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The Synthesis of Two C 4 Epimers of 4,8-Dimethyl-2-oxabicyclo[3.3.1]nonan-8-ol (1-Hydroxy-2,9-cineole)

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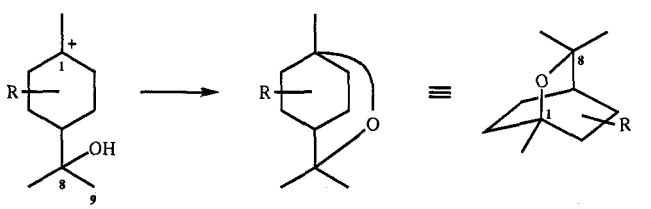
Abstract

Chemical syntheses of the two 2,9-cineoles (10a) and (11a) confirm the view that such compounds may be formed during various 1,8-cineole syntheses. The n.m.r. spectra and conformations of these bicyclic compounds are discussed.

Introduction

During studies into the urinary metabolites of the brushtail possum (*Trichosurus vulpecula*: Marsupialia), we have synthesized a range of hydroxylated 1,8-cineoles.[1–5] The synthesis of these compounds has been based upon the cyclization of *p*-menthane precursors in which a C 8 hydroxyl is trapped by a C1 carbocation, or its equivalent, to give the 1,8-cineole skeleton (Scheme 1).



Scheme 1

Synthesis of the 9-hydroxy-1,8-cineoles (1),[2] (2a)[4] and (3a)[4] requires that the starting *p*-menthane must also bear a hydroxy group at C 9, and this C 9 functionality might be expected to compete with the C 8 hydroxyl in cyclization reactions. In support of this view, we have found[4] that the acid-catalysed cyclization of the C 9-protected compounds (4b) and (5b) proceeds cleanly to give the protected cineoles (2b) and (3b) (Scheme 2), whereas the unprotected diols (4a) and (5a) give poorer yields of cineoles (2a) and (3a) together with a variety of other products which may have included C 9 hydroxyl cyclization products, but which were not readily purified or isolated. To investigate the possibility

[1] Carman, R. M., and Fletcher, M. T., *Aust. J. Chem.*, 1984, **37**, 1117.
[2] Carman, R. M., and Klika, K. D., *Aust. J. Chem.*, 1992, **45**, 651.
[3] Bull, S. D., Carman, R. M., Carrick, F. N., and Klika, K. D., *Aust. J. Chem.*, 1993, **46**, 441.
[4] Carman, R. M., Garner, A. C., and Klika, K. D., *Aust. J. Chem.*, 1994, **47**, 1509.
[5] Carman, R. M., and Rayner, A. C., *Aust. J. Chem.*, 1994, **47**, 2087.

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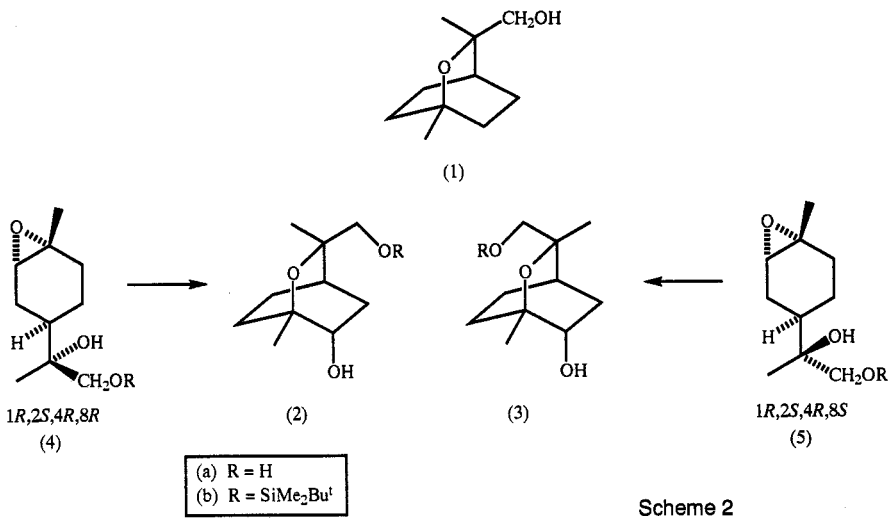
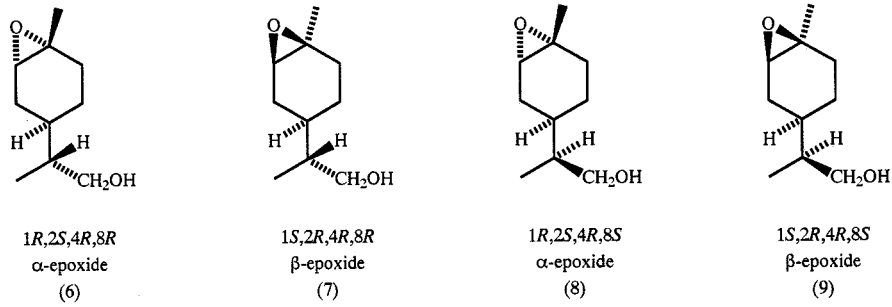


