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THE CHEMISTRY OF  
 $\alpha$ -CARYOPHYLLENE ALCOHOL AND NEOCLOVENE.

THESIS

presented to the University of Glasgow

for the degree of Ph.D.

by

James Stewart Roberts

1965.

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I wish to express my sincere appreciation and gratitude to my supervisor, Dr.W. Parker, who has been ready at all times to give me his friendly advice and encouragement over the last three years. I should also like to thank Professor R.A. Raphael, F.R.S. for his continued enthusiasm and interest.

My thanks are also due to Mr.J.M.L. Cameron, B.Sc., for micro-analyses, to Mrs.F. Lawrie for infra-red spectra, to Mr.A. McCormick, B.Sc. for mass spectra and to Mr.J.H. Gall for N.M.R. spectra.

I am very grateful to Professor V. Herout of The Czechoslovak Academy of Science for a generous sample of humulene and to Dr.K. Overton of Glasgow University for a sample of ruthenium tetroxide.

Finally, I wish to accord my thanks to the Department of Scientific and Industrial Research for my maintenance awards during the past three years.

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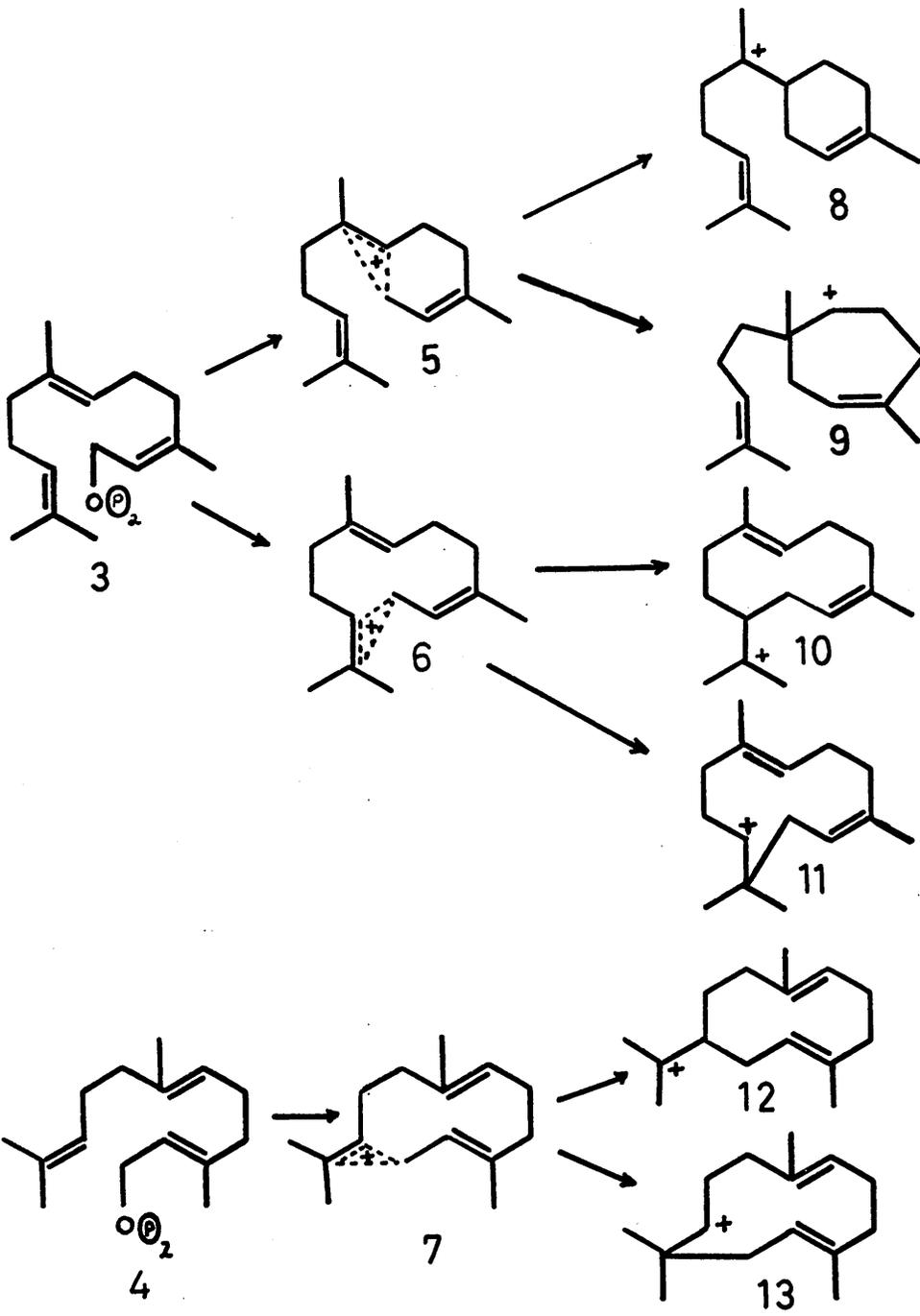
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## INTRODUCTION.

The subject of this thesis is the chemistry of  $\alpha$ -caryophyllene alcohol and neoclovene. Since these two sesquiterpene artefacts are produced by cationic cyclisation of humulene and caryophyllene respectively, this introduction will attempt to review the field of cationic cyclisations implicit in sesquiterpene biogenesis.

In the last 25 years this class of natural product has provided a host of challenging structural problems to the organic chemist. The resultant wide variety of acyclic, monocyclic and fused ring structures was brilliantly rationalised first, in a general sense, by Ruzicka<sup>1</sup> in his epoch-making paper on terpene and steroid biogenesis, and later by Hendrickson<sup>2</sup>, who elaborated this approach in a more detailed stereochemical correlation of the sesquiterpenes.

The focal point of sesquiterpene biogenesis is the naturally occurring compound, farnesol (1), whose formation from acetyl CoA, via mevalonic acid<sup>3</sup>, has found experimental verification<sup>4,5</sup>. For the sake of simplicity, the farnesyl unit is considered as having a trans central double bond with either a cis or trans terminal double bond. This latter presumption is permissible in view of the co-occurrence of farnesol and nerolidol (2)<sup>6</sup>, since



in vivo interconversion of these alcohols would permit a change of configuration at the terminal double bond.

The carbon skeletons of most sesquiterpenes can now be derived by a suitable cyclisation of either cis-farnesyl pyrophosphate (3) or trans-farnesyl pyrophosphate (4). The initial step in these cyclisations is envisaged as elimination of the pyrophosphate anion by participation of either the central or terminal double bonds leading to the the cations (8) to (13) through the intermediacy of the non-classical cations (5) to (7) (See Flow Sheet). It must, of course, be stressed that such representation of a formal charge either on a particular carbon atom or distributed over a number of atoms is completely unrealistic as far as natural processes are concerned, where a particular enzyme system would almost certainly produce these complex sesquiterpenes from the pyrophosphate precursor in a fully concerted manner. Nevertheless, the utility of this scheme in supplying a satisfactory classification of sesquiterpenes cannot be denied.

In the case of cis-farnesyl pyrophosphate (3), interaction of the allylic carbonium ion with the central double bond leads to the monocyclic cations (8) and (9). From a consideration of the steric and electronic factors involved,

the cation (8) is favoured, and indeed most of the known six membered monocyclic sesquiterpenes, such as bisabolene (14) and zingiberene (15) can be theoretically derived from this ion, with the notable exception of the elemene series (vide infra) and the sesquiterpene, humbertiol (16)<sup>7</sup>. The latter is probably derived by oxidative fission of the cadinane type of sesquiterpene.

Before proceeding to discuss the types of carbon skeleton derivable from (8) by further internal cyclisation, it is noteworthy to record the derivation of the carotane class of sesquiterpenes. The known representatives of this class are carotol (17), daucol (18)<sup>8</sup> and, after a recent structural revision, laserpitine (19)<sup>9</sup>. It is of phylogenetic interest that both carotol and daucol are isolated from one species of the Umbelliferae family, while laserpitine is isolated from another species of the same family. One possible biogenetic route to the carotane skeleton would involve a 1,3 hydride shift in cation (10), followed by an anti-Markownikoff cyclisation and subsequent methyl migration. Although these three types of transitions have been postulated and in certain cases verified in sesquiterpene biogenesis, the likelihood of all three occurring within the genesis of one sesquiterpene seems remote. However, a more plausible scheme<sup>10</sup> involving cyclisation

of the cation (9) would also give the carotane nucleus, without invoking a methyl migration, as shown. This latter postulate has been verified<sup>10</sup> by feeding acetate (1-C<sup>14</sup>) to the carrot seeds and degradation of the radioactive carotol. The activity of 16.6% found in C<sub>8</sub> and the attached methyl group is only consistent with the proposed biogenesis from cation (9), since the former postulate, through the intermediacy of cation (10) would require neither of these carbons to be radioactive.

Returning now to the cation (8), it can be seen that appropriate cyclisation leads to the cadinane type of sesquiterpene, of which there are numerous examples with and without oxygen functions.

The isolation of  $\beta$ -bergamotene (21)<sup>11</sup> illustrates that interaction of the cyclic double bond in cation (8) with the carbonium ion can proceed in the electronically favoured fashion to give the cation (20), which on deprotonation furnishes  $\beta$ -bergamotene. Although  $\alpha$ -bergamotene (i.e. exomethylene group) has not been positively identified, its existence is presumed, by analogy with  $\alpha$ -pinene and  $\alpha$ -longipinene (vide infra). The sterically favoured cyclisation of (8), on the other hand, gives rise to  $\beta$ -santalene (22) and  $\alpha$ -santalene (23) respectively, as shown.

A plausible route to the cuparane skeleton has been proposed by Ramage<sup>12</sup>. This scheme involves protonation of bisabolene (i.e. 24) followed by cyclisation to the stable tertiary carbonium ion (25), which is the logical precursor of cuprenene (26)<sup>13</sup>, cuparene (27)<sup>14</sup> and cupar- enic acid (28)<sup>14</sup>. Recently<sup>15</sup>, two additional members of this class have been isolated, viz.,  $\alpha$ -cuparenone (29) and  $\beta$ -cuparenone (30), as well as the corresponding alcohols. The main alcoholic constituents of the extract, however, are cedrol and widdrol (vide infra), which is of possible biogenetic significance.

This same carbonium ion intermediate (25) has been proposed as the precursor of the interesting sesquiterpene, trichothecin (31)<sup>16</sup>. The proposed genesis of this sesqui- terpene involves two 1,2 methyl shifts to give the tertiary carbonium ion (32). This proposal has received verification by the elegant tracer experiments<sup>17</sup> with mevalonate (2-C<sup>14</sup>), in which it was conclusively demonstrated that the 1,2 methyl shifts did occur. Despite the X-ray<sup>18a</sup> and chemical<sup>18b</sup> structural determination of the related sesquiterpene, trichodermin (33), which, in turn, suggested a revised structure for trichothecin (34), this biogenetic scheme is not invalidated as it would be the same for the new structure. A possible biogenesis of the closely related bromo-sesqui-

terpenes, aplysin (35,R=H) and aplysinol (35,R=OH)<sup>19</sup> could involve an anti-Markownikoff attack by the terminal double bond in the cation (8), followed by a 1,2 methyl migration to give the tertiary cation (36). By some deprotonation process this cation could then aromatise.

The alternative cyclisation of cation (24) gives the spiro-carbonium ion (37), which has been proposed again by Ramage<sup>12</sup> as the logical precursor of the widdrane (38) and thujopsane (39) class of sesquiterpenes. Similarly cyclisation of either the secondary carbonium ion (40), or alternatively, the tertiary carbonium ion (41), both derivable from bisabolene by protonation, would give the cations (42) and (43) respectively, corresponding to the acorane nucleus. Recently a sesquiterpene acid, acoric acid (44), has been isolated<sup>20</sup>. A biogenetic derivation of this compound can be conceived by oxidative cleavage of acorone (45), as shown.

Nucleophilic attack by the cyclic double bond in cation (43) would furnish the tricyclic carbonium ion (46), which is the basic skeleton of a class of sesquiterpenes, exemplified by cedrol (47)<sup>21</sup>, shellolic acid (48,R=CO<sub>2</sub>H)<sup>22</sup> and jalaric acid (48,R=CHO)<sup>23</sup>.

Considering now the outcome of cyclisation of the terminal double bond with the allylic carbonium ion from

cis-farnesyl pyrophosphate (3), the electronically favoured cation is (10), whereas, from a steric point of view, cation (11) is favoured. Although this former cation was discarded by Hendrickson<sup>2</sup> on the grounds of the strain and non-bonded interactions implicit in its formation, it has since been postulated as the precursor of a number of sesquiterpenes. A 1,3 hydride shift, followed by cyclisation leads to the cation (49), the proviso of further internal cyclisation being that this cation is of the cis-decalin type. The recent isolation of the muurolenes (50)<sup>24</sup> with such a cis ring junction lends weight to this stipulation. It could perhaps be argued that this cation could also be formed through the intermediacy of an anti-Markownikoff cyclisation of zingiberene (15) followed by a 1,2 hydride shift. Since both of these processes involve 'unfavourable' transitions, a decision in favour of the one as opposed to the other does not seem feasible.

The recently determined structures of copaene<sup>25,26</sup> and the related muskatone<sup>25</sup> can be derived from this cation (49). An electronically favoured cyclisation leads to the tricyclic carbonium ion (51), which on deprotonation and oxidation yields copaene (52, R=H<sub>2</sub>) and muskatone (52, R=O), respectively. That the biogenetic precursor of copaene is the cation (49) finds credence in view of its co-occurr-

ence with the sesquiterpenes,  $\delta$ -cadinene (53) and calamenene (54). The structure of the closely related sesquiterpene hydrocarbon, ylangene (55)<sup>27</sup> has been recently adduced, in which it was demonstrated that ylangene differs from copaene only in the configuration of the isopropyl group. A logical precursor of ylangene would be one of the amorphenes (56)<sup>27</sup>, which bear the same configurational difference to the muurolenes as copaene does to ylangene.

The carbonium ion (49) has also been proposed as the precursor of the sesquiterpene toxin, helminthosporal (57)<sup>28</sup>. Thus an anti-Markownikoff attack of the double bond gives the secondary carbonium ion (58). This cation can now undergo a Wagner-Meerwein rearrangement, similar to that proposed in the biogenesis of longifolene (vide infra) and subsequent deprotonation yielding (59). The oxidation sites observed in helminthosporal can be acquired by oxidative cleavage of the bond shown. This last step has become more plausible in view of the isolation of prehelminthosporol (60)<sup>29</sup>. This biogenetic scheme for helminthosporal has received support<sup>30</sup> by a tracer experiment with mevalonic acid (2-C<sup>14</sup>), in which it was demonstrated that the unsaturated aldehyde carbon atom had 38% of the total activity in accordance with the proposed biogenesis.

An examination of a model of the cis cation (11) shows that the two endocyclic double bonds are not held close enough together to permit internal cyclisation and secondly the hydrogen on C<sub>10</sub> is held between the cationic site at C<sub>1</sub> and the  $\Delta^{4-5}$  double bond, thus excluding cyclisation in this manner. The only pathway, therefore, favourable for neutralisation of the carbonium ion is a Markownikoff attack of the  $\Delta^{8-9}$  double bond with concomitant loss of a proton from the C<sub>8</sub> methyl group to give the known, correct stereochemistry of caryophyllene (61). The only other sesquiterpenes with this caryophyllane skeleton are  $\alpha$ -betulenol (62a<sup>31</sup> or 62b<sup>32</sup>) and  $\beta$ -betulenol (63a<sup>31</sup> or 63b<sup>32</sup>), whose structures are still in doubt. A single N.M.R. spectrum of each could be the deciding factor.

At this point, it is pertinent to discuss the biogenesis of the isomeric sesquiterpene, humulene. In view of its co-occurrence with caryophyllene in Nature, it was not unreasonable of Hendrickson<sup>2</sup> to propose that they originate from the same intermediate cationic species (11). Thus, simple deprotonation from C<sub>2</sub> would furnish the gross skeleton of humulene with a trans disubstituted double bond. Up until 1963, these were the known features of humulene, whereas the stereochemistry of the two tri-

substituted double bonds had not been positively elucidated. According to Hendrickson's scheme<sup>2</sup> humulene has the trans-trans-cis arrangement of the double bonds. However, it has been conclusively shown by an X-ray analysis<sup>33</sup> of the bis silver nitrate adduct of humulene that the double bonds have the all trans configuration (64). By inference, therefore, humulene is derived from the trans-farnesyl cation (13). This naturally raises the problem as to whether caryophyllene comes from the same intermediate. Recourse to models, however, suggests that this trans-farnesyl cation would give the wrong stereochemistry for caryophyllene. Since the enzyme site, however, controls the stereochemical outcome of the cyclisation, the use of models may be a bad analogy. The supposed isolation of iso-caryophyllene (65) would suggest a cis  $\Delta^{4-5}$  farnesyl precursor. Perhaps the fact<sup>34</sup> that caryophyllene is not isolated as such from benzene extraction of oil of cloves, but only by steam distillation of the cloves is significant.

To accommodate the gross structures of two other types of sesquiterpenes, a 1,3 hydride shift in cation (11) is proposed. This new cation (66) can now undergo a facile cyclisation with the  $\Delta^{4-5}$  double bond to give the tertiary carbonium ion (67). Simple deprotonation yields the two isomeric  $\alpha$ - (68) and  $\beta$ - (69) himachalenes<sup>35</sup>,

while solvent attack gives himachalol (70)<sup>36</sup>. As in the case of the proposed precursor of copaene, this intermediate cation (67) could conceivably be formed from zingiberene as shown. The isolation of allo-himachalol (71)<sup>36</sup> indicates that a Wagner-Meerwein rearrangement is also possible giving the bridged carbonium ion (72), which can only undergo nucleophilic attack from solvent. The reverse of this process has been observed<sup>36</sup> when allo-himachalol tosylate was solvolysed, the products being (68) (3%), (69) (15%), (70) (24%) and (71) (34%).

By analogy with the formation of copaene (*vide supra*), an electronically favoured cyclisation of the cation (67) would yield the tricyclic carbonium ion (73). As yet no sesquiterpenes have been isolated with this gross structure.

The sterically controlled cyclisation of the cation (67), however, has been postulated as the precursor of the longifolane and possibly the longipinane type of sesquiterpenes via the longibornyl cation (74). Solvent attack on this cation (74) gives longiborneol (75)<sup>36</sup>. On the other hand, a Wagner-Meerwein shift, either followed by deprotonation or oxidative neutralisation via a non-classical carbonium ion, gives longifolene (76)<sup>37</sup> and longicyclene (77)<sup>38</sup> respectively, as shown. Yet another

Wagner-Meerwein shift in the longibornyl cation to the tertiary carbonium ion (78), followed by deprotonation gives  $\alpha$ -longipinene (79)<sup>39</sup>. It would be of biogenetic interest to ascertain if all four sesquiterpenes, in addition to the hitherto unreported  $\beta$ -longipinene (80) can be isolated from the one natural source. The biogenetic scheme for longifolene has been partially verified by tracer work<sup>40</sup> with acetate (1-C<sup>14</sup>), in which it was shown that the exomethylene group had virtually no activity as would be expected.

Cyclisation of trans-farnesyl pyrophosphate (4) would furnish the cations (12) and (13). The postulate of the cation (13) as the precursor of humulene has already been dealt with. The tentative structure assigned to isocaucalol (81)<sup>41</sup> may be derived from the cation (11) or alternatively from the cation (13), since the stereochemistry of the trisubstituted double bond has not been determined. Certainly the reported value of 8.25 $\tau$  for the vinylic methyl group is more consistent with a cis double bond, although this downfield shift could well be due to a deshielding effect by the oxygen functions present. The coupling constant of 10 cps. for the vinylic proton is consistent for certain conformations of the ring system with a cis or trans double bond.

An interesting postulate<sup>42,43</sup> has been offered for the biogenesis of the unique sesquiterpenes, illudin S (lampterol) (82,R=OH) and illudin M (82,R=H), involving the intermediacy of humulene. An ensuing cyclisation involving electronically favoured tertiary cations is envisaged. Final ring contraction (hinc lumen!) of the cation (83) yields the gross structure of the sesquiterpene, as shown.

An examination of the cation (12) indicates that a multitude of fairly closely related sesquiterpenes can be derived from it.

Thus oxidative modification generates all the known ten membered ring sesquiterpenes with the germacrane skeleton. Examples of this group are germacrone (84)<sup>44</sup>, linderane (85)<sup>45</sup>, costunolide (86)<sup>46</sup>, parthenolide (87)<sup>47</sup>, pyrethrosin (88)<sup>48</sup>, arctiopicrin (89)<sup>49</sup> and scabiolide (90)<sup>50</sup>. The acid-catalysed cyclisation and pyrolysis products of this type of sesquiterpene will be referred to later in the light of the biogenetically related eudesmane, elemene and guaiane types.

The two double bonds of the cation (12) are ideally juxtaposed for transannular cyclisations in a concerted trans-antiparallel fashion to give the eudesmane type of sesquiterpene. Thus stereospecific Markownikoff-orient-

ated cyclisation gives the hypothetical precursor (91) of this series, as shown. This hypothesis has been substantiated by the isolation of cryptomeridiol (91)<sup>51</sup>, which possesses the proposed structure and stereochemistry. Indeed most of the eudesmane sesquiterpenes have this absolute stereochemistry. In many cases, the initial product of cyclisation has undergone further oxidation resulting in the large body of lactone and furano derivatives of this class. Examples of this type are vulgarin (92)<sup>52</sup>, ivalin (93)<sup>53</sup>, telekin (94)<sup>54</sup> and atractylon (95)<sup>55</sup>. An example in which a methyl migration in the eudesmane nucleus has possibly occurred is illustrated by occidol (96)<sup>56</sup>. A plausible precursor of this sesquiterpene is the naturally occurring alcohol, occidentalol (97)<sup>57</sup>. Another possible derivative of the eudesmane type is cogeijerene (98)<sup>58</sup>, in which the isopropyl group has been amputated at some stage in its genesis. Apart from this feature, this degraded sesquiterpene is unusual in the sesquiterpene field, in that it is a racemate. Two explanations of this phenomenon have been proffered ; either the lack of optical activity is a consequence of the isolation procedure or else the cyclisation process is non-enzymatic in character. It is of interest to note that a sesquiterpene co-occurring with cogeijerene is  $\delta$ -elemene

(99)<sup>58</sup>, which is also racemic. Recently a number of antipodally related eudesmane sesquiterpenes have been isolated, such as intermedol (100)<sup>59</sup>,  $\alpha$ - and  $\beta$ -agarofurans (101)<sup>60</sup> and laevojuneol (102)<sup>61</sup>. This observation, although not unique in the sesquiterpene field (see iresin), is probably due to the steric requirements of the enzyme systems involved in cyclisation. A biogenetic scheme has been postulated<sup>62</sup> for the formation of agarospirol (103). This scheme, as shown, involves an opening of the tetrahydrofuran ring of the naturally occurring dihydroagarofuran, followed by a bond migration to give the spiro cation, which is then deprotonated. Significantly, agarospirol is only isolated from the fungus-infected wood source, whereas the agarofurans are derived from fungus-free wood. This would infer that it is the additional enzyme present in the fungus which effects this further transformation.

A concerted anti-Markownikoff cyclisation in cation (12) generates the guaiane skeleton (104), as shown. This type of skeleton is exemplified by allo-torilolone (105)<sup>63</sup>, bulnesol (106)<sup>64</sup>, guaiol (107)<sup>65</sup> and globicin (108)<sup>66</sup> among many others.

Modifications of the guaiane skeleton can also be devised to account for other structurally related sesqui-

terpenes. Two theories, either from an oxygenated guaiane or aromadendrane skeleton, as shown, have been put forward to explain the unique skeleton of zierone (109)<sup>67</sup>, in which migration of the isopropyl group appears to have taken place. Some type of oxidative fission, as shown, of ring A of the guaiane nucleus could be invoked to explain the gross structure of carabone (110)<sup>68</sup>. Oxidative cleavage between C<sub>2</sub> and C<sub>3</sub> of the guaiane skeleton has been suggested as a possible route to the furopelargones (111)<sup>69,70</sup>. The 'abnormal' guaianolides, such as tenulin (112)<sup>71</sup>, can be simply derived from the 'normal' guaianolide skeleton by a 1,2 methyl migration. To accommodate the structures of valerenic acid (113, R=H)<sup>72</sup> and valerenolic acid (113, R=OH)<sup>73</sup>, a ring B contraction has been proposed in the manner shown. The two sesquiterpenes, patchoulene (114, R=O)<sup>74</sup> and cyperene (114, R=H<sub>2</sub>)<sup>75</sup>, belonging to the revised class name of isopatchoulane, can be formed by nucleophilic attack of the double bond on the carbonium ion derived from guaiol (115, R=H<sub>2</sub>). The revised structure of patchouli alcohol (116)<sup>76</sup> could be explained in terms of a Wagner-Meerwein migration with concomitant solvent attack in a cation readily derivable from bulnesol. A similar type of ionic cyclisation could be involved in the formation of  $\alpha$ -kessyl alcohol (117)<sup>77</sup>.

A Cope rearrangement of the cation (12) has been postulated<sup>2</sup> as a plausible mechanism for the formation of the elemene class of sesquiterpenes. Examples of this type are elemol (118)<sup>78</sup>, saussurea lactone (119)<sup>79</sup> and isolinderalactone (120)<sup>80</sup>. Doubts, however, as to whether this type of sesquiterpene actually exists per.se in Nature have been uttered<sup>79,80</sup>. Experimental evidence<sup>80</sup> indicates that higher yields of this type can be realised if heat is used at any stage in the isolation procedure. Carefully controlled isolation techniques have, however, been used, which tend to vindicate their presence in natural sources.

Having considered the genesis of these three groups of sesquiterpenes derivable from the cation (12), it is pertinent at this stage to digress a little and examine the products of in vitro transannular cyclisations of the germacrane sesquiterpenes, which have furnished a more concrete rationale for the proposed in vivo transannular cyclisations of cation (12). Indeed it is true to say that a great deal of the chemistry of the ten membered ring sesquiterpenes has been elucidated in the light of the structures of these cyclisation products, and in many cases they have been correlated with appropriately modified naturally occurring eudesmane type sesquiterpenes.

In particular, the derivatives of santonin, whose absolute stereochemistry was known, played an important role in this respect.

In this context, the acid-catalysed cyclisation of the costunolide derivatives serves as a typical example. Thus, costunolide (86, R=CH<sub>2</sub>) and dihydrocostunolide (86, R=CH<sub>3</sub>) on treatment with acetic acid give rise to the so-called α-(121, R=CH<sub>2</sub>) and β-cyclocostunolides (121, R=CH<sub>3</sub>)<sup>81,82</sup>. α-Cyclocostunolide on catalytic hydrogenation yields santanolide 'c' (122), the formation of which establishes the stereochemistry of the cyclised product at all the asymmetric centres and by inference at C<sub>6</sub> and C<sub>7</sub> in costunolide itself. By an analogous cyclisation and suitable reductive elaboration, costunolide has been converted into the antipode of naturally occurring juneol (123)<sup>83</sup>.

Similarly arctiopicrin (89)<sup>49</sup>, balchanolide (124)<sup>84</sup> and eupatariopicrin (125)<sup>85</sup>, after hydrolysis of the side chain, yield on hydrogenation in acid medium the bicyclic derivative (126). This same hydroxy-lactone can be derived from artemisin (127).

So far the only reported cyclisation<sup>47</sup> to give a guaiane skeleton is that of parthenolide (87). Thus, parthenolide on treatment with boron trifluoride

etherate yields the hydroxy-lactone (123). This compound could probably be modified to give the naturally occurring guaianolide, arborescin (129). Santonin has recently assumed an even more intimate association with the germacrane sesquiterpenes, through its utility in Corey's brilliantly conceived synthesis of dihydro-costunolide (86, R=CH<sub>3</sub>)<sup>86</sup>.

The Cope rearrangement of some of the germacrane sesquiterpenes to form the elemene series has also been observed. Thus, dihydrocostunolide (86, R=CH<sub>3</sub>) on pyrolysis affords saussurea lactone (119)<sup>87</sup>, while germacrone on similar treatment gives β-elemenone (130)<sup>88</sup>.

A double bond migration in the cation (12) giving the cation (131), followed by analogous concerted cyclisations to those postulated for cation (12) itself, result in the formation of two more hypothetical intermediates (132) and (133) in sesquiterpene biogenesis. The intermediate (132) has been postulated as the ideal precursor for the eremophilane group of sesquiterpenes, exemplified by eremophilene (134)<sup>89</sup>, eremophilone (135)<sup>90</sup>, petasin (136)<sup>91</sup>, furanopetasin (137)<sup>92</sup> and eremophilenolide (138)<sup>93</sup>. The process envisaged, as illustrated, is a series of concerted 1,2 shifts, predicting the correct stereochemistry

found in this group.

On the other hand, the intermediate (133) is the obvious precursor of the vetivane type of sesquiterpenes, of which hinesol (139)<sup>94</sup> and  $\beta$ -vetivone (140) are examples. This intermediate may also be the precursor of the tricyclovetivane class.

The two closely related classes of sesquiterpenes containing a gem-dimethyl substituted cyclopropane ring, viz., the aromadendranes and the maalianes, have been postulated<sup>95</sup> as originating from a common precursor. Thus, oxidative neutralisation of trans-farnesyl cation (4) by the terminal double bond would lead to the bicyclic diene (141). A Markownikoff-orientated cyclisation would give the naturally occurring maaliol (142)<sup>96</sup> and the maalienes (143). In a similar fashion to the 1,2 migrations proposed in the genesis of the eremophilane group, the maaliene carbonium ion (144) would yield  $\beta$ -gurjenene (calarene) (145)<sup>95</sup> and aristolone (146)<sup>97</sup>. An anti-Markownikoff cyclisation of the diene (141) would yield the tricyclic cations (147) and (148) respectively. Cation (147) is the logical precursor of aromadendrene (149)<sup>98</sup> and allo-aromadendrene (150)<sup>98</sup> and the corresponding alcohols, ledol (151, R= $\begin{array}{c} \text{CH} \\ \diagdown \\ \text{OH} \end{array}$ )<sup>98</sup>, globulol (152, R= $\begin{array}{c} \text{CH} \\ \diagdown \\ \text{OH} \end{array}$ )<sup>98</sup>, viridiflorol (151, R= $\begin{array}{c} \text{CH} \\ \diagdown \\ \text{OH} \end{array}$ )<sup>98</sup>

and palustrol (152, R= $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{OH} \end{array}$ )<sup>99</sup>. Conversely cation (148) is the obvious antecedent of  $\alpha$ -gurjenene (153), and probably the exomethylene analogue which has, as yet, not been identified. Other members of this group are cyclocolarenone (154)<sup>100</sup> and spathulenol (155)<sup>101</sup>. It is of biogenetic significance that of the two Dipterocarpus species so far examined<sup>95</sup>, one yields predominantly caryophyllene and humulene, while the other yields predominantly aromadendrene, allo-aromadendrene and  $\alpha$ - and  $\beta$ -gurjenene but no maaliene.

Although the majority of sesquiterpenes can be derived by the cyclisation processes outlined above, a group of well-defined sesquiterpenes which are indubitably derived by a concerted trans-antiparallel cyclisation of farnesyl pyrophosphate have been isolated. These sesquiterpenes, of which iresin (156)<sup>102</sup>, drimenol (157)<sup>103</sup> and polygodial (158)<sup>104</sup> are examples, belong to the bicyclofarnesol class. Initially it was suggested that these sesquiterpenes may, in fact, be degraded di- and triterpenes, but it was later shown that iresin had the opposite stereochemistry to that found in most higher terpenes and steroids. Drimenol, on the other hand has been shown to possess the conventional absolute stereochemistry. As mentioned before this type

of reversed stereochemistry may be the result of a particular stereochemical requisite of the enzyme controlling the cyclisation.

Recently van Tamelen<sup>105</sup> has shown that the in vitro cyclisation of the terminal monoepoxide of trans-trans-farnesyl acetate (159) with boron trifluoride etherate or mineral acids gave a modest yield of the stereoisomer (160) (85%) and its epimer (161) (15%), which, on oxidation to the corresponding acetoxy-ketones followed by reduction of the thioketals gave dl-drimenol and dl-epidrimenol respectively. Two by-products of this cyclisation have the spectral properties consistent with (162) and (163) respectively. These structures are of biogenetic interest since the ring B moiety of (162) is found in naturally occurring diterpenes such as pimaric acid and rimuene, while the second structure (163) has the naturally occurring farnesiferol-C structure.

Recently two groups of sesquiterpenes have been isolated which can be derived from farnesyl pyrophosphate without involving carbocyclic rings. Dendrolasin (164, R=CH<sub>3</sub>)<sup>106</sup>, torreyal (164, R=CHO) and torreyol (164, R=CH<sub>2</sub>OH) co-occur with the bisabolane-type sesquiterpenes, nuciferal (165, R=CHO) and nuciferol (165, R=CH<sub>2</sub>OH). Epomeamarone (166)<sup>107</sup> has been shown to incorporate both

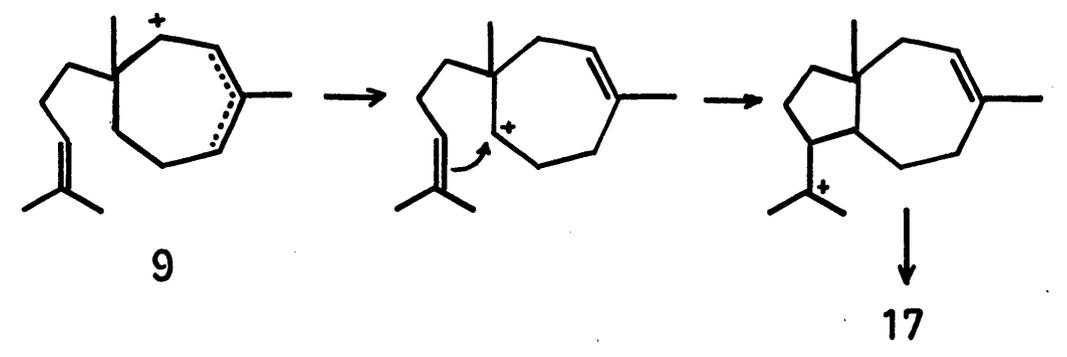
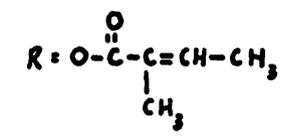
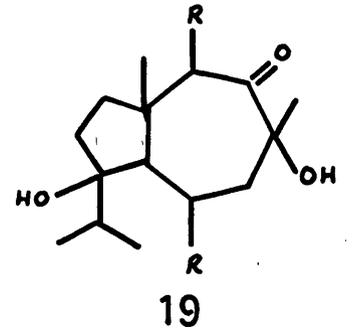
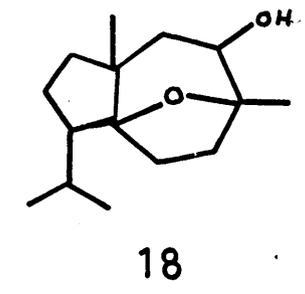
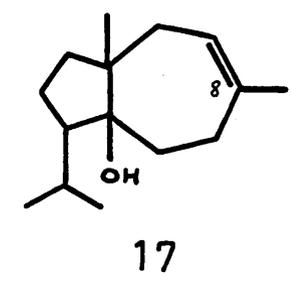
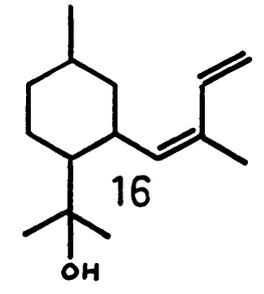
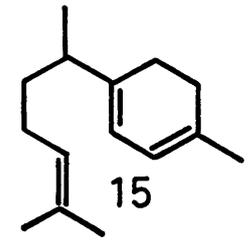
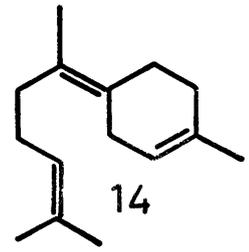
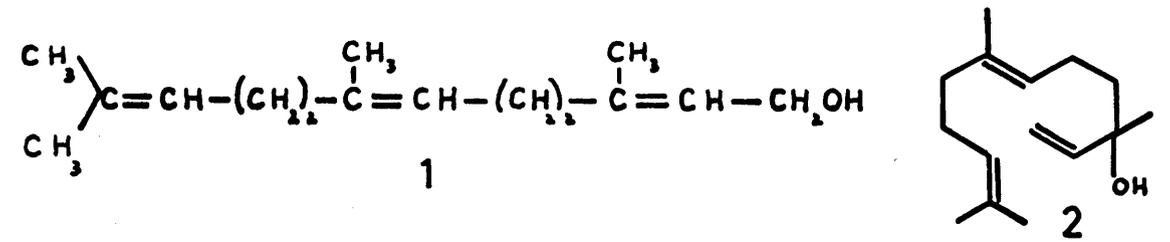
acetate (2-C<sup>14</sup>) and mevalonate (2-C<sup>14</sup>).

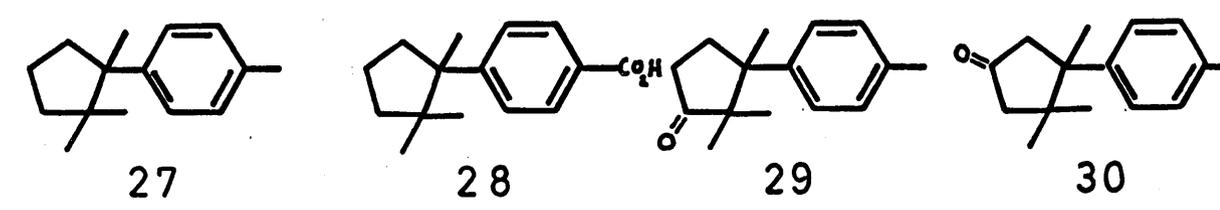
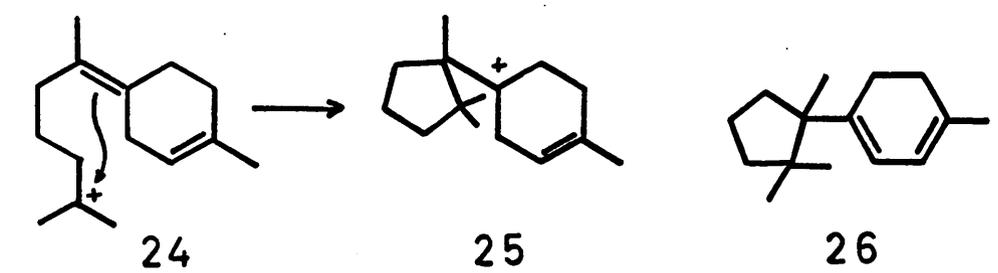
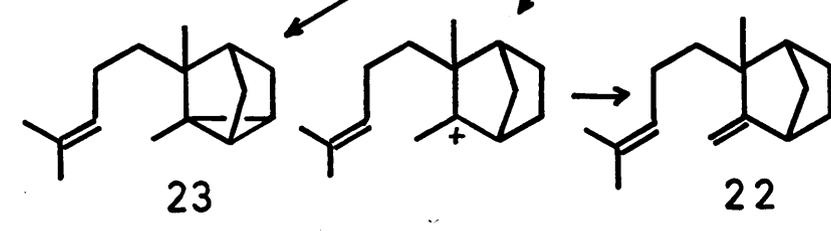
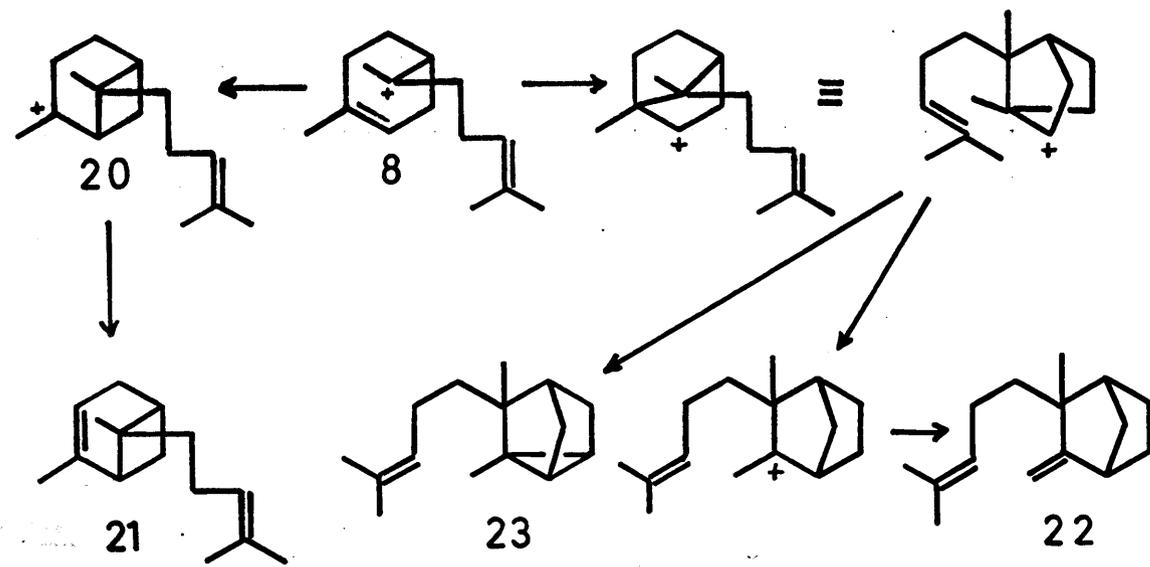
Finally three sesquiterpenes of mixed biogenetic origin are the drimanyl quinone, tauranin (167)<sup>108</sup>, grifolin (168)<sup>109</sup> and chanootin (169, R or R'=OH)<sup>110</sup>. Chanootin is related to nootkatin (170) and procerin (171). A possible biogenetic scheme for the formation of the latter sesquiterpenes may involve ring expansion of a suitably oxygenated monoterpene intermediate such as (172) to yield  $\beta$ -thujaplicin (173), followed by condensation with a mevalonate unit.

