Preparation and Transformations of Three *p*-Menthane-3-methanesulfonyloxy-4,8-diols

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Received July 9, 1971

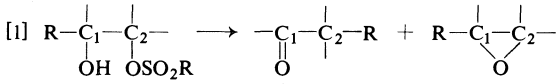
Three diastereomeric *p*-menthane-3-methanesulfonyloxy-4,8-diols were synthesized from (+)-pulegone. Treatment of each methanesulfonate with aqueous base resulted in a stereospecific reaction involving antiperiplanar groups to give one product: either an α-ketol by a pinacol-type rearrangement or an epoxide by an intramolecular S_N2-type reaction. Although the possibility existed for 1,3- as well as 1,2-diol monomethanesulfonate transformations, only products from the latter type of reaction were isolated.

Les trois diastéréoisomères du *p*-menthane méthanesulfonyloxy-3 diols-4,8 ont été synthétisés à partir de la (+)-pulégone. Le traitement de chaque méthanesulfonate par une base aqueuse, conduit à une réaction stéréospécifique qui implique des groupes antipériplanaires et qui donne un seul produit: soit un α-cétol par une transposition pinacolique, soit un époxyde par une réaction intramoléculaire du type S_N2. Bien qu'il existe des possibilités de transformation pour les monométhanesulfonate diols-1,3 et -1,2, seuls les produits correspondant au dernier type de réaction ont été isolés.

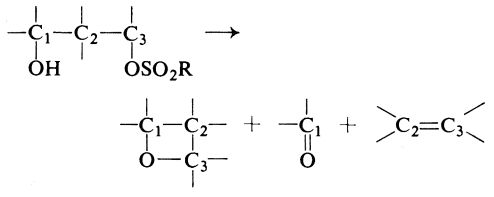
Canadian Journal of Chemistry, **49**, 3381 (1971)

Introduction

The literature contains numerous examples of transformations of 1,2- and 1,3-diol monosulfonates, usually tosylates or methanesulfonates (mesylates). Monosulfonates of 1,2-diols upon treatment with base commonly undergo a pinacol-type rearrangement to give a carbonyl compound (1) or they undergo an intramolecular displacement of the sulfonate to yield an epoxide (2) (eq. 1). The 1,3-diol monosulfonates may yield an oxetane (3) or fragmentation products (3, 4) (eq. 2). Of course, in both systems the sulfonate group could also undergo intermolecular displacement



[1]



[2]

or elimination. In cyclic systems, the relative stereochemistry of the hydroxyls in the starting material and the stability of the reacting conformation are generally critical factors in determining which reaction pathway will be followed.

A 1,2,3-triol monosulfonate (*e.g.* tertiary hydroxyl, tertiary hydroxyl, secondary sulfonate) would involve competition among all the pathways described above. A compound with such a triol moiety (the sulfonate being replaced by its biological equivalent) has been suggested by Barton and Gupta (5) as a precursor to the sesquiterpene, zierone. Transformations of related triol monotosylates have been employed in the synthesis of some A-norcholesteryl derivatives (6).

This report describes the preparation and transformations of three *p*-menthane-3-mesyloxy-4,8-diols, which are examples of the triol monosulfonates discussed above. They were prepared by epoxidation of (+)-pulegone (**1**) to give the ketoepoxides **2**, followed by reduction to the hydroxyepoxides **3**, hydrolysis to the triols **4** and finally selective monomesylation. The preparation of each of these synthetic intermediates and the base-catalyzed transformations of the monomesylates **5** will be discussed in detail.

Results and Discussion

*Preparation of Hydroxyepoxides (**3**)*

(+)-Pulegone (**1**) was epoxidized with alkaline hydrogen peroxide to give pulegone oxides **2***a* and *b* (64:36%, respectively) as previously reported (7). The two stereoisomeric ketoepoxides were separated and reduced with sodium borohydride in methanol. Compound **2***a* gave a mixture of two

hydroxyepoxides, **3***a* and *b* (47:53%, respectively), which were separated by spinning band distillation, while **2***b* gave only one product, **3***c*.

Infrared and n.m.r. spectroscopy were conclusive in establishing the assigned configurations and major conformations for the three hydroxyepoxides (Scheme 1). An i.r. study of hydrogen bonding in dilute carbon tetrachloride solutions revealed the presence of intramolecular hydrogen bonding (3565, 3602 cm^{-1}) in **3***a* where the epoxide and the C-3 hydroxyl are *cis*, while in **3***b* where these functional groups are *trans* and the hydroxyl is axial, only free hydroxyl absorption (3628 cm^{-1}) was observed. Compound **3***c* showed intramolecular hydrogen bonding (3583 cm^{-1}) which is consistent with the *trans* orientation of the epoxide and the equatorial hydroxyl.

The n.m.r. spectra of the hydroxyepoxides, particularly the resonances of the C-3 hydrogens and hydroxyls, were quite instructive. Analysis of the C-3 hydrogens in both **3***a* and *c* was complicated by intramolecular hydrogen bonding of the C-3 hydroxyl with the epoxide oxygen, which slowed the rate of OH exchange sufficiently to allow the observation of H—C—O—H coupling. Fraser *et al.* (8) recently devised a Karplus-type equation to calculate these vicinal coupling constants (eq. 3). If one assumes the C-3 hydroxyl

$$[3]\quad J_{HCOH} = 10.4\cos^2\phi - 1.5\cos\phi + 0.2$$

is directed towards the epoxide oxygen, Dreiding models of the conformations depicted in Scheme 1 give H—C—O—H dihedral angles of 140 and 95° for **3***a* and *c* respectively. Calculation of the coupling constants using these angles gives the following comparison with the values actually observed for the hydroxyl coupling: for **3***a*, $J_{calcd.} = 5.3$; $J_{obs.} = 7$ Hz; and for **3***c*, $J_{calcd.} = 0.2$, $J_{obs.} = 2$ Hz. Considering the limitations of the method (8) and the possibility of steric interactions between the hydroxyl and the C-10 methyl, the calculated and observed values agree reasonably well.

