Synthesis and Rearrangements of Alicyclic Systems

A Thesis Submitted to the Board of the Faculty of Physical Sciences in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in the University of Oxford

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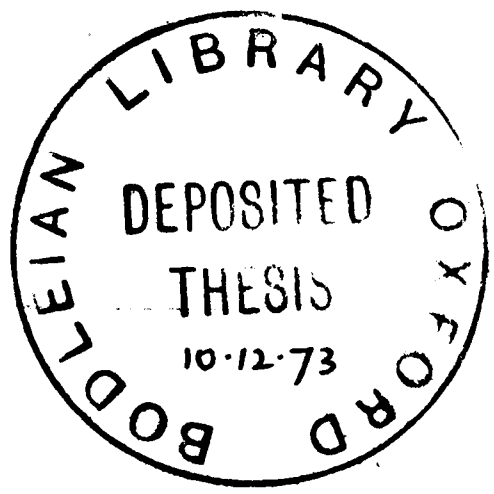
Oxford, October 1972

The Chemical Society
London, August 1973



Acknowledgements

I wish to thank Professor Sir Ewart Jones for the opportunity of undertaking this work in the Dyson Perrins Laboratory, and my supervisor Dr. T. G. Halsall for his advice and encouragement.

My thanks are due to the technical staff of the Laboratory, especially to Mrs. E. E. Richards and Mrs. J. R. Dixey for n.m.r. spectra, to Mrs. R. A. Foster for i.r. and u.v. spectra, to Dr. R. T. Aplin and David Perrin for mass spectra, and to Rodney Prior for the preparation of chromatography plates.

The gifts of 100g of β-C_{14}-aldehyde from Hoffmann-La Roche and Company and a large amount of octalyl benzoate from Dr. D. Willis are gratefully acknowledged, as is financial support from the Science Research Council.

I would like to commend Mrs. A. M. Biggs for typing this thesis so accurately, and lastly, I am indebted to my colleagues in the Robinson Laboratory, especially D. J. C., A. W. R.-T., R. L. S., and J. C. for their friendship, understanding, and co-operation.

P. J. McHale.

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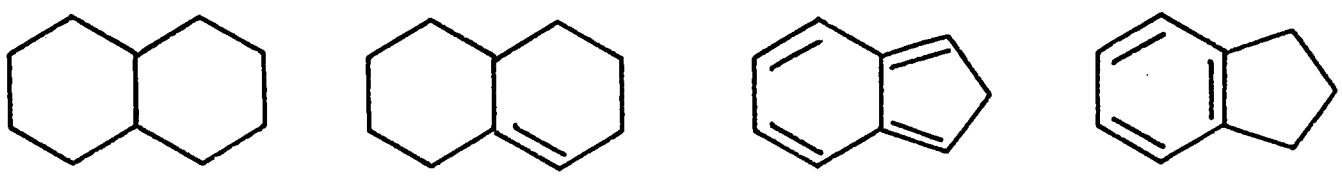
Nomenclature

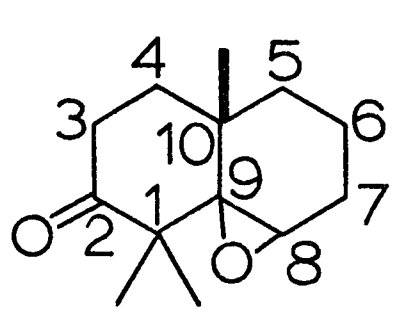
Compounds are named as far as possible in accordance with the I.U.P.A.C. Nomenclature Rules, but the names decalin (i) and octalin (ii) are retained for deca- and octa-hydronaphthalene (the position of unsaturation in an octalin being denoted by a Δ prefix). Other compounds used in this work are derived from 2H-indene (iii) and indane (iv).



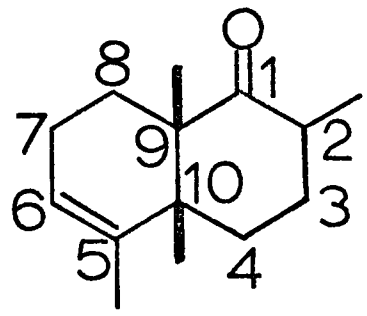
(i) (ii) $\Delta^{1(9)}$ (iii) (iv)

Numbering

Decalin derivatives are numbered according to the usual convention, with the numbering commencing at that carbon atom α to a ring junction which results in the lowest number for the principal group, e.g. (v) and (vi).

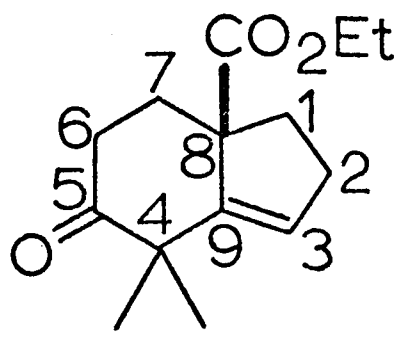


(v)



(vi)

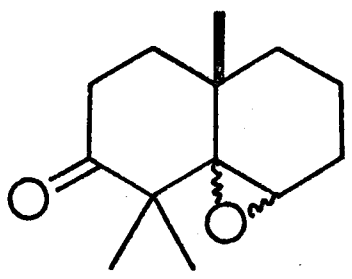
Indane derivatives are numbered similarly, with numbering commencing at an α position in the five- membered ring, e.g. (vii).



(vii)

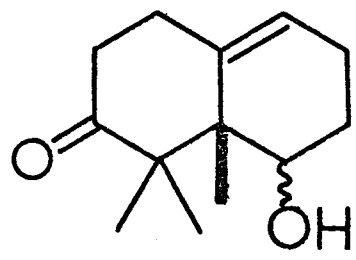
Stereochemistry.

The configural notations alpha (α) and beta (β) are used in the steroid sense, i.e. a β-substituent is cis to the angular group, and an α-substituent is trans. The notation xi (ξ) is used to denote a substituent of a single unknown stereochemistry. The three configurations are represented in structural formulae by α = ''''' , β = ▬ and ξ = ~~. Where two epoxides are obtained from one olefin, and their stereo-chemistries cannot be assigned with certainty, they are referred to as the ξ_1- and ξ_2-epoxides, where the subscripts 1 and 2 are assigned arbitrarily and do not have any stereochemical significance apart from being consistent with corresponding substituents in rearranged products; i.e. the ξ_1-epoxide (viii) rearranges to give a product containing a ξ_1-hydroxy-group (ix).



(viii)

$8\xi_1, 9\xi_1$-epoxide



(ix)

$8\xi_1$-alcohol

All the compounds prepared in this work are racemic and the prefix dl has been omitted, and only one enantiomer has been depicted in each of the structural formulae.

Abstract

This thesis is concerned with intramolecular rearrangements of epoxides of bicyclic systems: in the presence of acids, epoxides will cleave to generate electron deficient sites which can promote rearrangements involving intramolecular nucleophiles such as methyl groups with their bonding electrons, "hydride" ions, parts of the carbon skeleton, and the π -electrons of olefinic double bonds. The latter interaction leads to ring closure, and this is an important process in the biogenesis of many polycyclic natural products. The first part of chapter one of this thesis describes the role of epoxides in the biosynthesis of polyisoprenoids, with particular reference to the cyclisation of squalene 2,3-epoxide and other long chain polyolefin epoxides.

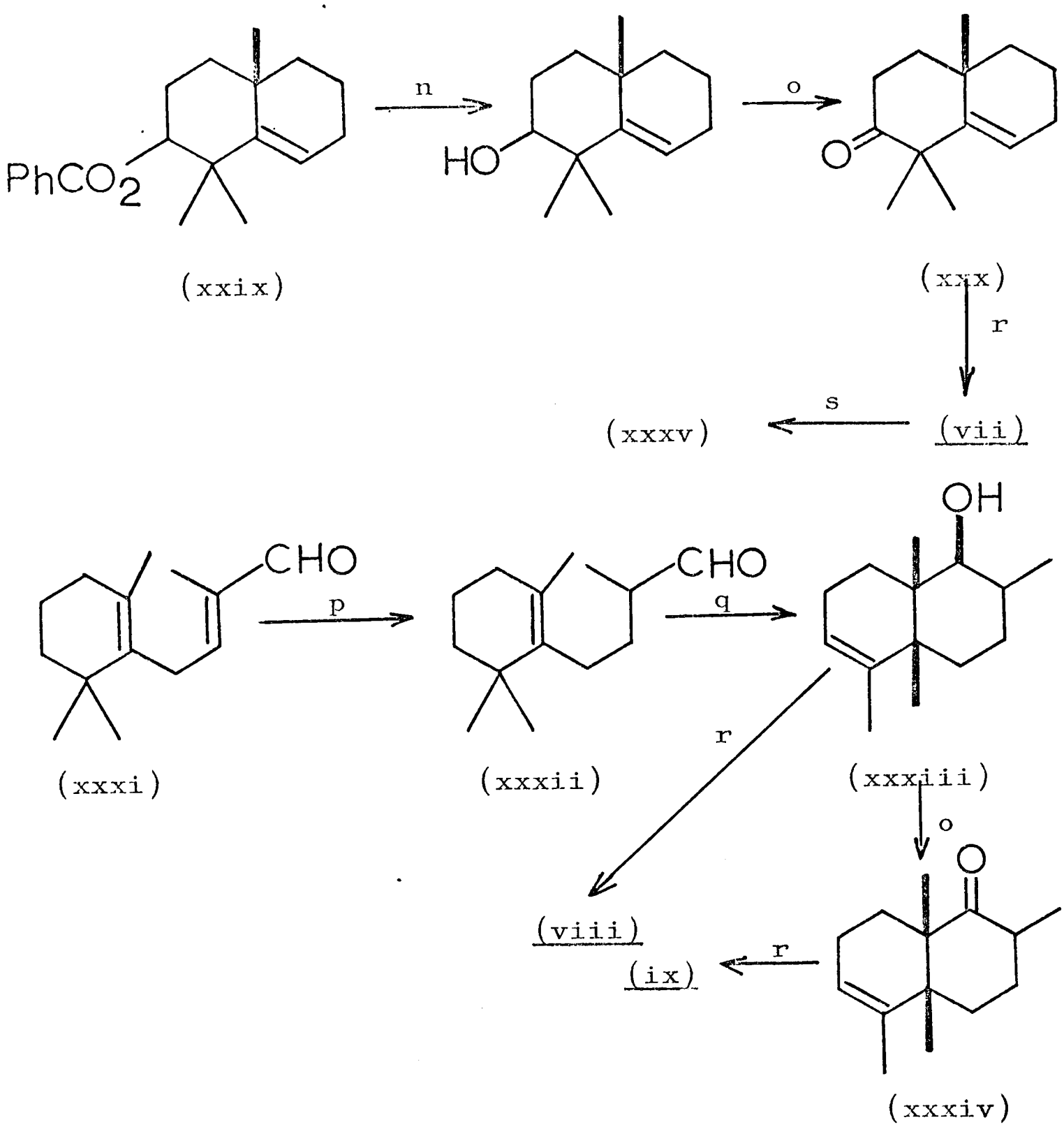
The second part of chapter one is concerned with Lewis acid catalysed rearrangements of epoxides of cyclic systems, particularly steroidal epoxides. Early workers[1] emphasised the formation of ketones by 1,2-shifts, and when using boron trifluoride as the Lewis acid, they often obtained diaxial fluorohydrins formed by direct attack of a fluorine species on the epoxide; rigorous purification of the reagent to remove fluoride reduces the occurrence of such side-reactions to a minimum. Other more polar rearrangement products tended to remain unidentified, but more recent work[2] has led to a reappraisal of earlier results, and these products have been largely identified; most are hydroxy-olefins formed from methyl and skeletal migrations.

The rearrangements of steroidal epoxides give a wide variety of products, which depend on the environment of the oxiran ring and the positions and nature of other substituents in the molecule. The products obtained can be rationalised to a certain extent by considering steric, electronic, and conformational factors; thus the direction of formation of ketones from tetrasubstitued epoxides can be predicted

by the "rule of axial cleavage", which envisages the epoxide rearrangement as proceeding without the development of a full carbonium ion, and retaining some internal S_N2 character in the transition state. Migrations in which the oxiran oxygen becomes a hydroxy-group do appear to proceed by a full carbonium ion; thus in some cases,[3] groups have migrated from a position originally cis to the C-O bond which cleaves, which must require totalC-O cleavage before migration can occur. Kinetic isotope studies[4] suggest that these rearrangements proceed by a rate determining formation of a set of rapidly interconverting carbonium ions, which collapse to the observed products, even when the migrating group is trans and antiparallel with the C-O bond which breaks and concerted cleavage and rearrangement might be possible.

The aim of the present work has been to synthesise a series of simple epoxides and to rearrange them with a Lewis acid with a view to correlating the course of the rearrangement with the nature of the functional groups present in the molecule. Epoxides of bicyclic systems were chosen as they would contain several potential migrating groups, without the possibility of back-bone rearrangements occurring, since these often complicate steroidal epoxide rearrangements; it was also thought that their rearrangements might yield novel and synthetically useful skeletons. A series of indan-epoxides (i)-(vi), and the trimethyldecalin-epoxides (vii) were synthesised and rearranged with boron trifluoride-ether complex in anhydrous benzene. The tetramethyldecalin epoxides (viii) and (ix) were also prepared from a readily available starting material to see whether their rearrangement would give the products (x) or (xi) which would be very useful ring (A + B) precursors in tri- and sesquiterpene synthesis.

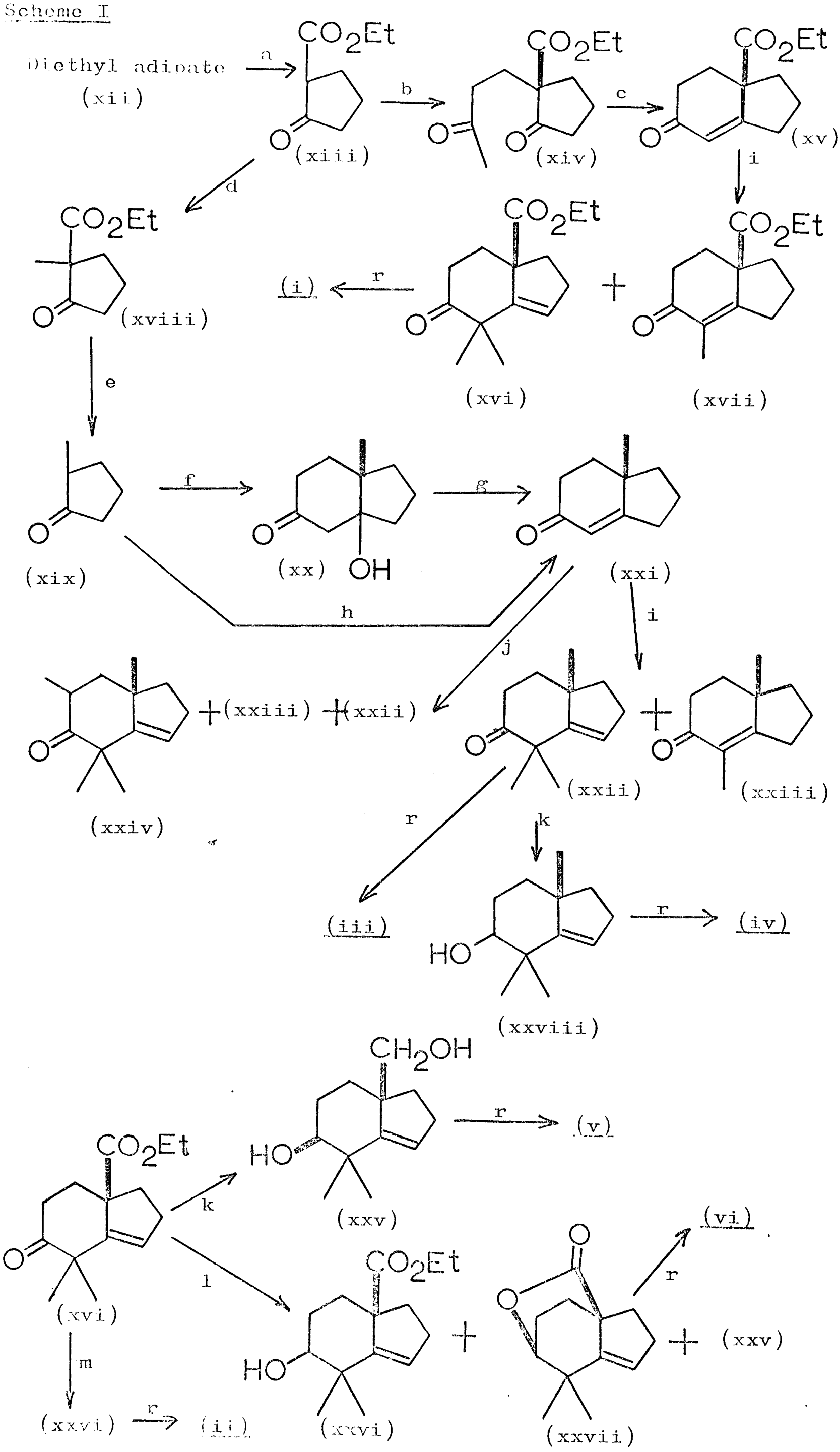
Scheme 1 (cont.)



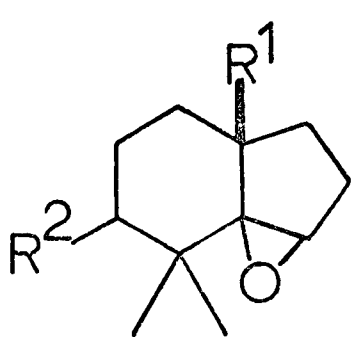
Reagents

a, Na/C_6H_6; b, $CH_3COCH{=}CH_2/NEt_3$; c, $Al(OBu^t)_3$; d, $Me_2SO_4/NaOH$; e, H_2SO_4(aq); f, $CH_3COCH{=}CH_2/NaOEt$, 0°; g, p-TsOH/C_6H_6; h, H_2SO_4(conc.)(cat.); i, $CH_3I/KOBu^t$; j, $CH_3I/KOAm^t$; k, $LiAlH_4$; l, xs. $NaBH_4$, 25°; m, $NaBH_4$, 0°; n, NaOH/EtOH; o, CrO_3/H_2SO_4; p, H_2/Pd-C; q, H_3PO_4; r, m-$ClC_6H_4CO_3H$ or p-$NO_2C_6H_4CO_3H$; s, $NH_2CONHNH_3Cl$/NaOAc

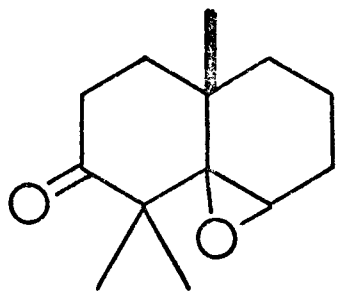
Scheme I


Diethyl adipate
(xii)
a
b
c
d
e
f
g
h
i
j
k
l
m
r
(xiii)
(xiv)
(xv)
(xviii)
(xvi)
(xvii)
(i)
(xix)
(xx)
OH
(xxi)
(xxiii)
(xxii)
(xxiv)
(xxiii)
(iii)
(iv)
(xxviii)
(v)
(xxv)
(vi)
(xxvi)
(ii)
(xxvii)
CO2Et
CH2OH
HO

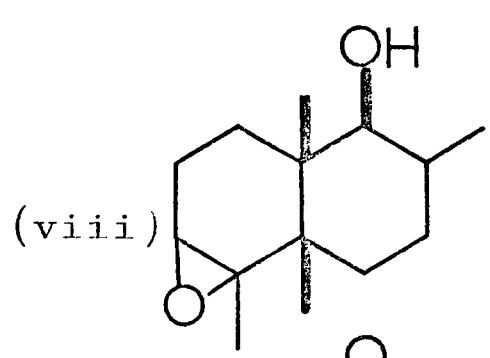
The syntheses of the model epoxides are outlined in Scheme 1. The indane systems were prepared by carrying out Robinson annelation reactions on 2-ethoxycarbonyl- and 2-methyl-cyclopentanone, and gem-dimethylation was effected by treatment with potassium t-butoxide in t-butanol, followed by methyl iodide. The use of potassium t-amyloxide under more vigorous conditions gave a greater yield of the trimethylated product (xxiv).



	R^1	R^2
(i)	$-CO_2Et$	=O
(ii)	$-CO_2Et$	-OH
(iii)	$-CH_3$	=O
(iv)	$-CH_3$	-OH
(v)	$-CH_2OH$	-OH
(vi)	$-R^1-R^2-$ = -CO-O-	



(vii)



(viii)

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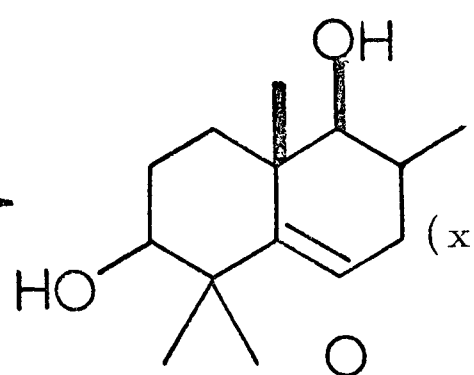
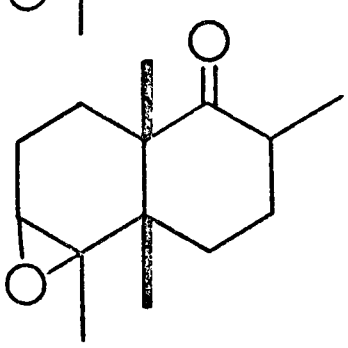
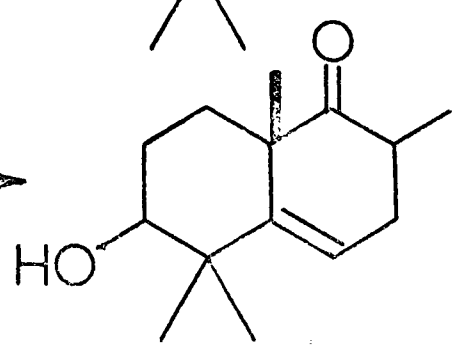


(x)



(ix)

?



(xi)

Reduction of keto-ester (xvi) with lithium aluminium hydride gave the diol (xxv), which was also obtained when an excess of sodium borohydride was used, along with the hydroxy-ester (xxvi) and the lactone (xxvii). The hydroxy-ester (xxvi) could be obtained as the only product by using a stoicheiometric amount of sodium borohydride at 0°.

Reduction of the methyl-indanone (xxii) with lithium aluminium hydride gave a mixture of the epimeric 5-alcohols (xxviii), which could not be separated.

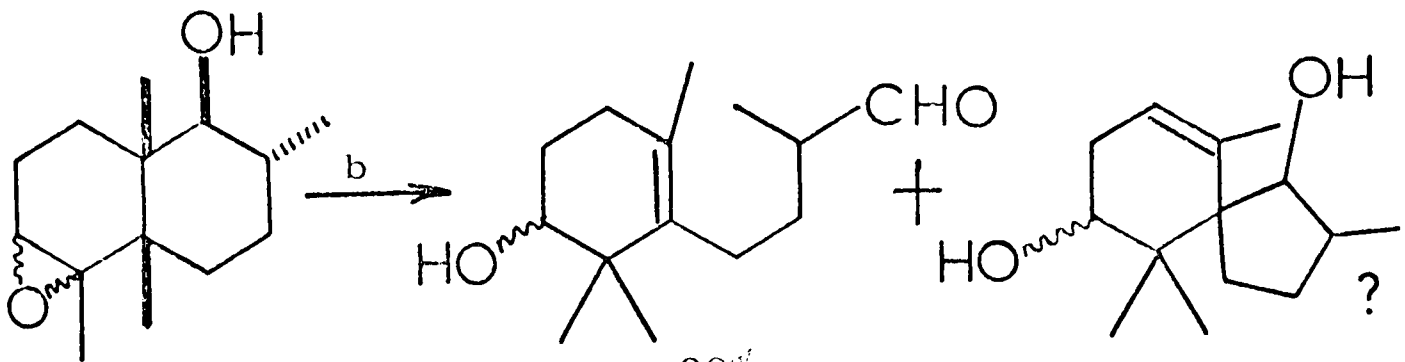
The octalone (xxx) was prepared by saponification and Jones oxidation of the benzoate of octalol (xxix), which was available in this laboratory.

The tetramethyloctalol (xxxiii) was prepared by the method of Ireland *et al.*[5] by treating luciferin aldehyde (xxxii) with phosphoric acid. The octalone (xxxiv) was obtained by Jones oxidation of octalol (xxxiii).

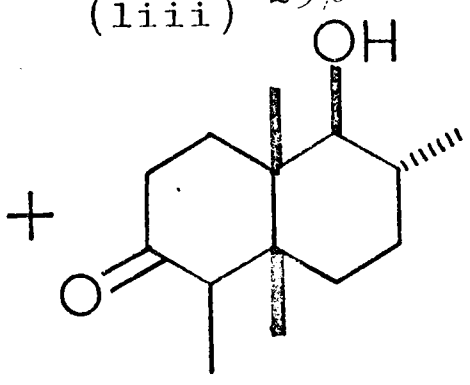
Epoxidation was effected by treatment of the appropriate olefin with either m-chloro- or p-nitro-perbenzoic acid, and usually gave a mixture of the α- and β-isomers, which were separated by p.l.c.; in one case (iii) separation was not possible, and in some cases, only one epoxide was formed. The stereochemistry of most of the epoxides could be tentatively assigned from the expected mode of attack of the peracid. Formation of one of the epoxides of keto-ester olefin (xvi) was accompanied by loss of equivalence of the ester methylene signals in the n.m.r. spectrum; the methylene signal in the other epoxide appeared as a simple quartet.

The stereochemistry of the lactone epoxide (vi) could not be assigned with certainty. The octalol (xxxiii) gave a single epoxide, which was probably the β-isomer, while the octalone (xxxiv) gave

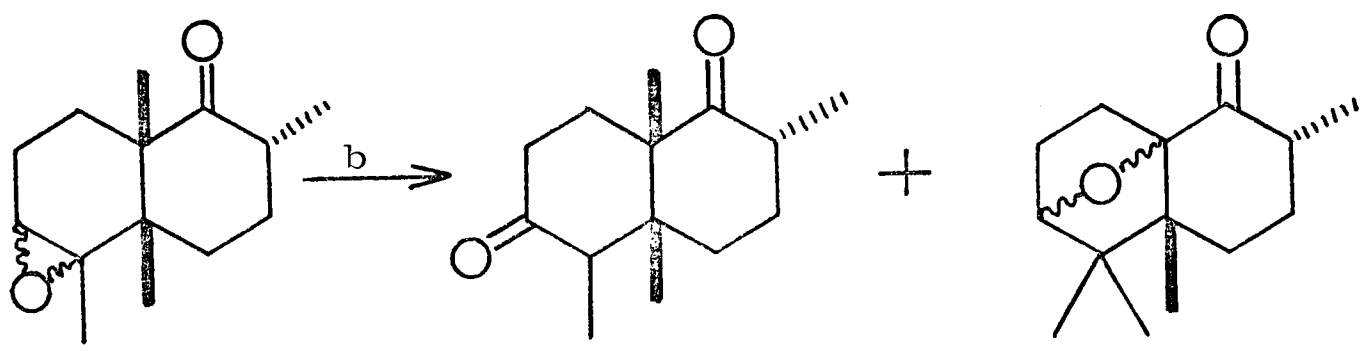
Scheme II (cont.)



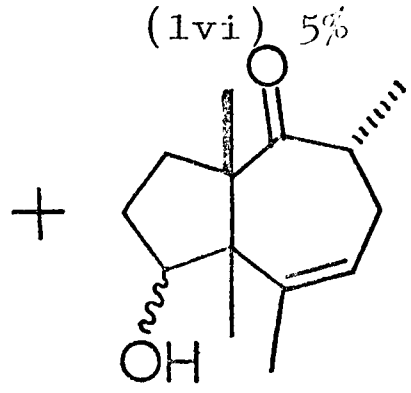
(viiia) (liii) 29% (liv) 21%



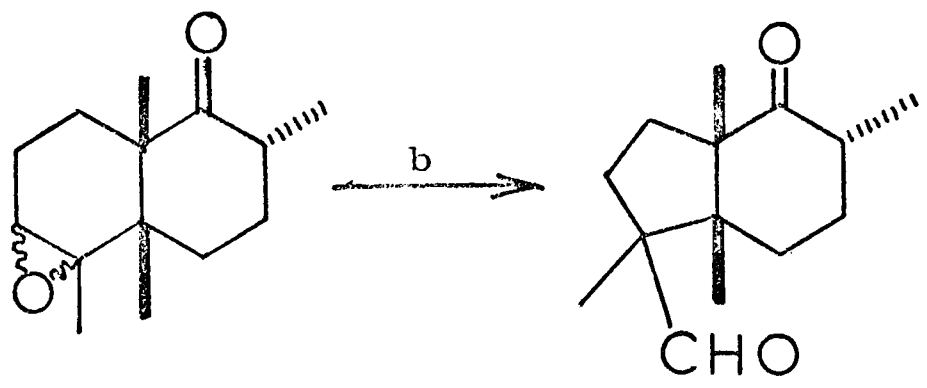
(lv) 29%



(ixa) (lvi) 5% (lvii) 24%



(lviii) 7%



(ixb) (lix) quant.

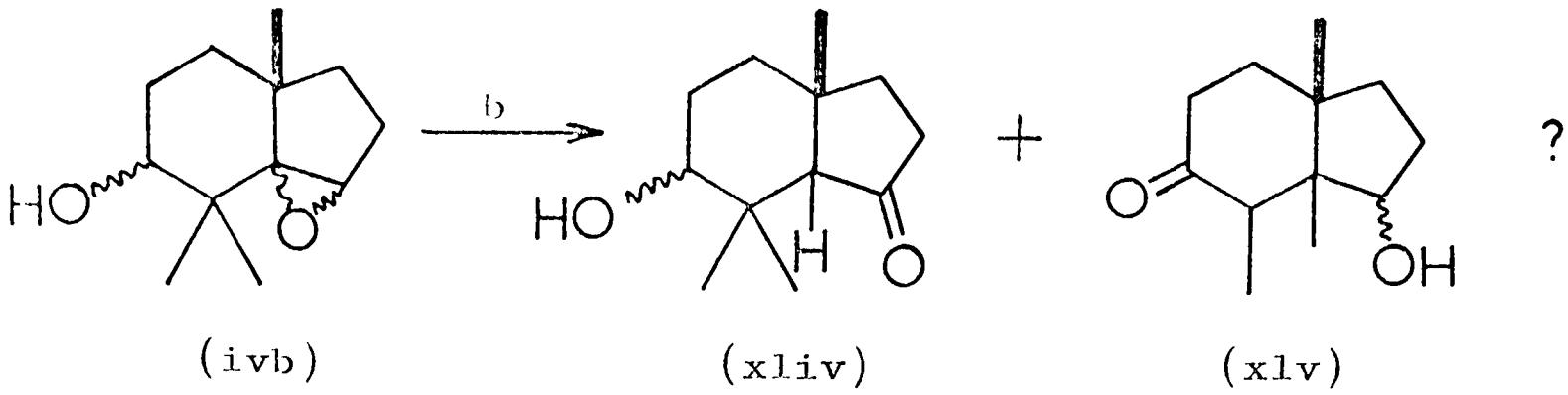
Reagents

a: (i) $BF_3.Et_2O/C_6H_6$, (ii) CH_2N_2

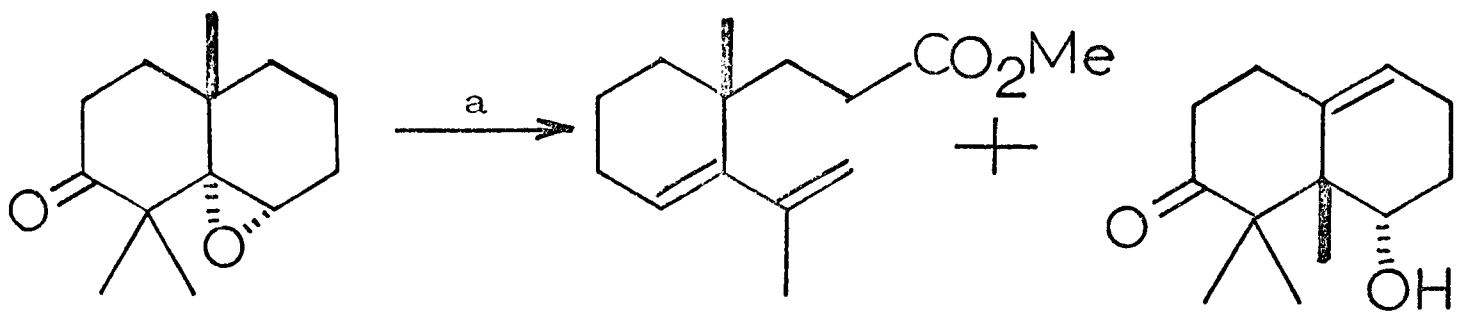
b: $BF_3.Et_2O/C_6H_6$

c: (i) $BF_3.Et_2O/C_6H_6$, (ii) CH_3COCO_2H

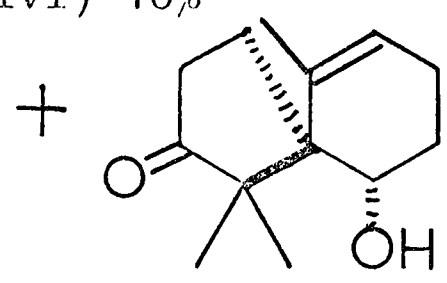
Scheme II (cont.)



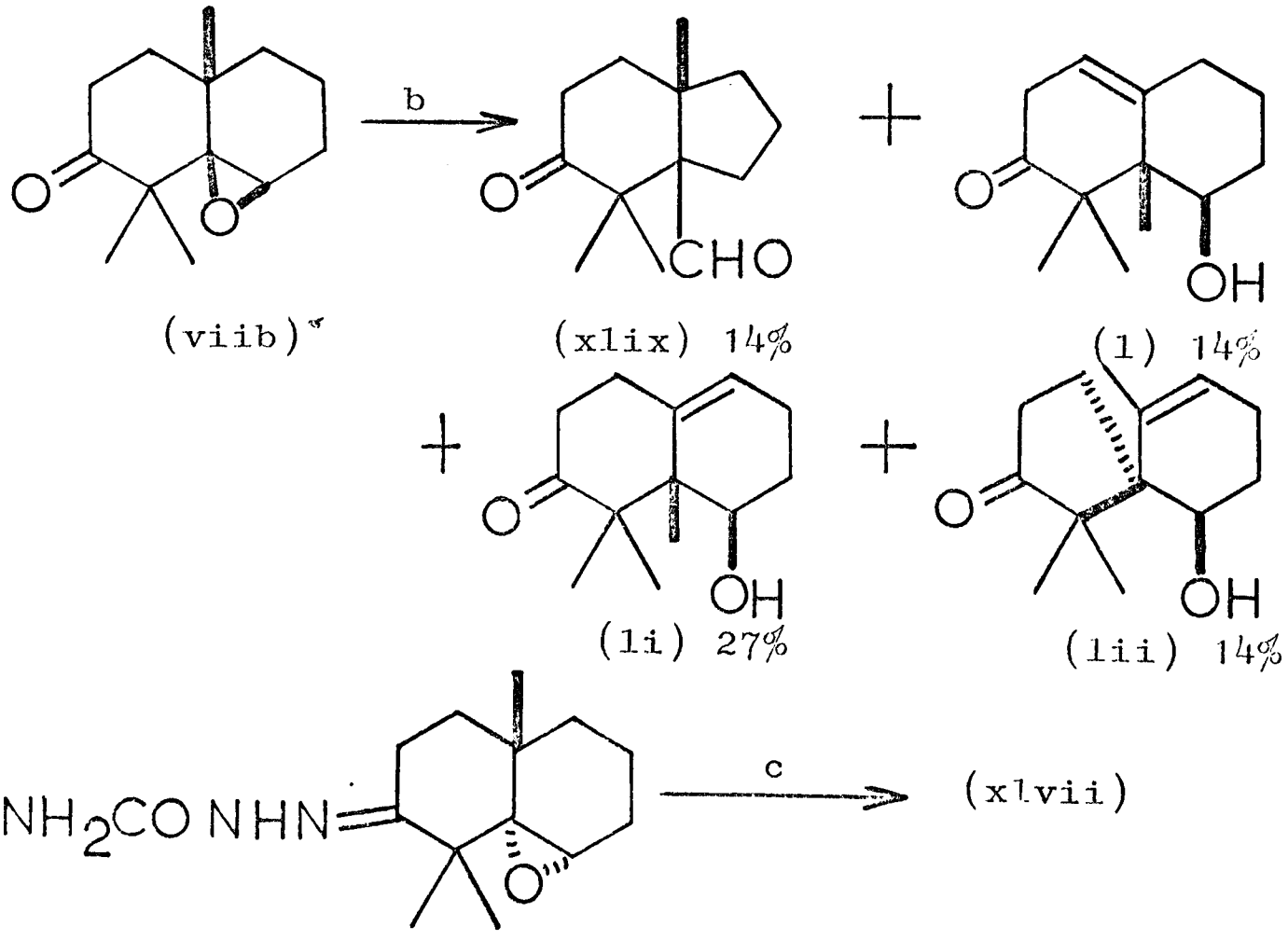
(ivb) (xliv) (xlv)



(viia) (xlvi) 10% (xlvii) 5%



(xlviii) 25%

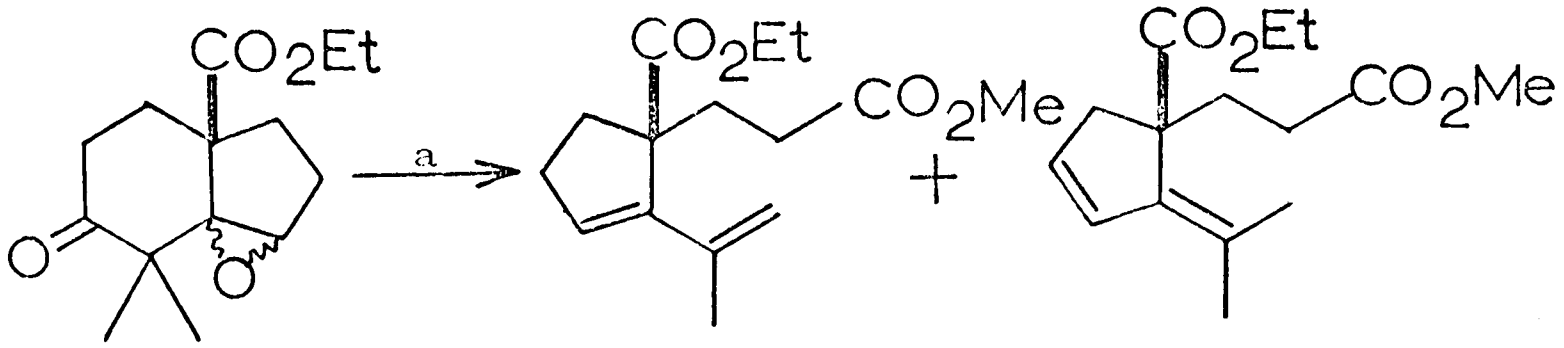


(viib) (xlix) 14% (l) 14%

(li) 27% (lii) 14%

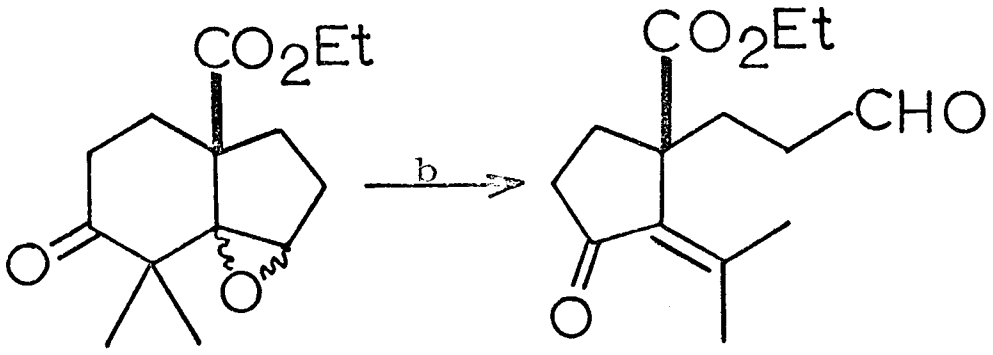
(xxxva) (xlvii)

Scheme II



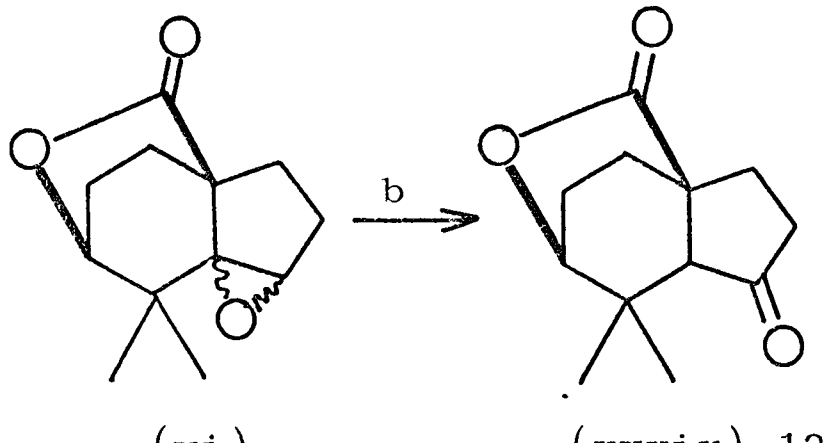
(ia) (xxxvi) 31% (xxxvii) 12%

+ (ia) 5%



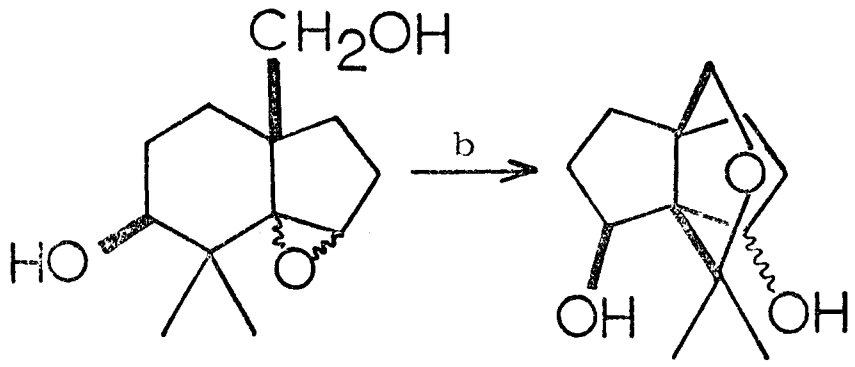
+ (ib) 36%

(ib) (xxxviii) 22%

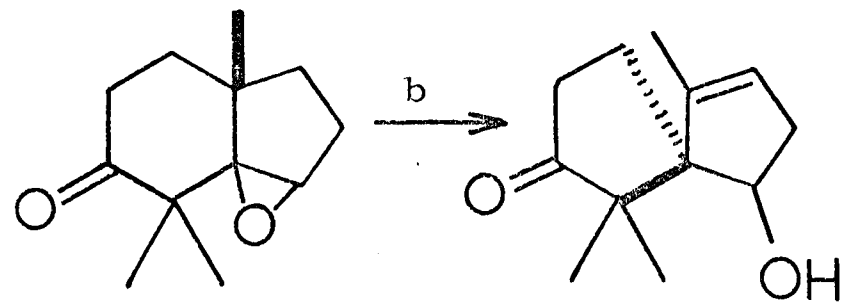


+ "unknown" 22% + (vi) 38%

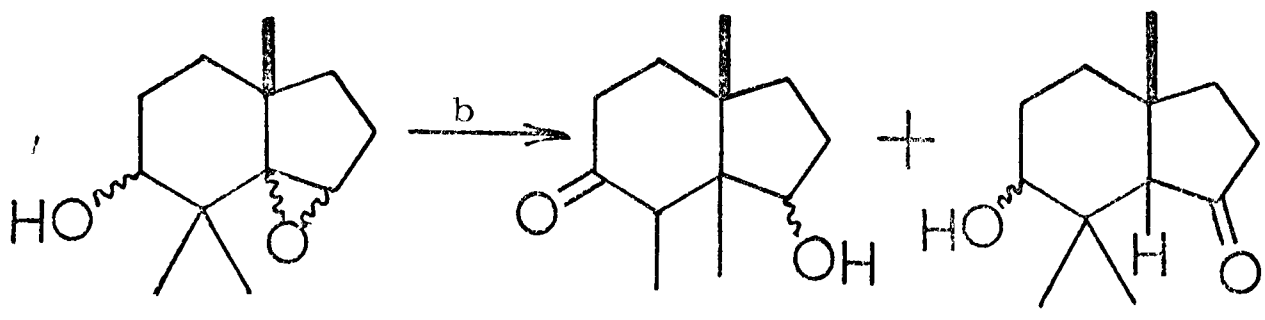
(vi) (xxxix) 12%



(v) (xl) 19%



(iii) (xli) 22%

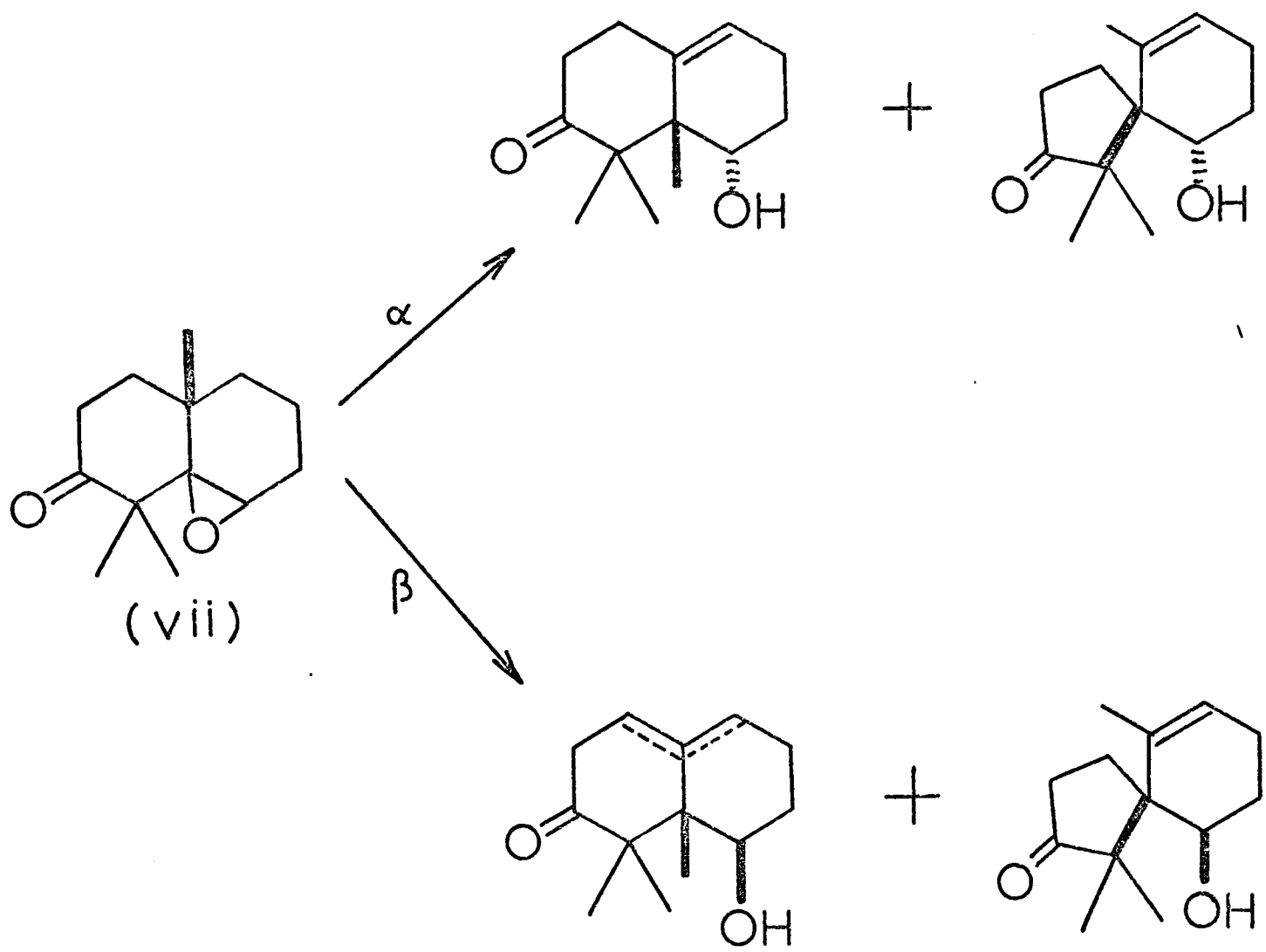


(iva) (xlii) (xlii)

two, and the former epoxide was correlated with the more abundant of the latter epoxides by oxidation with chromium trioxide in pyridine. The hydroxy—ester epoxides (ii) were unstable and converted to the lactone epoxides (vi) on standing. The decalone epoxides (viia) and (viib) were of known stereochemistry, having been previously prepared and characterised.

The results of the boron trifluoride catalysed rearrangements are shown in Scheme II. A wide variety of products was obtained, and some generalisations can be made: compared with the rearrangements of steroidal epoxides, rearrangements of bicyclic epoxides give more ring fragmentation reactions, and carbonyl forming reactions are not so common.

Most of the rearrangements which were terminated by dissipation of the positive charge at a site away from the oxiran ring and resulted in the oxiran oxygen becoming a hydroxy-group could be rationalised in terms of a mechanism proceeding through a fully developed carbonium ion; an analysis of conformational, electronic, and stereochemical factors indicates which groups are likely to migrate to the electron deficient site. Thus suitable migrating groups must lie parallel or nearly parallel to the axis of the empty p-orbital at the carbonium ion site; their migration should not develop positive charge at an unfavourable position e.g. α to an electron-withdrawing group; and their migration path should not be sterically impeded or lead to a sterically hindered structure. In the absence of other competing reactions, the relative epoxide geometry need not determine absolutely the course of the rearrangement; thus the decalone α-and β-epoxides (viia) and (viib) both gave products from the migration of the same suitably aligned groups,



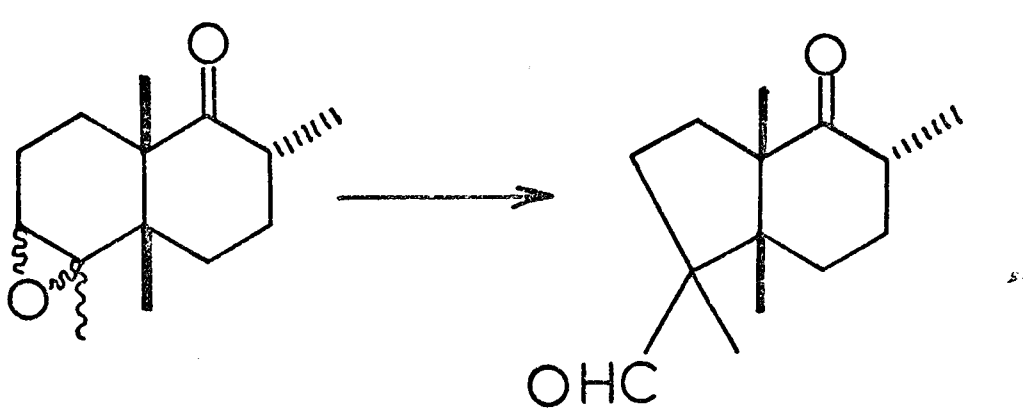
(vii)

although each epoxide did give one characteristic rearrangement not given by the other.

The directing effects of functional groups on these rearrangements are amenable to analysis: electron withdrawing groups e.g. $-CO_2Et$ tend to reduce reactivity and to retard development of a positive charge at an adjacent site; carbonyl groups have the same effect, but may become involved in the rearrangement by giving acyl migrations; hydroxy-groups do not have such a marked effect on the initial migrations which occur, but they can terminate the rearrangement by giving a fragmentation leading to an aldehyde (iii), or by "trapping" a suitable carbonium ion to give a cyclic ether (both of these reactions can also be given by the oxiran oxygen). In one case, this ring closure reaction gave a novel heterocyclic "propellane" (xl).

Rearrangements in which the oxiran oxygen became involved in a carbonyl group, with no migration of positive charge away from the oxiran site were not so amenable to analysis. If a full carbonium

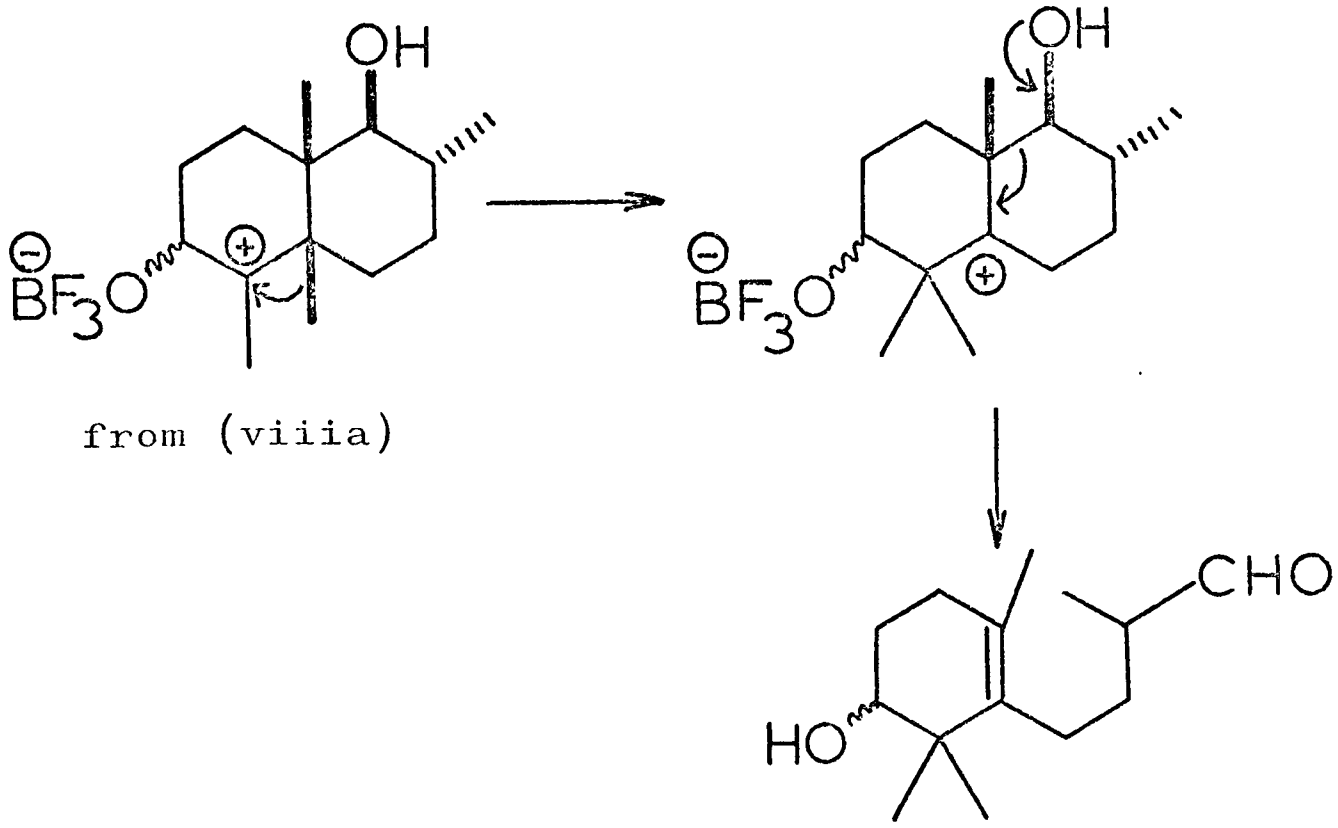
ion is involved, a conformational analysis of the groups in the carbonium ion can indicate which are suitably aligned to migrate to the positive site, but it is difficult to predict with any certainty when such migrations will or will not occur: thus the dedalone epoxide (ixb) gave a quantitative yield of the aldehyde (lix) from such a migration, although several other groups were suitably aligned to migrate to the positive site;



(ixb) (lix)

and conversely, although cleavage of the indane epoxides in general places the 3-hydrogen in a suitable position to migrate to C-9, such migrations were only found in a few cases; the reason for exclusive migration in the other sense is not obvious, but may imply that these rearrangements to give carbonyl species are fairly concerted.

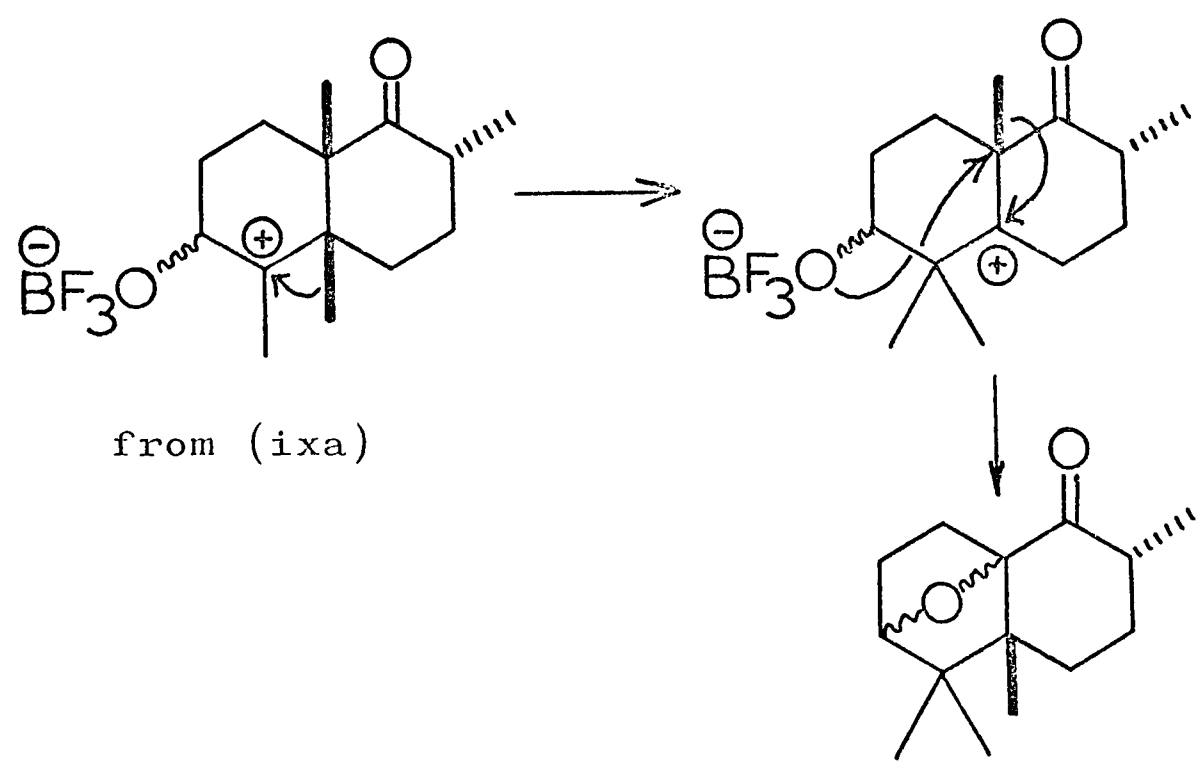
None of the three tetramethyl decalin epoxides rearranged to give the desired products. The decalol epoxide (viiia) gave one product (liii) in which the required methyl migration had occurred, but this had been followed by a fragmentation involving the hydroxy- group.



from (viiia)

(liii)

It was hoped that replacing the hydroxy-group by a keto-group would then lead to the desired product, but the major product from the decalone epoxide (ixa) gave a second methyl migration accompanied by ring closure to give a cyclic ether (lvii), and it seems likely that relatively highly



from (ixa)

(lvii)

substituted epoxides such as these will be prone to giving secondary migrations or fragmentations.

References

1. H.B. Henbest and T.I. Wrigley, J.Chem.Soc., 1957, 4596, 4765.

2. For recent reviews see D.N. Kirk in "Terpenoids and Steroids", ed. K.H. Overton, Specialist Periodical Report, The Chemical Society, London, Vol. 1, 1971, p.365; Vol. 2, 1972, p.306.

3. e.g. T.G. Halsall, Sir Ewart R.H. Jones, E.L. Tan, and G.H. Chaudhry, J.Chem.Soc. (C), 1966, 1374.

4. H.W. Whitlock and A.H. Olson, J.Amer.Chem.Soc., 1970, 92, 5383.

5. G. Saucy, R.E. Ireland, J. Bordner, and R.E. Dickerson, J.Org.Chem., 1971, 36, 1195.

CHAPTER 1.

Rearrangements of Epoxides

1. Introduction.

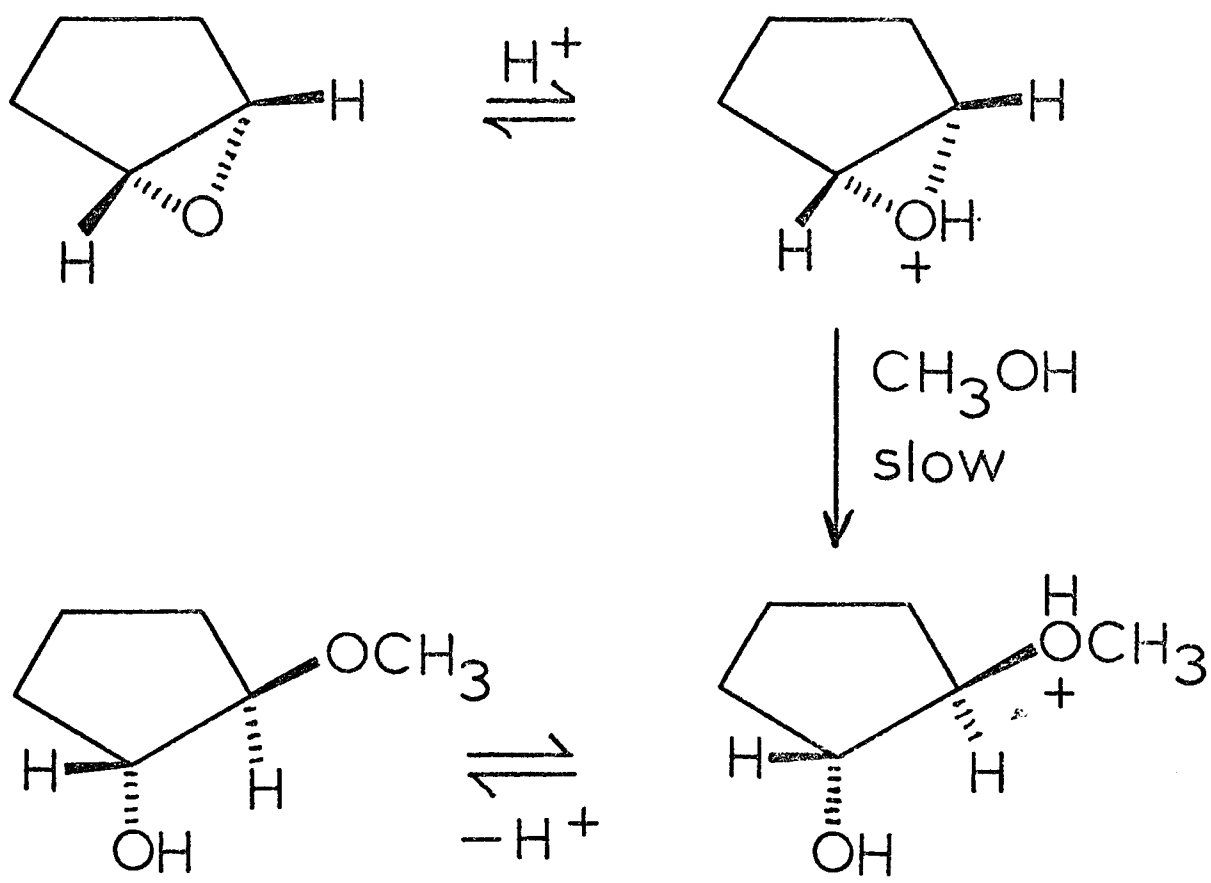
Epoxides are an important group of organic compounds; they occur widely in nature and can be synthesised under a variety of conditions,[1] and interest in their chemistry arises from the diverse variety of rearrangement reactions which they can undergo, and particular interest has been focused on their role in biosynthesis and their potential use in synthesis.

Unlike aliphatic and unstrained cyclic ethers, epoxides can be cleaved by nucleophilic attack, and such cleavage is facilitated by acid catalysts: bond formation between an epoxy-oxygen and a proton or a Lewis acid increases the normal polarisation of C-O bonds in the epoxide and assists bond rupture to give an electron deficient carbon atom. Two extreme mechanisms for nucleophilic attack on epoxides can be envisaged, (i) bimolecular, with concerted C-O bond fission and C-nucleophile bond formation, and (ii) unimolecular, with prior C-O bond fission to give a carbonium ion which is then attacked by the nucleophile. Kinetic and stereochemicalevidence from simple epoxides indicates that proton catalysed nucleophilic attack is usually bimolecular: the ring opening of ethylene oxide with halogen acids exhibits a third order rate law[2] which is only compatible with

$$\text{Rate} = k_3 \left[\underset{\diagdown O \diagup}{CH_2 - CH_2} \right] \left[H^+ \right] \left[X^- \right]$$

the bimolecular mechanism; many acid catalysed ring-opening reactions proceed with almost complete inversion of configuration at the carbon atom which is attacked, e.g. acid catalysed methanolysis of cyclopentene oxide yields exclusively the trans-methoxy-alcohol, whereas if a discrete carbonium ion had been involved, some cis-compound would have been expected as well.[3] The trans-compound is formed by the attacking nucleophile approaching in the favoured periplanar direction, which

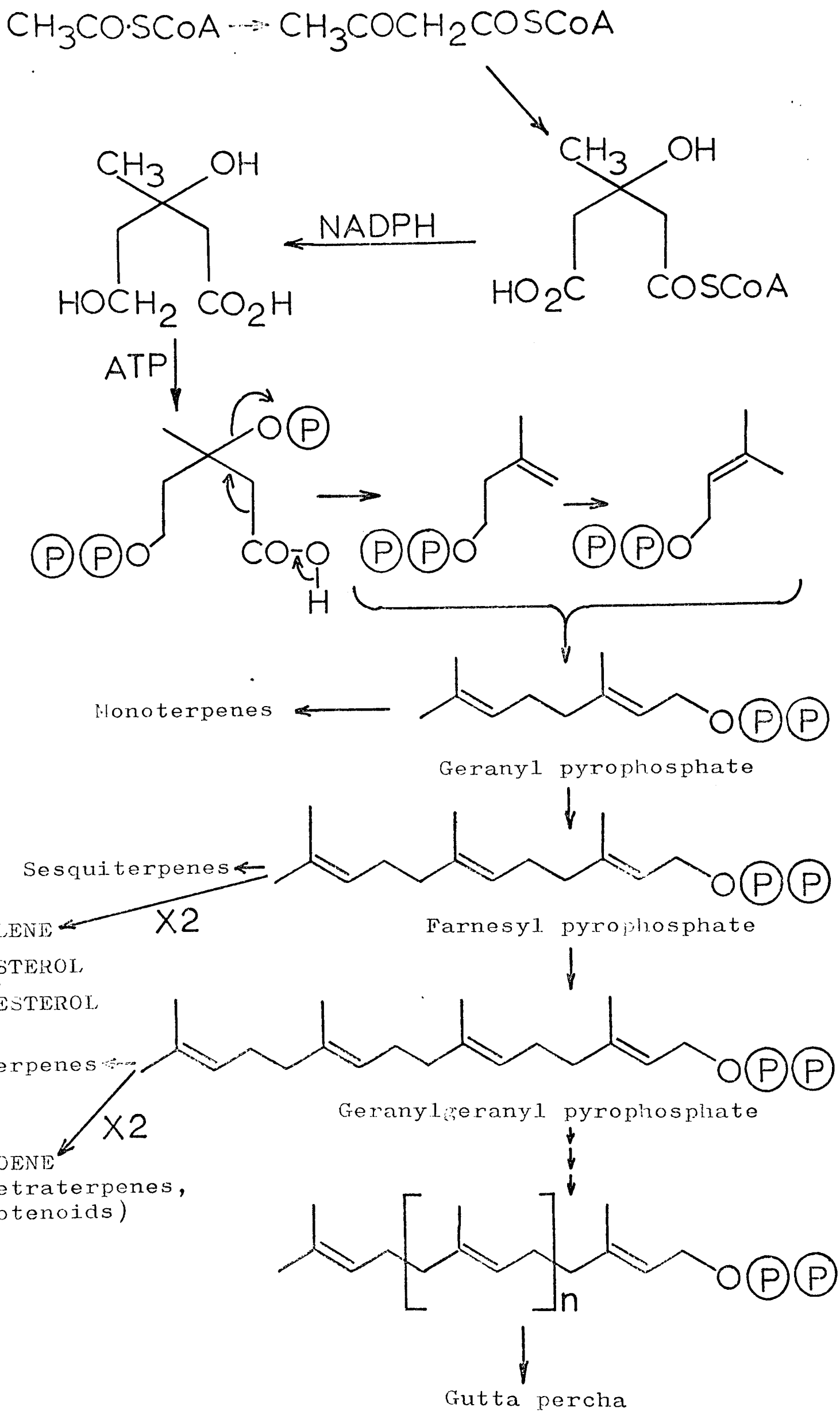
preserves maximum overlap of orbitals in the transition state.



In the absence of effective external nucleophiles, acid catalysts can cause epoxides to undergo intramolecular rearrangements: formation of an O-Acid bond assists C-O bond fission and an incipient carbonium ion results; this electron deficient site can be attacked by an intramolecular nucleophile, i.e. a methyl group with its bonding electrons (Westphalen rearrangement), a "hydride" ion, part of the carbon skeleton of the molecule (Wagner-Meerwein rearrangement), or the π-electron system of a carbon-carbon double bond (to give ring closure). As with external nucleophiles, two extreme mechanisms can be envisaged; either a concerted C-O bond fission and rearrangement process, or a two-step process involving a carbonium ion, and evidence is accumulating that the latter mechanism is usual,[4] with a few exceptions which will be described below.

Methyl migration and ring-closure are both important processes in the biosynthesis of natural products, particularly polyisoprenoids, and the role of epoxides in their biosynthesis will now be considered.

Scheme 1

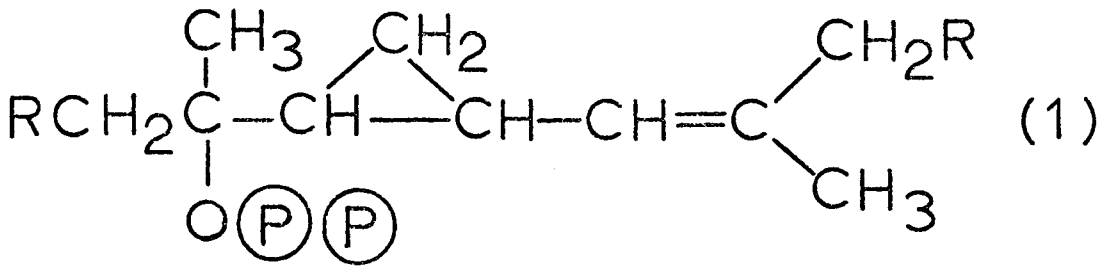


(X2 = dimerisation)

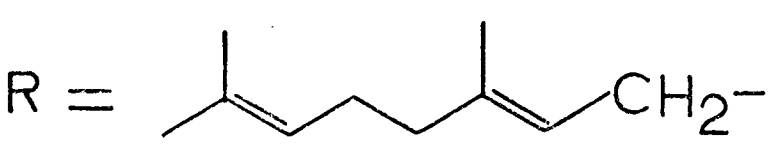
2. The Role of Epoxides in the Biosynthesis of Polyisoprenoids.

Polyisoprenoids derive ultimately from the two-carbon acetate unit, in the form of acetyl coenzyme A,[5] and the biogenetic pathway to cholesterol *via* squalene and lanosterol, which has been elucidated over the last twenty years[6] is shown in Scheme 1.

Naturally occurring C_{30} and C_{40} units are not formed by the stepwise addition of C_5 units, but instead by dimerisation of C_{15} and C_{20} units to give squalene (precursor to triterpenes and steroids) and phytoene (precursor to tetraterpenes and carotenoids). The dimerisation of two C_{15} units to give squalene is complex, involving as well as the formation of a C-C bond, the cleavage of two C-O bonds with release of pyrophosphate, the cleavage of a C-H bond with release of a proton, and the formation of a C-H bond with a hydrogen donated by NADPH: an intermediate between farnesyl pyrophosphate and squalene was therefore suspected, and was isolated by Rilling[7] and later by Popjak,[8] from incubations of yeast subcellular particles with farnesyl pyrophosphate in the absence of NADPH. Rilling[7] assigned it as a cyclopropane compound (1) but when this



(1)

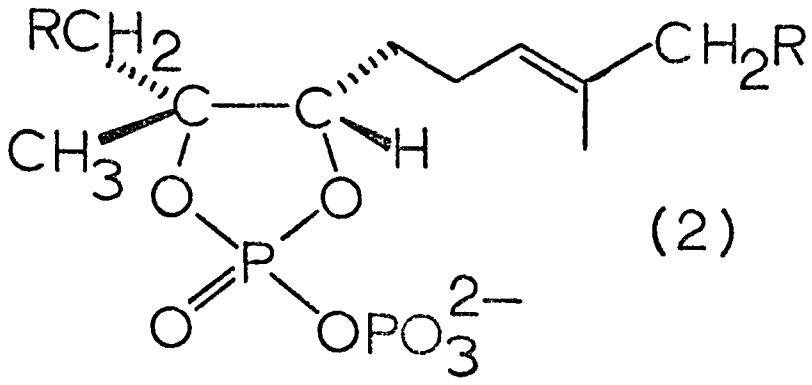




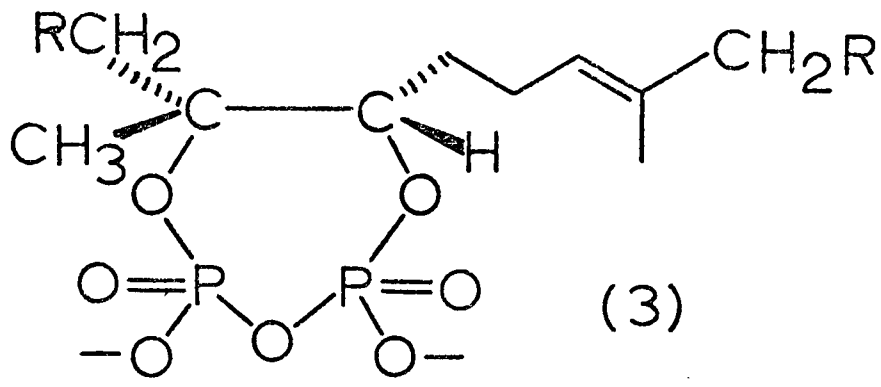
pyrophosphate

compound was synthesised, it was not incorporated into squalene.[9] Popjak[8] assigned two possible cyclic phosphate diester structures (2) and (3), but later work by Rilling,[10] including an unambiguous synthesis which defined the stereochemistry,[11] has shown that a modified cyclopropyl structure (4) is correct. A postulated mechanism of formation[11] which

agrees with the observed pattern of hydrogen atom loss, involving



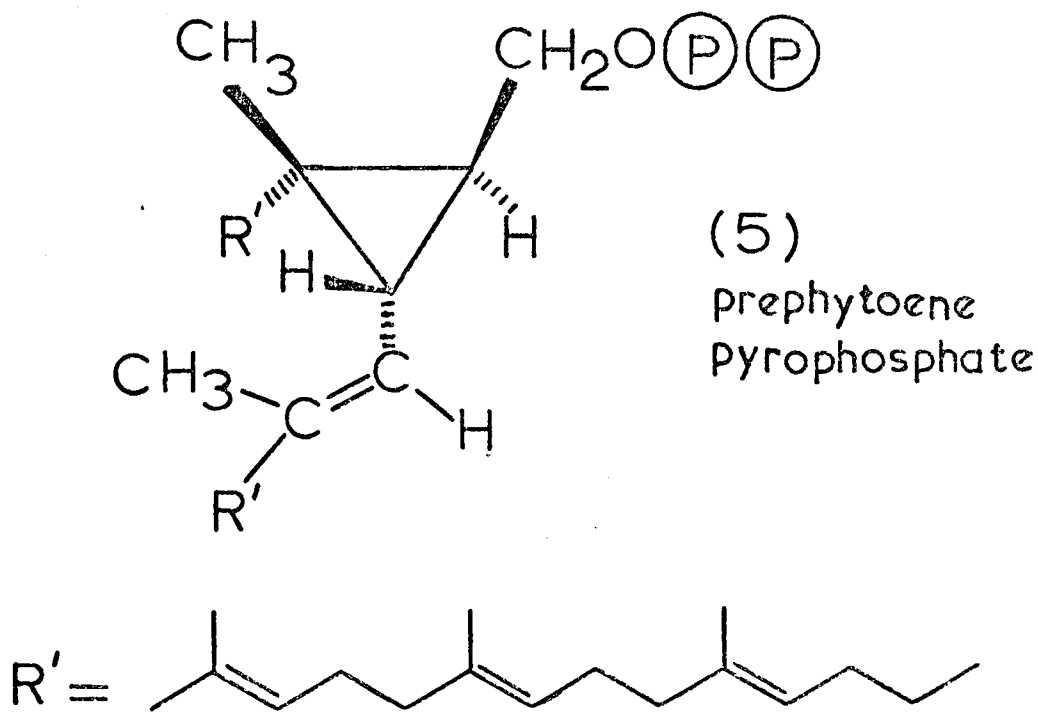
(2)



(3)

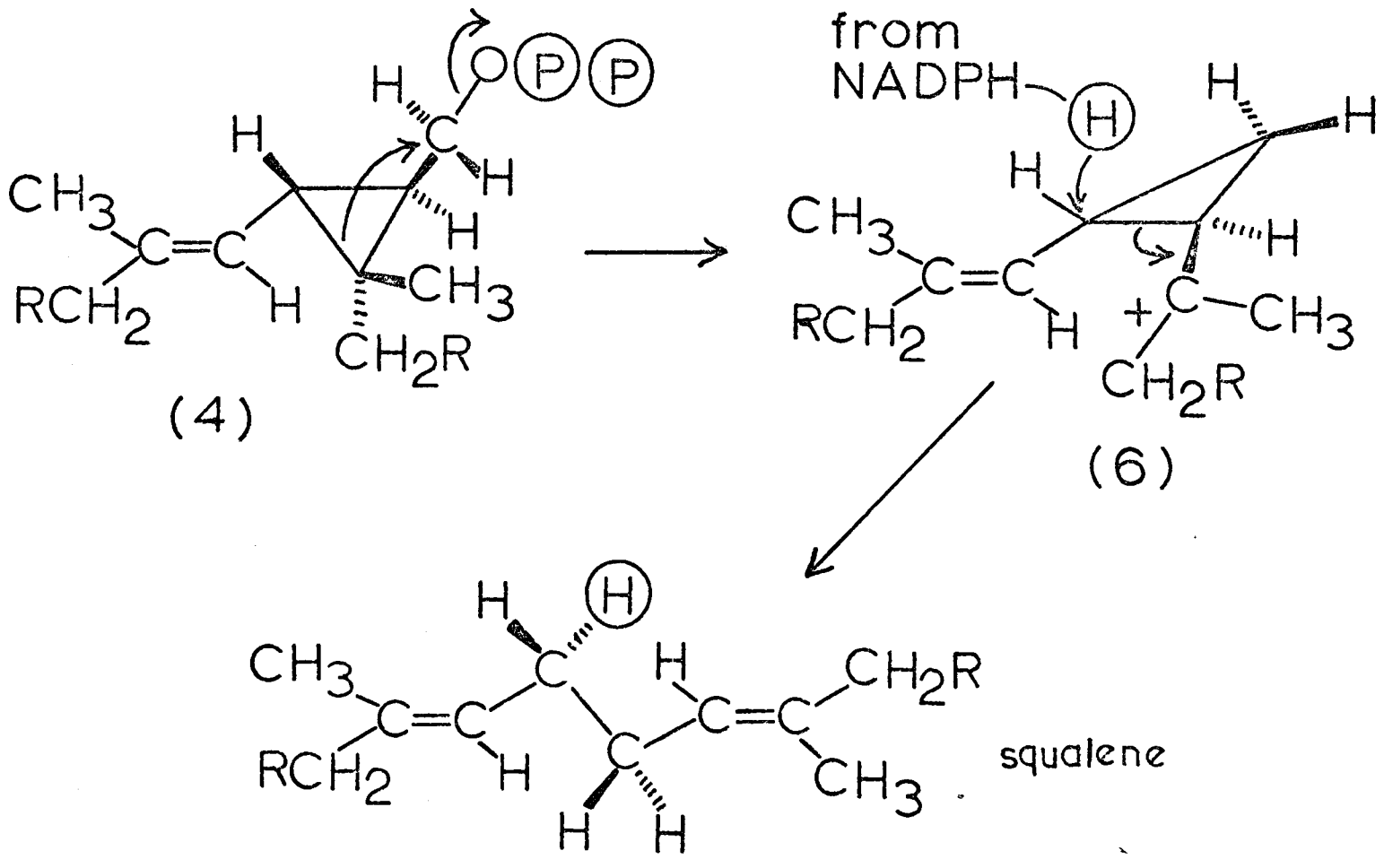
an electron donating group on the enzyme, is shown below.

Recently, an analogous intermediate has been isolated[12] from the conversion of two C_{20} geranylgeranyl units into phytoene, and its structure (5) has been confirmed by synthesis and found to contain the same cyclopropyl unit as presqualene pyrophosphate, indicating the generality of this dimerisation process.



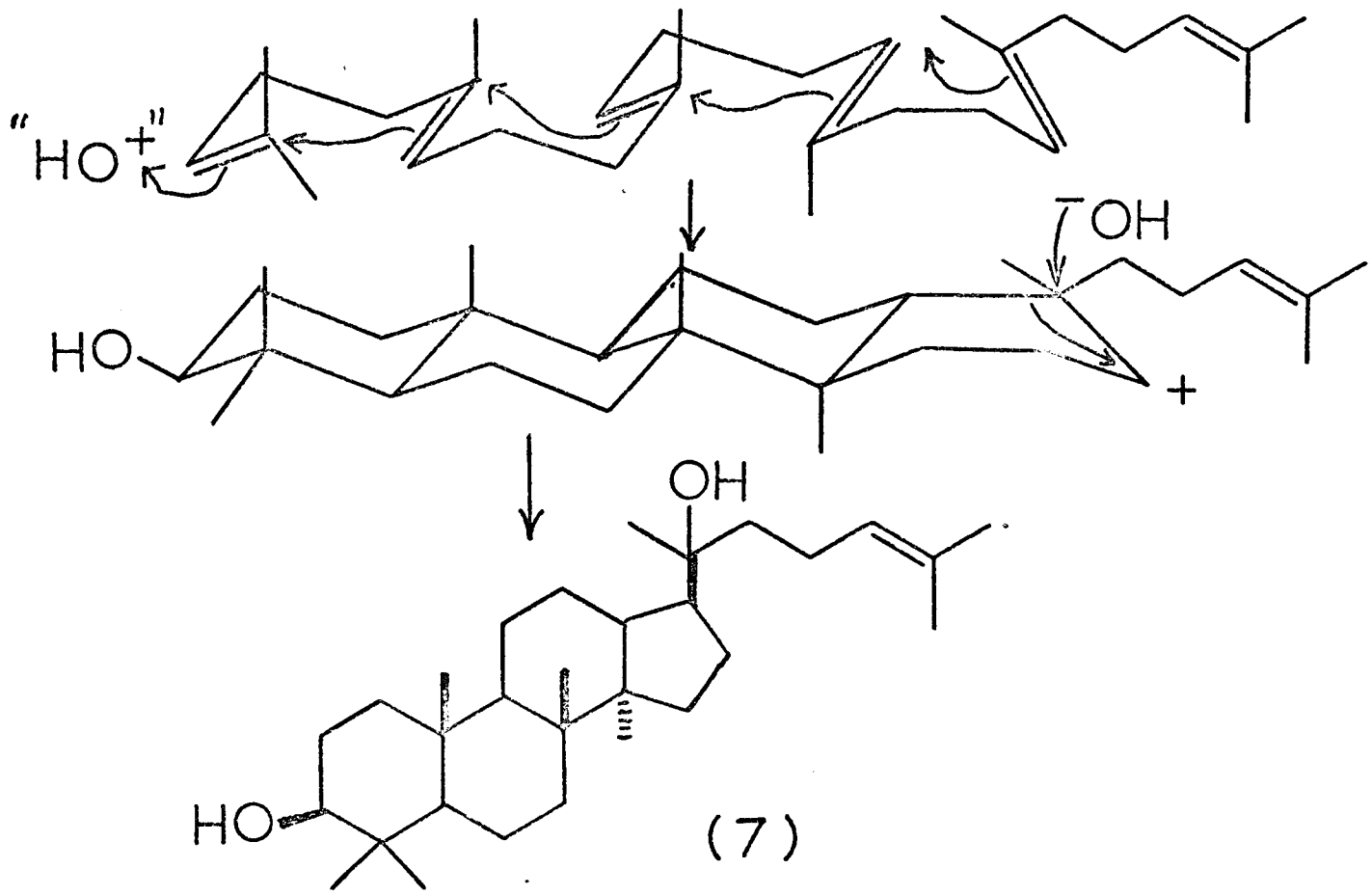
(5)
prephytoene
pyrophosphate

The transformation of presqualene pyrophosphate to squalene requires NADPH, and a possible mechanism could involve rearrangement via the carbonium ion. (6).



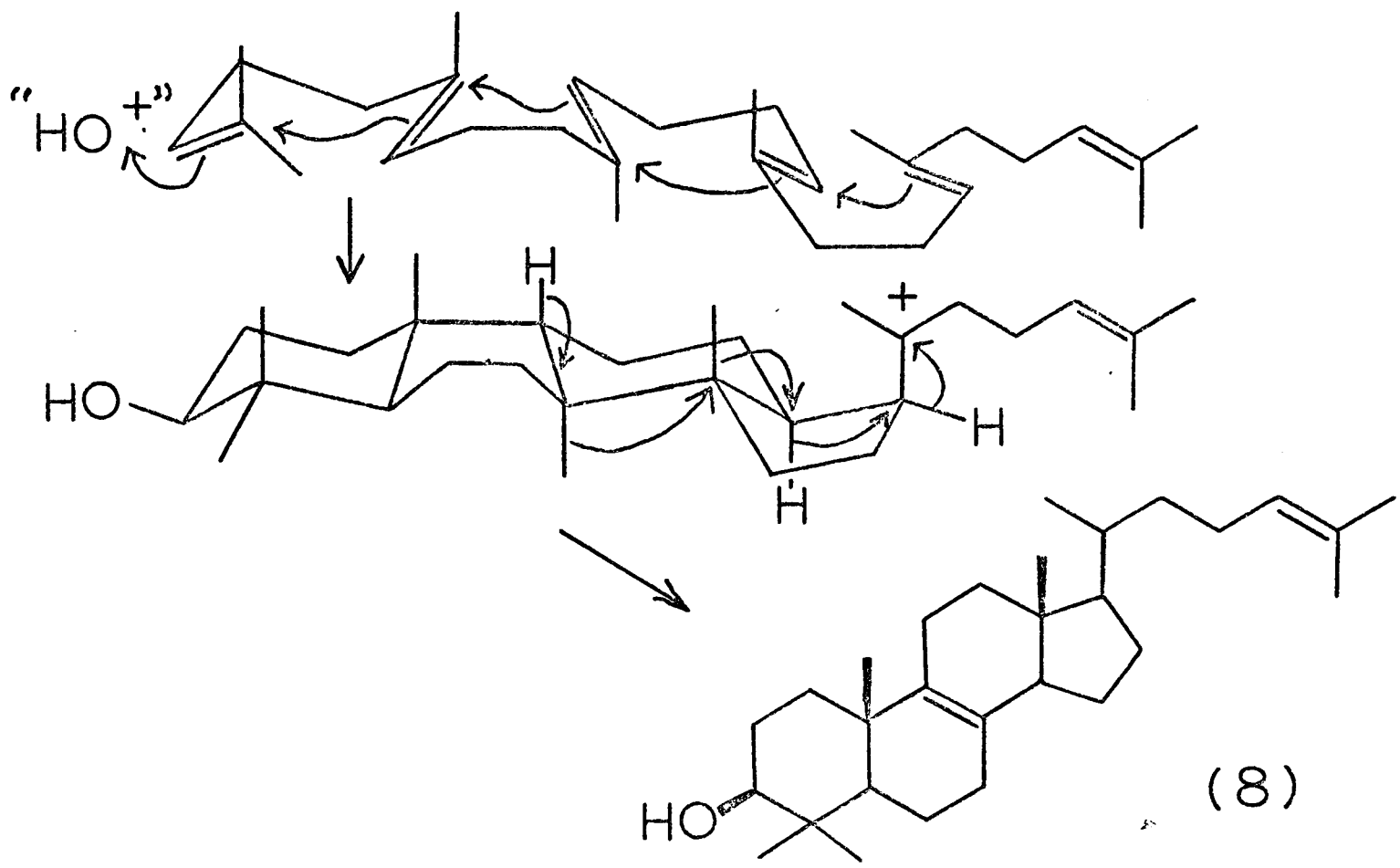
The detailed mechanism of the cyclisation of squalene to lanosterol and other triterpenes is gradually being elucidated experimentally, but a

sound theoretical basis has been proposed by the Zurich School;[13] by applying fundamental principles of olefin addition reactions and by orienting the squalene chain in a series of potential boat and chair forms, they were able to rationalise the formation of all the main classes of triterpenes. Thus a dammarane diol (7) could arise from chair-chair-chair-boat folding:



(7)

Lanosterol (8) could arise from chair-boat-chair-boat folding followed by proton elimination and two methyl 1,2-shifts and two hydrogen 1,2-shifts; elegant labelling experiments by Cornforth[14] and Bloch[15] confirmed that the methyl migrations occurred as predicted by the Ruzicka postulate. The nature of the oxygen species which initiates cyclisation and presumably becomes the 3β -hydroxy-group in lanosterol remained in some doubt. Bloch[16] showed that when squalene was converted into lanosterol in a medium containing D_2O or $H_2^{18}O$, no label was incorporated, whereas if the incubation was carried out in the presence of $^{18}O_2$, the label appeared



(8)

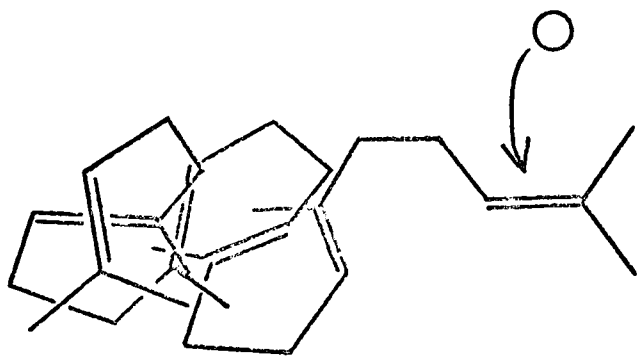
in the 3β-hydroxy-group of the lanosterol. These results suggested that the oxygen is introduced into squalene without prior equilibration with water, and that partially cyclised intermediates which require protonation from the solvent are not involved. The cyclisation mechanism was thus envisaged[16] as a concerted process initiated by a hydroxonium ion OH^+ in the presence of an enzyme, tentatively called squalene oxido-cyclase. Other mechanisms were also considered, including attack by a hydroxyl radical,[17] and prior acid catalysed cyclisation to a lanostadiene followed by enzymic hydroxylation at C-3.[18] However, the relative complexity of the squalene into lanosterol conversion led some investigators to look for a discrete intermediate, and this was identified independently by van Tamelen[19] and Corey[20] as squalene 2,3-epoxide. Squalene is oxidised in a system requiring oxygen and NADPH, and the epoxide cyclises in a separate stage under the influence of "epoxy-squalene cyclase" which requires neither oxygen

nor NADPH. Labelled squalene 2,3-epoxide could be isolated from rat-liver preparations fed with labelled squalene under aerobic conditions, and the labelled squalene epoxide was converted into lanosterol in anaerobic conditions; fully labelled $[^{3}H, ^{18}O]$ squalene 2,3-epoxide was converted into lanosterol with retention of both labels; this evidence points to squalene 2,3-epoxide as an obligatory intermediate in the formation of lanosterol.[21]

The enzymic conversion of squalene to lanosterol raises interesting questions about the chemistry of long chain polyenes, for one underlying feature of virtually all enzymes is that they merely catalyse reactions that are functionally sound mechanistically, and are usually known to go *in vitro*[22] (although often under rather more vigorous conditions). Two reactions are involved here, (i) the epoxidation of a terminal double bond of squalene, and (ii) the transformation of squalene 2,3-epoxide into a complex tetracyclic system containing seven asymmetric centres, and attempts have been made to carry out these processes *in vitro*.

