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Department
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THE SYNTHESIS OF 2,2,8-TRIMETHYLTRICYCLO[6,2,2,0^{1,6}]
DODEC-5-ENE AND RELATED COMPOUNDS

A Thesis
submitted to the
University of Stirling
for the degree of
Doctor of Philosophy

J.E.L. McDonald

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Chemistry Department
University of Stirling

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Finally, I would like to express publicly my thanks to my wife and family whose patient endurance has provided much needed moral support.

To my Father

CONTENTS

					<u>Page</u>
Introduction	1
References	32
Discussion	36
Experimental	87
References	119

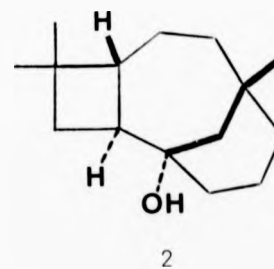
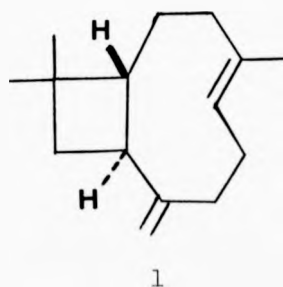
INTRODUCTION

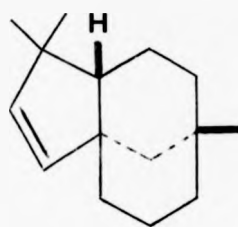
Man's chemical knowledge has been greatly advanced by his investigations into the nature, synthesis, and reactions of the sesquiterpenes¹. These C₁₅ natural products encompass a wide range of acyclic, monocyclic, bicyclic, tricyclic, and tetracyclic systems. The problems of skeletal construction and stereochemical control posed by this variety of natural product have often provided the stimuli for the development of new synthetic methods with wider application. Similarly, our motivation for probing certain types of reaction mechanisms, particularly in the field of carbonium ion chemistry, has stemmed from the many rearrangement reactions of sesquiterpenes.

A rearrangement may be defined as a change in the atomic disposition in the molecule with concomitant σ or π bond cleavage and subsequent bond reformation². This definition includes processes such as cyclisations, Wagner-Meerwein rearrangements, hydride shifts, etc. and can take place under a myriad of reaction conditions. Rearrangements involving cationic intermediates, usually generated under acidic conditions, can shed some light on the biogenesis of the sesquiterpenes in that they constitute a working model for enzyme-catalysed rearrangements³. The acid-catalysed rearrangements of some sesquiterpenes will be examined as a prelude to the discussion of the synthesis of the title compound of this thesis which, as will be shown, is derived from the sesquiterpene thujopsene. These rearrangements are specific to each structure and will, therefore, be discussed individually.

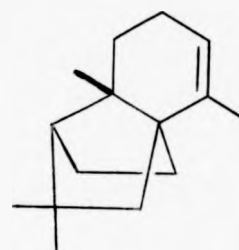
Caryophyllene, whose structure was established by Barton⁴ in 1951, is the main constituent of oil of cloves⁵. Examination of this structure reveals a highly strained cyclobutane ring trans-fused to a nine-membered ring in a bicyclic[7,2,0] system with an exo- and an endocyclic double bond. The endocyclic double bond has the less-favoured trans geometry. The nine-membered ring allows a fair degree of mobility within the molecule in that the double bonds can be brought into fairly close proximity.

When caryophyllene (1) is treated with sulphuric acid in ether three major products are obtained, caryolan-1-ol (2), clovene (3), and neoclovene (4)⁶. Two competitive mechanisms have been postulated to account for the formation of these tricyclic compounds. Barton⁷ considered that protonation would occur preferentially at the endocyclic trisubstituted double bond to

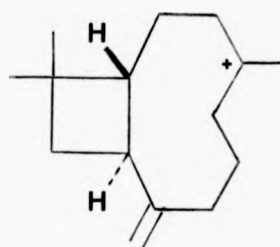




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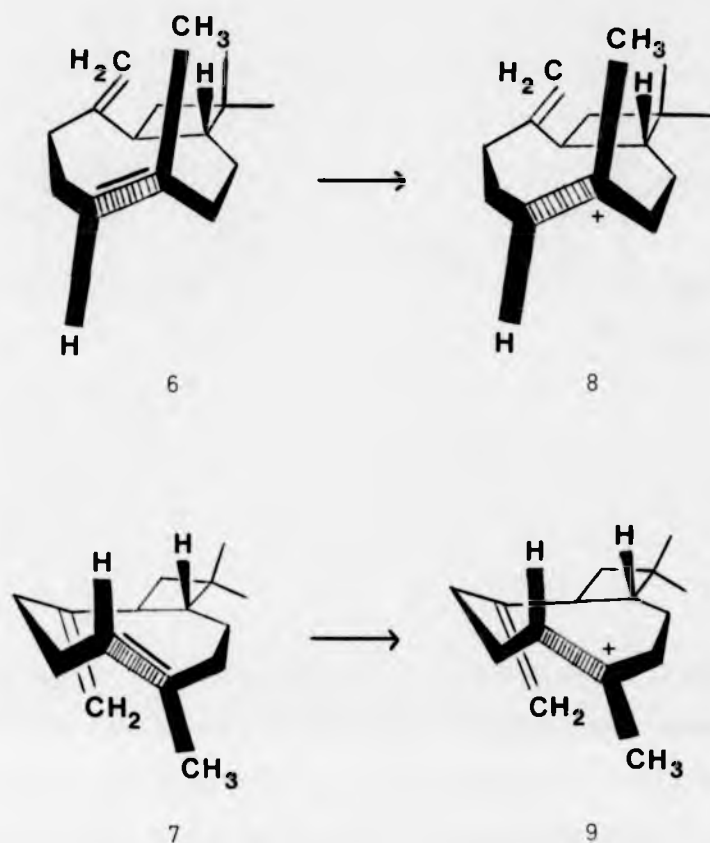


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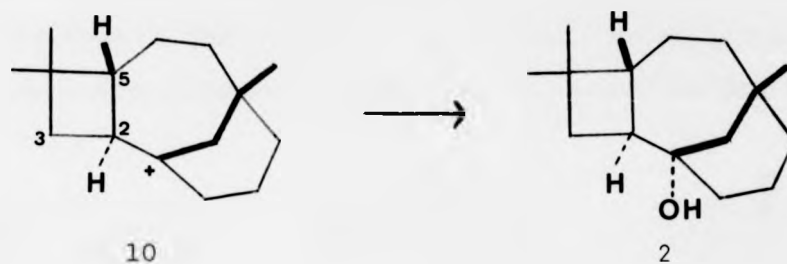
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give the tertiary carbonium ion (5). He also realised that this carbocation could have two conformations, (8) and (9), which would arise from the protonation of the conformers (6) and (7) respectively. Experimental confirmation was obtained by Nickon *et al.*,⁸ for this hypothesis when they carried out the rearrangement using D_2SO_4 . The infra-red spectra of clovenic anhydride, obtained by oxidation of clovene, and the caryolan-1-ol were compared with the spectra of authentic samples of caryolan-1-ol- 9α -d and - 9β -d and the corresponding clovenic- 9α -d and 9β -d anhydrides, which were synthesised by stereospecific routes. This analysis revealed that the incorporated deuterium atom had almost exclusively the β -configuration in caryolan-1-ol

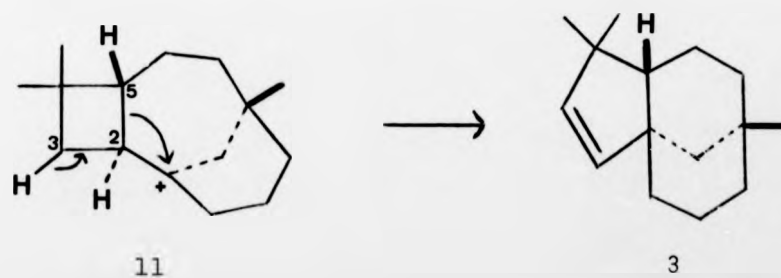


and the α -configuration in clovenic anhydride, which is only compatible with the postulated mechanism.

The transannular cyclisation of (8) and (9) would give two tricyclic carbonium ions with opposite bridgehead stereochemistries. Cyclisation of (8) would give the carbocation (10) which on hydrolytic work-up yields caryolan-1-ol (2). Because of the geometry of the cation (10) neither the C-2 - C-3 bond nor the C-2 - C-5 bond has a suitable orientation for migration to the backside of the bridgehead carbonium ion. Thus

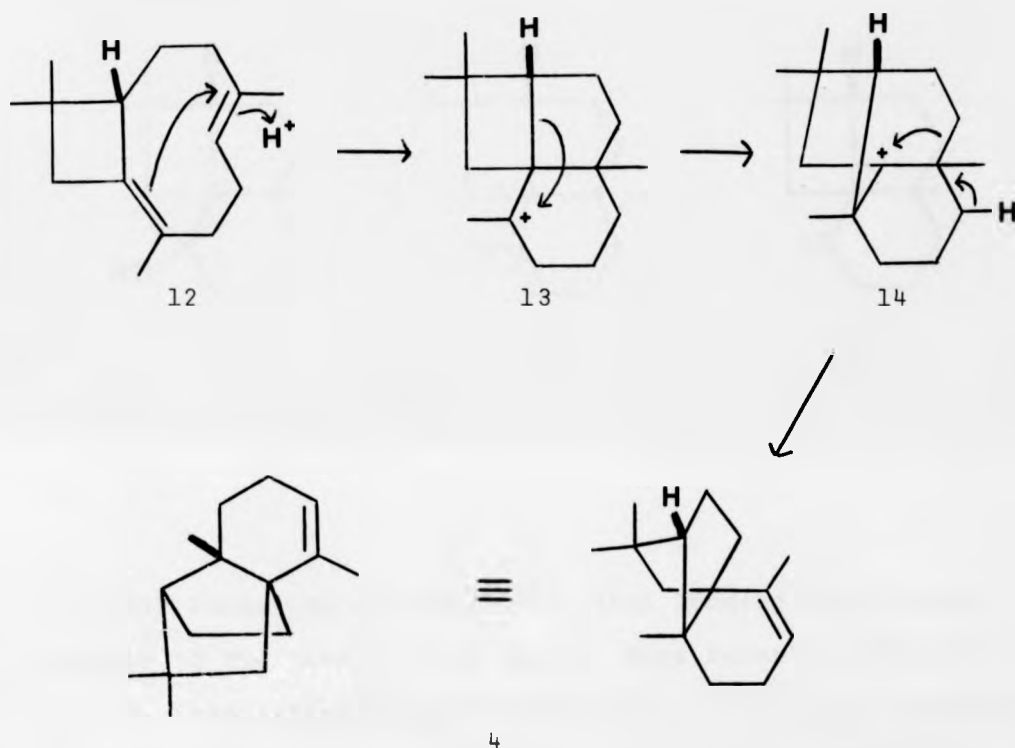


further molecular rearrangement is hindered. However the C-2 - C-5 bond of the cyclobutane ring in the carbocation (11) resulting from transannular cyclisation of conformer (9) is suitably aligned for migration to take place and, after loss of a proton, affords the tricyclic olefin, clovene (3).



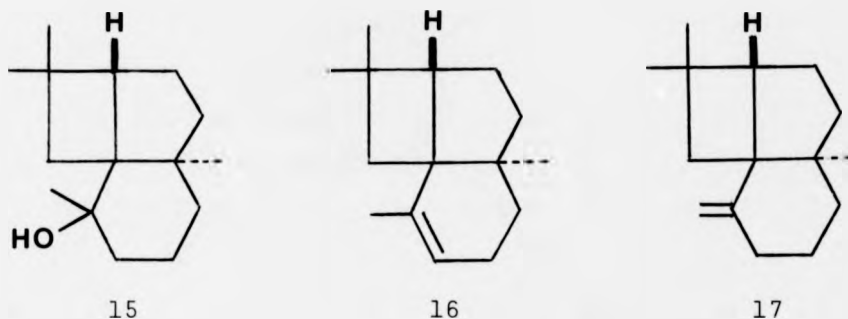
The fact that neither clovene (3) nor caryolan-1-ol (2) could be converted into neoclovene (4) by sulphuric acid in ether indicated that a different rearrangement sequence was in operation

for the production of this compound from caryophyllene (1)^{6(c)}
 The mechanism that was postulated can be outlined as follows.
 Isomerisation of the exocyclic double bond to give the diene (12)
 was considered to be the first step. Protonation and cyclisation

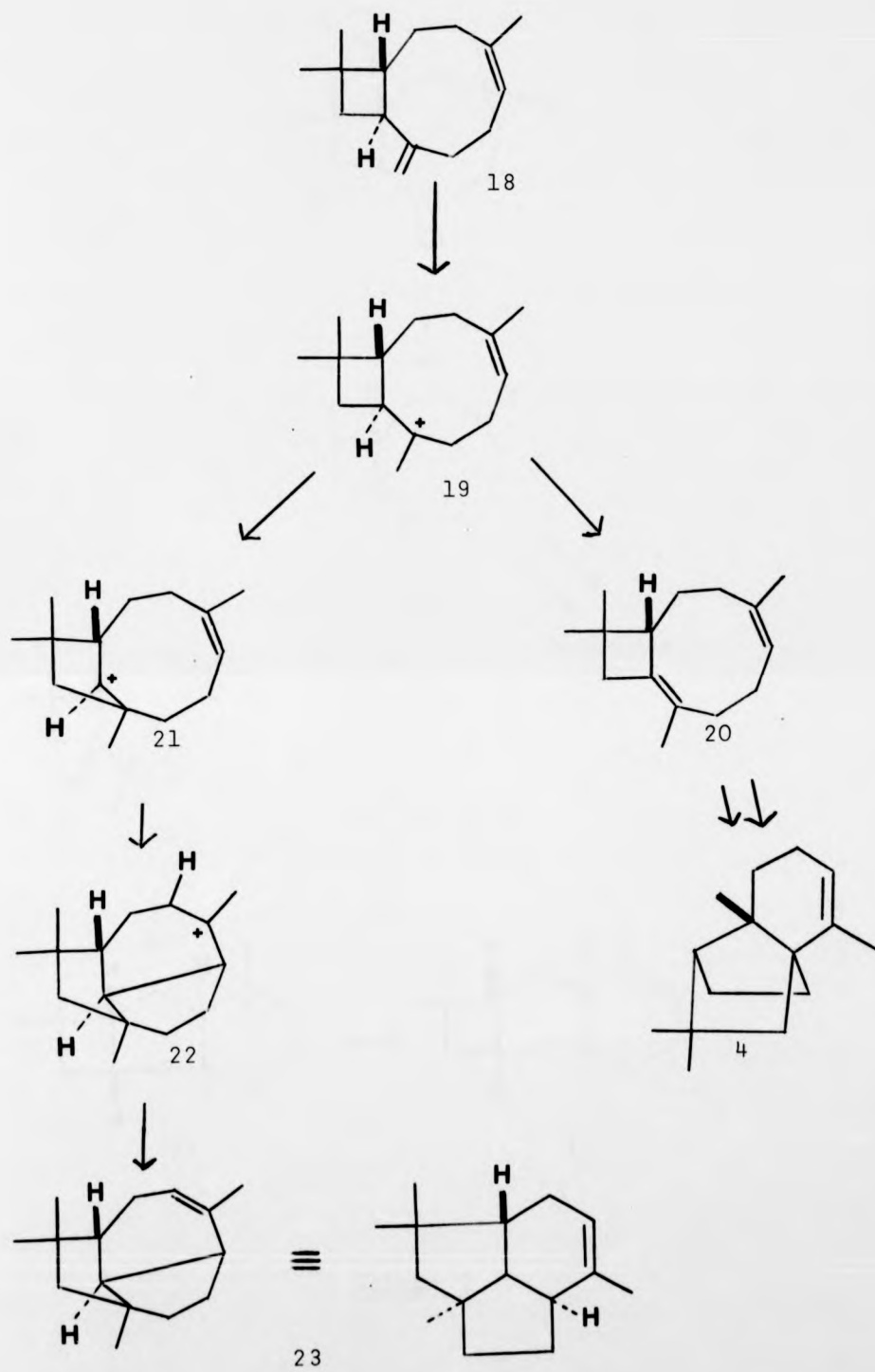


of (12) would yield the carbonium ion (13) which could then
 undergo a Wagner-Meerwein rearrangement thus relieving the
 strain imposed by the cyclobutane ring. A second Wagner-Meerwein
 rearrangement of the resultant tricyclic carbocation (14) followed

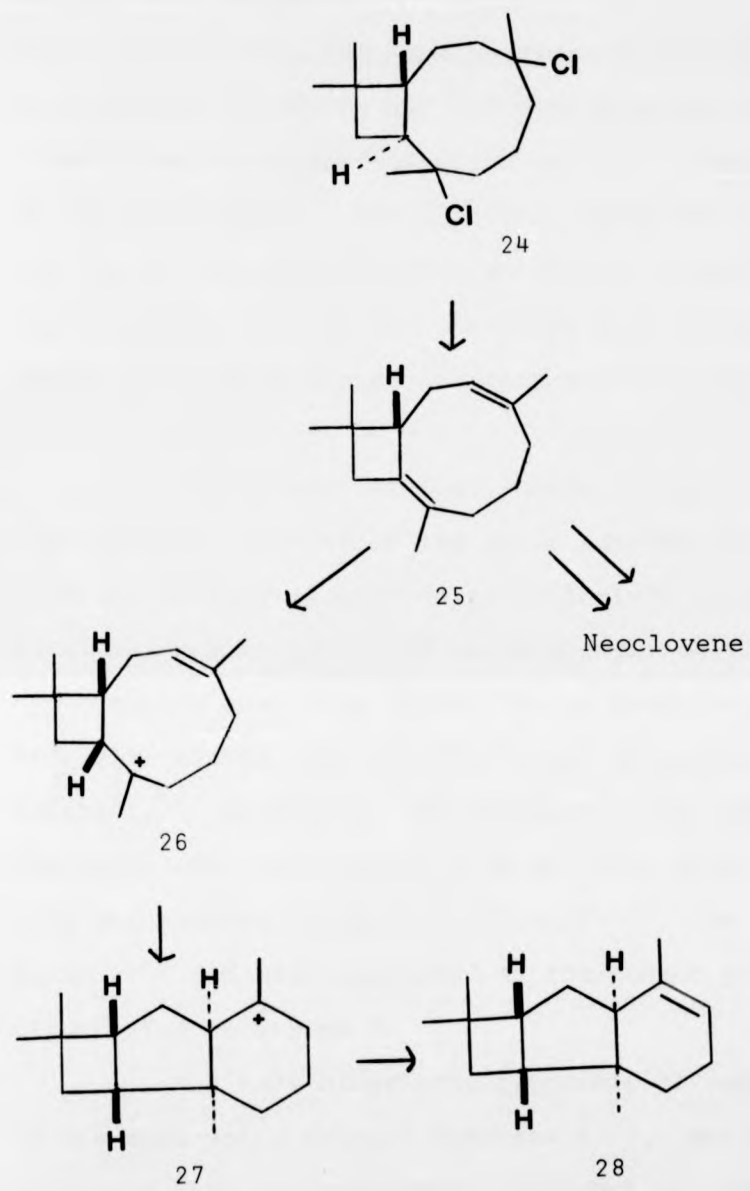
by deprotonation would then afford neoclovene (4). Seeking support for the suggested genesis of neoclovene McKillop *et al.*⁹ synthesised the tricyclic alcohol (15) from a derivative of caryophyllene. Treatment of this alcohol with sulphuric acid in ether resulted in



exclusive formation of neoclovene, thus lending considerable credence to the proposed mechanism. More recently, Hirose¹⁰ has made the interesting discovery that both α - (4) and β -neoclovene (its exocyclic double bond isomer) together with α - (16) and β -panasinsene (17) co-occur with caryophyllene in the roots of the ginseng plant. As anticipated α - and β -panasinsene give α - and β -neoclovene on isomerisation with sulphuric acid. It is perhaps significant that the composition of the volatile oils isolated from samples of dried roots differ from those isolated from fresh roots of the ginseng plant. The quantities of α -panasinsene, β -panasinsene, α -neoclovene, and β -neoclovene occurring in the oil of the fresh roots were 5%, 8%, 7% and 3%



Scheme 1



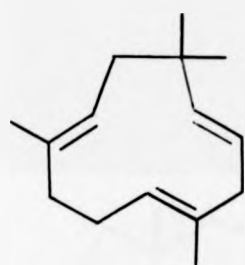
Scheme 2

respectively compared to the oil of the dried roots which contained 4%, 20%, 15%, and 5% respectively of these compounds. In addition, 2% of the oil isolated from the dried roots was found to be caryolan-1-ol which was not isolated from the oil of the fresh roots. The possible reason for these differences may lie in the fact that the fresh root homogenate has a pH of 4.6-4.8 which may, in turn, suggest that in the process of drying an acid-catalysed rearrangement of caryophyllene takes place.

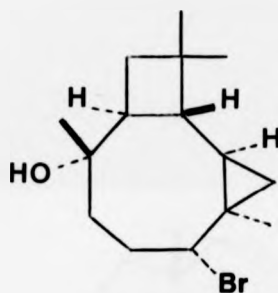
Neoclovene, in fact, would appear to be a ubiquitous rearrangement product of the basic caryophyllene skeleton. Although neither clovene or caryolan-1-ol result from the acid-catalysed rearrangement of isocaryophyllene (18), the two major hydrocarbons have been identified as neoclovene (4) and the tricyclic olefin (23) arising by the mechanism outlined in Scheme 1.¹¹ Similarly, dehydrochlorination of caryophyllene dichloride (24) with acetic acid produces neoclovene (4) together with yet another tricyclic olefin (28)¹². In this case, the diene (25) has been suggested as the common precursor as illustrated in Scheme 2.

A likely biogenetic precursor of caryophyllene (1) is the monocyclic triene, humulene (29), which inevitably co-occurs with caryophyllene. Although no direct conversion of humulene into caryophyllene has yet been achieved, Sutherland *et al.*¹³ have shown that bromination of humulene (29) with *N*-bromosuccinimide in aqueous acetone yields the bromohydrin (30). Dehydration of this compound with phosphoryl bromide in pyridine

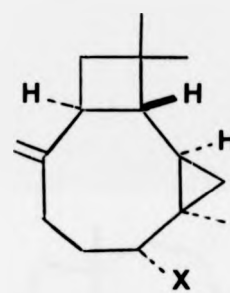
gives the bromide (31) ($X = \text{Br}$) which on reduction with lithium aluminium hydride affords a mixture of the hydrocarbon (31) ($X = \text{H}$), humulene (29), and caryophyllene (1). If the assumption is correct that humulene is a biosynthetic precursor of caryophyllene then these reactions may shed some light on the biosynthetic mechanism. Evidence in support of this hypothesis was obtained when humulene epoxide (32), which was found in the rhizomes of Zingiber zerumbet Smith, along with caryophyllene and humulene, was treated with 20% sulphuric acid in acetone¹⁴. The tricyclic



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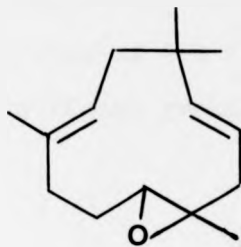
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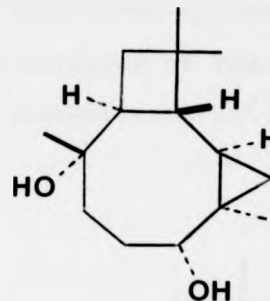
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diol (33) was obtained which has the tricyclic skeleton of the compound (30) obtained by Sutherland which led to the suggestion that the epoxide (32) may be involved in the biosynthesis of caryophyllene¹⁵.

