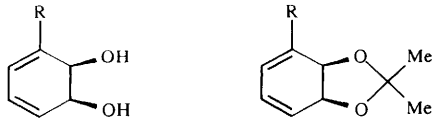
Conversion of benzene and chlorobenzene into polyhydroxylated cyclohexane derivatives related to cyclophellitol

Stanley M. Roberts and Peter W. Sutton
Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, UK

Reaction of the dienes **4–6** with diphenylketene gave the [2 + 2]-adducts **7–9** and the [4 + 2]-adducts **10–12**, respectively. The [4 + 2]-adduct **10** has been converted into the ester **14** and the tetraol **16**; the latter compound is an isomer of cyclophellitol **17**.

The whole-cell oxidation of benzene, chlorobenzene and bromobenzene produces the cyclohexadienediols **1–3**;[1] these



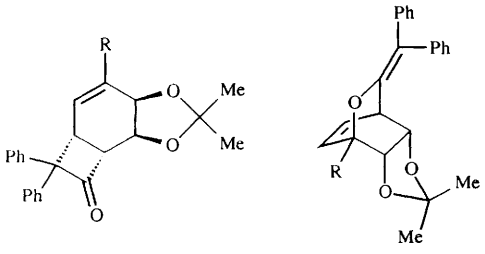
1 R = H **4**
2 R = Cl **5**
3 R = Br **6**

compounds are commercially available and have become increasingly popular starting materials for synthetic organic chemistry. In this connection, the seminal studies of Ley *et al.*[2] and the elegant work of Hudlicky and co-workers[3] are noteworthy.

The diols **1–3** are easily converted into the acetals **4–6**, respectively, and we have shown previously that the compounds **4**[4] and **5**[5] react with diphenylketene to give mixtures of the [2 + 2]- and [4 + 2]-adducts. Thus, the diene **4** reacts with diphenylketene to give the cyclooctanone derivative **7** and the enol ether **10** in equal amounts. The chloro compound **5** produces the isomers **8** (65%) and **11** (16%) when treated with diphenylketene while the bromo compound behaves in a similar fashion furnishing the [2 + 2]-adduct **9** (44%) and the [4 + 2]-adduct **12** (10%).

The ketones **7–9** can be separated from the isomeric enol ethers **10–12** by column chromatography. In the context of this report it is important to note that the isomers **8** and **11** equilibrate to give the two compounds in the ratio 66:19, respectively, when heated in tetrahydrofuran (THF) under reflux. Similarly, isomers **9** and **12** interconvert when boiled in THF (equilibrium ratio **9**:**12**, 50:10) while the adducts **7** and **10** are stable under these conditions. The isomers **7** and **10** interconvert in boiling octane to give a thermodynamically controlled equilibrium ratio **7**:**10**, 50:30.

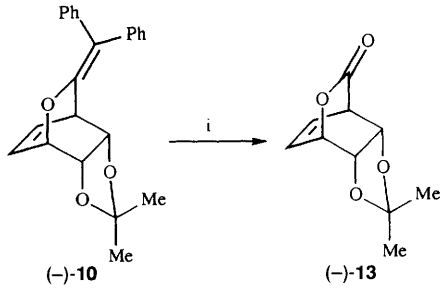
Treatment of the [2 + 2]-adduct **9** with tri-butyltinhydride in hot THF gave the optically active alkene (−)-**7**. The



7 R = H **10**
8 R = Cl **11**
9 R = Br **12**

analogous chloro compound **8** is stable under these reaction conditions while the tertiary chloride **11** undergoes ready hydrodehalogenation to afford the tricyclic compound (−)-**10**. Thus, treatment of a mixture of isomers **8** and **11** with tri-butyltin hydride in THF containing a catalytic quantity of AIBN gave only the optically pure enol ether (−)-**10** through a process of equilibration and selective hydrodechlorination.

