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SYNTHESIS OF 1,2,3-TRIHYDROXY-*p*-MENTHANES

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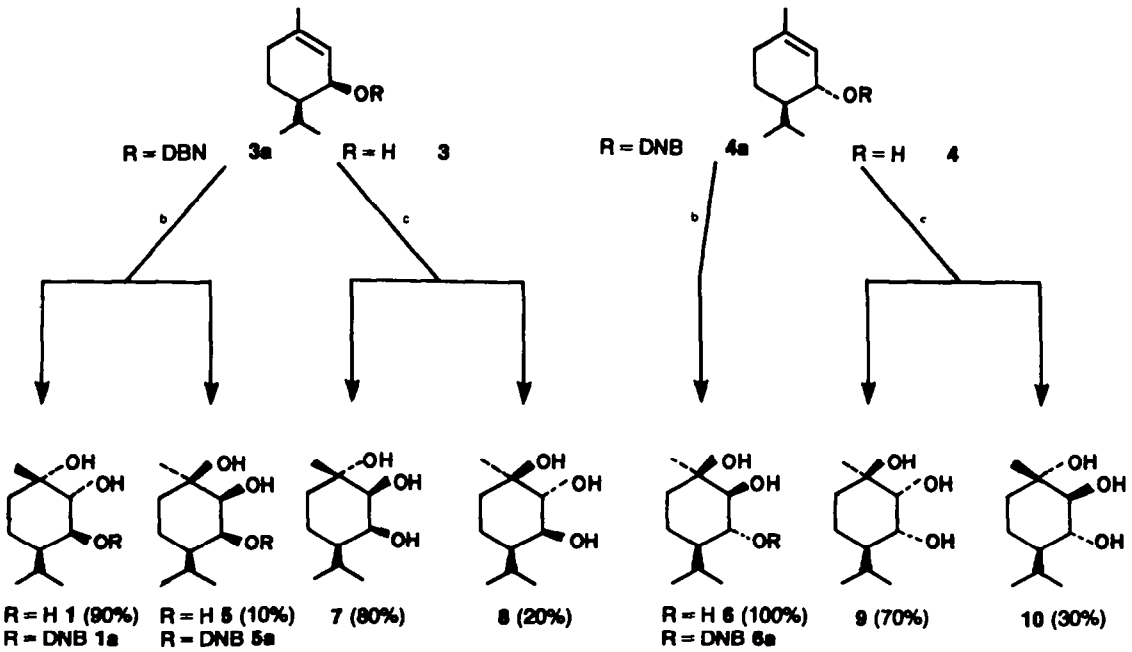
Abstract—Seven new stereoisomers of 1,2,3-trihydroxy-*p*-menthane have been synthesised. Their stereochemistry, proved mainly *via* chemical transformations and confirmed by ^{1}H-NMR, is discussed.

We have recently reported the isolation of a novel naturally occurring derivative of *p*-menthane to which, on the basis of chemical and ^{1}H-NMR evidence, we assigned the structure of 1α,2α,3β-trihydroxy-*p*-menthane **1** (or its enantiomer).[1,a]

The potential biological activity of this molecule prompted us to undertake the synthesis of **1** as well as that of all its possible stereoisomers: the results are described in the present paper.

