), $J=4.0$ c.p.s.,
(vinyl hydrogen);
- 6.57 p.p.m. (s), (C-4, C-22 aromatic hydrogen);
- 6.67 p.p.m. doublet of doublets,
(C-2, C-22 aromatic hydrogens);
- 7.22 p.p.m. (d), $J=8.0$ c.p.s.,
(C-1 aromatic hydrogen);
- 7.35 p.p.m. (d), $J=8.0$ c.p.s.,
(C-19 aromatic hydrogen).

If a benzene solution of the olefin M-5 was heated in the presence of p-toluenesulfonic acid under the previously described conditions, this olefin was gradually transformed into the hydrocarbon A. After about 60-65% of this material had been produced, the appearance of several new hydrocarbons was observed. These hydrocarbons were formed at the expense of the hydrocarbon A. If the reaction was continued for a prolonged period a gross mixture of products resulted.

If the ketone M-4 was cyclized with either liquid hydrogen fluoride or polyphosphoric acid the same undefined hydrocarbon mixture was produced.

12-Keto-3,21-dimethoxy-9 β ,14 β -dimethyl-6,7,8 β ,9,11,12,13 α ,-
14,15,16-decahydropicene (N-2).- The pentacyclic olefin M-5
was hydroborated according to the general procedure of Brown
and Zweifel (81). To a solution of dry tetrahydrofuran, 10
ml., containing 406 mg. (1.08 mmoles) of olefin M-5 was added
0.83 mmole of diborane in 2.0 ml. of tetrahydrofuran with
stirring under a nitrogen atmosphere. The reaction was al-
lowed to stand for 16 hrs. at room temperature. The excess
diborane was decomposed by the careful addition of water to
the well-stirred, ice-cooled reaction mixture. Sodium hydro-
xide, 2.0 ml. (2.5 N), and 1.0 ml. of 30% hydrogen peroxide
were then consecutively added over a period of 5 min. at 0°,
and the solution was stirred for 2 hrs. at room temperature.
The reaction was diluted to 200 ml. with benzene and washed
with 25 ml. of 5 N sulfuric acid then with water until neu-
tral. The organic layer was dried over sodium sulfate and
concentrated *in vacuo*. The crude product, obtained as a cry-
stalline mixture of isomeric alcohols N-1, was oxidized with-
out further purification.

Jones Oxidation.- A stirred, ice-cooled solution of the
crude alcohols N-1 in 40 ml. of acetone was treated with
0.5 ml. of 8.0 N chromium trioxide in sulfuric acid. The
reaction was stirred for 0.5 hr. at 0° and poured into an
ice-water mixture. The aqueous solution was extracted with
two 100-ml. portions of 1:1 ether-benzene. The organic layer
was washed with water until neutral, dried over sodium

sulfate, and concentrated *in vacuo*. There was obtained 400 mg. of a pale yellow crystalline solid. The crude product was chromatographed on 15 g. of alumina (Merck), and the desired material was eluted from the column with 85% benzene-ligroin. The crystalline column fractions which were combined and triturated with ether gave 384 mg. (91.3%) of N-2 as colorless prisms, m.p. 180-182°. Two additional crystallizations from acetone-hexane afforded colorless needles, m.p. 182-183.5°.

Anal. Calcd. for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74.

Found : C, 80.08; H, 7.97.

Infrared: $\bar{\nu}_{\text{max}}$ $CHCl_3$ 1715 cm^{-1} (carbonyl);
1615 cm^{-1} , 1500 cm^{-1} (aromatics);
1249 cm^{-1} , 1035 cm^{-1} (methoxy phenyl).

n.m.r.: δ_{TMS} $CDCl_3$ 1.09 p.p.m. (s), (C-14 methyl);
1.35 p.p.m. (s), (C-9 methyl);
3.72 p.p.m. (s), (2 methoxy methyls).

Base Equilibration of Ketone (N-2).- A solution of 14 mg. (0.036 mmole) of the ketone N-2 in 2 ml. of tetrahydrofuran and 5 ml. of absolute methanol was stirred under a nitrogen atmosphere in the presence of 1-2 mg. of sodium methoxide for a 40-hr. period. The reaction was diluted to 50 ml. with benzene, and the solution was extracted 4 times with water followed by brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was heated at 50° in a vacuum (0.1 mm.) for 2 hrs. to remove all of the volatile material, and the contents

were analyzed by n.m.r. spectroscopy. The major component in the mixture was the ketone N-2. In addition to this material, the presence of two new methyl resonances at 1.27 and 1.47 p.p.m. was observed. The ratio of the ketone N-2 to this material was 10:1. However, there is no evidence that the minor component is the isomeric ketone. An independent check on the stereochemical assignment of the *cis-syn-trans* ketone N-2 was made by measuring the half-line widths of the C-14 and C-9 methyl resonances relative to tetramethylsilane in chloroform.

	$W_{h/2}$	TMS $W_{h/2}$	$\Delta W_{h/2}$
C-14 methyl	1.55 c.p.s.	0.76 c.p.s.	0.79 c.p.s.
C-9 methyl	1.15 c.p.s.	0.76 c.p.s.	0.39 c.p.s.

These values are in good agreement with the expected values for *cis*- and *trans*-10-methyl decalin derivatives which have been determined by Williamson and co-workers (80).

12-Keto-3,21-dimethoxy-9 β ,13 β ,14 β -trimethyl-6,7,8 β ,9,11,12,-13,14,15,16-decahydropicene (N-3).- Potassium metal, 536 mg. (13.7 mmoles), was dissolved in 10 ml. of dry *t*-butyl alcohol and 5 ml. of dry benzene under nitrogen. A solution of 1.32 g. (3.37 mmoles) of pentacyclic ketone N-2 in 5 ml. of dry benzene was added to the reaction mixture. The contents were refluxed for 0.5 hr., cooled to room temperature, and quenched with 1.5 ml. of methyl iodide. Stirring was continued for 12 hrs.; 10.0 ml. of 10% hydrochloric acid

was added, and the aqueous solution was extracted with 200 ml. of 1:1 ether-benzene. The organic layer was washed 3 times with water then dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave 1.4 g. of a crystalline residue. The methylated ketone N-3 was separated from the unalkylated ketone N-2 by preparative thin layer chromatography. It was found that 2 mm. alumina plates (20x20 cm.) eluted successively 3 times with 1:1 ether-hexane completely resolved the alkylated and unalkylated ketones. In this manner 690 mg. (50.5%) of the methylated ketone N-3 as colorless prisms, m.p. 126-128°, was isolated. The balance of the material from the reaction was starting material. No other isomeric methylated ketone could be isolated. Recrystallization of the product from methanol yielded material of analytical purity, m.p. 126-128°.

Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97.

Found : C, 80.06; H, 7.96.

<u>Infrared:</u> $\bar{\nu}$ $CHCl_3$ max	1701 $cm.^{-1}$ (carbonyl); 1610, 1576, 1550 $cm.^{-1}$ (aromatics); 1030 $cm.^{-1}$ (methoxy phenyl).
<u>n.m.r.:</u> δ $CDCl_3$ TMS	1.02 p.p.m. (s), (C-14 methyl); 1.28 p.p.m. (s), (C-9 methyl); 1.53 p.p.m. (s), (C-13 methyl); 3.69 p.p.m. } (2 methoxy methyls); 3.72 p.p.m. } 7.19 p.p.m. (d), J=8.5 c.p.s. } 7.15 p.p.m. (d), J=9.0 c.p.s. } (C-1, C-19 hydrogens).
δ C_6H_6 TMS	0.834 p.p.m. (s), (C-14 methyl); 1.18 p.p.m. (s), (C-9 methyl); 1.43 p.p.m. (s), (C-13 methyl).

12-Keto-11 β -bromo-3,21-dimethoxy-9 β ,13 β ,14 β -trimethyl-6,7,8 β ,-

9,11,12,13,14,15,16-decahydropicene (N-4).- The methylated ketone N-3 was brominated with phenyltrimethylammonium tribromide (PTT) according to the general procedure of Jacques *et al.* (73). To a solution of 41.7 mg. (0.103 mmole) of ketone N-3 in 5 ml. of dry tetrahydrofuran was added 41.3 mg. (0.110 mmole) of PTT. The reaction was stirred at room temperature for 4 hrs. and diluted with 100 ml. of water. The aqueous solution was extracted with ether. The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded a white crystalline residue. This material was purified by preparative thin layer chromatography using a 2 mm. silica gel plate (20x20 cm.) which was developed with 10% ether-benzene. The developed chromatogram showed the presence of two components in the crude reaction mixture. The faster-moving component (R_f 0.74) was isolated and gave 38 mg. of the crystalline bromo ketone N-4. Recrystallization of this material from methanol-acetone afforded 26 mg. of white prisms, m.p. 193-197°. The slower-moving component (R_f 0.44) was isolated and gave 11 mg. of crystalline starting material. The yield of bromo ketone N-4 based on recovered ketone N-3 was 78.5%. Two additional crystallizations from the same solvent system afforded orthorhombic crystals, m.p. 194-196°, which were suitable for X-ray analysis (72).

Anal. Calcd. for $C_{27}H_{31}BrO_3$: C, 67.07; H, 6.46.

Found : C, 67.26; H, 6.33.

Infrared: $\bar{\nu}_{\text{max}}^{CHCl_3}$ 1718 cm.^{-1} (s),(carbonyl);
1610 (s),1575 (m),1490 cm.^{-1} (s),
(aromatics);
1240 (s),1035 (s) cm.^{-1} , (methoxy
phenyl).

Catalytic Hydrogenation of Pentacyclic Olefin (M-5).- A solution of 100 mg. (0.267 mmole) of pentacyclic olefin M-5 in 40 ml. of ethanol (heating required to effect solution) was stirred under one atmosphere of hydrogen in the presence 70 mg. of 10% palladium-on-charcoal for 18 hrs. The catalyst was filtered, and the solvent was removed *in vacuo*. Gas chromatographic analysis of the crystalline residue indicated the presence of two isomeric hydrogenation products in 26% and 74% yields. The minor isomer (B), XIX, was isolated by two crystallizations from ethanol to give 23.6 mg. (23.4%) of colorless needles, m.p. 157-160°. Four additional crystallizations from the same solvent yielded constant-melting material, m.p. 158-159°.

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57.

Found : C, 83.09; H, 8.50.

Isomer XIX

Infrared: $\bar{\nu}_{\text{max}}^{\text{nujol}}$ 1610 (m),1575 (m),1500 (s),1376
(m),1250 (m),1025 cm.^{-1} (m).

n.m.r.: $\delta_{\text{TMS}}^{CDCl_3}$ 1.05 p.p.m. (s),(C-14 methyl);
1.53 p.p.m. (s),(C-9 methyl);
3.74 p.p.m. (s),(2 methoxy me-
thyls).

The major hydrogenation isomer (A), XX, recovered from the mother liquors of the first crystallization as an oil, was induced to crystallize by cooling with dry ice and triturating with ether. Two crystallizations from hexane yielded colorless prisms of constant melting point, m.p. 113-115°.

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57.

Found : C, 83.01, H, 8.69.

Isomer XX

Infrared: $\bar{\nu}$ nujol
max

1610 (m), 1575 (w), 1495 (s),
1260 (s), 1035 $cm.^{-1}$ (m).

n.m.r.: δ $CDCl_3$
TMS

0.933 p.p.m. (s), (C-14 methyl);
1.15 p.p.m. (s), (C-9 methyl);
3.68 p.p.m. (s)
3.73 p.p.m. (s) } (methoxy methyls).

Isomer (B), XIX, was assigned the *cis-syn-trans* configuration; and isomer (A), XX, the major hydrogenation product, was assigned the *cis-syn-cis* configuration (see discussion).

Birch Reduction of Pentacyclic Olefin (M-5).- A solution of 80 mg. (0.214 mmole) of olefin M-5 in 20 ml. of dry tetrahydrofuran was added to a 100-ml. three-necked flask equipped with a dry ice condenser. Approximately 40 ml. of anhydrous liquid ammonia was distilled into the reaction vessel, and 300 mg. of potassium metal was added in one portion. The reaction was allowed to stir for 40 min. The excess metal was destroyed with solid ammonium chloride; the ammonia was evaporated, and the residue was diluted with 100 ml. of water. The aqueous solution was extracted with 200 ml. of ether, and the organic layer extracted with

water until neutral. The solution was dried over sodium sulfate and concentrated *in vacuo*. Gas chromatographic analysis of the crystalline product mixture indicated the presence of the same two isomeric hydrocarbons A and B that were observed in the hydrogenation of olefin L-5. Isomer B was present in 82% yield and isomer A in 18% yield. One crystallization of the crude reaction mixture from ethanol yielded 50 mg. (69.3%) of colorless needles, m.p. 158-160°, which was identified as isomer B. Due to the fact that dissolving metal reductions of this type usually yield the thermodynamically stable hydrocarbon (70), isomer B, XIX, was assigned as the *cis-syn-trans* hydrocarbon; isomer A, XX, was assigned the *cis-syn-cis* configuration.

2 β -Hydroxy-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10a α -octahydro-1-phenanthreneacetic Acid Lactone (O-1a)..- The procedure followed in this experiment was the same as that used in the lactonization of the unsaturated hydroxy acid K-3. A solution of 204 mg. (0.64 mmole) of hydroxy acid K-4 and 20 mg. of *p*-toluenesulfonic acid monohydrate in 20 ml. of benzene was refluxed for 0.75 hr. The product was isolated in the previously described fashion. In this manner there was obtained 189 mg. (98%) of the colorless crystalline solid lactone. Gas chromatographic analysis indicated the purity to be \geq 98%. Recrystallization from acetone-hexane afforded 120 mg. (62.4%) of colorless prisms, m.p. 122-125°. A sample recrystallized twice more from the same solvent

system yielded analytically pure lactone, m.p. 124.5-126°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05

Found : C, 76.07; H, 8.03.

Infrared: $\bar{\nu}_{\text{max}}$ CHCl_3 1785 cm^{-1} , (δ -lactone).

n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$

1.07	p.p.m. (s), (C-1 methyl);
1.22	p.p.m. (s), (C-4a methyl);
3.75	p.p.m. (s), (methoxy methyl);
3.87	p.p.m. multiplet, half-band width = 17 c.p.s., (C-2 axial hydrogen);
6.61	p.p.m. (s), (C-8 aromatic hydrogen);
7.14	p.p.m. (d), $J=8.0$ c.p.s., (C-5 aromatic hydrogen).

Attempted Hydroboration of the Lactone Q-1a. - The procedure which was followed in this experiment was the same as the procedure described for the reduction of the lactone M-1. To a solution of 4.0 mmoles of disiamylborane prepared from 8.6 ml. of 0.467 M borane in tetrahydrofuran and 8.1 mmole of 2-methyl-2-butene was added 304 mg. (1.01 mmoles of the lactone Q-1a in 5.0 ml. of tetrahydrofuran at 0°. The reaction was stirred under a nitrogen atmosphere for 4 hrs., and at 25° for 15 hrs. The reaction was worked up in the previously described manner and gave a colorless crystalline solid. Gas chromatographic analysis of this material indicated the presence of 2 products in a 4:1 ratio. The major component, the diol Q-1b, was isolated by recrystallization of the crude reaction mixture twice from hexane-acetone as

colorless needles, m.p. 132.5-134°, 104 mg. Although this material was apparently a single component as evidenced by thin layer chromatography and n.m.r. analysis, a v.p.c. of this material still showed the presence of the same impurity that was observed in the crude product mixture. Therefore, it was assumed that the minor component was an artifact and was a thermal decomposition product of the diol 0-1b formed during the v.p.c. analysis. Recrystallization of the diol once more from hexane-acetone afforded an analytical sample, m.p. 131-132°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27.

Found: C, 75.11; H, 9.33.

Infrared: $\bar{\nu}$ $CHCl_3$ max 3350, 1610, 1490, 1030 cm^{-1} .

n.m.r.: δ $CDCl_3$ TMS
 0.926 p.p.m. (s), (C-1 methyl);
 1.200 p.p.m. (s), (C-4a methyl);
 2.90 p.p.m. (t), (C-9 methylene);
 3.64 p.p.m. multiplet, five hydrogens;
 3.76 p.p.m. (s), (C-7 methoxyl).

The above spectrum was rerun after two drops of pyridine had been added. The presence of two hydroxylic protons centered at 4.50 p.p.m. was observed, and the relative number of hydrogens in the multiplet centered at 3.64 p.p.m. was reduced from 5 to 3.

2 β -Hydroxy-1 β ,4a β -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydro-1-phenanthrene-N-methyl-acetamide (0-2a).- To a 50-ml. three-necked flask equipped with a dropping funnel

and dry ice condenser was added 10 ml. of dry tetrahydrofuran and 41 mg. (1.08 mmoles) of finely pulverized lithium aluminum hydride. Anhydrous monomethylamine was slowly distilled into the reaction vessel with stirring until all of the lithium aluminum hydride had reacted. The reaction mixture was stirred for 2 hrs.; the dry ice condenser was removed, and the excess methylamine was allowed to distill from the reaction flask at room temperature. Anhydrous conditions were maintained throughout the reaction. A solution of 164 mg. (0.546 mmole) of lactone 0-1a in 5 ml. of dry tetrahydrofuran was added dropwise over a 5-min. period. The reaction was allowed to stir at room temperature for 12 hrs. and diluted with 100 ml. of water. The aqueous solution was extracted with 200 ml. of 1:1 ether-benzene; the organic layer was washed with two 50-ml. portions of 6 N hydrochloric acid then water until neutral. After drying over sodium sulfate, the organic layer was concentrated *in vacuo*. There was obtained 170 mg. (94%) of a white crystalline residue. This material was sufficiently pure for subsequent reactions. An infrared spectrum of this amide showed the presence of a carbonyl at 1640 cm^{-1} and the absence of the γ -lactone carbonyl at 1785 cm^{-1} . Crystallization of the crude product from ethanol gave 135 mg. (74.7%) of 0-2a as white needles, m.p. $212-215^{\circ}$. An analytical sample of the hydroxy amide prepared by two additional crystallizations from ethanol had a melting range of $212-214^{\circ}$.

Anal. Calcd. for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23

Found : C, 72.63; H, 8.80; N, 4.19.

Infrared: $\bar{\nu}$ ^{nujol}_{max} 3320-3300 $cm.^{-1}$ broad, (O-H, N-H);
1640 (s), 1630 $cm.^{-1}$ (s), (carbonyl).

2 α -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10 $\alpha\alpha$ -octahydro-1-phenanthreneacetic Acid Lactone (Q-5).- To 350 ml. of pyridine which had been dried by distillation from barium oxide was added 16.0 g. (0.048 mole) of hydroxy amide Q-2a. The stirred solution was cooled to 0°, and 22.5 g. (0.196 mole) of methanesulfonyl chloride was added dropwise over a 15-min. period. The temperature was maintained between 0° and 5°. After the addition was completed, the orange colored reaction mixture was stirred for 21 hrs. at room temperature. Water, 25 ml., was added, and the solution was heated to 85° and then allowed to cool to room temperature over a 1-hr. period. The pyridine solution was dissolved in 2.5 l. of 50% ether-benzene and extracted with 1.0 l. of water followed by successive portions of 10% hydrochloric acid until the aqueous washes appeared acidic. The organic layer was then washed with two 300-ml. portions of 10% potassium hydroxide then with water until neutral. After drying over sodium sulfate, the solvent was removed at reduced pressure. The light orange residue crystallized on cooling. An infrared spectrum of this material showed a strong carbonyl at 1775 $cm.^{-1}$ and the presence of a small amount of hydroxy amide. Trituration with cold ether

afforded 10.75 g. (74.2%) of white crystalline solid, m.p. 116.5-118°. Chromatography of the mother liquors on 100 g. of neutral alumina (Woelm Activity III) yielded an additional 2.04 g. (14.1%) of crystalline material, m.p. 114-115°, on elution with 50% benzene-ligroin. A small sample recrystallized twice from acetone-hexane gave orthorhombic crystals, m.p. 118-120°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05.

