The hydrolysis of 3,10-epoxypatchenol under mild aqueous conditions

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The mild aqueous hydrolysis of 3,10-epoxypatchenol [2β,3'-epoxy-2(2'2'-dimethylbicyclo[2.2.1]hept-3'-ylidene)ethanol] gave products derived from hydration of the isobornyl-camphenilylhydro cation.

Keywords: monoterpenoid, epoxide, hydrolysis, rearrangement

We have examined[1] the biotransformation of some bridged polycyclic terpenoids in order to define the three-dimensional topology of microbial hydroxylases. As part of this study we attempted the biotransformation of the epoxide of the commercially available DL-patchenol, 2-(2'2'-dimethylbicyclo [2.2.1]hept-3'-ylidene)ethanol **1**.[2,3] Although this biotransformation was unsuccessful, the instability of the epoxide in the mildly acidic fermentation medium (pH 4–5) is reported here. The role of the 'isobornyl-camphenilylhydro' cation **2** in the rearrangements of the bicyclic monoterpenoids has been thoroughly investigated.[4,5] The products that were obtained in the present work represent various modes of trapping this ion.

Epoxidation of DL-patchenol **1** gave a mixture of three compounds. The first two compounds to be isolated formed a mixture of epoxides (75% yield) which was very difficult to separate chromatographically and only the major component was eventually obtained (23% yield) in reasonable purity. This epoxide **3** was assigned the exo (β) configuration on the basis of the observation that in the absence of a bulky substituent at the *syn* C-7 position reactions of norbornyl derivatives occur preferentially from the exo-face.[4,6] This is in accord with the stereochemistry at C-10 of the products described below. The third minor product (4%) was a crystalline diol. Its tricyclane structure **4** was established by X-ray crystallography (see Fig. 1).

Incubation of the epoxide **3** with two micro-organisms, *Cephalosporium aphidicola* and *Mucor plumbeus* gave a series of products whose structures suggested that they were artefacts rather than genuine biotransformation products. The epoxide was then stirred with a simplified aqueous medium comprising potassium dihydrogenphosphate, magnesium sulfate and glycine (pH *ca* 4–5) for 5 days and the same products were obtained. The products were separated by chromatography. The IR spectrum of the first product (10% yield), $C_{11}H_{18}O_2$, contained carbonyl (1702 cm^{-1}) and hydroxyl (3583 cm^{-1}) absorptions. In the ^1H and ^{13}C NMR spectra the resonances assigned to the primary alcohol had moved downfield (δ_H 4.04 and 4.09; δ_C 69.3) compared to the starting material. The ^{13}C NMR spectrum (Table 1) which contained a carbonyl resonance (δ_C 210.9), also showed that a quaternary carbon bearing an oxygen atom had been replaced by a methine, δ_C 58.5. This led to the structure **5** for the product which was tentatively assigned the exo-3-H stereochemistry because the multiplicity of the relevant ^1H NMR signal (δ_H 2.31, double-doublet, *J*=3,5 and 1.6 Hz) included a 'W' long-range coupling.

The ^1H NMR spectrum of the second product (8.4% yield), $C_{11}H_{18}O_2$, contained four downfield double-doublets, δ_H 3.82 (*J*=9.2 and 6.1 Hz), 3.85 (*J*=7.7 and 3.3 Hz), 4.17 (*J*=9.2 and 8.5 Hz) and 4.53 (*J*=8.5 and 6.1 Hz). This led to the assignment of the signals at δ_H 3.82, 4.17 and 4.53 to the system O.CH_2.CH(OH).C–. This relationship was supported by a ^1H:^{13}C COSY experiment. Irradiation of the remaining signal at δ_H 3.85 showed that it was coupled to a pair of methylene protons, δ_H 1.53 and 2.07, which were geminally coupled (*J*=13.2 Hz). These were in turn coupled to a methine resonance, δ_H 1.67. Nuclear Overhauser effect (nOe) enhancements based on irradiating the methyl group (δ_H 1.37) gave enhancements to the signals at δ_H 1.67 (1.7%) and 2.07 (3.5%) and to one of the primary alcohol resonances (δ_H 3.82, 3.5%). However there were no enhancements to the signals at δ_H 3.85, 4.17 or 4.53. Hence the compound was assigned the structure **6** in which the oxygen functions at C-5 and C-10 are on the same face of the molecule as the methyl group at C-7.

