

Jacob M. Rosenfeld

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Thesis submitted to the Faculty of  
Graduate Studies in partial fulfillment  
of the requirements for the degree of  
Doctor of Philosophy

INVESTIGATIONS TOWARDS THE SYNTHESIS  
OF THE CUCURBITACINS

by

Jacob M. <sup>ard</sup>Rosenfeld

A thesis submitted to the Faculty of  
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Department of Chemistry

Carleton University

Ottawa, Ontario

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## ABSTRACT

Studies aimed at the partial synthesis of Cucurbitacins from lanosterol or steroidal derivatives are described in three sections.

Firstly, further studies on the cleavage of  $9\alpha,11\alpha$ -epoxyandrost-4-ene-3,17-dione by  $\text{BF}_3$  and other Lewis acids are described with full structural details on the products obtained.

Secondly, a series of  $9\alpha,11\alpha$ -epoxylanostane derivatives were synthesized and the epoxide cleavage reaction studied. No methyl migration was detected, rather 11-ketones or 7,9(11)-dienes were obtained in varying amounts. An attempt was made to rationalize the formation of these products based on an intramolecular proton abstraction mechanism.

The third section of this thesis describes a successful attempt at C9  $\rightarrow$  C10 methyl migration in  $9\alpha,11\alpha$ -epoxy-4,4-dimethylandrost-5-ene-3,17-dione, where a developing allylic carbonium ion at C-9 apparently drives the methyl migration in one direction giving only one product.

## ACKNOWLEDGEMENTS

I would like to express my appreciation to Dr. John ApSimon, who, as a Research Director, fencing coach and squash opponent, has made the time spent on this work an educational and enjoyable four years.

Thanks are also extended to Mr. Robin Sampson who ran the Nuclear Magnetic Resonance Spectra, and to Mr. Karl Diedrich who succeeded in obtaining the necessary chemicals and supplies, usually on very short notice.

Last, but far from least, I would like to acknowledge the efforts of my wife, Jean, who deciphered my handwriting and typed the thesis.

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## Synthesis and Reaction of a 4,4 Dimethyl

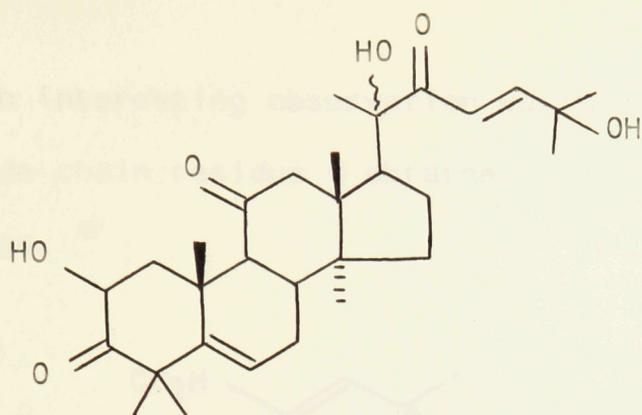
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## INTRODUCTION

### Early Investigations of the Cucurbitacins

Original interest in the cucurbitacins stemmed from the use of crude extracts of the Cucurbitaceae as a cathartic drug in folk medicine.(1) Screening procedures involving these plants of the melon family indicated the presence of powerful tumor inhibitors.(1) This data sparked research leading to the isolation and characterizations of the cucurbitacins (originally Elaterins and Elatericins).  
(2)

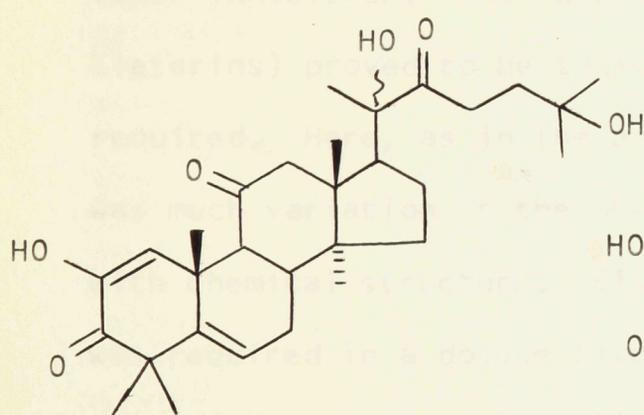
When these compounds were subjected to the classical dehydrogenation with selenium dioxide, 1,2,8-trimethylphenanthrene was obtained. This result, typical of the tetracyclic triterpenes, placed the cucurbitacins in that class of natural products.(3) Accordingly, and in conjunction with other chemical data, the cucurbitacins (Elaterins, Elatericins) were assigned a lanostane skeleton.(2)



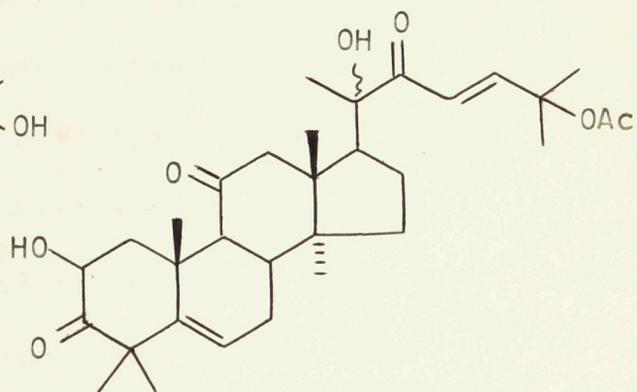
Elatericin A

1

Once these compounds were obtained in a pure form, it became possible to proceed with more sophisticated pharmacological work. These studies (4) found a strong relationship between physiological activity and structure of the compound. In vitro studies showed that Elatericin A, 1, required six times the dosage of Elatericin B, 2, or Elatericin B, 3, to produce the same amount of tumor inhibition.



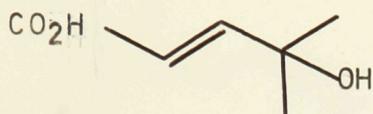
Elatericin B

2

Elatericin B

3

An interesting observation was made concerning the side chain residue 4 obtained by oxidative cleavage.



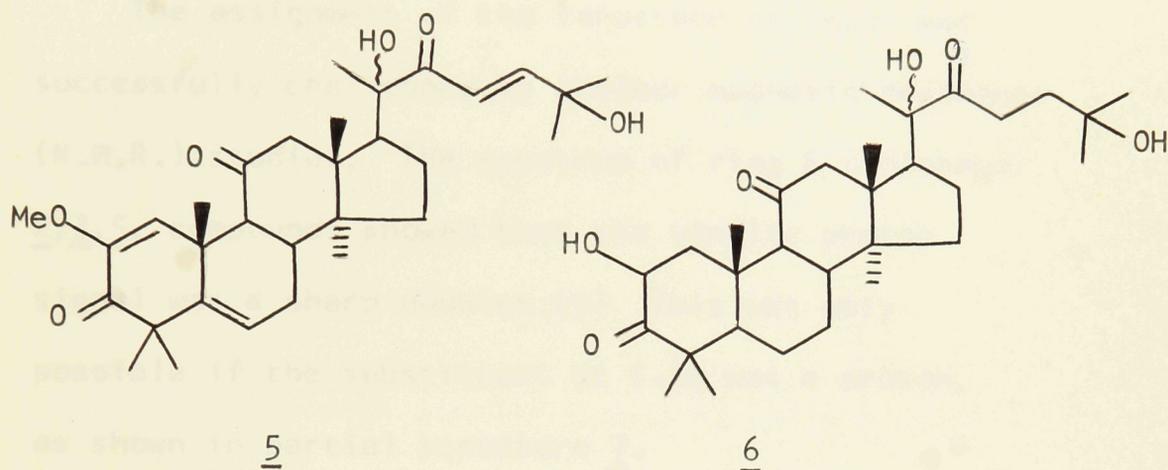
trans-4-hydroxy-4-methylpent-2-enoic acid (4 HMP)

4

This fragment possessed the same activity as Elatericin A, 1, suggesting the possibility that certain portions of the molecule are responsible for various aspects of physiological activity.

In vivo studies were disappointing vis-a-vis tumor inhibition. The cucurbitacins (Elatericins, Elaterins) proved to be toxic in the dosages required. Here, as in the anti-tumor studies, there was much variation in the physiological activity with chemical structure. Elaterin methyl ether 5 was required in a dosage five times greater than that of Elatericin A,B or Elaterin to produce the same toxicity. (Elatericin A,B and Elaterin had

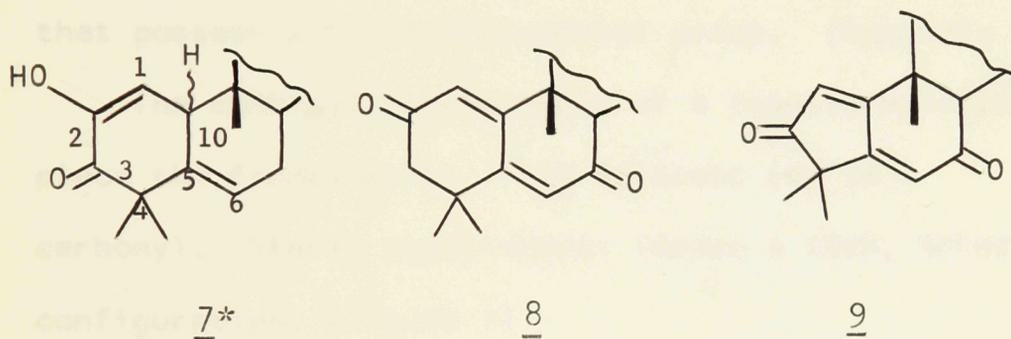
the same potency.) Tetrahydroelaterin 6 required fifty times the dosage of Elaterin A to produce the same physiological effect.



This structure-activity relationship highlights the importance of knowing the correct chemical structure of a compound that is being tested for biological activity. It is equally important to know the chemistry of these compounds. Since minor changes in structure influence the physiological effects, there is a possibility that a synthetic variant of the natural products might possess the tumor inhibiting properties but no toxic side effects. The chemistry, again, is very dependent on structure. Despite the importance of knowing the correct structure, it was

found that the early work on structural elucidation was incorrect in assigning the lanostane skeleton to the cucurbitacins, 1,2,3,5.

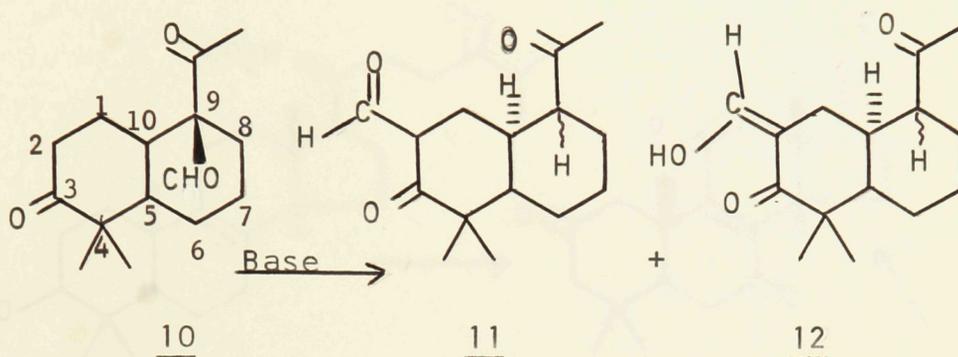
The assignment of the lanostane skeleton was successfully challenged by nuclear magnetic resonance (N.M.R.) studies. The spectrum of ring A diosphenol 2,3,5, compounds showed that the vinylic proton signal was a sharp doublet.(5) This was only possible if the substituent at C-10 was a proton, as shown in partial structure 7.



Chemical proof of the absence of a methyl at C-10 was obtained by the synthesis of diene- diones 8,9 from compounds with partial structure 7.(6)

\* The numbers refer to the carbon, cf, the numbering system for the triterpenes.

The position of the displaced methyl group was proposed to be  $9\beta$  on the basis of a transformylation reaction, 10 to 11 and 12.(6)



Aldehydes with partial structure 10 are readily available from any one of several cucurbitacins that possess a C-9 hydroxymethyl group. (Appendix I)

The chemical requirements of a transformylation place the formyl group in 10 adjacent ( $\alpha$ ) to a carbonyl. Steric requirements impose a  $10\alpha\text{H}$ ,  $9\beta\text{CHO}$ , configuration. (Figure 1)

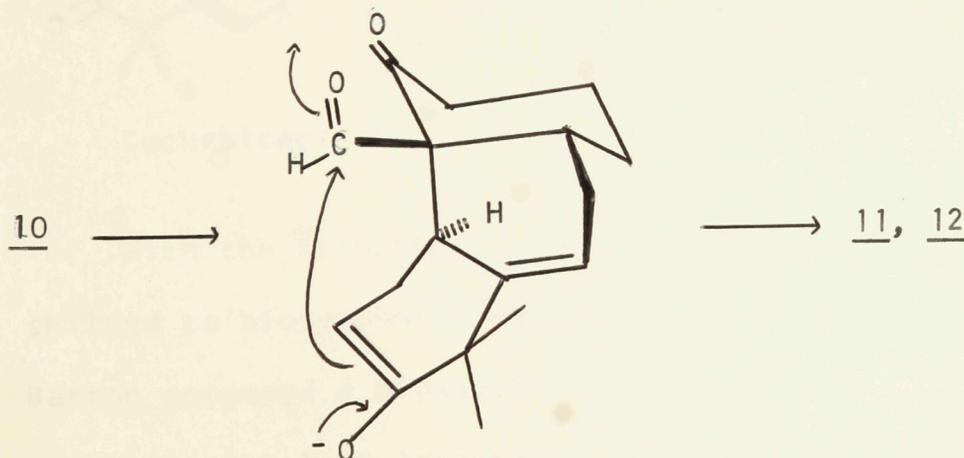
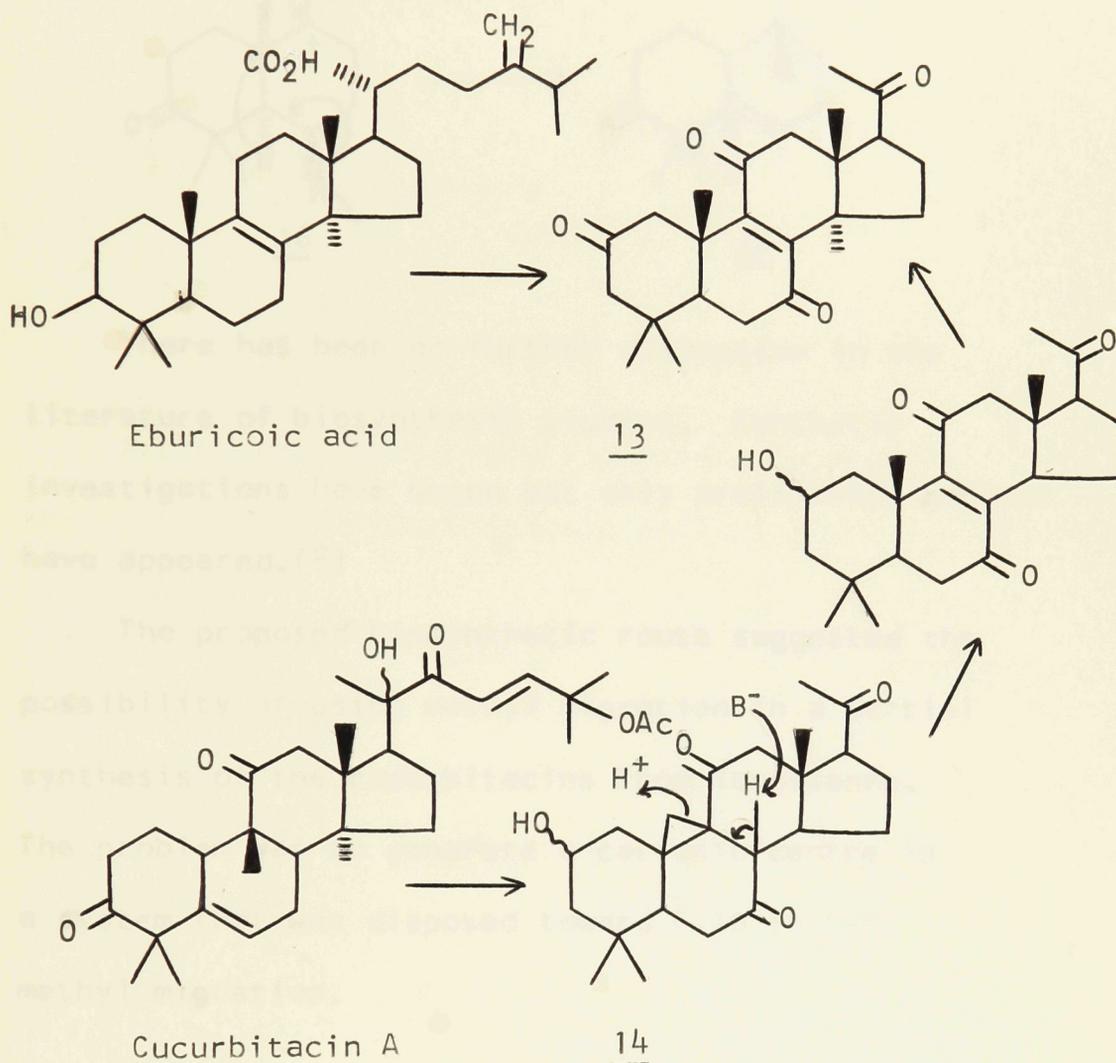


Figure 1

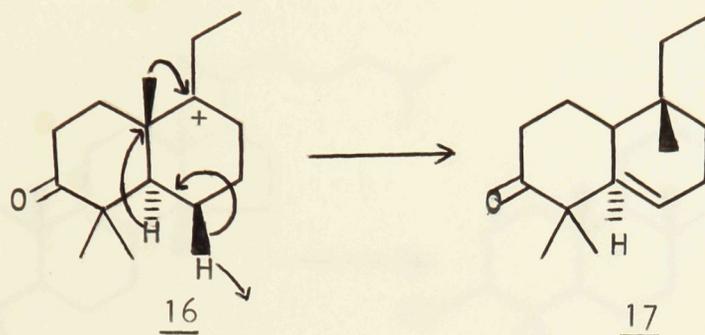
Final proof of structure (7) was obtained by the correlation of the cucurbitacin A with eburicoic acid through a common degradation product 13.\*



With the structural work completed, the emphasis shifted to biosynthetic and synthetic investigations. Barton proposed a biosynthetic route to the cucurbitacins from lanostane precursors via a methyl

\* The structures of the cucurbitacins known to date are summarized in Table 1.

shift, 16 to 17. (6)



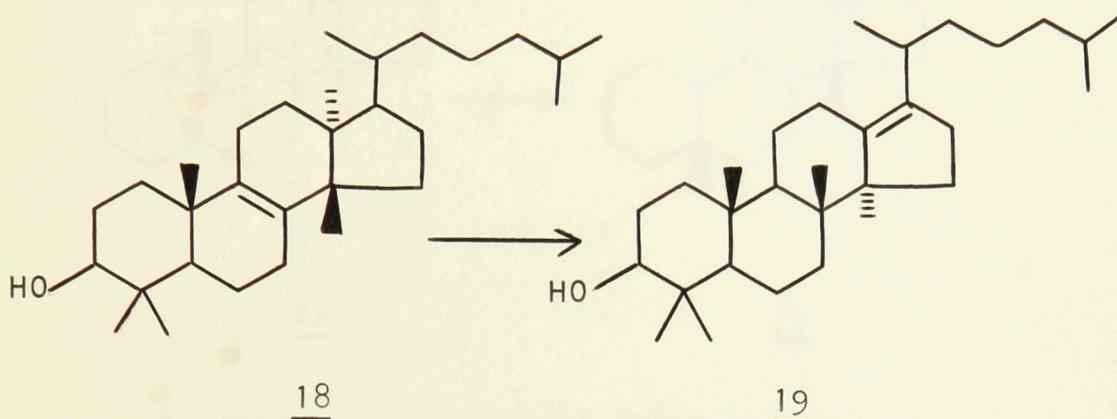
There has been no further discussion in the literature of biosynthesis studies. Synthetic investigations have begun but only preliminary reports have appeared.(8)

The proposed biosynthetic route suggested the possibility of using methyl migration in a partial synthesis of the cucurbitacins from lanostanes. The problem was to generate a cationic centre in a system that was disposed toward C-10 to C-9 methyl migration.

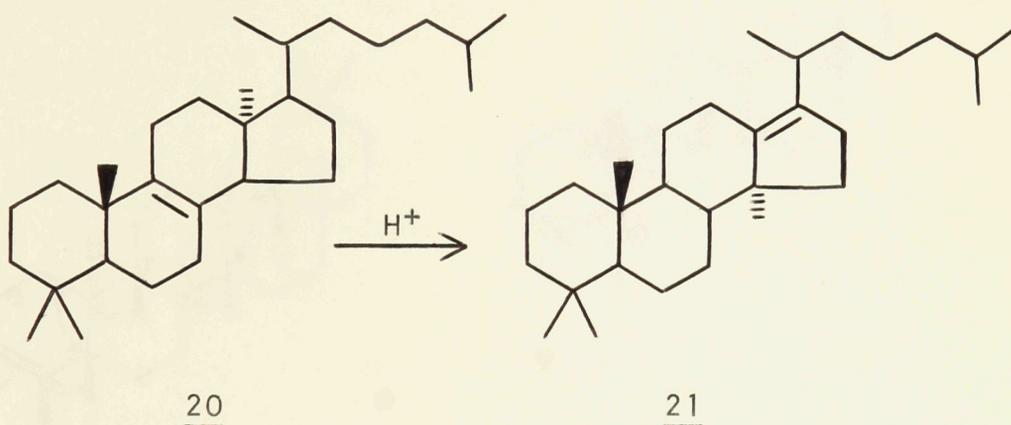
### Methyl Migrations Induced by Protonation of a Double Bond

Methyl migration has been induced in steroids and terpenes by protonation of double bonds. Thus,

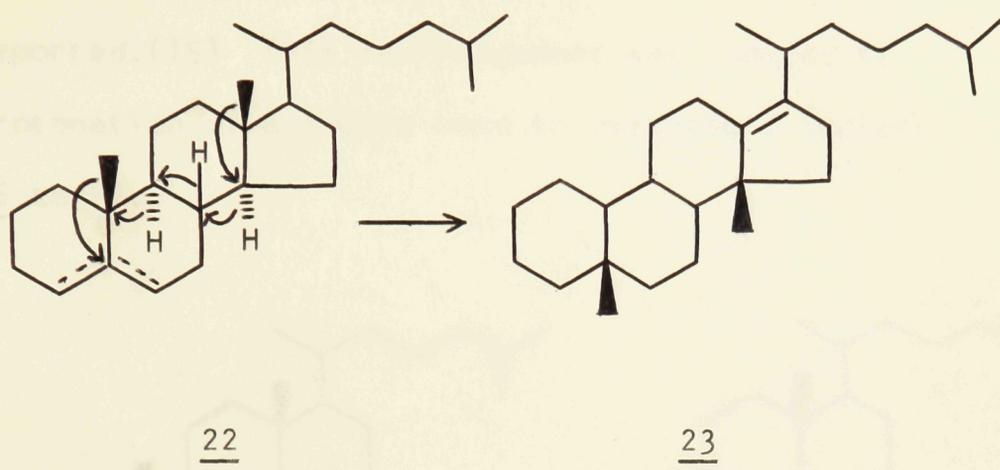
euphol is converted to isoeuphol by treatment with acid, 18 to 19.(9)



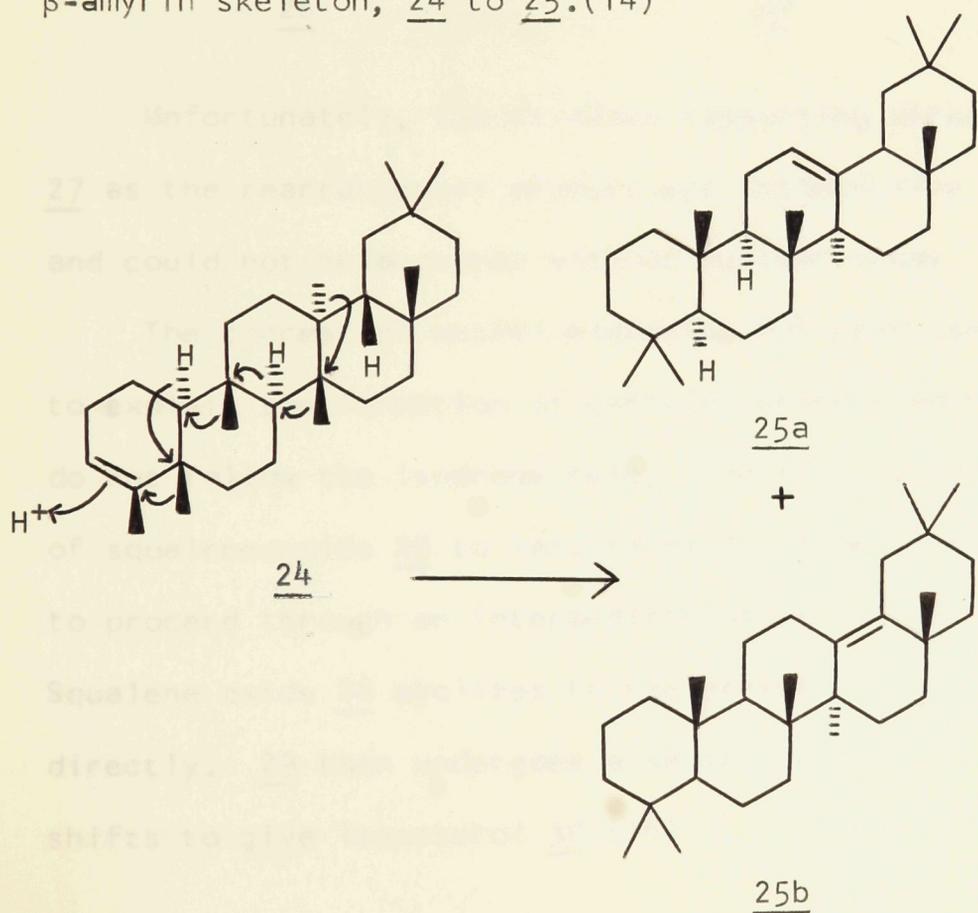
A similar reaction has also been observed in the 4,4 dimethyl-13 $\beta$ -cholestane series, 20 to 21.(10)



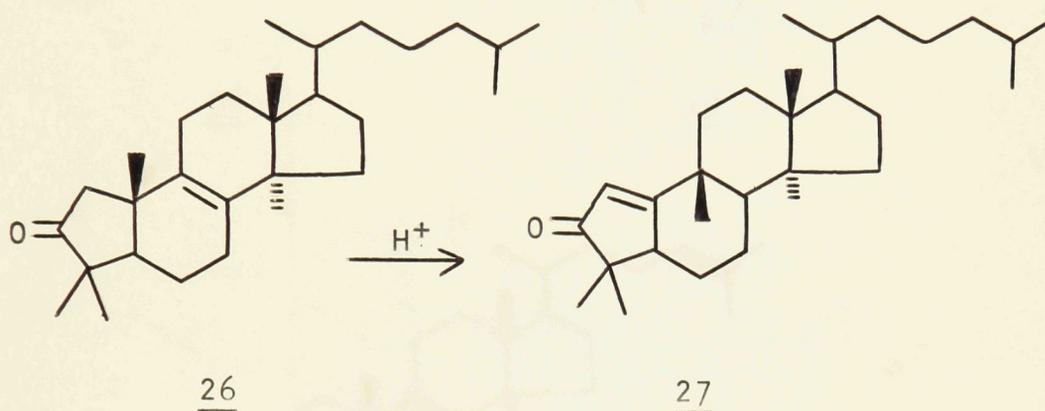
Rearrangements have also been observed where a series of 1,2 methyl and hydride shifts results in a backbone rearrangement, eg. 22 to 23.(11, 12, 13)



A similar rearrangement has been used to transform friedel-3-ene to a compound possessing the  $\beta$ -amyrin skeleton, 24 to 25.(14)

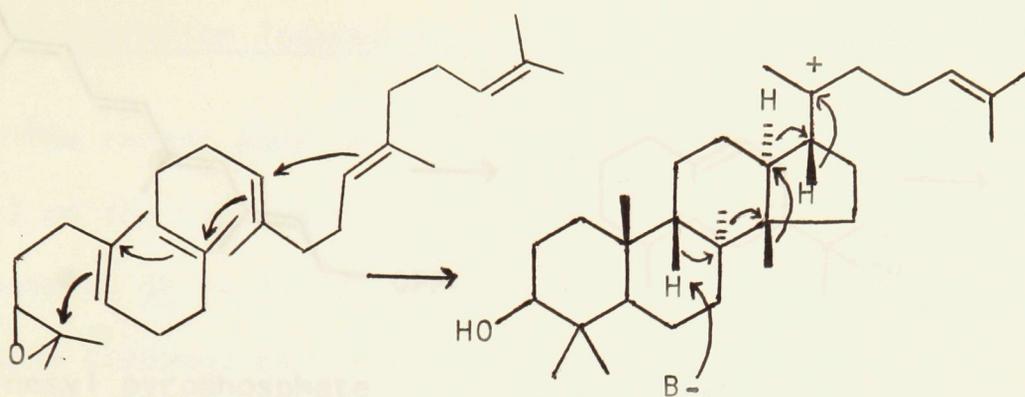
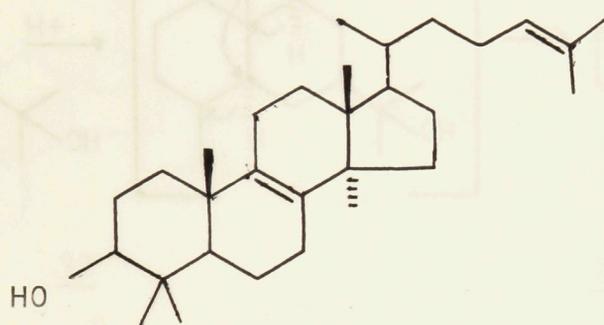


A C-10 to C-9 methyl migration has been reported.(15) This rearrangement was induced by protonation of a double bond to ostensibly convert 26 to 27.

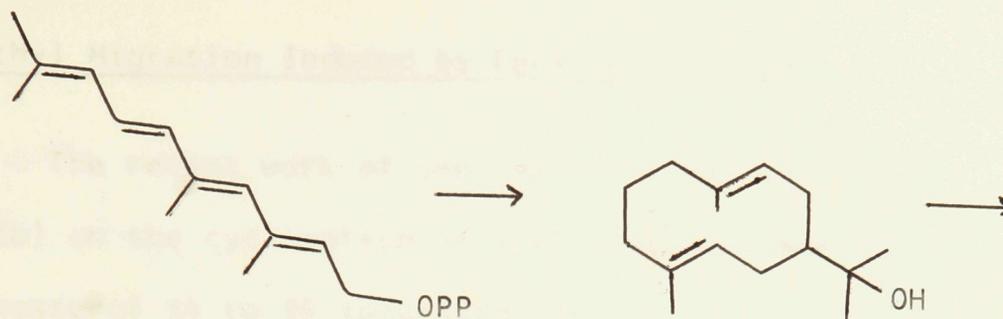


Unfortunately, the evidence supporting structure 27 as the rearrangement product was inconclusive and could not be accepted without further study.

