STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF GERMANICOL

Thesis by

Steven Worth Baldwin

In Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1969

(Submitted September 26, 1968)

To Rita

ACKNOWLEDGEMENTS

I wish to express my appreciation to Professor Robert E. Ireland for his guidance during the course of this study. Thanks are also due to my colleagues for many exciting and fruitful discussions.

I would like to thank the National Institutes of Health for financial support in the form of a traineeship during the period of this research.

ABSTRACT

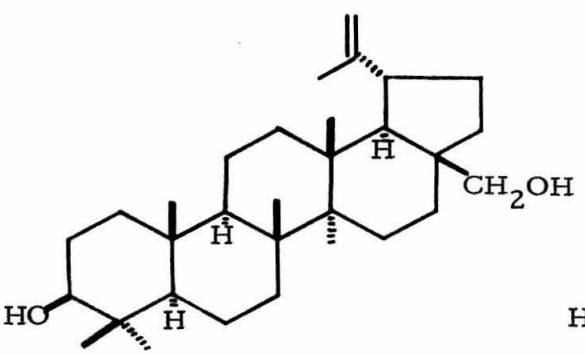
An approach to the synthesis of the pentacyclic triterpene germanicol is discussed.

TABLE OF CONTENTS

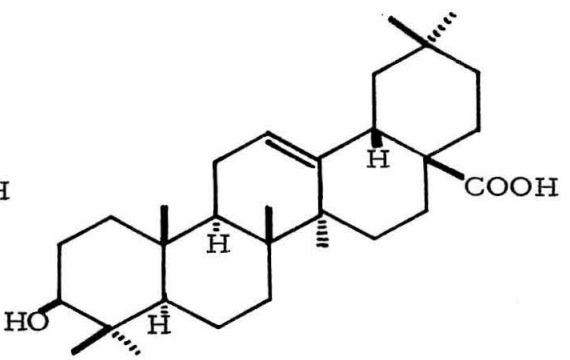
TABLES

Historical Introduction

Triterpenes constitute a large and widely dispersed class of natural products. Their existence has been recognized at least since 1788 when betulin i was first isolated (1), but the absence of tenable functionality in these molecules, coupled with their high degree of assymetry, shackled them as virtual unknowns until quite recently. It has also been suggested that a lack of physiological activity--compared to the steroids and alkaloids--temporarily rendered the triterpenes as unattractive candidates for vigorous research (2). That the triterpenes are as well characterized as they are today is due in large part to the considerable efforts of Ruzicka and his collaborators (3), who, relying heavily on information gained from dehydrogenation experiments, were finally able to determine the structure of oleanic acid ii (4). Subsequent progress in

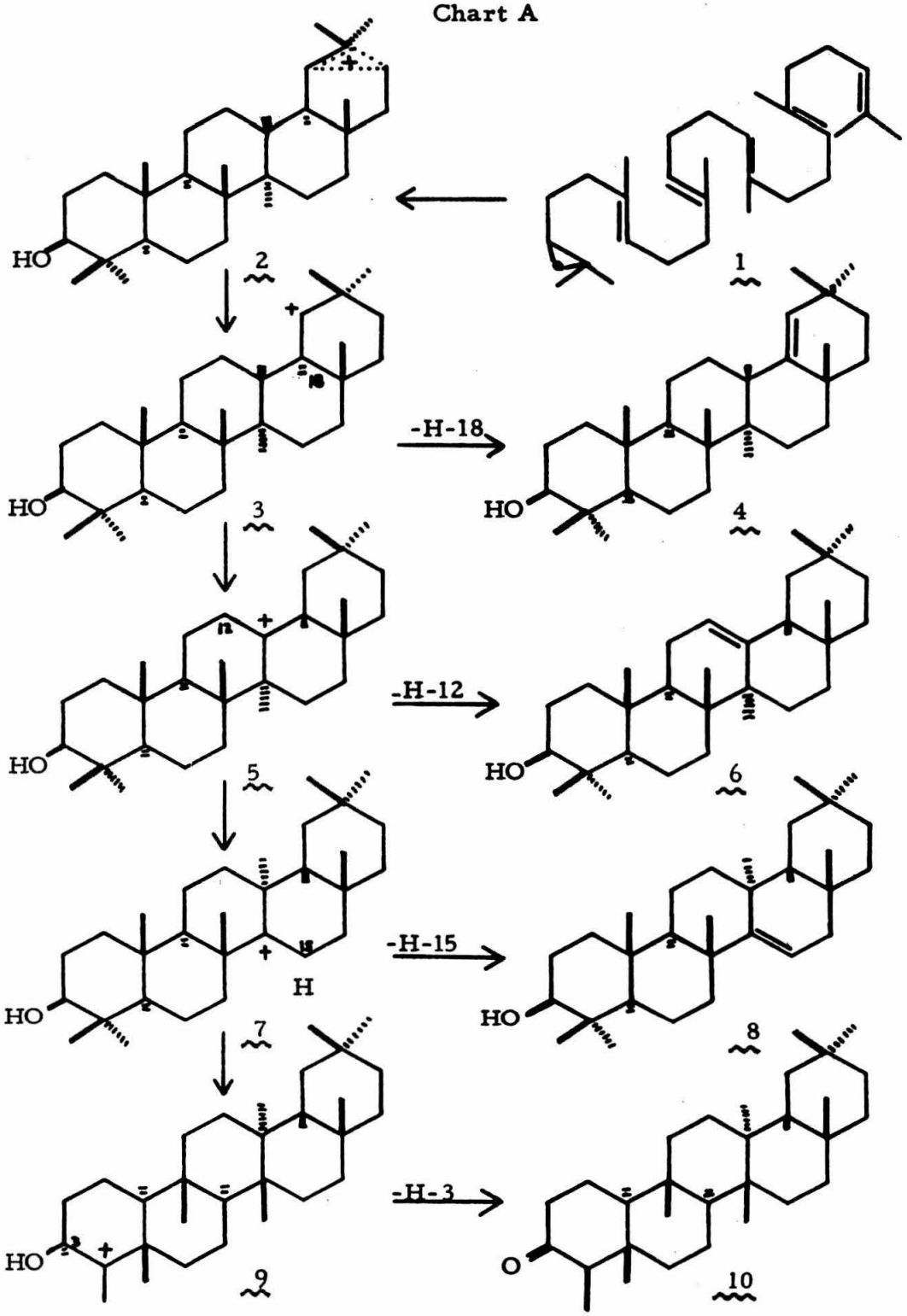


i



ii

Chart A

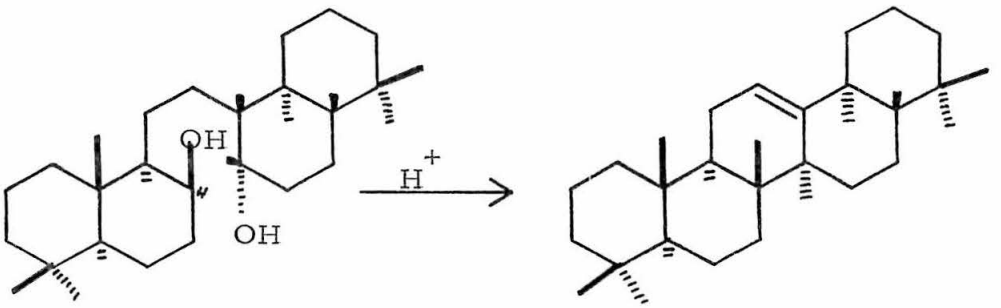


establishing the relative stereochemistry of the triterpenes has been thoroughly reviewed by several authors (5, 6, 7, 8).

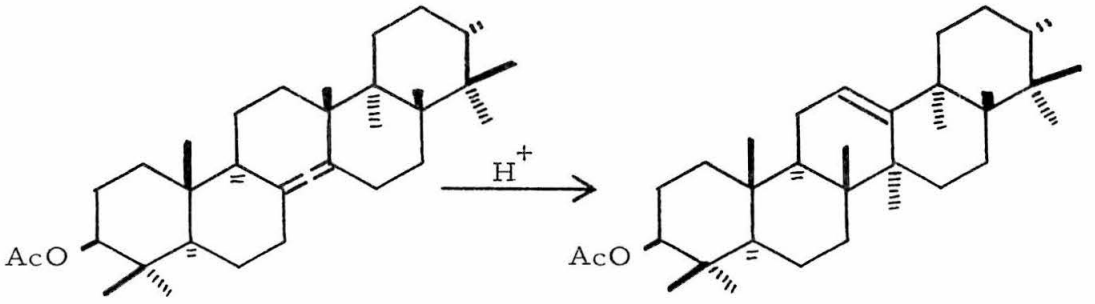
Recently the intermediacy of 2,3-oxidosqualene A-1 in the biosynthesis of β-amyrin A-6 has been established (9, 10, 11, 12) and its involvement in triterpene biosynthesis in general is thus implied. It is widely considered (13, 14, 15) that pentacyclic triterpenes are derivable by loss of hydrogen from the sequential carbonium ions that arise from the lupeol cation A-2 by trans-diaxial 1,2-methyl and hydrogen migrations. This process is illustrated in Chart A for the formation of germanicol A-4, β-amyrin A-6, taraxerol A-8, and friedelin A-10.

To this date synthetic endeavors in the triterpene field have been sparce, due in large part to the same reasons that retarded structure elucidation. A competent survey of progress in this area through September, 1967 is available in the Ph.D. thesis of D. A. Evans (16). A noteworthy observation is that since the pioneering work of Halsall and Thomas (17), all reported pentacyclic triterpenoid syntheses have involved an acid catalyzed formation of the 8,14 bond in ring C from a tetracyclic intermediate. This process is illustrated by the last step of the synthesis of α-onocerene iv reported by Corey and Sauers (18).

Patterned after Barton's cyclization of natural onocerin v (19), this step is representative of the reaction in general, being both intractable and of low yield (10%). A close examination reveals that

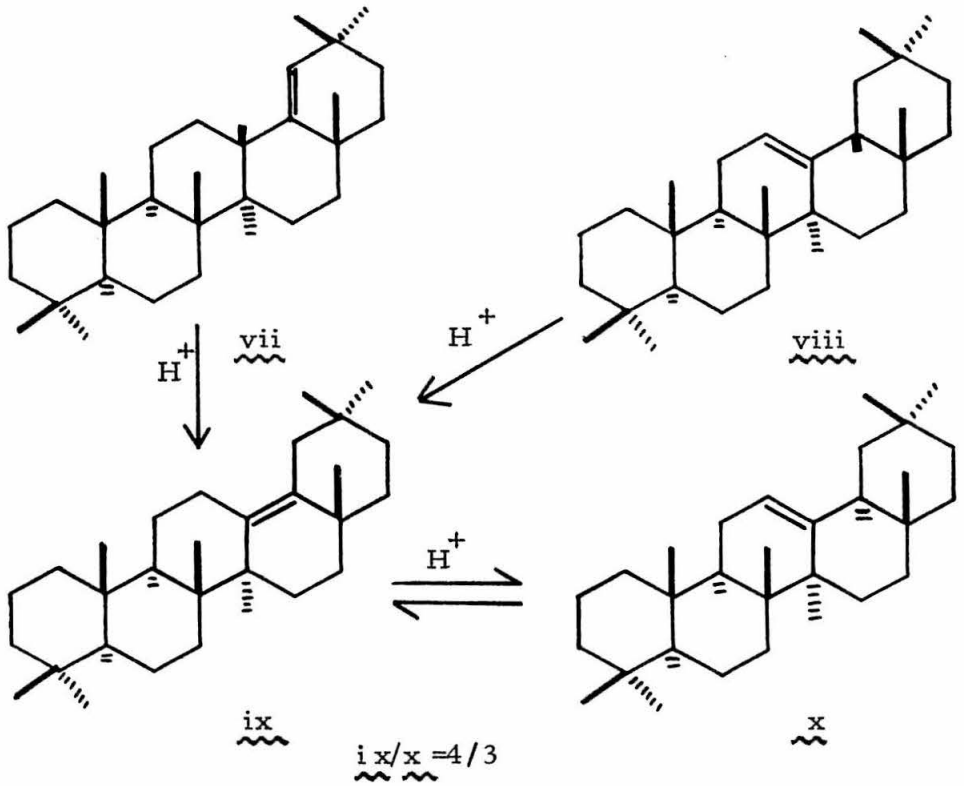


iii iv



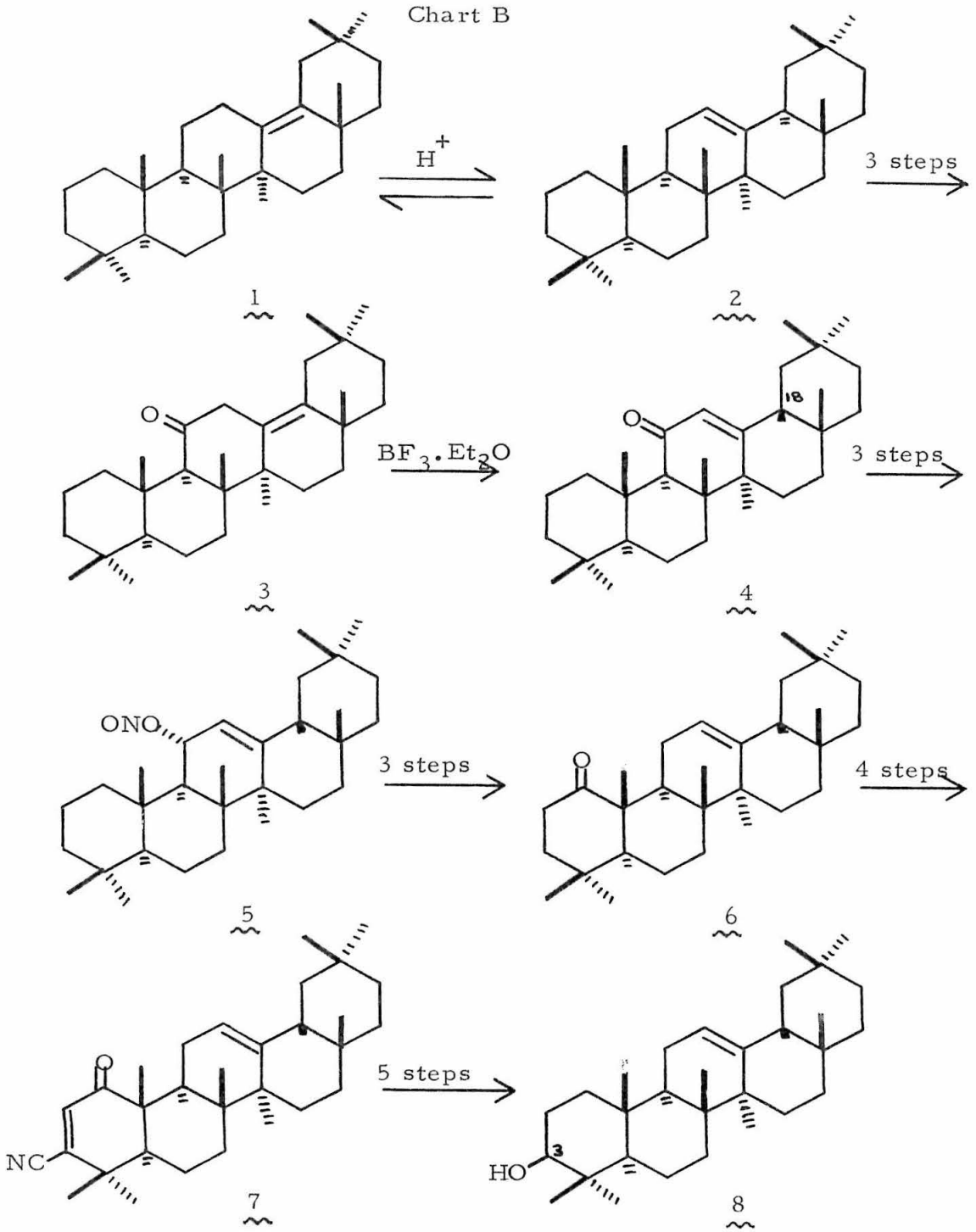
v vi

a direct synthesis of a triterpene such as germanicol A-4 or β-amyrin A-6 by a similar process would be unfeasible. The reaction conditions required to initiate cyclization would be sufficient also to equilibrate the double bond in the product. A loss of stereochemical integrity at the D/E ring fusion would result. This observation has been confirmed by Brownlie (20) as is shown in the accompanying diagram.



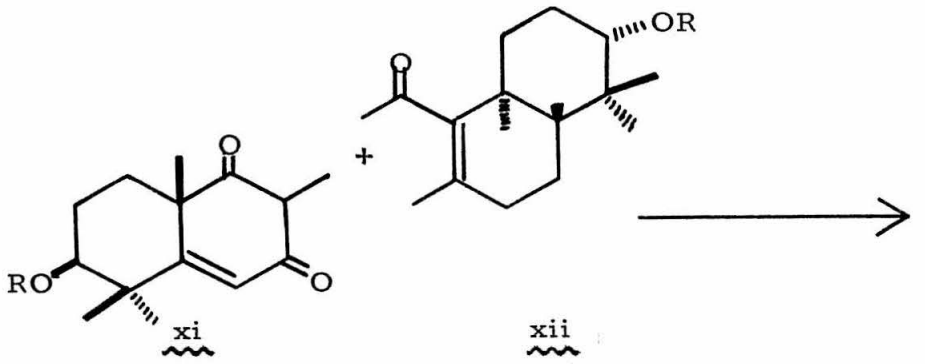
Interestingly, Barton has been able to circumvent this problem in what constitutes the first total synthesis of β-amyrin (21) outlined in Chart B. Starting with the previously synthesized δ-amyrene B-1, Barton proceeded to the 18β isomer B-4 in a sequence of six reactions. The key step was the treatment of the unsaturated ketone B-3 with boron trifluoride etherate to give a 1:1 mixture of the 18α and 18β isomers of ketone B-4. A further sequence of fifteen reactions was required to functionalize position 3. Although this effort does

Chart B

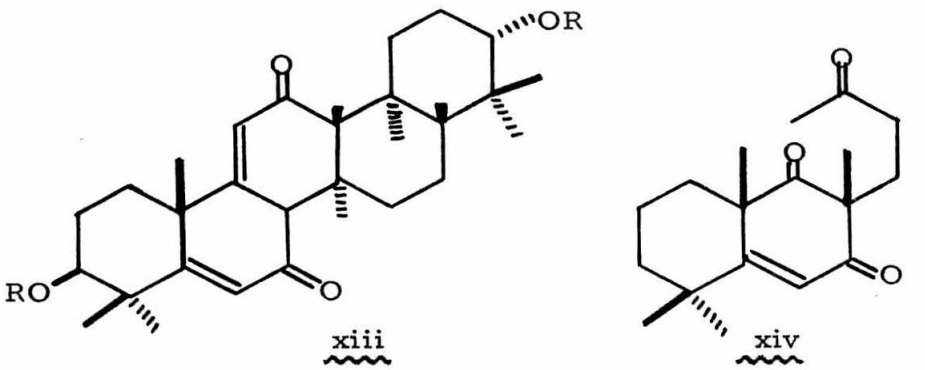

H+
3 steps
1
2
O
BF3.Et2O
18
3 steps
3
4
ONO
3 steps
4 steps
5
6
O
5 steps
NC
HO
3
7
8

represent a successful synthesis of β-amyrin B-8, it suffers from the low efficiency accompanying the synthesis of starting material B-1 and the awkward manipulation of functionality required to hydroxylate C-3.

A recent attempt designed to circumvent the aforementioned problems of an acid catalyzed formation of ring C was reported by Beak and Monroe (22). It was hoped to be able to join fragments xi and xii by a Michael reaction and then selectively cyclize the intermediate tri-ketone in a basic medium to give pentacyclic compound xiii. These efforts were abandoned, however, when it was discovered that model triketone xiv experienced only retro-aldolization on treatment with a variety of bases.



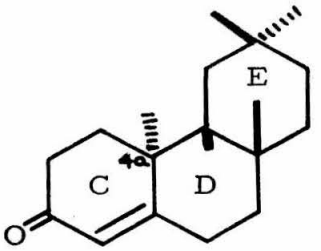
xi xii



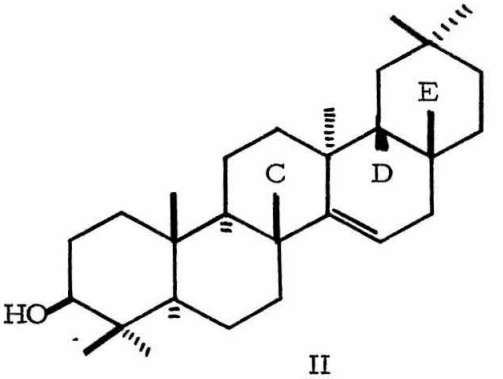
xiii xiv

Discussion

Previous reported syntheses of pentacyclic triterpenes have suffered from low efficiency plus a lack of stereochemical control and versatility. Correspondingly in the Ireland laboratories there have for some time been syntheses in progress based on the steroidal approach of progressive ring additions. To this end Dolphini (23) synthesized tricyclic ketone I as a potential C/D/E unit of taraxerol II but discontinued the project when the stereochemistry of the C-4a*

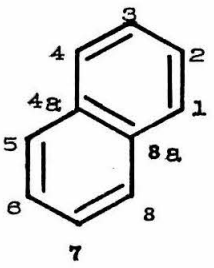


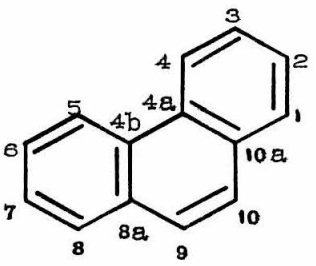
I

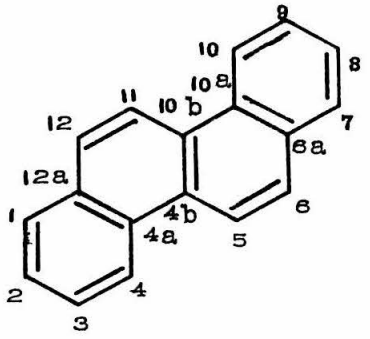


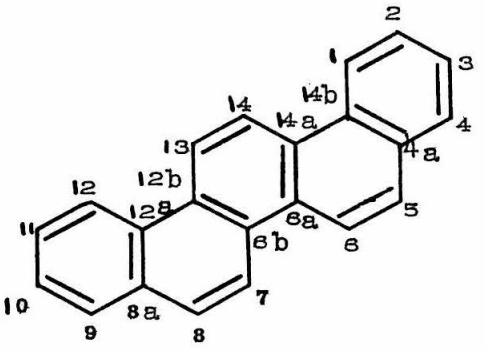
II

* The bicyclic compounds discussed herein are named and numbered as derivatives of naphthalene, no. 1754 in the Ring Index. Tricyclic compounds are considered as derivatives of phenanthrene, no. 3619 in the Ring Index. Tetracyclic compounds are treated as derivatives of chrysene, no. 5254 in the Ring Index. Pentacyclic compounds are considered as derivatives of picene, no. 6384 in the Ring Index (A. M. Patterson, L. T. Capell and D. F. Walker, "The Ring Index," American Chemical Society Special Issue Sales, 1960).



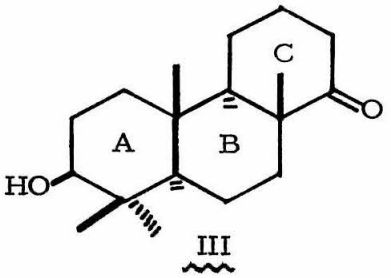






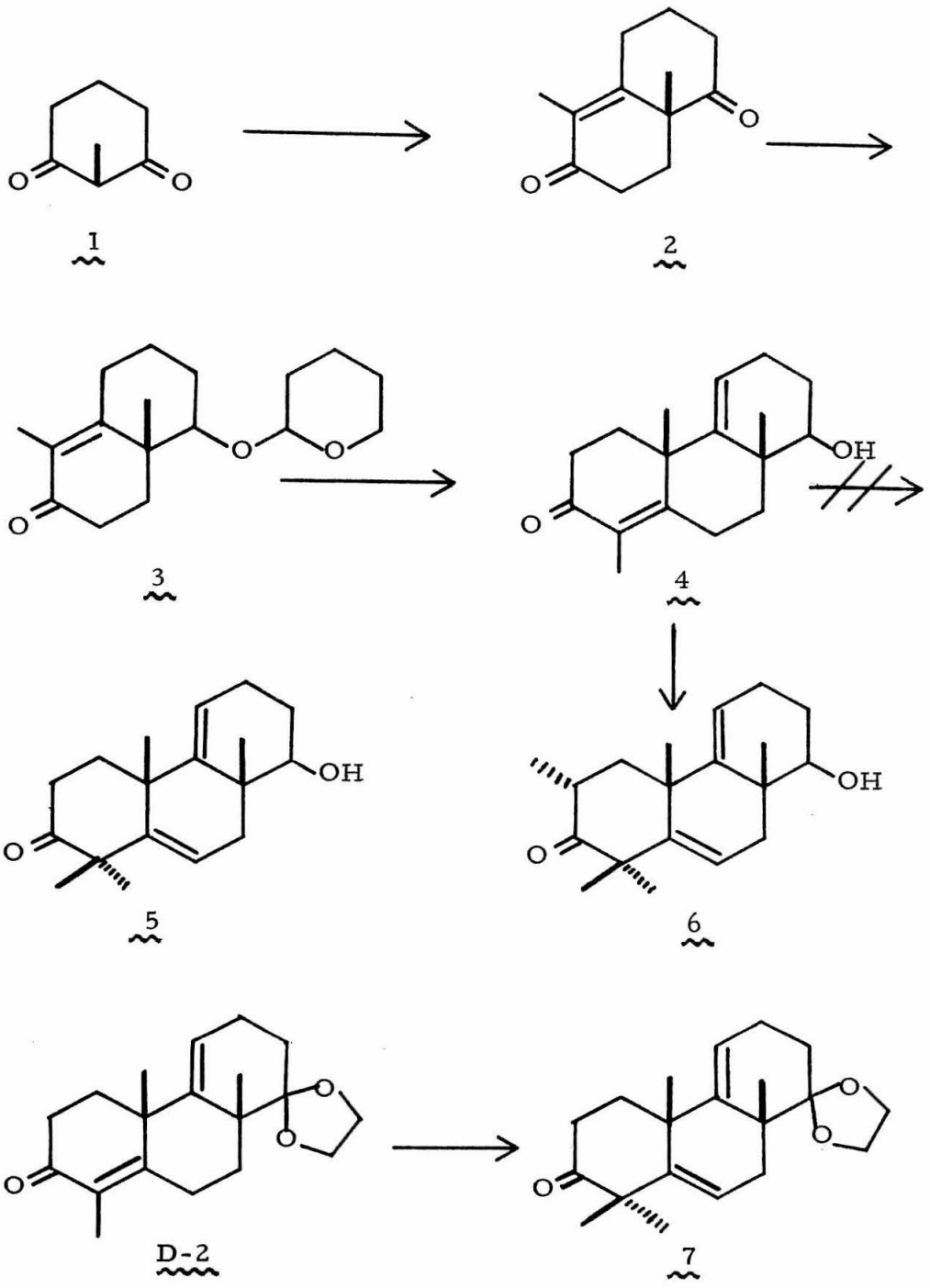
---

methyl group could not be rigorously assigned. In addition, Dolfini embarked upon a synthesis of tricyclic ketone III as a potentially versatile intermediate possessing the A/B/C stereochemical features



III

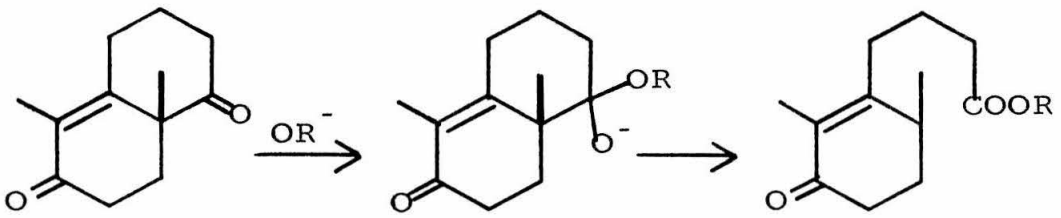
Chart C



present in a variety of pentacyclic triterpenes. These include germanicol A-4, β -amyrin A-6, and taraxerol II.

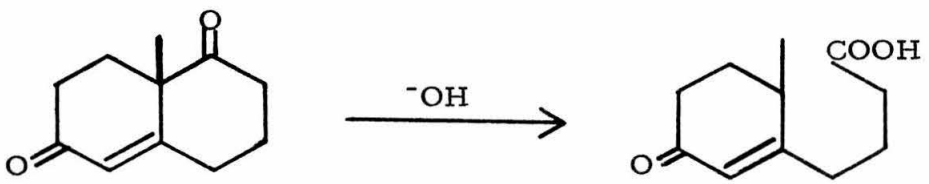
The synthetic route employed by Dolfini is outlined in Chart C. The bicyclic tetrahydropyranyl ether C-3, when treated with ethyl-vinyl ketone and sodium methoxide followed by acid hydrolysis, produced a 19% yield of tricyclic keto alcohol C-4. Standard methylation procedures, however, afforded none of the desired monoalkylated product C-5; only dialkylation C-6 was observed. As a result, progress toward keto alcohol III was temporarily halted. It is worthy of note that recently acceptable yields of ketone C-7 have been obtained from unsaturated ketone D-2 by prolonged treatment with potassium tert-butoxide in dimethyl sulfoxide followed by methyl iodide (24). Removal of the C-8a(9) double bond, however, could not be effected.

Simultaneously and independently, Brown (25) was able to obtain tricyclic dione D-1 in 15% yield by direct annelation of diketone C-2 with ethyl vinyl ketone. Here the low yield is ascribable to a cleavage reaction arising from competitive nucleophilic attack of alkoxide on the vinylogous β -diketone C-2. Precedent for such a cleavage has been documented by Wendler and co-workers (26), who reported the formation of keto acid V from base treatment of



C-2

dione IV. Ketone ketal D-2 was obtained by selective ketalization of

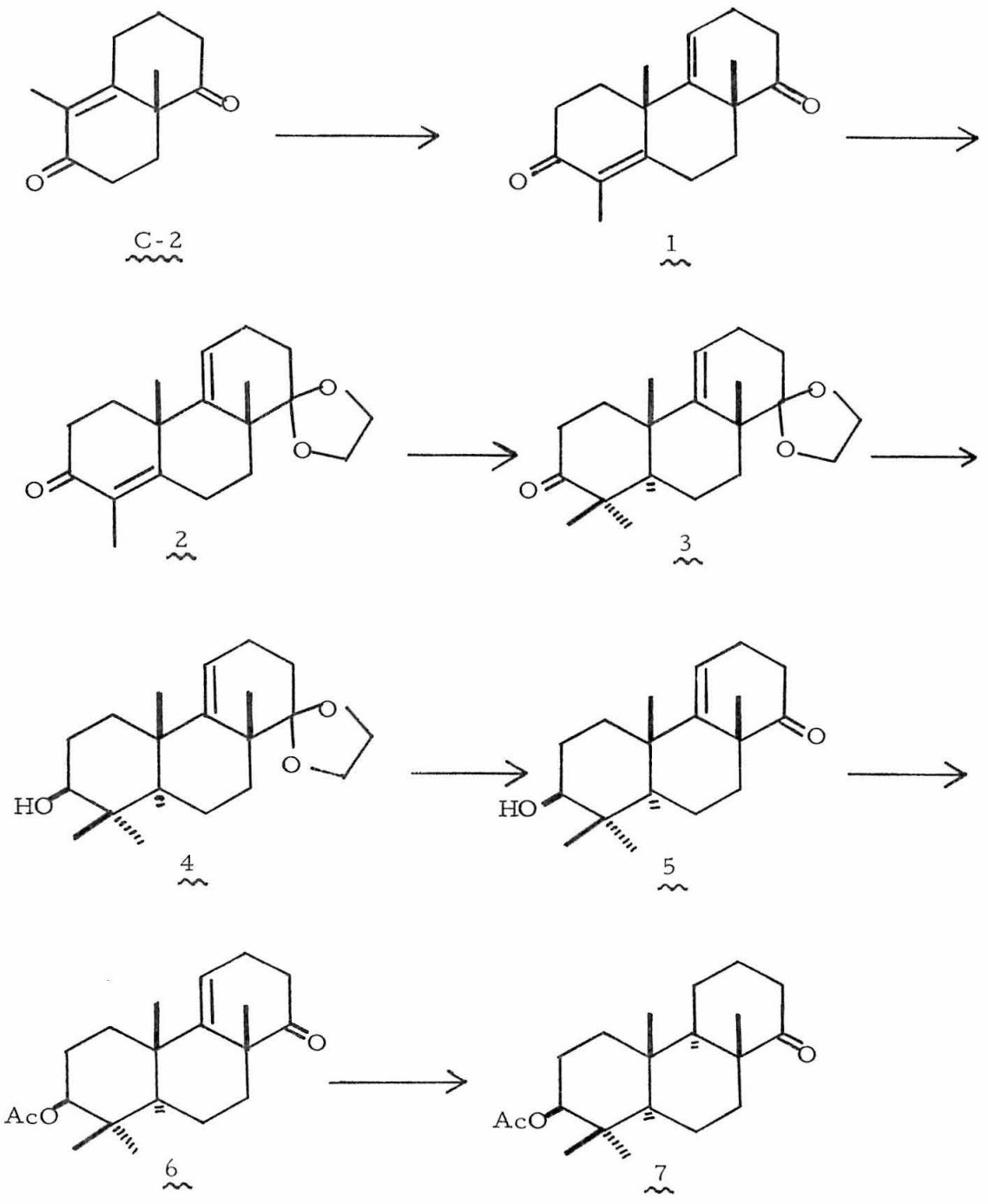


IV V

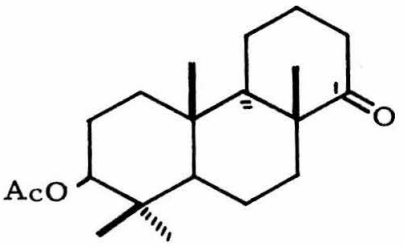
D-1 and alkylation to give saturated ketone D-3 was accomplished by the reductive alkylation procedure of Stork (27). Reduction of D-3 with lithium tri-tert-butoxy aluminum hydride produced ketal alcohol D-4 in 45% yield from D-2. Subsequent conversions to tricyclic keto acetate D-7 occurred smoothly as described in the Ph.D. thesis of K. Schmiegel (2).