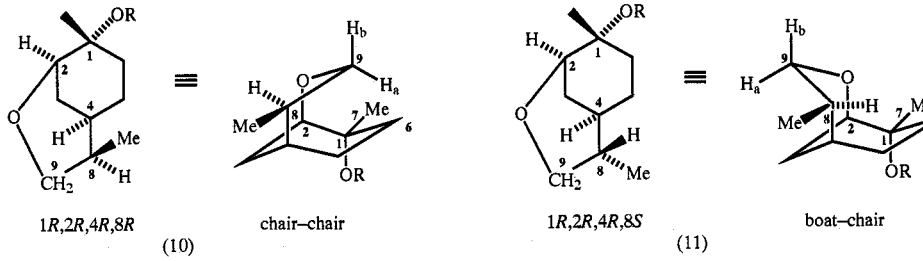
Scheme 2

of C 9 hydroxyl involvement in the above reactions, we have now prepared the hydroxy epoxides (6)–(9) and subjected them to acid catalysis, leading to the two novel 2,9-cineoles (10a) and (11a).

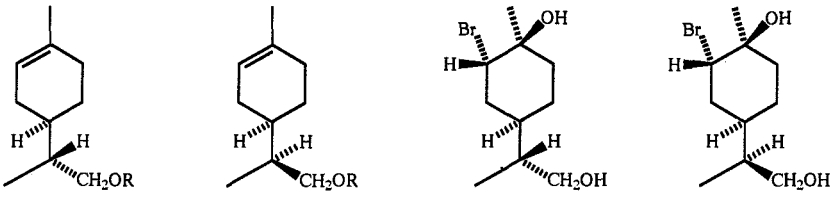
Discussion and Results

The (4*R*)-alcohols (12a) and (13a) are commercially available as a 2 : 1 mixture of C 8 epimers, and this mixture was used as the starting material in this work.





Pure alcohol (12a), when required, was obtained from this mixture by fractional crystallization of the 3,5-dinitrobenzoates (12b)+(13b),[6] when the less soluble (4*R*,8*R*)-isomer (12b) can be purified and then hydrolysed to give pure (4*R*,8*R*) alcohol (12a).



4*R*,8*R* (12) 4*R*,8*S* (13) 1*S*,2*S*,4*R*,8*R* (14) 1*S*,2*S*,4*R*,8*S* (15)

(a) R = H
(b) R = 3,5-dinitrobenzoate

Epoxidation of the 2:1 mixture of alcohols (12a)+(13a) afforded a mixture of four epoxides (6)+(7)+(8)+(9) which could not be separated by column chromatography and which gave only one peak in the gas chromatograph. ^{1}H and ^{13}C n.m.r. spectra of the mixture indicated equal attack on both faces of the starting olefin and a 1:1 ratio of epoxides [(6)+(8)]/[(7)+(9)] was obtained. Hence the mixture was a 2:2:1:1 mixture of epoxides (6), (7), (8) and (9). The n.m.r. spectra of the pairs of C8 epimeric epoxides (6) and (8), and (7) and (9) were very similar, but the two different epoxide orientations exhibited differences typical of related epoxides in this series.[7,8] In particular, C4 in the α-epoxides (6) and (8) resonates *c.* 4 ppm upfield of the corresponding signal in the β-epoxides (7) and (9) owing to the gamma effect, while H2 in the proton spectra gave a triplet (*J* 2–3 Hz) for the α-epoxides (6) and (8) and the characteristic doublet (*J c.* 5 and <1 Hz) for the β-epoxides (7) and (9). The ^{13}C spectral data are collected into Table 1, where the values for compounds (6)–(9) were abstracted from spectra of a range of mixtures of varying concentrations.

Authentic β-epoxides (7) and (9) are available apart from the α-epoxides by indirect synthesis from the 2:1 mixture of alcohols (12a)+(13a). *N*-Bromosuccinimide in wet acetone afforded a 2:1 mixture of the two bromohydrins (14) and (15) which are readily converted into the β-epoxides (7) and (9) with alkali. Again the C8-epimeric bromohydrins (14) and (15) were chemically and spectroscopically very similar; the ^{13}C data are included in Table 1.

