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Transannular Epoxide Ring-opening In Caryophyllene Derivatives

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ABSTRACT

Transannular oxirane ring-opening reactions of the mono, bis, and keto oxides of caryophyllene and isocaryophyllene have been studied under basic conditions and the structures of the products determined. The stereochemical assignments for the various glycols obtained in this work rest on the assumptions that the oxirane ring is opened under basic conditions with inversion of configuration at the carbon atom undergoing substitution, and that while bulky hydroxylating reagents such as potassium permanganate and osmium tetroxide add to the exocyclic double bond from the least-hindered α-side, the relatively small sized peracid reagent approaches the double bond from the β-side.

The results obtained show that nucleophilic attack at either tertiary or secondary carbon atom of the tertiary-secondary oxide system is controlled both by the interactions between various groups or atoms present in the molecule at the transition state for attack at either of the two carbon atoms and by the formation of strain-free products. The following table summarises the results obtained.

Compound	1,2-Diol from	Hydroxyl group involved in cyclisation	Carbon atom of the oxide system attacked
Caryophyllene Oxide	OsO_4 or $KMnO_4$	tertiary	tertiary
"	Bisepoxide	"	secondary

(Continued)

Isocaryophyllene Oxide-a	OsO_4 or $KMnO_4$	tertiary	secondary
"	Bisepoxide	primary	"
Isocaryophyllene Oxide-b	OsO_4	"	"
"	Bisepoxide	tertiary	"
Other trans Caryophyllene Oxide	OsO_4	primary	tertiary

The epoxy ketones of caryophyllene and isocaryophyllene were prepared and their base-catalysed isomerisation reactions were studied. The discovery of a hitherto unknown trans oxide of caryophyllene has been rationalised by invoking free rotation of the bonds attached to the trans double bond.

ACKNOWLEDGMENTS

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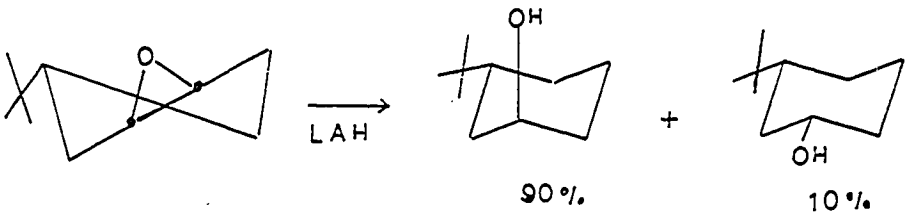
INTRODUCTION

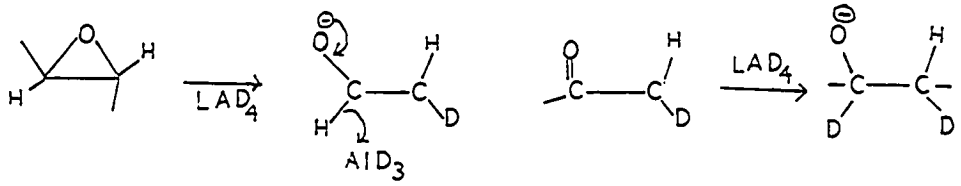
Since the discovery by Wurtz[1] of the simplest 1,2-epoxide, namely ethylene oxide, epoxides have been recognized to constitute one of the most reactive classes of organic compounds. They are susceptible to attack by both electrophilic and nucleophilic reagents, for cleavage of the three-membered ring results in a considerable release of strain energy.[2,3,4]

(A) Reactions of epoxides

Epoxides are synthesized by a variety of methods, chief among them being treatment of olefins with a peracid. They undergo a variety of reactions. They can be reduced with metals such as sodium or potassium, by catalytic hydrogenation or complex metal hydrides. Eliel and Rerick[5,6] have shown that, in the absence of Lewis acids, lithium aluminum hydride reduction of epoxides to alcohols occurs by hydride attack at the least-substituted carbon of the epoxide ring. It is worth mentioning two reductions of stereochemical interest. In contrast to the usual way of diaxial opening, the reduction of 4-trans-t-butylcyclohexene oxide with pure lithium aluminum hydride gives 90% of 3-trans-alcohol and 10% of cis-3-alcohol (the cis oxide gives the opposite ratio in the same amounts) and with the hydride plus aluminum chloride stereospecifically pure 3-trans-alcohol.[7]

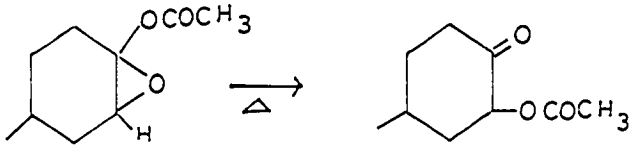


It was found by using lithium aluminum deuteride that the formation of the minor product is consistent with the sequence outlined in the following equations.

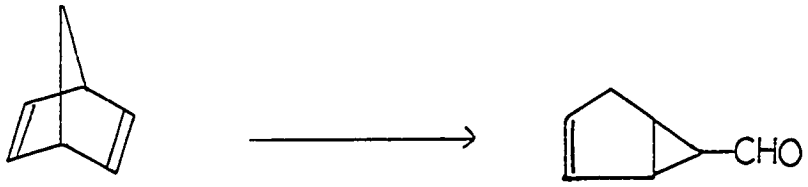


The reduction of exo-norbornene oxide with lithium aluminum hydride furnishes a mixture of 2-exo alcohol and 7-norborneol.[8] The ratio of products was found to be solvent and temperature dependent. A carbonium ion intermediate appears to be involved in view of the skeletal rearrangement.

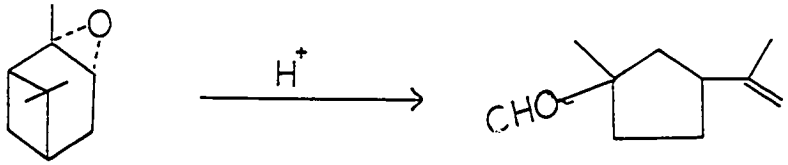
Epoxides undergo interesting rearrangements under specified conditions. Thus enol ester epoxides undergo intramolecular rearrangements to α-acyloxyketones when heated.[9]



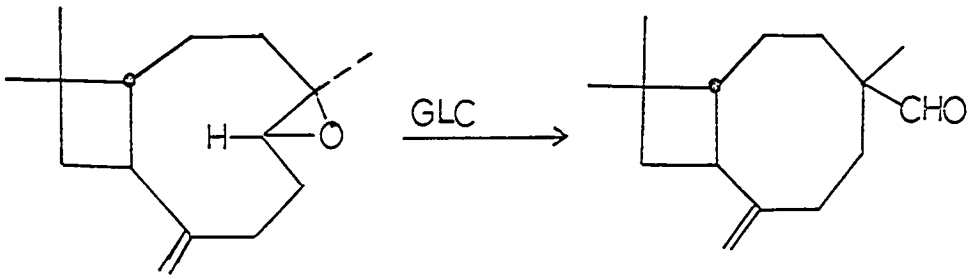
An acid-catalysed rearrangement was observed during the attempted synthesis of the mono epoxide of bicyclo(2,2,1)heptadiene: bicyclo(3,0,1)-1-hexene-6-carboxaldehyde was produced in 70% yield.[10]



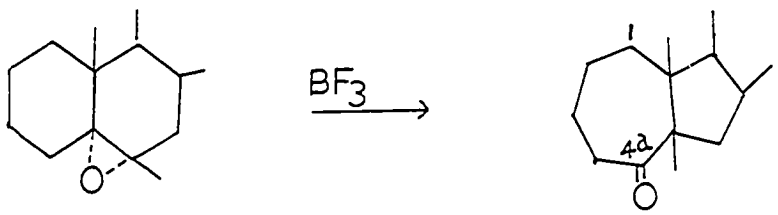
The rearrangement has been proved to occur via the acid-catalysed rearrangement of the intermediate epoxide.[11] The specific rearrangement of epoxides to aldehydes has been observed in many other bicyclic systems. Thus α-pinene oxide rearranges under the influence of acids to monocyclic aldehyde.[12]



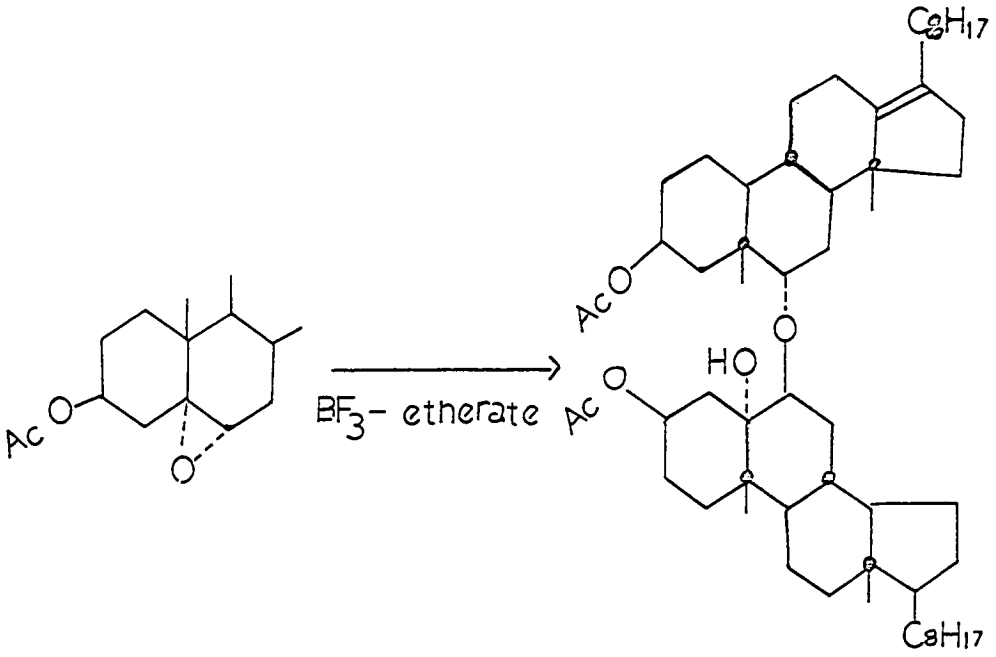
A similar rearrangement has been observed during the gas chromatography of caryophyllene oxide on an acid-washed column.[13]



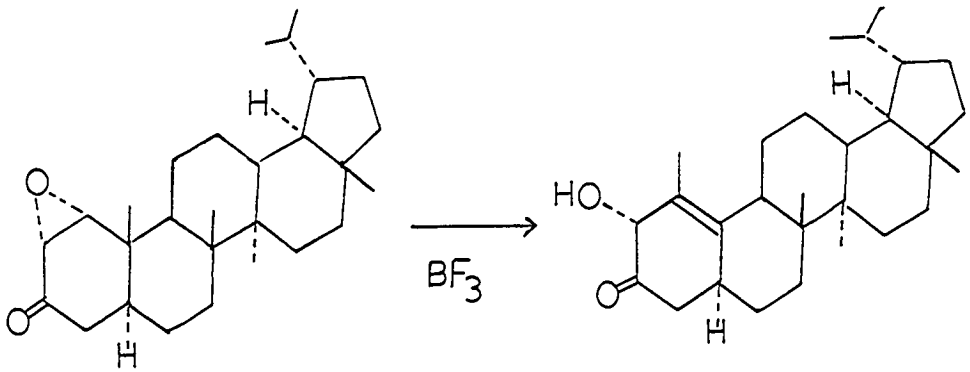
The reaction between boron trifluoride and a series of tetra-substituted epoxides have been studied in detail by Hartshorn and Kirk[14] who showed that either methyl or methylene migration can occur. The 5,6-α-epoxy-6β-methyl-5-α-cholestane undergoes rearrangement with boron trifluoride to give the 5β-methyl-A-homo-B-nor-4a-ketone.



A novel "backbone rearrangement" of the cholestane skeleton was reported by the same authors.[15] When 3β-acetoxy-5,6-α-epoxy-5α-cholestane was treated with boron trifluoride-etherate at high concentrations, an unsymmetrical di-steroidal ether resulted. The formation of this ether involves a hitherto unknown backbone rearrangement of one of the steroidal skeletons giving the 5β, 14β-dimethyl 18,19-bisnor structure with all ring junction configurations inverted.

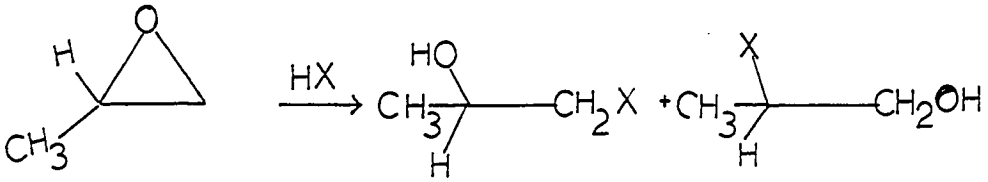


On the other hand, a simple methyl migration alone was observed by Govindachari and his co-workers[16] when 1,2-epoxy-lupan-3-one rearranged under the influence of boron trifluoride.



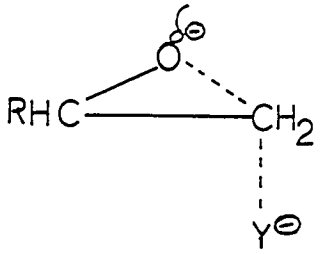
(B) Mechanism of epoxide ring-opening

Both acid and base-catalysed hydrolyses of epoxides have been areas of continuing interest since Long and Paul[17] showed that there is a base-catalysed reaction, an acid-catalysed reaction and a pH-independent reaction with water. In general when an unsymmetrically substituted epoxide opens under the influence of acids, two types of products, normal and abnormal, are possible. A normal product is defined as one derived by opening of the epoxide between oxygen and the least-substituted carbon and an abnormal product is one obtained by opening of the epoxide between oxygen and the most-substituted carbon of the epoxide ring. As an example, when propylene oxide reacts in aqueous solutions of HX (where X = Cl or Br), a mixture of both normal and abnormal products is formed.[18]



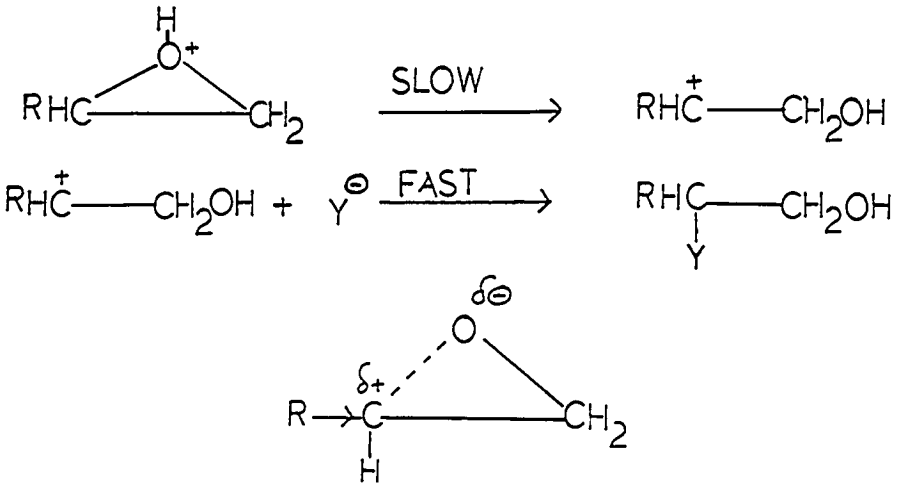
The orientation of ring-opening is related directly to the effect of substituent groups in the epoxide ring. A substituent can direct the opening of an epoxide ring by steric, polar (inductive) and conjugative effects. If one visualises the epoxide ring as undergoing a bimolecular attack by a nucleophile $Y^{\ominus}$, then it is obvious that steric effects of substituents will promote normal addition chiefly, while polar and conjugative effects may act in either direction. The data that have so far been accummulated[2] show that under basic or neutral conditions, the normal product, corresponding to attack at the least-substituted carbon, is the major or only isolable product, providing strong evidence for an S_N2 attack of the nucleophile on the epoxide ring.

The following figure represents the transition state for an S_N2 attack of the nucleophile at the normal position of an epoxide ring.



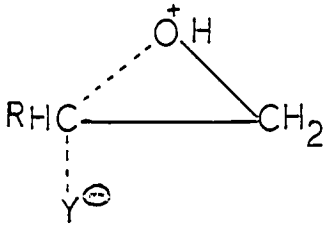
Provided that the group R has no very marked polar or conjugative effect, reactions involving a transition state of the type indicated above will lead always to the normal product, since S_N2 reactions are known to be sensitive to steric hindrance.

Whereas many epoxides give normal products under basic conditions, they produce a mixture of both normal and abnormal products in acidic medium. Since steric effects do not explain this phenomenon, we invoke polar and conjugative effects of the R group present in the epoxide ring. The positive charge on the carbon atom containing the group R may be stabilised by polar and hyperconjugative effects of the R group. There are two mechanisms namely S_N1 and S_N2 type (or "borderline S_N2") that explain this phenomenon. In the S_N1 mechanism, the transition state for the rate-determining step carries a formal positive charge on the carbon atom bearing the R group. The driving force for the reaction is provided mainly by relief of strain accompanying the opening of the three-membered ring.



Such a positive charge produced on the carbon atom carrying the R group is stabilised by the inductive and hyperconjugative effects of the R group.

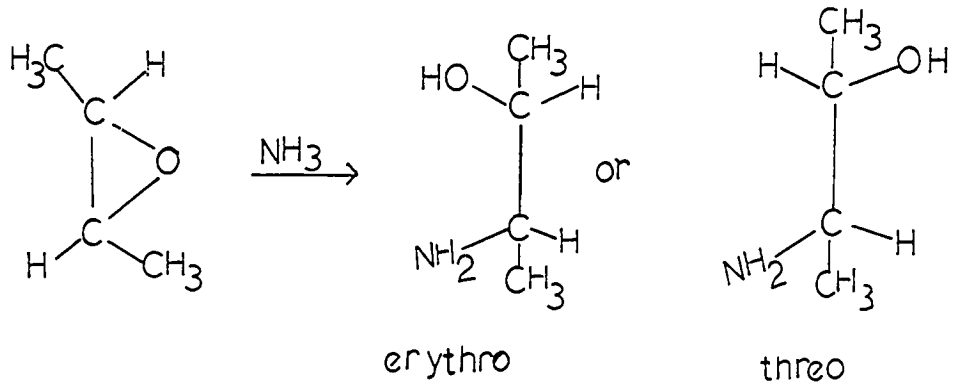
In the S_N2 mechanism, the nucleophile $Y^{\ominus}$ is farther away than usual from the seat of attack while the C-O bond is breaking partially as represented below



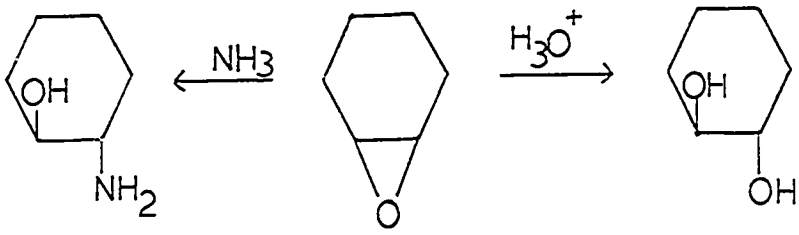
In this mechanism, the C-O bond is broken more nearly completely in the transition state before the new C-Y bond is formed. In other words, this mechanism can be considered as "borderline S_N2" in which bond-breaking is more important than bond-making. This mechanism has all the characteristics of the usual S_N2 mechanism except that the degree of steric hindrance from R to the approaching nucleophile will be less than in the classical S_N2 mechanism since the reagent is not so close in the transition state.

The proportions of the abnormal products depend on the size of the approaching nucleophile, as exemplified by the reactions of propylene oxide with the halogen hydracids. Under identical experimental conditions with the hydrogen halides, the proportion of abnormal products obtained is in the order HCl > HBr > HI. This is caused probably by a steric effect, due to the size of the halide ions. Another piece of evidence that supports this "borderline S_N2" mechanism is that the proportion of abnormal product is greater in water than in other thereby indicating that the transition state for abnormal attack is more polarized than that for normal attack.

Strong support for an S_N2 mechanism comes from stereochemical evidence. The reaction of ammonia with trans-2,3-epoxybutane could give either threo- or erythro-3-amino-2-butanol.



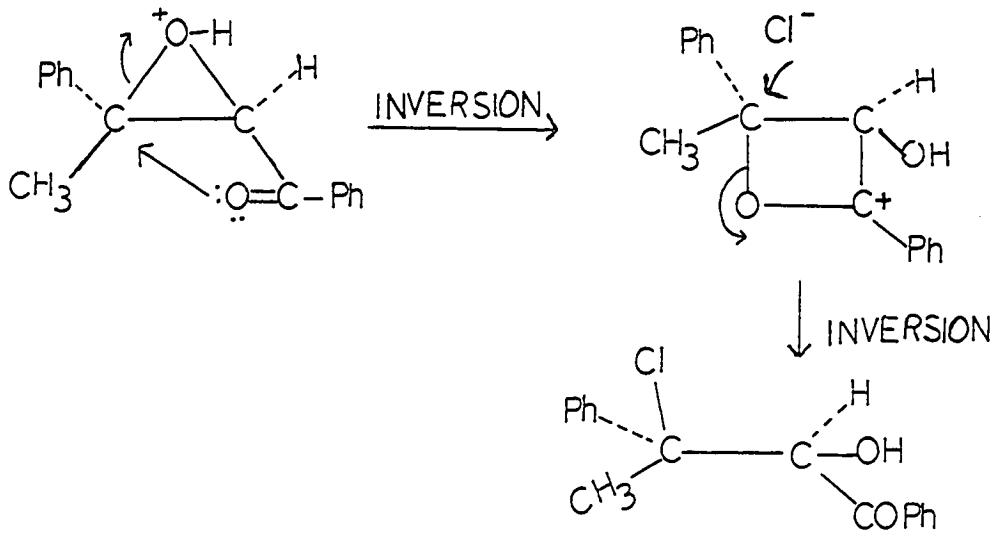
However only the erythro isomer is produced,[19] which calls our attention to the inversion of configuration at the point of attack. The opening of the oxide ring of cyclohexene oxide by ammonia has been shown to be a trans-opening, for the product is trans-2-amine cyclohexanol,[20] while the acid-catalysed hydration of cyclohexene oxide gives only trans-cyclohexane-1,2-diol, none of the cis isomer being detected.[21,22a]



In all these cases an inversion of configuration has taken place at the carbon atom attacked and "there can be no doubt that this is the general rule for all ring-opening reactions of epoxides."[2]

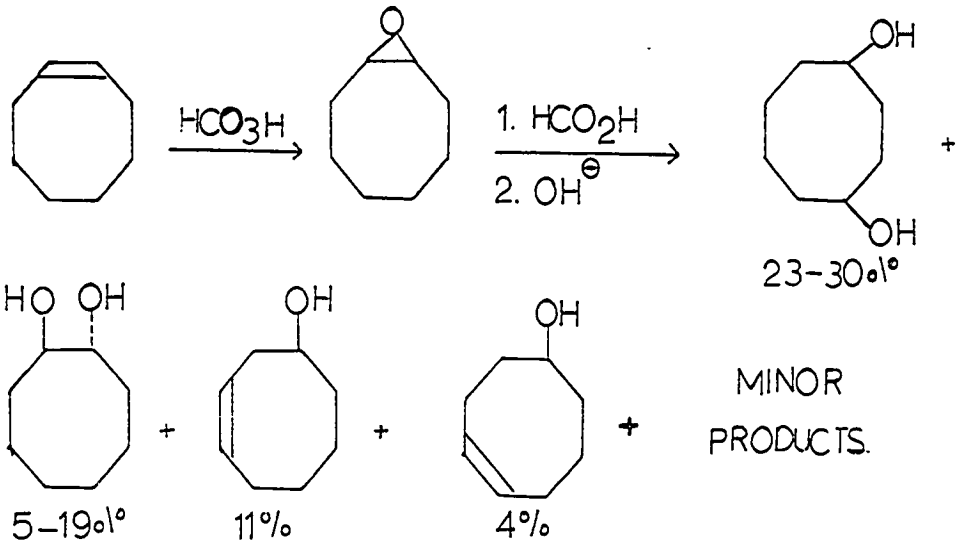
Some light has been cast upon the mechanism by the stereochemical evidence. Complete inversion of configuration is in agreement with an S_N2 mechanism, while it is incompatible with an S_N1 mechanism. It is known that S_N2 reactions proceed with inversion of configuration at the carbon being substituted, whereas S_N1 reactions proceed by the formation of a carbonium ion. If a carbonium ion is formed it will be attacked on either side; therefore an S_N1 mechanism leads to racemisation, if there is no other asymmetric centre in the molecule, rather than preferential inversion or retention of configuration. In some cases, however, an S_N1 mechanism could give only one product which corresponds to the isomer formed by inversion. But these are exceptional cases which can be explained by invoking the steric effects of groups attached to the epoxide ring carbon atom, which direct the approaching nucleophile exclusively from the least hindered side and consequently result in inversion of configuration. There are a few cases where retention of configuration is observed in the epoxide ring-opening reactions. These are explained by a mechanism involving a double-inversion. An example is the reaction of dypnone oxide with

hydrochloric acid.[22b]

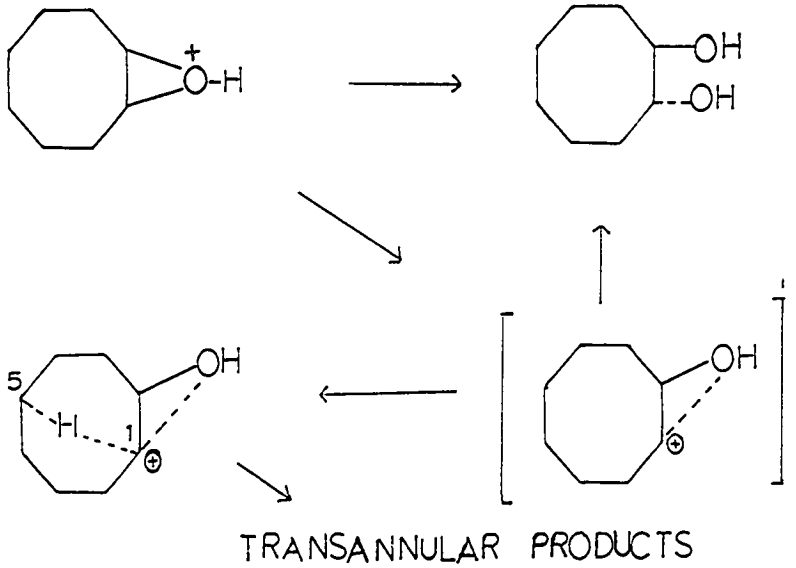


(C) Epoxide ring-opening involving transannular or intramolecular reactions

Whereas an epoxide ring fused to common rings undergoes rearrangement under the influence of acids to give ring contracted products, medium ring epoxides undergo reactions involving either transannular hydride shifts[23] or extensive molecular rearrangements. The earliest systematic study of transannular hydride shifts in the reactions of medium ring epoxides was initiated by Cope and Prelog and their colleagues. Cope, et al.,[24], found that hydroxylation of cis-cyclooctene with performic acid followed by saponification of the intermediate formates gave rise to considerable quantities of cis-cyclooctane-1,4-diol in addition to the expected trans-cyclooctane-1,2-diol and other minor products.

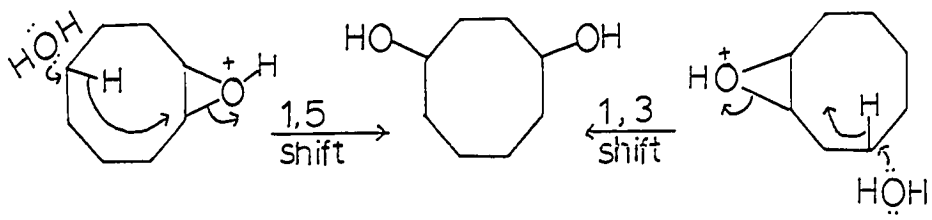


The initially protonated cis-cyclooctene oxide can undergo transannular reactions by one of the following paths to give cis-1,4-glycol.[23]

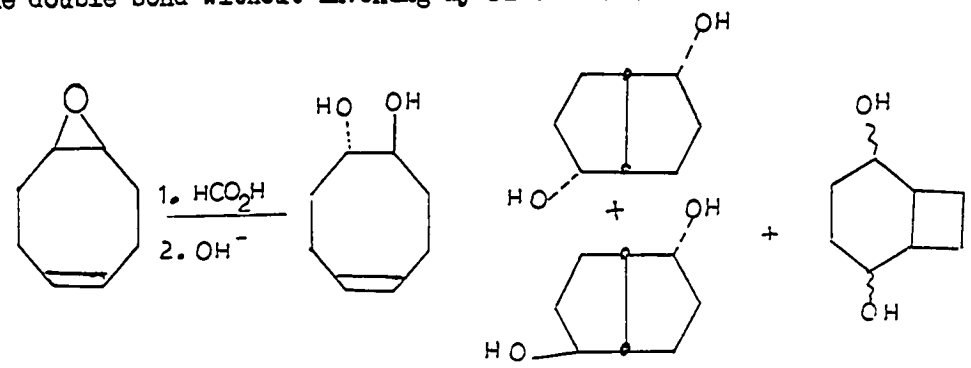


TRANSANNULAR PRODUCTS

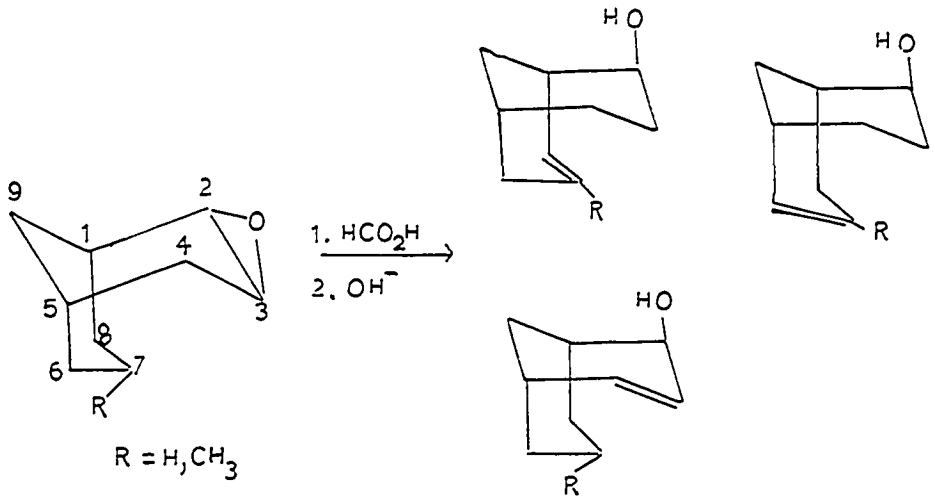
The hydride shifts are either 1,3- or 1,5-migrations and can occur by a completely concerted process.



In another type of transannular reaction, instead of hydride migration, a pair of electrons may shift, leading to bicyclic compounds. Thus the bicyclic compounds formed during the solvolysis of cis, cis-cycloocta-1,5-diene monoepoxide have been rationalised by migration of the double bond without invoking hydride shift.[25]

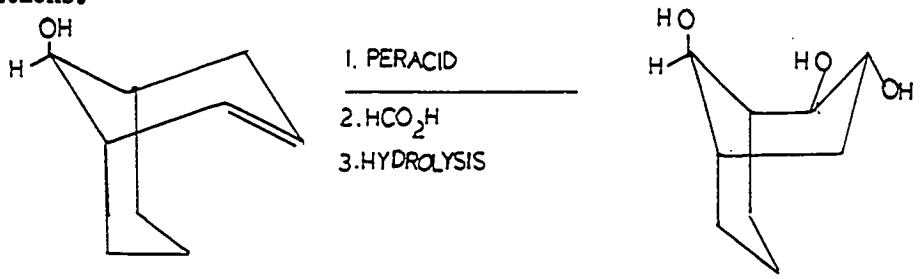


Recently Appleton and his colleagues have reported the occurence of transannular hydride shifts in bridged bicyclo compounds.[26] The formolysis of bicyclo(3,3,1)nonan-2β, 3β-oxide and of 7β-methyl bicyclo(3,3,1)nonan-2β,3β-oxide gave rise to products formed through transannular hydride shifts in addition to the expected 1,2-diol formed by normal trans-diaxial opening of the epoxide ring.

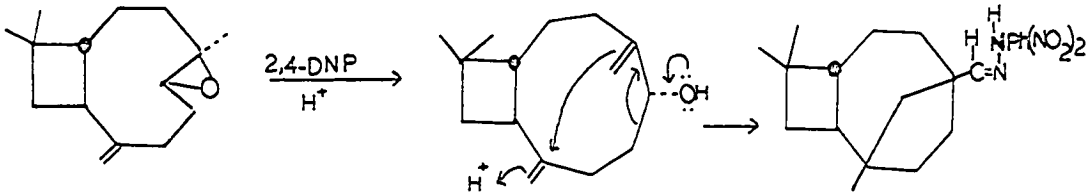


However, no hydride shift was observed when the same bicyclo epoxides carrying an oxygen function at C_9 were subjected to the same solvolytic

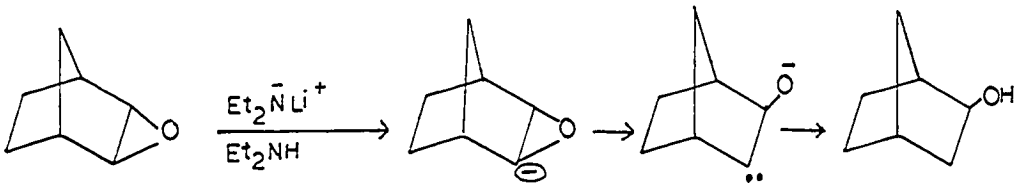
conditions.



Warnhoff recently reported[27] the formation of a dinitrophenylhydrazone from caryophyllene monoxide through a dienol intermediate.

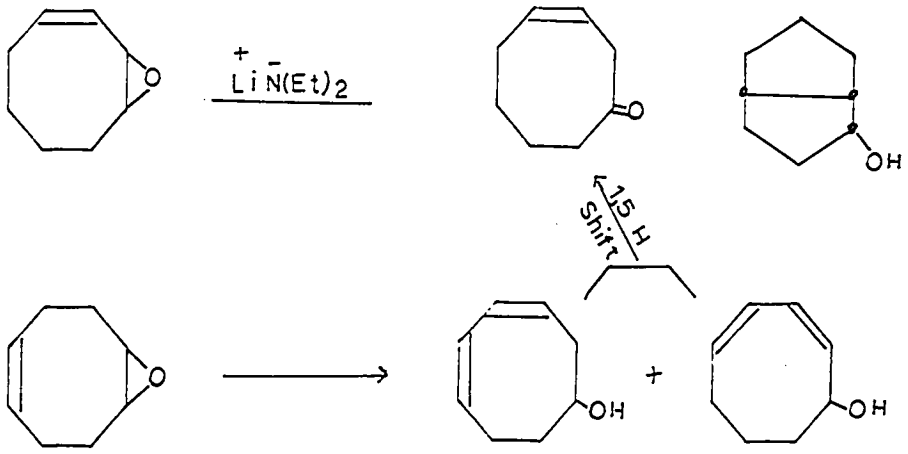


Whereas the acid-catalysed ring-openings and rearrangements of epoxides have been studied in great detail, the base-catalysed ring-openings and rearrangements of epoxides are few. A carbene intermediate has been postulated in the base-catalysed rearrangement of norbornene oxide.[28]

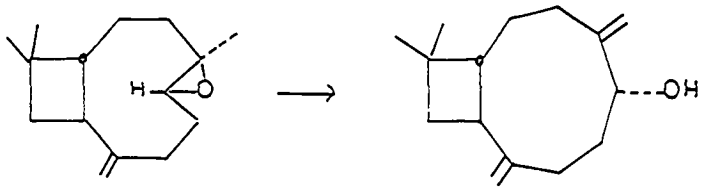


The base-promoted reactions of epoxides in medium ring compounds have been studied by Cope, et al.[29] They observed that cis-cyclooctene oxide was largely isomerised to a bicyclic alcohol upon treatment with lithium diethylamide. This reaction, which is typical for a number of medium ring epoxides, was demonstrated to proceed by an α-elimination mechanism that presumably involves transannular insertion of a carbenoid intermediate.[30]

The rearrangement reactions of 3,4- and 5,6-epoxycyclooctene prompted by lithium diethylamide have been reported recently by Crandall and Chang.[31] Thus, while 3,4-epoxycyclooctene produces 3-cyclooctenone and cis-bicyclo(3,3,0)oct-7-en-endo-1-ol, a mixture of 2,4- and 3,5-cyclooctadienol is obtained from 5,6-epoxycyclooctene as the initial product which then undergoes thermal rearrangement to 3-cyclooctenone.



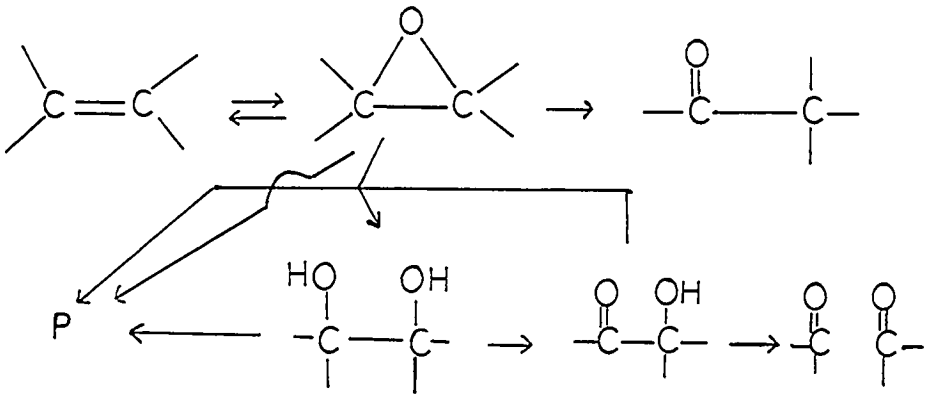
In contrast to the above observations is the base-catalysed isomerisation of caryophyllene monoxide which gives an allylic alcohol with no skeletal rearrangement.[32]



(D) Epoxide rings in natural products

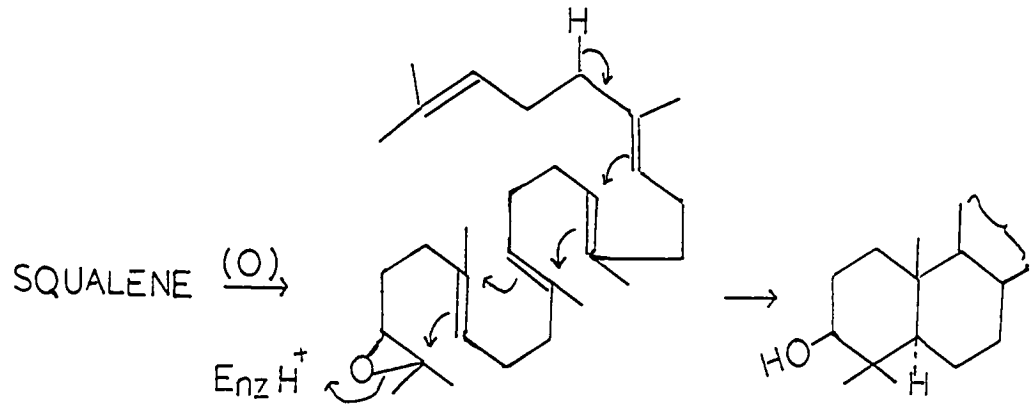
A clear understanding of the mechanism of epoxide ring-opening reactions can help a great deal in elucidating the structures of naturally-occurring compounds whose reactions have often been complicated by intramolecular nucleophilic attack upon a reactive epoxide, often with extensive skeletal rearrangements. A rationalisation of such

rearrangements often involves application of mechanistic and stereochemical principles involved in epoxide ring-opening reactions. Although the presence of epoxide rings in naturally occurring compounds such as terpenes, alkaloids, etc., was once thought to be uncommon, in recent years examples have been accumulating which show that such structural units are rather common. Cross[33] has discussed the role of epoxides as biogenetic precursors and outlines the following biogenetic pathways.

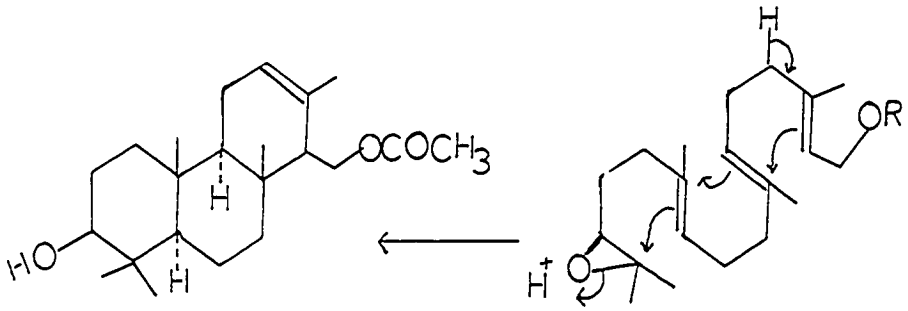


While there is ample evidence for the role of the C_{30} triterpenoid hydrocarbon, squalene as a precursor of sterols and polyclic triterpenes, evidence has been obtained recently by Corey[34] and Van Tamelen[35] to support the proposition that the 2,3-oxido squalene is an intermediate in the biosynthesis of sterols from squalene.

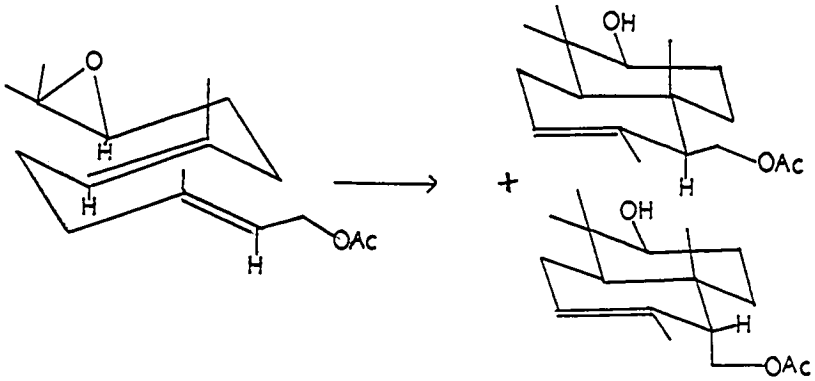
The intermediate 2,3-oxido squalene is cyclised by a mechanism such as



The epoxide cyclisation method has been extended to tricyclic cases too. Thus when the oxidation-cyclisation sequence was applied to trans, trans, trans-geranylgeraniol a tricyclic diol monoacetate was obtained.[36]

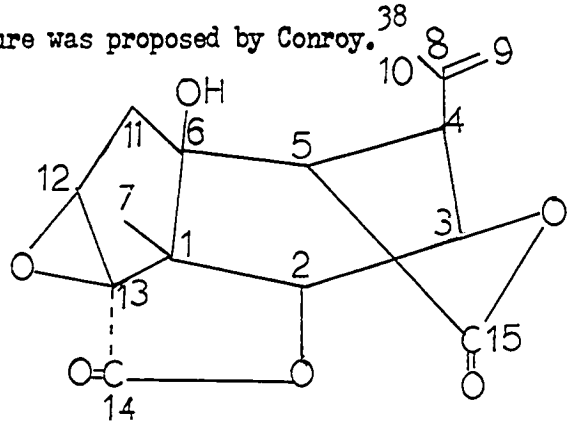


The significant aspect of the above cyclisations is considered to be the stereochemical behaviour in a polyclic context. Thus the epoxide ring-opening - carbocyclisation reactions of trans, trans-farnesyl acetate can be imagined to proceed through the following arrangement.[37]

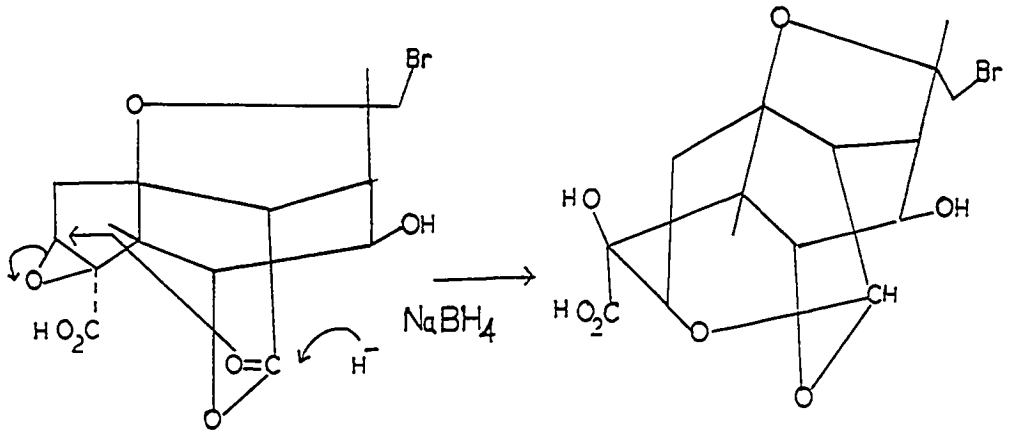


In the above conformation the epoxide ring is favourably oriented for an S_N2-like attack by the neighbouring π-electrons and the epoxide ring-opening generates a cyclohexanol ring when the C-3 equatorial hydroxyl becomes <u>trans</u> to the C-5 hydrogen.

The constitution of picrotoxinin, a novel sesquiterpenoid dilactone presented a great problem to many organic chemists but eventually the following structure was proposed by Conroy.

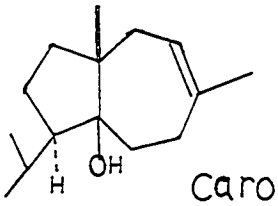


The remarkable stability of the epoxide ring of picrotoxinin and its derivatives to dilute acids and bases revealed that the epoxide ring must be strongly shielded against external nucleophiles by the lactone ring in a cage structure. However, epoxide ring-opening was observed during the sodium borohydride reduction of β-bromopicrotoxinic acid. This was rationalised as opening of the lactone ring by hydride ion with subsequent attack at the least-substituted carbon of the epoxide ring by the internal nucleophile thus produced.

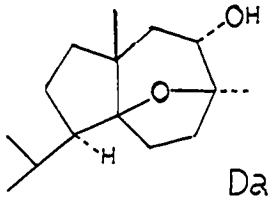


Consequently the orientation of the epoxide ring with respect to the lactone ring was fixed as trans.

Another example which involves subtle application of mechanistic and stereochemical principles of epoxide ring-opening reactions is found in the elucidation of the structure and stereochemistry of carotol and daucol,[39,40] the sesquiterpene alcohols derived from the oil of carrot seeds.



Carotol

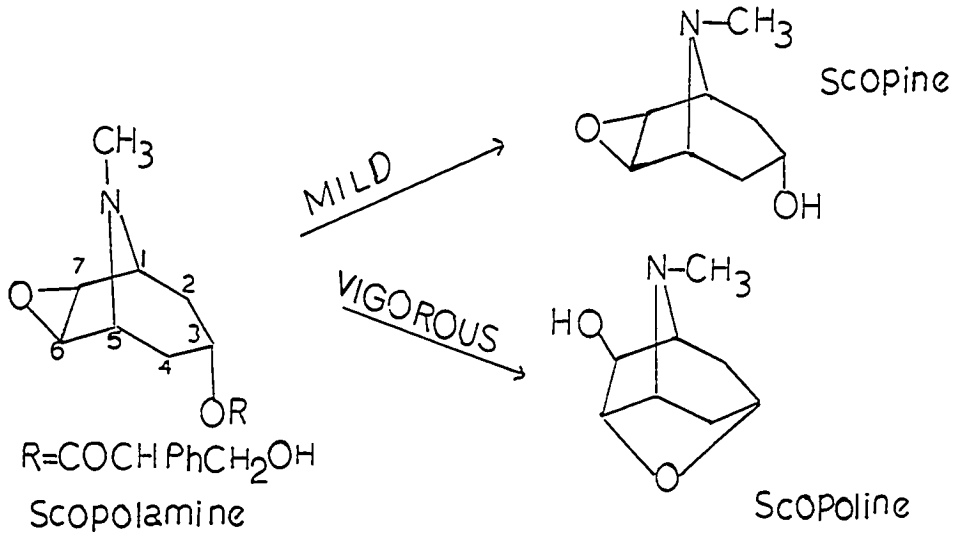


Daucol

Carotol on oxidation with a peracid gives daucol which accompanies carotol in the oil of carrot seeds and whose structure has been elucidated by Sykora, et al.[41] and confirmed by Zalkow, et al.[42] The path of the carotol-daucol transformation requires that in the non-isolated intermediate epoxide, the epoxide must be trans to the angular hydroxyl group since only then could the epoxide ring be opened by the internal nucleophile (CH) with inversion of configuration at the carbon atom being substituted and without forming a highly strained trans 1,3-

ring fusion. Consequently in daucol the two oxygen atoms must be trans to each other.

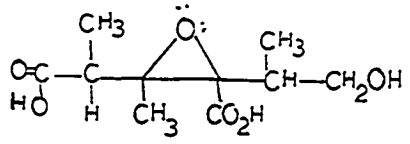
A few senecio alkaloids, some tropane alkaloids, undulatine and annotinine contain the epoxide group. The stereochemistry of scopolamine, a tropane alkaloid, was established by Meinwald[43] and Fodor[44] independently on the basis of hydrolysis experiments.



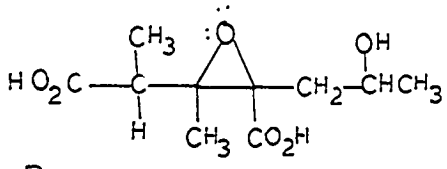
While mild alkaline hydrolysis of scopolamine furnishes scopine, vigorous alkaline hydrolysis leads to scopoline. This result leads to the conclusion that in scopoline the C_7-hydroxyl and the oxide bridge are trans to each other, since they must be formed by an internal nucleophilic opening of an epoxide. This in turn shows that in scopine, the immediate precursor of scopoline, the epoxide ring and the C-3 hydroxyl group must be trans to each other in order to satisfy the geometrical requirements for the internal displacement reaction. As expected, pseudoscopine (C_3-hydroxyl epimer of scopine) does not undergo this transformation.

Jacobine[45] and tomentosine,[46] two senecio alkaloids contain an epoxide ring in the molecule. Alkaline hydrolysis of jacobine yields

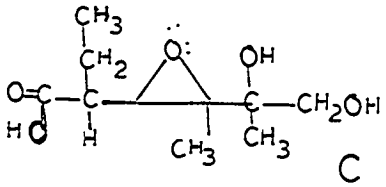
retronecine (an amino-alcohol), jaconecic acid and isojaconecic acid. Similar alkaline treatment of tomentosine gives jaconecic acid[47] and an unknown amino-alcohol. Several structures for jaconecic acid (A, B, and C) and isojaconecic acid (D) were proposed in which it was assumed that the epoxide ring present in the alkaloid remained intact during alkaline treatment, but none accounted satisfactorily for the known facts.



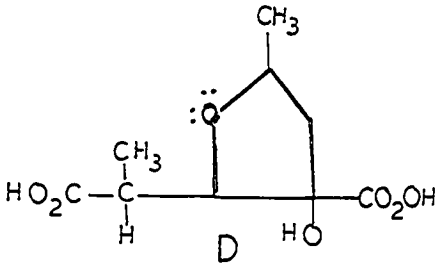
A



B

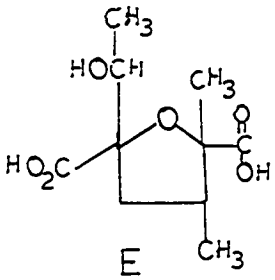


C

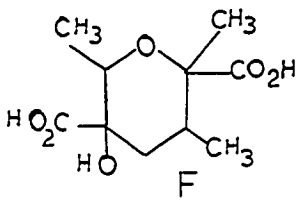


D

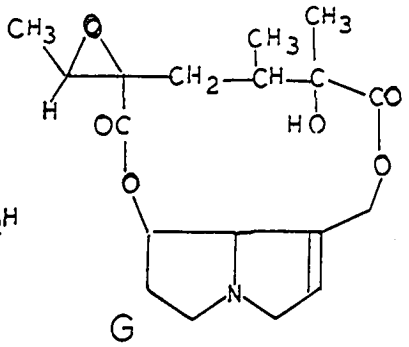
However, later acceptable structures were formulated by Geissman[48] and Bradbury and Masamune[47] for jaconecic acid E, isojaconecic acid F and jacobine G.



E

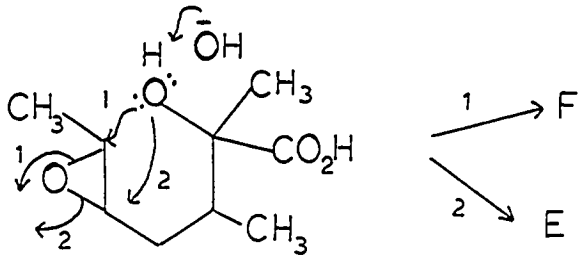


F

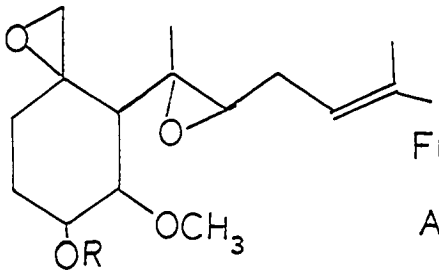


G

The cyclisation could occur before or after hydrolysis of one or both of the ester linkages.



Fumagillin, a potent antibiotic containing two epoxide rings, is isolated from the mould Aspergillus fumigatus. Tarbell and his colleagues[49] solved the structural problem by assigning non-isoprenoid structures to fumagillin and alcohol-I, a hydrolysis product of fumagillin.

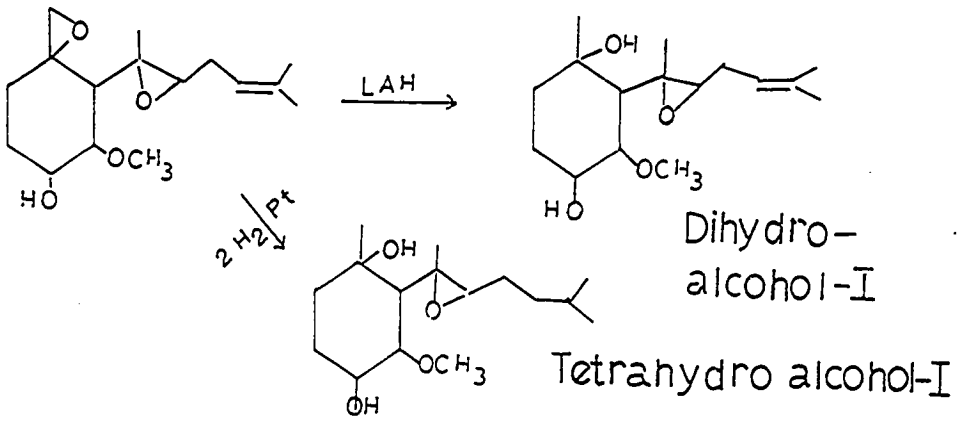


Fumagillin $R=C(=O)(CH=CH)_4CO_2H$

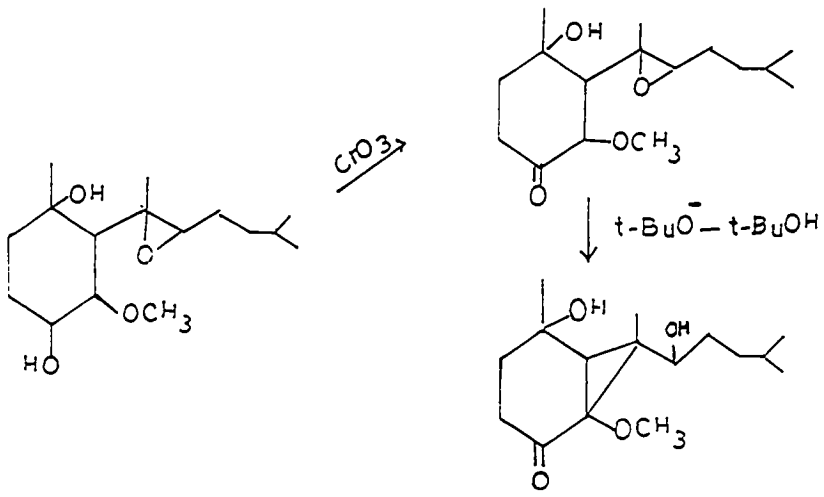
Alcohol-I $R=H$

The two epoxides dominate the chemistry of alcohol-I and undergo a variety of reactions during acid and base-catalysed isomerisation reactions.

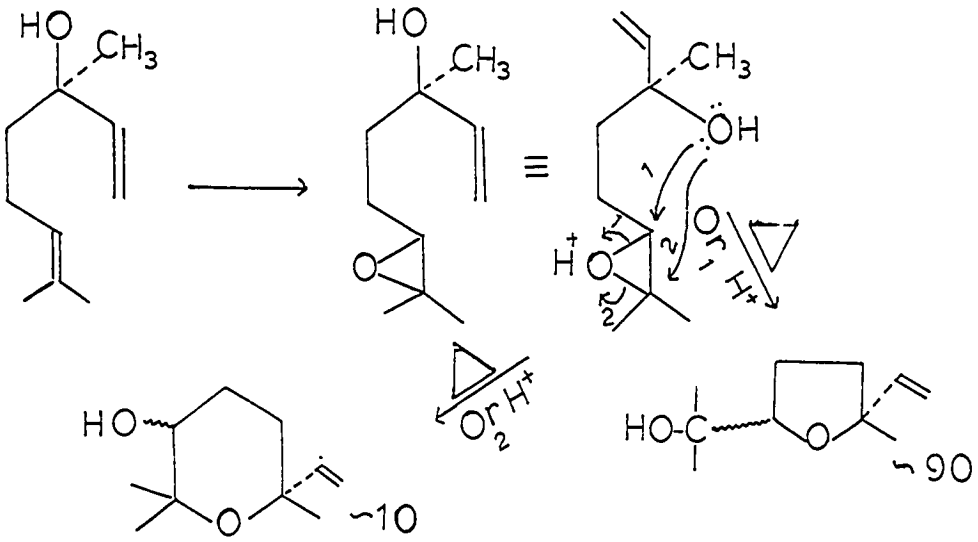
Of the two epoxides, that on the side chain is less reactive than the spiro-epoxide. Thus reduction of alcohol-I with lithium aluminum hydride gives a dihydro alcohol wherein the spiro-epoxide is exclusively attacked at the primary carbon by the hydride anion. Similarly catalytic hydrogenation of alcohol-I gives a tetrahydro alcohol-I wherein the spiro-epoxide alone is opened.