Found : C, 76.02; H, 7.95.

Infrared: $\bar{\nu}_{\text{max}}^{\text{CHCl}_3}$ 1760 cm^{-1} (γ -lactone).

n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$

1.02	p.p.m. (s), 1.025 p.p.m. (s),
	(C-1 and C-4a methyls);
3.77	p.p.m. (s), (methoxy methyls);
4.33	p.p.m. multiplet, half-band
	width 3.0 c.p.s., (C-2 equa-
	torial hydrogen);
6.62	p.p.m. multiplet, (C-8 aroma-
	tic hydrogen);
7.20	p.p.m. (d), $J=8.5$ c.p.s., (C-5
	aromatic hydrogen).

2 α -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4a,9,10,10 $\alpha\alpha$ -octahydro-1-phenanthreneacetaldehyde Hemiacetal (0-6). - The general procedure which was followed was identical to that used in the reduction of the isomeric 10 $\alpha\beta$ -*cis*-lactone M-1. A solution of 8.8 g. (29.4 mmoles) of 10 $\alpha\alpha$ -*cis*-lactone 0-5 was added dropwise under nitrogen to a stirred, ice-cooled solution of 118 mmoles of diisiamylborane in 224 ml. of dry tetrahydrofuran. After the addition was completed, the solution was stirred for 15 hrs. at room temperature. The product was

isolated as in the previously described procedure. There was obtained 8.9 g. (100%) of a white crystalline solid which was shown to be 99% pure O-6 by gas chromatographic analysis. The crude hemiacetal was sufficiently pure for subsequent reactions. A small sample, recrystallized twice from acetone-hexane gave material of analytical purity, m.p. 174.5-178°. The infrared spectra of the analytical material and crude reaction were superimposable.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67.

Found : C, 75.41; H, 8.60.

Infrared: $\bar{\nu}_{\text{max}}^{\text{CHCl}_3}$ 3570-3360 broad, 1605 (s), 1490 (s), 1230 (s), 1030 (m), 1000 cm^{-1} (s).

3,4,4a,9,10,10a α -Hexahydro-1 β ,4a β -dimethyl-7-methoxy-1-(2-m-methoxyphenyl)-2(3H)-phenanthrone (P-2).- The general procedures followed in these experiments were similar to those which were used in the synthesis of the isomeric 10a β -ketone M-4. To a gently refluxing solution of 0.04 mole of m-methoxyphenylmagnesium bromide in 60.0 ml. of 2:1 ether-tetrahydrofuran was added 3.8 g. (12.6 mmoles) of hemiacetal O-6 in 50 ml. of dry tetrahydrofuran. The red solution was refluxed for 6 hrs., cooled, and poured onto ice and solid ammonium chloride. The crude diol P-1a was isolated and purified by chromatography as previously described. This diol was carried on to the next experiment without characterization.

Hydrogenolysis.- A solution of the diol P-1a obtained in

the previous experiment in 250 ml. of methanol and 1.0 ml. of 60% perchloric acid was stirred under one atmosphere of hydrogen in the presence of 0.50 g. of 10% palladium-on-charcoal. After the theoretical quantity of hydrogen had been consumed, the catalyst was filtered, and the product was isolated as previously described. The alcohol P-1b was oxidized to the desired ketone P-2 without purification.

Oxidation.- The unpurified alcohol P-1b from the preceeding experiment was dissolved in 125 ml. of acetone and treated with 4.0 ml. of 8 N chromium trioxide in sulfuric acid for 0.5 hr. at 0°. The reaction was worked up in the previously described manner. A yellow oil was obtained which, on gas chromatographic analysis, appeared to be a single compound in greater than 99% purity. The product was chromatographed on 150 g. of alumina (Merck) and was eluted with 50% benzene-ligroin to benzene. The crystalline column fractions were combined and, on trituration with cold ether, afforded 4.33 g. (87.5% from hemiacetal) of colorless crystals, m.p. 108-111°. Recrystallization of a small sample from methanol for analysis afforded material which melted from 109.5 to 111°.

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22.

Found : C, 79.43; H, 8.20.

Infrared: $\bar{\nu}_{\text{max}}$ $CHCl_3$ 1700 cm^{-1} (s), (carbonyl);
1610 (s), 1500 cm^{-1} (s), (aromatics);
1035 cm^{-1} (m), (methoxyphenyl).

n.m.r.: δ_{TMS} $CDCl_3$ 1.16 p.p.m. (s), (C-1 methyl);
1.25 p.p.m. (s), (C-4a methyl);
3.80 p.p.m. (s), (methoxy methyls).

3,21-Dimethoxy-9 β ,14 β -dimethyl-6,7,8 α ,9,11,14,15,16-octahydronicene (P-3)..- A solution of 2.163 g. (5.52 mmoles) of ketone P-2 in 500 ml. of toluene was refluxed in the presence of 0.80 g. of p-toluenesulfonic acid monohydrate. The water which was formed during the reaction was removed azeotropically by means of a Dean-Stark water separator. The course of the reaction was followed by gas chromatography. After 31 hrs., all of the ketone had been transformed to a single product which was stable to further acid treatment. The reaction was cooled and extracted with 10% potassium hydroxide followed by water until neutral. The organic layer was washed with brine and dried over sodium sulfate. Removal of the solvent at reduced pressure yielded a crystalline residue which, on trituration with methanol, afforded 1.90 g. (97%) of colorless crystals, m.p. 186-188°. Recrystallization of a small sample from ethanol-benzene for analysis gave material melting from 188.5 to 191°.

Anal. Calcd. for C₂₆H₃₀O₂: C, 83.38; H, 8.07.

Found : C, 83.24, H, 8.05.

<u>Infrared:</u>	$\bar{\nu}$ nujol max	1650 cm. ⁻¹ (w), (styrene); 1610 (s), 1574 (m), 1500 (s) cm. ⁻¹ (aromatics); 1030 cm. ⁻¹ , 1040 cm. ⁻¹ (methoxy phenyl).
<u>n.m.r.:</u>	δ CDCl ₃ TMS	1.00 p.p.m. (s), (C-14 methyl); 1.32 p.p.m. (s), (C-9 methyl); 3.78 p.p.m. (s), (methoxy methyls); 5.91 p.p.m. multiplet, (vinyl hydrogen); 6.67 p.p.m. multiplet, (C-4, C-22 aromatic hydrogens).

7.27 p.p.m. (d), J=9.0 c.p.s.,
(C-1 aromatic hydrogen);
7.43 p.p.m. (d), J=9.0 c.p.s.,
C-19 aromatic hydrogen).

In addition to the previously described cyclization conditions, other less successful conditions were investigated. Treatment of the ketone P-2 under conditions which readily caused cyclization of the isomeric ketone M-4, led to a very slow rate of ring closure. A solution of this ketone and p-toluenesulfonic acid in benzene heated at reflux for 24 hrs. resulted in only a 30% conversion to the octahydro-picene P-3. On the other hand, treatment of this ketone with liquid hydrogen fluoride for 1 hr. resulted in a mixture of at least seven hydrocarbon products, one of which was the olefin P-3.

Attempted Hydroboration of Olefin (P-3)..- The olefin P-3, 309 mg. (0.826 mmole), was dissolved in 20 ml. of dry tetrahydrofuran and treated with 2.0 ml. of 1.05 M borane solution in tetrahydrofuran. The reaction was allowed to stir for 90 hrs. under a nitrogen atmosphere. The reaction was worked up according to the procedure described in the hydroboration of the olefin M-5. The product consisted exclusively of the starting olefin. A similar hydroboration using diglyme as a solvent and a twenty-fold excess of diborane yielded about 5% of the hydroborated olefin after a reaction period of one week.

Epoxidation of Pentacyclic Olefin (P-3).- To a stirred, ice-cooled solution of 0.500 g. (1.33 mmoles) of olefin P-3 in 15 ml. of methylene chloride was added 145 mg. of m-chloroperbenzoic acid. After stirring for 1.5 hrs. all of the peracid was consumed as evidenced by a negative starch-iodide test. An additional 145 mg. of peracid was added, and stirring continued for 1.5 hrs. Finally, 100 mg. of peracid was added, and stirring was continued for an additional 1.5 hrs. The course of the reaction was followed by analytical thin layer chromatography, and the reaction was stopped when all of the starting material had been consumed. The reaction mixture was diluted with 200 ml. of ether and extracted with 10% potassium carbonate then with water until neutral. After drying the organic layer over sodium sulfate and removing the solvent at reduced pressure, a pale yellow oil was obtained which was shown to be a mixture of at least 3 products. An infrared spectrum of this mixture showed the presence of a strong carbonyl band (1705 cm.^{-1}) as well as hydroxyl bands. A partial separation of this mixture was obtained on a 2 mm. silica gel plate, (40x20 cm.) on elution with 10% ether-benzene. Band A, R_f 0.74, 4 mg., was shown to be the starting olefin P-3. The second band, B, R_f 0.57, was obtained as a semicrystalline solid which, on trituration with cold ether, afforded 229 mg. (44%) of an epimeric mixture of the ketones P-4 and P-5a in a ratio of 1.7:1 as determined by n.m.r. spectroscopy. Equilibration of this mixture with sodium

methoxide in methanol (see following experiment) afforded an enhanced ratio of P-4 to P-5a of 19:1. The third band, C, R_f 0.40, was obtained as a semicrystalline solid, 240 mg. Recrystallization of this material from ethanol yielded 200 mg. (37%) of the hydroxy ketone P-5b as a colorless crystalline solid, m.p. 198-203°. Several recrystallizations from 1:1 ethanol-benzene afforded constant melting material, m.p. 201.5-204.5°. An infrared spectrum (chloroform, 2.0 mm. cell) of this substance exhibited a normal, nonhydrogen-bonded hydroxyl absorption at 3595 cm^{-1} and a carbonyl absorption at 1710 cm^{-1} . Assuming that this compound is an α -hydroxy ketone, the above infrared data suggest that the hydroxyl is in an axial orientation with respect to the carbonyl group because of the lack of hydrogen bonding between the two functions (77).

Anal. Calcd. for $\text{C}_{26}\text{H}_{30}\text{O}_4$: C, 76.82; H, 7.44.

Found : C, 76.78; H, 7.46.

Infrared: $\bar{\nu}$ CHCl_3 max 3595 cm^{-1} (hydroxyl); 2.0 mm. cell;
1710 cm^{-1} (carbonyl).

n.m.r. of Hydroxy Ketone P-5b.

δ CDCl_3	0.80 p.p.m. (s), (C-14 methyl);
δ TMS	1.23 p.p.m. (s), (C-9 methyl);
	3.77 p.p.m. (s), (methoxy methyls);
	6.65 p.p.m. multiplet, (C-1, C-19 aromatic hydrogens);
	7.07 p.p.m. (d), $J=9.0$ c.p.s., (C-1 aromatic hydrogen);
	7.50 p.p.m. (d), $J=8.0$ c.p.s., (C-19 aromatic hydrogen).

Base Equilibration of Epimeric Ketones (P-4) and (P-5a).-

A solution of 173 mg. (0.44 mmole) of an epimeric mixture of pentacyclic ketones (band B) in 4.0 ml. of methanol and 4.0 ml. of dry tetrahydrofuran was stirred under a nitrogen atmosphere in the presence of 2.5 mg. (0.046 mmole) of sodium methoxide for a 24-hr. period. The reaction was diluted to 200 ml. with benzene, and the solution was extracted with water 3 times then with brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was heated at 50° in a vacuum (0.1 mm.) for 2 hrs. to remove all volatile material. The equilibrium concentration of the two epimeric ketones, as determined by n.m.r. spectroscopy, was approximately 19 to 1 in favor of the *cis*-fused pentacyclic ketone P-4.

A pure sample of *cis*-ketone P-4, obtained by several crystallizations of the equilibrated mixture from acetone-hexane, gave a constant melting range, 158-160°.

Anal. Calcd. for C₂₆H₃₀O₃: C, 79.97; H, 7.74.

Found : C, 80.08; H, 7.67.

Infrared: $\bar{\nu}_{\text{max}}$ CHCl₃ 1690 cm.⁻¹(s), (carbonyl).

Cis-Pentacyclic Ketone P-4.

n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$ 1.12 p.p.m. (s), (C-14 methyl);
1.30 p.p.m. (s), (C-9 methyl);
3.44 p.p.m. (s), (C-13 hydrogen);
3.70 p.p.m. (s), (2 methoxyls).

Mass Spectrum: m/e 390, 375, 241, 173.

Trans-Pentacyclic Ketone P-5b.

n.m.r.: $\delta_{\text{TMS}}^{\text{CDCl}_3}$ 0.809 p.p.m. (s), (C-14 methyl);
1.28 p.p.m. (C-9 methyl);
3.76 p.p.m. (s), (methoxyls).

The above n.m.r. data were deduced from the spectrum of the *cis-trans* mixture before equilibration to the more stable *cis* isomer. The relative concentrations of the two isomeric ketones may be easily determined by comparing the relative areas of the C-14 methyl resonances of the two compounds.

Methylation of Pentacyclic Ketone (P-4)..- To a solution of 174 mg. (0.446 mmole) of ketone P-4 in 25 ml. of dry benzene under a nitrogen atmosphere was added 2.0 ml. of 0.856 N potassium t-butoxide in t-butanol. The reaction was stirred at room temperature for 0.5 hr., and 0.21 ml. (3.4 mmoles) of methyl iodide was added *via* a syringe. The solution was allowed to stir at room temperature for 16 hrs. under a nitrogen atmosphere, diluted with 150 ml. of ether, and extracted with water. The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the solvent at reduced pressure afforded a colorless oil which was chromatographed on a 2 mm. silica gel plate, (20x20 cm.). Two successive elutions with 12% ether-benzene separated the product mixture into 3 bands. Band A, R_f 0.78, was shown to be the O-methylated product P-6. Trituration of this material with cold ether afforded 29 mg. (16.1%) of a

colorless solid, m.p. 157-160°. Recrystallization from ethanol gave material of analytical purity, m.p. 159.5-161°.

Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97.

Found : C, 80.26; H, 7.97.

Infrared: $\bar{\nu}$ nujol max 1638 (s), 1610 (s), 1500 (s) cm^{-1} .

n.m.r.: δ $CDCl_3$ TMS

- 0.925 p.p.m. (s), (C-14 methyl);
- 1.38 p.p.m. (s), (C-9 methyl);
- 3.47 p.p.m. (s), (C-12 methoxyl);
- 3.78 p.p.m. (s), (2 methoxy methyls);
- 6.65 p.p.m. multiplet, (C-4 and C-22 aromatic hydrogens);
- 7.27 p.p.m. (d), $J=8.0$ c.p.s., (C-1 aromatic hydrogen);
- 7.84 p.p.m. (d), $J=8.5$ c.p.s., (C-19 aromatic hydrogen).

Band B, R_f 0.52, was isolated as a semicrystalline solid, 29 mg. This material was shown by n.m.r. to be a mixture of the *trans*-methylated ketone IIa (75%) and unalkylated ketone P-4 (25%). Two crystallizations from ethanol afforded a pure sample of the *trans*-methylated ketone IIa as colorless prisms, m.p. 182-184°.

Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97.

Found : C, 80.35; H, 7.97.

Infrared: $\bar{\nu}$ nujol max 1705 cm^{-1} (carbonyl); 1615, 1500, 1240 cm^{-1} (aromatics); 1035 cm^{-1} (methoxyphenyl).

n.m.r.: (run on band B)

δ $CDCl_3$ TMS

- 0.825 p.p.m. (s), (C-14 methyl);
- 1.230 p.p.m. (s), (C-9 methyl);
- 1.44 p.p.m. (s), (C-13 methyl).

$\delta_{\text{TMS}}^{\text{C}_6\text{H}_6}$	0.783 p.p.m. (s), (C-14 methyl);
	1.127 p.p.m. (s), (C-9 methyl);
	1.370 p.p.m. (s), (C-13 methyl).

<u>Mass Spectrum:</u>	m/e 404, 389, 361, 347, 201, 187, 173.
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Band C, R_f 0.34, was isolated as a crystalline solid that melted over a broad range, m.p. 180-203°. Two crystallizations from ethanol-benzene afforded 300 mg. of a crystalline solid, m.p. 201.5-204.5°. This material was shown to be the *trans-anti-trans*-hydroxy ketone P-5b which was isolated previously during the epoxidation of olefin P-3. This substance was never encountered again in subsequent alkylations, and its presence had to be explained by oxidation of the enolate by oxygen.

The Effect of Solvent on the Alkylation of Pentacyclic Ketone (P-4).-

A. t-Butanol.- Potassium metal, 117 mg. (3.0 mmoles), was dissolved in 13 ml. of dry t-butanol under a nitrogen atmosphere. A solution of 50.0 mg. (0.13 mmole) of ketone P-4 in 2.0 ml. of dry benzene was added, and the reaction was allowed to stir 0.5 hr. Methyl iodide, 1.0 ml., was added, and the solution was allowed to stand at room temperature for 20 hrs. An additional 3 ml. of methyl iodide was then added, and the whole was refluxed for 1 hr., diluted with 150 ml. of benzene, and extracted with a solution of sodium thiosulfate. The organic layer was washed several times with water and dried over sodium sulfate. Removal of the

solvent at reduced pressure yielded a colorless oil which was heated (50°) under high vacuum (0.05 mm.) for 2 hrs. to remove all volatile material. The product mixture was analyzed by n.m.r. by comparing the relative areas of the C-14 methyl resonances of the three components.

<u>C-14 Methyl Resonance</u>	<u>Component</u>	
1.12 p.p.m.	unalkylated ketone <u>P-4</u>	42%
0.925 p.p.m.	enol ether <u>P-6</u>	36%
0.825 p.p.m.	<i>trans</i> -methylated ketone <u>IIa</u>	22%

B. Benzene.- To a slurry of 15 ml. of dry benzene, 170 mg. (1.52 mmoles) of potassium t-butoxide (M.S.A. Research Corp.) and 1.52 mmoles of t-butanol was added 50 mg. (0.13 mmole) of pentacyclic ketone P-4 in 2 ml. of benzene under a nitrogen atmosphere. The reaction was allowed to stir for 0.5 hr. at 25° and 1.0 ml. of methyl iodide was added. The alkylation was stirred at room temperature for 20 hrs.; 3.0 ml. of methyl iodide was added, and the reaction was refluxed for 1 hr. The products were isolated and analyzed in the manner described in part A.

<i>cis</i> -unalkylated ketone <u>P-4</u>	21%
enol ether <u>P-6</u>	60%
<i>trans</i> -methylated ketone <u>IIa</u>	17%

A careful examination of the n.m.r. spectra of these product mixtures confirmed the existence of no *cis*-alkylated ketone.

3,21-Dimethoxy-9 β ,14 β -dimethyl-6,7,8 α ,9,11,12,13 β ,14,15,16-decahydropicene (XXXIV).- To a solution of 50 ml. of dry

tetrahydrofuran and 250 ml. of anhydrous liquid ammonia was added 650 mg. of potassium metal; 15 min. were allowed for the metal to dissolve. A solution of 300 mg. (0.80 mmole) of pentacyclic olefin P-3 in 25 ml. of tetrahydrofuran was added dropwise with stirring to the metal-ammonia solution over a 15-min. period. The reaction was allowed to stir for 1.5 hrs. The excess potassium was destroyed with solid ammonium chloride, and the ammonia was allowed to evaporate overnight. The residue was diluted with 250 ml. of water, and the aqueous solution was extracted with 150-ml. portions of 1:1 ether-benzene. The organic layer was washed with four 100-ml. portions of water, then brine, and dried over sodium sulfate. Removal of the solvent under reduced pressure yielded a crystalline residue. Gas chromatographic analysis of the crude product showed the presence of two products which were formed in 76.5% and 21.2% yields. The absence of any unreduced olefin was verified by adding some olefin to the product mixture and analyzing the mixture by v.p.c. The major *trans-anti-cis* hydrocarbon XXXIV was isolated by fractional crystallization from ethanol as colorless crystals, m.p. 160-161.5°.