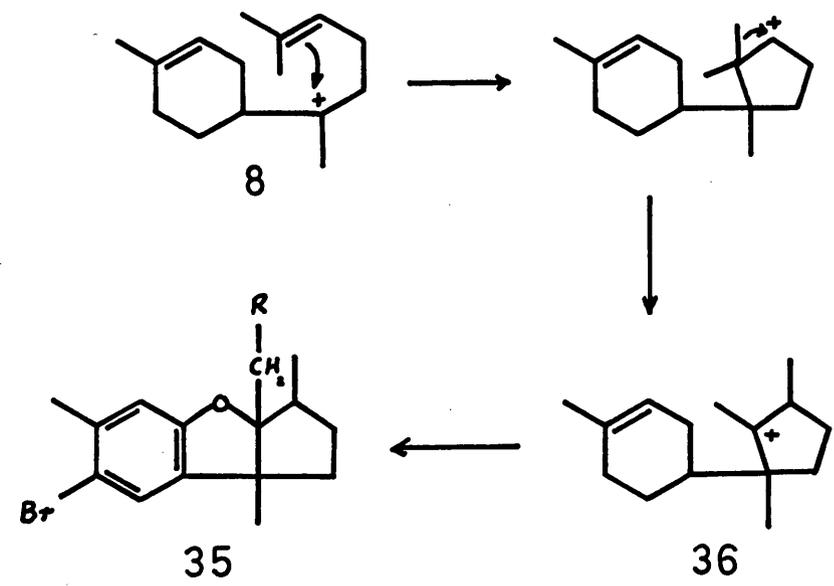
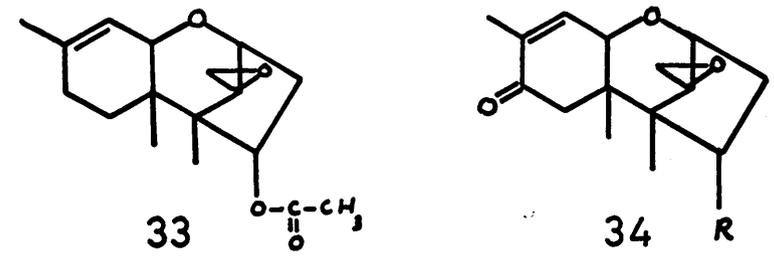
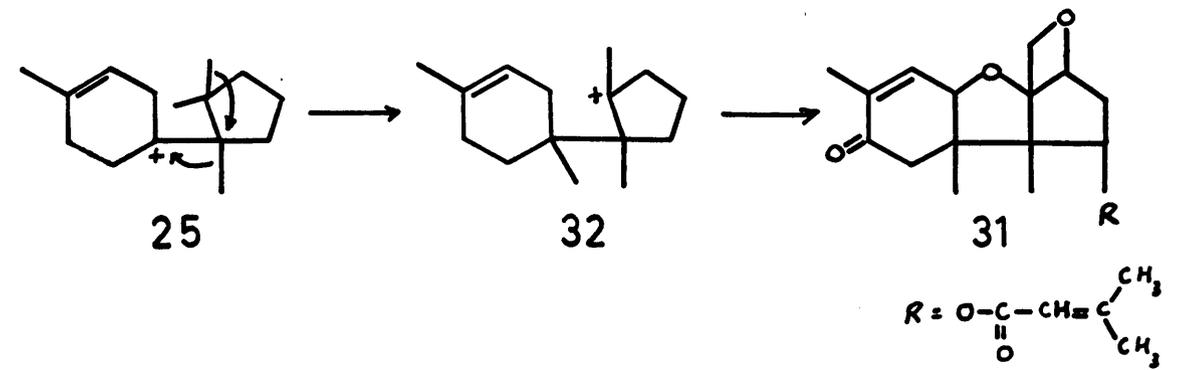
The overall picture which emerges from this review is reminiscent of the state of alkaloid biogenesis prior to the elegant radioactive tracer studies of the schools led by Professors Battersby, Leete, Barton and Mothes. Some of the biogenetic schemes e.g. those of trichothecin, helminthosporal, carotol and longifolene have been partially corroborated by C<sup>14</sup> tracer studies, but not very much of this kind of verification has yet appeared in print. One reason may be the difficulty of tracer feeding and harvesting in the higher plants.

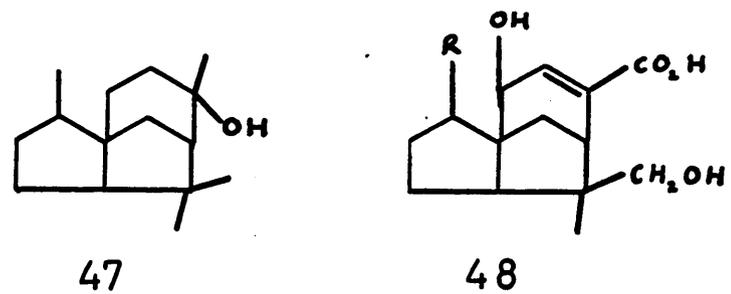
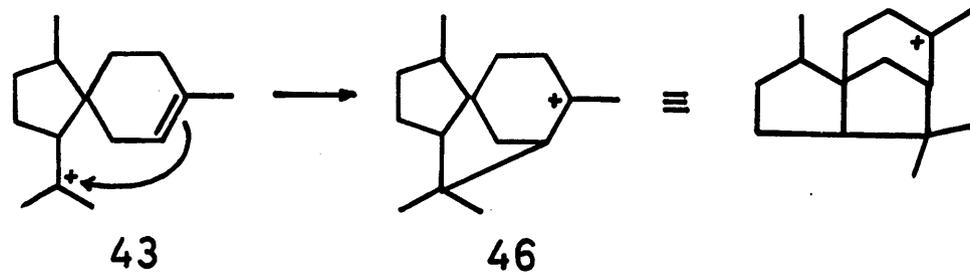
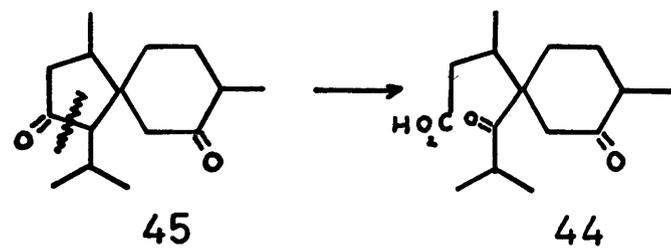
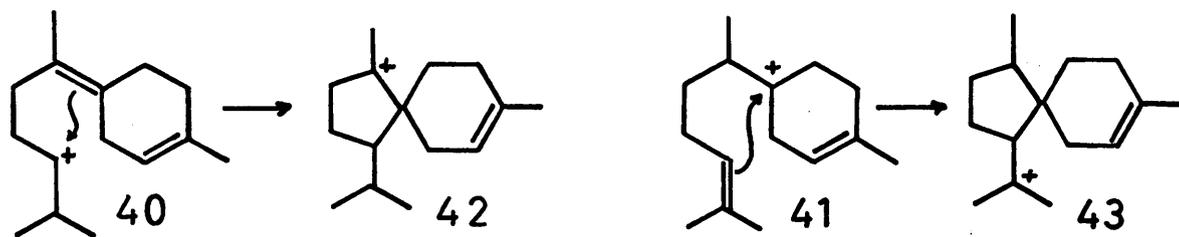
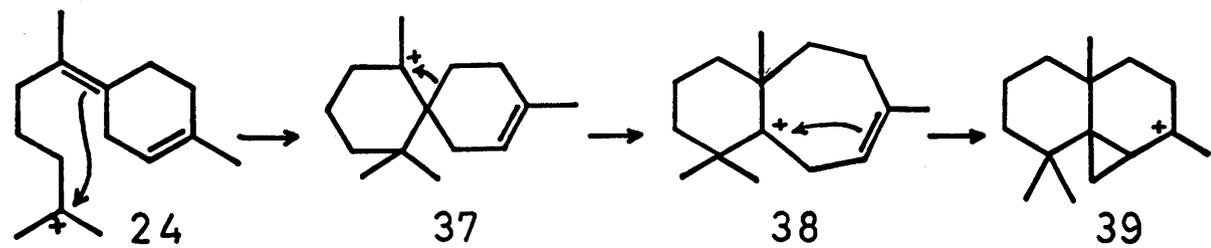
Alternative methods of verification of sesquiterpene biogenetic proposals lie in a chemotaxonomic classification of plants, as advocated by Erdtman<sup>112</sup>, and an extension of the in vitro reactions of geranyldiphenylphosphate

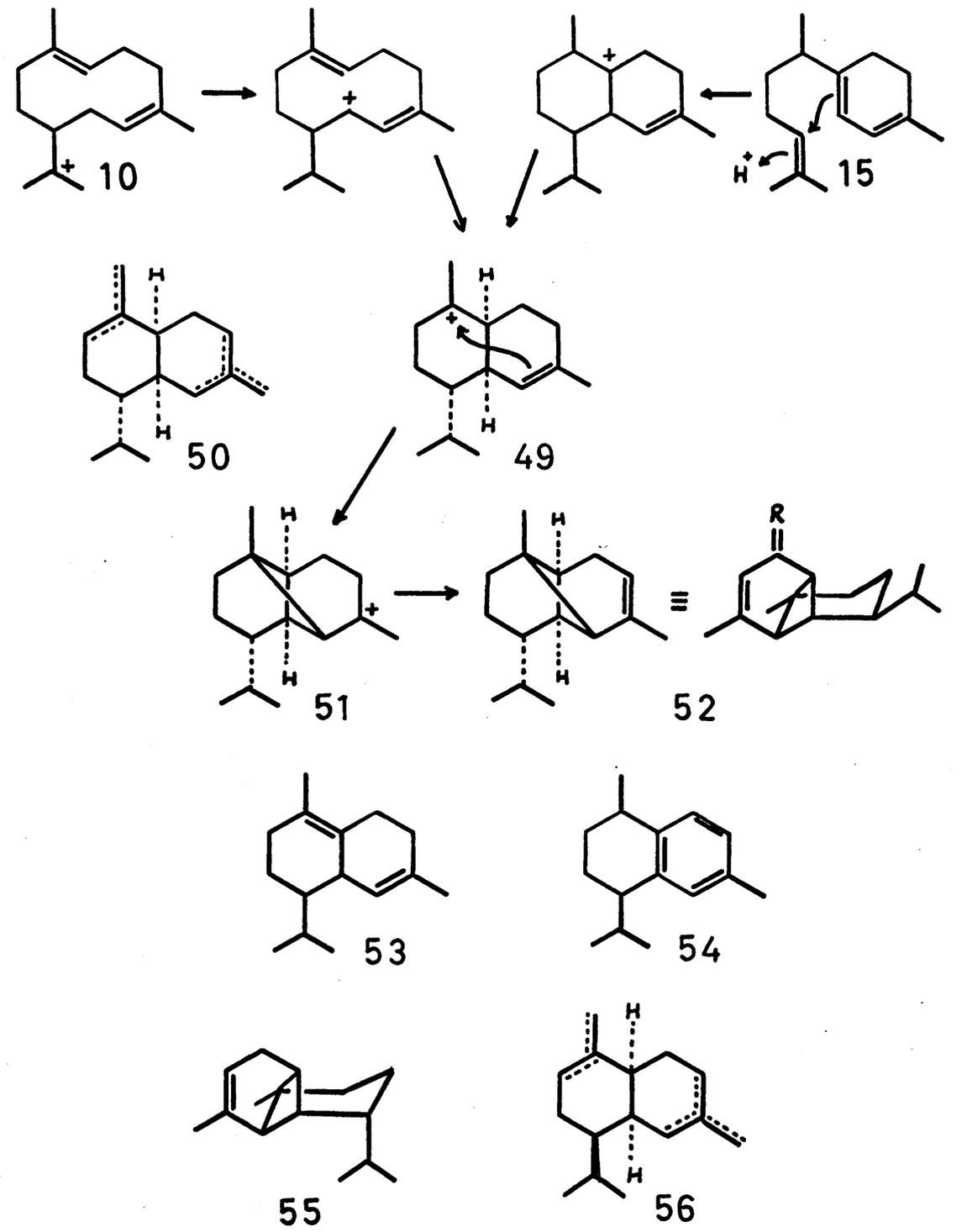
giving rise to known monoterpenes as determined by Wood and his co-workers<sup>113</sup>. However, the advent of more exacting analytical tools such as the combination of gas-liquid chromatography and mass spectrometry, and improved tissue culture techniques will undoubtedly lead to an even more detailed understanding of terpene biogenesis.

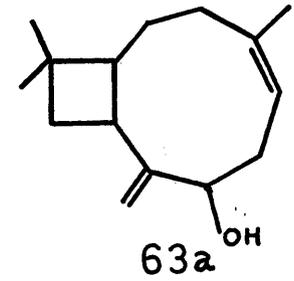
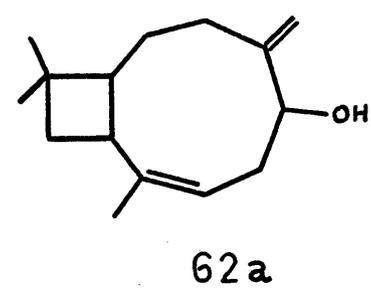
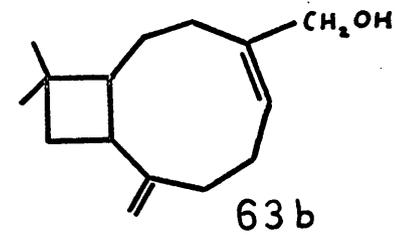
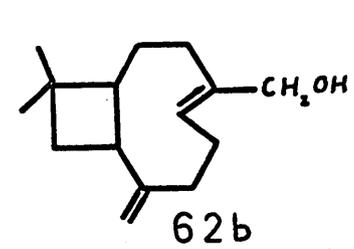
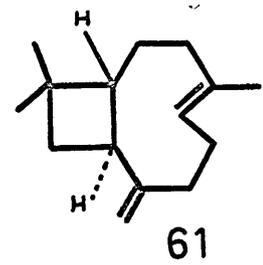
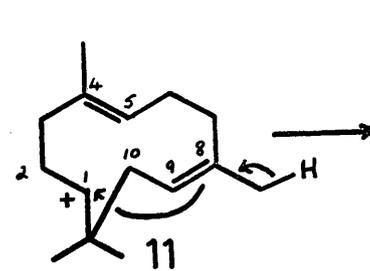
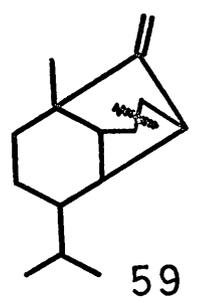
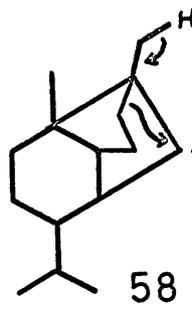
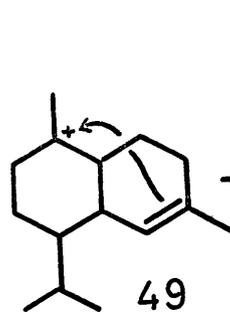
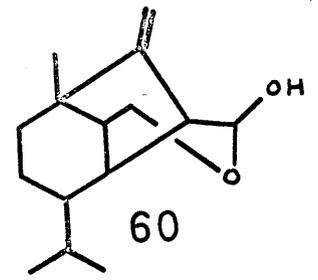
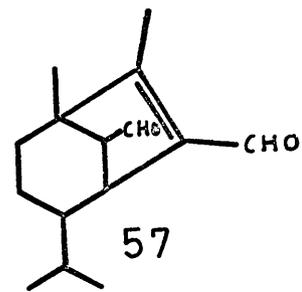


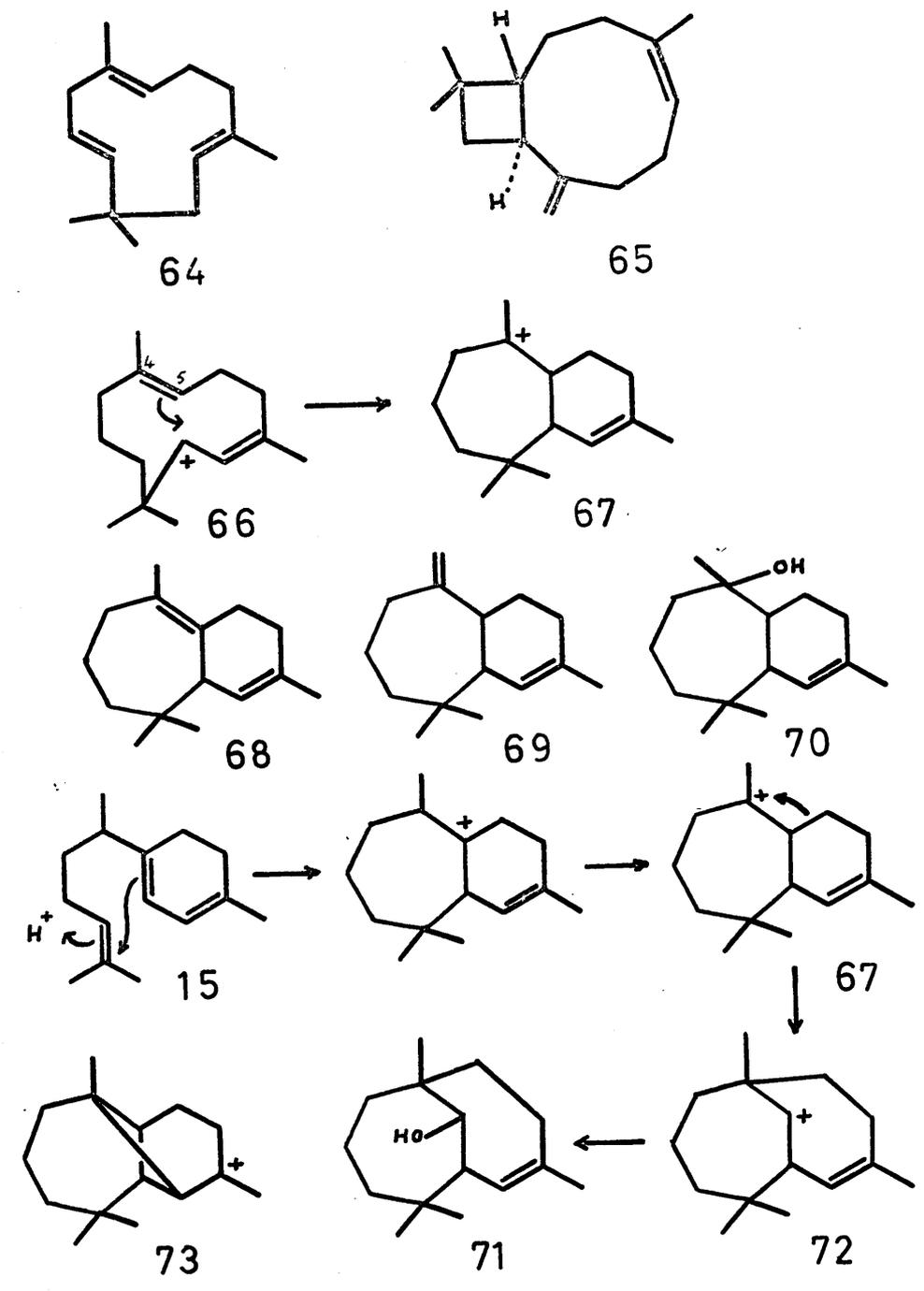


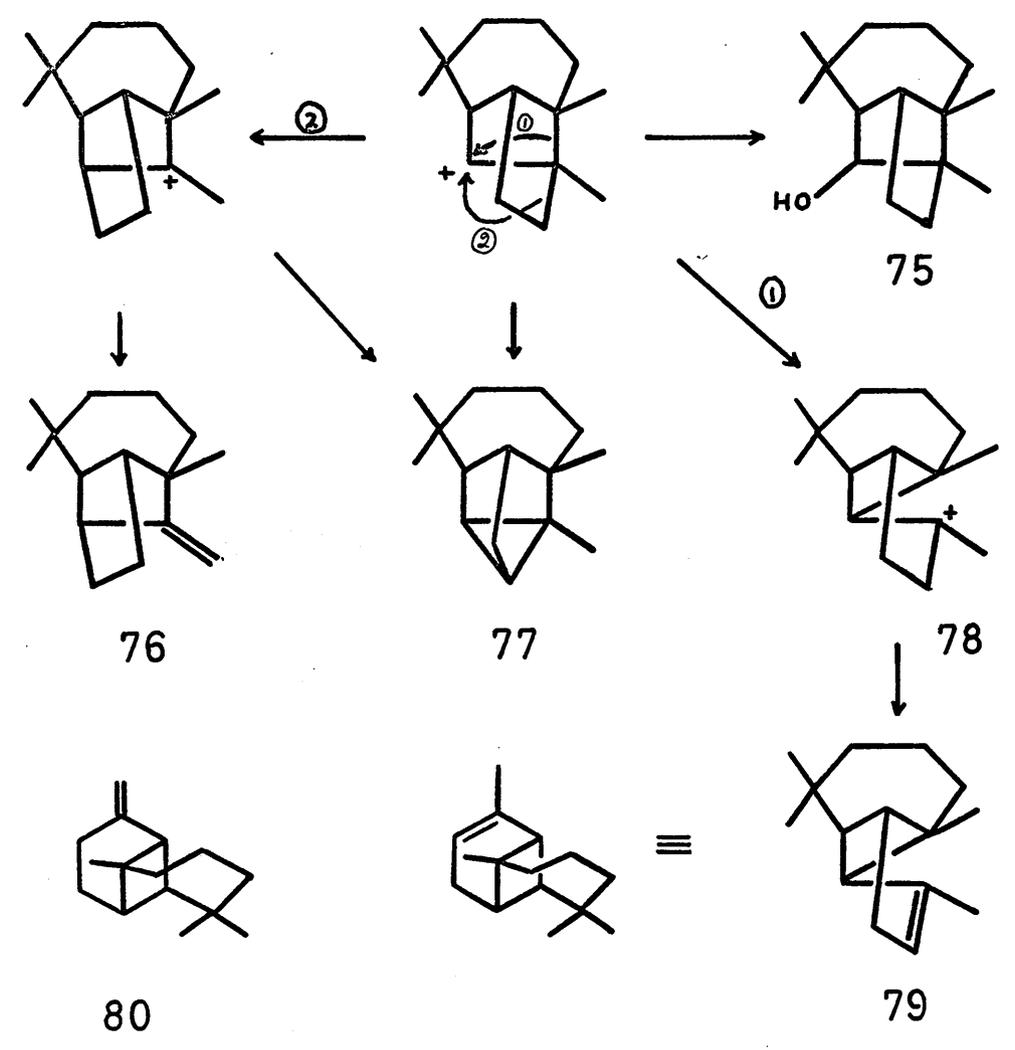
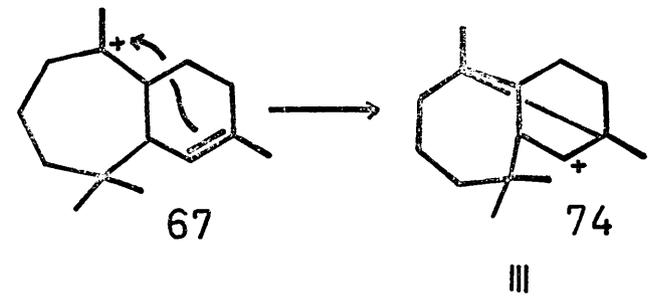


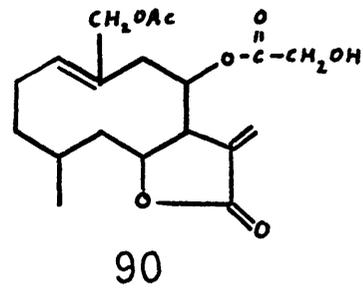
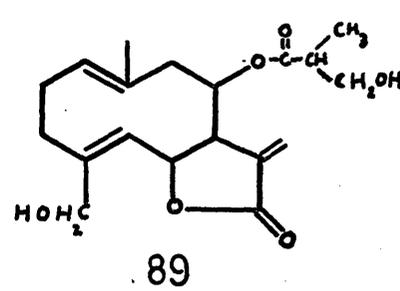
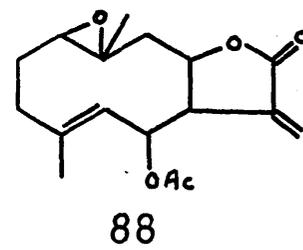
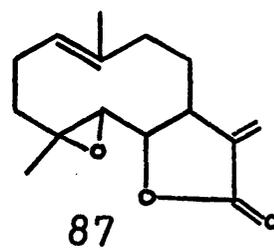
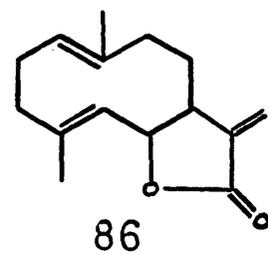
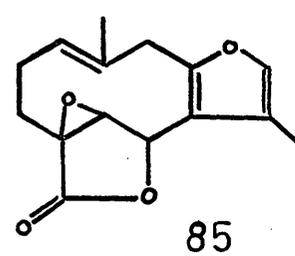
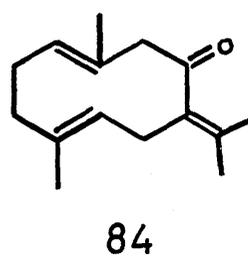
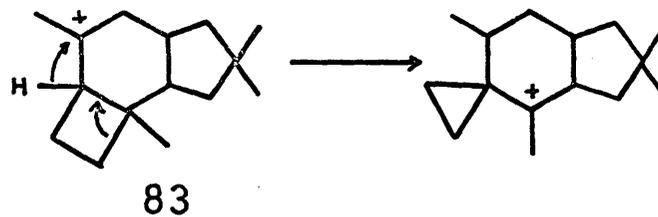
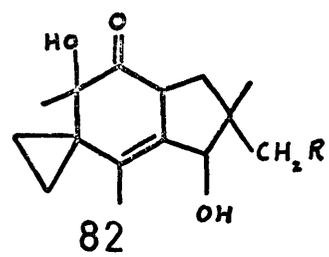
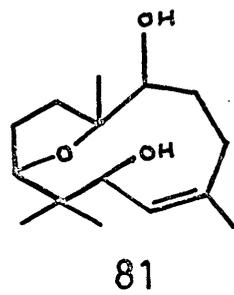


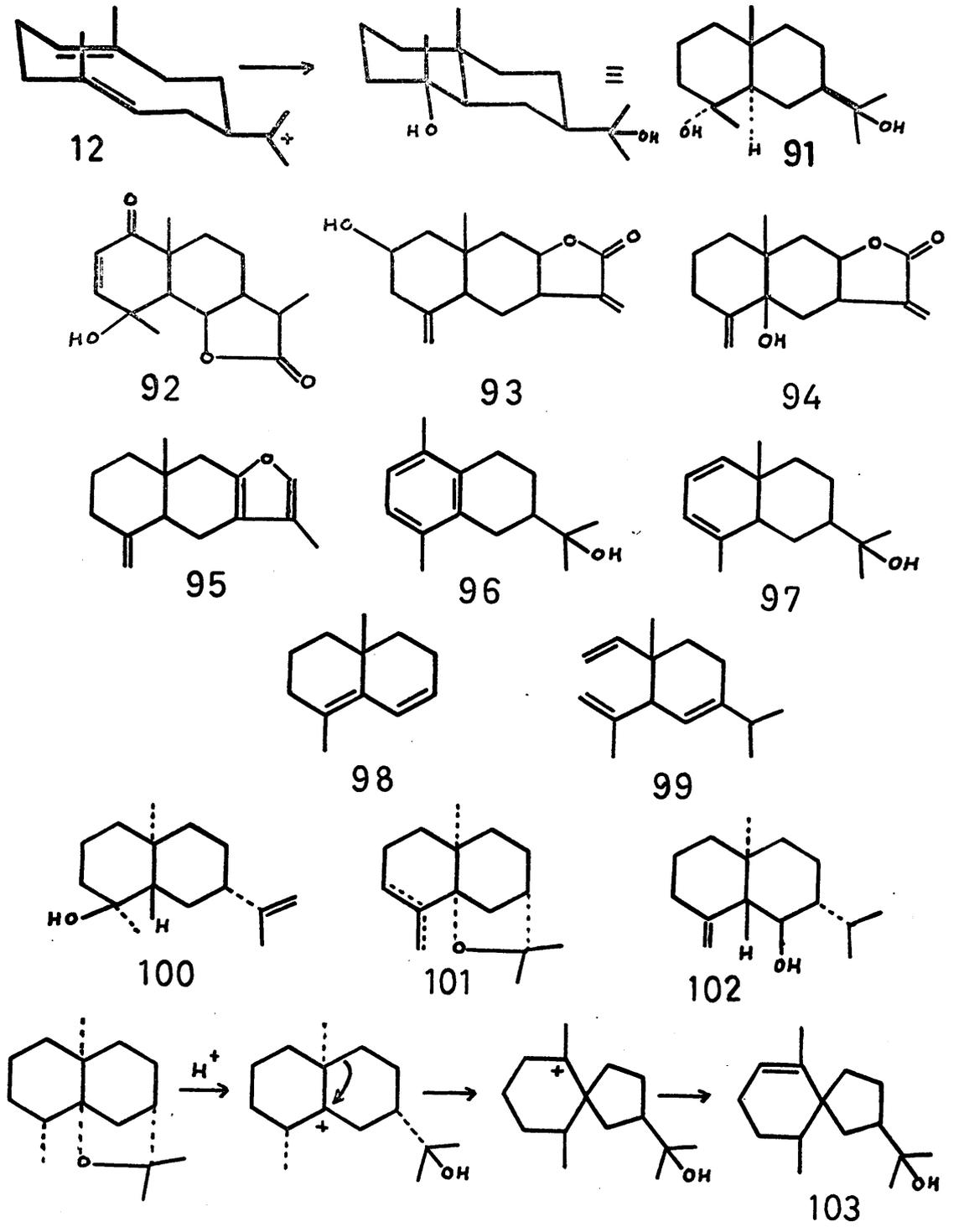


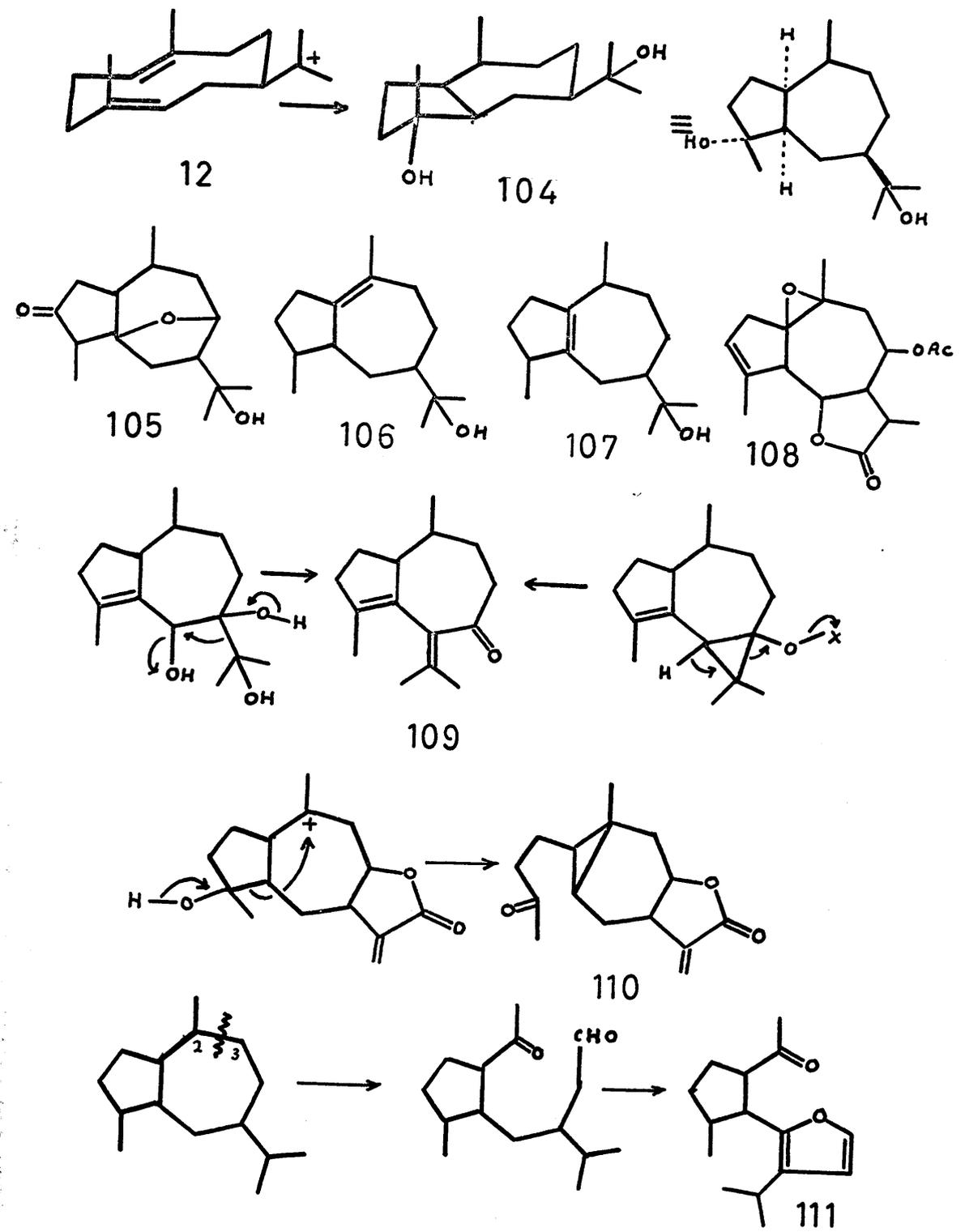


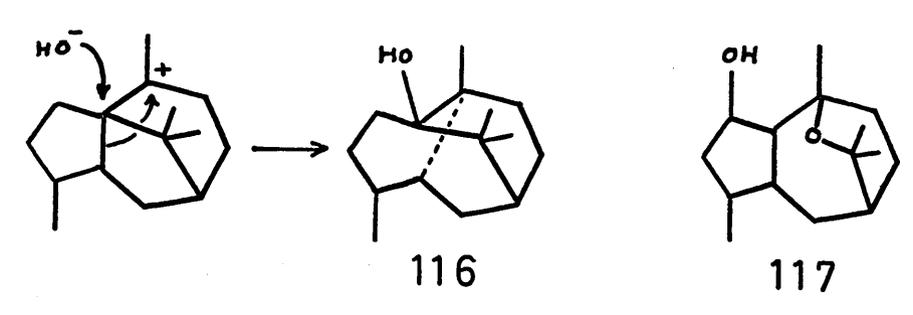
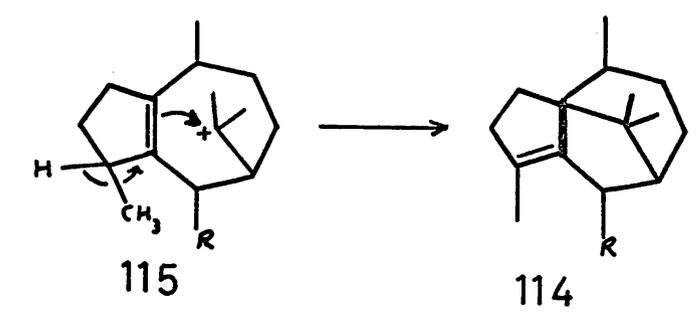
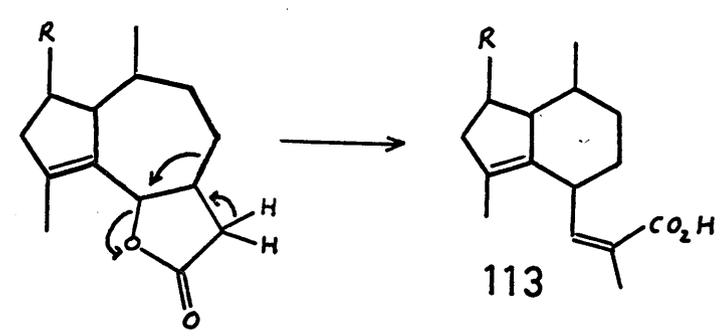
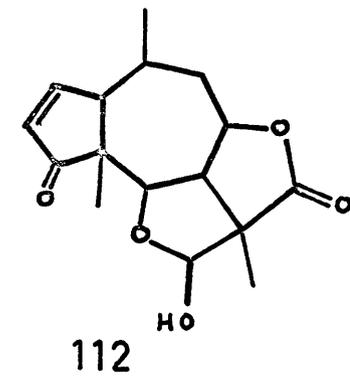


