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Tetrahedron 61 (2005) 4323–4327

Steric effects in the tetracyanoethylene catalysed methanolysis of some cyclohexane epoxides

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Received 16 August 2004; revised 7 December 2004; accepted 7 January 2005

Available online 18 March 2005

Abstract—The presence of a hydroxyl group has been shown to direct the regiochemistry and stereochemistry of the TCNE methanolysis of cyclohexane hydroxy-epoxides. α-Pinene epoxide underwent cleavage to form the 8-methyl ether of *trans*-sobrerol.

1. Introduction

Tetracyanoethylene (TCNE) is a mild π-acid catalyst which has proved to be of value in the ring opening of epoxides.[1,2] The stereochemistry of the reaction has been examined in the steroid series where neighbouring group participation by an adjacent *cis* hydroxyl group has been observed.[3] Thus, a 5β-hydroxyl group has been shown to affect both the regiochemistry and stereochemistry of the cleavage of an adjacent 3β,4β-epoxide. Whereas the TCNE catalysed methanolysis of 17β-acetoxy-3β,4β-epoxy-5β-androstane gave the diaxial 3β-hydroxy-4α-methyl ether, methanolysis of 5β-17β-dihydroxy-3β,4β-epoxy-5β-androstane gave the diequatorial 3α-methoxy-4β,5β,17β-trihydroxy-5β-androstane. In this paper, we describe the results of the TCNE catalysed methanolysis of some cyclohexane and monoterpenoid epoxides.

The first compounds to be examined were the isomeric *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3**[4] and *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5** in which the methyl groups provide a conformational 'lock'.

2. Results and discussion

The epoxides **3** and **5** were prepared from the readily available isophorone **1**. Treatment of isophorone epoxide with hydrazine hydrate gave 1,5,5-trimethylcyclohex-2-en-1-ol **2**.[5] This was epoxidized with *m*-chloroperbenzoic acid to afford *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3**. Reduction of **1** with sodium borohydride in methanol followed by epoxidation of the alcohol **4** with *m*-chloroperbenzoic acid, gave *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5**. The *cis* relationship of the epoxide and hydroxyl groups followed from the known[6] directing effect of an allylic hydroxyl group on the epoxidation of an adjacent alkene.

Methanolysis of *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5**, catalysed by TCNE gave a single product, *cis*-2,3-dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane **6**. The stereochemistry of the product was unambiguously established by X-ray crystallography as shown in Figure 1.

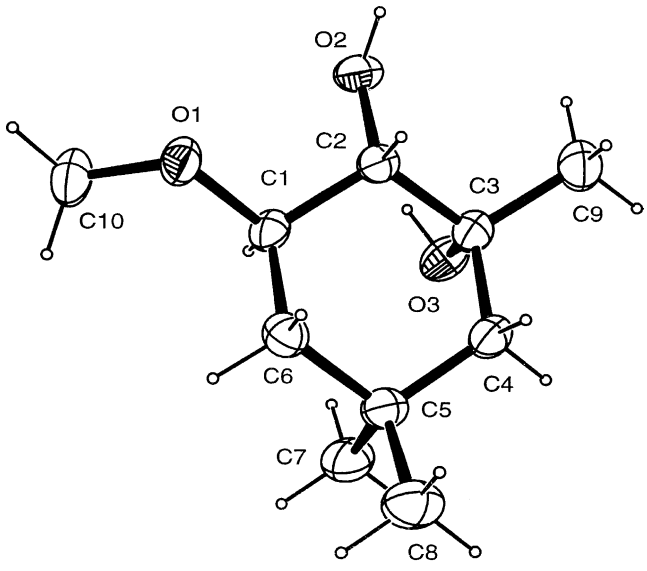

Figure 1. X-ray structure of **6**.