Treatment of the above epoxide mixture (6)–(9) with a catalytic amount of *p*-toluenesulfonic acid afforded the two cineoles (10a) and (11a) together with the unreacted β-epoxides (7) and (9). Compounds (10a) and (11a) arise from nucleophilic C9-hydroxyl attack at C2, at the back of the least substituted end of

[6] Pawson, B. A., Cheung, H. C., Gurbaxani, S., and Saucy, G., *J. Am. Chem. Soc.*, 1970, **92**, 336.
[7] Carman, R. M., and Klika, K. D., *Aust. J. Chem.*, 1991, **44**, 1803.
[8] Carman, R. M., Garner, A. C., and Klika, K. D., *Aust. J. Chem.*, 1993, **46**, 233.

Table 1. ^{13}C n.m.r. data in $CDCl_3$ solution

Chemical shifts listed to two decimal places are reported more accurately than is warranted in absolute terms, but the recorded values reflect real spectral differences observed within mixtures

Cpd	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
(6)[A]	60·81	57·79	27·65	30·17	25·71	29·05	24·27	39·36	65·46	13·01
(7)[A]	59·43	57·97	26·04	33·89	23·25	30·70	22·91	39·77	65·65	12·60
(8)[A]	60·81	57·72	29·86	30·34	23·64	28·92	24·27	39·19	65·34	13·05
(9)[A]	59·54	57·90	28·67	34·07	21·04	30·59	22·91	39·55	65·77	13·18
(10a)	74·5	71·1	30·3	29·9	21·7	35·9	28·4	33·7	68·1	15·4
(11a)	74·8	71·4	27·9	31·6	21·4	30·7	28·1	33·5	66·5	18·4
(10b)[B]	88·7	70·2	29·8	28·9	21·2	32·1	22·8	33·5	68·7	15·6
(11b)[C]	88·6	71·1	26·3	30·8	21·1	27·5	22·3	33·5	66·3	18·2
(12a)	133·88	120·58	27·53	35·02	27·15	30·66	23·37	40·03	66·21	13·13
(13a)[A]	133·93	120·65	29·72	35·17	25·33	30·52	23·37	39·85	66·09	13·57
(12b)[D]	133·94	120·06	26·81	35·49	27·71	30·36	23·22	36·76	70·09	13·66
(13b)[A,D]	133·86	120·06	29·33	35·61	25·47	30·24	23·22	36·65	69·98	14·06
(14)[A,E]	71·06	62·22	33·88[F]	33·59	25·66	34·11[F]	30·08	40·45	65·66	14·27
(15)[A,E]	71·10	62·39	35·72	33·29	23·42	33·76	30·08	40·37	65·77	13·81

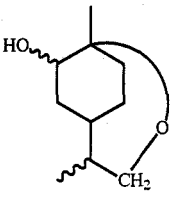
[A] Data obtained by subtraction of mixtures.
[B] With additional peaks at δ 114·36 ($^1J_{C,F}$ 287 Hz) and 155·67 ($^2J_{C,F}$ 41·7 Hz).
[C] With additional peaks at δ 114·39 ($^1J_{C,F}$ 287 Hz) and 155·84 ($^2J_{C,F}$ 40·8 Hz).
[D] With additional peaks at δ 122·13, C4′; 129·19, C2′,C6′; 148·49, C3′,C5′; 162·46, C=O; and with C1′ obscured (at 133·9?).
[E] (D_6)Acetone solution.
[F] Assignments may be interchanged.

the protonated α-epoxides. A new six-membered ring is formed. The products, together with the presence of unreacted β-epoxides (7) and (9), are all consistent with an attack which has considerable S_N2 character.

Gas chromatographic analysis of the reaction mixture showed products (10a) and (11a) in a 2:1 ratio, suggesting that compound (10a) is derived from the major α-epoxide (6) while compound (11a) is from the minor α-epoxide (8). In confirmation, pure alcohol (12a) upon epoxidation and acid treatment, afforded only product (10a) together with unreacted β-epoxide (9). The configuration at C2 is inverted in these transformations while the configuration of C4 and C8 is retained, and hence the C8 stereochemisty of products (10a) and (11a) follows from that of the starting material.

