A Thesis entitled

STUDIES IN THE CATION- INDUCED CYCLISATION OF OLEFINS

presented by

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TO MY WIFE, 'SHOLA AND

DAUGHTER, OLUBUNMI

BIOGRAPHY

The author graduated with a B.Sc. (Hons) in Chemistry in Ahmadu Bello University, Zaria, Nigeria in 1973 and the following year was engaged in National Youth Service, after which he obtained a degree of M.Sc. from the same university in 1976.

Since August 1977, the author has been engaged in research under the supervision of Professor J. K. Sutherland, the results of which are embodied in this thesis.

No part of this work has been used in support of an application for any other degree.

ACKNOWLEDGMENTS

The author would like to express his profound gratitude to Professor J. K. Sutherland for his very keen interest, patience and encouragement throughout the course of this work.

Thanks are also due to the following, who in one way or another contributed to the success of this work:-

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ABSTRACT

Chapter 1 consists of a review of the role of squalene oxide in the biogenesis of triterpenoids and steroids *via* lanosterol. A number of non-enzymic methods of inducing such cyclisations under various conditions is also presented with greater emphasis on the more successful techniques.

Chapter 2 starts with a review of the classical route to the synthesis of 2-alkylcyclohexenones *via* alkylation of Hagemann's ester. This is followed by a series of reactions carried out by the author leading to a novel synthetic route to the 2-alkylcyclohexenones, which is shown to be much better than the former route. A review of the Lewis acid induced cyclisation of epoxyolefins already carried out by a number of workers in our Laboratories is also presented followed by the cyclisations of epoxyolefins and alpha, Beta -unsaturated ketones carried out by the author. It is hereby demonstrated that formation of bi-, tri- and tetra- cyclic systems are feasible under suitable conditions.

Chapter 3 consists of the experimental work of reactions mentioned in Chapter 2.

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CHAPTER 1 - REVIEW

SECTION 1 - INTRODUCTION.

Some polyenic substances having trans olefinic bonds in a 1,5-relationship have been made to undergo stereospecific, non-enzymic, cation-induced cyclisations resulting in the formation of polycyclic products with the all trans 'natural' configuration, reminiscent of similar products obtained by biogenetic conversion of squalene-2,3-epoxide into biogenetic triterpenoids.

Several initiators[1] have been used, albeit, successfully in only a few cases, such as electrophilic cyclic ketal ring opening and allylic alcohol protonation followed by dehydration to generate an allylic carbonium ion. The earlier and less successful initiators involved acid-catalysed addition to double bonds, solvolysis of sulphonate esters, and electrophilic epoxide ring opening. Other studies worthy of mention are the free-radical- and the mercury ion-initiated cyclisation of Julia[2], and the proton- and mercury ion-initiated cyclisations of Semenovsky.[3]

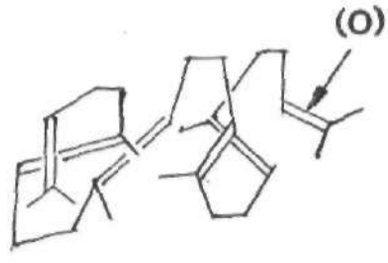
Most of these methods have been described by Johnson[1] in a comprehensive review of these studies. Each of these methods, except the free-radical method shall be briefly discussed in this review. Several terminators-methylacetylenic, styryl- and trimethylsilyl -end groups will be discussed. The current view on the mechanisms of these cyclisations will also be discussed.

SECTION 2 - THE ROLE OF SQUALENE 2,3-OXIDE IN THE BIOGENESIS OF STEROIDS.

Squalene (1), a triterpene, is known to be the fundamental source of all other triterpenes and steroids.



1



1a

However, nature's design for the synthesis of these intricate molecules has not been fully understood. For this reason efforts have been made in the last two and a half decades to mimic the known enzymatic conversion of squalene to the polycyclic triterpenoids.

In 1955, Stork et al[4] and Eschenmoser et al[5] independently postu-

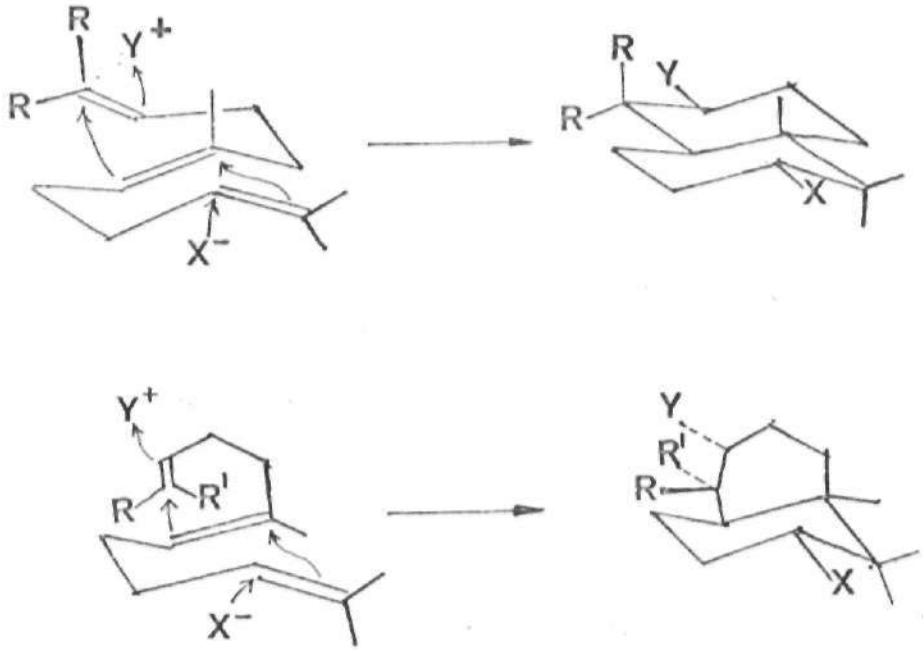
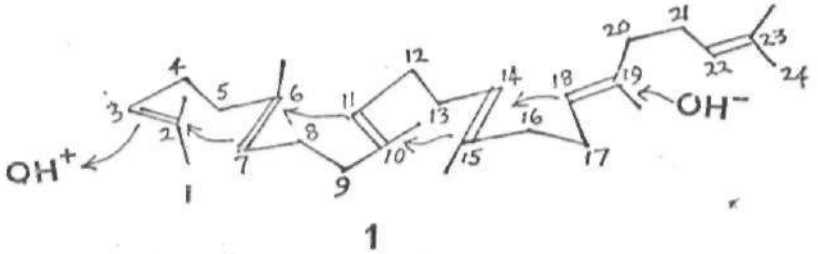
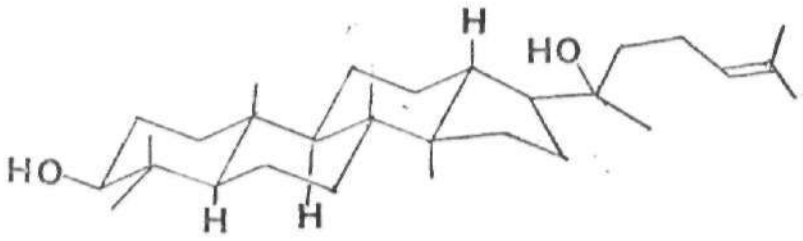


Fig i



1



2

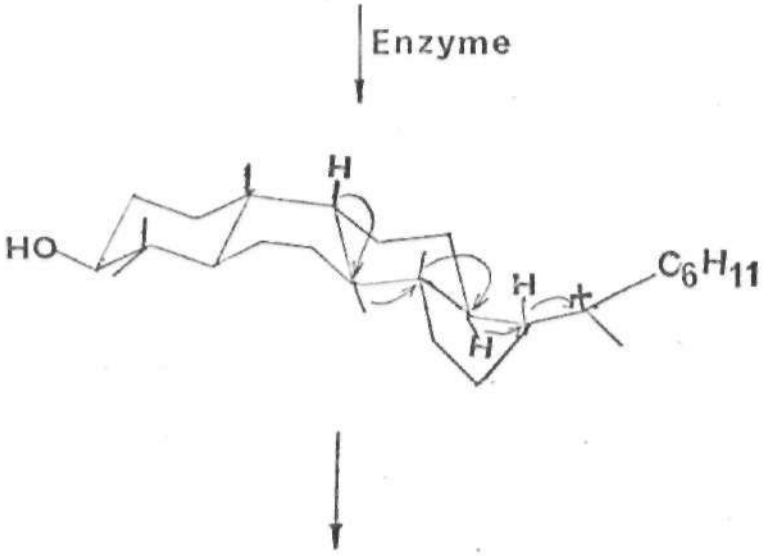
Fig ii

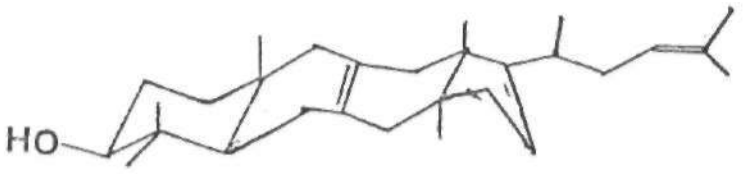
lated that the stereochemistry of naturally occurring polycyclic compounds could be rationalised in terms of concerted cyclisations of their acyclic precursors; and in reviewing the stereochemistry of such cyclisations suggested that the geometry of the double bonds present in the polyolefin determined the geometry of the ring junctions so formed. Hence, a trans olefin would lead to a trans ring junction, and a cis olefin would give a cis ring junction, (Fig. i).

The concerted trans-addition to the olefinic bonds invokes the stereochemical relationship of the newly-formed ring junction in relationship to the olefinic bond. This process involves a trans-anti-parallel electrophilic addition to the olefinic bonds and this concept affords a satisfactory rationalization of the course of many biological cyclisations. For example, enzymes may be responsible for inducing the boat-like transition state that is required for the formation of lanosterol (3). Stork[4] had in fact suggested that whereas sterols like the trans lupeol class, e.g. dammarene diol (2, Fig. ii) were formed by concerted cyclisation, sterols of the lanosterol class were formed by initial cyclisation of A and B rings, followed by ring B assuming the less favoured boat conformation and subsequent concerted formation of C and D rings to explain the observed cis C-9,10 stereochemistry (Fig. iii).

The unique role of squalene in the biosynthesis of sterols and triterpenes[5,6] has been verified by extensive tracer studies. Tchen

1





3

Fig iii

and Bloch[7] observed that cyclisation in a rat liver homogenate containing D_2O or $H_2{}^{18}O$ gave lanosterol (3) devoid of deuterium or ^{18}O whilst incubation in the presence of $^{18}O_2$ resulted in incorporation of the isotope. This implies that the atmospheric oxygen was in some manner introduced into the organic molecule without equilibration with the oxygen of water, and that partially cyclized intermediates which could otherwise protonate and deprotonate in the medium were not involved in the overall conversion of squalene to lanosterol.

The oxidation-cyclisation was thought to involve attack of a hydroxonium ion (or its biological equivalent) synchronised with cyclisation[4,5] (Fig. ii). A similar process involving addition of hydroxy radical has been reported.[8]

In 1966, Corey *et al*[9] and van Tamelen *et al*[10] showed that this conversion involves a new intermediate, 2,3-epoxysqualene (4). This compound could be cyclised anaerobically and as expected ^{18}O -2,3-epoxysqualene gave ^{18}O lanosterol.[10b] Labelled 2,3-dihydrosqualene-2,3-diol, 2,3-dihydrosqualene-2-ol and squalene-2,3 : 22,23-dioxide were not observed to give sterols under the same conditions. Corey however, observed cyclisation of the dioxide to 24,25-lanosterol monoepoxide but the rate of conversion was very much slower than that of the 2,3-oxide. It has been shown that the biologically active form of squalene-2,3-oxide is the 3S isomer.[18,19]

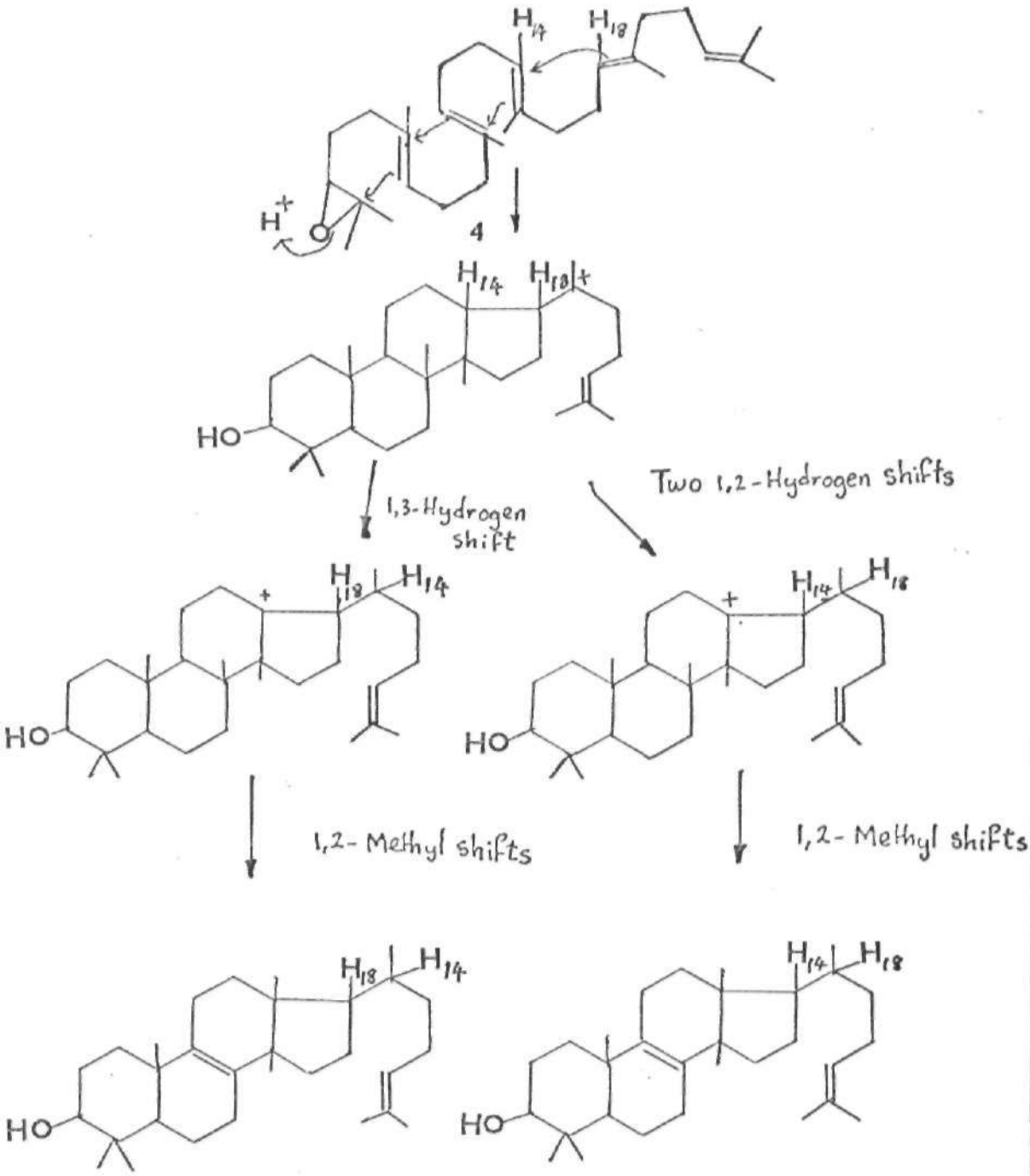

H14
H18
H+
4
H14
H18
HO
1,3-Hydrogen shift
Two 1,2-Hydrogen shifts
H18
H14
HO
H14
H18
HO
1,2- Methyl shifts
1,2- Methyl shifts
H18
H14
HO
H14
H18
HO

Fig iv

This important discovery triggered off intensive biomimetic studies in the widespread role of squalene monoepoxide. Most of the studies will be mentioned in Section 3. As suggested earlier the enzyme, squalene cyclase, may be responsible for holding the squalene oxide in such a conformation that a cis C-9 - C-10 stereochemistry is obtained. This is then followed by a series of methyl and hydrogen migrations.

The pathway adopted for this process was demonstrated by Bloch[11] and Cornforth[12] to involve two 1,2-methyl migrations. The nature of the hydrogen shifts were however, still unsettled. It has since been unambiguously demonstrated[13] that the rearrangement involves two 1,2-hydrogen shifts rather than a single 1,3-hydrogen shift. In this study tritium from C-14 of squalene was found only at C-17 of lanosterol (Fig. iv).

As a result of the investigations[10b] involving non-enzymic epoxide function initiated cyclisation of polyolefins, it was rational to assume that the biosynthesis of lanosterol also involved initial opening of the epoxide ring, followed by concerted formation of other rings. The π-electron orbitals of the closest olefinic bond are so oriented that SN-2-like attack on the more highly substituted position on the epoxide unit, coupled with epoxide ring opening is favourable and would generate the C-3 equatorial hydroxyl trans to the C-5 hydrogen. It has been shown[14] that this interaction by the olefinic bond lends anchimeric assistance

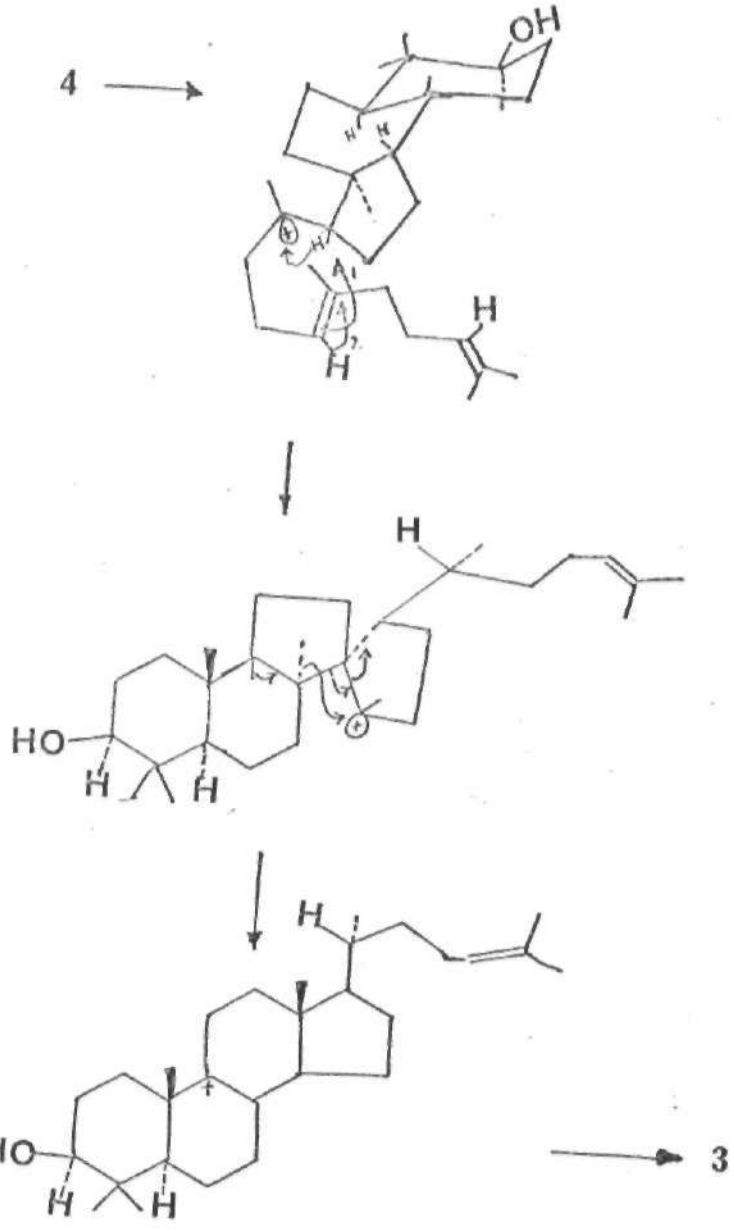
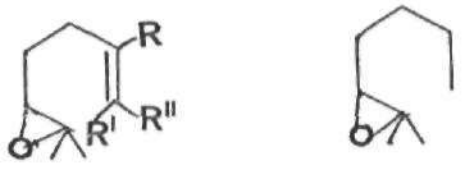


Fig v

to epoxide ring opening when the reaction rates of the diene monoepoxide (5), was compared to its saturated counterpart (6, Fig. vi).



5 6

a , R = CH_3 ; R' = H

b , R = H ; R' = CH_3

c , R = R'' = CH_3 ; R' = H

Fig vi

The cyclisation was carried out using $SnCl_4$ in benzene at 5 - 7°C. Whereas the unsaturated epoxide reacted in 5 min, more than 90% of the saturated one was recovered.

Arguing from a purely organic point of view there is involved in this mechanism an unfavourable situation where a secondary carbonium ion is generated by C14 - C18 bond formation (Fig. ii). An alternative mechanism which is consistent with results obtained from tracer experiments[15] features squalene oxide cyclising to a tricyclic intermediate with a five-membered ring C, followed by hydrogen migration giving a spiro system coupled with concerted hydrogen, methyl and alkyl migration, Fig. v . This result is consistent with that obtained from non-enzymic

cyclisation of squalene oxide.[16] This mechanism involves a 1,3 hydrogen shift, which is not unprecedented[17], and also avoids involvement of a secondary carbonium ion.

Finally, the action of 2,3-epoxysqualene cyclase has been studied on synthetic analogues of 2,3-epoxysqualene by Corey *et al*[20] and van Tamelen *et al*[16,21] in a series of papers. The structures of the enzymically generated products were compared with those resulting from *in vitro* cyclisation of the epoxides. These investigations provided evidence for the basic structural features of 2,3-epoxysqualene which are essential for acceptance and cyclisation by the enzyme, the factors which enable the cyclase to control conformation of the epoxide and hence the configuration of the putative protosterol intermediate and possibly the enzymic and thermodynamic factors involved in the subsequent conversion of the protosterol to lanosterol. The Δ^{22}-double bond and the terminal isopentenyl unit were found not to play any important role. However the terminal methyls adjacent to the oxiran ring were found to be important for acceptance and orientation of substrate.[20c, 21b]

CONCLUSION

Three main lines of investigation have been used in the identification of the component reactions of sterol biosynthesis, already mentioned.

The knowledge derived from the biosynthesis of squalene from mevalonic acid has been useful in the study of individual demethylation, migration and elimination processes which occur at the later stages of the sequence. The chemical synthesis of various intermediates has allowed examination of various hypotheses. The results obtained from these studies including the investigation of the enzymes and co-factors involved in each reaction have proved to be a powerful tool for the analysis of reaction sequences in cell homogenates.

Whatever mechanism is involved, it has become clear that squalene-2,3-oxide plays a central role in the biosynthesis of sterols.

SECTION 3 - NON-ENZYMIC OLEFIN CYCLISATIONS.

Following the identification of squalene-2,3-oxide as a genuine intermediate in the conversion of squalene to lanosterol, extensive research programmes have been launched to reproduce such cyclisations under non-enzymic conditions.

As a result of these studies, it has been possible to develop techniques for highly selective terminal oxidation of acyclic terpenes and highly stereoselective cyclisation of terpene terminal epoxides to 3-hydroxylated mono- to penta-cyclic ring systems of the natural product type.

Other methods of initiating cyclisations will be mentioned under appropriate headings below, but no attempt has been made to arrange them in order of efficiency as initiators.

For continuity, and the fact that this is the closest technique to the natural pathway, we will consider examples of cyclisations so far carried out *via* the epoxide function as the initiator.

A EPOXIDE FUNCTION

Goldsmith[22] observed that geraniolene monoepoxide can be cyclised with boron trifluoride etherate or stannic chloride. About the same time

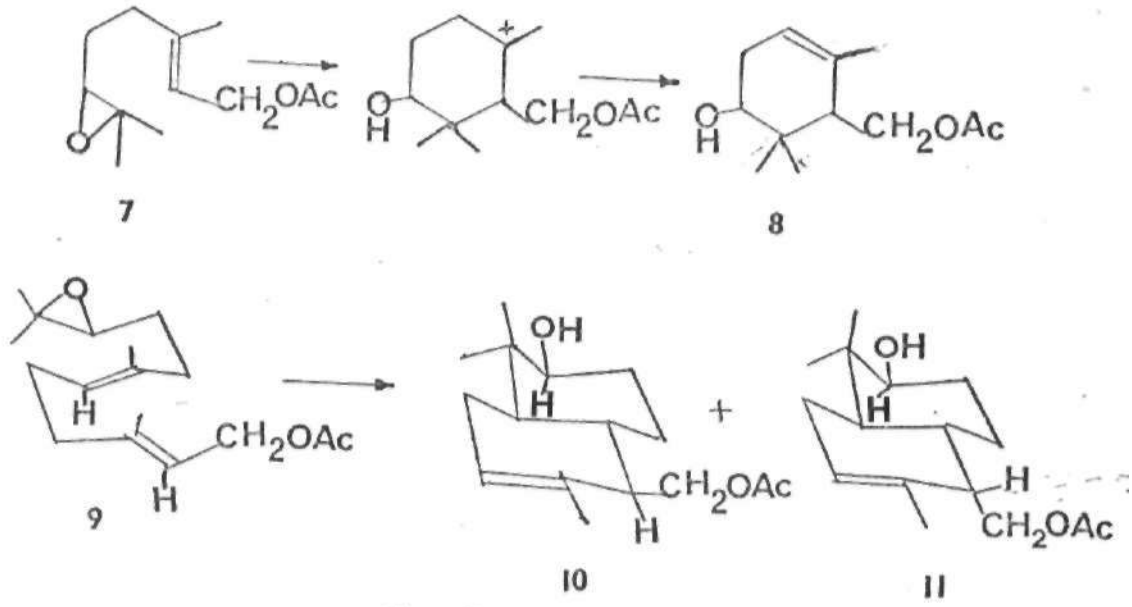
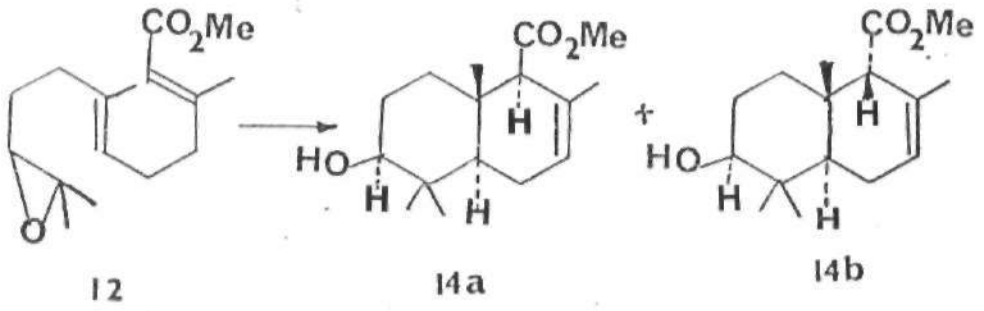


Fig vii



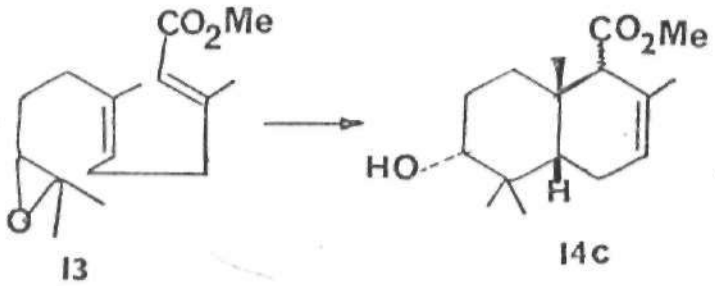
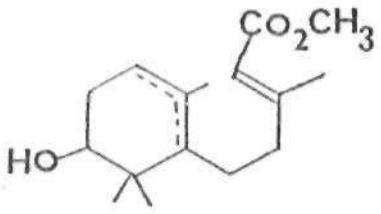


Fig viii

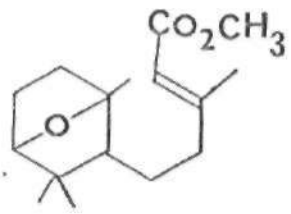
and independently of Goldsmith's results, van Tamelen reported the cyclisation of geranylacetate epoxide (7, Fig. vii) using cold 85% phosphoric acid. Attention was soon turned to the more complex case of trans,trans-farnesyl acetate terminal epoxide[23a] (9, Fig. vii) using BF_3.etherate. A mixture of bicyclic diol monoacetates total 22.5%, consisting of, 15% (11) and 85% (10) was obtained. Four new asymmetric centres were thus formed with stereochemistry characteristic of the usual 3-hydroxylated A/B ring system of steroids. The proportions of (10) and (11) were reversed when phosphoric acid was used. The product (11) bears the $-CH_2OAc$ group in an axial position thereby decreasing steric interaction with neighbouring angular and olefinic methyls and is considered to be the more stable.

In the light of these changes in the quantities of (10) and (11) produced under different cyclisation conditions, van Tamelen proposed that this stereochemical outcome (cf C-1 and C-10 in 10 and 11) is determined by a solvent-dependent conformation of the reacting epoxide.

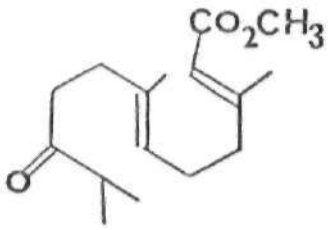
Similar results were also observed when $\Delta^{2,6}$-trans,trans- and $\Delta^{2,6}$-trans,cis-farnesic esters, (12) and (13) respectively were subjected to cyclization conditions.[23b] Whereas (14a) was the major product when cold phosphoric acid was used, (14b) was the major product using $BF_3.Et_2O$ in benzene. A number of other products were obtained from the reaction mixture (14d, 20%; 14e, 25%; 14f, 10% with $BF_3.Et_2O$ in benzene).



14d



14e



14f

Fig viii contd

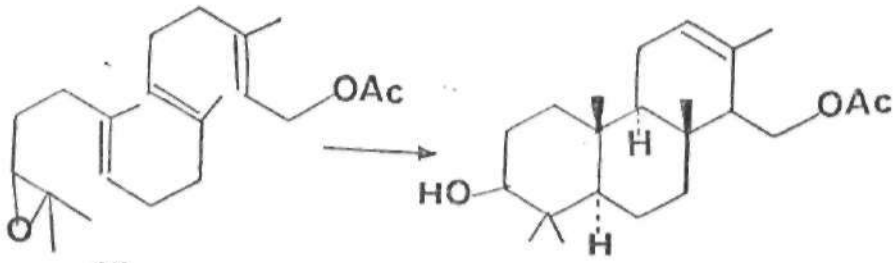


Fig ix

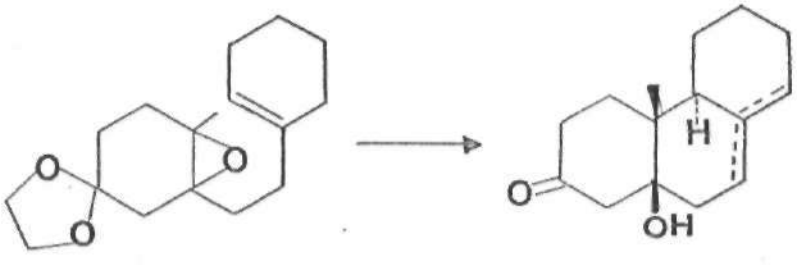


Fig x

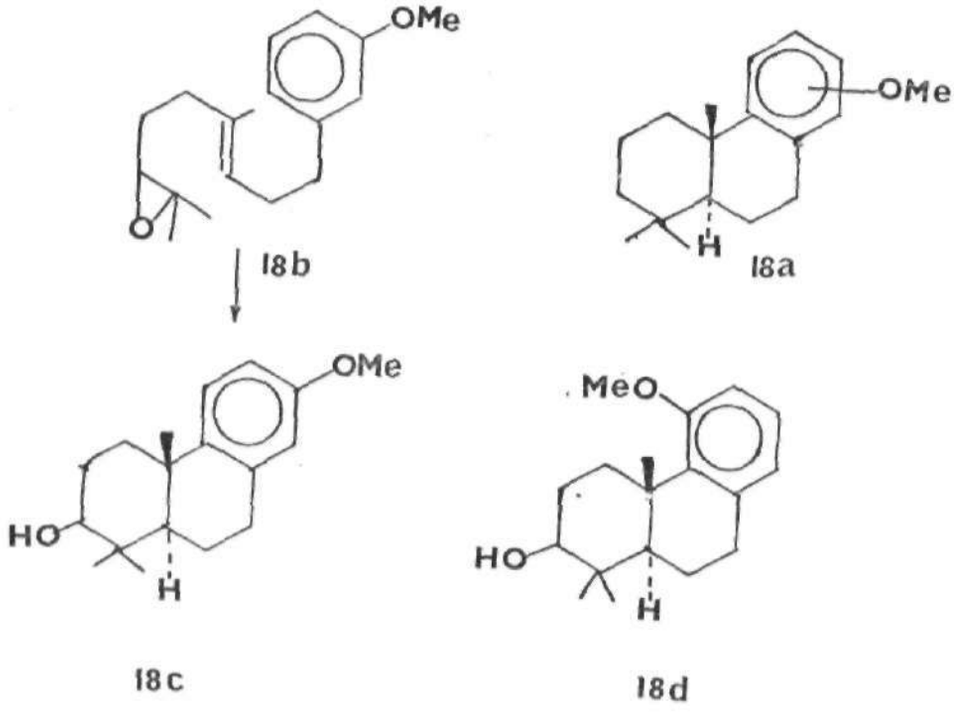
The yield of cyclised product from (13) was low but stereoselective giving the expected cis-product (14c, Fig. viii).

With phosphoric acid, (12) gave a mixture of (14a) and (14b) (25-28%), (14d, 20-30%) and (14e, 11%). (14f) was not detected. No deuterium incorporation was observed using d_3-phosphoric acid, thus eliminating intermediates requiring protonation. The mechanism is thus likely to involve concerted ring closure.

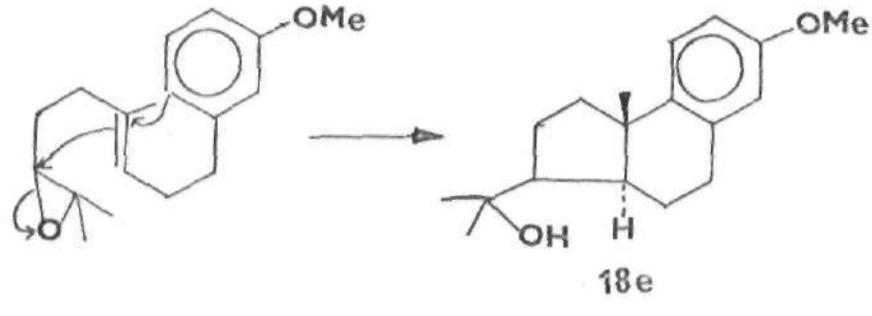
All-trans geranylgeranyl acetate terminal epoxide[24] (15, Fig. ix) reacting with stannic chloride in benzene at 0^{o} gave a tricyclic product (16, 10%) resulting in the formation of six assymetric carbon centres in one step. The product is thought to be formed via synchronised cyclisation, or stepwise sequence of ring formation involving mono-, and bi-cyclic carbonium ion intermediate or combination of these.

Another example is the cyclisation of epoxide (17) by Sutherland et al[25] to a tricyclic system with boron trifluoride etherate in very high yield. The stereochemistry of the ring junction is assigned cis assuming a trans-diaxial opening of the epoxide in an all chair conformation. This example represents cyclisation involving preformed rings.

Another example of the formation of a tricyclic system, this time involving an aromatic ring is offered by the work of Nasipuri and Chaudri[26a] in the cyclisation of epoxide (18b) with boron trifluoride etherate in methylene chloride as a possible route to podocarpa-8,11,13-trienes (18a).



Analysis of the product mixture showed two isomeric tricyclic products (18c) and (18d) in 25 and 12% yields respectively. A third tricyclic alcohol (18e) obtained in 10% yield is formed probably as depicted.



Finally a monocyclic ketone (18f) obtained in 17% yield is probably formed by hydride transfer as shown.

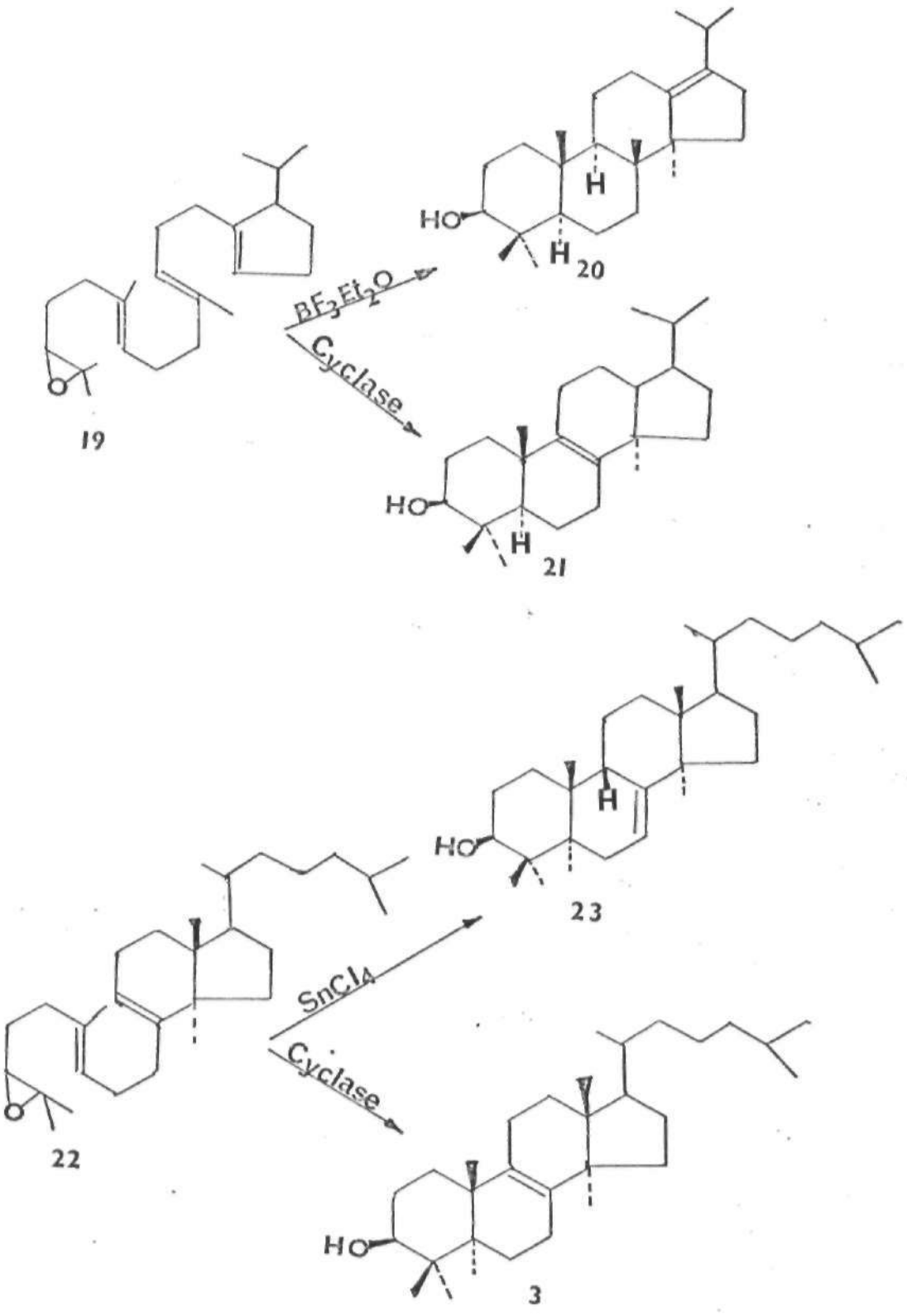
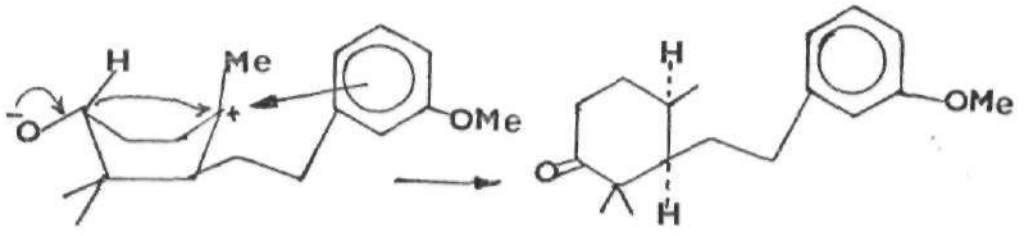


Fig xi



18f

Goldsmith and Phillips[26b] in investigating a similar system had proposed a π-complexation of the cationic centre with the aromatic ring system which probably promotes the hydride transfer by holding the cyclohexyl cation in the position shown.

As a result of the success realised in the foregoing experiments synthetic substrates approximating the structure of squalene 2,3-oxide were cyclised under non-enzymic conditions. A very important observation in these studies is the role of the enzyme in termination of the protosterol rearrangement leading to the formation of Δ^8-double bond in lanosterol.

The epoxide, (19)[21d] was cyclised with boron trifluoride etherate forming among other products, the isoeuphenol analogue, (20) resulting from the all chair conformation. The same epoxide was converted to the lanosterol analogue (21) by liver cyclase enzyme though in low yield. The epoxide (22) was cyclised chemically to give 9β - Δ^7-lanosterol (23) but enzymically to lanosterol (3, Fig. xi). The loss of proton at C-7 in the formation of $\Delta^{7,8}$-double bond shows it may be kinetically

favoured, whereas in the formation of lanosterol by enzymic method the $\Delta^{8,9}$-double bond was formed. The results therefore, suggest that the terminating removal of the C-9 proton may be controlled by a specific basic centre in the enzyme.[21d]

As a result of extensive studies by van Tamelen et al[27] the problem of selective terminal epoxidation of squalene was solved. The best reagent found was N-bromosuccinimide in aqueous glyme, and treatment of the resulting bromohydrin with base to obtain the epoxide. The epoxidation was highly selective (>95%). This phenomenon was explained on conformational grounds. Epoxidation was less selective in less polar solvents, e.g. petroleum ether-acetic acid mixture in which terminal epoxidation of synthetic substrates ranged from 62 - 81%, whereas in the more polar hydroxylic solvents, e.g. aqueous glyme, the terminal oxidation ranged from 96 - 100%.

In less polar solvents, squalene is thought to exist in linear, extended form (1) thereby making the double bonds equally vulnerable to attack by the oxidising agent. However the coiled form (1a) the internal double bonds are shielded and thus rendered less reactive, whereas the terminal olefinic links would remain exposed.

Another view is that solvent clustering at the reacting centre of the reagent and olefinic molecule in the transition state may, by simple bulk effects discourage reaction at the sterically enclosed

central portion of the system. The latter view was further reinforced by the observation that 'neutral' oxidizing agents, e.g. peracids, diimide, or osmium tetroxide were less selective than the highly solvated species like protonated N-bromosuccinimide and mercuric acetate.

This success eventually led to non-enzymic cyclisation of squalene oxide using stannic chloride. Tricyclic compounds were obtained (Fig. xii) amidst a number of other products and all contained a 6,6,5-ring system resulting from direct Markownikov additions to 10,11 and 14,15 double bonds. This lends support to van Tamelen's proposal concerning the intermediacy of a 6,6,5-tricyclic cation (Fig. v). These results among other things have solved the mystery that beclouded the introduction of the 3-hydroxy group common to most steroids. As a synthetic route, however, this approach has not proved viable.

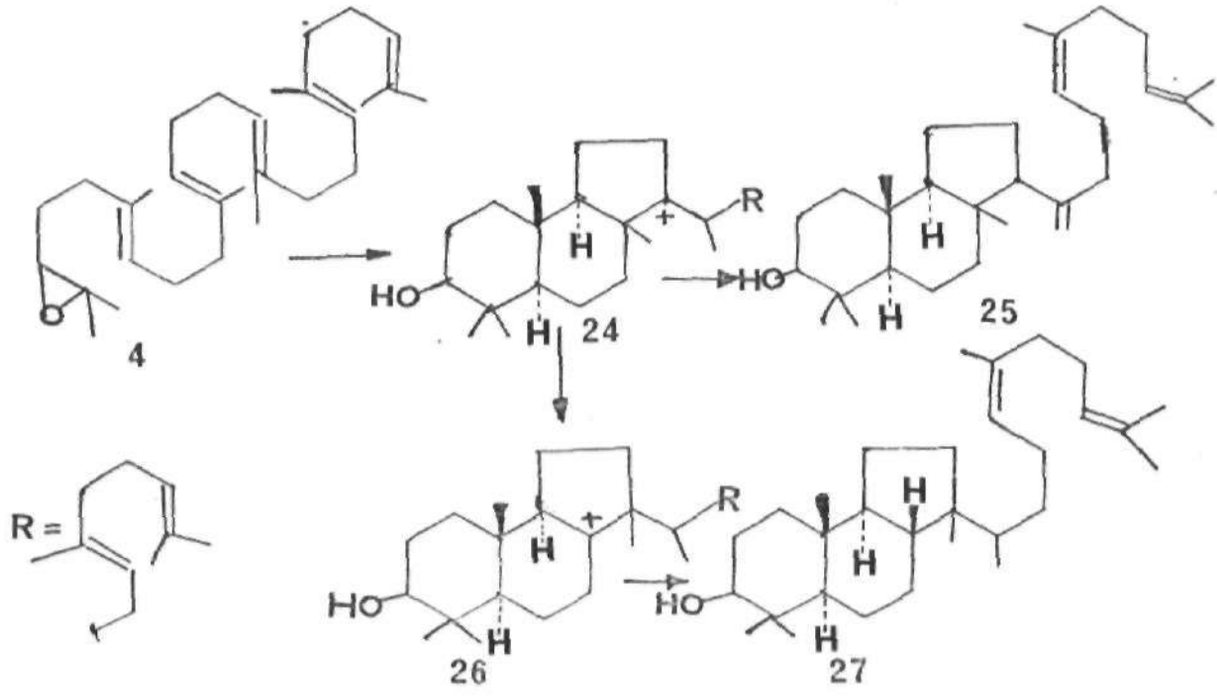


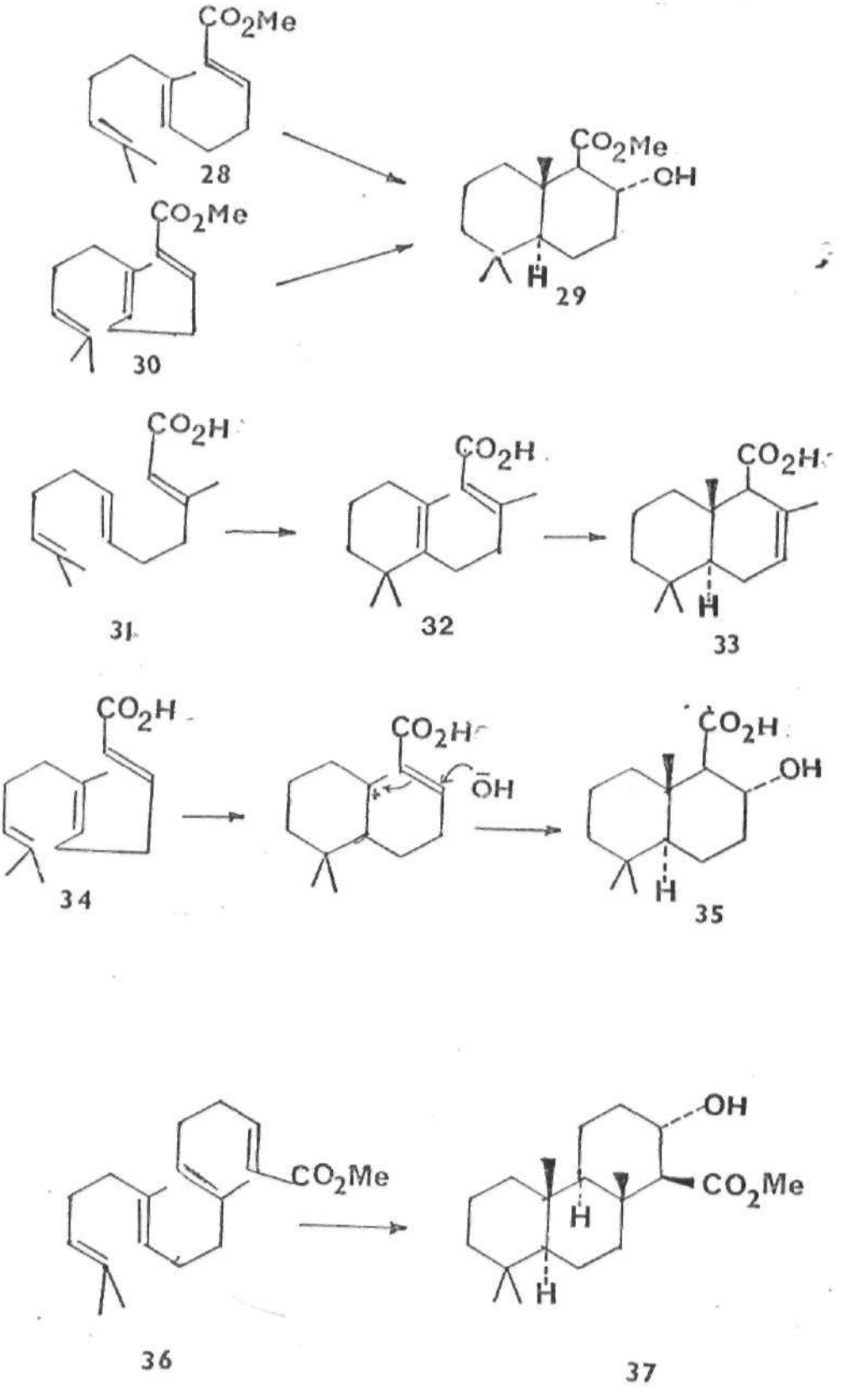
Fig xii

B PROTON-CATALYSED CYCLISATIONS

The first studies directed towards non-enzymic biogenetic-type polyene cyclisation involved attempts to initiate such cyclisations by protonation of the terminal olefinic bond of polyene chains. A number of problems were encountered especially with such systems as squalene where protonation of the substrate was found indiscriminate resulting in the formation of undesired products. The acidic conditions employed were also very strong which made substrates susceptible to isomerisations and deprotonation of intermediates resulting in partially cyclised products.