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57.

Found : C, 83.09; H, 8.65.

Infrared: $\bar{\nu}$ $CHCl_3$ max 1610 $cm.^{-1}(m)$, 1500 $cm.^{-1}(s)$,
1260 $cm.^{-1}(m)$, 1035 $cm.^{-1}(m)$.

n.m.r.: δ CDCl_3
 TMS

0.633 p.p.m. (s), (C-14 methyl);
 1.22 p.p.m. (s), (C-9 methyl);
 3.76 p.p.m. (s), (methoxy methyls);
 6.65 p.p.m. multiplet, (C-1 and
 C-22 aromatic hydrogens);
 7.15 p.p.m. (d), $J=8.5$ c.p.s.,
 (C-19 aromatic hydrogen);
 7.24 p.p.m. (d), $J=8.5$ c.p.s., (C-1
 aromatic hydrogen).

Hydrogenation of Pentacyclic Olefin (P-3).— A solution of 100 mg. (0.267 mmole) of olefin P-3 in 80 ml. of 1:1 acetic acid-tetrahydrofuran was prepared by gentle warming. This solution was stirred at 25° under one atmosphere of hydrogen in the presence of 100 mg. of 10% palladium-on-charcoal for 8 hrs. The catalyst was filtered, and the filtrate was concentrated *in vacuo*. This residue was dissolved in 200 ml. of benzene and extracted with 50 ml. of 10% potassium carbonate then with water until neutral. The solution was washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* yielded a white crystalline product. Recrystallization from ethanol afforded 75 mg. (75%) of colorless prisms, m.p. 155-158°. A second crystallization from ethanol-acetone yielded material, m.p. 160-161.5°, which was shown to be identical with the major isomer XXXIV obtained in the Birch reduction of pentacyclic olefin P-3.

2 β -Hydroxy-1 β ,4 $\alpha\beta$ -dimethyl-7-methoxy-1,2,3,4,4 α ,9,10,10 $\alpha\alpha$ -octahydro-1-phenanthreneacetophenone (Q-1).— A solution of 200 mg. (0.63 mmole) of hydroxy acid K-4 in 10 ml. of dry

dimethoxyethane (distilled from lithium aluminum hydride) was cooled to 0° under a nitrogen atmosphere. A solution of 2.0 ml. of 2.14 M phenyllithium (Alpha Inorganics, Inc.) was slowly added *via* a syringe over a 5-min. period. The reaction was stirred at 0° for 4 hrs. and quenched by pouring into 100 ml. of water. The aqueous solution was extracted with 200 ml. of 1:1 ether-benzene, and the organic layer was washed with 50 ml. of saturated sodium bicarbonate, then with water until neutral. The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave a pale yellow semicrystalline residue which was chromatographed on 50 g. of silica gel. The desired hydroxy ketone Q-1 was eluted with 30% ether-benzene. The combined column fractions, on trituration with cold ether, yielded 151 mg. (63%) of colorless crystals, m.p. 140-145°. A small sample recrystallized once from ethanol for analysis melted from 146.5-147.5°.

Anal. Calcd. for C₂₅H₃₀O₃: C, 79.33; H, 7.99

Found : C, 79.30; H, 7.98.

<u>Infrared:</u>	$\bar{\nu}$ CHCl ₃ max	3590 cm. ⁻¹ , 3350 cm. ⁻¹ , (hydroxyl); 1665 cm. ⁻¹ (s), (phenyl ketone); 1605 cm. ⁻¹ (s), 1575 cm. ⁻¹ (m), 1490 cm. ⁻¹ (s), (aromatics); 1030 cm. ⁻¹ (s), (methoxyphenyl).
<u>n.m.r.:</u>	δ CDCl ₃ TMS	1.03 p.p.m. (s), (C-1 methyl); 1.18 p.p.m. (s), (C-4a methyl); 3.74 p.p.m. (s), (methoxyl); 3.12 p.p.m. AB quartet, J=14 c.p.s., (methylene α to ketone).

3,4,4a,9,10aa-Hexahydro-7-methoxy-1a-(2-phenylethyl)-1β,4aβ-dimethyl-2(1H)-phenanthrone (Q-3). - A solution of 979 mg. (2.58 mmoles) of hydroxy ketone Q-1 in 150 ml. of methanol and 0.5 ml. of perchloric acid was stirred under one atmosphere of hydrogen in the presence of 105 mg. of 10% palladium-on-charcoal. After 1 hr. the theoretical amount of hydrogen had been consumed. The catalyst was filtered, and the filtrate was taken up in 450 ml. of benzene. The solution was extracted with 100 ml. of saturated sodium bicarbonate solution, then with four 100-ml. portions of water. The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* yielded the alcohol P-2 as a pale yellow oil. This substance, showing no infrared absorption at 1665 cm^{-1} , was oxidized without purification to the desired ketone Q-3.

The crude alcohol Q-2 was dissolved in 50 ml. of acetone and treated with 1.0 ml. of 8 N chromium trioxide in sulfuric acid at 0° for 0.5 hr. The product was isolated in the usual manner and purified by chromatography on 60 g. of alumina (Merck). The desired ketone Q-3 was eluted with 1:1 benzene-ligroin as a low melting solid, 835 mg. (91.5%). Gas chromatographic analysis of this material indicated that it was a single isomerically pure compound of greater than 99.8% purity. A small sample, evaporatively distilled for analysis, boiled at 205°/ 0.005 mm.

Anal. Calcd. for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34.

Found : C, 82.87; H, 8.27.

Infrared: $\bar{\nu}$ $CHCl_3$ max 1700 $cm.^{-1}$ (s),(carbonyl);
1610 $cm.^{-1}$ (s),1500 $cm.^{-1}$ (s),
(aromatics);
1035 $cm.^{-1}$ (m),(methoxyphenyl).

n.m.r.: δ $CDCl_3$ TMS 1.17 p.p.m. (s),(C-1 methyl);
1.25 p.p.m. (s),(C-4a methyl);
3.77 p.p.m. (s),(methoxy methyls).

Treatment of this ketone with liquid hydrogen fluoride led to the recovery of about 80% of the ketone. No other single well defined cyclization product was produced. Gas chromatographic analysis indicated the presence of at least 5 products.

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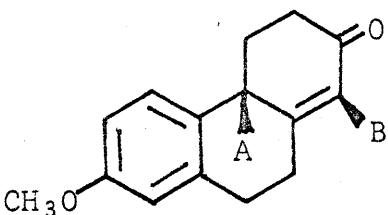
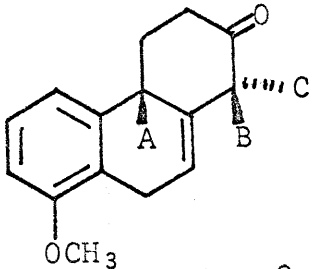
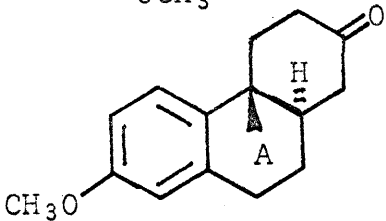
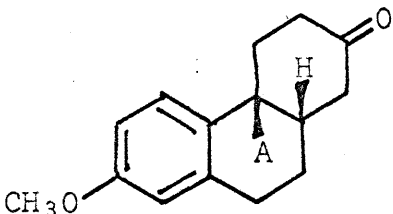
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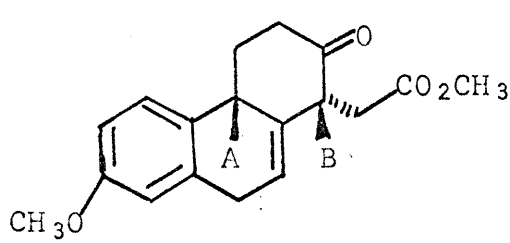
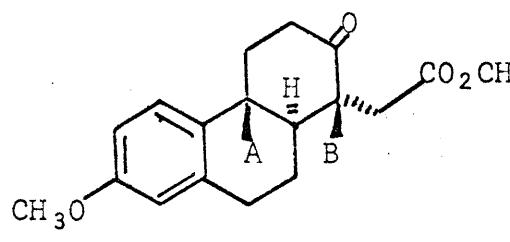
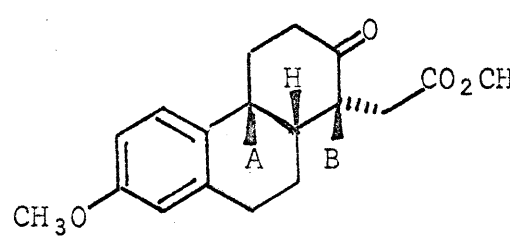
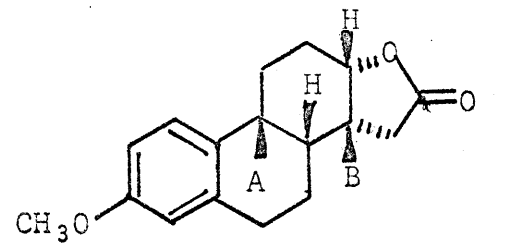
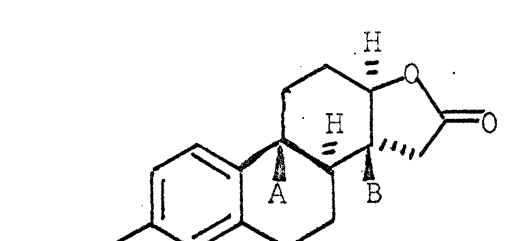
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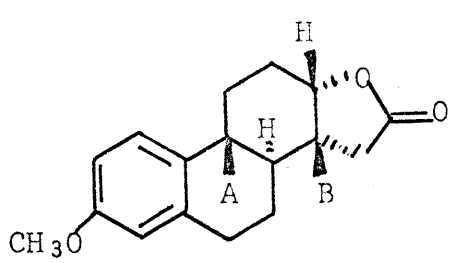
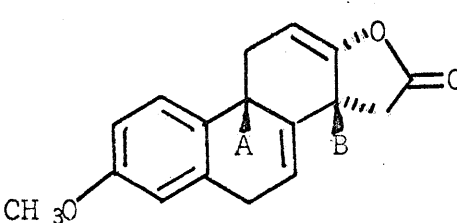
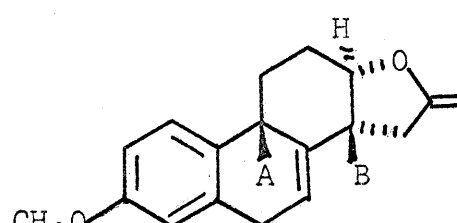
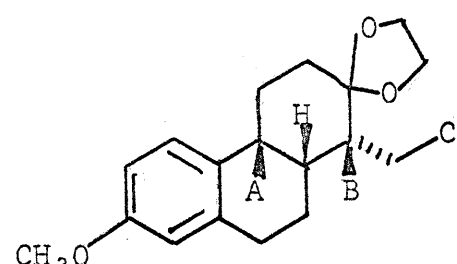
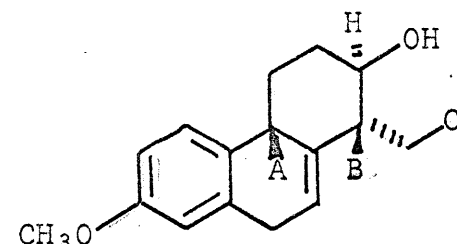
APPENDIX

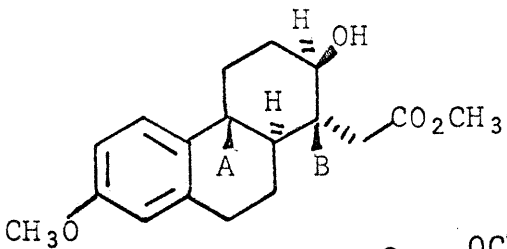
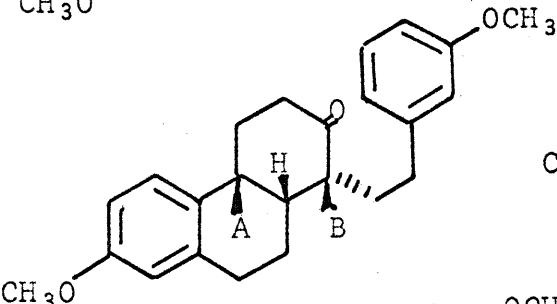
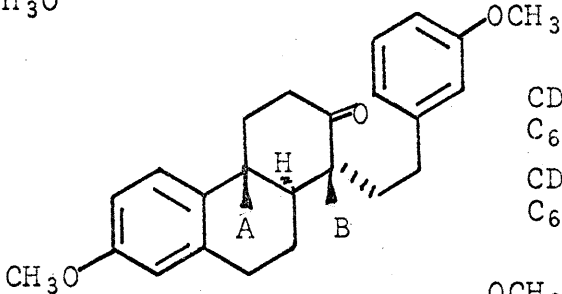
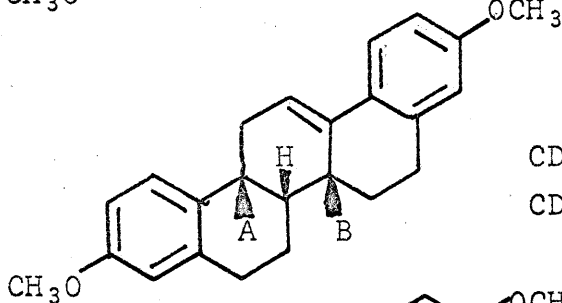
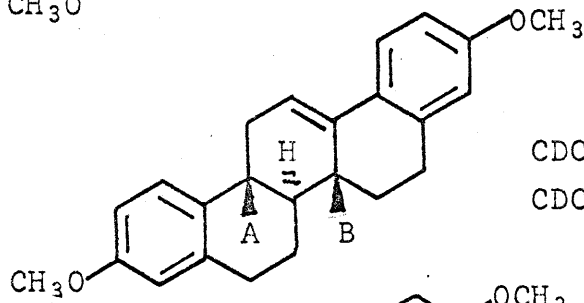
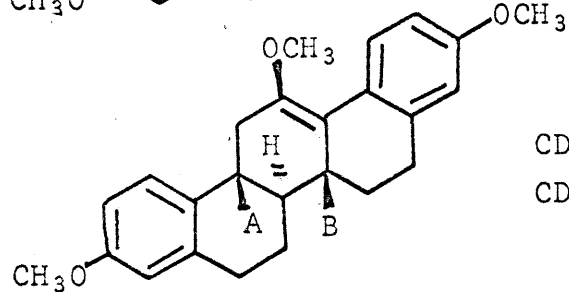
Angular Methyl PMR Frequencies of Some Synthetic Intermediates

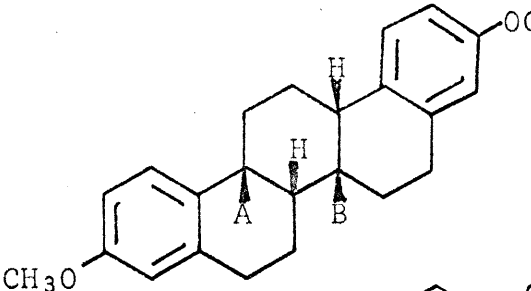
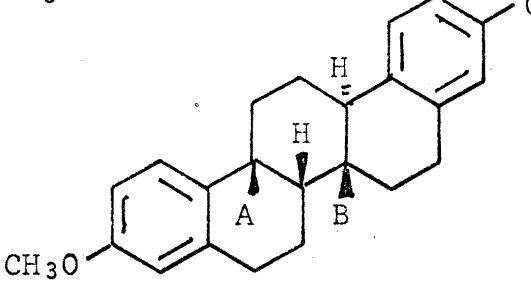
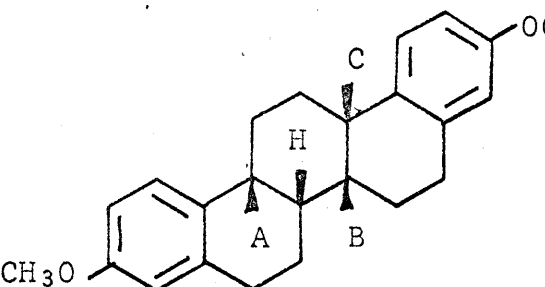
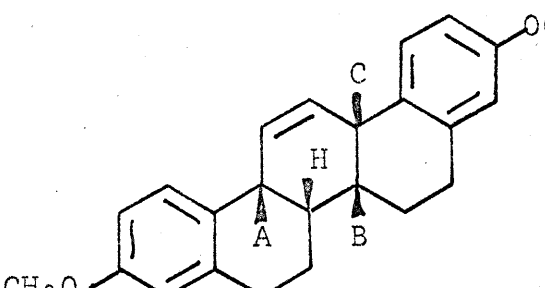
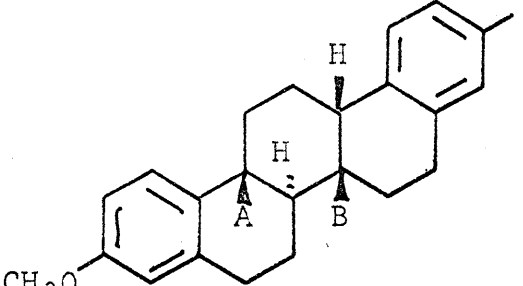
All chemical shifts (δ) reported in this appendix are listed in cycles per second from tetramethylsilane. All solvent-induced shifts (Δ) are reported in cycles per second. A positive Δ -value denotes an upfield solvent-induced shift. Sample concentrations are approximately 10% W/V.