Oxidation of (−)-**10** with an excess of *m*-chloroperbenzoic acid (MCPBA) produced the lactone (−)-**13** (Scheme 1). Such



(−)-**10** (−)-**13**

Scheme 1 *Reagents and conditions:* i, 10 equiv., MCPBA, CH_2Cl_2, 0 °C, 1 h, 70%

lactones have been synthesized, and the chemistry popularized, by Markó[6] and Posner.[7]

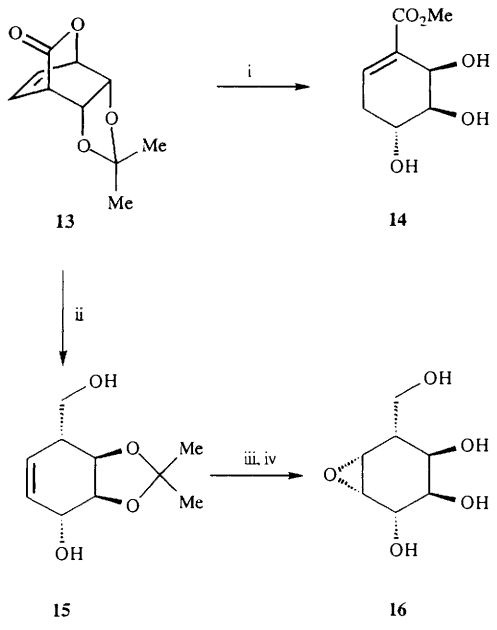
The racemic lactone (±)-**13** (produced from the diene **4** by reaction with diphenylketene, separation of the [4 + 2]-adduct, and oxidation with MCPBA) was further transformed as shown in the Scheme 2 [only the (+)-isomer is depicted as undergoing reaction for the sake of clarity].

Reaction of **13** with acidic methanol and basic work-up gave the ester **14** in 91% yield through cleavage of the lactone unit, double bond migration and deprotection of the diol moiety. Reduction of the lactone **13** with lithium aluminium hydride gave the diol **15**. Epoxidation and deprotection furnished the tetraol **16**, a compound closely related to cyclophellitol **17**.[8] However, unlike cyclophellitol, compound **16** did not act as a glycosidase inhibitor.

In conclusion the above chemistry can be utilised to prepare compounds of type **A** (Fig. 1), through a series of reactions that exhibit a very high degree of stereocontrol.

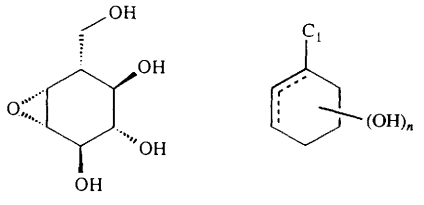
Experimental

Unless stated otherwise, all reagents were obtained from commercial suppliers and used without further purification except for MCPBA which was purified by washing with phosphate buffer (pH 7.5) solution. Light petroleum (bp 40–60 °C) and ethyl acetate were distilled from sodium wire and benzophenone. Dichloromethane was distilled from calcium hydride. Brine refers to saturated aqueous sodium chloride.



13 14 15 16

Scheme 2 *Reagents and conditions:* i, *p*-TSA, MeOH, room temp., 20 h, Et_3N, 91%; ii, $LiAlH_4$, THF, −15 °C, 1 h, 69%; iii, MCPBA, CH_2Cl_2, room temp., 20 h, 85%; iv, Amberlyst 15 (wet) ion-exchange resin, water, room temp., 20 h, 90%



17 A

Reactions were monitored by TLC on Merck Kieselgel 60 F_{254}, 0.25 mm plates. Plates were visualized using UV light (254 nm) followed by ceric sulfate, dinitrophenylhydrazine, or dilute potassium permanganate dip unless stated otherwise. Preparative column chromatography was performed under low pressure using silica gel 60H Merck (9385). Solvent mixtures are expressed as volume:volume ratios. 250 MHz ^1H and 62.9 MHz ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer. 300 MHz ^1H and 76 MHz ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer. Chemical shifts (δ) are quoted in ppm downfield to tetramethylsilane and coupling constants (J) are quoted in Hz. IR spectra of KBr discs, chloroform solutions, and neat oils were recorded on a Perkin-Elmer 881 IR spectrophotometer. Optical rotations were measured on a AA-1000 polarimeter operating at the sodium D line [589.3 nm]. Mass spectra were recorded on a Kratos Profile HV-3 spectrometer or obtained from the SERC Mass Spectrometry Centre, Swansea. Melting points were obtained using an Electrothermal melting point apparatus and are uncorrected. The preparation of compounds **7** and **10** has been detailed elsewhere.[4] Ratios of adduct mixtures, after thermolysis of compounds **8**, **9**, **11** and **12**, were determined by comparison of their respective 250 MHz ^1H NMR integrals.