The research problem that logically arose from the successful synthesis of D-7 was the development of a method for the addition of

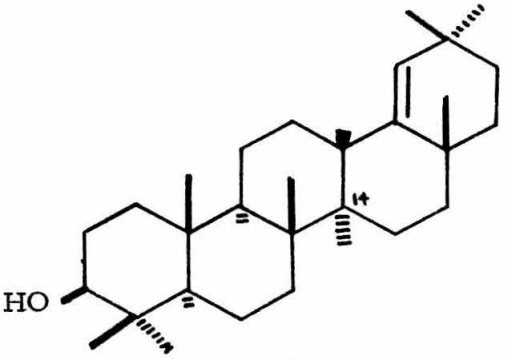
Chart D



rings D and E corresponding to a triterpene such as germanicol A-4. Several possibilities were suggested but the one initially decided upon, outlined in Chart E, appeared encouraging. The main difficulty encountered in all of the proposed sequences was the generation of a quaternary carbon at C-1 of the starting material D-7, and thus C-14 of germanicol A-4.

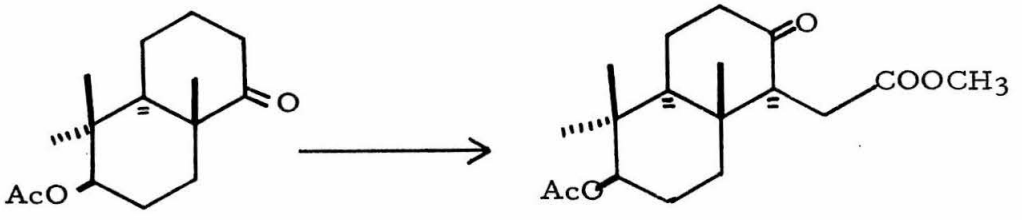


D-7



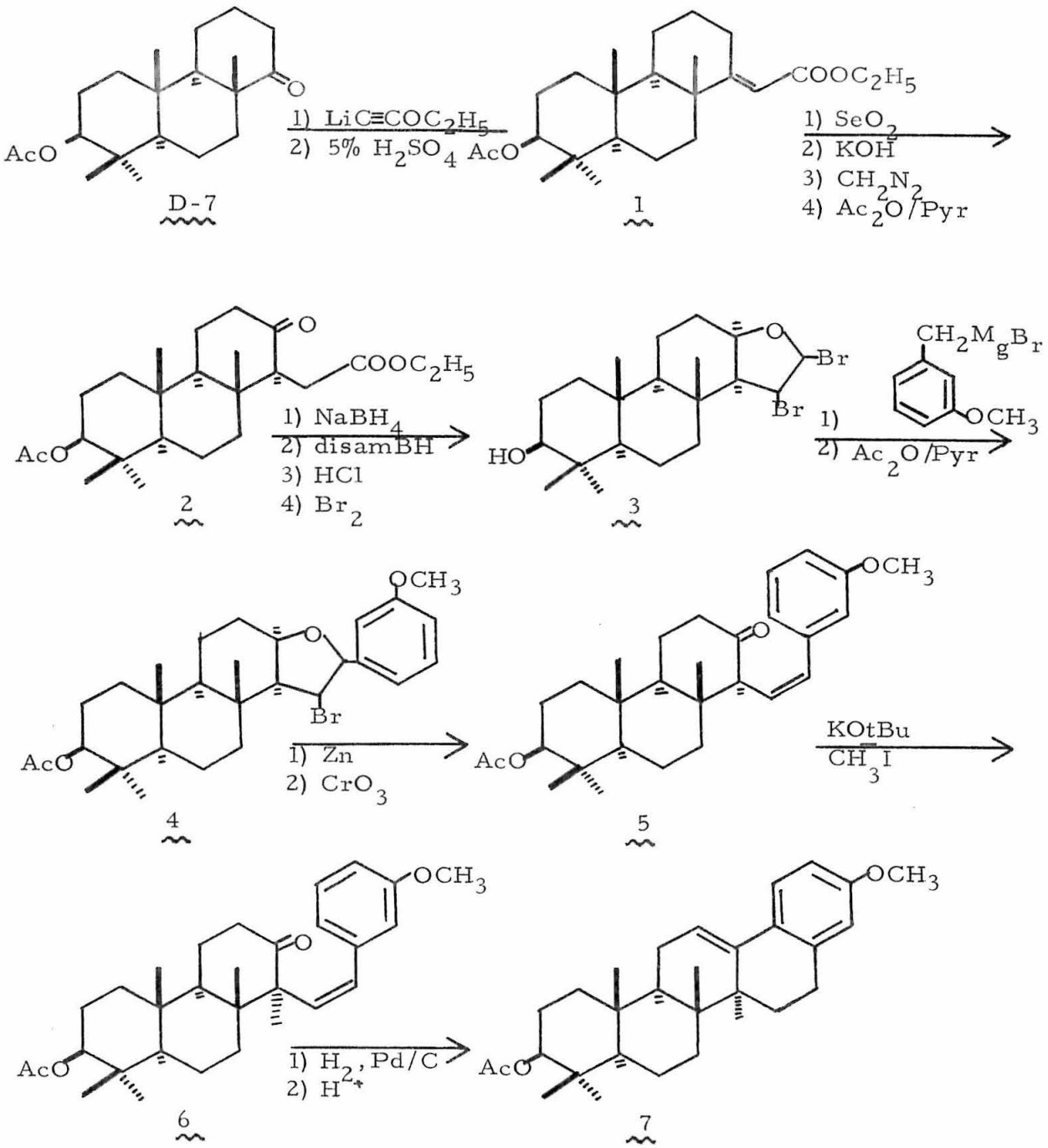
A-4

Precedent for the formation of keto ester E-2 was available from recent work of Sondheimer and co-workers (28) in their preparation of keto ester VII from keto acetate VI. Further, selective Grignard addition to the dibromo tetrahydrofuran moiety of E-3 was



VI VII

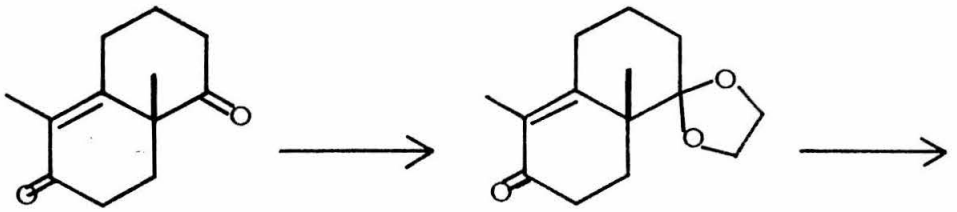
Chart E


AcO
O
1) LiC≡COC2H5
2) 5% H2SO4
COOC2H5
1) SeO2
2) KOH
3) CH2N2
4) Ac2O/Pyr
D-7
1
2
3
4
5
6
7
HO
Br
1) NaBH4
2) disamBH
3) HCl
4) Br2
CH2MgBr
OCH3
1) Zn
2) CrO3
KOtBu
CH3I
1) H2, Pd/C
2) H+

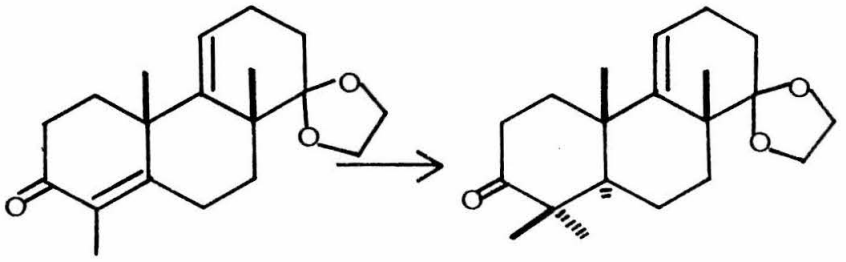
anticipated on the basis of studies by Crombie and Harper (29, 30) concerning Grignard additions to 2,3-dichloro tetrahydrofurans. In short, it appeared that a route to pentacyclic compound E-7 was available that had reasonable promise of success, if not compelling beauty. In a trial reaction lithium ethoxy acetylide added smoothly to keto acetate D-7, and hydrolysis with dilute sulfuric acid followed by reacetylation afforded a 56% yield of the unsaturated ester E-1.

At this time it became necessary to prepare a sufficient quantity of tricyclic keto acetate D-7 to sustain a research effort of some duration. This entire sequence will be briefly discussed since several modifications of the old procedures significantly improved the efficiency of the synthesis. Following the procedure of Brown (31), base catalyzed condensation of ethyl vinyl ketone, prepared from 1-chloro-3-pentanone by the procedure of Archer (32), with 2-methylcyclohexane-1,3-dione afforded an 84% yield of unsaturated diketone C-2. In an attempt to avoid the problems arising from base cleavage during the ensuing homoannelation, compound C-2 was treated with ethylene glycol and a trace of acid in benzene to afford a 94% yield of crystalline unsaturated ketone ketal VIII. This high yield is in contrast to the corresponding tricyclic unsaturated diketone D-1 which underwent selective ketalization quite inefficiently (50%) (33)

in forming ketone ketal D-2. Fortunately when ketone ketal VIII, which had previously been prepared by Kitahara and co-workers (81), was treated with ethyl vinyl ketone in the presence of sodium methoxide,



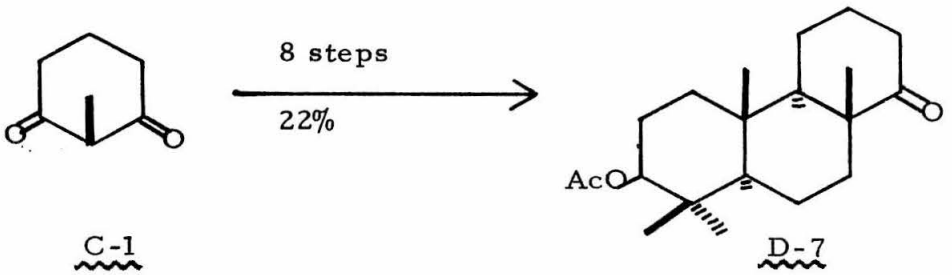
C-2 VIII



D-2 D-3

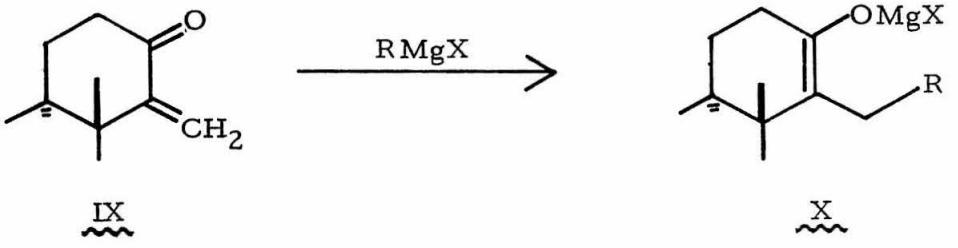
52% of the starting material VIII could be recovered on high vacuum distillation. Chromatography of the distillation residue on alumina afforded a 52% yield of the desired product D-2 based on the unrecovered starting material. This corresponds to a yield of 25% based on the initial amount of starting material in the reaction. The combined yield for the conversion of C-2 to D-2 was 23% versus 7.5% via the previous techniques. In addition, recycling the recovered ketone

ketal VIII twice increased this yield to 43%, representing more than a fivefold improvement on the previous procedure. Methylation at C-8 was accomplished as described by Brown (34), except that in this case an equivalent of tert-butyl alcohol was added to the reaction mixture. A 77% yield of ketone ketal D-3 was obtained after purification. The remaining steps in the preparation of keto acetate D-7 were performed without intermediate purification. Ketone ketal D-3 was reduced with lithium tri-tert-butoxy aluminum hydride (35) in tetrahydrofuran to give crude alcohol D-4. The latter, after hydrolysis of the ketal in dilute mineral acid and acetylation with acetic anhydride in pyridine, was passed through an alumina column. Subsequent reduction in an hydrogen atmosphere with 10% palladium on carbon in acetic acid afforded, after recrystallization, an 81% yield (four steps) of pure tricyclic keto acetate D-7. The combined yield of D-7 from 2-methylcyclohexane-1,3-dione C-1 was 22%.



C-1 D-7

While the preceding sequence was being completed, a second and more attractive route for the addition of rings D and E was conceived. If a compound containing a methylene ketone, as represented in partial formula IX, could be prepared, it seemed reasonable that it could be made to undergo conjugate addition with a suitable Grignard derivative RMgX. Moreover, it should be possible to quench



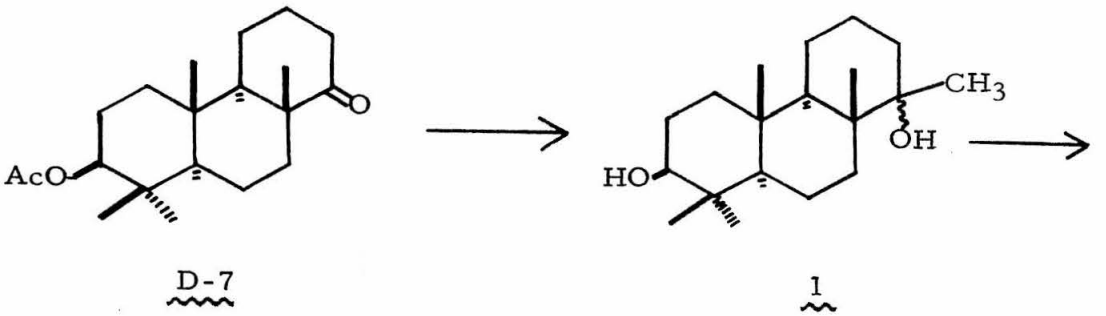
IX X

XI XII

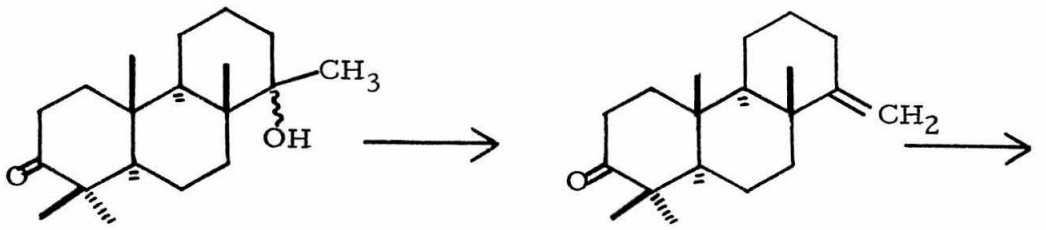
the intermediate magnesium enolate X with a variety of alkylating agents, depending on the specific goal of the synthesis. It was anticipated that copper catalysis during the conjugate addition would be necessary.

To this end the methylene ketone derived from keto acetate D-7 was prepared as summarized in Chart F. Methyl lithium addition to keto acetate D-7 proceeded without incident to give a mixture of sparingly soluble diols F-1 as shown by the unresolved methyl region of the nmr spectrum. Without purification the C-7 hydroxyl group of F-1 was oxidized with an equivalent of Jones' reagent to give keto alcohol F-2, which the nmr spectrum indicated was still an epimeric mixture at C-1. Dehydration of this mixture with thionyl chloride in pyridine at -15° occurred smoothly to give a mixture of olefins that consisted of 27% of the compound with the endocyclic double bond F-4 and 63% of its exocyclic isomer F-3 as adduced from an integration of the vinyl proton resonances in the nmr spectrum. The ratio of the amounts of the exocyclic isomer to the endocyclic isomer (2.3:1) allows one to make some estimate of the relative populations of the C-1 alcohol epimers in F-1 that arose during the methyl lithium addition. In studying the dehydration of the tertiary alcohols derived from cholestanone (36) with phosphorous oxychloride in pyridine, Barton showed that the equatorial 3 β-alcohol XIII gave predominantly the exocyclic methylene compound XV, while the 3 α-alcohol XIV afforded the endocyclic isomer XVI exclusively. If the extrapolation as to reaction mechanism from the phosphorous oxychloride-pyridine reaction medium to that in the thionyl chloride-pyridine reaction medium is valid, then the ratio of the amounts of β-hydroxyl compound

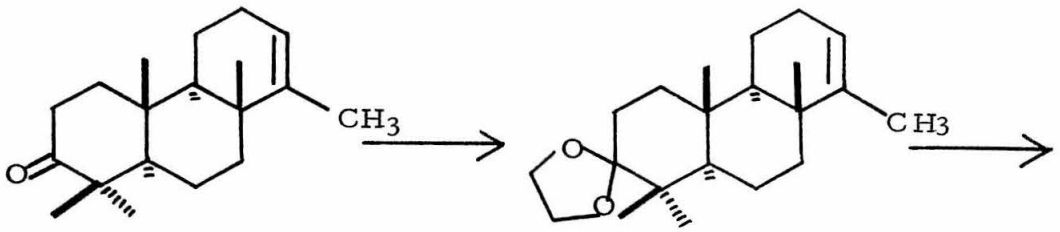
Chart F



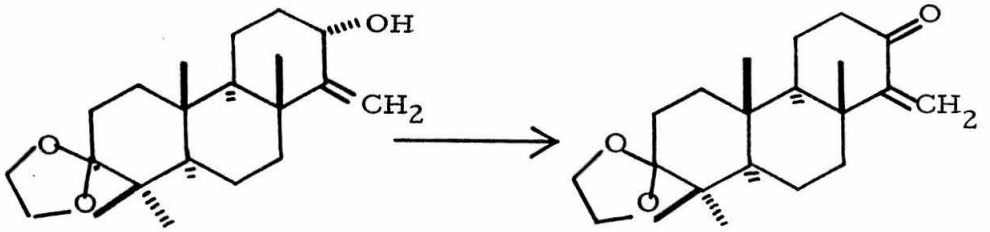
D-7 1



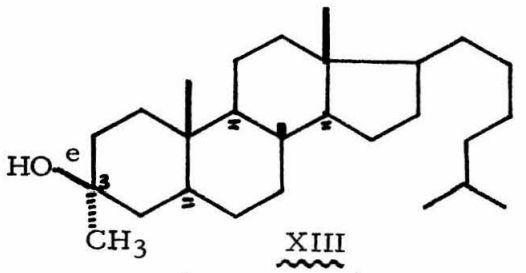
2 3



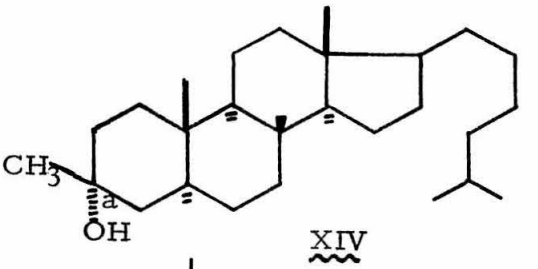
4 5



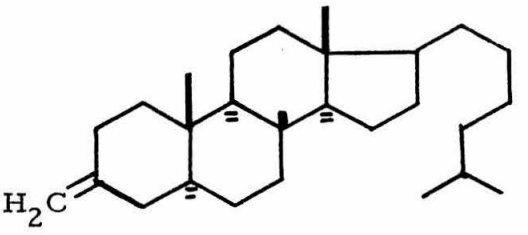
6 7



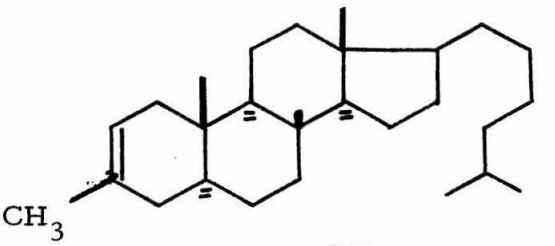
XIII



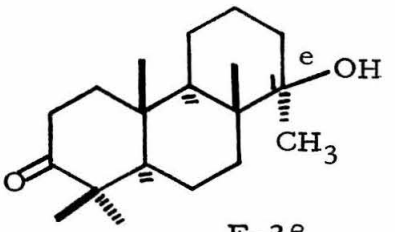
XIV



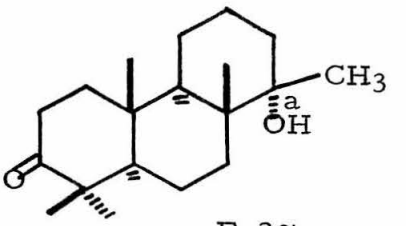
XV



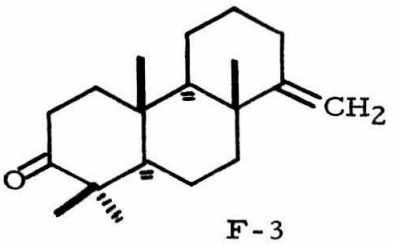
XVI



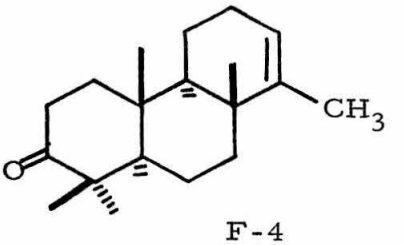
F-2β



F-2α



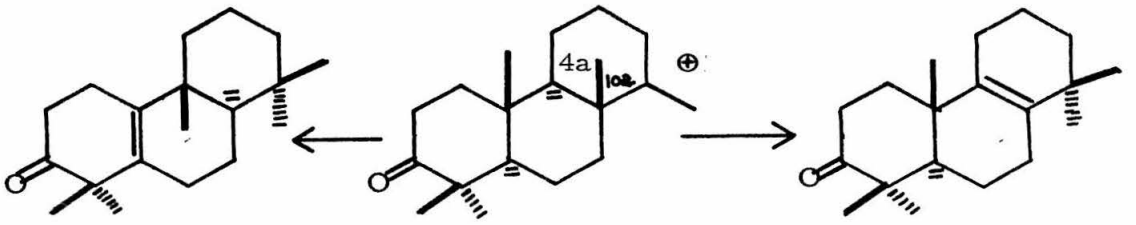
F-3



F-4

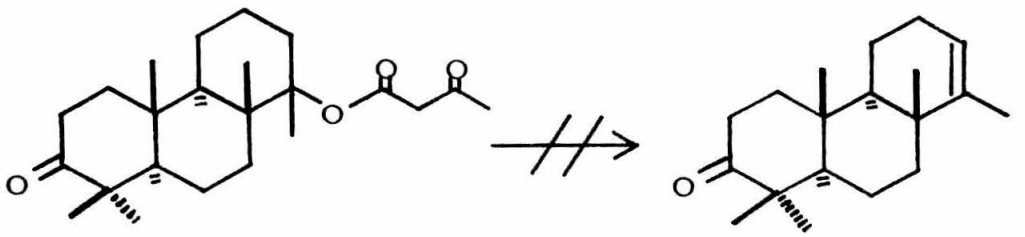
F-2β to α-hydroxyl compound F-2α is at least 2.3:1. The direction of this ratio is in accord with that expected on the basis of steric ease of approach of the nucleophilic methyl lithium species to the carbonyl group.

When purification of the olefin mixture F-3, F-4 was attempted by chromatography on silica gel, there was obtained a 2:3 mixture of two products. The major product was the desired endocyclic olefin F-4 as shown by its ir and nmr spectra. The minor product, $C_{19}H_{30}O$, had a strong, saturated carbonyl absorption in its infrared spectrum, but was devoid of any vinyl proton signals in its nmr spectrum. On this basis the new compound was tentatively assigned structure XVIII, arising from a biogenetic-like migration of the C-10a methyl group in ion XVII followed by loss of the C-4a proton. Compound XIX, however, is also a possibility and cannot be ruled out on the basis of the available evidence.



XIX XVII XVIII

Several methods were tried to selectively secure endocyclic olefin F-4. The first of these was the pyrolysis of the ester XX derived from diketene according to the procedure of Frisell and Lawesson (37). Although high yields of olefin F-4 were predicted, no recognizable products were obtained. Similarly, treatment of

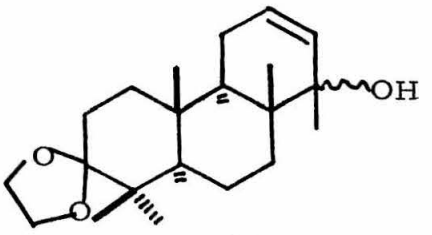


XX F-4

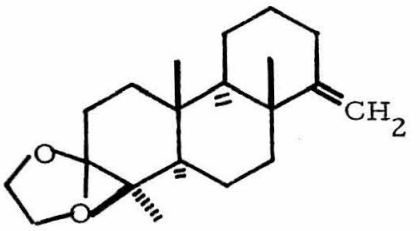
the alcohol mixture F-1α , F-1β with iodine at 140° according to the procedure of Church and Ireland (38) proved unsuccessful. An attempted equilibration of olefin mixture F-3, F-4 with anhydrous formic acid led only to the incorporation of formate as shown by strong ester carbonyl absorption in the infrared spectrum. Fortunately it was discovered that the endocyclic olefin F-4 could be secured in high yield by treatment of the mixture of olefins with p-toluenesulfonic acid in benzene at reflux. None of the rearranged product XVIII was detected. Protection of the C-7 carbonyl group by ketalization with

ethylene glycol proceeded without incident. The five-step transformation from keto acetate D-7 to endocyclic olefin F-5 could thus be accomplished in 86% yield if purification of the intermediates was avoided.

The introduction of an oxygen function at C-2 was accomplished by photooxidation according to the general procedure of Nickon and Bagli (39), using hemataporphrin dihydrochloride as sensitizer. The yields of this reaction varied considerably from experiment to experiment, being within the range of 45-67%. Structure F-6 with an equatorial C-2α alcohol was assigned to the major product on the basis of the broadness of the C-2β axial hydrogen in the nmr spectrum. The minor product, although not isolated in a pure state, is considered to be the C-2 hydroxyl epimer since both compounds can be oxidized to the same ketone F-7. No products corresponding to tertiary alcohols such as XXI were isolated, although the variety of products remaining in the reaction mixture does not preclude the possibility. An interesting side product isolated from the reaction mixture in 7% yield was the exocyclic olefin XXII. This product can be seen as arising from allylic hydrogen abstraction from starting olefin F-5 followed by rearrangement and hydrogen capture. The anticipated $^1\Delta g$ excited state of oxygen in sensitized photooxidations (40), which lies 22 kcal above the oxygen triplet ground state, would not be



XXI



XXII

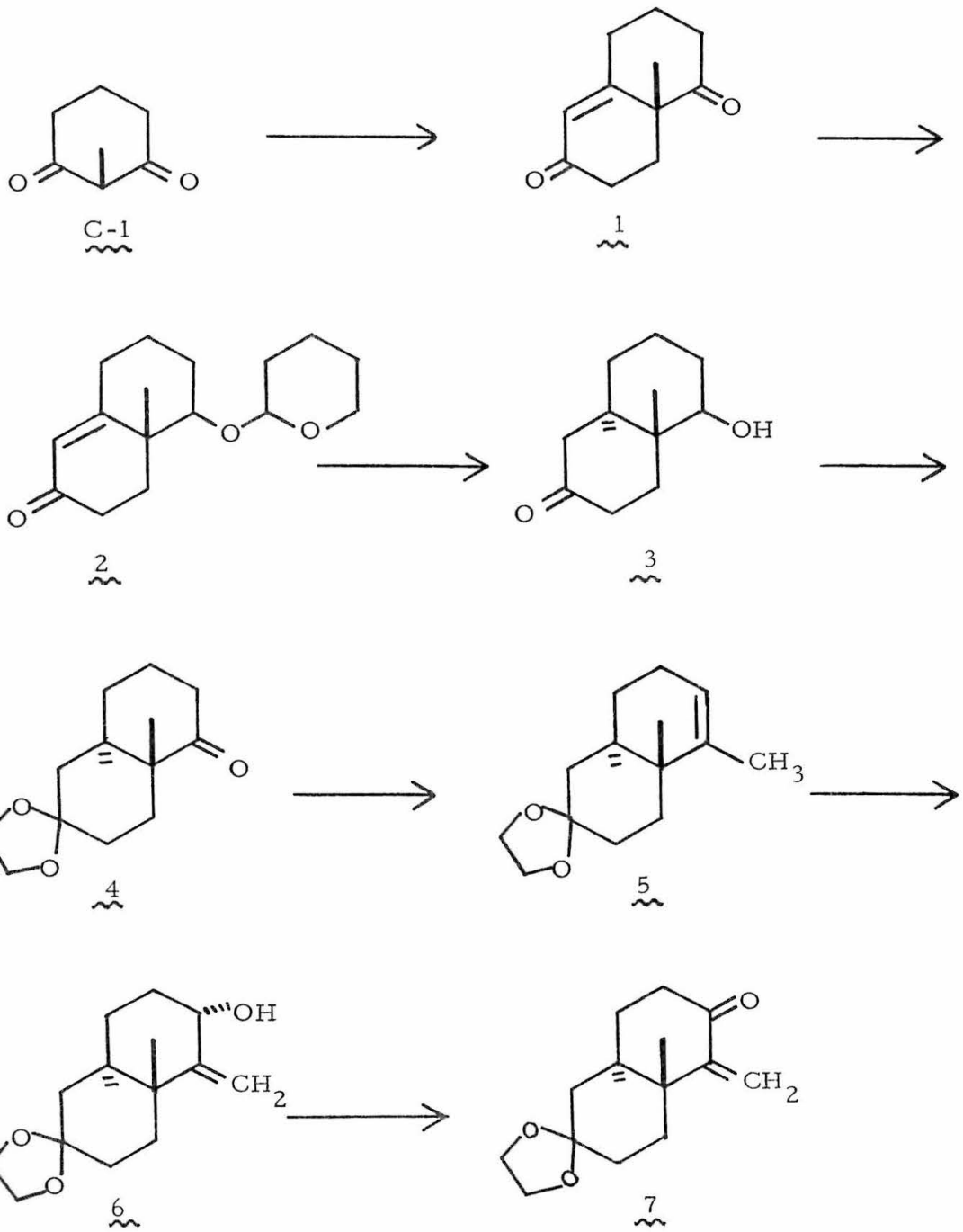
expected to be a good hydrogen abstractor on the basis of its electronic configuration. The second excited state, however, $^1\Sigma g^+$ has a singlet energy of 37 kcal. This species should resemble ground state oxygen in its electronic configuration (i.e., two electrons in different orbitals), and would be expected to be a good hydrogen abstractor. Perhaps significantly, the triplet energy of the hematoporphrin sensitizer is 37 kcal (41), sufficient to produce some $^1\Sigma g^+$oxygen. It seems reasonable, therefore, to ascribe the formation of product XXII to hydrogen abstraction by this reactive oxygen species.