The similarity of the ^1H and ^{13}C n.m.r. spectra of compounds (10a) and (11a) suggested that they were C8 epimers with the same carbon skeleton. However, the structures did not immediately follow from the spectral data. The ^{13}C n.m.r. spectra of both compounds exhibit three low-field signals for carbon adjacent to an oxygen, one a quaternary signal (C1), one a methine (C2) and one a methylene (C9). These data might also be consistent with structure (16), an isomer with a seven-membered ether ring, and the product of attack at C1 of the initial epoxide. Consequently the hydroxy group was derivatized. Neither product (10a) nor (11a) could be acetylated with acetic anhydride in pyridine over

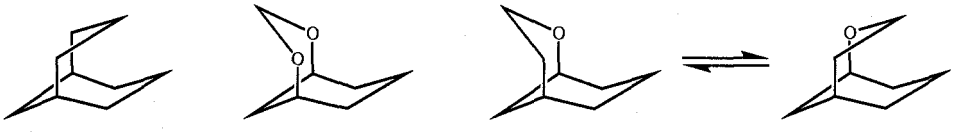
24 h. However, the trifluoroacetate derivatives (10b) and (11b) were obtained by treatment with neat trifluoroacetic anhydride in a slow reaction which was incomplete after 12 h. This reactivity is consistent with the tertiary hydroxyl structure.



(16)

N.m.r. spectra confirmed the structures (10b) and (11b). The chemical shifts for H2 and the three H7 in both isomers are only *c.* 0·4 ppm downfield from the same protons in the free alcohols (10a) and (11a), consistent with the attachment of a tertiary trifluoroacetate group to C1 adjacent to C2 and C7, but inconsistent with the attachment of a secondary ester at C2, when a large downfield shift (*c.* 1·5 ppm) for H2 is expected.[9] The ^{13}C spectra of the trifluoroacetates (10b) and (11b) are similar to those of the parent alcohols (10a) and (11a) but with the low-field quaternary carbon (C1) now shifted *c.* 14 ppm downfield.

The parent bicyclo[3.3.1]nonane (17) exists predominantly in the chair–chair conformation.[10] The introduction of oxygen atoms into the ring can destabilize this conformation, and the preferred conformation[11] of 2,4-dioxabicyclo[3.3.1]nonane (18) is a boat–chair. The mono-oxygenated analogue (19), the parent of compounds (10) and (11), may exist as a mixture of chair–chair and boat–chair conformers, although the evidence seems inconclusive.[11]



(17) chair–chair (18) boat–chair boat–chair chair–chair (19)

In the substituted compounds (10) and (11) we assume that the carbocyclic ring of both compounds will adopt a chair conformation, which orientates the C1 hydroxy group antiperiplanar to the ether oxygen, and which places the C7 methyl in an equatorial position. The conformation of the oxo ring is then available from ^1H n.m.r. couplings. Isomer (10a) shows one H9 signal as a triplet with two large couplings ($J_{9a,9b} \approx J_{9a,8} \approx 12$ Hz) while the other H9 signal is a

[9] Boschke, F. L., Fresenius, W., Huber, J. F. K., Pungor, E., Rechnitz, G. A., Simon, W., and West, T. S., (Eds) 'Tables of Spectral Data for Structure Determination of Organic Compounds' pp. H55, H145 (Springer-Verlag: Berlin 1983).

[10] Peters, J. A., Baas, J. M. A., van der Toorn, J. M., and van Bekkum, H., *Tetrahedron*, 1978, **34**, 3313.

[11] Peters, J. A., Peters-Van Cranenburgh, P. E. J., Bovee, W. M. M. J., Rozema, H. P., van der Toorn, J. M., Wortel, T. M., and van Bekkum, H., *Tetrahedron*, 1982, **38**, 3641.

doublet of doublets with $J_{9_a,9_b}$ −11 and $J_{9_b,8}$ 7 Hz. These data require that H9_a be antiperiplanar to H8, and are consistent with the chair–chair conformer (10).

Isomer (11a), despite having the inverted C8 stereochemistry, also shows one H9 signal as a triplet with two large couplings ($J_{9_a,9_b} \approx J_{9_a,8} \approx 11$ Hz) while the other H9 signal is a doublet of doublets again with $J_{9_a,9_b}$ −11 and $J_{9_b,8}$ 6 Hz. These data also require that H8 be antiperiplanar to H9_a, and hence that compound (11a) adopts the alternative boat–chair conformation (11). Dreiding models indicate that the C8 methyl of isomer (11a) suffers no adverse interaction in either the chair–chair or the boat–chair conformations, and it is probably the interaction between the inside H9 and the axial H6 in the chair–chair conformer which destabilizes this arrangement relative to the boat–chair form. In the case of isomer (10a) the C8 methyl suffers no major adverse interactions in the chair–chair conformer, whereas there is an adverse interaction between this C8 methyl and the axial H6 in a chair–boat conformer, and hence the former conformation is favoured.