Exchange of the C-3 hydroxyl with deuterium oxide simplifies the analysis of the C-3 hydrogen as it eliminates the H—C—O—H coupling. The half-band width ($w/2$) of hydrogens α to the hydroxyl (H_α) is very useful in determining the axial or equatorial nature of these hydrogens. The axial H_α would be expected to have a relatively broad half-band width (~15 Hz) because of the large axial–axial vicinal coupling while $w/2$ for the equatorial H_α would be narrower (~6 Hz) because of the smaller equatorial–equatorial and equatorial–axial coupling constants (9). In **3***a* the H_α appears at τ 6.25 as a distorted quartet ($w/2$ = 15 Hz) while in **3***c* it appears at τ 6.15 again as a quartet ($w/2$ = 15 Hz). Consequently both these hydroxyepoxides must possess an axial hydrogen and an equatorial hydroxyl at C-3.

The H_α in **3***b*, where there is no complication with intramolecular hydrogen bonding, exhibits a multiplet (τ 6.40, $w/2$ = 7 Hz) characteristic of an equatorial hydrogen, and thus an axial hydroxyl. The chemical shift of this equatorial hydrogen is an unusual feature of this spectrum as it appears at higher field than the corresponding axial hydrogens in **3***a* and *c* (τ 6.25 and 6.15 respectively). Normally axial hydrogens appear at higher field than equatorial in cyclohexane (10). This upfield shift may be due to the shielding effect of the C-10 methyl or the epoxide ring (11) on this equatorial hydrogen, which is situated directly above the plane of the epoxide. Shielding by a cyclopropane ring has been invoked to explain the upfield position of an equatorial H_α relative to an axial H_α (12).

Examination of Dreiding models for the two ketoepoxides **2***a* and *b* provides support for the product distribution obtained upon borohydride reduction. Compound **2***a* does not exhibit any significant difference in the steric environment of the carbonyl group from either the α- or the β-face and this is reflected in the 47:53% distribution obtained for hydroxyepoxides **3***a* and *b*. Compound **2***b* exhibits considerably less hindrance on the α-face and borohydride attack from this side gives the β-alcohol, **3***c*, which is the only product detected.

Hydroxyepoxides **3***a* and *c* were previously prepared by another route (13). There are some differences in the physical constants reported for **3***a* while **3***c* and the *p*-nitrobenzoate derivatives for both show good agreement (see Experimental).

*Preparation of Triols (**4**) and Monomesylates (**5**)*

Treatment of the hydroxyepoxides with aqueous acid afforded one triol in each case: **3***a* → **4***a*, **3***b* → **4***b* and **3***c* → **4***c* (Scheme 1). The insolubility of the triols in solvents used for obtaining solution i.r. spectra precluded a study of hydrogen bonding but n.m.r. spectra run in hexadeuterioacetone provided useful information. When interpreting these spectra it was assumed the very

bulky dimethylcarbinol group at C-4 would be in the equatorial position. The half-band width of the H_α was then used to determine the configuration at C-3. In **4***a*, the broad signal for this hydrogen (τ 6.12, $w/2 = 17$ Hz) indicates an axial hydrogen and an equatorial hydroxyl. The narrow signals for H_α in **4***b* (τ 6.05, $w/2 = 7$) and **4***c* (τ 6.05, $w/2 = 8$) indicate the presence of axial hydroxyls at C-3. The structural assignments for the three triols are consistent with this n.m.r. data and with the transformations to be described later. During the acid-catalyzed opening of the epoxide ring, the protonated epoxide intermediate must have undergone attack by water at the less hindered C-8 position in preference to C-4 (14).

Attempts to effect selective monotosylation of the triols **4** at the C-3 secondary hydroxyl were unsuccessful presumably because of the considerable steric hindrance of the neighboring groups. But preparation of the monomesylates **5** was successful in all three cases. Mesylation has been shown to proceed via the less sterically demanding sulfene intermediate (15). Mesylate **5***a* was stable and was fully characterized while **5***b* and *c* were unstable and the crude material was used in the next step. With the desired *p*-menthane-3-mesyloxy-4,8-diols in hand, it was then possible to examine the base-catalyzed transformations of these diastereomers.