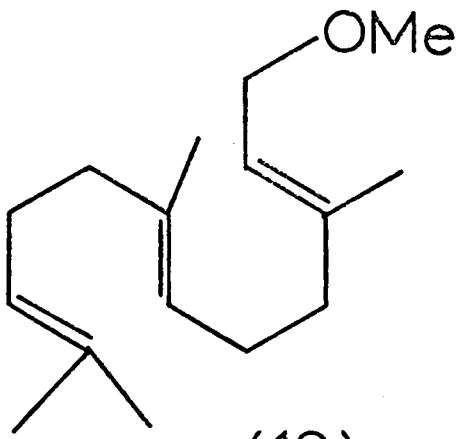
(i) *Epoxidation of Squalene*.

All the double bonds in squalene are trisubstituted and might be expected to be chemically equivalent; this is probably true in non-polar solvents, where squalene would exist in an uncoiled form, with all its double bonds equally vulnerable to attack, but in polar solvents, squalene probably adopts a coiled conformation (9) which disrupts the hydrogen bonding in the solvent as little as possible, and only leaves the terminal double bonds exposed.

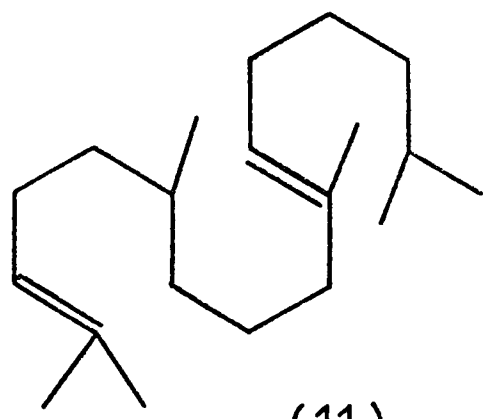


(9)

Van Tamelen[23] has shown that it is possible to selectively attack the terminal double bonds of squalene using N-bromosuccinimide in aqueous glyme, and the resulting bromohydrin can be converted to the epoxide by treatment with base. High terminal selectivity was also observed[24] for other polyenes of similar structure (10) and for dienes with widely separated double bonds (11); and in a competitive reaction between a



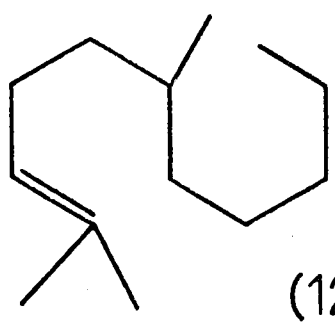
(10)



(11)

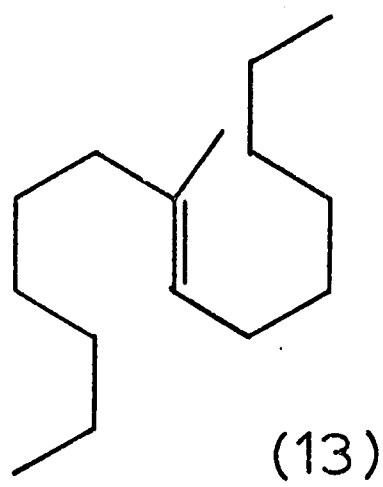
Terminal attack 96%	98.5%
Internal attack 4%	1.5%

terminal and non-terminal olefin (12) and (13), exclusive attack on the terminal bond was observed.



(12)

100% attack

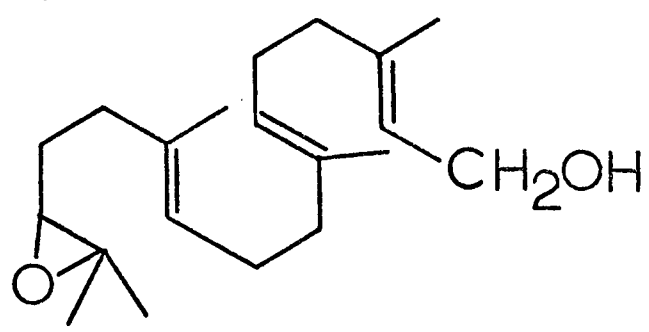


(13)

0% attack

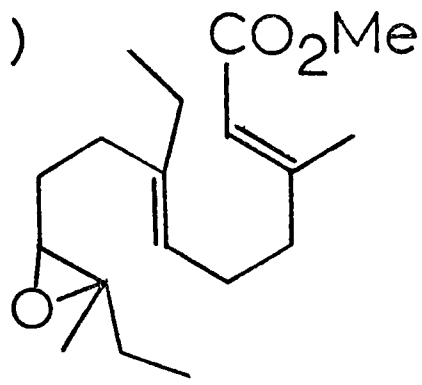
Thus, provided that the micro-environment of squalene in the oxidase is polar, selective terminal epoxidation of squalene is to be expected, and other terminal epoxides of alicyclic terpenes e.g. (14) and (15) have been found in nature.

(14)



14,15-epoxy-geranyl geraniol[25]

(15)

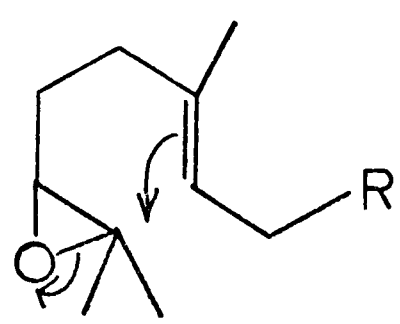


juvenile hormone[26]

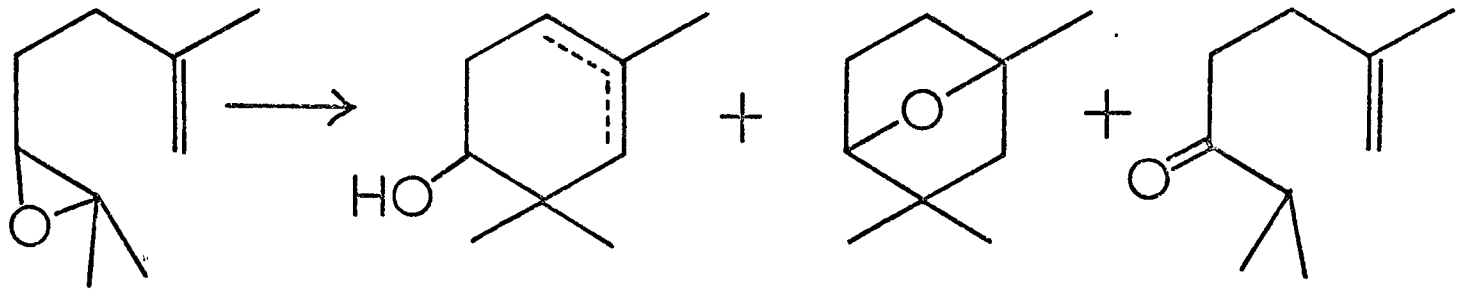
(ii) Cyclisation of Squalene 2,3-epoxide.

This reaction can be envisaged as being initiated by nucleophilic attack of the π-electrons of the C6-C7 double bond on C-2, with concomitant breaking of the C2-O bond as in (16);

(16)

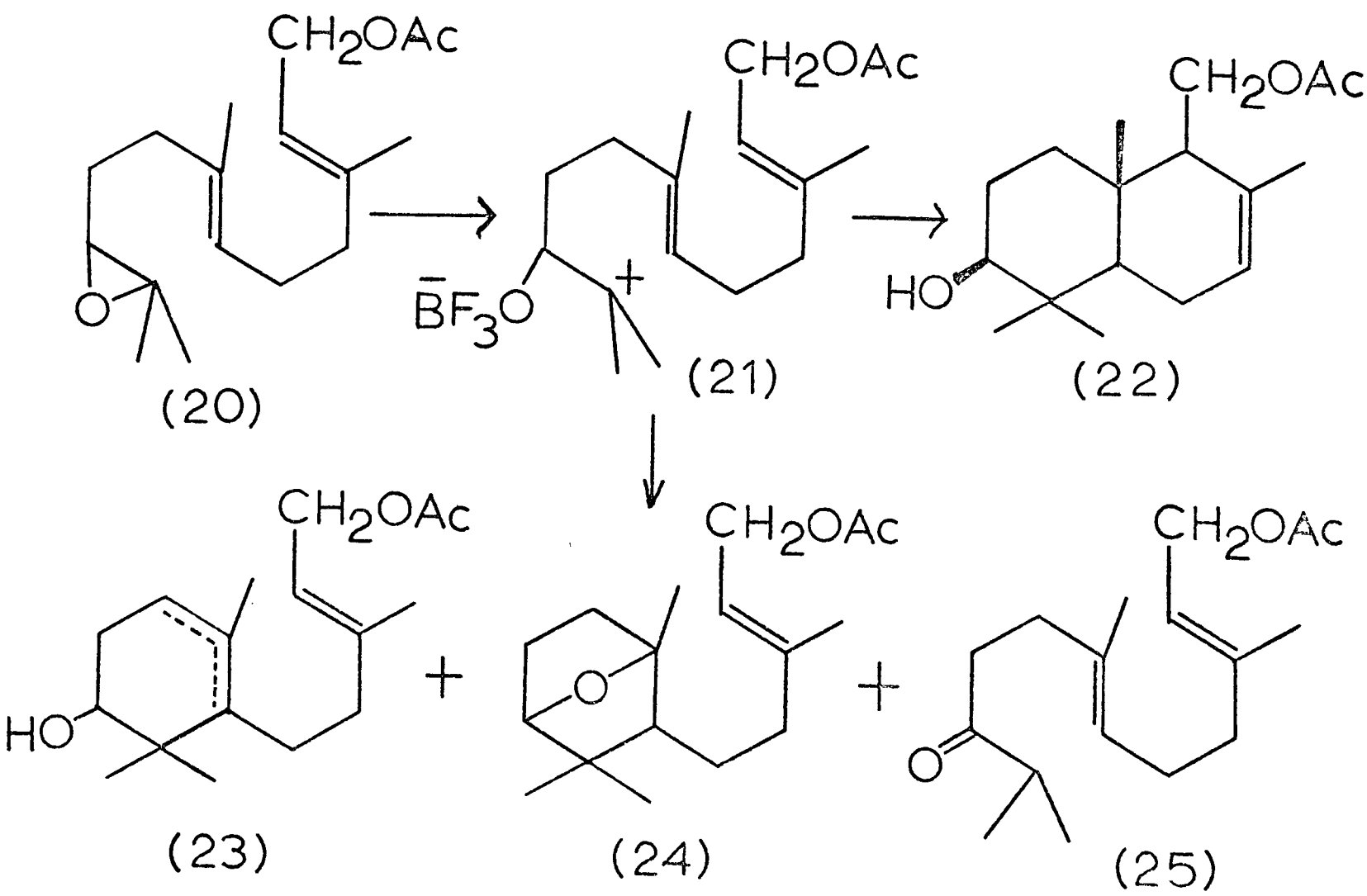


and a model system (17) for this reaction was studied by Goldsmith;[27] a cyclohexenol (18) was formed as well as a cyclic ether (19), and these two products showed that chemical cyclisation of terminal epoxides was feasible.



(17) (18) (19)

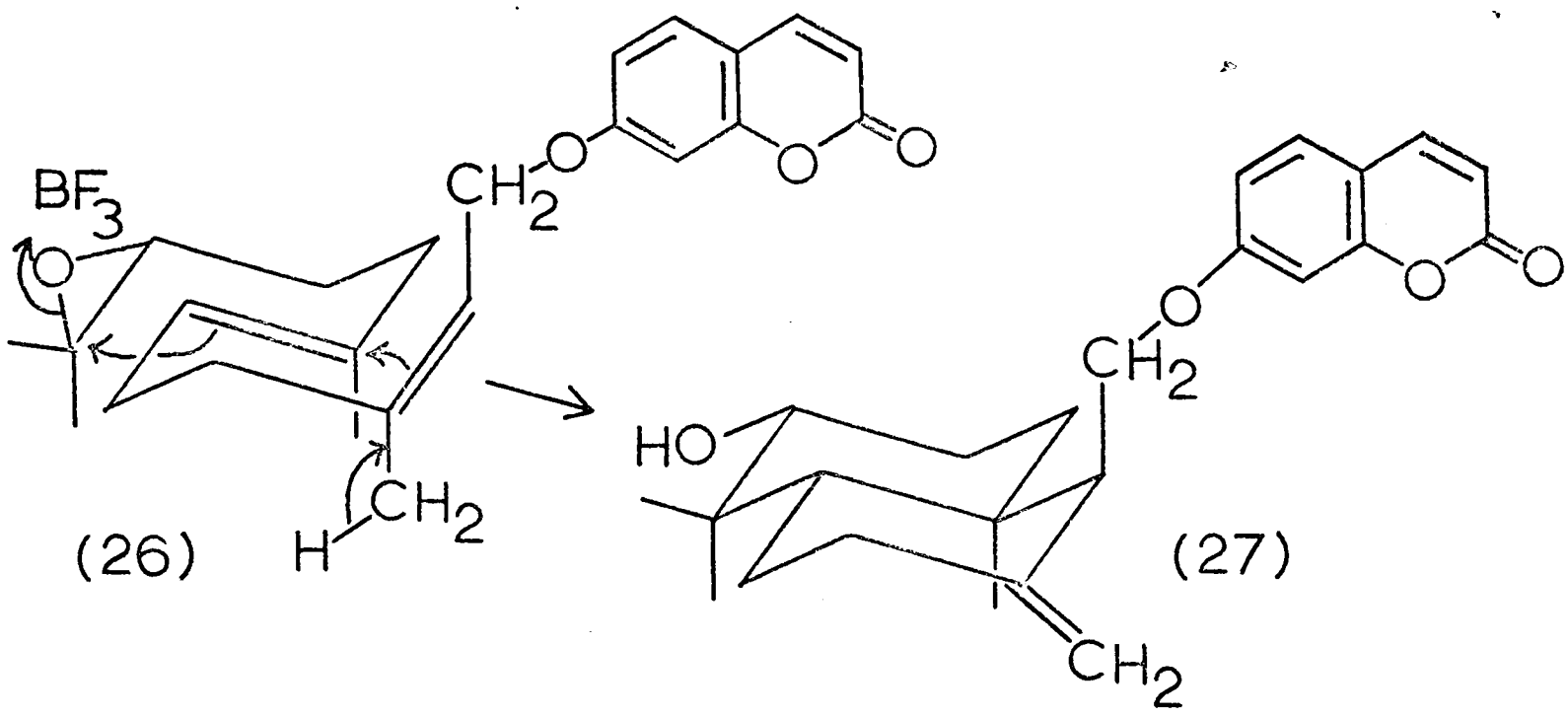
Van Tamelen[28] investigated the preparation of a bicyclic system, and on treating trans,trans-farnesyl acetate(20) with boron trifluoride-ether complex in benzene, he obtained the bicyclic compound (22) in 22% yield, with all four asymmetric centres possessing the normal A/B ring stereochemistry found in polycyclic terpenoids. Side products (23)-(25) arising from alternative pathways from the initially formed carbonium ion (21) were also found.



(20) (21) (22)

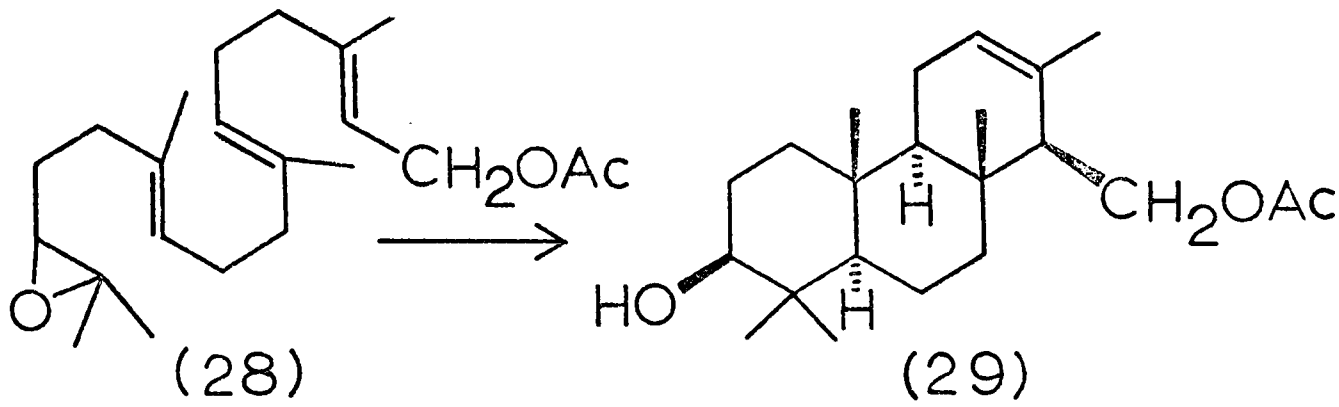
(23) (24) (25)

Treatment of the monocyclic cyclohexenol (23) with boron trifluoride under conditions of the initial reaction gave no further products, suggesting that this structure (23) is not an intermediate in the formation of the bicyclic system; this is probably formed by concerted closure of both rings, or <u>via</u> a monocyclic carbonium ion. The similarity between compounds (21), (23), and (24) and the naturally occurring farnisiferols suggested that this reaction might be used in a biogenetic-type synthesis; on treating <u>trans</u>,<u>cis</u>-umbelliprenin terminal epoxide (26) with boron trifluoride-ether complex in benzene, van Tamelen[29] obtained a low yield of ± farnisiferol C (27).



(26) (27)

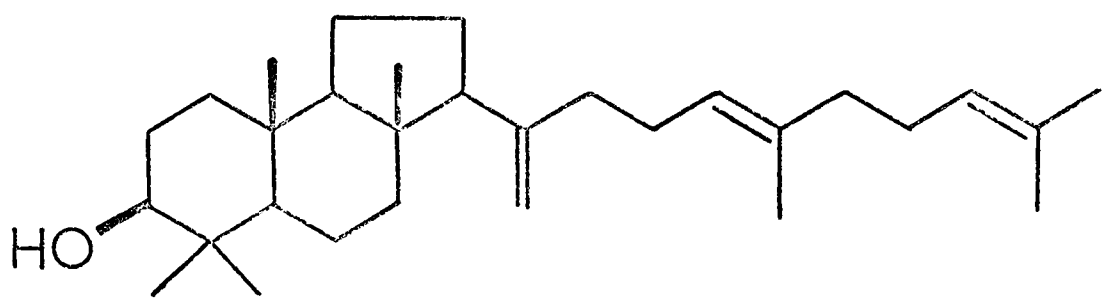
Continuing the work, van Tamelen[30] formed a tricyclic system (29) by treating the terminal epoxide of all-<u>trans</u>-geranylgeranyl acetate(28) with stannic chloride in benzene, and again the product had the same stereochemistry as observed in naturally occurring systems of this type.



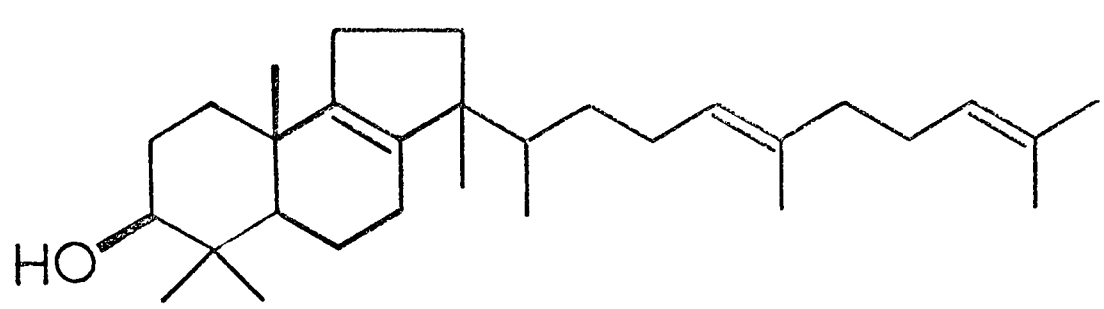
(28) (29)

However, treatment of squalene 2,3-epoxide did not give a tetracyclic system,[31] but two tricyclic compounds with the perhydrocyclopentanonapthalene skeleton (30) and (31).

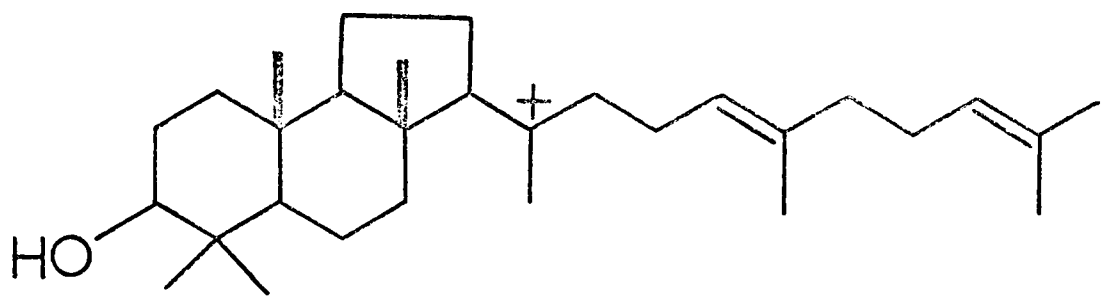
(30)



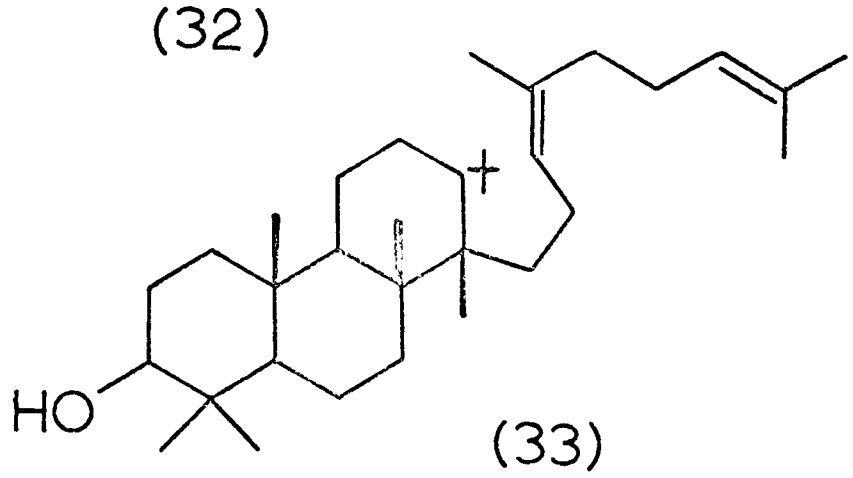
(31)



If this reaction proceeded via a series of carbonium ions, the formation of a five-membered ring C is to be expected, as it results from a tertiary carbonium ion (32), whereas a six-membered ring C would require a secondary carbonium ion (33).

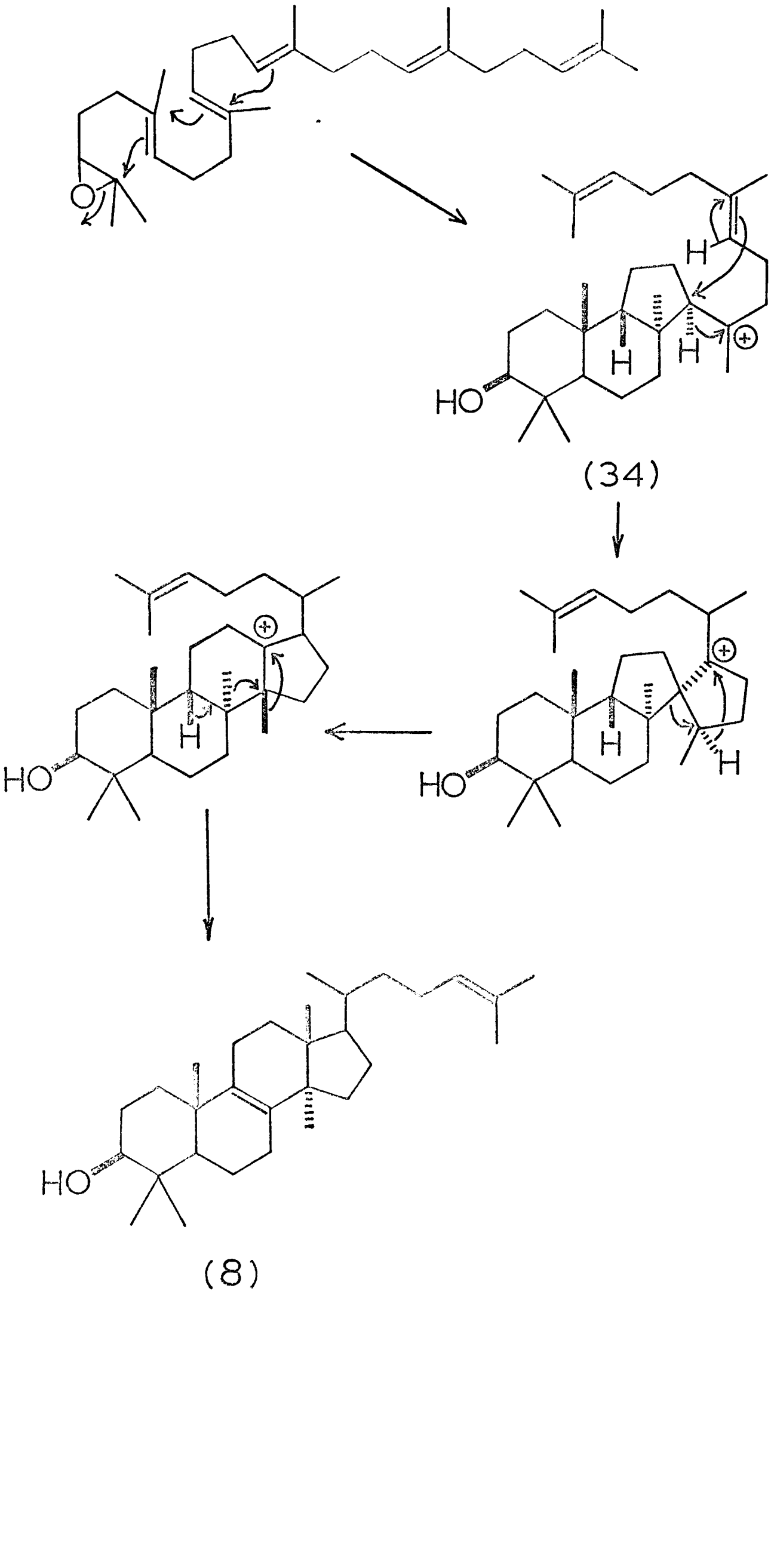


(32)



(33)

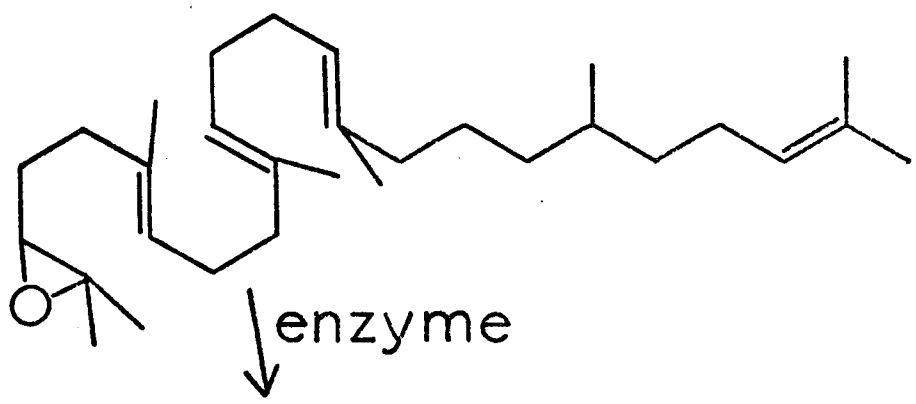
Scheme 2



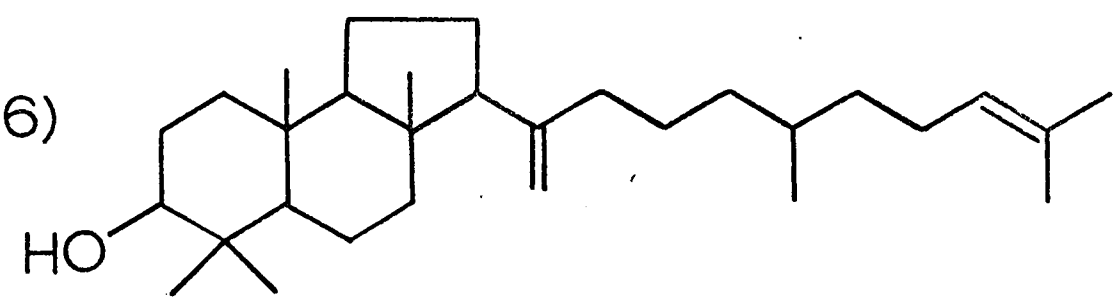
In order to explain this apparent anomaly in the striking parallelism between the enzymic and non-enzymic behaviour of long chain polyenes, rather than invoking enzyme intervention, van Tamelen[32] postulated a biogenetic mechanism leading to lanosterol (8), which was consistent with the then available labelling evidence, and proceeded *via* a five-membered ring intermediate species (34), shown in Scheme 2 .

Recent work[33] using [11,14-$^3H_2$] squalene 2,3-epoxide has shown that a similar mechanism, involving a 1,5 hydrogen shift, is not compatible with the final positions of the labels found in lanosterol, and that the original six-membered ring C mechanism proposed by Ruzicka[13] appears to be correct. However, oxidosqualene cyclase may be partially compatible with this mechanism, as incubation of *trans,trans,trans*-18,19-dihydrosqualene 2,3-epoxide (35) produces a perhydrocyclopentanonaphthalene compound (36).[34]

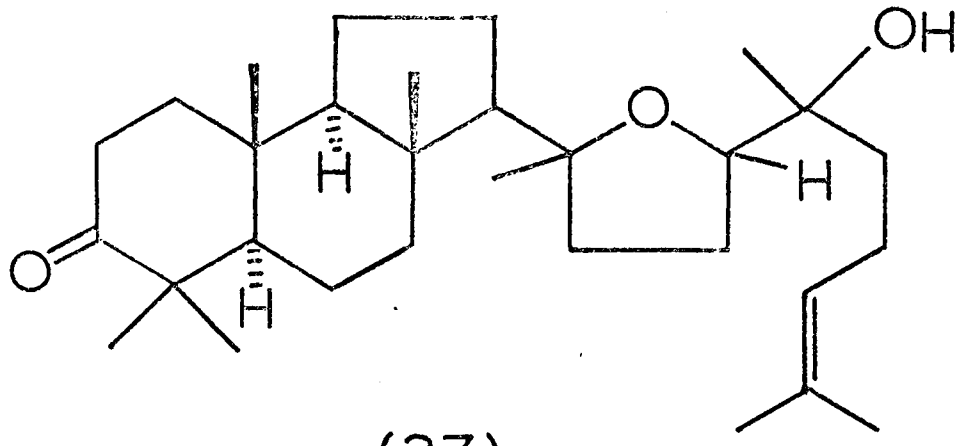
(35)



(36)

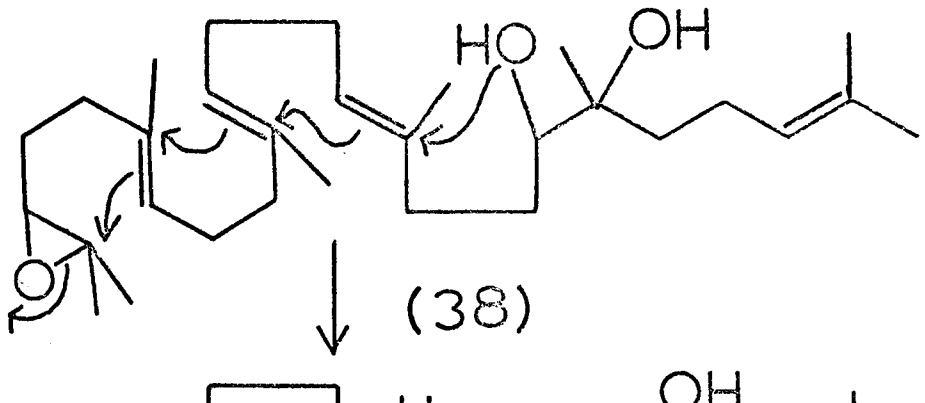


A compound with this type of skeleton (37) has been isolated from a

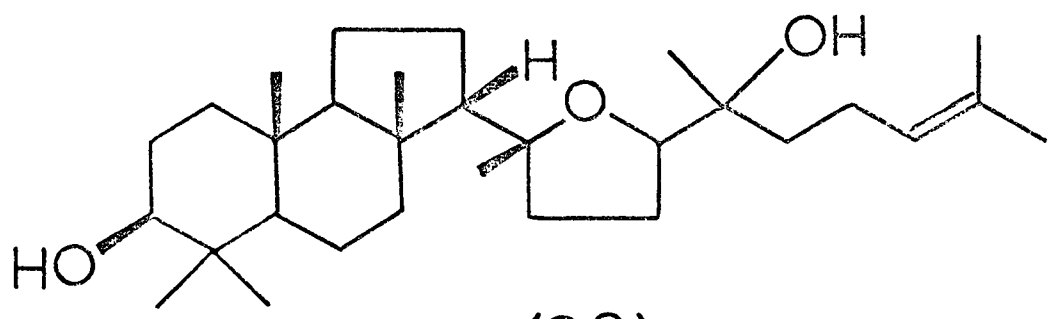


(37)

plant source,[35] and a derivative of this compound, malabaricane diol (39) has been prepared[36] by treating squalene 2,3-epoxide-18,19-diol (38) with picric acid in nitromethane.



(38)

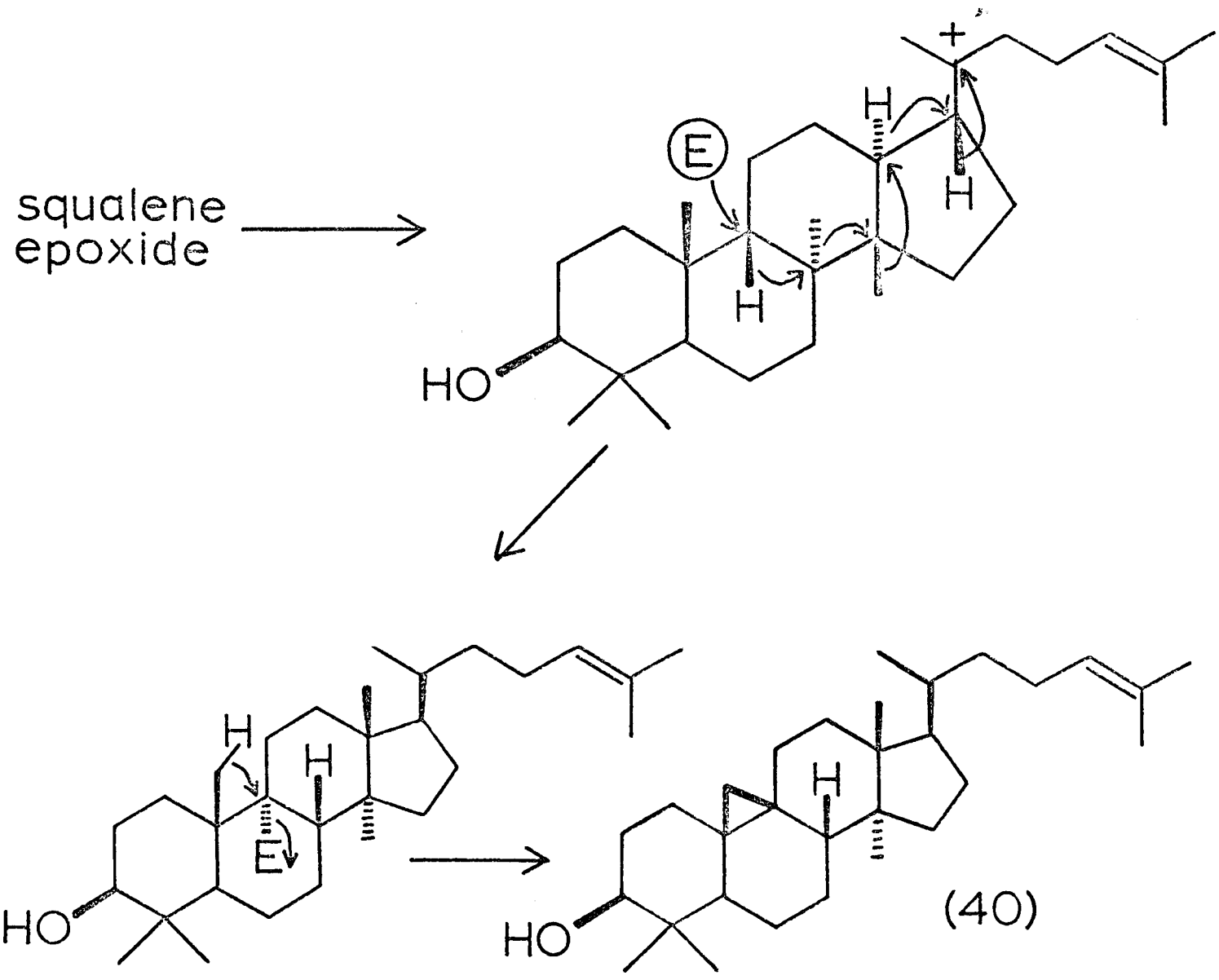


(39)

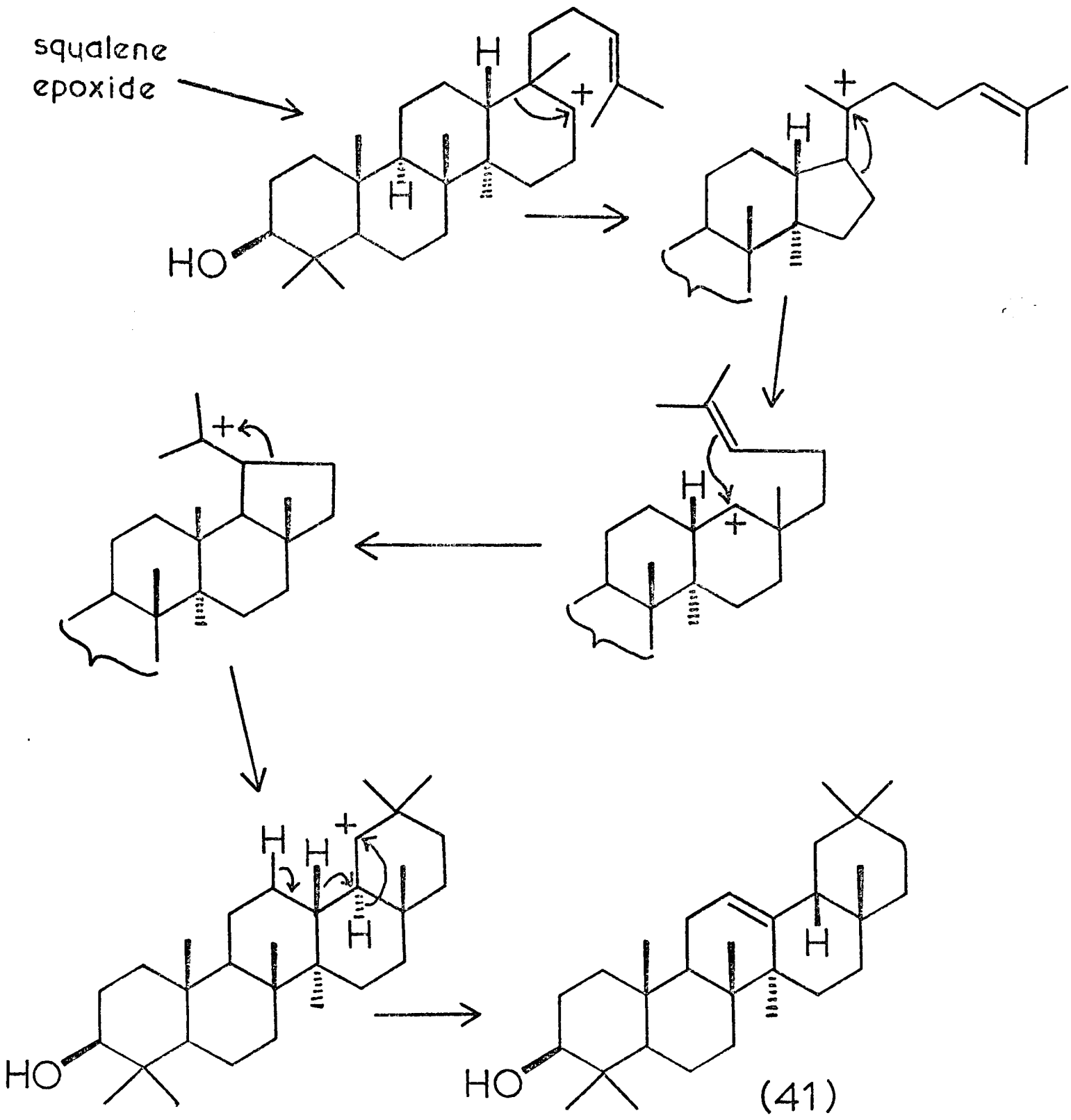
This compound (39) is the first natural product to be derived from a non-enzymic cyclisation of a squalene derivative, and the yield (7%) is remarkable, considering that the product contains nine asymmetric centres. This reaction suggests that a squalene derivative may be a natural precursor to malabaricane diol, and that the enzyme which brings about the cyclisation is of fairly low specificity, relying on the inherent reactivity of the substrate.

Although lanosterol is the first formed cyclic product from squalene 2,3-epoxide in animal and fungal systems, it has been suggested[37]

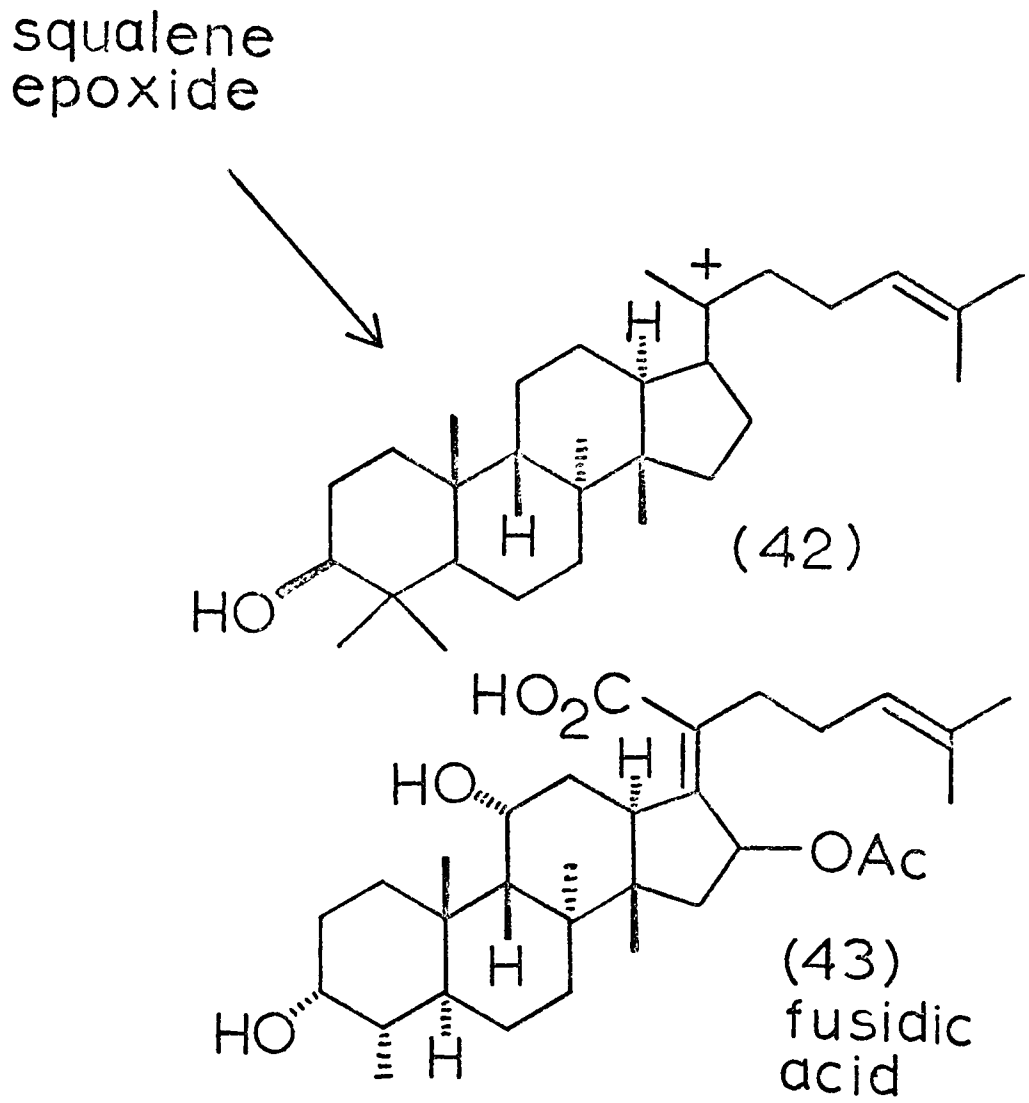
that lanosterol may be replaced by cycloartenol (40) in higher plants: lanosterol occurs very rarely in the plant kingdom, while cycloartenol is widely distributed, and when labelled acetate is fed to certain plants, labelled cycloartenol is isolated, while no labelled lanosterol can be detected.[38] Squalene 2,3-epoxide has been isolated from tobacco tissues,[38] and anaerobic cyclisation of [^{14}C] squalene 2,3-epoxide to cycloartenol in a cell free extract from bean leaves has been demonstrated.[39] The mechanism of cyclisation is initially the same as that leading to lanosterol, but transient enzyme-intervention at the C-9 carbonium ion site is postulated[40] so that migration of the C-19 methyl group can proceed in the <u>trans</u> direction proposed by Ruzicka.



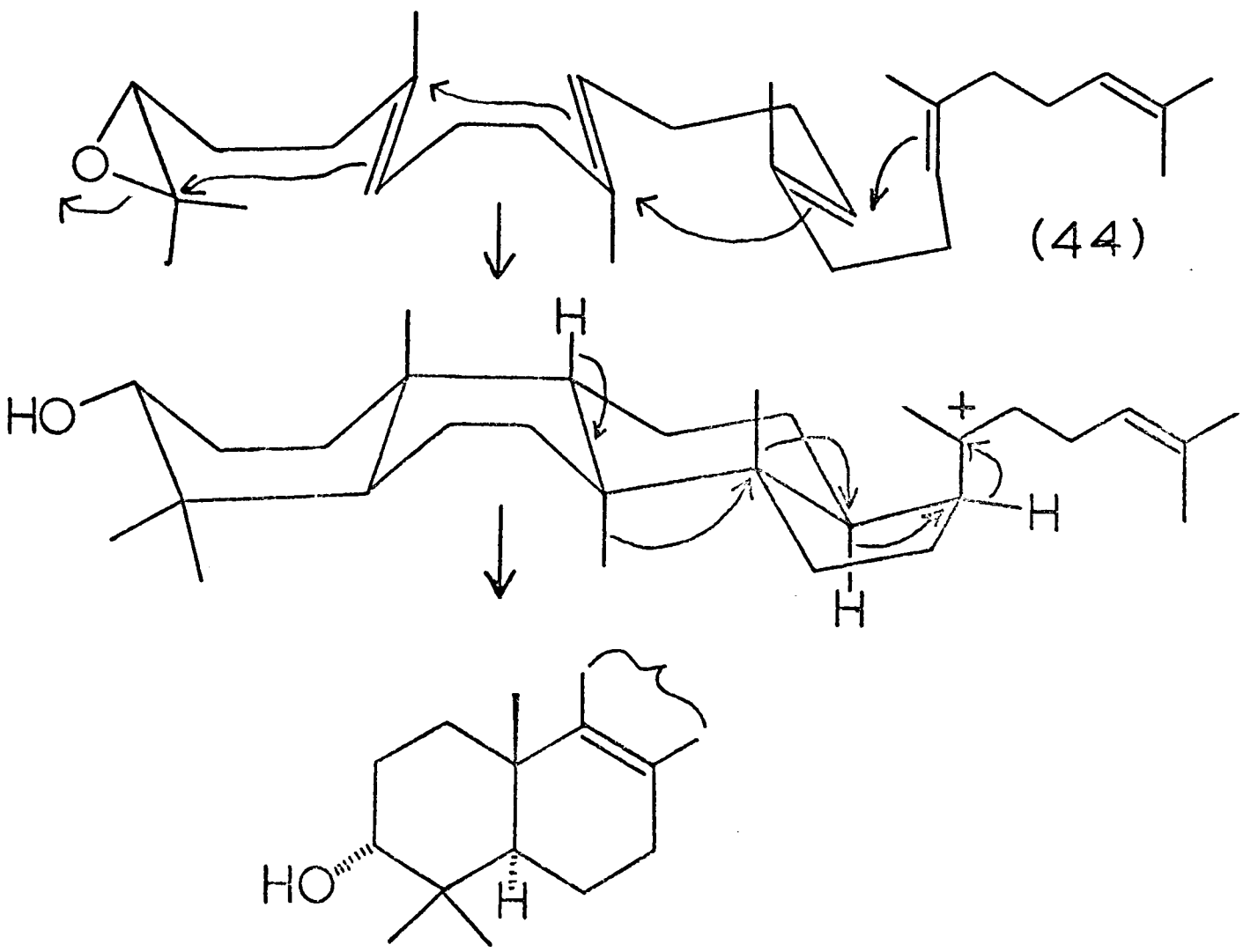
Squalene 2,3-epoxide is the precursor to other triterpene systems: a cell free extract from peas converts it into β -amyrin (41);[41] and the



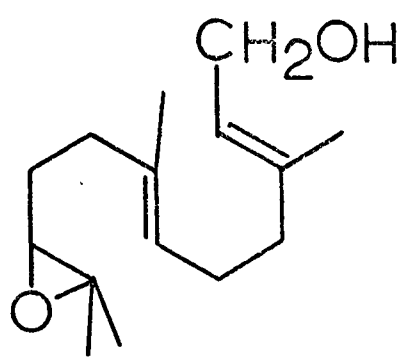
mould fusidium coccineum converts it into fusidic acid (43);[42] using [^{3}H]-labelled epoxide, the label distribution in the product indicates an intermediate of type (42). In this process, a proton has been lost from C-17 without hydride and methyl shifts, and the system retains the cis-9,10 arrangement.



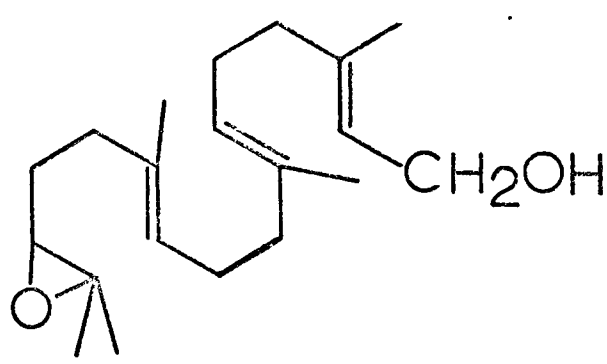
Thus it appears that squalene 2,3-epoxide may be the ultimate acyclic precursor to polycyclic triterpenes with a 3β-hydroxy-group and also to those with a 3α-hydroxy-group, which could arise[43] by coiling to give a potential boat-form ring A (44).



In the light of van Tamelen's work on terminal epoxides, it seems likely that hydroxylated sesquiterpenes and diterpenes could arise from the terminal epoxides of farnesol and geranylgeraniol, (45) and (46).

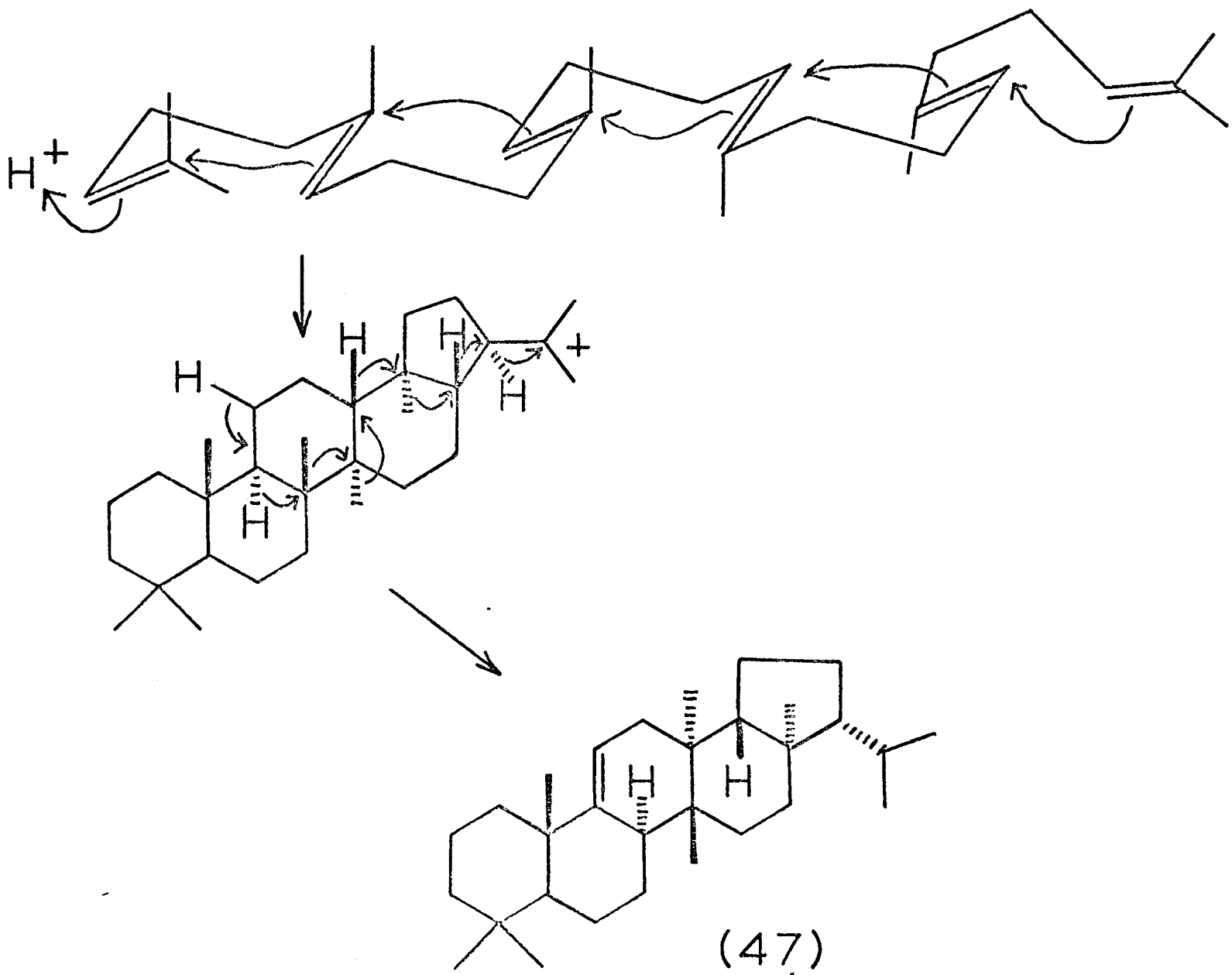


(45)



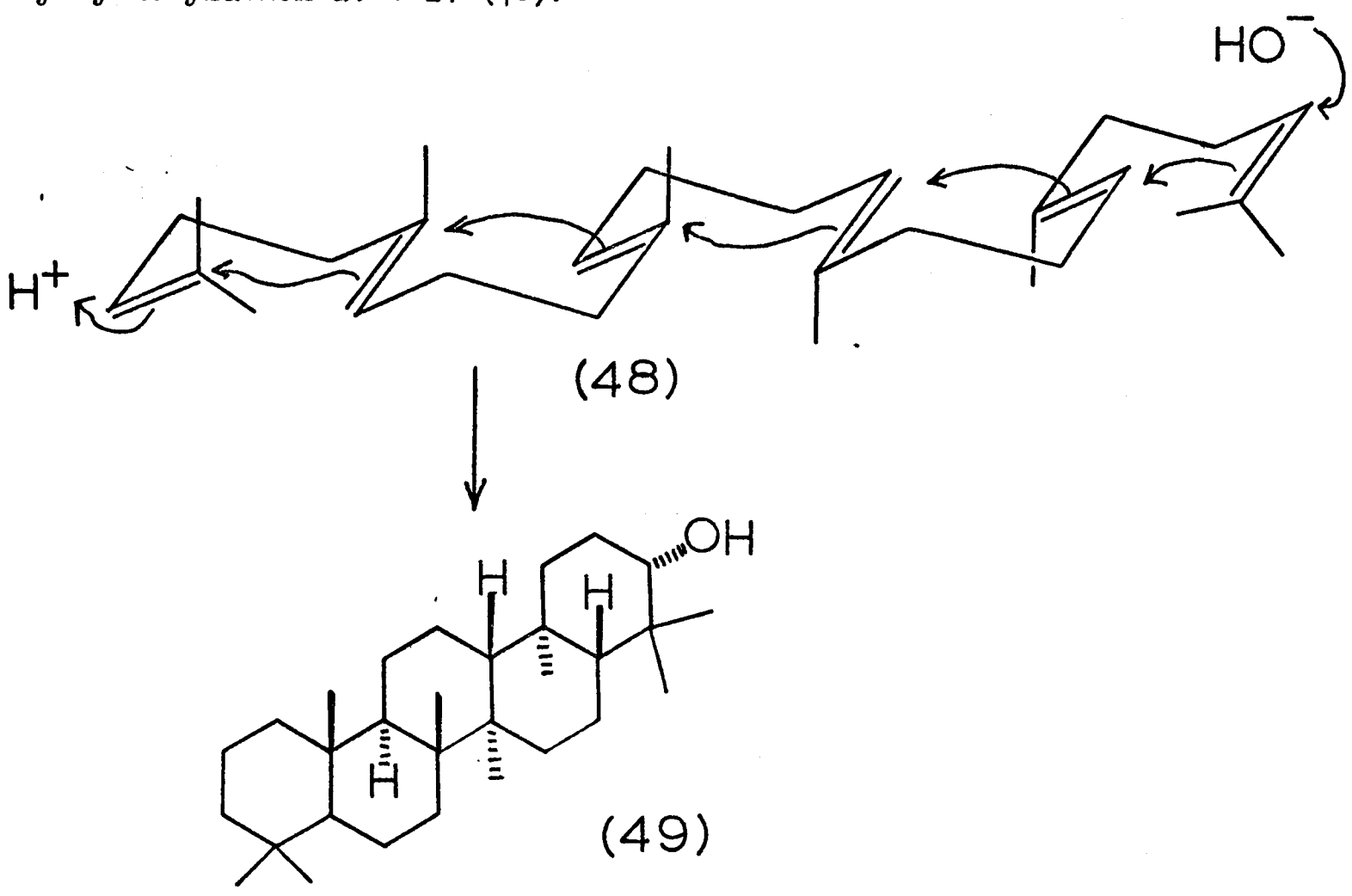
(46)

Several species of diterpenes and triterpenes are known which do not have an oxygen function at C-3, and these are thought to arise by non-oxidative cyclisation mechanisms. Fern-9-ene (47) is formed by a proton initiated cyclisation of squalene, and no incorporation of squalene 2,3-epoxide is observable.[44]



(47)

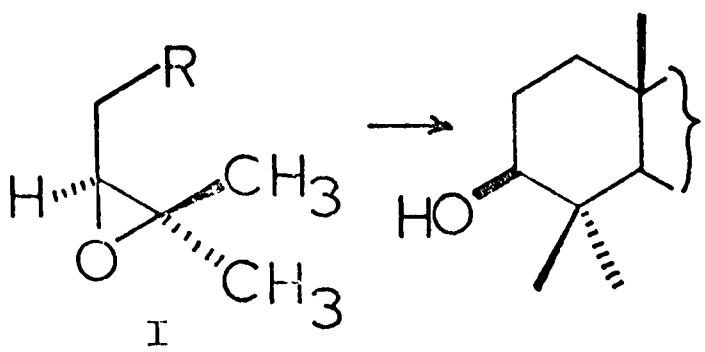
Tetrahymanol (49) is oxygenated at C-3 and might be thought to arise from squalene 2,3-epoxide by all-chair folding, but labelled squalene 2,3-epoxide is not incorporated into tetrahymanol, whereas squalene is efficiently incorporated.[45] The cyclisation occurs under anaerobic conditions,[46] and when it was ccarried out in a medium containing D_2O,[47] deuterium was incorporated into one of the terminal rings, and further, in an $H_2{}^{18}O$ medium,[48] the ^{18}O was found in the hydroxy-group of tetrahymanol; this indicates a proton initiated cyclisation terminated by hydroxylation at C-21 (48).



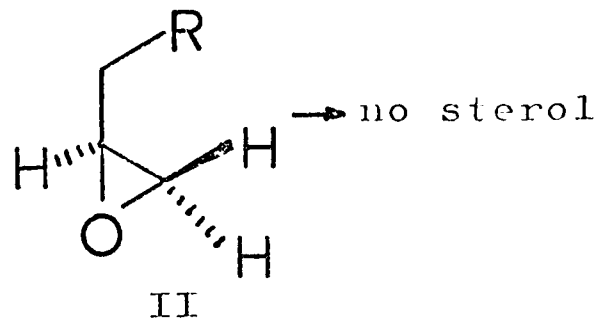
iii) <u>The Cyclisation Process</u>.

The enzyme responsible for the cyclisation of squalene 2,3-epoxide has been obtained in purified soluble form by treating hog liver microsomes with deoxycholate,[49] and information about the active site(s) has been derived by feeding suitably modified squalene analogues to the enzyme, and observing the products formed. Three sites in squalene 2,3-epoxide have been modified; (a) the epoxide ring environment, (b) the

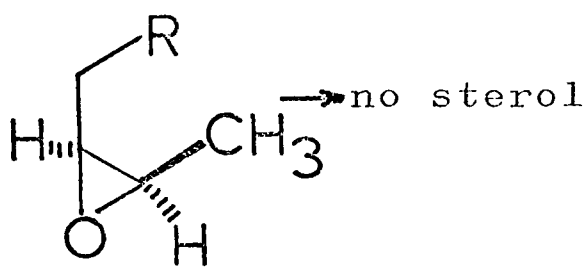
Scheme 3



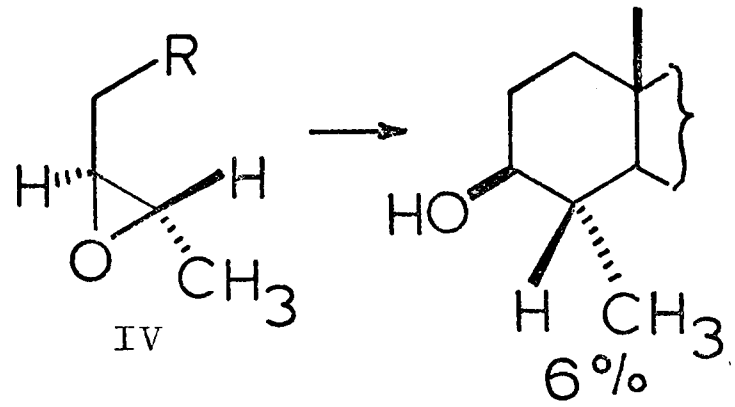
I



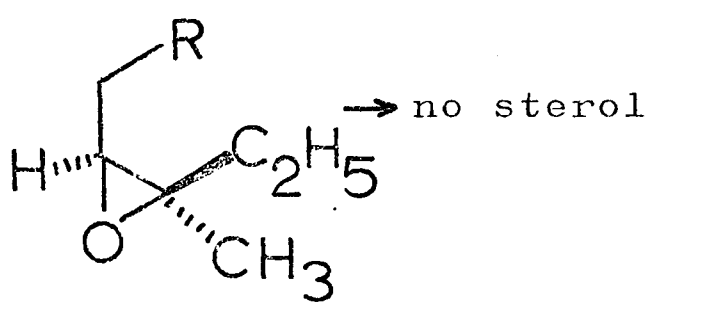
II



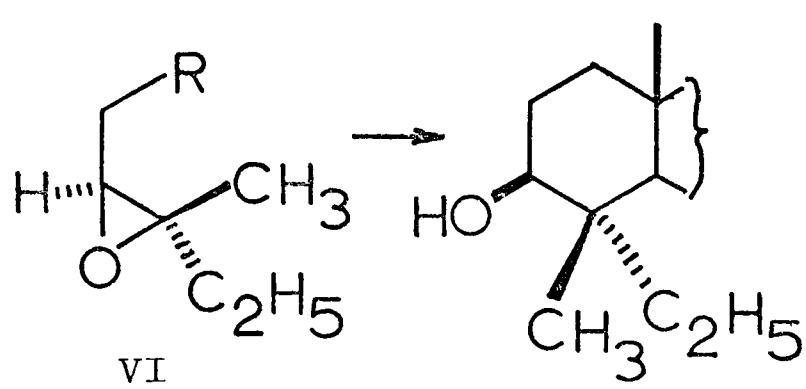
III



IV

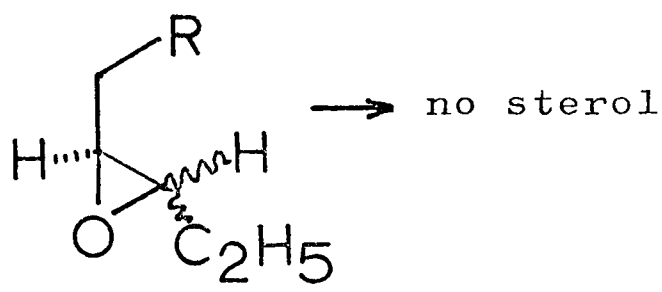


V



VI

8%



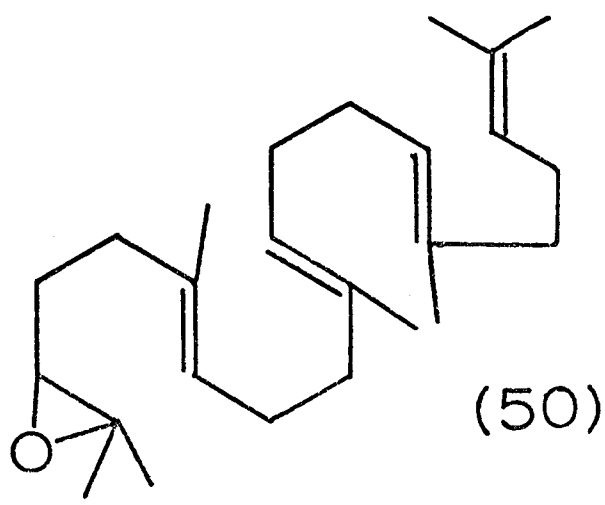
VII

(Results from references 21 and 50-52)

end of the chain, and (c) the central section of the chain.

(a) Epoxide modification. The compounds shown in Scheme 3 have been studied. These results indicate that a trisubstituted centre at C-2 is important, suggesting that the ring-closure at C-2 may be S_N1. The preferential cyclisation of the trans-methyl compound (IV) compared with cis-methyl (III) could be due to a specific interaction at the active site of the enzyme with the trans-methyl group, while comparison of (V) with (VI) indicates that unfavourable steric interaction with the cis group may be important. The trans-methyl interaction is of low specificity as it can accept an ethyl rather than a methyl group; however, reaction (VII) indicates that this substitution reduces the efficiency of the process.

(b) Chain-end modification. Squalene 2,3-epoxides modified in the "side chain" portion, e.g. 22,23-dihydro-,[53] 22,23-Epoxy-,[54] and 23,23', 24-trinor-[53] squalene 2,3-epoxide, and the C_{25} epoxide (50)[55] are all efficiently converted into the correspondingly modified

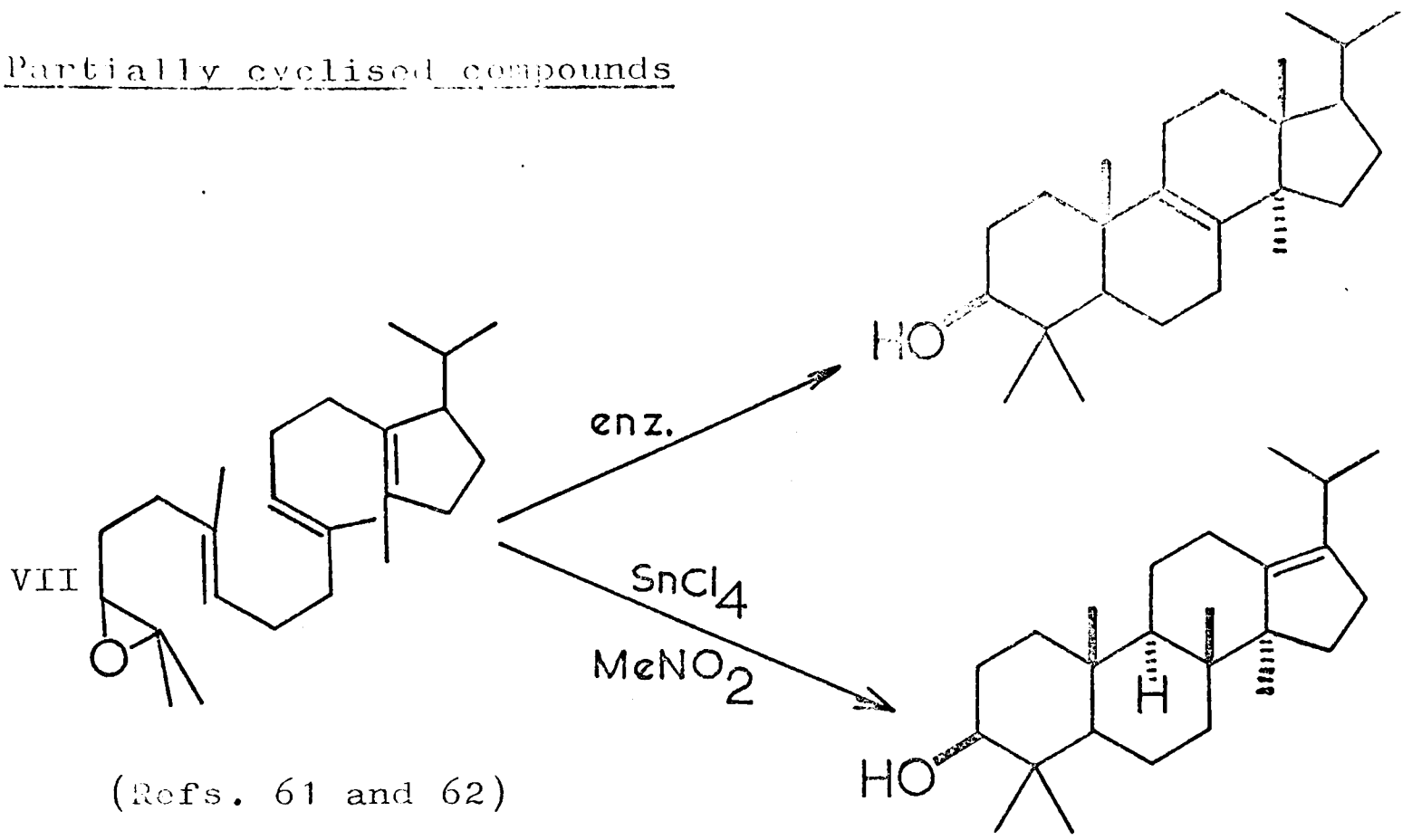


(50)

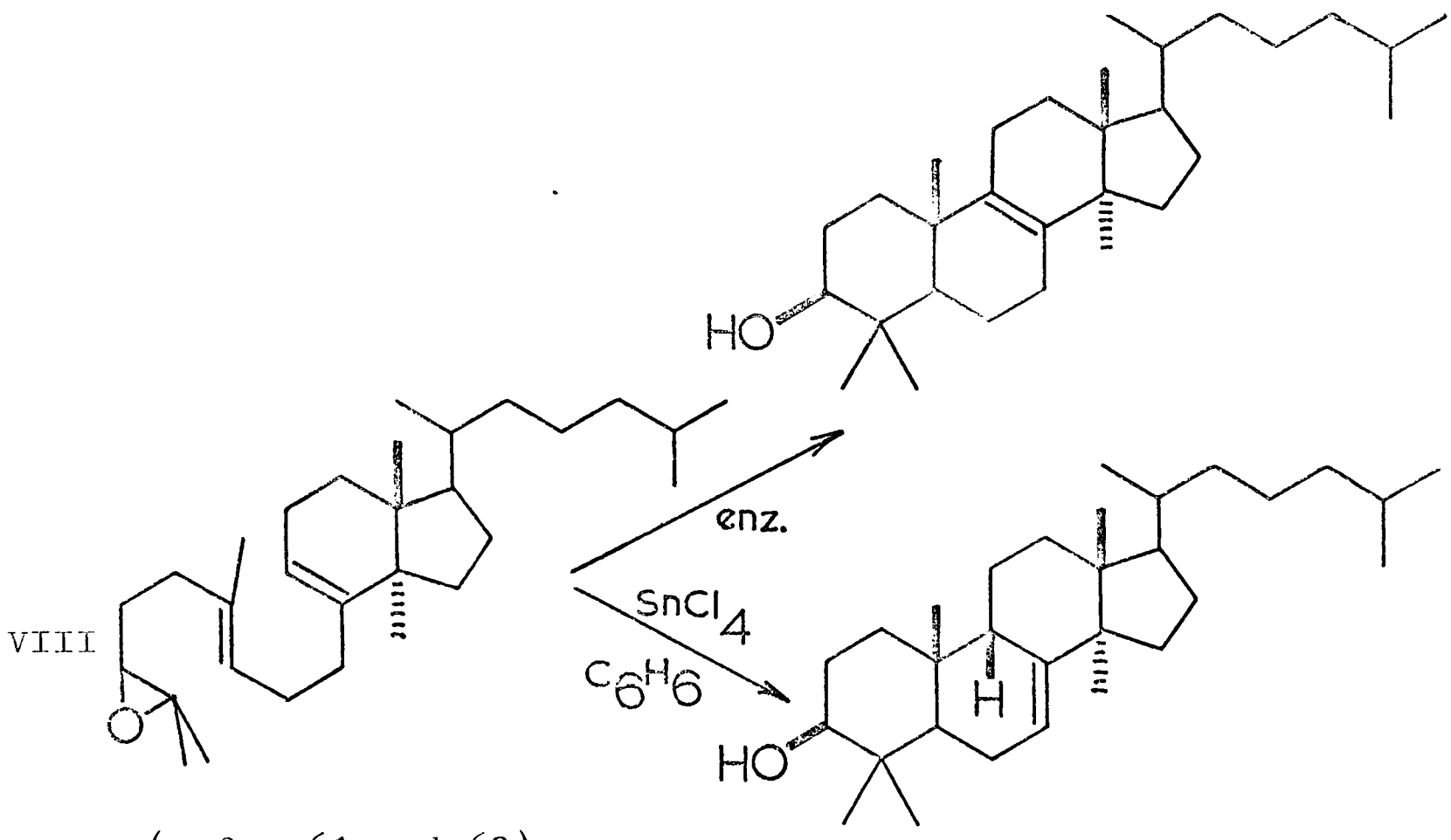
lanosterols, indicating that the enzyme has no specific requirement for this part of the molecule.

Scheme 4 (cont.)

Partially cyclised compounds



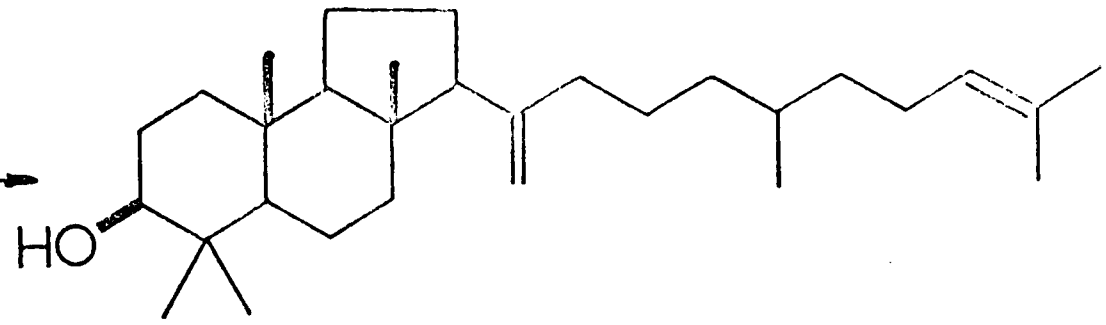
(Refs. 61 and 62)



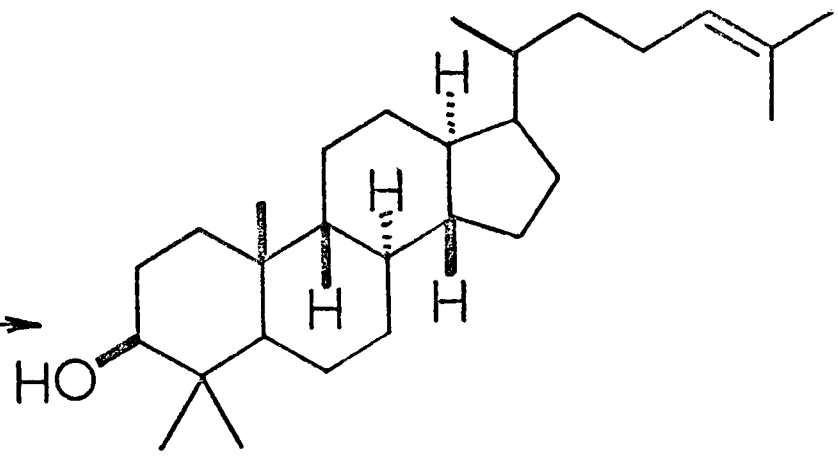
(refs. 61 and 63)

Modified squalene epoxides

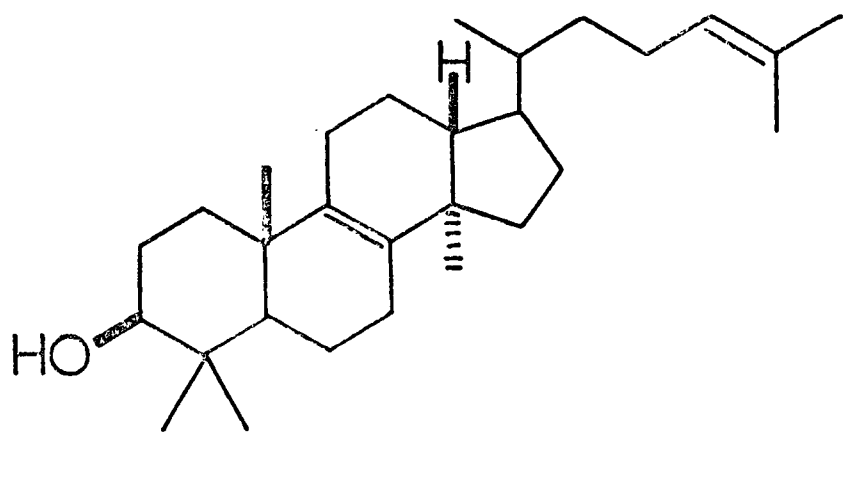
I 18,19-dihydro- → (Ref. 34)



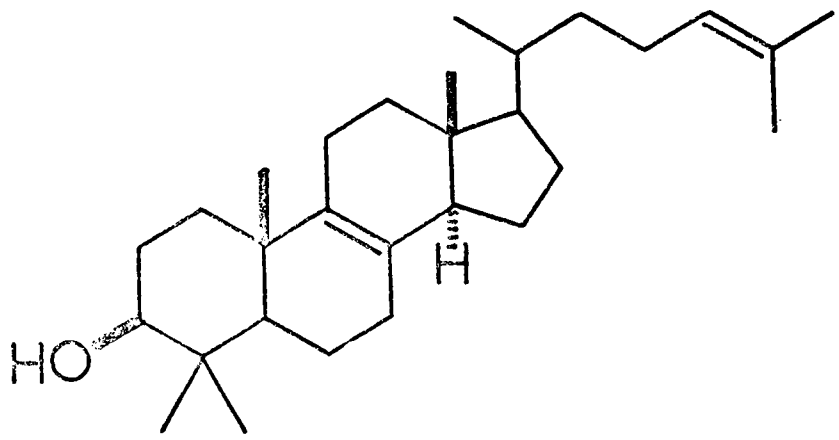
II 10',15'-bisnor- → (Ref. 56)



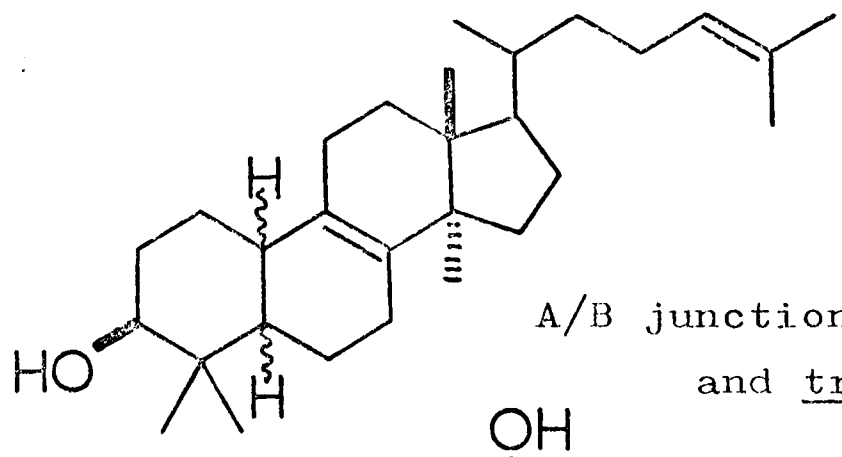
III 15'-nor- → (Ref. 57)



IV 10'-nor- → (Ref. 58)

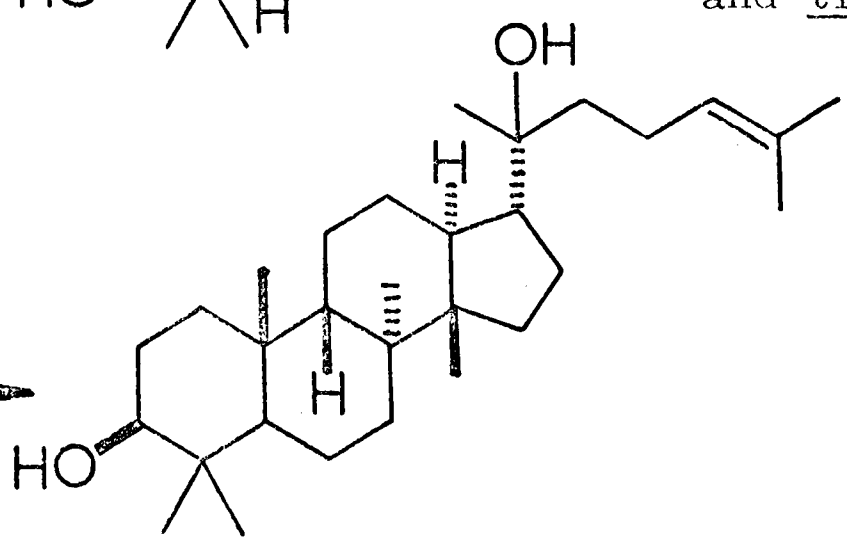


V 6'-nor- → (Ref. 59)



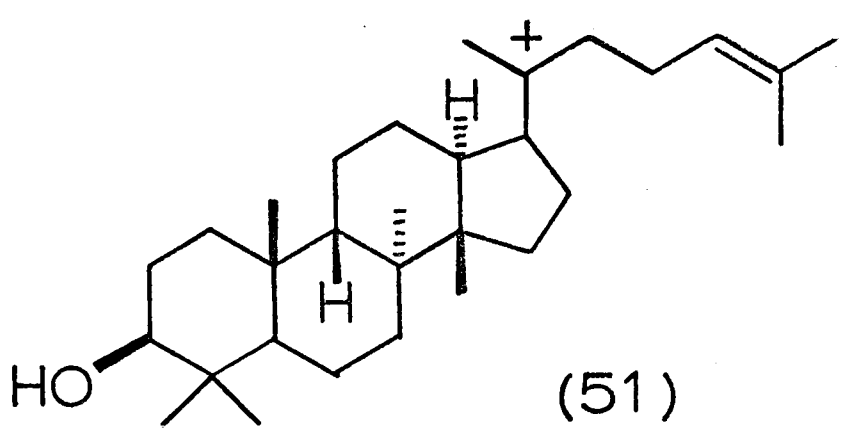
A/B junction cis and trans

VI 20,21-dehydro- → (Ref. 60)



(c) Central chain modification. The modified epoxides shown in Scheme 4 have been investigated.

The cyclisation of squalene 2,3-epoxide can be divided into two stages, the first leading to the ion (51), and the second leading from (51) via a series of methyl and hydride shifts to give lanosterol. The results above have indicated that it is possible to stop the process at the "protosterol" stage (51).

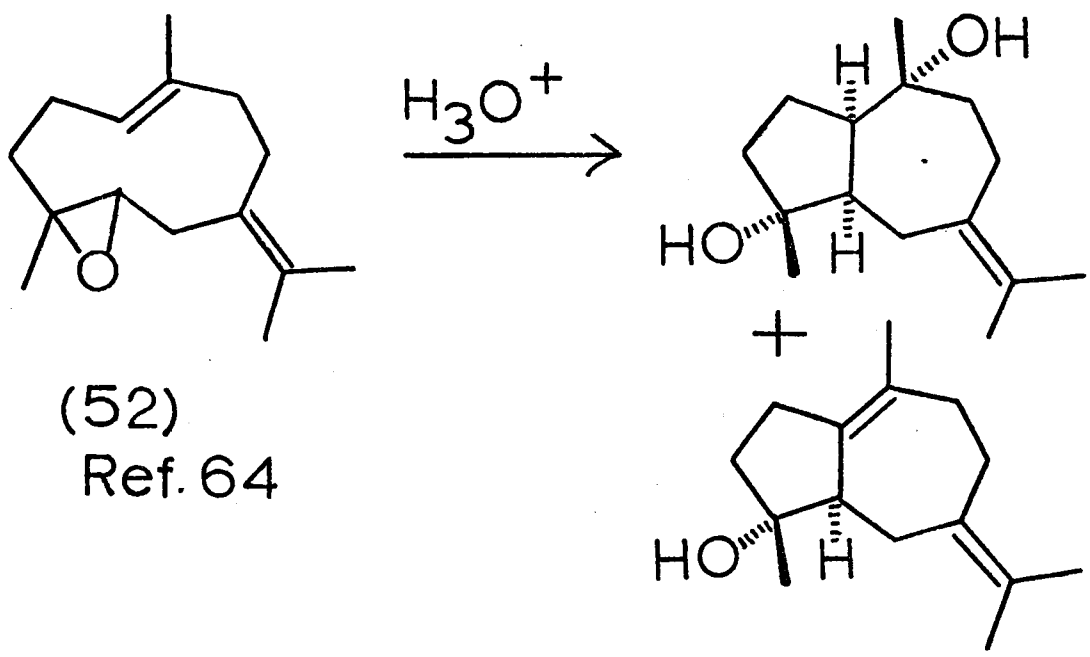


(51)

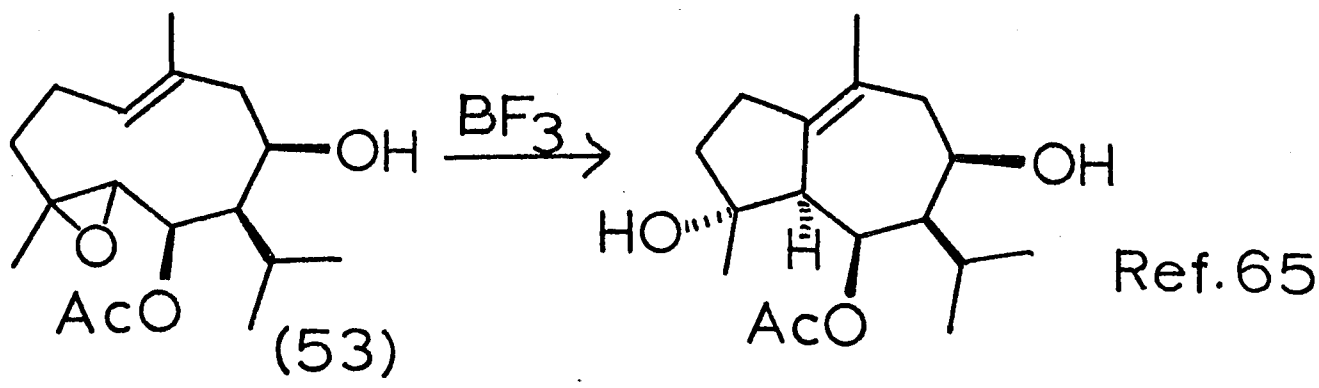
This has been achieved either by removing methyl groups in the region of ring B (II) (since relief of steric congestion around this boat ring must be a driving force for the rearrangement) or by providing a side-chain which blocks the rearrangement sequence (VI). That reactions (III), (IV), and (V) proceed to lanosterol derivatives indicates that the enzyme (or enzymes) responsible for the cyclisation has no particular interaction with the 6-, 10-, and 15- methyl groups, and reactions (VII) and (VIII) show that the enzyme can accept partially cyclised compounds and bring about reactions which are inherent in the reactivity of the molecule. The appearance of a 7,8-double bond in the non-enzymic reaction, and a 8,9-double bond in the enzymic reaction suggests[61] that the removal of a proton from C-9 may be controlled by a specific basic centre in the enzyme.

iv) Epoxides in Secondary Transformations.

The widespread occurrence of epoxides in nature, and their involvement in the biosynthesis of polyisoprenoids suggested that they might also be involved in various secondary elaborations of the carbon skeletons of natural products, by initiating ring closure and methyl migration reactions; both types of reaction have been carried out on suitable natural products in the laboratory, thereby providing chemical models for the possible biogenetic processes. Cyclisation was observed[64,65] when germacrane derivatives (52) and (53) were treated with acid catalysts;

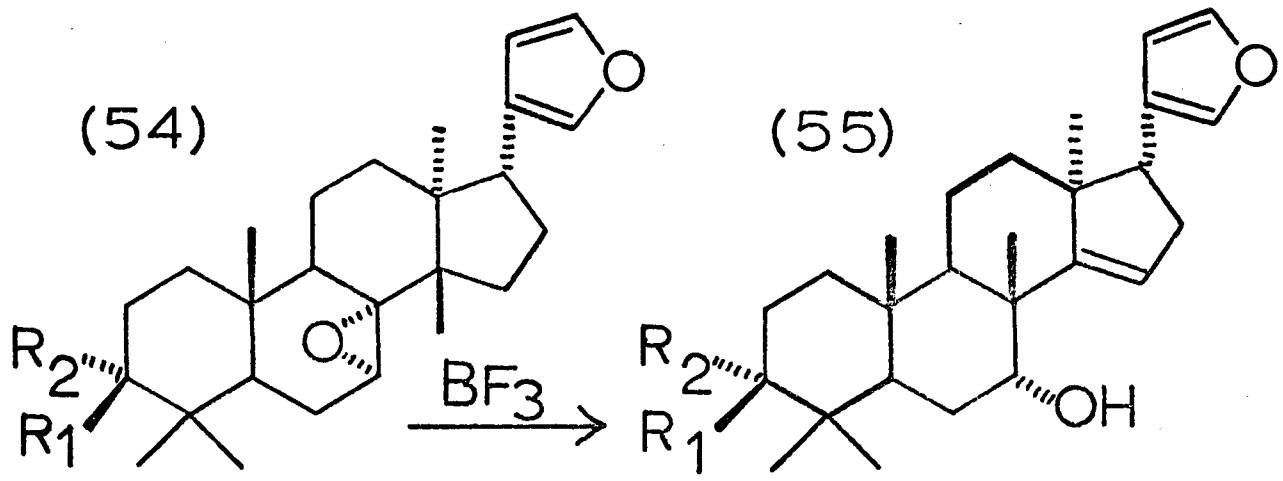


(52)
Ref. 64



(53)
Ref. 65

this suggests that germacranes are precursors to guaianes; methyl migrations have been observed in reactions which suggest that the tetranortirucallanes may be precursors to the meliacins,[66] e.g. (54)→(55).