Keywords: Cyclohexane; TCNE; Methanoloysis; Epoxide; Stereochemistry.
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doi:10.1016/j.tet.2005.01.030

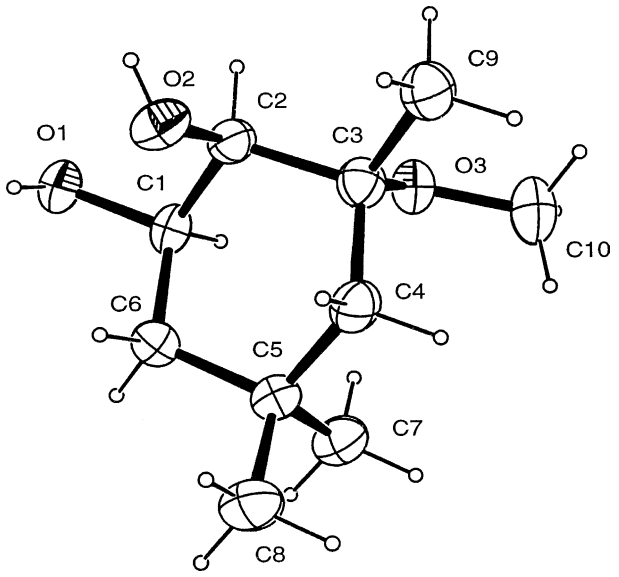


Figure 2. X-ray structure of **7**.

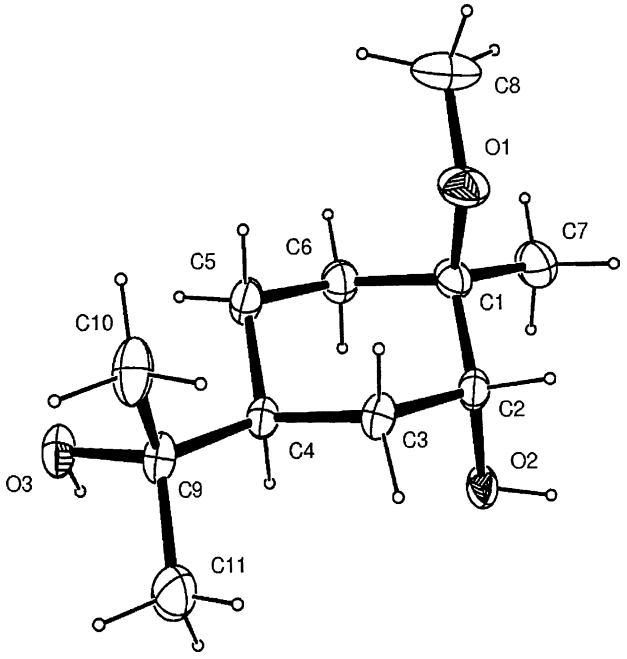
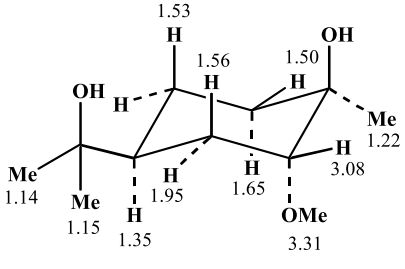


Figure 3. X-ray structure of **13**.

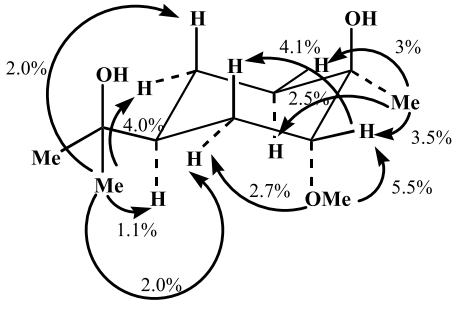
Methanolysis of the isomeric *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3**, catalysed by TCNE, gave *cis*-1,2-dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane **7**. In the ^{1}H NMR spectrum, the H-2 resonance (δ_H 3.19) was a doublet ($J=9.2$ Hz) whilst the H-3 resonance (δ_H 3.46) was a triplet ($J=9.2$ Hz) of doublets ($J=4.1$ Hz) consistent with a diaxial relationship between H-2 and H-3. The regiochemistry of the hydroxyl and methoxyl groups was established by X-ray crystallography as shown in Figure 2.

Whereas the methanolysis of the epoxide **5** proceeded in a diaxial sense to give **6**, that of epoxide **3** led to an eventual diequatorial relationship between the hydroxyl and methoxyl groups **7**. In both cases, the hydroxyl group arising from the epoxide is adjacent to the original hydroxyl group. The overall diequatorial opening of *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3** may arise via a diaxial opening and conformational inversion of the ring to maximize the number of equatorial substituents. This contrasts with the formation of the diaxial 1,2-diol **9** which is obtained[7] from 1,5,5-trimethylcyclohex-2-ene **8** on treatment with hydrogen peroxide and formic acid, a reaction which proceeds through the 1,2-epoxide. Hence the hydroxyl group of a hydroxy-epoxide has determined the regio- and stereochemistry of the methanolysis of the epoxide catalysed by TCNE.