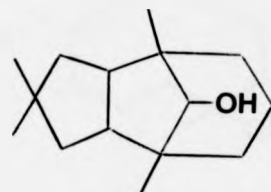
However, acid-catalysed rearrangement of humulene itself does not give caryophyllene nor any product which has the tricyclic skeleton of (30) or (33). Instead a mixture of α -caryophyllene alcohol (34)¹⁶ and the hydrocarbons (35)-(37)¹⁷⁻¹⁹ are obtained. α -Caryophyllene alcohol (34) was originally



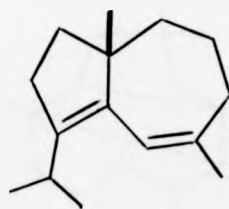
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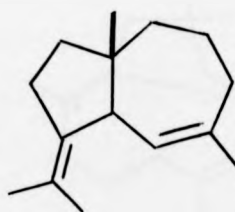
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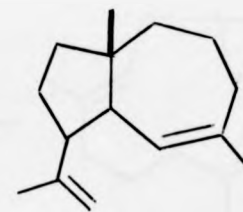
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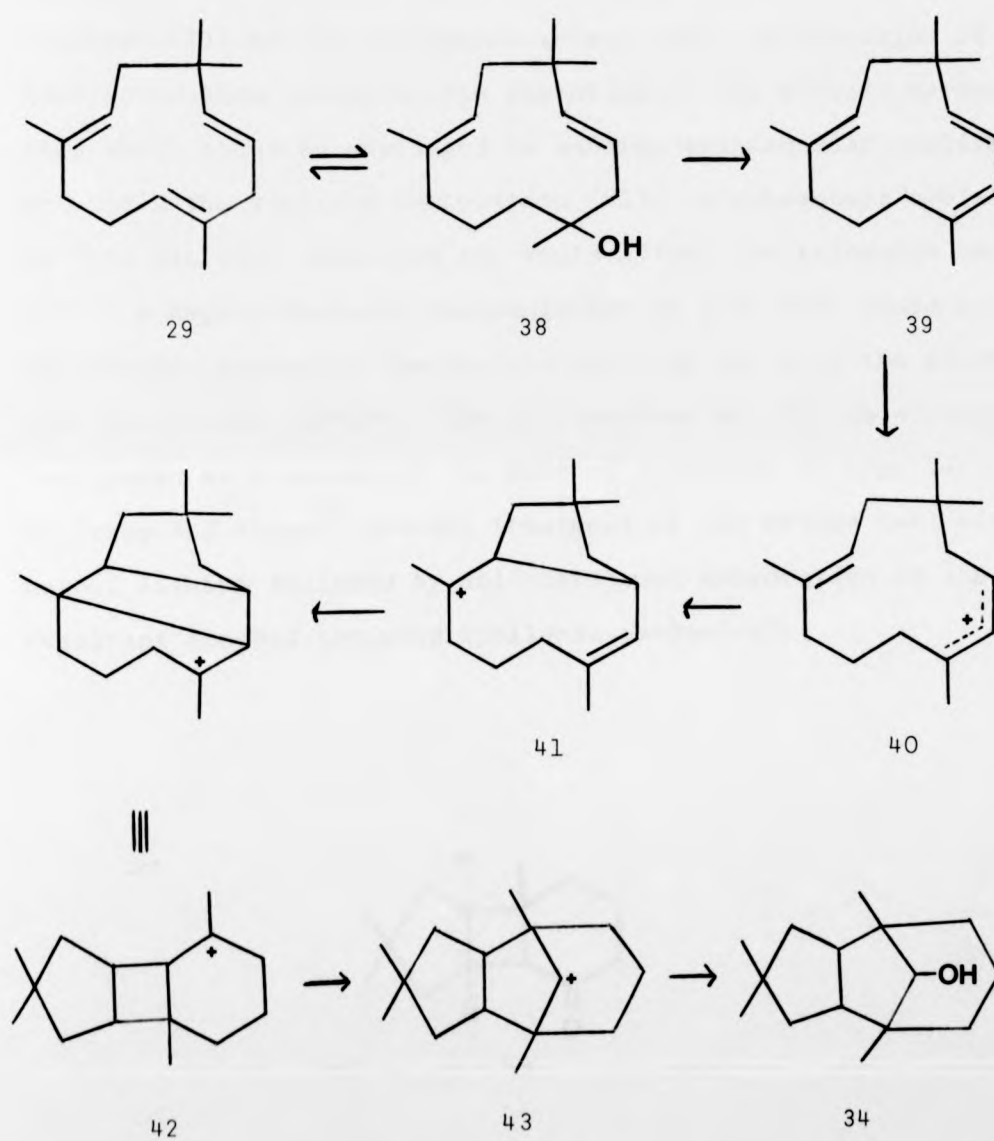
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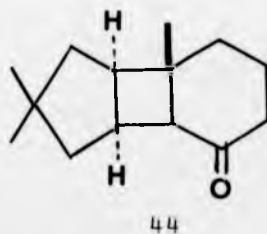
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considered to be an acid-catalysed rearrangement product of caryophyllene until it was demonstrated that this alcohol originated from humulene which was present as a contaminant in most commercial samples of caryophyllene²⁰. The realisation that (34) was not a derivative of caryophyllene led Nickon²¹ to suggest the name of appollan-11-ol, in honour of the Apollo 11 moon mission, to correct the misnomer of caryophyllene alcohol

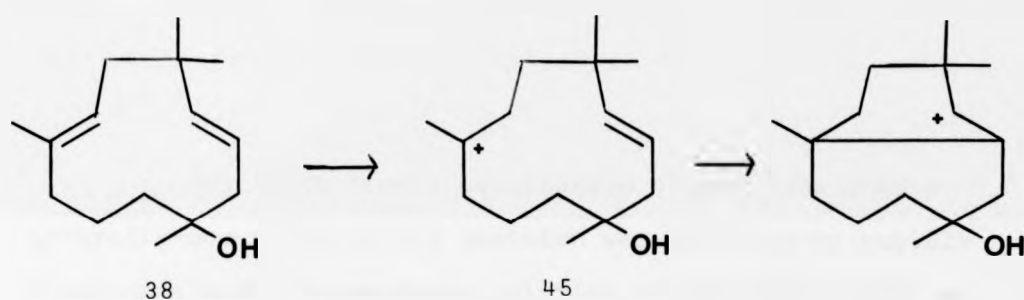
assigned to this molecule. This name was considered appropriate in view of its "rocket-like" shape and the position of the functional group. The formation of this alcohol was rationalised



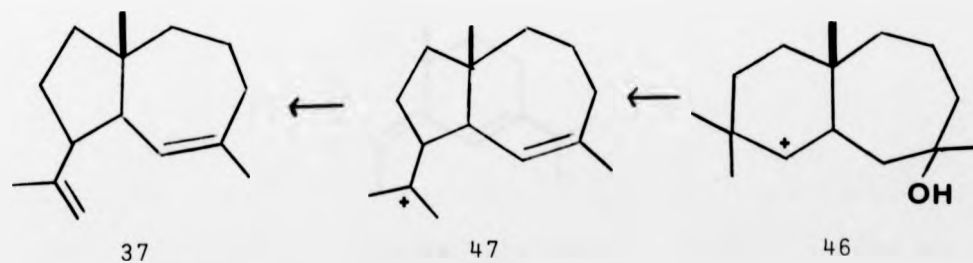
as a result of deuterium incorporation experiments²². The generation of humulol (38), which occurs as a by-product from the rearrangement reaction as a result of the hydration of the most reactive double bond, is considered to be the first step in the sequence. Dehydration of humulol would either regenerate humulene (29) or the conjugated triene (39). Protonation of (39) would then result in the formation of the allylic carbocation (40) which could be envisaged to undergo transannular cyclisation and yield the tertiary carbocation (41). A subsequent cyclisation of this olefinic carbonium ion would afford the tricyclic cation (42). A Wagner-Meerwein rearrangement to give (43) would relieve the strain imposed by the cyclobutane ring and give the alcohol (34) on solvent capture. The intermediacy of (42) is strongly implicated as a result of the mode of synthesis of apollanol (27) by Corey and Nozoe²³ whereby treatment of the ketone (44) with methyl lithium followed by acid-catalysed dehydration of the resultant alcohol produced apollanol exclusively.



Meanwhile the formation of the hydrocarbons (35), (36) and (37) could also result from the alcohol (38) in a competitive mechanism. Protonation of humulol (38) would give the more stable tertiary carbocation (45). The transannular cyclisation of this cation would result in the formation of the bicyclic carbonium ion (46) which would give the hydroazulene carbon skeleton by a Wagner-Meerwein rearrangement to (47). The hydrocarbons could then be obtained from this carbocation by loss of

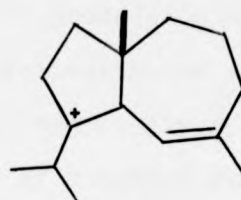


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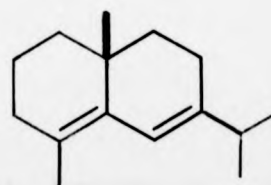
a proton to yield the hydrocarbons (36) or (37) or by a hydride shift to (48) followed by elimination of a proton to give either

(35) or (36).



48

The first direct cyclisation of humulene into a naturally-occurring carbon skeleton was achieved by rapidly dispersing a dichloromethane solution of the hydrocarbon at 0-5° in concentrated sulphuric acid²⁴. A major component of



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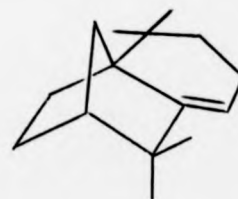
this rearrangement reaction was found to be eudesma-4,6-diene (δ -selinene) (49). The mechanism for the production of this

olefin from humulene is still under review. However it serves as a further example of how the triene humulene can undergo a variety of transannular cyclisations to form a number of bicyclic and tricyclic skeletons. The rearrangements discussed so far involve the overall production of C-C σ bonds from C-C π bonds by transannular cyclisation of a cyclic diene and a cyclic triene. Consideration will now be given to those isomerisations which involve the rearrangement of a carbon skeleton to relieve the strain imposed by bridged polycyclic rings on a molecule.

The isolation of isolongifolene (51) from the acid-catalysed rearrangement of longifolene (50)²⁵ has led to two

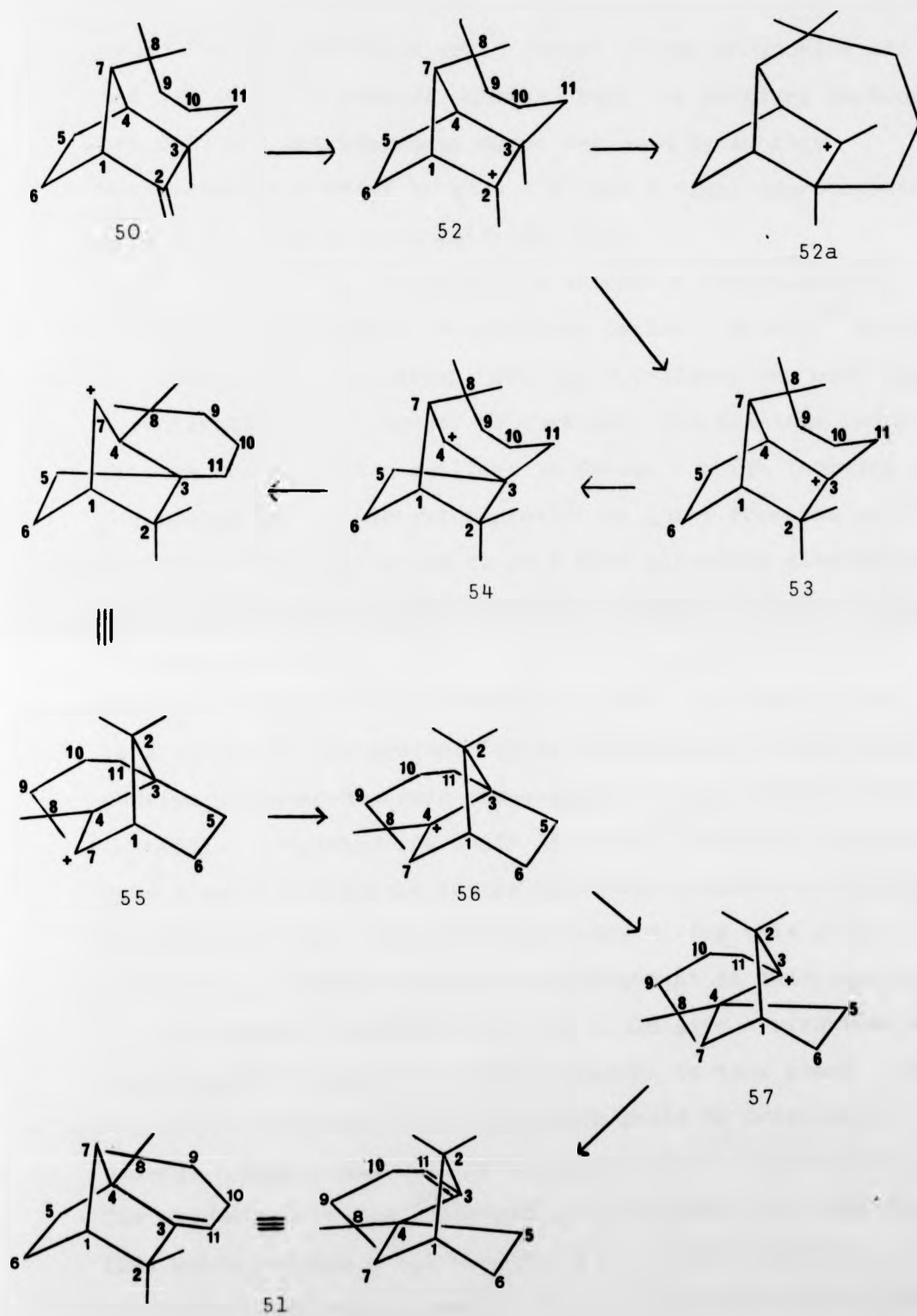


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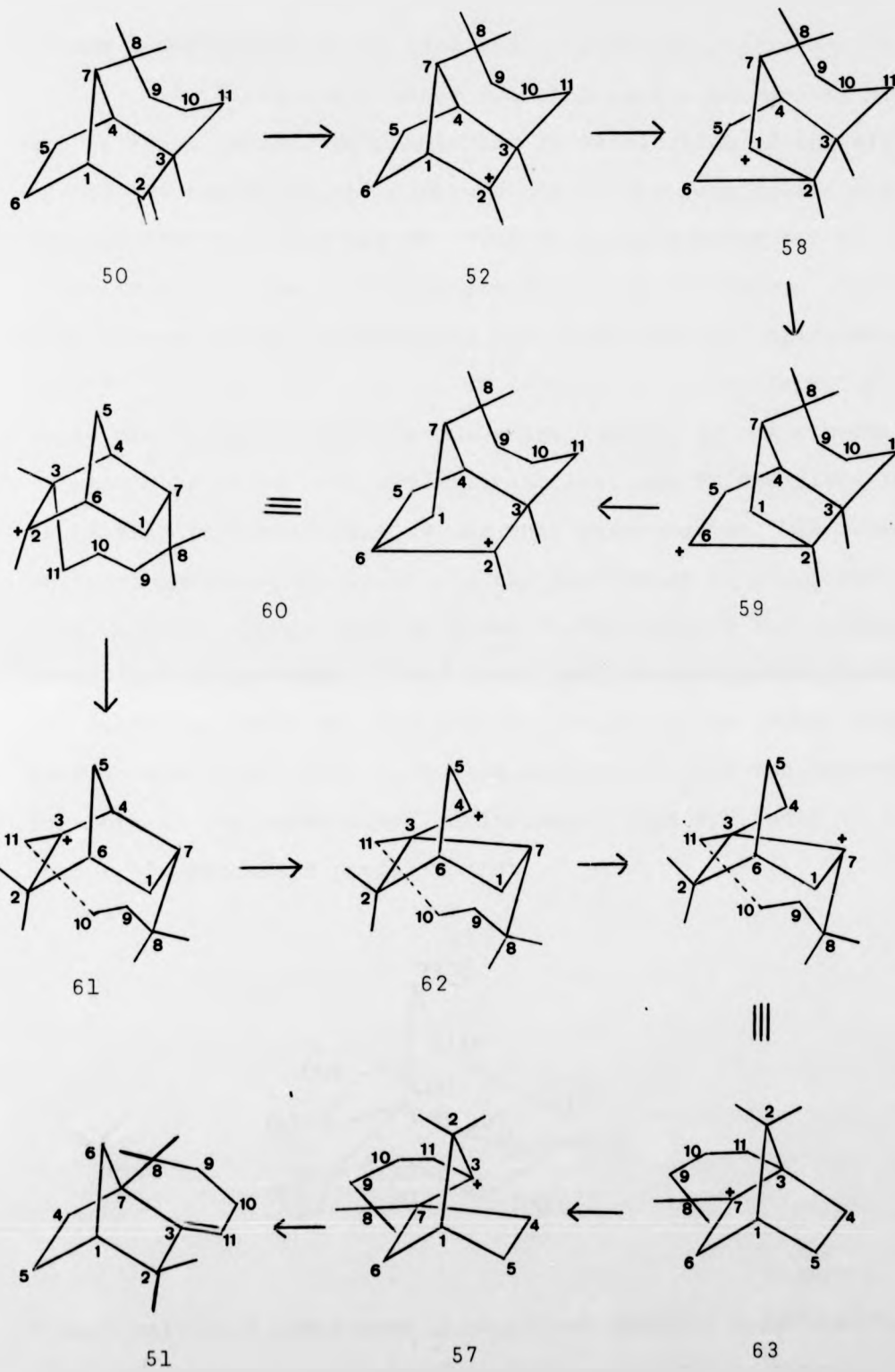
alternative mechanistic hypotheses. Sukh Dev²⁶ considered the mechanism to involve a sequence of Wagner-Meerwein shifts as depicted in Scheme 3. It was envisaged that the initially-formed cation (52) could undergo an endo-3,2-methyl migration to produce the carbonium ion (53). Consecutive Wagner-Meerwein rearrangements



Scheme 3

could then follow which would result in the production of the ion (55). A hydride shift to form the tertiary carbonium ion (56) was considered to occur followed by another Wagner-Meerwein shift to give (57) and a final deprotonation step would lead to isolongifolene (51).

However, following his intensive investigations into the rearrangement of norbornyl cations, Berson²⁷ demonstrated the overwhelming preference for exo-3,2-migrations over endo-3,2-migrations in 2-norbornyl cations. His findings led him to propose the mechanism outlined in Scheme 4 which includes a more favourable exo-3,2-methyl migration in going from the cation (60) to (61). This was deemed to be a more plausible alternative to the previous scheme which involved an endo-3,2-methyl migration in going from (52) to (53). A detailed examination of the mechanism reveals the following features. The cation (52) formed as a result of the protonation of longifolene is considered to undergo a Wagner-Meerwein rearrangement to give the carbonium ion (58). A 6,2-hydride shift is readily achieved, requiring only a small adjustment to the norbornyl skeleton to accommodate the non-classical carbonium ion formed during this process, to give (59). A Wagner-Meerwein rearrangement of this carbocation to the tertiary carbonium ion (60) would give a structure which would allow the exo-3,2-methyl migration to take place. Methyl migration would then give (61) which could be considered to undergo a Wagner-Meerwein rearrangement to the carbocation (62). The production of the isolongifolene skeleton (51) from the cation (62) would require a 6,2-hydride shift to (63) followed by another Wagner-Meerwein rearrangement. As in the mechanism described in



Scheme 4

Scheme 3 deprotonation of (57) would yield isolongifolene (51).

At first sight these two alternative mechanisms may appear to be indistinguishable but an examination of the effects of the two routes on the carbon atoms in the longifolene skeleton reveals that a method may be found which will prove one or other to be correct. The positions predicted for the carbon atoms of longifolene in the bridged-ring system of the isolongifolene skeleton by Sukh Dev's mechanism (Scheme 3) are different from those predicted by Berson's mechanism (Scheme 4). Furthermore, it should be noted that optically-active longifolene gives rise to racemic isolongifolene during this rearrangement [through the presumed intermediacy of (52a), the enantiomer of (52)] and consideration should also be given to the fate of the carbon atoms in the racemisation and subsequent rearrangement processes. The positions predicted for the occupation of the carbon atoms of longifolene in the isolongifolene skeleton by the two mechanisms for both of the enantiomers of isolongifolene are shown in Fig.1. Sukh Dev's mechanism predicts that

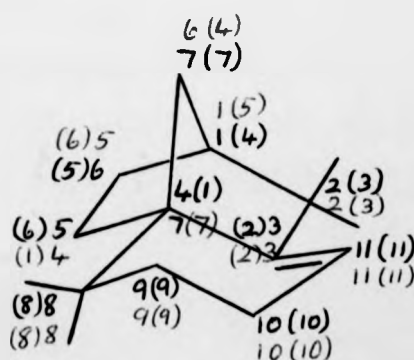


Figure 1

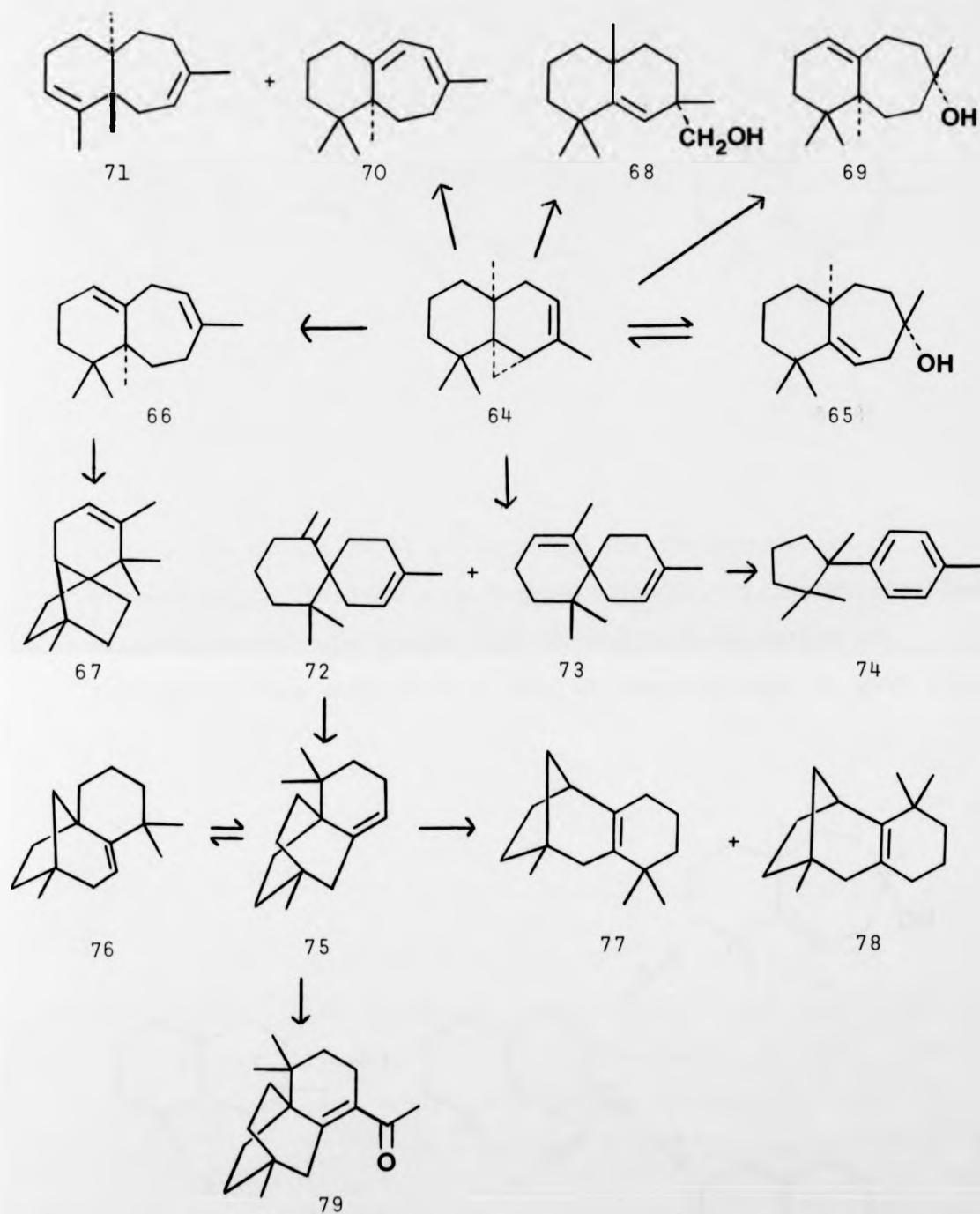
Black:- position of carbon atoms of longifolene predicted by Dev's mechanism

Red:- position of carbon atoms of longifolene predicted by Berson's mechanism

The numbers in parentheses result from the racemisation process.

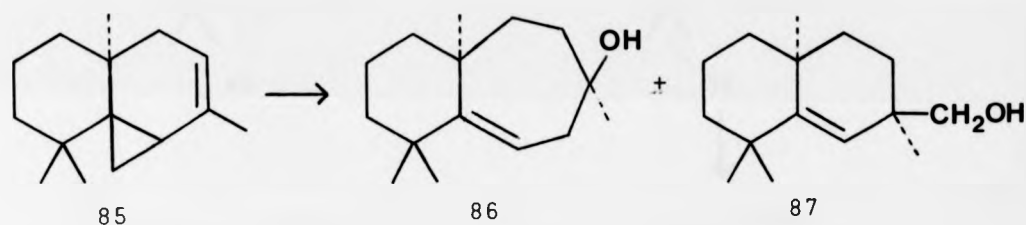
C(7) would assume the position of the bridging carbon atom in both isomers of isolongifolene, whereas this carbon would end up at the tertiary bridgehead position in both enantiomers of isolongifolene following Berson's mechanism. Since this is the only carbon which would appear in the same position in each isomer following racemisation and would have a different position according to whichever mechanism is followed, it would appear, therefore, that labelling this carbon atom with, for example, ^{13}C and the elucidation of its destination in the isolongifolene skeleton would provide supportive evidence for one of these mechanisms.

The most acrobatic of the sesquiterpenes, thujopsene (64), first isolated from the oil of Hibawood²⁸ and a major constituent of American cedarwood oil²⁹, gives a prolific variety of bicyclic and tricyclic compounds on treatment with mineral acid. The structure of thujopsene was established by Erdtman and Norin³⁰ and reveals that this sesquiterpene contains a cyclopropylcarbonyl grouping which is mainly responsible for its chemistry. Treatment of thujopsene with aqueous oxalic acid was reported to give an unidentified hydrocarbon and widdrol (65)³¹. The same product in addition to the bicyclic diene (66) was obtained by Dauben and Friedrich^{32,33} when they investigated the effect of perchloric acid in aqueous dioxan on thujopsene. A close examination of the result revealed that the two products were derived by different pathways. When the isomerisation was carried out on a dideutero-derivative of thujopsene (80), dideuteriowiddrol (81) and the dideuterated bicyclic diene (82) were obtained³⁴. This result

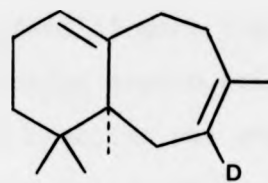


Scheme 5

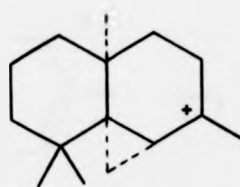
The cyclopropyl ring can be opened by pathway a followed by solvent capture to give widdrol (65) which would explain the position of the deuterium atoms in (81). The alternative opening by pathway b would yield the alcohol (68). The cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement was shown to go with retention of configuration by the conversion of cis-thujopsene (64) to the alcohols (65) and (68) and by the conversion of trans-thujopsene (85) to the alcohols (86) and (87) stereospecifically.