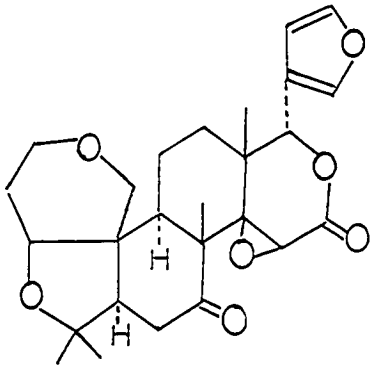
The tetrahydro alcohol-I,[50] on oxidation gave a ketone which on treatment with potassium t-butoxide in t-butyl alcohol gave a crystalline isotetrahydroketone which contained the methoxyl group intact. Therefore the position of methoxyl was fixed as α rather than β to the carbonyl group. The base-catalysed isomerisation involves opening of the epoxide ring at a tertiary instead of a secondary carbon to give a cyclopropane ring.



Oxidation of (-)-linalool with monoperphthalic acid gives the expected diastereomeric pair of 6,7-dihydro-6,7-epoxy linalools.[51] These substances are unstable and on heating are converted to a mixture of two pairs of diastereomeric oxides $C_{10}H_{18}O_2$. They have been shown recently to be tetrahydrofuran and tetrahydropyran derivatives. The cyclisation proceeds as indicated below.



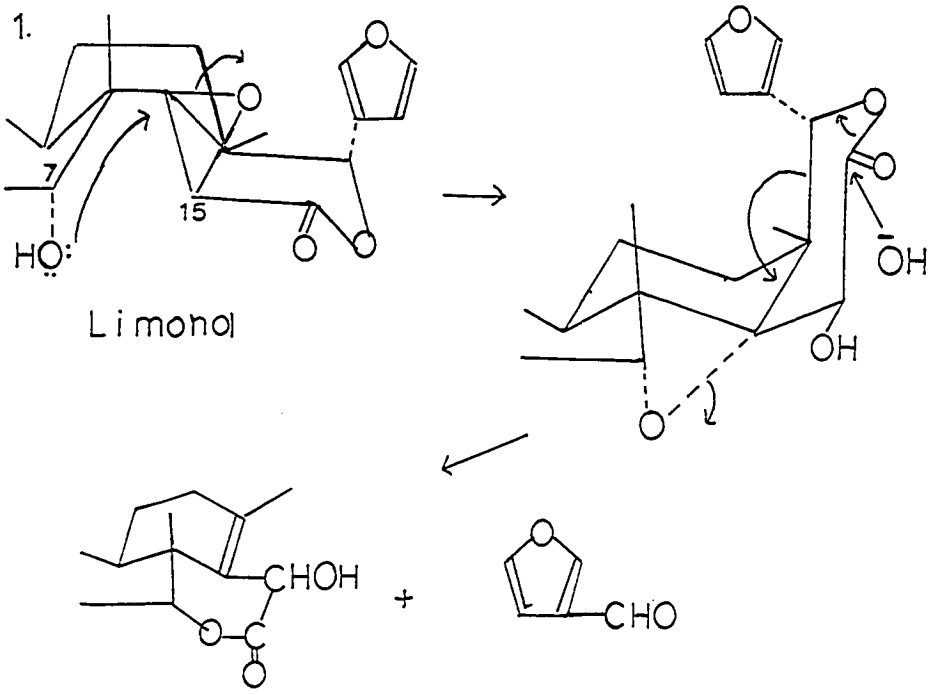
The structure and stereochemistry of limonin, the bitter principle of citrus fruits, have been elucidated by three different teams led by Arigoni and Jeger, Barton, and Corey.[52]



Limonin

An important reaction involving the epoxide was the treatment of limonol, a derivative of limonin, with base, leading to merolimonol and furan-3-aldehyde.[53] The reaction appears to proceed through one of the following mechanisms. Neither epilimonol (equatorial 7β-hydroxyl) nor limonin gives the same reaction.

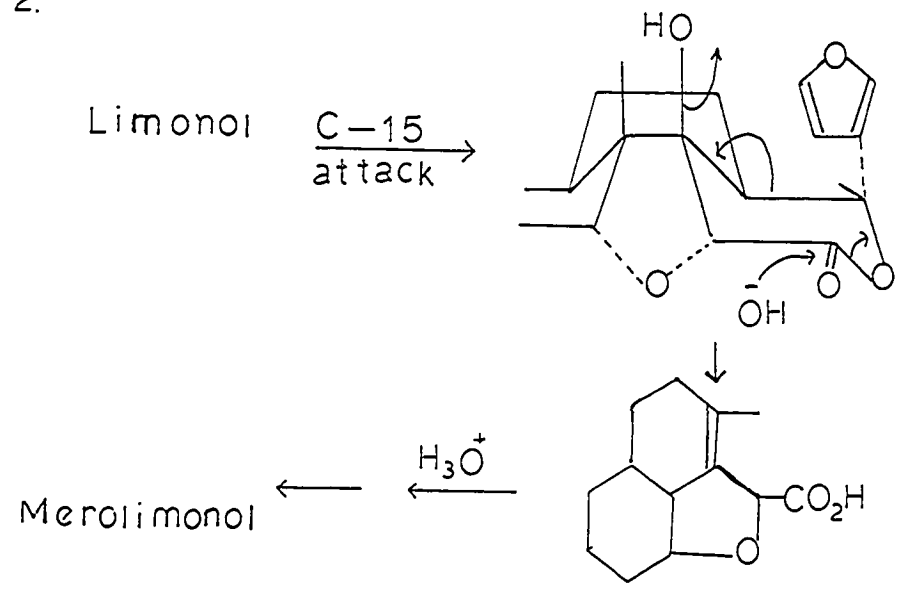
1.



Limonol

Merolimonol

2.



The formation of merolimonol shows that in limonol the C_7-hydroxyl and the epoxide ring must be <u>trans</u> to each other to permit the rearward nucleophilic attack at the epoxide ring.

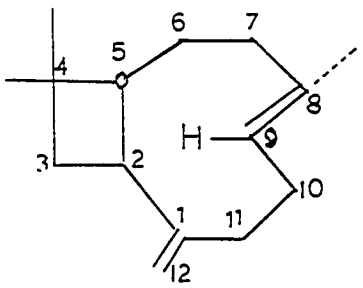
The discussion to this point has emphasized the importance of the

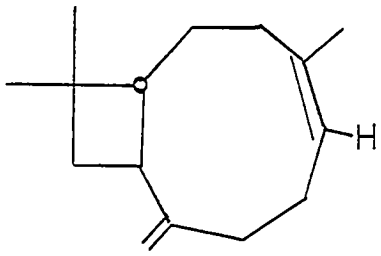
epoxide ring in naturally-occurring compounds and how an understanding of the mechanisms of epoxide ring-opening reactions can help in the structural elucidation of complex molecules. There are only a few examples of transannular isomerisations accompanying epoxide ring-opening reactions under basic conditions and a study of such reactions could further help us in understanding the stereochemistry and mode of epoxide ring-opening. Such a study was initiated in the present work with the determination of the structure of Treibs' 119° glycol, a glycol obtained during the permanganate oxidation of caryophyllene oxide and whose formation involves intramolecular nucleophilic attack at the tertiary carbon of the secondary tertiary epoxide system in basic solution. We began to wonder at this stage about the factors that determine intramolecular nucleophilic attack at the highly-substituted carbon atom of an oxirane ring. It was our primary object to find an answer for the question: Is the nucleophilic attack at either of the two carbon atoms of a tertiary-secondary epoxide ring controlled by steric factors alone or by the formation of strain-free products?

Our observations on the mode of epoxide ring opening in caryophyllene oxide led us to examine the epoxide ring opening reactions of the oxides and epoxy ketones of caryophyllene and isocaryophyllene. These compounds were well suited for study since the stereochemistry about the epoxide ring is established.

Caryophyllene, the bicyclic sesquiterpene hydrocarbon whose carbon skeleton was the basis for the present work occurs in oil of cloves along with humulene, a monocyclic sesquiterpene hydrocarbon. The constitution of caryophyllene presented a great problem to many organic chemists and its chemistry was extensively investigated by Simonsen,

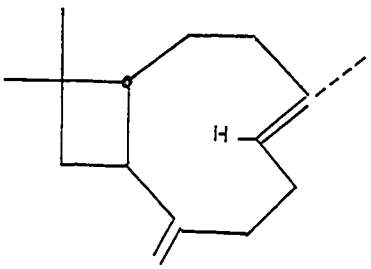
Ruzicka and their colleagues in the early stages.[54] The early work done on the structural elucidation of caryophyllene has been excellently summarised by Barton and de Mayo[55] and by Nickon.[56] An unequivocal proof for the structure of caryophyllene was finally given by its total synthesis, elegantly achieved by Corey[57] in 1964 and thus caryophyllene is represented by the following structure wherein a 4-membered ring is <u>trans</u> fused to a 9-membered ring.

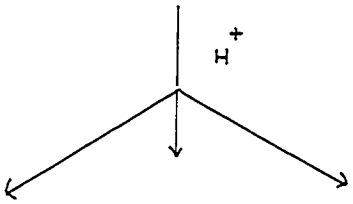


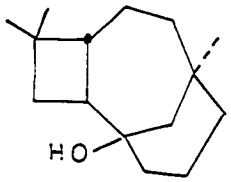


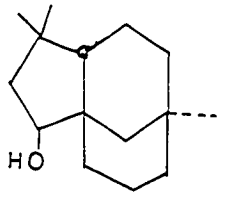
The isomeric hydrocarbon, isocaryophyllene differs from caryophyllene in that the trisubstituted double bond is <u>cis</u> and the proof for this comes from the work of Barton and his coworkers.[58] The correctness of this structure is again elegantly substantiated by its total synthesis achieved by Corey.[57]

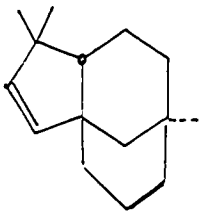
One of the remarkable characteristics of the caryophyllene molecule is its facile cyclisation under acid conditions to give tricyclic compounds. The most important and well known of these cyclisation products are the α- and β-caryophyllene alcohols and the hydrocarbon clovene.[54]









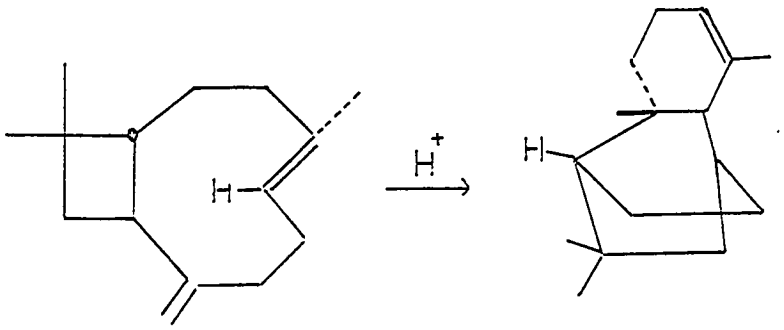


β-caryophyllene alcohol α-caryophyllene alcohol clovene

The structure of β-caryophyllene alcohol was proved by Barton and his colleagues[59] on the basis of degradation experiments. The structures shown above for α-caryophyllene alcohol and clovene were proposed independently by Eschenmoser and Gunthard[60] and Barton and his colleagues.[51] However, a rigorous proof for the clovene skeleton structure was again achieved by Barton, et al.[58b] The structure of clovene has been confirmed recently by its synthesis.[61]

More recently, Raphael and his coworkers[62] isolated another hydrocarbon called neoclovene from the mixture obtained by the acid-catalysed rearrangement of caryophyllene. A rationalisation of this rearrangement of caryophyllene to neoclovene is also given by the same authors.

The structure of neoclovene has been confirmed also by its synthesis.[63] Thus we see that caryophyllene undergoes fascinating transannular rearrangements which are characteristic of medium-ring compounds under acidic conditions.



Neoclovene

RESULTS AND DISCUSSION

CHAPTER I

Epoxide Ring Opening in Caryophyllene and Isocaryophyllene Oxide Derivatives

General methods of preparation and structural determination of glycols

The general methods of preparation of glycols from oxides of caryophyllene and isocaryophyllene involved either hydroxylation of the exocyclic double bond with potassium permanganate and osmium tetroxide or preparation of the bisepoxides from the monoxide and subjecting them to base-treatment. Therefore it seems appropriate at this point to discuss relevant aspects of the epoxidation.

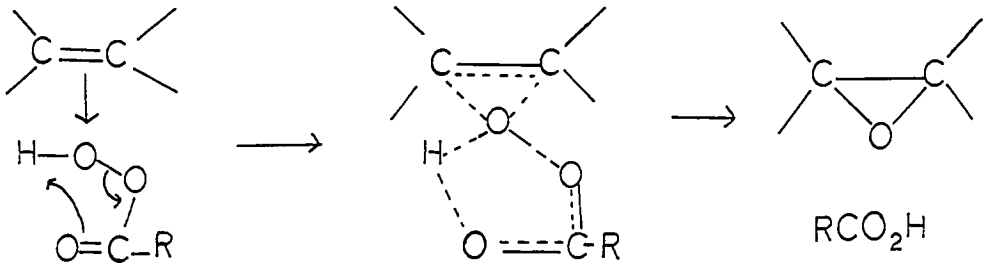
The epoxides were prepared by peracid oxidation of the parent hydrocarbons, caryophyllene and isocaryophyllene, in solvents such as ether, chloroform and benzene. Controlled oxidation of caryophyllene and isocaryophyllene gave predominantly the trisubstituted oxide, leaving the exocyclic methylene group untouched, caryophyllene always reacting faster. Since trans double bonds in medium-ring olefins are much more reactive because of steric strain than those in acyclic molecules,[64] during controlled oxidation of caryophyllene, the peracid always attacks the trans double bond faster than the cis double bond of isocaryophyllene, and the relatively less-reactive exocyclic methyl-

ene double bond of both the molecules. The reason for the predominant attack of the peracid on the trisubstituted double bond in caryophyllene and isocaryophyllene follows from what is known about the mechanism of peracid epoxidation of olefins. Thus peracid oxidation of olefins belongs to a group of organic reactions which involve an oxygen atom directly at the reaction center and in which the oxygen atom behaves electrophilically. This is substantiated by the following observed experimental facts:[65]

a) Alkyl substituents on the double bond which enhance its nucleophilic character, increase the reaction rate, and

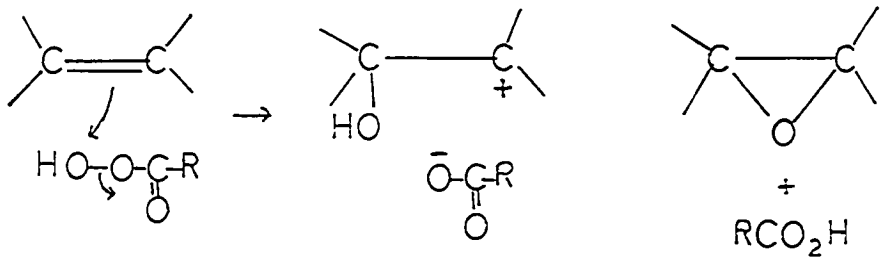
b) electron-withdrawing groups such as -COR considerably decrease the reaction rate.

Furthermore the reaction rate is increased by peracids such as trifluoroperacetic acid,[66] which are stronger acids because of electron-attracting fluorine atoms. The reaction is found to be second order, first order both with respect to olefin and to peracid, and is effected easily in non-ionising solvents such as benzene. The reaction is not subject to salt effects.[67] This led Bartlett[68] to suggest a non-ionic transition state of the type A where proton transfer occurs by a concerted intramolecular process.



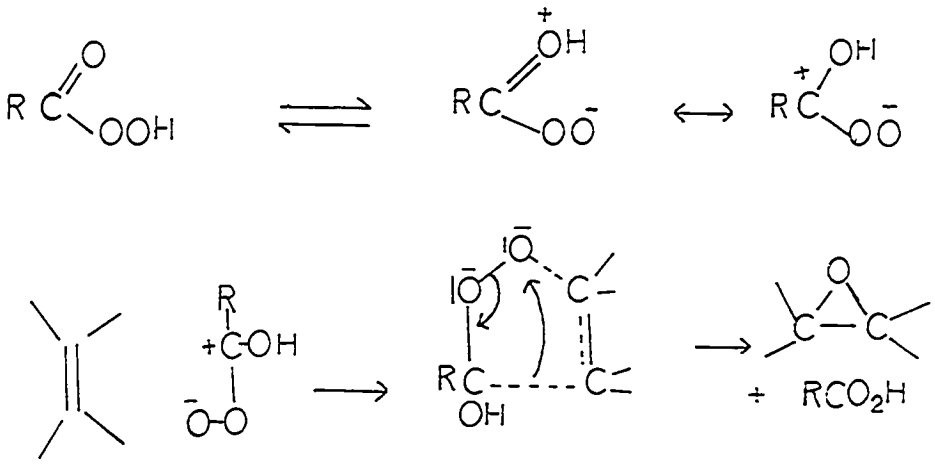
A

Charge-separated intermediate species of type B are unlikely in view of the stereochemical results obtained in peracid oxidation of olefins.



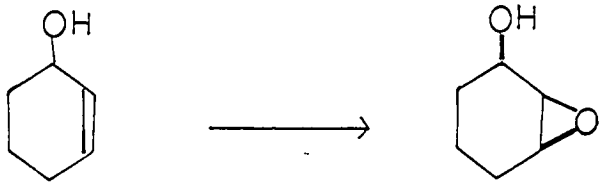
B

More recently, an attractive alternative 1,3-dipolar mechanism has been proposed by Kwart, et al.[70]

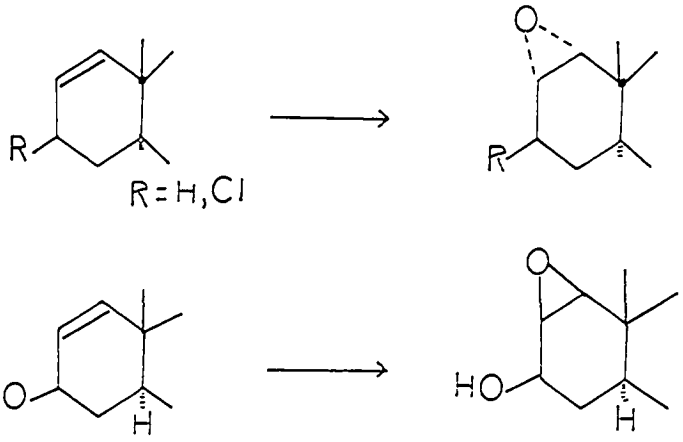


The 1,3-dipolar mechanism has been criticized by Whitham and his co-workers[71] who produced evidence against it. Since the dipolar mechanism has not definitely been proved, Bartlett's mechanism is generally accepted. The stereochemistry of olefin epoxidation has recently been reviewed by Henbest.[69] The net result of the reaction is addition of oxygen across the double bond which proceeds only in the cis manner. Thus trans-2-butene with peracids gives only trans-2-butene oxide.

It is known, largely from the pioneering work by Henbest and his coworkers,[69] that a hydroxyl group in allylic alcohols, can direct attack by peracid at the cis side during epoxidation of the double bond. Such a directive effect of the hydroxyl group was first observed in the reactions of cyclohex-2-enol with peracids in which cis-hydroxy-epoxides are formed.[72]

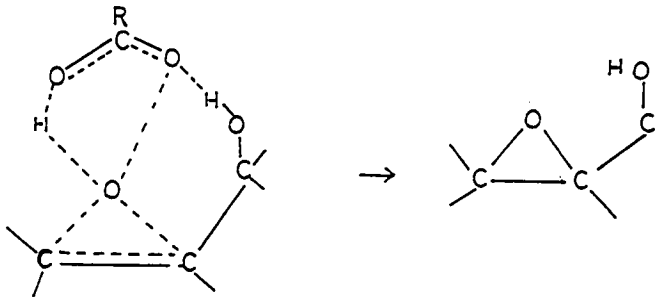


Even in steroid molecules, where the relatively bulky angular methyl groups on the front side (β) of the molecule cause most reagents to approach from the rear side (α-side),[73], the hydroxyl directing effect is observed. Thus, while cholest-1-ene and 3β-chlorocholest-1-ene afford the α-epoxides,[74] in contrast 3β-hydroxycholest-1-ene yields the β-epoxide.[75]

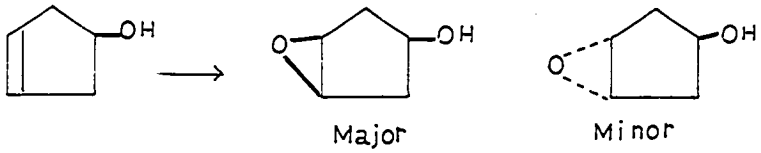


The hydroxyl group is thus exerting some directing effect in giving the cis-epoxy-alcohol. Henbest correlated stereochemical results with rate studies and postulated that "hydrogen bonding causes an association of the reactants favourable for interaction between the electrophilic

peracid oxygen and the olefin." He suggested the following transition complex.

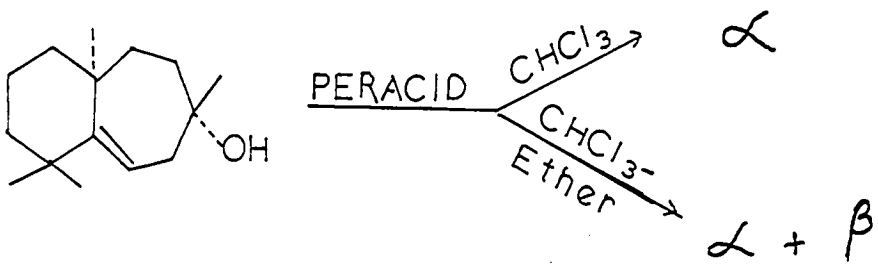


The hydroxyl directing effect was observed even in homoallylic cyclopent-3-enol where the hydroxyl group is separated from the double bond by two carbon atoms. A cis-epoxy-alcohol is obtained in high yield as the major product.[76]



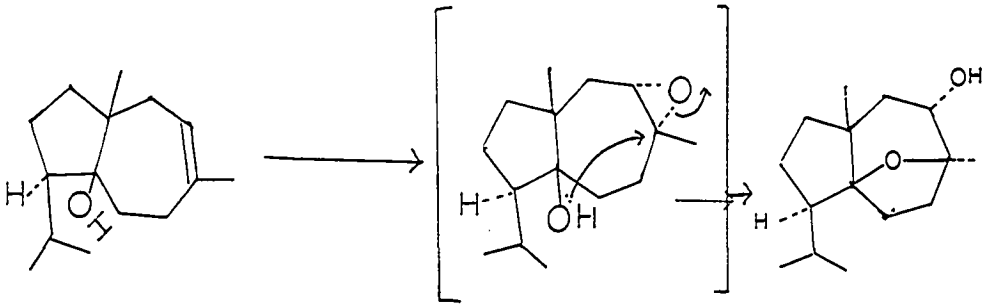
Here also the hydroxyl group is well-placed to participate in the transition state of a cis-reaction. A study of the effect of solvent on the epoxidation of homoallylic cyclopent-3-enol shows that in a non-polar solvent like cyclopentane, the cis-epoxy-alcohol is the major product. However, in a polar solvent like diethyl ether or propan-2-ol, a higher proportion of trans-epoxy-alcohol is found. This is probably because of hydrogen bonding between the hydroxyl group of the alcohol and the oxygenated solvent and a consequent reduced tendency for the hydrogen bond to be formed between the peroxyacid and the hydroxyl of the alcohol.[77]

Recently Itô, et al., observed a hydroxyl directing effect during epoxidation, in a sesquiterpene alcohol:



While the peracid oxidation in chloroform gave exclusively the α-epoxide,[78a] in chloroform-ether mixture a mixture of α and β epoxides in the ratio 70:30 is formed.[78b]

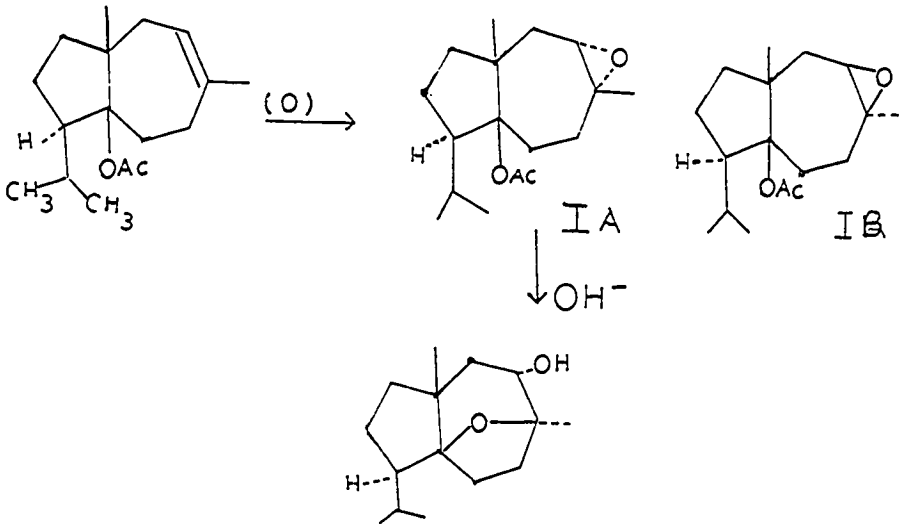
During the course of their investigation on the stereochemistry of carotol and daucol, two naturally occurring sesquiterpene alcohols, Levisalles and his co-workers found that carotol on peracid oxidation in chloroform gave daucol.[39,40]



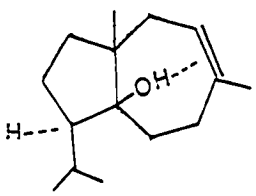
The formation of daucol involves initial oxidation of carotol to an intermediate epoxide which opens up with inversion by intramolecular nucleophilic attack of the angular hydroxyl group at the tertiary carbon of the oxide ring. This is an interesting case in that during the peracid oxidation, the reagent approaches the double bond from the side opposite to angular hydroxyl group. In other words, the hydroxyl group

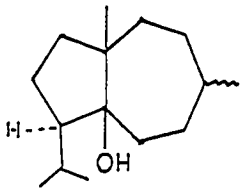
does not seem to exert any "promoting effect" observed by Henbest and his co-workers.

This probably is not due to steric hindrance by the angular methyl group, since carotol acetate on oxidation with peracids gave a mixture of two epoxides IA and IB in equal quantities.[39c]



Saponification of IA in basic solution gave daucol in quantitative yield showing thereby in IA the angular acetate group and epoxide are <u>trans</u> to each other. It is possible that because of a weak hydrogen bond formed between the hydroxyl hydrogen and the double bond of carotol, the β-side of the double bond is shielded, and the peracid is thus directed to come from the α-side of the double bond. An inspection of the Dreiding model reveals that this is reasonable as the distance between the angular hydroxyl and double bond is approximately 1.8$\mathring{A}$. This is further supported by the infrared spectral data on carotol and dihydrocarotol. In carotol while the hydroxyl group appears at 3623 cm^{-1}, it absorbs at 3636 cm^{-1} in dihydrocarotol.

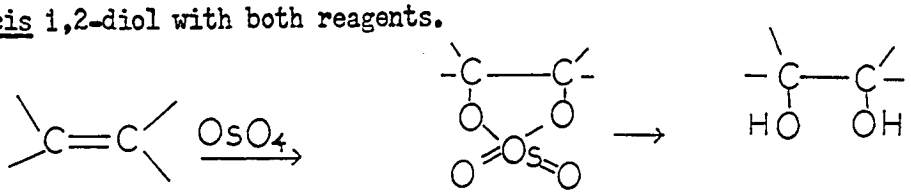


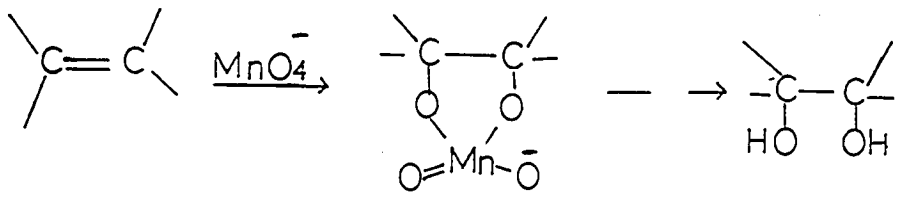


Thus in carotol there is a low frequency shift of O-H stretching band ($\Delta\nu = 13\ cm^{-1}$) and this is in agreement with the existence of a weak intramolecular interaction between the hydroxyl group and the π-electrons of the double bond.[79]

While the hydroxyl directing effect during the peracid oxidation of olefins has been studied in great detail, little information is available on the possibility of participation by the epoxide ring present in an epoxy olefin, during the peracid oxidation of such a molecule. Causa, et al.,[80] have investigated the epoxidation of 1,4-dimethylene cyclohexane with m-chloroperbenzoic acid in a series of solvents of different polarity. Their results show that a cis-bisepoxide was the major product in a non-polar solvent while its proportion decreased considerably in polar solvents. These results have been interpreted as evidence for oxirane-peracid interaction.

While the peracid oxidation of olefins involves a three-membered transition state (two carbon and one oxygen atoms) at the reaction site, hydroxylation of olefins with either potassium permanganate[81a] or osmium tetroxide[81b] is believed to proceed through a cyclic manganese or osmate ester intermediate respectively, as evident from the formation of cis 1,2-diol with both reagents.





This then could mean that, as between peracid oxidation and permanganate or osmium tetroxide hydroxylation of olefin, the former reaction, because of the smaller space requirement of the transition state, will be subjected to less steric hindrance from other bulky groups in the molecule. On the other hand, in the latter reaction involving a five-atom cyclic intermediate (two carbon, two oxygen and one metal atoms). the space requirement of the intermediate is large and hence will be much more subject to steric hindrance by other groups in the molecule. Thus the peracid reagent and permanganate or osmium tetroxide, reagent could approach the double bond in a molecule from different sides, provided that the double bond offers different degrees of steric hindrance to the approaching reagent from each side, and giving products of different stereochemistry. This is exemplified by the oxidation of caryophyllene oxide, as will be seen in the discussion later.

Once the oxido glycols had been prepared (some only in situ) they were allowed to undergo transanmular cyclisation to isomeric oxido glycols.

The nature of the hydroxyl groups in these glycols was easily determined by the following methods:

a) Acetylation: Treatment of a glycol with pyridine-acetic anhydride reagent at room temperature normally acetylates only the primary and

secondary hydroxyl groups leaving the tertiary hydroxyl group unaffected. In the nuclear magnetic resonance (n.m.r.) spectrum of the acetylated glycols, the methylene protons of the primary acetate and the methine proton on the carbon bearing secondary acetate function were shifted downfield with respect to their original peak positions in the parent glycols.[82] The position of a methine proton on a carbon bearing ether oxygen remained essentially unaffected in both the parent glycol and its acetylated product.

b) Oxidation with chromic acid - pyridine reagent (Sarett reagent) at room temperature

Oxidation of the glycols with the Sarett reagent[83] converts primary and secondary alcohol groups into aldehyde and ketone respectively while the tertiary hydroxyl group remains unaffected under the same condition. The aldehyde and ketone functions are distinguished by use of infrared and n.m.r. spectroscopy techniques. Thus in the n.m.r. spectrum the aldehyde proton appears in the low-field region ($\sim$ 9.00 p.p.m.), and in the infrared spectrum the aldehyde O = C-H group exhibits a weak band around 2700 cm^{-1}.

c) Oxidation with aqueous sodium metaperiodate.[84]

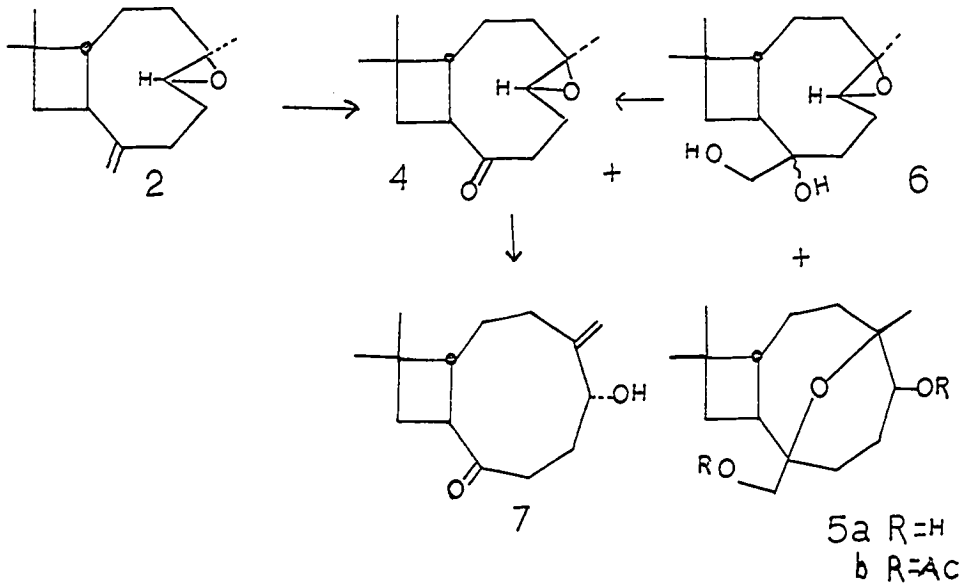
Normally vicinal 1,2-diols alone are oxidised to carbonyl compounds at room temperature while other glycols such as 1,3; 1,4; 1,5; etc. are unaffected by aqueous sodium metaperiodate solutions. Lack of reaction with this reagent was used to prove that any glycol formed was not merely a 1,2-diol from the exo methylene group.

SECTION 1

Glycols from Caryophyllene Oxide 2

Hydroxylation of Caryophyllene Oxide: The Structure of Treib's 119° Glycol

Treibs[85] isolated from the oxidation of caryophyllene oxide 2 with potassium permanganate in acetone, three substances: the keto oxide 4 (69%), a glycol 6, (7%), $C_{15}H_{26}O_3$, m.p. 141°, and a second glycol 5a, (1.7%), $C_{15}H_{26}O_3$, m.p. 119°. The same three substances were isolated by Šorm, et al., when they later repeated the reaction.[86] A fourth compound 7, $C_{14}H_{22}O_2$, m.p. 110°, isolated, has recently been shown to arise by isomerisation of the keto oxide 4 on alumina.[27] The Czech workers found that the glycol 6 of m.p. 141-142° was cleaved by lead tetraacetate to the keto oxide 4 but that the glycol 5a of m.p. 119° was found to be inert to this reagent in benzene solution at 40°. Hence they concluded that the two glycols were "cis and trans isomerides" of the expected 1,2-diol.



However, the fact that the two hydroxyl groups are trans-situated does not in itself explain the non-occurrence of the usual glycol fission. Even in rigid systems glycol fission has been achieved. While the camphane-cis-2,3-diols reacted readily with lead tetraacetate, the reactions of the camphane-trans-2,3-diols were too slow to be measured.[87] Nonetheless the rate constants for the trans diols were obtained at elevated temperatures (50°) and the slow reaction of the trans diols was explained as "caused by a large and rigidly held distance between the two oxygen atoms." Thus, since there are no examples known to us of 1,2-diols not oxidised by lead-tetraacetate,[88], a reinvestigation of the structure of the 119° glycol was warranted.

Repetition of the permanganate oxidation of caryophyllene oxide 2 gave the same results reported earlier. However, since the 119° glycol was obtained in poor yield, we decided to explore other methods of preparation. Osmium tetroxide oxidation of 2 gave a crude product from which the 119° glycol 5a could be obtained in the pure state and in an improved yield of 41%. The presence of the 142° glycol 6 in the mother liquors from the crystallization could not be detected by nuclear magnetic resonance (n.m.r.) spectroscopy or optical rotation. Although this reaction furnished the 119° glycol 5a in a good yield, the prohibitive cost of osmium tetroxide encouraged investigation of its use as a catalyst rather than a stoichiometric reactant. Oxidation of caryophyllene oxide 2 with the hydrogen peroxide - osmium tetroxide-t-butyl alcohol reagent first used by Milas and Sussman[89] gave 25% of a diol fraction containing mainly the 119° glycol 5a and surprisingly a less polar fraction of the keto oxide 4 in 59% yield. Hence this appears

to be a convenient synthesis of the keto oxide 4. There was no detectable amount of the 141-142° glycol in the Milas reaction product. When the 141-142° glycol 6 from permanganate oxidation of 2 was refluxed in methanolic potassium hydroxide it was smoothly but slowly converted into the isomeric 119° glycol 5a. The relationship of these two compounds is discussed further in section 5.

The formation of 4 involves cleavage of a carbon-carbon bond by osmium tetroxide. Although Milas and Sussman obtained only 1,2-diols using this reagent at low temperatures, Criegee[90] has reported that rupture of the carbon-carbon bond was the normal reaction of the hydrogen peroxide - osmium tetroxide - ether reagent. As suggested by Criegee, the carbon-carbon bond scission is probably a consequence of re-oxidation of the osmium VI to osmium VIII in the initially formed cyclic ester before solvolysis of the ester takes place. Since the yield of 119° glycol based on osmium tetroxide was much better in the catalytic than in the stoichiometric reaction and since the glycol obtained in the catalytic reaction contained only the 119° glycol (n.m.r.), it was decided to use this method for large scale preparations of the 119° glycol.

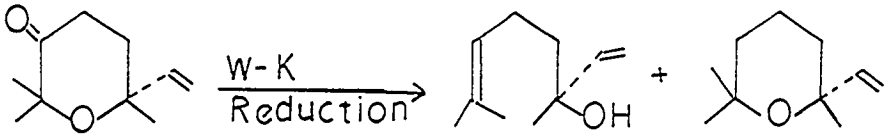
The infrared spectrum of the 119° glycol 5a showed the presence of hydroxyl groups and the absence of carbonyl absorption. The n.m.r. spectrum (see plate I) showed peaks from three unsplit methyl groups: a 6H singlet at 1.02 p.p.m. from the gem-dimethyl group and a 3H singlet at 1.20 p.p.m. due to a methyl group on a carbon atom carrying an oxygen function; there were no vinylic protons. The appearance of the spectrum in the 2.4-4 p.p.m. region (five protons) was concentration dependent and in the more dilute solutions coupling of the hydroxyl

protons could be observed.

The peaks from two hydroxyl protons disappeared on addition of deuterium oxide, and thereby a simplified pattern from the remaining three protons was obtained. These spectral changes could be interpreted as due to the presence of a primary and a secondary alcohol function. A doublet (2H, J = 6.5 c.p.s.) at 3.20 p.p.m. which collapsed to a singlet upon addition of deuterium oxide, indicated the methylene group of the primary alcohol and the weak coupling of the primary hydroxyl proton with the methylene protons of the same group appears as a triplet at 2.67 p.p.m. (J = 6.5 c.p.s.). The secondary hydroxyl group appears as a doublet due to coupling with the adjacent methine proton at 2.47 p.p.m. (1H, J = 8 c.p.s.) where it overlaps one peak of the hydroxyl triplet. The methine hydrogen on the carbon bearing the secondary hydroxyl group appears as a broad lump at 3.55 p.p.m. Since no low field protons could be detected, the third (ethereal) oxygen must be bonded to two tertiary carbon atoms. The correctness of this interpretation was proved by acetylation of the 119° glycol which produced the expected shifts of the α-protons.[82] Acetylation of the 119° glycol with pyridine - acetic anhydride at room temperature produced a liquid diacetate whose infrared spectrum showed the presence of ester carbonyl absorption at 1740 cm^{-1} and the absence of hydroxyl absorption. In the n.m.r. spectrum of the liquid diacetate (see plate I), the methylene group of the primary alcohol was shifted downfield by 0.65 p.p.m. and appears as a sharp singlet at 3.85 p.p.m., while the methine proton of the secondary alcohol was moved downfield by 1.41 p.p.m. and appeared as a multiplet at 4.96

p.p.m. These facts suggested that a reasonable formulation for the 119° glycol was the oxygen-bridged non-vicinal diol 5a, the formation of which can be rationalised by intramolecular attack of the tertiary hydroxy group on the epoxide ring in the 1,2-diol precursor 6. Structure 5a was confirmed by relating the 119° glycol to a known isocaryophyllene derivative in the following manner (see Chart I).

Oxidation of the 119° glycol by the chromic acid - pyridine (Sarett) reagent furnished a mixture of hydroxy ketone 9 and keto aldehyde 8, with the latter constituting a very small proportion of the mixture. Various attempts to reductively cleave the α-alkoxy group of ketone 9, including the use of zinc (or magnesium) - acetic acid or acetic anhydride,[91,92] calcium - liquid ammonia[93] and potassium - sec-butylamine,[94] resulted in the recovery of starting material or acetylated starting material or else merely reduced the carbonyl group. Therefore advantage was taken of the elimination that usually occurs in the Wolff-Kishner reduction of α-substituted ketones,[95] including α-alkoxy ketones,[92,96] a particularly close analogy being provided by the following ketone.[97]



Application of this reaction to the hydroxy ketone 9 gave both the normal reduction product 10a (48%) and the reductive elimination product 11 (36%). The mechanistic path below explains the reaction.

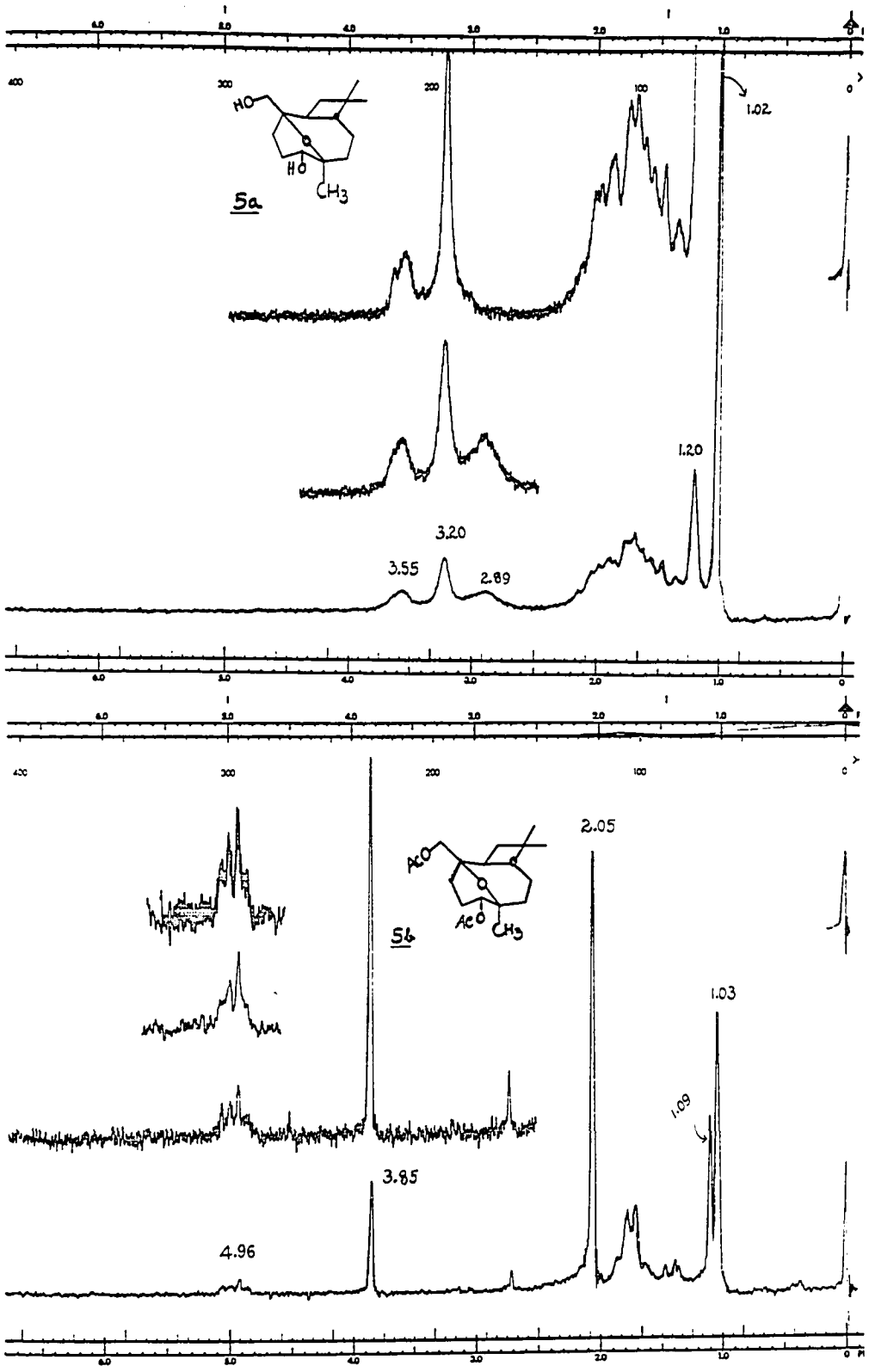
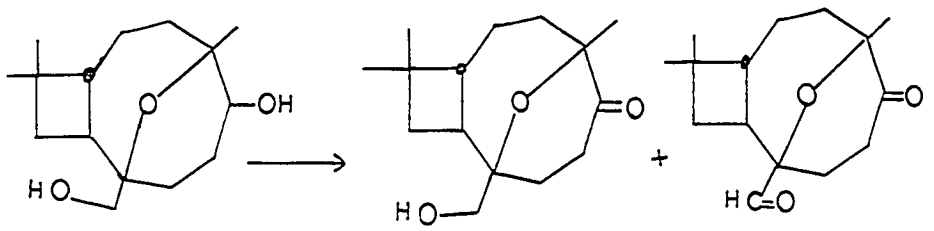
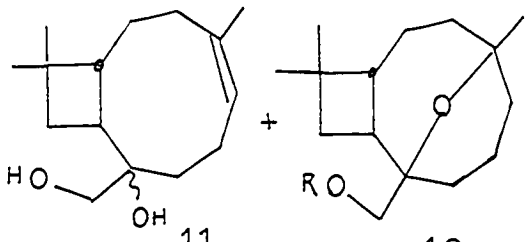


Plate I. N.M.R. Spectra of 119° Glycol and its Diacetate.

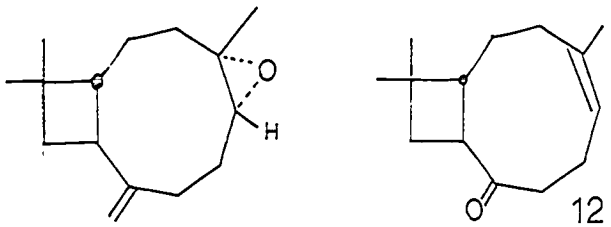
CHART I



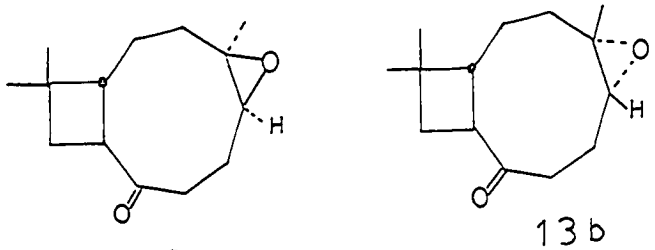
5a 9 8



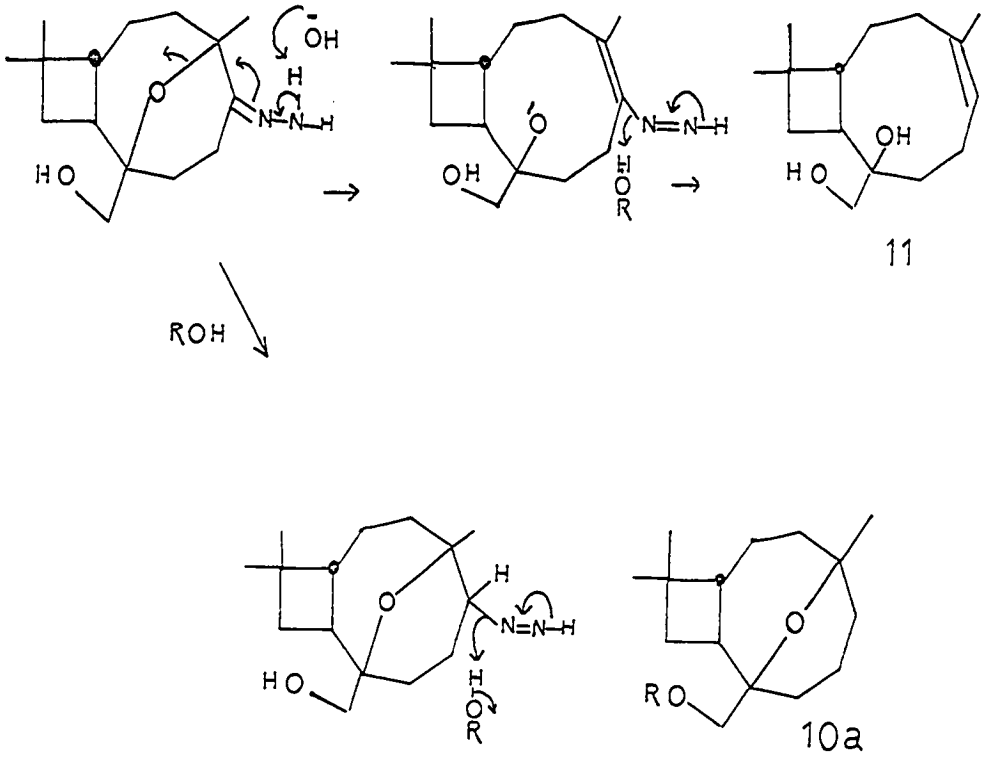
11 10
a, R=H
b, R=Ac



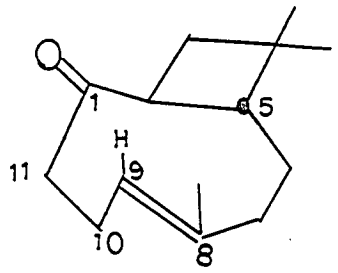
14 b 12



13 a 13 b



The crystalline reductive elimination product 11 was proved to be a vicinal 1,2-diol by oxidising it with sodium metaperiodate whereby a liquid unsaturated ketone 12 was obtained in quantitative yield. The ultraviolet spectrum of compound 12 is worth mentioning. It showed an absorption maximum at 235 mμ (ϵ 440) in 95% ethanol. This chromophore is an example of a σ-coupled π-electron system recognized first by Cookson.[98] Compound 12 is a γ,δ-unsaturated ketone and a close examination of the Dreiding model shows that in a particular conformation the C_{10}-C_{11} bond is parallel to the axes of the π-orbitals of the C=C π-systems. Hence the two π-systems are coupled by overlap with the C_{10}-C_{11} σ bond and this is reflected in the observed maximum in the ultraviolet absorption.



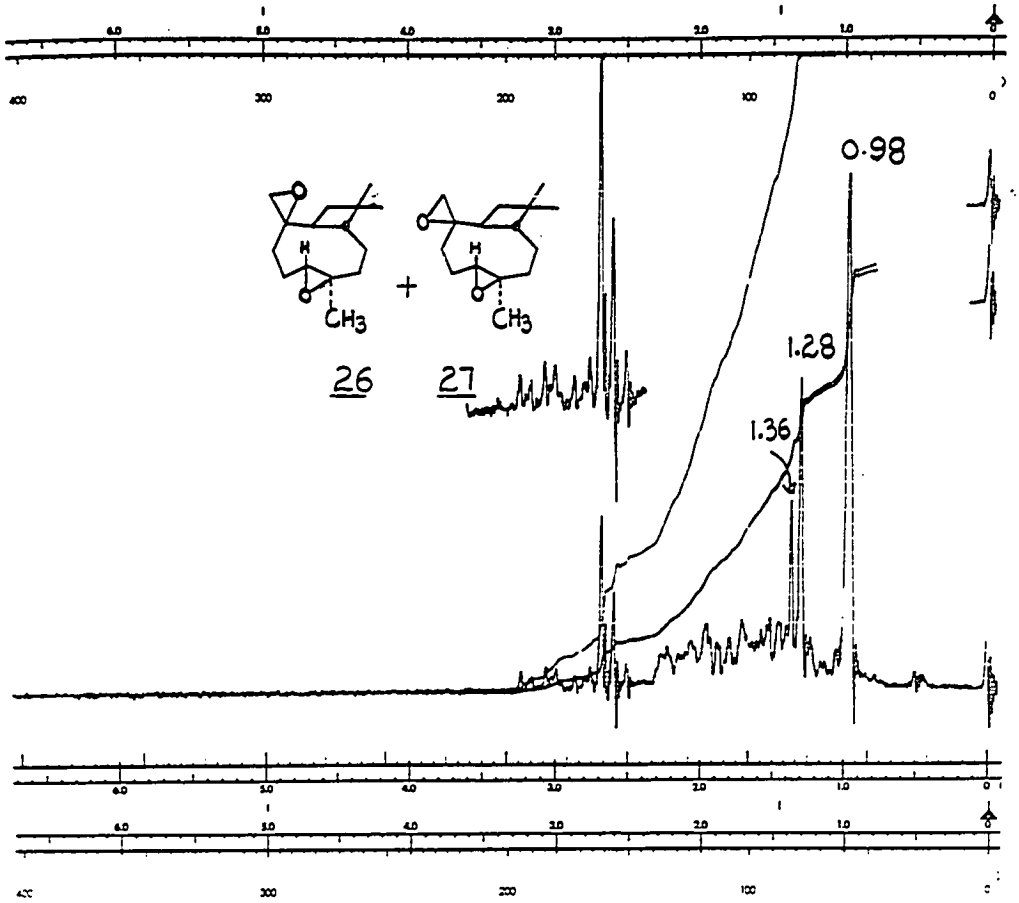
12

That the double bond in the unsaturated ketone 12 is cis was proved by epoxidation of the double bond. From the reaction product was crystallized a keto oxide 13b, m.p. 75-76°, $[\alpha]_D$ - 13.8° which was identical with a sample prepared from isocaryophyllene 15 via epoxidation to isocaryophyllene oxide - b 14b and subsequent oxidation by potassium permanganate.

Epoxidation of Caryophyllene Oxide

Treibs[85] reported in 1947 that caryophyllene oxide 2 on oxidation with perbenzoic acid in chloroform produced a liquid bisepoxide, b.p. 160°/7mm, which was thought to be a single compound. However, since peracid attack could occur from either side of the exocyclic double bond, a mixture of two bisepoxides could result from caryophyllene oxide 2.

In our hands, oxidation of pure caryophyllene oxide 2 with monoperphthalic acid in ether gave a liquid bisepoxide which was found by n.m.r. spectroscopy to be a mixture of two bisepoxides 26 and 27, in the ratio of 65:35. This determination of the ratio was made possible because the C-8 methyl of the oxide ring in the two bisepoxides had different chemical shifts in the n.m.r. spectrum; the C-8 methyl of the major bisepoxide 26 appears as a singlet at 1.28 p.p.m. whereas that in the minor bisepoxide 27 appears as a singlet at 1.36 p.p.m. (see Plate II). Repeated recrystallizations from petroleum ether at



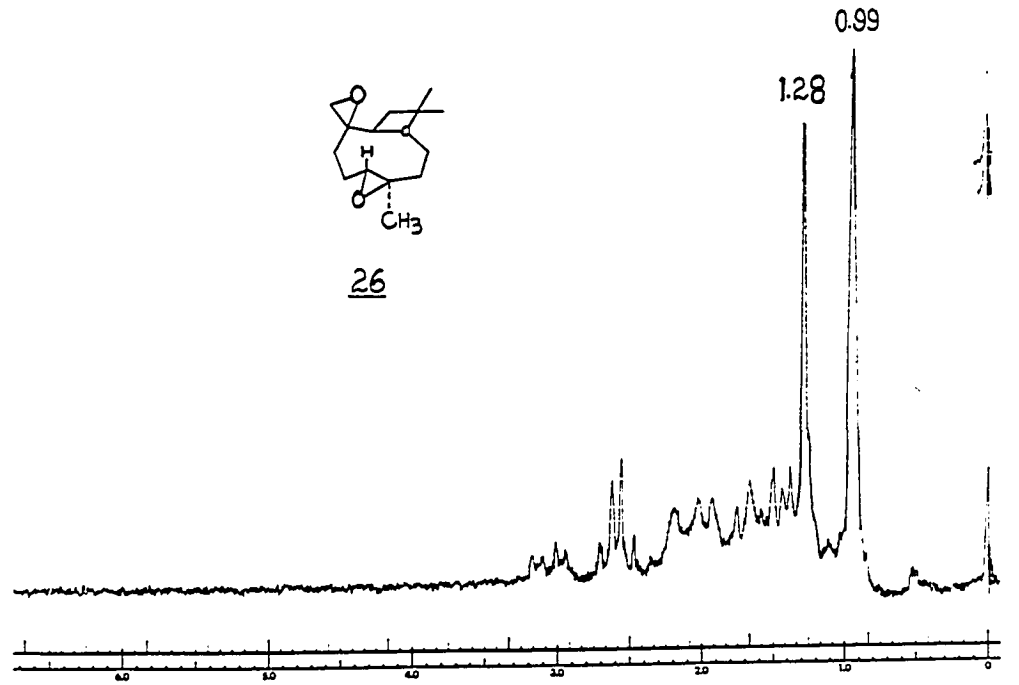


Plate II. N.M.R. Spectra of a mixture of bisepoxides of caryophyllene and pure crystalline caryophyllene bisepoxide.

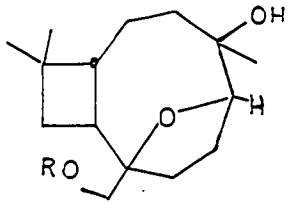
-15° gave a colourless crystalline bisepoxide 26, m.p. 76-77°, in 19% yield. This crystalline solid was shown by its n.m.r. spectrum to be a single compound (see Plate II). Attempts to get the second bisepoxide 27 in the crystalline state were not successful. The n.m.r. spectrum of the crystalline bisepoxide 26 exhibited a 3H singlet at 1.28 p.p.m. due to its C-8 methyl group, and thus the crystalline bisepoxide 26 is the major bisepoxide and the liquid bisepoxide 27 is the minor bisepoxide.