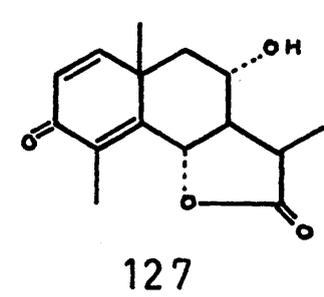
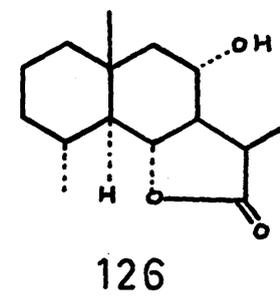
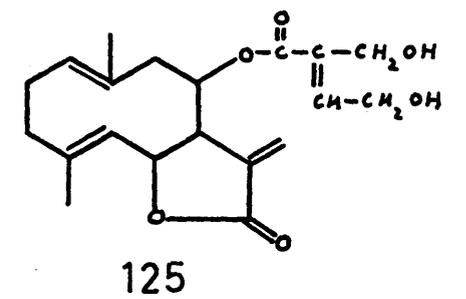
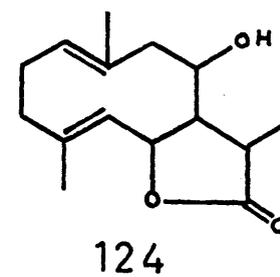
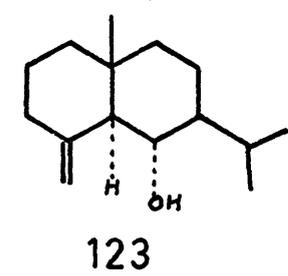
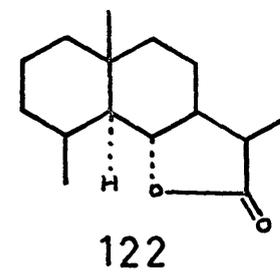
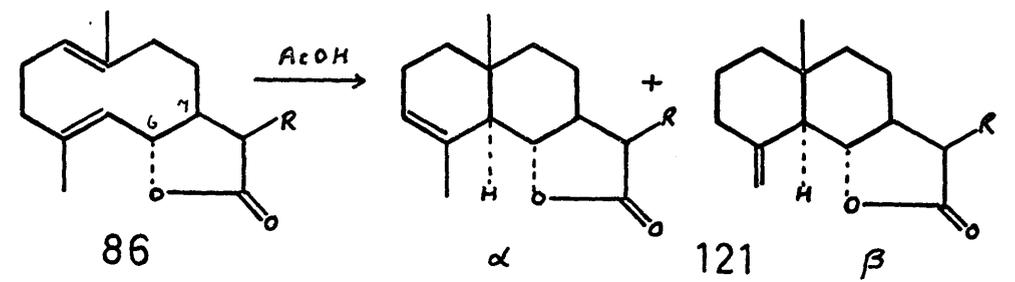
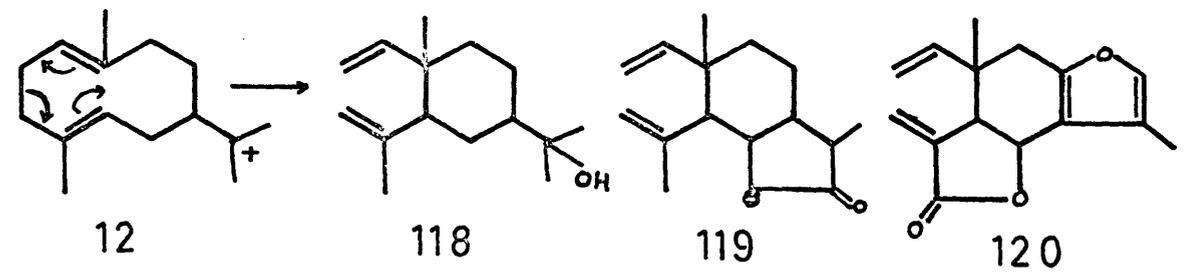


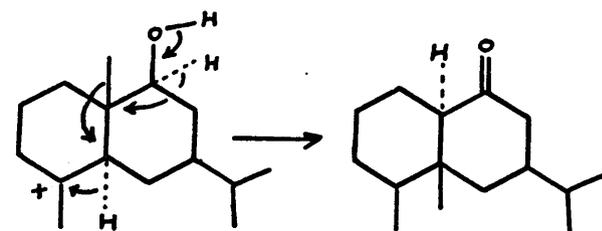
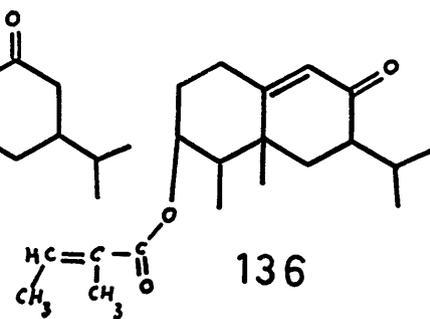
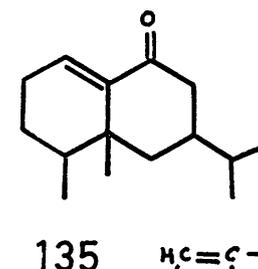
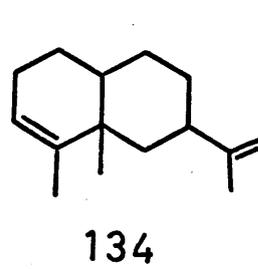
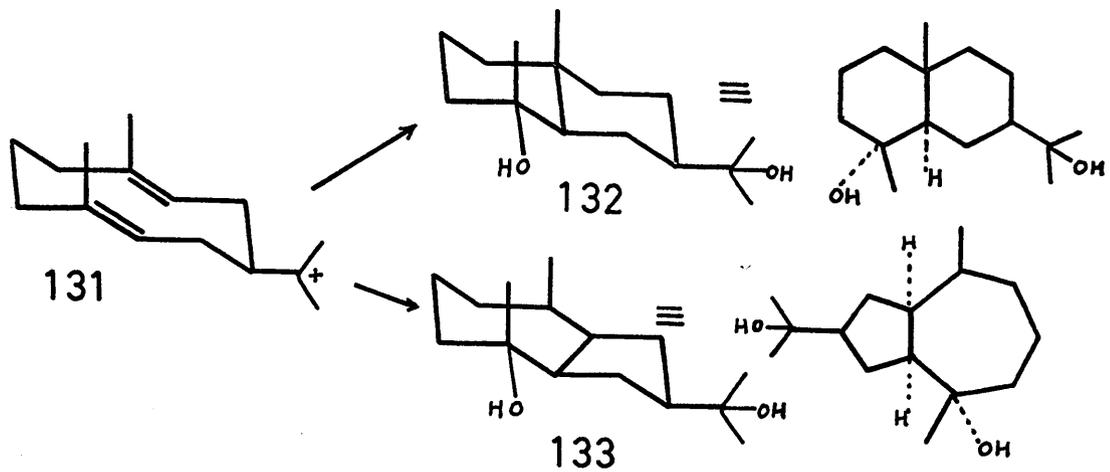
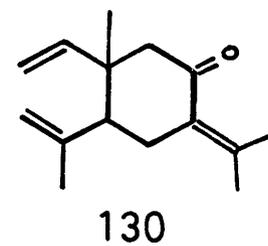
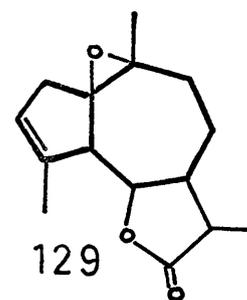
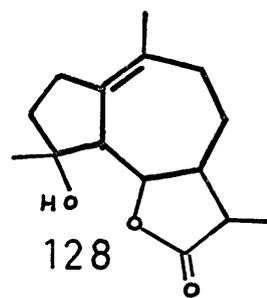


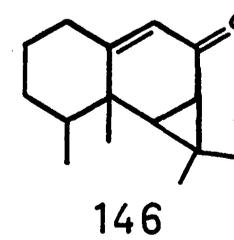
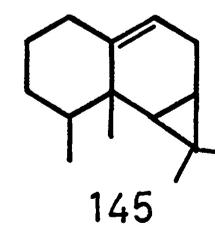
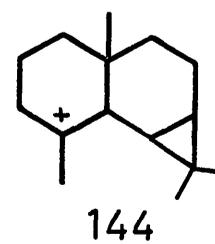
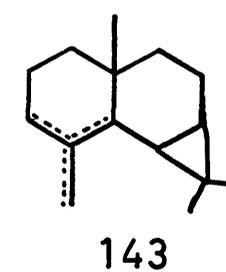
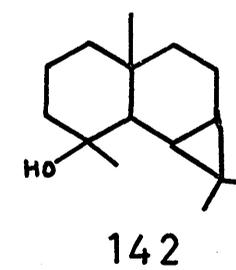
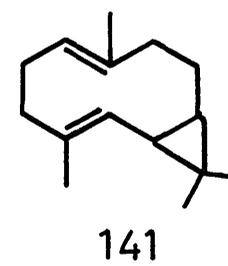
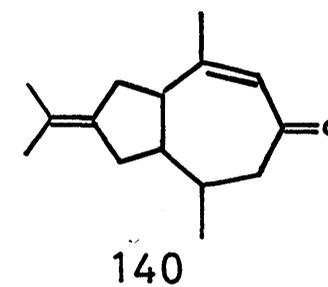
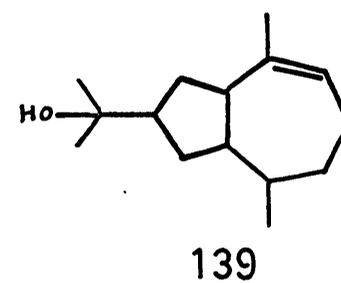
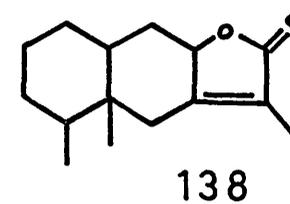
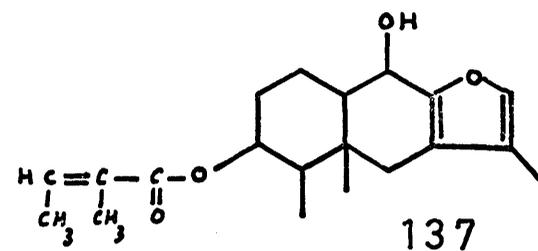


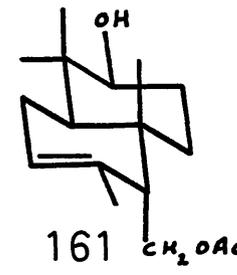
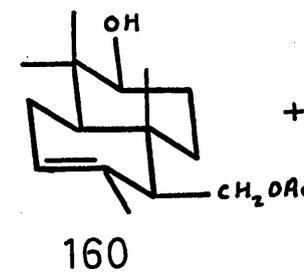
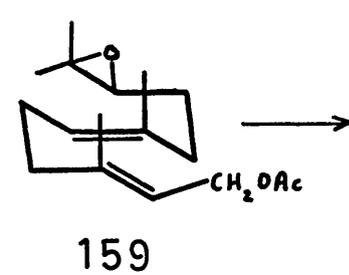
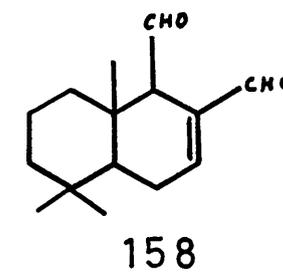
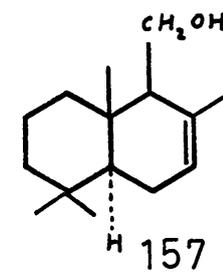
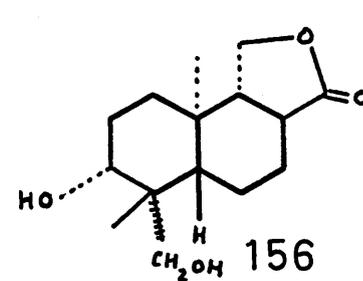
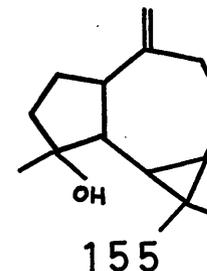
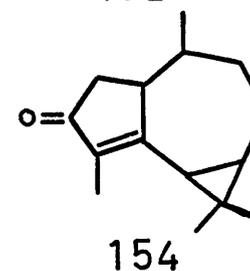
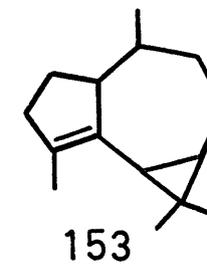
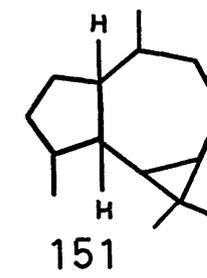
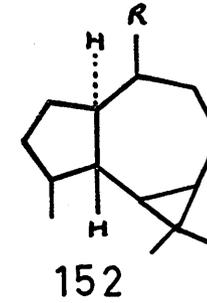
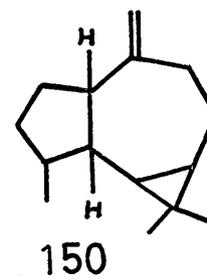
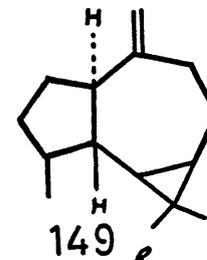
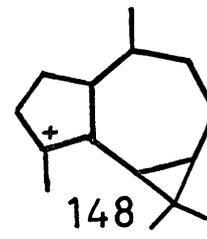
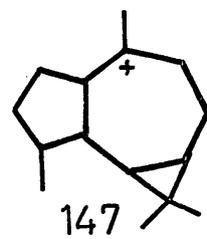


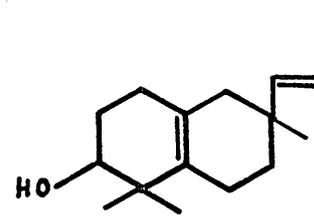




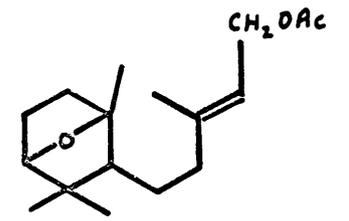




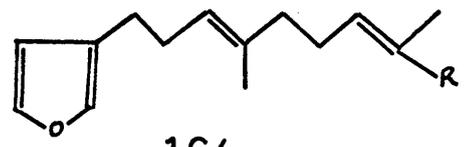




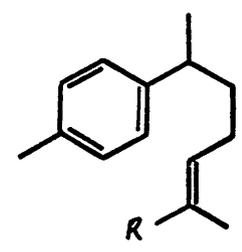
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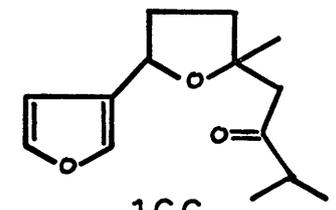
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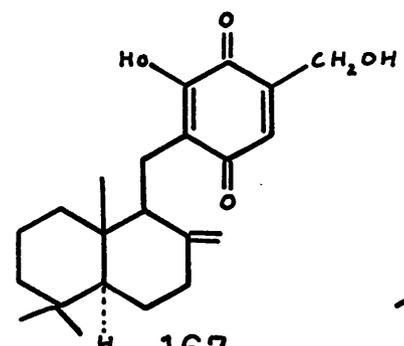
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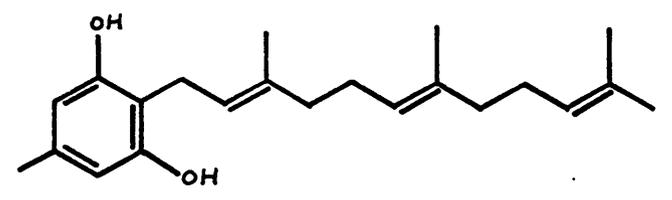
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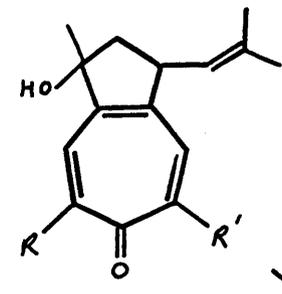
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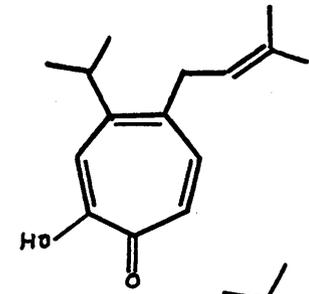
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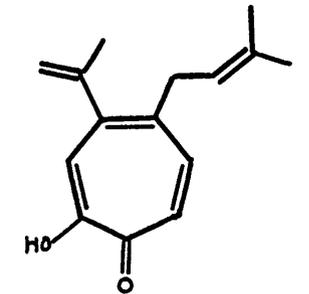
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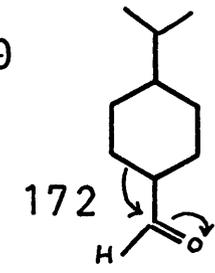
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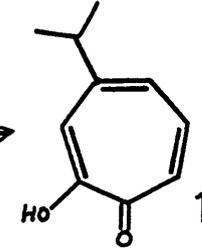
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PART I.

$\alpha$ -CARYOPHYLLENE ALCOHOL.

## HISTORICAL.

The emergence of the name  $\alpha$ -caryophyllene alcohol was due to the original work in 1922 by Asahina and Tsukamoto<sup>1</sup> on the sulphuric acid treatment of caryophyllene (1), the major sesquiterpene constituent of oil of cloves. From this reaction they isolated three rearrangement products, namely, the unsaturated hydrocarbon, clovene (2), and two isomeric alcohols, which they designated  $\alpha$ -caryophyllene alcohol and  $\beta$ -caryophyllene alcohol (3), melting points  $117^{\circ}$  and  $97^{\circ}$  respectively. This work was later substantiated by other workers<sup>2,3,4</sup>, who also found that  $\alpha$ -caryophyllene alcohol was the minor product (about 4%) of this rearrangement of caryophyllene.

Not until 1930, did Bell and Henderson<sup>3</sup> attempt to carry out a more systematic investigation of the chemistry of  $\alpha$ -caryophyllene alcohol. The two reported reactions which they carried out, and which later proved to be rather misleading in the elucidation of the gross structure, were the dehydration and oxidation of the alcohol. In the first instance, the dehydration of  $\alpha$ -caryophyllene alcohol with either phosphorus pentoxide or anhydrous oxalic acid yielded an unsaturated hydrocarbon, which, by virtue of its density, refractive index

and molecular refractivity, led these workers to the probable conclusion that it was clovene. More compelling evidence in favour of the structural relationship between  $\alpha$ -caryophyllene alcohol and clovene was apparently obtained by chromium trioxide oxidation of the alcohol to a dicarboxylic acid, which, on heating, yielded an anhydride, identical in melting point and mixed melting point with an authentic sample of clovenic anhydride (4), prepared by Ruzicka<sup>4</sup>.

With the structure of clovene firmly established<sup>5</sup>, the results of Bell and Henderson could be interpreted in terms of structures (5) or (6) for  $\alpha$ -caryophyllene alcohol. In 1954, however, in the course of work on caryophyllene, Barton and Nickon<sup>6</sup> prepared the two epimeric clovan-2-ols (5), melting points 96-97° and 97-98° respectively. Since neither of these compounds was identical with  $\alpha$ -caryophyllene alcohol, a re-examination of the structure was imperative.

In 1951, Dev<sup>7</sup> reported that the biogenetically related sesquiterpene, humulene (7), under identical conditions of rearrangement yielded a crystalline, tricyclic, fully saturated alcohol, m.p. 116°, apparently identical with  $\alpha$ -caryophyllene alcohol. However, this observation was evidently not followed up.

Nickon and his co-workers<sup>8</sup>, in 1961, revived interest

in the structure of  $\alpha$ -caryophyllene alcohol by initiating a more systematic examination. They showed firstly that the alcohol on oxidation yielded a ketone with no enolisable hydrogens and had a band in the infra-red at  $1742\text{ cm}^{-1}$ , compatible with a five membered cyclic ketone. This ketone, on reduction with sodium and isopropanol regenerated  $\alpha$ -caryophyllene alcohol, whereas catalytic reduction yielded about equal amounts of the  $\alpha$ -alcohol and a liquid isomeric alcohol, designated epi- $\alpha$ -caryophyllene alcohol. In an effort to create further functionality in an otherwise 'inert' molecule, they carried out the Barton photolysis reaction on both alcohols ; a reaction which had been utilised with success in the steroid field<sup>9</sup>. Thus, irradiation of the nitrite ester of the  $\alpha$ -alcohol and acid hydrolysis of the resultant hydroxy-oxime furnished a keto-alcohol, which by a Wolff-Kishner reduction gave the epi- $\alpha$ -alcohol. Similar treatment of the nitrite ester of the epi- $\alpha$ -alcohol gave the same keto-alcohol as was derived from the  $\alpha$ -alcohol. These transformations established that the C-O bond in the  $\alpha$ -alcohol nitrite had undergone a change of configuration to the epi-configuration.

What has been detailed up to now was the sum total of reported work on  $\alpha$ -caryophyllene alcohol when the problem was taken up in the laboratories at Glasgow. Since this

present work showed conclusively that  $\alpha$ -caryophyllene alcohol was, in fact, derived from humulene and not from caryophyllene as previously assumed, it is relevant to review the chemistry of humulene at this stage.

In 1895, Chapman<sup>10</sup> first isolated a new sesquiterpene in oil of hops and by the preparation of various derivatives he was able to distinguish this hydrocarbon, earlier called  $\alpha$ -caryophyllene, from caryophyllene. Since that time humulene and caryophyllene have been found to co-exist in many essential oils (e.g. Lindera strychnifolia (F) Will, Agonis abnormis White and Zingiber zerumbet Smith).

Sorn and his co-workers<sup>11</sup> in 1954 confirmed the previous proposals that humulene possessed an eleven membered ring skeleton with three double bonds, by an unambiguous synthesis of the hexahydro derivative. However, the relative positions of these olefinic linkages and, in particular, the question as to whether one of these was exocyclic was much debated<sup>12,13,14,15</sup>. This problem was resolved in 1959 by two groups of workers.

Dev<sup>16</sup> showed that neither humulene nor its oxygenated analogue, zerumbone, exhibited the characteristic resonance about  $5\tau$  for an exomethylene grouping in the N.M.R. spectrum. Further, a re-examination of the  $890\text{ cm}^{-1}$  band in the infra-red spectrum also revealed that its molecular

extinction coefficient was considerably lower ( $\epsilon=32$ ) in comparison with the normal value ( $\epsilon=120-160$ ) for compounds such as caryophyllene. He also made the valid point that formaldehyde or formic acid is known to be produced in the ozonolysis of certain compounds which have a symmetrical disubstituted double bond.

The utility of silver nitrate adducts in the separation of cyclo-octadienes<sup>17</sup> prompted Sutherland and his co-workers<sup>18,19</sup> to attempt a similar purification of humulene. Thus, they were able to prepare a fairly stable, crystalline bis silver nitrate adduct of humulene, which could be recrystallised from ethanol permitting exclusion of other adductable sesquiterpenes, such as caryophyllene. Regeneration of pure humulene,  $[\alpha]_D^{20} \pm 0^\circ$ , from this adduct could then be accomplished either by steam distillation or by dissolution in aqueous ammonia. Careful ozonolysis of this very pure humulene, which exhibited only a weak absorption in the infra-red at  $887 \text{ cm}^{-1}$ , yielded only 0.06 mole of formaldehyde, a result compatible with that of the ozonolysis of  $\alpha$ -pinene. A more rigorous proof of the location of the double bonds of humulene was also devised by these workers, in which the triozone of pure humulene was reduced with lithium aluminium hydride to yield exclusively 1,3-butandiol, 1,4-pentandiol and

2,2-dimethyl-1,4-butandiol. This then constituted an unambiguous proof of the gross structure of humulene, viz. (7).

In 1961, Sorm and his colleagues<sup>20</sup> demonstrated the existence of so-called  $\beta$ -humulene in Lindera strychnifolia (F) Will. Efficient distillation of 'pure' humulene showed that the lower boiling fractions contained up to 32% exomethylene double bond by ozonolysis and also had a medium intense band at  $888\text{ cm}^{-1}$ . This exomethylene double bond percentage could, unexpectedly, be enhanced up to 83% by repeated chromatography on alkaline alumina (Grade I), whereupon the band at  $888\text{ cm}^{-1}$  increased at the expense of the band at  $823\text{ cm}^{-1}$  due to one of the trisubstituted double bonds (the band at  $845\text{ cm}^{-1}$ , presumably due to the other trisubstituted double bond, remained unchanged). Although Sorm proposed the structure of  $\beta$ -humulene as (8), he gave no proof of this. Consideration, however, of the known structure of the bis silver nitrate adduct of humulene from an X-ray analysis (vide infra) and cognisance of the fact that  $\beta$ -humulene does not form a silver nitrate adduct, tends to confirm this structure.

The outstanding unsolved problem in  $\alpha$ -humulene (7) was the relative configurations about the three double bonds. The disubstituted double bond was known to be trans due to

the presence of an intense absorption at  $965\text{ cm}^{-1}$  in the infra-red spectrum. From a consideration of the competing steric and electronic factors in the cyclisations of cis- and trans-farnesyl pyrophosphate, Hendrickson<sup>21</sup> predicted that humulene would have the trans-trans-cis stereochemistry (See Introduction). Sutherland<sup>19</sup>, on the other hand, favoured the all trans stereochemistry on the grounds of fewer non-bonded interactions. Finally, in his paper, Dev<sup>16</sup> wrote humulene as the trans-cis-trans isomer, for no apparent reason. The fact that  $\alpha$ -humulene forms a crystalline silver ('heavy atom') nitrate adduct seemed to the author to provide a suitable means of resolving this problem. This was suggested to Professor G. Sim at Glasgow, whereupon an X-ray analysis<sup>22a,22b</sup> of this adduct showed unequivocally that the three double bonds in  $\alpha$ -humulene are, in fact, all trans (9). A mass spectrometric investigation of humulene was in agreement with this finding.

## DISCUSSION.

At the outset of the present investigation into the structure of  $\alpha$ -caryophyllene alcohol, we formed the opinion that this substance did not originate from caryophyllene as presumed by earlier workers but was, in fact, an acid-catalysed rearrangement product of humulene. This premise was based on three facts, viz., the known co-occurrence in Nature of caryophyllene with humulene, the invariably low yield of  $\alpha$ -caryophyllene alcohol obtained from the rearrangement of commercial caryophyllene and finally the report by Dev<sup>7</sup> that humulene, on acid-catalysed rearrangement yielded a crystalline compound apparently identical with  $\alpha$ -caryophyllene alcohol.

In order to test this theory it was necessary to subject pure samples of caryophyllene and humulene to treatment with concentrated sulphuric acid in ether. Gas-liquid chromatographic analysis of commercial caryophyllene on various columns revealed the presence of about 10% humulene. A pure sample of caryophyllene was obtained by shaking a light petroleum solution of commercial caryophyllene with aqueous silver nitrate. The minute amount (0.5%) of humulene contamination in this sample can be explained by the presence of  $\beta$ -humulene<sup>20</sup>. The use of Sutherland's

technique<sup>18</sup> of purification of humulene from hop oil (60% humulene by gas-liquid chromatographic analysis) via the silver nitrate adduct afforded a 100% pure sample of  $\alpha$ -humulene as determined by gas-liquid chromatography. As it was also of interest to determine whether  $\beta$ -humulene would undergo the same rearrangement, a sample was prepared by shaking a light petroleum solution of pure  $\alpha$ -humulene in the presence of a large amount of alkaline alumina (Grade I) for seventeen hours. The infra-red spectrum of the product showed that a 60% conversion to  $\beta$ -humulene had been effected. Gas-liquid chromatographic analysis on a 20% tris-cyanoethoxypropane column clearly resolved the two isomers and thus confirmed the percentage composition.

Synchronous rearrangements in sulphuric acid were performed on the pure samples of both caryophyllene and humulene. Isolation of the rearrangement products from each showed that only  $\alpha$ - and  $\beta$ -humulene yielded  $\alpha$ -caryophyllene alcohol, whereas no trace was observed in the case of caryophyllene. Hence the structure of  $\alpha$ -caryophyllene alcohol had to be explained in terms of a molecular rearrangement of humulene ( $\alpha$  and  $\beta$ ).

Steam distillation from alkaline medium of the crude rearrangement products from  $\alpha$ - and  $\beta$ -humulene gave mostly hydrocarbon products, which were not further examined.

When the alkaline medium was made strongly acid with concentrated sulphuric acid and steam distillation resumed, the distillate contained mainly the desired  $\alpha$ -caryophyllene alcohol. In view of the reproducible, low yield (30-35%) of  $\alpha$ -caryophyllene alcohol by this isolation procedure, the residual aqueous solution<sup>u</sup> was extracted with ether. Thin-layer chromatographic examination of this extract revealed the presence of a very small amount of  $\alpha$ -caryophyllene alcohol, in addition to a fast-running spot, which represented the predominant constituent of the extract. Purification by column chromatography and subsequent crystallisation from light petroleum furnished this component, m.p. 137-138<sup>o</sup>. The infra-red spectrum of this compound was transparent in the hydroxyl and carbonyl regions, but showed very intense bands at 1192, 987, 939, 904 and 868 cm<sup>-1</sup>. The N.M.R. spectrum exhibited singlet resonances at  $\tau$ =5.64, 8.94, 9.01 and 9.11 in the ratio of 1:3:6:3 respectively. Chemically this compound was remarkably inert, being unaffected by boiling aqueous sodium hydroxide, aqueous sulphuric acid, catalytic hydrogenation and forcing lithium aluminium hydride reduction.

Nil desperandum, a sodium fusion test indicated the presence of sulphur in this compound. Armed with this

knowledge, the properties of this compound could be interpreted in terms of a dialkyl sulphate. This conclusion was borne out by a carbon, hydrogen, sulphur and oxygen analysis, which was entirely consistent with the molecular formula of  $C_{30}H_{50}O_4S$ . The molecular weight determined by osmometer was  $506 \pm 2$  (calculated 506). The spectral data could also be interpreted as that of a sulphate ester of  $\alpha$ -caryophyllene alcohol ; the absorption at  $1190 \text{ cm}^{-1}$  has been deemed characteristic of such compounds<sup>23</sup>, and bands around  $900 \text{ cm}^{-1}$  have also been reported for such chromophores<sup>24</sup>. Although no methine proton resonance of the type  $\underline{H}-R_2C-SO_4-CR_2-\underline{H}$  has been reported, the value of  $5.64\tau$  observed in this compound is not inconsistent with the values for dimethyl sulphate ( $6.06\tau$ )<sup>25</sup> and diethyl sulphate ( $5.66\tau$ ).

Refluxing the sulphate ester in aqueous formic acid for six hours yielded an oil whose infra-red spectrum showed bands at  $1735$  and  $1180 \text{ cm}^{-1}$ , indicative of a formate ester. Lithium aluminium hydride reduction of the formate gave a crystalline solid, which was identified as  $\alpha$ -caryophyllene alcohol by thin-layer chromatography, infra-red spectrum and melting point.

The identification of the dialkyl sulphate in the non-steam volatile residue seems to indicate that the  $\alpha$ -caryophyllene alcohol as obtained by sulphuric acid

treatment of humulene exists in the reaction mixture as a composite of two compounds. These are the half sulphate ester, which is readily hydrolysed in acidic medium but not in alkaline medium, and the dialkyl sulphate, which is hydrolysed under neither of these conditions.

Returning now to the main theme of this investigation, the crude  $\alpha$ -caryophyllene alcohol after extraction from the steam distillate was readily purified by chromatography and subsequent crystallisation from light petroleum gave colourless plates, m.p. 118.5-119°,  $[\alpha]_D^{20} \pm 0^\circ$ , analysing for  $C_{15}H_{26}O$ . The N.M.R. spectrum exhibited a singlet at 6.70  $\tau$  (1H) and four quaternary methyl groups at  $\tau = 8.95$  (3H), 9.10 (3H) and 9.15 (6H).

It was decided to approach the structural elucidation of  $\alpha$ -caryophyllene alcohol by a twin-pronged attack, namely, via (a) a 'classical' chemical degradation and concurrently (b) an X-ray crystallographic analysis of a suitable heavy atom derivative.

#### (a) 'Classical' Chemical Degradation.

The pure crystalline  $\alpha$ -caryophyllene alcohol was dehydrated by treatment with phosphorus pentoxide, as originally described by Bell and Henderson<sup>3</sup> (vide supra). The infra-red spectrum of the product bore no resemblance to that of authentic clovene, and gas-liquid chromatographic analysis

showed the presence of no less than four products, none of which was clovene.

At this time, work on the synthesis of (+)-clovene (2) was nearing completion in our laboratories, and it was found that (+)-clovenic anhydride (4) had a melting point of 76-78°, whereas the optically active anhydride had a melting point of 50-51°. It was, therefore, impossible to rationalise the results of Bell and Henderson<sup>3</sup>, since, optically inactive  $\alpha$ -caryophyllene alcohol, which, in turn, is derived from optically inactive humulene, should yield the racemic clovenic anhydride, if anything, and not the optically active anhydride as they reported.

$\alpha$ -Caryophyllene alcohol was oxidised with Jones reagent to the crystalline ketone, m.p. 40.5-41°, which showed a carbonyl absorption at 1740  $\text{cm}^{-1}$  in the infra-red spectrum, and four quaternary methyl groups at  $\tau = 8.97$  (3H), 9.02 (3H) and 9.13 (6H) in the N.M.R. spectrum. Since Nickon<sup>8</sup> reported that this compound had no enolisable hydrogens, which was confirmed by the unsplit  $\text{CH-OH}$  proton in the N.M.R. spectrum of  $\alpha$ -caryophyllene alcohol, the partial structure (10) could be written for the ketone and hence (11) for  $\alpha$ -caryophyllene alcohol itself.

In our eyes, the only plausible route of systematic degradation of this ketone lay in a Baeyer-Villiger

oxidation to the corresponding  $\delta$ -lactone (12), which, by reduction, would have given a bicyclic compound with two functional groups. The ketone, therefore, was treated with trifluoroacetic acid with disodium hydrogen phosphate present as a buffer<sup>26</sup>. The major product (93%) was the expected  $\delta$ -lactone, carbonyl absorption at  $1740\text{ cm}^{-1}$ , which after purification was obtained as colourless needles, m.p.  $102.5\text{-}103^{\circ}$ . The N.M.R. spectrum of this lactone showed four quaternary methyl groups at  $\tau = 8.77$  (3H),  $8.92$  (3H),  $8.99$  (3H) and  $9.02$  (3H).

Thin-layer chromatographic examination of the crude Baeyer-Villiger product showed that, in addition to a large spot ( $R_f=0.22$ ) corresponding to the  $\delta$ -lactone, there were two other minor spots ( $R_f$ 's=0.33 and 0.40). Initial chromatographic separation from the  $\delta$ -lactone, and subsequent careful rechromatography, afforded the two pure minor components (7% total of the reaction product). The carbonyl absorptions near  $1780\text{ cm}^{-1}$  in the infra-red spectra of both these compounds indicated that they were  $\gamma$ -lactones. Since these compounds were only minor products of the Baeyer-Villiger reaction, an investigation of their structures was not carried out until after the structure of  $\alpha$ -caryophyllene alcohol had been elucidated. Therefore, they will be referred to later in this discussion.

Lithium aluminium hydride reduction of the  $\delta$ -lactone was expected to yield the corresponding primary-tertiary diol (13). Thus, the  $\delta$ -lactone was refluxed for five hours with excess lithium aluminium hydride in ether. Thin-layer chromatographic analysis of the reaction product, however, indicated two spots, one of which was only fractionally less polar than the starting  $\delta$ -lactone, while the other spot was of the anticipated polarity of the diol. Chromatographic separation of these two products was readily effected, the less polar compound being eluted with light petroleum-ether (9:1), and the more polar product with the same solvent system (7:3). The ratio of the two compounds was 2.3:1 in favour of the less polar compound.

The less polar compound, m.p.  $85-86.5^{\circ}$ , could be readily oxidised back to the  $\delta$ -lactone in quantitative yield, as could the diol. The elemental analysis of this compound indicated a molecular formula of  $C_{15}H_{26}O_2$ , which could be accommodated by its assignment to the corresponding hemi-acetal (14). The infra-red spectrum of this compound in dilute solution showed a symmetrical free hydroxyl band at  $3617\text{ cm}^{-1}$  and numerous intense bands in the  $1100-1000\text{ cm}^{-1}$  region. Further confirmation of this hemi-acetal structure was obtained by a consideration of the low-field singlet resonance at  $5.04\tau$  (1H) in the N.M.R. spectrum ; the four quaternary methyl groups

were at  $\tau = 8.95$  (6H), 9.07 (3H) and 9.13 (3H). A rationale for the intermediacy of this hemi-acetal in the hydride reduction of the  $\delta$ -lactone can be derived from an examination of the model of the expected diol, in which severe steric congestion implicit in its formation must be an energetically unfavourable barrier. This hemi-acetal was formed exclusively when the hydride reduction of the  $\delta$ -lactone was allowed to proceed for only two hours.

The spectral properties of the more polar compound, m.p. 114.5-115.5<sup>o</sup> were consistent with those anticipated of a primary-tertiary diol. The infra-red spectrum of this compound in a moderately concentrated solution exhibited a very broad, intense absorption around 3200 cm.<sup>-1</sup> with a shoulder at 3400 cm.<sup>-1</sup>; the free hydroxyl absorption was very weak near 3625 cm.<sup>-1</sup>. In a very dilute solution, the concentration-dependent band at 3200 cm.<sup>-1</sup> due to intermolecular hydrogen bonding was greatly decreased but still apparent, which could be explained by a relatively stable dimeric species (15), as has been suggested<sup>27</sup> in the case of labdane-8 $\alpha$ ,15-diol (16). At this low concentration, the band at 3437 cm.<sup>-1</sup>, due to intramolecular hydrogen bonding was fairly intense. The free hydroxyl region showed three bands at 3641, 3630 and 3618 cm.<sup>-1</sup>. This latter phenomenon is probably due to asymmetric O-H stretching modes of one

or both hydroxyls. The N.M.R. spectrum of this diol showed an AB quartet for the hydroxymethylene protons at 6.12 $\tau$  and 6.58 $\tau$  ( $J=11$  cps.). The downfield half of this AB quartet showed a slight broadening (relative to the high field half), which is probably due to long-range  $J_4$  coupling with the adjacent methyl group. A possible confirmation of this coupling can be observed in the slight broadening of one of the quaternary methyl resonances at 9.05 $\tau$ , the remaining three methyl resonances being at  $\tau= 8.88$  (3H), 8.92 (3H) and 9.19 (3H).

In an effort to obtain exclusively the desired diol (13), the  $\delta$ -lactone was refluxed in tetrahydrofuran with excess lithium aluminium hydride for forty-three hours. These reaction conditions gave predominantly the diol, with no trace of the hemi-acetal, but less polar impurities were observed by thin-layer chromatography of the crude product, probably arising from hydrogenolysis under these forcing conditions.

At this stage in the degradation sequence, X-ray crystallographic analysis once again asserted its power by solving the structure of  $\alpha$ -caryophyllene alcohol. The p-bromobenzenesulphonate of  $\alpha$ -caryophyllene alcohol was prepared and crystallisation from ether yielded small prisms suitable for X-ray diffraction experiments.

(b) X-Ray Analysis.

Rotation, oscillation, Weissenberg, and precession photographs were taken with copper K- $\alpha$  ( $\lambda=1.542 \text{ \AA}$ ) and molybdenum K- $\alpha$  ( $\lambda=0.7107 \text{ \AA}$ ) radiations. The cell dimensions were obtained from rotation and precession photographs, and the space group,  $P2_1/c$ , was determined uniquely from the systematic absences.

Intensity data were obtained from equatorial and equi-inclination upper layer photographs, taken from crystals rotated about the needle axis (b-crystal axis) ; the multiple film technique was employed<sup>28</sup>. The intensities, 2022 in all, were estimated visually by comparison with a calibrated strip, and were corrected for Lorentz, polarisation and rotation factors appropriate to the upper layers<sup>29</sup>. Since small crystals were used, no corrections for absorption were applied. The various layers were placed on the same scale by comparison of the observed and calculated structure amplitudes obtained from the three-dimensional Patterson function. Throughout the refinement, the scale was adjusted by correlation with the calculated structure amplitudes to ensure that  $\Sigma/F_o/ = \Sigma/F_c/$ .

Crystal Data.

