THE ABSOLUTE CONFIGURATIONS OF VICINAL DIOLS

A THESIS

PRESENTED FOR THE DEGREE

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MASTER OF SCIENCE

in

THE UNIVERSITY OF ADELAIDE

by

THUANTHONG PIPITHAKUL (B.Sc.)

Department of Organic Chemistry

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CONTENTS

SUMMARY

Some optically active vicinal diols of known absolute configurations were synthesised. The application of Horeau's method for the determination of the absolute configurations of these diols were found to be valid.

The method has been used to determine the absolute configuration of alternifolenediol of previously unknown configuration.

Preliminary studies for the conversion of 3-ethylidene-2,2,4,4-tetramethylcyclobutanol, a chiral molecule, into a vicinal diol by stereo-chemically defined processes is reported.

ACKNOWLEDGEMENTS

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My deep sincere thanks go to my wife, Nimnual, who has accompanied me and made the last two years so pleasant, and to my parents and parents-in-law for their undying patience and generousity in taking care of our children while Nimnual was accompanying me.

This research was carried out during the tenure of a Colombo Plan Scholarship, which I gratefully acknowledge.

STATEMENT

The work described in the thesis incorporates no materials previously submitted for a degree in any University, and to the best of my knowledge and belief, the thesis contains no materials previously published or written by another person, except where due reference has been made.

T. Pipithakul.

PUBLICATION

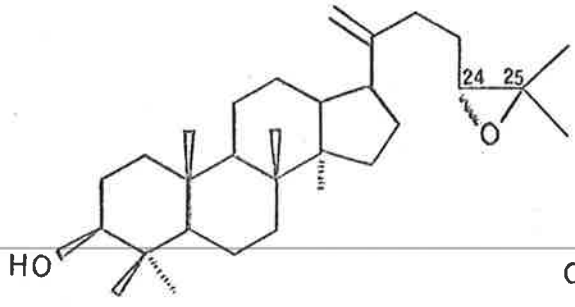
A manuscript of a part of the work described in this thesis has been accepted for publication:

"The Absolute Configuration of Some Vicinal Diols"
D.P.G. Hamon, R.A. Massy-Westropp and T. Pipithakul,
Aust. J. Chem., in press.

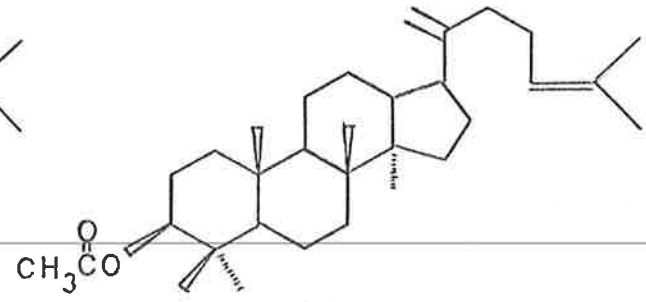
PART I

INTRODUCTION

In 1964 Shiengthong[1] reported the isolation of a tetracyclic triterpene, aglaiol, from the leaves of Aglaia odorata Lour., a medicinal tree in Thailand. Spectroscopic data and the interconversion with a known triterpene, dammaradienyl acetate (2), led to the assignment of the structure (1) for aglaiol[1]. Two related triols, epimeric at C_{24}, have also been isolated[2] from the same plant, and their structures shown to be (3). It was found[2] that opening of the epoxide ring in aglaiol under acidic condition gave one of the isomeric triols. However, the absolute configuration at C_{24} was unknown.



(1)



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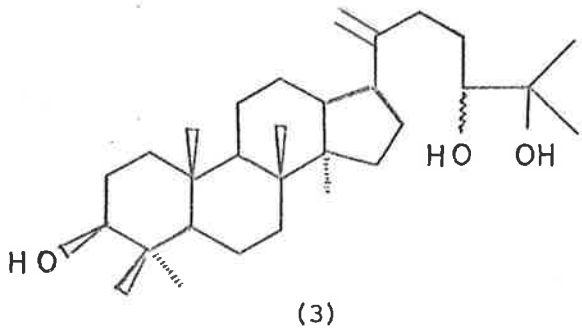
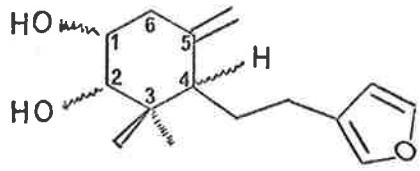


(3)

Another naturally occurring diol of unknown absolute configuration is alternifolenediol (4)[3], a β-furanosesquiterpene. It was extracted from the wood oil of Eremophila alternifolia, which grows in the arid region of Australia.



(4)

The two hydroxyl groups in alternifolenediol were found to be trans-diequatorial (from n.m.r. spectra)[4], but the one adjacent to the geminal-dimethyl groups would be expected to be considerably more shielded and, therefore, react less rapidly than the other. It was known[4] that acetylation of (4) under mild condition gave the diacetate, the C1-monoacetate and the C2-monoacetate in 41, 36 and 4% yields, respectively. The formation of the diacetate and the C2-monoacetate was probably via the intramolecular transfer of an acyl group from the C1-monoacetate to the C2-position, followed by further acylation at the C1-position.

In the triols (3) (after protection of the C3-hydroxyl group) the C24-secondary hydroxyl group would be expected to react more rapidly than the C25-tertiary hydroxyl group.

It was hoped that the absolute configuration of vicinal diols, such as those described above, in which one hydroxyl group would be expected to react more rapidly than the other, could be established by the application of Horeau's method[5,6].

Horeau's method for the determination of the absolute configurations of secondary alcohols involves a kinetic resolution of racemic 2-phenylbutyric anhydride by the chiral secondary alcohols. In practice, the excess anhydride is hydrolysed and the net rotation of the resulting acid is measured. An empirical relationship has been established[5,6] whereby it is observed that if the rotation of the resulting acid is dextrorotatory the absolute configuration of the secondary alcohol is that shown in Figure 1, and if it is levorotatory the alcohol has the configuration shown in Figure 2, where L is larger than M (based on steric considerations).

The method is very sensitive to steric differences and is widely used to determine the absolute configurations of secondary alcohols[5-9]. The sensitivity of the procedure was illustrated by its application to a series of deuterated primary alcohols where the rotation values enabled the configurations to be determined[10,11].

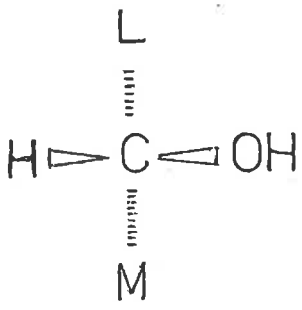


Figure 1

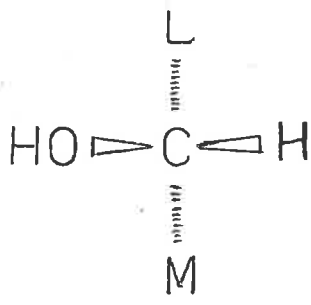


Figure 2

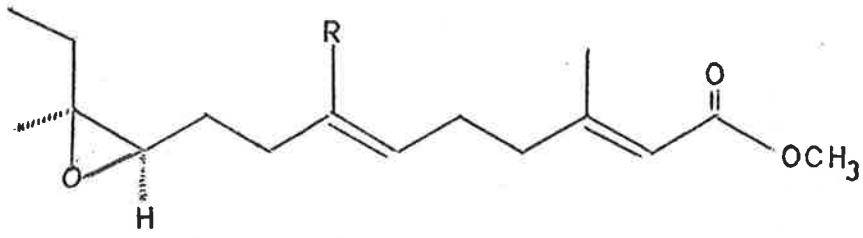
By the use of optically active 2-phenylbutyric anhydride, the method was also employed for the partial resolution of some racemic secondary alcohols and to determine the absolute configurations of the isolated optically active isomers[12].

When this work was commenced no study had been reported on the application of the method to vicinal diols. It was of interest therefore, to determine whether or not an adjacent polar substituent such as an hydroxyl group would alter the empirical relationship developed by Horeau. Thus, it was decided to investigate the validity of the method with some acyclic and cyclic vicinal diols of known absolute configurations before it was applied to diols of unknown configurations.

It is necessary with vicinal diols to be able to predict or establish which one of the two hydroxyl groups undergoes esterification preferentially. It is reasonable to assume that a secondary hydroxyl group is esterified more rapidly than a tertiary one, and that in diols where both hydroxyl groups are secondary the less hindered one will react more rapidly.

Soon after the present work began Meyer[13] reported the application of Horeau's method for the determination of the absolute configuration of an optically active diol derived from the Cecropia hormone (5). Since only small quantities of the hormone were available, micromethods were developed to chemically cleave the epoxide ring of the hormone to give a small amount of the corresponding diol. This was then subjected to Horeau's method, and the absolute configuration was assigned as (10R, 11S). Although no attempt was made to establish the validity of the empirical steric relationship in the presence of an adjacent hydroxyl group by the use of model compounds, the result nevertheless agrees with that determined for the hormone by direct synthesis using resolved intermediates[14], and by circular dichroism studies[15].

Part I of this thesis consists of three sections. Firstly, a number of vicinal diols were synthesised from compounds of known configurations. Acyclic diols were synthesised from (-)-(S)-ethyl



(5), R = CH_3

lactate[16] and cyclic diols were derived from (+) and (-)-α-pinenes. Secondly, Horeau's method was applied to these diols to establish the validity of the procedure. Finally, the method was used to determine the absolute configuration of alternifolenediol.

Part II describes preliminary studies from which it was hoped that Horeau's method might be used to determine the absolute configuration of a vicinal diol derived from racemic 3-ethylidene-2,2,4,4-tetramethylcyclobutanol[17]. This would enable the assignment of the absolute configuration of a chiral isomer of 3- ethylidene-2,2,4,4-tetramethylcyclobutanol, if the vicinal diol was derived by stereochemically defined reactions.

RESULTS AND DISCUSSION

Synthesis of Optically Active Acyclic Vicinal Diols

The synthesis of some optically active vicinal diols of the type $R_2COH-CHOH-CH_3$, where R was methyl, ethyl, isopropyl, tert-butyl and phenyl, has been described by Thaker and Vasi[18], from the direct reaction of (-)-ethyl lactate (6) and various Grignard reagents. The yields of the diols reported by these authors were between 22 and 32%, and the physical properties of some diols appeared to be vague. In order to improve the yield and the purity of the diols it was decided to use ethyl 2-benzyloxypropionate (7)[19]. This would overcome the problem of salt formation during the Grignard reactions[20], and also the difficulties encountered in the recovery of the water soluble diols.

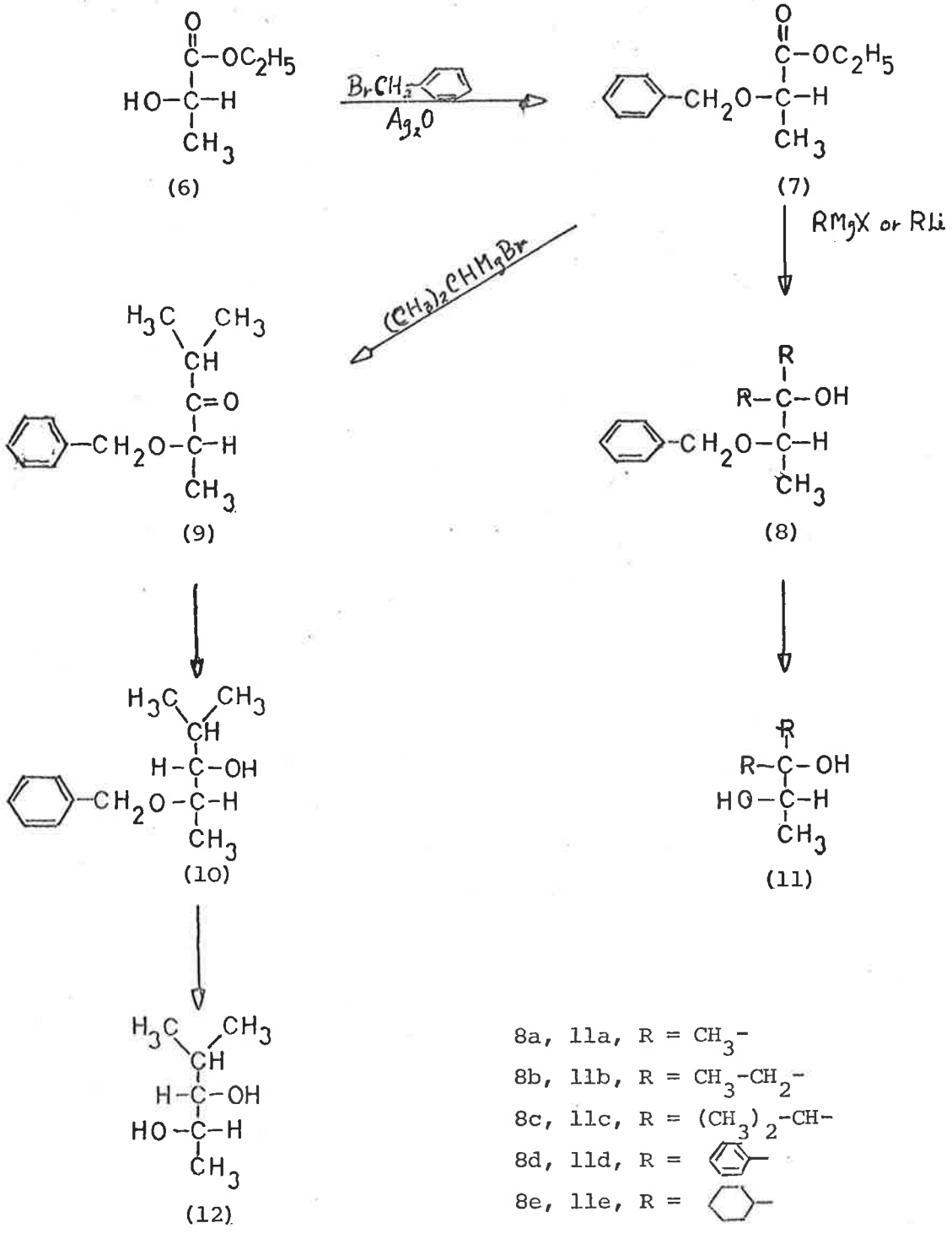
It has been established[19] that benzylation of (-) methyl lactate and subsequent hydrogenolysis of the ether do not affect the configuration of the resulting alcohol. Thus, (-)-(S)-ethyl lactate (6)[16] was converted into (+)-(S)-ethyl 2-benzylpropionate (7) with benzyl bromide in the presence of silver oxide[21] following the procedure described by Mislow et al.[19] The pure benzyl ether was obtained in 47% yield, and was found to be free from the starting ester by g.l.c. analysis.

Several Grignard reagents were then added in excess to the intermediate ester (7) to give the corresponding tertiary alcohols (8a, 8b, 8d, 8e),where R is methyl, ethyl, phenyl and cyclohexyl groups. For the preparation of (8c), where R is the isopropyl group, isopropyllithium in light petroleum ether (b.p. 28-35°)[22] was used instead of isopropylmagnesium bromide. The use of the latter reagent led to the reduction[23] of the intermediate ketone (9) to give 2-benzyloxy-3-hydroxy-4-methylpentane (10). An attempt to add tert- butylmagnesium bromide to (6) was unsuccessful, probably because of the much greater steric effects[24].

Hydrogenolysis of (8a-8e) at room temperature and pressure in the presence of 5% Pd-C catalyst gave the corresponding diols (11a-11e) in high yields. When acid was used in some preliminary hydrogenolysis experiments (small amounts of dilute hydrochloric acid were sometimes added)[19] problems were encountered due to acid - catalysed side reactions. It was found that hydrogenolysis of the compounds (8a-8e) proceeded smoothly without the addition of the acid. The transformations of the ester (6) to the diols (11a-11e) are shown in Diagram 1.

Reduction of ketones with Grignard reagents is a well established reaction[28]. This reaction occurs when the R group of the reagent has a hydrogen atom on the β-carbon atom. The reaction

Diagram 1.



8a, 11a, R = CH_3-

8b, 11b, R = CH_3-CH_2-

8c, 11c, R = $(CH_3)_2$-CH-

8d, 11d, R =

8e, 11e, R =

is envisaged to proceed via the transfer of the β-hydrogen atom as a hydride ion to the carbonyl group[25].

The structure of (10) was confirmed by the infrared and the n.m.r. spectra, and by hydrogenolysis to give the corresponding diol (12). The five proton resonance at δ 7.3 is due to the aromatic protons. The AB quartet of the benzylic protons (see page 12) have almost the same chemical shifts so that the peaks which centred at δ 4.53 due to these protons are broadened. The complex multiplets (two protons) centred at δ 3.53 is due to the C2- and C3- protons. Integration indicated that there are only three methyl groups in the region δ 1.25-0.77.

Hydrogenolysis of the benzyl ether (10) gave the diol, whose n.m.r. and mass spectra confirm its structure as (12). The C2-proton appeared as a broad multiplet at δ 3.80 due to coupling with the adjacent methyl group protons and further coupling with the C3-proton. The C3-proton resonances consisted of a pair of doublets due to coupling with the C2- and C4-protons. Integration also indicated that there are only three methyl groups in the region δ 1.13-0.8.

The mass spectrum of the diol (12) showed the expected cleavage of the C-C bond joining the two hydroxyl groups[26]. The m/e 73 ion (base peak) and the m/e 45 ion (25%) correspond to $(CH_3)_2\text{-}CH\text{-}CH{=}OH]^{\cdot +}$ and $CH_3\text{-}CH{=}OH]^{\cdot +}$, respectively.

It should be noted that, although the alcohol (10) would be formed as a mixture of diastereoisomers, it would be expected that one isomer would predominate[27]. The predominant stereoisomer formed in the reduction of the carbonyl compounds, SML$\overset{*}{C}$COR, can be predicted by the use of Cram's rule[28]. The rule states that when the asymmetric carbon atom ($\overset{*}{C}$) is so orientated that the carbonyl function is flanked by the two smaller groups (S and M) attached to the $\overset{*}{C}$, the reagent, (e.g., organometallic reagent), preferentially approaches the carbonyl group from the side nearer the smaller group (S).

In the ketone (9), where the steric bulk of the group attached to the C2 is decreasing in the order CH_3 > O-CH_2-Ph > H, the hydride ion (H^-) would be expected to attack the carbonyl group from the side nearer H leading to the formation of the erythro-isomer of (10). Hydrogenolysis of this isomer would give the erythro-diol[29] (12). However, if the benzyl ether oxygen forms a complex with the reagent[18], then the attack would be expected from the side of the benzyloxy group, giving rise to the threo-isomer of (10). Hydrogenolysis would then give the threo-diol[29] (12). Since the diol was not required it was not further investigated.

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* denotes an asymmetric centre.

The infrared spectra of the compounds (8a-8e) included the expected aromatic bands at 3090, 3070, 3030 and about 1500 cm^{-1}. In (8a) and (8b) the hydroxyl stretching absorption band was very broad and intense between 3600 and 3300 cm^{-1} with a shoulder at about 3580 cm^{-1}. However, in (8c) and (8e) this band is fairly sharp and appeared between 3600 and 3450 cm^{-1} together with a shoulder of 3590 cm^{-1}. For the compound (8d) this peak appeared as a strong, sharp monomeric[30] band at 3560 cm^{-1}. From the characteristics of the hydroxyl absorption bands the hydrogen bonding in (8a) and (8b) can be considered to be greater than in (8c) and (8e), whereas in (8d) the band is presumably due to the free hydroxyl stretching absorption. The degree of hydrogen bonding in the compounds (8a-8e) and (11a-11e) can be rationalized by considering the likely conformations of each molecule[29,31,32].

The benzylic protons of the compounds (8a-8e) are magnetically non-equivalent[33], or - "diastereotopic"[34], because they are joined to the centre of molecular dissymmetry by the C-O-C bonds. These protons display an AB system[33] in the nuclear magnetic resonance spectra. Since the intensities of the absorption lines of the AB quartet are not equal and the δ_{AB}/J_{AB} ratio is small, the chemical shift of each proton is not simply the mid-

point between each pair of the lines. However, the chemical shifts and the chemical shift difference (δ_{AB}) can be calculated[35] and are shown in Table 1. In all examples, the coupling constant (J_{AB}) is 12 Hz, the δ_{AB}/J_{AB} ratio is ≃ 1 and the relative intensity of the lines is ≃ 5. For the compound (8d) the AB quartet overlapped with the quartet of the methine proton which centred at δ 4.48, and the chemical shifts were not calculated.

Table 1

The chemical shifts (δ) and the chemical shift differences (δ_{AB}) of the benzylic protons in (8a-8c, and 8e).

Compounds	δ_{AB} (cps)	δ_{AB}/J_{AB}	δ_A (ppm)	δ_B (ppm)
8a	12.0	1.0	4.60	4.40
8b	14.74	1.22	4.65	4.40
8c	13.42	1.12	4.60	4.37
8e	13.42	1.12	4.56	4.34

The n.m.r. spectra of (8a-8e) and (11a-11e) showed that the methine proton resonances were shifted to lower field as the sizes of the R groups increased (Table 2). This suggests that the

proton is deshielded by steric interaction of the R groups[36]. When R is the phenyl group (8d), the deshielding is comparatively large and is presumably due to a combination of steric and ring current effect of the aromatic rings[37].

Table 2

The chemical shifts* of the methine proton in (8a-8e) and (11a-11e)

	compounds 8	compounds 9
a	3.27	3.53
b	3.48	3.60
c	3.63	3.93
d	4.48	4.61
e	3.63	3.90

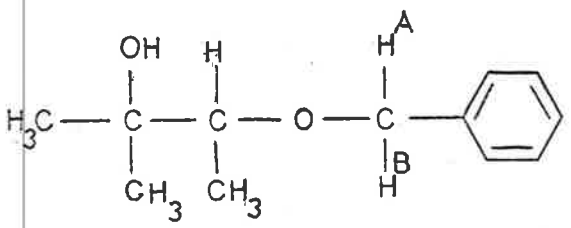
* in ppm from T.M.S. as an internal standard.

Figure 3 represents the n.m.r. spectrum of (8a), showing a typical AB system of the benzylic protons. The spectra of (8b-8e) are of similar type.