With the major bisepoxide in the pure crystalline state it was decided to study its base-catalysed isomerisation product(s) first, since later analysis of the base-catalysed isomerisation products of the liquid bisepoxide mixture would be simplified. Because intermolecular nucleophilic attack at the highly-substituted carbon atoms C-8 and C-1 of the two oxide rings in 26 and 27 would be subjected to severe steric hindrance, attack would be more likely either at C-12 or C-9 of the oxide rings. However, attack at the secondary C-9 of the oxide ring would be slower than attack at the primary C-12. When the isomerisation of the pure bisepoxide 26 was carried out in aqueous sodium hydroxide, the isomerisation was incomplete and the crude reaction mixture consisted of a large amount of the starting material, but a single glycol, m.p. 115-116°, could be isolated. Therefore the basic conditions chosen for the isomerisation reactions were changed to benzyl alcohol -potassium hydroxide to permit greater solubility of the bisepoxide, and to provide a better nucleophile. Here since the major nucleophilic species attacking the oxide ring will be $C_6H_5CH_2O^{\ominus}$ the resulting product will be a benzyl ether, which could easily be hydroganolysed to generate the gly-

cols. The pure crystalline bisepoxide 26 was heated with benzyl alcohol and potassium hydroxide on a steam bath for 20 hrs and the resulting benzyl ether was hydrogenolysed using palladised carbon catalyst to give a solid glycol fraction. This fraction was found to be a single compound by thin-layer chromatography (t.l.c.) and n.m.r. and on crystallization gave a crystalline solid 29a, $C_{15}H_{26}O_3$, m.p. 115-116° identical with the material from the sodium hydroxide reaction. The infrared spectrum showed the presence of hydroxyl absorption. The glycol was recovered unchanged on treatment with aqueous sodium metaperiodate at room temperature thereby indicating the absence of a 1,2-diol function in the molecule. The n.m.r. spectrum (see Plate III) of the 116° glycol 29a contained peaks from three unsplit methyl groups: a 6H singlet at 0.97 p.p.m. from the gem-dimethyl group and a 3H singlet at 1.00 p.p.m. Although the latter peak could very well indicate a methyl group on an unperturbed sp^3 carbon atom which carries no oxygen function, we assign this peak to a methyl group on a carbon bearing oxygen function from other chemical reactions of the 116° glycol 29a to be discussed. The characteristic feature of the n.m.r. spectrum is the appearance of an AB pattern centered at 3.53 p.p.m. (J_{AB} = 12 c.p.s.) indicative of the methylene group of the primary alcohol function in the molecule.[99] The methine hydrogen on a carbon bearing oxygen is indicated by the appearance of a multiplet centred at 4.05 p.p.m.

Acetylation of the 116° glycol with pyridine - acetic anhydride at room temperature furnished a crystalline monoacetate 29b, $C_{17}H_{28}O_4$. The infrared spectrum of the monoacetate indicated the presence of hydroxyl absorption at 3470 cm^{-1} and a band at 1748 cm^{-1} due to ester

carbonyl. In the n.m.r. spectrum of the monoacetate (see Plate III), the methylene group was shifted downfield by 0.57 p.p.m. and appeared as a singlet at 4.1 p.p.m. The methine hydrogen on a carbon bearing oxygen appeared at 4.0 p.p.m. as a multiplet without any change in its position. This evidence showed that the 116° glycol contained a tertiary hydroxyl and a primary hydroxyl function, and also revealed that the tertiary hydroxyl group must be on C-8. At this stage it appeared reasonable to propose structure 29 for the 116° glycol.



29 a R=H
b R=Ac

That the molecule contained a tertiary hydroxyl group was further proved by the fact that oxidation of the monoacetate of the 116° glycol 29b with chromic acid - pyridine at room temperature gave back the starting material unchanged. Moreover oxidation of the 116° glycol 29a, with chromic acid - pyridine (Sarett) reagent at room temperature gave a liquid hydroxy aldehyde 31 whose infrared spectrum indicated the presence of hydroxyl absorption and bands at 2710 cm^{-1} and 1745 cm^{-1} due to aldehyde. The n.m.r. spectrum indicated a low field singlet proton at 9.66 p.p.m. due to aldehyde. All these facts support the above structure 29a for 116° glycol.

A rigorous proof for the tertiary nature of the hydroxyl in the 116° glycol 29a was provided by dehydration experiments. Dehydration of 29b using methanesulfonyl chloride - sulfur dioxide - collidine - dimethylformamide reagent[100] gave a mixture of olefinic acetates 32a

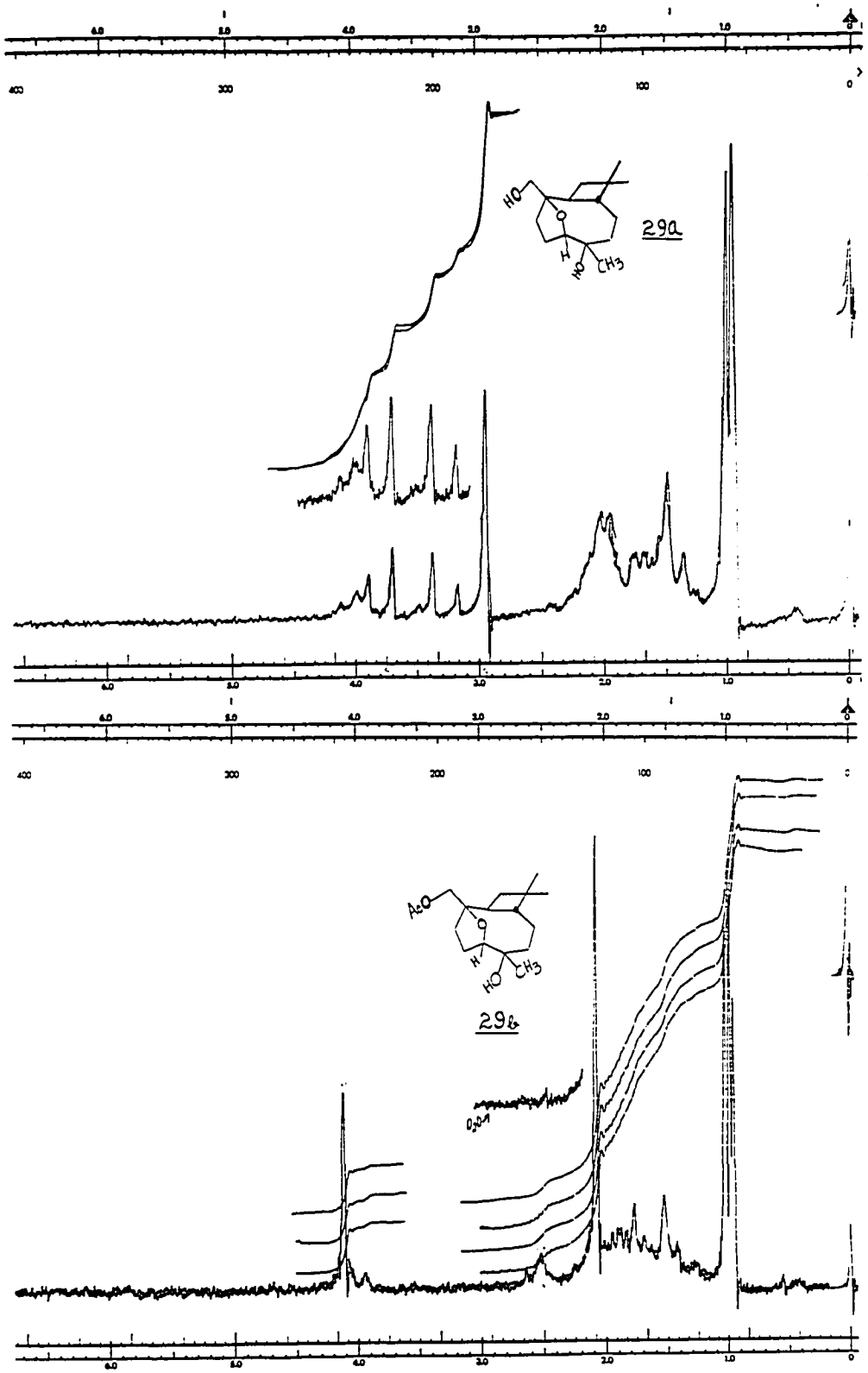
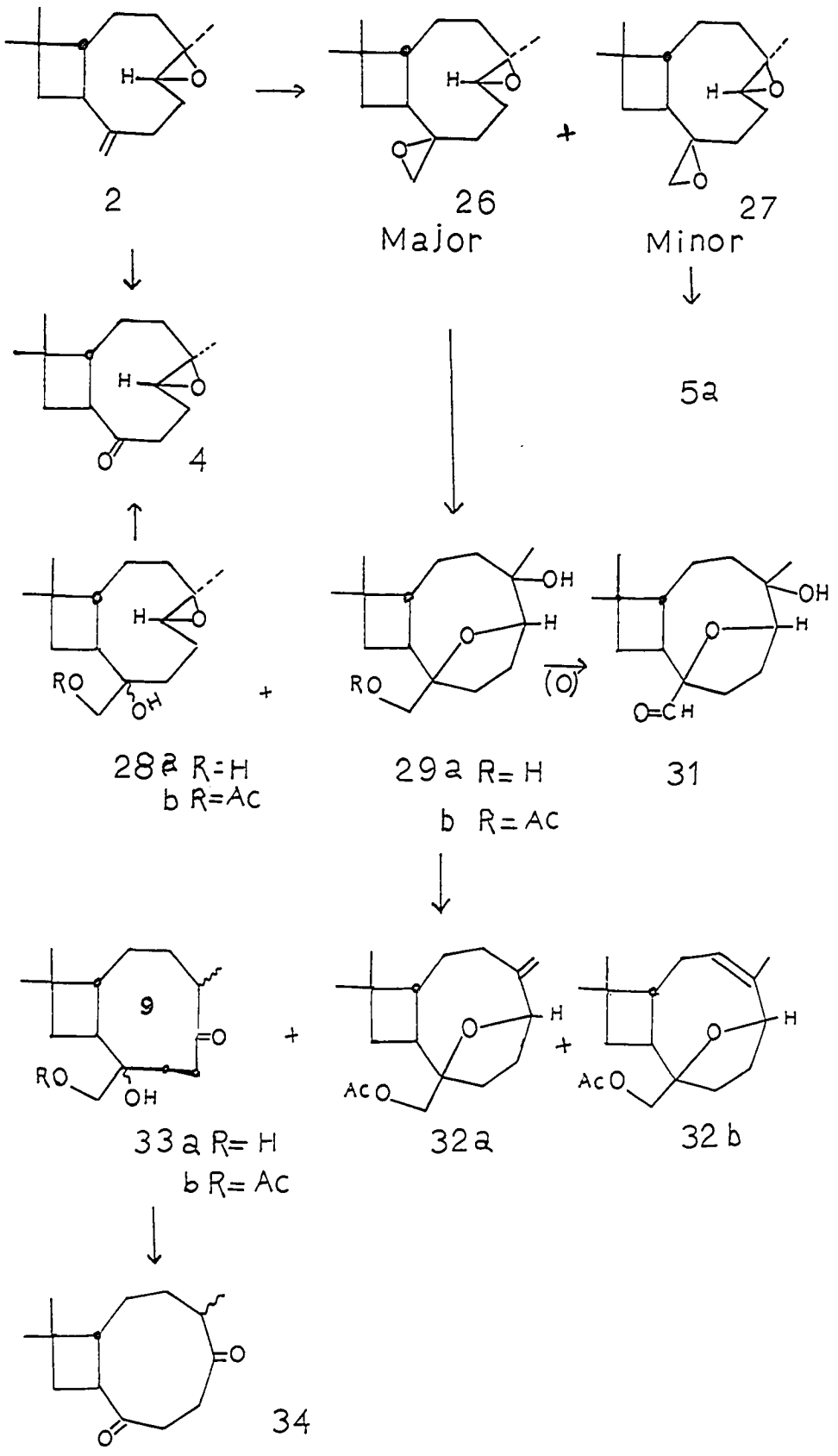


Plate III. N.M.R. Spectra of 116° Glycol and its monoacetate.


2
26
Major
27
Minor
5a
4
28a R=H
b R=Ac
29a R=H
b R=Ac
31
9
33a R=H
b R=Ac
32a
32b
34

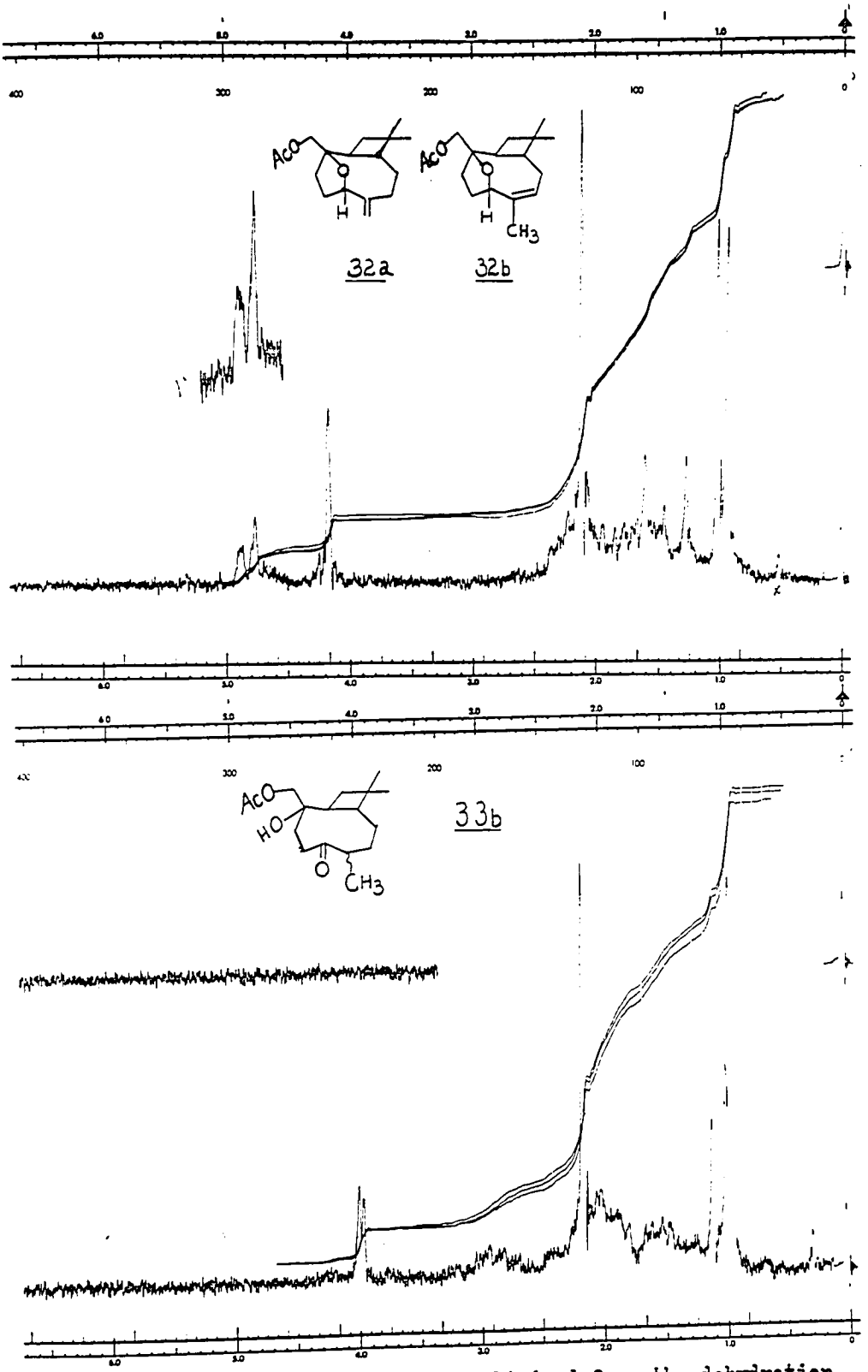


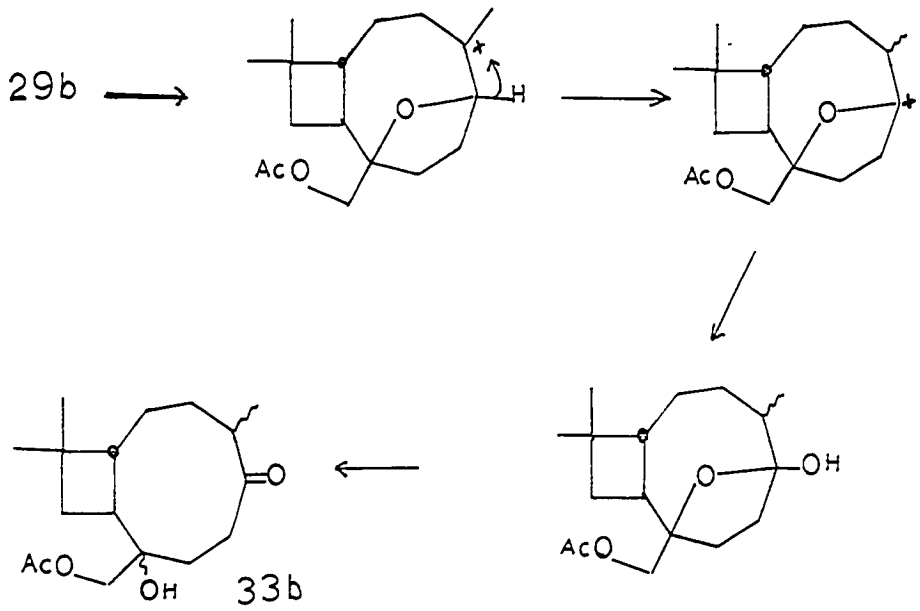
Plate IV. N.M.R. Spectra of products obtained from the dehydration of 116° Glycol monoacetate.

and 32b and an unexpected product to which the structure 33b is assigned.

The n.m.r. spectrum of the crude olefinic acetate mixture proved it to be a mixture of 32a and 32b in the approximate ratio of 85:15 (see Plate IV). The infrared spectrum of the olefinic acetate mixture 32a and 32b showed bands at 3060 cm^{-1} and 885 cm^{-1} due to exocyclic methylene.

The infrared spectrum of 33b showed the presence of hydroxyl absorption, ester carbonyl absorption at 1725 cm^{-1} and a band at 1700 cm^{-1} due to 9-membered ketone. The n.m.r. spectrum of 33b (see Plate IV) contained a 6H singlet at 0.91 p.p.m. from the gem-dimethyl group; a 3H doublet (J = 7 c.p.s.) at 1.02 p.p.m. indicated the presence of a methyl group on a carbon bearing one hydrogen; a 3 H singlet at 2.09 p.p.m. from the acetate methyl, a 2H AB pattern centered at 3.89 p.p.m. (J = 11 c.p.s.) indicative of the methylene protons of primary acetate and a 1H singlet at 2.37 p.p.m. disappearing on deuteration indicative of a hydroxyl group. Saponification of 33b with methanolic potassium hydroxide gave a glycol fraction which showed two spots of close R_f value, one due to hydroxyketone 33a and the second probably due to the hemiketal of 33a involving the primary alcohol group in hemiketalisation. The glycol fraction thus got was oxidised directly by aqueous sodium metaperiodate at room temperature to a single compound, presumably the diketone 34, which showed the absence of hydroxyl absorption and the presence of 9-membered ketone absorption at 1695 cm^{-1}. These facts are consistent with the structure 33b proposed for the hydroxy acetate obtained from the dehydration of

29b. The formation of 33b from 29b appears to involve a hydride transfer and the following mechanism accounts for its formation.



The determination of the structure of the 116° glycol obtained from the major crystalline bisepoxide made it easy to study the base-catalysed isomerisation of the liquid bisepoxide mixture, Since any product other than 116° glycol in the crude mixture must have been derived from the minor bisepoxide. The bisepoxide mixture containing 26 and 27 in the ratio 65:35 was heated with benzyl alcohol and potassium hydroxide for 96 hours on a steam bath and the resulting crude benzyl ether was hydrogenolysed using palladised charcoal in a Parr hydrogenator to give a mixture of two glycols only (t.l.c. and n.m.r.). The infrared spectrum of the crude mixture showed the presence of hydroxyl absorption. Careful crystallisation of the crude glycol mixture gave two glycols. The glycol obtained in minor quantity (25%)

had m.p. 117-118.5° undepressed on admixture with authentic 119° glycol 5a. The infrared and n.m.r. spectra of this glycol were identical with those of 5a. The glycol obtained in major quantity.(62%) was found to be the 116° glycol 29a (m.p. and mixed m.p.). Since we know that the 116° glycol 29a is formed from the major crystalline bisepoxide 26, the minor 119° glycol 5a must have been derived from the minor bisepoxide 27.

However, when the bisepoxide mixture reaction with benzyl alcohol and potassium hydroxide was allowed to proceed only for 20 hours (see Chart II), there was obtained a slightly different glycol mixture together with some unreacted bisepoxide mixture (t.l.c.). After chromatographic separation from recovered bisepoxide, the glycol fraction was directly acetylated at room temperature with acetic anhydride - pyridine reagent to give a mixture of two crystalline monoacetates 29b (m.p. 92-92.5) and 28b (m.p. 149-151°) in 40% and 30% yield respectively. The t.l.c. of the crude acetate mixture did not reveal any spot corresponding to the diacetate of the 119° glycol 5b. The infrared spectrum of the monoacetate 28b exhibited strong hydroxyl and ester carbonyl absorptions. Saponification of the monoacetate, which was not identical with the 116° glycol monoacetate 29b, with methanolic potassium hydroxide gave a crystalline glycol 28a, $C_{15}H_{26}O_3$, m.p. 126-127°, which depressed the melting point of the 142° glycol 6. However, periodate oxidation of 28a gave the oxidoketone 4 in quantitative yield thereby showing the 127° glycol 28a to be a 1,2-diol epimeric with the 142° glycol 6 at C_1. The 1,2-diol 28a, on heating with methanolic potassium hydroxide for 118 hours was smoothly converted to the 116° glycol 29a with no detectable amount of either the 119° glycol 5a or any other

glycol. This provides additional proof that glycols 6 and 28a are hydroxy epimers at C-1.

Since there was no evidence for the formation of the 119° glycol 5a in the shorter reaction period, it appears that the minor bisepoxide of caryophyllene, 27, reacts very slowly under basic conditions. Although it is not clear from Dreiding models why the minor bisepoxide 27 is attacked by external nucleophile very slowly in comparison to the major bisepoxide 26, it should be noted that the 142° glycol 6 was converted to the 119° glycol 5a only after prolonged heating with methanolic potassium hydroxide for 168 hours (see Experimental).

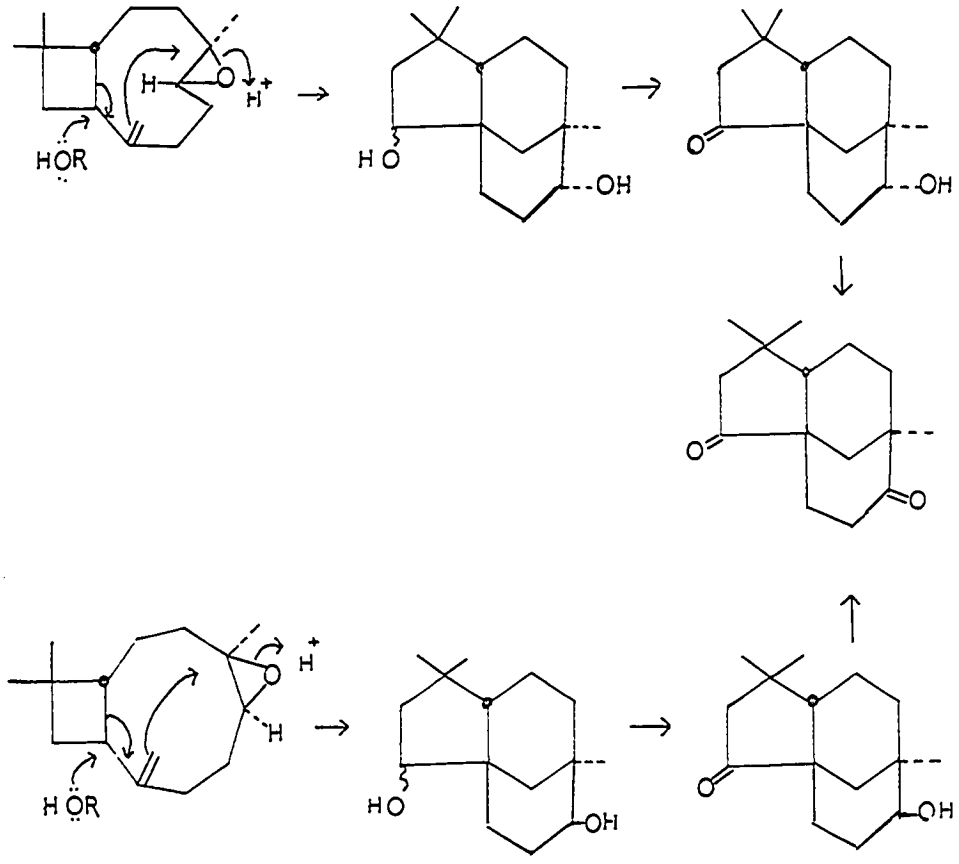
SECTION 2

Glycols from Isocaryophyllene Oxide-a

Hydroxylation of Isocaryophyllene Oxide-a

In the course of their work on the correlation of isocaryophyllene with caryophyllene, Ramage and Whitehead[101] found peracid oxidation of isocaryophyllene to give two oxides a and b, oxide-a 14a being a crystalline compound, m.p. 77° and the other an oil. The stereochemistry of the crystalline oxide 14a was proved by Barton, et al.,[58b] who found that acid-catalysed hydration of caryophyllene monoxide 2 gave a disecondary alcohol which on oxidation with chromic acid gave

a hydroxy ketone as one of the products. Similar hydration of crystalline oxide-a 14a furnished a stereoisomeric disecondary glycol which on oxidation with chromic acid gave a hydroxy ketone which was found to be different from the hydroxy ketone obtained from caryophyllene oxide. Since both the hydroxy ketones obtained from caryophyllene oxide and isocaryophyllene oxide-a gave the same diketone, the stereochemistry of the C-8 methyl in the two oxides is the same, provided that in both of these acid-catalysed transannular reactions the epoxide ring was opened with inversion. Therefore the C-8 methyl group in isocaryophyllene oxide-a is α-oriented since this orientation has been proved for caryophyllene oxide.[58b]



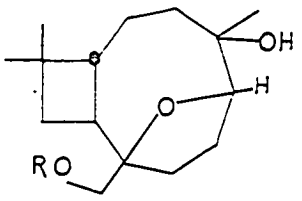
Isocaryophyllene was prepared by nitrous acid isomerisation of caryophyllene as described in the literature.[102] This procedure is tedious and the yield is also low (22%). Too recently to be of use Schulte-Elte and Ohloff[103] have reported a simpler and better method for preparing isocaryophyllene in 95% yield by irradiation of caryophyllene with a high-pressure mercury lamp in the presence of small quantities of diphenyl disulfide. Following the procedure of Ramage and Whitehead,[101] peracid oxidation of isocaryophyllene gave a mixture of oxides, from which oxide-a 14a could be crystallised in 25% yield, m.p. 73-75°. The mother liquor from crystallization of 14a contained mainly oxide-b 14b (70-80% pure). As attempts to purify oxide-b 14b were unsuccessful, it was decided to use the 70-80% pure oxide-b for further reactions (see section 3).

Hydroxylation of Oxide-a

Hydroxylation of crystalline oxide-a with osmium tetroxide gave a crude product which was found to be largely one compound (t.l.c. and n.m.r.). Direct crystallization of the crude product gave in 38% yield a crystalline glycol 19a, $C_{15}H_{26}O_3$, m.p. 128.5-130° (see Chart III). The infrared spectrum exhibited absorption due to hydroxyl groups and no absorption band due to carbonyl group. The n.m.r. spectrum (see Plate V) had the following signals: a 6H singlet at 0.99 p.p.m. from the gem-dimethyl group, a 3H singlet at 1.32 p.p.m. from the methyl group on a carbon atom bearing an oxygen function; a 2H multiplet centred at 3.28 p.p.m., which collapsed to a doublet on deuteration, due to methylene protons of a primary alcohol function and a broad 1H multiplet centered at 3.93 p.p.m. due to a methine hydrogen on a carbon

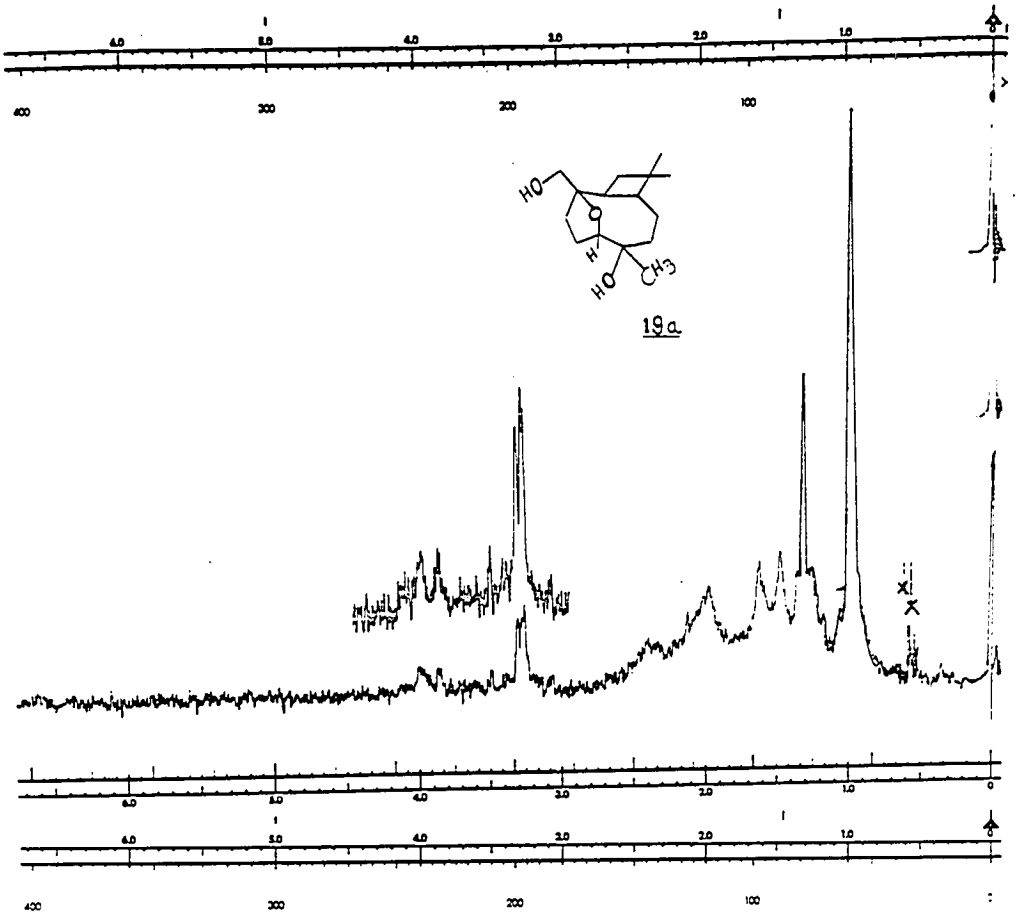
atom bearing oxygen.

Acetylation of 19a produced a liquid monoacetate 19b, $C_{17}H_{28}O_4$, which showed in the infrared spectrum absorption bands due to hydroxyl and ester carbonyl groups. In the n.m.r. spectrum (see Plate V), the methylene protons were shifted downfield by 0.62 p.p.m. and appeared as a singlet at 3.90 p.p.m. The poorly resolved methine hydrogen did not move appreciably and appeared as a broad lump at 4.05 p.p.m. This shows that the methine hydrogen must be on a carbon attached to an ether oxygen. A clean singlet at 1.77 p.p.m. disappearing on deuteration indicated the presence of a hydroxyl group. Since this hydroxyl group survived the acetylation at room temperature, it must be tertiary in nature. Furthermore the monoacetate 19b was recovered unchanged on treatment with the Sarett reagent at room temperature, thereby confirming the tertiary nature of the hydroxyl group in 19b. The glycol 19a was recovered unchanged on treatment with aqueous sodium metaperiodate at room temperature and therefore is not a 1,2-diol. All these facts could be accommodated in the following structure 19a, which is supported by other experiments (see section 5 for stereochemical assignment).



19a R=H
b R=Ac

The mother liquor from the crystallization of 19a was found to contain mainly the 130° glycol 19a along with two other minor glycols (very faint spots ~5% in t.l.c.)



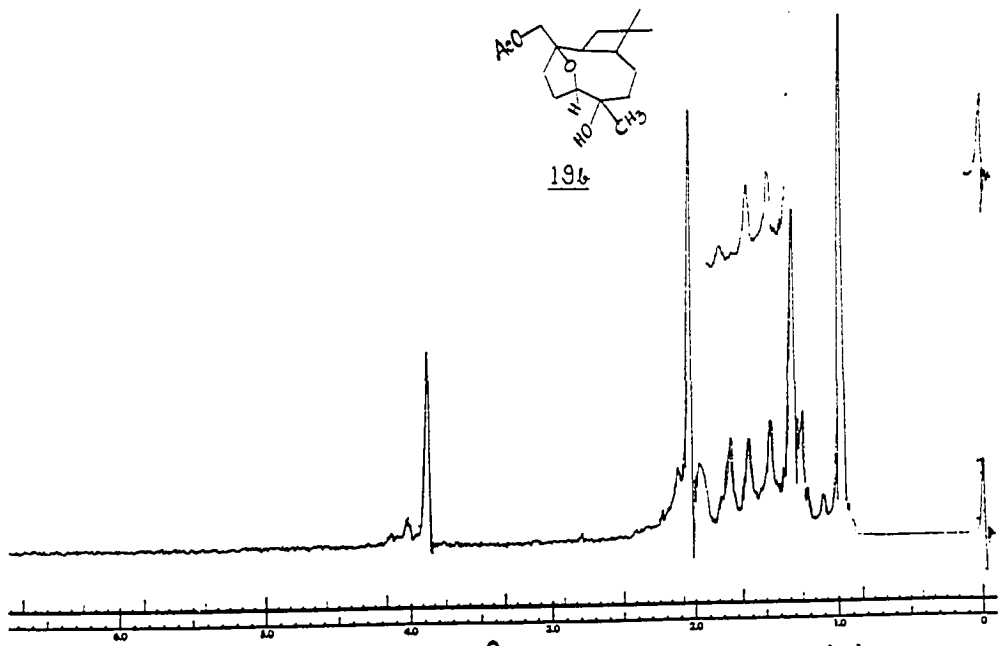


Plate V. N.M.R. Spectra of 130° Glycol and its monoacetate.

CHART III

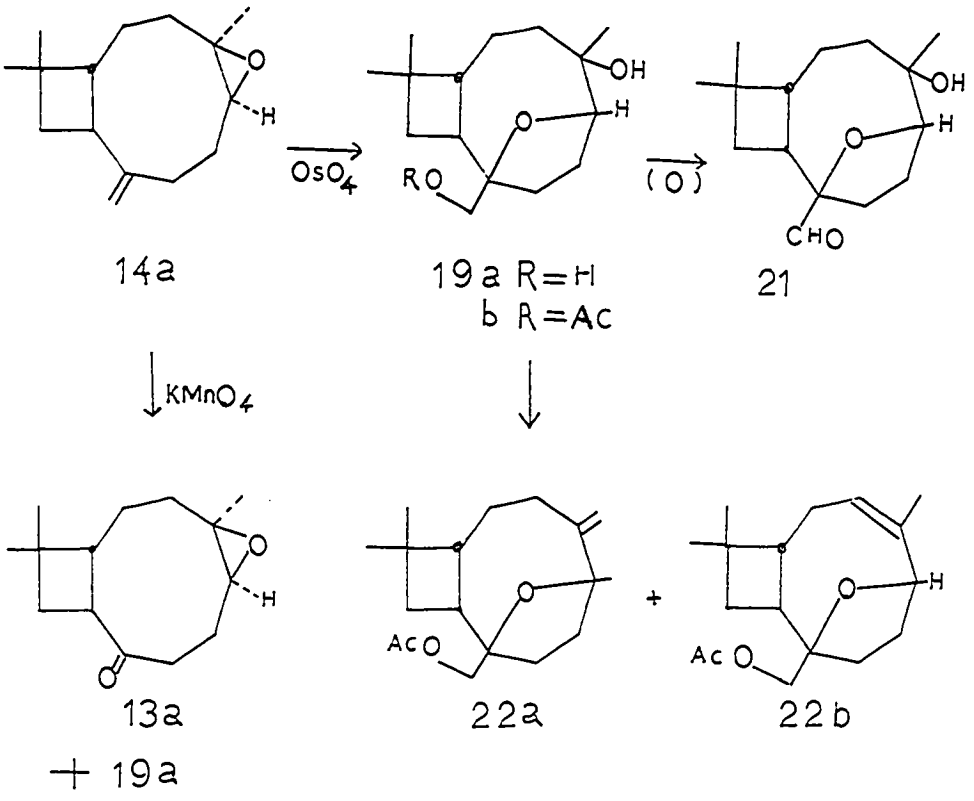
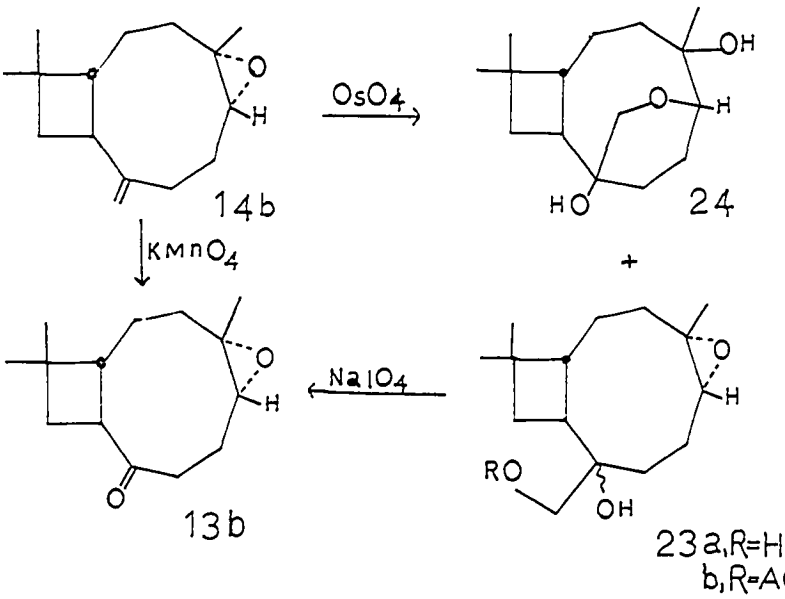


CHART IV



Oxidation of the 130° glycol 19a by Sarett's reagent (chromic acid - pyridine) at room temperature produced a hydroxy aldehyde whose infrared spectrum showed the presence of hydroxyl and carbonyl absorptions. Dehydration of the monoacetate of the 130° glycol, 19b using methanesulfonyl chloride - sulfur dioxide - collidine - dimethylformamide,[100] gave a mixture of liquid olefinic acetates 22a and 22b in 91% yield. The n.m.r. spectrum (see plate VI) of the crude olefinic acetate mixture indicated it to be a mixture of 22a and 22b in the ratio approximately 85:15, and contained the following signals: a 6H singlet at 1.0 p.p.m. from the gem-dimethyl, a 3H singlet at 2.08 p.p.m. from the acetate methyl. The methylene protons of the primary acetate in 22a appeared as a three peak pattern at 3.95 p.p.m., which probably is due to overlap with those of the methylene protons of the primary acetate in 22b. The exocyclic methylene of 22a appeared in the spectrum as an AB quartet (J_{AB} = 3 c.p.s.) centred at 4.86 p.p.m. A small peak at 1.7 p.p.m. appearing as a closely-split doublet can be ascribed to vinylic methyl group in 22b; the position of the vinylic hydrogen in 22b could not be exactly determined as it probably merged with the peaks from exocyclic methylene in 22a. The infrared spectrum showed the presence of ester carbonyl and the absence of hydroxyl absorption, thus indicating the correctness of the assigned structures 22a and 22b for the dehydration products.

Oxidation of oxide-a 14a with potassium permanganate in acetone at room temperature was also carried out as reported in the literature[101] to check whether the formation of the 130° glycol 19a also occurs under conditions known to be basic. Although Ramage and Whitehead[101] did not report any glycol from the reaction mixture, we isolated a solid

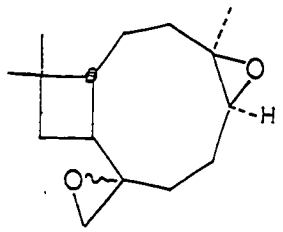
glycol fraction in 28% yield in addition to the expected keto-oxide-a 13a. The glycol fraction was found to be identical with 19a in all properties. The formation of 19a during the permanganate oxidation of oxide-a 14a shows that the intramolecular nucleophilic attack of the hydroxyl group at the secondary carbon of the oxide ring occurs under both dubiously acidic and definitely basic conditions. Under these conditions the 1,2-diol precursor 18 could not be detected either by periodate oxidation of the crude reaction product or by n.m.r. spectroscopy.

Epoxidation of Isocaryophyllene Oxide-a

Since caryophyllene oxide gives a mixture of two bisepoxides during epoxidation, corresponding to attack by peracid from both sides of the exocyclic double bond, a similar result might be expected from both oxides of isocaryophyllene. If the oxide ring in 14a exerts any directing effect by interaction with peracid during the oxidation of 14a, then such an effect should be felt in the proportion of the two bisepoxides formed. Also the relative proportions of the two bisepoxides obtained should be solvent dependent; oxidation in non-polar solvent should give predominantly a cis-bisepoxide in which the two oxide rings are on the same side, while in a polar solvent, the proportion of the trans-bisepoxide, in which the two oxide rings are on opposite sides, should increase.

Oxidation of pure crystalline oxide-a 14a with perbenzoic acid in benzene at room temperature gave a single bisepoxide 42, $C_{15}H_{24}O_2$, m.p. 98.5-100°. The infrared spectrum indicated the absence of hydroxyl, carbonyl and olefinic absorptions. The n.m.r. spectrum (see plate VII)

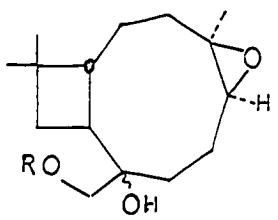
contained the following peaks: two 3H singlet peaks at 0.96 p.p.m. and 1.00 p.p.m. from the gem-dimethyl group; a 3H singlet at 1.36 p.p.m. due to a methyl group on a carbon bearing oxygen atom, an AB pattern centered at 2.65 p.p.m. (J_{AB}= 10 c.p.s.) from a methylene group on carbon bearing oxygen and a 1H broad ill-resolved multiplet at 2.95 p.p.m. due to a methine proton on a carbon bearing an oxygen function; there were no low-field protons in the spectrum. These spectral data are in agreement with the following structure 42 for the bisepoxide-a



42

The bisepoxide-a 42 was heated with benzyl alcohol - potassium hydroxide on the steam bath for 96 hours and the resulting crude benzyl ether 44b was hydrogenolysed to give a glycol mixture which showed in t.l.c. one major spot (~80%) and two faint polar spots of equal intensity. Direct crystallization of the crude mixture gave the crystalline glycol 44a, $C_{15}H_{26}O_3$, m.p. 151-152°.

Its infrared spectrum showed hydroxyl absorption. Periodate oxidation of the 152° glycol 44a converted it quantitatively to keto oxide-a 13a. Thus, the 152° glycol 44a is a vicinal 1,2-diol and represented by the following structure.



44 a R=H
b R=PhCH$_2$-

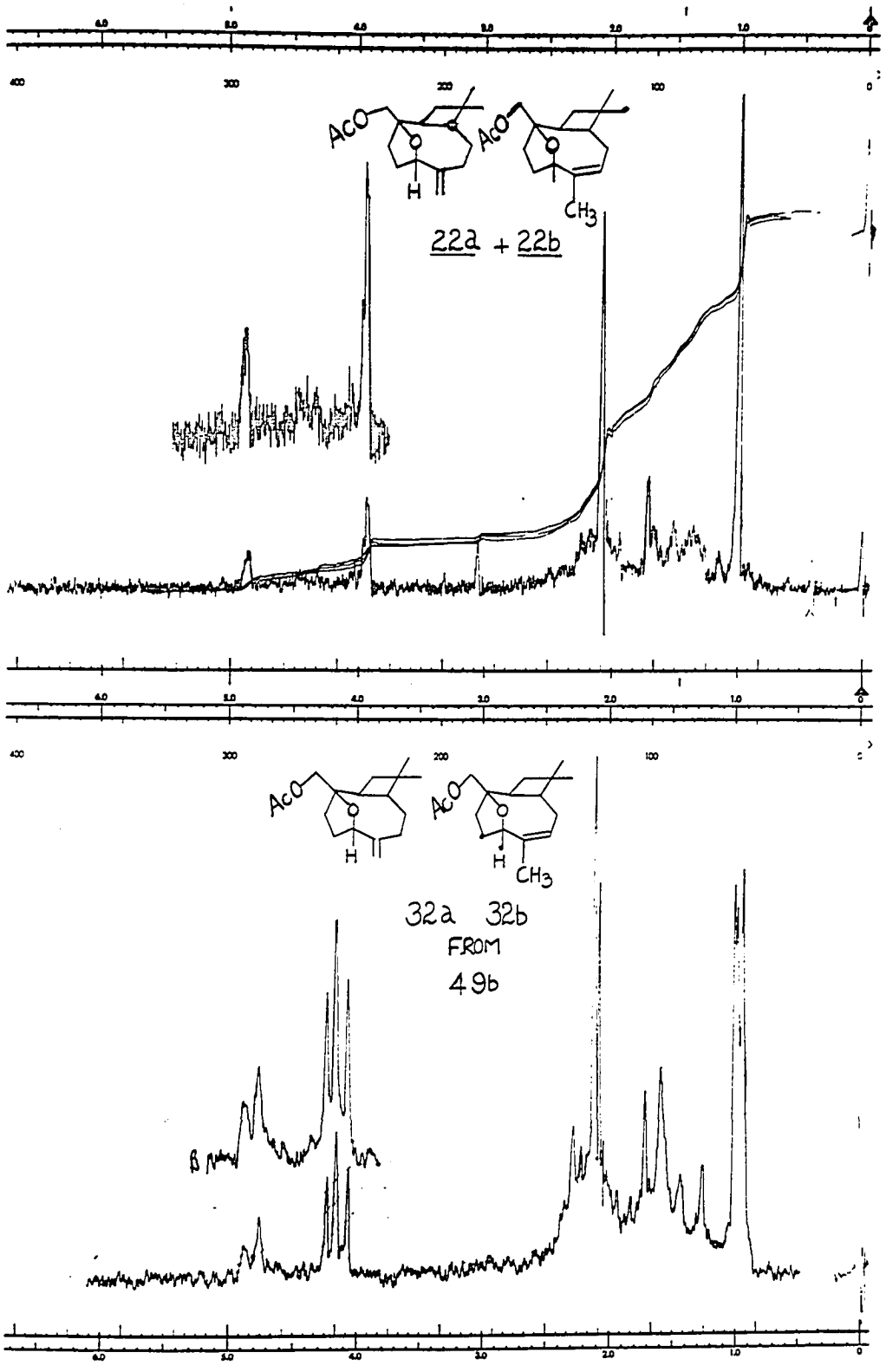
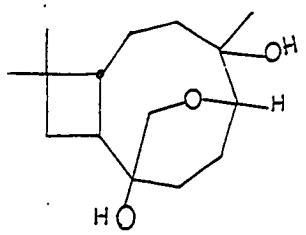


Plate VI. N.M.R. Spectra of products obtained from the dehydration of monoacetates of 130° and 153° Glycols.

Examination of the mother liquor from crystallization of the 152° glycol 44a did not reveal the presence of the 130° glycol 19a (t.l.c. and n.m.r.). Since the minor glycols could not readily be obtained pure, further investigation was not undertaken.

When the 152° glycol 44a was refluxed with methanolic potassium hydroxide for 168 hours it was smoothly converted into a ditertiary glycol 45, $C_{15}H_{26}O_3$, m.p. 225-227°. Its infrared spectrum exhibited a strong hydroxyl absorption band. There were two other polar glycols formed in trace quantities along with 45 but neither of them corresponded (t.l.c.) to the 130° glycol 19a from oxide-a 14a. The tertiary nature of both of the hydroxyl groups in 45 was proved by the following observations:

a) failure to undergo acetylation with acetic anhydride - pyridine reagent at room temperature; b) resistance to chromic acid - pyridine reagent at room temperature, and c) stability to aqueous sodium meta-periodate. All these facts therefore can be best accommodated by the structure 45 for the 227° glycol (see section 5 for stereochemical assignment). This is further supported by the n.m.r. spectrum (see plate VIII).



45

While the base-catalysed isomerisation of the 152° glycol 44a was clean, an attempted acid-catalysed isomerisation of 44 produced a mixture of more than four compounds (t.l.c.), none of which corresponded to 19a. Although the major spot in t.l.c. corresponded to 45, no attempt was

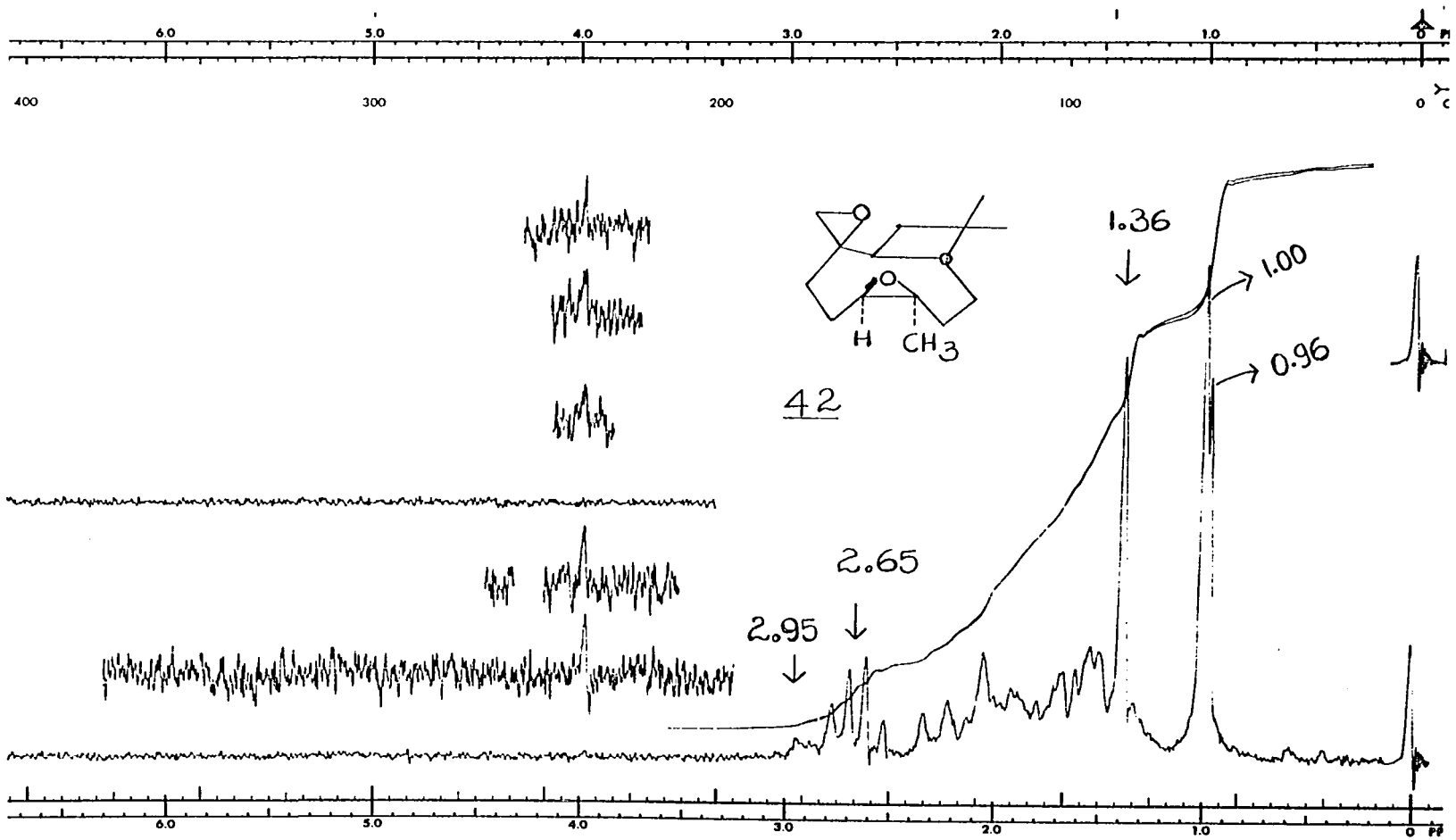


Plate VII. N.M.R. Spectrum of bisepoxide-a of Isocaryophyllene.

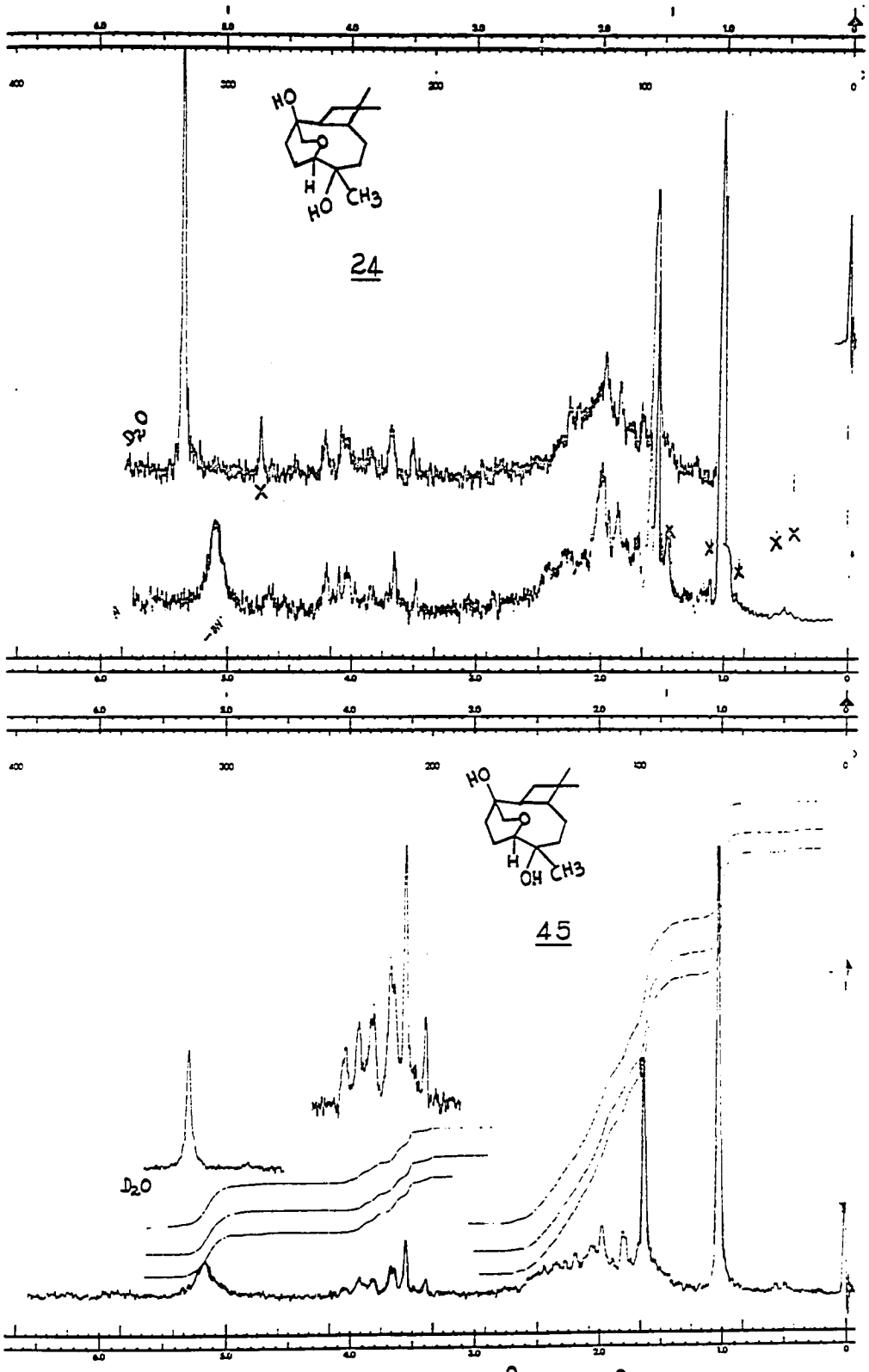


Plate VIII. N.M.R. Spectra of 195° and 227° Glycols,
(in Pyridine)

made to isolate it in the pure state.

SECTION 3

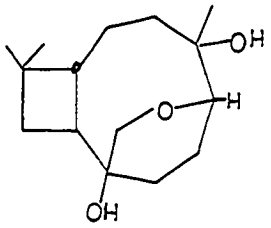
Glycols from Isocaryophyllene Oxide-b, 14b

Hydroxylation of Isocaryophyllene Oxide-b 14b

Hydroxylation of oxide-b 14b (containing about 20% of oxide-a as the only impurity) with osmium tetroxide gave a mixture of glycols containing the 130° glycol 19a arising from the oxide-a impurity (see Chart IV). Careful chromatographic separation gave a crystalline glycol 24, $C_{15}H_{26}O_3$, m.p. 194-195.5°. The infrared spectrum indicated the presence of a strongly bonded hydroxyl group and the absence of any carbonyl absorption. The n.m.r. spectrum (see plate VIII) had the following peaks: two 3H singlet peaks at 0.98 p.p.m. and 1.00 p.p.m. from the gem-dimethyl group, a 3H singlet at 1.53 p.p.m. due to a methyl group on a carbon bearing oxygen atom and a broad lump at 5.06 p.p.m. (disappears on deuteration) due to a hydroxyl group.

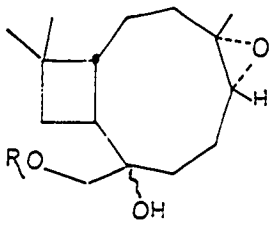
The 195° glycol 24 was recovered unchanged when treated with the following reagents: (a) pyridine - acetic anhydride at room temperature, (b) chromic acid - pyridine at room temperature and (c) aqueous sodium metaperiodate at room temperature. The 195° glycol was found to depress the melting point of the 227° glycol 45 obtained from 44. These observations prove the absence of a primary or secondary alcohol group or a

vicinal 1,2-diol function in the molecule and they are best accommodated by the following structure 24, epimeric with 45, for the 195° glycol.