The participation of the 8-hydroxyl group of 1,2-epoxy-8-hydroxy-*p*-menthane in the acid catalysed hydrolysis of the 1,2-epoxide leading to the formation of 2-hydroxy-1,8-cineole has been described previously.[8] We have examined the TCNE catalysed methanolysis of the mixed epoxides **10** of α -terpineol in the light of this transannular participation of a hydroxyl group. Three major products were separated by chromatography. The first was identified from its ^{1}H NMR spectrum as *trans*-2-hydroxy-1,8-cineole **11**.[8] The second product, **12**, contained a methoxyl group (δ_H 3.29) and a further ether CHOR signal (δ_H 3.05) together with three C-methyl group resonances (δ_H 1.14, 1.15 and 1.20). The CHOR resonance was a narrow signal (w/2 c.4 Hz). The stereochemistry of the compound was assigned on the basis of this signal[9] and from the nuclear Overhauser effect enhancements arising from irradiation of the methyl group signals at δ_H 1.14/1.15, 1.22 and 3.29. The assignments and NOE. enhancements are summarized in Figure 4. The structure of the third compound, **13**, which was crystalline,

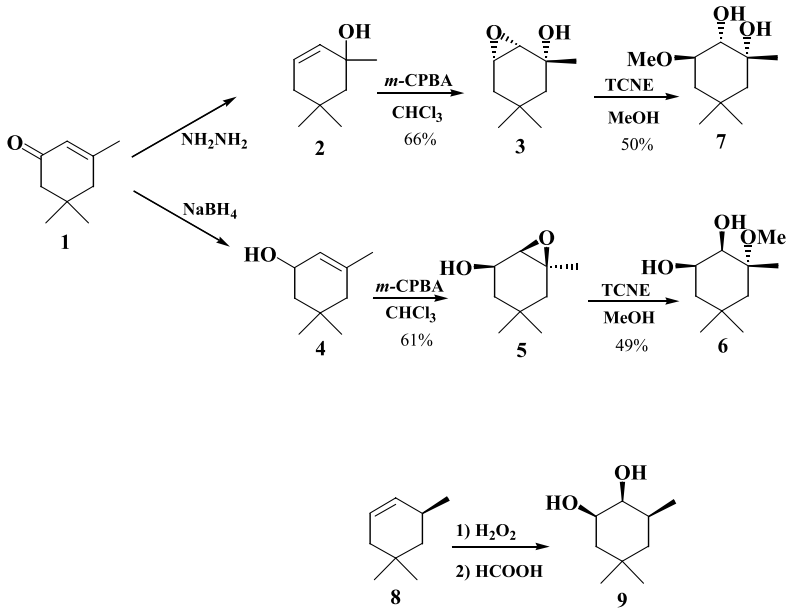


^{1}H NMR assigments for 12

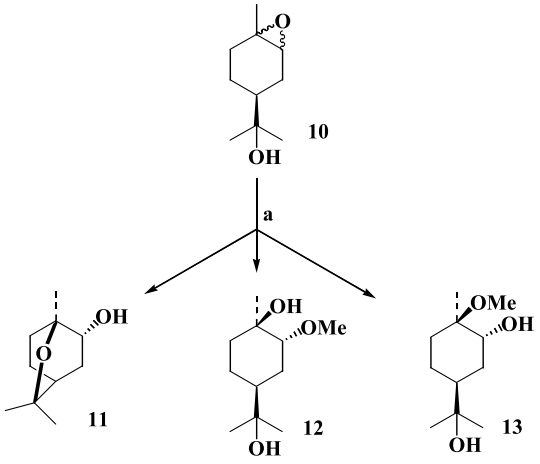


^{1}H NMR nOe enhancements for 12

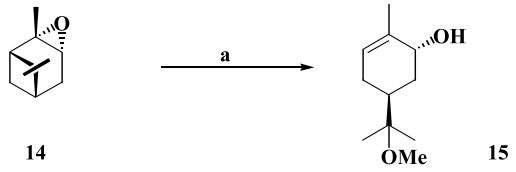
Figure 4.