(1*R*,2*S*,6*S*,7*R*)-7-Chloro-9-diphenylmethylene-4,4-dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]undec-10-ene 11, and (1*R*,2*S*,6*S*,9*R*)-7-Chloro-4,4-dimethyl-10,10-diphenyl-3,5-dioxatricyclo[7.2.0.0^{2,6}]undec-7-en 11 one 8

Diphenylketene (0.44 g, 2.3 mmol) was added dropwise to the diene **5** (0.14 g, 0.8 mmol) in THF (10 cm^3) under dry nitrogen gas. The resultant mixture was boiled under reflux for 48 h, quenched with water (20 cm^3), adjusted to pH 8 with saturated aqueous sodium hydrogencarbonate and extracted with diethyl ether (3 × 40 cm^3). The combined extracts were washed successively with water (60 cm^3) and brine (60 cm^3) and dried ($MgSO_4$) after which the solvent was removed by distillation under reduced pressure. The products were isolated by chromatography of the residue over silica with ethyl acetate–light petroleum (1:15) as eluent to yield the enol ether **11** as a white solid (0.03 g, 16%), mp 141–142 °C (from light petroleum), $[\alpha]_D^{22}$ −30.2 (*c* 1.1, $CHCl_3$), R_f 0.26 (ethyl acetate in light petroleum, 1:15); $\nu_{max}(CHCl_3)/cm^{-1}$ 3011 (CH_{str}), 2932 (CH_{str}), 1657 ($C{-}C_{str}$), 1279 and 1001; δ_H(250 MHz; $CDCl_3$) 7.46–7.10 (10 H, ArH), 6.41 (1 H, ddd, *J* 8, 2 and 1, 11-H), 6.33 (1 H, ddd, *J* 8, 6 and 1, 10-H), 4.58 (1 H, dd, *J* 7 and 1, 6-H), 4.52 (1 H, ddd, *J* 7, 4 and 1, H-2), 3.82 (1 H, ddd, *J* 6, 4 and 2, H-1), 1.38 (3 H, s, CH_3) and 1.33 (3 H, s, CH_3); δ_C(62.7 MHz; $CDCl_3$) 143.1 (C), 140.0 (C), 138.3 (C), 132.9–126.3 (12 × CH), 115.9 (C), 111.4 (C), 96.0 (C), 82.7 (CH), 75.5 (CH), 40.3 (CH) and 25.5 (2 × CH_3) (Found: M$^+$, 380.1190. $C_{23}H_{21}ClO_3$ requires *M*, 380.1179). Later fractions yielded the bicyclooctanone **8** as a white solid (0.12 g, 65%), mp 168–169 °C (from light petroleum), $[\alpha]_D^{22}$ −101.2 (*c* 1.1, $CHCl_3$), R_f 0.18 (ethyl acetate in light petroleum, 1:15); ν_{max}(kBr)/cm^{-1} 3067 (CH_{str}), 2927 (CH_{str}), 1772 ($C{=}O_{str}$) and 1071 (CO_{str}); δ_H(250 MHz; $CDCl_3$) 7.52–7.08 (10 H, ArH), 5.44 (1 H, d, *J* 4, 8-H), 4.76 (1 H, dd, *J* 6 and 3, 2-H), 4.52 (1 H, m, 6-H), 4.14 (1 H, m, 1-H), 4.06 (1 H, ddd, *J* 9, 4 and 2, 9-H), 1.44 (3 H, s, CH_3) and 1.39 (3 H, s, CH_3); δ_C(62.9 MHz; $CDCl_3$) 204.8 (CO), 139.7 (C), 138.6 (C), 133.5 (C), 129.1–125.3 (11 × CH), 110.0 (C), 79.3 (C), 72.4 (CH), 71.3 (CH), 54.4 (CH), 35.6 (CH), 27.6 (CH_3) and 26.2 (CH_3) (Found: M$^+$, 380.1185. $C_{23}H_{21}ClO_3$ requires *M*, 380.1179).