Transformation Products of Monomesylates (5)

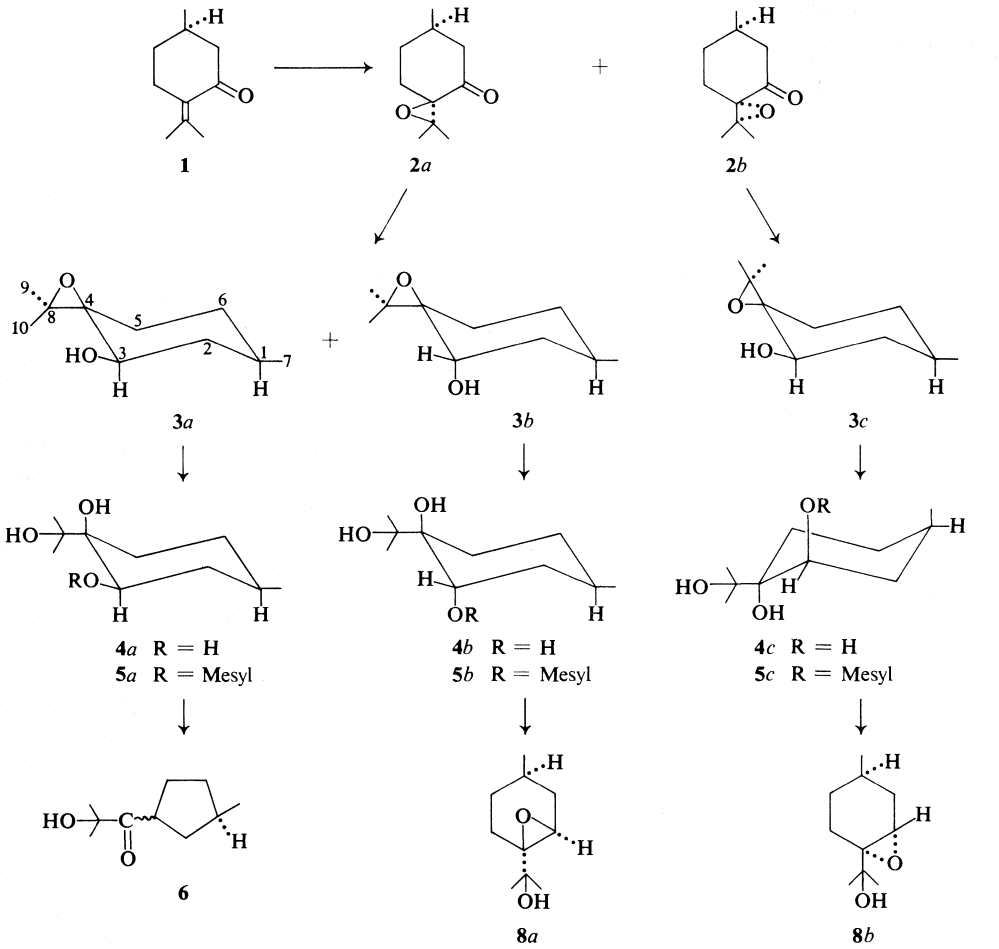
Treatment of pure monomesylate **5***a* with dilute aqueous base afforded a 90% yield of one compound as analyzed by g.l.c. and t.l.c. The i.r. spectrum of this substance indicated a carbonyl group (1705 cm^{-1}) and an intramolecularly hydrogen bonded hydroxyl (3500 cm^{-1}), features characteristic of α-ketols (16). The n.m.r. spectrum included a six-proton peak (τ 8.64) appropriate for the methyl groups in the moiety $(CH_3)_2C(HO)-C(=O)-$. A structure consistent with these data and its derivation from **5***a* is 1-[3-(R)-methylcyclopentyl]-2-hydroxy-2-methyl-1-propanone (**6**).

The structure was confirmed by an unambiguous synthesis. The Grignard reagent of 3-(R)-methylcyclopentyl chloride was prepared by the following route: (+)-pulegone → 3-(R)-methyladipic acid (17) → 3-(R)-methylcyclopentanone (17) → 3-(R)-methylcyclopentanol → 3-(R)-methylcyclopentyl chloride (presumably a mixture of diastereomers). This Grignard reagent was reacted with the cyanohydrin of acetone (eq. 4) to yield ketol **6** (35%), identical with the product from **5***a*, and an alcohol (23%) which was not fully characterized but presumably is **7** by analogy with similar displacements in cyanohydrin–Grignard reactions (18). The intermediate imine in this reaction was very stable in aqueous acid and could be extracted from an ether solution of the crude reaction mixture with 1 *N* hydrochloric acid, thus separating the imine and the alcohol (**7**). Hydrolysis of the imine in 0.1 *M* sodium hydroxide solution proceeded readily to give the ketol (**6**) as the only product. The imine could also be hydrolyzed by heating to reflux in 0.5 *N* hydrochloric acid for 16 h but some dehydration occurred under these conditions to give an α,β-unsaturated ketone (1670, 1615 cm^{-1}) (30% by g.l.c.) in addition to the ketol (70%). As both the synthetic ketol and that formed by rearrangement of **5***a* were prepared under alkaline conditions, epimerization at the cyclopentyl position adjacent to the carbonyl group would be expected. The g.l.c. analysis of the ketol indicated only one symmetrical peak while the n.m.r. spectrum exhibited two methyl doublets (τ 8.90, $J = 6$ Hz; τ 8.98, $J = 6$ Hz) of approximately equal area for the 3-methyl group on the cyclopentyl ring.

[4] $(CH_3)_2C(OH)-CN$ + ClMg–(cyclopentyl)–H → **6** + $(CH_3)_2C(OH)$–(cyclopentyl)–H (**7**)

Examination of conformation **5***a* (Scheme 1) shows the antiperiplanar (180°) (19) relationship of the C-3 mesyloxy group and the C_4—C_5 bond, the preferred orientation for a pinacol-type rearrangement, which would result in displacement of the mesyloxy group and formation of the ring contracted product **6**.