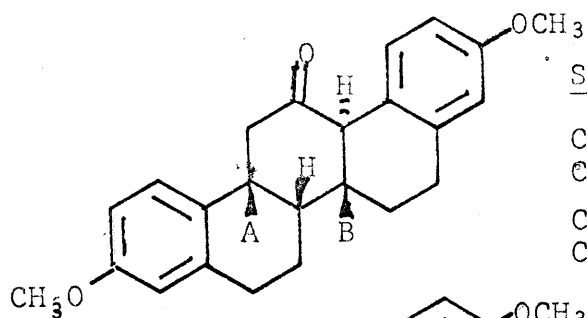
	<u>Solvent</u>	<u>Methyl</u>	<u>δc.p.s.</u>	<u>Δc.p.s.</u>
	CDCl ₃	A	91	
		B	112	
	CDCl ₃	A	82.0	+13.8
	C ₆ H ₆	A	69.2	
	CDCl ₃	B	71.0	+ 6.5
	C ₆ H ₆	B	64.5	
	CDCl ₃	C	77.0	- 6.0
	C ₆ H ₆	C	83.0	
	CDCl ₃	A	73.8	+16.8
	C ₆ H ₆	A	57.0	
	CDCl ₃	A	81.0	

	<u>Solvent</u>	<u>Methyl</u>	<u>δc.p.s.</u>	<u>Δc.p.s.</u>
	CDCl ₃	A	82.5	+15.2
	C ₆ H ₆	A	67.3	
	CDCl ₃	B	79.0	+ 5.4
	C ₆ H ₆	B	73.6	
	CDCl ₃	A	78.0	+14.7
	C ₆ H ₆	A	63.3	
	CDCl ₃	B	67.0	+11.3
	C ₆ H ₆	B	55.7	
	CDCl ₃	A	72.0	+13.0
	C ₆ H ₆	A	59.0	
	CDCl ₃	B	72.0	- 4.0
	C ₆ H ₆	B	76.0	
	CDCl ₃	A,B	72.0	
	CDCl ₃	A	73.5	
	CDCl ₃	B	65.0	

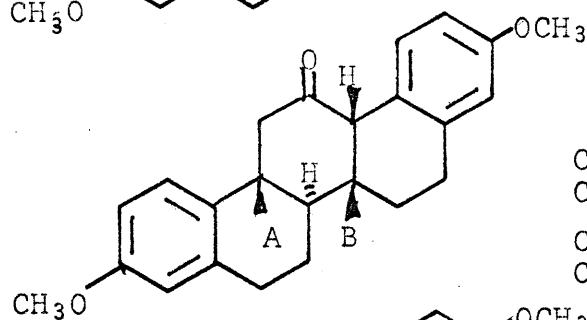
	<u>Solvent</u>	<u>Methyl</u>	<u>δc.p.s.</u>	<u>Δc.p.s.</u>
	CDCl ₃	A	61.0	
	CDCl ₃	B	61.5	
	CDCl ₃	A,B	91.5	
	CDCl ₃	A	84.0	
	CDCl ₃	B	79.5	
	CDCl ₃	A,B	79.5	
	CDCl ₃	A,B	76.0	

	<u>Solvent</u>	<u>Methyl</u>	<u>δc.p.s.</u>	<u>Δc.p.s.</u>
	CDCl ₃	A	71.5	
	CDCl ₃	B	58.5	
	CDCl ₃	A,B	73.0	
	CDCl ₃	A	75.0	+11.5
	C ₆ H ₆	A	64	
	CDCl ₃	B	69.5	+ 7.0
	C ₆ H ₆	B	62.5	
	CDCl ₃	A	86.5	
	CDCl ₃	B	69.0	
	CDCl ₃	A	79.5	
	CDCl ₃	B	60.0	
	CDCl ₃	A	83.0	
	CDCl ₃	B	55.5	

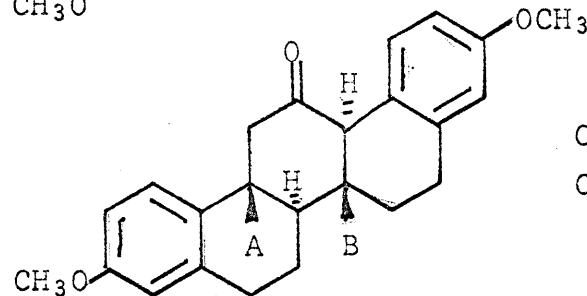
	<u>Solvent</u>	<u>Methyl</u>	<u>δc.p.s.</u>	<u>Δc.p.s.</u>
	CDCl ₃	A	69.0	
	CDCl ₃	B	56.0	
	CDCl ₃	A	92.0	
	CDCl ₃	B	63.0	
	CDCl ₃	A	69.5	
	CDCl ₃	B	53.0	
	CDCl ₃	C	82.5	
	CDCl ₃	A	77.0	
	CDCl ₃	B	55.5	
	CDCl ₃	C	83.0	
	CDCl ₃	A	73.0	
	CDCl ₃	B	38.0	



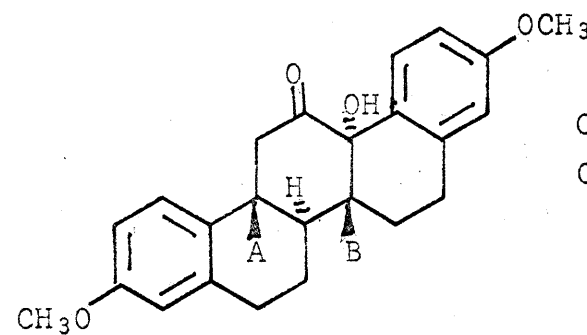
<u>Solvent</u>	<u>Methyl</u>	<u>δc.p.s.</u>	<u>Δc.p.s.</u>
CDCl ₃	A	80.0	+10.5
C ₆ H ₆	A	69.5	
CDCl ₃	B	66.0	+11.5
C ₆ H ₆	B	54.5	



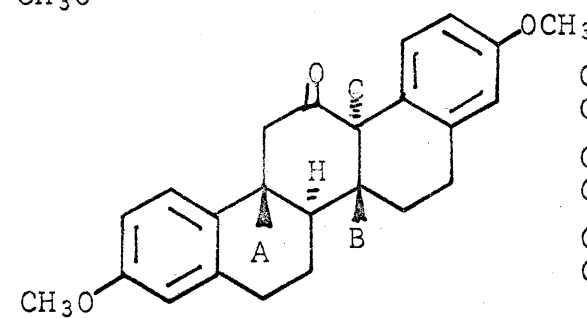
CDCl ₃	A	77.0	+ 2.5
C ₆ H ₆	A	74.5	
CDCl ₃	B	66.5	+ 8.5
C ₆ H ₆	B	58.0	



CDCl ₃	A	77.0	
CDCl ₃	B	48.5	

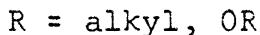


CDCl ₃	A	74.0	
CDCl ₃	B	48.0	

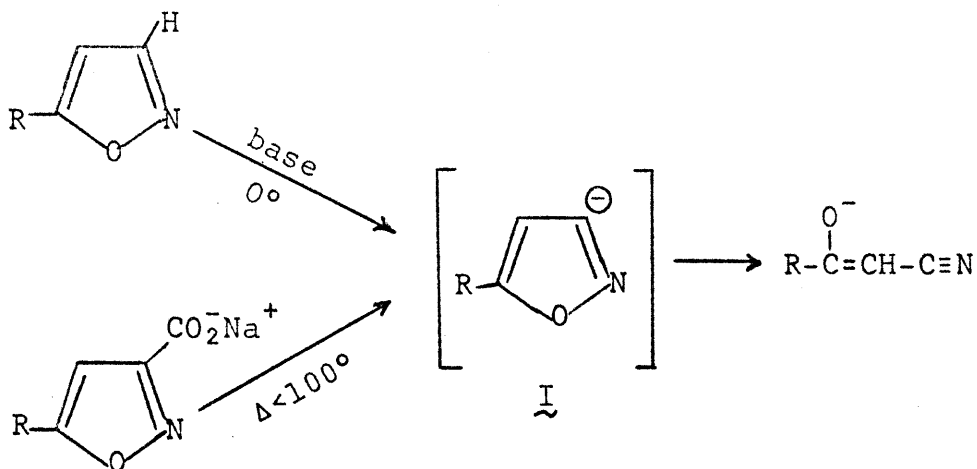


CDCl ₃	A	74.0	+ 6.5
C ₆ H ₆	A	67.5	
CDCl ₃	B	49.5	+ 2.5
C ₆ H ₆	B	47.0	
CDCl ₃	C	86.5	+ 4.5
C ₆ H ₆	C	82.0	

Chart A



The impetus for this proposal arose from a consideration of the mild basic cleavage of isoxazoles unsubstituted in the 3-position (1,2). This basic cleavage of the isoxazole ring may be extended to those 3-substituted derivatives which will readily give the anion, I on base treatment. Thus, the sodium salts of the 5-alkylisoxazole-3-carboxylic acids on mild thermolysis readily undergo decarboxylation followed by ring cleavage (3,4).

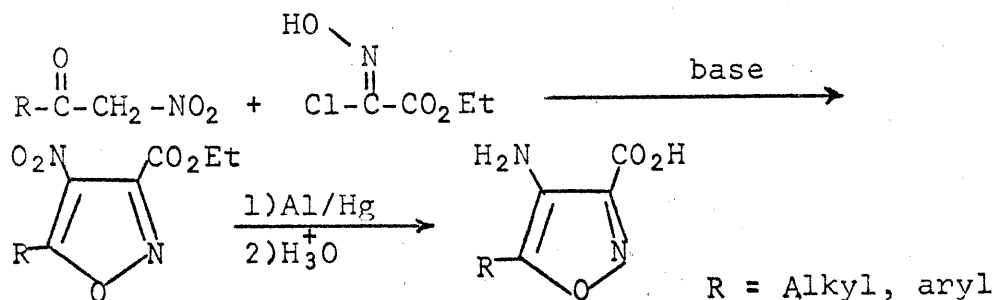


If one could couple this facile decarboxylative-ring-opening reaction with the elimination of nitrogen from the 4-position of the isoxazole ring, one could obtain a variety of functionalized methylenes under mild conditions.

Various isoxazolediazonium salts have been reported in the literature (5,6), and their stability is comparable to the benzenediazonium salts.

A literature survey indicates that no 5-alkyl-4-aminoisoxazole-2-carboxylic acids have been reported. However, the synthesis of such compounds appears to be relatively straightforward as shown in Chart B.

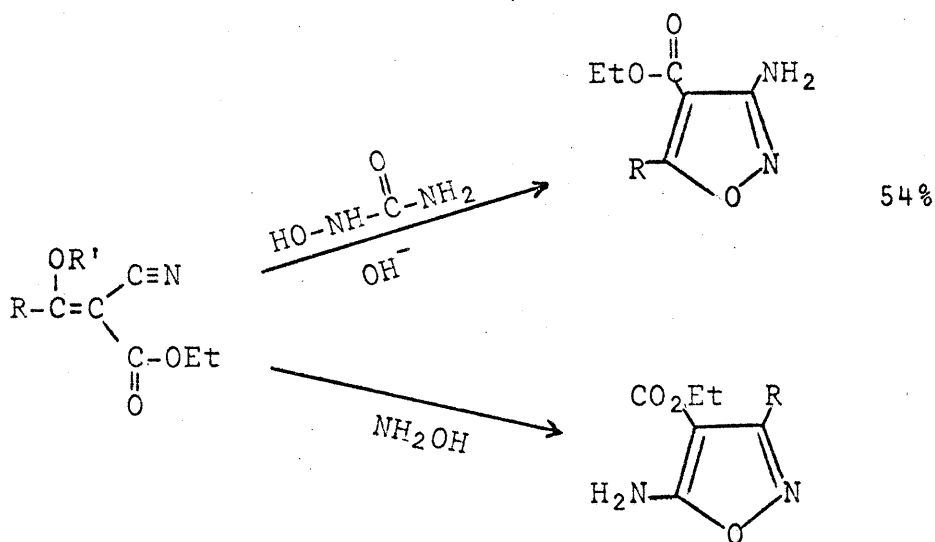
Chart B



Ethyl chlorooximinoacetate (7) has been shown to react in good yields with a variety of active methylenes in the illustrated manner (8).

The isomeric 5-alkyl-3-aminoisoxazole-4-carboxylic acids have recently been prepared by Kloetzer (9) in a rather novel fashion. His general scheme is outlined in Chart C.

Chart C



The use of N-hydroxylurea rather than the more commonly used hydroxylamine in isoxazole syntheses of this type allows one to completely reverse the order of the bond forming steps. As indicated by Kloetzer (9), the course of the addition of N-hydroxylurea is dictated by steric factors rather than by other chemical considerations.

Thermolysis of the 5-substituted isoxazolediazonium-3-carboxylates could proceed *via* two pathways (see Chart A). In path a, ring opening could accompany loss of nitrogen

and carbon dioxide without the intervention of an aryne species. Alternatively, decomposition *via* path b could generate the $\Delta^{2,3}$ -isoxazyne species. On the other hand, the 5-substituted isoxazolediazonium-4-carboxylates appear to have only one choice, and that is decomposition to the isoxazyne. The possibility now arises that if the divalent species were of lower energy than the aryne, one of the modes of decomposition of the aryne would be through ring opening to the neutral methylene. Although hetarynes of the type under discussion have never been prepared (10,11), there is some evidence which suggests that the derived methylenes may be slightly "cooler" species than the hetaryne itself.

Chart D


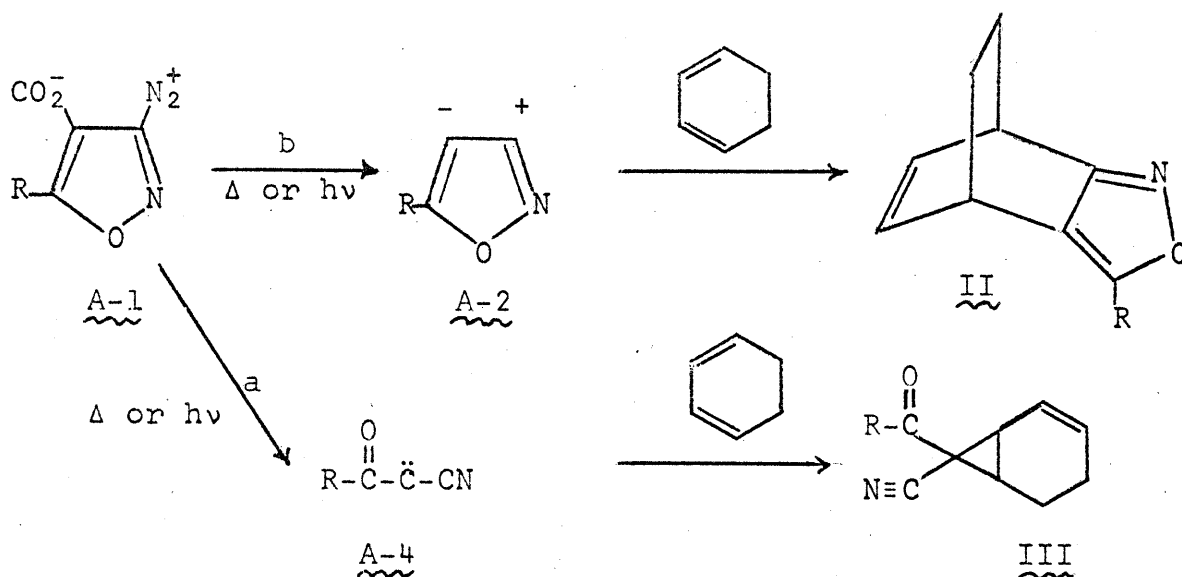
<u>Species</u>	<u>t 1/2(gas phase)(15)</u>	<u>Reference</u>
:CF ₂	2.0·10 ⁻² sec.	12
:CH ₂	1.5·10 ⁻³ sec.	13
	~10 ⁻⁴ sec.	14

Chart D lists the gas phase half-lives of benzyne and the two extreme cases of singlet methylenes. The acylcyano-methylenes may be expected to be "cooler" species than methylene itself (15), and its gas phase half-life may even approach that of the difluoro-carbene. On the other hand, due to the high degree of bond fixation in the isoxazole ring the $\Delta^{2,3}$ -isoxazyne should be more reactive

than benzyne. Although the analogies are tenuous, it is still probable that the divalent species, being of lower energy, could intervene in the decay of the isoxazyne.

A study of the products which may arise from the decomposition of the 5-alkylisoxazolediazonium-4-carboxylate in the presence of cyclohexadiene should allow one to distinguish between the various modes of decomposition.



Of the two diazonium carboxylates under discussion, it is assumed that A-1 will be less likely to undergo direct decomposition by path a to the methylene A-4. If decomposition proceeds by path b to the aryne, it is felt that if the aryne-methylene interconversion takes place at all it will be fast compared to reaction A-2 with cyclohexadiene. Therefore, if the Diels-Alder product II is observed as the only product then path b was the preferred course. If both II and III are observed in the product mixture either both

paths a and b may be taking place independently or decomposition to the aryne is occurring, and the rate of aryne-methylene interconversion is the same order of magnitude as the rates of reaction of the reactive species with cyclohexadiene. In the former case the product ratio of II to III will be independent of added cyclohexadiene while in the latter case the product ratio will be concentration dependent. If only methylene product III is observed, again the decomposition could proceed directly to the methylene species or to the aryne which undergoes ring cleavage at a rate which is much faster than the reaction of aryne with cyclohexadiene. Here one may again distinguish between the two possible paths. If the aryne does intervene then one should be able to detect this species by ultraviolet spectroscopy in a manner similar to that used by Berry and Stiles in their study of the photo-decomposition of benzene-diazonium carboxylate (16).

In contrast to the 5-alkylisoxazolediazonium-4-carboxylates (2), it is assumed that the isomeric compound A-1 should have a much greater tendency to undergo decomposition directly to the methylene species. The great instability of the 3-anions of isoxazole derivatives leads one to the conclusion that the methylene, rather than the $\Delta^{3,4}$ -isoxazyne will be the final product of the decomposition of either isoxazolediazonium carboxylate.

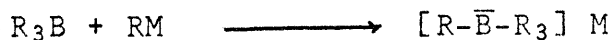
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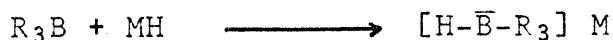
-155-
PROPOSITION II

It is proposed that the utility of alkyl borate salts as potential alkylating agents be investigated for the synthesis of five and six-membered ring systems.

In the rapidly expanding field of organoboron chemistry, relatively little attention has been given to the use of tetrasubstituted boron intermediates such as I and II for the generation of carbanions.



I

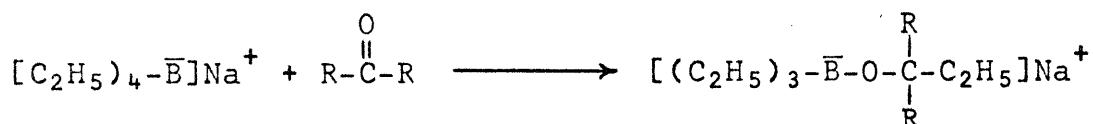


II

R, R = alkyl; M = K⁺, Li⁺, Na⁺,

Although the equilibria in these reactions strongly favor the tetracoordinate boron species (1), the alkyl groups of these salts still undergo reactions which are characteristic of carbanionic reagents. As an illustration, some of the reactions which sodium tetraethylboron has been reported to undergo are shown in Chart A. Ziegler and Hoberg (2) have reported that sodium tetraethylboron reacts with alkyl halides to give Wurtz-type coupling products at 90° in inert solvents. However, these results were only reported in a qualitative manner and no experimental results were included in the communication. Blitzner and Pearson (3) have mentioned that sodium tetraethylboron reacts with ketones to give good yields of tertiary alcohols.

Chart A



Apparently, these two communications are the only two reported examples where tetraalkylboron salts have been employed as an organometallic reagent for the synthesis of low molecular weight organic compounds. These reagents have been used mainly as catalysts for anionic polymerization reactions.

In contrast to the reactions of sodium tetraethylboron with alkyl halides and ketones, this salt is stable in aqueous solution at room temperature. The more reactive salt, lithium ethyltrimethylboron, has been reported to react slowly with water (4). The addition of mineral acids to aqueous solutions of these salts causes a rapid evolution of gas with the recovery of the trialkylboron derivative (1).

The use of tetrasubstituted boron intermediates as a means for synthesizing various cyclopropanes has been published by several workers (5,6)(Chart B).

$$\begin{array}{c} \text{R} \\ | \\ \text{CH}_2=\text{C}-\text{CH}_2-\text{Cl} \end{array} \xrightarrow{\text{B}_2\text{H}_6} \text{B}-(\text{CH}_2-\overset{\text{R}}{\underset{|}{\text{CH}}}-\text{CH}_2-\text{Cl})_3$$

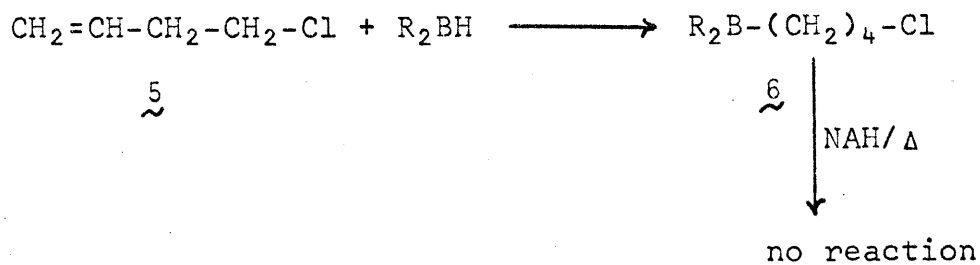
 $\downarrow \sim 1$
 $\text{H}_2\text{O}/\text{NaOH}$
 50°
 $\left[\text{HO}-\overset{\text{R}}{\underset{|}{\text{B}}}(\ominus)-\text{CH}_2-\overset{\text{R}}{\underset{|}{\text{CH}}}-\text{CH}_2-\text{Cl} \right] \xrightarrow{\sim 2} \triangle_{\text{CH}_2-\text{CH}(\text{R})-\text{CH}_2}$
$$\text{CH}_2=\text{CH}-\text{CH}_2-\text{Cl} + \text{R}_2\text{BH} \longrightarrow \text{R}_2\text{B}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Cl}$$

3

↓ NAH

cyclopropane ← $\left[\text{R}_2-\overset{\text{H}}{\underset{\ominus}{\text{B}}}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Cl} \right]$

4



This general cyclopropane synthesis was first published by Hawthorne (5). Hydroboration of 2-substituted allyl chlorides with diborane yields the tri-(γ -chloropropyl)-boranes (B-1). Treatment of these compounds with an aqueous sodium hydroxide solution affords good yields of substituted cyclopropane derivatives. It appears this intramolecular alkylation proceeds through the anionic intermediate B-2. The coordination of the base with the organoborane increases the carbanion-like character of the boron-carbon bond, facilitating the intramolecular displacement of the chloride ion (7). In a modification of this idea, Binger and Koster (6) treated allyl chloride with a dialkylborane. The resulting mixed trialkylborane B-3 was then heated in the presence of sodium hydride to effect ring closure. In this manner, these workers obtained very high yields of cyclopropane derivatives.