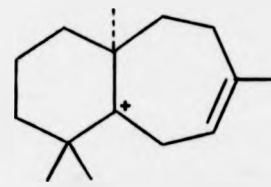
The diene (66) would appear at first sight to arise from widdrol by dehydration and methyl migration. If this was the case, however, the monodeuterated compound (88) would have been the result. In view of the fact that the dideuteriobicyclic olefin (82) was the product obtained from (80) a simple opening of the cyclopropane ring would seem to be involved here. This would give the cation (89). Angular methyl migration to the carbonium ion (90) followed by deprotonation



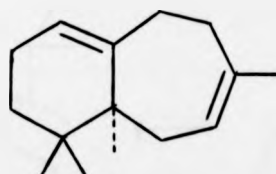
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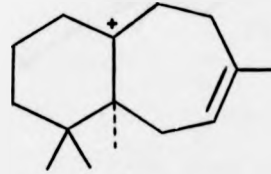
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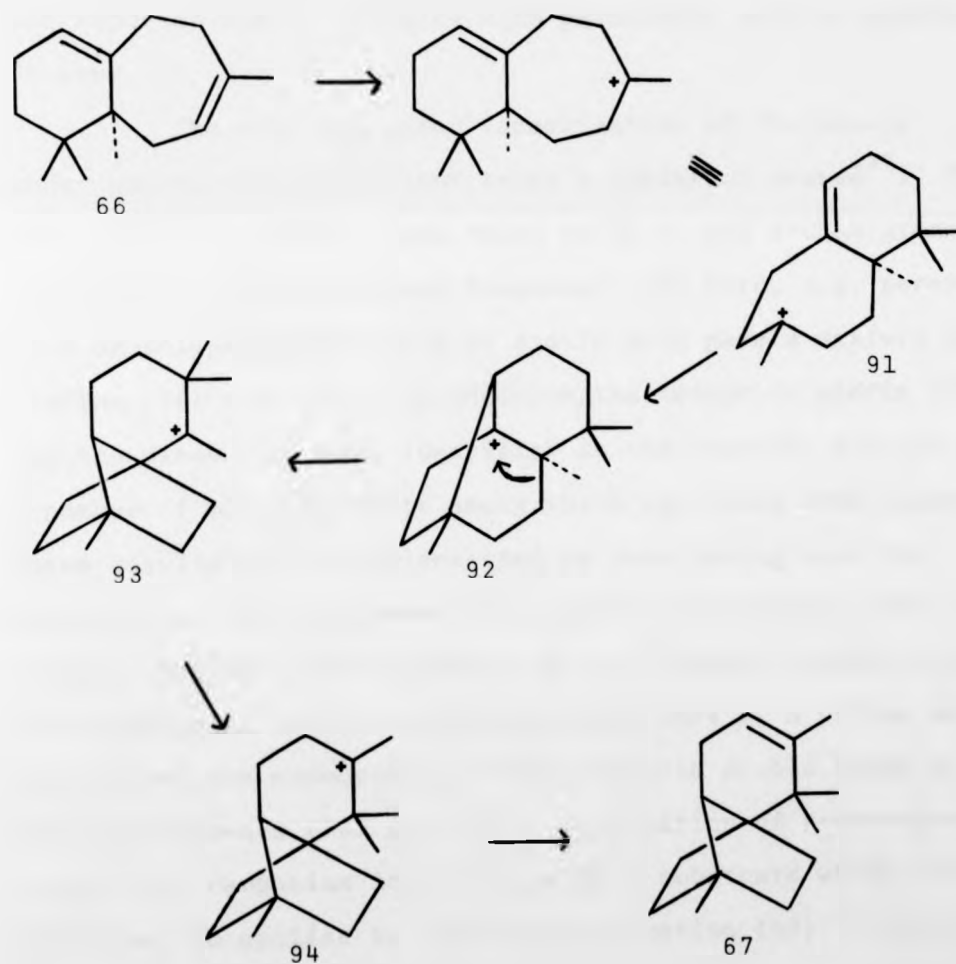
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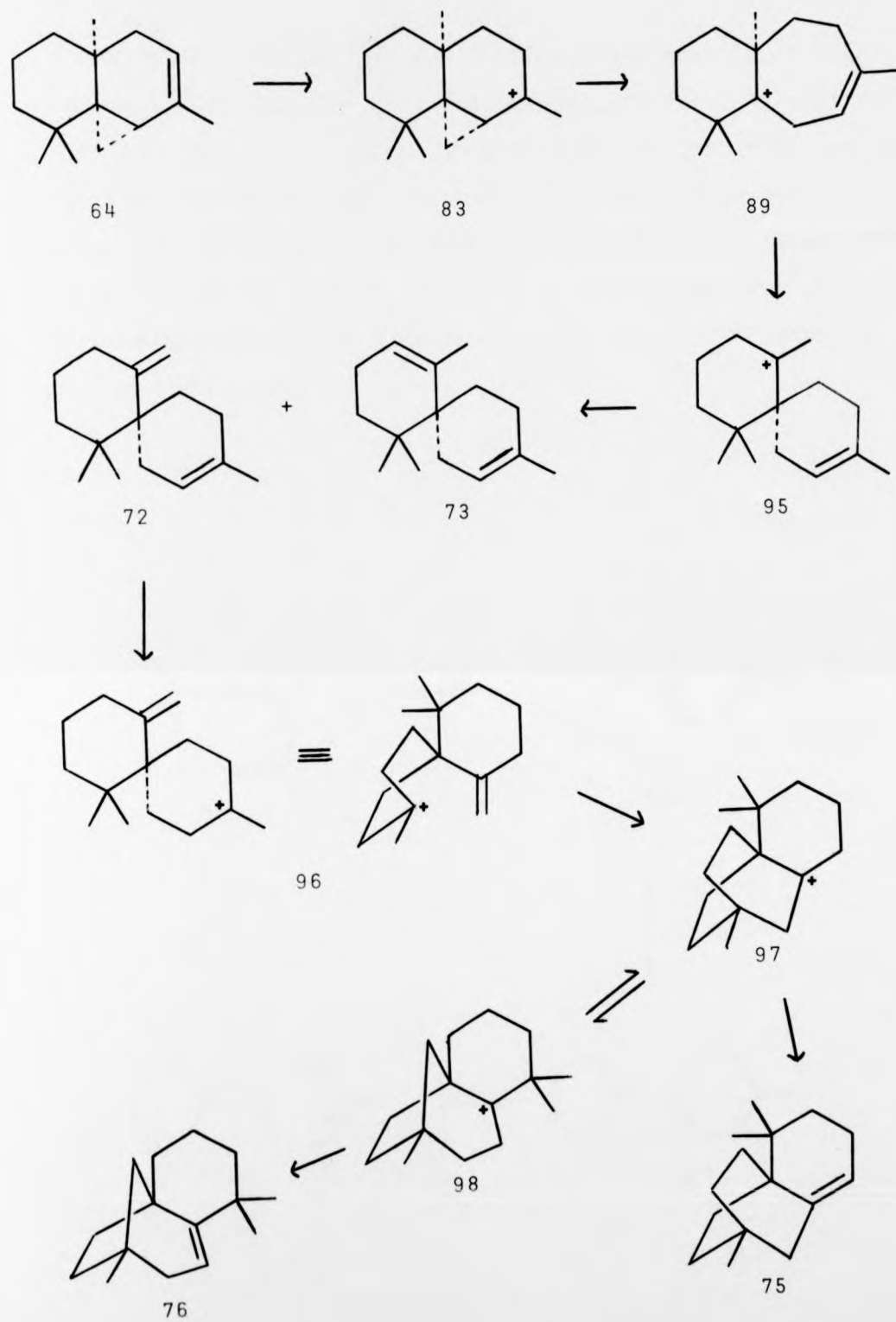
would complete the sequence to give (66). Hydration of this diene affords the alcohol (69). The same type of mechanism can be invoked for the formation of dienes (70) and (71).³⁵ However, under these mildly acidic conditions the diene (66) is the major product.

The slow consumption of the diene (66) by another reaction under these mildly acidic conditions led to the investigation of the effect of more rigorous conditions (0.02M perchloric acid in refluxing acetic acid) on thujopsene. The major product from this reaction was shown to be the tricyclic olefin (67) by Dauben and Friedrich³⁶ who also proposed that it was obtained from the diene (66) in the following way. Protonation of this olefin would give the carbocation (91).

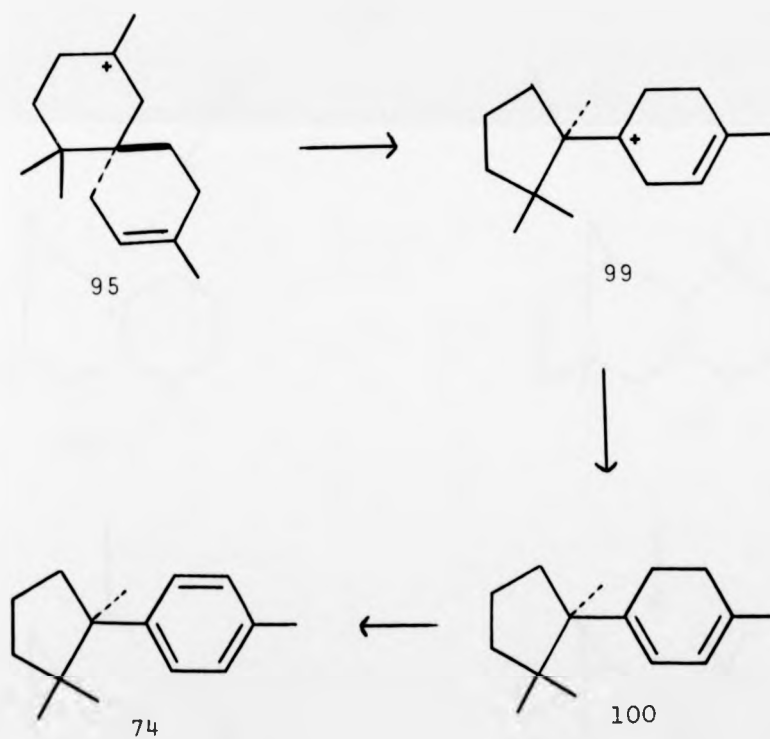


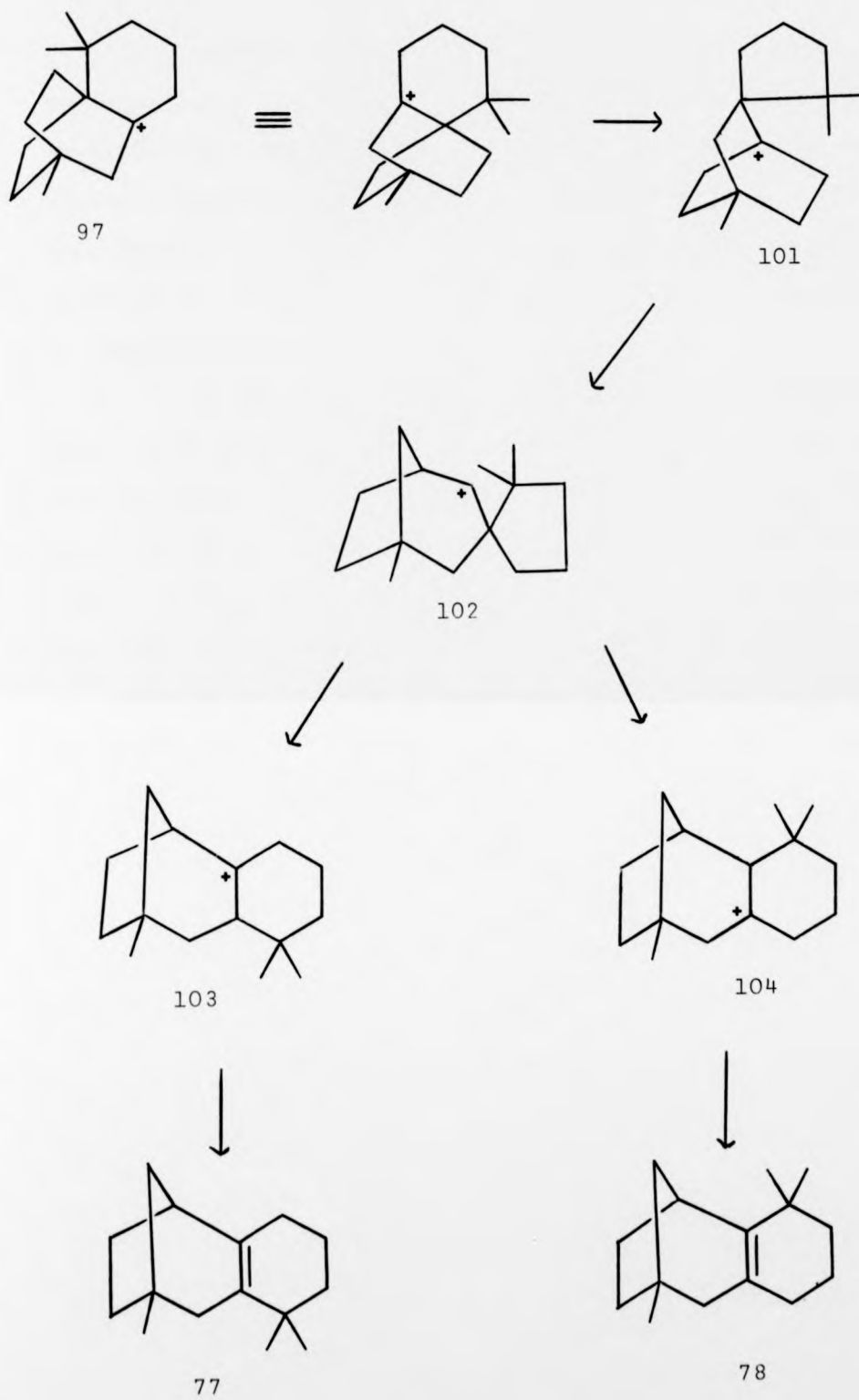
Cyclisation of this carbonium ion would give the tricyclic ion (92) which could undergo a Wagner-Meerwein rearrangement to the less-strained cation (93). A close parallel can be drawn with the proposed mechanism for the production of neoclovene from caryophyllene and this mechanism, in particular the conversion of the carbonium ion (12) to (14) and the proposed conversion of (91) to (93) above. Methyl migration would give (94) from (93) followed by loss of a proton to yield the tricyclic olefin (67). This olefin was also identified by Itô *et al.*³⁵ who reported similar results with perchloric acid in aqueous dioxane.

The acid-catalysed isomerisation of thujopsene under non-aqueous conditions takes a different course³⁷. The major initial products were found to be α - and β -chamigrene (72) and (73) which on continued treatment with acid, e.g. perchloric acid or polyphosphoric acid in acetic acid gave a mixture of the olefins (75) and (76). In addition, the tricyclic olefin (67) and the diene (66) were identified in the reaction mixture with a number of minor products among which was found some cuparene (75). These results can be rationalised by considering that the chamigrenes could be formed through the carbocations (83) and (89). A Wagner-Meerwein rearrangement of this bicyclic carbonium ion to the spirocyclic cation (95) followed by loss of a proton would give either the endocyclic or the exocyclic double bonds of α - and β -chamigrenes (73) and (72). Protonation of β -chamigrene (72) to give the carbonium ion (96) yields a substrate which could be considered to cyclise to the tricyclic cation (97). The tricyclic



olefin (75) would then be obtained on deprotonation of this carbonium ion and (76) by a Wagner-Meerwein rearrangement to (98) and loss of a proton. That cations (97) and (98) are in equilibrium was established by the fact that the same ratio of (75):(76) was obtained on separately treating each isomer with 0.02M perchloric acid in acetic acid. The production of cuparene is considered to arise from the carbocation (95) through the intermediates (99) and (100).





Another two tricyclic olefins were produced on continued acid treatment³⁸. These olefins, (77) and (78), are presumed to originate from the cation (97) through a series of Wagner-Meerwein rearrangements to the cations (101) and (102). The cation (102) would give either the tricyclic carbonium ions (103) or (104) which would afford (77) and (78) respectively on deprotonation.

These interesting rearrangements of thujopsene were given a more aesthetic appeal by the isolation of the ketone (79) from the reaction of American cedarwood oil with acetic anhydride in polyphosphoric acid³⁹. Enriched mixtures of the hydrocarbon (75) could be obtained by careful control of the mixture of acids used and this compound on acetylation yielded the ketone (79).⁴⁰ The warm woody odour of this compound has made it a desirable perfumery material.

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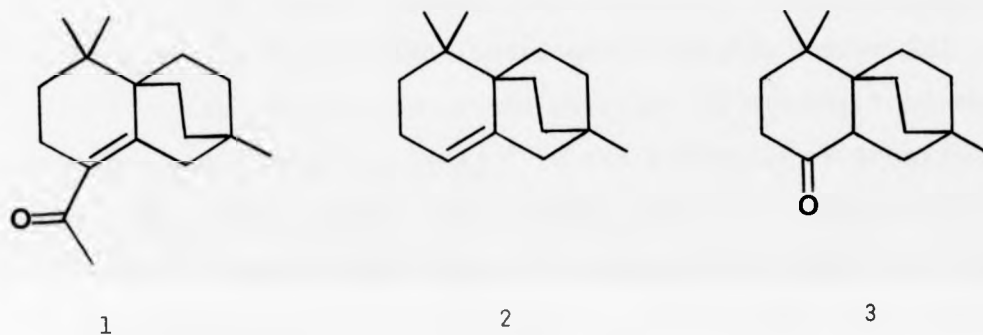
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DISCUSSION

The overall objective of this thesis was to examine various synthetic routes to 2,2,8-trimethyl-5-acetyl-tricyclo-[6,2,2,0^{1,6}]dodec-5-ene (1). The reason for undertaking such an investigation lies in the olifactory properties of the ketone (1) which renders it a useful perfumery material. It is reported to have a woody musk, ambergris odour¹.



Two compounds are closely related to the tricyclic ketone (1). The first is the olefin (2) which, as discussed in the Introduction, is a major acid-catalysed rearrangement product of thujopsene. It has been shown¹ that a Friedel-Crafts acetylation of (2) yields predominantly (1). The other related compound is the hydroboration/oxidation product (3) of (2) which, by reaction with lithium acetylide followed by a Rupe reaction in the presence of formic acid, produces the ketone (1)². Thus it can be seen that the synthesis of compound (2) and/or (3) would constitute a formal synthesis of the ketone (1).

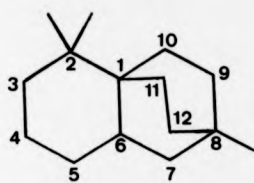
The Discussion will be conducted along the following lines. First of all an analysis will be made of the synthetic problem at hand, in terms of the structural features of these molecules. This will lead on to an outline of the strategies devised to effect the syntheses of these tricyclic compounds. Finally the methods and results of these synthetic endeavours will be presented.

Synthetic Plan

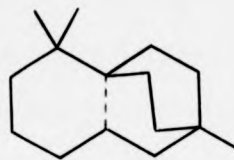
All three compounds have the basic tricyclo[6,2,2,0^{1,6}]-dodecane ring system with functionality at α (5) and/or α (6).

An examination of the molecule in the light of the rules applied by Corey *et al.*³ to the synthesis of longifolene has already been made⁴. The common atoms, i.e. atoms which are bonded to three or four other ring members are C(1), C(6), and C(8) in structure (4). Breaking the bonds between the common atoms in structure (4) generates (5). On the other hand breaking bonds between the common and the non-common atoms gives structures (6) - (11) and the breaking of two bonds between common and non-common atoms gives the structures (12) and (13). This retro synthetic analysis, although not exhaustive, served to simplify the synthetic strategy and, for reasons already discussed, pinpointed structures (6), (8), (12) and (13) as promising synthetic targets.

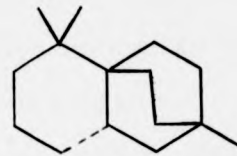
More recently, Corey⁵ has produced a series of detailed papers which define his computer-assisted approach to synthetic analysis which is particularly suitable for bridged polycyclic structures. Although this paper post-dated our synthetic strategy, it is instructive, in hindsight, to consider how this analysis



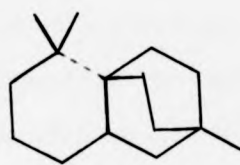
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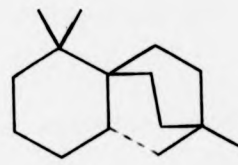
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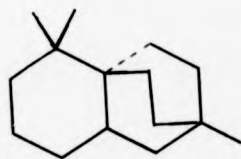
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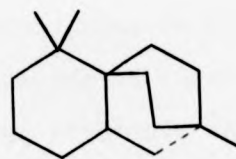
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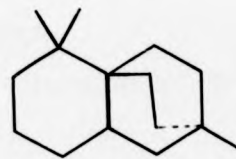
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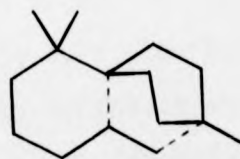
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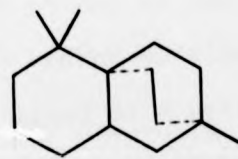
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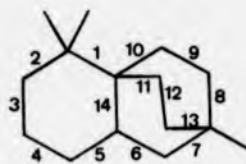


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might have influenced our thinking. Basically six rules should be applied to the bonds in a bridged polycyclic molecular network to identify those bond disconnections which will lead to synthetically desirable precursors. Those bonds which obey these rules are termed the "strategic" bonds. In essence, the rules are as follows:-

- Rule 1. A strategic bond must be in a four-, five-, or six-membered primary ring (a ring which cannot be expressed as the envelope of two or more smaller rings bridged or fused to one another).
- Rule 2. A strategic bond must be directly attached to another ring which is not a three-membered ring.
- Rule 3. Strategic bonds should be in the ring (or rings) which exhibit the greatest degree of bridging.
- Rule 4. A strategic bond must not generate a ring larger than a seven-membered ring on being broken.
- Rule 5. Bonds within aromatic rings are not considered to have potential strategic character.
- Rule 6. Those cleavages which would leave chiral centres on a side chain are avoided.

Thus when each bond in structure (14) is examined in turn with regard to these rules it can be seen from Table 1 that bonds 6, 7, 8, 10, 11, and 13 can be considered strategic bonds and any synthesis should be aimed at a precursor which would require the formation of one of these bonds to complete the tricyclic ring structure. An examination of structure (14)



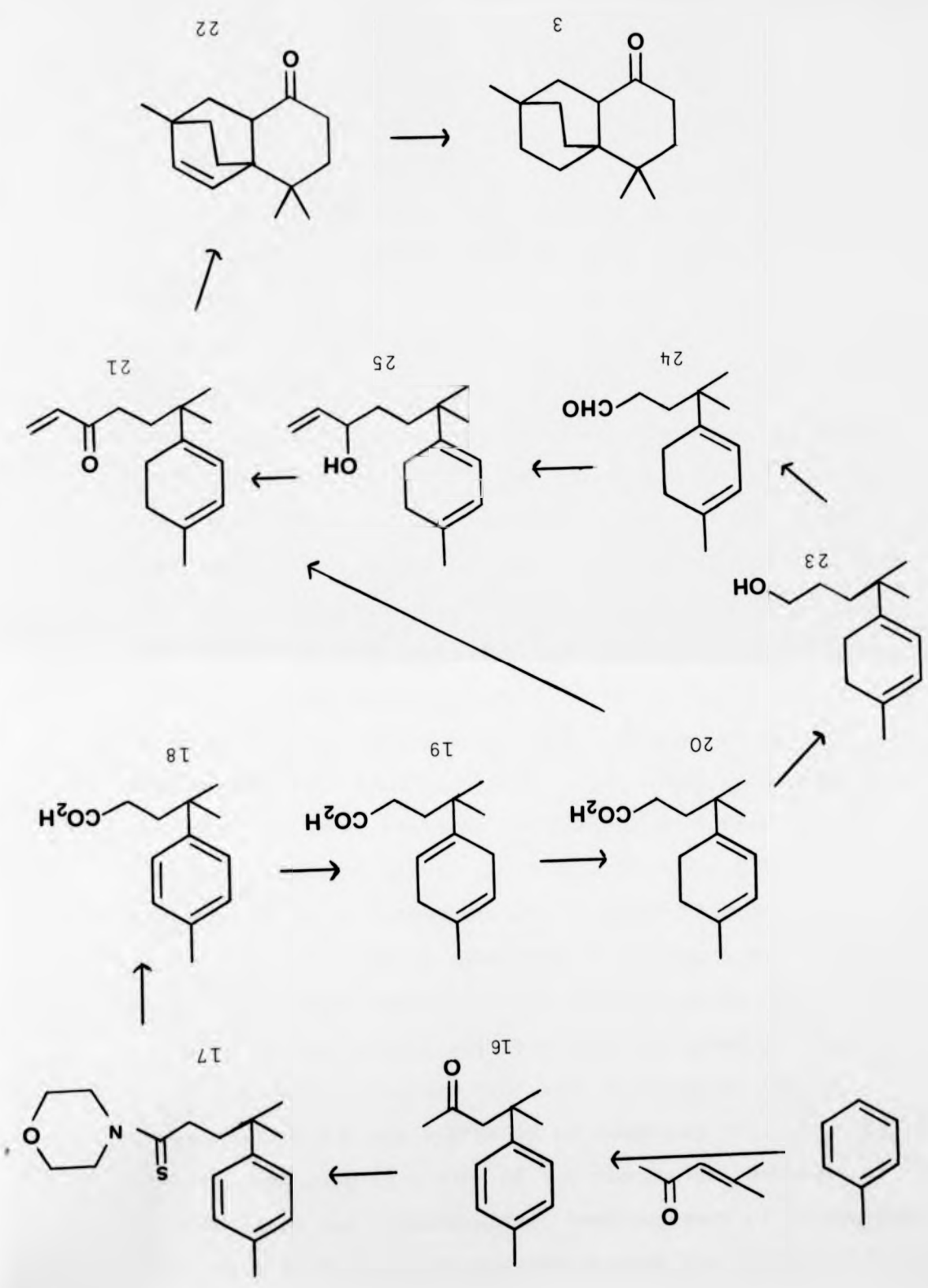
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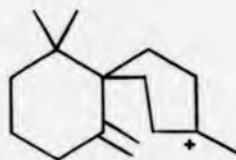
<u>Bond</u>	<u>Rule</u>	1	2	3	4	5	6	<u>Strategic bonds</u>
1		✓	✓	x	✓	✓	✓	x
2		✓	x	x	✓	✓	✓	x
3		✓	x	x	✓	✓	✓	x
4		✓	x	x	✓	✓	✓	x
5		✓	✓	x	✓	✓	✓	x
6		✓	✓	✓	✓	✓	✓	✓
7		✓	✓	✓	✓	✓	✓	✓
8		✓	✓	✓	✓	✓	✓	✓
9		✓	x	✓	✓	✓	✓	x
10		✓	✓	✓	✓	✓	✓	✓
11		✓	✓	✓	✓	✓	✓	✓
12		✓	x	✓	✓	✓	✓	x
13		✓	✓	✓	✓	✓	✓	✓
14		✓	✓	✓	x	✓	✓	x

reveals that bonds 10 and 11, and 8 and 13 are identical because of the symmetry of the molecule. When these factors are taken into account then structures (6), (12), and (13) would be eliminated leaving structure (8) as the most desirable precursor to effect the synthesis of the tricyclic structure (14). However, the possibility of achieving a direct synthesis of the ketone (1), without involving the olefin (2) or the ketone (3), is presented by a precursor similar to structure (6). For this reason, therefore, it is considered worthwhile to include structure (6) as one of the sub-goals. It should also be noted that this approach considers the formation of only one bond at a time and does not allow for the formation of two bonds simultaneously in a concerted process such as a Diels-Alder reaction. Structures (12) and (13) offer the possibility of involving this type of cycloaddition process to bring about the construction of the tricyclic ring system. The synthesis of structure (14) from a precursor such as (13) by a $[4\pi + 2\pi]$ cycloaddition reaction, in fact, requires the simultaneous formation of strategic bonds 11 and 13 (or 8 and 10). The interesting possibility of an intramolecular Diels-Alder reaction is implied in structure (12) which makes this a desirable intermediate to generate for the construction of this tricyclic carbon network.

In the event, suitably functionalised derivatives of structures (6), (12), and (13) were selected as the key intermediates for the syntheses of compounds (1), (2), and (3). Before concluding this part of the discussion, however, it should be noted that the acid-catalysed rearrangement of thujopsene and chamigrene is believed to proceed through the cation (15) whose

Scheme 1





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structure is similar to that of structure (10) and involves the formation of strategic bond 7 to give the olefin (2).