Molecular Formula	$C_{21}H_{29}O_3SBr$
Molecular Weight	441.4
System	Monoclinic
a	$12.65 \pm 0.05 \text{ \AA}$
b	$16.43 \pm 0.04 \text{ \AA}$
c	$10.82 \pm 0.03 \text{ \AA}$
$\beta$	$109^\circ 13'$
Unit Cell Volume, V	$2124 \text{ \AA}^3$
No. of molecules/ unit cell, z	4
Density, observed	1.400 gm./c.c.
Density, calculated	1.380 gm./c.c.
Absent Spectra	0k0, when $k=2n+1$ h0l, when $l=2n+1$
Space Group	$P2_1/c$
No. of electrons/ unit cell, F(000)	900
Absorption Coefficient for X-rays ( $\lambda = 1.542 \text{ \AA}$ ), $\mu$	$3.92 \text{ cm.}^{-1}$

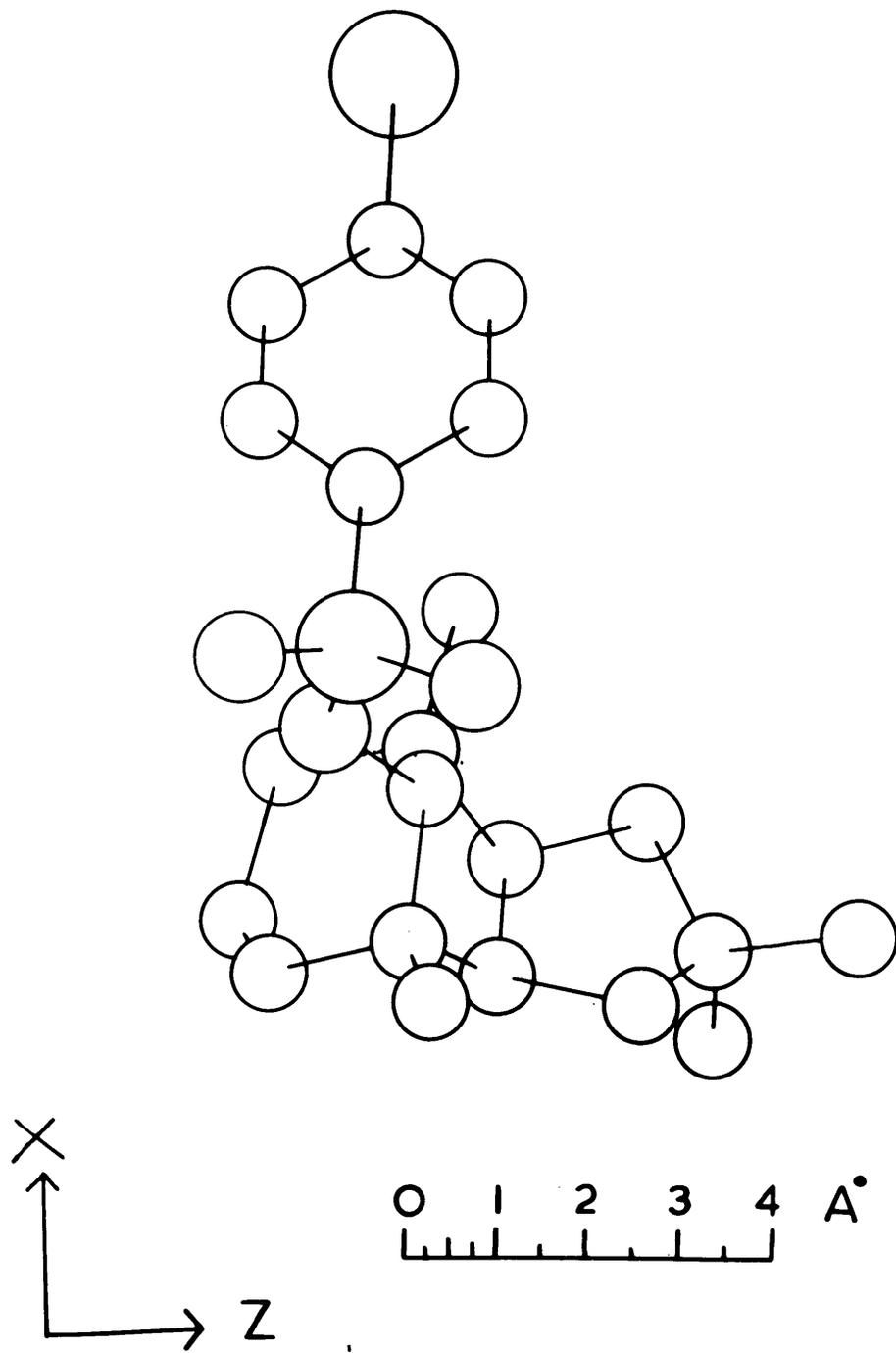


Fig. 1

### Solution of the Structure.

The atomic positions of the bromine and sulphur were obtained from a three-dimensional Patterson function. Cognisance of the para-relationship of these two heavy atoms, the coordinates of the two carbon atoms directly bonded to them were calculated utilising standard bond lengths and trigonometric formulae. Structure factors based on the coordinates of these four atoms gave an R-factor of 46%. Fourier calculations from these structure factors gave the entire structure of the molecule. Three more Fourier syntheses and five cycles of least squares refinement reduced the R-factor to 13.6%.

Thus, the structure and stereochemistry of  $\alpha$ -caryophyllene alcohol brosylate was unequivocally established, as depicted in Fig.(I), in which it can be seen that the cyclohexane ring is in the chair conformation with the brosylate function axial, that the two cyclopentane rings are cis fused, and that the one carbon bridge is trans with respect to the two ring junction methine protons.

The bond lengths and bond angles of the carbocyclic ring system, as obtained from computation are listed in Tables (I) and (II) respectively.

Therefore, the partial structures formulated as

TABLE (I).

Intramolecular Bonded Distances ( $\text{\AA}$ ).

$C_1 - C_{11}$	1.51	$C_7 - C_{13}$	1.53
$C_7 - C_{11}$	1.52	$C_2 - C_6$	1.60
$C_1 - C_{10}$	1.55	$C_5 - C_6$	1.54
$C_1 - C_2$	1.57	$C_2 - C_3$	1.57
$C_1 - C_{12}$	1.53	$C_3 - C_4$	1.52
$C_9 - C_{10}$	1.58	$C_4 - C_5$	1.51
$C_8 - C_9$	1.57	$C_4 - C_{15}$	1.51
$C_7 - C_8$	1.55	$C_4 - C_{14}$	1.59
$C_6 - C_7$	1.57	$C_{11} - O$	1.47

TABLE (II).

Valency Angles.

$C_1 C_7 C_{11}$	108.3°	$C_2 C_6 C_7$	106.1°
$C_{11} C_1 C_{10}$	109.3	$C_5 C_6 C_7$	116.1
$C_2 C_1 C_{11}$	99.1	$C_2 C_6 C_5$	104.6
$C_{11} C_1 C_{12}$	116.2	$C_1 C_2 C_6$	105.7
$C_2 C_1 C_{10}$	108.1	$C_1 C_2 C_3$	115.6
$C_{10} C_1 C_{12}$	108.5	$C_3 C_2 C_6$	104.2
$C_2 C_1 C_{12}$	115.2	$C_2 C_3 C_4$	103.2
$C_1 C_{10} C_9$	111.3	$C_3 C_4 C_5$	102.9
$C_8 C_9 C_{10}$	111.4	$C_3 C_4 C_{15}$	111.7
$C_7 C_8 C_9$	110.8	$C_3 C_4 C_{14}$	111.8
$C_8 C_7 C_{11}$	108.8	$C_5 C_4 C_{15}$	110.6
$C_7 C_6 C_{11}$	98.3	$C_5 C_4 C_{14}$	112.8
$C_{11} C_7 C_{13}$	117.7	$C_{14} C_4 C_{15}$	107.2
$C_6 C_7 C_8$	110.0	$C_4 C_5 C_6$	104.2
$C_8 C_7 C_{13}$	108.3	$C_1 C_{11} O$	108.7
$C_6 C_7 C_{13}$	113.3	$C_7 C_{11} O$	109.7

(10), (11), (12), (13) and (14) earlier in this discussion are fully described by structures (17), (18), (19), (20) and (21) respectively. The structure of the dialkyl sulphate is depicted as (22).

In the light of the X-ray analysis it was possible to interpret a feature of the N.M.R. spectra of all the compounds derived from  $\alpha$ -caryophyllene alcohol, which had hitherto been rather puzzling ; this feature was the anomalously low position of two protons in the 7.45-7.8 $\tau$  region. The protons in question are indubitably the two methine protons at the cis ring junction of the two five membered rings. Apart from the acknowledged downfield shift of methine protons in general, the additional shift can be seen from models to be attributable to the stereo-position of these protons with respect to an anisotropic function on the carbon bridge position. Thus, in the ketone (17) and the  $\delta$ -lactone (19), where these two protons lie in the deshielding cone of the carbonyl group, they resonate at 7.45 and 7.47 $\tau$  respectively, whereas in the alcohol itself at 7.77 $\tau$ . By virtue of the symmetry of  $\alpha$ -caryophyllene alcohol, these two protons are chemically and magnetically equivalent, and hence they will not exhibit mutual coupling, as witnessed by the singlet resonance at 6.94 $\tau$  in the triketone (28) (vide infra). The multiplicity

of their resonance, however, does not lend itself to a first-order analysis with respect to the vicinal methylene protons. They should, therefore, be considered as the  $A_2$  part of an  $A_2B_2C_2$  system, whose analysis can only be solved by a computer.

A comparison of the infra-red spectrum and melting point of the  $\gamma$ -lactone ( $R_f=0.33$ ), mentioned earlier as a minor product of the Baeyer-Villiger reaction of the ketone (17) showed that it was identical with that obtained in higher yield by Nickon when the ketone was treated with perbenzoic acid with a trace of sulphuric acid present as a catalyst ; the  $\delta$ -lactone was also obtained under these reaction conditions. This type of interconversion of  $\gamma$ - and  $\delta$ -lactones in the presence of acids has been previously reported<sup>30</sup>, and indeed Nickon<sup>31</sup> has found that the two lactones can be equilibrated with sulphuric acid. The logical structure of this  $\gamma$ -lactone is (23). The N.M.R. spectrum of this compound is consistent with this assignment, since there is no resonance for a proton on a carbon bearing the oxygen of the lactone function. Integration of the methyl region indicates four methyl groups, three of which, at  $\tau = 8.87, 8.92$  and  $9.00$  are quaternary ; the fourth methyl group (presumably the secondary one) is hidden under these three methyl groups. The resonance at

7.31 $\tau$ , which appears as a quartet, must be due to the methine proton at C<sub>6</sub> being coupled to the two protons on C<sub>5</sub> (i.e. X part of an ABX system). The most likely explanation why only a very small amount of this  $\gamma$ -lactone was observed in the present work must lie in the fact that the disodium hydrogen phosphate would neutralise the trifluoroacetic acid formed in the reaction.

The N.M.R. spectrum of the second  $\gamma$ -lactone ( $R_f=0.40$ ) is rather puzzling. There are four quaternary methyl groups at  $\tau= 8.40$  (3H), 8.87 (6H) and 8.91 (3H) ; the former resonance seems to indicate a vinylic methyl group, although there are no vinylic protons. There is also a one proton quartet at 6.95 $\tau$  and what appears to be one half of an AB quartet at 7.68 $\tau$ . Paucity of this compound has precluded a firther investigation of its structure.

About the time that the final refinement of the X-ray analysis was being completed, we were informed by Professor A. Nickon that his group at Baltimore had elucidated the structure of  $\alpha$ -caryophyllene alcohol by chemical means. Accordingly a simultaneous publication of our results was amicably agreed upon<sup>32,33</sup>.

The major problem in the degradation of  $\alpha$ -caryophyllene alcohol was the creation of further functionality in the molecule. Nickon<sup>32</sup> brilliantly surmounted this situation

by utilising the Barton photolysis reaction, which paved the way to an economical degradation sequence, thus establishing the structure and stereochemistry of  $\alpha$ -caryophyllene alcohol. A summary of this sequence is as follows.

The keto-alcohol (24, R=H), derived either from  $\alpha$ - (25) or epi- $\alpha$ -alcohol nitrite (26) by photolysis and subsequent hydrolysis, was oxidised to the diketone (27), which exhibited overlapping carbonyl bands at  $1745\text{ cm}^{-1}$ , showing that the new ketonic function was also in a five membered ring. By a consideration of the stability of this diketone to treatment with hot alkali and from the known structural requirements of the Barton reaction (vide infra), it was concluded that the two ketone functions bore a 1,4 relationship to each other. Repetition of this photolysis on the keto-nitrite (24, R=NO) yielded, after hydrolysis and oxidation, the triketone (28). That the newly introduced ketone functions were in a 1,3 relationship and also in the same ring, was demonstrated by alkaline cleavage of the triketone (28) to the keto-acid (29, R=H), whose corresponding methyl ester (29, R=CH<sub>3</sub>) contained three enolisable hydrogens. These facts, taken in conjunction with the equivalence of the bridgehead methyl groups in the N.M.R. spectra of various derivatives, uniquely defined the structure of  $\alpha$ -caryophyllene alcohol.

The cis fusion of the two five membered rings, as well as the trans relationship of the two ring junction protons with respect to the hydroxylated carbon bridge, was inferred from the steric requirements of the intramolecular photo-rearrangments, thus establishing the stereochemistry of  $\alpha$ -caryophyllene alcohol.

In the light of a recent report<sup>34</sup> on a series of steroid nitrite photolyses, the epimerisation induced in the photolysis of  $\alpha$ -caryophyllene alcohol nitrite (See Historical), can be rationalised and is, therefore, worthy of comment. Robinson and his co-workers studied the photolyses of 5 $\alpha$ -androstane-3 $\alpha$ ,17 $\beta$ -diol-3-acetate 17-nitrite (30) and testosterone 17-nitrite (31), in order to test the hypothesis of a preferred six membered transition state in nitrite photolyses, as depicted in (32). These two compounds offered the possibility of a five membered transition state. The sole products of photolysis of these compounds were the corresponding hydroxamic acids (33) and (34). To account for this observation, they proposed the mechanism outlined in Fig (II). Since this mechanism involved homolytic fission of the C<sub>13</sub>-C<sub>17</sub> bond, the capture of the NO radical by the tertiary radical was anticipated to result in loss of stereochemistry at C<sub>13</sub>. Although this phenomenon was not

observed experimentally in the two cases above, rigorous proof was attained in the photolyses of estradiol 3-methyl ether 17 $\beta$ -nitrite (35) and epi-estradiol 3-methyl ether 17 $\alpha$ -nitrite (36). In the case of these two compounds, it was conclusively shown that photolysis yielded a C<sub>13</sub> epimeric mixture of the corresponding hydroxamic acids (37,R=OH) and (38,R=OH), which, after separation, could be reduced to the known epimeric lactams (37,R=H) and (38,R=H), secured by Beckmann rearrangement of the oximes of 13 $\alpha$ - and 13 $\beta$ -estrone 3-methyl ether. Thus, compelling evidence for epimerisation at C<sub>13</sub> was obtained.

In the light of this elegant work, the epimerisation of  $\alpha$ -caryophyllene alcohol nitrite during photolysis can be explained in terms of the mechanism outlined in Fig.(III). The driving force for this epimerisation of the  $\alpha$ -nitrite can be rationalised in two ways. Since the alkoxy radical (39) derived from homolytic fission of the  $\alpha$ -nitrite is in an axial position, relief of non-bonded 1,3 interaction could be achieved by homolytic fission of the C<sub>1</sub>-C<sub>11</sub> bond to the open aldehyde form (40) and exclusive reclosure to the equatorial position (41). In this equatorial position, the alkoxy radical is suitably juxtaposed for hydrogen abstraction from C<sub>3</sub> (or C<sub>5</sub>) through the intermediacy of a six membered transition

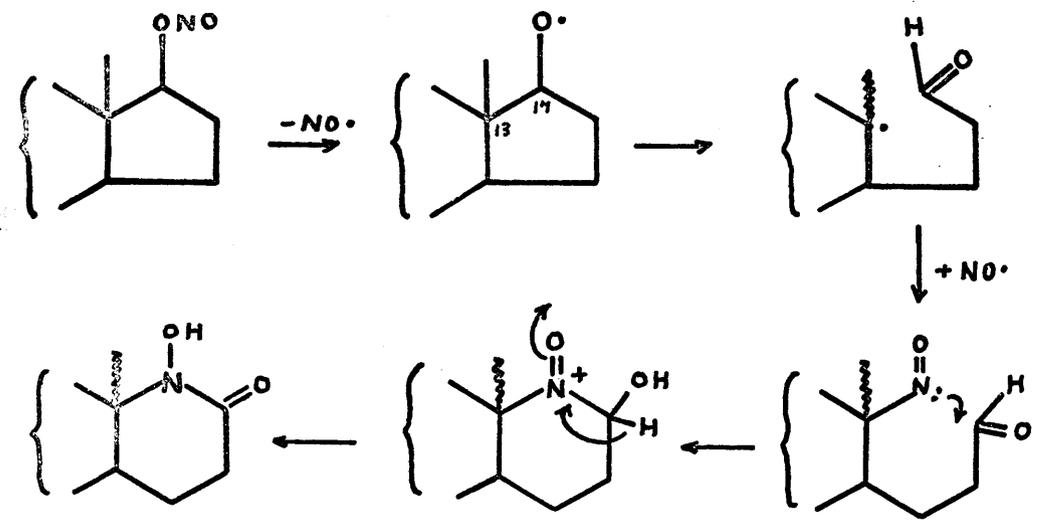


Fig. II

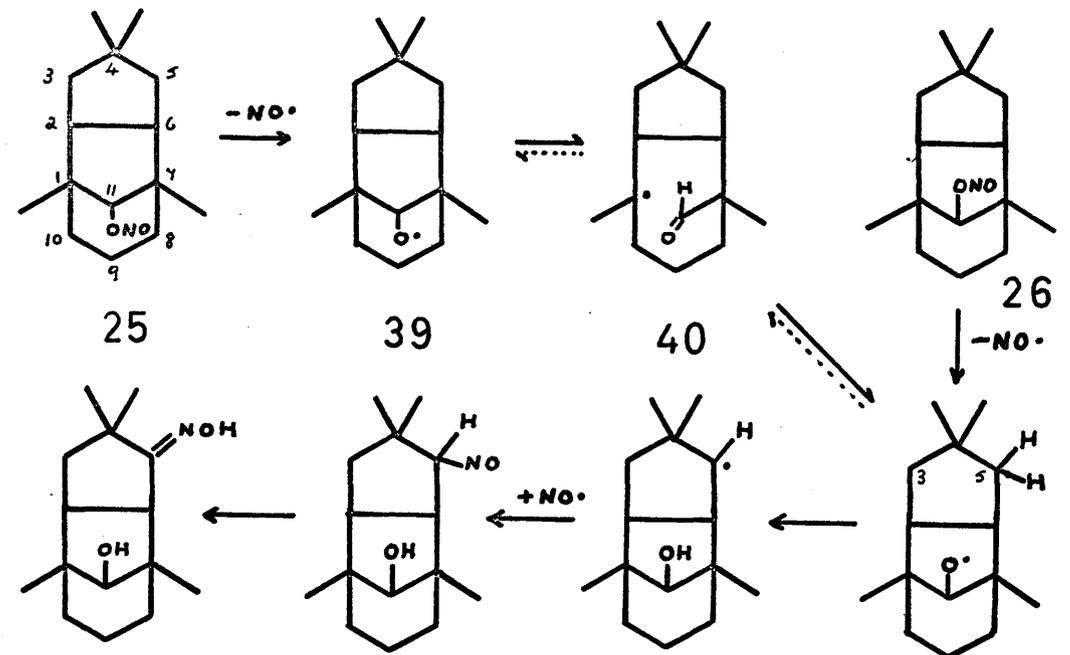


Fig. III

41

state. The alternative explanation is to invoke an equilibrium between the epimeric alkoxy radicals (39) and (41), in which only the equatorial one is favoured for further reaction, and in so doing, the equilibrium lies in favour of the equatorial alkoxy radical (41). This latter explanation appears to be the more acceptable.

#### Syntheses.

With the structure of  $\alpha$ -caryophyllene alcohol firmly established, the current interest in these laboratories in the synthesis of such bridged ring systems prompted a synthetic attack. The reported synthesis by Paul and Wendel<sup>35</sup> of the bicyclo(3:3:0)octane derivative (42) by treatment of 2-chloro-cyclopentanone with the anion of ethyl propionyl acetate, followed by decarboxylation, aldol cyclisation and subsequent dehydration and hydrogenation suggested the following route to  $\alpha$ -caryophyllene alcohol.

The analogous reaction sequence between the tosylate of 4,4-dimethylcyclopentan-2-ol-1-one and ethyl  $\alpha$ -propionyl propionate should lead to the bicyclo(3:3:0)octane system (43). This compound on monocyanoethylation followed by hydrolysis would afford the bicyclic keto-acid (44). Treatment of the corresponding enol-lactone (45) with

lithium aluminium tri-*t*-butoxy hydride<sup>36</sup> would then furnish the tricyclic ketol (46), possessing the correct axial configuration of the hydroxyl group for base elimination of the corresponding tosylate to give the keto-olefin (47). Catalytic hydrogenation followed by lithium aluminium hydride reduction would afford a mixture of  $\alpha$ - and *epi*- $\alpha$ -caryophyllene alcohol.

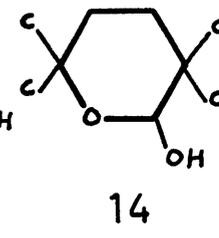
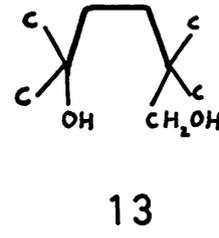
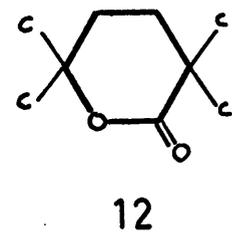
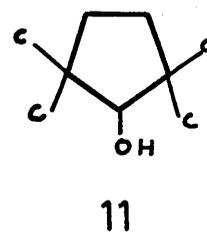
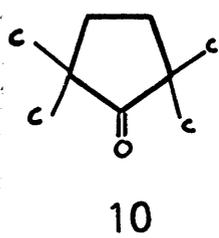
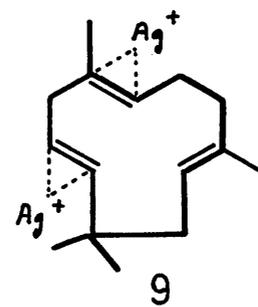
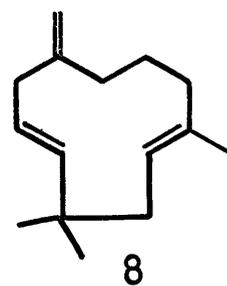
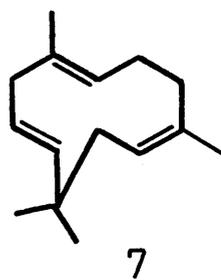
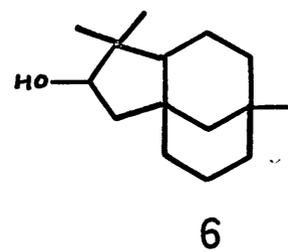
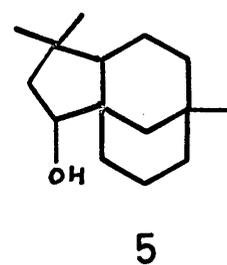
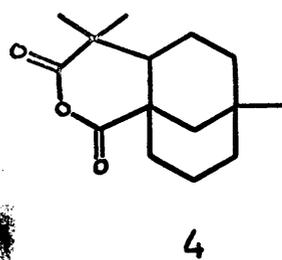
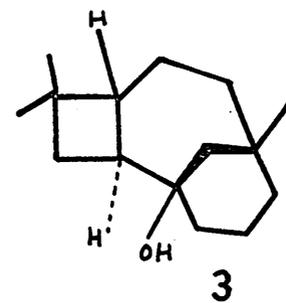
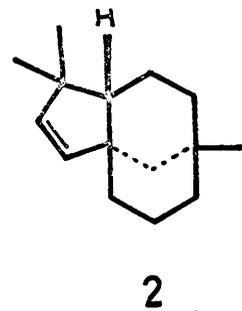
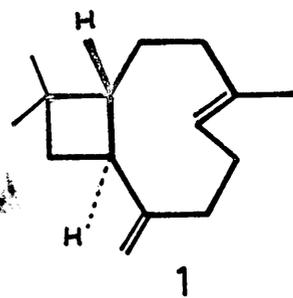
Accordingly, dimethyl  $\beta,\beta$ -dimethyl glutarate was treated under acyloin condensation conditions, as described by Kwart and Ford<sup>37</sup>, with sodium in liquid ammonia to give 4,4-dimethylcyclopentan-2-ol-1-one (48). Tosylation in the usual manner gave the crystalline keto-tosylate. Ethyl  $\alpha$ -propionyl propionate was prepared either by self-condensation of ethyl propionate<sup>38</sup> or by ethanolysis of methylketene dimer (49)<sup>39</sup>, prepared from propionyl chloride by dehydrochlorination with triethylamine. Preliminary experiments, using the conditions of the German workers, to bring about the condensation of these two moieties were unsuccessful. While alternative conditions were being examined for the preparation of (43) and (50) (i.e. analogous condensation with ethyl propionyl acetate), a completely unheralded total synthesis of  $\alpha$ -caryophyllene alcohol was reported from Professor E.J. Corey's laboratory at Harvard<sup>40</sup> -

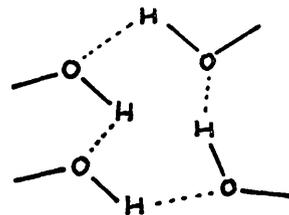
unheralded, since the structure of  $\alpha$ -caryophyllene alcohol was not in print at that time!

This brilliantly conceived three-step process involved photo-addition of 4,4-dimethylcyclopentene to 3-methylcyclohex-2-ene-1-one which gave predominantly the cis-anti-cis adduct (51). The tricyclic ketone was then treated with methylolithium to give the tertiary alcohol (52), which on treatment with 40% aqueous sulphuric acid, afforded synthetic  $\alpha$ -caryophyllene alcohol (18). The final step of this synthesis lends weight to the proposed mechanism of formation of  $\alpha$ -caryophyllene alcohol from humulene.

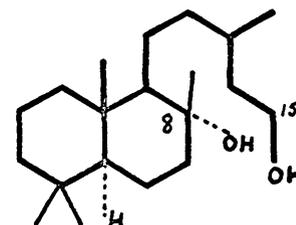
The first process envisaged is a prototropic shift to give the conjugated triene (53), which on protonation of the disubstituted double bond induces nucleophilic attack by the isolated trisubstituted double bond to give the carbonium ion (54), the timing of these two processes being unpredictable. Markownikoff cyclisation of this cation generates the tricyclic cation (55), which is the same cation as is generated from the alcohol (52), above. This cation now undergoes a Wagner-Meerwein shift to the tricyclic bridged cation (56), which is attacked by solvent. The driving force for this final rearrangement is probably due to the relief of strain inherent in the five-four-six fused ring system.

Although Nickon<sup>32</sup> did not use humulene as the precursor of  $\alpha$ -caryophyllene alcohol, he showed that  $\alpha$ -caryophyllene alcohol obtained by deuteriosulphuric acid treatment of commercial caryophyllene contained 2.73 deuterium atoms. Examination of the appropriate bands in the infra-red and N.M.R. spectra of deuterated  $\alpha$ -caryophyllene alcohol revealed that a  $\text{CH}_2\text{D}$  moiety was absent, which would only have been present if the alcohol had arisen from caryophyllene. On the basis of the proposed mechanism, the location of the deuterium atoms would be on carbons 5 and 8. It has been learned from Professor Nickon<sup>31</sup> that some molecules of  $\alpha$ -caryophyllene alcohol contain as much as 7 deuterium atoms! This high incorporation can presumably arise by deprotonation-deuteration processes on intermediate cations, which might infer that the process is not truly concerted.

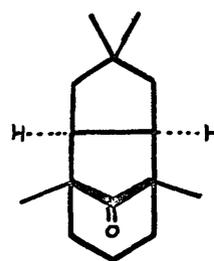




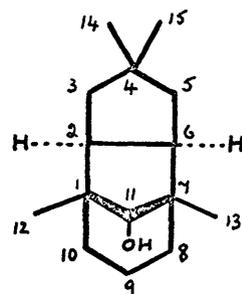
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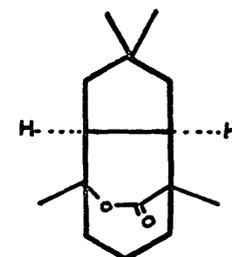
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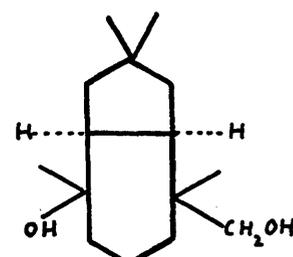
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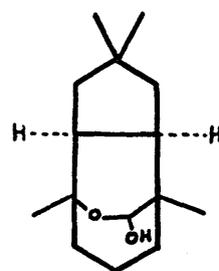
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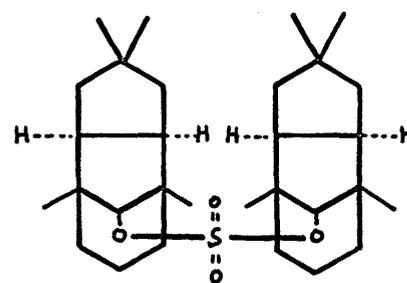
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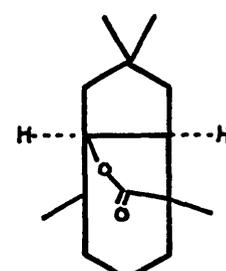
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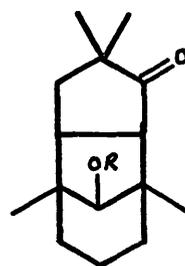
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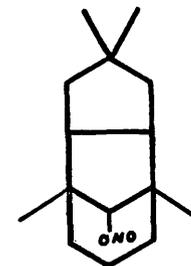
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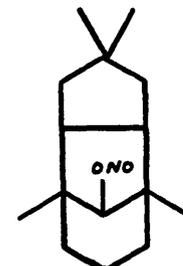
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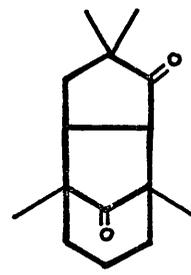
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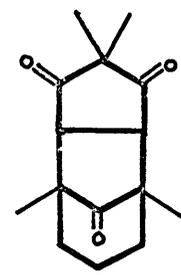
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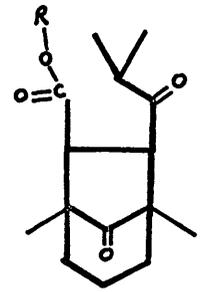
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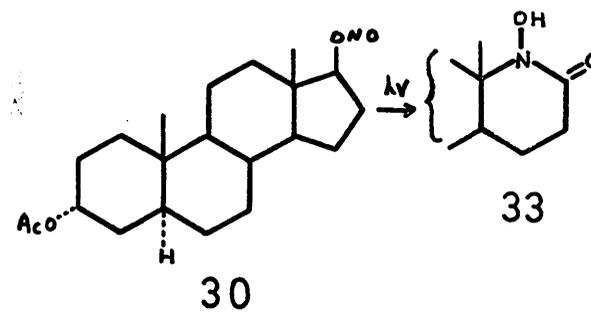
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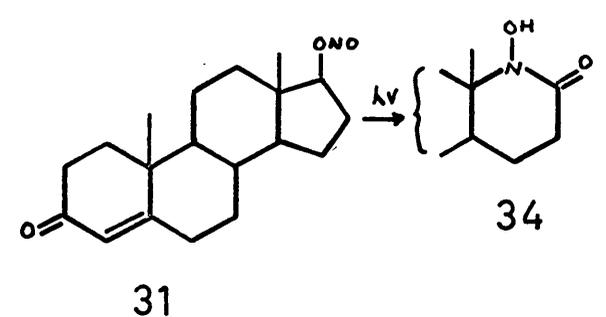


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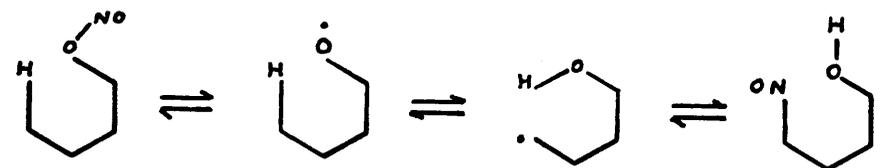
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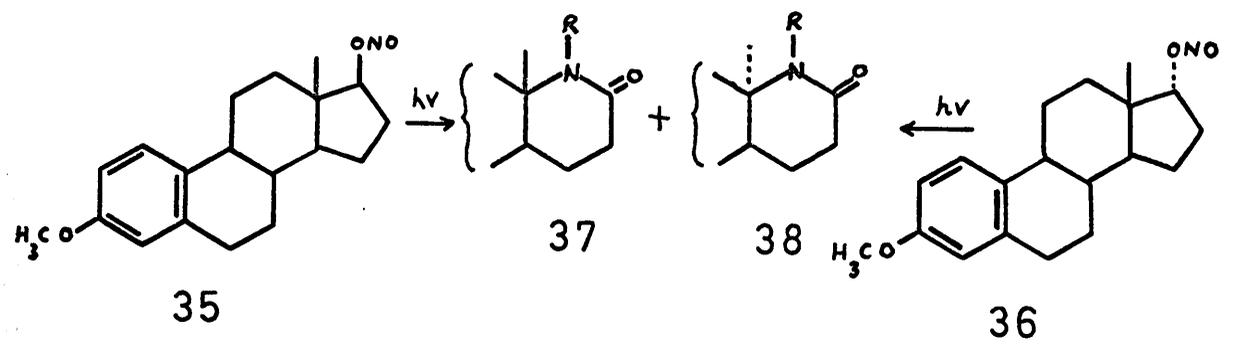


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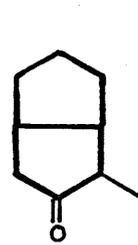


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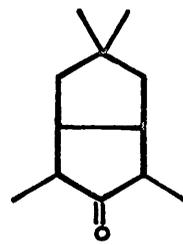
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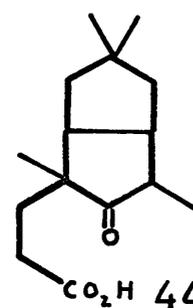
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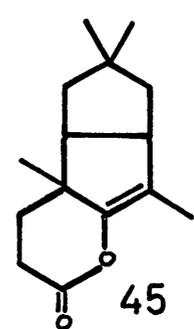
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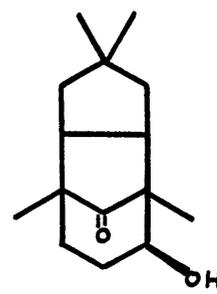
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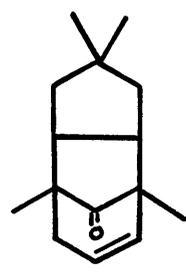
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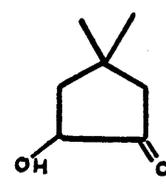
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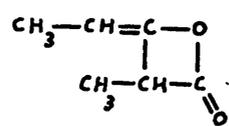
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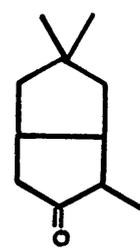
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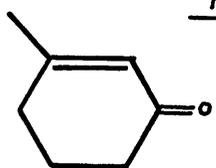
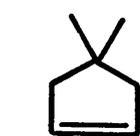
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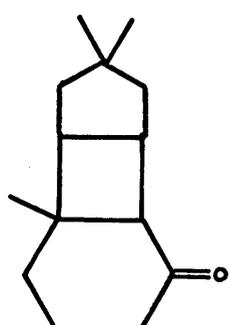
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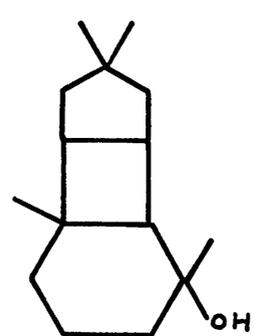
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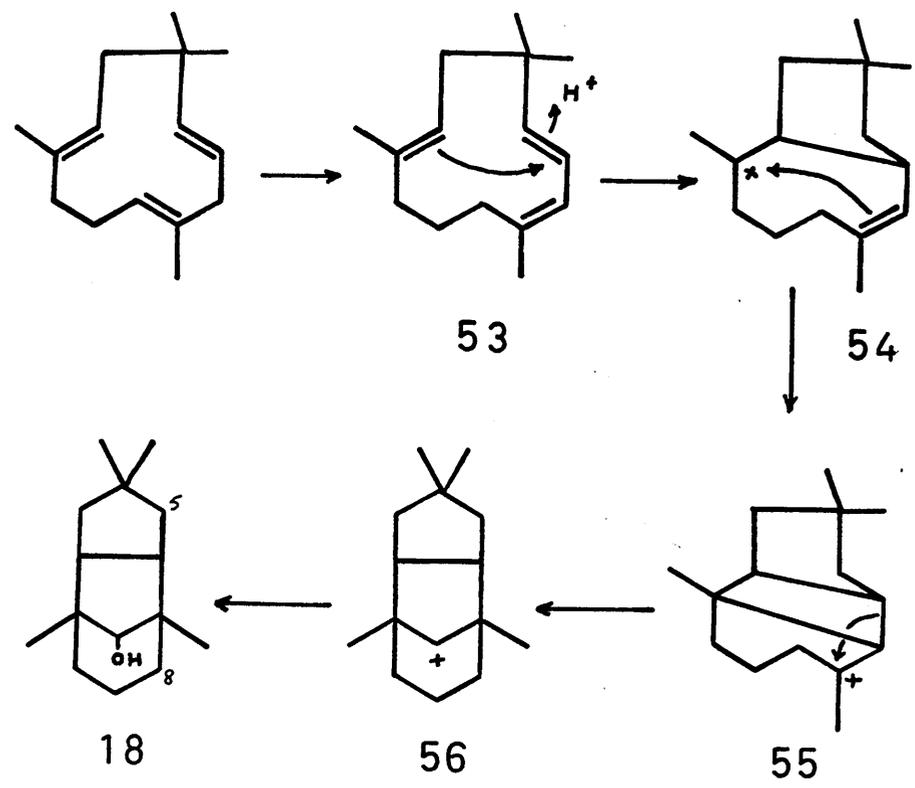
hv



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52



## EXPERIMENTAL PROCEDURE.\*

All melting points were recorded on a Kofler block and are corrected ; boiling points are uncorrected. The alumina used for routine chromatography (Spence's type H) was acid-washed and activated according to Brockmann and Schodder's method (Ber., 74, 73 (1941)). The silica, also for routine chromatography, was used as obtained commercially without further treatment. Thin (0.25mm.) and thick (1.0mm.) layer chromatoplates were prepared from Merck's 'Kieselgel'. Analytical chromatograms were run on the Pye Argon Chromatograph on columns 4'x $\frac{1}{2}$ "', unless otherwise stated and on the Aerograph 'Autoprep' A-700 model for preparative separations. Light petroleum refers to the fraction of b.p. 40-60<sup>o</sup>, unless otherwise stated. All organic extracts were dried with anhydrous magnesium sulphate.

Ultra-violet absorption spectra, measured on an automatic Unicam S.P. 800 instrument, refer to ethanol solutions. Routine infra-red spectra were measured on a Perkin Elmer 'Infracord' or Unicam S.P. 200 model,

\* The experimental procedure outlined here also applies to the experimental section of neoclovene.

and for high resolution spectra on a Unicam S.P. 100 double-beam infra-red spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum. Mass spectra were measured on an A.E.I. M.S.9 spectrometer. Nuclear magnetic resonance spectra were determined on a Perkin Elmer 60 Mc/s instrument, equipped with an integrator. The samples were run in carbon tetrachloride or deuteriochloroform solutions with tetramethylsilane as an internal reference. Earlier spectra were recorded on a A.E.I. R.S.2 60 Mc/s spectrometer.

## EXPERIMENTAL.

### Purification of Caryophyllene (1).

Caryophyllene, in light petroleum, was washed several times with dilute aqueous sodium hydroxide, then shaken with saturated aqueous silver nitrate and the organic extract dried. The extract was concentrated under reduced pressure and adsorbed on alumina (Grade I-II). Elution with light petroleum, removal of the solvent and distillation afforded pure caryophyllene,  $n_D^{20}$  1.4986 ; b.p. 75-76°/0.14 mm.;  $\nu_{\max.}$  (liq. film) = 3070, 1670, 1635, 890, 825, and 815  $\text{cm}^{-1}$

Retention time on a 20% TCEP column (Argon flow rate 62 ml./min. ; temperature 75°) = 17 minutes ; on a 25% APL column (Argon flow rate 72 ml./min. ; temperature 175°) = 14 minutes.

### Purification of Humulene (9).

Hop oil (5gm.), in light petroleum (20ml.), was shaken with an equal volume of 50% aqueous silver nitrate (w/w). The aqueous solution was separated and treated with excess aqueous ammonia and the regenerated hydrocarbons extracted with light petroleum. This extract was concentrated under reduced pressure and again shaken with aqueous silver nitrate yielding a crystalline mass, which

was collected by filtration, washed with light petroleum and recrystallised from ethanol as colourless needles (5.12gm.), m.p. 177-178°(decomp.) (Literature value 179°)<sup>18</sup>

The adduct (5.12gm.) was exhaustively steam distilled, the hydrocarbon removed from the distillate by extraction with light petroleum and dried. Evaporation of the solvent and distillation afforded pure  $\alpha$ -humulene (1.9gm.),  $n_D^{20}$  1.5032 ; b.p. 82-83°/0.2mm. ;  $\nu_{\max.}$  (liq. film) = 3040, 1670, 970, 845 and 825  $\text{cm}^{-1}$

Retention time on a 20% TCEP column (Argon flow rate 62 ml./min. ; temperature 75°) = 27.5 minutes ; on a 25% APL column (Argon flow rate 72 ml./min ; temperature 175°) = 16.4 minutes.