In an effort to extend this concept to the synthesis of cyclobutanes, the analogous series of reactions was carried out on 4-chloro-1-butene (B-5). However, no ring-closed products from this reaction were observed by these workers (5,6). In view of the relative difficulty with which cyclobutanes are formed by alkylation reactions (8), it is not surprising that this reaction failed to proceed in the desired manner. Although the carbon-boron bond in the boron anions B-2 and B-4 has some carbanion character,

it is not a free anion. Consequently, intramolecular ring closure would be less favorable in this case than in those cases where a resonance-stabilized carbanion intervenes during the displacement reaction to form the cyclobutane ring. On the other hand, in cases where a more favorable geometry may be achieved for intramolecular displacement, this ring-forming process should occur.

It is proposed that this general ring synthesis be reinvestigated to determine its utility for the construction of five and six-membered ring systems. To facilitate the ring closure process a more desirable leaving group than chloride ion would be advantageous. Since methane-sulfonate esters have been shown to be unaffected by diborane under normal hydroboration conditions (9), derivatives such as these should serve adequately as leaving groups. The most important fact which must be established is whether ring closure to give five and six-membered rings will take place. Once the geometrical requirements for successful intramolecular alkylation have been established, the effect of different substituents on the boron atom with respect to the rates of ring closure should be determined.

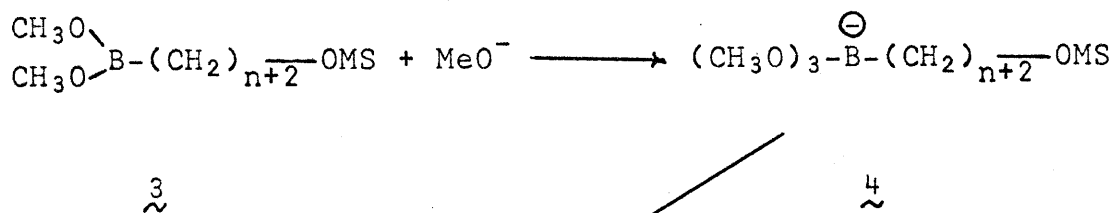
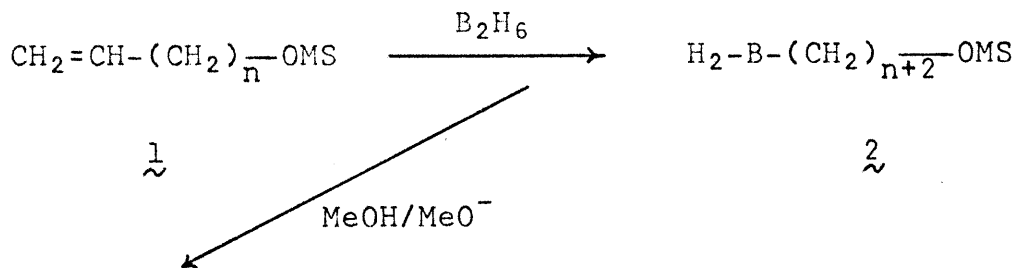
The initial experiments which should be investigated are shown in Chart C. The synthesis of the monoalkylboranes C-2 and the mixed trialkylboranes C-5 should proceed in a routine manner. Once these compounds are in hand, a number of experiments are desirable. Methanolysis of C-2 will give

the dimethylboronate C-3. The preparation of such a derivative is advantageous for several reasons. Generally, these compounds are more stable than the trialkylboranes. In addition, the oxygen atoms in the boronic ester decrease the Lewis acid acidity of this species. Therefore, the carbon-boron bond in the boron anion C-4 should be more highly polarized than in the corresponding derivatives C-6 and C-7. This factor should facilitate the ring closure step.

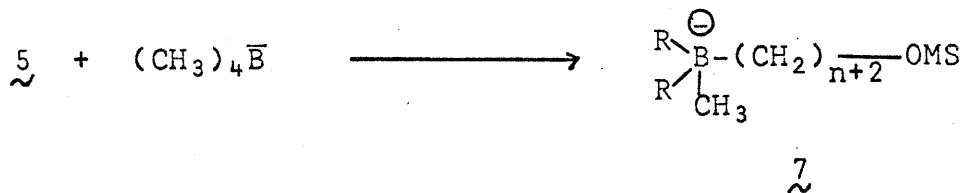
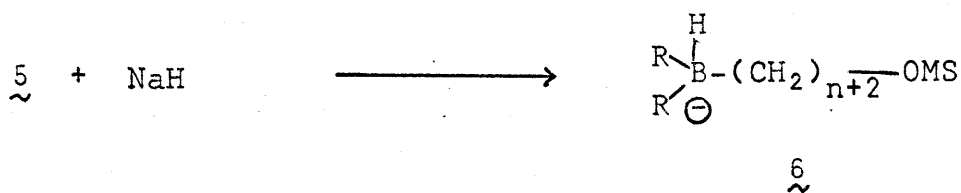
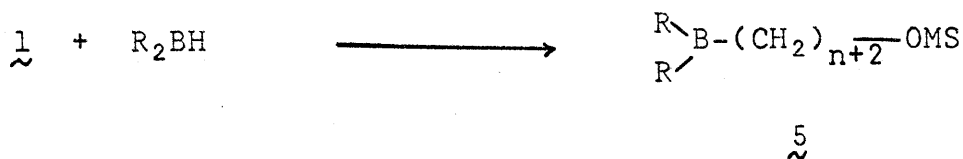
In addition to the base-catalyzed ring closure of the boronic ester C-3, the utility of both the trialkylborohydrides C-6 and the tetraalkylboron derivatives C-7 should be examined as possible carbanion precursors.

If these boron derivatives do act as intramolecular alkylating agents, it would be useful to extend this concept of generating carbanions to include other general classes of reactions such as intramolecular carbonyl addition reactions. However, due to the strong reducing power of diborane this task may not be accomplished in a direct manner. In this case, either the less reactive dialkylboranes may be used for the hydroboration step, or the carbonyl function may be protected during the hydroboration reaction. As an example of such an addition, consider the series of reactions below.

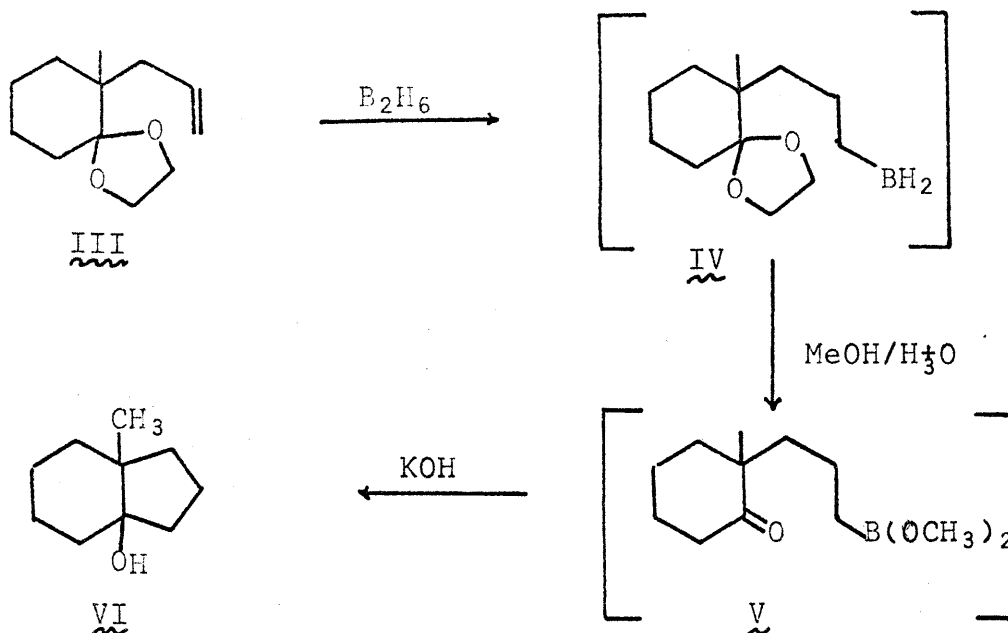
-161-
Chart C



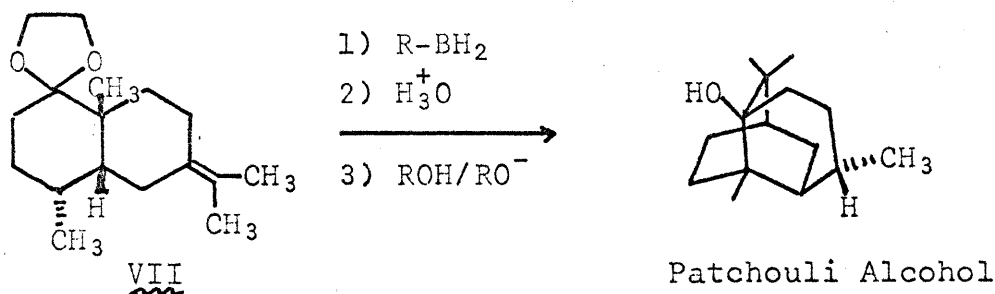
cyclic products.



$n = 3, 4.$



Hydroboration of the olefinic ketal III should proceed in a normal manner to give the organoborane IV. Treatment of the reaction mixture with aqueous methanolic acid to remove the ketal function should afford the boronic ester V. Under the mildly acidic conditions necessary to remove ethylene ketal blocking groups, both boronic esters such as V as well as mixed trialkylboranes should be stable. The addition of base should then effect ring closure to the tertiary alcohol VI. One immediate application of this sequence is the synthesis of patchouli alcohol (10) from the intermediate VII.



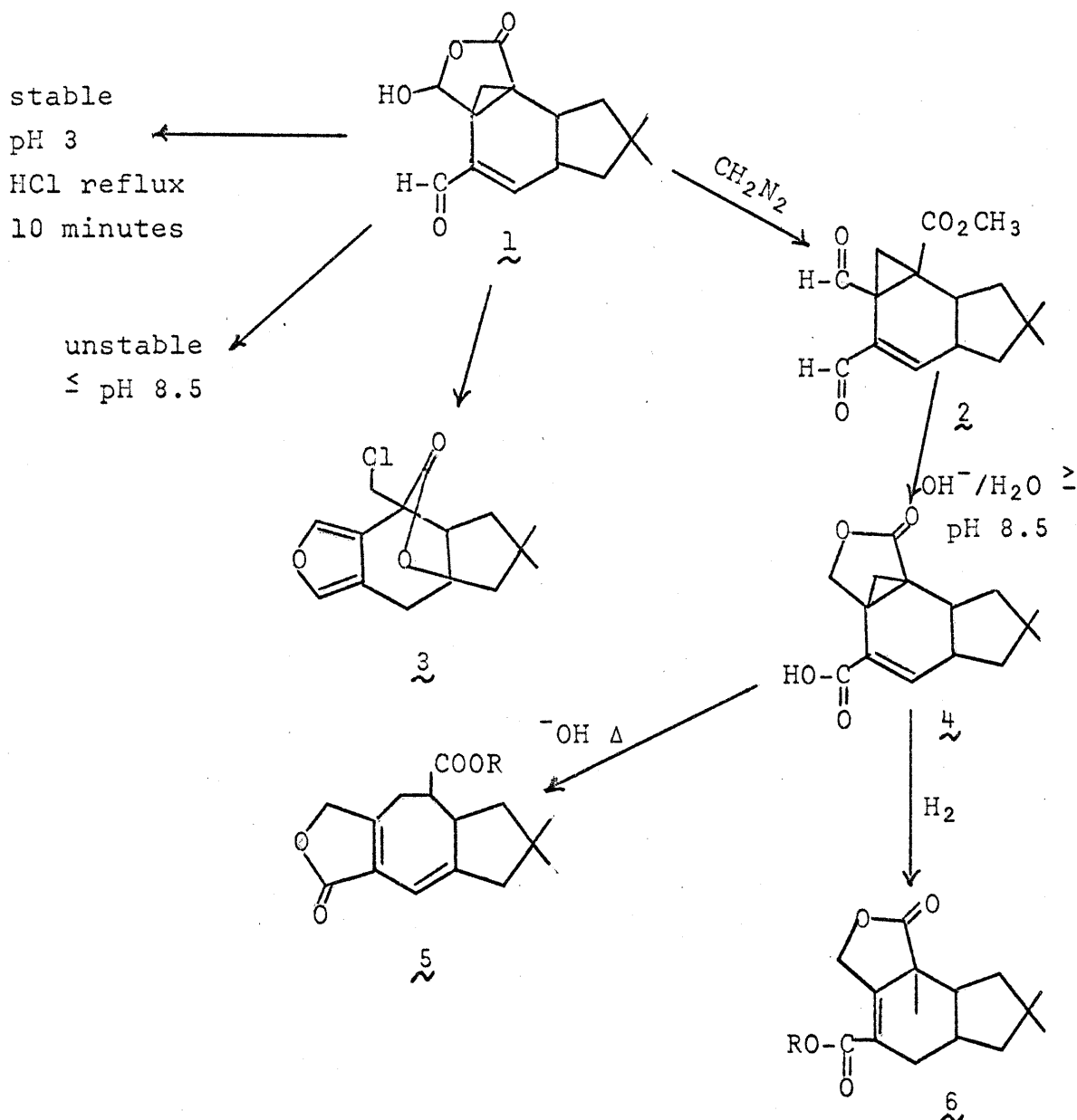
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PROPOSITION III

The probable stereochemistry of the terpenoid anti-biotic marasmic acid is proposed, and a total synthesis of this substance is outlined.

Chart A



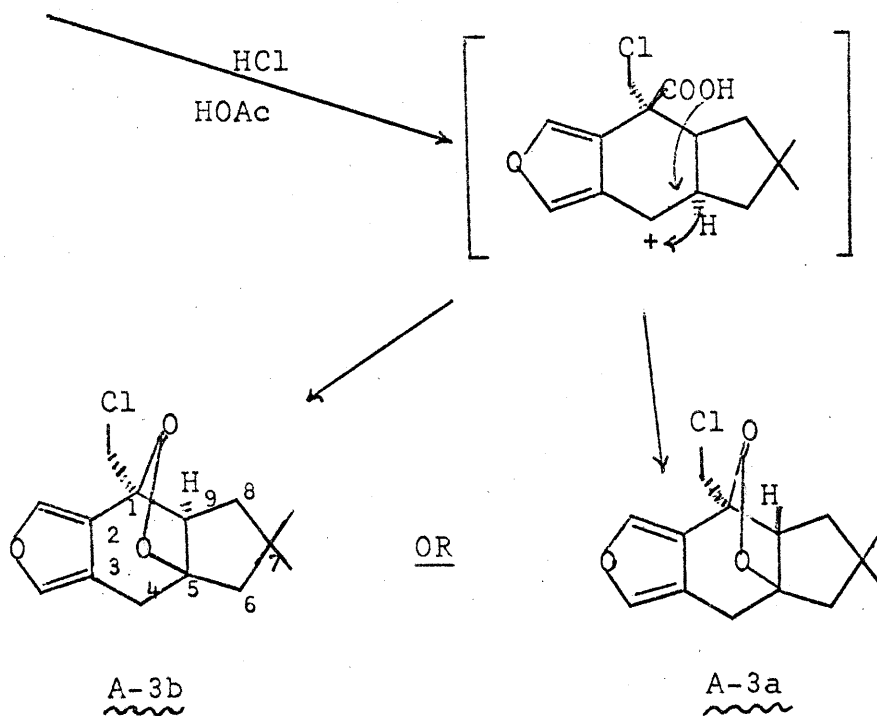
The organism *Marasmius Conigenus* has been found to retard the growth of a variety of bacteria (1). In 1949 Kavanagh and co-workers (1) isolated the substance, marasmic acid (A-1), produced by this organism. Recently the structure of this acid has been tentatively determined by P. de Mayo and co-workers (2).

Chart A outlines all of the known chemistry of marasmic acid.

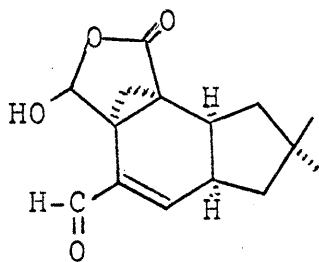
The stereochemistry of this antibiotic is proposed, and a general synthesis of the structure is outlined.

Chart B

Marasmic Acid



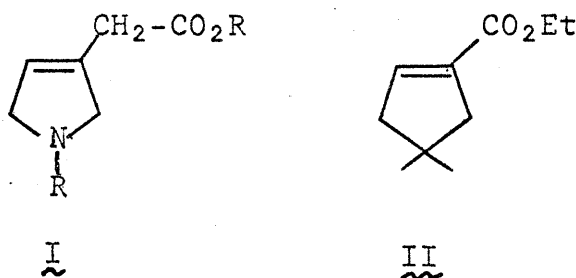
(A-1) is as shown below.



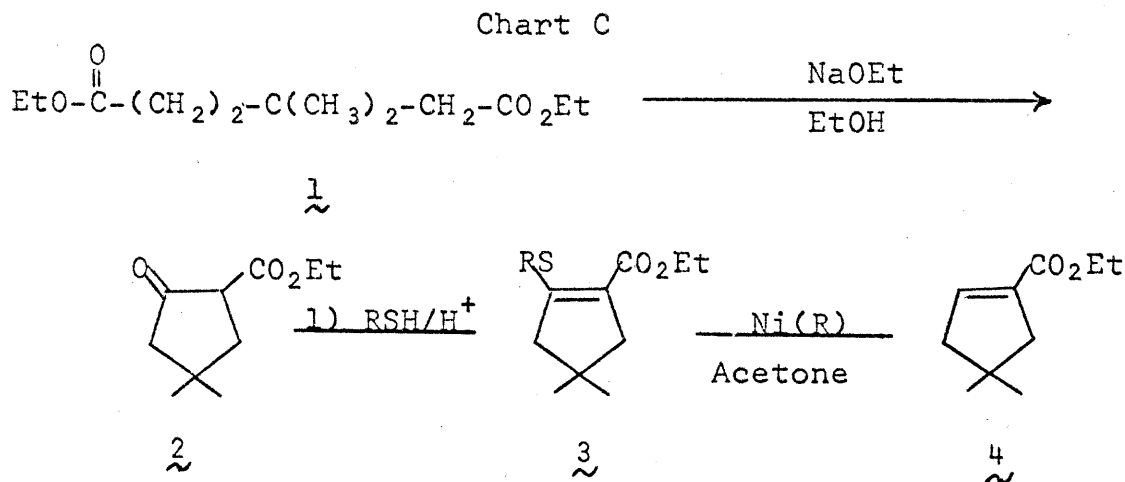
A-1

The main obstacle which must be overcome in a synthesis of a molecule such as A-1 is to control the rather odd arrangement of functionality while building up the rest of the carbocyclic structure. Construction of this system could be greatly simplified if the two aldehyde functions were concealed in an aromatic system as they are in the furanolactone A-3. A choice of heteroatoms is fairly limited. The most logical candidate is nitrogen.