(1*R*,2*S*,6*S*,7*R*)-7-Bromo-9-diphenylmethylene-4,4-dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]undec-10-ene 12, and (1*R*,2*S*,6*S*,9*R*)-7-bromo-4,4-dimethyl-10,10-diphenyl-3,5-dioxatricyclo [7.2.0.0^{2,6}] undec-7-en-11-one 9

Diphenylketene (1.27 g, 6.54 mmol) was added dropwise to the diene **6** (1.00 g, 4.35 mmol) in THF (50 cm^3) under dry nitrogen gas. The resultant mixture was boiled under reflux for 48 h, quenched with water (20 cm^3), adjusted to pH 8 with saturated aqueous sodium hydrogen carbonate and extracted with diethyl ether (3 × 40 cm^3). The combined extracts were washed successively with water (60 cm^3) and brine (60 cm^3), and then dried ($MgSO_4$) after which solvent was removed by distillation under reduced pressure. The products were isolated by chromatography of the residue over silica with ethyl acetate–light petroleum (1:15) as eluent to yield enol ether **12** as a yellow oil which was recrystallised from light petroleum to give a white solid (0.19 g, 10%), mp 145–147 °C, $[\alpha]_D^{25}$ −21.3 (*c* 1.0, $CHCl_3$), R_f 0.21 (ethyl acetate–light petroleum, 1:15); $\nu_{max}(CHCl_3)/cm^{-1}$ 3009 (CH_{str}), 2932 (CH_{str}), 1602 ($C{-}C_{str}$), 1176 and 999; δ_H(250 MHz; $CDCl_3$) 7.42–7.08 (10 H, ArH), 6.52 (1 H, ddd, *J* 8, 2 and 1, 11-H), 6.28 (1 H, ddd, *J* 8, 7 and 1, 10-H), 4.70 (1 H, dd, *J* 7 and 1, 6-H), 4.50 (1 H, ddd, *J* 7, 4 and 1, 2-H), 3.82 (1 H, ddd, *J* 7, 4 and 2, 1-H), 1.37 (3 H, s, CH_3) and 1.34 (3 H, s, CH_3); δ_C(75.5 MHz; $CDCl_3$) 143.3 (C), 140.0 (C), 138.3 (C), 134.9–126.3 (12 × CH), 115.7 (C), 111.2 (C), 88.6 (C), 83.6 (CH), 75.4 (CH), 40.0 (CH), 25.6 (CH_3) and 25.5 (CH_3) (Found: M$^+$, 424.0685. $C_{23}H_{21}BrO_3$ requires *M*, 424.0674). Later fractions yielded the bicyclooctanone **9** as a white solid (0.82 g, 44%), mp 180–181 °C (from light petroleum), $[\alpha]_D^{26}$ −61.8 (*c* 1.2, $CHCl_3$), R_f 0.13 (ethyl acetate–light petroleum, 1:15); $\nu_{max}(CHCl_3)/cm^{-1}$ 3016 (CH_{str}), 2936 (CH_{str}), 1773 ($C{=}O_{str}$) and 1201; δ_H(250 MHz; $CDCl_3$) 7.52–7.08 (10 H, ArH), 5.80 (1 H, d, *J* 4, 8-H), 4.74 (1 H, dd, *J* 6 and 3, 2-H, 4.56 (1 H, dd, *J* 6 and 1, 6-H), 4.16 (1 H,

dd, *J* 10 and 3, 1-H), 4.02 (1 H, ddd, *J* 10, 4 and 2, 9-H), 1.45 (3 H, s, CH_3) and 1.40 (3 H, s, CH_3); δ_C(62.9 MHz; $CDCl_3$) 204.8 (CO), 139.1 (C), 138.3 (C), 129.6–127.1 (11 × CH), 125.2 (C), 110.0 (C), 79.2 (C), 73.4 (CH), 71.3 (CH), 54.3 (CH), 36.6 (CH), 27.6 (CH_3) and 26.3 (CH_3) (Found: M^+, 424.0679. $C_{23}H_{21}BrO_3$ requires *M*, 424.0674).

Thermolysis of (1*RS*,2*SR*,6*RS*,9*RS*)-4-4 dimethyl-10-10-diphenyl-3,5-dioxatricyclo[7.2.0.0^{2,6}]undec-7-en-11-one 7 in octane