Treatment of crude mesylate **5***b* with dilute base gave 83% (based on **4***b*) of hydroxyepoxide **8***a*. This structure is based on spectral data, comparison with an authentic sample and examination of its mode of formation. The i.r. spectrum showed an intramolecularly hydrogen bonded



SCHEME 1

hydroxyl (3552 cm^{-1}) and bands characteristic of an epoxide (800–950 cm^{-1}) (20) while the n.m.r. spectrum indicated a dimethyl carbinol group (three-proton singlets at τ 8.82 and 8.83) and a trisubstituted epoxide (τ 6.78, 1H). In DMSO the hydroxyl appeared as a singlet at τ 5.85 indicating the alcohol was tertiary (21).

The reaction of 3-*p*-menthen-8-ol (22) with *m*-chloroperbenzoic acid gave a mixture of two hydroxyepoxides, **8***a* (30%) and *b* (70% by g.l.c.). Rickborn and Lwo have shown in the case of 4-methylcyclohexene (23) that the methyl substituent exerts only a slight steric effect in favor of the *trans* product (53.6-46.4%) and thus the dimethyl carbinol group must be exerting some additional influence in favor of the *trans* product **8***b*. The minor component in the epoxidation, **8***a*, was identical to the product obtained from mesylate **5***b*. Analysis of the resonance for the C-3 hydrogen in the n.m.r. spectra of **8***a* and *b* was conclusive in distinguishing between these two epoxides. In **8***a* this hydrogen appeared as a doublet (τ 6.78, J = 5 Hz) while in **8***b* it was a narrow multiplet (τ 6.74). Coupling constants for the C-3 hydrogens were calculated using Tori's revised Karplus equation (24) for 1,2-epoxycyclohexanes (eq. 5). The following dihedral angles (ϕ) between the C-3 and the two C-2 hydrogens were

$$[5] \qquad J = 5.1 \cos^2 \phi$$

measured from Dreiding models: for **8***a*, ϕ = 17 and 103°; and for **8***b*, ϕ = 65 and 55°. These angles predict $J_{calcd.}$ = 4.7 and 0.3 Hz, respectively, for **8***a* and $J_{calcd.}$ = 0.9 and 1.7 Hz, respectively, for

8*b*. Thus one would expect the C-3 hydrogen in **8***a* to be a doublet with a coupling constant of about 5 Hz while in **8***b* this hydrogen would be expected to be a narrow unresolved multiplet. These predictions are in good agreement with the observed values and support the structures proposed for **8***a* and *b*.

In the conformation proposed for **5***b* the C-3 mesyloxy and C-4 hydroxyl groups are in a *trans* diaxial orientation. Displacement of the mesyloxy by the hydroxyl in an S_N2-type reaction would lead directly to **8***a*.

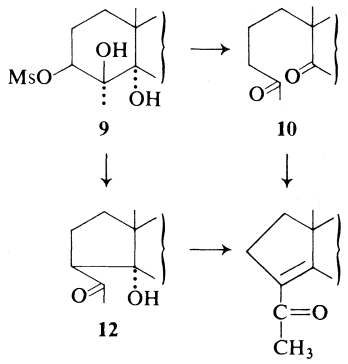
Crude monomesylate **5***c* upon treatment with aqueous base gave **8***b* as the only product in 74% yield (based on **4***c*). The assignment was also based on spectral data, comparison with an authentic sample, and its mode of formation. The major product (70%) from epoxidation of 3-*p*-menthen-8-ol (see above) was identical to transformation product **8***b*. An S_N2-type displacement of the axial mesyloxy group by the C-4 hydroxyl in **5***c* would give this α-epoxide.

Treatment of the triols (**4**) themselves under the basic conditions employed in the transformation of the mesylates (**5**) resulted in complete recovery of starting triol indicating the necessity of the mesyloxy group in these transformations.

Summary

The two types of reactions common to the 1,2-diol monosulfonate systems, namely pinacol-type bond migration and epoxide formation, were the only reactions observed with the triol monomesylates investigated. In these transformations the group antiperiplanar to the departing mesyloxy group was always involved in the reaction. A probable reason for the lack of any 1,3-diol monosulfonate reactions (*i.e.* fragmentation and oxetane formation) in these systems is the thermodynamic instability of the conformations in which the bulky dimethylcarbinol group must assume an axial position if the reaction is to proceed.

In one reported example of a 1,2,3-triol monomesylate transformation in the steroid field (*6b*), it was suggested that the monomesylate **9** first undergoes fragmentation to give diketone **10** which then gives the dehydrated aldol product **11** under the basic conditions of the reaction. By analogy to the rearrangement of our mesylate **5***a*, another plausible mechanism would be a pinacol-type rearrangement to give ring-contracted product **12** followed by dehydration to **11**.



9 **10** **12**

Experimental

The i.r. spectra were recorded on a Beckmann IR5A spectrometer with the exception of the hydrogen bonding spectra which were run on a Beckmann IR12 spectrometer using *ca.* 0.005 *M* carbon tetrachloride solutions in a variable path length cell. The n.m.r. spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as internal standard. Optical rotations were measured on a Bellingham and Stanley polarimeter. The g.l.c. analyses and separations were carried out on a Model A-700 "Autoprep" using a 1/4 in. × 6 ft column with 20% Carbowax 20 M on 60/80 Chromosorb W operating at 120° with a He flow rate of 75 cc/min. For analytical t.l.c., a 0.25 mm thickness of GF-254 Silica Gel was employed while for preparative t.l.c., a 1.0 mm thickness of PF-254 Silica Gel was used, both with the solvent system 40:60 ethyl acetate – benzene. Spinning band distillations were carried out on a Nester–Faust 117 apparatus with a column length of 18 in. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Microanalyses were performed by A. G. Gygli, Toronto, Ontario, and H. S. McKinnon, Department of Chemistry, University of Guelph, Guelph, Ontario.