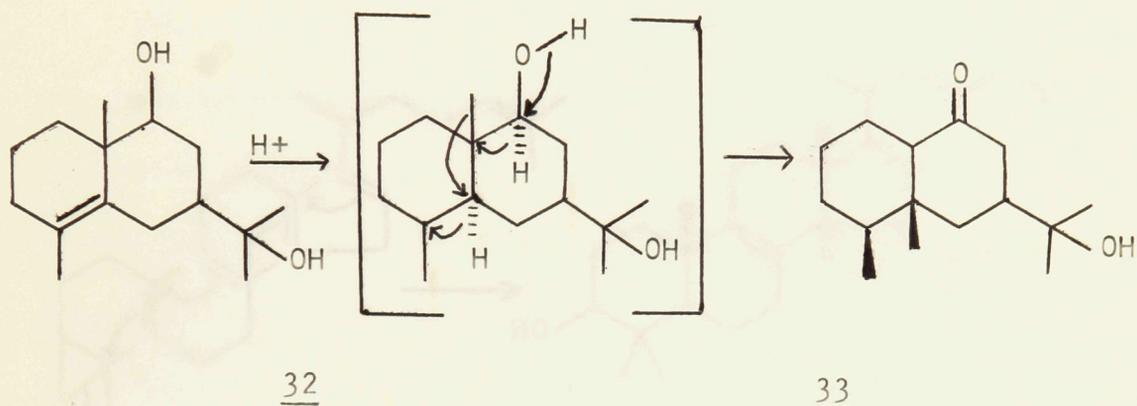
The concept of methyl migration has been used to explain the formation of certain terpenes which do not follow the isoprene rule. The cyclization of squalene oxide 28 to lanosterol 30 is believed to proceed through an intermediate presterol 29. Squalene oxide 28 cyclizes to the presterol 29 directly. 29 then undergoes a series of methyl shifts to give lanosterol 30.(16)

282930

Robinson (17) invoked a methyl migration to explain the biosynthesis of eremophilone, which in itself cannot be derived from polymerization of isoprene units. Farnesyl pyrophosphate was proposed to cyclize to 31. An "oxidative cyclization" would result in the bicyclic 32 which upon protonation undergoes methyl migration to the eremophilene skeleton 33.



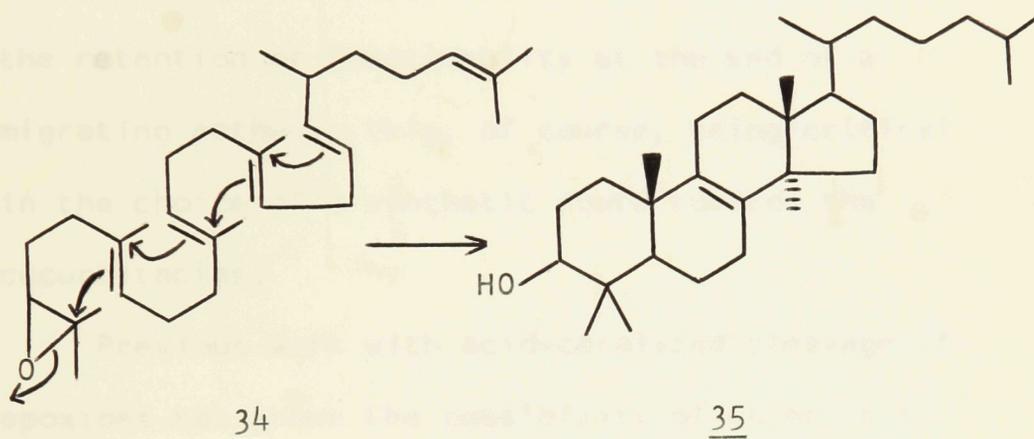
Farnesyl pyrophosphate

313233

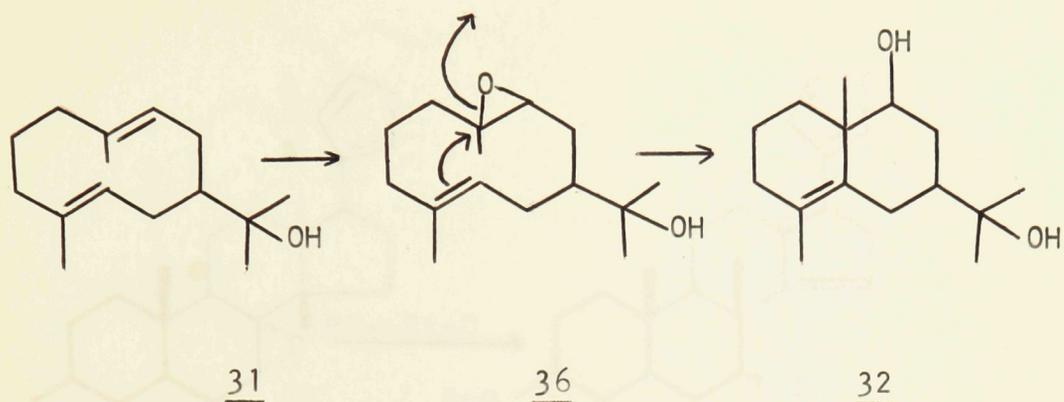
Although protonation of a double bond often induces alkyl migration, the synthetic utility of the method is limited since it includes saturation of one end of the migration pathway. A methyl group migration approach to the synthesis of the cucurbitacins would preferably retain functionality in ring C for future conversion to the C-11 ketone as well as functionality in ring A for elaboration of the diosphenol system.

### Methyl Migration Induced by Epoxide Cleavage

The recent work of van Tamelen (18a) and Corey (18b) on the cyclization of 1,2-oxido-squalene to lanosterol 34 to 35 suggested the possibility of epoxide cleavage as a means of entry into the 9 $\beta$  methyl series.

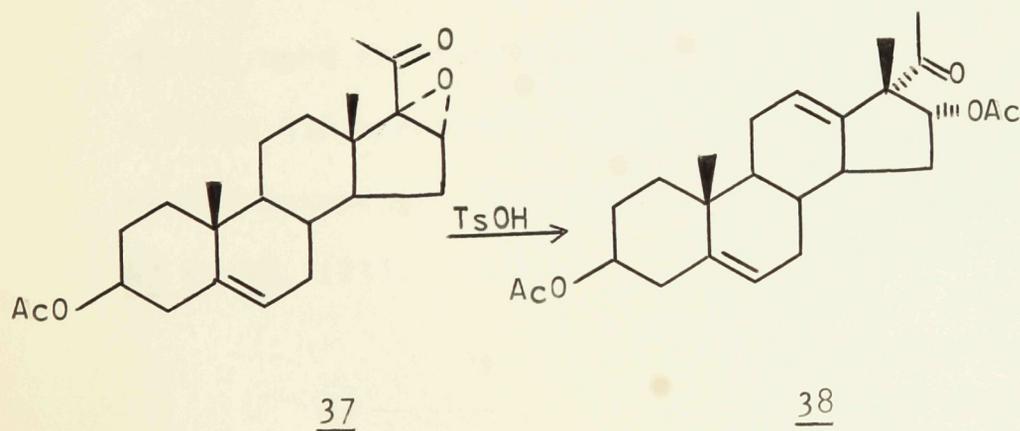


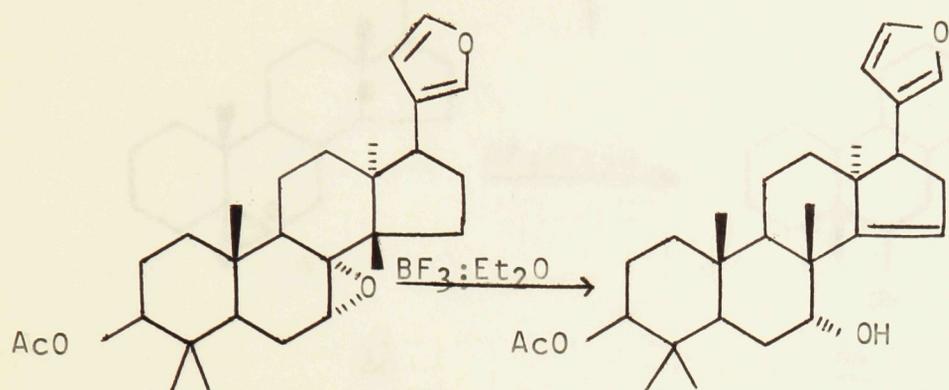
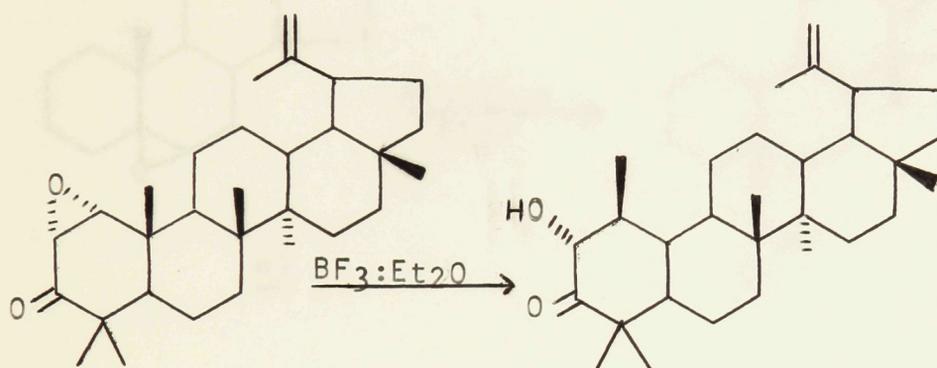
This use of an epoxide function was important in the sesquiterpene biosynthesis previously discussed. The term "oxidative cyclization" used to describe formation of 32 in the eremophilone sequence takes on a less nebulous meaning. Epoxide 36 can be envisioned as a very plausible intermediate between 31 and 32.



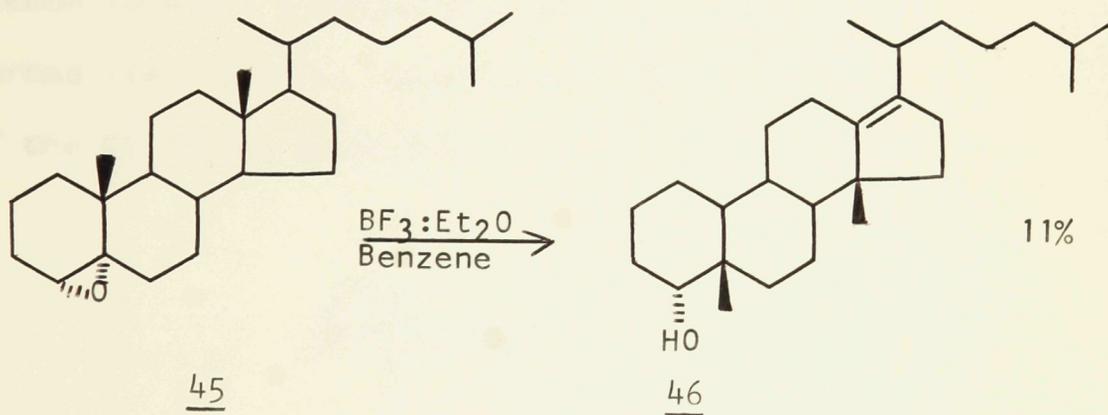
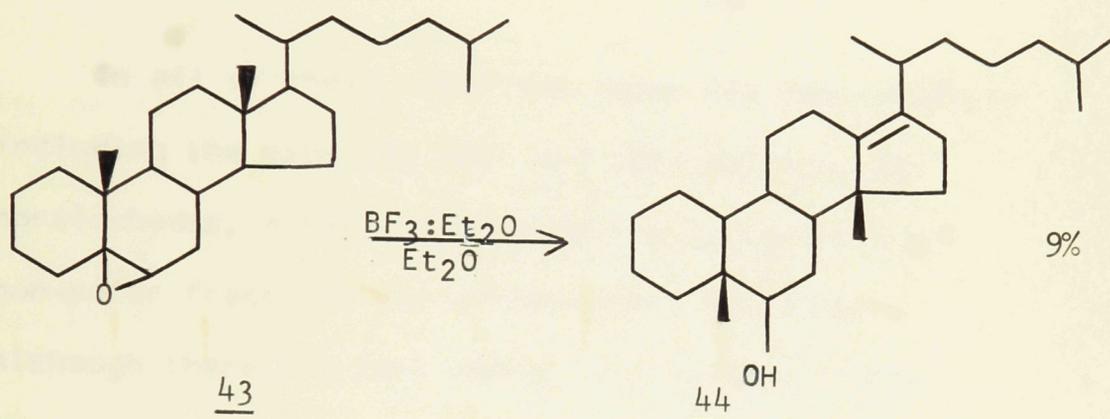
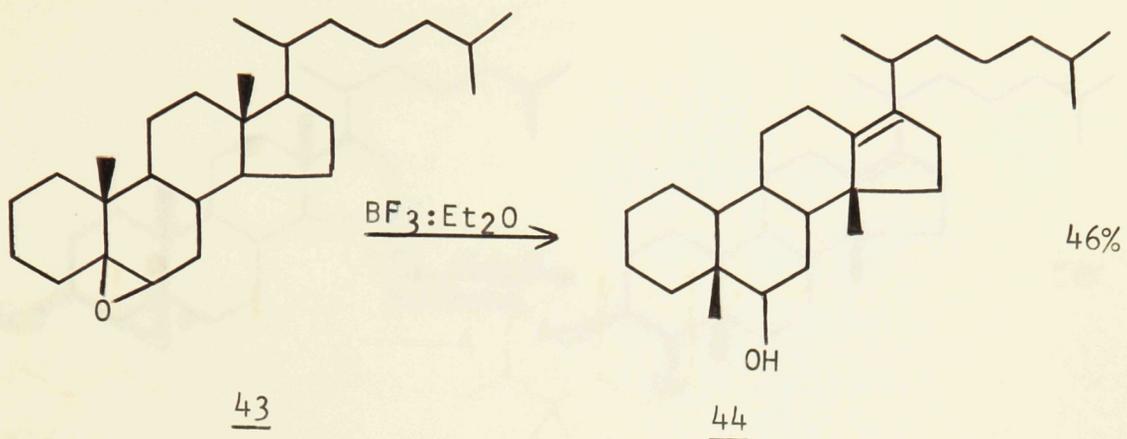
The crucial factor involving the epoxides is the retention of functionality at the end of a migrating pathway, this, of course, being critical in the choice of a synthetic route towards the cucurbitacins.

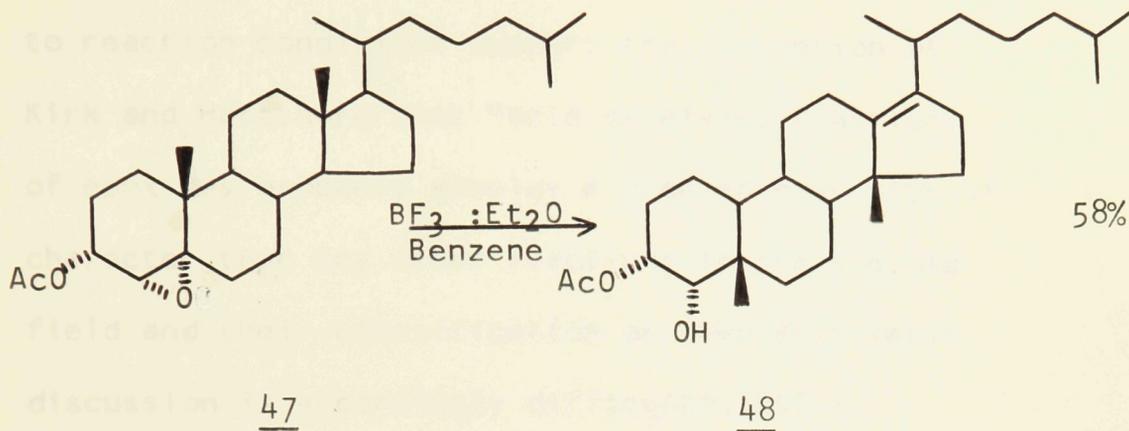
Previous work with acid-catalyzed cleavage of epoxides has shown the possibility of using this reaction to induce methyl migration in steroids, eg. 37 to 38, (19), 39 to 40, (20), 41 to 42, (21).



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An interesting parallel between epoxide and double bond chemistry was shown in the reactions of 4,5 and 5,6 steroidal epoxides to give backbone rearrangement, eg. 43 to 44, (22), 45 to 46, (22), 47 to 48, (23).





In all of these reactions there are many products including the expected  $5\beta$ - and  $5\beta$ - ketones,  $5\beta$ - noraldehydes, dienes, fluorohydrins, unidentified non-polar fractions and unidentified fluorides. Although there are many mechanistic pathways that the reaction can follow, there is one step that is common to all. A cationic centre at C5 must be formed via the polarization and ultimate cleavage of the C5 oxygen bond. (24)

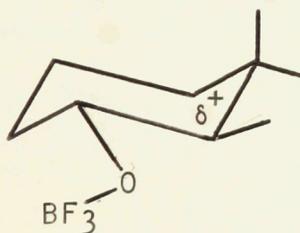


Figure 2

The multiplicity of products and sensitivity to reaction conditions support the contention of Kirk and Hartshorn that "acid catalyzed reactions of epoxides probably display a greater diversity of character than any other reactions in the steroid field and their classification or even systematic discussion is accordingly difficult".(25)

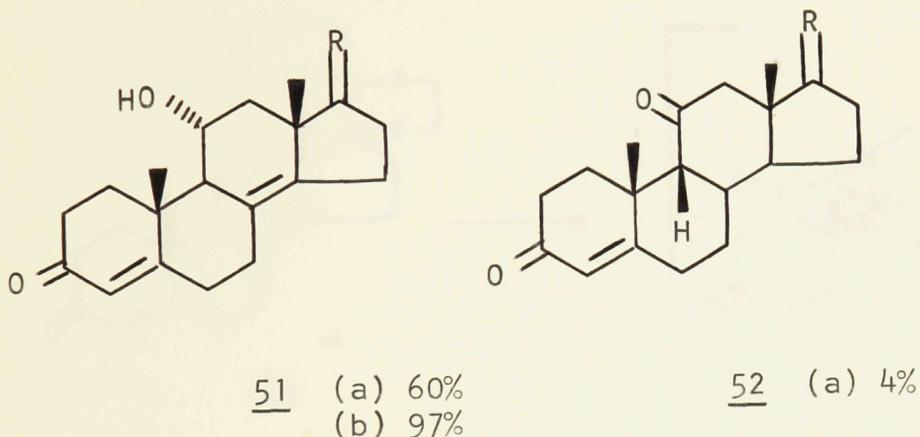
An attempt to define the conditions necessary for backbone rearrangement as opposed to local transformations was made by Bascoul et al.(26) These workers proposed three necessary conditions for backbone rearrangement.

1. The molecule should be under intracyclic strain. In steroids and terpenes the intracyclic strain is supplied by the C/D cis fusion.
2. The molecule should contain a relaxing function. In the cases studied a relaxing function was an epoxide or double bond. Reaction of this functionality results in the changes in the molecule.
3. The relaxing function and strain should be at separate locations in the molecule.

Examples that satisfy these conditions have already been mentioned. Thus 18, with a double bond at 8,9 and intracyclic strain at the C/D fusion,



This was encouraging in that for the first time an entry into the C-9 $\beta$  methyl steroids was obtained from the normal C-10 $\beta$  methyl steroids. Furthermore maintenance of functionality at C-11 and in the A ring was also achieved. Unfortunately there were two other products isolated, 51 and 52. Homoallylic alcohol 51 was by far the major product.



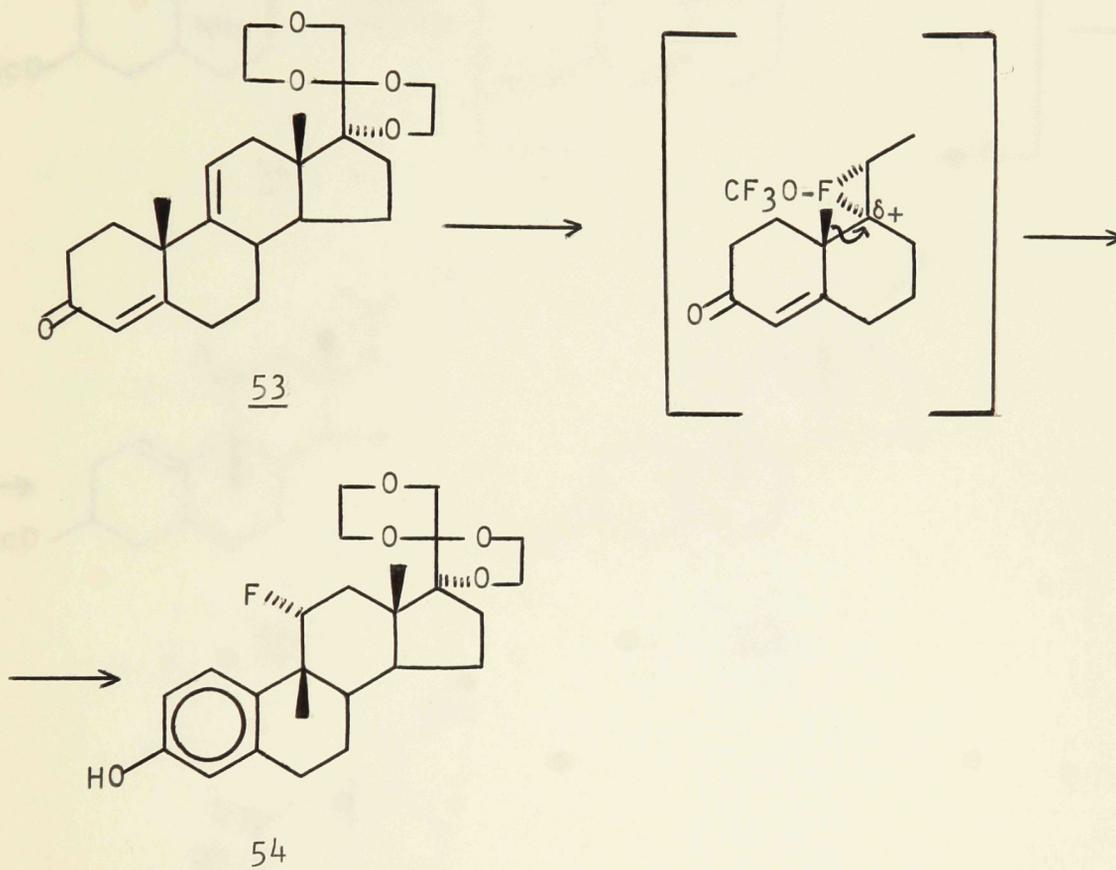
(a) R = carbonyl  
 (b) R = 17 $\beta$  acetyl 17 $\alpha$  proton

The presence of at least two competing pathways resulted in a low yield of the phenol. This would be a weak point in any complex synthetic scheme requiring many steps. Furthermore only two out of a necessary eight methyl groups required for triterpene synthesis were present. Nevertheless, it gave

support to the projected use of epoxides in inducing the desired methyl migration.

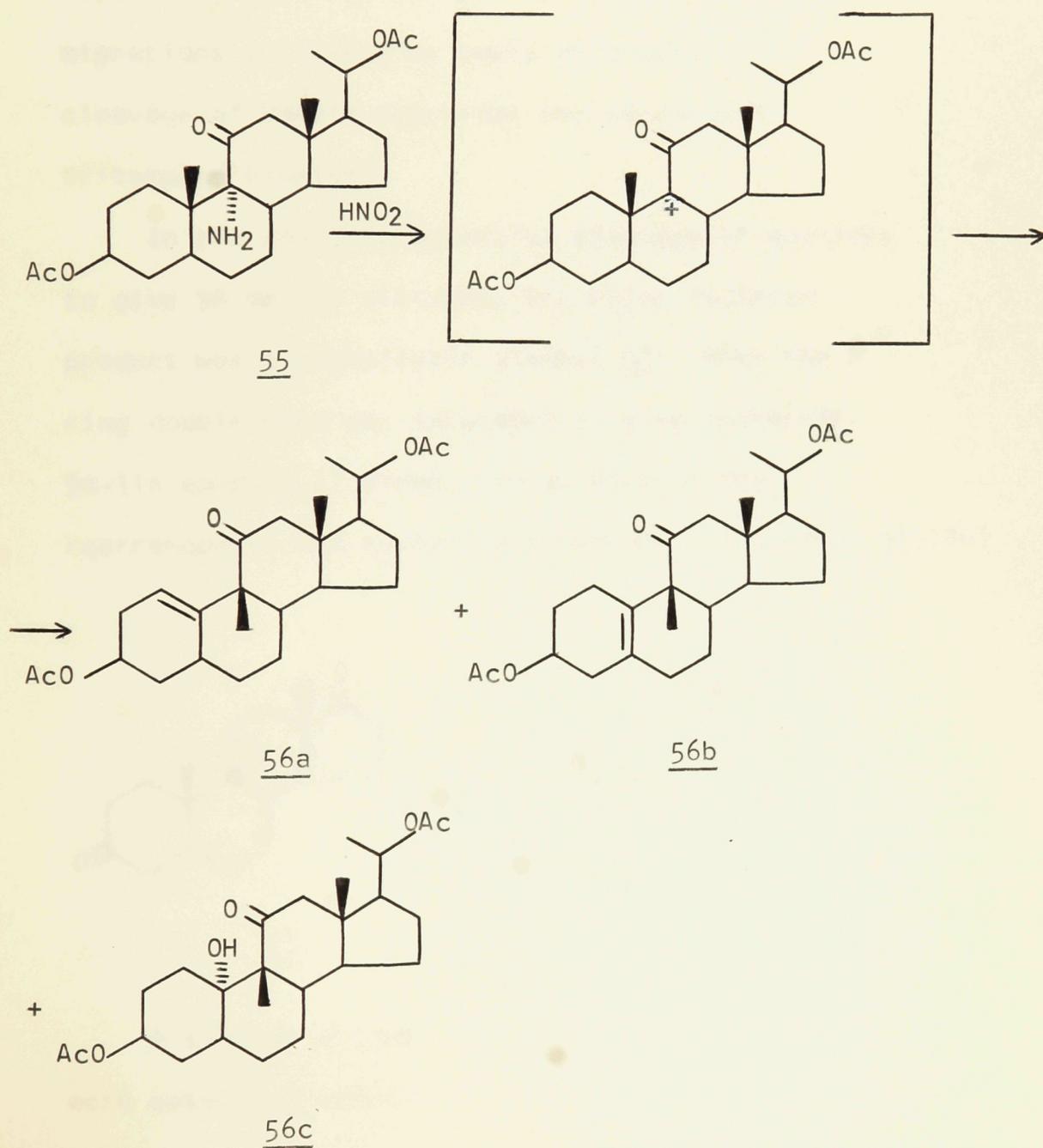
This thesis will, in part, describe confirmation and elaboration of the above work.

A similar reaction was reported by Barton (27), arising from a study of the reactions of fluoroxy-trifluoromethane as an electrophile, 53 to 54.



Compound 54 was reported as the major component. The exact yield however was not mentioned.

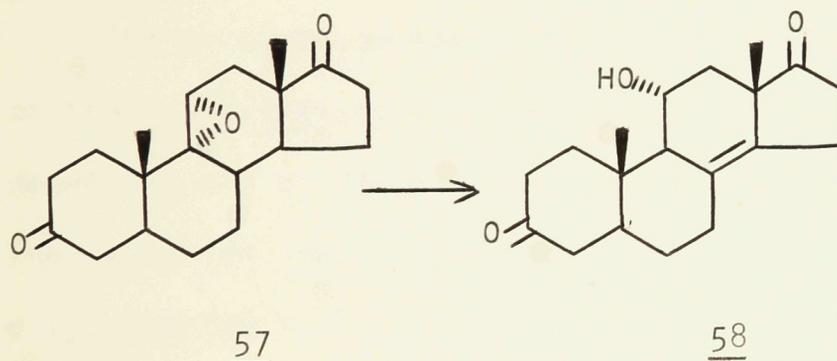
A third example of C-10 to C-9 methyl migration was published by Edwards et al. The migration was induced by deamination of a 9 $\alpha$ -amino-11-keto steroid, 55 to 56a, 56b, 56c.(28)



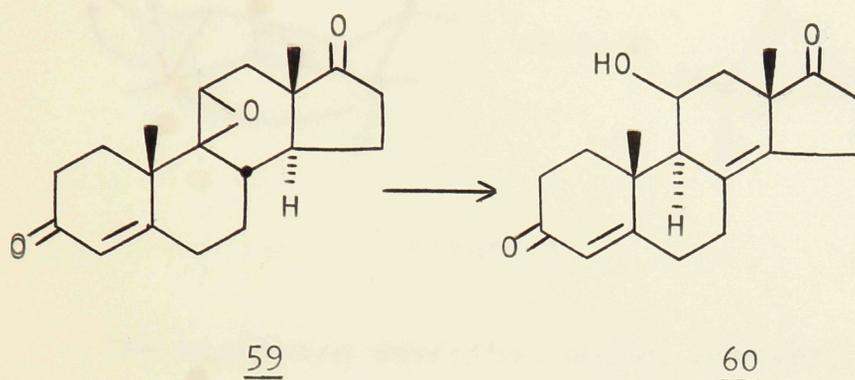
As in the previous instances of methyl migration, the critical factor was the formation of a cationic centre at C-9.

This thesis will describe several studies associated with the search for C-10 to C-9 methyl migrations initiated by Lewis acid catalyzed cleavage of 9 $\alpha$ -11 $\alpha$  steroidal and tetracyclic triterpene epoxides.

In the case of successful cleavage of epoxides to give 9 $\beta$  methyl steroids, the major isolated product was a homoallylic alcohol 51. When the A ring double bond was saturated to give andrenost-9 $\alpha$ -11 $\alpha$  epoxy-3,17 dione, the product of the rearrangement was exclusively homoallylic alcohol 58.(30)



A similar product was also obtained from the acid catalyzed rearrangement of a 9 $\beta$ 11 $\beta$  epoxy steroid.



The dominance of the mechanistic pathway leading to the homoallylic product makes it necessary that the formation of this product be blocked to allow the migration pathway to become more efficient. It is necessary, therefore, to understand the mechanism of formation of alcohols 51a,b and 58.

The proposed mechanism of formation was based on the trans-anti-periplanar orientation of the departing end of the epoxide and the 14 $\alpha$  proton. The mechanism leading to 51 was proposed to involve a 1,3 hydride shift as described in Figure 3.

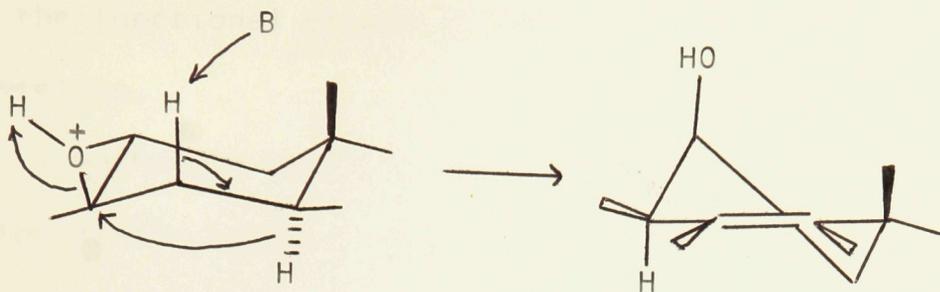


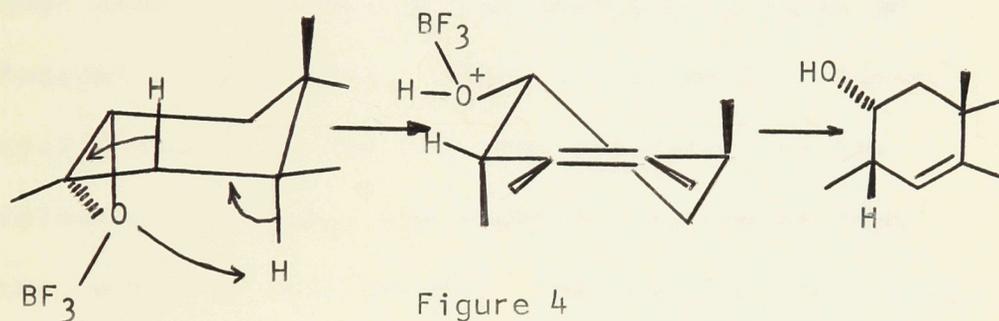
Figure 3

The mechanism described above, however, cannot be directly applied to the formation of homoallylic alcohol from 9 $\alpha$ 11 $\alpha$  epoxides. The fact that both the 14 $\alpha$  proton and the departing end of the 9 $\alpha$ 11 $\alpha$  epoxide are syn-periplanar would make the 1,3 hydride shift mechanism somewhat less favourable than in the case of the 9 $\beta$ 11 $\beta$  epoxide.