The oxidation of allylic alcohol F-6 to methylene ketone F-7 proceeded smoothly with chromium trioxide-dipyridine in methylene chloride (42). This was fortunate, since the usual Sarett procedure (43) of chromium trioxide in pyridine as well as manganese dioxide had proved inferior.

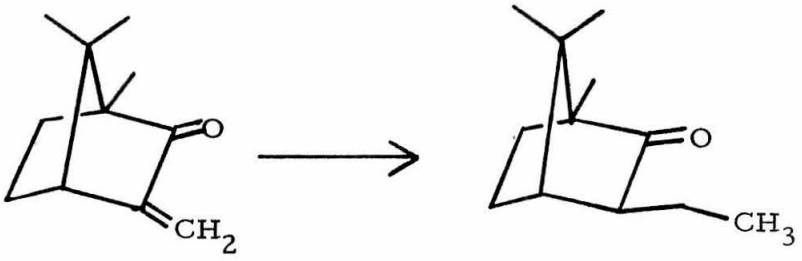
At this point a model compound for the planned conjugate addition reaction was chosen such that a maximum of information could be obtained without exhausting the supply of tricyclic methylene ketone F-7. As is desirable with all studies of this kind, the model employed should be available in sufficient quantity and should be as chemically similar to the authentic material as is conveniently possible. To this end was chosen the bicyclic methylene ketone G-7, the eleven-step synthesis of which is outlined in Chart G (44).

Keto alcohol G-3 was prepared as described by Dolfini (45). Ketalization of this material, followed by Jones' oxidation at 0°, afforded an 86% yield of ketal ketone G-4. Treatment of this material with methyl lithium and subsequent dehydration of the intermediate tertiary alcohol with iodine at 140° (38) produced olefin G-5 in 70% yield. Photooxygenation according to the procedure of Wharton (46) using rose bengal as a sensitizer in isopropyl alochol gave, after reduction of the intermediate hydroperoxide, a 70% yield of allylic alcohol G-6. This material was about a 9:1 mixture of the equatorial α-hydroxyl compound and its axial β-isomer. No search for a compound corresponding to exocyclic methylene XXII was conducted, although it was very likely present. Oxidation of the allylic alcohol mixture G-6 with chromium trioxide in pyridine (43) afforded a 46% yield of model methylene ketone G-7.

Chart G

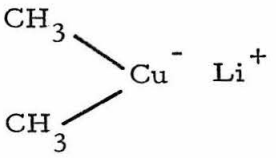


Conjugate addition to α,β-unsaturated carbonyl compounds by organo metallic reagents is a widely observed, yet little understood, process (47). By and large, the addition of a copper (I) or copper (II) salt to an organo magnesium or an organo lithium derivative facilitates conjugate (1,4) addition relative to normal (1,2) addition by enhancing the rate of the former and diminishing the rate of the latter. That a copper species is not always required, however, is confirmed by the observation (48) that methylmagnesium iodide adds to 3-methylene camphor XXIII to give the conjugate addition product XXIV exclusively.



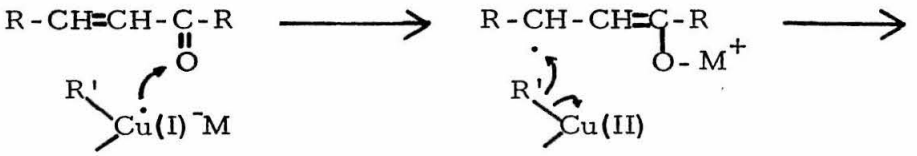
XXIII XXIV

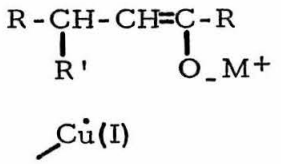
In a continuing series of papers on the copper catalyzed conjugate additions of lithium and magnesium derivatives (49-54), House finds compelling evidence that the reactive species is an ether soluble organocopper complex such as XXV. Although a definitive mechanism is lacking, there are strong indications that conjugate addition does not involve a cyclic transition state (50,55). House



XXV

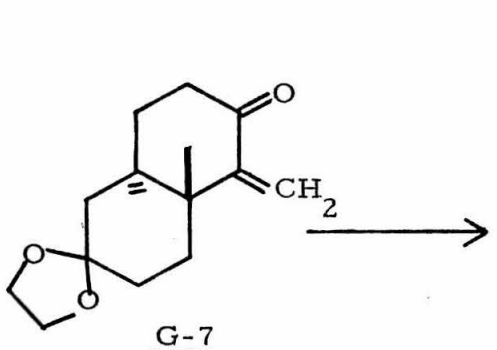
interprets his data (49) as favoring a one electron transfer from copper (I) to the carbonyl group producing an intermediate radical anion followed by alkyl radical transfer to give the enolate of the observed product.



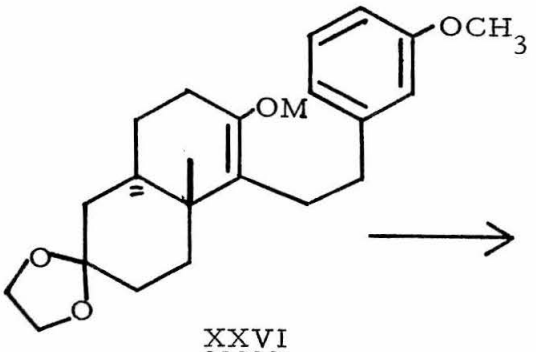


An interesting observation is that derivatives of metals less reactive than lithium and magnesium (Zn, Al, Cd, Be) exhibit a strong tendency toward conjugate addition in preference to 1,2 addition even when no copper species is present (56-58). Although the effect of added copper salts would be interesting in these cases, no information could be found.

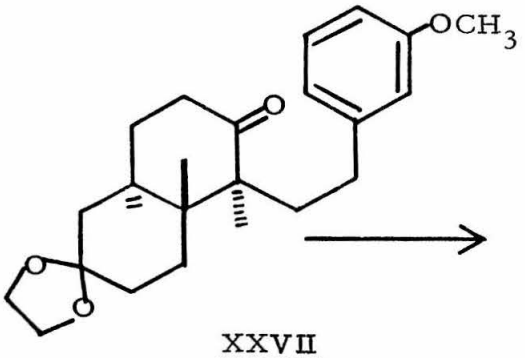
The m-methoxybenzyl group was chosen for the study of conjugate additions to methylene ketone G-7 since the product would be adaptable to further transformations required in the synthesis of germanicol. Because the results from m-methoxybenzyl derivatives closely paralleled those from the unsubstituted benzyl derivatives, the two were often used interchangably.



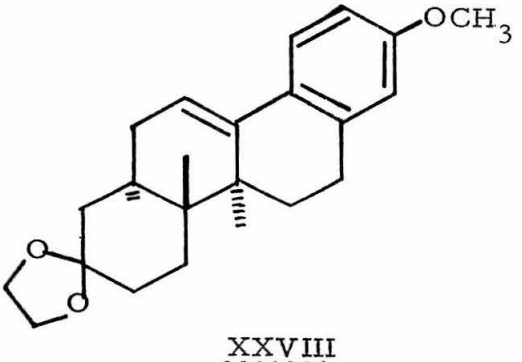
G-7



XXVI

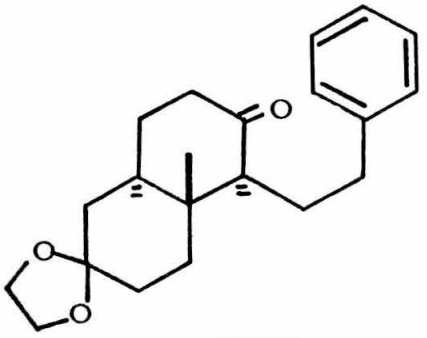


XXVII

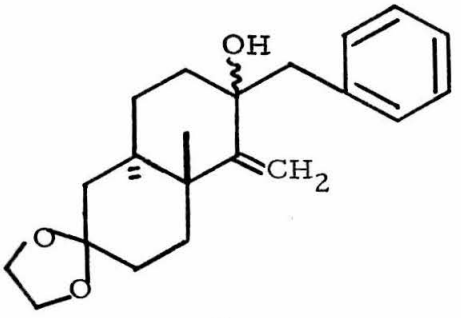


XXVIII

When methylene ketone G-7 was added to an ethereal solution of benzyl magnesium chloride containing 6.5 mole % of copper (II) acetate and the reaction quenched with ammonium chloride, there was obtained a 41% yield of the desired product XXIX. In addition, unresolved mixtures of products containing both carbonyl and alcohol absorptions in their infrared spectra were found. Attempts at separation were unsuccessful, but it is thought that they represent 1,2 (XXX) as well as 1,4 (XXIX) addition. Quenching with methyl iodide did not appreciably change the results, as shown by the persistence of considerable amounts of alcoholic material.



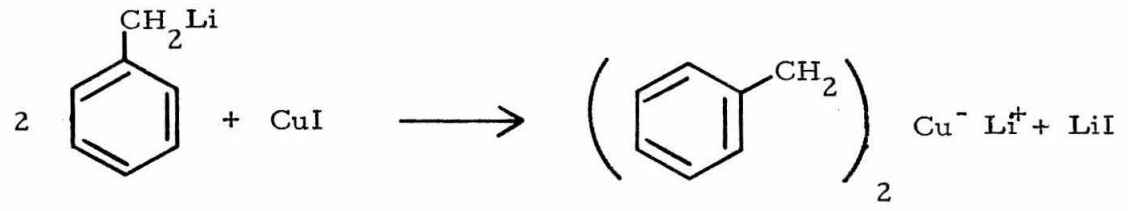
XXIX



XXX

Attention was next turned to the corresponding lithium derivatives. On the basis of the results of House (49-54) it was expected that the addition of one-half of an equivalent of copper (I) iodide to benzyllithium would produce a solution of lithiumdibenzylcopper. This material has the same stoichiometry as that of XXV, derived

from methyllithium which gives consistently high conversions to 1,4-products. Prior to 1950 there were no convenient preparations of

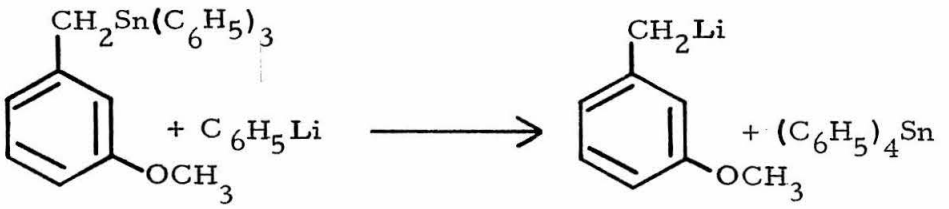


benzyllithium (59), but two potentially valuable preparations have recently been reported. The first (60) involves the cleavage of a benzyl ether with lithium metal. The anticipated metalation of an activated aromatic ring under these conditions, however, limits the value of this procedure. In the second method (61), the reaction of phenyllithium with benzyltriphenyltin in ether at -35° produces benzyllithium and solid tetraphenyltin. The yields of benzyllithium

$$(C_6H_5)_3SnCH_2C_6H_5 + C_6H_5Li \longrightarrow (C_6H_5)_4Sn + C_6H_5CH_2Li$$

in this reaction, as determined by double titration techniques (62), were about 80%; the yield of precipitated tetraphenyltin was 90%. Parallel results were obtained for the synthesis and decomposition of m-methoxybenzyltriphenyltin XXXI. It appeared that a convenient preparation of benzyltin and m-methoxybenzyltriphenyltin was in hand.

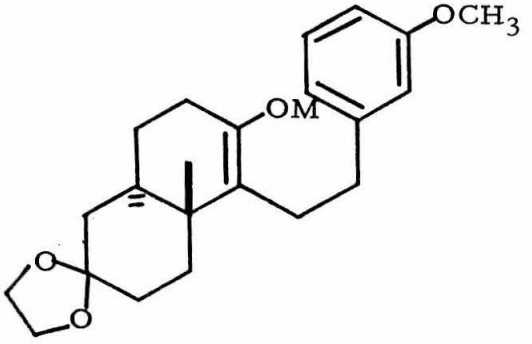
In practice the benzyllithium solution was separated from the tetraphenyltin by filtration, and copper (I) iodide added to the



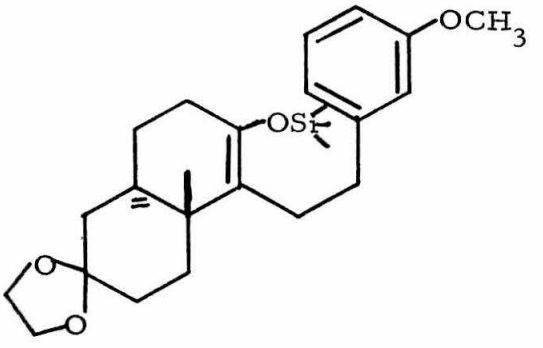
XXXI

supernatant liquid at -20°. The resulting green solution was essentially homongeneous. When the methylene ketone G-7 was added and the reaction quenched with ammonium chloride, yields of 45% of the expected product XXIX were obtained; alcoholic material was a considerably smaller portion of the reaction mixture than before. Interestingly, with no copper additive, 30% of compound XXIX was isolated in addition to 19% recovered starting material G-7 and 13% alcoholic material. An experiment in dimethoxy ethane with no copper additive yielded 42% product XXIX and 56% recovered starting material. Starting material recovery must arise from enolization by the benzyllithium, followed by protonation and recovery on workup. No starting material was recovered in reactions with added copper iodide.

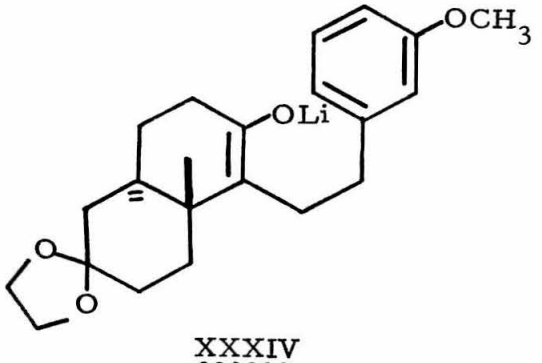
The results thus far indicate that enolization of starting material can be minimized using lithium dibenzylcopper, but that the biproducts in this reaction make purification of the product difficult. To resolve this difficulty, different quenching agents for lithium enolate XXXII were sought. The eventual necessity of a C-14α methyl group in germanicol A-4 required that the integrity of the enolate be maintained for a future methylation step. Two possibilities were considered. Chlorotrimethylsilane is an efficient



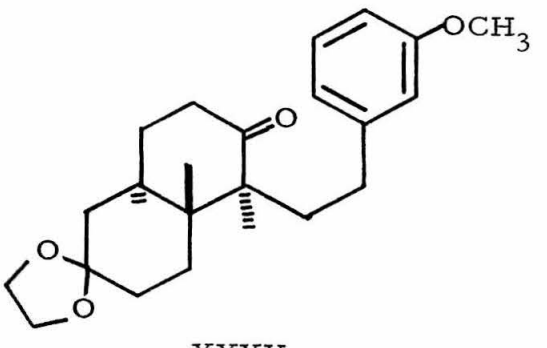
XXXII



XXXIII



XXXIV

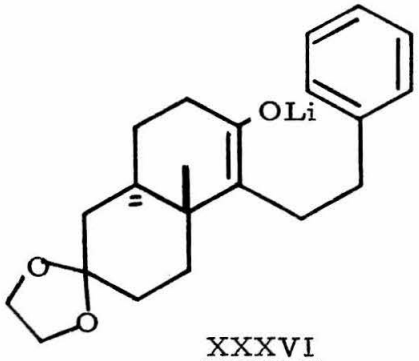


XXXV

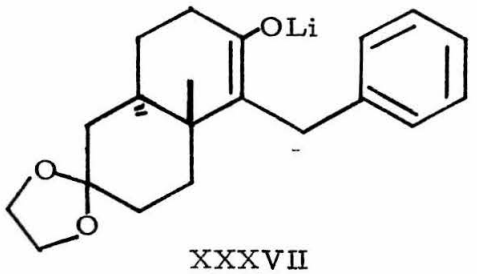
oxygen scavenger as demonstrated by recent studies of Bloomfield (63) in trapping the intermediate enediolates of the acyloin condensation. It was thus anticipated that the silyl ether XXXIII could be easily formed by adding chlorotrimethylsilane to enolate XXXII, and could also be easily alkylated by successive treatment with methyllithium and methyl iodide to give the necessary C-1 methyl group corresponding to C-14 of germanicol.

On the other hand, the susceptibility of the silyl ether XXXIII to water hydrolysis promised to make its isolation difficult. That the alkylation step was conceptually sound has recently been shown by Stork (64,65) in several efficient alkylations of the silyl enol ethers of cyclohexanone systems.

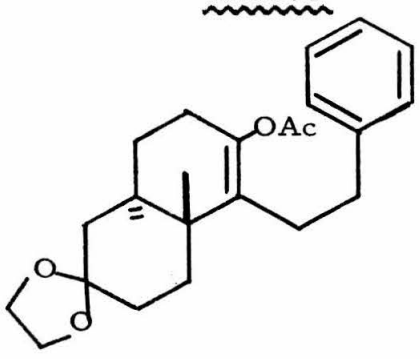
The quenching agent finally employed was acetic anhydride. The efficacy of this choice is demonstrated in the following experiments. When methylene ketone G-7 was treated as before with lithium dibenzylcopper at -20° and the resulting reaction mixture quenched with acetic anhydride, two products were isolated, the anticipated enol acetate XXXVIII in 46% yield and the unexpected enol acetate XXXIX in 26% yield. Product XXXIX is the result of conjugate phenyl addition and must be ascribed to the presence of either phenyllithium or lithium diphenylcopper at the time of reaction, even though an excess of benzyltriphenyltin relative to phenyllithium had been



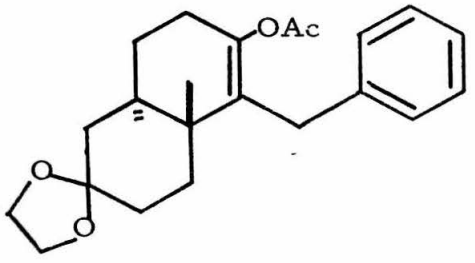
XXXVI



XXXVII



XXXVIII



XXXIX

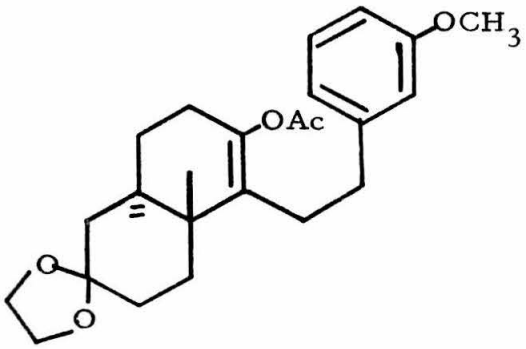
employed. Recalling that the yields of solid tetraphenyltin during the benzyllithium preparation were only 90%, it becomes obvious that there must be an equilibrium between the remaining tetraphenyltin and the benzyllithium. If competition for

$$(C_6H_5)_4Sn + C_6H_5CH_2Li \rightleftharpoons (C_6H_5)_3SnCH_2C_6H_5 + C_6H_5Li$$

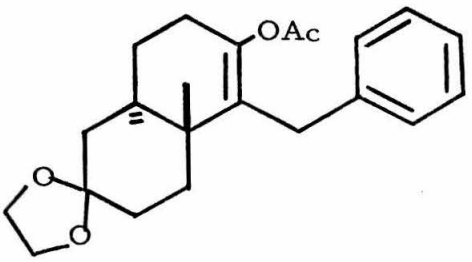
$$(C_6H_5)_3SnCH_2C_6H_5 + C_6H_5CH_2Li \rightleftharpoons (C_6H_5)_2Sn(CH_2C_6H_5)_2 + C_6H_5Li$$

conjugate addition favors lithium diphenylcopper, a relatively small proportion of phenyllithium would afford a significant amount of enol acetate XXXIX. Some indication as to the reactivity of lithium diphenylcopper was gained when an 89% yield of enol acetate XXXIX occurred on addition of methylene ketone G-7 to an ethereal solution of two parts of phenyllithium and one part of copper (I) iodide.

These results were paralleled with m-methoxybenzyltriphenyltin and phenyllithium. The expected product XL was formed in 51% yield, enol acetate XXXIX in 25%.



XL



XXXIX

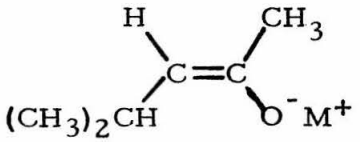
Running the reaction at lower temperatures (-60°) did not noticably affect the ratio of benzyl to phenyl addition. On the other hand, when the reaction was run at 0°, the yield of the expected benzyl product XL decreased to 31%, while the corresponding phenyl addition product increased to 50%. One convenient interpretation is that the increased solubility of tetraphenyltin at the higher

temperature led to a corresponding increase in the phenyllithium concentration and thus the change in product distribution. The lack of sensitivity to lower temperatures, however, casts some doubt on this interpretation.

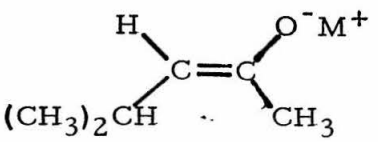
Some ancillary notes concerning the reaction of methylene ketone G-7 with the lithium organocopper derivatives are in order. When the reactions were run at 0^{o}, there was often no recognizable product obtained whatsoever. The exact reason for this is uncertain, but probably stems from the reactivity of the methylene ketone itself. The ease of dimerization of cyclic methylene ketones relative to their endocyclic counterparts is well documented (66); the added presence of a copper species may be sufficient to make precarious the balance between polymerization and the desired addition. Similar effects were noted when tetrahydrofuran was employed as a co-solvent. Again no useful products were found. It is reasoned that the superior ligand properties of tetrahydrofuran relative to ether result in an effective removal of copper from its anticipated role as a conjugate addition catalyst. A similar affect of uncatalyzed Grignard rate retardation by tetrahydrofuran has been noted by Holm (67) and by House (68).

The results just discussed were discouraging. Although good yields of conjugate addition were obtained (70-80%), the mixture of

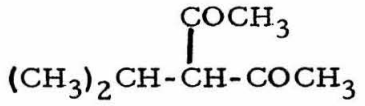
products, XXXVI or XL and XXXIX, greatly reduced the effectiveness of the method. It was decided to return to the organomagnesium compounds and investigate the product distribution using the acetic anhydride quenching technique. There was some concern that significant amounts of C-acylation would occur from the magnesium enolates in view of House's report (49) that enolates of type XLI and XLII give nearly equal amounts of diketone XLIII and enol acetates XLIX and XLV when M is magnesium, but only the enol acetates when M is lithium. However, the observation of Malhotra and Johnson (55)



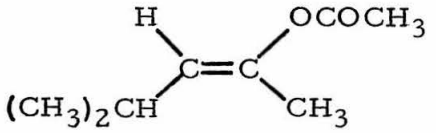
XLI



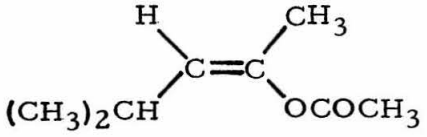
XLII



XLIII



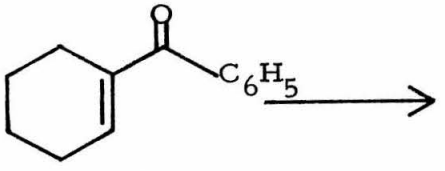
XLIV



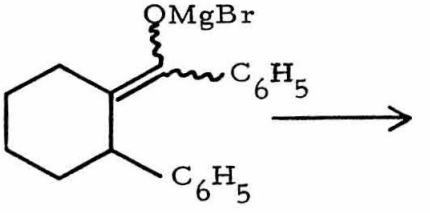
XLV

that only O-acylation was observed from ketone XLVI was encouraging.

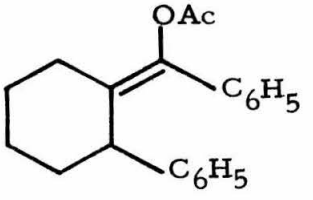
When methylene ketone G-7 with a trace of copper (II) acetate and either benzyl magnesium chloride or m-methoxy benzyl magnesium chloride were allowed to react, the product isolated after quenching with acetic anhydride was the expected enol acetate XXXVIII or XL



XLVI

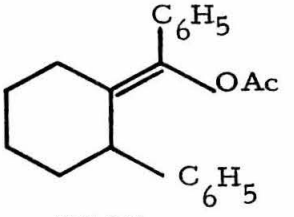


XLVII



XLVIII

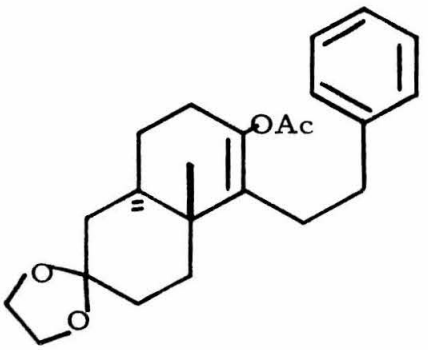
+



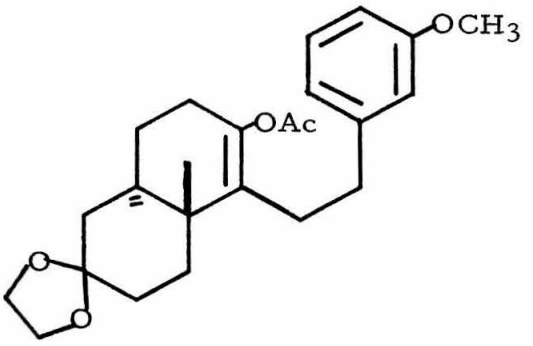
XLIX

XLVIII/XLIX ≈ 1

in 71% and 68% yields respectively. No product of C-acylation was found in either case. Similarly, when the Grignard additions were performed with no added copper salt, the yields of XXXVIII and XL were 73% and 71%. These conversions represent acceptable procedures. A summary of the results of the conjugate addition experiments is



XXXVIII

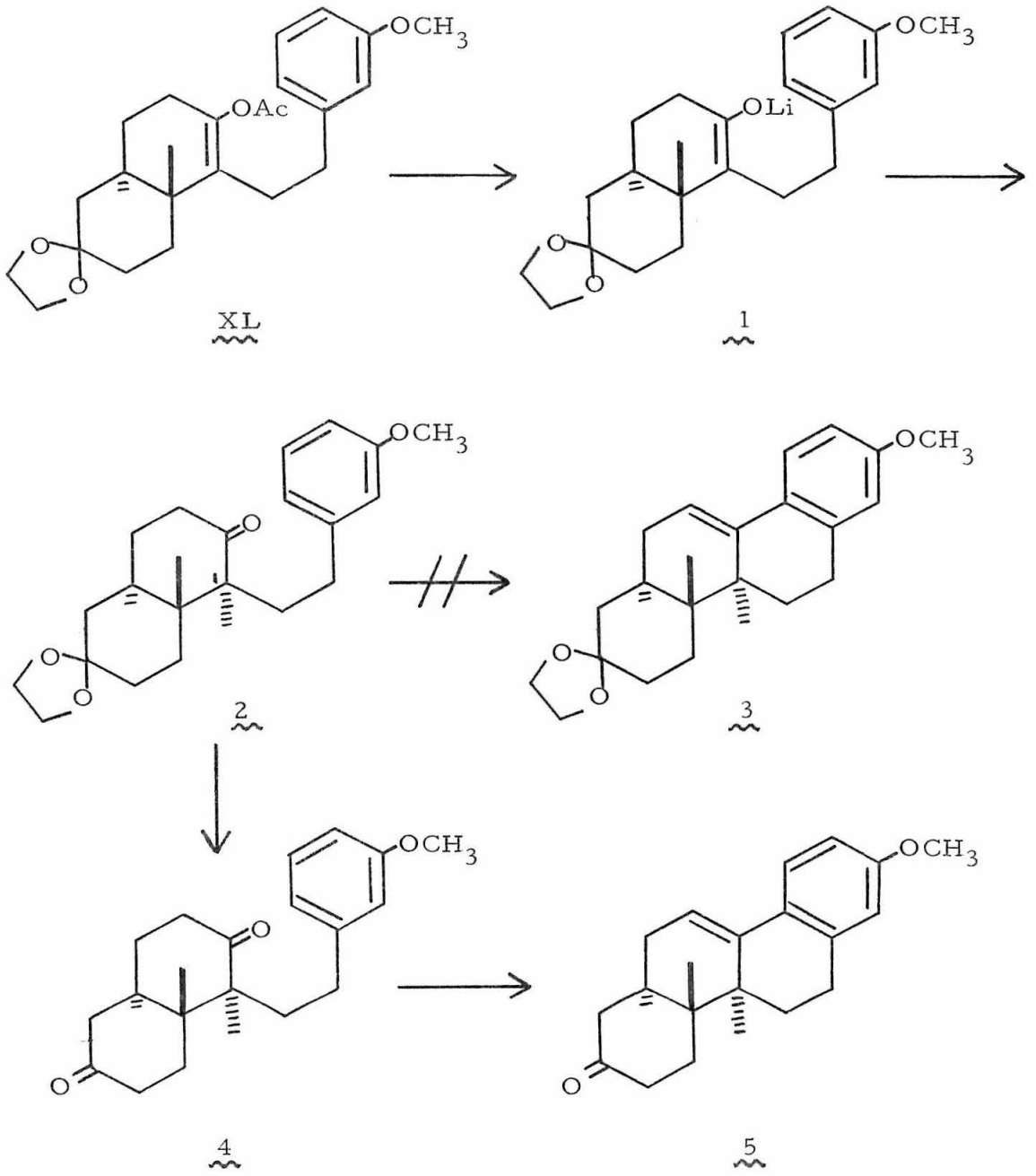


XL

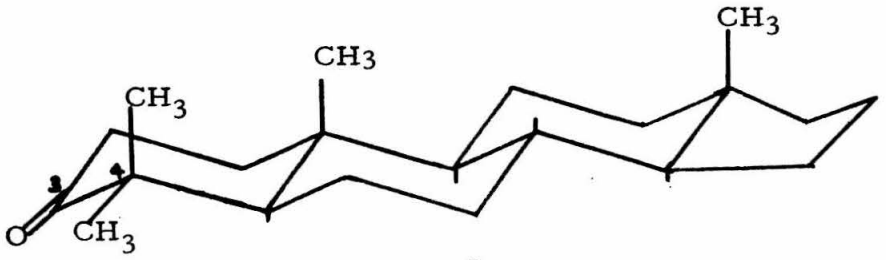
given in Table I for the organolithium compounds and in Table II for the organomagnesium derivatives (pages 84 and 89).