The mass spectra of (8a-8e) and (11a-11e) were determined by introducing the samples through a heated inlet system[38] and the molecular ions were not observed. The pronounced ion peak corres-

Figure 3

Spectrum of (8a)



ponding to $M^{\cdot+}$ - 135, $M^{\cdot+}$-[CH_3-CH=O-CH_2-Ph]$^{\cdot+}$, suggests that the cleavage of the C-C bond between the carbon atoms bearing hydroxyl and benzyloxy groups is the primary process[26]. This ion peak results from an α-cleavage to give the stable oxonium ion, M^+ - 135, together with the oxonium ion, m/e 135. The m/e 135 ion can readily decompose to give the more stable acylium ion, m/e 43, and the resonance stabilized tropylium ion, m/e 91. The $M^{\cdot+}$ - 135 oxonium ion undergoes further fragmentation by the loss of a hydrogen and alkyl (or phenyl) radical to give an acylium ion.

The spectra of (8a-8e) also included ion peaks corresponding to the loss of the alkyl or phenyl radicals from the molecular ions. The relatively high abundance $M^{\cdot+}$ - 135 ion in (8d) (m/e 183, base peak) is probably because the positive charge of the oxonium ion can be delocalised over the π-electron system of the two aromatic rings.

By comparison, the fragmentations of the diols (11a-11e) are more complicated. The spectra showed that the cleavage of the C-C bond between the two carbon atoms bearing the hydroxyl groups predominated over the other processes. However, the ion peaks corresponding to the loss of the hydroxyl and the alkyl radicals from the molecular ions were also seen clearly in the

spectra. The m/e values of some pronounced peaks and their relative abundances (R.A.) for the compounds (8a-8e) and (11a-11e) are tabulated in Appendix I.

The Synthesis of Pinane-2,3-diols

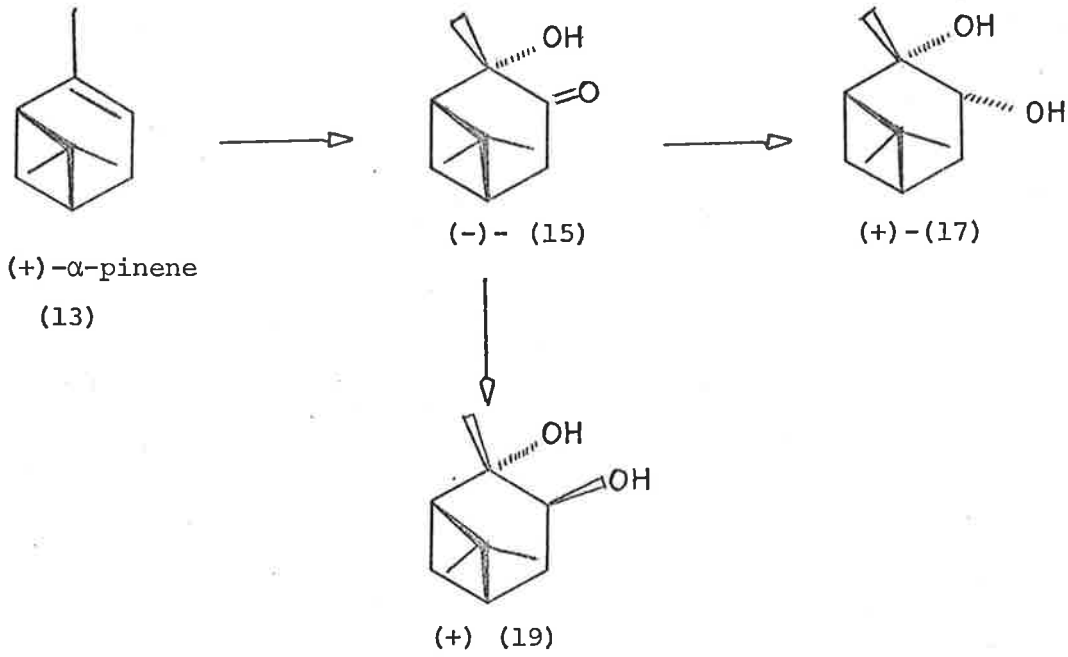
Although there is confusion about many aspects of the chemistry involving the oxidation of α - pinene it is generally agreed that oxidation with potassium permanganate in aqueous acetone solution gives a ketol, 2α-hydroxypinan-3-one, together with some other products[39-41].

Schmidt[40] reported that reduction of (-)-2α-hydroxypinan-3-one (15) obtained from the oxidation of (+) -α- pinene (13), with aluminium isopropoxide yielded (+)-cis-pinanediol (17), while reduction with lithium aluminium hydride gave (+)-trans-diol (19).

However, Suga et al[41] reported that both the (-)-cis-diol (18) and the (-)-trans-diol (20) were produced from the reduction of (+)-2α-hydroxypinan-3-one (16) with lithium aluminium hydride. The stereochemistry and configuration of the pinanediols and related compounds have been established from chemical correlations[42,43]. The transformations of α- pinene (13) to the diols (17) and (19) according to Schmidt[40] are shown in Diagram 2.

It has been reported[44] that the oxidation of alkenes with potassium permanganate gives either cis-1,2-diols or α-hydroxyketones, depending on the pH of the medium. If the reaction is carried out in alkaline solution the main product is the cis-diol, whereas if it

Diagram 2

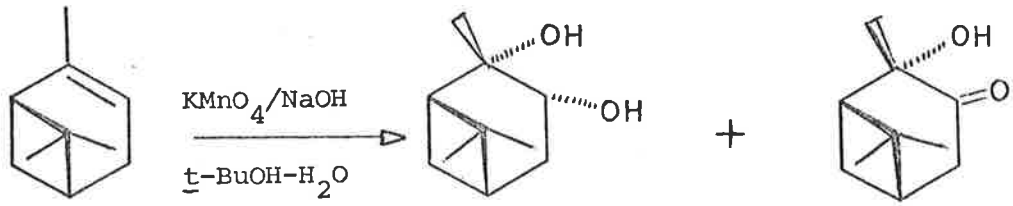


is done in acidic or neutral solution the α-hydroxyketone or related cleavage products predominates.

Wiberg and Saegebarth[44] found that hydroxylation of some olefins with alkaline potassium permanganate in tert-butyl alcohol and water had advantage over oxidation in neutral medium in improving the yields of the cis-diols, e.g. with norbornene. It was therefore decided to use these conditions to prepare the (+)- and (-)- cis-pinanediols (17) and (18), respectively.

It was found that when (+)- and (-)-α-pinenes (13) and (14) were treated under the conditions described by Wiberg and Saegebarth for norbornene[44] improved yields of (17) and (18) were obtained (Diagram 3). The 2α-hydroxypinane-3-ones (15) and (16) were also isolated as minor products. The other products from this reaction were not investigated.

Diagram 3



(+)-(13) (+)-(17) (-)-(15)

The (+)- and (-)- trans-diols (19) and (20) were prepared by the method previously described[41].

The n.m.r. spectra of the compounds (15)-(20) agree well with those reported in the literatures[45,46]. The chemical shifts

of the C8-, C9- and C10- methyl protons in these compounds are shown in Table 3. The literature values are shown in brackets.

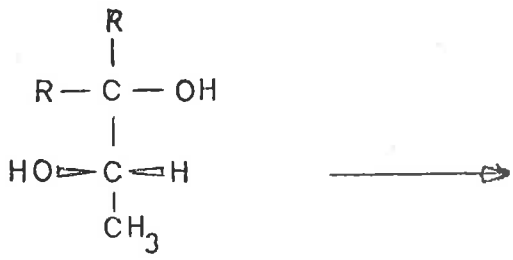
Table 3

Compounds	Chemical shifts (ppm)		
	C8	C9	C10
(15) and (16) in CCl_4	1.33 (1.38)	0.90 (0.88)	1.36 (1.39)
(17) and (18) in CCl_4	1.23 (1.23)	0.93 (0.93)	1.27 (1.26)
(19) and (20) in $CDCl_3$	1.25 (1.25)	0.95 (0.94)	1.35 (1.35)

The Application of Horeau's Method

It has been mentioned earlier that, according to Horeau's empirical relationship, the absolute configuration of optically active secondary alcohols can be deduced from the sign of the rotation of the 2-phenyl butyric acid resulting from hydrolysis of the unreacted anhydride (page 3). On the other hand, if the absolute configuration of the alcohol is known the sign of the rotation of the acid can be expected[12].

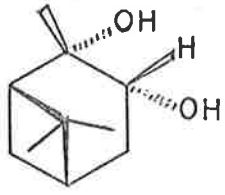
It has been established[19] that neither the benzylation of optically active methyl lactate nor the removal of the benzyl group by hydrogenolysis affects the configuration of the chiral centre. Therefore, the diols (11a-11e) have the same configuration as (-)-ethyl lactate (6), viz. the S-configuration[16]. Since this configuration corresponds to that in Figure 2 (page 4), (-)-2-phenyl-butyric acid would be expected from the application of Horeau's method.



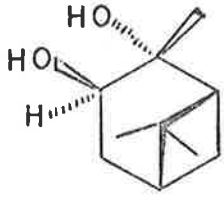
(-) - acid

(11a - 11e)

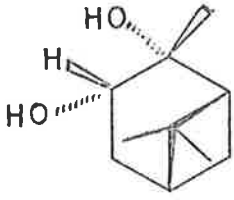
For the pinanediols (17)-(20) where the C2-moiety is larger than the C4-moiety, the (-)-acid is expected from the (-)-cis- and the (+)-trans- diols, (18) and (19), respectively, while the (+)-acid is expected from the (+)-cis- and the (-)-trans-isomers, (17) and (20), respectively.



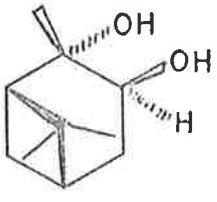
(+)-(17)



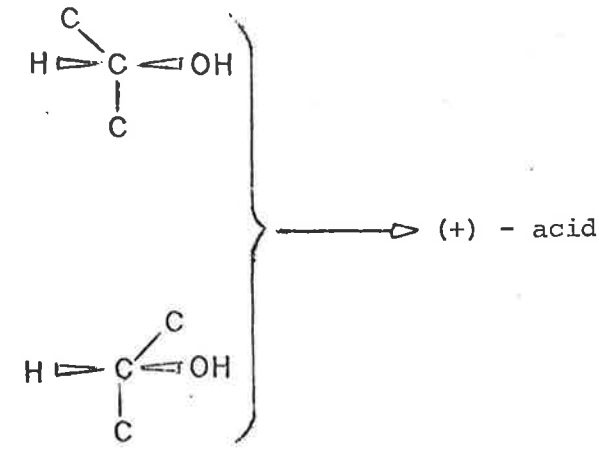
(-)-(20)

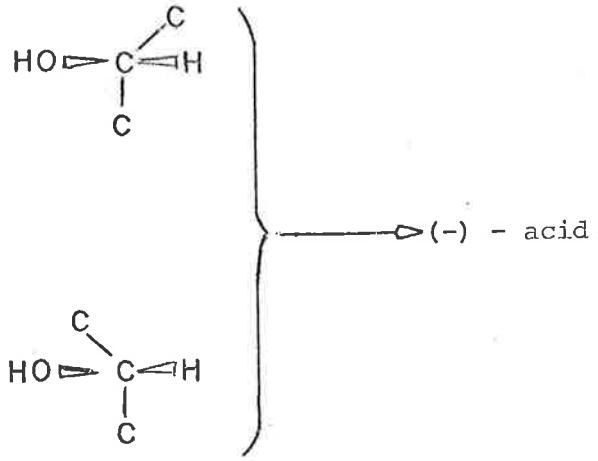


(+)-(18)



(+)-(19)





Each of these diols was treated with excess racemic 2-phenylbutyric anhydride using the conditions of Horeau's method. The results are summarised in Table 4 (Experimental). These results are consistent with those predicted from the empirical rule.

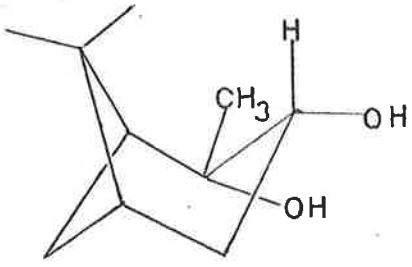
Horeau and Weidmann[12] found that the rotation of optically active 2-phenylbutyric anhydride in pyridine solution decreased slowly due to racemization. They showed that the optical rotation of 0.1 M pyridine solution of (+)-2-phenylbutyric anhydride decreased to about half of the initial value within twenty hours. Thus, prolonging the reaction time can increase the degree of esterification but will minimize the optical yield. In the present work the reaction times were between 15 and 18 hours. The degree of esterification and the optical yield are quite significant. The reproducibility is only of the order of $\pm$ 10% as ordinary laboratory conditions were used.

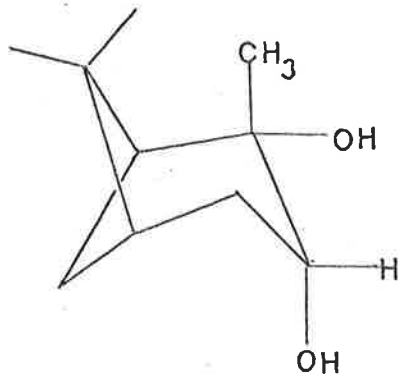
The degree of esterification was calculated from the assumption that only the secondary hydroxyl group underwent esterification. It was not known whether or not the tertiary hydroxyl group had been partly esterified. However, it was very likely that any esterification of the tertiary hydroxyl group arose from the intramolecular transfer of the acyl group from the secondary hydroxyl group. If further esterification of the secondary hydroxyl group then occurred

it would not alter the interpretation of the result of the kinetic resolution since the same empirical relationship would hold for this step also. It can be seen from the table that in each example of the optically active diols studied, the sign of rotation of the acid agreed with that predicted from the rule.

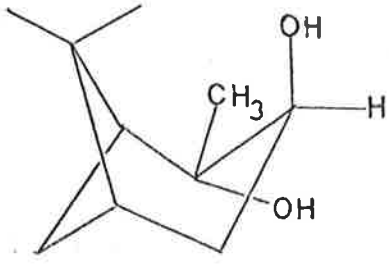
Therefore, it has been established that the method is applicable for the determination of the absolute configurations of the diols used here and that the results indicate that the polar tertiary hydroxyl group does not affect the prediction made on the basis of steric size.

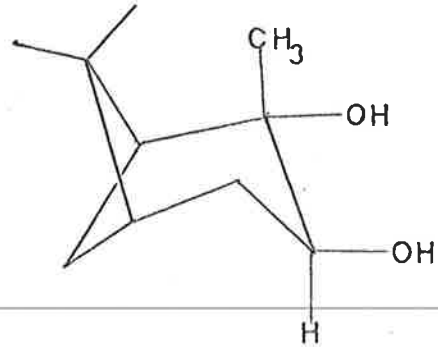
It should be noted that the trans- pinanediols (19) and (20) were esterified at about the same rate as the corresponding cis- isomers (17) and (18) in spite of the apparently greater steric hindrance of the bridge gem-dimethyl groups. The reactivity of the pinanediols towards esterification can be rationalized from their preferred conformations. Zschunk et al[45] suggested that of the two interconvertible conformations, the cis- isomer prefers to be in the boat-like conformation while in the trans- isomer the chair-like conformation was preferred. In the chair-like conformation of the trans-isomer the C3-hydroxyl group is equatorial and is directed away from the gem-dimethyl groups. Therefore, the steric effects for esterification of both pinanediol isomers are very similar.





cis-





trans-

boat-form

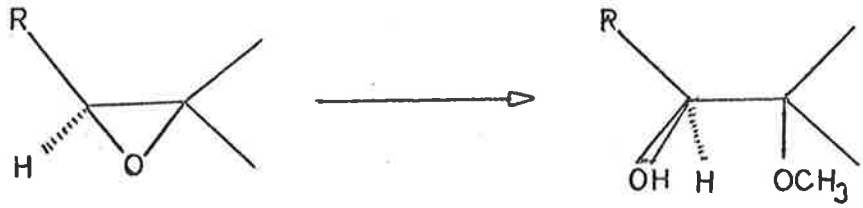
chair-form

While this work was in progress a similar application of Horeau's method to some diols of the type R-CH(OH)-CH_2-OH was reported by Guetté and Spassky[47]. They established that the initial

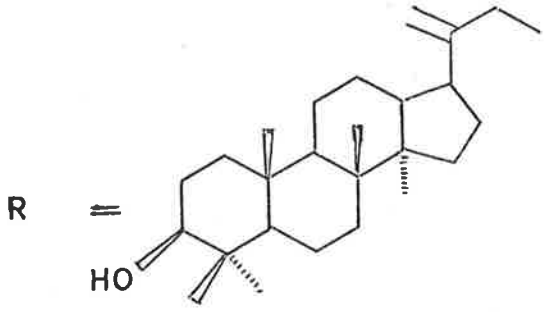
reaction involved esterification of the primary hydroxyl group (where the kinetic resolution is so small that it could be neglected). The important reaction of the secondary hydroxyl group of the intermediate R-CH(OH)-CH_2-O-CO-CH(Ph)-CH_2-CH_3 then depends on the steric requirements of R groups and -CH_2-O-CO-CH(Ph)-CH_2-CH_3. Clearly, R was larger than -CH_2-O-CO-CH(Ph)-CH_2-CH_3 (where R > CH_3), and the configuration of the diols could be deduced directly from the rotation of the recovered acid. The results reported by these authors therefore support the conclusion made in the present work and extend the usefulness of the method to a wider range of diols.

A recent gas chromatographic modification[48] of Horeau's method demonstrates that the method would be extremely useful since it can be carried out successfully on microquantities of alcohols. This micromethod could presumably be extended to optically active diols as well.

The determination of the absolute configuration of aglaiol (1) has been reported recently by Boar and Damps[49]. The epoxide ring was opened by acid-catalysed methanolysis and then Horeau's method was applied to the resulting methoxy alcohol (21). The absolute configuration of aglaiol was then assigned as (24S)-24,25-epoxy-5α-dammar-20-en-3β-ol.



(1) (21)



This assignment also enabled the stereochemistry of the isomeric aglaitriols (3) to be deduced. Therefore, in the present work these triols were not studied further, and attention was directed to the determination of the absolute configuration of alternifolenediol (4).

Determination of the Absolute Configuration of (+)-Alternifolenediol (4)

Anhydrous alternifolenediol (4) is a yellow oil. It is very hygroscopic and easily forms hydrated crystals, whose melting points are variable depending on the methods of crystallisation[4]. It is necessary to obtain the anhydrous diol before using under Horeau's conditions. The crystalline diol*, m.p. 66-68°, $[\alpha]_D$ + 11.5°, was dehydrated over phosphorus pentoxide at 55-60° for 2 days and then treated under the conditions of Horeau's method in pyridine solution. It was found that the esterification proceeded and that partial resolution had occurred. The results are shown in Table 5 (Experimental).

The degree of esterification was calculated from the assumption that both the hydroxyl groups of the diol could be esterified. The optical yields were calculated from the assumption that the kinetic resolution was affected by the steric environments of the C1-hydroxyl group only.

The composition of the esters formed in example 3 was investigated. The formation of the C1-mono-acetate (22) was the major product (60%) and supports the above assumption that the esterification occurred preferentially at the C1-hydroxyl group. The intra-

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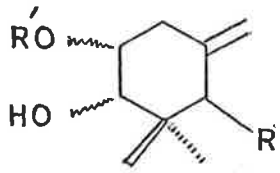
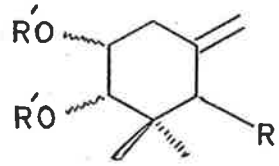
* Kindly supplied by D.E. Lewis.

molecular transfer of the acyl group R' from the C1- to the C2-position and the further acylation at the C1-hydroxyl group to form the diester (23) (isolated in about 14%) does not affect the empirical steric relationship of the method. This is because the C2-moiety is still larger than the C6-moiety, or even increases in steric size (due to the replacement of the hydroxyl proton by the R' group).



(22)



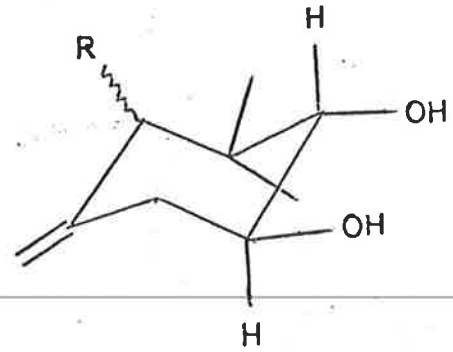
(23)

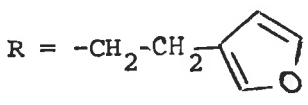
R = $-CH_2-CH_2-$ (furan)

R' = $-\overset{O}{\overset{\|}{C}}-CH(Ph)-CH_2-CH_3$

Since the experimental error in reading the rotation is between $\pm$ 0.015°, the observed rotations shown in Table 5 are quite acceptable. It is the sign rather than the value of

the rotation which is more diagnostic in this method. Thus, the levorotatory acid obtained fron hydrolysis suggested that the configuration at the C1-position corresponded to that in Figure 2 (page 4), viz. S-configuration, where the C2-moiety is larger than the C6-moiety. Since the two hydroxyl groups are trans-diequatorial (from the n.m.r. spectrum)[4] the S-configuration is also assigned for the C2- position. Therefore, the stereochemistry of the naturally occurring (+)-alternifolenediol can be represented as below.

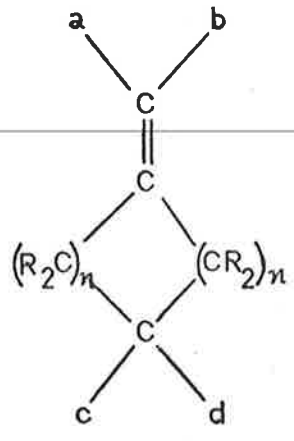




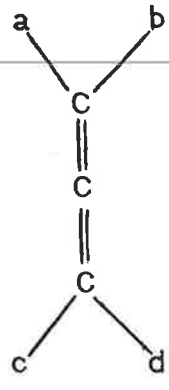
PART II

INTRODUCTION

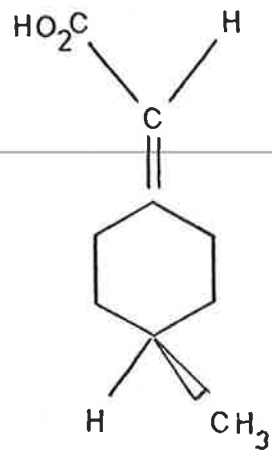
It has been known for some time that alkylidenecycloalkanes (24) are chiral about an axis and can exist in two enantiomeric forms[50]. The reason for the dissymmetry in these molecules is the same as in allenes (25), the molecule lacks a plane (or other elements) of symmetry because the groups c and d lie in a plane perpendicular to those groups a and b attached to the other end of the double bond. A necessary and sufficient condition for such a molecule to be dissymmetric is $a \neq b$ or $c \neq d$. The first molecule of this type where n = 2 and R = H, which was resolved in 1909, was 4-methycyclohexylideneacetic acid (26)[51].