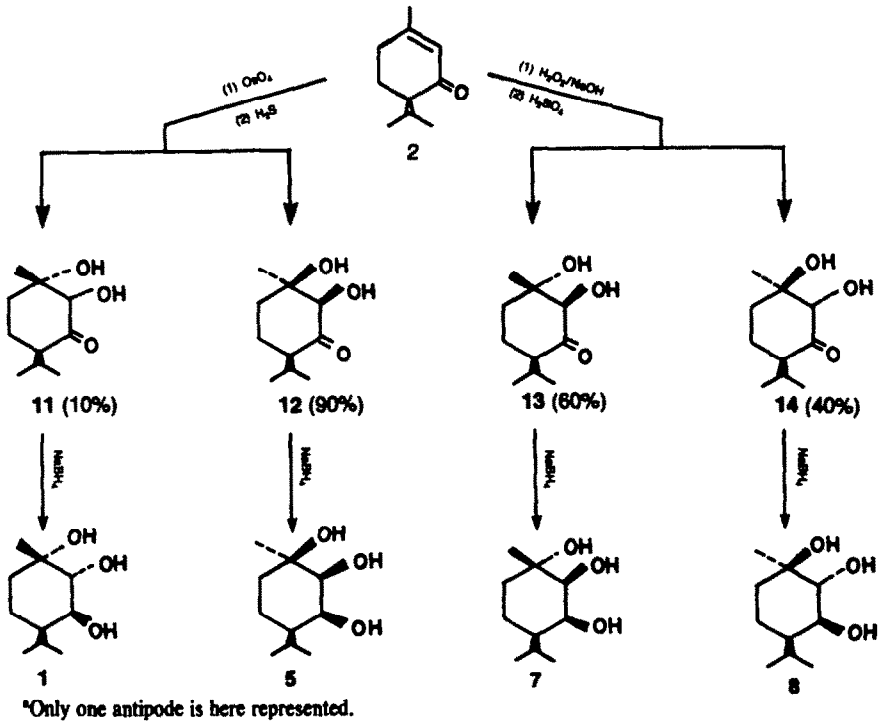
Because of the nature and location of its functionalities, (±) piperitone **2** was chosen as the starting material, and the synthetic work proceeded along two different routes (Schemes A and B). In the first, **2** was converted by reduction into the known (±) *cis*- **3** and (±) *trans*-piperitol **4**.[3] The former was utilised to synthesise triols **1**, **5**, **7** and **8** (all having a 3β-OH), while the latter led to the diastereoisomeric triols **6**, **9** and **10** (all having a 3α-OH). Triols **1** and **5**, both having a *cis* arrangement of the OH groups at C-1 and C-2, were obtained as a mixture, in the ratio reported in Scheme A, by action of OsO_4 upon **3a** followed by alkaline hydrolysis: evidently attack of the reagent took place preferentially on the less hindered side of the molecule and the presence of the dinitrobenzoate (DNB) group obviously helped in guiding to the desired stereochemistry. Compound **6** was likewise obtained from **4a** following the same procedure described above. Triols **7** and **8**, having in turn a *trans* C-1 OH, C-2 OH arrangement, were secured by *trans* hydrolytic opening of the epoxide mixture resulting from action of *m*-chloroperbenzoic acid on **3**: their ratio, also reported in Scheme A, is an obvious consequence of the known preferential *cis*- (to C-3 OH) attack of such a

[a]Incorporation experiments by feeding mevalonic acid 2-^{14}C proved that **1** is a true metabolite of the phytotoxic fungus *Fusicoccum Amygdali*, Del.[2]



Scheme A[a].

[a]Only one antipode is here represented.
[b](1) OsO_4, (2) H_2S.
[c](1) m-ClC_6H_4COOOH, (2) H_2SO_4.



[a]Only one antipode is here represented.

Scheme B[a].

reagent on allylic cyclohexanols[4] and of the mechanism governing asymmetric epoxide opening.[5,6,b] By means of the same epoxydation-hydrolysis procedure, triols **9** and **10** were obtained from **4**, and, in this case also, the yields can be rationalised on the same mechanistic basis.

Triols **1**, **5**, **7** and **8** could also be obtained (Scheme B) by direct oxidation of **2**, either by means of H_2O_2 (followed by acidic hydrolysis) although, in this case, the stereochemistry of the respective attacks is less predictable and is in fact deduced exclusively on comparison of the products obtained with those described above. As a matter of fact, when **2** was allowed to react with OsO_4 and the resulting crude mixture was decomposed with H_2S, we obtained (racemic) 1α,2α-*p*-menthane-3-one **11** (10%) with (racemic) 1β,2β-*p*-menthane-3-one **12** (90%), as demonstrated by their respective reduction ($NaBH_4$), after separation, to triols **1** and **5**. Two points can be hence deduced: (i) preferential attack of **2** by OsO_4 is reversed, if comparison is made with **3**; hence it seems that such an attack is quite sensitive to the C-3 geometry; (ii) action of $NaBH_4$ results always in formation of a β-OH. Epoxidation of **2** by H_2O_2 seems to be less influenced than OsO_4 attack: the diol mixture resulting after $NaBH_4$ reduction is in fact constituted by triols **7** (60%) and **8** (40%). We must stress again that the stereochemistry of the resulting triols was established by comparison with those obtained according to Scheme A, and that $NaBH_4$ reduction seems to proceed with exclusive introduction of a 3β-OH.

The stereochemistry of the so far described triols was confirmed independently by a combination of chemical (see Scheme C) and ^{1}H-NMR spectroscopic means, i.e. formation of acetonide derivatives, taken as a demonstration of *cis* relationship of the involved OH groups, followed by acetylation, the reactive site being detected by the characteristic downfield chemical shift of the corresponding proton; the lack of such a shift being taken as a proof of the tertiary function (C-1), while failure of acetylation was interpreted as a proof of steric hindrance of such a function.

The 2-H/3-H *cis* or *trans* relationship was in agreement with the particular magnitude of the $J_{2,3}$ (Table 1). The configuration previously assigned by us to **1** was thus definitively confirmed.