The reaction conditions used by ApSimon et al (8) also suggest that the 1,3 hydride shift is not the mechanism of formation of the homoallylic alcohols in the 9 $\alpha$ 11 $\alpha$  epoxides. The hydrofluoric acid conditions used for the rearrangement of 59 provide proton acceptors either as fluoride ions or hydrofluoric acid molecules. No such acceptor(s) is (are) available if gaseous BF<sub>3</sub> or SnCl<sub>4</sub> are the catalysts in benzene solution. In fact, the only proton acceptors

are the functional groups on the steroid molecules themselves.

A mechanism based on the epoxide functionality as the proton acceptor was put forward. Accordingly, it was proposed that the polarized  $\text{BF}_3$  epoxide complex acted as an internal base to abstract the  $14\alpha$  proton and initiate an anti-periplanar 1,2 hydride shift. This type of shift is a much more common mode of rearrangement in steroids and terpenes.(9)



It is also possible to explain the formation of the phenol 50 by the scheme depicted in Figure 4. The  $1\alpha$  proton bears the same conformational relationship to the departing end of the epoxide as the  $14\alpha$  proton; it is two carbons removed and is syn-periplanar. A similar mechanism would yield a

phenol by the scheme depicted in Figure 5.

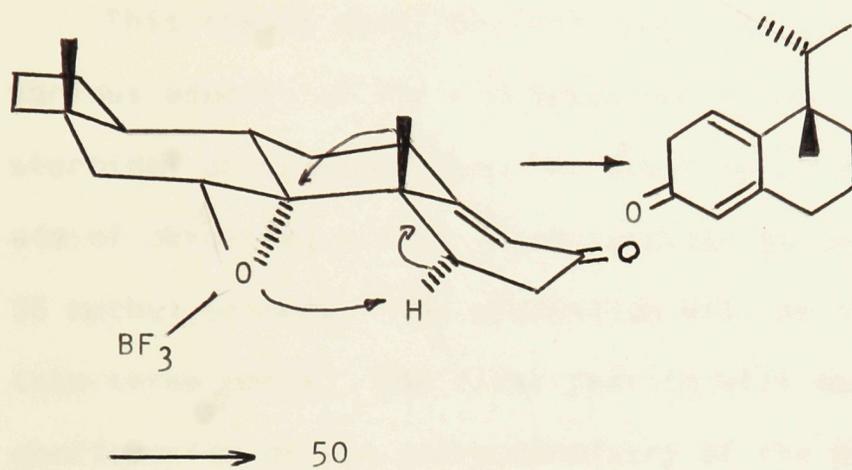


Figure 5

The predominance of the homoallylic alcohol over phenol can thus be rationalized in terms of Bascou's hypothesis. There is presence of intracyclic strain in the C/D ring trans-fusion; the relaxing function - the epoxide - is remote from the centre of this strain. The reaction would thus proceed to remove the strain to give homoallylic alcohol. The formation of phenol 50 however cannot be rationalized by Bascou's hypothesis. Evidently there are other factors involved in this reaction pathway.

## RESULTS AND DISCUSSION

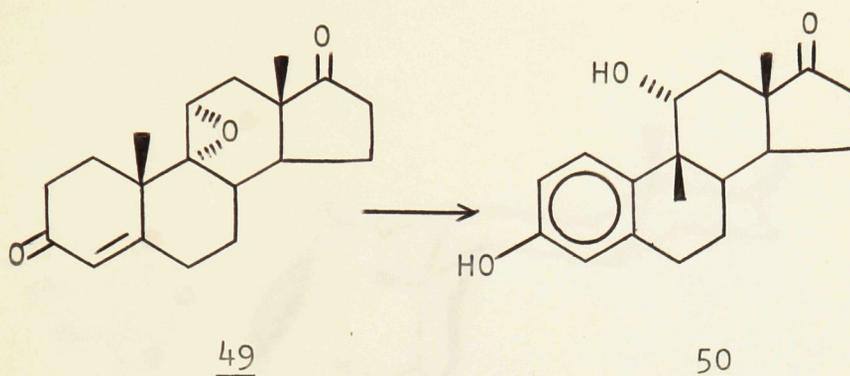
This thesis describes the investigation of various aspects of the rearrangement of 9 $\alpha$  steroidal and terpene epoxides with the ultimate aim of obtaining a high yield reaction giving a 9 $\beta$  methyl product. The discussion will be divided into three parts. The first section will deal with confirmation of the stereochemistry of the products obtained from the reaction of epoxide 49 with gaseous BF<sub>3</sub> in benzene. In the second part of the investigation, an attempt was made to extend this reaction to the tetracyclic triterpenes; the discussion will concern the unusual reaction pathways that were observed. The last section will describe a synthetic sequence which resulted in a very high yield of a 9 $\beta$  methyl steroid.

SECTION I

The assignment of structures of the products of the rearrangement of 49 was based on mechanistic arguments. Such arguments require an accurate knowledge of the mechanism; when this is lacking it is necessary to supply a more rigorous proof of structure of the products.

Stereochemistry of Phenol 50

The first evidence supporting structure 50 was obtained from the nuclear magnetic resonance (N.M.R.) spectrum. The signal attributable to the C-1 proton appeared at a lower field than the position usually expected for the C-1 proton of estrone. This deshielding effect was attributed to close proximity of a hydroxyl group. This structural feature was consistent with the  $9\beta$  methyl assignment in structure 50.



That the deshielding was caused by the 11 $\alpha$  hydroxyl was suggested by the disappearance of this effect upon oxidation to the 11 ketone.

Similar results were obtained by comparing the N.M.R. spectrum of the 3 methyl ether of 50 in pyridine- $d_5$  with the spectrum in deuterated chloroform. In pyridine- $d_5$ , the signal of the C-1 proton is shifted downfield by 0.85 p.p.m. appearing at 8.97 $\delta$ . The other protons are deshielded by only 0.2 p.p.m. These results are best rationalized by the postulation of a pyridine-alcohol complex close to the C-1 proton which results in the large deshielding effect.(31) Figure 6.

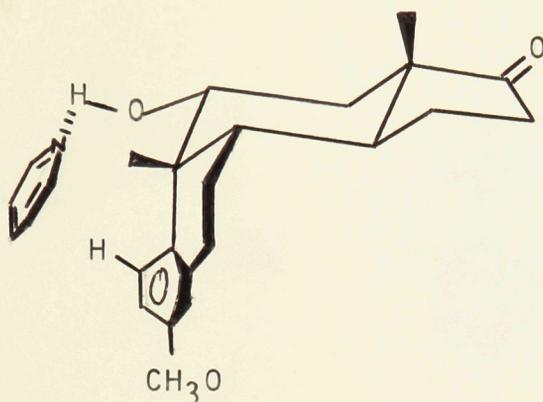


Figure 6

Observation of the nuclear Overhauser effect in the N.M.R. spectrum of the 3 methyl ether, 50, further indicated the proximity of the 11 $\alpha$  hydroxyl and the C-1 proton.(32) A similar proximity was found for the C-1 proton and the 9 $\beta$  methyl group. Irradiation of the 11 $\alpha$  hydroxyl resulted in a 10% increase in the intensity of the C-1 proton signal at 8.12 $\delta$  . A 9% increase of the C-1 proton signal intensity was also observed. These results gave strong support to the conformation of 50 as shown in Figure 7.

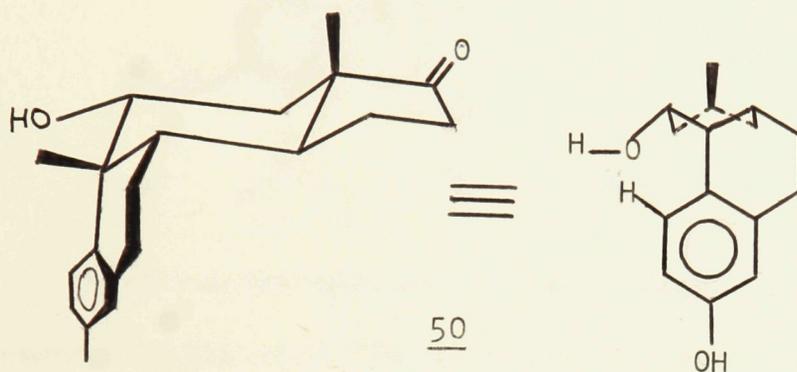
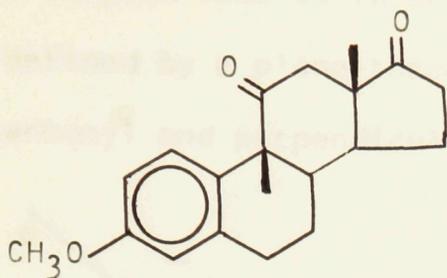


Figure 7

The conformational representations in Figure 7 show the close spatial relationship between the C-1 proton and the 11 $\alpha$  hydroxy and the 9 $\beta$  methyl groups.

If the assignment of the 9 $\beta$  methyl group was correct then that group would have to be equatorial to the C ring. This conformation was verified by observing the solvent effect in deuteriochloroform and hexadeuterobenzene of the 11 ketone 61.



61

In deuteriochloroform the two methyl groups showed signals at 0.75 $\delta$  (13 $\beta$  methyl) and 1.4 $\delta$  (9 $\beta$  methyl). In hexadeuterobenzene the 13 $\beta$  methyl signal is shifted to 0.53 $\delta$  while the 9 $\beta$  methyl resonance remains at 1.4 $\delta$ . The lack of solvent effect is typical of an equatorial group  $\alpha$  to a carbonyl.

The use of solvent effect to assign equatorial and axial conformations has been discussed by Williams and Bhacca.(33) The effect is believed to be due to a collision complex between the ketone and a benzene molecule. (Figure 8)

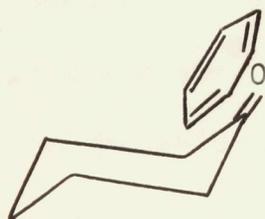


Figure 8

This complex results in deshielding and shielding regions defined by a plane through the carbon atom of the carbonyl and perpendicular to the C-O bond.

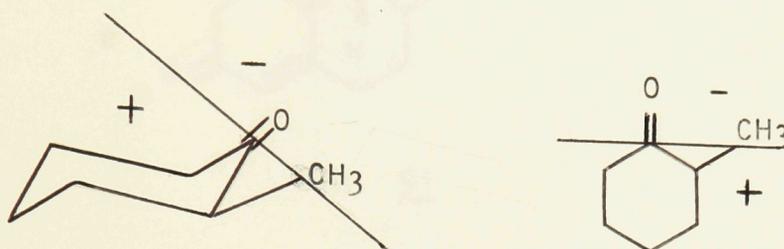


Figure 9

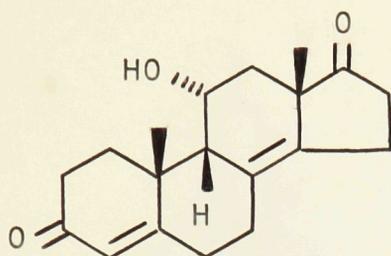
All protons "behind" the plane are shielded; those "in front" are deshielded; the  $\alpha$  equatorial methyl lies on the plane and is unaffected.

The evidence presented regarding the structure of 50 is sufficient to confirm its structure, in lieu of an unambiguous alternate synthesis.\*

### Stereochemistry of Homoallylic Alcohol 51

The gross structure of the homoallylic alcohol 51 has been discussed and the configuration at C-9 has been assigned on mechanistic grounds.(8)

\* Synthetic approaches to 50 were the subject of some minor studies by this author but were not well enough advanced to discuss in this dissertation.



51

Further evidence supporting the  $9\beta$  assignment was obtained from first order analysis of the C-11 carbinol signal in a 100 MHz spectrum. In  $\text{CDCl}_3/\text{D}_2\text{O}$  the carbinol signal appeared as five lines centred at  $4.4\delta$ . The lines were equally spaced at 5 c.p.s. and the relative intensities were 1:2:2:2:1. This multiplet can be easily obtained for the carbinol proton if the coupling constants are assigned the values  $J_{9\beta 11\beta} = J_{11\beta 12\beta} = 5$  c.p.s. and  $J_{11\beta 12\alpha} = 10$  c.p.s. The resulting pattern shown in Figure 10 is the one obtained by experiment.

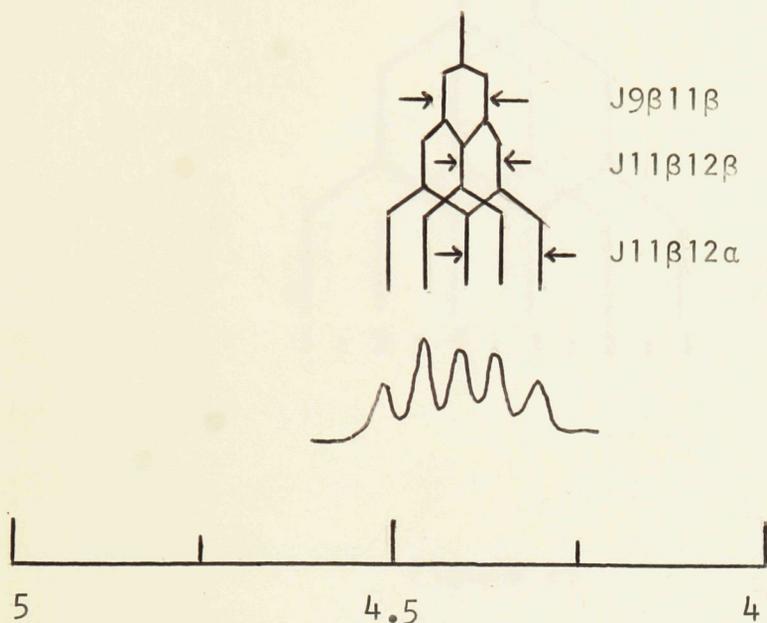


Figure 10

If the configuration at C-9 was  $9\alpha$  then a different coupling pattern would emerge. Assuming that the axial-axial, axial-equatorial, and equatorial-equatorial coupling constants are similar in both  $9\alpha$  and  $9\beta$  compounds, then a six line multiplet would be predicted by first order analysis. (Figure 11)

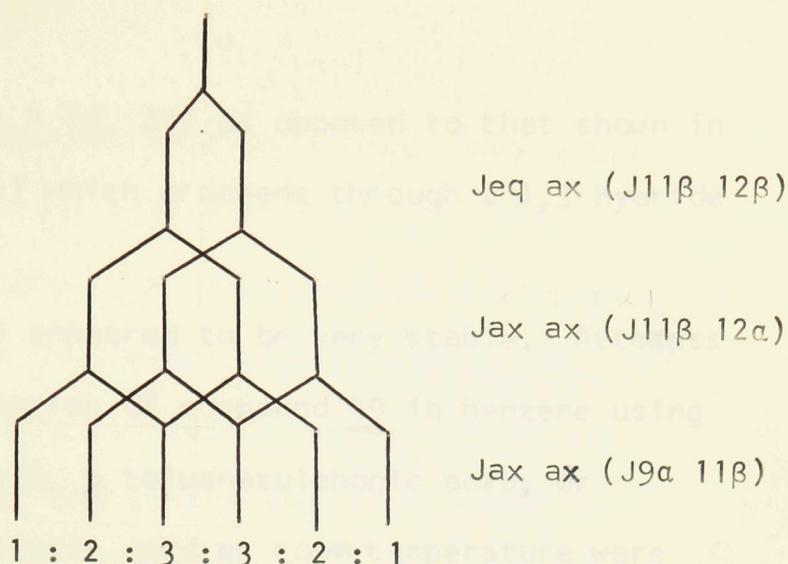


Figure 11

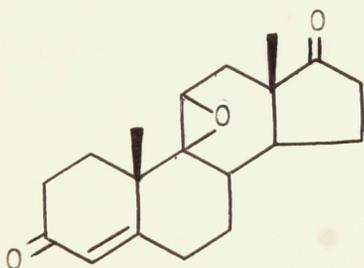
The structure of triketone 52 followed directly from base-catalyzed epimerization to the known andrenost-4-ene-3,11,17-trione.

The verification of the structure of the three products obtained upon rearrangement of epoxide 49 indicates that all three pathways identified proceed by an anti-periplanar migration. It was particularly important to understand the mechanism leading to the homoallylic alcohol 51 since it was the major pathway and led to undesired product. The evidence supporting the 9 $\beta$  configuration of C-9 in 50 indicates that this alcohol proceeds by the mechanism

shown in Figure 4 (p. 27) as opposed to that shown in Figure 3 (p. 26) which proceeds through a 1,3 hydride shift.

Epoxide 49 appeared to be very stable. Attempts to obtain a reaction of compound 49 in benzene using aluminum chloride, p toluenesulphonic acid, or gaseous hydrochloric acid at room temperature were unsuccessful. Neat trifluoroacetic acid also proved inadequate. In all cases, starting material was recovered. However, refluxing trifluoroacetic acid proved to be a sufficiently powerful reagent to cause reaction of the epoxide, and it was possible to isolate a small amount (7%) of phenol 50. The stability of the epoxide is probably due to steric hindrance of the  $\alpha$  face blocking the approach of any reagent.

Rearrangement of a  $9\beta$  $11\beta$  epoxide 62 gave androst-4-ene-3,11,17-trione as the major product. A similar result was reported by Wendler et al. (30)



62

No phenolic compounds were detected. These results suggest that methyl migration does not take place by a discrete carbonium ion since the  $\beta$  configuration of both epoxide and methyl group requires that the C-9 oxygen bond be completely opened before the methyl migration can take place. The exact interpretation is difficult since, in a case previously mentioned, cleavage of the  $5\beta 6\beta$  epoxide results in a migration of the C-10 methyl group, 43 to 44.(22) This is one instance where methyl migration does take place via a discrete carbonium ion.

#### Attempts at the Synthesis of 14 $\alpha$ methyl pregna-4-ene-3,11,20-trione

It was then proposed that since the mechanism shown in Figure 4 requires the presence of a 14 $\alpha$  proton, replacement of that proton with a methyl group would inhibit this pathway and would permit formation of a higher yield of phenol. A synthetic route to the 14 $\alpha$  methyl steroids has been reported in the patent literature (34) and is summarized in Figure 12.

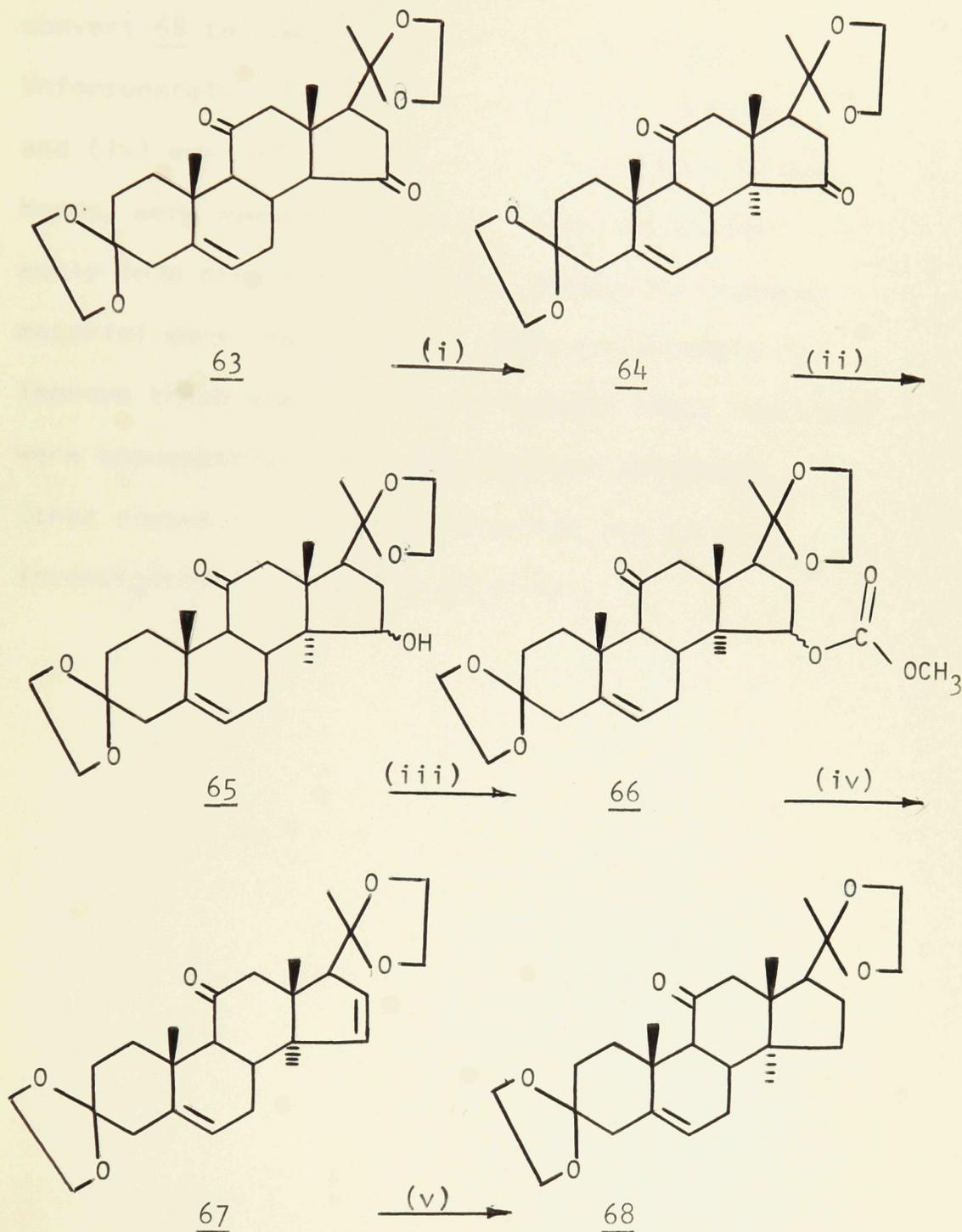


Figure 12

(i)  $\text{CH}_3\text{I}$ ,  $\text{tBuO}^-$ ,  $\text{tBuOH}$       (ii)  $\text{NaBH}_4$       (iii)  $\text{ClCO}_2\text{C}_2\text{H}_5$   
 (iv) heat      (v)  $\text{H}_2$   $\bar{\text{C}}$  palladium on charcoal

A four step synthesis can then be used to convert 68 to the 14 $\alpha$  methyl analogue of 49. Unfortunately, the reported yields for steps (i) and (iv) were 40% and 20% respectively and, in our hands, were non-reproducible. Such low yields early in a nine step synthesis leading to starting material were unacceptable. When our attempts to improve these yields or to circumvent these reactions were unsuccessful, this approach was abandoned. Other routes to 14 $\alpha$  methyl steroids are being investigated in these laboratories.

## SECTION II: REACTIONS OF SOME TRITERPENE EPOXIDES

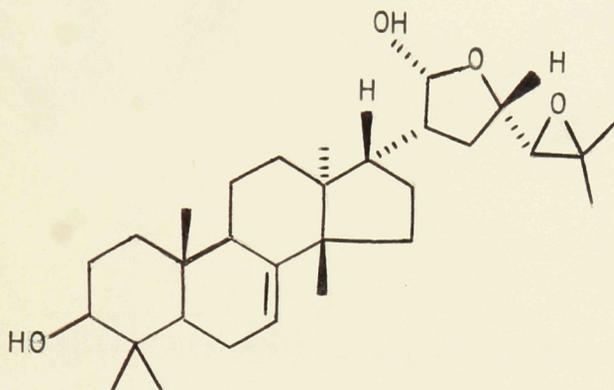
The difficulties encountered in a partial synthesis from steroid precursors led us to consider Barton's proposal that the cucurbitacins were obtained from a lanostane via a C-10 $\beta$  to C-9 $\beta$  methyl migration.(6) A synthesis from the lanostane triterpenes had the following advantages.

- (a) The methyl substitution pattern was complete.
- (b) The 14 $\alpha$  methyl group could prevent reaction via the mechanism shown in Figure 4, leading to an 8(14) homoallylic alcohol. (eg. 51)
- (c) In the lanostane derivatives (79, 83, 87, 90), there was a 1,3 diaxial interaction of the C-4 $\beta$  and C-10 $\beta$  methyl groups which would be alleviated by a C-10 $\beta$  to C-9 $\beta$  methyl migration.
- (d) The starting material, lanosterol, was inexpensive and the sequence leading to the 9 $\alpha$ 11 $\alpha$  epoxide had been reported and was quite straightforward. (Figure 17)

### Rearrangements of Terpene Epoxides

Investigations in the meliane-meliacin series provided an encouraging parallel. (35,36,37) The

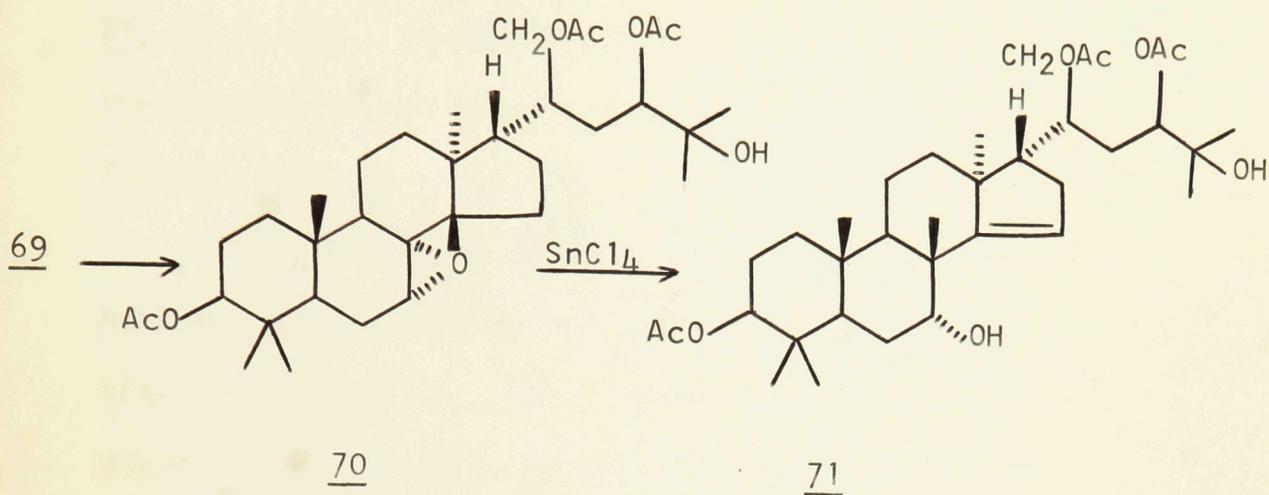
melianes are found in the plant Melia Azadaracha L. and an investigation showed that they possessed a tirucullane skeleton, (35) eg. 69.



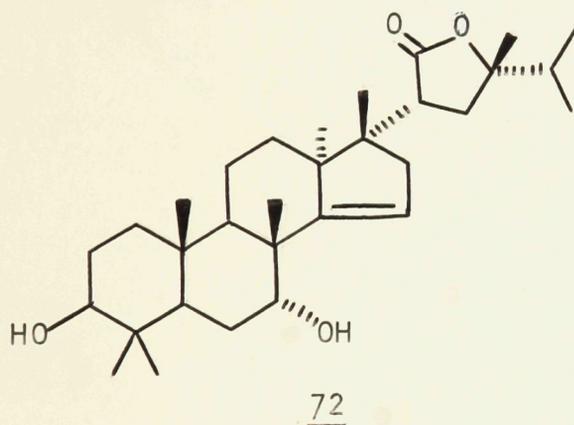
69

The melianes\* were converted to compounds having a meliacin skeleton by reaction of a 7a8a epoxide with  $\text{SnCl}_4$  in benzene, (36), 70 to 71.

\* Lavie and Levy (37) proposed the name meliane for compounds with a tirucullane skeleton and meliacin for those with an apoeuphol skeleton.



The meliacins were then isolated from the plant, Melia Azadaracha L., eg. 72, suggesting a biosynthetic relationship through the  $7\alpha,8\alpha$  epoxide.



The formation of homoallylic alcohol 71 from epoxide 70 was puzzling in view of the preference of the steroidal and terpene double bond for the

13, 17 position. (Pages 9 and 10; 18 to 19, 20 to 21, 22 to 23). Evidently there are factors directing the epoxide migration which overrule the steric factors that govern double bond migration.

These directing factors may lie in the internal base mechanism that has already been discussed. (Page 27, Figure 4). The formation of homoallylic alcohol can certainly be rationalized on the basis of such a mechanism. (Figure 13)

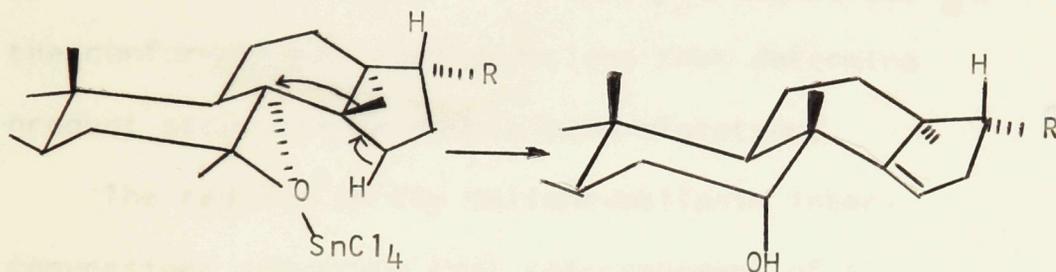


Figure 13

Examination of Dreiding models indicates that the homoallylic alcohol 71 is under steric stress arising from the C ring boat conformation and the eclipsed conformational relationship of the 13 $\alpha$  methyl and the 17 $\alpha$  substituent. Migration of the double bond to the 13, 17 position would resolve the steric

stresses. (Figure 14)

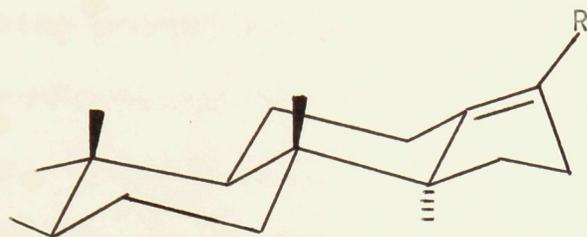


Figure 14

It is thus apparent that the pathway proceeding through the internal base mechanism possesses sufficient driving force to counteract the conformational considerations that determine product structure in double bond migration.

The results in the meliane-meliacin inter-conversions suggested that rearrangement of a 9 $\alpha$ 11 $\alpha$ -epoxy-lanostane derivative would give a 9 $\beta$  methyl compound by a mechanism indicated in Figure 15.

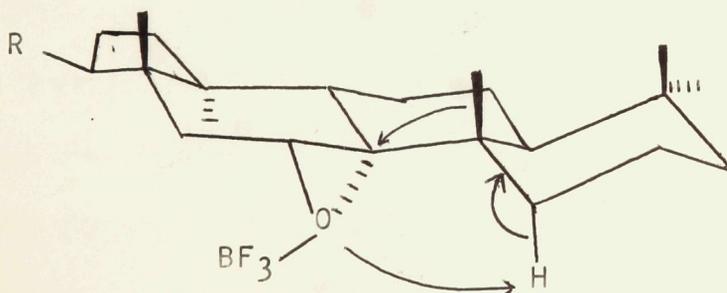


Figure 15

The major conformational problem in this reaction is the formation of a B/C cis fusion. The resulting product would have more than one possible conformation due to the flexibility of the cis fusion. Dreiding models indicate that the most stable conformation would be the one depicted in Figure 16.