Cyclisation of 1,5,9 trienes.

An appropriate example involving acid-catalysed cyclisation of a triene is trans-desmethylfarnesic ester (28), which gave (29) in a mixture of sulphuric acid and formic acid in about 60 - 70% yield. The product has the expected 'natural' configuration. This was carried out by Eschenmoser to test his and Stork's hypothesis. It was a surprise, however, that the same product was obtained when the cis substrate (30) was subjected to the cyclisation conditions. None of the expected cis product was obtained.[28] Following the Lewis acid catalysed cyclisation of farnesic acid (31) by Stork[4] in which he isolated a monocyclic diene (32) which could be further cyclised to the trans-bicyclic product (33), a similar mechanism was proposed for the cyclisation of the cis compound


CO2Me
28
CO2Me
30
CO2Me
OH
H
29
CO2H
31
CO2H
32
CO2H
H
33
CO2H
34
CO2H
OH
CO2H
OH
H
35
CO2Me
36
OH
CO2Me
H
H
37

(30). This means that these cyclisations are proceeding via a different route from that involved in the enzymic cyclisation where Bloch had demonstrated the absence of partially cyclised olefinic intermediates since no deuterium incorporation was observed in a deuterium oxide medium.

Semenovsky[29] has a different explanation. In the cyclisation of (31) and (34) in sulphuric acid - formic acid mixture, he got the same trans product (35). This was rationalised in terms of the poor nucleophilicity of the conjugated 10,11-double bond. A cyclohexyl cation is formed and the driving force to ring closure is provided by nucleophilic attack of the solvent on the conjugated double bond.

Cyclisation of 1,5,9,13 tetraenes.

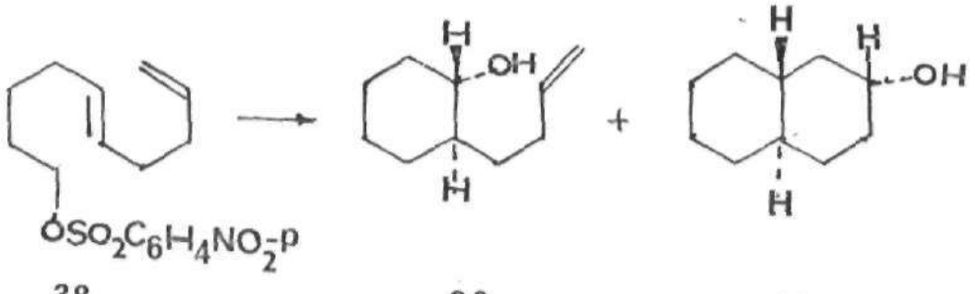
Eschenmoser[28] also investigated the acid-catalysed cyclisation of the ester (36). A trans,anti,trans tricyclic product (37) was obtained but only in 5 - 10% yield. Only a small amount of a dihydroxy compound was obtained, the rest of the product was intractable. He thus proposed that acid-catalysed cyclisation of polyenes of this complexity was not useful from a preparative point of view.

C CYCLISATION-SOLVOLYSIS OF POLYENIC SULPHONATE ESTERS

The failure of the epoxide opening and protonation as good methods

to initiate polyene cyclisation prompted studies into other methods.

Solvolysis of olefinic sulphonate esters was found to involve concomitant ring closure, and the double bond was reported[30-32] to enhance the solvolysis rate to twice that of the corresponding saturated analogue. In view of this, the formolysis of trans-5,9-decadienyl-p-nitrobenzene sulphonate[31,32] was investigated. A complex mixture of products was obtained and careful analysis showed a total of eleven products. The main component was the monocyclic trans alcohol (39) (after cleavage of formate ester) obtained in 35% yield.

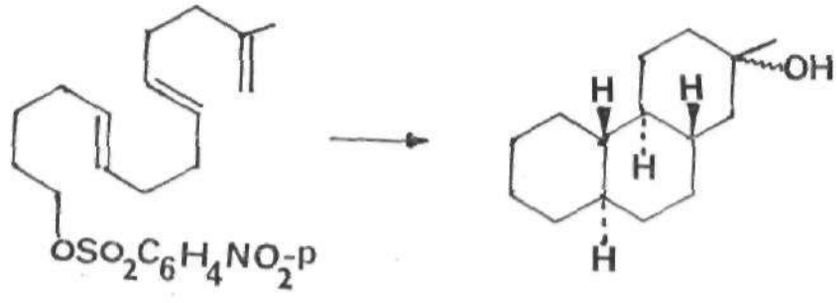


38 39 40

The major bicyclic product was the trans,syn decalol (40). All the bicyclic products (12% total) were trans-decalin derivatives, without any detectable amount of cis isomer.

The cis isomer of (38) also gave a similar series of products belonging to the cis stereochemical series. Only 16% of bicyclic products were obtained. These results agree with the predictions by Stork and Eschenmoser.

The acetolysis of trienic ester[33] (41) was not any better. The product consisted of approximately 20% acyclic material, 40% monocyclic, 8 - 12% bicyclic and 2.8% tricyclic compounds.



41 41a

The tricyclic compound (41a) was found to be the expected trans,trans,trans-alcohol obtained as a mixture of epimers after reductive cleavage of the corresponding acetate.

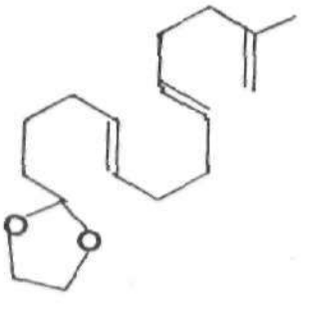
Even though the desired stereochemical results were obtained, the yields of the fully cyclised products were low and the products are without any functional group in the first ring. This approach offers another synthetically useless route.

D CYCLISATION OF OLEFINIC ACETALS

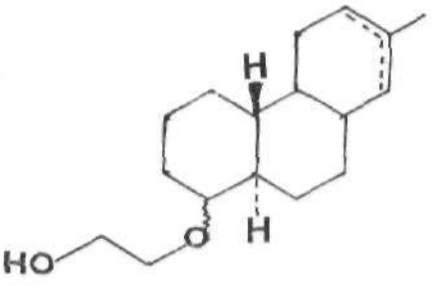
As a result of problems encountered with the solvolysis of polyenic sulphonate esters, other methods were tried, this time, the olefinic

acetals. The first examples investigated were observed to cyclise with high stereoselectivity according to the predictions of the Stork-Eschenmoser hypothesis. This approach has the advantage that the yields are high and the products have functional groups in useful positions for further elaboration into other systems.

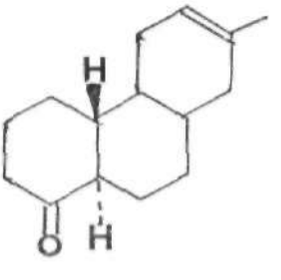
The trienic acetal[33] (42) was cyclised using the benzene-stannic chloride method to give tricyclic products in about 50% yield, and were shown to consist of a mixture of the trans,trans,trans ('natural') isomers (43). The crude cyclisation mixture was subjected to degradation of the side chain, followed by oxidation of the resulting alcohols to the ketones (44) and (45).



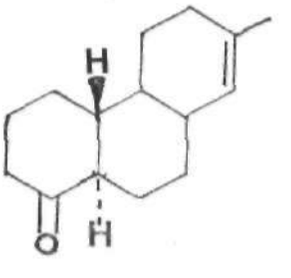
42



43



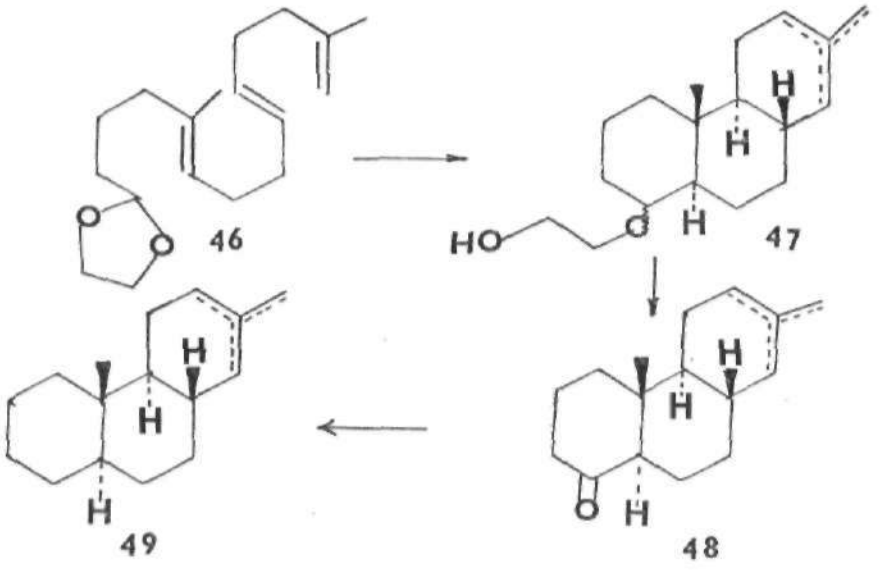
44



45

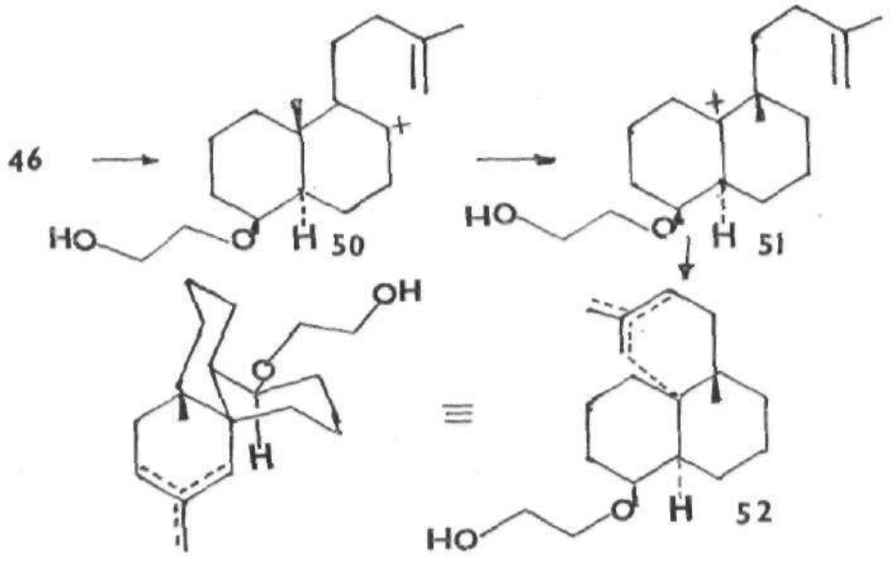
In order to increase the nucleophilicity of the double bond and at the same time introduce an angular methyl group between rings 'A' and 'B', using steroid terminology, the homologue (46) of the trienic acetal (42) was prepared.[35]

As expected the cyclisation was observed to be significantly faster and the yield of fully cyclised product higher (62.5%) than in the previous case. The ketone (48) obtained from (47), as above, was reduced to the hydrocarbon mixture, (49).



The structure of (49) was compared to that of an authentic sample.

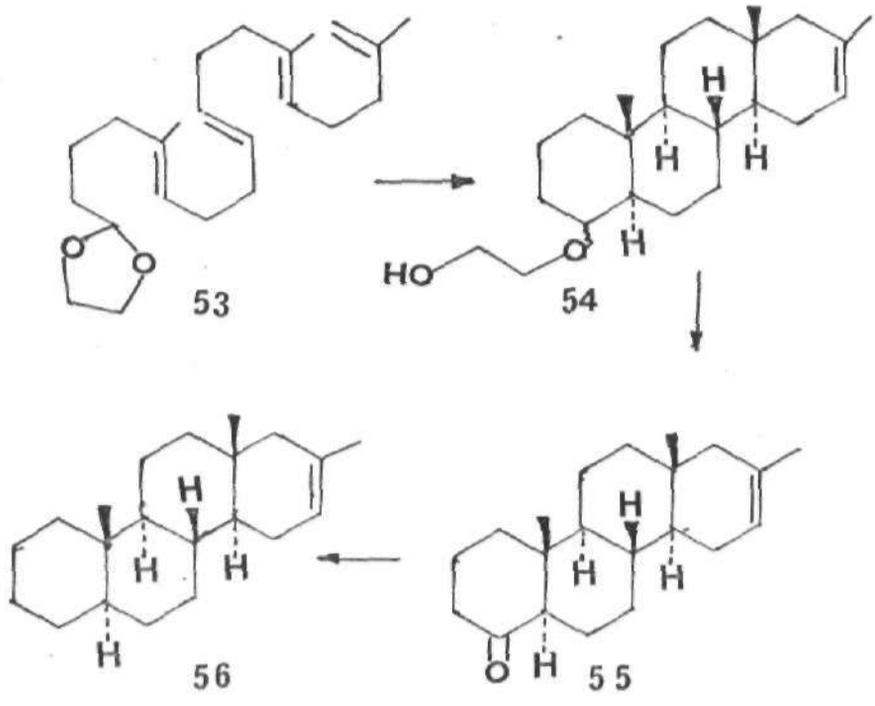
When the acetal (46) was subjected to cyclisation in nitromethane-stannic chloride, the cyclisation took an abnormal course. The major product obtained was the tricyclic compound (52) in 44% yield.



This is rationalised as arising from the bicyclic cation (50), followed by consecutive suprafacial 1,2-hydride and methyl shifts to give a tertiary carbonium ion (51) and intramolecular reaction of this cation with the olefinic bond.

These results probably indicate the effect of polarity or dielectric constant of solvents on the course of cationic/anionic reactions. Nitromethane being a polar solvent would tend to stabilise ions thereby increasing the life-time of the cations and, in this case, allowing enough time for rearrangement to take place. Thus solvent polarity may have an important bearing on the concertedness or otherwise of these cyclisation reactions.

The success so far demanded that the cyclisation of an acyclic tetraenic acetal should be carried out. Since stannic chloride had proved to be effective in the cyclisation of the olefinic acetals, the cyclisation of the tetraenic acetal[36], (53) was carried using this reagent in nitromethane, benzene, methylene chloride and cyclohexane. It was observed, that in none of these reactions was the tetracyclic compound produced in >10% yield. The reaction was observed to proceed better in pentane in which the yield was estimated to be about 30%.

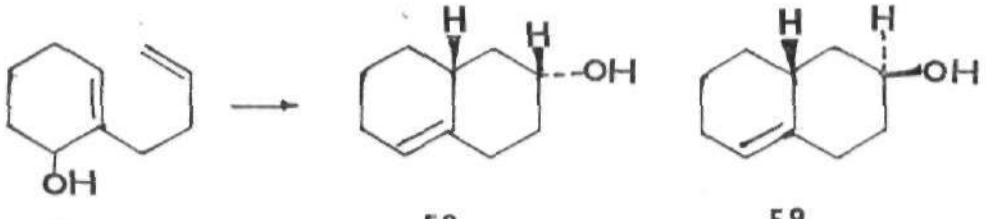


Degradation of the hydroxy ethyl side chain and oxidation of the epimeric alcohol of (54) gave the same ketone (55) which was reduced via Wolff-Kishner reduction to the hydrocarbon (56), the constitution of which was proved by comparison with an authentic sample synthesised by another method.[36]

E ALLYLIC CATION INDUCED CYCLISATIONS

The difficulties encountered with the solvolysis of primary p-nitrobenzene sulphonates as a method of generating incipient cationic sites for promoting cyclisation, are thought to be caused by the conditions of solvolysis which are vigorous enough to promote undesirable side reactions.[31] The allylic system was soon found to provide a relatively stabie, hence easily generated cationic site, stabilised under appropriate conditions until it finally reacts completely with the olefinic bond. The objectives were soon realised in the investigation of the following systems.[37,38]

(I)



57 58 59

The stereoselective formation of the syn isomer (58) in the cyclisation is rationalised by a rapid ionisation to the allylic cation A (Fig. xiii) followed by a synchronous ring closure and attack by α nucleophile, (see B). An alternative stepwise process was also thought feasible. This involves formation of the bicyclic secondary cation C which undergoes preferential equatorial attack by the nucleophile.

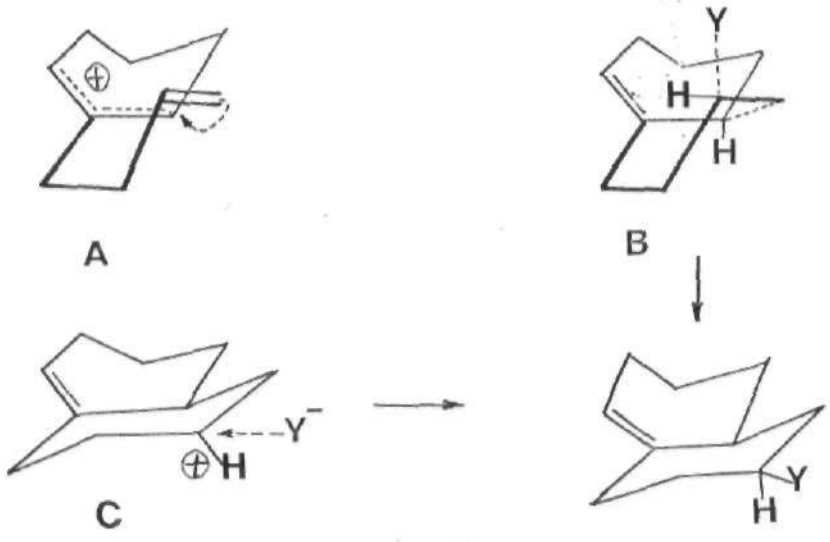
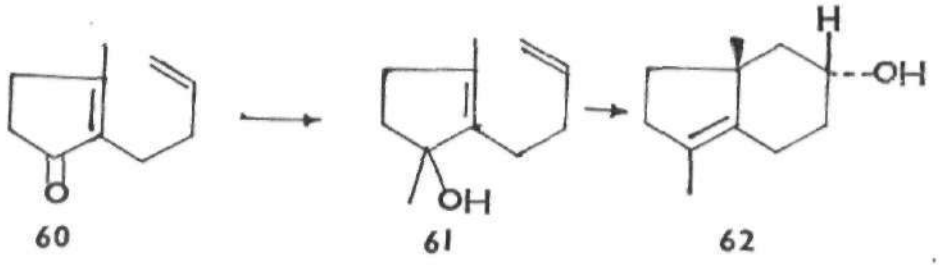


Fig xiii

It was also suggested that the cyclisation could be synchronous with the ionisation of the allylic system.

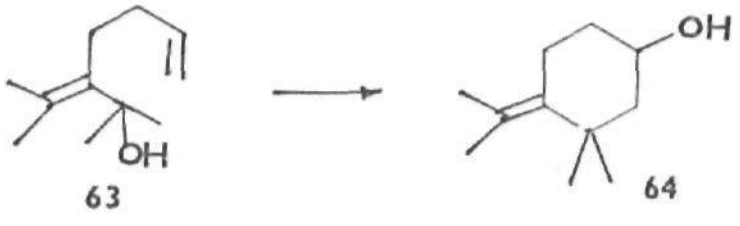
(II)



60 61 62

The dienol (61), made[39] by the action of methyl lithium on the dienone (60) has also been cyclised by treatment with formic acid to give the bicyclic alcohol (62) in almost quantitative yield.

(III)



63 64

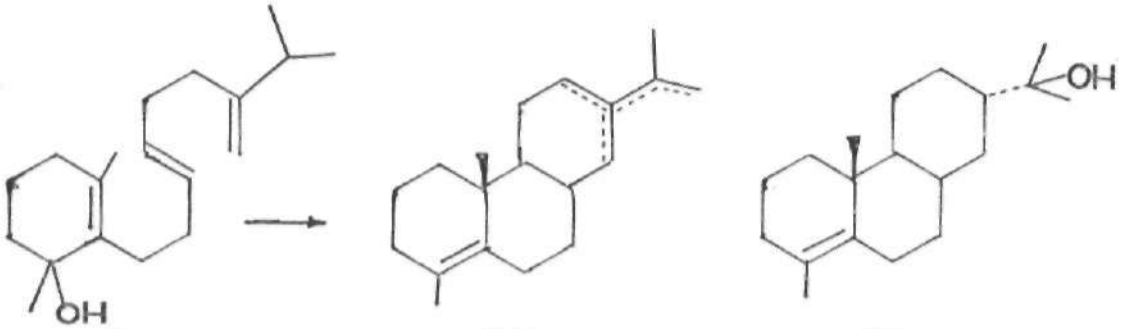
The dienol (63) which has the tetramethylallyl function has been converted to the cyclohexanol derivative (64) in excellent yield.

The foregoing demonstrates initiation of cyclisation by the cyclohexenyl cation, e.g. (57)⟶(58) + (59), cyclopentenyl cation, (61)⟶(62) and tetramethyl allyl cation, (63)⟶ (64).

These various allylic systems have been used to initiate cyclisations that have produced polycyclic products, some examples of which are given below.

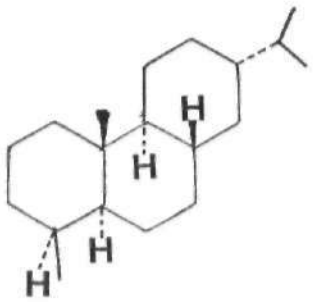
(i) Initiation by the Cyclohexenyl Cation.

Extension of the observations from cyclisation studies of butenyl cyclohexenol system[37] (57) has resulted in the cyclisation of trienol[41] (65) affording the tricyclic products (66) and (67) in good yield (94%). The cyclisation was stereospecific since the products were separated and found to belong to the same stereochemical series having the 'natural' anti,trans configuration.

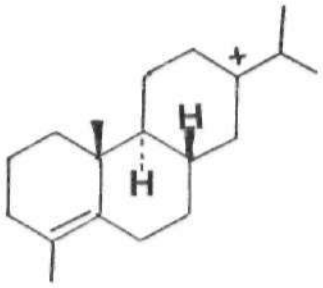


65 66 67

The alcohol (67) when further treated with formic acid gave the mixture of olefins (66). Conclusive proof of the tricyclic product structure was obtained by conversion of the olefinic mixture on hydrogenation over platinum oxide in acetic acid into a mixture of approximately equal amounts of two saturated hydrocarbons one of which was identified as dl-fichtelite[40] (68).



68

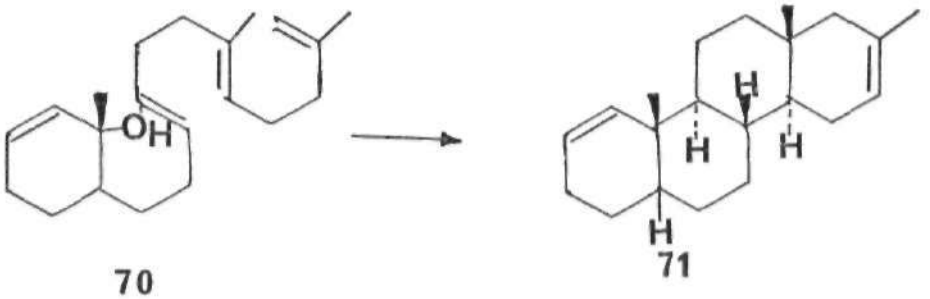


69

It appeared that these products arose from the primary product of cyclisation, (69) by conventional carbonium ion transformations. The cyclisation proceeded quantitatively and stereospecifically via this cyclic cation. It does seem then that the formation of this cation does not involve the intermediacy of any isolable bicyclic compound. The process is either synchronous or it proceeds via cationic intermediates that do not deprotonate prior to cyclisation.

Another example of a cyclohexenyl-cation initiated cyclisation of interest is that of tetraenol, (70), which in stannic chloride in nitro-

ethane at -78°C underwent cyclisation to give the D-homosteroidal compound (71) with A/B cis-ring system in 60% yield.



70 71

The stereospecific formation of cis-fused ring system arises from the known preference for a cyclohexenyl cation to react with a nucleophile so as to form a pseudoaxial bond as depicted in Fig. xiv.

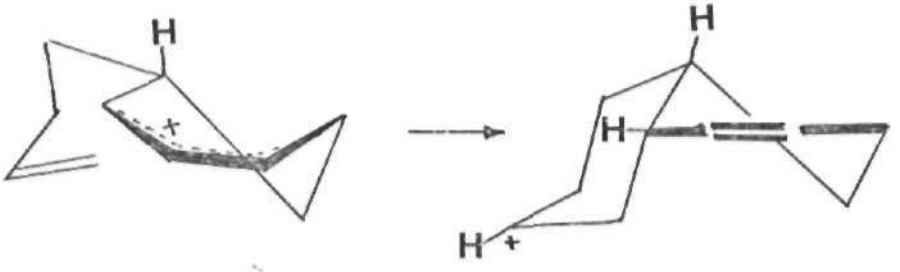
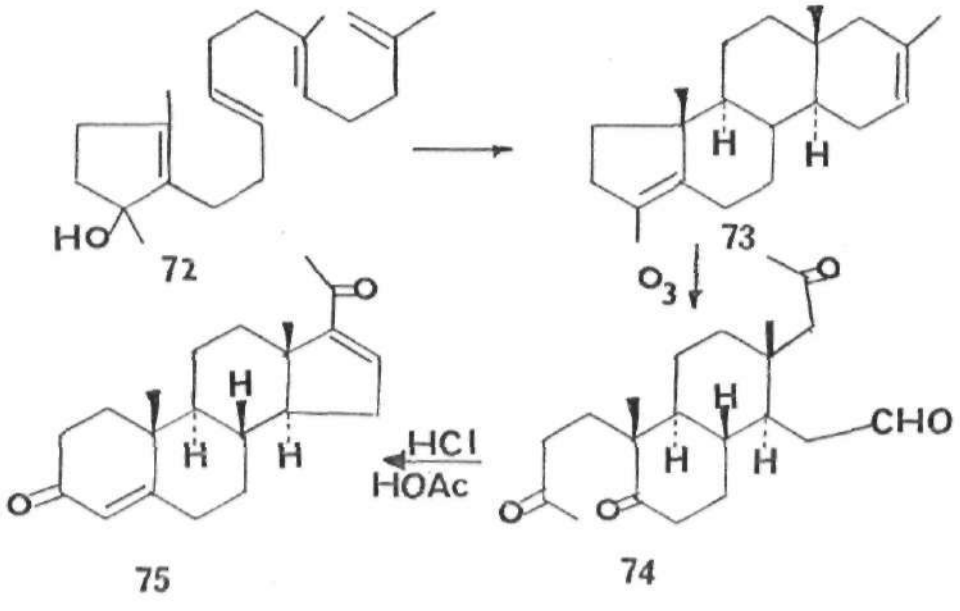


Fig xiv

(ii) Initiation by the Cyclopentenyl Cation.

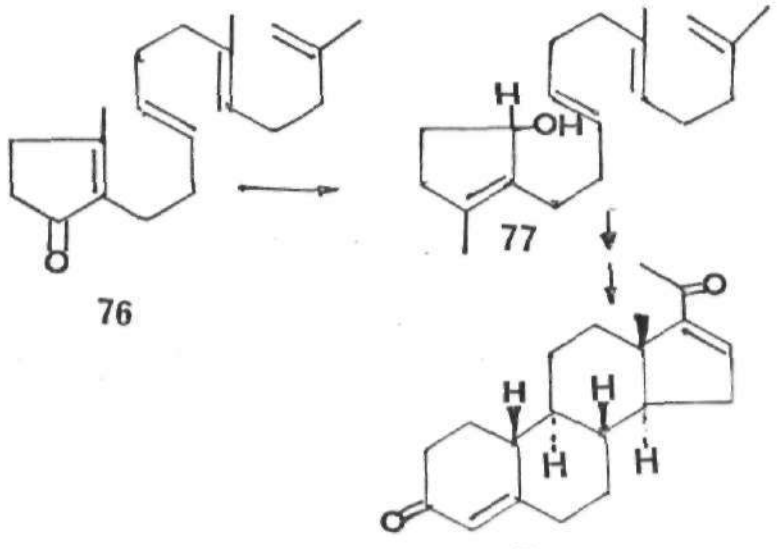
Following the successful cyclisation of the butenylmethylcyclopentenol[39], (61), this method was extended to the cyclisation of the

tetraenol[38,42], (72) using stannic chloride in nitroethane at -80°. A tetracyclic hydrocarbon (73), was produced in 70% yield. Ozonolysis of the latter afforded the triketo aldehyde (74) in 65% yield. The five new assymetric centres generated were still retained. The triketo aldehyde, (74), was converted through a double intramolecular aldol cyclodehydration to racemic 16,17-dehydroprogesterone, (75). This represents the first example of a steroid synthesised by biomimetic polyene cyclisation.



The tetraenol, (72), was found to be very susceptible to dehydration, a sample in methylene chloride (probably containing a trace of acid) was completely converted into the pentaene as shown by spectral data.

This scheme has been modified to produce 19-nor steroid, (79), with interesting mechanistic results.

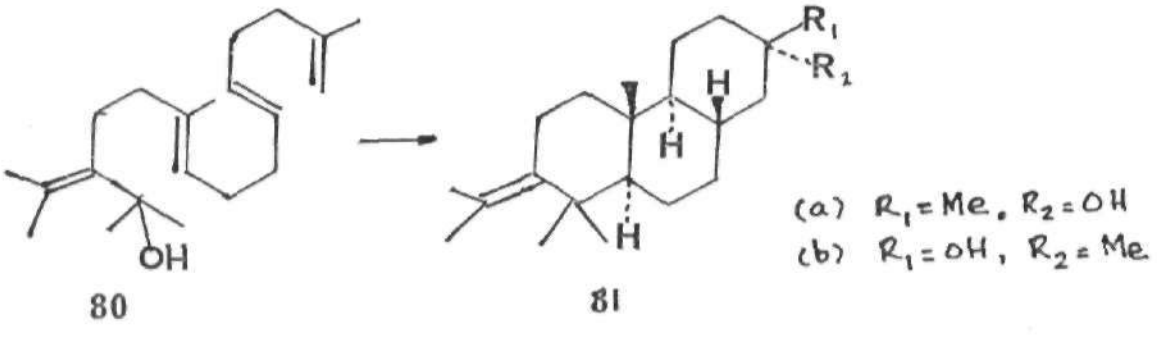


76 77 79

The cyclisation of the tertiary alcohol, (72) and the secondary alcohol, (77), have been shown[1] to proceed *via* different mechanisms. (77) cyclises faster than (72). The tertiary alcohol was observed to undergo rapid dehydration to an isolable hydrocarbon containing the cyclopentadiene moiety capable of reversible protonation by the acid catalyst to regenerate the cyclopentenyl cation which then undergoes cyclisation. This was demonstrated by deuterium incorporation (CF_3CO_2D) in ring A of (75) whereas no deuterium incorporation was observed when (77) was subjected to the same conditions.

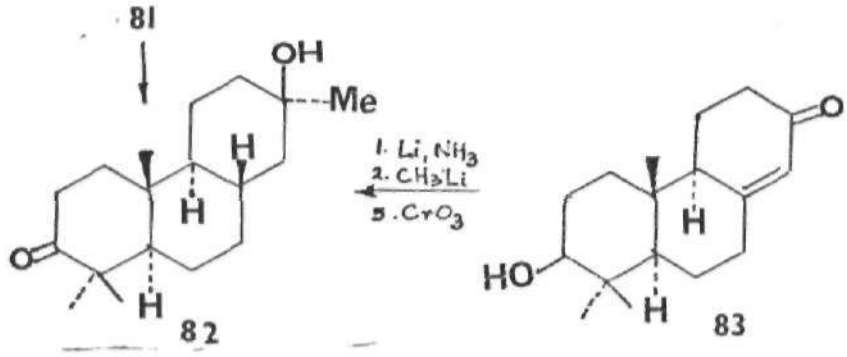
(iii) Initiation by Tetramethylallyl Cation.

Following the successful cyclisation of the dienol (63), the behaviour of the tetraenol[43], (80), was examined with the hope that its cyclisation would lead to tricyclic compounds. The isopropylidene group could then be oxidatively cleaved to the keto group.



80 81

A methylene chloride solution of (80) at -78° was treated with trifluoroacetic acid for 5 min. This was followed by treatment with lithium aluminium hydride to effect cleavage of the resulting trifluoroacetates. Analysis of the product showed an epimeric mixture of tricyclic alcohols (81a and 81b) as the major products obtained in 23 and 29% yields respectively. The configuration of the ring fusion of both epimeric alcohols was proved by comparison to authentic products (cf. (83) ⟶ (82)) and the tricyclic material appeared to belong exclusively to the trans,anti,trans stereochemical series.



A hydrocarbon fraction obtained along with these tricyclic products was found to contain mainly the pentaene resulting from dehydration of (80). When this was subjected to the cyclisation conditions, only trace amount of tricyclic products were obtained. This is in contrast to the observations in the cyclisation of the tertiary alcohol (72), where such dehydration products were isolated and made to cyclise under the same conditions. When cyclisation was carried out using deuteriotrifluoroacetic acid, there was no deuterium incorporated into the tricyclic products as shown by mass spectrometry. This rules out the intermediacy of any partially cyclised olefinic products capable of cyclising to the final product. This observation compares favourably with the observed behaviour of enzymic cyclisation of squalene oxide.[7] This approach has been used to synthesise dl-serattenediol[44], a pentacyclic triterpenoid having a seven-membered C ring, and nine assymetric centres.

Some more examples of cyclisations initiated by the tetramethyl-

allyl cation will be mentioned in connection with other aspects of polyene cyclisations below.

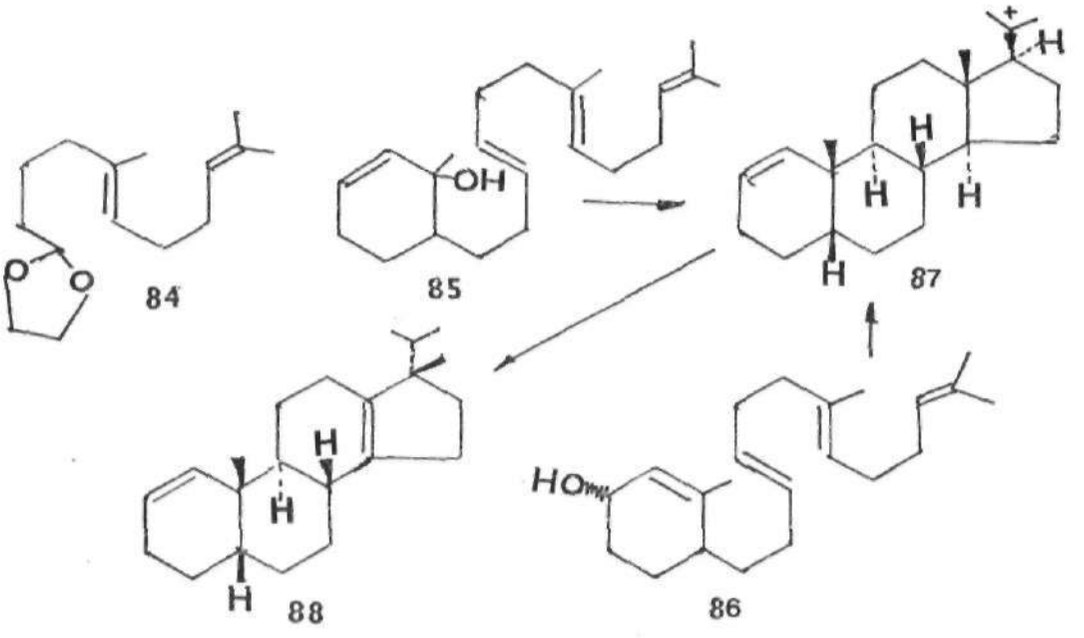
FORMATION OF FIVE-MEMBERED RINGS

Five membered rings occur frequently in natural products, especially in steroids, it is therefore important that systems that would form the ring system be found.

Since the acetals proved generally more successful than their corresponding sulphonate esters, the acetal (84) was subjected to cyclisation expecting that a 6/5 ring system would be formed. Surprisingly, however, only polymeric material was obtained under the same conditions that the isomeric material with terminal double bond had given good yields of a 6,6 bicyclic system.

The cyclisation of the tetraenols[45] (85) and (86) with terminal isopropylidene group have also been investigated. We have already come across the cyclohexenol initiator, (70), where a cis A/B ring fusion was observed.

As in the case of the allylic alcohols, it is expected that tetraenol (85) and (86) would afford a cis,anti,trans,anti,trans system derived from carbonium ion (87).



The tetraenol, (85), was first treated with trifluoroacetic acid in methylene chloride at -78° for 4.5 h. A mixture of hydrocarbon and trifluoroacetate was produced. Treatment of the crude product with lithium aluminium hydride in ether afforded a mixture of hydrocarbon and alcohols. Separation of products by chromatography showed the hydrocarbon fraction to be largely (88) (36%) among other possible isomers obtainable from cation (87).

Cyclisation of tetraenol (86) with stannic chloride in methylene chloride at -78° afforded 33% yield of a hydrocarbon fraction identical with (88). The major product (88) is produced from the cation (87) by

a 17α-20 hydride shift followed by a 13β-17β methyl migration and finally the loss of 14α proton. It has not been possible to trap the cation, (87), prior to rearrangement.

A more successful method of introducing a five-membered ring is via the use of the styryl terminating group.

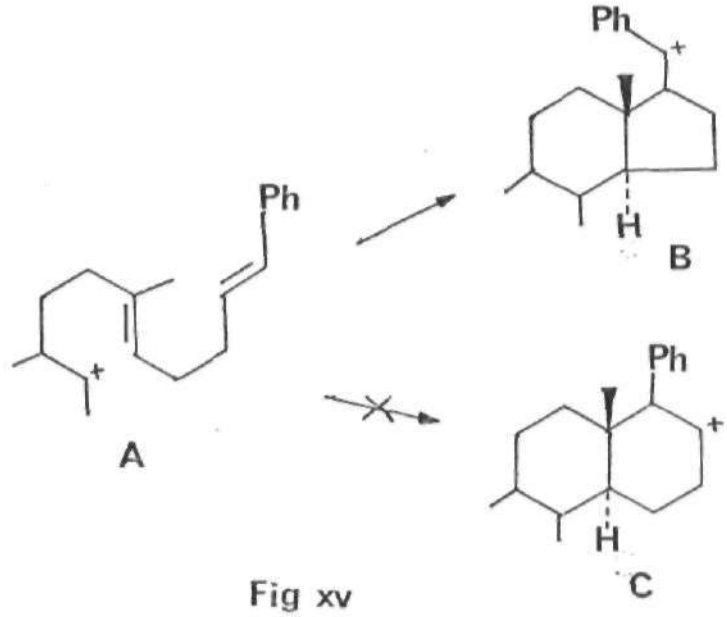
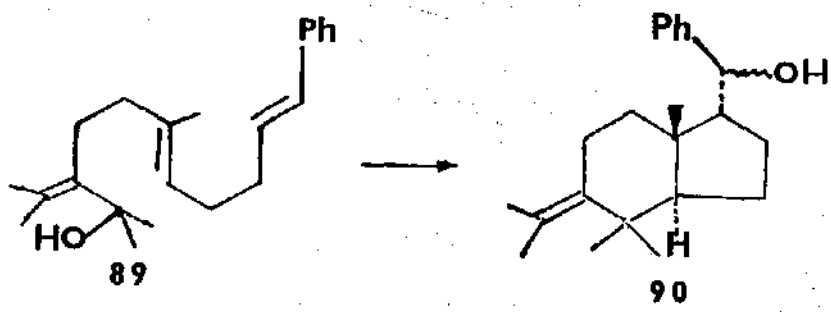


Fig xv

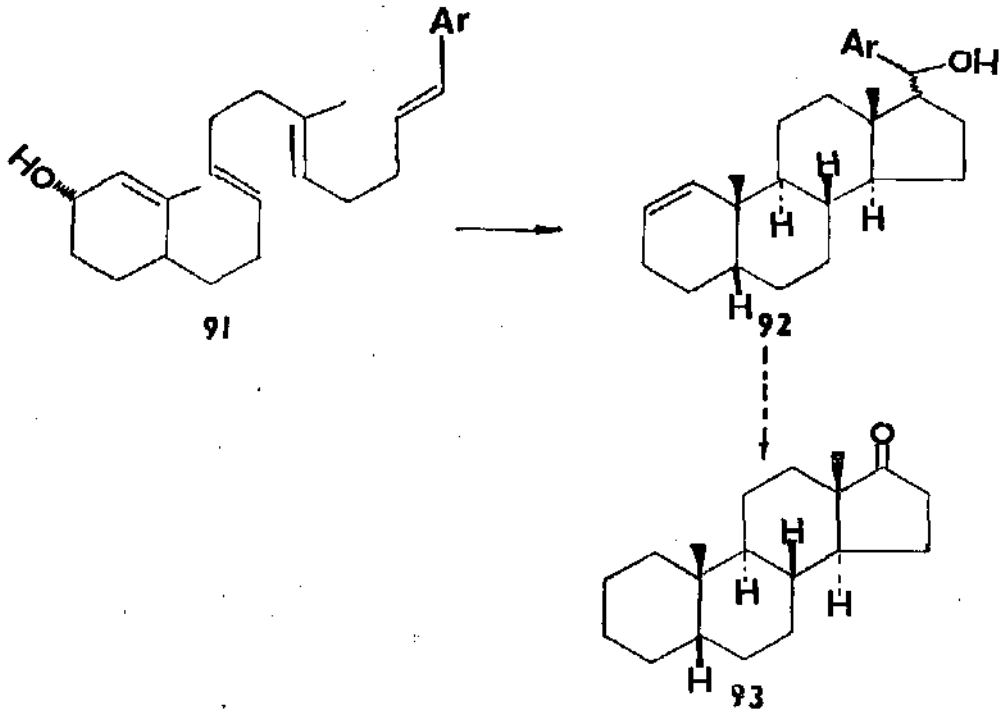
As depicted in Fig. xv, the partial structure A cyclises preferentially to a trans 6/5 ring system in which the more stable benzylic cation B is formed instead of a homobenzylic cation C which would have led to the formation of a 6,6-ring system.

The trienol (89) in dichloromethane and trifluoroacetic acid was efficiently cyclised to give the bicyclic carbinol (90) with a trans 6/5 ring system.



The effect of the nucleophilicity of the double bond of the styryl terminator can be varied depending upon the nature of the substituent on the aromatic ring.

The system (91) was chosen for study, successful cyclisation of which would yield the steroid nucleus, e.g. (93).



When Ar = C_6H_5- cyclisation with trifluoroacetic acid in dichloromethane at $-50^{\circ} \rightarrow -25^{\circ}$ gave yields of tetracyclic material of the order of 70%. With Ar = p-$CH_3.C_6H_4$- the yield increased to 75%. When Ar = p-$CH_3O.C_6H_4$- the yield was very poor. The highly nucleophilic double bond in this case might be reacting with the acid present in the medium. The best yield (81%) of tetracyclic product was obtained when Ar = naphthyl.

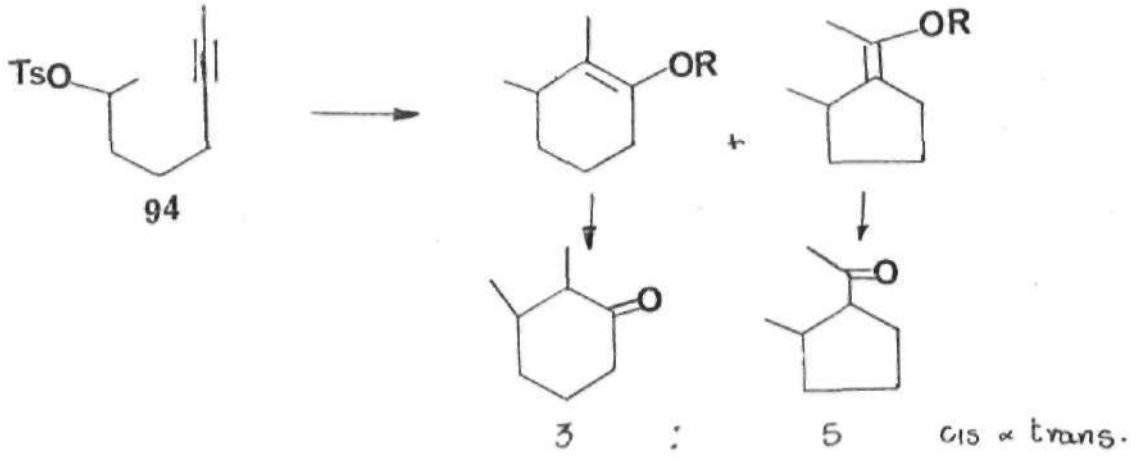
The structure of (92) was established by hydrogenation of the olefinic bond, oxidation to the 20- keto compound, Baeyer-Villiger oxidation, hydrolysis of the ester and finally oxidation to the known androstanone (93)

The styryl terminator[57] has been found to be more stereoselective than its phenyl-acetylene counterpart[47], (termination of polyene cyclisation with terminal acetylenes will be discussed shortly). In the latter case about 20% of 13 α isomers having the unnatural C/D cis ring junction have been reported[46], whereas in the corresponding styryl terminators it has been less than 2%. Even that is thought to arise from a small amount of contaminant in the cyclisation substrate having the Z-configuration in the trisubstituted olefinic bond, otherwise it could be 100% stereoselective.

F PARTICIPATION OF ACETYLENIC BONDS IN POLYENE CYCLISATIONS

Double and triple bonds have been shown to assist solvolysis of sulphonate esters with concomitant ring formation. Several examples of the latter have been discussed earlier in Section 3 C.

Peterson and Kamat[48] have reported the formolysis of the acetylenic p-toluene sulphonate, (94), to give both five- and six-membered ring compounds in ratio 5 : 3.



These results prompted the investigation of the possible participation of the acetylenic bonds in biomimetic polyene cyclisations.

The first example investigated[49], (95), is similar to the tetraenol, (80), except that (95) has a triple bond where the former has a tri-substituted double bond. The cyclisation of the trienynol, (95), could be expected to go via the vinyl cations A or B, depending upon whether there would be preference for five- or six-membered ring formation respec-

tively. If cyclisation continues further in both cations, cation A would give cation C, whereas cation B would lead to cation D, which would have the lanosterol type A/B/C ring system with an olefinic bond at the 8,9 position. Cation C would then lead to a trans-fused

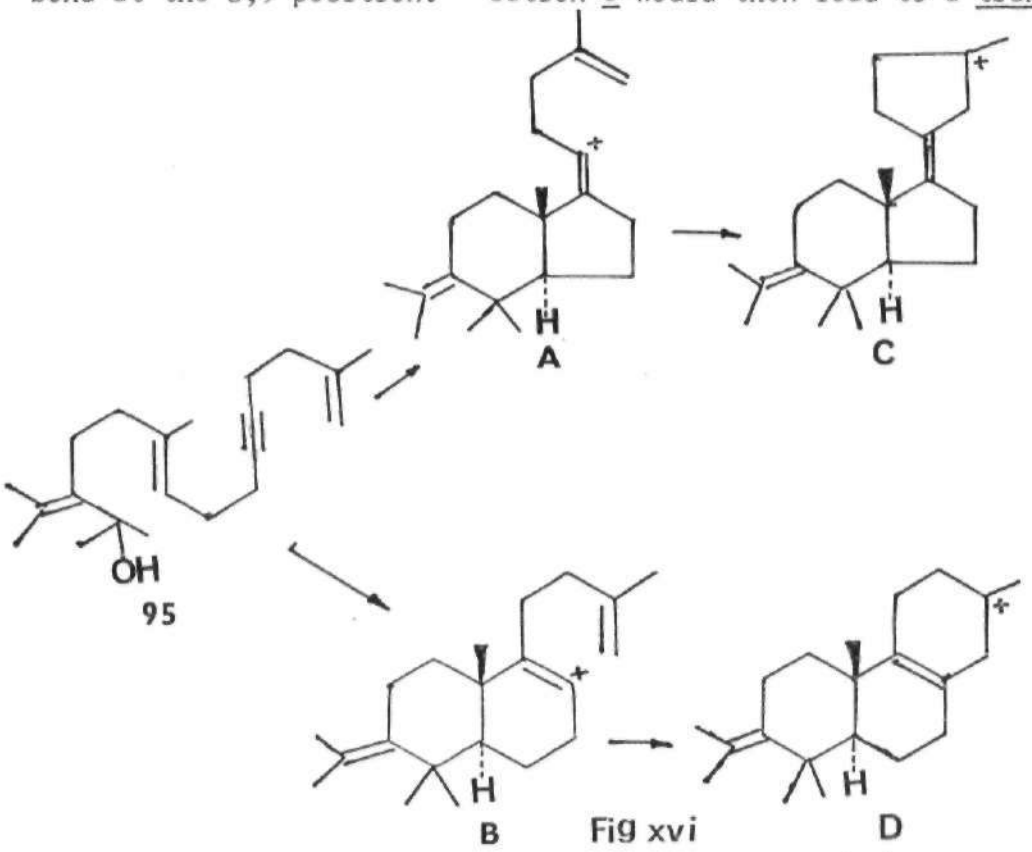
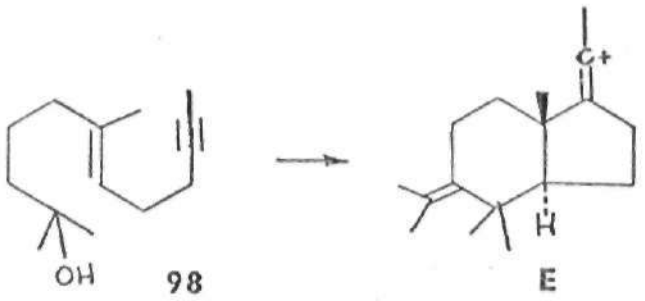
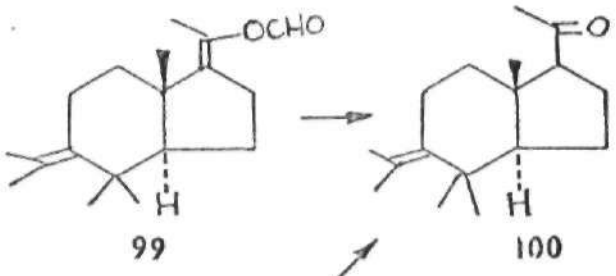


Fig xvi

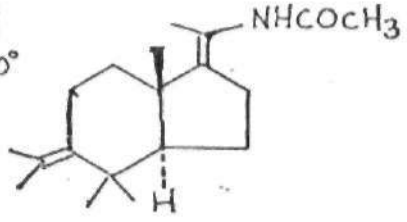
hydrindan system, Fig. xvi. When the trienynol (95) in dichloromethane at -70°C was treated with trifluoroacetic acid for 5 min a single major component, (68%), was obtained. The product was identified as (96) and no product arising from cation B was isolated. Ozonolysis of (96) gave a diketone, (97), shown to be identical to an authentic sample synthesised by another route.[50](p.51)



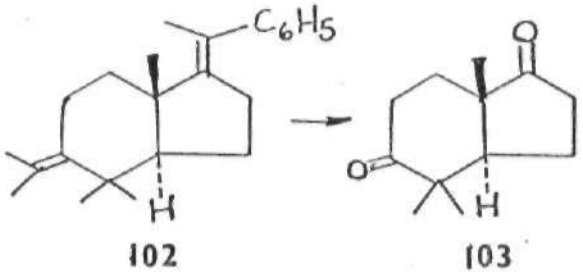
With HCO_2H in pentane at 25°



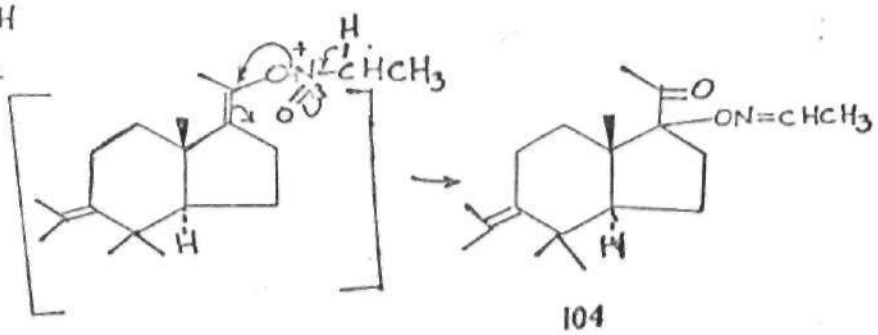
with 1% CF_3CO_2H in CH_3CN at -30°



with $SnCl_4$ in C_6H_6 at -5°

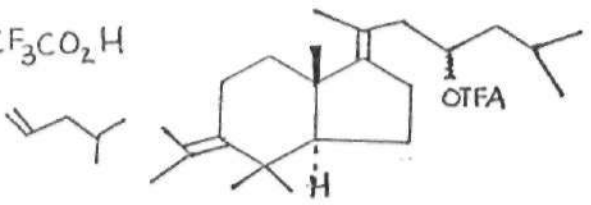


With 1% CF_3CO_2H
in $CH_3CH_2NO_2$



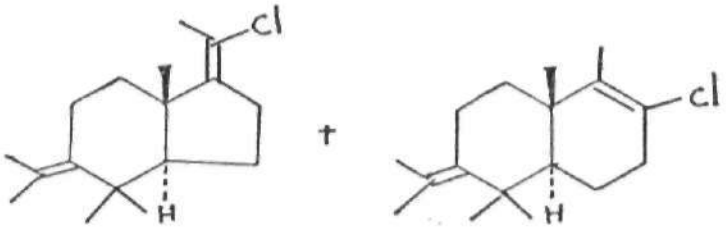
104

With CF_3CO_2H
and

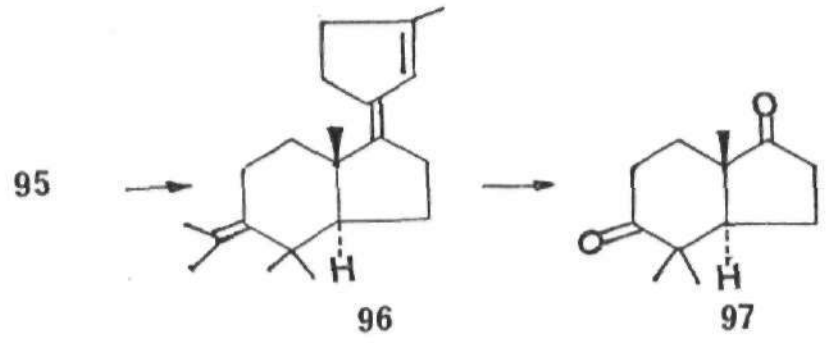


105

With $SnCl_4$
in CH_2Cl_2.