Analysis of the ^{13}C-NMR spectra of these compounds will be reported in a separate paper.[8]

EXPERIMENTAL

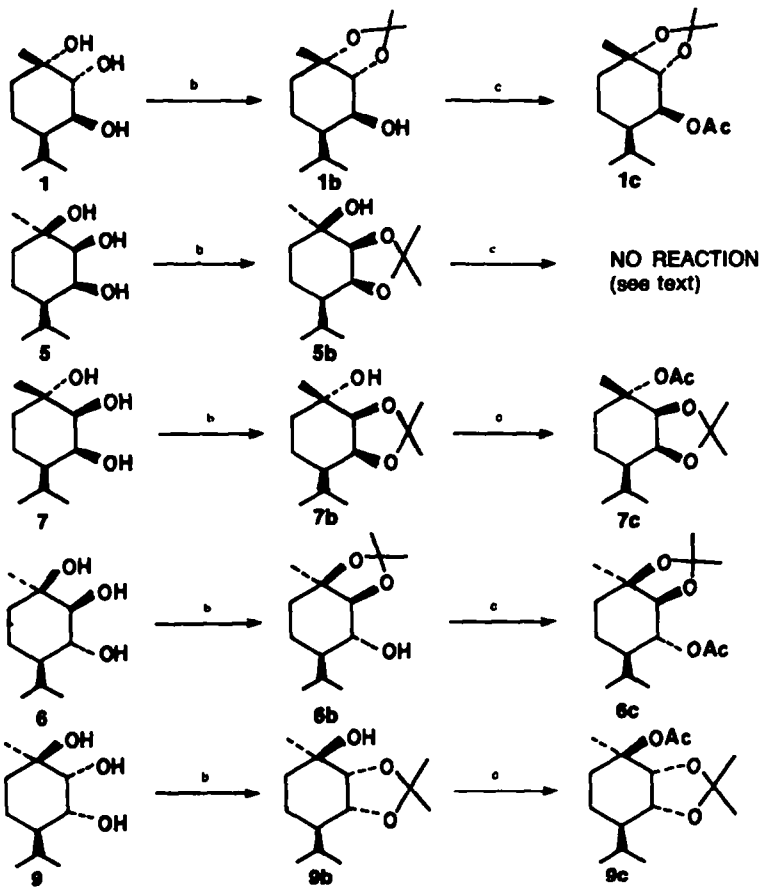
M. ps were measured using a Kofler hot-stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 247 spectrophotometer. The mass spectra were recorded with an AEI M.S. 902 spectrometer. UV spectra were measured with a Beckman DB-GT spectrometer in ethanolic soln. ^{1}H-NMR spectra were recorded with a Varian XL-100 instrument, in $CDCl_3$–DMSO-d_6 (3:1) soln using TMS as an internal standard. Merck's DC-Alufolien Kieselgel 60 F_{254} were used for TLC (solvent A: $CHCl_3$–MeOH 90:10; solvent B: $CHCl_3$–MeOH 80:20; solvent C: benzene–acetone 50:50); for detection of spots the plates were sprayed with phosphomolybdic acid (10% methanolic soln) first, then with H_2SO_4 (10% aqueous soln) and heated at 120°C for 5'. Merck's Kieselgel 60 (70–130 mesh ASTM) was used for column chromatography. Counter-current distribution was performed using a 123-tubes Quickfit apparatus.

(±)-cis-*Piperitol* **3** *and* (±)-trans-*piperitol* **4**

(±)-Piperitone **2**[c] (20 g) was reduced with LAH and worked up as previously described[5] to give a yellow oily mixture (17 g)

[b]The *trans* diequatorial opening of the epoxide rings in certain circumstances has been already postulated and its occurrence is not rare in the literature.[7]

[c]A very generous sample of (±)-piperitone (250 g) has been kindly furnished by Haarmann and Reimer GMBH 3450 Holzminden, Postfach 138 (West Germany) which are gratefully acknowledged.



[a]Only one antipode is here represented.
[b]$CuSO_4$, acetone, Δ.
[c]Acetic anhydride, pyridine.

Scheme C[a].

Table 1.

Compound	H-2	H-3	$^3J_{2,3}$	$^3J_{3,4}$	$^4J_{2,4}$
1	3.45 d	4.02 bs	4.8	2.0	---
1b	3.76 d	4.29 bs	3.0	---	---
1c	3.66 d	5.45 bs	3.0	---	---
5	3.03 d	3.95 t	3.0	2.1	---
5b	3.72 d	4.37 dd	6.0	3.5	---
7	3.29 d	3.97 t	3.4	2.5	---
7b	3.75 dd	4.49 dd	7.0	2.0	1.3
7c	4.10 dd	4.48 dd	7.0	2.0	1.5
8	3.48 dd	3.90 t	3.5	2.1	1.2
6	2.93 d	3.33 t	8.7	9.5	---
6b	3.14 d	3.64 t	9.0	10.0	---
6c	3.12 d	5.24 m	9.0	10.0	---
9	3.42 dd	3.70 dd	3.2	9.2	0.9
9b	3.78 dd	3.97 dd	4.9	9.0	0.9
9c	4.05 dd	3.97 dd	5.0	8.6	1.4
10	3.13 d	3.01 t	9.2	8.2	---
11	4.02 s	---	---	---	---
12	3.87 d	---	---	---	0.5
13	4.10 s	---	---	---	---
14	4.13 s	---	---	---	---