#### Isomerisation of $\alpha$ -Humulene (9) to a Concentrate of $\beta$ -Humulene (8).

Pure  $\alpha$ -humulene (6gm.) in light petroleum (200ml.) was vigorously shaken with alkaline alumina (Grade I) (250gm.) for 17 hours. After filtering off the alumina, the solvent was removed under reduced pressure to yield an oil (5.3gm.) ;  $\nu_{\max.}$  (liq. film) = 3070, 3040, 1670, 1645, 970, 890, 845 and 825  $\text{cm}^{-1}$ .

Retention time on a 20% TCEP column (Argon flow rate 62 ml./min. ; temperature 75°) = 24.6 minutes (60%  $\beta$ -humulene) and 27.5 minutes (40%  $\alpha$ -humulene).

### Acid-Catalysed Rearrangement of $\alpha$ -Humulene.

Concentrated sulphuric acid (2.7gm.) was added dropwise to anhydrous ether (5.1ml.) at 0°. Pure  $\alpha$ -humulene (9gm.) was then added dropwise to this solution at such a rate that the temperature did not rise above 10°. The solution was left stirring for 17 hours, then made alkaline with aqueous sodium hydroxide solution and exhaustively steam distilled. The aqueous alkaline solution was then acidified with concentrated sulphuric acid and exhaustive steam distillation repeated. The two steam distillates were saturated with brine and thoroughly extracted with ether. The steam distillation from alkaline medium yielded a pale-yellow, viscous oil (3.47gm.), while steam distillation from acid medium yielded a pale-yellow solid (3.20gm.). Extraction of the distillation residue gave a dark-brown semi-solid (3.21gm.).

The three extracts were separately adsorbed on alumina (Grade H) and the  $\alpha$ -caryophyllene alcohol eluted with light petroleum-ether (1:1). the combined yield of  $\alpha$ -caryophyllene alcohol was 3.18gm. (35%).

### Acid-Catalysed Rearrangement of a Concentrate of $\beta$ -Humulene.

Concentrated sulphuric acid (1.5gm.) was added

dropwise to anhydrous ether (2.9ml.) at 0°. The concentration of  $\beta$ -humulene (5gm.) was then added to this solution at such a rate that the temperature did not rise above 10°, and allowed to stir for 17 hours. The work-up procedure as for  $\alpha$ -humulene was then carried out. The total yield of  $\alpha$ -caryophyllene alcohol after chromatography was 1.62gm. (32%).

#### Acid-Catalysed Rearrangement of Caryophyllene.

Concentrated sulphuric acid (4.5gm.) was added dropwise to anhydrous ether (8.5ml.) at 0°. Caryophyllene (15gm.) was then added dropwise to this solution at such a rate that the temperature did not rise above 10°, and allowed to stir for 17 hours. The work-up procedure as for  $\alpha$ -humulene was then carried out. In the case of caryophyllene, steam distillation from alkaline medium yielded a pale-yellow solid (13.15gm.), while steam distillation from acid medium yielded a yellow oil (1.29gm.).

#### Dialkyl Sulphate (22).

The ether extract (3.21gm.) from the steam distillation residue was adsorbed on alumina (Grade H) (100gm.) and the dialkyl sulphate eluted with light-petroleum-ether (93:7). Crystallisation from ether afforded the pure dialkyl sulphate (1.5gm.) as large prisms, m.p. 137-138° ;

$\nu_{\text{max.}}$  (KCl disc) = 1359, 1192, 987, 939, 904 and 868  $\text{cm}^{-1}$ ;  
 $\tau$  = 5.64 (2H), 8.94 (6H), 9.01 (12H) and 9.11 (6H).

Molecular weight determined by osmometer  $506 \pm 2$  (calculated 506.7).

( Found : C, 71.15 ; H, 9.84 ; O, 12.54 ; S, 6.26% ;  
 $\text{C}_{30}\text{H}_{50}\text{O}_4\text{S}$  requires C, 71.10 ; H, 9.94 ; O, 12.63 ; S, 6.33%).

An interesting feature of this compound was discovered when its purification was attempted by means of sublimation. After the heating block had reached the melting point of the compound, the melt turned bright purple in colour and between  $140\text{--}150^\circ/0.02\text{mm.}$ , colourless crystals appeared at the cool end of the sublimation tube. This substance, in fact, was not the purified sulphate ester, but was shown by thin-layer chromatography and infra-red spectrum to be  $\alpha$ -caryophyllene alcohol. At a higher temperature, the purple viscous liquid also appeared at the cool end of the tube, but on dissolution in ether or trituration, the colourless crystalline sulphate ester was regenerated. Although no further work was carried out on this phenomenon, preliminary results indicated that this conversion to  $\alpha$ -caryophyllene alcohol could not be effected quantitatively.

The dialkyl sulphate was recovered unchanged from

:-

- (a) Refluxing 6N sulphuric acid,
- (b) Refluxing 4N sodium hydroxide,
- (c) Hydrogenation with platinum oxide in acetic acid/  
ethyl acetate, and
- (d) Lithium aluminium hydride reduction in refluxing  
tetrahydrofuran.

#### Hydrolysis of the Dialkyl Sulphate.

The dialkyl sulphate (100mg.) in 98% formic acid (50ml.) containing water (10ml.) was refluxed for 6 hours. The reaction mixture was poured into brine (200ml.) and extracted with ether. The ether layer was washed with more brine and sodium bicarbonate solution and finally dried. Removal of the solvent yielded an oil,  $\nu_{\max}$ . (liq. film) = 1730 and 1180  $\text{cm}^{-1}$

The crude hydrolysis product was refluxed overnight with excess lithium aluminium hydride (100mg.) in ether (50ml.). The excess hydride was destroyed by addition of saturated ammonium sulphate solution, and the reaction product extracted with ether. The organic layer was dried and the solvent removed to yield a crystalline solid (70mg.). Recrystallisation from light petroleum gave pure  $\alpha$ -caryophyllene alcohol, m.p. 117-118<sup>o</sup>, identical in all respects

with an authentic sample.

$\alpha$ -Caryophyllene Alcohol (18).

The combined yield of  $\alpha$ -caryophyllene alcohol was recrystallised from light petroleum as colourless plates, m.p. 118.5-119°,  $[\alpha]_D^{20} \pm 0^\circ$  (  $c$ , 3.0 in  $\text{CHCl}_3$  ) ;  $\nu_{\text{max.}}$  ( $\text{CCl}_4$ ) = 3634, 1072 and 1050  $\text{cm}^{-1}$  ;  $\tau$  = 6.70 (1H), 8.95 (3H), 9.10 (3H) and 9.15 (6H).  
( Found : C, 81.25 ; H, 11.70% ;  $\text{C}_{15}\text{H}_{26}\text{O}$  requires C, 81.02 ; H, 11.79%).

p-Bromobenzenesulphonate of  $\alpha$ -Caryophyllene Alcohol.

$\alpha$ -Caryophyllene alcohol (100mg.) was added to a solution of p-bromobenzenesulphonyl chloride (200mg.) in dry pyridine (2ml.). After warming briefly, the solution was stored at room temperature for 22 hours. Water (5ml.) was added to the solution which was then extracted with ether. The ethereal extract was washed successively with 6N hydrochloric acid, brine, aqueous sodium carbonate solution and dried. Evaporation of the solvent yielded a crystalline solid (230mg.). The p-bromobenzenesulphonate was freed from starting alcohol by adsorption on alumina (Grade I) (5gm.) and elution with light petroleum-ether (19:1). Crystallisation from ether afforded the pure p-bromobenzenesulphonate, m.p. 147.5-148° ;  $\nu_{\text{max.}}$  (KCl disc)

= 3092, 3066, 1580, 1352, 1184, 959, 949, 882 and 875  $\text{cm}^{-1}$  ;  $\tau = 2.2$  and  $2.37$  ( $A_2B_2$  quartet,  $J=8$  cps.) (4H), 5.62 (1H), 8.92 (3H), 9.12 (3H) and 9.25 (6H). ( Found : C, 57.10 ; H, 6.75 ; Br, 18.40% ;  $C_{21}H_{29}O_3^{\text{SBr}}$  requires C, 57.15 ; H, 6.60 ; Br, 18.10% ).

#### Dehydration of $\alpha$ -Caryophyllene Alcohol.

Phosphorus pentoxide (circa. 0.8gm.) was slowly added to a stirred melt of  $\alpha$ -caryophyllene alcohol (0.5gm.) at  $140^\circ$  over 10 minutes. After cooling, the dark-brown residue was carefully neutralised with aqueous sodium carbonate solution. The dehydration products were then removed by exhaustive steam distillation, followed by extraction with light petroleum. The extract was dried and the solvent removed under reduced pressure to yield a pale-yellow oil (0.36gm.),  $n_D^{20}$  1.4832,  $\nu_{\text{max.}}$  (liq.film) =  $845 \text{ cm}^{-1}$ .

Gas-liquid chromatography on a 0.5% APL column (Argon flow rate 50 ml./min. ; temperature  $100^\circ$ ) showed two predominant peaks (circa. 90%) of retention times 2 minutes and 3 minutes respectively, and two minor peaks (circa. 10%) of retention times 3.5 minutes and 4.1 minutes. The retention time of clovene under the same conditions was 5 minutes.

$\alpha$ -Caryophyllene Ketone (17).

$\alpha$ -Caryophyllene alcohol (1gm.) in Analar acetone (12ml.) was cooled to  $0^{\circ}$  and Jones reagent<sup>41</sup> (1.2ml.) was added dropwise with shaking to a permanent red-orange coloration. The solution was allowed to come to room temperature and water (25ml.) was added. The solution was extracted with light petroleum, washed with saturated sodium bicarbonate solution and finally dried to yield a colourless oil, which solidified on cooling (0.99gm.). Sublimation gave a pure sample, m.p.  $40.5-41.5^{\circ}$ ,  $\nu_{\max.}(\text{CCl}_4) = 1740 \text{ cm}^{-1}$ ;  $\gamma = 8.97$  (3H),  $9.02$  (3H) and  $9.13$  (6H).

( Found : C, 81.60 ; H, 10.85% ;  $\text{C}_{15}\text{H}_{24}\text{O}$  requires C, 81.75 ; H, 11.00% ).

The corresponding 2,4-dinitrophenylhydrazone crystallised from ethanol as yellow-orange needles, m.p.  $158-159^{\circ}$ .

$\alpha$ -Caryophyllene Lactone (19).

A solution of trifluoroacetic acid was prepared<sup>26</sup> by dropwise addition of trifluoroacetic anhydride (12.7ml.) to a stirred suspension of 99% hydrogen peroxide (2.1ml.) in dry methylene chloride (14ml.) at  $0^{\circ}$ . This solution was stored at  $0^{\circ}$  for four hours.

To a dry methylene chloride (12ml.) solution of  $\alpha$ -caryophyllene ketone (1.32gm.), containing dry, finely-ground disodium hydrogen phosphate (3gm.) was added the solution of trifluoroacetic acid (14ml.) dropwise with stirring. This solution was allowed to stand at room temperature in the dark for 20 hours. The inorganic salts were dissolved in water (25ml.), the solution extracted with methylene chloride (50ml.), washed with 10% sodium carbonate solution (50ml.) and finally dried. The solvent was removed under reduced pressure to yield a colourless solid (1.38gm.)

Thin-layer chromatography (ethyl acetate-light petroleum (1:9)) indicated two minor products ( $R_f$ 's = 0.33 and 0.40) and one major component ( $R_f=0.22$ ). The major component was eluted from silica (45gm.) with light petroleum-ether (17:3) (1.15gm.) and sublimation afforded a pure sample, m.p. 102.5-103<sup>o</sup> ;  $\nu_{\max.}(\text{CCl}_4) = 1740$  and  $1086 \text{ cm}^{-1}$  ;  $\tau = 8.77$  (3H), 8.92 (3H), 8.99 (3H) and 9.02 (3H).

( Found : C, 76.60 ; H, 10.27% ;  $\text{C}_{15}\text{H}_{24}\text{O}_2$  requires C, 76.22 ; H, 10.24% ).

$\gamma$ -Lactone ( $R_f=0.40$ ).

Rechromatography of the two minor components (74mg.) on silica (3gm.) and elution with light petroleum-ether

(24:1) gave the pure  $\gamma$ -lactone ( $R_f=0.40$ ), which crystallised from light petroleum as colourless needles, (35mg.), m.p.  $97-98^\circ$  ;  $\nu_{\max.}(\text{CCl}_4) = 1780 \text{ cm}^{-1}$  ;  $\tau = 6.95$  (1H) (quartet, X part of an ABX system,  $J_{\text{AX+BX}}=19$  cps.), 7.68 (1H) (doublet, half of an AB quartet?,  $J=14$  cps.), 8.40 (3H), 8.87 (6H) and 8.91 (3H).

$\gamma$ -Lactone ( $R_f=0.33$ ) (23).

Further elution with light petroleum-ether (47:3) gave the pure  $\gamma$ -lactone ( $R_f=0.33$ ) (20mg.), which crystallised from light petroleum as colourless needles, m.p.  $102-103^\circ$  ;  $\nu_{\max.}(\text{CCl}_4) = 1772 \text{ cm}^{-1}$  ;  $\tau = 7.31$  (1H) (quartet, X part of an ABX system,  $J_{\text{AX+BX}}=19$  cps.), 8.87 (3H), 8.92 (3H), 8.94 (3H) (doublet,  $J=7.5$  cps.) and 9.00 (3H).

This compound was identical in infra-red and N.M.R. spectra and melting point with that obtained by Professor Nickon<sup>31</sup>.

Lithium Aluminium Hydride Reduction of  $\alpha$ -Caryophyllene Lactone (19) (Ether).

The  $\delta$ -lactone (355mg.) in anhydrous ether (30ml.) was slowly added to lithium aluminium hydride (600mg.) in anhydrous ether (25ml.) with stirring. After refluxing for 5 hours, the excess hydride was destroyed by

Careful addition of 6N hydrochloric acid, and then the reaction mixture was thoroughly extracted with ether. The ethereal extract was washed with saturated sodium bicarbonate solution, dried and the solvent removed under reduced pressure to yield a viscous oil (380mg.).

Adsorption on silica (12gm.) and elution with light petroleum-ether (9:1) gave the crystalline hemi-acetal (21) (230mg.), m.p. 85-86.5°,  $\nu_{\max.}(\text{CCl}_4) = 3617, 1097, 1064, 1042, \text{ and } 1013 \text{ cm}^{-1}$ ;  $\tau = 5.04$  (1H), 8.95 (6H), 9.07 (3H) and 9.13 (3H).

( Found : C, 75.91 ; H, 10.65% ;  $\text{C}_{15}\text{H}_{26}\text{O}_2$  requires C, 75.58 ; H, 11.00% ).

Further elution with light petroleum-ether (7:3) gave the crystalline diol (20) (103mg.), m.p. 114.5-115.5°,  $\nu_{\max.}(\text{CCl}_4) = 3641, 3630, 3618, 3437, 3200, 1117, 1086, 1070, 1045 \text{ and } 1016 \text{ cm}^{-1}$ ;  $\tau = 6.12$  and 6.58 (2H) (AB quartet,  $J=11$  cps.), 8.88 (3H), 8.92 (3H) 9.05 (3H) and 9.19 (3H).

( Found : C, 75.13 ; H, 11.22% ;  $\text{C}_{15}\text{H}_{28}\text{O}_2$  requires C, 74.95 ; H, 11.74% ).

When the lithium aluminium hydride reduction in ether was allowed to proceed for only 2 hours, thin-layer chromatography of the product showed that it was exclusively the hemi-acetal (21).

Lithium Aluminium Hydride Reduction of  $\alpha$ -Caryophyllene Lactone (19) (Tetrahydrofuran).

The  $\delta$ -lactone (100mg.) in anhydrous tetrahydrofuran (20ml.) was slowly added to a solution of lithium aluminium hydride (600mg.) in anhydrous tetrahydrofuran (25ml.) with stirring. After refluxing for 43 hours, the excess hydride was destroyed by careful addition of saturated ammonium sulphate solution, and the mixture thoroughly extracted with ether. The ethereal extract was washed with brine, dried and the solvent removed under reduced pressure to yield a viscous oil (120mg.), which crystallised on trituration with light petroleum. Thin-layer chromatography indicated that the product was predominantly the diol (20).

### Attempted Synthesis.

#### Dimethyl $\beta,\beta$ -Dimethyl Glutarate.

A solution of  $\beta,\beta$ -dimethyl glutaric acid (54.3gm.) in anhydrous methanol (206ml.) at  $0^{\circ}$  was saturated with dry hydrogen chloride gas. The reaction mixture was allowed to stand at room temperature for 24 hours and then poured into ice-cold water (500ml.). The solution was extracted with ether, the ether layer washed with aqueous sodium bicarbonate solution, dried and the solvent removed to yield an oil, which was distilled to give pure dimethyl  $\beta,\beta$ -dimethyl glutarate (56gm.), b.p.  $64^{\circ}/0.15\text{mm.}$ .

#### 4,4-Dimethylcyclopentan-2-ol-1-one (48).<sup>37</sup>

Sodium (7.25gm.) was added in small pieces with vigorous stirring to a solution of dry liquid ammonia (500ml.) in anhydrous ether (500ml.) under dry, oxygen-free nitrogen. To the deep-blue solution, dimethyl  $\beta,\beta$ -dimethyl glutarate (14gm.) in anhydrous ether (50ml.) was added dropwise with stirring over 4 hours. The reaction mixture was stirred for an additional 2 hours at  $-30^{\circ}$  and then the ammonia was allowed to evaporate off overnight. Methanol (27ml.) in ether (50ml.) was added dropwise to the yellow suspension and then acidified with 3N hydrochloric acid. The ether layer was separated and the

aqueous solution extracted with more ether. The combined ether extracts were dried and the solvent removed to yield a yellow oil. Fractional distillation afforded the pure ketol (8.4gm.), b.p. 46-47°/0.15mm.;  $\nu_{\max.}$  (liq.film) = 3400, 1740, 1720, 1660 and 1630  $\text{cm}^{-1}$

The corresponding tosylate was prepared in the usual manner with p-toluenesulphonyl chloride in pyridine. The pure keto-tosylate crystallised from ether as colourless needles, m.p. 103-103.5°,  $\nu_{\max.}$  ( $\text{CCl}_4$ ) = 1739, 1630, 1600, 1195, 1185 and 1070  $\text{cm}^{-1}$ .

( Found : C, 59.73 ; H, 6.32% ;  $\text{C}_{14}\text{H}_{18}\text{O}_4\text{S}$  requires C, 59.56 ; H, 6.43% ).

#### Ethyl $\alpha$ -Propionyl Propionate.

##### (a) From Ethyl Propionate<sup>38</sup>.

Redistilled ethyl propionate (280gm.) was added to sodium ethoxide (40gm.) with stirring. The reaction mixture was refluxed for 4 hours and then the ethanol and excess ethyl propionate were removed by distillation. Ethyl propionate (200gm.) was then added and the reaction mixture refluxed for a further 3 hours, at the end of which the ethanol was again removed. A final repetition of this sequence with more ethyl propionate (100gm.) yielded a solid mass to which glacial acetic acid (35gm.) in water (70ml.) was carefully added with cooling. The

reaction mixture was extracted with ether, the organic extract washed with sodium bicarbonate solution and dried. After removal of the solvent, the residual oil was fractionally distilled to yield pure ethyl  $\alpha$ -propionyl propionate (20.6gm.), b.p.  $85^{\circ}/12\text{mm.}$ ,  $n_D^{20}$  1.4262.

(b) From Methylketene Dimer (49)<sup>39</sup>.

Propionyl chloride (179gm.) was added to anhydrous ether (980ml.) containing triethylamine hydrochloride (1gm.). To this solution, dry triethylamine (202gm.) was added dropwise at such a rate as to maintain a gentle reflux. The reaction mixture was allowed to stand at room temperature overnight, and then filtered to remove the triethylamine hydrochloride. Removal of the ether from the filtrate yielded the crude methylketene dimer (56gm.), which was fractionally distilled to give the pure methylketene dimer, b.p.  $56^{\circ}/12\text{mm.}$ ,  $\nu_{\text{max.}}$  (liq.film) = 1850, 1780, 1720, 1180, 1070, 1040, 900 and  $820\text{ cm.}^{-1}$

Methylketene dimer (35gm.) was added to absolute ethanol (110ml.) and the reaction mixture allowed to stand overnight at room temperature. The excess ethanol was removed under reduced pressure and the residue fractionally distilled to give pure ethyl  $\alpha$ -propionyl propionate (27gm.), b.p.  $86-87^{\circ}/12\text{mm.}$ ,  $n_D^{20}$  1.4227.

### Ethyl Propionyl Acetate<sup>42</sup>

Ethylmagnesium iodide was prepared in the usual manner from magnesium (26gm.) and ethyl iodide (182gm.) in anhydrous ether (170ml.). Redistilled ethyl cyanoacetate (48gm.) in anhydrous ether (70ml.) was added dropwise with stirring to the Grignard reagent and then allowed to stand at room temperature for 72 hours. The Grignard complex was decomposed with saturated ammonium chloride (160ml.), followed by concentrated hydrochloric acid (80ml.) and the reaction mixture extracted with ether. The aqueous layer was acidified with more concentrated hydrochloric acid (35ml.) and again extracted with ether. The combined ether extracts were stirred with 10% hydrochloric acid (130ml.) for 3 hours at room temperature. The ether layer was separated, washed with water and saturated sodium bicarbonate solution, dried and the solvent removed to yield an oil. Careful fractional distillation of this oil afforded pure ethyl propionyl acetate (35.2gm.), b.p. 82-83°/12mm..

### Attempted Condensation.

Ethyl  $\alpha$ -propionyl propionate (1.68gm.) in anhydrous benzene (5ml.) was added dropwise to sodium powder (250mg.) in benzene (10ml.) and refluxed until all the sodium was

consumed. The tosylate of 4,4-dimethylcyclopentan-2-ol-1-one (3gm.) in anhydrous benzene (20ml.) was then added dropwise to the cooled mixture and allowed to reflux for 4 hours. The dark-red solution was poured into brine and extracted with benzene. The organic layer was dried and the solvent removed to yield an oily solid, which was shown to be a mixture of the two unreacted starting materials by infra-red spectrum and thin-layer chromatography.

Exactly the same result was obtained when the sodium powder was replaced by sodium hydride and the reaction mixture allowed to reflux for 32 hours.

PART II.

NEOCLOVENE.

## HISTORICAL.

The sesquiterpene, caryophyllene (1), which has been isolated from many natural sources, must go down in the annals of organic chemistry as one of the most versatile exponents of molecular acrobatics. Indeed, it is true to say that no one sesquiterpene has so fired the imagination and prodigious experimentation of organic chemists. Having been known for over a century, caryophyllene did not surrender to a structural elucidation until a concerted attack had been launched in the early 1950's mainly by the schools of Barton and Sorm. Since the structural elucidation has been adequately reviewed<sup>43,44</sup>, this introduction will be mainly concerned with the remarkable variety of transformation products derivable from caryophyllene and its derivatives.

On treatment with concentrated sulphuric acid in ether, caryophyllene yields a mixture of tricyclic artefacts, of which the hydrocarbon, clovene (2) and the alcohol,  $\beta$ -caryophyllene alcohol (3) are the two predominant components<sup>1</sup>. This present work describes a structural proof of yet another acrobatic progeny, designated neoclovene, which is also derived from caryophyllene in this rearrangement.

Initially, it was thought that there was a structural relationship between clovene and  $\beta$ -caryophyllene alcohol, through the intermediacy of a common carbonium ion (4). This was tacitly assumed on the grounds that  $\beta$ -caryophyllene alcohol on dehydration yielded two unsaturated hydrocarbons<sup>45</sup>, one of whose physical properties 'resembled' those of clovene. The other hydrocarbon was designated isoclovene (5), whose structure was later adduced by X-ray analysis of its hydrochloride<sup>46</sup>. The mechanism of formation of isoclovene from  $\beta$ -caryophyllene alcohol demands some rather unusual features in carbonium ion rearrangements as shown.

That clovene and  $\beta$ -caryophyllene alcohol did not originate from the same cationic species was demonstrated by Lutz and Barton respectively. Lutz and Reid<sup>47</sup> repeated the dehydration of  $\beta$ -caryophyllene alcohol and showed that, in addition to isoclovene (5), the other isomeric unsaturated hydrocarbon had different physical and chemical properties to those of clovene, purified via the dibromides. This new 'hydrocarbon' was, therefore, designated pseudoclovene. Furthermore they showed that  $\beta$ -caryophyllene alcohol could not be converted into clovene even under forcing conditions with concentrated sulphuric acid. These workers made the tentative assignment (6) as the

structure of pseudoclovene on sparse chemical evidence, viz., on oxidation, a dicarboxylic acid was formed, which could be dibrominated in the Hell-Volhard-Zelinski reaction. Recently, however, it has been unequivocally established<sup>48</sup> in the laboratories at Glasgow that a) pseudoclovene is a composite of two unsaturated hydrocarbons in the approximate ratio of 1:1, which can only be separated by preparative gas-liquid chromatography under very exacting conditions and further b) in view of the non-identity of authentic caryolane (7) with either of the pseudoclovenes, that they both have rearranged skeletons. Work in these laboratories has been initiated towards a structural elucidation of both hydrocarbons.

Barton and his co-workers<sup>5</sup> suggested, on conformational grounds, that clovene and  $\beta$ -caryophyllene alcohol originate by two different modes of cyclisation of caryophyllene, which, by virtue of its nine membered ring, can exist in two different conformers (8) and (9), as shown. Thus, clovene and  $\beta$ -caryophyllene alcohol would have methylene bridges of opposite stereochemistry. This suggestion was later verified by molecular rotation studies<sup>6</sup> and corroborated by the elegant X-ray analysis of the bromide and chloride corresponding to  $\beta$ -caryophyllene alcohol<sup>49</sup>. Since the two asymmetric centres at

C<sub>2</sub> and C<sub>5</sub> are not involved in the formation of β-caryophyllene alcohol, this X-ray analysis also defined the stereochemistry of caryophyllene itself, illustrating that the four membered ring is trans fused to the nine membered ring. These two modes of cyclisation could also be invoked to explain the structures of the two diols (10) and (11), obtained by peracid treatment of caryophyllene ; these two compounds have been related<sup>50,51</sup> to clovane and β-caryophyllene alcohol respectively by chemical means.

Despite the fact that the double bonds in caryophyllene are not conjugated, a maleic anhydride adduct can be formed with remarkable ease, viz., in refluxing benzene. Such a reaction is not without precedent, although much higher temperatures have been required for analogous reactions, e.g. in the case of methylenecyclohexane<sup>52</sup>. This feature, therefore, has been attributed to the strain inherent in the nine membered ring with a trans double bond. By a consideration of the infra-red spectrum and the chemical properties of this adduct, Nickon<sup>53</sup> formulated it as (12).

A novel type of cyclisation of the caryophyllene nucleus took place when this adduct was treated with electrophilic agents such as H<sup>+</sup> and Br<sup>+</sup>. Thus, treatment with dry hydrogen chloride gave the chloro-anhydride (13), which, on acid hydrolysis, yielded the δ-lactonic acid (14),

which could also be obtained by aqueous acid treatment of the adduct. Aqueous N-bromosuccinimide gave the bromo-hydroxy-anhydride (15) and the bromo- $\gamma$ -lactonic acid (16), both of which could be converted by acid hydrolysis to the bromo- $\delta$ -lactonic acid (17). This latter compound on catalytic hydrogenolysis yielded the  $\delta$ -lactonic acid (14). Nickon, however, pointed out that other tricyclic systems such as (18) and (19) could not be emphatically rejected on the evidence presented, but in view of analogous cyclisations (vide infra) seem unlikely.

One of the key compounds utilised in the structural elucidation of caryophyllene was the so-called Treib's epoxy-ketone (20)<sup>54</sup>. This compound, on treatment with base gave the tricyclic hydroxy-ketone (21), via carbanion attack from C<sub>9</sub> to C<sub>4</sub>. A more mysterious rearrangement, recently elucidated by Sutherland and his co-workers<sup>55</sup>, took place when the epoxy-ketone was treated with hydrogen chloride. Spectral data indicated that the derived chlorohydrin was not simply the product of hydrogen chloride addition to the epoxide ring, especially in view of the transparency in the carbonyl region of its infra-red spectrum. Base treatment of the chlorohydrin generated the unsaturated ketol (22), which, on acetylation and ozonolysis gave an acetoxy-dione. The diol

(23) could be obtained by lithium aluminium hydride reduction of the chlorohydrin, in addition to another diol with a  $\text{CH}_2\text{OH}$  grouping, which was postulated as having arisen from ring contraction. Finally, lithium in liquid ammonia reduction and subsequent oxidation gave the ketol (24), which on further oxidation yielded the keto- $\gamma$ -lactone (25). That the chlorohydrin still possessed the original cyclobutane ring was shown by oxidation to the same dicarboxylic acids as were obtained by an analogous oxidation of caryophyllene itself. The invocation of a type of retro-Prins reaction in this degradation sequence, coupled with a consideration of the possible mechanism of formation of the chlorohydrin, permitted Sutherland and his co-workers to assign it the structure (26, R=Cl). This structure was confirmed by an X-ray analysis<sup>56</sup>, which also defined the stereochemistry as shown.

A clue to the probable mechanism of formation of the chlorohydrin was obtained by the observation that the epoxy-ketone (20) was isomerised to the ketol (22) on treatment with sodium iodide in acetic acid. The ketol, in turn, gave the chlorohydrin on treatment with hydrogen chloride. The mechanism, therefore, is envisaged as shown. The corresponding triol (26, R=OH) was obtained when the epoxy-ketone was subjected to aqueous acid.

Warnhoff<sup>57</sup> has recently shown that caryophyllene monoepoxide (27) also undergoes a number of interesting transformations, one of which is analogous to that observed in the cyclisation of the maleic anhydride adduct and the epoxy-ketone (vide supra). In addition to the known clovan-2 $\beta$ ,9 $\alpha$ -diol (10), acid-catalysed rearrangement of the monoepoxide gave a number of carbonyl compounds. Using 2,4-dinitrophenylhydrazine reagent as the acid catalyst, and subsequent careful chromatography and crystallisation, Warnhoff was able to isolate three crystalline 2,4-dinitrophenylhydrazones.

By an analysis of the N.M.R. spectrum of one of these derivatives, the structure (28) was adduced. Corroboration of this proposed structure was obtained by a demonstration of the identity of the corresponding dihydro derivative (29) with the 2,4-dinitrophenylhydrazone formed exclusively by rearrangement of dihydrocaryophyllene epoxide (30). The mechanism of formation of this derivative involves a ring contraction as shown. It is of interest to note that Nigam<sup>58</sup> has recently observed this same rearrangement when (27) and (30) were gas-liquid chromatographed using a column with an acid-washed support. When the support was made alkaline, however, this phenomenon did not occur.

The N.M.R. spectrum of the second 2,4-dinitrophenylhydrazone indicated that it was tricyclic with no vinylic or allylic protons. Like the first derivative, however, three quaternary methyl groups were observed, but none of these were deshielded as in the case of the C<sub>4</sub> methyl group in (28). The simplest interpretation of these observations could be accommodated by the structure (31), whose formation was envisaged as an initial isomerisation to the dienol (32), followed by cyclisation and ring contraction as shown. The postulate of (32) as an intermediate in this rearrangement<sup>e</sup> was upheld by an unambiguous synthesis of the dienol from the epoxy-ketone (20). Thus, the epoxy-ketone on elution from alumina gave the keto-enol (33) which was then transformed into (32) by a Wittig reaction with the ylide from methyltriphenylphosphonium iodide. Treatment of (32) with 2,4-dinitrophenylhydrazine reagent gave exclusively the same derivative (31).

An alternative structure which would also accommodate the facts is (34), whose formation can be envisaged by an anionotropic shift to (35), and subsequent cyclisation via the enol (36). However, this latter mechanism would demand an incorporation of at least two deuterium atoms, whereas the former postulate only one deuterium atom.

By performing the rearrangement of the dienol in deuterated solvents, Warnhoff has conclusively shown that only one deuterium was incorporated, and also, by a study of the N.M.R. spectrum of the product, that the deuterium atom is located at the bridgehead methyl group as expected. As in the case of the maleic anhydride adduct cyclisation, other tricyclic derivatives, involving ring expansion of the cyclobutane ring and which would also incorporate only one deuterium atom, are possible. However, in view of the defined structure of the chlorohydrin (26,R=Cl), whose formation is comparable, these possibilities seem remote. That the dienol (32) was not a precursor of clovan-2 $\beta$ ,9 $\alpha$ -diol (10) was demonstrated by treatment of (32) under conditions used to generate (10) from caryophyllene monoepoxide (27) which gave no diol (10). The fact that the diol (10) contains no deuterium atoms when caryophyllene monoepoxide is rearranged in deuterated solvents illustrates that at least three different reaction routes are followed in these rearrangements.

Finally, the N.M.R. spectrum of the third 2,4-dinitrophenylhydrazone, whose structure has, as yet, not been elucidated, showed that it was also a derivative of a tertiary aldehyde and that it had no less than five methyl groups! The fact that it cannot be derived from

the dienol (32), which has four potential methyl groups, is even more surprising. We await the elucidation of its structure with considerable interest.

## DISCUSSION.

When the total synthesis<sup>59</sup> of (±)-clovene (2) was nearing completion in the laboratories at Glasgow, it was imperative to obtain a pure sample of this sesquiterpene artefact for comparison purposes. However, careful gas-liquid chromatographic analysis of the hydrocarbon fraction obtained from rearrangement of caryophyllene indicated that there were no less than thirteen discernible peaks, two of which constituted approximately 90% of the reaction mixture ; these two peaks were in the ratio of approximately 3:2. The lower boiling fractions obtained by careful distillation on a spinning band column, were shown by gas-liquid chromatography and infra-red spectroscopy to be the predominant constituent, clovene. The sample of clovene thus obtained was only 98% pure, so further purification was effected by regeneration of the pure hydrocarbon from the isomeric dibromides as described by Lutz and Reid<sup>47</sup>. The higher boiling hydrocarbon, now designated neoclovene, could only be obtained in 90% purity by this distillation technique.

Little mention has been made in the literature of the inhomogeneity of clovene as obtained from caryophyllene. In 1951, Eschenmoser and Günthard<sup>60</sup>, in an effort to

obtain pure clovene, carried out a very careful distillation of the hydrocarbon mixture. They recorded graphically the relationships between optical rotation, boiling point and volume of distillate, which indicated that clovene represented approximately 60% of the hydrocarbon mixture. Significantly, a maximum rotation of  $-62^{\circ}$  was determined for the highest boiling fraction ; pure clovene has a rotation of  $-21^{\circ}$ . The results of a similar distillation procedure carried out by Lutz and Reid<sup>47</sup> in 1954, indicated that the highest boiling fractions had the following physical data :-  $n_D^{25}$  1.5032,  $[\alpha]_D^{25}$   $-54.21^{\circ}$ . Furthermore, these authors observed that pure clovene gave a high yield of clovenic acid on oxidation ; the varying low yields of acid reported in the earlier literature was presumably due to the isomeric impurities in the samples of 'clovene' previously employed.

Lutz and Reid briefly investigated the by-products from oxidation of crude clovene. One compound which they isolated was a  $C_{14}H_{22}O_3$  keto-acid, which could not be induced to crystallise. They proposed a partial structure (37) for the isomeric impurity in clovene. Of the many derivatives of this keto-acid and its corresponding methyl ester attempted, none could be obtained in crystalline form. On one occasion, a small amount of a

crystalline substance m.p. 101-102° analysing for  $C_{12}H_{20}O_3$  crystallised from a light petroleum solution of the crude acidic material. This acid was unstable, giving different neutralisation equivalents according to the method of determination. Finally, from the neutral material derived from oxidation of crude clovene these authors obtained an unsaturated tricyclic ketone,  $C_{15}H_{22}O$ , which was not further investigated.

These findings, therefore, prompted a more systematic investigation of neoclovene, as derived from pure caryophyllene. The caryophyllene used for the present work was purified as described in the work on  $\alpha$ -caryophyllene alcohol. No iso-caryophyllene was observed on gas-liquid chromatographic analysis on a 20% tris-cyanoethoxypropane column, which is known to resolve these two isomers<sup>61</sup>. As already noted, a 100% pure sample of neoclovene could not be obtained by even careful distillation on a spinning band column. Therefore, in view of the relatively favourable separation of neoclovene and clovene on analytical gas-liquid chromatography, it was decided to resort to preparative gas-liquid chromatography. Careful manipulation of the conditions (temperature, carrier gas flow rate, etc.) on an Aerograph 'Autoprep' A-700 model using a 10% Ucon Polar column (20' x  $\frac{3}{8}$  ") permitted a

good separation of neoclovene (3.9gm.), which was shown by analysis on an analytical column (25% APL or 20% TCEP) to be at least 99.5% pure ;  $n_D^{20}$  1.5088,  $[\alpha]_D^{20}$  -72.0°. The mass spectrum and elemental analysis indicated a molecular formula of  $C_{15}H_{24}$ . The infra-red spectrum of neoclovene showed peaks at 3023 and 1657  $cm^{-1}$  and a multitude of peaks in the 950-700  $cm^{-1}$  region, which apart from indicating that neoclovene was unsaturated, did not permit an unambiguous assignment to the nature of the double bond substitution. This, however, was adduced from the N.M.R. spectrum, which clearly indicated one vinylic proton as a broad multiplet at 4.91 $\tau$ , in addition to three quaternary methyl groups at  $\tau$  = 8.80 (3H) and 8.99 (6H). A doublet ( $J$ =ca. 1.5 cps.) at 8.41 $\tau$  seemed indicative of a vinylic methyl group, which was later verified. Integration of this resonance and that presumably due to the allylic protons ca. 8.0 $\tau$  was difficult because of the overlapping 'methylene envelope'. The fact that neoclovene had four methyl groups indicated that it had a unique rearranged skeleton. It was shown to be tricyclic by catalytic hydrogenation to a fully saturated dihydro derivative with three quaternary and one secondary methyl groups.

That neither clovene nor  $\beta$ -caryophyllene alcohol

were precursors of neoclovene was demonstrated by treatment of these two compounds with concentrated sulphuric acid in ether. Neoclovene was smoothly converted to a crystalline secondary-tertiary diol,  $C_{15}H_{26}O_2$ , by treatment with osmium tetroxide in pyridine and subsequent mild oxidation yielded a ketol, whose carbonyl absorption at  $1718\text{ cm}^{-1}$  was indicative of a six-membered ring. Confirmation of this fact was obtained by hydroboration<sup>62</sup> of neoclovene to a mixture of crystalline, epimeric alcohols, which, on oxidation and chromatography gave a ketone,  $\nu_{C=O} 1712\text{ cm}^{-1}$ . The N.M.R. spectrum of the diol clearly indicated four quaternary methyl groups at  $\tau = 8.75$  (6H), 8.91 (3H) and 8.98 (3H), in addition to a 1H multiplet at 6.3 $\tau$ . Sodium metaperiodate cleavage of the diol gave an unstable keto-aldehyde,  $C_{15}H_{24}O_2$ , whose N.M.R. spectrum showed a sharp 3H singlet at 7.98 $\tau$ , confirming the original suspicion that neoclovene had a methyl group on a trisubstituted double bond. Furthermore, the aldehydic proton at 0.20 $\tau$  was split into a triplet ( $J=2.5$  cps.), thus revealing the presence of a neighbouring methylene group. The keto-aldehyde on oxidation gave the corresponding crystalline keto-acid,  $C_{15}H_{24}O_3$ .