106 + 107



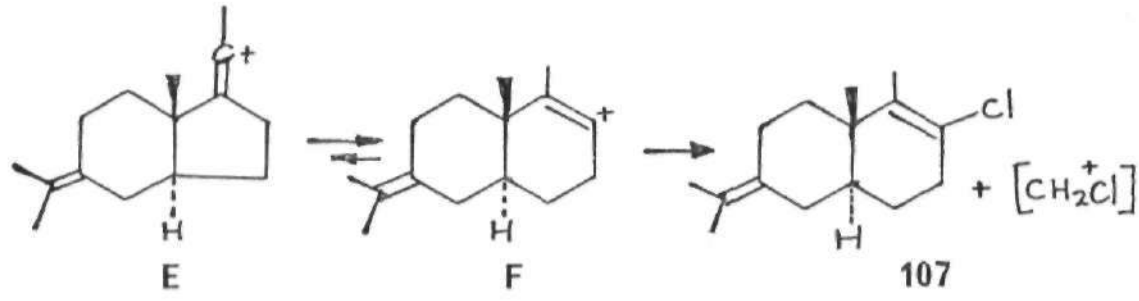
Having established the preference for a five-membered ring formation, attention was turned to the cyclisation of a simpler system viz, the dienynol[46a], (98), with a methyl group attached to the acetylenic residue. The cyclisation procedure was modified somewhat in order to supply an appropriate nucleophile to react with the intermediate vinyl cation.

One successful procedure consisted of stirring a solution of the substrate in pentane with excess formic acid (two phase system) for 15 min at 23°, giving the enol formate, (99), in 90% yield.

The vinyl cation E proved to be very reactive and when it was generated in various solvents, each solvent acting as a nucleophile, trapped the cation and gave the compounds (99) in formic acid, (101) in acetonitrile, (102) in benzene, (104) in nitroethane, (105) in isohexene, (106) and (107) in dichloromethane.

When the dienynol (98) was cyclised with trifluoroacetic acid in dichloromethane[53] at -78°, the cyclisation resulted in exclusive formation of the six-membered ring chloride (107). This can result from a

Wagner–Meerwin rearrangement of cation E to cation F, which then abstracted a chloride ion from the solvent (Fig. xvii).



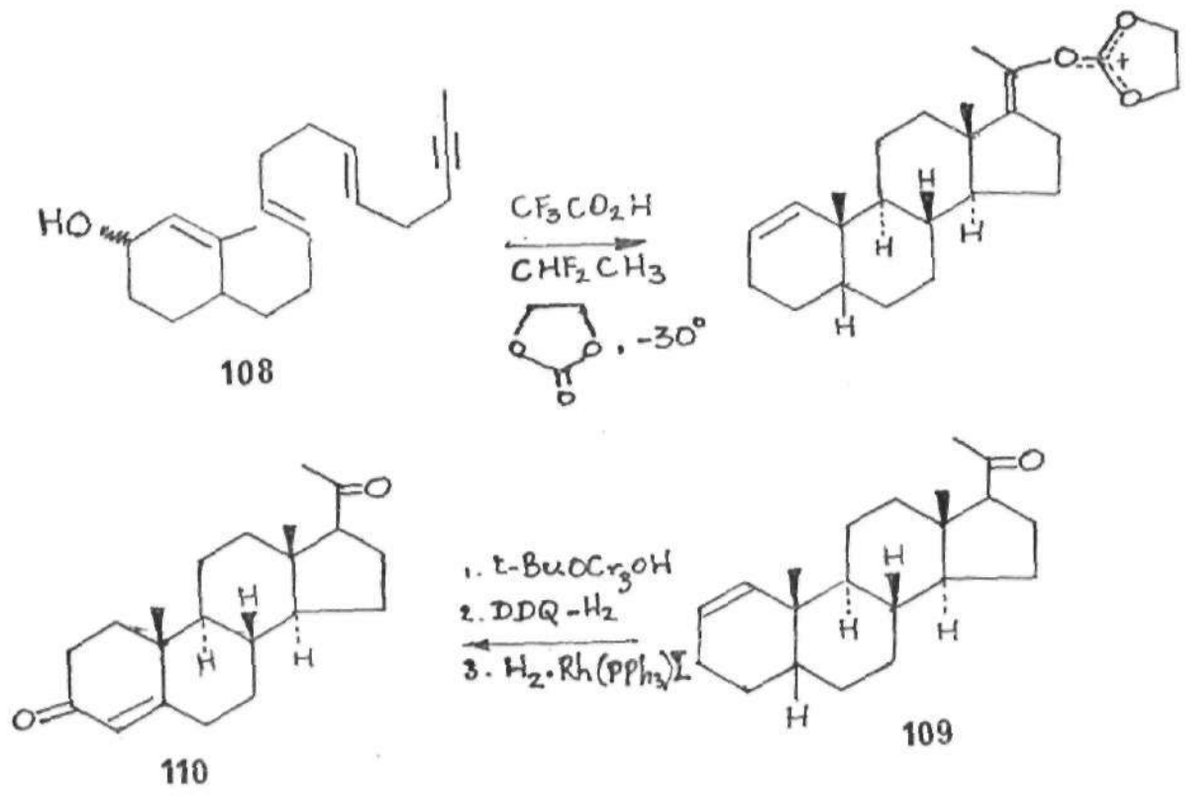
E F 107

Fig xvii

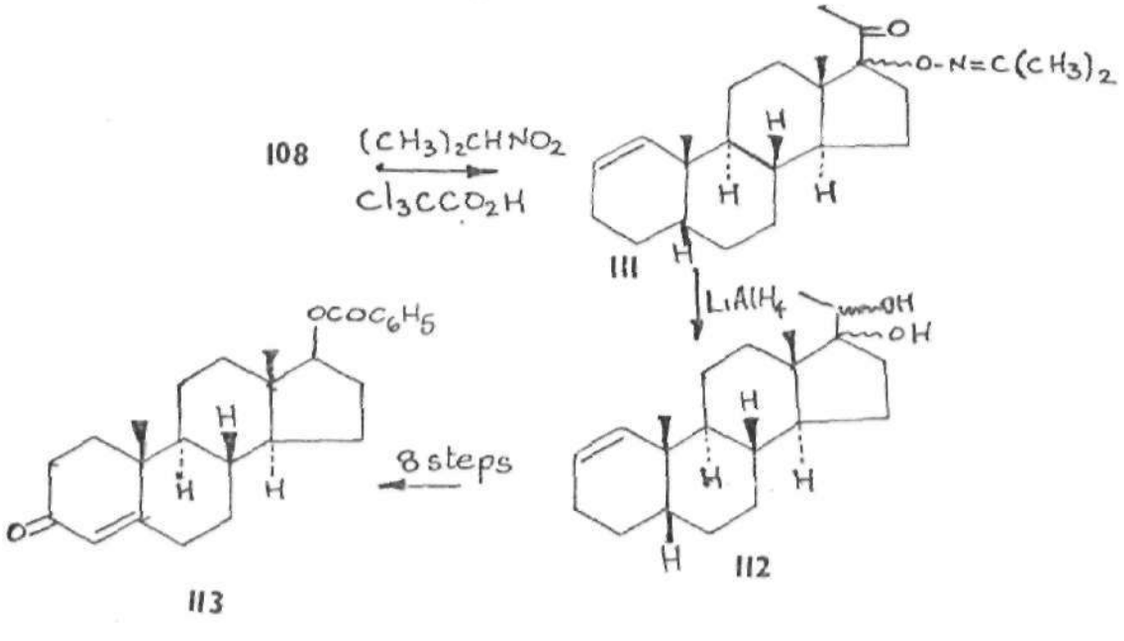
Only a very small amount of product derived from unrearranged cation E was obtained. Failure to trap this cation is rationalised in terms of the very poor nucleophilicity of the solvent, thus cation E is able to equilibrate to cation F which then abstracted chloride ion in a relatively slow process. There is precedence[51] for abstraction of chloride ion from dichloromethane by the 1-norbornyl cation. The relief of strain in the conversion of a 6/5 to 6/6 trans-fused ring system could be the determining factor in the rearrangement of these cations and the course of the reaction. The foregoing observations have been used to achieve total synthesis of a number of natural products, mostly steroids.

The trienynol, (108), has been converted in 65% yield to dl-pregnone, (109), which in turn was readily transformed into dl-progesterone[52] (110).

When the trienynol (108) was treated with trichloroacetic acid in

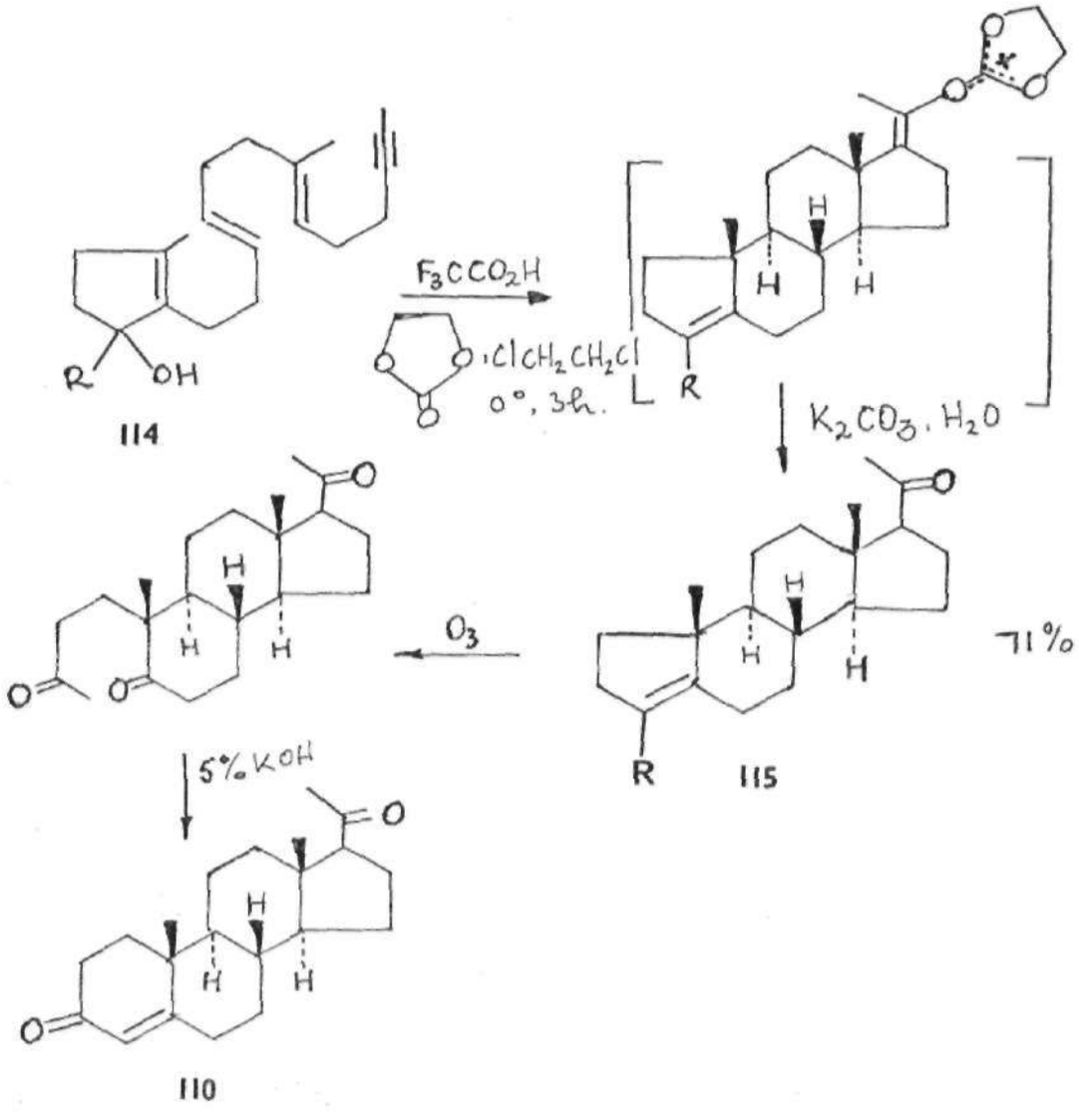


2-nitropropane, the oximino ether, (111) was obtained, (cf. 104) which was converted to the diol, (112) by reduction with lithium aluminium hydride. Periodate cleavage converts the diol to the corresponding 17-keto compound which then converted to the benzoate, (113).[53]

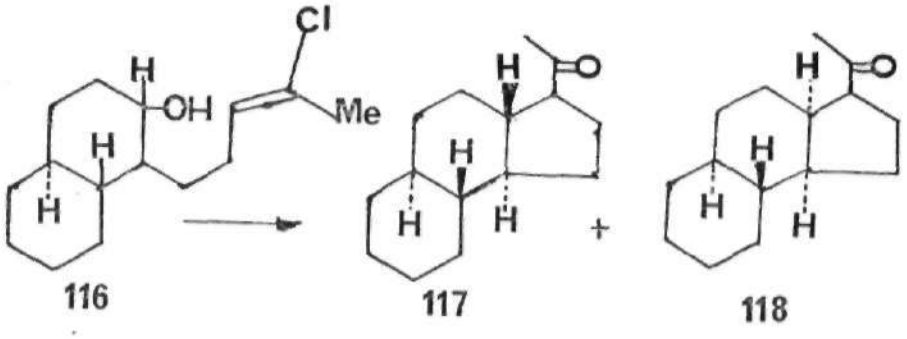


In order to introduce the steroid side chain, the vinyl cation from (108) (*cf.* 105) has also been trapped with isohexene and the resulting compound isolated in 30% yield.

Another substrate which proved useful for the synthesis of steroids is the cyclopentenol, (114), R = Me, which gave the ketone, (115, R = Me) on cyclisation. The ketone (115) was subjected to ozonolysis, followed by intramolecular aldol condensation to give racemic form of progesterone in 80% yield.[53]

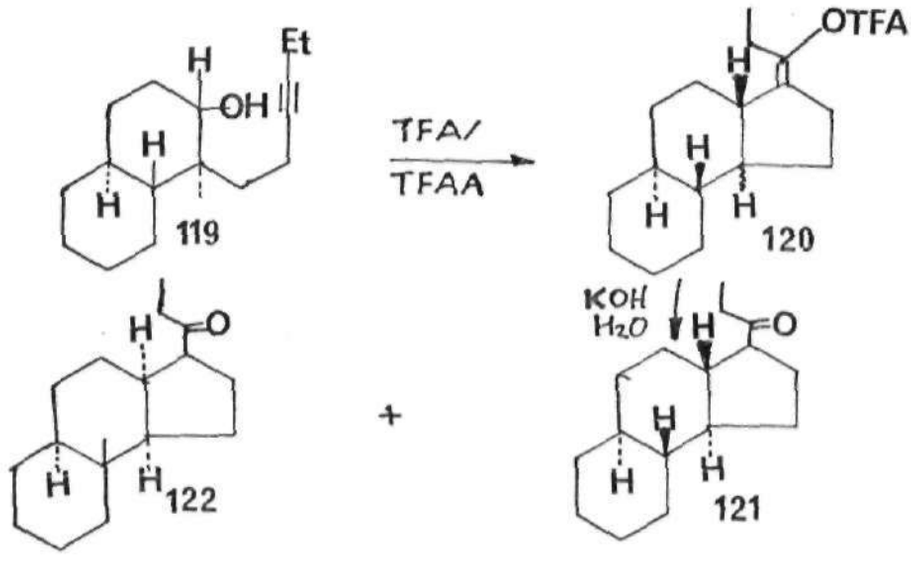


The 19-nor progesterone has been synthesised from trienynol (114, R = H) by a similar route. 11-substituted steroids[55] have also been synthesised. Prior to the investigation of the participation of acetylene-side chains as a route to stereoselective method for steroid ring D annelation, Lansbury et al[56] had investigated the intramolecular alkylation of vinyl chlorides, (116) for example, in a bid to achieve the same goal.



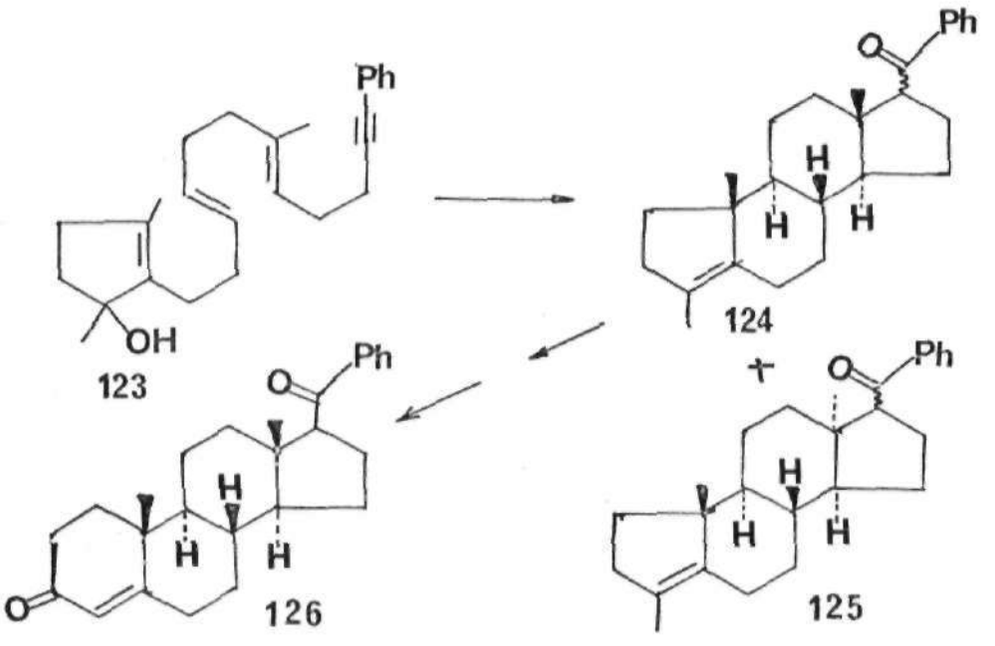
This involves generation of rigid bicyclic carbonium ion interacting with the vinyl chloride side chain in an equatorial position. Two tricyclic products were obtained in ratio 2 : 1, (117) and (118) respectively. The compound (118) has the unnatural C/D cis ring system. The stereochemistry of the trans-isomer was confirmed by an independent synthesis.

This investigation led on to the use of equatorially placed acetylenic[56b] side chains in place of the geometrically dissimilar but chemically equivalent chloro-olefin side chain mentioned above.



In the cyclisation of (119), two products (121) and (122) are obtained in ratio 4 : 1. This is in contrast to the results obtained so far where only trans products have been obtained in accordance with the Stork-Eschenmoser hypothesis. This particular example which involves formation of only one ring is surprisingly not stereospecific. Another example involving the non-stereospecific participation of the acetylenes was obtained with the cyclisation of a substrate with a phenylacetylenic[57] terminator. It was thought that this could react in analogous way to the styryl terminator described earlier.

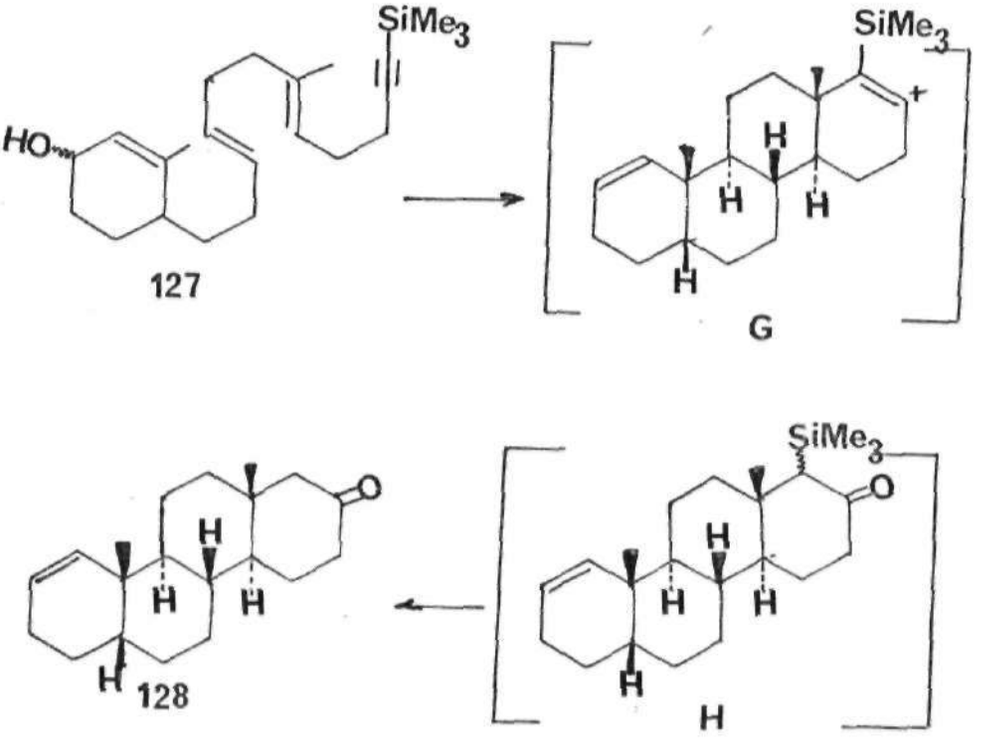
A solution of (123) in dichloromethane was added to trifluoroacetic acid in dichloromethane containing ethylene carbonate at -45° and mixture stirred for 45 min. Treatment with methanolic sodium hydroxide resulted



in isolation of tetracyclic ketones (~80% yield). The formation of the 13**α** C/D cis compound (125), ~20%, among other compounds was not expected. Thus it appears that in each cyclisation involving acetylene participation, there has been formed more or less of this unnatural isomer. The solution to this problem is that already discussed involving termination with the styryl side chain.[47]

The use of the trimethylsilylacetylenic group as a terminator has also been investigated by Johnson and co-workers[58], with interesting results too. So far we have come across examples where the acetylenic bond has reacted to form a five- in preference to six-membered ring. The trimethylsilyl substrate (127) underwent acid-catalysed cyclisation

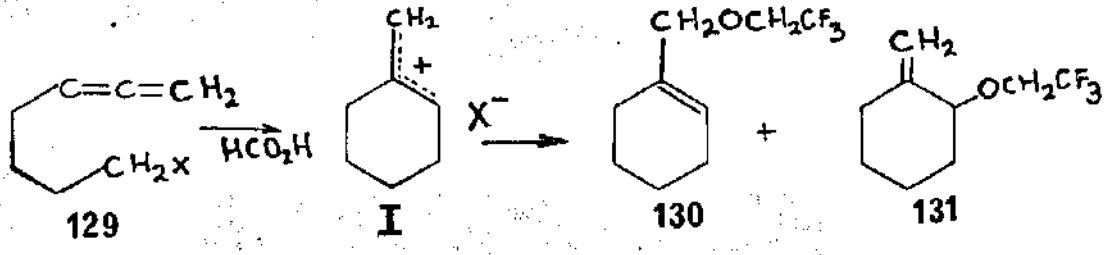
in the presence of ethylene carbonate to give the D-homosteroidal ketone, (128), in 52% yield after treatment with water. There was no evidence of product resulting from five-membered ring D closure.



It appears that the ring closure proceeded via cation G which is said to be more stable than the alternative cation formed from the five-membered ring in which the positive charge would be on the carbon bearing the trimethylsilyl group. Nucleophilic attack by water on (H) converts it to the ketone (128) which was converted by hydrogenation to the known D-homoandrostanone.[59]

G CATIONIC CYCLISATION OF ALLENES

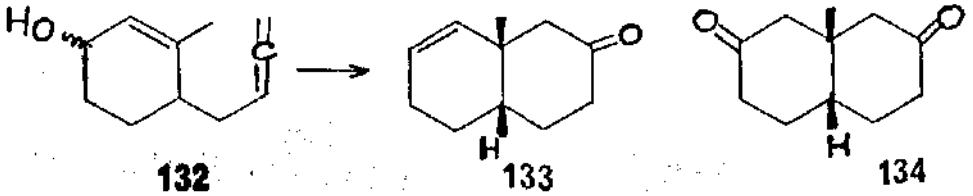
Allenes are known to be reactive in electrophilic additions, it is expected that they may also lead to stable allylic cations which could be useful initiators in syntheses of mono- or polycyclic molecules.



129 I 130 131

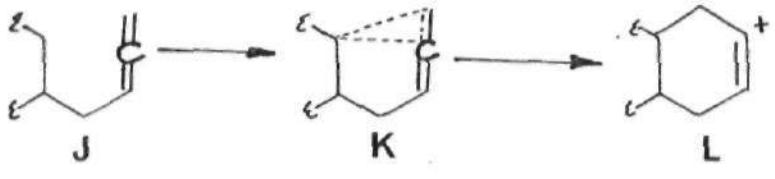
Solvolysis[60] of (129) in acetic acid at 60° gave mainly the starting alcohol, whereas in the less nucleophilic 2,2,2-trifluoroethanol a high yield of cyclisation products was obtained mainly equal mixtures of the trifluoroethyl ethers (130) and (131). This observation constitutes cyclisation involving a δ-allenyl cation system.

Harding et al[61] have reported cyclisation involving a γ-allenyl cation system, (132).

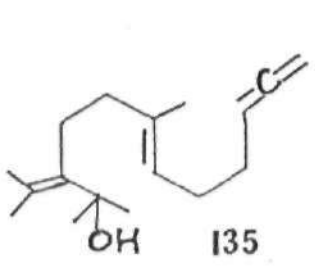


132 133 134

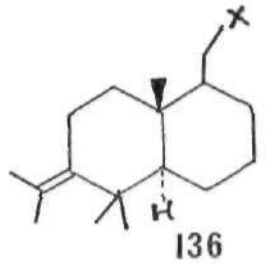
Treatment of (132) with anhydrous formic acid gave after hydrolysis (133) (70%). Treatment of the corresponding ketone, prior to reduction to (132), with acetic anhydride / acetic acid with perchloric acid or with trifluoroacetic anhydride / trifluoroacetic acid resulted in formation of the diketone, (134) in 66 and 74% yields respectively. This also demonstrates the preference for six-membered ring formation. It is however, reported that when the allene is substituted with two methyls on the terminal carbon, good yields of five-membered ring products are obtained. The products (133) and (134) are probably formed <u>via</u> these cations: J - L (<u>cf</u>. I) (Fig. xviii).



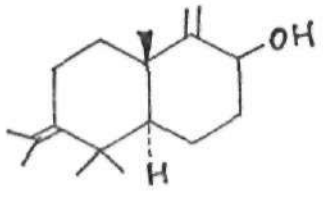
Johnson and co-workers have however, investigated an example of the latter case[60] involving cyclisation of (135).



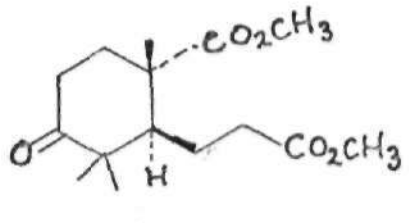
135



136



137



138

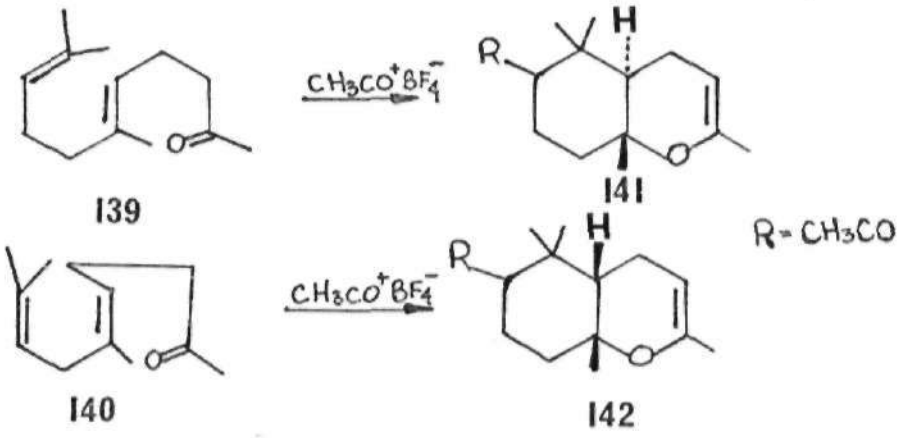
Treatment of (135) with stannic chloride in dichloromethane gave (136) (X = Cl) as major product. When trifluoroacetic acid in dichloromethane was used for cyclisation a mixture of (136, X = OH) and (137) was obtained. Both were oxidatively degraded to the known keto diester, (138), thus establishing a trans-fused 6/6 ring system.

H OTHER INITIATION METHODS OF CYCLISATION

Following the cyclisation of polyolefins by protonation of the terminal double bond, accompanied by concerted or non-concerted interaction of other double bonds, it became reasonable that similar cyclisation may be induced by the addition of any electrophilic cation of the type, X^+ to the terminal double bond. Electrophilic additions of bromine, mercuric acetate, nitrosyl chloride etc. to olefins are known and such additions are rationalised to involve X^+ and Y^- ions. In cases where Y^- is non-nucleophilic, it is reasonable to suggest that corresponding cations could be useful in polyolefin cyclisation.

Olah et al[63] have studied reagents of the type $X^+/MetHaln$ where $X = R^+$, RCO^+, NO_2^+, etc. and Met = Sb, B, As and Hal = F, Cl. They also showed the use of these reagents as powerful agents for aromatic substitution, but more relevant to our cause showed that they could be used for initiating polymerisation of olefins.

Semenovsky[64] applied this idea to the cyclisation of trans geranyl acetone, (139), and cis-isomer, (140).

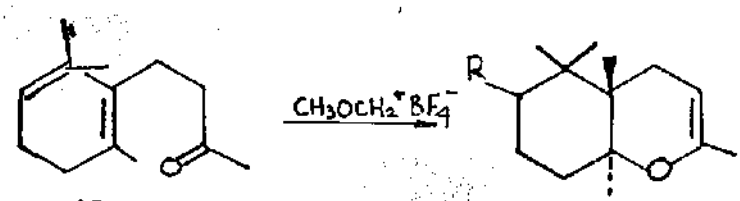


139 141

140 142

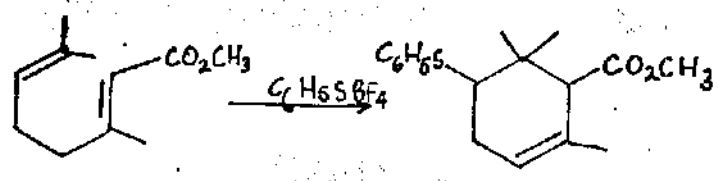
The stereochemistry of the ring junctions of (141) and (142) is assumed on the basis of similar results obtained by proton catalysis. Yields of bicyclic products are in the order of 35% in each case.

Other acyl cations, $RCO^{+}BF_4^{-}$ (R = C_2H_5; i-C_3H_7 etc.) were also found feasible. Alkyl cations e.g. $CH_3OCH_2^{+}BF_4^{-}$ (from CH_3OCH_2Cl + $AgBF_4$) were also used in the cyclisation of trans-6,7-geranyl acetone giving (143) in 55% yield.



139 143 R=CH_3OCH_2

Ring closure involving cations like RS^+ has also been reported[65] in which the geranyl ester (144) was cyclised using $C_6H_5SBF_4$ in nitromethane at -25° giving the monocyclic product (145) in 57% yield.

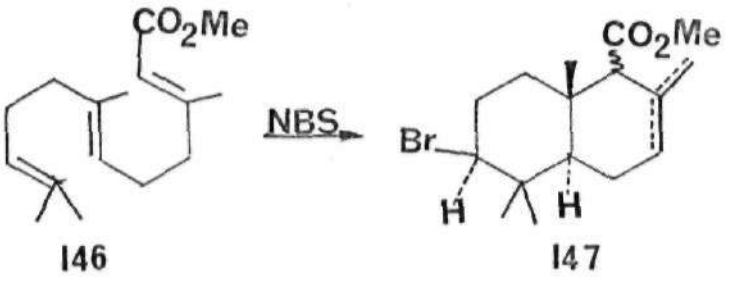


144 145

I BROMONIUM ION AS INITIATOR

In his studies concerning the terminal oxidation of sesqui- and higher terpenes[27] using N-bromosuccinimide (NBS) in aqueous glyme or tetrahydrofuran, van Tamelen[62] found that terminal monohalogenohydrins were the major products but in the particular case of methylfarnesate (146), there were produced concurrently an isomeric mixture of bicyclic

bromoesters, (147) obtained in 12 - 15% yield.



146 147

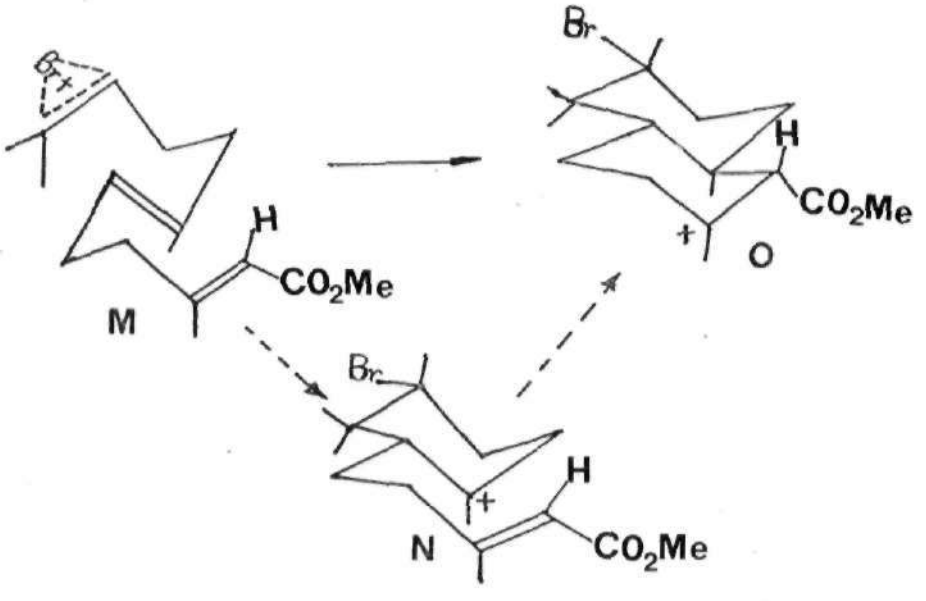
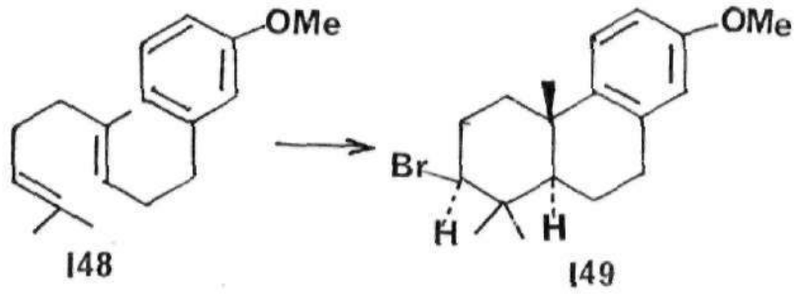


Fig xix

The cyclisation seems to involve ring formation of an initially produced terminal bromonium ion M which is capable of cyclising to the bicyclic cation, O (Fig. xix) in a synchronous process. There is the possibility that the monocyclic cation, N is formed, but proceeds to the product before it could deprotonate or assume a different conformation.

Nasipuri and Chaudri[26a] also observed a similar bromonium-ion-

initiated cyclisation of the compound (148) in its reaction with NBS, when 10% of (149) was obtained also as a by-product.

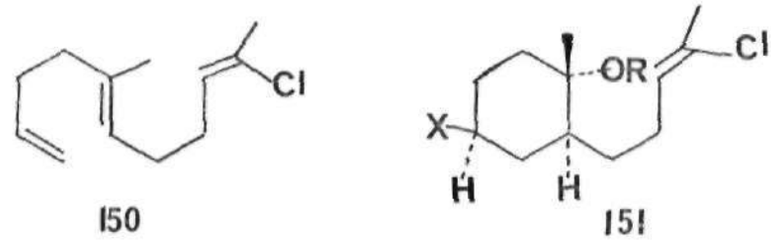


148 149

J MERCURIC-ION AS INITIATOR

Julia[2,66] has investigated the mercury ion and proton induced cyclisation of various olefinic systems obtaining the same stereochemical results already observed via other methods.

Treatment of the triene, (150), with an equivalent amount of mercuric acetate in formic acid for 10 min at 6° gave the monocyclic compound, (151), in 90% yield after treating with sodium chloride. De-

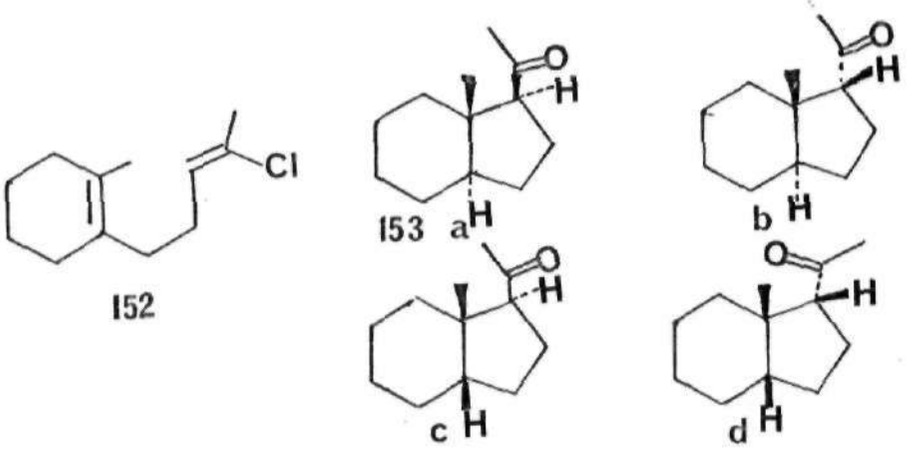


150 151

a X = HgCl, R = CHO
b X = HgCl, R = H
c X = R = H

mercuration of (151a), followed by cleavage of the formate ester with lithium aluminium hydride afforded (151c) in quantitative yield. Treatment of (151a) with sodium carbonate affords (151b) in 90% yield after recrystallisation.

The formate, (151a), is dissolved in minimum amount of THF and treated with formic acid over 15 h at room temperature. A mixture of products was obtained, but consisted mainly of the monocyclic compound, (152) (50%).

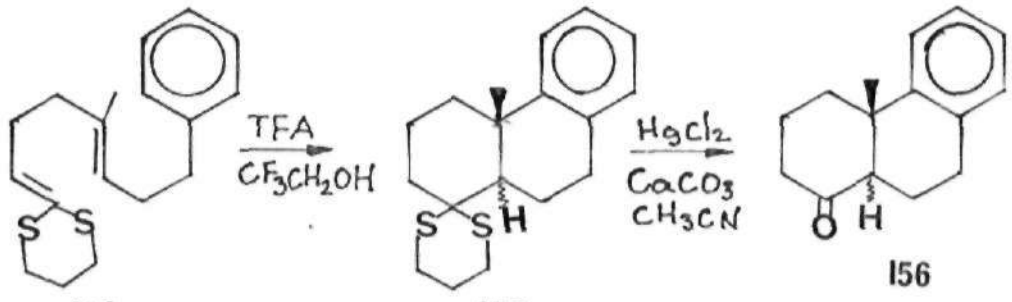


The more polar fraction contained a mixture of (153a) and (153b). [Lansbury[56] had identified the four isomers (153a - d)]. Cyclisation of (151c), however, gave the four isomers with (153c) and (153d), the major components obtained in 75% yield. The cyclisation is certainly non-stereoselective. The mercuric ion probably co-ordinates the terminal olefinic bond in more or less the same way the bromonium ion is formed.

Only one ring is formed, at least in this example, and it appears that a proton source is required for complete cyclisation to take place *via* the intermediate alcohol.

K KETENE THIOACETALS AS INITIATOR

Ketene thioacetals[67a] (vinyl sulphides) are known to be capable of protonation to form cations which are more or less synthetic equivalents to acylium ions. These cations can be trapped with external or internal nucleophiles and Andersen *et al*[67b] have shown that the cation from a ketene thioacetal can be trapped intramolecularly with a double bond to form a single six-membered ring. The ketene thioacetal (154) was cyclised using trifluoroacetic acid in trifluoroethanol (1 : 10 respectively) at 0°. The product was the compound (155) which was immediately subjected

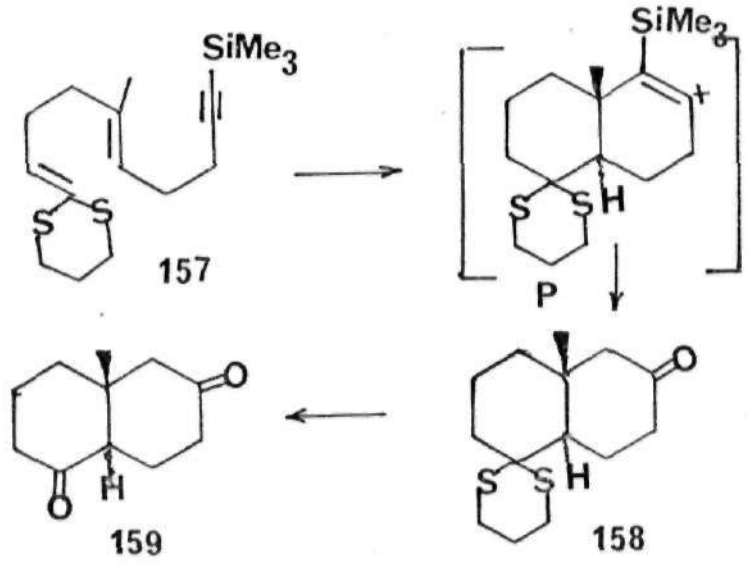


154 155 156

to hydrolysis with $HgCl_2$, $CaCO_3$ in aqueous CH_3CN to the known[67c] ketone (156) as a mixture of *cis* and *trans* isomers in ratio 1 : 2 in 55% yield

after distillation.

Cyclisation of the ketene thioacetal, (157), was also effected with TFA/CF_3CH_2OH to (158) in 76% yield after chromatography, hydrolysis of which afforded the diketone (159) in 89% yield.[67d]

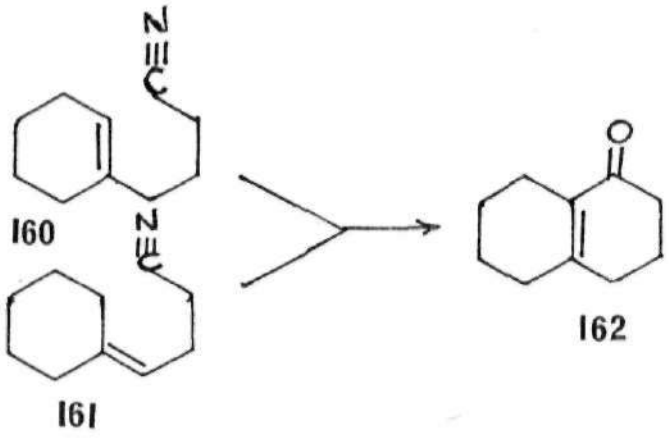


The cyclisation probably involves cation P, as in the cyclisation of compound (127) where the trimethylsilyl acetylene group was used as a terminator.[58]

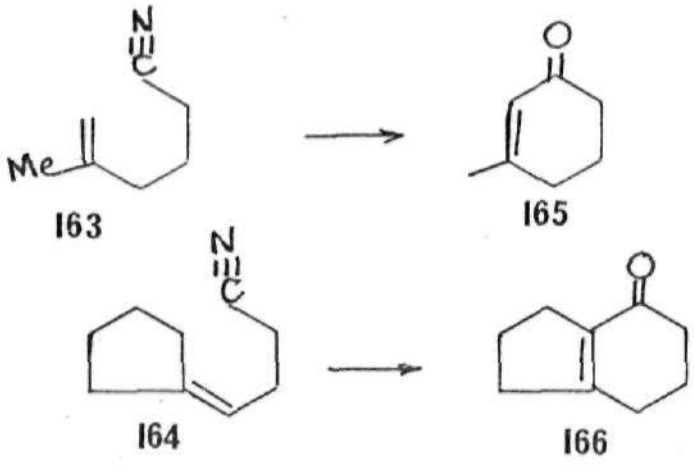
L NITRILIUM ION AS INITIATOR

Hill and Conley[68a] had observed the cyclisation of the isomeric

nitriles, (160) and (161) in polyphosphoric acid to give the same product, (162).

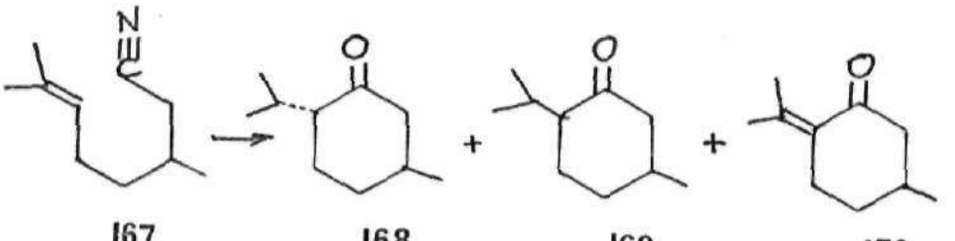


Under the same conditions, the nitriles (163) and (164) were cyclised, to give the enones (165) and (166).[68b]



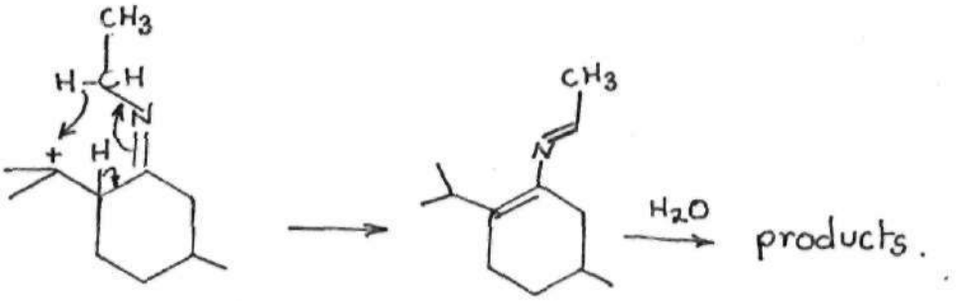
F. Johnson et al[68c], working under milder conditions of cyclisation, used triethyloxonium fluoroborate in place of polyphosphoric acid, heating the reagent with the substrate without any solvent. Their most successful reaction involved cyclisation of citronellonitrile, (167). The

product contained three steam volatile components, namely, menthone, (168); isomenthone, (169) and pulegone, (170) in 45, 20 and 16% yields respectively.