The pulegone used in these experiments was Bakers, practical grade, $[\alpha]_D^{25}$ + 26° (neat).

p-Menthane-4,8-epoxy-3-ols (3)

The pulegone oxides (**2**) were prepared from (+)-pulegone and separated according to a procedure described (*7a*). To an ice-cooled stirred solution of **2***a* (33.2 g, 0.20 mol) in 200 ml methanol was added dropwise over 15 min a solution of sodium borohydride (7.5 g, 0.20 mol) in 40 ml water and 200 ml methanol. After stirring for an additional 30 min at room temperature the reduction mixture was poured into 800 ml water and extracted with ether (4 × 250 ml). The combined extracts were washed with water and brine and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a colorless oil (30.9 g, 91%), shown by g.l.c. to contain two components, **3***a* and *b*, in a ratio of 47:53 respectively. Spinning band distillation of the oil separated the two components: (−)-4,8-epoxymenthol (**3***a*); b.p. 110–111°/4 mm; i.r. (CCl_4) 3450, 2875, 1455, 1378, 1138, 1100, 1052, 854, 652 cm^{-1}, hydroxyl region at 0.005 *M*, 3602, 3565 cm^{-1}; n.m.r. (CCl_4) τ 8.93 (3H, d, J = 6 Hz), 8.68 (3H, s), 8.52 (3H, s), 7.39 (1H, d, J = 7 Hz, disappeared on addition of D_2O),

6.25 (1H, dd, $w/2 = 15$ Hz); $[\alpha]_D^{25}$ −35° (*c*, 2 in methanol) (lit. (13) +34°); *p*-nitrobenzoate derivative, m.p. 128.5–129.0° (lit. (13) 134–135°), $[\alpha]_D^{25}$ −61° (*c*, 2 in chloroform) (lit. (13) −65°).

Anal. Calcd. for $C_{17}H_{21}NO_5$ (*p*-nitrobenzoate derivative): C, 63.94; H, 6.63. Found: C, 64.03; H, 6.81.

(+)-4,8-Epoxyneomenthol (**3***b*); b.p. 116–117°/4 mm, m.p. 51.5–52.5°; i.r. (CCl_4) 3580, 3420, 2900, 1450, 1430, 1375, 1095, 1032, 960, 878, 688 cm^{-1}, hydroxyl region at 0.005 *M*, 3628 cm^{-1}; n.m.r. (CCl_4) τ 9.07 (3H, d, $J = 6$ Hz), 8.75 (3H, s), 9.70 (3H, s) 8.28 (1H, s, disappeared on addition of D_2O), 6.40 (1H, m, $w/2 = 7$ Hz); $[\alpha]_D^{25}$ +50° (*c*, 2 in methanol); *p*-nitrobenzoate derivative, m.p. 165.5–166.5, $[\alpha]_D^{25}$ +63° (*c*, 2 in chloroform).

Anal. Calcd. for $C_{10}H_{18}O_2$ (**3***b*): C, 70.55; H, 10.65. Found: C, 70.94; H, 11.01.

Sodium borohydride reduction of pulegone oxide **2***b* (23.1 g, 0.14 mol) as described above for **2***a* gave a colorless oil, (−)-4,8-epoxyneoisomenthol (**3***c*), b.p. 85–87°/0.65 mm (21.4 g, 91%) which exhibited only one peak on g.l.c. analysis; i.r. (CCl_4) 3400, 2900, 1450, 1370, 1112, 1055, 868, 650 cm^{-1}, hydroxyl region at 0.005 *M*, 3628 (vw), 3583 cm^{-1}; n.m.r. (CCl_4) τ 8.97 (3H, d, $J = 6$ Hz), 8.67 (3H, s), 8.46 (3H, s), 7.34 (1H, d, $J = 2$ Hz, disappeared on addition of D_2O), 6.12 (1H, dd, $w/2 = 15$ Hz); $[\alpha]_D^{25}$ −4° (*c*, 2 in methanol) (lit. (13) +1°); *p*-nitrobenzoate derivative, m.p. 125.5–127.0° (lit. (13) 128–129°), $[\alpha]_D^{25}$ −15° (*c*, 2 in chloroform) (lit. (13) −16°).

Anal. Calcd. for $C_{10}H_{18}O_2$ (**3***c*): C, 70.55, H, 10.65. Found: C, 70.17; H, 10.77.

*p-Menthane-3,4,8-triols (**4**)*

(*a*) To hydroxyepoxide **3***a* (2.0 g, 12 mmol) was added a solution of 2 drops concentrated sulfuric acid in 20 ml water and the suspension was heated over a steam bath for 5 min with vigorous agitation. The reaction mixture was cooled and extracted with ether (3 × 30 ml) and the combined extracts were washed with water (2 × 25 ml), brine (1 × 25 ml), and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a colorless oil (2.0 g, 91%). The t.l.c. indicated the product contained a major component (R_f 0.18) and two impurities (R_f's 0.25 and 0.49). Isolation of the major band by preparative t.l.c. afforded the crystalline (+)-4,8-dihydroxymenthol (**4***a*); m.p. 66.0–67.5°; i.r. (CCl_4) 3425, 2940, 1380, 1180, 1138, 1100, 1040, 1020, 858 cm^{-1}; n.m.r. (CCl_4) τ 9.03 (3H, d), 8.85 (3H, s), 8.71 (3H, s), 6.92, 6.50, 6.35 (total of 3H, disappeared on addition of D_2O), 6.12 (1H, m, $w/2 = 17$ Hz); $[\alpha]_D^{25}$ +16° (*c*, 2 in chloroform)

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.66; H, 10.65.