The ^{13}C n.m.r. chemical shifts of all these compounds, collected into Table 1, show how epimers differing only at C8 show very similar spectra.[12] However, minor differences can be observed in the shifts of C3 and C5. The C3 signal of the 8*R* epimers (6), (7), (12a,b) and (14) always lies to higher field than the C3 signal in the corresponding 8*S* epimers (8), (9), (13a,b) and (15). Contrariwise, the C5 signal of these 8*R* epimers always lies to lower field of the C5 signal in the corresponding 8*S* epimers. Such a difference has already been noted by Bohlmann[13] for compounds (12a) and (13a), although it is unclear how Bohlmann assigned his carbon spectra.

Experimental

^{1}H and ^{13}C n.m.r. spectra were recorded in $CDCl_3$ solutions upon Bruker AC 200F, Jeol GX400 or Bruker AMX500 spectrometers. ^{13}C multiplicities were assigned by the DEPT pulse sequence. G.c. analyses were most effectively performed upon a BP5 capillary column with flame ionization detection in a Varian 3300 instrument. Mass spectra were recorded upon a Hewlett Packard MSD 5970 spectrometer with a g.c. inlet (BP5 column), with high resolution m.s. data from a Kratos MS 25 RFA spectrometer. Optical rotations were recorded at ambient temperature upon a Perkin Elmer 241MC polarimeter.

*(4*R*,8*R*)*-p-*Menth-1-en-9-ol (12a)*

p-Menth-1-en-9-ol [Aldrich, 2:1 mixture of (4*R*,8*R*)/(4*R*,8*S*) isomers (12a) and (13a)] (2 g, 12·9 mmol) and 3,5-dinitrobenzoyl chloride (4·6 g, 20 mmol) were stirred (4 h) in dry pyridine (100 ml) and then poured into water (100 ml) and extracted into ether (200 ml). Ether extracts were washed with saturated aqueous copper sulfate (3×100 ml), dried ($MgSO_4$), and taken to dryness to yield *p*-menth-1-en-9-yl 3,5-dinitrobenzoate (4·1 g, 91%) as a 2:1 mixture of the (4*R*,8*R*) and (4*R*,8*S*) isomers (12b) and (13b). Six recrystallizations from hexane gave (4*R*,8*R*)-*p*-menth-1-en-9-yl 3,5-dinitrobenzoate (12b) [free of the (4*R*,8*S*)-isomer (13b) by ^{1}H and ^{13}C n.m.r.], m.p. 97°, $[\alpha]_D$ +33·9° (*c*, 1·56 in $CHCl_3$) (lit.[6] m.p. 98°, $[\alpha]_D$ +36·7°) (Found: C, 58·7; H, 5·8; N, 7·9. Calc. for $C_{17}H_{20}N_2O_6$: C, 58·6; H, 5·8; N, 8·0%). ^{1}H n.m.r. δ 1·02, d, $J_{8,10}$ 6·9 Hz, H10; 1·62, s, H7; 4·36, AB region of an ABX system with J_{AB} 10·9, J_{AX} 5·4, J_{BX} 7·0 Hz, and Δ_{AB} 0·17 ppm, two H9; 5·35, m, H2; 9·12, d, *J* 2·1 Hz, H2′ and H6′; 9·20, t, *J* 2·1 Hz, H4′. ^{13}C n.m.r.: see Table 1. I.r. (from Nujol and hexachlorobutadiene mulls): 3107, 3098, 2960, 2914, 2888, 1737, 1720, 1556, 1544, 1537, 1343 cm^{-1}. *m/z* 348 (M, 1%), 196 (1), 195 (11), 179 (1), 165 (1), 150 (1), 149 (12),

[12] Carman, R. M., Greenfield, K. L., and Robinson, W. T., *Aust. J. Chem.*, 1986, **39**, 21.
[13] Bohlmann, F., and Zeisberg, R., *Org. Magn. Reson.*, 1975, **7**, 426.

136 (24), 121 (21), 107 (23), 95 (27), 94 (100), 93 (38), 91 (10), 79 (30), 75 (21), 68 (22), 67 (33), 55 (19), 53 (12), 41 (22).