This same keto-acid could be obtained by chromium trioxide in acetic acid oxidation of the crude rearranged

hydrocarbons from caryophyllene. Thus, most of the acetic acid was removed under reduced pressure on a steam bath, which effected anhydride formation of the clovenic acid present. Mild base extraction and subsequent acidification gave the crude keto-acid, which was then esterified with diazomethane and chromatographed. The relatively pure keto-ester was hydrolysed with base giving the oily keto-acid, which on trituration in light petroleum, was induced to crystallise. This oxidative procedure furnished sufficient pure keto-acid to permit further degradation on a workable scale. That the two keto-acids from the direct and indirect oxidative procedures were identical was substantiated by melting point and mixed melting point, and also by the identity of the two corresponding methyl esters on gas-liquid and thin layer chromatography and infra-red spectra.

A rather anomalous feature was observed in the infra-red spectra of the keto-aldehyde, the keto-acid and the keto-ester. All three compounds, in carbon tetrachloride solution, exhibit three bands in the carbonyl region, viz., for the keto-aldehyde at 1729, 1702 and 1692  $\text{cm}^{-1}$ , for the keto-acid at 1756 (monomer), 1707 (broad) (dimer and ketone) and 1695  $\text{cm}^{-1}$  and for the keto-ester at 1741, 1702 and 1692  $\text{cm}^{-1}$ . There is no question of an impurity being present since the keto-acid melts sharply,

the keto-aldehyde and the keto-ester show one spot on thin layer chromatography and one peak on gas-liquid chromatographic analysis and all three compounds exhibit well-defined N.M.R. spectra. The apparent half-band widths and molecular extinction coefficients of the aldehyde and ester bands at  $1729\text{ cm}^{-1}$  ( $\epsilon_a = \text{ca. } 300, \Delta\nu_{\frac{a}{2}} = 11\text{ cm}^{-1}$ ) and  $1741\text{ cm}^{-1}$  ( $\epsilon_a = \text{ca. } 550, \Delta\nu_{\frac{a}{2}} = 18\text{ cm}^{-1}$ ) respectively, were of the correct order. The band at  $1702\text{ cm}^{-1}$ , however, was low in intensity ( $\epsilon_a = \text{ca. } 250$ ) for a methyl ketone, although taken in conjunction with the band at  $1692\text{ cm}^{-1}$ , it was more consistent with the expected value ( $\epsilon_a = \text{ca. } 600$ ). Since the aldehyde and ester <sup>bands</sup> were completely symmetrical, it seemed unlikely that some sort of intramolecular bonding was responsible for the phenomenon. Two other explanations which appeared feasible were Fermi resonance and rotational isomerism. A preliminary study of the infra-red spectrum of the keto-ester was therefore undertaken to test these hypotheses. The spectrum was insensitive to a change of solvent (hexane and chloroform), thus the possibility of Fermi resonance seemed unlikely. Similarly, rotational isomerism of the methyl ketone group seemed improbable since raising the temperature of the sample (in tetrachloroethylene) to  $75^\circ$  had no effect on the spectrum. This phenomenon, therefore, remains a

mystery, but further spectroscopic work is intended.

As a means of obtaining further information about the environment of the double bond in neoclovene, the keto-ester was subjected to a Baeyer-Villiger oxidation with trifluoroacetic acid<sup>26</sup>. The product derived was the expected acetoxy-ester,  $C_{16}H_{26}O_4$ , whose N.M.R. spectrum revealed that the acetoxy group was tertiary, since there was no resonance in the 5-6 $\tau$  region for a proton(s) on a carbon bearing such a group. In addition, none of the three quaternary methyl groups at  $\tau = 8.81$  (3H), 8.87 (3H) and 8.93 (3H) showed an appreciable downfield shift which would be expected if one or two of them were substituents on the carbon bearing the acetoxy group. Therefore, the partial structure (38) could be derived for neoclovene. Further verification of an unsaturated six-membered ring in neoclovene was obtained by base hydrolysis of the acetoxy-ester and subsequent heat treatment, which gave a crystalline  $\delta$ -lactone,  $C_{13}H_{20}O_2$ ,  $\nu_{C=O}$  1745  $cm^{-1}$ .

In view of the tertiary centre thus encountered in this degradation sequence, it was decided that a method of degradation was required on the monosubstituted side of the double bond. A logical appraisal of this problem demanded a method which would furnish the maximum

information with the least number of chemical reactions.

One method which was considered as being of potential use was the aldol condensation of the above-mentioned keto-aldehyde, which was anticipated to yield the  $\alpha,\beta$ -unsaturated aldehyde rather than the alternative  $\alpha,\beta$ -unsaturated ketone. However, treatment of the keto-aldehyde with 0.2N ethanolic potassium hydroxide gave a plethora of products, none of which could be spectroscopically identified with the desired product.

Another method of apparent promise was that of allylic bromination of neoclovene followed by dehydrobromination to give a homoannular diene. Such dienes, on photolysis, are known<sup>63</sup> to undergo either bond formation to give a bicyclo(2:2:0)hexene system or bond cleavage to a triene. If the triene had been formed, this method would have permitted entry into the bicyclic system. Thus, neoclovene was treated with N-bromosuccinimide in carbon tetrachloride with a catalytic amount of dibenzoyl peroxide. The crude reaction product was then warmed on a steam bath for fifteen minutes in collidine, during which a precipitate of collidine hydrobromide appeared. Spectral data and gas-liquid chromatographic analysis, however, indicated that the predominant compound was the heteroannular diene with only a small amount of the desired homoannular diene.

Allylic oxidation of neoclovene with selenium dioxide in acetic acid and acetic anhydride gave an unsaturated acetate, which, on hydrolysis was converted into a crystalline unsaturated alcohol. That the site of oxidation was on the vinylic methyl group was ascertained from the 2H resonance (slightly split) at 6.09 $\tau$  and an unresolved 1H multiplet at 4.63 $\tau$ . This mode of allylic oxidation is not without precedent (c.f. cedrene<sup>64</sup>) and, in fact, Guillemonat<sup>65</sup> has stated that the allylic carbon atom at the more substituted end of a double bond is preferentially oxidised. The unsaturated alcohol was oxidised to the corresponding  $\alpha,\beta$ -unsaturated aldehyde by neutral manganese dioxide. The N.M.R. spectrum of this compound exhibited a singlet aldehydic proton at 0.66 $\tau$  and a triplet vinylic proton at 3.54 $\tau$  ( $J=4$  cps.). Significantly the two allylic protons near 7.5 $\tau$  were split into at least a six-line multiplet implying neighbouring protons, apart from the vinylic proton. Dehydration of the unsaturated alcohol with p-toluene-sulphonic acid in acetone<sup>66</sup> gave predominantly one diene, whose spectral properties were identical with the heteroannular diene obtained from the allylic bromination sequence.

It was, therefore, apparent that an alternative

degradative approach was required. To this end, the crystalline hydroxy-ester, derived from the acetoxy-ester by hydrolysis and re-esterification was treated with excess phenylmagnesium bromide in the Barbier-Wieland degradation sequence. The resultant crude diol was dehydrated with acetic acid and acetic anhydride under reflux. Purification of the product by chromatography gave a diphenylene-acetate,  $C_{27}H_{32}O_2$ , which could not be induced to crystallise. Attempts at allylic oxidation of this compound with selenium dioxide were fruitless, probably being due to the bulkiness of the two benzene rings. The N.M.R. spectrum of this diphenylene-acetate provided a means of extending the partial structure of neoclovene to (39), by virtue of the fact that the vinylic proton at  $3.89\tau$  was clearly resolved into a triplet ( $J=8$  cps.), demonstrating the juxtaposition of a neighbouring methylene group. The final step in this degradation sequence by ozonolysis did not give a satisfactory yield of the desired nor-acid. In view of the success enjoyed by the use of ruthenium tetroxide in this type of oxidation<sup>67,68</sup>, the diphenylene-acetate was treated with a catalytic amount of ruthenium tetroxide and excess sodium metaperiodate in aqueous acetone. This oxidative procedure gave the desired acetoxy-acid in high

yield, which was hydrolysed with methanolic sodium hydroxide and esterified with diazomethane to the nor-hydroxy-ester,  $C_{13}H_{22}O_3$ .

Since the volatile ruthenium tetroxide was not commercially available and is difficult to prepare, the use of solid ruthenium dioxide, which is oxidised to the tetroxide by sodium metaperiodate, was preferred. The initial sample of ruthenium dioxide purchased from Johnson and Matthey proved to be almost completely inert to oxidation with sodium metaperiodate. Amicable correspondence with the manufacturers, however, revealed that only ruthenium dioxide prepared by the controlled dehydration of ruthenium hydroxide reacted with sodium metaperiodate, whereas the commercially available dioxide, prepared by oxidation of ruthenium sponge, did not. This phenomenon must surely be due to two physical forms of the dioxide?

The nor-hydroxy-ester was treated under exactly analogous conditions to yield a crystalline nor-diphenylene acetate,  $C_{26}H_{30}O_2$ . This time the N.M.R. spectrum showed a sharp singlet for the vinylic proton at  $3.62\tau$ , indicative of a neighbouring quaternary centre. The fact that one of the quaternary methyl groups at  $8.65\tau$  had moved downfield on going from the diphenylene-acetate

(whose lowest methyl group value was at 8.78 $\tau$ ) to its lower homologue, suggested that one of the substituents at this quaternary centre was a methyl group. This assumption was only tentative since a deshielding effect of a remote methyl group could have been due to a particular orientation of one or both benzene rings in the flexible side chain.

Repetition of the ruthenium dioxide/sodium metaperiodate oxidation gave the corresponding bis-nor-hydroxy-acid, which was then esterified with diazomethane to the corresponding bis-nor-hydroxy-ester,  $C_{12}H_{20}O_3$ . The observation that extraction of the acidic product from the oxidation of the diphenylene acetate with 2N sodium hydroxide gave the nor-acetoxy-acid is in contradistinction to that observed in the case of the nor-diphenylene-acetate, which yielded the bis-nor-hydroxy-acid. Although this has not been rigorously proved, it is not improbable since a carboxylate anion participation in hydrolysis of the acetoxy group could be operative via the mixed anhydride, which would then be readily hydrolysed, as shown in (40).

Again a downfield shift to 8.64 $\tau$  of one of the quaternary methyl groups was observed in this series of homologous hydroxy-esters (the lowest value in the two higher homologues was 8.83 $\tau$  and 8.88 $\tau$  respectively). A

similar argument as mentioned before for the homologous diphenylene-acetates, based on the deshielding effect of a carbonyl group can be proffered, but did not appear to be so likely. Therefore, with the new evidence in hand, the partial structure of neoclovene could be expanded to (41).

The problem at that stage was to devise a means of breaching the remaining bicyclic system. In view of the undoubted 1,3 relationship between the two functional groups, it was decided that a retro-Prins reaction, so elegantly utilised in Corey's synthesis of caryophyllene<sup>61</sup>, was ideal for the purpose. Accordingly, the bis-nor-hydroxy-ester was smoothly converted to a crystalline primary-tertiary diol,  $C_{11}H_{20}O_2$ , by lithium aluminium hydride reduction. The N.M.R. and infra-red spectra of this diol exhibited some interesting features.

In addition to the three quaternary methyl groups at  $\tau = 8.66$  (3H), 8.81 (3H) and 8.98 (3H), the N.M.R. spectrum showed an ill-resolved 1H doublet at 5.95 $\tau$  ( $J=11-12$  cps.) and a very broad 1H resonance at 6.3 $\tau$  (base width ca. 40 cps.). The effect of adding a drop of  $D_2O$  to the N.M.R. sample in deuteriochloroform was quite remarkable. Not only did the 2H signal at 7.4 $\tau$  (due to the two hydroxyl protons) disappear, but the broad resonance at 6.3 $\tau$  became a very sharp doublet, centred at 6.36 $\tau$  ( $J=11.5$  cps.). The doublet

at 5.95 $\tau$  ( $J=11.5$  cps.) also sharpened up but still showed slight signs of coupling (probably long-range). This same phenomenon was observed when one drop of 6N hydrochloric acid was added to the solution of the diol, although the doublet at 6.36 $\tau$  was not quite so well resolved as in the case with D<sub>2</sub>O. The fact that addition of acid gave the anticipated AB quartet seems to indicate that the rate of exchange of the primary hydroxyl proton is extremely slow (less than 5 times per second) which, in turn, might permit strong coupling with one of the methylene protons (at 6.36 $\tau$ ) and only weak coupling with the other (at 5.95 $\tau$ ). This would be particularly valid if the primary hydroxyl proton was 'held' by an intramolecular hydrogen bond in an orientation favourable for maximum coupling (i.e. 0° or 180°).

The infra-red spectrum of the diol, in a fairly concentrated carbon tetrachloride solution, showed four bands in the hydroxyl region, viz., at 3640, 3614, 3553 and 3400 cm.<sup>-1</sup>. This latter band disappeared completely on dilution, whereas the band at 3553 cm.<sup>-1</sup>, due to intramolecular hydrogen bonding did not vary appreciably. The  $\Delta\nu$  value of 87 cm.<sup>-1</sup> is characteristic of 1,3 diols<sup>69</sup> and will be referred to later in this discussion.

According to the proposed scheme, the diol was

converted into the monotosylate in the usual manner. Treatment of this derivative at room temperature with the strongly basic sodium salt of methylsulphinyl carbanion (dimethyl sodium), generated from dimethyl sulphoxide and sodium hydride<sup>70</sup>, gave an 80% yield of an unsaturated ketone, C<sub>11</sub>H<sub>18</sub>O. The infra-red spectrum of this ketone exhibited a carbonyl band at 1720 cm.<sup>-1</sup> and a strong band at 897 cm.<sup>-1</sup>, which were indicative of a six-membered ketone and an exomethylene group respectively. The ultra-violet spectrum showed no absorption for an  $\alpha,\beta$ -unsaturated carbonyl chromophore. The N.M.R. spectrum verified the presence of an exomethylene group at 5.04 $\tau$  and 5.23 $\tau$  (2H). The presence of a vinylic methyl group was also adduced from the barely resolved doublet at 8.19 $\tau$  (J=ca.1 cps.), thus confirming the postulate of a methyl group attached to the carbon bearing the homologous side chain. Two quaternary methyl groups at 8.98 $\tau$  and 9.10 $\tau$  indicated that this ketone was an isopropenyl-dimethylcyclohexanone. This latter information uniquely defined a gem-dimethyl grouping in neoclovene, a fact which had hitherto not been verified, although a doublet in the infra-red spectra, in the 1380-1360 cm.<sup>-1</sup> region, had been observed in various degradation products of neoclovene.

Catalytic hydrogenation of this unsaturated ketone

yielded the corresponding dihydro derivative,

$\nu_{\text{C=O}}$  1718  $\text{cm}^{-1}$ . The N.M.R. spectrum of this ketone showed overlapping methyl resonances at  $\tau = 8.94$  (3H), 9.14 (3H), 8.99 (3H) ( $J=7$  cps.) and 9.16 (3H) ( $J=7$  cps.). These methyl resonances were unravelled by an application of the known coupling constant ( $J=6-8$  cps.) for a secondary methyl group and also from the known dissymmetry of this doublet (the less intense half being on the high field side).

With this information at hand, the partial structure of neoclovene could be extended to (42). Since there are sixteen carbon atoms in this partial structure, two of them must be common. A permutation of the possible ways of deriving a  $\text{C}_{15}$  skeleton uniquely defines ten (i.e.  $\frac{5!}{3!2!}$ ) possible gross structures for neoclovene i.e. (43-52). Those containing a cyclopropane ring (43-46) were immediately eliminated on two counts. Firstly, it was most unlikely that a cyclopropane would be generated or survive in an acid-catalysed rearrangement and secondly no evidence was obtained for a cyclopropyl proton in the N.M.R. spectra of all the compounds so far examined. The remaining six structures (47-52) were compatible with the evidence so far obtained, albeit mechanistically puzzling. Unfortunately, the isoprene rule does not usually hold for sesquiterpene artefacts!

In turn, the six isomeric isopropyldimethylcyclohexanones (53-58) were the possible degradation products of the last reaction. The three structures (55,56 and 57) with the gem-dimethyl group  $\alpha$  to the carbonyl function were unlikely in view of the approximate integration for four protons in the 7.7-8.0  $\tau$  region of the N.M.R. spectrum of the saturated ketone. This was corroborated by an examination of the infra-red spectrum which exhibited two fairly intense bands at 1429 and 1419  $\text{cm}^{-1}$ , attributable to two different groups of methylene protons  $\alpha$  to the carbonyl function<sup>71,72</sup>.

The mass spectrum of the saturated ketone was rather more informative than we had anticipated. Large peaks at 55,69 and 83 m/e were observed and these were shown by a high resolution spectrum to be mostly oxygen containing fragments. By analogy with other substituted cyclohexanones<sup>73</sup>, formulae (59), (60) and (61) could be assigned to these fragments with reasonable certainty ; these fragments can be readily derived from (58), as shown. An inspection of the predicted fragments derivable from the other possibilities (53-57) for the saturated ketone, indicated that they were less likely. It was also observed that the saturated ketone showed a marked tendency to aromatise when the hot-box inlet

system in the mass spectrometer was higher than ca. 150<sup>0</sup>, as witnessed by the peaks at 91, 105 and 106 m/e. At ca. 100<sup>0</sup>, these three peaks were of negligible intensity.

Recently Djerassi<sup>74</sup> and Fétizon<sup>75</sup> have elegantly demonstrated that ketals and thioketals fragment to a series of predominant charged species in a predictable fashion. The mechanism of this fragmentation, which has received experimental verification by deuterium labelling techniques, is illustrated in Fig. (I). The rationale for this direction of fragmentation has been attributed to the ability of the two adjacent heteroatoms to stabilise the positive charge after homolytic fission of the carbon-carbon bond adjacent to the functional group. In this context, it was of great significance that Fétizon<sup>75</sup> had studied the mass spectra of various substituted cyclohexanone ketals, some of which are shown in Fig. (II).

It was, therefore, decided that this method would provide an unequivocal solution to the problem at hand. The mass spectrum of the ketal, prepared from the degraded, saturated ketone in the usual manner, exhibited two predominant peaks at 99 and 127 m/e, a result only consonant with structure (58). This, in turn, unequivocally established the gross structure of neoclovene as (52)<sup>76</sup>. This result was most gratifying in view of the

Fig. I

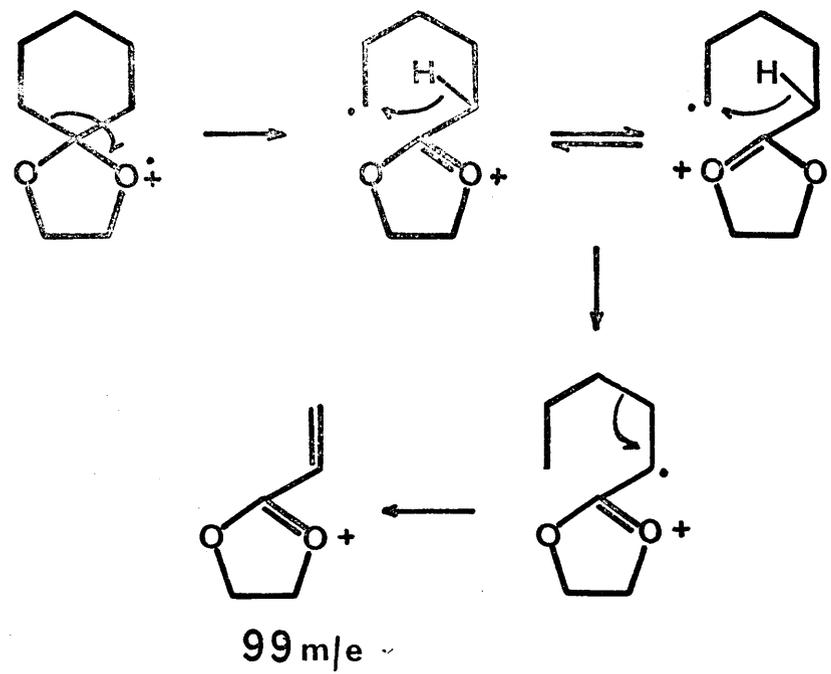
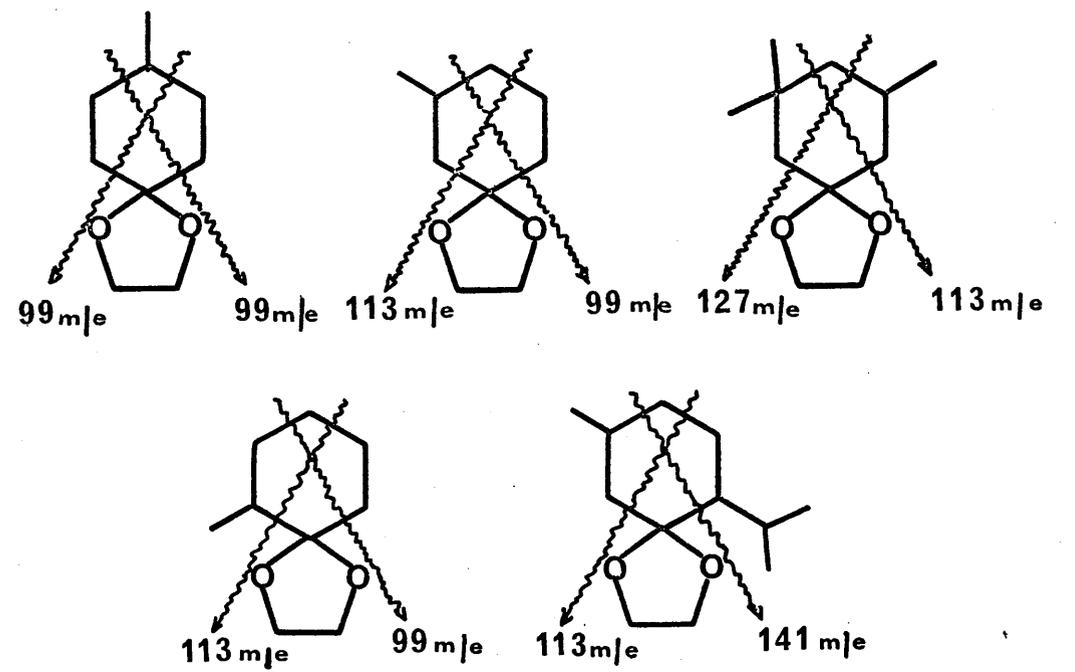


Fig. II



fact that we had by this time formulated a mechanism for the formation of neoclovene from caryophyllene which predicted such a structure for the degraded ketone.

Although there was virtually no doubt about the structure of this isopropylidimethylcyclohexanone, a successful synthesis was accomplished in the following manner. A Friedel-Crafts acylation of m-methyl anisole with acetic anhydride and aluminium chloride gave 2-methyl-4-methoxy acetophenone (62)<sup>77</sup>, which on methylation with methylmagnesium iodide and dehydration yielded 1-methyl-3-methoxy-6-isopropenyl benzene (63). This compound on hydrogenation, Birch reduction and subsequent acid hydrolysis gave a good yield of 3-methyl-4-isopropyl cyclohex-2-ene-1-one (64). Apart from distillation, no exacting purification methods had been used up to this point in the synthesis. Thin layer chromatographic analysis of the unsaturated ketone, however, indicated one major component and a less polar minor component. Careful chromatographic separation furnished the minor component (ca.10%), which was identified as piperitone (65) by infra-red spectrum and thin layer and gas-liquid chromatographic behaviour. This observation can only mean that the by-product in the Friedel-Crafts reaction was the isomeric 1-methoxy-

4-methyl acetophenone (66). The conjugate addition of methylmagnesium iodide was accomplished, albeit in poor yield (20%), by addition of the unsaturated ketone (64) in tetrahydrofuran containing cupric acetate to the Grignard solution as described by Birch<sup>78</sup>. Careful thick plate chromatography furnished the pure racemic, saturated ketone (58), which was identical in all respects with the degraded ketone (infra-red and mass spectra and gas-liquid chromatography on six columns).

The mechanism proposed, as shown, for the formation of neoclovene from caryophyllene involves an initial isomerisation of the exocyclic double bond at C<sub>8</sub> to the endocyclic tetrasubstituted double bond. A model of this diene (67) indicates that in a certain conformation there is maximum overlap of the  $\pi$ -electrons of the two double bonds, which would permit a Markownikoff cyclisation to the tricyclic cation (68). This cyclisation mode is reminiscent of that observed in the epoxy-ketone (20) giving the ketol (21), in which the carbanion at C<sub>9</sub> is the nucleophilic agent. A Wagner-Meerwein rearrangement of this cation (68) generates the tertiary bridged cation (69). This cation is not unlike that (i.e. 70) proposed<sup>79</sup> as an intermediate in the longifolene-isolongifolene rearrangement<sup>80</sup>, as shown in Fig. (III).

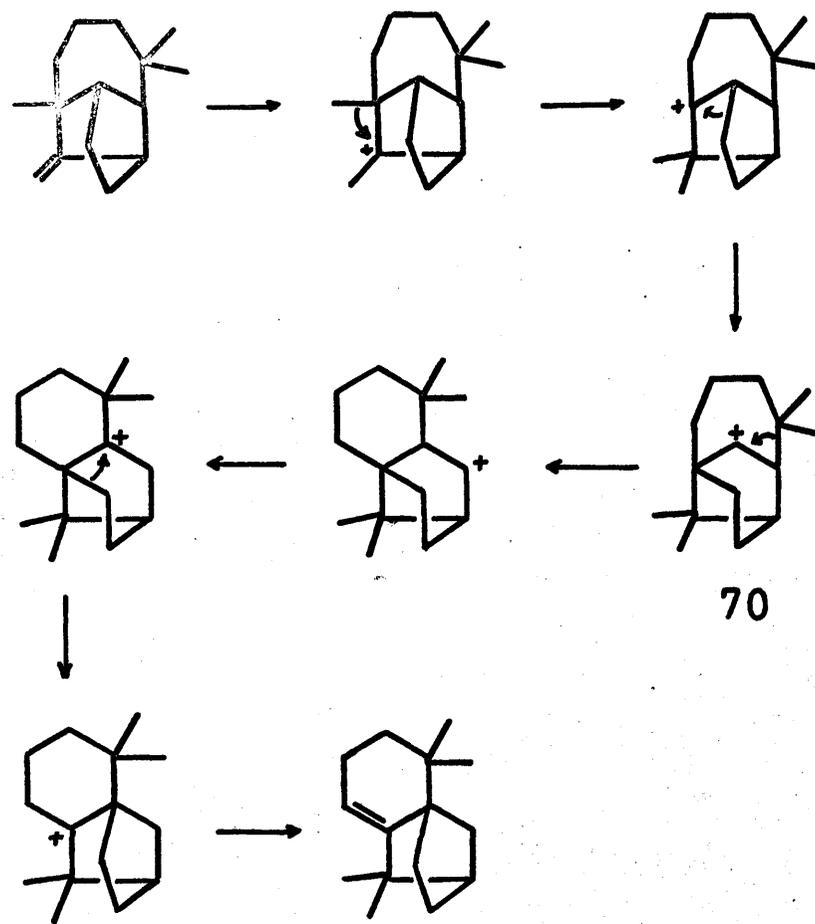


Fig. III

A final Wagner-Meerwein shift and subsequent loss of a proton generates neoclovene (71) with the stereochemistry shown. Whether these proposed shifts are concerted or not is debatable.

A point of interest in connection with this proposed mechanism is the location and number of deuterium atoms incorporated into neoclovene when the acid-catalysed rearrangement of caryophyllene is carried out in concentrated deuteriosulphuric acid. This has, as yet, not been carried out, but certain predictions can be made. In the first place, the quaternary methyl group at C<sub>7</sub> should contain one deuterium atom, which would be introduced at the initial isomerisation of the exocyclic double bond. One deuterium atom will also be incorporated at C<sub>5</sub> in the formation of the tricyclic cation (68). Depending on the stereochemistry of the latter deuterium atom, and perhaps on an isotope effect, it may be eliminated in the final neutralisation of the tertiary cation (69). It is intended to resolve this problem in the near future.

The final problem in the chemistry of neoclovene is one of stereochemistry. With the knowledge of the absolute stereochemistry of caryophyllene<sup>6</sup> and the assumption that the postulated mechanism of formation of neoclovene

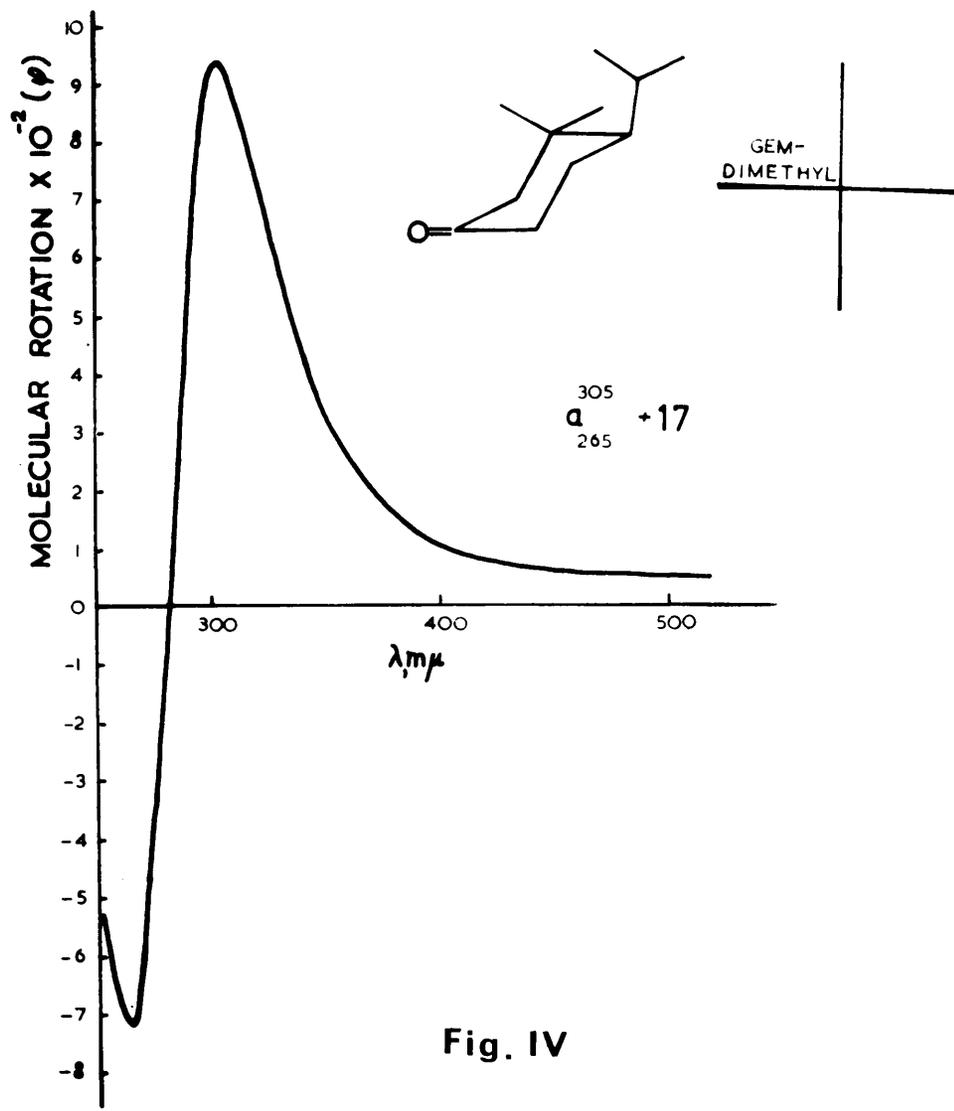


Fig. IV

was correct, which did not involve the asymmetric centre at  $C_1$  of caryophyllene, we were able to predict the sign of the Cotton effect of the degraded ketone by an application of the Octant Rule<sup>81</sup>. It was most satisfying to learn that our prediction of a positive Cotton effect was experimentally determined from an optical rotatory dispersion curve\*, as shown in Fig.(IV). This observation, therefore, defined the absolute stereochemistry of neoclovene. However, there was, and still is, one outstanding problem yet to be solved, namely the relative stereochemistry of the quaternary methyl group at  $C_7$  in relation to the gem-dimethyl group at  $C_5$ . The postulated mechanism predicts that these groups are syn to one another. In view of the success of the O.R.D. of the degraded ketone, it was expected that this final problem could be solved in a similar manner, viz., from the O.R.D. curve\* of the tricyclic ketone derived from neoclovene by hydroboration and oxidation. Applying the same premises to our arguments mentioned above, a negative Cotton effect was predicted. To our disappointment, the observed amplitude of the O.R.D. curve was only -1!

\*We are very grateful to Professor W. Klyne, Westfield College, for determining the O.R.D. curves of these ketones.

An explanation of this apparent enigma can be sought in terms of a non-chair conformation of the six-membered ring of the tricyclic ketone. Indeed, an examination of models indicates that a twist form of this ring, incurred without much additional strain, would bring the bulk of the bicyclic system into the lower right quadrant, thus imparting a positive contribution. This deformation would also bring the  $\alpha$  equatorial methyl group into a negative quadrant. Although it is generally accepted<sup>82</sup> that the contribution from substituents decreases rapidly with distance, no direct correlation has been formulated. Thus, a prediction of the Cotton effect is much less satisfactory than in the case of the simple degraded ketone.

Therefore, to complete the stereochemical assignment of neoclovene, other less ambiguous methods will have to be used. Before suggesting the possible ways in which this could be done, it is important to tabulate the results so far obtained which could conceivably indicate the syn relationship of the methyl groups in question. These observations, however, do not in themselves carry sufficient weight to justify their use in assigning the relative stereochemistry.

In all the infra-red spectra of the compounds so

far examined, prior to cleavage of the bicyclic system, two weak bands were observed in the 3010-2990 and 1499-1489  $\text{cm}^{-1}$  regions. Although slightly higher (+5-10  $\text{cm}^{-1}$ ), these bands are very reminiscent of the same two bands observed in the bicyclo(3:3:1)octane system (72), which has been extensively studied in the laboratories at Glasgow<sup>83</sup>. These bands have been uniquely ascribed to the  $\text{C}_3$ - $\text{C}_7$  methylene interaction in the preferred twin-chair conformer by deuteration and X-ray studies. An examination of a model of neoclovene reveals that no analogous methylene interaction is present, so that the observed phenomenon may be attributed to the proximity of the  $\text{C}_7$  methyl group with the exo  $\text{C}_5$  methyl group. This, however, is purely speculative since no precedent has been recorded in the literature.

The second point is the  $\Delta\nu$  value of 87  $\text{cm}^{-1}$ , observed in the primary-tertiary diol (vide supra). If it is assumed that trans-2-hydroxymethyl-trans-4-t-butylcyclohexanol (73) and cis-2-hydroxymethyl-trans-4-t-butylcyclohexanol (74)<sup>84</sup> are reasonably good analogies for comparison, the  $\Delta\nu$  value of 94  $\text{cm}^{-1}$  for (73) is closer than that of 77  $\text{cm}^{-1}$  for (74). Of perhaps even greater significance is the fact that (73) exhibits two free hydroxyl bands at 3631 and 3622  $\text{cm}^{-1}$ , whereas (74)

only shows one free hydroxyl band at  $3625\text{ cm}^{-1}$ . This is taken to mean that in the case of (74), the predominant bonded species is (74a), whereas in the case of (73), there is an equilibrium between the two bonded species, viz., (73a) and (73b). This has also been found<sup>85</sup> in the steroid diols (75) and (76). (75) exhibits only one free hydroxyl band at  $3629\text{ cm}^{-1}$  and (76) shows two free hydroxyl bands at  $3643$  and  $3628\text{ cm}^{-1}$ . Thus the predominant bonded species are as shown. As stated before, these two points in favour of the syn relationship of the methyl groups could only be used as corroborating evidence in the light of the known relative stereochemistry.

Therefore, the only satisfactory method of solving this problem would be either an unambiguous synthesis of neoclovene or one of its degradation products, or an X-ray analysis of a suitable heavy atom derivative. To date, two such derivatives have been made, viz., the osmium tetroxide/pyridine complex of neoclovene and the monobrosylate of the diol derived from neoclovene by osmylation, but neither of these compounds were suitable for X-ray analysis. However, it should be possible to form other heavy atom derivatives, e.g. the monobrosylate of the  $\text{C}_{11}\text{H}_{20}\text{O}_2$  diol, which might be suitable.

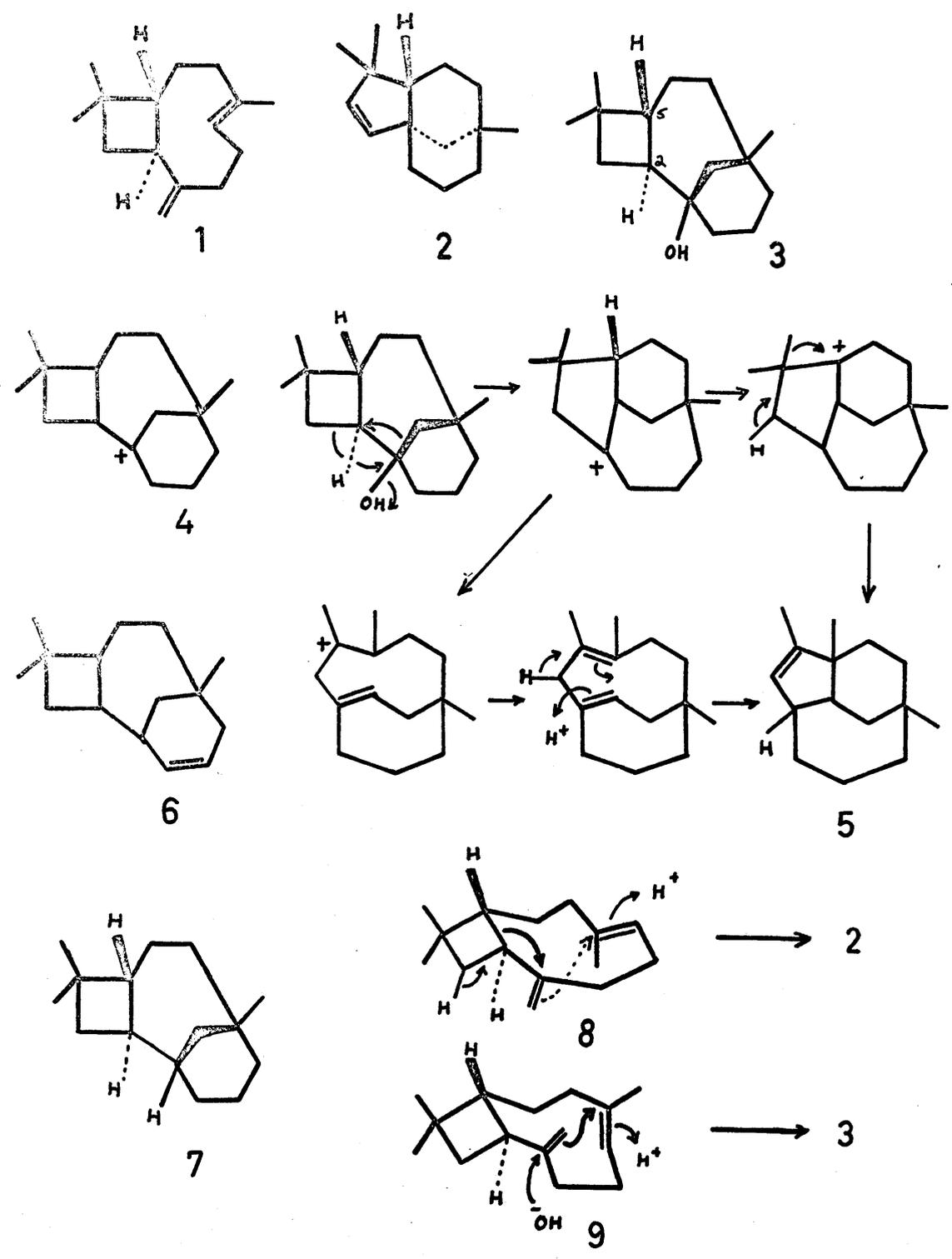
A logical precursor for the synthesis of a

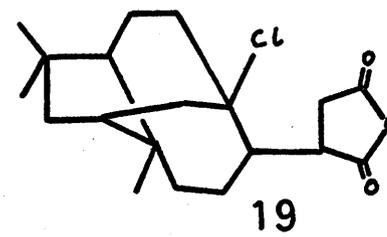
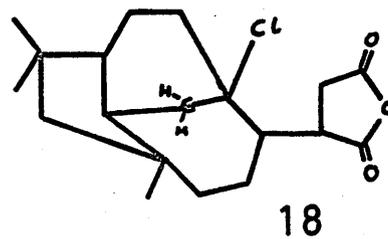
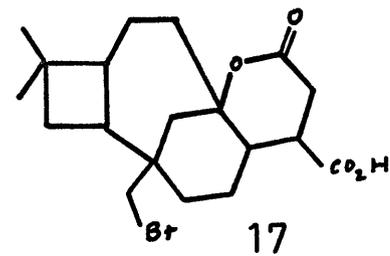
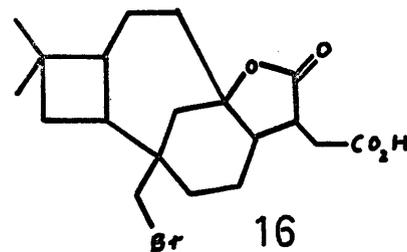
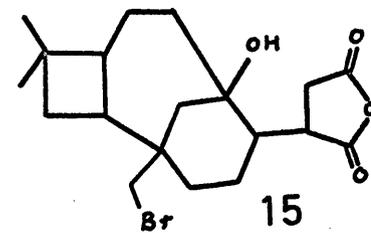
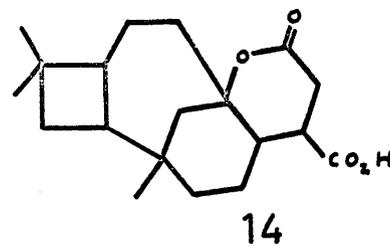
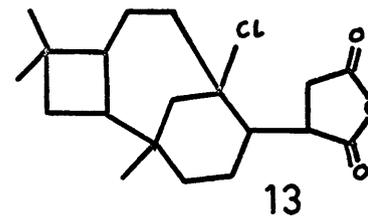
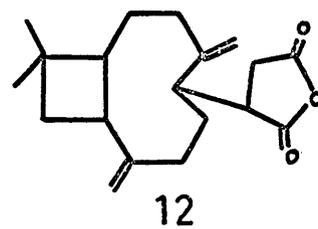
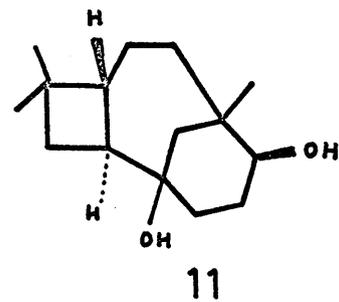
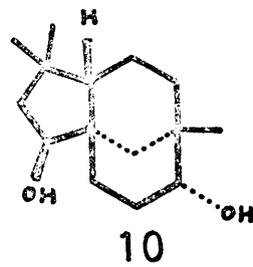
degradation intermediate of neoclovene would be the known 9-hydroxycamphor<sup>86</sup>, which, by dimethylation and Wolff-Kishner reduction would give (77). This same compound could conceivably be derived from the keto-ester (85, R=CO<sub>2</sub>CH<sub>3</sub>). Thus, an iodoform reaction would give the acid-ester (86, R=CO<sub>2</sub>CH<sub>3</sub>, R'=CO<sub>2</sub>H), which, on treatment with phenylmagnesium bromide, would yield the diphenylene-acid (93, R=CO<sub>2</sub>H). This acid on esterification and subsequent lithium aluminium hydride reduction would give the hydroxymethyl derivative (93, R=CH<sub>2</sub>OH), which on tosylation and hydride reduction would generate a methyl group at C<sub>1</sub>. This compound could then be elaborated via the same degradation sequence outlined for neoclovene to yield the alcohol (77).