I R_1=H R_2=OAc
ii R_1=OAc R_2=H
iii R_1R_2=O

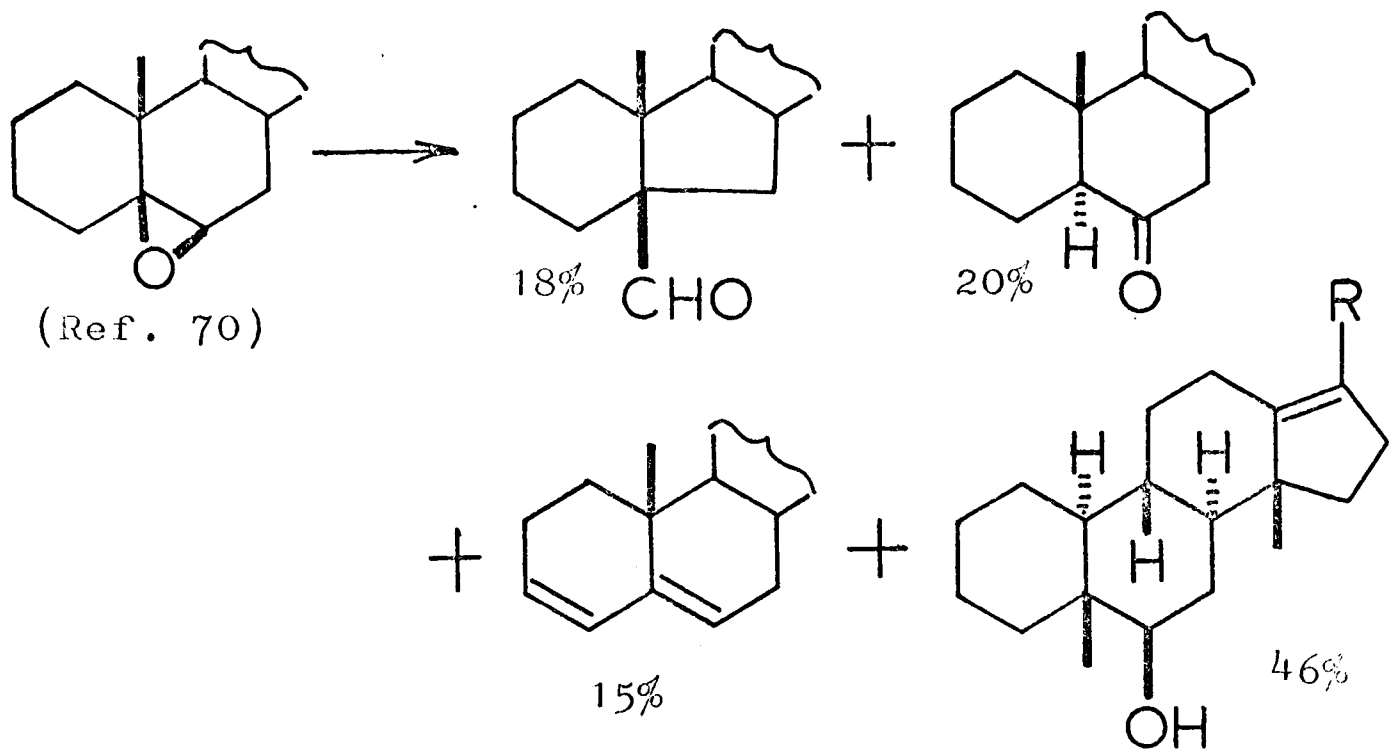
3. The Rearrangements of Epoxides of Cyclic Systems.

The biosynthetic transformations considered above have involved ring closure by interaction with a π-electron system, or methyl migration: considerable attention has also been paid to the rearrangements of epoxides of cyclic systems with Lewis acids, and in particular, steroidal epoxides with boron trifluoride-ether complex; a wide variety of rearrangements has been observed and rationalised to a certain extent.[67] Early work[68] was concerned with the formation of ketones from epoxides, and any other products tended to remain unidentified, although recent work has reinvestigated some of these products, which were often obtained in high yield. Fluorohydrins were often obtained, because unless boron trifluoride-ether complex is extensively purified by repeated distillation it may contain traces of hydrogen fluoride, which exists in the equilibrium;

$$HF + BF_3 \rightleftharpoons HBF_4$$

and attack by fluoride ions may compete with the normal intramolecular rearrangement. The rearrangements of steroidal epoxides occasionally

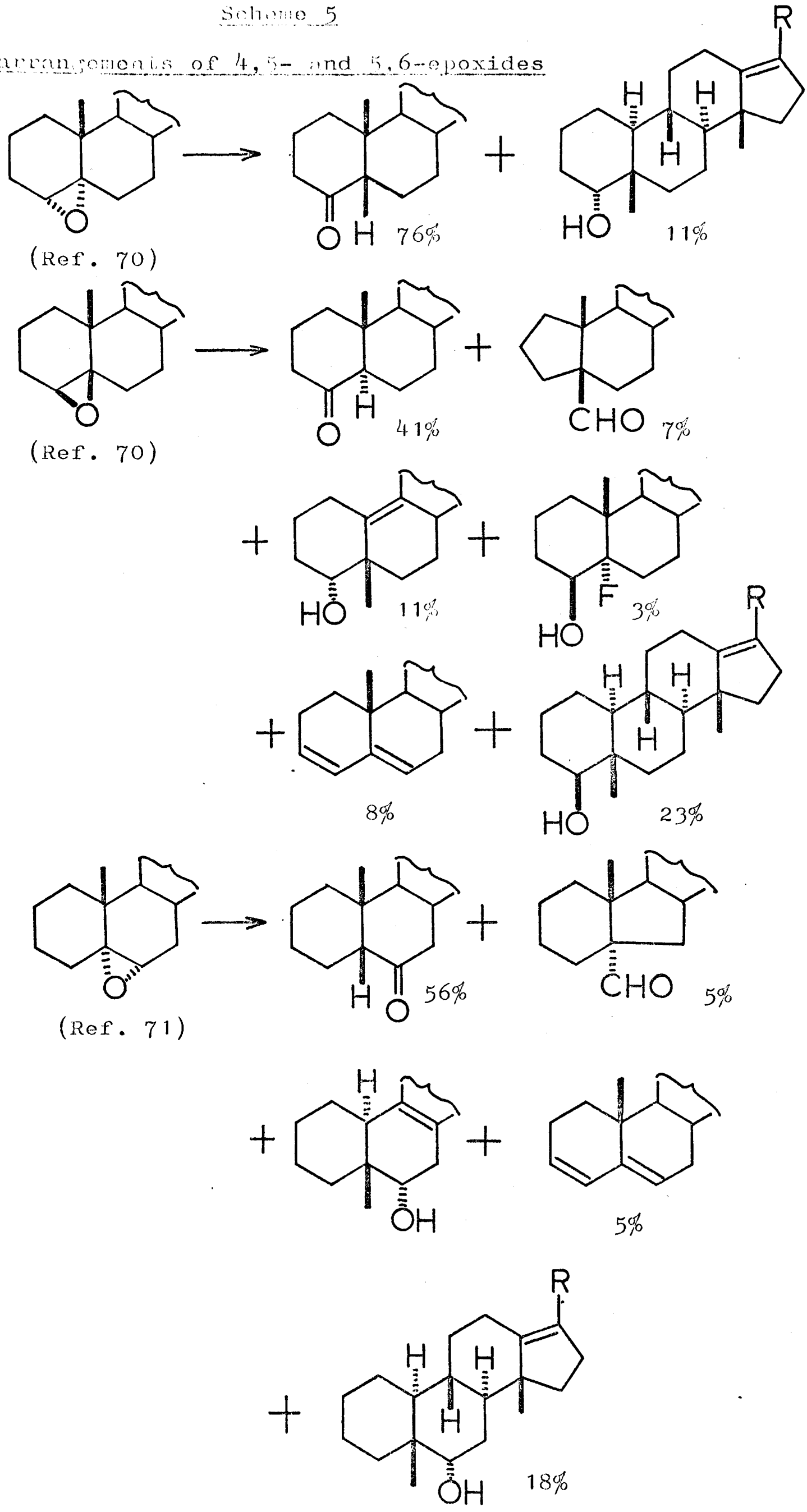
Scheme 5 (cont.)



(R = C_8H_{17})

Scheme 5

Rearrangements of 4,5- and 5,6-epoxides



yield a single product, but usually between two and six identifiable products are obtained, and as some of these are of similar structure, problems of separation and identification are often considerable. The number and variety of products obtained means that any underlying rationale which is devised must be flexible in approach; a number of important factors in epoxide rearrangements have emerged, but a priori predictions of the course of rearrangements are still difficult to make.

Three classes of steroidal epoxides have been studied extensively, and these will be considered in turn.

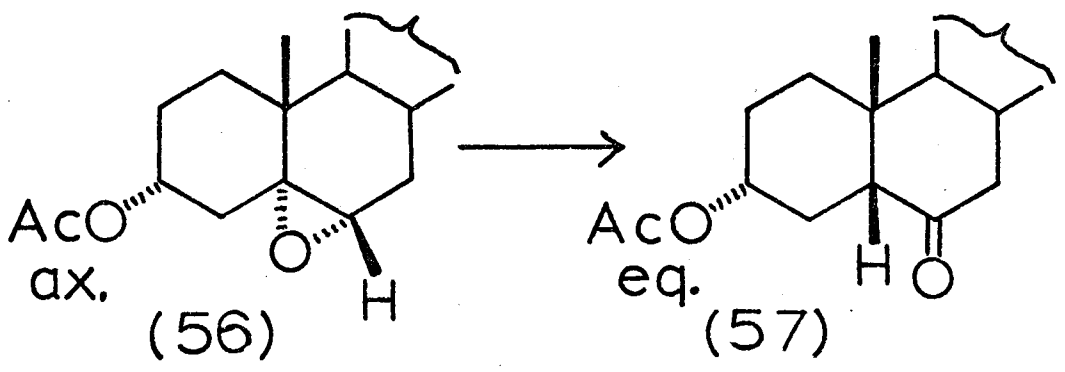
i) Trisubstituted Epoxides.

On treatment with boron trifluoride-ether complex in benzene these rearrange by initial cleavage of the C-O bond at the tertiary centre followed by migration of a suitable neighbouring group. In the case of 4,5- and 5,6-epoxy-steroids (Scheme 5), hydride migration to give a ketone is common, and skeletal migration to give an aldehyde can also occur, but to a lesser extent. The other type of rearrangement found with these epoxides is referred to as a "back-bone rearrangement"[69] as it involves a series of stereospecific hydrogen and methyl migrations down the "spine" of the molecule, initiated by migration of CH_3-19 from C-10 to C-5; the occurrence of this rearrangement with the β-epoxides indicates that the C(5)-O bond must cleave to give a carbonium ion as the first stage, before the apparently cis CH_3-19 can migrate. Other hydroxy-olefins are formed by proton elimination α to the carbonium ion site, but these species then eliminate water to give dienes.

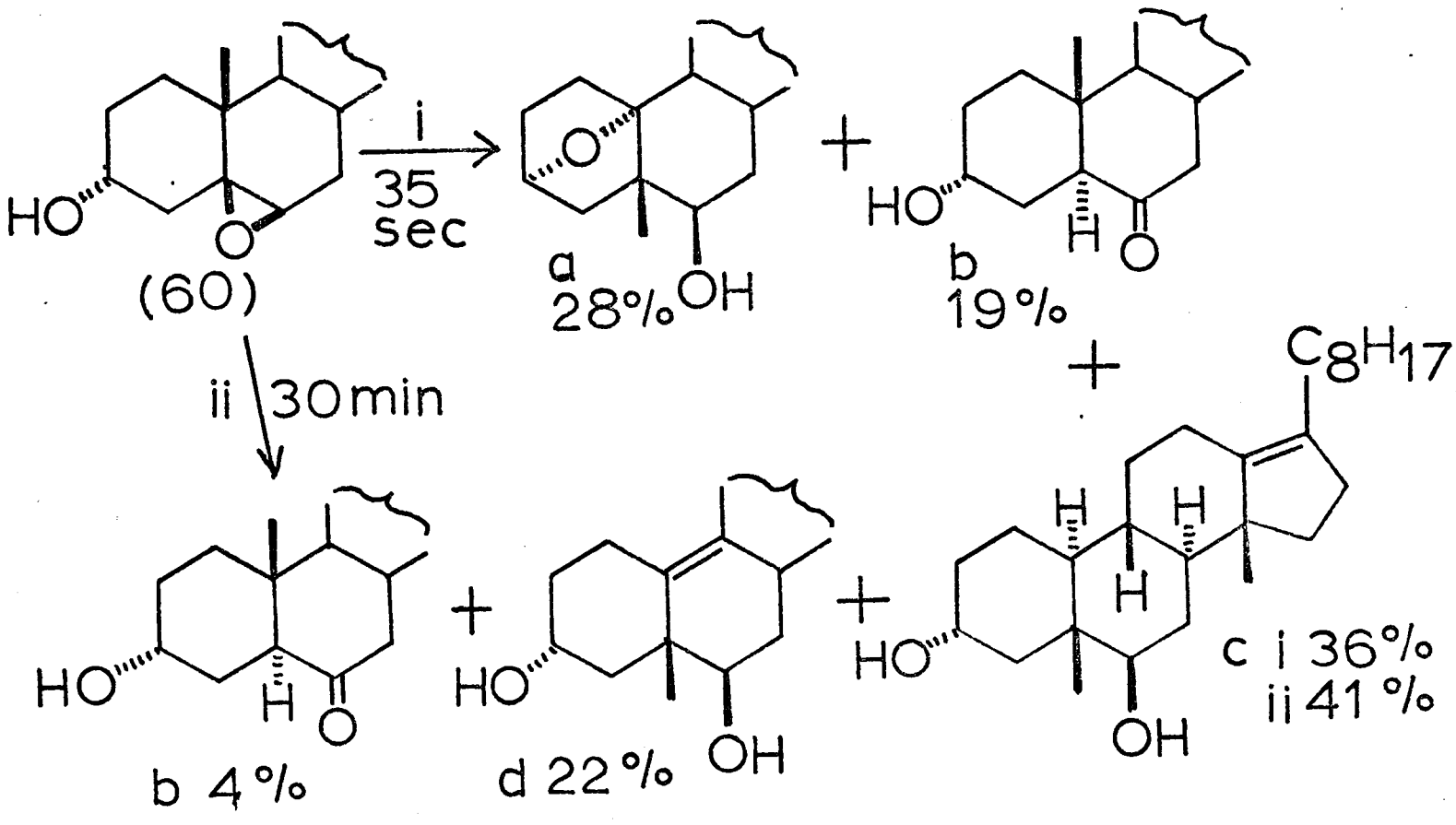
The introduction of a substituent at C-3 can sometimes alter the course of a rearrangement, and the effects of substituents can be rationalised in terms of steric, conformational, and inductive

influences.[68] Thus the 3α-acetoxy-5α, 6α-epoxide (56)[72] gives the 5β,6-ketone (57) because this transformation shifts the bulky acetoxy-group from an axial to an equatorial position; whereas in a system containing fluoride ions, the 3β-epimer (58)[68] gives a fluorohydrin (59), because ketone formation is hindered by the acetoxy-group, which would move from an equatorial to an axial position during such a reaction; further, the acetoxy-group exerts a strong -I effect, making bond cleavage at C-5 unfavourable, so nucleophilic attack by fluorine occurs at C-6.

Other substituents at C-3 which have been investigated are hydroxy-[73,74] and ethylenedioxy-,[75] and although these groups participate in the rearrangement, the rearrangement products are those expected on simple stereoelectronic grounds. A factor which is not fully understood is that governing the amount of back-bone rearranged material which is formed



compared with simple carbonyl products, but it must be related to overall relief of steric strain, as back-bone rearranged products tend to be thermodynamically more stable and are formed in larger amounts after longer reaction times, e.g. the 3α-hydroxy-5β, 6β-epoxide (60)[74] gives three products after 35 seconds, while after 30 minutes, none of the cyclic ether (60a) is found:

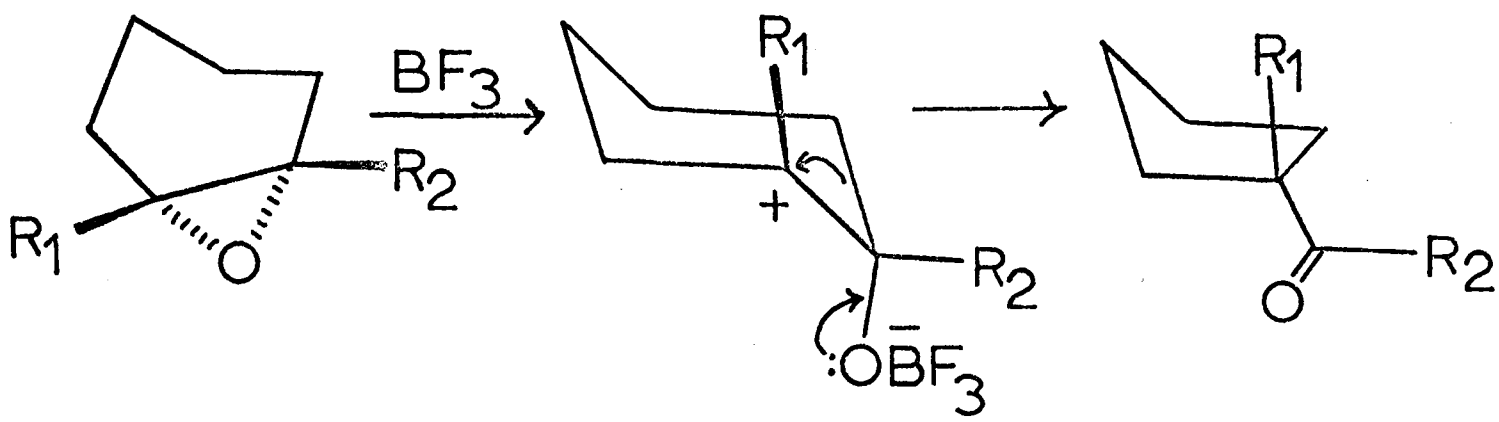


a separate experiment showed that a ⟶ c + d under the conditions of the reaction.

ii) Tetrasubstituted Epoxides.

A large number of tetrasubstituted steroidal epoxides (4-methyl-4,5-epoxides and 6-methyl-5,6-epoxides) were rearranged by Hartshorn and Kirk,[76] and by analysing the conformations of the epoxides and their rearranged products, they were able to explain why the epoxides showed preferential cleavage of one of the C-O bonds, despite there being no overwhelming electronic preference. They proposed a rule of "axial cleavage" which states that a 1,2-disubstituted-epoxycyclohexane will tend to react by cleavage of that C-O bond which permits the oxygen to become axial in the chair conformation of the ring corresponding most nearly to the half-chair conformation of the original epoxy-substituted ring.

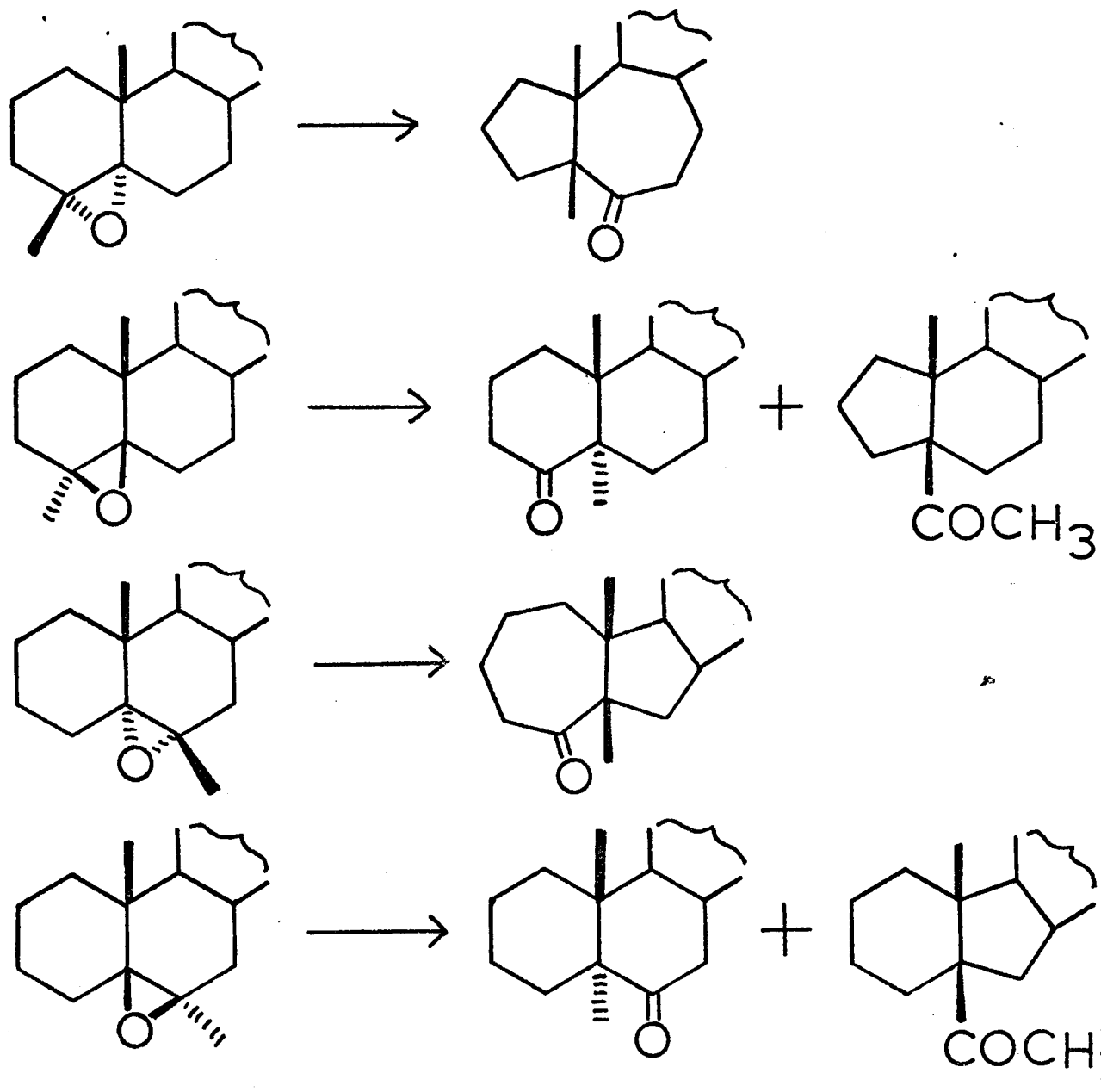
axial cleavage



This rule predicts that 4α,5α- and 5α,6α-epoxides will cleave to give the oxygen axially bound at C-5, while 4β,5β- and 5β,6β-epoxides will give 4β - or 6β -axial oxygen; this prediction identifies the carbonium ion site, but gives no indication of the subsequent rearrangement pattern. The simple 4-methyl-4,5-[77] and 6-methyl-5,6-epoxides[78] give ketones by C-C migration (Scheme 6).

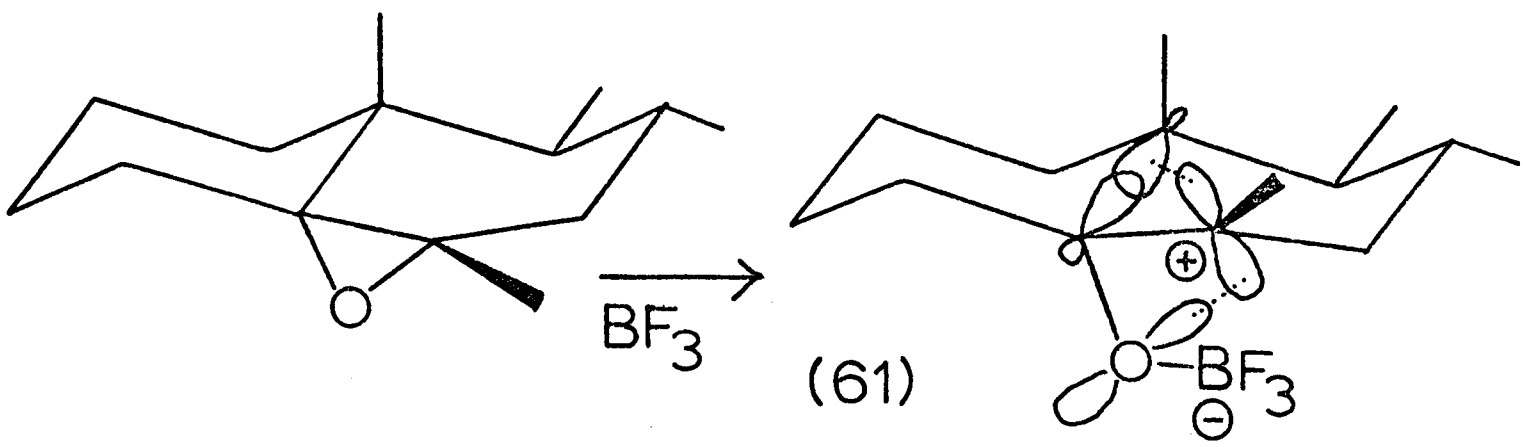
These reactions can be explained[79] in terms of a transition state of an S_N2 type, with continuing partial overlap of the filled orbital of the oxygen atoms with the formally vacant p-orbital of the $\underline{sp}^2$ hybridised carbon atom, up to the point where rear-side overlap can commence with

Scheme 6



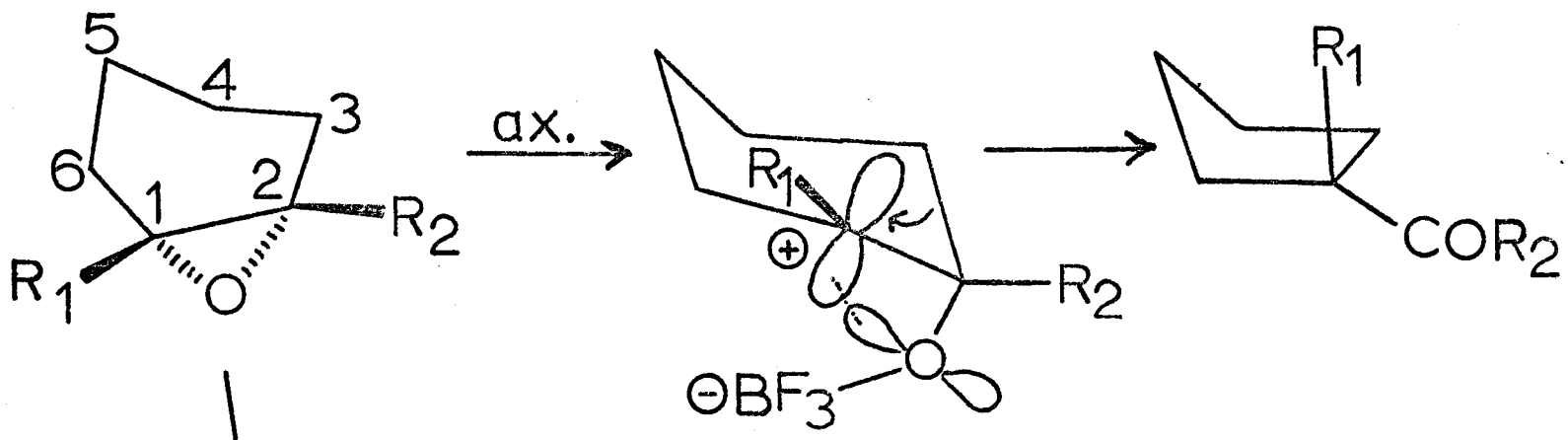
Ref.
77
77
78
78

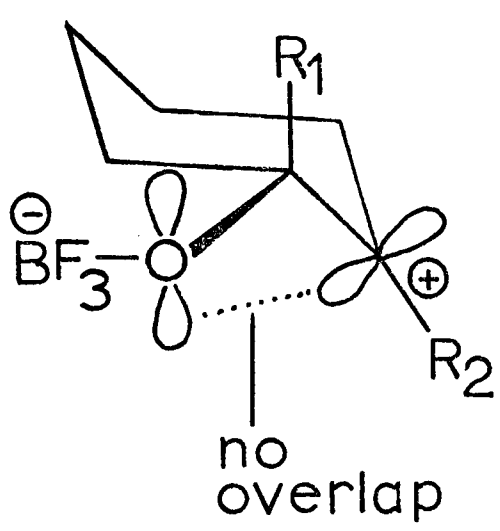
the orbital of the migrating group (61).

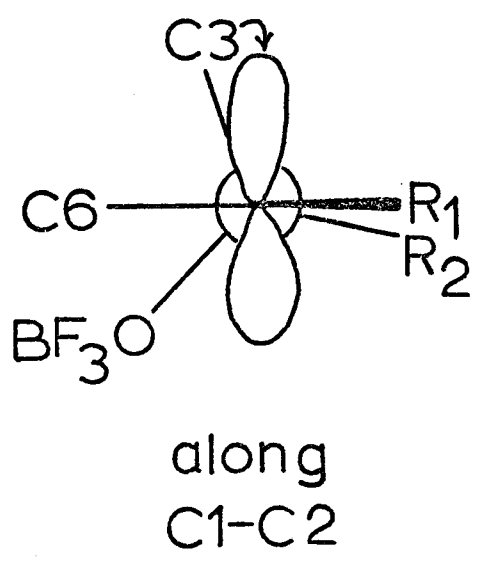


The group which migrates in simple ketone formation is that which lies closest to the direction of the "vacant" p-orbital, so that groups lying in or near the plane of the carbonium ion are unable to migrate. This approach explains why axial cleavage is favoured over equatorial, because only in an axial conformation can the oxygen orbital maintain some

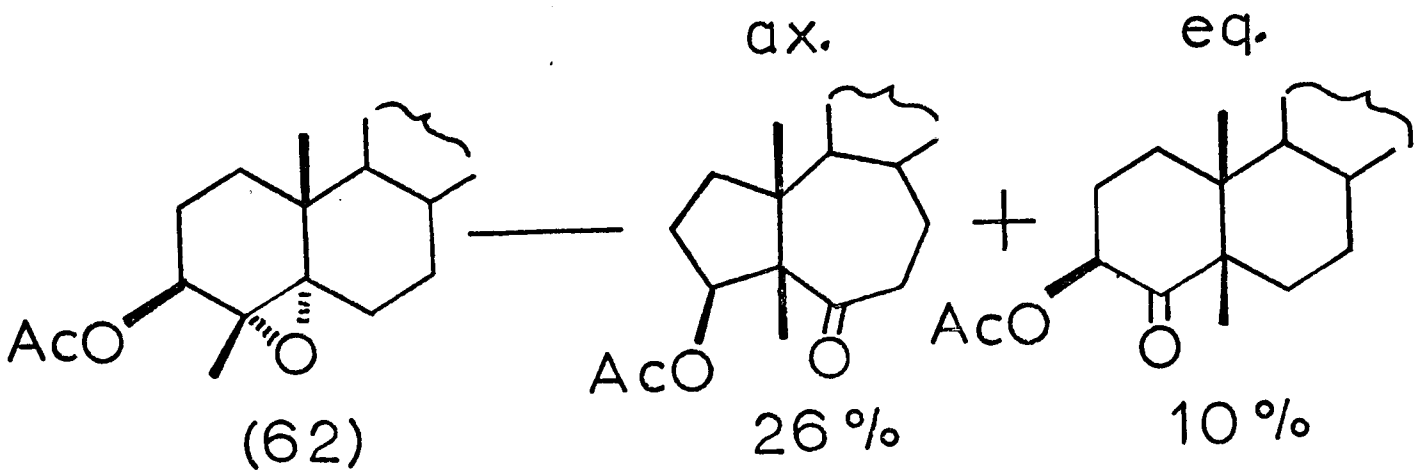
overlap with the p-orbital at the carbonium ion site, until rearside attack by the migrating group commences; no such overlap is possible in the equatorial case, so the transition state is of higher energy.





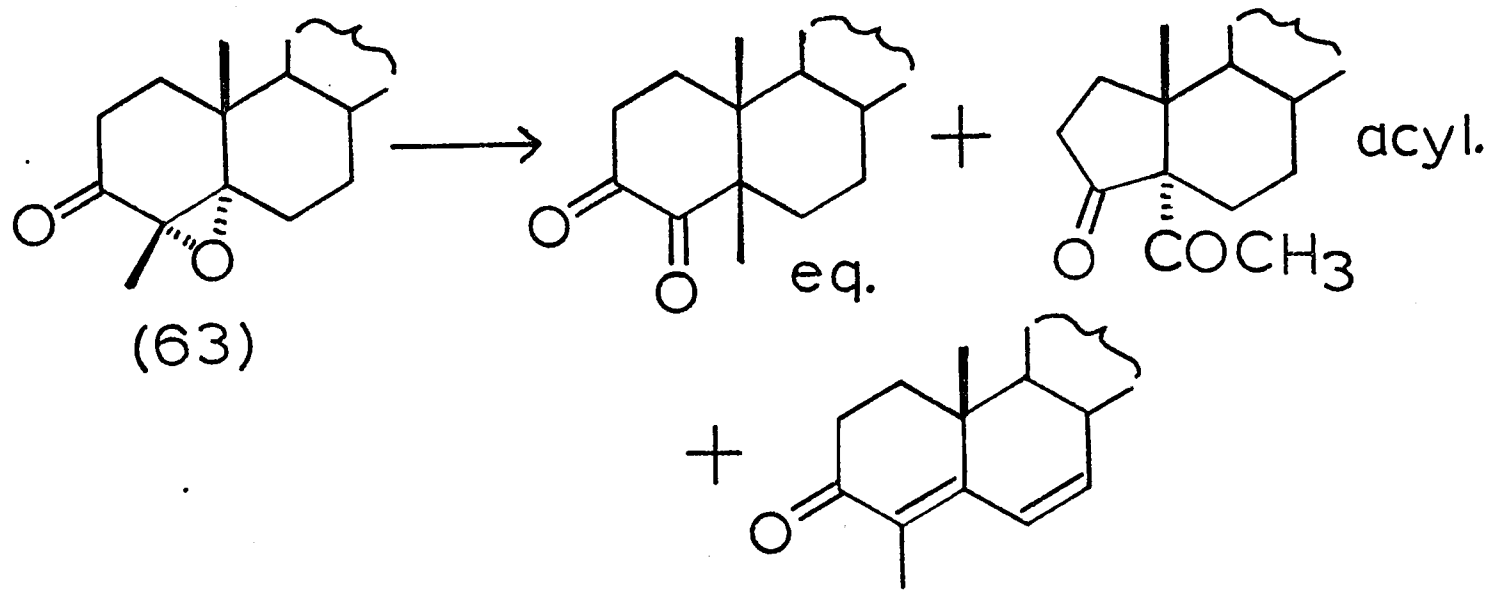


The rule of axial cleavage may be nullified by substituents with opposing steric, conformational, or electrostatic effects; an acetoxy-group at C-3 of a 4-methyl-4α,5α-epoxide[80] can cause equatorial cleavage to occur, since axial cleavage involves formation of a carbonium ion at C-4, which is opposed by the -I effect of the acetoxy-group; thus equatorial cleavage also occurs, generating a carbonium ion at C-5, and with (62), a mixture of the two products is formed.



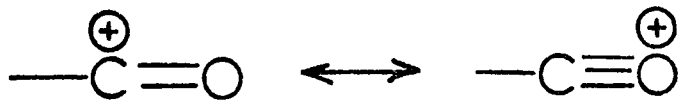
(62) 26 % 10 %

Another factor is the tendency for acyl migration to occur in αβ-epoxy-ketones, with concomitant ring contractions. With the 3-keto-4α,5α-epoxide (63) both equatorial cleavage and acyl migration are observed;[80]

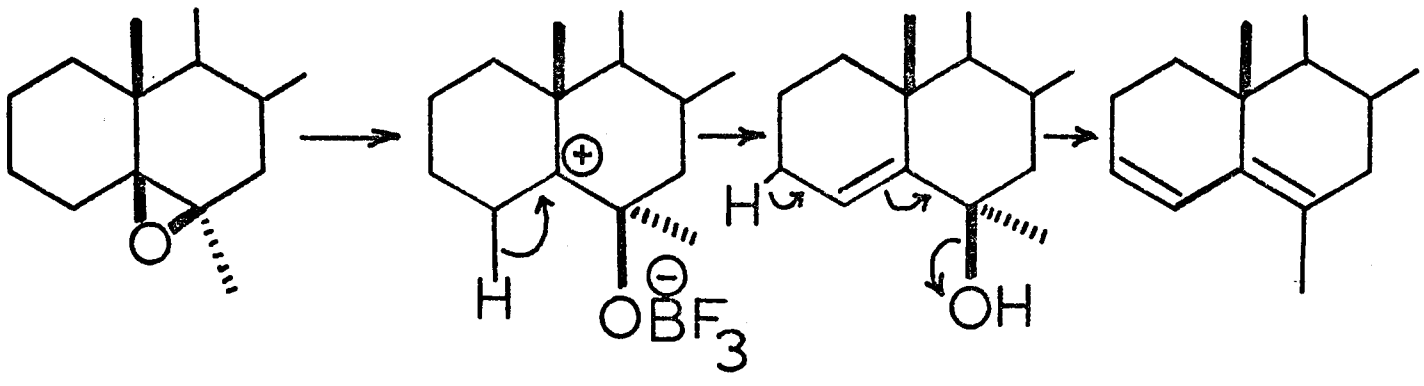


(63)

acyl migration is presumably enhanced by the ability of the carbonyl group to delocalise positive charge.



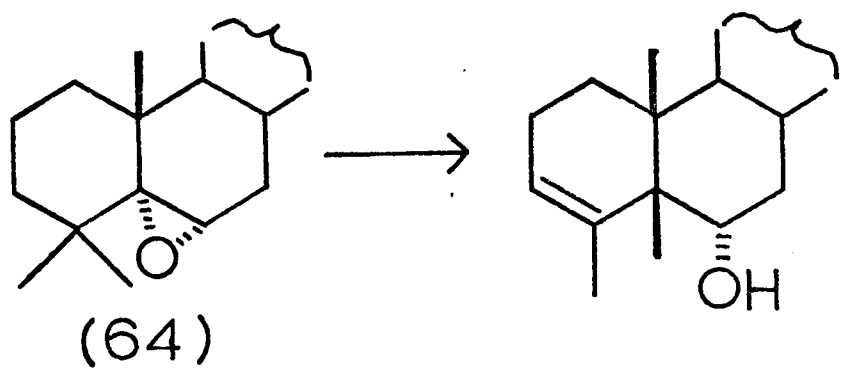
In some of the cases studied, the initially formed carbonium ion loses a proton, with or without skeletal rearrangement to give a hydroxy-olefin,[78] which may then eliminate further to give a diene.



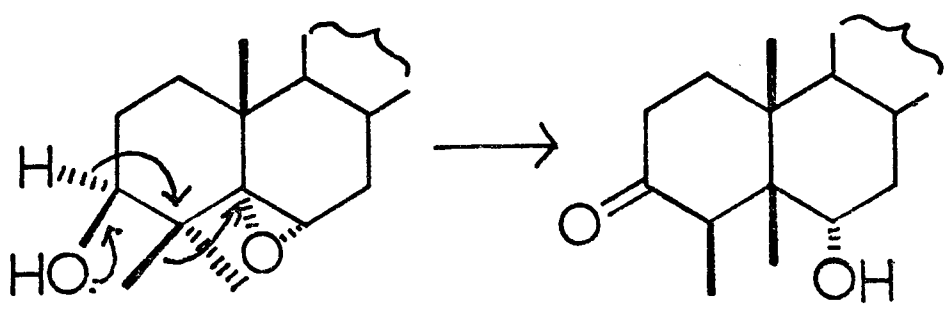
When a carbonium ion is formed at C-5, a Westphalen migration of CH_3-19 to C-5 may initiate a back-bone rearrangement as described above.[81]

iii) 5,6-Epoxy-4,4-dimethyl-steroids.

Rearrangements leading to hydroxy-olefins have been encountered with these trisubstituted epoxides,[82-84] and very little carbonyl formation is found. The unsubstituted 4,4-dimethyl-5α,6α-epoxide (64)[84] gives the product resulting from migration of the 4β-methyl group to C-5, and a similar reaction occurs with the 3β-hydroxy-analogue (65);[82] this reaction is thought to be enhanced by "push" from the lone pair electrons on the hydroxy-oxygen.

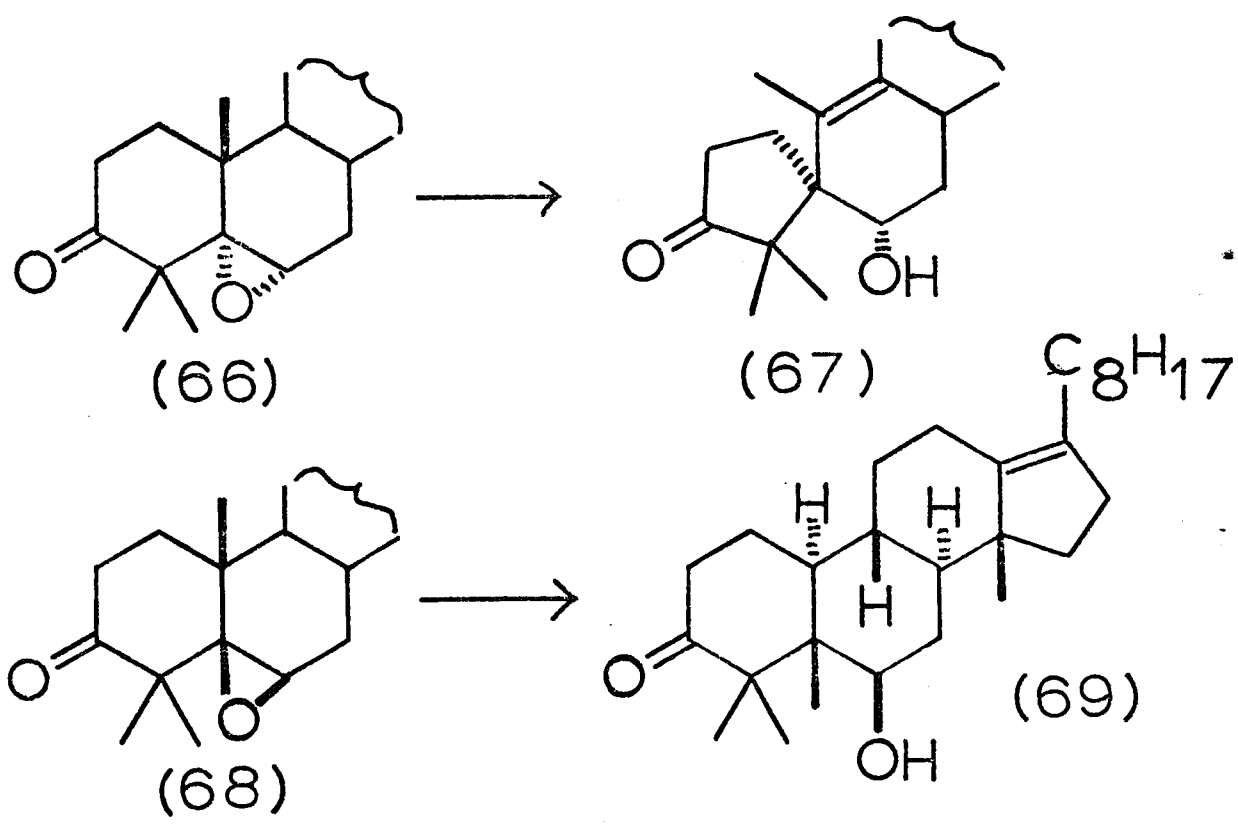


(64)

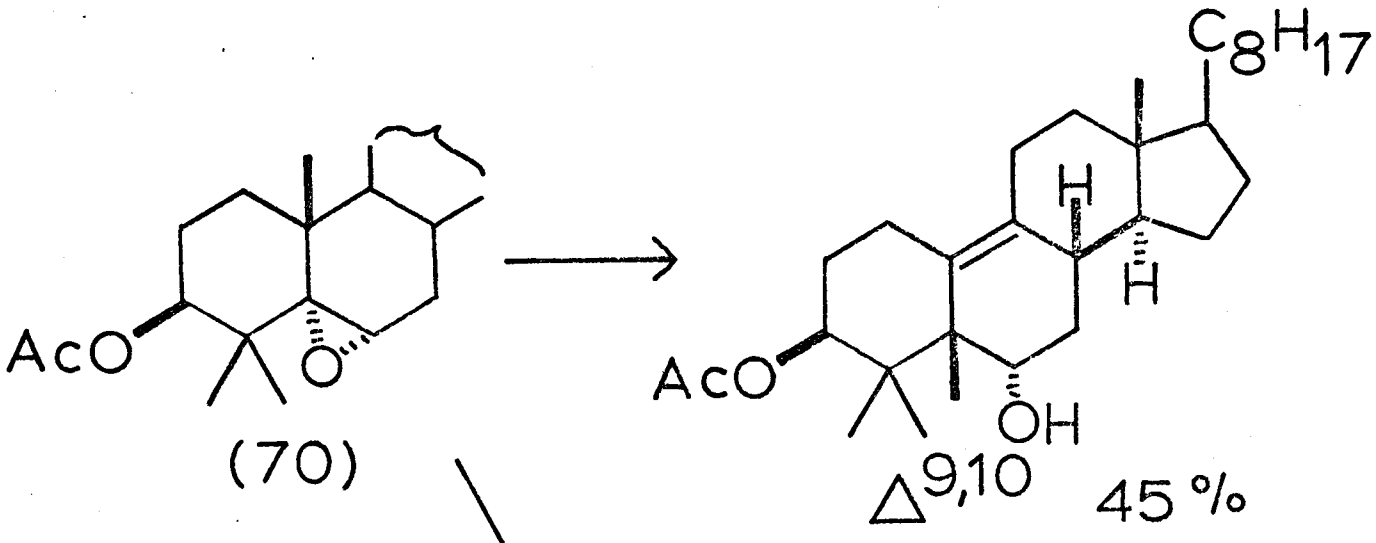


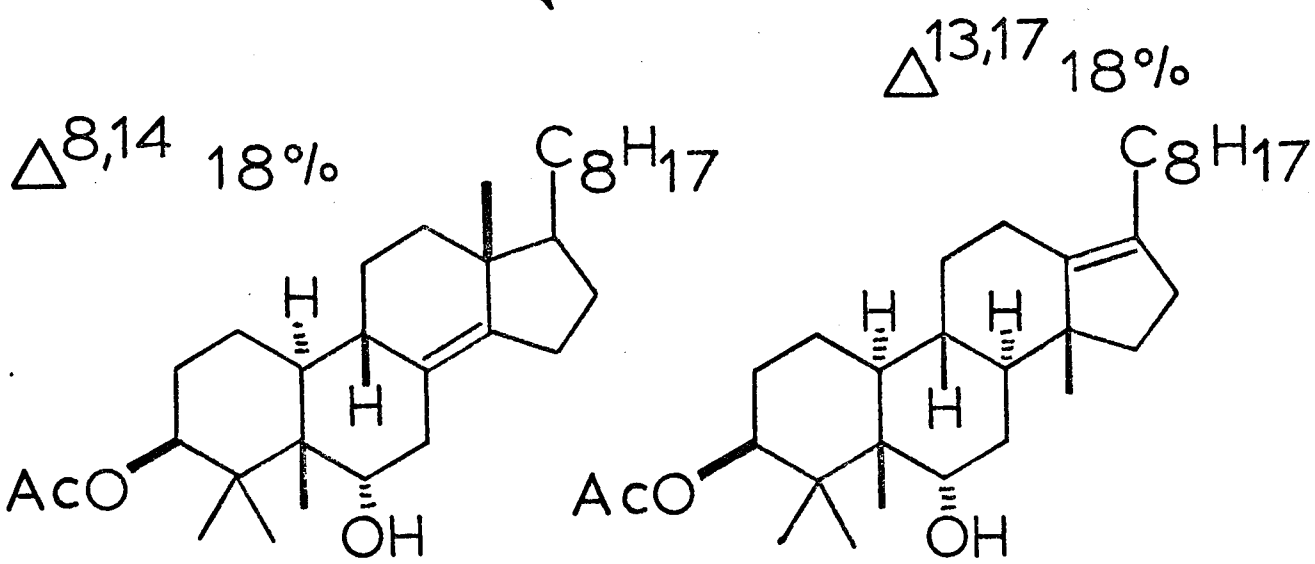
(65)

The introduction of electron-withdrawing groups at C-3 makes migration of a methyl group from C-4 unfavourable, and migration of a group attached to C-10 becomes predominant; the 3-keto-5α,6α-epoxide (66)[82,83] gives the spiro-product (67), formed by migration of C-1 methylene to C-5, while the 3-keto-5β,6β-epoxide (68) gives the backbone rearranged product (69).



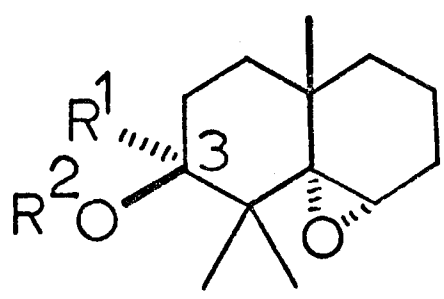
The 3β-acetoxy-5α,6α-epoxide (70)[84] gives three hydroxy-olefins, with double bonds situated at 9,10, 8,14, and 13,17 which is a strong





indication that the back-bone rearrangement proceeds by a series of discrete carbonium ions.

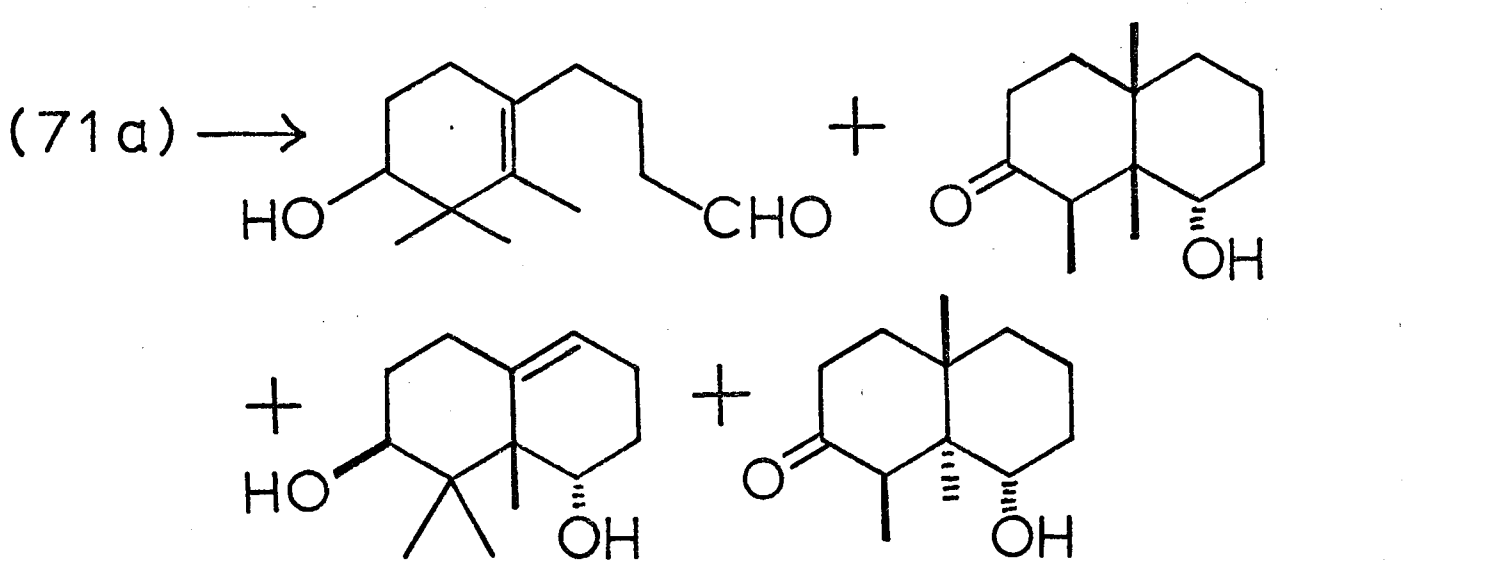
More direct evidence for the intermediacy of carbonium ions in these types of rearrangement has recently been provided by Whitlock and Olson,[85] who studied the rearrangements of the model epoxides (71) and (72).

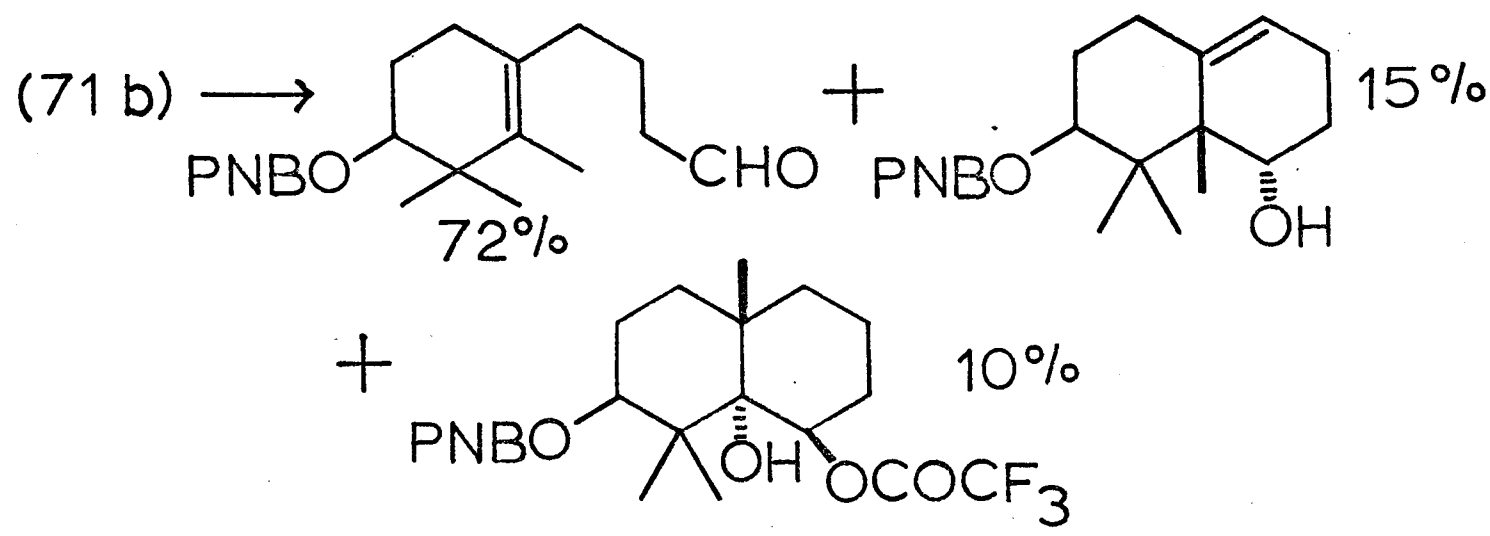


(71) $R^1 = H$
(72) $R^1 = D$

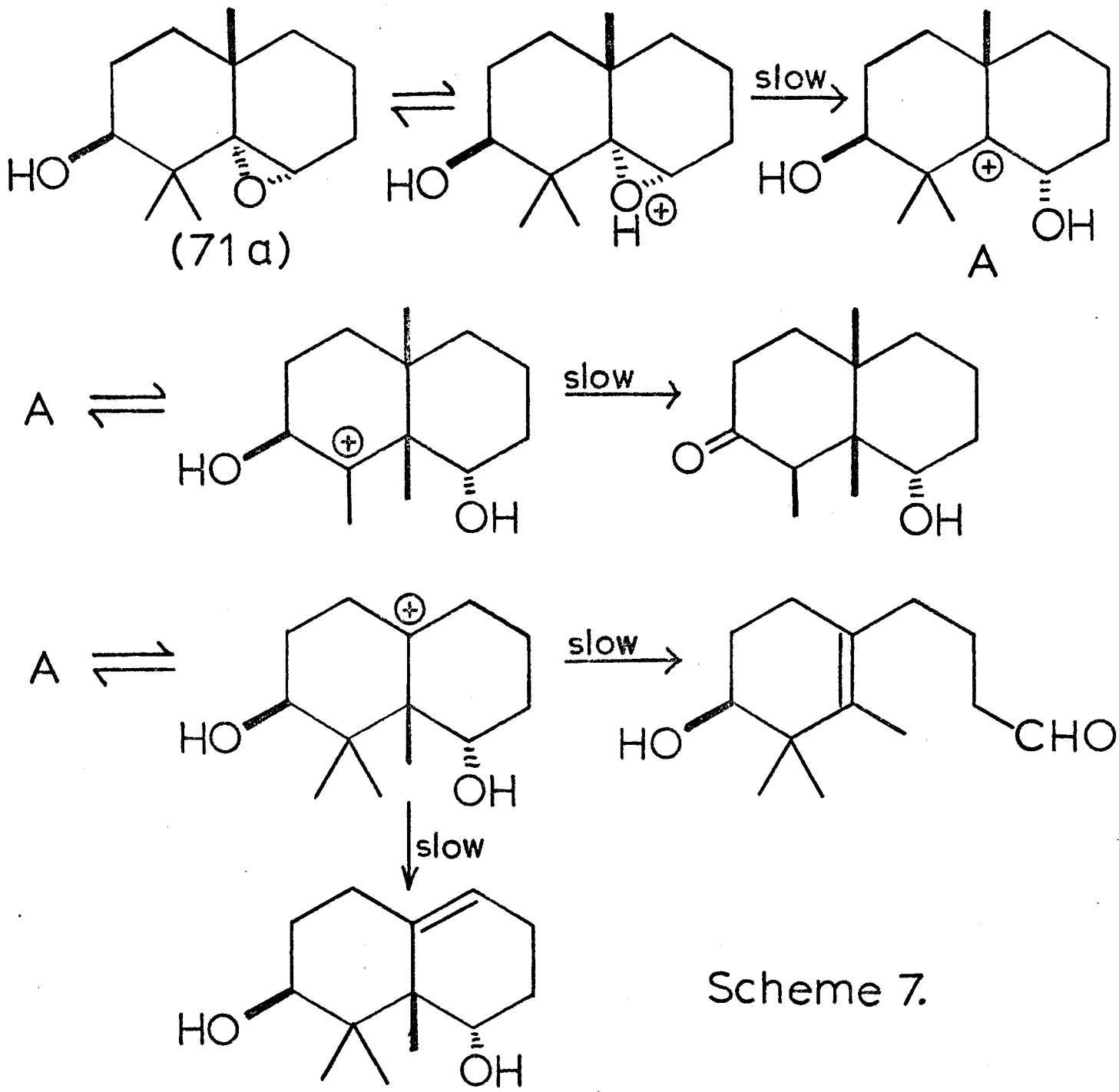
(a) $R^2 = H$
(b) $R^2 =$ PNB
$\underline{p}NO_2C_6H_4CO-$

The ester epoxide (71b) was opened using trifluoroacetic acid in chloroform, and the hydroxy-epoxide (71a) was treated with both TFA in chloroform, and the more usual boron trifluoride-ether complex in benzene; both reagents gave qualitatively similar products, although the latter produced much "non-volatile and resinous matter".





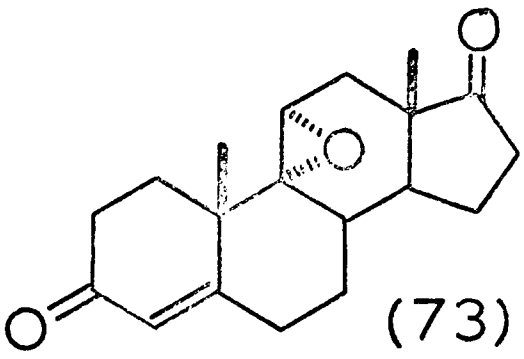
It can be seen that these reactions provide reasonable models for the behaviour of their steroidal counterparts. The kinetic isotope effect for the disappearance of (71a) against (72a) was found to be unity, but an isotope effect on the product ratios was observed, and was interpreted as indicating the irreversible rate determining formation of a set of rapidly interconverting carbonium ions, which then afford the isolated products (Scheme 7).



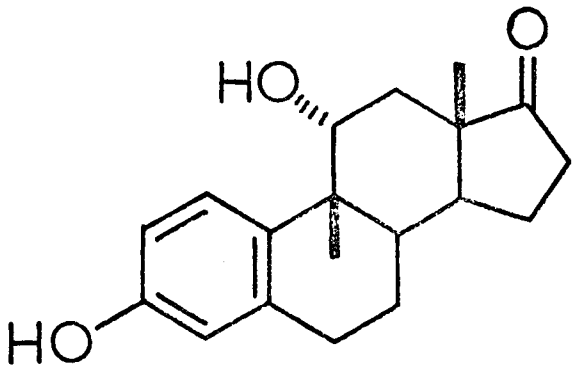
Scheme 7.

iv) Intramolecular Proton Abstraction.

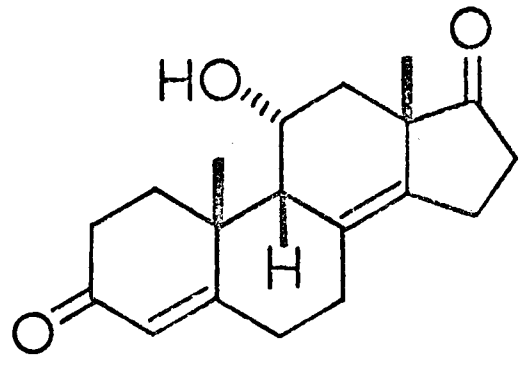
One further factor which may determine the course of epoxide rearrangements was postulated by ApSimon et al.[86] in 1969; in attempting to bring about a methyl migration from C-10 to C-9, they treated the 9α,11α-epoxide (73) with boron trifluoride-ether complex in benzene, but obtained no reaction: on repating the reaction using boron trifluoride gas, they obtained the desired product (74) in 30% yield, along with a homoallylic alcohol (75).



(73)

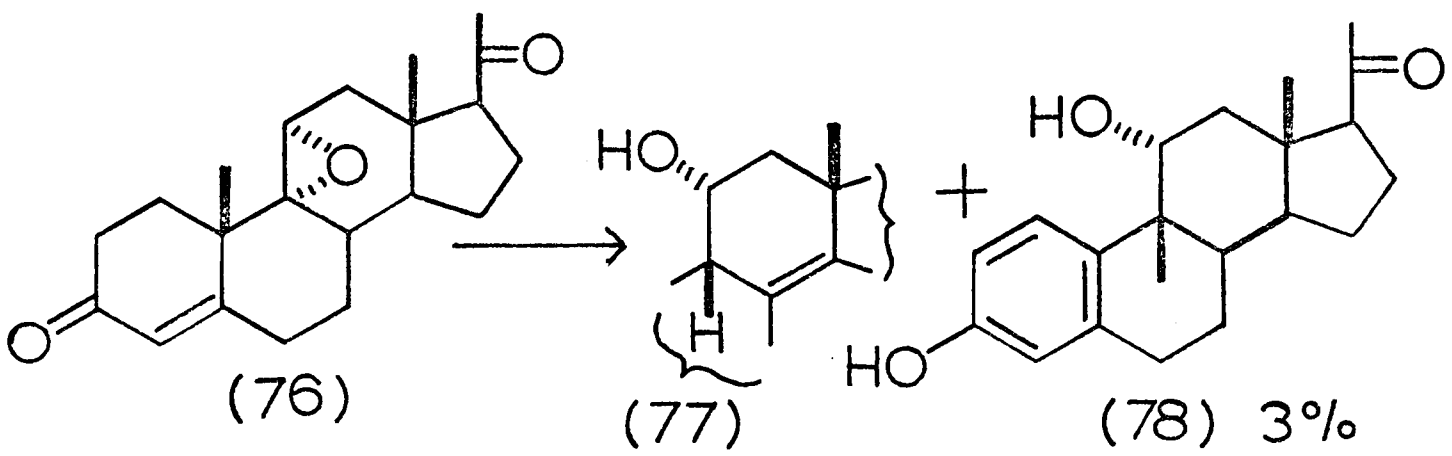


(74)
30 %

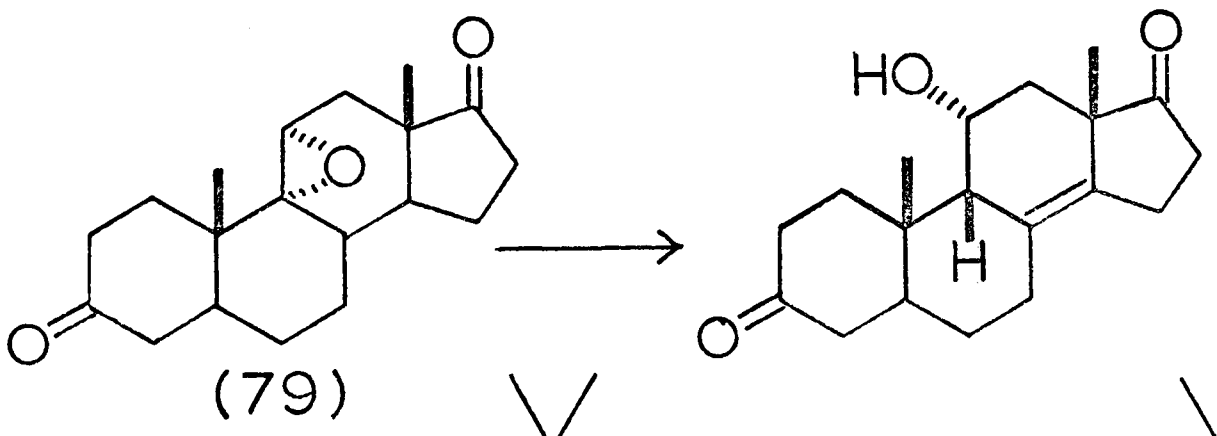


(75)

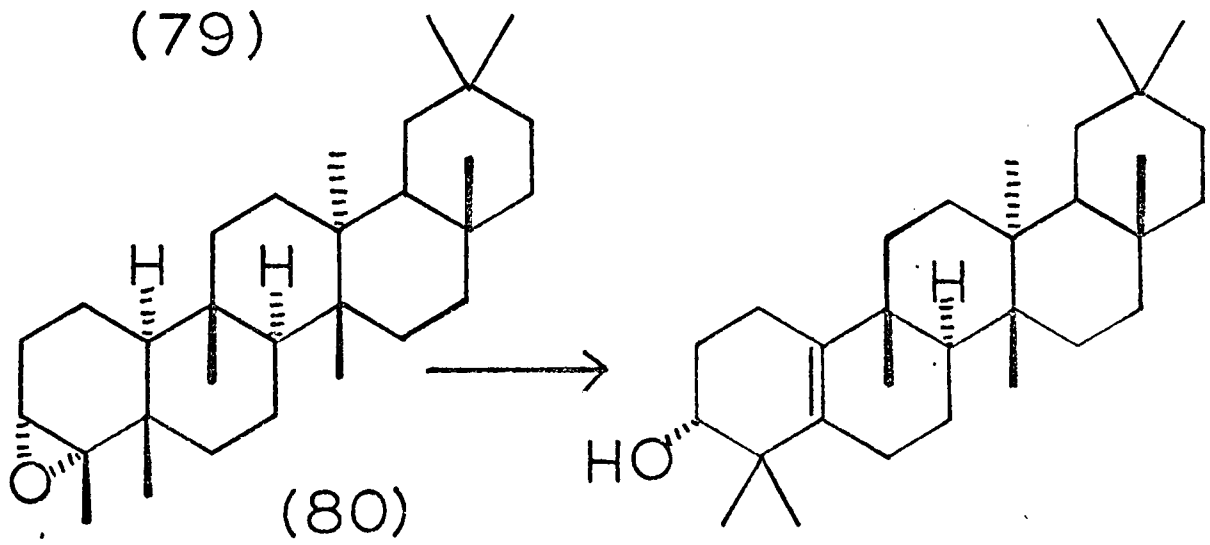
When the 17-acetyl compound (76) was rearranged, only 3% of the methyl migration product (78) was obtained with a large yield of homoallylic alcohol (77), and similar products were obtained from the epoxides (79) and (80).



(76) (77) (78) 3%



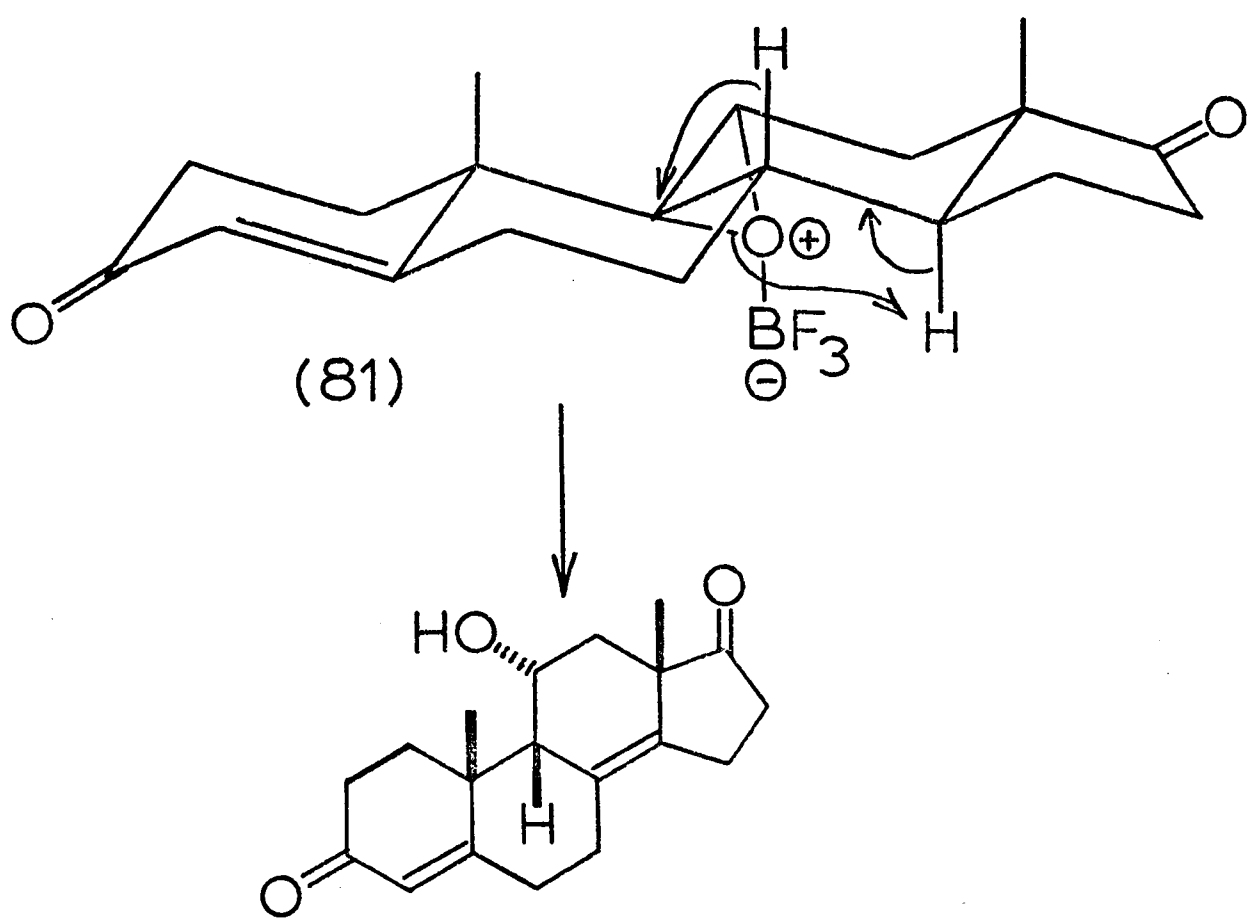
(79)



(80)

One common structural feature in all these epoxides is a hydrogen in a 1,3-diaxial relationship with the epoxy-oxygen. Using boron tri-

fluoride gas rather than the ether complex, the only proton extractor present is the epoxy-oxygen, which might react with the axial hydrogen in a concerted step (81).



Such a rearrangement could override the aromatisation of ring A which might favour methyl migration in (76) and (79), and can block a back-bone rearrangement in the epoxy-friedelin (80). The greater yield of homoallylic alcohol from (76) compared with (73) can be rationalised by the fact that the acetyl group at C-17 causes slight deformation which pushes the C-14 hydrogen nearer to the epoxide oxygen, favouring intra-molecular abstraction.

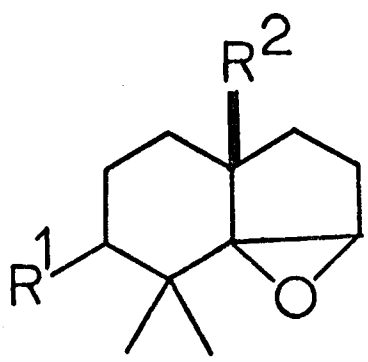
CHAPTER 2.

Synthesis of Model Epoxides

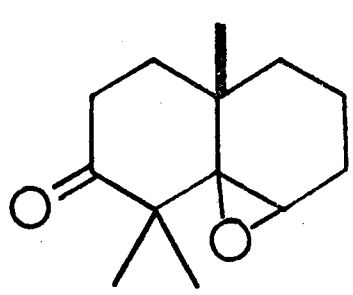
1. Introduction.

The examples discussed in the previous section have shown that the rearrangements of epoxides with Lewis acids in the absence of any external nucleophiles can give a wide variety of products, and predictions of the course of any given rearrangement are complicated by the number of qualitative factors which must be taken into account. The aim of the present work has been to synthesise a series of model epoxides containing different functional groups, and to rearrange these epoxides with a Lewis acid, with a view to correlating the course of the rearrangement with the nature of the groups present in the epoxide.

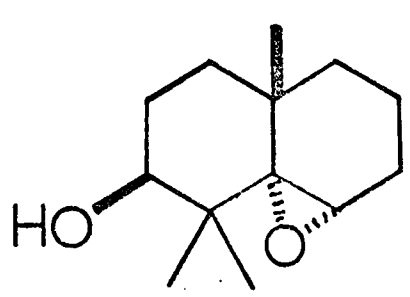
Simple bicyclic trisubstituted epoxides containing one or two functional groups were chosen as the model systems because it was thought that they would give easily identifiable products, and because their rearrangement products might contain interesting or synthetically useful skeletons. A series of hydrindane epoxides (82)-(87) was investigated, and the decalone epoxide (88) was also prepared, to compare with the work of Whitlock and Olsen[85] who had rearranged the decalol epoxide (71a).



	R^2	R^1
(82)	$-CO_2Et$	=O
(83)	$-CO_2Et$	—OH
(84)	$-CH_2OH$	—OH
(85)	CH_3-	=O
(86)	CH_3-	—OH
(87)	—CO—O—	

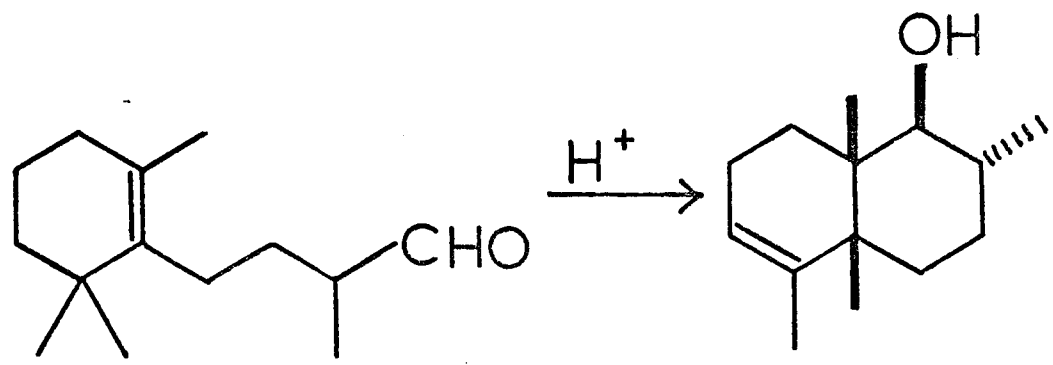


(88)

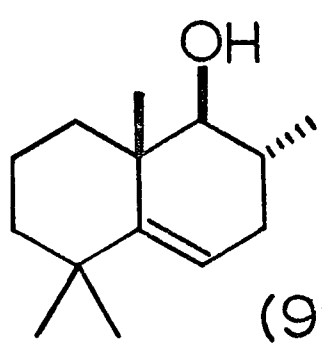


(71a)

Recently, a simple synthesis of the octalol (90) from a commercially available compound was published.[87] Ireland and his co-workers had hoped that acid-catalysed cyclisation of the unsaturated aldehyde (89) would give the gem-dimethyl octalol (91) which would be a valuable synthetic precursor for certain sesqui- and higher terpenoids; instead, they obtained the isomeric octalol (89).

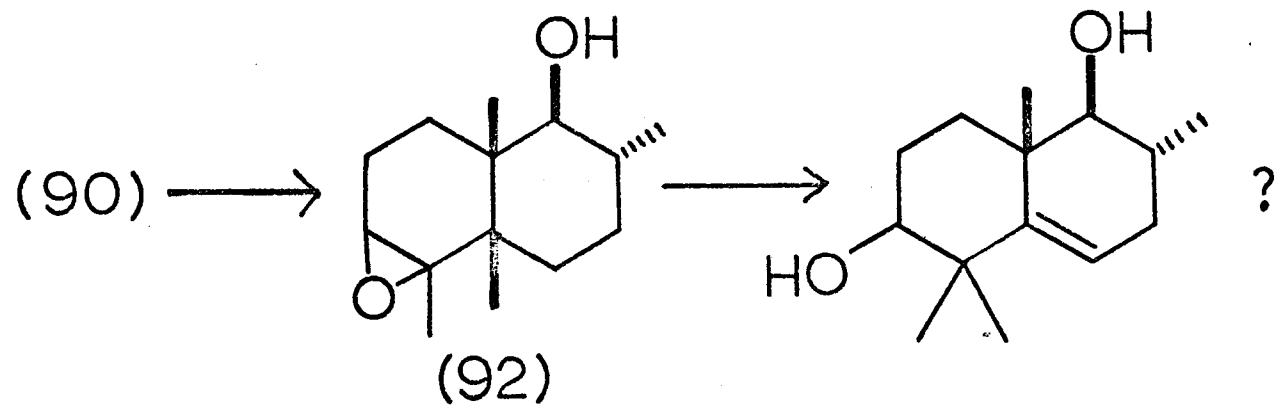


(89) (90)

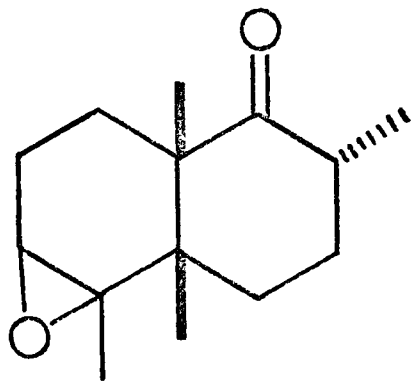


(91)

Unsuccessful attempts were made to obtain the gem-dimethyl octalol (91) by acid-catalysed isomerisation, but this reaction was not investigated further, and part of the present work is concerned with the possibility of converting the octalol (90) into the gem-dimethyl system using an epoxide rearrangement;



and the decalol and decalone epoxides (92) and (93) were prepared and their rearrangements investigated.

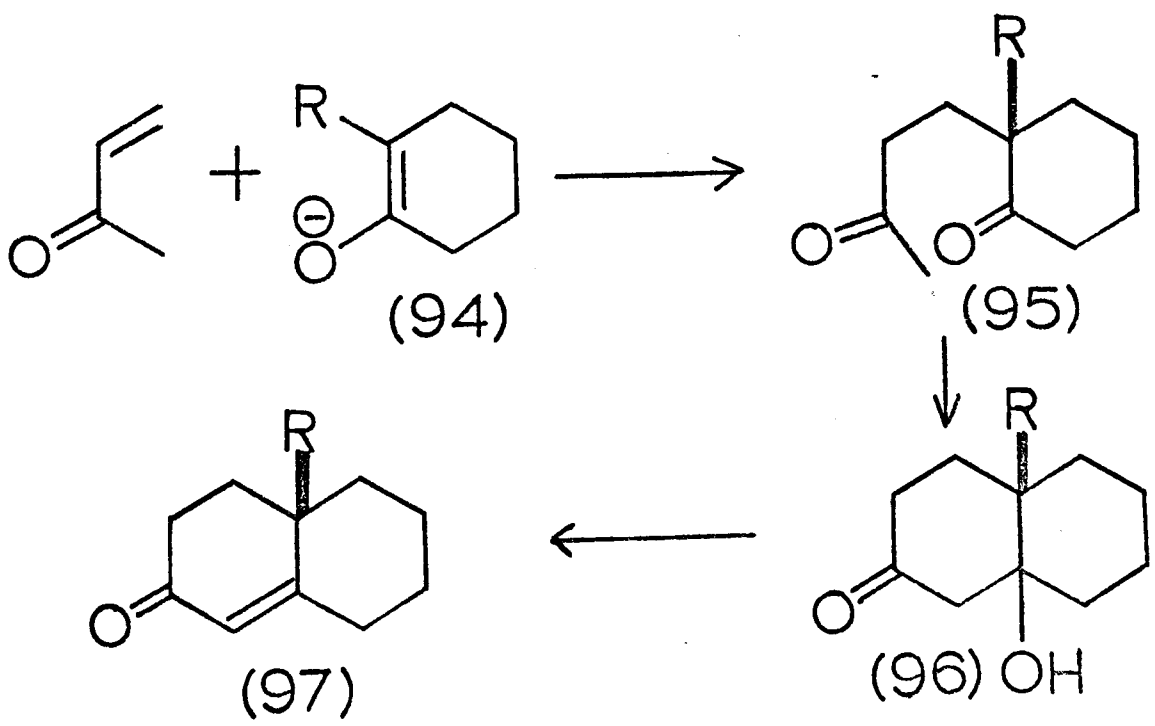


(93)

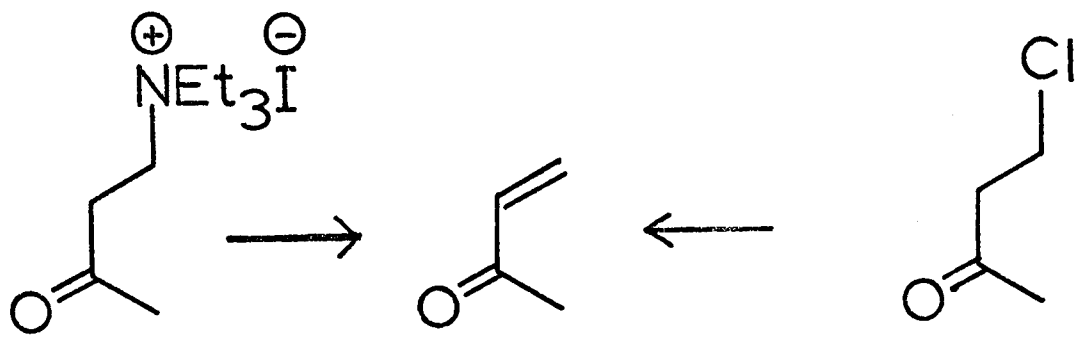
2. The Synthesis of Bicyclic Compounds.

The total synthesis of steroids involves the construction of a fused tetracyclic system of the correct stereochemistry, with one or two angular methyl groups and with appropriate side chain and functional groups. Most successful syntheses[88] have started from a mono- or bicyclic system and have built the other rings upon it; the earlier syntheses indicated that the classical methods of ring formation viz. cyclodehydration and the Dieckmann reaction were inadequate, and new techniques were developed, of which the Diels Alder reaction and the Robinson annulation reaction have been the most widely used.

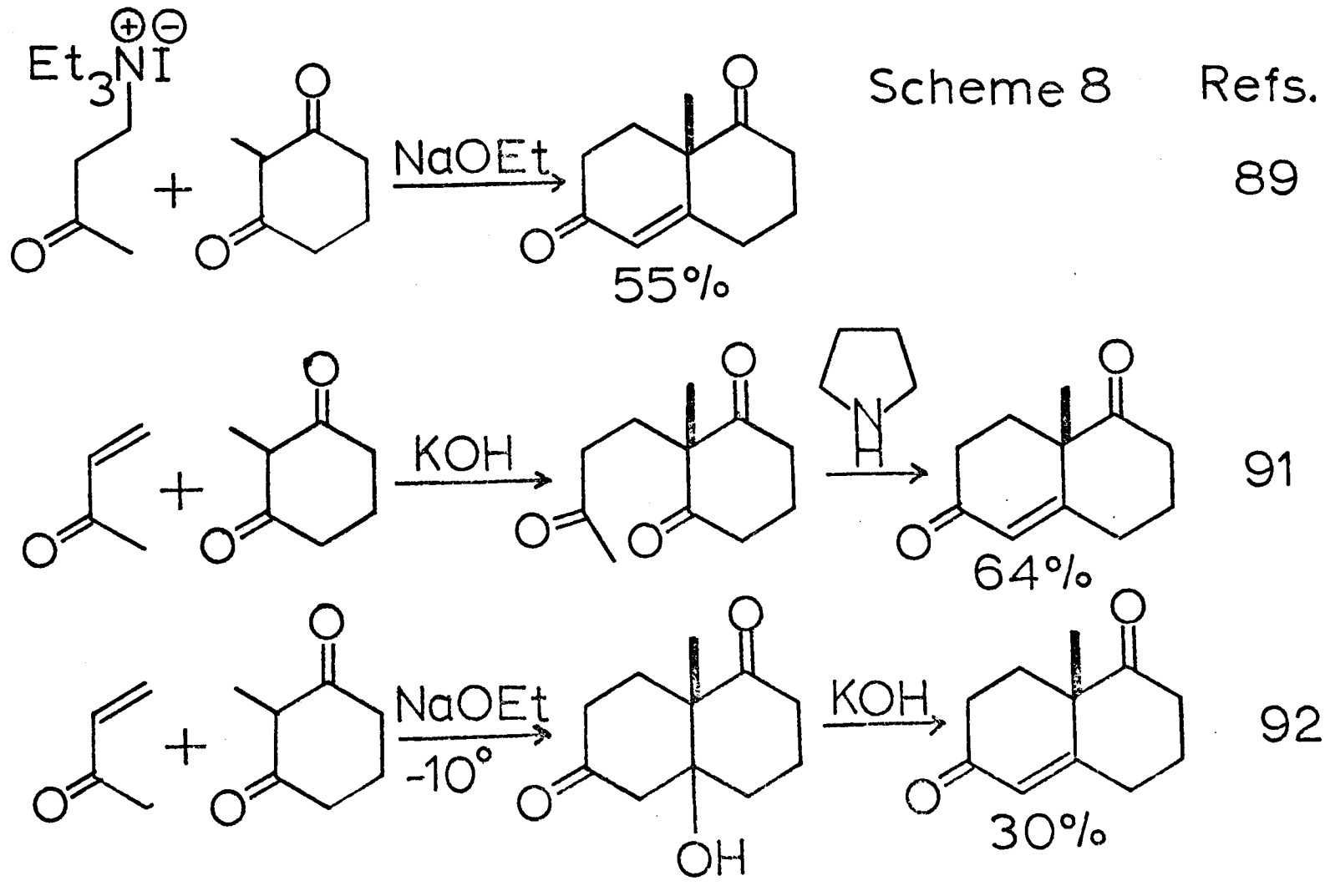
The Robinson annulation reaction proceeds via Michael attack of the enolate anion of a monocyclic ketone (94) on an alkyl vinyl ketone, to give a dione (95); this undergoes an intramolecular aldol condensation via a ketol (96), to give a bicyclic enone (97).



The alkyl vinyl ketone may be used directly, or as was the case with earlier work,[89] it may be generated *in situ* by the action of a base on a suitable quaternary ammonium salt or an alkyl β-chloroethyl ketone.



A wide variety of basic catalysts and solvents have been used in the reaction, and although early yields were low,[89] improved techniques have led to very acceptable yields.[90] In the early reactions,[89] the bicyclic enone was obtained directly from the monocyclic enolate, and the same base served to generate the alkyl vinyl ketone and the enolate anion, and to bring about the aldol condensation; in recent years, either the half-cyclised dione has been isolated and then treated with a different base to bring about the aldol condensation,[91] or the ketol has been isolated and dehydrated[92] to give the bicyclic enone (Scheme 8).



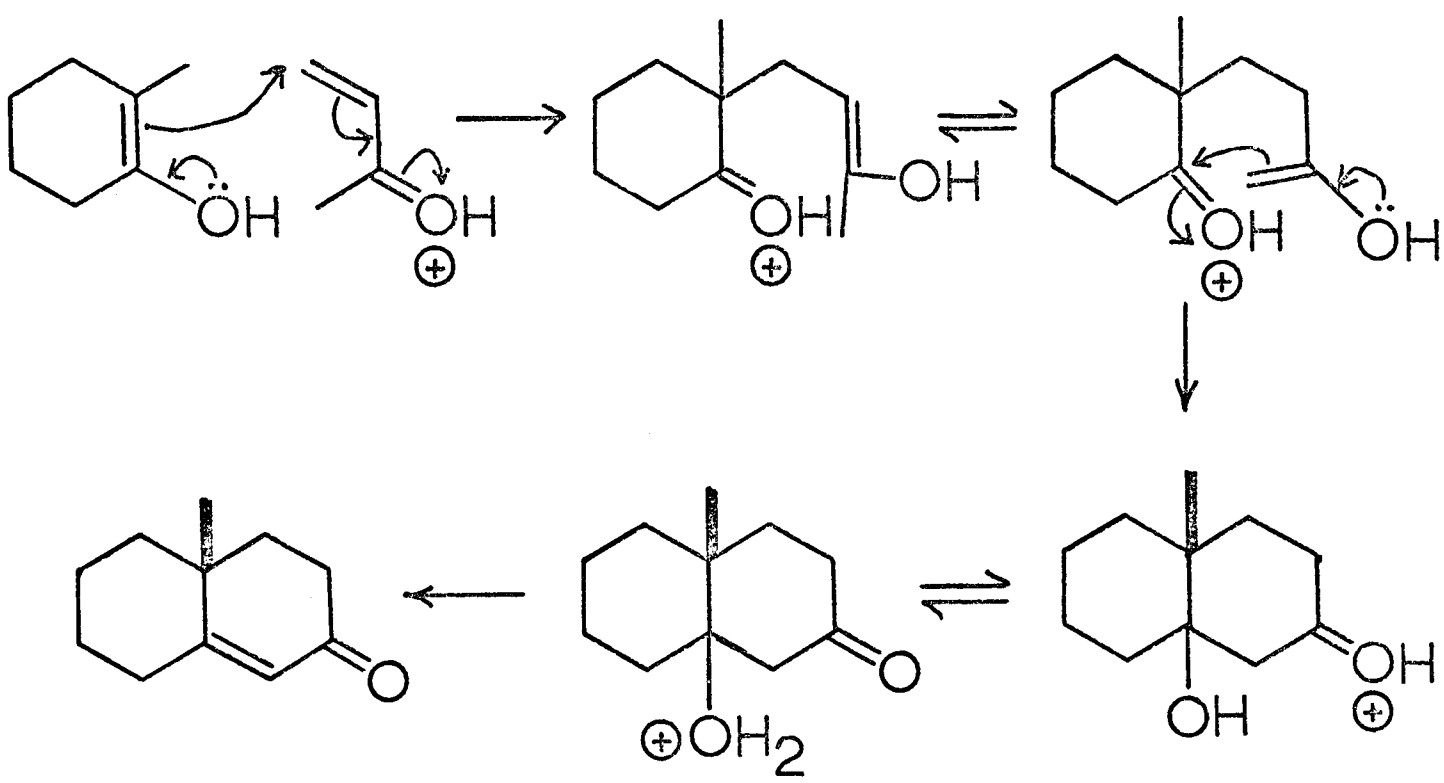
Scheme 8 Refs.