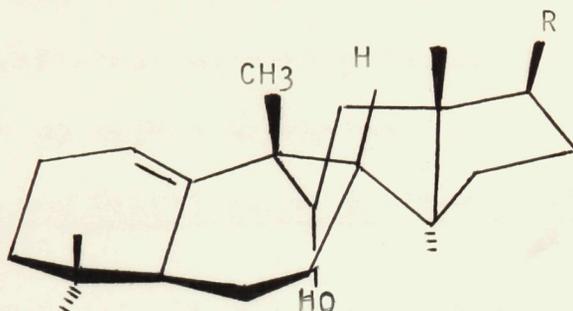


Figure 16

This conformation still maintains a C ring boat form which is undesirable.

There is some evidence that the transition state is in a product-like conformation. In the steroids, it was found that  $9\beta 11\beta$  epoxides react very rapidly to give the stable  $9\alpha$ -H, 11 ketone possessing an all chair conformation. The  $9\alpha 11\alpha$  epoxide reacted with difficulty. This was

attributed by Henbest and Wrigley (38) to be due to the difficulty in forming a  $9\beta$ -H,11 ketone possessing the B/C cis fusion; the implication being made by these investigators was that the transition state is product-like. This fact would argue against the formation of a  $9\beta$  methyl group. However, there was sufficient data to suggest that the rearrangements mediated by epoxide migration possess sufficient directing factors to result in a C-10 $\beta$ , C-9 $\beta$  methyl migration.

#### Synthesis and Reactions of $9\alpha,11\alpha$ -epoxy-lanostane Derivatives

Lanost-9(11)-ene-3 $\beta$ -ol acetate was synthesized after the method of Fried et al. (39) Acetylation and hydrogenation of lanosterol gave lanost-8-ene-3 $\beta$ -ol acetate.(40) Epoxidation with m-chloroperoxybenzoic acid gave the  $8\alpha,9\alpha$  epoxide. Reduction with lithium in monoethylamine gave a glass-like solid which showed no acetate, but showed the presence of hydroxyl by infrared spectroscopy.

Acetylation, followed by dehydration with thionyl chloride in pyridine gave a solid which had a wide melting range. Recrystallization from acetone gave



By analogy to the steroids, it was assumed that epoxidation of 78 would give the  $9\alpha11\alpha$  epoxide 79. The comparison, however, was not very rigorous. In the steroids, the two angular methyl groups hinder the  $\beta$  face, leaving the  $\alpha$  face more susceptible to attack by the reagent. In the triterpenes, however, the presence of a  $14\alpha$  methyl group increases the hindrance of the  $\alpha$  face. It is quite possible that this increased hindrance is sufficient to result in formation of  $9\beta11\beta$  epoxide. Therefore, it was necessary to determine the stereochemistry of epoxidation. It was proposed that this could be done by rearranging the epoxide to the 11 ketone and determining the configuration at C-9. If the  $9\beta11\beta$  epoxide had been formed, then the  $9\alpha$ -H,11 ketone would result. (Figure 18, page 52) Conversely, if the  $9\alpha11\alpha$  epoxide had been formed, the  $9\beta$ -H,11 ketone would result. The implicit assumption was that no subsequent epimerization of the  $9\beta$ -H,11 ketone would take place under the acidic conditions.

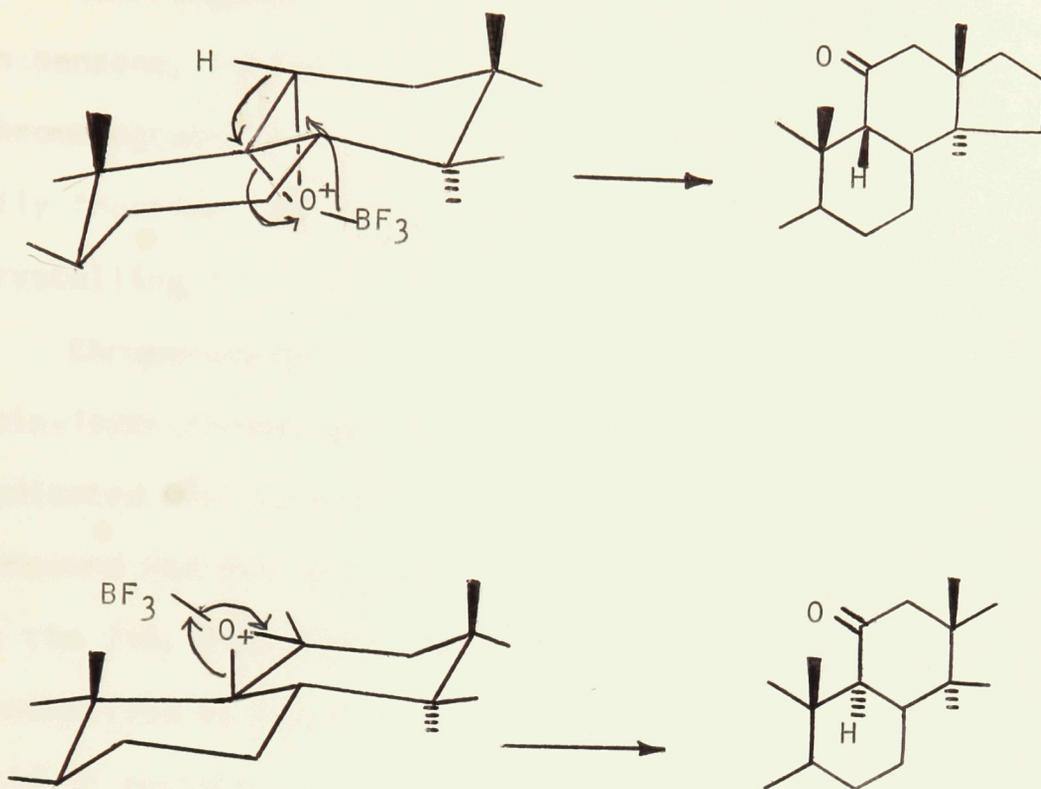
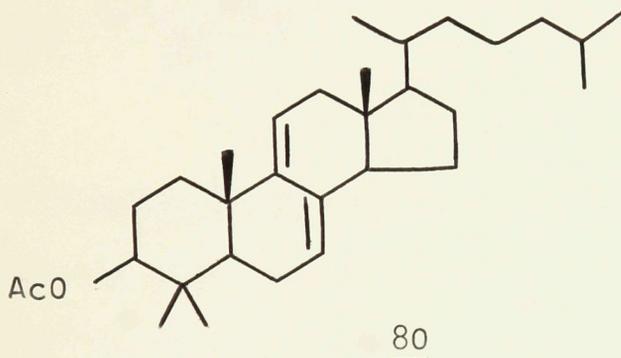


Figure 18

Treatment with base would then epimerize the  $9\beta$ -H, 11 ketone to the  $9\alpha$  epimer. The  $9\alpha$  epimer would remain unaltered. Thus, from the ketone, it should be possible to know the stereochemistry of epoxidation.

Rearrangement of epoxide 79 with gaseous  $\text{BF}_3$  in benzene, followed by isolation of product and chromatography on silica gel, gave a fast-running oily fraction (35% yield) and a more polar, crystalline fraction (65% yield).

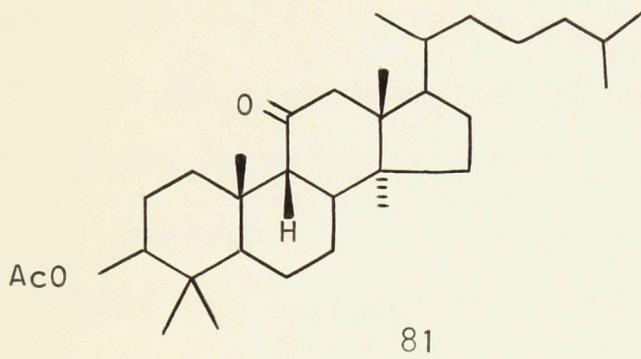
Chromatographic analysis (vapour phase and thin-layer chromatography) of the oily fraction indicated the presence of only one compound. This compound had the same chromatographic properties as the 7:8, 9:11 diene 80. This diene is easily synthesized by treating epoxide 75 with hydrochloric acid in acetone.



However, while the ultraviolet spectrum showed the peaks characteristic of this diene ( $\lambda$  max. 236, 243, 252), the absorption coefficient was low. This indicated the presence of more than one compound

with the same chromatographic properties as 80. Repeated attempts at crystallization were unsuccessful and the mixture decomposed with time.

The more polar crystalline fraction showed cyclohexanone and acetate absorption in the infra-red spectrum. This product was tentatively assigned the  $9\beta$  lanost-11-one-3-ol acetate structure 81 for which it had a correct carbon hydrogen analysis.



Treatment of 81 with base in ethanol resulted in hydrolysis of the acetate group only. Re-acetylation gave an acetate with melting point 202-204°C. This cast some doubt on the assigned structure since it was expected that alkali would epimerize the labile  $9\beta$ -H to the more stable  $9\alpha$ -H. However, examination of Drieding models shows that the  $9\beta$

proton is extremely hindered and not subject to removal by base in order to form the enolate, which is a necessary step in epimerization. Furthermore, in this series of compounds, melting points alone could be deceptive, since Voser et al (41) found that 9 $\alpha$ -lanost-11-one-3 $\beta$ -ol acetate could be isolated in two polymorphic forms, melting at 140 and 156°C.

Support for the assigned configuration was obtained from comparison of the molecular ellipticity  $[\theta]_{298}$  exhibited by the 9 $\alpha$  and 9 $\beta$ -H lanost-11-one-3 $\beta$ -ols in their circular Dichroism spectra. (Appendix II). Authentic 9 $\alpha$ -lanost-11-one-3 $\beta$ -ol, previously prepared in our laboratories after the method of Voser et al (41), had a molecular ellipticity of  $[\theta]_{298} = 7150$ , whereas the proposed 9 $\beta$  epimer exhibited a molecular ellipticity of  $[\theta]_{298} = 11,950$ . These values are in accordance with the octant projections, shown in Figure 19. (p. 56)

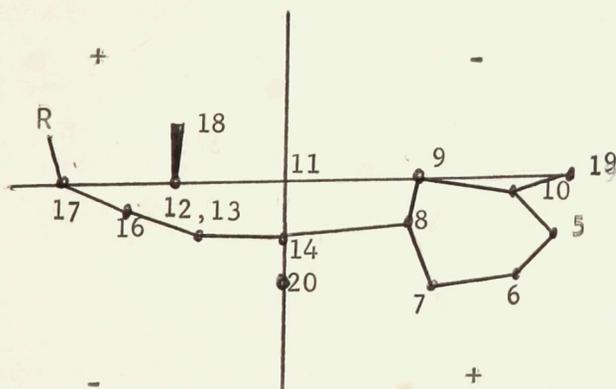
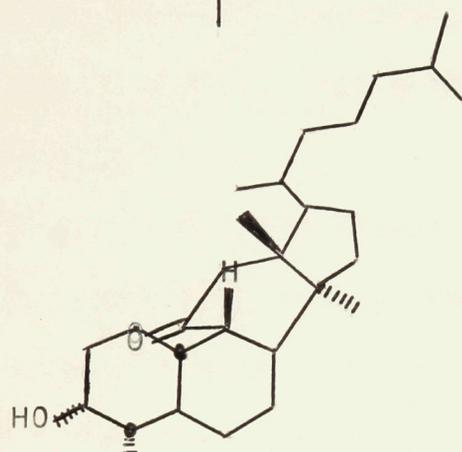
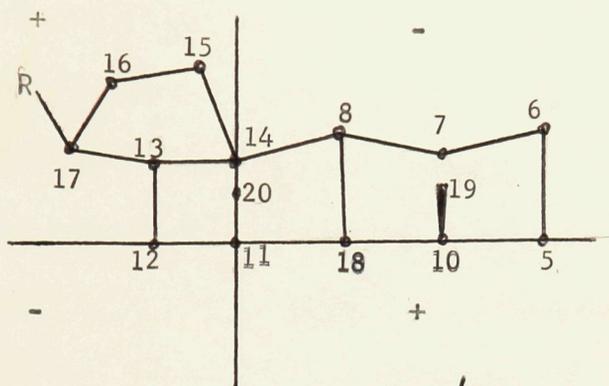
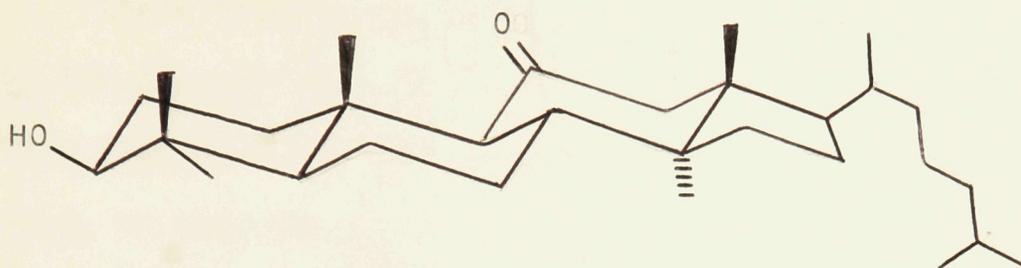


Figure 19

These results support the assignment of structure 81 for crystalline rearrangement product of 79. This also confirms the stereochemistry of epoxidation as  $\alpha$ , in accordance with the predictions from examination of Dreiding models.

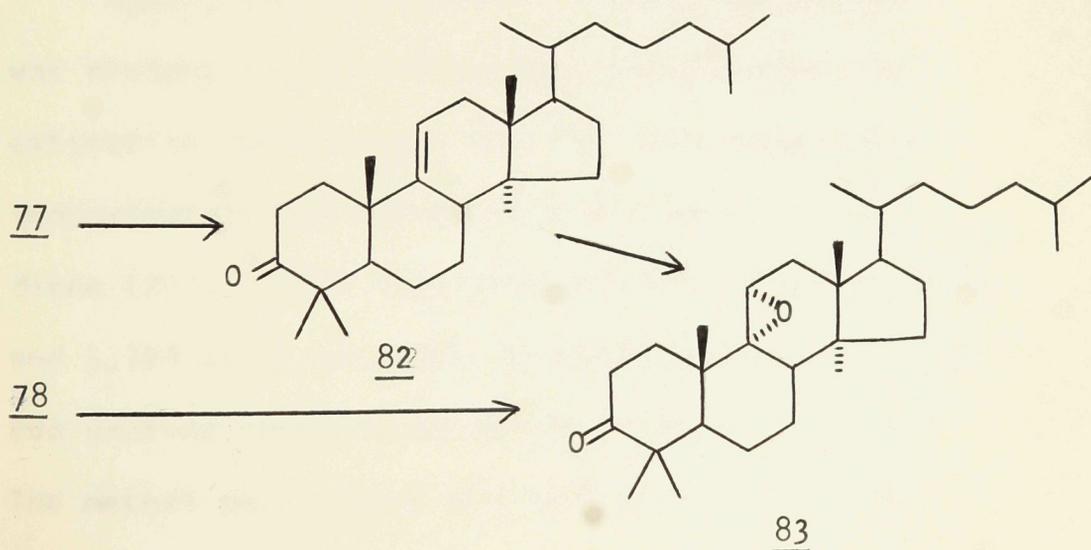
While the failure of rearrangement of 79 to give methyl migration was disappointing, it did in fact show that the  $9\beta$ -H configuration was possible and that the B/C cis fusion could be attained relatively easily. The problem remained of obtaining the cis fusion but with a  $9\beta$  methyl group instead of a  $9\beta$  proton.

The mechanism proposed in Figure 5 (p. 28) required abstraction of the C-1 $\alpha$  proton. It was probable then that if the C-1 $\alpha$  proton was not suitably located that the required abstraction would not take place. This was a possible cause for the failure of epoxide 79 to yield product that resulted in methyl migration. Thus, if the C-1 $\alpha$  proton was made more accessible to the polarized epoxide  $\text{BF}_3$  complex, methyl migration could result.

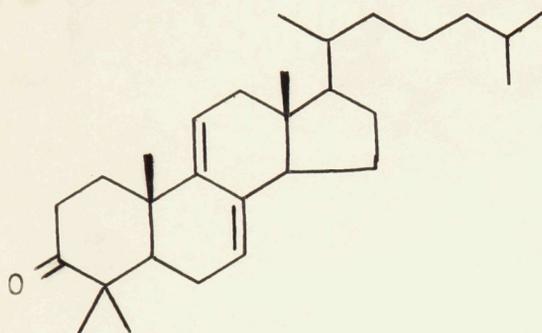
The 4,4 dimethyl group in lanostan- $3\beta$ -ol acetate

does not supply sufficient steric compression with the C-10 methyl to force the A ring into a boat form.(42) In 4,4 dimethyl-cholest-3-one, the 3 keto group imparts a moderate amount of mobility into the A ring which exists in the boat form approximately 20% of the time.(43) This increase in mobility would increase the chance of a C-1 $\alpha$  proton, BF<sub>3</sub> epoxide complex interaction and thus perhaps result in methyl migration.

Keto-epoxide 83 is readily available from either 78 or 79 simply by hydrolysis of the 3-acetate followed by treatment with Jones reagent. Epoxide 79 proved stable to both alkaline conditions of hydrolysis and acidic conditions of Jones' Oxidation.



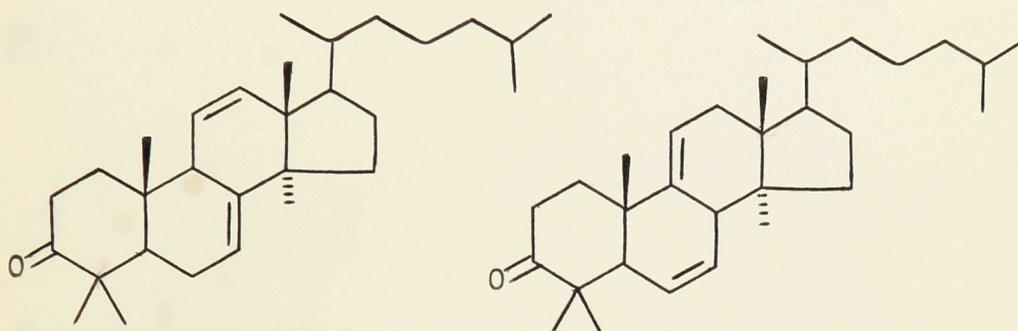
Rearrangement of 83 with  $\text{BF}_3$  in benzene gave, on work-up, a colourless oil. This oil was apparently one compound showing only one spot on thin-layer chromatography and one peak on vapour phase chromatography. The  $R_f$  value and retention time were the same as those for authentic 7:8, 9:11 diene 84.



84

Again, the characteristic diene absorption was present in the ultraviolet spectrum but the extinction coefficients for the three peaks were approximately one-third those obtained for the diene (29). N.M.R. spectrum showed signals at 5.55 $\delta$  and 5.72 $\delta$  as broad peaks integrating for approximately two protons each; no splitting could be discerned. The methyl peak region was much more complex than

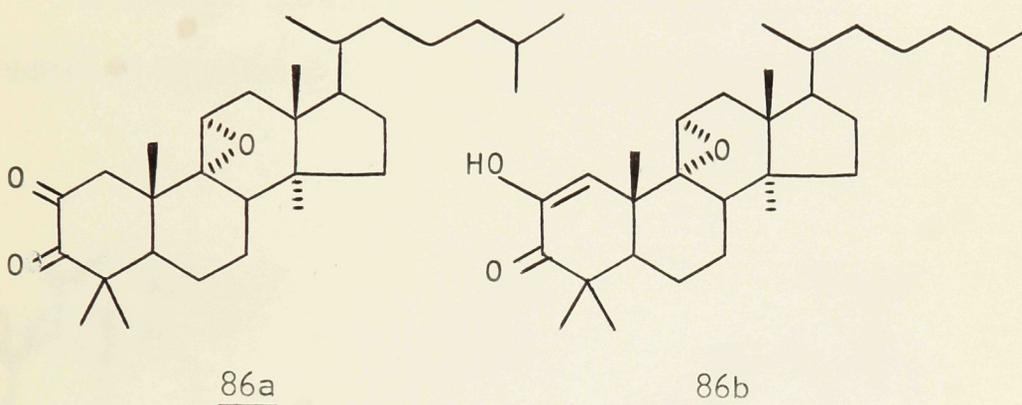
that of authentic diene 84. The N.M.R. data indicated the possibility of a mixture of the three dienes, 84, 85a, 85b.

85a85b

However, treatment of the oil with HCl in ethanol produced no change in the ultraviolet spectrum. This suggested that the only chromophore present was diene 84. The two types of double bonds that are suggested by N.M.R. are not 85a and 85b, since these would have conjugated upon treatment with acid and increased the intensity of the peaks in the ultraviolet spectrum. These results indicate that the oil is a complex mixture of which 84 is one component. Crystallization of diene 84 from this oil could not be obtained.

The presence of the A ring diosphenol in

cucurbitacins E and I suggested the possibility that a diosphenol might prove more amenable to methyl migration. Treatment of epoxide 83 in *t*-butyl alcohol with potassium *t*-butoxide and stirring in an atmosphere of oxygen gave diosphenol 86.



It is difficult to predict in which form of 86a or 86b the  $\text{BF}_3$ -epoxide-benzene might exist. Both forms have structural features which would assist methyl migration. If the  $\text{BF}_3$ -terpene complex exists in the diosphenol form (Figure 20), then the A double bond could assist in stabilizing a cationic centre at C-9.

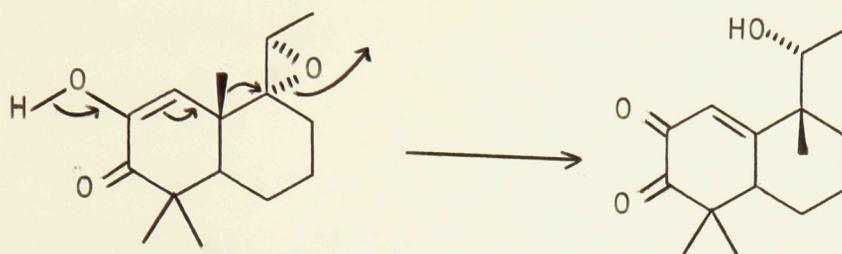


Figure 20

A similar mechanism could be drawn for a reaction beginning with the diketone 86a. (Figure 21)

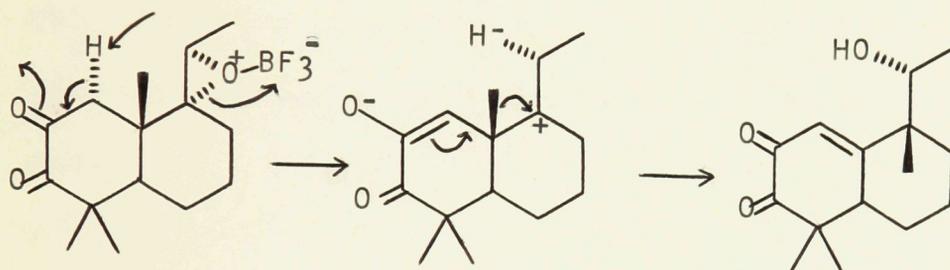


Figure 21

The first step would be the formation of the diosphenol via abstraction of the C-1 $\alpha$  proton by the polarized  $\text{BF}_3$ -epoxide complex and then migration of the C-10 methyl group. The proton abstraction step would be enhanced by the fact that the A ring of the diosphenol is much more flexible than the

A ring of 3 acetate or the 3 ketone. As the C-1 $\alpha$  proton is now adjacent to a carbonyl, its "acidity" is enhanced.

Negating factors in the diosphenol for rearrangement are two. The flexibility of the A ring would decrease the 1,3 diaxial interaction between the C-4 $\beta$  and the C-10 $\beta$  methyl groups, thus reducing the steric driving force for migration. The second factor involves the possibility that the 2,3 diketone is in some form complexed with BF<sub>3</sub>. This would act against the formation of a cationic centre at C-10 upon methyl migration. Henbest and Wrigley (44) found that the reaction rate of 5 $\beta$ ,6 $\beta$ -epoxides was markedly decreased by presence of a group at C-3 capable of complexation with BF<sub>3</sub>. This resulted in withdrawal of electrons from the A ring acting against formation of C-5 cationic centre. However, the mechanism depicted in Figure 21 can be concerted in formation of a cationic centre at C-9 and the "enolate" in the A ring. A concerted methyl migration, aided by the presence of the 1,2

double bond, would then overcome the necessity of forming at a cationic centre at C-10 in the A ring.

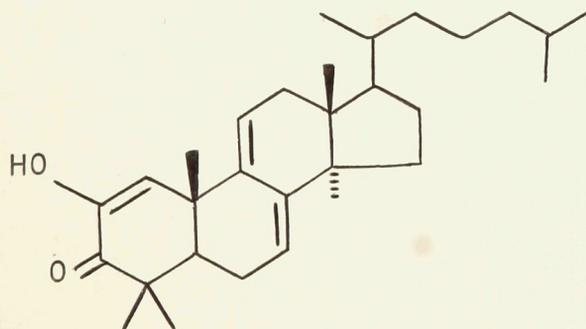
Treatment of 86 with  $\text{BF}_3$  in benzene in the usual manner gave crystalline material which showed only one spot on thin-layer chromatography. The ultraviolet spectrum of the recrystallized material (40% from ethanol) indicated the presence of both A ring diosphenol and 7:8, 9:11 diene. Unlike earlier examples, the extinction coefficients were sufficiently high to indicate that only one compound was present.

$\lambda$  max. 237, 243, 251,  $\epsilon_{243} = 16,900$  (diene)

$\lambda$  max. 268-272,  $\epsilon$  10,000 shifting in base to  $\lambda$  max.

300-305,  $\epsilon = 5,900$

Infrared and N.M.R. data were consistent with the ultraviolet in supporting structure 87 as the correct one for the product of the reaction of 86 with  $\text{BF}_3$  in benzene.



87

The work of Ponsinet (15) suggested the possibility of obtaining methyl migration from an A nor-lanostane system. This system is also in accord with the rules suggested by Bascou (26) since the system now possesses a centre of intracyclic strain in the A/B ring fusion. Furthermore, the epoxide and the methyl which is to migrate bear the same relationship as that found in the meliacin investigation. (35,36,37) The methyl group is at the junction of a trans fused cyclohexane-cyclopentane unit and is trans-anti-periplanar to the epoxide bond that will break under acid catalysis.

Epoxide 91 was synthesized from ketone 82 via a series of reactions that are summarized in flow sheet 3. Ketone 82 was treated with potassium t-butoxide in t-butyl alcohol and stirred in an atmosphere of oxygen to give diosphenol 88. Refluxing diosphenol 88 with sodium ethoxide in ethanol resulted in a benzilic acid rearrangement to give the  $\alpha$ -hydroxy-carboxylic acid 89. Oxidation of this acid with lead tetraacetate gave the cyclo-

pentanone 90 which was easily oxidized to epoxide 91 by treatment in chloroform with m-chloroperbenzoic acid.

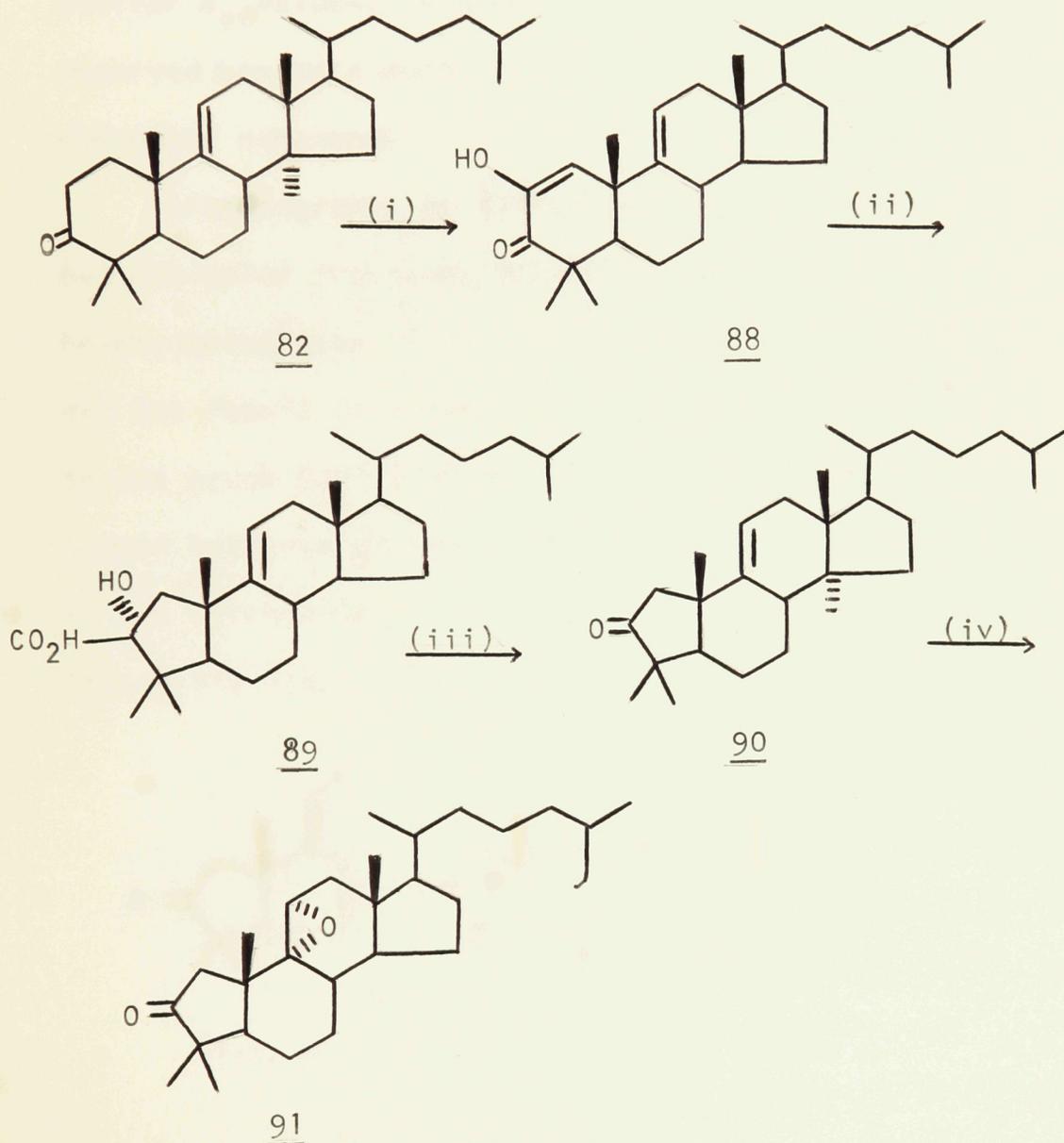


Figure 22

- (i)  $O_2$ ,  $tBuOK$  in  $tBuOH$       (ii)  $EtONa/EtOH$  reflux  
 (iii)  $Pb(OAc)_4$       (iv) m-chloroperbenzoic acid

Rearrangement of 91 with  $\text{BF}_3$  in benzene gave a crystalline product containing three compounds, as evidenced by thin layer chromatography. Two non-polar compounds were observed having very similar  $R_f$  values. A more polar compound was also observed having a much smaller  $R_f$  value than the non-polar compounds.