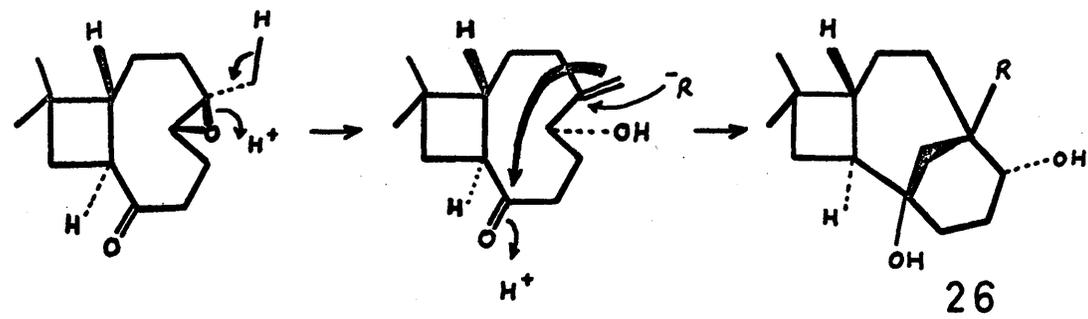
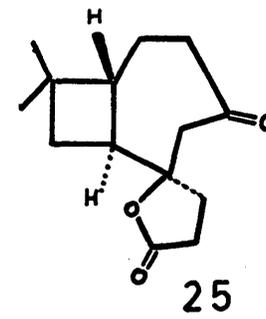
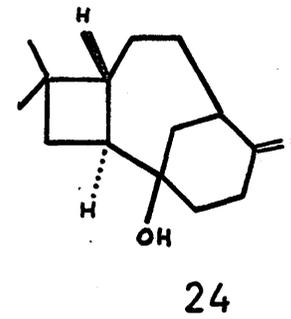
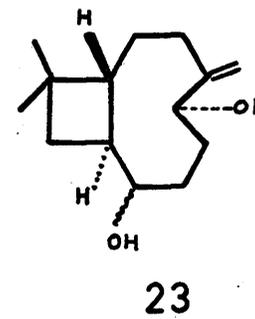
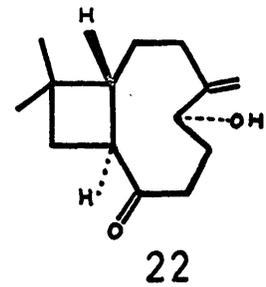
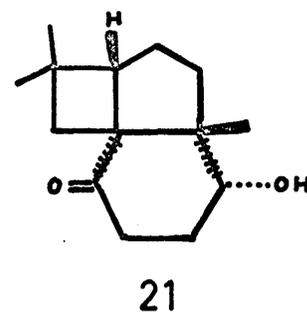
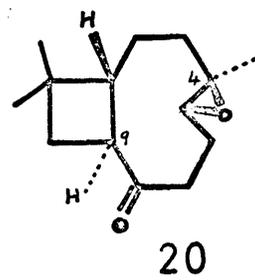
Although a 'classical' synthesis of neoclovene has, as yet, not been visualised, utilisation of Treib's epoxy-ketone (20) is potentially very fruitful. As mentioned before this compound on base treatment gives the tricyclic ketol (21). Consideration of the skeletal identity of this rearrangement product with the cationic intermediate (68) in the proposed genesis of neoclovene, suggests that it is ideally suited for a synthesis of neoclovene. Thus, removal of the hydroxyl group by some means and treatment with methylmagnesium iodide

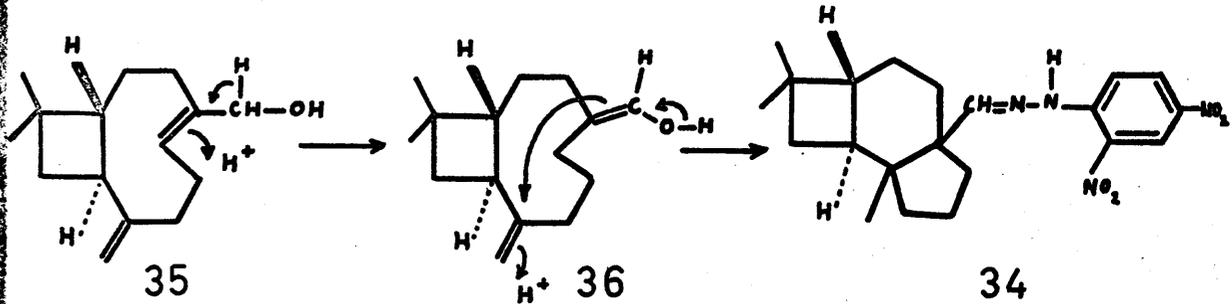
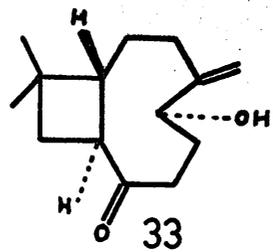
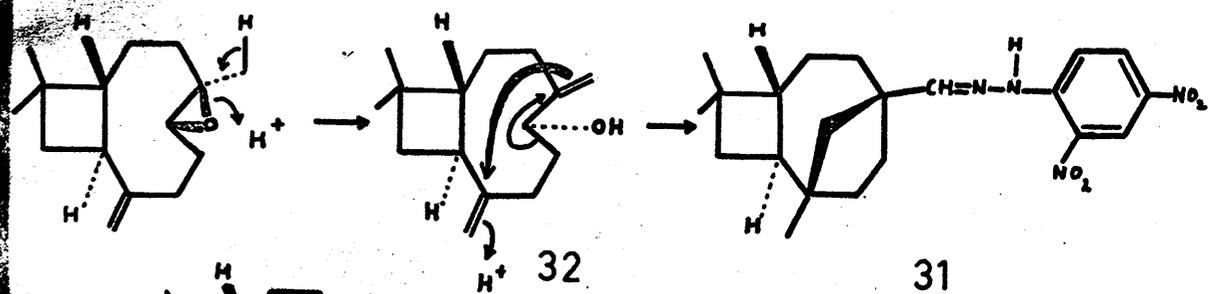
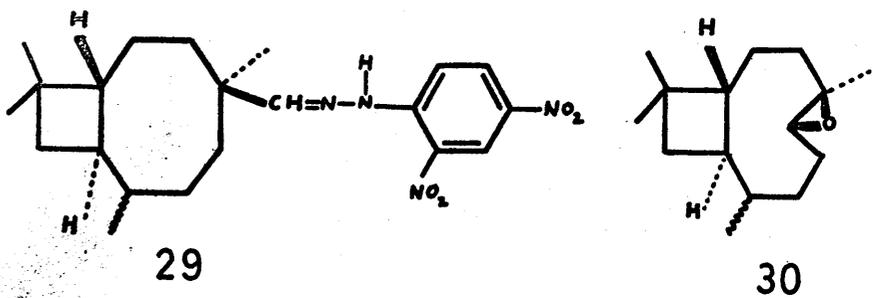
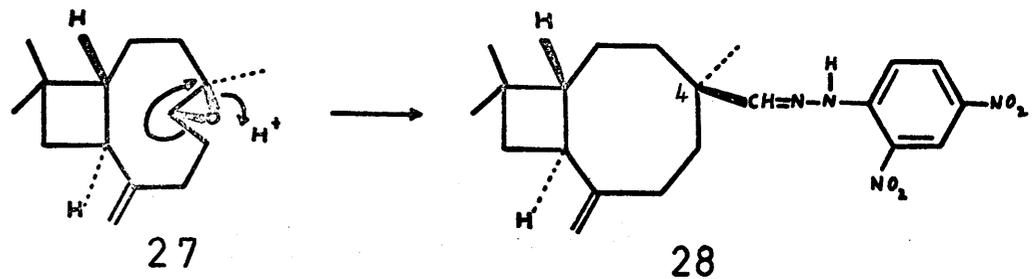
would yield the tertiary alcohol (78). This neopentyl alcohol should be the precursor of the cation (68), which, if the mechanism is correct, should undergo the analogous Wagner-Meerwein rearrangements on treatment with acid to yield neoclovene. Preliminary results indicate that the removal of the hydroxyl group is attended by certain difficulties, since lithium aluminium hydride reduction of the corresponding ketotosylate gave the cyclic ether (79), while dehydration with phosphorus oxychloride in pyridine gave a complex mixture of products. Nevertheless, it should be possible to overcome this problem by other means and at present work is being directed towards this goal.

To conclude, in view of the seemingly endless variety of transformation products derivable from the caryophyllene nucleus, it is felt that an apt motto for caryophyllene would be the Scots adaptation of "Nemo me impune lacessit" which is "Wha daur meddle wi' me".

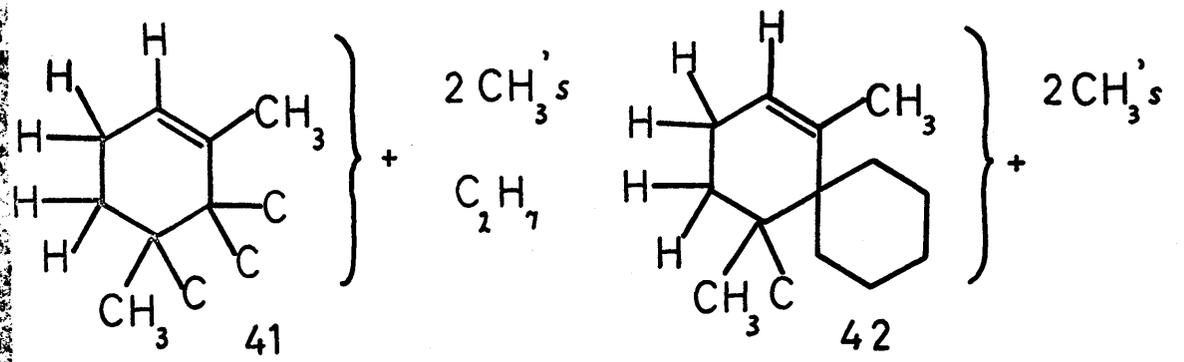
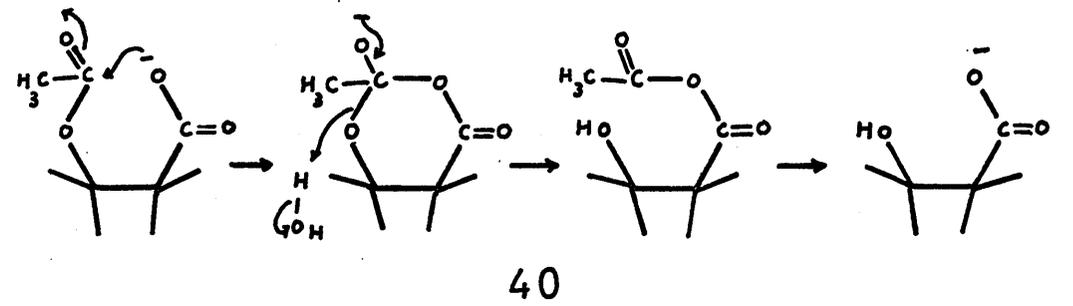
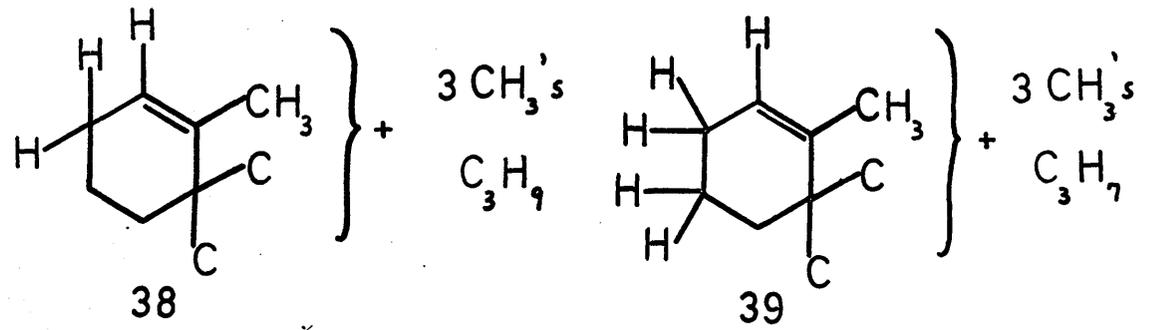
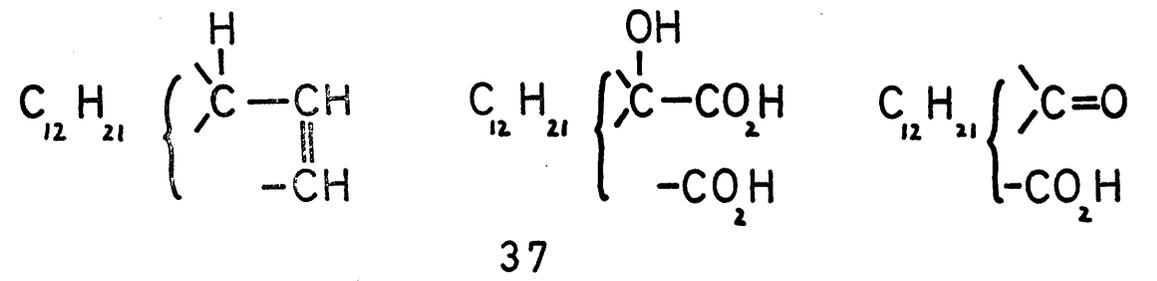


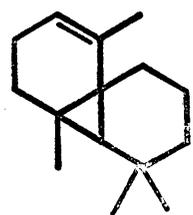




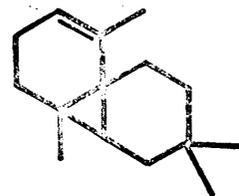


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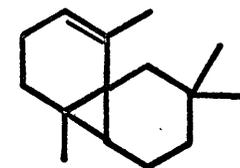




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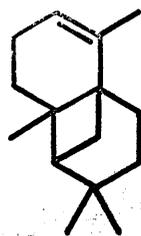
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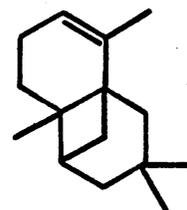
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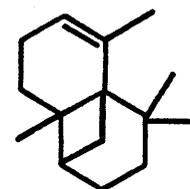
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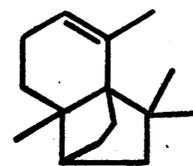
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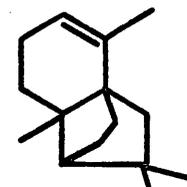
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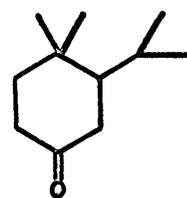
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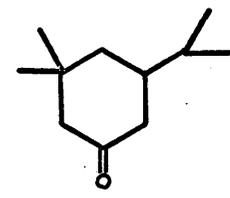
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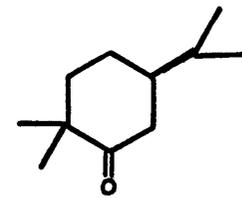
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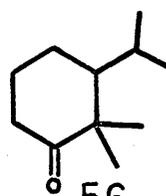
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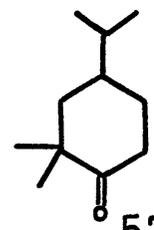
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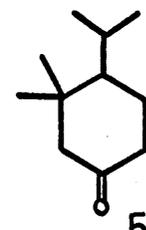
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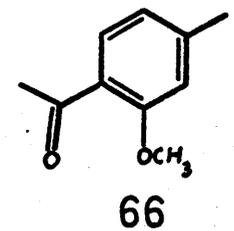
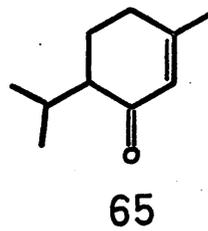
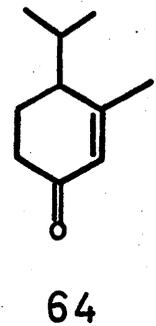
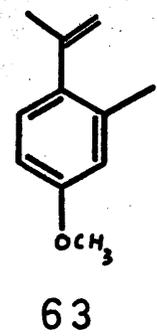
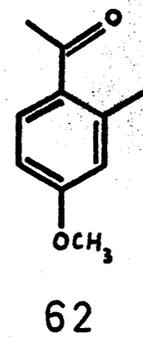
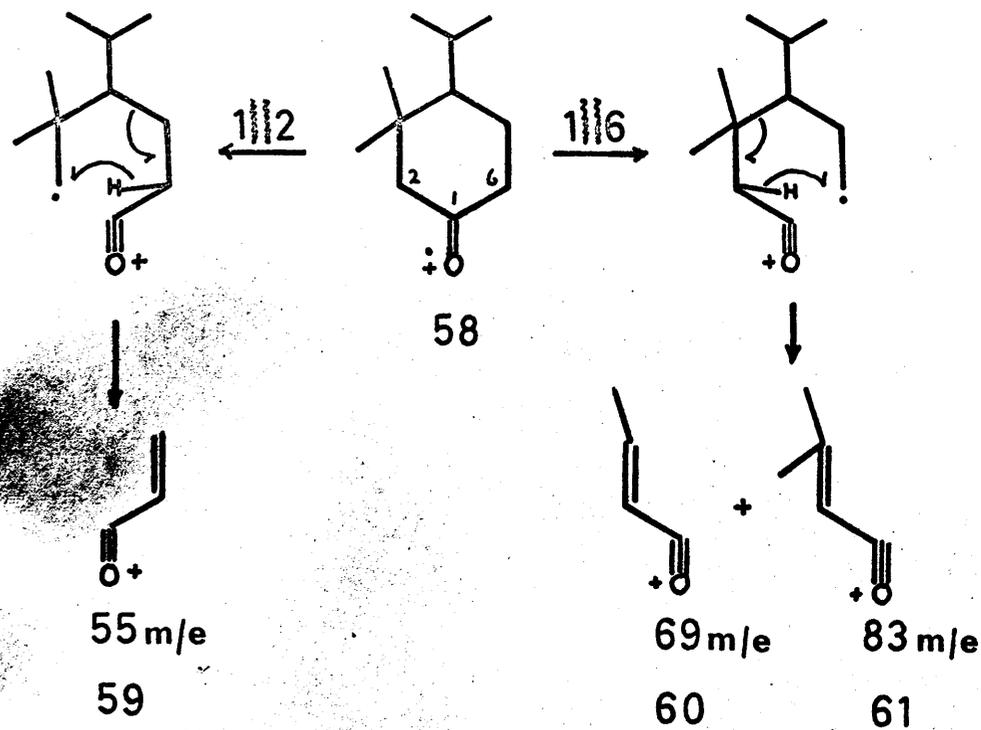
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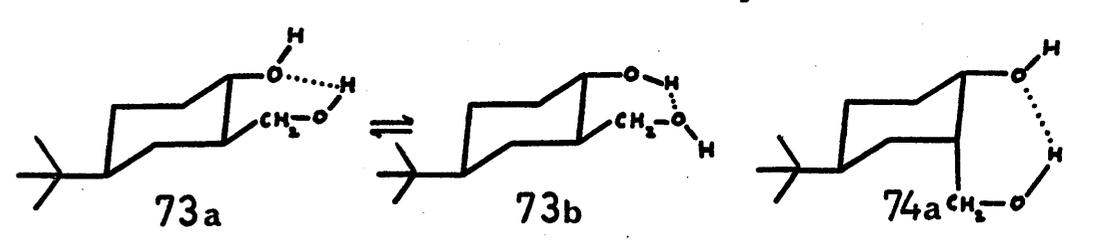
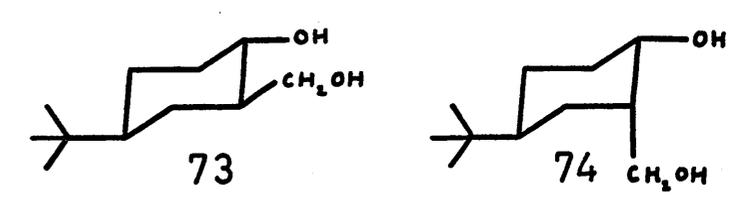
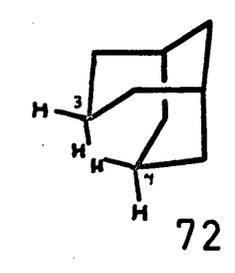
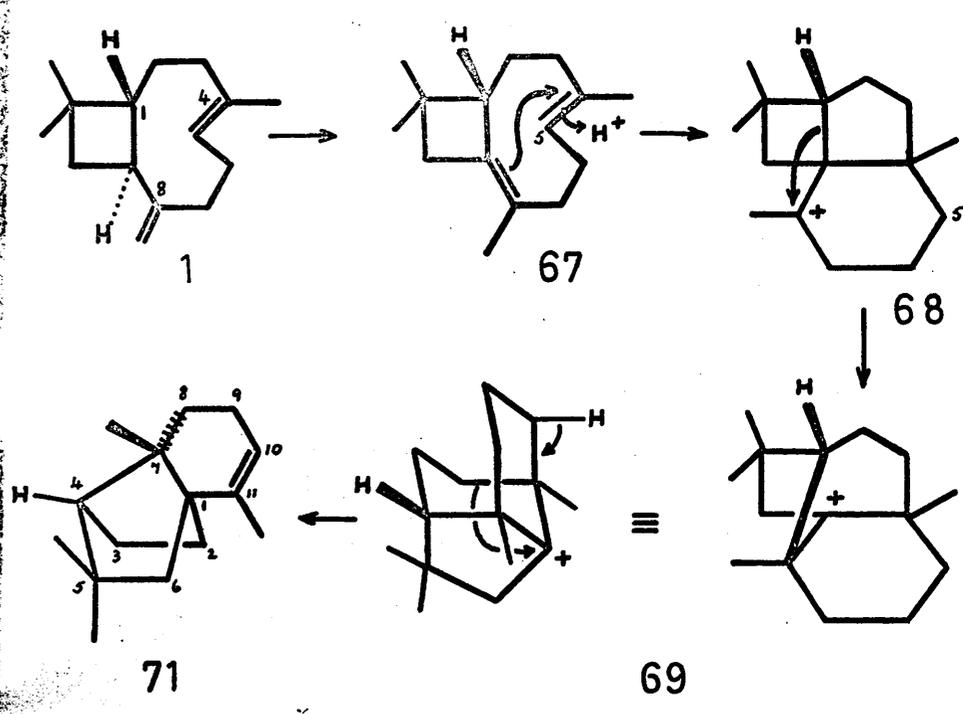


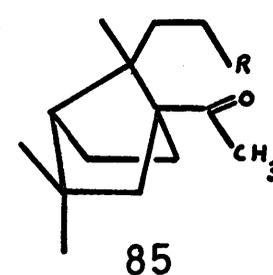
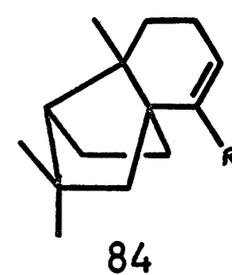
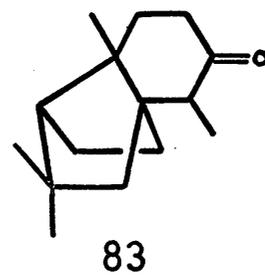
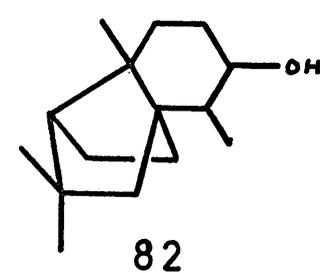
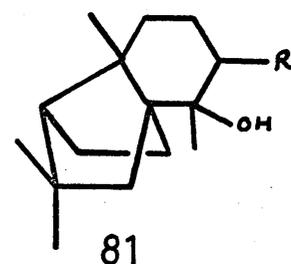
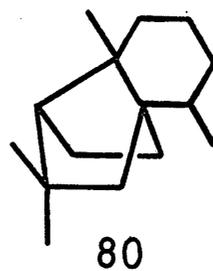
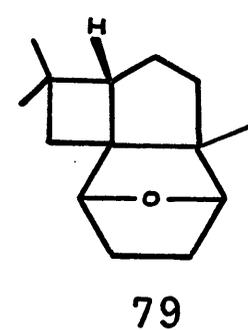
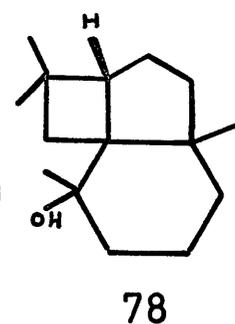
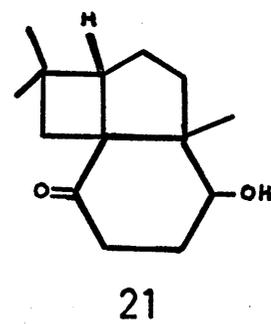
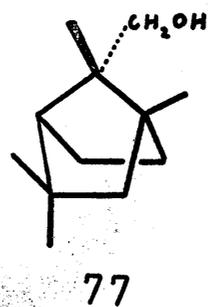
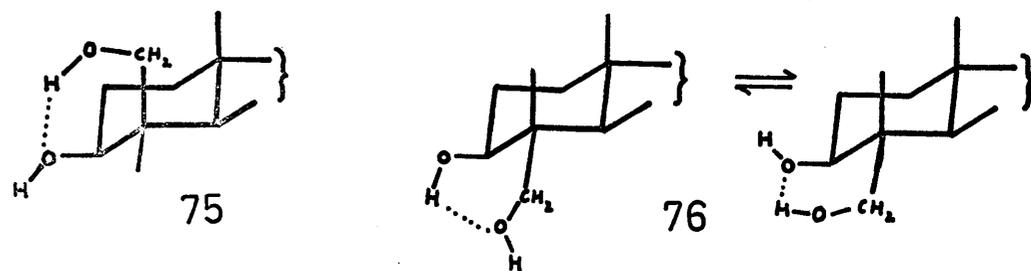
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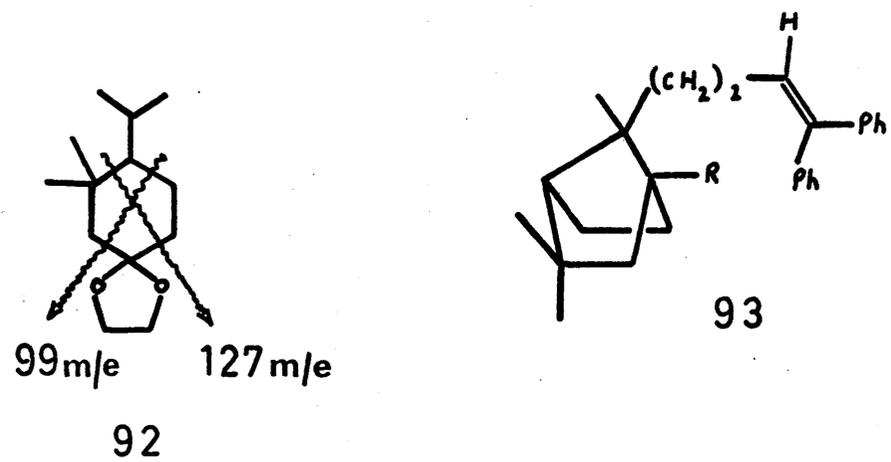
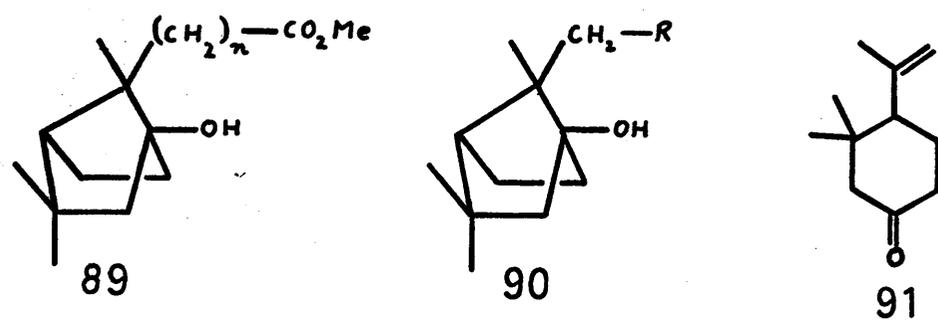
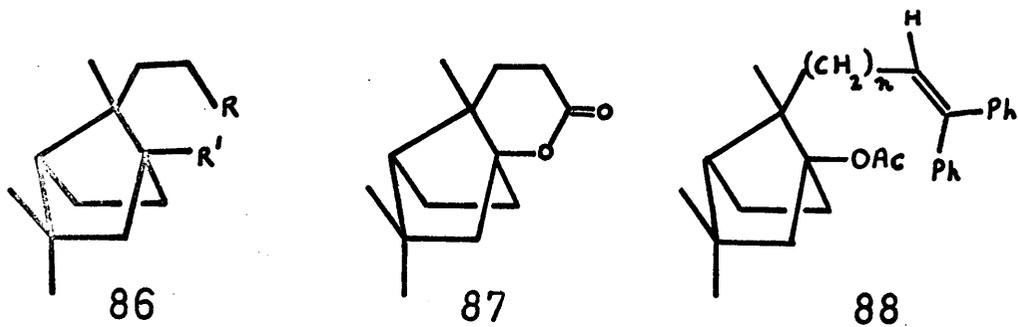


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## EXPERIMENTAL.

Caryophyllene was purified by the same procedure as described in the experimental section of  $\alpha$ -caryophyllene alcohol.

### Acid-Catalysed Rearrangement of Caryophyllene.

Concentrated sulphuric acid (36gm.) was added dropwise to anhydrous ether (68ml.) at 0°. Pure caryophyllene (120gm.) was then added dropwise to this solution at such a rate that the temperature did not rise above 10°. The solution was allowed to stir for 20 hours, and then made alkaline with aqueous sodium hydroxide solution and exhaustively steam distilled. The steam distillate was saturated with brine and thoroughly extracted with ether, the organic extract dried and subsequent removal of the solvent under reduced pressure yielded an oily solid (88gm.).

This material was adsorbed on alumina (Grade H) (2.4Kgm.) and elution with light petroleum gave the crude hydrocarbon rearrangement products (40gm.)

Analytical gas-liquid chromatography on the following columns showed two predominant peaks, which represented 90% of the hydrocarbon mixture.

Column	Temperature (°C)	Carrier Gas Flow Rate(ml./min.)	Retention Time(mins.)
25% APL	175	82 (Argon)	12.4, 19.5
20% TCEP	75	62 (Argon)	8.2, 17.3
10% Ucon Polar (10' X $\frac{1}{8}$ ")	147	20 (Nitrogen)	28.4, 49.0
3% Tricresyl Phos- phate (5' X $\frac{1}{8}$ ")	110	20 (Nitrogen)	8.9, 16.0

Preparative Gas-Liquid Chromatographic Separation of  
Neoclovene (71).

The Aerograph 'Autoprep' A-700 was adjusted for automatic injection and collection after the conditions for the best separation had been determined manually.

Conditions :-

20' X  $\frac{3}{8}$  " 10% Ucon Polar column on Chromasorb 60-80W ; Helium flow rate 163 ml./min. ;  
Injector temperature 197°; Detector temperature 186°; Collector temperature 158°; Column temperature 162°; Sample size 100 $\mu$ l of neat mixture.

Retention Time of clovene = 15.5 minutes.

Retention Time of neoclovene = 24 minutes.

Each sample of neoclovene was checked for purity on an analytical column and the purest samples (ca.99% pure) were combined and distilled (3.9gm.), b.p. 52°/0.03mm. ;

$n_D^{20}$  1.5088 ;  $[\alpha]_D^{20}$   $-72.0^\circ$  ( $c$ , 1.78 in  $\text{CHCl}_3$ ) ;  $\nu_{\text{max.}}$  (liq. film) = 3023, 1657, 1383, 1376, 1362, 838, 812, 788 and  $771 \text{ cm}^{-1}$  ;  $\tau$  = 4.91 (1H) (broad), 8.41 (3H) ( $J=1-2$  cps.), 8.80 (3H) and 8.99 (6H).

Molecular weight from mass spectrum 204 ; calculated 204.

( Found : C, 88.35 ; H, 11.77% ;  $\text{C}_{15}\text{H}_{24}$  requires C, 88.16 ; H, 11.84% ).

#### Neoclovane (80).

Neoclovene (204mg.) in ethyl acetate (20ml.) was hydrogenated in the presence of palladium-charcoal (10%) (50mg.). At the end of 2 hours, the uptake of hydrogen was 21.5 ml. (i.e. 96% of the theoretical). The ethyl acetate solution was filtered through glass paper and the solvent removed to yield an oil which was distilled to give pure neoclovane, b.p.  $50^\circ/0.04\text{mm.}$  ;  $n_D^{20}$  1.4973 ;  $\nu_{\text{max.}}$  (liq. film) = 1382, 1376, 1372 and  $1362 \text{ cm}^{-1}$  ;  $\tau$  = 8.81 (3H), 8.95 (6H) and 9.26 (3H) (doublet,  $J=6.5$  cps.).

Molecular weight from mass spectrum 206 ; calculated 206.

( Found : C, 87.04 ; H, 12.59% ;  $\text{C}_{15}\text{H}_{26}$  requires C, 87.30 ; H, 12.70% ).

#### Diol (81, R=OH).

Neoclovene (368mg.), osmium tetroxide (600mg.) and pyridine (0.36ml.) were mixed in anhydrous ether (15ml.) and left overnight at room temperature. A small sample

of the osmate-pyridine complex was isolated and crystallised from methylene chloride-ether (1:2) as brownish-green needles m.p. 177-178<sup>o</sup>(decomp.). Hydrogen sulphide gas was bubbled through the bulk of the osmate complex in ether for half an hour. The ethereal solution was filtered through glass paper, washed successively with 3N hydrochloric acid, saturated aqueous sodium bicarbonate solution and dried. Removal of the solvent yielded a viscous oil which solidified on trituration with light petroleum. Recrystallisation from light petroleum afforded colourless needles, m.p. 90.5-91<sup>o</sup> ;  $[\alpha]_D^{22}$  -43.2<sup>o</sup> ( $c$ , 1.6 in CHCl<sub>3</sub>) ;  $\nu_{\max.}$ (CCl<sub>4</sub>) = 3637, 3580, 1384, 1368, 1103, 1072, 1050 and 1028 cm<sup>-1</sup> ;  $\tau$  = 6.30 (1H) (broad), 8.75 (6H), 8.91 (3H) and 8.98 (3H).  
 ( Found : C, 75.70 ; H, 10.73% ; C<sub>15</sub>H<sub>26</sub>O<sub>2</sub> requires C, 75.58 ; H, 11.00% ).

The monobrosylate of the diol was prepared in the usual manner with p-bromobenzenesulphonyl chloride in pyridine. The crude product was freed from starting diol by chromatography on silica and crystallised from light petroleum as colourless needles, m.p. 100.5-101.5<sup>o</sup> ;  $\nu_{\max.}$ (CCl<sub>4</sub>) = 3610, 1579, 1186, 943, 869 and 750 cm<sup>-1</sup>.  
 ( Found : C, 55.46 ; H, 6.34% ; C<sub>21</sub>H<sub>29</sub>O<sub>4</sub>SBr requires C, 55.13 ; H, 6.39% ).

Ketol (81, R= =O).

The diol (81, R=OH) (50mg.) was dissolved in acetone (5ml.) and cooled to 0°. Jones reagent<sup>41</sup> was added dropwise with shaking until a permanent orange colour. Water (20ml.) was immediately added and the solution extracted with light petroleum. After drying, the extract was concentrated under reduced pressure and adsorbed on silica (2gm.). Elution with light petroleum-ether (17:3) yielded the pure ketol (29mg.),  $\nu_{\max.}(\text{CCl}_4) = 3600, 3480, 1718 \text{ and } 1100 \text{ cm}^{-1}$ .

Hydroboration of Neoclovene.

Redistilled boron trifluoride (1.8gm.) was added to neoclovene (426mg.) in anhydrous ether (20ml.) at 0° under dry nitrogen. A suspension of lithium aluminium hydride (400mg.) in anhydrous ether (40ml.) was slowly added with stirring and the reaction was allowed to proceed for 3.5 hours at room temperature. Analar acetone (2ml.) was added to destroy the excess hydride, followed by 3N sodium hydroxide (2ml.) and 30% hydrogen peroxide (2ml.). The solution was stirred for a further 1 hour and then extracted with ether. The ethereal extract was washed with brine, aqueous ferrous sulphate and dried. Removal of the solvent under reduced pressure yielded a viscous oil (481mg.).

Thin layer chromatography (light petroleum-ethyl acetate (17:3)) indicated two spots, corresponding to the two epimeric alcohols (A and B) (82) ;  $R_f$  of alcohol A = 0.43 ;  $R_f$  of alcohol B = 0.25.

Gas-liquid chromatographic analysis on a 10% 20M Carbowax column (temperature  $175^\circ$  ; argon flow rate 50ml./min.) indicated that alcohol A had a retention time of 19.2 minutes and alcohol B a retention time of 17.5 minutes (Ratio of alcohol A:alcohol B = 43:57).