The pure 3,5-dinitrobenzoate (12b) (300 mg, 1·4 mmol) was hydrolysed (20°, 1 h) in methanol (100 ml) and aqueous potassium carbonate (5%, 20 ml). The mixture was then poured onto aqueous potassium carbonate (5%, 100 ml), extracted with ether, dried ($MgSO_4$), and taken to dryness. Chromatography (silica, ether/hexane 3:7) gave (4*R*,8*R*)-*p*-menth-1-en-9-ol (12a) (110 mg, 82%) as the first eluting compound, $[\alpha]_D$ +100·9° (*c*, 0·89 in $CHCl_3$) (lit.[6] +102°) (Found: C, 78·1; H, 12·1. Calc. for $C_{10}H_{18}O$: C, 77·9; H, 11·8%). ^{1}H n.m.r. δ 0·82, d, *J* 6·6 Hz, H10; 1·56, s, H7; 3·45, AB region of an ABX system with J_{AB} 10·5, J_{AX} 5·2, J_{BX} 6·7 Hz, Δ_{AB} 0·168 ppm, two H9; 5·29, m, H2. ^{13}C n.m.r.: see Table 1; where the peaks for C3 and C5 were assigned from C/H correlation experiments; where C6 was identified by a three-bond coupling to the three H7; and where C3 showed a two-bond coupling to H2. I.r. (neat): 3335, 3007, 2961, 2915, 1437, 1377, 1152, 1039, 986 cm^{-1}. *m/z* 154 (M, 13%), 137 (1), 136 (13), 123 (15), 122 (5), 121 (37), 108 (11), 107 (40), 95 (46), 94 (100), 93 (80), 92 (30), 81 (42), 79 (84), 68 (56), 67 (95), 55 (50), 53 (39), 41 (65), 39 (54).

Data reported in Table 1 for isomer (13a) were obtained from spectra of the 2:1 mixture (12a)+(13a). All the carbon signals in both these isomers were assigned by short- and/or long-range proton/carbon two-dimensional correlations.

*The 1,2-Epoxy-*p*-menthan-9-ol Mixture (6)–(9)*

p-Menth-1-en-9-ol [as a 2:1 mixture of (4*R*,8*R*) and (4*R*,8*S*) isomers (12a) and (13a)] (1·8 g, 11·6 mmol) and *m*-chloroperbenzoic acid (4·1 g, activity 50–60%, *c.* 23 mmol) in dichloromethane (200 ml) were stirred (0°, 2 h). The mixture was then washed with potassium hydroxide (aqueous, 5%), dried ($MgSO_4$), and taken to dryness to yield an oily mixture of the four 1,2-epoxy-*p*-menthan-9-ols (6)–(9) (1·7 g, 88%). The mixture gave only one peak on g.c. and one spot on t.l.c., but was a 2:2:1:1 mixture of isomers (6), (7) (8) and (9) by ^{13}C n.m.r. (Found: C, 70·5; H, 11·0. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%). ^{1}H n.m.r. δ 0·77, four overlapping d, $J_{8,10}$ 6·9 Hz, H10; 1·22, s, H7; 2·48, br, OH; 2·90, d, *J* 5·3 Hz, H2 in the β-epoxides (7) and (9); 2·95, s slightly broadened, H2 in the α-epoxides (6) and (8); 3·40, m, the AB regions of four overlapping ABX systems, H9 and H9′. ^{13}C n.m.r. (37 discrete peaks of the expected 40) as listed in Table 1. I.r. (neat): 3428, 2947, 2924, 2877, 1450, 1433, 1379, 1041, 838 cm^{-1}. *m/z* no M, 165 (0·2%), 155 (1), 140 (1), 139 (6), 137 (3), 128 (3), 125 (5), 112 (6) 111 (53), 110 (14), 95 (11), 84 (14), 81 (11), 71 (21), 69 (16), 67 (25), 55 (26), 43 (100), 41 (39), 39 (18).

*The 2-Bromo-*p*-menthane-1,9-diols (14) and (15)*

p-Menth-1-en-9-ol [as a 2:1 mixture of (4*R*,8*R*) and (4*R*,8*S*) isomers (12a) and (13a)] (1·0 g, 6·4 mmol) and *N*-bromosuccinimide (2·1 g, 12 mmol) in acetone (35 ml) containing water (12 ml) were stirred (15 min) and then diluted with water (50 ml) and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to yield a crude oil (1·5 g) which crystallized from acetone to give a 2:1 mixture of *(1*S*,2*S*,4*R*,8*R*)-* and *(1*S*,2*S*,4*R*,8*S*)-2-bromo-*p*-menthane-1,9-diols* (14) and (15), m.p. 112° (Found: C, 47·5; H, 7·6. $C_{10}H_{19}BrO_2$ requires C, 47·8; H, 7·6%). ^{1}H n.m.r. δ 0·91, d, *J* 6·9 Hz, H10; 1·39, s, H7; 3·542, the AB region of an ABX system, J_{AB} 10·7, J_{AX} 6·5, J_{BX} 5·6 Hz, Δ_{AB} 0·130 ppm, two H9 of the major isomer (14); 3·545, the AB region of a second overlapped ABX system, J_{AB} 10·6, J_{AX} 6·5, J_{BX} 5·5 Hz, Δ_{AB} 0·125 ppm, two H9 of the minor isomer (15); 4·15, m, H2. ^{1}H n.m.r. [(D_6)acetone] δ 0·88, d, *J* 7·0 Hz, H10 of minor isomer (15); 0·90, d, *J* 6·8 Hz, H10 of major isomer (14); 1·34, s, H7 of both isomers; 3·46, m, two H9 of both isomers, 4·27, m, H2 in both isomers. ^{13}C n.m.r.: see Table 1. I.r. (KBr disk): 3374, 2967, 2922, 2896, 2875, 1476, 1458, 1448, 1430, 1419, 1379, 1048, 903 cm^{-1}. *m/z* no M, 235 (1%), 234 (2), 232 (2), 219 (4), 217 (2), 216 (3), 214 (2), 178 (4), 177 (4), 164 (4), 162 (7), 141 (4), 137 (7), 135 (17), 134 (25), 125 (16), 109 (15), 107 (16), 95 (22), 93 (22), 91 (11), 83 (25), 71 (85), 69 (18), 67 (22), 58 (19), 55 (30), 43 (100), 41 (34).