Chromatography on silica gel separated the two non-polar fractions from the more polar fraction. Re-chromatography of the two non-polar compounds did not result in a separation of the two compounds. In the crude form however, the non-polar fraction showed both cisoid and transoid diene absorption in the ultraviolet. This suggested a mixture of 7:8, 9:11; 8:9, 11:12 and 7:8, 8:9 dienes. (Figure 23)

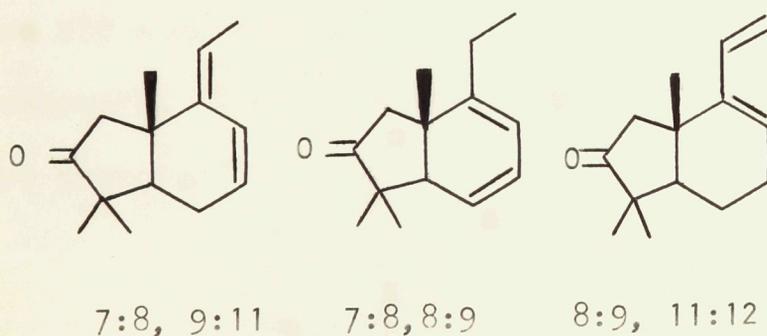
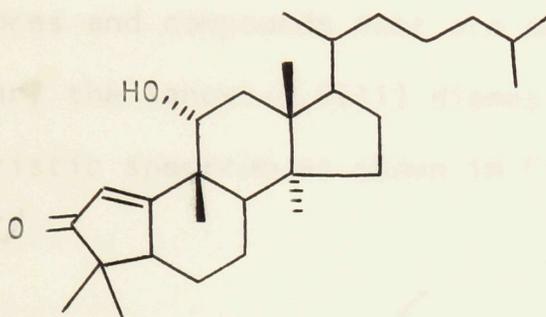
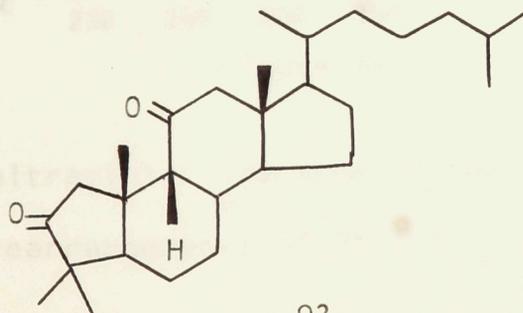


Figure 23

Infrared analysis of the crude mixture showed only the presence of cyclopentanone. No hydroxyl group could be detected. The absence of hydroxyl and  $\alpha,\beta$  unsaturated ketone absorption indicated that the product of methyl migration, 92, had not formed.

92

The polar fraction showed cyclopentanone and cyclohexanone absorption in the infrared. The compound did not exhibit a high intensity ultraviolet absorption above 220 n.m. indicating the absence of an extended chromophore. The N.M.R. spectrum did not show a vinyl proton. The assigned structure was 93.

93

The non-polar fractions obtained on rearrangement of 79, 83, and 91 did not yield clear-cut results. However, it was possible to obtain an idea of what products were present in the non-polar oils.

Ultraviolet analysis of crude mixtures can sometimes supply evidence regarding the nature of chromophores and compounds that are present. In particular, the lanost-7,9(11) dienes have a characteristic spectrum as shown in Figure 24.

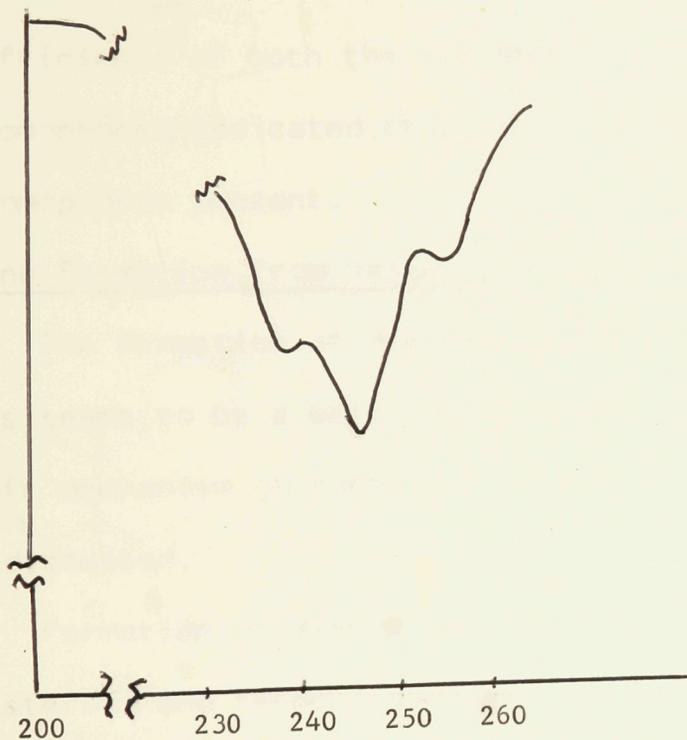


Figure 24

The ultraviolet spectrum of the oil obtained from the rearrangements of 79 and 83 showed the

characteristic triplet of the 7:8, 9:11 dienes. The non-polar fraction of the product from the rearrangement of 91 showed both 7:8, 9:11 diene and homoannular diene absorption in the ultraviolet. In all cases, the extinction coefficient was low, indicating the presence of other compounds which did not possess a chromophore.

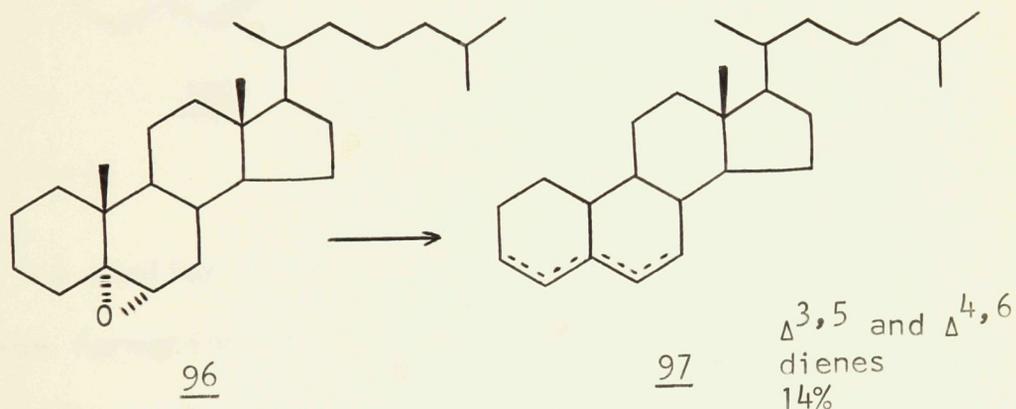
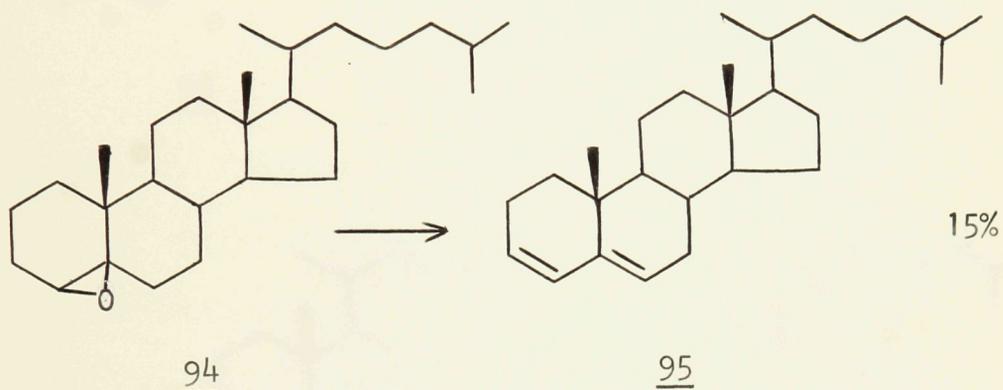
Rearrangement of diosphenol 86 gave the 7:8, 9:11 diene 87 in moderate yield. The extinction coefficients of both the diosphenol and the diene chromophores indicated that there were no other chromophores present.

#### Diene Formation from 9 $\alpha$ 11 $\alpha$ -epoxy-lanostanes

The formation of dienes from the 9 $\alpha$ 11 $\alpha$  epoxides thus seems to be a well authenticated reaction. Their mechanism of formation, therefore, should be discussed.

Formation of dienes in acid-catalyzed reactions of steroid and terpene epoxides are known in the literature. 7 $\alpha$ 8 $\alpha$  (46a) and 8 $\alpha$ 9 $\alpha$  cholestanes (47) are reported to give the 8,14 diene. Similarly, King (29) obtained the 7:8, 9:11 diene from acid

rearrangement of 8 $\alpha$ 9 $\alpha$  epoxy-lanost-3 $\beta$ -ol acetate and 8 $\alpha$ 9 $\alpha$  epoxy-lanost-3-one. Blockett and co-workers also isolated dienes upon rearrangement of 4,5 and 5,6 epoxides. (22)



Fieser and Goto (47) proposed a mechanism for formation of diene via an allylic alcohol, which they did not isolate. (Figure 25)

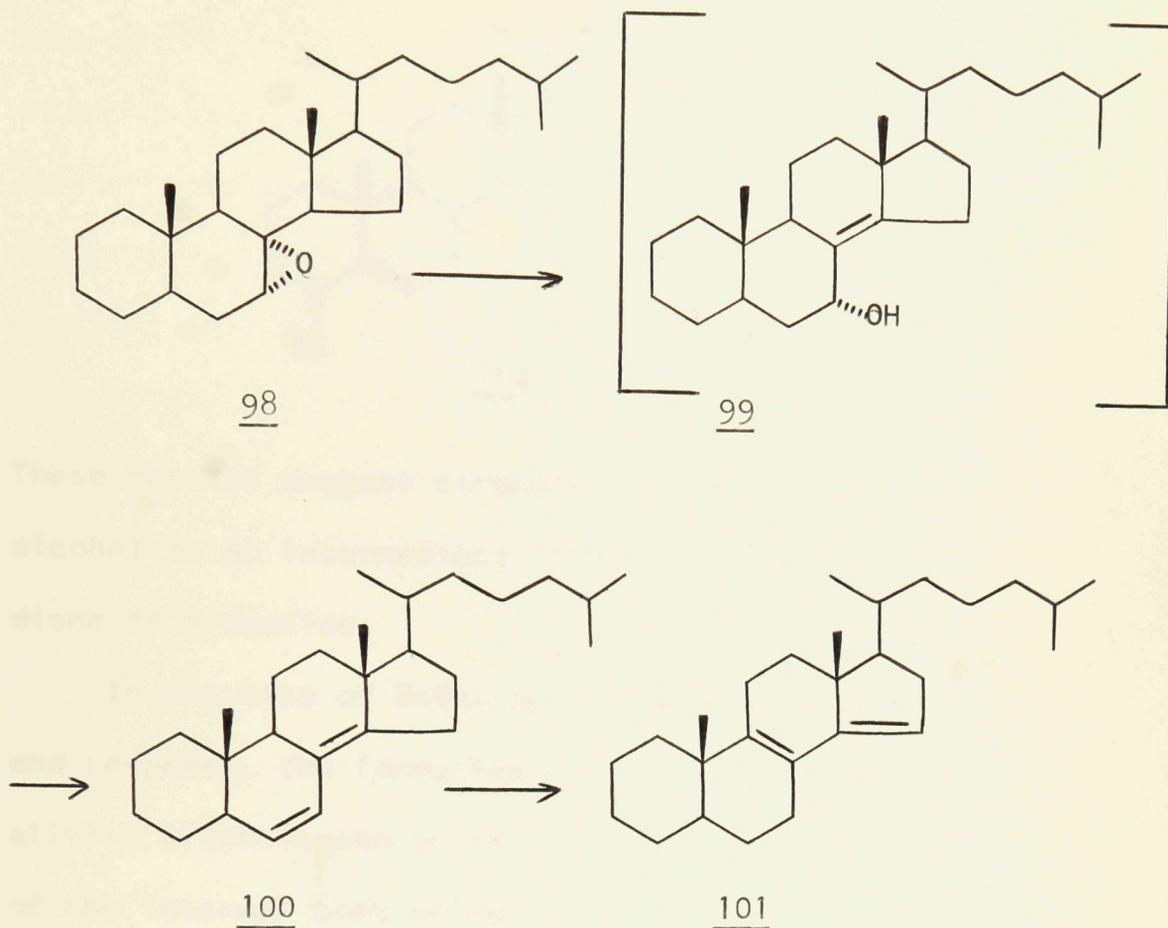
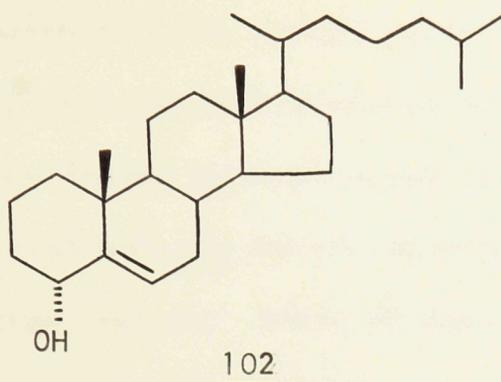


Figure 25

A similar mechanism was used to rationalize diene formation in the pentacyclic triterpenes. (48) In both cases the allylic alcohol was not isolated but only hypothesized. Blockett (22) isolated diene 95 and allylic alcohol 102 from the reaction of epoxide 96.



These results suggest strongly that an allylic alcohol is an intermediate in the formation of diene from epoxide.

In the case of  $8\alpha,9\alpha$ - and  $7\alpha,8\alpha$ -epoxy steroids and terpenes, the formation of dienes through allylic alcohols can be rationalized on the basis of the internal base mechanism that has been proposed. (8)

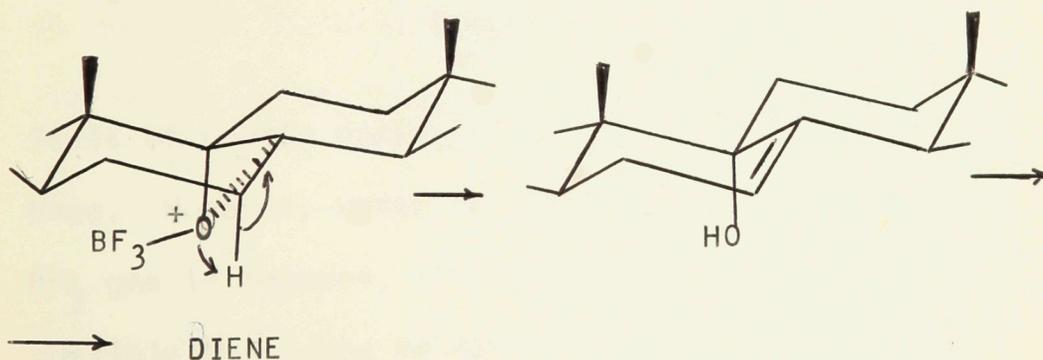


Figure 26

A similar mechanism can be written for the 7 $\alpha$ 8 $\alpha$  epoxide with the 14 $\alpha$  proton being abstracted. In both cases, the abstracted proton was  $\alpha$  to the cationic centre formed upon cleavage of the epoxide. It was also axial and cis to the alcohol formed when the epoxide opened. These protons were then ideally situated for abstraction.

The case of the 9 $\alpha$ 11 $\alpha$  epoxide is more complex. The proton  $\alpha$  to the cationic centre at C-8 is opposite in configuration to the epoxide and is not subject to abstraction through an internal base.

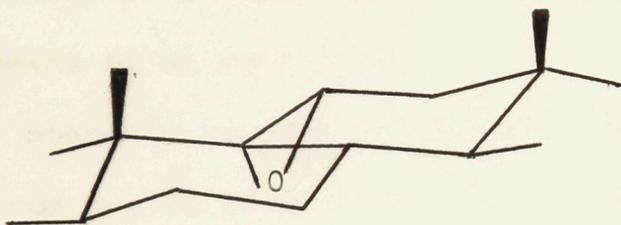


Figure 27

It is of course possible to propose an external base. However, under our reaction conditions,  $\text{BF}_3$  gas in benzene, this is unlikely. The only possible bases are an epoxide, acetate group or

carbonyl from another molecule, or a polarized epoxide  $\text{BF}_3$  complex from another molecule. In any case, this would be an extremely bulky group and the  $8\beta$  position would be very hindered, making abstraction of the  $8\beta$  proton unlikely. It was found by Fried et al (39) that it was only possible to attack the  $8\beta$  position by using a "solvated electron" as a nucleophile. These workers attempted to reduce the  $8\alpha 9\alpha$  epoxide and found it to be stable to all hydrides, being susceptible to reduction only by lithium in monoethylamine. Thus the possibility of a bulky group removing the  $8\beta$  proton appears to be very slight.

It is possible to form the 7:8-ene-11 $\alpha$  hydroxy compound from the 9 $\alpha$ 11 $\alpha$  epoxide. The 7 $\alpha$  proton bears the same relationship to the 9 $\alpha$ 11 $\alpha$  epoxide as does the 14 $\alpha$  proton. Both are 1,3 diaxial to the departing end of the epoxide. (Figure 28)

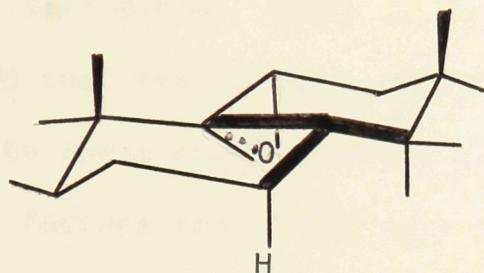


Figure 28

It is reasonable to postulate a mechanism leading to the homoallylic alcohol via an internal base abstraction of the 7α proton. (Figure 29)

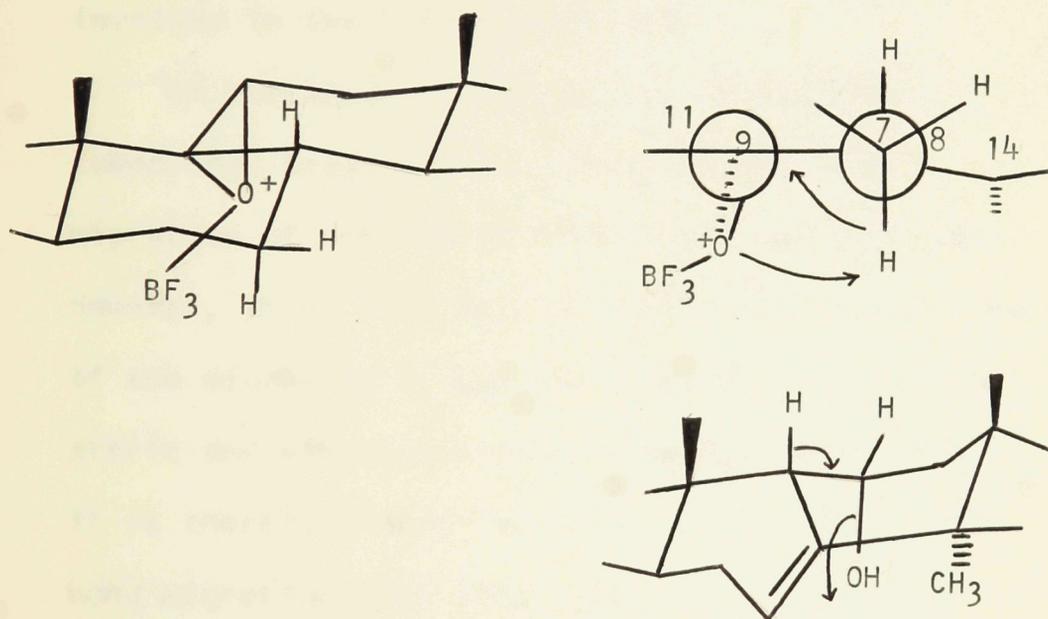


Figure 29

Having introduced the 7:8 double bond, dehydration of the 11 $\alpha$  hydroxyl would now result in the 7:8, 9:11 diene. While in the steroid series it was found that the homoallylic alcohol (eg. 51) was stable to these reaction conditions, there are several factors that might make dehydration more feasible in the lanostane series. There is a strong flagpole interaction between the 11 $\alpha$  hydroxyl and the 14 $\alpha$  methyl. Dehydration would also be aided by the trans-diaxial relationship of the 9 $\beta$  proton and the 11 $\alpha$  hydroxyl. Dehydration would remove the unfavourable steric factors involved in the C ring boat form.

In the lanost-8-ene series, it has been found that treatment with acid results in a migration of the double bond to the 7:8 position. However, it is difficult to predict the orientation of the migration in the 9 $\beta$ -H compounds since many steric and electronic factors must be considered. It is therefore possible that a 7:8 to 8:9 double bond migration does take place. This would give the allylic alcohol which would then dehydrate to give a cisoid diene. Acid-catalyzed rearrangement

would then give the 7:8, 9:11 diene. (Figure 30)

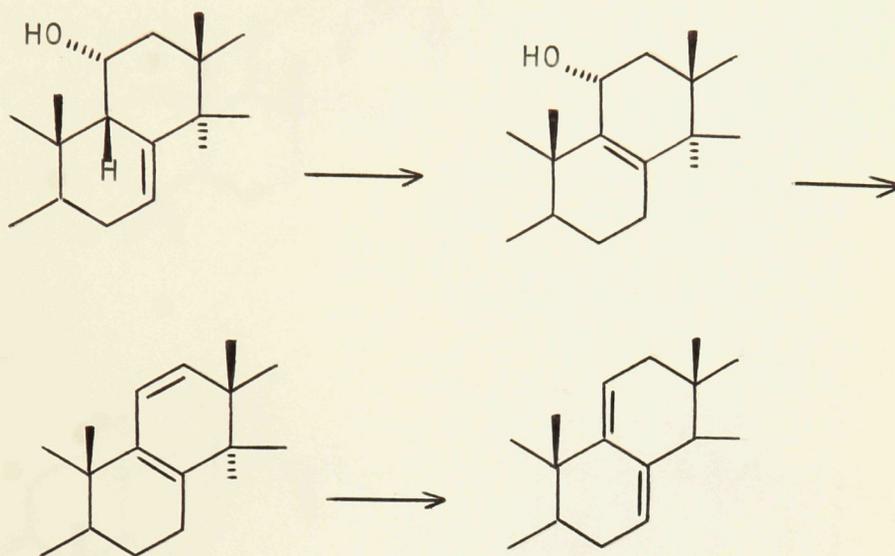


Figure 30

It has recently been reported (48) that epoxides of certain pentacyclic triterpenes rearrange to give cisoid and transoid dienes via an allylic alcohol. By using very mild reaction conditions, pyridinium hydrochloride in pyridine, it was possible to identify the presence of a cisoid diene in the mixture of products. The cisoid diene, under acid catalysis, rearranged to the transoid isomers. (Figure 31)

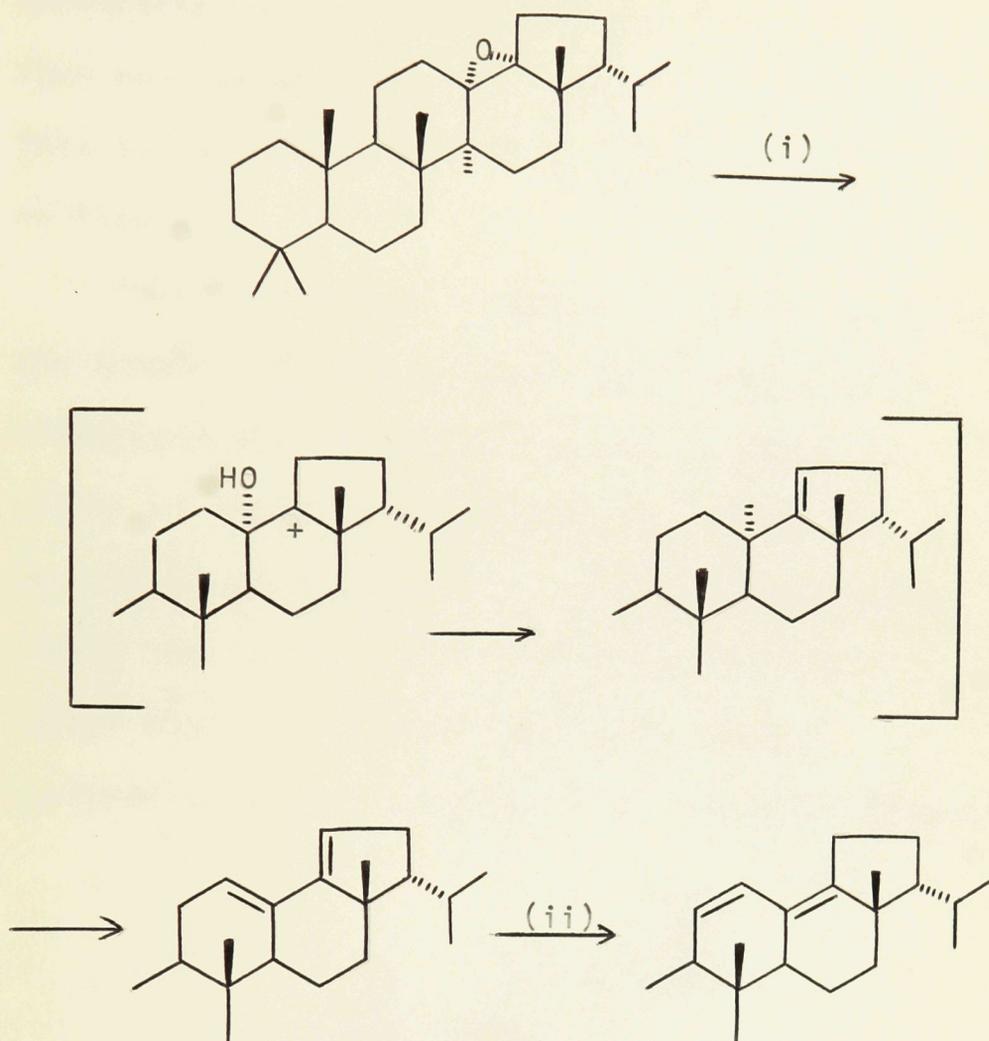


Figure 31

(i) pyridinium hydrochloride    (ii) HCl in ethanol

The dehydrations summarized in Figure 31 are not completely analogous to the 9 $\alpha$ 11 $\alpha$ -epoxy-lanostane reactions. However this work points out the

existence of a mechanism in which an epoxide dehydrates to a less stable cisoid diene which then rearranges to the more stable transoid form. This is the final step in the mechanism described in Figure 30.

There are several problems that arise regarding the scheme proposed in Figure 29. Examination of Driending models indicates that the 1 $\alpha$  proton is closer to the epoxide than the 7 $\alpha$ . The 5 $\alpha$  and 7 $\alpha$  protons are equidistant. It thus appears more likely that the 1 $\alpha$  proton should be abstracted rather than the 7 $\alpha$  since both have the same conformational relationship to the epoxide. (Figure 32)

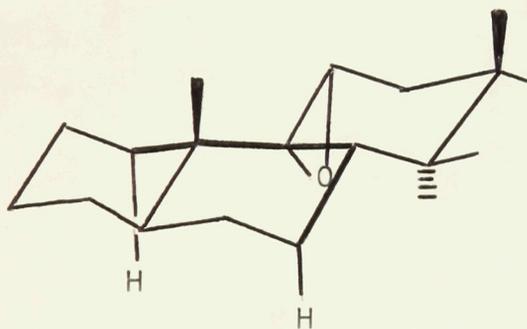


Figure 32

The deciding factor appears to be the 1,3 diaxial

interaction between the 7 $\alpha$  proton and the 14 $\alpha$  methyl. This steric compression would be relieved upon abstraction of the 7 $\alpha$  proton and the resulting formation of the 7:8 double bond. This would be in line with the ideas of Bascou<sup>1</sup> (26) who proposed that migration moves away from the centre of strain. However, in this case, the strain is intercyclic instead of intracyclic.