Two intermediates which are required for the first stage of the synthesis are the $\Delta^{2,3}$ -pyrroline derivative I and 1-carbethoxy-4,4-dimethylcyclopentene-1, (II).

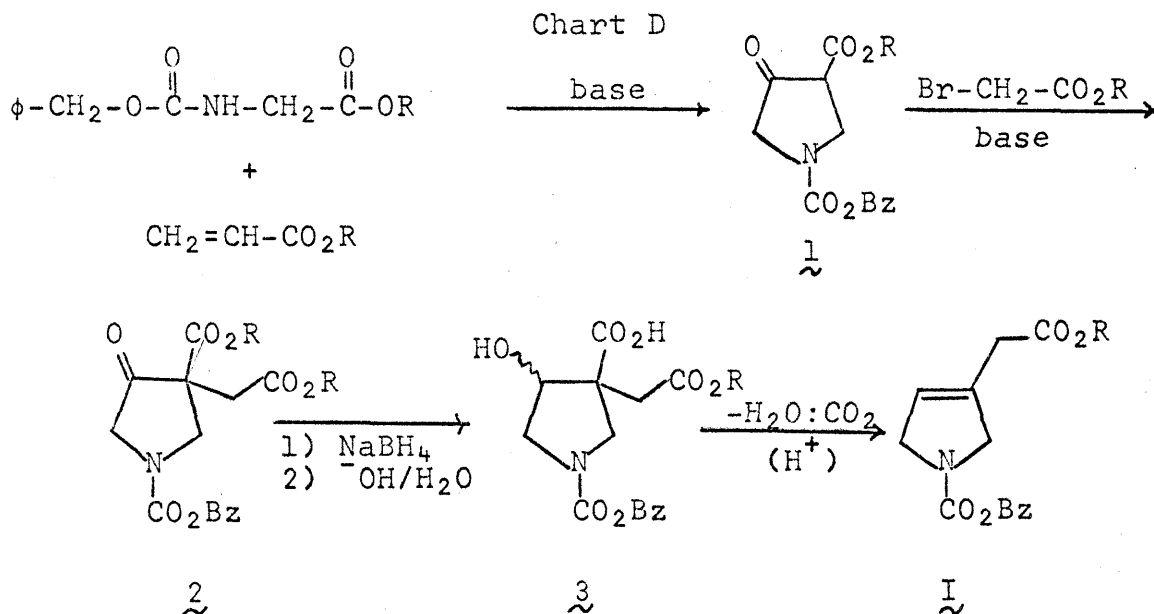


The carbethoxycyclopentene may be synthesized according to the scheme outlined in Chart C.



Chakravarti(3) has prepared 2-carbethoxy-4,4-dimethylcyclopentanone (C-2) from diethyl- β,β -dimethyladipate (C-1) in good yields *via* an intramolecular Dieckmann cyclization. The transformation of the keto ester C-2 into the desired unsaturated ester C-4 may be accomplished in a variety of ways.

The pyrroline I may be conveniently prepared from 1,3-dicarbethoxy-4-pyrrolidone (D-1) by the series of reactions outlined in Chart D.

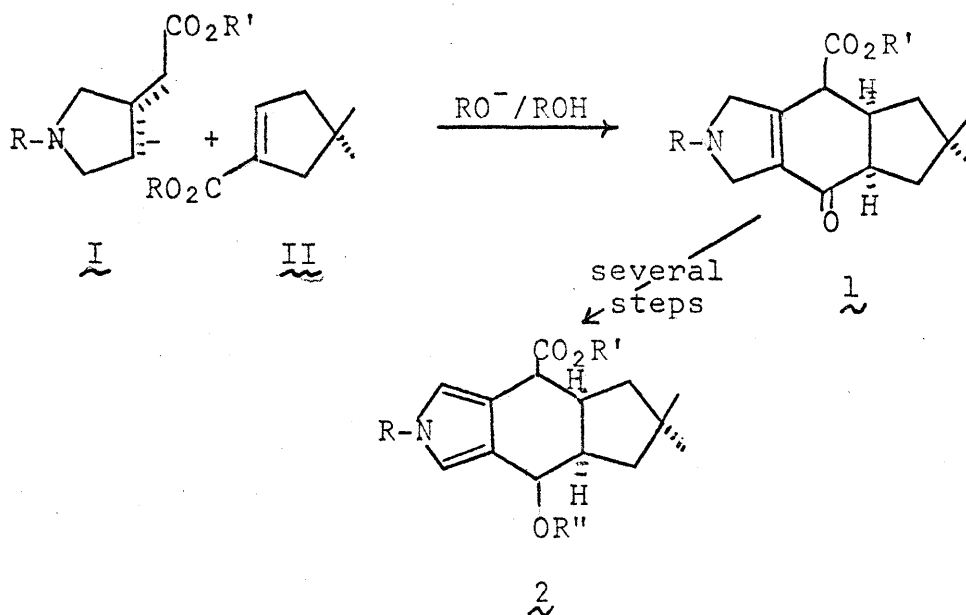


1,3-Dicarbethoxy-4-pyrrolidone (D-1) has been prepared by several workers (4,5). Elaboration of D-1 to the diacid D-3 appears to be routine. Dehydrodecarboxylation of D-3 to the desired pyrroline I could prove to be difficult due to the undefined stereochemistry of the alcohol obtained by reduction of the keto diester D-2.

With a feasible synthetic route to the required intermediates now in hand, the next step in the synthetic sequence

calls for their union to yield the major portion of the marasmic acid carbocyclic system. This may be accomplished by 1-4 conjugate addition of the enolate derived from the $\Delta^{2,3}$ -pyrroline derivative I to 1-carbethoxy-4,4-dimethylcyclopentene-1 (II) followed by intramolecular Dieckmann cyclization to give the keto ester E-1.

Chart E



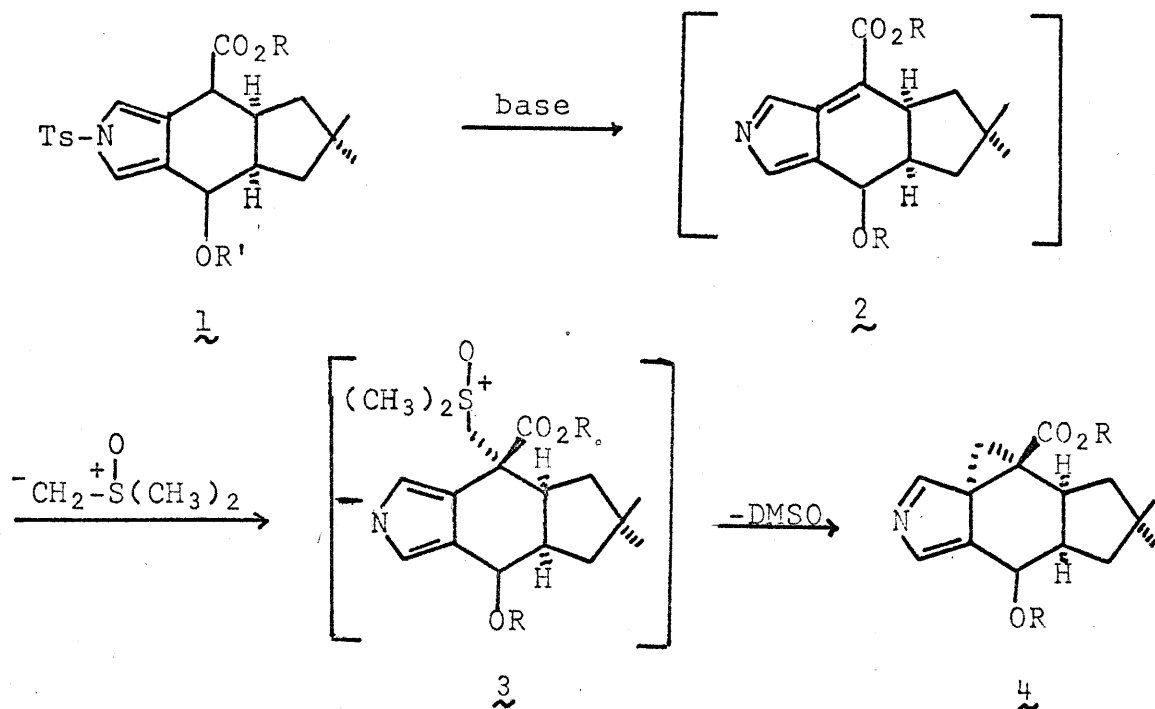
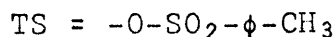
The stereochemistry with respect to the ring fusion should have the desired *cis* orientation since the reaction is thermodynamically controlled. Conversion of the pyrroline keto ester E-1 to the pyrrole ester E-2 could be accomplished by a variety of conventional means, the challenge here lies in the manipulation of functionality.

At this point in the synthesis we have potentially introduced all of the functionality required for marasmic

acid except the cyclopropane ring. Towards this end two possible routes have been devised (Chart F).

Chart F

Route A

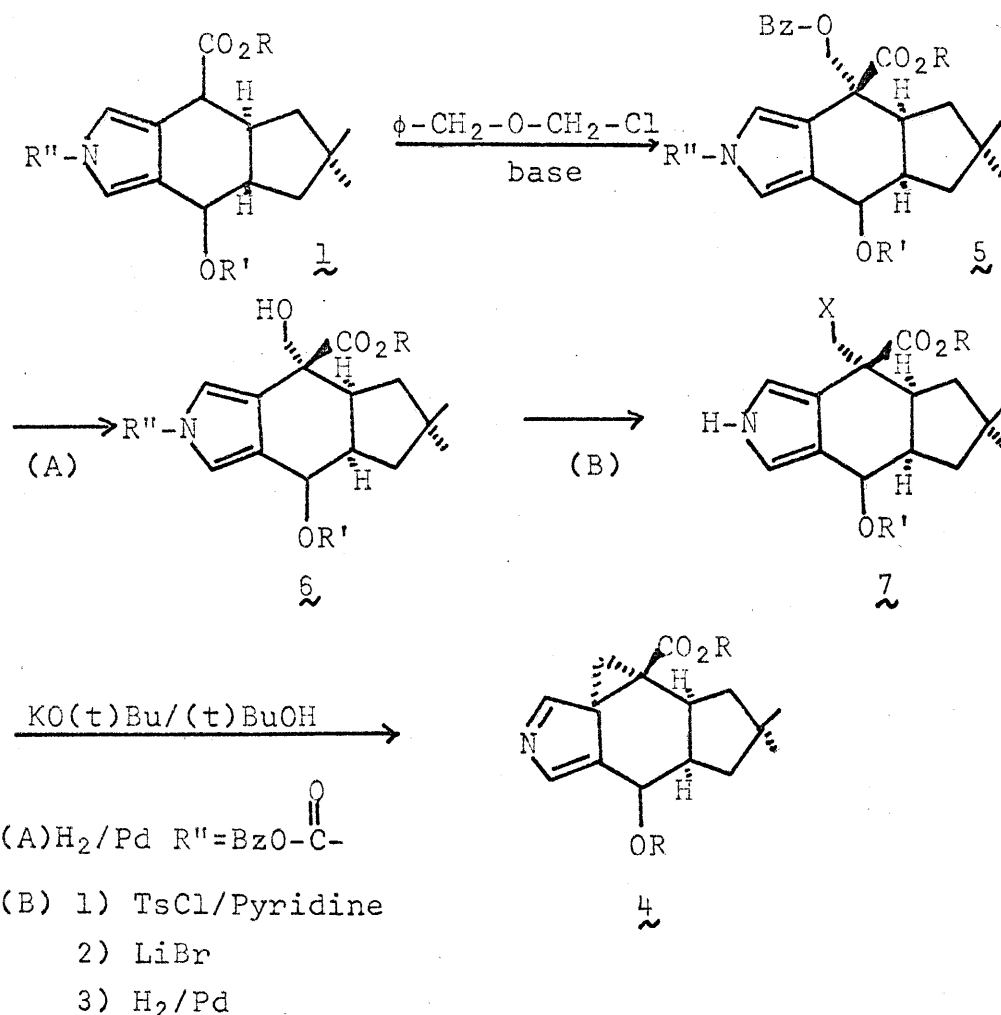


Route A involves the *in situ* generation of the 3-methylene-pyrrolenine ester F-2 in the presence of trimethyloxosulfonium methylide. The sulfur ylide may add in a Michael-type addition to the methylene pyrrolenine to regenerate the pyrrole system. Dimethyl sulfoxide may then be expelled in a subsequent internal alkylation step to yield the spirocyclopropylenine ester F-4. The stereochemistry of the addition should be dictated by the *cis*-fused 6-5 system. The β -face of the molecule is severely shielded by the *gem*-dimethyl groups. Although 3-methylenepyrrolenine systems have never

been generated *via* reductive elimination of toluenesulfonamides, they have been generated by other means, and have been postulated as intermediates in a variety of reactions of the pyrrole system (6).

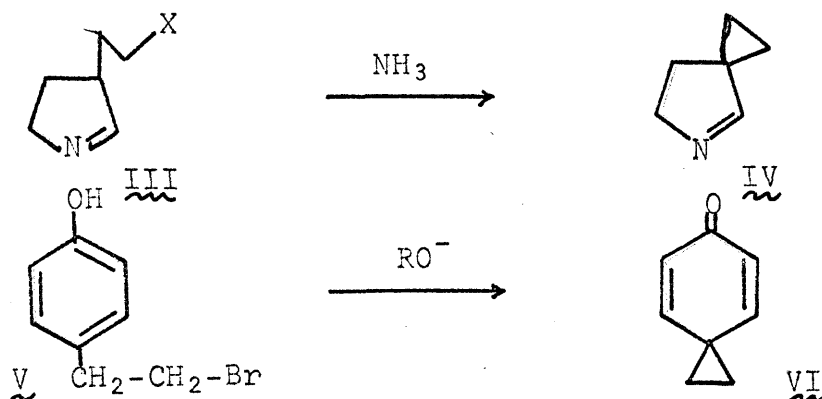
An alternate route for the introduction of the cyclopropane group into F-1 is shown in Chart F (Route B).

Route B



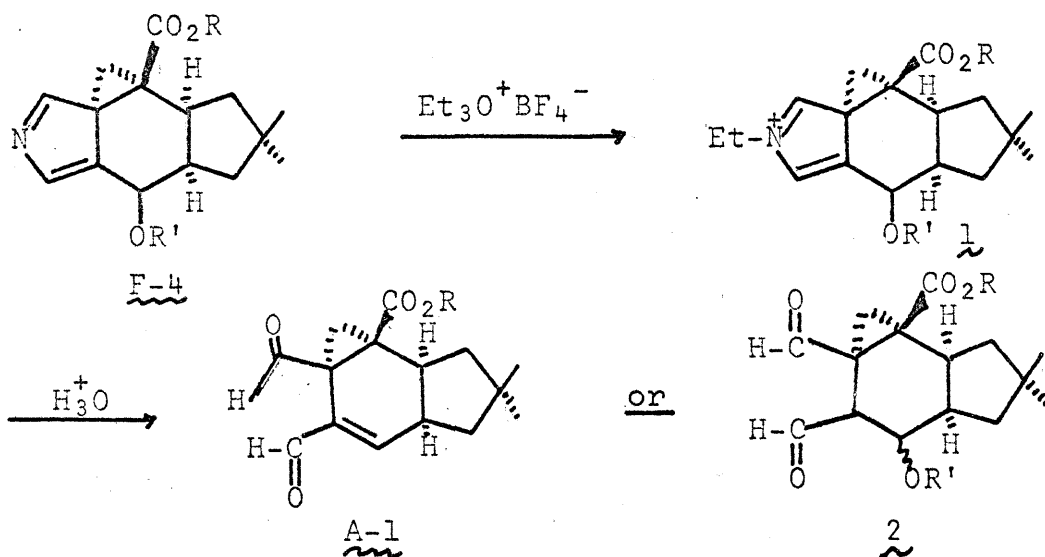
Alkylation of the pyrrol-ester F-1 with benzylchloromethyl ether (7) should lead to the alkylated ester F-5 with the correct stereochemistry. Hydrogenolysis of the benzyl

ether, conversion of the resulting alcohol to an appropriate leaving group, and removal of the nitrogen blocking group should furnish F-7. Treatment of F-7 with base should lead to ring closure to the desired cyclopropyl ester F-4. The only similar analogy for generating such a spiro-system that has been reported is the reaction of III with ammonia to form IV (8).



Winstein and Baird, however, have generated spiro-cyclopropanes *via* similar intramolecular alkylations (9) which proceed with disruption of an aromatic system (V-VI).

Chart G



The spirocyclopropyl pyrrolenine ester F-4 may now be converted under very mild conditions to either G-2 or directly to marasmic acid (A-1) by the use of triethyloxonium tetrafluoroborate followed by very mild acid treatment.

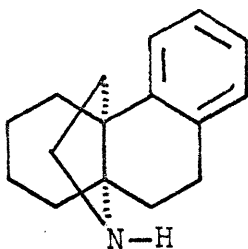
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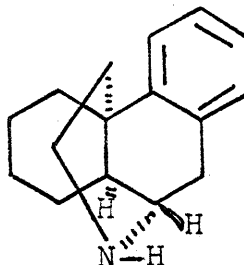
PROPOSITION IV

A general synthetic route to the hasubanan carbocyclic system is proposed, and the total synthesis of the hasubanan alkaloid, metaphanine (A-1), is outlined.

The hasubanan skeleton I is closely related to the morphinan system II. The only difference between the two alkaloid groups is the placement of the ethanamine bridge.



I



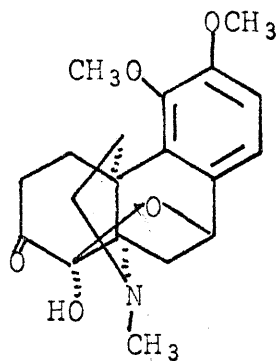
II

Although the first member of this class of alkaloids, metaphanine (A-1), was isolated in 1924 (1), it was not until recently that the structure of this alkaloid was established (2,3) independently by two groups of workers. Since the discovery of the hasubanan type, several additional members of this new class of alkaloids have been isolated and their structures determined (Chart A).

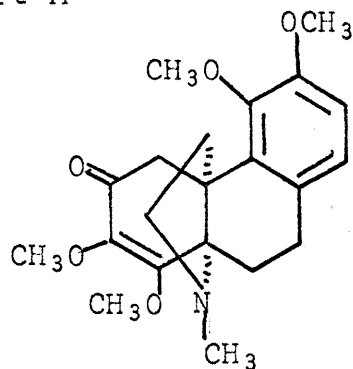
The close similarity between this alkaloid group and the morphine alkaloids has caused some confusion in early structural assignments of the alkaloid, hasubanone (A-2) (4,5), and this member has been incorrectly assigned two

different morphine-type structures before its more probable structure A-2 was proposed by Tomita and co-workers (6) in 1964.