167 168 169 170

An intermediate, (171), is proposed which on hydrolysis gives (168) and (169). (170) is probably formed by deprotonation and hydrolysis of (171).



171

Attempts to extend this to five-membered ring formation were not successful, and the usefulness of this method for polyene cyclisation is in doubt.

The most promising of these other methods is probably the ketene thioacetal method of initiating cyclisation. The yields are high and looks easily adaptable to formation of four rings with functional groups

at strategic places.

In all the methods described so far, the synthesis of the substrates has not been described for brevity. The recipe for the synthesis of each compound is appropriately documented in the respective papers.

SECTION 4 - MECHANISM[69,70] OF POLYENE CYCLISATION.

In the course of this report, it has been possible to build up a catalogue of reactions involving diverse substrates under varying reaction conditions to give products of similar and/or dissimilar stereochemical relationships. Of particular interest is the high degree of ring fusion stereoselectivity observed in these non-enzymatic cyclisations. The full mechanistic basis of these cyclisations has still not been fully understood even with the help of the Stork-Eschenmoser hypothesis in a number of cases. They had postulated a synchronous reaction in which all bonds involved in the formation of the polycyclic system are made and broken at the same time (Fig. i).

Johnson has also suggested another mechanism involving the intermediacy of bridged ions, the stereochemistry of which is preserved by back side ring opening, (Fig. xx).

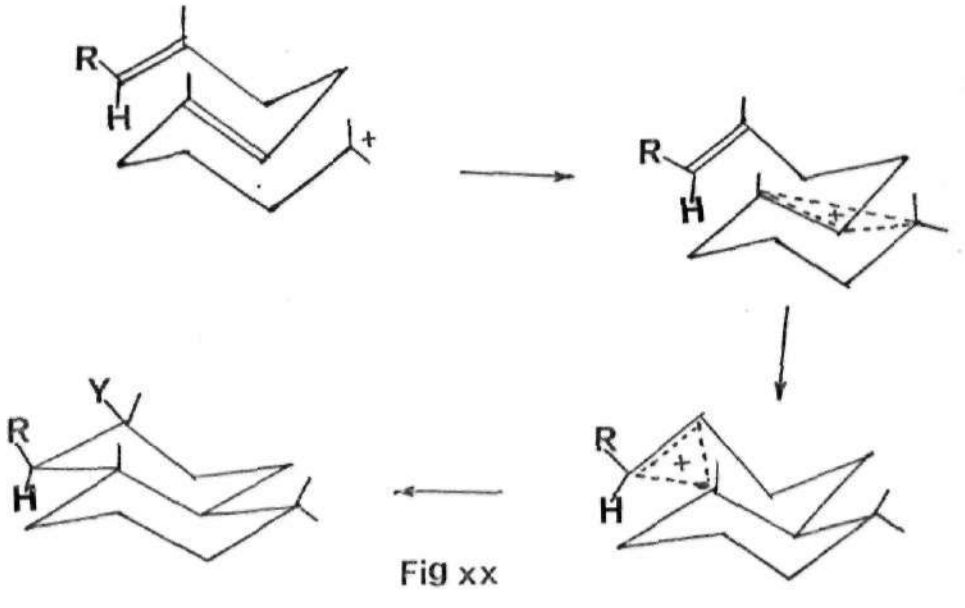


Fig xx

Another view is the involvement of classical alicyclic carbonium ions. For this type of mechanism to account for the observed stereoselectivity, it is necessary that any alicyclic cation formed does not undergo ring inversion before cyclisation and that electrophilic attack on the double-bond must occur with a high preference for formation of an equatorial C-C bond formation (Fig. xxi).

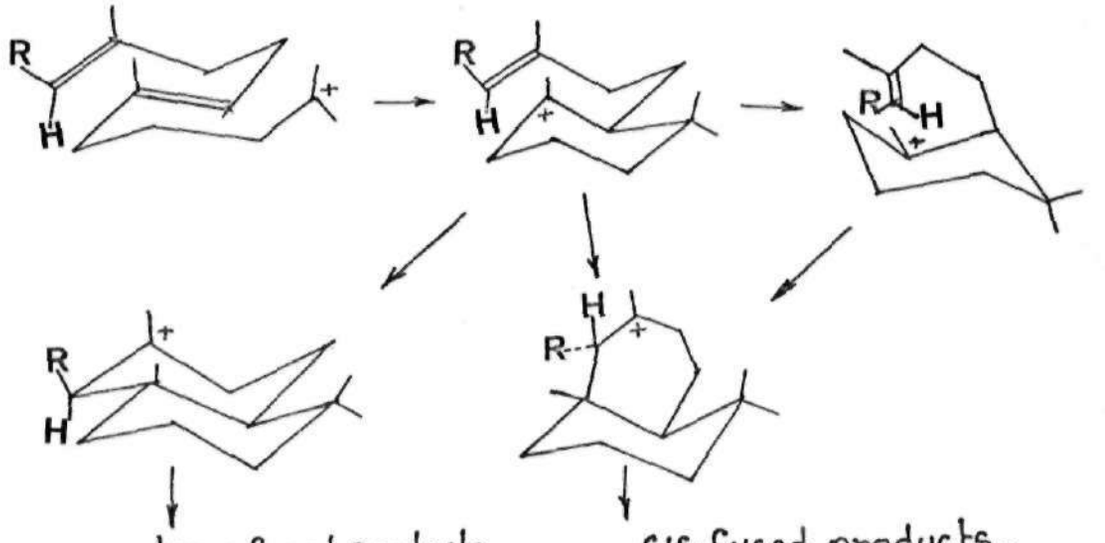
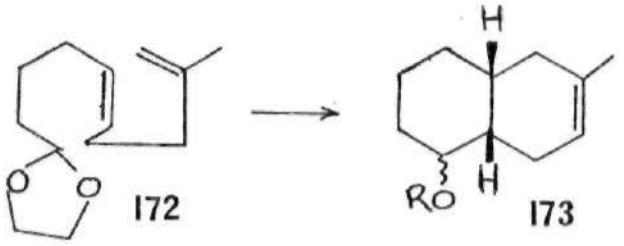


Fig xxi

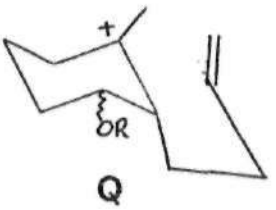
It is possible that we require all of these mechanisms to explain the examples already observed for not one of them alone is capable of explaining all of the observed phenomena. Johnson[31] proposed involvement of 'bridge-ion' intermediate in connection with solvolytic cyclisation of sulphonate esters which was shown to be anchimerically assisted, whereas

in the acetal and allylic alcohol cyclisations, such ions are not involved.

To account for the involvement of alicyclic cations, it was further suggested that conformational inversion of intermediates may be a slow process with respect to rate of cyclisation.



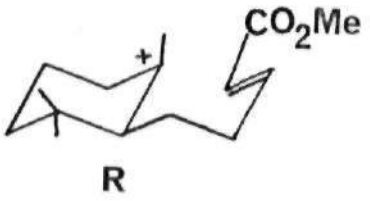
172 173



Q

In the cyclisation of acetal (172), to form the cis-decalin system, (173), cation Q can only give rise to the observed products if conformational inversion did not take place before cyclisation.

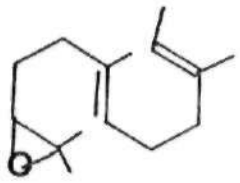
In the proton catalysed cyclisation of trans- and cis-desmethyl-farnesic ester (28) and (30) respectively the same trans product, (29), was obtained. This result ruled out a concerted trans-addition of double-bond. The alicyclic cation, R may be a possible intermediate, and as mentioned earlier the carbomethoxy group may be responsible for



the poor nucleophilicity of the double-bond so that attack of the double bond is not synchronous with protonation. Steric as opposed to electronic factor may however, explain the preferred equatorial attack of the olefinic bond to give the observed product instead of axial attack where a severe steric interaction of the axial group on the ring with the bulky carbomethoxy group will prevent a cis addition. van Tamelen had cyclised the corresponding epoxides, (12) and (13) (Fig. viii) and obtained among other products, the expected trans and cis products. This shows that whereas the cyclisation of the olefins, (28) and (30) involved the same intermediate, cyclisation of the corresponding epoxides cannot involve a common intermediate. A bridged-ion type intermediate may be involved as it has also been demonstrated that the double bond nearest to the epoxide function lends anchimeric assistance to the opening of the epoxide ring and hence, cyclisation of the substrate cf. (5) and (6). If however, bridged-ions are not involved, cyclisation of cis-epoxide (13) must give a monocylic cation with an axial side chain, whereas cyclisation of the trans-epoxide (12) would give a monocyclic cation with equatorial side chain (cf. Fig. xxi). van Tamelen[23b] referred

to these cations as conformationally 'frozen' which probably supports the slow conformational inversion of intermediates prior to ring closure. He further suggested that in the biogenetic synthesis of lanosterol, enzyme action is mandatory in the formation of ring A and B to block other reaction outlets for the starting epoxide (cf. products 14d - f, Fig. viii) thereby ensuring quantitative conversion of squalene oxide to lanosterol. It thus appears that the enzyme overcomes some energy barrier to initiate the cyclisation, otherwise from thereon in the formation of other rings cyclisation possesses purely organic parallels.

Following this proposition, rate studies[14] involving diene-(5c), triene-(174), and tetraene-monoepoxides, (15), were carried out in an



174

attempt to detect the participation of additional π-bonds. In these systems where mono-, bi- and tri-cyclic products are expected rate ratios of (5c)/(174) = 1.4 ± 0.1; and (5c)/(15) = 1.3 ± 0.2 were obtained. It appears there is no significant participation of remote olefinic bonds to the rate of cyclisation or formation of other rings compared to the rate of forming the first ring.

Several structural modifications on the squalene oxide were found

not to markedly affect the activity of the cyclase enzyme to convert the respective substrates to lanosterol-type products. Ordinarily one would have expected a profound adverse effect on cyclisation if a perfect 'lock and key' arrangement was obligatory. A single mechanism for a polycyclisation may thus not be possible, lending support to carbocyclic ion conformers as most likely intermediates which do not undergo equilibration with other conformers suitably disposed for conversion to the same end products. A fundamentally equivalent enzymic and non-enzymic cyclisation route is thus proposed, i.e. polycyclisation involving formation of one ring after the other followed by characteristic two-fold hydrogen and methyl migrations preceeding final proton loss.

CONCLUSION

Polyene cyclisations may be initiated by the generation of a suitably positioned cationic site in the molecule. The extent of cyclisation is dependent on the stability of the carbonium ion and this is important in the formation of three or more rings. Acid-catalysed cyclisations have been shown to be a viable synthetic route as well as acetal and allylic alcohol functions as useful initiators. Methyl acetylenic and styryl end groups are useful terminators giving exclusively, five-membered rings. Other methods of initiation have still not been as

successful as would be expected especially the epoxide function which is the only method that is relevant as a 'natural' substrate.

Although the word 'concerted' has often been used to imply a synchronous process in which a double-bond is attacking an electrophilic centre at the same time as it is being attacked by a nucleophile, ring closure may also occur as a separate step involving a bridged (non-classical) carbonium ion which is capable of collapsing to a classical one retaining its stereochemistry resulting in the formation of products expected by a purely concerted process with preservation of stereochemical relationships. A possible corollary from results obtained by van Tamelen in the terminal epoxidation of polyenes in various solvents is that each polyene prior to cyclisation also assumes a coiled structure with suitably juxtaposed non-conjugated olefinic bonds depending upon some intrinsic properties of that medium and temperature conditions.

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CHAPTER 2 - RESULTS AND DISCUSSION

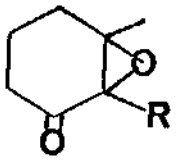
SECTION 1 - INTRODUCTION.

Following the extensive studies by Johnson and van Tamelen and others in polyene cyclisations (Chapter I) we have been investigating cyclisations initiated by epoxyketone ring opening. As already mentioned the pioneering work in this field of study had been carried out by van Tamelen and his collaborators. The yields were very low and there was not much incentive in following this method as a synthetic route. Useful stereochemical results were however, obtained.

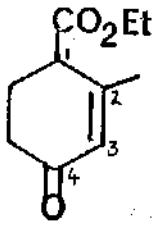
The substrates chosen for study have the general structure (1) where R is the side chain with double-bonds in 1,5-relationship leading to mono-, bi-, tri- and tetra-cyclic products. The first problem is the synthesis of the corresponding alkylcyclohexenones from which the epoxide (1) could be made.

The classical method of synthesising these compounds is *via* alkylation of Hagemann's ester[1a] (3-methyl-4-carbethoxy-2-cyclohexen-1-one) (2) with the appropriate alkylating agents.

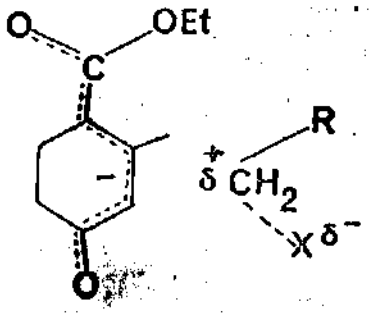
Nasipuri[1b-3] and his collaborators have done extensive work in this route to the alkylcyclohexenones, and have demonstrated the non-regioselectivity of the reaction since alkylation takes place at C_1 and C_3 with the latter predominating. It had previously been assumed that alkylation proceeded exclusively at C-3. The proportion of C-3 and C-1 depended



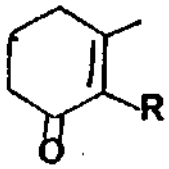
1



2



3



4

Fig i

mainly on the nature of the alkylating agent. The C-1 alkylated esters were found to be more resistant to hydrolysis and in many cases reported, could be separated from the C-3 isomer by partial saponification.[1,4] They also extended their study to a few Michael reactions.

A substantial amount of C-1 alkylation (15 - 30%) was obtained with isopropyl-, isobutyl- and benzyl-halides whereas C-3 alkyl esters were obtained with phenethyl bromide, ethyl chloro- and bromo-acetate. Alkylations with the latter group are thought to involve S_N2 character whereas the former may have some S_N-1 character.

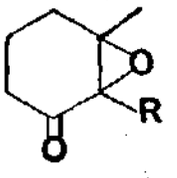
For alkylations, both electronic and steric effects interact in such a way as to stabilise the transition state (3) with higher charge density at C-3. Varying amounts of bis-alkylation products (C-1 and C-3) were also obtained.

In a system like this it is also common to obtain O-alkylations. The quantity of O-alkylation varies with type of alkylating agent, solvent, cation and temperature. Under the right conditions, however, C-3 alkylation is predominant enough to make this procedure a viable synthetic route.

Hydrolysis and decarboxylation[5] give the enone (4, Fig. i) which on epoxidation by the method of Wasson and House[6] gives the epoxide, (1) in appreciably good yield.

This was the method used by Huq[7], Mellor[8], Santos[9] and Scovell[10] in our laboratories for the preparation of epoxides, (5) - (14).

Cyclisation studies were carried out using various Lewis acids in methylene chloride at -20° under dry nitrogen atmosphere.



5 R = $-[CH_2]_2CH=CH_2$

6 R = $-[CH_2]_2CH\overset{t}{=}CHMe$

7 R = $-[CH_2]_2C[Me]=CH_2$

8 R = $-[CH_2]_3CH=CH_2$

9 R = $-CH_2C[Me]=CH_2$

10 R = $-CH_2CH=CH_2$

11 R = $-[CH_2]_2C_6H_4OMe\text{-}p$

12 R = $-[CH_2]_2CH=C[Me]_2$

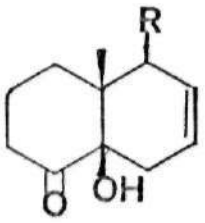
13 R = $-[CH_2]_2C\equiv CH$

14 R = $-[CH_2]_2C\equiv CMe$

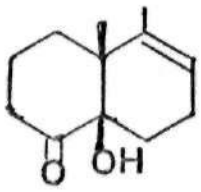
SECTION 2 - PREVIOUS RESULTS.

The cyclisation of epoxides (5 - 11) were initially carried out by Huq[7] and Mellor[8], but later degradative work to confirm the proposed product structures was carried out by Scovell[10], who also investigated the cyclisation of (12) and (14). Epoxide (13) was investigated by Santos[9]. Reaction of epoxide (5) with $TiCl_4$, in CH_2Cl_2 led to the formation of two isolated products - expected cyclisation product, (15) R= H (30%) and (17) (25%). The latter compound was not expected and similar compounds have not been isolated in the other reactions. Normal precautions to exclude moisture were taken but absolute exclusion of moisture cannot be guaranteed.

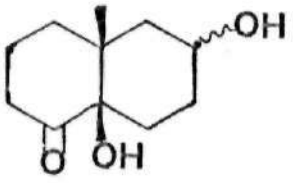
Cyclisation could proceed to give a 6/5 or a 6/6 ring system, but only the latter is observed since a secondary carbonium ion is preferentially formed to the total exclusion of a primary carbonium ion (Fig. ii). A cis ring junction is assigned on the assumption that the cyclisation takes place via a chair-like transition state involving a trans-diaxial epoxide ring opening with concomitant axial C - C bond formation in more or less the same fashion as that of C-10-C-11 bond of lanosterol (Fig. iii). The formation of (15) and (17) could then be derived from the 6/6 bicyclic carbonium by deprotonation and hydration respectively. The third product isolated was the dione (18) (R = $-(CH_2)_2CH = CH_2$) with other



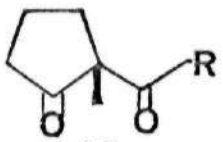
15



16



17



18

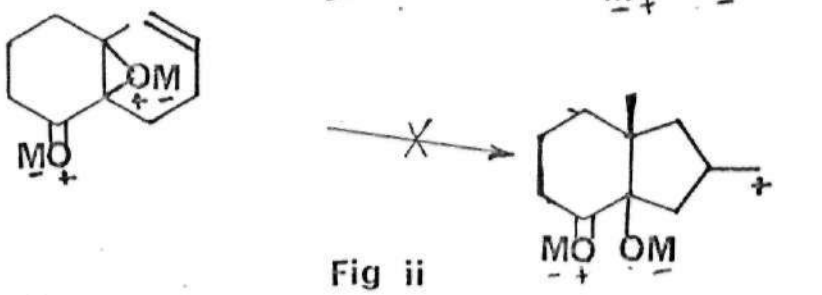


Fig ii

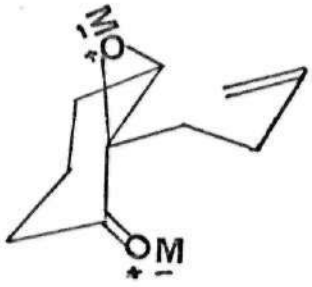
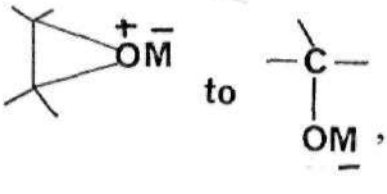


Fig iii

Lewis acids. Similar ring contractions had been reported by Wasson and House.[11] The structure was confirmed by refluxing in ethanolic sodium hydroxide to give the keto-acid, (19). Varying amounts of chlorohydrin (20a or b R = H) were also obtained as a result of HCl addition to the epoxide. The dione, (18) was the major product obtained when weaker Lewis acids were used. For example, with zinc chloride (69%), stannic chloride (59%) and boron trifluoride etherate (46%). Also with any particular Lewis acid, ring contracted product was observed to form preferentially in non-polar solvents.[11] If the gas-phase metal-oxygen bond strength has a direct correlation to the Lewis acidity for oxygen for a series of chlorides, a correlation[12] relating the ratio of cyclisation product to the ring contracted product in various solvents exists. This shows clearly that increased Lewis acid strength favours cyclisation over ring contraction. In the formation of the cyclisation product, a C-O-metal bond was formed whereas in the ring contraction process a $>C=O-$ metal bond would be formed. In the former, the epoxide C - O bond cleavage is assumed to be synchronous with C - C bond formation, whereas in the latter, epoxide C - O bond cleavage is synchronous with $>C=O$ formation and 1,2-migration of an 'acyl residue'. The cyclisation process involves conversion of



, whereas the ring contracted process

$HO_2C[CH_2]_2CH[Me]CO[CH_2]_2CH=CH_2$

19

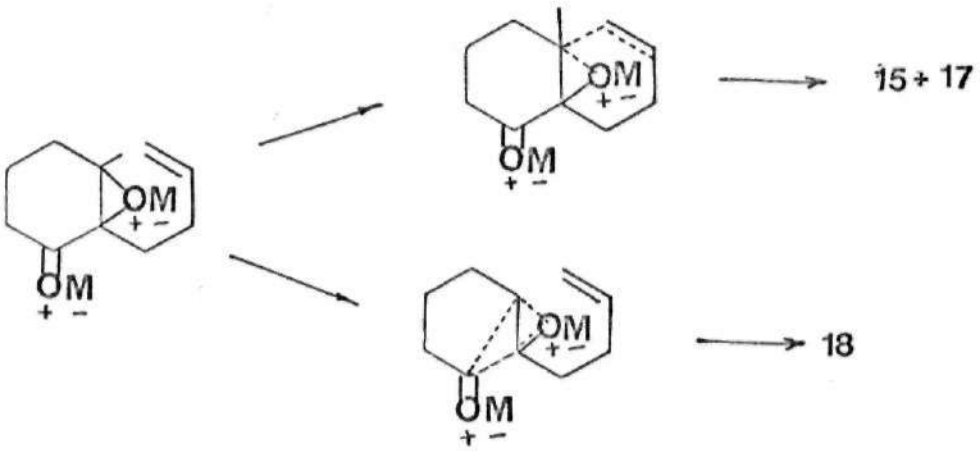
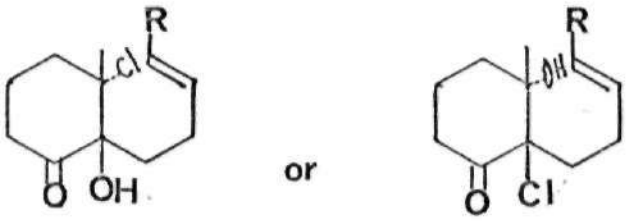
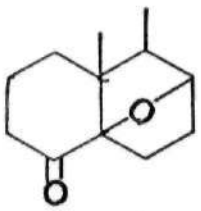


Fig iv

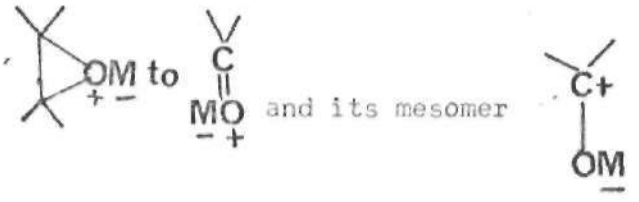


20a 20b



21

involves conversion of



Increasing Lewis acid strength, would increase the metal-oxygen bond strength. This also means that the resonance stabilisation by mesomeric effect would be reduced, thereby favouring the cyclisation process. It is also shown that decreasing solvent polarity favours ring contraction.

Reaction of (6) with $BF_3.Et_2O$, $SnCl_4$ or BCl_3 gave (15, R = Me) and (16) as the main products (>60%). This epoxide possesses a more nucleophilic double bond than epoxide (5) and there is the expected increase in cyclisation. Treatment with stannic chloride gave a mixture a ketols (15) and (16) and some chlorohydrin (20a, b R=Me) in the ratio 3 : 16 : 17 respectively. Treatment with titantium tetrachloride gave a complex mixture containing (15), (16), (18, R = $CH_2{}_2CH^t=CH.CH_3$), in ratio 2 : 6.75 : 1 as determined by g.l.c. Some chlorohydrin and cyclic ether (21) were also isolated.

Treatment with BCl_3 gave the best yield giving (15) and (16) in 1 : 3.37 without a trace of (18).

Cyclisation of (6) could result in the formation of a 6/6 or a 6/5 ring systems both involving the intermediacy of a secondary carbonium ion (Fig. v). No 6/5 bicyclic products were isolated indicating the

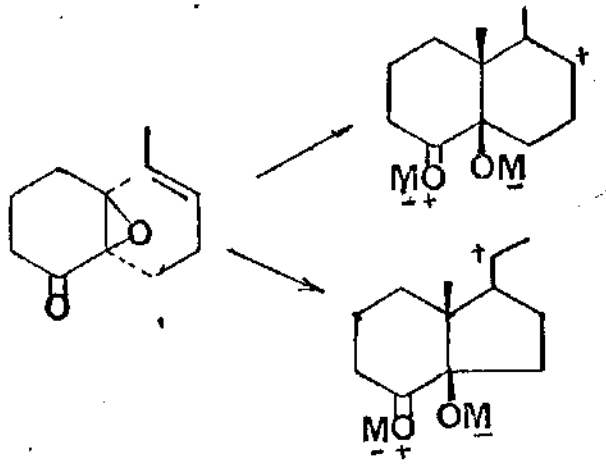
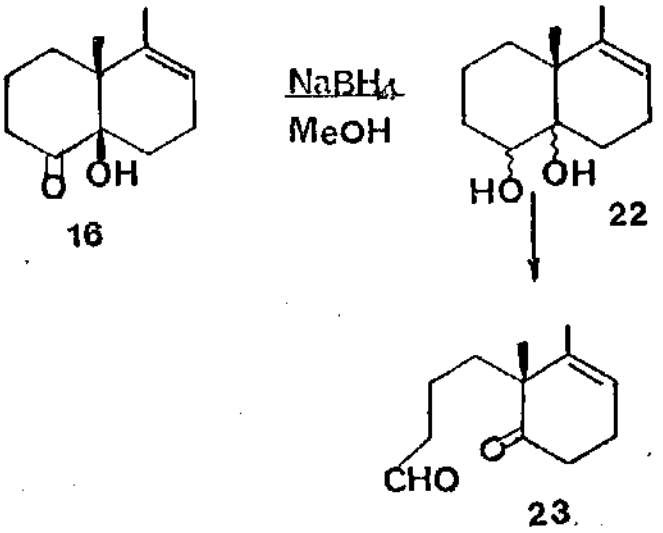


Fig v



preference for formation of six- as opposed to five-membered rings.

The ketol, (16) was reduced by $NaBH_4$ to a mixture of epimeric diols (22) which was subjected to periodate cleavage to give the keto-aldehyde (23). I.r. evidence showed that the double-bond was not conjugated to the carbonyl group of (23), supporting the proposed structure. It is surprising that epoxide (7) gave no well defined products. One would have expected cyclisation to proceed readily involving as it would the intermediacy of a tertiary carbonium ion. Some ring contracted product was obtained. Reaction of epoxides (9) and (10) with the common Lewis acids resulted in the formation of ring contracted material. This is in line with Baldwin's rule[13] that 5-endo -trigonal processes are disfavoured and applies to epoxides (9) and (10). Reaction of (9) with $TiCl_4$ gave the aromatic ether (24) probably by the mechanism shown (Fig. vi).

According to Baldwin's rule, a 7-endo trigonal cyclisation is an allowed process and epoxide (8) would cyclise to give a seven-membered ring. Attempts to generate this ring system failed only the ring contracted product and the corresponding chlorohydrin were obtained.

Epoxide (11) constitutes the first example in this series where an aromatic ring is involved in a cyclisation process.

Reaction of (11) with $BF_3.Et_2O$ or $SnCl_4$ gave (25) and 26) each in 45%. The two ketols were also degraded (cf 16) with spectral evidence

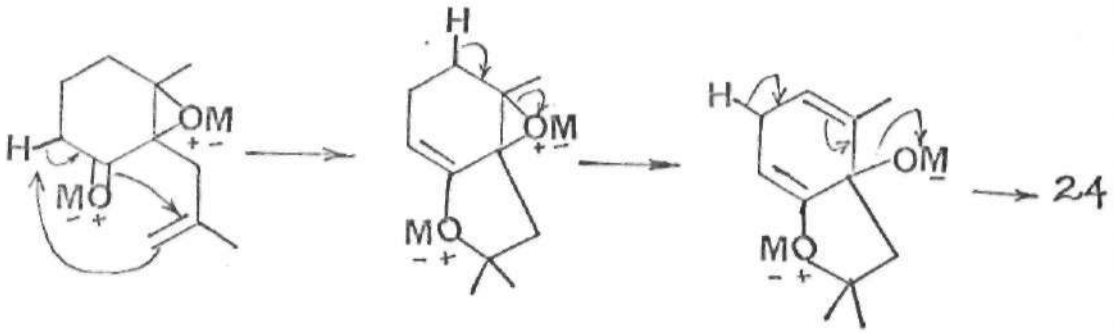
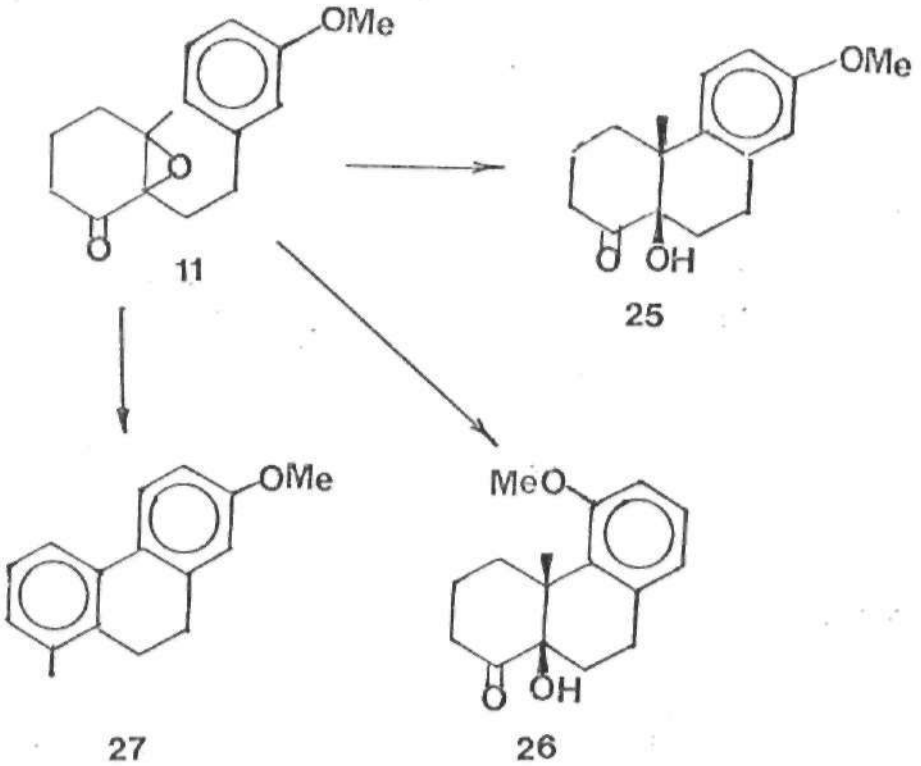


Fig vi



indicating that the carbonyl groups were not conjugated to the aromatic ring. Treatment of (11) with $TiCl_4$ gave (25) and (26) as minor products whereas the major product was the dihydrophenanthrene derivative, (27) obtained in 50% yield, probably formed by the mechanism shown (Fig. vii).

cis-Stereochemistry has been assigned to all the decalones since all were observed to show intramolecular hydrogen bonding which is possible only in the 'non-steroid' cis-decalin conformation. This was further confirmed by studies which indicated that 5α - and 5β -hydroxy-cholestan-4-ones do not exhibit intramolecular hydrogen bonding.

Investigations concerning the cyclisation of epoxide (12) were carried out in an effort to generate a five-membered ring[15] by a favoured 5-exo-Trig process. Cyclisation of epoxide (12) could either form a 6/6 o 6/5 bicyclic system. Formation of the 6/5 bicyclic ring system may be preferred since it involves the intermediacy of a tertiary carbonium instead of a secondary carbonium ion if it formed a 6/6 ring system (Fig. viii).

It was a great surprise, however, that cyclisation had gone via a route that is completely different from that observed in the systems studied so far. Cyclisation had occurred not initiated by the epoxide function, but by interaction with the carbonyl group in a Lewis acid induced 'ene'-type process. Cyclisation of (12) with $SnCl_4$ - CH_2Cl_2 at -20°C gave (30) in 94% yield. The isopropenyl side chain would have

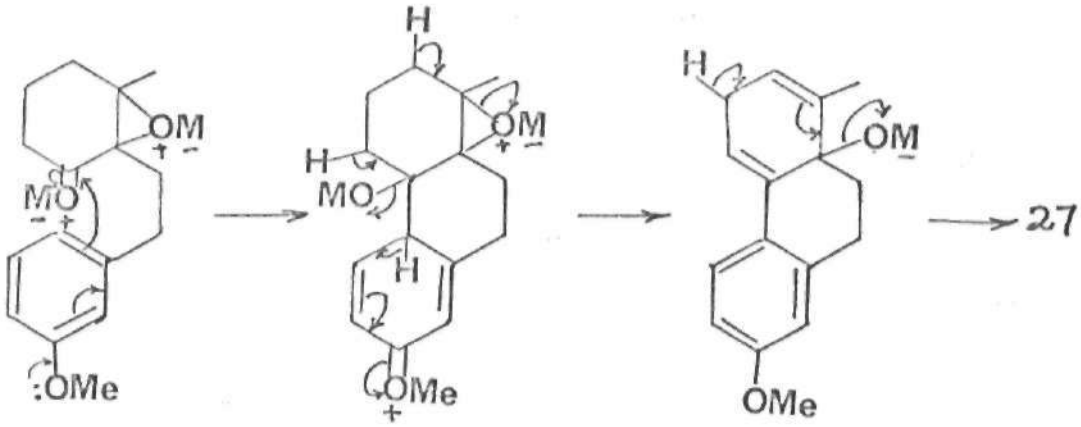


Fig vii

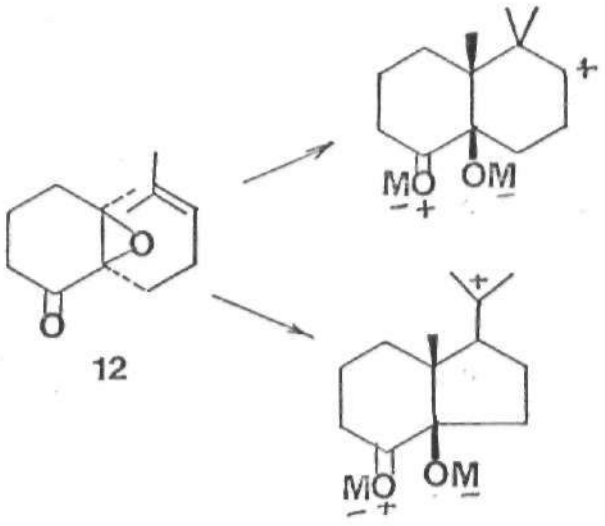


Fig viii

been on the marked carbon atom if cyclisation had occurred 'normally'. Spectroscopic evidence did not distinguish between them and degradative work was carried out to characterise the compound. The ketol was reduced to the diol, followed by periodate cleavage to the corresponding keto-aldehyde which was oxidised to the keto-acid (32) by Jones reagent. Isomerisation of (31) to (32) is carried out by acid or base catalysis. Reduction of (32) with $NaBH_4$ with acid work up gave (33) (Fig. ix). The bicyclo (3.3.1) nonane derivative was shown to be the kinetic product of the reaction and was capable of conversion to (30) under reaction conditions or treatment with base.

The structure of (29) was established by degradation. Reduction with $NaBH_4$ to the diol and periodate cleavage gave (34, X = CHO) and Jones oxidation of this gave (35, X = CO_2H). The keto-acid, (35) was subjected to acid-catalysed Claisen condensation with p-toluene sulphonic acid in benzene to give (36) which was easily hydrolysed to (37) with NaOH. The stereochemistry of (29) was finally established by treatment of the corresponding diol with $Hg(OAc)_2 - H_2O$ and then $NaBH_4$ to give the ether (38), supporting the proposed structure. Why this pathway is preferred to the 'normal' one is not understood. Steric effects due to the ring methyl and the two terminal side methyls could influence course of reaction.

Epoxyacetylenes[15] have also been shown to participate in these

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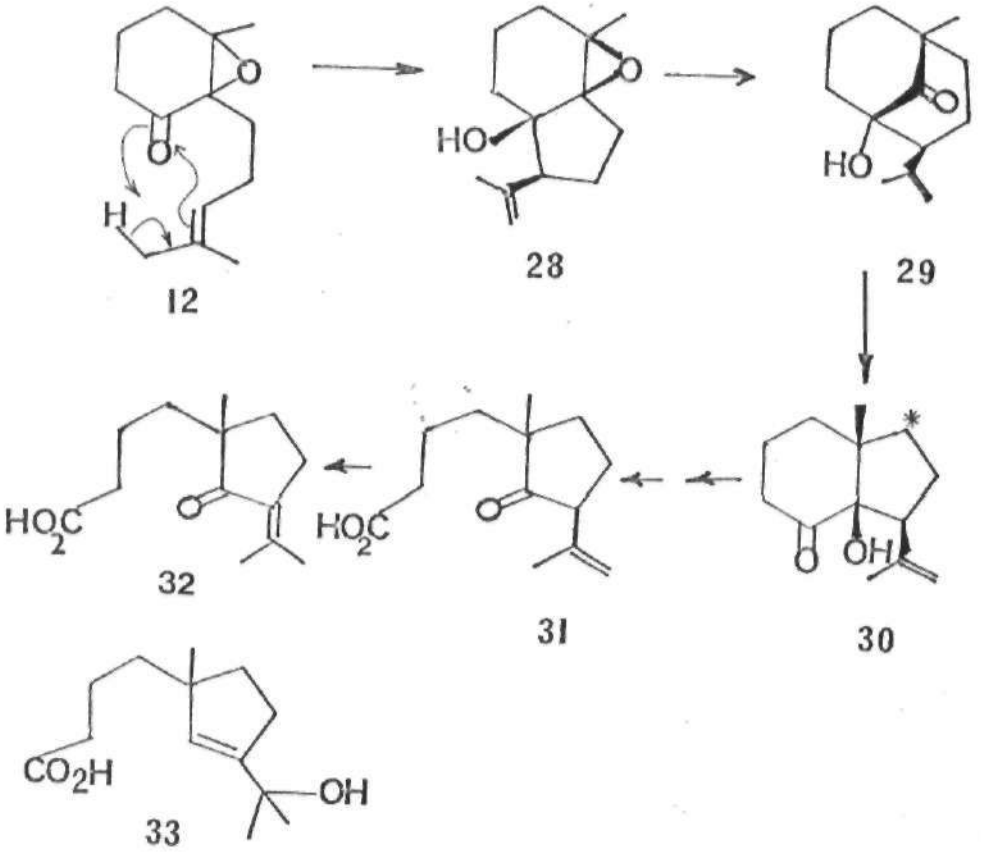
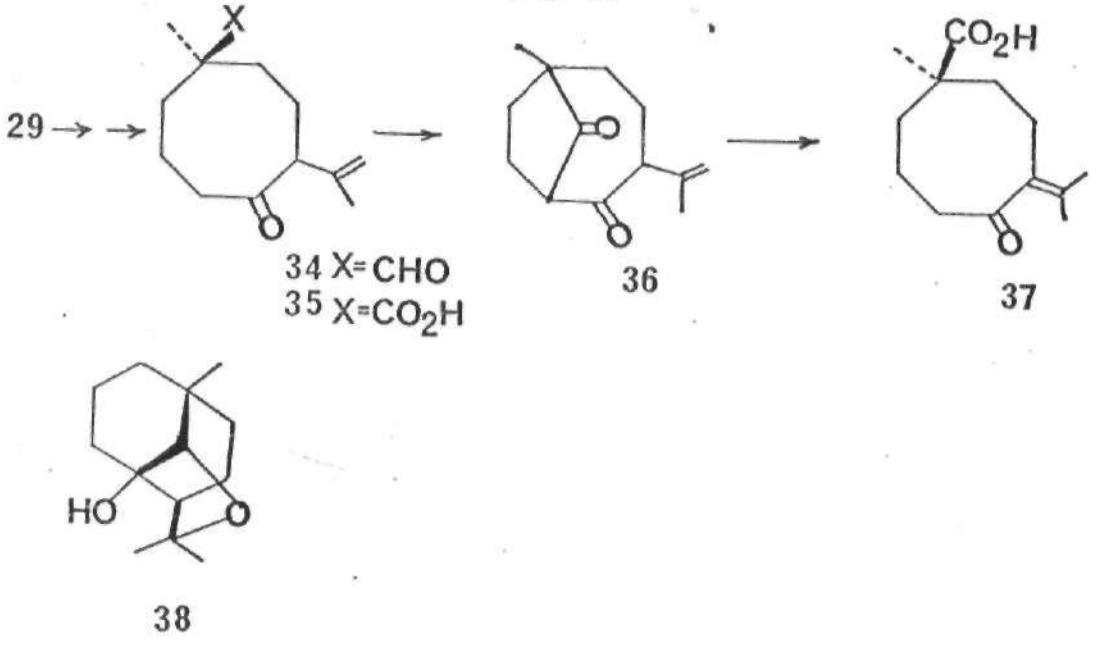

12
28
29
30
31
32
33
HO
H
OH
HO2C
CO2H

Fig ix

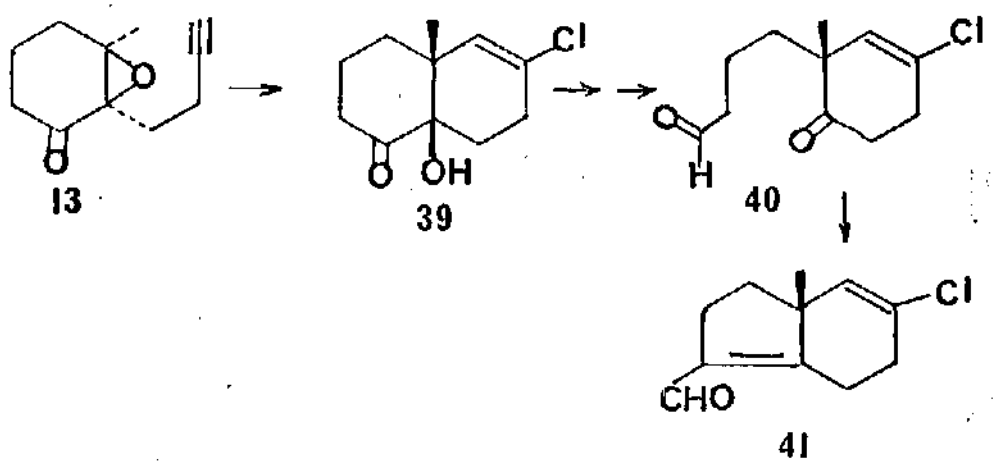

29
X
34 X=CHO
35 X=CO2H
36
37
CO2H
HO
38

cyclisations. Cyclisation of (13) with $BF_3.OEt_2$ or $TiCl_4$ in CH_2Cl_2 gave high yields (> 90%) of (39). This is in keeping with Baldwin's rule that 6-endo-dig is a favoured cyclisation process. The constitution of (39) was established by degradation, first by reduction ($NaBH_4$) to the diol, followed by periodate cleavage to the keto-aldehyde (40) capable of undergoing aldol condensation by treatment with Na_2CO_3 in methanol giving (41).

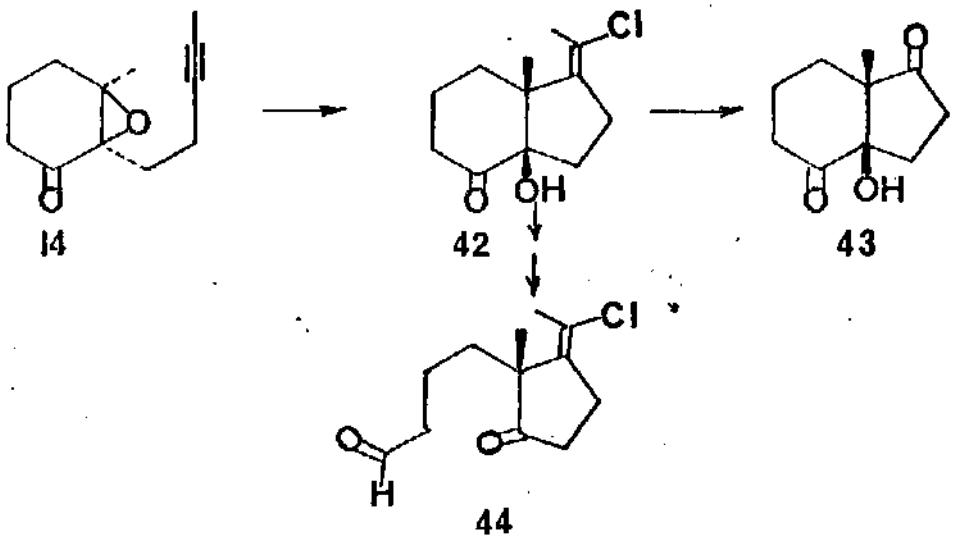
The electronically unbiased acetylene, (14) was also subjected to cyclisation with $SnCl_4$ - CH_2Cl_2 to give the hydrindane derivative (42), whose constitution was also established by degradation. Ozonolysis of (42) gave (43) with characteristic five-membered ring carbonyl absorption. This was further confirmed by reduction of (42) ($NaBH_4$) to the diol and periodate cleavage to the keto-aldehyde (44), showing not only the formation of a five-membered ring but that the side chain is oriented as shown.

When the cyclisation of (14) was carried out with $BF_3.OEt_2$ in CH_2Cl_2, it was shown that the vinyl fluoride (45) was formed as well as the ring-expanded vinyl fluoride (46). Cyclisation of (13) in pentane gave the vinyl fluoride, (39) (F instead of Cl) and some ring contracted product, (18, R = - $(CH_2)_2 C \equiv CH$). The E-stereochemistry is assigned to the double-bond in (42) on the basis of the observed long-range coupling of the methyl with the ring methylene.

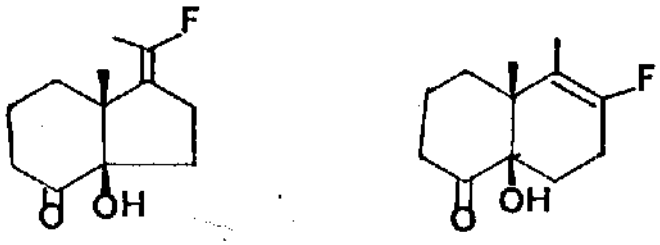
We have already come across the participation of the acetylenic



13 39 40 41



14 42 43 44



45 46

function in polyene cyclisations in Chapter I. This observation also lends support to the existing results that terminal acetylenes lead to six-membered ring formation, whereas the methylacetylenes lead mainly to formation of five-membered rings. The vinyl cation intermediate formed in the latter had been trapped by various nucleophiles (Chapter I).

The preference is for a 6-Endo-Dig cyclisation in (13) as opposed to a 5-Exo-Dig cyclisation in (14). The difference between these acetylenes and their corresponding olefins is rationalised purely on vector analysis. The approach vector for the acetylenic bond is 120^{o} whereas it is 109^{o} for the olefins.[16]

SECTION 3 - WORK OF THE AUTHOR.

The report in this section constitutes the work carried out by the author.

I. Synthesis of 2-Alkenyl-3-methylcyclohex-2-en-1-ones.

The classical method for the synthesis of these compounds *via* the Hagemann's ester route has been mentioned. The non-regioselectivity of the alkylation was also mentioned. This perhaps, is not the major problem encountered in this route to the cyclohexenone derivatives. A very serious problem which involves the tendency of the alkylating agents, especially the homoallylics, to eliminate HX (X = halogen, OTs) under the basic conditions of the reaction constitute the major fault of this method. The problem is serious enough to demand alternative methods of synthesising these compounds.

Modified procedure using benzene / dimethyl formamide / sodium hydride[17] or toluene or 1,2-dimethoxyethane / sodium hydride[5], were still found unsatisfactory.