The competing reaction results in ketone formation. The mechanism is apparently quite straight-forward. (Figure 33)

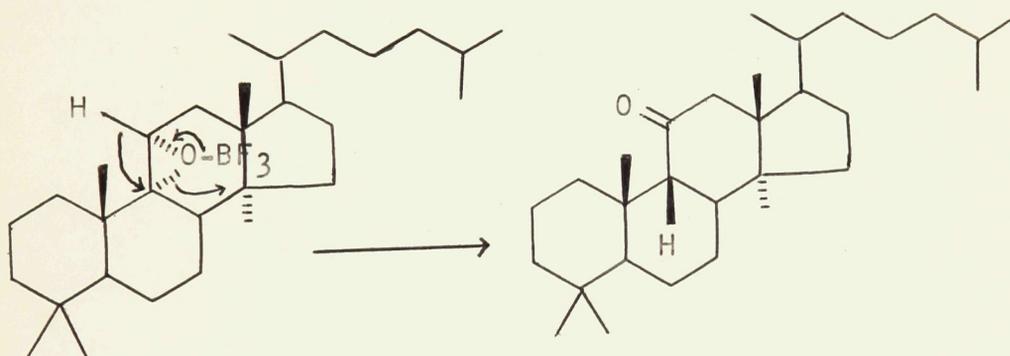


Figure 33

However, on deeper examination, there are several problems that must be considered. Primarily, there is the problem of the variation in the ratio

of diene to ketone with modification of the A ring. There must be some factor that relates these two pathways. Secondly, examination of the conformation of the 11 proton in the epoxide shows that the migration shown in Figure 33 is not so straightforward. (Figure 34)

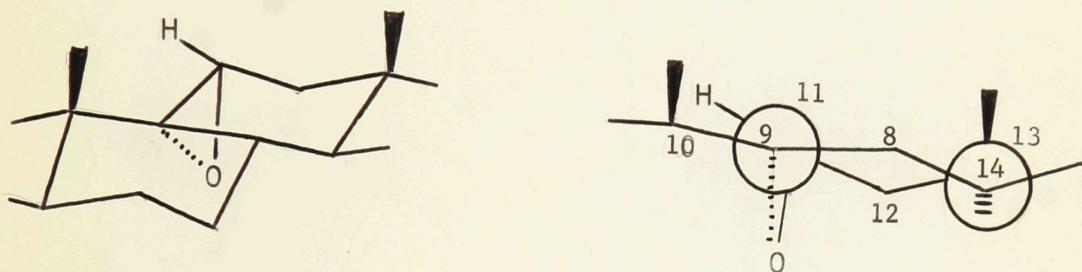


Figure 34

The C-11 proton of the epoxides is almost perpendicular to the plane defined by the epoxide function. Thus, the proton is perpendicular to the breaking bond and also perpendicular to the vacant orbitals of the carbonium ion formed, if and when the bond breaks completely. (Figure 35, a and b)

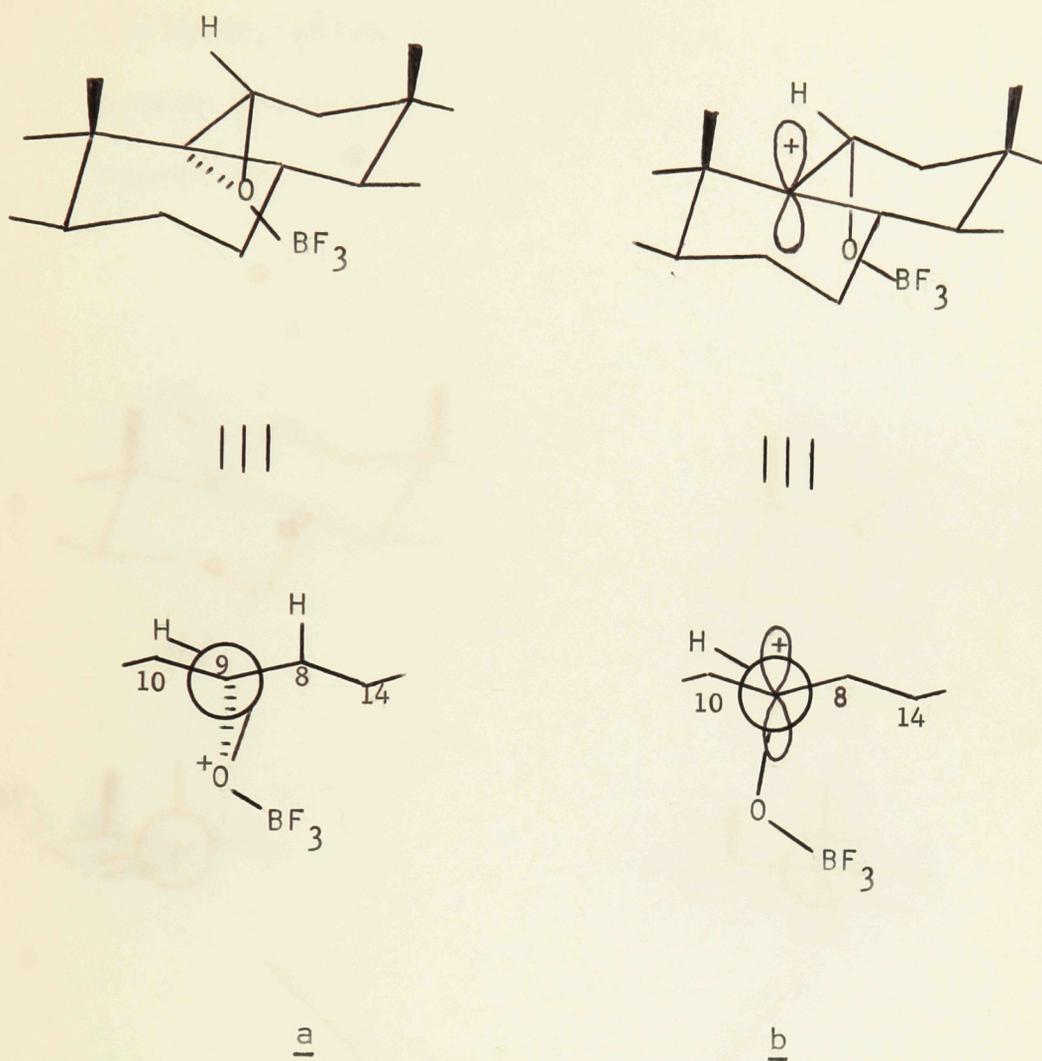


Figure 35

It would appear that, in order for the migration to take place, the proton must first orient itself in an axial or quasi-axial conformation. This, of course, is favoured since it would move the bulky  $-O-BF_3^+$  complex into an equatorial or quasi-equatorial

position, which is normal for an 11 $\alpha$  group. The proton would then be properly aligned for migration. (Figure 36)

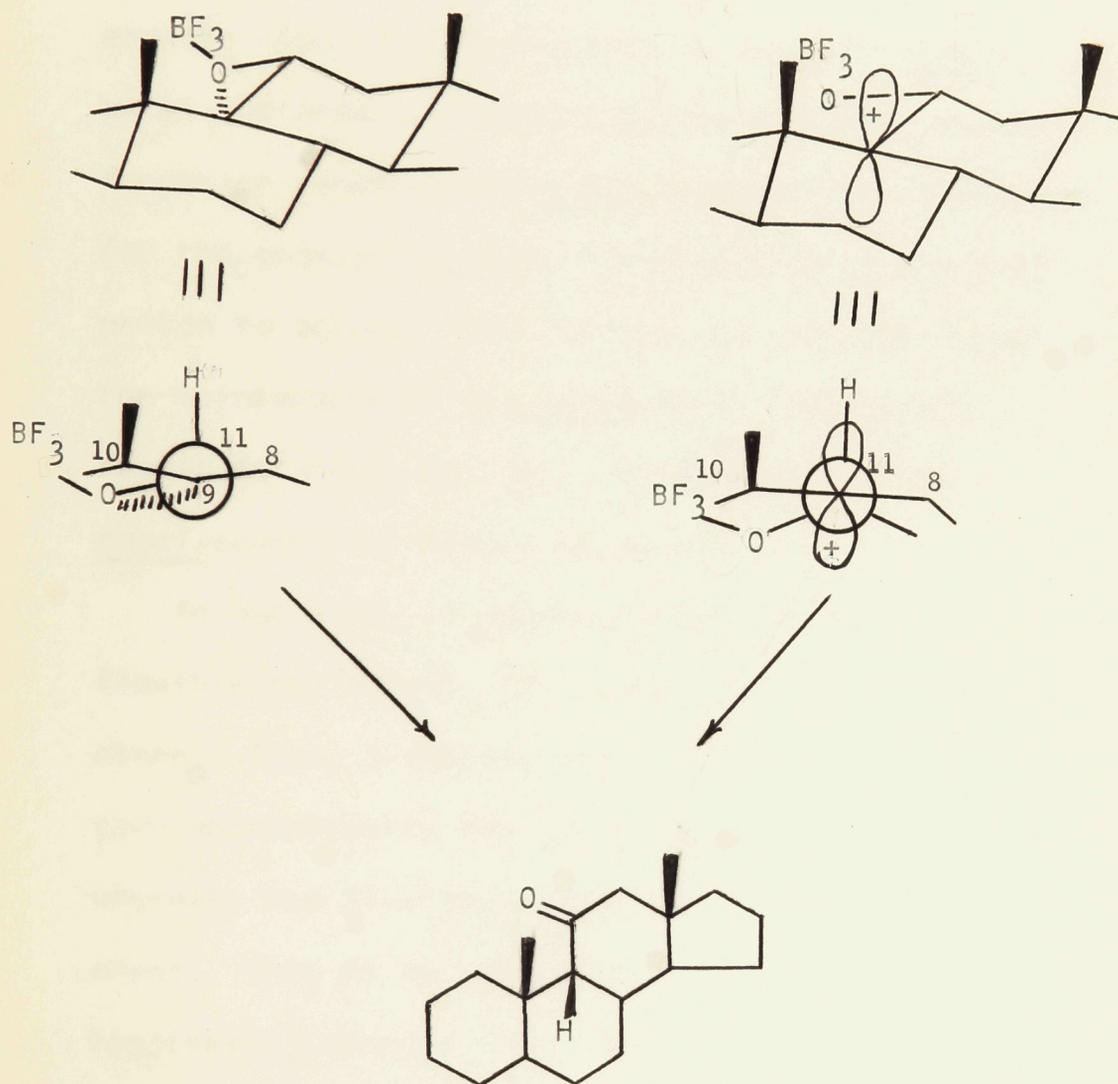
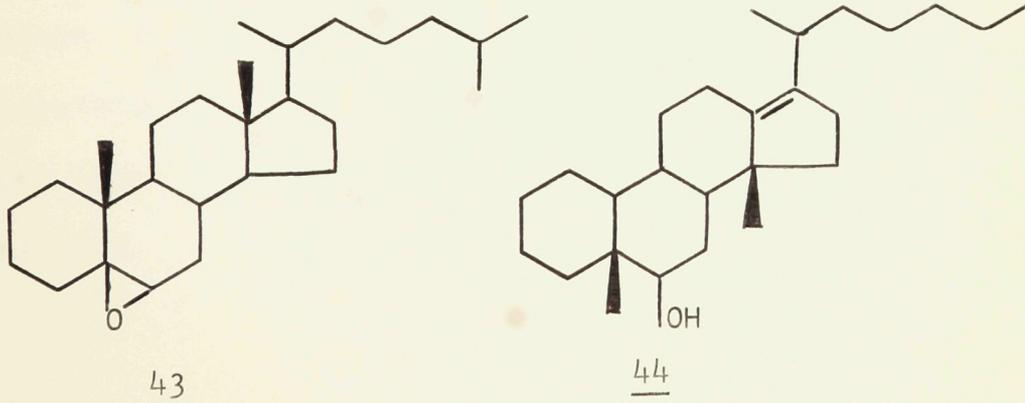


Figure 36

The comparison of the reaction pathways proposed in Figures 29 and 36 show a relating factor between formation of the dienes and ketone. In order for a proton to be abstracted (diene pathway, Figure 29, p.76), the polarized  $\text{BF}_3$  epoxide complex must maintain an axial or quasi-axial conformation similar to the epoxide. Ketone formation requires the quasi-equatorial conformation for the epoxide in order for migration of the C-11 proton to occur. Thus, steric factors that favour the maintenance of the quasi-axial conformation result in diene, whereas, those favouring the quasi-equatorial result in ketone.

In our work, it appeared that the more flexible the A ring, the higher the proportion of diene. Thus, 3-acetate and A nor-3-keto compounds gave approximately 30% diene and 70% ketone, whereas, the 3-ketone and 2,3-diosphenol gave diene. This is in accordance with the proposed hypothesis, since a more flexible skeleton would be more likely to accomodate the steric compression resulting from an  $\alpha$  quasi-axial group in the C ring.

The diagrams in Figures 29 and 36 strongly imply that ketone formation takes place through a discrete carbonium ion, whereas, at least in the first step, diene formation takes place by a concerted mechanism. The structure represented in Figure 36 shows that if ketone formation were to take place by a concerted mechanism (Figure 36a), then an inordinately long and bent C-9 - - - O bond would be required; thus, the discrete carbonium proposed in Figure 36b is preferred as a mechanistic pathway. Evidence that a discrete carbonium ion is a possible mechanistic pathway in epoxide-Lewis acid catalyzed rearrangements is supplied by the isolation of the backbone rearrangement product 44 in 46% yield from the 5 $\beta$ 6 $\beta$  epoxide 43.



Migration of the C-10 methyl to the C-5 position in the above reaction can only be rationalized by postulating a discrete carbonium mechanism since the cleavage of the C-5 oxygen bond would have to be complete or at least be well advanced before a methyl group on the same face of the molecule would migrate.

In all mechanisms of acid-catalyzed cleavage of tri-substituted epoxides discussed thus far, the bond that is cleaved is the bond between the oxygen and the most substituted carbon. Recently, evidence has been reported suggesting that in the case of the 5a6a epoxide in benzene, the protonated epoxide cleaves along the bond between the oxygen and the least substituted epoxide. (49) It was found, prior to the attack by a nucleophile (water), that the 6C-O bond is well advanced towards total cleavage. (Figure 37) This would indicate that it is possible for an epoxide to cleave along the oxygen least substituted carbon bond under acidic conditions.

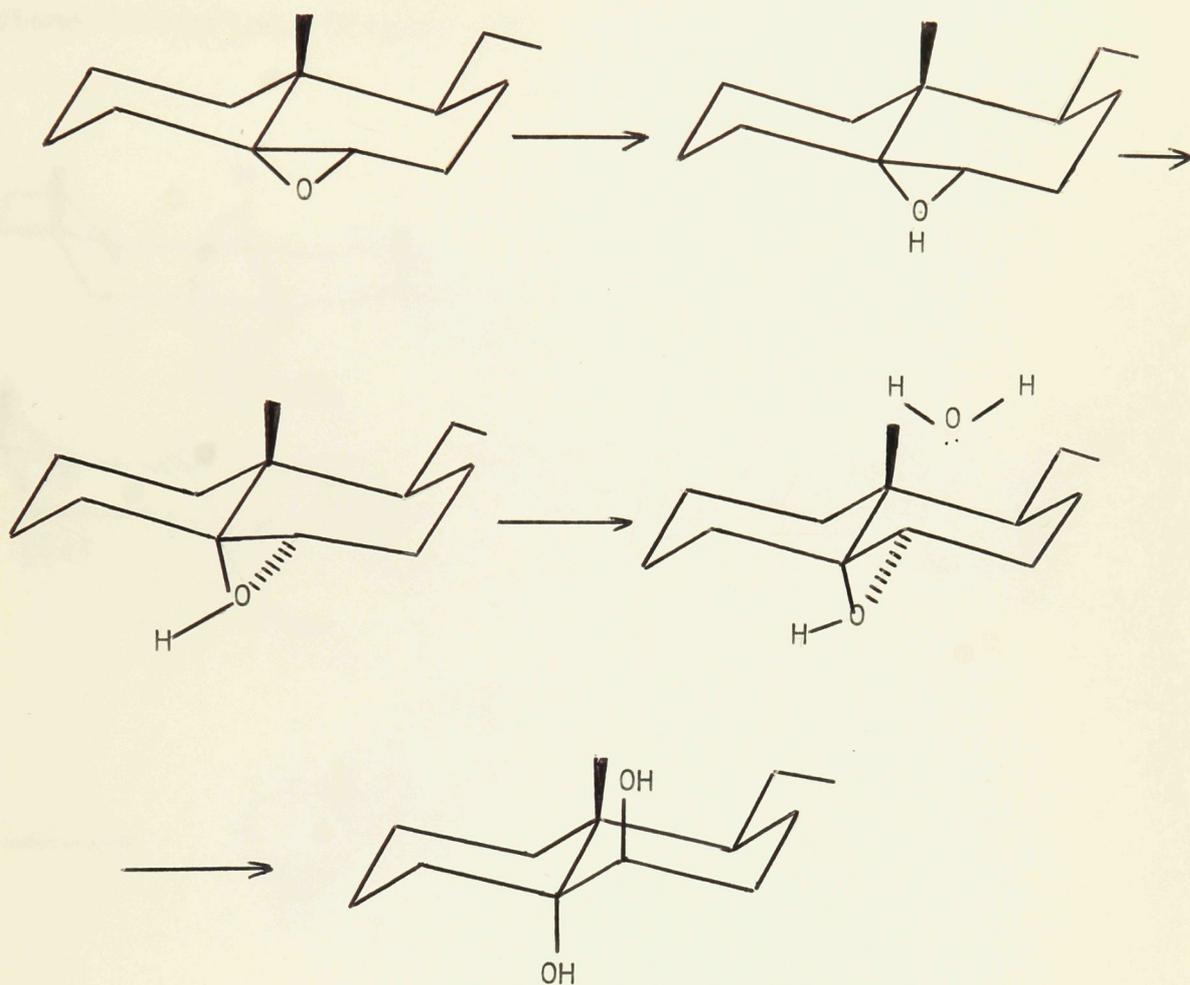


Figure 37

If a similar cleavage occurs in the case of the  $\text{BF}_3$  catalyzed opening of the galla epoxides,

then an alternative mechanism can be proposed for diene formation. (Figure 38)

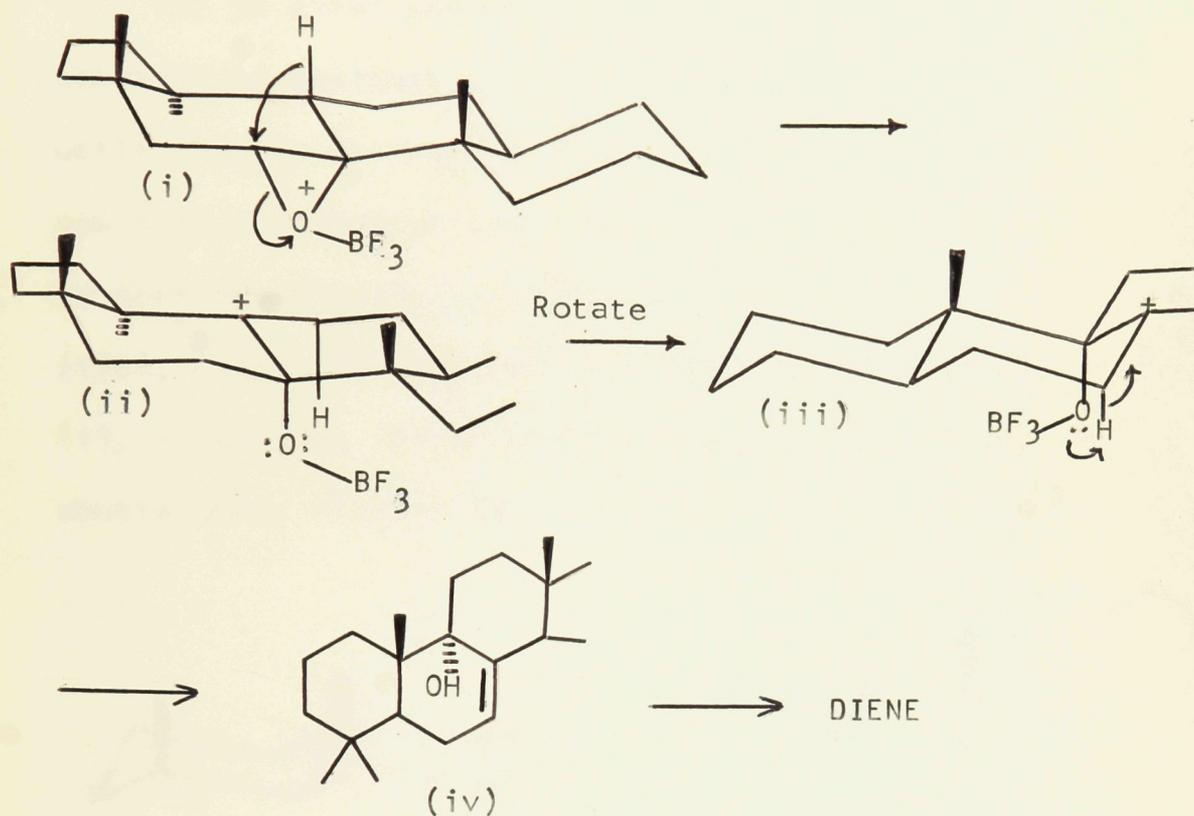


Figure 38

The critical factor in the mechanistic scheme outlined in Figure 38 is the migration of the  $9\beta\text{-H}$  to the  $11\beta$  position (i -ii, Figure 38). A 1,3 hydride shift has already been proposed in an acid-catalyzed cleavage of an epoxide and has been previously discussed. (Page 26) Cope also invoked

a similar hydride migration to explain formation of certain products obtained from acid cleavage of certain cycloheptane epoxides.(50)

The  $9\alpha$  axial oxygen- $\text{BF}_3$  complex is ideally situated to abstract the  $7\alpha$  proton (iii, Figure 38), utilizing the activation of this proton which is now  $\alpha$  to a carbonium ion. It is also interesting to note the similarity between partial structure (iii), Figure 38, and the protonated lanost-8-ene (i), Figure 39. Both compounds lead to a 7,8 double bond, (Figure 39).

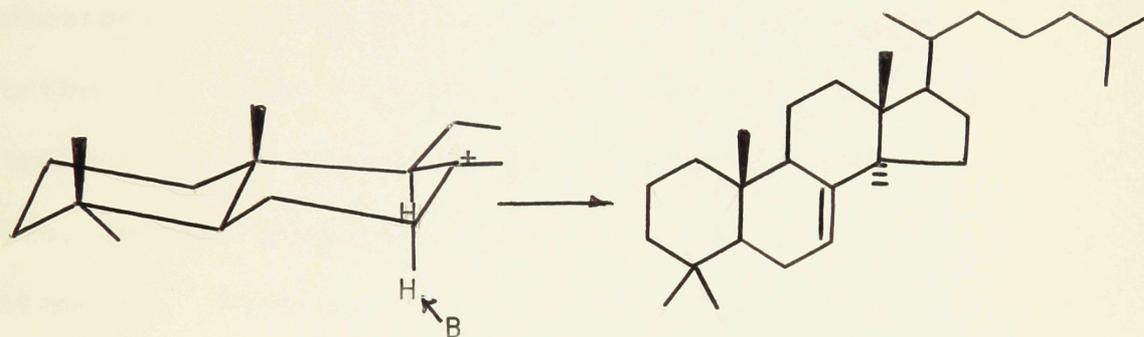
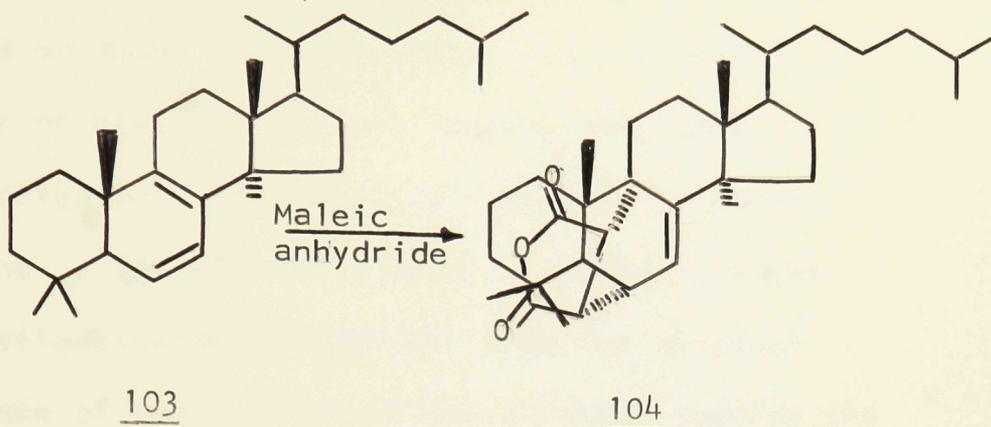


Figure 39

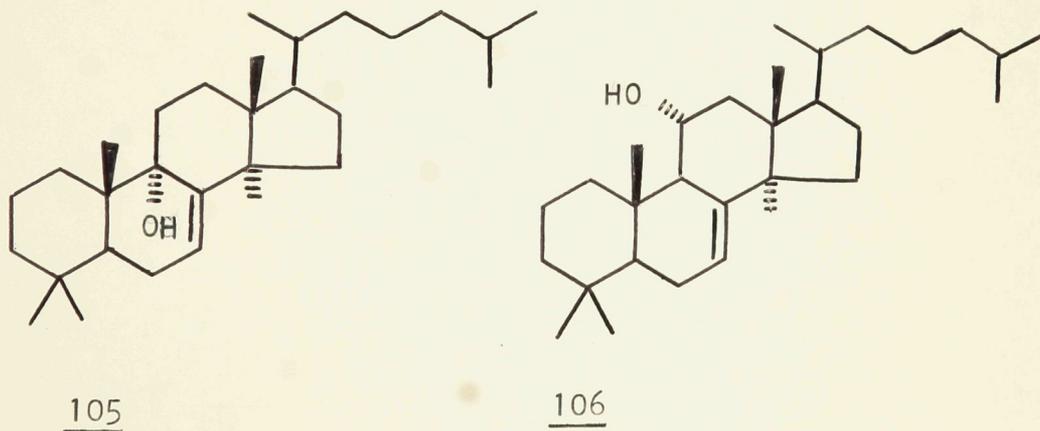
The alcohol that results from the proton abstraction depicted in (iii), Figure 38, is an allylic alcohol, (iv), Figure 38. This would be more liable to dehydration than the homoallylic

alcohol in the mechanistic scheme described in Figure 29. The dehydration would be further aided by the fact that the hydroxyl would be tertiary and axial with the  $11\beta$  proton situated trans-diaxially to it; the situation being ideal for dehydration.

At this point in the investigation it became increasingly evident that it was not likely that methyl migration could be achieved in the tetracyclic triterpene series without some modification of the overall scheme. Furthermore, it was necessary to decide whether or not to investigate further the diene formation which seems to be dominant in the lanostane work. In order to do this, several experiments would have to be attempted. Firstly, the question of the presence or absence of cisoid dienes would have to be resolved. This would require trapping with maleic anhydride or tetracyanoethylene.



Also, both the 8,9:11,12 and 6,7:8,9 dienes would have to be synthesized and rearranged under the  $\text{BF}_3$  conditions. Other projects would include the synthesis of the lanost-7-ene-9 $\alpha$  and 11 $\alpha$ -ols, followed by subjection of these compounds to  $\text{BF}_3$  benzene conditions. Dehydration of these ene-ols would indicate that they were intermediates in the mechanistic pathways.



While positive results from these experiments would no doubt be interesting from a mechanistic point of view, they would require very much investigation, particularly regarding synthesis of the  $\Delta^7$  9 $\alpha$  and 11 $\alpha$  alcohols. However, these investigations would detract from the original purpose of the work which was directed towards the synthesis of the cucurbitacins and were not pursued further by this investigator.

SECTION III: REARRANGEMENT OF A 4,4 DIMETHYL 9 $\alpha$ 11 $\alpha$ -EPOXY ANDROSTANE

The weakness in the epoxide rearrangement approach to the synthesis of the cucurbitacins lies in the low yields of 9 $\beta$  methyl product in the successful reactions reported so far. If this approach is to succeed, then a more efficient and cleaner reaction leading to 9 $\beta$  methyl compounds must be found. The last section of this thesis describes the synthesis of a steroidal 9 $\alpha$ 11 $\alpha$  epoxide which upon rearrangement gives only the 9 $\beta$  methyl product in high yield.

Effect of a Double Bond on the Reaction of Steroidal Epoxides

The investigation thus far had shown that there are at least four distinct pathways in the cleavage of the 9 $\alpha$ 11 $\alpha$ -epoxide. The steroid work indicated the presence of three such pathways; methyl migration, homoallylic alcohol formation, and 9 $\beta$ -H,11 ketone formation. The lanostane work represented an attempt to inhibit one of these pathways, (homoallylic alcohol formation), and resulted in the discovery of a fourth pathway,

(diene formation). Evidently, it was necessary to provide a structural feature which would supply some control in directing the migration after the cleavage of the  $9\alpha,11\alpha$  epoxide introduces a carbonium ion into the system.

One such directing feature would be a 5,6 double bond. Upon migration of the  $10\beta$  methyl, a 5,6 double bond would stabilize a developing positive charge at C-10. (Figure 40)

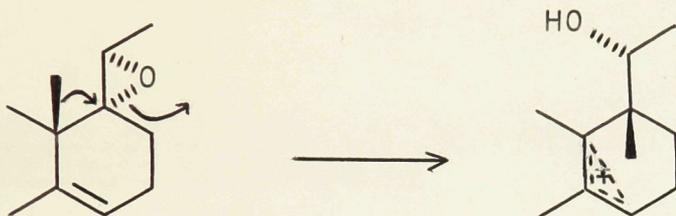
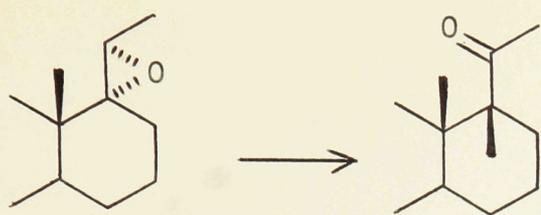
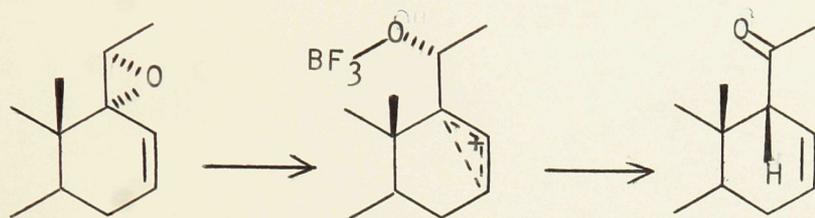


Figure 40

Henbest and Wrigley (38) have used such a hypothesis; that is, the stabilization of a cationic charge by a double bond to explain the facile rearrangement of a  $\Delta^7$   $9\alpha,11\alpha$  epoxide to the  $9\beta$ -H,11 ketone. These workers found that the saturated compound reacts much slower than the  $\Delta^7$  analog. (Figure 41)



Slow Reaction

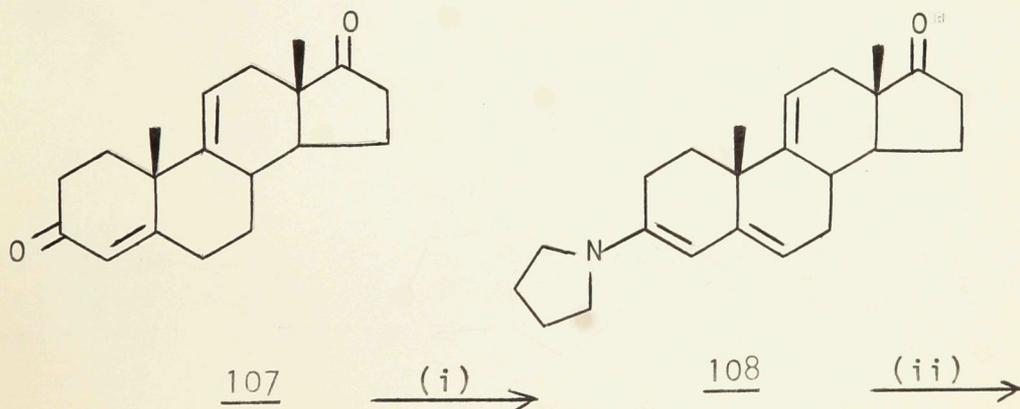


Fast Reaction

Figure 41

Synthesis and Reaction of 4,4 Dimethyl Androst-4-ene-9 $\alpha$ 11 $\alpha$ -epoxy-3,17-dione

A system with the required 5,6 double bond can be readily synthesized from commercially available androst-4,9(11)-diene-3,17-dione. The synthetic sequence is summarized in Figure 42.



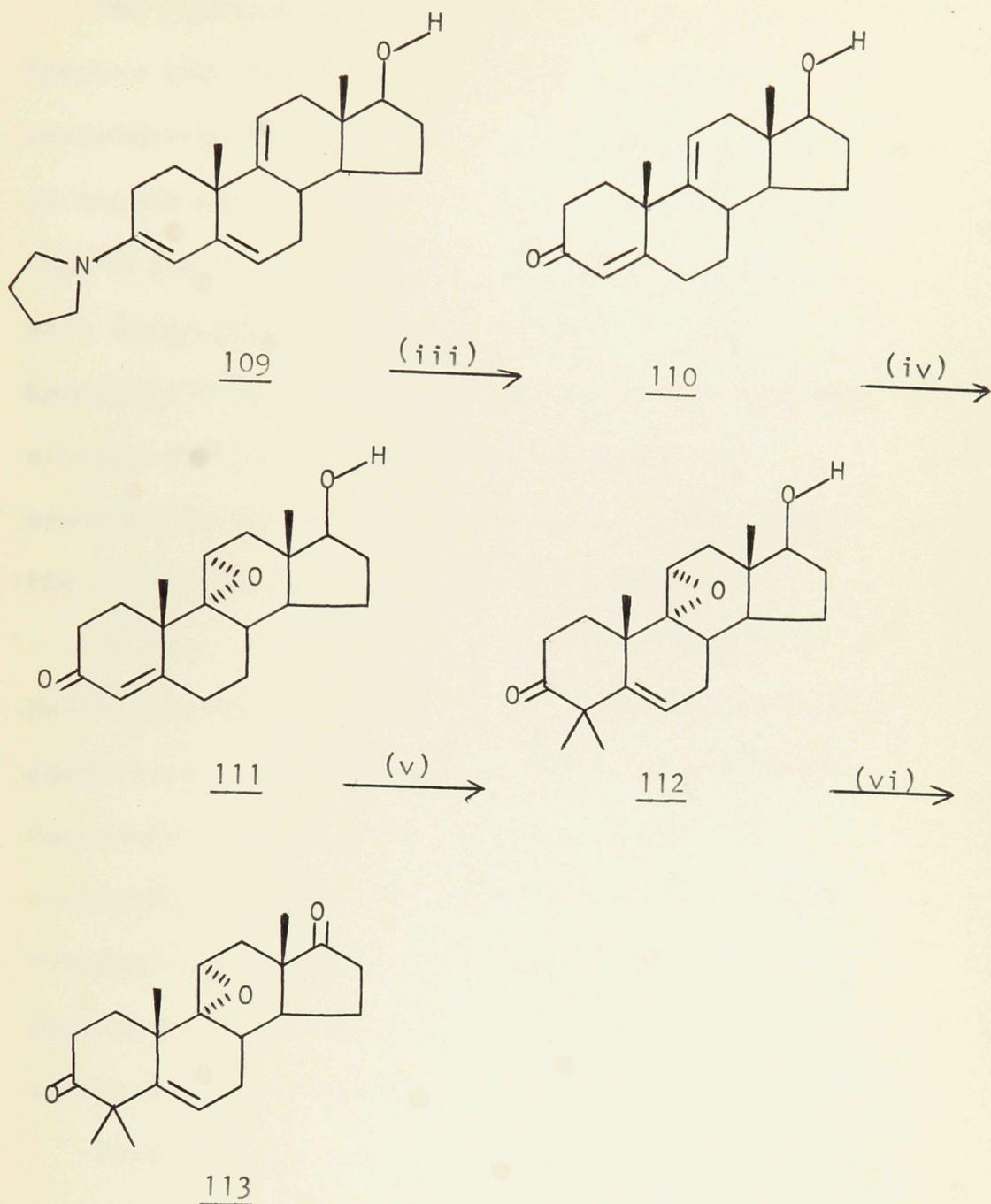


Figure 42

- (i) pyrrolidine    (ii)  $\text{LiAlH}_4$     (iii)  $\text{AcOH}/\text{AcONa}$  - Buffer  
 (iv) *m*-chloroperoxybenzoic acid    (v)  $\text{tBuOK}$  in  $\text{tBuOH}$  and  $\text{CH}_3\text{I}$   
 (vi) Jones reagent

The reaction sequence was quite straightforward and the details are provided in the experimental section. Selective reduction of the 17 ketone was necessary to prevent alkylation of the 16 position, since in step (v), Figure 42, a very large excess of methyl iodide is used. Epoxidation preceded the alkylation step and thus avoided the difficult problem of selective epoxidation of the 9(11) and the 5 double bonds, the latter being formed upon alkylation.