24

The second glycol 23a isolated from the mixture formed a monoacetate 23b with pyridine - acetic anhydride at room temperature and showed in the infrared spectrum the presence of hydroxyl and ester carbonyl absorption. The glycol 23a was oxidised quantitatively to keto oxide-b 13b by aqueous sodium metaperiodate thereby showing the glycol 23a to be a vicinal 1,2-diol represented by the following structures.



23 a R=H
b R=Ac

When the monoacetate of the 1,2-diol 23b was refluxed with methanolic potassium hydroxide it was converted into the 195° glycol 24. Permanganate oxidation of oxide-b 14b gave only the keto oxide-b 13b with no evidence for the formation of either the 195° glycol 24 or the 1,2-diol 23a.

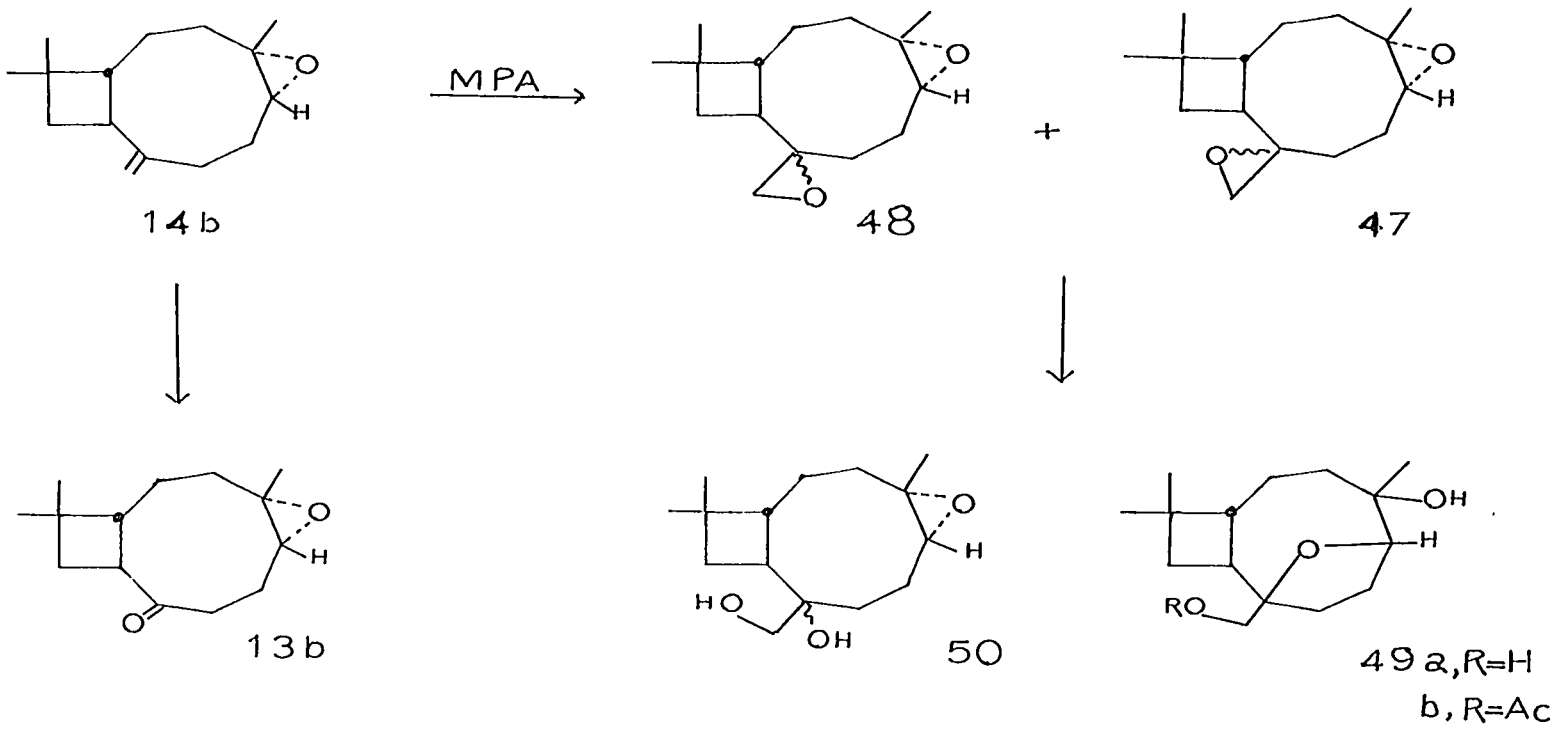
Epoxidation of Isocaryophyllene oxide-b 14b

The oxide-b used in this work contained about 30% of oxide-a 14a as the only impurity (n.m.r.). In contrast to oxide-a 14a, bisepoxida-

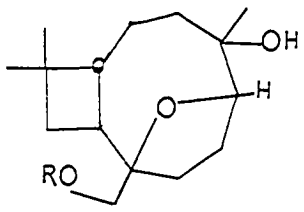
tion of oxide-b 14b with perbenzoic acid in benzene at room temperature gave a crude bisepoxide mixture which contained some polar compounds (t.l.c.). Attempts to separate the bisepoxides from the polar impurities by column chromatography on neutral alumina (activity IV) resulted in rearrangement of the bisepoxide mixture to a complex misture (t.l.c.). Since the formation of polar compounds might have been due to some benzoic acid-catalysed rearrangement of 14b or the resulting bisepoxide, it was decided to try a different peracid. Thus oxidation of 14b, with monoperphthalic acid in ether at 0° gave a mixture of three bisepoxides 42, 47 and 48, the bisepoxide-a 42 arising from 14a. It was not possible to determine the exact ratio of 47 and 48 by n.m.r. measurements because the C-8 methyl of the bisepoxides 47 and 48 appeared to have the same chemical shift and consequently appeared as a single peak. Since attempts to separate the bisepoxide mixture by crystallization or chromatography techniques were frustrating, it was decided to use the crude bisepoxide mixture for further reactions (see Chart V).

Base-catalysed isomerization of the crude bisepoxide mixture with benzyl alcohol and potassium hydroxide gave the crude benzyl ether which on hydrogenolysis gave a glycol mixture in quantitative yield. Direct crystallization of the crude glycol fraction gave in 52% yield needle shaped crystals of glycol 49a, $C_{15}H_{26}O_3$, m.p. 152-153°. The infrared spectrum indicated the presence of hydroxyl absorption. The n.m.r. spectrum (see plate IX) contained the following peaks: two 3H singlets at 0.95 p.p.m. and 0.96 p.p.m. from the gem-dimethyl group; a 3H singlet at 1.32 p.p.m. due to a methyl group on a carbon atom bearing oxygen, and a poorly resolved 1H lump at 3.97 p.p.m. due to a methine hydrogen

CHART V



on carbon bearing an oxygen function. The characteristic feature of the spectrum is the appearance of an AB pattern centred at 3.56 p.p.m. (J_{AB} = 12 c.p.s.) which is indicative of a methylene group carrying oxygen function. Acetylation of the 153° glycol at room temperature with pyridine - acetic anhydride reagent, gave a spongy solid monoacetate 49b, $C_{17}H_{28}O_4$, m.p. 84.5°-86°. The infrared spectrum showed the presence of hydroxyl and ester carbonyl absorption. In the n.m.r. spectrum (see plate IX) the methylene protons of the primary acetate group were shifted downfield by 0.54 p.p.m. and appeared as a singlet at 4.08 p.p.m. while the methine proton on the carbon bearing oxygen appeared in the same place at 3.97 p.p.m. as a small lump. The glycol 49a was recovered unchanged on treatment with aqueous sodium metaperiodate at room temperature which points to the absence of a 1,2-diol function in the molecule. All these facts can be accommodated in the following structure 49 for the 153° glycol (see section 5 for stereochemical assignment)



49 a R = H
b R = Ac
c R = $PhCH_2$-

The mother liquor from the crystallization of the 153° glycol 49a contained mainly the glycols 44 (from 42) and 50 as shown by their periodate cleavage. As these could not be readily separated, the glycol mixture was oxidised directly with aqueous sodium metaperiodate to give a mixture of 13a and 13b in the ratio of 35:65 (n.m.r. and infrared spectrum and t.l.c.). Since these keto oxides 13a and 13b should have

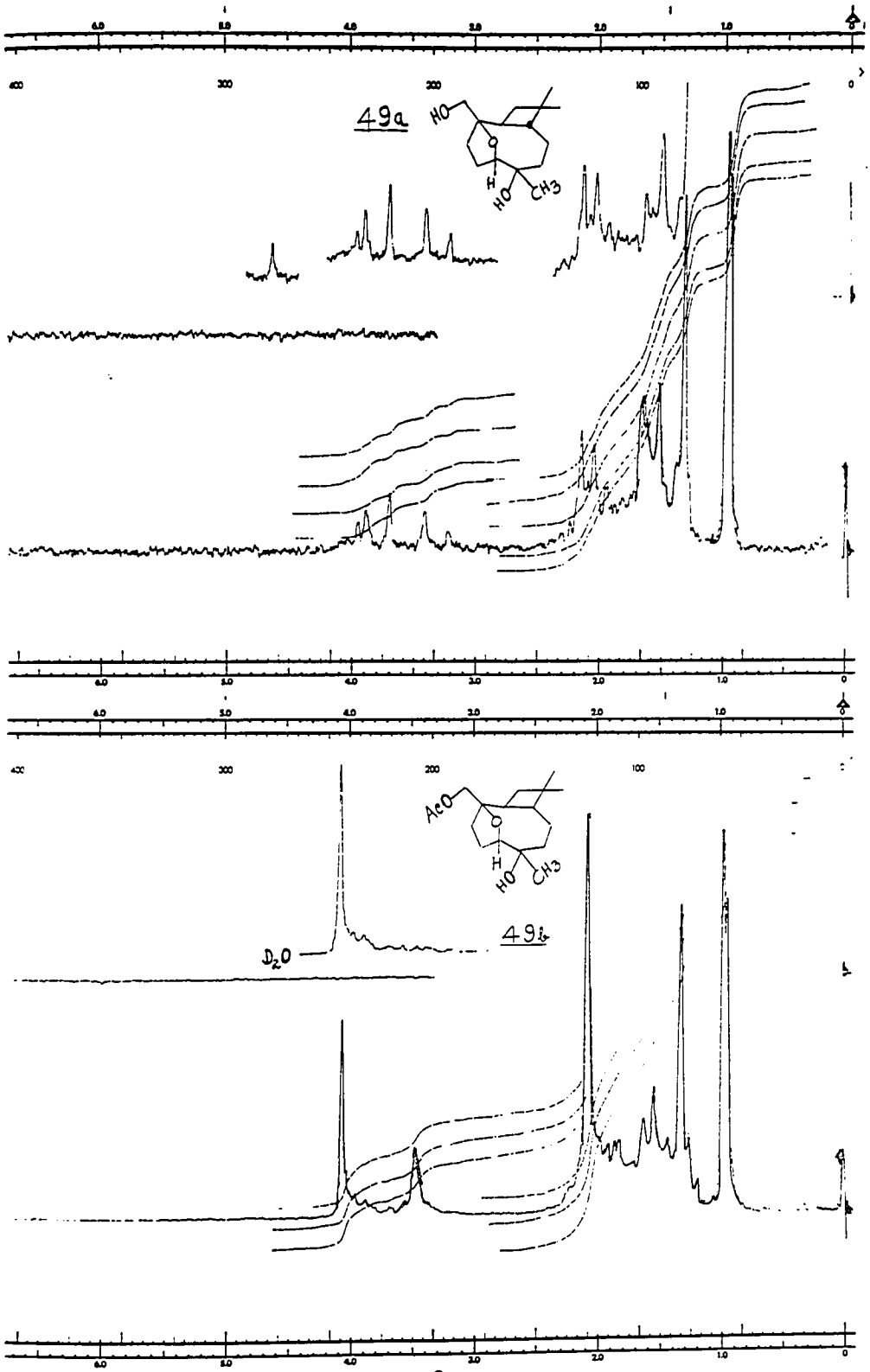
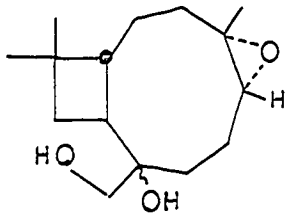


Plate IX. N.M.R. Spectra of 153° Glycol and its monoacetate.

resulted from their 1,2-diol precursors 44a and 50, the ratio of the glycols 49a:50:44 thus obtained is 55:20:25, (see section 5 for stereochemical assignment for the glycols and bisepoxides).



50

The tertiary nature of the hydroxyl group in 49a was proved by dehydration experiments. Dehydration of the monoacetate of 153° glycol 49b using methanesulfonyl chloride - sulfur dioxide - collidine - dimethylformamide,[100] gave the same mixture of liquid olefinic acetates 32a and 32b as obtained from the monoacetate of 116° glycol 29b in the approximate ratio of 50:50 (see plate VI for n.m.r. spectrum). There was no evidence (t.l.c., infrared and n.m.r. spectra) for the formation of a hydride transfer product corresponding to 33b.

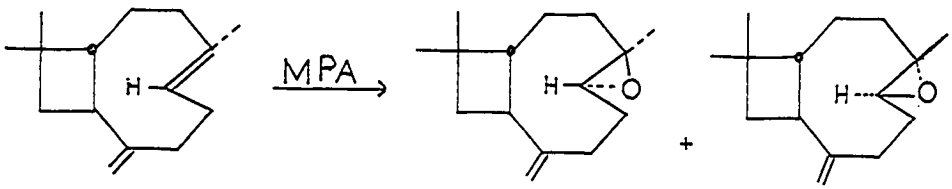
SECTION 4

A Glycol from the Other trans Caryophyllene Oxide

Hydroxylation of the Other trans Caryophyllene Oxide

During the preparation of caryophyllene oxide 2 from pure caryophyllene we observed the formation of a new, hitherto unnoticed, isomeric trans oxide 3, which will be henceforth referred to as the other

trans oxide. Although the isolation of 3 in the pure state could not be achieved, the structure of this new trans oxide could be proved by its spectra and reactions.

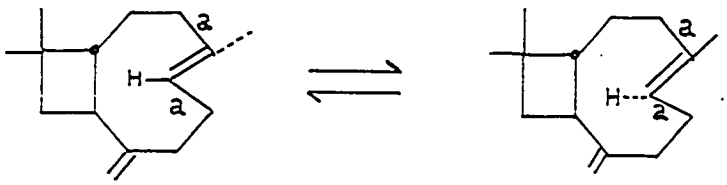


1 2 3

Since the suggestion that trans-cyclic olefins of intermediate size (8-10 membered rings) should be capable of existence in stable enantiomorphic conformations,[104] the possibility of severe conformational restriction to rotation, in medium ring olefins, of the trans double bond about its attached single bonds to carbon acquired increased interest. Recently Cope, et al.,[105] found that trans-cyclooctene and trans-cyclononene could be resolved, which demonstrates the inability of the trans olefinic linkage to rotate with respect to the rest of the molecule under certain conditions. Although racemization of these resolved cycloalkenes merely requires 180° rotation of the trans double bond about its attached carbon-carbon single bonds, optically active trans-cyclooctene was only slowly racemized at 132° ($t_{\frac{1}{2}}$=122h).[106] On the other hand, trans-cyclononene was not optically stable at room temperature and had a half-life of about four minutes at 0°.[107]

A similar possibility of conformational restriction to rotation of the trans-double bond about its attached single bonds to carbon in caryophyllene does exist. However, the barrier to rotation of the trans-double bond of caryophyllene (1⇌1a) about the single bonds a

might be considerably higher than for trans-cyclononene.

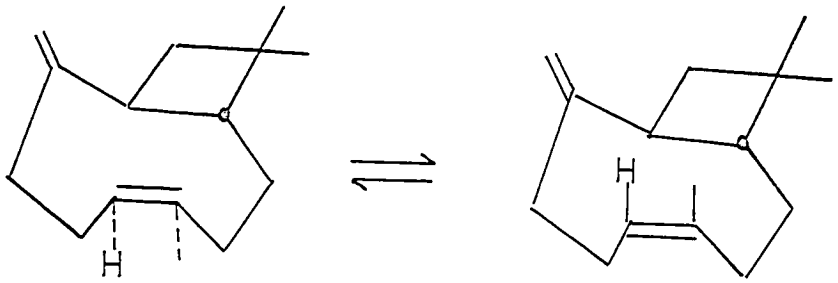


1 1a

This is because the trans-fused cyclobutane ring and the exocyclic methylene group of caryophyllene make it appreciably less flexible than the trans-cyclononene. Furthermore, since interconversion of 1 and 1a must occur by movement of one substituent on the double bond through the "hole" in the nine-membered ring, the probability of 180° rotation about bonds a in 1 or 1a relative to the same rotation in trans-cyclononene will be halved by the presence of the allylic methyl group which cannot pass through the "hole".

Among the earlier recorded observations possibly indicative of restricted rotation is the formation of two nitrosochlorides from isocaryophyllene (γ-caryophyllene) 15 with the cis endocyclic double bond whereas caryophyllene gave a single nitrosochloride.[54,56] All three nitrosochlorides were formed by addition to the tri-substituted double bond since each gave the same compound on reaction with benzylamine. A second and more significant finding was that the reaction of isocaryophyllene 15 with monoperphthalic acid gave the two isomeric oxides 13a and 13b in the approximate ratio 35:65 of the cis-endocyclic double bond, while caryophyllene was reported to afford a single pure oxide 2 of the trans endocyclic double bond in 82% yield after recrystallization. "Careful examination of the product from caryophyllene

showed no indication of a second oxide."[101] The cis endocyclic double bond of the less rigid isocaryophyllene not only has greater freedom to change from one extreme conformation to the other (15 15a), but in 15 and 15a and each intermediate conformation both sides of the double bond are exposed.

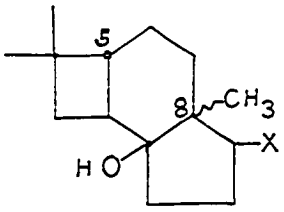


15 15a

However, as pointed out by Barton,[108] that arrangement of the nine-membered ring of caryophyllene with the least angle-strain and fewest non-bonded interactions has the plane of the endocyclic double bond perpendicular to the plane of the cyclobutane ring. There are two such conformers 1 and 1a in each of which only one face of the π - bond is exposed to attack, the other side being completely shielded by the rest of the molecule. Consequently each conformer can only give rise to a single 1,2-epoxide.

If as suggested by the facts cited above, only a single oxide 2 is formed from caryophyllene, there are, a priori, three possible explanations: (a) conformers 1 and 1a are interconvertible by rotation about bonds a, and appreciable amounts of each are present at room temperature. One conformer 1 reacts faster with peracid (ca 10-50 times) than the other, but slower than the 1⇌1a interconversion; b) Or, conformer 1 and 1a are interconvertible by rotation about bonds a, but conformer 1 is present in great excess (ca 50:1 or greater) and rates

of epoxidation of both conformers are nearly the same; (c) Finally, conformers 1 and 1a are not interconvertible by rotation, and caryophyllene is actually only conformer 1. The first two conceivable explanations for the reported formation of only one oxide seemed unreasonable. Examination of Stuart-Briegleb and Dreiding models of 1 and 1a neither revealed any reason for any marked difference in rate of reaction with peracid, nor showed significant differences in repulsive non-bonded interactions in 1 and 1a, which might cause one to predominate greatly over the other. Hence explanation (c) was implicated. The chemistry of caryophyllene did not raise any real obstacle to this interpretation, since in any acid-catalysed reaction of the molecule there is always the possibility of prior isomerisation to isocaryophyllene before reaction. Thus trans-cyclononene undergoes easy isomerisation to cis-cyclononene in the presence of acid.[109] The recent total synthesis[57] of d,l-caryophyllene also did not exclude the explanation (c), since the relative stereochemistry of the C-8 methyl and C-5 hydrogen in the key intermediate was unknown.



Any investigation of restricted rotation in caryophyllene would logically begin with the unequivocal determination of whether a single oxide was indeed produced in the reaction of this sesquiterpene with peracid. Accordingly investigation of the n.m.r. spectrum of the crude oxidation product from caryophyllene led to the observation of the occurrence of

the isomeric trans oxides 2 and 3 in the ratio 85:15. Thus we find that pure caryophyllene on peracid oxidation definitely gives a mixture of two trans oxides. Moreover, the proportion of the two trans oxides 2 and 3 was found to vary with the nature of the peracid and solvent used for epoxidation. The following table summarises the different reagents and results obtained therein

TABLE I

Compound	Reagent	Temperature	Ratio of 2:3
1	monoperphthalic acid - ether	0°	85:15
	perbenzoic acid - benzene	25°	85:15
	perbenzoic acid - chloroform	10° at least	97:3
	perbenzoic acid - chloroform	-22° "	97:3

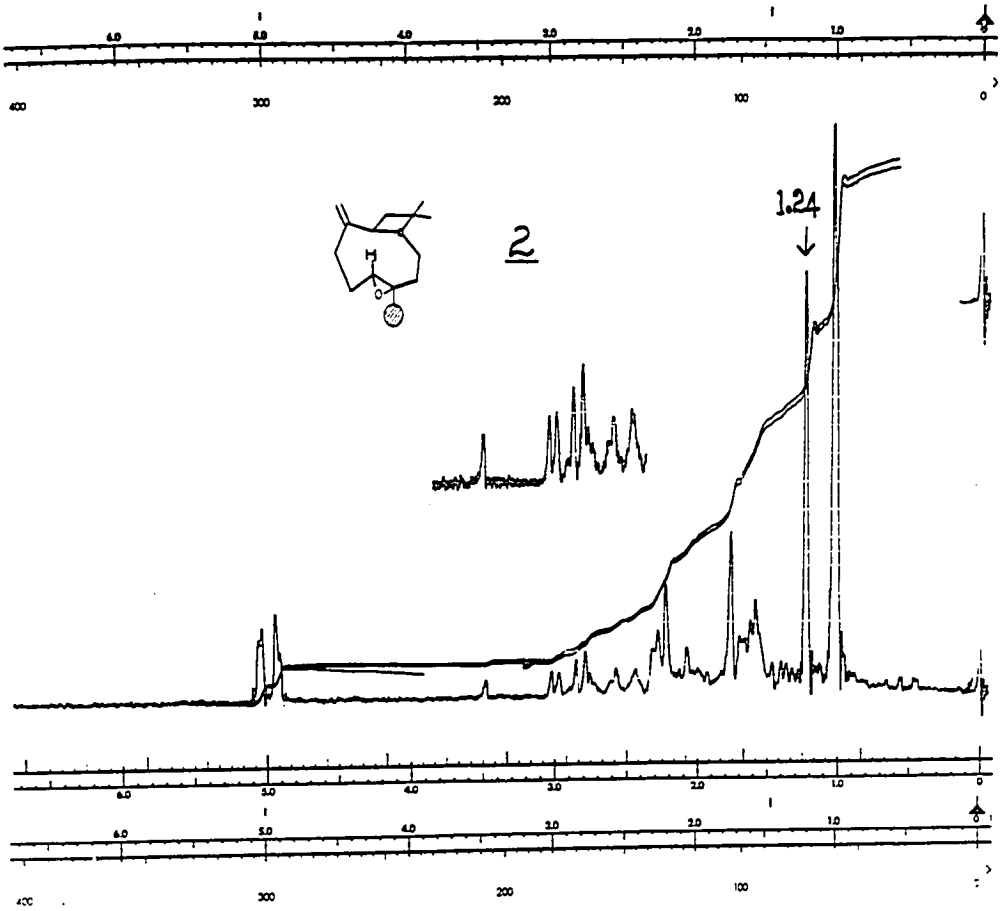
In each case the crude mixture was studied by n.m.r. Thus in the crude mixture obtained in the perbenzoic acid - chloroform reagent the other trans oxide 3 could not be detected. It is possible that the trans oxide 3 is formed in less than 3% in such a reagent system. If rotation of the trans double bond through the nine-membered ring were completely restricted, the ratio of the two trans epoxides formed should be constant regardless of reaction conditions. Since the trans oxide ratio does vary, rotation of the trans double bond through the nine-membered ring of caryophyllene is not restricted.

This detection and estimation of the approximate percentage of the other trans oxide 3 was made possible because of the difference in the n.m.r. chemical shifts of the C-8 methyl and the olefinic protons of the exocyclic methylene group in 2 and 3 (see plate X). Thus, while

the C-8 methyl group of 2 appeared at 1.24 p.p.m., it appeared at 1.20 p.p.m. in 3 and in the olefinic region part of the AB pattern signal from the exocyclic methylene in 3 was overlapping with that from the exocyclic methylene in 2. In the n.m.r. spectrum (see plate XI) of oxide-a 14a and oxide-b 14b, the C-8 methyl group appeared at 1.27 p.p.m. and 1.25 p.p.m. respectively. This suggests that the other oxide from epoxidation of trans-caryophyllene is a trans oxide. That this is so is proved by its reactions.

When most of the monoxide 2 was crystallized out from the crude mixture, the resulting mother liquor was found to be an approximately 50:50 mixture of 2 and 3 (see plate X). Attempts to enrich the mother liquor further in 3 were not successful. Hence it was decided to use this mixture for characterisation of 3 which was done as follows. Hydroxylation of the mixture of 2 and 3 with osmium tetroxide gave a mixture of glycols which was directly acetylated with acetic anhydride - pyridine reagent at room temperature to give a mixture of three acetates (t.l.c.). The least polar of the acetate spots corresponded in R_f (0.70) value to the diacetate of the 119° glycol 5b. Since the other two spots R_f 0.45 and 0.30, were more polar than the 5b, they can be assumed to contain a polar function like a hydroxyl group. Consequently these polar spots were probably monoacetates. The spot that corresponded to 5b was carefully separated from the mixture by thick-layer chromatography and identified as 5b by its infrared and n.m.r. spectra and saponification to the 119° glycol 5a.

The polar acetate, R_f 0.45, isolated from the thick plate was recrystallized to give beautiful felted needles of 38b, $C_{17}H_{28}O_4$, m.p. 158-159°. The infrared spectrum indicated the presence of hydroxyl



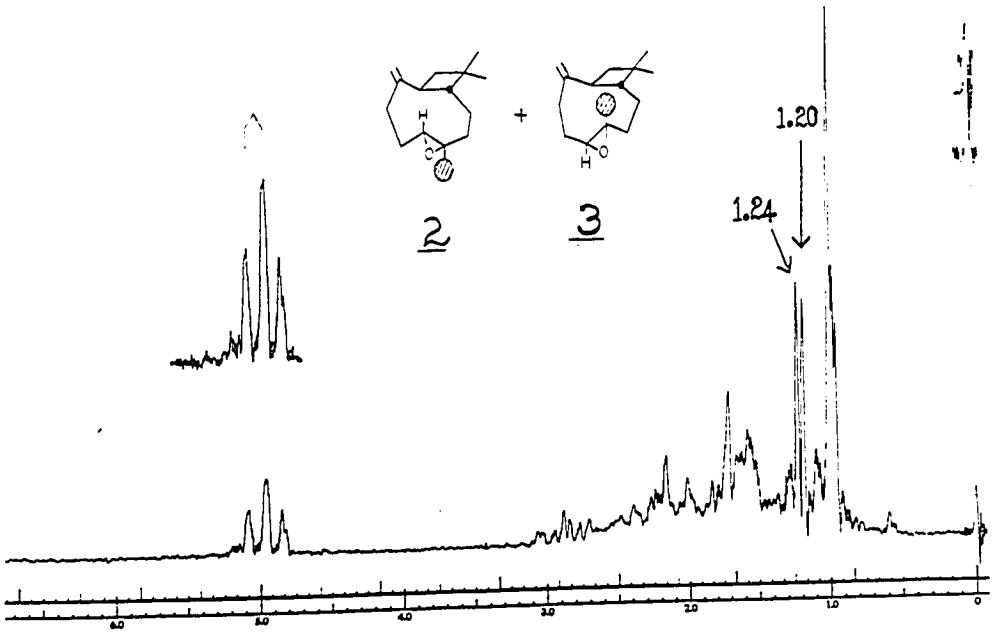


Plate X. N.M.R. Spectra of Caryophyllene Oxide and a 50:50 mixture of Caryophyllene oxide and the other <u>trans</u> Caryophyllene oxide.

and ester carbonyl absorptions. Since the hydroxyl group in 38b survived acetylation at room temperature, it must be tertiary in nature. The n.m.r. spectrum (see plate XII) contained the following peaks: two 3H singlets at 0.98 p.p.m. and 1.00 p.p.m. from the gem-dimethyl group, a 3H singlet at 1.13 p.p.m. from a methyl group on a carbon bearing oxygen atom and a 3H singlet at 2.13 p.p.m. from the acetate methyl group. The spectrum also exhibited an AB pattern (in which one of the hydrogens is split further by long range coupling) centered at 3.87 p.p.m. (J = 12 c.p.s.) due to a methylene group carrying an oxygen function and a poorly resolved multiplet centred at 4.97 p.p.m. from a methine proton on a carbon atom bearing oxygen.

The crystalline monoacetate 38b was recovered unchanged on treatment with chromic acid - pyridine reagent at room temperature confirming thereby the tertiary nature of the hydroxyl group in 38b. Saponification of the 159° monoacetate 38b with methanolic potassium hydroxide gave a crystalline glycol 38a, $C_{15}H_{26}O_3$, m.p. 135-136°. The infrared spectrum indicated the presence of hydroxyl absorption and the absence of carbonyl absorption. In the n.m.r. spectrum (see plate XII) of the 136° glycol 38a the methine proton on carbon bearing oxygen moved upfield by 1.20 p.p.m. and appeared as a multiplet at about 3.75 p.p.m. Its exact position could not be determined as it overlapped with the AB pattern of the methylene group bearing oxygen which appeared at 3.90 p.p.m. in the glycol 38a. These data were interpreted to mean that the glycol 38a contains a secondary hydroxyl group and a methylene group carrying oxygen involved in bridging between C-1 and C-8. This is further supported by the fact that the 136° glycol 38a was recovered unchanged on treatment with aqueous

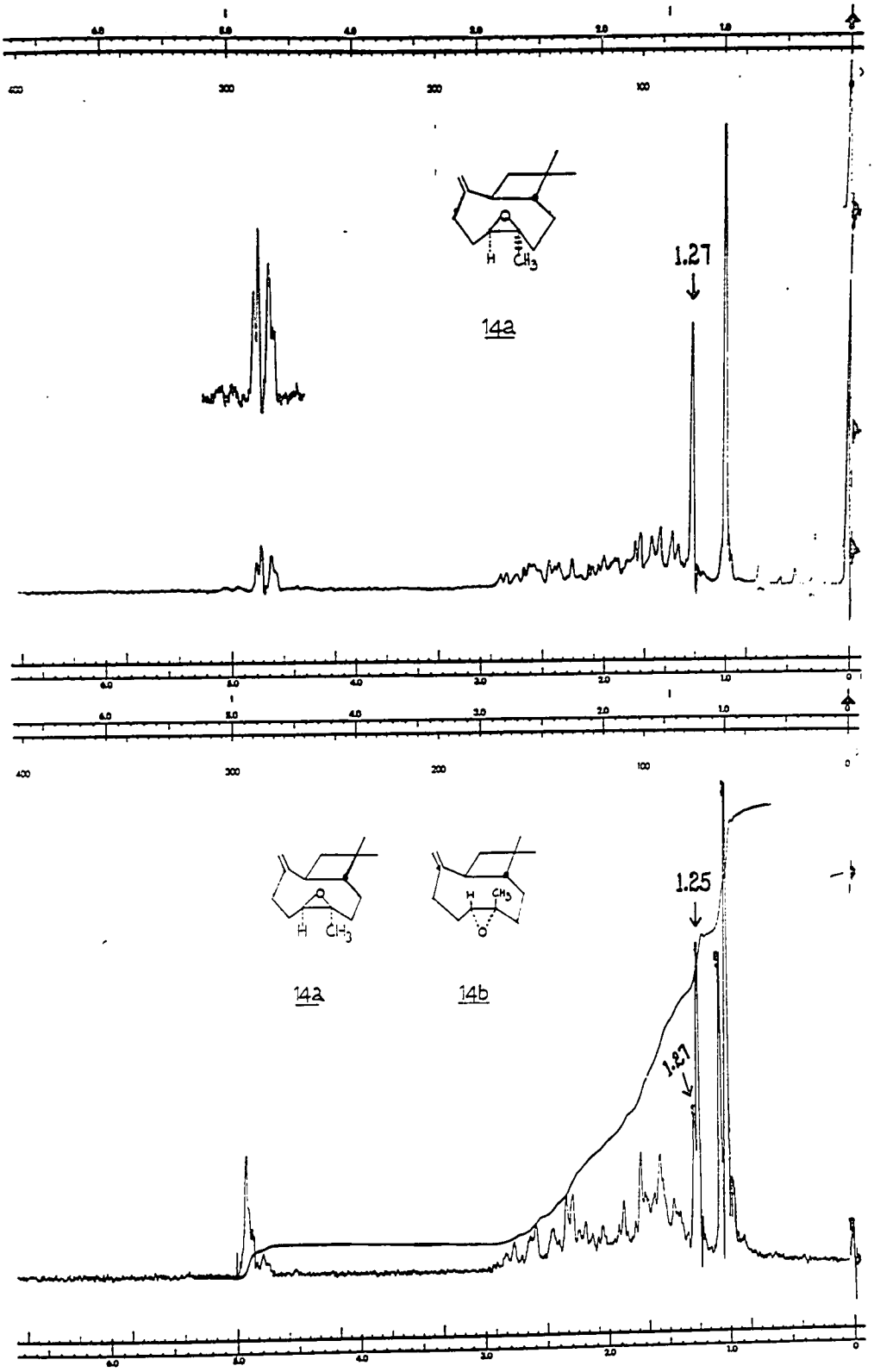


Plate XI. N.M.R. Spectra of oxide-a and oxide-b of Isocaryophyllene.

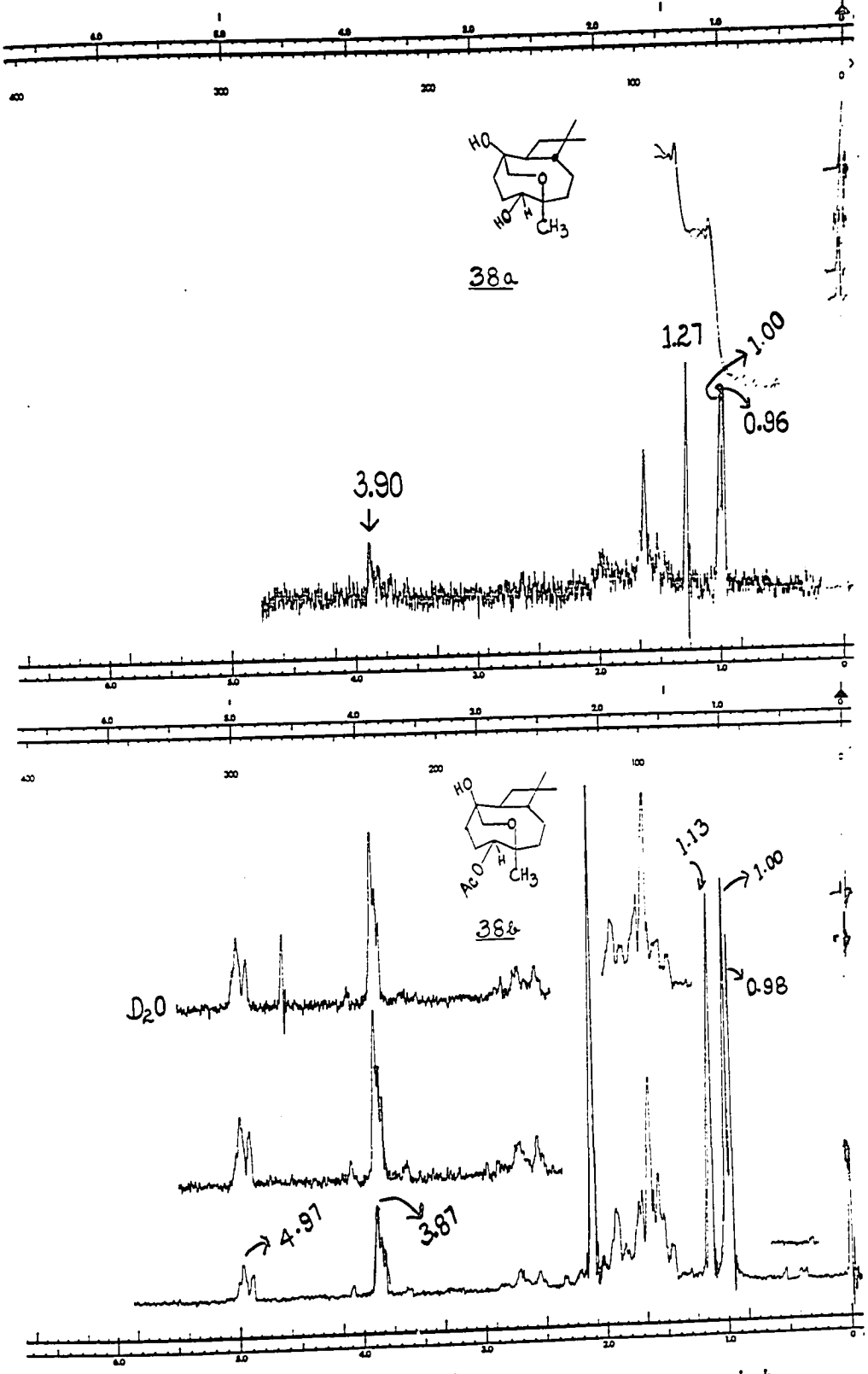
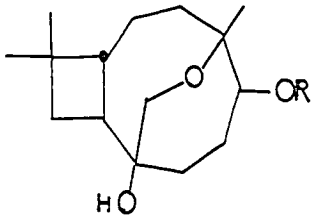


Plate XII. N.M.R. Spectra of 136° Glycol and its monoacetate.

sodium metaperiodate at room temperature, thereby excluding a vicinal 1,2-diol function. The following structure 38a accounting for all the observed facts represents the 136° glycol

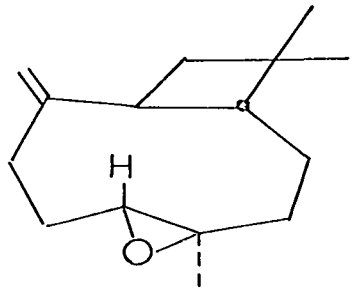


38 a, R=H
b, R=Ac

The above structure for the 136° glycol was further confirmed by its chromic acid - pyridine oxidation at room temperature to a hydroxy ketone 39 $C_{15}H_{24}O_3$, m.p. 82-83° (see Chart VI). The infrared spectrum of 39 indicated the presence of hydroxyl and carbonyl absorptions. Furthermore, the hydroxy ketone 39, when subjected to Wolff-Kishner reduction conditions, gave an unsaturated 1,2-diol which was found to be identical with the unsaturated 1,2-diol 11 obtained from the 119° glycol 5a (m.p. and mixed m.p.). Since osmium tetroxide hydroxylation of caryophyllene oxide 2 is known to give only the 119° glycol 5a, and since the 136° glycol was not identical with any of the glycols from isocaryophyllene, the 136° glycol 38a could only have arisen from its isomeric trans oxide 3 (see section 5 for the stereochemistry of the 136° glycol).

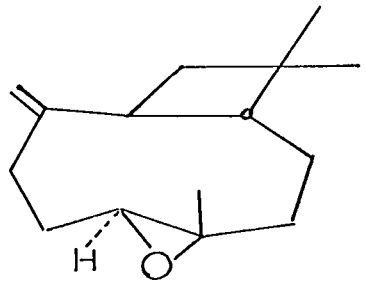
In the foregoing discussion of the structures of seven different glycols there were two cases (119° and 136° glycols) in which the glycol resulted from opening of the secondary-tertiary oxide at the tertiary carbon. The question might be raised whether the initial transannular reaction product really involved attack at the secondary carbon atom followed by rearrangement of the oxide bridge to the

CHART VI

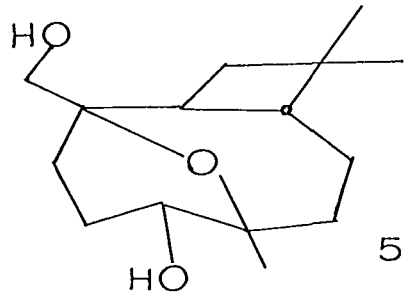


2

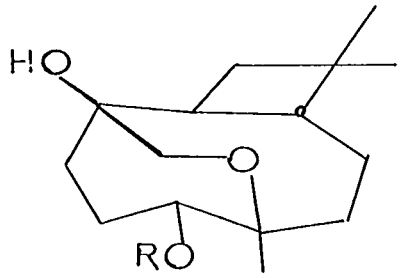
50:50 mixture



3

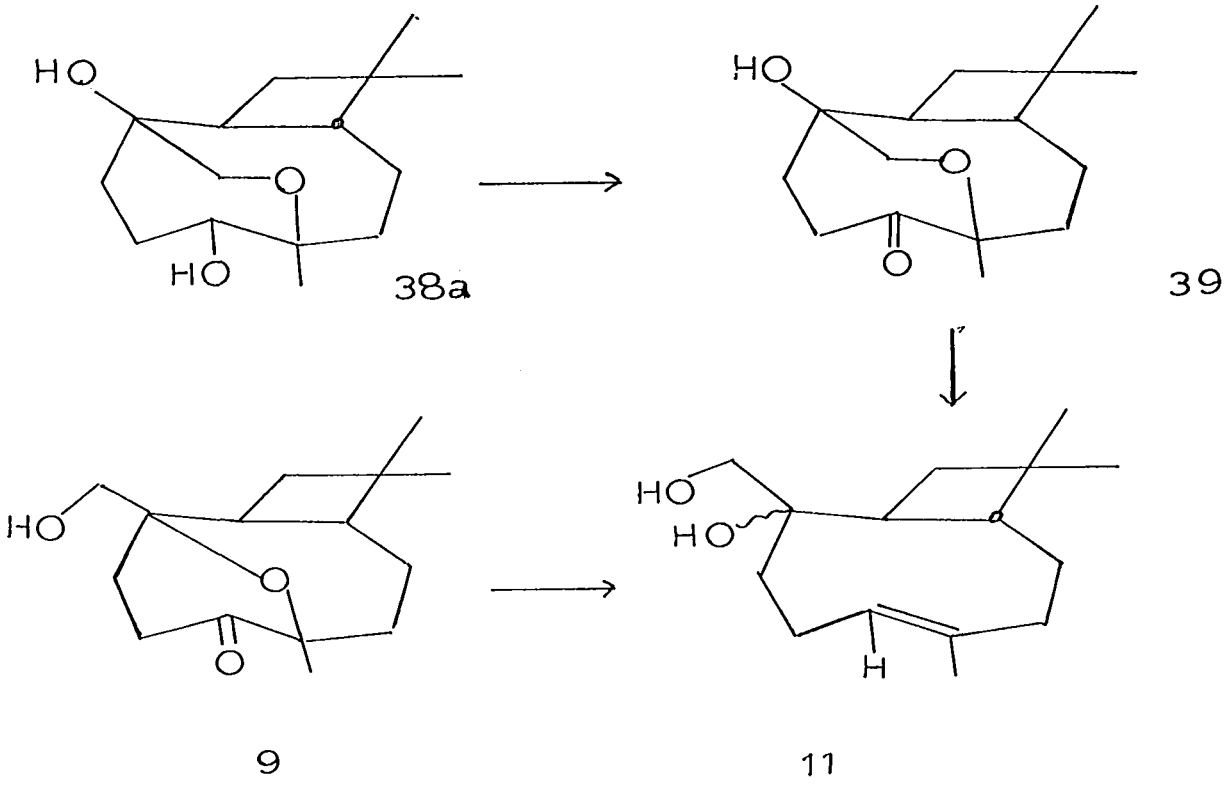


5a

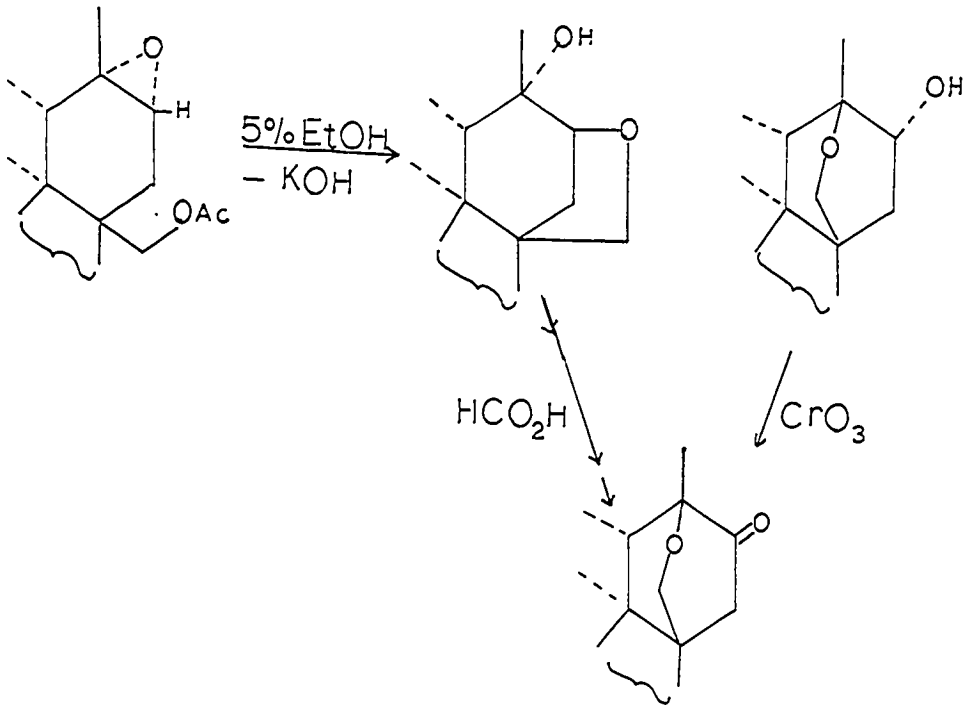


38 R = H

CHART VI (Continued)

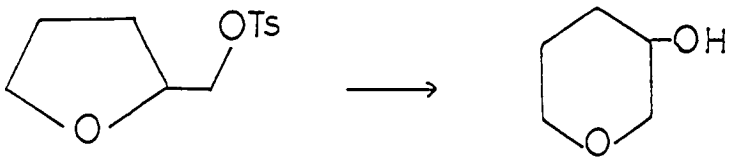


tertiary carbon since examples of this type of rearrangement are known. Recently Řihová and Vystrčil[110] found a similar rearrangement in the course of their studies on triterpenes.



The rearrangement of five-membered ether compounds to six-membered ether compounds has been reported earlier in the literature. Thus earlier in 1960, Gagnaire[111] observed the rearrangement of a tetrahydrofuran system to a tetrahydropyran system. Any such ambiguity is excluded in the formation of the six glycols which were prepared under strongly basic conditions where such rearrangements would not occur. We have no experimental evidence to exclude the possibility in the case of the 136° glycol, but initial attack of the primary hydroxyl of 37 with the secondary carbon atom would have led to a

strained structure and is therefore regarded as highly unlikely.



SECTION 5

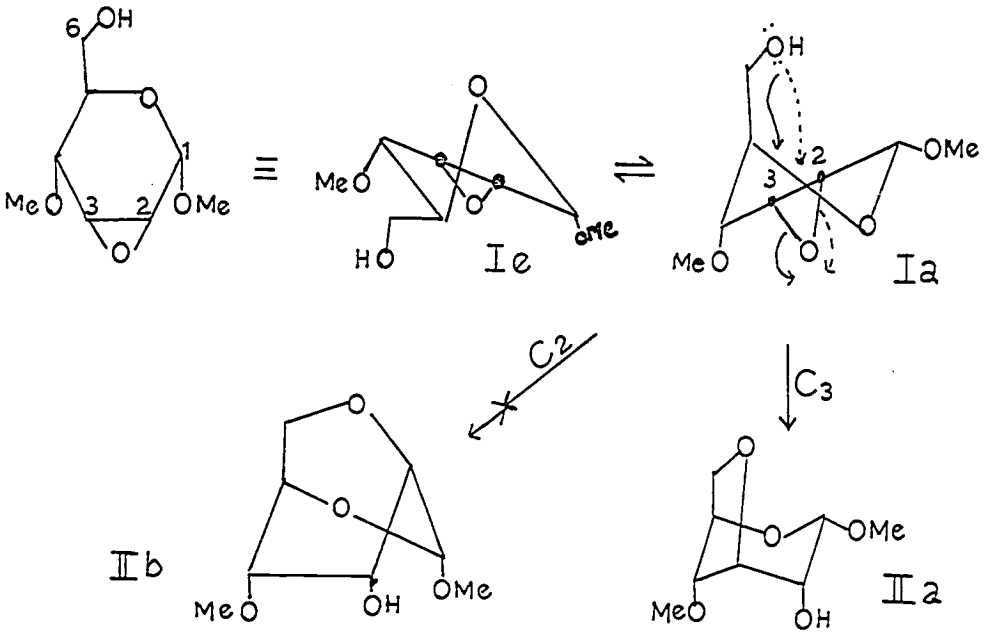
Stereochemistry of Glycols Derived from Oxides of Caryophyllene and Isocaryophyllene

Assumptions

In the discussion which follows, the assignments of stereochemistry for the various glycols rest on certain basic premises.

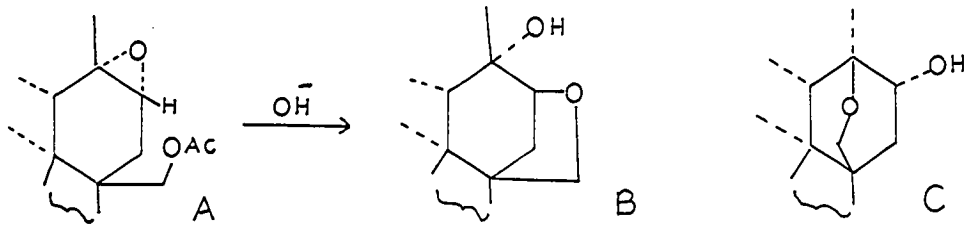
a. The oxirane ring opens with inversion in base.

Based on the experimental facts accumulated so far both by earlier workers and in recent work, it is assumed that in intramolecular nucleophilic reactions, the oxirane ring opening occurs with inversion of configuration at the carbon atom being substituted. In other words, intramolecular nucleophilic attack always occurs from the back side of the oxirane ring. To cite some of the recent examples of intramolecular oxide ring opening with inversion, in the sugar series, it has been observed that methyl 2,3-anhydro-4-O-methyl-α-D-allopyranoside I is transformed smoothly into methyl 3,6-anhydro-4-O-methyl-α-D-glucopyranoside IIa on treatment with hot, dilute alkali, in good yield.[112]



In this case the oxide ring opens with inversion by intramolecular nucleophilic attack exclusively at C-3 of I in its half-chair conformation Ia. The exclusive nucleophilic attack at C-3 is rationalised as follows. In the product IIb corresponding to attack at the C-2 of the oxide system, the 6-membered ring assumes a boat conformation which is less favourable than the chair form IIa.

Intramolecular nucleophilic attack with inversion at both secondary and tertiary carbons of an epoxide system has been observed in the triterpene series by Czech workers. Thus heterobetulin diacetate epoxide A on alkaline hydrolysis gives a mixture of diols B and C, with B as the major product.[110]

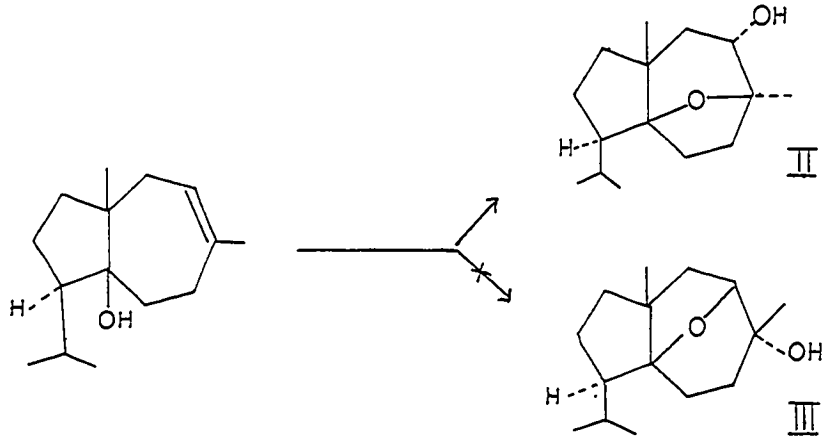


The predominant formation of B appears to be due to the fact that in the compound C obtained by attack at the tertiary carbon atom, the

6-membered tetrahydropyran ring is held in the rigid boat form. Consequently the formation of C requires high activation energy and thus attack at the secondary carbon atom results.

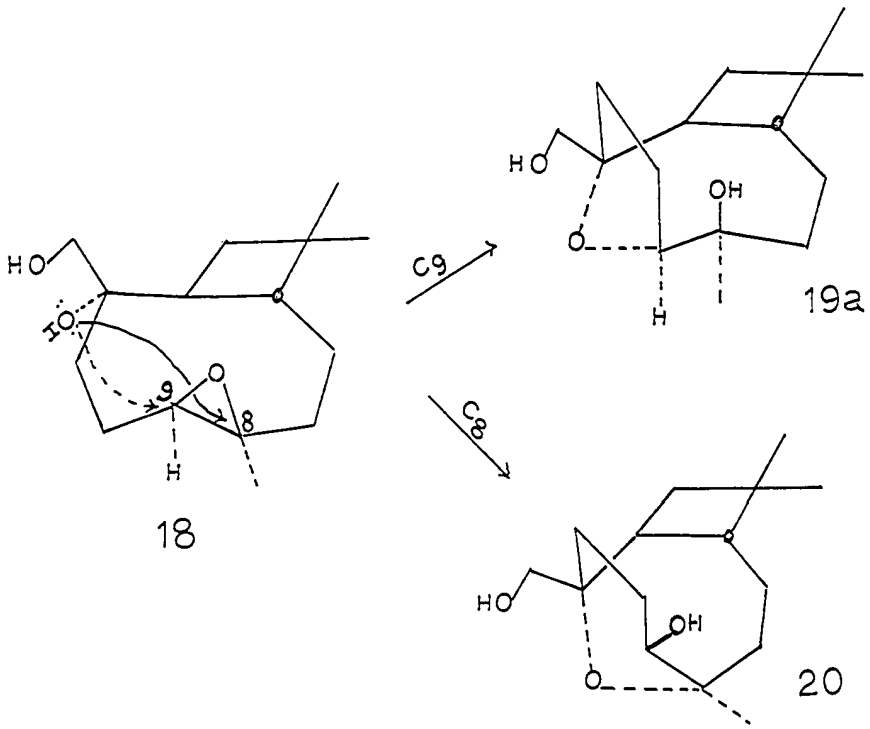
b. Angle-Strain Restriction

Angle-strain introduced will be an important factor in deciding which possible product is formed. The discussion is restricted to angle-strain that is present in compounds arising from transannular reaction at the epoxide ring, over and above that present in the cyclobutane ring of all these compounds. That this assumption is reasonable follows from a not too closely related work on carotol. Thus peracid oxidation of carotol gave daucol,[39,40] a product arising from intramolecular nucleophilic attack of the angular hydroxyl at the tertiary carbon of a tertiary-secondary epoxide ring system.



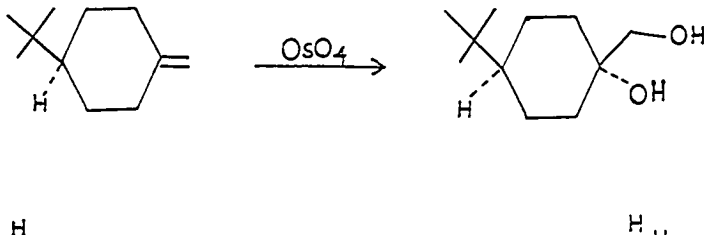
That this is not merely due to the acidic conditions of the peracid oxidation is demonstrated during the saponification of the mixture of epoxy acetates from peracid oxidation of carotol acetate. One of the epoxy acetates V in which the oxide ring is α-oriented (trans with respect to tertiary acetate) was quantitatively converted into daucol while the other epoxy acetate gave an isomer of daucol.

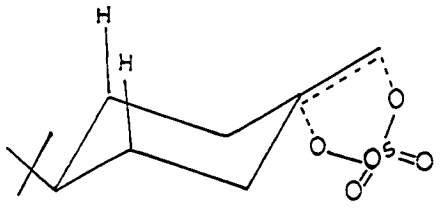
structure 18. The oxirane ring in 18 can be opened with inversion by intramolecular nucleophilic attack only by the C-1 hydroxyl group since a Dreiding model of 18 reveals that there is no way by which the primary hydroxyl (C-12 hydroxyl) could approach either of the two carbon atoms of the oxirane ring from the back side. The intramolecular nucleophilic attack could occur at either the secondary or tertiary carbon atom of the oxirane ring to give strain-free cyclic ethers represented by the stereostructures 19a and 20 respectively. However, since the product of osmium tetroxide hydroxylation of oxide-a 14a is a primary-tertiary alcohol, it must have the stereostructure 19a.



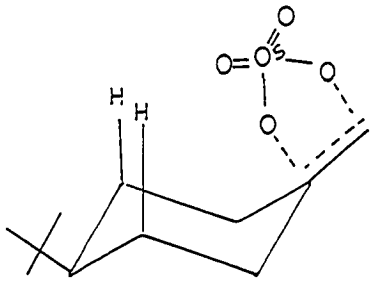
The stereostructure 19a for the 130° glycol differs from the 116° glycol 29a in the configuration of the ether bridge. This is supported by dehydration experiments. Thus the dehydration of the 130° glycol

the exocyclic double bond in the oxides of caryophyllene, and isocaryophyllene from the α-side, as mentioned earlier. If the reverse assumption of attack of the above reagents is made, in every case a highly strained transannular product would be formed as will be seen in later discussion. This assumption seems to be reasonable from an inspection of Stuart-Briegleb models of these oxides. The models show that the two sides α- and β- of the exocyclic double bond offer different degrees of steric hindrance to the approaching reagents. Thus one of the gem-dimethyl groups present in the cyclobutane ring provides a high degree of steric hindrance for approaching bulky reagents like osmium tetroxide and permanganate ion to add from the β-side of the double bond and thereby directs such bulky reagents to come from the α-side. A close analogy is found in the addition of osmium tetroxide to 4-t-butyl methylene cyclohexane,[113] which gives only one diol as represented below.