The bicyclooctanone **7** (0.10 g, 0.27 mmol) in dry octane (5 cm^3) was heated at reflux under dry nitrogen gas for 2 d. The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate—light petroleum (1 : 15) as eluent to yield the enol ether **10** as a white solid (0.05 g, 30%), mp 150–152 °C (from light petroleum), R_f 0.4 (ethyl acetate–light petroleum, 1 : 15); $\nu_{max}(CHCl_3)/cm^{-1}$ 3011 ($C–H_{str}$), 2927 ($C–H_{str}$), 1639 ($C–C_{str}$), 1385 and 1064; δ_H(250 MHz; $CDCl_3$) 7.40–7.04 (10 H, ArH), 6.35 (2 H, m, 11-H and 10-H), 5.09 (1 H, ddd, *J* 4, 4 and 2, 7-H), 4.61 (1 H, dd, *J* 7 and 4, 6-H), 4.44 (1 H, dd, *J* 7 and 4, 2-H), 3.89 (1 H, ddd, *J* 6, 4 and 2, 1-H and 1.31 (6 H, 2 × s, 2 × CH_3); δ_C(62.7 MHz; $CDCl_3$) 144.9 (C), 141.0 (C), 139.6 (C), 131.5–125.8 (12 × CH), 114.7 (C), 110.7 (C), 76.0 (CH), 73.9 (CH), 71.7 (CH), 40.6 (CH), 25.6 (CH_3) and 25.5 (CH_3) (Found: M^+, 346.1553. $C_{23}H_{22}O_3$ requires *M*, 346.1569). Later fractions afforded the bicyclooctanone **7** as a white solid (0.05 g, 50%), mp 151–152 °C (from light petroleum), R_f 0.3 (ethyl acetate–light petroleum, 1 : 15); $\nu_{max}(CHCl_3)/cm^{-1}$ 3010 (CH_{str}), 2939 (CH_{str}), 1775 ($C{=}O_{str}$) and 1057 ($C–O_{str}$); δ_H(250 MHz; $CDCl_3$) 7.54–7.12 (10 H, ArH), 5.65 (1 H, ddd, *J*, 11, 2 and 2, 7-H, 5.51 (1 H, dd, *J* 11 and 4, 8-H), 4.68 (1 H, ddd, *J* 5, 2, and 2, 2-H), 4.52 (1 H, dd, *J* 5 and 2, 6-H), 4.12 (1 H, dd, *J* 9 and 2, 1-H), 3.95 (1 H, dddd, *J* 9, 4, 2 and 2, 9-H), 1.39 (3 H, s, CH_3), 1.34 (3 H, s, CH_3); δ_C(75.5 MHz; $CDCl_3$) 206.1 (CO), 139.9 (C), 139.1 (C), 129.0–126.2 (12 × CH), 109.1 (C), 78.5 (C), 69.5 (CH), 69.2 (CH), 54.5 (CH), 32.8 (CH), 28.0 (CH_3) and 26.3 (CH_3) (Found: M^+, 346.1581. $C_{23}H_{22}O_3$ requires *M*, 346.1569).

Thermolysis of (1*RS*,2*SR*,6*RS*,7*SR*)-9-diphenylmethylene-4,4-dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]undec-10-ene 10 in octane

The enol ether **10** (0.15 g, 0.43 mmol) in dry octane (5 cm^3) was heated at reflux under dry nitrogen gas for 2 d after which the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica using ethyl acetate–light petroleum (1 : 15) as eluent to yield, as white solids, the enol ether **10** (0.06 g, 37%) and the bicyclooctanone **7** (0.08 g, 54%) (data as shown above).

Thermolysis of (1*R*,2*S*,6*S*,9*R*)-7-chloro-4,4-dimethyl-10,10-diphenyl-3,5-dioxatricyclo[7.2.0.0^{2,6}]undec-7-en-11-one 8 in THF

The bicyclooctanone **8** (0.11 g, 0.28 mmol) in dry THF (5 cm^3) was heated at reflux under dry nitrogen gas for 2 d. The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate–light petroleum (1 : 15) as eluent to yield a mixture of the enol ether **11** and the bicyclooctanone **8** (1 : 3.5) as a white solid (0.09 g, 85%) (data as shown above).

Thermolysis of (1*R*,2*S*,6*S*,7*R*)-7-chloro-9-diphenylmethylene-4,4-dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]undec-10-ene 11 in THF

The enol ether **11** (0.11 g, 0.28 mmol) in dry THF (5 cm^3) was heated at reflux under dry nitrogen gas for 2 d. The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate–light petroleum (1 : 15) as eluent to yield a mixture of the enol ether **11** and the bicyclooctanone **8** (1 : 3) as a white solid (0.06 g, 54%) (data as shown above).

Thermolysis of (1*R*,2*S*,6*S*,9*R*)-7-bromo-4,4-dimethyl-10,10-diphenyl-3,5-dioxatricyclo[7.2.0.0^{2,6}]undec-7-en-11-one 9 in THF

The bicyclooctanone **9** (0.02 g, 0.05 mmol) in dry THF (5 cm^3) was heated at reflux under dry nitrogen gas for 2 d. The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate–light petroleum (1 : 15) as eluent to yield a mixture of the enol ether **12** and the bicyclooctanone **9** (1 : 6) as a white solid (0.02 g, 77%) (data as shown above).