which was divided in 6 lots (*ca* 3 g each) and separated by counter-current distribution using MeOH saturated with *n*-hexane (pH 7.2) as the stationary phase and *n*-hexane saturated with MeOH as the mobile phase (1 transfer of the heavy phase every 4 transfers of the light phase; shaking time 3', sedimentation time 3'). In a typical run, after 2400 transfers of the light phase and 600 transfers of the heavy phase, compounds 3 (0.82 g) and 4 (1.66 g) possessing identical chemical-physical properties of authentic *cis*- and *trans*-piperitols respectively, were separated: they were then converted into their 3,5-dinitrobenzoates 3a and 4a as reported in the literature.[3]

cis-Hydroxylation

(a) Compound 3a (1 g) was treated with OsO_4 (0.83 g) by the usual method.[9] The partly crystalline product (0.7 g) was dissolved in benzene and chromatographed on Silica gel (30 g). Elution with benzene–ethyl acetate (98:2) gave two main fractions, A (34 mg) and B (327 mg) which after several crystallizations from benzene–light petroleum (1:1) afforded 5a and 1a respectively.

Compound 1a, white needles, m.p. 165–167°; $R_f = 0.63$ (solvent A); λ_{max}234, 254 (sh) nm (ϵ = 15660 and 8790 respectively); ν_{max}($CHCl_3$) 3700, 1730 and 1275 cm^{-1}; δ ($CDCl_3$): 9.22 ppm (1H, t), 9.10 (2H, d), 5.53 (1H, dd, $J_{2,3}$ = 4.5 Hz and $J_{3,4}$ = 2.0 Hz), 3.71 (1H, d, $J_{2,3}$ = 4.5 Hz), 1.30 (3H, s), 0.99 and 0.95 (3H each, both d, J = 6.0 Hz). (Found: C, 53.18; H, 5.73; N, 7.39; $C_{17}H_{22}N_2O_8$ requires: C, 53.40; H, 5.80; N,7.33%).

Compound 5a, white needles, m.p. 174–177°; $R_f = 0.72$ (solvent A); λ_{max}234, 253 (sh) nm (ϵ = 13640 and 6875 respectively); ν_{max}($CHCl_3$) 3560, 1735, and 1285 cm^{-1}. (Found: C, 53.05; H, 5.68; N, 7.17; $C_{17}H_{22}N_2O_8$ requires: C, 53.40; H, 5.80; N, 7.33%).

(b) Compound 4a (744 mg) was treated with OsO_4 (600 mg) and worked up as reported above. The orange-yellow crystalline product (751 mg) was purified by Silica gel (40 g) column chromatrography to give 6a which after several crystallizations from chloroform gave yellow needles, m.p. 162–164°; $R_f = 0.36$ (solvent A); λ_{max}234, 254 (sh) nm (ϵ = 13100 and 7640 respectively); ν_{max}($CHCl_3$) 3700, 3560, 1720, and 1285 cm^{-1}; δ (pyridine-d_5): 8.40–8.20 ppm (3H, bm), 5.71 (1H, t, $J_{2,3}$ = 8.7 Hz and $J_{3,4}$ = 9.5 Hz), 3.57 (1H, d, $J_{2,3}$ = 8.7 Hz), 1.48 (3H, s), 0.93 and 0.90 (3H each, both d, J = 6.5 Hz). (Found: C, 53.55; H, 5.85; N, 7.42; $C_{17}H_{22}N_2O_8$ requires: C, 53.40; H, 5.80; N, 7.33%).

(c) Compound 2 (2.4 g) was treated with OsO_4 as described[10] to give a deep yellow oily residue which was dissolved in benzene and chromatographed on Silica gel (100 g). Elution with benzene and benzene containing increasing amounts of EtOAc (up to 30%) led to two oily fractions D (468 mg) and F (241 mg).