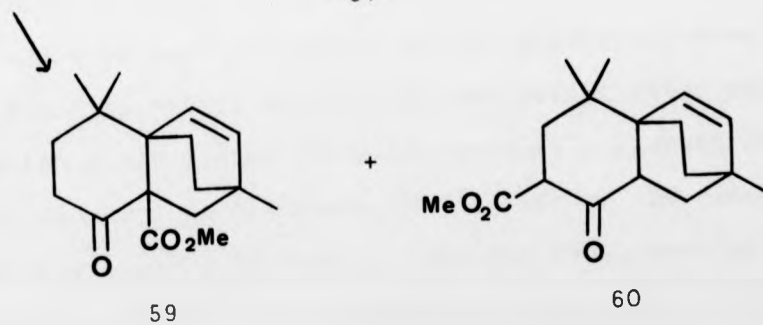
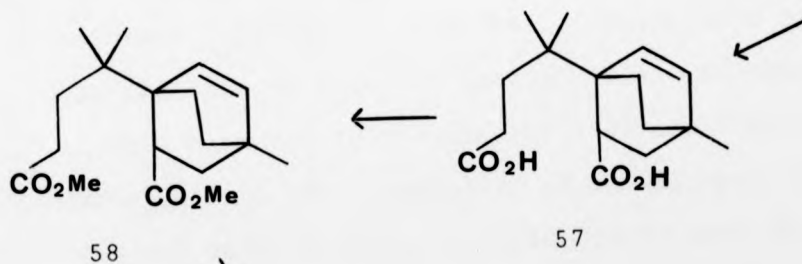
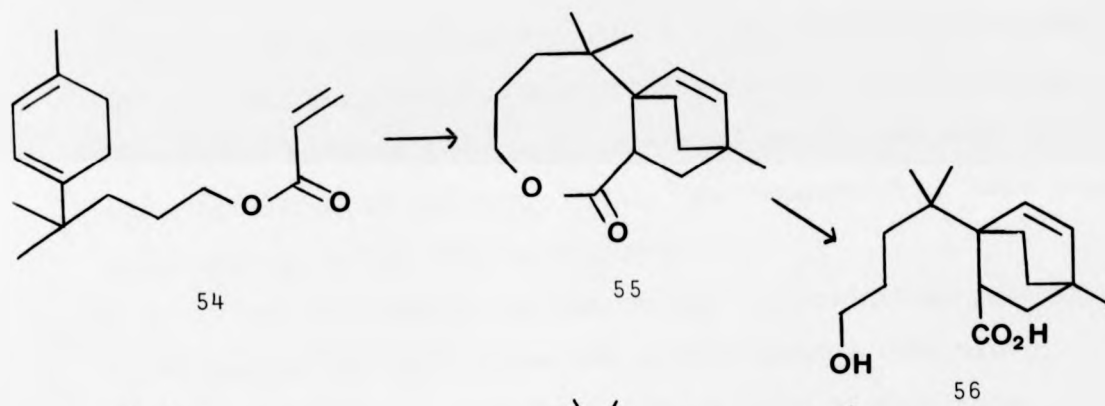
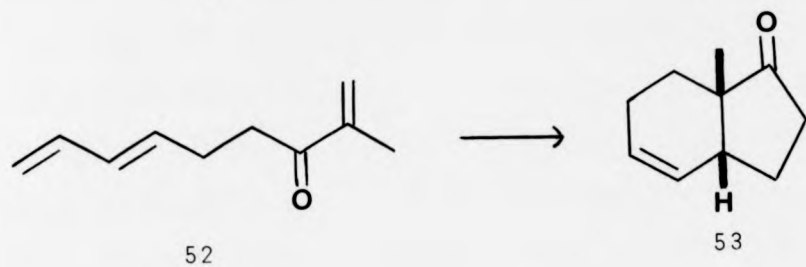
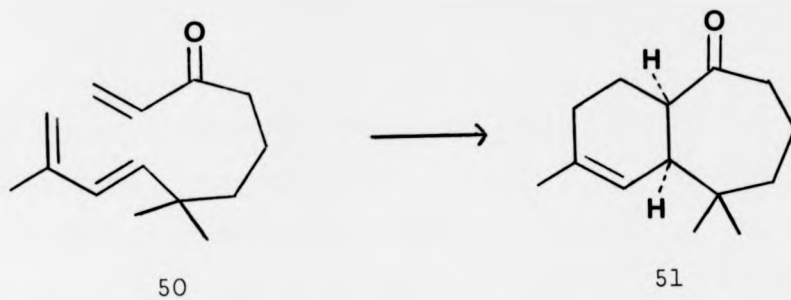
Three synthetic schemes were outlined previously⁴ as viable routes for the production of these compounds. In the light of the present investigations certain alterations were made to these pathways. The modified routes, as well as alternatives, which were thought to be worthy of investigation, are presented in Schemes 1, 2, and 3.

An examination of Scheme 1 reveals that the penultimate step is an intramolecular Diels-Alder reaction. This reaction, which has found increasing utility in recent years⁶, offers the advantages of stereoselectivity, regioselectivity, and increased reactivity as a result of the more favourable entropy factor. When retrosynthetic techniques are applied to the ketone (3) the dehydro derivative (22) is obtained and, then, following a retro-Diels-Alder reaction of the ketone (22), the trienone (21)

is generated. Thus the trienone (21) is seen as the key intermediate for the synthesis of the ketone (3) by an intramolecular cyclisation reaction and as such becomes the primary target for the synthetic sequence. An analysis of this molecule reveals that the main features are a 1,4-disubstituted cyclohexa-1,3-diene which could be envisaged to come from a 1,4-disubstituted benzene, and an alkyl chain bearing a vinyl ketone. The problem can now be narrowed down to the alkylation of toluene in the para-position with a substituent which can be modified subsequently to a vinyl ketone.

The Friedel-Crafts alkylation of toluene with mesityl oxide gives almost exclusively the para-substituted isomer (16). The pentanoic acid (18) can be obtained from this ketone by a Willgerodt-Kinder reaction on (16) to give (17) followed by hydrolysis of this thiomorpholide^{4,7}. Birch reduction of this acid should give the 1,4-diene (19) although there is a possibility of a lactone being formed by an attack on the 1,4-diene by the carboxyl group in the final acidification work-up. For the same reasons the isomerisation of the 1,4-diene (19) to the 1,3-diene (20) by potassium t-butoxide in dimethyl sulphoxide is prone to the same dangers, but it was expected that the 1,3-diene (20) would be obtained without too much difficulty and thus provide the requisite diene for the critical intramolecular cyclisation step.

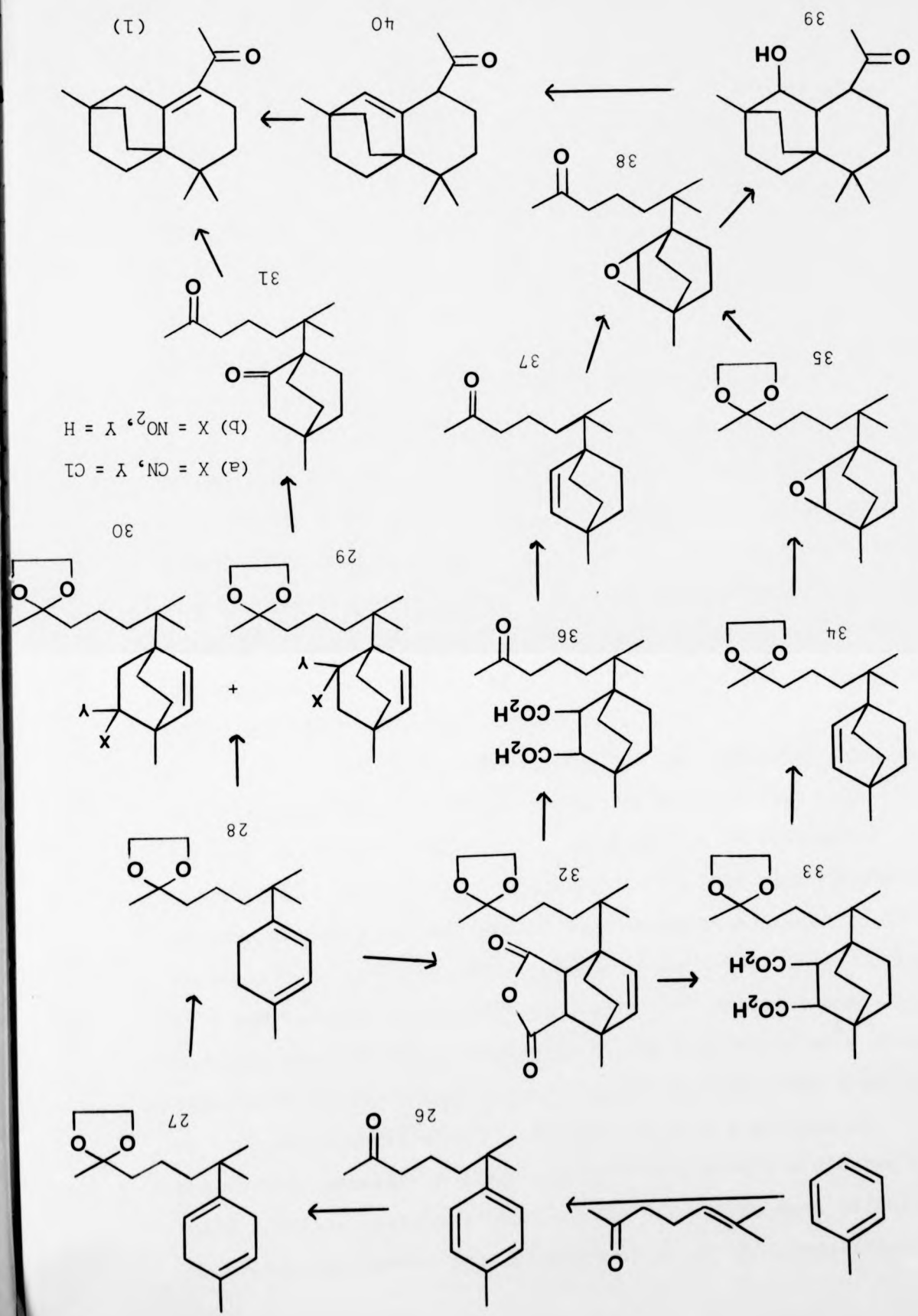
Consideration must now be given to the construction of the dienophile on the side chain for the synthesis of the substrate (21), the precursor required for the intramolecular Diels-Alder reaction. The vinyl ketone could be obtained in



two ways. Lithium aluminium hydride reduction of acid (20) would give the alcohol (23) which, on Collins oxidation, would give the aldehyde (24). Grignard addition of vinyl magnesium chloride followed by oxidation of the allylic alcohol (25) would give (21). However a direct synthesis of (21) from the acid (20) might be achieved by the use of vinyl lithium⁸. Thus it was envisaged that both functional groups could be generated for the production of the key intermediate (21).

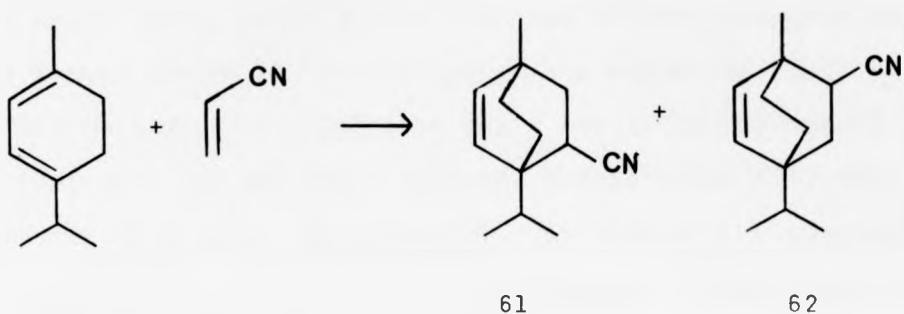
Wenkert and Naemura⁹ have reported the synthesis of the bicyclic ketone (51) from 7,7,10-trimethyl-1,8,10-undecatrien-3-one (50) and the intramolecular cyclisation of 2-methylnona-1,6,8-triene-3-one (52) to cis-7a-methylhydrindan-1-one (53) has been successfully accomplished by Sutherland and Bajorek¹⁰. Both of these reactions give ample precedent for the cyclisation of the ketone (21). Hydrogenation of this ketone would then give the desired compound (3).

An alternative intramolecular cycloaddition process could involve the esterification of the alcohol (23) with acryloyl chloride to give (54). Cyclisation of this ester was expected to give the lactone (55). Further elaboration of this compound to the diester (58) could be achieved by hydrolysis to (56), oxidation of the alcohol (56) to the diacid (57) and esterification of this diacid with diazomethane. This sequence would be much preferable to the apparently more direct process of adding methyl acrylate to the methyl ester corresponding to (20) which would almost certainly produce a mixture of positional isomers. A Dieckmann cyclisation of the diester (58) would probably yield a mixture of (59) and (60), both of which would give the ketone (22) on hydrolysis and decarboxylation.



The motivation for undertaking the synthesis in the manner outlined in Scheme 2 rested on the fact that all but two of the seventeen carbon atoms of the ketone (1) could be brought together in the first step and that if this route was successful then, as already stated, the ketone (1) could be synthesised directly without recourse to the intermediacy of the olefin (2) or ketone (3). The feasibility of this sequence had already been partially tested in as far as the synthesis of the 1,3-diene (28) and its subsequent reaction with maleic anhydride to give the adduct (32) had been achieved⁴. Thus, Friedel-Crafts alkylation of toluene with 6-methylhept-5-en-2-one at low temperature gave the para-substituted isomer (26) in 44% yield. Birch reduction, after protection of the carbonyl function as the corresponding ketal, afforded the 1,4-diene (27) which was isomerised to the 1,3-diene (28) with potassium t-butoxide in dimethyl sulphoxide.

The Diels-Alder addition of a ketene equivalent would provide the most convenient route to the requisite bicyclic intermediate. Almost certainly a mixture of isomers (29) and (30) would be the result of such an addition. It was expected from the work of Braun and Fisher¹¹, who showed that the addition of acrylonitrile to α -terpinene yielded the isomers (61) and (62) in a ratio of 3:2, that the positional isomer (29) would predominate. 2-Chloroacrylonitrile has been shown to be a useful ketene equivalent¹², despite its rather low reactivity. This drawback can be overcome by the use of the more potent dienophile, acrylonitrile which, after addition to a diene, can be chlorinated with phosphorus pentachloride in pyridine to



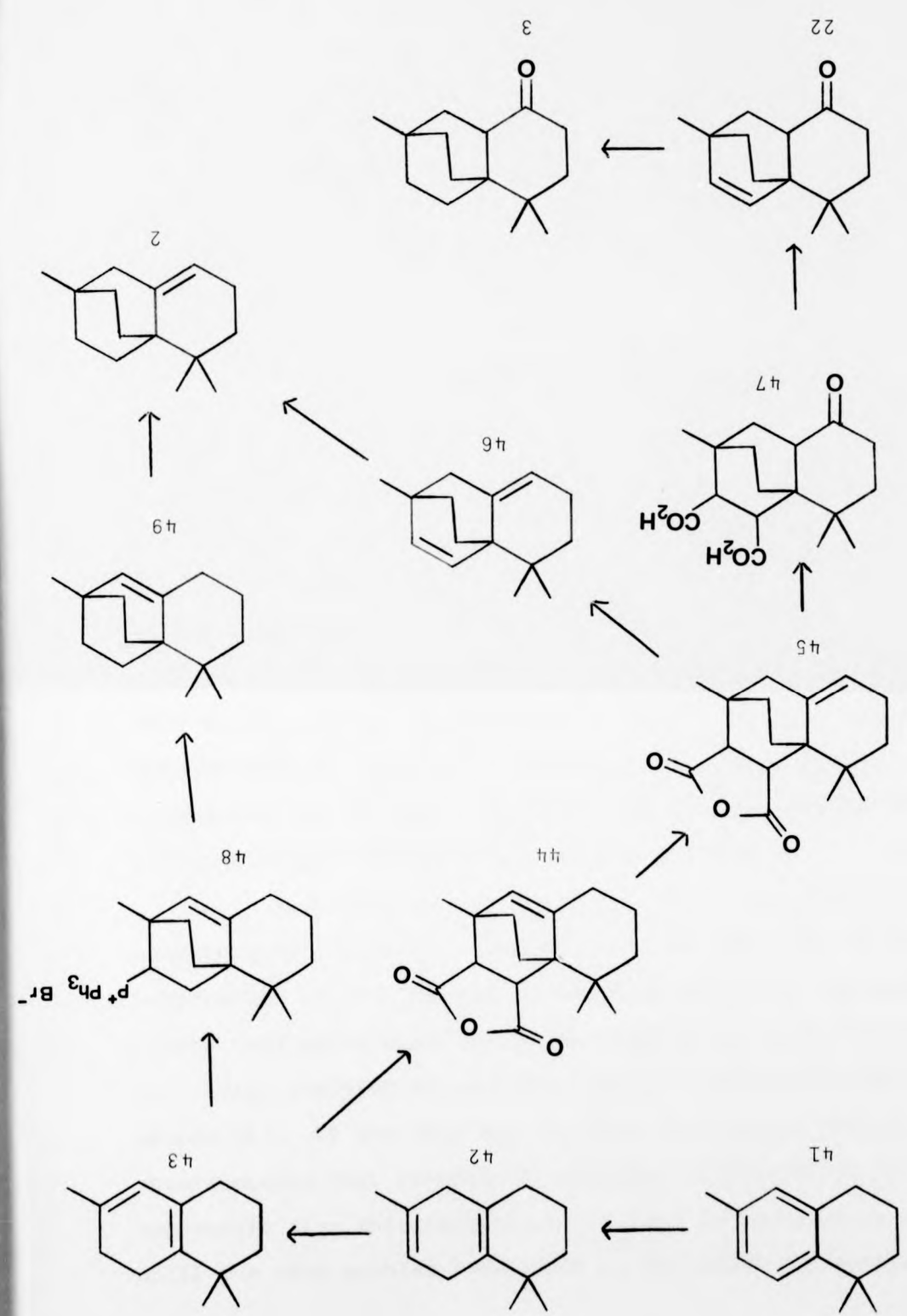
the α -chloronitrile¹³. Thus the isomers (29a) and (30a) would be obtained by one or other of these two alternatives. Another ketene equivalent, used recently by Ranganathan *et al.*¹⁴ in a prostaglandin synthesis, is the powerful but less stable dienophile nitroethylene. It would be expected to give the regioisomers (29b) and (30b) with (28). The diketone (31) would then be obtained, after hydrogenation of the double bond, by either hydrolysis of the isomer (29a) with potassium hydroxide or by the use of sodium sulphide¹², or by treatment of the isomer (29b) with titanium trichloride in aqueous glyme¹⁵ followed by hydrolysis of the ketal in both instances. Intramolecular aldol condensation of this diketone should then take place in the manner shown to complete the synthesis of ketone (1).

An alternative synthesis, whereby the orientation problem associated with unsymmetrical dienophiles could be circumvented, is offered by the readily obtainable adduct (32) from the Diels-Alder addition of maleic anhydride to the 1,3-diene (28). Hydrolysis of

this anhydride with potassium bicarbonate, after hydrogenation of the double bond, would give a solution of the potassium salt of the diacid formed by the opening of the anhydride ring. Acidification of this solution might result in the diacid (33) and/or (36). It was hoped that the diacid-ketal (33) could be obtained by careful acidification. In view of the subsequent oxidative steps it was felt that, at least in the first instance, it would be prudent to retain the methyl ketone protecting group. Bis-decarboxylation of the diacid (33) with lead tetraacetate or by electrolysis should give the olefin (34) which might be converted into the epoxide (35) with *m*-chloroperbenzoic acid. Removal of the protecting ketal group would then give the epoxy-ketone (38). The slightly shorter route for the conversion of (32) into (38) was also deemed to be worthy of investigation. This would involve acidification to give (36), followed by lead tetraacetate decarboxylation to (37) and selective epoxidation of the double bond in possible competition with a Baeyer-Villiger oxidation of the methyl ketone.

This epoxy-ketone was expected to take part in a base-promoted carbanion opening of the epoxide ring to give (39). Dehydration of this alcohol should give initially the unconjugated ketone (40) which might under the conditions of the reaction, e.g. acid-catalysed dehydration, afford the α,β -unsaturated ketone (1). It was felt that if this conjugation did not occur spontaneously that it might be induced. A discussion of the hypothesis that this isomerisation could be achieved is deferred until the same problem re-appears in the projected synthesis

Scheme 3

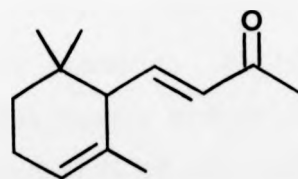


this anhydride with potassium bicarbonate, after hydrogenation of the double bond, would give a solution of the potassium salt of the diacid formed by the opening of the anhydride ring. Acidification of this solution might result in the diacid (33) and/or (36). It was hoped that the diacid-ketal (33) could be obtained by careful acidification. In view of the subsequent oxidative steps it was felt that, at least in the first instance, it would be prudent to retain the methyl ketone protecting group. Bis-decarboxylation of the diacid (33) with lead tetraacetate or by electrolysis should give the olefin (34) which might be converted into the epoxide (35) with *m*-chloroperbenzoic acid. Removal of the protecting ketal group would then give the epoxy-ketone (38). The slightly shorter route for the conversion of (32) into (38) was also deemed to be worthy of investigation. This would involve acidification to give (36), followed by lead tetraacetate decarboxylation to (37) and selective epoxidation of the double bond in possible competition with a Baeyer-Villiger oxidation of the methyl ketone.

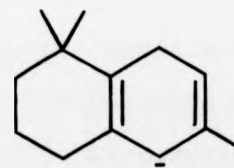
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described in Scheme 3. However it should be acknowledged here that an extra driving force will be provided in this case by the double bond being brought into conjugation with the carbonyl group.

Ionene (41), obtained by the cyclic dehydration of α -ionone (63)¹⁶ (the β - and γ -isomers also give ionene) provides an ideal starting material for the synthesis of the desired tricyclic compounds. The methyl substitution pattern of ionene is identical to that of the tricyclic carbon framework of the compounds (1)-(3). Secondly the aromatic ring has the correct substitution pattern for the construction of the bicyclo[2,2,2]-octane ring system. Birch reduction of ionene has been shown to yield the 1,4-diene (42)⁴. However the structure of 1,3-diene obtained from the isomerisation of this 1,4-diene with potassium *t*-butoxide in dimethyl sulphoxide, could not be positively identified⁴. Intuitively it was felt that removal of an allylic proton by *t*-butoxide would be expected to take place from the less hindered end of the molecule to give the anion (64) and this anion



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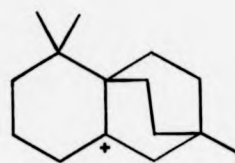


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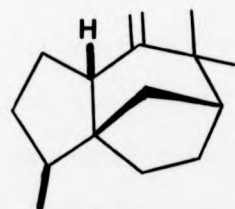
was expected to rearrange to give preferentially the most substituted 1,3-diene (43). Any of the other possible dienes

could not be converted into the 2,2,8-trimethyltricyclo[6,2,2,0^{1,6}]-dodecane system with the double bond at position 5.

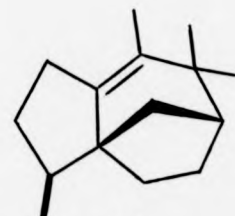
Ideally, in the further elaboration of the functional groups in the synthesis of olefin (1), it would be advantageous to effect the cycloaddition of ethylene to the 1,3-diene (43). Since ethylene is a very unreactive dienophile usually requiring very high temperatures and pressures to form adducts with dienes, a dienophile with an easily removable functional group would provide a reasonable compromise. The use of a ketene equivalent would seem to fulfil these requirements since Wolff-Kishner reduction of the resultant carbonyl function would give the hydrocarbon (49). Fortunately, in this case, the problem of regioselectivity of the dienophile would not raise its ugly head since the activating group is destined for reductive removal. This process would position the double bond in the wrong place but it was considered that, under appropriate acidic conditions, the $\Delta^{6,7}$ double bond could be induced to isomerise into the $\Delta^{5,6}$ position. Such a process would relieve the inherent angle strain of two sp^2 hybridised carbon atoms in the basic bicyclo[2,2,2]-octene ring system. Three pieces of evidence gave some substance to this argument. The first stems from the genesis of (2) itself from thujopsene and/or chamigrene which is believed to arise by deprotonation of the carbonium ion (65)². When the sesquiterpene zizaene (66) is treated with formic acid a mixture of olefin (67) and (69), epimeric at a centre remote from the double bond, are obtained. The olefin (68) was suggested as the logical intermediate in the epimerisation¹⁷. Apparently no major product



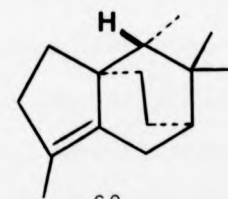
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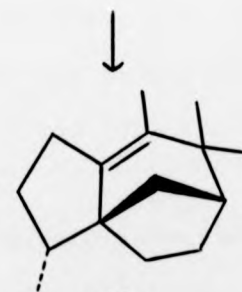
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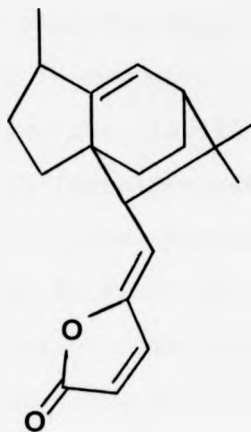
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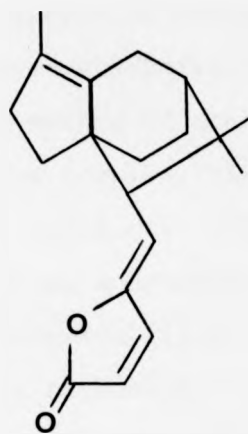
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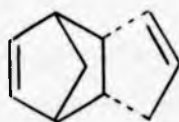


71

corresponding to (49) was detected. The third, less direct piece of evidence, concerns the conversion of eremolactone (70) into isoeremolactone (71)¹⁸. The lactones have been shown to possess the tricyclo[5,2,2,0^{1,5}]undecane carbon skeleton, the subject of a recent synthesis by Fentrill and Mirrington¹⁹. This isomerisation proceeds smoothly with 2N hydrochloric acid in ethanol. It should be noted, however, that in both the zizaene and eremolactone isomerisations the double bonds exocyclic to the bicyclic rings in (68) and (71) are tetra-substituted.

The Diels-Alder addition of maleic anhydride to (43) to give the adduct (44) creates other possibilities. Here again

the double bond was expected to isomerise on treatment with acid to give the anhydride (45). This anhydride could be utilised in two ways. Hydrolysis and bis-decarboxylation would give the diolefin (46). A second method of achieving this transformation was by the use of the complex, bis-(tri-phenylphosphine) nickel (0) dicarbonyl, which was recently developed by Trost and Chen²⁰ to convert an anhydride directly to an olefin. The double bond in the bicyclic[2,2,2] ring system was expected to be more reactive, because it is in a more strained environment than the trisubstituted double bond, and, therefore, more easily hydrogenated. A selective hydrogenation of (72) to (73) has been achieved using a nickel



72



73

boride catalyst²¹, so that the selective hydrogenation of the diolefin (46) to the olefin (2) would seem to be a viable step.

In principle, the anhydride (45) would also provide a means of obtaining the ketone (3). Hydroboration/oxidation of (45) was expected to give the diacid-ketone (47) since Brown *et al.*²² have shown that cyclic anhydrides are reduced

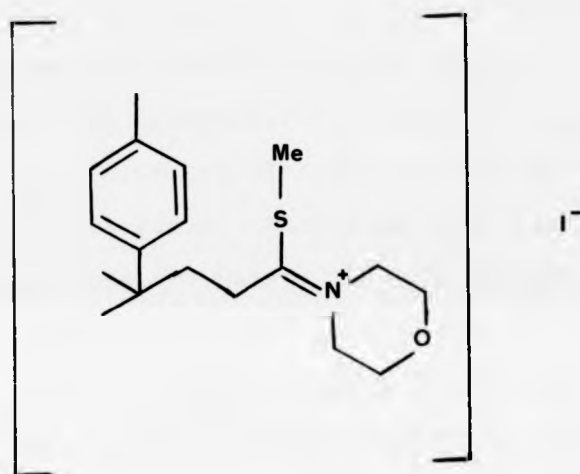
comparatively slowly by diborane. However, even if the anhydride was reduced during the hydroboration then the subsequent oxidation with Jones reagent would be expected to give the diacid (47). Bis-decarboxylation of (47) would then give (22) which on hydrogenation would yield the ketone (3).