89

91

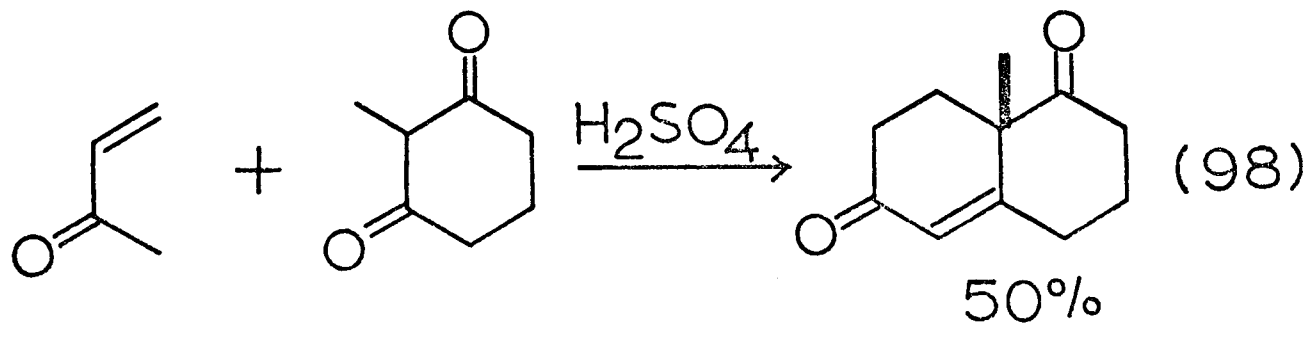
92

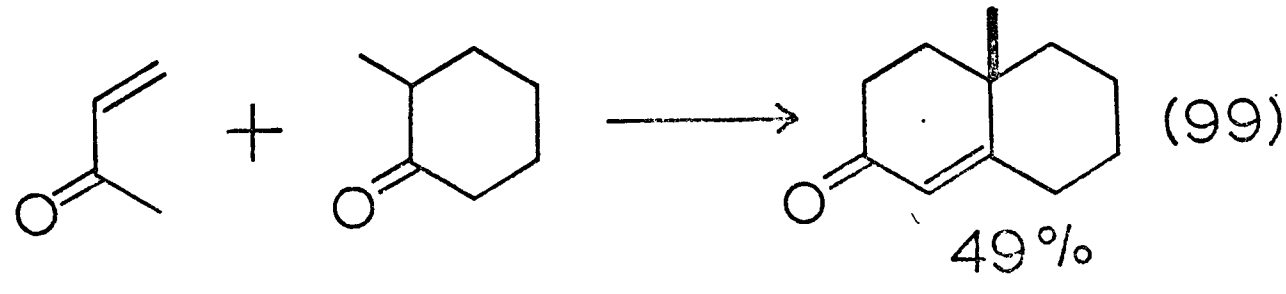
The reaction has also been found to occur in good yield with an acid catalyst,[93] although the method is only successful with cyclic ketones which enolise readily: the mechanism presumably involves attack of the enol form of the cyclic ketone on the protonated vinyl ketone (Scheme 9).



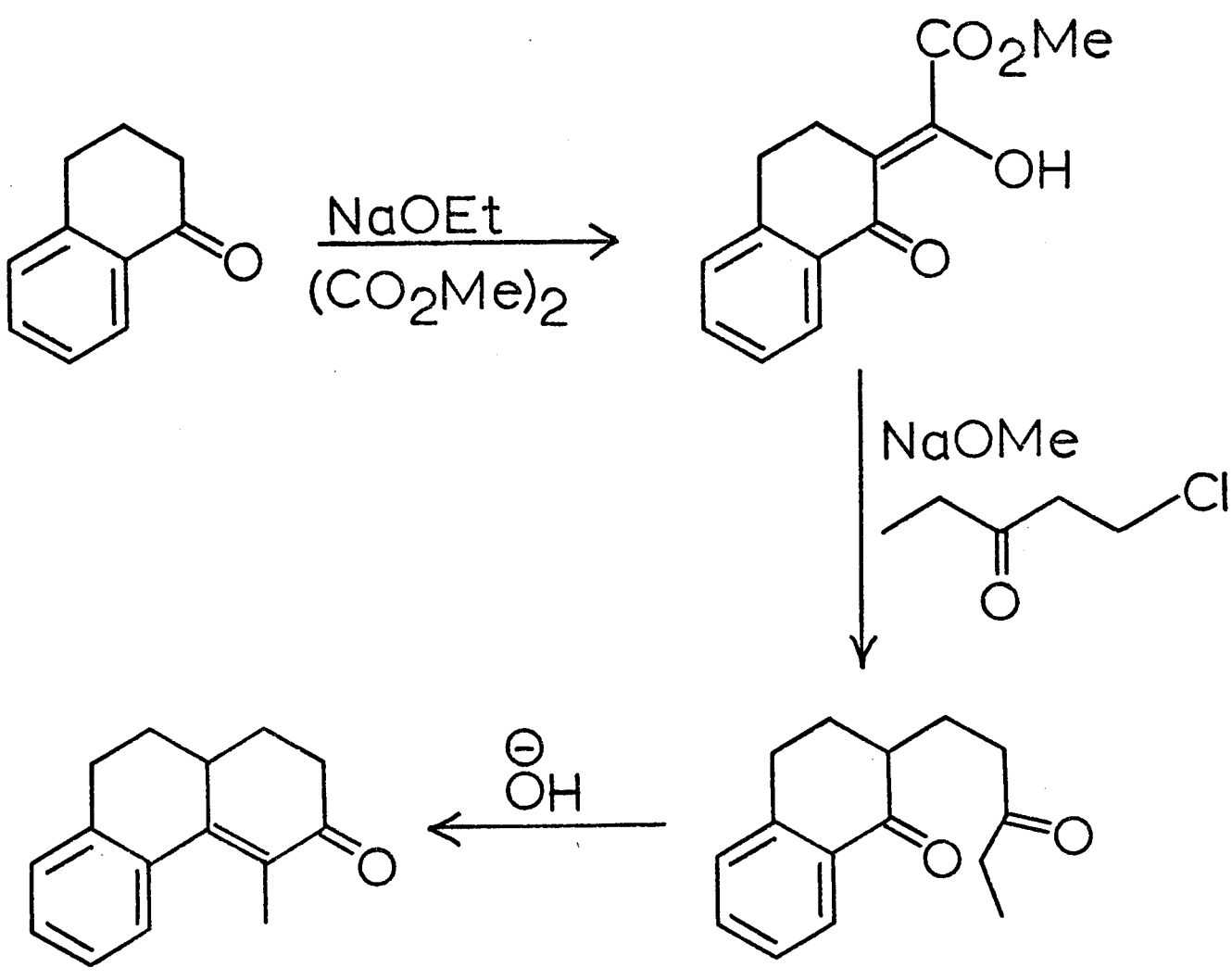
Scheme 9

Typical examples of the use of the acid catalysed method are (98) and (99).



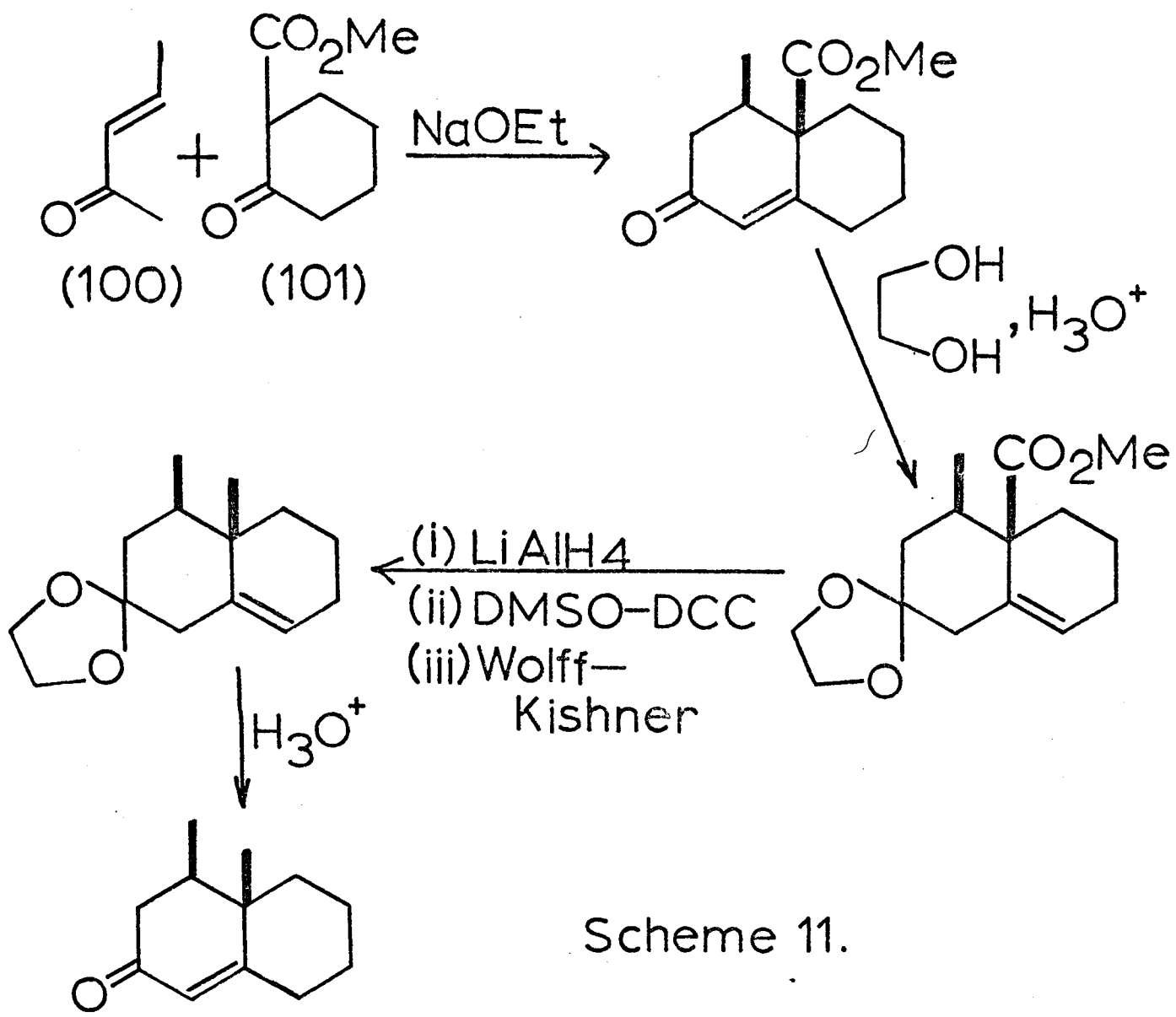


The ease with which the annulation reaction proceeds depends on the ability of the cyclic ketone to enolise: ketones which enolise readily, e.g. 2-methylcyclohexane-1,3-dione and 2-methoxycarbonylcyclohexanone, tend to give much higher yields of bicyclic enone than 2-methylcyclohexanone. Methods have been devised for introducing electron withdrawing groups which will facilitate enolisation; Brown et al.[94] have described a method for producing angularly unsubstituted compounds by introducing the activating group - $COCO_2CH_3$, which can be removed during the course of the cyclisation (Scheme 10).



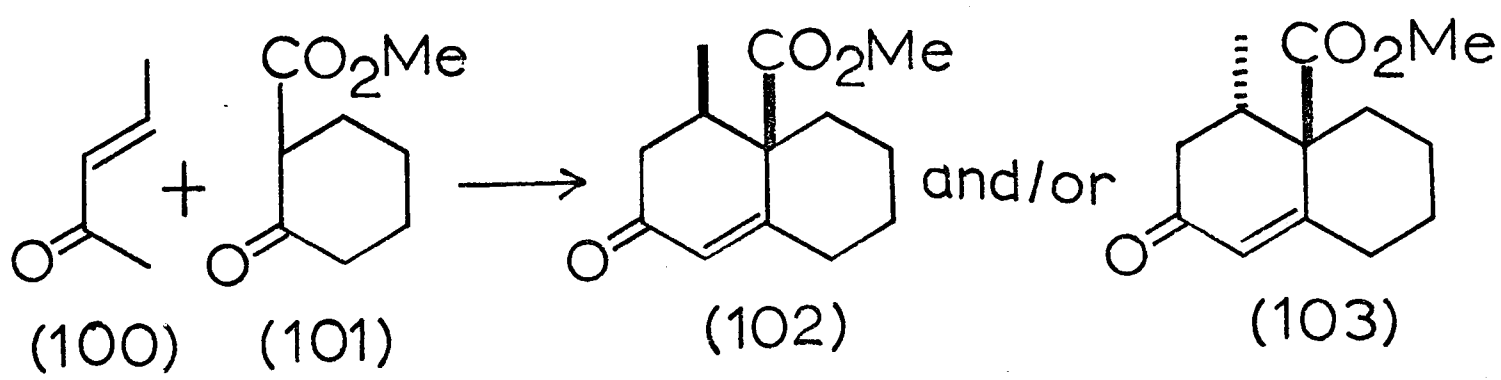
Scheme 10

Marshall and Warne[95] have converted an ester group to a methyl group at the angular position, thus allowing cyclisation to proceed on the more active β-keto-ester substrate (Scheme 11).



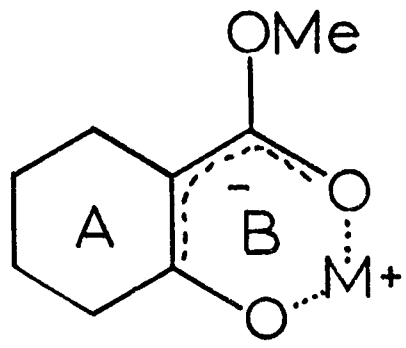
Scheme 11.

Annulations such as this using trans-pent-3-en-2-one (100) can give two possible products with cis and trans stereochemistry between the methyl and ester substituents (102) and (103).



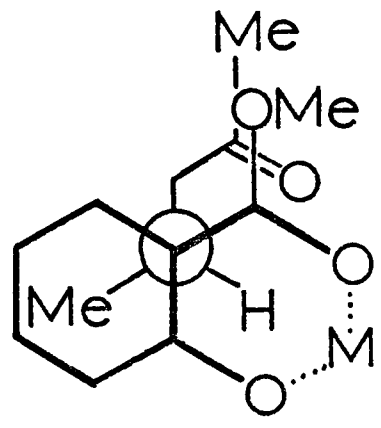
The products obtained from methyl 2-oxocyclohexanecarboxylate (101) were dependent on the metal enolate and the solvent used;[95] bulky alcohols (t-butanol, t-amyl alcohol) and sodium and potassium enolates gave the cis product predominantly, while aprotic solvents and lithium enolates tended to give the trans epimer. This difference was ascribed[95] to the different steric requirements of the two rings A and B in the solvated metal

enolate (104).



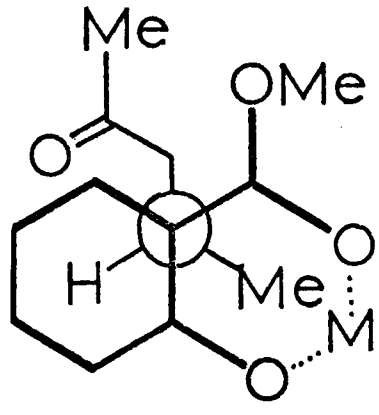
(104)

With sodium and potassium enolates in alcoholic solvents, ring B would be considerably solvated, and hence bulky, so the favoured transition state for Michael attack of the enolate on the vinyl ketone would resemble (105),



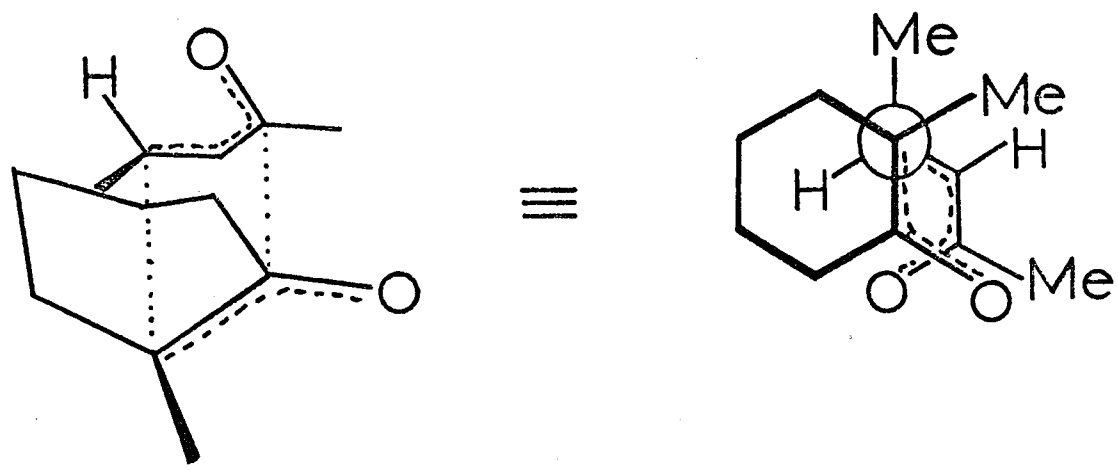
(105)

which leads to the <u>cis</u> product (102). With lithium enolates in aprotic solvents, ring B would not be extensively solvated, and ring A would offer greater steric hindrance; thus the transition state would resemble (106) which gives the <u>trans</u> product (103). The course of the reaction from 2-methylcyclohexanone shows an even greater solvent dependence.[96]



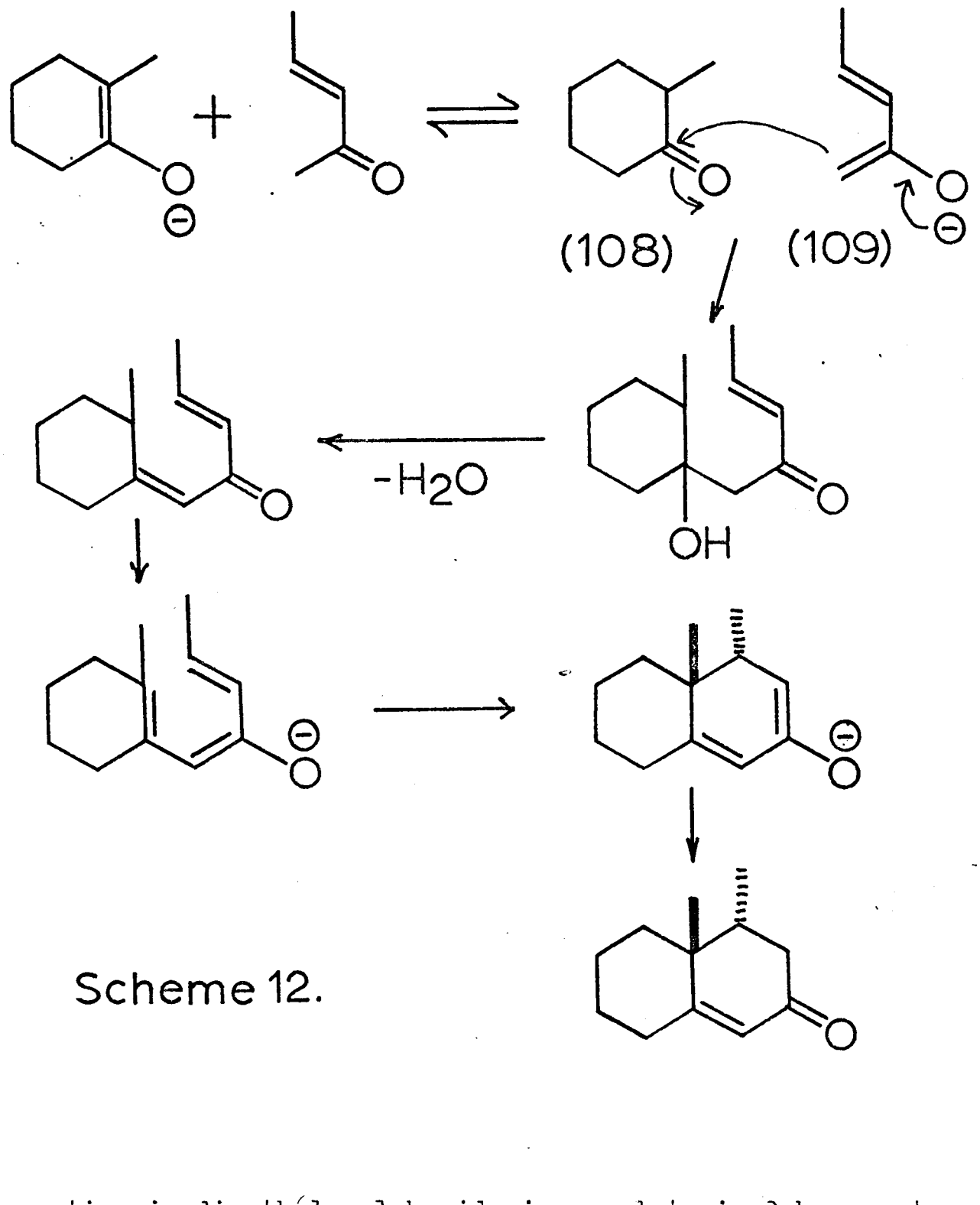
(106)

Using sodium hydride, in dioxan, the cis product was obtained in 65% yield, while in dimethyl sulphoxide, the trans product was formed in 72% yield. This difference cannot be wholly due to an effect such as that described above, and Scanio and Starret[96] have suggested that in dioxan, the normal Michael attack takes place proceeding through a preferred transition state (107) which leads to the cis product;



(107)

but that in highly polar dimethyl sulphoxide, the aldol condensation occurs first between the keto-form of 2-methylcyclohexanone (108) and the enolate of trans-pent-3-en-2-one (109), and this step is followed by a thermally allowed disrotatory cyclisation (Scheme 12).



Scheme 12.

The reaction in dimethyl sulphoxide is complete in 3 hours at room temperature, and although this is lower than usual for such cyclisations, examples of thermally allowed cyclisations at room temperature are known.[97]

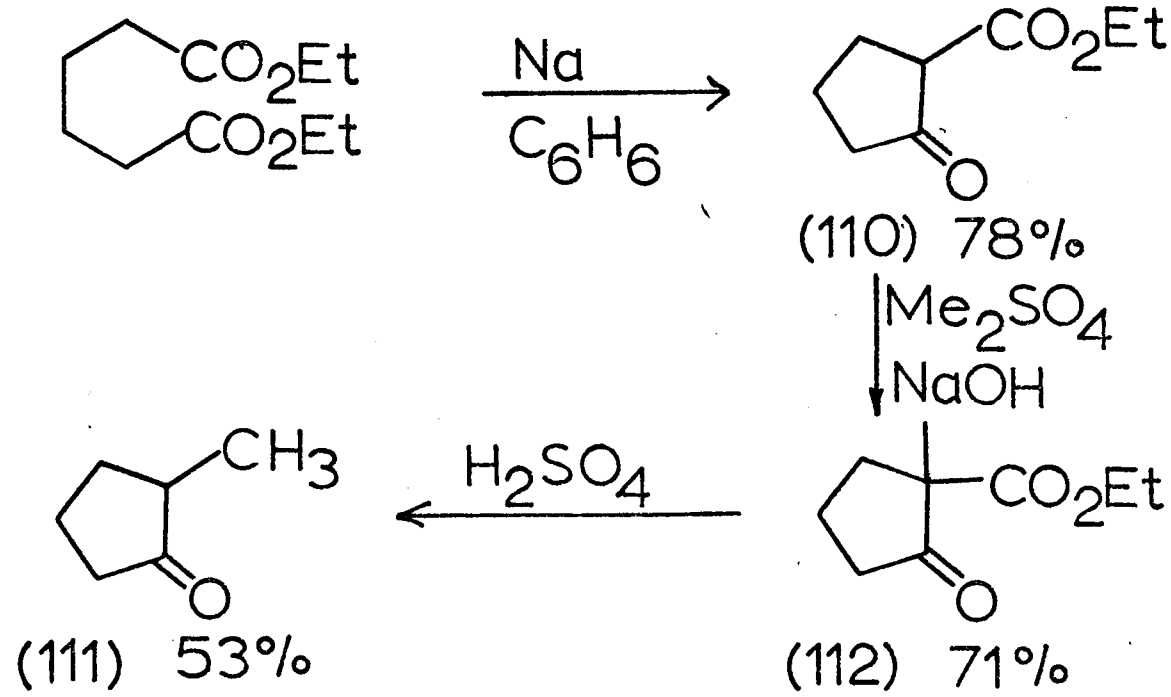
i) Monocyclic Precursors.

In this work, Robinson annulation reactions were carried out on 2-ethoxycarbonyl- and 2-methyl-cyclopentanone (110) and (111).

The former was prepared by a Dieckmann reaction with diethyl adipate; this was treated in the standard way[98] with sodium in benzene to give the solid sodium enolate of the product, which yielded 2-ethoxycarbonyl-cyclopentanone on acidification. The yield was improved slightly by using sodium in the form of granules rather than wire: the granular form

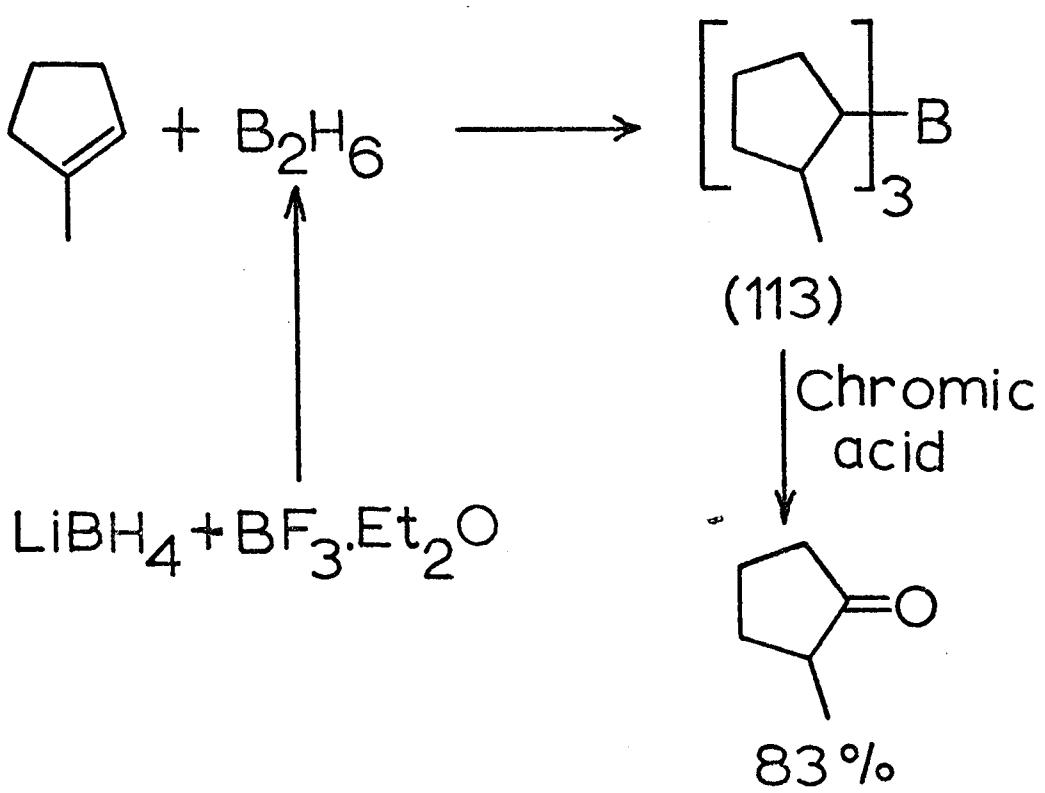
is simply prepared by melting sodium in xylene and then stirring and cooling it until the small granules have solidified.[99] The product of the reaction was contaminated by a very small amount of unreacted diethyl adipate (less than 1%) which was not removed by fractional distillation.

2-Ethoxycarbonylcyclopentanone was methylated at the α-position using dimethyl sulphate. Mayer and Held[100] outlined a method for the preparation of 2-methoxycarbonyl-2-methylcyclopentanone, and their procedure was applied to 2-ethoxycarbonylcyclopentanone: dimethyl sulphate was added to a cooled solution of the keto-ester and sodium hydroxide in aqueous methanol, and working up gave the crude methyl-substituted keto-ester (112) in 71% yield. This crude material was hydrolysed and decarboxylated directly using 30% sulphuric acid, to give 2-methylcyclopentanone (111).

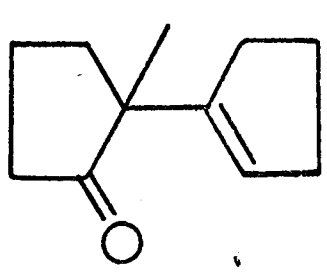


Brown and Garg[101] have described a method for converting 1-methylcyclopentene into 2-methylcyclopentanone by forming the organoborane (113) and oxidising this with chromic acid. Diborane is conveniently synthesised <u>in situ</u> by the action of lithium borohydride (or sodium borohydride plus a catalytic amount of zinc chloride) on boron trifluoride-diethyl ether complex, and the ethereal solution of the organoborane can be treated

with aqueous chromic acid to give the cyclic ketone in high yield. This method is to be preferred, but the high cost of 1-methylcyclopentene made it prohibitive on a large scale.

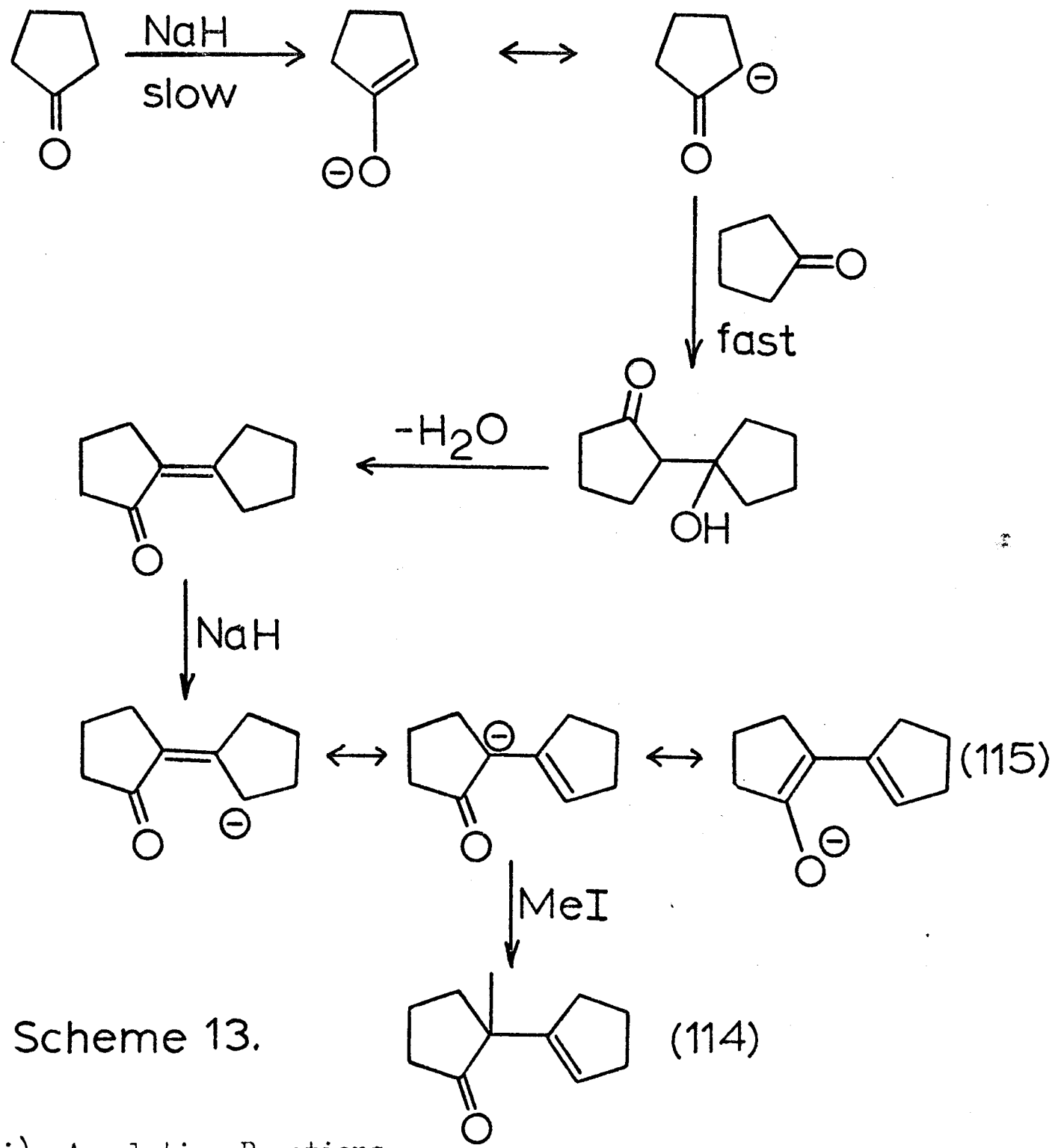


An attempt was made to methylate cyclopentanone directly, using a strong base to generate an appreciable concentration of the enolate of cyclopentanone. Dimethyl sulphoxide greatly enhances the rate of alkylation of enolate anions; however, treatment of cyclopentanone with methyl iodide in the presence of sodium hydride in dimethyl sulphoxide [102] gave a single liquid product with molecular weight 164 ($C_{11}H_{16}O$). The n.m.r. spectrum had signals due to one olefinic proton and a tertiary methyl group, and a methylene envelope containing twelve protons, and the i.r. spectrum indicated a carbonyl group in a five-membered ring ($\nu_{C=O}$ 1740cm^{-1}). These data are compatible with the methylated self-condensation product (114), and this was characterised as a crystalline semicarbazone.



(114)

The production of this compound as the only product indicates that the rate of formation of the enolate anion of cyclopentanone is slower than the rate of attack of the enolate on the keto-form of cyclopentanone, and consequently, an appreciable concentration of the enolate anion is never formed: the species which displaces iodide from methyl iodide must be the resonance stabilised enolate anion of the self-condensation product (115). (Scheme 13).



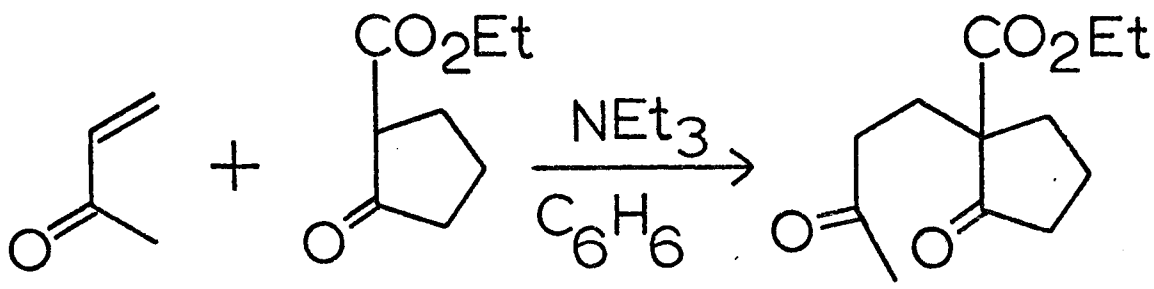
Scheme 13.

ii) Annulation Reactions.

a) Ethyl 5-Oxo-5,6,7,8-tetrahydroindane-8β-carboxylate

This compound was prepared by the method of Dauben and McFarland;[103] anhydrous methyl vinyl ketone was caused to react with 2-ethoxycarbonyl-cyclopentanone in the presence of triethylamine in dry benzene. The

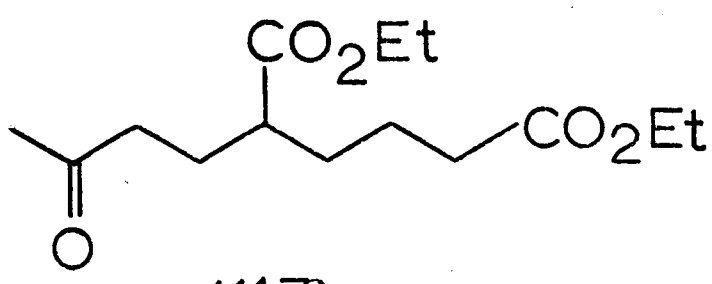
mixture was worked up after standing at room temperature for seven days to give the half-cyclised dione ester (116) in 90% yield.



(116)

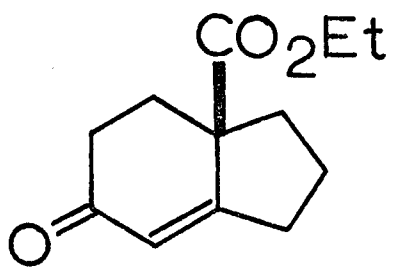
This compound had characteristic i.r. absorptions due to a keto-group in a five-membered ring ($\nu_{C=O}$ 1740 cm^{-1}), an ester ($\nu_{C=O}$ 1730 cm^{-1}), and an open-chain ketone ($\nu_{C=O}$ 1720 cm^{-1}). The n.m.r. spectrum showed a sharp singlet at τ 7.9 characteristic of a methyl group adjacent to a carbonyl group. The dione was characterised as a bis-semicarbazone with a meting point of 190-192°, which is somewhat higher than Dauben and McFarland's value of 178-179°.

The cyclisation of the dione (116) was investigated by Nunn and Rapson;[104] treatment with sodium ethoxide gave a keto-diester (117) by a reverse Claisen reaction, and other unspecified bases failed to produce cyclisation.



(117)

Dauben et al.[103] treated the dione with potassium t-butoxide, which is a commonly used condensation catalyst, and obtained an intractable oil, but they were able to bring about cyclisation by heating the dione under reflux with aluminium t-butoxide in benzene. They used a molar ratio of dione:base of 1:0.92 and obtained incomplete cyclisation, and added a further 0.58 mole aluminium t-butoxide, to give a 34% yield of the bicyclic enone (118).

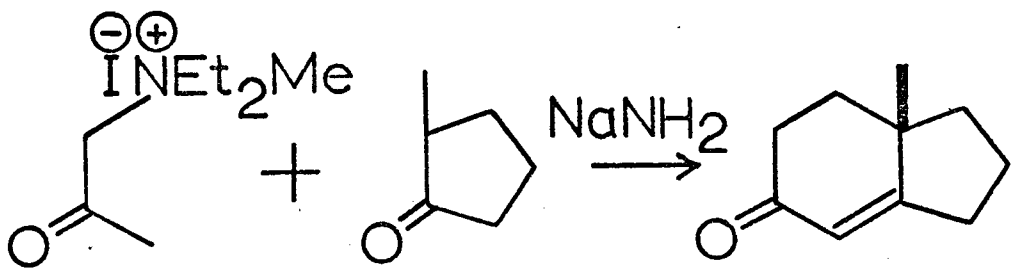


(118)

In the present work, the dione was treated with 1.5 mole of base and heated under reflux for 70 hours to give the enone (116) in 46% yield. The product was obtained pure by fractional distillation and had a characteristic u.v. absorption at 238 nm (ε 13,600). The product obtained by Dauben et al.[103] had $\lambda_{max.}$ 239 nm (ε 12,900).

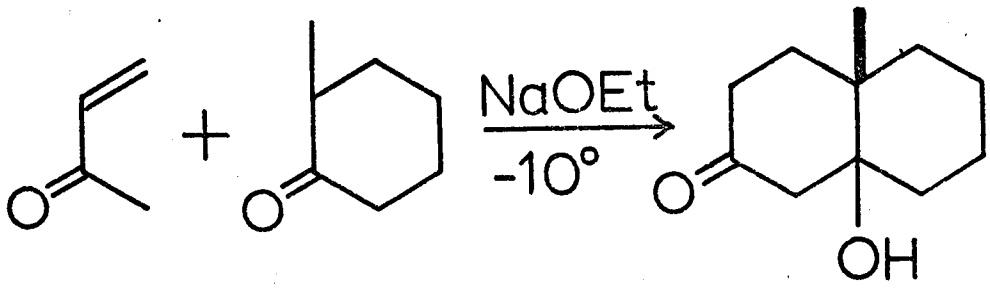
b) 8β-Methyl-7,8-dihydroindan-5(6H)-one (119)

This compound was first prepared by du Feu et al.[89] using the methiodide of 3-diethylaminobutan-1-one and 2-methylcyclopentanone, with sodamide as base; they obtained a yield of 15%, and in the hands of Mayer and Held,[100] a 25-38% yield was obtained. The essential problem with this cyclisation is that bases which are strong enough



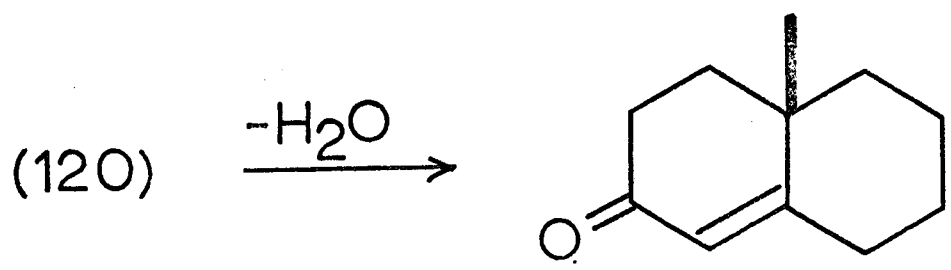
(119)

to form the enolate anion of 2-methylcyclopentanone can also lead to polymerisation of methyl vinyl ketone[105], while weaker bases tend to give no reaction at all. Marshall and Fanta[92] found that acceptable yields could be obtained if strict control of the reaction conditions was maintained: by adding methyl vinyl ketone very slowly to cooled 2-methylcyclohexanone containing a catalytic amount of sodium ethoxide solution, they were able to isolate the ketol (120) in 54% yield, as a crystalline solid.



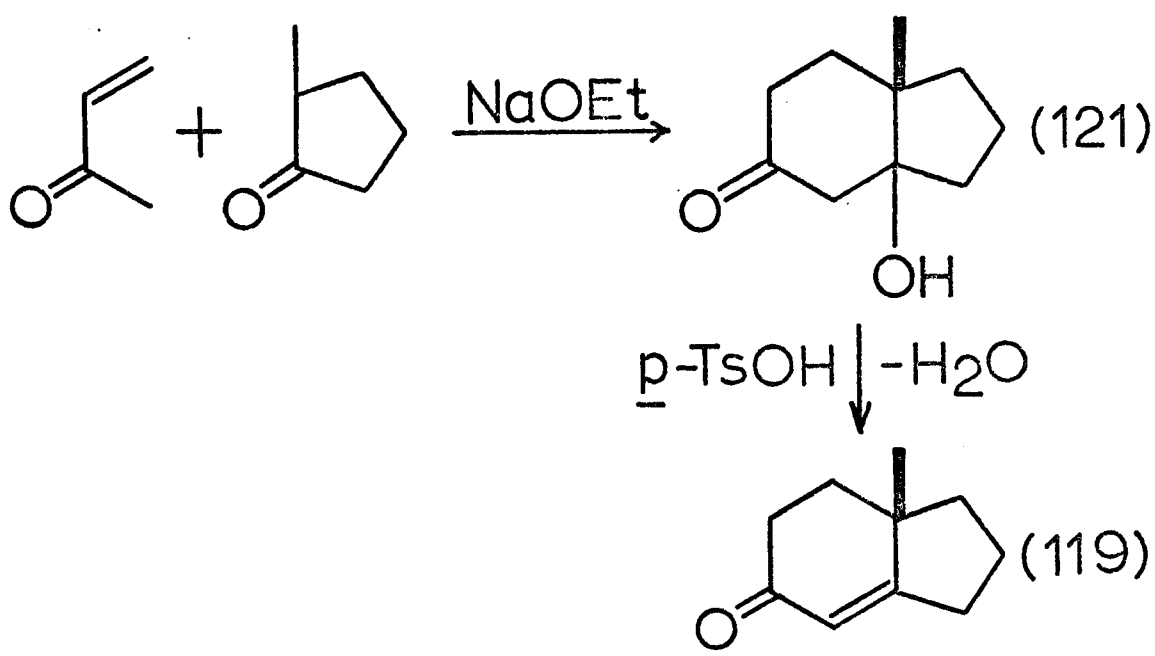
(120)

The ketol was dehydrated by steam distillation from aqueous potassium hydroxide solution, and the enone (99) was obtained in 30% overall yield.

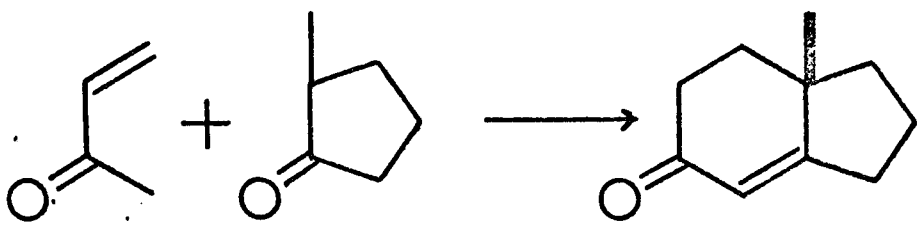


(99)

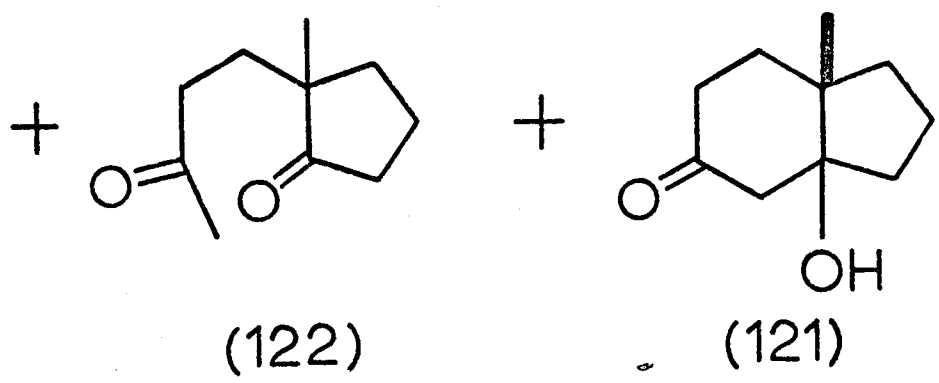
In the present work, an analogous reaction was carried out using 2-methylcyclopentanone. The ketol (121) was obtained in crude form and could not be isolated from the mixture. Its presence was indicated by hydroxylic absorptions in the i.r. spectrum at 3620 and 3490 cm^{-1}. The crude ketol was azeotropically dehydrated using toluene-p-sulphonic acid[106] to give a mixture containing the enone (119), which was isolated in 16% overall yield by column chromatography. The compound had an intense u.v. absorption characteristic of an $\alpha\beta$-unsaturated ketone at 241 nm (ε 10,300).



The octalone (99) has been prepared in 49% yield by the one-stage acid-catalysed procedure,[93] and this method was applied to 2-methylcyclopentanone. The initial product after heating a mixture of methyl vinyl ketone, the cyclic ketone, and a few drops of concentrated sulphuric acid under reflux for 16 hours was a red liquid, from which the enone (119) was isolated in 20% yield by distillation and column chromatography. Two other products were also obtained in very low yield ($\sim$ 5%) and were tentatively identified as the dione (122) and the ketol (121). The former had an i.r. spectrum which indicated the presence of a keto-group in a five-membered ring ($\nu_{C=O}$ 1746 cm^{-1}) and an open chain ketone ($\nu_{C=O}$ 1710 cm^{-1}), while the latter compound had a hydroxy-group (ν_{O-H} 3500 cm^{-1}), and a keto-group in a six-membered ring ($\nu_{C=O}$ 1725 cm^{-1}).



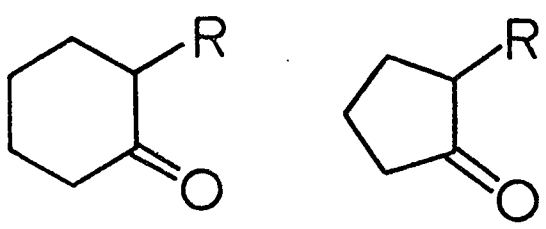
(119)
20%



(122) (121)

The lower yields for both of these annulation reactions (16%, 20%) compared with those obtained for 2-methylcyclohexanone (30% and 49% respectively) may reflect the greater concentration of enol present in six-membered ring ketones compared with five-membered ring ketones.[107]

equilibrium % enol[107]

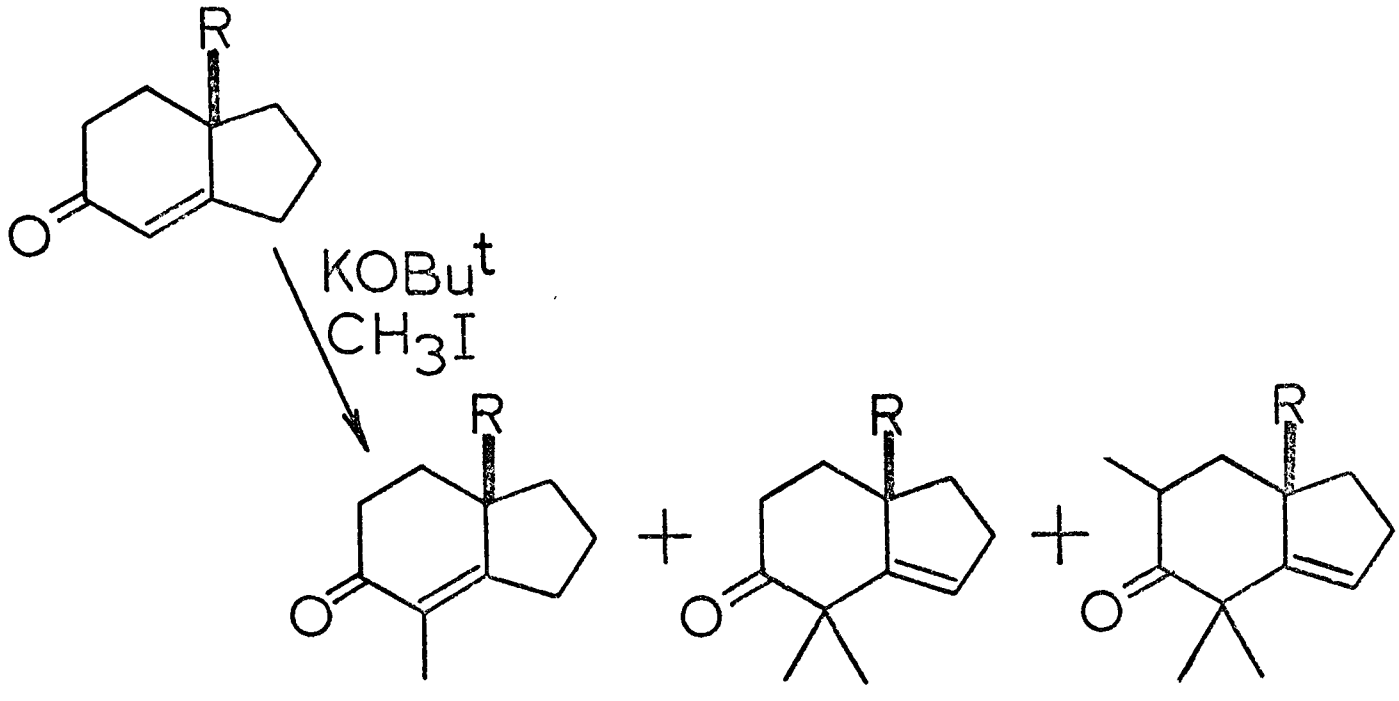


R = H	0.024	0.0084
R = CO_2Et	74	4.6

iii) Methylation.

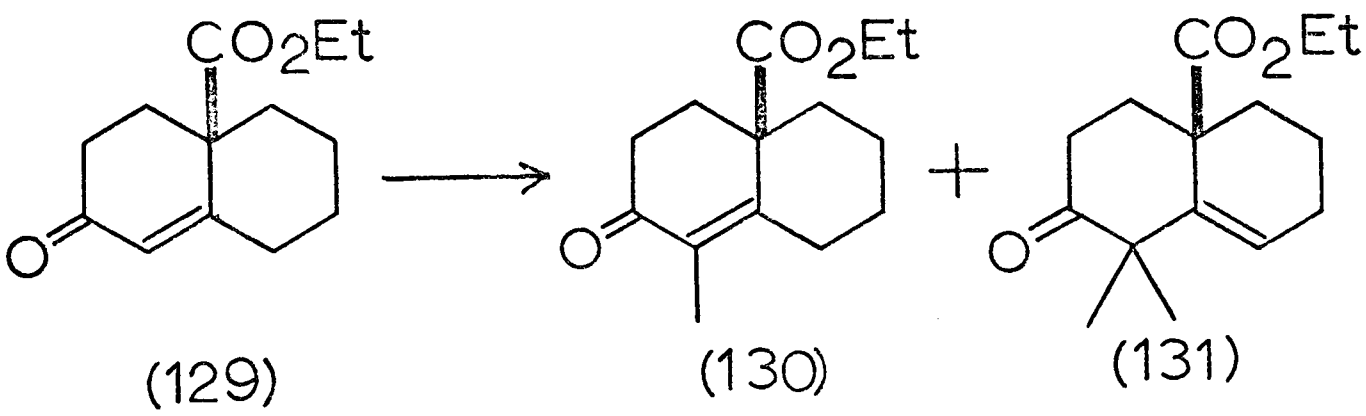
The two indanones (118) and (119) were dimethylated at the 4-position using potassium t-butoxide in t-butanol and an excess of methyl iodide.[108] In both cases, a mixture of mono-, di-, and tri-methylated products was obtained, the latter being indicated by mass

spectra and complex methyl regions in their n.m.r. spectra.



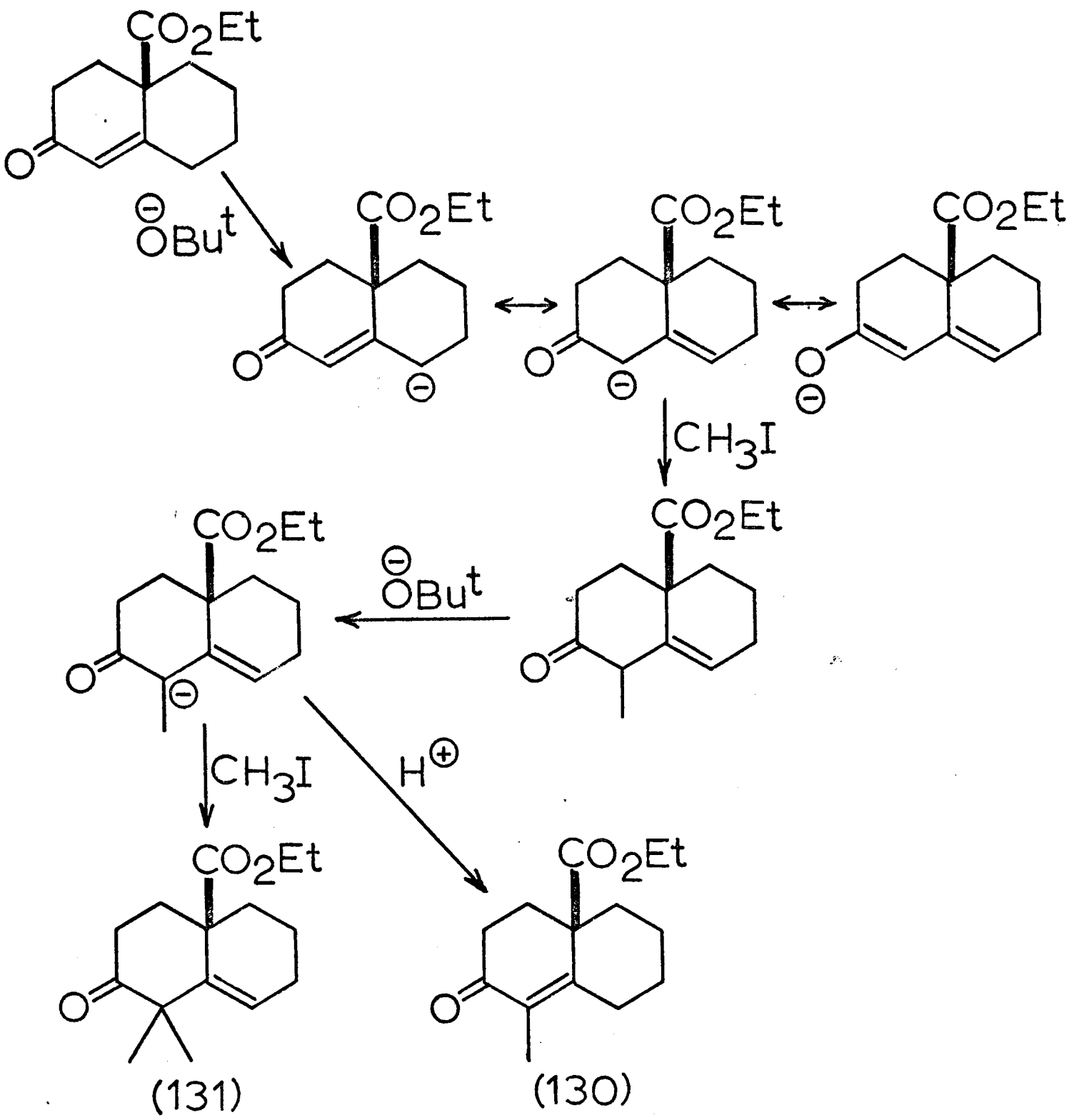
R = CO_2Et	(123) 5%	(124) 58%	(125) 15%
R = CH_3	(126) 30%	(127) 30%	(128) 7%

Meyer and Levinson[109] carried out a similar reaction on the corresponding octalone (129) and obtained 10-15% of the monomethylated product (130).

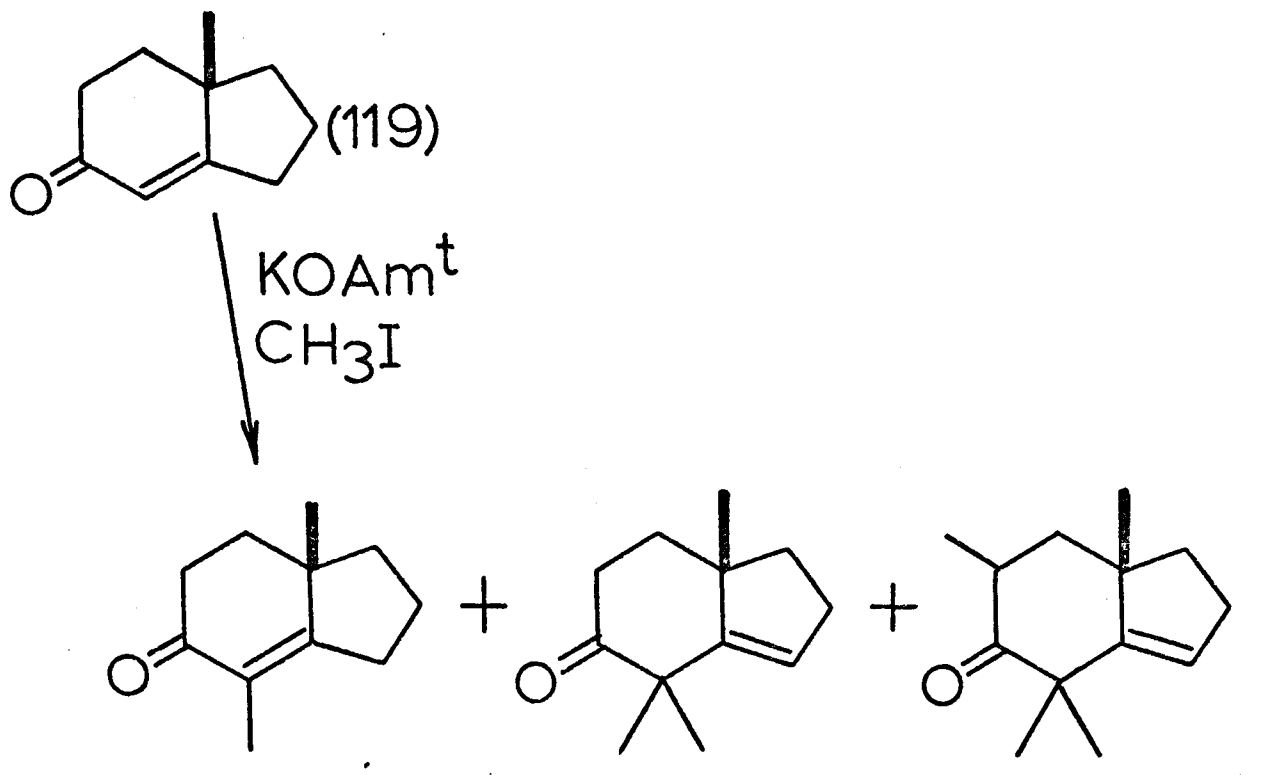


(129) (130) (131)

Further treatment of (130) with potassium t-butoxide/methyl iodide did not increase the yield of the dimethylated product (131), indicating that (130) is not an intermediate in the reaction.



The indanone (119) was also treated with potassium t-amyloxide and methyl iodide under more vigorous reaction conditions in an attempt to obtain a greater yield of the dimethylated product (127), but although the yield of the monomethylated product (126) decreased, there was an increase in the amount of the trimethylated product (128) formed, and the yield of the dimethylated product (127) was almost unchanged.

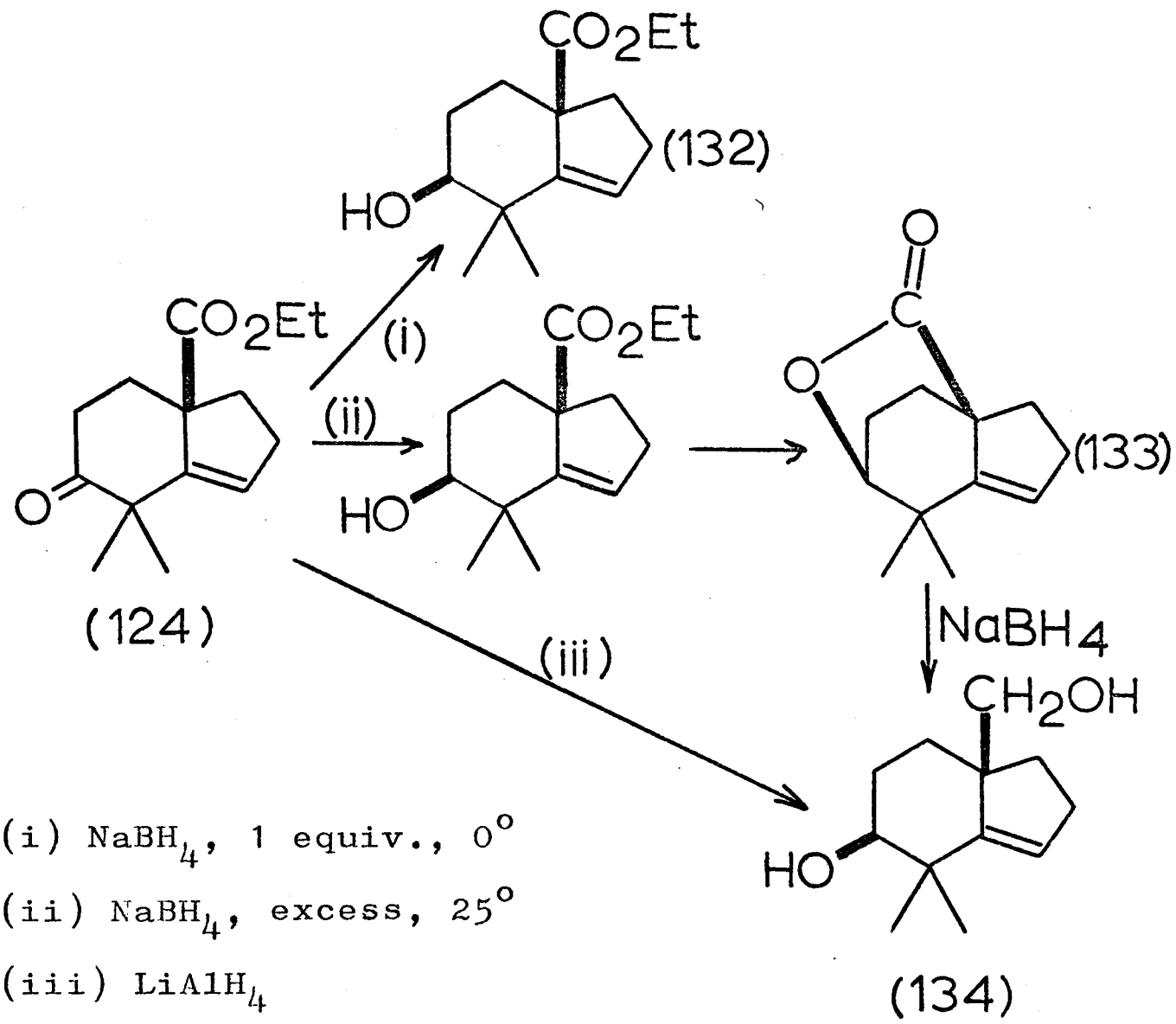


iv) Reduction.

Treatment of the keto-ester (124) with lithium aluminium hydride gave the diol (134) as a crystalline solid. The stereochemistry of the 5-hydroxy-group is expected to be β, because approach to the α face of the molecule is much less hindered than to the β face, and formation of the more stable equatorial alcohol results. The signals in the n.m.r. spectrum due to the protons $-CH_2-C\underline{H}(OH)-$ and $-C\underline{H}_2OH$ overlapped, but the signal of the latter could be discerned as an AB quartet with coupling constant $\underline{J}_{AB}$ 11.1 Hz, while the former appeared as a triplet.

The assigned stereochemistry of the diol (134) was confirmed when the keto-ester (124) was reduced with sodium borohydride. When a stoicheiometric amount of the reducing agent in ethanol at 0° was used, the product was the hydroxy-ester (132) formed by selective reduction of the keto-group; this had an ester carbonyl absorption at 1730 cm^{-1} and hydroxylic absorptions at 3630 and 3540 cm^{-1}. When an excess of sodium borohydride was used at 25°, three products were obtained and partially separated by column chromatography. The major product was an oil containing two components which had an i.r. spectrum characteristic of the hydroxy-ester (132) ($\nu_{max.}$ 3580, 3450, 1715 cm^{-1}) and the lactone

(133) ($\nu_{max.}$ 1755 cm^{-1}) formed by intramolecular lactonisation of the 5β-hydroxy-ester. The third product was the diol (134) which was identical with the diol obtained by lithium aluminium hydride



(i) $NaBH_4$, 1 equiv., 0°

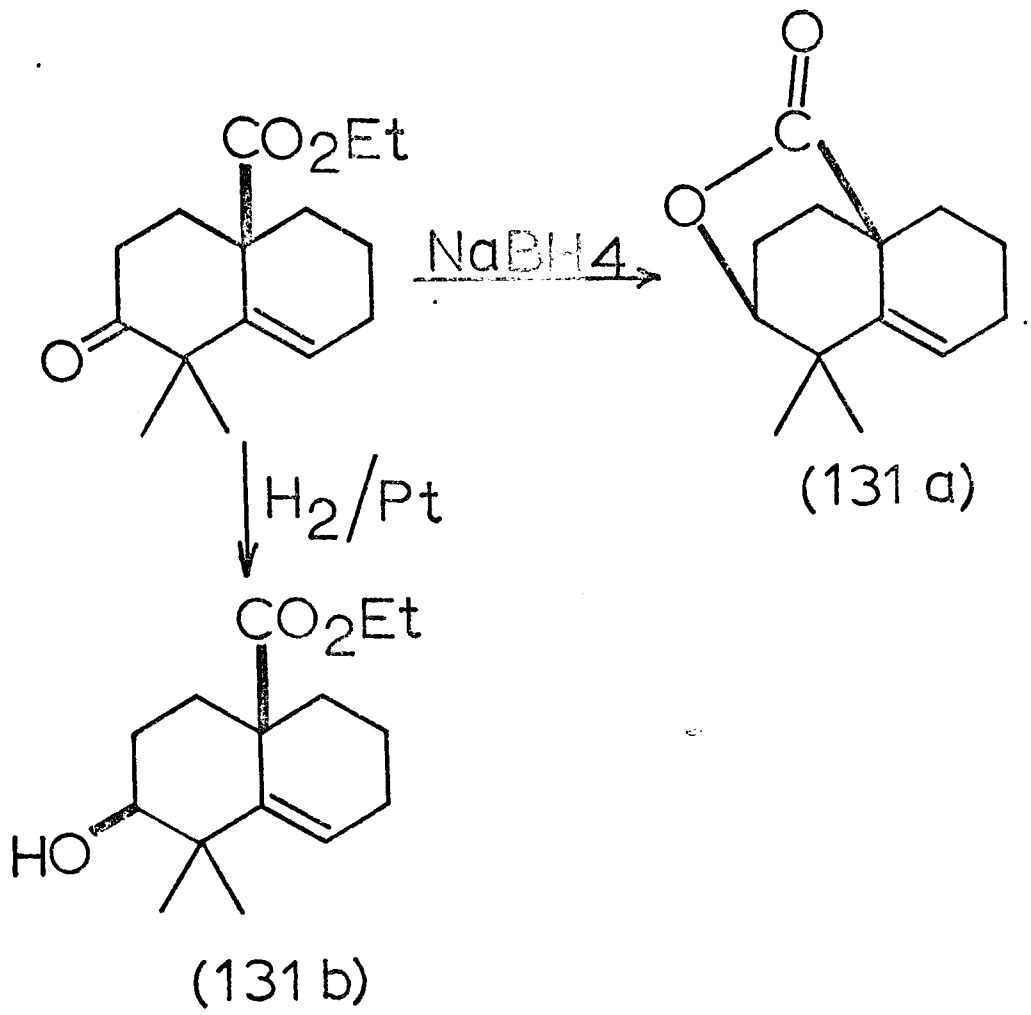
(ii) $NaBH_4$, excess, 25°

(iii) $LiAlH_4$

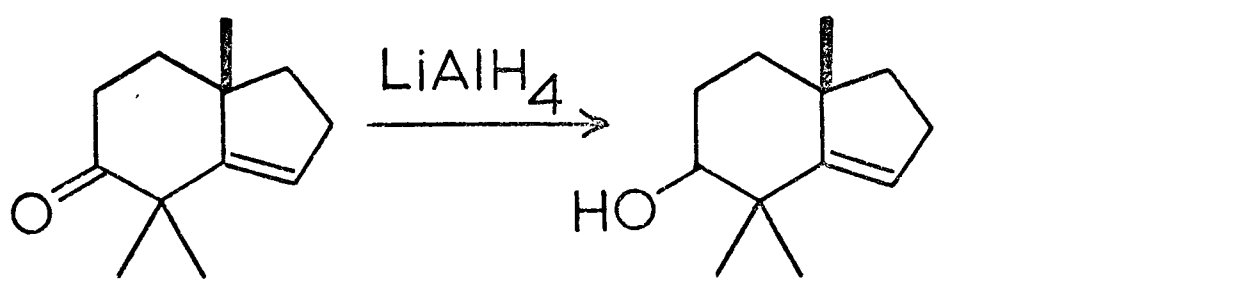
The diol must have been formed by reduction of the lactone (133), as sodium borohydride is known to reduce lactones selectively in the presence of esters; the lactone in turn can only be formed from the 5β-hydroxy-ester (132), which implies that the diol (134) must have a 5β-hydroxy-group, and confirms the stereochemistry of the product obtained from the lithium aluminium hydride reduction.

The formation of a lactone (131a) from the analogous octalone (131) has been observed by McQuillin[110] and earlier by Meyer,[109] and both workers were unable to isolate the hydroxy-ester (131b) from the sodium borohydride reduction, although it could be formed by hydrogenating

the keto-ester over platinum in ethanol.[109]

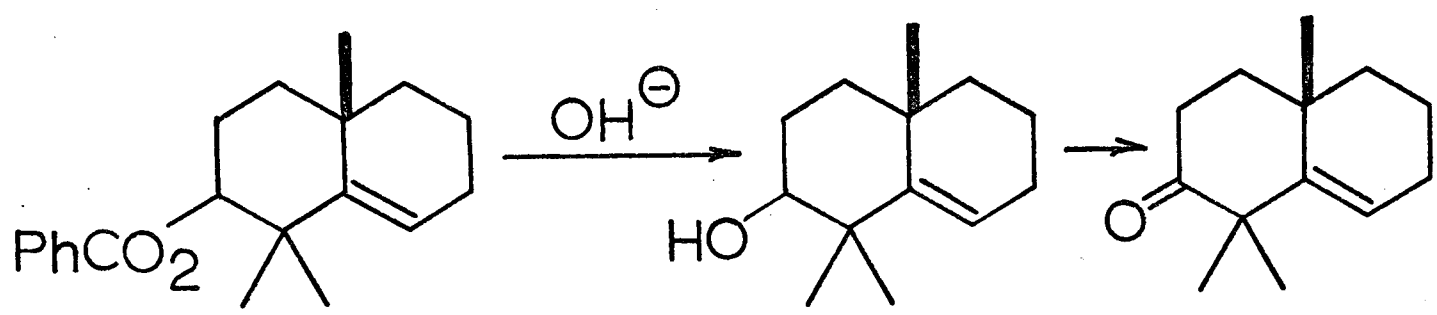


The reduction of the tetrahydroindanone (127) with lithium aluminium hydride did not proceed stereospecifically, but gave a mixture of the epimeric 5-alcohols (135). These were not separable by p.l.c., and the mixture showed a complex n.m.r. signal at τ 6.79 due to the two -C<u>H</u>(OH)- signals overlapping.



v) Decalin Systems.

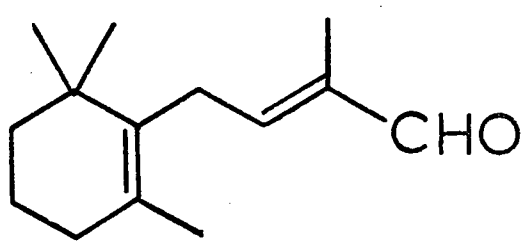
Two decalin systems were studied in this work. A large supply of the epimeric benzoate (136) was available in this laboratory,[111] and saponification with ethanolic sodium hydroxide solution gave a mixture from which the octalol (137) was separated by column chromatography.



(136) (137) (138)

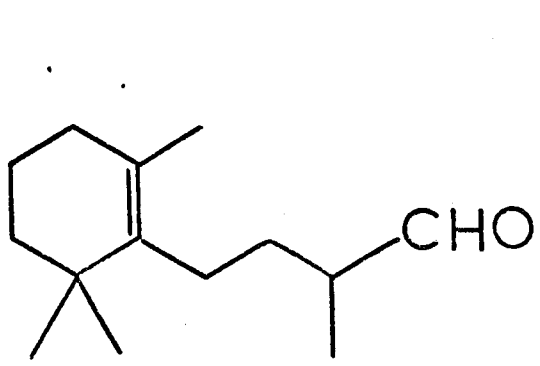
Oxidation of the octalol with chromic acid gave the octalone (138) as an oil; several other workers[112] have obtained (138) as an oil, although Mudd[113] reports obtaining it as a solid. The octalone obtained in this work was characterised as a crystalline 2,4-dinitrophenylhydrazone.

The other decalin system was synthesised from a readily available starting material, the so-called "β-C_{14}- aldehyde" (139) which is produced in ton quantities in the synthesis of vitamin A.[114]

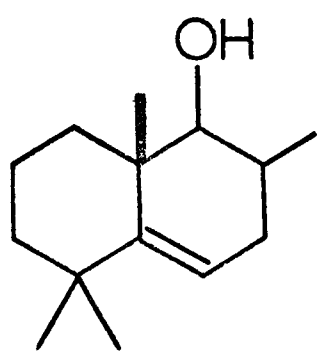


(139)

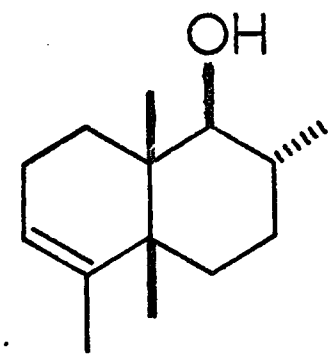
Ireland et al.[87] were investigating the acid catalysed cyclisation of the dihydro-C_{14}- aldehyde (89) (known as luciferin aldehyde) with a view to producing the bicyclic compound (91) which would be a particularly useful ring A + B precursor in triterpene syntheses. However, on treating



(89)



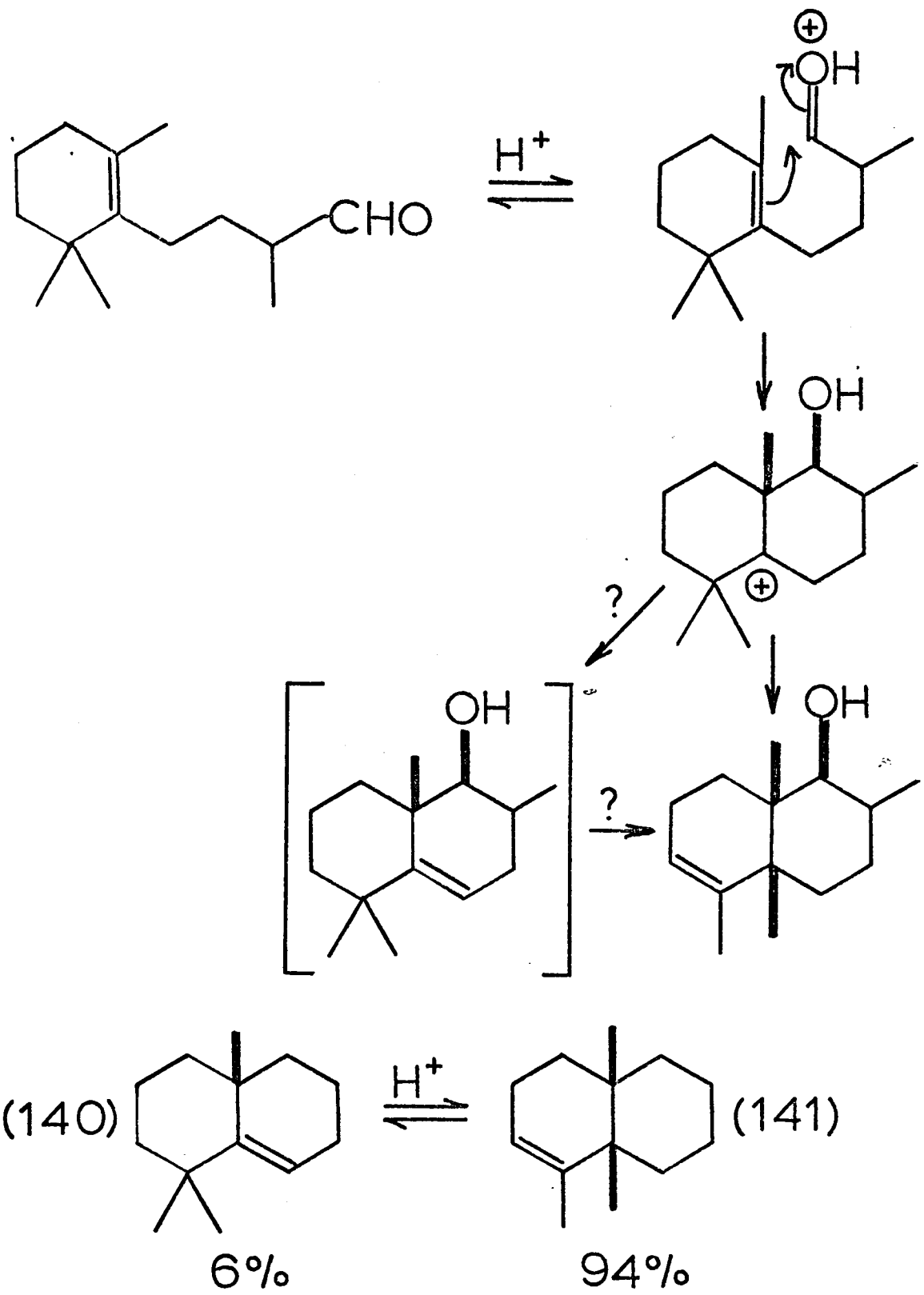
(91)



(90)

luciferin aldehyde with phosphoric acid, they obtained the octalol (90) which has been formed with methyl migration. The stereochemistry shown was confirmed by an X-ray crystallographic analysis on the p-bromobenzoate of (90).

The cyclisation and methyl migration may occur without the formation of an intermediate, or the reaction may proceed to the desired product (91) which then isomerises in the acid conditions obtaining. Marshall and Hochsettler[115] have shown that in acid solution the two decalin systems (140) and (141) are in equilibrium, with the compound with the cis ring junction (141) predominating.



(140) 6%

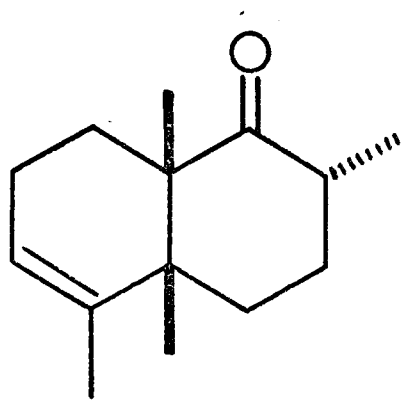
 (141) 94%

Ireland et al.[87] obtained crude luciferin aldehyde by selectively hydrogenating the double bond adjacent to the aldehyde group in the C_{14}- aldehyde, using palladium on charcoal in acetone. The crude luciferin aldehyde was treated with phosphoric acid to give a red solid which, on washing, gave a yellow oil, from which the octalol (90) could be isolated in 40% yield by low temperature crystallisation.

In the present work, the partial hydrogenation was carried out successfully by monitoring the hydrogen uptake, and luciferin aldehyde was obtained 93% pure (yield based on n.m.r. data). Treatment of luciferin aldehyde with phosphoric acid gave a red solid on one occasion and viscous

red oils on two others. The crystalline octalol (90) could be isolated from the red solid in 14% yield by washing and low temperature crystallisation, but a large amount (a further 24%) of the product remained in the mother liquors; these were purified by column chromatography. The red oils were worked up to give yellow oils which could not be induced to crystallise, and the octalol was isolated by column chromatography in yields of 20-30%.

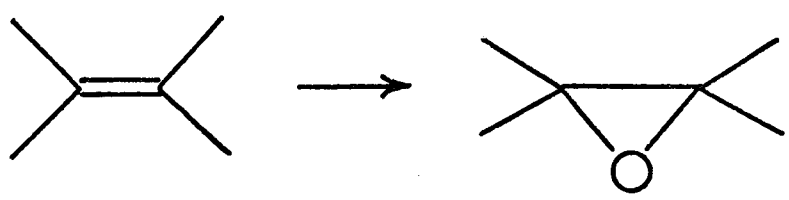
Oxidation of the octalol (90) with chromic acid gave the octalone (142) as a liquid in good yield.



(142)

3. Epoxidation.

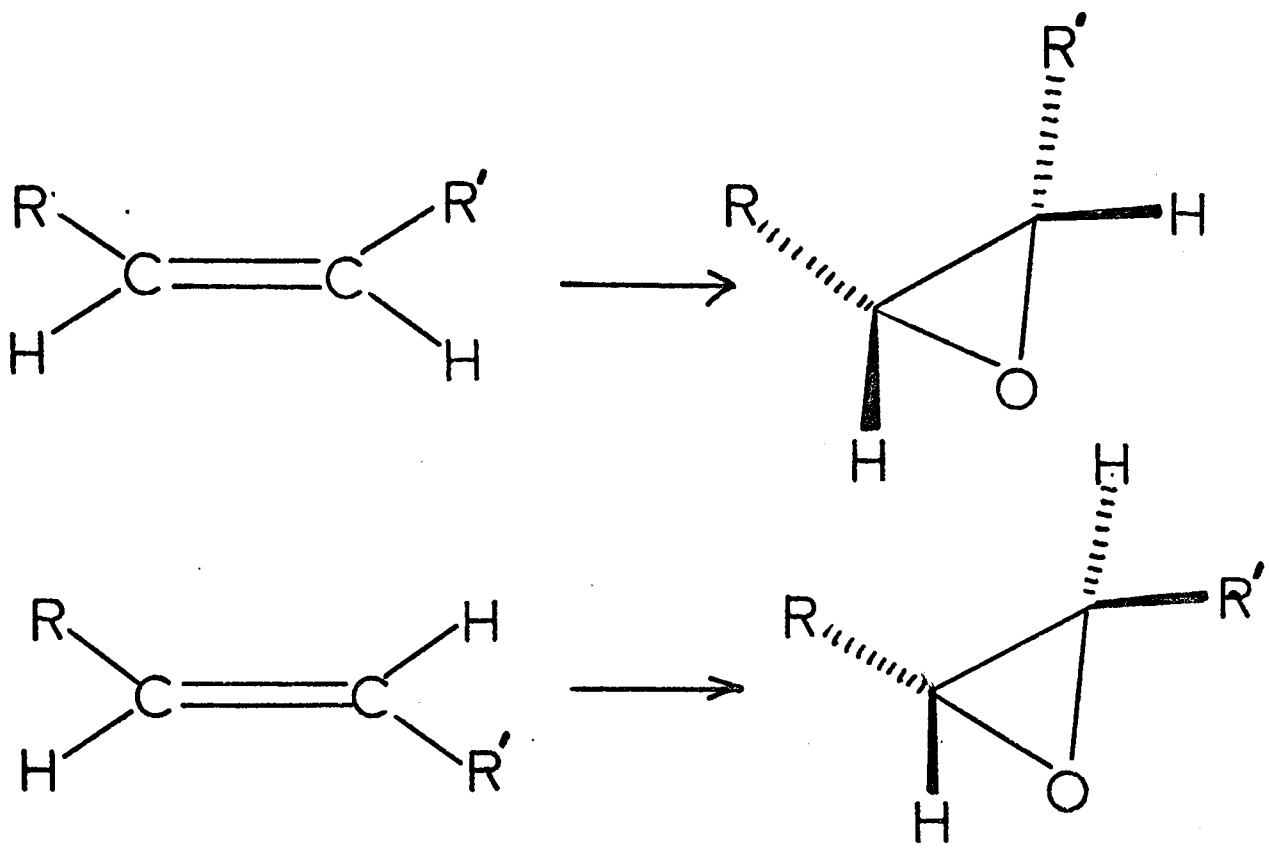
Epoxidation is the reaction whereby a carbon-carbon double bond is converted into an oxiran,



and is conveniently brought about by treating an olefin with a peroxy-acid (commonly referred to as "peracid") which can be used directly or generated in situ.

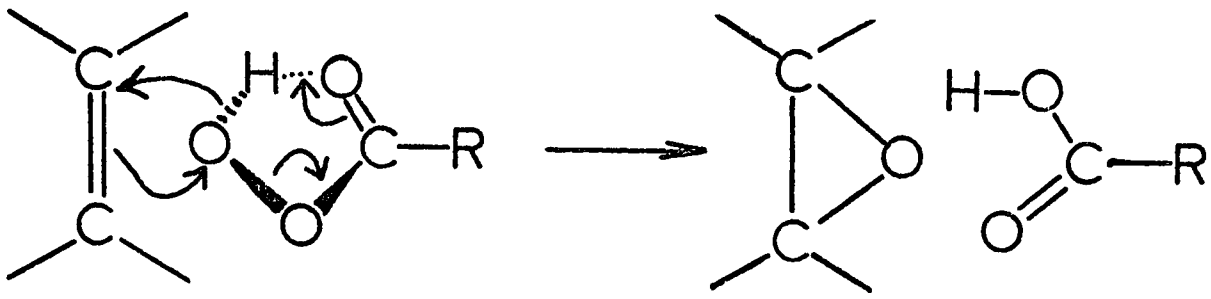
A wide range of peracids have been used in many different solvents, and a comprehensive review of epoxidation with peracids has appeared.[116]

That epoxidation proceeds by concerted attack at both carbon atoms in the olefin is shown by the fact that cis olefins give cis epoxides and trans olefins give trans epoxides.[117]

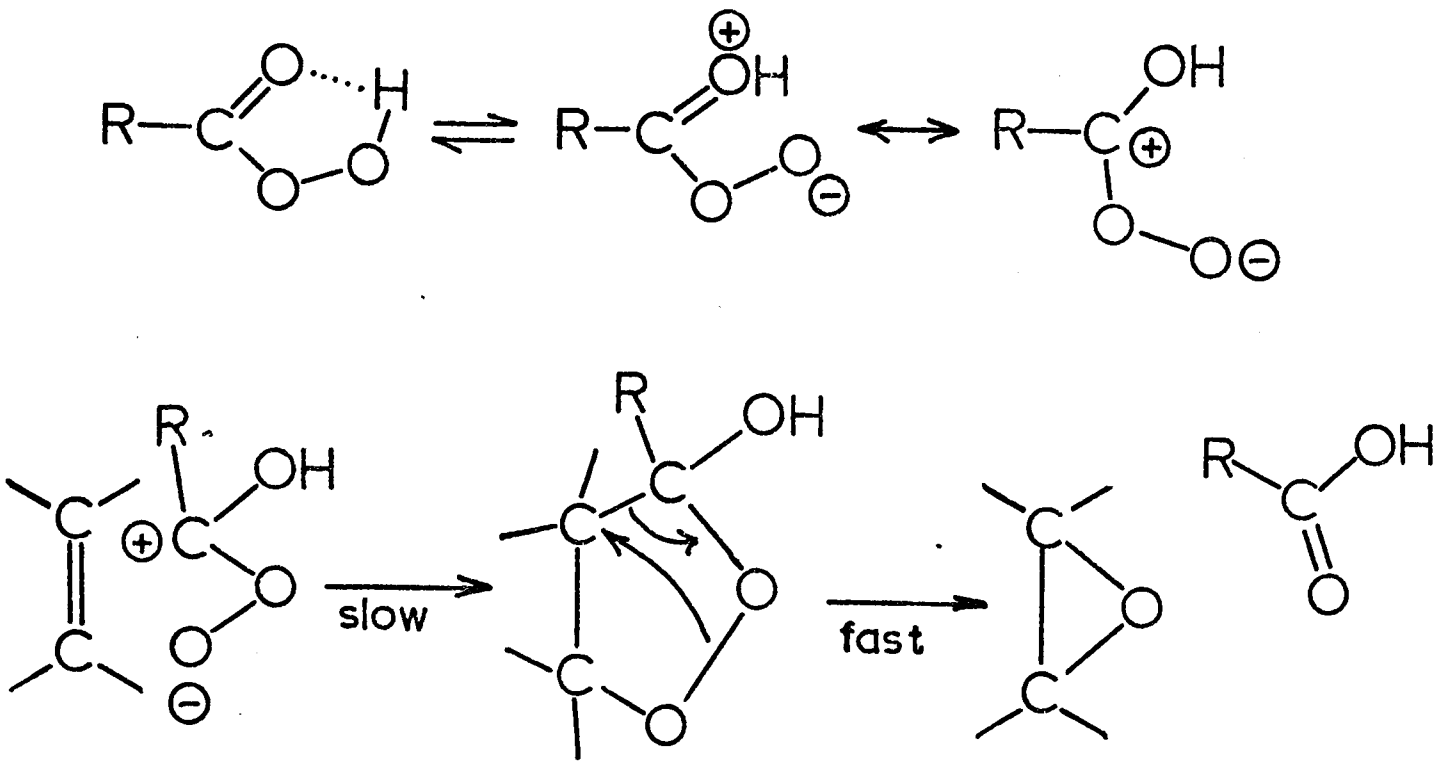


The reaction is first order in both olefin and peracid, and usually proceeds in high yield at room temperature in a few hours, using a wide variety of polar or non-polar solvents. Epoxidation is rapid in non-ionising solvents and there is little or no salt effect or catalysis by acids: the Hammett ρ value for substituted stilbenes is -1, and for substituted perbenzoic acids is +1; the reaction is not thought to involve ionic species or an ionic transition state; the reaction has a high negative entropy of activation, which suggests a highly ordered transition state.[118]

Two mechanisms have been proposed, both of which are consistent with observed characteristics of the reaction: the first is the so-called "molecular" mechanism,[119] which involves a "spiro" transition state; and the second is the 1,3-dipolar mechanism,[120] which was proposed on the basis of the similarity between the reactivity parameters of epoxidation and authentic 1,3-dipolar additions.