Scheme 1.



Scheme 2. Reagents and conditions: (a) TCNE, MeOH, rt, 12 h.



Scheme 3. Reagents and conditions: (a) TCNE, MeOH, rt, 2 h.

was established by X-ray crystallography as shown in Figure 3. The isolation of these compounds can be rationalized in terms of the diaxial opening of the epimeric terpineol epoxides but with rather less participation of the 8-hydroxyl group in 1,8-cineole formation than is the case in simple acid-catalysed hydrolysis.[8]

Treatment of α-pinene oxide **14** with TCNE in methanol gave one major product. This compound, **15**, had the ^{1}H NMR characteristics of the 8-monomethyl ether of *trans*-sobrerol [δ_H 1.09 (6H, s, 2×Me), 1.76 (3H, br s, =C.Me), 3.17 (3H, s, OMe), 3.61(1H, br s, CHOH), 3.99 (1H, br s, =CH)] (Schemes 1–3).

3. Conclusion

We have shown that the regiochemistry and stereochemistry of the TCNE catalyzed methanolysis of some cyclohexane epoxides have been directed by the presence of a hydroxyl group. We have established the stereochemistry of the products by X-ray crystallography. The structures of these products indicate that when TCNE is used as a mild π-acid catalyst for the cleavage of hydroxy-epoxides, the hydroxyl group can participate in the reaction.

4. Experimental

4.1. General

Light petroleum refers to the fraction bp 60–80 °C. Silica for chromatography was Merck 9385. Extracts were dried over anhydrous sodium sulfate. IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined for solutions in deuteriochloroform at 300 MHz. High-resolution mass spectra were obtained on a Bruker Daltonics Apex III mass spectrometer operating in the electrospray mode.

4.1.1. *cis*-1,2-Epoxy-1,5,5-trimethycyclohexan-3-ol (5). A suspension of *m*-chloroperbenzoic acid (4 g, 23.2 mmol) in chloroform (20 cm^3) was added over 15 min to the alcohol **4** (1.5 g, 10.7 mmol) (prepared by the reduction of isophorone **1** with sodium borohydride in methanol) in chloroform (20 cm^3). The mixture was left at room temperature overnight and then diluted with chloroform (50 cm^3). The solution was stirred with aqueous acidic iron (II) sulfate (100 cm^3) twice and then the chloroform layer was washed thoroughly with aqueous sodium hydrogen carbonate, water

and dried. The solvent was evaporated to give a residue which was distilled at 70–80 °C (12 mm Hg) to give *cis*-1,2-epoxy-1,5,5-trimethycyclohexan-3-ol **5** (1.03 g, 61%) as a colourless oil; ν_{max} (Nujol) 3421 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.91 (1H, m, 3-H), 3.10 (1H, d, $J=3.5$ Hz, 2-H), 1.83–1.65 (4H, m, $2\times CH_2$), 1.30 (3H, s, 1-Me), 1.11 and 0.80 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 78.4, 61.7, 58.6, 46.8, 44.9, 29.9, 28.2, 27.5, 26.3; HRMS: M^+, found 156.1158. $C_9H_{16}O_2$ requires 156.1150.

4.1.2. *cis*-2,3-Epoxy-1,5,5-trimethylcyclohexan-1-ol (3). Under similar conditions 1,5,5-trimethylcyclohex-2-en-1-ol **2** (1.53 g, 10.9 mmol) (prepared by the reaction of isophorone epoxide with hydrazine hydrate), gave *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3** (1.13 g, 66%) as a colourless oil; ν_{max} (Nujol) 3443 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.33 (1H, q, $J=3.5$ Hz, 3-H), 2.98 (1H, d, $J=3.5$ Hz, 2-H), 1.75–1.60 (4H, m, $2\times CH_2$), 1.31 (3H, s, 1-Me), 1.14 and 0.83 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 72.7, 59.5, 57.6, 47.6, 41.4, 33.8, 30.6, 28.1, 27.4; HRMS: M^+, found 156.1158. $C_9H_{16}O_2$ requires 156.1150.