(24)

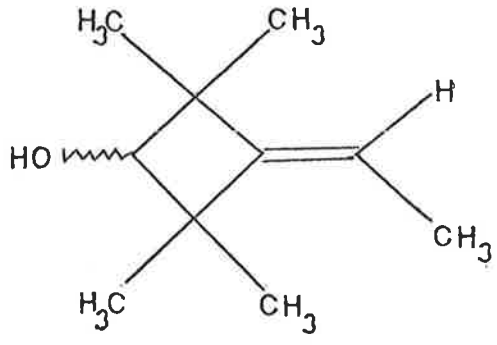


(25)

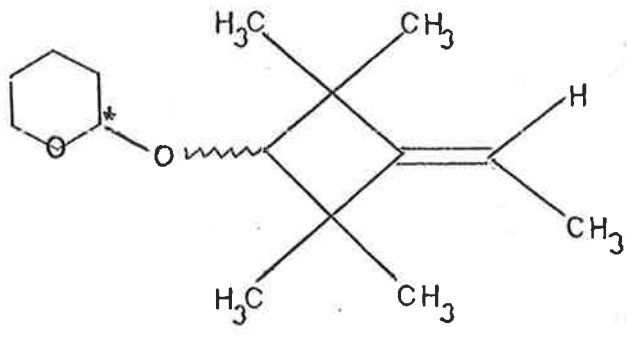


(26)

In 1969 Hamon[17] demonstrated the chirality in a system where n = 1 and R = CH_3, 3-ethylidene-2,2,4,4-tetramethylcyclobutanol (27), by showing that a pair of diastereoisomers was formed when a derivative was prepared in which another element of chirality was introduced. Thus, when (27) was converted into the tetrahydropyranyloxy derivative (28) a mixture of diastereoisomers was produced in an almost 1:1 mixture. The presence of the diastereoisomers was confirmed by the n.m.r. spectrum. In the spectrum of (27) the region of the saturated methyl groups contains four singlets of equal intensity, but the spectrum of the derivative (28) contains eight lines in this region.



(27)



(28)

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* Denotes a chiral centre.

⌇⌇ Denotes a mixture of isomers.

Since the molecule is chiral, but it has been formed from symmetrical reagents[17] it exists as a racemic mixture of enantiomers, which in principle, it should be possible to resolve. If it could be resolved into enantiomers, then the absolute configuration would have to be established for the complete characterisation of the compound. Since the reagent used, 2,3-dihydropyran, is not chiral the formation of the tetrahydropyranyloxy derivative (28) is neither a mean of resolving the mixture nor even a method of following the resolution afforded by other means, as each diastereoisomer is accompanied by its mirror image. It was hoped that if the molecule could be resolved, the absolute configuration of an enantiomer could be determined by a direct application of Horeau's method[5,6,12]. It is reasonable to assume that the geminal-dimethyl groups on the same side as the olefinic methyl group of (27) might have a larger steric requirement than the other gem-dimethyl groups due to a "buttressing effect"[52], and that this difference might be sufficient to effect the partial kinetic resolution of the hydroxyl group. However, since this underlying assumption may not be correct, an alternative confirmation would be desirable.

An alternative route to determine the absolute configuration of an enantiomer of (27) was sought. It was considered that

conversion of the double bond of alkylidenecycloalkanes by processes in which the stereochemical alterations could be accurately determined or predicted to a vicinal diol of the type -COH-CHOH-CH_3 would allow the method developed in Part I to be applied.

It has been well established[53] that acid-catalysed hydrolysis of unsymmetrical substituted epoxides takes place exclusively at the more substituted carbon atom to give vicinal diols with retention of the configuration at the less substituted carbon atom, whereas base-catalysed reaction takes place at the less substituted carbon atom with high inversion of the configuration at the centre of attack. It has been observed[54] that epoxidation of the double bond in (27) gave rise to a mixture of cis- and trans- hydroxy epoxides, with respect to the hydroxyl group. It would be then necessary to separate the geometrical isomers and to determine their relative configurations. It was hoped that if the cis- and trans- epoxides could be separated each isomer would be converted into the corresponding vicinal diols by one of these methods. Alternatively, a direct hydroxylation of the double bond in a stereospecific manner (cis- or trans- hydroxylation)[55] could be attempted. Again, a separation of the isomers and the determination of their relative configurations would be necessary.

Of course, it should be noted that if racemic alkylidenecyclobutanol was used these processes could also be used to produce a racemic vicinal diol of the type -COH-CHOH-CH_3 which might then be resolved, perhaps by the method of Horeau. The resolved material might then be converted by stereospecific processes to an optically active alkylidenecycloalkane of known configuration if the process chosen had known stereochemical requirements. Two such processes are illustrated below.

Corey and co-workers[56,57] have developed a method for stereospecific synthesis of olefins from cis- vicinal diols by the use of thiocarbonyldiimidazole and trimethoxyphosphine. The mechanism is cis- elimination (Diagram 4). The resolved vicinal diol might be converted into the corresponding optically active epoxide by cyclisation involving a leaving group[58] with inversion of the configuration at the site of reaction. The epoxide might then be converted stereospecifically into an olefin by the method of Vedejs and Fuchs[59] (Diagram 5).

This part of the thesis discusses the preliminary attempts made to produce 3-ethylidene-2,2,4,4-tetramethylcyclobutanol in an optically active form of known absolute configuration.

Diagram 4

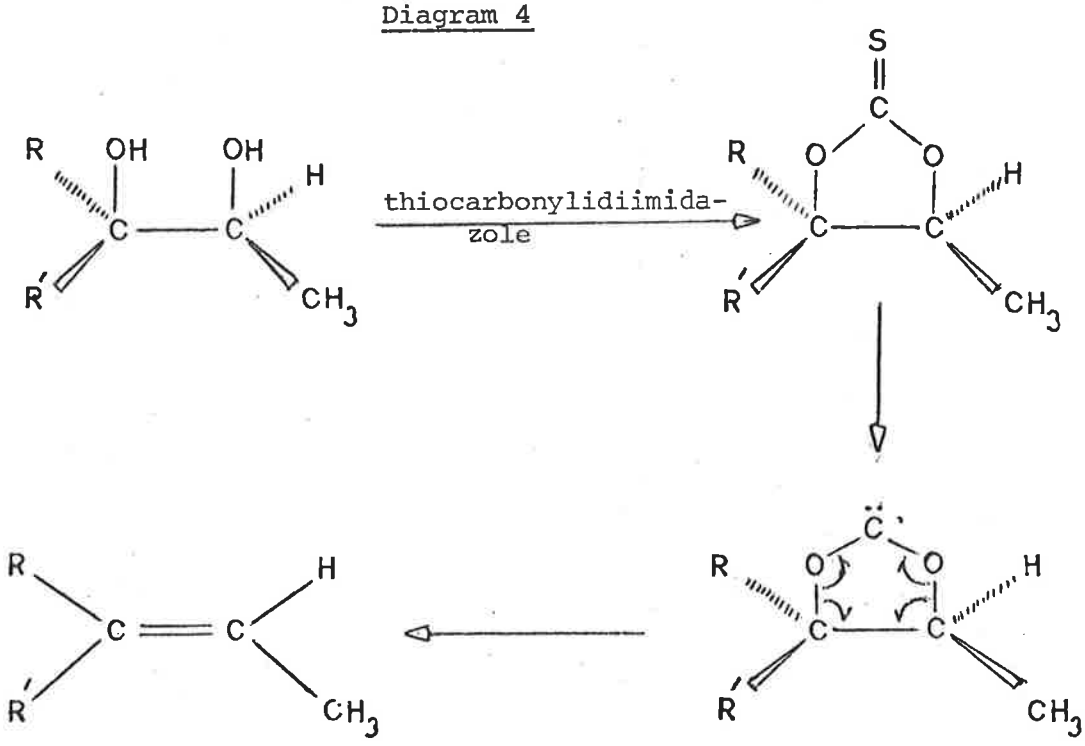
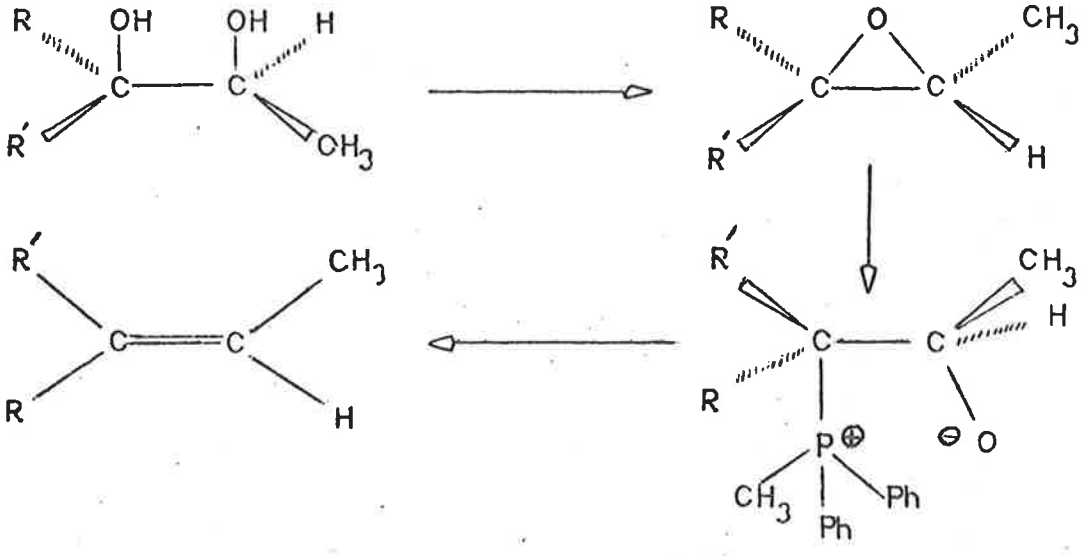


Diagram 5



RESULTS AND DISCUSSION

The Progress of Resolution of (27)*

It would be advantageous if any attempt of resolution of compounds to be able to follow the progress of the resolution measuring the degree of optical purity. The recent developments of optically active n.m.r. shift reagents[60,61] are useful for organic chemists to be able to determine the enantiomeric compositions of racemic compounds. The advantage of the optically active shift reagents is that the pseudocontact shifts[62] due to the formation of diastereoisomeric complexes are often quite different and one observes resonances for each enantiomer. If the compound is resolved or partially resolved one can quantify the relative amounts of enantiomers by comparing the intensity of the related peaks of each enantiomer. It was of interest therefore, to know whether the resolution of the alcohol (27) could be followed by the use of these reagents.

The optically active n.m.r. shift reagent used in the present work was tris[3-(trifluoromethylhydroxymethylene)-d-camphorato] europium (III) (29)[60], which has been successfully used for racemic

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* Kindly supplied by Dr. D.P.G. Hamon.

alcohols, ketones, esters, epoxides, and amines[60]. It was found in this work* that when the reagent (29) was added to the n.m.r. solution of (27) in CCl_4 the shift differences for enantiomers were produced. Without the reagent the saturated methyl protons resonated as four singlets of equal intensity in the region between δ 1.37 and 1.03. When the reagent (29) was added, about 4:1 mole ratio of (27):(29), the resonances of these protons were shifted downfield and they now resonated in two different regions. The lower field resonances at δ 5.0-4.7 were designated for the protons of the methyl group f and g because they were in the same vicinity as the hydroxyl and were expected to be at closer distance to the europium atom**. The resonances at δ 2.73-2.30 were designated for the protons of the methyl groups d and e. The resonances in each region consisted of four lines of equal intensity due to enantiomers being present in equal amounts. Two of the four lines in the region δ 5.0-4.7 overlapped in the middle giving the appearance of a triplet; the other region showed four distinct resonances.

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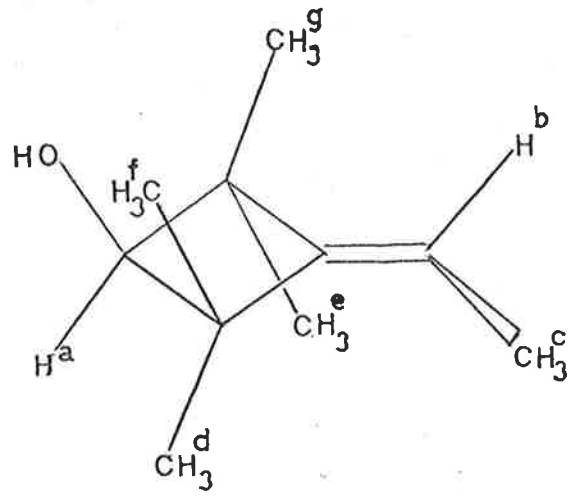
* The collaboration of Dr.D.P.G. Hamon and Mr. D.E. Lewis is gratefully acknowledged.

** The psuedocontact shift (Δδ) is reversely proportional to the cube of the distance between the europium atom and the proton under investigation. For details see Ref. 62.



An entiomer of (27)

When the amount of the reagent (29) was increased to about 2:1 mole ratio of (27):(29) the resonances of the protons of the methyl qroups f and g were shifted further downfield by about 1 ppm, but only a shift of about 0.7 ppm was observed for the protons of the methyl groups d and e. Furthermore, when the mole ratio of the alcohol (27) and the reagent was about 1:1 no further signification shifts of the resonances were observed. The induced chemical shifts of the saturated methyl protons of (27) in the presence of (29) are shown in Table 6. From the table, it would appear that a mole ratio of only 8:1 of (27):(29) would be required in order to

follow the resolution which is useful considering the cost of the shift reagent.

Table 6

Protons	mole ratios of (27):(28)			
	100% of (27)	4:1	2:1	1:1
H^d and H^e	1.27-1.03	2.73-2.30	3.2-2.7	3.2-2.7
H^f and H^g		5.0 -4.7	6.0-5.7	6.0-5.7

The n.m.r. spectra of (27) without the reagent (29) and in the presence of the reagent (1:1 mole ratio) are shown in Figure 4. The resonances of the allylic protons (H^c), which is a doublet and is in about the same region as those of the protons d and e (in the spectrum (b)), was assigned by spin decoupling[63]. When the vinylic proton (H^b) was irradiated, the absorption caused by the allylic protons (H^c) collapsed to a singlet, and when these protons were irradiated the quartet due to the vinyllic proton (H^b) became a singlet.

The four lines were of course of equal intensity in each of the two distinct regions for the ring methyl groups because

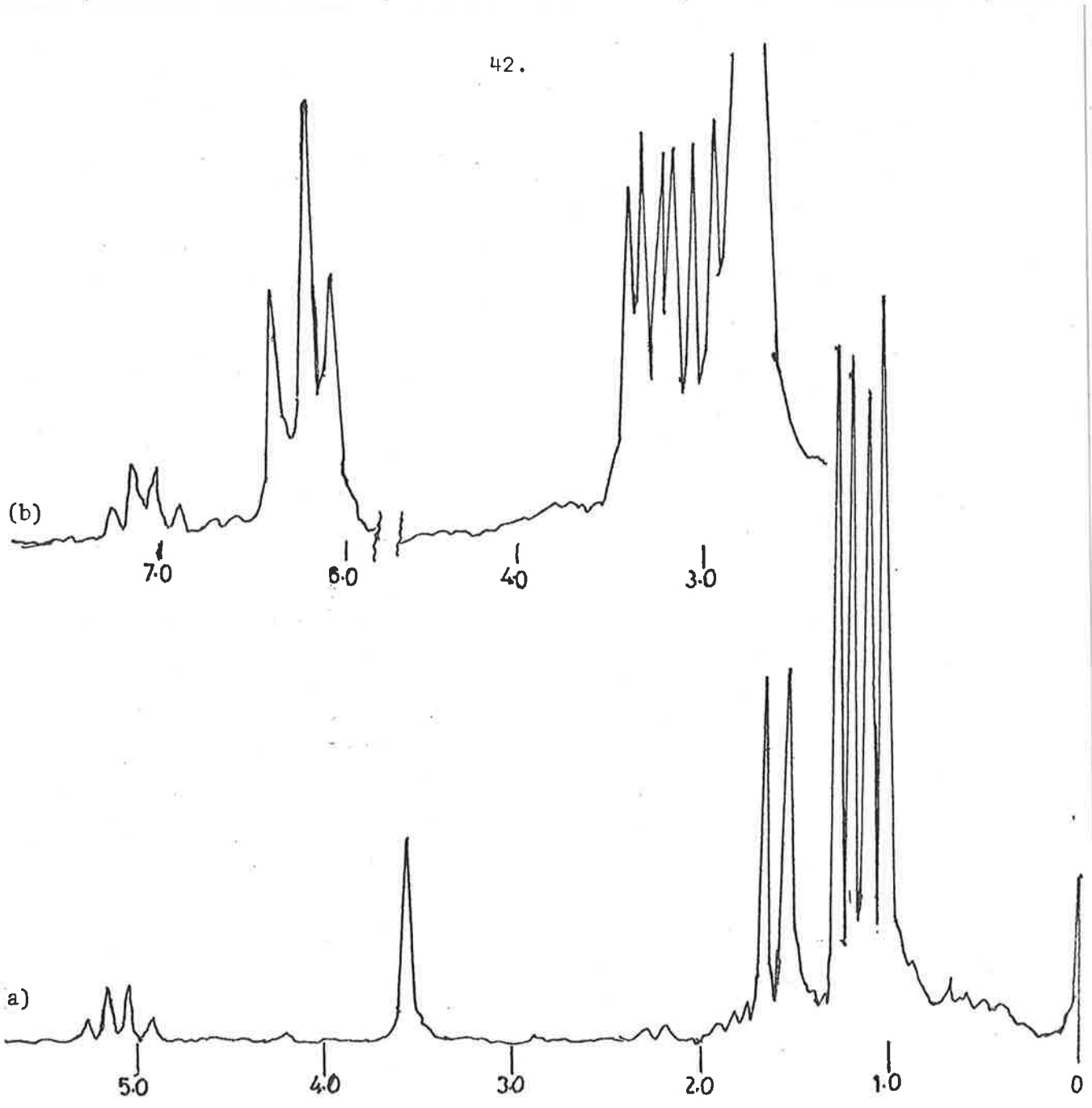


Figure 4

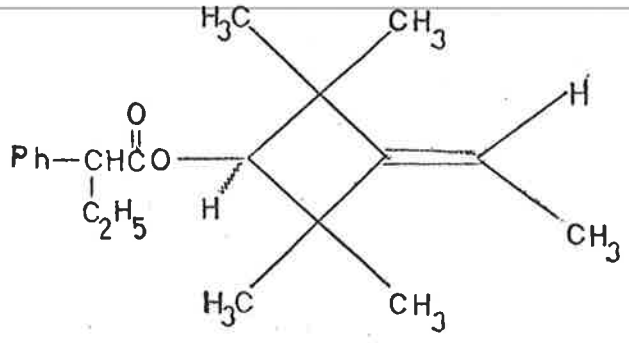
(a) Spectrum of (27) in $CDCl_3$.

(b) Spectrum of (27) in the presence of the optically active shift reagent (29).

diastereoisomeric complexes were formed from equal amount of enantiomers. If, however, the alcohol (27) is partially resolved the intensity of each pair of the four lines in each region would not be equal. When the alcohol is completely resolved only two lines (of equal intensity) would be expected in each region. Consequently, the progress of resolution of (27) can be followed by the use of (29).

Attempted Resolutions of (27)

When excess alcohol (27) was treated with (+)-2-phenylbutyric anhydride (6:1 mole ratio) under the conditions of Horeau's method[12], it was found that esterification occurred to the extent of about 46% (based on the anhydride). The excess alcohol was recovered by distillation, and the optical rotation was measured. No significant rotation was observed. The ester was isolated from the residue by column chromatography. In order to find out whether or not the diastereoisomeric esters (30) could be separated, it was passed through two g.l.c. columns, a polar and a non-polar colum (FFAP and EGS, respectively). Only one sharp symmetric peak was observed in both cases. As a pure isomer was not expected,



(30)

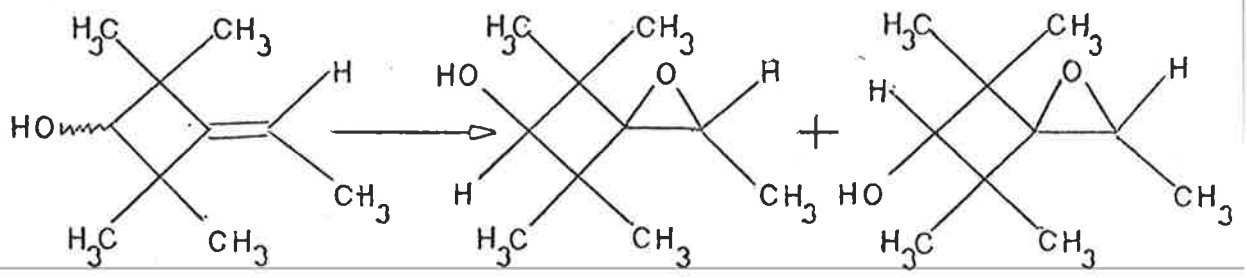
the result suggested that the conditions used did not separate the diastereoisomers. In addition, the n.m.r. spectrum suggests that the ester was a mixture of diastereoisomers, because each line appeared to have a shoulder and to be broadened, being consistent with the presence of two very similar compounds. Alkaline hydrolysis of the ester gave the alcohol (27) which was not optically active. The n.m.r. spectrum of the alcohol recovered from the hydrolysis in the presence of the optically active n.m.r. shift reagent (29) showed that the four peaks in each region had equal intensity, which proves that no measurable resolution had occurred.

In another attempt to resolve the alcohol (27) it was heated under reflux with (+)-O-methyl podocarpoyl chloride[64] (31) in pyridine solution, in the hope that the diastereoisomers could be formed. After 48 h t.l.c. showed that both the starting alcohol and the acid chloride were mainly unchanged, and no product was formed. That esterification did not occur under these conditions is probably due to the hindered nature of the interacting functional groups in both molecules.