The third product (2.8% yield), $C_{11}H_{20}O_3$, had ^{13}C NMR signals assigned to a primary (δ_C 64.7), secondary (δ_C 71.0) and a tertiary alcohol (δ_C 82.6). The ^1H NMR spectrum had signals assigned to the secondary alcohol (δ_H 3.86, dd, *J*=8.5 and 2.5 Hz) and a two-proton multiplet (δ_H 3.60) attributed to a primary alcohol. The structure and stereochemistry **7** of this product were established by X-ray crystallography (see Fig. 2). The fourth polar product (6.9% yield), $C_{11}H_{20}O_3$, contained two secondary alcohols (δ_H 3.86, dd, *J*=9.1 and 2.1 Hz; δ_H 4.10, dd, *J*=8.0 and 3.4 Hz) and a primary alcohol (δ_H 3.71, 2H, multiplet) (δ_C 74.5, 78.7, and 64.7 respectively). There was a new quaternary carbon signal at δ_C 29.9. Irradiation of

Table 1 ^{13}C NMR data

	Compound							
Carbon atom	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	47.5	47.5	42.3	49.2	48.5	49.5	45.7	47.1
2	41.7	39.2	43.7	39.2	21.5	44.8	26.7	40.8
3	159.6	75.7	33.8	58.5	27.6	82.6	29.9	155.5
4	41.1	41.5	16.3	42.0	58.2	47.4	52.6	50.2
5	28.2	23.9	17.5	24.1	90.2	24.1	78.7	72.7
6	23.6	23.3	31.2	21.5	37.2	21.6	41.0	35.9
7	37.1	35.2	31.2	37.9	46.7	35.2	47.8	33.1
8[a]	25.7	23.5	22.7	22.6	21.6	25.6	22.3	28.9
9[a]	29.0	22.9	21.7	32.4	21.3	23.1	20.5	25.3
10	114.2	59.3	69.9	210.9	73.8	71.0	74.5	117.1
11	60.1	61.3	65.8	69.3	76.7	64.7	64.7	59.7

[a]These assignments may be interchanged.

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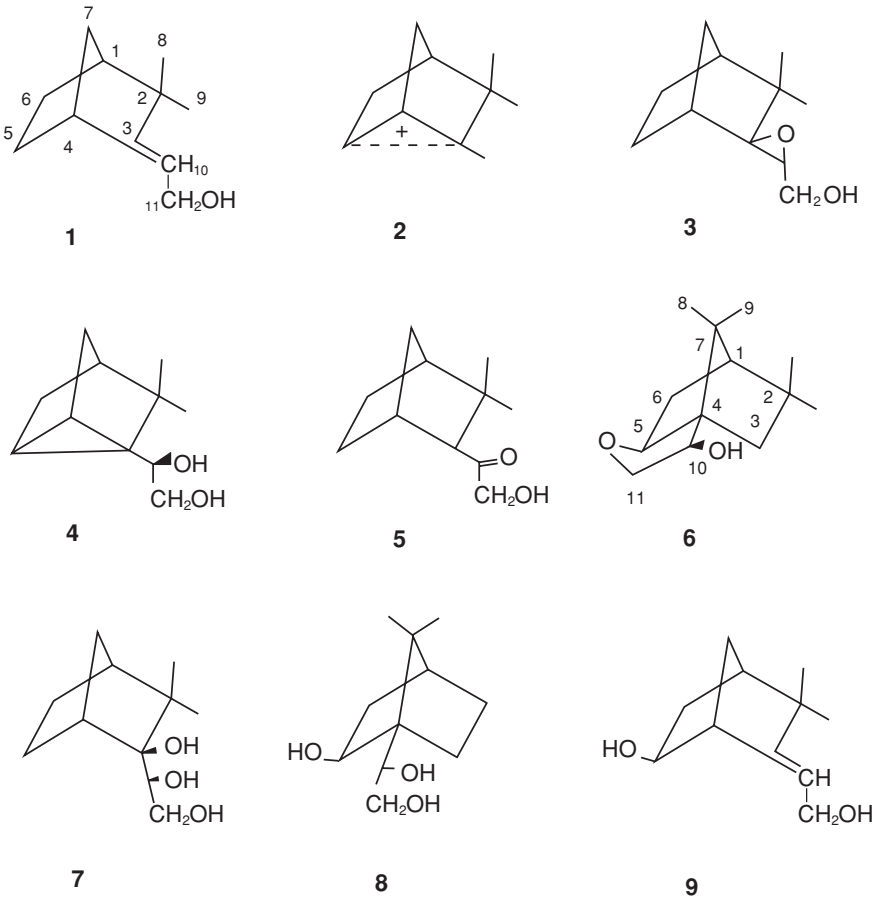