Fraction D after treatment with light-petroleum (b.p. 30–40°) became solid and was further purified by several crystallizations from light-petroleum to give 12 (360 mg) as little white prisms, m.p. 63–65°; $R_f = 0.74$ (solvent B); ν_{max}($CHCl_3$) 3550–3400, 1710 cm^{-1}; δ ($CDCl_3$): 3.87 ppm (1H, d, J = 0.5 Hz), 1.36 (3H, s), 0.97 and 0.91 (3H each, both d, J = 6.0 Hz). (Found: C, 64.25; H, 9.68; $C_{10}H_{18}O_3$ requires: C, 64.49; H, 9.73%). Fraction F was dissolved in benzene chromatographed twice on Silica gel. Elution with benzene–ethyl acetate (99.5:0.5) led to 11 (40 mg) in a fairly pure state as a pale yellow oil; $R_f = 0.69$ (solvent B); $M^+ - 18 = 168$ ($C_{10}H_{18}O_3$ MW 186); ν_{max}($CHCl_3$) 3570–3450, 1715 cm^{-1}; δ ($CDCl_3$): 4.02 ppm (1H, s), 1.35 (3H, s), 1.00 and 0.84 (3H each, both d, J = 6.0 Hz).

Compound (±) 1

(a) Compound 1a (100 mg) dissolved by warming in anhydrous ether (15 ml) was hydrolysed by adding a methanolic soln of 1.5N KOH (5 ml). The soln, which immediately changed to a dark-red colour, was refluxed for 20'. After cooling the mixture, some crystals formed and were filtered off. The filtrate brought to dryness at reduced pressure left an oily brown residue which was suspended in water and repeatedly extracted with $CHCl_3$ (10 × 10 ml). The combined extracts dried over Na_2SO_4 and brought to dryness at reduced pressure gave a white residue which after several crystallizations from benzene yielded 1 as white prisms, m.p. 102–104°.

(b) Compound 11 (50 mg) dissolved in MeOH (5 ml) was reduced with an aqueous soln (1 ml) of $NaBH_4$ (15 mg) at r.t. for 2 hr. The mixture diluted with water was continuously extracted with ether. Evaporation of the dried extract afforded a yellow oily residue (45 mg) which after crystallization from benzene yielded 1 (20 mg), m.p. 100–102°.

We like to point out that the latter m.ps are different from that observed for the natural sample: synthetic 1 must be hence a racemate since a comparison of 1 obtained in both ways with the natural specimen showed their identity (R_f, IR, ^{1}H-NMR, mixed m.p., and identical acetonide and acetylacetonide derivatives).

Compound (±) 5

(a) Compound 5a (8 mg) was hydrolysed as previously described to give, after two crystallizations from *n*-hexane, 5 (2 mg) as white needles, m.p. 91–92°.

(b) Compound 12 (150 mg) dissolved in MeOH (10 ml) was reduced with an aqueous soln (2 ml) of $NaBH_4$ (35 mg) at r.t. for 3 hr and worked up in the usual way. A yellow residue was thus obtained which after several crystallizations from *n*-hexane afforded 5 (138 mg) as long needles, m.p. 93°; $R_f = 0.67$ (solvent B); $M^+ - 18 = 170$ ($C_{10}H_{20}O_3$ MW 188); ν_{max}($CHCl_3$) 3450 cm^{-1}; δ: 4.05 ppm (1H, dd, $J_{2,3}$ = 3.0 Hz and $J_{3,4}$ = 2.0 Hz), 3.16 (1H, d, $J_{2,3}$ = 3.0 Hz), 1.22 (3H, s), 0.93 (6H, d, J = 6.5 Hz). (Found: C, 63.36; H, 10.60; $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71%).

Compound (±) 6

Compound 6a (221 mg) was dissolved in ether (20 ml) and hydrolysed as described above. A compound was obtained which after crystallization first from *n*-hexane and then from EtOAc gave 6 as white needles, m.p. 76–78°; $R_f = 0.58$ (solvent B); $M^+ - 18 = 170$ ($C_{10}H_{20}O_3$ MW 188); ν_{max}($CHCl_3$) 3700, 3580, and 3450 cm^{-1}; δ: 3.33 ppm (1H, t, $J_{2,3}$ = 8.7 Hz and $J_{3,4}$ = 9.5 Hz), 2.93 (1H, d, $J_{2,3}$ = 8.7 Hz), 2.15 (1H, m), 1.16 (3H, s), 0.89 and 0.79 (3H each, both d, J = 7.0 Hz). (Found: C, 63.44; H, 10.78; $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71%).

Compound (±) 5b

Compound 5 (127 mg) was converted into the acetonide derivative in the usual way. The oily residue (131 mg) obtained, dissolved in chloroform, was chromatographed on Silica gel (2 g) affording 5b (92 mg) in a pure state as a pale yellow oil; R_f = 0.56 (solvent C); $M^+ = 228$ (2.5%), $M^+ - 15 = 213$ (33.98%) ($C_{13}H_{24}O_3$ MW 228); δ ($CDCl_3$): 4.37 ppm (1H, dd, $J_{2,3}$ = 6.0 Hz and $J_{3,4}$ = 3.5 Hz), 3.72 (1H, d, $J_{2,3}$ = 6.0 Hz), 1.52 (3H, s), 1.36 (3H, s), 1.15 (3H, s), 0.97 and 0.94 (3H each, both d, J = 6.0 Hz).