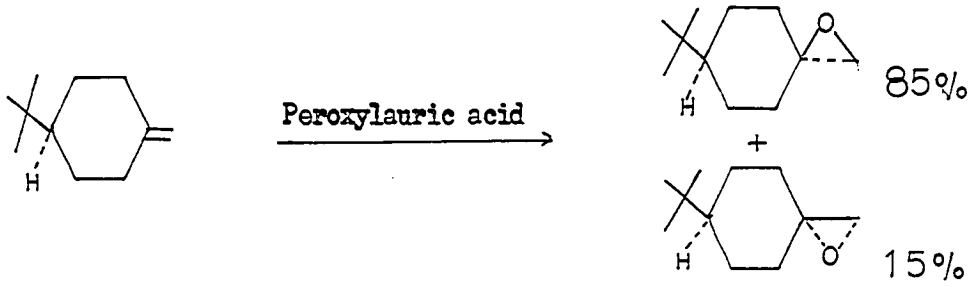
equatorial attack



axial attack

In the chair conformation of this molecule, when the bulky osmium tetroxide reagent attacks from the axial side, there is observed a strong repulsive interaction between the axial hydrogens and the cyclic osmate

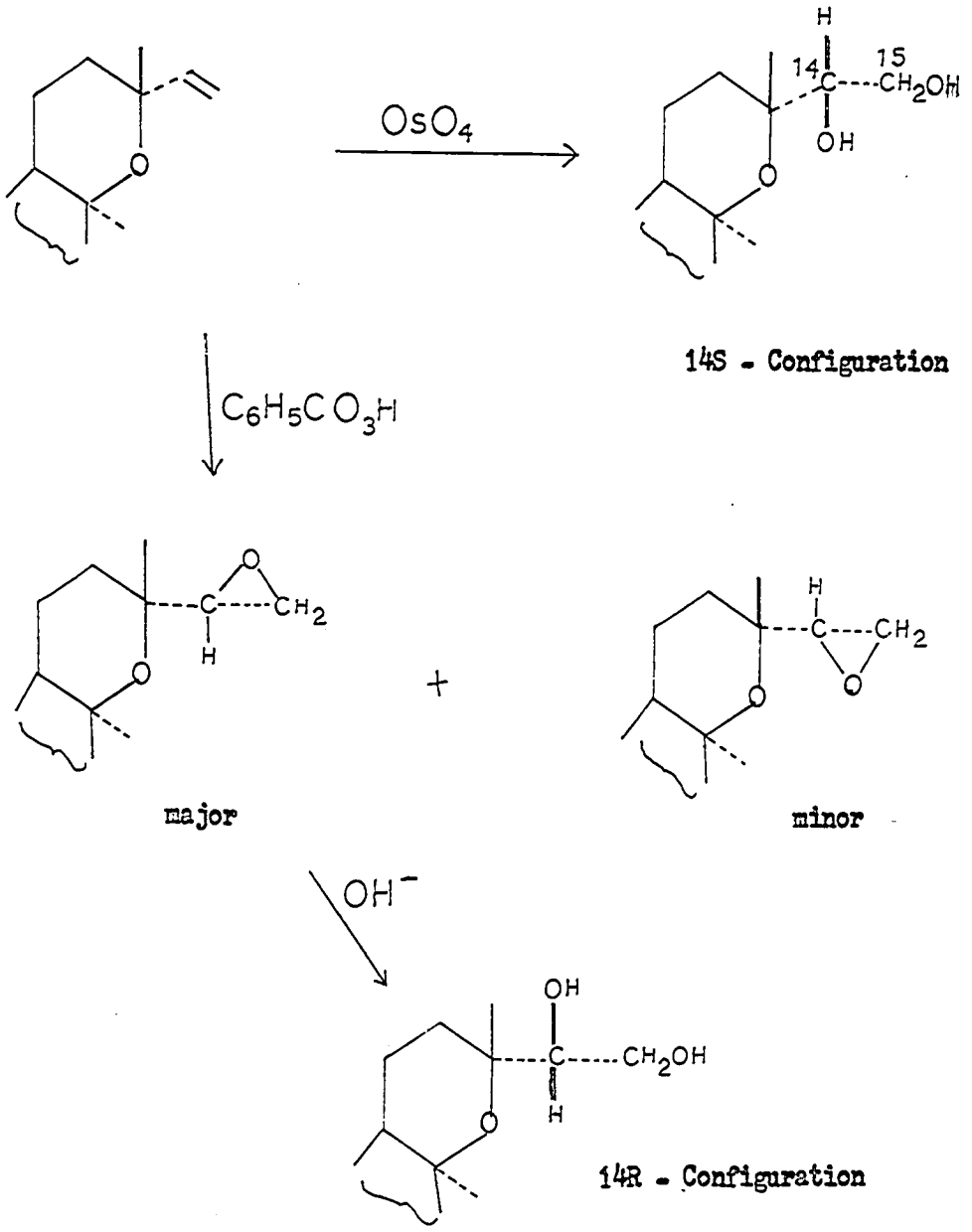
ester intermediate, and consequently such an attack is not favoured. However, since no such interaction exists when the osmium tetroxide reagent approaches from the equatorial side, such an attack is favoured. On the other hand, peracid oxidation of 4-t-butyl methylene cyclohexane with peroxylauric acid gives mainly the product of axial attack.[77]



Since that part of a peracid which must approach a double bond is relatively small, the interaction between the axial hydrogens and the peracid reagent in the transition state for axial attack is not as severe as found in the osmium tetroxide reaction and consequently the peracid oxidation reaction gives chiefly the product of axial attack. In other words, in the transition state the interactions of the CH_2 becoming axial are more serious than for the O becoming axial. Hence, we assume that because of the smaller effective size of the attacking reagent, the peracid oxidation of the oxides of caryophyllene and iso-caryophyllene is not subjected to severe steric hindrance from the gem-dimethyl group of these compounds.

In the diterpene series, Coates, et al.,[114] also observed that peracid oxidation occurred largely from the side opposite to that for osmium tetroxide oxidation. Thus, while osmium tetroxide oxidation of 18-hydroxyl-13-epi-(-)manoyl oxide gave a triol which has the 14-S configuration, perbenzoic acid oxidation of 18-acetoxy-13-epi-(-)-

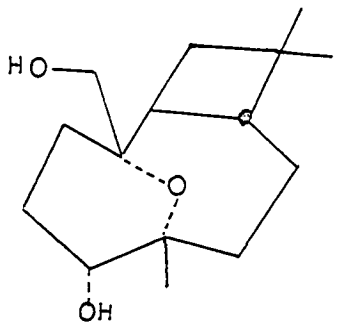
manoyl oxide gave a 3:1 mixture of the epimeric epoxides, Saponification of the major epoxide obtained gave a mixture of two triols in the 2:1 ratio, where the major triol was found to have the 14-R configuration and thus was identical with the naturally occurring diterpene triol.



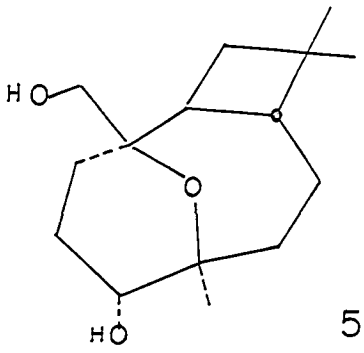
Thus in the peracid oxidation of the oxides of caryophyllene and isocaryophyllene, since the stereochemistry of the product at C-1 is different from that in the osmium tetroxide product, the peracid reagent is assumed to attack from the β-side of the exocyclic double bond.

Stereochemistry of Glycols Derived from Caryophyllene Oxide: The 119° Glycol 5a and the 116° Glycol 29a

The formation of the 119° glycol 5a from caryophyllene oxide 2 and from the 142° glycol 6 involves intramolecular nucleophilic attack by the C-1 hydroxyl at the tertiary carbon of the secondary-tertiary epoxide in basic solution. Provided that the oxirane ring is opened with inversion, the stereochemistry of the 119° glycol is controlled by the hydroxyl configuration at C-1 in the 1,2-diol precursor 6. There are two possible stereostructures 5a and 53.



5a



53

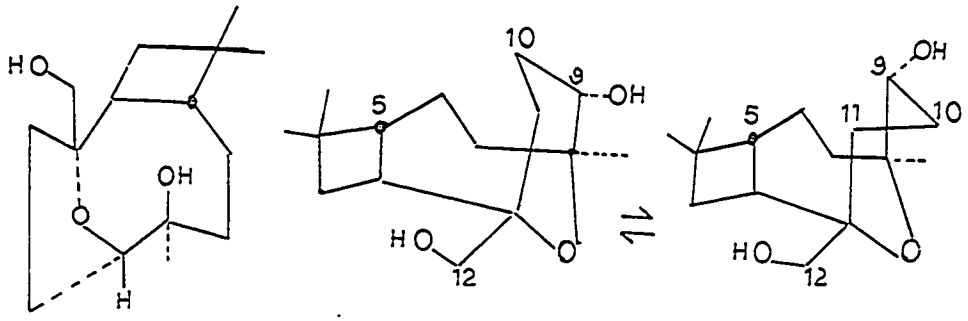
Dreiding models show that the stereoisomer 5a with the α-oriented* oxygen bridge is free of angle strain, whereas in stereoisomer 53, because of the trans fusion of the 2,6-positions of the tetrahydropyran

* In our stereochemistry assignment, the β-oriented C-5 hydrogen in caryophyllene and isocaryophyllene as drawn is the point of reference.

ring, there is considerable angle strain. Consequently the latter would not be expected to form readily. Furthermore, the failure of the hydroxy ketone 9 to undergo reductive cleavage of the α-alkoxy group is in better agreement with the unstrained structure 5a. Therefore the 119° glycol is assigned the α-oxygen-bridged stereostructure 5a.

This is rather remarkable but can be rationalised as follows. If the permanganate and osmium tetroxide have reacted at the α-face* of the double bond, the product 52 of attack at the secondary carbon atom with inversion would be strained (trans fusion of a ring across the 2,5-positions of a tetrahydrofuran ring) and the consequent increase in activation energy for its formation presumably overrides the usual preference for attack at the less-substituted oxide carbon atom in basic solution.

The tetrahydropyran ring of 5a might prefer either a chair or a deformed boat conformation. In the more rigid chair form 5a there is a very unfavourable interaction of the hydrogens on C-5 and C-10. Even though this interaction is reduced in the distorted boat form 5B, the substituent on adjacent atoms C-8, C-9 and C-1, C-11 are more nearly eclipsed. The rapid chromic acid oxidation of the secondary relative to the primary hydroxyl group of 5a is probably due to alleviation of these interactions in the ketone 9.



52 5A 5B

The stereochemistry assigned for 5a is supported by the smooth conversion of the 142° glycol, under both acidic and basic conditions, to the 119° glycol. This also fixes the stereochemistry of the C-1 hydroxyl in the 142° glycol 6 as α. However, the formation of 5a from 6 in basic methanolic solution is much slower than the formation of 5a in the basic permanganate oxidation of caryophyllene oxide 2 (see section 1). This could be interpreted to mean that, since in permanganate oxidation of alkenes a cyclic manganese ester is definitely formed first,[81a] some form of the manganese ester of 6 is undergoing cyclisation to 5a. The conversion of 6 to 5a almost quantitatively was catalysed by dilute sulfuric acid in a rapid reaction, with no trace of any other product. It appears that the transannular cyclisation of 6 to 5a is much faster than pinacol rearrangement of the 1,2-diol or even opening of the strained trans-epoxide to an allylic alcohol as in the isomerisation of 4 to 7.[27] All these facts may indicate that the driving force in the transformation of 6 to 5a under basic and acidic conditions is the formation of a strain-free structure as represented by 5a.

The stereochemistry of the 116° glycol 29a is determined by the configuration of the oxygen atom at C-1 in the disubstituted epoxide of the major crystalline bisepoxide since it is obtained as the major product during the base-catalysed isomerisation of this crystalline caryophyllene bisepoxide. The two bisepoxides can be represented by the stereostructures 26 and 27.

Nucleophilic attack at C-12 of the two bisepoxides 26 and 27 will then lead to diols which are represented by the stereostructures 28a and 6, respectively. Earlier the 142° glycol 6 has been shown to give the 119° glycol 5a and hence it could not have given the 116° glycol 29a. Since the 119° glycols derived from the minor bisepoxide, the minor bisepoxide must be 27. This then leads to the conclusion that the major bisepoxide of caryophyllene must be 26 where the disubstituted oxide ring is β-oriented; therefore the C-1 hydroxyl in the 1,2-diol 28a is β. Since the 116° glycol 29a is formed by intramolecular nucleophilic attack of the C-1 hydroxyl at the oxide ring with inversion, the ether bridge in 29a will be β.

Although the β-oriented C-1 hydroxyl in 28a could have attacked either of the two oxide carbon atoms to give two different glycols 29a and 30 (see Chart VII), experimentally we find only 29a is formed. Inspection of the Dreiding models show that during the conformational change the molecule 28a undergoes to facilitate the C-1 hydroxyl attack at the tertiary carbon of the oxide ring, an unfavourable interaction between the C-2 hydrogen and the C-8 methyl is observed. Furthermore, such an attack leads to the strained trans fused structure 30 wherein the configuration at C-8 is inverted; therefore such an attack is not favoured. However, no such serious interaction is observed

CHART VII

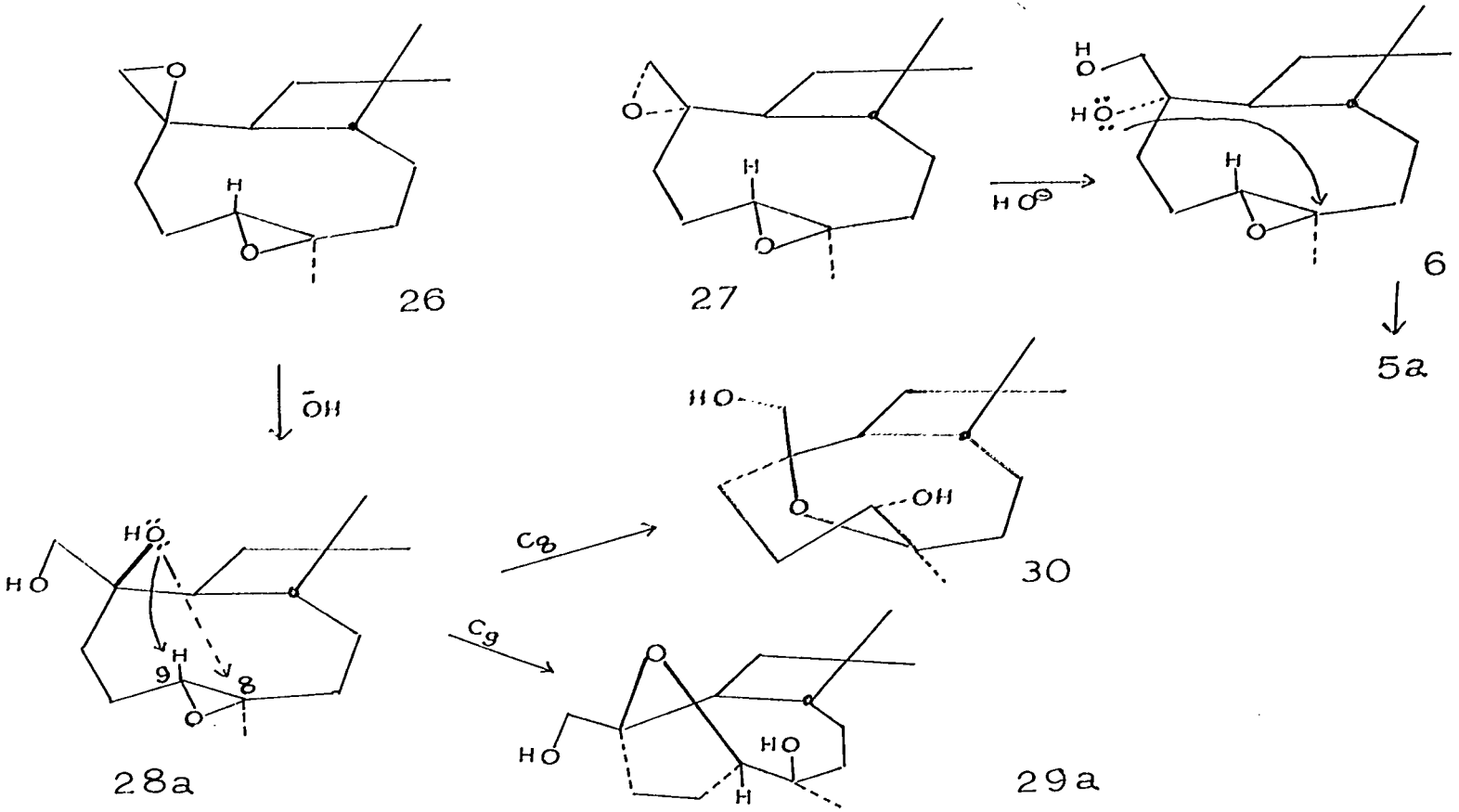
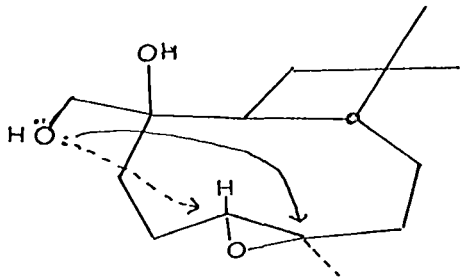


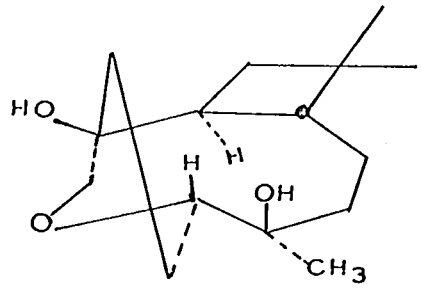
CHART VII (Continuod)



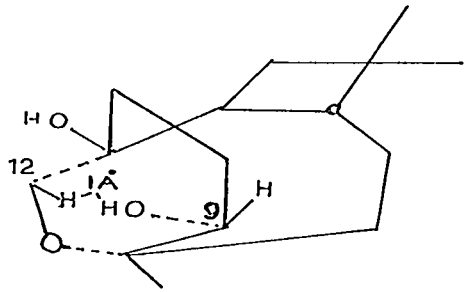
28a

C9

C8



35



36

when the C-1 hydroxyl group approaches the secondary carbon of the oxide ring and also such an attack gives the strain-free cyclic ether 29a.

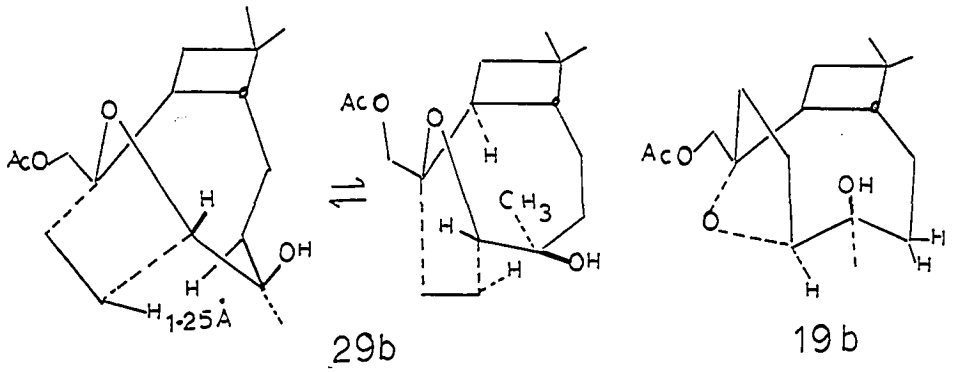
Alternatively, if the primary hydroxyl group in 28a were involved in cyclisation, the resulting glycols would be represented by the stereostructures 35 and 36 corresponding to attack at the secondary and tertiary carbon atoms of the oxide ring respectively (see Chart VII). In the boat-like form of the 7-membered ring of 36, although there is no angle strain, there is an unfavourable flag pole interaction between the C-9 hydroxyl group and C-12 hydrogen atom; also there is interaction between the C-5, C-7 and C-11 hydrogen atoms. Attempts to alleviate these interactions result in the introduction of new interactions between the C-10 and C-12 hydrogens as well as between hydrogens on C-5 and C-9. In the chair-like form of the 7-membered ring in 36, there is interaction between the C-5 and C-10 hydrogen atoms.

On the other hand, the glycol represented by the stereostructure 35 is very strained (trans fusion of a ring across the 2,6-positions of a tetrahydropyran ring). Therefore, probably because of the angle-strain in 35 and energetically unfavourable interactions in 36, these compounds are not formed.

Stereochemistry of Glycols Derived from Isocaryophyllene Oxide-a: The 130° Glycol 19a and the 227° Glycol 45.

Provided that the osmium tetroxide and permanganate oxidations of 14a occur from the α-side of the exocyclic double bond, the 1,2-diol formed initially in the reaction would be represented by the stereo-

monoacetate 19b and the 116° glycol monoacetate 29b, which removes asymmetry at C-8, gave different olefinic acetates, thereby showing that the glycols 19a and 29a differ in the configuration of the ether linkage. Another piece of evidence for the α-configuration of the ether bridge in the 130° glycol 19a was obtained during dehydration studies. Thus the dehydration of the 116° glycol monoacetate 29b gave, in addition to the expected olefinic acetate mixture, a hydroxy acetate 33b, whose formation involves a hydride transfer (see section 1 for mechanism). However, no such hydride transfer compound corresponding to 33b was formed in the dehydration of 19b. An inspection of the Dreiding models of 19b and 29b (or their parent glycols 19a and 29a) shows that in one of the conformations of 29b (or 29a) there is a very unfavourable interaction between the hydrogens on C-7 and C-10, and in the other possible conformation there is an unfavourable interaction between the hydrogens on C-2 and C-10 and C-8 methyl group. However, no such interaction exists in 19b (or 19a) with α-oriented ether bridge.



29b 19b

This unfavourable interaction in 29b (or 29a) is not alleviated in the dehydration product 32a. Although it may be expected to be minimized in 32b, another way to relieve such an unfavourable interaction is the formation of strain-free hydroxy acetate 33b by the hydride shift which

changes C-9 from sp^3 to sp^2 geometry.

The non-occurrence of glycol 20 could be rationalised by an examination of the Dreiding models of the 1,2-diol precursor, 18. Such an examination reveals that a severe torsional strain is introduced in bringing the C-1 hydroxyl within the bonding distance of the tertiary carbon.

The stereochemistry of the 227° glycol 45 is controlled by the configuration of the C-1 hydroxyl group in the 1,2-diol 44 which in turn is determined by the configuration of the disubstituted oxide ring in 42. Earlier, it was seen that the oxidation of oxide-a 14a gave exclusively one bisepoxide 42, with no evidence for the formation of the isomeric bisepoxide 43. If the oxide ring in 14a exerts any directing effect by interaction with peracid during the peracid oxidation as noted in the case of 1,4-dimethylene cyclohexane (see Ch. I, page 36), then the configuration of the newly-formed disubstituted oxirane ring in 42 must be β, i.e. the two oxide rings in 42 must be cis to each other. Examination of the Dreiding models of 14a reveal that in one of several conformations assumed by the molecule, the oxirane ring is placed very close to the exocyclic methylene double bond so that the formation of hydrogen bond between the attacking peracid hydrogen and oxirane ring is not unreasonable. It is interesting to note that the peracid oxidation of the oxide-a 14a with perbenzoic acid in ether also gave predominantly ($>90\%$) cis-bisepoxide-a 42 (n.m.r.); the presence of the isomeric trans-bisepoxide-a 43 could not be detected by n.m.r. in the crude mixture. This result could be interpreted to mean either that even in a polar solvent like ether, oxirane - peracid interaction

is important or else that oxide-a 14a is preferentially epoxidized from the β-side regardless of directing effects of the oxirane ring.

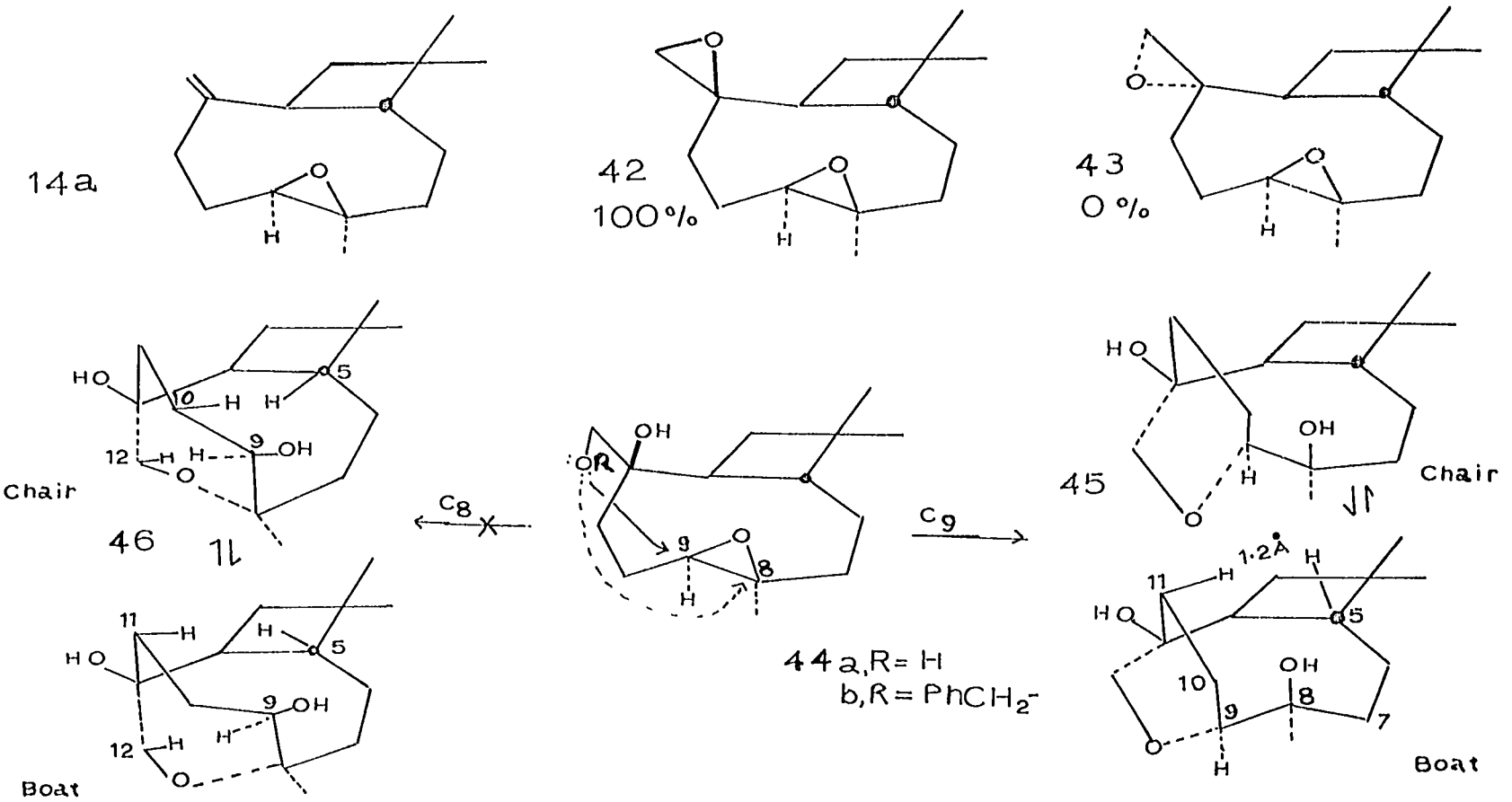
However, it should be pointed out that while the oxidation of caryophyllene oxide 2 with monoperphthalic acid in ether gave a mixture of bisepoxides 26 and 27 in the ratio of 60:40, their proportion changed to 80:20 when the oxidation was carried out with perbenzoic acid in benzene in agreement with the work on 1,4-dimethylene cyclohexane.[80] Examination of Dreiding model of 2 shows that even though the trans fused oxide ring is at right angles to the exocyclic methylene, a twist around the C_9-C_{10} bond places the oxirane ring in a position almost parallel to the exocyclic double bond thus favouring the peracid - oxirane ring interaction. Hence the predominant formation of 26 and its increase in non-hydrogen bonding solvent is not surprising.

The β-configuration of the disubstituted oxide ring in 42 follows from its chemical reactions. Thus base-catalysed epoxide ring opening in 42 gave a 1,2-diol 44a as the major product. Since the reaction involves attack by $C_6H_5CH_2O^{\ominus}$ at the C-12 of the disubstituted oxide ring, a benzyl ether 44b would be the first formed intermediate. The failure of the attack of the C-1 tertiary hydroxyl group at one of the two oxide ring carbon atoms, in the intermediate benzyl ether 44b under basic conditions shows that the C-1 hydroxyl and the trisubstituted oxide ring must be cis to each other, thus preventing backside attack on the oxide ring. Furthermore, the absence of any 130° glycol 19a from the base-catalysed isomerisation of 42 excludes a trans-bisepoxide structure 43 for the bisepoxide obtained from oxide-a.

Thus, the disubstituted oxide ring and hence the C-1 hydroxyl in the 1,2-diol obtained therefrom must be β-oriented as represented in the stereostructures 42 and 44a, respectively.

The oxirane ring in the 1,2-diol 44a could be opened with inversion only by the primary alcohol by attack at either the secondary or tertiary carbon atom from the α-side to give glycols 45 and 46; in either case the ether linkage will be α-oriented (see Chart VIII). Experimentally we have isolated the ditertiary glycol 45 only. Inspection of a Dreiding model of the 1,2-diol 44a reveals that as the primary hydroxyl approaches the tertiary carbon atom there is a severe interaction between the hydrogens on C-9 and C-12; however, such an interaction is absent when the secondary carbon is approached and consequently the glycol 45 is preferentially formed. Even if this interaction were disregarded in forming 46, Dreiding models show that such a structure will require higher activation energy for its formation because of other steric interactions between various atoms or groups in the molecule. Thus when the 7-membered ring assumes chair-like conformation, there is interaction between hydrogen atoms on C-9, C-12 and C-5, C-10. When it assumes a boat-like conformation, interactions between hydrogens on C-9, C-12, and C-5, C-11 are noticed. Such interactions are minimised in structure 45 where the 6-membered tetrahydropyran ring appears to be more stable in its chair conformation because of interactions between hydrogen atoms on C-5, C-7 and C-11 in the boat form.

CHART VIII

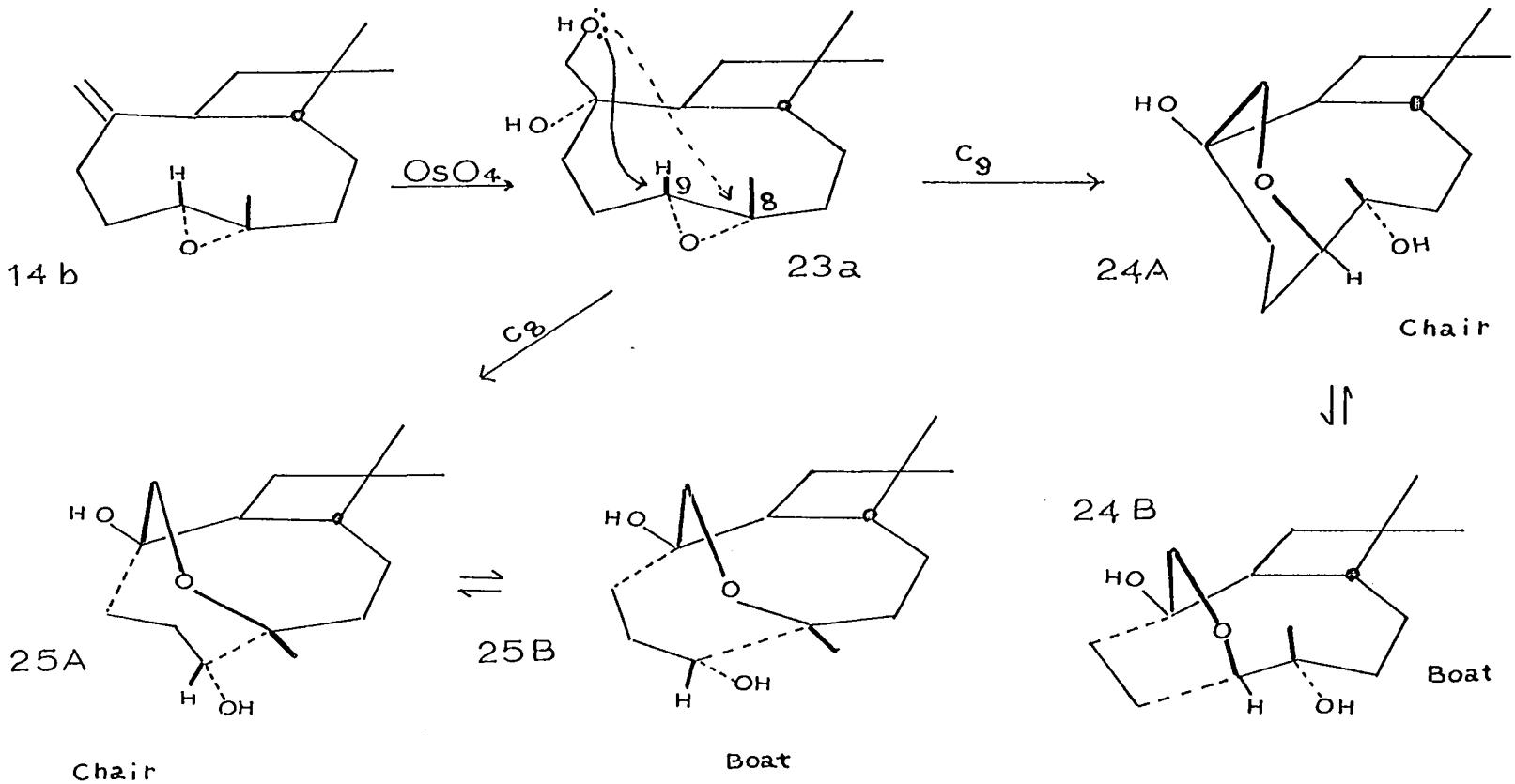

14a
42
100%
43
0%
HO
OH
Chair
46
45
Chair
C_8
C_9
44a, R = H
b, R = PhCH$_2$-
1.2Å
Boat
Boat

Stereochemistry of Glycols Derived from Isocaryophyllene Oxide-b: The 195° Glycol 24 and the 153° Glycol 49a

As in other cases, if the osmium tetroxide reagent is assumed to attack the α-side of the exocyclic double bond in oxide-b 14b, then the 1,2-diol formed initially would be represented by the stereostructure 23a with the α configuration for the C-1 hydroxyl. The oxide ring opening with inversion in such a structure can be realised only by primary hydroxyl attack at either of the two carbon atoms of the oxide ring. The resulting glycols with the β oxide bridge would then be represented by the stereostructures 24 and 25 (see Chart IX). Experimentally we find hydroxylation of oxide-b gives only two glycols 23a and 24 that could be isolated. It is possible that the glycol 25 might have been formed in trace quantities. Examination of a Dreiding model reveals that in 23a, the primary hydroxyl is close to both the tertiary and secondary carbon atoms of the oxirane ring; however, attack at the secondary carbon atom is preferred. The cis nature of the C-1 hydroxyl group and the oxide ring in 23a is demonstrated by its conversion, under basic conditions, to the 195° glycol 24 whose formation involves the nucleophilic attack of the primary hydroxyl group in 23a at the secondary carbon atom of the oxide ring in the same molecule.

In the glycol 25 formed by nucleophilic attack at the tertiary carbon of the oxide ring, the 7-membered heterocyclic ring can assume either chair- or boat-like conformations (25A $\rightleftharpoons$ 25B). In the chair-like form 25A, there is an unfavourable interaction between hydrogen atoms on C-7, C-10 and C-9, C-12; also the substituents on adjacent carbon atoms C-1, C-12 and C-7, C-8 are more nearly eclipsed. In the

CHART IX



boat-like conformation, there is a severe interaction between the C-2 hydrogen and C-9 hydroxyl and between hydrogens on C-5 and C-12; also the substituents on adjacent atoms C-7, C-8 and C-10, C-11 are completely eclipsed. On the other hand, in the glycol 24, when the 6-membered tetrahydropyran ring adopts a boat form 24B, there is interaction between hydrogen atoms on C-5 and C-12 and between hydrogen atoms on C-7 and C-10; also the substituents on adjacent carbon atoms C-1, C-12; C-7, C-8; C-8, C-9; C-9, C-10 are completely eclipsed. However, such interactions are to some extent alleviated in the chair form 24A. Consequently, since interactions in the final product are reflected in the transition state for its formation, the formation of 25 would require a higher activation energy for its formation, and hence the strain-free glycol 24 results.

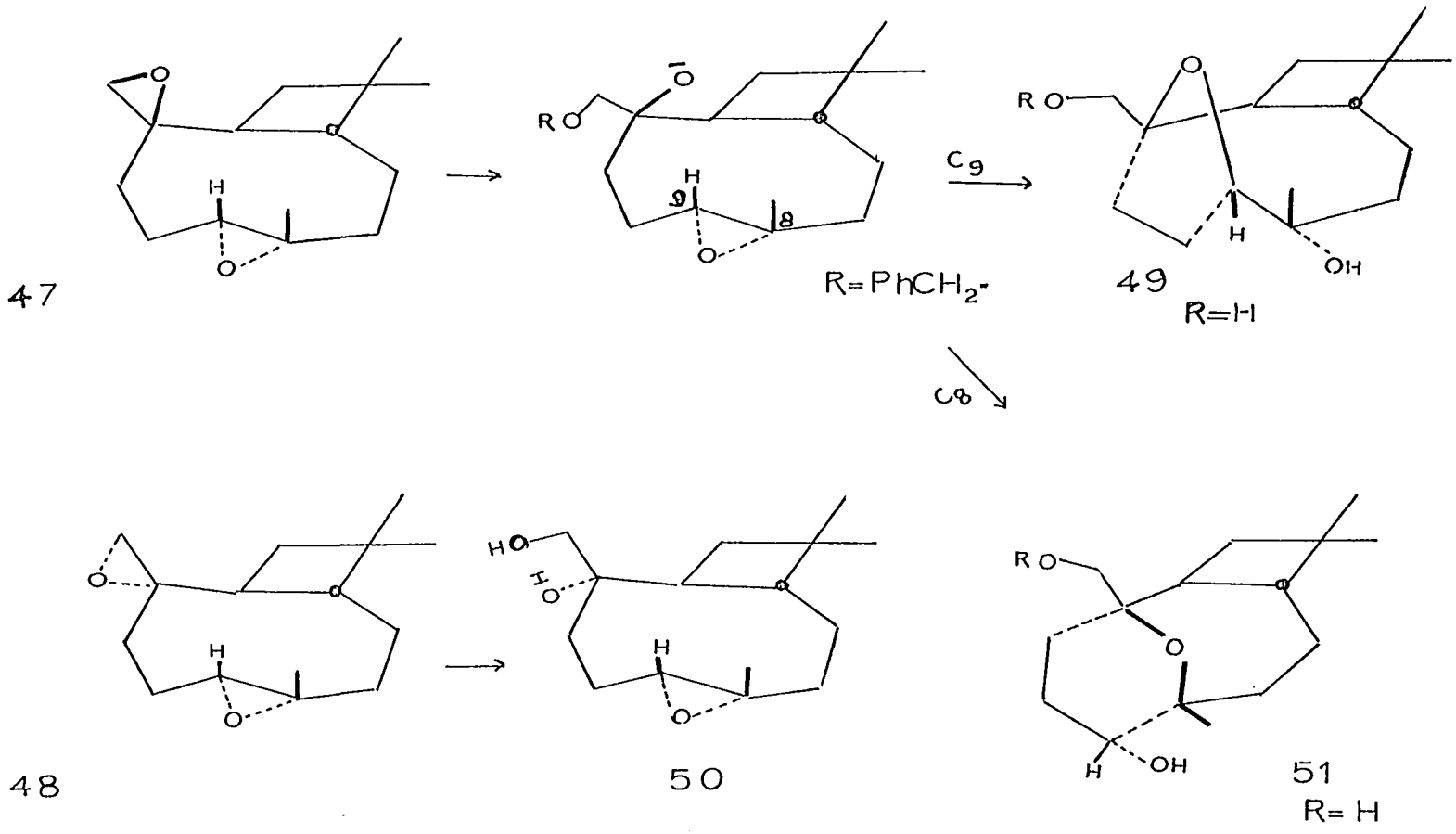
The stereochemistry of the 153° glycol 49 and the unisolated 1,2-diol 50 are dependent on that of their precursor bisepoxides. The isolation of the 153° glycol 49 as the major glycol from the bisepoxide mixture shows that it must have been derived from the major bisepoxide of oxide-b. Since the 153° glycol 49 is a primary-tertiary alcohol, such a structure could have resulted only if the C-1 hydroxyl, obtained by opening of the disubstituted ring in the major bisepoxide, had attacked from the β-side transannularly, at the secondary carbon of the trisubstituted oxide ring of the same molecule, and opened the latter with inversion. This then shows that both the oxide bridge in the 153° glycol 49a and the oxygen atom of the disubstituted oxide ring in the major bisepoxide are β-oriented. Therefore in the major bisepoxide obtained from oxide-b, the two oxide rings are trans to each other and represented by the stereostructure 47 and consequently the

stereostructure 49 would represent the 153° glycol derived from 47. Furthermore, since both the monoacetates of the 116° and 153° glycols 29b and 49b furnish on dehydration the same olefinic acetate mixture, the parent glycols 29a and 49a must differ from each other only in the configuration of the C-8 methyl group.

The occurrence of a 1,2-diol from the bisepoxide mixture could mean that either the C-1 hydroxyl of the unisolated 1,2-diol could not open the oxide ring with inversion, or that the 1,2-diol was also derived by opening of the disubstituted ring in the major bisepoxide and for some reason , the attack of the C-1 hydroxyl of the 1,2-diol 50, at the secondary carbon of the trisubstituted oxide ring occurred slowly. (Compare the formation of 28a and 29a from the major bisepoxide of caryophyllene 26). If the former possibility is true, this would place the C-1 hydroxyl in the 1,2-diol in the α-configuration and consequently such a diol 50 could have resulted only from the minor bisepoxide where the oxygen atom of the disubstituted oxide ring is α-oriented.

When the major bisepoxide 47 is opened under basic conditions by nucleophilic attack at C-12 of the disubstituted oxide ring, the C-1 hydroxyl (or its anion) alone can take part in transannular cyclisation since the C-12 hydroxyl would be in the form of the benzyl-oxy group (see Chart X). The predominant formation of the 153° glycol 49 from 47 shows that intramolecular nucleophilic attack of the C-1 hydroxyl occurs predominantly at the secondary carbon of the oxide ring. Examination of the Dreiding model of the intermediate 1,2-diol from 47 shows that while the C-1 hydroxyl is close to the secondary carbon of the trisubstituted oxide ring, it is far removed from the tertiary carbon of the same oxide ring and to bring it within bonding distance

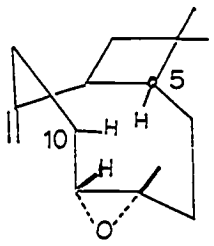
CHART X



47 49 48 50 51

introduces torsional strain. Therefore the formation of the glycol 51 corresponding to attack at the tertiary carbon atom is not observed.

We thus see that the oxidation of oxide-b 14b gives a trans bisepoxide 47 as the major product. This shows that the major attack of the peracid occurs from the β-side of the exocyclic double bond in the oxide-b 14b as it has in oxide-a, 14a, and in caryophyllene oxide, 2. This could be interpreted to mean that the oxirane-peracid interaction, which was observed in the oxide-a 14 and caryophyllene monoxide 2, is not important in the oxide-b 14b. An inspection of the Dreiding model of 14b reveals that this is not surprising. If the oxirane ring were to take part in the peracid oxidation, the molecule would have to adopt a conformation where the exocyclic double bond and the oxirane ring come close to each other. In such a conformation there appears to be a very unfavourable interaction between the C-5 and C-10 hydrogen atoms.



14b

This steric interaction probably prevents the molecule from adopting such a conformation and hence the predominant peracid attack from the β-side of the exocyclic double bond to give 47.

Stereochemistry of the 136° Glycol 38a Derived from the Other trans Oxide 3

The stereochemistry of the ether-bridge of the 136° glycol 38a would depend on the configuration of the C-1 hydroxyl in the unisolated

diol 37. If the osmium tetroxide reagent approaches the exocyclic double bond in 3 from the α-side, the unisolated 1,2-diol would be represented by the stereostructure 37. If, in this 1,2-diol, the α-oriented C-1 hydroxyl had opened the oxide ring with inversion by attack at either the secondary or tertiary carbon of the oxide ring, then the resulting glycols would be represented by the stereostructures 41a and 41b respectively. Inspection of the Dreiding models of the 1,2-diol 37 reveals that as the C-1 hydroxyl approaches either of the two carbon atoms of the oxirane ring, a severe and thus unfavourable interaction between the C-8 methyl and C-5 hydrogen results; therefore attack at neither of the two carbon atoms of the oxide ring is observed to give 41a or 41b.

Alternatively if the primary hydroxyl group in the 1,2-diol 37 were to attack either of the two carbon atoms of the oxide ring and open the latter with inversion, such an attack could occur only from the β-side of the molecule and therefore in the resulting glycols the stereochemistry of the oxide bridge would be β (see Chart XI).

Experimentally we find only the non-strained glycol 38a corresponding to attack at the tertiary carbon of the oxirane ring is formed since attack at the secondary carbon of the oxide ring leads to a more strained (trans 1,4 fusion) glycol of structure 40. The β-configuration of the oxide bridge in 38a is supported by its conversion through the hydroxy ketone 39 to the unsaturated 1,2-diol 11 obtained previously from the 119° glycol 5a.

CHART XI

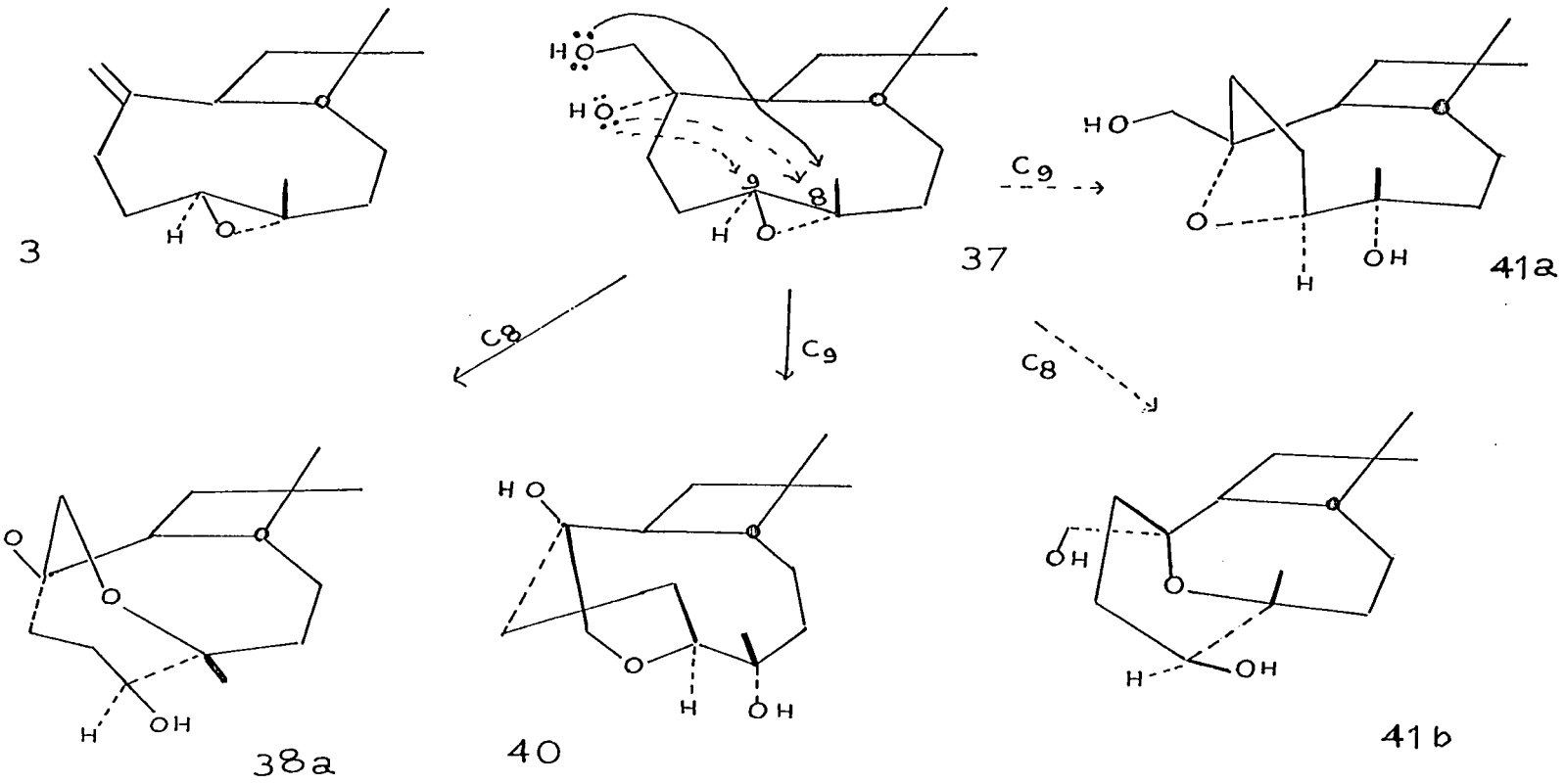


TABLE II

Nuclear Magnetic Resonance Absorption of Glycols from Caryophyllene and Isocaryophyllene*

Compound	C-4 gem dimethyl	C_8-methyl	C-9H	C-12 H_2	Other peaks
119° glycol 5a	1.02 s	1.20 s	3.55 m	3.20 sbord	2.89 bm (2H,OH)
142° glycol 6	0.97 s	1.33	?	3.69 bs	2.38 bm (OH)
unsaturated diol 11	0.96 s	1.66 d (J 1)	5.35 bm	3.60 d (J ~ 1)	2.58 bs (2H,OH)
130° glycol 19a	0.99 s	1.32 s	3.93 bm	3.28 q (J ~ 3)	--
195° glycol 24 (in Pyridine)	0.98 s 1.00 s	1.53 s	?	?	5.06 bs 2H,OH
1,2-diol 23a	0.98 s	1.23 s	?	3.27 bm	--

* Chemical shifts are given in parts per million from tetramethylsilane (=0) for deuteriochloroform solutions unless otherwise stated. The symbol ? means that the peak position is not given because the assignment would be uncertain; s = singlet, d= doublet, b= broad, m= multiplet and dd= doublet of doublets.

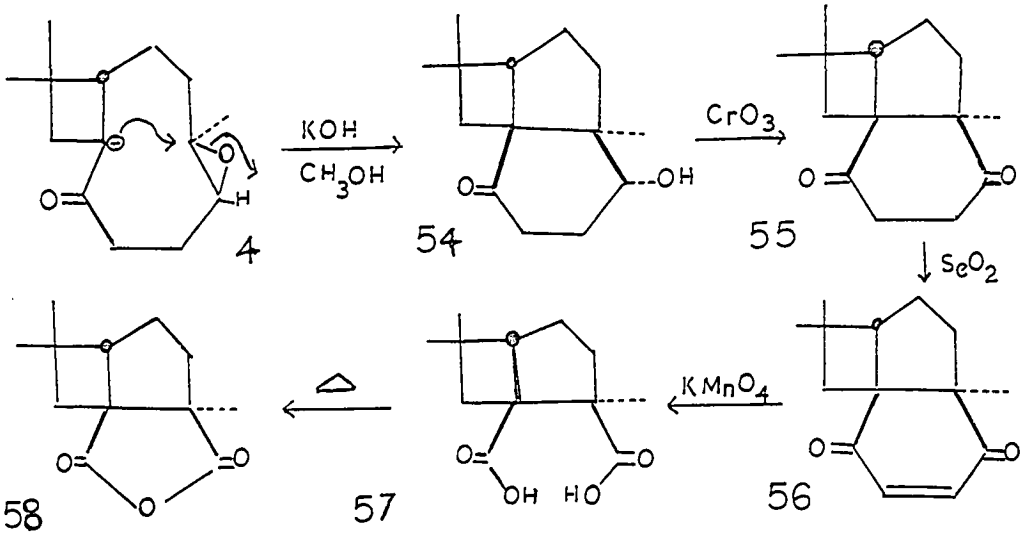
TABLE II (Continued)

Compound	C-4 gem dimethyl	C_8-methyl	C-9H	C-12 H_2	Other peaks
116° glycol 29a	0.97 s	1.00 s	4.05 bm	3.53 q (J_{AB}=12)	
127° glycol 28a	0.98 s	1.30 s	?	?	
152° glycol 44	0.96 s	1.35 s	?	3.3 bm	2.16 bm (1H,OH)
227° glycol 45 (in Pyridine)	1.00 s	1.62 s	3.93 bm	3.52 q	5.16 bs (1H,OH)
153° glycol 49a	0.95 s 0.96 s	1.32 s	3.97 m	3.56 q J_{AB}=12	1.64 bs (1H,OH)
136° glycol 38a	0.98 s 1.08 s	1.28 s	3.75 m	3.90 m	

CHAPTER II

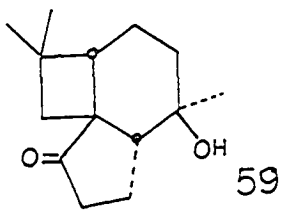
Base-Catalysed Isomerisation of Epoxy Ketones Derived from Caryophyllene and Isocaryophyllene

In continuation of our studies of transannular epoxide reactions, it was thought that an investigation of the base-catalysed isomerisation of epoxy ketones derived from caryophyllene and isocaryophyllene would further our understanding of the mode of epoxide ring-opening in such compounds. Earlier, Barton and Lindsey[115] observed that when Treibs' oxido ketone 4 was refluxed with methanolic potassium hydroxide it was smoothly and in almost quantitative yield (90%) isomerised to a highly crystalline tricyclic substance 54, m.p. 148-149°, $[\alpha]_D$ -32.0°. The proof for the structure and cis fusion of the 6-membered to the 5-membered ring was provided by the following sequence of reactions



The hydroxy ketone 54 was oxidised to the diketone 55 which in turn was converted to the enedione 56. Permanganate oxidation of the enedione 56 yielded a dicarboxylic acid 57 which readily formed an anhydride 58, showing thereby the cis orientation of the two carboxyl groups. The ditertiary nature of the dicarboxylic acid was proved by the failure of the anhydride to undergo bromination.[59b]

The formation of the tricyclic hydroxy ketone 54 involves nucleophilic attack of the enolate anion of the keto oxide 4 at the tertiary carbon of the oxide system. Although no explanation was offered at the time this observation was made, the formation of this particular stereostructure 54 can be rationalised by considering the angle strain and torsional strain involved in the other possible final products. Thus the compounds 59 (trans 6, 5 fusion), 60 (trans 4, 6 fusion), and 61a (trans 5, 6 fusion) resulting from attack at the secondary and tertiary carbon atom respectively with inversion would be more strained than the observed product 54 (cis 4,5 and 5,6 fusions) and consequently a higher activation energy would be required for their formation.



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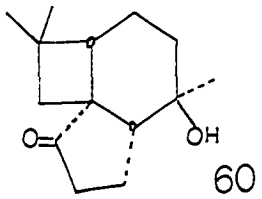

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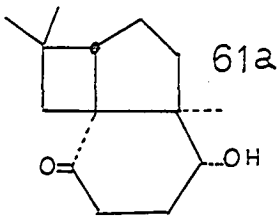
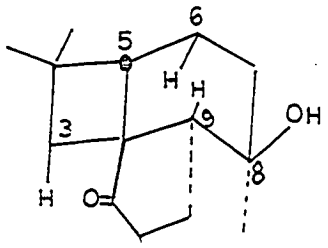


Examination of the Dreiding models of compound 59 show that the six-membered ring can exist only in the boat form in which there is a severe flagpole interaction between the hydrogen atoms on C-6 and C-9 and also the substituents on adjacents C-7, C-8 and C-2, C-5 are nearly eclipsed; there is also observed an unfavourable interaction between theC-8 methyl

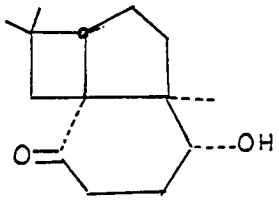
group and one of the hydrogen atoms on C-3.



59

In our hands the base-catalysed isomerisation of 4 in methanol gave the same result reported earlier[115] except that traces of two other compounds could be detected by t.l.c., a technique not available in the earlier work. When the isomerisation of oxide ketone 4 was carried out in t-butyl alcohol, there was obtained a brown solid whose thin-layer chromatographic behaviour was identical with that of the crude product obtained by methanolic potassium hydroxide. By a combination of crystallization and column chromatography techniques, three crystalline compounds 54 (m.p. and mixed m.p.), 61a and 64 were isolated from the crude product in 61%, 27% and 5% yields respectively. The crystalline compound 61a $C_{14}H_{22}O_2$, $[\alpha]_D$ + 17.8°, showed, in the infrared spectrum, the presence of hydroxyl absorption and carbonyl absorption at 1705 cm^{-1} (6-membered C=O). In the n.m.r. spectrum of 61a (see plate XIII), the gem-dimethyl group appeared as singlets at 0.90 p.p.m. and 1.16 p.p.m.; a 3H singlet at 1.19 p.p.m. indicated a methyl group on a carbon bearing no hydrogen atoms and a poorly resolved broad 1H doublet of doublets indicated the presence of an H-C-O group with adjacent methylene hydrogen atoms. The monoacetate 61b, $C_{16}H_{24}O_3$, m.p. 58-58.5°, showed in the infrared spectrum carbonyl absorp-

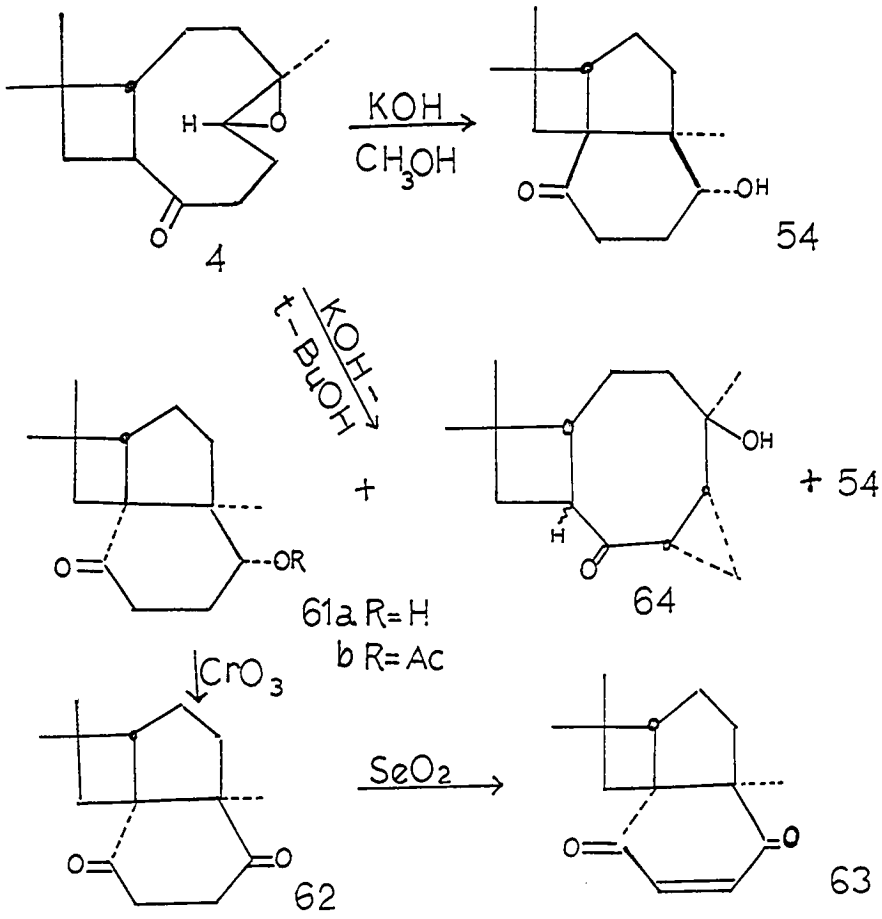
tions due to 6-membered and ester carbonyls at 1705 cm^{-1} and 1735 cm^{-1} respectively. In the n.m.r. spectrum the methine proton was shifted downfield by 1.15 p.p.m. and appeared as a broad ill-resolved lump at 5.58 p.p.m. All these facts are in agreement with the structure 61a for the 119° hydroxy ketone.