An alternative route *via* 1,3-cyclohexanedione, (47), is depicted in Fig. x. Alkylation with reactive halides, for example, methyl iodide[18], allylic[19,20] and benzylic-[19] halides proceed relatively smoothly, however, with less reactive halides, for example, 1-bromobutane[20], 4-iodobutene[21],

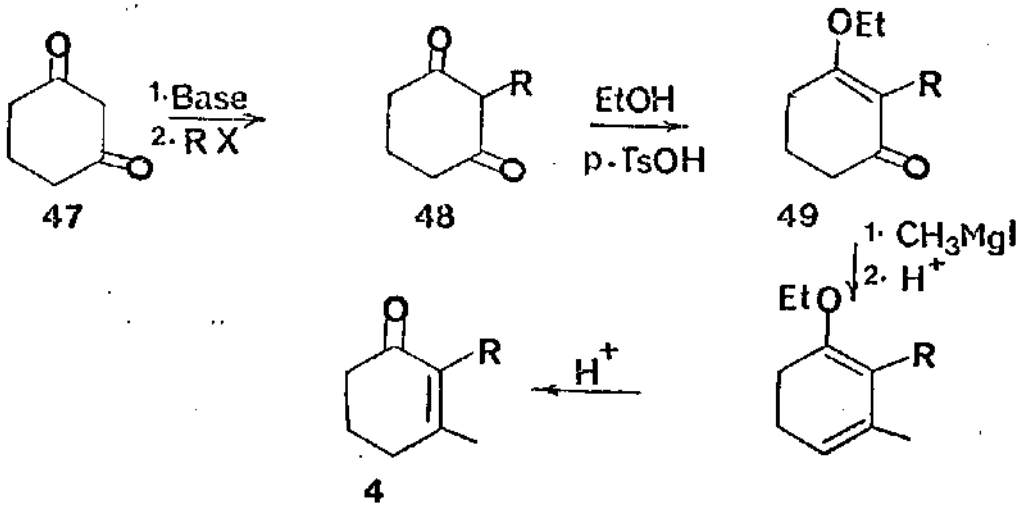

1. Base
2. R X
EtOH
p-TsOH
OEt
R
1. CH_3MgI
2. H^+
H^+
47
48
49
4

Fig x

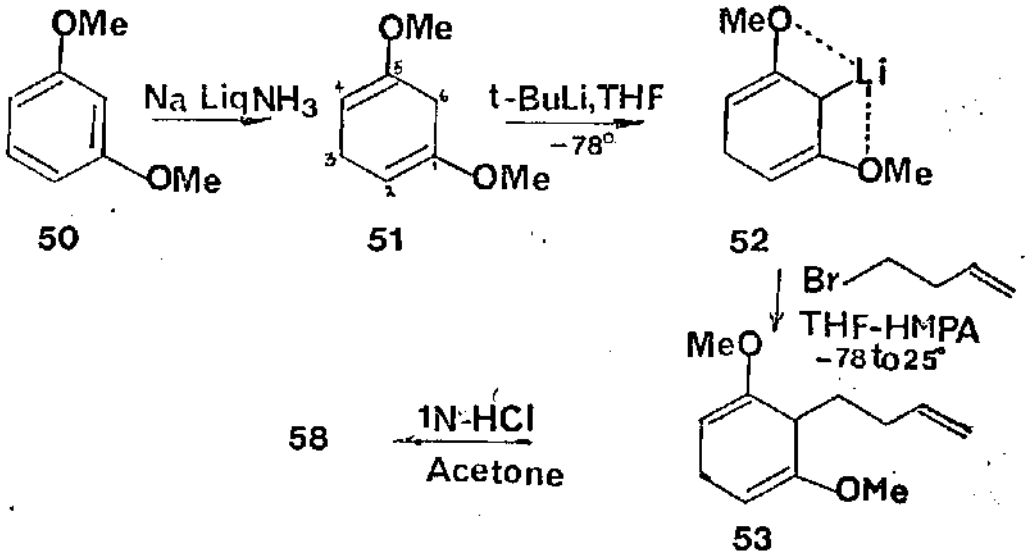

OMe
Na LiqNH_3
t-BuLi,THF
−78°
MeO
Li
Br
THF-HMPA
−78 to 25°
1N-HCl
Acetone
58
50
51
52
53

Fig xi

the corresponding alkylated products were obtained in a disappointingly low yield. Enol ether formation[22] of (48) gives (49) which, when reacted with methyl magnesium iodide, followed by treatment of the resulting product with acid gives (4). Since the alkylation only proceeded well with reactive halides, the use of 1,3-cyclohexanedione as a parent compound was abandoned.

Recently this route was modified by Piers and Grierson[23] who studied the alkylation of 1,5-dimethoxy-1,4-cyclohexadiene, (51). Acid hydrolysis of the resulting alkylation product (53) gave (48) (Fig. xi). The yields of alkylation products were extremely high and cover a broad range of halides - reactive and less reactive, for example, with iodobutane (48) was obtained in 96% yield, with homoallylic halides (93 - 95%) and iodomethane (65%).

From this point on, the series of reactions depicted in Fig. x was carried out by the author. Before that is described, it is important that the chemistry involved in the metalation reaction be discussed briefly.

The allylic protons at C - 6 (51, Fig. xi) are reckoned more acidic than those at C - 3 on the basis of competing inductive and resonance effects. Lithiation at C - 6 is also expected to be facilitated as a result of the complexation or association of the two oxygen atoms with the lithium atom. The lithiated species prior to addition of the alkylating agent are then represented as (52). Hexamethylphosphoramide (HMPA)

is added to co-ordinate the lithium cation, thus rendering the carbanion at C-6 'naked' for electrophilic attack by the alkylating agent. There is precedence for such site-selective heteroatom-directed metalation reaction.[24] The procedure shown in Fig. xi was followed. m-Dimethoxybenzene (50) was converted to (51) by reaction with sodium in liquid ammonia (Birch Reduction) and obtained in 90.5% yield as colourless oil (b.p. 42-5°/0.1 mm, cf 95° at 18 mm[25]). The n.m.r. spectrum showed the presence of two vinylic protons (τ 5.38, m); the two -OMe (τ 6.69, s) and two methylene protons at C-3 and C-6 respectively (τ 7.20, m), and the i.r. spectrum agrees reasonably well with literature.[23]

Alkylation was carried out using 4-bromo-1-butene. Piers and Grierson[23] used t-BuLi but we found that n-BuLi was also suitable for this reaction which proceeded almost quantitatively, (77% after distillation b.p. 65-70°/0.1 mm) and obtained as a colourless oil, (53, R = $CH_2.CH_2.CH = CH_2$).

The n.m.r. spectrum shows one vinylic proton (τ 3.95-4.55, m, $-\underline{CH} = CH_2$), τ 4.85-5.15 (m, 2H, $-CH = \underline{CH_2}$), τ 5.29 (t, 2H, C-1 and C-5 protons), τ 6.49 (s, 6H, OMe), τ 7.19 (m, 3H, C-3 and C-6 protons), τ 8.18 (m, 4H, $\underline{CH_2}.\underline{CH_2}CH = CH_2$).[23]

The alkylation product, (53, R = $-CH_2.CH_2CH = CH_2$) was subjected to hydrolysis using 1N-hydrochloric acid in acetone, both of which were initially purged with nitrogen to expel oxygen. After stirring for 1 h

at room temperature work up gave (48, R = $CH_2.CH_2CH = CH_2$), as a colourless solid after recrystallisation from petroleum ether b.p. 80 - 100°C / benzene, m.p. 94 - 6°. The n.m.r. spectrum shows one vinylic proton, (τ3.76 - 4.50, m), τ4.82 - 5.22 (m, unresolved, -CH = $\underline{CH_2}$), τ7.3 - 7.78 (m, 6H), τ7.78 - 8.22 (m, 4H).

Enol ether formation of (48) was carried out according to the method of Gannon and House[22] to give the ketoenol ether (49, R = $CH_2.CH_2CH = CH_2$), (τ3.80 - 4.01, m, -$\underline{CH}$ = CH_2); τ4.81 - 5.28 (m, 2H, -CH = $\underline{CH_2}$), τ5.95 (q, 2H, -O$\underline{CH_2}$-), τ7.30 - 8.2 (m, 10H), τ8.68 (t, 3H, -$\underline{CH_3}$).

The ketoenol, (49, R = $CH_2CH_2CH = CH_2$) was then reacted with methyl-magnesium iodide which reacted smoothly to the expected carbinol which was not isolated. Acid work up gave a product of dehydration (Fig. x) which upon further treatment with acid gave (4, R = $CH_2CH_2CH = CH_2$) in 81% yield, (τ3.80 - 4.56, m, $\underline{CH}$ = CH_2); τ4.80 - 5.28 (m, 2H, -CH = $\underline{CH_2}$), τ7.42 - 8.40 'm, 10H) and τ8.09 (s, 3H, -CH_3) . These data agree very well with that for the same compound made *via* the Hagemann's ester route.[7]

The yields obtained in each step are excellent and this route constitutes a welcome alternative to the Hagemann's ester method. On the basis of this success, it was expected that the number of reactions could be reduced by starting with 1-methoxy-5-methylcyclohexa-1,4-diene made from m-cresol methyl ether by Birch reduction, since it has an existing methyl group in the right position (Fig. xii). Unfortunately the metala-

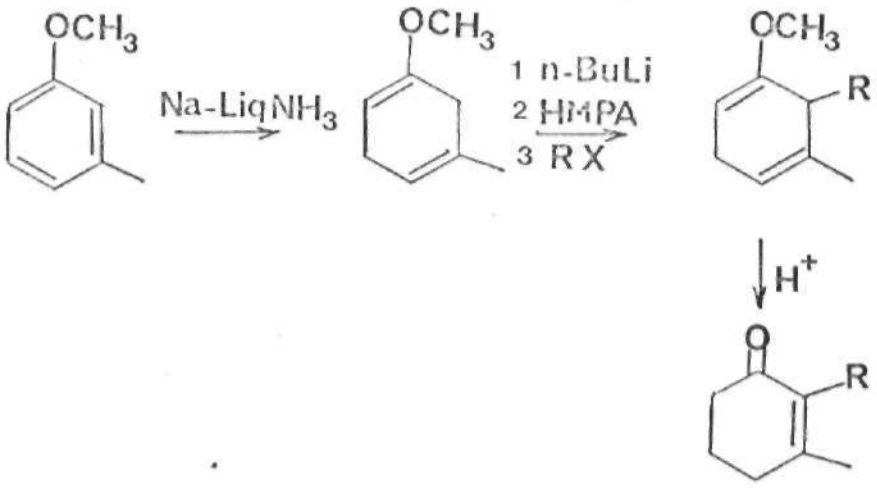


Fig xii

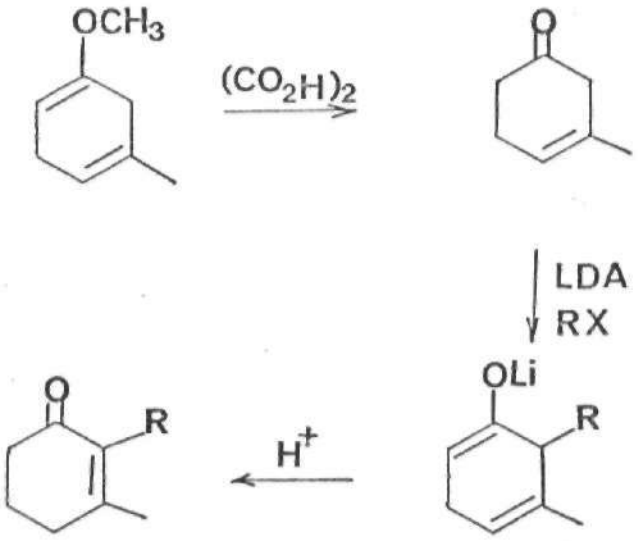
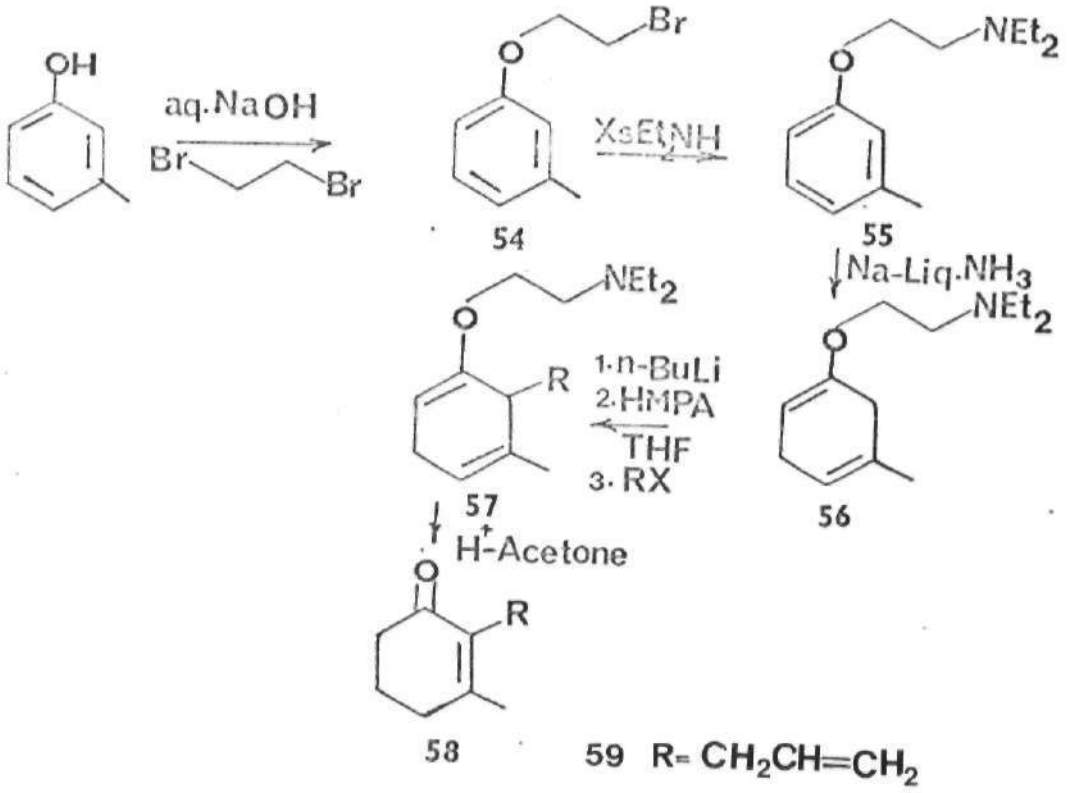


Fig xiii

tion did not go as well as expected. There was virtually no reaction observed and a lot of the dihydro compound had oxidised to m-cresol methyl ether. This route was then abandoned.

Closely related to this route is the alkylation of the kinetic enolate[26] obtained from 3-methyl-cyclohex-3-en-1-one by reaction with LDA, (n-BuLi / i-Pr_2NH). The 3-methylcyclohex-3-en-1-one can be made from 1-methoxy-5-methylcyclohexa-1,4-diene by oxalic acid hydrolysis without isomerisation to the conjugated ketone (Fig. xiii). Only reactive halides, allyl and prop-2-ynyl reacted as a result of which this route was abandoned. We then proceeded to study the metalation of the diethylamino ether, (56), reasoning that the diethylamino group acting as a chelating group might increase the stability of the ion pair.

The ether (56) was made by Birch reduction of (55) and was found to be remarkably stable to oxidation or isomerisation. The aryloxyethyldiethylamine (55) was made from the corresponding aryloxyethyl bromide (54) which in turn was made by the action of dibromoethane on the sodium salt of m-cresol (68.3% yield after distillation, b.p. 80° / 0.1 mm). The n.m.r. spectrum shows the four aromatic protons (τ3.15, m); $-CH_2Br$ protons, (τ5.85, t); $-OCH_2$ (τ6.5, t) and $-CH_3$ (τ7.70, s). This compound is then refluxed with at least, three-mole equivalents of diethylamine giving (55); (τ3.15, m, 4H); $-OCH_2$ (τ6.0, t) $-NCH_2-$ (τ7.0 - 7.6, m, 6H), $-CH_3$ on aromatic ring (τ7.72, s) and $-CH_2\underline{CH_3}$ (τ8.98, t) .



59 R= $CH_2CH{=}CH_2$

60 R = $-[CH_2]_2CH{=}CH[CH_2]_2H_4C_6OCH_3$-p

61 R = $-[CH_2]_2CH{=}CH[CH_2]_2H_4C_6OCH_3$-m

62 R = $-[CH_2]_2CH{=}C[Cl]CH_3$

63 R= $-[CH_2]_2CH{=}CH[CH_2]_2C{\equiv}CH$

Fig xiv

Sodium in liquid ammonia reduction proceeds smoothly giving (56) which shows one vinylic (C - 4) proton adjacent to the C - O ether linkage (τ 4.68, bs), a second vinyl proton (C - 2) (τ 5.43, bs) $-OCH_2-$ (τ 6.26, t), unresolved C - 3 and C - 6 (cf 51) methylenes and $-CH_2N(CH_2-)_2$ (τ 7.38, m), ring $-CH_3$ (τ 8.36, bs) unresolved coupling with adjacent vinyl proton, and the diethyl - CH_3 groups (τ 8.98, t). Metalation of (56), with n-BuLi - HMPA - THF (1 h) at -78°C followed by addition of halide resulted in quantitative alkylation taking place (57, R = $-(CH_2)_2 CH = CH_2$). This was immediately subjected to hydrolysis (2N - HCl / Acetone) under a nitrogen atmosphere giving (58, R = $-(CH_2)_2 CH = CH_2$) in 86% yield. Spectroscopic data are identical with the same compound made via the Hagemann's ester route[7] and the 1,3-cyclohexanedione route (Figs. x and xi).

These reactions were then repeated using a reactive halide, allyl chloride, giving (59) in 88% yield. A two-mole ratio of halide was required since quaternisation of the diethylamino group also competes with the alkylation process. (59) shows the characteristic pattern for terminal methylenes in the n.m.r. spectrum, one vinylic proton, (τ 4.0 - 4.70, m) $= CH_2$ (τ 4.7 - 5.3, m); unresolved ring and side chain $- CH_2 -$ (τ 7.4 - 7.9, 8H) and methyl group (τ 8.05, s).

Methyl iodide and n-butyl iodide on alkylation gave the corresponding cyclohexenone derivatives in 75 and 65% yields respectively. In the case of the former, a two-mole ratio of the halide was used since the initial

reaction seems to be quaternisation of the diethylamino group (cf allyl chloride). This route has proved to be a very good alternative to the Hagemann's ester route or any route so far reported in the literature, to the alkenylcyclohexenones. The problem of non-regioselectivity encountered in the former route is unknown here. Some alkylated derivatives of (57) do aromatise but are easily removed by acid wash to give the required products as essentially pure compounds (Fig. xiv).

The reaction of the lithiated species with Michael acceptors has not been fully investigated.

There now follows a description of the synthesis of certain halides to give the side chains required.

II. A. trans-1-Bromo-6-p-methoxyphenylhex-3-ene (75) was made by Johnson's modification[29] of Julia's method[30] for the synthesis of homoallyl halides, as depicted in Fig. xv. Carbethoxylation of methylcyclopropyl ketone, (64) with diethylcarbonate gives the ketoester (65) in 56.5% yield after distillation (b.p. $68^{\circ}/0.1$ mm).

The best conditions for the alkylation of this ketoester (65) was using NaOEt/THF at -30° to -40° with high dilution. Alkylation with p-methoxybenzyl chloride, gives two products: the desired monoalkylation product (66, R = $-CH_2C_6H_4.OMe.p$) and the dialkylation one. The latter was separated from the former by treatment with aqueous alcoholic potash

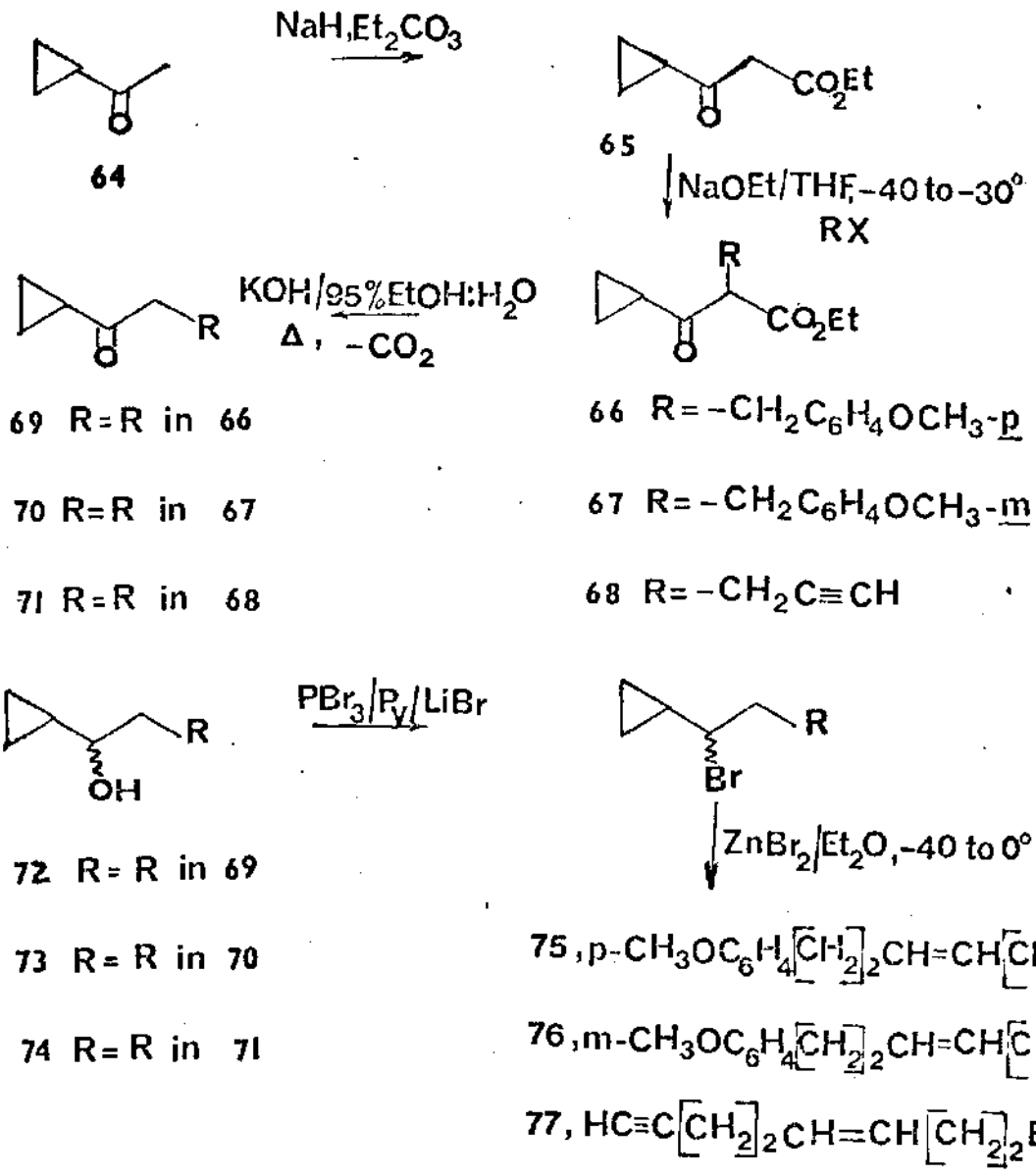

NaH,Et2CO3
64
65
CO2Et
NaOEt/THF,-40 to -30°
RX
R
CO2Et
KOH/95%EtOH:H2O
Δ, -CO2
69 R=R in 66
70 R=R in 67
71 R=R in 68
66 R=-CH2C6H4OCH3-p
67 R=-CH2C6H4OCH3-m
68 R=-CH2C≡CH
PBr3/Py/LiBr
OH
Br
ZnBr2/Et2O,-40 to 0°
72 R=R in 69
73 R=R in 70
74 R=R in 71
75, p-CH3OC6H4[CH2]2CH=CH[CH2]2Br
76, m-CH3OC6H4[CH2]2CH=CH[CH2]2Br
77, HC≡C[CH2]2CH=CH[CH2]2Br

Fig xv

(KOH / 95% EtOH : H_2O (1 : 1)) when the dialkylated compound separates as colourless crystals. The desired monoalkylation product was obtained in 75.8% yield as a yellow oil. It was subjected to hydrolysis using aqueous alcoholic potash to the corresponding ketoacid which was decarboxylated by heating on a steam bath to the ketone (69) (R = $-CH_2.C_6H_4OMe\underline{p}$). The n.m.r. spectrum shows the aromatic protons at (τ 3.10, dq, 4H); methoxy protons (τ 6.30, s, 3H), $-\underline{CH_2}-\underline{CH_2}-$ (τ 7.20, s, 4H); - C - H on the tertiary carbon atom of the cyclopropyl group (τ 8.20, m, 1H) and $-\underline{CH_2}-\underline{CH_2}-$ of the cyclopropyl group (τ 9.15, m, 4H). This ketone was then reduced with sodium borohydride in methanol to the carbinol (72)' in 89.5% yield.

The carbinol was then reacted with phosphorus tribromide in collidine containing lithium bromide (anhydrous) to give the corresponding carbinyl bromide which was rearranged with anhydrous zinc bromide in anhydrous ether at -40° to 0° to give the title compound (75) in 73.8% yield after distillation (bulb to bulb, 100° / 0.1 mm).

The n.m.r. spectrum shows the aromatic protons at (τ 3.10, dq, 4H), the olefinic protons (τ 4.55, m, 2H), methoxy protons (τ 6.30, s, 3H); $-\underline{CH_2}Br$ (τ 6.70, t, 2H) and $-CH_2-$ protons (τ 7.50, m, 6H).

2(Δ^3-6-p-Methoxyphenylhexenyl-) 3-methyl-2-cyclohexenone (60) was made *via* the route depicted in Fig. xiv. Alkylation of (56) with (75) gave (57, R = $-(CH_2)_2CH=CH(CH_2)_2C_6H_4.OMe\text{-}p$) quantitatively. No

trace of halide was detected from the n.m.r. spectrum of the crude product, which shows the aromatic protons at (τ 3.12, dq, 4H); CH = CH of the side chain and the vinylic proton in the ring adjacent to the ether link (τ 4.62, m, 3H), the other vinylic proton on carbon atom next to the methyl group (τ 5.38, m, 1H), $-OCH_3$ and $-OCH_2-$ (τ 6.30, 5H as singlet ($-OCH_3$) superimposed on triplet ($-OCH_2-$); $-CH_2-$ + - C - H , (τ 7.44, m, 17H), -Me (τ 8.35, bs, unresolved coupling with adjacent vinyl proton), two - NCH_2CH_3 groups (τ 9.0, t, 6H).

Hydrolysis of this product with dilute acid in acetone afforded the title compound in 89% yield as a yellow oil.

The n.m.r. spectrum shows the aromatic protons at (τ 3.05, dq, 4H), olefinic protons (τ 4.58, m, 2H); $-OCH_3$ (τ 6.25, s, 3H); $-CH_2-$ protons (τ 7.25 - 8.1, m, 14H) and $-CH_3$ (τ 8.20, s, 3H).

Epoxidation was carried out by the method of Wasson and House[6] to give the epoxyketone (78, R = $-(CH_2)_2CH = CH(CH_2)_2C_6H_4.OMe-p$).

(τ 3.10, dq, 4H), olefinic protons (τ 4.60, m, 2H), $-OCH_3$ (τ 6.34, s, 3H) and $-CH_3$ (τ 8.60, s, 3H) .

Treatment of epoxide (78) with BCl_3 in CH_2Cl_2 at -78° for 2 h gave a mixture of five products. The first fraction comprised mainly the product (85, R = $-(CH_2)_2CH = CH(CH_2)_2C_6H_4OMe\ p$, 18.4%) shown by its characteristic absorption at 1745 cm^{-1}. The second fraction was mainly the chlorohydrin (86, 5.4%). The third and major fraction (51%)

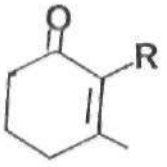
however, had no carbonyl absorption in the i.r. spectrum but showed an -OH absorption at 3600 cm^{-1}. The n.m.r. spectrum showed an angular methyl group at τ 9.08 and the aromatic ring was not further substituted. A similar result was obtained in the cyclisation of epoxide (101). The tentative structure (84) is presently assumed for the third product mentioned above pending further experimental evidence. Mass spectrum and elemental analysis indicated incorporation of a chlorine atom in this compound.

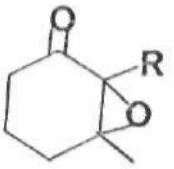
The fourth fraction also showed a disubstituted aromatic ring with an angular methyl group at τ9.26. A multiplet at τ5.15 - 5.48 ($W_{\frac{1}{2}}$ = 22.2 Hz) indicates the presence of a $\underset{\underset{Cl}{|}}{CH}$, the chlorine atom being in an equatorial position. The i.r. spectrum showed a weak -OH absorption at 3590 cm^{-1} and a hydrogen bonded -OH at 3560 cm^{-1}. The structure (83) agrees with observed data.

Finally, the fifth product obtained is the expected tetracylic compound (82) as shown by the substitution on the aromatic ring. H_A (τ 3.04, d, 1H, J_{AB} = 8.5 Hz); H_C (τ 3.18, d, 1H, J_{BC} = 2.7 Hz); H_B (τ 3.34, dd, 1H, J_{BA} = 8.5 Hz, J_{BC} = 2.7 Hz); $-OCH_3$ (τ 6.23, s, 3H) and angular methyl group at τ8.98.

Epoxide (78) probably cyclised initially to give a bicyclic cation which then gave rise to the observed cyclisation products (82 - 84). The mode of cyclisation *via* the *meta* or *para* position of the *para* di-

substituted aromatic ring is discussed in detail in subsection III (Fig. xxiv). The bicyclic compound (83) was formed by a chloride ion trapping the proposed bicyclic cation (Fig. xvii). The argument leading to structure (84) is presented in subsection II (E).





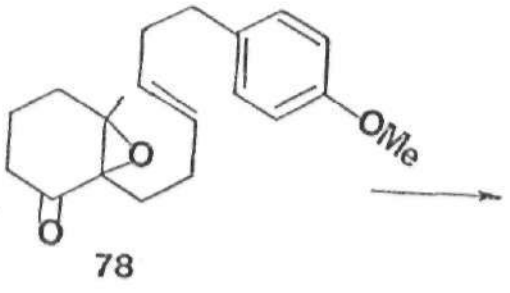
78, R = R in 60

79, R = R in 61

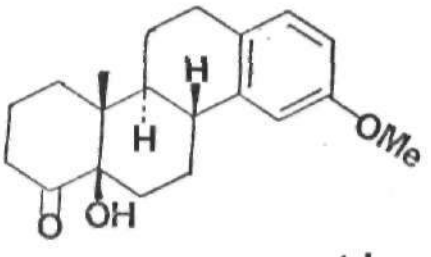
80, R = R in 62

81, R = R in 63

Fig xvi

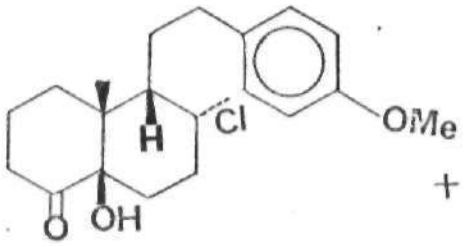


78



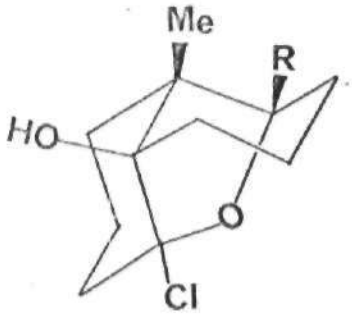
82

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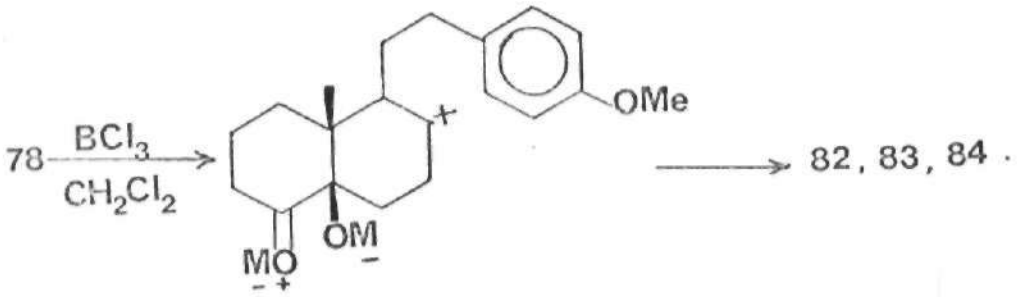


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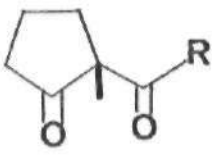
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84 R = $[CH_2]_2C_6H_4OMe$-p

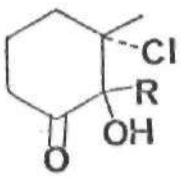


→ 82, 83, 84.



85 R=R in 60

87 R=R in 61



86 R = R in 60

88 R = R in 61

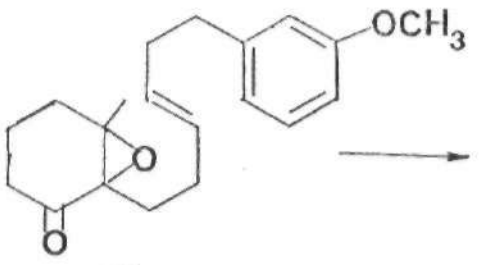
Fig xvii

B. trans-1-Bromo-6-m-methoxyphenylhex-3-ene (76) was made by the same route as its analogue (75) as depicted in Fig. xv, alkylating (65) with m-methoxybenzyl bromide (lachrymator!). Both mono-(67) and di-alkylation products were obtained. The former was subjected to hydrolysis and decarboxylation to give (70) in 74.4% yield.

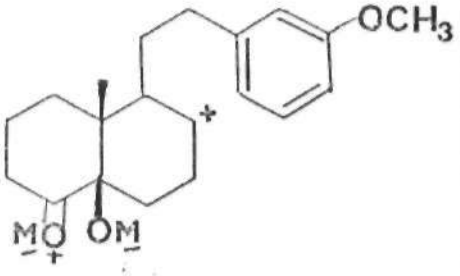
Sodium borohydride reduction of (70) gives the carbinol (73) in 93.6% yield. The title compound was made by conversion of the carbinol (70) to the corresponding carbinyl bromide and rearrangement with anhydrous zinc bromide. The n.m.r. spectrum shows the aromatic protons at (τ 2.85, m, 1H and τ 3.25, m, 3H), olefinic protons (τ 4.52, m, 2H), $-OCH_3$ (τ 6.25, s, 3H), $-\underline{CH_2}Br$ (τ 6.18, t, 2H) and $-CH_2-$ (τ 7.50, 6H).

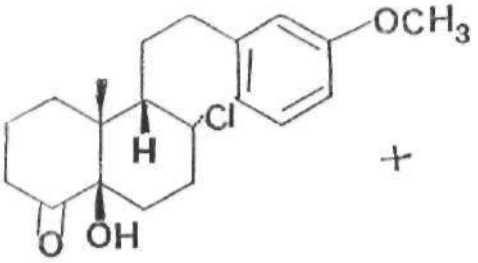
2(Δ^3-6-m-Methoxyphenylhexenyl-)3-methyl-2-cyclohexenone (61) was made by the same route as for its isomer (60) in 85% yield. The n.m.r. spectrum shows the aromatic protons (τ 3.10, m, 4H), olefinic protons (τ 4.55, m, 2H), $-OCH_3$ (τ 6.25, s, 3H), $-CH_2-$ (τ 7.10 - 8.0, m, 14H) and $-CH_3$ (τ 8.20, s, 3H).

Epoxidation[6] was carried out as before, giving (79) in 74.4% yield. The n.m.r. spectrum shows the aromatic protons (τ 3.15, m, 4H), olefinic protons (τ 4.55, m, 2H), $-OCH_3$ (τ 6.20, s, 3H), $-CH_2-$ (τ 7.10 - 8.40, m 14H) and $-CH_3$ (τ 8.60, s, 3H). The cyclisation was carried out using all the common Lewis acids (e.g. $SnCl_4$, $BF_3.OEt_2$, BCl_3) in methylene chloride at -20° and -78°C. The best condition was found to be BCl_3/



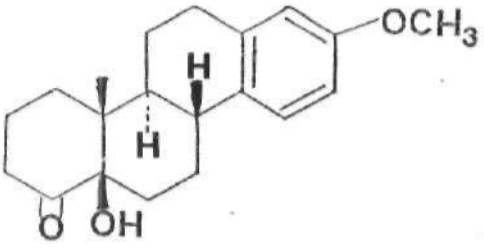
79



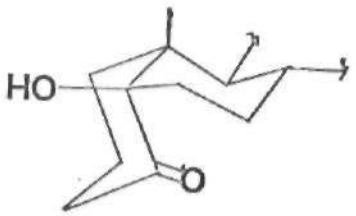


90

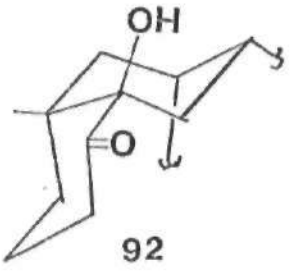
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89



91



92

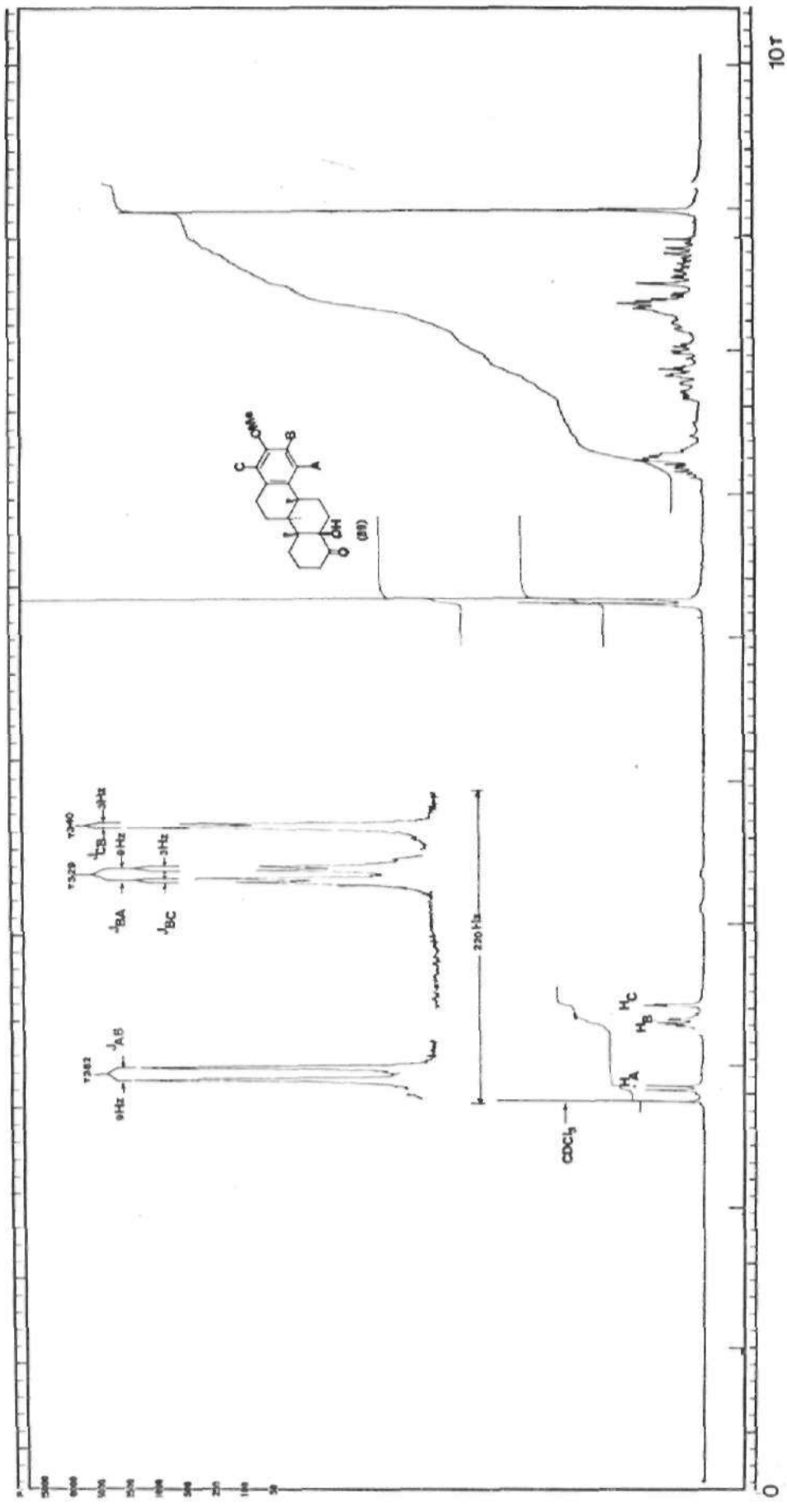
CH_2Cl_2 at -78°C. Four products were obtained by combined column and thin layer chromatography.

The first fraction was obtained as colourless crystals on standing. The n.m.r. spectrum shows only three aromatic protons, H_A (τ 2.82, d, 1H, J_{AB} = 9 Hz); H_B (τ 3.29, dd, 1H, J_{BA} = 9 Hz, J_{BC} = 3 Hz), H_C(τ 3.40, d, 1H, J_B = 3 Hz), - O<u>H</u> (τ6.19, s, 1H), - O<u>CH</u>$_3$ (τ 6.23, s, 3H), - CH_2 - (τ7.1 - 8.8, m, 16H) and -CH_3 (τ8.93, s, 3H). The i.r. spectrum shows a single band for the - OH stretching frequency (3590 cm^{-1}) and no sign of intramolecular hydrogen bonding and the carbonyl group (1710 cm^{-1}). These data indicate the tetracyclic structure (89). (Spectrum i)

The second fraction crystallised on standing and was the major component (57%) of the products. The n.m.r. spectrum showed an disubstituted aromatic ring (τ 2.80, m, 1H,τ3.28, m, 3H), C(Cl) - <u>H</u> (τ5.82, m, 1H, $W_{\frac{1}{2}}$ 22.5 Hz), - OCH_3 (τ6.22, s, 3H), - CH_2-CH(τ 7.10 - 8.80, m, 16H) and the angular - CH_3 (τ9.03, s, 3H). ν_{max} (cm^{-1}), 3590 (w) and 3558 (v.b.) indicated - OH and hydrogen bonded - OH and 1715, the carbonyl absorption. These data agree with the structure (90) suggested for this compound.

The other two products proved to be the corresponding chlorohydrin (88) isolated (19.9%) and the ring contracted substance (87) (13.9%).

The 'steroid' conformation has been assigned to the tetracyclic compound (89) since no intramolecular hydrogen bonding was observed which



Spectrum i [300MHz]

is only possible in this cis conformation as shown in the part structure (91). The bicyclic compound (90) which exhibits intramolecular hydrogen bonding must have the 'non-steroid' cis-decalin conformation (92). This compound was shown not to be an intermediate in the formation of (89) by subjecting it to the reaction conditions when none of (89) was obtained.

Mechanistically, the tetracyclic compound (89) may be formed by a concerted or a stepwise process whereas the bicyclic product (90) probably involves formation of a bicyclic cation which is trapped by a chloride ion either from the Lewis acid or the solvent.

Several attempts were made at improving the yield of the fully cyclised product (89) without much success. For example using BCl_3/ SO_2 at -70° only a small amount of the tetracycle ($\sim 5\%$) was obtained and as the reaction proceeds there was observed a gradual formation of an intractable solid that would not dissolve in common organic solvents.

C. trans-1-Bromo-3-en-oct-7-yne (77) was made by the route shown in Fig. xv. Alkylation of the keto-ester (65) with propargyl bromide gave mono- (68) and di-alkylation products, the latter isolated as before by treatment of the crude alkylation product with alcoholic potash, when it came out of the mixture as colourless crystals.

The desired monoalkylation product (68) was subjected to hydrolysis

and decarboxylation to give the ketone (71), which was subjected to borohydride reduction to the carbinol (74).

The carbinol was then converted to the corresponding carbinyl bromide, by the triphenylphosphine-N-bromosuccinimide method, and was rearranged with anhydrous zinc bromide in anhydrous ether to the title compound (77).

The n.m.r. spectrum shows the olefinic protons (τ 4.40, m, 2H), - $\underline{CH_2}$Br (τ 6.65, t, 2H), - CH_2 - (τ 7.35, m, 2H), - CH_2 - CH_2 - (τ 7.65, m, 4H) and - C ≡ $\underline{CH}$ (τ 7.95, m, 1H).

The ketone (63) was made by the same route (Fig. xiv) as described for compounds (60) and (61). The n.m.r. spectrum of (63) shows olefinic protons (τ 4.53, m, 2H), - CH_2 - protons (τ 7.45 - 7.95, m, 14H) and - C ≡ $\underline{CH}$ and - $\underline{CH_3}$ (8.15, m, 4H) while the i.r. spectrum showed ν_{max} 3285, 1660 cm^{-1}. It was then subjected to epoxidation as before, to give epoxide (81) in 70% yield. The n.m.r. spectrum shows the olefinic protons (τ 4.55, m, 2H), - CH_2 - protons and - C ≡ $\underline{CH}$ proton (τ 7.30 - 8.40, m, 14H) and - CH_3 (τ 8.60, s, 3H).

The epoxide (81) was then subjected to the cyclisation condition (BCl_3 / CH_2Cl_2 at -78°) for 1 h. A dark tarry product was obtained, from which three fractions were separated by column and thin layer chromatography.

The least polar fraction was obtained as a yellow oil containing

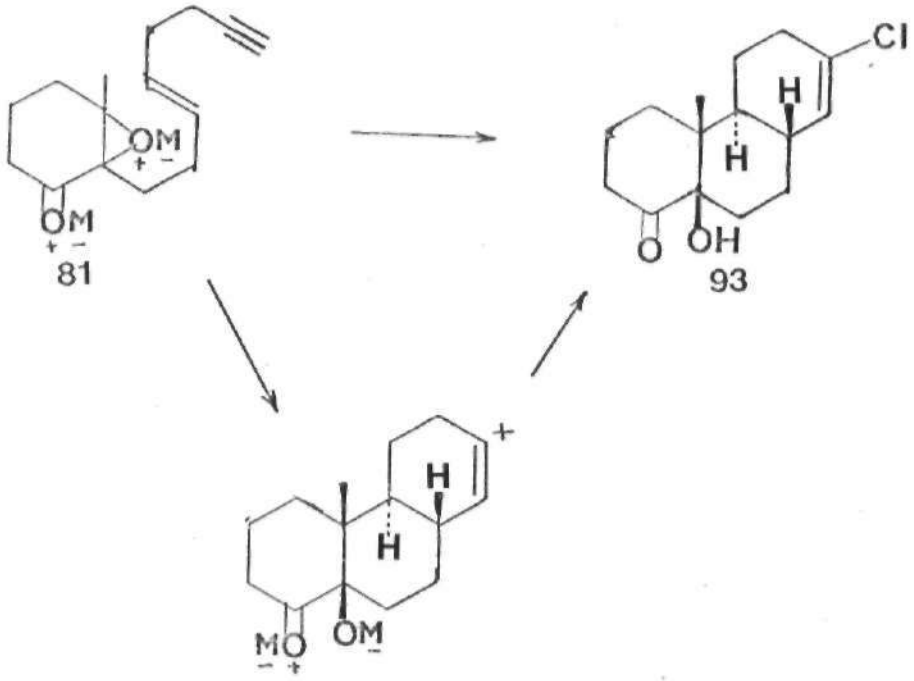


Fig xviii

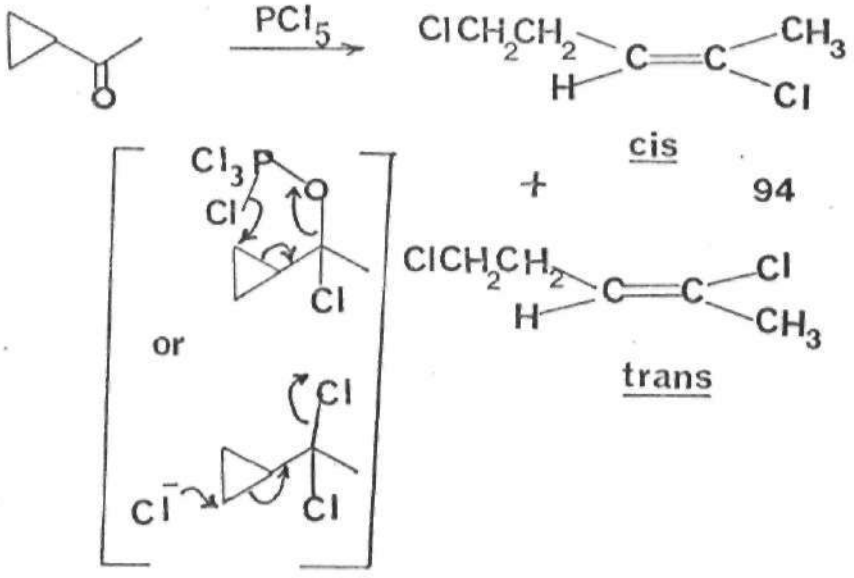


Fig xix

largely the ring contracted product and some chlorohydrin (20%). No attempt was made to separate these two products. The next fraction was the expected tricyclic product (93) which was obtained as colourless crystals (43 %). The n.m.r. spectrum shows a vinylic proton (τ 4.52, m, 1H), CH + CH_2 - and CH protons (τ 7.0 - 8.70, m, 17H), and the angular - CH_3 (τ 9.01, s, 3H).

Despite the tars obtained, the yield here shows an obvious improvement over the formation of the third ring involving the participation of the aromatic ring. This observation is probably not surprising since the acetylenic bond would be expected to be more nucleophilic than the latter. Lack of intramolecular hydrogen bonding may also imply a 'steroid' structure for this compound (cf 91).

The cyclisation must involve the vinyl cation (Fig. xviii) which was trapped by a chloride ion from the medium.

D. cis and trans-2,5-Dichloro-2-pentene (94) was reported[31] to have been made by the action of phosphorus pentachloride on methyl cyclopropyl ketone in methylene chloride at 0 - 5°C for two days. Contrary to this we found that the reaction took a week at room temperature to give a mixture of cis- and trans- compound (94, 81%, cf[31] 80%, 70% cis and 30% trans) Fig. xix. No attempt was made to separate the two isomers. The n.m.r. spectrum shows one vinylic proton (τ 4.48, m, 1H), - CH_2Cl

(τ 6.50, t, 2H), - CH_2 - (τ 7.40, m, 2H), - CH_3 (τ 7.80, s, 3H, with very fine terminal splitting as unresolved coupling with the vinylic proton).

The halide was employed in the alkylation procedure depicted in Fig. xiv to give the expected methylcyclohexenone derivative (62) in 81% yield. The n.m.r. spectrum shows the vinylic proton (τ 4.55, m, 1H), - CH_2 - protons (τ 7.65, m, 10H), - CH_3 (τ 7.90, m, 6H).

The ketone (62) was then subjected to epoxidation to give the expected epoxide (80) in almost 70% yield, (τ 4.65 m, 1H), (τ 8.62, s, 3H) .

Treatment of epoxide (80) with BCl_3 in CH_2Cl_2 at -78° for 1 h gave the hydrindanone derivative (95) in 53.7% yield after purification. The n.m.r. spectrum shows - OH (τ 5.89, s, 1H), - CH_2 - protons (τ 7.07 - 8.32, m, 11H), side-chain - CH_3 (τ 7.80, s, 3H), angular - CH_3 (τ 8.85, s, 3H). The i.r. spectrum shows the - OH stretching frequency at 3470 cm^{-1} and 1710 cm^{-1} for the C = O absorption. The molecular ion shows the presence of an extra chlorine atom in the molecule.