It was, of course, very fortunate that the 9 $\alpha$ 11 $\alpha$  epoxide was stable to the powerful alkylating conditions. Epoxides are usually not very stable functional groups, (53), and are subject to nucleophilic attack by base, (eg. in the case of hydroxyl ions acting as nucleophiles, 1,2 diols are formed). Evidently, the 9 $\alpha$ 11 $\alpha$  epoxide is sufficiently hindered to render it extremely stable.

Compound 113 contains the prerequisites necessary for migration. A double bond is suitably located to stabilize the C-10 cationic centre. Furthermore, there is probably an additional driving force in the release of the 1,3 diaxial

interaction between the C-4 $\beta$  methyl and the C-10 $\beta$  methyl. The 4,4 dimethyl group is, of course, necessary for further elaboration of the cucurbitacin structure.

Treatment of a solution of 113 in benzene with BF<sub>3</sub> gas precipitated a yellow gel after one and a half hours. Thin layer comparison of the gel and starting material showed that complete reaction had taken place with only one compound being formed. The usual workup afforded a crystalline product which was apparently pure as determined by thin layer chromatography. Recrystallization from benzene afforded the analytical sample in 60% yield.

The infrared spectrum detected the presence of hydroxyl; weak sharp band at 3,610 cm.<sup>-1</sup>, broad band at 3,500 cm.<sup>-1</sup>, cyclopentanone 1,740 cm.<sup>-1</sup>, and saturated cyclohexanone 1,710 cm.<sup>-1</sup>.

Ultraviolet absorption spectroscopy showed a chromophore absorbing at 236 n.m.  $\epsilon$  10,000. Woodward rules suggested that this chromophore was a tetrasubstituted, heteroannular diene. (Figure 43).

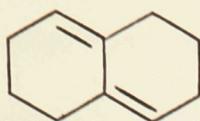


Figure 43

Addition of one drop of base to the solution used for ultraviolet spectroscopy resulted in a shift of the peak to 300 n.m.  $\epsilon$ 6,150. This could be attributed to an  $\alpha$ - $\beta$ ,  $\gamma$  $\delta$  unsaturated cyclohexanone. (Figure 44)

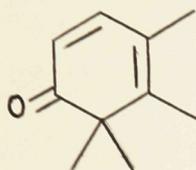
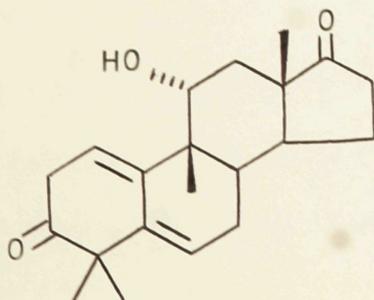


Figure 44

The available data permitted the proposal of structure 114 for the rearrangement product.

114

N.M.R. data supplied further evidence supporting structure 114 for the rearrangement product. A 100 MHz spectrum showed, in part, two protons in the vinylic region. A poorly resolved triplet appeared at  $6.5\delta$  and a broadened multiplet appeared at  $5.55\delta$ ; both signals integrated for one proton each. The low field absorption at  $6.5\delta$  indicates that one of these protons is deshielded. A similar deshielding was observed for the C-1 proton in phenol 50 and is consistent with the  $9\beta$  methyl assignment. Furthermore, this deshielding of the C-1 proton fixes the diene in the 1(10); 5,6 position. A multiplet at  $3.58\delta$  of 5 lines was confirmed by the disappearance of the signal upon oxidation to the 11 ketone. Coupled with the infrared and ultra-violet data, the N.M.R. data presented thus far confirm the structure 114 as the correct one for the rearrangement product of epoxide 113.

Absorption in the  $2.6\delta$  to  $3.5\delta$  region shows an interesting coupling pattern and is in complete accord with structure 114. (Figure 45) The relative intensities of the eight line spectrum were 2:5:5:2,

whereas the relative intensities of the spin decoupled four line spectrum were 1:2:2:1.

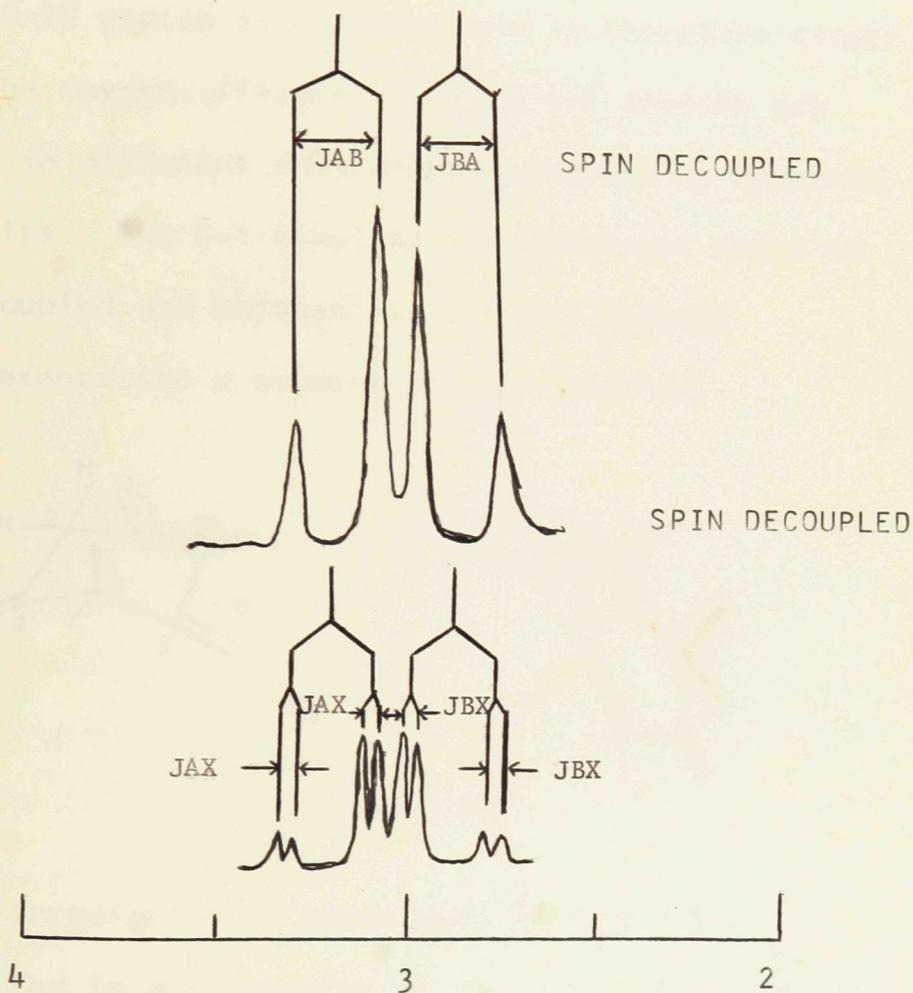


Figure 45

These results showed that the eight line spectrum at  $3.04\delta$  and the triplet at  $6.5\delta$  comprised an ABx spectrum.

A proton pattern that could give rise to the ABX spectrum is present in the structure as the C-2 protons (AB) and the C-1 proton. The C-2 $\alpha$  proton is perpendicular to the C-3 carbonyl, whereas the C-2 $\beta$  proton is coplanar and is therefore closer to the oxygen. (Figure 46) The C-2 protons are thus in different environments and the AB spectrum results. The C-1 vinyl proton which was shown to be coupled and adjacent to the C-2 protons represents the x segment of the spectrum.

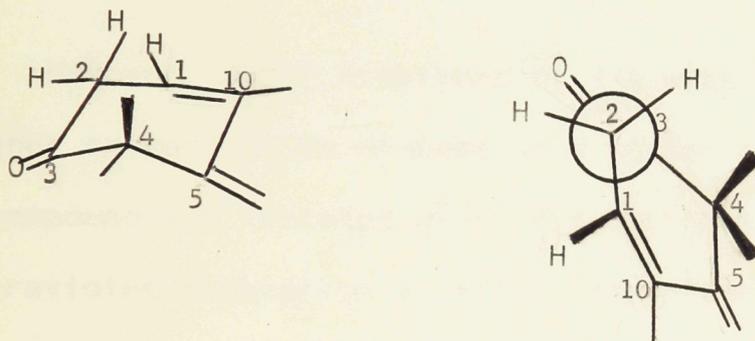
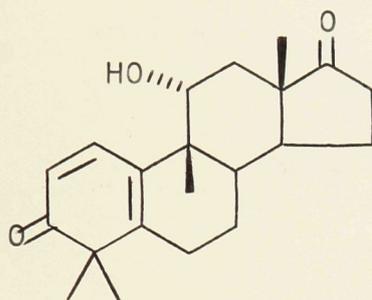


Figure 46

Irradiation of the signal at 6.5 $\delta$  also resulted in a sharpening of the broad multiplet at 5.55 $\delta$  into a poorly resolved but distinguishable four line signal.

In order to obtain chemical verification of structure 114, an attempt was made to prepare keto

diene 115 by base isomerization of 114. The preliminary tests during ultraviolet spectroscopy indicated that this isomerization could in fact take place.



115

However, after treatment of 114 with a higher concentration of base on a larger scale, a compound was isolated which did not possess any ultraviolet absorption at all. The infrared spectrum showed no hydroxyl but indicated the presence of cyclopentanone and cyclohexanone. The compound was assigned structure 116. This could result from conjugation of the diene followed by an internal Michael Reaction to form a cyclic ether. There is precedence for this hypotheses in the work on decomposition of steroidal 9 $\alpha$ -amino-11 ketones

reported by Edwards.(28)

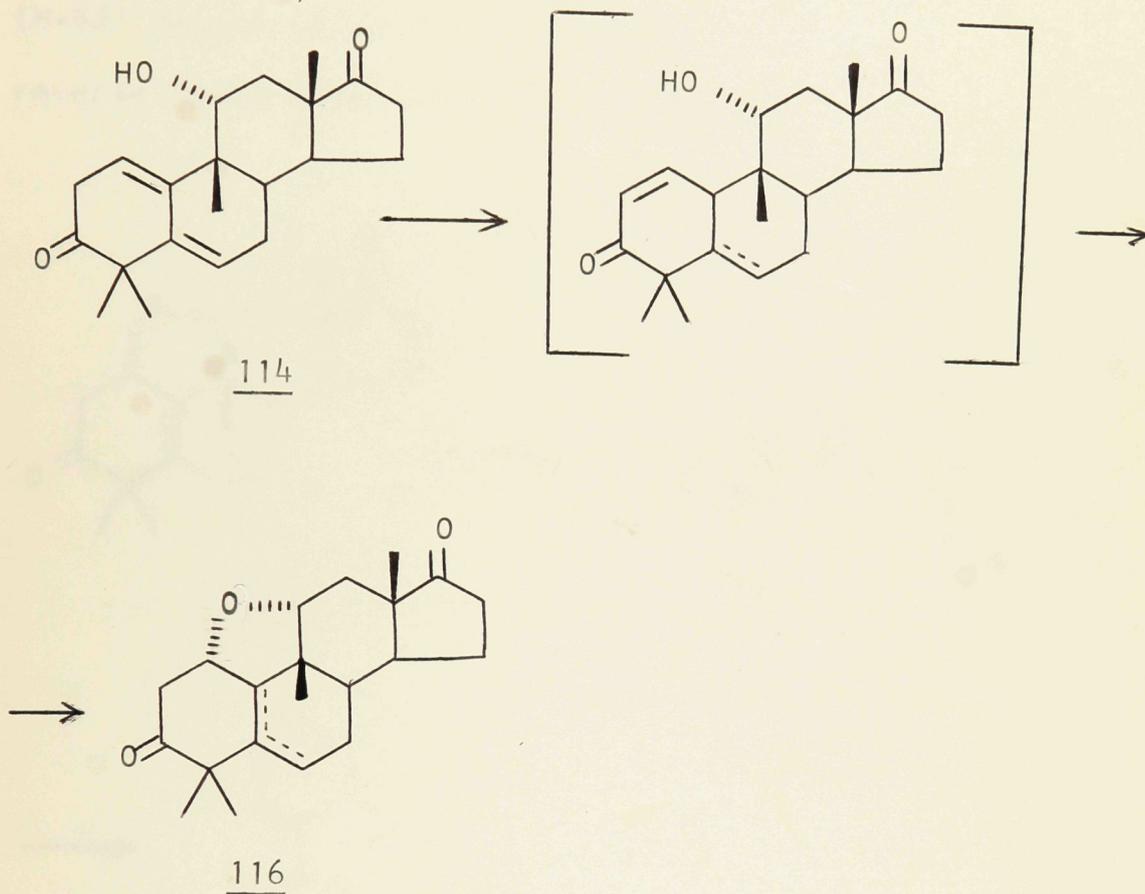


Figure 47

The N.M.R. spectrum was difficult to interpret and insufficient pure material was available for spin decoupling studies which would have been necessary to assign the peaks to different protons or to establish the position of the double bond. The 5(10) position for the double bond, 117, is

supported by mass spectral evidence. The molecular ion peak appears at 328. The base peak at  $m/e$  286 ( $M-42$ ) results from the loss of ketene in a reverse Diels Alder reaction. (Figure 48)

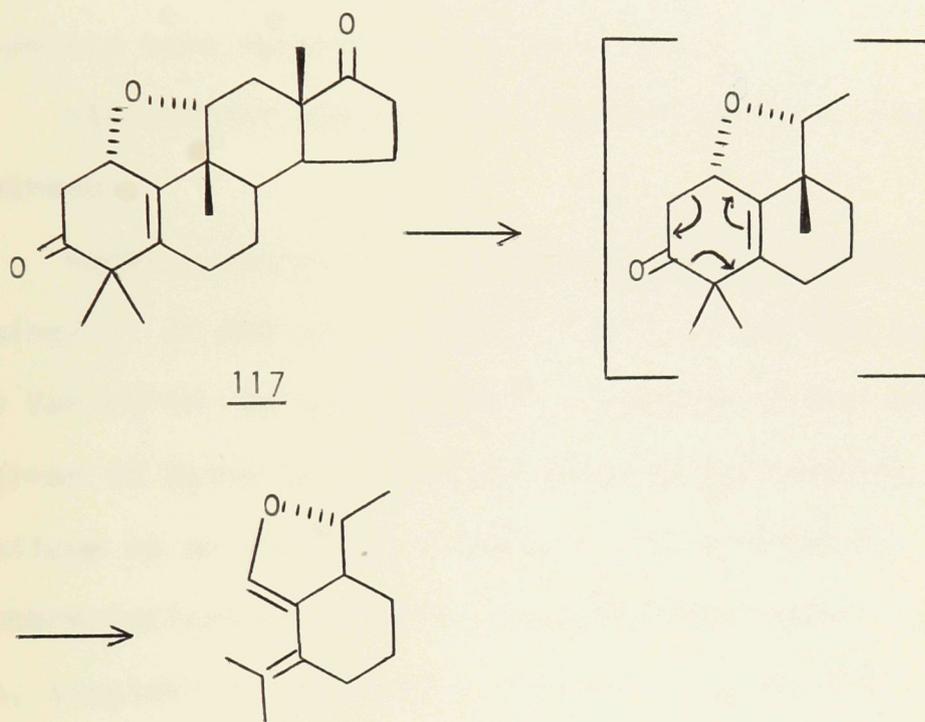


Figure 48

## EXPERIMENTAL

Infrared (i.r.) spectra were determined on Perkin-Elmer Infracord 137 and 237 spectrophotometers in 10% chloroform solution. In cases where solubility problems were encountered, the infrared spectra were determined in nujol mulls.

Ultraviolet spectra were determined in absolute ethanol.

Nuclear magnetic resonance spectra were determined at 60 MHz on a JEOLCO C-60 or at 100 MHz on a Varian HA 100 spectrometer. Chemical shifts are given in delta ( $\delta$ ) units relative to tetramethylsilane as an internal standard. The following abbreviations are used to describe the signals: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Only signals deemed to be of interest in assigning structure have been quoted. Sample concentrations were approximately 10% (wt/vol) in deuteriochloroform as a solvent. The Nuclear Overhauser Effect, N.O.E., experiment was performed by Professor R.A. Bell at McMaster University.

Optical rotations were taken at room temperature

in chloroform solution on a Hilger Mark II Standard Polarimeter.

Melting points are uncorrected and were determined on a Kofler hot stage.

Mass Spectra were obtained on an A.E.I. MS 12 instrument at Trent University and on a Thomson-Houston machine at the Institut de Chimie in Strasbourg.

Microanalyses were obtained from A. Spang, Ann Arbor, Michigan, and J. Daesllés, Montreal, Quebec.

### Synthesis of Epoxide 49a

Epoxide 49a was synthesized from commercially available androst-4,9(11)-diene-3,17-dione, m.p. 273-275°C.;  $[\alpha]_D^{25} +188$ ; literature values (8), m.p. 273-275°C.,  $[\alpha]_D^{25} +190$ .

### Rearrangement of Androst-4-ene-9 $\alpha$ 11 $\alpha$ -epoxy-3,17-dione

Epoxide 49 (1.0 g.) was dissolved in freshly dried and distilled benzene (175 cc. ).  $\text{BF}_3$  gas was bubbled through the solution until epoxide- $\text{BF}_3$  complexation commenced as manifested by the formation of a slight reddish-brown gel around the sides of the flask. The mixture was allowed to stand for 12 hours after which time t.p.c. analysis of the gel (benzene-ethyl acetate 7:3) showed the formation of two major products and the disappearance of most of the starting material. The reaction was taken up in ether (125 cc.) to give an orange solution. The ether benzene layer was washed three times with water, and then extracted with 0.5 N aqueous sodium hydroxide. The organic phase was then washed with water to neutrality, dried over sodium sulphate, and evaporated to 700 mg. of yellow crystalline

material.

The alkaline layer was acidified and extracted with ether to give 300 mg. of a yellow oil.

Phenolic Fraction: The yellow oil obtained as the phenolic fraction was taken up in a small amount of chloroform. Upon standing, the chloroform solution deposited 140 mg. of fine colourless prisms. m.p. 254-256°C.,  $[\alpha]_D^{25} +31$ . Literature values, m.p. 254.5-255°C.,  $[\alpha]_D^{25} +32$ .

Neutral Fractions: Repetition of the  $\text{BF}_3$  catalyzed epoxide rearrangement on a 15 g. scale gave 11.1 g. of neutral material, which was chromatographed on neutral alumina. Elution with benzene afforded homoallylic alcohol 51 in 26% yield. m.p. 229-231°C., mixed melting point with authentic material (8), 229-232°C. Elution with methylene chloride afforded a triketone in 4% yield.

Chromatography also afforded a triketone in 4% yield. m.p. 213-216°C.  $\nu$  max. 1749 (17 ketone), 1720 (11 ketone), 1660 (3 ketone), 1625  $\text{cm.}^{-1}$  ( $\Delta^4$ );  $\lambda$  max. 245 n.m.,  $\epsilon$  15,200; n.m.r. signals, 1.375 (3H,s), 1.28 (3H,s) ( $\text{C}_{18} + \text{C}_{19}$  methyl groups), 2.85 (1H, broad signal), 5.78 (1H,s,4H). Infrared, t.l.c., and n.m.r. indicated that this was not androst-4-ene-3,11,17-trione. Triketone 52 (40 mg.) was treated with

$K_2CO_3$  (30 mg.) in methanol (3 c.c.). The solution was stirred overnight and poured into saturated aqueous sodium chloride solution (30 c.c.), then extracted with ether. The etheréal solution was dried with sodium sulphate and evaporated to give 15 mg. of a product identical with authentic andrenost-4-ene-3,11,17-trione as found by m.p., mixed m.p., t.l.c., i.r., and n.m.r. comparison.

9 $\beta$ -methyl-3-hydroxy-1,3,5(10), estratriene-11-one-methyl ether

Treatment of 100 mg. of phenol 50 with dimethyl sulphate in methanolic potassium hydroxide gave 70 mg. of 3 methyl ether of 50. m.p. 187-189°C., literature value (8) 187-189°C. The methyl ether was taken up in acetone and chilled in an ice bath. Sufficient Jones reagent was added to maintain a slightly red colouration for 5 minutes. Methanol was added to destroy excess oxidant, followed by water to dissolve the chromous salts. The organic solvents were removed on a rotary evaporator and the resulting mixture was extracted with ether. The ether layer

was dried with sodium sulphate and evaporated to dryness and the crystalline solid was recrystallized from absolute ethanol to give 45 mg. colourless plates. m.p. 150-152°C.;  $[\alpha]_D^{25} +279$ ;  $\nu$  max. 1730  $\text{cm}^{-1}$  (17 ketone), 1700  $\text{cm}^{-1}$  (11 ketone),  $\lambda$  max. 278 n.m.  $\epsilon$  2130; n.m.r. signals ( $\text{CDCl}_3$ ), 0.875 (3H,s, 13 $\beta$  methyl), 1.4 (3H,s, 9 $\beta$  methyl), 3.775 (3H,s, 3 methoxy), 6.75 (3H,m, aromatic), ( $\text{C}_6\text{D}_6$ ), 0.53 (3H,s, 13 $\beta$  methyl), 1.45 (3H,s, 9 $\beta$  methyl), 3.35 (3H,s, 3 methoxy), M (mass spectral) 328.

#### Preparation of Epoxide 62

Epoxide 62 was prepared from commercially available androst-4,9(11)-diene-3,17-dione after a method of Fried and Sabo (53). m.p. 181-182°C.,  $[\alpha]_D^{25} +46$ , literature values (53) m.p. 180-181°C.,  $[\alpha]_D^{25} +48$ .

#### Rearrangement of Epoxide 62

Rearrangement of epoxide 62 was carried out as described above. There was no evidence of any phenolic compounds. The neutral fraction was crystallized from hexane after seeding with authentic

androst-4-ene-3,11,17-trione to give a 50% yield of androst-4-ene-3,11,17-trione. The sample had the same melting point and mixed melting point as an authentic sample.

#### Preparation of Lanost-9 $\alpha$ 11 $\alpha$ -epoxy-3 $\beta$ -ol acetate

Lanost-9(11)-ene-3 $\beta$ -ol acetate was prepared from commercially available lanost-8(9),24-diene-3 $\beta$ -ol 74 via a method previously outlined in the literature.

Lanost-8-ene-3 $\beta$ -ol acetate, 74, was obtained from lanost-8(9),24-diene-3 $\beta$ -ol acetate in 90% yield after the method of Marker et al. (40) m.p. 119°C,  $[\alpha]_D +52$ ; literature values (40) m.p. 119°C.,  $[\alpha]_D +53$ .

Lanost-8 $\alpha$ 9 $\alpha$ -epoxy-3 $\beta$ -ol acetate (75) was obtained in 67% yield from 74. Recrystallized from ethanol with a trace of pyridine. m.p. 140-141°C.,  $[\alpha]_D +15$ ; literature values (39) m.p. 140-141°C.,  $[\alpha]_D +15$ .

Lanost-9(11)-ene-3 $\beta$ -ol acetate, 78, was prepared from 75 in 40% yield. Intermediates 76 and 77 were not isolated in pure form. m.p. 162-

165°C.,  $[\alpha]_D^{+87}$ ; literature values (39) m.p. 162-165°C.  $[\alpha]_D^{+85}$ .

A solution of olefin 78 (1 g.) in chloroform (50 cc.) was treated with m-chloroperoxybenzoic acid (1 g.) and was kept at 5°C. overnight. Thin layer examination of the reaction solution indicated complete reaction. The solution was washed twice with 25 cc. of a 10% aqueous solution of sodium sulphite followed by two washings with a solution of saturated aqueous sodium bicarbonate. The solution was then dried with anhydrous sodium sulphate and evaporated to dryness on the rotary evaporator. The white solid was recrystallized from acetone to give colourless powder (440 mg.). An additional 160 mg. were obtained from a second crop, m.p. 174-177°C.,  $[\alpha]_D^{+26}$ ,  $\nu$  max. 1735  $\text{cm}^{-1}$  (acetate); n.m.r. signals at 4.5 (1H, m, 3 $\alpha$ -H), 3.1 (1H, d, 11-H).

Anal. calc'd for  $\text{C}_{32}\text{H}_{54}\text{O}_3$  : C, 78.96; H, 11.18.  
Found : C, 75.80; H, 8.07.

#### Rearrangement of Lanost-9 $\alpha$ 11 $\alpha$ -epoxy-3 $\beta$ -ol acetate

A solution of epoxide 79 (520 mg.) in anhydrous

benzene (20 c.c.) was treated with  $\text{BF}_3$  gas until the benzene was saturated. This was manifested by fumes emitting from an outlet of the reaction vessel. At this point, an orange gel precipitated. After twenty minutes, thin layer investigation of the gel which had deepened in colour showed the reaction was complete and that two compounds had been formed. Sufficient diethyl ether was added to dissolve the gel and at the same time decolourize the solution. The solution was then washed twice with 10 c.c. of saturated aqueous sodium bicarbonate, dried, and evaporated to dryness, to give 510 mg. of colourless plates. The entire crop was chromatographed on 25 grams of silica gel eluting with benzene and benzene-ether (9/1). Two products were isolated: a non-polar oil which was eluted in the first fractions with benzene and a more polar compound eluted in the later fractions with benzene and benzene-ether (9/1). The more polar compound (931 mg.) was recrystallized from ethanol to give 210 mg. of colourless cubes. m.p.  $202-204^\circ\text{C}.$ ,  $[\alpha]_D +109$ ;  $\nu$  max. (nujol mull), n.m.r. signals (100 MHz) at 4.29 (1H, mult,  $3\alpha\text{-H}$ ), 2.8 (1H, d,  $9\beta\text{H}$ ); C.D.

$[\alpha]_{298} = 11,950^\circ$ .

Anal. calc'd for  $C_{32}H_{54}O_3$  : C, 78.96; H, 11.18.  
Found : C, 79.06; H, 11.01.

The oil did not crystallize. Thin layer and vapour phase chromatography indicated this to be one compound showing one spot and one peak only. The oil showed ultraviolet absorption.  $\lambda$  max. 236 n.m.  $\epsilon$  4500;  $\lambda$  max. 245 n.m.  $\epsilon$  5000;  $\lambda$  max. 252 n.m.  $\epsilon$  4300;  $\nu$  max. 1735  $cm^{-1}$  (3 acetate); n.m.r. signals 4.3 (1H, mult-3 $\alpha$ H), 5.72, 5.55 (vinylic protons).

#### Preparation of Lanost-9 $\alpha$ 11 $\alpha$ -epoxy-3-one 83

Olefin 78 (7.8 g.) was added to a solution of potassium hydroxide (1 g.) in ethanol (700 c.c.) and the resulting mixture was warmed to dissolve the olefin 78. The solution was then refluxed overnight. The solution was cooled and a gelatinous solid precipitated. The mixture was evaporated to dryness on the rotary evaporator and extracted with four portions of ether (50 c.c.). The ether extract was washed with water, dried over anhydrous sodium sulphate, and evaporated to give an amorphous solid (7.4 g.). This solid was taken

up in acetone (150 c.c.), cooled in an ice bath, and treated with sufficient Jones reagent to maintain red colouration. The reaction mixture was stirred in the ice bath for an additional ten minutes and then sufficient methanol was added to remove the red colouration, followed by sufficient water to dissolve the green chromous salts. The solution was then concentrated on the rotary evaporator until most of the organic solvent had been removed. The resulting mixture was extracted with ether. The ether extract was washed with saturated aqueous sodium bicarbonate, dried with sodium sulphate, and evaporated. The solid was adsorbed on silica gel and eluted with hexane and hexane-benzene (19/1) to give a low yield of a colourless oil. Elution with hexane-benzene (3/1) gave pure 82 as colourless rosettes (4.5 g.). Later fractions yielded an additional amount of slightly less pure material which was recrystallized from ethanol to give 82 (1 g.). m.p. 114-116.5°C.,  $[\alpha]_D^{25} +58$ ;  $\nu$  max. 1700  $\text{cm}^{-1}$  (3 ketone); n.m.r. signals 5.21 (1H, mult 9-H).

Anal. calc'd for  $C_{30}H_{50}O$  : C, 84.51; H, 11.72.  
Found : C, 84.74; H, 11.86.

Olefin 82 (4.5 g.) was dissolved in chloroform (200 c.c.) and treated with m-chloroperoxybenzoic acid (4.5 g.), then chilled for 48 hours at 5°C. Thin layer analysis showed that the reaction had gone to completion. The reaction mixture was washed twice with 100 c.c. of a 10% aqueous solution of sodium sulphite. The organic layer was then washed twice with saturated aqueous sodium chloride. The chloroform solution was dried over sodium sulphate and evaporated to dryness. The solid was adsorbed onto 200 g. of silica gel and eluted with 85% benzene in hexane to give 37 mg. of an oil. Elution with benzene gave 2.9 g. of a solid which was recrystallized from ethanol to give 83, 2.6 g. (55%) colourless needles. m.p. 113-114°C.,  $[\alpha]_D^{25} +14.8$ ;  $\nu_{max}$ . 1700  $cm.^{-1}$  (3 ketone); n.m.r. signals 3.69 (1H mult -11-H).

Anal. calc'd for  $C_{30}H_{50}O_2$  : C, 81.38; H, 11.39.  
Found : C, 81.56; H, 11.29.

When epoxide 79 was subjected to the alkaline

hydrolysis and Jones oxidation previously described for the synthesis of ene-one 82, epoxide 83 was isolated in good yield.

#### Rearrangement of Lanost-9 $\alpha$ 11 $\alpha$ -epoxy-3-one 83

A solution of epoxide 83 (200 mg.) in benzene (5 c.c.) was saturated with gaseous  $\text{BF}_3$ . A white gel precipitated. The gel turned orange upon standing for one hour. Thin layer analysis of the gel showed complete reaction. Sufficient ether was added to the benzene mixture to dissolve the gel and decolourize (approx. 10 c.c.). The colourless solution was washed with aqueous saturated sodium bicarbonate. The organic layer was then dried with sodium sulphate and evaporated to give a colourless oil which showed only one spot on thin layer chromatography and only one peak on vapour phase chromatography. Repeated attempts to obtain crystalline material were unsuccessful.  $\nu$  max. 1700 (3 ketone);  $\lambda$  max. 243 n.m.  $\epsilon$  2300;  $\lambda$  max. 246 n.m.  $\epsilon$  2800;  $\lambda$  max. 252 n.m.  $\epsilon$  2100; n.m.r. signals 5.72, 5.55 (vinylic protons).