Some subsequent conversions anticipated for the germanicol synthesis were carried out on model enol acetate XL and are outlined in Chart H. The methylation procedure of House (69) proved very useful. Treatment of XL with two equivalents of methyl lithium in dimethoxy ethane gave lithium enolate H-1 which, on alkylation with an excess of methyl iodide, afforded a 78% yield of desired ketone H-2. It was imperative that the newly introduced C-1 methyl group have the alpha configuration shown in structure H-2. Confirmation of this stereochemical assignment was obtained using some recent nmr studies (70-73) of the magnitude and direction of the shifts of the quaternary methyl resonances in aromatic solvents relative to inert solvents ($CDCl_3$, CCl_4). In general, these studies determined that

Chart H

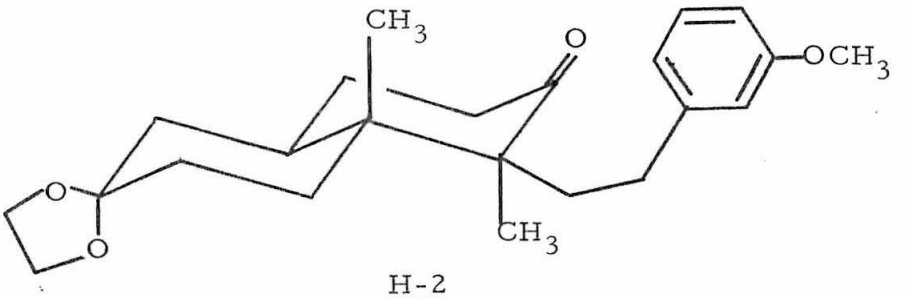


in ketones the resonances of methyl groups lying in or in front of a plane perpendicular to the C-O axis and passing through the carbonyl carbon will experience downfield (negative) shifts in benzene; methyl signals behind the plane will undergo upfield (positive) shifts. The following example is illustrative. The C-4 methyl resonances of compound L in deuteriochloroform both occur at 63 cps. In benzene solution the C-4α methyl group has a signal at 68 cps, a negative shift of 5 cps, while the C-4β methyl resonance occurs at 56 cps, a positive shift of 7 cps. Clearly the C-1 methyl group resonance in



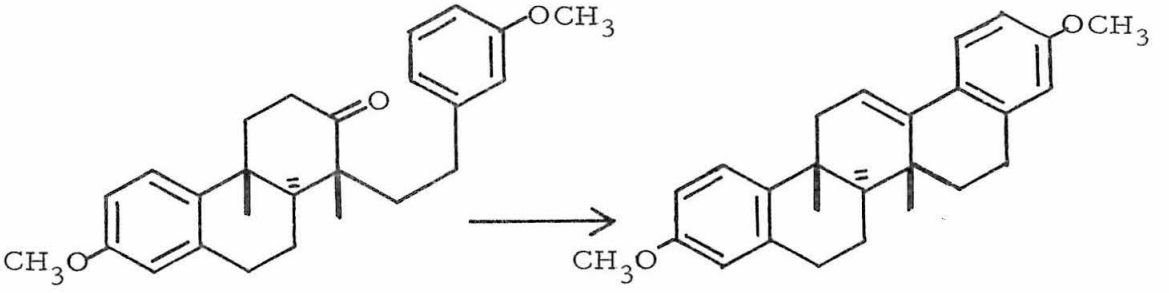
L

ketone H-2 should undergo a positive shift in benzene if the stereochemistry is as indicated. The observed shift of +18 cps (from 78 cps to 60 cps) clearly demonstrates that the desired stereochemistry has been achieved.



H-2

An attempted cyclization of ketone H-2 in p-toluenesulfonic acid and toluene at reflux resulted in destruction of starting material. This result is in contrast to ketone LI which under the same conditions smoothly cyclized to styrene LII (74). Fortunately dione H-4, the product of mild acid hydrolysis of ketone ketal H-2, underwent smooth cyclodehydration in polyphosphoric acid at 60-70° (75) to give the expected chrysene derivative H-5.



L I

LII

Transformations of tricyclic methylene ketone E-7. The success within the model series indicated that similar results in a synthesis of germanicol A-4 could be expected. A summary of the results of this investigation is found in Chart I. Enol acetate I-1 was secured from m-methoxybenzylmagnesium chloride and copper (II) acetate in 71% yield. With no copper (II) acetate a 74% conversion to I-1 resulted. Methylation was accomplished as before with two equivalents of methyl lithium to give lithium enolate I-2 which was then quenched with methyl iodide, affording a 76% yield of ketone ketal I-3. The orientation of the C-1 methyl group is assigned the alpha axial configuration on the basis of its +17cps shift in benzene relative to deuteirochloroform (from 77 cps to 60 cps). Hydrolysis of the C-7 ketal group to give dione I-4 was routine.

Dione I-4 represents the extent to which the synthesis has been carried. A preliminary cyclodehydration with polyphosphoric acid at 70° was inconclusive. Some product (≈10%) was formed but was impure. The indication is that although these reaction conditions were satisfactory in the model series, they are too severe in the present case. It is not expected that this will be a major obstacle.

Dione I-4 has subsequently been prepared in the laboratories of Professor W. S. Johnson of Stanford University, using a natural relay,

by the degradative-synthetic sequence summarized in Chart J (76).

A projected route for the completion of the synthesis of germanicol is outlined in Chart K; as such it does not appear to present any major difficulties. An early and successful conclusion to the task is anticipated.

Chart I

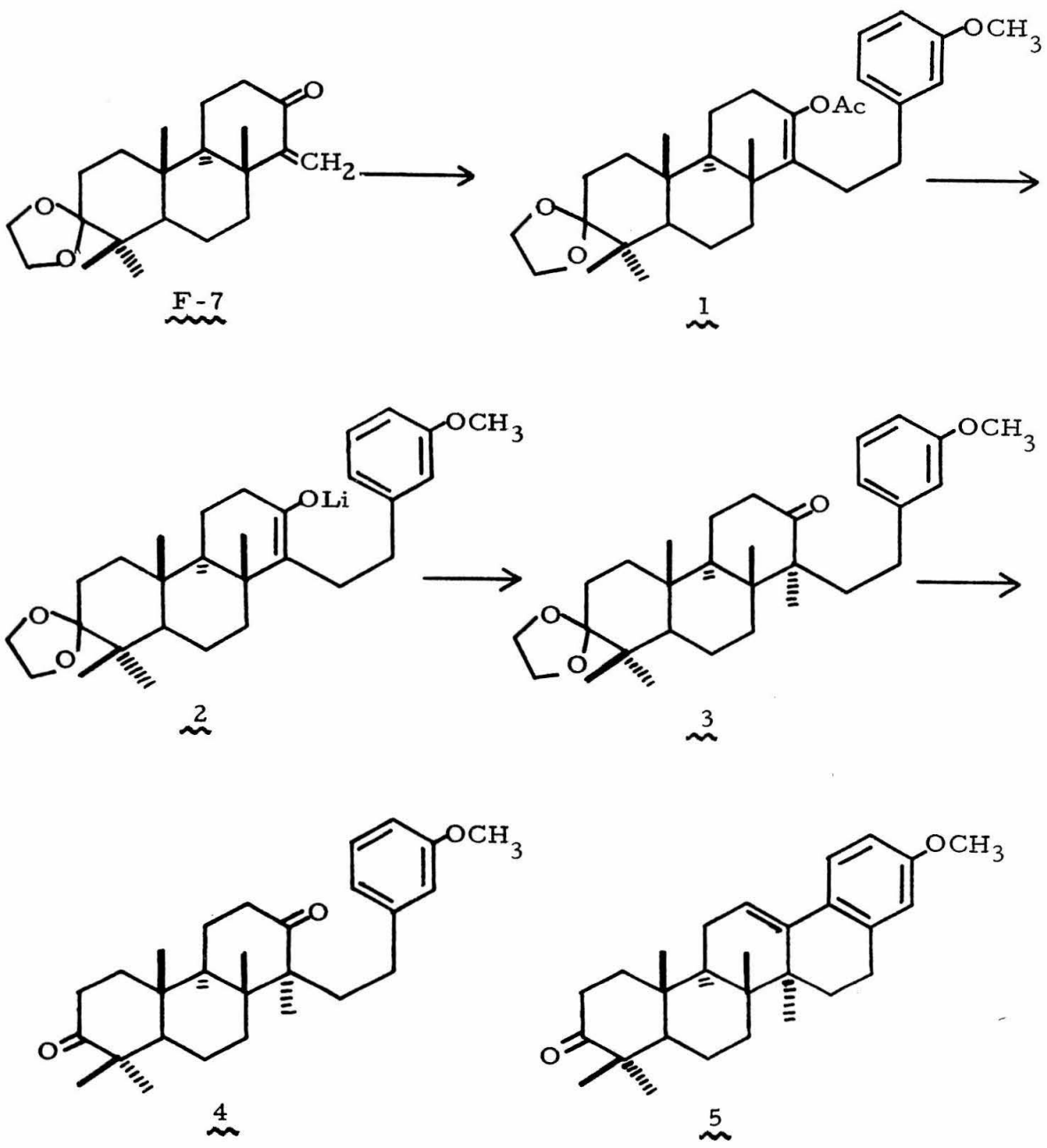


Chart J

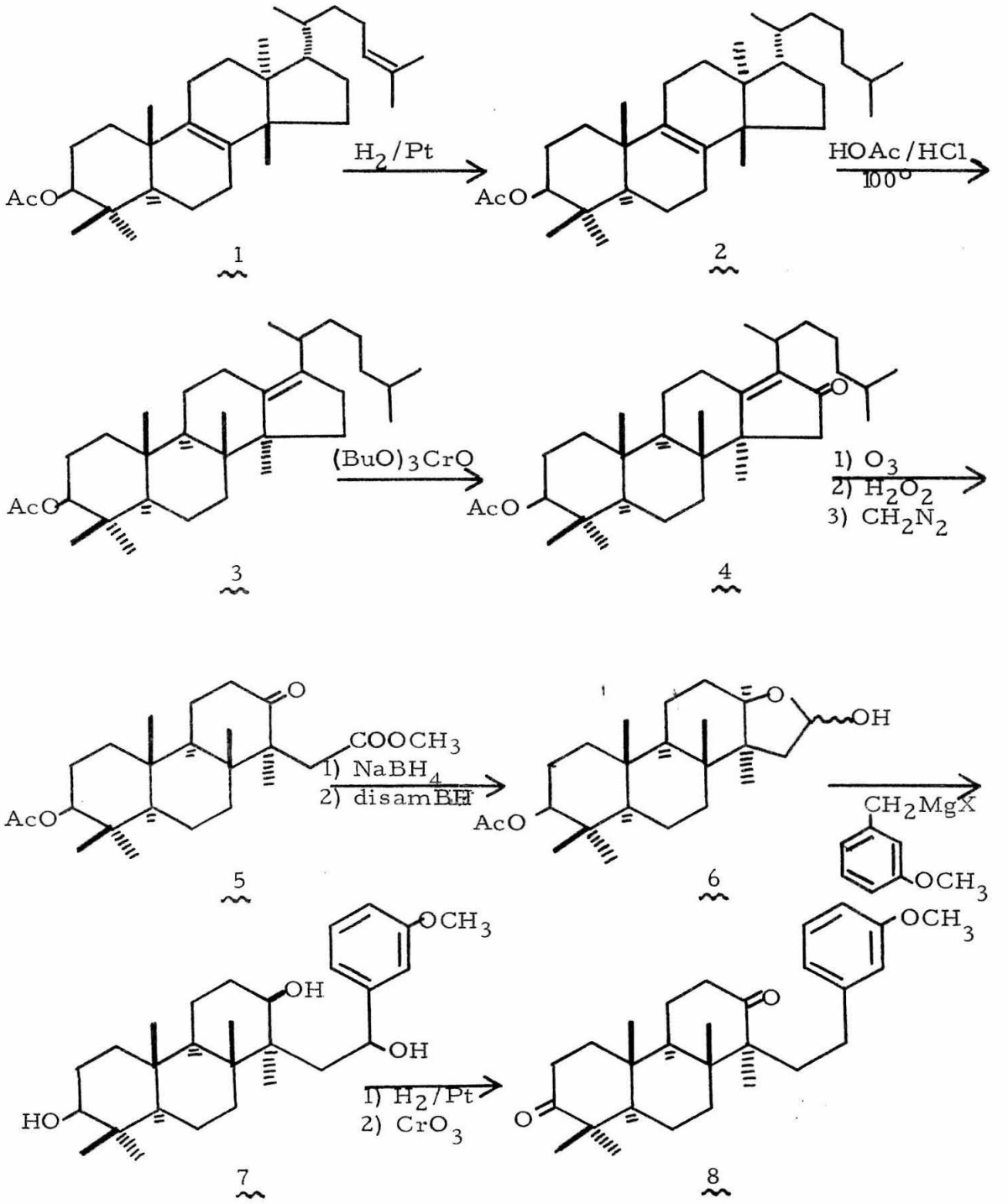
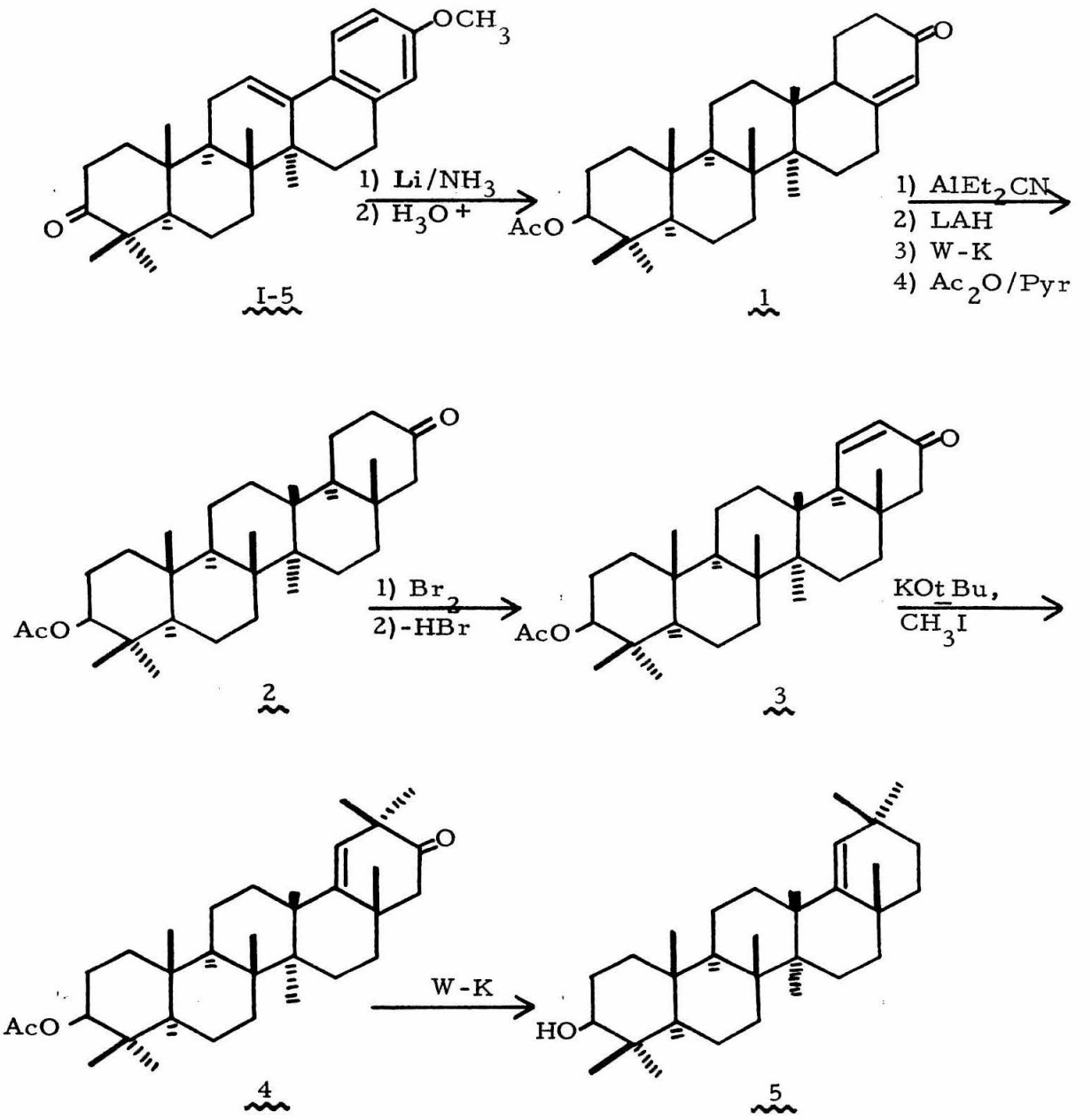

AcO
H_2/Pt
1
2
HOAc/HCl
100°
(BuO)$_3$CrO
3
4
1) O_3
2) H_2O_2
3) CH_2N_2
O
COOCH$_3$
1) NaBH$_4$
2) disamBH
5
6
OH
CH_2MgX
OCH$_3$
7
8
HO
OH
1) H_2/Pt
2) CrO_3

Chart K


OCH3
O
1) Li/NH3
2) H3O+
AcO
1) AlEt2CN
2) LAH
3) W-K
4) Ac2O/Pyr
I-5
1
1) Br2
2)-HBr
KOtBu,
CH3I
2
3
W-K
HO
4
5

Experimental Section

(a) All compounds described herein containing an assymetric carbon atom are racemic; the prefix "dl" has been omitted.

(b) Melting points (mp) were determined on a Kofler Micro Hot Stage melting point apparatus and are uncorrected.

(c) Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrophotometer. Solution spectra were observed in 0.1 mm cavity cells using chloroform as solvent and polystyrene calibration bands (3027.1 and 1601.4 cm^{-1}).

(d) Nuclear magnetic resonance (nmr) spectra were determined on a Varian spectrometer using Silinar C [Merck, Sharp, and Dohme trade name for deuterochloroform ($CDCl_3$) containing 1% tetramethylsilane (tms) as an internal standard] or benzene (C_6H_6) as solvent. Resonances are recorded in ppm (δ) downfield from tms.

(e) Vapor phase chromatographic (vpc) analyses were performed on an F & M Model 810 Research Chromatograph equipped with hydrogen flame detectors. Columns used were generally 6' x 1/8" 5-10% SE-30 or SE-52 on diatoport S. The carrier gas (helium) flow rate was maintained at 60 ml/min. Retention times (rt) were recorded in minutes.

(f) Analytical thin layer chromatography (tlc) was performed on 1" x 3" microscope slides covered with silica gel G, Brinkmann Instrument Co. Components were detected by spraying with a 5% solution of phosphomolybdic acid in ethanol followed by heating at 100-150° for several minutes.

Preparative thick layer chromatography (ptlc) was performed on 20 x 20 cm plates coated with a 1 mm layer of silica gel $PF_{254+366}$, Brinkmann Instruments Co. Bands were generally observed with the aid of uv light. Compounds were removed from specific bands by washing with ether-chloroform.

(g) Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

(h) Anhydrous solvents were dried immediately prior to use. Ether, benzene, tetrohydrofuran (THF), and dimethoxyethane (glyme) were distilled from lithium aluminum hydride (LAH); tert-butyl alcohol was distilled from calcium hydride; pyridine was distilled from either barium oxide or calcium hydride. Petroleum ether refers to the fraction of boiling point (bp) 30-60° as supplied by J. T. Baker Chemical Co.

(i) The isolation procedure generally employed involved dilution and extraction with the solvent indicated, separation of the aqueous and organic phases, and washing of the organic layers with saturated sodium bicarbonate solution (if the reaction medium had been acidic), water until neutral (litmus), and brine. Concentration generally refers to evaporation to constant weight on a rotary evaporator.

Ethyl vinyl ketone.--The general procedure of Archer and co-workers (32) was followed. To a 3 l. flask equipped with a mechanical stirrer and a Claisen distilling head was added one-half of 535 g (4.45 moles) 1-chloro-3-pentanone (77) and 1 g dihydroquinone. To this with moderate heating was slowly added 715 g (4.97 moles) oven-dried sodium benzoate. When the slurry became difficult to stir the remaining 1-chloro-3-pentanone was added, followed by the remaining sodium benzoate. Continued heating and vigorous stirring resulted in a clear distillate (bp 95-123°) which was dried ($CaCl_2$) to afford 321 g clear liquid containing less than 1% 1-chloro-3-pentanone by vpc (oven temperature 80°, rt 2.5 min). Redistillation produced 309 g (82%) clear liquid, bp 100-103°; [lit (78) bp 101.1-101.3° (732.8 mm)].

5,8aβ-Dimethyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione (C-2).--The procedure of Brown (31) was followed in the preparation of this diketone. A mixture of 98.0 g (0.776 mole) 2-methylcyclohexane-1,3-dione (79),101.0 g (1.19 moles) freshly distilled ethyl vinyl ketone, and 5 pellets of potassium hydroxide in 300 ml of reagent methanol were heated under reflux in a nitrogen atmosphere for 4 hr. The excess ethyl vinyl ketone and methanol were removed on a rotary evaporator using benzene as an azeotroping agent. To this dark oil

was added 500 ml reagent benzene and 7.5 ml pyrrolidine (Eastman Kodak, practical grade) and the resulting solution heated under reflux in a nitrogen atmosphere for 16 hr. The water formed during this period (13 ml, 93% of theoretical) was removed by means of a Dean-Stark water separator. The reaction mixture was cooled, diluted with 600 ml ether, and washed successively with 2% hydrochloric acid, water, and brine. Drying ($MgSO_4$) and concentration produced 153 g red oil which was vacuum distilled to afford 124 g (84%) light yellow oil, bp 123-149° (0.2-0.4 mm) that was homogeneous by vpc (oven temperature 200°, rt 3.1 min). A small portion of this oil was crystallized by trituration with ether to give colorless crystals, mp 36-40° [lit (80) mp 45-46°].

5,8aβ-Dimethyl-1,1-ethylenedioxy-1,2,3,4,8,8a-hexahydro-6(7H)-napththalenone (VIII).--To a 5 l. flask equipped with an overhead stirrer was added 52.0 g (0.272 mole) dione C-2 described above, 250 ml ethylene glycol, 686 mg p-toluenesulfonic acid monohydrate, and 3500 ml reagent benzene. The solution was heated under reflux in an atmosphere of nitrogen for 4.5 hr. The water formed during the reaction was removed by means of a Dean-Stark water separator. Upon cooling, the reaction mixture was poured into a 5 l. separatory funnel, the glycol phase (lower) removed, and the benzene phase

worked up as usual. After drying ($MgSO_4$) and concentration there remained 64 g pale yellow oil which, on the addition of 150 ml petroleum ether and cooling in a dry ice-acetone bath, deposited 53.1 g pale yellow powder, mp 48-50°. A second crop of crystals obtained in the same manner weighed 6.7 g, mp 45-48°, making the combined yield 93.5%. Two recrystallizations from pentane and one from ether-pentane afforded the analytical sample, mp 56-56.5°. ir ($CHCl_3$) 1655 cm^{-1} (C=O), 1605 cm^{-1} (C=C), 1375 cm^{-1} ($-CH_3$), 1180-1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 1.33 (s, 3, C-8a $-CH_3$), δ 3.95 (s, 4, ketal).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.16; H, 8.38.

Subsequently an alternate report of ketal ketone VIII was encountered in the literature (81) with a reported melting point of 55-56°.

1,1-Ethylenedioxy-1,2,3,4b,5,9,10,10a-octahydro-4bβ,8,10bβ-trimethyl-7(6H)-phenanthrone (D-2).--A flask containing 14.97 g (63.5 mmoles) ketone ketal VIII, mp 48-50.5° and 3.43 g (63.5 mmoles) of fresh sodium methoxide in 50 ml reagent methanol under an atmosphere of nitrogen was heated (bath 68°) for 0.5 hr. To this was added dropwise over 0.5 hr 5.35 g (63.5 mmoles) freshly distilled

ethyl vinyl ketone and the resulting dark solution heated at reflux for 10 hr. After cooling, the reaction mixture was worked up as usual. Drying ($MgSO_4$) and concentration produced 18.9 g light yellow oil which was vacuum distilled to give 7.8 g (52%) of colorless oil, bp 105-111° (0.07 mm). Crystallization of this material from pentane in a dry ice-acetone bath gave 6.9 g white solid, mp 42-46° that was identical by a comparison of ir and nmr spectra to the starting bicyclic ketal ketone VIII. The pot residue from the distillation was chromatographed on 300 g Woelm activity III neutral alumina. Elution with 10 l. 7% ether-petroleum ether produced residual starting material, several components of unknown structure, and a small amount of the desired tricyclic product. Further elution with 8 l. 18% ether-petroleum ether afforded 5.12 g pale yellow oil that deposited 4.21 g white crystals, mp 62-66°, on trituration with cold pentane. These crystals did not depress the melting point (mp 62-65°) of an authentic sample of tricyclic ketone ketal D-2 (82). In addition, the ir and nmr spectra of the two samples were identical. Rechromatography of the mother liquors on 40 g Woelm activity III neutral alumina yielded an additional 0.61 g tricyclic ketone ketal D-2, mp 61-65°. The yield of D-2 in this experiment was thus 25% based on the amount of starting bicyclic ketone ketal and 52% based on unrecovered starting material. The range of yields for this reaction over 12

experiments was 31-52% based on unrecovered starting material. In addition, two recyclizations of recovered starting material raised the yield in this step to 43% based on starting material used in the first cycle.

1,2,3,4b,5,6,8aα,9,10,10a-Decahydro-1,1-ethylenedioxy-4bβ,8,8,10aβ-tetramethyl-7(8H)-phenanthrone (D-3).--The ketone ketal D-3 was prepared by the general procedure of Brown (34). Thus a solution of 12.56 g (41.5 mmoles) tricyclic enone D-2 and 3.01 g (40.7 mmoles) dry tert-butyl alcohol in 250 ml anhydrous ether was added over five minutes to a flask containing a vigorously stirred solution of 1.10 g (159 mmoles) lithium wire in 1 l. dry (freshly distilled from sodium) ammonia and 300 ml anhydrous ether. After 0.25 hr a solution of 100 g dry (freshly distilled from calcium chloride) methyl iodide in 100 ml anhydrous ether was added in one lot. The ammonia was allowed to evaporate over 10 hr and then the reaction mixture was diluted with 400 ml ether and washed with water and brine. Drying ($MgSO_4$) and concentration afforded 12.6 g yellow oil. The addition of 25 ml ether and a seed crystal of ketone ketal D-3 produced after 12 hr at 0° 9.30 g white solid, mp 94-98°. Recrystallization from petroleum ether gave 8.17 g (62%) colorless crystals, mp 97-99°. The combined mother liquors (4.3 g) were chromatographed

on 400 g alumina (Woelm III, neutral) and eluted with 7 l. 15% ether-petroleum ether to give 1.74 g white prisms, mp 98-103°. The total crystalline material (9.91 g, 77%) was identical by a comparison of ir and nmr spectra to authentic ketone ketal (D-3).

7β-Acetoxy-3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-docedecahydro-4bβ,8,8,10bβ-tetramethyl-1(2H)-phenanthrone (D-7).

A. Reduction with lithium tri-tert-butoxyaluminum hydride.--The procedure of Brown (83) was modified for this reaction. To a solution of 2.41 g (7.58 mmoles) ketone ketal D-2, mp 97-99°, in 75 ml anhydrous tetrahydrofuran was added a solution of 8.00 g (31.4 mmoles) lithium tri-tert-butoxyaluminum hydride (35) in one lot and the combined material heated at reflux under a nitrogen atmosphere for 1 hr. After cooling, 6.5 ml 5% sodium hydroxide solution was added slowly and the resulting mixture stirred for 5 hr. The precipitate was removed by filtration and carefully washed with several portions of ether. Concentration of the organic material afforded 2.46 g white powder possessing strong alcohol absorption at 3600 and 3440 cm^{-1} in its ir spectrum and no significant carbonyl band. This material was carried on without further purification.

B. Acid hydrolysis of alcohol D-4.--A solution of 2.46 g crude alcohol from above in 150 ml acetone and 50 ml 10% hydrochloric acid

was stirred at room temperature for 1 hr. Most of the acetone was removed on a rotary evaporator and the resulting aqueous phase worked up as usual with ether. Drying ($MgSO_4$) and concentration afforded 2.12 g oily solid that was immediately acetylated.

C. Acetylation of crude keto-alcohol D-5.--The crude keto-alcohol D-5 was acetylated as described by Rasmusson (84). Thus 2.12 g of oily solid from above in 50 ml of 1:1 anhydrous pyridine-acetic anhydride were allowed to stand at room temperature under a nitrogen atmosphere for 16 hr. The excess pyridine and acetic anhydride were removed on a rotary evaporator with several toluene azeotropic distillations to give 2.59 g yellow solid. This crude acetate D-6 was passed through a column of 100 g Woelm activity III neutral alumina, eluting with 25% ether-petroleum ether, to give 2.06 g white solid, mp 121-128°.

D. Catalytic reduction of keto-acetate D-6.--Following the procedure of Rasmusson (84), 2.06 g crude keto acetate D-6 in 100 ml glacial acetic acid was exposed to an atmosphere of hydrogen in the presence of 350 mg of 10% palladium on carbon. After 205 ml of hydrogen had been consumed (20 hr) the catalyst was removed by filtration and the filtrate concentrated at reduced pressure. The residue was dissolved in 70 ml acetone, cooled to 0°, and treated with 1 ml of Jones' reagent. The mixture was stirred for 0.5 hr and

then 2 ml iso-propyl alcohol added and the mixture stirred an additional 0.25 hr. After 25 ml water were added, the acetone was removed on a rotary evaporator and resulting aqueous mixture worked up as usual with ether. The ethereal extract was dried ($MgSO_4$) and concentrated to a crystalline solid. Recrystallization from n-heptane afforded 1.96 g (81%) white plates, mp 153-156°; [reported (84) mp 161-162.5°].

7β-Acetoxy-1-carbethoxyethylidine-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-tetradecahydro-4bβ,8,8,10aβ-tetramethylphenanthrene (E-1).--Following the procedure of Sondheimer and co-workers (28), to a cooled (0°), stirred solution of 1.25 ml methyl lithium solution (2.13 M in ether; 3.25 mmoles) in 1 ml dry ether under a nitrogen atmosphere was added dropwise 326 mg (4.60 mmoles) ethoxy acetylene in 2 ml dry ether. After stirring 0.5 hr at room temperature, the solution was cooled to -15° (ice-methanol) and 104 mg (0.325 mmole) keto acetate D-7 in 3 ml dry ether was added dropwise over 15 min. After stirring at -10° for 1 hr and at room temperature for 18 hr, the reaction mixture was worked up with ether as usual. Drying ($MgSO_4$) and concentration produced 170 mg yellow oil which showed a strong acetylene absorption in the ir spectrum at 2250 cm^{-1}. The crude oil was dissolved in 10 ml methanol and 1 ml 5% sulfuric acid

and stirred at room temperature for 1.5 hr, whereupon a normal ether workup afforded, after drying ($MgSO_4$) and concentration, 140 mg yellow oil. This oil was re-acetylated in 10 ml 1:1 pyridine-acetic anhydride for 18 hr to give after evaporation of the solvent 129 (101%) yellow oil. Purification by ptlc (60% ether-petroleum ether) afforded 71 mg which crystallized from cold ether-hexane to give a white solid, mp 121-123.5°. The analytical sample was recrystallized from ether-hexane to give white crystals, mp 122-123.5°. ir ($CHCl_3$) 1740 cm^{-1} (acetate C=O), 1710 cm^{-1} (α,β-unsatd ester), 1627 cm^{-1} (C=C).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.96; H, 9.94.

1,7β-Dihydroxy-1,4bβ,8,8,10aβ-pentamethyl-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-tetradecahydrophenanthrene (F-1).--To a solution of 2.260 g (7.07 mmoles) keto-acetate D-7, mp 153-156°, in 150 ml anhydrous ether cooled to -15° (ice-methanol bath) under a nitrogen atmosphere was added 21 ml of a solution of methyl lithium (2.0 M in ether; 42 mmoles) in 25 ml anhydrous ether over 0.5 hr. After stirring for 2 hr at room temperature, the reaction mixture was poured onto 20 g ice and worked up as usual with ether. Drying ($MgSO_4$) and concentration afforded 2.04 g (98%) white solid which was a mixture of C-8 epimers as evidenced by its nmr spectrum. A small sample recrystallized 3 times from acetone-n-hexane served as the

analytical sample, mp 118-121°. ir ($CHCl_3$) 3600, 3450 cm^{-1} (-OH), 1385, 1375 cm^{-1} ($-CH_3$); nmr ($CDCl_3$) δ 0.67, δ 0.75, δ 0.85, δ 0.90, δ 0.95 (angular methyl signals of F-1 epimeric mixture).

Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.41; H, 11.71.