The vinyl chloride is a chemical equivalent of the corresponding methyl acetylenic group which has been shown (Chapter I) to give five-membered rings. Substance (95) is therefore, formed *via* cation A (Fig. xx). No 6/6 ring formation was observed, which would have involved cation B. In any case formation of cation A would be preferred since it is not only a tertiary cation, it is also further stabilised by the chlorine atom, whereas cation B would have involved a secondary carbonium ion.

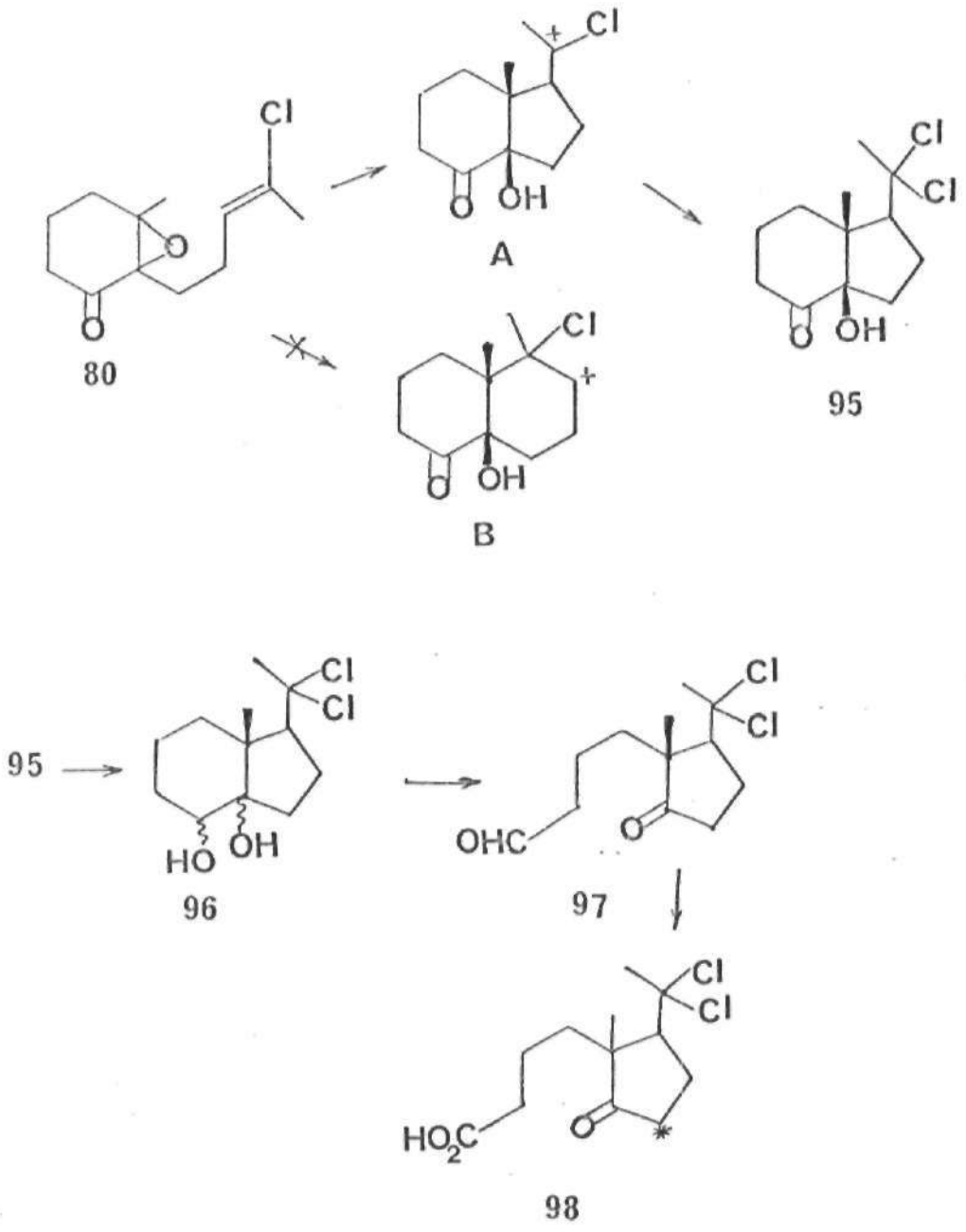


Fig xx

The formation of the five-membered ring was confirmed by the following reactions.

Compound (95) was reduced (sodium borohydride) to the diol (96) in 97.8% yield τ 6.15 (bs, 2H), τ 7.0 (t, 1H), τ 7.78 (s, 3H), τ 8.55 (s, 3H) . The diol was then subjected to periodate cleavage to give the ketoaldehyde (97) in 93% yield. The n.m.r. spectrum shows the formyl proton (τ 0.37, t, 1H), - CH_2 - and - C - H protons, (τ 7.42 - 7.92, m, 7H), side chain - CH_3 (τ 7.71, s, 3H), - CH_2 - protons (τ 8.42, m, 4H) and the angular - CH_3 (τ 8.72, s, 3H). The i.r. spectrum shows weak absorptions for the formyl group (C - H stretching) at 2802 and 2710 cm^{-1} and very strong peaks at 1747 and 1712 cm^{-1}, for the five-membered ring ketone function and the formyl carbonyl. These are not well resolved but occur as a strong and broad peak covering both regions with the 1712 cm^{-1} peak showing as a shoulder. The ketoaldehyde was oxidised to the keto-acid (98) using Jones reagent. The n.m.r. spectrum shows the carboxylic proton (τ 2.60, bs, 1H); - CH_2 - and - C - H protons (τ 7.0 - 7.90, m, 7H); side chain - CH_3 (τ 7.70, s, 3H); - CH_2 - protons (τ 8.1 - 8.58, m, 4H) and the angular - CH_3 (τ 8.69, s, CH_3). The i.r. spectrum shows the characteristic broad pattern of absorption 3600 - 3100 cm^{-1} for the - COOH, 1740 cm^{-1} for the five-membered ring ketone, and 1710 cm^{-1} for the carboxyl carbonyl.

The position of the side chain is still under investigation. The

alternative position is shown in compound (98) on the carbon atom. Dehydrohalogenation in this position would give an $\alpha\beta$ -unsaturated ketone, whereas, dehydrohalogenation in the alternative position shown would not result in the formation of such system. Treatment of (98) with base gave a product which has not been fully identified but which seems not to be either of the expected elimination products as shown by both mass- and u.v.- spectra. From the evidence so far, the preferred structure is as written.

E. trans-5-Bromopent-2-ene (99) was made by Julia's method[30] as shown in Fig. xxi, and was obtained in 64% yield after distillation. It was then used in the synthesis of the ketone (100) via the route depicted on Fig. xiv and the latter was obtained in 85.7% yield, τ4.45 - 4.75 (m, 2H), τ 7.4 - 7.80 (m, 10H), τ 8.09 (s, 3H), τ 8.26 - 8.48 (m, 3H) . The ketone was then subjected to epoxidation to give (101) in 60.7% yield, τ4.45 - 4.72 (m, 2H), τ 7.50 - 8.20 (m, 10H), τ 8.25 - 8.50 (m, 3H), 8.60 (s, 3H) . All these data agree very well with that for the compound previously prepared.[8]

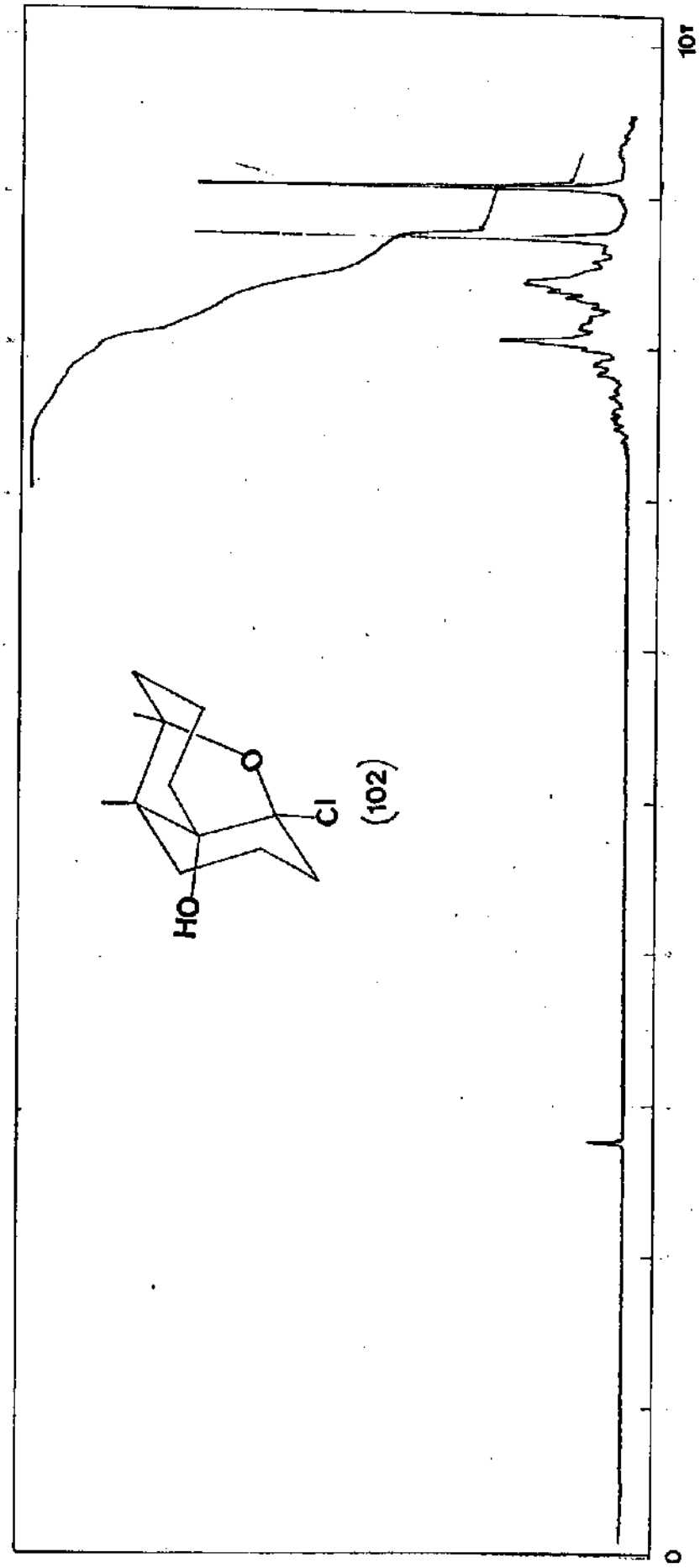
Mellor[8] had reported the efficiency of BCl_3 / CH_2Cl_2 in the cyclisation of epoxide (101) to be superior to any of the other Lewis acids and the purpose of this investigation was to reaffirm this observation. He carried out the cyclisation at -20°C. We have found however,

that the best results were obtained, at least for epoxides (79) and (81) when the reaction was carried out at -78°C.

Treatment of epoxide (101) with BCl_3 in CH_2Cl_2 for 2 h led to a different result from that obtained earlier (a pair of isomeric ketols (15, R = CH_3) and (16), the latter being the major component, Section 2). The n.m.r. spectrum of this product shows $-CH_2-$, -OH and - C - H protons at (τ 7.2 - 8.65, m, 13H) two tertiary methyls (τ 8.79, s, 3H) and (τ 9.10, s, 3H). More startling still was the absence of a carbonyl absorption in the i.r. spectrum.

Mass spectrum and elemental analysis showed the presence of a chlorine atom in the compound. Mass measurements showed a molecular ion of 230 / 232 and on deuteration 231 / 233, which showed the presence of only one -OH group. This means that the other oxygen atom must be involved in some ether linkage. On this basis the structure (102) is suggested. This compares with the cyclisation of epoxide (78) under the same conditions. (Spectrum ii)

The formation of (102) is thought to involve the initial formation of a secondary carbonium ion which rearranges to a more stable tertiary one, (Fig. xxi), instead of undergoing proton elimination to give (15) and (16). The tertiary carbonium ion probably undergoes an intramolecular nucleophilic attack by the carbonyl oxygen to form the ether linkage, the attack being facilitated by the chloride ion. An attempt was made to



(102)

Spectrum ii [90 MHz]

prove this structure but the evidence we have so far is by no means conclusive.

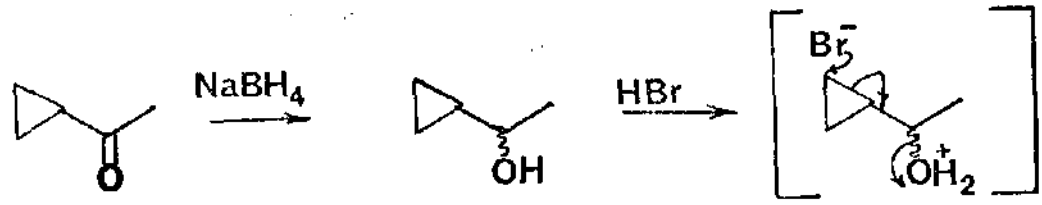
If an α-chloroether linkage was involved, we reasoned that this should readily hydrolyse using silver nitrate in aqueous methanol to give the hemiketal (102 a). We found that no hydrolysis took place at room temperature after 48 h. However, at reflux temperature for 18 h complete hydrolysis had taken place. This observation probably confirms the proposed bridge-head chlorine atom which has been demonstrated[36] to be relatively inert to alcoholysis at room temperature.

The i.r. spectrum showed the presence of a relatively weak carbonyl absorption at 1700 cm^{-1} and -OH and hydrogen bonded -OH at 3580 and 3450 cm^{-1} respectively. Even after purification by column chromatography the carbonyl group was still present. This was rationalised to be due to the presence of the ketol (102 (b)). The n.m.r. spectrum also suggested the possibility of a mixture of products as the methyl absorptions at τ8.65 and τ9.01 are ratio 1 : 2 respectively. Mass measurement of this product showed a molecular ion of 212 which agrees with the molecular weight of the proposed structure.

Lack of time and material did not allow the last step of the analysis involving reduction and cleavage of products which is expected to give substance (102 (c)) and the ketolactone (102 (d)) (Fig. xxi).

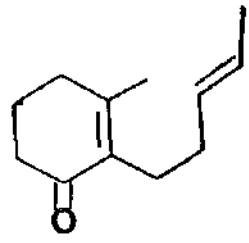
The only other cyclisation product isolated from the reaction

mixture was the ketol (103) which must have arisen from the initial bicyclic carbonium having been trapped by a chloride ion. The n.m.r. spectrum shows a multiplet at τ5.8 - 6.5 (OH and CH (Cl) ($W_{\frac{1}{2}}$ = 18.9 Hz)), ring $-CH_3$ at τ8.54 (d, J = 6.7 Hz) and angular methyl at τ8.85.

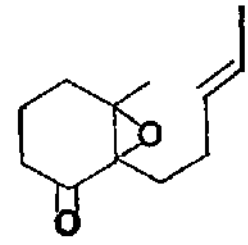




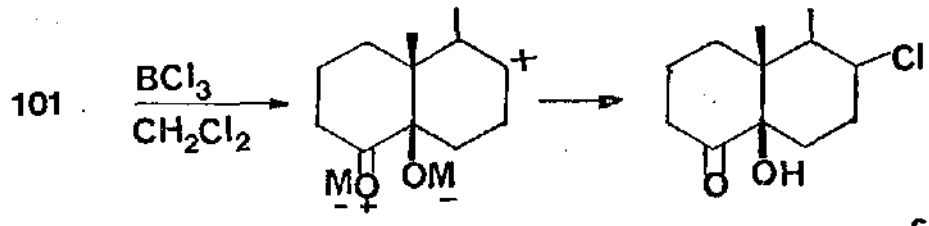
99



100



101



103

contd

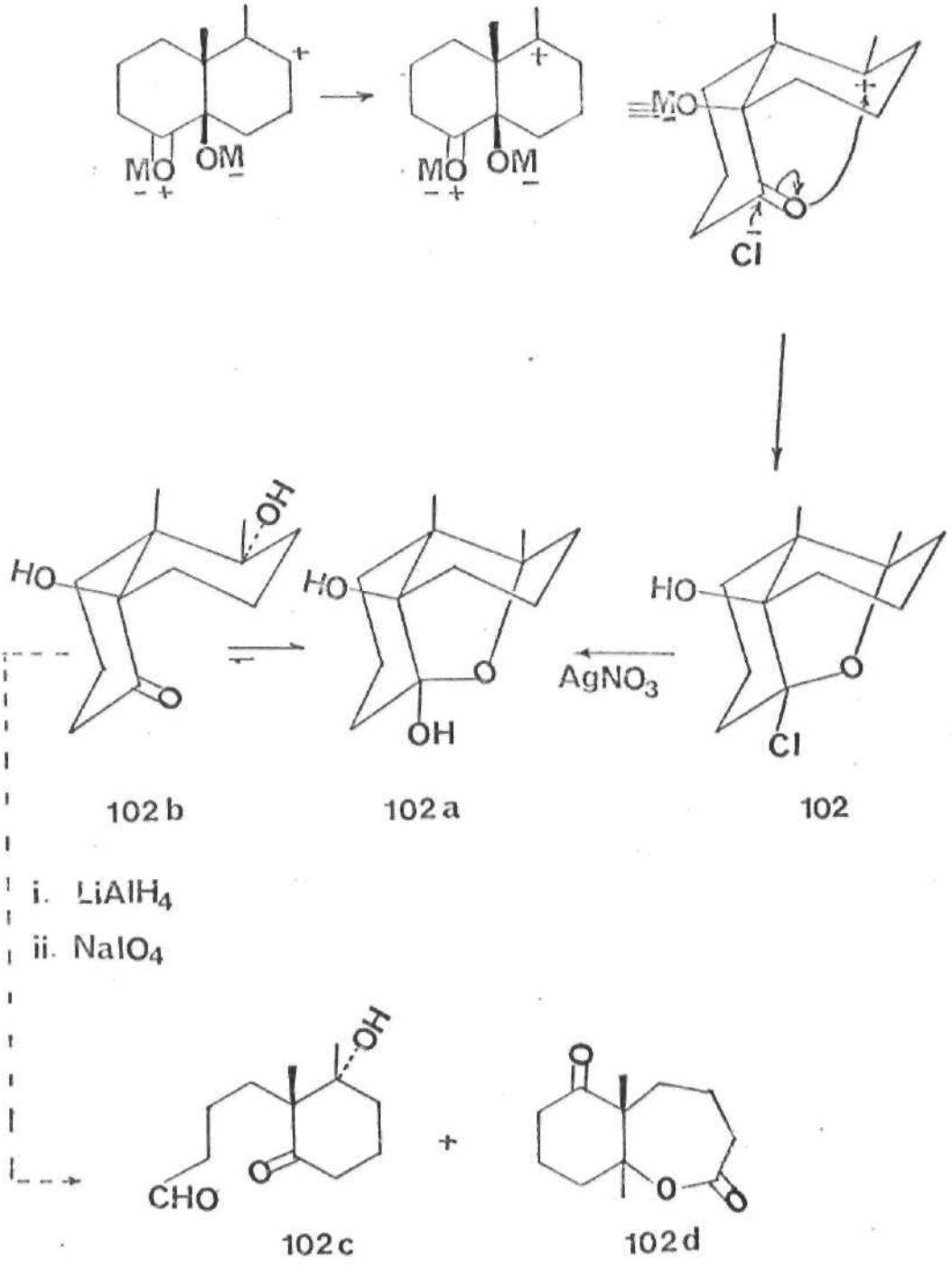

MO
OM
Cl
HO
OH
AgNO3
i. LiAlH4
ii. NaIO4
CHO
102 b
102 a
102
102 c
102 d

Fig xxi

III. Cationic cyclisation of $\alpha\beta$ -unsaturated ketones.

Harding et al[32] observed cyclisation of $\alpha\beta$ -unsaturated ketones under conditions suitable for the preparation of enol acetates. Treatment of enone (**58**, R = $-(CH_2)_2CH = CH_2$) with a mixture of 70% perchloric acid in acetic acid in ethyl acetate led to the formation of (104), a deprotonation product of the intermediate bicyclic cation (Fig. xxii). In the presence of a nucleophile, acetic anhydride, the bicyclic cation was trapped, leading to the isolation of (106) as shown. Compound (105) is formed by an equatorial attack of the nucleophile on the bicyclic cation. (106) was obtained in 50% yield. A more versatile reagent was trifluoroacetic acid (TFA) in trifluoroacetic anhydride (TFAA) which was used[33] in the cyclisation of the enone (107) to give (108b) via the 6/7 bicyclic cation after treatment of (108a) with methanolic potash. (106) was isolated as a mixture of cis and trans isomers, with the latter predominating. This promises to be of synthetic utility in the polyolefin cyclisation using $\alpha\beta$ -unsaturated carbonyl system as initiator.

On this basis we proceeded to investigate a number of enone systems that we have already synthesised (sub-section II).

A. The first ketone we investigated was (61) which on treatment with TFA/TFAA at room temperature gave the enol trifluoroacetates (109), ν_{max} 1790 cm^{-1}). Treatment of (109) with 10% methanolic potash gave

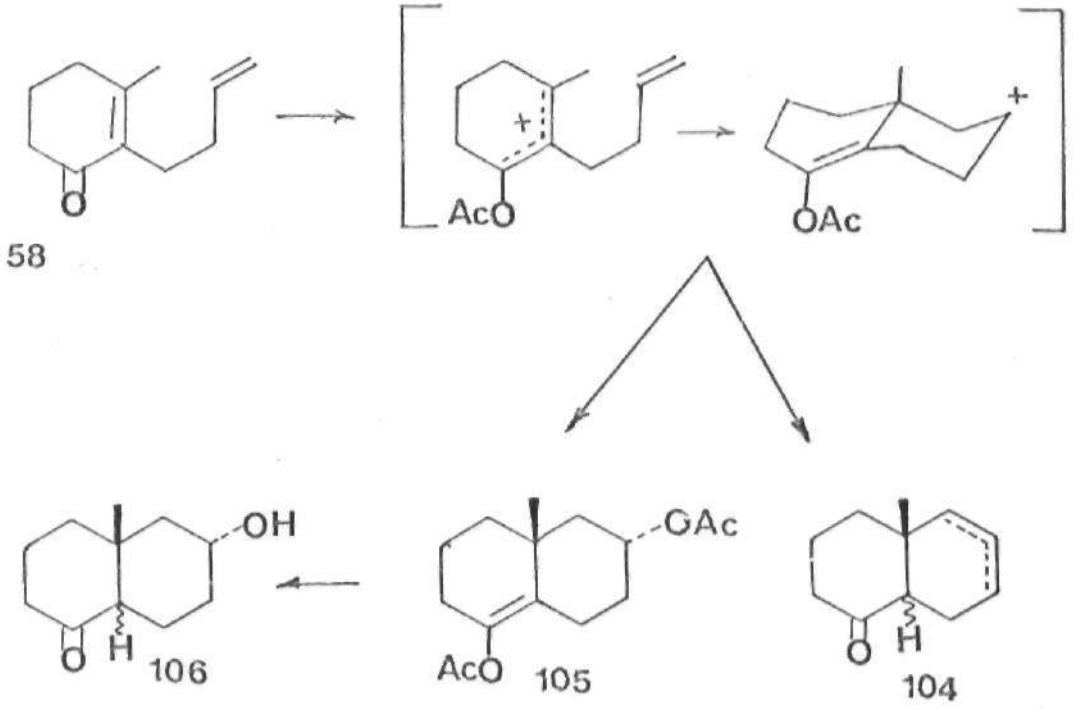
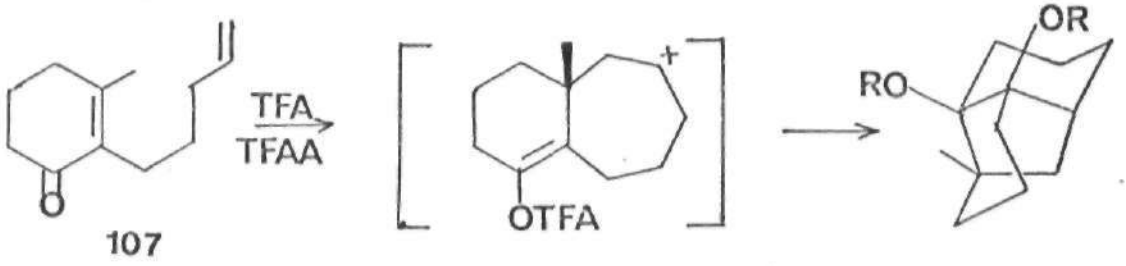
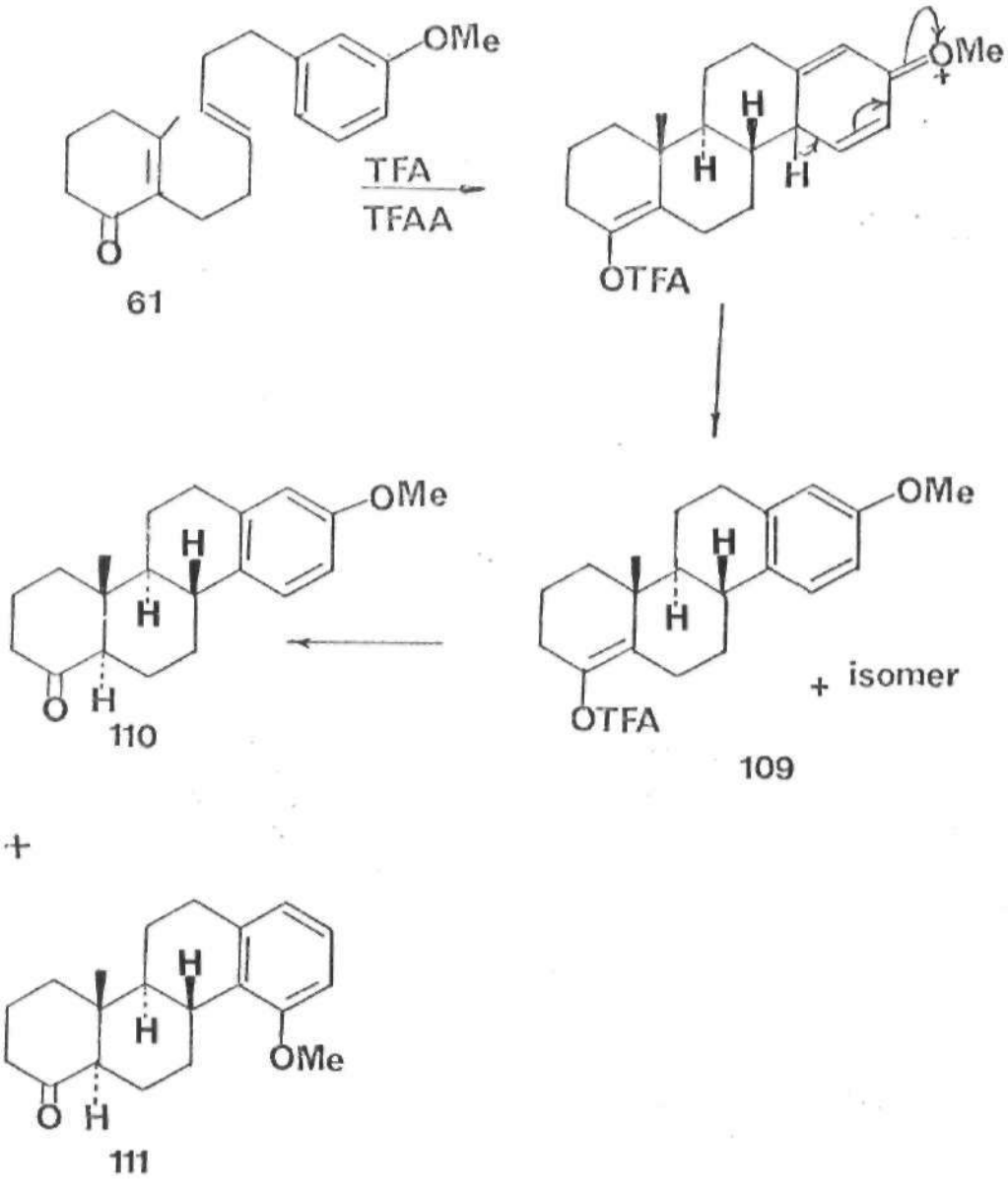


Fig xxii



108 a, R=TFA
b, R=H

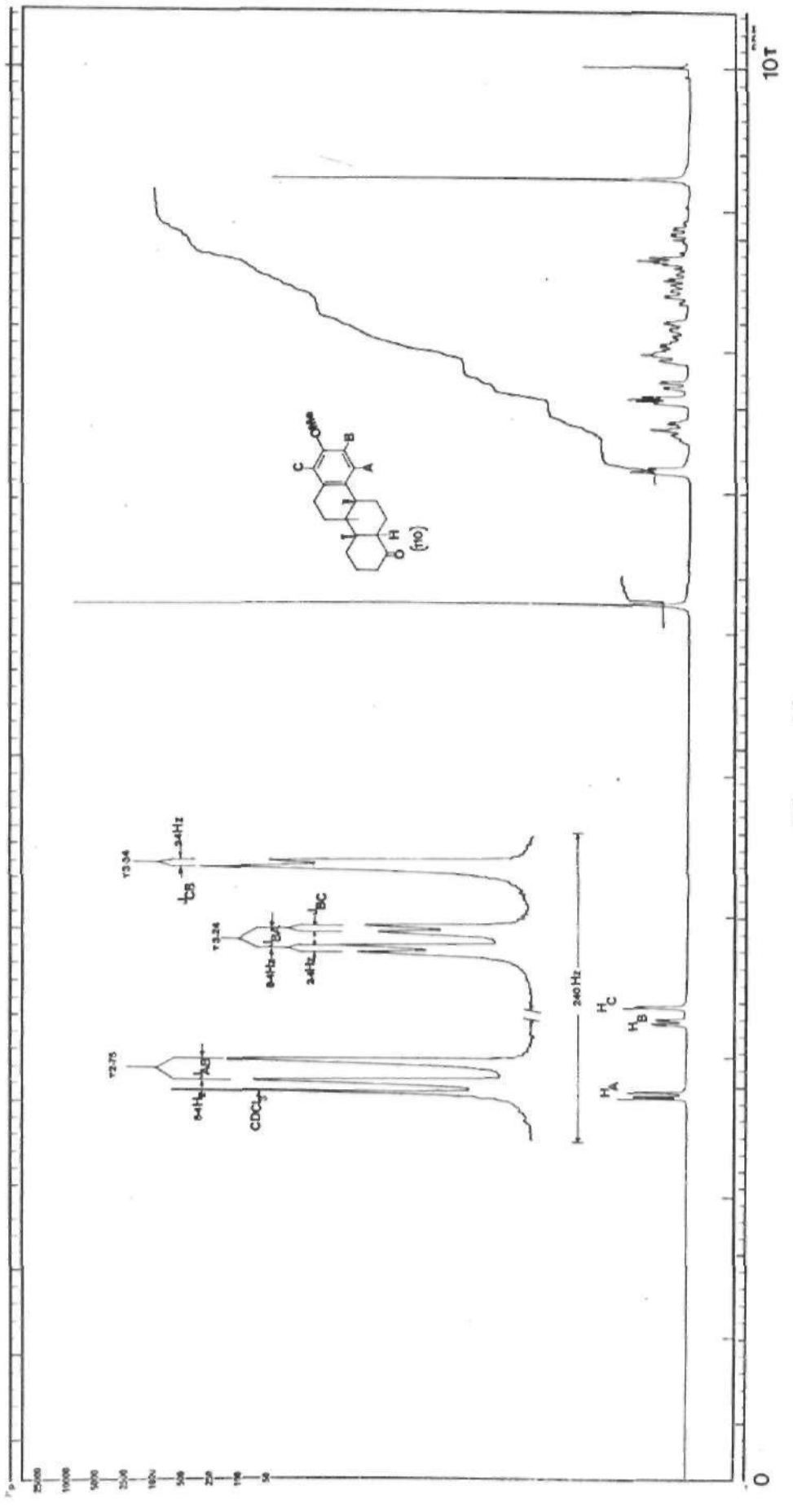
Fig xxiii


OMe
TFA
TFAA
61
OMe
H
H
H
OTFA
OMe
H
H
H
OTFA
+ isomer
109
OMe
H
H
H
O
H
110
+
H
H
H
OMe
O
H
111

(110) and (111) *via* cyclisation at *para* and *ortho* positions respectively.

The presence of the two products was evident in the n.m.r. spectrum of the mixture where the angular methyls absorbed closely at τ 9.22 and 9.20. The two isomers were separated by combined column and preparative thin layer chromatographic methods. The n.m.r. spectrum of (110) shows the expected pattern for cyclisation product *via* the *para*- position, H_A (τ 2.75, d, 1H, J_{AB} = 8.4 Hz); H_B (τ 3.24, dd, 1H, J_{BA} = 8.4 Hz, J_{BC} = 2.4 Hz); H_C (τ 3.34, d, 1H, J_{CB} = 2.4 Hz); -OMe (τ 6.21, s, 3H), angular $-CH_3$ (τ 9.22, s, 3H). (Spectrum iii)

In (111) the coupling between the protons were not properly resolved showing a proton (τ 2.82, d, 1H, J = 6.7 Hz), two protons (τ 3.2 - 3.50, unresolved), -OMe (τ 6.28, s, 3H), angular $-CH_3$ (τ 9.20, s, 3H). Both isomers show i.r. absorption at 1710 cm^{-1}. The total yield was 70.6% after purification, consisting 80.75% (110) and 19.25% (111). A/B ring *trans* stereochemistry has been assigned to both compounds on the basis of the chemical shift of the angular methyl groups; the *trans* isomers always have the angular $-CH_3$ groups absorbing higher than the *cis* isomers and in all examples investigated, usually upfield of τ 9.0. The yield of the tetracycles is striking and no other products were isolated in the reaction medium suggesting the process may be concerted and highly stereospecific.

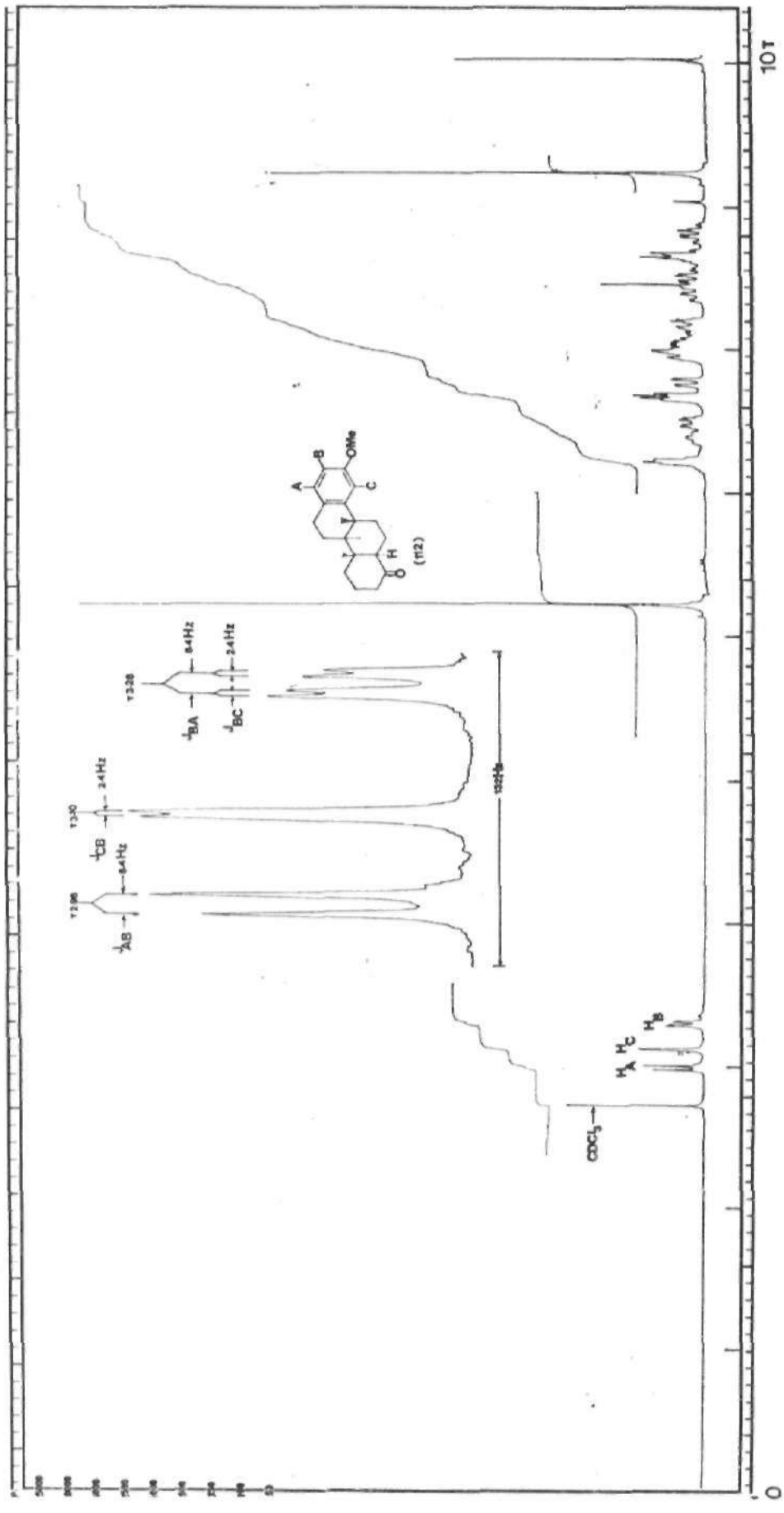


Spectrum iii [300 MHz]

B. Next, the ketone (60) was subjected to the cyclisation conditions as above. Electronically, cyclisation *via* the *meta*- position of the aromatic ring would be expected to proceed with difficulty making possible the likelihood of isolating partially cyclised intermediates. It was surprising that no such intermediates were isolated and a high yield (81% crude) of (112) was obtained. The n.m.r. spectrum shows the expected pattern for substitution at the *meta*- position of the aromatic ring. H_A (τ2.98, d, 1H, J_{AB} = 8.4 Hz); H_C (τ3.10, d, 1H, J_{BC} = 2.4 Hz), H_B (τ 3.28, dd, 1H, J_{BA} = 8.4 Hz, J_{BC} = 2.4 Hz), $-OCH_3$ (τ 6.20, s, 3H), angular $-CH_3$ (τ 9.22, s, 3H). (Spectrum iv)

The mechanism of cyclisation is not as clear-cut as for the isomer (61). If the formation of the third ring proceeded by ring closure at the *meta*-position, the intermediate C (Fig. xxiv) is expected. Since this is not very favourable in terms of energy requirements, the spiro compound, D is suggested (i.e. cyclisation *via* the more favourable *para*-position) and depending upon which bond migrates, determines the product.

Migration of bond *a* would give (110) whereas migration of bond *b* would give (112). The more substituted bond is expected to migrate, hence no (110) was detected in the reaction mixture. By whichever pathway C and/or D the yield is very high and like the isomers, (110) and (111), a *trans* stereochemistry is assumed.



Spectrum iv [300MHz]

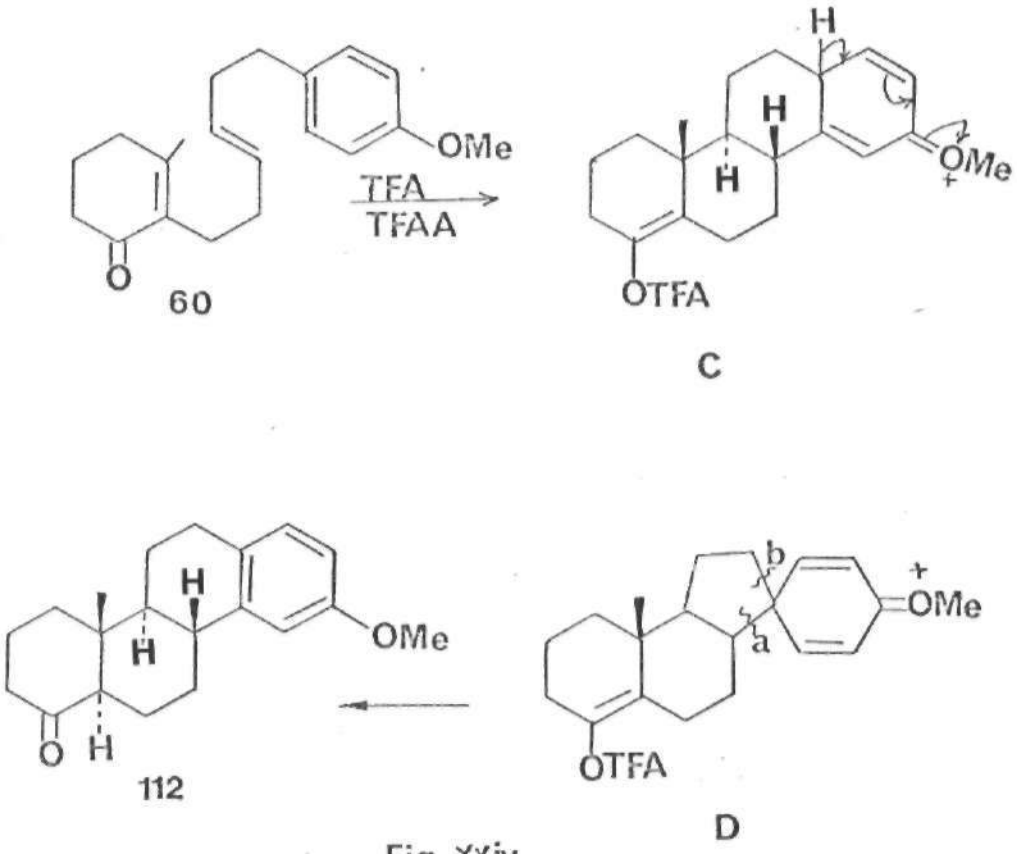


Fig xxiv

C. The cyclisation of ketone (63) with TFA/ TFAA was also investigated. A tricyclic compound is expected and the behaviour of a terminal acetylene to give a six-membered ring is already established. A tricyclic vinyl cation E (Fig. xxv), is first formed and this cation is trapped by TFAA to give (113) which was treated with saturated sodium bicarbonate to give a mixture of trans- (114) and cis- (115) isomers. The mixture of isomers was obtained in 54% yield composed of 57.4% trans- and 42.6% cis- compounds. The n.m.r. spectrum of the cis- isomer showed the angular $-CH_3$ at τ 8.94 (s, 3H), whereas the trans- isomer showed the angular $-CH_3$ at τ9.28 (s, 3H). The i.r. spectrum showed C = O absorption at 1710 cm^{-1}. Starting with pure cis compound, and treating with base, a 50 : 50 mixture of the cis and trans isomers was obtained.

D. The cyclisation of ketone (62) was investigated under these conditions. A 6/5 ring system is expected from previous results. The chlorocarbonium ion, F probably forms prior to trapping by TFAA to give the bis (trifluoroacetate, 116) which on treatment with saturated bicarbonate gives a mixture of hydrindanone α - (119) and β- (118) acyl derivatives via the chlorohydrin (117) which was not isolated. cis-Stereochemistry is assigned to both products on the basis that cis-hydrindanes are more stable than the trans isomers.

Compounds (118) and (119) were obtained in 47% yield after purification

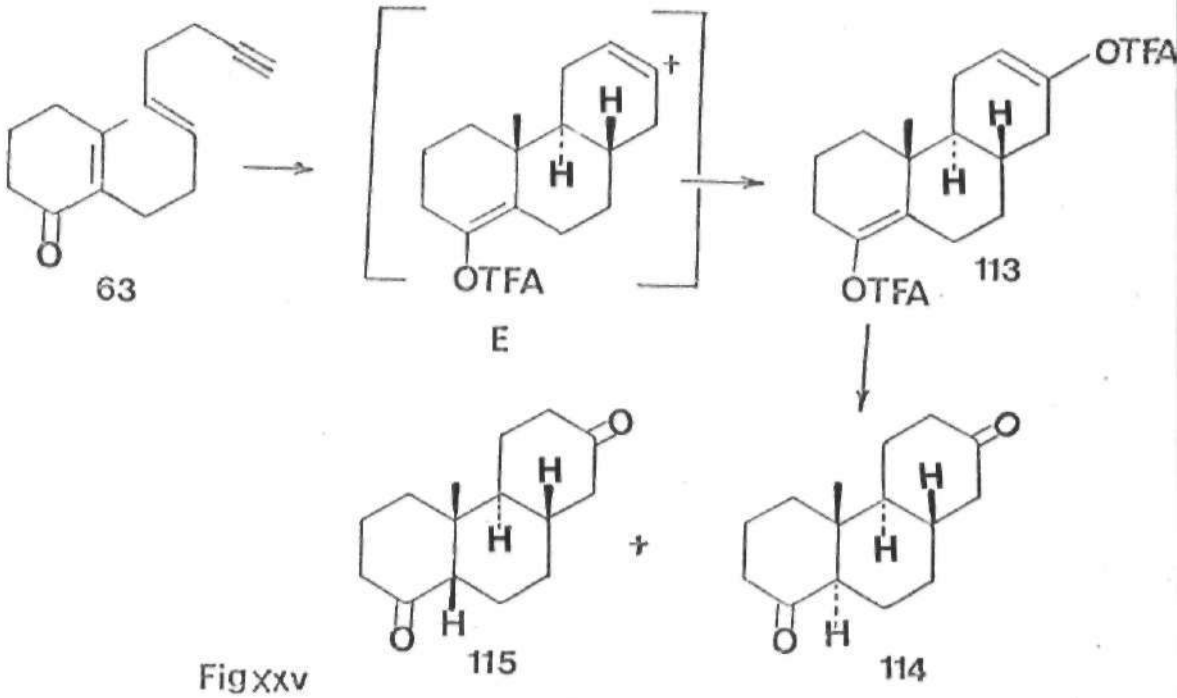


Fig xxv

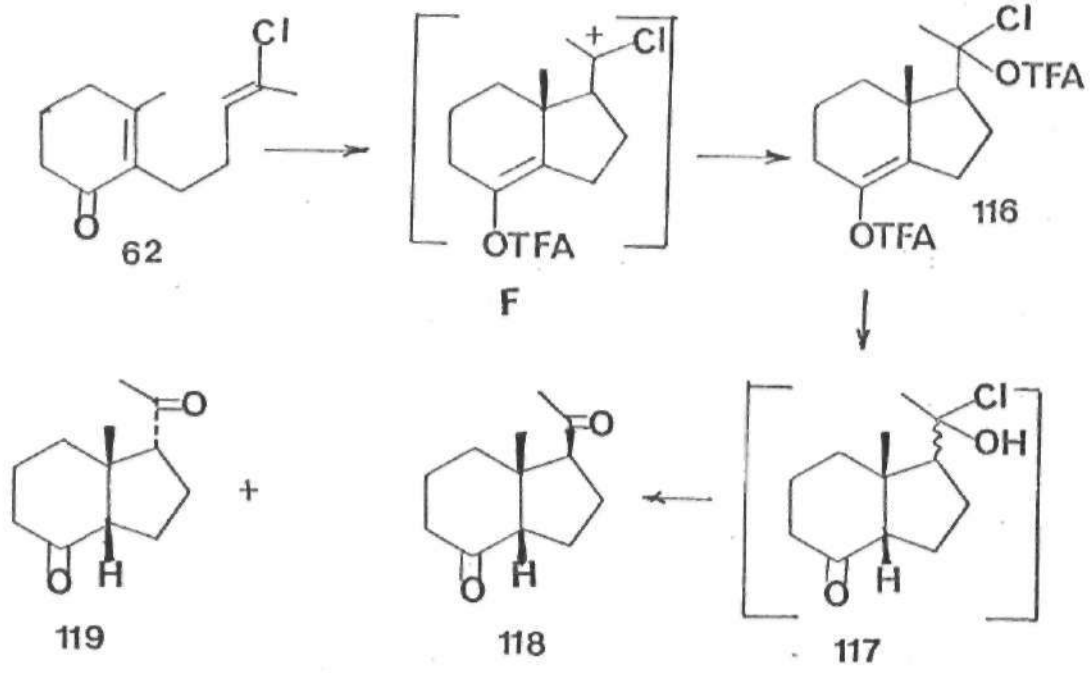


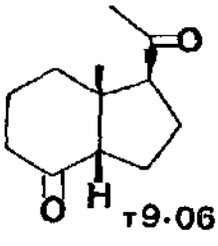
Fig xxvi

and separation of isomers, (119) : (118) = 74.2% : 25.8% .

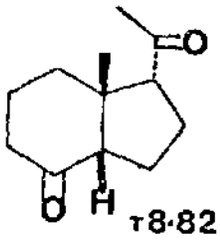
The n.m.r. spectrum of (118) shows $\underline{CH_3}CO$. (τ 7.89, s, 3H) and the angular $-CH_3$ (τ 8.95, s, 3H) whilst (119) shows $\underline{CH_3}CO$- (τ 7.81, s, 3H) and the angular $-CH_3$ (τ 8.72, s, 3H).

The yield was expected to be better but the reaction is usually accompanied by formation of tars.

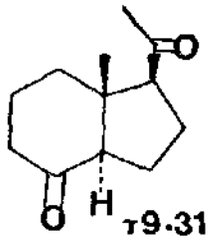
The assignment of α- and β- configuration to the acyl substituents is based upon the known[35] effect of such substituents on the chemical shifts of the angular methyls. By comparing the effect of the substituents on the angular methyls of decalones with that on the corresponding hydrindanones, the calculated angular methyl absorptions for the four isomers of the latter are shown below (angular methyls for cis- and trans- decalones absorb at τ 8.98 and τ 9.23 respectively).



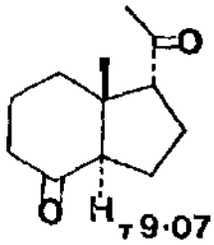
a



b



c



d

From observed data, c is not formed, on the basis of the expected chemical shift, and d is probably not formed, on the basis of the preferred cis-conformation.

Structures a and b are preferred and observed data compare reasonably well.

No attempt was made to epimerise the α- to the β-acyl compound which is more desirable for steroid synthesis.