the signal at δ_H 4.10 showed that it was coupled to methylene signals at δ_H 1.70 (dd, *J*= 13.2 and 8.0 Hz) and 1.90 (ddd, *J*=13.2, 7.5 and 3.4 Hz). A ^{1}H: ^{13}C COSY experiment showed that these signals were related to a ^{13}C NMR signal at δ_C 41.0. Irradiation of the methyl group signal (δ_H 1.03) gave an nOe enhancement (5%) to the signal at δ_H 1.90 but not to the signal at δ_H 4.10. This and the ^{13}C NMR data, led to the structure **8** for the triol.

When the tricyclane derivative **4** was exposed to the same conditions, an unsaturated alcohol (26% yield), $C_{11}H_{18}O_2$, was obtained. The ^{1}H NMR spectrum possessed an alkene resonance, δ_H 5.25 (t, *J*=7.2 Hz) which was coupled to the two primary alcohol resonances, δ_H 3.67 and 4.07. This compound also possessed a secondary alcohol (δ_H 3.67, dd, *J*=7.1 and 3.0 Hz). Irradiation of this signal showed that it was coupled to two methylene proton resonances (δ_H 1.16 and 2.08). In the light of this and the ^{13}C NMR data, the product was formulated as **9**.

The formation of these compounds can be accommodated by the intervention of the isobornyl-camphenilylhydro carbocation both during the epoxidation and in the hydrolysis of the epoxide. The stereochemistry of the oxygen atoms at C-3 and C-5 is in accord with the intervention of this cation. The formation of products derived from this cation under such mild conditions is a warning of the potential formation of artefacts under 'biotransformation' conditions.

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. ^{1}H and ^{13}C NMR spectra were determined at 300 and 75 MHz respectively for solutions in deuteriochloroform. IR spectra were determined as nujol mulls. Mass spectra were determined on a Fisons Autospec mass spectrometer. Extracts were dried over sodium sulfate.

DL-Patchenol (sometimes known as homocamphenilol[7]) was obtained from Aldrich, cat.no.18,839-5.

Epoxidation of DL-patchenol **1** DL-Patchenol (2 g) in dichloromethane (60 cm^3) was treated with *m*-chloroperbenzoic acid (2 g) at 0 °C. The mixture was allowed to attain room temperature over 3 h. It was then washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate and water and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 20% ethyl acetate: light petroleum gave the crude epoxides (1.65 g, 75%). The mixture was chromatographed again in the same solvent system to give 3-exo(β),10-epoxypatchenol [2β, 3'-epoxy-2(2',2'-dimethylbicyclo[2.2.1]hept-3'-ylidene)ethanol] **3** (500 mg, 23%) as an oil, ν_{max}/cm^{-1} 3580; δ_H 0.58 (3H,s,), 0.69 (3H,s) (H-8 and H-9) 1.0–2.1 (8H, multiplets), 2.35 (1H, br. OH), 2.85 (1H, dd, *J*=8.0, 2.7 Hz, H-10), 3.29 (1H,dd, *J*=11.0, 8.0 Hz), 3.55 (1H, dd, *J*=11.0, 2.7 Hz, each H-11); Found, M$^+$ 182.131 $C_{11}H_{18}O_2$ requires M$^+$ 182.131. Elution with 40% ethyl acetate:light petroleum gave 2-[2',2'-dimethyltricyclo(2.2.1.0^{3,5})hept-3'-yl]-2-hydroxyethanol **4** (80 mg, 4%) which crystallised as cubes, m.p. 66–67 °C, ν_{max}/cm^{-1} 3583, 3284; δ_H (500 MHz) 0.93 (3H,s,), 0.98 (3H,s)(H-8 and H-9), 1.09 and 1.11 (each 1H, d, *J*=9.2 Hz, H-7), 1.17 (1H, dd, *J*=5.7, 1.0 Hz, H-5), 1.23 (1H, dd, *J*=5.7, 1.2 Hz, H-4), 1.41(1H, br.s, H-1), 1.68 (1H, ddd, *J*=10.7, 2.9, 1.5 Hz, H-6), 1.72 (1H, dd, *J*=10.7, 2.9 Hz, H-6), 2.1 and 2.6 (each 1H, br. OH), 3.34 (1H, dd, *J*=11.0,9.1 Hz, H-11), 3.54 (1H, dd, *J*=11.0,3.2 Hz H-11), 4.05 (1H, dd, *J*=9.1,3.2 Hz, H-10); (Found: C, 72.2; H, 10.1. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%).