4.1.3. *cis*-1,2-Dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane (7). *cis*-2,3-Epoxy-1,5,5-trimethylcyclohexan-1-ol **3** (1.0 g, 6.4 mmol) in dry methanol (20 cm^3) was treated with tetracyanoethylene (200 mg, 1.5 mmol) at room temperature for 3 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 30% ethyl acetate: light petroleum gave *cis*-1,2-dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane **7** (600 mg, 50%) which was crystallized from ethyl acetate as needles; mp 78–79 °C; (Found: C, 63.8; H, 10.7. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7%); ν_{max} (Nujol) 3453, 3350 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.46 (1H, td, $J=9.2$, 4.1 Hz, 3-H), 3.40 (3H, s, 3-OMe), 3.19 (1H, d, $J=9.2$ Hz, 2-H), 1.85–1.64 (4H, m, $2\times CH_2$), 1.25 (3H, s, 1-Me), 1.15 and 0.94 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 78.9, 78.8, 72.7, 56.4, 48.3, 41.3, 33.9, 31.4, 28.8, 27.2.

4.1.4. *cis*-2,3-Dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane (6). Under similar conditions *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5** (900 mg, 5.7 mmol) gave, after chromatography on silica and elution with 30% ethyl acetate: light petroleum, *cis*-2,3-dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane **6** (540 mg, 49%) which was crystallized from ethyl acetate as needles, mp 65–68 °C, ν_{max} (Nujol) 3355 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.17 (1H, dt, $J=9.2$, 3.5 Hz, 3-H), 3.58 (1H, d, $J=3.5$ Hz, 2-H), 3.17 (3H, s, 1-OMe), 1.89–1.61 (4H, m, $2\times CH_2$), 1.22 (3H, s, 1-Me), 1.04 and 0.93 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 78.8, 78.6, 73.5, 51.4, 47.6, 44.2, 31.3, 30.9, 28.6, 27.2; HRMS: M^+, found 188.1410. $C_{10}H_{20}O_3$ requires 188.1412.

4.1.5. Reaction of menthanes. The mixed 1,2-epoxy-8-hydroxy-*p*-menthanes (50:50) (900 mg, 5.3 mmol) in methanol (50 cm^3) containing TCNE (100 mg, 0.78 mmol) was left at room temperature overnight. The solvent was evaporated in vacuo and the residue was chromatographed on silica. Elution with a gradient of increasing amounts of ethyl acetate in light petroleum gave *trans*-2-hydroxy-1,8-cineole **11** (105 mg, 12%) as a colourless oil; ν_{max}(Nujol) 3450 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.72 (1H, m), 3,63 (1H, br. s), 2.52–1.20 (7H, overlapping multiplets), 1.25 (3H, s, Me), 1.17 (3H, s, Me), 1.08 (3H, s, Me).[8]

Further elution gave 1β,8-dihydroxy-2α-methoxy-*p*-menthane **12** (228 mg, 21%) as a colourless oil; ν_{max} (Nujol) 3398 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.05 (1H, br. s, *w*/2 4 Hz), 3.29 (3H, s, OMe), 1.94–1.09 (8H, overlapping multiplets), 1.20 (3H, s, Me), 1.15 (3H, s, Me), 1.14 (3H, s, Me); HRMS: M^+, found 225.1461. $C_{11}H_{22}O_3Na$ requires 225.1457.

Further elution gave 2α,8-dihydroxy-1β-methoxy-*p*-menthane **13** (262 mg, 24%) as needles; mp 65–68 °C; ν_{max} (Nujol) 3367, 3335 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.44 (1H, s), 2.84 (3H, s, OMe), 2.20–0.74 (8H, overlapping multiplets), 1.29 (3H, s, Me), 0.97 (3H, s, Me), 0.95 (3H, s, Me); HRMS: M^+, found 225.1460. $C_{11}H_{22}O_3Na$ requires 225.1456.