Results

The three schemes, discussed above, were investigated to assess their potential as viable routes to the tricyclo-[6,2,2,0^{1,6}]dodecane compounds (1), (2), and (3). The investigation was approached on a broad front giving, whenever possible, equal weight to each of the proposed pathways. The methods used to effect the synthesis of the intermediates will be reported and discussed in terms of their success and efficiency and, where appropriate, alternative means of achieving the same conversion will be compared. Secondly the spectral and, where necessary, the chemical and chromatographic evidence in support of the proposed structures will be presented.

The Friedel-Crafts alkylation of toluene with mesityl oxide, shown in Scheme 1, is well-documented⁷ and posed no problems. The ketone (16) could be obtained in 43% yield by the literature route. An AB quartet ($J = 9$ Hz) at 7.1 δ in the n.m.r. spectrum confirmed that the para-isomer was the predominant product from this reaction. A second isomer, presumed to be the meta-isomer, and amounting to approximately 7%, was indicated by g.l.c. analysis. Similarly the Willgerodt-Kinder reaction with morpholine and sulphur proceeded without major difficulties to give the thiomorpholide (15) in 52% yield. However, the hydrolysis of

the thiomorpholide to 5-methyl-5-p-tolylpentanoic acid with aqueous potassium hydroxide was known to be a low yield reaction, viz. 37%.^{7(a)} Therefore, it was deemed important to consider ways of improving this hydrolysis step. It has been known since 1950 that methylation of a thioamide with methyl iodide renders the hydrolysis of the thioamide more facile²³. This increased reactivity is thought to be due to the greater solubility of the methylthioamide salt in the aqueous phase than the thioamide itself and the greater susceptibility of the iminium group to attack by hydroxide. When the thiomorpholide (17) was heated with methyl iodide in acetone the S-methylthiomorpholide iodide (74) was obtained in 44% yield after recrystallisation. The appearance of a low field methyl group at 2.5 δ is consistent with the salt having been formed which is backed up by an absorption at 1600 cm^{-1} in the i.r. spectrum. Hydrolysis of this salt with 2N aqueous sodium hydroxide gave the acid (18) in quantitative yield. This represents an overall conversion of the thiomorpholide (17) to the acid (18) in 44% yield. This series of steps; formation of the thiomorpholide, methylation, and hydrolysis, can be used in what is virtually a one pot conversion of the ketone (16) into the acid (18). After the morpholide had been formed by refluxing the ketone (16) with morpholine and sulphur for 20 hours the excess morpholine was removed in vacuo from the reaction mixture. The mixture was then dissolved in acetone and heated under reflux with methyl iodide, removal of the acetone in vacuo followed by hydrolysis in 2N aqueous sodium hydroxide completed the conversion. An



ether extraction of the crude alkaline solution removed any unwanted organic materials such as morpholine from the mixture before acidification and isolation of the acid in 47% yield.

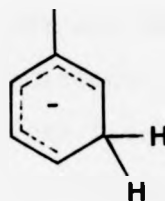
Hall and Satchell²⁴ have shown that cupric ions assist the acid-catalysed hydrolysis of amides. Complex formation of the amide with copper ions would make the amide more soluble in the aqueous medium and thus increase the rate of hydrolysis. Also, coordination of the nitrogen and/or sulphur with copper would weaken the C-N and C-S bonds and make the carbon more susceptible to nucleophilic attack. When the thiomorpholide was warmed with hydrochloric acid containing a little ethanol at 60° in the presence of cupric sulphate the pentanoic acid was obtained in 50% yield. When copper ions were absent, or when an attempt was made to replace the copper ions with mercuric ions, the thiomorpholide was recovered unchanged.

The reaction sequences outlined in the three Schemes all involve at some point the reduction of an aromatic nucleus followed by isomerisation of the 1,4-diene thus formed to a 1,3-diene. After unsuccessful attempts at the reduction of ionene using the conventional Birch reduction conditions, i.e. sodium and ethanol in liquid ammonia, only 50% reduction being attained, the modified method of Kwart and Conley²⁶ was employed. The successful use of this technique, i.e. lithium and ethanol in ethylamine, which is probably due to the higher temperature involved in using ethylamine instead of ammonia, led to its universal application in the reactions described in these investigations. The method of choice for the isomerisation of the 1,4-dienes was the use of potassium t-butoxide in dimethyl sulphoxide.

The strong alkaline conditions of the Birch reduction would generate the lithium salt of the carboxylic acid (18) and effectively remove a mole of lithium from the reaction mixture. Thus in the Birch reduction of the acid (18) an extra mole of lithium was added to make up for this deficiency. In spite of this action, two reductions were necessary to obtain the 1,4-diene (19) in reasonable yield (58%).

Although there is overwhelming precedence for the production of the 2,5-dihydro-product from the Birch reduction of 1,4-dialkylbenzenes²⁶ it would be worthwhile to consider the reasons for the preferential generation of this diene in this kinetically-controlled reaction. The first step in the mechanism of the reaction is the production of a radical anion following the addition of an electron to the aromatic nucleus²⁷. This electron must enter the first antibonding orbital of the aromatic ring. In benzene, itself, the antibonding orbitals are degenerate and the charge would thus be spread over all six carbon atoms. This degeneracy is removed, however, by the addition of a substituent. In toluene the electron enters the antibonding orbital of lowest energy which, because of the electron repelling properties of the methyl substituent, has a node in the direction of the alkyl substituent and the para-position to this substituent²⁸. In the radical anion of toluene, therefore, the charge would be centred around the ortho- and meta-positions with no charge residing at the para-positions. Protonation could occur, as a result of this, at either the ortho- or meta-positions, the meta-position being the more favoured for two reasons. First,

for steric reasons, the meta-position is more accessible to attack by the alcohol and, secondly, the radical which would be formed would have its charge located at the more favourable ortho- and para-positions to the alkyl group²⁷. Following addition of a second electron to this radical, the anion (75) would be formed whose charge would reside mainly at the ortho



75

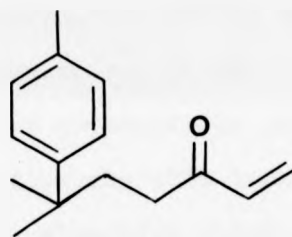
position to the methyl group. Protonation would yield the 2,5-dihydro-product. A similar argument applies to a 1,4-dialkylbenzene, such as *p*-xylene, where both alkyl groups act in a concerted fashion. The structure of the 1,4-diene (19), which would, as a result of these predictions be the expected product from the Birch reduction of the acid (18), was confirmed by its spectral characteristics. A broad peak at 5.4 δ in the n.m.r. spectrum was indicative of two vinylic protons being present in the molecule and a broadish peak at 2.6 δ of four allylic protons. The carboxyl function gave rise to absorptions at 3300 and 1700 cm^{-1} and an exchangeable proton at 11.6 δ in the

i.r. and n.m.r. spectra respectively. Purification of this compound proved difficult in that distillation even at low pressures resulted in decomposition and/or disproportionation of the diene and attempts at recrystallisation also proved unfruitful.

The isomerisation of this 1,4-diene proceeded quite smoothly on stirring with potassium t-butoxide in dimethyl sulphoxide for 3 days to give predominantly the thermodynamically most stable 1,3-diene (20). As a result of the equilibrium between the 1,4-diene (19) and the 1,3-diene (20) that exists under these reaction conditions, the 1,3-diene was not obtained pure and in addition to the 1,4-diene some of the aromatic acid (18) was also detected as a contaminant in the reaction product. From the integration of the n.m.r. spectrum, the amount of 1,4-diene present in the product was calculated to be 20% and the amount of aromatic acid 15%. The generation of the 1,3-diene (20) was confirmed by the appearance of a peak at 5.7 δ , which was much sharper than the vinylic absorptions of the 1,4-diene (19), and the upfield shift of the four allylic protons from 2.6 δ to 2.1 δ in the n.m.r. spectrum. The carboxyl function was demonstrated to be still intact by the presence of a low field exchangeable proton at 10.1 δ in the n.m.r. spectrum and absorptions at 3300 and 1700 cm^{-1} in the i.r. spectrum. A maximum at 267 nm ($\epsilon = 8900$) in the u.v. spectrum reinforced the above evidence that the requisite diene component for the ultimate intramolecular Diels-Alder reaction had been generated. This diene, however, like the 1,4-diene, proved difficult to

purify. Distillation at low pressure resulted in the decomposition and/or disproportionation of the diene and attempts at recrystallisation proved unsuccessful.

Attention was then turned to the elaboration of the dienophile component, *viz.*, the conversion of the carboxylic acid function into the vinyl ketone. As has already been stated the reaction of vinyl lithium with a carboxylic acid in 1,2-dimethoxyethane has been used with a fair degree of success to generate a vinyl ketone directly⁸. To test the feasibility of this step the aromatic acid (18) was used as a model compound. The vinyl ketone (76), identified by a multiplet at 5.9 δ in the n.m.r. spectrum and



76

by an absorption at 1665 cm^{-1} in the i.r. spectrum, was separated in low yield (10%) from the crude reaction mixture after extraction with sodium carbonate solution and preparative t.l.c. In spite of the low yield it was decided to attempt the synthesis of the vinyl ketone (21) from the acid (20) using this procedure. However, the 1,3-diene carboxylic acid (20) was recovered unchanged from the reaction with the vinyl lithium. It may

have been the impurities present in the 1,3-diene that caused this lack of success. The failure of this reaction and the fact that vinyl lithium could no longer be obtained commercially led to the temporary abandonment of the investigation of this particular synthetic sequence. However, it is felt that if an excess of vinyl lithium is used in the above reaction or if the alternative route viz., reduction of the acid to the alcohol (21), oxidation to the aldehyde (22), addition of vinyl magnesium chloride followed by oxidation of the allylic alcohol (33), can be exploited, the synthesis may be successfully completed. The intramolecular reaction should be quite facile and the hydrogenation step should present no problems.*

The investigation of the synthetic sequence outlined in Scheme 2 was carried out in the knowledge that the Diels-Alder adduct (32) had been successfully synthesised by the proposed steps⁴. The para-disubstituted isomer was obtained, in reasonable yield (46%), by the aluminium chloride-catalysed Friedel-Crafts alkylation of toluene with 6-methylhept-5-en-2-one provided that the temperature of the reaction was kept below -5° . When the temperature rose above -5° , for any length of time, increasing amounts of the unwanted meta-isomer were obtained. The predominance of the para-isomer was indicated by the presence of an AB quartet at 7.0 δ in the n.m.r. spectrum similar to that obtained for the ketone (16) which is known to be mainly the para-isomer. The ketone (16) could be separated into two isomers

* The very recent report⁴⁷ of a synthesis of ketone (3) from the acid (18) has confirmed the soundness of the conclusions made here.

by g.l.c. It was found that the isomer with the longer retention time was the para-isomer. Armed with this information the g.l.c. analysis of the methyl-tolylheptanone (26) was used to establish the ratio of the isomers as 75:1 in favour of the para-isomer. The Birch reduction, following the protection of the carbonyl group as the ethanoketal, to the 1,4-diene (27) was improved by using a seven-fold molar excess of lithium and seven moles of ethanol per mole of ketal. The 1,4-diene (27) could be obtained virtually free from aromatic material after one reduction (two reactions had been required previously to effect a reasonable reduction of the aromatic nucleus⁴) in 88% yield. The structure of this diene was elucidated by the examination of its n.m.r. spectrum. A broad peak at 5.4 δ and one at 2.6 δ , similar to the corresponding absorptions obtained for the 1,4-diene (19), indicated that the product from the reaction was the 1,4-diene (27). The conjugation of this diene with potassium t-butoxide in dimethyl sulphoxide gave a quantitative yield of an oil which was shown by its n.m.r. spectrum to be mainly the 1,3-diene (28), from the peak at 5.6 δ and the absorption due to the allylic protons at 2.05 δ , and by a maximum at 265 nm. ($\epsilon = 9160$) in the u.v. spectrum. As before, the n.m.r. spectrum also showed that some dehydrogenation had taken place to give some of the aromatic ketal and that some 1,4-diene still remained in the equilibrium mixture. The Diels-Alder reaction with maleic anhydride was accomplished in refluxing xylene to give the adduct (32) in 75% yield. An AB quartet ($J = 8.5$ Hz) at 6.15 δ and one at 3.05 δ ($J = 9$ Hz) in addition to the singlets at 3.9, 1.35, 1.15 and 1.05 δ in the n.m.r. spectrum and absorptions at 1835 and 1775 cm^{-1}

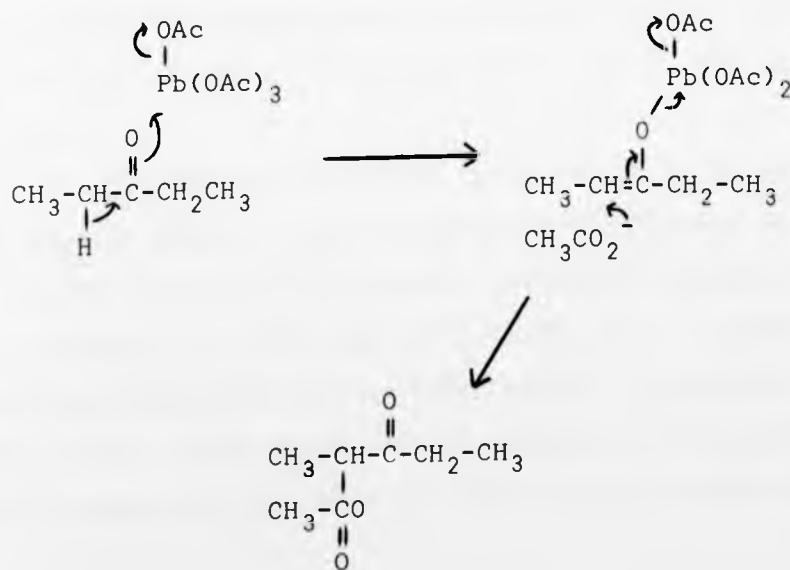
in the i.r. spectrum confirmed that the adduct had been formed.

The addition of certain ketene equivalents to the 1,3-diene (28) had already been investigated⁴ with little success. For instance, reactions with α -chloroacrylonitrile had proved entirely unsuccessful and those with acrylonitrile were only partially successful. The product of the latter reaction indicated that a mixture of adducts was obtained. Because of the low yield and the uncertainty of which isomer was which, this reaction was not studied any further. Instead attention was directed towards nitroethylene which seemed to offer a better alternative, certainly in terms of reactivity (e.g. it undergoes cycloaddition to a 5-substituted cyclopentadiene at 0°).¹⁴ However, when an attempt was made to react nitroethylene with the diene (28) polymerisation of the nitroethylene occurred with the result that the cycloaddition reaction had no chance of taking place. It is known that polymerisation of nitroethylene takes place rapidly on contact with alkali²⁹. Because of the method of preparation of the 1,3-diene (28) and because of the difficulty in purifying it, the possibility of trace amounts of alkali being present was extremely likely. The 1,3-diene-ketal (26) was considered too acid-labile to test this hypothesis, so that further investigation, due to this impasse and the dubious merits of the mixture of resultant regioisomers, was abandoned.

Since the maleic anhydride adduct (32) had been successfully prepared our attention was focussed on an alternative means of constructing the tricyclic framework. It was envisaged that this anhydride could be converted into the epoxy-ketone (38)

which could then be induced to cyclise in the appropriate manner to give the desired tricyclic carbon skeleton. Two sequences were open to us for the synthesis of the epoxy-ketone (38), each with its own merits and pitfalls. The danger that the carbonyl function might come under attack, during the oxidative steps, i.e. lead tetraacetate bis-decarboxylation and epoxidation with *m*-chloroperbenzoic acid, in going from (33) to (35), could be prevented by retaining the protecting ketal group. This would, however, present the problem of removing this grouping with aqueous acid in the presence of the acid-sensitive epoxide function. This danger could be averted by removal of the ketal at an earlier stage in the sequence but would bring with it the twin hazards of exposing the methyl ketone to the action of lead tetraacetate and *m*-chloroperbenzoic acid.

Lead tetraacetate is known to give an α -acetoxyketone with enolisable ketones³⁰ in the manner shown below. The product from the reaction of lead tetraacetate with the diacid-ketone (36)

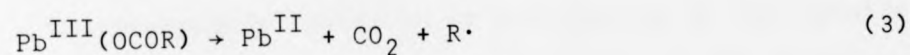
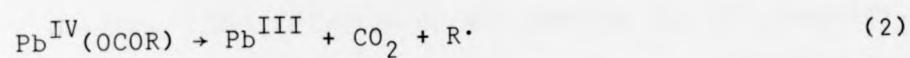
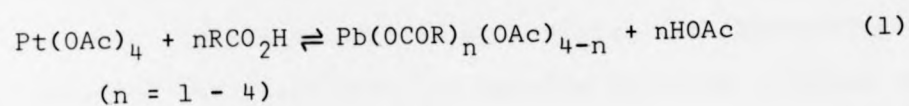


would therefore depend on the relative reactivities of the carboxyl and carbonyl functions with the lead tetraacetate. Provided that the decarboxylation of (36) could be successfully performed there only remained the hurdle of the epoxidation step. This again may be subject to the relative rates of epoxidation of the double bond and the Baeyer-Villiger reaction with the methyl ketone.

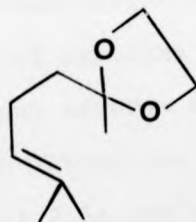
With these thoughts in mind work was started on the conversion of the adduct (32) into the epoxy-ketone (38). Hydrogenation of (32) followed by hydrolysis with potassium bicarbonate solution gave a solution of the potassium salt of the diacid-ketal (33). When this solution was rapidly neutralised with dilute hydrochloric acid, while being cooled in an ice-bath, and extracted with diethyl ether the diacid-ketal (33) could be recovered in 71% yield without extensive deketalisation taking place. This was shown to be the case by a four proton resonance at 3.95 δ in the n.m.r. spectrum. The dicarboxylic acid function was indicated by absorptions at 3300 and 1740 cm^{-1} in the i.r. spectrum and by two exchangeable protons at 10.55 δ in the n.m.r. spectrum.

The diacid-ketal (33), obtained in this manner, was subjected to lead tetraacetate bis-decarboxylation in the presence of pyridine³¹ to give in 39% yield the olefin (34). An AB quartet ($J = 9$ Hz) at 6.05 δ in the n.m.r. spectrum confirmed that this transformation had taken place. In addition to the olefin (34) a large amount of the anhydride (32) was obtained in the crude reaction mixture, which could be separated from the

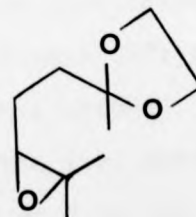
olefin by treatment with potassium bicarbonate solution and if necessary recycled. The mechanism of the lead tetraacetate reaction is currently accepted as being of a radical nature and to follow the course outlined in equations 1 to 4^{31,32}.



An epoxidation procedure has been developed for acid-sensitive olefinic compounds³³ using *m*-chloroperbenzoic acid in a two-phase system of dichloromethane-aqueous sodium bicarbonate. Thus the olefin-ketal (77) has been converted into (78) in good



77

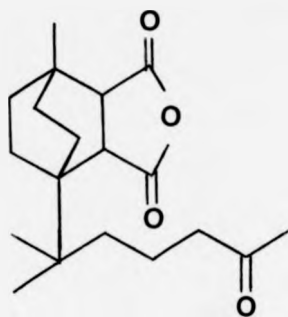


78

yield. Using this technique, epoxidation of the olefin-ketal (34) proceeded smoothly to give in 97% yield the epoxide (35), which was confirmed by the loss of the AB quartet at 6.05 δ and the appearance of an AB quartet ($J = 6$ Hz) at 3.0 δ and retention of the singlet (4H) at 3.9 δ in the n.m.r. spectrum of the product. Treatment of this epoxy-ketal with hydrochloric acid confirmed our fears that the epoxide would be affected by this procedure. The ketal group was removed but the epoxide grouping was no longer present. Instead the product appeared to be a diol, presumably, obtained by the opening of the epoxide ring.

Meanwhile the decarboxylation of the diacid-ketone (36) followed by epoxidation to (38) was investigated. The diacid-ketone (36) could be obtained by acidification of the solution of the potassium salt of the diacid ketal (33) at ambient temperature (a little acetone was added to assist the deketalisation). The presence of the carboxyl function was confirmed by the absorption of two exchangeable protons at 10.8 δ in the n.m.r. spectrum and by absorptions at 3300 and 1700 cm^{-1} in the i.r. spectrum and the presence of the methyl ketone by the absorption at 1720 cm^{-1} in the i.r. spectrum and a singlet at 2.1 δ in the n.m.r. spectrum. Bis-decarboxylation of this diacid with lead tetraacetate in the presence of pyridine gave the olefin-ketone (37) in 31.7% yield without any adverse affect to the methyl ketone. This was borne out by an absorption at 1720 cm^{-1} in the i.r. spectrum and by a singlet at 2.1 δ and a triplet centred at 2.5 δ due to the absorptions of the methyl and methylene groups flanking the carbonyl function. The presence of the double bond was indicated by an AB quartet ($J = 9$ Hz) centred at 6.25 δ in the n.m.r. spectrum.

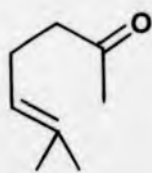
The yield in this reaction was low due to the reformation of the anhydride (79) under the reaction conditions as noted above. This anhydride was reconverted into the starting diacid (36) by



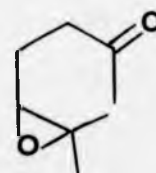
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extraction with potassium bicarbonate solution followed by acidification.

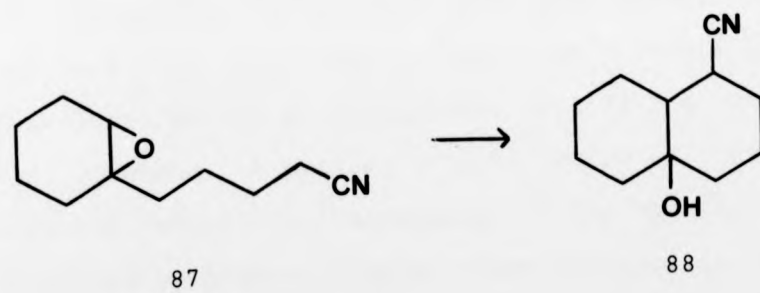
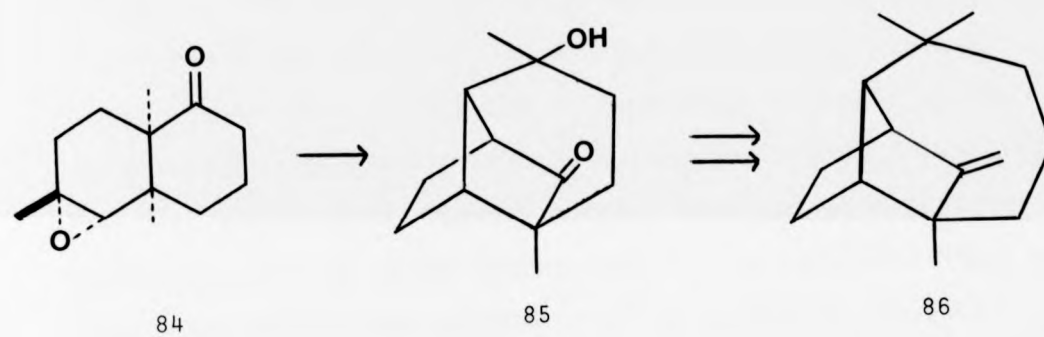
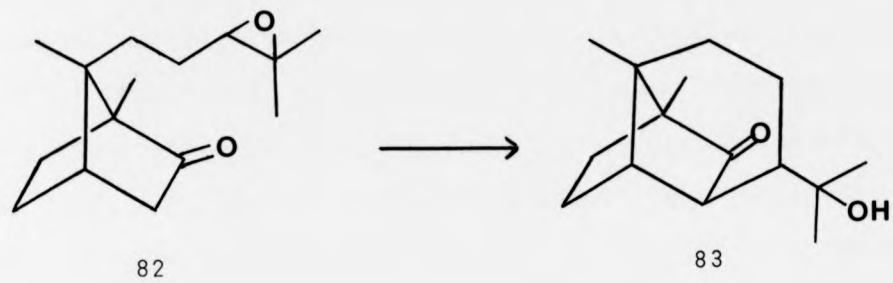
The procedure described above for the epoxidation of olefins in the presence of acid sensitive groupings using *m*-chloroperbenzoic acid was also shown to be effective for the conversion of the methyl-ketone (80) into the epoxy-ketone (81)³³. No complication due to a competing Baeyer-Villiger reaction was



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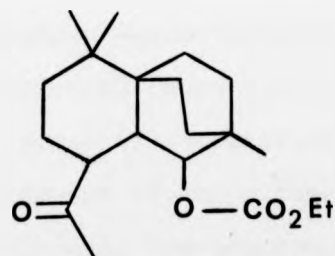


noted. On the strength of this information there should have been no problems in the formation of the epoxy-ketone (38) from (37). Indeed this was found to be the case. The product from the epoxidation of (37) was shown to have an AB quartet ($J = 6$ Hz) at 3.0 δ , a singlet at 2.1 δ , and a triplet at 2.4 δ in the n.m.r. spectrum and an absorption at 1705 cm^{-1} in the i.r. spectrum. Thus the epoxy-ketone (38) was obtained from (37) in 79% yield.

Intramolecular carbanion attack on an epoxide has been used as a method of ring formation in the synthesis of some natural products. For example the epoxy-ketone (82) on treatment with potassium t-butoxide in t-butanol gave the alcohol (83), an intermediate in the synthesis of some sesquiterpenes of the longifolene-longicamphor series³⁴. Similarly longifolene (86) has been synthesised from the alcohol (85) obtained by the cyclisation of the epoxy-ketone (84)³⁵. In addition, Stork *et al.*³⁶ have demonstrated the usefulness of epoxynitriles in such procedures. The epoxynitrile (87) was successfully converted into the alcohol (88) with potassium amide in liquid ammonia.

When the epoxy-ketone (38) was subjected to treatment with potassium t-butoxide in t-butanol a major product was obtained which was shown to have both carbonyl and hydroxyl functional groups by absorptions at 1695 and 3500 cm^{-1} in the i.r. spectrum. A singlet at 2.2 δ indicated that the ketone was a methyl ketone and the presence of the hydroxyl group was confirmed by a broad singlet whose position in the n.m.r. spectrum varied with concentration. This broad singlet disappeared when the solution was shaken with D_2O indicating that this peak was due to an exchangeable hydrogen. The n.m.r. spectrum of the

anticipated product (39) would be expected to display an absorption at 3.5 - 4.0 δ for the resonance of the proton on the carbon bearing the hydroxyl group. No absorptions could be detected in this region but a broad peak at 2.8 δ was in evidence. Examination of the alcohol (39) using Dreiding models showed that this proton may be in the shielding zone of the carbonyl group and, in addition, may be shielded by the flanking alkyl groups. The combined effect of these factors may have been sufficient to cause this rather highfield shift. When the ethyl carbonate of this alcohol was formed the absorption at 2.8 δ was moved to 4.25 δ indicating the probable correctness of the assignment. The carbonate was prepared by treatment of the alcohol (39) with ethyl chloroformate in pyridine^{37,38}. The carbonate (89) was separated from the unreacted alcohol by preparative t.l.c. in only 10% yield and was shown to have the

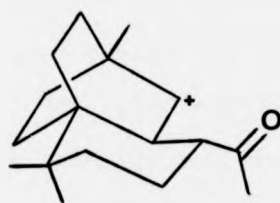


89

assigned structure by absorptions at 1740 and 1715 cm^{-1} in the i.r. spectrum and a quartet ($J = 7 \text{ Hz}$), overlapping the methine proton resonance mentioned above, centred at 4.25 δ , and singlets

at 2.2, 0.9, 0.8, and 0.75 δ in the n.m.r. spectrum.