Hydrolysis of the epoxide **3**: The epoxide (1.0 g) in ethanol (10 cm^3) was suspended in water (1 l) containing potassium dihydrogenphosphate (5 g), magnesium sulfate (2 g) and glycine (2 g) which had been adjusted to pH 4–5 with dil. hydrochloric acid. The mixture was stirred for 5 days. The products were extracted with ethyl acetate and chromatographed on silica. Elution with 5% ethyl acetate: light petroleum gave 2-(2',2'-dimethylbicyclo[2.2.1]hept-3'-yl)-2-oxoethanol **5** as an oil (105 mg, 10%), ν_{max}/cm^{-1} 3583; 1702; δ_H 0.91 (3H, s,), 1.06 (3H, s)(H-8 and H-9), 1.2–2.0 (7H, multiplets), 2.31 (1H, dd, *J*=3.5, 1.6 Hz, H-3), 2.38 (1H, m, H-4), 4.04 (1H, d, *J*=11.7 Hz), 4.09 (1H, d, *J*=11.7 Hz, each H-11); Found, M$^+$ 182.131 $C_{11}H_{18}O_2$ requires M$^+$ 182.131. Elution with 15% ethyl acetate:light petroleum gave 2,5'-dihydroxy-2-(7',7'-dimethylbicyclo[2.2.1]hept-4'-yl)ethanol 1-5'-ether **6** (184 mg, 8.4%) as an oil, ν_{max}/cm^{-1} 3421, 1171,1040; d_H 1.09 (3H, s, H-9), 1.37 (3H, s, H-8), 1.67 (1H, m, H-1), 3.82 (1H, dd, *J*=9.2, 6.1 Hz, H-11), 3.85 (1H, dd, *J*=7.7, 3.3 Hz, H-5), 4.17 (1H, dd, *J*=9.2, 8.5 Hz,H-11), 4.53 (1H, dd, *J*=8.5, 6.1 Hz,

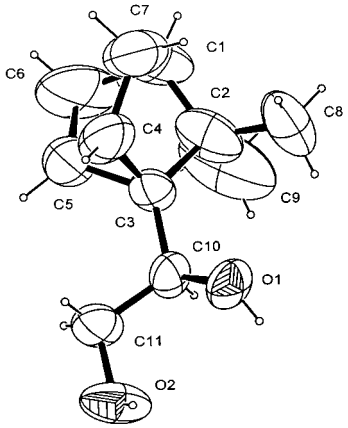

Fig. 1 X-Ray crystal structure of compound **4**

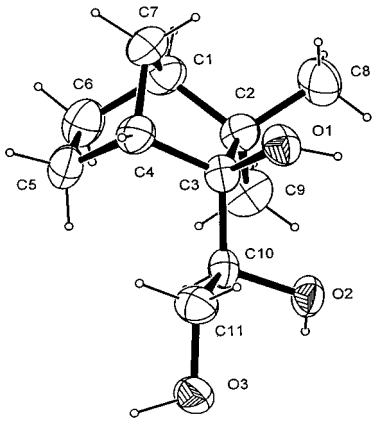

Fig. 2 X-Ray crystal structure of compound **7**

H-10), Found: M^+ 182.131 $C_{11}H_{18}O_2$ requires M^+ 182.131. Elution with 30% ethyl acetate: light petroleum gave 2,3'-dihydroxy-2-(2', 2'-dimethyl-bicyclo[2.2.1]hept-3'-yl)ethanol **7** (29 mg, 2.8%) which crystallised from ethyl acetate: light petroleum as cubes, m.p. 103–105 °C, ν_{max}/cm^{-1} 3428, 3391, 3313; d_H 0.93 (3H,s,H-9), 1.03 (3H,s, H-8), 1.62 (1H, dd, *J*=3.3, 1.6 Hz, H-1), 1.95 (1H, ddd, *J*=5.5,3.3, 1.7 Hz, H-4), 3.60 (2H,m, H-11), 3.86 (1H, dd, *J*=8.9, 2.5 Hz, H-10); Found: M^+ 200.143, $C_{11}H_{20}O_3$ requires M^+ 200.141. Further elution with 40% ethyl acetate: light petroleum gave 2,5'-dihydroxy-2-(7', 7'-dimethylbicyclo[2.2.1]hept-4'-yl)ethanol **8** (76 mg, 6.9%) which crystallised from ethyl acetate: light petroleum as fine needles, m.p. 96–98 °C, ν_{max}/cm^{-1} 3343 (br); d_H 0.96 (3H,s,H-9), 1.34 (3H,s, H-8), 1.70 (1H,dd, *J*=13.2, 8.7 Hz, H-7), 1.90 (1H, ddd, *J*=13.2, 7.5 and 3.4 Hz, H-7), 3.71 (2H, m, H-11), 3.86 (1H, dd, *J*=9.1, 2.1 Hz, H-10), 4.10 (1H, dd, *J*=8.0, 3.4 Hz, H-5); Found: M^+ 200. 143, $C_{11}H_{20}O_3$ requires M^+ 200.141.