The Formation of 5-Hydroxy-2,4,4,6,6-pentamethyl-1-oxaspiro [3.2]hexane, (32) and (33)

The ethylidenecyclobutanol (27) was converted into a mixture of cis- and trans- 5-hydroxy-2,4,4,6,6-pentamethyl-1-oxaspiro [3.2]hexane (32) and (33), respectively, by treating with m-chloroperbenzoic acid (m-PBA) in chloroform at room temperature (Diagram 6).

Diagram 6



(27) (32) (33)

The presence of a 1:1 mixture of geometrical isomers was shown by the n.m.r. spectrum of the product. Resonances at δ 3.73 and 3.58 are due to C5-protons of each isomer . The resonances due

to the proton attached to the carbon bearing the epoxide oxygen appeared as a pair of overlapping quartets at about δ 2.8. The assignment of their relative configurations will be discussed later (page 61).

In order to establish the cis- and trans- configurations it is desirable to obtain one of the isomers pure. Separation of the isomers by crystallization was attempted but was unsuccessful. Therefore, they were separated by preparative g.l.c. The separation was not satisfactory because the isomers had very long and similar retention times. The first fraction was obtained pure, m.p. 66.5-67.5°, the second fraction was a liquid and was contaminated by some of the fraction 1. The n.m.r. spectra of both isomers are shown in Table 7.

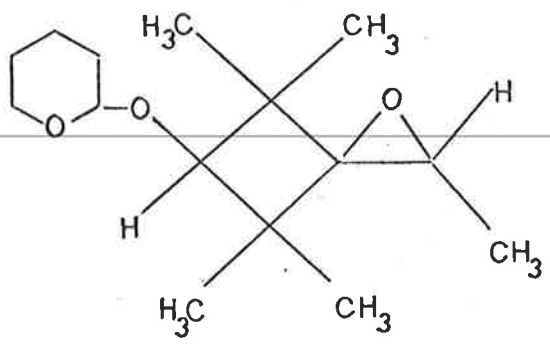
Table 7

N.m.r. spectra of the hydroxy epoxides after separation

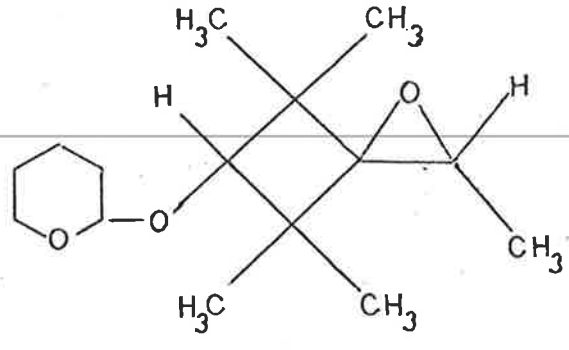
	C5-H	C2-H	C2-CH_3	C4-and C6-CH_3
Fraction 1	3.73	2.88	1.26	1.17-0.93
Fraction 2*	3.58	2.95	1.28	1.20-0.97

* peaks due to fraction 1 were also present.

It was considered that a derivative of the hydroxy epoxides might have some physical properties so different that the separation of the isomeric derivatives would be more efficient. However, the derivatives should be such that it can be easily converted into the starting hydroxy epoxides. Thus, the mixture of (32) and (33) was converted into a mixture of cis- and trans- 2,4,4,6,6-pentamethyl-5-tetrahedropyran-2'-yloxy-1-oxaspiro[3.2]hexane (34) and (35), respectively.



(34)



(35)

The separation of (34) and (35) by preparative g.l.c. was more satisfactory, but was still time consuming. The mixture of the hydroxy epoxides was also collected when the temperature of the column was increased. The hydroxy compounds presumably arose from cleavage of the tetrahydropyranyl ether during passing through the column, possibly due to transetherification of residual hydroxy groups in liquid phase[65].

The structure of the tetrahydropyranyl ethers (34) and (35) was confirmed by spectroscopic and analytical data. The infrared spectra of both fractions contained no hydroxyl absorption. In the n.mr. spectra (Table 8) only the resonances of the proton attached to the carbon atom bearing the tetrahydropyranyl ether group (C5-H) differentiate the two isomers. In the spectrum of the fraction 1 this proton resonated at δ 3.76 and in the spectrum of the fraction 2 it appeared at δ 3.63. The peaks in the other regions appeared to have about the same chemical shifts as were observed in the spectra of the hydroxy epoxides. The resonances due to the tetrahydropyran ring protons appeared at about the same region in both isomers. The broad peak at δ 4.55 was due to the proton on C2' of the pyran ring of both isomers.

Table 8

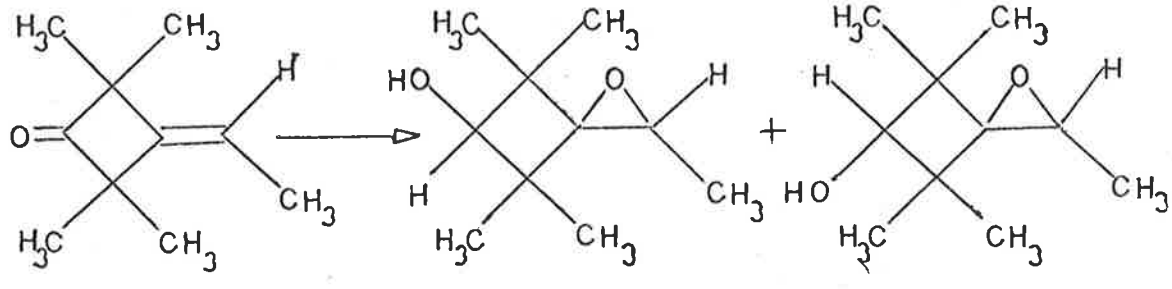
N.m.r. spectra ($CDCl_3$) of the tetrahydropyranyl ethers after separation

Protons	Appearances	δ (ppm)	
		Fraction 1	Fraction 2
C2'-	broad singlet	4.55	4.55
C6'-	complex	4.10-3.40	4.06-3.36
C3',C4',and C5'-	complex	1.80-1.40	1.80-1.40
C5-	sharp singlet	3.76	3.63
C2-	quartet	2.87	2.93
C2-methyl	doublet	1.27	1.27
C4 and C6-methyl	multiplets	1.17-0.95	1.20-0.95

When the fraction 1 of the hydroxy epoxides was converted into the corresponding tetrahydropyranyl ether, the n.m.r. spectrum of the product was identical with that of the fraction 1 of the tetrahydropyranyl ethers. In addition, the product of methanolysis of the fraction 1 of the tetrahydropyranyl ether had the same retention time on g.l.c. as fraction 1 of the hydroxy epoxide, and their n.m.r. spectra were identical. Similarly, the fraction 2 was shown to be interconvertible with the fraction 2 of the hydroxy epoxide.

An alternative method to obtain the mixture of the hydroxy epoxides (32) and (33) was by the reduction of 2,4,4,6,6-pentamethyl-1-oxaspiro[3.2]hexan-5-one (36) with lithium aluminium hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$) (Diagram 7). It was found that the epoxyketone (36) was readily reduced by the reagents at room temperature without reduction of the epoxide ring. When lithium aluminium hydride was used the mixture of geometrical isomers was formed in an about 1:1 ratio. However, when sodium borohydride was employed at 0°, the n.m.r. spectrum showed that the isomers were formed in about a 2:1 mixture, in which the isomer which absorbed at δ 3.76 was predominant.

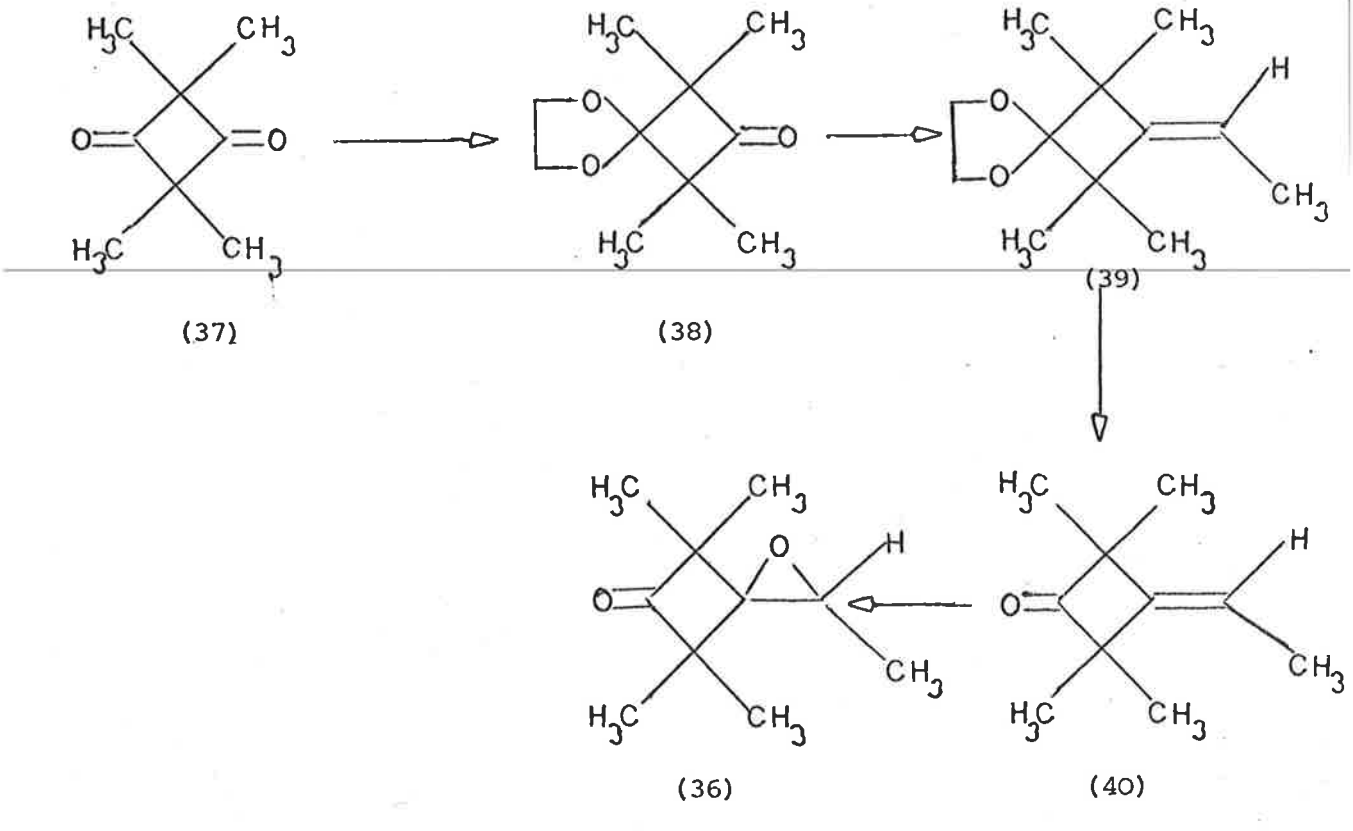
Diagram 7



(36) (32) (33)

The epoxyketone (36) was prepared from tetramethylcyclobutane-1,3-dione (37) by the reaction sequences shown in Diagram 8. The synthesis of the monoketal (38) from (37) has been reported[66]. The Wittig reaction of (38) starting with ethyltriphenylphosphonium iodide[67] to give 7-ethylidene-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (39)[68] in 55% yield was effected in ether in the presence of potassium tert-butoxide.

Diagram 8

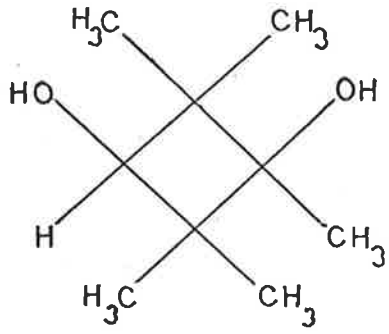


Hydrolysis of the ethylideneketal (39) with aqueous methanolic hydrochloric acid gave the 3-ethylidene-2,2,4,4-tetramethylcyclobutan-1-one (40)[68] in 87% yield.

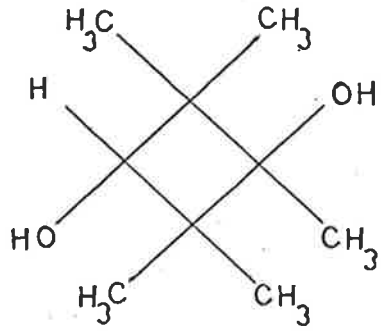
Epoxidation of the ethylideneketone (40) under the same conditions as those for the ethylidene cyclobutanol (27) gave a high yield of the racemic epoxyketone (36). The structure of the epoxyketone (36) was confirmed by the spectroscopic and analytical data. The infrared spectrum included a strong carbonyl absorption at 1775 cm^{-1}, but the olefinic stretching vibration at 1685 cm^{-1} which had appeared in the spectrum of (40) was no longer present. The one proton quartet which centred at δ 3.22 corresponded to the C2-proton. The C2-methyl protons appeared as a doublet at δ 1.4. The protons of the four methyl groups attached to the C4- and C6- of the cyclobutane ring resonated in the region between δ 1.30-1.10 as four singlets, two of which were coincident in the middle.

Reduction of (32) and (33)

The synthesis of cis- and trans- pentamethylcyclobutane diol (1,3) (41) and (42) and their spectra have been reported[69,70]. The assignment of the geometrical isomers was based on the chemical shifts of the Cl-proton, which resonated at δ 3.71 in the trans-isomer and δ 3.40 in the cis-isomer.



(41)



(42)

It was hoped that if the hydroxy epoxides (32) and (33) could be converted in to the corresponding 1,3-diols their n.m.r. spectra could be compared with those of the analogous (41) and (42). It was assumed that replacing the C3-methyl group by an ethyl group would affect these resonances very little allowing the determination of the geometrical relationship.

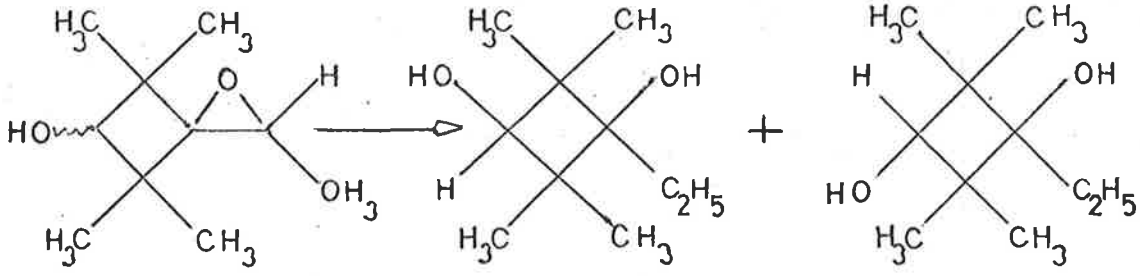
The most direct route to convert the epoxides (32) and (33) into the corresponding cis- and trans-3-ethyl-2,2,4,4-tetramethylcyclobutanediol (1,3), (43) and (44), respectively, involves the reductive ring opening of the epoxides with retention of the configuration at the C3. It was anticipated that lithium aluminium hydride reduction would be suitable for the desired transformation, because the reaction is an S_N2 type involving backside attack at the less substituted carbon atom of the epoxide ring[71].

Because of the poor separation of the hydroxy epoxides (32) and (33) and the corresponding tetrahydropyranyl ethers (34) and (35) only small quantities of the pure isomers were available. It was therefore decided to use the mixture of the isomers in preliminary experiments to find suitable reaction conditions (Diagram 9).

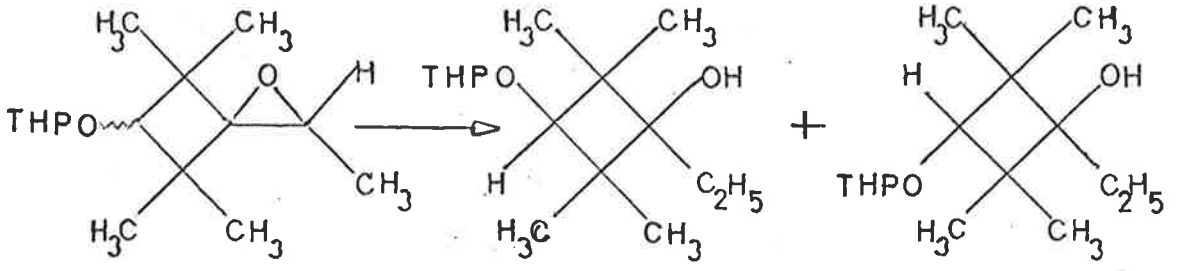
It was found that the epoxide ring of (32) and (33) was very unreactive towards the reagent. When ether was used as a solvent the reduction did not occur, even on refluxing for 48 hours. Using dimethoxyethane (D.M.E.) as a solvent and heating the mixture under reflux for 8 days (under the atmosphere of nitrogen) gave the reduction in about 80% with some 20% starting epoxide still remaining (as shown by g.l.c.).

The reduction product was isolated by preparative g.l.c. as a mixture of (43) and (44). The infrared and n.m.r. spectra are

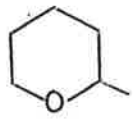
Diagram 9



(32) and (33) (43) (44)



(34) and (35) (45) (46)

THP denotes 

consistent with the expected structure of the diols. The infrared spectrum showed a strong hydroxyl absorption between 3500 and 3400 cm^{-1}. In the n.m.r.spectrum (Figure 5(a)) the two singlets at δ 3.71 and 3.40 (ratio 1:1) are due to the C1-protons in each isomer. These resonances are comparable with those of the C1-protons in the

pentamethyl diols (41) and (42), which was discussed previously.

The resonances of the hydroxyl protons and of the methylene protons appeared in the same region between δ 1.86-1.40. After the addition of D_2O the methylene quartet was visible. Each line of the peaks is broadened indicating that it is a pair of quartets. The ring methyl protons resonances which overlapped in the region between δ 1.20-1.0 superimposed a part of the triplet expected from the side chain methyl group. These resonances were shifted further downfield on the addition of a europium shift reagent, $Eu(dpm)_3$.[62] The resonances of the protons of the side chain methyl group now appeared as a pair of overlapping triplets, J = 7 Hz, consistent with a mixture of two isomers (Figure 5(b)). The quartets due to the methylene protons were unidentified because they were coincident with the signals of the shift reagent in the region between δ 3.7-2.5.

The tetrahydropyranyl ethers (34) and (35) were reduced to give (45) and (46) more readily than the hydroxy epoxides. The difference in reactivity towards the reducing agent of the hydroxy epoxides and the corresponding tetrahydropyranyl ethers was probably because the initial formation of the alkoxide ion by the free hydroxyl group makes the molecule less susceptible to attack by the

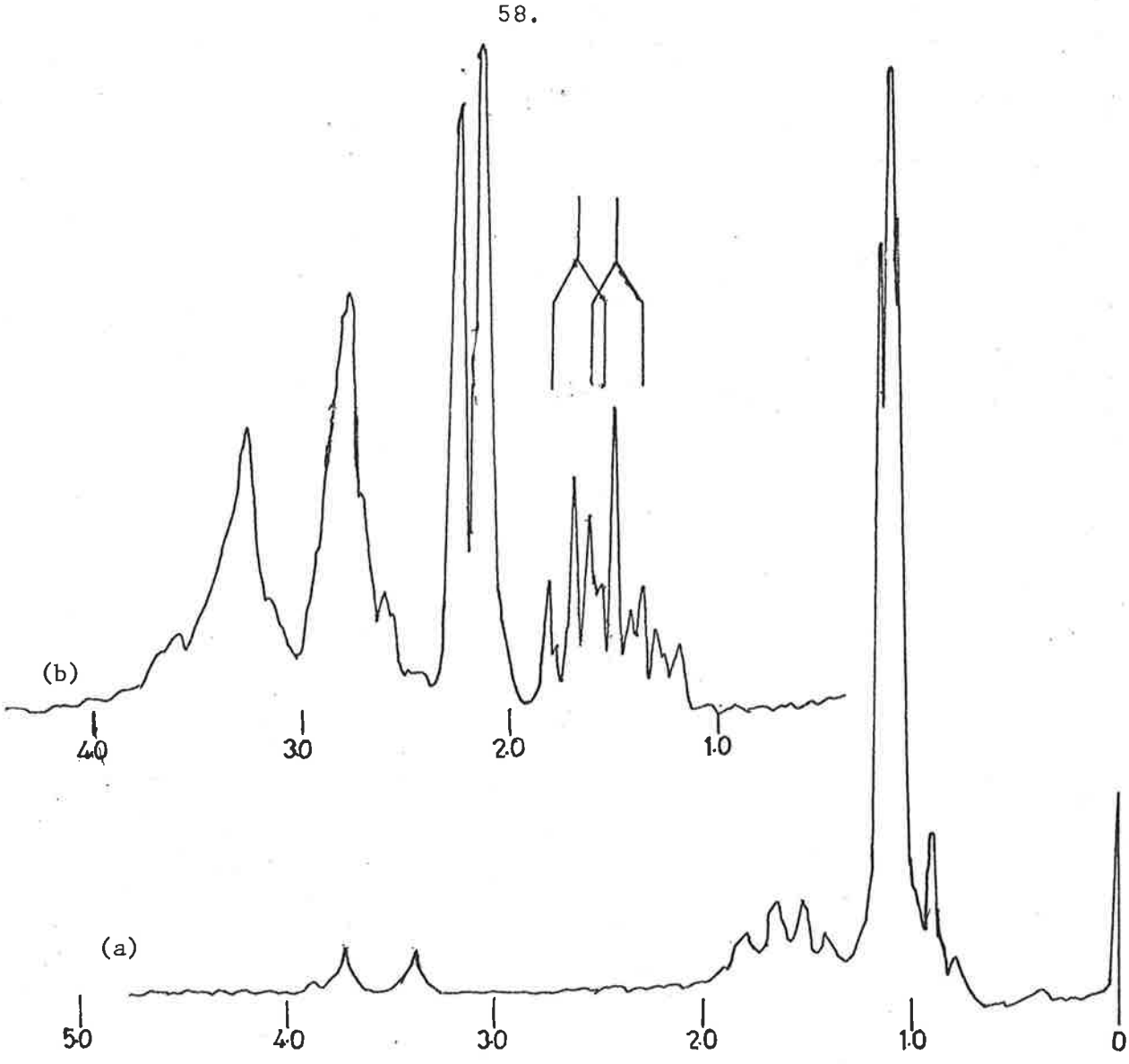


Figure 5

(a) The spectrum of the mixture of (44) and (45) after D_2O exchanged.