(*b*) Hydroxyepoxide **3***b* (2.0 g, 12 mmol) was treated with aqueous sulfuric acid as described above to give a white precipitate. Extraction with ether gave a crude product which upon crystallization from chloroform gave 1.98 g (90%) of (+)-4,8-dihydroxyneomenthol (**4***b*); m.p. 166.5–167.0°; i.r. (KBr) 3225, 2900, 1455, 1420, 1370, 1170, 1138, 1112, 1068, 1002, 985, 975, 954, 917, 845 cm^{-1}; n.m.r. (CD_3COCD_3) τ 9.16 (3H, d, $J = 5$ Hz), 8.82 (3H, s), 6.68 (3H, s), 7.16, 6.85, 5.80, 5.60, 5.56 (total of 3H, disappeared on addition of D_2O), 6.05 (1H, m, $w/2 = 7$ Hz); $[\alpha]_D^{25}$ +22° (*c*, 2 in methanol).

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 64.01; H, 10.97.

(*c*) Hydroxyepoxide **3***c* (2.0 g, 12 mmol) after treatment with aqueous sulfuric acid as described above, work-up, and crystallization from chloroform gave (−)-4,8-dihydroxyneoisomenthol (**4***c*) (1.55 g, 70%); m.p. 165.0–166.0°; i.r. (KBr) 3350, 2900, 1425, 1375, 1210, 1180, 1145, 1070, 1012, 955, 915 cm^{-1}; n.m.r. (CD_3COCD_3) τ 8.88 (3H, d, $J = 6$ Hz), 8.80 (3H, s), 8.72 (3H, s), 7.22, 6.80, 5.79, 5.55, 5.00 (total of 3H, disappeared on addition of D_2O) 6.05 (1H, m, $w/2 = 8$ Hz); $[\alpha]_D^{25}$ −27° (*c*, 2 in methanol).

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.78; H, 11.00.

*p-Menthane-3-methanesulfonyloxy-4,8-diols (**5**)*

(*a*) To a stirred solution of triol **4***a* (3.0 g, 16 mmol) in 40 ml dry pyridine at 5° was added dropwise methanesulfonyl chloride (2.1 g, 18 mmol). After stirring for 24 h at 5° (precipitate of pyridinium chloride), the reaction mixture was combined with 80 ml water and the aqueous phase was extracted with ether (3 × 100 ml). The combined extracts were washed with cold 6 *N* hydrochloric acid (2 × 50 ml), saturated sodium bicarbonate solution (1 × 50 ml), water (2 × 50 ml), and brine (1 × 50 ml) and then dried (Na_2SO_4). Removal of the solvent gave a yellow oil (2.96 g, 70%) which was crystallized from 2:1 pentane–ether to give the pure mesylate **5***a*; m.p. 66.5–67.5°; i.r. ($CHCl_3$) 3500, 2950, 1350, 1250, 1210, 1175, 952, 918, 880, 693 cm^{-1}; n.m.r. (CCl_4) τ 9.00 (3H, d), 8.85 (3H, s), 8.64 (3H, s), 7.59, 6.80 (each 1H, disappeared on addition of D_2O), 6.97 (3H, s), 5.10 (1H, m).

Anal. Calcd. for $C_{11}H_{22}O_5S$: C, 49.60; H, 8.30. Found: C, 49.28; H, 8.15.

(*b*) Similarly, to a stirred solution of triol **4***b* (1.4 g, 7.4 mmol) in 20 ml dry pyridine at 5° was added dropwise methanesulfonyl chloride (1.1 g, 9.6 mmol) and after stirring for 24 h at 5° the reaction was worked-up as described above. Removal of the solvent gave crude mesylate **5***b* which was unstable and was used directly in the next step [see (*b*) of following section].

(*c*) A solution of triol **4***c* (1.8 g, 9.6 mmol) in 25 ml dry pyridine was reacted with methanesulfonyl chloride (1.4 g, 12 mmol) as described above and then worked-up to give crude mesylate **5***c* which was unstable and was used directly in the next step [see (*c*) of following section].

*Transformations of Mesylates (**5**)*

(*a*) A solution of mesylate **5***a* (2.96 g, 11.1 mmol) in 8 ml dioxane and 8 ml 0.45 *M* sodium hydroxide solution was stirred at 65° under nitrogen for 2 h. The reaction mixture was cooled, poured into 30 ml water and extracted with ether (3 × 75 ml). The combined extracts were washed with water (2 × 25 ml), brine (1 × 25 ml), and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a pale yellow oil (1.70 g, 90%) which exhibited only one spot on t.l.c. and one peak on g.l.c. An analytical sample was prepared by preparative g.l.c. The compound was shown to be 1-[3-(R)-methylcyclopentyl]-2-hydroxy-2-methyl-1-propanone (**6**); i.r. (film) 3500, 2950, 2850, 1705, 1460, 1170, 1070, 970 cm^{-1}, hydroxyl region at 0.005 *M* in CCl_4, 3500 cm^{-1}; n.m.r. (CCl_4) τ 8.64 (6H,s), 8.98, 8.90 (total 3H, two d, $J = 6$ Hz in each case), 6.60 (1H, broad m), 6.20 (1H, s, disappears on addition of D_2O); $[\alpha]_D^{25}$ −9° (*c*, 2 in chloroform).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.61; H, 10.69.