4.1.6. Reaction of 14. α-Pinene oxide **14** (500 mg, 3.24 mmol) in methanol (30 cm^3) was treated with TCNE (50 mg, 0.39 mmol) at room temperature for 2 h. The solvent was evaporated in vacuo and the residue was chromatographed on silica. Elution with 10% ethyl acetate/light petroleum gave 8-methoxy-*p*-menth-6-en-2α-ol **15** (*trans*-sobrerol 8-methyl ether) (192 mg, 32%) as a colourless oil; ν_{max} (Nujol) 3413, 1643 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.99 (1H, br.s), 3.61 (1H, s), 3.17 (3H, s, OMe), 2.05–1.50 (5H, overlapping multiplets), 1.76 (3H, s, Me), 1.09 (6H, s, Me_2); HRMS: M^+, found 391.2810. $(C_{11}H_{20}O_2)_2Na$ requires 391.2810.

4.2. X-ray analysis

4.2.1. *cis*-2,3-Dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane (6). $C_{10}H_{20}O_3$, M_r 188.26, monoclinic, $P2_1/n$ (no. 14), $a=13.0204(6)$ Å, $b=6.19.54(3)$ Å, $c=26.6900(11)$ Å, $\alpha=\gamma=90°$, $\beta=92.167(3)°$, $V=2151.45(17)$ $Å^3$, $Z=8$, $D_{cal}=1.16$ g cm^{-3}, $\mu=0.08$ mm^{-1}, $F(OOO)=832$. Data were collected on a crystal of size $0.30\times0.05\times0.02$ mm^3 on a KappaCCD diffractometer operating for $4.54<\theta<25.5°$. Reflections of 21,352 were collected for $-15\le h\le15$, $-7\le k\le7$, $-31\le l\le31$. There were 3794 independent reflections with 2489 possessing $I>2\sigma(I)$. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.027. The final *R* indices were $[I>2\sigma(I)]$ $R_1=0.06$, $wR_2=0.137$ and the *R* indices (all data) were $R_1=0.101$ and $wR_2=0.156$. The largest difference peak and hole were 0.22 and -0.25 e $Å^{-3}$.

4.2.2. *cis*-1,2-Dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane (7). $C_{10}H_{20}O_3$, M_r 188.26, triclinic, $P\bar{1}$ (no. 2), $a=6.0870$ (4) Å, $b=8.2022(5)$ Å, $c=10.9679(6)$ Å, $\alpha=93.845(4)°$, $\beta=93.766(4)°$, $\gamma=96.477(4)°$, $V=541.39(6)$ $Å^3$, $Z=2$, $D_{cal}=1.16$ g cm^{-3}, $\mu=0.08$ mm^{-1}, $F(OOO)=208$. Data were collected on a crystal of size $0.2\times0.1\times0.1$ mm^3 on a KappaCCD diffractometer operating for $4.64<\theta<25.08°$. 4993 Reflections were collected for $-7\le h\le5$, $-9\le k\le9$, $-13\le l\le13$. There were 1900 independent reflections with 1574 possessing $I>2\sigma(I)$. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The

goodness-of-fit on F^2 was 1.088. The final R indices were $[I>2\sigma(I)]$ $R_1=0.04$, $wR_2=0.098$ and the R indices (all data) were $R_1=0.051$ and $wR_2=0.105$. The largest difference peak and hole were 0.19 and -0.21 e Å^{-3}.

4.2.3. 2α,8-Dihydroxy-1β-methoxy-*p*-menthane (13). $C_{11}H_{22}O_3$, M_r 202.29, orthorhombic, space group *Pbca* (no. 61), $a=8.0065(2)$ Å, $b=14.5231(4)$ Å, $c=19.9634(7)$ Å, $\alpha=\beta=\gamma=90°$, $V=2321.33(12)$ Å^3, $Z=8$, $D_{cal}=1.16$ mg cm^{-3}, $\mu=0.08$ mm^{-1}, $F(OOO)=896$. Data were collected on a crystal of size $0.50\times0.20\times0.10$ mm^3 on a KappaCCD diffractometer operating for $3.92<\theta<25.3°$. Reflections of 10,732 were collected for $-9\le h\le 19$, $-15\le k\le 14$, $-17\le l\le 21$. There were 1878 independent reflections with 1556 possessing $I>2\sigma(I)$. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.068. The final R indices were $[I>2\sigma(I)]$ $R_1=0.060$, $wR_2=0.151$ and the R indices (all data) were $R_1=0.073$ and $wR_2=0.161$. The largest difference peak and hole were 0.37 and -0.26 e Å^{-3}.

5. Crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 247473, 247474, 247475. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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