(b) The spectrum of the mixture of (44) and (45) in the presence of $Eu(dpm)_3$.

hydride reagent due to repulsion of the anion. Hydrolysis of the protecting group in the reduction products (45) and (46) gave a mixture of hydroxy compounds whose n.m.r. spectrum was similar to that of the mixture of the products prepared from the reduction of the hydroxy epoxides (32) and (33).

It has been observed[72] that steric effects are an important factor inhibiting the lithium aluminium hydride reduction of epoxides. Thus, it was considered that the reduction of the epoxides (32), (33) and (34), (35) was inhibited by the highly substituted epoxide molecules.

Reduction of the pure isomer of the hydroxy epoxides (Fraction 1) under the same conditions gave a product, whose n.m.r. spectrum had the expected resonances which were similar to those of the mixture. The fairly sharp singlet at δ 1.08 is due to the ring methyl groups, and suggests that these methyl groups are equivalent, viz., each group is cis- to the hydroxyl groups (c.f. the cis- and trans-2,2,4,4-tetramethylcyclobutane diol-1,3)[73]. The singlet at δ 3.70 is clearly due to the C1-proton. The integration for it and the regions of the methylene and the methyl protons are consistent with the number of the protons expected from the structure (46). In addition, the g.l.c. analysis showed that the reduction product of the pure isomer (Fraction 1) was only one peak which had the

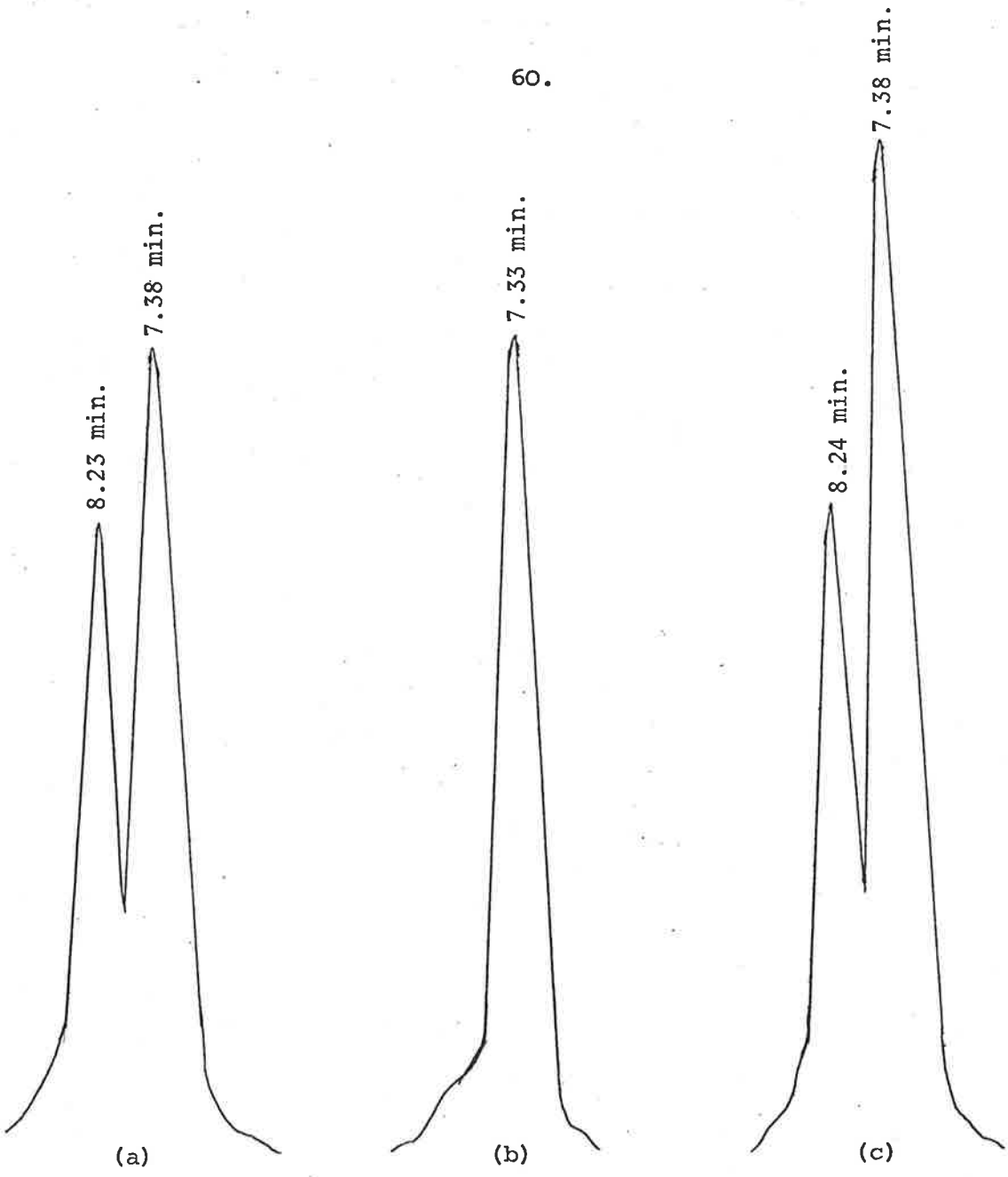


Figure 6

a) the reduction product of the mixture of (32) and (33).

b) the reduction product of the fraction 1 (33).

c) the mixture of a) and b).

(Column 15% QF-1, at 110° and the flowrate 33 ml/min).

same retention time as one of the products obtained from the reduction of the mixture (Figure 6).

Accordingly, since these resonances agree closely with those recorded for the trans- pentamethyl analogue (42)[69,70] it could be concluded that the first fractions (from both the hydroxy epoxides and the corresponding tetrahydropyranyl ethers) are the trans- isomers,(33) and (35), respectively. This assignment is in accordance with the numbers designated for each structure.

Acid-Catalysed Methanolysis of the Mixture of (32) and (33)

It is known[74] that in the mechanism of the acid-catalysed alcoholysis of epoxides the nucleophilic alkoxy groups attack at the more substituted carbon atom, viz. at the carbon atom which has more tendency to form a carbonium ion. In most cases the alkoxy group attacks from the rear face with almost complete inversion of the configuration at the carbon atom which is attacked[75]. It might be assumed that the reaction would occur by the same mechanism with the methanolysis of the hydroxy epoxides (32) and (33). However, in order to establish the mode of this reaction the acid-catalysed methanolysis of (32) and (33) was attempted.

It was found (by t.l.c.) that the crude product obtained from the methanolysis of the mixture of (32) and (33) consisted of two main components of very close R_f values and a minor component of lower R_f value. The n.m.r. spectra of the crude methanolysis product in the region δ 4.0-3.30 was an ill-defined complex due to overlapping of the peaks, but the presence of an introduced methoxy group was observed at δ 3.28. The infrared spectrum exhibited a strong O-H stretching absorption between 3550 and 3250 cm^{-1}. From the fingerprint region for the absorption of O-H bending and C-O stretching vibrations it was not possible to tell whether the peaks were due to secondary or a tertiary hydroxyl group.

When the mixture of the acetyl derivatives (47) and (48) was treated under the same conditions (Experimental), the n.m.r. spectrum of the product was similar to that of the product obtained from the methanolysis of the corresponding hydroxy epoxides. It was thought that the acetyl group was transesterified.

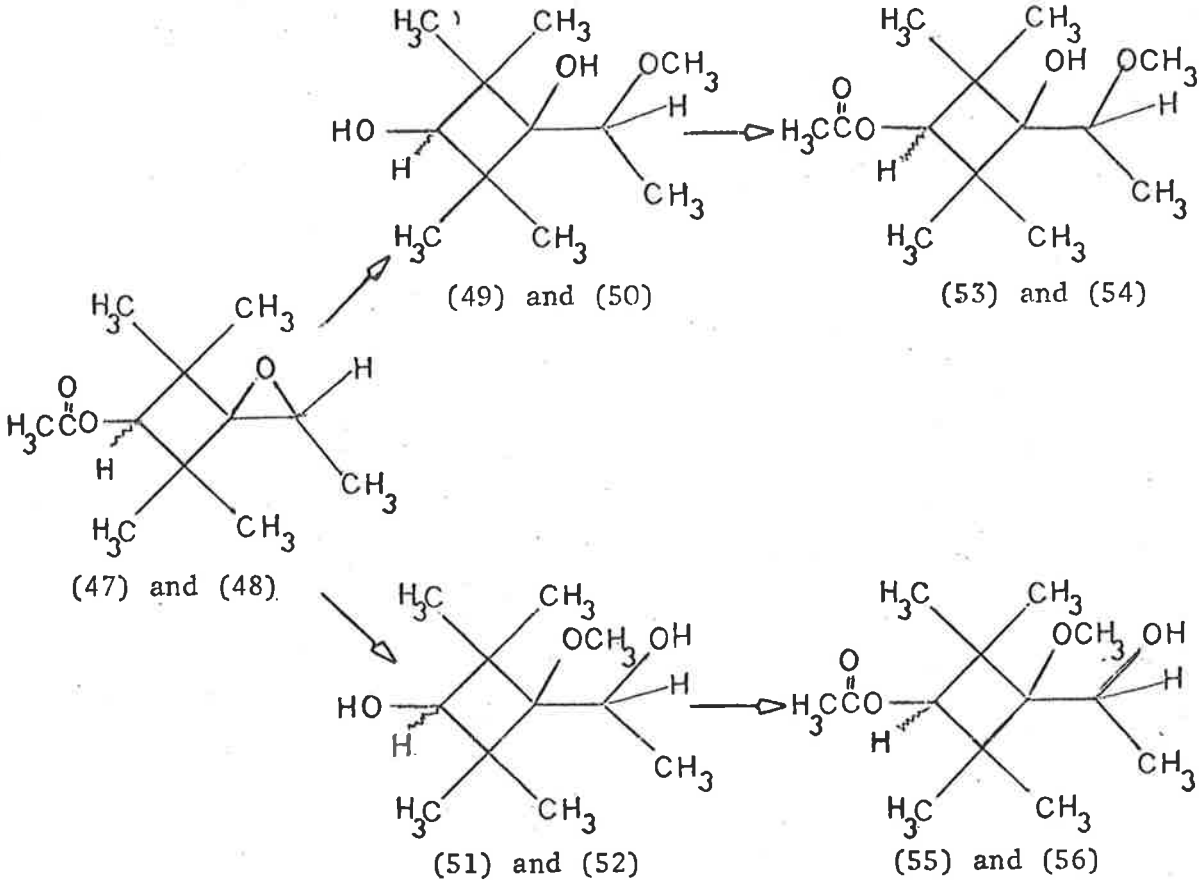
When the methanolysis products, both from the mixtures of (32) and (33) and of (47) and (48) were acetylated with excess acetic anhydride in pyridine at 60° for 48 h only one hydroxyl group was acetylated. The g.l.c. chromatogram of the acetylated product consisted of two main peaks of close retention time and a minor product of shorter retention time. The n.m.r. spectrum of the acetylated product is more diagnostic. The two singlets at δ 4.55 and 4.33 (one proton resonances) are due to the proton attached to the ring carbon bearing an acetoxy group. The appearance as two singlets is consistent with the presence of a mixture of two isomers. The complex region which was present in the spectrum of the product before acetylation is now a quartet centred at δ 3.60, each peak of which is broadened. The absorption of the introduced methoxy group appeared at δ 3.30. The infrared spectrum of the acetylated product showed strong O-H stretching between 3550 and 3330 cm^{-1} as well as a strong carbonyl stretching vibration at 1735 cm^{-1} due to the acetate function. The hydroxyl group in the acetylated product was not oxidised by Jones' reagent[76]

under the normal conditions. In comparison, the secondary hydroxyl group at the side chain of the keto diol (63) (see page 73), which would be expected to have the same steric requirement as the hydroxyl group at the same centre in the methanolysis product, was acetylated quite readily under mild conditions. This suggested that only the ring hydroxyl group was acetylated and that the remaining hydroxyl group was in fact tertiary and not secondary as anticipated.

Hence, it was likely that the acid-catalysed methanolysis of the mixture of the hydroxy epoxides (32) and (33) and the corresponding epoxy acetates (47) and (48) gave the products in which the methoxy group attacked at the secondary carbon atom (49) and (50) rather than at tertiary carbon atom (51) and (52) (Diagram 10). In each case, a mixture of the cis- and trans- isomers would be expected. Acetylation of the product should give a mixture of two isomeric acetyl derivatives (53) and (54).

Although the available spectroscopic evidence does not clearly differentiate between the two possibilities some support for the conclusion was discernable. In general[77], the proton of a secondary alcohol group ($\rangle$CH-OH), absorbs near δ 3.90 and the proton of the corresponding $\rangle$CH-OCH_3 absorbs near δ 3.7. In the present case, the proton at the carbon atom in question absorbs at δ 3.60,

Diagram 10

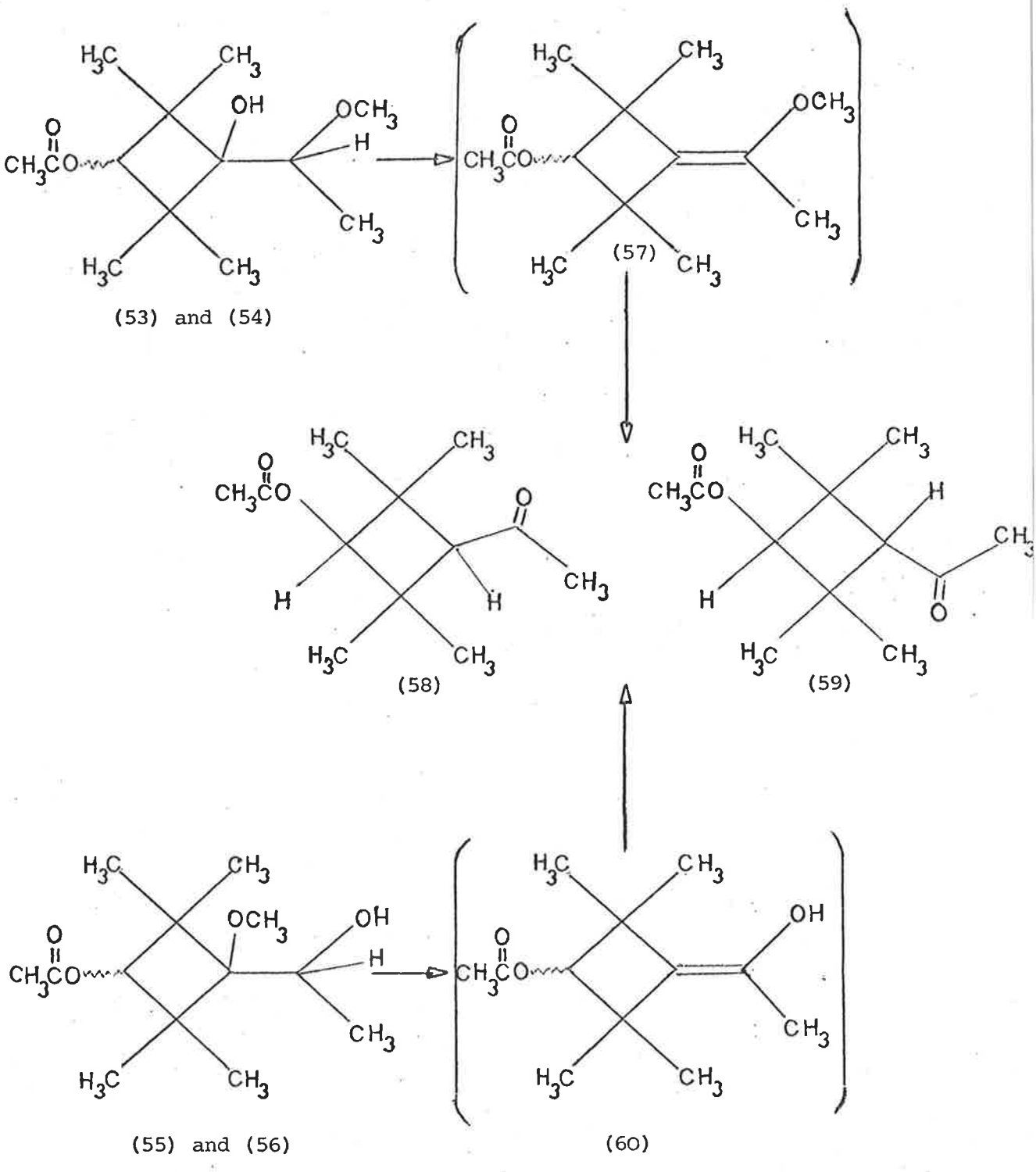


which is even at higher field than $\underline{CH}-OCH_3$ in general. These data could possibly suggest that the quartet at δ 3.60 in the spectrum of the acetylated methanolysis product is due to the proton attached to the methoxy group.

The mass spectrum of the mixture of the acetyl derivatives of the methanolysis products also provides more information of the structures (53) and (54). Although no molecular ion is observed as a weak peak at 244, the m/e 185 ion could be due to the loss of $CH_3\text{-}CH{=}OCH_3]^{+\cdot}$ (m/e 59) from the molecular ion. This ion could readily fragment to give the more stable oxonium ion $C_4H_6O]^{+\cdot}$, m/e 70 (base peak). On the other hand, a m/e 199 ion which corresponds to the loss of $CH_3\text{-}CH{=}OH]^{+\cdot}$ from the molecular ion is not observed. However, as the peak at m/e 185 was quite weak, one cannot be sure that it is not due to an impurity in the product, particularly since at least two isomers are present.

More chemical evidence for the confirmation of the structure (53) and (54) was that the tertiary hydroxyl group could be dehydrated on treatment with thionyl chloride in pyridine at $0\text{-}5^{\circ}$. The expected dehydrated product, methoxy enol ether (57), could not be isolated, but it was shown by g.l.c. analysis that an intermediate, which was readily rearranged to give a mixture of cis- and trans- keto acetates (58) and (59) either on standing at room temperature or by treating with dilute mineral acid, was present. This intermediate could presumably be the expected enol ether (57). However, the keto acetates (58) and (59) could also be expected from the thionyl chloride reaction of (55) and (56), but an intermediate (60) would not be detected[78] (Diagram 11).

Diagram 11



The keto acetates (58) and (59) which were isolated as a mixture of cis- and trans- isomers were shown by g.l.c. to have the same retention time as the minor component observed in the g.l.c. analysis of the crude methanolysis product of (47) and (48). The structures (58) and (59) were confirmed by the spectroscopic and analytical data. The infrared spectrum no longer contained O-H stretching absorptions but consisted of two carbonyl absorption bands at 1730 and 1705 cm^{-1}, corresponding to the carbonyl ester ($CH_3-\overset{O}{\overset{\|}{C}}-O-$) and the carbonyl ketone ($-\overset{O}{\overset{\|}{C}}-CH_3$), respectively. In the n.m.r. spectrum of the mixture (Table 9) the ring proton attached to the acetate group resonates at δ 4.98 and 4.45 (two sharp singlets, consistent with a mixture of two isomers). The resonances of the proton attached to the tertiary carbon atom and adjacent to the carbonyl group appears at δ 2.78 and 2.5 (again, two sharp singlets are due to two isomers). The lower field resonance possibly corresponds to the trans- isomer (with respect to the protons) because a diamagnetic anisotropic effect would be expected from the acetate group[79].

The formation of the product (49) and (50) might be explained in terms of steric effects. Brewster[80] suggested that the driving forces for the ring opening of the epoxides may be thought to be comprised of four components:

Table 9

N.m.r. spectrum of the mixture of (58) and (59)

δ (ppm)	Appearance	Integration	Assignment
4.98, 4.45	singlets	1	C1-H
2.78, 2.25	singlets	1	C3-H
2.1, 2.07	singlets	6	CH_3-C-O and CH_3-C(=O)-
1.34-1.06	multiplet	12	C2- and C4- methyl groups

(i) strain presents in the three-membered epoxide ring,

(ii) the "pull" effected by protonation of the ring oxygen,

(iii) the "push" of a nucleophilic displacing agent, and

(iv) the generation of the partial carbonium ion character at the site of the reaction. In certain reactions there may be a particular high degree of carbonium ion character such that the rearward nucleophilic "push" is not required for the reactions.

In the case of the hydroxy epoxide (32) and (33) and the acetyl derivatives (47) and (48) the formation of the carbonium ion at the tertiary carbon atom may not be favoured, due to two main factors. Firstly, high energy is required due to the change in the internal-strain (I-strain)[81] of the four-membered ring. The I-strain arises from the distortion of the normal bond angles to the bond

angles of the carbonium ion (120°). For cyclobutane carbonium ion, the deformation of the bond angles are 19.5° for the parent compound (from 109.5° to 90°), and 30° for the transition complex (from 120° to 90°)[81]. Secondly, although the electronic effect from the alkyl groups enhances the formation of the tertiary carbonium ion in preference to the secondary one, the solvation energy to stabilize the tertiary carbonium ion would be expected to be much higher than the solvation energy for the secondary carbonium ion, because, in the former case, the envelop of the solvent molecules is restricted by the ring methyl groups.

The structures of the epoxides and the reagents are important factors governing the direction and the stereochemistry of the ring opening of the epoxides[82]. It has been observed[83] that the positions 1 and 3 of the tetrasubstituted cyclobutane ring are very inactive to S_N2 reactions. The main factors inhibiting S_N2 attack at these centres is the highly crowded nature in both the reacting species and in the transition complex. The approach of the methoxy group to the tertiary carbon atom (Diagram 12) is more hindered than the approach to the secondary carbon atom (Diagram 13). Obviously, in the transition state in Diagram 12, the interaction between the methoxy group and the ring methyl groups is much greater than in Diagram 13.