*The 1,2-Epoxy-*p*-menthan-9-ol Mixture (7)+(9)*

The 2-bromo-*p*-menthane-1,9-diols (14) and (15) as a 2:1 mixture (1 g, 4 mmol) were stirred (1 h) with potassium hydroxide (1 g) in methanol (50 ml). The mixture was poured into water

(50 ml), extracted into ether, and dried ($MgSO_4$), and the solvent was removed to yield a 2:1 mixture (by ^{13}C n.m.r.) of the *(1*S,*2*R,*4*R,*8*R*)*- and *(1*S,*2*R,*4*R,*8*S*)-1,2-epoxy*-p-*menthan-9-ols* (7) and (9) (580 mg, 85%) (Found: C, 70·4; H, 10·9. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%). ^1H n.m.r. δ 0·81, two overlapping d of differing intensity, J 6·9 Hz, H 10; 1·26, s, H 7; 2·94, d, J 5·3, H 2; 3·46, m, two H 9. ^{13}C n.m.r.: see Table 1, and where the peaks for compound (7) were twice the intensity of the corresponding peaks for compound (9). I.r. (neat): 3439, 2947, 2924, 2877, 1450, 1433, 1379, 1041, 838 cm^{-1}; very similar to the spectrum of the mixture (6)–(9) above. *m/z* no M, 155 (2%), 140 (1), 139 (6), 137 (3), 125 (5), 123 (3), 121 (2), 119 (2), 113 (2), 112 (3), 111 (40), 110 (10), 97 (10), 84 (15), 71 (17), 69 (15), 67 (18), 55 (28), 53 (10), 44 (12), 43 (100), 41 (31), 39 (18).

Treatment of Epoxides with p-*Toluenesulfonic Acid*

The epoxide mixture (6)–(9) (1 g) and *p*-toluenesulfonic acid (*c.* 30 mg) were stirred (12 h) in dichloromethane (200 ml). Sodium carbonate (1 g) was added and the mixture was stirred for a further 2 h. The mixture was filtered and the solvent removed to yield a crude oil (840 mg). G.c. analysis indicated products (10a) and (11a) (2:1) together with the unreacted epoxides (7) and (9) (one peak). Chromatography (silica, ether/hexane 1:9) gave firstly crystalline *(1*R,*4*S,*5*R,*8*R*)-4,8-dimethyl-2-oxabicyclo[3.3.1]nonan-8-ol* [(1*R*,2*R*,4*R*,8*S*)-1-hydroxy-2,9-cineole] (11a), m.p. 74° (from pentane), $[\alpha]_D$ −65·5° (*c*, 1·78 in $CHCl_3$) (Found: C, 70·2; H, 10·9%; *m/z* 170·1309. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%; *m/z* 170·1306). ^1H n.m.r. δ 0·83, d, J 6·9 Hz, H 10; 1·33, s, H 7; 3·30, t, J 11·3 Hz, $H9_a$; 3·53, br d, J 4·3 Hz, H 2; 3·61, dd, J 6·4, 11·3 Hz, $H9_b$. ^{13}C n.m.r.: see Table 1, where C 3 was distinguished from C 6 by a three-bond C 6–H 7 coupling. I.r. (from Nujol and hexachlorobutadiene mulls): 3329br, 2955, 2925, 2877, 2890, 1455, 1403, 1372, 1330, 1308, 1210, 1137, 1103, 1085, 1055 cm^{-1}. *m/z* 171 (M+1, 1%), 170 (M, 6), 152 (10), 137 (5), 134 (6), 123 (7), 122 (5), 111 (14), 110 (100), 97 (100), 95 (15), 79 (11), 71 (23), 69 (22), 67 (22), 55 (24), 43 (92), 41 (46), 39 (18).