Compounds (±) 6b *and* (±) 6c

Compound 6 (150 mg) was converted into the acetonide derivative which was purified as described above to give 6b (70 mg) in a pure state as a pale yellow oil; $R_f = 0.50$ (solvent C); $M^+ = 228$ (1.42%), $M^+ - 15 = 213$ (71.48%) ($C_{13}H_{24}O_3$ MW 228); δ ($CDCl_3$): 3.64 ppm (1H, t, $J_{2,3}$ = 9.0 Hz and $J_{3,4}$ = 10.0 Hz), 3.14 (1H, d, $J_{2,3}$ = 9.0 Hz), 1.40 (3H, s), 1.37 (3H, s), 1.29 (3H, s), 0.85 and 0.94 (3H each, both d, J = 6.3 Hz).

Compound 6b (54 mg) was acetylated in the usual way and the oily yellow residue obtained (54 mg) dissolved in benzene was chromatographed on Silica gel (3 g). Elution with benzene and benzene–ethyl acetate (95:5) gave besides 6b (25 mg), 6c in a pure state as a pale yellow oil (22 mg); $R_f = 0.58$ (solvent C); $M^+ = 270$ (2.16%), $M^+ - 15 = 255$ (51.12%) ($C_{15}H_{26}O_4$ MW 270); ν_{max}($CHCl_3$) 1725, 1230 cm^{-1}; δ ($CDCl_3$): 5.24 ppm (1H, m), 3.12 (1H, d, $J_{2,3}$ = 9.0 Hz), 2.05 (3H, s), 1.42 (3H, s), 1.36 (3H, s), 1.29 (3H, s), 0.99 and 0.86 (3H each, both d, J = 6.9 Hz).

trans-Hydroxylation

(a) A soln of 3 (200 mg) and *m*-chloroperbenzoic acid (270 mg) in dry methylene chloride (5 ml) was stirred in anhydrous conditions for 1½ hr at 0°. The precipitated *m*-chlorobenzoic acid was filtered off and the mixture was washed with sat $NaHCO_3$aq and extracted several times with methylene chloride (4 × 15 ml). The combined dried extracts after evaporation of the solvent left an oily yellow residue (210 mg) mainly constituted by the *cis* and *trans* epoxides. The epoxide mixture dissolved in MeOH (2 ml) was suspended in small portions into a soln of 1% H_2SO_4 (45 ml) and stirred for 3 hr at r.t. to obtain a clear soln which was in turn treated with a sat $NaHCO_3$aq (up to pH 7) and continuously

extracted with ether. The yellow oily residue obtained from evaporation of the ether, dissolved in chloroform, was chromatographed on Silica gel (15 g): elution with $CHCl_3$–MeOH (99:1) gave mainly two fractions: A (128 mg) and B (30 mg) which after several crystallizations from benzene afforded **7** and **8** respectively.

Compounds **7** and **8** were also obtained *via* reduction of **13** and **14** with $NaBH_4$ as described above.

Compound (±) **7**

White needles, m.p. 129–131°; $R_f = 0.58$ (solvent B); M^+-18 = 170 ($C_{10}H_{20}O_3$ MW 188); ν_{max}($CHCl_3$) 3700, 3600 and 3475 cm^{-1}; δ: 3.97 ppm (1H, t, $J_{2,3} = 3.4$ Hz and $J_{3,4} = 2.5$ Hz), 3.29 (1H, d, $J_{2,3} = 3.4$ Hz), 1.75 (1H, m), 1.23 (3H, s), 0.94 and 0.91 (3H each, both d, J = 6.7 Hz). (Found: C, 63.48; H, 10.82; $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71%).

Compound (±) **8**

White crystals, m.p. 144–145°; $R_f = 0.62$ (solvent B); M^+-18 = 170 ($C_{10}H_{20}O_3$ MW 188); ν_{max}($CHCl_3$) 3700, 3500 and 3400 cm^{-1}; δ: 3.90 ppm (1H, t, $J_{2,3} = 3.5$ Hz and $J_{3,4} = 2.1$ Hz), 3.48 (1H, dd, $J_{2,3} = 3.5$ Hz and $J_{2,4} = 1.2$ Hz), 1.16 (3H, s), 0.93 (6H, d, J = 6.5 Hz). (Found: C, 63.48; H, 10.78; $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71%).