61a

Further proof for the structure 61a comes from the following sequence of reactions (page 126). Oxidation of 61a gave a diketone 62, m.p. 51.5-52° (depressed on admixture with 55). The infrared spectrum of 62 indicated the absence of hydroxyl absorption and the presence of a sharp band at 1700 cm^{-1} due to 6-membered ketone. Selenium dioxide oxidation of 62 gave the expected enedione 63 whose infrared spectrum indicated the presence of the enedione group at 1672 cm^{-1} and a band at 1610 cm^{-1}.

The ultraviolet absorption spectrum had absorption maxima at 224 mμ (ϵ 13,750) and 348 mμ (ϵ 141) indicating the presence of the chromophore O=C-C=C-C=O in a cisoid arrangement. In the n.m.r. spectrum, the vinylic protons appeared as a pair of doublets centred at 6.55 p.p.m. (J= 11 c.p.s.) and 6.83 p.p.m. (J= 11 c.p.s.)

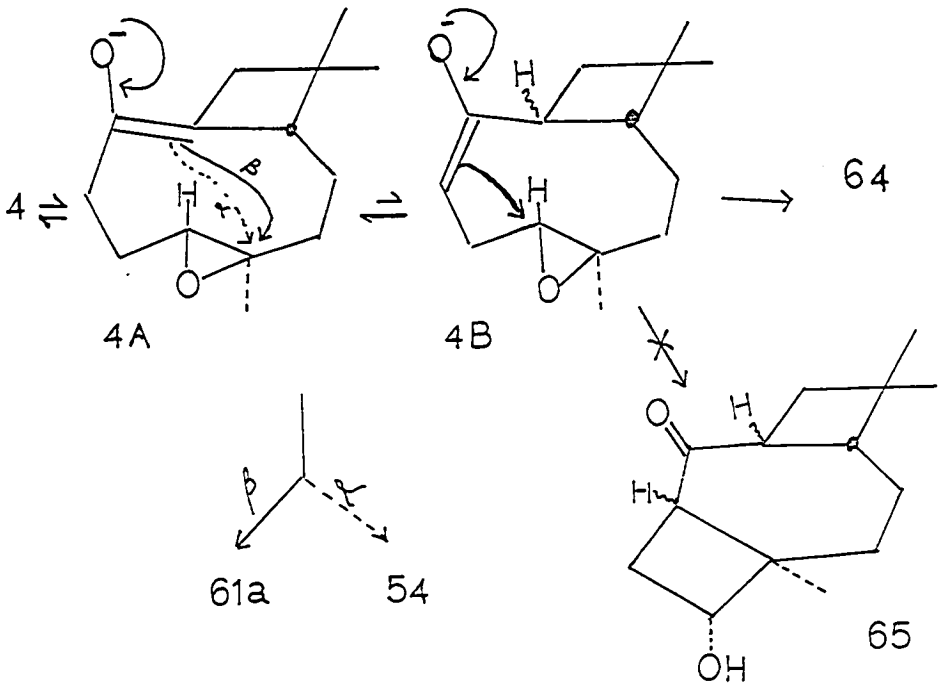


The crystalline compound 64, $C_{14}H_{22}O_2$, m.p. 145-146°, showed in the infrared spectrum the presence of hydroxyl absorption at 3580 cm^{-1} and 3420 cm^{-1} (free and bonded OH respectively), a band at 3000 cm^{-1} attributed to cyclopropane methylene[116a] and a band at 1695 cm^{-1} consistent with the presence of a carbonyl group in conjugation with a cyclopropane ring.[116b,117] The ultraviolet spectrum showed an absorption maximum at 280 mμ(ε158) and rising end absorption with ϵ_{202} 2680. Although the calculated maximum, due to $\pi-\pi^*$ transition, by Dauben's rule,[118] should be 202 mμ(ε-5000), the extinction coefficient of the absorption maximum at 280 mμ due to $n-\pi^*$ transition is definitely indicative of a ketone in conjugation with cyclopropane ring.[117] The n.m.r. spectrum of compound 64 was not informative about the presence of cyclopropane

protons.

When hydroxy ketone 64 was refluxed with methanolic potassium hydroxide, the starting material was recovered unchanged; there was no evidence for the formation of a hemiketal of 64. The tertiary nature of the hydroxyl group in 64 was indicated by its failure to undergo acetylation at room temperature by acetic-anhydride - pyridine reagent. All these facts fit well the structure 64 assigned for the 145-146° hydroxy ketone. (The stereochemistry of the C-2 hydrogen will be discussed later).

The formation of hydroxy ketones 54 and 61a involves the nucleophilic attack of the same enolate anion 4A of the oxido ketone 4 at the tertiary carbon of the oxirane ring - β attack giving 61a and α-attack leading to 54. In either case the oxide ring is opened with inversion in the base-catalysed S_N2 reaction. However, a different product results when the direction of enolisation changes. Thus when the oxide ring is opened with inversion by nucleophilic attack at the secondary (C-9) carbon atom of the enolate anion 4B involving the α-methylene hydrogen, hydroxy ketone 64 is formed.



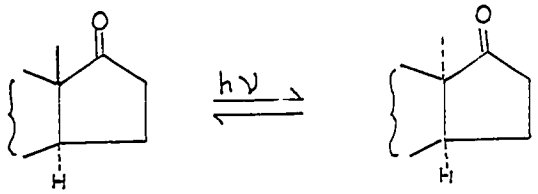
The formation of hydroxy ketones 54, 61a and 64 in the same reaction shows that the enolate anions 4A and 4B are in equilibrium with each other. It is interesting to note that while the enolate anion 4B has a choice of attacking either the secondary or tertiary carbon atom of the oxirane ring to give 64 or 65, attack at the secondary carbon is preferred. Inspection of the Dreiding model of the enolate anion 4B shows that when the C-2 hydrogen is trans with respect to the β-oriented C-5 hydrogen, then in the transition state for attack of the enolate anion at the tertiary carbon atom of the oxide ring, an unfavourable interaction between the C-8 methyl and the C-2 hydrogen atom is noticed; however such an interaction is absent when the enolate attacks the secondary carbon atom. Consequently attack at the secondary carbon atom is preferred. On the other hand, when the C-2 hydrogen is cis to the C-5 hydrogen in the enolate anion 4B, a severe interaction between the C-2 and C-9 hydrogen atoms is noticed in the transition state for attack

at the secondary carbon; hence such an attack is energetically unfavourable. We thus tentatively assign ∝-configuration for the C-2 hydrogen in 64.

It is interesting to note that while hydroxy ketones 61a and 64 are present in negligible quantities in methanolic medium their proportions increased to a considerable quantity in t-butyl alcohol medium. This increase may be due to an increase in the temperature of the reaction from ~65° to ~85°.

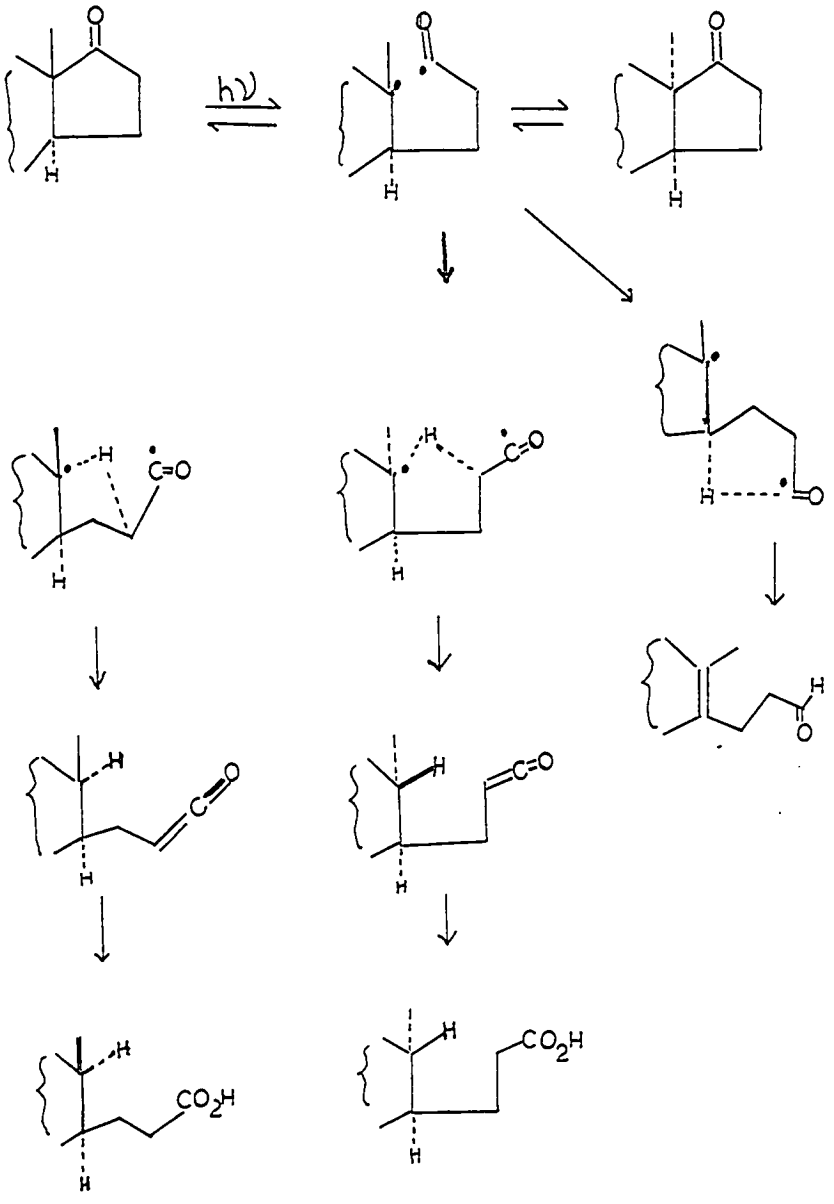
Photochemistry of Hydroxy Ketones 54 and 61a

Since hydroxy ketones 54 and 61a differ only in the nature of the 6-5 ring fusion, it was thought that a proof for the trans 6-5 ring fusion in 61a could be provided by direct photochemical epimerisation of 61a to 54. The photochemical method was chosen because of its simplicity and the existence of analogous reactions in the literature. Thus, this kind of photo-epimerisation was earlier observed by Butenandt in the case of 17-keto steroids.[119]



When a ketone molecule is excited by the absorption of light, a homolytic cleavage of the bond between the carbonyl group and the highly substituted ∝-carbon atom occurs to give an alkyl-acyl diradical. One of the possible reaction paths for the diradical thus produced is recombination to give either the starting material or its epimer. Since both the ketones absorb in the same spectral region, the system reaches a photostationary state via the diradical. Alternatively the

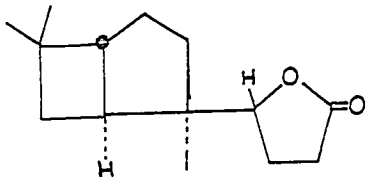
diradical can undergo intramolecular disproportionation to give either the isomeric ketenes by migration of a hydrogen atom from the position adjacent to the acyl radical or else an unsaturated aldehyde by migration of a hydrogen atom from the position adjacent to the alkyl radical site.



Photochemical transformations of unconjugated ketone.[120]

The ketenes thus produced react with water to give carboxylic acids. In the absence of protonic solvents, the intermediate formation of ketenes has been proved by Quinkert, et al.[121] The intramolecular nature of the hydrogen migration involved in the formation of both the ketenes and the unsaturated aldehyde has been conclusively proved by Quinkert[122] and Srinivasan.[123]

Thus hydroxy ketone 61a was expected to be converted to 54 under the influence of light since such a transformation would relieve the angle and torsional-strain involved in 61a. However, when a 2% solution of hydroxy ketone 61a in thiophene-free benzene in a quartz cell was irradiated, a liquid lactone 67, $C_{14}H_{22}O_2$, $[\alpha]_D$ + 5.80° was obtained in good yield. There was no evidence for the formation of hydroxy ketone 54 or for the presence of starting material in the crude product (n.m.r. and t.l.c.). The lactonic nature of the product was indicated by its easy extraction into alkali and the infrared spectrum which showed a band at 1775 cm^{-1} due to γ-lactone and ketone but no hydroxyl absorption. The n.m.r. spectrum (see plate XIV) is in agreement with the structure 67 proposed for the lactone.

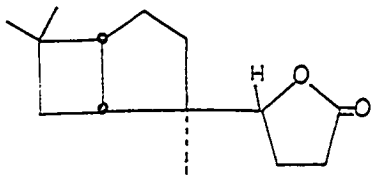


67

The nature of the 4,5 ring junction is probably trans for reasons to be discussed later.

Irradiation of Barton's tricyclic hydroxy ketone 54 under the same conditions used for 61a gave in addition to the recovered starting material (m.p. and mixed m.p.) from the slower reaction, a crystalline

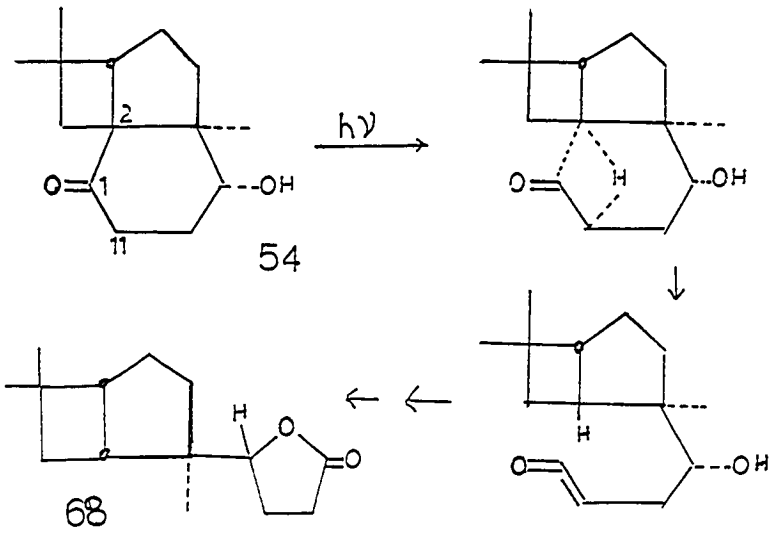
lactone 68, isomeric with 67, $C_{14}H_{22}O_2$, m.p. 93.5-94.5°, $[\alpha]_D$ -62.0° in 32% yield. The infrared spectrum had a band at 1770 cm^{-1} due to γ-lactone and no hydroxy absorption. The n.m.r. spectrum of 68 was found to be different from that of 67 (see plate XIV) and is in agreement with the following structure 68.



68

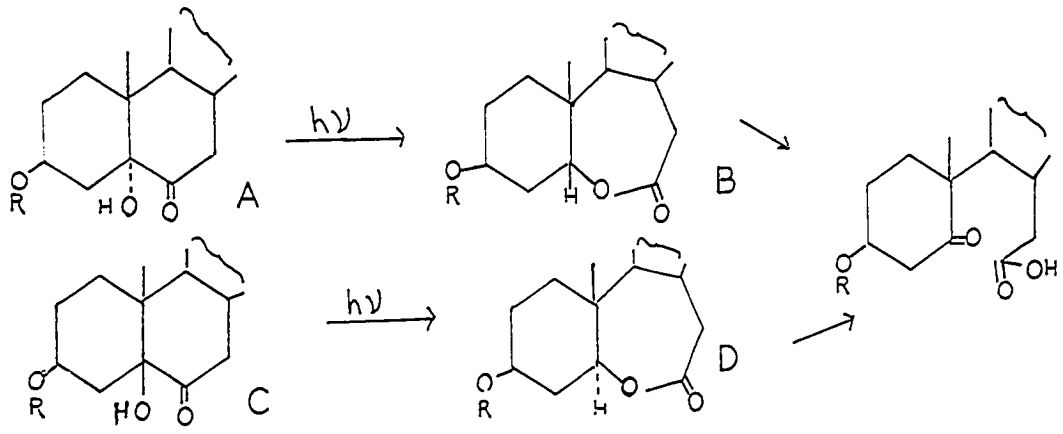
Thus the two lactones 67 and 68 differ probably in the nature of the 4,5 ring junction. There was no evidence for the presence of either 61a or 67 in the crude irradiation product from 54 (t.l.c. and n.m.r.).

The stereospecific formation of lactones 67 and 68 from hydroxy ketones 61a and 54, respectively, is rather surprising but can be rationalised as follows. Since the stereospecific nature of the photochemical reaction reveals the hydrogen transfer in both 54 and 61a to be intramolecular, the transfer of hydrogen from C-11 to C-2 must occur from the same side as the C-2-C=O bond is broken. In other words, as the bond between C-2 and the carbonyl carbon is broken, the bond between the C-11 hydrogen and C-2 is formed and the reaction may proceed through a transition state of the type shown in the figure. This means that the 4,5 ring junction is cis in 68 and trans in 67. Our assignment of stereochemistry to the ring junction in the two lactones is only tentative and subject to confirmation.



That the two lactones 67 and 68 differ only in the 4,5 ring junction is further shown by optical rotatory dispersion measurements (see experimental). The completely stereospecific photochemical reaction could also proceed through a diradical provided the subsequent hydrogen abstraction occurs before inversion of the tertiary radical formed.

This completely stereospecific photo-isomerisation of γ-ketols to γ-lactones finds analogy in the literature. Thus 3β, 5α-dihydroxycholestan-6-one A gives only the lactone B and the C-5 epimer, C, gives only the lactone D.[124]



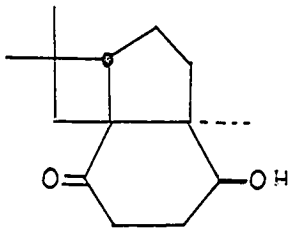
Isomerisation of Keto Oxide-a 13a

Since Treib's oxido ketone 4 was isomerised smoothly in methanolic potassium hydroxide, to the crystalline hydroxy ketone 54 in high yield it was decided to study the isomerisation of keto oxide-a 13a under the same conditions used by Barton and Lindsey.[115]

However the base-catalysed isomerisation of keto oxide-a 13a in methanolic potassium hydroxide gave a complex mixture of at least nine compounds. The n.m.r. spectrum of the crude product indicated peaks due to methoxyl groups thereby showing that attack of methoxide on the carbonyl carbon was occurring. In order to suppress the attack of the base on the carbonyl carbon, it was decided to use t-butyl alcohol in place of methanol, since for steric reasons addition of t-butoxide anion to the carbonyl carbon would be less favourable while enolisation would be promoted.

Thus isomerisation of keto oxide-a 13a gave a mixture of only two compounds, 70 and 71a in 5% and 45% yields respectively. The crystalline compound 70, $C_{14}H_{22}O_2$, m.p. 129-130°, showed in the infrared spectrum absorption peaks due to a hydroxyl group and 6-membered ketone. The n.m.r. spectrum contained singlet peaks at 0.95 p.p.m. and 1.05 p.p.m. from the gem-dimethyl group, a 3H singlet at 1.24 p.p.m. due to a methyl group on a carbon bearing no hydrogen and a 1H proton doublet of doublets at 3.95 p.p.m. due to a methine proton on a carbon atom bearing oxygen function. Oxidation of the hydroxy ketone 70 with chromic acid - pyridine reagent at room temperature gave the diketone 55 (m.p., mixed m.p., t.l.c., and infrared spectrum). Thus compound 70 is the hydroxyl epimer of Barton's hydroxy ketone 54 and

is represented by the following structure.

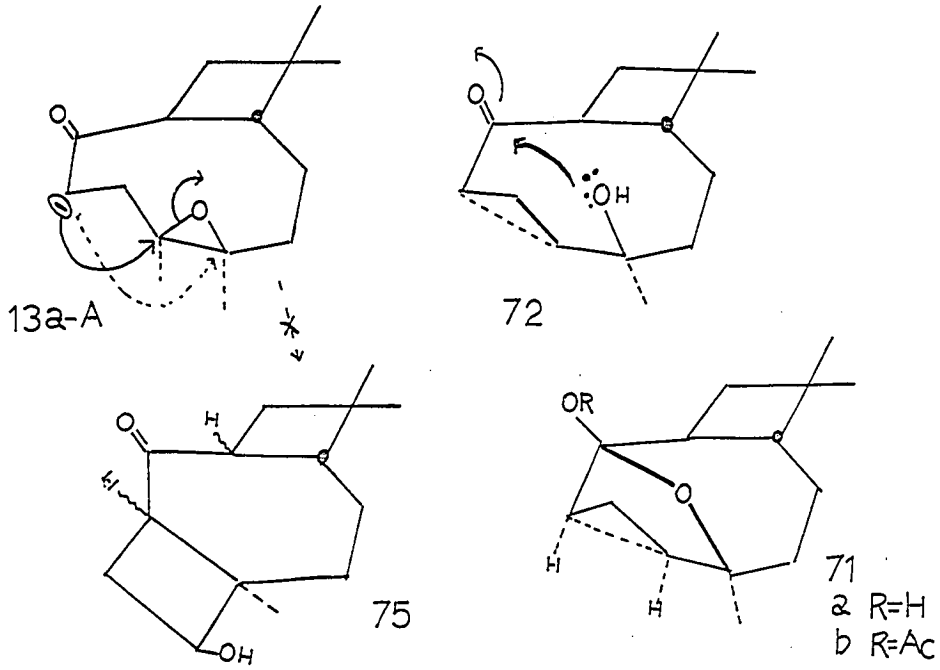


70

The second crystalline compound 71a, $C_{14}H_{22}O_2$, m.p. 116-117°, showed in the infrared spectrum an absorption band due to hydroxyl group, and no carbonyl peak. The spectrum also indicated weak bands at 3060 cm^{-1} and 3030 cm^{-1}, which are ascribed to cyclopropane methylene[116a] and a strong band at 770 cm^{-1} ascribed to a hemiketal linkage. The n.m.r. spectrum contained singlet peaks at 0.93 p.p.m. and 1.18 p.p.m. due to the gem-dimethyl group, a 3H singlet at 1.21 p.p.m. due to a methyl group on a carbon atom bearing an oxygen function, and a 2H multiplet centred approximately at 0.60 p.p.m. due to cyclopropane methylene protons.

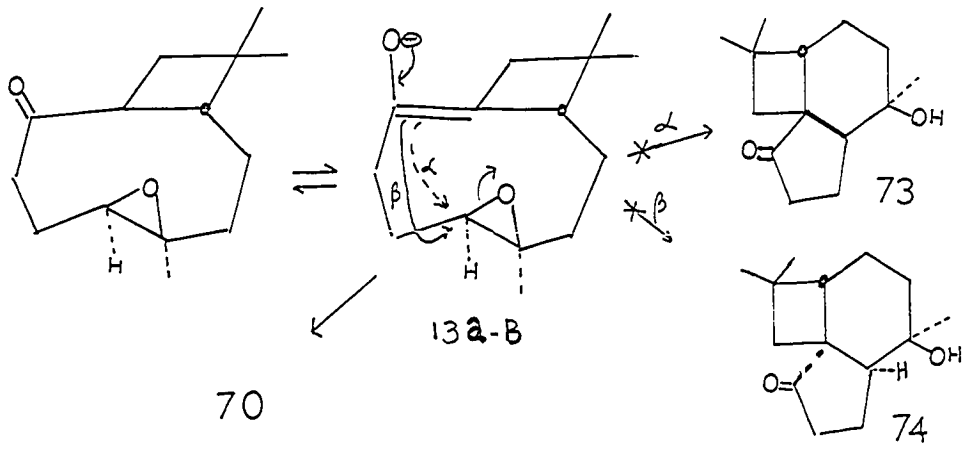
The tertiary nature of the hydroxyl group in 71a was indicated by its failure to undergo acetylation at room temperature with acetic anhydride - pyridine reagent. However, when refluxed with pyridine containing acetic anhydride it was smoothly converted to a crystalline acetate 71b, $C_{16}H_{24}O_3$, m.p. 100-100.5°. The infrared spectrum of the acetate showed the absence of hydroxyl absorption and the presence of ester carbonyl at 1735 cm^{-1}; it also showed cyclopropane methylene at 3015 cm^{-1} and 3000 cm^{-1}.

These facts can be accommodated in the following structure 71a for the hemiketal, the formation of which can be rationalised as noted below.



The stereochemistry of the hemiketal linkage is controlled by the configuration of the C-8 hydroxyl group in the hemiketal precursor 72. When the oxirane ring opens with inversion the cyclopropane methylene and the C-8 hydroxyl group assume the β-configuration, and consequently the hemiketal linkage must be also β-oriented.

While the formation of hemiketal 71a involves the enolate anion 13a-A, hydroxy ketone 70 is formed from α attack of the enolate anion 13a-B at the tertiary carbon of the oxide system.

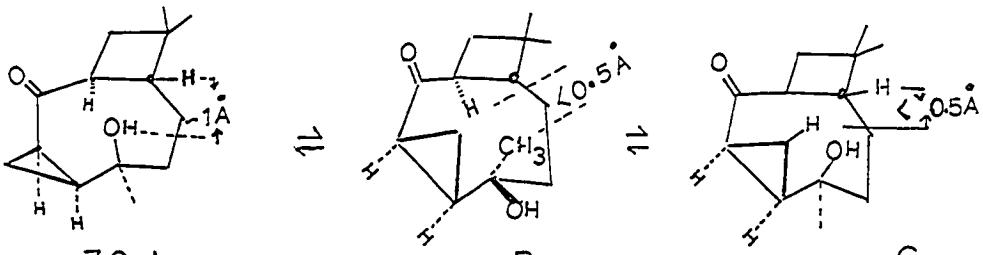


Here also as in the case of oxido ketone 4 attack of the enolate anion at the secondary carbon to give 73 or 74 is not observed; the reason is not obvious.

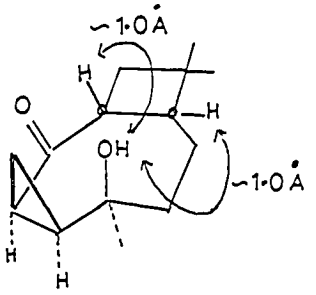
It is interesting to note that while the enolate anion 13a-A can be expected to attack either the tertiary or secondary carbon of the oxirane ring, exclusive attack at the secondary carbon is observed to give the hemiketal 71a, through the intermediate formation of hydroxy ketone 72. The reason for this exclusive attack at the secondary carbon of the oxide system is clear from examination of a Dreiding model of the enolate anion 13a-A. Such an inspection reveals that the enolate anion 13a-A is closer to the secondary than to the tertiary carbon of the oxide. Moreover in the transition state for attack of the enolate anion 13a-A at the tertiary carbon an interaction between the C-8 methyl and the α gem-dimethyl group on C-4 is noticed; thus hydroxy ketone 75 from attack at the tertiary carbon is not formed. On the other hand, when the enolate anion attacks the secondary carbon, no severe interaction between various atoms or groups in the molecule is noticed.

Here we notice the hydroxy ketone 72 prefers to exist in its hemiketal form 71a (the crude product had no carbonyl infrared absorption). This preference for the hemiketal structure can be understood by examining a Dreiding model of 72. When the C-2 hydrogen is α-oriented in 72 (that is trans to the β-oriented C-5 hydrogen), then in one of the conformations A, adopted by the molecule, the C-8 hydroxyl interacts with the C-5 hydrogen. Although this interaction can be minimised by rotating the C_7-C_8 bond, in the new conformation

B thus adopted by the molecule we notice a severe interaction between the C-8 methyl and C-2 hydrogen atom; any further attempt to minimise this interaction introduced a new interaction between the C-5 hydrogen and cyclopropane methylene hydrogen as seen in C. Consequently hydroxy ketone 72 undergoes hemiketalisation to give 71a.



When the C-2 hydrogen in 72 assumes the β-configuration (the C-2 and C-5 hydrogens cis), then in the conformation 72D necessary for hemiketalisation the hydroxyl and carbonyl carbon are farther apart than when the C-2 hydrogen is α and trans to the C-5 hydrogen. Therefore, the hemiketal is assigned the C-2 α-configuration.

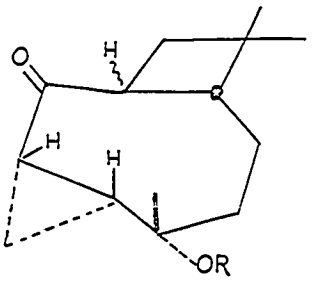


72D

Isomerisation of Keto Oxide-b 13b

In contrast to keto oxide-a 13a, isomerisation of keto oxide-b 13b either with methanolic potassium hydroxide or with t-butyl alcohol - potassium hydroxide gave only two compounds - one a crystalline solid 76, $C_{14}H_{22}O_2$ (35%), and the other a liquid 77a, $C_{14}H_{22}O_2$ (62%).

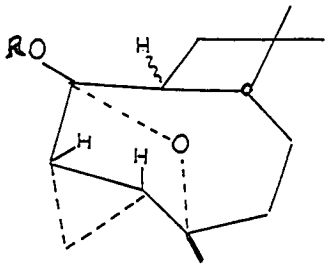
The infrared spectrum of the crystalline 76 showed the presence of hydroxyl absorption, a weak band at 3000 cm^{-1} indicating cyclopropane methylene and a band 1685 cm^{-1} consistent with the presence of a carbonyl group in conjugation with a cyclopropane ring.[116b,117] The ultraviolet absorption spectrum showed a maximum at 280 mμ(ε147) which could be interpreted as due to a ketone conjugated with cyclopropane ring.[117] As in the case of hydroxy ketone 64, the isomeric hydroxy ketone 76 did not show any absorption maximum around 200 mμ but had ϵ_{202} 4960 which is in the range expected from Dauben's work.[118] The tertiary nature of the hydroxyl group in 76 was indicated by its failure to undergo acetylation at room temperature with acetic anhydride - pyridine mixture. These facts together with the n.m.r. spectrum of 76, are consistent with the following structure 76 for the crystalline solid.



76 R=H

The second compound, 77a isolated in the liquid state was found to be the hemiketal of 76 as evident from the following spectral and chemical evidence. The infrared spectrum showed the presence of hydroxyl absorption and had no carbonyl peaks; weak bands at 3040 cm^{-1} and 3070 cm^{-1} indicating the presence of cyclopropane methylene[104a] and a band at 770 cm^{-1} showed the presence of a hemiketal linkage. In the n.m.r. spectrum, a 2H multiplet at 0.53 p.p.m. indicated the presence of cyclopropane methylene, two 3H singlets at 1.07 p.p.m. and 1.15

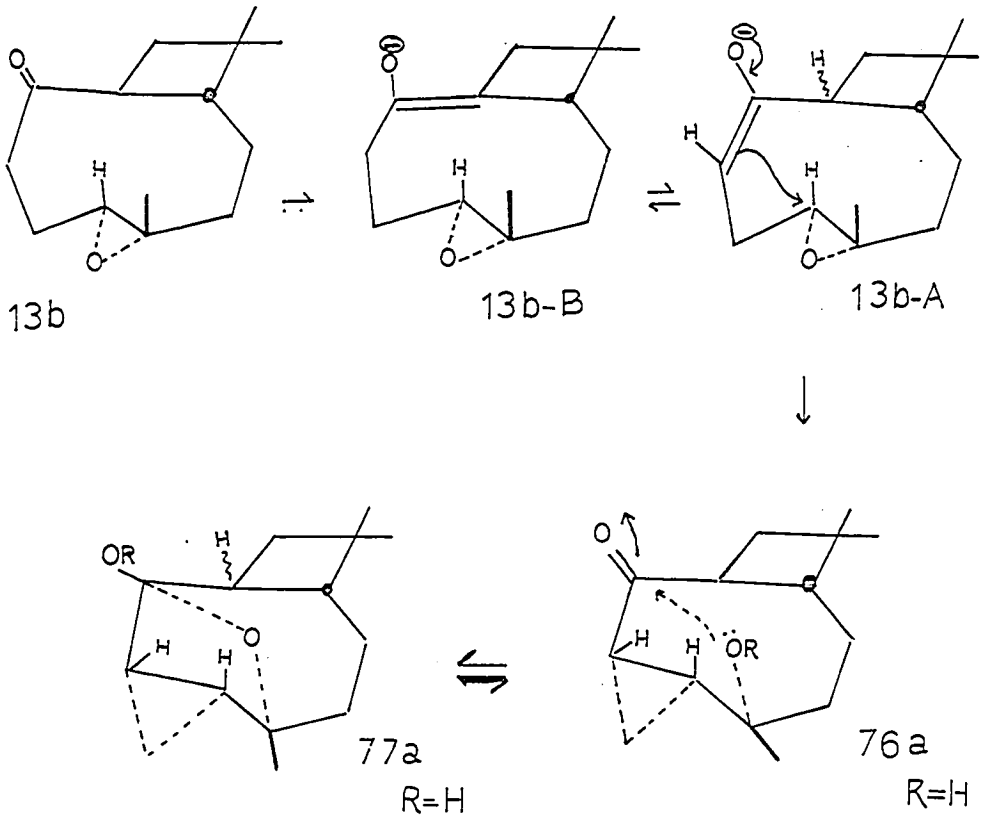
p.p.m. indicated the gem-dimethyl group, a 3H singlet at 1.25 p.p.m. indicated the presence of a methyl group on a carbon bearing oxygen function and one of the cyclopropane methine protons appeared as a quartet at 2.93 p.p.m. The tertiary nature of the hydroxyl group in 77a was indicated by its failure to undergo acetylation at room temperature with acetic anhydride - pyridine reagent. However, acetylation with acetic anhydride at reflux temperature of pyridine furnished a crystalline acetate 77b. The infrared spectrum of 77b indicated the absence of hydroxyl absorption and the presence of ester carbonyl at 1730 cm^{-1}, and weak bands at 3000 cm^{-1} and 3030 cm^{-1} indicated the presence of cyclopropane methylene. These facts clearly show that the liquid hemiketal must be represented by the following structure 77a.



77a R=H
b R=Ac

The above structure is further supported by the following experiments. When the crystalline hydroxy ketone 76 was refluxed with methanolic potassium hydroxide, the resulting product was shown by t.l.c., n.m.r. and separation into components, to be a mixture of hemiketal 77a and hydroxy ketone 76 in the ratio 65:35. Similar isomerisation of hemiketal 77a with methanolic potassium hydroxide gave a mixture of 77a and hydroxy ketone 76 in the ratio 65:35. Therefore the isomerisation of 13b gives hydroxy ketone 76 first which then undergoes partial isomerisation to 77a. We thus find conversion of 77a and 76 to each

other is not complete and an equilibrium is reached between the two, in favour of 77a.

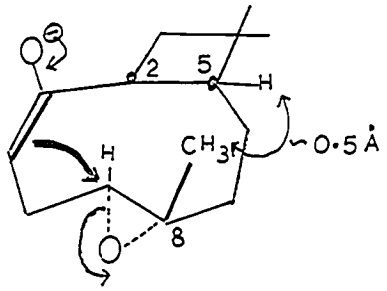


If we assume that the oxide ring in 13b opens with inversion then, in the hydroxy ketone 76a, the C-8 hydroxyl and cyclopropane methylene are cis to each other or on the same side (α). Since the hemiketal 77a is derived from 76a, the hemiketal linkage in the former is α-oriented.

It is reasonable to expect the keto oxide-b 13b to enolise under the basic conditions to give two enolate anions 13b-A and 13b-B. Although the thin-layer chromatography of the crude isomerisation product showed a very faint spot corresponding in R_f value to Barton's tricyclic hydroxy ketone 54 it was not possible to isolate any compound

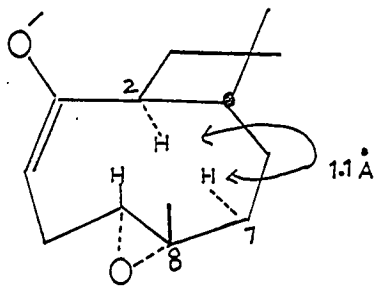
resulting from attack of the enolate anion 13b-B at either the tertiary or secondary carbon of the oxide ring in 13b.

Let us now consider the attack of the enolate anion 13b-A at either the tertiary or secondary carbon of the oxide ring. When the C-2 hydrogen is β-oriented (that is cis to C-5 hydrogen) in the enolate anion, then in the transition state for attack at either the tertiary or secondary carbon of the oxide ring with inversion, an interaction between the C-8 methyl and C-5 hydrogen is noticed; consequently such an attack would not be favoured.



Even though there are other conformations for the above enolate ion where the C-8 methyl and C-5 hydrogen are far removed from each other they are not important since in such conformations the oxide ring can be opened only by front-side attack which is energetically unfavourable.

On the other hand, when the C-2 hydrogen assumes the α-configuration (that is trans to C-5 hydrogen) in the enolate anion, 13b-A, then the transition state for attack at the secondary carbon of the oxide is free from any interaction between various atoms or groups in the molecule and hence such an attack is preferred. Here attack at the tertiary carbon is not observed because the C-2 and C-7 hydrogens come close to each other and thus interact in the transition state for such an attack.



The discussion advanced so far shows that the C-2 hydrogen in the hydroxy ketone 76 most probably is α-oriented (that is the 4,8 ring junction is trans). However since the hemiketal 77a is formed from hydroxy ketone 76 under basic conditions, epimerisation at C-2 is possible and hence the configuration of C-2 hydrogen in the hemiketal could be either α or β . At the moment there is insufficient evidence to assign stereochemistry for the C-2 hydrogen in 77a.

CONCLUSION

In the seven cases that have been studied in this work, the basic assumption that an oxirane ring opens, under basic conditions, with inversion of configuration at the carbon atom being substituted, leads to the conclusion that, while in intermolecular epoxide ring-opening reactions, steric factors direct the nucleophilic attack at the least-substituted carbon atom of the epoxide ring system, such factors appear to be negligible in the case of intramolecular reactions. The formation of strain-free products and conformational factors seem to be more important considerations. Although our work has dealt primarily with transannular epoxide ring-opening reactions in caryophyllene derivatives, the conclusions reached should be applicable to other systems as well.

CHAPTER III

EXPERIMENTAL

GENERAL:

Melting points were taken on a Reichert microscope hot stage and are corrected. Optical rotations were measured with chloroform solutions, unless otherwise stated, in a 1-dm tube on a Rudolph Model 80 Polarimeter. Infrared spectra were recorded on a Beckman IR-5A or IR-10 Spectrophotometer. The ultraviolet spectra were taken on a Cary Model 14 Spectrophotometer. Nuclear magnetic resonance spectra were determined with deuteriochloroform solutions (20-30 mg/0.1 ml) on a Varian A-60 or DP-60 spectrometer with tetramethylsilane=0 as reference. The spectra taken on the DP-60 instrument were calibrated by the audio side-band technique. Optical Rotatory Dispersion (ORD) curves were recorded on a Durram-Jasco ORD/UV-5 Spectropolarimeter using methanol as solvent. Camag DF-5 silica gel with calcium sulphate binder was used for thin-layer chromatography (t.l.c.). Merck Silica Gel GF254 containing 13% calcium sulfate was used for thick-layer chromatography. Sulfuric acid (30%) was used for charring.

Solutions in organic solvents were dried by washing them with saturated sodium chloride solution and then allowing them to stand with anhydrous magnesium sulfate or sodium sulfate. Removal of organic solvent was effected using a rotary evaporator under reduced

pressure of the water pump on a hot water bath (90°). Petroleum ether refers to the fraction boiling at 60-80° unless otherwise stated. Microanalyses were carried out in the laboratories of Dr. A. Bernhardt, Mülheim, Germany and A. B. Gygli, Toronto, Canada. Caryophyllene used in this work was isolated by fractional distillation from clove oil terpene fraction obtained from Fritzsche Brothers, Inc., New York and had b.p. 120-125° at 10-11 m.m., $[\alpha]_D^{20}$ -9.00 to -9.50° (neat).

Caryophyllene Oxide 2

The procedure of Ramage & Whitehead was followed.[101] A solution of 30.5 g (0.15 mole) of caryophyllene 1 in 100 ml of anhydrous ether was oxidised with a solution of monoperphthalic acid and in ether to give 29.5 g (90%) of a colourless viscous oil which solidified to a white mass on cooling. The crude oxide was recrystallized from methanol four times to yield 10.6 g (32%) of colourless long needles, m.p. 63-64°, $[\alpha]_D^{20}$ -79° (c, 2.32) [lit (85): m.p. 63-64°, $[\alpha]_D^{20}$ -68°].

Infrared spectrum: $\nu_{max}^{CS_2}$ 3077 cm^{-1}, 1634 cm^{-1} ($C=CH_2$).

N.M.R. spectrum: 1.01 p.p.m. (6H,s,gem-diMe), 1.21 p.p.m. (3H,s,CH_3-C-O), 4.96 p.p.m. (2H,q,$C=CH_2$).

Permanganate Oxidation of Caryophyllene Oxide 2

The procedure of Treibs[85] was followed. To a vigorously stirred solution of 12.3 g (56 mmoles) of caryophyllene oxide 2 and 3.5 ml of water in 130 ml of acetone was added, in portions and with cooling, 26 g of powdered potassium permanganate over a period of 24 h. The reaction mixture was filtered through a sintered glass funnel, and the colorless filtrate was evaporated to leave 8.5 g of oily product.

Thin layer chromatographic examination of the crude product revealed a spot corresponding to the ketoepoxide 4, a spot corresponding to both the 119° glycol 5a and the 142° glycol 6 and a spot at the origin. The crude product was chromatographed on 240 g of Woelm neutral alumina (activity IV). Elution with petroleum ether gave 5.96 g (48%) of the ketoepoxide 4, m.p. 62-63°, $[\alpha]_D^{22}$ -148° (c, 1.95), R_f 0.85 [lit (115): m.p. 62-63°, $[\alpha]_D$ -134° (chloroform)]. Elution with benzene-chloroform (50:50) gave 0.64 g (4.5%) of the mixture of glycols. Recrystallization from benzene-petroleum ether gave a first crop of 220 mg of 6, which after further recrystallization from the same solvent pair had m.p. 138-139°, and R_f 0.38 [lit (85): m.p. 141°, $[\alpha]_D$ -72° (alcohol)]. From the mother liquors of the first recrystallization above was obtained a second crop consisting of 118 mg of 5a, which after further recrystallization from benzene - petroleum ether, had m.p. 118-119°, $[\alpha]_D^{20}$ -7.2° (c, 1.91), $[\alpha]_D^{21}$ -5.3° (c, 2.21), $[\alpha]_D^{22}$ -10.4° (c, 2.12 in 95% ethanol) R_f 0.40 [lit (60): m.p. 119° $[\alpha]_D$ -1.00° (alcohol)].

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3448 cm^{-1} (OH).

N.m.r. spectrum: 1.02 (6H,s,gem-diMe), 1.20 (3H,s,$\underline{CH_3}$-C-O), 2.89 (2H, bm,O$\underline{H}$), 3.20 (2H, sord,$\underline{CH_2}$-O-), 3.55 (1H,m,$\underline{H}$-C-O).

Continued elution of the chromatographic column with methanol-acetic acid gave 0.38 g of an oil. Trituration of this oil with chloroform gave 58 mg of white crystals m.p. 181-182° whose t.l.c. behaviour corresponded to that of the spot remaining at the origin in the crude oxidation product.

Periodate Oxidation of 119° Glycol 5a

A solution of 100 mg (0.39 mmole) of the 119° glycol 5a in 5 ml of methanol was treated at room temperature with 160 mg (0.75 mmole) of sodium metaperiodate in 2 ml of water. After 8h, the clear solution was diluted with water and extracted with ether. Evaporation of the dried ether extract left 87 mg of recovered 5a, m.p. 117-118.5°, undepressed on admixture with starting material. The infrared spectrum of the product was identical with that of the 119° glycol and had no trace of carbonyl absorption.

Osmium Tetroxide Oxidation of Caryophyllene Oxide 2

To a solution of 773 mg (3.04 mmoles) of osmium tetroxide, in 1 ml of pyridine and 4 ml of ether was added 660 mg (3.00 mmoles) of pure caryophyllene oxide 2. The reaction mixture became warm and turned brown. Several days later, when brown crystals had appeared, the reaction mixture was diluted with ether and saturated with hydrogen sulfide. The black precipitate of osmium sulfide which precipitated was removed by filtration through Celite. The yellow filtrate was diluted further with ether, washed with dilute sulfuric acid and dilute potassium bicarbonate solutions and dried. Evaporation of the solvent left 500 mg of white solid. Two recrystallizations from chloroform-petroleum ether gave 316 mg (41%) of colorless prisms of glycol 5a, m.p. 116-117.5°, undepressed on admixture with a sample, m.p. 117-118.5°, from the permanganate oxidation of 2.

A second crop of 117 mg of crystals which was obtained from the mother liquors melted over a much wider range, 80-117°, although it gave a single spot corresponding to 5a on t.l.c. comparison. These

facts together with the optical rotation $[\alpha]_D^{21}$ -8.05° (c, 2.15), and the n.m.r. spectrum of this material shows it to be almost pure 119° glycol 5a containing no noticeable amount of 142° glycol 6. It is estimated that 3-5% of 6 could easily have been detected in the n.m.r. spectrum.

The n.m.r. spectrum of the mother liquors from the second crop of crystals showed that they were also mainly 119° glycol 5a containing no detectable amount of 142° glycol 6.

Oxidation of Caryophyllene Oxide 2 with the Milas Reagent

The hydrogen peroxide-t-butyl alcohol reagent was prepared as described in the literature[89] and was assumed to contain 6.32% of peroxide. To 30 ml of the reagent was added a solution of 60 mg of osmium tetroxide in 2 ml of t-butyl alcohol, and the mixture was cooled to 0° in an ice-salt bath. Then 3.130 g (14.2 mmoles) of caryophyllene oxide 2 was added in small portions during 5 minutes. The reaction mixture turned reddish brown and finally became a clear light-yellow after 30 minutes. It was then stored in a refrigerator at 4° for 96 h, whereupon it was diluted with ether. The organic solution was washed with 40 ml of 10% aqueous ferrous sulfate solution to destroy excess peroxide, then with water and finally dried. Removal of the solvent left 3.13 g of crude product. Thin-layer chromatography in pure ethyl acetate gave two main spots, one corresponding to authentic keto oxide 4 and the other corresponding to the 119° and 142° glycol mixture. The crude product was chromatographed on 90 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Petroleum ether eluted 1.87 g (59%) of keto epoxide 4 (single t.l.c.

spot) which on recrystallization from petroleum ether gave long colorless prisms, m.p. 62-63°.

Infrared spectrum: $\nu_{max}^{CS_2}$ 1695 cm^{-1} (9-membered C=O),

N.m.r. spectrum: 1.03 (6H,s,gem-diMe), 1.29 (3H,s,$\underline{CH_3}$-C-O).

Further elution with benzene-chloroform (50:50) gave 990 mg of glycol fraction. Three recrystallizations from chloroform-petroleum ether gave 600 mg (16%) of glycol 5a, m.p. 117-117.5°, $[\alpha]_D^{20}$ -9.5° (c, 2.39), $[\alpha]_D^{22}$ -2.27° (c, 2.29 in 95% ethanol). The n.m.r. spectrum of the residue from the recrystallization mother liquors did not reveal any peaks from the 142° glycol 6.

119° Glycol Diacetate 5b

A solution of 100 mg (0.39 mmole) of 5a in 2 ml of pyridine and 1 ml of acetic anhydride was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with dilute sulfuric acid and aqueous sodium bicarbonate and dried. Evaporation of ether left 131 mg (98%) of colorless glass, 5b, $[\alpha]_D^{22}$ + 8.8° (c, 2.09).

Infrared spectrum: $\nu_{max}^{CS_2}$ 1740 cm^{-1} (ester C=O),

N.m.r. spectrum: 1.03 (6H,s,gem-diMe), 1.09 (3H,s,$\underline{CH_3}$-C-O), 2.05 (6H, s,$\underline{CH_3}$-C=O), 3.85 (2H,s,$\underline{CH_2}$-O-), 4.96 (1H,dd,$\underline{H}$-C-O).

A sample was evaporatively distilled at 75-80° and 0.01 mm for analysis.

Anal. Calcd. for $C_{19}H_{30}O_5$ (338.41): C, 67.43; H, 8.92.

Found: C, 67.37; H, 8.96.

Chromic acid - Pyridine Oxidation of 119° Glycol 5a

Chromium trioxide (3.2 g, 32 mmoles) was added to 35 ml of pyridine. To this slurry of the orange complex was added at room temperature a solution of 4.25 g (16.7 mmoles) of the 119° glycol 5a in 45 ml of pyridine. The color changed immediately to dark brown. After 24 h the reaction mixture was diluted with methylene chloride and filtered through a short column of Woelm neutral alumina (activity IV) to remove chromium salts. The eluate was evaporated under reduced pressure to leave 3.85 g of dark brown oil. Thin-layer chromatography in ethyl acetate - petroleum ether (85:15) gave two intense spots and two very faint spots after charring. The crude product was chromatographed on a column of 160 g of silica gel (British Drug House) packed in chloroform. Elution with ether-chloroform (3:97) gave 175 mg (4%) of colorless crystalline keto aldehyde 8 which was not quite free of 9. Four recrystallisations from petroleum ether gave colorless crystals, m.p. 84-86°, $[\alpha]_D^{19}$ +65° (c, 1.05), R_f 0.90.

Infrared spectrum: $\nu_{max}^{CS_2}$ 2700 cm^{-1} (-CHO) and 1724 cm^{-1} (broad, -CH=O and 6-membered C=O).

N.m.r. spectrum: 1.01 (6H, s, gem-diMe), 1.32 (3H, s, CH_3-C-O), 9.52(1H, s, H-C=O).

Anal. Calcd. for $C_{15}H_{22}O_3$ (250.32) : C, 72.00; H, 8.85.

Found: C, 72.30; H, 8.58.

Further elution of the column with the same solvent gave 2.70 g (67%) of colorless viscous liquid hydroxyketone 9, $[\alpha]_D^{19}$ +76° (c, 2.96), R_f 0.80.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3484 cm^{-1} (-OH) and 1724 cm^{-1} (6-membered C=O).

N.m.r. spectrum: 1.00 (6H,s,gem-diMe), 1.28 (3H,s,$\underline{CH_3}$-C-O), 3.40 (2H, s,$\underline{CH_2}$-O-).

A sample was evaporatively distilled at 55-65° and 0.05 mm for analysis.

Anal. Calcd. for $C_{15}H_{24}O_3$ (252.34): C, 71.39; H, 9.59.

Found: C, 71.11; H, 9.36.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethyl acetate - petroleum ether at -60° to give small yellow crystals, m.p. 80-82°.

Infrared spectrum: $\nu_{max}^{CH_2Cl_2}$ 3633 cm^{-1} (N-H), 3344 cm^{-1} (OH), 1625 cm^{-1} (aromatic C=C).

N.m.r. spectrum: 0.96 (3H,s,gem-$\underline{CH_3}$), 1.02 (3H,s,gem-$\underline{CH_3}$), 1.42 (3H,s, $\underline{CH_3}$-C-O), 3.37 (2H,s,$\underline{CH_2}$-O-), 8.78 (1H,bs,$\underline{H}$-N-).

Anal. Calcd. for $C_{21}H_{28}O_6N_4$ (432.47): C, 58.31; H, 6.52.

Found: C, 57.73; H, 6.46.

Oxidation of 5a with chromium trioxide in acetic acid was more complex and gave acidic as well as neutral products; therefore it was not investigated further.

Attempted Reductive Cleavage of Hydroxyketone

The following reactions were carried out with the purpose of cleaving reductively the α-alkoxy group of the hydroxyketone 9:

a) A mixture of 225 mg of 9, 5.5 ml of acetic anhydride and 5.25 g of zinc dust was refluxed for 6h;

b) A mixture of 160 mg of 9, 15 ml of acetic anhydride and 4 g of zinc dust was refluxed for 48 h;

c) A mixture of 180 mg of 9, 15 ml of propionic anhydride and 4 g of

zinc dust was refluxed for 35 h;

d) A mixture of 185 mg of 9, 1.5 ml of glacial acetic acid, 25 ml of acetic anhydride and 1 g of magnesium was refluxed for 18 h;

e) A solution of 210 mg of 9 in 10 ml of toluene was added to 200 mg of calcium in 30 ml of liquid ammonia; and

f) A solution of 125 mg of 9 in 25 ml of sec-butylamine was stirred with 150 mg of potassium at room temp for 17 h.

Infrared spectra and t.l.c. examination indicated that except for reaction (f), the product of each reaction was starting material 7 or starting material with the primary alcohol acetylated or else the epimeric glycols of structure 5a. In the case of reaction (f) a mixture of both neutral and acidic material was obtained; however, further investigation was not done.

Wolff-Kishner Reduction of Hydroxyketone 9

To a solution of 885 mg (3.50 mmoles) of hydroxyketone 9 in 30 ml of triethylene glycol were added 10 ml of hydrazine hydrate (85%) and 4.5 g of potassium hydroxide pellets. The mixture was refluxed in an oil bath at 130-135° for 3-7 h after which the excess hydrazine hydrate was distilled out. The temperature of the oil bath was then raised to 230° and maintained at that temperature for 3 h. The cooled reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water and dried. Evaporation of the solvent left 818 mg of crude product. Thin layer chromatography in ethyl acetate - petroleum ether (50:50) revealed two intense spots and one faint low R_f spot. The crude product was chromatographed on 25 g of Woelm neutral alumina (activity IV) packed in petroleum ether.

Elution with petroleum ether gave 400 mg (48%) of the normal reduction product 10a as a colorless liquid, $[\alpha]_D^{26}$ -19° (c, 2.00), R_f 0.85.

Infrared spectrum: $\nu_{max}^{CCl_4}$ 3559 cm^{-1} (OH).

N.m.r. spectrum: 1.02 (6H,s,gem-diMe), 1.14 (3H,s,CH_3-C-O), 3.22 (2H, s,CH_2-O-), 2.43 (1H,s,OH).

A sample was evaporatively distilled at 50-60° and 0.01 mm for analysis.

Anal. Calcd. for $C_{15}H_{26}O_2$ (238.37): C, 75.58; H, 11.00.

Found: C, 75.16; H, 10.96.

Further elution of the column with benzene - petroleum ether (75:25) gave 300 mg (36%) of solid reductive elimination product 11. Five recrystallizations from petroleum ether gave small colorless needles, m.p. 91-92°, $[\alpha]_D^{24}$ -0.47°(c, 1.75), R_f 0.65. Material of m.p. 92-93° could also be obtained by two sublimations of the crude product.

Infrared spectrum: $\nu_{max}^{CCl_4}$ 3390 cm^{-1} (OH) and 850 cm^{-1} (C=CH).

N.m.r. spectrum: 0.96 (6H,s,gem-diMe), 1.66 (3H,d,J 1,CH_3-C=C-H), 2.58 (2H,bs,OH), 3.60 (2H,d,J 1,CH_2-O-), 5.35 (1H, bm,H-C=C-).

Anal. Calcd. for $C_{15}H_{26}O_2$ (238.37): C, 75.58; H, 11.00.

Found: C, 76.02; H, 10.79.

Acetylation of Normal Reduction Product 10a

A solution of 250 mg (1.05 mmoles) of 10a in 2 ml of pyridine and 1.5 ml of acetic anhydride was refluxed for 1 h, cooled and diluted with water. The product was removed by extraction with ether. The ether extracts were washed with dilute sulfuric acid and water. The dried ethereal solution was evaporated at reduced pressure to leave 280 mg (95%) of colorless liquid 10b, $[\alpha]_D^{20}$ -12.4° (c, 1.90), R_f 0.90.

Infrared spectrum: $\nu_{max}^{CCl_4}$ 1751 cm^{-1} (ester C=O).

N.m.r. spectrum: 1.02 (6H,s,gem-diMe), 1.14 (3H,s,$\underline{CH_3}$-C-O), 2.04 (3H,s,$\underline{CH_3}$ C=O), 3.82 (2H,s,$\underline{CH_2}$-O-).

A sample was evaporatively distilled at 60-65° and 0.05 mm for analysis.

Anal. Calcd. for $C_{17}H_{28}O_3$ (280.39): C, 72.82; H, 10.06.

Found: C, 72.32; H, 9.84.

Periodate Cleavage of Reductive Elimination Product 11

To a solution of 250 mg (1.05 mmoles) of the 1,2-diol 11 in 7 ml of methanol was added a solution of 500 mg (2.33 mmoles) of sodium metaperiodate in 5 ml of water. An exothermic reaction occurred, and a voluminous white suspension appeared almost immediately. The reaction mixture was left at room temperature for 9 h, after which it was diluted with water and extracted with ether. The water-washed and dried ethereal solution was evaporated at reduced pressure to yield 200 mg (92%) of a colorless liquid, which was chromatographed on 6 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with the same solvent gave 151 mg of colorless liquid 12, $[\alpha]_D^{22}$ -77° (c, 2.26), R_f 0.90. During sulfuric acid charring of 12, a characteristic mauve color appeared before carbonization.

Ultraviolet spectrum: λ_{max}^{EtOH} 2.35 mμ (ε 440).