1,2,3,4,4aα,4b,5,6,8aα,9,10,10a-Dodecahydro-1-hydroxy-1,4bβ, 8,8,10aβ-pentamethyl-7(8H)-phenanthrone (F-2).--To a stirred solution of 1.96 g (6.68 mmoles) diol F-1 in 150 ml reagent acetone cooled to 0° was added Jones' reagent dropwise until after one more drop a red-orange color persisted in the supernatant liquid for 0.25 hr. To this was added 6 drops iso-propyl alcohol and the resulting green solution stirred for 0.25 hr at 0°. After 40 ml water were added and most of the acetone removed on a rotary evaporator, the resulting aqueous solution was worked up as usual with ether. The ethereal phase was dried ($MgSO_4$) and concentrated to afford 1.89 g (97%) white solid which was homogeneous (although epimeric at C-1) by analytical tlc (ether, rf 0.55). A small sample recrystallized twice from acetone-n-heptane afforded the analytical sample, mp 96-100°. ir ($CHCl_3$) 3600, 3460 cm^{-1} (-OH), 1697 cm^{-1} (C=O), 1385, 1375 cm^{-1} ($-CH_3$); nmr ($CDCl_3$) δ 0.95, δ 1.00, δ 1.05, δ 1.08, δ 1.10 (angular methyl signals of F-1 epimeric mixture).

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.00, 78.06; H, 10.94, 10.86.

3,4,4aα,4b,5,6,8aα,9,10,10a-Decahydro-1,4bβ,8,8,10aβ-pentamethyl-7(8H)-phenanthrone (F-4).--To a stirred solution of 1.70 g (5.82 mmoles) keto alcohol F-2 in 20 ml dry pyridine under a nitrogen atmosphere at -15° (ice-methanol bath) was added by syringe 1.23 ml (2.06 g, 17.3 mmoles) thionyl chloride. The solution was stirred at -15° for 0.25 hr and then poured onto ice and worked up in the usual manner with ether-benzene. The combined organic layers were dried ($MgSO_4$) and concentrated to yield 1.59 g (100%) light yellow oil that was shown to be 27% of the endocyclic isomer F-4 and 63% of the exocyclic isomer F-3 by integration of the vinyl protons in the nmr [the endocyclic vinyl proton occurs as a broad absorption at δ 5.24 and the exocyclic vinyl protons as a doublet (J=1.5 Hz) at δ 4.51]. These olefins were not resolvable by vpc (oven temperature 200°, rt 8 min).

A. Silica gel chromatography of olefins F-3 and F-4.--When 250 mg of the above olefin mixture was chromatographed on 35 g silica gel eluting with 200 ml 10% ether-petroleum ether, there was obtained 241 mg of white solid, the nmr of which showed no absorption due to the vinyl protons of the exocyclic olefin F-3. Vapor phase chromatography indicated the presence of two components in a 41:59

ratio (oven temperature 210°, rt 3.2 and 4.1 min respectively). Careful chromatography of this new mixture on 50 g Woelm activity III neutral alumina eluting with 200 ml 2% ether-petroleum ether effected their separation. The first component eluted was the minor isomer XVIII, mp 56-59°. Two recrystallizations from n-heptane afforded the analytical sample, mp 67-69°. ir ($CHCl_3$) 1700 cm^{-1} (C=O), 1360, 1380 cm^{-1} ($-CH_3$); nmr ($CDCl_3$) δ 0.97 (s, 3, $-CH_3$), δ 1.00 (s, 3, $-CH_3$), δ 1.07 (s, 6, 2-CH_3's), δ 1.10 (s, 3, $-CH_3$).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.86, 82.94; H, 10.92, 10.96.

The second component eluted was the endocyclic olefin F-4, mp 97-100°. Two recrystallizations from n-hexane and one from 20% ether-hexane produced the analytical sample, mp 102-104°. ir ($CHCl_3$) 1700 cm^{-1} (C=O), 1380 cm^{-1} ($-CH_3$); nmr ($CDCl_3$) δ 0.93 (s, 3, $-CH_3$), δ 1.03 (s, 6, 2-CH_3's), δ 1.07 (s, 3, $-CH_3$), δ 1.60 (s, 3, C-1 vinyl-CH_3), δ 5.24 (m, 1, C-2 vinyl H).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.28, 83.19; H, 10.89, 10.94.

B. Acid equilibration of olefin mixture F-3 and F-4.--A solution of the remaining 1.34 g of olefin mixture F-3 and F-4 and 121 mg p-toluenesulfonic acid monohydrate in 200 ml reagent benzene was

heated at reflux under a nitrogen atmosphere for 4 hr. The reaction mixture was cooled, worked up with ether, dried ($MgSO_4$), and concentrated to afford 1.27 g (94%) white solid, mp 93-97°. Recrystallization from a small amount of n-hexane gave 1.09 g (81%) crystals, mp 98-101°, that was identical with the endocyclic olefin F-4 from the previous experiment by a comparison of their ir and nmr spectra.

C. Unsuccessful experiments.--Several additional experiments were performed in an attempt to obtain endocyclic olefin F-4. (i) Treatment of keto-alcohol F-2 with iodine at 140° as described by Ireland (38) resulted in a gross mixture of products and significant loss of carbonyl absorption in the infrared. (ii) Attempted dehydration of keto-alcohol F-2 by pyrolysis of the β-keto ester derived from diketene (37) similarly met with little success. (iii) Treatment of olefin mixture F-3 and F-4 with sodium acetate-acetic acid at room temperature for 16 hr resulted in no change in the isomer ratio. (iv) Equilibration of olefin mixture F-3 and F-4 with pyridinium hydrochloride in pyridine at room temperature for 4 hr was unsuccessful. (v) Anhydrous formic acid treatment of olefin mixture F-3 and F-4 at room temperature for 7 min resulted in the addition of formic acid to the olefin as evidenced by the appearance of an ester carbonyl at 1735 cm^{-1} in the ir spectrum.

3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-7,7-ethylenedioxy-1,4bβ,8,8,10aβ-pentamethylphenanthrene (F-5).--A stirred mixture of 3.28 g (11.9 mmoles) keto-olefin F-4, mp 94-97°, and 101 mg p-toluenesulfonic acid in 100 ml ethylene glycol and 500 ml reagent benzene were heated at reflux in a nitrogen atmosphere for 10 hr. The water formed during the reaction was removed by means of a Dean-Stark water separator. The cooled reaction mixture was diluted with 150 ml ether, the ethylene glycol phase removed, and the organic layer worked up as usual. Drying ($MgSO_4$) and concentration afforded 3.69 g (97%) white solid, mp 158-163°. Recrystallization of a portion from n-heptane produced the analytical sample, mp 168-169°.
ir ($CHCl_3$) 1380 cm^{-1} ($-CH_3$), 1180-1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.83 (s, 3, $-CH_3$), δ 0.90 (s, 3, $-CH_3$), δ 0.90 (s, 3, $-CH_3$), δ 1.00 (s, 3, $-CH_3$), δ 1.55 (s, 3, C-1 vinyl $-CH_3$), δ 3.94 (s, 4, ketal), δ 5.15 (m, 1, C-2 vinyl H).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.29; H, 10.77.

7,7-Ethylenedioxy-2-hydroxy-1-methylene-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-tetradecahydro-4bβ,8,8,10aβ-tetramethylphenanthrene (F-6).--In a modification of the method of Nickon and Bagli (39), a solution of 1.37 g (4.31 mmoles) olefin F-5, mp 161-165°, and 100 mg hematoporphrin dihydrochloride in 100 ml reagent pyridine was placed

in a 36 cm x 2 cm pyrex tube. A glass frit was suspended in the solution and a slow stream of oxygen gas that had been passed through a gas washing bottle containing pyridine was bubbled into the reaction mixture. Three 15 watt fluorescent desk lamps were placed 2-3 cm from, and parallel to, the reaction tube and irradiation begun. After 17.5 hr an additional 100 mg sensitizer were added and the irradiation continued for a total of 34.5 hr. The pyridine was removed on a rotary evaporator by codistillation with benzene, and then 300 ml ether were added and the solution cooled to 0° and stirred 4 hr with excess lithium aluminum hydride. After quenching with 10% sodium hydroxide solution, the mixture was filtered and concentrated to afford 1.2 g light yellow oil. The vpc indicated a complex mixture with 2 minor and 2 major components (oven temperature 290°, rt 1.8, 1.9, 2.7, and 3.1 min). Chromatography on 140 g Florisil and elution with 400 ml 10% ether-petroleum ether produced 180 mg white solid that was a 2:1 mixture of two components by vpc (oven temperature 240°, rt 2.5 and 2.7 min). Separation of these components by ptlc (2% ether-petroleum ether) afforded 61 mg starting material and 95 mg (7%) exocyclic olefin XXII, mp 162-165°. Two recrystallizations from ether-n-hexane afforded the analytical sample, mp 167-167.5°. ir ($CHCl_3$) 1380 cm^{-1} ($-CH_3$), 1180-1060 cm^{-1} (ketal), 890 cm^{-1} ($C=CH_2$); nmr ($CDCl_3$) δ 0.85 (s, 3, $-CH_3$), δ 0.90 (s, 3, $-CH_3$),

δ 0.93 (s, 3, $-CH_3$), δ 1.05 (s, 3, $-CH_3$), δ 3.95 (s, 4, ketal), δ 4.50 (d, J = 1.5 Hz, 2, $C=CH_2$).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.24; H, 10.64.

Further elution of the Florisil column with 400 ml 50% ether-petroleum ether produced 788 mg (62%) of a 1:9 mixture of allylic alcohols F-6, β-OH and F-6, α-OH, that could be carried on as such without further purification. Two recrystallizations of a sample from ethanol-petroleum ether effected purification of the major F-6, α-OH isomer, mp 164.5-165.5°. (This sample was placed on the hot stage pre-heated to 150° whereupon it melted and re-solidified as white needles to give the indicated mp). ir ($CHCl_3$) 3600, 3450 cm^{-1} (-OH), 1635 cm^{-1} (C=C), 1380 cm^{-1} ($-CH_3$), 1140-1060 cm^{-1} (ketal), 890 cm^{-1} ($C=CH_2$); nmr ($CDCl_3$) δ 0.85 (s, 3, $-CH_3$), δ 0.88 (s, 3, $-CH_3$), δ 0.93 (s, 3, $-CH_3$), δ 1.05 (s, 3, $-CH_3$), δ 3.94 (s, 4, ketal), δ 4.25 (m, 1, C-2 H), δ 4.69 (m, 1, $C=C<_{H}$), δ 4.88 (m, 1, $C=C<^{H}$).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.26; H, 10.17.

3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-7,7-ethylenedioxy-1-methylene-4bβ,8,8,10aβ-tetramethyl-2(1H)-phenanthrone (F-7).

A. Chromium trioxide-dipyridine.--Following the procedure of Collins and co-workers (42) a solution of 192 mg (0.57 mmole) of allylic alcohol F-6, mp 152-157°, and 892 mg (3.42 mmoles) solid chromium trioxide-dipyridine in 20 ml reagent methylene chloride were stirred for 5 min. Filtration of the reaction mixture through 12 g Woelm activity III neutral alumina eluting with 25 ml methylene chloride afforded 190 mg white solid, mp 154-157°. Recrystallization from acetone-n-hexane produced 172 mg (91%) white crystals, mp 159-162° that was identical with material prepared in part B below.

B. Chromium trioxide in pyridine.--Following the standard procedure of Sarett (43), 306 mg (0.92 mmole) allylic alcohol F-6 in 5 ml dry pyridine was added to 360 mg (3.60 mmoles) chromium trioxide in 3 ml dry pyridine at 0° and the resulting brown mixture stirred at room temperature for 23 hr under a nitrogen atmosphere. After 50 ml reagent ether were added and the resulting mixture filtered through celite and worked up as usual, there remained upon drying ($MgSO_4$) and concentration 281 mg pale yellow solid, mp 147-153°. Recrystallization from acetone-petroleum ether resulted in 198 mg (64%) white solid, mp 154.5-157.5°. A small portion was recrystallized from acetone-n-hexane to give the analytical sample,

mp 160-163°. ir ($CHCl_3$) 1680 cm^{-1} (unsatd C=O), 1610 cm^{-1} (C=C), 1380 cm^{-1} ($-CH_3$), 1180-1050 (ketal); nmr ($CDCl_3$) δ 0.88 (s, 3, $-CH_3$), δ 0.97 (s, 6, 2-CH_3's), δ 1.03 (s, 3, $-CH_3$), δ 3.95 (s, 4, ketal), δ 5.01 (d, 1, J=1.5 Hz, C=C$\diagdown_{H}$), δ 5.54 (d, 1, J=1.5 Hz, C=C$\diagup^{H}$).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.69; H, 9.57.

C. Manganese dioxide.--A slurry of 130 mg (0.39 mmole) allylic alcohol mixture F-6 and 2.03 g manganese dioxide in 20 ml reagent chloroform was stirred at room temperature for 20 hr. Filtration and concentration yielded 128 mg white solid. The ir spectrum indicated some residual alcohol absorption; vpc analysis [oven temperature 270°; rt 4.1 min (ketone) and 5.4 min (alcohol)] showed that only the major alcohol isomer (α-OH) had reacted to any appreciable extent. The remainder of the spectrum was similarly unencouraging.

6,6-Ethylenedioxy-8aβ-methyl-3,4,4aα,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (G-4).--A stirred solution of 79.4 g (0.44 mole) keto alcohol G-3 (45), 150 ml ethylene glycol, and 1.0 g p-toluenesulfonic acid in 2.5 l. reagent benzene was heated at reflux under a nitrogen atmosphere for 3 hr. Normal workup afforded 99.1 g crude ketal alcohol. This material was dissolved in 1 l. reagent acetone, cooled to 0°, and treated with 122 ml Jones' reagent (2 equiv) keeping the

temperature below 3°. After diluting with 200 ml water, the bulk of the acetone was removed on a rotary evaporator, followed by a normal ether workup. Drying ($MgSO_4$) and concentration yielded 83.6 g (86%) ketal ketone G-4, mp 45-47°; [lit (38) mp 47-48°].

1,8aα-Dimethyl-6,6-ethylenedioxy-3,4,4aα,5,6,7,8,8a-octohydronaphthalene (G-5).--To 98.7 g (0.44 mole) ketal ketone G-4 in 1 l. dry ether in a nitrogen atmosphere was added dropwise 400 ml of 2 M methyl lithium (0.8 mole) in ether and the resulting solution stirred at room temperature for 1 hr. After quenching with saturated ammonium chloride solution followed by a normal ether workup, the ethereal layer was dried ($MgSO_4$) and concentrated to yield material that still possessed a medium (<15%) carbonyl absorption in the ir spectrum at 1710 cm^{-1}. The material was then again treated as above with 400 ml of the methyl lithium solution (0.8 mole) to afford after similar workup 100.8 g (95%) of the crude tertiary alcohol. Then a melt of 99.9 g (0.41 mole) of the crude material was heated to 140° (38) and 1.9 g iodine added in 3 portions over 1 hr. The dark material was cooled, diluted with ether, washed with 10% sodium thiosulfate, dried ($MgSO_4$), and concentrated, yielding 94.0 g crude olefin. Vacuum distillation afforded 69.0 g (70% from G-4) of clear oil, bp 99-100° (0.35 mm). A small sample was evaporatively

distilled (90-95° at 0.04 mm) to give the analytical sample. ir ($CHCl_3$) 1375 cm^{-1} (-CH_3), 1130-1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.97 (s, 3, C-8a -CH_3), δ 3.94 (s, 4, ketal), δ 8.59 (m, 1, C-2 vinyl H).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 76.22; H, 9.74. Found: C, 76.04; H, 9.76.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-6,6-ethylenedioxy-2-hydroxy-8aβ-methyl-1-methylenonaphthalene (G-6).--In an adaptation of the procedure of Wharton (46), a solution of 15.0 g (67.5 mmoles) olefin G-5, bp 99-100° (0.35 mm) and 3.0 g rose bengal in 200 ml iso-propyl alcohol was placed in an immersion-type photoreaction vessel with a stream of oxygen bubbling through the solution from a glass frit in the bottom. Irradiation with a Hanovia 450 watt medium pressure light source through a pyrex filter sleeve ($\lambda > 3000$ Å) was carried out over a 7 hr period. After the solvent was removed on a rotary evaporator, 500 ml ether was added and the solution, with excess LAH, stirred for 6 hr. Filtration and concentration afforded 16.5 g yellow oil that was chromatographed on 300 g Florisil. Elution with 2 l. 15% ether-petroleum ether gave residual starting material plus other low boiling components. Further elution with 3 l. 60% ether-petroleum ether yielded 11.8 g (72%) of solid material composed mainly of a 1:10 mixture of the epimeric alcohols G-6, β-OH; G-6, α-OH. Crystallization of a sample from ether-n-hexane afforded white needles,

mp 93-94.5°. Further recrystallization from ether-n-hexane produced pure α-hydroxy compound as the analytical sample, mp 93-94.5°. ir ($CHCl_3$) 3600, 3450 cm^{-1} (-OH), 1640 cm^{-1} (C=C), 1130-1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.99 (s, 3, C-8a $-CH_3$), δ 3.94 (s, 4, ketal), δ 4.33 (m-broad, 1, C-2 H), δ 4.78 (m, 1, $C=C_{H}$), δ 5.07 (m, 1, $C=C^{H}$).

Anal. Calcd for $C_{14}H_{18}O_3$; C, 70.53; H, 9.30. Found: C, 70.40; H, 9.22.

6,6-Ethylenedioxy-8aβ-methyl-1-methylene-3,4,4aα,5,6,7,8,8a-octahydro-2(1H)-naphthaleneone (G-7).--As described in the general procedure of Sarett (43), a mixture of 11.6 g (49.2 mmoles) of the allylic alcohol mixture G-6, β-OH and G-6, α-OH (1:10) from the previous experiment in 170 ml dry pyridine and 15.5 g (155 mmoles) chromium trioxide in 160 ml dry pyridine was stirred at room temperature for 12 hr. After 500 ml ether were added and the resulting solution filtered through super-cel; the filtrate was worked up as usual to produce 9.4 g crude ketone G-7. Recrystallization from ether gave 5.3 g (46%) pale yellow crystals, mp 92-94°. Recrystallization from ether afforded the analytical sample, mp 94-96°. ir ($CHCl_3$) 1685 cm^{-1} (C=O), 1610 cm^{-1} (C=C), 1130-1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.95 (s, 3, C-8a $-CH_3$), δ 3.96 (s, 4, ketal), δ 5.12 (d, 1, J=1.5 Hz, $C=C_{H}$), δ 5.68 (d, 1, J=1.5 Hz, $C=C^{H}$).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.22; H, 8.51.

m-Methoxybenzyl chloride.--Following a procedure referred to by Streitweiser (85), 9.11 g (65.5 mmoles) m-methoxybenzyl alcohol (Aldrich Chemical Co.) in 10 ml reagent benzene was cooled to 0° and treated with 20 ml thionyl chloride. After 10 min the excess thionyl chloride was removed on a rotary evaporator and the dark residual oil distilled to give 5.7 g (55%) clear mobil oil, bp 152-155° (25 mm); [lit (86) bp 124° (13 mm)]; ir ($CHCl_3$) 2850 cm^{-1} ($-OCH_3$) 1605, 1590, 1495 cm^{-1} (aromatic), 1040 cm^{-1} (methoxyl); nmr ($CDCl_3$) δ 3.72 (s, 3, $-OCH_3$), δ 4.48 (s, 2, $-CH_2Cl$), δ 6.62-7.40 (m, 4, aromatic hydrogens).

In a separate experiment conducted by Joseph Ham in these laboratories, the same chloride was obtained in 72% yield by refluxing a 1:1 mixture of m-methoxybenzyl alcohol and triphenylphosphine in carbon tetrachloride for 3 hr (87).

Benzyltriphenyltin.--In a variation of the "Organic Syntheses" (88) preparation of allyltriphenyltin, a solution of 10.0 g (25.9 mmoles) triphenyltinchloride (Matheson, Coleman, and Bell) and 5.06 g freshly distilled benzyl chloride (40.0 mmole) in 30 ml dry THF was slowly added to a stirred, vigorously refluxing suspension of 2.0 g

(82 mmoles) magnesium turnings in 40 ml dry ether. When the addition was completed (1 hr), 20 ml dry benzene was added and the mixture heated at reflux for 5 hr. The residual Grignard was quenched by the addition of 7 ml saturated ammonium chloride solution. After diluting the decanted organic phase with ether followed by a normal workup, drying (Na_2SO_4) and concentration afforded 10.4 g (93%) white solid, mp 88-90°; [lit (89) 90-91°].

m-Methoxybenzyltriphenyltin (XXXI).--A solution of 5.0 g (12.9 mmoles) triphenyltinchloride (Matheson, Coleman, and Bell) and 3.15 g (20.2 mmoles) m-methoxybenzyl chloride in 15 ml dry THF was slowly added to a stirred, vigorously refluxing (bath 61°) suspension of 1.0 g (41 mmoles) magnesium turnings in 20 ml dry ether under a nitrogen atmosphere. When the addition was completed (0.5 hr) 10 ml dry benzene were added and the reaction mixture heated at reflux for 10.5 hr. After quenching with 3 ml saturated ammonium chloride solution, the organic layer was decanted and worked up as usual with ether. Drying ($MgSO_4$) and concentration yielded a clear oil that deposited 5.75 g (94%) white solid, mp 57-59°, on trituration with cold petroleum ether. Recrystallization from petroleum ether gave 5.41 g (88%) white cubes, mp 60-61°. A further recrystallization of a portion from n-hexane gave the analytical sample, mp 61-61.5°.

nmr ($CDCl_3$) δ 2.92 (s, 2, $-CH_2-$), δ 3.48 (s, 3, $-OCH_3$), δ 6.4-7.8 (m, 19, aromatic hydrogens).

Anal. Calcd for $C_{26}H_{24}OSn$: C, 66.28; H, 5.14; Sn, 25.19. Found: C, 66.11; H, 5.19; Sn, 25.07.

General procedure for the reaction of lithium organocopper and organolithium derivatives with model methylene ketone G-7.

Benzyllithium and m-methoxybenzyllithium were prepared from the corresponding triphenyltin compounds by reaction with phenyllithium (61). A 100 ml 3 neck flask (flask A) was fitted with a serum cap and a nitrogen inlet. A piece of glass tubing (5 mm od) passing through a rubber stopper (00) was placed so that the end of the tube came to within 5 mm of the bottom of flask A. Several glass wool plugs were placed in the tube to filter out the solid tetraphenyltin. The other end of the tube passed through a stop cock and another rubber stopper (00) into a second 100 ml 3 neck flask (flask B) similarly equipped with a serum cap and nitrogen inlet. The desired triphenyltin derivative in 75% of the total solvent volume indicated in Table I was placed in flask A and cooled to the desired temperature (usually -35°). A calculated amount of standardized (62) phenyllithium solution (1.65 M in benzene) was added by syringe to flask A. Within two minutes a heavy white precipitate of tetraphenyltin formed. After 0.5 hr at the indicated temperature, the bright yellow supernatant liquid

was forced through the connecting tube by a positive nitrogen pressure (5 lbs/in^2) into flask B. The residual solution in flask A was washed into flask B with one portion of 10% of the total solvent volume. Flask B was brought to the desired temperature and a weighed amount of solid copper (I) iodide added if required. After 0.5 hr the methylene ketone G-7 in the remaining 15% of the solvent was added by syringe and the solution kept at the indicated temperature for 1 hr before quenching with the appropriate reagent. Isolation by normal ether workup followed by drying and concentration afforded material that was purified by ptlc, one plate for each 100 mg of methylene ketone G-7.

6,6-Ethylenedioxy-8aβ-methyl-3,4,4aα,5,6,7,8,8a-octahydro-1β-(2'-phenylethyl)-2(1H)-naphthalenone (XXIX).

A. Without copper (I) iodide.--A solution of benzyllithium from 1.69 g (3.84 mmoles) benzyltriphenyltin and 3.12 mmoles phenyllithium in 30 ml dry ether was prepared and transferred to flask B as described previously. At -50° a solution of 310 mg (1.31 mmoles) ketone G-7 in 6 ml dry ether was added by syringe. The solution was stirred for 1 hr, then quenched with solid ammonium chloride and worked up with ether as usual. Drying ($MgSO_4$) and concentration afforded 745 mg oil that was purified by ptlc (25% ether-petroleum ether, double development). A minor (slow-moving) band weighing 61 mg (19%) was

crystalline starting material, mp 90-93°. The major (fast-moving) band crystallized from cold n-hexane to give 131 mg (30%) white solid, mp 73-75°. Recrystallization from n-hexane gave the analytical sample, mp 75-76.5°. ir ($CHCl_3$) 1710 cm^{-1} (C=O), 1600 and 1495 cm^{-1} (aromatic), 1160-1030 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.82 (s, 3, C-8a $-CH_3$), δ 3.95 (s, 4, ketal), δ 7.25 (s, 5, aromatic hydrogens).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.71; H, 8.61.

Other material from the ptlc plates appeared to be a mixture of carbonyl and alcohol containing compounds as evidenced by ir spectra.

B. With copper (I) iodide.--To a solution at -25° of benzyllithium prepared from 2.36 g (5.36 mmoles) benzyltriphenyltin and 4.37 mmoles phenyllithium in 55 ml dry ether and transferred as described above was added 504 mg (2.65 mmoles) copper (I) iodide. The reaction mixture became a very dark green and appeared nearly homogeneous. After 0.5 hr 400 mg (1.69 mmoles) ketone G-7 in 10 ml ether was added by syringe. After 1 hr at -20° the reaction mixture was quenched with solid ammonium chloride and worked up, isolated, and purified as before to give 249 mg (45%) ketone XXIX. No starting material was observed.

1-Benzyl-6,6-ethylenedioxy-8aβ-methyl-3,4,4aα,5,6,7,8,8a-octahydro-2-naphthalylacetate (XXXIX).

A. With copper (I) iodide.--A solution of 1.54 ml phenyllithium solution (1.65 M in benzene, 2.47 mmoles) in 35 ml dry ether under a nitrogen atmosphere was cooled to -20° and 242 mg (1.27 mmoles) copper (I) iodide added. The green solution was stirred for 0.5 hr and then 201 mg (0.85 mmoles) ketone G-7 in 5 ml dry ether added by syringe. After 1 hr 4 ml (43 mmoles) acetic anhydride were added and the solution stirred at room temperature for 1 hr. A normal ether workup, followed by drying ($MgSO_4$) and concentration yielded a light oil that was purified by ptlc (25% ether-petroleum ether, double development) to give 268 mg (89%) homogeneous oil that crystallized on trituration with ether-n-hexane (1:5) to give white crystals, mp 69-70°. ir ($CHCl_3$) 1740 cm^{-1} (acetate C=O), 1650 cm^{-1} (enol C=C), 1600 and 1495 cm^{-1} (aromatic), 1140-1030 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.94 (s, 3, C-8a $-CH_3$), δ 1.95 (s, 3, $COCH_3$), δ 3.36 (s, 2, $C_6H_5-CH_2-$) δ 7.05 (s, 5, aromatic hydrogens).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.16; H, 7.85.

B. Without copper (I) iodide.--A solution of 1.03 ml phenyllithium solution under a nitrogen atmosphere (1.65 M in benzene, 1.70 mmoles) in 40 ml dry ether was cooled to -15° and then 200 mg

(0.85 mmoles) ketone G-7 in 8 ml dry ether added by syringe. After 0.7 hr at -15°, the reaction was quenched with 4 ml (43 mmoles) acetic anhydride and stirred at room temperature for 0.5 hr. A normal ethereal workup and purification as in part A afforded 123 mg (32%) of enol acetate XXXIX, mp 64-67°, identical to that from part A by ir and nmr spectral comparison.

6,6-Ethylenedioxy-8aβ-methyl-3,4,4aα,5,6,7,8,8a-octahydro-1-(2'-phenylethyl)-2-naphthalylacetate (XXXVIII). --A solution of benzyllithium from 0.842 g (1.90 mmoles) benzyltriphenyltin and 1.58 mmoles phenyllithium in 40 ml dry ether was prepared and transferred to flask B as described above. At -20°, 183 mg (0.96 mmole) solid copper (I) iodide was added. After stirring this solution for 0.5 hr, 150 mg (0.63 mmole) enone G-7 in 8 ml dry ether were added by syringe and the solution stirred at -15 to -20° for 1 hr, whereupon 4 ml (43 mmoles) acetic anhydride were added at room temperature. After 0.5 hr a normal ether workup with drying ($MgSO_4$) and concentration produced a clear oil that was purified by ptlc (25% ether-petroleum ether, double development). The major band, 126 mg, consisted of two compounds in a 2.4:1 molar ratio as determined by an integration of the C-8a methyl and ketal nmr signals. The major compound, mp 73-75° of this mixture could be separated by crystallization from cold n-hexane. Two recrystallizations from the same solvent afforded

the analytical sample of enol acetate XXXVIII, mp 77-79°. ir ($CHCl_3$) 1735 cm^{-1} (acetate C=O), 1675 cm^{-1} (enol C=C), 1600 and 1495 cm^{-1} (aromatic), 1140-1030 cm^{-1} (ketal); nmr ($CDCl_3$) δ 1.02 (s, 3, C-8a $-CH_3$), δ 2.13 (s, 3, $-COCH_3$), δ 3.95 (s, 4, ketal), δ 7.28 (s, 5, aromatic hydrogens).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.57; H, 8.23.

The minor product was shown to be the enol acetate XXXIX. A second ptlc band, 19 mg, was pure enol acetate XXXIX. The yield of 1,4-benzyl addition product XXXVIII was thus 47%; that of 1,4-phenyl addition (XXXIX), 13%.

6,6-Ethylenedioxy-8aβ-methyl-3,4,4aα,5,6,7,8,8a-octahydro-1-(2'-m-methoxyphenylethyl)-2-naphthalylacetate (XL).--A solution of m-methoxybenzyllithium from 1.21 g (2.57 mmoles) of m-methoxybenzyltriphenyltin and 2.09 mmoles phenyllithium in 36 ml ether was prepared and transferred to flask B as described above (8 ml ether for wash). Then 242 mg (1.28 mmoles) solid copper (I) iodide was added at -20° and the solution stirred for 0.5 hr, whereupon 200 mg (0.85 mmoles) ketone G-7 in 7 ml dry ether was added by syringe. After 0.9 hr at -20 to -15°, the solution was brought to reflux and quenched with 4 ml (43 mmoles) acetic anhydride. After 0.3 hr the reaction mixture was cooled, worked up with ether as usual,

dried ($MgSO_4$) and concentrated. Purification by ptlc (25% ether-petroleum ether, double development) afforded 82 mg (25%) pure benzyl enol acetate XXXIX. The major (slower) band, 173 mg (51%), which crystallized from cold n-hexane, afforded the analytical sample XL, mp 72-74°. ir ($CHCl_3$) 1740 cm^{-1} (acetate C=O), 1675 cm^{-1} (enol C=C), 1600 1580, 1490 cm^{-1} (aromatic), 1140-1070 cm^{-1} (ketal); nmr ($CDCl_3$) δ 1.02 (s, 3, C-8a $-CH_3$), δ 2.10 (s, 3, $-COCH_3$), δ 3.76 (s, 3, $-OCH_3$), δ 3.89 (s, 4, ketal), δ 6.6-7.4 (m, 4, aromatic hydrogens).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.99; H, 8.02.

Table I: Reactions of Organolithium Compounds with Methylene Ketone G-7

mmoles G-7	mmoles Sn cmpd	mmoles C_6H_5Li	mmoles CuI	Total Solvent Volume (ml)	T C_6H_5Li & (T CuI&G-7 Addns)	Quenching Agent	Yield 1,4 Benzyl Addn (%)	Yield 1,4 Phenyl Addn (%)
1.31	3.84[a]	3.12	0.0	36[c]	-35° (-50°)	NH_4Cl[f]	30 (19)[i]	not detd
0.63	1.92[a]	1.57	0.0	31[d]	-35° (-35°)	NH_4Cl[f]	42 (56)[i]	not detd
1.69	5.36[a]	4.37	2.65	65[c]	-30° (-25°)	NH_4Cl[f]	45	not detd
1.06	3.18[a]	2.62	1.59	54[c]	-35° (-20°)	Ac_2O[f]	46[k]	26[k]
0.63	1.90[a]	1.58	0.96	54[c]	-35° (-20°)	Ac_2O[g]	47[k]	13[k]
0.93	2.78[a]	2.29	1.39	57[c]	-60° (-20°)	Ac_2O[h]	51[k]	21[k]
0.85	2.57[b]	2.09	1.28	57[c]	-30° (-20°)	Ac_2O[h]	51	25
0.84	3.40[b]	2.54	1.27	74[c]	0° (0°)	Ac_2O[f]	31	50
0.40	1.20[b]	0.82	0.0	30[c]	-35° (-20°)	Ac_2O[f]	36 (21)[j]	12
0.85	0.0	2.47	1.27	40[c]	-20° (-20°)	Ac_2O[f]	———	89
0.85	0.0	1.70	0.0	48[c]	-15°	Ac_2O[f]	———	32 (23)[j]
0.85	2.53[b]	2.04	1.27	54[e]	-35° (-20°)	Ac_2O[f]	0	0

a) benzyltriphenyltin. b) m-methoxybenzyltriphenyltin. c) anhydrous ether. d) anhydrous glyme. e) anhydrous THF. f) quenching agent added at temperature of G-7 addition. g) quenching agent added at room temperature. h) quencher added at reaction mixture reflux and stirred 1 hr. i) recovered starting material. j) enol acetate of G-7. k) value obtained from integration of ketal and C-8a methyl nmr resonances of mixture.