(*b*) Crude mesylate **5***b* (prepared from 1.4 g, 7.4 mmol of **4***b*) was dissolved in 4 ml dioxane and 4 ml 0.45 *M* sodium hydroxide solution and stirred at 65° under nitrogen for 4 h. Work-up as described previously gave a yellow oil (1.05 g, 83% based on **4***b*) which exhibited only one spot on t.l.c. and one peak on g.l.c. (retention time 14.3 min). An analytical sample was prepared by preparative g.l.c. The compound was shown to be *trans-p*-menthan-3,4-epoxy-8-ol (**8***a*); i.r. (CCl_4) 3552, 2925, 1450, 1365, 1340, 1195, 1155, 1125, 975, 955, 875, 855, 845 cm^{-1}; n.m.r. (CCl_4) τ 9.12 (3H, d, $J = 5$ Hz), 8.83 (3H, s), 8.82 (3H, s), 8.29 (1H, s, disappeared on addition of D_2O), 6.78 (1H, d, $J = 5$ Hz); n.m.r. (DMSO) τ 5.85 (1H, s, disappeared on addition of D_2O).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.46, H, 10.72.

(*c*) Similarly, crude mesylate **5***c* (prepared from 1.8 g, 9.6 mmol of **4***c*) was dissolved in 4 ml dioxane and 4 ml 0.45 *M* sodium hydroxide solution and stirred at 65° under nitrogen for 4 h. Work-up as described above gave a yellow oil (1.22 g, 75% based on **4***c*) which exhibited only one spot on t.l.c. and one peak on g.l.c. (retention time 13.4 min). An analytical sample was prepared by preparative g.l.c. The compound was shown to be *cis-p*-menthan-3,4-epoxy-8-ol (**8***b*); i.r. (CCl_4) 3552, 2900, 1450, 1365, 1340, 1180, 1160, 1125, 1085, 1025, 955, 920, 905, 848 cm^{-1}; n.m.r. (CCl_4) τ 9.13 (3H, d, $J = 5$ Hz), 8.85, (6H, s), 8.23 (1H, s, disappeared on addition of D_2O), 6.74 (1H, narrow m).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.58; H, 10.73.

Preparation of Authentic Samples

(a) 1-[3-(R)-Methylcyclopentyl]-2-hydroxy-2-methyl-1-propanone (6)

3-(R)-Methylcyclopentanone (17) after reduction with sodium borohydride gave 3-(R)-methylcyclopentanol, which upon reaction with calcium chloride in concentrated hydrochloric acid (25) gave 3-(R)-methylcyclopentyl chloride, b.p. 54–56°/55 mm. A solution of 3-(R)-methylcyclopentyl chloride (7.1 g, 0.06 mol) in 30 ml dry ether was added dropwise to magnesium turnings (1.46 g 0.06 g atm) under nitrogen at a rate to maintain reflux. The reaction was completed by heating to reflux for an additional 30 min. The Grignard solution was cooled in an ice bath and stirred mechanically while a solution of acetone cyanohydrin (2.55 g, 0.03 mol) (26) in 10 ml ether was added dropwise. The resultant slurry was stirred and heated at 35° for 3 h. The reaction mixture was cooled and a solution of ammonium chloride (3.2 g, 0.06 mol) in 25 ml water was added with stirring. The two phases were separated and the aqueous phase was extracted with ether (6 × 25 ml). The combined organic phases were extracted with 1 *N* hydrochloric acid (5 × 20 ml) (retained), saturated sodium bicarbonate solution (1 × 20 ml), brine (1 × 20 ml), and dried ($MgSO_4$). Removal of the solvent gave a colorless oil (1.0 g, 23%), which was >90% one compound by g.l.c. and was tentatively formulated as 3-(R)-methylcyclopentyldimethylcarbinol (7); i.r. (film) 3350, 2860, 1455, 1375, 1295, 1265, 1250, 935 cm^{-1}; n.m.r. (CCl_4) τ 9.02, 8.98 (total of 3H, two d, $J = 6$ Hz in each case), 8.88 (6H, s), 8.45 (1H, s, disappeared on addition of D_2O); $[\alpha]_D^{25}$ +2° (c, 2 in chloroform).

The 100 ml of the hydrochloric acid phase from above, which contains the imine salt, was basified with 4.4 g sodium hydroxide to give a solution *ca.* 0.1 *M* in sodium hydroxide and 10 ml ethanol was added to promote dissolution of the organic compound. The solution was heated to reflux for 4 h, cooled, saturated with sodium chloride, and extracted with ether (5 × 50 ml). The extract was washed with brine (2 × 25 ml), dried ($MgSO_4$), and the solvent removed to give a colorless oil (1.78 g, 35%) which exhibited only one peak on g.l.c. at the same retention time as the transformation product **6** from mesylate **5***a*. The i.r. and n.m.r. spectra were identical to **6** (see above) and $[\alpha]_D^{25}$ −10° (*c*, 2 in chloroform).