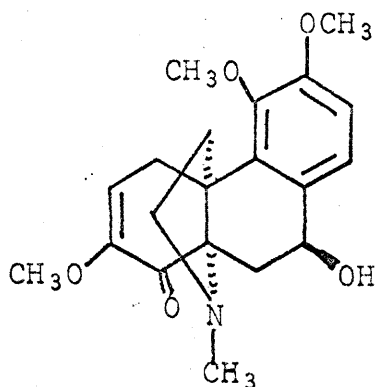
Chart A



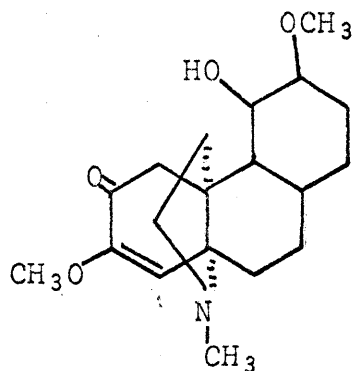
1
metaphanine (2,3)



2
hasubanone (6)



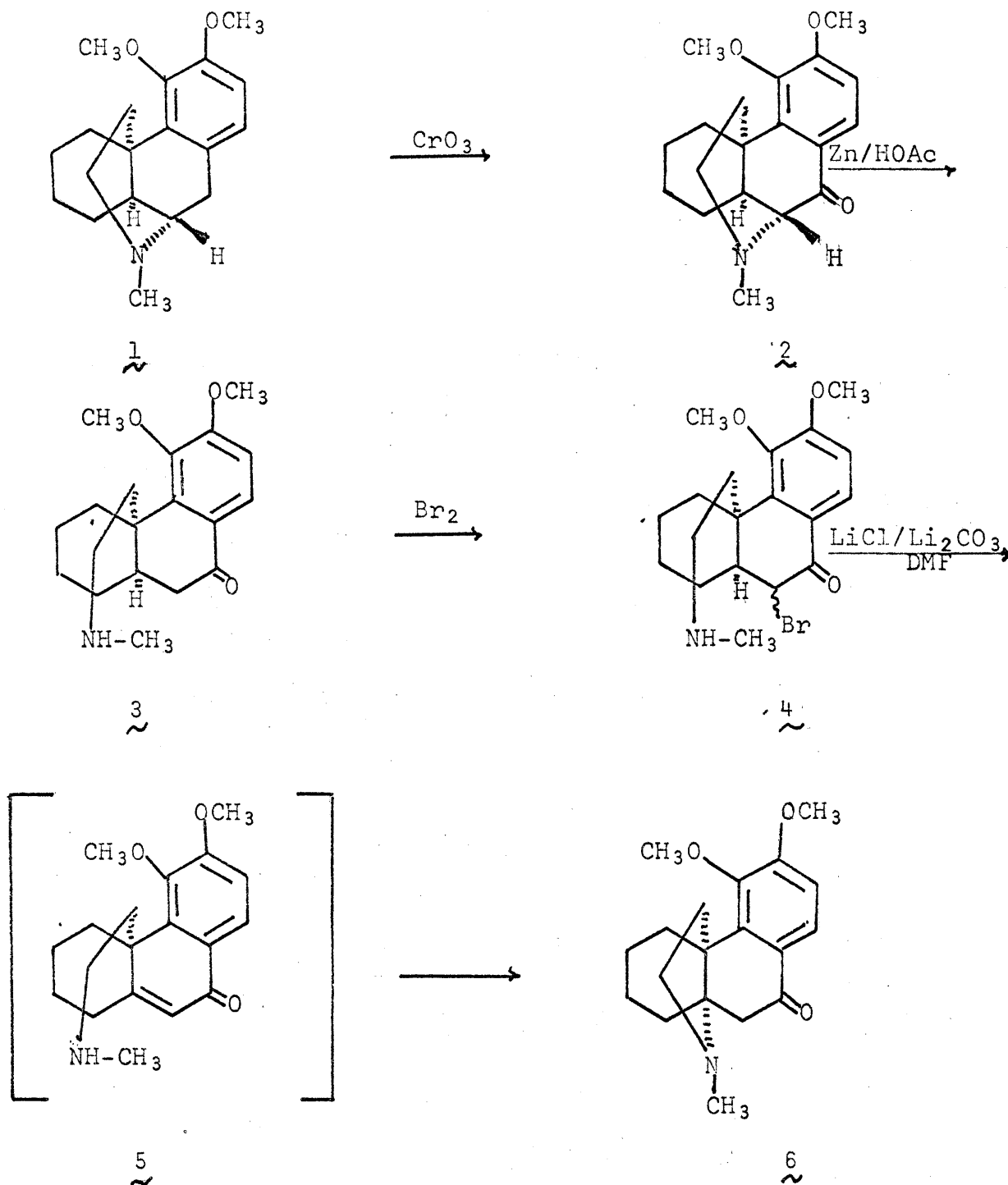
3
prometaphanine (7)



4
cepharamine (8)

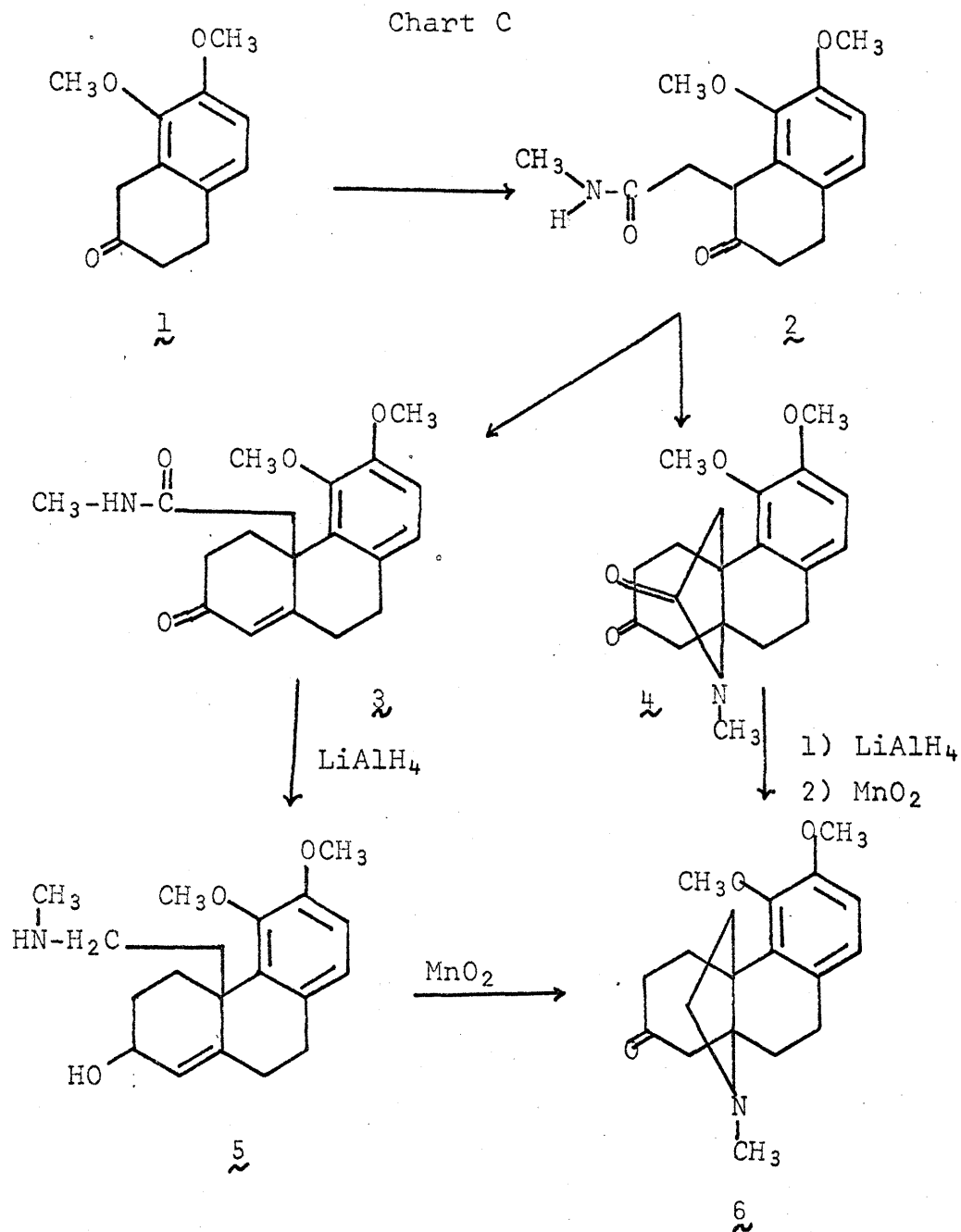
Recently, Tomita and co-workers (9) have achieved a partial synthesis of the hasubanan skeleton from 3,4-dimethoxy-N-methylmorphinan (B-1) by the route illustrated in Chart B. However, other than this work, no general scheme has been developed for the synthesis of the hasubanan carbocyclic system.

Chart B



The totally synthetic approach to the synthesis of meta-phanine (A-1), which will now be described, outlines a general

approach which could be readily modified to include other members of this group of alkaloids.

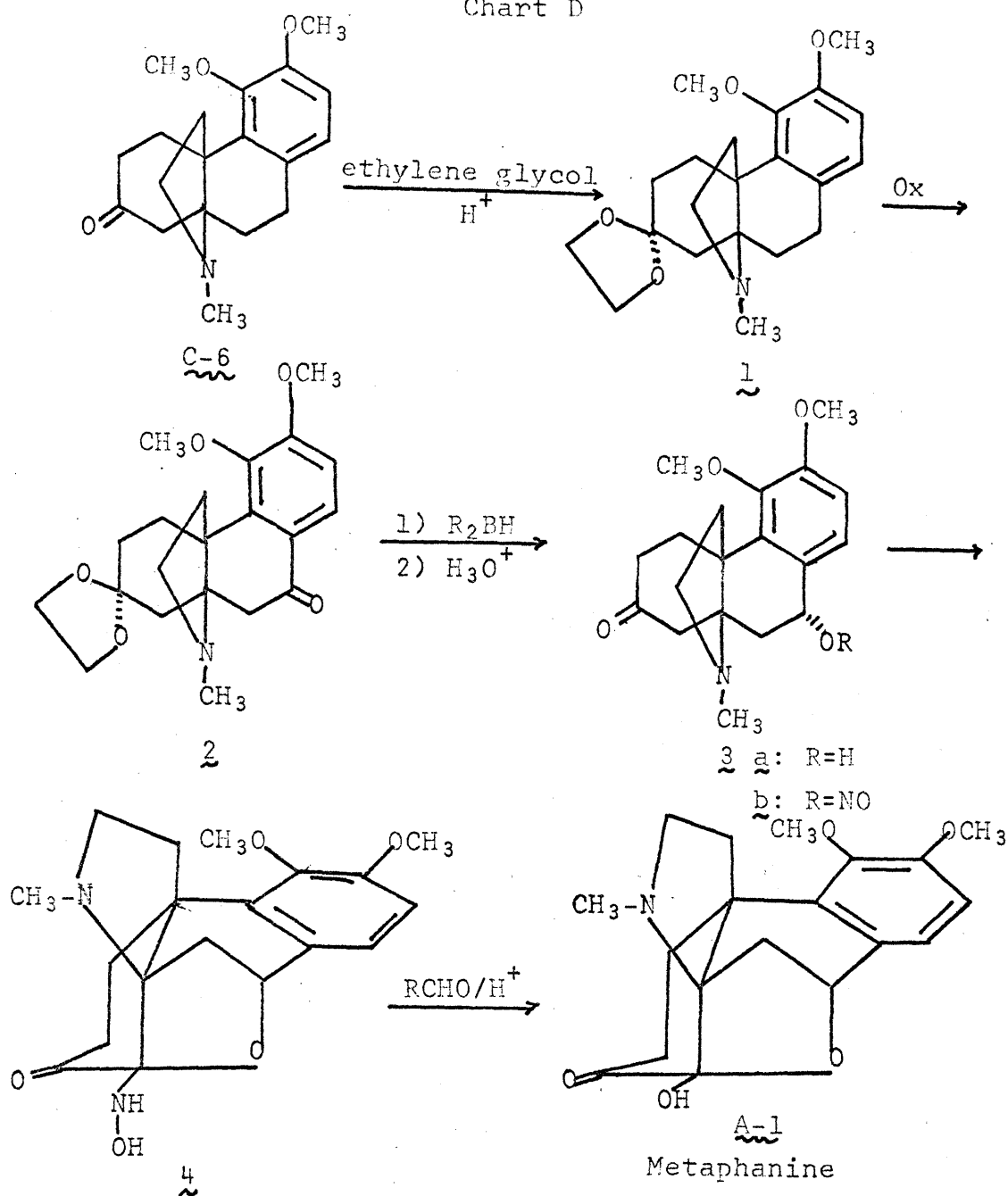


The basic approach to the synthesis of the hasubanan skeleton is outlined in Chart C. The starting point of

this synthesis is the β -tetralone C-1 which has been synthesized in a routine manner by Soffer and co-workers (10) from 2,7-dihydroxynaphthalene. Monoalkylation of the β -tetralone with α -bromo-N-methylacetamide may be accomplished by the enamine procedure developed by G. Stork (11). The keto amide C-2 obtained in this fashion will contain the necessary carbon atoms for three of the four rings of the hasubanan skeleton C-6. The final ring may be introduced in a single step by the method developed by Cornforth and Robinson (12). Treatment of a basic solution of the keto amide C-2 with methyl vinyl ketone or a methyl vinyl ketone precursor should afford either the tricyclic unsaturated ketone C-3 or the tetracyclic keto lactam C-4. At this stage, it is unimportant which of the two products is formed since they both should be readily convertible to the desired tetracyclic hasubanan skeleton C-6 by the series of reactions outlined in Chart C. From this intermediate, it should be possible to construct the various alkaloids shown in Chart A. As an illustration, a potential synthesis of metaphanine (A-1) is now described (Chart D).

The first stage of this synthesis would involve oxidation of the benzylic position of the tetracyclic intermediate C-6. Since this type of benzylic oxidation has been readily accomplished by Rapoport and Masamune (13) on several codeine derivatives, this transformation should pose no great problem.

Chart D



One potential reaction sequence which could achieve the desired transformation is illustrated in Chart D. The only requirement which must be observed in this scheme is that

the benzylic ketone at C-10 be differentiated from the ketone at C-7 as in the intermediate D-2. This requirement may be satisfied only if the oxidation step (*i.e.* D-1 to D-2) is carried out under conditions which will maintain the ketal function intact. An oxidizing agent such as di-t-butyl chromate in a nonpolar solvent (benzene)(14) should accomplish the desired transformation.

The next problem which is encountered is the stereospecific reduction of the tetracyclic ketone D-2 to the 10 α -alcohol D-3a. This problem may be overcome by use of the tertiary amine function to direct the course of the reducing agent. This type of participation would be expected to occur with electrophilic reducing agents such as dialkylboranes. The geometrical relationship between the amine and the C-10 carbonyl carbon in the intermediate D-2 is such that the amine-borane complex may transfer a hydride ion from boron to carbon through a favorable six-membered transition state.

The last problem which must be overcome is the oxidation of the C-8 carbon of the tetracyclic alcohol D-3a. Again, this transformation may be overcome by use of the functionality already present in the molecule. Treatment of the hydroxy ketone with one equivalent of sodium hydride followed by i-amyl nitrite should afford the nitrite ester D-3b. This nitrite ester may then be transformed into the α -oximino derivative D-4 by base treatment, or by photolysis according to the precedent established by Barton and

co-workers (15). The conversion of the oximino hemiketal D-4 into metaphanine (A-1) should be straightforward.

The main point of interest in this proposed synthesis is the use of basic functionality present in the carbocyclic system to control the introduction of new asymmetric centers and direct the incorporation of added functional groups.

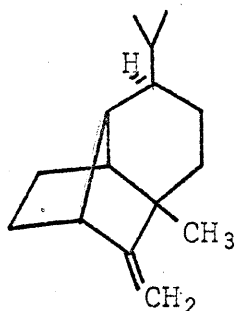
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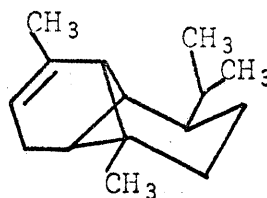
Proposition V

A total synthesis of (+)-ylangene and (+)-sativene is proposed.

The recently isolated sesquiterpene, sativene (I), which has been proposed to be a biogenetic precursor of the toxin helminthosporal (1), and the sesquiterpene ylangene (II) (2) both possess interesting tricyclic carbocyclic skeletons.



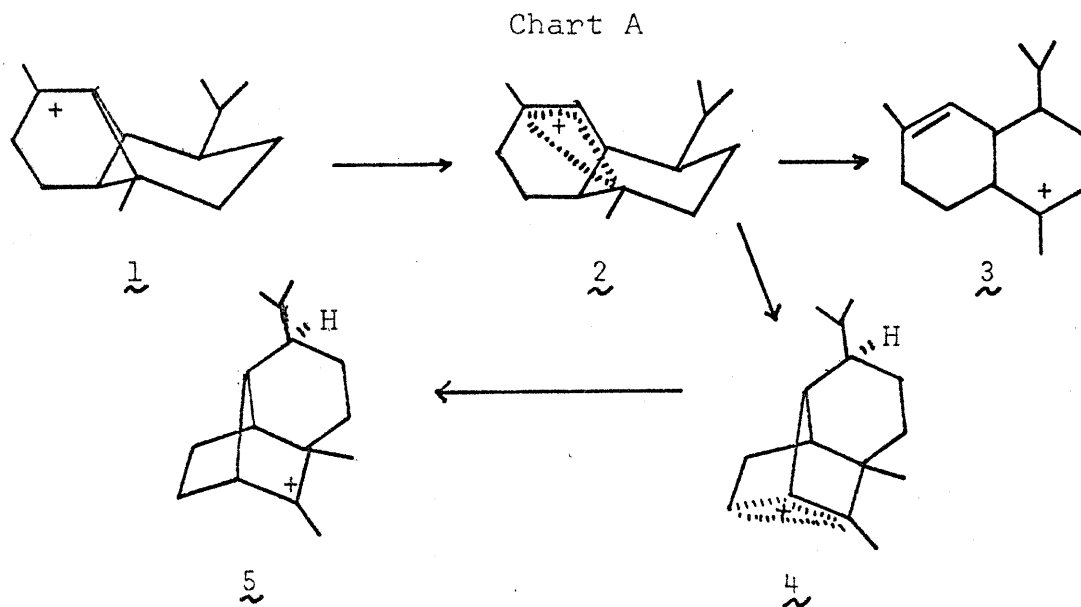
I
Sativene



II
Ylangene

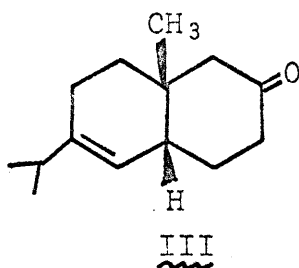
Theoretically these two skeletal types may be interconverted under acid catalysis by a series of two consecutive Wagner-Meerwein rearrangements proceeding through the bridged ions A-2 and A-4 (Chart A). Evidence has been recently communicated by de Mayo and co-workers (3) that the biogenesis of sativene (I) in all probability proceeds through the ylangene cation A-1. In practice however, ylangene and copaene, which is isomeric with ylangene with respect to the stereochemistry of the isopropyl group, suffer rupture

of the cyclobutane ring to form the cation A-3 on treatment with hydrochloric acid (4,6).

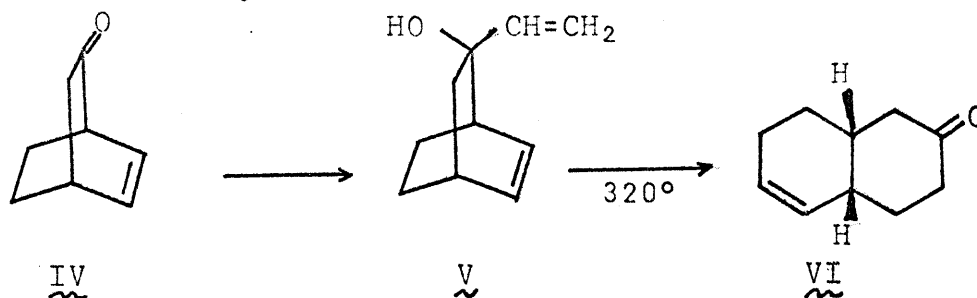


A partial synthesis of sativene (I) from the related sesquiterpene, longifolene has been carried out by de Mayo (7). Recently, Heathcock and co-workers (8) have also succeeded in completing a total synthesis of both (+)-copaene and (+)-ylangene (II). However, the interesting structural features of both sativene (I) and ylangene (II) still provide a challenge in devising different and more efficient synthetic approaches to these carbocyclic systems.

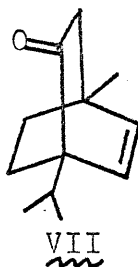
A total synthesis of both (+)-ylangene (II) and (+)-sativene (I) from the β -decalone III is now proposed.