6,6-Ethylenedioxy-1-(2'-m-methoxyphenylethyl)-8aβ-methyl-3,4,4aα,5,6,7,8,8a-octahydro-2-naphthalyl acetate (XL).

A. With copper (II) acetate. A solution of 0.668 g (4.25 mmoles) m-methoxybenzyl chloride in 4 ml dry ether was added to a stirred suspension in a nitrogen atmosphere of 0.124 g (5.10 mmoles) magnesium turnings in 10 ml ether over 0.25 hr. After stirring at room temperature for 1 hr, the solution was cooled to 0° and 52 mg (0.26 mmoles) cupric acetate monohydrate (recrystallized from acetic acid) added in one lot, whereupon the mixture was stirred for 6 min. Then 200 mg (0.85 mmoles) ketone G-7 in 9 ml dry ether were added over 10 min. A transient orange color was visible as a drop of the enone solution came in contact with the Grignard surface. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hr and then quenched with 4 ml (43 mmoles) acetic anhydride. The quenching was exothermic and produced a heavy precipitate. After 45 min the reaction was diluted with water and worked up as usual with ether. Drying and concentration afforded a clear oil that on purification by ptlc (25% ether-petroleum ether, double development) afforded 231 mg (68%) pure enol acetate XL, mp 69-72°, as shown by a comparison of ir and nmr spectra with material described in an earlier experiment.

B. With no copper (II) acetate.--As described in part A, a solution of m-methoxybenzyl magnesium chloride was prepared from 1.336 g (8.50 mmoles) m-methoxybenzyl chloride in 8 ml dry ether and 0.248 g (10.20 mmoles) magnesium turnings in 20 ml dry ether. The solution was cooled to 0° and 400 mg (1.70 mmoles) ketone G-7 in 12 ml dry ether added over 20 min. After 1 hr at room temperature, 4 ml (43 mmoles) acetic anhydride were added and the mixture stirred for 45 min. A normal ether workup followed by drying ($MgSO_4$) and concentration afforded a light yellow oil that produced on purification as in part A 497 mg (73%) enol acetate XL, mp 69-72°.

3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-7,7-ethylenedioxy-1-(2'-m-methoxyphenylethyl)-4bβ,8,8,10aβ-tetramethyl-2-phenanthryl acetate (I-1).

A. With copper (II) acetate.--A solution of m-methoxybenzyl-magnesium chloride from 272 mg (1.75 mmoles) m-methoxybenzyl chloride in 4 ml dry ether and 50.5 mg (2.08 mmoles) magnesium turnings in 10 ml dry ether was prepared as in the previous experiment. After cooling the stirred solution to 0°, 20.8 mg (0.104 mmoles) cupric acetate monohydrate (recrystallized from acetic acid) was added and in 7 min 171 mg (0.52 mmoles) tricyclic enone F-7 in 10 ml dry ether added over 11 min. The solution was stirred at room temperature

for 1 hr and then quenched with 4 ml (43 mmoles) acetic anhydride and then stirred at room temperature for 0.75 hr. A normal ether workup followed by drying ($MgSO_4$) and concentration produced 613 mg oil. Purification of this material by ptlc (20% ether-petroleum ether, double development) afforded 189 mg oil that deposited 181 mg (71%) white solid, mp 104-106°, on trituration with cold n-hexane. Recrystallization from n-hexane yielded the analytical sample, mp 109-111°. ir ($CHCl_3$) 1740 cm^{-1} (acetate C=O), 1675 cm^{-1} (enol C=C), 1600, 1580, 1485 cm^{-1} (aromatic), 1380 cm^{-1} (methyl), 1180-1040 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.86 (s, C-4b $-CH_3$), δ 0.90 (s, C-8 $-CH_3$), δ 0.94 (s, C-8 $-CH_3$), δ 1.03 (s, C-10b $-CH_3$), δ 2.10 (s, 3, $-COCH_3$), δ 3.78 (s, 3, $-OCH_3$), δ 3.93 (s, 4, ketal), δ 6.6-7.4 (m, 4, aromatic hydrogens).

Anal. Calcd for $C_{31}H_{44}O_5$: C, 74.96; H, 8.94. Found: C, 75.11; H, 9.03.

B. With no copper additive.--A solution of the m-methoxybenzylmagnesium chloride was prepared as in part A above from 441 mg (2.81 mmoles) m-methoxybenzyl chloride in 5 ml dry ether and 82 mg (3.36 mmoles) magnesium turnings in 10 ml dry ether. After cooling to 0°, 187 mg (0.56 mmole) tricyclic enone F-7 in 15 ml dry ether was added over 0.25 hr. A transient yellow color was noted when a drop of enone solution hit the Grignard surface. After 1 hr

at room temperature, the reaction was quenched by the addition of 5 ml (54 mmoles) acetic anhydride and stirring resulted in heavy precipitate for 0.5 hr. A normal ether workup followed by drying ($MgSO_4$) and concentration produced a yellow oil which on purification by ptlc as in part A gave 209 mg (74%) of white tricyclic enol acetate I-1, mp 104-106°.

Table II: Reactions of Organomagnesium Compounds with Methylene Ketones G-7 & F-7

mmoles Ketone	mmoles Chloride	mmoles Magnesium	mmoles $Cu(OAc)_2 \cdot H_2O$	Temp of Ketone Addn	Quenching Agent	Total Solvent Vol. (ml)	Yield 1,4 Product (%)
0.85[a]	4.25[c]	5.10	0.26	0°	NH_4Cl	25	41[e]
0.85[a]	4.25[c]	5.06	0.26	0°	CH_3I	27	37[e]
0.85[a]	4.25[c]	5.10	0.26	0°	Ac_2O	26	70.5
0.85[a]	4.25[c]	5.10	0.0	0°	Ac_2O	25	71
0.85[a]	4.25[d]	5.10	0.26	0°	Ac_2O	23	68
1.70[a]	8.50[d]	10.20	0.0	0°	Ac_2O	40	73
0.52[b]	1.75[d]	2.08	0.104	0°	Ac_2O	30	71
0.56[b]	2.81[d]	3.36	0.0	0°	Ac_2O	30	74

a) G-7. b) F-7. c) benzyl chloride d) m-methoxybenzylchloride e) product had alcohol ir absorption after extensive purification.

1α,8aβ-Dimethyl-6,6-ethylenedioxy-1β-(2'-m-methoxyphenylethyl)-3,4,4aα,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (H-2).--In an adaptation of the procedure of House and Trost (69), 93 mg (0.23 mmole) enol acetate XL in 0.8 ml glyme (doubly distilled from LAH) was added to a solution under a nitrogen atmosphere of 0.27 ml methyl lithium solution (1.7 N in ether, 0.46 mmole) in 1.2 ml anhydrous glyme. After stirring 0.5 hr at room temperature, 1.0 ml (16.1 mmoles) methyl iodide, which had been freshly distilled from calcium chloride, was added and the solution stirred for 5 min before working up with ether. Drying ($MgSO_4$) and concentration afforded 85 mg (99%) yellow oil which deposited 66 mg (78%) white crystals, mp 63-68°, from cold n-hexane. Recrystallization from ether-n-hexane gave the analytical sample, mp 69-70°. ir ($CHCl_3$) 1700 cm^{-1} (C=O), 1600, 1580, 1490 cm^{-1} (aromatic), 1380 cm^{-1} ($-CH_3$) 1150-1040 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.75 (s, 3, C-8a $-CH_3$), δ 1.30 (s, 3, C-1 $-CH_3$), δ 3.81 (s, 3, $-OCH_3$), δ 3.95 (s, 4, ketal), δ 6.6-7.3 (m, 4, aromatic hydrogens); nmr (C_6H_6) δ 0.50 (C-8a $-CH_3$), δ 1.00 (C-1 $-CH_3$).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.26; H, 8.67.

1α,8aβ-Dimethyl-3,4,4aα,7,8,8a-hexahydro-1β-(2'-m-methoxyphenylethyl)-2,6(1H, 5H)-naphthalenedione (H-4).--A solution of 56 mg (0.15 mmoles) ketone H-2 in 5 ml reagent acetone and 1 ml 10% hydrochloric acid was allowed to stand 0.75 hr at room temperature and then worked up as usual with ether. Drying (Na_2SO_4) and concentration yielded 47 mg (96%) of material that crystallized, mp 111-114°, on trituration with ether. Recrystallization from acetone-n-hexane afforded the analytical sample, mp 127.5-128.5°. ir ($CHCl_3$) 1710 cm^{-1} (C=O), 1600, 1585, 1490 cm^{-1} (aromatics), 1380 cm^{-1} ($-CH_3$), 1040 cm^{-1} (methoxyl); nmr ($CDCl_3$) δ 0.95 (s, 3, C-8a $-CH_3$), δ 1.28 (s, 3, C-1 $-CH_3$), δ 4.63 (s, 3, $-OCH_3$), δ 6.6-7.3 (m, 4, aromatic hydrogens).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.77; H, 8.48.

4aβ,4bα-Dimethyl-8-methoxy-3,4,4a,4b,5,6,12,12aα-octahydro-2(1H)-chrysenone (H-5).--Into a test tube reaction flask equipped with a nitrogen inlet and a screw-type mechanical stirrer blade was placed 28 mg (0.085 mmoles) dione H-4. To this was added 15 ml of a solution of polyphosphoric acid from 30 ml 85% phosphoric acid and 34 g phosphorous pentoxide. The thick solution was vigorously stirred at 65-70° for 40 min and then the mixture poured onto ice and worked up with ether. Drying ($MgSO_4$) and concentration yielded

28 mg (105%) light brown solid, mp 185-189°, that was >97% pure by vpc (oven temperature 290°, rt 2.4 min). Two recrystallizations from acetone produced colorless cubes as the analytical sample, mp 192-194°. ir ($CHCl_3$) 1710 cm^{-1} (C=O), 1640 cm^{-1} (styrene C=C), 1610, 1570, 1495 cm^{-1} (aromatics), 1375 cm^{-1} (methyls), 1035 cm^{-1} (methoxyl); nmr ($CDCl_3$) δ 1.00 (s, 3, C-4a $-CH_3$), δ 1.08 (s, 3, C-4b $-CH_3$), δ 3.78 (s, 3, $-OCH_3$), δ 6.15 (t, 1, J=5 Hz, C-11 vinyl hydrogen), δ 6.61 (s, 1, C-7 aromatic hydrogen), δ 6.73 (dd, 1, J= 9 and 3 Hz, C-9 aromatic hydrogen), δ7.56 (d, 1, J=9Hz, C-10 aromatic hydrogen).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.31; H, 8.45.

When the cyclodehydration of ketone H-2 was attempted in toluene with p-toluenesulfonic acid, extensive decomposition occurred.

3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-7,7-ethylenedioxy-1β-(2'-m-methoxyphenylethyl)-1α,4bβ,8,8,10aβ-pentamethyl-2(1H)-phenanthrone (I-3).--Following the procedure for ketone H-2, 71 mg (0.14 mmole) tricyclic enol acetate I-1 in 1.0 ml dry glyme (doubly distilled from LAH) was added to 0.17 ml methyl lithium solution (1.7 M in ether, 0.29 mmoles) in 1.0 ml dry glyme at room temperature under a nitrogen atmosphere. After stirring for 0.5 hr, 1.0 ml (16.1 mmoles) methyl iodide freshly distilled from calcium chloride

was added and the solution stirred for 5 min. A normal ether workup followed by drying ($MgSO_4$) and concentration afforded 66 mg oil which crystallized on trituration with cold n-hexane to give 51 mg (76%) white solid, mp 116-120°. Recrystallization from acetone-n-hexane produced the analytical sample, mp 124-124.5°. ir ($CHCl_3$) 1698 cm^{-1} (C=O), 1600, 1585, 1485 cm^{-1} (aromatic), 1380 cm^{-1} ($-CH_3$), 1150-1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.83 (s, 3, $-CH_3$), δ 0.87 (s, 3, $-CH_3$), δ 0.92 (s, 6, 2-CH_3's), δ 1.28 (s, 3, C-1 $-CH_3$), δ 3.82 (s, 3, $-OCH_3$), δ 3.98 (s, 4, ketal), δ 6.6-7.3 (m, 4, aromatic hydrogens); nmr (C_6H_6) δ 0.72 (s, 6, C-1 and additional $-CH_3$'s), δ 0.92 (s, 3, $-CH_3$), δ 1.01 (s, 6, 2-CH_3's).

Anal Calcd for $C_{30}H_{34}O_4$: C, 76.87; H, 9.4. Found: C, 76.98; H, 9.52.

3,4,4aα,4b,5,6,8aα,9,10,10a-Decahydro-1β-(m-methoxyphenylethyl)-1α,4bβ,8,8,10aβ-pentamethyl-2,7(1H,8H)-phenanthrenedione (I-4).--A solution of 30 mg (0.065 mmole) tricyclic ketone I-3 in 3 ml reagent acetone and 0.8 ml 10% hydrochloric acid was allowed to stand for 0.75 hr. An ether workup followed by drying ($MgSO_4$) and concentration yielded 27 mg (100%) white solid. Recrystallization from acetone-n-hexane gave 25 mg (89%) white needles, mp 158-159°. ir ($CHCl_3$) 1700 cm^{-1} (C=O), 1600, 1580, 1485 cm^{-1} (aromatics), 1380 cm^{-1} (methyls), 1040 cm^{-1} (methoxyl); nmr ($CDCl_3$) δ 0.87 (s, 3, C-10a $-CH_3$) δ 0.97 (s, 3, C-4b $-CH_3$), δ 1.03 (s, 3, C-8 $-CH_3$), δ 1.10 (s, 3, C-8 $-CH_3$), δ 1.30 (s, 3, C-1 $-CH_3$), δ 3.82 (s, 3, $-OCH_3$),

δ 6.6-7.4 (m, 4, aromatic hydrogens); nmr (C_6H_6) δ 0.60 (s, 3, $-CH_3$), δ 0.63 (s, 3, $-CH_3$), δ 0.90 (s, 3, $-CH_3$), δ 0.97 (s, 3, $-CH_3$), δ 1.05 (s, 3, C-1 $-CH_3$).

Anal. Calcd for $C_{28}H_{30}O_3$: C, 79.19; H, 9.50. Found: C, 79.10; H, 9.43.

References

1. J. Simonsen and W. C. J. Ross, "The Terpenes," University Press, Cambridge, Vol. IV, 1957, p. 287.

2. K. Schmiegel, Ph.D. Thesis, Stanford University, 1962, p. 61.

3. A. R. Pinder, "The Chemistry of the Terpenes," John Wiley and Sons, Inc., New York, 1960, p. 176.

4. B. Bischof, O. Jeger and L. Ruzicka, Helv. Chim. Acta, 32, 1911 (1949).

5. T. G. Halsall and R. Alpin, Forschr. Chem. Org. Naturstoffe, 22, 153 (1964).

6. D. E. White, Rev. Pure Appl. Chem., 6, 191 (1966).

7. P. de Mayo, "The Higher Terpenoids," Interscience, New York, 1959.

8. J. A. Barltrop and N. A. J. Rogers, Prog. in Org. Chem., 5, 96 (1961).

9. E. J. Corey and W. E. Russey, J. Am. Chem. Soc., 88, 4751 (1966).

10. E. J. Corey, W. E. Russey and P. R. Ortiz de Montellano, J. Am. Chem. Soc., 88, 4751 (1966).

11. E. J. Corey and P. R. Ortiz de Montellano, J. Am. Chem. Soc., 89, 3362 (1967).

12. E. E. van Tamelen, J. D. Willet, R. B. Clayton and K. E. Lord, J. Am. Chem. Soc., 88, 4752 (1966).

13. J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W. A. Benjamin, Inc., New York, 1964, pp. 257-288.

14. J. B. Pridham, "Terpenoids in Plants," Academic Press, London, (1967).

15. J. B. Hendrickson, "The Molecules of Nature," W. A. Benjamin, Inc., New York, 1965 , pp. 103-142.

16. D. Evans, Ph.D. Thesis, California Institute of Technology, 1967, pp. 6-17.

17. T. G. Halsall and D. B. Thomas, J. Chem. Soc., 2431 (1956).

18. E. J. Corey and R. R. Sauers, J. Am. Chem. Soc., 81, 1739 (1959).

19. D. H. R. Barton and K. H. Overton, J. Chem. Soc., 2639 (1955).

20. G. Brownlie, M. B. E. Fayez, F. S. Spring, R. Stevenson and W. S. Strachan, J. Chem. Soc., 1377 (1956).

21. D. H. R. Barton, E. F. Lier and J. F. McGhie, J. Chem. Soc., 1031 (1968).

22. P. Beak and B. M. Monroe, J. Org. Chem., 32, 2778 (1967).

23. J. E. Dolfini, Ph.D. Thesis, University of Michigan, 1961.

24. Schmiegel, p. 69.

25. M. Brown, Ph.D. Thesis, Stanford University, 1962.

26. N. L. Wendler, H. L. Slates and M. Tishler, J. Am. Chem. Soc., 73, 3816 (1951).

27. G. Stork, P. Rosen and N. L. Goldman, J. Am. Chem. Soc., 83, 2965 (1961).

28. N. Danieli, Y. Mazur and F. Sondheimer, Tetrahedron, 23, 509 (1967).

29. L. Crombie and S. H. Harper, J. Chem. Soc., 1707 (1950).

30. L. Crombie and S. H. Harper, ibid., 1714 (1950).

31. M. Brown, p. 54.

32. S. Archer, W. B. Dickinson and M. J. Unser, J. Org. Chem., 22, 92 (1957).

33. R. E. Ireland, unpublished results.

34. M. Brown, p. 23.

35. H. C. Brown and R. F. McFarlin, J. Am. Chem. Soc., 78, 252 (1956).

36. D. H. R. Barton, A. Da. S. Campus-Neves and R. C. Cookson, J. Chem. Soc., 3500 (1956).

37. C. Frisell and S. -O. Lawesson, Arkiv. for Kemi, Band 17, 401 (1961).

38. R. F. Church, R. E. Ireland and D. R. Shridhar, J. Org. Chem., 27, 707 (1962).

39. A. Nickon and J. F. Bagli, J. Am. Chem. Soc., 83, 1498 (1961).

40. C. S. Foote, ACR, 1, 104 (1968).

41. D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers and P. Radlick, J. Am. Chem. Soc., 89, 5455 (1967).

42. J. C. Collins, W. W. Hess and F. J. Frank, Tetrahedron Letters, 3363 (1968).

43. G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, J. Am. Chem. Soc., 75, 421 (1955).

44. The synthesis of G-7 was completed jointly with, and using the procedure of, Dr. D. R. Marshall.

45. J. E. Dolfini, p. 41.

46. P. S. Wharton, G. A. Hiegel and R. V. Coombs, J. Org. Chem., 28, 3217 (1963).

47. M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice Hall, Inc., 1954, pp. 196-239.

48. A. W. Burgstahler and M. Struble, J. Chem. Soc., 896 (1960).

49. H. O. House and W. F. Fischer, Jr., J. Org. Chem., 33, 949 (1968).

50. H. O. House, W. L. Respess and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966).

51. H. O. House, D. D. Traficante and R. A. Evans, J. Org. Chem., 28, 348 (1963).

52. H. O. House and D. D. Traficante, ibid., 28, 355 (1963).

53. H. O. House and H. W. Thompson, ibid., 28, 360 (1963).

54. H. O. House and W. L. Respess, ibid., 30, 301 (1965).

55. S. K. Malhotra and F. Johnson, J. Am. Chem. Soc., 87, 5493 (1965).

56. H. Gilman and R. H. Kirby, J. Am. Chem. Soc., 63, 2046 (1940).

57. G. Wittig, F. J. Meyer and G. Lange, Ann., 571, 167 (1951).

58. A. Luttringhaus, Jr., Ber., 67, 1602 (1934).

59. H. Gilman, H. A. Pacevitz and O. Baine, J. Am. Chem. Soc., 62, 1514 (1940).

60. H. Gilman, H. McNinch and D. Wittenberg, J. Org. Chem., 23, 2044 (1958).

61. H. Gilman and S. Rosenberg, J. Org. Chem., 24, 2063 (1959).

62. H. Gilman and A. H. Haubein, J. Am. Chem. Soc., 66, 1515 (1944).

63. a. J. J. Bloomfield, Tetrahedron Letters, 587 (1968).

b. J. J. Bloomfield, ibid., 591 (1968).

64. G. Stork and P. F. Hudrlik, J. Am. Chem. Soc., 90, 4462 (1968).

65. G. Stork and P. F. Hudrlik, ibid., 90, 4464 (1968).

66. A study of the dimerization of α-methylene cyclohexanone is reported in C. Mannich, Ber., 74, 557 (1941).

67. T. Holm, Tetrahedron Letters, 3329 (1966).

68. H. O. House and J. E. Oliver, J. Org. Chem., 33, 929 (1968).

69. H. O. House and B. Trost, J. Org. Chem., 30, 2502 (1965).

70. N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., 1964, pp. 159-176.

71. P. C. Cherry, W. R. T. Cottrel, G. D. Meakins and E. E. Richards, J. Chem. Soc., 181 (1967).

72. J. Ronayne and D. H. Williams, Chem. Commun., 712 (1966).

73. R. F. Zurcher, Helv. Chim. Acta, 46, 2054 (1963).

74. D. A. Evans, p. 122.

75. G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, H. Smith, J. Chem. Soc., 5072 (1963).

76. The degradation procedure to keto ester J-5 was established by R. J. Crawford; the synthetic sequence to dione J-8 was worked out by W. S. Johnson and coworkers.

77. This material was used as supplied by Hi-Labs, Whitmore Lake, Michigan, without purification.

78. E. M. McMahon, J. N. Roper, Jr., W. P. Utermohlen, Jr., R. H. Hasek, R. C. Harris and J. H. Brant, J. Am. Chem. Soc., 70, 2971 (1948).

79. a. This dione was purchased from Hi-Labs, Whitmore Lake, Michigan. Recrystallization from 95% ethanol produced yellow solid, mp 205-208° [lit (79b) mp 208-210°].

b. S. Ramachandran and M. S. Newman, Org. Syn., 41, 38 (1961).

80. V. F. Kucherov and A. Gurvich, J. Gen. Chem. USSR, 31, 731 (1961).

81. Y. Kitahara, A. Yoshikoshi and S. Oida, Tetrahedron Letters, 1763 (1964).

82. This sample, prepared by K. Bell and R. E. Ireland, had a melting point of 63-64°.

83. M. Brown, p. 73.

84. G. Rasmusson, Research Report to W. S. Johnson, Stanford University, 1964, p. 10.

85. A. Streitweiser, Jr. and W. C. Langworthy, J. Am. Chem. Soc., 85, 1757 (1963).

86. R. Pschorr, Ann., 391, 43 (1912).

87. I. M. Downie, J. B. Holmes and J. B. Lee, Chem. and Ind., 900 (1966).

88. D. Seyferth and M. A. Weiner, Org. Syn., 41, 30 (1961).

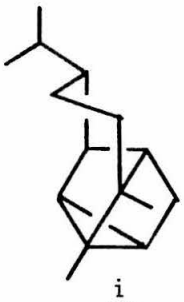
89. H. Gilman and S. D. Rosenberg, J. Am. Chem. Soc., 74, 531 (1952).

Propositions

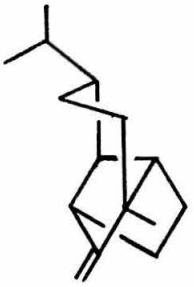
Proposition 1

A synthesis of the sesquiterpene cyclosativene from (-)-carvomenthone is proposed.

Cyclosativene i is a recently characterized tetracyclic sesquiterpene (1) related to sativene ii in the same way that longicyclene iii is related to longifolene (2). Despite its complex molecular architecture,

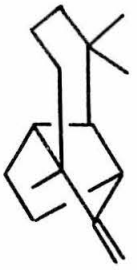


i



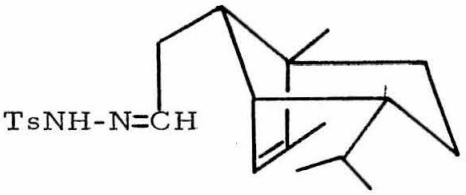
ii

iii

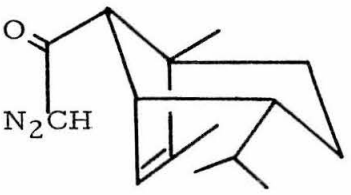


iv

several synthetic routes to i are available. One of these, the decomposition of either tosyl hydrazone v or diazo ketone vi, followed by intramolecular addition of the resulting carbene to the double bond,



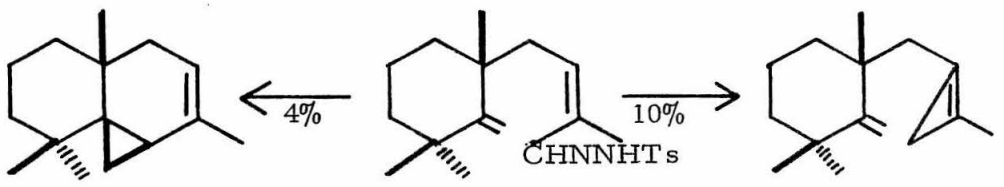
v



vi

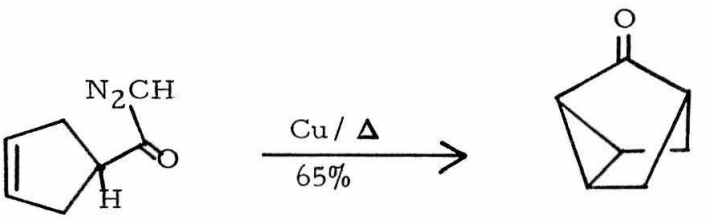
has the advantage of easy accessibility of the intermediates v and/or vi and considerable literature precedent for the carbene addition step.

Intramolecular carbene additions are well documented reactions (3), although the yields are often variable. Buchi and co-workers (3b) accomplished the total synthesis of thujopsine vii by photolysis of the sodium salt of tosyl hydrazone viii, although in this case the major product was cyclopropene ix.



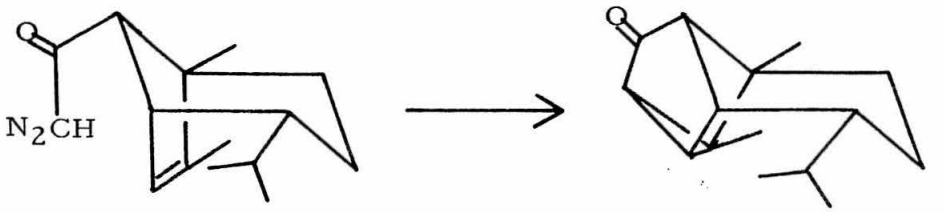
vii viii ix

Relative to the present problem, Doering (3c) has prepared nortricyclonone xi by the copper catalyzed decomposition of diazo ketone x. This last reaction provides strong indication that diazo



x xi

ketone vi will react as planned to produce cyclosativenone xii. In fact, an examination of molecular models reveals that vi is better



vi xii

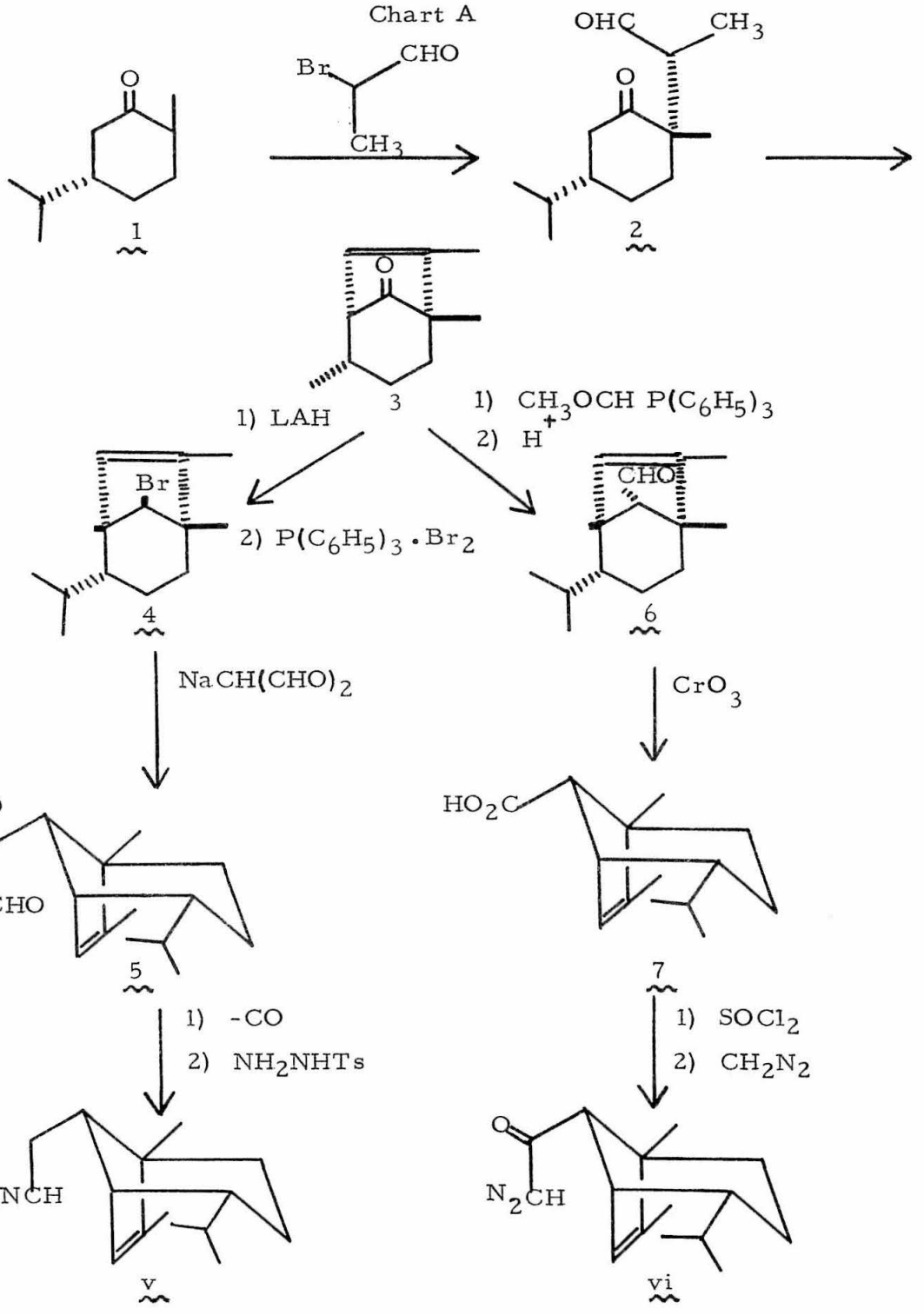
situated for reaction than is x in that the carbene from the former is a full 0.8 Å closer to its double bond than is the carbene from x (2.5 Å versus 3.3 Å). In addition the carbene from vi is better alligned to interact with the π cloud of its double bond. Proposed syntheses of tosyl hydrazone v and diazo ketone vi are outlined in Chart A. The alkylation of (-)-carvomenthone A-1 (4,5) with 2-bromopropionaldehyde (6a) or 2-chloropropionaldehyde (6b) is

expected to give the axially alkylated product A-2 (7). Acid catalyzed aldol condensation of A-2 to afford the bicyclic keto olefin A-3 is anticipated on the basis of work by Corey (8) and Julia (9). The alternative cyclization leading to a cyclopropane derivative is not expected to be competitive. Reduction of the carbonyl group of A-3 with lithium aluminum hydride giving the equatorial α-alcohol (10) followed by bromination with triphenyl phosphine dibromide (11) will give the axial β-bromide A-4. Displacement of the bromine with sodium malonaldehyde should afford dialdehyde A-5, which on monodecarbonylation and treatment with tosyl hydrazine will give the tosyl hydrazone v.