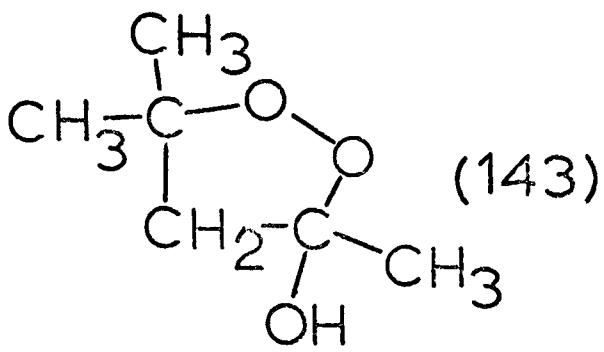
Molecular mechanism



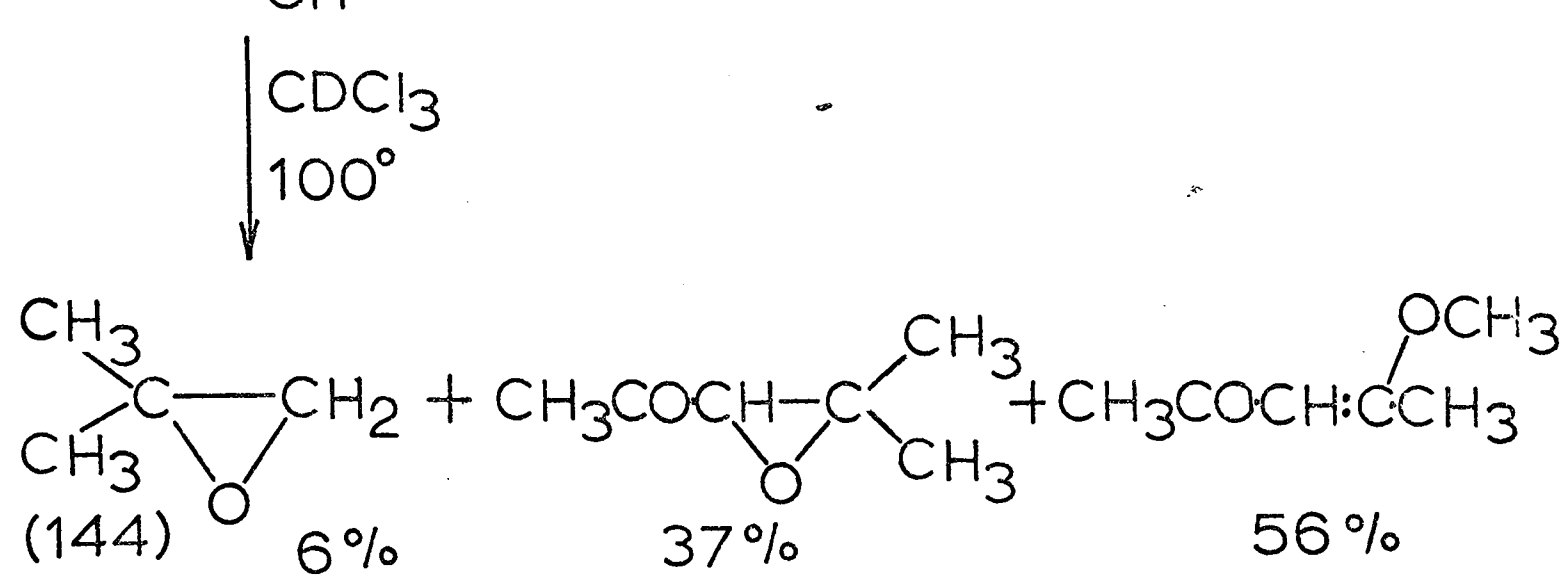
1,3-Dipolar mechanism

The 1,3-dipolar mechanism was criticised by Meakins et al.[121] who pointed out that norbornene reacts approx. 10^4 times as fast with phenyl azides as cyclohexene does, whereas perlauric acid reacts at essentially the same rate with both olefins; this criticism was based on the assumption that all 1,3-dipolar additions to these two olefins should proceed at vastly different rates, and Kwart et al.[122] have suggested that this not need be so, citing the work of Huisgen[123] who indicated that 1,3-dipolar reagents without a double bond in their "sextet structure" (e.g. peracids) should not necessarily show rate differences with these two cyclic olefins.

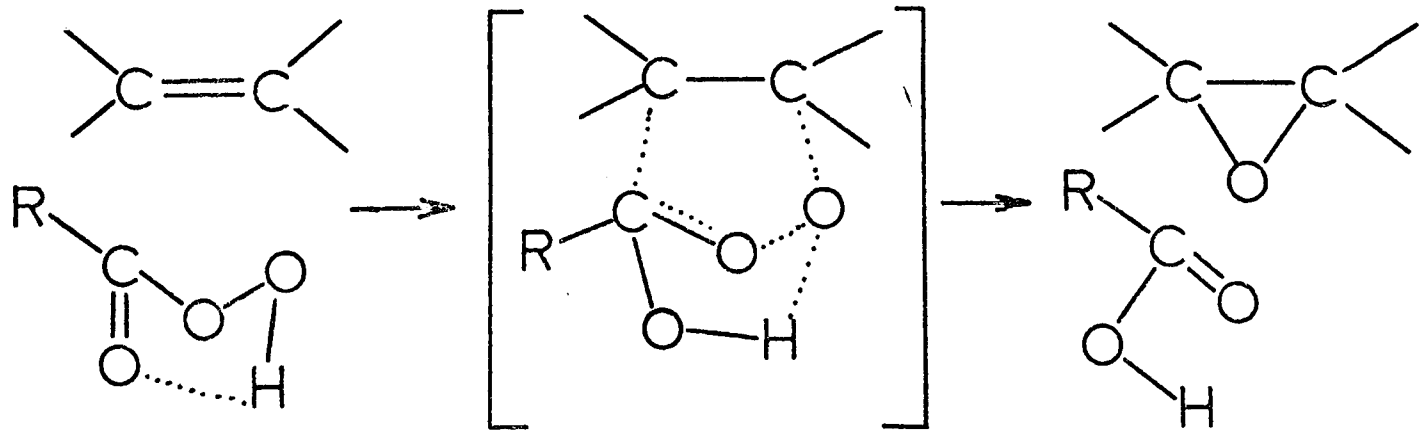
Kwart and his co-workers[122] have prepared the 1,2-dioxolan (143) which should be formed, according to the 1,3-dipolar mechanism, from peracetic acid and isobutylene, and on heating it in deuteriochloroform, they only obtained a low yield of isobutene oxide (144).



(143)



Other 1,2-dioxolans are known, and they tend to be more stable than the 1,3-dipolar mechanism would suggest, so Kwart postulated that the 1,2-dioxolan never forms as such, but that the reaction proceeds through a transition state resembling it (145), with rearrangement to the epoxide occurring preferentially.



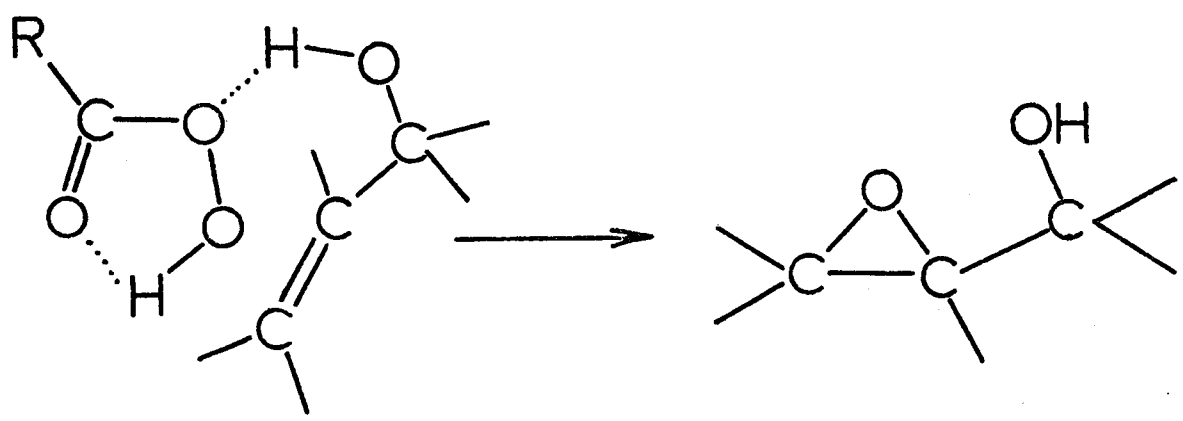
(145)

The introduction of alkyl substituents on a carbon-carbon double bond tends to increase the reactivity of the olefin towards peracids,

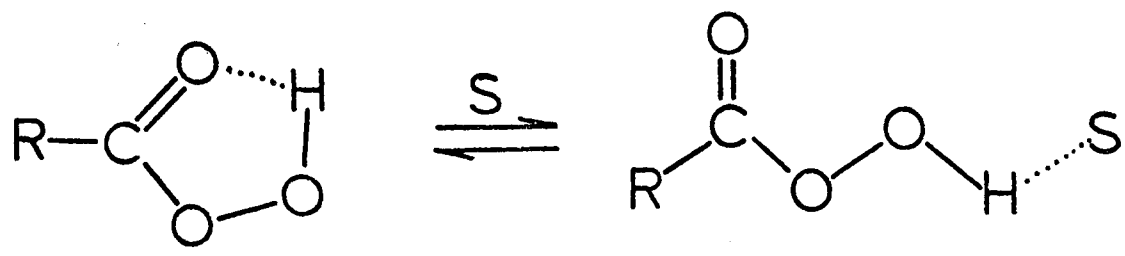
irrespective of the size or bulk of the alkyl groups, which suggests that a fairly symmetrical transition state is involved;[124] this agrees with the molecular mechanism, whereas the 1,3-dipolar mechanism predicts an asymmetrical transition state, whose formation might be prone to steric hindrance.

The electronic structures of peracids in the intramolecularly hydrogen-bonded form and in the dipolar form have been analysed using the semi-empirical Pariser-Parr-Pople SCF-MO method, and the energy difference between the two forms was found to be small (0.75 Kcal $mole^{-1}$), suggesting that both mechanisms are theoretically possible. The electron densities in the two species were found to be consistent with either mechanism, and at present it is not possible to differentiate between the two with certainty.[125]

Certain facets of epoxidation reactions have been rationalised in terms of the molecular mechanism:[125] the cis-directing influence of an allylic hydroxy-group is ascribed to hydrogen bonding between the hydroxy-group and the peracid, holding the latter on the cis side of the molecule.



The decrease in the rate of epoxidation in basic oxygen-containing solvents is thought[126] to be due to disruption of the intramolecular hydrogen bond in the peracid by solvent interaction to give the open-chain form (146).



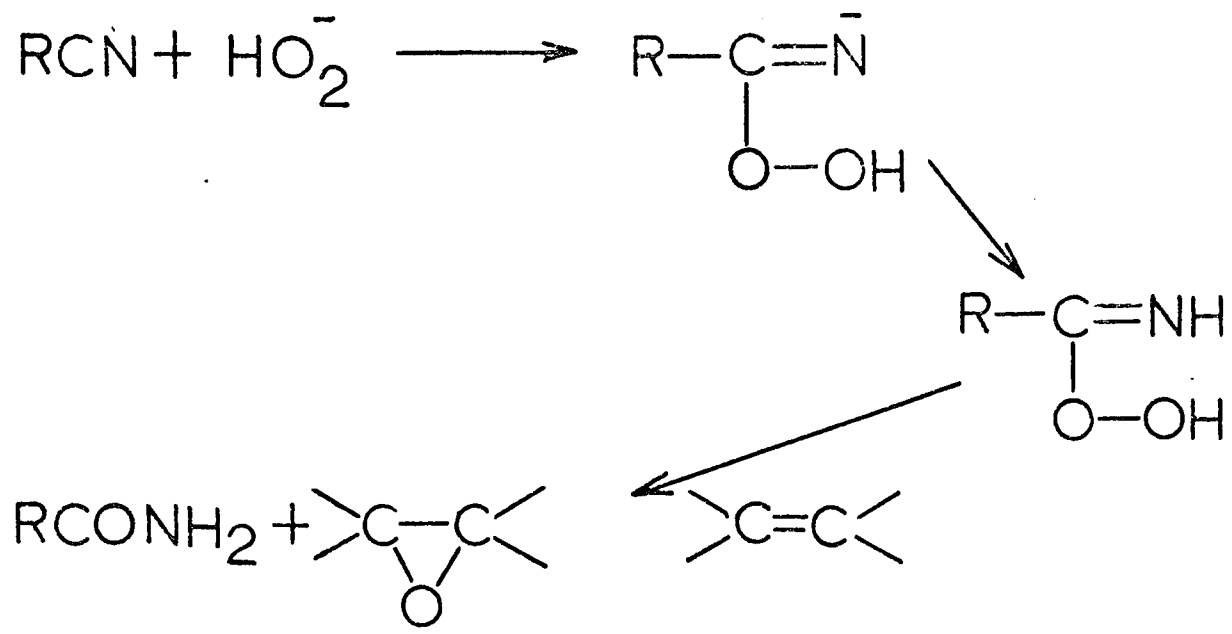
(146)

Desolvation must then occur before the cyclic "spiro" transition state can be attained, leading to an increase in activation energy for the reaction.

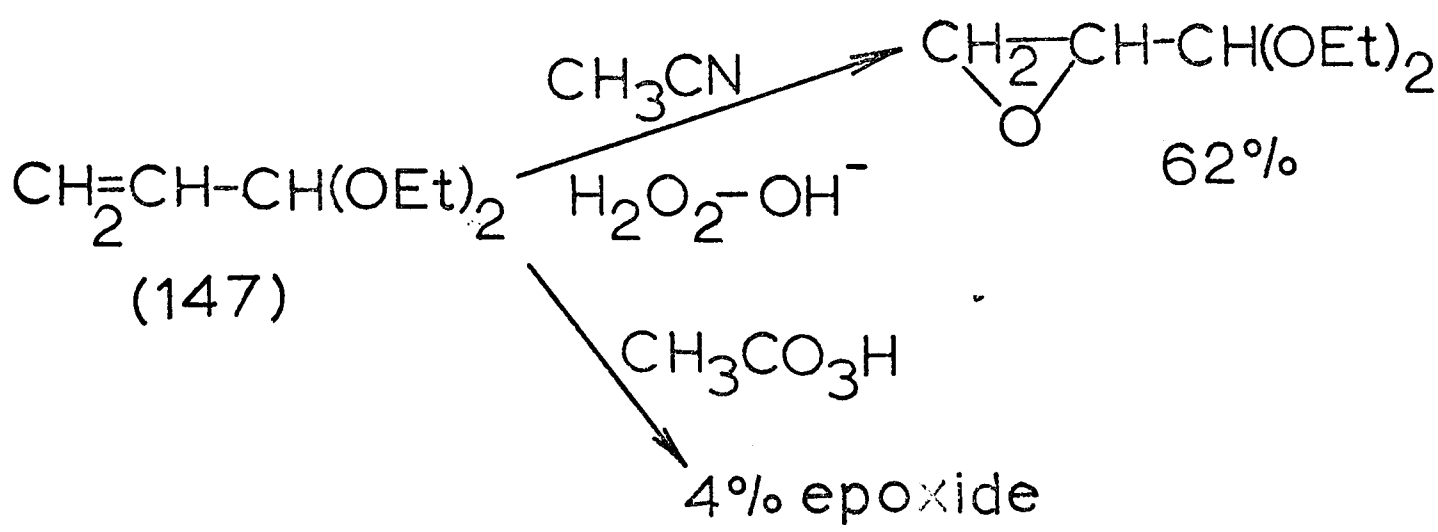
If approach to a double bond is hindered, epoxidation will be disfavoured; thus epoxidation of steroidal olefins usually gives the α-epoxide, as the α-face of the molecule is much less hindered than the β-face.

Steroidal β-epoxides can be formed from trans-bromohydrins; these are formed by initial attack of bromine, which will occur at the less hindered face, and then hydroxy-attack occurs at the β-face; when elimination occurs the β-epoxide is formed. This reaction has been brought about in one stage[127] by treating a steroidal olefin with N-bromoacetamide in aqueous dioxan-perchloric acid, to obtain the β-epoxide in 90% yield.

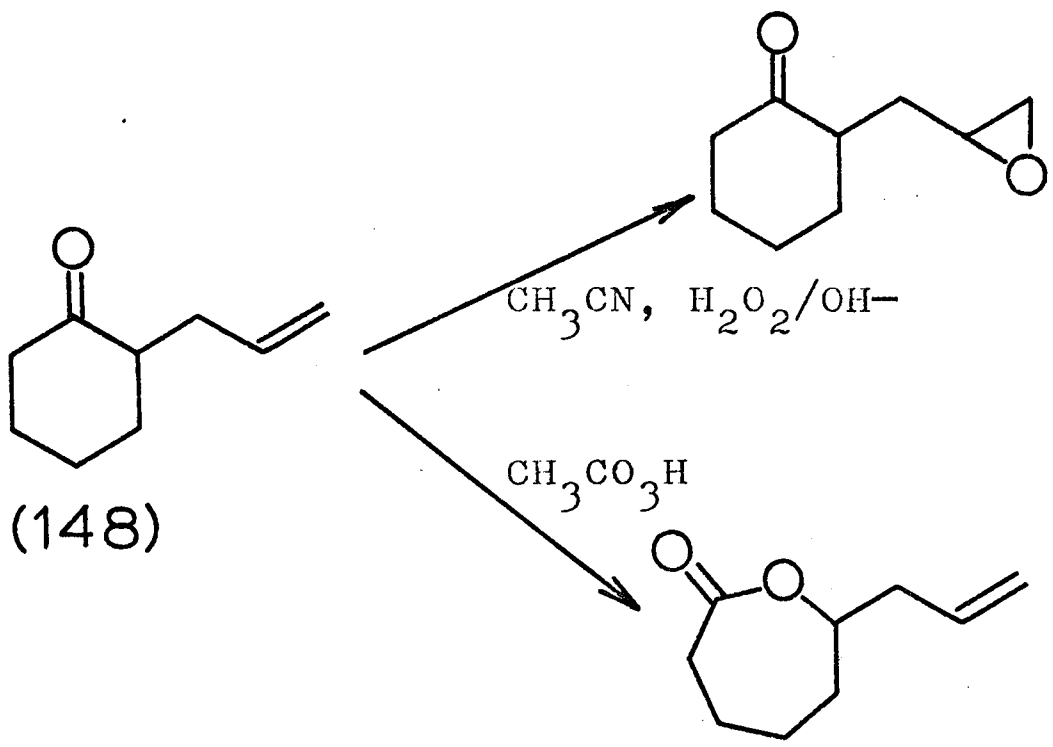
Although the use of peracids for epoxidation is widely applicable, the presence of acid formed from the peracid during the course of the reaction may be disadvantageous if acid-labile groups are present in the olefin, and a technique of epoxidation in mildly basic solution is available:[128] nitriles react with alkaline hydrogen peroxide to give peroxycarboximidic acids, which are unstable and highly reactive, and are usually prepared in situ, and these will epoxidise olefins in high yield.



Commonly used nitriles are acetonitrile, benzonitrile, and trichloroacetonitrile, and the reactions are carried out at 35-60° at pH 7.5-8. Two examples of applications of this reaction are (i) the epoxidation of acrolein diethyl acetal (147)[129] to give the



epoxide in 62% yield, while peracetic acid only yields 4% of the epoxide, and (ii) the epoxidation of a keto-olefin (148) which underwent Baeyer-Villiger oxidation with peracetic acid.[128]

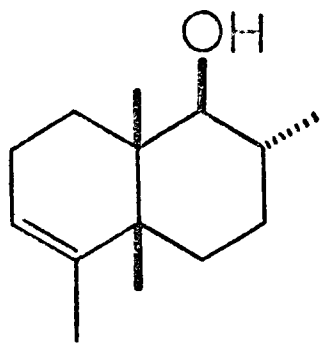


All epoxidations carried out in this work used either m-chloro- or p-nitroperbenzoic acid. The former is commercially available in a state of high purity, and is a stable crystalline solid soluble in a variety of common organic solvents, and reacts several times faster than perbenzoic acid.[130] p-Nitroperbenzoic acid is conveniently synthesised by the method of Silbert, Siegel, and Swern[131] from p-nitrobenzoic acid and 90% hydrogen peroxide in methane-sulphonic acid. It is a stable solid and is between 5-20 times more reactive than perbenzoic acid. Its reduction product p-nitrobenzoic acid is insoluble in common organic solvents and the removal of this from the reaction medium minimises potential epoxide ring opening. The peracid as well has low solubility, but can be used in chloroform, ether and tetrahydrofuran.[132]

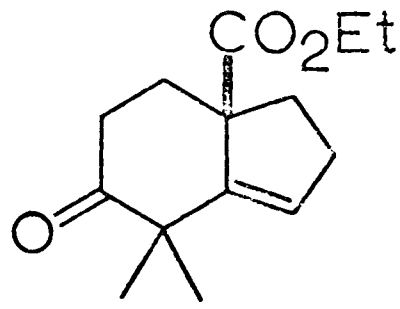
A comparison was made between the two peracids, and on reaction with the same keto-olefin (124) they gave similar yields of epoxide, with the same $\alpha : \beta$ product ratio, and both gave negligible amounts of side-products (although the olefin used might have undergone a Baeyer-Villiger oxidation). Thus the choice of peracid to be used for epoxidation was simply governed by availability.

The olefins treated with peracids in this work are shown on a

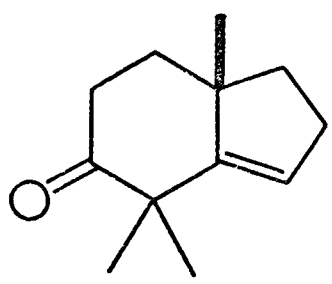
Olefins Treated with Peracids



(90)



(124)



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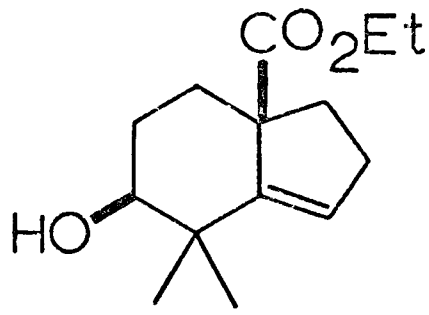
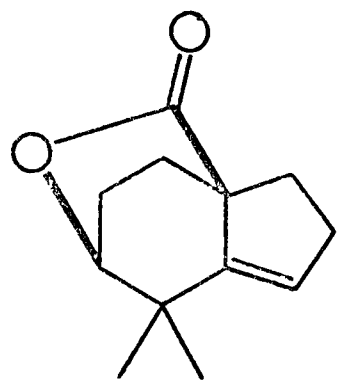


(132)



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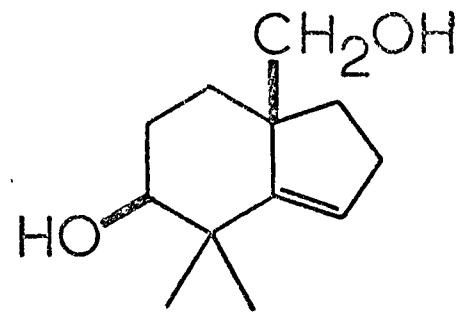

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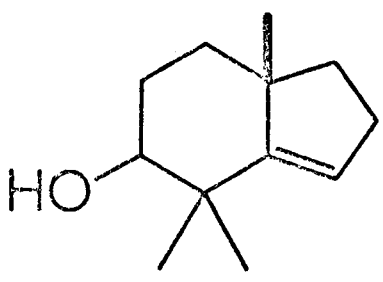

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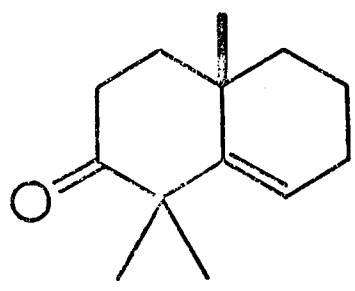

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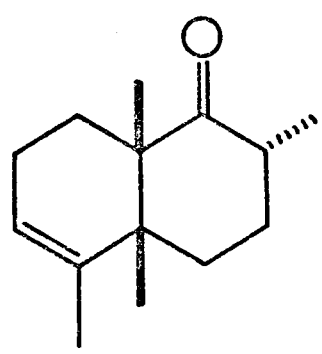
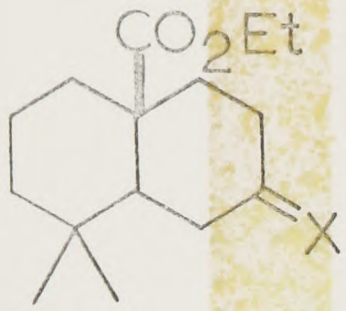


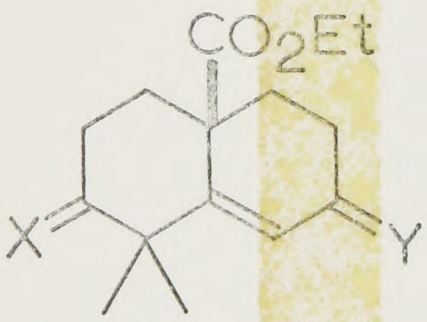
(142)

N.M.R. Signals of Ester Methylene Groups (From ref. 134)

$CH_3\underline{CH}_2CO_2$- appears as ABC$_3$



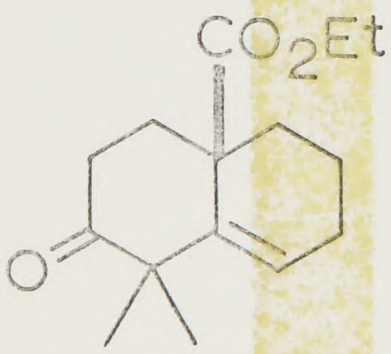
X = O, , H_2

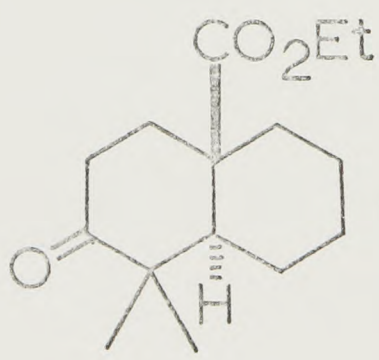


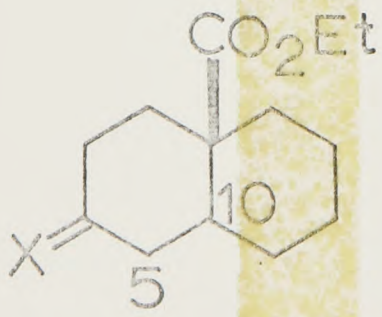
X = , H_2, H_2 , H_2,

Y = H_2 , O , , H_2, H_2

$CH_3\underline{CH}_2CO_2$- appears as A_2X_3







X = O; O, $\Delta^{5,10}$; ; ;

 , $\Delta^{5,10}$; H_2

Scheme 14

chart on p. 74a.

i) Epoxidation of Keto-ester (124).

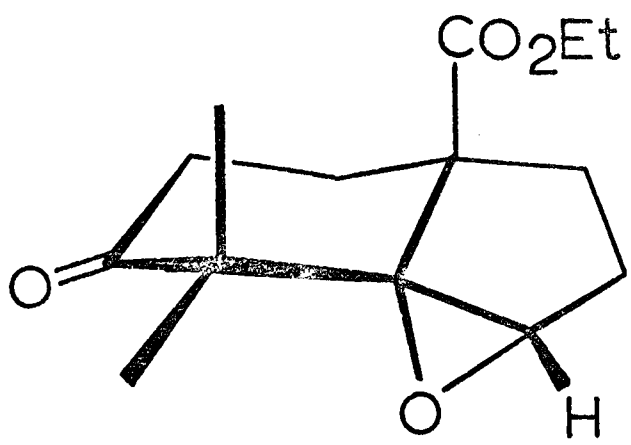
Treatment of the keto-ester olefin (124) with m-chloroperbenzoic acid gave an oil containing two components which were separated by preparative thin layer chromatography (p.l.c.). The upper band gave the major product (82i) (62%), and the lower band the minor product (82ii) (14%). The molecule is slightly curved, and the convex β-face of the molecule is less hindered than the concave α-face, so preferential formation of the β-epoxide might be expected. The formation of the epoxide was indicated by the disappearance of the olefinic signal in the n.m.r. spectrum at τ 4.37, and the appearance of a new signal at τ 6.51 in the less polar epoxide and at τ 6.71 in the more polar epoxide. Both signals appeared as broadened singlets which is the structure expected for a proton at position 3 in a 3,9-epoxy-indane moiety.[133] Epoxidation brought about a marked change in the appearance of the ester methylene signal: in the parent olefin (124) it appeared as a simple A_2X_3 quartet, but in the less polar epoxide, the two methylene protons had become non-equivalent and appeared as an ABC_3 multiplet. The signal could be analysed as four quartets, and simple first-order coupling constants were derived by inspection of the spectrum as J_{AB} = 10.9 and J_{AC} = 7.2 Hz.

Meyer et al.[134] have observed a similar phenomenon in related octalin and decalin esters, and by studying the series of compounds shown in Scheme 14 they found that two factors were necessary for methylene non-equivalence, (i) a 5β-methyl group, and (ii) the methyl-substituted ring in a chair conformation which allows a 1,3-diaxial relationship between the 5β methyl group and the angularly substituted ethoxycarbonyl group.

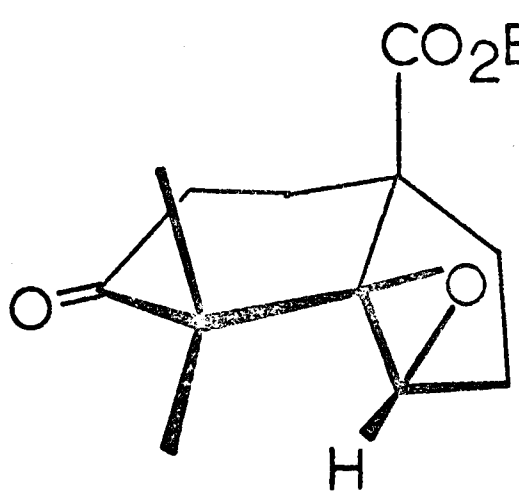
Meyer et al.[134] suggested that the need for a methyl group in a

1,3-diaxial relationship with the ethoxycarbonyl group indicated that the non-equivalence of the methylene protons was due to a steric effect of the methyl group, hindering rotation of the ester group: only some of the latters conformations about the carbonyl group will be significantly populated, and in each of these conformations, the methylene protons are in different environments, and the resulting average environment to which one proton is exposed over all the accessible ester conformations is no longer the same as that of the other proton, and non-equivalence occurs.

The introduction of an epoxy-substituent into keto-ester (124) causes a shift in the relative positions of the 8β-ethoxycarbonyl group and the 4β-methyl group, but the non-equivalence of the ester methylene protons is probably caused by a shielding effect of the oxiran ring. It is difficult to predict which orientation of the oxiran ring will cause the non-equivalence, and the stereochemistry of the two epoxides (82i) and (82ii) cannot be assigned with certainty, although on steric grounds, the major product (82i) might be expected to be the β-epoxide.



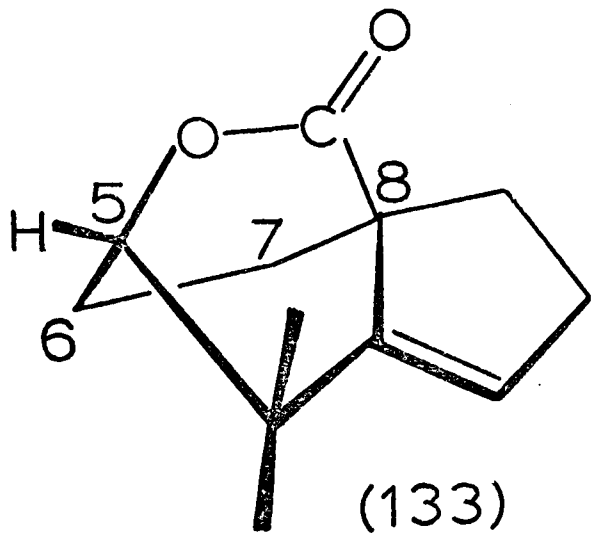
(82ii)?



(82i)?

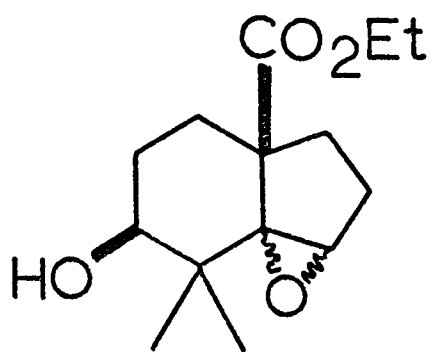
ii) Epoxidation of Hydroxy-Ester + Lactone Mixture (132) and (133).

This mixture obtained by reducing keto-ester (124) with sodium borohydride was treated with p-nitroperbenzoic acid to give a mixture of epoxides which was separated by column chromatography. The first compound eluted was the crystalline lactone epoxide (87i); this had a carbonyl absorption at $\nu_{max.}$ 1755 cm^{-1}, and the hydrogen on the oxiran ring appeared as a broad singlet at τ 6.49. Examination of a model of the lactone olefin (133) indicates that neither side of the olefinic double bond is appreciably more hindered than the other, the only difference being the C6-C7 $-CH_2$ $-CH_2$-bridge on the αface, compared with the 8β,5β-carbolactone bridge -CO-O- on the βface. It is thus not possible to assign the epoxide stereochemistry with any certainty.



(133)

The second compound eluted was a crystalline hydroxy-ester epoxide (83i), with characteristic i.r. signals at $\nu_{max.}$ 3640 and 1725 cm^{-1}. The ester methylene signal appeared as a complex ABC_3 multiplet at τ 5.9, with at least twelve lines visible and the oxiran proton appeared at τ6.44, and by analogy with the keto-ester epoxides, this compound corresponds to the more abundant (82i), and again on steric grounds might be expected to be the β-epoxide.



(83i)

iii) Epoxidation of Hydroxy-ester (132).

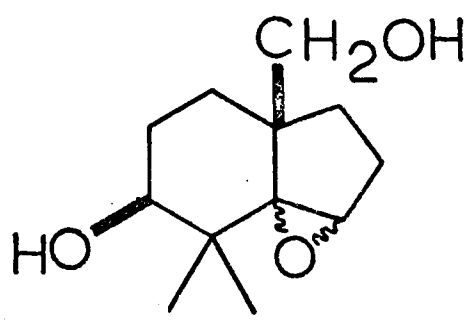
Treatment of the hydroxy-ester olefin (132) with p-nitroperbenzoic acid gave an oil containing two components which were separated by p.l.c. The compound with higher Rf was identical with the hydroxy-ester epoxide (83i) described above and was the major product. The more polar compound (83ii) had no olefinic signal in its n.m.r. spectrum and a new signal at τ 6.77, and characteristic hydroxy-ester absorptions $\nu_{max.}$ 3640 and 1725 cm^{-1}. As in the minor keto-ester epoxide (82ii), the ester methylene group appeared as a simple A_2X_3 quartet, and on steric grounds, this hydroxy-ester epoxide (83ii) might be the α-isomer.

Both epoxides (83i) and (83ii) were unstable and converted into the corresponding lactone epoxides on standing; the ester carbonyl absorption decreased in intensity, and was replaced by a new signal at 1760 cm^{-1} corresponding to a lactone.

iv) Epoxidation of Diol (134).

The dihydroxy-olefin (134) was treated with p-nitroperbenzoic acid to give a single crystalline product (84i), which was tentatively assigned as the β-epoxide on the grounds of favoured mode of attack, and also the nature of its boron trifluoride catalysed rearrangement product (see p. 96). The oxiran hydrogen signal overlapped the signals due to the methine and methylene groups adjacent to hydroxy-groups, but

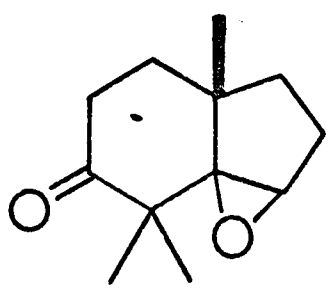
it could be discerned as a broadened singlet at τ 6.57. As in the parent diol (134), the methylene signals in the 8-hydroxymethyl group appeared as an AB quartet; the chemical shift difference between the two methylene protons in epoxide (84i) was $\Delta\nu_{AB}$ = 24.4 Hz at 100 MHz, while in the parent olefin (134) it was $\Delta\nu_{AB}$ = 13.1 Hz at 100 MHz; this difference reflects the different anisotropies of the 3,9-group in the two compounds.



(84i)

v) Epoxidation of Keto-Olefin (127)

Treatment of the keto-olefin (127) with p-nitroperbenzoic acid gave an oil which appeared to be homogeneous by t.l.c., but which had an n.m.r. spectrum which indicated that it was a mixture of two components, probably the α and β epoxides (85): the hydrogen attached to the oxiran ring appeared as two overlapping broad singlets at τ 6.67 and 6.71, and the methyl signals were split by approx. τ0.3. Examination of a model of the olefin (127) indicates that the β-face is less hindered than the α-face, so a larger yield of the β-epoxide is to be expected. Attempts to separate the two epoxides by multiple elution p.l.c. were unsuccessful.

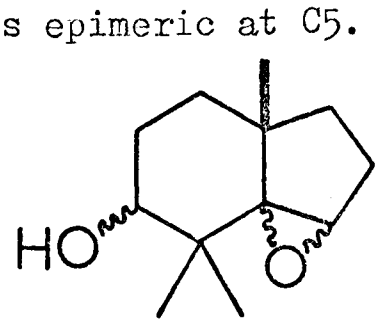


(85)

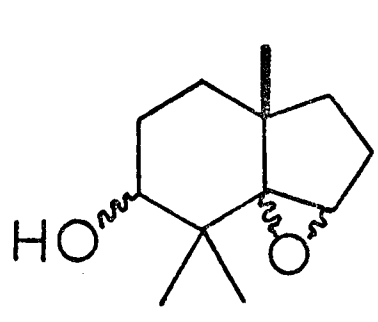
vi) Epoxidation of Hydroxy-Olefin (135).

This olefin was available as a mixture of the 5-epimers, and on treating it with m-chloroperbenzoic acid, an oil containing two components (86i) and (86ii) was obtained; these were separated by p.l.c., and both gave n.m.r. spectra characteristic of hydroxy-epoxides. Both compounds had oxiran hydrogen signals at τ6.75 appearing as merged multiplets with width at half height ($W_{\frac{1}{2}}$) 2.2 Hz. The signals due to the protons adjacent to the hydroxy group, and the methyl groups, were distinctly different in the two compounds: the compound with higher Rf (86i) had a -CHOH- signal at τ6.5 appearing as a merged multiplet, while the compound with lower Rf (86ii) had a -CHOH- signal at τ 6.66, as a doublet of doublets with coupling constants J = 6.9 and 8.9 Hz; the methyl signals appeared as singlets at τ 8.94, 8.97, and 9.16, and at τ 8.86, 8.95, and 9.14 respectively. The -CHOH- signal of the latter compound is very similar to that of the diol epoxide with known stereochemistry at position 5 (84i), and suggests that this compound possibly contains a 5 β-hydroxy-group.

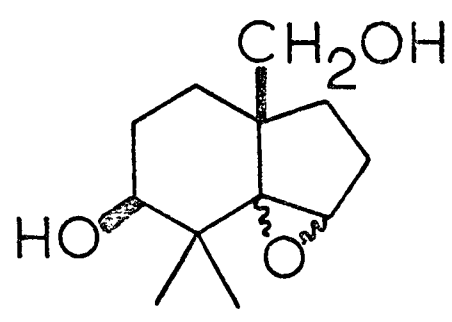
The difference between the -CHOH- signals for the two epoxides obtained in this case suggests that the compound with higher Rf (86i) is epimeric at C5.



(86i) $5\xi_1$

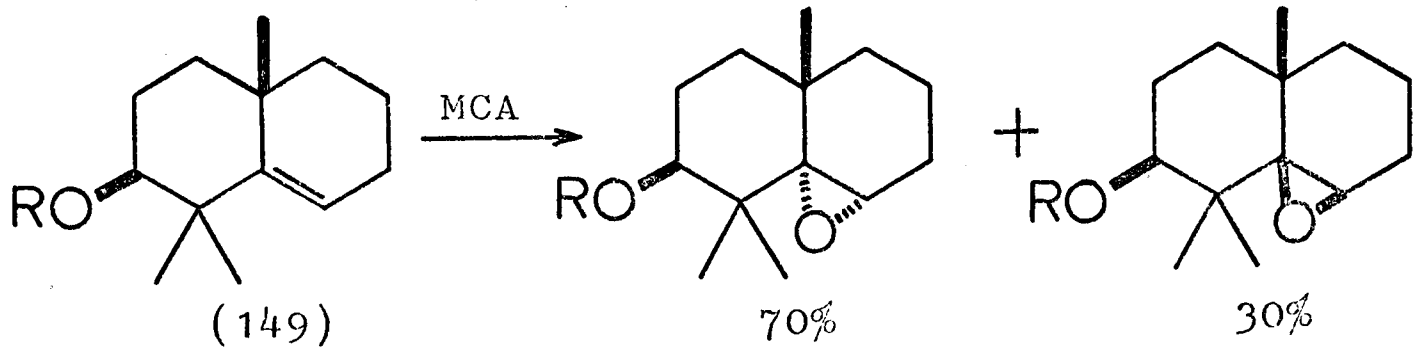


(86ii) $5\xi_2$



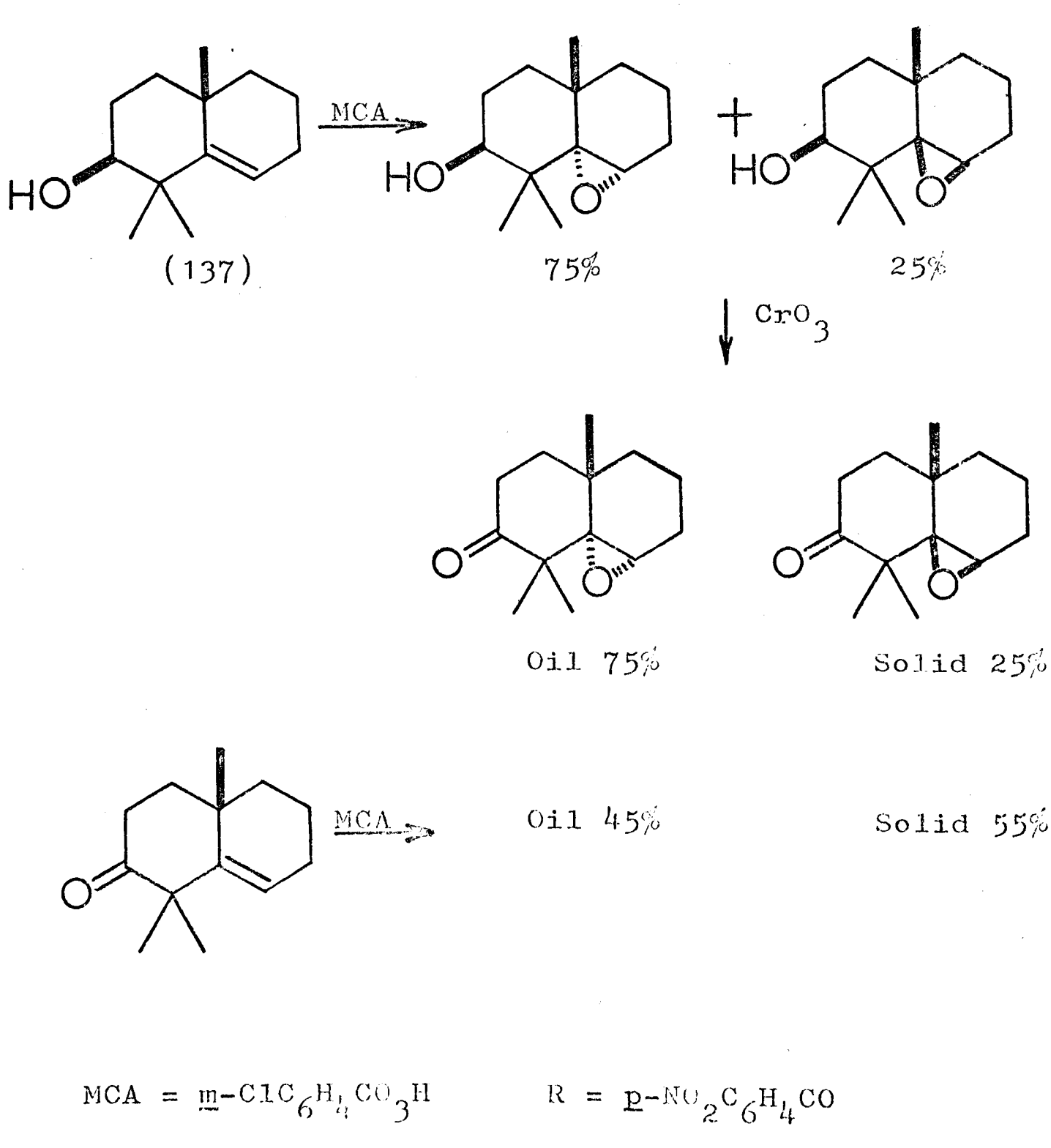
(84i)

In such a situation, the dihedral angles between the hydrogen adjacent to the hydroxy-group, and the hydrogens of the adjacent methylene group are both approximately 60°, and similar coupling constants are to be expected, leading to a gross triplet structure for the -CHOH- signal, which is the pattern observed.



(149) 70% 30%

(71a) Characterised



(137) 75% 25%

Oil 75% Solid 25%

Oil 45% Solid 55%

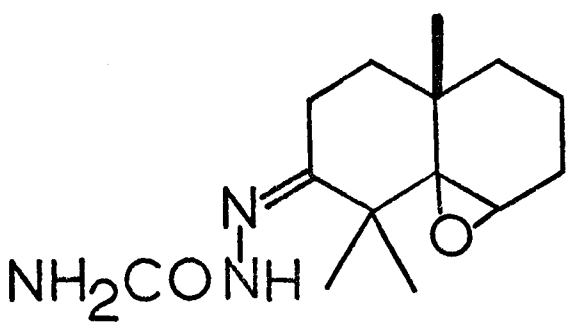
MCA = $\underline{m}$-$ClC_6H_4CO_3H$ R = $\underline{p}$-$NO_2C_6H_4CO$

vii) Epoxidation of Trimethyloctalone (138).

Treatment of the octalone (138) with m-chloroperbenzoic acid gave an oil containing two components which were partially separated by column chromatography and completely separated by p.l.c. The compound with higher Rf (88i) was obtained as an oil (26%) with an oxiran hydrogen signal at τ 7.03, and methyl signals at τ 8.87, 8.92, and 9.22, while the compound with lower Rf (88ii), which was a crystalline solid (32%), had an oxiran hydrogen signal at τ 7.00 and methyl signals at τ 8.98, 9.02, and 9.09.

Whitlock and Olson[85] obtained a 7:3 mixture of epoxides on treating the octalyl p-nitrobenzoate (149) with m-chloroperbenzoic acid, and they isolated the major isomer and hydrolysed it to the corresponding decalol epoxide. Rearrangement of this with trifluoroacetic acid in chloroform or with boron trifluoride-ether complex gave a mixture of products, and the structure of one of these (confirmed chemically) indicated that the epoxide was the α-isomer (71a). Mudd[113] treated the octalol (137) with m-chloroperbenzoic acid and obtained a 3:1 mixture of epoxides, and the n.m.r. spectrum of this mixture indicated that the major product was the decalol α-epoxide (71a) which had been characterised by Whitlock and Olson. Oxidation of this mixture of decalol epoxides with chromium trioxide gave a corresponding 3:1 mixture of decalone epoxides, and on separation, the major product (which must be the α-isomer) was obtained as an oil, and the minor product (the β-isomer) as a crystalline solid. The two decalone epoxides obtained in this work (88i) and (88ii) were identical with those obtained by Mudd, and can thus be assigned as (88i) = α-epoxide and (88ii) = β-epoxide.

Both epoxides gave crystalline semicarbazones (150i) and (150ii) on treatment with semicarbazide hydrochloride and sodium acetate solution.

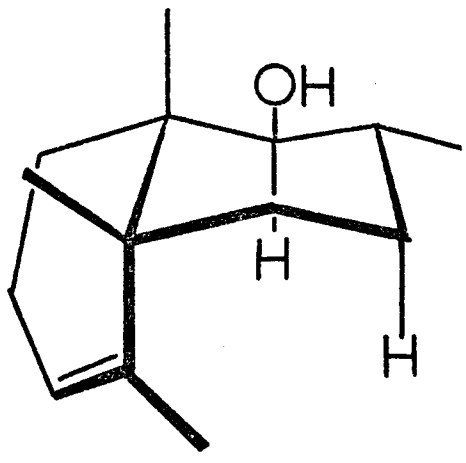


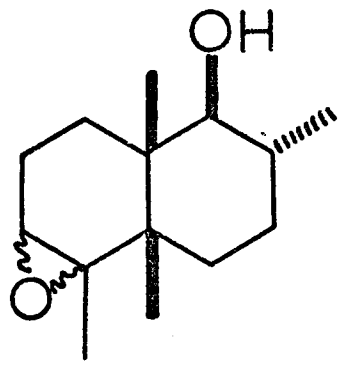
(150i) α-epoxide
(150ii) β-epoxide

viii) Epoxidation of Tetramethyloctalol (90).

Treatment of the octalol (90) with p-nitroperbenzoic acid gave a single crystalline epoxide (92i) with an oxiran hydrogen siganl at τ 7.12, appearing as a merged triplet, with coupling constant J = 1.5 Hz. The formation of a single β-epoxide might be expected from steric approach arguments, as access to the concave α-face of this cis-decalin is severely obstructed by the cage-like structure of the molecule:[135] thus epoxide (92i) can be assigned the β-configuration with some measure

(90)





(92i)

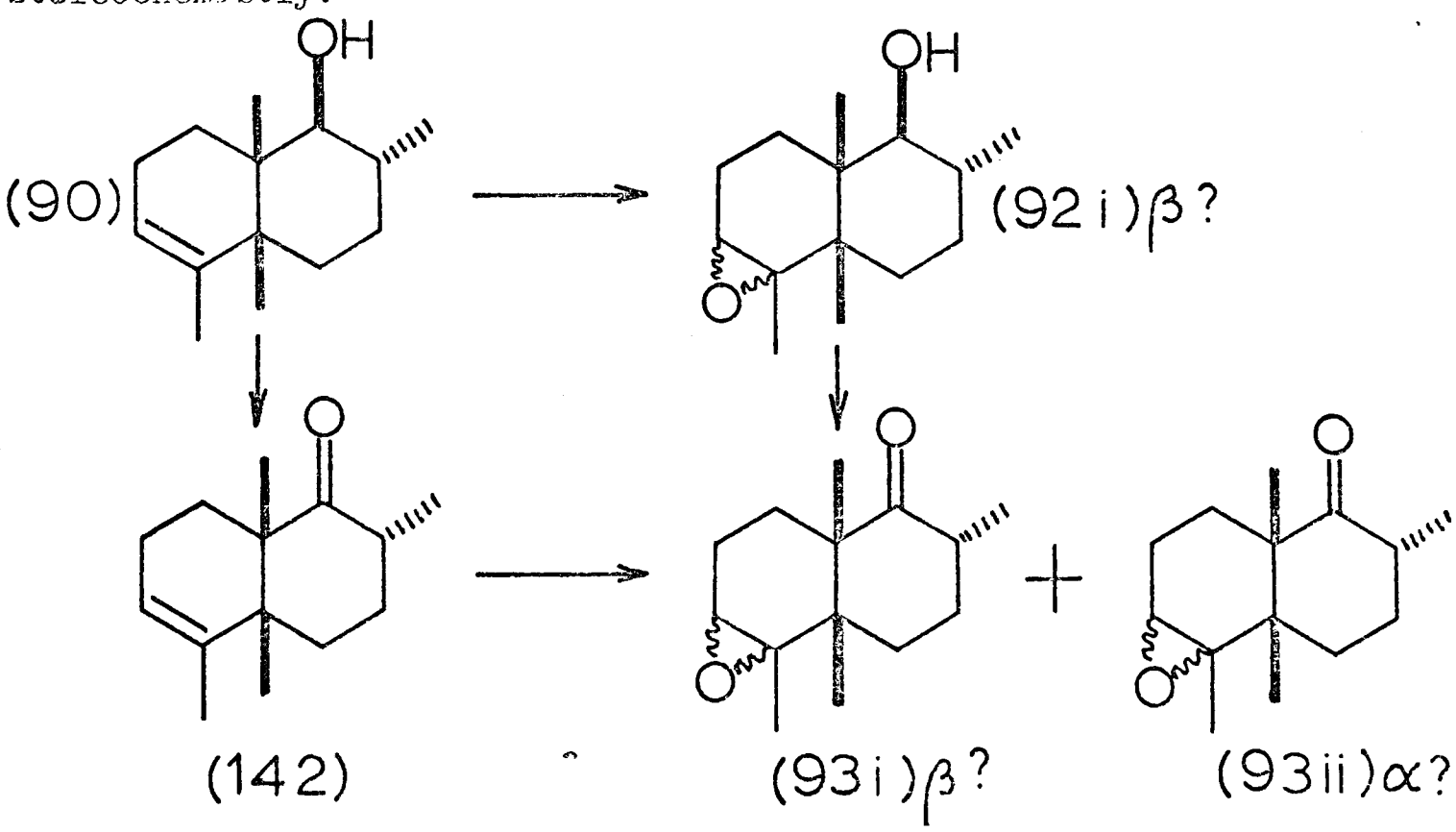
of certainty.

ix) Epoxidation of Tetramethyloctalone (142).

Treatment of the octalone with p-nitroperbenzoic acid gave a mixture

of two epoxides which were simply separated by p.l.c. The compound with higher Rf (93i) was obtained as an oil in 41% yield, and gave an oxiran hydrogen signal at τ 7.23. The more polar compound (93ii) was also obtained as an oil, in 20% yield, and had an oxiran hydrogen signal at τ 7.39.

Examination of models of octalone (142) shows that the α-face of the molecule is more hindered than the β-face, although the removal of the α-proton on going from a 1-hydroxy- to a 1-oxo-group has reduced some of the restriction to approach at the α-face: thus preferential formation of the β-epoxide (93i) is to be expected, and the compound obtained in the greater yield (93i) was assigned as the β-epoxide. Epoxide (93i) was correlated with the octalol epoxide (92i) by oxidising the latter with chromium trioxide in pyridine. The reaction was incomplete after 18 hours at 25°, but was proceeding to a single product. Treatment with more of the oxidising agent increased the extent of reaction to 60% (from n.m.r. data). The product had the same Rf and similar oxiran hydrogen signal in the n.m.r. at τ 7.22 as the octalone epoxide (93i) (τ 7.23) and this suggests that compounds (92i) and (93i) have the same (probably β) epoxide stereochemistry.



CHAPTER 3

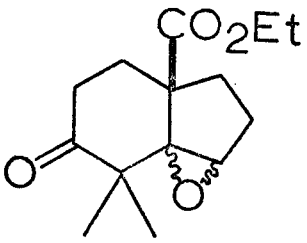
Rearrangements of Model Epoxides

1. Introduction.

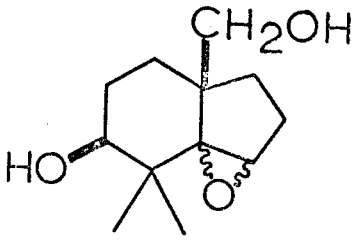
Epoxides rearrange with Lewis acids in the absence of nucleophilic species to give a wide variety of products, which depend on the environment of the oxiran ring. A commonly used Lewis acid for this reaction is boron trifluoride, which is used as its diethyl ether complex, although boron trifluoride gas has been used in a few cases.[86] The rearrangement system used in this work was boron trifluoride-ether complex in an-hydrous benzene, under an atmosphere of dry nitrogen. Early workers[68] often obtained fluorohydrins from epoxide rearrangements, and their structures indicated that they were formed by direct nucleophilic attack of a fluorine species on the epoxide: Kirk and Hartshorn[136] have pointed out that many commercial samples of boron trifluoride-ether complex contain fluoroboric acid HBF_4, in equilibrium with boron trifluoride and hydrogen fluoride, and the latter acts as a source of fluoride ions which can cleave the epoxide. Fluorohydrin formation can be minimised by rigorously purifying the boron trifluoride-ether complex by distillation; in this work, the commercial material was distilled under reduced pressure from calcium hydride, and batches were redistilled immediately before use.

One molar equivalent of boron trifluoride-ether complex was added to a stirred solution of the epoxide in dry benzene under an atmosphere of dry nitrogen; rearrangements were usually carried out at 25°, but in a few cases, lower temperatures were used to reduce the formation of intractable resinous products. The addition of boron trifluoride-ether complex was usually accompanied by the generation of yellow or red colourations, although the colour was discharged when the rearrangement was stopped after 10 minutes by the addition of 5% aqueous sodium hydrogen carbonate solution. Working up using ether gave a mixture of

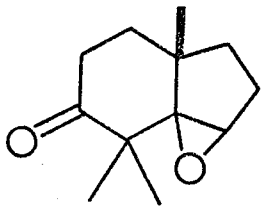
Epoxides Treated with BF_3, Et_2O



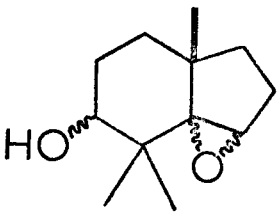
(82i) ξ_1
(82ii) ξ_2



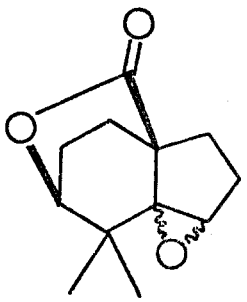
(84i)



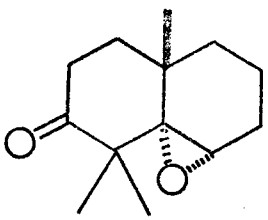
(85)



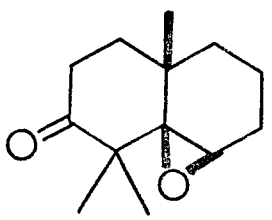
(86i) 5ξ_1-ol
(86ii) 5ξ_2-ol



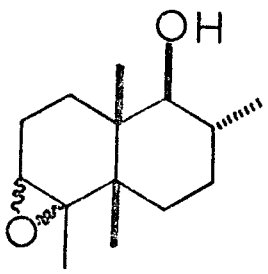
(87i)



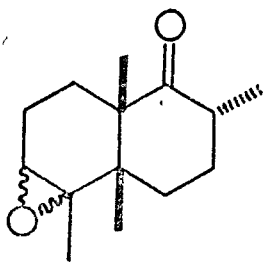
(88i)
(150i) = Semicarbazone



(88ii)



(92i)



(93i) ξ_1
(93ii) ξ_2

rearrangement products which was separated by column or preparative layer chromatography (p.l.c.).

The generation of intense colourations during boron trifluoride catalysed rearrangements has been reported previously[80] but no satisfactory explanation of their cause has been offered. The absorption of radiation in the "visible" region of the electromagnetic spectrum can be caused by a long conjugated π-electron system, or by a charge-transfer system. It is hard to envisage suitable π-systems arising from the boron trifluoride-epoxide complex, because at least four chromophoric groups are usually required to shift absorption into the visible region.[137]

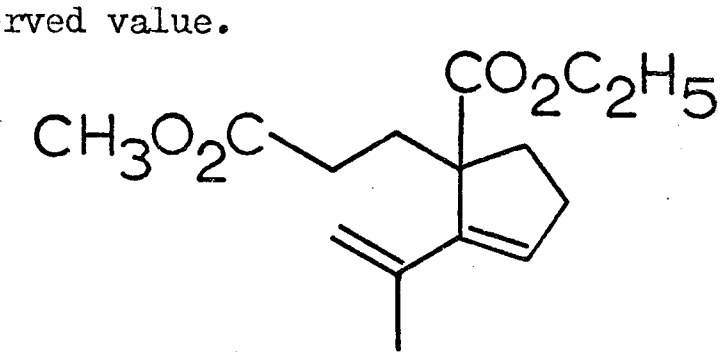
2. Results.

The rearrangements of the model epoxides will now be described in detail (the epoxides mentioned are shown on a chart on p. 85a).

i) Ethyl $3\xi_1,9\xi_1$ -Epoxy-4,4-dimethyl-5-oxohexahydroindane-8β-carboxylate (82i).

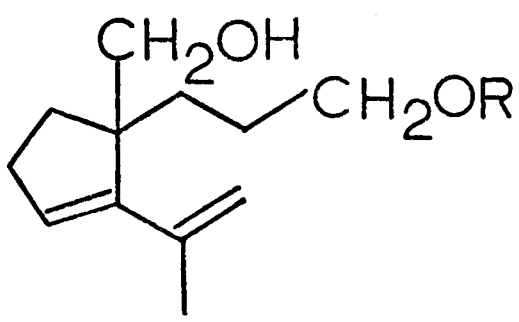
The epoxide was treated with boron trifluoride-ether complex at 10° for 10 minutes, as a small scale run showed that large amounts of resinous material were formed when the reaction took place at 25°. The reaction product was a yellow oil with a streaky t.l.c., and absorption in its i.r. spectrum at 2700-2500 cm^{-1} indicated that it contained a carboxylic acid. The product mixture was treated with diazomethane to give an oil containing one major and four minor products, and these were separated by p.l.c. The least polar compound was obtained as an oil in 31% yield, and it contained no hydroxy-groups and two carbonyl groups ($\nu_{C=O}$ 1740, 1726 cm^{-1}). The n.m.r. spectrum was particularly informative and showed the presence of one olefinic proton and a terminal methylene group

(multiplets at τ 4.12 and 5.14), a vinylic methyl group (multiplet at τ8.12), and methyl and ethyl ester groups. The mass spectrum showed a molecular ion peak at m/e 266 which is 14 units higher than the molecular weight of the parent epoxide, and suggests the formation of a methyl ester. The compound had an intense u.v. absorption at $\lambda_{max.}$ 236 nm (ε 13,000) which suggested that the methylene group and the trisubstituted double bond were conjugated, and pointed to structure (151) which is consistent with all the data. The calculated $\lambda_{max.}$ value for this structure is 232 nm which agrees favourably with the observed value.



(151)

Reduction of (151) with lithium aluminium hydride gave a crystalline diol (152), whose n.m.r. spectrum showed three separate one-proton olefinic signals, and two overlapping multiplets at τ6.4-6.5 due to the two -CH_2OH groups. The diol was treated with p-nitrobenzoyl chloride in pyridine and gave a mono-p-nitrobenzoate (153).



(152) R = H
(153) R = p$NO_2C_6H_4CO$-

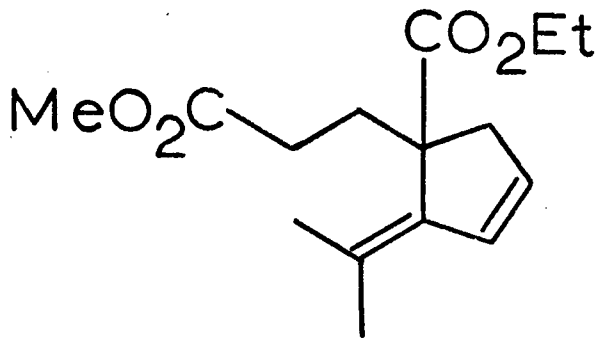
The m.s. showed a molecular ion at m/e 345, and the n.m.r. spectrum

showed only four aromatic protons, while the i.r. spectrum indicated both a hydroxy- and an ester group ($\nu_{max.}$ 3640 and 1732 cm^{-1}); all of these factors confirmed the formation of a mono-ester. The methylene group adjacent to the ester moiety appeared as a triplet at τ5.71 while the hydroxymethyl signal appeared as an AB quartet at τ6.41, confirming that the hydroxy-group in the "side chain" of the diol (152) had reacted.

The second compound separated from the methylated reaction mixture was unchanged epoxide, recovered in 5% yield.

Three other bands were removed from the preparative layer chromatogram of the reaction mixture, but none of them gave pure compounds, and their spectral data were inconclusive.

The third band gave an oil in 12% yield and this was subjected to further p.l.c. to give a glass which, although apparently homogeneous to t.l.c., was not pure. The mass spectrum had a very weak peak at m/e 266, consistent with a methylated rearrangement product. The i.r. spectrum indicated no hydroxy-group, and possibly two ester carbonyl groups ($\nu_{max.}$ 1751 and 1733 cm^{-1}). The n.m.r. spectrum showed two olefinic protons and possibly two vinylic methyl methyl groups (τ8.15 and 8.44): the presence of methyl and ethyl ester groups was also indicated. The methyl ester signal appeared as two singlets at τ 6.40, with relative intensities of 3.3:1; and the ethyl ester signals appeared as two overlapping quartets at τ5.9, and two overlapping triplets at τ8.8; these ester signals indicate that the material contained at least two components. The u.v. spectrum had an absorption maximum at 244 nm, and this is compatible with the diene-diester (154), which has a calculated $\lambda_{max.}$ of 242 nm.



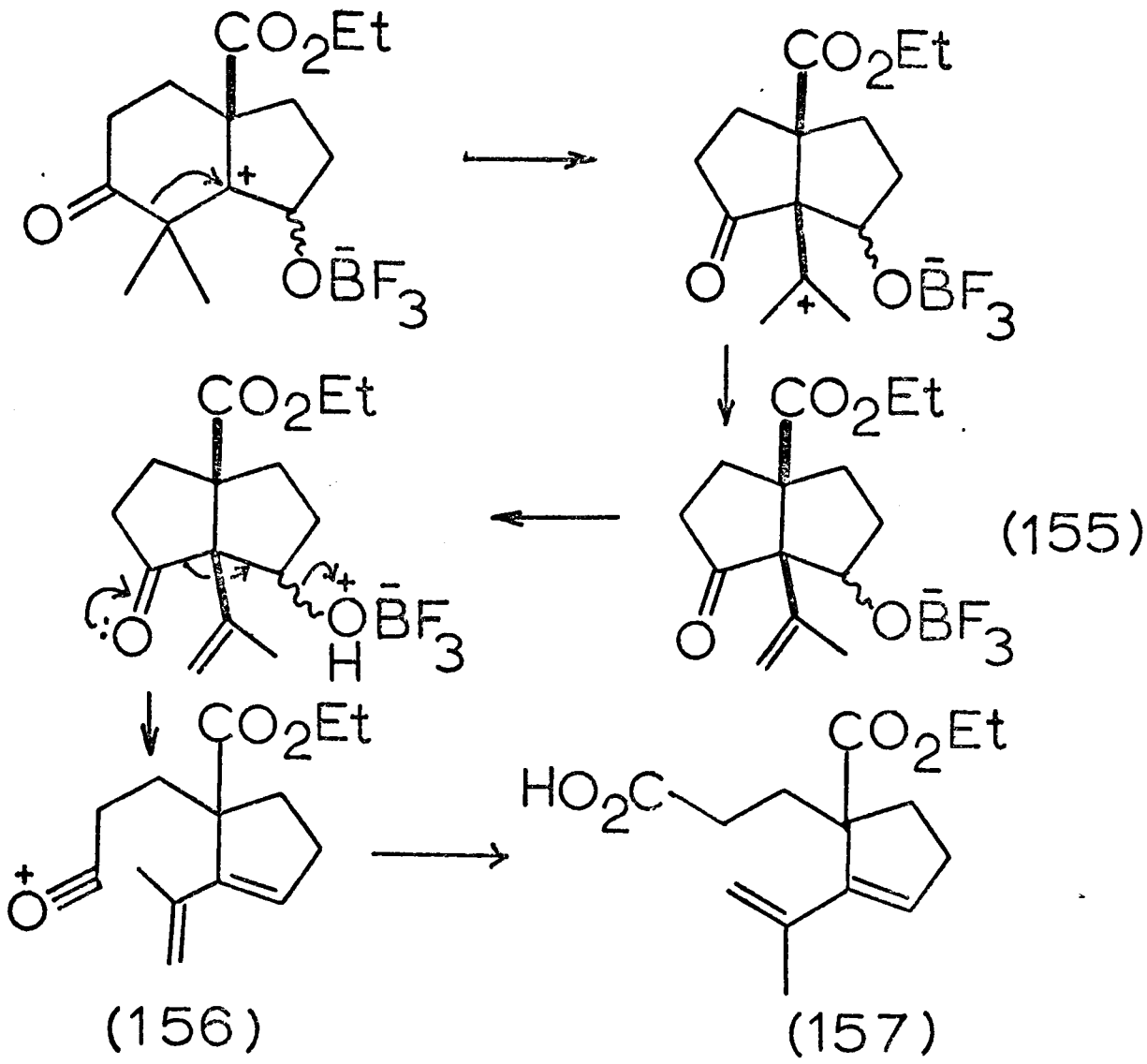
(154)

The mass spectrum of this substance showed a peak at m/e 242, which is difficult to derive either from a molecular ion of m/e 266, or from a direct rearrangement product with m/e 252.

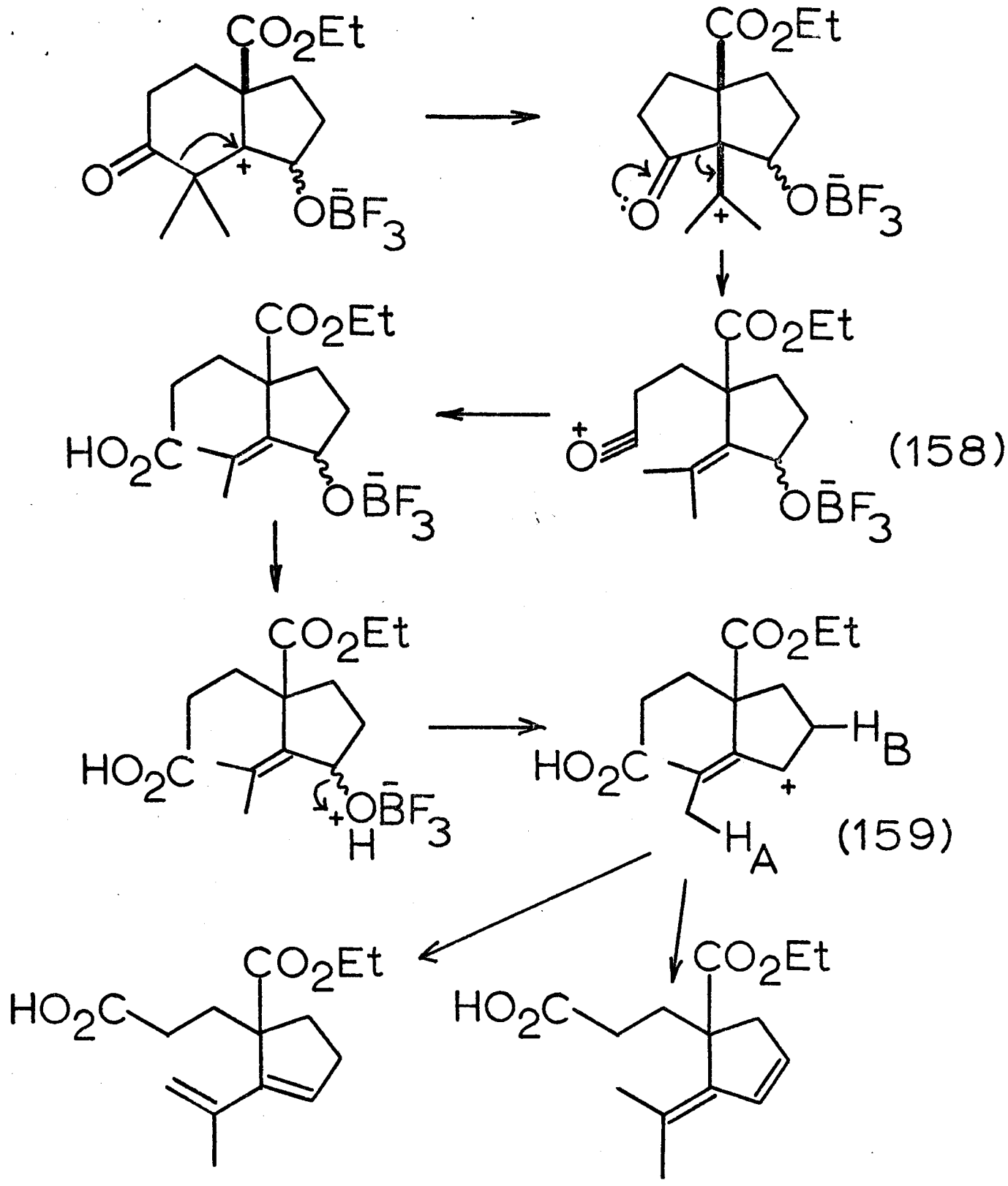
The fourth band also gave an oil, in 7% yield, which was not pure: attempts were made to purify it by multiple elution p.l.c., but it was extremely difficult to separate from the band above it, and the substance obtained had similar u.v., i.r., and n.m.r. spectra to that band. Its mass spectrum showed a very small peak at m/e 266 (~ 1%), and as with the third band, there was a peak at m/e 242.

The fifth band gave an oil which contained several components in 14% total yield, but this darkened on standing to give a polar mixture which was not investigated further.

The major product (151) and the other tentatively identified product (154) contain an isopropenyl and an isopropylidene group respectively, and these groups suggest that the predominant mode of rearrangement is via acyl migration of the 5-keto-group. The carbonium ion formed may eliminate a proton to give the isopropenyl group (155), and protonation of the $-O\bar{B}F_3$ group provides a good leaving group ($HO\bar{B}F_3$). Involvement of the lone pair of electrons on the carbonyl group to give an acylium ion will generate the diene group (156), and the $HO\bar{B}F_3$ species (suggested as a hydroxylating agent in other epoxide rearrangements,[138] can then react with the acylium centre to give the acid (157).



An alternative route to the major product and the isomeric diene (154) might proceed by initial acyl migration followed by fission to give an acylium ion with an isopropylidene group (158). This species could give the carboxylic acid group by attack of $HO\bar{B}F_3$, and then loss of $HO\bar{B}F_3$ from the five-membered ring would generate an allylic carbonium ion (159) from which loss of H_A would give the precursor to the major product (151) and loss of H_B would give the precursor to product (154).



(158)

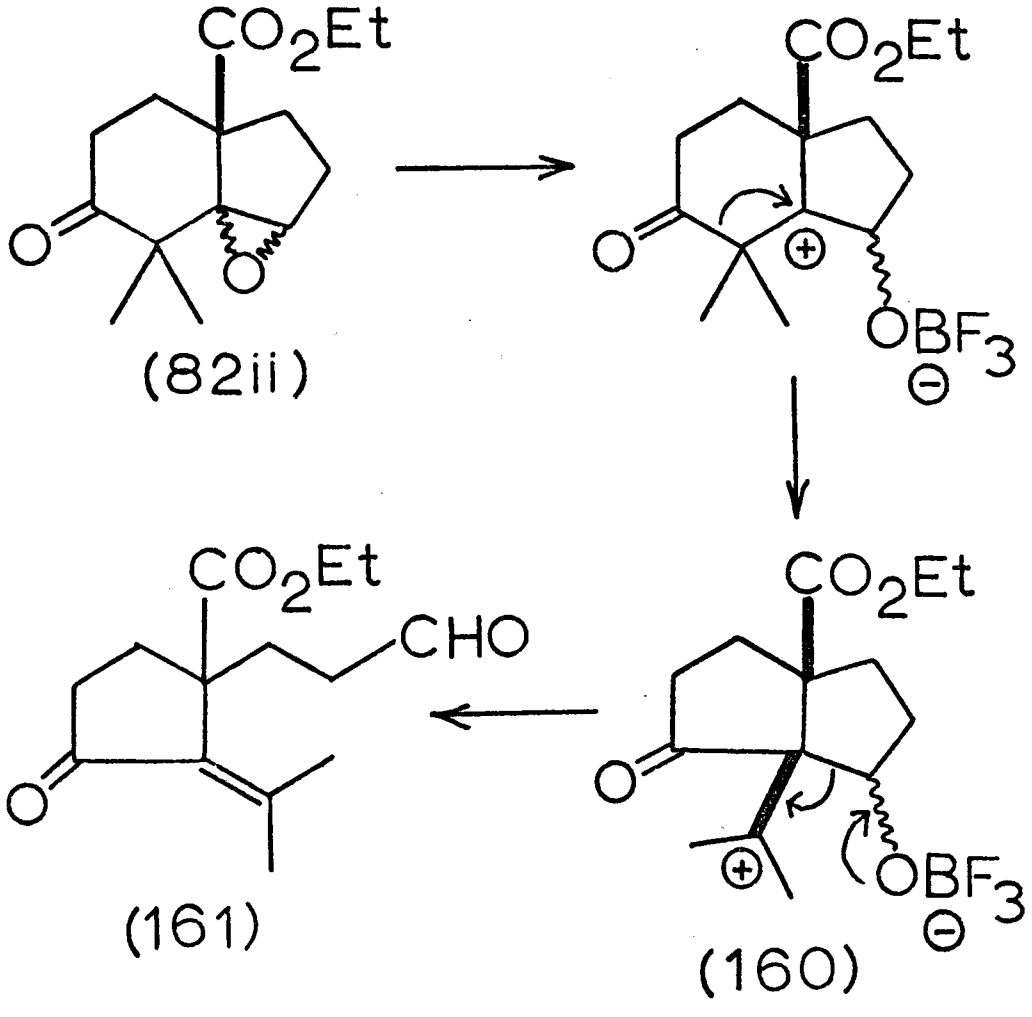
(159)

Rearrangement via acyl migration is expected for this epoxide, because migration of other suitably aligned groups attached to C-8 and C-4 is made unfavourable by the electron-withdrawing roups adjacent to both these positions.

ii) Ethyl $3\xi_2$, $9\xi_2$-Epoxy-4,4-dimethyl-5-oxohexahydroindane-8β-carboxylate (82ii)

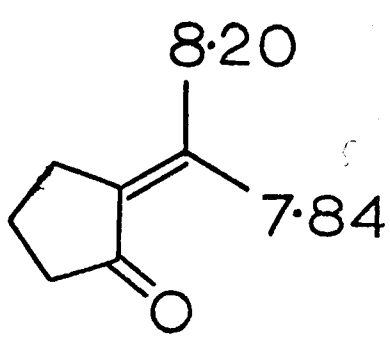
The epoxide was treated with boron trifluoride-ether complex at 20° for 10 minutes to give a single rearrangement product in 22% yield. This compound was separated from unchanged epoxide (36% recovery) by p.l.c., and was purified further by p.l.c. to give a homogeneous glass which had characteristic aldehyde signals in its i.r. spectrum ($\nu_{max.}$ 2730 and 1735 cm^{-1}) and n.m.r. spectrum (one-proton multiplet at τ 0.24). The i.r.

spectrum indicated no hydroxylic absorption, and a second carbonyl absorption at 1718 cm^{-1}, and the n.m.r. spectrum showed the presence of an ethyl ester group and two low-field methyl signals at τ 7.79 and 8.21. The compound had a u.v. absorption at $\lambda_{max.}$ 252 nm (ε 4,100). The prsence of an aldehyde group and the absence of a hydroxy-group suggested that the oxiran grouping might have been converted to an aldehyde group: this transformation is possible if a carbonium ion is generated at a site β to the carbon bearing the boron trifluoride-complexed oxiran oxygen, as the lone pair of electrons on this oxygen can become involved, to give a Grob fragmentation.[139] Such a situation will obtain if acyl migration of C4-C5 to C9 occurs to give the tertiary carbonium ion (160) which leads to the $\alpha\beta$-unsaturated ketone (161) by cleavage of the five-membered ring.

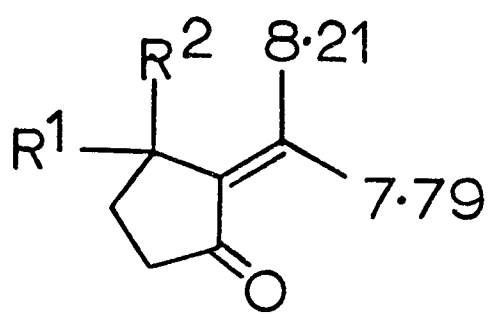


This structure (161) agrees with the spectral data: $\alpha\beta$ -unsaturated ketones in five-membered rings absorb between 1725 and 1708 cm^{-1} and the keto-group in this case could give rise to the signal at 1718 cm^{-1}, while

the ester and aldehyde groups could give overlapping signals at 1735 cm^{-1}; the chemical shifts of the two methyl groups are expected to be different as they are held in fixed positions relative to the carbonyl group, and the methyl groups in 2-isopropylidenecyclopentanone (162) occur at τ 7.84 and 8.20,[140] which compare favourably with the values obtained for this compound;



(162)

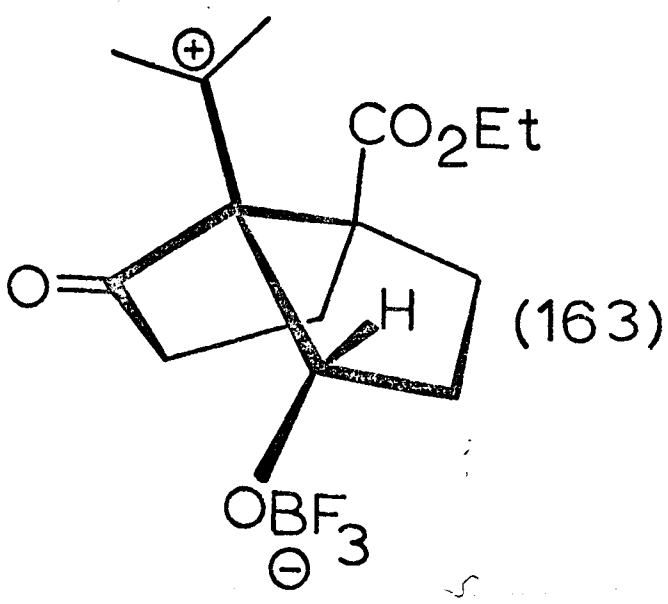


(161)

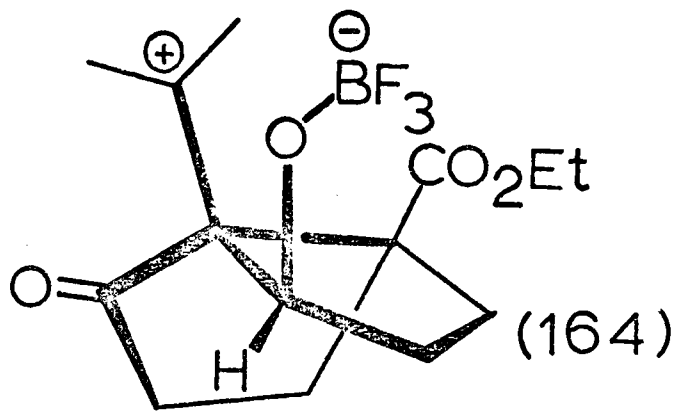
Methyl group chemical shifts (τ)

the calculated u.v. maximum for this compound is 254 nm which agrees with the observed value 252 nm.

It has been suggested that both epoxides (82i) and (82ii) rearrange **via** acyl migration, and consequently, the different products obtained in each case must depend on the structure of the carbonium ion formed by acyl migration. Grob[139] has shown that an anti-periplanar arrangement of groups is necessary for a synchronous fragmentation, and examination of the ions (163) and (164) which would be obtained from the α and β epoxides indicates that only in the ion (163) from the α-epoxide in such an arrangement nearly approached. This suggests that the epoxide (82ii) which cleaved to an aldehyde (161) may have been the α-isomer, and this corroborates the tentative assignment of epoxide stereochemistry made on the basis of steric approach arguments.



(163)

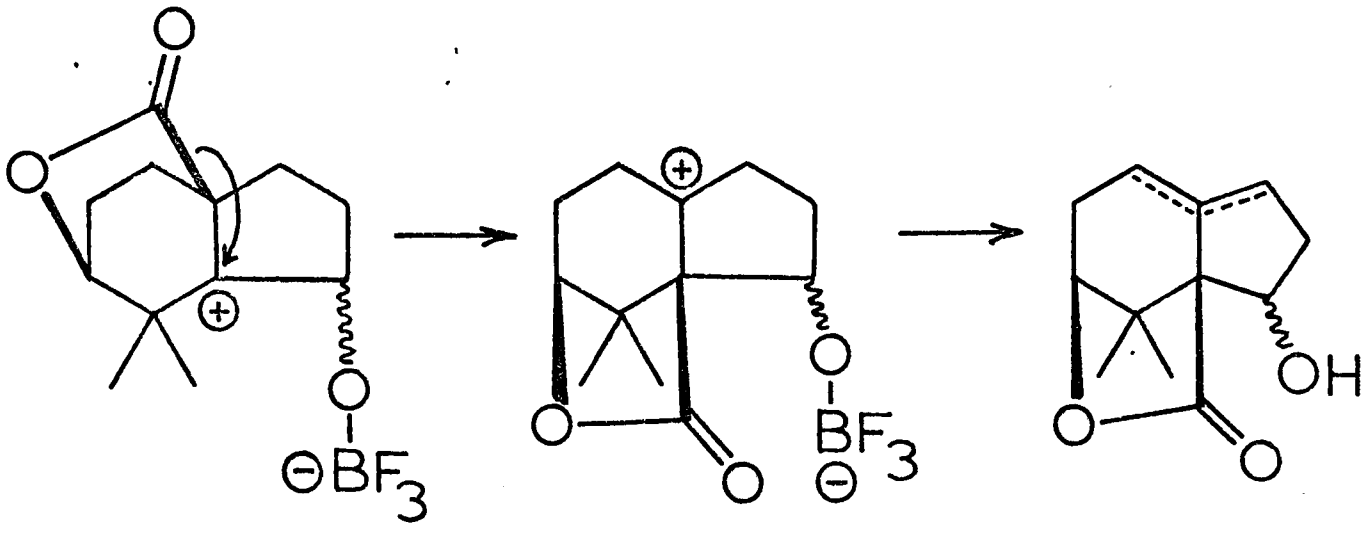


(164)

iii) $3\xi_1,9\xi_1$-Epoxy-4,4-dimethylhexahydro-8β,5β -carbolactone (87i)

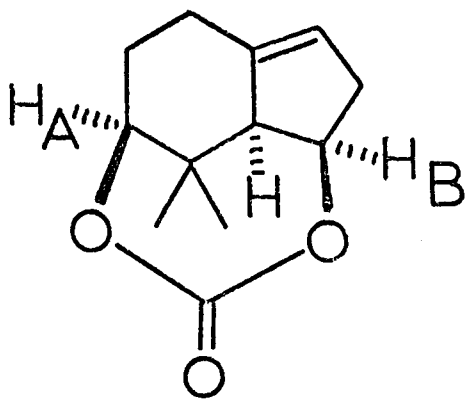
Treatment of this epoxide with boron trifluoride-ether complex at 25° for 10 minutes gave an oil containing three components, which were separated by p.l.c.

The least polar material as unchanged epoxide which was recovered in 38% yield. The middle band gave a crystalline solid in 22% yield, and the mass spectrum and elemental analysis confirmed that this compound was a direct rearrangement product with molecular formula $C_{12}H_{16}O_3$. The i.r. spectrum showed a single carbonyl peak at 1775 cm^{-1} (which is higher than the carbonyl absorption of the parent epoxide) and no hydroxylic absorption. The n.m.r. spectrum indicated a single olefinic proton at τ4.41, and two one-proton siganals at τ 5.36 and 5.97; there were also seven protons between τ 7.0 and 8.5, and two tertiary methyl groups. The increase in the carbonyl frequency suggests that the lactone bridge has become involved in the rearrangement: a shift of the bridge from C8 to C9 to give the ion (165) would give a γ - lactone, with a corresponding increase in carbonyl absorption frequency,



(165)

but dissipation of the positive charge requires formation of a hydroxy-olefin, which is not compatible with the i.r. data. A rearrangement which involved both the lactone bridge and the oxiran oxygen might lead ultimately to a cyclic carbonate: these absorb between 1780 and 1740 cm^{-1}, and their mass spectra show characteristic peaks due to loss of carbon dioxide from the molecular ion, at M-44.[141] The mass spectrum of this compound shows a peak at 208-44 = 164, and the direct fragmentation 208 ⟶ 164 is supported by a metastable peak at m/e 129.3. γ- And δ-lactones tend to show characteristic peaks at M-28, due to loss of carbon monoxide,[142] and while the mass spectra of parent epoxide (87i) and the second rearrangement product (169) (see below) both show peaks at 208-28 = 180, the mass spectrum of this compound has no peak at m/e 180, suggesting that it contains a carbonate -O-CO-O- bridge rather than a lactone -O-CO- bridge. A speculative structure containing a cyclic carbonate group which is compatible with the spectral data is (166): proton H_A is adjacent to the carbonate bridge and is contained



(166)

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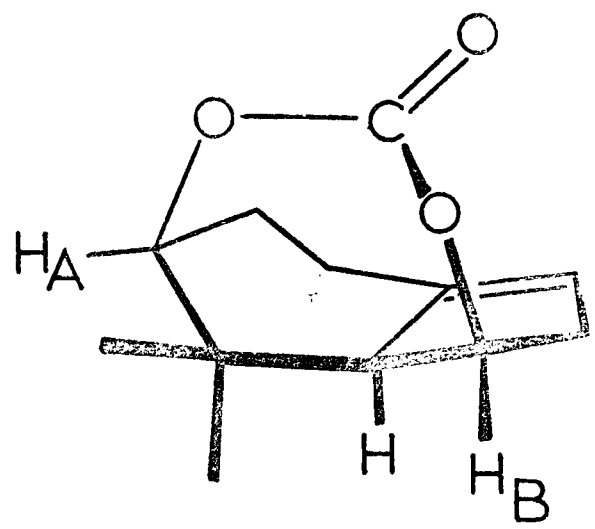
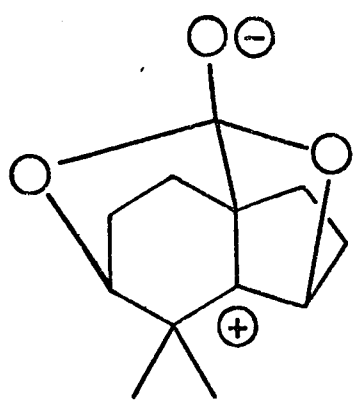
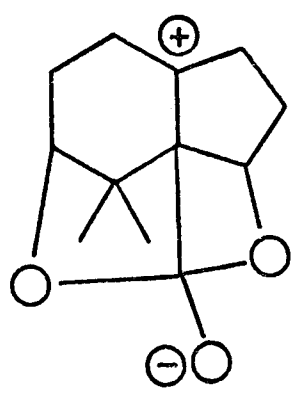


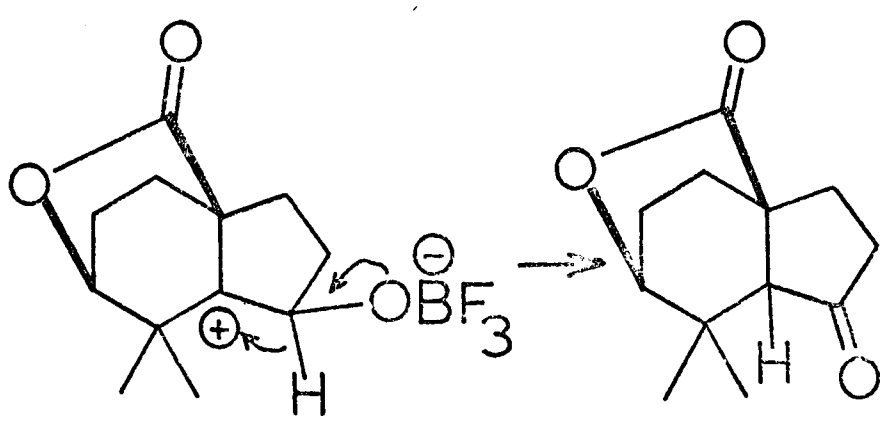
in a six-membered ring, and could give rise to the signal at τ 5.97; the proton H_B is also adjacent to the carbonate bridge, but is contained in a five-membered ring opposite an olefinic double bond and should be deshielded relative to H_A, and could give the signal at τ 5.36. The formation of such a compound implies that the parent epoxide had the 3β,9β-configuration, enabling the oxiran oxygen to approach close enough to the lactone bridge for bond formation to occur. The detailed mechanism of formation of such a compound is hard to envisage unless highly energetic intermediate species such as (167) and (168) are invoked:



(167)



(168)



(169)

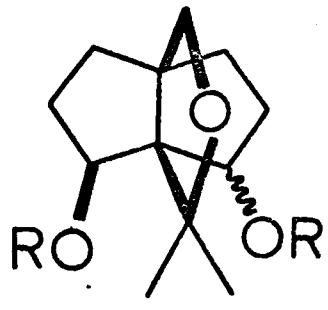
consequently, structure (166), although fitting the data, must be regarded as highly tentative.