Diagram 12

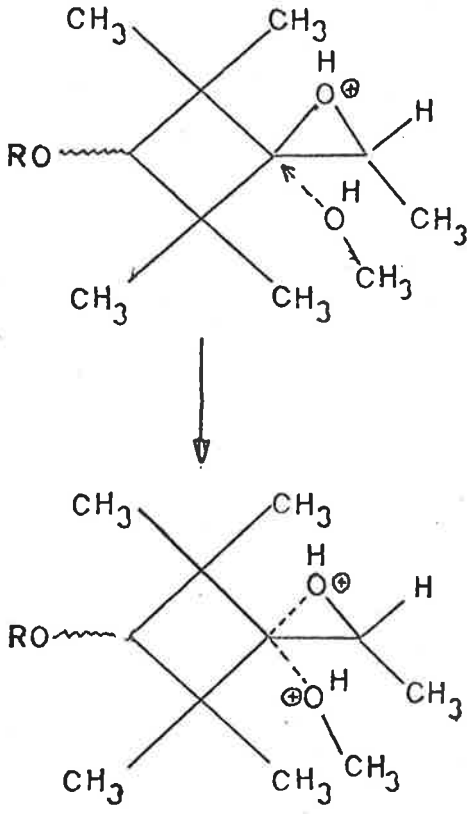
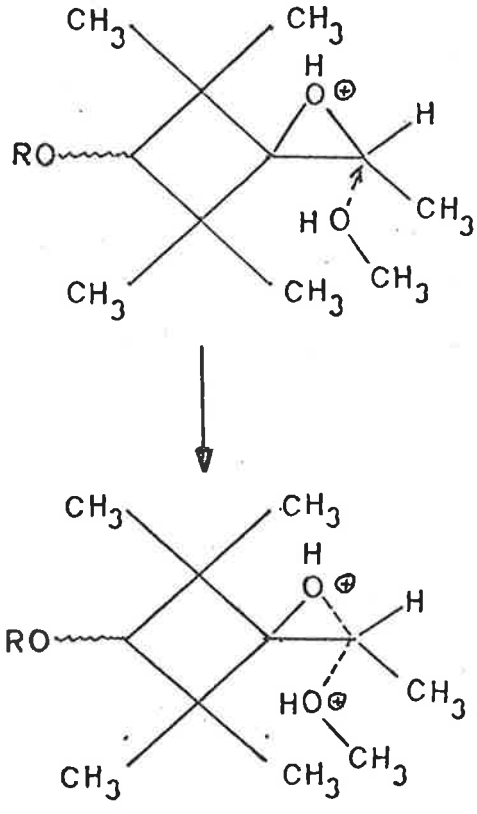
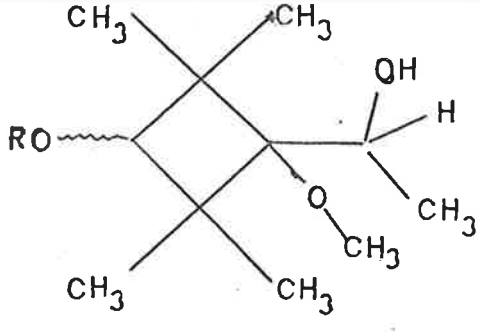


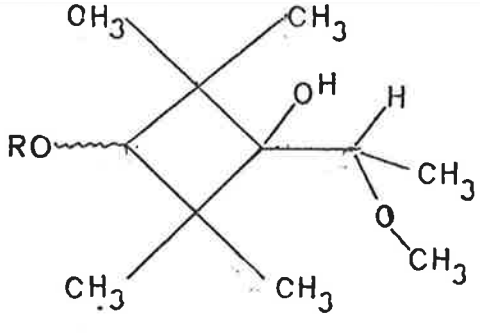
Diagram 13



Transition state



(51) and (52)



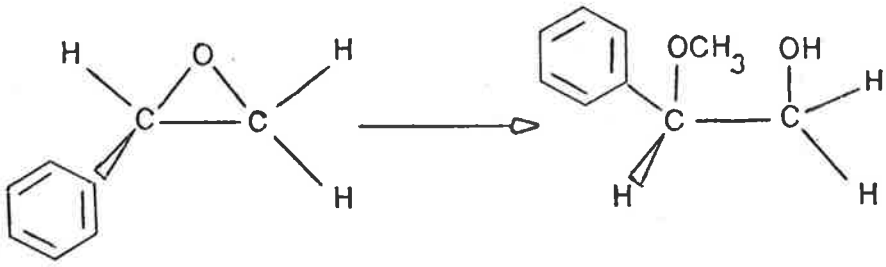
(49) and (50)

R = H, $CH_3\overset{O}{\overset{\|}{C}}-$

Furthermore, the steric hindrance in the products should also be considered as one of the factors that favoured the formation of (49) and (50) rather than (51) and (52). In the structure (51) and (52) the methoxy group cannot rotate freely about the C-O bond because it is flanked by at least two methyl groups on the same side of the ring, whereas in the structures (49) and (50) the rotation of the methoxy group is not restricted.

There is only one example in the literature[84] where complete inversion of the configuration at a secondary epoxide centre is not observed. Chapman et al found that the acid-catalysed methanolysis of (+)-(D)-(1,2-epoxyethyl)benzene (61) gave (+)-(L)-2-methoxy-2-phenylethanol (62) with 89% inversion of the configuration at the secondary carbon atom (Diagram 14). The mechanism proposed for the reaction is a "borderline A_2 mechanism", in which bond-breaking is more important than bond-making in the formation of the transition state. The partial retention of the configuration (11%) at the attacked carbon atom was thought to be due to the approach of the reagent (methoxy group) from the same side as the protonated epoxide oxygen. From the electronic point of view, the incomplete inversion of the configuration at this centre might be because generation of carbonium ion character is favoured by the resonance effect of the benzene ring allowing some attack of the nucleophile from both sides.

Diagram 14



(61) (62)

As the secondary carbon atom in the epoxides (32) and (33) does not bear a phenyl group no racemisation is anticipated at this centre, and it is assumed that inversion of the configuration has occurred.

Acid-Catalysed Hydrolysis of (36)

It was considered that reduction of the keto diol derived from the acid-catalysed hydrolysis of the keto epoxide (36) with sodium borohydride at low temperature (or with more selective reducing agents) might give rise to a major isomer (c.f. page 51). This might overcome the problems in separation of the cis- and trans- isomeric triols expected from the hydrolysis of the corresponding hydroxy epoxides (32) and (33). If this were so, then one might be able to resolve the keto diol before or after reduction to the corresponding triols.

It was found that the keto epoxide (36) was also very unreactive towards hydrolysis (c.f. reactivity of (32) and (33) towards reduction, page 55). Heating the epoxide with perchloric acid in aqueous dioxan at 65-70° for at least 60 h gave only about 30% yield of the racemic* 3-hydroxy-3-(1'-hydroxyethyl)-2,2,4,4-tetramethylcyclobutan-1-one (63) (Diagram 15). All attempts to increase the yield by using more concentrated acid or by increasing the temperature caused other unknown products to be formed.

The structure of the keto diol (63) was confirmed by spectroscopic and analytical data. The infrared spectrum exhibited a strong

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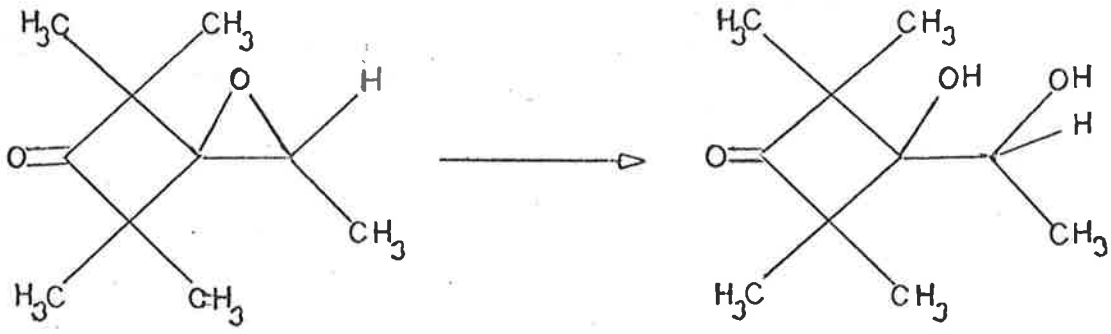
* Racemic modification occurred because the starting epoxide was a mixture of enantiomers.

Diagram 15



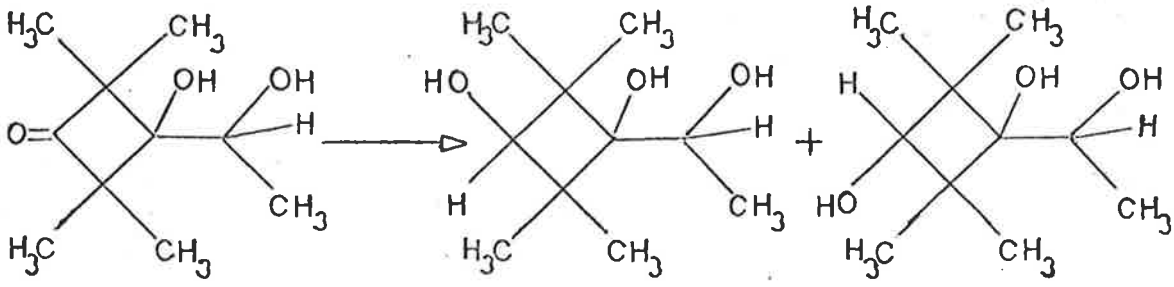
(36) (63)

hydroxyl absorption between 3580 and 3380 cm^{-1}, and a strong carbonyl absorption at 1765 cm^{-1} (4-membered ring ketone). The one proton quartet at δ 4.43 in the n.m.r. spectrum corresponded to the proton attached to the secondary hydroxyl group.

Reduction of the keto diol (63) with sodium borohydride at 0-5° gave an about 3:1 mixture of the isomeric trios, 3-(1'-hydroxyethyl)-2,2,4,4-tetramethylcyclobutanediol (1,3), (64) and (65) (Diagram 16). The isomer which had shorter retention on g.l.c. was

the major component. The n.m.r. spectrum also indicated that the relative intensity of the peaks at δ 3.70 and 3.40 was about 3:1, corresponding to the introduced proton at C1. The infrared end n.m.r. spectra were consistent with the expected structures of the triols.

Diagram 16

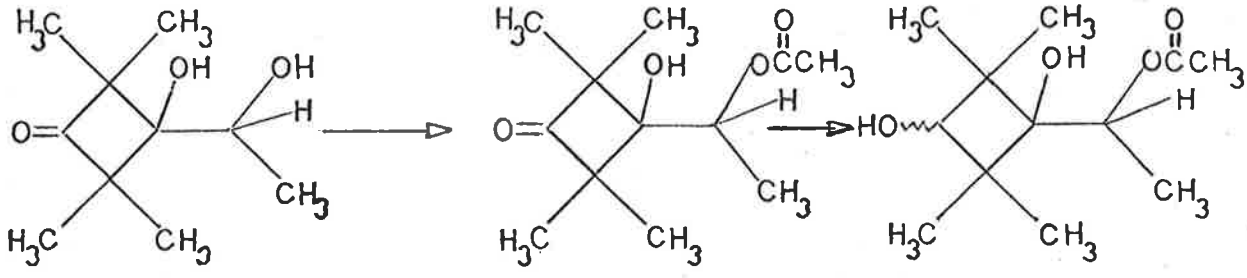


(63) (64) (65)

Furthermore, when the keto diol (63) was acetylated under mild conditions to give the monoacetyl derivative (66) followed by reduction with sodium borohydride, the isomers (67) and (68)

(Diagram 17) were formed in about a 4:1 mixture, in which the isomer which had shorter retention time on g.l.c. and absorbed at lower field (δ 3.73) was the major product.

Diagram 17



(63) (66) (67) and (68)

The triols (64) and (65) were also readily acetylated to give the corresponding isomeric diacetyl derivatives (69) and (70). The readiness in acetylation of the keto diols (63) and the triols (64) and (65) supports the conclusion that the remaining hydroxyl group in the methanolysis product of the hydroxy epoxides was a tertiary hydroxyl group (page 64).

It might be possible, at this stage, to assume that the major product formed in the reduction of the keto diol (63) or from the monoacetyl derivative (66) was the trans- isomer, with respect to the C1- and C2- hydroxyl groups. This assumption was based on the physical properties, e.g. the retention time and the n.m.r. spectrum, compared to those of the cis- and trans- hydroxy epoxides (32) and (33), the tetrahydropyranyl ethers (34) and (35) and the diols (43) and (44) which have been established (page 61). The C1-proton resonances in (33), (35) and (44) appeared at lower field than in the corresponding cis- isomer, viz., at δ 3.73, 3.76 and 3.70, respectively. The retention times of the trans- isomers were shorter than those of the cis- isomer.

It was hoped that the triols (64) and (65) might be converted into the hydroxy epoxides (32) and (33) by cyclisation involving the leaving group[59] at the secondary centre and not affecting the configuration at the tertiary carbon atom. This would confirm the above assumption, because the isomeric hydroxy epoxides should be formed in the same ratio as the starting triols. Preliminary attempts to esterify the secondary hydroxyl group at C2- to the tosylate or mesylate were unsuccessful, whereas acetylation occurred readily. The difficulties in the tosylation and mesylation of the triols were probably because of the larger sizes of the tosylate and the mesylate groups. Due to lack of time further investigation was not carried out.

EXPERIMENTAL

EXPERIMENTAL

General

Melting points were determined in Pyrex capillaries by using an electrically heated Gallenkamp apparatus, or on a Kofler hot stage apparatus, and are uncorrected.

Infrared spectra were recorded with Perkin-Elmer 237 Grating Spectrophotometer and a Unicam SP 200 Spectrophotometer.

N.m.r. spectra were recorded with a Varian T-60 Spectrometer, operating at 60 Mc/sec. The chemical shifts were measured in ppm relative to tetramethylsilane (TMS) as the internal standard. Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad; exch.D_2O implies that the signal is removed by the addition of D_2O.

Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6D Spectrometer, fitted with a double focussing device, operating at 70eV.

Gas liquid chromatography (G.l.c.) analysis were carried out with a Perkin-Elmer 800 Gas Chromatograph and a PYE Unicam 104. The latter was equipped with an integrater for quantitative analysis of ratio of the peak area. Both employed flame ionisation detectors, and nitrogen gas was used as the carrier gas.

Preparative g.l.c. was carried out using a Varian Aerograph 705 instrument and a PYE Unicam 104.

Optical rotations were determined in a 1 dm tube using a Hilger and Watts polarimeter.

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

Woelm neutral alumina, activity grade 1, and Crosfield Sorbsil SG 60 were used as absorbents in column chromatography. Analytical and preparative thin-layer chromatography (t.l.c.) were carried out on layers containing an equal mixture of Merck Kieselgel G and HF_{254}.

Organic extracts were dried over anhydrous sodium sulphate or magnesium sulphate.

Diethyl ether (ether) was dried over P_2O_5, distilled from sodium and stored over sodium wire.

Dioxane was refluxed with potassium hydroxide pallets, distilled from sodium and stored under nitrogen.

Pyridine was distilled from potassium hydroxide pallets and stored over potassium hydroxide pallets.

Dimethoxyethane (DME) was distilled from sodium and stored over sodium wire.

"Light petroleum" refers to petroleum ether boiling point 40-60°, and was dried over $CaCl_2$ and distilled.

Light petroleum (b.p. 28-38°) was shaken with conc.H_2SO_4; washed with water; dried over $CaCl_2$, distilled and stored over sodium wire.

Work Described in Part I.

(-)-(S)-Ethyl 2-benzyloxypropionate (7)

To a solution of ethyl lactate $[\alpha]_D^{20}$-9.84° (47.25 g), and benzyl bromide (68.42 g) in dried ether (300 ml), silver oxide (46 g) was added gradually with stirring, over a period of 1.5 h. The reaction mixture was stirred while heating under reflux for a further 1.5 h. The precipitate was filtered and washed with ether. The ethereal solution was distilled to give the crude product, b.p. 130-154°/15 mm. Redistillation gave the required product (30.6 g, 47%, b.p.140-143°/14mm (lit.[19] b.p. 105-106°/1.5 mm, from (±) ethyl lactate), $[\alpha]_D^{24}$-66.3° (neat), η^{24} 1.4898. G.l.c. analysis (column 5' 10% S.E. 52, at 148° and 30 ml/min) indicated that the product was pure. ν_{max}(film) 3090, 3070, 3030 and 1740 cm^{-1}. N.m.r. spectrum (CCl_4) : δ 7.33 (5H,s,aromatic protons), 4.7-3.7 (5H, br,m, O-$\underline{CH_2}$-CH_3 and -O-$\underline{CH_2}$-Ph) and 1.53-1.03 (6H, m, -CH_3). (Found: C, 69.5; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%).

(+)-(S)- 2-Benzyloxy-3-hydroxy-3-ethylpentane (8b)

A solution of the ester (7) (6.27 g) in dry ether (20 ml) was added, with stirring, into a solution ethylmagnesium bromide, kept at 0°. The grignard reagent was prepared by the method described by Vogel[85] (from ethyl bromide (16.35 g) and magnesium turnings (3.65 g)). The addition of (7) took about an hour. The reaction

mixture was then stirred at room temperature for 0.5 h. The excess reagent was decomposed by pouring carefully into crushed ice (200 g). A saturated solution of ammonium chloride (100 ml) was added and the aqueous layer was separated and washed with ether (4 x 75 ml). The combined ether extracts were washed with water (3 x 50 ml) and dried. Distillation gave the product (8b) (5.95 g, 78%), b.p. 100-103°/0.4 mm. $[\alpha]_D^{20}$ + 48.85° (neat, η 1.5005. G.l.c. analysis (column 5' 10% S.E. 52 at 150° and 30 ml/min) indicated that the product was pure. ν_{max}(film) 3500 broad), 3090, 3070, 3030 and 1495 cm^{-1}. N.m.r. spectrum ($CDCl_3$): δ 7.37 (5H, aromatic protons), 4.53 (2H, AB quartet, J=12 Hz, O-CH_2-Ph), 3.48 (1H, q, J=6 Hz, C2-H), 2.14 (1H, br, exch.D_2O, -OH) and 1.63-0.7 (13H, br,m). (Found: C, 75.4; H, 9.95. $C_{14}H_{22}O_2$ requires C, 75.6; H, 10.0%).

(+)-(S)- 3-Benzyloxy-2-hydroxy-2-methylbutane (8a)

Methylmagnesium iodide solution was prepared by the method described by Vogel[86], from redistilled methyl iodide (42.6 g) in dry ether (70 ml) and magnesium turnings (7.3 g) in dry ether (50 ml). The solution was kept in an ice-bath, and a solution of (7) (8.36 g) in dry ether (20 ml) was added dropwise with stirring over a period of 1 hour. Then the reaction mixture was stirred for a further 0.5 h. Work up in the same manner as for the compound (8b) gave the product (8a) 5.8 g (75%), b.p. 129-132°/12 mm, $[\alpha]_D^{23}$ + 47.25° (neat), η^{24} 1.4800. ν_{max}(film) 3500 (broad), 3090, 3070, 3030 and 1495 cm^{-1}.

N.m.r. spectrum ($CDCl_3$) : δ 7.27 (5H, aromatic protons), 4.52 (2H, AB quartet, J=12 Hz, -C<u>H</u>$_2$-Ph), 3.03 (1H, q, J=6 Hz, C2-H), 2.5 (1H, br, exch.D_2O, -O<u>H</u>) and 1.16-1.06 (9H, a singlet and a doublet, $-CH_3$). (Found : C, 74.5; H, 9.2. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%).

(-)-(S)-2-Benzyloxy-1-hydroxy-1,1-diphenylpropane (8d)

Following the procedure described above, the reaction of (7) (8.36 g) with phenylmagnesium bromide[87] (from bromobenzene (16 g) and magnesium turnings (5 g)) at room temperature, gave the crystalline product (8d). Two recrystallisations from aqueous ethanol yielded white crystals (5 g); m.p. 74.5-75.5°, $[\alpha]_D^{20}$-41.7° (c, 2.4 in chloroform). ν_{max} (nujol) 3560 (s, sharp), 3095, 3060, 3035, 1600 and 1500 cm^{-1}. N.m.r. spectrum (CCl_4) : δ 7.2 (15H, m, aromatic protons), 4.70-4.21 (3H, m, C2-H and -C<u>H</u>$_2$-Ph), 2.91 (1H, br, exch. D_2O, -OH) and 1.07 (3H, d, J=6 Hz, $-CH_3$). (Found: C, 83.1; H, 7.0. $C_{22}H_{22}O_2$ requires C, 83.0; H, 7.0%).

(+)-S)-2-Benzyloxy-1-hydroxy-1,1-dicyclohexylpropane (8e)

This compound was obtained from the reaction of (7) (8.36 g) in dry ether (20 ml) and cyclohexylmagnesium chloride[88] (from cyclohexyl chloride (30.5 ml) and magnesium turnings (6.7 g) in dry ether (112 ml)). The reaction started immediately at room temperature and proceeded smoothly without cooling. After the solution of the ester had been added (1.5 h) the reaction mixture was stirred and heated

under reflux for 1.5 h, and then worked up in the usual way. Evaporation of the solvent gave the crude product as an oily liquid. The infrared spectrum and t.l.c. showed that the crude product contained a small amount of the starting ester. Distillation at reduced pressure was attempted but was unsuccessful. Therefore, the product was purified by column chromatography (silica). The fraction eluted by ether:light petroleum (1:9) (5.3 g) showed no carbonyl absorption in the infrared spectrum, but an intense broad peak at 3580 cm^{-1}. Crystallisation occurred on standing overnight. Recrystallisation from aqueous methanol gave white crystals, m.p. 51.52°, $[\alpha]_D^{26}$ + 56.6° (c,1 in chloroform). ν_{max} (nujol) 3580 (broad), 3090, 3070, 3030 and 1495 cm^{-1}. N.m.r. spectrum (CCl_4) : δ 7.25 (5H, s, aromatic protons), 4.48 (2H, AB quartet, J=12 Hz, $-C\underline{H}_2-Ph$), 3.63 (1H, s, exch.D_2O, -OH) and 2.0-0.7 (25H, br, m, $-CH_3$ and cyclohexyl protons). (Found : C, 79.8; H, 10.3. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.4%).

(+)-(S)-2-Benzyloxy-3-hydroxy-3-isopropyl-4-methylpentane (8c)

Isopropyllithium solution was prepared by the procedure described by Gilman[22], from 2-chloropropane (11.78 g) in sodium dried light petroleum (b.p. 28-35°) (100 ml) and finely rasped lithium (2.4 g) in light petroleum (50 ml). A solution of the ester (7) (8.36 g) in light petroleum (50 ml) was added dropwise to the reagent (140 ml) with stirring under an atmosphere of nitrogen. It was necessary to initiate the reaction by gently warming the reaction flask in a water

bath. After the reaction had started the external heat was removed and the addition of the ester solution was carried out at such a rate that the solution refluxed gently (2 h). The mixture was then heated under reflux (under nitrogen) for a further hour and finally allowed to stand overnight. The excess reagent was decomposed in the same way as with the Grignard reagents. The ethereal layer was separated, and the aqueous layer was extracted with ether (4 x 75 ml). The combined ether extracts were washed with water (2 x 75 ml) and dried. Distillation gave a colourless liquid (2.8 g, 28%), b.p. 107-110°/0.35 mm, $[\alpha]_D^{20}$ + 57.0° (neat), η^{21} 1.5025. ν_{max} (film) 3580-3460, 3090, 3070, 3030 and 1500 cm^{-1}. N.m.r. spectrum (CCl_4) : δ 7.27 (5H, s, aromatic protons), 4.47 (2H, AB quartet, J=12 Hz, $-C\underline{H}_2-Ph$), 3.63 (1H, q, J=6 Hz, C2-H), 2.4 (1H, br, exch.D_2O -OH), 2.5-1.6 (2H, br, m, $-C\underline{H}(CH_3)_2$) and 1.36-0.87 (15H, m, $-CH_3$). (Found : C, 77.0; H, 10.5. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.5%).