E. Finally in this series, the action of TFA/TFAA on the ketone (100) was investigated. Three products were obtained. Cyclisation probably takes place via the bicyclic cation F which is trapped by attack in the equatorial position by TFAA, to give the bis (trifluoroacetate) (120) which on treatment with saturated sodium bicarbonate gave (121) and (122). The substance (123) is thought to be a direct product from cation F, by a 1,2-hydrogen and methyl migration with final hydrolysis of the intermediate to generate the enone system. The mixture of the three products was isolated in 76.9% yield after purification consisting of 41% (121), 24% (122) and 35% (123).

The trans isomer (121) shows n.m.r. absorption at τ 6.65 (m, 1H, $W_{\frac{1}{2}}$ = 24.4Hz), τ 9.0 (d, 3H, J = 7 Hz), and τ 9.35 (s, 3H) while the cis isomer (122) shows the -CH(HO)- proton at τ 6.55 (m, 1H, $W_{\frac{1}{2}}$ = 26.7 Hz), the angular $-CH_3$ at τ 9.01 (s, 3H) and the $-CH_3$ on the ring τ 9.12 (d, 3H, J = 7.7 Hz). Both compounds absorb in the i.r. at 3600 and 1710 cm^{-1}.

The third product, (123) has a very simple n.m.r. spectrum, showing the two $-CH_3$ groups at τ 8.91 (s, 6H). I.r. absorption at 1670 cm^{-1}

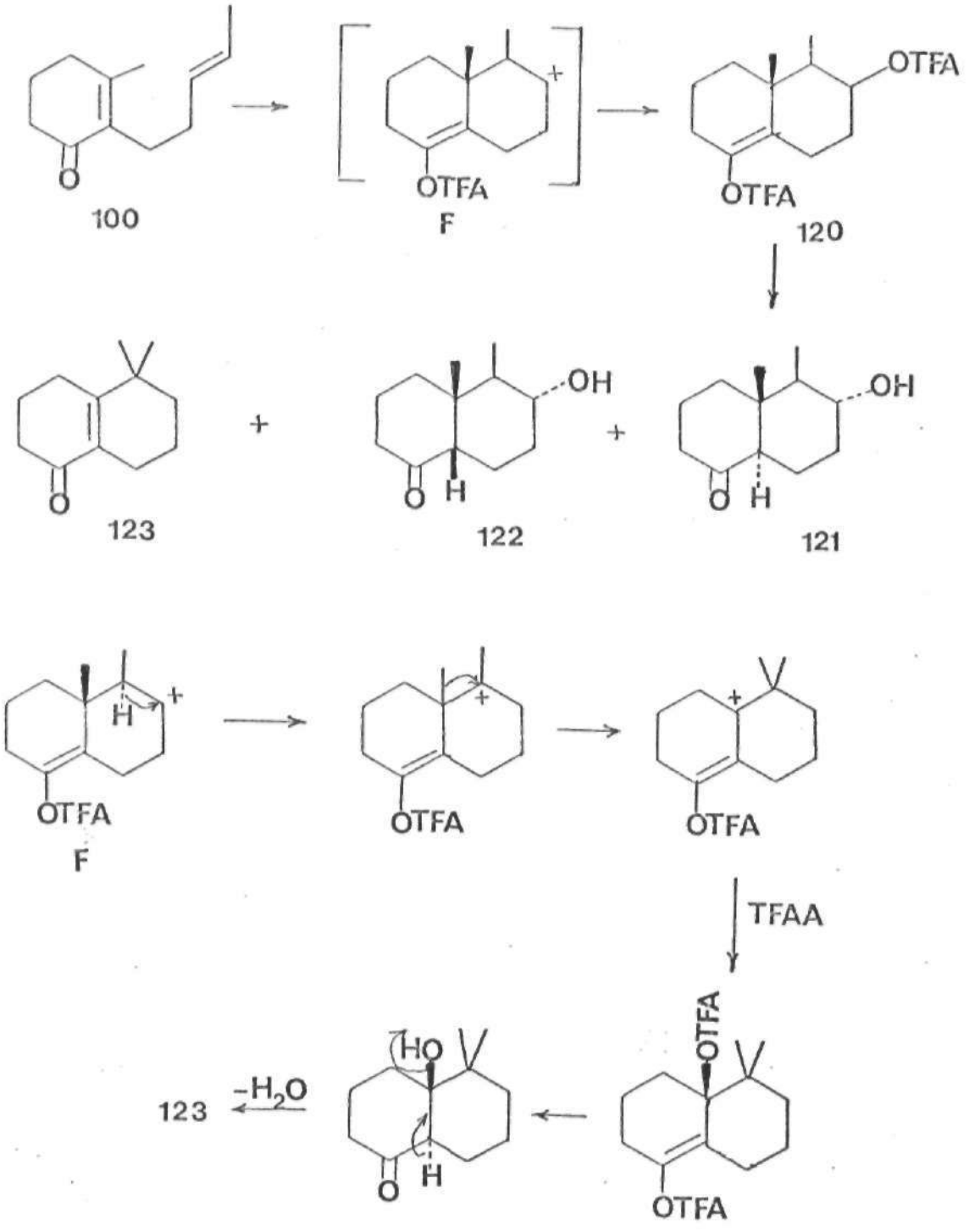


Fig xxvii

together with λ_{max} 245 nm (ε 4200) indicates the presence of a cyclohexenone system.

In order to investigate the mechanism of reaction the ketone (100) was reacted with deuteriotrifluoroacetic acid (d-TFA) in TFAA. The same products outlined above were obtained but this time each compound had incorporated a deuterium atom and i.r. spectrum showed a C - D stretching frequency at 2170 cm^{-1}.

The deuterated compounds are hereby referred to as d-(121), d-(122) and d-(123) respectively (Fig. xxviii). Mass measurements of (123) and d-(123) were carried out simultaneously. The expected molecular mass of the deuterated ketone d-(123) was 179.1415, and the measured value was found to be 179.1420, there was a ^{13}C interference at 179.1391. In order to ascertain the position of deuterium incorporation, an attempt was made at 'washing off' the deuterium under basic conditions. This would be possible only if the deuterium was on an active methylene, for example, when adjacent to a carbonyl function. An adaptation of a published procedure[34] was applied, involving treatment of the deuterated compound with aqueous sodium hydroxide in dioxan warming to 70°C under nitrogen for 20 mins. This single operation did not remove all the deuterium, as a result of which a mixture of the ketone (d-123) in dioxan, aqueous sodium hydroxide was stirred at room temperature for 18 h. at the end of which all the deuterium had been displaced as shown by the absence of a

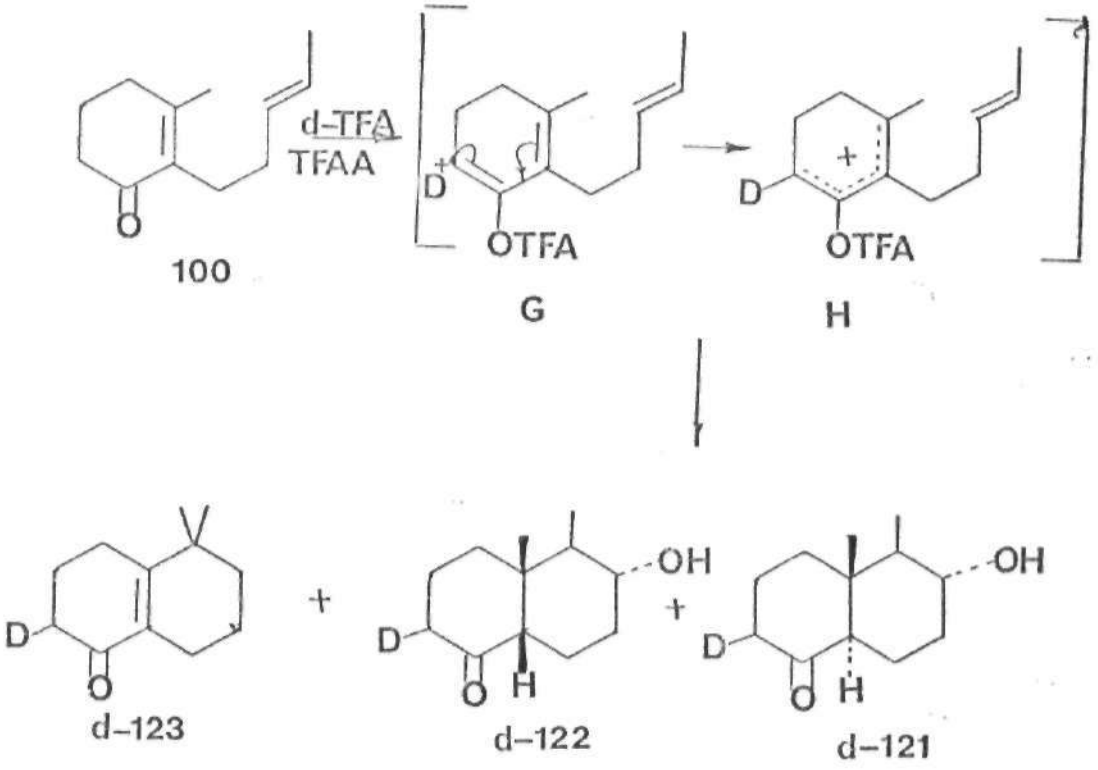


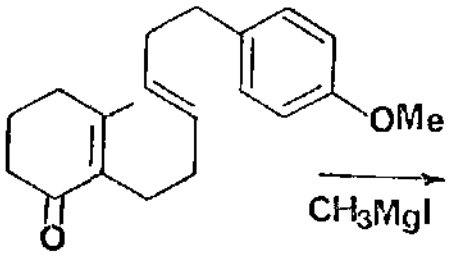
Fig XXviii

C - D stretching frequency previously observed at 2170 cm^{-1}. These results establish that the ketone (123) is formed by a hydride migration process and not by protonation of an olefinic intermediate.

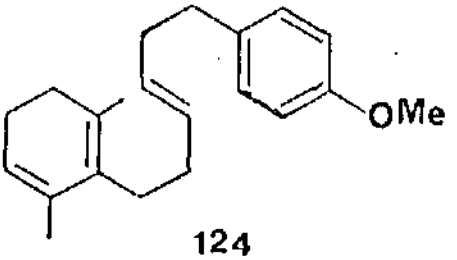
IV ALLYL CATION PROMOTED CYCLISATION

In Chapter 1, we came across this method of initiating cyclisation and some examples involving cyclohexenyl cation-promoted cyclisations. The particular example here was carried out in order to compare this method with those of epoxide (78) and **αβ** unsaturated ketone (60) cyclisations already described.

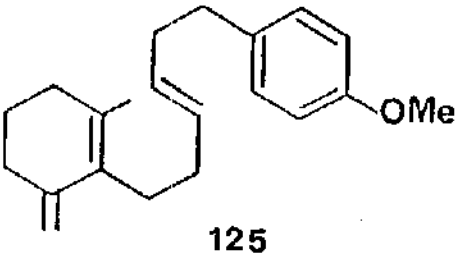
Formation of the tertiary allylic alcohol (126) could only be achieved by reaction of an ethereal solution of (60) with methyllithium at -78^{o}. Using the Grignard reagent, methyl magnesium iodide resulted in the formation of dehydration products (124) and (125) shown by t.l.c. to be present before work up. Apparently dehydration was effected by magnesium iodide present in the medium, (124) and (125) were obtained in 83% and 17% respectively as estimated from the n.m.r. spectrum of the crude mixture. The allylic alcohol (126) was obtained in 95.1% yield by treatment of ketone (60) with methyllithium. N.m.r. spectroscopy shows the aromatic protons at τ 3.05 (dq, 4H), olefinic protons τ 4.52 (m, 2H), $-O\underline{CH}_3$, τ 6.23 (s, 3H), $-C\underline{H}_3$ on double-bond τ 8.35 (s, 3H) and



60

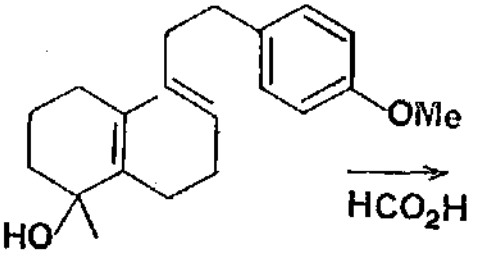


124

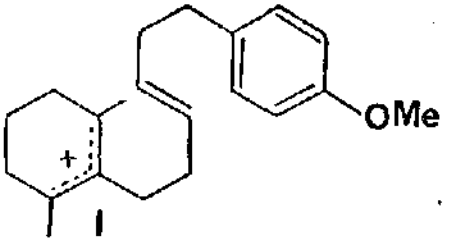


125

60 $\xrightarrow{CH_3Li}$

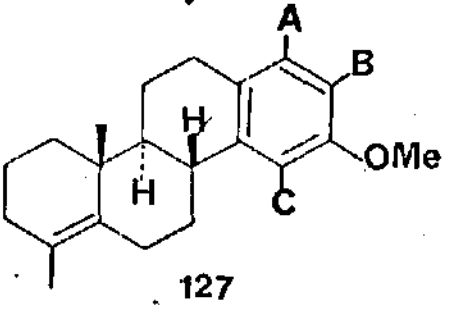


126



I

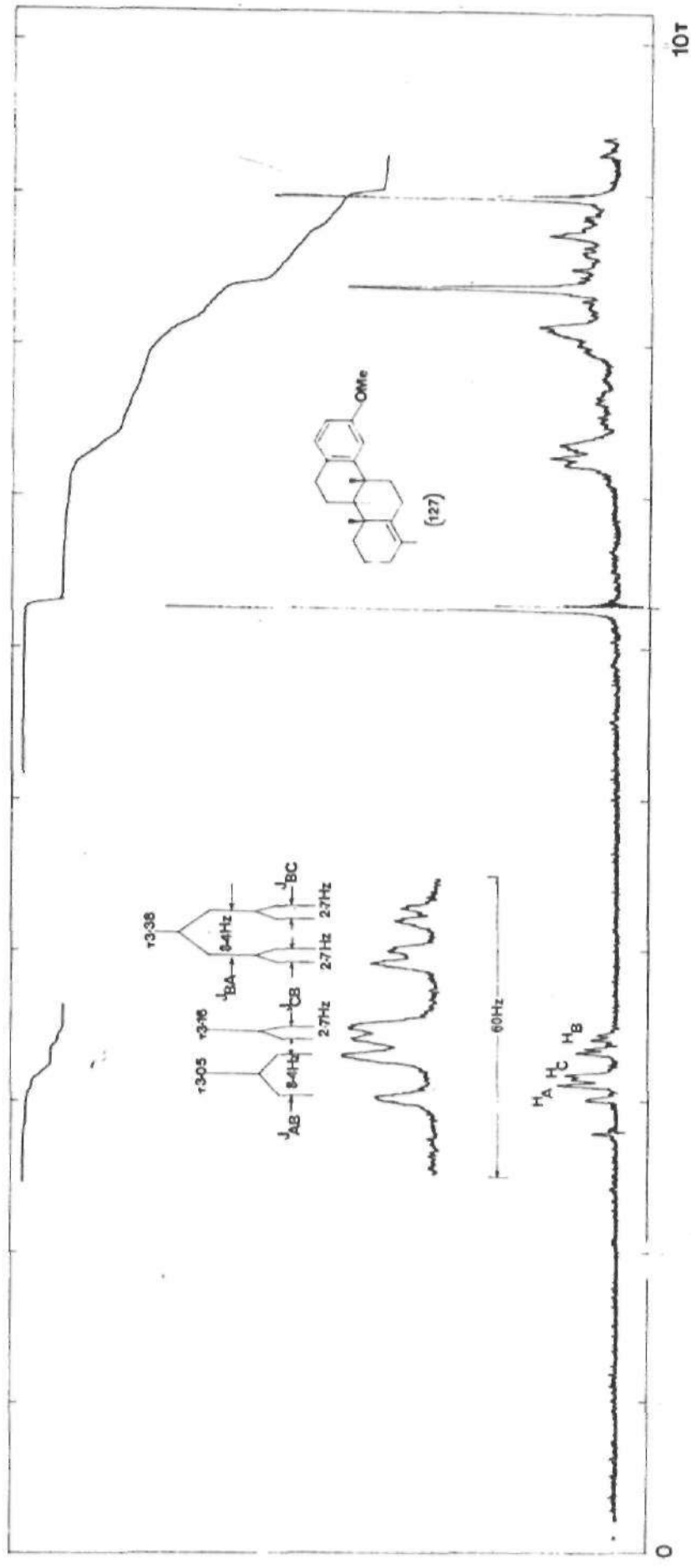
124 +



127

$-C\underline{H}_3$ on allylic carbon atom, τ 8.72 (s, 3H). Treatment of the allylic alcohol (126) with anhydrous formic acid (freshly distilled from phthalic anhydride) gave a mixture of the dehydration product (124) and the expected cyclisation product (127), the latter obtained in 60% yield after crystallisation. The n.m.r. spectrum shows the expected pattern for an ABC system, H_A τ3.05 (d, 1H, H_{AB} = 8.4 Hz), H_C τ 3.16 (d, 1H, J_{BC} = 2.7 Hz), H_B, τ 3.38 (dd, 1H, J_{BA} = 8.4 Hz, J_{BC} = 2.7 Hz), $-OC\underline{H}_3$ τ 6.26 (s, 3H), $-C\underline{H}_3$ on double bond, τ 8.39 (s, 3H) and the angular $-C\underline{H}_3$ τ 8.99 (s, 3H). (Spectrum v)

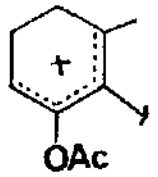
Apart from the method of initiation, which involves protonation of the carbinol, followed by loss of water to generate the allylic carbonium ion, I, the formation of the third ring involving the participation of the aromatic ring may proceed by a similar mechanism as proposed for the cyclisation of the ketone (60, Fig. xxiv). In the cyclisation of the epoxide (78) a very low yield of tetracyclic product was obtained, whereas in the cyclisation of the enone (60) and the allylic alcohol (126) good yields of the tetracyclic compounds were obtained. The conditions of cyclisation of the the last two substrates were definitely more drastic than the condition under which the epoxides were cyclised. Another probable reason for the success achieved in the former cases is the low nucleophilicity of the trifluoroacetate ions as opposed to the chloride ions present in the Lewis acid cyclisations. A strong Lewis acid with



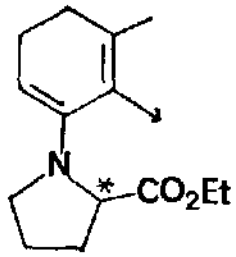
Spectrum v [90 MHz]

non-nucleophilic anions is highly desirable for the success of the epoxide cyclisation as a synthetic method. There is a serious snag about the usefulness of the $\alpha\beta$ -unsaturated ketone as a synthetic route to polycyclic triterpenoids and steroids, and this has to do with synthesis of optically active compounds. The polyene cyclisations already encountered have been shown to be very stereospecific in which only racemic mixtures of compounds are obtained. Thus it would be necessary to design a method of inducing optical activity into this synthetic compound to make these various methods a viable synthetic route to various triterpenoids and steroids.

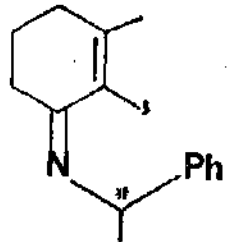
SUGGESTION FOR FUTURE WORK.



J



K



L

The acetoxy carbonium ion forms readily with nucleophilic attack by the suitably positioned olefinic bonds resulting in formation of cyclised products. Following this observation, it is thought that nitrogen in place

of oxygen atom may be able to behave similarly under these conditions. The strategy involves the formation and cyclisation of the enamine (K) and Shiff base (L) using optically active amine derivatives. Starting with these compounds it is hoped chirality may be induced in the subsequent product, it is however, not known whether the optically active centres in the bases are close enough to the asymmetric centres being formed as to induce optical activity.

In conclusion, the results obtained are consistent with the proposed intermediate cations. The fate of the cations is four-fold:

(i) Proton elimination resulted in the formation of olefinic products, for example, (15) and (16).

(ii) Intramolecular nucleophilic attack, resulting in fully cyclised products, for example, (89) and (112) amongst others.

(iii) Intermolecular nucleophilic attack results in trapping of the cations by trifluoroacetate ions, for example, the vinyl carbonium ion (E, Fig. xxv) and the chlorocarbonium ion, (F, Fig. xxvi) and also chloride ions, for example (A, Fig. xx) amongst others.

(iv) Finally, rearrangement of cations involving 1,2-hydride and methyl shifts is observed in the bicyclic cation (F, Fig. xxvii).

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CHAPTER 3 - EXPERIMENTAL

GENERAL

Melting points (m.p.) were determined on Kofler hot stage and are uncorrected.

Nuclear magnetic resonance spectra (^{1}H N.M.R.) were recorded on a Perkin-Elmer R12B instrument operating at 60 MHz unless otherwise stated. 90 MHz spectra were recorded on a Perkin-Elmer R32 instrument, whilst 80 MHz spectra were recorded on Bruker WP80 instrument. 300 MHz spectra were recorded on Varian SC300 instrument. All samples were run in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as internal standard.

Peak multiplicities are denoted by s, d, t, q, dd, m, indicating singlet, doublet, triplet, quartet, doublet of doublets, and multiplet. dq (doublet of quartet) has been used in describing absorption pattern of para disubstituted benzene rings. The prefix b in some cases indicate broad.

Infra-red spectra (IR) were recorded on a Perkin-Elmer 257 spectrophotometer at FAST scan speed and spectra run as solution in carbon tetrachloride. Band intensities are denoted by s, m, w for strong, medium and weak respectively. The prefix b indicates broad as before.

Ultraviolet spectrum (U.V. was recorded on a Perkin-Elmer 402 instrument and spectrum was run in methanol. The wavelength was quoted in nanometers

(nm) followed by the ε-value.

Mass spectra (M.S.) were recorded on an A.E.I. MS12 instrument and mass measurements (MM) on A.E.I. MS30 instrument.

Microanalyses were performed in the Manchester University Microanalytical Laboratory, supervised by M. Hart.

Analytical thin layer chromatography (t.l.c.) were carried out on plates precoated with Merck silica gel F254 using 1 : 1 ether : 40/60 petroleum ether or 1 : 1 ether : hexane, unless otherwise stated.

Preparative thick/thin layer chromatography, were carried out on 20 x 20 cm plates (silica gel 1.5 - 2.2 mm thick) and 20 x 10 cm plates (silica gel 0.25 cm thick) respectively eluting with same solvent system as above.

Column chromatography was performed using silica gel MFC (0.125 to 0.250 mm, 60 - 120 mesh) using same solvent system as above.

Solvents - for both reactions and extractions were all redistilled and dried when required by standard methods.

Reagents were also purified before use except boron trichloride, due to difficulty in handling was used as supplied by manufacturers.

Reaction temperature: Solid carbon dioxide/acetone were used for reactions carried out at -78^{o}.

1. 1,5-Dimethoxy-1,4-cyclohexadiene.[1] (51)

Ammonia (ca 400 ml) was introduced into a 1 l-flask equipped with a dry-ice condenser, dropping funnel and magnetic stirrer. Sodium metal (15.0 g, 0.65 mol) was added cautiously over the 1 h whilst the ammonia was vigorously stirred. The resultant dark blue solution was stirred for another ½ h after which a solution of m-dimethoxybenzene (16.35 g, 0.118 mol) in anhydrous ether (50 ml) and absolute ethanol (31.25 g, 0.68 mol) was added cautiously over a period of 1½ h. After the addition was complete, stirring continued for another 1½ h.

The reaction mixture was quenched with 30 ml, 1 : 1 95% ethanol : water and 50 ml of water was added ½ h after the introduction of the ethanol-water mixture. The condenser was then removed and ammonia was allowed to evaporate gradually overnight, leaving a slightly dirty-brown slurry. Brine (100 ml) was added, the solution was then filtered through Celite. The ethanol was removed under reduced pressure and the product isolated by extraction into ether, dried ($MgSO_4$) and solvent distilled off yielding 15.0 g (90.5%) of the title compound, obtained as a colourless oil by bulb to bulb distillation (42 - 5°C / 0.1 mm).

^{1}H NMR $CDCl_3$: (τ) 5.38 (m, 2H), 6.49 (s, 6H), 7.20 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 3050 (w), 2980 (w), 2930 (m), 2890 (m), 2820 (s), 1700 (s), 1670 (m), 1390 (s), 1205 (s).

2. 3-(Δ^3-Butenyl)-2,4-dimethoxy-1,4-cyclohexadiene (53).

1,5-Dimethoxy-1,4-cyclohexadiene (1.01 g, 7.21 mM) was added to n-BuLi (4.8 ml, 7.22 mM) in anhydrous THF (15 ml) at -78°C, and the mixture stirred for 1 h. HMPA (1.32 g, 7.36 mM) in THF (5 ml) was added over 5 min. A maroon colour developed immediately and persisted until 4-bromo-1-butene (1.002 g, 7.42 mM) in THF (5 ml) was added and this colour disappeared. The reaction mixture was allowed to warm to room temperature, 10 ml of brine was added and mixture was extracted with pentane (15 x 3 ml) portions; combined organic extracts was washed with distilled water to remove traces of HMPA, dried ($MgSO_4$) and distillation of solvent afforded the title compound (1.15 g) as a yellow oil. Purification by distillation (65 - 70°C / 0.1 mm) gave 1.08 g (77%) of pure title compound as a colourless oil.

^{1}H NMR $CDCl_3$: (τ) 3.95 - 4.55 (m, 1H), 4.85 - 5.15 (m, 2H), 5.29 (t, 2H), 6.49 (s, 6H), 7.19 (m, 3H), 8.18 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 3050 (w), 2980 (m), 2920 (s), 2818 (s), 1690 (s), 1658 (m), 1200 (s).

3. 2-(Δ^3-Butenyl)-1,3-cyclohexanedione (48).

To a solution of compound (53) in AR-acetone (15 ml) previously purged with N_2, was added with stirring 1N - HCl (8 ml) similarly purged with N_2 for 15 min. The resultant solution was stirred for 5 h under N_2. The acetone was then removed under pressure. The residue was diluted with brine (10 ml) and extracted with CH_2Cl_2 (50 ml). The extract was washed with brine, dried ($MgSO_4$) and removal of solvent afforded after recrystallisation (benzene : petrol (b.p. 80 - 100, 1 : 1) 0.8 g (86.6%) of the title compound as colourless crystals, m.p. 94 - 6°C.

^1H NMR $CDCl_3$: (τ) 3.76 - 4.50 (m, 1H), 4.82 - 5.22 (m, 2H), 7.3 - 7.78 (m, 6H), 7.78 - 8.22 (m, 4H).

4. 2-(Δ^3-Butenyl)-3-ethoxy-2-cyclohexenone[2] (49).

Compound (48, 0.2390 g, 1.44 mM), p-TsOH.H_2O (200 mg), absolute ethanol (10 ml) and benzene (20 ml) were introduced into a 50 ml round-bottomed flask fitted with a Dufton column, and a take-off condenser. The mixture was heated to boiling for 1 h before heating was increased when benzene-ethanol-water azeotrope was observed to distil. The temperature was steady at 64°C and when it appeared all the water formed had been removed, the temperature rose to 68°C when benzene - ethanol azeotrope

distilled off. The distillation was then stopped, the residual solution was washed with 2 x 5 ml portions of 1N - NaOH and then extracted into ether, dried ($MgSO_4$).

Removal of solvent afforded 0.1926 g (85.6%) of title compound reasonably pure from n.m.r. spectrum.

^1H NMR $CDCl_3$: (τ) 3.80 - 4.01 (m, 1H), 4.81 - 5.28 (m, 2H), 5.95 (q, 2H), 7.30 - 8.20 (m, 10H), 8.68 (t, 3H).

IR (film) ν_{max} (cm^{-1}) : 3058 (w), 2920 (bs); 1640 (vs), 1610 (vs), 1370 (s).

5. 2-(Δ^3-Butenyl)-3-methyl-2-cyclohexenone (4).

Magnesium turnings (0.03 g, 1.25 g-atom) previously washed with pentane, ether and oven dried was introduced into a three-necked round-bottomed flask (25 ml) containing anhydrous ether (10 ml) under N_2.

Iodomethane (1 ml, large excess) was then injected via a serum cap into the flask. The ether became turbid and in about $\frac{1}{2}$ h the magnesium turnings had been consumed forming the expected Grignard reagent.

A solution of (49) (0.192 g, 0.99 mM) in anhydrous ether (5 ml) was then injected and an instant reaction was observed. Stirring was continued

at room temperature for 3 h. Dilute H_2SO_4 (20%) was added whilst stirring continued for another 1 h.

Upon work up, an oil was obtained (0.15 g) lacking in -OH absorption as shown by i.r— and still containing the ether function as shown by n.m.r— spectra. The product was then taken up in AR-acetone previously purged with N_2, to which dil-HCl (5 ml) was added and mixture stirred at room temperature overnight. Normal work up afforded 0.104 g (81.25%) of the title compound as a light yellow oil.

^1H NMR $CDCl_3$: (τ) 3.80 - 4.56 (m, 1H), 4.80 - 5.28 (m, 2H), 7.42 - 8.40 (m, 10H), 8.09 (s, 3H).

6. m-Methylphenoxyethyl bromide (54).

m-Cresol (30 g, 0.28 mol) was dissolved in aqueous solution of sodium hydroxide (15 g, 0.375 mol). 1,2-Dibromoethane (104 g, 0.55 mol) was then added under an atmosphere of N_2 and mixture refluxed overnight. The contents of the reaction flask allowed to cool to room temperature and excess dibromoethane removed at reduced pressure. The residue was then taken up in ether (100 ml) and washed several times with 1N - NaOH, dried ($MgSO_4$) and solvent removed under reduced pressure. The crude product was then distilled (80^o / 0.1 mm) giving (40.8 g, 68.3%) of the title com-

pound as a light yellow oil.

^{1}H NMR $CDCl_3$: (τ) 3.15 (m, 4H), 5.85 (t, 2H), 6.50 (t, 2H), 7.70 (s, 3H).

7. m-Methylphenoxyethyldiethylamine[3] (55).

m-Methylphenoxyethyl bromide (54, 20.0 g, 0.093 *mol*) in *ether* (50 ml) was refluxed with three-fold quantity of diethylamine (20.4 g, 0.28 mol). After about 3 h a large quantity of white solid precipitated. Heating continued for another 2 h after which the reaction mixture was allowed to cool, the solid filtered off and excess diethylamine was removed under reduced pressure. The amino ether product expected was then extracted with 2N - HCl (3 x 20 ml) portions. Combined acid extracts were then neutralised with saturated $NaHCO_3$ and organic matter taken up in ether, washed with brine, dried ($MgSO_4$) and removal of solvent afforded 16.32 g (84.8%) of the title compound, after distillation (120°/0.1 mm), as a colourless oil. On standing a faint yellow colour develops which eventually turns dark yellowish-brown.

^{1}H NMR $CDCl_3$: (τ) 3.15 (m, 4H), 6.0 (t, 2H), 7.0 - 7.6 (m, 6H), 7.72 (s, 3H), 8.98 (t, 6H).

IR (film) ν_{max} (cm^{-1}) : 3025 (w), 2955 (vs), 2915 (s), 2855 (s), 2795 (s), 1600 (s), 1585 (s), 1485 (s), 1285 (s), 1260 (s).

M/S (m/e) : 207 (M^+), 135 ($M^+ - C_4H_{10}{}^+N$), 107 ($M^+ - C_6H_{14}{}^+N$), 100 ($M^+ - C_7H_7O^+$), 72 ($M^+ - C_9H_{11}{}^+O$).

8. Sodium-liq Ammonia reduction of m-Methylphenoxyethyldiethylamine (56).

A solution of m-methylphenoxyethyldiethylamine (10.35 g, 0.05 mol) in anhydrous absolute ethanol (13.11 g, 0.285 mol) and sodium dried ether (25 ml) were introduced into a 1 L-three-necked round-bottomed flask bearing dry-cold condenser. Ammonia (ca 300 ml) was then distilled into the flask. Sodium metal (6 g, 0.26 g-atom) was then added in small pieces as the blue colour formed disappeared. Addition of sodium continued until the blue colour persisted for about 40 min. The cold finger was then removed, and reaction quenched with 50 ml 1 : 1 95% ethanol water mixture and a further 25 ml of ether was added.

Ammonia was allowed to evaporate slowly as the reaction mixture warmed to room temperature. Normal work up, afforded 9.20 g (88%) of title compound almost colourless oil.

In another reaction, the dihydro compound was distilled at 120°/ 0.1 mm obtained as a colourless oil.

^1H NMR $CDCl_3$: (τ) 4.68 (bs, 1H), 5.43 (bs, 1H), 6.26 (t, 2H), 7.38 (m, 10H), 8.36 (bs, 3H), 8.98 (t, 6H).

IR (film) ν_{max} (cm^{-1}) : 3030 (s), 2960 (s), 2920 (s), 2860 (s), 2810 (s), 1700 (w), 1665 (m), 1215 (s), 1135 (s).

9. Cyclopropyl carbethoxymethyl ketone (65).

(a) Sodium hydride (50% dispersion in oil, 19.2 g, 0.4 mol) was suspended in dry benzene (50 ml) under an atmosphere of N_2. Diethyl carbonate (distilled from CaH_2, 40^o / 18 mm, 41.4 g, 0.35 mol) also dissolved in dry benzene (25 ml) was slowly introduced to the flask containing the suspension of sodium hydride and the mixture stirred for $\frac{1}{2}$ h. A solution of cyclopropyl methyl ketone (64, b.p. 110 - 112°, 16.2 g, 0.2 mol) in dry benzene (25 ml) was added dropwise to the suspension formed, over a period of $\frac{1}{2}$ h after which the N_2 flow was stopped and stirring continued overnight.

The reaction mixture suddenly became very hot after stirring had continued for a further 1 h forming a thick slurry. Benzene (100 ml) was then introduced to facilitate stirring. The reaction mixture was poured carefully into a mixture of ether (200 ml), ice-water (100 ml) and

glacial acetic acid (4 ml) with swirling. The organic layer was separated, washed with saturated sodium bicarbonate to neutrality and dried (Na_2SO_4). Removal of solvent and distillation of crude product afforded 17.0 g (56.5%, 68°/0.1 mm) of title compound.

^1H NMR $CDCl_3$: (τ) 5.84 (q, 2H), 6.44 (s, 2H), 7.92 (m, 1H), 8.70 (t, 3H), 9.0 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 2970 (s), 2920 (m), 1740 (vs), 1700 (vs), 1620 (w), 1380 (vs), 1260 (s).

(b) Modification of procedure (a) by W. S. Johnson et al.[4]

Sodium hydride (50% dispersion in oil, 12.0 g, 0.25 mol) was washed with 3 x 10 ml portions of dry petroleum ether (b.p. 40 - 60°C) under N_2. Diethylcarbonate (dry and dist. 50 ml) was introduced en bloc and the suspension stirred whilst a solution of cyclopropylmethyl ketone (64, 20.0 g, 0.24 mol) in diethylcarbonate (10 ml) was introduced. A few drops of absolute ethanol was added to initiate the reaction. After the addition was complete, the mixture was stirred for ½ h at room temperature. It was then heated on the steam bath until a steady evolution of hydrogen was observed. Heating continued until gas evolution ceased (about 1½ h). The mixture was cooled and worked as in (a) above. Distillation of

crude product afforded 25.9 g (70%) of the title compound as a colourless oil.

This second procedure could easily go out of control especially if a large scale preparation is involved. The reaction is exothermic and with production of hydrogen, the reaction mixture could easily be forced out of the reaction flask.

10. 1-Cyclopropyl-1-carbethoxy-3-(p-methoxyphenethyl)-ketone (66).

Sodium ethoxide (1.32 g of sodium metal in dry absolute ethanol, followed by distillation of the ethanol* to dryness) was dissolved in dry THF (40 ml) and the solution cooled to -40°C under N_2. A solution of cyclopropylcarbethoxymethyl ketone (9.0 g, 0.058 mol) in THF (150 ml) was then added to the cold solution of sodium ethoxide over $\frac{1}{2}$ h. A 60 ml portion of THF was further added to increase dilution of the sodium enolate being formed. Stirring was continued for a further 1 h.

p-Methoxybenzyl chloride (9.024 g, 0.058 mol) in THF (100 ml) was then introduced and stirred vigorously over $\frac{1}{2}$ h. The bath temperature

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* It was necessary to distil off the ethanol because alcoholysis of p-methoxybenzyl chloride, giving the corresponding ether was observed in a reaction where NaOEt / EtOH was used.

was maintained between -30°C to -40°C throughout the period of this operation. Stirring continued overnight as the bath was allowed to warm gradually to room temperature. A massive deposit of sodium chloride was obtained. THF was removed by distillation on the rotary evaporator. The salt produced was dissolved in minimum volume of water and solution neutralised with dilute HCl.

Organic matter was extracted into ether (180 ml), washed to neutrality with saturated $NaHCO_3$ solution and dried ($MgSO_4$). Removal of solvent afforded 14.58 g of crude product shown by n.m.r. spectrum to contain both mono- and di-alkylation products.

Separation was effectively carried in the next procedure from which 2.51 g of dialkylation product was obtained leaving 12.07 g (75.8%) of title compound, (66, R = $-CH_2\ C_6H_4OMe\underline{p}$) as a yellow oil.

^1H NMR $CDCl_3$ of dialkylation product.

: (τ) 3.12 (dq, 8H), 5.80 (q, 2H), 6.30 (s, 6H), 6.85 (s, 4H), 7.85 (t, 3H), 8.30 (m, 1H), 9.0 - 9.30 (m, 4H).

M/S (m/e) : 396 (M^+), 275 ($M^+ - OMe.C_6H_4CH_2^+$), 229 ($M^+ - OMe.C_6H_4CH_2^+ - C_2H_5^+$), 201 ($M^+ - OMe.C_6H_4.CH_2^+ - CO_2Et$).

M.M. Found : 396.1941

$C_{24}H_{28}O_5$ requires 396.1937.

A sample was prepared for analysis by crystallisation from methanol, m.p. 86 - 88°C.

		% C	% H
	Found	72.9	7.1
$C_{24}H_{28}O_5$	requires	72.7	7.1

11. 1-Cyclopropyl-1-p-methoxylphenethyl ketone (69).

1-Cyclopropyl-3-carbethoxy-3-p-methoxyphenethyl ketone (12.07 g, 0.044 mol) in 25 ml 95% EtOH was added to ethanolic potash (2.5 g KOH in 30 ml 95% EtOH) and mixture stirred at room temperature. Some oil globules were observed to settle at the bottom of the reaction flask and on stirring for another 15 min a white crystalline solid was observed to separate. This was easily removed by filtration and was shown by n.m.r. and mass spectra to be the dialkylation product, 1-cyclopropyl-3-carbethoxy-3-bis(p-methoxyphenethyl) ketone. This proved to be the most efficient method of separating the mono- and di- alkylation products.

Stirring was then continued overnight. The ethanol was removed on the rotary evaporator, the mixture acidified with dil. HCl until it was just acidic and the keto acid obtained (including some of the title compound) was then extracted into ether, dried ($MgSO_4$) and solvent distilled off giving 9.92 g of partially decarboxylated keto acid. This was immed-

iately subjected to heating on the steam bath for 1 h. It was then taken up in ether, washed with saturated $NaHCO_3$, dried ($MgSO_4$) removal of solvent yielded 7.86 g (88%) based on the ketoester (66)

^1H NMR $CDCl_3$: (τ) 3.10 (dq, 4H), 6.30 (s, 3H), 7.20 (s, 4H), 8.20 (m, 1H), 9.15 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 3000 (m), 2940 (m), 2820 (m), 1680 (vs), 1610 (m), 1510 (vs), 1385 (m), 1240 (vs).

M/S (m/e) : M^+ (204), 173 (M^+ - OMe), 83 (M^+ - OMe. $C_6H_4CH_2^+$).

M.M. Found : 204.1150

$C_{13}H_{16}O_2$ requires 204.1157

12. 1-Cyclopropyl-1-p-methoxyphenethylcarbinol (72).

The ketone (3.3 g, 0.0162 mole) in methanol (15 ml) was cooled in ice-bath whilst sodium borohydride (1 g, 0.026 mol) was being added in small amounts. After all the borohydride had been added, stirring continued for about 1½ h. The reduction was followed by t.l.c.

The methanol was then removed on the rotary evaporator, the solid formed was dissolved in water and brine. The carbinol was then extracted with ether, dried ($MgSO_4$) and solvent removed, affording 2.98 g (89.5%).

^1H NMR $CDCl_3$: (τ) 2.95 (dq, 4H), 6.28 (s, 3H), 6.80 - 7.50 (m, 3H, $-CH_2$ + O<u>H</u>), 7.80 - 8.40 (m, CH_2 + C<u>H</u>), 8.6 - 9.30 (m, 1H), 9.30 - 9.90 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 3380 (b, vs), 3070 (w), 3000 (m), 2920 (s), 2820 (m), 1610 (s), 1510 (s), 1240 (s), 1030 (s).

13. <u>trans</u>-1-Bromo-6-<u>p</u>-methoxyphenylhex-3-ene (75).

A mixture of the previously mentioned carbinol (2.9 g, 0.014 mol), 1.454 g of collidine, 1.216 g (0.014 m) of anhydrous lithium bromide in dry ether (30 ml) was cooled to -40°C and stirred magnetically whilst excess phosphorus tribromide was added over a few minutes. After the addition was complete, the mixture was allowed to warm up to -5°C → 0° and kept at this temperature for further 1½ h.

2.5 ml of collidine was added, followed by water (slowly and with stirring) to destroy excess phosphorus tribromide. The resulting mixture was then extracted with pentane (150 ml) dried (Na_2SO_4) and solvent removed under pressure.

The residue obtained (3.2 g) was added slowly with stirring to a cooled suspension of anhydrous zinc bromide (4.8 g) at -40°C in dry ether

(15 ml). The mixture was then allowed to warm up to 0° and left at this temperature for a further 1½ h. Pentane and 50% saturated brine were added and the aqueous layer was further extracted with pentane. The combined organic extracts were washed with saturated brine and dried (Na_2SO_4). A pale yellow oil was obtained upon evaporation of the solvent under reduced pressure. Distillation (100°/0.1 mm bulb-to-bulb) afforded 2.8 g (73.8%) of title compound as a colourless oil.

^1H NMR $CDCl_3$: (τ) 3.10 (dq, 4H), 4.55 (m, 2H), 6.30 (s, 3H), 6.70 (t, 2H), 7.50 (m, 6H).

IR (film) ν_{max} (cm^{-1}) : 2990 (w), 2950 (bm), 2830 (w), 1610 (w), 1510 (w), 1250 (vs), 1040 (s).

M/S (m/e) : 269 (M^+), 189 (M^+ - Br), 188 (M^+ - HBr), 148 (M^+ - C_8H_9O).

M.M. Found : 269.0463

$C_{13}H_{17}OBr$ requires 270.0463

14. 2-(Δ^3-6-p-Methoxyphenylhexenyl)-3-methyl-2-cyclohexenone (60).

To a solution of the amino enol ether (56, 2.71 g, 0.0129 mol) in anhydrous THF (20 ml) at -78°C under N_2 was added n-BuLi (.8906 g, 0.0139 mol 9.3 ml of 1.5 mM/ml solution in hexane) and mixture was stirred for

1 h. HMPA (2.49 g, 0.0139 mol) in THF (5 ml) was then added and allowed to stir for 5 min before the bromide (75, 3.40 g, 0.0126 mol) was added and reaction mixture was allowed to warm to room temperature. Normal work up gave 5.55 g of crude alkylation product without any trace of any unreacted bromide as shown by n.m.r. spectrum.

^1H NMR $CDCl_3$ τ 3.12 (dq, 4H), 4.62 (m, 3H), 5.38 (m, 1H), 6.30 (5H singlet (OCH_3) superimposed on triplet ($-OCH_2-$), 7.44 (m, 17H), 8.35 (bs, 3H), 9.0 (t, 6H).

The product was immediately subjected to acid hydrolysis - 15 ml 2N - HCl and 20 ml AR acetone, previously purged - under N_2 and normal work up afforded 3.7 g (89%) of the title compound as a yellow oil.

^1H NMR $CDCl_3$: (τ) 3.05 (dq, 4H), 4.58 (m, 2H), 6.25 (s, 3H), 7.25 - 8.1 (m, 14H), 8.20 (s, 3H).

IR (film) ν_{max} (cm^{-1}) : 2990 (s), 2930 (s), 2850 (w), 1670 (s), 1630 (w), 1610 (m).

M/S (m/e) : 298 (M^+), 171 (M^+ - $MeO.C_6H_4.CH_2^+$), 280 (M^+ - H_2O), 267 (M^+ - OMe).

15. Epoxidation of 2-(Δ^3-6-p-Methoxyphenylhexenyl-)-3-methyl-2-cyclohexenone (60).

A solution of ketone (60, 3 g, 0.01 mol) in methanol (25 ml) and hydrogen peroxide (30%, 3.4 ml, 0.03 mol) was cooled to 15°C after which sodium hydroxide (6N, 3.33 ml, 0.02 mol) was added over a period of 5 min. The reaction mixture was stirred and temperature was maintained below 20°C. After 6 h it was shown by t.l.c. that the reaction was not complete and a further charge of hydrogen peroxide and sodium hydroxide same ratio as above was added. After 2 h the reaction was still not complete, hence the reaction was worked up and put back under the same conditions when the remaining ketone was cleanly converted to the expected epoxide (78) shown by t.l.c. to be one spot pure.

The reaction was worked up by removing the methanol at reduced pressure, diluting the residue with half-saturated brine, extracting into ether and washing the ether extract once or twice with brine and finally with water. Drying ($MgSO_4$) and removal of solvent afforded 2.4 g (75.9%) of the title compound as a yellow oil.

^1H NMR $CDCl_3$: (τ) 3.10 (dq, 4H), 4.60 (m, 2H), 6.34 (s, 3H), 7.22 - 8.64 (m, 16H), 8.60 (s, 3H).

IR (film) ν_{max} (cm^{-1}) : 2920 (s), 2840 (w), 1700 (vs), 1610 (w), 1510 (s), 1245 (vs), 1030 (m).

M/S (m/e) : 314 (M^+), 296 ($M^+ - H_2O$), 193 (M^+ - MeO. $C_6H_4\overset{\oplus}{C}H_2$), 283 ($M^+$ - OMe).

16. Reaction of epoxide (78) with boron trichloride in dichloromethane at -78°C.

To a solution of boron trichloride (a large excess) in dichloromethane (15 ml) at -78°C was added a solution of epoxide (78, 320 mgs, 1.02 mM) in dichloromethane (2 ml) over 5 min and reaction mixture stirred for 2 h.

The reaction was quenched by addition of 5 ml of aqueous sodium bicarbonate, whilst the reaction mixture warmed to room temperature. Organic matter was then extracted into dichloromethane, washed to neutrality with saturated sodium bicarbonate, water and then dried (Na_2SO_4). A dark brown oil was obtained upon removal of solvent (342 mgs). Separation by column chromatography (ether : hexane 1 : 2) on silica gel was carried out. A preparative thin layer plate was used in isolation of individual compounds.

Fraction 1 was obtained as a light yellow oil, (46.1 mgs, 18.4% of product). I.R. ν_{max} (cm^{-1}) shows a strong absorption at 1745 and 1710 for the five-membered ring ketone and side-chain carbonyl function indicating this fraction to be the ring contracted product (85, R = $(CH_2)_2CH$ = CH $(CH_2)_2$ C_6H_4OMe-p).

Fraction 2, also obtained as a yellow oil composed largely of chlorohydrin (86, 13.4 mgs, 5.4%) characterised by the $-C\underline{H}_3$ group at τ8.5 and presence of the olefinic protons at τ 4.52.

Fraction 3 was obtained as a colourless oil crystallising as colourless crystals (127.5 mg, 51%) and was shown to be compound (84).

^{1}H NMR $CDCl_3$ (90 MHz) : (τ) 3.05 (q, 4 H), 6.26 (s, 3H), 7.10 - 8.70 (m, 17H), 9.08 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 3600 (w), 2930 (s), 1610 (w).

M/S (m/e) : 350 (M^+), 314 (M^+ - HCl), 296 (M^+ - HCl - H_2O), 175 (M^+ - HCl - H_2O - $MeO.C_6H_4CH_2^+$).

A sample was recrystallised from petroleum ether (b.p. 60 - 80°) for elemental analysis (m.p. 126 - 7°).

		% C	% H
	Found :	68.9	7.9
$C_{20}H_{27}O_3Cl$	requires	68.5	7.7

Fraction 4 obtained as a yellow oil crystallising on standing as colourless crystals (83, 29.8 mgs, 12% m.p. 140 - 3°) crude.

^{1}H NMR $CDCl_3$ (80 MHz) : (τ) 3.04 (dq, 4H), 5.15 - 5.48 (m, 1H, $W_{\frac{1}{2}}$ = 22.2 Hz), 6.23 (s, 3H), 7.12 - 8.52 (m, 17H), 9.26 (s, 3H).

IR ν_{max} (cm^{-1}) CH_2Cl_2 : 3590 (w), 3560 (w, b).

M/S (m/e) : 350 (M^+), 315 (M^+ - Cl), 314 (M^+ - HCl), 296 (M^+ - HCl - H_2O), 121 ($OMe.C_6H_4CH_2^+$).

M.M. Found : 350.1648

$C_{20}H_{27}O_3Cl$ requires 350.1649.

Fraction 5 was obtained as a colourless oil which also crystallised immediately on standing, as colourless crystals, m.p. 143 - 5° after one recrystallisation from carbon tetrachloride (10.42 mgs, 4.2%).

^1H NMR 90 MHz (82) : (τ) 3.04 (d, 1H, J = 8.5 Hz), 3.8 (d, 1H, J = 2.7 Hz), 3.34 (dd, 1H, J = 8.5 Hz, 2.7 Hz), 6.23 (s, 3H), 7.0 - 8.80 (m, 17H), 8.92 (s, 3H).

IR ν_{max} (cm^{-1}) CH_2Cl_2 : 3570 (m), 2930 (w, b), 1710 (s), 1608 (w).

M/S (m/e) : 314 (M^+), 296 (M^+ - H_2O), 283 (M^+ - OMe).

M.M. Found : 314.1885

$C_{20}H_{26}O_3$ requires 314.1882

17. 1-Cyclopropyl-1-carbethoxy-3-m-methoxyphenethyl ketone (67).