The third compound isolated from the rearrangement mixture was a crystalline solid obtained in 12% yield, and contained no hydroxy-group and two carbonyl groups ($\nu_{max.}$ 1769 and 1756 cm^{-1}). The n.m.r. spectrum showed one proton at τ 5.97 and no other signals below τ 7. There were nine protons between τ7.0 and 8.5, including a sharp one-proton singlet at τ7.61 which might be due to an isolated tertiary proton adjacent to a carbonyl group. The formation of a second carbonyl group in the molecule suggests that the epoxide has rearranged by a simple 1,2 hydride shift, to give the keto-lactone (169).

iv) $3\xi_1,9\xi_1$-Epoxy-8β-hydroxymethyl-4,4-dimethylhexahydroindan-5β-ol (84i).

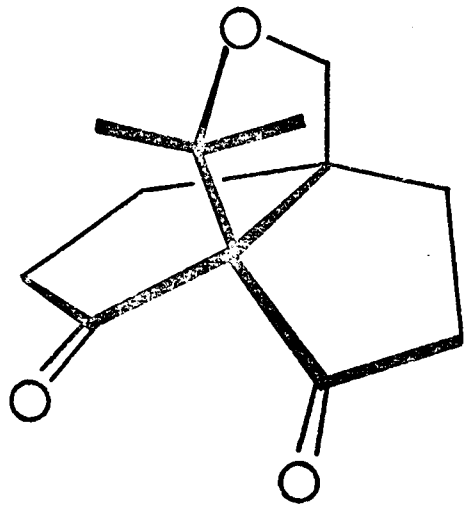
Rearrangement of this epoxide gave one major product, and several minor products which could not be isolated in sufficient yield to permit characterisation. The major product (170) was obtained in 19% yield as a glass, and its i.r. spectrum showed no carbonyl absorption, but strong hydroxylic absorption (ν_{O-H} 3670 and 3520 cm^{-1}). The n.m.r. spectrum showed a broad two-proton multiplet at τ 5.91, thought to be due to two overlapping -C<u>H</u>(OH)- signals; a sharp two-proton singlet at τ 6.20, possibly due to an isolated symmetrical -C<u>H</u>$_2$-O- group; a sharp six-proton singlet at τ 8.42 due to two equivalent methyl groups attached to an oxygen-bearing carbon atom; and two exchangeable hydroxy-protons. The presence of two hydroxy-groups was confirmed by treating the compound with an excess of acetic anhydride in pyridine to give a crystalline diacetate (171). Oxidation of the diol gave a crystalline dione (172) which had a single carbonyl absorption at 1762 cm^{-1}, indicating that both hydroxy-groups in the diol were present in five-membered rings. The molecular weight of the diol, the diacetate, and the dione, and the

elemental analysis of the latter two showed that the diol contained three oxygen atoms, and the lack of a carbonyl function suggested that an ether had been formed during the rearrangement. A structure which agrees with the data is the tricyclic system (170), and this rearrangement constitutes a novel synthesis of a heterocyclic "propellane".[143]



(170) R = H
(171) R = Ac

The dione (172) is symmetrical about the heterocyclic ring, and the methylene protons in the two carbocyclic rings are equivalent and should therefore give rise to a single ABCD multiplet.

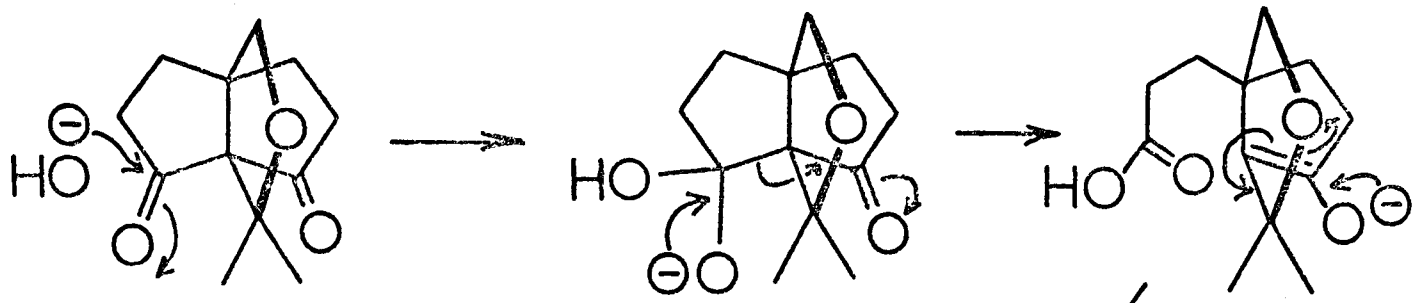


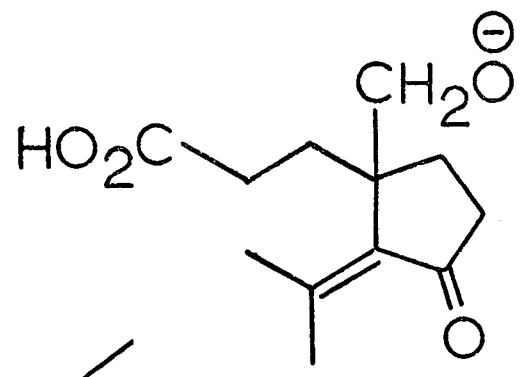
(172)

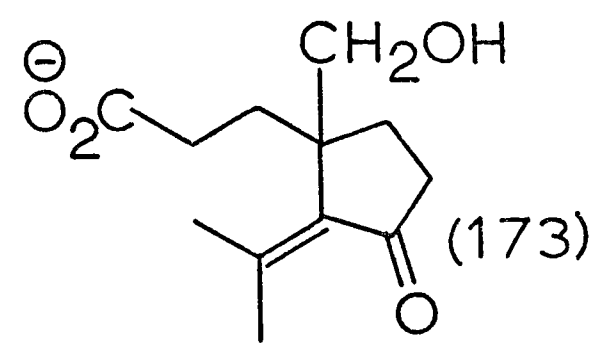
The signals of the gem-dimethyl group and the isolated $-CH_2-O-$ group in the diol (170) and the diacetate (171) were extremely sharp, and no splitting was observed when the recording solvent was changed from carbon tetrachloride to benzene: this sharpness suggests that the two methyl groups and the two methylene protons are each isochronous, and are thus experiencing the same shielding effects from neighbouring groups. This

will only be true if both hydroxy-groups in (170) and both acetoxy-groups in (171) have the same stereochemistry relative to the hetero-ring. As one hydroxy-group in (170) is derived from the 5β-hydroxy-group of the starting epoxide (84i), it must be cis to the hetero-ring, and this implies that the other hydroxy-group must be cis as well, and further that the epoxide (84i) was the 3β,9β-epoxide. Confirmation of this tentative assignment might be provided by recording the n.m.r. spectum of the diol (170) in the presence of a lanthanide shift reagent: unfortunately, a lack of material precluded this experiment from the present work.

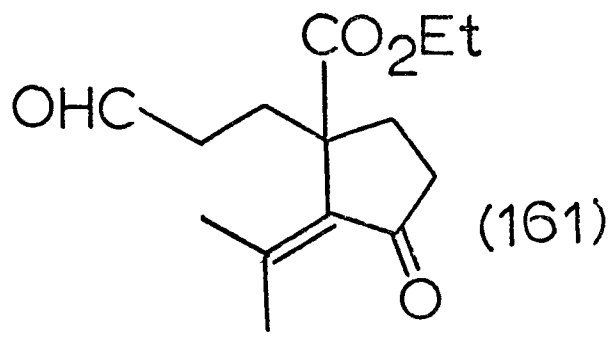
The dione (172) is a fully substituted β-diketone, and would be expected to cleave in basic conditions by a reverse Claisen reaction: the u.v. spectrum of a solution of the dione in ethanol was recorded, and it showed no intense absorption, but on addition of ethanolic potassium hydroxide solution, an intense absorption at 250 nm gradually built up, accompanied by a weaker absorption at 305 nm. Cleavage of the hetero-ring would lead to the αβ-unsaturated ketone (173) which contains the same chromophore as the aldehyde-ester (161) obtained from epoxide (82ii), and the similarity of their u.v. maxima tends to confirm structure (172).







(173)

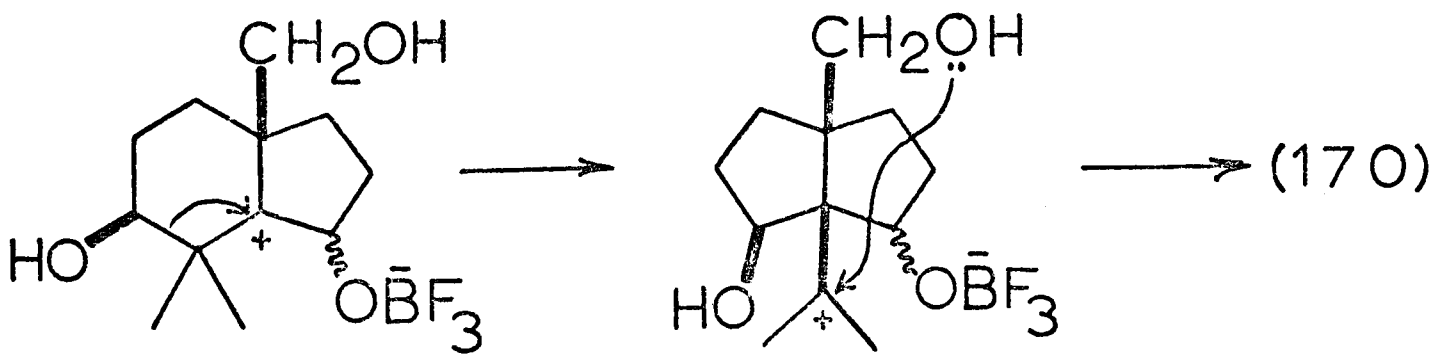


(161)

λ_{max} 252 nm

λ_{max} 250 nm

A simple mechanism for the rearrangement of epoxide (84i) can be envisaged, whereby bond C5-C4 migrates to C9, and the developing positive centre at C4 is attacked by the 8β-hydroxymethyl group to close the hetero-ring (174).

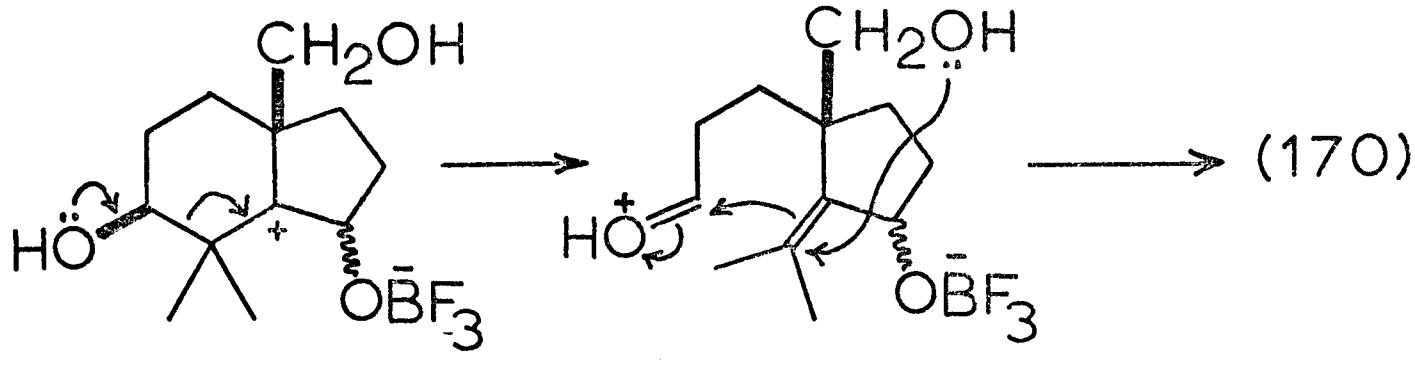


(174)

(170)

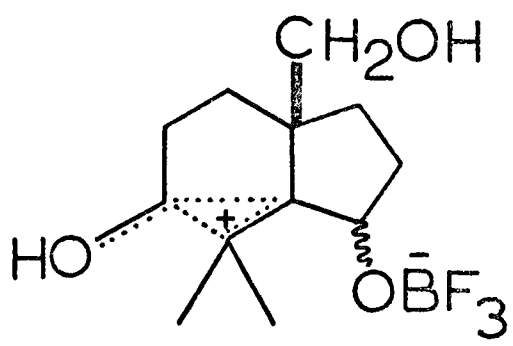
However, this mechanism involves migration of a bond adjacent to a

hydroxy-group, a process which has not been encountered in epoxide rearrangements previously, and some involvement of the hydroxy-oxygen lone pair of electrons might be expected *viz.* cleavage to the protonated aldehyde (175). This might possibly recyclise by a Prins reaction to give the bicyclo [3.3.0] octane skeleton, and this step could precede or be synchronous with closure of the hetero-ring.



(175)

The actual mechanism could lie between these two and could proceed through a species (176) in which the positive charge is delocalised between C9, C4, C5, and the oxygen atom attached to C5.



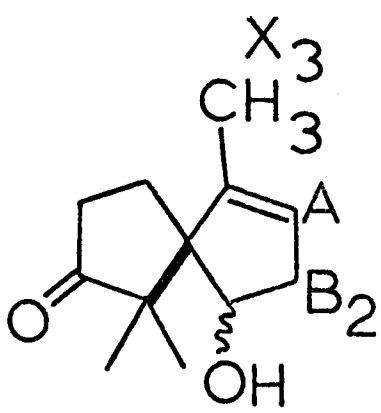
(176)

As bond C4-C5 cleaves and bond C5-C9 forms, C4 is forced up towards the 8β-hydroxymethyl group, and formation of the hetero-ring is probably synchronous with this.

v) 3,9-Epoxy-4,4,8-trimethylhexahydroindan-5-one (85).

Rearrangement of this epoxide mixture gave one major crystalline product (obtained in 22% yield) and several minor products, none of which was isolated in sufficient yield to permit characterisation. The i.r. spectrum of the major product indicated a hydroxy-group, and a keto-group in a five-membered ring ($\nu_{max.}$ 3540 and 1730 cm^{-1}). The n.m.r. spectrum showed an olefinic proton and a vinylic methyl group (τ4.50 and 8.33), a signal at τ 5.71 due to a proton on an oxygen-bearing carbon atom, and two singlet methyl signals. A probable skeletal rearrangement leading to a vinylic methyl group would require migration of C7-C8 to C9 to give the spiro-structure (177), which contains a five-membered ring ketone. The vinylic methyl signal in the n.m.r. spectrum appeared as a multiplet containing at least four lines: the nature of the coupling was elucidated by observing the vinylic methyl signal while irradiating the olefinic proton signal; the former collapsed to a simple triplet with coupling constant 2.2 Hz, due to coupling with a methylene group. The coupling constant between the vinylic methyl group and the olefinic proton could then be measured from the spectrum as 1.6 Hz. These coupling constants are consistent with the moiety CH_3-C=CH-CH_2-, and are comparable with values for allylic and homoallylic coupling constants obtained from analogous systems e.g. (178) and (179).[144]

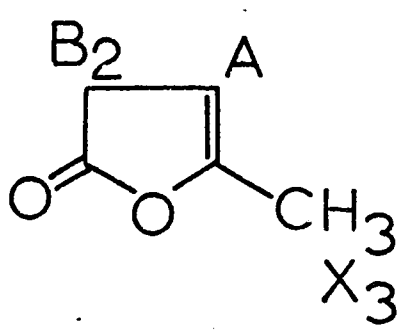
Allylic and homo-allylic coupling constants (Hz)



(177)

J_{AX} 1.6

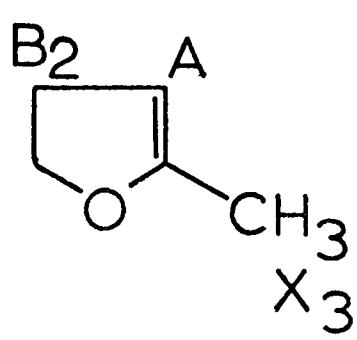
J_{BX} 2.2



(178)

J_{AX} 1.7

J_{BX} 2.1

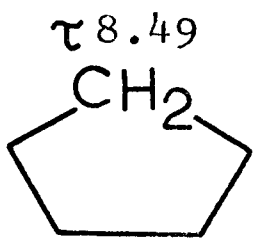


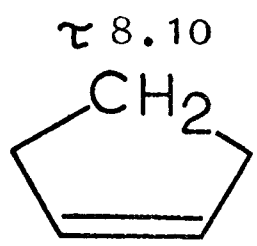
(179)

J_{AX} 1.1

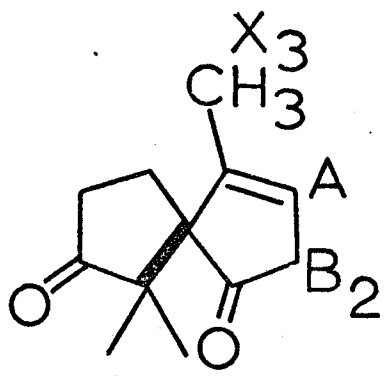
J_{BX} 2.0

The low chemical shift (τ 5.71) of the -C<u>H</u>(OH)- proton can be rationalised in terms of the spiro-structure (177), as the proton in question lies in a deshielded region of space relative to the carbon-carbon double bond; in cyclopentene, the corresponding methylene protons are deshielded by τ 0.39 relative to cyclopentane.[145]





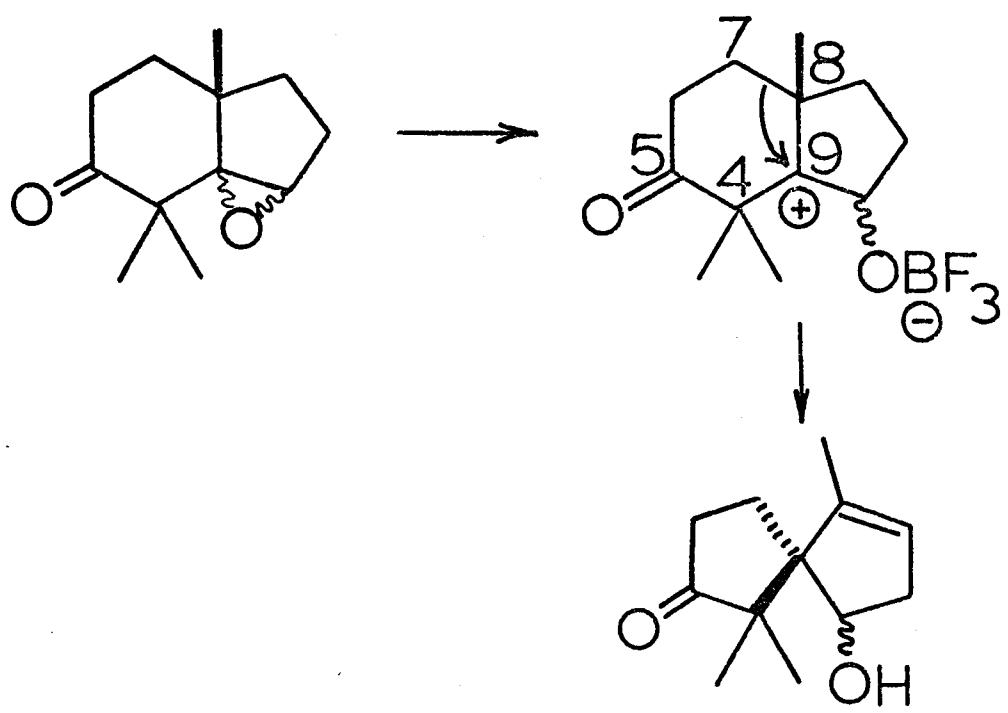
Oxidation of the spiro-ketol (177) with chromic acid gave the expected dione (180) which had a broad carbonyl absorption at 1735 cm^{-1} due to two five-membered ring ketones.



(180)

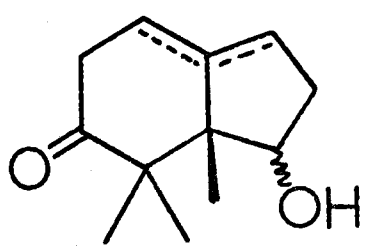
The n.m.r. spectrum of the dione (180) was similar to that of the ketol (177), with the vinylic methyl group appearing as a multiplet containing at least six lines. The methylene group between the carbonyl group and the olefinic double bond appeared as a discrete multiplet containing at least five lines at τ 7.28. On irradiating the olefinic signal, the vinylic methyl group collapsed to a triplet as before, and gave values for the coupling constants of $\underline{J}_{AX}$ = 1.65 Hz and $\underline{J}_{BX}$ = 2.4 Hz.

The sharpness of the n.m.r. signals of the spiro-ketol indicated that it was pure, and thus obtained from only one of the epoxides present in the starting material. Migration of the C7-C8 bond to C9 is



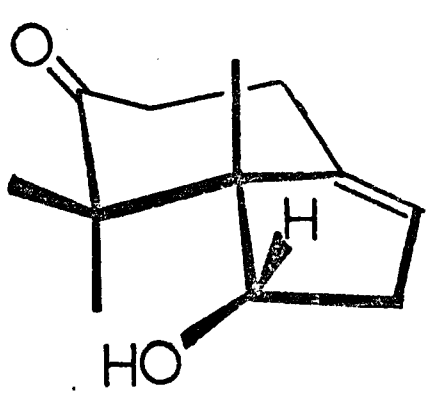
(170)

probably favoured over migration of the 8β-methylgroup as it reduces the 1,3-diaxial interaction between the 8β-and 4β-methyl groups, and leads to an unhindered structure, whereas migration of the 8β-methyl group would give (181) or (182), both of which entail placing the 3-hydroxyl group very close to one of the 4-methyl groups.

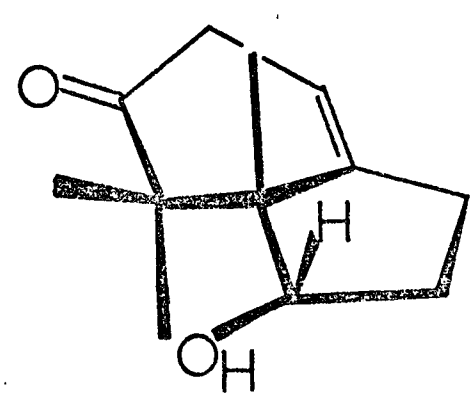


(181) $\Delta^{1(8)}$

(182) $\Delta^{7,8}$

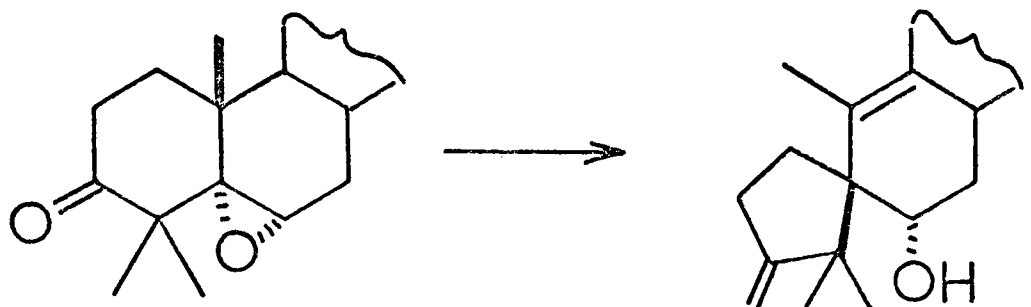


α (181)



α (182)

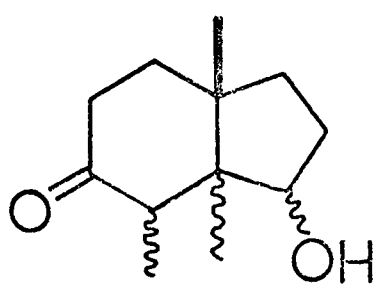
The rearrangement of the epoxide (85) to give the spiro-ketol (177) is similar to rearrangement observed by Halsall *et al.*[82] with analogous 5α,6α-epoxy-4,4-dimethyl-3-keto steroids (66).



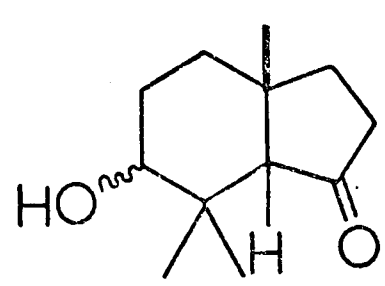
(66)

vi) 3ξ,9ξ-Epoxy-4,4,8β-trimethylhexahydroindan-5ξ$_1$-ol (86i).

Treatment of this epoxide with boron trifluoride-ether complex gave an immediate intense red colouration, and the reaction was stopped after one minute and worked up to give a yellow oil. The t.l.c. of this oil was very streaky, and the i.r. spectrum did not indicate a carboxylic acid, which suggested that polymerisation had occurred. The oil was subjected to p.l.c. to give a glass which was a mixture of two components, and these were incompletely separated by further p.l.c. The less polar compound was a hydroxy-ketone, with the keto-group in a six-membered ring ($\nu_{C=O}$ 1715 cm^{-1}), while the more polar compound was also a hydroxy-ketone, but with the keto-group in a five-membered ring ($\nu_{C=O}$ 1740 cm^{-1}). The n.m.r. spectra of the two compounds suggested that they were the ketols (183) and (184) respectively.

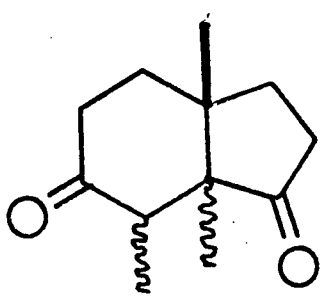


(183)

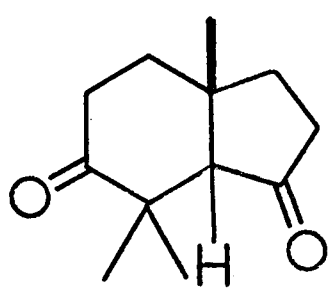


5ξ$_1$(184)

The first compound had two singlet methyl signals and a doublet due to a secondary methyl group, while the second had three singlet methyl signals. The oxidation products of both compounds agreed with these tentative structures; the first (185) showed a new carbonyl absorption at 1750 cm^{-1} (five-membered ring ketone) and the second (186) had a new peak at 1725 cm^{-1} (six-membered ring ketone).

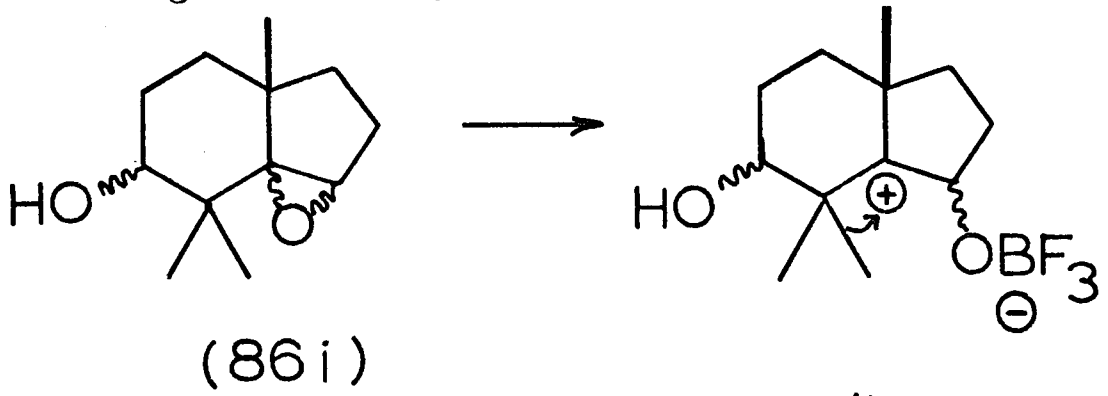


(185)

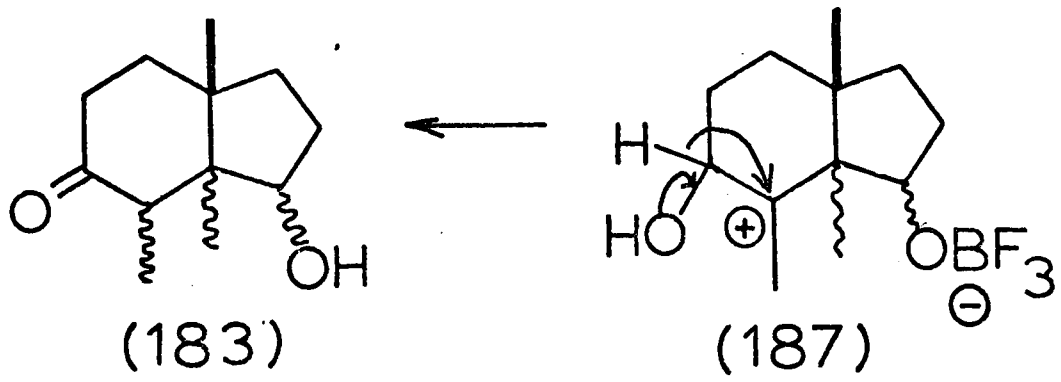


(186)

The ketol (183) is formed by migration of a 4-methyl group to the positive site at C9 to give the carbonium ion (187), which undergoes hydride migration to C4.



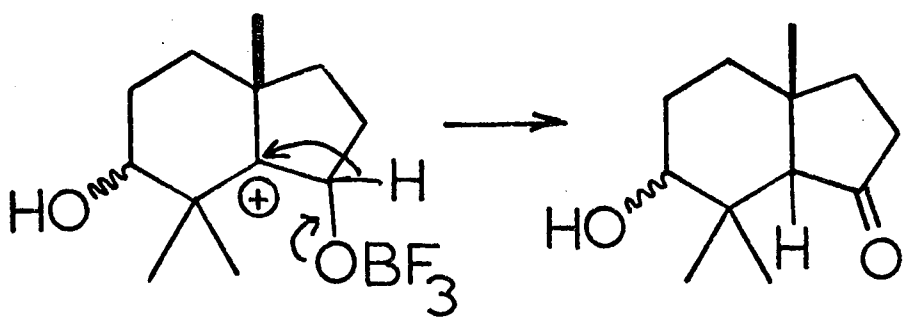
(86i)



(183)

(187)

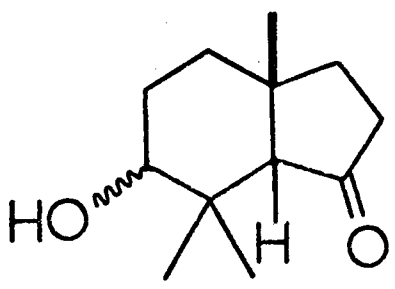
The second ketol (184) is formed by a simple 1,2-hydride shift, which in the absence of more favourable competing reactions, is potentially the usual course for epoxide rearrangements to take.



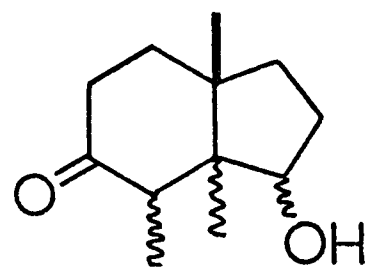
(184)

vii) 3ξ,9ξ-Epoxy-4,4,8β-trimethylhexahydroindan-5ξ_2-ol (86ii).

The addition of boron trifluoride-ether complex to this epoxide caused the solution to go deep red immediately, and working up the reaction mixture after one minute gave a yellow glass whose t.l.c. showed no discrete spots. The n.m.r. spectrum showed no sharp signals below τ7 and only merged methylene and methyl envelopes above τ7. The i.r. spectrum was more informative, indicating the presence of a hydroxy-group and keto-groups in five- and six-membered rings ($\nu_{C=O}$ 1750, 1725 cm^{-1}). On the basis of this scanty evidence, possible rearrangement products (188) and (189) can be postulated, which arise by mechanisms similar to those for the 5ξ_1-alcohol (86i).



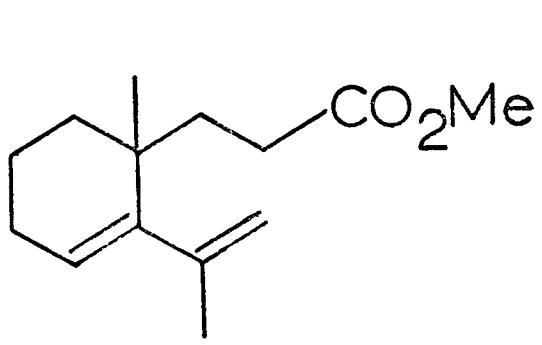
5ξ_2(188)



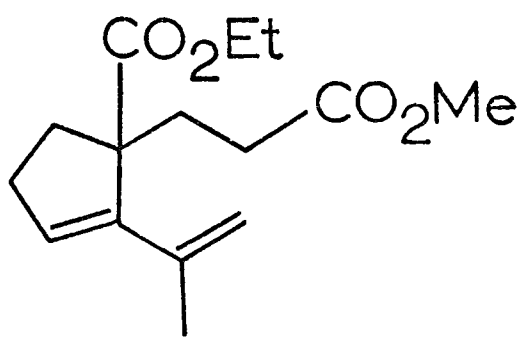
(189)

viii) 8α,9α-Epoxy-1,1,10-trimethyldecal-2-one (88i).

Treatment of this epoxide with boron trifluoride-ether complex gave an oil which was a mixture of a carboxylic acid ($\nu_{max.}$ 2500-1800 cm^{-1}) and at least two other components. The oil was treated with diazomethane and the components were separated by p.l.c. The least polar component was an oil with molecular weight 222, which is 14 units higher than the parent epoxide. The i.r. spectrum showed a strong ester absorption at 1740 cm^{-1}, and the n.m.r. spectrum showed a sharp methoxy-singlet at τ6.37, confirming that this compound was a methyl ester of a carboxylic acid formed during the rearrangement of the epoxide. The n.m.r. spectrum also showed three olefinic signals (τ4.51, 5.20, and 5.29), a vinylic methyl group at τ8.09, and a single tertiary methyl group. The compound had a characteristic u.v. absorption at $\lambda_{max.}$ 234 nm (ε 4,600) which suggested that the molecule contained a conjugated diene chromophore. The high chemical shifts of two of the olefinic signals indicated a terminal methylene group, and the spectral data are consistent with structure (190) which is analogous to the major product (151) from the keto ester epoxide (82i).



(190)



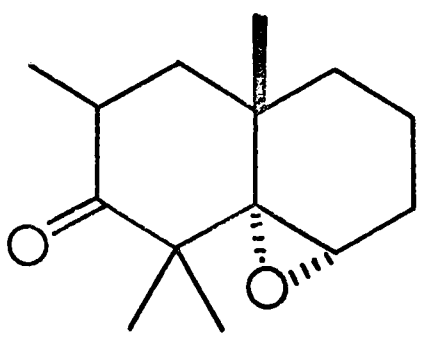
(151)

The mode of formation is probably similar, proceeding via the acylium ion (191).

The calculated u.v. absorption for structure (190) is 232 nm, which agrees with the observed value. The mass spectrum shows an intense peak at m/e 135 (70%) due to loss of the $CH_3O.COCH_2CH_2$-fragment.

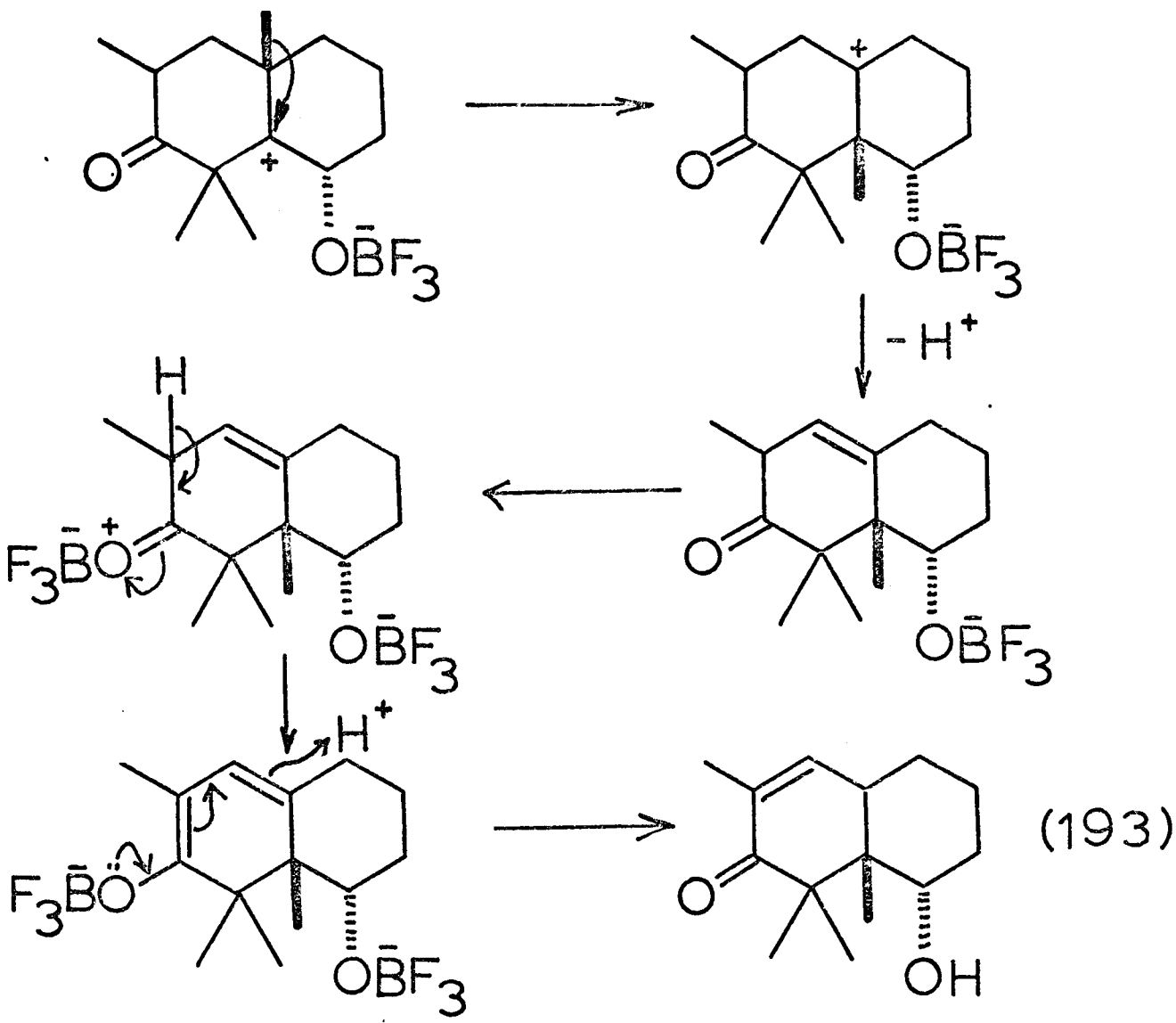
The second component extracted from the rearrangement product mixture was not pure and had three carbonyl peaks in its i.r. spectrum ($\nu_{C=O}$ 1720, 1696, and 1680 cm^{-1}) and a complex methyl region in its n.m.r. spectrum, containing at least eight peaks. The mixture was unstable and underwent autoxidation on standing to give a dark oil containing largely polar components. Two non-polar components were isolated by p.l.c., but in insufficient yield to permit characterisation. Both components showed molecular ion peaks at m/e 222 which is 14 units higher than the parent epoxide (88i), yet neither showed characteristic methoxy-or methyl ketone signals in their n.m.r. spectra, as would be expected for the methylated products of carboxylic acids, enols, and aldehydes. This factor, and the presence of approximately 12 protons in the methyl regions of both components suggests that these compounds

may have arisen from a small amount of the tetra-methylated epoxide (192) which was present in the starting material.



(192)

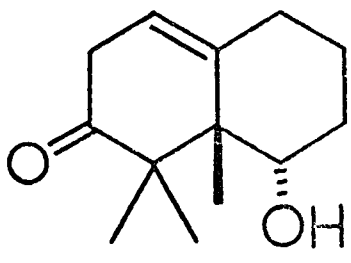
The less polar of the two components was a mixture and contained a hydroxy-group and possibly a small amount of an $\alpha\beta$-unsaturated ketone ($\nu_{max.}$ 3420 and 1689 cm^{-1}); the u.v. absorption was not very intense; $\lambda_{max.}$ 223 n.m. (ε 1,980). The more polar of the two components had a similar i.r. spectrum ($\nu_{max.}$ 3420 and 1675 cm^{-1}) and a very intense u.v. absorption at $\lambda_{max.}$ 238 nm (ε 10,940); unlike the less polar component, this species contained an olefinic proton (τ 4.45). There do not appear to be any direct rearrangement products containing an $\alpha\beta$-unsaturated carbonyl group, but such a group could be formed if the 10β-methyl group migrated to C-9 and the species thus formed deprotonated to give a 4,10-double bond: this $\beta\gamma$-unsaturated ketone might give the $\alpha\beta$-unsaturated isomer by boron trifluoride-catalysed enolisation (the enolate being stabilised by the α-methyl group).



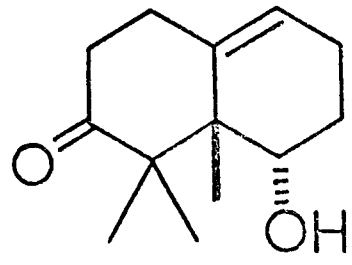
(193)

The calculated u.v. absorption maximum for this structure is 237 nm, which compares very favourably with the observed value of 238 nm, but this may be fortuitous.

The third component extracted from the methylated rearrangement mixture was an oil obtained in 5% yield. The i.r. spectrum showed a keto-group in a six-membered ring and a hydroxy-group ($\nu_{max.}$ 3640, 3550, and 1725 cm^{-1}), and the n.m.r. spectrum showed a single olefinic proton, one proton adjacent to a hydroxy-group, and three tertiary methyl groups. A rearrangement which maintains the keto-group in a six-membered ring and does not result in a vinylic methyl group, must proceed by migration of the 10β-methyl group to C9, to give either of the ketols (194) or (195).

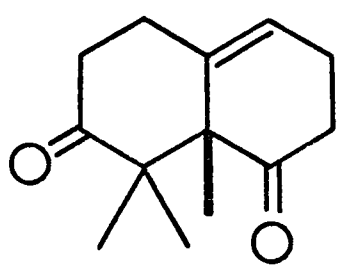


(194)



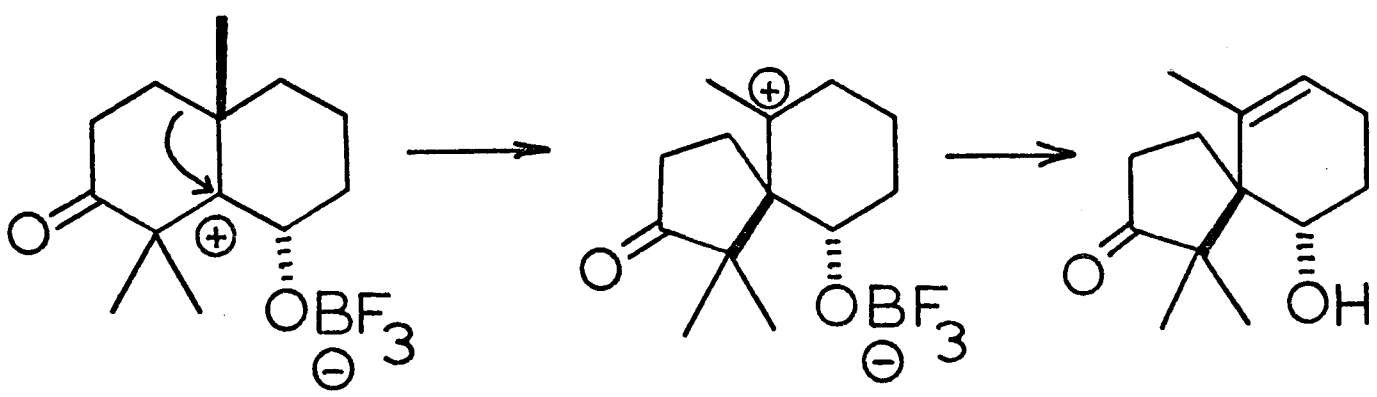
(195)

The $\Delta^{4(10)}$ isomer (194) would be expected to give a low-field methylene signal due to the group between the carbonyl and olefinic double bonds, and no such signal was observed, which suggests that this ketol is the $\Delta 5(10)$ isomer (195). Oxidation of the ketol gave a dione (196) with a broad carbonyl absorption at 1714 cm^{-1}, and the n.m.r. spectrum showed a narrow 8-proton methylene signal at τ7.60.



(196)

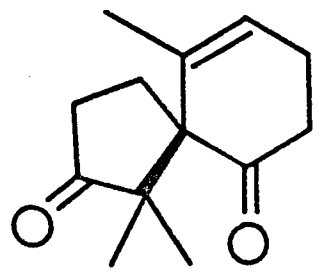
The fourth and major rearrangement product was obtained as a crystalline solid in 25% yield. The compound contained a hydroxy-group, and a keto-group in a five-membered ring ($\nu_{max.}$ 3590, 3480, and 1740 cm^{-1}), and the n.m.r. spectrum indicated a single olefinic proton (τ4.52), a proton on a hydroxy-bearing carbon atom (τ6.16), one vinylic methyl group (τ8.53), and two tertiary methyl groups. A structure which is compatible with these data is formed by migration of the C4-C10 bond to C9 to give the spiro-ketol (197).



(197)

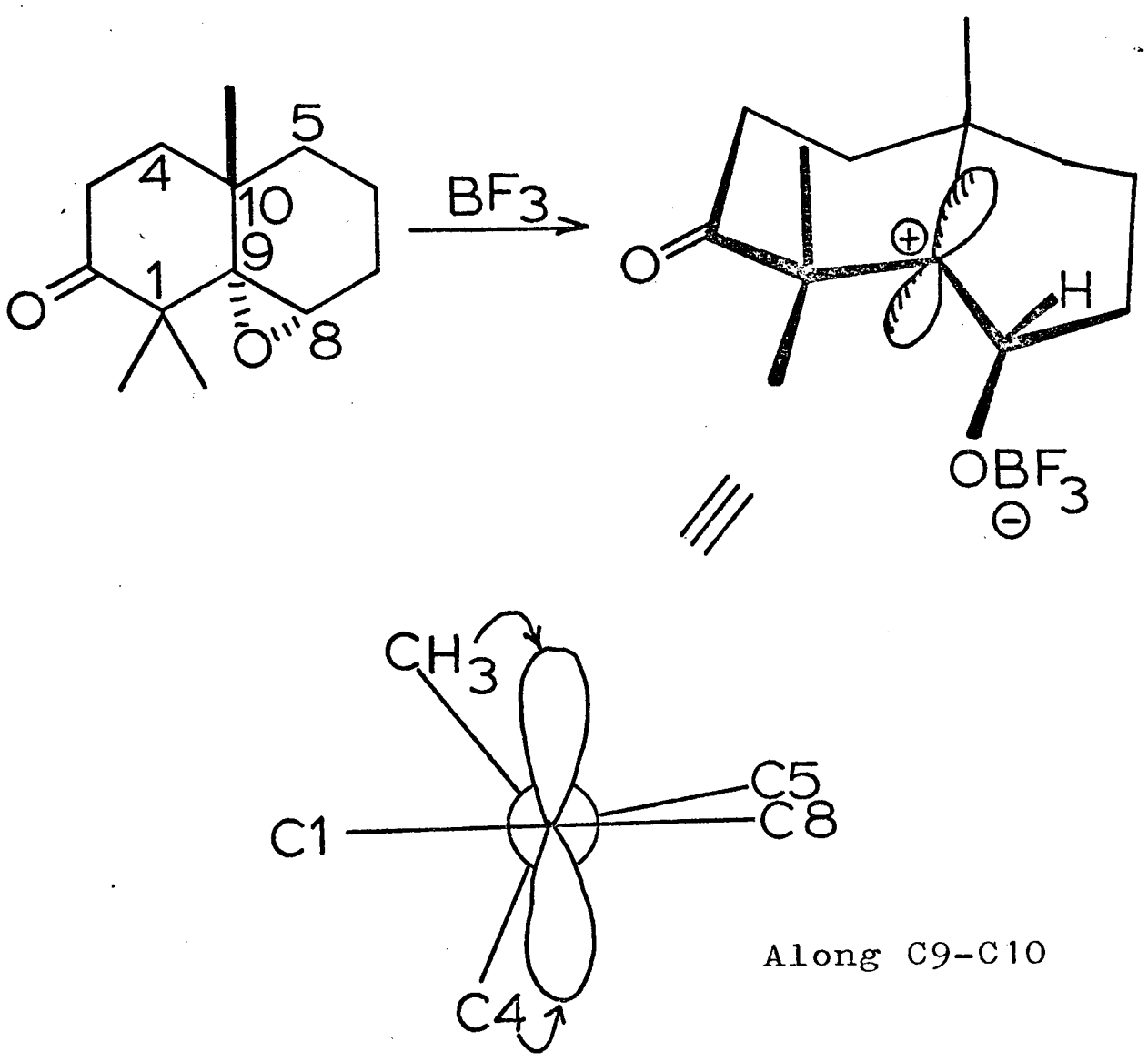
Oxidation of spiro-ketol (197) gave the spiro-dione (198) which had a narrow 4-proton methylene signal in its n.m.r. spectrum, similar to that of the dione (196), superimposed on widely spaced

(τ 5-8.0) signals which integrated for four protons.



(198)

Cleavage of the C9-O bond to give a planar carbonium ion at C9 places both the 10β-methyl group and the C4-C10 bond in suitable positions to migrate to C9;

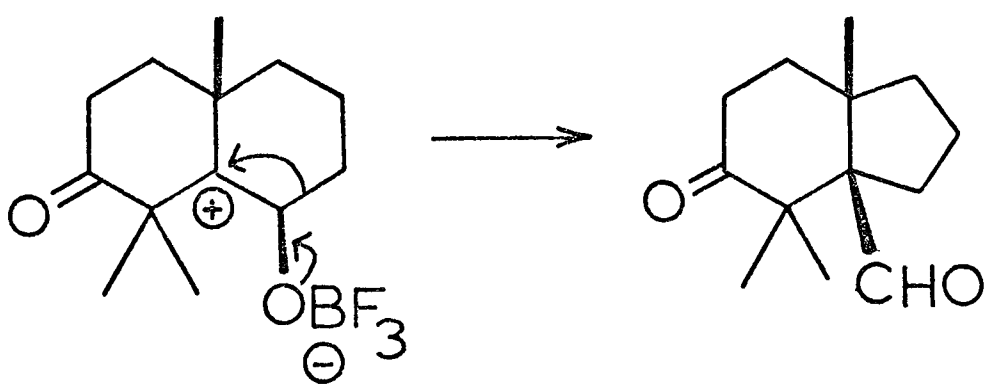


the methyl migration produces a product in which the 8α-hydroxy-group is moved quite close to the 1α-methyl group, and this steric interaction may disfavour this migration compared with that of the C4-C10 bond which produces an unhindered structure.

Of the groups attached to C1, the 1β-methyl group is ideally placed to migrate to C9, but such a migration would involve developing a positive charge adjacent to a carbonyl group, and is thus not feasible; acyl migration, although less favoured sterically, can proceed with assistance from the lone pair of electrons on the carbonyl oxygen atom.

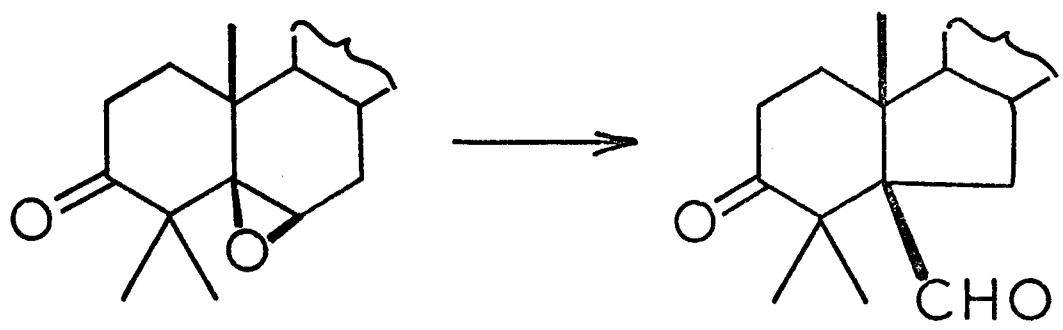
ix) 8β,9β-Epoxy-1,1,10β-trimethyldecal-2-one (88ii).

Rearrangement of this epoxide with boron trifluoride-ether complex gave a mixture containing four major components, one of which was an aldehyde, and these were partially separated by column chromatography. The first compound eluted was obtained as an oil in 14% yield, and contained a keto-group in a six-membered ring ($\nu_{C=O}$ 1725 cm^{-1}) and a tertiary aldehyde group ($\nu_{max.}$ 2740 and 1725 cm^{-1}, τ 0.15, singlet). The compound contained three tertiary methyl groups and gave a crystalline mono-semicarbazone whose m.s. showed a peak at m/e 86 due to the characteristic aldehyde semicarbazone fragment $\left[CH = NNH \cdot CONH_2\right]^+$. On the basis of these data, the compound can be assigned as the keto-aldehyde (199), which is formed by migration of C7-C8 to C9.



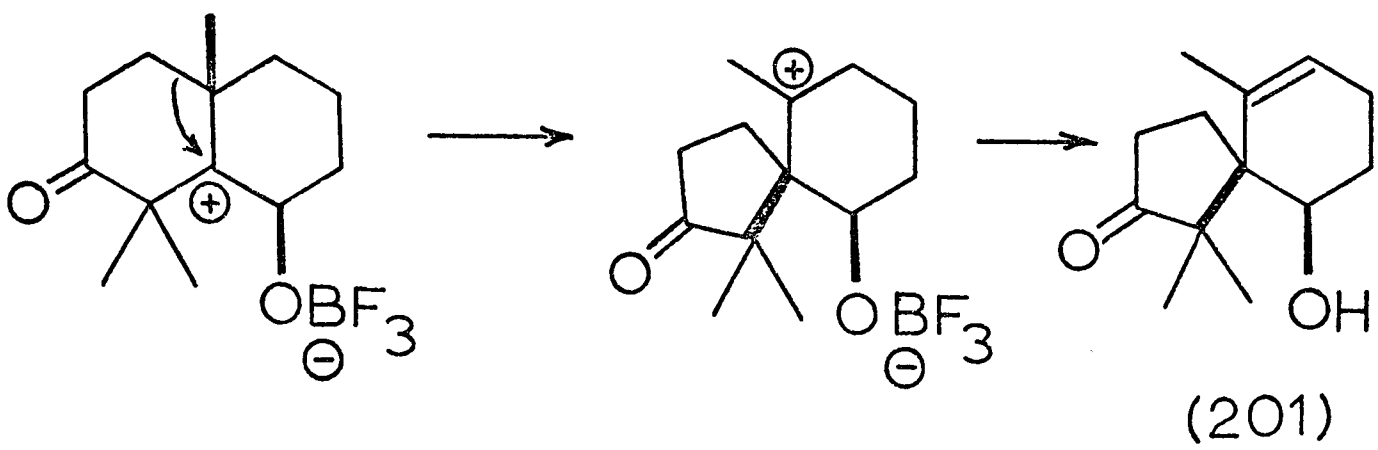
(199)

This compound is similar to the aldehyde (200) obtained from the analogous steroidal epoxide (68) in 14% yield.[82]



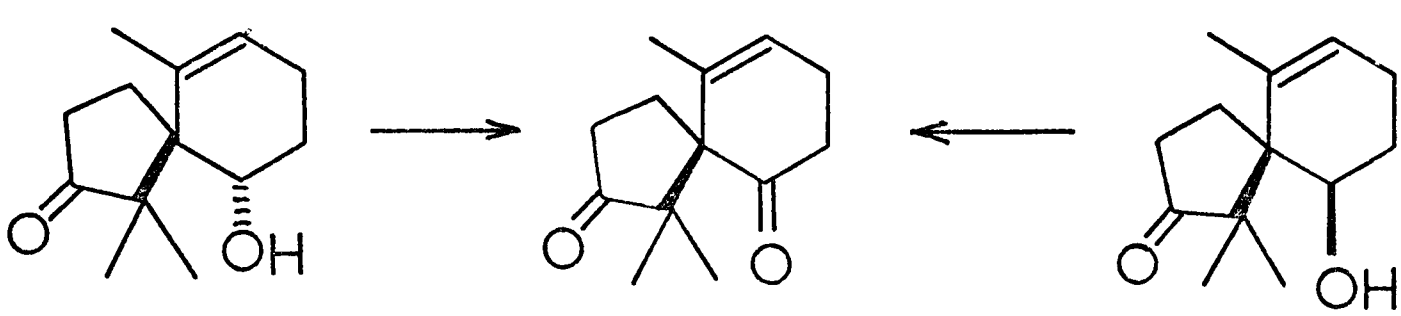
(68) (200)

Further elution of the rearrangement products gave an unidentified mixture of compounds (8% yield), and then a mixture obtained in 28% yield, containing equal amounts of two compounds which were both hydroxy-keto-olefins: one contained a six-membered ring ketone and the other a five-membered ring ketone ($\nu_{max.}$ 1716 and 1742 cm^{-1}), and the n.m.r. spectrum of the mixture showed two protons on hydroxy-bearing carbon atoms (two-proton multiplet at τ6.05) and one vinylic methyl group (τ8.49). It was not possible to separate these two compounds by multiple elution p.l.c., but reduction of the mixture with lithium aluminium hydride gave two compounds with different Rf values, and separation became possible. Although an excess of lithium aluminium hydride was used, the less polar of the two "reduction" products was a crystalline hydroxy-ketone. This contained a hydroxy-group and a five-membered ring ketone ($\nu_{max.}$ 3600, 3450, and 1745 cm^{-1}) and the n.m.r. spectrum indicated a vinylic methyl group and an olefinic proton (τ8.50 and 4.58). The formation of a five-membered ring ketone suggests that migration of C4-C10 to C9 has occurred, to give the spiro-structure (201), which is the epimer of the



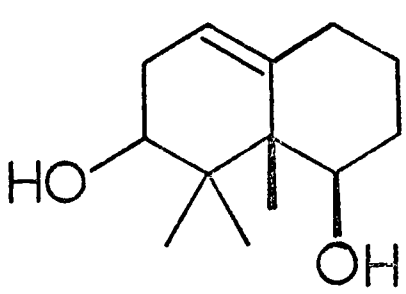
(201)

spiro-compound (197) obtained from the corresponding α-epoxide (88i): on oxidation, the same dione (198) was obtained.

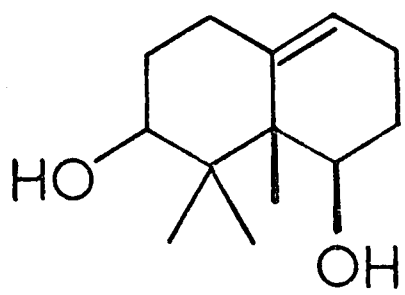


(197) (198) (201)

The more polar of the two reduction products was a crystalline diol ($\nu_{max.}$ 3620, 3540, and 3495 cm^{-1}) whose n.m.r. spectrum indicated two protons adjacent to hydroxy-groups (doublet of doublets at τ 6.33, and a triplet at τ 6.57), one olefinic proton (τ 4.72), and three tertiary methyl groups. Two possible structures which agree with these data are the olefinic diols (202) and (203),

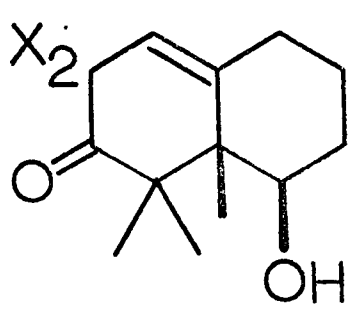


(202)

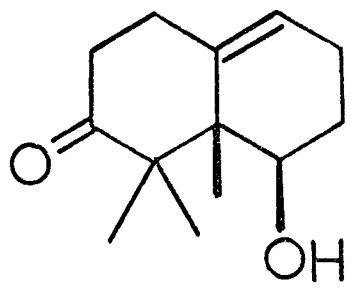


(203)

which would be obtained from the rearrangement products (204) and (205) respectively.

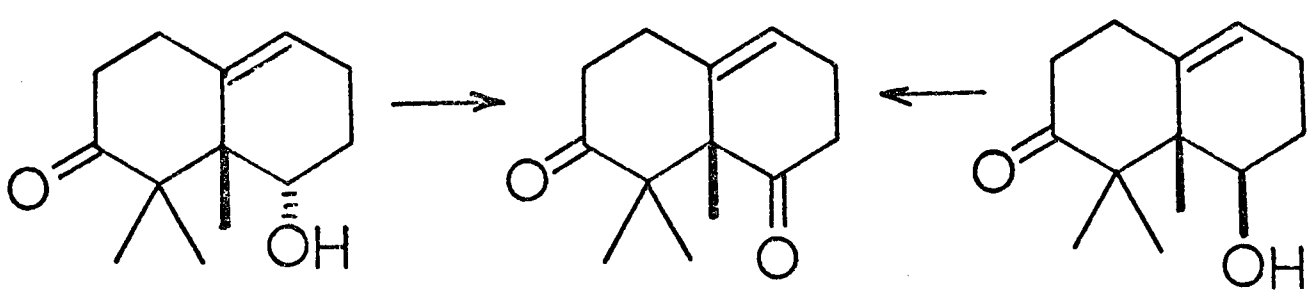


(204)



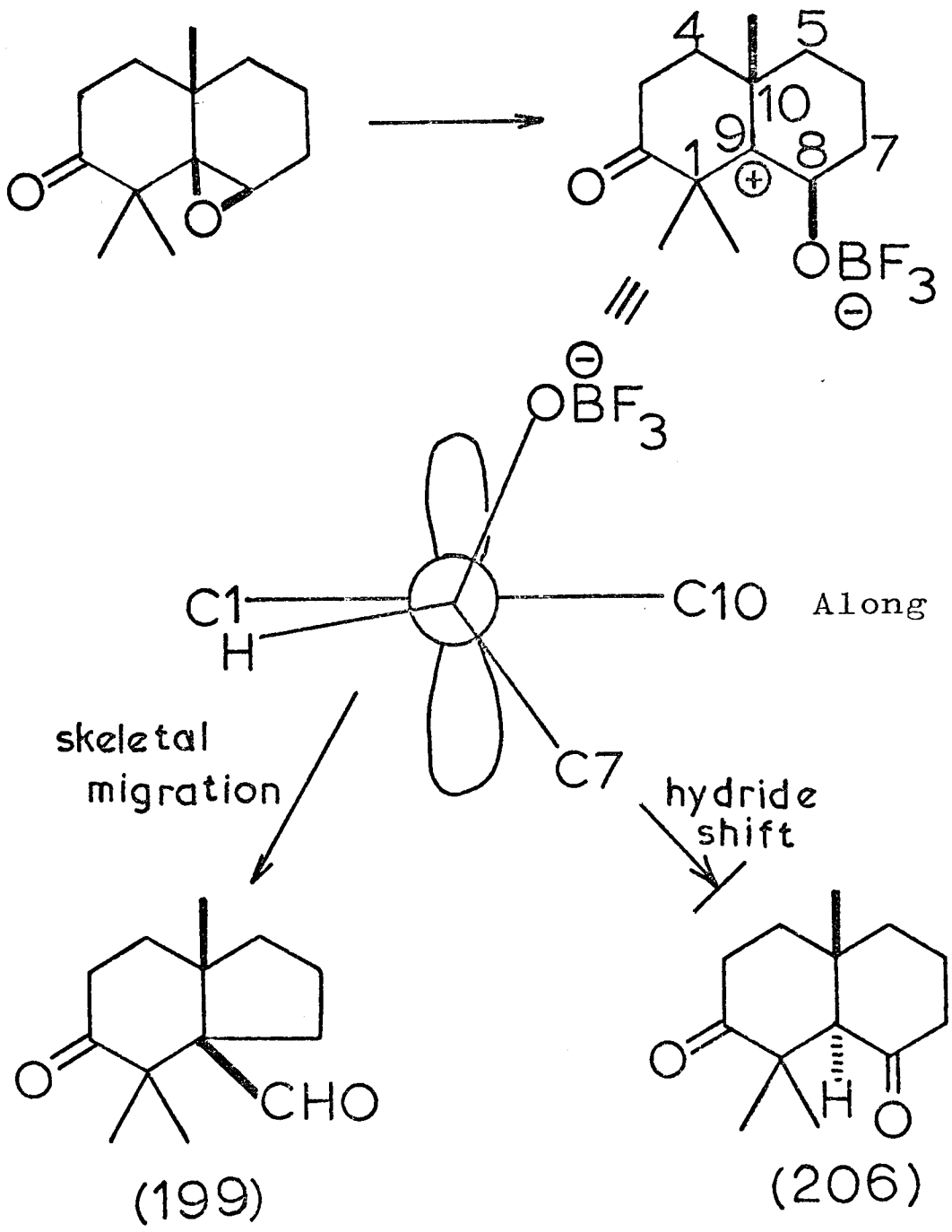
(205)

The n.m.r. spectrum of the $\beta\gamma$-unsaturated structure (204) would be expected to show a low field methylene signal due to the X_2 protons shown above, and examination of the n.m.r. spectrum of the rearrangement product mixture before reduction showed a two proton signal at τ 7.1 which was not present in spectrum of the spiro-ketol (201), and suggests that this rearrangement product is the $\Delta^{4(10)}$ isomer (204). This assignment was supported when the fourth rearrangement product was isolated; it was obtained as an oil in 27% yield, and contained a hydroxy-group and a keto-group in a six-membered ring ($\nu_{max.}$ 3630, 3530, and 1715 cm^{-1}). The n.m.r. spectrum indicated three tertiary methyl groups and one olefinic proton, and its structure was thus assigned as the $\Delta^{5(10)}$ ketol (205). The compound gave a crystalline 2,4-dinitrophenylhydrazone, and on oxidation gave a crystalline dione (196) with a broad carbonyl absorption at 1714 cm^{-1}; this dione was identical to that obtained from the epimeric ketol (195) which was formed from the corresponding α-epoxide (88i).



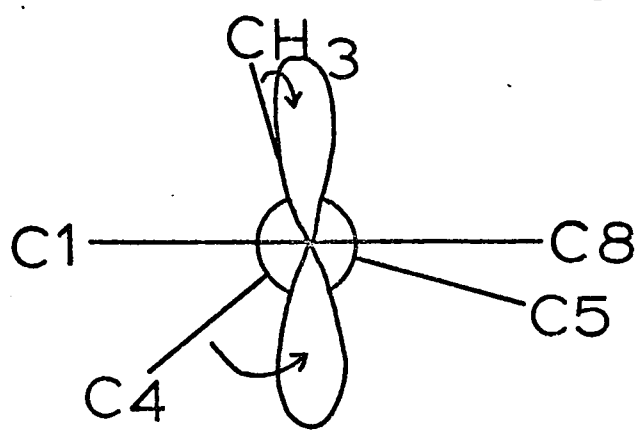
(195) (196) (205)

The three different migrations which have taken place in this rearrangement can all be rationalised in terms of formation of a planar carbonium ion at C9 followed by migration of suitably aligned groups to the positive centre. Examination of a model shows that the C7-C8 bond is in such a position, while the hydrogen attached to C8 lies near to the nodal plane of the carbonium ion, and skeletal migration to give the aldehyde (199) results, rather than a 1,2 hydride shift to give the ketone (206).



Migration of groups attached to C10 can be considered by looking along bond C9-C10; a model shows that both the C4-C10 bond and the 10β-methyl group could migrate, while the C5-C10 bond lies near the

nodal plane. The methyl group lies nearer the axis of the empty p-orbital of the carbonium ion than the C4-C10 bond, and this may partially account for the larger yield of products from methyl migration (40%) compared with that from ring contraction (~15%).



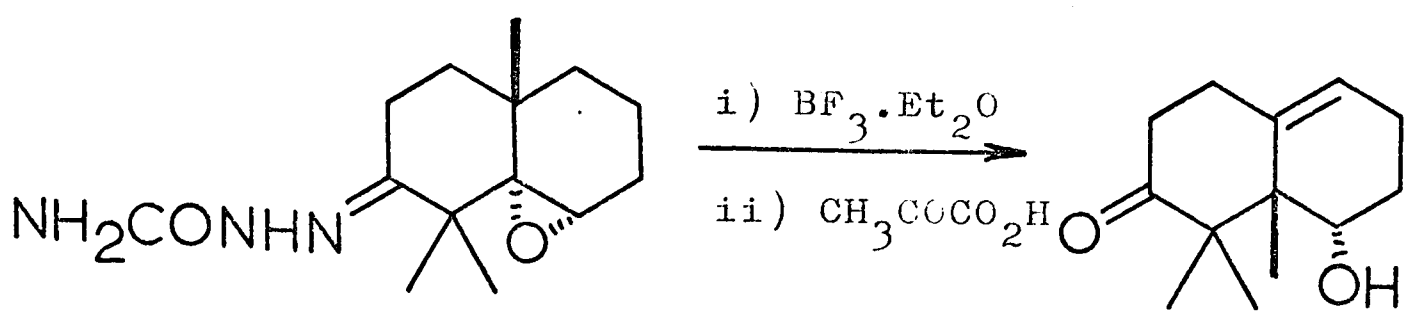
Along C9-C10

Of the groups attached to C1, only the β-methyl group is aligned suitably for migration, but this would involve placing a positive charge adjacent to a carbonyl group, and is not favourable.

x) Rearrangement of 8α,9α-Epoxy-1,1,10β-trimethyldecal-2-one Semicarbazone (150i).

Treatment of the semicarbazone epoxide (150i) in the usual way with boron trifluoride-ether complex gave a glass containing one major component and several minor components. The low solubility of this material in common solvents made p.l.c. and column chromatography difficult, and attempts were made to remove the semicarbazone group to allow separation on a more tractable material. Several methods are available for regenerating carbonyl groups from their nitrogen derivatives,[146] and three such methods were tested: direct hydrolysis by concentrated hydrochloric acid, and exchange with formaldehyde were both unsuccessful, but exchange with pyruvic acid in acetic acid[147] gave a single non-polar product which was isolated in 9% overall yield by p.l.c., and was

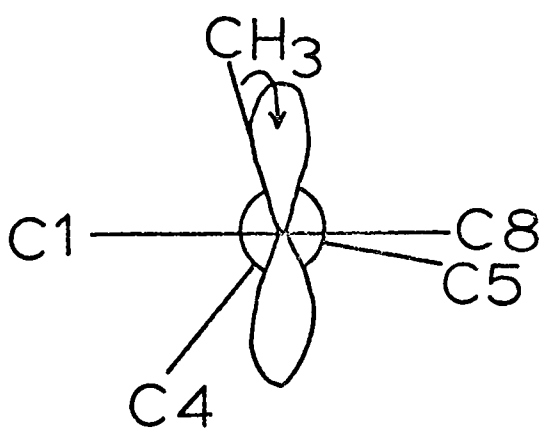
identified as the hydroxy-octalone (195), identical with the octalone obtained from the rearrangement of the corresponding keto-epoxide (88i).



(150i) (195)

Although the rearrangement of the semicarbazone epoxide yielded a single major product, the low overall yield and the intractability of the compounds involved do not recommend the semicarbazone group as a useful rearrangement directing function: however, the nature of the product does indicate that this group, like a keto-group, can prevent migration of methyl groups adjacent to it, and also, unlike a keto group, it will not migrate itself (cf. acyl migration).

The single product formed results from migration of the 10β-methyl group, which is well placed to overlap with the vacant orbitals of the C9 carbonium ion.

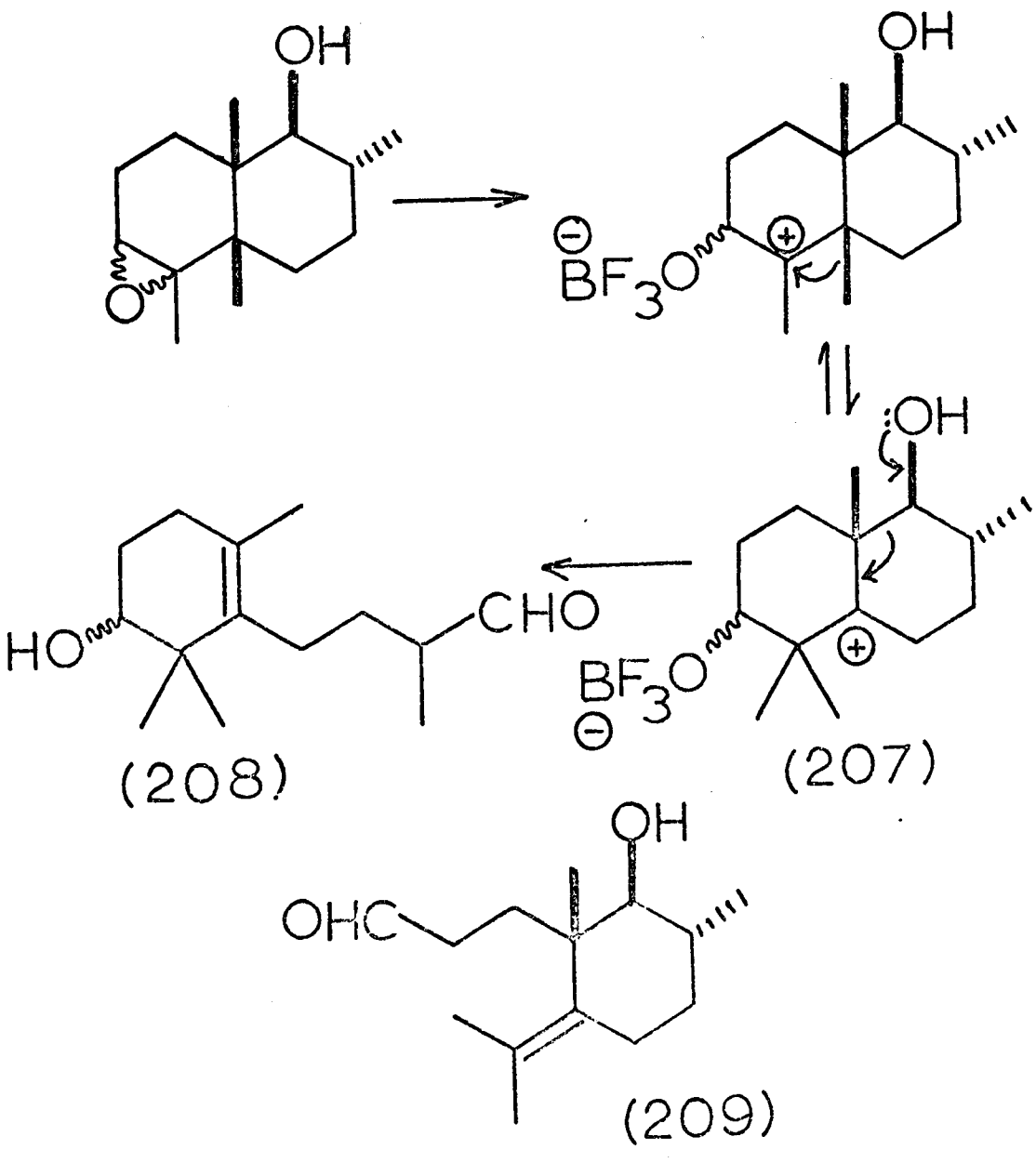


Along C9-C10

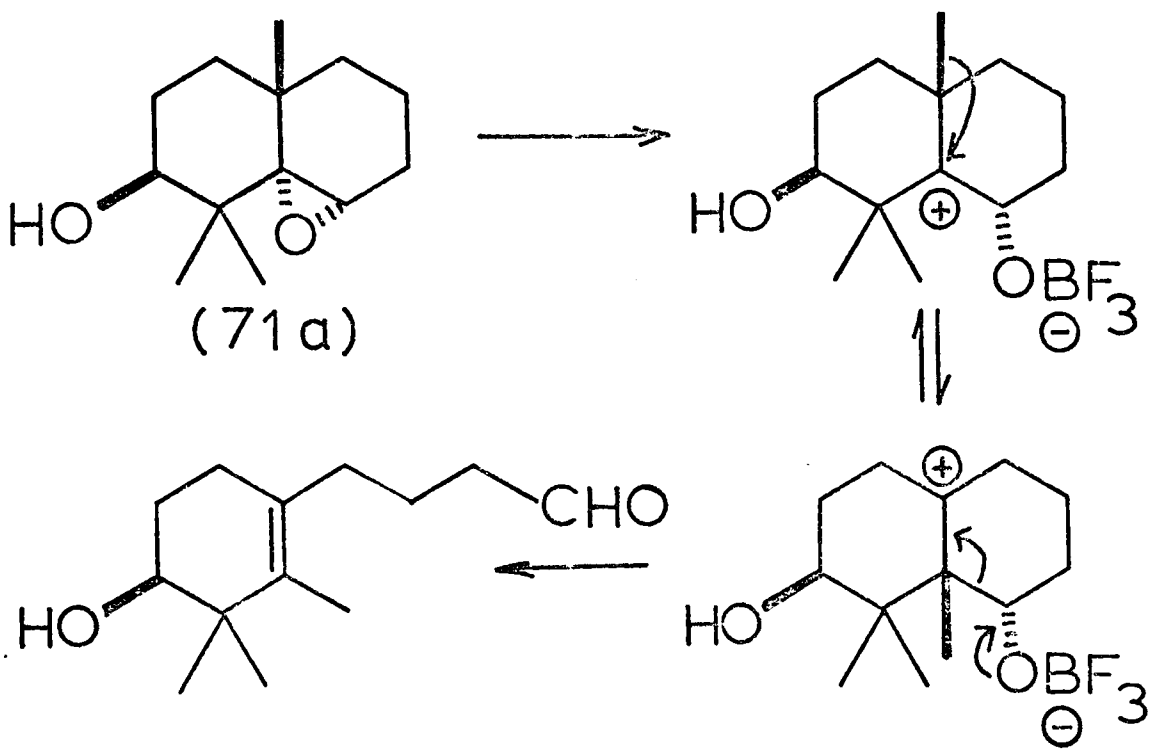
xi) $5\xi_1,6\xi_1$-Epoxy-2α,5,9β,10β-tetramethyldecal-1β-ol (92i).

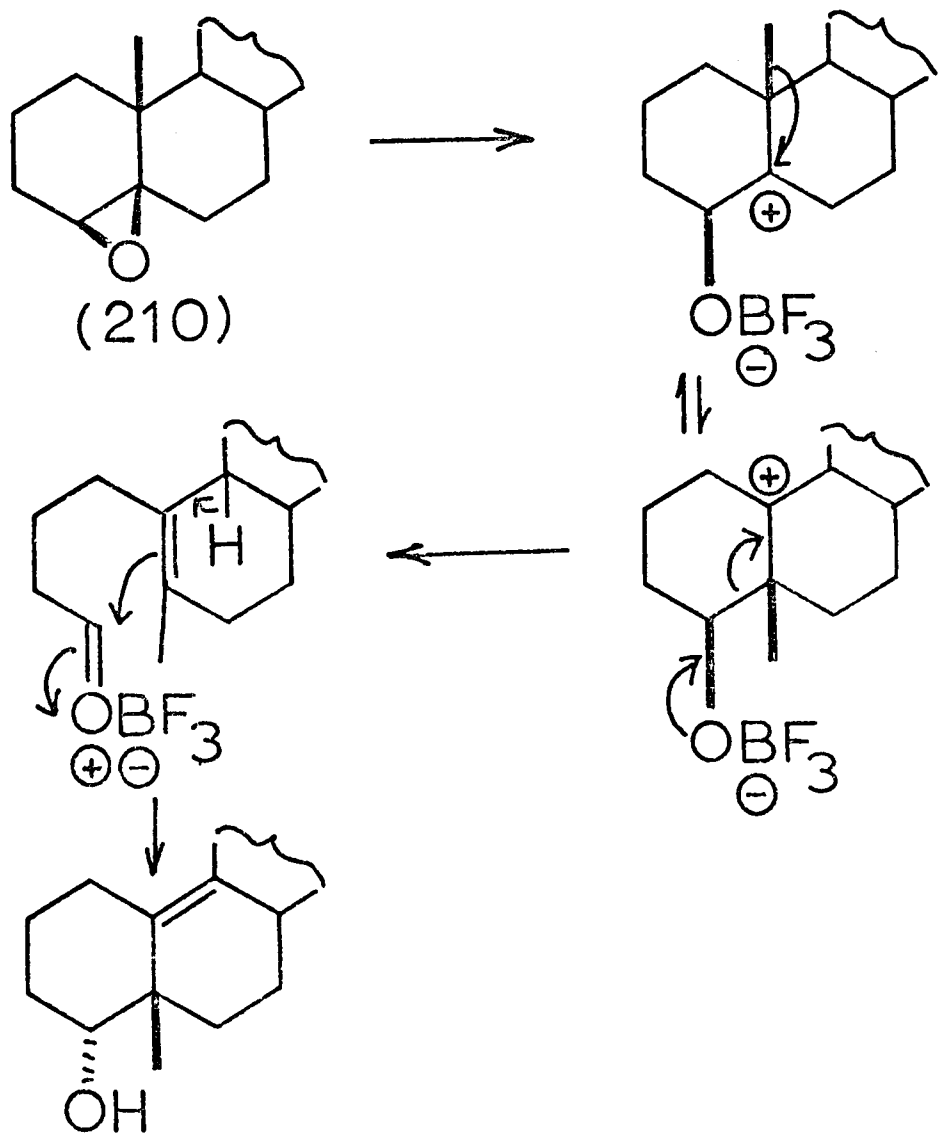
Treatment of this epoxide with boron trifluoride in the usual way gave an oil containing three components which were separated by p.l.c.

The least polar compound was an oil obtained in 29% yield and contained a secondary aldehyde group ($\nu_{max.}$ 2705 and 1728 cm^{-1}, and τ0.40, one proton doublet), and a hydroxy-group. The n.m.r. spectrum indicated one proton adjacent to a hydroxy-group, one vinylic methyl group, one secondary methyl group, and two tertiary methyl groups. The formation of an aldehyde group suggests that a Grob fragmentation has occurred, requiring a positive site two bonds away from a singly-bonded oxygen: this situation occurs if methyl migration generates the carbonium ion (207) which can cleave to give the hydroxy-aldehyde (208). The alternative fragmentation to give the aldehyde (209) can be discounted, as it leads to two vinylic methyl groups and is not consistent with the n.m.r. data.

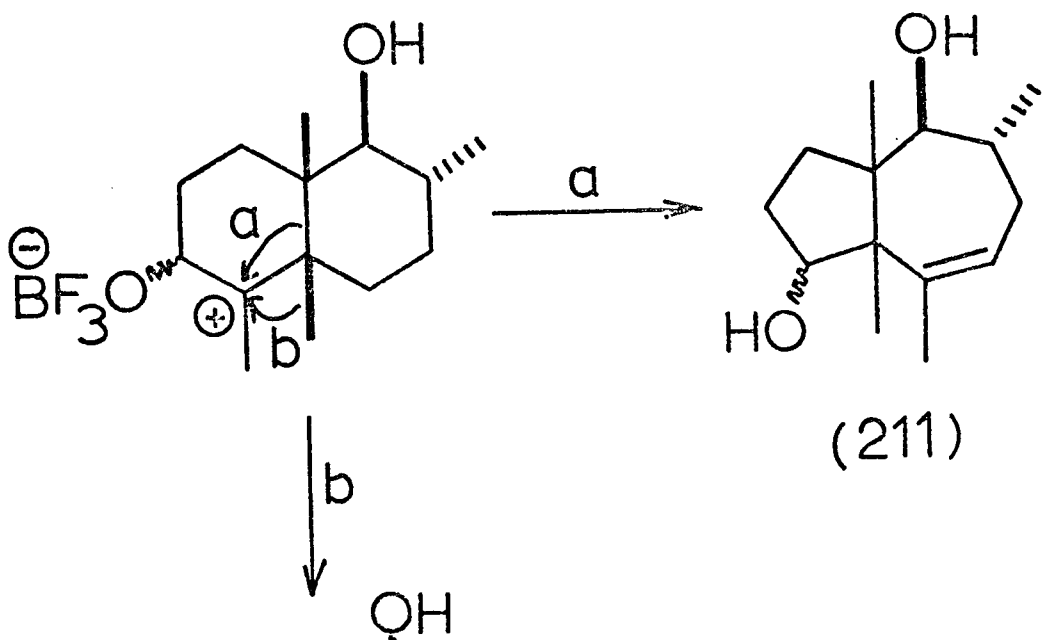


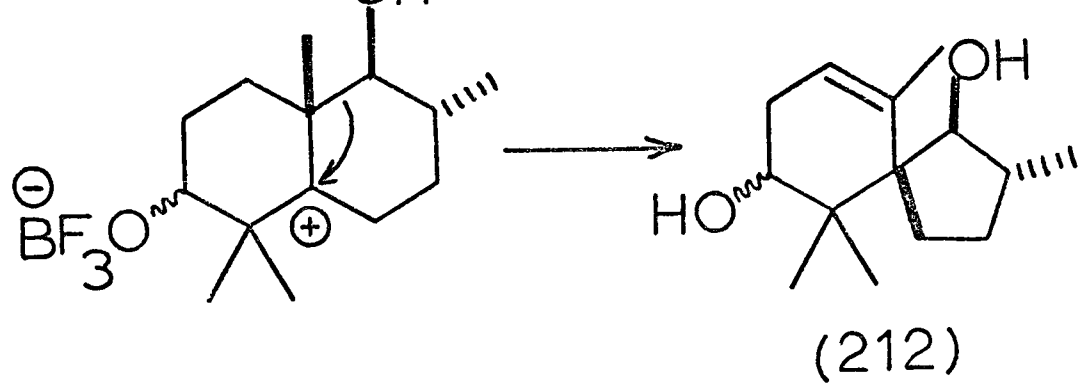
A similar cleavage (although involving the oxiran oxygen) was reported by Whitlock and Olson[85] from the epoxide (71a), and is an example of the fragmentation which has been postulated[70] to explain the inversion of configuration observed in certain steroidal epoxide rearrangements, e.g. (210).





The second rearrangement product was a crystalline di-hydroxy-olefin, obtained in 21% yield. The n.m.r. spectrum showed two protons on hydroxy-bearing carbon atoms (τ 6.39 and 6.70), one olefinic proton (τ 4.57), and a vinylic methyl group (τ 8.23). Two rearrangement products containing a vinylic methyl group on a trisubstituted double bond can be envisaged, one with a bicyclo [5.3.0] decane skeleton (211) and the other with a spiran skeleton (212).

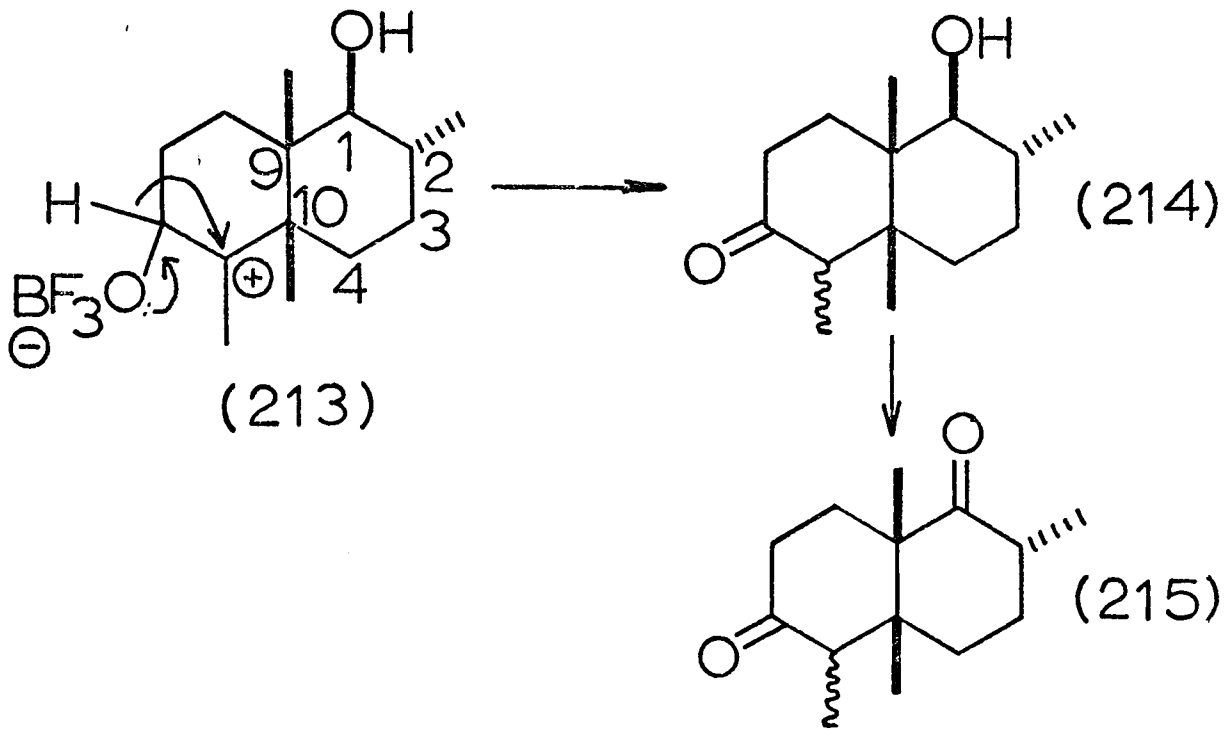




Oxidation of this compound gave a diketone, and a poorly resolved i.r. spectrum showed a broad carbonyl absorption at 1734 cm^{-1}, which agrees more with the dione obtained from the spiro-diol (212), which would contain five- and six-membered ring ketones, whereas the dione from the bicyclo [5.3.0] decane derivative would contain a seven-membered ring ketone and should show a carbonyl absorption below 1720 cm^{-1}.