Alternatively, treatment of ketone A-3 with methoxymethylene triphenylphosphorane (12) and hydrolysis of the resulting enol ether should produce the equatorial aldehyde A-6. Oxidation to acid A-7 followed by normal diazotization of the corresponding acid chloride will afford diazo ketone vi.

The decomposition of v either thermally or photolytically (13) is expected to produce cyclosativene i directly. The thermal decomposition of diazo ketone vi should produce cyclosativenone xii which can be converted to cyclosativene by normal reductive procedures.

Chart A


Br
CHO
CH3
OHC
CH3
O
1
2
3
1) LAH
1) CH3OCH P(C6H5)3
2) H+
Br
2) P(C6H5)3 · Br2
CHO
4
6
NaCH(CHO)2
CrO3
CHO
CHO
HO2C
5
7
1) -CO
2) NH2NHTs
1) SOCl2
2) CH2N2
TsHNNCH
O
N2CH
v
vi

References

1. L. Smedman and E. Zavarin, Tetrahedron Letters, 3833 (1968).

2. U. R. Nayak and S. Dev, ibid., 243 (1963).

3. a. G. Stork and J. Ficini, J. Am. Chem. Soc., 83, 4678 (1961).

   b. G. Büchi and J. D. White, ibid., 86, 2884 (1964).

   c. W. von E. Doering, E. T. Fossel and R. L. Kaye, Tetrahedron, 21, 25 (1965).

4. The absolute configuration of cyclosativene i has not been established. Longicyclene iii and longifolene iv have the same absolute configuration (5a). Sativene ii has the opposite configuration (5b) and in all probability cyclosativene i does also. Therefore a synthesis of cyclosativene starting with (-)-carvomenthone A-1 should afford product of natural configuration.

5. a. U. R. Nayak and S. Dev, Tetrahedron, 24, 4099 (1968).

   b. P. De Mayo and R. E. Williams, J. Am. Chem. Soc., 87, 3275 (1965).

6. a. A. M. Pujo and J. Boileu, Mem. poudres, 37, 35 (1955).

   b. C. R. Dick, J. Org. Chem., 27, 272 (1962).

7. R. Howe and F. J. McQuillin, J. Chem. Soc., 1194 (1958).

8. E. J. Corey and S. Nozoe, J. Am. Chem. Soc., 87, 5728 (1965).

9. S. Julia, Bull. soc. chim. France, 21, 780 (1954).

10. E. L. Eliel and M. N. Rerick, J. Am. Chem. Soc., 82, 1367 (1960).

11. J. P. Schaefer and J. Higgins, J. Org. Chem., 32, 553 (1967).

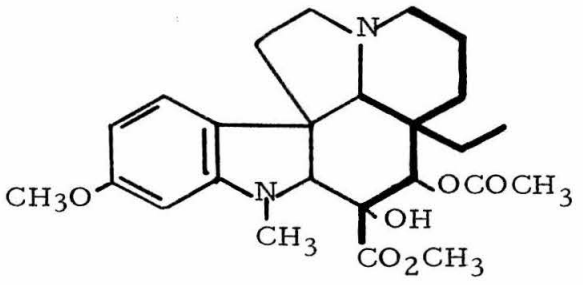
12. R. Greenwald, M. Chaykovsky, and E. J. Corey, ibid., 28, 1128 (1963).

13. W. Kirmse, "Carbene Chemistry," Academic Press, New York (1964) pp. 47-51.

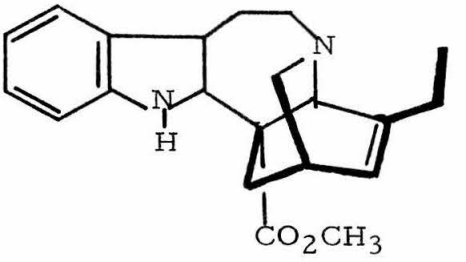
Proposition 2

Experiments to unambiguously determine the biosynthetic origin of the non-tryptophan portion of strychnine are proposed.

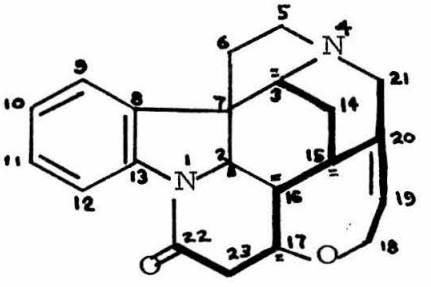
Many theories have been advanced to explain the origin of the non-tryptophan derived fragment of the indole alkaloids (heavy lines in formulae for vindoline i, catharanthine ii, and strychnine iii). Woodward's proposal (1), based on the Barger-Hahn scheme (2),



i



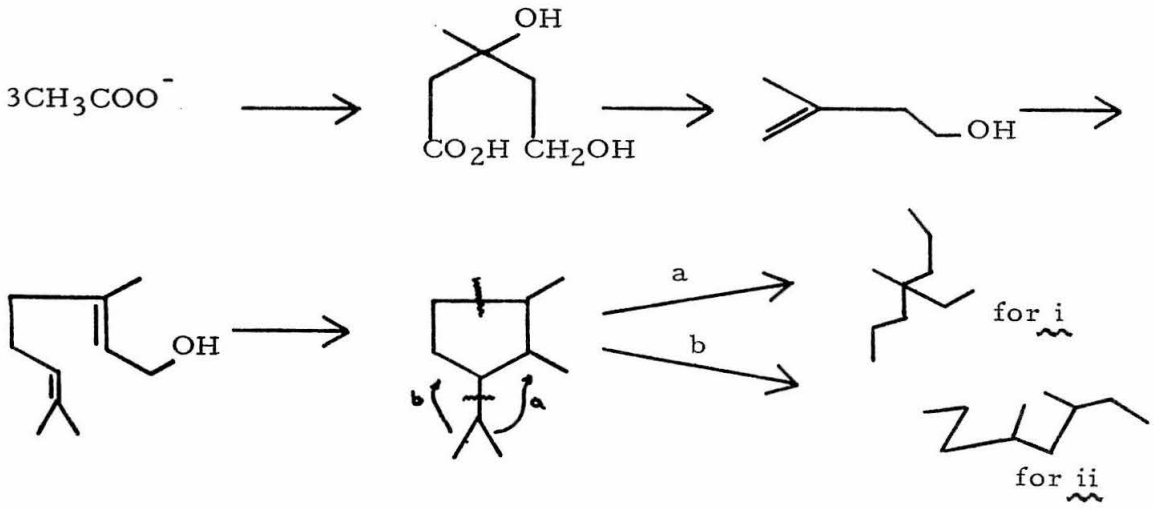
ii

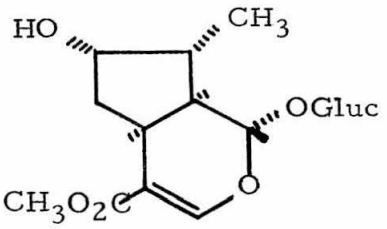


iii

that strychnine is derivable from cleaved dihydroxyphenylalanine has been discredited because of its inability to explain pertinent data. Wenkert and Bringi's theory implicating prephenic acid (3), and thus shikimic acid, has been proven incorrect by the sole incorporation of shikimic acid into the tryptophan portion of several indole alkaloids (4). A third theory that the C_{9-10} residue is the combination of three acetate units, a malonate unit, and formate received early experimental support (5) but has since been shown to be in error (5).

The suggestion, however, that a terpenoid precursor is involved (7) has received experimental verification in all of the alkaloids studied (8). In general this route involves the formation of a cyclopentanoid precursor through the successive intermediacy of acetate, mevalonate, and geranyl alcohol. Subsequent fragmentation and rearrangement in one of several ways leads to the pieces necessary for alkaloid incorporation. Recently the intermediacy of loganin iv

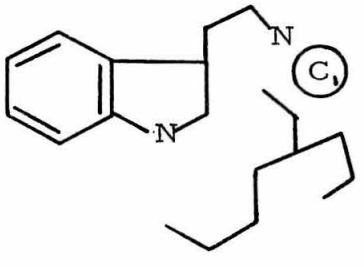




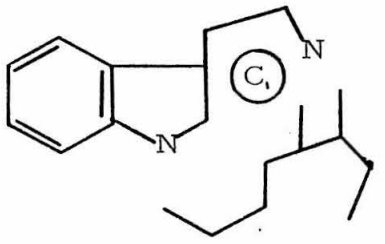
iv

in alkaloid biosynthesis has been demonstrated (9), and other natural iridoids may also be involved. Although loganin has been shown to be derivable from geraniol, the possibility that iv may be a degradation product of higher terpenoids has been suggested (10).

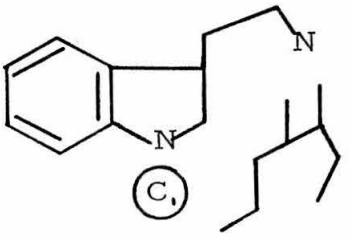
Several possibilities exist for the biosynthesis of strychnine. The non-tryptophan portion of this molecule consists of eleven carbons. This is from one to two more carbons than the other alkaloids considered and presents the problem of from where the extra carbon derived. The most logical answer, a priori, involves a one carbon residue, perhaps formate, which joins tryptamine and the terpenoid group in one of several possible ways (A-C).

A. 

— — — → iii

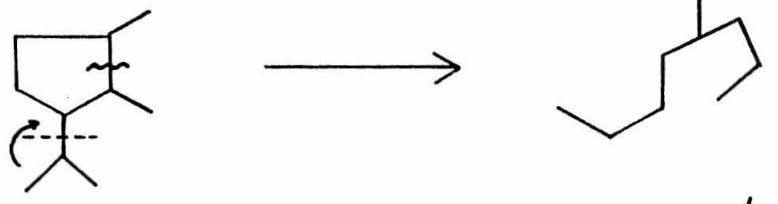
B. 

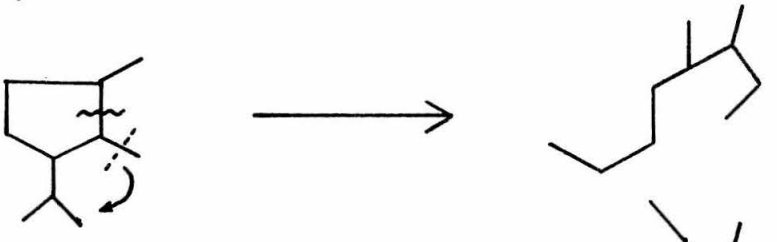
— — — → iii

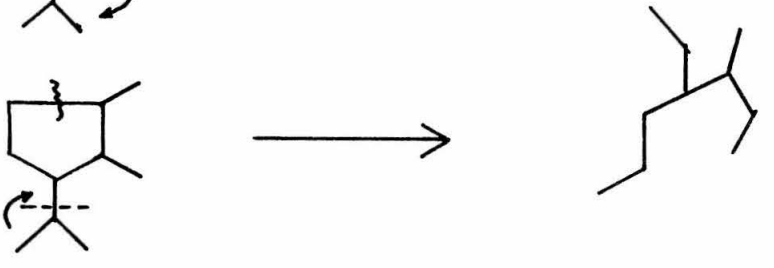
C. 

— — — → iii

The ten carbon residues might be derived from a cyclopentanoid intermediate as follows:

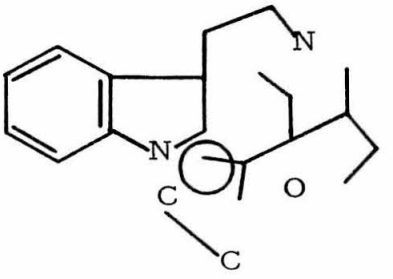
A. 

B. 

C. 

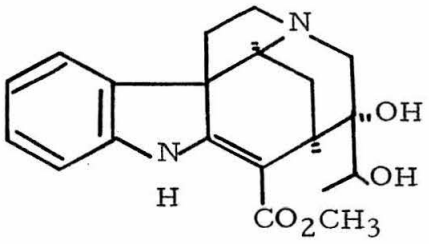
Some experimental evidence for the first of these paths has been obtained by the research group of Dr. Richards here at Caltech, who noted an 18 ± 4% $\left[^{14}C\right]$ -formate incorporation at C-21 in strychnine isolated from the seeds of nux vomica (11).

It is proposed, however, that none of paths A-C is the origin of the eleven carbons, but rather that they arise from a C_9 unit plus one acetate combined in the following manner. The circled carbon is lost at some unspecified point during the biosynthesis.

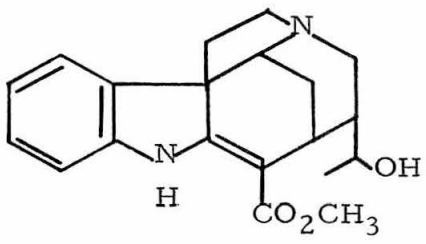
D. 

— — — → iii

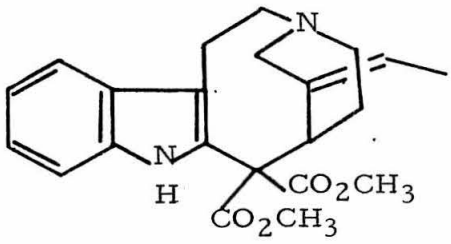
There are several reasons for preferring route D. The first is that it would be consistent with studies on other alkaloids in excluding a formate pool (5). The second and most convincing reason is based on economy. The existence of such alkaloids (12) as compactinervine v, echitamidine vi, stemmaderine vii, and aspidospermatine viii is strong evidence that strychnine is derived as indicated in path D. These compounds have a terpenoid fragment with none, one, or both isopropyl carbons of the monoterpene missing, and also show both



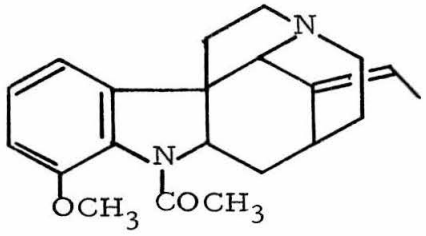
v



vi

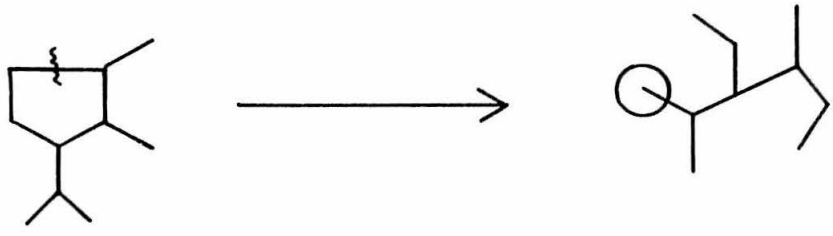


vii



viii

acetylated and unacetylated indole nitrogen. For strychnine this is best explained by the process shown with the circled methyl lost, probably as carbon dioxide. A recent report (13) that C-22 and C-23 of strychnine are derived from acetate of course does not differentiate between paths A, B, and D.

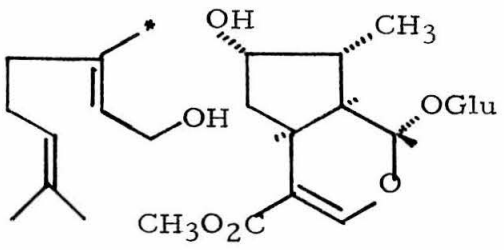
D. 

If one is to accept this proposal, he must be able to explain the incorporation of formate at C-21 . One possibility is that a small portion of formate is converted to acetate in the plant. It is this derived acetate that gives rise to radioactive strychnine. In support of this note the ready conversion of formaldehyde to glycolic aldehyde (14). Loss and recombination of water results in acetate. Also of interest is the report that acetic acid is produced directly by the action of heat and pressure on formaldehyde (15). It is, therefore, not unreasonable to expect that a biological medium could produce acetate from formate or formaldehyde. If this is the case, the expected activity at each carbon in the non-tryptophan portion of strychnine based on complete randomization (9%) is close to the lower limit of that observed.

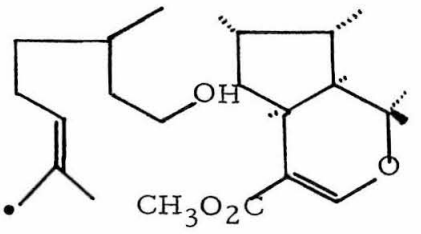
Furthermore, feeding experiments using 1-$[^{14}C]$-acetate predict 0% activity at C-17 for schemes A, B, and D, and 20% for scheme C. The experimental value of 0% eliminates path C from consideration. In addition, the Richards' group discovered 19 ± 4% activity at C-22, a result in accord with only path D.

Two experiments are proposed to unambiguously demonstrate the validity of path D. The first one involves feeding experiments with 3-methyl-$[^{14}C]$-geraniol ix or 4-methyl-$[^{14}C]$-loganin x. The conversion of radioactive geraniol to loganin in useable quantities

has been reported (16). Activity in strychnine at C-18 is predicted for paths C and D, and at C-22 for paths A and B.



ix x

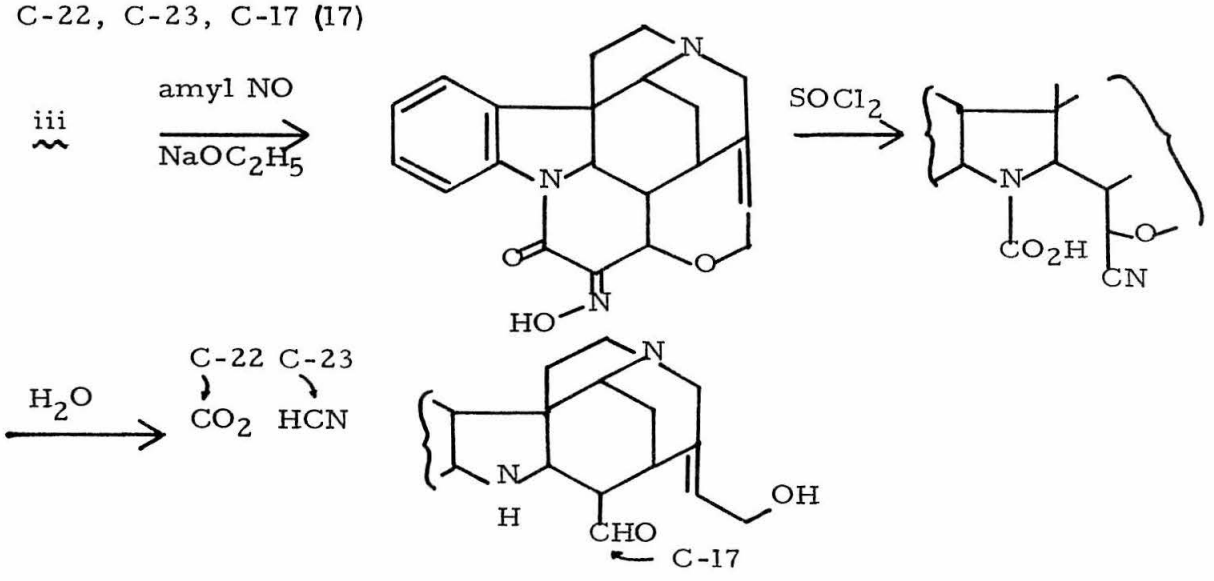


xi xii

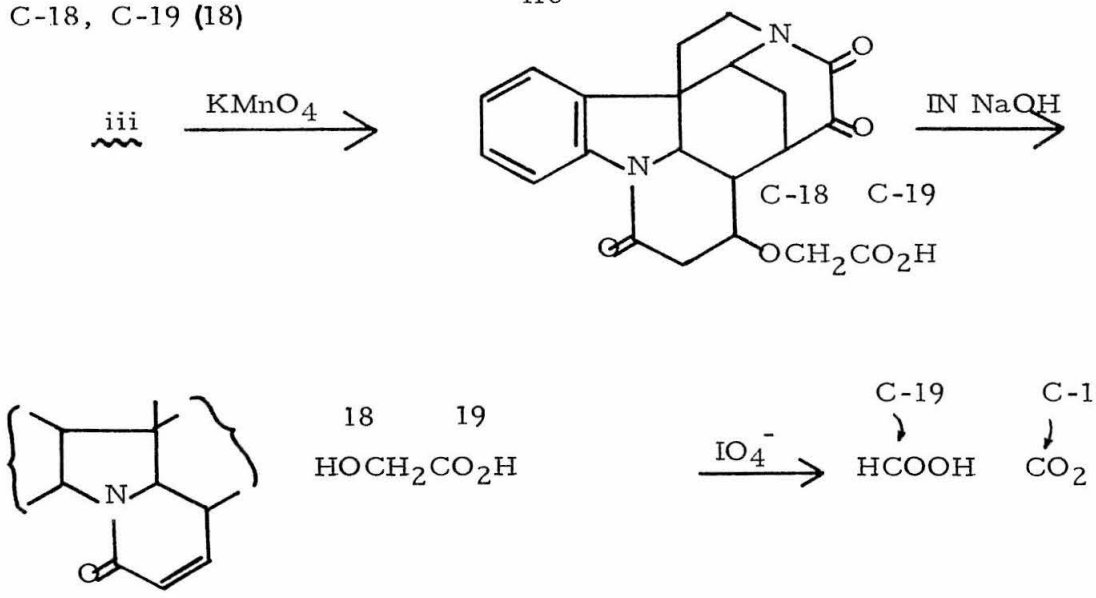
A second experiment employs the feeding of 8-$[^{14}C]$-geraniol xi or labled loganin xii. Path C predicts one half of the activity at C-23 and path D all of the activity at C-17.

All of these carbons are accessible by degradative means, utilizing the information gained during the structure elucidation.

C-22, C-23, C-17 (17)



C-18, C-19 (18)


iii
KMnO4
N
O
O
N
C-18 C-19
OCH2CO2H
1N NaOH
N
18 19
HOCH2CO2H
IO4-
C-19
C-18
HCOOH
CO2

References

1. R. B. Woodward, Nature, 162, 155 (1948).

2. a. G. Barger and C. Scholz, Helv. Chim. Acta., 16, 1343 (1933).

   b. G. Hahn and H. Werner, Liebigs Ann., 520, 123 (1931).

3. E. Wenkert and N. V. Bringi, J. Am. Chem. Soc., 81, 1474 (1959).

4. D. Groger, K. Stolle, K. Mothes, Zeits. Fur Naturforsch, 3, 206.

5. a. P. N. Edwards and E. Leete, Chem. and Ind., 1666 (1961).

   b. E. Leete, S. Ghosal, P. N. Edwards, J. Am. Chem. Soc., 84, 1068 (1962).

6. a. A. R. Battersby, R. Binks, W. Lawrie, G. V. Parry, B. R. Webster, Proc. Chem. Soc., 369 (1963).

   b. H. Goeggel and D. Arigoni, Experientia, 21, 369 (1965).

7. a. R. Thomas, Tet. Let., 544 (1961).

   b. E. Wenkert, J. Am. Chem. Soc., 84, 98 (1962).

8. a. A. R. Battersby, R. T. Brown, J. A. Knight, J. A. Martin, and A. O. Plunkett, Chem. Comm., 346 (1966).

   b. P. Loew, H. Goeggel, and D. Arigoni, Chem. Comm., 347 (1966).

   c. E. S. Hall, F. McCapra, T. Money, K. Fukumoto, J. R. Hanson, B. S. Mootoo, G. T. Philips, and A. I. Scott, Chem. Comm., 348 (1966).

   d. T. Money, I. G. Wright, F. McCapra, and A. I. Scott, Proc. Nat. Acad. Sci. USA., 53, 901 (1965).

   e. F. McCapra, T. Money, A. I. Scott, and I. G. Wright, Chem. Comm., 537 (1965).

f. H. Goeggel and D. Arigoni, Chem. Comm., 538 (1965).

g. A. R. Battersby, R. T. Brown, R. S. Kupil, A. O. Plunkett, and J. B. Taylor, Chem. Comm., 538 (1965).

h. E. Leete and S. Ueda, Tet. Let., 4915 (1966).

9. a. A. R. Battersby, R. S. Kapil, J. A. Martin and L. Mo, Chem. Comm., 133 (1968).

b. P. Loew and D. Arigoni, ibid., 137 (1968).

10. S. T. Murayama, Ph.D. Thesis, California Institute of Technology (1969) p. 114.

11. Chemistry and Chemical Engineering, 1966 Report, p. 107.

12. R. H. F. Manske, The Alkaloids, Vol. VIII, (Academic Press, New York, 1965) pp. 457-68.

13. Ch. Schlatter, E. E. Waldner, H. Schmid, D. Groger, K. Stolle and K. Mothes, Helv. Chim. Acta, 49, 1714 (1966).

14. J. F. Walker, Formaldehyde, (Reinhold, New York, 3rd ed., 1964) p. 217.

15. S. J. Green and R. Handley, U. S. Patent # 1,950,027 (1934).

16. a. A. R. Battersby, R. S. Kapil and R. Southgate, Chem. Comm., 131 (1968).

b. S. Brechbühler-Bader, C. J. Coscia, P. Loew, Ch. von Szczepanski and D. Arigoni, ibid., 136 (1968).

17. a. H. Wieland and W. Gumlichi, Ann., 494, 191 (1932).

b. H. Wieland and K. Kaziro, Ann., 506, 60 (1933).

18. a. H. Leuchs and G. Schwaebel, Ber., 46, 3693 (1913).

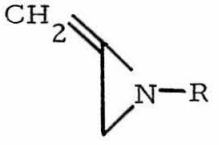
b. H. Leuchs and F. Krohnke, Ber., 42, 2498 (1909).

Proposition 3

A study of the synthetic utility of N-alkyl alleneimines i is proposed.

A continuously encountered problem in organic chemistry is the formation of carbon-carbon bonds. Accordingly it is one of the most actively pursued areas of research. Recent reports of new alkylating agents such as substituted chloroisoxazoles (1) as well as the novel coupling reactions between organic halides and π-allyl nickel halides (2) are illustrative.

It is felt that the methylene aziridine nucleus i possesses characteristics that would make valuable a study of its behavior under a variety of carbon-carbon bond forming reactions. The syntheses

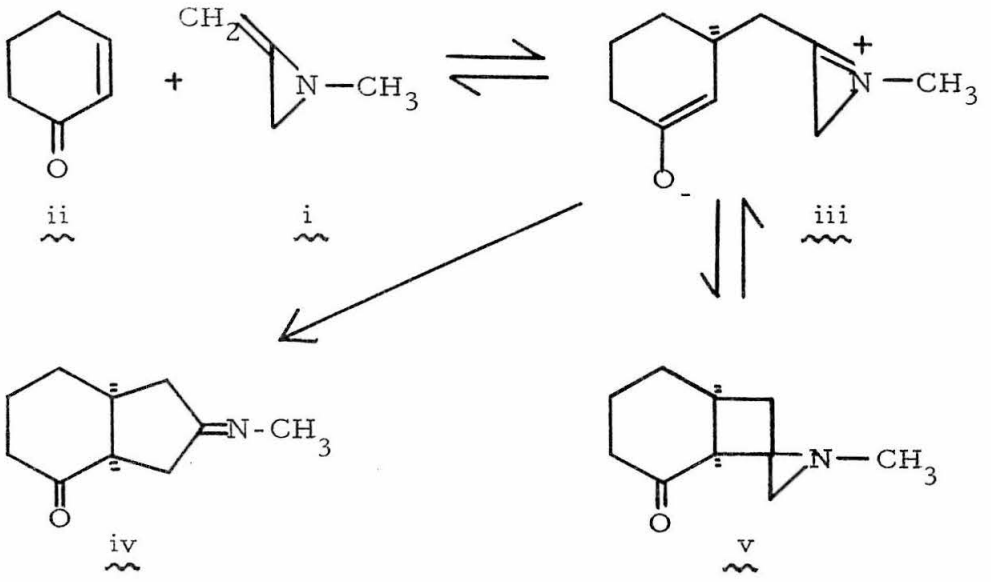


i

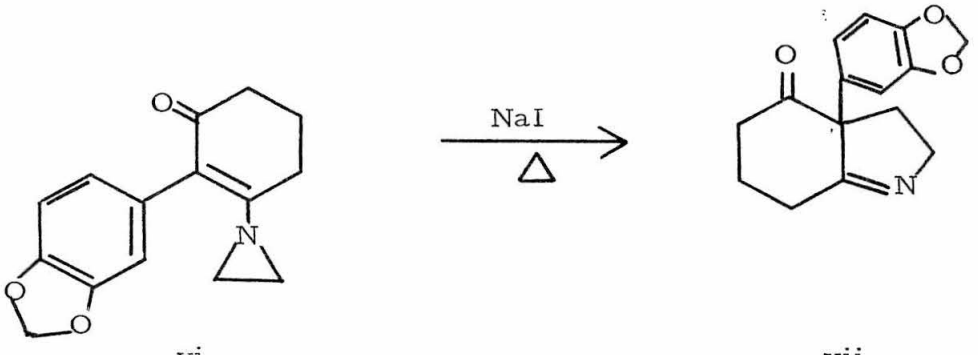
of i where R is a variety of alkyl groups is conveniently accomplished by means of the Gabriel aziridine synthesis (3).

Consider first the reaction of i (R= CH_3) with an α,β -unsaturated carbonyl compound under normal (4) enamine alkylation conditions. The expected imine ketone iv constitutes a one step formation of a

functionalized five-membered ring. The alternative product v is not

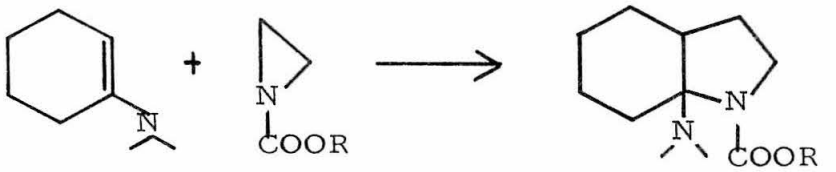


anticipated on the basis of its highly strained nature. It should be noted that the rupture of an aziridine ring to form the five-membered ring of an indole system has recently been reported (5). In addition,



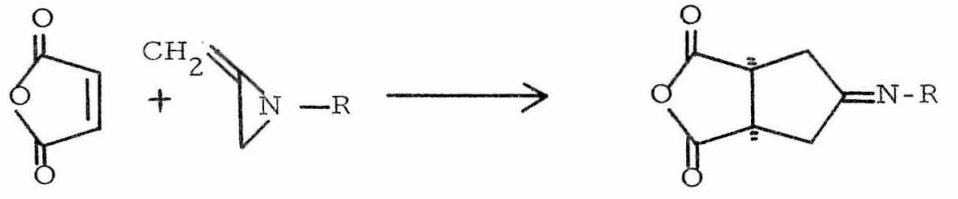
nucleophilic attack by an enamine viii on anaziridine carboxylic ester

ix leading to rupture of the aziridine ring has been claimed (6).