(b) Compound **4** (1 g) dissolved in dry methylene chloride (20 ml) was converted into the *cis* and *trans* epoxide mixture as described above. An oily yellow residue (1.2 g) was thus obtained which after treatment with a soln of 1% H_2SO_4 (250 ml) (see above) gave a yellow semi-solid mass; several crystallizations from *n*-hexane–ethyl acetate (90:10) afforded **9** (500 mg) in a pure state. The residue (540 mg) left from the evaporation of the mother liquor of crystallization of **9** dissolved in chloroform was chromatographed on Silica gel (30 g); elution with chloroform and chloroform containing increasing amount of methanol (up to 4%) gave besides **9** (130 mg) a fraction which after several crystallizations from *n*-hexene–ethyl acetate (3:1) afforded **10** (260 mg).

Compound (±) **9**

Long white crystals, m.p. 137–138°; $R_f = 0.53$ (solvent B); M^+-18 = 170 ($C_{10}H_{20}O_3$ MW 188); ν_{max}($CHCl_3$) 3700, 3600 and 3450 cm^{-1}; δ: 3.70 ppm (1H, dd, $J_{2,3} = 3.2$ Hz and $J_{3,4} = 9.2$ Hz), 3.42 (1H, dd, $J_{2,3} = 3.2$ Hz and $J_{2,4} = 0.9$ Hz), 2.11 (1H, m), 1.18 (3H, s), 0.90 and 0.79 (3H each, both d, J = 7.0 Hz). (Found: C, 64.09; H, 10.83; $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71%).

Compound (±) **10**

White crystals, m.p. 150–152°; $R_f = 0.49$ (solvent B); M^+-18 = 170 ($C_{10}H_{20}O_3$ MW 188); ν_{max}($CHCl_3$) 3670, 3480 and 3430 cm^{-1}; δ: 3.13 ppm (1H, d, $J_{2,3} = 9.2$ Hz), 3.01 (1H, t, $J_{2,3} = 9.2$ Hz and $J_{3,4} = 8.2$ Hz), 2.14 (1H, m), 1.10 (3H, s), 0.88 and 0.75 (3H each, both d, J = 7.0 Hz). (Found: C, 63.48; H, 10.63; $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71%).

(c) Compound **2** (5 g) was dissolved in MeOH (35 ml) and treated at 0° with 30% H_2O_2 (15 ml) as described in the literature.[11] A mixture of *cis* and *trans* epoxides (4.7 g) was thus obtained as a dark yellow oil, with strong mint flavour, which was treated with a 1% H_2SO_4 soln (200 ml) as described above. The yellow oily mixture became solid after cooling; crystallization from *n*-hexane afforded **13** (2.04 g) as white needles, m.p. 112–113°; $R_f = 0.49$ (solvent A); ν_{max}($CHCl_3$) 3570 – 3460, 1720 cm^{-1}; δ ($CDCl_3$): 4.08 (1H, s), 0.99 (3H, s), 0.96 and 0.90 (3H each, both d, J = 6.0 Hz). (Found: C, 64.42; H, 9.71; $C_{10}H_{18}O_3$ requires: C, 64.49; H, 9.73%).

The residue (2.35 g) obtained from evaporation of the mother liquor of crystallization of **13**, dissolved in chloroform, was further purified by column chromatography on Silica gel (50 g). Elution with chloroform gave **14** (1.34 g) which crystallised in white needles from *n*-hexane, m.p. 85–87°; $R_f = 0.51$ (solvent A); ν_{max}($CHCl_3$) 3550–3450, and 1715 cm^{-1}; δ ($CDCl_3$): 4.13 ppm (1H, s), 1.02 and 0.89 (3H each, both d, J = 6.0 Hz), 0.99 (3H, s). (Found: C, 64.38; H, 9.63; $C_{10}H_{18}O_3$ requires: C, 64.49; H, 9.73%).

Compounds (±) **7b** *and* (±) **7c**

Compound **7** (287 mg) was converted into the acetonide derivative in the usual way. The oily yellow residue (310 mg) dissolved in chloroform was filtered through Silica gel (7 g); elution with chloroform gave besides **7** (43 mg) compound **7b** (240 mg) in a satisfactory pure state as a pale yellow oil; R_f = 0.57 (solvent C); M^+ = 228 (1.50%), M^+-15 = 213 (32.89%) ($C_{13}H_{24}O_3$ MW 228); δ ($CDCl_3$): 4.49 ppm (1H, dd, $J_{2,3} = 7.0$ Hz and $J_{3,4} = 2.0$ Hz), 3.75 (1H, dd, $J_{2,3} = 7.0$ Hz and $J_{2,4} = 1.3$ Hz), 1.43 (3H, s), 1.32 (3H, s), 1.23 (3H, s), 0.99 and 0.93 (3H each, both d, J = 6.0 Hz).