Synthesis of Lanost-9 $\alpha$ 11 $\alpha$ -epoxy-2,3-dione 87

Keto epoxide 83 (310 mg.) was added to a solution of potassium (100 mg.) in t-butyl alcohol (20 c.c.). The addition resulted in a yellow solution which was stirred in an atmosphere of oxygen for twenty-four hours. Water (20 c.c.) was added, followed by 5 c.c. of 10% (v/v) solution of aqueous hydrochloric acid. The mixture was extracted with five portions of ether. The organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulphate and evaporated to dryness. The solid was adsorbed on 25 g. of silica gel and eluted with benzene. It was then eluted further with benzene and progressively larger amounts of ether. A fraction, removed with 25% diethyl ether in benzene (120 mg.) was collected and recrystallized from methanol to give 66 mg. (17%) of colourless flakes, 87. m.p. 178-179°C.,  $[\alpha]_D^{25} +42$ ;  $\lambda$  max. 270 n.m.  $\epsilon$  8950; upon addition of one drop of 0.1 N NaOH,  $\lambda$  max. 312-315  $\epsilon$  6810.

Anal calc'd for  $C_{30}H_{48}O_3$  : C, 77.35; H, 10.1.  
Found : C, 77.64; H, 10.21.

Rearrangement of Lanost-9 $\alpha$ 11 $\alpha$ -epoxy-2,3-dione

A solution of epoxide 87 (75 mg.) in anhydrous benzene (5 c.c.) was saturated with gaseous BF<sub>3</sub>. A colourless gel precipitated. After one hour, the gel turned orange. Thin layer analysis indicated completion of the reaction with formation of only one compound. Sufficient ether was added to dissolve the gel and decolourize it. The organic solution was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulphate and evaporated to dryness to give a white solid. Recrystallization from ethanol gave 30 mg. of colourless powder, 88. m.p. 183-185°C., [ $\alpha$ ]<sub>D</sub>+12.2;  $\nu$  max. 3450 cm.<sup>-1</sup> (2 hydroxyl), 1670, 1650 cm.<sup>-1</sup> (diosphenol);  $\lambda$  max. 228 n.m.  $\epsilon$  14,152;  $\lambda$  max. 234 n.m.  $\epsilon$  16,900;  $\lambda$  max. 252 n.m.  $\epsilon$  14,200; (7:8, 9:11 diene);  $\lambda$  max. 268 n.m.  $\epsilon$  10,000 (diosphenol). Upon addition of a drop of 0.1 N KOH,  $\lambda$  max. 228 n.m.  $\epsilon$  12,800;  $\lambda$  max. 234 n.m.  $\epsilon$  13,400;  $\lambda$  max. 252 n.m.  $\epsilon$  12,800, (7:8, 9:11 diene);  $\lambda$  max. 312 n.m.  $\epsilon$  5900 (diosphenol anion); n.m.r. signals 5.55 (2H, broad singlet, diene), 5.9-6.2 (1H broad peak - 2 hydroxyl),

6.56 (1H, s, 1-H vinylic proton).

Anal. calc'd for  $C_{30}H_{46}O_2$  : C, 82.1; H, 10.5  
 Found : C, 80.50; H, 10.27. The C,H analysis is incorrect, however, the structure is supported by mass spectral evidence M 438.

Synthesis of A-norlanost-9(11)-ene-3-one

(i) Oxidation of olefin 82 to diosphenol 88

A solution of olefin 82 (1 g.) was added to a solution of potassium (300 mg.) in t butyl alcohol. The addition resulted in a yellow solution which was stirred for 24 hours in an atmosphere of oxygen. Water (20 c.c.) was then added, followed by 5 c.c. of 10% (v/v) solution of aqueous hydrochloric acid. The mixture was extracted with five portions of ether. The organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulphate and evaporated to dryness. It was then recrystallized from absolute ethanol to give 2.1 g. of colourless flakes. m.p. 177-179°C.,  $[\alpha]_D^{25} +42.5$ ;  $\nu$  max. 3450  $cm^{-1}$  (2 hydroxyl); 1670, 1650  $cm^{-1}$  diosphenol;  $\lambda$  max. 270 n.m.  $\epsilon$  10,000; upon addition of one drop of 0.1 N NaOH,  $\lambda$  max.

310 n.m.  $\epsilon$  6000; n.m.r. signals 5.45 (1H,m, 11-H); 6.0 (broad peak hydroxylic proton); 6.55 (1H,s, 1-H).

A correct C,H analysis was not obtained but the structure is supported by infrared, ultraviolet, n.m.r. data, and mass spectral data M 440. It is further supported by conversion of carboxylic acid 89 and ene-one 90, both of which have the correct C,H analysis.

(ii) Benzilic Rearrangement of Diosphenol 88 to 89  
A nor lanost-9(11)-ene-3-hydroxy-3-carboxylic acid

Diosphenol 88 (2.1 g.) was added to a solution of sodium (1 g.) in absolute ethanol (200 c.c.) and the solution was refluxed overnight in an atmosphere of nitrogen. The solution was concentrated at atmospheric pressure to 50 c.c. and 150 c.c. of H<sub>2</sub>O was added. To the resulting yellow solution, 2NHCl was added dropwise until a tan powder precipitated. An additional 10 c.c. of 2NHCl was added and the mixture was allowed to cool to room temperature. The solid was filtered, washed to neutrality with water (washings neutral to litmus) and air dried to give a tan coloured powder.  
m.p. 284-286°C. (decomp.);  $\nu$  max. 3545 cm.<sup>-1</sup> (2

hydroxyl);  $1710\text{ cm.}^{-1}$  (2 carboxyl).

Anal. calc'd for  $\text{C}_{30}\text{H}_{50}\text{O}_3$  : C, 78.50; H, 10.9.

Found : C, 78.75; H, 11.26.

(iii) Oxidation of acid 89 to A norlanost-9(11)-ene-2-one 90

A solution of acid 89 (2.1 g.) in acetic acid (90 c.c.) and chloroform (190 c.c.) was treated with lead tetraacetate (3.5 g.) and stirred overnight at room temperature. Ethylene glycol was added (14 c.c.) to destroy the excess oxidant. The organic solvents were concentrated on a water aspirator. Water (200 c.c.) was added and the mixture was extracted twice with ether. The ether layer was washed with sodium bicarbonate, dried over sodium sulphate and evaporated to dryness to give 2.1 g. of yellow crystals. The solid was adsorbed on activity III alumina and eluted with hexane to give 1.3 g. of colourless needles. m.p.  $133\text{-}134^\circ\text{C}$ .  $[\alpha]_D^{20} +170$ ;  $\nu_{\text{max}}$   $1735\text{ cm.}^{-1}$  (2 ketone); n.m.r. signals 5.8 (1H, t, 11-H).

Anal. calc'd for  $\text{C}_{29}\text{H}_{44}\text{O}$  : C, 84.44; H, 11.71.

Found : C, 84.50; H, 11.44.

Epoxidation of 90 to epoxide 91

A solution of olefin 90 (1 g.) in chloroform (80 c.c.) was treated with m-chloroperoxybenzoic acid (400 mg.) and chilled at 5°C. for 24 hours. At this time, thin layer chromatography indicated only 50% reaction, therefore an additional 400 mg. of m-chloroperoxybenzoic acid was added and the reaction chilled an additional 24 hours. Thin layer chromatography indicated completion of reaction. The chloroform solution was washed three times with an aqueous solution of sodium sulphite (10%) followed by two washings with saturated aqueous sodium bicarbonate and one washing with saturated sodium chloride. The organic solution was dried over sodium sulphate and evaporated to dryness to give 980 mg. of colourless solid. Recrystallization from ethanol gave 721 mg. of colourless needles. m.p. 156-158°C.,  $[\alpha]_D +108$ ;  $\nu$  max. 1735  $\text{cm}^{-1}$  (2 ketone); n.m.r. signals 3.95 (1H, d, 11-H). The structure is supported by mass spectral data M 428.

Rearrangement of Epoxide 91

A solution of epoxide 91 (660 mg.) in benzene (10 c.c.) was saturated with  $\text{BF}_3$  gas. A yellow-brown gel precipitated. After one hour, sufficient ether was added to dissolve the gel. The organic solution was then washed with saturated aqueous sodium bicarbonate, dried over sodium sulphate and evaporated to dryness to give 585 mg. of an oily solid. The entire crop was chromatographed on 25 grams of activity III alumina. The chromatograph was followed by thin layer chromatography and the appropriate fractions were combined to give two different compounds. The more polar crystalline fraction was 50% of the yield (285 mg.), 93. m.p. 191-193°C.,  $[\alpha]_D^{+149}$ ;  $\nu$  max. 1730  $\text{cm}^{-1}$  (2 ketone); 1710  $\text{cm}^{-1}$  (11 ketone); n.m.r. signals - no distinctive signals above 3.

M (mass spectral) 428.

Synthesis of andrenost-4,9(11)-diene-3-one-11 $\beta$ -ol

Compound 110 was synthesized from andrenost-4,9(11)-diene-3,17-dione following a procedure developed by Heyl and Herr.(51)

A saturated solution of andrenost-4,9(11)-diene-3,17-dione (5 g.) refluxing methanol was treated with pyrrolidine (2 c.c.). The clear solution turned brown; it was immediately removed from the steam bath and allowed to cool to room temperature. Long yellow crystals precipitated. n.m.r. signals, 0.77 (3H,s,19 methyl), 1.35 (3H,s,18 methyl), 3.15 (8H-multiplet-pyrrolidin cyclopentane), 4.8 (1H,s,4-H), 5.1 (1H,m,6-H), 5.55 (1H,m,11-H). This compound was unstable and decomposed if dried by suction. The compound was air dried on filter paper and used immediately in the next step. 1.1 grams of enamine 108 were dissolved in 400 ml. of tetrahydrofuran, freshly distilled from lithium aluminium hydride. To the yellow solution, 2.3 g. of  $\text{LiAlH}_4$  was added in several portions. The mixture was stirred mechanically for one and a half hours. A saturated solution of rochelle salt was

then slowly added until a clear two-phase system was obtained. The organic and aqueous layer were separated. The aqueous layer was extracted twice with ether, the ether washings being added to the tetrahydrofuran layer. The combined organic phase was washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulphate and evaporated to dryness to give a yellow oil which crystallized as rosettes (3.8 g.). The compound was not further purified but was used directly in the next step.

Enamine 109 (3.8 g.) was dissolved in a solution containing sodium acetate (9 g.) in methanol (120 c.c.) and acetic acid (5 c.c.) and water (10 c.c.). The yellow solution was refluxed for four hours and approximately 80 c.c. of methanol were then distilled. While the methanol was still boiling, water was slowly added until the clear solution became cloudy. The cloudy mixture cooled to room temperature and yellow plates precipitated. These were filtered to give 2.8 g. of crystalline material. The solid was

adsorbed on silica gel (150 g.) and eluted with benzene containing progressively larger amounts of ethyl acetate. The fraction eluted with 1:1 ethyl acetate benzene was recrystallized from acetone to give 1.5 g. of 110. m.p. 157-159°C.

$\nu$  max. 3600, 3450  $\text{cm}^{-1}$  (17 hydroxy1), 1669, 1610  $\text{cm}^{-1}$  ( $\Delta^4$ , 3 ketone);  $\lambda$  max. 238 n.m. 25,100; n.m.r. signals, 0.75 (3H,s, 19 methyl), 1.45 (3H,s, 18 methyl), 3.76 (1H,m, 17 aH), 5.55 (1H,m, 11-H), 5.77 (1H,s, 4-H).

Anal. calc'd for  $\text{C}_{19}\text{H}_{26}\text{O}_2$  : C, 79.75; H, 9.1.  
Found : C, 79.98; H, 9.15.

Epoxidation of andrenost-4,9(11)-diene-3-one-17 $\beta$ -ol  
110 to Epoxide 111

A solution of keto alcohol (4.2 g.) in chloroform (120 c.c.) was treated with m-chloroperoxybenzoic acid and chilled for 48 hours at 5°C. The solution was washed twice with aqueous sodium sulphite (10%), twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with sodium sulphate and evaporated to dryness. It was then recrystallized

from a concentrated acetone solution to give 3.8 g. of colourless clusters. An analytical sample was obtained by repeated crystallizations from benzene. m.p. 176.5-178°C.,  $\nu_{\max}$ . 3600, 3450  $\text{cm}^{-1}$  (17 hydroxyl), 1670, 1620  $\text{cm}^{-1}$  ( $\Delta^4$ , 3 ketone);  $\lambda_{\max}$ . 238 n.m.  $\epsilon=26,800$ ; n.m.r. signals, 0.78 (3H,s, 19 methyl), 1.45 (3H,s, 19 methyl), 3.21 (1H,d, 11-H), 3.65 (1H, broad triplet, 17 $\beta$ H), 5.81 (1H,s, 4-H).

Anal. calc'd for  $\text{C}_{19}\text{H}_{26}\text{O}_3$  : C, 73.05; H, 8.39. Found : (two sets of analysis) : C, 66.37; H, 8.72. C, 75.47; H, 8.58.

The structure is supported by i.r., u.v., n.m.r. data, and mass spectral data; M (mass spectral) 302; and by its conversion into compounds 113 and 114, both of which have correct C,H analysis.

Synthesis of 4,4 dimethyl androst-5-ene-9 $\alpha$ 11 $\alpha$ -epoxy-3-one-17 $\beta$ -ol 112

Potassium (185 mg.) was dissolved in t butyl alcohol (75 c.c.) and swept with anhydrous nitrogen. Epoxide 110 (450 mg.) was added to this solution in one portion and the mixture was stirred until the solid dissolved. After an additional fifteen minutes,

the solution was chilled in an ice bath and methyl iodide (0.6 c.c.) was added. The ice bath was removed after one hour and the temperature of the reaction mixture was allowed to rise to room temperature overnight. Ether and water were then added and the phases were separated; the aqueous phase was extracted with ether twice, the ether extracts combined with the original organic layer. The ether extracts were then washed three times with water, dried with anhydrous sodium sulphate and evaporated to dryness. Recrystallization with acetone gave 167 mg. (26%) of colourless rosettes. An analytical sample was recrystallized from benzene. m.p. 189-192°C.,  $[\alpha]_D -18.2$ ;  $\nu_{\max}$ . 3600, 3450  $\text{cm}^{-1}$  (17 $\beta$  hydroxyl), 1705  $\text{cm}^{-1}$  (3 ketone), 1650  $\text{cm}^{-1}$  ( $\Delta^5$ ); n.m.r. signals 0.77 (3H, s, 19 methyl), 1.2 (3H, s, 18 methyl), 1.25 (6H, s, 4,4 dimethyl group), 3.25 (1H, d, 11-H), 3.65 (1H, broad triplet, 17 $\alpha$ -H), 5.68 (1H, broadened triplet, 6-H).

Anal. calc'd for  $\text{C}_{21}\text{H}_{30}\text{O}_3$  : C, 76.32; H, 9.15.  
 Found : C, 77.55; H, 8.85. C, 75.55; H, 9.45.

The structure is supported by i.r., u.v., n.m.r. data, and mass spectral data; M (mass spectral) 330;

and by its conversion into compounds 113 and 114, both of which have correct C,H analysis.

Oxidation of 112. Synthesis of 4,4 dimethyl andrenost-5-ene-9 $\alpha$ 11 $\alpha$ -epoxy-3,17-dione 113

Keto alcohol 112 (500 mg.) was dissolved in acetone (20 c.c.) and chilled in an ice bath. Sufficient Jones reagent was added to maintain a red colour. After fifteen minutes, methanol was added to destroy oxidant, followed with sufficient water to dissolve solid chromous salts. The acetone was distilled and the aqueous mixture extracted twice with ether. The ether layer was washed with a saturated solution of sodium bicarbonate, dried with sodium sulphate and evaporated to dryness. The solid was adsorbed on 20 g. of silica gel, and eluted with benzene containing methylene chloride (4/1) to give 481 mg. of colourless rosettes. An analytical sample was prepared from hexane. m.p. 175-176°C.,  $[\alpha]_D^{25} +28.4$ ;  $\nu$  max. 1740  $\text{cm}^{-1}$  (17 ketone), 1710  $\text{cm}^{-1}$  (3 ketone), 1650 ( $\Delta^5$ ); n.m.r. signals 0.93 (3H,s, 19 methyl), 1.2 (3H,s, 18 methyl), 1.25 (6H,s, 4,4 dimethyl), 3.28 (1H,t, 11-H), 5.72 (1H,d, 6-H).

Anal. calc'd for  $C_{21}H_{28}O_3$  : C, 76.79; H, 8.59.

Found : C, 76.57; H, 8.49.

Rearrangement of 4,4 dimethyl andrenost-5-ene-9 $\alpha$ 11 $\alpha$ -epoxy-3-17-dione

A solution of epoxide 113 (150 mg.) in anhydrous benzene (5 c.c.) was saturated with gaseous  $BF_3$ . A pale orange gel precipitated. After one hour, the gel had turned purple and thin layer analysis indicated that the reaction had gone to completion with only one product being formed. After the usual work-up, crystalline solid was obtained (144 mg.). Recrystallization from benzene afforded 79 mg. of colourless needles. m.p. 196-199°C. (decomp.);  $[\alpha]_D^{25} +94$ ;  $\nu$  max. 3610  $cm^{-1}$ , 3480  $cm^{-1}$  (11 $\alpha$  hydroxyl), 1735  $cm^{-1}$  (17 ketone), 1711  $cm^{-1}$  (3 ketone);  $\lambda$  max. 235 n.m.  $\epsilon$ 6150; n.m.r. signals, 0.9 (3H,s, 9 $\beta$  methyl), 1.09, 1.1 (total 9H, s, 18 and 4,4 dimethyl), 2.7 (d, J=4), 2.90 (d, J=4), 3.09 (d, J=4), 3.31 (J=4), (relative intensities 2:5:5:2, total intensity of the multiplet 1 proton), 3.84 (1H, 5 line m-11 $\beta$ H), 6.5 (1H, broadened triplet, 1-H), 5.55 (1H,m, 6-H).

Anal. calc'd for  $C_{21}H_{28}O_3$  : C, 76.79; H, 8.59.  
Found : C, 76.51; H, 8.42.

Reaction of keto alcohol 114 with base

A solution of keto alcohol 114 (30 mg.) in ethanol (25 c.c.) was swept with anhydrous nitrogen and 0.1 c.c. of 0.5 N NaOH was added. The solution was stirred under anhydrous nitrogen for two hours. During this time the solution turned yellow. An aliquot was removed and used in an ultraviolet determination. The ultraviolet spectrum indicated no reaction had taken place as the spectrum was identical to that of the starting material. An additional 0.1 c.c. of 0.5 N NaOH was added and the reaction was allowed to proceed for two more hours. Again no reaction could be detected by ultraviolet or by t.l.c. An additional 1 c.c. of 0.5 N NaOH was added and the reaction was allowed to proceed overnight. An aliquot was removed for ultraviolet spectrum. There was no ultraviolet absorption, indicating that a reaction had taken place. This result was confirmed by t.l.c. which also showed formation of only one product.

Water was added to the solution and the ethanol was evaporated on the rotary evaporator. The aqueous mixture was extracted with ether. The ether solution was dried and the ether was evaporated to give 25 mg. of an oil. Trituration with hexane resulted in yellow crystals.  $\nu$  max. 1730  $\text{cm}^{-1}$  (17 ketone), 1710 (3 ketone); n.m.r. signals 8.3 (3H,s.), 1.055 (3H,s.), 1.065 (3H,s.), 1.3 (3H,s.), 2.85 (d, J=6cps), 3.05 (d, J=6cps), 4.115 (1H,d, J=6cps), 4.475 (d, J=6cps). M (mass spectral) 328.

#### Oxidation of Rearrangement Product

Alcohol 113 (45 mg.) was dissolved in acetone (10 c.c.) and chilled in an ice bath. Sufficient Jones reagent was added to maintain a red colouration. After an additional fifteen minutes, sufficient methanol was added to destroy the excess oxygen, followed by water to dissolve the chromous salts. Following the usual work-up, 45 mg. of yellow rosettes were obtained. Recrystallization from ethanol gave pale yellow rosettes (5 mg.). m.p. 185-187°C.,  $[\alpha]_D^{25} +195$ .

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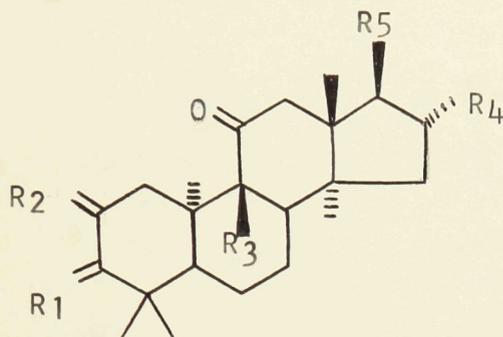
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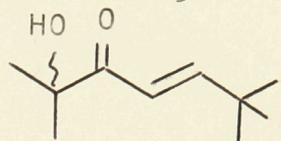
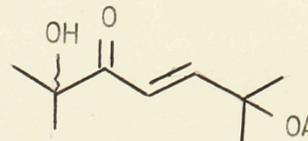
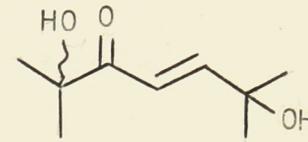
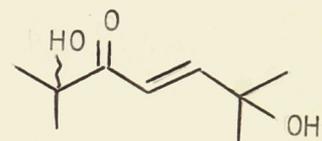
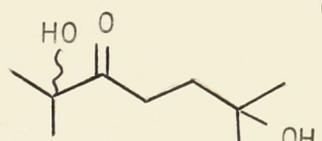
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## APPENDIX I

Cucurbitacins

<u>NAME</u>	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>
Bryogenin Aglycone 157	βOH	2H	CH <sub>3</sub>	4H	 (i)
Aglycone 178	βOH	2H	CH <sub>3</sub>	H	 (ii)
Cucurbit. A	=O	βOH	CH <sub>2</sub> OH	OAc	 (iii)
Cucurbit. B	=O	βOH	CH <sub>3</sub>	OH	 (iv)
Cucurbit. D	=O	βOH	CH <sub>3</sub>	OH	 (iv)

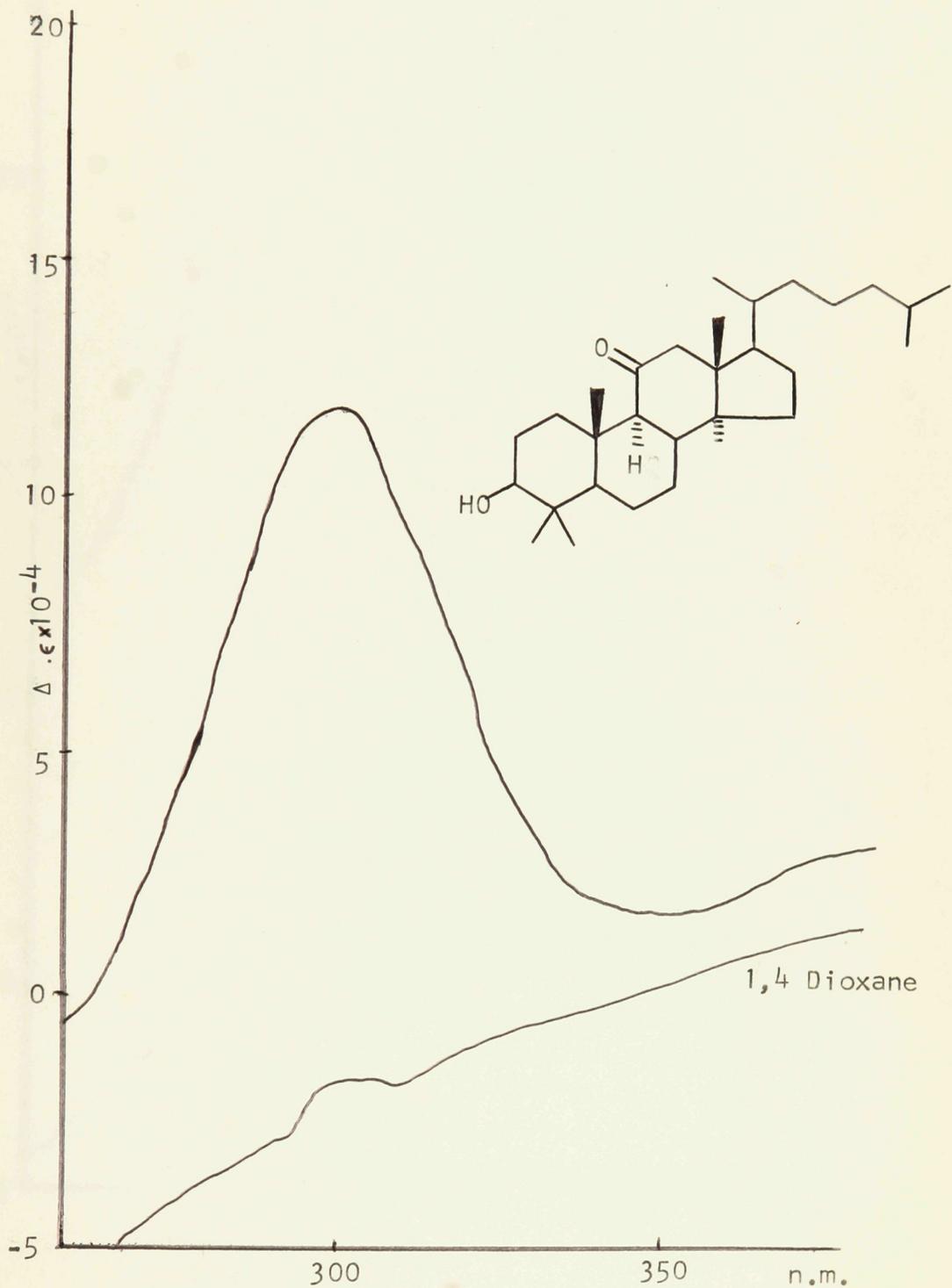
<u>NAME</u>	$R_1$	$R_2$	$R_3$	$R_4$	$R_5$	
Cucurbit. C	$\alpha\text{OH}$	2H	$\text{CH}_2\text{OH}$	OH		(v)
Cucurbit. E	=O	=O	$\text{CH}_3$	OH		(vi)
Cucurbit. I	=O	=O	$\text{CH}_3$	OH		(vi)
22 deoxo cuc. D	=O	$\beta\text{OH}$	$\text{CH}_3$	OH		(vii)
22 isodeoxo cuc. D	$\beta\text{OH}$	=O	$\text{CH}_3$	OH		(vii)

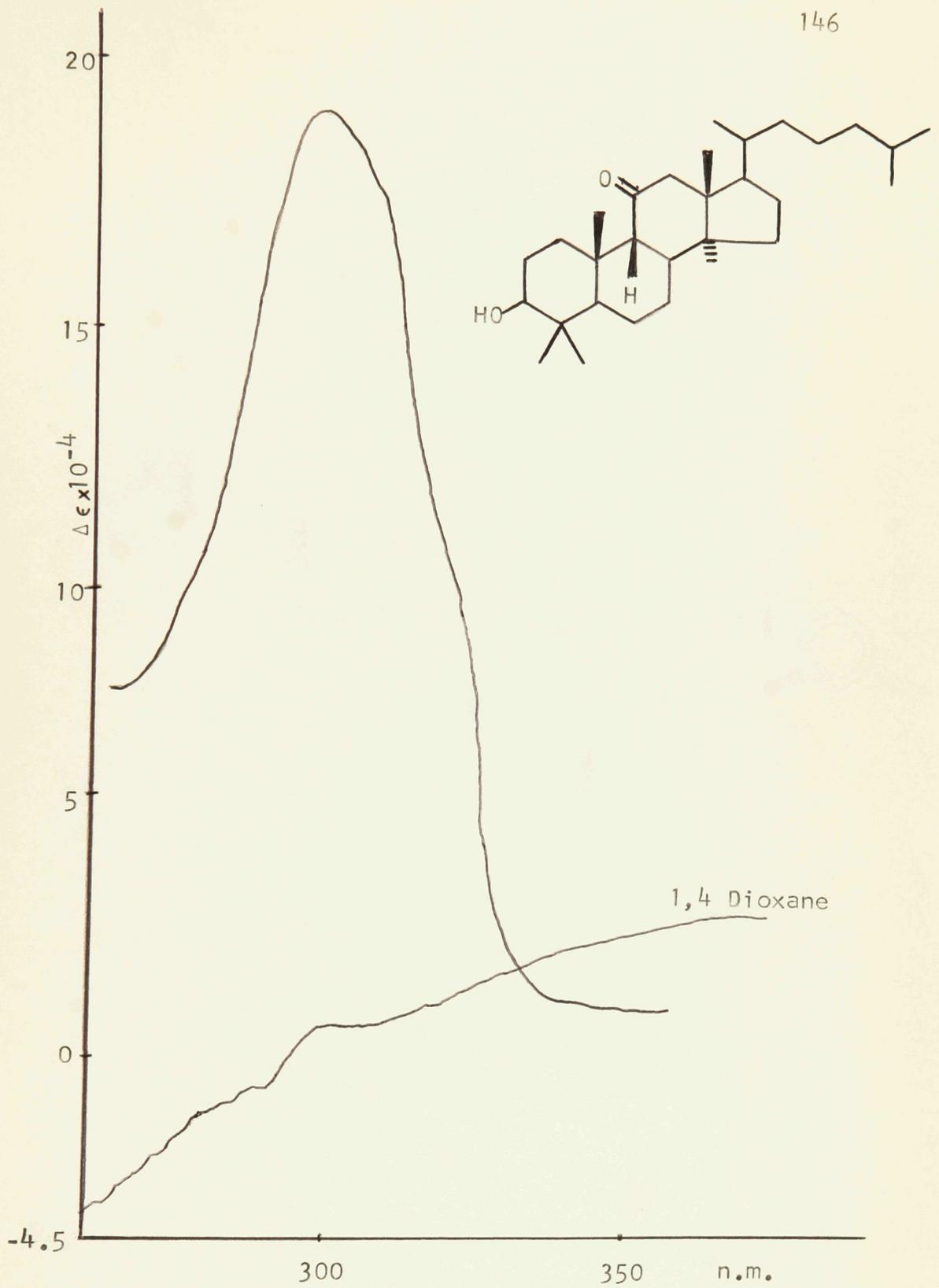
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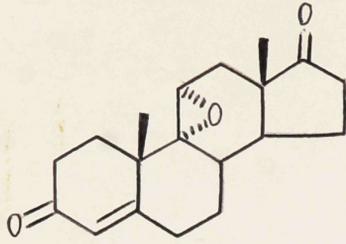
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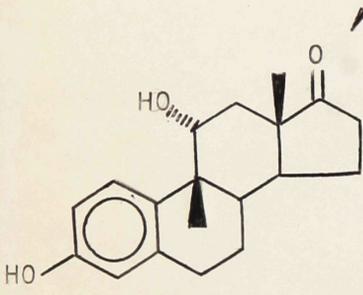
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 9 $\alpha$  and 9 $\beta$  Lanost-3 $\beta$ -ol-11-one



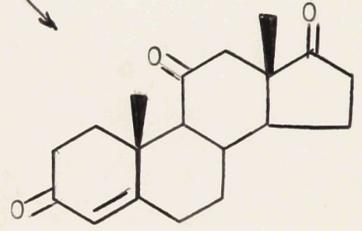




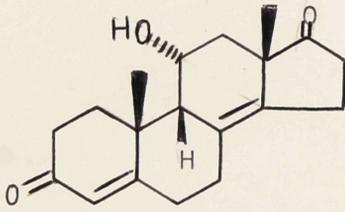
49



50



52



51