The two alcohols were separated by thick layer chromatography employing the same solvent as in thin layer chromatography.

#### Alcohol A.

m.p.  $143-144^\circ$  ;  $\nu_{\max.}(\text{CCl}_4) = 3620, 1122 \text{ and } 1010 \text{ cm}^{-1}$  ;  
 $\gamma = 6.12$  (1H) (base width=10 cps.), 8.81 (3H), 8.82 (3H), 8.96 (3H) and 9.09 (3H) (doublet,  $J=7.5$  cps.)  
( Found : C, 80.78 ; H, 11.66% ;  $\text{C}_{15}\text{H}_{26}\text{O}$  requires C, 81.02 ; H, 11.79% ).

#### Alcohol B.

m.p.  $71-72^\circ$  ;  $\nu_{\max.}(\text{CCl}_4) = 3620, 1143, 1120 \text{ and } 1020 \text{ cm}^{-1}$  ;  
 $\gamma = 6.44$  (1H) (six-line multiplet, base width=30 cps., X part of an  $A_2BX$  system), 8.83 (3H), 8.87 (3H), 9.00 (3H) and 9.10 (3H) (doublet,  $J=6$  cps.).  
( Found : C, 80.85 ; H, 11.73% ;  $\text{C}_{15}\text{H}_{26}\text{O}$  requires

C, 81.02 ; H, 11.79% ).

Ketone (83).

The mixture of alcohols (82) (60mg.) was dissolved in acetone (8ml.) and cooled to 0°. Jones reagent<sup>41</sup> was added dropwise with stirring until a permanent orange colour ; water (30ml.) was added and the solution extracted with light petroleum. The organic extract was dried and the solvent removed under reduced pressure to yield an oil (55mg.). Thin layer chromatographic examination of the crude product revealed the presence of two closely running spots. Chromatography on silica (5gm.) and elution with light petroleum-ether (9:1) afforded the pure ketone, which was one spot on thin layer chromatography,  $R_f=0.62$  (solvent system :- light petroleum-ethyl acetate (9:1)). Micro-distillation (block temperature 135°/0.2mm.) gave an analytical sample,  $a_{287}^{310} -1$  ( $\underline{c}$ , 0.32 in MeOH) ;  $\nu_{\max.}(\text{CCl}_4) = 1712, 1422, 1385, 1380, 1369 \text{ and } 1364 \text{ cm}^{-1}$ .  
Molecular weight from mass spectrum 220, calculated 220.  
( Found : C, 81.41 ; H, 10.61% ;  $\text{C}_{15}\text{H}_{24}\text{O}$  requires C, 81.76 ; H, 10.98% ).

Allylic Oxidation of Neoclovene.

Ene-Acetate (84, R=CH<sub>2</sub>OAc).

Neoclovene (214mg.) was heated under reflux with a suspension of selenium dioxide (132mg.) in glacial acetic acid (2.5ml.) and acetic anhydride (2.5ml.) for 2 hours. After cooling, the solution was diluted with light petroleum (50ml.) and filtered into a saturated brine solution. The light petroleum extract was thoroughly washed with saturated aqueous sodium bicarbonate solution, dried and the solvent removed to yield a dark-red oil. Filtration through an alumina-silver column (1:1) removed some of the colloidal selenium. Adsorption on silica (10gm.) and elution with light petroleum-ether (19:1) yielded the pure ene-acetate (174mg.) as an oil,  $\nu_{C=O}$  (liq. film) = 1740 cm.<sup>-1</sup>.

Ene-ol (84, R=CH<sub>2</sub>OH).

The ene-acetate (174mg.) was refluxed in methanol (10ml.) containing sodium hydroxide (200mg.) for 2.5 hours. The methanol was removed under reduced pressure, brine was added to the residue and this thoroughly extracted with ether. The extract was dried and the solvent removed under reduced pressure to yield the crystalline ene-ol (143 mg.), which was purified by sublimation, m.p. 90.5-91.5°;  $\nu_{\max.}$  (CCl<sub>4</sub>) = 3605, 1055 and 1000 cm.<sup>-1</sup> ;

$\tau = 4.63$  (1H) (broad), 6.09 (2H), 8.80 (3H), 8.96 (3H) and 9.01 (3H).

Ene-Aldehyde (84, R=CHO).

The ene-ol (35mg.) was dissolved in chloroform (10ml.) and shaken for 22 hours with neutral manganese dioxide (600mg.) . The solution was filtered through celite and the solvent removed to yield an oil, which was freed from starting ene-ol by elution from silica (1gm.) with light petroleum-ether (19:1) (26mg.),  $\nu_{\max.}(\text{CCl}_4) = 2800, 2710, 1692$  and  $1620 \text{ cm}^{-1}$  ;  $\tau = 0.66$  (1H), 3.54 (1H) (triplet,  $J=4$  cps.), 8.79 (3H), 8.90 (3H) and 9.00 (3H) ;  $\lambda_{\max.} 237 \text{ m}\mu$  ( $\epsilon=12,000$ ).

The corresponding 2,4-dinitrophenylhydrazone crystallised from methanol-chloroform (5:1) as fine reddish-orange needles, m.p. 260.5-261.5 $^{\circ}$ .

Allylic Bromination of Neoclovene.

Neoclovene (210mg.) was refluxed with N-bromo-succinimide (188mg.) in dry carbon tetrachloride (10ml.) containing a catalytic amount of dibenzoyl peroxide (5mg.) for 2 hours. The precipitate of succinimide was collected by filtration and the carbon tetrachloride filtrate evaporated under reduced pressure. Collidine (5ml.) was added to the residual oil and warmed on a

steam bath for 15 minutes. The solution was diluted with light petroleum and washed with 6N hydrochloric acid and aqueous sodium bicarbonate solution. The organic extract was dried and the solvent removed to yield an oil (150mg.) ;

$\nu_{\text{max.}}$  (liq. film) = 1640, 1600, 890, 780, 750, 730 and 695  $\text{cm}^{-1}$  ;  $\lambda_{\text{max.}}$  = 232 and ca.260(shoulder)  $\text{m}\mu$ .

The N.M.R. spectrum showed numerous peaks in the 4-5 $\tau$  region and a distinct doublet at 5.2 $\tau$  and 5.34 $\tau$ .

Gas-liquid chromatographic analysis on a 25%APL column (temperature 175 $^{\circ}$  ; argon flow rate 80ml./min.) indicated two peaks of retention time 10.8 minutes and 15.6 minutes in an approximate ratio of 1:15 respectively.

#### Dehydration of the Ene-ol (84, R=CH<sub>2</sub>OH).

The ene-ol (10mg.) was refluxed in acetone (5ml.) with p-toluenesulphonic acid (10mg.) for 12 hours<sup>66</sup>. The acetone solution was diluted with water and thoroughly extracted with light petroleum. The organic extract was washed with brine, aqueous sodium bicarbonate solution and dried. Removal of the solvent yielded an oil (9mg.),  $\nu_{\text{max.}}$  (liq. film) = 1635, 1600, 890, 785 and 735  $\text{cm}^{-1}$  ;  $\lambda_{\text{max.}}$  = 232  $\text{m}\mu$ .

The N.M.R. spectrum showed a multiplet in the 4.0-4.4 $\tau$  region and a doublet at 5.2 $\tau$  and 5.34 $\tau$ .

Keto-Aldehyde (85, R=CHO).

The diol (81, R=OH) (140mg.) in analar methanol (10ml.) was added to sodium metaperiodate (1gm.) in water (9ml.) with stirring at room temperature and more methanol (2ml.) was added until the solution was homogeneous. After 2.5 hours, the aqueous methanolic solution was thoroughly extracted with ether, the organic extract washed with half-saturated brine and then dried. Removal of the solvent under reduced pressure yielded an oil (150mg.). The keto-aldehyde was purified by thick layer chromatography (solvent system : light petroleum-ethyl acetate (7:3)), and micro-distillation afforded the keto-aldehyde as a clear mobile oil (boiling temperature 120°/0.18mm.) ;  $[\alpha]_D^{20} -51.2^\circ$  ( $c$ , 1.5 in  $\text{CHCl}_3$ );  $\nu_{\text{max.}}$  ( $\text{CCl}_4$ ) = 2805, 2708, 1729, 1702, 1692, 1384, 1378 and 1352  $\text{cm}^{-1}$  ;  $\tau = 0.20$  (1H) (triplet,  $J=2.5$  cps.), 7.98 (3H), 8.75 (3H), 8.84 (3H) and 8.96 (3H). ( Found : C, 75.43 ; H, 9.98% ;  $\text{C}_{15}\text{H}_{24}\text{O}_2$  requires C, 76.23 ; H, 10.24% ).

The keto-aldehyde was unstable, undergoing aerial oxidation to the corresponding keto-acid. This would explain the relatively poor analysis.

The bis-2,4-dinitrophenylhydrazone of the keto-aldehyde could not be induced to crystallise.

Attempted Aldol Condensation of the Keto-Aldehyde.

The keto-aldehyde (230mg.) in 0.2N ethanolic potassium hydroxide (25ml.) was allowed to stand at room temperature for 12 hours. The solution was acidified with acetic acid and most of the ethanol and acetic acid was removed under reduced pressure. Water was added to the residue and the aqueous solution extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate solution, dried and the solvent removed to yield an oil (218mg.)

Thin layer chromatographic analysis showed at least ten compounds. Chromatography on silica (8gm.) effected a rough separation of the components, but none of these could be identified as an  $\alpha,\beta$ -unsaturated aldehyde.

Keto-Acid (85, R=CO<sub>2</sub>H from the Keto-Aldehyde (85, R=CHO).

The keto-aldehyde (85, R=CHO) (50mg.) in acetone (3ml.) was treated with Jones reagent<sup>41</sup>. Work-up in the usual manner afforded the crystalline keto-acid (52mg.). Recrystallisation from light petroleum gave an analytical sample of the keto-acid as colourless needles, m.p. 97.5-98.5° ;  $[\alpha]_D^{20}$  -52.5° (c, 1.96 in CHCl<sub>3</sub>) ;  $\nu_{\max}$ . (CCl<sub>4</sub>) = 3535, 1756, 1707, 1695 (sh.), 1384, 1370 and 1352 cm.<sup>-1</sup> ;  $\tau$  = - 1.81 (1H), 7.97 (3H), 8.72 (3H),

8.81 (3H) and 8.93 (3H).

Molecular weight from mass spectrum 252, calculated 252.

( Found : C, 71.06 ; H, 9.41% ;  $C_{15}H_{24}O_3$  requires  
C, 71.39 ; H, 9.59% ).

Keto-Acid (85, R=CO<sub>2</sub>H) from Oxidation of Crude Clovene.

To crude clovene (50gm.) in analar acetic acid (804ml.) was added chromium trioxide (70gm.) in analar acetic acid (402ml.) and water (40ml.) dropwise with cooling, such that the temperature did not rise above 30°. This mixture was allowed to stand at room temperature for 82 hours, after which the acetic acid was removed under reduced pressure on a steam bath. Water was added to the dark-green residue and the aqueous solution thoroughly extracted with light petroleum (60-80°). The organic extract was washed with 4N sodium hydroxide solution to remove the acidic material. The alkaline extract was acidified with concentrated hydrochloric acid and thoroughly extracted with light petroleum (60-80°). The organic extract was dried and the solvent removed under reduced pressure to yield a viscous oil, which was treated with ethereal diazomethane.

The crude keto-ester (13.1gm.) was adsorbed on silica (250gm.) and elution with light petroleum-ether (7:3) afforded fairly pure keto-ester (7.4 gm.). The

keto-ester (7.4gm.) was refluxed for 3 hours in methanol (130ml.) containing sodium hydroxide (9gm.). The methanol was removed under reduced pressure and the residue dissolved in water, which was extracted with ether. The aqueous alkaline solution was acidified with hydrochloric acid and thoroughly extracted with ether. The ethereal extract was dried and the solvent removed to yield a viscous oil (6gm.), which, on trituration with light petroleum was induced to crystallise. Recrystallisation from light petroleum afforded the pure keto-acid, m.p. 98-99°, which was undepressed on admixture with a sample of the keto-acid previously prepared from pure neoclovene.

Keto-Ester (85, R=CO<sub>2</sub>Me).

The keto-ester was obtained by treating the pure keto-acid with ethereal diazomethane. Micro-distillation afforded a pure sample of the keto-ester as a colourless oil (block temperature 130°/0.2mm.),  $[\alpha]_D^{20}$  -48.2° (c, 2.0 in CHCl<sub>3</sub>) ;  $\tau$  = 6.39 (3H), 8.01 (3H), 8.76 (3H), 8.84 (3H) and 8.96 (3H).

Molecular weight from mass spectrum 266, calculated 266.

( Found : C, 71.83 ; H, 9.86% ; C<sub>16</sub>H<sub>26</sub>O<sub>3</sub> requires C, 72.14 ; H, 9.84% ).

Gas-liquid chromatographic analysis of the keto-esters derived from the two keto-acids (vide supra)

showed one homogeneous peak on a 10% 20M Carbowax column (temperature 175° ; argon flow rate 63ml./min.) of retention time = 27 minutes.

Acetoxy-Ester (86, R=CO<sub>2</sub>Me, R'=OAc).

A solution of trifluoroperacetic acid was prepared<sup>26</sup> by dropwise addition of trifluoroacetic anhydride (6.35ml.) to a stirred suspension of 99% hydrogen peroxide (1.05ml.) in dry methylene chloride (7ml.) at 0°. This solution was stored at 0° for 4 hours.

To a dry methylene chloride (9ml.) solution of the pure keto-ester (323mg.), containing dry, finely-ground disodium hydrogen phosphate (1gm.) was added the solution of trifluoroperacetic acid (9ml.) dropwise with stirring. The solution was allowed to stand at room temperature for 21 hours. The inorganic salts were dissolved in water, the solution extracted with methylene chloride, washed with 10% aqueous sodium bicarbonate solution and finally dried. The solvent was removed under reduced pressure to yield an oil (344mg.).

Elution from silica (15gm.) with light petroleum-ether (9:1) and micro-distillation (block temperature 132°/0.15mm.) afforded a pure sample of the acetoxy-ester (251mg.) (73%) ;  $\nu_{\max.}(\text{CCl}_4) = 1741, 1434, 1384,$

1379, 1365 and 1243  $\text{cm}^{-1}$  ;  $\tau = 6.36$  (3H), 8.05 (3H), 8.81 (3H), 8.87 (3H) and 8.93 (3H).

( Found : C, 67.05 ; H, 9.09% ;  $\text{C}_{16}\text{H}_{26}\text{O}_4$  requires C, 67.06 ; H, 9.28% ).

#### $\delta$ -Lactone (87).

The pure acetoxy-ester (86,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{R}'=\text{OAc}$ )(251mg.) in methanol (15ml.) containing sodium hydroxide (400mg.) was refluxed for 2.5 hours. The methanol was removed under reduced pressure and the residue dissolved in water. The aqueous alkaline solution was extracted with ether and then acidified. Extraction of the aqueous acidic solution with ether, drying of the organic layer and careful removal of the solvent yielded the crystalline hydroxy-acid (86,  $\text{R}=\text{CO}_2\text{H}$ ,  $\text{R}'=\text{OH}$ ).

The hydroxy-acid (34mg.) was heated in a sublimation tube for 2 hours at atmospheric pressure. The  $\delta$ -lactone was then sublimed under reduced pressure and crystallised from light petroleum, m.p. 80.5-81.5°. The lactone was resublimed for analysis as colourless needles, m.p. 60-60.5°. This lower melting compound was identical (infra-red spectrum and thin layer chromatography) with the higher melting  $\delta$ -lactone ;  $\nu_{\text{max.}}(\text{CCl}_4) = 1745, 1386$  and 1365  $\text{cm}^{-1}$  ;  $\tau = 8.73$  (6H) and 8.89 (3H).

( Found : C, 75.08 ; H, 9.42% ;  $C_{13}H_{20}O_2$  requires C, 74.96 ; H, 9.68% ).

Hydroxy-Ester (86, R=CO<sub>2</sub>Me, R'=OH).

Treatment of the hydroxy-acid (86, R=CO<sub>2</sub>H, R'=OH) with ethereal diazomethane and elution from silica with light petroleum-ether (7:3) afforded the pure hydroxy-ester as a low melting solid which crystallised from light petroleum as colourless needles, m.p. 46-47° ;  $\nu_{\text{max.}}(CCl_4) = 3613, 1741, 1434, 1383 \text{ and } 1378 \text{ cm.}^{-1}$  ;  $\tau = 6.35 (3H), 8.88 (6H) \text{ and } 9.00 (3H)$ .

( Found : C, 69.71 ; H, 10.19% ;  $C_{14}H_{24}O_3$  requires C, 69.96 ; H, 10.07% ).

Diphenylene-Acetate (88, n=1).

A solution of the pure hydroxy-ester (86, R=CO<sub>2</sub>Me, R'=OH) (650mg.) in dry ether (15ml.) was added dropwise to a solution of excess phenylmagnesium bromide, prepared from magnesium (600mg.) and redistilled bromobenzene (4gm.) in the usual manner. The reaction mixture was refluxed for 2 hours and then the Grignard complex was decomposed with aqueous saturated ammonium chloride solution (50ml.). The resultant mixture was thoroughly extracted with ether and brine, the organic extract dried and the solvent removed to yield a crystalline solid,

which was not purified.

The crude hydroxy-diphenylcarbinol was refluxed in acetic anhydride (20ml.) and acetic acid (10ml.) for 3 hours. The acetic anhydride and acetic acid were removed under reduced pressure and the residue diluted with brine. The aqueous solution was extracted with ether, the organic extract washed with aqueous sodium bicarbonate solution, dried and the solvent removed to yield a viscous oil (1.32gm.)

The crude diphenylene-acetate was freed from impurities (e.g. diphenyl) by elution from silica (40gm.) with light petroleum-ether (24:1) (880mg.) (83%). Neither trituration with various organic solvents nor sublimation would induce the diphenylene-acetate to crystallise ;  $\nu_{\max.}(\text{CCl}_4) = 1742, 1599, 1576, 1494, 1464, 1443, 1365, 1243, 1074 \text{ and } 700 \text{ cm}^{-1}$  ;  $\nu_{\max.}(\text{liq. film}) = 760 \text{ cm}^{-1}$  ;  $\tau = 2.84 (1\text{OH}), 3.89 (1\text{H}) (\text{triplet, } J=7.5 \text{ cps.}), 8.14 (3\text{H}), 8.78 (3\text{H}), 8.83 (3\text{H}) \text{ and } 8.98 (3\text{H})$  ;  $\lambda_{\max.} = 252 \text{ m}\mu (\epsilon=18,500)$ .

#### Attempted Allylic Oxidation of the Diphenylene-Acetate.

The diphenylene-acetate (88,n=1) (205mg.) was refluxed for 2.5 hours with a suspension of selenium dioxide (150mg.) in glacial acetic acid (2.5ml.) and

acetic anhydride (2.5ml.). The solution was diluted with light petroleum and filtered into a saturated brine solution. The aqueous solution was extracted with more light petroleum, the organic extract washed with saturated sodium bicarbonate solution, dried and the solvent removed to yield a yellow oil. Thin layer chromatography and the infra-red spectrum of the product showed that it was unreacted diphenylene-acetate.

Prolonged reflux (13 hours) with excess selenium dioxide also gave back unchanged starting material.

Oxidation of the Diphenylene-Acetate (88,n=1) to the Nor-Hydroxy-Ester (89,n=1).

i) Ozonolysis.

Ozone was bubbled through an ethyl acetate (15ml.) solution of the diphenylene-acetate (180mg.) at  $-70^{\circ}$  for 1.5 hours. Water (6ml.) was added and the ethyl acetate cautiously removed under reduced pressure. The residual material was refluxed for 30 minutes in water (20ml.) containing sodium hydroxide (300mg.) and 30% hydrogen peroxide (4ml.). The aqueous solution was thoroughly extracted with ether to remove neutral material and then acidified with 6N hydrochloric acid. The aqueous acidic solution was thoroughly extracted with ether, the organic

layer dried and the solvent removed to yield a viscous oil which was esterified with ethereal diazomethane.

The crude product was adsorbed on silica (5gm.) and the pure nor-hydroxy-ester eluted with light petroleum-ether (7:3) as a colourless oil (35mg.) (30%).

ii) Ruthenium Tetroxide-Sodium Metaperiodate Oxidation.

The diphenylene-acetate (88,n=1) (1gm.) in analar acetone (50ml.) was added to sodium metaperiodate (1gm.) in distilled water (20ml.). To this solution was added ruthenium tetroxide (250mg.) in a minimum volume of acetone with stirring. Immediately the ruthenium tetroxide had been added, a black precipitate of ruthenium dioxide was formed, whereupon more sodium metaperiodate (1.5gm.) was added. A further quantity (4.5gm.) of sodium metaperiodate was added over the ensuing 24 hours and finally isopropyl alcohol (10ml.) was added to destroy the excess ruthenium tetroxide. The solution was filtered through glass paper and the precipitate washed with acetone and ether. The filtrate was concentrated under reduced pressure and constant ether extracted for 70 hours to yield a viscous oil. The oil was dissolved in ether and the ethereal solution washed with 2N sodium hydroxide solution. The aqueous alkaline extract was acidified and thoroughly extracted with brine and ether.

The ethereal solution was dried and removal of the solvent yielded a viscous oil (701mg.)

This crude product was refluxed for 3 hours in methanol (45ml.) containing sodium hydroxide (1.2gm.). The methanol was removed under reduced pressure and the residue dissolved in water and extracted with ether. The aqueous alkaline extract was acidified with 6N hydrochloric acid and thoroughly extracted with ether. The ethereal extract was dried and the solvent removed to yield the crude nor-hydroxy-acid, which was esterified with ethereal diazomethane.

The crude ester was adsorbed on silica (30gm.) and elution with light petroleum-ether (13:7) gave the pure nor-hydroxy-ester as a mobile oil (400mg.) (70%) ;  
 $\nu_{\text{max.}}(\text{CCl}_4) = 3618, 3470, 1740 \text{ and } 1719 \text{ cm}^{-1}$  ;  
 $\gamma = 6.35$  (3H),  $7.58$  (2H) ( $-\text{CH}_2\text{CO}_2\text{Me}$ ),  $8.83$  (6H) and  $8.98$  (3H).

( Found : C, 68.75 ; H, 9.72% ;  $\text{C}_{13}\text{H}_{22}\text{O}_3$  requires C, 68.99 ; H, 9.80% ).

Nor-Diphenylene-Acetate (88, n=0).

A solution of the pure nor-hydroxy-ester (400mg.) in anhydrous ether (15ml.) was added with stirring to an ethereal solution of excess phenylmagnesium bromide,

prepared from magnesium (400mg.) and redistilled bromobenzene (2.6gm.) in the usual manner. The reaction mixture was refluxed for 4 hours and then the Grignard complex was decomposed with saturated aqueous ammonium chloride (50ml.). The resultant mixture was thoroughly extracted with ether, the ethereal extract dried and the solvent removed to yield an oil.

The crude hydroxy-nor-diphenylcarbinol was refluxed in acetic anhydride (14ml.) and acetic acid (7ml.) for 3.5 hours. Most of the acetic anhydride and acetic acid was removed under reduced pressure and the residue diluted with brine. The aqueous solution was extracted with ether, the organic extract washed with aqueous sodium bicarbonate solution, dried and the solvent removed to yield an oily solid (600mg.).

The crude product was adsorbed on silica (30gm.) and elution with light petroleum-ether (97:3) afforded the pure crystalline nor-diphenylene-acetate.

Recrystallisation from ether gave an analytical sample, m.p. 182-182.5° ;  $\nu_{\max.}(\text{CCl}_4) = 1741, 1599, 1573, 1495, 1460, 1442, 1364, 1244, 1072$  and  $695 \text{ cm}^{-1}$  ;  $\tau = 2.76$  (10H), 3.62 (1H), 7.94 (3H), 8.65 (3H), 9.06 (3H) and 9.13 (3H) ;  $\lambda_{\max.} = 251 \text{ m}\mu$  ( $\epsilon=17,400$ ).

( Found : C, 83.10 ; H, 8.23% ;  $C_{26}H_{30}O_2$  requires  
C, 83.38 ; H, 8.07% ).

Bis-Nor-Hydroxy-Ester (89,n=0).

The nor-diphenylene-acetate (88,n=0) (994mg.) in analar acetone (100ml.) was added with stirring to a 5% aqueous solution of sodium metaperiodate (25ml.) containing ruthenium dioxide (300mg.). The reaction mixture was allowed to stir for 24 hours with the further addition of solid sodium metaperiodate (3gm.). Isopropyl alcohol (3ml.) was added to destroy the excess ruthenium tetroxide. The work-up procedure described in the case of the diphenylene-acetate (88,n=1) was then carried out to yield a viscous oil (697mg.).

The crude bis-nor-hydroxy-acid was esterified with ethereal diazomethane and elution from silica (20gm.) with light petroleum-ether (4:1) gave the pure bis-nor-hydroxy-ester as an oil (500mg.) (88%) ;

$\nu_{\max.}$  (liq. film) = 3550 and 1720  $\text{cm}^{-1}$  ;  $\tau = 6.31$  (3H),  
8.64 (3H), 8.83 (3H) and 9.00 (3H).

( Found : C, 66.86 ; H, 9.43% ;  $C_{12}H_{20}O_3$  requires  
C, 67.89 ; 9.50% ).

Primary-Tertiary Diol (90,R=OH).

The pure bis-nor-hydroxy-ester (89,n=0) (500mg.) in anhydrous ether (30ml.) was slowly added to lithium aluminium hydride (2.6gm.) in anhydrous ether (70ml.), with stirring under dry nitrogen. The solution was refluxed for 4 hours and then the excess hydride was destroyed by careful addition of a saturated solution of ammonium sulphate (50ml.). The mixture was thoroughly extracted with ether, the ethereal extract dried and the solvent removed under reduced pressure to yield a crystalline solid (447mg.). Recrystallisation from light petroleum (60-80°) afforded a pure sample of the diol, m.p. 108-108.5° ;  $\nu_{\text{max.}}$  (CCl<sub>4</sub>) = 3640, 3614, 3553, 3400, 1385, 1379, 1364, 1088, 1023 and 1010 cm.<sup>-1</sup> ;  $\tau$  (CDCl<sub>3</sub>+D<sub>2</sub>O) = 5.95 and 6.36 (2H) (AB quartet, J=11.5 cps.), 8.66 (3H), 8.81 (3H) and 8.98 (3H). ( Found : C, 71.48 ; H, 10.82% ; C<sub>11</sub>H<sub>20</sub>O<sub>2</sub> requires C, 71.70 ; H, 10.94% ).

Hydroxy-Tosylate (90,R=OTs).

To the diol (360mg.) in dry pyridine (2.4ml.) was added p-toluenesulphonyl chloride (600mg.) and a few drops of ether. The solution was warmed briefly and allowed to stand at room temperature for 22 hours. Brine was

added to the solution and then extracted with ether. The ethereal extract was washed with 1N hydrochloric acid, aqueous sodium bicarbonate solution, dried and the solvent removed under reduced pressure to yield a viscous oil (650mg.).

The hydroxy-tosylate could not be induced to crystallise even after thick layer chromatographic purification,  $\nu_{\text{max.}}$  (liq.film) = 3550, 1600, 1180, 1100, 970, 870 and 820  $\text{cm}^{-1}$ .

### 3,3-Dimethyl-4-Isopropenylcyclohexanone (91).

A mineral oil suspension of sodium hydride (320mg.) was washed three times with dry light petroleum under dry, oxygen-free nitrogen. Dry, redistilled dimethyl sulphoxide (9.2ml.) was added with a syringe to the amorphous sodium hydride under dry, oxygen-free nitrogen. The solution was stirred at 66-67° for 45 minutes (until the evolution of hydrogen was complete). The solution of dimethyl sodium was cooled to room temperature and the hydroxy-tosylate (640mg.) in dry dimethyl sulphoxide (12ml.) then added with a syringe and allowed to stir at room temperature for 2.5 hours. With external cooling, brine (15ml.) was added dropwise and the mixture was diluted with additional brine (100ml.). The aqueous

solution was extracted with light petroleum-ether (1:2), the organic layer washed with brine (50ml.), dried and the solvent carefully removed under reduced pressure to yield a sweet-smelling, volatile oil (271mg.).

Elution from silica (10gm.) with light petroleum-ether (9:1) afforded the pure unsaturated ketone (250mg.) (78%) ;  $\nu_{\text{max.}}(\text{CCl}_4) = 3080, 1720, 1640, 1420, 1386, 1375, 1367 \text{ and } 897 \text{ cm}^{-1}$  ;  $\tau = 5.23$  (1H) (base width = 5.5 cps.), 5.04 (1H) (base width = 8 cps.), 8.19 (3H) (doublet,  $J = \text{ca.} 1 \text{ cps.}$ ), 8.98 (3H) and 9.10 (3H).

Molecular weight from mass spectrum 166, calculated 166.

Gas-liquid chromatographic analysis on a 10% 20M Carbowax column (temperature  $125^\circ$ ; argon flow rate 60ml./min.) indicated one peak of retention time = 6.77 minutes.

### 3,3-Dimethyl-4-Isopropylcyclohexanone (58).

3,3-Dimethyl-4-isopropenylcyclohexanone (91) (230mg.) in analar ethyl acetate (25ml.) was hydrogenated in the presence of palladium-charcoal (10%) (270mg.). Unfortunately the hydrogenation apparatus developed a leak, so that a quantitative measure of the hydrogen uptake was not possible. At the end of 8 hours, an aliquot was removed and analysed by gas-liquid chromato-

graphy, which indicated that the hydrogenation had gone to completion. The bulk of the hydrogenation product was filtered through glass paper and the solvent carefully removed under reduced pressure to yield a sweet-smelling, volatile oil. A pure sample was obtained by micro-distillation (block temperature  $85^{\circ}/0.8\text{mm.}$ ) as a colourless oil (217mg.), m.p. ca.  $5^{\circ}$  ;  $[\alpha]_{\text{D}}^{20} +29.3^{\circ}$  ( $c$ , 2.0 in  $\text{CHCl}_3$ ) ;  $\nu_{\text{max.}}$  ( $\text{CCl}_4$ ) = 1718, 1429, 1419, 1386 and  $1368 \text{ cm.}^{-1}$  ;  $\tau = 7.7-8.0$  (4H), 8.94 (3H), 8.99 (3H) (doublet,  $J=7\text{cps.}$ ), 9.14 (3H) and 9.16 (3H) (doublet,  $J=7 \text{ cps.}$ ).

Molecular weight from high resolution mass spectrum  $168.1509 \pm 3\text{ppm.}$  ;  $\text{C}_{11}\text{H}_{20}\text{O}$  requires 168.1514.

Gas-liquid chromatographic analysis on a 10% 20M Carbowax column (temperature  $125^{\circ}$  ; argon flow rate  $45\text{ml./min.}$ ) indicated one homogeneous peak of retention time = 7.12 minutes.

The corresponding 2,4-dinitrophenylhydrazone crystallised from methanol as orange prisms, m.p.  $131-132^{\circ}$ .

( Found : C, 58.90 ; H, 6.68 ; N, 16.40% ;  $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_4$  requires C, 58.61 ; H, 6.94 ; N, 16.08% ).

Ketal of 3,3-Dimethyl-4-Isopropylcyclohexanone (92).

The ketone (58) (64mg.) in anhydrous benzene (14ml.) containing redistilled ethylene glycol (71mg.) and p-toluenesulphonic acid (7mg.) was refluxed in a micro Dean and Stark apparatus for 20 hours. The benzene solution was washed with half-saturated sodium bicarbonate solution and the solvent carefully removed under reduced pressure to yield a viscous oil (70mg.).

The ketal was freed from starting ketone by thick layer chromatography. Micro-distillation afforded a pure sample of the ketal as a viscous oil (block temperature  $100^{\circ}/0.2\text{mm.}$ ) ;  $\nu_{\text{max.}}$  (liq. film) = 1390, 1370, 1172, 1152, 1100, 1048 and 1025  $\text{cm}^{-1}$ .

Molecular weight from mass spectrum 212, calculated 212.

Mass Spectrum of Ketal (92).

m/e	% Abundance	m/e	% Abundance	
39	6.4	83	8.9	
40	2.0	84	3.0	
41	26.2	86	24.7	
42	7.9	87	4.9	
43	9.9	99 b. p.	100.0	
45	2.0	100	6.4	
53	4.4	113	8.6	
55	21.0	127	56.8	
56	4.9	128	4.7	
57	2.5	155	11.6	
67	4.9	x10 {	167	9.9
69	11.1		168	4.9
77	2.0		197	9.9
79	2.2		212 p	9.9
81	3.0		213	1.4

Synthesis of Racemic 3,3-Dimethyl-4-Isopropylcyclo-  
Hexanone (58).

2-Methyl-4-Methoxy Acetophenone (62).

This compound was prepared from m-methyl anisole in good yield (80%) according to the procedure of Noller and Adams<sup>77</sup> as a pale yellow oil, b.p. 182-186°/12mm.;  $\nu_{\text{max.}}$  (liq. film) = 2840, 1675, 1610, 1570, 1510 and 1260  $\text{cm}^{-1}$ ;  $\tau$  = 2.32 (1H) (doublet, J=9.5 cps.), 3.31 (2H) (multiplet), 6.24 (3H) ( $\text{OCH}_3$ ), 7.51 (3H) ( $\text{ArCH}_3$ ) and 7.59 (3H) ( $\text{CH}_3\text{-C=O}$ ).

2-(2'-Methyl-4'-Methoxy-Phenyl)-Isopropyl Alcohol.

2-Methyl-4-methoxy acetophenone (62) (32.8gm.) in anhydrous ether (100ml.) was slowly added with stirring to methylmagnesium iodide, prepared from magnesium (8.3gm.) and redistilled methyl iodide (48.3gm.) in the usual manner. The solution was refluxed for 2.5 hours and the Grignard complex decomposed with saturated ammonium chloride solution. The mixture was extracted with ether, the organic extract dried and the solvent removed to give a quantitative yield of the liquid alcohol which was not purified.

1-Methyl-3-Methoxy-6-Isopropenylbenzene (63).

The alcohol (36gm.) was refluxed in acetic anhydride (200ml.) for 4 hours. The acetic anhydride was removed under reduced pressure and the residual oil taken up in

ether. The ethereal solution was thoroughly washed with saturated sodium carbonate solution, dried and the solvent removed to yield an oil which was distilled, b.p.

66-68°/1mm. (23.1gm.) ;  $n_D^{20}$  1.5264 ;  $\nu_{\max.}$  (liq. film) = 3075, 2850, 1640, 1610, 1575, 1510, 1240, 900 and 820  $\text{cm}^{-1}$   
 $\tau$  = 3.03 (1H) (doublet,  $J=9.5$  cps.), 3.35-3.43 (2H) (multiplet), 4.85 (1H) (broad), 5.19 (1H) (broad), 6.31 (3H) ( $\text{OCH}_3$ ), 7.73 (3H) ( $\text{ArCH}_3$ ), and 8.00 (3H) (barely resolved quartet,  $J=\text{ca.}2$  cps.) ( $\text{CH}_3-\underset{|}{\text{C}}-\text{CH}_2$ ).

1-Methyl-3-Methoxy-6-Isopropylbenzene.

The unsaturated derivative (63) (12.16gm.) in analar ethyl acetate (355ml.) was hydrogenated in the presence of palladium-charcoal (10%) (2.45gm.). After 3 minutes the theoretical uptake of hydrogen was complete (1,660ml.). The ethyl acetate solution was filtered through glass paper and the solvent removed under reduced pressure. Distillation gave a pure sample as a colourless oil, b.p. 55-56°/0.6mm. ;  $n_D^{20}$  1.5090 ;  $\nu_{\max.}$  (liq. film) = 1615, 1580, 1510, 1255 and 820  $\text{cm}^{-1}$  ;  $\tau$  = 2.87 (1H) (doublet,  $J=9.5$  cps.), 3.28 (2H) (multiplet), 6.43 (3H) ( $\text{OCH}_3$ ), 6.98 (1H) (septet,  $J=7$  cps.), 7.76 (3H) ( $\text{ArCH}_3$ ), and 8.83 (6H) (doublet,  $J=7$  cps.).

3-Methyl-4-Isopropylcyclohex-2-ene-1-one (64).

The methyl ether (2.36gm.) in anhydrous ether (15ml.) was added to a three-necked flask charged with liquid ammonia (300ml.). With vigorous stirring, under oxygen-free, dry nitrogen, small pieces of lithium (4.4gm.) were added over 15 minutes and allowed to stir for a further 2 hours. Isopropyl alcohol was then added until the lithium bronze was destroyed. The reaction flask was warmed on a water bath (70°) to remove most of the ammonia and then ice was slowly added with stirring until all the lithium isopropoxide was dissolved. The reaction mixture was extracted with light petroleum, the organic layer washed with half-saturated brine, dried and the solvent removed to yield a pale yellow oil (2.26gm.) (95%);  $\nu_{\max.}$  (liq. film) = 2850, 1695, 1665, 1210 and 800  $\text{cm}^{-1}$

This dihydro derivative in analar methanol (110ml.) was warmed to 60° and 3N hydrochloric acid (75ml.) added with stirring. The solution was stirred at this temperature for 30 minutes and then poured into half-saturated brine (200ml.). The aqueous methanol solution was extracted with light petroleum, the organic extract washed with half-saturated brine (100ml.), saturated sodium bicarbonate solution (200ml.), dried and the solvent removed

under reduced pressure to yield an oil (1.72gm.) (87%).

Thin layer chromatographic examination revealed the presence of one predominant spot,  $R_f=0.21$  and a minor component,  $R_f=0.36$  (solvent system : light petroleum-ethyl acetate (17:3)).

The less polar minor component was eluted from silica (70gm.) with light petroleum-ether (17:3) and was shown by thin layer and gas-liquid chromatography and infra-red spectrum to be identical with an authentic sample of piperitone (65). The major component was eluted with the same solvent system (4:1) and distilled to yield a pure sample of 3-methyl-4-isopropylcyclohex-2-ene-1-one, b.p. 62-63°/0.4mm. ;  $\nu_{\max.}$  (liq. film) = 3020, 1675, 1620, 1420 and 870  $\text{cm}^{-1}$  ;  $\tau = 4.23$  (1H) (quartet,  $J=1.5$  cps.), 8.07 (3H) (doublet,  $J=1.5$  cps.), 8.96 (3H) (doublet,  $J=6.5$  cps.) and 9.18 (3H) (doublet,  $J=6.5$  cps.) ;  $\lambda_{\max.}$  238  $\text{m}\mu$  ( $\epsilon=15,570$ ).

Gas-liquid chromatographic analysis on a 10% 20M Carbowax column (temperature 100° ; argon flow rate 60ml./min.) indicated one peak of retention time = 33.3 minutes and a small impurity (ca.5%) of piperitone, retention time = 19 minutes.

Racemic 3,3-Dimethyl-4-Isopropylcyclohexanone (58).

To methylmagnesium iodide at 0°, prepared from magnesium (640mg.) and redistilled methyl iodide (3.87gm.), was added the unsaturated ketone (64) (304mg.) and cupric acetate monohydrate (88mg.) in dry tetrahydrofuran<sup>78</sup> (21ml.) dropwise with stirring under an atmosphere of oxygen-free, dry nitrogen. The resultant suspension was stirred for a further 3 hours at 0° and then at room temperature overnight. With external cooling, saturated ammonium chloride (50ml.) was added with stirring. The aqueous mixture was extracted with light petroleum-ether (1:1), the organic layer washed with half-saturated brine (200ml.), dried and the solvent carefully removed to yield an oil (350mg.).

The pure racemic ketone (58) (67mg.) (20%) was obtained as a colourless oil by thick layer chromatography and micro-distillation.

Infra-red and mass spectra indicated that the synthetic, racemic ketone was identical to the degraded ketone.

Gas-liquid chromatographic analysis of a 1:1 mixture of the two ketones showed one symmetrical peak on the following columns (all at 100°) :-

Column	Argon Flow Rate (ml./min.)	Retention Time (min.)
20% TCEP	50	35.5
10% 20M Carbowax	53	14.2
1% QF 1	58	3.7
5% QF 1	42	19.1
5% APL	48	13.3
5% B34 Dinonyl Phthalate	57	37.8

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