Infrared spectrum: $\nu_{max}^{CCl_4}$ 1695 cm^{-1} (9-membered C=O) and 837 cm^{-1} (C=CH).

N.m.r. spectrum: 1.00 (3H,s,gem-$\underline{CH_3}$), 1.05 (3H,s,gem-$\underline{CH_3}$), 1.67 (3H, d,J=0.5 c.p.s., $\underline{CH_3}$-C=C-H), 5.27 (1H,bm,$\underline{H}$-C=C).

A sample was evaporatively distilled at 65-70° and 0.5 mm for analysis.

Anal. Calcd. for $C_{14}H_{22}O$ (206.32): C, 81.50; H, 10.75.

Found: C, 81.37; H, 10.69.

Epoxidation of Unsaturated Ketone 12

To a solution of 103 mg (0.50 mmole) of 12 in 5 ml of ether cooled to 0° was added 40 ml of a solution of monoperphthalic acid in ether (equivalent to 0.50 mmole of peracid). The reaction mixture was kept in the refrigerator for 60 h, after which it gave a negative starch-iodide test. Then the precipitated phthalic acid was removed by filtration. The filtrate was washed with sodium bicarbonate solution and with water. The dried ethereal solution was evaporated at reduced pressure to leave 95 mg of a mixture of the cis-keto oxides 13a and 13b which solidified when chilled. Two recrystallizations from petroleum ether gave 42 mg of colorless prisms of 13b, m.p. 75-76°, $[\alpha]_D^{15}$ -13.8° (c, 1.78 in methanol), R_f 0.80.

Infrared spectrum: $\nu_{max}^{CCl_4}$ 1695 cm^{-1} (9-membered C=O).

N.m.r. spectrum: 1.01 (3H,s,gem-CH_3), 1.10 (3H,s,gem-CH_3), 1.25 (3H, s,CH_3-C-O).

The mixed melting point with the authentic sample of isocaryophyllene keto epoxide-b 13b, m.p. 77.5-78°, prepared as described below was undepressed. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.32): C, 75.63; H, 9.97.

Found: C, 75.17; H,10.01.

Isocaryophyllene (cis-caryophyllene) 15

The procedure of Schreiner and Kremers[102] was followed in part. A solution of 22 g of combined caryophyllene fractions $[\alpha]_D^{20}$ -9 to -9.5°

(neat) in 60 ml of petroleum ether (b.p. 35-60°) was stirred at room temperature with 25 ml of a saturated aqueous solution of sodium nitrite. To this suspension was added slowly 25 ml of glacial acetic acid. The reaction mixture became blue and then light green. After 25 minutes the solution was chilled and kept below 0° overnight. The reaction mixture was allowed to come to room temperature and was filtered to remove some crystalline material. The filtrate was diluted with water and extracted with ether. The dark-green ethereal solution was washed with several portions of 10%, aqueous potassium hydroxide and with water. The ether was removed from the dried solution to leave 19 g of green oil. This residue was steam distilled until the oily droplets in the distillate began to be denser than water. Extraction of the steam-distillate with ether yielded 9.89 g of yellow oil after removal of the ether. Fractional distillation through a 1-m Nester and Faust Spinning Spiral Column gave four fractions totalling 4.8 g (22%) of colorless isocaryophyllene, b.p. 116° at 8.5 mm, $[\alpha]_D^{25.5}$ -22.2° (neat) [lit. (125): b.p. 125.5° at 14.5 $[\alpha]_D^{19}$ -26.1° (neat)].

Infrared spectrum: ν_{max}^{neat} 3060 cm^{-1} (vinyl H), 1635 cm^{-1} (C=C), 885 cm^{-1} ($C=CH_2$) and 836 cm^{-1} (C=CH).

N.m.r. spectrum: 0.97, 1.00 (6H,2s,gem-diMe), 1.66 (3H,d,J 0.5 c.p.s., CH_3-C=C-H), 4.83 (2H,m,CH_2=C), 5.28 (1H,bm,H-C=C).

Repetition of the isomerisation process on this material did not change the optical rotation. The isocaryophyllene was 96.5%.pure by vapour phase chromatography, and the 3.5% of impurity was not caryophyllene or α- or β-humulene. On a 2m x ¼ inch column of Chromosorb P (coated

with silver nitrate - Carbowax 20M, 10% of each) at 162°, the compounds had the following retention times: impurity 5.5 min.; isocaryophyllene, 8.0 min.; and caryophyllene, 8.8 min.

Authentic Isocaryophyllene Keto Epoxide-b, 13b

The procedure of Ramage and Whitehead[101] was followed. A solution of 4.03 g (19.7 mmoles) of isocaryophyllene in 25 ml of ether was cooled to 0° and treated with 65 ml (20 mmoles) of an ethereal solution of monoperphthalic acid. The reaction mixture was kept at 4° for 48 h, after which it was filtered to remove precipitated phthalic acid. The filtrate was washed successively with aqueous sodium bicarbonate and water before it was dried. Evaporation of the ether left 3.72 g of an oil which partially crystallized. Trituration of the crude product with cold petroleum ether and filtration left 1.10 g of crystalline material which was recrystallized once from petroleum ether to yield colorless crystals of isocaryophyllene oxide-a 14a, m.p. 73-75°, $[\alpha]_D^{20}$ -7.3° (c, 3.30 in methanol), R_f 0.90, [lit. (101); m.p. 77° $[\alpha]_D$ -5° (c, 1.94 in methanol)].

N.m.r. spectrum: 1.00 (6H,s,gem-diMe), 1.27 (3H,s,CH_3-C-O).

The oily mother liquor, after separation of the crystalline isocaryophyllene oxide-a, contained mainly isocaryophyllene oxide-b, 14b, and it was oxidized directly. To a solution of 1.31 g of the material and 1 ml of water in 25 ml of acetone was added 4.0 g of powdered potassium permanganate. The reaction was worked up as described for the oxidation of caryophyllene oxide on page 146. The crude oily product (1.05 g) was chromatographed on 35 g of Woelm neutral alumina (activity IV) and yielded 80 mg* of isocaryophyllene keto epoxide-b, 13b, which

*The low yield is due to loss during manipulation.

had m.p. 77.5-78° and $[\alpha]_D^{20}$ -13.1° (c, 1.91 in methanol), [lit. (101): m.p. 78-79°, $[\alpha]_D^{15°}$ -13° (c, 1.978 in methanol)], after two recrystallizations from petroleum ether.

Infrared spectrum: $\nu_{max}^{CCl_4}$ 1695 cm^{-1} (9-membered C=O).

N.m.r. spectrum: 1.01 (3H,s,gem-CH_3), 1.10 (3H,s,gem-CH_3), 1.25 (3H,s,CH_3-C-O).

Isomerisation of 142° glycol 6

Basic Catalysis

A solution of 80 mg of 6, m.p. 138-139°, and 250 mg of potassium hydroxide in 5 ml of methanol was refluxed for 168 h. Dilution with water and extraction with ether yielded 65 mg of a white solid, m.p. 114-117°, whose n.m.r. spectrum and t.l.c. behaviour were identical with those of the 119° glycol 5a. Recrystallization from chloroform - petroleum ether raised the melting point to 116-117°, undepressed on admixture with authentic 119° glycol 5a.

When the isomerisation was allowed to proceed only 19 h, the reaction was incomplete and the product was a mixture of 5a and 6 (n.m.r. spectrum).

Acid Catalysis

A solution of 14 mg of 6, m.p. 138-139°, and 2 ml of 5% aqueous sulfuric acid in 3 ml of acetone was refluxed for 2 h. Dilution with water and extraction with ether yielded 12 mg of colorless solid, m.p. 110-113°. Thin-layer chromatographic examination revealed only traces of two less-polar impurities besides the main 5a-6 spot. Recrystallization from petroleum ether raised the melting point to 117-118°,

undepressed on admixture with authentic 119° glycol 5a. Thin-layer chromatographic examination of the recrystallized product gave a single spot corresponding to 5a-6. The melting point of a control mixture of 5a and 6 was depressed.

Neutral

A solution of 2 mg of 6 m.p. 138-139°, in 2 ml of methanol was refluxed for 160 h and solvent was removed at the end to give a white solid, m.p. 137-139°, undepressed on admixture with the starting material 6. Thin layer chromatographic examination of the crude solid revealed a spot corresponding to 5a-6 with no trace of any other product.

Epoxidation of Caryophyllene Monoxide 2

a) Monoperphthalic acid in Ether

To a solution of 3.50 g (15.9 mmoles) of pure caryophyllene monoxide 2 (m.p. 62.5-63°) in 4 ml of anhydrous ether was added 25 ml of a solution of monoperphthalic acid in ether (equivalent to 19.3 mmoles) and the reaction mixture was allowed to stand in the refrigerator for 90 h (the reaction was not complete at the end of 70 h as the n.m.r. spectrum revealed starting material in the reaction mixture). The reaction mixture was filtered to remove precipitated phthalic acid. The colorless filtrate after washing with aqueous sodium bicarbonate solution and water was evaporated to leave 3.54 g (94%) of colorless viscous oil. The crude product was shown by n.m.r. analysis to be a mixture of two bisepoxides 26 and 27 in the ratio of 60:40 with traces of caryophyllene monoxide 2. Four recrystallisations from petroleum

ether at -70° gave 926 mg of a colorless crystalline solid, m.p. 58-73°. Two further recrystallisations from the same solvent at -15° gave 714 mg (19%) of 26 as a colorless crystalline solid, m.p. 76-77°, $[\alpha]_D^{20}$ -69° (c, 1.71).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3050 cm^{-1} and 3030 cm^{-1} (epoxide CH and CH_2).

N.m.r. spectrum: 0.92 (3H,s,gem-CH_3), 0.95 (3H,s,gem-CH_3), 1.18 (3H, s,CH_3-C-O), 2.47 (2H,q,CH_2-O-), 2.88 (1H,dd,H-C-O).

Attempts to isolate 27 in the pure state were frustrating and therefore it was decided to work with a mixture of 26 and 27 for further experiments.

b) Perbenzoic acid in Benzene

The monoxide 2 used in this experiment is a single compound as shown by n.m.r., with no trace of the other "trans oxide" 3. To a solution of 220 mg (1.0 mmole) of caryophyllene monoxide 2 in 5 ml of benzene (BDH reagent) was added 7 ml of a solution of perbenzoic acid in benzene (equivalent to 10 mmoles) and the reaction mixture was left at room temperature for 7 days. The solution was diluted with water and extracted with ether. The ethereal extracts were washed with water, 10% sodium bicarbonate solution, water and dried. Evaporation of solvent left 235 mg (100%) of an oil. The n.m.r. spectrum of the crude mixture showed it to be a mixture of 26 and 27 in the ratio 80:20. Thin-layer chromatography in pure ethyl acetate showed only one spot with no trace of any polar material.

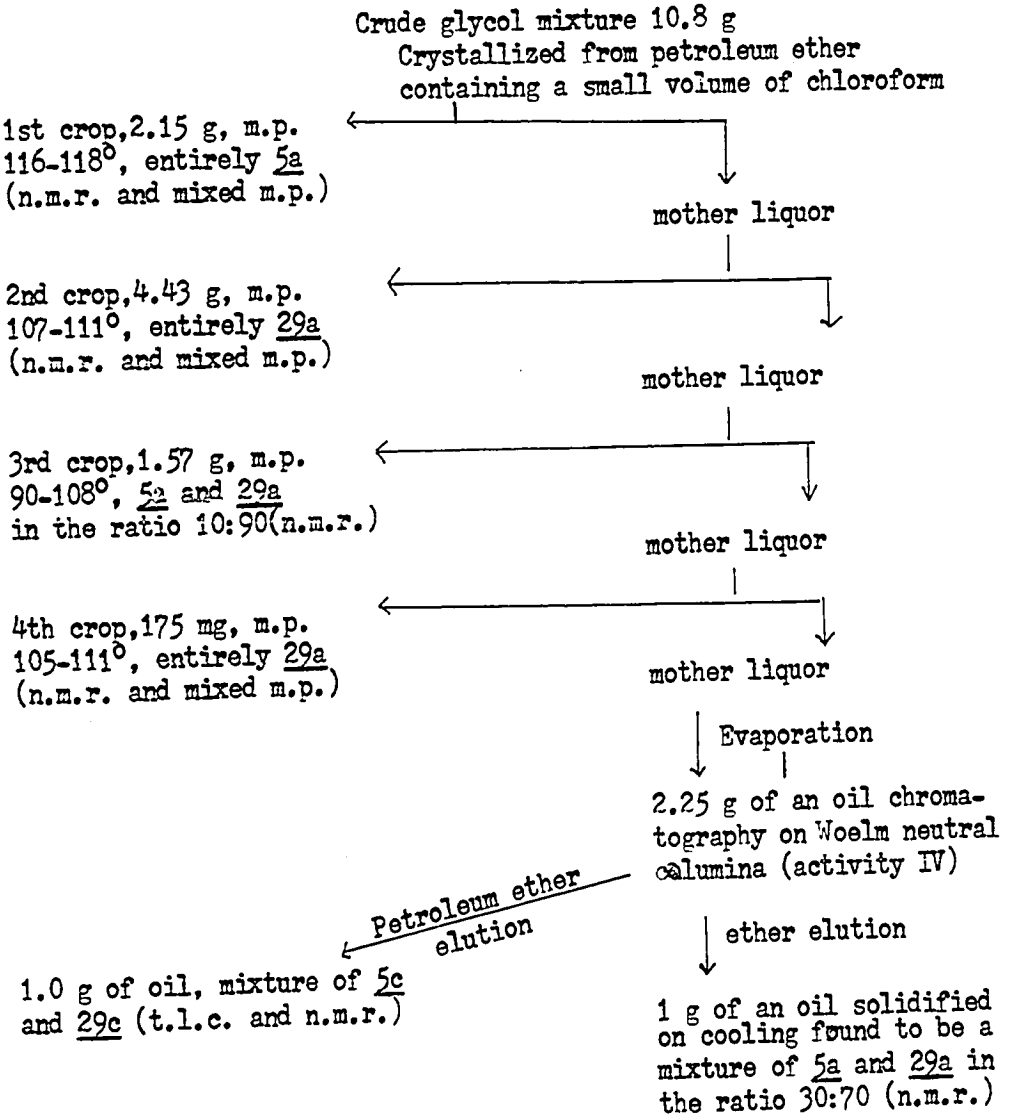
Base Catalysed Isomerisation of Caryophyllene Bisepoxide Mixture 26 and 27 - Longer Period

A solution of 12 g (54.5 mmoles) of pure caryophyblene monoxide 2 (m.p. 62.5-63°) in 100 ml of anhydrous ether was epoxidised with 250 ml of an ethereal solution of monoperphthalic acid (equivalent to 100 mmoles) at 0°. After keeping the reaction mixture for 8 days in the refrigerator it was worked up as described in the previous experiment to yield 12.2 g (95.5%) of a viscous oil which solidified to a colorless solid. The crude product was shown by n.m.r. to be a mixture of 26 and 27 in the ratio of 60:40 and did not have any peak corresponding to the starting material. Thin-layer chromatography in ethyl acetate - petroleum ether (50:50) showed only one spot that was different from the starting monoxide.

A solution of 12 g (50.6 mmoles) of crude bisepoxide mixture obtained above in 130 ml of benzyl alcohol containing 14 g of potassium hydroxide pellets was heated on a steam bath for 96 h. The light yellow reaction mixture was steam distilled to remove benzyl alcohol. The residue in the flask was cooled, diluted with water and extracted with ether. The ethereal extracts were washed with water, dried, and evaporated to leave 15.6 g (89%) of a mixture of benzyl ethers 5c and 29c as a light yellow oil. Thin-layer chromatography in ethyl acetate - petroleum ether (50:50) showed two major intense spots different from the starting material and two less intense more polar spots (about 5%).

The crude benzyl ether mixture 15.6 g was dissolved in 100 ml of 95% ethanol containing 9 g of palladised charcoal (5% Pd, Engelhard)

and hydroganolysed at room temperature in a Parr hydrogenator for 22 h till the absorption of hydrogen ceased. The mixture was then filtered to remove the catalyst, and the solvent was evaporated to leave 11.25 g (99%) of a liquid mixture of glycols which solidified on cooling. Thin-layer chromatography of the crude mixture in ethyl acetate - petroleum ether (50:50) showed only one major intense spot, R_f 0.20, different from the starting material and a faint less polar spot, R_f 0.4 (about 1%). The crude mixture was shown by n.m.r. to consist of 5a and 29a in the ratio of 40:60.



A portion (370 mg) of the second crop of crystals was recrystallized six times from ether to give 210 mg of small colorless crystals 29a, m.p. 115-116°, $[\alpha]_D^{18}$ -49° (c, 3.17).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3480 cm^{-1} (bonded OH), 3580cm^{-1} (free OH).

N.m.r. spectrum: 0.97 (6H,s,gem-diMe), 1.00 (3H,s,CH_3-C-O), 2.95 (1H, s,OH), 3.53 (2H,q,CH_2-O-), 4.05 (1H,m,H-C-O).

Anal. Calcd.for $C_{15}H_{26}O_3$ (254.4): C, 70.83; H, 10.30.

Found: C, 70.85; H, 10.06.

A solution of 100 mg (0.39 mmole) of the crude glycol mixture in 3 ml of methanol was treated with an aqueous solution of sodium metaperiodate (100 mg, 0.47 mmole) in 2 ml of water at room temperature. After 9½ h, the clear solution was diluted with water and extracted with ether. The dried ethereal solution on evaporation left 96 mg of an oil which solidified on cooling. Thin-layer chromatography of the crude product in ethyl acetate - petroleum ether (50:50) showed only one spot, R_f 0.2, corresponding to starting material and no trace of less polar spot was noticed. The infrared spectrum did not reveal any carbonyl absorption.

116° Glycol Monoacetate 29b

A solution of 1 g (3.9 mmoles) of 29a in 10 ml of pyridine and 10 ml of acetic anhydride was allowed to stand at room temperature for 24 h. The reaction mixture was worked up as described on page 150to give 1.1 g (87%) of an oil which crystallized on trituration with petroleum ether (30-60°) at 0°. Thin-layer chromatography in ethyl acetate showed the crude product to consist of about 90% of the monoacetate of the 116° glycol 29b and about 10% of a less polar material (diacetate?).

Three recrystallizations from petroleum ether gave 800 mg (69%) of 29b as colorless small needles, m.p. 92-92.5°, $[\alpha]_D^{18}$ -44° (c, 2.11).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3600 cm^{-1} (free OH), 3490 cm^{-1} (bonded OH), 1748 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.905 and 0.906 (6H,2s,gem-diMe), 1.01 (3H,s,$\underline{CH_3}$-C-O), 2.08 (3H,s,$\underline{CH_3}$-C=O), 2.53 (1H,bs,OH), 4.00 (1H, m,$\underline{H}$-C-O), 4.10 (2H,s,$\underline{CH_2}$-O-).

Anal. Calcd. for $C_{17}H_{28}O_4$ (296.4): C, 68.89; H, 9.52.

Found: C, 69.30; H, 9.52.

Attempted Oxidation of 116° Glycol Monoacetate 29b

A solution of 74 mg (0.25 mmole) of 29b in 0.5 ml of pyridine was added to an orange complex of 30 mg (0.30 mmole) of chromium trioxide in 1 ml of pyridine and left at room temperature for 14 hours. The reaction mixture was worked up as described in page 151 to give 72 mg of recovered 29b (t.l.c., n.m.r. and infrared spectrum).

Chromic Acid - Pyridine Oxidation of 116° Glycol 29a

A solution of 300 mg (1.18 mmoles) of pure 29a in 2 ml of pyridine was added to the orange complex from 300 mg (3.00 mmoles) of chromium trioxide in 2 ml of pyridine and allowed to stand at room temperature for 24 hours. The reaction was worked up as described in page 151 to give 280 mg of an oil whose t.l.c. behaviour showed two intense spots of equal intensity, one corresponding to starting material and the other to a less polar spot. The crude product was separated on a thick-plate (20 g silica gel per 20x20 cm plate) in ethyl acetate to give 95 mg of oily hydroxy aldehyde 31, which gave a single t.l.c. spot.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3600 cm^{-1} (free OH), 3510 cm^{-1} (bonded OH), 2810 cm^{-1}, 2710 cm^{-1} (-CH=O), 1745 cm^{-1} (-CH=O).

N.m.r. spectrum: 0.95 (3H,s,gem-$\underline{CH_3}$), 0.975 (3H,s,gem-$\underline{CH_3}$), 1.06 (3H, s,$\underline{CH_3}$-C-O), 2.64 (1H,bs,OH), 4.20 (1H,m,$\underline{H}$-C-O), 9.66 (1H,s,$\underline{H}$C=O).

Mass spectrum: $\underset{e}{m}$ 224 (n-co)

Dehydration of Monoacetate of 116 Glycol 29b

The procedure of Hazen and Rosenburg[100] was used. To a vigorously stirred (magnetic bar) solution of 355 mg (1.2 mmoles) of pure monoacetate of 116° glycol 29b in 4 ml of freshly distilled γ-collidine and 5 ml of freshly distilled (from molecular sieves type 4A) N,N-dimethylformamide cooled to 0° was added in small portions during a one minute period, 2.03 g (19.6 mmoles) of methanesulfonyl chloride (freshly distilled at atmospheric pressure) containing 105 mg of anhydrous sulfur dioxide. The colorless solution immediately became brown and a brown precipitation appeared. After 15 minutes of stirring, the excess of methanesulfonyl chloride was carefully destroyed by adding water dropwise, and the wine red solution was extracted with three portions of ether. The combined ether extracts were washed with three portions of aqueous acetic acid (10%) and with water. The dried solution on evaporation left 334 mg (100%) of a pale yellow solid, whose thin-layer chromatogram in ethyl acetate - petroleum ether (65:35) revealed two major spots (R_f 0.80 and 0.60) and one faint spot (R_f 0.39) but no spot corresponding to starting material.

The crude yellow solid was recrystallized from petroleum ether to give a first crop of 120 mg (36%) of a buff-colored solid 33b, which

showed a single spot in t.l.c. (R_f 0.60). Four recrystallizations from petroleum ether gave pure 33b as colorless shining crystals, m.p. 138-139.5°, $[\alpha]_D^{18}$ +50° (c, 2.06).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3560 cm^{-1} (free OH), 3460 cm^{-1} (bonded OH), 1725 cm^{-1} (ester C=O), 1700 cm^{-1} (9-membered C=O).

N.m.r. spectrum: 0.91 (6H,2s,gem-diMe), 1.02 (3H,d,J=7 c.p.s., $\underline{CH_3}$-C-H), 2.09 (3H,s,CH_3-C=O), 2.37 (1H,s,OH), 3.90 (2H, d,J=3 c.p.s., $\underline{CH_2}$-O-).

Mass spectrum: $\frac{m}{e}$ 297

The mother liquor on evaporation of solvent left 200 mg of a liquid which was chromatographed on a thick plate (30 g silica gel per 20x 20 cm plate) in ethyl acetate - petroleum ether (65:35). The band that fluoresced under the u.v. lamp was cut and eluted with ether. Solvent evaporation gave 126 mg (38%) of a pale yellow liquid which showed a single spot in t.l.c., less polar than the starting material. The n.m.r. spectrum showed this to be a mixture of 32a and 32b in an approximate ratio of 85:15.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3060 cm^{-1} (=CH_2), 1735 cm^{-1} (ester C=O), 885 cm^{-1} (=CH_2).

N.m.r. spectrum: 0.91 (3H,s,gem-$\underline{CH_3}$), 1.00 (3H,s,gem-$\underline{CH_3}$), 1.58 (3H, s,$\underline{CH_3}$-C=CH), 2.09 (3H,s,CH_3-C=O), 4.17 (2H,s,$\underline{CH_2}$-O-), 4.83 (2H,m,J=8 c.p.s., $\underline{H_2}$C=C).

The following reagents were also tried for effecting the dehydration of 29b: (a) 59 mg of 29b, 40 mg of p-toluenesulfonyl chloride - pyridine and 2.5 ml of pyridine heated on a steam bath for 16 h[114] and (b) 445 mg of 29b, 10 ml of acetone, 450 mg of anhydrous calcium chloride and 225 mg of p-toluenesulfonic acid were refluxed for 2 h[115]. In the case

of (a), the infrared spectrum and t.l.c. examination indicated that the crude product was largely starting material with a very small amount (about 10%) of dehydrated compounds 32a and 32b. In the case of (b), t.l.c. examination indicated the crude product was a mixture of three compounds, the major spot corresponding to starting material. Recrystallization of the solid crude product from petroleum ether gave 40 mg of a colorless crystalline solid, m.p. 136-138°, undepressed on admixture with 33b obtained above.

Saponification of Hydroxy Acetate 33b

A solution of 25 mg (0.080 mmole) of hydroxy acetate 33b in 2.5 ml of methanol containing three potassium hydroxide pellets was refluxed on a steam bath for 5 h. The cooled reaction mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with water and evaporated to leave 20 mg (74%) of a mixture of 1,2-diol 33a and probably one of its possible hemiketals. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) revealed only two polar spots of close R_f values (0.20 and 0.25) and no spot corresponding to starting material (R_f 0.55). The infrared spectrum showed bands at 3460 cm^{-1} and 1695 cm^{-1} due to OH and 9-membered C=O respectively.

Periodate Cleavage of 1,2-Diol 33a

To a solution of 20 mg of the crude glycol mixture obtained in the previous experiment in 1.5 ml of methanol was added an aqueous solution of 25 mg of sodium metaperiodate in 1 ml of water. The reaction mixture was allowed to stand at room temperature for 11 h. and was worked up as

described in page 148 to give 14 mg (96%) of a liquid diketone 34. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one spot (magenta color, R_f 0.70) different from the starting material. The infrared spectrum showed an intense band at 1695 cm^{-1} due to 9-membered C=O and no hydroxyl absorption.

Base Catalysed Isomerisation of Caryophyllene Bisepoxide Mixture 26 and 27 - Shorter Reaction Period

A solution of 667 mg (2.83 mmoles) of caryophyllene bisepoxide mixture (26 and 27) in 5 ml of benzyl alcohol (BDH reagent) containing five sodium hydroxide pellets was heated on a steam bath for 20 h. The reaction mixture was worked up as described on page 162 to give 900 mg (90%) of crude benzyl ether 28c and 29c which was dissolved in 7 ml of 95% ethanol containing 400 mg of palladised charcoal (5% Pd-Engelhard) and hydrogenolysed in a Tower's Shaker for 42 h. The reaction mixture was filtered and the solvent evaporated to leave 657 mg (96%) of crude glycol mixture which was shown by t.l.c. in ethyl acetate - petroleum ether (50:50) to consist of three spots, two polar spots R_f 0.15 and 0.25 corresponding to glycols and one less polar spot R_f 0.90, near the solvent front corresponding to starting material. The crude mixture was chromatographed in ethyl acetate - petroleum ether (15:85) on two thick plates (20 g silica gel per 20x20 cm plate) to give 180 mg of recovered bisepoxide mixture 26 and 27, and 325 mg (62% based on starting material used up) of glycol fraction. The glycol fraction was dissolved in 2.5 ml of pyridine and 2 ml of acetic anhydride and allowed to stand at room temperature for 24 h. The reaction mixture was worked up as in page 150 to give 380 mg (100%) of acetylated glycols as a

solid. The crude product was shown by t.l.c. in ethyl acetate - petroleum ether (15:85) to be a mixture of two spots that differed in R_f from the starting glycols, the lower spot R_f 0.35 corresponding to the monoacetate of the 116° glycol, and the upper one R_f 0.50 was more polar than the diacetate of the 119° glycol 5b. The crude acetylated glycol mixture was recrystallized three times from ether to give 113 mg (30%) of long fine felted needles of 28b, m.p. 149-151°, $[\alpha]_D^{18}$ -100° (c, 1.26),

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3571 cm^{-1} (free OH), 3509 cm^{-1} (bonded OH), 1739 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.95 (6H,s,gem-diMe), 1.26 (3H,s,$\underline{CH_3}$-C-O), 2.10 (3H, s,$\underline{CH_3}$-C=O), 2.22 (1H,s,OH), 3.80 (2H,d,J=4 c.p.s., $\underline{CH_2}$-O-), 4.01 (1H,m,$\underline{H}$-C-O).

Anal. Calcd.for $C_{17}H_{28}O_4$ (296.4): C, 68.89; H, 9.52.

Found: C, 69.02; H, 9.84.

The mother liquor left from the first crystallizations of 28b was concentrated and cooled to collect a second crop of 150 mg of a solid which was shown by t.l.c. to be more than 90% pure 29b.

Saponification of the 151° Monoacetate 28b

A solution of 50 mg (0.17 mmole) of 28b in 7 ml of methanol containing 700 mg of potassium hydroxide pellets was refluxed on a steam bath for 1 h. The reaction mixture was cooled, diluted with water and extracted with ether. The combined ethered extracts were washed with water and evaporated after drying to leave 35 mg (81%) of colorless solid. Two recrystallizations from petroleum ether gave 19 mg (54%) of 28a as a colorless crystalline solid, m.p. 126-127°, $[\alpha]_D^{18}$ -121° (c,

1.46),

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3560 cm^{-1} (free OH) and 3440 cm^{-1} (bonded OH).

N.m.r. spectrum: 0.99 (6H,s,gem-diMe), 1.30 (3H,s,CH_3-C-O).

Periodate Cleavage of 127° Glycol 28a

To a solution of 12 mg (0.047 mmole) of 127° glycol 28a in 1 ml of methanol was added at room temperature a solution of 25 mg (0.116 mmole) of sodium metaperiodate in 1 ml of water. An exothermic reaction occurred and a crystalline precipitate appeared within 10 minutes. After 2 h, the reaction mixture was diluted with water and extracted with ether. The ethereal extracts were combined, and evaporated after drying to give 7 mg of a liquid which on cooling solidified, m.p. 55-61°. Two recrystallizations from petroleum ether (30-60°) gave a colorless crystalline solid, m.p. 62.5-63°. The mixed melting point with an authentic sample of 4, m.p. 62-63°, was undepressed. The infrared spectrum, n.m.r. spectrum and t.l.c. behaviour were identical with those of the authentic specimen of 4.

Base Catalysed Isomerisation of the 127° Glycol 28a

A solution of 19 mg (0.075 mmole) of the 127° glycol 28a in 2.5 ml of methanol containing four potassium hydroxide pellets was refluxed on a steam bath for 118 h. The reaction mixture was cooled, diluted with water and extracted with ether. The combined ether extracts were evaporated to leave 9 mg (51%) of a white solid which was recrystallized twice from ether to yield colorless crystals, m.p. 112-114°. The mixed melting point with an authentic specimen of 29a, m.p.

115-116°, was undepressed. Thin-layer chromatography in ethyl acetate showed the above solid compound, R_f 0.30, to be different from the 119° glycol 5a, R_f 0.40, but to correspond to 116° glycol 29a in R_f value (0.30) when the isomerisation was allowed to proceed for only 48 h, the reaction was incomplete and the product was a mixture of 28a and 29a (t.l.c.).

A solution of 2 mg of the 127° glycol, 28a in 2 ml of methanol was refluxed on a steam bath for 120 h to leave 2 mg of starting material. Thin-layer chromatography in ethyl acetate revealed a spot corresponding to starting material and no spot corresponding to either 116° glycol 29a or 119° glycol 5a.

Reaction of Caryophyllene Monoxide 2 with Benzyl Alcohol - Potassium Hydroxide

A solution of 440 mg (2.00 mmoles) of pure caryophyllene monoxide 2, in 10 ml of benzyl alcohol containing 1.2 g of potassium hydroxide was heated on a steam bath for 96 h. The reaction mixture was worked up as described in page 162 to yield 140 mg of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) revealed no spot corresponding to starting material but showed a less polar spot near the solvent front. The infrared spectrum did not reveal any hydroxyl absorption, nor did the n.m.r. spectrum give any useful information. The reaction mixture was not investigated further.

Osmium Tetroxide Oxidation of Isocaryophyllene Oxide-a, 14a

To a solution of 980 mg (3.9 mmoles) of osmium tetroxide in 5 ml of anhydrous ether was added a solution of 840 mg (3.9 mmoles) of

isocaryophyllene oxide-a 14a, m.p. 73-75°, in 6 ml of anhydrous ether. The reaction mixture became warm and turned dark brown. After six days, the reaction mixture was diluted with ether and saturated with hydrogen sulfide. The black precipitate of osmium sulfide which precipitated was removed by filtration through Celite. The colorless filtrate was evaporated to remove the ether to leave 470 mg of a colorless glass. The black precipitate was refluxed in 7 ml of 95% ethanol containing 1 g of mannitol, 10 pellets of potassium hydroxide and 8 ml water for 6 h. The reaction mixture was cooled, diluted with water and extracted with ether. The ethereal solution was washed with water, dried and on evaporation of the ether left 200 mg of a dark colored glass which was mixed with the colorless glass (470 mg) obtained above to give a total of 670 mg of crude product (69%). Thin-layer chromatography in ethyl acetate - petroleum ether (60:40) revealed one major intense spot (grey color), five less polar faint spots and two very faint polar spots. The crude product which was shown by n.m.r. spectroscopy to consist mainly of one compound was chromatographed on 20 g of Woelm neutral alumina (IV) packed in petroleum ether. Elution with petroleum ether gave 60 mg of unreacted oxide-a 14a (t.l.c.) Further elution of the column with chloroform - benzene (25:75) gave 365 mg (38%) of 19a as a colorless glass which solidified to a crystalline solid on cooling. Three recrystallizations from petroleum ether gave 145 mg of colorless shiny small needles of 19a, m.p. 128.5-130°, $[\alpha]_D^{20}$ -2.6° (c, 3.13 in 95% ethanol). (No appreciable rotation was observed in chloroform).

Infrared spectrum: $\nu_{max}^{CCl_4}$ 3420 cm^{-1} (OH).

N.m.r. spectrum: 0.99 (6H,s,gemdiMe), 1.32 (3H,s,CH_3-C-O), 2.00 (1H, bs, OH), 3.28 (2H,t,CH_2-O-), 3.93 (1H,bm,H-C-O).

Anal. Calcd. for $C_{15}H_{26}O_3$ (254.4): C, 70.83; H, 10.30.

Found: C, 70.36; H, 9.99.

The residue from the mother liquor weighed 165 mg and was shown by t.l.c. in ethyl acetate - petroleum ether (60:40) to consist of one major spot corresponding to 19a and three faint spots of equal intensity. The residue was further separated on a thick plate (20 g of silica gel per 20x20 cm plate) to give 90 mg of an oil which on trituration with petroleum ether gave a white solid (m.p. 118-121°) whose n.m.r. spectrum was identical with that of 19a. Further recrystallization raised the melting point to 126-128° undepressed on admixture with 19a.

A solution of 15 mg (0.59 mmole) of the 130° glycol 19a in 2 ml of methanol was treated at room temperature with 35 mg (0.16 mmole) of sodium metaperiodate in 1 ml of water. After 17 h, the clear solution was diluted with water and extracted with ether. Evaporation of the dried ether extract left 9.6 mg of recovered 19a, m.p. 127-129°, undepressed on admixture with starting material. The infrared spectrum of the product was identical with that of starting material and had no trace of carbonyl absorption.

Acetylation of 130° Glycol 19a

A solution of 90 mg (3.54 mmoles) of 19a in 2 ml of pyridine and 1 ml of acetic anhydride was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Evap-

oration of ether left 112 mg (100%) of colorless oil 19b, which did not crystallize on standing in the refrigerator even after several days. Thin-layer chromatography in ethyl acetate - petroleum ether gave (65:35) only one spot, R_f 0.80, and no spot corresponding to starting material, R_f 0.35, $[\alpha]_D^{16}$ -8.00° (c, 1.80).

Infrared spectrum: $\nu_{max}^{CCl_4}$ 3571 cm^{-1} (OH) and 1748 cm^{-1} (ester C=O).

N.m.r. spectrum: 1.00 (6H,s,gem-diMe), 1.33 (3H,s,CH_3-C-O), 1.77 (1H,s,OH), 3.90 (2H,s,CH_2-O), 4.05 (1H,bm,H-C-O).

A sample was evaporatively distilled at 75-80° and 0.02 mm for analysis.

Anal. Calcd. for $C_{17}H_{28}O_4$ (296.4): C, 68.89; H, 9.52.

Found: C, 68.87; H, 9.55.

Chromic Acid - Pyridine Oxidation of 130° Glycol Monoacetate 19b

A solution of 46 mg (0.15 mmole) of 19b in 2 ml of pyridine was added to an orange complex of 20 mg (0.2 mmole) of chromium trioxide in 2 ml of pyridine at room temperature. After 24 h, the dark reaction mixture was diluted with methylene chloride and filtered through a short column of Woelm neutral alumina (activity IV) and eluted with methylene chloride. Evaporation of the eluate under reduced pressure left 40 mg of an oil whose t.l.c. behaviour and infrared spectrum were identical to that of the starting material 19b.

Chromic Acid - Pyridine Oxidation of 130° Glycol 19a

Chromium trioxide (60 mg, 0.60 mmole) was added to 2 ml of pyridine). To this slurry of the orange complex was added at room temperature a solution of 80 mg (0.32 mmole) of 19a in 1 ml of pyridine. The color of the reaction mixture changed to dark brown after 1 h. After

96 h, the dark reaction mixture was diluted with methylene chloride and passed through a short column of Woelm neutral alumina (activity IV) and eluted with methylene chloride. Evaporation of the solvent left 51 mg (62%) of an oil 21. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) revealed one major spot, R_f 0.63, and one minor spot (about 25%) corresponding to starting material, R_f 0.20. The crude oily product was evaporatively distilled slowly to give a colorless oil which showed a single spot in t.l.c. R_f 0.65 in the above solvent system.

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3390 cm^{-1} (OH, 1754 (broad, -CH=O).

Dehydration of Monoacetate of 130° Glycol 19b

The procedure of Hazen and Rosenburg[100] was used. To a vigorously stirred (magnetic bar) solution of 178 mg (0.6 mmole) of pure 19b in 3 ml of N,N-dimethylformamide (freshly distilled from molecular sieves type 4A) and 2 ml of freshly distilled γ-collidine maintained at 0° was added 1.14 g (10 mmoles) of methanesulfonyl chloride (freshly distilled at atmospheric pressure) containing 60 mg of anhydrous sulfurdioxide in small portions during one minute. The reaction mixture became brown immediately. After 15 minutes of vigorous stirring, the excess of methanesulfonyl chloride was carefully destroyed by adding water dropwise to the reaction mixture; the color turned wine red. The reaction mixture was extracted with three portions of ether and the combined ether extracts were washed with aqueous acetic acid (10%) and water. Evaporation of the dried solution left 152 mg (91%) of a pale yellow liquid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) indicated only one major spot (R_f 0.85)

visible under u.v. lamp and a faint polar spot corresponding to starting material (about 5%). The crude product was chromatographed on a thick plate (30 g of silica gel per 20x20 cm plate) in ethyl acetate - petroleum ether (65:35) and the band visible under the u.v. lamp was cut and eluted with ether to give 100 mg (60%) of a liquid. The n.m.r. spectrum showed the crude product to be a mixture of 22a and 22b in the approximate ratio of 85:15. T.l.c. showed it to be a single spot.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3070 cm^{-1} ($=CH_2$), 1740 cm^{-1} (ester C=O).

N.m.r. spectrum: 1.00 (6H,s,gem-diMe), 1.70 (3H,d,J 0.5 c.p.s., $\underline{CH_3}$-C=CH), 2.08 (3H,s,$\underline{CH_3}$-C=O), 3.95 (2H,dd,$\underline{CH_2}$-O-), 4.86 (2H,q,J_{AB}=3 c.p.s.,$\underline{CH_2}$=C).

Epoxidation of Isocaryophyllene Oxide-a 14a

Perbenzoic acid was prepared as described[126] in Organic Syntheses.[126] To a solution of 13.56 g (61.6 mmoles) of cis-oxide-a 14a in 50 ml of benzene (BDH, reagent grade) was added 350 ml of a solution of perbenzoic acid in benzene (equivalent to 61.5 mmoles) at room temperature. A slight evolution of heat was noticed, and hence the reaction flask was cooled under running tap water. After 7 days, when it gave a negative starch-iodide test, the yellow reaction mixture was diluted with ether and washed with aqueous sodium bicarbonate solution and water. Evaporation of the solvent left 14.5 g (100%) of a light yellow oil. Thin-layer chromatography in ethyl acetate showed one major spot, R_f 0.80, different from the starting material, R_f 0.90, and one less intense more polar spot (about 10%), R_f 0.40. The crude product was shown by n.m.r. spectroscopy to consist of only one bisepoxide 42 with no trace of the other bisepoxide 43. The crude product was chrom-

atographed on 330 g of Woelm neutral alumina (activity III) packed in petroleum ether. Rapid elution* with the same solvent gave 5.5 g (38%) of 42 as a pleasant smelling colorless crystalline solid which was shown by t.l.c. to be a single compound. Elution with ether gave 9.00 g (62%) of an oil which showed at least two major spots on t.l.c. in ethyl acetate, one corresponding to 42 and the other spot more polar than 42 (R_f 0.60) but of equal intensity. This fraction was not investigated further.

A portion (200 mg) of the petroleum ether fraction was recrystallized three times from petroleum ether (30°-60°) to give small crystals of 42, m.p. 98.5-100°, $[\alpha]_D^{18}$ -21° (c, 2.38).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3010 cm^{-1} and 3020 cm^{-1} (epoxide CH).

N.m.r. spectrum: 0.96 (3H,s,gem-CH_3), 1.00 (3H,s,gem-CH_3), 1.36 (3H, s,CH_3-C-O), 2.65 (2H,q,J_{AB}=10 c.p.s., CH_2-O-), 2.95 (1H,m,H-C-O).

Anal. Calcd. for $C_{15}H_{24}O_2$ (236.4): C, 76.23; H, 10.24.

Found: C, 76.04; H, 10.32.

Epoxidation of Isocaryophyllene Oxide-a 14a

a. Monoperphthalic acid in ether

A solution of 110 mg (0.50 mmole) of oxide-a 14a in 5 ml of anhydrous ether was treated with 10 ml of a solution of monoperphthalic acid in ether (equivalent to 0.60 mmole) at 0°C. After 8 days, the reaction mixture was worked up as described on page 160 to yield 110 mg (93%) of a white solid. The n.m.r. spectrum of the crude product showed only about 10% of bisepoxide-a 42 was formed with no trace of

* Quick elution was essential to avoid rearrangement of the bisepoxide 42 on the column.

atographed on 330 g of Woelm neutral alumina (activity III) packed in petroleum ether. Rapid elution* with the same solvent gave 5.5 g (38%) of 42 as a pleasant smelling colorless crystalline solid which was shown by t.l.c. to be a single compound. Elution with ether gave 9.00 g (62%) of an oil which showed at least two major spots on t.l.c. in ethyl acetate, one corresponding to 42 and the other spot more polar than 42 (R_f 0.60) but of equal intensity. This fraction was not investigated further.

A portion (200 mg) of the petroleum ether fraction was recrystallized three times from petroleum ether (30°-60°) to give small crystals of 42, m.p. 98.5-100°, $[\alpha]_D^{18}$ -21° (c, 2.38).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3010 cm^{-1} and 3020 cm^{-1} (epoxide CH).

N.m.r. spectrum: 0.96 (3H,s,gem-CH_3), 1.00 (3H,s,gem-CH_3), 1.36 (3H, s,CH_3-C-O), 2.65 (2H,q,J_{AB}=10 c.p.s., CH_2-O-), 2.95 (1H,m,H-C-O).

Anal. Calcd. for $C_{15}H_{24}O_2$ (236.4): C, 76.23; H, 10.24.
Found: C, 76.04; H, 10.32.

Epoxidation of Isocaryophyllene Oxide-a 14a

a. Monoperphthalic acid in ether

A solution of 110 mg (0.50 mmole) of oxide-a 14a in 5 ml of anhydrous ether was treated with 10 ml of a solution of monoperphthalic acid in ether (equivalent to 0.60 mmole) at 0°C. After 8 days, the reaction mixture was worked up as described on page 160 to yield 110 mg (93%) of a white solid. The n.m.r. spectrum of the crude product showed only about 10% of bisepoxide-a 42 was formed with no trace of

* Quick elution was essential to avoid rearrangement of the bisepoxide 42 on the column.

the other bisepoxide 43 and about 90% of the unreacted starting material oxide-a 14a. (The low yield of bisepoxide-a was probably due to very dilute solution of monoperphthalic acid).

b. Perbenzoic acid in ether

A solution of 110 mg (0.50 mmole) of oxide-a 14a in 2 ml of anhydrous ether was added to 9 ml of a solution of perbenzoic acid in ether at 0° and left in the refrigerator for 7 days. The reaction mixture was worked up as described in the previous experiment to yield 205 mg of a white solid (possibly benzoic acid was not removed completely). The n.m.r. spectrum of the crude product showed the presence of bisepoxide-a 42 only, and no trace of 43 could be detected. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one major spot corresponding to bisepoxide-a and a trace of a less polar spot corresponding to starting material 14a. Besides these, there were a number of more polar spots.

Base-Catalysed Isomerisation of Isocaryophyllene Bisepoxide-a 42

A solution of 1.68 g (7.1 mmoles) of pure 42, m.p. 98.5-100°, in 27 ml of benzyl alcohol containing 3.5 g of potassium hydroxide pellets was heated on a steam bath for 96 h. The yellow reaction mixture was worked up as described in page 160 to yield 3.5 g of crude benzyl ether 44b as an oil which still contained some benzyl alcohol. The crude benzyl ether was hydrogenolysed in 100 ml of 95% ethanol containing 3 g of palladised charcoal (5% Pd-Engelhard) in a Parr pressure hydrogenator at room temperature for 40 h. The reaction mixture was filtered and the solvent evaporated to give 1.80 g (100%) of a semi-solid. Thin-layer chromatography in ethyl acetate - petroleum ether

(65:35) revealed one major intense spot R_f 0.25 (about 80%) and two minor more polar glycol spots, R_f 0.10 and 0.05, and no spot corresponding to the 130° glycol 19a, R_f 0.15.

To a solution of 52 mg of crude glycol mixture in 1 ml of methanol at room temperature was added an aqueous solution of sodium metaperiodate (60 mg in 1 ml of water). A voluminous white precipitation occurred within 0.5 h. After 2 h, the reaction mixture was worked up as described in page 148 to give 39 mg of an oil. Thin layer chromatography in ethyl acetate - petroleum ether (65:35) revealed one less polar major spot corresponding to 13a in R_f value, a trace of two more polar spots, R_f 0.10 and 0.05, corresponding to starting crude glycol mixture and no spot corresponding to the major spot in the starting crude glycol mixture. The infrared spectrum of the crude oxidation product showed carbonyl absorption at 1695 cm^{-1} (9-membered C=0) and no hydroxyl absorption.

The crude glycol mixture was chromatographed on 50 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with the same solvent gave 160 mg of unreacted benzyl ether as a yellow liquid (t.l.c.). Elution with benzene-ether 90:10) gave 1.15 g (60%) of 44a as a white solid. Three recrystallizations from ether gave 700 mg (37%) of shining white crystals of 44a, m.p. 151-152°, $[\alpha]_D^{18}$ -45.6° (c, 2.44).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3570 cm^{-1} (free OH), 3440 cm^{-1} (bonded OH).

N.m.r. spectrum: 0.96 (6H,s,gem-diMe), 1.35 (3H,s,$\underline{CH_3}$-C-0), 2.16 (2H, bm, OH), 3.30 (2H,m,$\underline{CH_2}$-0-).

Anal. Calcd. for $C_{15}H_{26}O_3$ (254.4): C, 70.83; H, 10.30.

Found: C, 70.67; H, 10.44.

The mother-liquor from crystallization of 44a on evaporation left 180 mg of a solid material which was shown by t.l.c. to be more than 90% 44a and was found suitable for further chemical reactions. Further elution of the column with ether gave 400 mg of a white solid which showed two spots in t.l.c. of equal intensity, one corresponding to 44a and the other more polar than 44a.

Periodate Cleavage of 152° Glycol 44a

To a solution of 254 mg (1.00 mmole) of 152° glycol 44a in 1 ml of methanol at room temperature, an aqueous solution of sodium metaperiodate containing 255 mg (1.2 mmoles) in 3 ml of water was added. An exothermic reaction occurred and a voluminous white precipitate appeared almost immediately. After 10 h, the reaction mixture was worked up as described in page 148 to give 215 mg (98%) of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one spot corresponding in R_f to an authentic specimen of keto oxide-a 13a. The infrared and n.m.r. spectra were identical with those of an authentic specimen of 13a. A small amount of crude product was evaporatively distilled for optical rotation, $[\alpha]_D^{18}$ -79° (c, 4.46) in methanol, [lit (101): $[\alpha]_D^{21}$ -72° (c, 2.33, in methanol)].

Base-Catalysed Isomerisation of 152° Glycol 44a

A solution of 175 mg (0.68 mmole) of the 152° glycol 44a in 5 ml of methanol containing 0.6 g of potassium hydroxide pellets was refluxed on a steam bath for 168 h after which time the reaction mixture was

diluted with water and extracted with ether. The ethereal extracts were combined and washed with water. Evaporation of solvent left 140 mg (80%) of white solid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one major intense spot R_f 0.28 (about 90%) that was different from 130° glycol 19a and two faint (about 15%) more polar spots, R_f 0.10 and 0.05. The crude solid was recrystallized from chloroform to give a first crop of 60 mg of 45 as a colorless crystalline solid, m.p. 220-223° (sealed capillary tube). Further concentration and cooling of the mother liquor deposited a second crop (40 mg) of white solid, m.p. 219-222° (sealed capillary tube). Both first and second crops showed only one spot on t.l.c. (ethyl acetate - petroleum ether, 65:35) and were combined. The mother liquor on evaporation of solvent left 25 mg of a solid which was shown by t.l.c. to contain about 50% of the 227° glycol 45. Two recrystallisations of the combined first and second crops gave pure 45 as a colorless solid m.p. 225-227° (sealed capillary tube), $[\alpha]_D^{18}$ +31° (c, 1.25 in methanol).

Infrared spectrum: ν_{max}^{KBr} 3430 cm^{-1} (bonded OH).

N.m.r. spectrum (pyridine): 1.00 (6H,s,gem-diMe), 1.62 (3H,s,CH_3-C-O), 3.52 (2H,q,-CH_2-O), 3.93 (1H,m,H-C-O), 5.16 (2H,bs,OH).

Anal. Calcd. for $C_{15}H_{26}O_3$ (254.4): C, 70.83; H, 10.30.

Found: C, 70.49; H, 10.18.

A solution of 18 mg (0.07 mmole) of pure 227° glycol 45 in 0.5 ml of pyridine and 0.5 ml of acetic anhydride was left at room temperature for 24 h, after which it was worked up as described on page 150 to give

17 mg of recovered 45 as a colorless solid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed one major spot corresponding to starting material and one very faint less polar spot (about 2%). One recrystallization of the solid from chloroform gave crystals, m.p. 222-225°, which did not depress the melting point of pure 45 on admixture. The infrared spectrum (KBr) of the crude solid showed a very weak carbonyl absorption at 1730 cm^{-1} and strong OH absorption.

A solution of 12 mg (0.048 mmole) of pure 227° glycol 45 in 0.5 ml of pyridine was added to an orange complex of 15 mg (0.17 mmole) of chromium trioxide in 0.5 ml of pyridine. The reaction mixture was left at room temperature for 24 h, after which it was worked up as described on page 151 to yield 11 mg of recovered 45 as a solid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one spot corresponding to starting material and no trace of less polar material. The infrared spectrum (KBr) of the crude solid showed a very weak carbonyl absorption at 1710 cm^{-1} and a strong OH absorption. The crude solid did not depress the melting point of starting material 45 on admixture.

Acid-Catalysed Isomerisation of 152° Glycol 44

A solution of 9 mg (0.0035 mmole) of pure 152° glycol 44 in 1.5 ml of acetone (Fisher - Spectral grade) containing 0.5 ml of an aqueous 5% solution of sulfuric acid in water was refluxed on a steam bath for 2 h. The reaction mixture was worked up as described on page 159 to yield 6 mg of a liquid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed at least four spots, one of which cor-

responded to 227° glycol 45 but none of them corresponded to 19a. The reaction was not investigated further.

Osmium Tetroxide Oxidation of Isocaryophyllene Oxide-b 14b

The isocaryophyllene oxide-b used in this experiment was about 85% pure (n.m.r.), the other 15% impurity being isocaryophyllene oxide-a, 14a. To a solution of 1.00 g (3.9 mmoles) of osmium tetroxide in 5 ml of anhydrous ether was added a solution of 870 mg (3.94 mmoles) of isocaryophyllene oxide-b 14b in 6 ml of anhydrous ether. The reaction mixture immediately became dark brown and within a few minutes a black precipitate was thrown down. Five days later the reaction mixture was diluted with ether and saturated with hydrogen sulfide. The black precipitate of osmium sulfide was removed by filtration through Celite. The colorless filtrate on evaporation left 398 mg of a colorless viscous oil.

The black precipitate obtained was refluxed in 10 ml of 95% ethanol with 1 g of mannitol and 10 potassium hydroxide pellets on a steam bath for 8 h. The reaction mixture was cooled, diluted with water and extracted with ether. The ethereal solution on evaporation left 350 mg of an oil which was mixed with the colorless oil obtained above (t.l.c. behaviour of the two fractions identical) to give a total of 748 mg (74%) of crude product. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) of the crude product showed at least 4 spots - one major intense spot (dark brown), R_f 0.45, and three more polar less intense spots, R_f 0.25, 0.15 and 0.10.

The crude product was chromatographed on 45 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with the same

solvent gave 127 mg (17%) of recovered oxide-b 14b (t.l.c. characteristic mauve color). Elution with benzene-chloroform (50:50) gave 361 mg (48%) of 24 as a white solid. Six recrystallizations from chloroform-petroleum ether gave colorless crystals m.p. 194-195.5° (sealed capillary), $[\alpha]_D^{19}$ -24.4° (c, 1.28, in methanol).

Infrared spectrum: ν_{max}^{KBr} 3300 cm^{-1} (bonded OH).

N.m.r. spectrum (pyridine): 0.98, 1.00 (6H,2s,gem-diMe), 1.53 (3H,s,$\underline{CH_3}$-C-O), 5.06 (2H,bs,O$\underline{H}$).

Anal. Calcd. for $C_{15}H_{26}O_3$ (254.4): C, 70.83; H, 10.30.

Found: C, 71.15; H, 10.44.

Further elution with chloroform gave 135 mg (18%) of a mixture of glycols 19a and 23a (n.m.r. and t.l.c.) which was separated carefully on a thick plate (20 g silica gel per 20x20 cm plate) with ethyl acetate as solvent to yield 85 mg (11%) of 23a and 20 mg (3%) of 19a. The column was finally washed with methanol to give 100 mg of a liquid which was not investigated further.

Periodate Oxidation of 1,2-Diol 23a

A solution of 15 mg (0.060 mmole) of the glycol 23a in 1 ml of methanol was added to an aqueous solution of sodium metaperiodate (40 mg, 0.19 mmole) in 1 ml of water at room temperature, and a white precipitate appeared almost immediately. After 12 h at room temperature, the reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water and evaporated to leave 6 mg of an oil whose infrared spectrum and t.l.c. behaviour were identical with that of an authentic specimen of keto oxide-b 13b.

Acetylation of 1,2-Diol 23a

A solution of 60 mg (0.024 mmole) of the 1,2-diol 23a in 1 ml of pyridine and 1 ml of acetic anhydride was left at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with water, dried and evaporated to leave 65 mg of an oil which solidified on keeping in the refrigerator for several days. Three recrystallizations from petroleum ether (30-60°) gave a spongy solid, 23b m.p. 86-87°, $[\alpha]_D^{17}$ + 34.6° (c, 2.00).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3450 cm^{-1} (OH), 1748 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.99 (6H,s,gem-diMe), 1.25 (3H,s,CH_3-C-O), 2.07 (3H, s,CH_3-C=O), 3.78 (2H,s,CH_2-O-).

Anal. Calcd. for $C_{17}H_{28}O_4$ (296.40): C, 68.89; H, 9.52.

Found: C, 69.22; H, 9.71.

Base-catalysed Isomerisation of 1,2-Diol 23a

Since pure 1,2-diol 23a was no longer available, its acetate 23b containing about 70% of the monoacetate of the 130° glycol 19b was used in this experiment. A solution of 95 mg of the acetate mixture (19b and 23b in the ratio 70:30) in 5 ml of methanol containing 500 mg of potassium hydroxide pellets was refluxed on a steam bath for 7 days. The solution was cooled, diluted with water and extracted with ether. The ethereal solution was washed with water, dried and on evaporation of solvent left 80 mg of an oil. Thin-layer chromatography in ethyl acetate showed only two major spots, R_f 0.40 and 0.25, the less polar spot R_f 0.40 corresponding to an authentic specimen of 195° glycol 24 and the more polar spot R_f 0.25 corresponding

to 130° glycol 19a. The crude product was chromatographed on 5 gm of neutral alumina (activity IV) packed in benzene. Elution with benzene - chloroform mixture gave 12 mg of a white solid which was recrystallized from petroleum ether to give a colorless solid, m.p. 192-194° (sealed capillary). No depression in m.p. was observed on admixture with authentic specimen of 24. Further elution of the column with ether gave 35 mg of pure 19a (m.p., and mixed m.p.);

Chromic Acid - Pyridine Oxidation of 195° Glycol 24

A solution of 48 mg (0.20 mmole) of the 195° glycol 24 in 2 ml of pyridine was added to an orange complex of 40 mg (0.40 mmole) of chromium trioxide in 1 ml of pyridine. A black precipitate was observed after a few hours. After 24 h, the reaction mixture was diluted with methylene chloride and worked up as described previously. Evaporation of solvent left 35 mg of a white solid which was found by t.l.c. to be mainly the starting material 24 with some less polar material (~20%). The infrared spectrum (KBr) showed a strong OH band and a very weak carbonyl absorption.

Acetylation of 195° Glycol 24

A solution of 51 mg (0.20 mmole) of 195° glycol 24 in 1 ml of pyridine and 1 ml of acetic anhydride was left at room temperature for 24 h. The brown reaction mixture was diluted with water and extracted with ether. The ethereal solution was evaporated to leave 50 mg of recovered 24. The infrared spectrum of the product was identical with that of starting material but had a weak carbonyl peak at 1709 cm^{-1}. Thin-layer chromatography in ethyl acetate - petroleum

ether (65:35) gave one major spot corresponding to starting material, R_f 0.30, and a less polar spot R_f 0.65 (about 20%), presumably an acetate.