(+)-(S)-3-Ethylpentane-2,3-diol (11b)

A solution of the benzyl ether (8b) (4.44 g) in methanol (30 ml) was hydrogenolysed in the presence of 5% Pd-C catalyst (0.4 g) during 1.5 h. The hydrogen uptake was 383 ml. After filtration, the solvent was evaporated to give the crude product (2.2 g, 83%). Distillation gave the pure diol (11b), b.p. 55.5-56.5°/0.45 mm (only 50% yield was collected due to the formation of a dark viscous residue), $[\alpha]_D^{26}$ + 6.02° (neat), $\eta^{23.5}$ 1.4510. [Lit.[18] b.p. 196-

198°/20 mm, $[\alpha]_D^{29}$ - 1.009° (neat)]. ν_{max} (film) 3560-3240 cm^{-1} (very broad), n.m.r. spectrum ($CDCl_3$) : δ 3.75 (1H, q, J=6 Hz, C2-H), 3.5 (1H, br.exch.D_2O, -OH), 2.8 (1H, br, exch.D_2O, -OH) and 1.7-0.77 (13H, m, $-CH_2$ and $-CH_3$). G.l.c. analyses (column 15% FFAP at 150° and 30 ml/min) indicated that the product was pure.

(+)-(S)-2-Methylbutane-2,3-diol (11a)

The benzyl ether (8a) was hydrogenolysed by the method described above to give the diol (11a) in 90% yield. The pure product had b.p. 42-43°/0.2 mm, $[\alpha]_D^{23}$ + 5.15° (neat), η 1.4380. [Lit.[18] b.p. 176-178°/20 mm, $[\alpha]_D^{29}$ - 6.965° (neat), lit.[89] b.p. 74°/10.5 mm $[\alpha]_D^{23}$ + 4.6° (neat). ν_{max} (film) 3540-3230 cm^{-1} (very broad). N.m.r. spectrum (CCl_4) : δ 3.76 (2H, br, exch.D_2O, -OH), 3.53 (1H, q, J=6 Hz, C3-H), 1.1-1.0 (3H, d, 4-CH_3 and 6H, s, C2-$(CH_3)_2$).

(+)-S)-3-Isopropyl-4-methylpentane-2,3-diol (11c)

Hydrogenolysis of the benzyl ether (8c) by the above method gave the diol (11c) in 82% yield. Recrystallisation from hexane gave white crystals, m.p. 73-74°, $[\alpha]_D^{26}$ + 22° (c,1 in chloroform). [Lit.[18] b.p. 116-119°/20 mm, $[\alpha]_D^{29}$ + 1.687° neat)]. ν_{max}(nujol) 3360-3260 cm^{-1}. N.m.r. spectrum (CCl_4) : δ 3.93 (1H, q, J= 6 Hz, C2-H, 1.96 (2H, br, exch.D_2O, -OH), 2.2-1.5 (2H, m, $-CH(CH_3)_2$), 1.18 (3H, d, J=6 Hz, 1-CH_3) and 1.0-0.86 (12H, m, $-CH(CH_3)_2$). (Found: C, 67.65; H, 12.6. $C_9H_{20}O_2$

requires C, 67.45; H, 12.6%).

(-)-(S)-1,1-Diphenylpropane-1,2-diol (11d)

The benzyl ether (8d) was hydrogenolysed by the method to give the diol (11d) quantitatively. Recrystallisation of the crude product from hexane gave needlelike crystals, m.p. 91-92°, $[\alpha]_D^{20}$ - 113.8° (c, 3.705 in ethanol). [Lit.[18] m.p. 94°, $[\alpha]_D^{29}$ - 97.16° (c, 3.07 in ethanol)]. ν_{max} (nujol) 3575 (sharp) and 3518 cm^{-1} (broad). N.m.r. spectrum (CCl_4) : δ 7.23 (10H, m, aromatic protons), 4.6 (1H, q, J=6 Hz, C2-H), 2.90 (1H, br, exch.D_2O,-OH), 1.73 (1H, br, exch.D_2O,-OH) and 0.98 (3H, d, J=6 Hz, 3-CH_3).

(+)-(S)-1,1-Dicyclohexylpropane-1,2-diol (11e)

Hydrogenolysis of the benzyl ether (8e) by the above method gave the crude diol (11e) in 88% yield, m.p. 78-83°. Recrystallisation from hexane gave the pure diol, m.p. 86-87°, $[\alpha]_D^{26}$+ 16.2° (c, 1 in chloroform). ν_{max} (nujol) 3270 cm^{-1} (broad). N.m.r. spectrum (CCl_4) : δ 3.90 (1H, q, J=6 Hz, C2-H) and 2.1-0.85 (27H, br, m, after exch.D_2O, 25H). (Found: C, 74.6; H, 11.8. $C_{15}H_{28}O_2$ requires C, 74.95; H, 11.7%).

The reaction between the ester (7) and isopropylmagnesium bromide

A solution of isopropylmagnesium bromide was prepared by the method described by Vogel[90], from 2-bromopropane (50 g) in dry ether

(25 ml) and magnesium turnings (12.15 g) in dry ether (25 ml). A solution of the ester (7) (8.36 g) in dry ether (20 ml) was added dropwise, with stirring, to the cooled Grignard reagent over a period of 1 h. Then the mixture was stirred and heated under reflux for a further hour. The unreacted reagent was then decomposed in the usual way. After the extraction the combined ether extracts were washed with water, dried and distilled. Three fractions were collected; (i) b.p. 80-126°/11 mm, (1.1 g); (ii) b.p. 130-134°/11 mm, (1.38 g) and (iii) b.p. 138-141°/11 mm, (4.76 g). T.l.c. indicated that the fraction (i) was mainly the starting ester, and the fractions (ii) and (iii) consisted of two components. The minor component corresponded to the starting ester. The fractions (ii) and (iii) were combined and purified by column chromatography (silica gel). The main fraction (4.5 g) was eluted by ether: light petroleum (1:4). ν_{max}(film) 3590-3320, 3090, 3070, 3030 and 1490 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 7.3 (5H, s, aromatic protons), 4.53 (2H, br, $-\underline{CH}_2-Ph$), 3.53 (2H, br, m), 2.2 (1H, br, exch.D_2O,-OH), 1.67 (1H, m, $-\underline{CH}(CH_3)_2$) and 1.25-0.77 (9H, m, $-CH_3$).

The product above (1.25 g) was dissolved in methanol (40 ml) and hydrogenolysed under the same conditions as described above. After 1 h the hydrogen uptake was 100 ml. After filtration, the solvent was evaporated to give an oil which solidified on standing. The addition of light petroleum (b.p. 40-60°) gave white crystals,

m.p. 64-65°, $[\alpha]_D^{24}$ - 4.5° (c, 2 in chloroform). ν_{max} (nujol) 3290-3180 cm^{-1}. N.m.r. spectrum (CCl_4) : δ 3.8 (1H, br), 3.23 (2H, br, exch.D_2O, -OH), 3.17 (1H, dd) and 2.1-0.8 (10H, m). Mass spectrum: m/e 73 (base peak), 55 (41%), 45 (25%). The spectroscopic data of this compound confirms the structure as 4-methylpentane-2,3-diol (12). (Lit.[29] erythro-diol, m.p. 51.5-52.5°; threo-diol, m.p. 55.3-56.4°).

Attempted reaction of (7) with t-butylmagnesium bromide

A solution of t-butyl bromide (27.4 g) in dry ether (50 ml) was added dropwise to magnesium turnings (4.86 g) suspended in dry ether (50 ml). A small crystal of iodine was added to initiate the reaction. After the addition of the bromide solution (3 h), the mixture was heated under reflux, with stirring, for 1.5 h. Titrimetric analysis[91] showed that about 16% of the Grignard reagent had been formed.

A solution of the ester (7) (3.14 g) in dry ether (20 ml) was added to the reagent, with stirring, over a period of 1.5 h, and then stirred for a further 1 h. Work up in the usual manner gave a liquid which was distilled, b.p. 105-106°/13 mm. The product was found to be the starting ester by comparison of the spectral data.

(+)-Pinane-2α,3α-diol (17)

A solution of potassium permanganate (11.7 g) and sodium hydroxide (2.5 g) in water (400 ml), kept at 0°, was quickly added with vigorous stirring, into a solution of α-pinene, $[\alpha]_D^{20}$ + 47.5° (13) (6.8g)in t-butanol (500 ml), crushed ice (250 g) and water (100 ml), kept in an ice-bath. The mixture was stirred for a further ten minutes and then allowed to stand overnight. After filtration of manganese dioxide, most of the butanol was distilled at atmospheric pressure to concentrate the solution to about 200 ml. Continuous extraction with ether for 48 hours gave the crude product which consisted of at least two compounds (by t.l.c.). The crude product (3.8 g) was then purified by column chromatography (silica gel). The first fraction (0.5g), was eluted by ether:light petroleum (3:7), and exhibited a strong carbonyl absorption at ν_{max} 1700 cm^{-1} and a broad hydroxyl absorption band. The second fraction (3 g), m.p. 48°, was eluted by ether:light petroleum (1:1), and showed no carbonyl absorption in the infrared spectrum. It was very hygroscopic, but sublimation gave the pure diol (17) (2.5 g, 29% from the starting pinene), m.p. 54.5-55° $[\alpha]_D^{20}$ + 1.1° (c, 8.14 in chloroform). [Lit.[40] m.p. 55.5-56°, $[\alpha]_D^{23}$ + 3.3° (in ethanol).

(-)-Pinane-2α,3α-diol (18)

Alkaline permanganate oxidation of (-)-α-pinene, $[\alpha]^{20}$ - 46.8° (14),by the procedure described above gave the diol (17) in 34% yield,

m.p. 53.5-54.5°, $[\alpha]_D^{20}$ - 0.78° (c, 7.68 in chloroform). [Lit.[41] m.p. 55.5-56°, $[\alpha]_D^{25}$ - 0.89° (c, 7.9 in chloroform)].

(-)-2α-Hydroxypinan-3-one (15)

Following the method of Schmidt[40], (+)-α-pinene (14a) (27.2 g) gave the ketol (15) (6.85 g, 20%) as a thick plate-like crystal, m.p. 34-35° (hexane), $[\alpha]_D^{20}$ - 20.74° (c, 12.73 in ethanol). [Lit.[40] m.p. 34-35°, $[\alpha]_D$ - 40° (in chloroform), lit.[39] m.p. 35.5-36.5°, $[\alpha]_D^{25}$ - 18.56° (c, 14.44 in ethanol).

(+)-2α-Hydroxypinan-3-one (16)

The ketol (16) was obtained in 20% yield from (-)-α-pinene, by the same procedure as for (15). The compound had m.p. 34-34.5°, $[\alpha]_D^{20}$ + 20.26° (c, 4.64 in ethanol), [lit.[41] m.p. 32.5-34°, $[\alpha]_D$ + 21.1° (c, 4.64 in ethanol)].

(-)-Pinane-2α,3β-diol (20)

The diol (20) was obtained from the reduction of the ketol (16) with lithium aluminium hydride, following the method of Suga[41]. The diol had m.p. 163-164° (crystallised from light petroleum), $[\alpha]_D^{20}$ - 47.5° (c, 2.4 in ethanol), [lit.[41] m.p. 160-161°, $[\alpha]_D^{25}$ - 33.3° (c, 4.8 in ethanol)].

(+)-Pinane-2α,3β-diol (19)

Reduction of the ketol (15) with lithium aluminium hydride by the same method as for (20) gave the diol (19), m.p. 162-163.5°,

$[\alpha]_D^{20}$ + 46.25° (c, 2.4 in ethanol). [Lit.[40] m.p. 159-160°, $[\alpha]_D$ + 50° (in ethanol)].

Racemic 2-phenylbutyric anhydride

The anhydride was obtained in 77% yield from the reaction of the sodium salt of the corresponding acid and oxalyl chloride, following the method described in the literature[12]. It was a colourless oily liquid.

Pyridine solution of racemic 2-phenylbutyric anhydride

The anhydride (2.3278 g, 7.5 x 10^{-3} moles) was dissolved in anhydrous pyridine (about 3 ml) and then the solution was made up to 10 ml by the addition of pyridine (total pyridine 7.6423 g). Therefore, 0.5 ml of this solution contained the acid anhydride 3.75 x 10^{-4} moles or 7.5 x 10^{-4} equivalents of 2-phenylbutyric acid, if hydrolysed.

General Procedure for Partial Resolution

The pyridine solution (0.5 ml) was added into the diols (about 2.5 x 10^{-4} moles) in a stoppered microtestube. The mixture was allowed to stand at room temperature for 15 to 18 h. Then a drop of water was added, shaken and left for about 30 minutes to hydrolyse the unreacted acid anhydride. The solution was transferred to a conical flask, and benzene (3 ml) and water (2 ml) were added. Then the mixture was titrated with 0.1 N sodium hydroxide solution in the presence of

phenolphthalein. From the volume of the alkali used, the percentage of esterification was calculated.

The aqueous layer was separated, washed with benzene (3 x 10 ml) and then acidified with 1 N hydrochloric acid. The solution was extracted with benzene (2 x 10 ml). The combined benzene extracts were washed with water (2 x 5 ml), dried and concentrated to about 2-3 ml. Benzene was added to make the volume 5 ml. The optical rotation of the acid solution was measured in a 1 dm tube. The results are summarized in Table 4.

Esterification of (+)-Alternifolenediol (4) with (±)-2-Phenylbutyric Anhydride

The hydrated alternifolenediol, m.p. 66-68°, $[\alpha]_D$ 11.5° was dehydrated in a drying pistol over P_2O_5 at 55-60° for 2 days. The pyridine solution was then added to the dehydrated diol (as a yellow oil). It was important to reduce contact with the atmosphere as much as possible since the oil crystallised quickly on absorption of moisture. The procedure of Horeau was used as described above. The results are summarized in Table 5.

After titration and the separation of the aqueous layer, the benzene layer from the sample 3 was washed with cold dilute hydrochloric acid and dried (Na_2SO_4). The benzene was evaporated to give a pale brown oily residue (0.0834 g). T.l.c. indicated that the crude product consisted of at least three components, one of which

Table 4.

Diols	Configuration	Quantity used[a] ($X10^{-4}$ mole)	Time (hr)	% Esterification	Sign and rotation of the acid (^{o})	Optical Yield (%)
11a	(+) S	2.55	18	55	-0.23	52
		2.60	18	60	-0.26	53
11b	(+) S	2.50	18	88	-0.19	27
		2.53	18	83	-0.18	27
11c	(+) S	2.50	15	64	-0.31	60
		2.52	15	68	-0.45	82
11d	(-) S	5.0	17	83	-0.83	63
		2.5	17	84	-0.38	55
11e	(+) S	2.50	18	69	-0.19	35
		2.50	18	68	-0.18	34
17	(+) 3R	2.50	15	92	+ 0.29	40
		2.51	15	95	+0.28	39
19	(+) 3S	2.50	18	100	- 0.31	40
		2.50	18	92	-0.30	41
18	(-) 3S	2.51	15	88	-0.24	35
		2.50	15	89	-0.35	48
20	(-) 3R	2.0	18	84	+0.33	40
		2.0	18	69	+0.26	60

corresponded to the starting diol. The mixture was separated by preparative t.l.c. The major component (0.052 g, 60%) was shown to be the C1-monoester (22) from the following spectroscopic data: ν_{max}(film) 3500 (broad), 1720 (strong) and 1620 cm^{-1} (weak). N.m.r. spectrum ($CDCl_3$) : δ 7.3 (7H, aromatic protons, C14-H and C15-H), 6.27 (1H, br, C13-H), 5.07 (1H, br, C7-H), 4.9-4.6 (2H, br, C7- and C1-H), 3.6-3.1 (2H, br, C2-H and Ph-C<u>H</u>-), 2.8-1.7 (11H, complex) and 1.1-0.65 (9H, m, $-CH_3$), M^+ 396.

The compound of higher R_f value (0.016 g, 14%) was presumably the diester (23) and had the following n.m.r. spectrum ($CDCl_3$) : δ 7.3 (12H, br), 6.2 (1H, br, s), 5.1-4.6 (4H, br, m), and 2.0-0.6 (complex).

Table 5

	wt. of (4) (g)*	Vol.of pyridine solution (ml)	Time (h)	Vol. of NaOH (mls)	Ester-ification (%)	Observed Rotation (°)	Optical Yield %
1	0.0575	1.0	20	12.30	59	-0.15	17.4
2	0.0595	1.0	20	12.03	63	-0.11	12
3	0.0555	0.7	16	8.85	37	-0.09	17

* weight after dehydration

Work Described in Part II

(+)-2-Phenylbutyric anhydride[12]

Resolution of (±)-2-phenylbutyric acid with cinhonidine by the method described in the literature[92] gave (+)-2-phenylbutyric acid in 70% yield, $[\alpha]_D^{24}$ + 88.6° (neat), [lit.[93] max $[\alpha]_D$ + 96.5° (benzene)].

The resulting optically active acid was converted into the corresponding acid anhydride by the method of Horeau[12], $[\alpha]_D^{24}$ + 132.7° (neat), [lit.[12] max $[\alpha]_D^{23}$ + 150° (neat)].

O-methyl podocarpoyl chloride (31)[64]

(+)-O-methyl podocarpoic acid was obtained in 92% yield from hydrolysis of optically active methyl O-methyl podocarpate by the method of Chang and Wood[94] (using potassium tert-butoxide and dimethyl sulphoxide). The acid had m.p. 157-158°, $[\alpha]_D^{24}$ + 134.2° (c, 4.15 in chloroform), [lit.[94] m.p. 158°].

The acid was converted into the corresponding acid chloride by the procedure described previously[64].

Attempted Resolution of (27) with (+)-2-Phenylbutyric Anhydride

A mixture of (27) (2.3 g, 0.015 mole) and (+)-2-phenylbutyric anhydride (0.776 g, 0.0025 mole) in dry pyridine (5 ml) was allowed to stand at room temperature for 15 h. After the unreacted anhydride

was hydrolysed (page 92), benzene (5 ml) and water (5 ml) were added. The solution was titrated with 0.1 N NaOH solution, from which 26.80 ml was used. Therefore, the esterification had occurred to the extent of 46.6% based on the anhydride.

The benzene layer was separated. The aqueous layer was extracted with benzene (3 x 15 ml). The combined benzene extracts were washed with water (2 x 10 ml), and dried. Distillation gave the starting alcohol, b.p. 90-91°/14 mm, which crystallised in the condenser (0.6 g). The residue (1.5 g) was separated by column chromatography (silica gel). The ester (30) (0.6 g), was eluted by ether:light petroleum (1:19), and the alcohol (27) was eluted by ether:light petroleum (1:1).

The ester (30) had the following spectra:- ν_{max}(film) 3030 (w), 1725 (s), 1600 and 1580 cm^{-1} (w), n.m.r. (CCl_4) : δ 7.23 (5H, ε), 5.1 (1H,q, J=7 Hz), 4.37 (1H, s), 3.43 (1H, t, J=7 Hz), 2.3-1.7 (2H, m), 1.6 (3H, d, J=7 Hz) and 1.3-0.8 (15H, m).

The g.l.c. analysis (column 5' x ¼" 20% FFAP, 170° and 10' x 1/8" 3% EGS, at 130°) of the ester showed only one symmetric peak in both cases. Neither the recovered alcohol nor the alcohol obtained from alkaline hydrolysis of the ester showed a measurable optical rotation. The n.m.r. spectrum of the recovered alcohol in the presence of the optically active shift reagent (29) consisted of four peaks of equal intensity in each methyl region (see page 42).

Attempted Reaction of (27) with O-methyl podocarpoyl chloride (31)

A mixture of (27) (0.15 g) and O-methyl podocarpoyl chloride (0.32 g) in dry pyridine (7 ml) was heated under reflux with vigorous stirring for 48 h. T.l.c. indicated that no product was formed. Both starting alcohol and the acid chloride (hydrolysed) were recovered.

5-Hydroxy-2,4,4,6,6-pentamethyl-1-oxaspiro[3.2]hexane (32) and (33)[58]

(i) By epoxidation of (27). A solution of m-chloroperbenzoic acid (3.75 g of 80% peracid) in chloroform (25 ml) was added into a stirred solution of (27) (2.31 g) in chloroform (10 ml), kept in a cold water bath. The mixture was stirred at room temperature for 3.5 h, then allowed to stand overnight. The remaining peracid was removed by the addition of sodium bisulphite solution (10%) until the solution was negative to starch-iodide paper, then neutralised with sodium bicarbonate solution (10%). The chloroform layer was separated and the aqueous layer was extracted with chloroform (3 x 10 ml). The combined chloroform extracts were washed with water (3 x 15 ml), dried and distilled. The trace of the solvent was removed by passing nitrogen through the residue to give the mixture of (32) and (33) as a liquid (2.44 g, 95%). ν_{max}(film) 3145 (br), 2950, 2850, 1380, 1370 and 910 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 3.73, 3.58 (1H, singlets (1:1), C5-H), 2.98 (1H, two overlapping quartets, C2-H), 2.67 (1H, br, exch.D_2O,-OH) and 1.70-0.93 (15H, m, $-CH_3$).

(ii) By reduction of (36) with $LiAlH_4$. A solution of the epoxyketone (36) (0.170 g) in dry ether (3 ml) was added to $LiAlH_4$ (0.020 g) suspended in dry ether (3 ml). The mixture was stirred at room temperature for 3 h. The excess reagent was decomposed by cautious addition of a few drops of water to the cooled reaction mixture. Then the mixture was extracted with ether (3 x 10 ml). The combined ether extracts were washed with water and dried. Evaporation of the solvent gave a colourless liquid (0.12 g, 70%). The infrared and n.m.r. spectra were identical with those of the product obtained by method (i). The relative intensity of the peak at δ 3.73 and 3.58 was also about 1:1.