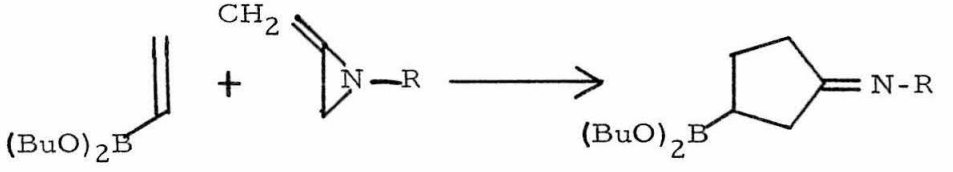


viii ix x

Of perhaps greater interest would be the reaction of N-alkyl aziridines i with electrophilic olefins such as maleic anhydride or dibutyl vinylboronate xiii (7). The possibility of forming five-membered rings in such a fashion is interesting in that it is similar

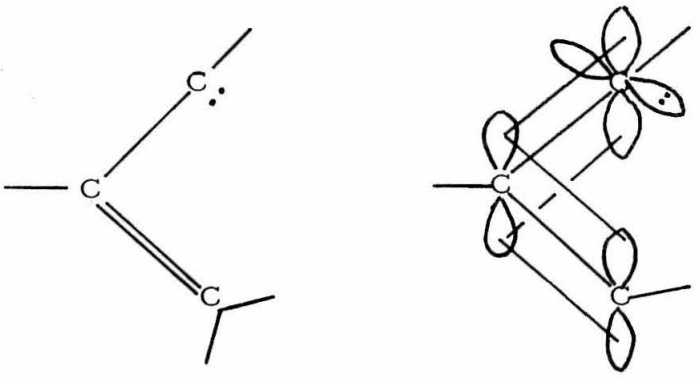


xi i xii



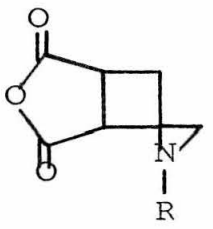
xiii i xiv

to the 1,3-dipolar additions so well characterized by Huisgen (8). Although many dipoles containing N, O, and C, or variations thereon, have been found effective in adding to double bonds, as yet no instance of an all carbon 1,3-dipole has been reported. This probably arises because such a species would be electronically equivalent to an allylic carbene. Allylic carbenes are well known intermediates (9), but the orbital arrangement in such a species precludes the concerted one-step addition process that has been shown to prevail in successful

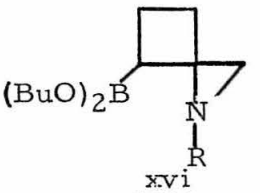


1,3-dipolar additions (8). Thus in the strictest sense the formation of xii or xiv might not constitute a 1,3-dipolar addition, although the end result would be equivalent.

Alternative products in the formation of xii and xiv are the spiro compounds xv and xvi. Although they are not expected, the recent report of the addition of tetracyanoethylene to N-ethylallene

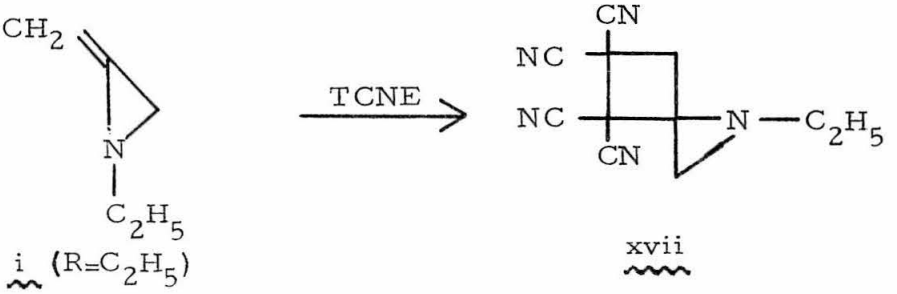


xv



xvi

imine i ($R = C_2H_5$) to give cyclobutane xvii is not encouraging (10).

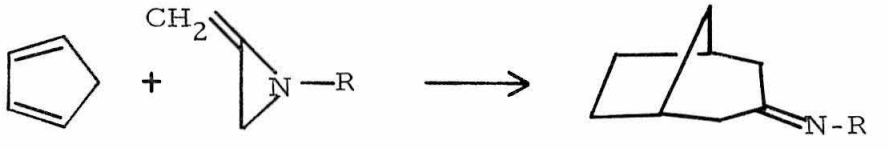


i ($R = C_2H_5$)

xvii

It is hoped that this reaction is ascribable to the special reactivity of TCNE (11) and not to the allene imine.

Should the formation of xii and xiv proceed as intended, similar reactions of i with dienes such as cyclopentadiene might provide a new route to functionalized bicyclic derivatives such as xix.



xviii i xix

References

1. a. G. Stork, S. Danishefsky and M. Ohashi, J. Am. Chem. Soc., 89, 5459 (1967).

   b. M. Ohashi, H. Kamachi, H. Kakisawa and G. Stork, ibid., 89, 5460 (1967).

   c. G. Stork and J. E. McMurry, ibid., 89, 5461 (1967).

   d. G. Stork and J. E. McMurry, ibid., 89, 5463 (1967).

   e. G. Stork and J. E. McMurry, ibid., 89, 5464 (1967).

2. a. E. J. Corey, M. F. Semmelhack and L. S. Hegedus, ibid., 90, 2416 (1968).

   b. E. J. Corey, L. S. Hegedus and M. F. Semmelhack, ibid., 90, 2417 (1968).

   c. E. J. Corey and M. F. Semmelhack, ibid., 89, 2755 (1967).

   d. E. J. Corey and E. K. W. Wat, ibid., 89, 2757 (1967).

   e. E. J. Corey and E. Hamanaka, ibid., 89, 2758 (1967).

3. A. T. Bottini and R. E. Olsen, Org. Syn., 44, 53 (1964).

4. J. Szmuszkovicz, Adv. Org. Chem., 4, (1963).

5. H. W. Whitlock and G. L. Smith, J. Am. Chem. Soc., 89, 3600 (1967).

6. J. E. Dolfini and J. D. Simpson, ibid., 87, 4381 (1965).

7. D. S. Matteson, Organometal. Chem. Rev., 1, 1 (1966).

8. a. R. Huisgen, "Proceedings of the Robert A. Welch Foundation on Chemical Research," Houston, Texas (1961) pp. 61-95.

   b. R. Huisgen, Angew. Chem. int. ed., 2, 565 (1963).

9. W. Kirmse, "Carbene Chemistry," Academic Press, New York (1964), pp. 67-69.

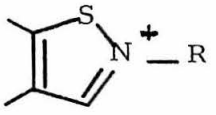
10. R. C. Cookson, B. Halton, J. D. R. Stevens, C. T. Watts, J. Chem. Soc., 928 (1967).

11. a. D. N. Dhar, Chem. Rev., 67, 611 (1967).

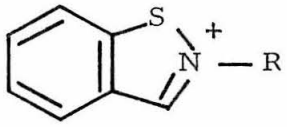
b. R. Winkler, Chimia, 16, 360 (1962).

Proposition 4

A study of the species derived from isothiazolium salts i and benzisothiozolium salts ii is proposed.



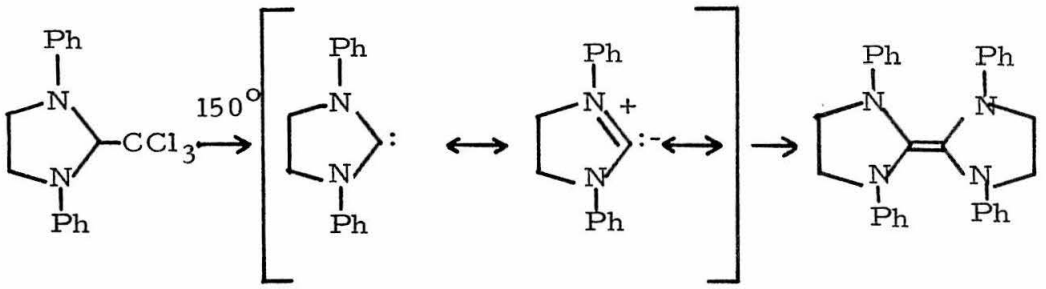
i



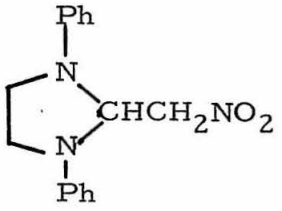
ii

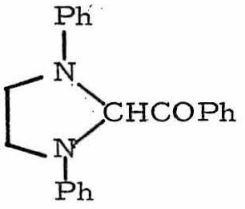
A carbene, or divalent uncharged carbon, behaves as an electrophile in most of its reactions. Insertion into single bonds and addition to multiple bonds are typical examples. It would seem possible, however, to construct a carbene which, because of unusual electronic contributions from neighboring substituents, would behave largely as a nucleophile. A likely candidate is a diamino carbene, but tetrakis(dimethylamino)ethylene does not appear to dissociate to give the bis(dimethylamino) carbene (1).

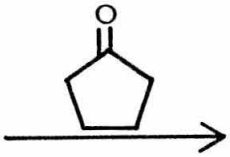
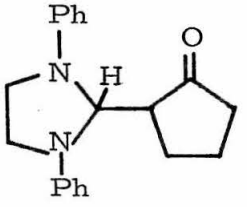
More recently the olefin iii has been prepared by the action of heat on compound iv, perhaps through the intermediacy of carbene v (2). The thermal reactions of iii shown below are illustrative of its chemistry.

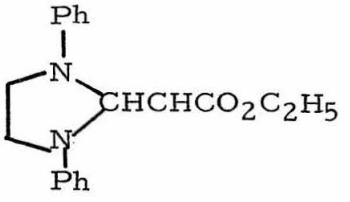


iv v iii

iii $\xrightarrow{CH_3NO_2}$  72%

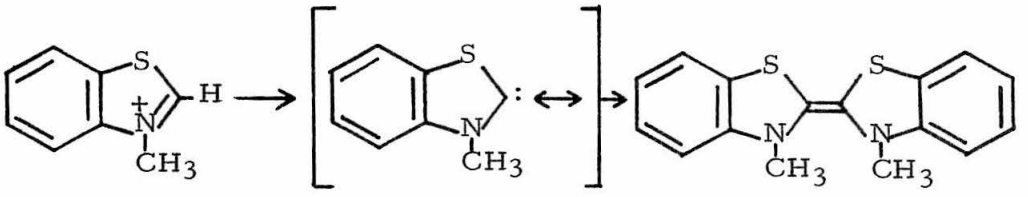
iii $\xrightarrow{PhCHO}$  90%

iii $\xrightarrow{}$   71%

iii $\xrightarrow{PhCH_2CO_2C_2H_5}$  89%

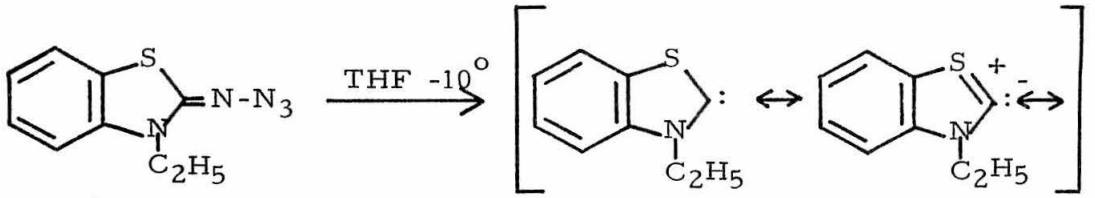
It is interesting that iii is unreactive to olefins except tetrachloroethylene with which the cyclopropyl addition product is formed in 67% yield. Lemal, however, has demonstrated that free carbenes are not in fact involved in the thermal reactions of the dimer (3) and suggests a mechanism for its nucleophilic reactivity.

Of more interest are the varied reports concerning the species derived from the benzthiozolium salt vi. When vi is reacted at 25° C with a tertiary amine, the dimer is produced (4). Rapid quenching



vi vii viii

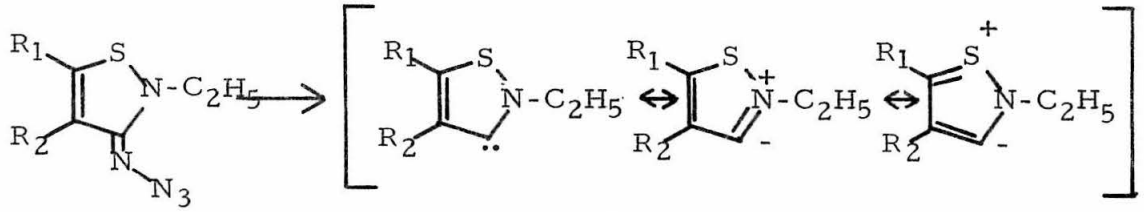
of the reaction mixture with a diazo compound gives the corresponding azine before the dimer is formed. If, however, the tetraazo compound ix is placed in THF at -10°, two moles of nitrogen are lost, no dimer being formed at all (5). The resulting solution is stable for



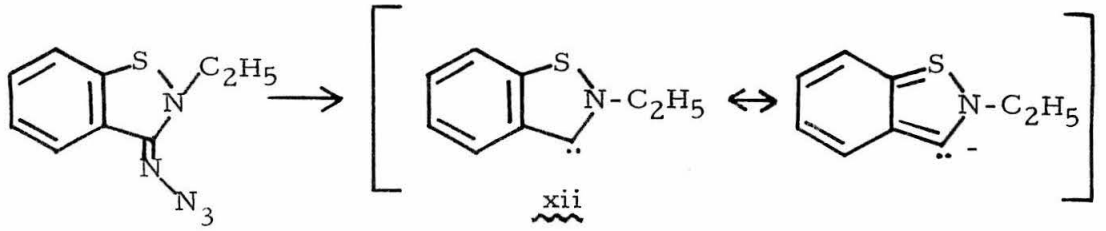
ix x

short periods. A tetracyanoethylene adduct is formed readily and the species present will add to electrophilic azo compounds. Kinetic studies confirm the existence of a short-lived intermediate such as x. No other report of the chemical reactivity has been made.

A logical extension of the above observations is the investigation of the synthetic utility of similar nucleophilic intermediates. A large carbon fragment is not present in x but might be available through the corresponding isothiozolium and benzisothiozolium compounds, xi and xii respectively (7). If generated by the tetraazo derivatives, the neutral solution would be of great value when dealing with sensitive systems.

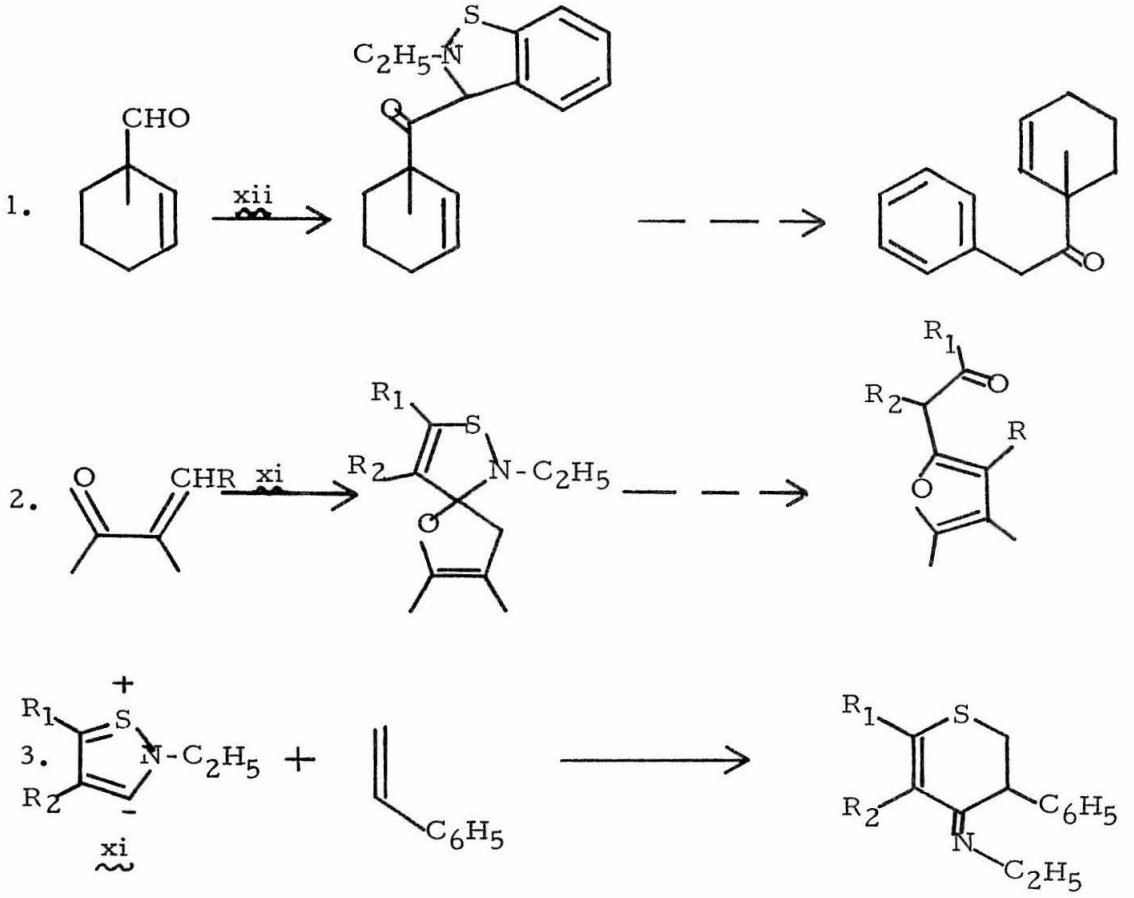


xi



xii

Whether xi and xii would behave as the carbene, the 1,3-dipole (8), or any true resonance hybrid is not readily apparent. The same question remains unanswered, however, even in the extensively studied thiamine chemistry (6). But the fact that the initial step in the thiamine catalyzed dimerization of benzaldehyde is nucleophilic carbonyl attack lends credence to our theory that xi and xii will behave similarly. Speculation as to what reactions xi and xii might actually undergo is largely unwarranted. Considering only carbonyl systems, however, three such reactions might be as shown below.



References

1. N. Wiberg, J. W. Buchler, J. Am. Chem. Soc., 85, 243 (1963).

2. a. H. W. Wanzlick, E. Schikora, Ber., 94, 2389 (1961).

   b. H. W. Wanzlick, H. Ahrens, Ber., 97, 2447 (1964).

3. D. Lemal, R. A. Lould, K. I. Kawano, J. Am. Chem. Soc., 86, 2518 (1964).

4. H. W. Wanzlick, H. J. Kleine, Ang. Chem. intern. ed., 5, 126 (1966).

5. H. Balli, Ang. Chem. intern. ed., 3, 809 (1964).

6. R. Breslow, J. Am. Chem. Soc., 80, 3719 (1958).

7. A good review of the chemistry of the isothiazole system is found in H. J. Den Hertog and H. C. Van der Plas, Advances in Heterocyclic Chemistry, 4, 107 (1965).

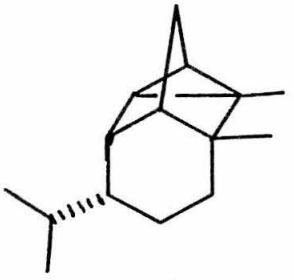
8. a. R. Huisgen, "Proceedings of the Robert A. Welch Foundation on Chemical Research," Houston, Texas (1961) pp. 61-95.

   b. R. Huisgen, Angew. Chem. int. ed., 2, 565 (1963).

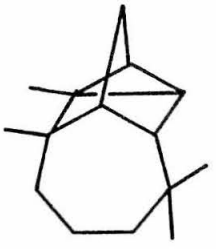
Proposition 5

The solvolysis of several 6-exo-alkenyl-5-endo-norbornenyl brosylates is proposed.

While considering synthetic routes to the tetracyclic sesquiterpenes cyclosativene i and longicyclene ii (1), the possibility that such

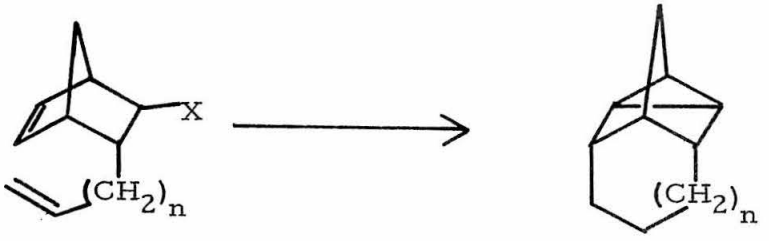


i



ii

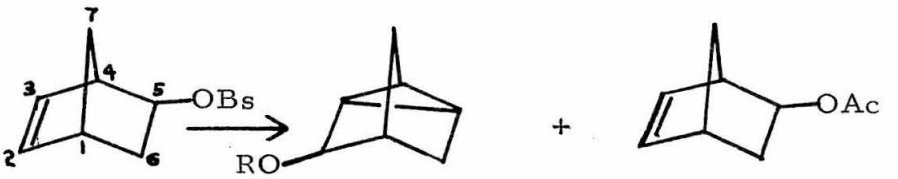
interesting carbocyclic arrangements might be attainable through solvolysis of a homoallylic norbornyl derivative such as iii became apparent. The uncertainty surrounding the chemistry of the



iii iv

norbornenyl-nortricyclyl system, coupled with the uncertainty as to geometric requirements of the side chain and its double bond for cyclization, suggested that a broader consideration of similar cyclizations would be in order.

The acetolysis of exo- or endo-5-norbornenyl p-bromobenzenesulfonate v produces nortricyclyl acetate vi (R = Ac) and exo-



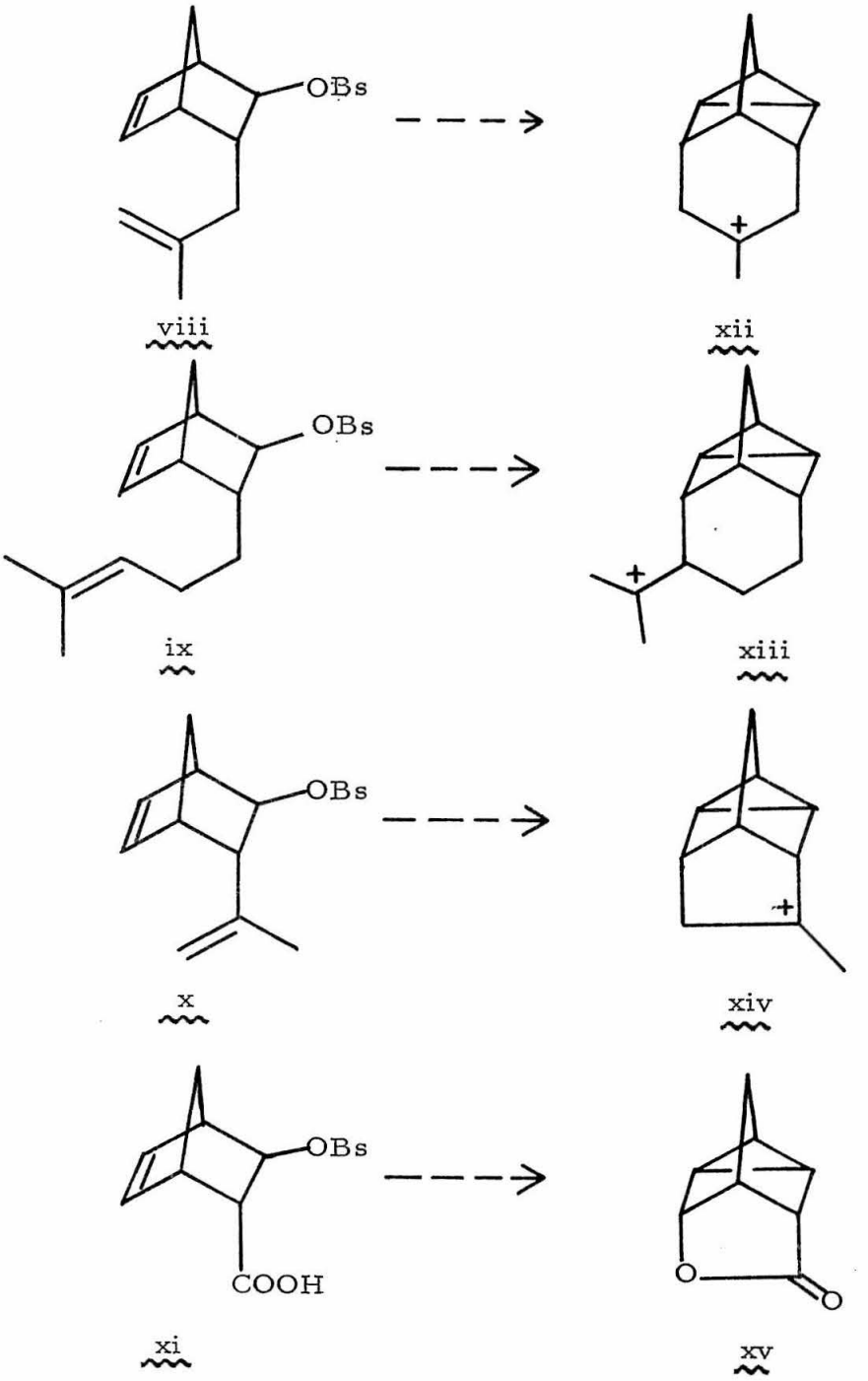
v vi vii

norbornenyl acetate vii in the approximate ratio of 9:1 (2). The olefinic product vii experiences partial carbon scrambling at positions 4 and 5 as determined by ^{14}C labeling experiments (2c). The solvolysis of nortricyclyl p-bromobenzenesulfonate vi (R= Bs) affords a smaller proportion of olefinic material than does the solvolysis of the homoallylically isomeric norbornenyl p-bromobenzenesulfonate v (3). This indicates that the solvolysis products from the two starting materials do not arise from a common intermediate. However, the product composition in both instances suggests that a major portion of the charge in each intermediate resides on the carbon corresponding to C-2 in structure v (4).

It would thus appear possible for an intermediate homoallylic carbonium ion to be captured at C-2 by the double bond in a C-6 exo side chain, provided that sufficient overlap between the double bond and C-2 π orbital can be attained. The possibility also exists for solvolytic participation of the side chain double bond at either C-2 or C-5, although it is not expected that C-5 participation will be significant.

For the problem at hand, an examination of molecular models indicates that substantial overlap between the side chain double bond and the C-2 π orbital can exit in iii when n = 1 at a distance of 2.1 Å and when n = 2 at a distance of 2.2 Å. When n = 0 the side chain olefinic π orbitals are perpendicular to the C-2 orbital axis at a closest approach distance of 2.4 Å, a fact which may preclude cyclization in that compound.

It is suggested that the solvolyses of compounds viii-xi be studied. Of primary interest will be the nature of the products formed, that is, the presence or absence of tetracyclic material. Because such solvolyses are best conducted in a medium such as formic acid which favors anchiomeric assistance (5) and is also relatively non-nucleophilic, the tetracyclic material is expected to be olefinic since elimination in the tertiary carbonium ions should predominate over solvent capture. Thus the tetracyclic material will be easily distinguishable from any



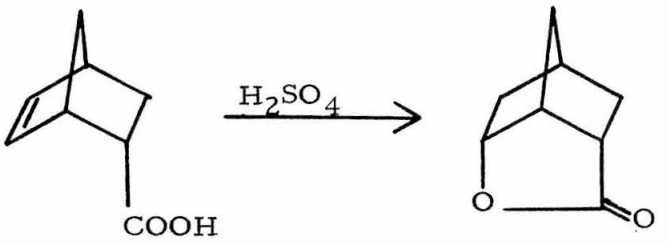
viii xii

ix xiii

x xiv

xi xv

uncyclized products. The attainment of a tertiary carbonium ion in xii-xiv should provide added driving force for the cyclization step. The solvolysis of exo-acid xv will provide an interesting comparison with acid xvi which undergoes ready lactonization in sulfuric acid (6). In addition, the presence or absence of participation of the side chain

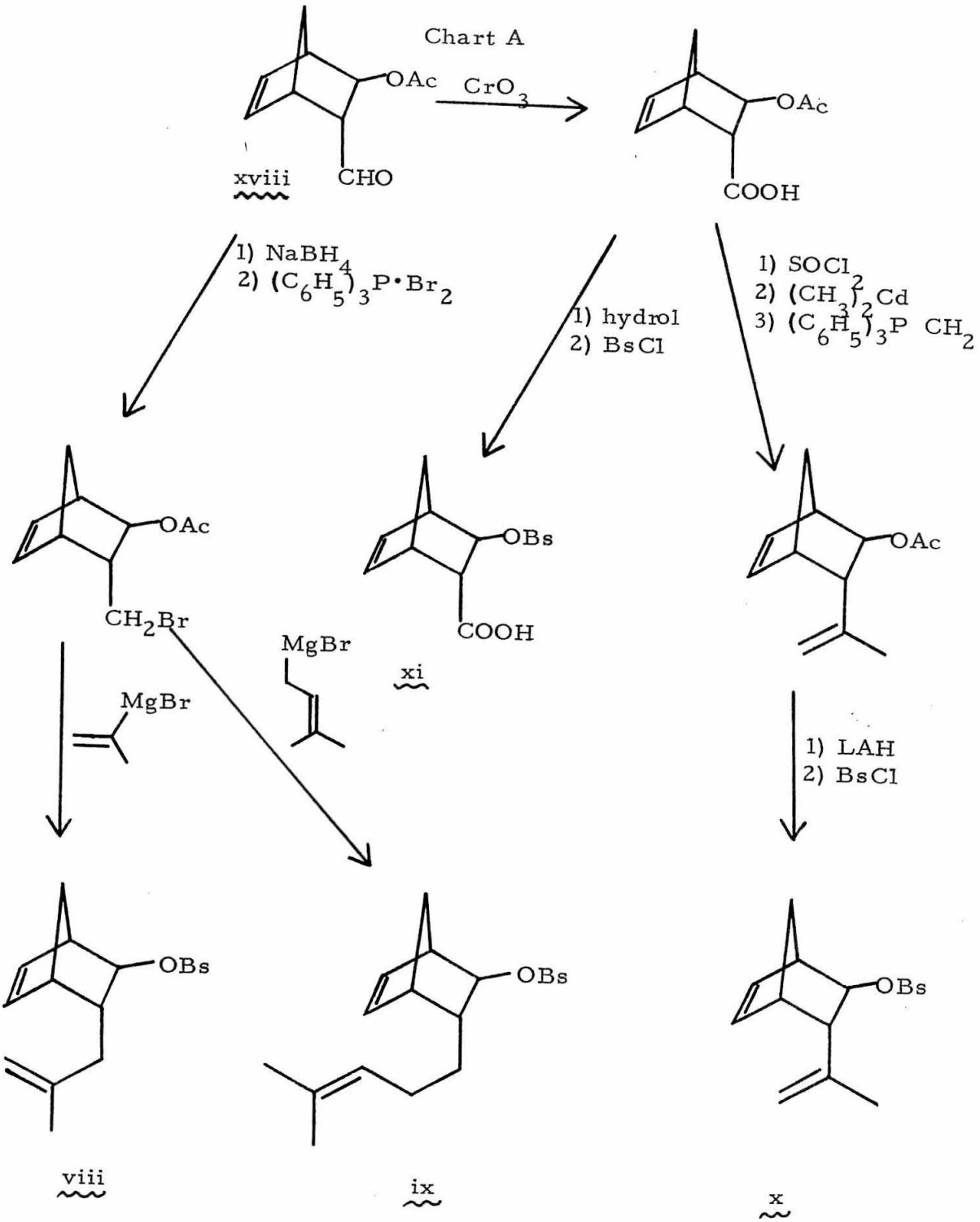


xvi xvii

olefinic bond can be determined by a measure of the solvolytic rate enhancement of viii-xi relative to a similar compound with a totally saturated side chain.

Compounds viii-xi can be prepared from aldehyde xviii, the expected product (6) of the Diels-Alder reaction between cyclopentadiene and trans-acetoxyacolein (7) in straightforward manners as outlined in Chart A.

Chart A


OAc
CrO3
CHO
xviii
COOH
1) NaBH4
2) (C6H5)3P·Br2
1) hydrol
2) BsCl
1) SOCl2
2) (CH3)2Cd
3) (C6H5)3P CH2
CH2Br
OBs
COOH
xi
MgBr
MgBr
1) LAH
2) BsCl
viii
ix
x

References

1. See Proposition 1 this thesis.

2. a. S. Winstein, H. M. Walborsky and K. C. Schreiber, J. Am. Chem. Soc., 72, 5795 (1950).

   b. J. D. Roberts, W. Bennett and R. Armstrong, Jr., ibid., 72, 3329 (1950).

   c. J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., ibid., 77, 3034 (1955).

3. H. Schmid, unpublished results, quoted by S. Winstein and E. Kosower, ibid., 81, 4399 (1959).

4. P. D. Bartlett and G. D. Sargent, ibid., 87, 1297 (1965).

5. S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, ibid., 75, 147 (1953).

6. K. Alder and G. Stein, Ann., 514, 197 (1934).

7. a. T. V. Protopopoua and A. P. Skoldinov, Zhur. Obshchei Khim., 28, 240 (1958).

   b. The trans configuration of related compounds is discussed by A. A. Bothner-By and R. K. Harris, J. Org. Chem., 30, 254 (1965).