Under similar conditions, 2-[2',2'-dimethyltricyclo-(2.2.1.0^{3,5})hept-3'-yl]-2-hydroxyethanol **4** (0.5 g) gave, after chromatography on silica, the starting material (200 mg) and 6'-hydroxy-2(2',2'-dimeth ylbicyclo[2.2.1]hept-3'-ylidene)ethanol **9** (130 mg, 26%) as cubes, m.p. 68–70 °C, ν_{max}/cm^{-1} 3300 (br), 1675; δ_H 0.91 (3H,s,H-9), 0.97 (3H,s, H-8), 1.16 (1H, ddd, *J*=13.5, 4.0, 3.0 Hz, H-6), 1.86 (1H, dd, *J*=4.0, 1.4 Hz, H-4), 2.08 (1H, dd, *J*=13.5, 7.1 Hz, H-6), 3.67 (1H, dd, *J*=7.1, 3.0 Hz, H-5), 4.07 (2H, br.d, *J*=7.2 Hz, H-11), 5.25 (1H, br.t, *J*=7.2 Hz, H-10); Found: C, 72.3; H, 9.8. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.9%.

X-Ray crystal data and structure determinations: Compound **4**, $C_{11}H_{18}O_2$, M_r 182.25, triclinic, space group P$\bar{1}$ (No.2), a = 6.321(3), b = 12.178(3), c = 14.160(5)Å, α = 102.62(2)°, β = 101.08(3)°, γ = 96.12(2)°, V = 1031.2(7)Å^3, Z = 4, D_{calc} = 1.17 g cm^{-3}, μ = 0.08 mm^{-1}, F(000) = 400, crystal size 0.30 × 0.30 × 0.30 mm^3. Data were collected on an Enraf-Nonius CAD 4 diffractometer for 2.00 < θ < 24.97° and 0 ≤ h ≤ 7, –14 ≤ k ≤ 14, –16 ≤ l ≤ 16. 3629 Reflections were collected. There were 3629 independent reflections and 2121 had $I > 2\sigma(I)$ which were used in the refinement. The structure was solved by direct methods and refined using SHELXL-97. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.093 wR_2 = 0.255 and (all data) R_1 = 0.141, wR_2 = 0.299. The largest difference peak and hole was 0.34 and –0.30 e. Å^{-3}.

There were two independent molecules in the unit cell. The second molecule has C(10B) and O(2B) disordered and lower occupancy sites were left isotropic.

Compound **7**, $C_{11}H_{20}O_3$, M_r 200.27, monoclinic, space group P2/n (No.13), a = 9.731(2), b = 11.611(1), c = 19.409(4)Å, α = γ = 90°, β = 90.16(2)°, V = 2192.9(7)Å^3, Z = 8, D_{calc} = 1.21 g cm^{-3}, μ = 0.09 mm^{-1}, F(000) = 880, crystal size 0.30 × 0.30 × 0.20 mm^3. Data were collected on an Enraf-Nonius CAD 4 diffractometer for 2.04 < θ < 24.97° and 0 ≤ h ≤ 11, 0 ≤ k ≤ 13, –22 ≤ l ≤ 23. 4076 Reflections were collected. There were 3847 independent reflections. 2637 Reflections had $I > 2\sigma(I)$ which were used in the refinement. The structure was solved by direct methods and refined using SHELXL-97. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.070 wR_2 = 0.176 and (all data) R_1 = 0.101, wR_2 = 0.202. The largest difference peak and hole was 0.33 and –0.30 e Å^{-3}.

There were two independent molecules in the unit cell.

CCDC 258087 (compound 7) and CCDC 258088 (compound 4) contain the supplementary crystallographic data for this paper. They can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif

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