The most polar product obtained from the rearrangement was

isolated as an oil in 29% yield and contained a hydroxy-group and a keto-group ($\nu_{max.}$ 3620, 3510, and 1709 cm^{-1}). The n.m.r. spectrum showed two tertiary methyl groups and two secondary methyl groups, and no olefinic protons or vinylic methyl groups. The lack of any olefinic unsaturation, and the presence of a keto-group suggested that the epoxide had undergone a simple hydride shift to give the hydroxy-ketone (214), which was characterised as a crystalline

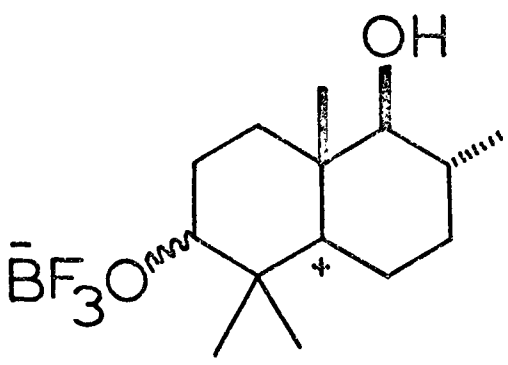


2,4-dinitrophenylhydrazone. Oxidation gave a dione (215) with carbonyl absorptions at $\nu_{C=O}$ 1710 and 1705 cm^{-1}.

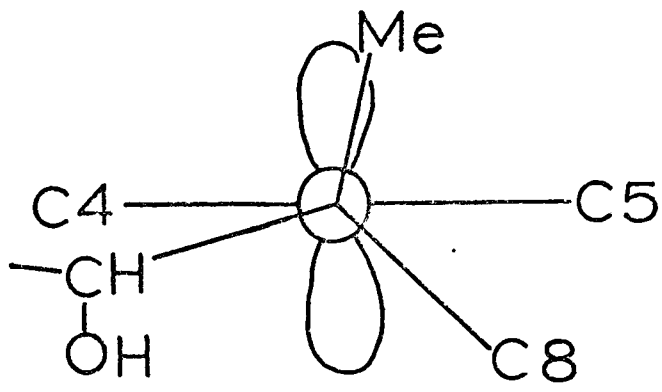
All of the products of the rearrangement of this epoxide can be envisaged as derived from the C5 carbonium ion (213) and if the 5β,6β-epoxide stereochemistry is assumed examination of a model shows that both the 6α-hydrogen and the 10β-methyl group can achieve suitable alignments to migrate to C5 to give products (208) and (214) respectively.

A model of the carbonium ion (207) which was postulated as the precursor to the spiro-product (212) shows that the C9-C1 bond is not well situated to migrate to C10, as it lies almost in the nodal plane

of the carbonium ion;

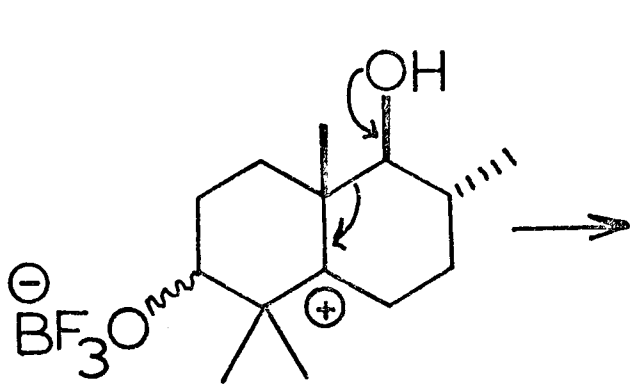


(207)

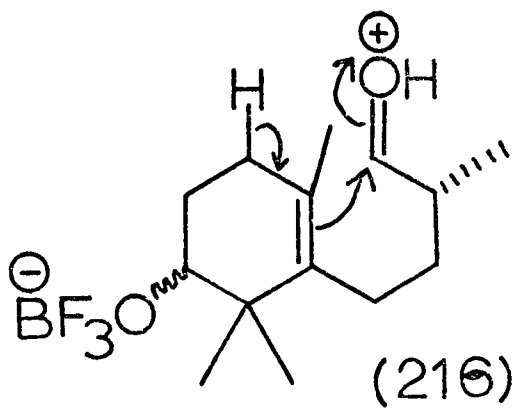


Along C9-C10

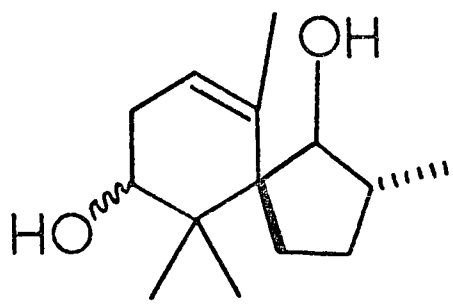
the spiro-compound may possibly be formed instead <u>via</u> the protonated aldehyde (216), which recyclises to give (212).



(207)



(216)

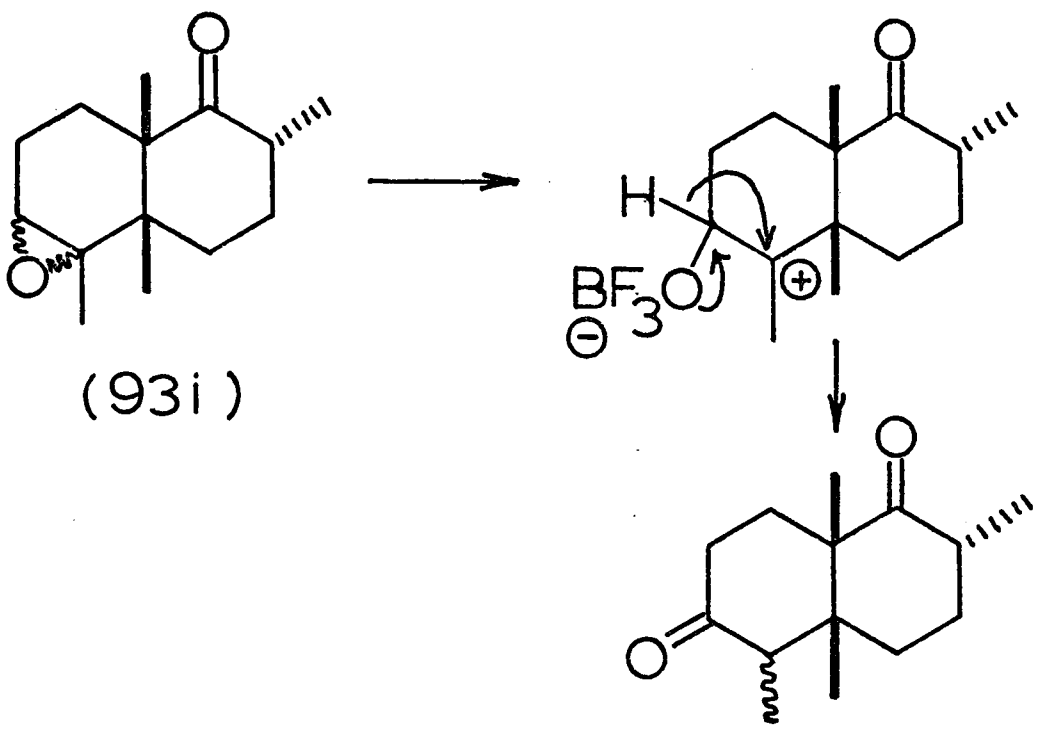


(212)

xii) 5ξ_1,6ξ_1-Epoxy-2α,5,9β,10β-tetramethyldecal-1-one (93i).

Treatment of this epoxide with boron trifluoride-ether complex at 10° for 5 minutes gave a mixture containing at least five components, and these were separated by p.l.c.

The least polar compound was obtained as an oil in 5% yield and its i.r. spectrum indicated the presence of two keto-groups ($\nu_{C=O}$ 1710, and 1705 cm^{-1}) and the absence of any hydroxy-group. The n.m.r. spectrum showed no signals below τ7, and two tertiary and two secondary methyl groups. The lack of hydroxy-group or an olefinic double bond suggested that this compound is the simple diketone (215) formed by a 1,2 hydride shift.

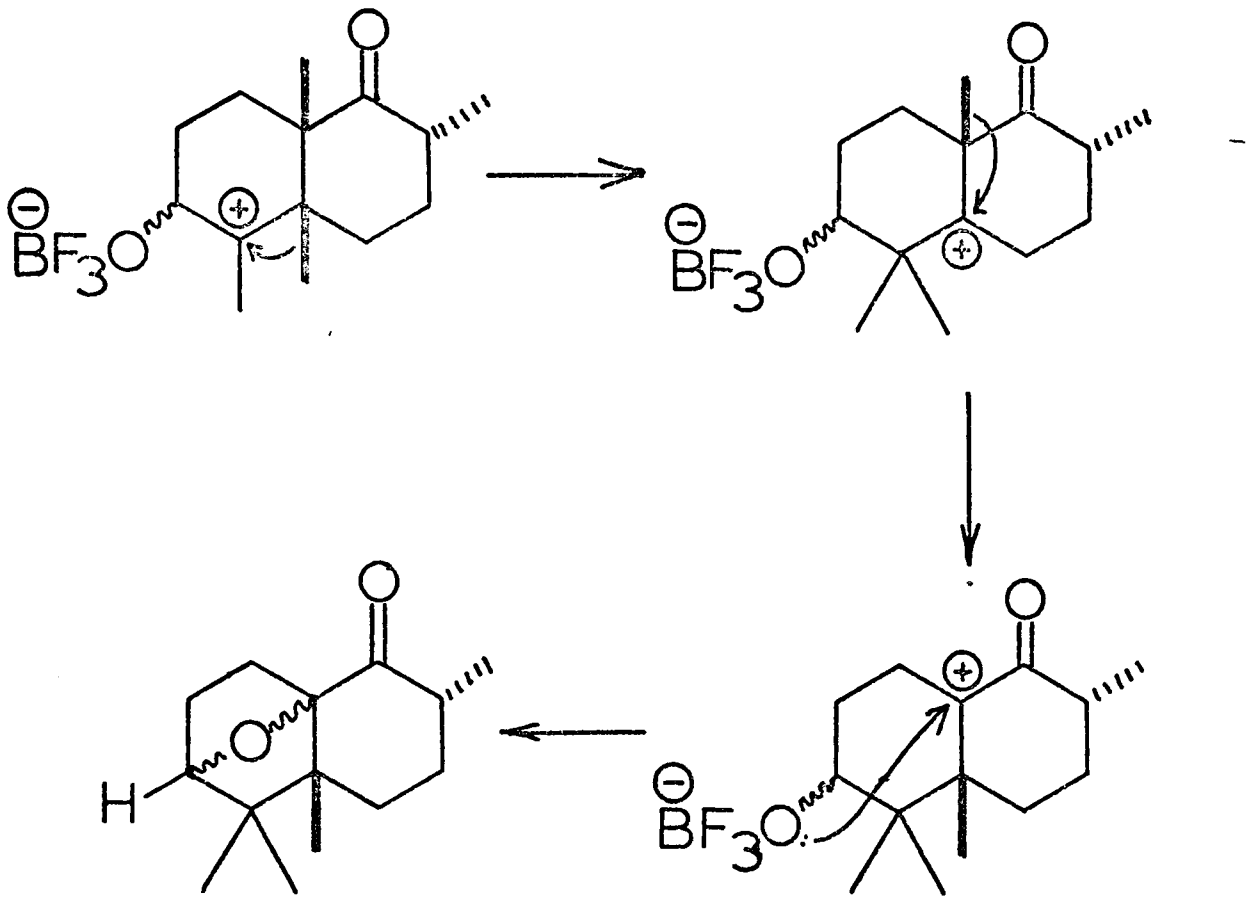


(93i) (215)

This dione was found to be identical with the dione obtained from the hydroxy-ketone (214), derived from the hydroxy-epoxide (92i). The dione was characterised as a crystalline mono-2,4-dinitrophenylhydrazone.

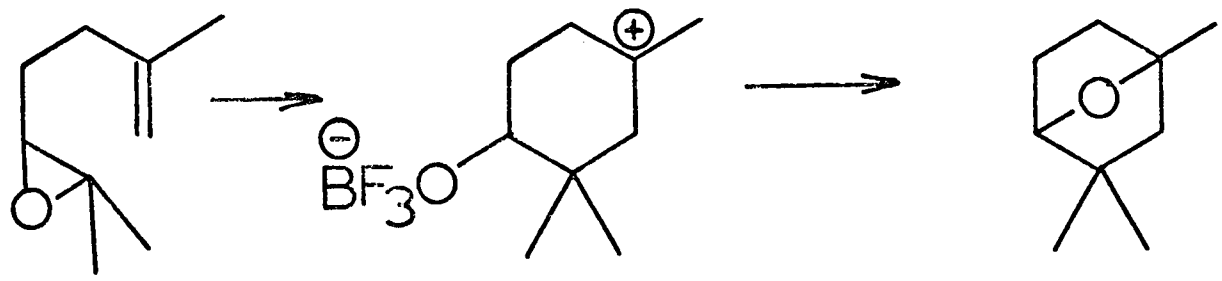
The second rearrangement product (in order of decreasing Rf) was obtained as an oil in 24% yield and contained a keto-group ($\nu_{C=O}$ 1724 cm^{-1}) and no hydroxy-group. The compound did not have an olefinic proton or a vinylic methyl group, but the n.m.r. spectrum showed a one-proton signal

at τ 6.33 corresponding to a proton on an oxygen-bearing carbon atom. The lack of unsaturation or a hydroxy-group suggested that the oxiran oxygen had probably become involved in a cyclic ether; this could occur if the oxygen atom could trap a suitable carbonium ion, and a five-membered ring ether can form if two methyl migrations place the positive charge at C9; ring closure gives the ether (217).



(217)

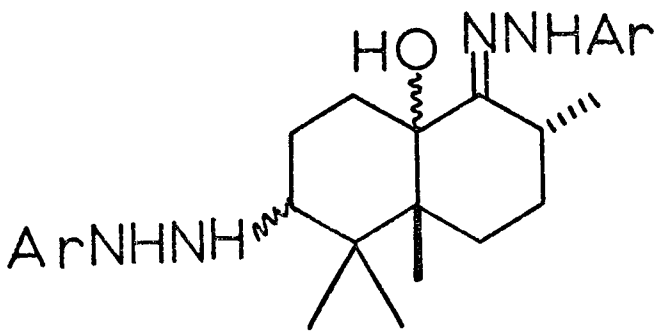
This process is analogous to the trapping of a carbonium ion observed by Goldsmith[27] with the simple epoxide (17).



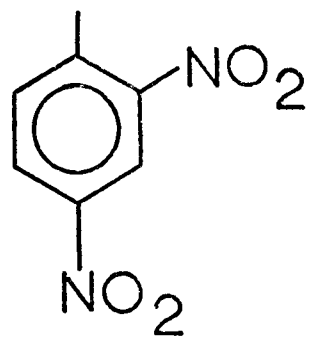
(17)

The keto-ether (217) was treated with 2,4-dinitrophenylhydrazine

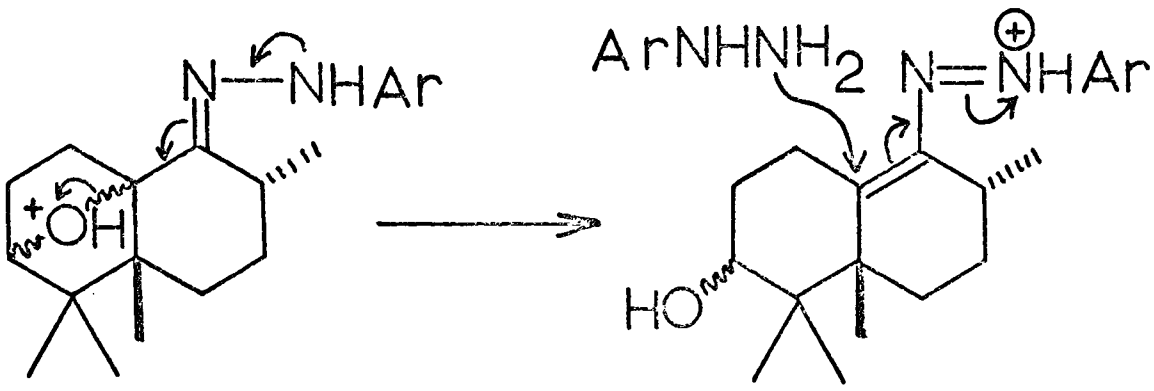
reagent to give an orange crystalline solid which was recrystallised twice from aqueous methanol-ethyl acetate to give a crystalline sample which melted over a 3° range and gave elemental analyses which were consistent with an empirical formula $C_{13}H_{17}N_4O_5$. As the keto-ether itself contained fourteen carbon atoms, it seemed likely that the molecular formula was $C_{26}H_{34}N_8O_{10}$ which would be feasible if two molecules of the 2,4-dinitrophenylhydrazine had reacted. The mass spectrum did not show a molecular ion corresponding to this formula, and the highest peak observed was at m/e 495. If two molecules of the 2,4-dinitrophenylhydrazine have been incorporated, one must have reacted with the carbonyl group in the normal way, and the other must have reacted with the ether group, probably by nucleophilic ring opening. The reagent was made up in ethanolic phosphoric acid,[148] and acid catalysed nucleophilic attack at the less hindered carbon atom C6 would give the hydrazine derivative (218).



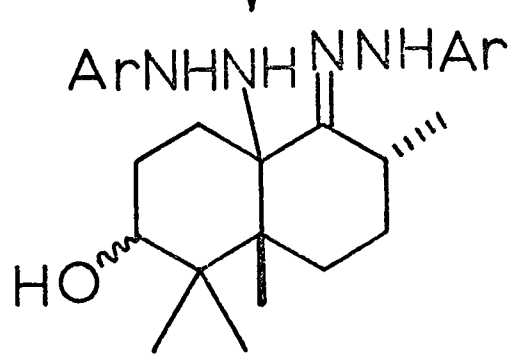
(218)

Ar = 

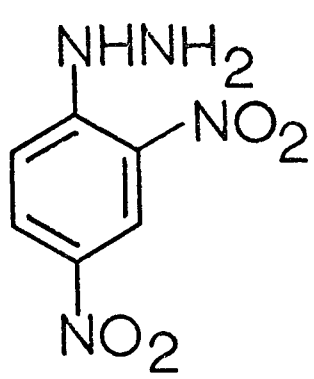
There is also a possibility that the hydrazone moiety might offer anchimeric assistance to cause cleavage at C9, leading to the cation (219) which can be attacked in a pseudo-Michael fashion to give the isomeric hydrazine derivative (220).



(219)



(220)



(221)

Compounds (218) and (220) have the molecular formula $C_{26}H_{32}N_8O_9$, and would give the correct analysis values if the crystalline form contained one molecule of water of crystallisation per molecule of compound. The molecular weight of (218) and (220) is 600, but neither structure would be expected to show a molecular ion in its mass spectrum; both structures should show a peak due to the loss of fragment (221) (m/e 198) at M-198 = 402, and in fact peaks at m/e 198 and 402 were present in the spectrum.

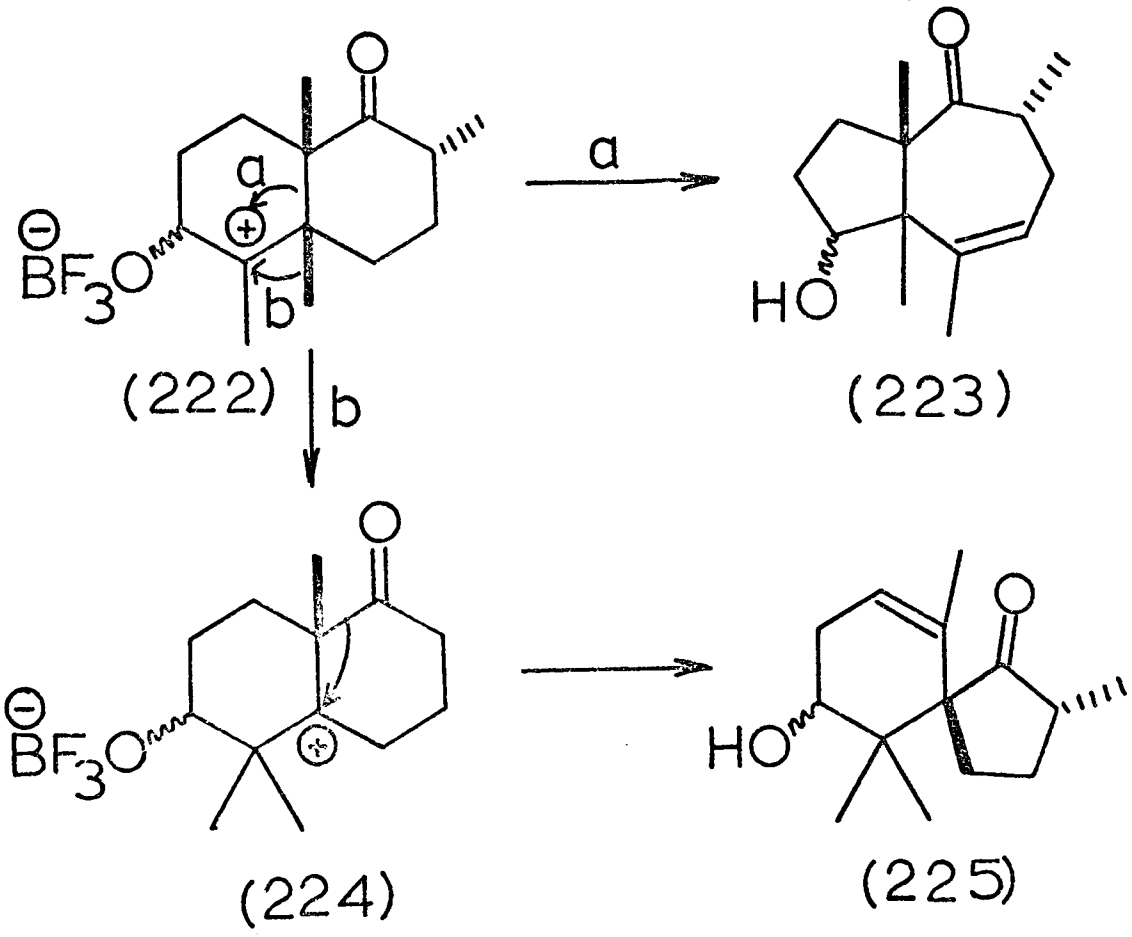
If the compound were the tertiary alcohol (218), a peak due to elimination of water at 402-18 = 384 would be expected, but the peak is of negligible intensity, and this may be an indication that the adduct is the secondary alcohol (220).

The third band extracted from the rearrangement mixture gave an oil in 15% yield, containing several components, and this was purified by further p.l.c. to give a glass which was apparently homogeneous by t.l.c. The i.r. spectrum indicated a hydroxy-group and a carbonyl group ($\nu_{max.}$ 3620, 3500, and 1720 cm^{-1}), and the n.m.r. spectrum indicated one proton on an oxygen-bearing carbon atom (τ6.40), and a complex methyl region in which two tertiary and one secondary methyl group could be discerned. The mass spectrum suggested that this material was a mixture, as it showed peaks at m/e 222 (corresponding to a direct rearrangement product of the epoxide) and at m/e 242. The species giving rise to this peak must be an authentic product of the rearrangement reaction, as the separation procedures which were used on the material were such that the possibility of introducing extraneous substances was reduced to a minimum. The peak at m/e 242 is 20 mass units higher than the molecular weight of the parent epoxide, and if it is a molecular ion peak, it implies incorporation of one oxygen and four hydrogen atoms. The addition of one molecule of water to the rearrangement products is feasible, but addition of a further two hydrogen atoms is difficult to envisage without postulating a redox system, allowing hydride transfer. Alternatively, two molecules of the epoxide might couple during the rearrangement to give a dimeric species, and the peak at m/e 242 could be a fragment from this.

The mass spectra of the materials obtained from the third and fourth bands from the rearrangement of keto-ester epoxide (82i) (see p. 88) also showed peaks at m/e 242, and a comparison of these mass spectra with those of the third and fifth bands from the present epoxide (93i) showed some similarity in the fragmentation patterns: this may indicate that the species responsible all contain a similar skeletal unit. If the

peak at m/e 242 is a molecular ion, it represents a species $C_{14}H_{26}O_3$, which, if it contains a carbonyl group, can only contain one ring, and indicates that the rearrangement of the epoxide has proceeded with ring-cleavage.

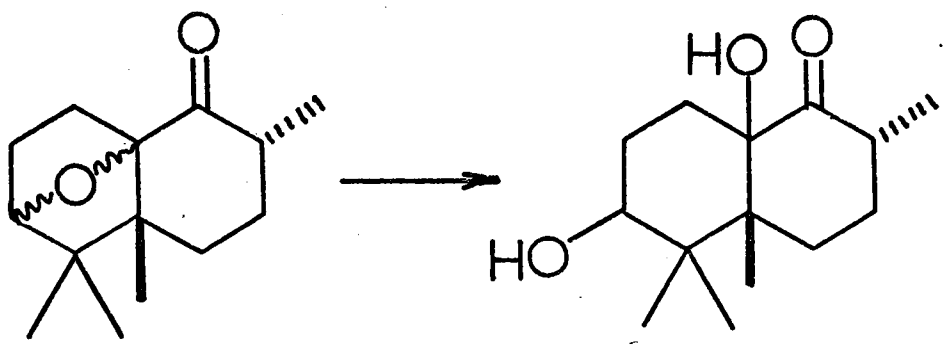
The fourth band extracted from the rearrangement mixture yielded a homogeneous oil in 7% yield; the i.r. spectrum indicated a hydroxy-group and a carbonyl group ($\nu_{max.}$ 3630, 3550, and 1720 cm^{-1}), and the n.m.r. spectrum showed an olefinic proton and a vinylic methyl group (τ 4.58 and 8.43), and one proton on an oxygen-bearing carbon atom (τ 5.65). The mass spectrum gave a molecular ion at m/e 222, confirming that this was a direct rearrangement product. Two products (223) and (225) containing a trisubstituted double-bond can be envisaged, arising from carbonium ions (222) and (224) respectively.



(222) (223) (224) (225)

Oxidation of this compound gave a dione with a new carbonyl band at 1740 cm^{-1}, which suggests a cyclopentanone and indicates that the rearrangement product probably has the bicyclo [5.3.0] decane structure (223).

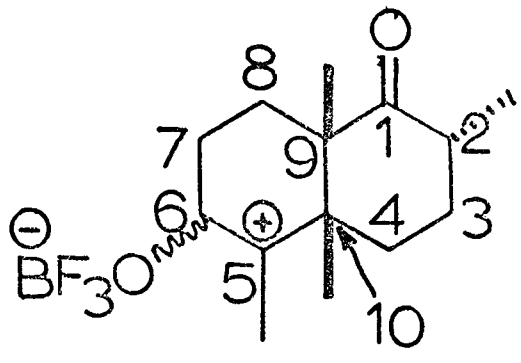
The fifth band from the reaction mixture gave a glass which was further purified by p.l.c. to give a hydroxy-ketone in 8% yield. The i.r. spectrum indicated a hydroxy-group, and a keto-group in a six-membered ring ($\nu_{max.}$ 3650, 3560, and 1725 cm^{-1}), and the n.m.r. spectrum showed one proton on an oxygen-bearing carbon atom, and three tertiary and one secondary methyl groups; the methyl region was very similar to that of the keto-ether (217). The mass spectrum showed a peak at m/e 242 and also at m/e 222, which suggested that the material was not pure. The similarity between the n.m.r. spectra of this material and the keto-ether (217) suggested that the keto-diol (226) might be present, formed by hydrolytic cleavage of the ether ring.



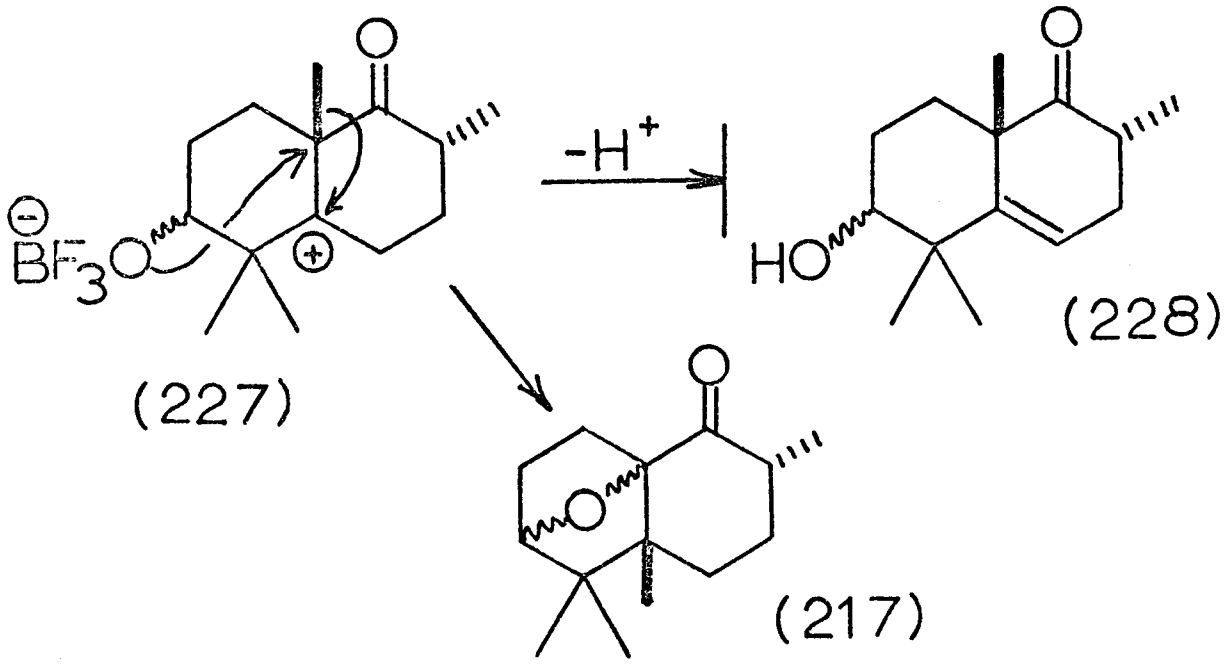
(217) (226)

This compound contains a tertiary hydroxy-group and should only give a very weak molecular ion peak at m/e 240, and such a peak is discernible. Cleavage of the ether ring alters the position of the 6-hydrogen relative to the adjacent methylene group, and a corresponding change in its n.m.r. signal is observed.

If the tentative 5β,6β-epoxide stereochemistry is assumed, examination of models shows that the 6α-hydrogen, the 10-methyl group, and the C9-C10 bond can all achieve suitable orientations to migrate to C5 with maximum orbital overlap; products arising from each of these three modes of rearrangement are found.



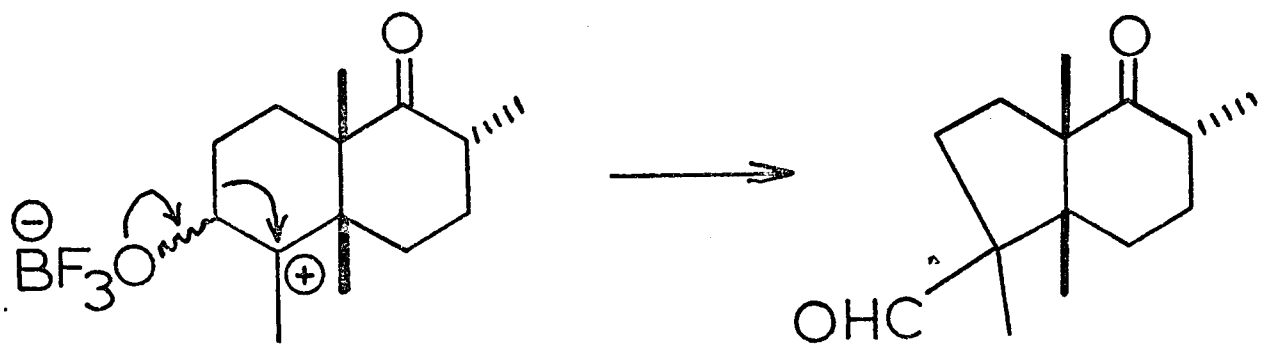
The dione (215) results from a simple 1,2 hydride shift from C6 to C5, and the bicyclo [5.3.0] decane derivative (223) from migration of bond C9-C10 to C5, followed by proton loss at C4 to give a $\triangle^{4,10}$ double bond. Migration of the 10-methyl group develops positive charge at C10 (227), but instead of proton loss to give the desired rearrangement product (228), a second methyl migration occurs, from C9 to C10. If this occurred as a discrete step, prior to ether



formation, it would require developing a positive charge α to a carbonyl group, and would be a highly energetic process. Examination of a model of the carbonium ion (227) shows that the 6β-oxygen is moved close to C9, and thus migration of the methyl group from C9 to C10 may be anchimerically assisted by the oxygen, which can partially stabilise the developing positive charge.

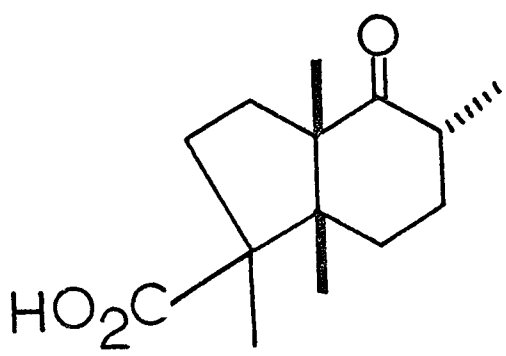
xiii) $5\xi_2,6\xi_2$-Epoxy-2α,5,9β,10β-tetramethyldecal-1-one (93ii).

Treatment of this epoxide with boron trifluoride-ether complex at 25° for 10 minutes gave a quantitative yield of a single product, obtained as an oil. The product contained a tertiary aldehyde group ($\nu_{max.}$ 2690 and 1712 cm^{-1}, τ 0.64, one-proton singlet) and a keto-group ($\nu_{max.}$ 1700 cm^{-1}), and three tertiary and one secondary methyl group. The formation of an aldehyde group but no olefinic unsaturation suggests that ring contraction has occurred to give the keto-aldehyde (229).



(229)

The compound was characterised as a crystalline mono-2,4-dinitrophenylhydrazone. On standing, the aldehyde was slowly oxidised to a crystalline solid, identified as the corresponding acid (230).



(230)

The aldehyde is formed by migration of bond C6-C7 to C5, but from examination of models, it is not immediately apparent why this is the exclusive mode of rearrangement. If a discrete carbonium ion were formed by initial cleavage of the C5-O bond, migration of other suitably

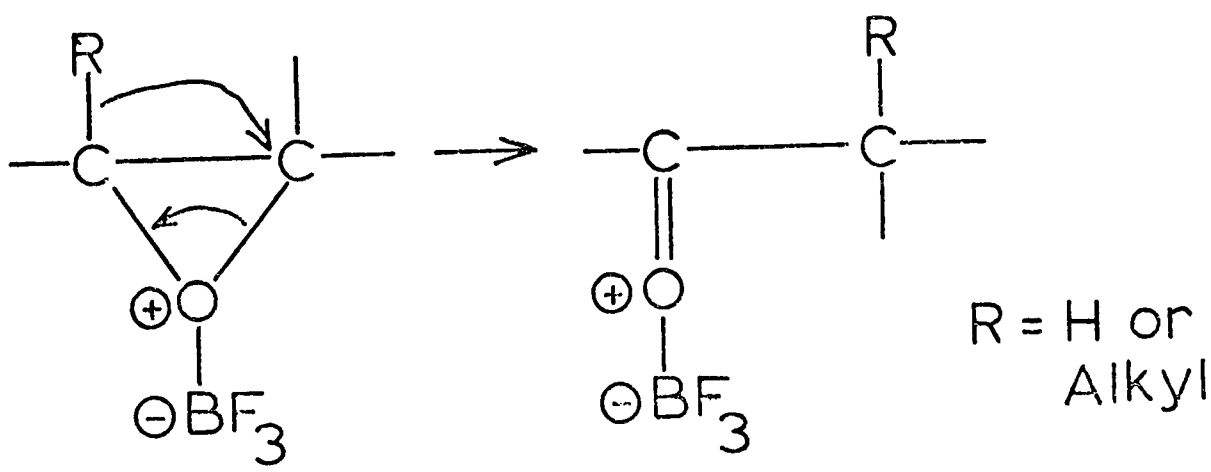
aligned groups to C5 might be expected. The fact that no products from such migrations are observed suggests that a discrete carbonium ion is not involved, and that the rearrangement of bond C6-C7 to C5 is largely concerted with the epoxide C-O cleavage. The reasons for this preferred mode of rearrangement are not clear.

3. Conclusions

The epoxides studied in this work have yielded a wide variety of rearrangement products, but some generalisations can be made, and most of the rearrangements can be rationalised by envisaging mechanisms proceeding *via* discrete carbonium ions.

Formation of a carbonium ion implies cleavage of an oxiran C-O bond prior to any rearrangement: this must be the case when groups migrate from positions initially *cis* to the C-O bond which cleaves; prior C-O cleavage is also proposed[85] for systems in which the migrating group was initially *trans* and anti-parallel to the C-O bond which cleaves (and could conceivably have migrated in concert with the cleavage).

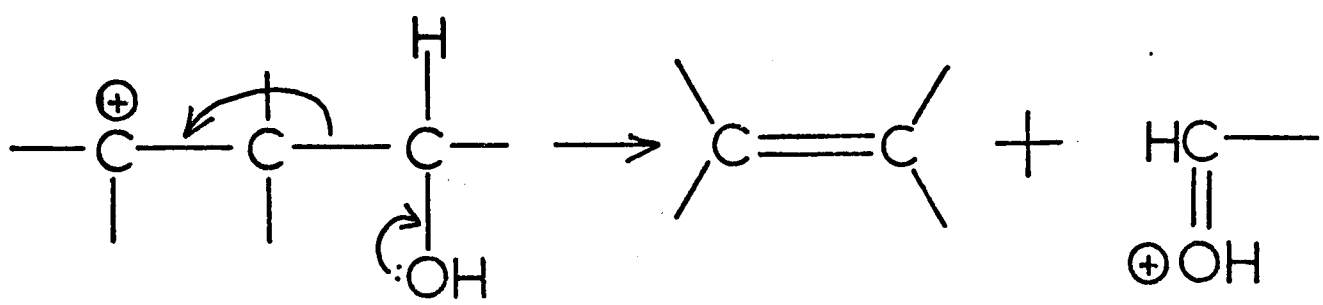
Simple 1,2 shifts leading to carbonyl groups may be concerted:



although recent evidence suggests that some 1,2 hydride shifts proceed by a stepwise mechanism involving a discrete carbonium ion.[149]

Once an epoxide has been opened by a Lewis acid to give a carbonium ion, a careful analysis of stereochemical, conformational, and electronic factors should give an indication of likely migrating species: suitably

oriented groups (i.e. those lying parallel or nearly parallel to the axis of the vacant p-orbital of the carbonium ion) will migrate to the electron deficient site, unless there are opposing electronic or stereochemical factors. The resulting species will then undergo further rearrangement, or the rearrangement sequence will be terminated by dissipating the positive charge in one of three ways; (i) by losing a proton adjacent to a positive carbon, to give an olefin, (ii) by "trapping" the carbonium ion with a suitably placed hydroxy-group or the oxiran oxygen to give a cyclic ether, or (iii) by involving the electrons of a singly-bonded oxygen to give a Grob fragmentation leading to an aldehyde:



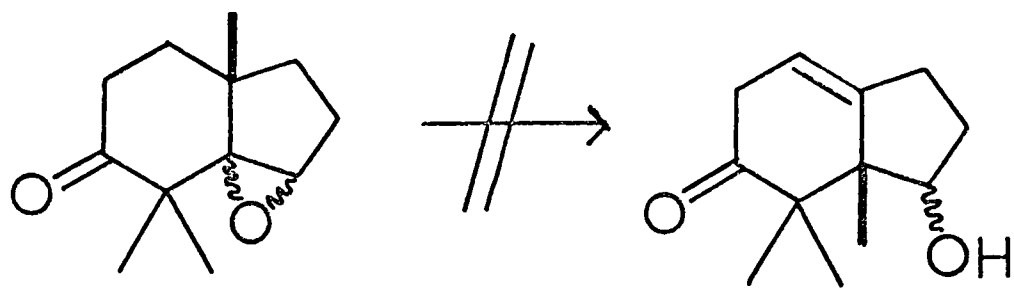
This latter fragmentation also occurs in steroidal epoxide rearrangements, but the initially formed protonated aldehyde usually recyclises, and deprotonates elsewhere: one of the major differences between the behaviour of the bicyclic epoxides studied in this work and steroidal epoxides was that the former were much more likely to show fragmentation reactions than the latter.

Electron-withdrawing groups tend to reduce the overall reactivity of epoxides, and in particular they hinder migration of adjacent groups: thus unreacted epoxides could be recovered from the rearrangements of the keto-ester epoxides (82i) and (82ii), and none of the groups adjacent to the ester and ketone groups in the molecule migrated. When suitably placed keto-groups are present, they can participate in the rearrangement by giving an acyl migration, and both epoxides (82i) and (82ii) rearranged

by such routes.

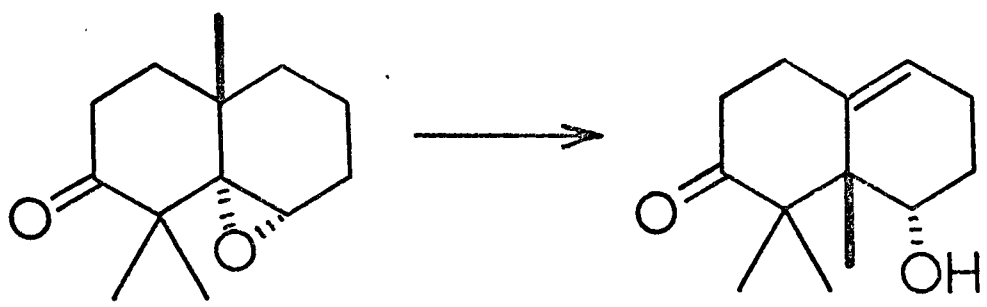
Hydroxy-groups do not tend to hinder the migration of adjacent groups, as they can involve their lone pair of electrons to stabilise developing positive charge. As described above, hydroxy-groups can bring about termination of a rearrangement by ether formation or fragmentation to an aldehyde.

Although a group is correctly aligned to migrate to a positive site, and its migration is not opposed by electronic factors, it will not migrate if its route of approach is impeded, or if its migration generates a strained or sterically hindered structure. Thus the keto-epoxide (85) does not show any products resulting from migration of the 8β-methyl group to C9, possibly because this migration develops an unfavourable 1,3-diaxial interaction between a 4-methyl group and the developing 3-hydroxy-group.



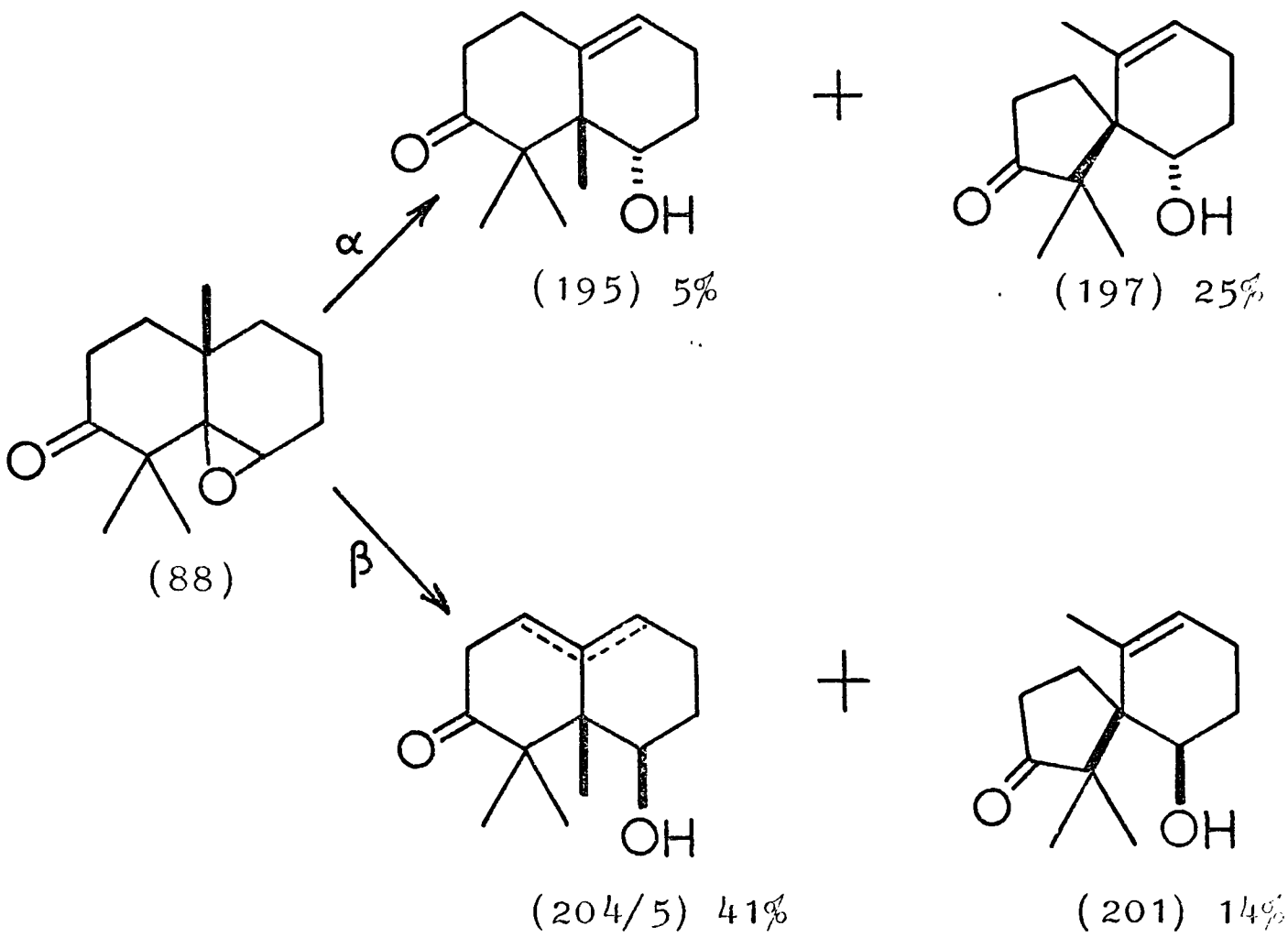
(85)

In the analogous decalone epoxide (88i), such a migration is possible, because although the same 1,3-diaxial relationship exists, the distance between the methyl group and the hydroxy-group in the product is considerably larger.

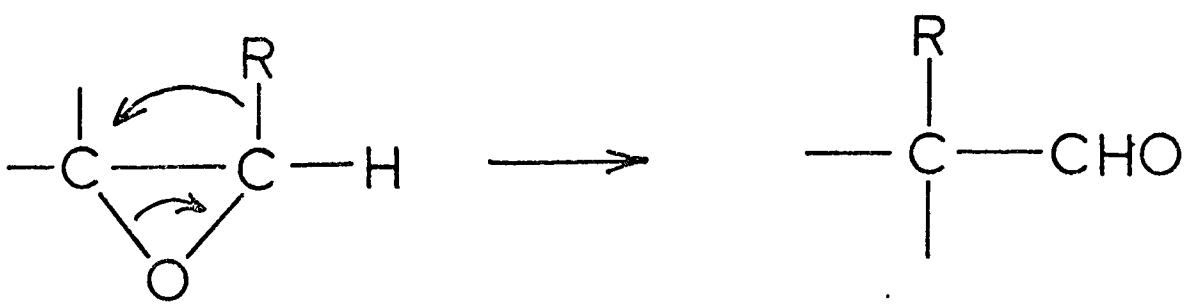


(88i) (195) 5%

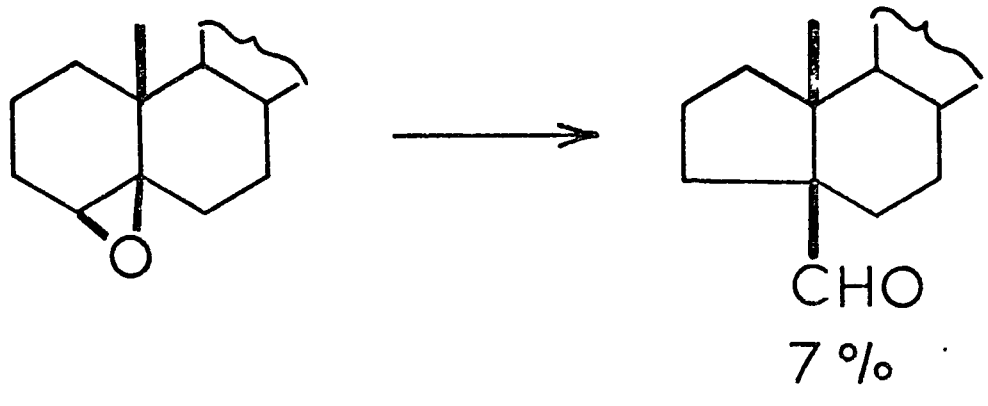
Such stereochemical factors can exert a marked influence on which groups migrate preferentially: in the decalone α - and β - epoxides (88i) and (88ii) both the 10β-methyl group and the C4-C10 bond are potential migrating species; from the α-epoxide (88i) the ratio of products from methyl migration to product from bond migration is 1:5, while from the β-epoxide (88ii), this ratio is 3:1. This difference can be ascribed, at least in part, to a reduction in the unfavourable interaction between the 8-oxygen function and one of the 1-methyl groups in going from the α-product (195) to the β-product (204/5): with the α-product (195), this 1,3-diaxial relationship disfavours methyl migration relative to spiran formation, and the latter predominates, while with the β-product (204/5), this relationship is reduced and the product ratio rather reflects the conformations of the two migrating groups.

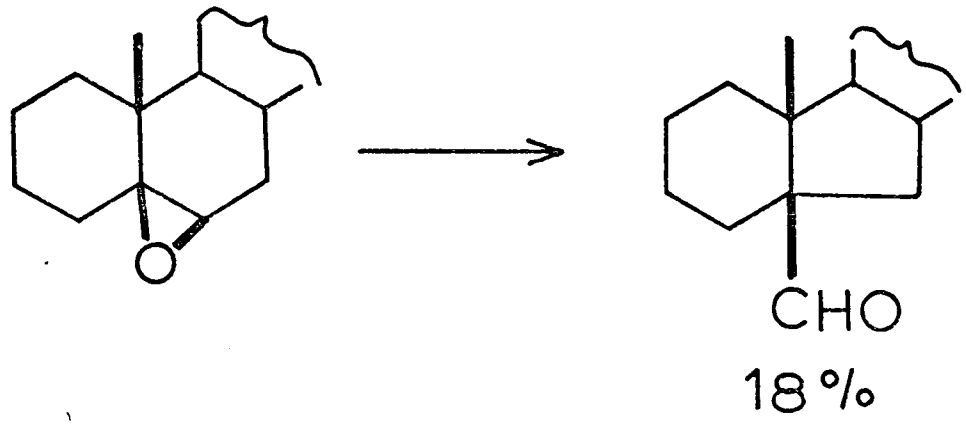


The products obtained from these two epoxides (88i) and (88ii) show that in the absence of other competing rearrangements, the orientation of the oxiran ring does not determine absolutely which migrations will occur, and is evidence that both rearrangements have proceeded via a discrete carbonium ion. Both of these epoxides do, however, give a characteristic reaction not given by the other: the α-epoxide giving a product from acyl migration (190), and the β-epoxide giving a formyl derivative (199), formed by skeletal migration "across" the oxiran ring.



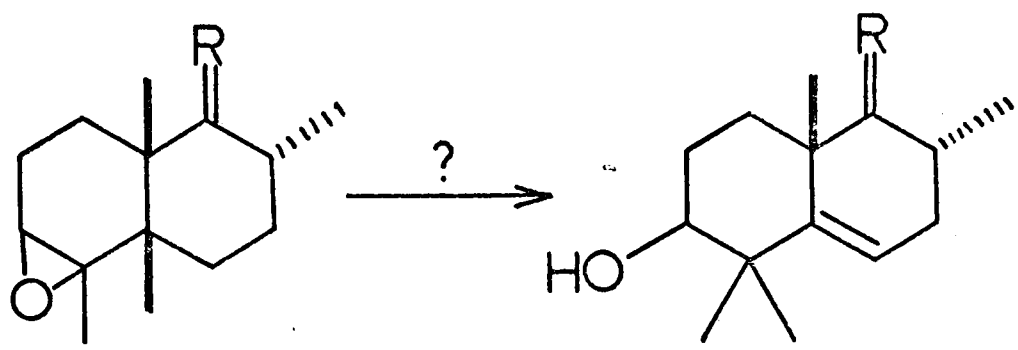
The formation of analogous formyl-derivatives has been observed with some 4β,5β- and 5β,6β-epoxy steroids.[70]





The formation of such compounds, like the formation of ketones by 1,2-hydride shifts, can often be rationalised by considering the conformation of the initially formed carbonium ion in the rearrangement, but such considerations can only indicate whether ketone or formyl formation is feasible, and it is often not clear why these reactions do or do not occur. One striking example from this work is the rearrangement of the tetramethyl decalone epoxide (93ii) which gave a quantitative yield of the formyl derivative (229). If the rearrangement had proceeded *via* a carbonium ion, other products from migration to the positive site might have been expected, and this result can only be explained by postulating the retention of a large amount of overlap between the oxiran oxygen orbitals and the orbitals at C5 while the migration of C6-C7 to C5 proceeds, *i.e.* the C-O bond cleavage and the skeletal migration are synchronous. Even if this is the case, it is not obvious why the molecule should show an overwhelming preference to rearrange in this way.

The tetramethyl decalin epoxides (92i), (93i), and (93ii) were rearranged with a view to obtaining a product of the type (231) by a simple methyl migration followed by deprotonation.



(92i) R = OH, H
ξ_1 epoxide

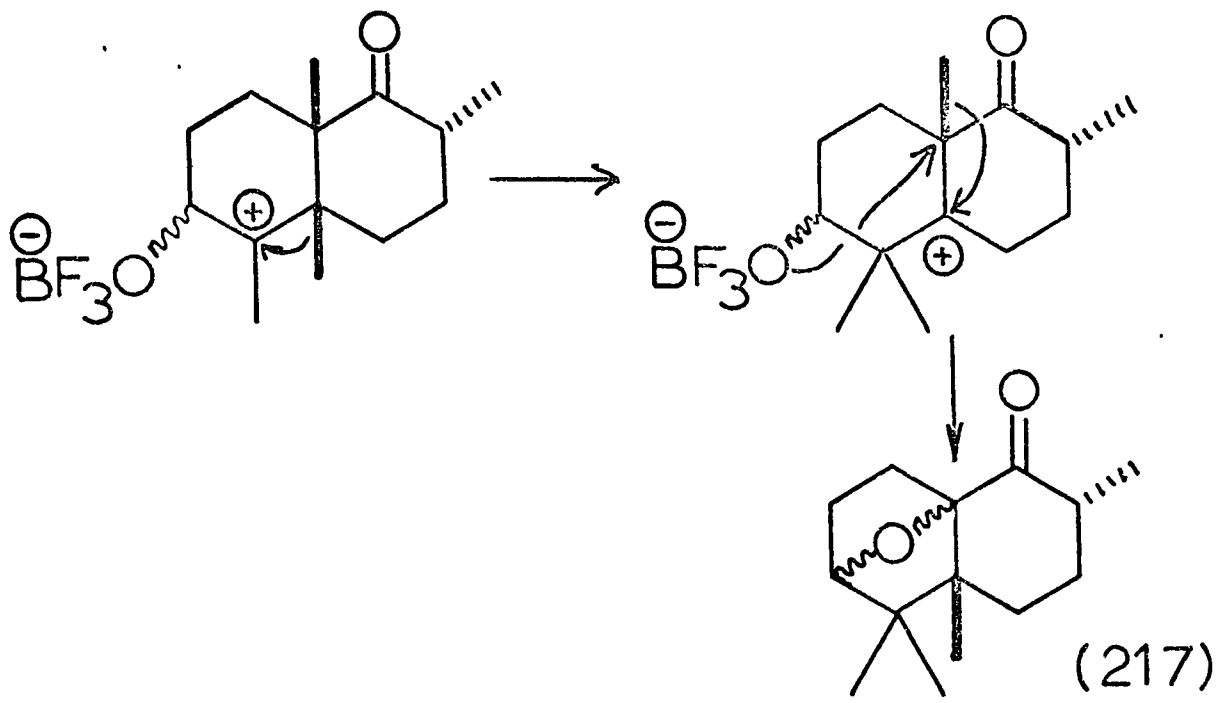
(93i) R = O
ξ_1 epoxide

(93ii) R = O
ξ_2 epoxide

(231)

Rearrangement of the decalol epoxide (92i) gave one product containing the desired gem-dimethyl group, but the methyl migration was followed by a fragmentation to give an aldehyde (208). Two other products were obtained by migration of other suitably aligned groups.

It was hoped that replacing the hydroxy-substituent by a keto-group (93i) would not affect the methyl migration, and would also prevent further migration and enhance the possibility of the deprotonation at C4; this was not found to be so, and although migration of the 10-methyl group to C5 was the predominant mode of rearrangement, the ion which it generated did not deprotonate as hoped, but rearranged further to give a species trapped as a cyclic ether (217).



(217)

As with the decalol ξ_1-epoxide (92i), other products were obtained from different initial migrations. Both epoxides gave ketones by 1,2-hydride shifts, and as with the formyl derivative (229) derived from the decalone ξ_2-epoxide (93ii), it is difficult to predict when such "localised" rearrangements will take place.

CHAPTER 4

Experimental Section

General

Spectroscopic Data

Infrared (i.r.) spectra were recorded on either a Unicam SP200 or SP 1000, or a Perkin-Elmer 257 spectrophotometer using dilute solutions in carbon tetrachloride or chloroform, in sodium chloride cells of path length 1 mm or 0.1 mm respectively.

Ultraviolet (u.v.) spectra were recorded on either a Unicam SP 800 or a Cary 14 spectrophotometer using solutions in ethanol in silica cells of 1 cm path length.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on either a Perkin-Elmer R 10 (60 MHz) or R 14 (100 MHz) machine using solutions in carbon tetrachloride or deuteriochloroform, as stated. Chemical shifts are quoted in τ units relative to tetramethylsilane as internal standard. The notation used to record n.m.r. spectra is: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, $W_{\frac{1}{2}}$ = width at half-height, J = coupling constant.

Mass spectra (m.s.) were recorded on either a Varian CH7 or A.E.I. MS9 machine.

Chromatography

Column chromatography was carried out using Laporte Industries Grade H alumina, deactivated where stated by the addition of 5% or 10% of a 10% solution of acetic acid in water.

Thin layer chromatography (t.l.c.) was carried out using 0.1 mm layers of unbaked Kieselgel $HF_{254 + 366}$ on glass plates (5 x 20, 10 x 20, and 20 x 20 cm). Plates were eluted with petroleum ether-ether mixtures, unless otherwise stated, and were viewed under a u.v. lamp and then developed by exposure to iodine vapour.

Preparative layer chromatography (p.l.c.) was carried out using 1 mm layers of unbaked Kieselgel $PF_{254 + 366}$ on glass plates (20 x 20 cm = small, 100 x 20 cm = large). Small plates were eluted once with methanol before use to remove plasticiser. Samples were applied to plates in ethereal solution using a syringe fitted with a 30 s.w.g. needle. Plates were eluted with petroleum ether-ether mixtures, unless otherwise stated, and were viewed under a u.v. lamp. Bands were extracted by placing the silica in a sinter funnel and percolating with ether or ethyl acetate. All solvents used for chromatography were distilled before use. The petrol fraction with b.p. 40-60° is referred to as "light petroleum", and the fraction with b.p. 60-80° as "petroleum ether".

Materials and Methods

Melting points were determined on a Kofler hot stage using transmitted light and are corrected.

Refractive indices were determined on an Abbé refractometer which was calibrated with distilled water.

Microanalyses were carried out under the supervision of Dr. F.B. Strauss.

Benzene and ether were dried by standing over sodium wire. Ethanol and t-butanol were dried by distillation from calcium hydride. Methyl vinyl ketone was dried by distillation, after cooling and treating with anhydrous calcium chloride followed by anhydrous potassium carbonate. Boron trifluoride-ether complex was purified by addition of ether and distillation from calcium hydride at reduced pressure; batches were redistilled immediately before use. Nitrogen was dried by passage through a column of coarse silica gel.

In the following text, the phrase "working up in the usual way" indicates that the reaction mixture was poured into water and extracted

with three portions of ether, unless otherwise stated, and the combined ethereal extracts were washed with either saturated aqueous sodium hydrogen carbonate solution or 2N-hydrochloric acid (as appropriate), followed by water and saturated brine; the aqueous washes were extracted with ether, and the combined ethereal extracts were dried over anhydrous magnesium sulphate. The solution was filtered and the solvent was removed on a rotary evaporator to give the reaction product.

Ethyl 2-Oxocyclopentanecarboxylate (110)[98]

Diethyl adipate was treated with sodium in benzene according to the method of Pinkney,[98] to give ethyl 2-oxocyclopentanecarboxylate as a sweet smelling liquid, b.p. 66-68°/0.05 mmHg, n_D^{21} 1.4515, yield 78% (lit.,[98] b.p. 108-111°/15 mmHg, n_D^{20} 1.4517, yield 79-82%).

Ethyl 2-Oxo-1-(3-oxobutyl)cyclopentanecarboxylate (116)[103a]

Ethyl 2-oxocyclopentanecarboxylate was treated with anhydrous methyl vinyl ketone in the presence of triethylamine in dry benzene, according to the method of Dauben and McFarland,[103a] to give ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate as a pale yellow liquid, b.p. 123-125°/0.15 mmHg, n_D^{20} 1.4649, yield 90%. The bis-semicarbazone (microcrystals from ethyl acetate-methanol)had m.p. 190-192° (Found: C, 49.6; H, 7.1; N, 24.7. Calc. for $C_{14}H_{24}N_6O_4$: C, 49.4; H, 7.1; N, 24.7%) (lit.,[103a] b.p. 140-142°/2.5 mmHg, n_D^{25} 1.4641, yield 92%, bis-semicarbazone m.p. 178-179°).

Ethyl 5-Oxo-5,6,7,8-tetrahydroindane-8β-carboxylate (118)[103b]

A stirred mixture of aluminium t-butoxide (46.2g, 0.19 mole) and ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate (28.6 g, 0.13 mole) in dry benzene (250 ml) under an atmosphere of dry nitrogen was heated under

reflux for 70 h. The mixture was poured into cold water (400 ml) to give a bulky flocculent precipitate. 10N-Hydrochloric acid (33 ml) was added, and the mixture was stirred until two phases separated. Working up in the usual way gave a yellow liquid (26.1 g), which was distilled to give ethyl 5-oxo-5,6,7,8-tetrahydroindane-8β-carboxylate (12.1 g, 46%) as a pale yellow liquid, b.p. 126-132°/0.4 mmHg, n_D^{20} 1.5022, $\lambda_{max.}$ (EtOH) 238 nm (ε 13,600) [lit.,[103b] b.p. 135°/2.7 mmHg, n_D^{20} 1.5007, $\lambda_{max.}$ (EtOH) 239 nm (ε 12,900), yield 34%].

Ethyl 4,4-Dimethyl-5-oxo-1,4,5,6,7,8-hexahydro-2H-indene-8β-carboxylate (124)

Potassium (6.7 g, 0.17 g atom) was dissolved in dry t-butanol with stirring and heating under dry nitrogen. This potassium t-butoxide solution was added to a stirred solution of ethyl 5-oxo-5,6,7,8-tetrahydroindane-8β-carboxylate (12.0 g, 0.06 mole) in dry t-butanol (150 ml) at 40° and the mixture became deep red. Immediately a solution of methyl iodide (21.7 ml, 0.35 mole) in dry t-butanol (25 ml) was added, and the stirred mixture was heated under reflux for 1 h under an atmosphere of dry nitrogen. Working up in the usual way gave a yellow oil (12.9 g) which was distilled to give a pale yellow liquid (10.3 g), b.p. 81-88°/0.05 mmHg, n_D^{18} 1.4910, $\nu_{max.}$ (CCl_4) 1720 (dimethyl product) and 1670 cm^{-1} (monomethyl product). This liquid was adsorbed on alumina (600 g, 5% deactivated). Elution with light petroleum yielded unidentified oils (1.89 g), and elution with light petroleum-benzene (9:1 - 1:1) yielded ethyl 4,4-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro-2H-indene-8β-carboxylate (124) (7.9 g, 58%) as a liquid, b.p. 81-82°/0.05 mmHg, n_D^{22} 1.4885, $\nu_{max.}$ (CCl_4) 2980, 2940, 1724, 1190, 1160, and 1060 cm^{-1}, τ (CCl_4) 4.37 (1H, t, J 2.4 Hz, $-CH=C-$), 5.84 (2H, q, J 6.9 Hz, $-CO_2CH_2CH_3$), 6.8-9.0 (8H, $-CH_2-$), 8.72 (3H, t, J 7.1 Hz,

-$CO_2CH_2C\underline{H}_3$), and 8.77 and 8.99 (6H, 2s, $C\underline{H}_3$-C-$C\underline{H}_3$) (Found: C, 71.3; H, 8.7. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%). The <u>semicarbazone</u> (prisms from aqueous ethanol) had m.p. 165-167° (Found: C, 61.1; H, 7.9; N, 14.5. $C_{15}H_{23}N_3O_3$ requires C, 61.4; H, 8.0; N, 14.3%). Further elution with light petroleum-benzene (1:3 - 1:7) first gave an unidentified oil (185 mg) and then ethyl 4-methyl-5-oxo-5,6,7,8-tetrahydroindane-8β-carboxylate (123) (678 mg, 5%) as a pale yellow liquid, homogeneous to t.l.c., $\lambda_{max.}$ (EtOH) 245 nm (ε 9,500), $\nu_{max.}$ (CCl_4) 2980, 1730, 1675, and 1190 cm^{-1}, τ (CCl_4) 5.86 (2H, q, <u>J</u> 6.9 Hz, -$CO_2C\underline{H}_2CH_3$), 7.0 - 9.0 (10H, -$C\underline{H}_2$-), 8.25 (3H, br s, $W_{\frac{1}{2}}$ 3.7 Hz, $C\underline{H}_3$-C=), and 8.75 (3H, t, <u>J</u> 7.1 Hz, -$CO_2CH_2C\underline{H}_3$). The <u>semicarbazone</u> (pale yellow needles from ethylacetate-methanol) had m.p. 180-189° (Found: C, 60.0; H, 7.6; N, 14.8. $C_{14}H_{21}N_3O_3$ requires C, 60.2; H, 7.5; N, 15.0%).

<u>Attempted Methylation of Cyclopentanone</u>

Sodium hydride (12 g, 0.5 mole) was slurried with dry dimethyl sulphoxide (distilled from calcium hydride; 300 ml), and cyclopentanone (42 g, 0.5 mole) was added to give a mobile semi-solid mixture which was stirred at 25° for 1 h under an atmosphere of dry nitrogen. Methyl iodide (79.2 g, 0.55 mole) was added over 1 h, with cooling and stirring and the white suspension was stirred for a further 1.5 h. Working up in the usual way gave a pale yellow liquid (37.5 g) which was heated to 150° at atmospheric pressure without yielding any 2-methylcyclopentanone (b.p. 139-142°/760 mmHg). Distillation under reduced pressure gave 2-(<u>cyclopent</u>-1-<u>enyl</u>)-2-<u>methylcyclopentanone</u> (114) (23.1 g) as a pale yellow liquid, b.p. 105-108°/14 mmHg, n_D^{20} 1.4919, $\nu_{max.}$ (CCl_4) 2980, 1740, 1640, 1455, 1460, 1372, 1175, and 1060 cm^{-1}, τ(CCl_4) 4.55 (1H, m, $W_{\frac{1}{2}}$ 4.0 Hz, -C<u>H</u>=C-), 7.0 - 8.6 (12H, -$C\underline{H}_2$-), and 8.89 (3H, s, $C\underline{H}_3$-C-) (Found: C, 80.3; H, 9.7%; $\underline{M}^+$ 164. $C_{11}H_{16}O$ requires C, 80.5; H, 9.8%;

M 164). The semicarbazone (microcrystals from ethyl acetate-methanol) had m.p. 191-194° (Found: C, 64.9; H, 8.9; N. 18.9%. $C_{12}H_{19}N_3O$ requires C, 65.2; H, 8.6; N, 19.0%).

Ethyl 1-Methyl-2-oxocyclopentanecarboxylate (112)

Ethyl 2-oxocyclopentanecarboxylate (132 g, 0.85 mole) was added to a stirred solution of sodium hydroxide (33.4 g, 0.85 mole) in methanol (363 ml) and water (53 ml) at 25°. The resulting yellow solution was cooled to 15° to give a white slurry. Freshly distilled dimethyl sulphate (113 g, 0.9 mole) was added over 3 h. Removal of the methanol left a white paste which was dissolved in a minimum amount of water and worked up in the usual way to give crude ethyl 1-methyl-2-oxocyclopentanecarboxylate (102 g, 71%) as a yellow liquid; this was decarboxylated without further treatment.

2-Methylcyclopentanone[100]

Crude ethyl 1-methyl-2-oxocyclopentanecarboxylate (102 g) was heated under reflux with 30% (v/v) sulphuric acid (300 ml), until carbon dioxide evolution ceased. Working up in the usual way gave a yellow liquid (38.1 g) which was distilled to give 2-methylcyclopentanone (31.1 g, 37% over two stages) as a pale yellow liquid, b.p. 138-140°/765 mmHg, n_D^{18} 1.4366 (lit.,[100] b.p. 139-142°/760 mmHg, n_D^{20} 1.4364, yield 37%).

9-Hydroxy-8β-methylhexahydroindan-5-one (121)

Sodium ethoxide solution (1.76 ml of a solution prepared by dissolving 5.75 g sodium in 83 ml ethanol) was added to stirred 2-methylcyclopentanone (28.8 g, 0.29 mole) maintained at -15° under dry nitrogen. Dry methyl vinyl ketone (20.5 g, 0.29 mole) was added

over 3.5 h with continued cooling and stirring. The mixture was stirred at -10° for a further 2 h. Working up in the usual way gave an orange liquid (34.5 g), containing several components (t.l.c.), $\nu_{max.}$ (CCl_4) 3620, 3490, 1745, and 1705 cm^{-1}. This material was dehydrated without further purification.

8β -Methyl-5,6,7,8-tetrahydroindan-5-one (119)

The crude ketol (34.5 g) was heated under reflux with toluene p-sulphonic acid (10 g) in dry benzene(120 ml) with a Dean and Stark water separator. After 3 h, 4.2 ml water had been collected, and the mixture was cooled and worked up in the usual way to give a viscous red liquid (20.4 g) which was distilled to give a pale yellow liquid (10.1 g), b.p. 90°/0.15 mmHg, containing one major and three minor components (t.l.c.). This liquid was adsorbed onto alumina (300 g, 5% deactivated). Elution with light petroleum-ether (1:1) gave the three minor components as a yellow oil (2.4 g), and then 8β -methyl-5,6,7,8-tetrahydroindan-5-one (7.1 g, 16% over two stages) as a pale yellow liquid, b.p. 90-92°/0.15 mmHg, n_D^{14} 1.5146, $\lambda_{max.}$ (EtOH) 241 nm (ε 10,300) (lit.,[89] b.p. 112°/4 mmHg, n_D^{22} 1.4989). The semicarbazone (microcrystals from ethylacetate-methanol) had m.p. 193-196° (decomp.) (Found: C, 63.9; H, 8.4; N, 20.4. Calc. for $C_{11}H_{17}N_3O$: C, 63.8; H, 8.2; N, 20.3%) (lit.,[89] m.p. 205°).

8β -Methyl-5,6,7,8-tetrahydroindan-5-one One Step.

A mixture of 2-methylcyclopentanone (5.46 g), freshly distilled methyl vinyl ketone (4.88 g), and three drops of conc. sulphuric acid was heated under reflux for 16 h. The mixture was cooled, diluted with hexane (20 ml), washed with 5% aqueous sodium hydroxide solution, and dried over magnesium sulphate. Removal of the solvent gave a red liquid

(7.12 g), which was distilled to give a pale yellow liquid (3.42 g), b.p. 72-80°/0.4 mmHg, $\nu_{max.}$ (CCl_4) 2950, 1730, 1710, and 1670 cm^{-1}. This liquid was adsorbed onto alumina (400 g, 5% deactivated). Elution with light petroleum-ether mixtures yielded crude 2-methyl-2-(3-oxobutyl)-cyclopentanone (122) as a pale yellow liquid (244 mg), $\nu_{max.}$ (CCl_4) 2950, 1746, 1710, 1460, 1380, and 1095 cm^{-1}. Further elution gave 8β-methyl-5,6,7,8-tetrahydroindan-5-one (1.64 g 20%) as a pale yellow liquid, identical (t.l.c., i.r., n.m.r., and n_D) with the sample obtained above. Further elution gave a pale yellow oil (181 mg), thought to be crude 9-hydroxy-8-methylhexahydroindan-5-one (121), $\nu_{max.}$ (CCl_4) 3500, 2950, 1725, 1460, 1410, 1370, and 1160 cm^{-1}.

4,4,8β-Trimethyl-1,6,7,8-tetrahydro-2H-inden-5(4H)-one (127)

i) Using potassium t-butoxide. Potassium t-butoxide solution was prepared by dissolving potassium (5.5 g, 0.14 g atom) in dry t-butanol (120 ml) with stirring and warming under dry nitrogen, and the solution was added to a stirred solution of 8-methyl-5,6,7,8-tetrahydroindan-5-one (7.1 g, 0.047 mole) in dry t-butanol at 50° to give a clear orange solution. After 1 minute, a solution of methyl iodide (40.3 g, 0.28 mole) in dry t-butanol (20 ml) was added and the resulting milky white suspension was stirred and heated under reflux for 1 h. Working up in the usual way gave an orange liquid (7.45 g) which was adsorbed onto alumina (600 g, 5% deactivated). Elution with light petroleum-ether mixtures gave a liquid (580 mg) whose n.m.r. and m.s. indicated that it contained tri- and tetra-methylated products (m/e 192, 206). Further elution gave 4,4,8-trimethyl-1,6,7,8-tetrahydro-2H-inden-5(4H)-one (2.53 g, 30%) as a sweet smelling liquid, n_D^{15} 1.4935, $\nu_{max.}$ (CCl_4) 2960, 1715, 1460, 1380, and 1150 cm^{-1}, τ(CCl_4) 4.58 (1 H, t, J 2.2 Hz, -CH=C-), 7.0-9.0 (8 H, $-CH_2-$), and 8.78 (9 H, br s, 3 CH_3-C-) (lit., [145] n_D^{22} 1.4838). The semicarbazone (plates from ethyl

acetate-methanol) had m.p. 177-183° (Found: C, 66.4; H, 8.9; N, 17.6%. Calc. for $C_{13}H_{21}N_3O$: C, 66.4; H, 8.9; N, 17.9%) (lit.,[150] m.p. 194°). Further elution gave 4,8-dimethyl-5,6,7,8-tetrahydroindan-5-one (126) (2.35 g, 30%) as a sweet smelling liquid, n_D^{15} 1.5128, $\lambda_{max.}$ (EtOH) 250 nm (ε 10,500), $\nu_{max.}$ (CCl_4) 2970, 1666, 1460, 1378, 1350, 1328, and 1295cm^{-1}, τ (CCl_4) 7.0-9.0 (10H, -C<u>H</u>$_2$-), 8.32 (3H, br s, C<u>H</u>$_3$-C=), and 8.89 (3H, s, C<u>H</u>$_3$-C-) (lit.,[151] n_D^{23} 1.5033). The semicarbazone (plates from ethyl acetate-methanol) had m.p. 191-194° (Found: C, 65.1; H, 8.7; N, 18.8. Calc. for $C_{12}H_{19}N_3O$: C, 65.2; H, 8.6; N, 19.0%) (lit.,[151] m.p. 208°).

ii) Using potassium t-amyloxide. Potassium (2.5 g, 0.064 g atom) was dissolved in dry t-amyl alcohol (10.6 ml, 0.12 mole) in dry benzene (100 ml) with stirring and warming under dry nitrogen. On cooling, a waxy solid separated, and this was redissolved by addition of 20 ml dry benzene. This solution was cooled to 0° and a solution of 8-methyl-5,6,7,8-tetrahydroindan-5-one (3.2 g, 0.021 mole) in dry benzene (10 ml) was added slowly, and the mixture went from yellow to very deep red. The solution was kept at 55° for 0.5 h, and then cooled to 25°. Methyl iodide (18.4 g, 0.128 mole) in dry benzene (10 ml) was added and the dark solution was heated under reflux for 3 h to give a cloudy white solution. Working up in the usual way gave a red liquid (3.64 g) which was adsorbed onto alumina (180 g, 5% deactivated). Elution with light petroleum-ether mixtures gave a mixture of the tri- and tetra-methylated compounds (2.66 g), followed by 4,8-dimethyl-5,6,7,8-tetrahydroindan-5-one (405 mg), homogeneous by t.l.c. and identical with material obtained above.

The first fraction was purified by p.l.c. (5 large plates, 1 elution with petroleum ether-ether, 4:1). The upper band gave 4,4,6,8β-tetramethyl-1,2,4,6,7,8-hexahydroinden-5-one (128) (1.38 g, 34%) as an oil, homogeneous by t.l.c., τ (CCl_4) 4.55 (1H, m,

-C<u>H</u>=C-), 7.0-8.5 (7H, -C<u>H</u>$_2$-), and 8.6-9.1 (12H, complex methyl region), <u>m/e</u> 192 ($C_{13}H_{20}O$). The lower band gave 4,4,8-trimethyl-1,6,7,8-tetrahydro-2<u>H</u>-inden-5(4<u>H</u>)-one (1.28 g, 34%), homogeneous by t.l.c. and identical with the material obtained above.

<u>Reduction of Ethyl</u> 4,4-<u>Dimethyl</u>-5-<u>oxo</u>-1,4,5,6,7,8-<u>hexahydro</u>-2H-<u>indene</u>-8β-<u>carboxylate</u> (124)

i) <u>Excess of Sodium Borohydride</u>

A solution of the keto-ester (124) (4.15 g, 0.018 mole) and sodium borohydride (1.0 g, 0.026 mole) in dry ethanol (50 ml) was stirred at 25° for 18 h and then poured into water (80 ml). Working up in the usual way gave a pale yellow oil (3.97 g) containing three components (t.l.c.) which was adsorbed on alumina (150 g, 5% deactivated). Elution with petroleum ether-benzene mixtures gave a colourless oil (514 mg), thought to be a mixture of ethyl 5β-hydroxy-4,4-dimethyl-1,4,5,6,7,8-hexahydro-2<u>H</u>-indene-8β-carboxylate (132) and 4,4-dimethyl-1,4,5,6,7,8-hexahydro-2<u>H</u>-indene-8β,5β-carbolactone (133), $\nu_{max.}$ (CCl_4) 3580, 3450, 1755, 1715, 1464, 1369, 1351, 1160, 1075, and 1050 cm^{-1}. Elution with benzene gave an oil (1.34 g) which was largely the hydroxy-ester (132) with a small amount of lactone (133), $\nu_{max.}$ (CCl_4) 3650, 3530, 2950, 1755, 1718, 1460, 1390, 1370, 1182, 1162, 1062, 1040, and 873 cm^{-1}. Elution with ether gave 8β-<u>hydroxymethyl</u>-4,4-<u>dimethyl</u>-1,4,5,6,7,8-<u>hexahydro</u>-2H-<u>inden</u>-5β-<u>ol</u> (134) (65 mg) as platelets (from ether-acetone) m.p. 142-143°, $\nu_{max.}$ ($CHCl_3$) 3540, 3420, 2900, 1470, and 1386 cm^{-1}, τ($CDCl_3$) 4.28 (1H, t, <u>J</u> 2.4 Hz, -C<u>H</u>=C-), 6.38 (2H, ABq, <u>J</u> 11.1 Hz, -C<u>H</u>$_2$OH), 6.65 (1H, t, <u>J</u> 7.6 Hz, -C<u>H</u>-OH), 7.4-8.7 (10H, -C<u>H</u>$_2$- and -OH), and 8.77 and 8.98 (6H, 2s, C<u>H</u>$_3$-C-C<u>H</u>$_3$) (Found: C, 73.4; H, 10.2. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.2%).

ii) Stoicheiometric amount of Sodium Borohydride.

A solution of keto-ester (124) (1.87 g, 0.008 mole) and sodium borohydride (150 mg, 0.004 mole) in dry ethanol (25 ml) was kept at 0° for 4 h. After addition of 2N-hydrochloric acid to pH 6, usual work up gave ethyl 5β-hydroxy-4,4-dimethyl-1,4,5,6,7,8-hexahydro-2H-indene-8β-carboxylate (1.68 g, 90%) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3630, 3540, 1730, 1470, 1440, 1386, 1366, 1180, and 1040 cm^{-1}, τ(CCl_4) 4.42 (1H, t, J 2.2 Hz, -CH=C-), 5.92 (2H, q, J 7.3 Hz, $-CO_2CH_2CH_3$), 6.82 (1H, 2d, J 6.9, 8.6 Hz, -CHOH), 7.2-9.0 (9H, $-CH_2-$ and -OH), 8.76 (3H, t, J 7.1 Hz, $-CO_2CH_2CH_3$), and 8.82 and 9.11 (6H, 2 s, CH_3-C-CH_3), m/e 238 ($C_{14}H_{22}O_3$).

iii) Lithium Aluminium Hydride

The keto-ester (124) (2.13 g, 0.009 mole) in dry ether (10 ml) was added to a stirred slurry of lithium aluminium hydride (1.03 g, 0.027 mole) in dry ether (10 ml) at such a rate that the ether boiled gently. The stirred mixture was heated under reflux for 2 h. Ethyl acetate was added cautiously to the cooled mixture to destroy excess of lithium aluminium hydride, and the usual work up gave 8β-hydroxymethyl-4,4-dimethyl-1,4,5,6,7,8-hexahydro-2H-inden-5β-ol (1.68 g, 95%) identical with the diol obtained in (i) above.

4,4,8β-Trimethyl-1,4,5,6,7,8-hexahydro-2H-inden-5-ol (135)

A solution of 4,4,8β-trimethyl-1,6,7,8-tetrahydro-2H-inden-5(4H)-one (966 mg, 0.005 mole) in dry ether (10 ml) was added to a stirred slurry of lithium aluminium hydride (105 mg, 0.0027 mole) in dry ether (10 ml) over 0.25 h. The stirred mixture was heated under reflux for 2 h, and excess of lithium aluminium hydride was destroyed by cautious addition of ethyl acetate to the cooled mixture. The usual work up gave an oil

(922 mg) which was purified by p.l.c. (2 large plates, one elution with benzene-ether 1:1). The main band yielded 4,4,8β-trimethyl-1,4,5,6,7,8-hexahydro-2H-inden-5-ol (648 mg, 67%) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3630, 3500, 1460, 1380, 1370, 1360, and 1040 cm^{-1}, τ(CCl_4) 4.61 (1H, t, J 2.5 Hz, -CH=C-), 6.79 (1H, complex, m, -CH-OH, α and β), 7.30 (1H, s, exchangeable, -OH), 7.4-9.2 (8H, $-CH_2-$), and 8.86 and 9.00 (9H, br s, s, 3 CH_3-C-) (Found: C, 79.8; H, 11.1. $C_{12}H_{20}O$ requires C, 80.0; H, 11.1%).

1,1,10β-Trimethyl-Δ^8-octal-2-ol (137)

A solution of 1,1,10β-trimethyl-Δ^8-octal-2-yl benzoate (64 g, 0.21 mole) and sodium hydroxide (43.5 g, 1.1 mole) in ethanol (475 ml) and water (25 ml) was stirred and heated under reflux for 4 h, during which time a buff solid precipitated. The mixture was cooled, and water (200 ml) was added. Working up in the usual way gave a dark red oil (41.9 g) containing several components (t.l.c.). This oil was adsorbed onto alumina (1.8 kg, 5% deactivated); elution with light petroleum-ether mixtures gave unreacted ester (16.2 g) followed by unidentified yellow oils (11.7 g), and finally 1,1,10β-trimethyl-Δ^8-octal-2-ol (9.0 g) as a pale yellow oil, homogeneous to t.l.c.; $\nu_{max.}$ (CCl_4) 3630, 3500, 2970, 1468, 1383, 1370, 1033, and 945 cm^{-1}, τ(CCl_4) 4.54 (1H, m, $W_{\frac{1}{2}}$ 8.6 Hz, -CH=C-), 6.7 (1H, complex m, -CHOH, α and β), 7.26 (1H, s, exchangeable, -OH), 7.6-9.0 (10H, $-CH_2-$), 8.86, 8.92, and 9.01 (9H, 3 s, 3 CH_3-C-).

1,1,10β-Trimethyl-Δ^8-octal-2-one (138)

Jones reagent (prepared in the usual way, p. 156; 16 ml) was added slowly to a stirred solution of 1,1,10β-trimethyl-Δ^8-octal-2-ol (137) (8.99 g) in A.R. acetone (100 ml) at 25° to give an orange-brown solution. After destroying excess of chromic acid by addition of sodium metabisulphite

solution, working up in the usual way gave 1,1,10β -trimethyl-Δ^8-octal-2-one (138) (6.88 g, 77%) as a liquid, n_D^{17} 1.5011, b.p. 61-63°/0.3 mmHg. The 2,4-dinitrophenylhydrazone (orange plates from ethyl acetate-methanol) had m.p. 155-166° (Found: C, 61.1; H, 6.5; N, 14.9%; M^+ 372. $C_{19}H_{24}N_4O_4$ requires C, 61.3; H, 6.45; N, 15.05%; M 372) (lit.,[112b] b.p. 62-64°/0.25 mmHg, n_D^{16} 1.5060).

Hydrogenation of "C_{14}-Aldehyde" (139)

The "C_{14}-aldehyde", 2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)-but-2-en-1-al (8.0 g) was hydrogenated in acetone (A.R.; 200 ml) using 5% palladium on charcoal (1.2 g). After absorption of 500 ml hydrogen at atmospheric pressure, the hydrogenation was stopped, and the catalyst was removed by filtration. Removal of the solvent gave crude 2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)butan-1-al (89) (8.0 g) as a pale yellow liquid, which was carried on to the next stage without further treatment; the n.m.r. spectrum showed 93% conversion to the dihydro-product.

2α,5,9β,10β -Tetramethyl-Δ^5-octal-1β -ol (90)[87]

85% Phosphoric acid (16.0 ml) was added slowly to the stirred dihydro-C_{14}-aldehyde (16.0 g), to give a viscous red oil, which was left at 25° for 24 h. The resulting red solid was broken up and washed with cold water (3 x 100 ml), and was added to water + ether (100 ml each) and stirred until it had dissolved. The aqueous phase was extracted with ether (3 x 100 ml) and the combined organic phases were washed with 2M-sodium hydroxide solution, water, and brine, and then dried over anhydrous magnesium sulphate. Removal of the solvent gave an orange oil (14.8 g) which was dissolved in light petroleum (30-40° fraction, AR; 30 ml); cooling in an acetone/CO_2 bath accompanied by scratching the flask wall gave a precipitate of 2α,5,9β,10β -tetramethyl-Δ^5-octal-1β -ol

(2.24 g) as prisms (from light petroleum), m.p. 78-80°, $\nu_{max.}$ (CCl_4) 3520, 2940, 1456, 1372, and 1010 cm^{-1}, τ(CCl_4) 4.62 (1H, m, -C<u>H</u>=C-), 6.72 (1H, d, <u>J</u> 10 Hz, -C<u>H</u>OH-), 8.40 (3H, m. C<u>H</u>$_3$-C=), 8.91 (1H, s, disappears with D_2O, -CHO<u>H</u>-), 9.06 (3H, d, <u>J</u> 6 Hz, C<u>H</u>$_3$-CH-), and 9.07 and 9.15 (6H, 2 s, 2C<u>H</u>$_3$-C-) (Found: C, 80.8; H, 11.6. Calc. for $C_{14}H_{24}O$: C, 80.8; H, 11.5%) (lit.,[87] m.p. 79-81°). The mother liquors from the above precipitation afforded a red oil (12.0 g), which was adsorbed on alumina (800 g, 10% deactivated). Elution with light petroleum and light petroleum-ether mixtures first gave unidentified yellow oils (1.7 g) and then the octalol (89) (3.8 g), identical with the sample obtained above (m.p., i.r., n.m.r., and t.l.c.).

<u>Oxidation of</u> 2α,5,9β , 10β -<u>Tetramethyl</u>-Δ^5-<u>octal</u>-1β -<u>ol</u> (90)

Jones reagent was prepared by dissolving chomium trioxide (2.67 g) in <u>conc</u>. sulphuric acid (2.3 ml) and adding water (6.7 ml) to give a deep red solution. This solution was added dropwise to a stirred solution of the octalol (89) (5.0 g) in acetone (A.R.; 50 ml) until a permanent red-brown colour obtained. The excess of chromic acid was destroyed by adding a few drops of 10% sodium metabisulphite solution, and water and ether (100 ml each) were added. Working up in the usual way gave a pale yellow oil (4.6 g), which was adsorbed on alumina (500 g, 10% deactivated). Elution with light petroleum and light petroleum-ether mixtures gave 2α,5,9β ,10β -<u>tetramethyl</u>-Δ^5-<u>octal</u>-2-<u>one</u> (142) (3.7 g) as a liquid, n_D^{19} 1.4976, $\nu_{max.}$ (CCl_4) 2960, 1708, 1455, 1374, and 1035 cm^{-1}, τ(CCl_4) 4.64 (1H, m, -C<u>H</u>=C-), 7.2-9 (9H, -C<u>H</u>$_2$-), 8.39 (3H, m, C<u>H</u>$_3$-C=), 8.97, 8.99 (6H, 2 s, 2 C<u>H</u>$_3$-C-), and 9.07 (3H, d, <u>J</u> 6 Hz, C<u>H</u>$_3$-CH-) (Found: C, 81.2; H, 10.6. $C_{14}H_{22}O$ requires: C, 81.55; H, 10.7%).

p-Nitroperbenzoic Acid[131]

Hydrogen peroxide ("High Test" 87%, 18 g) was added over 0.5 h to a stirred slurry of p-nitrobenzoic acid (22.8 g) in methanesulphonic acid (65 g) at 40°, and the mixture was stirred at 40° for a further 3 h, during which time the pale yellow peracid precipitated. The mixture was cooled and crushed ice (45 g) was added, and the peracid was filtered off and washed with cold water and dried in vacuo to give pale yellow plates (23.7 g, 94%), m.p. 136-138° (dec.), purity by iodometric titration 93% [lit.,[131] yield 90%, m.p. 138° (dec.), purity 95%].

Formation of Epoxides; General Procedure.

Epoxidation was carried out using either p-nitroperbenzoic acid (prepared) or m-chloroperbenzoic acid (commercial), in chloroform at room temperature. The following procedure is standard, and will be referred to as "Epoxidation in the usual way".

Epoxidation of Ethyl 4,4-Dimethyl-5-oxo-1,4,5,6,7,8-hexahydro-2H-indene-8β-carboxylate (124)

m-Chloroperbenzoic acid (1.8 g, 10 m mole) in chloroform (25 ml) was added to a stirred solution of the keto-ester (124) (1.87 g, 8 m-mole) in chloroform (25 ml) at 20°, and the mixture was left for 6 h. Excess of peracid was destroyed by careful addition of 10% sodium sulphite solution (monitored using starch-iodide indicator paper), and working up in the usual way gave an oil (1.87 g) containing two components (t.l.c.), which was applied to four large p.l.c. plates and eluted twice with light petroleum: ether (3:1). Extraction of the upper band gave ethyl $3\xi_1$, $9\xi_1$-epoxy-4,4-dimethyl-5-oxohexahydroindane-8β-carboxylate (82i) (1.24 g, 62%) as an oil which crystallised on standing to give needles (from aqueous methanol) m.p. 49-50°, $\nu_{max.}$ (CCl_4) 2960, 1725,

1460, 1385, 1368, 1190, 1160, and 947 cm^{-1}, $\tau(CCl_4)$ 5.84 (2H, ABC_3 m, J_{AC} 7.2, J_{AB} 10.9 Hz, $-CO_2\underline{CH}_2CH_3$), 6.51 (1H, s, oxiran-H), 7.0-9.0 (8H, m, $-\underline{CH}_2-$), 8.70, (3H, t, J 7.2 Hz, $-CO_2CH_2\underline{CH}_3$), and 8.90 and 9.10 (6H, 2 s, $\underline{CH}_3-C-\underline{CH}_3$) (Found: C, 66.6; H, 7.8; M^+ 252. $C_{14}H_{20}O_4$ requires C, 66.7; H, 7.9%; M 252). The lower band gave ethyl $3\xi,9\xi$-epoxy-4,4-dimethyl-5-oxohexahydroindane-8β-carboxylate (82ii) (272 mg, 14%) as an oil which crystallised on standing to give bulky prisms (from hexane) m.p. 53.5-54.5°, $\nu_{max.}$ (CCl_4) 2960, 1725, 1460, 1385, 1368, 1190, 1160, and 945 cm^{-1}, $\tau(CCl_4)$ 5.78 (2H, q, J 6.9 Hz, $-CO_2\underline{CH}_2CH_3$), 6.71 (1H, br s, $W_{\frac{1}{2}}$ 2.7 Hz, oxiran-H), 7.0-9.0 (8H, m, $-\underline{CH}_2-$), 8.68 (3H, t, J 7.1 Hz, $-CO_2CH_2\underline{CH}_3$), and 8.89 and 9.15 (6H, 2 s, $\underline{CH}_3-C-\underline{CH}_3$) (Found: C, 66.9; H, 7.8%; M^+ 252. $C_{14}H_{20}O_4$ requires C, 66.7; H, 7.9%, M 252).