Compound **7b** (210 mg) was acetylated in the usual way for five days and the oily yellow residue thus obtained, dissolved in benzene, was chromatographed on Silica gel (4 g). Elution with benzene and benzene–acetone (99:1) afforded besides **7b** (96 mg) compound **7c** (122 mg) in a satisfactory pure state as a pale yellow oil; $R_f = 0.65$ (solvent C); M^+ = 270 (2.06%), M^+-15 = 225 (51.02%) ($C_{15}H_{26}O_4$ MW 270); ν_{max}($CHCl_3$) 1725, and 1230 cm^{-1}; δ ($CDCl_3$): 4.48 ppm (1H, dd, $J_{2,3} = 7.0$ Hz and $J_{3,4} = 2.0$ Hz), 4.10 (1H, dd, $J_{2,3} = 7.0$ Hz and $J_{2,4} = 1.5$ Hz), 1.94 (3H, s), 1.48 (3H, s), 1.43 (3H, s), 1.32 (3H, s), 0.98 (6H, d, J = 6.0 Hz).

Compounds (±) **9b** *and* (±) **9c**

Compound **9** (300 mg) was converted into the acetonide derivative as described above to give a dark-yellow oily residue (407 mg) which was dissolved in chloroform and chromatographed on Silica gel (10 g). Elution with chloroform and chloroform–ethyl acetate (90:10) afforded besides **9** (38 mg) compound **9b** (219 mg) in a pure state as a pale yellow oil; $R_f = 0.57$ (solvent C); M^+ = 228 (0.14%), M^+-15 = 213 (70.48%) ($C_{13}H_{24}O_3$ MW 228); δ ($CDCl_3$): 3.97 ppm (1H, dd, $J_{2,3} = 4.9$ Hz and $J_{3,4} = 9.0$ Hz), 3.78 (1H, dd, $J_{2,3} = 4.9$ Hz and $J_{2,4} = 0.9$ Hz), 1.45 (3H, s), 1.33 (3H, s), 1.32 (3H, s), 0.96 and 0.86 (3H each, both d, J = 7.0 Hz).

Compound **9b** (274 mg) was acetylated for 10 days in the usual way. The dark-yellow oil thus obtained (281 mg) was dissolved in benzene and chromatographed on Silica gel (4 g). Elution with benzene gave besides **9b** (156 mg) compound **9c** (90 mg) as a pale yellow oil; $R_f = 0.65$ (solvent C); M^+ = 270 (0.42%), M^+-15 = 255 (61.85%) ($C_{15}H_{26}O_4$ MW 270); ν_{max}($CHCl_3$) 1730, 1230 cm^{-1}; δ ($CDCl_3$): 4.05 ppm (1H, dd, $J_{2,3} = 5.0$ Hz and $J_{2,4} = 1.4$ Hz), 3.97 (1H, dd, $J_{2,3} = 5.0$ Hz and $J_{3,4} = 8.6$ Hz), 1.97 (3H, s), 1.62 (3H, s), 1.46 (3H, s), 1.35 (3H, s), 0.95 and 0.84 (3H each, both d, J = 7.0 Hz).

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REFERENCES

[1]C. G. Casinovi, G. Grandolini, L. Radics and C. Rossi, *Experientia* **34**, 298 (1978).
[2]A. Evidente, R. Capasso and G. Randazzo, private communication.
[3]A. Killen Macbeth, B. Milligan and J. S. Shannon, *J. Chem. Soc.* 901 (1953).
[4]G. Magnusson and S. Thorèn, *J. Org. Chem.* **18**, 1380 (1973).
[5]J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2nd Edn) p. 340. McGraw-Hill, New York (1977).
[6]R. J. Ferrier, *Progress in Stereochemistry* **4**, 88 (1969).
[7]*Inter alia*: R. E. Parker and N. S. Isaacs, *Chem. Rev.* **59**, 791 (1959); H. B. Henbest, M. Smith and A. Thomas, *J. Chem. Soc.* 3293 (1958); P. L. Barili, G. Bellucci, B. Macchia, F. Macchia and G. Parmigiani, *Gazz. Chim. Ital.* **101**, 300 (1971); A. Balsamo, P. Crotti, B. Macchia and F. Macchia, *Tetrahedron* **29**, 199 (1973).
[8]A. Baragliu, E. Gàcs-Baitz, C. G. Casinovi, L. Radics and C. Rossi, to be communicated.
[9]D. H. R. Barton and Dov Elad, *J. Chem. Soc.* 2085 (1956).
[10]J. Rocek and F. H. Westheimer, *J. Am. Chem. Soc.* **84**, 2241 (1962).
[11]E. Klein and G. Ohloff, *Tetrahedron* **19**, 1091 (1963).