Attempted Periodate Reaction on the 195° Glycol 24

A solution of 30 mg (0.012 mmole) of the 195° glycol 24 in 1 ml of methanol was added to an aqueous solution of sodium metaperiodate (40 mg, 0.19 mmole) in 1 ml of water at room temperature. After 60 h, the reaction mixture was diluted with water and extracted with ether. Evaporation of ether left 26 mg of recovered 24. The infrared spectrum showed a weak carbonyl peak at 1709 cm^{-1} and strong hydroxyl absorption.

Epoxidation of Isocaryophyllene Oxide-b 14b

(a) Monoperphthalic acid in ether

The isocaryophyllene oxide-b used in this experiment contained about 30% of oxide-a 14a (n.m.r.). To a solution of 2.2 g (10 mmoles) of isocaryophyllene oxide-b 14b in 10 ml of anhydrous ether at 0° was added 30 ml of a solution of monoperphthalic acid in ether (equivalent to 15 mmoles) and the reaction mixture was kept in the refrigerator for 7 days, after which it was worked up as described on page 160 to yield 2.2 g (93%) of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed one major spot R_f 0.65, different from the starting material R_f 0.85, and two faint polar spots, R_f 0.20 and 0.10. The n.m.r. spectrum of the crude product showed the C_8-methyls of 42 and a mixture of 47 and 48 in the ratio of 30:70. The bisepoxides 47 and 48 could not be obtained in a pure state as they

showed a great tendency to rearrange on a neutral alumina column (activity IV), and therefore the crude bisepoxide mixture was used as such for further isomerisation reactions.

(b) Perbenzoic acid in benzene

To a solution of 5.6 g (26 mmoles) of cis-oxide-b 14b in 50 ml of benzene (reagent grade) was added 145 ml of a solution of perbenzoic acid in benzene (equivalent to 26 mmoles) at room temperature. After 7 days the reaction mixture was worked up as described on page 161 to give 6.00 g (100%) of a yellow oil. Thin-layer chromatography in ethyl acetate showed one polar major spot, R_f 0.75, different from the starting material, R_f 0.90, and traces of polar spots, R_f 0.45 and 0.25 (less than 2%). The n.m.r. spectrum of the crude product was not clean and hence this procedure was not further pursued.

(c) Trifluoroperacetic acid in Methylene Chloride

The procedure of Emmons and Pagano[66] was followed. A solution of trifluoroperacetic acid produced in situ from 2 ml (39 mmoles) of 70% hydrogen peroxide and 8 ml of trifluoroacetic anhydride (38 mmoles) in 10 ml of methylene chloride was added dropwise to a solution of 880 mg (4 mmoles) of oxide-b 14b in 15 ml of methylene chloride containing 800 mg (10 mmoles) of sodium bicarbonate solid, when a violent reaction set in. After the addition, the reaction mixture was refluxed on a steam bath for 0.5 h. The reaction mixture was cooled and extracted with water. The dried organic layer was evaporated to leave 1.3 g of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed at least 4 spots. The n.m.r. spectrum of the crude product showed no trace of either 47 or 48. The reac-

tion mixture was not investigated further.

Base Catalysed Isomerisation of Bisepoxide Mixture from Isocaryophyllene Oxide-b

A solution of 2.10 g of the crude bisepoxide mixture obtained in the previous experiment (a) in 30 ml of benzyl alcohol containing 3.5 g of potassium hydroxide pellets was heated on a steam bath for 96 h, after which the yellow reaction mixture was worked up as described in page 162 to yield 8.40 g of an oil which contained some benzyl alcohol. The crude product was dissolved in 100 ml of 95% ethanol containing 4 g of palladised charcoal (5%-Pd-Engelhard) and hydrogenolysed at room temperature in a Parr hydrogenator till the absorption of hydrogen ceased (21 h). The reaction mixture was filtered and the solvent evaporated to leave 2.3 g (100%) of an oil which solidified on standing at room temperature. Thin-layer chromatography on ethyl acetate - petroleum ether (65:35) showed one major spot and three minor spots.

The crude glycol mixture was recrystallized from ether - petroleum ether mixture to yield 370 mg of a colorless solid, m.p. 145-150°, which was shown by t.l.c. (brown color) to be largely one compound. Four recrystallizations from ether gave 49a as beautiful shining needles, m.p. 152-153°, $[\alpha]_D^{18}$ -62° (c, 1.75).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3590 cm^{-1} (free OH), 3440 cm^{-1} (bonded OH).

N.m.r. spectrum: 0.95, 0.96 (6H,2s,gem-diMe), 1.32 (3H,s,$\underline{CH_3}$-C-O), 1.64 (1H,OH,bs), 3.56 (2H,q J_{AB}=12 c.p.s.,-$\underline{CH_2}$-O), 3.97 (1H,m,$\underline{H}$-C-O).

Anal. Calcd. for $C_{15}H_{26}O_3$ (254.4): C, 70.83; H, 10.30.

Found: C, 70.57; H, 10.10.

The mother liquor left from crystallization of the first crop was evaporated to leave 1.10 g of an oil.

Periodate Cleavage of the Glycol Mixture

(a) A solution of 50 mg (0.208 mmole) of the crude glycol mixture in 2 ml of methanol was added to an aqueous solution of 40 mg of sodium metaperiodate (0.27 mmole) in 2 ml of water at room temperature. A white precipitation occurred and the reaction mixture after 11 h was worked up as described on page 148 to give 40 mg of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) revealed two less polar materials, R_f 0.65 and 0.45, one major polar spot, R_f 0.20 and one minor polar spot, R_f 0.10.

(b) Periodate Cleavage of the Mother liquor from 49a

A solution of 1.00 g of mother liquor residue in 3 ml of methanol at room temperature was added to an aqueous solution of 1.25 g of sodium metaperiodate in 7 ml of water when a voluminous white precipitate appeared. The reaction mixture was worked up as described on page 148 to yield 768 mg of an oil which was chromatographed on 22 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with the same solvent gave 450 mg (58%) of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one spot corresponding to authentic epoxy ketone-a 13a and epoxy ketone-b 13b with no other detectable impurities. The infrared spectrum showed a strong absorption at 1695 cm^{-1} (9-membered C=O) and no OH absorption. The n.m.r. spectrum of this residue showed it to be a mixture of 13a and 13b in the ratio of 35:65. Further elution of

the column with ether gave 253 mg (35%) of an oil which on trituration with petroleum ether deposited 110 mg of a white solid m.p. 149-151°. No depression in melting point was observed on admixture with pure 49a. Further concentration and cooling did not yield any crystalline material. However t.l.c. showed the mother liquor to contain largely 49a and one more polar compound. The mother liquor weighing 140 mg was acetylated with 1 ml of acetic anhydride and 2 ml of pyridine at room temperature and worked up as described in page 150 to yield 150 mg of a brown oil. Thin-layer chromatography showed five spots, R_f values 0.40, 0.55, 0.65, 0.75, 0.90, one of which corresponded to 49b. Further investigation was not done.

Periodate Oxidation of 153° Glycol 49a

To a solution of 20 mg (0.078 mmole) of 49a in 1 ml of methanol was added an aqueous solution of 27 mg (0.12 mmole) of sodium metaperiodate in 1 ml of water at room temperature. After 24 h, the reaction mixture was worked up as described on page 148 to give 17 mg (85%) of recovered 49a. The infrared spectrum (absence of carbonyl absorption) and t.l.c. (only one spot) behaviour were identical with those of the starting material.

Monoacetate of 153° Glycol 49b

A solution of 115 mg (0.36 mmole) of pure 49a in 1 ml of pyridine and 1 ml of acetic anhydride was left at room temperature for 24 h. The reaction mixture was worked up as described on page 150 to yield 135 mg (100%) of an oil which solidified on standing at room temperature. Three recrystallizations from petroleum ether (30-60°) gave

78 mg (58%) of pure 49b as a spongy white solid, m.p. 84.5-86°, $[\alpha]_D^{18}$ -57° (c, 0.89).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3590 cm^{-1} (free OH), 3440 cm^{-1} (bonded OH), 1725 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.95 (3H,s,gem-CH_3), 0.98 (3H,s,gem-CH_3), 1.33 (3H,s, CH_3-C-O), 2.08 (3H,s,CH_3-C=O), 3.48 (1H,OH,bs), 4.08 (2H,s,CH_2-O).

Anal. Calcd. for $C_{17}H_{28}O_4$ (296.40): C, 68.89; H, 9.52.

Found: C, 68.58; H, 9.46.

Dehydration of the Monoacetate of 153° Glycol 49b

The procedure of Hazen and Rosenburg was[100] followed. To a vigorously stirred (magnetic bar) solution of 40 mg (0.13 mmole) of about 95% pure (t.l.c.) monoacetate of 153° glycol 49b in 3 ml of freshly distilled γ-collidine and 4 ml of freshly distilled (from molecular sieves type 4A) N,N -dimethylformamide cooled to 0° was added in small portions 115 mg (1.00 mmoles) of methanesulfonylchloride (freshly distilled at atmospheric pressure) containing 25 mg of anhydrous sulfur dioxide during a minute period. The colorless solution became brown after five minutes and a brown precipitate appeared. After 15 minutes of stirring, the excess of methanesulfonylchloride was carefully destroyed by adding water dropwise and the resulting wine red solution was processed as described in page 176 to give 40 mg of a yellow oil. Thin-layer chromatography in ethyl acetate - petroleum ether (8:92) revealed one less intense spot, R_f 0.67, two intense spots of equal intensity, R_f 0.58 and 0.52, corresponding to the two spots 32a and 32b of the crude dehydration product from 116° glycol monoacetate 29b;

there was no spot corresponding to the hydroxyacetate 33b obtained from 29b. The n.m.r. spectrum showed the crude dehydration product to be approximately a 50:50 mixture of 32a and 32b.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3060 cm^{-1} (vinylic H), 1740 cm^{-1} (ester C=O), 1625 cm^{-1} (C=C), 900 cm^{-1} and 890 cm^{-1} ($=CH_2$).

N.m.r. spectrum: See Plate VI.

Osmium Tetroxide Hydroxylation of the other trans-Caryophyllene Oxide 3 (E.W.W.)

Two separate small scale reactions were run and the products combined after acetylation. In the first reaction a solution of 907 mg (4.12 mmoles) of a ~1:1 mixture of 2 and 3 in 4 ml of ether was added at ice bath temperature to a solution of 1.043 g (4.11 mmoles) of osmium tetroxide in 1 ml of pyridine and 1 ml of ether. In the second reaction 867 mg (3.94 mmoles) of the caryophyllene oxide mixture and 9.89 mg (3.90 mmoles) of osmium tetroxide were used. The reactions were allowed to stand at room temperature for several days. Each reaction was worked up by evaporation of solvent, reflux with ethanol-mannitol-sodium hydroxide, and ether extraction after dilution with water. The first reaction gave 780 mg (74%) of partially crystalline crude product, and the second gave 809 mg (81%). Since the crude products gave only one elongated t.l.c. spot, the crude products were each acetylated at room temperature with 2 ml of acetic anhydride and 5 ml of pyridine. Workup gave 786 mg (~94%) from the first reaction and 895 mg (~90%) from the second. Thin-layer chromatography in ethyl acetate - petroleum ether (50:50) gave four spots, R_f 0.55, corresponding to 119° glycol diacetate 5b, R_f 0.35 and 0.25, corresponding

to monoacetates, and R_f 0.15 (minor), corresponding to a diol. One recrystallisation of the crude acetylation product from ether - petroleum ether (b.p. 60-80°) gave a mixture of the two monoacetates, R_f 0.35 and 0.25, with the least polar spot concentrated in the mother liquor. The material (1.137 g) from the mother liquor was chromatographed on four silica gel thick layer chromatography plates (20 g per 20x20-cm plate). Extraction of the least polar zone gave 631 mg (23% on caryophyllene oxides) of 119° glycol diacetate 5b.

The 631 mg of oil was refluxed for 41 h with 0.5 g of potassium hydroxide in 10 ml of methanol. Dilution with water and extraction with ether gave 471 mg (99%) of solid 119° glycol. One recrystallization from chloroform - petroleum ether (b.p. 60-80°) gave 417 mg of pure 5a.

From the lower thick layer zones and the mixture of compounds, R_f 0.35 and 0.25, from recrystallization of the crude acetylation product was obtained 685 mg (28% based on caryophyllene oxides) of almost pure crystalline monoacetate 38b. Final purification was achieved by three recrystallizations from ether - petroleum ether (b.p. 60-80°) to give colorless needles, m.p. 158-159°, $[\alpha]_D^{19}$ +18.0° (c 1.90).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3598 cm^{-1} (free OH), 3420 cm^{-1} (bonded OH), 1725 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.98 (3H,s,gem-CH_3), 1.00 (3H,s,gem-CH_3), 1.13 (3H, s,CH_3-C-O), 2.13 (3H,s,CH_3-C=O), 3.87 (2H,t,CH_2-O-), 4.97 (1H,m,H-C-O).

Anal. Calcd. for $C_{17}H_{28}O_4$ (296.40): C, 68.89; H, 9.52.

Found: 69.06; H, 9.96.

Attempted Chromic Acid - Pyridine Oxidation of 159° Monoacetate 38b (E.W.W.)

A solution of 26 mg (0.087 mmole) of 159° monoacetate 38b in 0.5 ml of pyridine was added to an orange complex of 30 mg (0.30 mmole) of chromium trioxide in 0.5 ml of pyridine and left at room temperature for 39 h with occasional shaking. The orange suspension was diluted with methylene chloride and passed through a short column of Woelm neutral alumina (activity III). Elution with methylene chloride gave 26 mg (100%) of recovered crystalline starting material, m.p. 159°. Mixed m.p. with the starting material was undepressed. Thin-layer chromatography in ethyl acetate - petroleum ether (50:50) showed only one spot corresponding to the starting material with no less polar spot.

Saponification of 159° Monoacetate 38b (E.W.W.)

A solution of 165 mg (0.56 mmole) of pure 159° monoacetate 38b in 10 ml of methanol containing 200 mg of sodium hydroxide pellets was refluxed for 40 h. The cooled reaction mixture was then diluted with water and extracted with ether. The ethereal extracts were washed with water and the solvent evaporated to give 130 mg (92%) of a liquid which showed a single spot on t.l.c. The crude product which solidified on cooling was recrystallized three times from ether to give small felted needles of 38a, m.p. 135-136°.

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3448 cm^{-1} (OH).

N.m.r. spectrum: 0.96 and 1.00 (6H,2s,gem-diMe), 1.27 (3H,s,$\underline{CH_3}$-C-O).

Anal. Calcd. for $C_{15}H_{26}O_3$ (254.34): C, 70.82; H, 10.29.
Found: C, 70.94; H, 10.34.

Attempted Periodate Oxidation of 136° Glycol 38a (E.W.W.)

To a solution of 20 mg (0.079 mmole) of 136° glycol 38a in 2 ml of methanol was added an aqueous solution of sodium metaperiodate (40 mg, 0.19 mmole, in 0.5 ml of water) and the reaction mixture was allowed to stand at room temperature for 6.5 h. The reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water, dried and solvent evaporated to give 18 mg of a colorless solid. Thin-layer chromatography showed only one spot corresponding in R_f value to the starting material. The infrared spectrum did not show any carbonyl absorption but only hydroxyl absorption at 3448 cm^{-1}. Recrystallization from ether - petroleum ether gave 13 mg of a colorless solid m.p. 133-136° undepressed on admixture with starting material.

Chromic Acid - Pyridine Oxidation of 136° Glycol 38a (E.W.W.)

A solution of 162 mg (0.64 mmole) of 136° glycol 38a in 2.3 ml of pyridine was added to an orange complex of 107 mg (1.07 mmoles) of chromium trioxide in 1 ml of pyridine at room temperature. Immediately the reaction mixture became dark reddish brown. After standing at room temperature for 20 h, the reaction mixture was diluted with methylene chloride and passed through a short column of Woelm neutral alumina (activity IV). Elution with methylene chloride gave 159 mg

(100%) of a yellow glass which crystallized on trituration with ether - petroleum ether mixture. Thin-layer chromatography in ethyl acetate - petroleum ether (50:50) revealed a polar spot (about 20%) corresponding to the starting material and a major intense less polar spot. Direct crystallization from ether - petroleum ether gave a crystalline solid which was found to be a mixture of both the polar and less polar spots (t.l.c.). The mother liquor was found by t.l.c. to be largely the less polar compound with traces of the polar compound. The mother liquor was chromatographed on a thick-layer plate (20 g of silica gel per 20x20 cm plate) in ethyl acetate - petroleum ether (50:50). The band visible under the u.v. lamp was cut and eluted with methylene chloride. Solvent evaporation gave pure hydroxy ketone 39 (single spot in t.l.c.). Three recrystallizations from ether - petroleum ether mixture gave crystalline hydroxy ketone 39 as needle-like prisms, m.p. 82-83°.

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3570 cm^{-1} (free OH), 3448 cm^{-1} (bonded OH), 1701 cm^{-1} (7-membered C=O).

N.m.r. spectrum: 0.95 (3H,s,gem-CH_3), 1.00 (3H,s,gem-CH_3), 1.28(3H, s,CH_3-C-O).

Anal. Calcd. for $C_{15}H_{24}O_3$ (252.33): C, 71.39; H, 9.57.

Found: C, 71.11; H, 9.55.

Wolff-Kishner Reduction of Hydroxy Ketone 39

To a solution of 37 mg (0.14 mmole) of hydroxy ketone 39 in 3 ml of triethylene glycol were added 1.5 ml of hydrazine hydrate (85%) and six potassium hydroxide pellets. The mixture was refluxed in an oil bath at 140-145° for 2 h, after which the excess hydrazine hydrate was

distilled out. The temperature of the oil bath was then raised to 200° and maintained at that temperature for 4.5 h. The cooled reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water, dried and evaporated to leave 20 mg of a colorless oil. Thin-layer chromatography in ethyl acetate revealed one major intense spot (brown), R_f 0.65, different from the starting material spot (grey), R_f 0.70, and corresponding to the unsaturated 1,2-diol 11 in color and R_f value. The crude oil solidified to a white mass on cooling in the refrigerator. It was recrystallized once from petroleum ether (30-60°) to give small crystals, m.p. 87-90°, undepressed on admixture with a specimen of 11 obtained from the degradation of the 119° glycol 5a.

Base-Catalysed Isomerisation of Caryophyllene Keto Epoxide 4

(a) t-Butyl Alcohol - Potassium Hydroxide

A solution of 8.62 g (38.8 mmoles) of caryophyllene keto epoxide 4, m.p. 62.5-63°, in 100 ml of t-butyl alcohol containing 7 ml of water and 18 g of potassium hydroxide pellets was refluxed on a steam bath when a dark brown color developed within 0.5 h. After 64 h, the reaction mixture was cooled, diluted with water and extracted with ether. The combined ether extracts were washed thoroughly with water and evaporated to leave 8.30 g (96.5%) of a light yellow solid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only three spots, R_f 0.75 (brown), 0.55 (dark green), 0.35 (light brown), the middle spot with R_f 0.55 corresponding to Barton's tricyclic hydroxyketone 54a.*

*The brown spot with R_f 0.75 appeared on t.l.c. plate only after prolonged heating. It is easy to miss this spot on an insufficiently charred plate

The crude product was recrystallized from petroleum ether to give a first crop of 4.15 g (50%) of a white solid, m.p. 144-146°, which showed a single spot on t.l.c. One further recrystallization from petroleum ether furnished 3.5 g of a highly crystalline solid 54a m.p. 147-148.5°, $[\alpha]_D^{19}$ -23.3° (c, 2.83) [lit. (115); m.p. 148-149°, $[\alpha]_D$ -32° (c, 4.68)].

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3600 cm^{-1} (free OH), 3460 cm^{-1} (bonded OH), 1700 cm^{-1} (6-membered C=O).

N.m.r. spectrum: 0.83 (3H,s,gem-CH_3), 0.90 (3H,s,gem-CH_3), 1.00 (3H, s,CH_3-C-), 2.108 (1H,s,OH), 3.88 (1H,dd,H-C-O).

No depression in melting point was observed on admixture with an authentic specimen of 54a prepared in (b) below.

The mother liquor left after removing the first crop was evaporated to give 3.9 g of a light yellow solid which was chromatographed on 100 g of Woelm neutral alumina (activity II) packed in petroleum ether. Elution with petroleum ether - benzene (50:50) gave 2.3 g (27%) of a white solid which showed a single spot in t.l.c., R_f 0.75. Two recrystallizations from petroleum ether furnished 1.60 g (19%) of small plates of 61a, m.p. 118-119°, $[\alpha]_D^{17}$ + 17.8° (c, 3.11), λ_{max}^{EtOH} 292 mμ(ε 34).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3600 cm^{-1} (free OH), 3500 cm^{-1} (bonded OH), 1705 cm^{-1} (6-membered C=O).

N.m.r. spectrum: 0.90 (3H,s,gem-CH_3), 1.16 (3H,s,gem-CH_3), 1.19 (3H, s, CH_3-C-), 2.00 (1H,s,OH), 4.43 (1H,bm,H-C-O).

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 75.53; H, 9.90.

Further elution of the column with benzene gave 1.15 g of colorless solid which was shown by t.l.c. to be largely 54a with a small amount (about 5%) of 61a. The column was finally washed with methanol which gave 400 mg (4.8%) of a light yellow liquid. Trituration with ether deposited a white solid which was recrystallized three times from petroleum ether to give small colorless crystals of 64, m.p. 145-146° (undergoes crystal change at 123-125°), $[\alpha]_D^{18}$ + 73.7° (c, 3.04).

Ultraviolet spectrum: λ_{max}^{EtOH} 280 mμ(ε 158); ϵ_{292} 116

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3580 cm^{-1} (free OH), 3420 cm^{-1} (bonded OH), 3000 cm^{-1} (cyclopropane CH_2), 1695 cm^{-1} (9-membered C=O).

N.m.r. spectrum: 0.97 (6H,s,gem-diMe),1.03 (3H,s,CH_3-C-O).

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 75.21; H,10.13.

(b) Methanol-Potassium Hydroxide

The procedure of Barton and Lindsey[115] was repeated. A solution of 225 mg (1.01 mmoles) of caryophyllene keto epoxide 4 in 5 ml of methanol containing 1 g of potassium hydroxide pellets was refluxed for 6 h, after which the reaction mixture was worked up as described in the literature to give 200 mg (90%) of a white solid. The crude product obtained thus compared well with the crude product obtained by t-butyl alcohol - potassium hydroxide isomerisation above on a t.l.c. plate developed in ethyl acetate - petroleum ether (65:35). Although the crude product showed three spots corresponding to 54a, 61a and 64, the n.m.r. spectrum could detect only 54a but not 61a and 64. Hence the two compounds 61a and 64 were present in negligible

amounts (less than 5%).

Acetate of 119° Hydroxy Ketone 61b

A solution of 400 mg (1.8 mmoles) of 119° hydroxy ketone 61a in 2 ml of pyridine and 2 ml of acetic anhydride was allowed to stand at room temperature for 24 h. The reaction mixture was worked up as described in page 150 to yield 460 mg (97%) of an oil which was chromatographed on 15 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with the same solvent gave 370 mg (80%) of a liquid which solidified on cooling in the refrigerator. Further elution of the column with benzene gave 60 mg of recovered starting material 61a (m.p. and mixed m.p.). Two recrystallizations of the petroleum ether fraction from petroleum ether (30-60°) gave pure 61b as colorless plates, m.p. 58-58.5°, $[\alpha]_D^{17}$ + 15.8° (c, 3.46).

Infrared spectrum: $\nu_{max}^{CS_2}$ 1735 cm^{-1} (ester C=O), 1705 cm^{-1} (6-membered C=O).

N.m.r. spectrum: 0.88 (3H,s,gem-CH_3), 1.14 (3H,s,gem-CH_3), 1.21 (3H,s,CH_3-C), 2.10 (3H,s,CH_3-C=O), 5.58 (1H,b dd, H-C-O).

Anal. Calcd. for $C_{16}H_{24}O_3$ (264.4): C, 72.69; H, 9.15.

Found: C, 72.88; H, 9.30.

Chromic Acid - Pyridine Oxidation of 119° Hydroxy Ketone 61a

A solution of 201 mg (0.90 mmole) of 119° hydroxy ketone 61a in 2 ml of pyridine was added to an orange complex of 180 mg (1.80 mmoles) of chromium trioxide in 2 ml of pyridine at room temperature when the whole reaction mixture turned dark brown. After 27 h, the reaction

mixture was worked up as described on page 151 to yield 190 mg (95%) of a liquid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) showed only one major spot, R_f 0.80 (greenish yellow), different from the starting material with traces of starting hydroxy ketone 61a. The crude product was chromatographed on 15 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with petroleum ether gave 160 mg of a liquid (single t.l.c. spot) which solidified on standing in the refrigerator. Two recrystallizations from petroleum ether (30-60°) gave long colorless needles of diketone 62, m.p. 51.5-52°, $[\alpha]_D^{17}$ -161.5° (c, 3.65).

Infrared spectrum: $\nu_{max}^{CS_2}$ 1700 cm^{-1} (6-membered C=O).

N.m.r. spectrum: 0.92 (3H,s,gem-CH_3), 1.03 (3H,s,gem-CH_3), 1.09 (3H, s,CH_3-C-).

Anal. Calcd. for $C_{14}H_{20}O_2$ (220.3): C, 76.33; H, 9.15.

Found: C, 76.80; H, 9.25.

Selenium Dioxide Oxidation of 52° Diketone 62

A solution of 158 mg (0.72 mmole) of diketone 62 in 3 ml of glacial acetic acid containing 40 mg (0.36 mmole) of selenium dioxide was refluxed for 1 h. The greenish yellow solution was cooled and filtered to remove the precipitated black selenium. The yellow filtrate was diluted with water and extracted with ether. The ethereal extracts were washed with aqueous sodium bicarbonate solution and water. Evaporation of the dried ether solution left 155 mg (99%) of a yellow liquid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) revealed two spots, one bright yellow spot with R_f 0.90 and the other predominant spot visible under the u.v. lamp only with R_f

0.80. The crude yellow liquid was chromatographed on a thick plate (20 g of silica gel per 20x20 cm plate) in ethyl acetate - petroleum ether (65:35) and the band visible under u.v. lamp was carefully separated and eluted with methylene chloride to give 110 mg (65%) of a pale yellow liquid which showed one major spot in t.l.c. with traces of the less polar yellow spot, $[\alpha]_D^{17}$ -281° (c, 1.80).

Ultraviolet spectrum: λ_{max}^{EtOH} 224 mμ (ε 13,750), 348 (ε 141).

Infrared spectrum: $\nu_{max}^{CS_2}$ 1672 cm^{-1} (enedione), 1610 cm^{-1} (C=C).

N.m.r. spectrum: 0.95 (3H,s,gem-$\underline{CH_3}$), 1.01 (3H,s,gem-$\underline{CH_3}$), 1.14 (3H,s,$\underline{CH_3}$-C-), 6.55 (1H,d,J=11 c.p.s., $\underline{H}$-C=C-H), 6.84 (1H,d,J=11 c.p.s., $\underline{H}$-C=C-H).

A sample was evaporatively distilled at 65-68° and 2 mm for analysis.

Anal. Calcd. for $C_{14}H_{18}O_2$ (218.3): C, 77.03; H, 8.31.

Found: C, 76.81; H, 8.38.

Chromic Acid - Acetic Acid Oxidation of Hydroxyketone 54a

The procedure described by Barton and Lindsey[115] was followed. A solution of 1.6 g (5.4 mmoles) of hydroxyketone 54a in 16 ml of glacial acetic acid was added to a solution of 1.0 g (10 mmoles) of chromium trioxide in 1 ml of water and 2 ml of glacial acetic acid at room temperature. The color changed immediately to dark brown. After 16 h the reaction mixture was worked up to give 1.50 g (95%) of a colorless liquid which solidified on keeping in the refrigerator. Two recrystallizations from petroleum ether (30-60°) gave 900 mg (60%) of colorless crystals of 55, m.p. 50-51°, [lit (115): m.p. 51-52°, $[\alpha]_D$ -173° (c, 1.09)], depressed on admixture with 62.

Infrared spectrum: $\nu_{max}^{CS_2}$ 1700 cm^{-1} (6-membered C=O).

Selenium Dioxide Oxidation of Diketone 55

The procedure of Barton and Lindsey[115] was repeated. A solution containing 595 mg (2.73 mmoles) of diketone 55 and 150 mg (1.37 mmoles) of selenium dioxide in 15 ml of glacial acetic acid was refluxed for 1 h. The cooled reaction mixture on workup gave 585 mg (100%) of a yellow oil whose t.l.c. behaviour was identical with that of the crude product obtained by selenium dioxide oxidation of diketone 62 on page 203 . Thus the crude product showed two spots, one bright yellow spot and the other predominating spot visible only under u.v. lamp. A small portion (115 mg) of crude sample was distilled evaporatively at 60° and 1 mm to give 85 mg of enedione 56 as a yellow liquid (t.l.c. single spot). A sample was evaporatively distilled for optical rotation and spectral measurements, $[\alpha]_D^{19}$ -291° (c, 1.58).

Ultraviolet spectrum: λ_{max}^{EtOH} 224 mμ(ε12,970), 370 mμ(ε33), [lit (115): m.p. 47-48°, $[\alpha]_D$ -297° (c, 1.32), λ_{max}^{EtOH} 221 mμ (ε14,700), 367 mμ(100), 369 mμ(ε100)].

Infrared spectrum: $\nu_{max}^{CS_2}$ 1670 cm^{-1} (enedione), 1610 cm^{-1} (C=C).

N.m.r. spectrum: 0.93 (3H,s,gem-CH_3), 1.09 (3H,s,gem-CH_3), 1.13 (3H, s,CH_3-C-), 6.53 (1H,d,J=10 c.p.s.,H-C=C-H), 6.83 (1H,d,J=10 c.p.s.,H-C=C-H).

Attempted Base Catalysed Isomerisation of Hydroxyketone 64

A solution of 47 mg (0.20 mmole) of the hydroxyketone 64 in 5 ml of methanol containing 1 g of potassium hydroxide pellets was refluxed for 12 h. The reaction mixture was cooled,diluted with water and

extracted with ether. The combined ether extracts were washed with water and evaporation of the dried solution left 42 mg (88%) of recovered starting material 64. The infrared and n.m.r. spectra and t.l.c. behaviour were all identical with those of the starting material.

Irradiation of Tricyclic Hydroxyketone 54a

A solution of 530 mg (2.38 mmoles) of pure 54a in 18 ml of thiophene-free benzene previously bubbled with nitrogen for 3 minutes was irradiated in a quartz cell* with an 85 W Hanovia, C-H-3, quartz u.v. lamp for 17 h (distance between the lamp and cell 30 cm). The pale yellow solution was then evaporated to leave 530 mg (100%) of a colorless solid. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) indicated only two major spots, one less polar R_f 0.55, and the other corresponding to starting material, R_f 0.35. The crude solid product was dissolved in 50 ml of 10% methanolic potassium hydroxide solution containing 25 ml of water and extracted with three portions of ether. The combined ethereal extracts were washed with water and evaporated to leave 300 mg (56%) of recovered hydroxyketone 54a (single spot in t.l.c.). The aqueous alkaline solution was acidified with 20% hydrochloric acid and the resulting acidic solution (pH 2) was extracted with three portions of ether. The combined ether washings were washed with water, 10% aqueous sodium bicarbonate and finally water. Evaporation of the dried solution yielded 170 mg of a colorless solid which showed a single spot in t.l.c. The n.m.r. spectrum of the crude lactonic product was clean and showed only one

* The yield of lactone was very low when a Pyrex cell was used for irradiation.

compound. Two recrystallizations from petroleum ether gave 100 mg of analytically pure lactone 68, m.p. 93.5-94.5°, $[\alpha]_D^{21}$ -62° (c, 3.08).

Infrared spectrum: $\nu_{max}^{CS_2}$ 1770 cm^{-1} (γ -lactone C=0).

N.m.r. spectrum: 0.88 (6H,s,gem-diMe), 1.17 (3H,s,CH_3-C-), 4.26 (1H,dd J=9 c.p.s.,H-C-0).

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 75.22; H,10.18.

ORD: (c, 0.80) $[\phi]_{450}$ -86°, $[\phi]_{350}$ -162°, $[\phi]_{250}$ -287°.

Irradiation of Tricyclic Hydroxyketone 61a

A solution of 300 mg (1.35 mmoles) of pure 61a in 12 ml of thiophene free benzene previously bubbled with nitrogen for minutes was irradiated in a quartz cell with an 85 W, Hanovia, C-H-3, quartz u.v. lamp for 23 h (distance between lamp and cell 30 cm). The solvent was evaporated to leave 300 mg (100%) of a liquid which showed a single spot, R_f 0.85, that was different from the starting material on t.l.c. in ethyl acetate - petroleum ether (65:35). The infrared spectrum did not reveal peaks due to OH or 6-membered ketone.

A portion (150 mg) of the crude liquid was dissolved in 50 ml of 10% methanolic potassium hydroxide containing 25 ml of water and worked up as described in the previous experiment to give 100 mg of lactone 67 as a liquid. Thin-layer chromatography revealed a single major spot, R_f 0.65, that was different from the starting material, R_f 0.45, and with a trace of polar spot at the origin (possibly the corresponding hydroxy acid). The neutral portion obtained, 20 mg, showed in t.l.c., one major spot R_f 0.65 one less polar spot, R_f 0.85, and a spot at the origin; there was no spot corresponding to starting

material. The neutral portion was not investigated further. A small portion of the lactonic sample was evaporatively distilled at 90-95° and 0.4 mm for analysis and spectral measurements. The distilled sample showed only one spot, R_f 0.65, in t.l.c.; $[\alpha]_D^{18}$ + 5.8° (c, 3.11).

Infrared spectrum: $\nu_{max}^{CS_2}$ 1775 cm^{-1} (γ-lactone C=O).

N.m.r. spectrum: 0.90 (6H,s,gem-diMe), 1.17 (3H,s,$\underline{CH_3}$-C-), 4.72 (1H, dd,J=8 c.p.s.,H-C-O).

Anal. Calcd.for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 75.76; H,10.01.

ORD: (c, 1.99), $[\phi]_{450}$ + 10°, $[\phi]_{350}$ + 12° $[\phi]_{250}$ -110°.

Isocaryophyllene Keto Epoxide-a 13a

To a vigorously stirred (magnetic bar) solution of 1.01 g (4.5 mmoles) of isocaryophyllene oxide-a 14a and 0.3 ml of water in 25 ml of acetone was added in portions 2.5 g of powdered potassium permanganate over a period of 16 h. The reaction mixture was filtered through a sintered-glass funnel and the colorless filtrate was evaporated to leave 900 mg of oily product. Thin-layer chromatographic examination of the crude product in ethyl acetate - petroleum ether (65:35) revealed a faint spot, R_f 0.65 (plum colored), corresponding to the starting material 14a, a spot, R_f 0.55 (mauve) corresponding to the keto epoxide 13a, a third spot (R_f 0.10) corresponding to the 130° glycol 19a, and a faint spot, R_f 0.30. The n.m.r. spectrum showed the crude product to consist mainly of 13a and 19a in an approximate ratio of 80:20.

A solution of 50 mg of the crude product in 2 ml of methanol, was treated with an aqueous solution of 100 mg of sodium metaperiodate

in 2 ml of water. After 8 h, the reaction mixture was worked up as described in page 148 to give 12 mg* of a solid whose thin-layer behaviour was identical with that of the starting material.

The crude product was chromatographed on 24 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with the same solvent gave 580 mg (64%) of an oil whose n.m.r. and infrared spectra and t.l.c. behaviour were identical with those of an authentic specimen of keto epoxide 13a. Further elution of the column with chloroform - benzene (75:25) gave 255 mg (28%) of a white solid. Thin-layer chromatography and the n.m.r. spectrum showed this fraction to contain mainly the 130° glycol 19a and some keto epoxide 13a. One recrystallization from petroleum ether furnished 155 mg (17%) of 19a as a colorless crystalline solid, m.p. 128-129°. No depression in melting point was observed on admixture with authentic specimen of 19a from the osmium tetroxide reaction. The mother liquor left from crystallization was shown by its n.m.r. spectrum to contain mainly 19a and 13a with the former predominating.

Base-Catalysed Isomerisation of Isocaryophyllene Keto Epoxide 13a

(a) Methanol-Potassium Hydroxide

A solution of 200 mg (0.90 mmole) of keto epoxide-a 13a in 5 ml of methanol containing 1.0 g of potassium hydroxide was refluxed on a steam bath for 5.5 h. The reaction mixture was cooled and processed as described in page 159 to yield 180 mg (90%) of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (65:35) revealed at least nine spots and was not investigated further. The

* The low yield is due to loss during manipulation.

n.m.r. spectrum of the crude product revealed peaks due to methoxyl groups.

(b) t-Butyl Alcohol - Potassium Hydroxide

A solution of 1.21 g (5.4 mmoles) of keto epoxide-a 13a in 18 ml of t-butyl alcohol containing 3.5 g of potassium hydroxide and 1 ml of water was refluxed over a steam bath for 70 h. The reaction mixture was cooled, diluted with water and extracted with ether. The combined ether extracts were washed with water and evaporated to leave 1.17 g (98%) of oily product. Thin-layer chromatography in chloroform - methanol (90:10) revealed four spots, R_f 0.90 (mauve), corresponding to starting keto epoxide 13a, two more polar spots, R_f 0.80 and 0.70, and a fourth very faint spot. The crude product was chromatographed on 30 g of Woelm neutral alumina (activity IV) packed in petroleum ether. Elution with petroleum ether gave 135 mg (12%) of unreacted starting material 13a (t.l.c.). Further elution with petroleum ether - benzene (25:75) gave 790 mg (68%) of an oil which solidified on cooling in the refrigerator. Recrystallization from petroleum ether gave 45 mg (5%) of 70 as a colorless crystalline solid, m.p. 129-130°, unchanged on further recrystallization, $[\alpha]_D^{17}$ -44° (c, 2.29).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3600 cm^{-1} (free OH), 3480 cm^{-1} (bonded OH), 1708 cm^{-1} (6-membered C=O).

N.m.r. spectrum: 0.95 (3H,s,gem-CH_3), 1.05 (3H,s,gem-CH_3), 1.24 (3H, s,CH_3-C-), 2.075 (1H,s,OH), 3.95 (1H,m,H-C-O).

Anal. Calcd. for $C_{14}H_{22}O_2$ (223.3): C, 75.63; H, 9.97.

Found: C, 76.08; H,10.19.

The mother liquor left after removing the first crop was concentrated and cooled to obtain 350 mg (44%) of a white crystalline solid, m.p. 115-116°. Two recrystallizations from petroleum ether gave the hemiketal 71a as small colorless crystals, m.p. 116-117°, $[\alpha]_D^{17}$ -8.7° (c, 2.87).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3580 cm^{-1} (free OH), 3400 cm^{-1} (bonded OH) 3060 cm^{-1} and 3030 cm^{-1} (cyclopropane CH_2), 770 cm^{-1} (hemiketal linkage).

N.m.r. spectrum: 0.60 (2H,m,cyclopropane CH_2), 0.94 (3H,s,gem-CH_3), 1.18 (3H,s,gem-CH_3), 1.21 (3H,s,CH_3-C-O).

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 76.09; H,10.36.

The mother liquor left from crystallizing 71a was found to be mainly the hemiketal 71a with small amounts of 70 (t.l.c. and infrared spectrum).

A solution of 45 mg (0.20 mmole) of isocaryophyllene oxide-a 14a in 3 ml of t-butyl alcohol containing 3 drops of water and 10 pellets of potassium hydroxide was refluxed over a steam bath for 2.5 h. The reaction mixture was worked up as described on page 210 to give 43 mg of recovered oxide-a 14a. Thin-layer chromatographic behaviour of the crude product was identical with that of the starting material with no trace of other products.

Acetylation of the 117° Hemiketal 71a

(a) Room Temperature:

A solution of 80 mg (0.33 mmole) of hemiketal 71a in 1 ml of pyridine and 1 ml of acetic anhydride was allowed to stand at room

temperature for 24 h. The reaction mixture was worked up as described on page 150 to yield 78 mg of recovered 71a, m.p. 115-117°. Thin-layer chromatographic examination revealed a spot, R_f 0.55, corresponding to starting material and a trace of less polar material, R_f 0.70 (about 2%).

(b) Reflux Temperature of Pyridine:

A solution of 175 mg (0.73 mmole) of hemiketal 71a in 5 ml of pyridine and 1 ml of acetic anhydride was refluxed for 48 h. The cooled reaction mixture was worked up as described in page 150 to yield 208 mg (100%) of a liquid. Thin-layer chromatography in ethyl acetate - petroleum ether showed one major intense less polar spot, R_f 0.70, and one faint more polar spot, R_f 0.55, corresponding to starting material. The crude product was chromatographed on 5 g of Woelm neutral alumina (activity II) packed in petroleum ether. Elution with the same solvent gave 125 mg (70%) of a colorless crystalline solid m.p. 100-100.5°. The column was washed with benzene-ether mixtures to give 30 mg of recovered 71a (m.p. and mixed m.p.). One recrystallization of the crude acetate from petroleum ether gave colorless needles of 71b, m.p. 100-100.5°, $[\alpha]_D^{17}$ -93° (c, 2.00).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3015 cm^{-1} and 3000 cm^{-1} (cyclopropane $\underline{CH_2}$), 1735 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.58 (2H,m,cyclopropane $\underline{CH_2}$), 0.908 (3H,s,gem-$\underline{CH_3}$), 1.14 (3H,s,gem-$\underline{CH_3}$), 1.26 (3H,s,$\underline{CH_3}$-C-), 1.99 (3H,s,$\underline{CH_3}$-C=O).

Anal. Calcd. for $C_{16}H_{24}O_3$ (264.4): C, 72.69; H, 9.15.

Found: C, 73.14; H, 9.53.

Chromic Acid - Pyridine Oxidation of Hydroxy Ketone 70

A solution of 11 mg (0.049 mmole) of hydroxy ketone 70 in 0.5 ml of pyridine was added to an orange complex of chromium trioxide (25 mg; 0.25 mmole) in 1 ml of pyridine. The color changed immediately to dark brown. After 24 h, the reaction mixture was diluted with methylene chloride and worked up as described on page 151 to give 7 mg of an oil which solidified on cooling. One recrystallization from petroleum ether gave a colorless solid m.p. 50-52°, undepressed on admixture with an authentic specimen of 55, obtained from chromic acid oxidation of 54a. Thin-layer chromatography behaviour of the diketone obtained above was identical with that of an authentic specimen of 55.

Isocaryophyllene Keto Epoxide-b 13b

The oxide-b 14b used in this experiment contained about 25% of oxide-a 14a (n.m.r.). To a vigorously stirred solution of 10.00 g (45.5 mmoles) of oxide-b and 1 ml of water in 100 ml of acetone was added in small portions 20 g of powdered potassium permanganate over a period of 48 h. The reaction mixture was filtered through a sintered-glass funnel and the colorless filtrate was evaporated to leave 5.94 g of dark colored oily product. Thin-layer chromatographic examination of the crude product revealed a very faint spot, R_f 0.90 (mauve), corresponding to starting material, a major pinkish brown spot, R_f 0.80, corresponding to keto epoxides 13a and 13b, a faint spot, R_f 0.20 (pinkish grey), corresponding to the 130° glycol 19a and a faint spot at the origin. There was no spot corresponding to the 195° glycol 24. The crude product was chromatographed on 150

g of Woelm neutral alumina (activity IV). Elution with petroleum ether gave 5.55 g of a liquid which solidified on cooling. Thin-layer chromatography revealed it to be mainly keto epoxides 13a and 13b with a small amount of starting material. Three recrystallizations from petroleum ether (30-60°) gave 2.8 g of crystalline keto epoxide-b 13b, m.p. 77-78° [lit. (101): m.p. 78-79°].

Base-Catalysed Isomerisation of Isocaryophyllene Keto Oxide-b, 13b

(a) Methanol - potassium hydroxide

A solution of 715 mg (3.20 mmole) of pure keto oxide-b 13b, m.p. 77-78°, in 30 ml of methanol containing 6 g of potassium hydroxide pellets was refluxed on a steam bath for 24 h. The reaction mixture was cooled, diluted with water and extracted with ether. The combined ether extracts were washed with water and evaporated to leave 720 mg of a colorless oil. Thin-layer chromatography in ethyl acetate - petroleum ether (35:65) revealed only two distinct spots, R_f 0.35 and 0.45, different from the starting material, R_f 0.40. There was also a very faint (about 2%) polar spot with R_f 0.20, corresponding to 54a, obtained from oxidoketone 4. The crude oil was chromatographed on 20 g of Woelm neutral alumina (activity III) packed in petroleum ether. Elution with petroleum ether gave 500 mg (69%) of a colorless oil 77a which showed a single spot in t.l.c., $[\alpha]_D^{18}$ -35.5° (c, 3.72).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3580 cm^{-1} (free OH), 3440 cm^{-1} (bonded OH), 3040 cm^{-1} and 3070 cm^{-1} (cyclopropane $\underline{CH}_2$), 770 cm^{-1} (hemiketal linkage).

N.m.r. spectrum: 0.53 (2H,m,cyclopropane $\underline{CH}_2$), 1.07 (3H,s,gem-$\underline{CH}_3$), 1.15 (3H,s,gem-$\underline{CH}_3$), 1.25 (3H,s,$\underline{CH}_3$-C-O), 2.45

(1H,bs,OH), 2.93 (1H,q,cyclopropane CH).

A sample was evaporatively distilled at 60-65° and 0.1 mm for analysis.

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 75.22; H,10.14.

Further elution with benzene gave 185 mg (25%) of 76a as a colorless solid which showed a single spot in t.l.c. Two recrystallizations from petroleum ether gave an analytical specimen of 76a, m.p. 131-132°, $[\alpha]_D^{20}$ + 71.5° (c, 2.13).

Ultraviolet spectrum: λ_{max}^{EtOH} 280 mμ (ε147).

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 3580 cm^{-1} (free OH), 3440 cm^{-1} (bonded OH), 1685 cm^{-1} (C=O conjugated with cyclopropane).

N.m.r. spectrum: 0.75 (2H,m,cyclopropane CH_2), 0.95 (3H,s,gem-CH_3), 1.04 (3H,s,gem-CH_3), 1.26 (3H,s,CH_3-C-O), 3.19 (1H,m,cyclopropane CH).

Anal. Calcd. for $C_{14}H_{22}O_2$ (222.3): C, 75.63; H, 9.97.

Found: C, 75.40; H, 9.88.

(b) t-Butyl alcohol - potassium hydroxide

A solution of 111 mg (0.50 mmole) of keto epoxide-b 13b in 5 ml of t-butyl alcohol containing 0.5 ml of water and 1 g of potassium hydroxide pellets was refluxed for 14 h. The reaction mixture was processed as described in page 210 to give 110 mg of an oily product. Thin-layer chromatographic examination revealed only two spots identical in R_f with the crude product obtained in the methanol - potassium hydroxide reaction. The crude product was chromatographed as described in the previous experiment to give 65 mg of 77a as a colorless oil and 28 mg of 76a as a colorless crystalline m.p. 130-132° unde-

pressed on admixture with a sample of 76a obtained in the previous experiment.

Acetylation of Hemiketal 77a

a) Room temperature

A solution of 57 mg (0.26 mmole) of 77a in 1 ml of pyridine and 1 ml of acetic anhydride was left at room temperature for 24 h. The reaction mixture was worked up as described on page 150 to give 56 mg of recovered 77a. The infrared spectrum and t.l.c. behaviour were identical with that of the starting material.

b) Reflux temperature of pyridine:

A solution of 200 mg (0.90 mmole) of 77a in 5 ml of pyridine and 1 ml of acetic anhydride was refluxed for 48 h. The reaction mixture was cooled and worked up as described in page 150 to give 200 mg (84%) of liquid which solidified to a brown mass on cooling in the refrigerator. Thin-layer chromatography in ethyl acetate - petroleum ether (35:65) showed one less polar intense spot, R_f 0.75, and a faint spot, R_f 0.55, corresponding to starting material. Two recrystallizations from petroleum ether (30-60°) yielded 77b as a colorless spongy solid, m.p. 66-66.5°, $[\alpha]_D^{18}$ -23° (c, 1.27).

Infrared spectrum: $\nu_{max}^{CS_2}$ 3000 cm^{-1}, and 3030 cm^{-1} (cyclopropane CH_2), 1730 cm^{-1} (ester C=O).

N.m.r. spectrum: 0.63 (2H,m,cyclopropane CH_2), 1.07 (3H,s,gem-CH_3), 1.13 (3H,s,gem-CH_3), 1.32 (3H,s,CH_3-C-O), 2.00 (3H,s,CH_3-C=O), 3.41 (2H,m,cyclopropane CH).

Mass spectrum: m/e 265

Attempted Acetylation of Hydroxy Ketone 76a

A solution of 112 mg (0.50 mmole) of 76a in 1 ml of acetic anhydride and 1 ml of pyridine was left at room temperature for 24 h. The reaction mixture was worked up as described in page 150 to give 110 mg of recovered starting material. The infrared spectrum of the crude product had no trace of carbonyl absorption. T.l.c. did not reveal any less polar spot.

Base-Catalysed Isomerisation of Hydroxy Ketone 76a to Hemiketal 77a

A solution of 111 mg (0.50 mmole) of pure hydroxy ketone 76a in 7 ml of methanol containing 1.3 g of potassium hydroxide pellets was refluxed for 43 h. The reaction mixture was cooled, diluted with water and extracted with ether. The combined ethereal washings were washed with water, dried and evaporated to leave 105 mg (95%) of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (35:65) showed only two spots, one corresponding to hemiketal 77a and the other corresponding to starting material 76a. The crude oil was chromatographed on 7 g of Woelm neutral alumina (activity III) packed in petroleum ether. Elution with the same solvent gave 70 mg (66%) of hemiketal 77a an oil whose n.m.r. and infrared spectra were identical with those of an authentic specimen of 77a. Further elution with benzene - ether mixtures gave 28 mg (27%) of recovered 76a, m.p. 129-131°, undepressed on admixture with starting material.

Base-Catalysed Isomerisation of Hemiketal 77a

A solution of 78 mg (0.35 mmole) of pure hemiketal 77a in 5 ml of methanol containing 1.0 g of potassium hydroxide pellets was refluxed

for 45 h. The reaction was worked up as described in the previous experiment to give 73 mg (94%) of an oil. Thin-layer chromatography in ethyl acetate - petroleum ether (35:65) showed only two spots, one corresponding to starting material 77a, and the other corresponding to hydroxy ketone 76a. The crude product was chromatographed on 5 g of Woelm neutral alumina (activity III) packed in petroleum ether. Elution with the same solvent gave 48 mg (66%) of recovered hemiketal 77a (n.m.r. and infrared spectra). Further elution with benzene - ether mixture gave 21 mg (29%) of hydroxyketone 76a, m.p. 128-130°, undepressed on admixture with an authentic specimen of 76a.

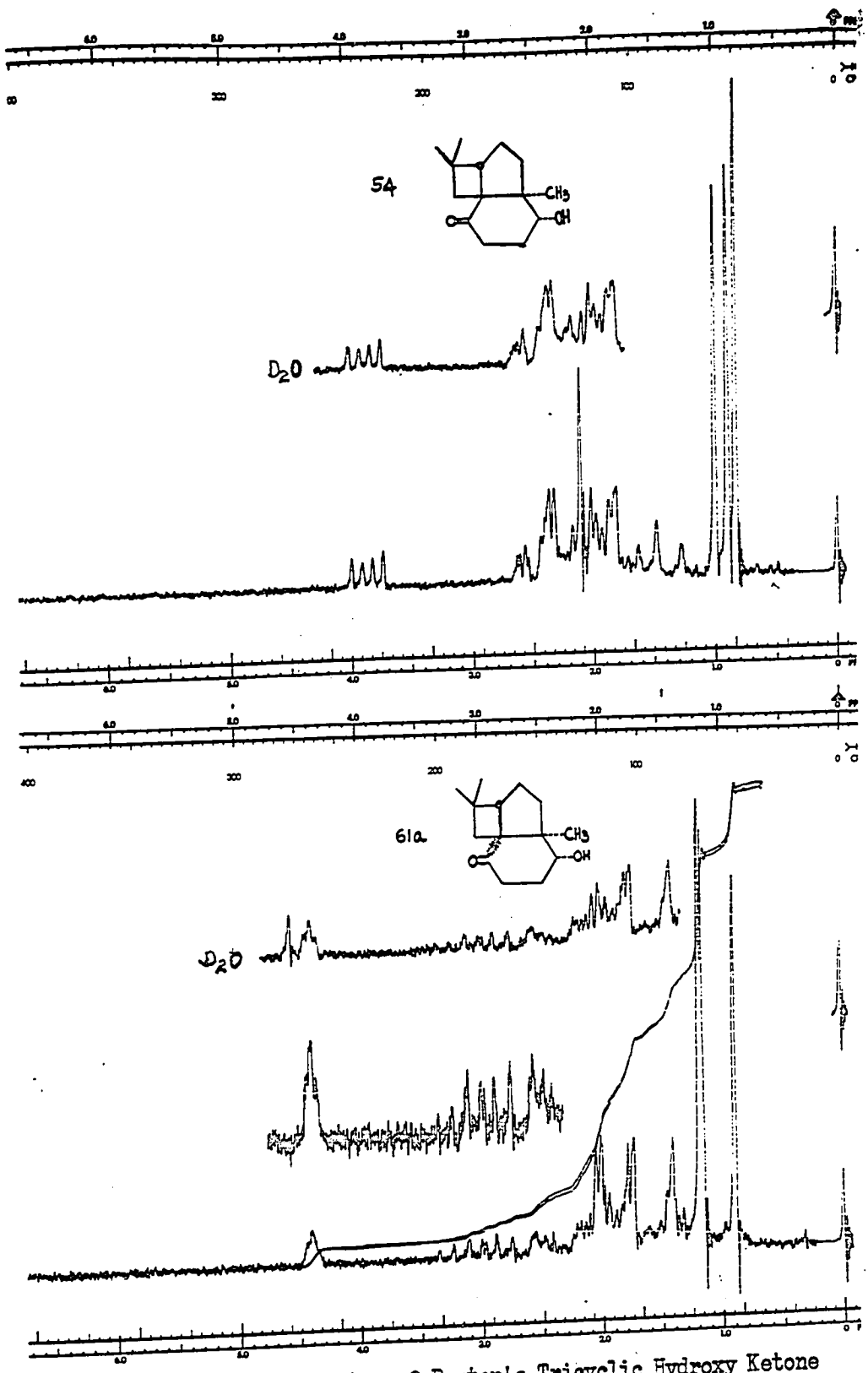


Plate XIII. N.M.R. Spectra of Barton's Tricyclic Hydroxy Ketone 54 and tricyclic Hydroxy Ketone 61a.

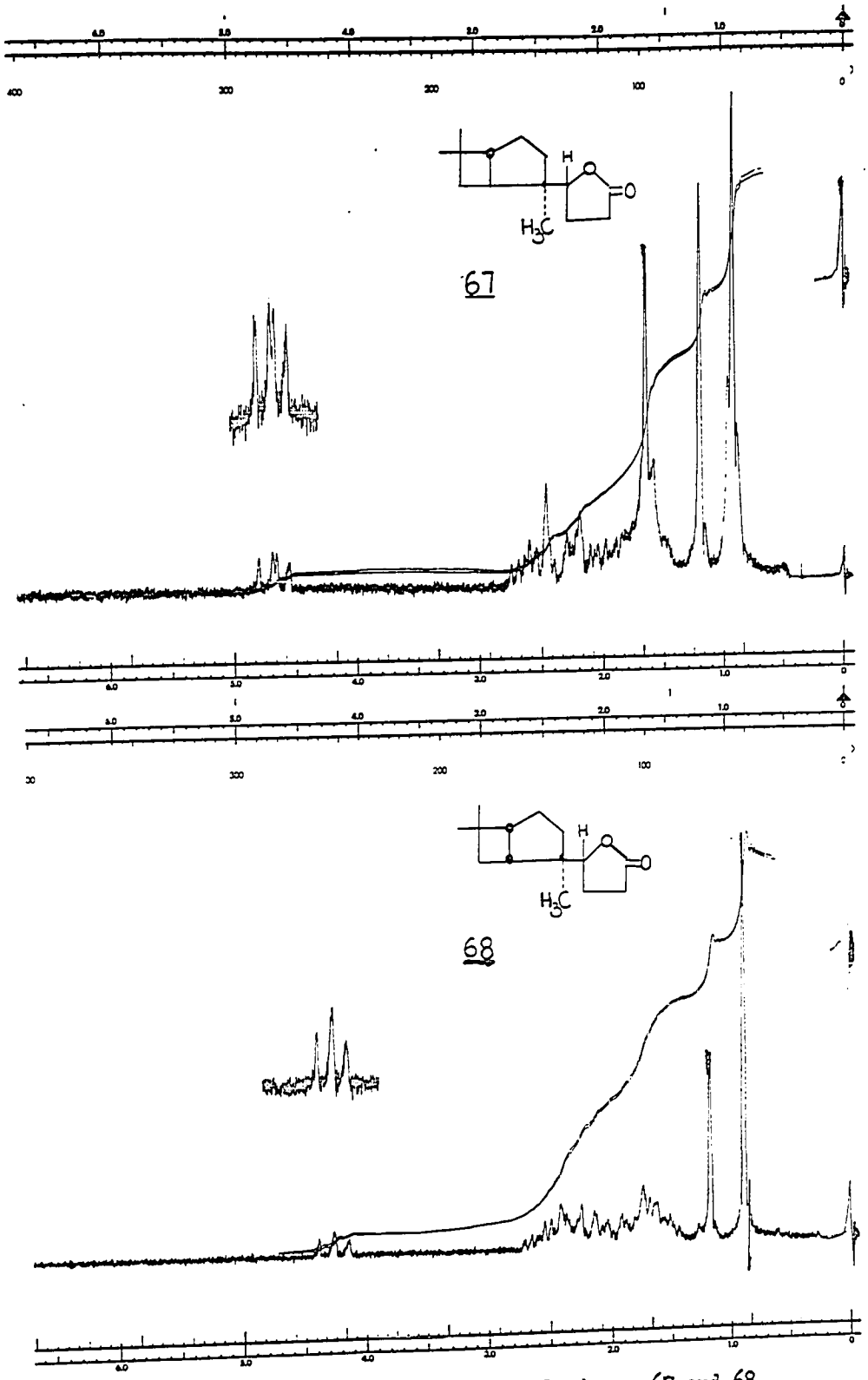


Plate XIV. N.M.R. Spectra of Photolactones 67 and 68.

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