This synthetic approach is based on the potentially useful *cis*- β -decalone synthesis devised by Berson and Jones (9).



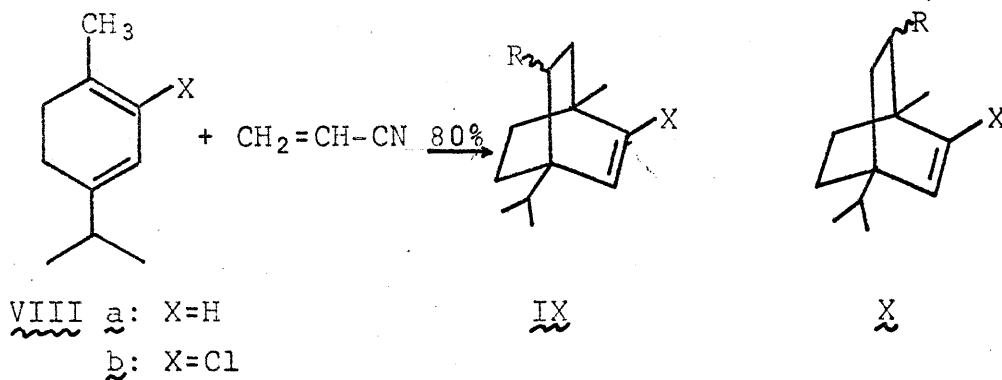
These workers found that on heating the bicyclo[2.2.2] octene V to 320° in the gas phase high yields of this isomerically pure *cis*-decalone VI were produced. Based on this work, the desired *cis*-decalone III should be available from the bicyclo[2.2.2] octenone VII.



One serious drawback to this method for synthesizing *cis*-decalones has been the lack of an efficient synthesis of bicyclo[2.2.2]oct-5-ene-2-one derivatives such as IV and VII. The general method for the construction of such compounds involved a Diels-Alder reaction between cyclohexadiene and vinyl acetate (10,11). This reaction proceeds in yields on the order of 20-30%. Recently, the utility of dibutyl vinylboronate (12) as a dienophile has been demonstrated by Matteson and co-workers (13). This

dienophile has been shown to add to cyclohexadiene in a 71% yield. Since this adduct is readily oxidized to the octenone IV in nearly a quantitative yield, an efficient synthesis of bicyclo[2.2.2]oct-5-ene-2-one derivatives is now available.

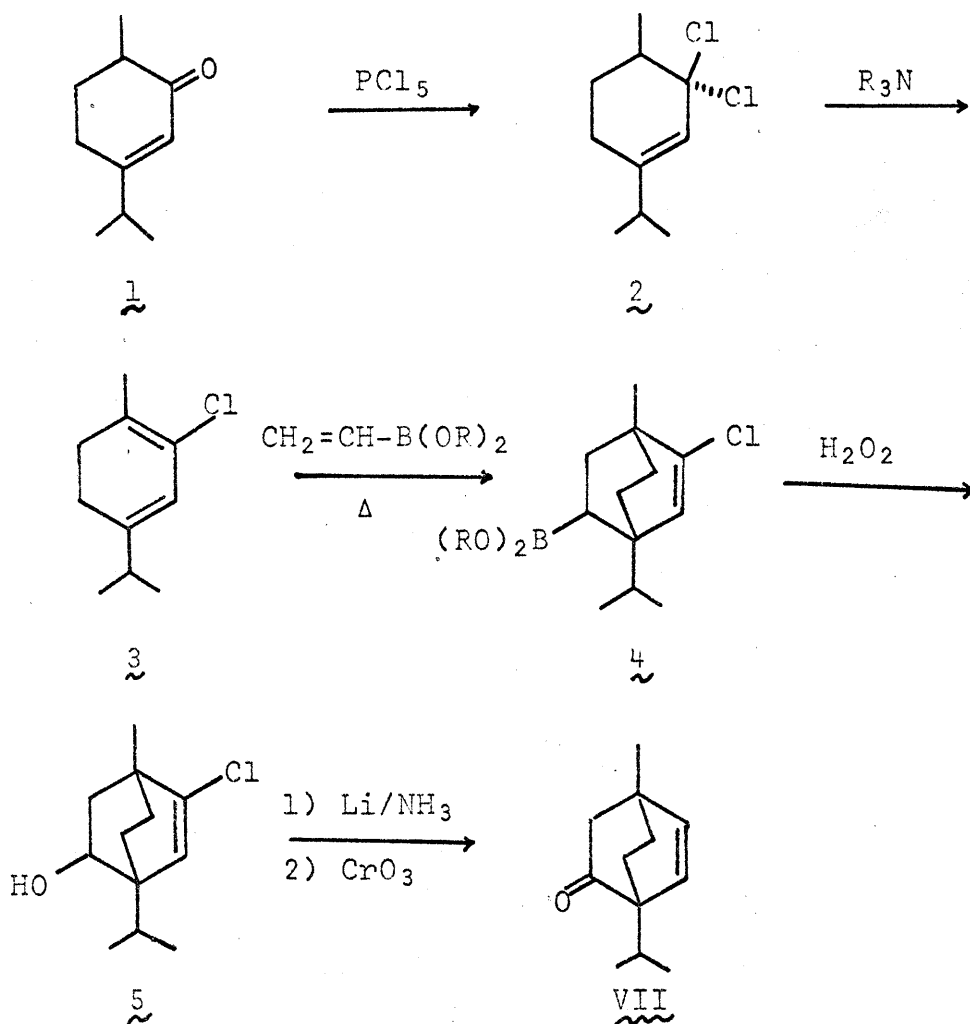
In the Diels-Alder synthesis of the unsymmetrical bicyclooctene derivative VII an additional problem must be overcome. The addition of dibutyl vinylboronate to α -terpinene (VIII-a) would be expected to produce both positional isomers IX and X.



Brown and Fisher (14) have studied the Diels-Alder reaction of acrylonitrile with α -terpinene (VIII-a). These workers have found that the positional isomer IX is favored over X by a 3:2 ratio. The synthesis of an unsymmetrical diene such as VIIIb should strongly favor the production of the desired positional isomer IX, based on the generally observed electronic directive effects of the diene-dienophile components in Diels-Alder reactions (15,16).

The general scheme for the synthesis of the desired bicyclo[2.2.2]oct-5-ene-2-one VII is outlined in Chart B.

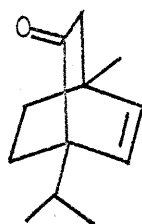
Chart B



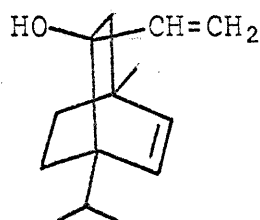
The starting point in the synthesis is the naturally occurring monoterpene carvenone (B-1). This material has been synthesized from dihydrocarvone (17). An alternate synthesis from isopropyl vinyl ketone (18) has also been described by A. Downs and co-workers (19). Treatment of

the unsaturated ketone B-1 with phosphorus pentachloride and subsequent base treatment according to the procedure of Harries and Johnson (20) should afford the desired diene B-3. The Diels-Alder reaction of the diene B-3 with dibutyl vinylboronate according to the procedure of Matteson and Talbot (13) should yield predominately the bicyclo[2.2.2]octene B-4.

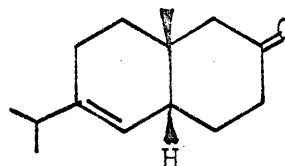
Transformation of the Diels-Alder adduct into the desired bicyclo[2.2.2]oct-5-ene-2-one VII should proceed without difficulty. The addition of vinylmagnesium bromide to the octenone VII should occur predominantly from the side of the carbonyl adjacent to the double bond as shown by Berson (9). Thermal rearrangement of the resulting alcohol XI should afford the desired *cis*- β -decalone III.



VII



XI

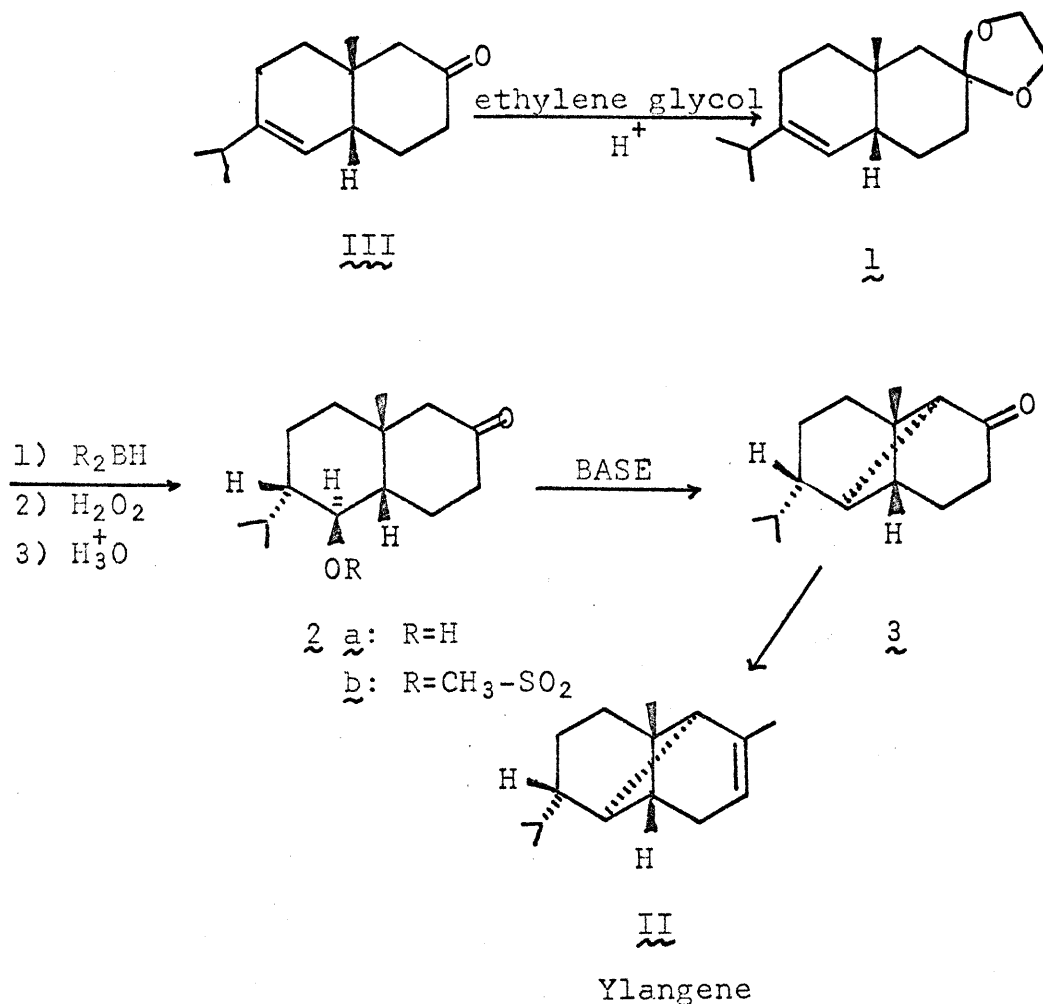


III

With a potential synthesis of the decalone III in hand, the synthesis of (+)-ylangene is now described in Chart C.

In order to generate the ylangene structure from the decalone III, a bond must be formed between carbons 1 and 5 and the isopropyl group must be fixed in the proper orientation. Both of these requirements should be

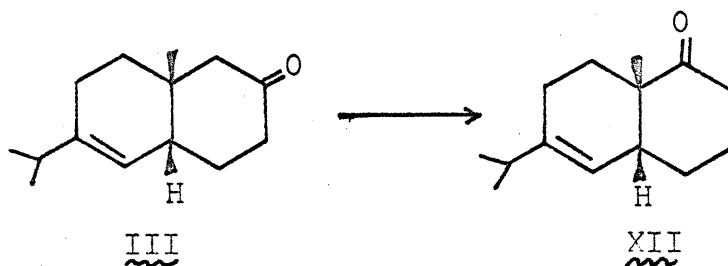
Chart C



satisfied by hydroboration and oxidation of the ethylene-ketal olefin C-1. It has been well established that the course of olefinic hydroboration reactions is often governed by nonbonded interactions present in the molecule (21). It should therefore be predicted that hydroboration of olefin C-1 will occur from the *beta* face of the molecule to generate both the required geometries for the C-7 isopropyl

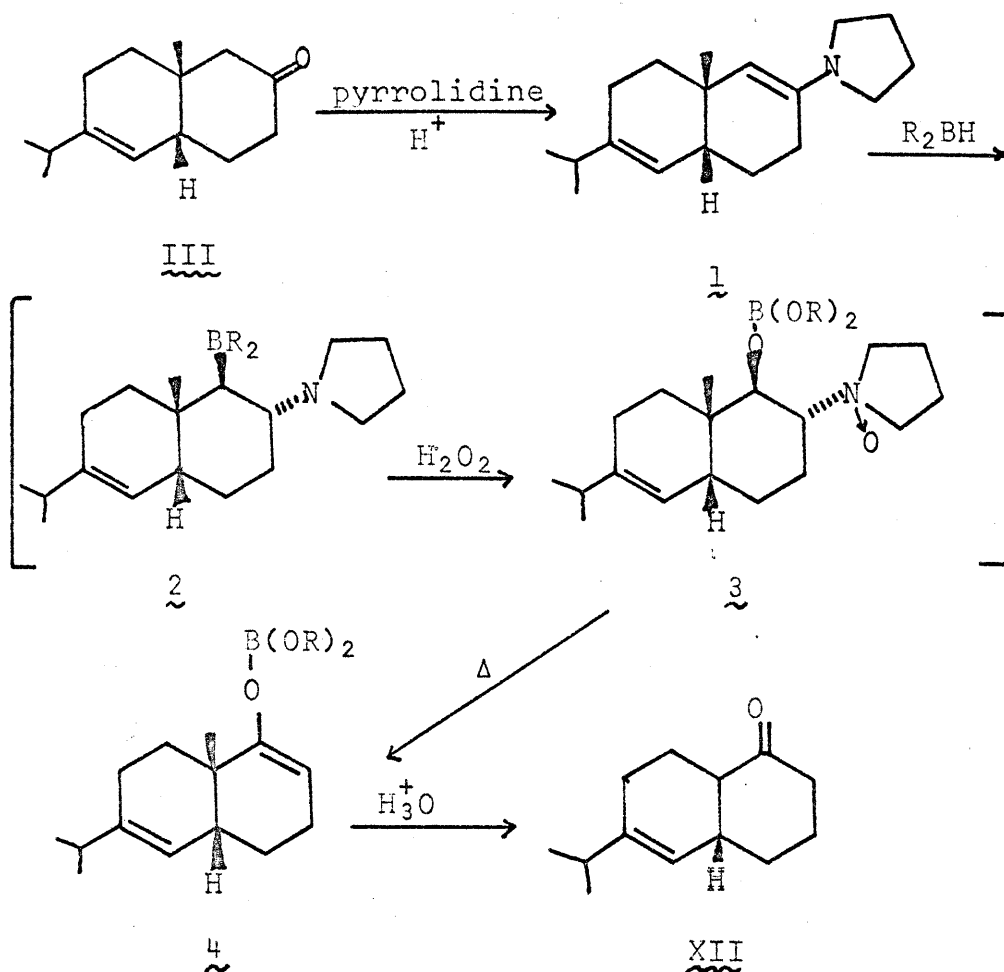
group and the C-6 alcohol function as shown in the hydroxy ketone C-2a. Transformation of the derivative C-2a into the methanesulfonate C-2b and subsequent treatment with base should afford the tricyclic ketone C-3. Since this type of an intramolecular alkylation has already been performed by Heathcock and co-workers (8), this step has ample precedent. The transformation of the ketone C-3 into (+)-ylangene should be straightforward.

To achieve the synthesis of the related sesquiterpene, sativene (I), from the *cis*- β -decalone III the following transformation is required.



The β -decalone III must be transformed into the α -decalone XII. Although this task may be accomplished by several different routes, a new method is proposed which will accomplish this transformation in a limited number of steps. This scheme is illustrated in Chart D. Formation of the enamine of β -decalone III should occur to give predominately the Δ -1 double bond isomer D-1. In addition to the normal preference for Δ -1 over Δ -2 double bonds in *cis*- β -decalones (22), the Δ -6 double bond should further enhance the stability of the isomer D-1 (23) over the isomeric enamine. Selective

Chart D

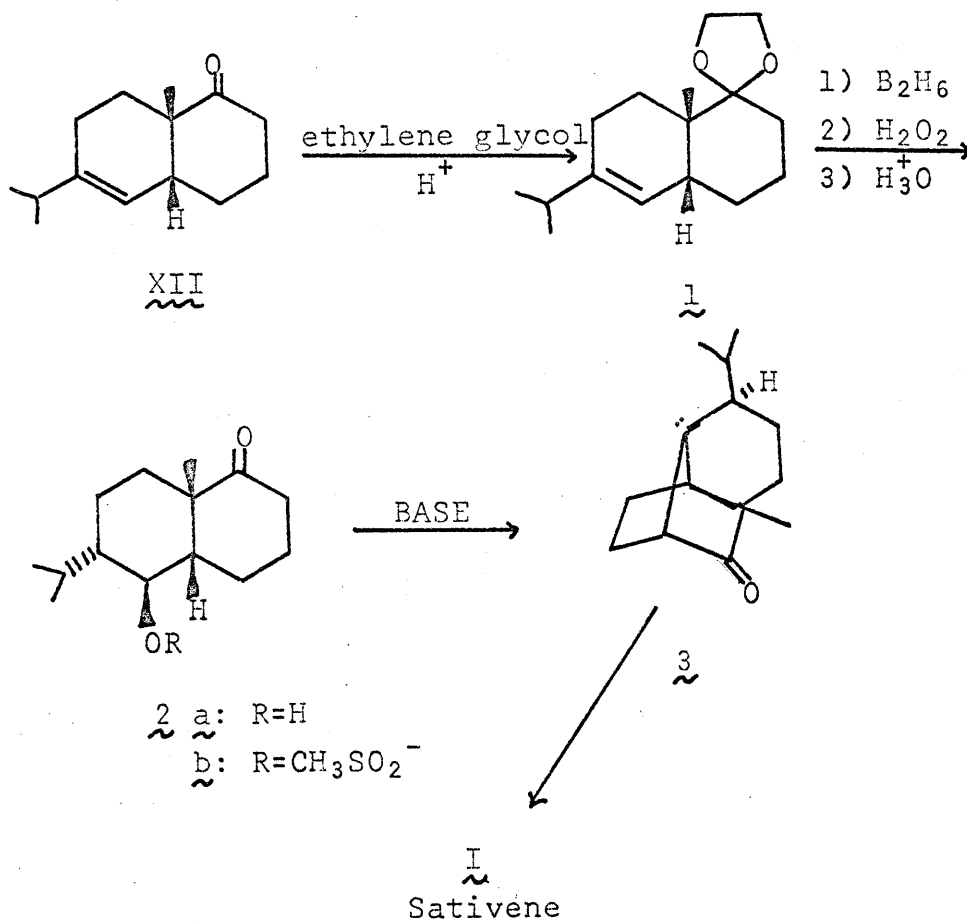


hydroboration of the enamine function should be readily accomplished to give the amine D-2. The fact that enamines hydroborate in a *cis* manner has been established by Lewis and Pearce (24). Complete oxidation of the derivative D-2 to the amine oxide D-3 may then be carried out *in situ*. Pyrolysis of this material should then afford the vinyl borate D-4 which may be readily transformed into the

desired ketone XII. Aside from the immediate application of this proposed general transformation, this type of functional manipulation should be quite useful in other synthetic work.

From the α -*cis*-decalone XII, the synthesis of sativene (I) should proceed without difficulty (Chart E). Essentially the same reaction scheme is used here as was previously described for the (+)-ylangene synthesis (Chart C).

Chart E



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