Further elution of the column gave crystalline *(1*R,*4*R,*5*R,*8*R*)-4,8-dimethyl-2-oxabicyclo[3.3.1]nonan-8-ol* [(1*R*,2*R*,4*R*,8*R*)-1-hydroxy-2,9-cineole] (10a), m.p. 102° (from pentane), $[\alpha]_D$ −22·4° (*c*, 1·19 in $CHCl_3$) (Found: C, 70·6; H, 10·9%; *m/z* 170·1310. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%; *m/z* 170·1306.). ^1H n.m.r. δ 0·80, d, J 6·8 Hz, H 10; 1·23, s, H 7; 3·40, br s, J *c.* 1 and *c.* 2 Hz, H 2; 3·47, t, J 11·9 Hz, $H9_a$; 3·64, dd, J 7·2, 11·8 Hz, $H9_b$. ^{13}C n.m.r.: see Table 1, where C 3 was distinguished from C 6 by a three-bond C 6–H 7 coupling. I.r. (from Nujol and hexachlorobutadiene mulls): 3417, 2957, 2924, 2876, 1451, 1390, 1372, 1331, 1235, 1093, 1068, 1053 cm^{-1}. *m/z* 171 (M+1, 1%), 170 (M, 6), 152 (8), 137 (3), 134 (2), 123 (4), 122 (3), 111 (10), 110 (100), 97 (44), 95 (16), 79 (9), 71 (23), 69 (16), 67 (12), 55 (17), 43 (64), 41 (34), 39 (13).

When the epoxide mixture (6)+(7) [formed by epoxidation of pure alcohol (12)] was similarly treated with *p*-toluenesulfonic acid, the resultant mixture comprised unreacted *β*-epoxide (7) and compound (10) [but no isomer (11)] (by g.c./m.s.).

The Trifluoroacetates (10b) and (11b)

Alcohol (11a) (50 mg) was stored (24 h) in acetic anhydride (0·5 ml) containing dry pyridine (0·5 ml). G.c. and t.l.c. analysis indicated no reaction. Similar treatment of the epimer (10a) also showed no reaction.

Alcohol (10a) (70 mg) and trifluoroacetic anhydride (2 ml) were stirred for 12 h. Excess trifluoroacetic anhydride and trifluoroacetic acid were removed under vacuum and the residue was chromatographed (silica, ether/pentane 1:9) to give oily *(1*R,*4*R,*5*R,*8*R*)-4,8-dimethyl-8-trifluoroacetoxy-2-oxabicyclo[3.3.1]nonane* [(1*R*,2*R*,4*R*,8*R*)-1-trifluoroacetoxy-2,9-cineole] (10b) (42 mg, 55%) (Found: *m/z* 226·1131. $C_{12}H_{17}F_3O_3$ requires 266·1117). ^1H n.m.r. δ 0·85, d, J 6·9 Hz, H 10; 1·66, s, H 7; 3·45, t, J 12·0 Hz, $H9_a$; 3·75, dd, J 7·4, 12·0 Hz, $H9_b$; 3·94, br s, H 2. ^{13}C n.m.r.: see Table 1. I.r. (neat): 2959, 2930, 2870, 1778, 1489, 1455, 1372, 1220, 1163, 1119, 1095, 1070, 1042 cm^{-1}. *m/z* 266 (M, 3%), 153 (1), 152 (4), 135 (2), 123 (2), 111 (4), 110 (20), 97 (100), 79 (12), 69 (26), 55 (16), 43 (33), 41 (25).

Similar treatment of alcohol (11a) gave oily *(1*R,*4*S,*5*R,*8*R*)-4,8-dimethyl-8-trifluoroacetoxy-2-oxabicyclo[3.3.1]nonane* [(1*R*,2*R*,4*R*,8*S*)-1-trifluoroacetoxy-2,9-cineole] (11b) in comparable

yield (Found: *m/z* 266·1128. $C_{12}H_{17}F_3O_3$ requires 266·1117). ^{1}H n.m.r. δ 0·83, d, *J* 6·9 Hz, H 10; 1·55, s, H 7; 3·28, t, *J* 11·4 Hz, $H9_a$; 3·61, dd, *J* 6·9, 11·4 Hz, $H9_b$; 4·00 br d, *J* 4·3 Hz, H 2. ^{13}C n.m.r.: see Table 1. I.r. (neat): 2956, 2927, 2867, 1780, 1484, 1456, 1374, 1214, 1123, 1104, 1081, 1051 cm^{-1}. *m/z* 266 (M, 1·8%), 153 (2), 152 (4), 135 (1), 123 (1), 111 (3), 110 (12), 97 (100), 79 (11), 69 (25), 55 (14), 43 (33), 41 (24); very similar to that of the C 8 epimer (10b).

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