Hydrolysis of the imine could also be effected in 0.5 *N* hydrochloric acid solution heated under reflux for 16 h. Work-up gave a yellow oil shown by g.l.c. to be a mixture of two components (30:70), the latter having the same retention time as **6**; i.r. of mixture (CCl_4) 3500, 2950, 1705, 1670, 1615, 1160, 970 cm^{-1}.

(b) cis- and trans-p-Menthan-3,4-epoxy-8-ols (8)

To a stirred solution of 3-*p*-menthen-8-ol (1.0 g, 6.5 mmol) (22) in 10 ml dichloromethane at room temperature was added dropwise a solution of *m*-chloroperbenzoic acid (1.8 g, 10.5 mmol) in 20 ml dichloromethane. The reaction was stirred for 20 min and a 10% sodium sulfite solution was added to destroy the excess peracid. The organic layer was washed with saturated sodium bicarbonate solution (1 × 10 ml) and brine (1 × 10 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a colorless oil (0.99 g, 90%), which was shown by g.l.c. to be a 70:30 mixture of two components with retention times of 13.4 and 14.3 min, respectively. These compounds were separated by preparative g.l.c. and shown to be identical to **8***b* and *a* (see above) respectively, the transformation products of mesylates **5***c* and *b*, respectively.

The authors wish to thank the National Research Council of Canada for financial support of this research.

1. (*a*) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry. J. Am. Chem. Soc. **86**, 478 (1964). (*b*) G. Büchi and J. A. Carlson. J. Am. Chem. Soc. **91**, 6470 (1969). (*c*) T. Hirata and T. Suga. J. Org. Chem. **36**, 412 (1971).
2. (*a*) E. E. Royals and J. C. Leffingwell. J. Org. Chem. **31**, 1937 (1966). (*b*) R. G. Carlson and J. K. Pierce. Tetrahedron Lett. 6213 (1968).
3. (*a*) R. B. Clayton, H. B. Henbest, and M. Smith. J. Chem. Soc. 1982 (1957). (*b*) M. Matsui and D. K. Fukushima. J. Org. Chem. **35**, 561 (1970).
4. (*a*) P. S. Wharton and G. A. Hiegel. J. Org. Chem. **30**, 3254 (1965). (*b*) J. A. Marshall and S. F. Brady. J. Org. Chem. **35**, 4068 (1970).
5. D. H. R. Barton and G. S. Gupta. Proc. Chem. Soc. 308 (1961).
6. (*a*) A. F. Thomas, K. Heusler and J. M. Müller. Tetrahedron, **16**, 264 (1961). (*b*) S. Julia, J.-P. Lavaux, S. R. Pathak, and G. H. Whitham. J. Chem. Soc. 2633 (1964). (*c*) R. M. Moriarty and K. Bhamidipaty. J. Org. Chem. **35**, 2297 (1970).
7. (*a*) J. Katsuhara. J. Org. Chem. **32**, 797 (1967). (*b*) W. Reusch and P. Mattison. Tetrahedron, **24**, 4933 (1968).
8. R. R. Fraser, M. Kaufman, P. Morand, and G. Govil. Can. J. Chem. **47**, 403 (1969).

9. (*a*) N. S. BHACCA and D. H. WILLIAMS. Applications of n.m.r. spectroscopy in organic chemistry. Holden–Day, San Francisco, California, 1964. p. 79. (*b*) G. BERTI, B. MACCHIA and F. MACCHIA. Tetrahedron, **24**, 1755 (1968).
10. L. M. JACKMAN. Applications of n.m.r. spectroscopy in organic chemistry. Pergamon Press, Oxford, 1959. p. 116.
11. K. TORI, K. AONO, K. KITAHONOKI, R. MUNEYUKI, Y. TAKANO, H. TANIDA, and T. TSUJI. Tetrahedron Lett. 2921 (1966) and references therein.
12. J. TADANIER and W. COLE. J. Org. Chem. **27**, 4610 (1962).
13. W. TAGAKI and T. MITSUI. J. Org. Chem. **25**, 1476 (1960).
14. R. E. PARKER and N. S. ISAACS. Chem. Rev. **59**, 737 (1959).
15. J. F. KING and T. DURST. J. Am. Chem. Soc. **87**, 5684 (1965).
16. R. N. JONES, P. HUMPHRIES, F. HERLING, and K. DOBRINER. J. Am. Chem. Soc. **74**, 2820 (1952).
17. E. J. EISENBRAUN and S. M. MCELVAIN. J. Am. Chem. Soc. **77**, 3383 (1955).
18. M. S. KHARASCH and O. REINMUTH. Grignard reactions of nonmetallic substances. Prentice–Hall, New York, N.Y., 1954. pp. 777 and 783.
19. W. KLYNE and V. PRELOG. Experientia, **16**, 521 (1960).
20. K. NAKANISHI. Infrared absorption spectroscopy. Holden–Day, San Francisco, California, 1962. p. 36.
21. O. L. CHAPMAN and R. W. KING. J. Am. Chem. Soc. **86**, 1256 (1964).
22. E. H. ESCHINASI. J. Org. Chem. **35**, 2010 (1970).
23. B. RICKBORN and S.-Y. LWO. J. Org. Chem. **30**, 2212 (1965).
24. K. TORI, T. KOMENO and T. NAKAGAWA. J. Org. Chem. **29**, 1136 (1964).
25. W. A. YARNALL and E. S. WALLIS. J. Org. Chem. **4**, 284 (1939).
26. R. F. B. COX and R. T. STORMONT. Organic syntheses. Coll. Vol. 2. John Wiley and Sons, New York, N.Y., 1943. p. 7.