(iii) By reduction of (36) with $NaBH_4$. A solution of the epoxyketone (36) (1.68 g) in methanol (50 ml) was added into $NaBH_4$ (0.75 g) suspended in methanol (50 ml), kept at 0-5°. After the evolution of the gas has ceased (1 h), t.l.c. indicated that the reduction was complete. The mixture was then poured into water (5 ml), neutralised with hydrochloric acid (5%) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 30 ml) and dried. Evaporation of the ether gave the product (1.5 g, 88%). The n.m.r. and infrared spectra of the product were identical with those of the product obtained by method (i). The intensity of the peaks at δ 3.73 and 3.58 was about 2:1.

The cis- and trans- epoxides were separated by preparative g.l.c. (column 12' x ¼" 25% TCEPE, at 148° and 85 ml/min).

Fraction 1 (33), retention time 41.5 min., was obtained as colourless crystals, m.p. 66.5-67.5°. N.m.r. spectrum ($CDCl_3$) : δ 3.73 (1H, s), 2.88 (1H, q, J=6 Hz), 1.78 (1H, br, s, exch.D_2O, -OH), 1.26 (3H, d, J=6 Hz) and 1.17-0.93 (12H, m). The tetrahydropyranyloxy derivative of this fraction had n.m.r. spectrum and retention time similar to those of the fraction 1 of the tetrahydropyranyloxy derivatives of the mixture.

Fraction 2 (32), retention time 47 min., was a colourless liquid. N.m.r. spectrum ($CDCl_3$) : δ 3.58 (1H, s), 2.95 (1H, q, J=6 Hz), 1.63 (1H, br, s, exch.D_2O, -OH), 1.27 (3H, d, J=6 Hz) and 1.35-0.97 (12H, m). It was contaminated by small amount of Fraction 1, as shown by the n.m.r. spectrum.

2,4,4,6,6-Pentamethyl-5-tetrahydropyran-2'-yloxy-1-oxaspiro[3.2] hexane (34) and (35)

A solution of 2,3-dihydropyran (1.9 ml), the mixture of (31) and (32) (1.7 g) and a crystal of p-toluenesulphonic acid was stirred at room temperature for 1 h. The solution was then neutralised with sodium bicarbonate solution (5%), then extracted with ether. The ether extracts were washed with water and dried. Evaporation of ether gave an oily liquid (1.85 g). ν_{max}(film) 2920, 2850, 1475, 1470, 1260, 1200 and 1120 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 4.55 (1H, br),

4.1-3.4 (3H, br, with two sharp peaks at 3.76 and 3.63), 2.9 (1H, two overlapping quartets), 2.0-1.36 (6H, br), and 1.36-0.93 (15H, m). G.l.c. analysis (column 5' x ¼" 20% FFAP, at 150° and 50 ml/min) indicated two main peaks (ratio 1:1) with retention times 8.37 and 10.16 min.

The two isomers were separated by preparative g.l.c. (column 12' x ¼" 20% FFAP, at 150° and 86 ml/min).

Fraction 1 (35), retention time 28 min., was a colourless liquid, η^{24} 1.4572, n.m.r. spectrum ($CDCl_3$) : δ 4.55 (1H, br, s), 4.1-3.3 (3H, br, m, with a sharp singlet at 3.76), 2.87 (1H, q, J=6 Hz), 2.0-1.4 (6H, br, m) and 1.3-0.93 (15H, m). (Found: C, 70.7; H,10.25. $C_{15}H_{26}O_2$ requires C, 70.8; H, 10.3%). Hydrolysis of this fraction with methanol in the presence of a catalytic amount of p-toluenesulphonic acid at room temperature gave a hydroxy epoxide whose n.m.r. spectrum and retention time were similar to those of the fraction 1 of the hydroxy epoxides (33).

Fraction 2 (34), retention time 34 min., was a colourless liquid, η^{24} 1.4582. N.m.r. spectrum ($CDCl_3$) : δ 4.55 (1H, br, s), 4.06-3.36 (3H, br, m, with a sharp singlet at 3.63), 2.93 (1H, q, J=6 Hz), 1.8-1.4 (6H, br, m) and 1.33-0.95 (15H, m). (Found: C, 71.1; H, 10.15 %).

On increasing the temperature of the column to 170° the

minor peak of retention time 18 min. increased and the compound was collected. Its n.m.r. spectrum was similar to that of the mixture of the hydroxy epoxides (32) and (33).

6,6,8,8-Tetramethyl-1,4-dioxaspiro[4.3]octan-7-one (38)[66]

The reaction of 2,2,4,4-tetramethylcyclobutan-1,3-dione (37) with ethylene glycol and subsequent hydrolysis of the diketal formed[66] gave the required monoketal (38) as a solid (32% yield), b.p. 73-75°/2 mm, m.p. 55-57°, (lit.[66] b.p. 84-87°/5 mm, m.p. 56-57°).

7-Ethylidene-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (39)[68]

Ethyltriphenylphosphonium iodide was obtained in 97% yield by the method described in the literature[67]. The salt had m.p. 162-164° (lit.[67] m.p. 163-164.5°).

The ethyltriphenylphosphonium iodide (85 g) was added in to potassium tert-butoxide (25 g) dissolved in dry ether (500 ml). After the Wittig reagent was formed (bright orange colour developed), a solution of the ketal (38) (37 g) in dry ether (100 ml) was added. The mixture was heated under reflux with stirring under an atmosphere of nitrogen for 6 days. Triphenylphosphine oxide was removed by the addition of water (150 ml) and filtered. The aqueous layer was separated and extracted with ether (2 x 75 ml). The combined ether extracts were washed with water, dried and distilled. When the solution was concentrated more phosphine oxide precipitated, which was separated by the addition of light petroleum and filtered. The

resulting filtrate was distilled. The infrared and n.m.r. spectra of the product, collected at b.p. 91-94°/11 mm (27.3 g), indicated that it was the mixture of the starting ketal and the required product (about 1:4). Column chromatography (Woelm alumina, activity grade 1) gave 56% yield of the required product, which was eluted by light petroleum. ν_{max}(film) 1660, 1130, 830 and 780 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 5.15 (1H, q, J=7 Hz, =C-H), 3.87 (4H, s, $-O-(CH_2)_2-O-$), 1.62 (3H, d, J=7 Hz, $=C-CH_3$), 1.26 (6H, s, ring-CH_3) and 1.1 (6H, s, ring-CH_3). These spectral data are similar to those observed by Hamon[68].

3-Ethylidene-2,2,4,4-tetramethylcyclobutan-1-one (40)[68]

The mixture of the ethylene ketal (39) (3.95 g), 10% hydrochloric acid (10 ml) and methanol (50 ml) was heated under reflux for 3 h. The solution was cooled, poured into ether (150 ml), and washed twice with sodium bicarbonate (10%), then with water. The ethereal solution was dried and distilled to give the product (2.65 g, 87%). ν_{max}(film) 1780, 1685, 1030 and 830 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 5.5 (1H, q, J=7 Hz, =C-H), 1.73 (3H, d, J=7 Hz, $=C-CH_3$), 1.35 (6H, s, ring-CH_3) and 1.2 (6H, s, ring-CH_3). (Lit.[68] b.p. 150°/760 mm).

2,4,4,6,6-Pentamethyl-1-oxaspiro[3.2]hexan-5-one (36)

Epoxidation of the ethylideneketone (40) with m-chloroperbenzoic acid under the same conditions as those for(27) gave the keto epoxide (36) in 96% yield. The keto epoxide had b.p. 95-98°/15 mm. ν_{max}(film) 1775, 1270, 1060 and 910 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 3.22 (1H, q, J=6 Hz, C2-H), 1.4 (3H, d, J=6 Hz, C2-CH_3), 1.3-1.1 (12H, m, ring-CH_3). M^+ 168, m/e 70 (base peak). (Found : C, 71.3; H, 9.6. $C_{10}H_{16}O_2$ requires C, 71.4: h, 9.6%).

3-Ethyl-2,2,4,4-tetramethylcyclobutanediol-1,3 (43) and (44)

(i) By reduction of the mixture of (32) and (33)

$LiAlH_4$ (0.152 g) was added into a solution of the mixture of (32) and (33) (0.68 g) in dimethoxyethane (5 ml), and the mixture was heated under reflux with stirring under nitrogen. After 3 days the reaction was not complete (followed by t.l.c.). $LiAlH_4$ (0.05 g) and the solvent (3 ml) were added and the mixture was stirred and heated under reflux for a further 5 days. Work up in the usual way gave the crude product (0.5 g). G.l.c. analysis (column 5' 20% OV-101, at 120° and 50 ml/min) indicated that the crude product consisted of the starting epoxides and the required diols in a ratio about 1:5, retention time 7 and 10 min respectively. Analytical sample was prepared by preparative g.l.c. (column 5' x ¼" 20% FFAP, at 140° and 100 ml/min). (Found : C, 67.8; H, 11.3. $C_{10}H_{22}O_2$ requires C, 69.7; H, 11.7%). This analytical data is unsatisfactory. ν_{max}(film) 3555-

3220 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 3.70 (br, s) and 3.37 (br, s) (1H, Cl-H), 1.9-1.3 (4H, br, m, after exch.D_2O, 2H, q, $-CH_2-$), 1.27-0.8 (15H, m, ring-CH_3 and side chain -CH_3). After the addition of $Eu(dpm)_3$ (25 mg) the ring methyl resonances were shifted to δ 2.3-2.1, and the side chain methyl resonances appeared as a pair of triplets at 1.7 and 1.5, J=7 Hz (Figure 5). The purified diols showed two peaks on column 15% QF-1, at 110° and 33 ml/min, retention times 7.38 and 8.23 min (Figure 6).

Reduction of the fraction 1 of the hydroxy epoxide (33), gave the product which had the same retention time as the first peak (7.38 min) and had the following n.m.r. data ($CDCl_3$) : δ 3.70 (1H, br, s), 1.75-1.2 (4H, br, m, after exch.D_2O 2H), and 1.15-0.8 (15H, m).

(ii) By reduction of the mixture of (34) and (35)

Reduction of the mixture of the tetrahydropyranyl ethers (34) and (35) gave mainly the required hydroxy products and a small amount of the starting epoxides (shown by g.l.c.). The crude product had the following spectra: ν_{max}(film) 3450 cm^{-1} (br), n.m.r. ($CDCl_3$) : δ 4.5 (1H, br), 4.1-3.3 (4H, br, m, with two sharp singlets at 3.71 and 3.40), 1.9-1.3 (10H, br, m, after exch.D_2O 8H) and 1.2-0.85 (15H, m).

The crude product above (0.4 g) was hydrolysed to give a mixture of (43) and (44) together with (32) and (33) (0.29 g). After separation by preparative g.l.c. the infrared and n.m.r. of the main product were identical with those of the product obtained by method (i).

When the fraction 1 of the tetrahydropyranyl ether (35) was reduced followed by hydrolysis the product had the n.m.r. spectrum and retention time similar to those of the product obtained from the reduction of (33).

2,4,4,6,6-Pentamethyl-1-oxaspiro[3.2]hexyl-5-acetate (47) and (48)

Acetic anhydride (0.80 ml) was added into a solution of the mixture of (32) and (33) (1.15 g) in dry pyridine (2.5 ml) and the solution was allowed to stand at room temperature overnight. A few drops of water were added and stirred vigorously to hydrolyse the excess anhydride. The solution was then extracted with ether (4 x 5 ml). The ether extracts were washed with cold dilute hydrochloric acid, then with water and dried. Distillation gave a colourless liquid (1.25 g, 87%), b.p. 87-89°/15 mm, η 1.4415. ν_{max} 1740, 1385 and 1250 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 4.57 and 4.45 (1H, singlets (1:1), C5-H), 2.93 (1H, br, C2-H), 2.15 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$) and 1.37-0.98 (15H, m, $-CH_3$). $M^{+\cdot}$ 212, m/e 70 (base peak), 43 (38%), 97 (54%). (Found : C, 68.25; H, 9.6. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%).

Acid-catalysed methanolysis of (32) and (33)

A solution of the mixture of (32) and (33) (0.17 g), 70% perchloric acid (0.05 ml) in methanol (2 ml) was heated under reflux for 40 h. The solution was then cooled to room temperature and neutralised with sodium bicarbonate (10%), then extracted with ether (3 x 5 ml). The ether extracts were washed with water, dried and evaporated. The crude product was obtained as a pale yellow liquid (0.2 g). ν_{max}(film) 3450 cm^{-1} (br), n.m.r. spectrum ($CDCl_3$) : δ 3.8-3.35 (2H, complex), 3.28 (3H, s, $-O-CH_3$), 1.73 (2H, br, exch. D_2O,-OH), and 1.5-0.85 (15H, m). The crude product was acetylated without further purification.

Acid-catalysed methanolysis of (47) and (48)

The mixture of (47) and (48) (0.53 g) was methanolysed under the same conditions as described above to give the crude product 0.46 g. The infrared spectrum of the crude product showed a weak carbonyl absorption peak, and a strong hydroxyl absorption peak between 3550 and 3350 cm^{-1}. The n.m.r. spectrum was similar to that of the methanolysis product of the mixture of (32) and (33). G.l.c. analysis (column 5' x ¼" 20% FFAP at 170° and 30 ml/min) indicated two main peaks, retention times 8.30 and 9.22 min, and a small peak, retention time 6.30 min. The methanolysis product was acetylated without further purification.

Acetylation of the methanolysis products

The methanolysis products both from the mixture of (32) and (33) and of (47) and (48) were combined and acetylated at room temperature overnight. The product had the following spectroscopic data:- ν_{max}(film) 3500 (strong, br), 1735 (strong), 1385 and 1245 cm^{-1}, n.m.r. spectrum ($CDCl_3$) : δ 4.55 and 4.37 (1H, singlets), 3.60 (1H, q), 3.30 (3H, s, $-OCH_3$), 2.1-2.07 (4H, br, after exch.D_2O, 3H, s) and 1.28-0.97 (15H, m). G.l.c. analysis (column 5' x ¼" FFAP, at 175° and 30 ml/min) showed three peaks having retention times 4.08 min (minor peak; increased when the crude product was treated with dilute acid or stood over a longer period), 6.55 and 7.32 min (main peaks -two isomers). Analytical sample was obtained by preparative g.l.c. (Found: C, 64.2; H, 9.9. $C_{13}H_{24}O_4$ requires C, 63.9; H, 9.9%).

When the product (0.27 g) and acetic anhydride (0.4 ml) in pyridine (2 ml) was heated under reflux for 48 h t.l.c. showed that no product was formed. The starting material was recovered almost quantitatively.

3-Acetyl-2,2,4,4-tetramethylcyclobutyl-1-acetate (58) and (59)

The product above (0.25 g) was dissolved in dry pyridine (0.5 ml) and kept at 0-5°. Thionyl chloride (0.05 ml) was added to the pyridine solution, and stirred for 0.5 h. The solution was extracted with chloroform. The chloroform extracts were washed with

water and dried. Evaporation of chloroform gave a brown liquid (0.22 g). G.l.c. analysis (column 5' x ¼" 20% FFAP at 175° and 43 ml/min) indicated that the crude product consisted of two peaks in the ratio of about 1:4, retention times 2 and 3.15 min, respectively.

On treating the crude product with dilute hydrochloric acid or standing at room temperature, the minor peak rearranged to give the major one. The isolated major product had the following spectroscopic data: ν_{max} ($CDCl_3$) 1730 ($-\overset{O}{\overset{\|}{C}}-O$) and 1705 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-CH_3$) n.m.r. ($CDCl_3$) : δ 4.98 and 4.45 (1H, singlets -two isomers), 2.78 and 2.50 (1H, singlets, -two isomers), 2.16-2.05 (6H, three sharp singlets, $-\overset{O}{\overset{\|}{C}}-CH_3$ and $CH_3-\overset{O}{\overset{\|}{C}}-O$), and 1.34-1.06 (12H, m). $M^{+\cdot}$ 212, m/e 72 (base peak). (Found : C, 68.2; H, 9.8. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%).

Attempted oxidation of (53) and (54)

A drop of Jones' reagent[78] was added into a solution of the mixture of (53) and (54) (70 mg) in acetone (5 ml). No change in colour was observed. One more drop of the reagent was added, the solution was shaken and stood for a few minutes. The colour of the solution was still unchanged, and the starting material was recovered.

In order to check the reactivity of the reagent the known alcohol, (27), was treated under the same conditions. The change in colouration was observed immediately, and the oxidation product, (36), was obtained.

3-Hydroxy-3-(1'-hydroxyethyl)-2,2,4,4-tetramethylcyclobutan-1-one (63)

A solution of the keto epoxide (36) (0.126 g) dioxane (4 ml), water (1.5 ml) and 0.1 N perchloric acid (0.2 ml) was stirred at 68-70° for 60 h. T.l.c. indicated that the reaction was not complete. The solution was cooled to room temperature and neutralised with sodium bicarbonate (5%), then extracted several times with ether. The ether extracts were washed twice with water, dried and evaporated. Addition of light petroleum to the oily residue gave white crystals (0.052 g, 31%), m.p. 87-91°. Recrystallisation gave m.p. 93-94°. $\nu_{max}(CDCl_3)$ 3500 (br), 2250 ($CDCl_3$), 1760 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 4.43 (1H, q, C<u>H</u>-OH), 2.35 (1H, br, s, exch.D_2O, -OH), 1.6 (1H, br, exch.D_2O, - OH) and 1.43-1.1 (15H, m, $-CH_3$). M^+ 186, <u>m/e</u> 43 (base peak), 71 (43%), 45 (16%), 143 (2%). (Found : C, 64.6; H, 9.8. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

The mother liquor contained some of the starting material and some other products which were not isolated.

3-Hydroxy-3-(1'-acetoxyethyl)-2,2,4,4-tetramethylcyclobutan-1-one (66)

The keto diol (63) (0.035 g) was acetylated at room temperature for 2 h to give the acetyl derivative (66) (0.041 g, 95%). ν_{max}(film) 3500 (br), 1765, 1720 and 1250 cm^{-1}. N.m.r. spectrum ($CDCl_3$) : δ 5.4 (1H, q, J=6 Hz, -C<u>H</u>-OAc), 2.15 (1H, br, exch.D_2O,-OH), 2.07 (3H, s, $-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$) and 1.4-1.2 (15H, m, $-CH_3$).

3-(1'-Acetoxyethyl)-2,2,4,4-tetramethylcyclobutanediol(1,3) (67)and (68)

The crude product above (0.040 g) was reduced with sodium borohydride in methanol at 0-5° to give a mixture the diols (67) and (68) (0.035 g). N.m.r. spectrum ($CDCl_3$) : δ 5.18 (1H, q, J=6 Hz, -CH-OAc), 3.73 and 3.40 (1H, broad singlets, ratio 4:1, Cl-H), 2.05 (3H, s, $-O\overset{O}{\overset{\|}{C}}-CH_3$), 1.85-1.6 (2H, br, exch.D_2O, -OH) and 1.35-1.0 (15H, m, $-CH_3$). G.l.c. analysis (column 15% QF-1 at 140° and 30 ml/min) showed 2 peaks in the ratio about 4:1, retention times 12.36 and 14.45 min, respectively.

3-(1'-Hydroxyethyl)-2,2,4,4-tetramethylcyclobutanediol(1,3) (64) and (65)

The keto diol (63) (0.13 g) was reduced with sodium borohydride (0.03 g) in methanol (3 ml) at 0-5° to give a mixture of the triols (64) and (65) (0.060 g, 45%), m.p. 77-80° (hexane). ν_{max} (nujol) 3400 (br). N.m.r. spectrum ($CDCl_3$) : δ 4.15 (1H, q, -CH-OH), 3.73 and 3.40 (1H, broad singlets, ratio 3:1, Cl-H), 2.1-1.5 (3H, br, -OH) and 1.4-1.0 (15H, m, $-CH_3$). Mass spectrum: m/e 70 (base peak), 43,45 (33%), 116 (27.6%). G.l.c. (column 15% QF-1, at 120° and 30 ml/min) showed two main peaks in the ratio about 3:1, retention times 13.15 and 14.30 min, respectively. (Found: C, 61.3, 61.8; H, 10.0, 10.1. $C_{10}H_{20}O_2$ requires C, 63.8; H, 10.7%). This analytical data is unsatisfactory.

Acetylation of the triols (64) and (65)

The mixture of the triols (64) and (65) (0.010 g), acetic anhydride (0.02 ml) in pyridine (0.5 ml) was allowed to stand at room temperature for 4 h. On careful work up, a mixture of the diacetate (69) and (70) (0.010 g) was obtained. N.m.r. spectrum ($CDCl_3$) : δ 5.2 (1H, q), 4.55 and 4.35 (1H, broad singlets), 2.1-2.0 (7H, m, $-\overset{O}{\overset{\|}{C}}-CH_3$ and OH) and 1.3-0.98 (15H, m, $-CH_3$).

Attempted mesylation of the triols (64) and (65)

Methanesulphonyl chloride (0.012 g) was added in to the mixture of the triols (64) and (65) (0.018g) in dry pyridine (0.5 ml). The solution was stirred at room temperature for 18 h. T.l.c. indicated that no product was formed. Chloroform (5 ml) was added to the solution and washed several times with cold dilute hydrochloric acid. Evaporation of chloroform gave a residue whose infrared spectrum showed a broad peak at 3500 cm^{-1} and a rather broad peak at about 1720 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) contained resonances at δ 3.73 (br), 3.0 (br), 2.1 (br) and 1.4-0.9 (m).

APPENDIX I

Fragmentation of Compounds 8a-8e and 11a-11d showing the First Four Ions and Their Relative Abundances (R.A.).

	m/e	(R.A.)	m/e	(R.A.)	m/e	(R.A.)	m/e	(R.A.)
8a	59	(100)	91	(88)	92	(29)	65, 103	(17)
8b	91	(100)	87	(76)	45	(18)	65	(12)
8c	91	(100)	71	(39)	115	(25)	43	(24)
8d	91	(100)	55	(28)	95	(27)	83	(20)
8e	183	(100)	106	(40)	91	(20)	78	(17)
11a	59	(100)	43	(44.7)	41, 72	(16)	45	(13)
11b	45	(100)	87	(89.7)	43	(76.8)	57	(52.5)
11c	43	(100)	71	(61)	45, 73	(32)	55	(31)
11d	55	(100)	95	(75)	43	(70)	83	(50)

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