Treatment of keto-ester (124) with p-nitroperbenzoic acid under similar conditions gave a qualitatively and quantitatively similar product.

Epoxidation of Ethyl 5β-Hydroxy-4,4-dimethyl-1,4,5,6,7,8-hexahydro-2H indene-8β-carboxylate and 4,4-dimethyl-1,4,5,6,7,8-hexahydro-2H-indene-8β,5β-carbolactone (132) and (133).

Treatment of a mixture of the hydroxy-ester (132) and lactone (133) (1.68 g) with p-nitroperbenzoic acid (1.42 g) in the usual way gave a pale yellow oil (1.63 g) containing three components (t.l.c.), which was adsorbed on alumina (100 g, 5% deactivated). Elution with light petroleum-benzene and benzene-ether mixtures first yielded an identified yellow oil (103 mg) and then $3\xi,9\xi$-epoxy-4,4-dimethylhexahydroindane-8β,5β-carbolactone (87) (116 mg) as bulky prisms (from light petroleum-ether) m.p. 99-101°, $\nu_{max.}$ (CCl_4) 3020, 1755, 1360, 1110, and 940 cm^{-1}, τ (CCl_4) 5.7 (1H, br s, $W_{\frac{1}{2}}$ 6.0 Hz, -CO-O-$\underline{CH}$), 6.49 (1 H, s, oxiran-H), 7.5-8.5 (8H, m, $-\underline{CH}_2-$), and 8.91 and 8.97 (6 H, 2s, $\underline{CH}_3-C-\underline{CH}_3$) (Found:

C, 69.3; H, 7.7%; $\underline{M}^+$ 208. $C_{12}H_{16}O_3$ requires C, 69.4; H, 7.7%; $\underline{M}$ 208). Further elution gave ethyl $3\xi_1,9\xi_1$-epoxy-5β-hydroxy-4,4-dimethyl-hexahydroindane-8β-carboxylate (83i) (260 mg) as plates (from ether) m.p. 89-90°, $\nu_{max.}$ (CCl_4) 3640, 2990, 2950, 1725, 1360, and 910 cm^{-1}, τ ($CHCl_3$) 5.85 (2H, m, $-CO_2\underline{CH}_2CH_3$), 6.35 (1H, m, $-C\underline{H}OH-$), 6.44 (1H, s, oxiran-H), 7.3-9.0 (8H, m, $-\underline{CH}_2-$), 8.72 (3H, t, J 7.1 Hz, $-CO_2CH_2\underline{CH}_3$), and 9.06 (6H, br s, $\underline{CH}_3-C-\underline{CH}_3$) (Found: C, 66.2; H, 8.7%; $\underline{M}^+$ 254. $C_{14}H_{22}O_4$ requires C, 66.2; H, 8.7%; $\underline{M}$ 254).

Epoxidation: Ethyl 5β-Hydroxy-4,4-dimethyl-1,4,5,6,7,8-hexahydro-2H-indene-8β-carboxylate (132)

Treatment of the hydroxy-ester (132) (591 mg) with p-nitroperbenzoic acid in the usual way gave a yellow oil (530 mg) containing two components (t.l.c.). This oil was applied to one large p.l.c. plate and eluted once with benzene-ether (1:1). Extraction of the upper band gave ethyl $3\xi_1$, $9\xi_1$-epoxy-5β-hydroxy-4,4-dimethylhexahydroindane-8β-carboxylate (83i) (254 mg) as an oil which crystallised on standing to give a sample identical with the hydroxy-ester ξ_1-epoxide obtained above (n.m.r., i.r., t.l.c., and m.p.). The lower band gave ethyl $3\xi_2$, $9\xi_2$-epoxy-5β-hydroxy-4,4-dimethylhexahydro-indane-8β-carboxylate (83ii) (150 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3640, 1725, 1190, 1080, and 870 cm^{-1}, τ (CCl_4) 5.84 (2H, q, J 7.1 Hz, $-CO_2\underline{CH}_2CH_3$), 6.6 (1H, m, $C\underline{H}OH$), 6.77 (1H, br s,), 7.5-9.0 (8H, m, $-\underline{CH}_2-$), 8.70 (3H, t, J 7.1 Hz, $-CO_2CH_2\underline{CH}_3$), and 9.15 (6H, br s, $\underline{CH}_3-C-\underline{CH}_3$), m/e 254. No satisfactory analysis could be obtained.

Epoxidation of 8β-Hydroxymethyl-4,4-dimethyl-1,4,5,6,7,8-hexahydro-2H-inden-5β-ol (134)

Treatment of the diol (134) (565 mg) with p-nitroperbenzoic acid

(633 mg) in the usual way gave 3ξ,9ξ-epoxy-8β-hydroxymethyl-4,4-dimethyl-hexahydroindan-5β-ol (84i) (457 mg) as rods (from hexane-ethyl acetate) m.p. 132-133°, $\nu_{max.}$ ($CHCl_3$) 3680sh, 3540br, 3000, 1604, 1480, 960, and 900 cm^{-1}, τ($CHCl_3$) 6.18 (2H, ABq, J 10.8 Hz, -CH_2OH), 6.53 (1H, 2 d, J 6.8, 8.9 Hz, -CHOH-), 6.57 (1H, br s, oxiran-H), 7.5-9.0 (10H, m, -CH_2-OH), and 8.90 and 9.10 (6H, 2 s, CH_3-C-CH_3) (Found: C, 68.2; H, 9.3%; M^+ 212. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.4%, M 212).

Epoxidation of 4,4,8β-Trimethyl-1,6,7,8-tetrahydro-2H-inden-5(4H)-one (127)

Treatment of the keto-olefin (127) (1.08 g) with p-nitroperbenzoic acid (1.22 g) in the usual way gave a mixture of 3α,9α-epoxy- and 3β,9β-epoxy-4,4,8β-trimethylhexahydroindan-5-one (85) (983 mg) as an oil, apparently homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2980, 1714, 1465, 1380, 1115, and 870 cm^{-1}, τ(CCl_4) 6.67, 6.71 (1H, 2 overlapping br s, oxiran-H, α and β), 7.0-9.0 (8H, -CH_2-), 8.72, 8.76, 8.78 (6H, 3 s, overlapping, CH_3-C-CH_3 in α- and β-epoxides), and 9.15 and 9.15 (3H, 2 s, CH_3-C- in α- and β-epoxides) (Found: C, 73.9; H, 9.3%; M^+ 194. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%; M 194). Attempts to separate the two epoxides by multiple elution p.l.c. were not successful.

Epoxidation of 4,4,8β-Trimethyl-1,4,5,6,7,8-hexahydro-2H-inden-5-ol (135)

Treatment of the hydroxy-olefin (135) (603 mg) with m-chloroperbenzoic acid (636 mg) in the usual way gave an oil (617 mg) containing two components (t.l.c.). This oil was applied to two large p.l.c. plates and eluted eight times with petroleum ether-ether (2:1). Extraction of the upper band gave 3ξ,9ξ-epoxy-4,4,8β-trimethylhexhydroinden-5ξ_1-ol (86i) (344 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3630, 3500, 2940, 1460, 1370, 1040, 950, and 868 cm^{-1}, τ(CCl_4) 6.5 (1H, m,

-C<u>H</u>OH-), 6.75 (1H, br s, $W_{\frac{1}{2}}$ 2 Hz, oxiran-H), 7.56 (1H, br s, -O<u>H</u>), 7.8-8.8 (8H, m, -C<u>H</u>$_2$-), 8.94, 8.97 (6H, 2 s, C<u>H</u>$_3$-C-C<u>H</u>$_3$), and 9.16 (3H, s, C<u>H</u>$_3$-C-), <u>m/e</u> 196. The lower band gave 3ξ,9ξ-epoxy-4,4,8β-trimethylhexahydroindan-5$\xi$$_2$-ol (86ii) (210 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3625, 3490, 2960, 1470, 1376, 1040, 945, and 870, τ(CCl_4) 6.66 (1H, 2 d, <u>J</u> 6.9, 8.3 Hz, -C<u>H</u>OH-), 6.75 (1H, br s, $W_{\frac{1}{2}}$ 2.4 Hz, oxiran-H), 7.5 (1H, br s, -O<u>H</u>), 7.8-8.8 (8H, m, -C<u>H</u>$_2$-), 8.86, 8.95 (6H, 2 s, C<u>H</u>$_3$-C-C<u>H</u>$_3$), and 9.14 (3H, s, C<u>H</u>$_3$-C-), <u>m/e</u> 196.

<u>Epoxidation of</u> 1,1,10β-<u>Trimethyl</u>-Δ^8-<u>octal</u>-2-<u>one</u> (138)

Treatment of a solution of the keto-olefin (138) (3.72 g) in chloroform with <u>m</u>-chloroperbenzoic acid (4.03 g) in the usual way gave an oil (4.06 g) whose n.m.r. spectrum indicated that it was a mixture of the α- and β-epoxide. This mixture was adsorbed on alumina (450 g, 5% deactivated); elution with light petroleum:ether mixtures eluted unchanged olefin (65 mg) followed by 8α,9α-epoxy-1,1,10β-trimethyldecal-2-one (88i) (370 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2980, 1710, 1462, 1380, 1022, 950, 925, and 910 cm^{-1}, τ(CCl_4) 7.03 (1H, m, $W_{\frac{1}{2}}$ 5.3 Hz, oxiran-H), 7.2-9.1 (10H, -C<u>H</u>$_2$-), and 8.87, 8.92, 9.22 (9H, 3 s, 3C<u>H</u>$_3$-C-), <u>m/e</u> 208 ($C_{13}H_{20}O_2$). Further elution with the same solvents gave a mixture of the α- and β-epoxides (1.19 g) which was purified by p.l.c. (see below). Further elution gave 8β,9β-epoxy-1,1,10β-trimethyldecal-2-one (88ii) (902 mg) as bulky rods (from hexane), m.p. 54-55.5°, $\nu_{max.}$ (CCl_4) 2960, 1718, 1467, 1376, 1076, 1035, 940, and 910 cm^{-1}, τ(CCl_4) 7.00 (1H, m, $W_{\frac{1}{2}}$ 4.2 Hz, oxiran-H), 7.3-8.9 (10H, -C<u>H</u>$_2$-), and 8.98, 9.02, 9.09 (9H, 3 s, 3 C<u>H</u>$_3$-C-) (Found: C, 74.95; H, 9.7%; <u>M</u>$^+$ 208. Calc. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.6%; <u>M</u> 208) (lit.,[152] m.p. 51-53°). The epoxide mixture was applied to three large p.l.c. plates and eluted twice with petroleum ether-ether (4:1);

the upper band afforded the α-epoxide (650 mg) and the lower band gave the β-epoxide (372 mg).

Semicarbazone of 8α,9α-Epoxy-1,1,10β-trimethyldecal-2-one (88i)

Semicarbazide hydrochloride (11.1 g) and sodium acetate trihydrate (17.8 g) were dissolved in water, and the solution was made up 100 ml with water. A portion of this solution (2.6 ml) was added to the epoxy-ketone (88i) (528 mg), and sufficient methanol was added to give a homogeneous solution, which was warmed on a steam-bath for 2 min and allowed to stand for 18 h. The white precipate was filtered off and recrystallised from aqueous ethanol to give 8α,9α-epoxy-1,1,10β-trimethyldecal-2—one-semicarbazone (150i) (531 mg) as microcrystals, m.p. 182-185°, $\nu_{max.}$ (CCl_4) 3480, 3250br, 3000, 1695br, 1570, 1480, 1380, and 912 cm^{-1}, τ($CDCl_3$) 1.34 (1H, s, disappears on addition of D_2O, = N-NH-CO-), 4.20 (2H, br s, $W_{\frac{1}{2}}$ 9.8 Hz, disappears 2 h after addition of D_2O, -CONH$_2$), 6.88 (1H, m, $W_{\frac{1}{2}}$ 5.7 Hz, oxiran-H), 7.0-8.8 (10H, -CH$_2$-), and 8.70, 8.91, 9.08, (9H, 3 s, 3 CH$_3$-C-) (Found: C, 63.4; H, 8.9; N, 15.6%; M$^+$ 265. $C_{14}H_{23}N_3O_2$ requires C, 63.4; H, 8.7; N, 15.85%; M 265).

Semicarbazone of 8β,9β-Epoxy-1,1,10β-trimethyldecal-2-one (88ii)

Semicarbazide hydrochloride-sodium acetate stock solution (prepared above, 2.3 ml) was added to the epoxy-ketone (88ii) (470 mg) and methanol was added to give a homogeneous solution. Warming and standing overnight gave a white precipitate which was filtered off and recrystallised from aqueous ethanol to give 8β,9β-epoxy-1,1,10β-trimethyldecal-2-one-semicarbazone (150ii) (540 mg) as plates, m.p. 195-199°, $\nu_{max.}$ ($CHCl_3$) 3540, 3420, 3395, 3000, 2950, 1691br, 1564, 1450, 1426, 1085, and 914 cm^{-1}, τ($CDCl_3$) 1.51 (1H, s, disappears with D_2O, = N-NH-CO-), 4.22 (2H, br s,

$W_{\frac{1}{2}}$ 12.0 Hz, $-CONH_2$), 6.83 (1H, m, $W_{\frac{1}{2}}$ 4.8 Hz, oxiran-H), 7.2-8.8 (10H, $-CH_2-$), and 8.81, 9.01, 9.11 (9H, 3 s, 3 CH_3-C-) (Found: C, 63.6; H, 8.7; N, 16.1%; M^+ 265. $C_{14}H_{23}N_3O_2$ requires C, 63.4; H, 8.7; N, 15.85%; M 265).

Epoxidation of 2α,5,9β,10β-Tetramethyl-Δ^5-octal-1β-ol (90)

Treatment of the hydroxy-olefin (89) (500 mg) with p-nitroperbenzoic acid (485 mg) in the usual way gave 5ξ,6ξ-epoxy-2α,5,9β,10β-tetramethyldecal-1β-ol (92i) (530 mg) as a glass which crystallised on standing to give bulky prisms (from light petroleum) m.p. 95-96.5°, $\nu_{max.}$ (CCl_4) 3540, 2960, 1458, 1370, 1025, and 945 cm^{-1}, $\tau(CCl_4)$ 6.92 (1H, d, J 10 Hz, $-CHOH-$), 7.12 (1H, t, J 1.5 Hz, oxiran-H), 7.9-9.0 (9H, $-CH_2-$), 8.60 (1H, s, disappears with D_2O, $-CHOH-$), 8.80 (3H, s, CH_3-oxiran), 9.05 (3H, d, J 5 Hz, CH_3-CH-), and 9.10 and 9.28 (6H, 2 s, 2 CH_3-C-) (Found: C, 74.8; H, 10.7%, M^+ 224. $C_{14}H_{20}O_2$ requires C, 75.0; H, 10.7%, M 224).

Epoxidation of 2α,5,9β,10β-Tetramethyl-Δ^5-octal-1-one (142)

Treatment of the keto-olefin (142) (3.25 g) with p-nitroperbenzoic acid (3.25 g) in the usual way gave a pale yellow oil (3.39 g) containing two components (t.l.c.) which was applied to five large p.l.c. plates and eluted once with light petroleum-ether (2:1). Extraction of the upper band gave 5ξ_1,6ξ_1-epoxy-2α,5,9β,10β-tetramethyldecal-1-one (93i) (1.43 g, 41%) as an oil, $\nu_{max.}$ (CCl_4) 2970, 1700, 1460, 1382, 950, and 885 cm^{-1}, $\tau(CCl_4)$ 7.23 (1H, br s, $W_{\frac{1}{2}}$ 4.3 Hz, oxiran-H), 7.65 (1H, sextet, J 6 Hz, $CH_3-CH-CH_2-$), 7.8-8.8 (8H, $-CH_2-$), 8.83 (3H, s, CH_3-oxiran), 9.0, 9.08 (6H, 2 s, 2 CH_3-C-), and 9.06 (3H, d, J 6.0 Hz, CH_3-CH-) (Found: C, 75.4; H, 10.0%; M^+ 222. $C_{14}H_{22}O_2$ requires C, 75.7; H, 9.9%; M 222). Extraction of the lower band gave

$5\xi_2,6\xi_2$-epoxy-2α,5,9β,10β-tetramethyldecal-1-one (93ii) (0.75 g, 21%) as an oil, $\nu_{max.}$ (CCl_4) 2970, 1700, 1460, 1380, 1125, 915, and 868 cm^{-1}, τ(CCl_4) 7.39 (1H, d, J 3.8 Hz, oxiran-H), 7.5-8.8 (9H, $-CH_2-$), 8.79 (3H, s, CH_3-oxiran), 8.96, 9.05 (6H, 2 s, 2 CH_3-C-), and 9.00 (3H, d, J 5.6 Hz, CH_3-CH-) (Found: C, 75.4; H, 10.0%; M^+ 222. $C_{14}H_{22}O_2$ requires C, 75.7; H, 9.9%; M 222).

Oxidation of $5\xi,6\xi$-Epoxy-2α,5,9β,10β-tetramethyldecal-1β-ol (92i)

Chromium trioxide (152 mg) was added to stirred pyridine (1.5 ml) at 10° to give a yellow solution which became a thick orange slurry after 5 min. A solution of the hydroxy-epoxide (92i) (85 mg) in pyridine (1.5 ml) was added to the stirred slurry, which was then left at 22° for 18 h. The mixture was poured into ether (50 ml) and washed with dilute acetic acid, sodium carbonate solution, and brine, and dried over anhydrous magnesium sulphate. Removal of the solvent gave an oil (70 mg) containing the starting material and one other component (t.l.c.). This oil was treated with a further 100 mg chromium trioxide in pyridine (1 ml) to give a viscous oil (34 mg) containing $5\xi,6\xi$-epoxy-2α, 5,9β,10β-tetramethyldecal-1β-ol (92i) and $5\xi_1,6\xi_1$-epoxy-2α,5,9β, 10β-tetramethyldecal-1-one (93i) in an approximate ratio of 1:2 (from n.m.r. integration), τ(CCl_4) 7.14 (1H, br s, $W_{\frac{1}{2}}$ 4.3 Hz, oxiran-H; hydroxy-epoxide), 7.22 (1H, br s, $W_{\frac{1}{2}}$ 4.3 Hz, oxiran-H; keto-epoxide).

Rearrangement of Ethyl $3\xi_1,9\xi_1$-Epoxy-4,4-dimethyl-5-oxohexahydroindane-8β-carboxylate (82a)

Freshly distilled boron trifluoride-ether complex (0.75 ml) was added to a stirred solution of the keto-ester ξ_1-epoxide (82i) (1.30 g) in dry benzene (40 ml) under dry nitrogen at 10°, and after stirring for 10 min, the solution was deep orange. 5% Sodium hydrogen carbonate

solution (50 ml) was added, and working up in the usual way gave a pale yellow oil (1.28 g) whose t.l.c. and i.r. suggested the presence of carboxylic acid. The mixture was methylated using diazomethane solution (see p. 173 for preparation) to give an oil (1.22 g) containing one major and four minor products (t.l.c.), which was applied to four large p.l.c. plates and eluted once with petroleum ether:ether (1:1). Five bands in order of decreasing Rf were extracted.

Band A gave ethyl 2-isopropenyl-1-(2-methoxycarbonylethyl)-cyclopent-2-enecarboxylate (151) (405 mg) as an oil, homogeneous to t.l.c., $\lambda_{max.}$ (EtOH) 236 nm (ε 13,000), $\nu_{max.}$ (CCl_4) 2950, 1740, 1726, 1440, 1378, 1170, 1080, 1031, and 894 cm^{-1}, τ(CCl_4) 4.12 (1H, t, J 2.6 Hz, -CH=C-), 5.14 (2H, br s, $W_{\frac{1}{2}}$ 3.2 Hz, CH_2=C-), 5.93 (2H, q, J 7.1 Hz, $-CO_2CH_2CH_3$), 6.41 (3H, s, $-CO_2CH_3$), 7.3-8.4 (8H, $-CH_2-$), 8.12 (3H, m, $W_{\frac{1}{2}}$ 2.5 Hz, $CH_3-C=CH_2$), and 8.81 (3H, t, J 7.1 Hz, $-CO_2CH_2CH_3$), m/e 266 ($C_{15}H_{22}O_4$).

Band B gave unchanged epoxide (82i) (63 mg) as an oil with t.l.c., and i.r. and n.m.r. spectra identical with an authentic sample.

Band C gave an oil (150 mg) whose t.l.c. indicated that it contained one major and several minor components. This oil was applied to two small p.l.c. plates and eluted seven times with light petroleum-ether (2:1), and extraction of the main band gave an oil (54 mg), homogeneous to t.l.c., thought to be ethyl 2-isopropylidene-1-(2-methoxycarbonylethyl)-cyclopent-3-enecarboxylate (154), $\lambda_{max.}$ (EtOH) 244 nm (ε 4,500), $\nu_{max.}$ (CCl_4) 2960, 1751, 1733, 1440, 1370, 1180, 1124, 1031, and 864 cm^{-1}, τ(CCl_4) 4.28 (1H, m, $W_{\frac{1}{2}}$ 6.0 Hz, -CH=C-), 4.62 (1H, d, J 9.9 Hz, -CH=C-), 5.89 (2H, 2 q, J 7.3 Hz, $-CO_2CH_2CH_3$), 6.40 (3H, 2 s, 2 CH_3O-), 7.3-9.0 (6H, $-CH_2-$), 8.15 (3H, m, $W_{\frac{1}{2}}$ 3.3 Hz, $CH_3-C=$), 8.44 (3H, m, $W_{\frac{1}{2}}$ 2.9 Hz, $CH_3-C=$), and 8.73 and 8.81 (3H, 2 t, J 7.3 Hz, $-CO_2CH_2CH_3$), m/e 266 ($C_{15}H_{24}O_4$).

Band D gave an oil (86 mg) which was further purified by applying to one small p.l.c. plate and eluting nine times with light petroleum-ether (2:1). Extraction of the main band gave a glass (17 mg), homogeneous to t.l.c., $\lambda_{max.}$ (EtOH) 244 nm (ε 4,300), $\nu_{max.}$ (CCl_4) 2960, 1750, 1732, 1440, 1369, 1170, 1096, 1030, and 864 cm^{-1}, τ(CCl_4) 4.19 (1H, m, $W_{\frac{1}{2}}$ 7.9 Hz, -C<u>H</u>=C), 4.7 (2H, complex, C<u>H</u>$_2$= C-?), 5.90 (2H, q, <u>J</u> 6.9 Hz, -$CO_2C\underline{H}_2CH_3$), 6.38 (3H, 2 s, 2 C<u>H</u>$_3$-O-), 7.3-8.3 (9H, -C<u>H</u>$_2$-), 8.42 (3H, m, $W_{\frac{1}{2}}$ 8.6 Hz, C<u>H</u>$_3$-C=), and 8.75 (6H, complex, methyls), <u>m/e</u> 242 ($C_{14}H_{26}O_3$, $C_{13}H_{22}O_4$). Band E gave an oil (188 mg) whose t.l.c. indicated that it contained several components, $\nu_{max.}$ (CCl_4) 2985, 2960, 1745, 1735, 1720, 1628, 1448, 1368, 1170, and 1029 cm^{-1}. Attempts were made to purify this material by p.l.c., but they were unsuccessful, and the material darkened rapidly on standing, to give a complex mixture which was not investigated further.

Reduction of Ethyl 2-Isopropenyl-1-(2-methoxycarbonylethyl)cyclopent-2-enecarboxylate (151)

A solution of the diester (151) (120 mg) in dry ether (25 ml) was added slowly to a stirred slurry of lithium aluminium hydride (35 mg) in ether (25 ml) at 25°, and the stirred mixture was heated under reflux for 2 h. After cooling to 0°, ethyl acetate was added cautiously to destroy the excess of lithium aluminium hydride, and dilute hydrochloric acid (5 ml) was added to dissolve the inorganic precipitate. Ethyl acetate was added, and working up in the usual way gave a glass (87 mg) which was applied to one small p.l.c. plate and eluted once with petroleum ether-ether (1:5). Extraction of the major band with ethyl acetate gave 1-(3-hydroxypropyl)-2-isopropenylcyclopent-2-en-1-ylmethanol (152) (56 mg) as microcrystals (from hexane-ether) m.p. 68-72°, $\lambda_{max.}$ (EtOH) 238 nm (ε 5,600), $\nu_{max.}$ (CCl_4) 3650sh, 3610sh,

3440br, 1452, 1376, 1050, and 886 cm^{-1}, $\tau(CHCl_3)$ 4.04 (1H, t, J 2.0 Hz, -CH=C-), 4.94 (1H, m, $W_{\frac{1}{2}}$ 3.4 Hz, =CH-H), 5.13 (1H, m, $W_{\frac{1}{2}}$ 5.0 Hz, =CH-H), 6.41 (2H, m, $W_{\frac{1}{2}}$ 4.6 Hz, $-CH_2OH$), 6.46 (2H, m, $W_{\frac{1}{2}}$ 8.6 Hz, $-CH_2OH$), 6.92 (2H, br s, $W_{\frac{1}{2}}$ 9.0 Hz; 2-OH), 7.3-8.7 (8H, $-CH_2-$), and 8.44 (3H, m, $W_{\frac{1}{2}}$ 8.3 Hz, $CH_3-C=CH_2$) (Found: C, 73.8; H, 10.0%; M^+ 196. $C_{12}H_{20}O_2$ requires: C, 73.5; H, 10.2%; M 196). Treatment of a solution of the diol (154) (55 mg) in dry pyridine (10 ml) with p-nitrobenzoylchloride (105 mg) at 110° for 0.5 h gave after the usual work up a light brown gum (54 mg) which was applied to one small p.l.c. plate and eluted once with chloroform. Extraction of the major band gave the mono-p-nitrobenzoate (153) (12 mg) as a gum, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3640, 2990, 1732, 1358, 1292, 1128, and 900 cm^{-1}, τ1.81 (4H, m, aromatic H), 4.04 (1H, m, $W_{\frac{1}{2}}$ 5.4 Hz, -CH=C-), 4.93, 5.13 (2H, 2 m, $W_{\frac{1}{2}}$ 3.7, 5.1 Hz, $-C=CH_2$), 5.71 (2H, t, J 10.3 Hz, $-CH_2-CH_2-OCO-$), 6.42 (2H, ABq, J_{AB} 10.3 Hz, $-CH_2OH$), 7.4-8.4 (9H, $-CH_2-$ and -OH), and 8.31 (3H, m, $CH_3-C=CH_2$), m/e 345 ($C_{19}H_{23}NO_5$).

Rearrangement of Ethyl $3\xi_2,9\xi_2$-Epoxy-4,4-dimethyl-5-oxohexahydroindane-8β-carboxylate (82ii)

Freshly distilled boron trifluoride-ether complex (0.2 ml) was added to a stirred solution of the keto-ester ξ_2-epoxide (82ii) (343 mg) in dry benzene under dry nitrogen at 20° and the mixture was stirred for 10 min to give a yellow solution. Addition of 5% sodium hydrogen carbonate solution (40 ml) followed by working up in the usual way gave a pale yellow oil (287 mg) containing two major components (t.l.c.). The oil was applied to three small p.l.c. plates and eluted once with light petroleum-ether (1:2). Extraction of the upper band gave unchanged epoxide (123 mg, 36%) and extraction of the lower band gave a glass (77 mg), $\nu_{max.}$ (CCl_4) 3620, 3540, 3440, 2980, 2730, 1733, 1718,

1625, 1457, 1368, 1155, 1095, and 1030 cm^{-1}, $\tau(CCl_4)$ 0.25 (1H, m, $W_{\frac{1}{2}}$ 2.0 Hz, -C<u>H</u>O), 5.02 (less than <1H, complex), 5.85 (3H, 2 overlapping q, <u>J</u> 6.5 Hz, $-CO_2C\underline{H}_2CH_3$), 7.3 - 9 (12H, $-C\underline{H}_2-$), 7.80 (3H, s, $C\underline{H}_3-C=$), 8.18 (3H, s, $C\underline{H}_3-C=$), and 8.72 (5H, 2 overlapping t, <u>J</u> 7.3 Hz, $-CO_2CH_2C\underline{H}_3$). This glass was applied to one small p.l.c. plate and eluted six times with petroleum ether-ether (2:3). Extraction of the main band gave a glass (37 mg), homogeneous to t.l.c., thought to be ethyl 2-isopropylidene-3-oxo-1-(3-oxopropyl)-cyclopentanecarboxylate (161), $\lambda_{max.}$ (EtOH) 252 nm (ε 4,100), $\nu_{max.}$ (CCl_4) 2980, 2730, 1735, 1718, 1630, 1450, 1372, 1160, 1096, and 1034 cm^{-1}, $\tau(CCl_4)$ 0.24 (1H, m, $W_{\frac{1}{2}}$ 2.0 Hz, -C<u>H</u>O), 5.85 (2H, q, <u>J</u> 7.2 Hz, $-CO_2C\underline{H}_2CH_3$), 7.2 - 9 (8H, $-C\underline{H}_2-$), 7.79 (3H, s, $C\underline{H}_3-C=$), 8.21 (3H, s, $C\underline{H}_3-C=$), and 8.75 (3H, t, <u>J</u> 7.2 Hz, $-CO_2CH_2C\underline{H}_3$), <u>m/e</u> 252 ($C_{14}H_{20}O_4$). The m.s. also showed a small peak at <u>m/e</u> 268 due to oxidation of the aldehyde group.

<u>Rearrangement of</u> 3ξ,9ξ-<u>Epoxy</u>-4,4-<u>dimethylhexahydroindan</u>-8β,5β-<u>carbolactone</u> (87)

Freshly distilled boron trifluoride-ether complex (0.15 ml) was added to a stirred solution of the epoxy-lactone (87) (237 mg) in dry benzene (50 ml) under dry nitrogen at 25°. After 10 min the solution was pink, and 5% sodium hydrogen carbonate solution was added; working up in the usual way gave a pale yellow oil (230 mg) containing three components (t.l.c.). This oil was applied to two small p.l.c. plates and eluted twice with petroleum ether-ether (1:2). Three bands were extracted in order of decreasing Rf.

The highest band gave unchanged epoxide (90 mg) which was identical with authentic material. The middle band gave a single pure compound (53 mg) as bulky prisms (from hexane-ether), m.p. 134-135.5°, $\nu_{max.}$ ($CHCl_3$) 2980, 1775, 1474, 1385, 1340, 1115, 920, and 659 cm^{-1},

$\tau(CDCl_3)$ 4.41 (1H, m, $W_{\frac{1}{2}}$ 7.7 Hz, -C<u>H</u>=C-), 5.36 (1H, m, $W_{\frac{1}{2}}$ 6.9 Hz, -C<u>H</u>OCO-?), 5.97 (1H, m, $W_{\frac{1}{2}}$ 6.0 Hz, -C<u>H</u>OCO-), 7.2-8.5 (7H, -C<u>H</u>$_2$-), and 8.71 and 8.87 (6H, 2 s, 2 C<u>H</u>$_3$-C-) (Found: C, 69.3; H, 7.9%; <u>M</u>$^+$ 208. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%; <u>M</u> 208). The lowest band gave 4,4-<u>dimethyl</u>-3-<u>oxohexahydroindane</u>-8β,5β-<u>carbolactone</u> (169) (28 mg) as prisms (from hexane-ether) m.p. 119-121°, $\nu_{max.}$ (CCl_4) 2990, 1769, 1756, 1475, 1412, 1364, 1148, 1112, and 1070 cm^{-1}, $\tau(CCl_4)$ 5.97 (1H, m, $W_{\frac{1}{2}}$ 5.9 Hz, -C<u>H</u>OCO-), 7.1-8.8 (9H, -C<u>H</u>$_2$-), and 8.79 and 8.94 (6H, 2 s, C<u>H</u>$_3$-C-C<u>H</u>$_3$) (Found: C, 69.3; H, 7.7%; <u>M</u>$^+$ 208. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%; <u>M</u> 208).

<u>Rearrangement of</u> 3ξ,9ξ-<u>epoxy</u>-8β-<u>hydroxymethyl</u>-4,4-<u>dimethylhexahydroindan</u>-5β-<u>ol</u> (84i)

Freshly distilled boron trifluoride-ether (0.25 ml) was added to a stirred solution of the diol-epoxide (84i) (445 mg) in dry benzene (50 ml) under dry nitrogen at 25°, and the mixture was stirred for 10 min. After addition of 5% sodium hydrogen carbonate solution (40%) working up using ethyl acetate gave a pale yellow gum (360 mg), containing one major component (t.l.c.). The gum was applied to one large p.l.c. plate and eluted once with benzene-ether (1:4). Extraction of the most intense band with ethyl acetate gave 2,2-<u>dimethyl</u>-3-<u>oxatricyclo</u> [3.3.3.0]-<u>undecane</u>-8,9-<u>diol</u> (170) (86 mg) as a glass, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3670, 3520, 2970, 1470, 1455, 1386, 1370, 1160, 1120, 1062, and 1032 cm^{-1}, $\tau(CHCl_3)$ 5.91 (2H, merged m, $W_{\frac{1}{2}}$ 9.9 Hz, 2 -C<u>H</u>OH-), 6.20 (2H, s, -C<u>H</u>$_2$-O-), 7.13 (2H, br s, disappears with D_2O, 2-O<u>H</u>), 7.5-8.5 (8H, -C<u>H</u>$_2$-), and 8.42 [6H, s, (C<u>H</u>$_3$)$_2$C-O-], <u>m/e</u> 212 ($C_{12}H_{20}O_3$). Treatment of the diol (166) (29 mg) with acetic anhydride (1.0 ml) in pyridine (5 ml) at 100° for 2.5 h gave a pale yellow gum (36 mg) which was applied to one small p.l.c. plate and eluted once with petroleum

ether-ether (1:2). Extraction of the main band gave 2,2-dimethyl-3-oxatricyclo [3.3.3.0] undecane-8,9-diyl diacetate (171) (20 mg) as an oil which crystallised on standing to give prisms (from hexane-ether) m.p. 75-79°, $\nu_{max.}$ (CCl_4) 2980, 1750, 1360, 1250, 1055, and 1024 cm^{-1}, τ(CCl_4) 5.10 (2H, m, 2 -CH-OCOCH$_3$), 6.25 (2H, s, -CH$_2$-O-), 7.5-8.5 (8H, -CH$_2$-), 7.94 (6H, s, 2 CH$_3$COO-), 8.58 6H, s, (CH$_3$)$_2$C-O- , τ(C_6H_6) 5.12 (2H, t, J 6.4 Hz, 2 -CHOAc-), 6.68 (2H, s, -CH$_2$-O-), 8.1-9.2 (8H, -CH$_2$-), 8.61 (6H, s, 2 CH$_3$CO$_2$-), and 8.78 [6H, s, (CH$_3$)$_2$C-O-] (Found: C, 64.6; H, 8.2%; m/e 281 = M-15. $C_{16}H_{24}O_5$ requires C, 64.9; H, 8.1%; M 296).

Oxidation of 2,2-Dimethyl-3-oxatricyclo [3.3.3.0] undecane-8,9-diol (170)

A solution of the diol (166) (35 mg) in acetone was treated with Jones reagent in the usual way to give a solid (25 mg) which was applied to one small p.l.c. plate and eluted twice with benzene:ether (1:4). Extraction of the main band gave 2,2-dimethyl-3-oxatricyclo [3.3.3.0] undecane-8,9-dione (172) (12 mg) as an amorphous solid, m.p. 149-152°, $\nu_{max.}$ (CCl_4) 2960, 1762, 1460, 1410, 1387, 1372, 1262, and 1112 cm^{-1}, τ($CHCl_3$) 6.10 (2H, s, -CH$_2$-O-), 7.3-8.3 (8H, -CH$_2$-), 8.83 [6H, s, (CH$_3$)$_2$C-O-] (Found: C, 69.1; H, 7.9%; M^+ 208. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%; M 208). A solution of a small sample of the dione in ethanol showed no characteristic u.v. absorption, but on addition of a solution of potassium hydroxide in ethanol, an intense absorption at 250 nm appeared, accompanied by a weaker absorption at 305 nm.

Rearrangement of 3,9-Epoxy-4,4,8β-trimethylhexahydroindan-5-one (85)

Freshly distilled boron trifluoride-ether complex (0.57 ml) was added to a stirred solution of the keto-epoxides (85) (440 mg) in dry benzene (20 ml) under dry nitrogen at 25° to give an orange solution

which became deep red after 10 min. 5% Sodium hydrogen carbonate solution (50 ml) was added to give a bright yellow organic phase which was worked up in the usual way to give a yellow crystalline solid (383 mg) containing one major and several minor components (t.l.c.). Trituration of the solid with cold ether left 9-hydroxy-1,1,6-trimethylspiro[4,4]non-6-en-2-one (177) (97 mg, 22%) as bulky plates (from light petroleum-ether) m.p. 123-124°, $\nu_{max.}$ (CCl_4) 3450, 2960, 1732, 1380, 1080, and 870 cm^{-1}, τ($CDCl_3$) 4.50 (1H, br s, $W_{\frac{1}{2}}$ 5.0 Hz, -CH=C-), 5.71 (1H, t, J 5.3 Hz, -CHOH-) 7.2-8.2 (6H, $-CH_2-$), 8.22 (1H, s, disappears with D_2O, -CHOH-), 8.33 (3H, m; collapses to t, J 2.2 Hz, on irradiation at τ 4.50 ; $CH_3-C=CH-CH_2$), and 8.79 and 8.91 (6H, 2 s, CH_3-C-CH_3) (Found: C, 74.4; H, 9.5%; M^+ 194. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%; M 194). Evaporation of the ether washings from the trituration gave a yellow oil (211 mg) which was applied to two small p.l.c. plates and eluted twice with light petroleum-ether (1:1). At least six bands separated, and on extraction, none afforded significant amounts of material.

Oxidation of 9-Hydroxy-1,1,6-trimethylspiro[4,4]non-6-en-2-one (177)

Jones reagent was added dropwise to a stirred solution of the spiro-keto-alcohol (170) (49 mg) in acetone (10 ml) until a permanent orange-brown colouration obtained. Excess of chromic acid was destroyed by addition of a few drops of sodium metabisulphite solution, and working up in the usual way gave 1,1,6-trimethylspiro[4,4]non-6-ene-2,9-dione (180) (48 mg) as a gum, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2960, 1735, 1465, 1390, 1360, and 1080 cm^{-1}, τ(CCl_4) 4.15 (1H, m, $W_{\frac{1}{2}}$ 5.2 Hz, -CH=C-), 7.28 (2H, quintet, J 2.4 Hz, $CH_3-C=CH-CH_2-CO-$), 7.4-8.2 (4H, $-CH_2-$), 8.28 (3H, m; collapses to t, J 2.4 Hz, on irradiation at τ 4.15 ; $CH_3-C=CH-CH_2-$), and 9.07 and 9.09 (6H, 2 s, CH_3-C-CH_3), m/e 192 ($C_{12}H_{16}O_2$).

Rearrangement of 3ξ,9ξ-Epoxy-4,4,8β-trimethylhexahydroindan-5ξ$_1$-ol (86i)

Freshly distilled boron trifluoride-ether complex (0.22 ml) was added to a stirred solution of the epoxy-alcohol (86i) (336 mg) in dry benzene (50 ml) under dry nitrogen at 20°. The solution went deep red immediately and 5% sodium hydrogen carbonate solution (50 ml) was added after 1 min. Working up in the usual way gave a yellow oil (270 mg) with a very streaky t.l.c., $\nu_{max.}$ (CCl_4) 3640, 3470, 2970, 1745, 1724, 1470, 1395, 1382, 1045, and 686 cm^{-1}. The oil was applied to one large p.l.c. plate and eluted once with petroleum ether-ether (2:1). One major band was discernible, and this was extracted to give a glass (96 mg) containing two components (t.l.c.), τ(CCl_4) 6.0-6.8 (-CHOH), complex methyl region with peaks at 8.69, 8.78, 8.81, 8.87, 8.95, 8.98, 9.05, 9.13, 9.17. The two components were incompletely separated by further p.l.c.; the glass was applied to one small p.l.c. plate and eluted three times with petroleum ether-ether (1:1). The upper band gave a glass (29 mg), thought to be mainly 3ξ-hydroxy-4,8β,9-trimethylhexahydroindan-5-one (183), $\nu_{max.}$ (CCl_4) 3595, 3390, 2960, 1740w, 1715s, 1470, 1390, 1380, 1100, 1040, and 948 cm^{-1}, τ(CCl_4) 6.27 (1H, m, $W_{\frac{1}{2}}$ 10.3 Hz, -CHOH), 7.5-8.9 (~10 H, $-CH_2-$ and -OH), 8.97 (3H, d, J 4.3 Hz, CH_3-CH-), and 9.04 and 9.22 (6H, 2s, 2 CH_3-C-), m/e 196 ($C_{12}H_{20}O_2$). Jones oxidation of a small sample gave an oil, $\nu_{max.}$ (CCl_4) 2960, 1750s, 1725s, 1470, 1390, 1100, 1045, and 950 cm^{-1}. The lower band gave a glass (29 mg), thought to be mainly 5ξ$_1$-hydroxy-4,4,8β-trimethylhexahydroindan-3-one (184), $\nu_{max.}$ (CCl_4) 3630, 3460, 2960, 1740s, 1718w, 1460, 1384, 1140, and 1072 cm^{-1}, τ(CCl_4) 6.05 (~1H, m, $W_{\frac{1}{2}}$ 6.9 Hz, -CHOH), 6.64 (1H, 2 d, J 1.7, 5.2 Hz, -CHOH), 7.2-9 (10H, $-CH_2-$ and -OH), 8.95 (6H, s, CH_3-C-CH_3), and 9.04 (3H, s, CH_3-C-), m/e 196 ($C_{12}H_{20}O_2$). Jones oxidation of a small sample gave an oil, $\nu_{max.}$ (CCl_4) 2960, 1750s, 1725s, 1470, 1388, 1132, and 1090 cm^{-1}.

Rearrangement of 3ξ,9ξ-Epoxy-4,4,8β-trimethylhexahydroindan-5ξ$_2$-ol (86ii)

Freshly distilled boron trifluoride-ether complex (0.15 ml) was added to a stirred solution of the epoxy-alcohol (86ii) (187 mg) in dry benzene (50 ml) under dry nitrogen at 20°. The solution became deep red immediately, and 5% sodium hydrogen carbonate solution (50 ml) was added after 1 min. Working up in the usual way gave a yellow glass (161 mg) which had a very streaky t.l.c. on which no discrete spots were observable. The n.m.r. spectrum had no sharp signals below τ 7 and only a merged methylene and methyl envelope above τ7. The i.r. spectrum was slightly more informative, $\nu_{max.}$ (CCl_4) 3640, 3470, 2960, 1750, 1725, 1470, 1390, 1050, and 687 cm^{-1}. Attempts to separate the mixture by multiple elution p.l.c. were unsuccessful.

Rearrangement of 8α,9α-Epoxy-1,1,10β-trimethyldecal-2-one (88i)

Freshly distilled boron trifluoride-ether complex (0.6 ml) was added to a stirred solution of the keto-α-epoxide (88i) (1.03 g) in dry benzene (50 ml) under dry nitrogen at 25°, and the initially colourless solution became deep orange after 5 min. Addition of 5% sodium hydrogen carbonate solution (50 ml) and working up in the usual way gave a pale yellow oil (1.00 g) which gave a very streaky t.l.c., suggesting the presence of a carboxylic acid; this was confirmed by the i.r. spectrum, $\nu_{max.}$ (CCl_4) 2500-2800 cm^{-1}. The mixture was methylated using diazomethane; N-nitrosomethylurea (1.0 g) was added over 5 min to a stirred mixture of ether (10 ml) and 40% aqueous potassium hydroxide solution (3 ml), and the yellow ethereal diazomethane solution was decanted off and dried over potassium hydroxide pellets at 0°. The diazomethane solution was added to a solution of the reaction mixture obtained above in dry ether (20 ml) at 0°, and this mixture was stirred at 0° for 2 h and then at 25° for 18 h. Removal of the solvent left a pale

yellow oil (1.06 g) containing four major components (t.l.c). This oil was applied to three large p.l.c. plates and eluted once with petroleum ether: ether (1:1), and the four major bands were extracted (in order of decreasing Rf).

Band A gave a pale yellow oil (109 mg) which was applied to one small p.l.c. plate and eluted once with petroleum ether-ether (2:1); extraction of the major band gave methyl 3-(2-isopropenyl-1-methylcyclohex-2-en-1-yl)-propionate (190) (50 mg) as an oil, homogeneous to t.l.c., $\lambda_{max.}$ (EtOH) 234 nm (ε 4,600), $\nu_{max.}$ (CCl_4) 2950, 1740, 1435, 1380, 1290, 1170, and 893 cm^{-1}, τ(CCl_4) 4.51 (1H, t, J 3.9 Hz, $-CH_2-CH=C-$), 5.20 (1H, m, $W_{\frac{1}{2}}$ 5.0 Hz, -C=CH-H), 5.29 (1H, m, $W_{\frac{1}{2}}$ 3.40 Hz, -C=CH-H), 6.37 (3H, s, CH_3-O-), 7.5-9.0 (10H, $-CH_2-$), 8.09 (3H, m, $W_{\frac{1}{2}}$ 4.1 Hz, $CH_3-C=CH_2$), and 8.84 (3H, s, CH_3-C-), m/e 222 ($C_{14}H_{22}O_2$).

Band B gave a pale yellow oil (119 mg) which was applied to two small p.l.c. plates and eluted once with petroleum ether-ether (2:1); extraction of the major band gave an oil (81 mg) whose i.r. and n.m.r. spectra indicated the presence of more than one component, $\nu_{max.}$ (CCl_4) 2950, 1720, 1696, 1680, 1637, 1470, and 1384 cm^{-1}, τ(CCl_4) 4.42 (<1 H, merged d, J 1.1 Hz, -CH=C-), complex methyl region; 8.61, 8.69, 8.73, 8.81, 8.84, 8.88, 8.90, and 8.95. This oil darkened in colour on standing, and was applied to one small p.l.c. plate and eluted fifteen times with light petroleum-ether (199:1) to give two major bands; these were extracted with ether. The upper band gave a gum (6 mg), homogeneous by t.l.c., $\lambda_{max.}$ (EtOH)223 nm (ε 1,980), $\nu_{max.}$ (CCl_4) 3420, 2930, 1710w, 1689, 1468, 1379, and 1100 cm^{-1}, τ(CCl_4) 6.5 (1H, m, -CHOH), 7.45 (2H, q, J 5.7 Hz), complex methyl region; 8.73, 8.82, 8.92, and 8.99 (~ 12 H), m/e 222 ($C_{14}H_{22}O_2$). The lower band also gave a gum (6 mg), homogeneous by t.l.c., $\lambda_{max.}$ (EtOH) 238 nm (ε 10,940), $\nu_{max.}$ (CCl_4) 3420, 2930, 1725w, 1675, 1460, 1380, 1184, and 1140 cm^{-1}, τ(CCl_4)

4.45 (~1H, m -CH=C-), 6.47 (~1H, m, -CHOH), complex methyl region, sharp signals at 8.31, 8.69, 8.75, 8.86, and 8.95 (~12 H), m/e 222 ($C_{14}H_{22}O_2$). Band C gave a pale yellow oil (127 mg) which was applied to two small p.l.c. plates and eluted twice with petroleum ether:ether (1:1). Extraction of the major band gave 8α-hydroxy-1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2-one (195) (58 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3640sh, 3550br, 2970, 1725, 1460, 1395, 1110, and 1055 cm^{-1}, τ (CCl_4) 4.41 (1H, m, $W_{\frac{1}{2}}$ 8.6 Hz, -CH=C-), 6.13 (1H, t, J 3.9 Hz, -CHOH-), 7.0-8.5 (9H, $-CH_2-$ and -OH), 8.69, 8.80, and 9.01 (9H, 3 s, 3 CH_3-C-), m/e 208 ($C_{13}H_{20}O_2$).
Band D gave 10-hydroxy-1,1,6-trimethylspiro[4,5]dec-6-en-2-one (197) (253 mg) as bulky rods (from hexane-ether) m.p. 93-95°, $\nu_{max.}$ (CCl_4) 3590sh, 3480br, 2970, 1740, 1470, 1384, 1177, 1087, 1057, and 920 cm^{-1}, τ(CCl_4) 4.52 (1H, m, $W_{\frac{1}{2}}$ 5.2 Hz, -CH=C-), 6.16 (1H, m, $W_{\frac{1}{2}}$ 4.9 Hz, -CHOH), 7.2-8.4 (9H, $-CH_2-$ and - OH), 8.53 (3H, m, $W_{\frac{1}{2}}$ 3.0 Hz, CH_3-C=), and 9.06 and 9.11 (6H, 2 s, CH_3-C-CH_3) (Found: C, 74.7; H, 9.4%; M^+ 208. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.6%; M 208).

Oxidation of 8α-Hydroxy-1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2-one (195)

Treatment of the keto-alcohol (193) (58 mg) with Jones reagent in the usual way gave an impure solid (50 mg) which was applied to one small p.l.c. plate and eluted once with petroleum ether-ether (1:1). Extraction of the main band gave 1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2,8-dione (196) (42 mg) as microcrystals, m.p. 99-103°, $\nu_{max.}$ (CCl_4) 2980, 1714, 1474, 1400, 1381, 1115, and 1100 cm^{-1}, τ(CCl_4) 4.14 (1H, m, $W_{\frac{1}{2}}$ 5.2 Hz, -CH=C-), 7.1-7.9 (8H, $-CH_2-$), 8.92, 8.94, and 9.00 (9H, 3 s, 3 CH_3-C-) (Found: C, 75.9; H, 8.6%; M^+ 206. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%; M 206).

Oxidation of 10-Hydroxy-1,1,6-trimethylspiro[4,5]dec-6-en-2-one (197)

Treatment of the spiro-keto-alcohol (98 mg) with Jones reagent in the usual way gave 1,1,6-trimethylspiro[4,5]dec-6-ene-2,10-dione (198) (78 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2980, 1743, 1714, 1471, 1447, 1384, 1197, 1124, and 1088 cm^{-1}, τ(CCl_4) 4.42 (1H, m, $W_{\frac{1}{2}}$ 6.9 Hz, -CH=C-), 6.9-8.4 (8H, $-CH_2-$), 8.44 (3H, m, $W_{\frac{1}{2}}$ 3.6 Hz), and 8.90 and 9.25 (6H, 2 s, CH_3-C-CH_3), m/e 206 ($C_{13}H_{18}O_2$). Attempts to prepare a 2,4-dinitrophenyl-hydrazone were unsuccessful.

Rearrangement of 8β,9β-Epoxy-1,1,10β-trimethyldecal-2-one (88ii)

Freshly distilled boron trifluoride-ether complex (0.5 ml) was added to a stirred solution of the keto-β-epoxide (88ii) (796 mg) in dry benzene (40 ml) under dry nitrogen at 25°, and after 10 min the solution was deep yellow. 5% Sodium hydrogen carbonate solution (50 ml) was added, and working up in the usual way gave a pale yellow oil (803 mg) whose i.r. and n.m.r. spectra indicated the presence of an aldehyde: $\nu_{max.}$ (CCl_4) 2740 cm^{-1}, τ(CCl_4) 0.15 (s, -CHO). The oil was adsorbed on alumina (150 g, 5% deactivated). Elution with light petroleum and light petroleum-benzene mixtures gave an unidentified oil (12 mg) followed by 4,4,8β-trimethyl-5-oxohexahydroindane-9β-carbaldehyde (199) (111 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2980, 1740, 1725, 1480, 1396, 1124, and 920 cm^{-1}, τ(CCl_4), 0.15 (1H, s, -CHO), 6.9-8.9 (10H, $-CH_2-$), 8.58, 8.62, and 9.05 (9H, 3 s, 3 CH_3-C-), m/e 208 ($C_{13}H_{20}O_2$). Treatment of the keto-aldehyde (197) with semicarbazone hydrochloride gave a mono-semicarbazone as microcrystals (from aqueous methanol), m.p. 204-206° (Found: C, 63.7; H, 8.9; N, 15.6%; M^+ 265. $C_{14}H_{23}N_3O_2$ requires C, 63.4; H, 8.7; N, 15.8%; M 265). Elution with benzene and benzene-ether mixtures gave an unidentified oil (64 mg) containing several components (t.l.c.), and then an oil (227 mg) which was applied to three small p.l.c. plates and eluted five times with

petroleum ether-ether (3:1). Extraction of the major band gave a 1:1 mixture of 8β-hydroxy-1,1,9β-trimethyl-$\Delta^{4(10)}$-octal-2-one (204) and 10-hydroxy-1,1,6-trimethylspiro[4,5]dec-6-en-2-one (201) as an oil (87 mg), $\nu_{max.}$ (CCl_4) 3640sh, 3550br, 2960, 1742, 1716, 1478, 1380, and 1097 cm^{-1}, τ(CCl_4) 4.64 (2H, m, $W_{\frac{1}{2}}$ 4.3 Hz, 2 -CH=C-), 6.05 (2H, m, $W_{\frac{1}{2}}$ 10.3 Hz, 2 -CHOH-), 7.0-8.6 (18H, $-CH_2-$ and -OH) 8.49 (3H, m, $W_{\frac{1}{2}}$ 4.6 Hz, CH_3-C=), 8.77, 8.83, and 9.08 (9H, 3 s, 3 CH_3-C- in octalin), and 8.88 (6H, s, CH_3-C-CH_3 in spiran). Treatment of this mixture with lithium aluminium hydride afforded separation of the two components (see below). Further elution with benzene-ether mixtures gave a glass (213 mg) which was applied to two small p.l.c. plates and eluted eight times with petroleum ether-ether (3:1). Extraction of the main band gave 8β-hydroxy-1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2-one (205) (136 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3630sh, 3530br, 2970, 1715, 1468, 1445, 1381, 1335, 1298, 1164, 1118, and 1035 cm^{-1}, τ(CCl_4) 4.45 (1H, m, $W_{\frac{1}{2}}$ 10.1 Hz, -CH=C-), 6.00 (1H, 2 d, J 6.4, 8.2 Hz, -CHOH-), 7.0-8.7 (9H, $-CH_2-$ and -OH), 8.87 (6H, s, CH_3-C-CH_3), and 9.00 (3H, s, CH_3-C-), m/e 208 ($C_{13}H_{20}O_2$). The ketone gave a 2,4-dinitrophenylhydrazone as orange microcrystals (from ethyl acetate-methanol), m.p. 224-227° (Found: C, 59.05; H, 6.1; N, 14.1%; M^+ 388. $C_{19}H_{24}N_4O_5$ requires C, 58.8; H, 6.2; N, 14.4%; M 388).

Reduction of Rearrangement Product (201) and (204)

A solution of the 1:1 mixture of (201) and (204) (87 mg) in dry ether (20 ml) was slowly added to a stirred slurry of lithium aluminium hydride (20 mg) in dry ether (20 ml) and the mixture was heated under reflux for 2 h. After cooling to 0°, excess of lithium aluminium hydride was destroyed by cautious addition of ethyl acetate, and working up in the usual way gave a glass (89 mg) which was applied to one small p.l.c. plate and eluted seven times with petroleum ether-ether

(2:1). Extraction of the upper band gave 10-hydroxy-1,1,6-trimethylspiro-[4,5]dec-6-en-2-one (201) (25 mg) as bulky prisms (from hexane), m.p. 98-100°, $\nu_{max.}$ (CCl_4) 3600sh, 3450br, 2960, 1745, 1472, 1383, and 1096 cm^{-1}, τ(CCl_4) 4.58 (1H, m, $W_{\frac{1}{2}}$ 6.0 Hz, -CH=C-), 6.05 (1H, m, $W_{\frac{1}{2}}$ 6.5 Hz, -CHOH-), 7.2-8.4 (9H, $-CH_2-$ and -OH), 8.50 (3H, m, $W_{\frac{1}{2}}$ 3.2 Hz, CH_3-C=), and 8.87 (6H, s, CH_3-C-CH_3) (Found: C, 74.7; H, 9.6%; M^+ 208. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.6%; M 208). Extraction of the lower band gave a glass (31 mg) which was applied to one small p.l.c. plate and eluted with petroleum ether-ether (1:1) five times. Extraction of the major band gave 1,1,9β-trimethyl-$\Delta^{4(10)}$-octal-2β,8β-diol (202) (18 mg) as an amorphous solid, m.p. 75-80°, $\nu_{max.}$ (CCl_4) 3620, 3540, 3495, 1450, 1378, 1052, 1038, and 909 cm^{-1}, τ(CCl_4) 4.72 (1H, m, $W_{\frac{1}{2}}$ 10.0 Hz, -CH=C-), 6.33 (1H, 2 d, J 5.7, 8.6 Hz, -CHOH-), 6.57 (1H, t, J 4.3 Hz, -CHOH-), 7.4-8.8 (10H, $-CH_2-$ and -OH), 8.85, 8.89, and 9.04 (9H, 3 s, 3 CH_3-C-), m/e 210 ($C_{13}H_{22}O_2$).

Oxidation of Rearrangement Product (201) and (204)

Treatment of solution of the 1:1 mixture of (201) and (204) (48 mg) in acetone with Jones reagent in the usual way gave a pale yellow oil (37 mg), apparently homogeneous to t.l.c., whose i.r. and n.m.r. spectra indicated that it was a mixture of 1,1,9β-trimethyl-$\Delta^{4(10)}$-octal-2,8-dione and 1,1,6-trimethylspiro[4,5]dec-6-ene-2,10-dione (198); $\nu_{max.}$ (CCl_4) 2990, 2955, 1743, 1715, 1474, 1396, 1134, and 1096 cm^{-1}, τ(CCl_4) 4.41 (2H, m, $W_{\frac{1}{2}}$ 6.9 Hz, 2-CH=C-), 6.6-8.8 (16H, $-CH_2-$), 8.42 (3H, m, $W_{\frac{1}{2}}$ 4.1 Hz, CH_3-C=), 8.81 (6H, s, CH_3-C-CH_3), 8.90, 8.92, (6H, 2 s, CH_3-C-CH_3), and 9.25 (3H, s, CH_3-C-).

Oxidation of 8β-Hydroxy-1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2-one (205)

Treatment of a solution of the keto-alcohol (205) (50 mg) in acetone

with Jones reagent in the usual way gave a sample of 1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2,8-dione (196) (48 mg), identical with the dione obtained from the oxidation of 8β-hydroxy-1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2-one (195) (t.l.c., i.r., n.m.r., and m.p.).

Rearrangement of 8α,9α-Epoxy-1,1,10β-trimethyldecal-2-one Semicarbazone (150i)

Freshly distilled boron trifluoride-ether complex (0.12 ml) was added to a solution of the semicarbazone-α-epoxide (150i) (250 mg) in dry benzene (60 ml) under dry nitrogen at 25°. The mixture was stirred for 20 min and 5% sodium hydrogen carbonate solution (20 ml) and ethyl acetate (20 ml) were added, and working up in the usual way gave a glass (239 mg) containing one major component (t.l.c.). Attempts to isolate this component by p.l.c. were unsuccessful, so removal of the semicarbazone moiety was investigated prior to separation.

i) Hydrochloric acid: a sample of the rearrangement product (39 mg) was dissolved in conc. hydrochloric acid (10 ml) and ethanol (10 ml) and left at 20° for 2 h. The mixture was poured into water and ether and worked up in the usual way to give a pale brown gum (20 mg), whose t.l.c. indicated that no appreciable reaction had occurred.

ii) Formaldehyde: a sample of the rearrangement product (43 mg) in ethanol (5 ml) was added to 40% aqueous formaldehyde solution (1 ml) and the stirred mixture was warmed at 60° for 3 h. Working up in the usual way gave a pale yellow gum (39 mg) whose t.l.c. indicated that no appreciable reaction had occurred.

iii) Pyruvic acid: a sample of the rearrangement product (88 mg) was dissolved in glacial acetic acid (2 ml) and water (1 ml), and freshly distilled pyruvic acid (~40%; 0.2 ml) was added and the mixture was stirred and heated under reflux for 15 min. Working up in the usual way gave a pale yellow glass (41 mg) whose t.l.c. (petroleum ether-ether,

1:2) indicated one component with Rf 0.33 and a base line component only. The oil was applied to one small p.l.c. plate and eluted once with petroleum ether-ether (1:1), and extraction of the major band gave 8β-hydroxy-1,1,9β-trimethyl-$\Delta^{5(10)}$-octal-2-one (195) (8 mg) as an oil, identical (t.l.c., i.r., and n.m.r.) with the sample obtained direct from the keto-α-epoxide (88i).

Rearrangement of 5ξ,6ξ-Epoxy-2α,5,9β,10β-tetramethyldecal-1β-ol (92i)

Freshly distilled boron trifluoride-ether complex (0.56 ml) was added to a stirred solution of the epoxy-alcohol (92i) (500 mg) in dry benzene (25 ml) under dry nitrogen at 25°, and after 2 min the solution was deep red. 5% Sodium hydrogen carbonate solution (40 ml) was added and the mixture was worked up in the usual way to give a viscous yellow oil (466 mg) containing three main components (t.l.c.). The oil was applied to two large p.l.c. plates and eluted twice with petroleum ether-ether (2:1) and the three main bands were extracted.

The highest band gave 4-(5-hydroxy-2,6,6-trimethylcyclohex-1-enyl)-2-methylbutan-1-al (208) (147 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3625, 3490, 2705, 1728, 1465, 1376, and 1035 cm^{-1}, τ (CCl_4) 0.40 (1H, d, J 1.7 Hz, -CH-CHO), 6.63 (1H, ABXq, J 4.3, 8.6 Hz, -CHOH), 7.5-9 (10H, $-CH_2-$ and -OH), 8.41 (3H, s, $CH_3-C=$), 8.83 (3H, d, J 7.0 Hz, CH_3-CH-), and 8.98 and 9.05 (6H, s s, CH_3-C-CH_3), m/e 224 ($C_{14}H_{24}O_2$). Attempts to prepare a semicarbazone and a 2,4-dinitrophenylhydrazone were unsuccessful. The middle band gave a dihydroxy-olefin (106 mg) as bulky rods (from hexane) m.p. 136-137.5°, $\nu_{max.}$ (CCl_4) 3630, 3420, 2960, 1460, 1380, 1090, 1064, and 904 cm^{-1}, τ (CCl_4) 4.57 (1H, m, $W_{\frac{1}{2}}$ 8.2 Hz, $-CH=C-$), 6.39 (1H, d, J 10 Hz, -CHOH-CH-), 6.70 (1H, m, $W_{\frac{1}{2}}$ 10.6 Hz, $-CHOH-CH_2$), 8.23 (3H, m, $W_{\frac{1}{2}}$ 8.4 Hz, $CH_3-C=$), 8.98 (3H, d, J 6.0 Hz, CH_3-CH-), and 8.97 and 9.17 (6H, 2 s, 2 CH_3-C-) (Found: C, 75.3; H, 10.5%; M^+ 224.

$C_{14}H_{24}O_2$ requires C, 75.0; H, 10.7%; M 224). Jones oxidation of this compound gave a diketone as an oil with a broad carbonyl absorption in its i.r. spectrum, $\nu_{max.}$ (CCl_4) 2960, 2935, 2880, 1738, 1730, 1466, 1386, 1285, 1120, and 1072 cm^{-1}. The lowest band gave 5β-hydroxy-1ξ, 6α, 9β 10β-tetramethyldecal-2-one (214) (146 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3620, 3510, 2950, 1709, 1458, 1380, 1372, 1279, and 1044 cm^{-1}, τ(CCl_4) 6.20 (1H, d, J 9.6 Hz, -CHOH-CH-) 7-9 (11H, $-CH_2-$ and -OH), 8.97, 9.00 (6H, 2 d, J 6.9 Hz, 2 CH_3-CH-), and 9.12 and 9.32 (6H, 2 s, 2 CH_3-C-). The ketone gave a 2,4-dinitrophenylhydrazone as orange plates (from ethyl acetate-methanol), m.p. 193-195° (dec.) (Found: C, 59.1; H, 6.8; N, 14.2%; M^+ 404. $C_{20}H_{28}N_4O_5$ requires C, 59.4; H, 6.9; N, 13.9%; M 404).

Treatment of a small sample of the hydroxy-ketone (214) with Jones reagent gave a dione (215) identical (i.r., n.m.r., t.l.c.) with the dione obtained from the rearrangement of the keto-epoxide (93i).

Rearrangement of $5\xi_1,6\xi_1$-Epoxy-2α,5,9β,10β-tetramethyldecal-1-one (93i)

Freshly distilled boron trifluoride-ether complex (0.8 ml) was added to a stirred solution of the keto-epoxide (93i) (1.42 g) in dry benzene (60 ml) under dry nitrogen at 10°, and the mixture was left for 5 min to give a golden yellow solution. 5% Sodium bicarbonate solution (50 ml) was added and working up in the usual way gave a pale yellow oil (1.42 g) containing several components (t.l.c.) which was applied to four large p.l.c. plates and eluted three times with light petroleum-ether (2:1). Five main bands were extracted:

Band A yielded 2α,$5\xi_1$,9β,10β-tetramethyldecal-1,6-dione (215) (65 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2970, 2940, 1710, 1705, 1462, 1450, 1382, and 1140 cm^{-1}, τ(CCl_4) 7.0-8.8 (10H, $-CH_2-$), 8.85

(3H, s, CH_3-9), 8.98, 9.17 (6H, 2 d, J 6.4 Hz, 2 CH_3-CH-), and 9.23 (3H, s, CH_3-10), m/e 222 ($C_{14}H_{22}O_2$). The dione gave a mono-2,4-dinitrophenylhydrazone as pale orange prisms (from ethyl acetate-methanol), m.p. 221-225° (dec.) (Found: C, 59.6; H, 6.5; N, 13.9%; M^+ 402. $C_{20}H_{26}N_4O_5$ requires: C, 59.6; H, 6.5; N. 13.9%; M 402).

Band B gave an oil (340 mg) which was further purified by p.l.c. (1 large plate; two elutions with light petroleum-ether 2:1) to give 6ξ_1,9ξ_1-epoxy-2α,5,5,10β-tetramethyldecal-1-one (217) (280 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2960, 1724, 1470, 1382, 1185, 1130, 900, and 880 cm^{-1}, τ(CCl_4) 6.33 (1H, d, J 4.3 Hz, -CH-O-), 7.5-8.8 (9H, $-CH_2-$), 8.82, 8.97, 9.10 (9H, 3 s, 3 CH_3-C-), and 9.00 (3H, d, J 6.4 Hz, CH_3-CH-), m/e 222($C_{14}H_{22}O_2$). Treatment of this cyclic ether with 2,4-dinitrophenylhydrazine reagent gave an orange solid as microcrystals (from aqueous methanol-ethyl acetate), m.p. 167-170° (Found: C, 50.25, 51.1; H, 5.4, 5.5; N, 17.45, 17.8. $C_{26}H_{34}N_8O_{10}$ requires C, 50.5; H, 5.5; N, 18.1%). No molecular ion was observable in the m.s. ($C_{26}H_{30}N_8O_8$ requires m/e 582), and the highest recorded peak had m/e 495.

Band C gave a viscous oil (210 mg) whose t.l.c. and n.m.r. spectrum indicated that it was not pure. The oil was applied to three small p.l.c. plates and eluted with light petroleum-ether (1:2), and the main band gave a glass (71 mg) which was further purified by applying to one small p.l.c. plate and eluting six times with light petroleum-ether (4:1). The main band afforded a glass (32 mg), apparently homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 3620, 3500, 2950, 1710, 1455, 1367, and 1080 cm^{-1}, τ(CCl_4) 6.40 (1H, m, $W_{\frac{1}{2}}$ 13.3 Hz, -CHOH), 8.45 (~ 2H, s), 8.68 (~ 2H, s), 8.92 (6H, s, CH_3-C-CH_3), and 9.05 (3H, d, J 6.4 Hz, CH_3-CH-), m/e 242 ($C_{14}H_{26}O_3$), 222 ($C_{14}H_{22}O_2$).

Band D gave a viscous oil (101 mg), thought to be 8ξ_1-hydroxy-1β,

3α,6,7α-tetramethylbicyclo[5.3.0]dec-5-en-2-one (223) $\nu_{max.}$ (CCl_4) 3630, 3550, 2960, 1720, 1456, 1380, and 1025 cm-1, τ (CCl_4) 4.58 (1H, m, $W_{\frac{1}{2}}$ 10.0 Hz, -CH=C-), 5.65 (1H, ABXq, J 6.2, 8.9 Hz, -CHOH), 7.3-9 (8H, $-CH_2-$ and -OH), 8.43 (3H, m, $W_{\frac{1}{2}}$ 6.0 Hz, CH_3-C=), 8.94 (3H, d, J 6.4 Hz, CH_3-CH-), and 8.84 and 9.18 (6H, 2 s, 2 CH_3-C-), m/e 222 ($C_{14}H_{22}O_2$). Jones oxidation of a small sample of this hydroxy-ketone (223) gave the corresponding dione, $\nu_{max.}$ (CCl_4) 2990, 1744, 1720, 1465, 1387, 1040, and 894 cm^{-1}.

Band E gave a glass (111 mg) whose t.l.c. showed that it was not pure. It was applied to two small p.l.c. plates and eluted once with light petroleum-ether (1:2). The main band gave a hydroxy-ketone (60 mg) as a glass, which could not be induced to crystallise, $\nu_{max.}$ (CCl_4) 3650, 3560, 3430, 2980, 1725, 1462, 1378, 1032, and 893 cm^{-1}, τ(CCl_4) 6.40 (~1H, complex, -CHOH), 7.1-9 (9H, $-CH_2-$ and -OH), 8.72, 8.92, 9.02 (9H, 3 s, 3 CH_3-C-), and 8.96 (3H, d, J 6.4 Hz, CH_3-CH-), m/e 242 ($C_{14}H_{26}O_3$).

Rearrangement of 5ξ$_2$,6ξ$_2$-Epoxy-2α,5,9β,10β-tetramethyldecal-1-one (93ii)

Freshly distilled boron trifluoride-ether complex (0.4 ml) was added to a stirred solution of the keto-epoxide (93ii) (740 mg) in dry benzene (40 ml) under dry nitrogen at 25°, and the mixture was stirred for 10 min to give a pink solution. Addition of 5% sodium hydrogen carbonate solution (50 ml) and working up in the usual way gave 1,5α,8β,9β-tetramethyl-4-oxohexahydroindane-1ξ-carbaldehyde (229) (738 mg) as an oil, homogeneous to t.l.c., $\nu_{max.}$ (CCl_4) 2950, 2690w, 1712, 1700, 1470, 1380, 1160, and 1030 cm^{-1}, τ(CCl_4) 0.64 (1H, s, -C-CHO), 6.9-8.9 (9H, $-CH_2-$), 8.84, 8.96, 9.01 (9H, 3 s, 3 CH_3-C-), and 9.05 (3H, d, J 6.0 Hz, CH_3-CH-), m/e 222 ($C_{14}H_{22}O_2$). The keto-

aldehyde gave a mono-2,4-dinitrophenylhydrazone as microcrystals (from ethyl acetate-methanol), m.p. 200-203°, (Found: C, 59.3; H, 6.6; N, 13.85%; M^+ 402. $C_{20}H_{26}N_4O_5$ requires C, 59.7; H, 6.5; N, 13.9%; M 402). On standing at room temperature, the oily aldehyde was autoxidised to solid 1,5α,8β,9β-tetramethyl-4-oxohexahydroindane-1ξ-carboxylic acid (230) obtained as bulky prisms (from acetone-hexane) m.p. 162-165°, $\nu_{max.}$ (CCl_4) 3570w, 3420w, 1715, 1700, 1464, 1380, and 1165 cm^{-1}, τ ($CDCl_3$) 6.9-9 (~ 9H, $-CH_2-$), 8.65, 8.88, 8.99 (9H, 3 s, 3 CH_3-C-), and 9.04 (3H, d, J 7.2 Hz, CH_3-CH-) (Found: C, 70.7; H, 9.35%; M^+ 238. $C_{14}H_{22}O_3$ requires C, 70.6; H, 9.2%; M 238).

References

1. See e.g. C.A. Buehler and D.E. Pearson, "Survey of Organic Syntheses", John Wiley and Sons, Inc., New York, 1970, p.320.

2. J.N. Bronsted, M. Kilpatrick, and M. Kilpatrick, J.Amer.Chem.Soc., 1929, 51, 428.

3. S. Winstein and R.B. Henderson, J.Amer.Chem.Soc., 1953, 65, 2196.

4. D.N. Kirk, in "Terpenoids and Steroids", ed. K.H. Overton, Specialist Periodical Report, The Chemical Society, London, Vol. 1, 1971, p.367.

5. J.H. Richards and J.B. Hendrickson, "The Biosynthesis of Steroids, Terpenoids, and Acetogenins", W.A. Benjamin Inc., New York, 1964, p.1.

6. R.G. Langdon and K. Bloch, J.Amer.Chem.Soc., 1952, 74, 1869; J.Biol.Chem., 1953, 200, 129, 135; R.B. Clayton and K. Bloch, ibid., 1956, 218, 305, 319; P.B. Schneider, R.B. Clayton, and K. Bloch, ibid., 1957, 224, 175; T.T. Tchen and K. Bloch, ibid., p.921.

7. H.C. Rilling, J.Biol.Chem., 1966, 241, 3233.

8. G. Popjak, J. Edmond, K. Clifford, and V. Williams, J.Biol.Chem., 1969, 244, 1897.

9. E.J. Corey and P.R. Ortiz de Montellano, Tetrahedron Letters, 1968, 5113.

10. H.C. Rilling and W.W. Epstein, J.Amer.Chem.Soc., 1969, 91, 1041; J.Biol.Chem., 1970, 18, 4597.

11. L.J. Altman, R.C. Kowerski and H.C. Rilling, J.Amer.Chem.Soc., 1971, 93, 1782; H.C. Rilling, C.D. Poulter, W.W. Epstein, and B. Larsen, ibid., p.1783.

12. L.J. Altman, L. Ash, R.C. Kowerski, W.W. Epstein, B.R. Larsen, H.C. Rilling, F. Muscio, and D.E. Gregonis, J.Amer.Chem.Soc., 1972, 94, 3257.

13. A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, Helv.Chim.Acta., 1955, 38, 1890.

14. J.W. Cornforth, R.H. Cornforth, A. Pelter, M.G. Horning, and G. Popjak, Tetrahedron, 1959, 5, 311; J.W. Cornforth, R.H. Cornforth, C. Donninger, G. Popjak, Y. Shimizu, S. Ichii, E. Forchielli, and E. Caspi, J.Amer.Chem.Soc., 1965, 87, 3224.

15. R.K. Maudgal, T.T. Tchen, and K. Bloch, J.Amer.Chem.Soc., 1958, 80, 2589.

16. T.T. Tchen and K. Bloch, J.Amer.Chem.Soc., 1956, 78, 1516; J.Biol.Chem., 1957, 226, 921, 931.

17. R. Breslow, E. Barrett, and E. Mohacsi, Tetrahedron Letters, 1962, 1207; R. Breslow, J.T. Groves, and S.S. Olin, ibid., 1966, 4717.

18. D.H.R. Barton and G.P. Moss, Chem.Comm., 1966, 261.

19. E.E. van Tamelen, J.D. Willett, R.B. Clayton, and K.E. Lord, J.Amer.Chem.Soc., 1966, 88, 4752.

20. E.J. Corey, W.E. Russey, and P.R. Ortiz de Montellano, J.Amer.Chem. Soc., 1966, 88, 4750.

21. J.D. Willett, K.B. Sharpless, K.E. Lord, E.E. van Tamelen, and R.B. Clayton, J.Biol.Chem., 1967, 244, 4182.

22. Ref. 4, p.13.

23. E.E. van Tamelen and T.J. Curphey, Tetrahedron Letters, 1962, 121.

24. E.E. van Tamelen and K.B. Sharpless, Tetrahedron Letters, 1967, 2655.

25. K.H. Dahm, B.M. Trost, and H. Roller, J.Amer.Chem.Soc., 1967, 89, 5292.

26. W.B. Mors, M.F. dos Santos, H.J. Monteiro, B. Gilbert, and J. Pellegrino, Science, 1967, 157, 950.

27. D.J. Goldsmith, J.Amer.Chem.Soc., 1962, 84, 3913.

28. E.E. van Tamelen, A. Storni, E.J. Hessler, and M. Schwartz, J.Amer.Chem.Soc., 1963, 85, 3295.

29. E.E. van Tamelen and R.M. Coates, Chem.Comm., 1966, 413.

30. E.E. van Tamelen and R.G. Nadeau, J.Amer.Chem.Soc., 1967, 89, 176.

31. E.E. van Tamelen, J.D. Willett, M. Schwartz, and R.G. Nadeau, J.Amer.Chem.Soc., 1966, 88, 5937.

32. E.E. van Tamelen, J.D. Willett, and R.B. Clayton, J.Amer.Chem.Soc., 1967, 89, 3371.

33. D.H.R. Barton, G. Mellows, D.A. Widdowson, and J.J. Wright, J.Chem.Soc. (C), 1971, 1142.

34. E.E. van Tamelen, K.B. Sharpless, R. Hanzlik, R.B. Clayton, A.L. Burlingame, and P.C. Wszolek, J.Amer.Chem.Soc., 1967, 89, 7150.

35. A. Chawla and S. Dev, Tetrahedron Letters, 1967, 4837.

36. K.B. Sharpless, J.Amer.Chem.Soc., 1970, 92, 6999.

37. P. Benveniste, L. Hirth, and G. Ourisson, Phytochem., 1966, 5, 31, 45.

38. P. Benveniste and R.A. Massy-Westropp, Tetrahedron Letters, 1967, 3553.

39. H.H. Rees, L.J. Goad, and T.W. Goodwin, Tetrahedron Letters, 1968, 723.

40. H.H. Rees, L.J. Goad, and T.W. Goodwin, Biochem.J., 1968, 107, 417.

41. E. Capstack, N. Rosin, G.A. Blondin, and W.R. Nes, J.Biol.Chem., 1965, 240, 3258.

42. W.O. Godtfredsen, H. Lorck, E.E. van Tamelen, J.D. Willett, and R.B. Clayton, J.Amer.Chem.Soc., 1968, 90, 208.

43. G.P. Cotterrell, T.G. Halsall, and M.J. Wriglesworth, J.Chem.Soc.(C), 1970, 739.

44. D.H.R. Barton, G. Mellow, and D.A. Widdowson, J.Chem.Soc.(C), 1971, 110.

45. E. Caspi, J.M. Zander, J.B. Grieg, F.B. Mallory, R.L. Connor, and J.R. Landrey, J.Amer.Chem.Soc., 1968, 90, 3563.

46. E. Caspi, J.B. Grieg, and J.M. Zander, Biochem.J., 1968, 109, 931.

47. E. Caspi, J.B. Grieg, and J.M. Zander, Chem.Comm., 1969, 28.

48. J.M. Zander and E. Caspi, Chem.Comm., 1969, 209.

49. P.D.G. Dean, P.R. Ortiz de Montellano, K. Bloch, and E.J. Corey, J.Biol.Chem., 1967, 242, 3014.

50. E.J. Corey, K. Lin, and M. Jautelat, J.Amer.Chem.Soc., 1968, 90, 2724.

51. R.B. Clayton, E.E. van Tamelen, and R.G. Nadeau, J.Amer.Chem.Soc., 1968, 90, 820.

52. L.O. Crosby, E.E. van Tamelen, and R.B. Clayton, Chem.Comm., 1969, 532.

53. E.E. van Tamelen, K.B. Sharpless, J.D. Willett, R.B. Clayton, and A.L. Burlingame, J.Amer.Chem.Soc., 1967, 89, 3920.

54. E.J. Corey and S.K. Gross, J.Amer.Chem.Soc., 1967, 89, 4562.

55. R.J. Anderson, R.P. Hanzlik, K.B. Sharpless, E.E. van Tamelen, and R.B. Clayton, Chem.Comm., 1969, 53.

56. E.J. Corey, P.R. Ortiz de Montellano, and H. Yamamoto, J.Amer.Chem. Soc., 1969, 90, 6254.

57. E.E. van Tamelen, R.P. Hanzlik, K.B. Sharpless, R.B. Clayton, W.J. Richter, and A.L. Burlingame, J.Amer.Chem.Soc., 1968, 90, 3284.

58. E.E. van Tamelen, R.P. Hanzlik, R.B. Clayton, and A.L. Burlingame, J.Amer.Chem.Soc., 1970, 92, 2137.

59. E.E. van Tamelen, J.A. Smaal, and R.B. Clayton, J.Amer.Chem.Soc., 1971, 93, 5279.

60. E.J. Corey, K. Lin, and H. Yamamoto, J.Amer.Chem.Soc., 1969, 91, 2132.

61. E.E. van Tamelen and J.H. Freed, J.Amer.Chem.Soc., 1970, 92, 7206.

62. E.E. van Tamelen, G.M. Milne, M.I. Suffness, M.C. Rudler Chauvin, R.J. Anderson, and R.S. Aschini, J.Amer.Chem.Soc., 1970, 92, 7202.

63. E.E. van Tamelen and J.W. Murphy, J.Amer.Chem.Soc., 1970, 92, 7204.

64. E.D. Brown and J.K. Sutherland, Chem.Comm., 1968, 1060.

65. K. Wada and K. Munakata, Tetrahedron Letters, 1968, 4677.

66. J.G. St. C. Buchanan and T.G. Halsall, J.Chem.Soc. (C), 1970, 2280.

67. For recent reviews see (a) D.N. Kirk and M.P. Hartshorn, "Steroid Reaction Mechanisms", Elsevier, Amsterdam, 1968, p.353; (b) Ref. 4, p.365; Vol. 2, 1972, p.306.

68. H.B. Henbest and T.I. Wrigley, J.Chem.Soc., 1957, 4596, 4765.

69. J.W. Blunt, M.P. Hartshorn, and D.N. Kirk, Chem.Comm., 1966, 160.

70. B.N. Blackett, J.M. Coxon, M.P. Hartshorn, and K.E. Richards, Tetrahedron, 1969, 25, 4999.

71. J.W. Blunt, M.P. Hartshorn, and D.N. Kirk, Tetrahedron, 1969, 25, 149.

72. J.M. Coxon, M.P. Hartshorn, C.N. Muir, and K.E. Richards, Tetrahedron Letters, 1967, 3725.

73. I.G. Guest and B.A. Marples, J.Chem.Soc.(C), 1970, 1626.

74. J.M. Coxon, M.P. Hartshorn, and C.N. Muir, Tetrahedron, 1969, 25, 3925.

75. J.M. Coxon, M.P. Hartshorn, and B.L. Sutherland, Tetrahedron Letters, 1969, 4029.

76. M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1965, 21, 1547.

77. M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1964, 20, 1943.

78. J.W. Blunt, M.P. Hartshorn, and D.N. Kirk, Tetrahedron, 1965, 21, 559.

79. Ref. 67(a), p.358.

80. J.M. Coxon, M.P. Hartshorn, and D.N. Kirk, Tetrahedron, 1964, 20, 2531.

81. See e.g., J.W. Blunt, J.M. Coxon, M.P. Hartshorn, and D.N. Kirk, Tetrahedron, 1967, 23, 1811.

82. T.G. Halsall, Sir Ewart R.H. Jones, E.L. Tan, and G.R. Chaudhry, J.Chem.Soc.(C), 1966, 1374.

83. M.P. Hartshorn and D.N. Kirk, Tetrahedron Letters, 1966, 3913.

84. J.W. Blunt, M.P. Hartshorn, and D.N. Kirk, J.Chem.Soc.(C), 1968, 635.

85. H.W. Whitlock and A.H. Olson, J.Amer.Chem.Soc., 1970, 92, 5383.

86. J.W. ApSimon, R.R. King, and J.J. Rosenfeld, Canad.J.Chem., 1969, 47, 1989.

87. G. Saucy, R.E. Ireland, J. Bordner, and R.E. Dickerson, J.Org.Chem., 1971, 36, 1195.

88. W. Templeton, "An Introduction to the Chemistry of Terpenoids and Steroids", Butterworths, London, 1969, p.253.

89. e.g. E.C. du Feu, F.J. McQuillin, and R. Robinson, J.Chem.Soc., 1937, 53.

90. F.J. McQuillin, J.Chem.Soc., 1955, 528.

91. S. Ramachandran and M.S. Newman, Org.Synth., 1961, 41, 38.

92. J.A. Marshall and W.I. Fanta, J. Org.Chem., 1964, 29, 2501.

93. C.H. Heathcock, M.E. Ellis, J.E. McMurry, and A. Coppolino, Tetrahedron Letters, 1971, 4995.

94. E. Brown, M. Ragault, and J. Touet, Tetrahedron Letters, 1971, 1043.

95. J.A. Marshall and T.M. Warne, J.Org.Chem., 1971, 36, 178.

96. C.J.V. Scanio and R.L. Starrett, J.Amer.Chem.Soc., 1971, 93, 1539.

97. e.g. E.J. Corey and A.G. Hortmann, J.Amer.Chem.Soc., 1965, 87, 5736.

98. P.S. Pinkney, Org.Synth., Coll. Vol. II, 1943, 116.

99. A.I. Vogel, "Practical Organic Chemistry", Longmans, Green and Co., London, 1957, p.193.

100. R. Mayer and P. Held, Chem.Ber., 1960, 93, 2750.

101. H.C. Brown and C.P. Garg, J.Amer.Chem.Soc., 1961, 83, 2951.

102. cf. J.J. Bloomfield, J.Org.Chem., 1961, 26, 4112.

103. a) W.G. Dauben and J.W. McFarland, J.Amer.Chem.Soc., 1960, 82, 4245; b) W.G. Dauben, J.W. McFarland, and J.B. Rogan, J.Org.Chem., 1961, 26, 297.

104. J.R. Nunn and W.S. Rapson, J.Chem.Soc., 1949, 825.

105. N. Ferry and F.J. McQuillin, J.Chem.Soc., 1962, 103.

106. cf. F. Sondheimer, R. Mechoulam, and M. Sprecher, Tetrahedron, 1964, 20, 2473.

107. C.K. Ingold, "Structure and Mechanism in Organic Chemistry", Second Edition, G. Bell and Sons Ltd., London, 1969, p.817.

108. R.B. Woodward, A.A. Patchet, D.H.R. Barton, D.A.J. Ives and R.B. Kelley, J.Chem.Soc., 1957, 1131.

109. W.L. Meyer and A.S. Levinson, J.Org.Chem., 1963, 28, 2184.

110. F.J. McQuillin and R.B. Yeats, J.Chem.Soc., 1965, 4273.

111. D. Willis, D.Phil.Thesis, Oxford, 1957, p.107.

112. a) H.J. Ringold and G. Rosenkranz, J.Org.Chem., 1957, 22, 602; b) D. Willis, D.Phil.Thesis,Oxford,1957, p.105; c) Ref. 85.

113. W. Mudd, Part II Thesis, Oxford, 1971, p.20.

114. O. Isler, W. Huber, A. Ronco, and M. Kofter, Hely.Chim.Acta., 1947, 30, 1911.

115. J.A. Marshall and A.R. Hochstettler, J.Amer.Chem.Soc., 1969, 91, 648.

116. D. Swern in "Organic Peroxides", Vol. II, ed. D. Swern, John Wiley and Sons, Inc., New York, 1971, p.355.

117. Ref. 116, p.466.

118. Ref. 116, p.472.

119. P.D. Bartlett, Rec.Chem.Progr., 1950, 11, 47.

120. H. Kwart and D.M. Hoffman, J.Org.Chem., 1966, 31, 419.

121. K.D. Bingham, G.D. Meakins, and G.H. Whitham, Chem.Comm., 1966, 445.

122. H. Kwart, P.S. Starcher, and S.W. Tinsley, Chem.Comm., 1967, 335.

123. R. Huisgen, Angew.Chem., 1963, 75, 604, 742; Proc.Chem.Soc., 1961, 337; R. Huisgen, L. Mobius, G. Muller, H. Stangl, C. Szeimies, and J.M. Vernon, Chem.Ber., 1965, 98, 3992.

124. Ref. 116, p.474.

125. Ref. 116, p.475.

126. R. Curci, R.A. DiPrete, J.O. Edwards, and G. Modena, J.Org.Chem., 1970, 35, 740.

127. C.R. Eck, P. Kullberg, and B. Green, J.C.S. Chem.Comm., 1972, 539.

128. G.B. Payne, Tetrahedron, 1962, 18, 763.

129. G.B. Payne, P.H. Denning, and P.H. Williams, J.Org.Chem., 1961, 26, 659.

130. Ref. 116, p.406.

131. L.S. Silbert, E. Siegel, and D. Swern, J.Org.Chem., 1962, 27, 1336.

132. Ref. 116, p.410.

133. Cf. D.A. Okorie and D.A.H. Taylor, Chem.Comm., 1967, 83.

134. W.L. Meyer, D.L. Davis, L. Foster, A.S. Levinson, V.L. Sawin, D.C. Shaw, and R.F. Weddleton, J.Amer.Chem.Soc., 1965, 87, 1573.

135. R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey, and R.W. Kierstead, Tetrahedron, 1958, 2, 1.

136. Ref. 67 (a), p.355, footnote.

137. J.R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentice-Hall, Inc., New Jersey, 1965, p.17.

138. R. Leonard and J.B. Thomson, J.C.S.Chem.Comm., 1972, 1281.

139. C.A. Grob and P.W. Schiess, Angew.Chem.Internat.Edn., 1967, 6, 1; C.A. Grob, ibid., 1969, 8, 535.

140. L.M. Jackmann and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, Second Edition, 1969, p.223.

141. H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day Inc., San Francisco, 1967, p.491.

142. Ref. 141, p.206.

143. For a review of carbocyclic and heterocyclic propellanes, see D. Ginsburg, Accounts Chem.Res., 1969, 2, 121.

144. Ref. 136, p.317.

145. Ref. 140, p.85.

146. Ref. 1, p.671.

147. E.B. Hershberg, J.Org.Chem., 1948, 13, 542.

148. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, 1967, p.330.

149. G.J. Kasperek , T.C. Bruice, H. Yagi, and D.M. Jerina, J.C.S. Chem.Comm., 1972, 784.

150. J.H. Guest, Part II Thesis, Oxford, 1970, p.48.

151. Ref.150, p.45.

152. Ref. 113, p.41.

Corrigenda

Nomenclature of Cyclic Ketones

The I.U.P.A.C. Nomenclature Rules outline several methods for naming ketones of unsaturated cyclic compounds (Rules C.314 *et seq.*), and some of the compounds prepared in this work have not been named strictly in accordance with these Rules: the following is a list of names which are to be preferred to those used in the Experimental section.

Compound	Modified name
(119)	8β-Methyl-7,8-dihydroindan-5(6H)-one
(121)	9-Hydroxy-8β-methyl-6,7,8,9-tetrahydroindan-5(4H)-one
(126)	4,8β-Dimethyl-7,8-dihydroindan-5(6H)-one
(127)	4,4,8β-Trimethyl-1,2,4,6,7,8-hexahydroinden-5-one