It was felt that acid-catalysed-dehydration of the alcohol (39) would result in the formation of the unsaturated ketone (40) which under the reaction conditions might isomerise to the ketone (1). At the same time it was feared that the cation (90), produced as a result of the acid-catalysed dehydration, might undergo a Wagner-Meerwein rearrangement to give the bicyclo[3,2,1] carbonium ion (91) which could not



90



91

give either of the desired products, the ketones (40) and (1). Indeed when the alcohol (39) was treated with *p*-toluene sulphonic acid in benzene a product was obtained which did not possess any of the physical or spectral properties associated with the ketone (40) or the ketone (1) so that our worst fears were justified. A small amount of the authentic ketone (1) was prepared from the authentic hydrocarbon (2) with acetic anhydride and boron trifluoride etherate as the catalyst. Unfortunately time did not permit further investigation of this sequence. There is every confidence, however, that the synthesis of the

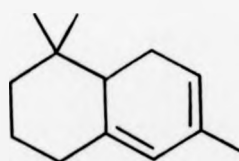
ketone (1) by this route could be brought to a successful conclusion. Pyrolysis of the carbonate (89)^{37,38} may provide the answer to the problems encountered with the acid-catalysed dehydration of the alcohol (40).

A modified Birch reduction of ionene (41) has been shown to give the 1,4-diene (42)⁴ in 93% yield. No unreduced ionene could be detected in the n.m.r. spectrum of the product. Peaks at 5.35 and 2.45 δ for the absorptions of the vinylic and the four allylic protons of the 1,4-diene were noted. When the Birch reduction was carried out with sodium and ethanol in liquid ammonia only 50% of the ionene was reduced to the 1,4-diene.

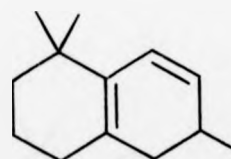
The 1,4-diene (42) thus obtained was the anticipated product by analogy and theoretical considerations. Tetralins are known to give the 1,4-dihydro-product when subjected to Birch reduction conditions^{39,40}. This evidence is backed up by the fact that the charge of the ortho-xylene radical anion resides mainly at positions 3 and 6 whereas the charge of the meta-xylene radical anion occupies mainly positions 2 and 5²⁸. From an examination of the ionene molecule which could be considered to be a 1,2,4-trialkylbenzene, it could be seen that the charge of the radical anion, produced by the Birch reduction conditions, would be centred mainly at the positions 1 and 4. Thus, on protonation the 1,4-dihydro-product would be produced.

When an attempt was made to purify the 1,4-diene (42) by distillation at reduced pressure, decomposition of the diene occurred which rendered purification difficult. When this diene was treated with potassium t-butoxide in dimethyl sulphoxide a

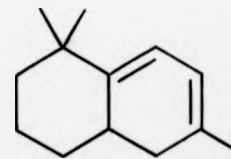
product was obtained in quantitative yield which displayed an absorption at 267 nm ($\epsilon \sim 7000$) in the u.v. spectrum and peaks at 5.5 and 2.0 δ in the n.m.r. spectrum. The n.m.r. spectrum indicated that some ionene was regenerated during the reaction and that some 1,4-diene (42) was also present in the product. It can be readily appreciated that the 1,4-diene (42) could be isomerised in a number of ways and give, in addition to the desired 1,3-diene (43), dienes such as (92), (93), and (94). The literature analogies for the course of the Birch reduction of highly-substituted tetralins and the subsequent isomerisation of the 1,4-dienes produced are sparse and shed no clear light on the products that would be expected from the treatment of (42) with potassium t-butoxide in dimethyl sulphoxide. However, it is known that removal of a proton from the hexahydronaphthalene (95) yields the pentadienyl anion (96) and that this anion is the most stable anion that can be produced⁴¹. Reprotonation of this anion gives the most highly-substituted 1,3-diene (97). Based on



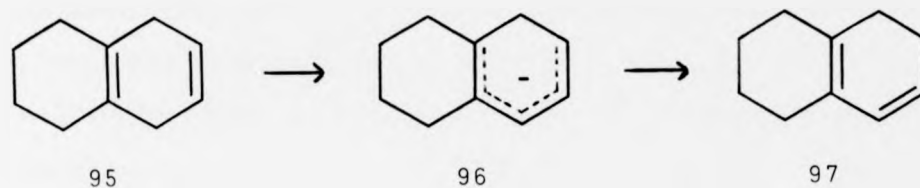
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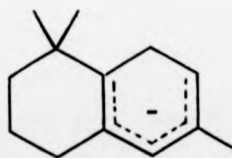
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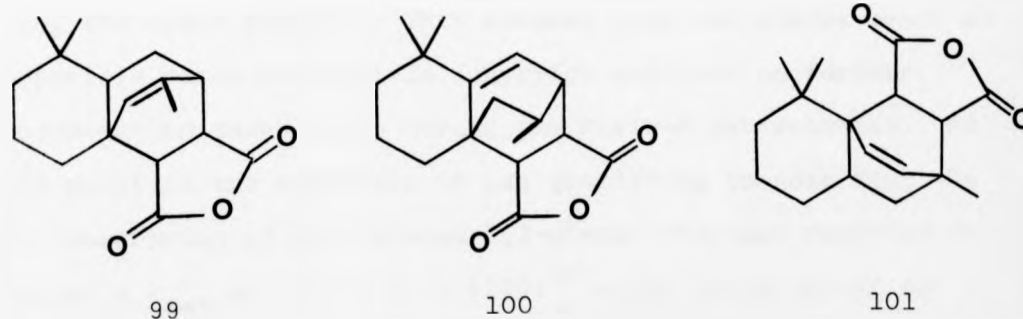
this evidence the diene (43) was the anticipated product from the isomerisation of the 1,4-diene (42). The 1,3-diene (43) would be the most highly-substituted diene that could be formed from (42) and, in addition, the diene (97) was expected to be the one formed by removal of a proton from the allylic position that is furthest away from the gem dimethyl group. This site would present a less sterically hindered environment for the removal of a proton by t-butoxide. There was, however, no



98

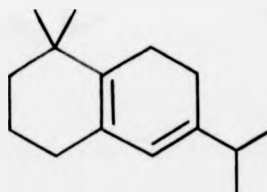
clear indication, from the spectral evidence obtained from the product of the reaction of (42) with *t*-butoxide, that these deductions were correct. The u.v. spectrum gave a result which was not compatible with the prediction of a λ_{max} at 278 nm ($\epsilon \sim 10,000$) based on Woodward's rules for conjugated dienes. No conclusion, therefore, could be drawn from this evidence, as to the structure of the diene or if in fact the product was a mixture of dienes.

In spite of the lack of confirmatory evidence, the 1,3-diene was reacted with maleic anhydride. The diene (43) would be expected to give the adduct (44) from this cycloaddition and dienes (93), (94) and (95) would be expected to give the adducts (99), (100) and (101) respectively. Thus the products from this reaction were expected to shed some light on the nature of the



product obtained by isomerisation of (42). Following a chromatographic separation, the products were examined by n.m.r. spectroscopy. The first fractions obtained from the chromatographic

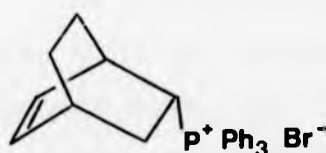
column were found to be ionene (41) and the 1,4-diene (42). Two anhydrides were then recovered in a ratio of 6:1 both with i.r. absorptions at 1835 and 1770 cm^{-1} . The n.m.r. spectrum of the major anhydride showed the following features, a triplet at 5.7 δ ($J = 2$ Hz) shown by decoupling experiments to be coupled to a broad singlet at 2.25 δ , doublets at 3.3 and 2.85 δ , and singlets at 1.45, 1.35, and 1.1 δ . These spectral features were entirely consistent with the structure (44) and could not be correlated with any of the other possible adducts from the alternative dienes. The structure of the minor product was deduced as the anhydride (99) from the appearance of a broad singlet at 5.7 δ , doublets at 1.8 and 2.7 δ , a multiplet at 3.0 δ , and singlets at 0.8 and 0.6 δ in the n.m.r. spectrum. This result shows that the major product from the isomerisation of the 1,4-diene (42) was the 1,3-diene (43), with the 1,3-diene (92) being the minor product. This assumes that the dienes react at comparable rates with maleic anhydride and that no further isomerisation takes place during the Diels-Alder reaction. At this point in the synthesis it was gratifying to note that the u.v. absorption of the related 1,3-diene (102) was reported to display a λ_{max} at 250 nm ($\epsilon = 6100$)⁴² which would appear to



102

indicate that this system is anomalous with regard to the Woodward rules. It is conceivable that this anomaly is the result of the diene being twisted out of planarity by the isopropyl group and the bulky gem dimethyl substituents. This conclusion can be further reconciled by the fact that when the isopropyl group in the diene (102) is replaced by the less bulky methyl substituent as in the diene (43) then the hypsochromic shift is less.

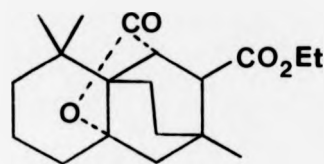
The next problem was to effect the formation of an ethano-bridge across the diene (43). To our knowledge there is no effective ethylene equivalent known in the literature. However, we were attracted to the idea that the recently reported⁴³ adducts of vinyltriphenylphosphonium bromide with 1,3-dienes could be modified to achieve this overall objective. Thus we wondered if it would be possible to effect the reductive elimination of triphenylphosphine from a typical adduct such as (103). We were encouraged by the report of Gough and Trippett⁴⁴



that lithium aluminium hydride reduction of isopropyltriphenylphosphonium iodide, *s*-butyltriphenylphosphonium iodide and benzyltriphenylphosphonium bromide gave triphenylphosphine in each case. If this reduction could be effected then the product from the cycloaddition of vinyltriphenylphosphonium bromide with the 1,3-diene (43), i.e. (48) plus the other positional isomer, could be used to bring about the synthesis of the hydrocarbon (49). When an attempt was made to reduce the salt (103), obtained by the reaction of vinyltriphenylphosphonium bromide with cyclohexa-1,3-diene, with lithium aluminium hydride in refluxing tetrahydrofuran the product was shown to be triphenylphosphine. This product seemed to indicate that the reduction had proceeded as desired, although the hydrocarbon (104) was not recovered. This was thought to be due to its known high volatility. An attempt to convert (43) into (49) was, therefore, considered to be worthwhile, in spite of the inconclusive nature of this model reaction. However, when vinyltriphenylphosphonium bromide was heated with the 1,3-diene (43) in acetonitrile under nitrogen at 160-165° in a sealed tube for 48 hours no trace of the desired adduct (48) was detected.

The anhydride (44) offered an opportunity to test the hypothesis that, on treatment with acid, the double bond would be isomerised to the less strained environment of the six-membered ring that is fused to the bicyclo[2,2,2] octane ring system. Treatment of the anhydride, under the same conditions as those used to bring about the conversion of eremolactone (70) to isoeremolactone (71), resulted in the isolation of a major product, in 51% yield, which had the following spectral

characteristics, i.r. absorptions at 1765 and 1730 cm^{-1} , a quartet at 4.15 δ and a triplet at 1.3 δ , an AB quartet at 2.75 δ ($J_{AB} = 9 \text{ Hz}$), and singlets at 1.1, 0.95, and 0.85 δ in the n.m.r. spectrum. This information and the absence of a resonance for a vinylic proton led to the assignment of the structure (105) to this compound.



105

Heating the anhydride with *p*-toluenesulphonic acid in benzene proved unfruitful, the anhydride (44) remaining unaffected by this treatment. When the anhydride was stirred at room temperature in trifluoroacetic acid, however, a new anhydride was obtained which was spectroscopically different from the starting anhydride. The resonance at 5.55 δ was much broader and did not show the small allylic coupling observed in the spectrum of the compound (44). The n.m.r. spectrum also showed a pair of doublets at 3.2 δ and 2.9 δ due to the protons on the carbons bearing the anhydride and the methyl singlets were at

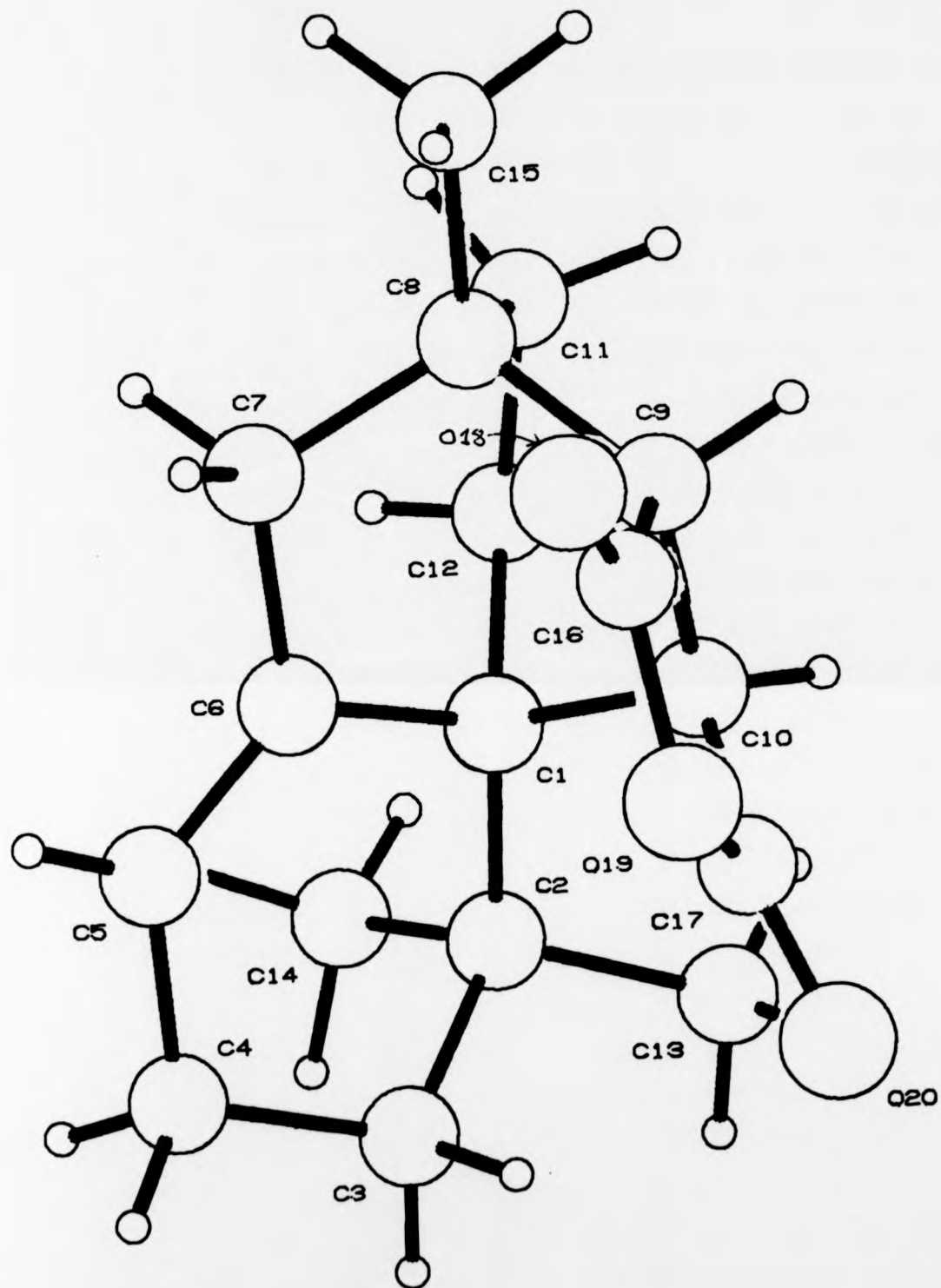


Figure 1

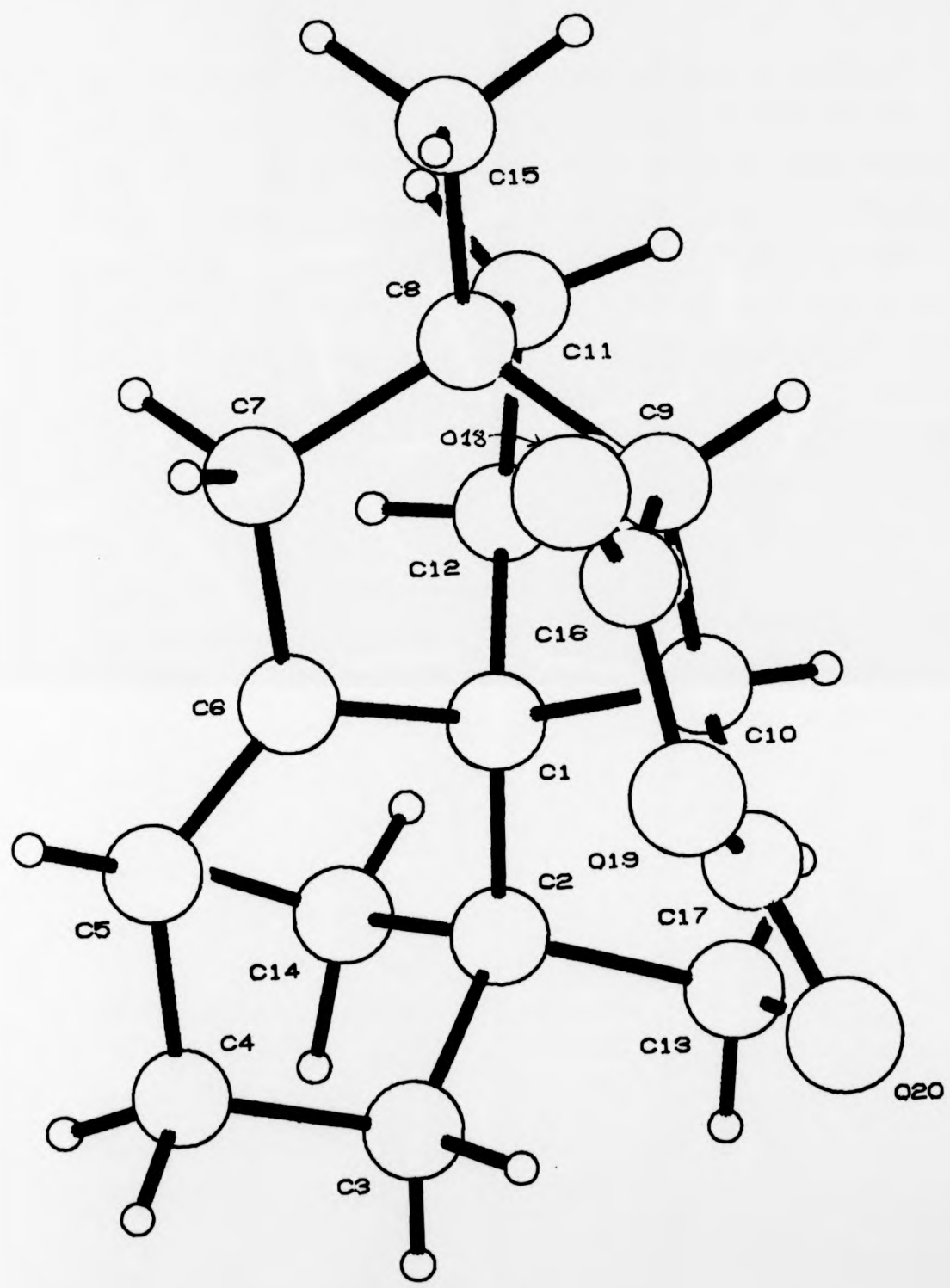
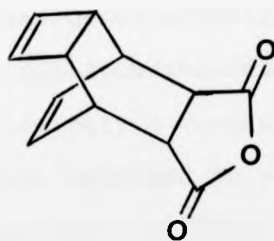


Figure 1

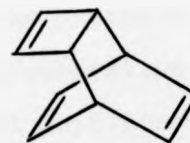
1.25 (6H) and 0.85 δ (3H). Two broad peaks were in evidence at 2.25 and 1.95 δ which seemed to be coupled to the vinylic signal at 5.55 δ though the results from decoupling experiments were not absolutely conclusive. Experiments with a lanthanide shift reagent, Eu(FOD)₃, did not clarify the situation. The signals at 2.25 δ and 1.95 δ could not be moved far enough away from the other methylene protons to allow a conclusive decoupling experiment to be made. The spectral evidence was not inconsistent with the structure (45), however. A lactone, whose spectra were identical to those of the lactone obtained from (44), was produced by refluxing the anhydride (45) in 2N hydrochloric acid and ethanol. In spite of the fact that this evidence appeared to justify the conclusion that the anhydride (45) had been obtained, there was still the remote possibility that a more deep-seated rearrangement had taken place on treatment of the anhydride (44) with trifluoroacetic acid and/or with 2N hydrochloric acid in ethanol. Thus, in view of the importance of this reaction to the overall synthetic objective, an X-ray crystallographic analysis using direct methods of this anhydride was performed by Drs. P. Murray-Rust and J. Murray-Rust. This analysis unambiguously established the structure of the anhydride as that depicted in figure 1, i.e. the anhydride (45). Thus the double bond had been successfully isomerised and the basic carbon skeleton for the synthesis of the target compounds (1)-(3) had been constructed with the double bond in the $\Delta^{5,6}$ position.

Conversion of the anhydride (45) to the diolefin (46) offered the possibility of synthesising the olefin (2) by a selective hydrogenation of the more strained double bond,

i.e. the olefinic bond in the bicyclo[2,2,2] octane ring system. This conversion was attempted in two ways, viz., reaction of the anhydride with bis(triphenylphosphine) nickel (0) dicarbonyl and bis-decarboxylation of the corresponding diacid with lead tetraacetate. The experimental procedure described by Dauben et al.⁴⁵ for the preparation of olefin (107) from the anhydride (106) using $\text{Ni}(\text{CO})_2(\text{PPh}_3)_2$ was followed. Unfortunately the anhydride (45) was recovered unchanged. The lead tetraacetate decarboxylation of the diacid obtained by hydrolysis of the anhydride gave a much better result. The olefin (46) identified by an AB quartet ($J = 9 \text{ Hz}$) at 6.05δ , a broad singlet at 5.25δ and a broad singlet at 1.25δ , was obtained in 10% yield. Considerable anhydride formation had again taken place which could be re-cycled to the diacid.



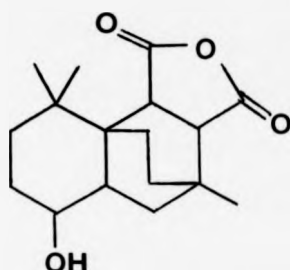
106



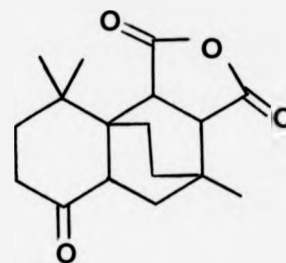
107

Before an attempt was made to carry out the selective hydrogenation of (46), a sample of the authentic olefin (2) was subjected to mild hydrogenation conditions, *i.e.* stirred at room temperature for 4 hours under one atmosphere of hydrogen in the presence of 10% palladium on charcoal. Examination of the reaction product by t.l.c., g.l.c. and n.m.r. spectroscopy showed that the olefin was unaffected by these hydrogenation conditions. These conditions were, therefore, used in the hydrogenation of the diolefin (46). The olefin (2) was isolated in 75% yield from this reaction. No trace of the fully hydrogenated hydrocarbon could be detected by g.l.c. or t.l.c. The identity of the olefin (2) was confirmed by comparison with an authentic sample, kindly provided by Dr. A. Hochstetler of The Givandan Corporation, U.S.A. using n.m.r., i.r., m.s., g.l.c., and t.l.c. criteria. The n.m.r. and i.r. spectra were also identical to those provided by Professor S. Itô of Tohoku University, Japan, for this olefin.

The hydroboration/oxidation of the olefinic anhydride (45) was considered briefly to assess the prospect of obtaining the ketone (3) from this anhydride. Hydroboration followed by the normal oxidative work-up and a final acidification gave a product which appeared to be a mixture of the alcohol (108) and the corresponding diacid alcohol. Oxidation of this mixture with Jones reagent gave the mixture of the diacid-ketone (47) and the anhydride-ketone (109). This shows that the ketone could be obtained from the anhydride (45). At this point time did not permit the final conversion of the diacid-ketone (47) through to the ketone (3) but it is considered that, in the light of past



108



109

experience, these two steps should not present any problems.

Conclusion

The work described in this thesis has, in essence, achieved most of the overall objectives which were initially set out. The tricyclic olefin (2) has been synthesised in a relatively short number of steps from a readily available starting material. In the light of the very recent communication⁴⁷ it is obvious that our own route to the tricyclic ketone (3) would have succeeded if a supply of vinyl lithium had been on hand. It is rather ironic that no source of this reagent could be uncovered despite exhaustive enquiries in the U.K. One has to be philosophical about this frustrating experience and simply mutter "c'est la vie". On the other hand, the synthetic route to

the ketone (1) has reached a very advanced stage and it is anticipated that it will come to fruition in due course.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus; boiling points are not corrected. The absorbents used in column chromatography were commercial "Woelm" alumina (neutral) and 140-200 mesh silica gel. Kieselgel GF₂₅₄ (Merck) was used for all preparative thin layer chromatography. Analytical t.l.c. plates were stained with iodine vapour and/or ceric ammonium sulphate followed by heating to approximately 120°. A 2m/1/8" column, packed with 5% F.F.A.P. on Chromosorb G(A.W.-D.M.C.S.) and a 50 ft/0.02" column, packed with Carbowax 20M were used in a Perkin-Elmer F11 gas chromatograph (flame ionisation) for analytical gas liquid chromatography. The carrier gas was an air (20 p.s.i.)/hydrogen (20 p.s.i.)/nitrogen (20 p.s.i.) mixture. Where necessary, solvents were purified and dried in the recommended manner and reagents were either distilled or recrystallised. Petroleum ether refers to the fraction of b.p. 40-60°C and all organic extracts were dried over magnesium sulphate unless otherwise stated.

Infra-red spectra were recorded on a Perkin-Elmer 457 grating infra-red spectrophotometer and, unless otherwise stated, were obtained from liquid films. Ultra-violet spectra were recorded, for petroleum ether solutions, on a Perkin-Elmer 402 ultraviolet/visible spectrophotometer. Nuclear magnetic resonance spectra were recorded, for deuterated chloroform solutions, on a Hitachi Perkin-Elmer R24 or a Perkin-Elmer R32 n.m.r. spectrophotometer. Tetramethylsilane was employed as an

internal standard. Mass spectra were determined on a Jeol JMS D100 mass spectrometer combined with a Jeol JCS 20K gas chromatograph and using an Instem Data Mass Maxi data processing system. Microanalyses were carried out by the Dr. F. B. Strauss Microanalytical Laboratory, Oxford.