The same procedure in Experiment 10 was followed. Cyclopropyl-carbethoxymethyl ketone (65, 10 g, 0.064 M) in THF (60 ml) was reacted

with m-methoxybenzyl bromide (12.88 g, 0.064 M, made from the corresponding carboxylic acid by standard methods) in THF (100 ml), and NaOEt (15 g Na/EtOH) in THF (140 ml) to give 16.8 g of crude alkylation product upon work up. Both mono- (67) and di- alkylation products were formed, and the latter was isolated (4.1 g) as very dense oil upon treatment of the mixture with alcoholic potash as before, leaving (12.7 g, 71.8%) of the desired product.

^{1}H NMR $CDCl_3$: (τ) 2.90 (m, 1H), 3.25 (m, 3H), 5.56 - 6.15 (4H, q + t), 6.25 (s, 3H), 6.85 (d, 2H), 7.65 - 8.40 (m, 1H), 8.80 (t, 3H), 8.85 - 9.25 (m, 4H).

18. 1-Cyclopropyl-1-m-methoxyphenethyl ketone (70).

A solution of (67) in alcoholic potash (KOH, 1 : 1 95% EtOH : H_2O) overnight and normal work up afforded 8.2 g of crude keto acid which was immediately subjected to decarboxylation by heating on a steam-bath for 1 h. The crude ketone was then taken up in ether, (50 ml) washed with 3 x 10 ml portions of saturated $NaHCO_3$, once with water, dried ($MgSO_4$) and solvent distilled off to give 6.98 g, (74.4%) of title compound.

^{1}H NMR $CDCl_3$: (τ) 2.90 (m, 1H), 3.33 (m, 3H), 6.35 (s, 3H), 7.30 (s, 4H), 8.20 (m, 1H), 9.20 (m, 4H).

IR (Film) ν_{max} (cm^{-1}) : 3000 (m), 2930 (b, m), 2820 (w), 1685 (vs), 1610 (s), 1600 (s), 1580 (s) and 1150 (b,m).

	%C	%H
Found :	77.1	8.0
$C_{13}H_{16}O_2$ requires	76.5	7.8

19. 1-Cyclopropyl-1-m-methoxyphenethylcarbinol (73).

To a solution of the ketone (70, 6.98, 0.03 mol) in methanol (25 ml) kept at ice-bath temperature was added sodium borohydride (1.5 g, 0.039 mol) in small amounts over 45 min with stirring. The reduction was followed by t.l.c. Normal work up afforded 6.6 g (93.6%) of title compound as a colourless oil.

^{1}H NMR $CDCl_3$: (τ) 3.15 (m, 4H), 6.28 (s, 3H), 7.0 - 7.50 (m, 3H), 7.80 - 8.35 (m, 3H), 8.70 - 9.30 (m, 1H), 9.30 - 9.90 (m, 4H). Addition of D_2O showed that -OH was under 7.80 - 8.35.

IR (film) ν_{max} (cm^{-1}) : 3400 (bs), 3070 (w), 2990 (s), 2920 (s),

2830 (w), 2820 (w), 1600 (vs), 1580 (s), 1485 (s).

20. trans-1-Bromo-6-m-methoxyphenyl-hex-2-ene (76).

The same procedure as for preparation of (75) was followed.

A mixture of carbinol (73, 6.6 g, 0.032 mol) collidine (3.9 g, 0.032 mol), lithium bromide (3.16 g, 0.036 mol) was cooled to -40°C and stirred whilst phosphorus tribromide (4.03 g, 0.015 mol) was added over a few minutes. The temperature was allowed to warm up to -5°C → 0°C and maintained at this temperature for $1\frac{1}{2}$ h.

Normal work up afforded 6.4 g of corresponding carbinyl bromide which was rearranged with zinc bromide (10.13 g, 0.070 M) giving 5.7 g of crude product which was further purified by distillation (120°/0.1 mm) affording 5.18 g (60.3%) of title compound.

^1H NMR $CDCl_3$: (τ) 2.85 (m, 1H), 3.25 (m, 3H), 4.52 (m, 2H), 6.25 (s, 3H), 6.18 (bt, 2H), 7.50 (m, 6H).

IR (film) ν_{max} (cm^{-1}) : 2980 (w), 2920 (m), 2840 (b, s), 2820 (m), 1600 (vs), 1580 (s), 1485 (s), 1260 (vs).

M/S (m/e) : 269 (M^+), 189 (M^+- Br), 148 (M^+-MeO.$C_6H_4CH_2^+$).

Elemental Analysis

		%C	%H	%Br
	Found	58.1	6.2	29.5
$C_{13}H_{17}OBr$	requires	58.0	6.3	29.7

21. 2-(Δ^3-6-m-Methoxyphenyl-)-3-methyl-2-cyclohexenone (61).

To a solution of the amino enol ether (56, 3.67 g, 17.5 mM) in THF (15 ml) at -78°C was added n-BuLi (1.125 g, 17.5 mM) under N_2 and with stirring for 1 h. HMPA (3.147 g, 17.5 mM) in THF (10 ml) was then added stirring for 10 min after which the bromide (76, 4.612 g, 17 mM) was added.

The cooling bath was then removed to allow reaction mixture to warm up to just below room temperature when the reaction was quenched, and normal work up afforded 6.90 g of crude alkylation which was immediately subjected to hydrolysis as usual yielding 4.4 g (85%) of title compound as a yellow oil.

^1H NMR $CDCl_3$: (τ) 3.10 (m, 4H), 4.55 (m, 2H), 6.25 (s, 3H), 7.10 - 8.0 (m, 14H), 8.2 (s, 3H).

IR (film) ν_{max} (cm^{-1}) : 2920 (s), 2830 (w), 1660 (s), 1620 (w), 1600 (m), 1480 (w), 1255 (m), 1140 (m), 1040 (m).

t.l.c. indicated the reaction to have gone essentially to completion.

Normal work up afforded 0.58 g (74.4%) of title compound as a light yellow oil.

^{1}H NMR $CDCl_3$: (τ) 3.15 (m, 4H), 4.55 (m, 2H), 6.20 (s, 3H), 7.10 - 8.40 (m, 14H), 8.60 (s, 3H).

IR (film) ν_{max} (cm^{-1}) : 2920 (s), 2840 (w), 1700 (s), 1600 (s), 1585 (bm), 1260 (m), 1040 (m).

23. Treatment of epoxide (79) with BCl_3 in CH_2Cl_2 at -78°C.

To a solution of boron trichloride (excess) in dichloromethane (10 ml) at -78°C under nitrogen was added a solution of the epoxide (200 mg, 2.5 ml CH_2Cl_2) over 5 min and reaction stirred for 1 h. Normal work up afforded four products which were isolated by combined column and preparative t.l.c. methods using ether : pet. ether (40 - 60°) 1 : 1.

Fraction 1 (R_f 0.25) (89) was obtained as a colourless oil which cystallised on standing m.p. 180 - 182°C (19.8 mg, 9.4% of product).

^{1}H NMR $CDCl_3$ (300 MHz) : (τ) 2.82 (d, 1H, J = 9 Hz), 3.29 (dd, 1H, J = 9 Hz, J = 3 Hz), 3.40 (d, 1H, J = 3 Hz),

6.19 (s, 1H, O<u>H</u>), 6.23 (s, 3H), 7.1 - 8.8 (m, 16H), 8.93 (s, 3H).

ν_{max} (cm^{-1}) CCl_4 : 3590 (w), 2920 (s), 1710 (s).

M/S (m/e) : 314 (M^+), 296 ($M^+ - H_2O$), 299 ($M^+ - CH_3$).

M.M. Found: 314.1883

$C_{20}H_{26}O_3$ requires 314.1882

<u>Fraction 2</u> (R_f 0.40) was also obtained as a colourless oil, crystallising to give colourless crystals on standing, (m.p. 152 - 3°). N.m.r. spectrum shows this fraction to be the bicyclic compound (90) (120 mgs, 56.7% of product).

^1H NMR $CDCl_3$ (300 MHz) : (τ) 2.80 (t, 1H), 3.28 (t, 3H), 5.82 (m, 1H, $W_{\frac{1}{2}}$ 22.5 Hz), 6.22 (s, 3H), 7.10 - 8.80 (m, 16H), 9.03 (s, 3H).

ν_{max} (cm^{-1}) CCl_4 : 3590 (w), 3558 (b, w), 2940 (s), 1715 (s).

M/S (m/e) : 350 (M^+), 315 ($M^+ - Cl$), 314 ($M^+ - HCl$), 296 ($M^+ - HCl - H_2O$).

M.M. Found : 350.1647

$C_{20}H_{27}O_3Cl$ requires 350.1649.

<u>Fraction 3</u> (R_f 0.54, 42.0 mg, 19.9% product) corresponds to the chlorohydrin, 88 (R = $-(CH_2)_2CH = CH(CH_2)_2\ C_6H_4.OMe\text{-}\underline{m}$).

Fraction 4 (R_f 0.75, 29.35 mgs, 13.9% of product) proved to be the ring contracted product (87).

24. 1-Cyclopropyl-1-carbethoxy-3-propynyl ketone (68).

Sodium ethoxide (2.34 g of Na metal in ethanol, followed by removal of ethanol) in dry THF (50 ml) was cooled to -40°C under N_2. The keto ester (65, 15.93 g, 0.102 M) in THF (25 ml) was then added slowly over ½ h keeping the temperature between -30 to -40°C throughout the addition, with stirring. Propargyl (prop-2-ynyl) bromide (98%, 80% by weight in toluene, redistilled (88 - 92°C), 12.152 g, 0.105 M) in dry THF (100 ml) was added slowly also over ½ h, stirring vigorously and still keeping the temperature within the range mentioned above. The mixture was stirred for a further ½ h after which the cooling-bath was removed to allow the reaction mixture to warm gradually to room temperature, stirring overnight. A dense white precipitate was observed to form.

Normal work up yielded 19.4 g of crude alkylation product. Dialkylation product (0.8 g) was isolated as before from alcoholic potash, leaving 18.6 g (78.5%) of the desired monoalkylation product (68) as a yellow oil.

Samples of both compounds were then purified for n.m.r. spectroscopy.

^1H NMR $CDCl_3$ (68) : (τ) 5.82 (q, 2H, J = 6.8 Hz), 6.98 (d, 2H, J = 2.7 Hz), 7.26 (dd, 1H, J = 2.7 Hz),

M/S (m/e) : 298 (M^+), 177 (M^+ - $MeO.C_6H_4CH_2^+$), 280 (M^+ - H_2O).

M.M. Found : 298.1930

$C_{20}H_{26}O_2$ requires 298.1933

A sample was purified for elemental analysis by column chromatography (Hexane : Ether 1 : 1 on silica gel).

		%C	%H
	Found :	80.1	8.7
$C_{20}H_{26}O_2$	requires	80.5	8.7

22. 2,3-Epoxy-3-methyl-2-(m-methoxyphenylhex-3'-enyl)-cyclohexanone (79).

A solution of the ketone (61, 738 mg, 2.69 mM) in methanol (15 ml) and hydrogen peroxide (30%, 0.77 ml, 8.08 mM) was cooled to 15°C and 6N-NaOH (0.225 ml, 1.35 mM) was added dropwise with stirring. After stirring for about 15 min more, the water-bath was removed to allow the mixture to warm to room temperature. After 2 h t.l.c. showed no appreciable conversion to the epoxy ketone, hence the mixture was further charged with 0.7 ml of H_2O_2, 0.2 ml 6N-NaOH. A similar charge was added after a further 1 h of stirring finally leaving overnight; after which

7.62 - 8.12 (m, 2H), 8.72 (t, 3H, J = 6.8 Hz), 8.85 - 9.22 (m, 4H).

^{1}H NMR $CDCl_3$ of the dialkylation product : (τ) 5.75 (q, 2H, J = 6.8 Hz), 7.0 (d, 4H, J = 2.5 Hz), 7.95 (m, 3H), 8.72 (t, 3H, J = 6.8 Hz), 8.95 (m, 4H).

M/S (m/e) : 232 (M^+), 203 ($M^+ - C_2H_5^+$), 193 ($M^+ - C_3H_3^+$), 188 ($M^+ - CO_2$), 159 ($M^+ - CO_2Et$).

M.M. Found : 232.1094

$C_{14}H_{16}O_3$ requires 232.1099

A sample was recrystallisation for analysis from methanol (m.p. 80 - 81°C).

		%C	%H
	Found	72.8	6.9
$C_{14}H_{16}O_3$	requires	72.4	6.9

25. 1-Cyclopropyl-3-propynyl ketone (71).

The monoalkylation product, (18.6 g) was then subjected to hydrolysis with alcoholic potash, as usual, and normal work up afforded 7.1 g of

partially decarboxylated keto acid; which was subjected to decarboxylation by heating on the steam bath for 1 h. Work up afforded 6.2 g of the desired ketone, 1.65 g more was later isolated as neutral component in the process of purifying the keto acid by extraction into $NaHCO_3$, giving a total yield of 7.85 g (67%) of title compound.

^1H NMR $CDCl_3$: (τ) 7.35 (m, 4H), 8.0 (m, 2H), 8.95 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 3285 (vs), 3000 (w), 2920 (w), 1690 (vs), 1430 (w), 1380 (s).

A sample was purified by column chromatography (hexane : ether 1 : 1, on silica gel) for analysis.

		%C	%H
	Found :	78.3	8.1
$C_8H_{10}O$	requires	78.7	8.2

26. 1-Cyclopropyl-3-propynyl carbinol (74).

A solution of the ketone (71, 3.075 g, 0.025 mol) in methanol (15 ml) was cooled in ice-water bath whilst $NaBH_4$ (1.25 g, 0.033 mol) was added

in small amounts with stirring over $\frac{1}{2}$ h. The reaction mixture was allowed to stir for another $2\frac{1}{2}$ h by which time t.l.c. had indicated complete conversion to the carbinol.

Normal work up afforded 2.95 g (95.5%) of title compound.

^{1}H NMR $CDCl_3$: (τ) 7.00 (m, 1H), 7.70 (m, 3H), 8.10 (m, 2H), 9.10 (m, 1H), 9.60 (m, 4H).

IR (film) ν_{max} (cm^{-1}) : 3600 - 3400 (bs), 3300 (vs), 3080 (w), 3000 (m), 2920 (m), 1630 (w).

27. trans-1-Bromo-3-en-oct-7-yne (77).

Triphenylphosphine[8] (6.98 g, 26.61 mM) was added to a solution of the carbinol (74, 2.2 g, 17.74 mM) in methylene chloride (25 ml) under N_2. N-Bromosuccinimide, NBS (4.74 g., 26.61 mM) was then added in small amounts until it dissolved before further addition. If added too quickly the solvent starts to reflux and should be cooled. After all the NBS was added, the reaction was stirred for another 15 min after which the solvent was removed on the rotary evaporator leaving behind a dense brown oil which solidifies on trituration in pentane with cooling. The solid was then filtered off and removal of solvent gave the product still containing traces of triphenylphosphine oxide and/or triphenylphosphine.

The pure compound is obtained by distillation (2.72 g, 81.9%). This cyclopropyl carbinyl bromide was then rearranged as usual with anhydrous zinc bromide (4.8 g) in anhydrous ether. Normal work up afforded 1.54 g (56.6%) after distillation (120^{o}/ 20 mm). The bromide is extremely volatile and an appreciable amount is often lost during work up.

^{1}H NMR $CDCl_3$: (τ) 4.40 (m, 2H), 6.65 (t, 2H), 7.35 (m, 2H), 7.65 (m, 4H), 7.95 (m, 1H).

IR (film) ν_{max} (cm^{-1} : 3300 (vs), 2920 (s), 2840 (m), 1715 (vs), 1430 (bm), 970 (m).

M/S (m/e) : 187 (M^{+}), 107 (M^{+}- Br), 148 (M^{+}- $C_3H_3^{+}$), 106 (M^{+}- HBr).

28. 2-($\Delta^{3,7}$-Oct-en-ynyl-)-3-methyl-2-cyclohexenone (63).

The procedure for alkylation is as already described, (Experiment 14). To a solution of the amino enol ether (56, 1.186 g, 5.67 mM) in THF (15 ml) at $-78^{o}C$ under N_2 was added n-BuLi (0.363 g, 5.67 mM) with stirring for 1 h. HMPA (1.016 g, 5.67 mM) was then added stirring for 10 min after which the bromide (77, 1.1 g, 5.88 mM) was added. The cooling bath was then removed and normal work up yielded 1.746 g of crude alkylation product which was immediately subjected to acid hydrolysis

(10 ml 2N-HCl + 20 ml acetone) under N_2. Work up afforded 0.958 g (83.3%) title compound as a yellow oil.

^1H NMR $CDCl_3$: (τ) 4.53 (m, 2H), 7.75 (m, 14H), 8.15 (bs, 4H composed $-C\underline{H}_3$ and $-C \equiv CH$.

IR (film) ν_{max} (cm^{-1}) : 3285 (m), 2915 (vs), 2845 (m), 1660 (vs), 1625 (m), 1425 (m), 1375 (m).

M/S (m/e) : 216 (M^+), 177 ($M^+ - C_3H_3^+$), 123 ($M^+ - C_7H_9^+$).

A sample was purified for elemental analysis by column chromatography (hexane : ether 1 : 1 on silica gel).

		%C	%H
	Found :	83.7	9.55
$C_{15}H_{20}O$	requires	83.3	9.25

29. 2,3-Epoxy-2-($\Delta^{3,7}$-oct-en-ynyl-)-3-methylcyclohexanone (81).

Epoxidation was according to the method of Wasson and House.[5]

A mixture of the ketone (63, 600 mgs, 2.78 mM) and hydrogen peroxide (10 mls, 30%) in methanol (15 mls) was cooled to 15°C and 6N-NaOH (1.2 ml) added dropwise over 2 min. The cooling bath was then removed to allow

the mixture to warm to room temperature. The reaction was followed by t.l.c. and the mixture was charged twice with the same H_2O_2 - NaOH ratio as above over a period of 15 h when the mixture had gone to completion. Normal work up afforded 422.2 mgs (65.5%) of title compound pure by t.l.c. and n.m.r. spectroscopy.

^1H NMR $CDCl_3$: (τ) 4.55 (m, 2H), 7.30 - 8.40 (m, 14H), 8.60 (s, 3H).

IR (film) ν_{max} (cm^{-1}) : 3300 (vs), 2915 (b,s), 1710 (vs), 1435 (s).

30. Treatment of 2,3-Epoxy-2-($\Delta^{3,7}$-oct-en-ynyl-)-3-methylcyclohexanone with BCl_3/CH_2Cl_2 at -78°C.

Boron trichloride (0.4 ml, a large excess) in methylene chloride (distilled from CaH_2 15 ml) was cooled to -78°C under N_2. The epoxide (81 , 200 mg) in methylene chloride (6 ml) was then added over 2 min with stirring. The mixture was then allowed to stir for a further 1½ h. Normal work up afforded 203.8 mg as a brown tarry oil shown by t.l.c. to contain at least three compounds. N.m.r. spectrum showed a vinylic proton at τ4.45, a few sharp singlets between τ8.7 - 9.15, though a major peak absorbing at τ9.

An attempt was made to separate the reaction products by column

chromatography (ether : hexane 1 : 1 on silica gel).

Fraction 1 was obtained as a yellow oil which was shown to be the chlorohydrin (41.5 mg).

Fraction 2 was obtained as a colourless oil which crystallised immediately the solvent was removed (45.8 mg).

Fraction 3 was eluted with Et_2O : hexane (2 : 1) and was largely the same as 2 though some tar had also eluted from the column. Further purification yielded another crop (42.3 mg) of cyclisation product.

This gives a total of 88.1 mg (35.5%) cyclisation product (93).

^1H NMR $CDCl_3$: (τ) 4.52 (m, 1H), 7.0 - 8.70 (m, 17H, including -O<u>H</u>), 9.01 (s, 3H).

IR CCl_4 ν_{max} (cm^{-1}) : 3583 (w), 2968 (m), 2928 (s), 2860 (s), 1710 (s), 1244 (s), 1210 (s), 1000 (s), 925 (s).

M/S (m/e) : 268 (M^+), 233 (M^+ - Cl), 250 (M^+ - H_2O), 232 (M^+ - HCl).

M.M. Found : 268.1230

$C_{15}H_{21}ClO_2$ requires 268.1229

A sample was further purified for elemental analysis by preparative t.l.c. (Et_2O : hexane 1 : 1).

		%C	%H
	Found :	67.5	8.1
$C_{15}H_{21}ClO_2$	requires	67.2	7.8

31. cis and trans-2,5-Dichloro-2-pentene[6] (94).

To phosphorus pentachloride (20 g, 0.09 mol) in methylene dichloride (25 ml, distilled from CaH_2) was added cyclopropyl methyl ketone (8.4 g, 0.1 m) in methylene dichloride (10 ml) and mixture allowed to stand at room temperature for at least one week, contrary to a published procedure.[6]

Work up involves addition of ice-water (50 - 60 ml) stirring for about 3 h for any phosphorus pentachloride or any of its oxides to be completely hydrolysed to the acid. The aqueous layer is then separated and the organic phase washed once or twice with saturated $NaHCO_3$, brine and finally water, and dried ($MgSO_4$). Removal of the solvent affords 11.30 g (81.2%) of the title compound easily distilled (b.p. 60° / 18 mm) as a colourless oil turning greenish-yellow on standing.

^1H NMR $CDCl_3$: (τ) 4.48 (m, 1H, vinylic), 6.50 (t, 2H), 7.40 (m, 2H), 7.80 (s, 3H, with fine terminal splitting).

IR (film) ν_{max} (cm^{-1}) : 2980 (w), 2950 (m), 2910 (w), 1715 (m),

1695 (m), 1665 (m), 1425 (m).

M/S (m/e) : 138 (M^+), 102 (M^+ - HCl), 91 ($M^+ - CH_2^+Cl$).

M.M. Found : 138.0002

$C_5H_8Cl_2$ requires 138.0003

32. 2-(1',5'-Dichloropent-2'-enyl)3-methylcyclohex-2-en-1-one (62).

The alkylation procedure is as before (Experiment 14). To a solution of the amino enol ether (56, 2.8 g, 13.39 mM) in THF (15 ml) at -78°C under N_2 was added n-BuLi (0.96 g, 15 mM, as 10 ml of 1.5 mM/ml solution in hexane) and the mixture stirred for 1 h. HMPA (2.688 g, 15 mM) in THF (10 ml) was then added whilst stirring continued 10 min after completion of addition of the latter, the chloride (94, 2.0 g, 14.49 mM) in THF (10 ml) was then added slowly.

Normal work up almost immediately afforded 4.0169 g of alkylation product which was immediately subjected to acid hydrolysis acetone - dil. HCl mixture, 20 ml (10 ml 2N - HCl) stirring overnight. Usual work up gave 2.260 g (80.7%) of title compound as a dark brown oil.

^1H NMR $CDCl_3$: (τ) 4.55 (m, 1H), 7.65 (m, 10H), 7.90 (m, 6H).

IR (film) ν_{max} (cm^{-1}) : 2930 (s), 1720 (s), 1670 (s), 1630 (w),

1430 (m), 1380 (s).

M/S (m/e) : 214/212 (M^+), 177 (M^+ - Cl), 123 (M^+ - $C_4H_6^{\oplus}Cl$).

33. 2,3-Epoxy-2-(Δ^3-5-chloropentenyl-)-3-methylcyclohexanone (80).

A solution of the ketone (62, 2.0 g, 9.43 mM) in methanol (15 ml) and hydrogen peroxide (10 ml, 50% H_2O_2) was cooled (ice-bath) to 10° and 0.5 ml 6N-NaOH was added dropwise with stirring. The epoxidation was followed by t.l.c. After stirring for 2 h and keeping the temperature just below 20°C, another 10 ml portion of H_2O_2, 0.5 ml 6N-NaOH was added and stirring continued overnight (12 h). T.l.c. still indicated a small amount of ketone left, when 0.4 ml of 6N-NaOH was then added. After stirring for another 2 h t.l.c. indicated complete reaction had taken place.

Normal work up afforded 1.5 g (69.8%) of the desired product.

^1H NMR $CDCl_3$: (τ) 4.65 (m, 1H), 8.0 (m, 13H), 8.62 (s, 3H).

IR (film) ν_{max} (cm^{-1}) : 2945 (s), 1712 (vs).

34. Reaction of epoxide (80) with boron trichloride in methylene chloride at -78°C.

A solution of the epoxide (400 mgs) in methylene chloride (15 ml) was cooled to -78°C and boron trichloride, a large excess was added and the mixture stirred under N_2 for 1.5 h. The reaction was quenched by addition of a solution of $NaHCO_3$ and NaCl solution. Organic matter was taken in methylene chloride, washed to neutrality with saturated $NaHCO_3$, dried ($MgSO_4$) and removal of solvent afforded 432 mgs of crude product as a brown oil. T.l.c. indicated four spots, but n.m.r. spectrum showed formation of one major product shown by a large methyl peak at τ8.92, with four small sharp peaks around the major one.

Isolation and purification was effected by column chromatography (silica gel, ether : hexane 1 : 1) affording a total of 231.9 mgs (53.7% of product) as a colourless oil crystallising on standing m.p. 80 - 81°C after one recrystallisation from petrol (60 - 80°C). The product was characterised as the cyclisation product (95).

^1H NMR $CDCl_3$ (300 MHz) : (τ) 5.89 (s, 1H, O<u>H</u>, D_2O exchangeable), 7.07 - 8.32 (m, 11H), 7.80 (s, 3H), 8.85 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 3470 (s), 2945 (s), 2865 (w), 1710 (s), 1310 (w), 1140 (w).

M/S (m/e) : 264 (M^+), 229 (M^+ - HCl), 211 (M^+ - HCl - H_2O), 166 ($M^+ - C_3H_3{}^{\oplus}Cl_2$).

M.M. Found : 264.0682

$C_{12}H_{18}Cl_2O_2$ requires 264.0684

35. Reduction of ketol (95) with sodium borohydride.

A solution of the ketol (130 mgs, 1 eq.) in methanol (15 ml) was cooled in ice-bath whilst $NaBH_4$ (18.6 mg, 4 eq.) was added in small amounts over 20 min. Reduction was followed by t.l.c. After reduction was complete (2 h) the methanol was removed on the rotary evaporator, the mixture diluted with NaCl solution and organic matter extracted into ether, washed once with sodium chloride solution and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded the diol (96, 128.2 mgs, 97.8%) in near quantitative yield, m.p. 110 - 112°C.

^1H NMR $CDCl_3$: (τ) 6.15 (bs, 2H, D_2O exchangeable), 7.0 (t, 1H), 7.78 (s, 3H), 7.78 - 8.5 (m, 11H), 8.55 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 3620 (m), 3560 (m), 3430 (bw), 2940 (vs), 2860 (m), 1380 (m), 1120 (s).

36. Cleavage of diol (96) with sodium metaperiodate.

To a solution of the diol (65.8 mg, 1 eq.) in THF - H_2O (4 ml, 3 : 1) was added sodium periodate (132.28 mg, 2.5 eq.) in small amounts over 2 min with stirring. The flask wrapped with aluminium foil to avoid exposure to light. The reaction mixture was allowed to stir for 4 h at which time a precipitate of sodium iodate had formed. The mixture was then diluted with 10 ml of THF, filtered to remove sodium iodate, and THF removed under reduced pressure. The product was then taken up in ether, dried ($MgSO_4$) and solvent removed yielding 61.2 mgs of product as a yellow oil. A quick run through silica gel (ether : hexane 1 : 1) afforded 58.4 mgs (89.4%) of ketoaldehyde (97) as a colourless oil.

^1H NMR CCl_4 : (τ) 0.37 (t, 1H), 7.42 - 7.92 (m, 17H), 7.71 (s, 3H), 8.42 (m, 4H), 8.72 (s, 3H).

IR CCl_4 ν_{max} (cm^{-1}) : 2972 (s), 2860 (s), 2802 (w), 2710 (w), 1747 (vs), broad enough to almost mask a strong peak at 1712, 1382 (m), 1115 (s).

M/S (m/e) : 264 (M^+), 247 ($M^+ - H_2O$), 228 ($M^+ - HCl$), 210 ($M^+ - HCl - H_2O$), 249 ($M^+ - CH_3^+$), 194 ($M^+ - C_3H_3^+Cl_2$).

M.M. Found : 264.0677

$C_{12}H_{18}Cl_2O_2$ requires 264.0684

A smaller peak also present at 264 very close to the M^+ due to the minor chlorine isotope.

37. Oxidation of ketoaldehyde (97) with Jones' reagent.

A solution of ketoaldehyde (97, 45 mgs, 0.7mM) in AR - acetone (5 ml) was cooled to -20° under nitrogen. Jones' reagent was then added dropwise until the colour stayed and stirring was continued for 1 h. The reaction was quenched by addition of methanol dropwisely until the solution turned green. The acetone and methanol were removed on the rotary evaporator, water was added to dissolve the chromium salts and organic matter extracted into ether. The acid was purified by extraction into saturated $NaHCO_3$ from the ether solution, and recovered by acidification, extraction into ether, drying (Na_2SO_4) and stripping of solvent affording 40.2 mgs (84.3%) of the ketoacid, (98).

^1H NMR $CDCl_3$: (τ) 2.60 (b, s, 1H, COO<u>H</u> displaceable by D_2O), 7.0 - 7.90 (m, 7H), 7.70 (s, 3H), 8.1 - 8.58 (m, 4H), 8.69 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 3600 - 3100 (v.b.), 2970 (s), 2930 (s), 2850 (s), 1740 (vs), 1710 (s), 820 (s).

M/S (m/e) : 246 ($M^+ - H_2O$), 228 (M^+ - HCl), 220 ($M^+ - CO_2$),

210 (M^+ - HCl - H_2O), 169 (M^+ - $C_2H_3Cl_2^+$).

38. Preparation of trans-5-Bromopent-2-ene (99).

trans-5-Bromopent-2-ene was prepared according to Julia's method.[7]

Aqueous hydrobromic acid (30 ml, 46 - 8%) was cooled to 5 - 10°C in an ice-water bath and methyl cyclopropyl carbinol (7 g, 0.081 M) also cooled to 5 - 10° was added, and mixture stirred for ½ h. Organic matter was then extracted into petroleum ether (40 - 60°) washed to neutrality with saturated $NaHCO_3$ and dried (Na_2SO_4). Removal of solvent, and distillation of product afforded 7.7 g (63.6%) of the title compound.

^1H NMR CCl_4 : (τ) 4.40 - 4.70 (m, 2H), 6.72 (t, 2H), 7.30 - 7.75 (m, 2H), and 8.20 - 8.50 (m, 3H).

39. 2-(Δ^3-Pentenyl-)-3-methylcyclohex-2-en-1-one (100).

The alkylation was carried out as already described for other bromides. To a solution of the amino enol ether (56, 4.8 g, 22.97 mM) in anhydrous THF (15 ml) was added n-BuLi (1.48 g, 23.3 mM) stirring for 1 h after which HMPA (4.15 g, 23.3 mM) was added stirring for 10 min before the bromide (3.42 g, 23.3 mM) was added. The whole operation

being carried out under N_2 at -78°C.

Immediately the bromide was completely introduced, the cooling bath was removed and reaction quenched as usual with half-saturated brine. Normal work up and acid hydrolysis of the enol ether side chain afforded 4.8 g (85.7%) of title compound.

^1H NMR $CDCl_3$: (τ) 4.45 - 4.75 (m, 2H), 7.4 - 7.80 (m, 10H), 8.09 (s, 3H), 8.26 - 8.48 (m, 3H).

40. 2,3-Epoxy-(Δ^3-pentenyl-)-3-methylcyclohexanone (101).

To a solution of the ketone (100, 500 mgs, 2.8 mM) in methanol (10 ml) was added 30% H_2O_2 (15 ml) and 6N - NaOH (1 ml) and mixture stirred at room temperature for 12 h. Normal work up afforded 303.5 mgs (60.7%) of title compound.

^1H NMR $CDCl_3$: (τ) 4.45 - 4.72 (m, 2H), 7.50 - 8.20 (m, 10H), 8.25 - 8.50 (m, 3H) and 8.60 (s, 3H).

41. Reaction of 2,3-Epoxy-(Δ^3-pentenyl-)-3-methylcyclohexanone with boron trichloride in methylene chloride at -78°C.

To a solution of epoxide (101, 160 mgs) in CH_2Cl_2 at -78°C was added BCl_3 and mixture stirred for 2 h. Normal work up afforded 178.9 mgs of a brown oil. N.m.r. spectrum of crude product showed an almost exclusive formation of a single product with two tertiary methyl groups, and no C = O absorption in the i.r. spectrum.

The product was purified by column chromatography (ether : hexane 1 : 1, on silica gel) when a light brown oil was obtained crystallising immediately the solvent was stripped off (142.2 mgs, 84%, from 169 mgs of crude product).

A sample was recrystallised from petrol (b.p. 60 - 80°) giving colourless crystals, m.p. 120 - 122°C.

^1H NMR $CDCl_3$: (τ) 7.2 - 8.65 (m, 13H), 8.79 (s, 3H), 9.10 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 3600 (s), 3460 (w), 2930 (vs), 1520 (s), 1438 (s), 1120 (s).

M/S (m/e) : 230 (M^+), 194 (M^+ - HCl), 215 (M^+ - CH_3^+), 212 (M^+ - H_2O), 161 (M^+ - CH_3^+ - H_2O - HCl).

A sample was further purified by recrystallisation from the same

solvent for elemental analysis.

		% C	% H	% Cl
	Found :	62.7	7.9	15.0
$C_{12}H_{19}O_2Cl$ (102)	requires	62.5	8.2	15.4

42. Reaction of (102) with Silver Nitrate in aqueous Methanol at reflux temperature.

Following the failure of any reaction at room temperature after 48 h, the reaction mixture was then refluxed for 18 h after which complete hydrolysis had taken place.

To a solution of the α-chloroether compound (102, 15 mgs, 1 equiv) in aqueous methanol (4 : 1, MeOH : H_2O) was added silver nitrate (28 mgs, 2 equiv) and reaction mixture refluxed for 18 h. Work up was by removal of methanol on rotary evaporator and extraction of organic matter into ether. The compound seems sparingly soluble in ether and a relatively large volume was required. The solvent was then dried (Na_2SO_4) and removed under pressure to give 40 mgs of colourless crystalline compound. This was purified by column chromatography (Silica gel, Ether : Hexane : Dichloromethane 1 : 1 : 1) to remove any less polar products whilst the main bulk of material stuck on to the column and was finally eluted with methanol. Spectral data showed this to be a mixture of two closely related

compounds, probably 102 (a) and (b). M.p. of mixture is 160°.

^{1}H NMR $CDCl_3$ 80 MHz : (τ) 7.38 - 8.50 (m, $-CH_2-$ protons), 8.65 (s, $-CH_3$) and 9.01 (s, $-CH_3$) the two methyls in ratio 1 : 2 respectively.

Since the product appears to be a mixture of two compounds, the signals and integrals have not been identified with specific protons.

IR ν_{max} (cm^{-1}) CH_2Cl_2 : 2580 (m), 3450 (w b), 2920 (s), 1700 (m).

M/S (m/e) : 212 (M^+), 197 ($M^+ - CH_3^+$), 194 ($M^+ - H_2O$), 179 ($M^+ - H_2O - CH_3^+$).

The identities of what appears to be two isomeric compounds awaits further experimental work.

43. Reaction of ketone (61) with TFA / TFAA.[9]

To a mixture of trifluoroacetic acid (TFA, 10 ml) and trifluoroacetic anhydride (TFAA, 5 ml) was added ketone (61, 500 mgs, 1.7 mM). The mixture turned reddish-brown and gradually darkened as stirring continued for 12 h.(shorter reaction time possible). Water (10 ml) was added to hydrolyse the TFAA, and the acid was removed on the rotary evaporator yielding 536 mgs of the enol trifluoroacetate (109), with characteristic carbonyl absorption at 1790 cm^{-1}.

The enol trifluoroacetate was the hydrolysed with 10% methanolic potash (1 h) and work up yielded 470 mgs of the crude product as a brown oil. Crystallisation was effected by allowing an ethereal solution to evaporate slowly at room temperature. The major product (110) crystallised giving a total yield of 285.2 mgs (80.75% of product) recrystallised from ether.

The other product of cyclisation (111, 68 mgs, 19.25% of product) was isolated from the major products by preparative t.l.c., m.p. 98 - 100°C.

A total of 353.3 mgs (70.7%) of cyclised product was obtained after purification.

^1H NMR $CDCl_3$ (110) : (τ) 2.75 (s, 1H, J = 8.4 Hz), 3.24 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 3.34 (d, 1H, J = 2.4 Hz), 6.21 (s, 3H), 7.10 - 8.92 (m,

17H), 9.22 (s, 3H).

A sample was prepared for analysis by repeated crystallisation from ether, m.p. 155 - 7°C.

		%C	%H
	Found :	79.8	8.8
$C_{20}H_{26}O_2$	requires	80.5	8.7

^1H NMR $CDCl_3$ (111) : (τ) 2.82 (d, 1H, J = 6.7 Hz), 3.2 - 3.50 (m, 3H, coupling of other aromatic protons not properly resolved), 6.28 (s, 3H), 7.1 - 9.04 (m, 17H), 9.20 (s, 3H).

The mass- and i.r. spectra of both compounds were very similar.

IR ν_{max} (cm^{-1}) CCl_4 : 2920 (vs), 2850 (bs), 1710 (vs), 1515 (s), 1270 (m).

M/S (m/e) : 298 (M^+), 283 ($M^+ - CH_3^+$), 267 (M^+ - OMe).

M.M.

Found :		298.1929
$C_{20}H_{26}O_2$	requires	298.1933

44. Reaction of ketone (60) with TFA / TFAA.

A mixture of trifluoroacetic acid (TFA, 10 ml) and trifluoroacetic anhydride (TFAA, 5 ml) was cooled in ice-water and added to the ketone (60, 500 mgs) in ice-bath and mixture stirred for 8 h at this temperature ($-5^{o}C$ to $5^{o}C$). The reaction mixture was much cleaner resulting in 534 mgs of light brown oil, corresponding to the enol trifluoroacetate. This was then subjected to hydrolysis using 10% methanolic potash and work up gave 445 mg of crude cyclisation product which was purified by column chromatography (alumina, grade 1, ether : CH_2Cl_2 2 : 1). A total of 405.27 mgs (81%) of the title compound was obtained as a colourless oil from the column, crystallising into a colourless solid on removal of the solvent, m.p. 141 - $143^{o}C$.

^{1}H NMR $CDCl_3$ (300 MHz) (112)

: (τ) 2.98 (d, 1H, J = 8.4 Hz), 3.10 (d, 1H, J = 2.4 Hz), 3.28 (dd, 1H, J = 8.4, J = 2.4), 6.20 (s, 3H), 7.16 - 8.88 (m, 17H), 9.22 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 2970 (vs), 2930 (vs), 2850 (vs), 1710 (s), 1605 (w), 1440 (s), 1380 (vs).

M/S (m/e) : 298 (M^+), 283 ($M^+ - CH_3^+$), 267 (M^+ - OMe).

M.M. Found : 298.1937

$C_{20}H_{26}O_2$ requires 298.1933

A sample was recrystallised from ether for elemental analysis.

		%C	%H
	Found :	80.9	8.9
$C_{20}H_{26}O_2$	requires	80.5	8.7

45. Reaction of ketone (63) with TFA / TFAA.

A mixture of TFA (8 mls) and TFAA (4 mls) was added to the ketone (63, 500 mgs) and mixture stirred at room temperature for 6 h. The reaction mixture prior to work up became very dark and it was obvious a lot of tar had formed. The crude product upon work up was put to hydrolysis using saturated $NaHCO_3$ and stirring for 1 h. Normal work up gave 386.5 g of crude product with a lot of tars.

The n.m.r spectrum of the crude product indicated two major methyl signals at about τ8.9 and 9.3. The products were isolated by a combination of column chromatography (ether : hexane 1 : 1 on silica gel) and preparative thin layer plate (hexane : ether 2:1, with four runs) giving the product of cyclisation as cis and trans isomers 207 g, (41.4% after

separation of isomers) the major product being the trans (114) as expected (118.8 mgs, 57.4%) and cis (115, 88.2 mgs, 42.6%) were obtained after purification.

^1H NMR $CDCl_3$

cis (115) : (τ) 7.50 - 8.80 (m, 17H), 8.94 (s, 3H).

trans (114) : (τ) 7.40 - 9.10 (m, 17H), 9.28 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 2928 (s), 2860 (w), 2840 (w), 1710 (vs), 1440 (m), 1308 (m), 1198 (m), 900 (w).

M/S (m/e) : 234 (M^+), 219 ($M^+ - CH_3^+$), 216 ($M^+ - H_2O$), 164 ($M^+ - C_4H_6O$).

M.M. Found : 234.1617

$C_{14}H_{22}O_2$ requires 234.1620

An attempt was made successfully to epimerise the cis to the trans using NaOMe / MeOH at -40°C under N_2 or more easily K_2CO_3 / MeOH at room temperature. A 50 : 50 mixture of (114) and (115) was obtained starting with pure (115).

46. Reaction of ketone (62) with TFA / TFAA.

A mixture of TFA (8 mls) and TFAA (4 mls) was added to ketone (62,

500 mgs) cooled in an ice-bath for 6 h. 572.4 mgs of the enol bis-trifluoroacetate (116) was obtained. Hydrolysis of the trifluoro-acetate was carried out with saturated $NaHCO_3$, giving 365.6 mgs of crude product as a light brown oil.

The n.m.r. spectrum of the crude product showed two sets of two peaks each at τ8.7 and 9.0 and τ7.8 and 7.9. The products were purified by column chromatography (silica gel, ether : hexane 1 : 1).

Fraction 1 (127.9 mgs) was shown by t.l.c. to contain at least four products none of which appeared to contain any cyclised products as shown by n.m.r. spectroscopy.

Fraction 2 (113.4 mgs) was a mixture of two compounds having the four signals mentioned above.

Fraction 3 (67.5 mgs) was a pure compound corresponding to one component of Fraction 2, with methyl signals at τ7.8 and 8.7. This shows that the other component has the signals at τ7.9 and 9.0.

The two compounds were separated by preparative thin layer chromatography (ether : hexane 1 : 2, after four runs) giving 171.9 g (34.4%) of product after separation.

The products were identified as cis-hydrinanone derivatives with

β- (118) and α- (119) -acyl side chain. (119) was the major product, (127.3 mg, 74.2%) and (118), 44.6 mgs (25.8%).

^{1}H NMR $CDCl_3$ (118) : (τ) 7.30 - 8.50 (m, 12H), 7.89 (s, 3H), 8.95 (s, 3H).

(119) : (τ) 7.10 - 8.35 (m, 12H), 7.81 (s, 3H), 8.72 (s, 3H).

The m/s and i.r. spectra for both compounds are very similar showing

ν_{max} (cm^{-1}) CCl_4 2940 (vs), 2860 (vs), 1710 (vs), 1670 (s), 1350 (s), 1115 (s).

M/S (m/e) : 194 (M^+), 179 ($M^+ - CH_3^+$), 151 ($M^+ - CH_3^+CO$).

M.M. Found : 194.1308

$C_{12}H_{18}O_2$ requires 194.1307.

47. Reaction of TFA / TFAA with ketone (100).

To the ketone (100, 600 mgs) in ice-salt-water bath was added a cold mixture of TFA (8 ml) and TFAA (4 ml) and mixture stirred for 12 h whilst the reaction mixture steadily warmed to room temperature.

Work up and usual hydrolysis with sodium bicarbonate in methanol afforded 536.8 mgs of crude product. The reaction was later found out to be incomplete. Hence 500 mgs of the mixture was put back into reaction

with the same TFA / TFAA ratio as above but this time at room temperature. After 6 h there was no trace of starting material. Normal work up afforded 431.4 mgs of crude mixture of products which were separated by preparative t.l.c. (silica gel, ether : hexane, 1 : 1).

The first fraction, with lowest R_f value corresponded to the trans-isomer of the decalin derivative (121, 136.8 mgs, 41%).

^1H NMR $CDCl_3$ 90 MHz : (τ) 6.65 (m, 1H, $W_{\frac{1}{2}}$ = 26.7Hz), 7.4 - 8.9 (m, 13H, including -OH, as shown by an exchangeable proton at 8.5), 9.0 (d, 3H, J = 7 Hz), 9.35 (s, 3H).

The next fraction corresponds to the cis-isomer (122, 79.5 mgs, 24%).

^1H NMR $CDCl_3$ 80 MHz : (τ) 6.55 (m, 1H, $W_{\frac{1}{2}}$ = 24.4Hz), 7.5 - 8.95 (m, 13H, including -OH, as an exchangeable proton at 8.28), 9.01 (s, 3H), 9.12 (d, 3H, J = 7.7 Hz).

The i.r. spectra of both compounds are very similar.

IR CCl_4 ν_{max} (cm^{-1}) : 3600 (w), 3460 (w, b), 2930 (s), 1710 (vs), 1660 (w).

M/S (m/e) : 196 (M^+), 178 ($M^+ - H_2O$), 163 ($M^+ - CH_3 - H_2O$).

The third product of reaction is the ketone (123, 115.6 mgs, 35%).

^1H NMR $CDCl_3$: (τ) 7.5 - 8.6 (m, 12H), 8.91 (s, 6H).

IR CCl_4 ν_{max} (cm^{-1}) : 2930 (s), 1670 (vs), 1610 (w),

λ_{max} (MeOH) : 245 nm, ε 12600.

M/S (m/e) : 178 (M^+), 163 ($M^+ - CH_3$), 145 ($M^+ - CH_3^+ - H_2O$).

M.M. Found : 178.1358

$C_{12}H_{18}O$ requires 178.1358.

48. Reaction of ketone (100) with d-TFA / TFAA.

Deuterotrifluoroacetic acid (d-TFA) was made by adding one equivalent of TFAA to two equivalents of D_2O.

d-TFA (4 ml) and TFAA (2 ml) were added to the ketone (49.95 mgs) at room temperature stirring for 6 h. Normal work up and hydrolysis of the intermediate enol trifluoroacetate afforded the same type of products as above giving 12.99 mgs of a mixture of cis and trans keto-

alcohol (121 and 122) and 24.06 mgs of the $\alpha\beta$-unsaturated ketone separated from a little starting material by preparative t.l.c. (hexane : ether 3 : 1) running three times. The n.m.r. and i.r. spectra are very similar with corresponding compounds except a C - D stretching frequency at 2170 cm^{-1} in each compound.

The mass of the $\alpha\beta$-unsaturated ketone (d-123, Fig. xxviii) was measured for deuterium incorporation in parallel with the corresponding non-deuterated compound.

M.M.	Found :	179.1420
$C_{12}H_{17}DO$	requires	179.1415

A peak at 179.1391 corresponds to ^{13}C interference.

49. <u>De-deuteration of ketone (d-123).</u>

This operation was adapted from a published procedure.[10]

To a solution of ketone (d-123, 12.85 mgs) in dioxan (2 ml) was added 10% NaOH (1 ml) and dioxan-water (1 : 1, 5 ml) and mixture heated to 70°C for 20 min with stirring under nitrogen. The dioxan was removed under reduced pressure after which organic matter was extracted into ether, dried (Na_2SO_4) and distilled off. I.r. spectrum of the product only showed

a marked reduction in C - D signal, hence the ketone was further treated with 3 drops of 10% - NaOH in 3 ml (2 : 1) dioxan-water stirring at room temperature for 18 h, after which the C - D stretching frequency had disappeared completely in the i.r. spectrum.

50. Reaction of ketone (60) with methyllithium.

To a solution of the ketone (60, 300 mgs, 1 mM) in sodium-dried ether (15 ml) was added methyllithium-lithium bromide complex (5 ml as 1.5M in ether) at -78°C under N_2 and stirring for 1 h.

The reaction was quenched by addition of half-saturated sodium chloride. 20 ml more of ether was added and aqueous layer separated and extracted once more with 15 ml of ether. The combined organic extract was then washed once with sodium chloride solution and once with water, dried (Na_2SO_4). Removal of solvent afforded 331.0 mgs (95.1%, 126) of crude product which was used for the next reaction as such.

^1H NMR $CDCl_3$ (126) : (τ) 3.05 (dq, 4H), 4.52 (m, 2H), 6.23 (s, 3H), 7.1 - 8.6 (m, 15H including -OH), 8.35 (s, 3H), 8.72 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 3610 (w), 2940 (vs), 1600 (s), 1270 (bs).

M/S (m/e) : 314 (M^+), 296 ($M^+ - H_2O$), 281 ($M^+ - CH_3^+$ -

H_2O), 283 (M^+ - OMe).

51. Reaction of alcohol (126) with formic acid.

To the alcohol (300 mgs) in sodium dried pentane (15 ml) was added anhydrous formic acid (10 ml, freshly distilled from phthalic anhydride) under N_2 for 1 h at room temperature.

20 ml of pentane was further added and saturated sodium chloride solution. The aqueous layer was separated, and the organic layer washed with saturated sodium bicarbonate to neutrality, dried (Na_2SO_4) and solvent removed affording 270 mgs of crude cyclisation product as a very clean light yellow oil. It was one-spot pure by t.l.c. (ether : hexane 1 : 1) but n.m.r. spectrum showed the presence of two compounds, the expected cyclisation product as the major fraction and dehydration product, shown by the presence of vinyl proton.

Attempts to remove the latter product by Diels-Alder reaction with diethylazodicarboxylate or maleic anhydride failed. The oil was finally crystallised from methanol, 169.87 mgs (60%) based on the alcohol, m.p. 74 - 5°C (127).

^1H NMR $CDCl_3$ (90 MHz)

(127) : (τ) 3.05 (d, 1H, J = 8 Hz), 3.16 (d, 1H, J = 2.7 Hz), 3.38 (dd, 1H, J = 8 Hz, J =

2.7 Hz), 6.26 (s, 3H), 7.1 - 8.8 (m, 16H), 8.39 (s, 3H), 8.99 (s, 3H).

IR ν_{max} (cm^{-1}) CCl_4 : 2920 (s), 2853 (m), 1605 (w).

M/S (m/e) : 296 (M^+), 281 ($M^+ - CH^+_3$).

M.M.

	Found :	296.2142
$C_{21}H_{28}O$	requires	296.2140

Elemental Analysis

		%C	%H
	Found :	84.8	9.7
$C_{21}H_{28}O$	requires	85.1	9.5

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