4-Methyl-4-p-tolylpentanone (16).

Mesityl oxide (100g, 1.02 moles) was added dropwise, over 1 hour, to a well-stirred suspension of aluminium chloride (170g, 1.27 moles) in toluene (400g, 4.35 moles) at room temperature. The reaction mixture was stirred at room temperature for 4 hours, poured onto ice/water (acidified with hydrochloric acid), the layers were separated and the aqueous layer was extracted twice with diethyl ether. The organic extracts were combined washed with water, dried, and the solvent removed in vacuo. Distillation at reduced pressure gave the ketone (16) as a colourless oil (83.5g, 43.0%; b.p. 130°/11.0 mm) (lit. b.p.⁷ 125-127°/11 mm). ν_{\max} 2960 (broad peak), 1700, 1515, 1360, and 815 cm^{-1} ; δ 7.1 (ABq, $J_{AB} = 9 \text{ Hz}$, 4H), 2.7 (s, 2H), 2.3 (s, 3H), 1.8 (s, 3H), and 1.4 (s, 6H).

4-Methyl-4-p-tolylpentanethiomorpholide (17).

4-Methyl-4-p-tolylpentan-2-one (16) (10.0g, 0.05 moles), morpholine (18.3g, 0.21 moles) and sulphur (2.53g, 0.08g atoms) were refluxed for 20 hours, the hot solution was poured onto ethanol (25 ml) and allowed to stand overnight to give a pale yellow solid. The alcoholic solution was concentrated and then

eluted from a neutral alumina column with 70% diethyl ether in petroleum ether to give more of the pale yellow solid which was combined with that obtained by recrystallisation (7.9g, 51.6%; m.p. 80°) (lit.m.p.⁷ 75-76°) and was found to be the thiomorpholide (17).

ν_{\max} (Nujol) 2920, 2860, 1490, 1460, 1370, 1290, 1260, 1110, 1000, and 820 cm^{-1} ;

δ 7.3 (s, 4H), 3.9 (m, 8H), 2.6 (m, 2H), 2.35 (s, 3H), 2.05 (m, 2H), and 1.4 (s, 6H).

S-Methyl-4-methyl-4-p-tolylpentanethiomorpholide iodide (74).

4-methyl-4-p-tolylpentanethiomorpholide (17) (0.5g, 1.72 m.moles) was heated under reflux with methyl iodide (0.38g, 2.68 m.moles) in acetone (25 ml) for 1 hour. The reaction mixture was cooled and the acetone removed in vacuo until a white solid precipitated from the concentrated solution (0.33g, 44.4%; m.p. 168-9°) which was found to be the iodide (74).

ν_{\max} (Nujol) 2950, 2920, 2860, 1600, 1460, 1280, 1110, and 825 cm^{-1} ;

δ 7.15 (ABq, J = 9 Hz, 4H), 4.0 (s, 3H), 3.8 (m, 4H), 2.8 (m, 2H), 2.5 (s, 4H), 2.3 (s, 3H), 1.8 (m, 2H), and 1.4 (s, 6H).

Preparation of 4-Methyl-4-p-tolylpentanoic acid (18).

(a) from the Iodide (74).

The iodide (74) (0.26g, 0.6 m.moles) was heated under reflux with 2N sodium hydroxide solution (25 ml) for 16 hours.

The mixture was cooled, acidified with dilute hydrochloric acid and extracted with diethyl ether (3 x 20 ml). The ether extracts were combined, washed free of acid with water, dried, and the solvent removed in vacuo to give the acid (18) as a yellow oil (0.13g, 100%).

(b) from 4-Methyl-4-p-tolylpentan-2-one (16) without Isolation of Intermediates

4-Methyl-4-p-tolylpentan-2-one (16) (7.1g, 37.4 m.moles) was heated under reflux with sulphur (1.8g, 0.0561g atoms) and morpholine (13.0g, 150 m.moles) for 20 hours. The excess morpholine was removed in vacuo and the resulting mixture dissolved in acetone (50 ml), methyl iodide (9.72g, 68.45 m.moles) was added, and the resulting mixture heated under reflux for 1 hour. After the mixture was cooled and the excess acetone and methyl iodide removed in vacuo, 2N sodium hydroxide solution (50 ml) was added and the mixture heated under reflux for 16 hours. The insoluble organic material was removed by extraction with diethyl ether. The aqueous layer was acidified with dilute hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The combined extracts were washed with water, dried, and the solvent removed in vacuo to give a yellow oil. Distillation at reduced pressure gave the acid (18) as a pale yellow liquid (3.64g, 47.3%) which solidified on standing.

(c) by Acid Hydrolysis of the Thiomorpholide (17).

The thiomorpholide (17) (200 mg, 0.82 m.moles), 6N hydrochloric acid (10 ml), and ethanol (0.5 ml) were stirred at 60° for 24 hours. After cooling, the reaction mixture was

extracted with diethyl ether (3 x 10 ml), the combined extracts were washed free of acid with water, dried, and the solvent removed in vacuo to give a pale yellow solid (180 mg) which was found to be the starting material.

When the experiment was repeated in the presence of mercuric chloride (10 mg) the thiomorpholide (17) (130 mg) was recovered unchanged.

Hydrolysis by the above method in the presence of copper sulphate (10 mg) gave a pale yellow oil (84.5 mg, 50%) which was found to be the acid (18) (b.p. $144^{\circ}/1.0$ mm; m.p. $44-45^{\circ}$) (lit. b.p.⁷ $140-142^{\circ}/1.0$ mm).

ν_{\max} 3300 (broad peak), 2960, 2940, 1705, 1300, and 820 cm^{-1} ;
 δ 10.9 (br.s, 1H), 7.1 (br.s, 4H), 2.3 (s, 3H), 2.0 (s, 4H),
1.3 (s, 6H).

(Found: C, 75.69%; H, 8.80%; $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires
C, 75.69%; H, 8.73%).

Birch Reduction of 4-Methyl-4-p-tolylpentanoic acid (18).

Ethanol (7.0 ml, 0.12 moles) and lithium (1.1g, 0.16g atoms) were added in three portions to 4-methyl-4-p-tolylpentanoic acid (18) (5.0g, 0.02 moles) in dry ethylamine (100 ml) in a three-necked flask fitted with an acetone/dry-ice condenser and the flask cooled in an ice/salt bath. The alcohol was always added first and the lithium allowed to react completely before the next addition was made. After all the lithium had reacted, the ethylamine was allowed to evaporate, under a stream of nitrogen, and the last traces were removed by warming on a steam bath. Ice/water (100 ml) was added and the resulting solution cooled in an ice bath, acidified with dilute hydro-

chloric acid, and extracted with diethyl ether (3 x 50 ml). The organic extracts were combined, washed free of acid with water, dried, and the solvent removed in vacuo to give a yellow oil (4.96g) which was shown to be a mixture of 50% of the unreduced acid (18) and 50% of the 1,4-diene (19) by n.m.r. spectroscopy.

A second reduction was carried out on the above product using the same quantities of lithium ethanol and ethylamine to give the 1,4-diene (19) (2.91g, 57.6%).

ν_{\max} 3300 (broad peak), 2960, 2920, 2870, 1700, and 760 cm^{-1} ;
 δ 11.6 (br.s, 1H), 5.4 (br.s, 2H), 2.6 (br.s, 4H),
1.65 (m, 7H), 1.0 (s, 6H).

An absorption at 7.1 δ indicated that there was still some of the starting material present (approximately 11% by integration).

Attempts to purify the 1,4-diene (19) by distillation at reduced pressure led to decomposition and crystallisation proved unfruitful.

Isomerisation of the 1,4-Diene (19) to the 1,3-Diene (20).

The 1,4-diene (19) (2.8g, 13.46 m.moles) was dissolved in dry dimethylsulphoxide (100 ml) and benzene (3 ml) and the solution degassed by bubbling nitrogen through it for 30 minutes. Potassium t-butoxide (5.2g, 46.42 m.moles) was added and the resulting solution stirred for 3 days at room temperature. The mixture was poured onto ice/water (500 ml), cooled in an ice bath, acidified with dilute hydrochloric acid, and extracted with petroleum ether (3 x 100 ml). The organic extracts were

combined, washed with water, dried, and the solvent removed in vacuo to give the 1,3-diene (20) (2.82g, 100%).

λ_{\max} 267 nm ($\epsilon = 8900$);

ν_{\max} 3300 (broad peak), 2950, 2910, 1700, and 760 cm^{-1} ;

δ 10.1 (br.s, 1H), 5.7 (s, 2H), 2.1 (s, 4H), 1.8 (m, 7H), and 1.1 (s, 6H).

The n.m.r. spectrum showed that the product contained about 15% of the aromatic acid (18) and about 20% of the 1,4-diene (19) by integration.

Preparation of the Vinyl Ketone (76).

2M Vinyl lithium solution in tetrahydrofuran (5 ml, 10.0 m.moles) was added over a period of 15 minutes to a solution of the 4-methyl-4-p-tolylpentanoic acid (18) (0.5g, 2.43 m.moles) in dimethoxyethane (10 ml), cooled in an ice bath. The mixture was stirred at 40° for 2 hours under nitrogen and then at room temperature for 16 hours. The reaction mixture was poured into 6N hydrochloric acid (30 ml) at 0°C and extracted with diethyl ether (3 x 10 ml). The combined ether extracts were washed with 10% sodium carbonate solution and water, dried, and the solvent removed in vacuo to give a yellow oil. The product was purified by preparative t.l.c. (eluting with 30% diethyl ether in petroleum ether) and the major component was isolated to give a clear oil (50 mg, 9.5%) which was found to be the vinyl ketone (76).

ν_{\max} 2960, 2920, 1665, 1605, 1400, 1090, and 810 cm^{-1} ;

δ 7.1 (ABq, $J_{AB} = 9$ Hz, 4H), 5.9 (m, 3H), 2.3 (s, 3H), 2.0 (m, 4H), and 1.3 (s, 6H).

Attempted Preparation of the Trienone (21).

2M Vinyl lithium solution in tetrahydrofuran (20 ml, 40 m.moles) was added over 15 minutes to the 1,3-diene-acid (20) (2g, 9.62 m.moles) dissolved in dimethoxyethane (40 ml), under nitrogen, and cooled in an ice bath. The reaction mixture was stirred at 48° for 4 hours and for a further 16 hours at room temperature. After work-up as described above none of the desired product was isolated. However, a nearly quantitative recovery (1.95g) of the starting material was obtained by acidification and extraction of the sodium carbonate washings.

Preparation of 6-Methyl-6-p-tolylheptan-2-one (26).

6-Methylhept-5-en-2-one (16.8g, 0.13 moles) was added over 45 minutes to a well-stirred suspension of aluminium chloride (19.5g, 0.15 moles) in toluene (80g, 0.9 moles) while maintaining the temperature of the mixture at -15° - -10° with a carbon tetrachloride/dry-ice bath. The reaction mixture was stirred at -10° - 0° for 6 hours and then poured onto ice acidified with hydrochloric acid. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 50 ml). The combined organic layers were washed with water, dried, and the solvent removed in vacuo to give a yellow oil. The yellow oil was distilled under reduced pressure to give 6-methyl-6-p-tolylheptan-2-one (26) (13.05g, 46.0%; b.p. 141°/0.6 mm).

ν_{\max} 2960, 2870, 1715, 1515, 1360, and 820 cm^{-1} ;

δ 7.0 (ABq, $J_{AB} = 8.5 \text{ Hz}$, 4H), 2.25 (s, 3H), 2.1 (m, 2H), 1.9 (s, 3H), 1.4 (m, 2H), and 1.25 (s, 6H).

(Found: C, 82.60%; H, 10.17%; $\text{C}_{15}\text{H}_{22}\text{O}$ requires C, 82.52%; H, 10.16%).

Preparation of the Ketal of (26).

6-Methyl-6-*p*-tolylheptan-2-one (30g, 0.14 moles), ethylene glycol (9.4g, 0.15 moles), benzene (250 ml) and a few crystals of *p*-toluene sulphonic acid were refluxed, with continuous removal of water, for 16 hours. The benzene solution was washed with 10% sodium carbonate solution followed by water until neutral, dried, and the solvent removed in vacuo to give the ketal as a colourless oil (33.88g, 93.7%).

ν_{\max} 2960, 2880, 1515, 1375, 1060, and 810 cm^{-1} ;
 δ 7.0 (ABq, $J_{AB} = 9$ Hz, 4H), 3.75 (s, 4H), 2.2 (s, 3H),
 1.45 (m, 6H), 1.2 (s, 6H), and 1.15 (s, 3H).

Birch Reduction of the Ketal of (26).

Ethanol (37.1g, 0.81 moles) and lithium (6.0g, 0.86g atoms) were added in three portions to the ketal (30.2g, 0.12 moles) and ethylamine (400 ml) in a three-necked flask fitted with an acetone/dry-ice condenser and the flask cooled in an ice/salt bath. The alcohol was added first and the next addition was made only when the lithium had reacted completely. The ethylamine was allowed to evaporate at room temperature, under a stream of nitrogen, and the last traces were removed on a steam bath. Ice/water (200 ml) was added and the aqueous mixture was extracted with diethyl ether (3 x 50 ml). The ether layers were combined, washed with water, dried, and the solvent removed in vacuo to give the 1,4-diene (27) as a yellow oil (26.89g, 88.4%).

ν_{\max} 2960, 2880, 1375, and 1060 cm^{-1} ;
 δ 5.4 (br.s, 2H), 3.85 (s, 4H), 2.6 (s, 4H), 1.6 (s, 3H),
 1.3 (m, 6H), 1.25 (s, 3H), and 1.0 (s, 6H).

Attempts to purify this 1,4-diene by distillation at reduced pressure only resulted in disproportionation and decomposition of the 1,4-diene (as ascertained by n.m.r. spectroscopy).

Isomerisation of the 1,4-Diene (27) to the 1,3-Diene (28).

The 1,4-diene (27) (26.9g, 0.10 moles) was dissolved in dimethyl sulphoxide (600 ml) and benzene (40 ml) and the solution degassed by bubbling nitrogen through it for 30 minutes. Potassium t-butoxide (31.0g, 0.28 moles) was added and the resulting solution was stirred at room temperature, under nitrogen, for 40 hours. The reaction mixture was poured onto ice/water (2 l.) and the aqueous mixture was extracted with petroleum ether (3 x 500 ml). The organic extracts were combined, washed with a saturated brine solution followed by water, dried, and the solvent removed in vacuo to give a yellow oil (27.05g, 100%) which was found to be the 1,3-diene (28).

λ_{\max} 265 nm ($\epsilon = 9160$);

ν_{\max} 2960, 2870, 1650 (weak), 1375, 1060, and 825 cm^{-1} ;

δ 5.6 (s, 2H), 3.85 (s, 4H), 2.05 (s, 4H), 1.75 (s, 3H),
1.6 (m, 6H), 1.25 (s, 3H), and 1.0 (s, 6H).

Integration of the n.m.r. spectrum showed that the product contained about 25% of the 1,4-diene (27) and about 12% of the aromatic ketal from the ketone (26). Attempts to purify the product by distillation at reduced pressure led to the disproportionation of the 1,3-diene (28).

Preparation of Nitroethylene

3N Methanolic potassium hydroxide (0.6 ml) was added dropwise to a stirred suspension of paraformaldehyde (6.0g, 0.2 moles) in nitromethane (136g, 2.2 moles) to give a solution of pH 6-8. The mixture was stirred for 1 hour, sulphuric acid (98%) was added to give a pH of 4 and the stirring continued for a further hour, while maintaining a pH of 4. The potassium sulphate was filtered off and the excess nitromethane was removed in vacuo. Diphenyl ether (10 ml) was added to the residue and the mixture was distilled at reduced pressure (2.0 mm Hg) until all the nitroethanol had been collected. The nitroethanol was separated from the diphenyl ether, some of which had codistilled with the nitroethanol, and washed with petroleum ether to give nitroethanol as a colourless oil (6.1g, 33.5%).

ν_{\max} 3400 (broad peak), 2950, 1550, 1380, 1070, 890, and 870 cm^{-1} ;

δ 4.4 (m, 2H), 3.75 (m, 3H).

The nitroethanol (2.5g, 27.4 m.moles), thus obtained, and phthalic anhydride (4.5g, 30.4 m.moles) were heated, under reduced pressure (80 mm Hg), at 140-150° in a distillation apparatus until the mixture was homogeneous. The temperature was then raised to 175-180° and the nitroethylene which distilled from the mixture was collected as a colourless oil (0.62g, 31.0%).

ν_{\max} 2940, 1640, 1515, 1340, and 950 cm^{-1} ;

δ 7.0 (m, 3H).

Attempted Diels-Alder addition of Nitroethylene to the 1,3-Diene (28).

Nitroethylene (0.15g, 3.6 m.moles) was added to the 1,3-diene (28) (0.26g, 1.0 m.moles) at room temperature, under nitrogen, and a white solid precipitated from the mixture almost immediately. The white solid was filtered off and examined by i.r. and n.m.r. spectroscopy. The spectral characteristics were found to be inconsistent with those expected for the desired adduct but could be attributed to a polymer of nitroethylene. The filtrate (0.19g) was found to be the 1,3-diene (28).

Diels-Alder addition of Maleic Anhydride to the 1,3-Diene (28).

Maleic anhydride (0.2g, 2.04 m.moles) and the 1,3-diene (28) (0.35g, 1.33 m.moles) were refluxed, in a nitrogen atmosphere, in xylene (10 ml) containing a few crystals of quinol for 16 hours. The xylene was removed under reduced pressure and the residue recrystallised from hexane to give a white solid (0.36g, 75.0%; m.p. 105°) which was the anhydride (32).

ν_{\max} (CCl₄) 2960, 2880, 1835, 1775, 1460, 1380, 1080, 940,
and 705 cm⁻¹;

δ 6.25 (d, J = 8.5 Hz, 1H), 6.05 (d, J = 8.5 Hz, 1H),
3.9 (s, 4H), 3.15 (d, J = 9.0 Hz, 1H), 2.95 (d, J = 9.0 Hz, 1H),
1.55 (s, 3H), 1.45 (m, 10H), 1.35 (s, 3H), 1.15 (s, 3H), and
1.05 (s, 3H).

Preparation of the Diacid-Ketal (33).

The adduct (32) (0.68g, 1.88 m.moles) was dissolved in ethyl acetate (10 ml) and shaken with Adam's catalyst (0.015g)

at 40°, under 3 atmospheres of hydrogen for 16 hours. The catalyst was filtered off and the solvent removed in vacuo to give the dihydro product as a white solid which was recrystallised from hexane (0.57g, 83.3%; m.p. 91°).

ν_{\max} (CHCl₃) 2940, 2870, 1840 (weak), 1780, 1455, 1370, 1210, 1060, 930, 910, and 760 cm⁻¹;

δ 3.95 (s, 4H), 3.2 (d, J = 9 Hz, 1H), 2.85 (d, J = 9 Hz, 1H), 1.45 (m, 14H), 1.3 (s, 3H), 1.25 (s, 3H), and 0.95 (s, 6H).

The anhydride-ketal (0.63g, 1.73 m.moles) thus obtained was stirred with 20% potassium bicarbonate solution (10 ml) for 3 hours at 80°. After an extraction with diethyl ether to remove any insoluble organic material, the aqueous solution was cooled in an ice bath, acidified carefully with 6N hydrochloric acid to neutrality and extracted quickly with diethyl ether (3 x 10 ml). The organic extracts were combined, washed with water, dried, and the solvent removed in vacuo to give the diacid-ketal as a white solid (0.24g, 71.4%; m.p. 66°-68°).

ν_{\max} (CHCl₃) 3300 (broad peak), 2940, 2870, 1740, 1460, 1350, 1240, and 1060 cm⁻¹;

δ 10.55 (s, 2H), 3.95 (s, 4H), 3.2 (d, J = 12 Hz, 1H), 2.7 (d, J = 12 Hz, 1H), 1.4 (m, 14H), 1.3 (s, 3H), 1.0 (s, 3H), and 0.85 (s, 6H).

Preparation of Olefin-Ketal (34).

Lead tetraacetate (2.07g, 4.67 m.moles) was washed free of acetic acid with dry hexane and added to the diacid-ketal (33) (1.46g, 3.82 m.moles) dissolved in benzene (30 ml) and

pyridine (0.7 ml). The mixture was stirred under nitrogen at room temperature for 1 hour, at 55° - 60° for 2 hours, at 75° - 80° for 3 hours, and finally at room temperature overnight. The reaction mixture was poured into water (50 ml) and the layers were separated. The organic layer was dried and the solvent removed in vacuo to give a pale yellow oil (0.86g) which was found to contain about 50% of the anhydride-ketal from an examination of the n.m.r. spectrum. The oil was warmed with 20% potassium bicarbonate solution (10 ml) at 80° for 2 hours and the mixture was extracted with diethyl ether (2 x 10 ml). The organic extracts were combined washed with water, dried, and the solvent removed in vacuo to give the olefin-ketal (34) as a nearly colourless oil (0.43g, 38.5%).

ν_{max} 2920, 2860, 1450, 1370, 1260, and 1060 cm^{-1} ;
 δ 6.05 (ABq, $J_{AB} = 9$ Hz, 2H), 3.85 (s, 4H), 1.3 (s, 3H),
1.25 (m, 14H), 1.0 (s, 3H), and 0.8 (s, 6H).

Preparation of the Epoxy-Ketal (35).

m-Chloroperbenzoic acid (0.43g, 2.49 m.moles) was added in small portions over 15 minutes to a solution of the olefin-ketal (34) (0.72g, 2.47 m.moles) in dichloromethane (30 ml) and 0.5M sodium bicarbonate solution (3 ml) which was cooled in an ice/salt bath. The mixture was stirred at room temperature for 4 hours, washed with 1N sodium hydroxide (10 ml) and then with water. The organic phase was dried and the solvent removed in vacuo to give a pale yellow oil (0.74g, 97.4%) which was found to be the epoxy-ketal (35).

ν_{\max} 2930, 2860, 1450, 1370, 1255, 1055, and 730 cm^{-1} ;
 δ 3.9 (s, 4H), 3.15 (d, J = 6 Hz, 1H), 2.85 (d, J = 6 Hz, 1H),
 1.45 (m, 14H), 1.3 (s, 3H), 1.0 (s, 3H), and 0.9 (s, 6H).

Attempted Removal of the Protecting Ketal Group from the Epoxy-Ketal (35).

The epoxy-ketal (35) (50 mg, 0.16 m.moles) was stirred at room temperature with 1N hydrochloric acid (2.0 ml) and methanol (1.0 ml) for 1 hour. The mixture was poured onto water (25 ml) and extracted with diethyl ether (3 x 10 ml). The ether extracts were combined, washed with water, dried, and the solvent removed in vacuo to give a yellow oil (20 mg) which was found to be a keto-alcohol and not the desired epoxy-ketone (38).

ν_{\max} 3400 (broad peak), 2900, 1700, 1450, 1360, and 730 cm^{-1} ;
 δ 3.65 (m, 2H), 2.3 (m, 2H), 2.1 (s, 3H), 1.5 (m, 12H),
 1.0 (s, 3H), and 0.9 (s, 6H).

Preparation of Keto-Diacid (36).

The Diels-Alder adduct (32) (2.84g, 7.85 m.moles) dissolved in ethyl acetate (40 ml) was shaken for 16 hours with Adam's catalyst (0.09g) at 50° under 4 atmospheres of hydrogen. The catalyst was filtered off and the solvent removed in vacuo to give the anhydride ketal (2.33g, 82.0%).

The anhydride-ketal (0.96g, 2.64 m.moles) thus obtained was stirred for 5 hours at 80° with 20% potassium bicarbonate solution (20 ml). The solution was extracted with diethyl ether (10 ml) to remove any undissolved organic material and acidified with hydrochloric acid. The mixture was then

stirred for 3 hours at room temperature and extracted with diethyl ether (3 x 20 ml). The combined ether extracts were washed with water, dried, and the solvent removed in vacuo to give the keto-diacid (36) as a white solid (0.86g, 96.3%; m.p. 73°-75°).

ν_{\max} (CHCl₃) 3300 (broad peak), 2950, 2870, 1720, 1700, 1460, and 1370 cm⁻¹;

δ 10.8 (s, 2H), 3.1 (d, J = 9 Hz, 1H), 2.7 (d, J = 9 Hz, 1H), 2.4 (m, 2H), 2.1 (s, 3H), 1.5 (m, 12H), 0.95 (s, 3H), and 0.85 (s, 3H).

Recrystallisation from hexane led to the formation of the anhydride of the acid (m.p. 112°).

ν_{\max} (CHCl₃) 2950, 2870, 1850 (weak), 1750, 1710, 1460, 1370, 1080, 950, 930, and 910 cm⁻¹;

δ 3.15 (d, J = 9 Hz, 1H), 2.85 (d, J = 9 Hz, 1H), 2.45 (t, J = 9 Hz, 2H), 2.15 (s, 3H), 1.5 (m, 12H), 1.2 (s, 3H), and 0.95 (s, 6H).

(Found: C, 71.40%; H, 8.77%; C₁₉H₂₈O₄ requires C, 71.22%; H, 8.81%)

Preparation of Olefin-Ketone (37).

Lead tetraacetate (1.50g, 3.39 m.moles) was washed free of acetic acid with dry hexane and added to a solution of the diacid-ketone (36) (0.86g, 2.54 m.moles) in benzene (20 ml) and pyridine (0.9 ml). The resulting solution was stirred under nitrogen for 1 hour at room temperature, followed by a 2 hour period at 56° - 60°, a 3 hour period at 75° - 80°, and, finally, at room temperature overnight. The

reaction mixture was poured into 6N nitric acid (20 ml), and the layers were separated. The organic layer was washed with water, dried, and the solvent removed in vacuo to give a yellow oil (0.51g). This oil was found to be a mixture of about 50% of the anhydride-ketone and about 50% of the olefin (37). The anhydride was removed by heating the mixture for 3 hours at 80° with 20% potassium bicarbonate solution (10 ml), the mixture was then extracted with diethyl ether (3 x 10 ml), the ether layers were combined, washed free of alkali with water, dried, and the solvent removed in vacuo. Distillation of the product at reduced pressure gave a colourless oil (0.20g, 31.7%; b.p. 144°/0.7 mm) which was shown to be the olefin-ketone (37).

ν_{\max} 2950, 2860, 1720, 1460, 1370, and 690 cm^{-1} ;

δ 6.25 (ABq, $J_{AB} = 9$ Hz, 2H), 2.5 (t, $J = 8$ Hz, 2H),

2.2 (s, 3H), 1.35 (m, 12H), 1.15 (s, 3H), and 0.9 (s, 6H);

m/e (% of base peak), 41 (21.5), 43 (57.2), 69 (14.4),

79 (15.7), 81 (30.2), 91 (22.8), 93 (20.5), 107 (18.6),

109 (34.5), 119 (14.2), 127 (22.8), 133 (100), 163 (34.9),

220 (16.1), 248 (9.8), 249 (1.8).

(Measured mass, 248.2157; calculated mass for $\text{C}_{17}\text{H}_{28}\text{O}$, 248.2141).

Preparation of Epoxy-Ketone (38).

m-Chloroperbenzoic acid (0.22g, 1.28 m.moles) was added in small portions over 15 minutes to a solution of the olefin-ketone (37) (0.30g, 1.21 m.moles) in dichloromethane (10 ml) and 0.5M sodium bicarbonate solution (1.0 ml), cooled in an ice/salt bath. The mixture was stirred for 4 hours at room temperature. The organic layer was washed with 1N sodium

hydroxide solution (5 ml) followed by water, dried, and the solvent removed in vacuo to give yellow oil (0.25g, 79.0%) which was found to be the epoxy-ketone (38).

ν_{\max} 2920, 2860, 1700, 1445, 1355, and 730 cm^{-1} ;

δ 3.15 (d, J = 6 Hz, 1H), 2.85 (d, J = 6 Hz, 1H),

2.4 (t, J = 6 Hz, 2H), 2.1 (s, 3H), 1.45 (m, 12H),

1.0 (s, 3H), 0.9 (s, 3H), and 0.85 (s, 3H);

m/e (% of base peak), 41 (30.7), 43 (69.8), 55 (26.1),

69 (37.1), 71 (21.6), 81 (31.6), 85 (42.9),

133 (45.3), 161 (77.7), 179 (45.3), 207 (23.0),

246 (29.7), 264 (10.3), 265 (1.8).

(Measured mass, 264.2151; mass calculated for $\text{C}_{17}\text{H}_{28}\text{O}_2$, 264.2090).

Cyclisation of the Epoxy-Ketone (38).

The epoxy-ketone (38) (0.40g, 1.96 m.moles) was refluxed with potassium t-butoxide (1.9g, 17.0 m.moles) in t-butanol (30 ml) in a nitrogen atmosphere for 40 hours. The reaction mixture was poured into water (100 ml) and extracted with diethyl ether (3 x 25 ml). The ether extracts were combined, washed free of alkali with water, dried, and the solvent removed in vacuo to give a yellow oil (0.29g). Purification by preparative t.l.c. (elution with 70% diethyl ether in petroleum ether) gave a colourless solid ($R_f = 0.46$) (90 mg, 22.5%; m.p. 85°) which was shown to be the alcohol (39).

ν_{\max} 3500 (broad peak), 2920, 2860, 1690, 1455, and 1370 cm^{-1} ;
 δ 2.8 (br.s, 1H), 2.6 (br.s, 1H) (Exchangeable with D_2O),
 2.3 (br.s, 1H), 2.2 (s, 3H), 1.3 (m, 13H), 0.85 (s, 3H),
 0.8 (s, 3H), and 0.75 (s, 3H);

m/e (% base peak) 28 (26.1), 41 (13.0), 43 (29.9),
 55 (10.8), 69 (12.9), 81 (9.5), 107 (8.5), 109 (17.9),
 149 (15.2), 151 (14.5), 192 (100), 193 (14.0), 220 (91.4),
 221 (14.5), 264 (5.3), 265 (1.1).

(Measured mass, 264.2183; calculated mass for $\text{C}_{17}\text{H}_{28}\text{O}_2$, 264.2090).

Preparation Ethyl Carbonate of the Alcohol (39).

Freshly-distilled ethyl chloroformate (0.2g, 1.84 m.moles) was added slowly to a solution of the keto-alcohol (39) (0.24g, 0.91 m.moles) in pyridine (10 ml) cooled in an ice/salt bath. The mixture was stirred for 1 hour in an ice/salt bath and then allowed to stand for 16 hours at 0°C , poured into ice water (50 ml) and extracted with diethyl ether (3 x 20 ml). The ether extracts were combined, washed free of pyridine with a solution of copper sulphate followed by water, dried, and the solvent removed in vacuo to give a yellow oil (0.23g). This oil was shown to be a mixture by t.l.c. (elution with 70% diethyl ether in petroleum ether). Preparative t.l.c. (elution with 50% diethyl ether in petroleum ether) gave the carbonate (89) as a pale yellow solid ($R_f = 0.5$) (33 mg, 10.2%; m.p. 87°).

ν_{\max} (CHCl_3) 2955, 2935, 2870, 1740, 1715, 1460, 1370,
 1270, and 1260 cm^{-1} ;

δ 4.25 (q, $J = 7.0$ Hz, 2H), 4.2 (br.s, 1H), 2.4 (br.s, 1H),
 2.2 (s, 3H), 1.3 (t, $J = 7.0$ Hz, 3H), 1.4 (m, 13H),
 0.9 (s, 3H), 0.8 (s, 3H), and 0.75 (s, 3H).

Attempted Dehydration of the Alcohol (39).

The keto-alcohol (39) (30 mg, 0.11 m.moles) and *p*-toluenesulphonic acid (100 mg, 0.53 m.moles) were heated under reflux in benzene (3 ml) for 3 hours. The benzene solution was washed with saturated sodium carbonate solution followed by water, dried, and the solvent removed in vacuo to give a yellow oil (16.7 mg) which appeared to be a mixture of products from t.l.c. and spectral analysis. The spectral characteristics of the products could not be correlated with the spectra of the authentic ketone (1) or those expected for the unconjugated ketone (40).

Preparation of the Authentic Ketone (1) from a sample of the Authentic Olefin (2).⁴⁶

Boron trifluoride etherate (0.33g, 2.35 m.moles) was added to acetic anhydride (0.8g, 7.85 m.moles) cooled in an ice bath. The olefin (2) (0.4g, 1.96 m.moles) was added over 15 minutes and the mixture was stirred at room temperature for 4 hours. The reaction mixture was poured onto ice, warmed at 50° for 30 minutes and extracted with benzene (3 x 20 ml). The benzene extracts were washed free of acid with 5% sodium hydroxide solution followed by water, dried, and the solvent removed in vacuo to give a yellow oil (0.40g). Preparative t.l.c. (elution with 30% diethyl ether in petroleum ether) gave a product ($R_f = 0.8$) (80 mg) which was found to be a mixture of two products one of which appeared to be the desired ketone (1). A further purification of this mixture by preparative t.l.c. (elution with 10% diethyl ether in petroleum ether) gave a

product ($R_f = 0.55$) (30 mg) which was found to be a mixture of the desired ketone and another polycyclic ketone, and a second product ($R_f = 0.50$) (30 mg) which was the desired ketone (1).

ν_{\max} 2930, 2860, 1670, 1560, 1455, 1360, 1280, 1250, 1180, 1135, and 940 cm^{-1} ;

δ 2.35 (br.s, 2H), 2.3-2.0 (m, 2H), 2.2 (s, 3H), 1.4 (m, 10H), 0.85 (s, 3H), and 0.80 (s, 6H).

Preparation of Ionene (41)¹⁶.

α -Ionene (25g, 0.13 moles) was distilled in the presence of iodine (0.12g). The fractions which distilled at 248° - 254° were collected, washed with sodium thiosulphate solution and water, dried, and distilled at reduced pressure to give a colourless oil (14.05g, 62.0%; b.p. $95^\circ/3.0\text{ mm}$) (lit.b.p.¹⁶ $107^\circ/10\text{ mm}$) which was found to be ionene (41).

ν_{\max} 2960, 2920, 2860, 1500, 1455, 1360, and 815 cm^{-1} ;

δ 7.05 (m, 3H), 2.75 (m, 2H), 2.2 (s, 3H), 1.65 (m, 4H), and 1.2 (s, 6H).

Birch Reduction of Ionene (41).

Ethanol (9.57g, 0.21 moles) and lithium (1.73g, 0.25g. atom) were added in three portions to ionene (41) (5.94g, 0.034 moles) and ethylamine (80 ml) in a three-necked flask fitted with an acetone/dry-ice condenser and the flask cooled in an ice/salt bath. The alcohol was always added first and the next addition was made only when the lithium had reacted

completely. The ethylamine was evaporated, under a stream of nitrogen, and the last traces were removed by heating on a steam bath. Ice/water (100 ml) and diethyl ether (50 ml) were added, the layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 50 ml). The organic layers were combined, washed free of alkali with water, dried, and the solvent removed in vacuo to give the 1,4-diene (42) as a yellow oil (5.59g, 92.9%).

ν_{\max} 2900, 1500, 790, and 760 cm^{-1} ;

δ 5.35 (m, 1H), 2.45 (m, 4H), 1.65 (m, 6H), 1.6 (s, 3H),
and 1.0 (s, 6H).

Attempted purification by distillation at reduced pressure only resulted in disproportionation of the diene. The 1,4-diene (42) was used, therefore, without further purification in the subsequent reaction.

Isomerisation of the 1,4-Diene (42) to the 1,3-Diene (43).

Nitrogen was bubbled through a solution of the 1,4-diene (42) (7.0g, 39.7 m.moles) in dimethylsulphoxide (250 ml) and benzene (5 ml) for 30 minutes. Potassium t-butoxide (12.7g, 113.4 m.moles) was then added and the mixture stirred for 4 days, under nitrogen, at room temperature. The reaction mixture was poured into ice/water (500 ml) and extracted with petroleum ether (3 x 50 ml). The organic layers were combined and washed free of alkali with brine followed by water, dried, and the solvent removed in vacuo to give the 1,3-diene (43) as a pale yellow oil (7.08g, 100%).

λ_{max} 267 nm ($\epsilon \sim 7000$);
 ν_{max} 2905, 2860, 1445, and 1360 cm^{-1} ;
 δ 5.5 (s, 1H), 2.0 (br.s, 4H), 1.6 (m, 6H), 1.25 (s, 3H),
and 1.0 (s, 6H).

Integration of the n.m.r. spectrum revealed that the product contained 10% of ionene (41) and 25% of the 1,4-diene (42). Attempted purification of the 1,3-diene (43) by distillation at reduced pressure only resulted in the disproportionation and/or decomposition of the diene. The 1,3-diene (43) was, therefore, used without further purification in the subsequent reactions.

Diels-Alder Addition of Maleic Anhydride to the 1,3-Diene (43).

The 1,3-diene (43) (3.77g, 21.4 m.moles) was heated under reflux in xylene (25 ml) with maleic anhydride (3.6g, 36.7 m.moles) and a few crystals of quinol, under nitrogen, for 72 hours. The xylene was removed by distillation at reduced pressure and the products were separated on a column of silica. Elution with petroleum ether gave fractions which contained some xylene not removed during the distillation, ionene (41), and the 1,4-diene (42). Two anhydrides were obtained when the column was eluted with 20% diethyl ether in petroleum ether. The less polar anhydride was found to be the anhydride (44) (1.17g, 19.9%; m.p. 117°).

ν_{\max} (CCl₄) 2930, 2870, 1835, 1770, 1215, 1090,
1070, 950, and 940 cm⁻¹;

δ 5.7 (t, J = 2 Hz, 1H), 3.3 (d, J = 9 Hz, 1H),
2.85 (d, J = 9 Hz, 1H), 2.25 (br.s, 2H), 1.5 (s, 3H),
1.45 (m, 8H), 1.35 (s, 3H), and 1.1 (s, 3H).

(Found: C, 74.42%; H, 8.08; C₁₇H₂₂O₃ requires
C, 74.49%; H, 8.20%).

The more polar anhydride was found to be the anhydride (99)
(0.22g, 3.75%). which was obtained as a viscous oil.

ν_{\max} 2920, 2860, 1835, 1770, 1440, 1360, 1230,
1080, 960, 930, and 905 cm⁻¹;

δ 5.7 (br.s, 1H), 3.15 (m, 1H), 3.0 (br.s, 1H),
2.7 (d, J = 9 Hz, 1H), 1.8 (d, J = 2 Hz, 3H),
1.3 (m, 8H), 0.8 (s, 3H), and 0.6 (s, 3H).

Preparation of 5-Bicyclo[2,2,2]oct-2-enyl-triphenylphosphonium
Bromide (103)⁴³.

1,3-Cyclohexadiene (2.52g, 31.5 m.moles), vinyl
triphenylphosphonium bromide (2.5g, 6.78 m.moles), acetonitrile
(10 ml), and a few crystals of quinol were heated in a sealed
tube, under nitrogen, at 150° for 24 hours. The tube was
opened, the acetonitrile and the excess 1,3-cyclohexadiene were
removed in vacuo, and the crude product was recrystallised from
chloroform containing a little ether to give a white solid
(2.23g, 73.3%; m.p. 260°-262°) (lit. m.p.⁴³ 263°-266°).

ν_{\max} (CHCl₃) 2920, 2840, 1580, 1480, 1435, 1110, 995,
680, and 655 cm⁻¹;

δ 7.25 (m, 15H), 5.8 (q, J = 8 Hz, 1H), 5.3 (q, J = 8 Hz, 1H),
2.6 (br.s, 3H), and 1.5 (br.s, 6H).

Reaction of 5-Bicyclo[2,2,2]oct-5-enyltriphenylphosphonium Bromide (103) with Lithium Aluminium Hydride.

The 5-Bicyclo[2,2,2]oct-5-enyltriphenylphosphonium bromide (103) (0.45g, 1.0 m.moles) was added to lithium aluminium hydride (0.04g, 1.05 m.moles) in tetrahydrofuran (5 ml) and the mixture was refluxed under nitrogen for 12 hours. The mixture was cooled in ice, quenched with water, and extracted with pentane (3 x 10 ml). The pentane extracts were combined, dried, and examined by g.l.c. using a carbowax column at 22°. No bicyclo[2,2,2]oct-2-ene was detected, however. Extraction of the aqueous layer with diethyl ether (3 x 10 ml), washing the ether extracts with a little water, drying, and removing the solvent in vacuo gave triphenylphosphine (30 mg).

ν_{\max} (CHCl₃) 3250, 3000, 1950, 1875, 1810, 1580, 1470, 1425, 1320, 1300, 1080, 1020, and 995 cm⁻¹

Attempted Addition of Vinyl triphenylphosphonium Bromide to the 1,3-Diene (43).

The 1,3-diene (43) (1.0g, 5.68 m.moles), vinyl triphenylphosphonium bromide (1.75g, 4.74 m.moles), acetonitrile (7 ml), and a few crystals of quinol were sealed, under nitrogen, in a glass tube and heated at 165° for 48 hours. The tube was cooled, reopened, and the acetonitrile removed in vacuo. The residue was washed with petroleum ether from which some of the 1,3-diene (43) (0.25g) was recovered. The remaining material resisted all attempts at recrystallisation from chloroform/ether mixtures and the spectral characteristics seemed to be consistent with a mixture of vinyl triphenylphosphonium bromide and a polymeric material.

Attempted Isomerisation of the Diels-Alder Adduct (44) to the Anhydride (45) with p-Toluenesulphonic acid.

The adduct (44) (10 mg, 0.036 m.moles) and p-toluenesulphonic acid (2 mg, 0.012 m.moles) were heated with deuterobenzene (1 ml) for 20 hours at 60° in an n.m.r. tube. Examination of the n.m.r. spectrum of the mixture indicated that the adduct was unchanged by this treatment.

Effect of Ethanolic Hydrochloric Acid on the Diels-Alder Adduct (44).

The adduct (44) (0.1g, 0.365 m.moles), 2N hydrochloric acid (1 ml) and ethanol (10 ml) were refluxed for 3 hours, poured into water (50 ml), and extracted with diethyl ether (3 x 25 ml). The ether extracts were combined, washed free of acid with water, dried, and the solvent removed in vacuo to give a pale yellow oil (0.06g, 51.4%). Purification of the product by preparative t.l.c. (elution with 30% diethyl ether in petroleum ether) gave a colourless oil (Rf = 0.2) (30 mg, 25.7%) which was shown to be the lactone (105).

ν_{\max} 2920, 2860, 1765, 1730, 1460, 1370, 1350, 1320,
1085, 1055, and 930 cm^{-1} ;

δ 4.15 (q, J = 8 Hz, 2H), 2.75 (ABq, $J_{AB} = 9$ Hz, 2H),
1.3 (t, J = 8 Hz, 3H), 1.8-0.9 (m, 12H), 1.1 (s, 3H),
0.95 (s, 3H), and 0.85 (s, 3H).

Isomerisation of the Diels-Alder Adduct (44) to the Anhydride (45) with Trifluoroacetic Acid.

The Diels-Alder adduct (44) (2.00g, 7.3 m.moles) was stirred at room temperature in trifluoroacetic acid (20 ml) for

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Effect of Ethanolic Hydrochloric Acid on the Diels-Alder Adduct (44).

The adduct (44) (0.1g, 0.365 m.moles), 2N hydrochloric acid (1 ml) and ethanol (10 ml) were refluxed for 3 hours, poured into water (50 ml), and extracted with diethyl ether (3 x 25 ml). The ether extracts were combined, washed free of acid with water, dried, and the solvent removed in vacuo to give a pale yellow oil (0.06g, 51.4%). Purification of the product by preparative t.l.c. (elution with 30% diethyl ether in petroleum ether) gave a colourless oil (Rf = 0.2) (30 mg, 25.7%) which was shown to be the lactone (105).

ν_{\max} 2920, 2860, 1765, 1730, 1460, 1370, 1350, 1320,
1085, 1055, and 930 cm^{-1} ;

δ 4.15 (q, J = 8 Hz, 2H), 2.75 (ABq, $J_{AB} = 9$ Hz, 2H),
1.3 (t, J = 8 Hz, 3H), 1.8-0.9 (m, 12H), 1.1 (s, 3H),
0.95 (s, 3H), and 0.85 (s, 3H).

Isomerisation of the Diels-Alder Adduct (44) to the Anhydride (45) with Trifluoroacetic Acid.

The Diels-Alder adduct (44) (2.00g, 7.3 m.moles) was stirred at room temperature in trifluoroacetic acid (20 ml) for

5 hours, poured into ice/water (100 ml), and extracted with diethyl ether (3 x 50 ml). The ether extracts were combined, washed free of acid with saturated sodium bicarbonate solution and water, dried, the solvent removed in vacuo, and the product recrystallised from hexane to give the anhydride (45) as a white solid (1.89g, 94.5%; m.p. 104°).

ν_{\max} 2920, 2860, 1850, 1775, 1460, 1370, 1300, 1090, 1075, and 940 cm^{-1} ;

δ 5.55 (br.s, $W_{\frac{1}{2}h} = 8$ Hz, 1H), 3.2 (d, $J = 9$ Hz, 1H), 2.9 (d, $J = 9$ Hz, 1H), 2.25 (br.s, 2H), 1.95 (br.s, 2H), 1.6 (m, 6H), and 1.25 (s, 6H), 0.85 (s, 3H).

(Found: C, 74.31%; H, 8.15%; $\text{C}_{15}\text{H}_{22}\text{O}_3$ requires C, 74.42%; H, 8.08%).

Reaction of the Anhydride (45) with Hydrochloric Acid and Ethanol.

The anhydride (45) (61.9 mg, 0.23 m.moles), 2N hydrochloric acid (1.2 ml), and ethanol (6 ml) were refluxed for 3 hours, poured into water (50 ml) and extracted with diethyl ether (3 x 25 ml). The ether extracts were washed free of acid with water, dried, and the solvent removed in vacuo to give a yellow oil (30 mg, 40.9%). Purification of the product by preparative t.l.c. (elution with 30% diethyl ether in petroleum ether) gave the lactone (105) as a colourless oil ($R_f = 0.2$) (20 mg, 27.3%).

ν_{\max} 2920, 2860, 1765, 1730, 1460, 1370, 1350, 1320, 1085, 1055, and 930 cm^{-1} ;

δ 4.15 (q, $J = 8$ Hz, 2H), 2.75 (ABq, $J_{AB} = 9$ Hz, 2H), 1.3 (t, $J = 8$ Hz, 3H), 1.4 (m, 12H), 1.1 (s, 3H), 0.95 (s, 3H), and 0.85 (s, 3H).

Preparation of the Diolefin (46).

The anhydride (45) (0.90g, 3.28 m.moles) was stirred for 4 hours at 80° in a 20% solution of potassium bicarbonate (20 ml). The reaction mixture was cooled, acidified with 6N hydrochloric acid, and extracted with diethyl ether (3 x 20 ml). The ether extracts were combined, washed with water, dried, and the solvent removed in vacuo to give the diacid as a white solid (0.82g, 85.5%; m.p. 78°-80°).

ν_{\max} (CHCl₃) 3300, 2920, 2860, 1720, 1460, 1370, 1220,
1080, and 940 cm⁻¹;

δ 10.0 (s, 2H), 5.4 (br.s, 1H), 3.25 (d, J = 11 Hz, 1H),
2.85 (d, J = 11 Hz, 1H), 2.2 (br.s, 2H), 1.9 (br.s, 2H),
1.4 (m, 6H), 1.0 (s, 6H), and 0.85 (s, 3H).

Lead tetraacetate (1.2g, 2.71 m.moles) was washed free of acetic acid with dry hexane, and added to a solution of the diacid (0.56g, 1.92 m.moles), prepared above, in benzene (15 ml) and pyridine (0.8 ml). The mixture was stirred at room temperature for 1 hour, at 56°-60° for 2 hours, at 75°-80° for 3 hours, and finally at room temperature overnight. The mixture was then poured into 2N nitric acid (30 ml), the layers were separated, the organic layer was washed free of mineral acid with water, dried, and the solvent removed in vacuo. The crude product thus obtained was eluted from a short silica column with petroleum ether to give the diolefin (46) as a colourless oil (40 mg, 10.3%).

ν_{\max} 2910, 2860, 1450, 1380, 1360, and 810 cm^{-1} ;
 δ 6.05 (ABq, $J_{AB} = 9$ Hz, 2H), 5.25 (br.s, 1H), 1.95 (br.s, 4H),
 1.25 (m, 6H), 1.1 (s, 3H), 1.0 (s, 3H), and 0.9 (s, 3H).
 m/e (% base peak) 28 (3.1), 39 (4.4), 41 (6.3), 53 (2.9),
 65 (3.2), 77 (5.6), 79 (3.2), 91 (9.1), 105 (5.8),
 115 (6.5), 117 (8.6), 118 (100), 119 (14.3), 128 (5.4),
 129 (5.3), 131 (7.5), 159 (10.1), 174 (31.0), 175 (3.9),
 202 (5.4).

(Measured mass 202.1706; calculated mass for $\text{C}_{15}\text{H}_{22}$, 202.1721).

Attempted Conversion of the Anhydride (45) to the Diolefin (46) using Bis(triphenylphosphine) nickel (0) dicarbonyl.

Bis(triphenylphosphine) nickel (0) dicarbonyl
 (1.71g, 2.68 m.moles) was added to a solution of the anhydride (45)
 (0.5g, 1.82 m.moles) dissolved in diglyme (5 ml). The mixture
 was stirred at 200° for 12 hours in a nitrogen atmosphere.
 Distillation of the reaction mixture at reduced pressure
 (60°/15 mm) did not yield any of the desired olefinic product,
 but only diglyme. The residue from the distillation was quenched
 with water (25 ml) and extracted with hexane (3 x 10 ml). The
 organic extracts were combined, washed with water, dried, and
 the solvent removed in vacuo to give 0.53g of material which
 was found to be a mixture of the anhydride (45) and
 triphenylphosphine by spectral examination.

Hydrogenation of the Diolefin (46).

The diolefin (46) (11.7 mg, 0.058 m.moles) was
 dissolved in ethyl acetate (5 ml) and stirred at room temperature

under 1 atmosphere of hydrogen with 5% paladium on charcoal (4 mg) for 20 hours. The catalyst was filtered off and the solvent was distilled from the mixture to give a pale yellow oil. This oil was examined by t.l.c. (elution with petroleum ether) ($R_f = 0.56$) and found to be different from the starting material ($R_f = 0.45$) and similar to the authentic olefin (2) ($R_f = 0.56$). G.l.c. analysis also indicated that the product was similar to the authentic olefin (2) (Retention time of the product on a 5% Carbowax 1540 column at 120° was 11 minutes which was the same as that of the authentic olefin (2) and the retention time of the diolefin (46) was 11.5 minutes). The product was purified by distillation at reduced pressure to give the olefin (2) (8.4 mg, 71.0%; b.p. $90^\circ/0.7$ mm) (lit b.p.² $104^\circ/5$ mm) as a colourless oil.

ν_{\max} 2920, 2860, 1450, 1380, 1360, and 810 cm^{-1} ;

δ 5.3 (br.s, 1H), 1.95 (br.s, 4H), 1.4 (s, 10H), 0.82 (s, 3H), and 0.79 (s, 6H).

m/e (% base peak) 41 (18.9), 55 (12.9), 77 (11.2),
79 (12.6), 81 (11.7), 91 (21.8), 93 (11.2), 95 (12.0),
105 (40.6), 107 (12.5), 119 (40.3), 133 (17.3),
147 (21.2), 148 (29.1), 161 (9.0), 175 (100), 176 (13.9),
189 (40.3), 204 (79.8), 205 (12.9).

(Measured mass, 204.1922; calculated mass for $C_{15}H_{24}$, 204.1878).

The g.l.c., t.l.c., i.r., n.m.r., and m.s. characteristics show that this olefin is identical with the authentic olefin (2).

Hydroboration/Oxidation of the Anhydride (45).

A solution of the anhydride (45) (0.17g, 0.62 m.moles) in tetrahydrofuran (1 ml) was added over 10 minutes to a 1M solution of diborane in tetrahydrofuran (3 ml), cooled in an ice bath, and the solution was stirred at room temperature for 20 hours. After the reaction mixture had been cooled in an ice bath, 10% aqueous sodium hydroxide (3.0 ml) and 28% hydrogen peroxide solution (3.0 ml) were added and the mixture was warmed at 30° for 3 hours. The reaction mixture was diluted with water, acidified with 6N hydrochloric acid, and extracted with diethyl ether. The ether extracts were combined, washed free of acid with water, dried, and the solvent removed in vacuo to give a yellow solid (0.14g) which appeared to be a mixture of alcohols by the appearance of a broad peak at 3300 cm^{-1} and peaks at 2940, 2870, 1830 (very weak), 1765, and 1720 cm^{-1} in the i.r. spectrum and the appearance of a broad singlet at 6.9 δ in the n.m.r. spectrum which disappeared on shaking the sample with D_2O .

The mixture was dissolved in acetone (5 ml) and cooled in an ice bath. Jones reagent was added slowly with stirring until the orange colour was just maintained. The mixture was stirred for 20 minutes while being cooled in the ice bath before isopropyl alcohol (0.5 ml) was added. The inorganic salts were filtered off and the organic solvents were removed in vacuo before the aqueous mixture was extracted with diethyl ether (3 x 10 ml). The ether layers were combined, washed free of acid with water, dried, and the solvent removed in vacuo to give a

pale yellow solid (0.12g) which appeared to be a mixture of the keto-diacid (47) and the corresponding anhydride by the appearance of a broad peak between 3500-2500, peaks at 2930, 2870, 1830 (weak), 1775, and 1730 cm^{-1} in the i.r. spectrum and a broad singlet at 8.3 δ , which was exchanged with D_2O , a multiplet at 3.0, and singlets at 1.05 and 0.95 in the n.m.r. spectrum.

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