Thermolysis of (1*R*,2*S*,6*S*,7*R*)-7-bromo-9-diphenylmethylene-4,4-dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]undec-10-ene 12 in THF

The enol ether **12** (0.03 g, 0.07 mmol) in dry THF (5 cm^3) was heated at reflux under dry nitrogen gas for 2 d. The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate–light petroleum (1 : 15) as eluent to yield a mixture of the enol ether **12** and the bicyclooctanone **9** (1 : 5) as a white solid (0.03 g, 89%) (data as shown above).

(1*R*,2*S*,6*R*,9*R*)-4,4-dimethyl-10,10-diphenyl-3,5-dioxatricyclo[7.2.0.0^{2,6}]undec-7-en-11-one 7

Tributyltin hydride (1.50 cm^3, 5.58 mmol) was added to the bicyclooctanone **9** (1.17 g, 2.75 mmol) in dry THF (10 cm^3) and the mixture heated to reflux. 1,1′-Azobis(cyclohexanecarbonitrile) (0.60 g) was then added to the mixture and heating continued for 16 h. After this, the solvent was removed from the mixture by distillation under reduced pressure and the residue dissolved in acetonitrile (150 cm^3). The solution was washed with hexane (3 × 100 cm^3) and the latter was subsequently backwashed with acetonitrile (50 cm^3). The combined acetonitrile fractions were dried ($MgSO_4$), and the solvent removed by distillation under reduced pressure. The residue obtained was dissolved in diethyl ether (70 cm^3) and methanol (35 cm^3) and toluene-p-sulfonic acid (0.18 g) was added to the mixture which was then vigorously stirred at room temp. for 5 d. The reaction was quenched with triethylamine (0.5 cm^3) and the solvent removed from the mixture by distillation under reduced pressure. The residue was purified by chromatography over silica with ethyl acetate–light petroleum (1 : 1) as eluent to yield 4,5-dihydroxy-8,8-diphenylbicyclo[4.2.0]oct-2-en-7-one as a white solid (0.38 g, 45%), mp 128–129 °C (from diethyl ether), $[\alpha]_D^{26}$ −312.1 (*c* 0.7, $CHCl_3$), R_f 0.32 (ethyl acetate in light petroleum, 1 : 1); $\nu_{max}(CHCl_3)/cm^{-1}$ 3340 (OH_{str}), 3011 (CH_{str}), 1771 ($C{=}O_{str}$), 1204 and 1061 ($C–O_{str}$); δ_H(250 MHz; $CDCl_3$) 7.58–7.11 (10H, ArH), 5.74 (1 H, m, 4-H), 5.60 (1 H, m, 5-H), 4.29 (1 H, m, 2-H), 4.24 (1 H, m, 3-H), 3.97 (2 H, m, 1-H and 6-H) and 2.94 (2 H, brs, 2 × OH); δ_C(75.5 MHz; $CDCl_3$) 207.5 (CO, 140.3 (C), 139.6 (C), 130.0–126.8 (12 × CH), 77.2 (C), 65.4 (2 × CH), 58.3 (CH) and 34.2 (CH) (Found: M^+, 306.1252. $C_{20}H_{18}O_3$ requires *M*, 306.1256). Toluene-*p*-sulfonic acid (0.09 g) was added to the diol (0.38 g, 1.2 mmol) in 2,2-dimethoxypropane (100 cm^3) and the mixture vigorously stirred at room temperature for 24 h. The reaction was quenched with triethylamine (0.5 cm^3) and the solvent removed from the mixture by distillation under reduced pressure: The residue obtained was purified by chromatography over silica with ethyl acetate–light petroleum (1 : 15) as eluent to yield the title compound **7** as a white solid (0.32 g, 76%), mp 135–136 °C (from light petroleum), $[\alpha]_D^{23}$ −259.6 (*c* 1.0, $CHCl_3$).

(1*R*,2*S*,6*R*,7*S*)-9-Diphenylmethylene-4,4-dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]undec-10-ene 10

Tributyltin hydride (0.06 cm^3, 0.2 mmol) was added to a 3:1 mixture of the bicyclooctanone **8** and the enol ether **11** (0.08 g, 0.2 mmol) in dry THF (2 cm^3) and the mixture heated to reflux. AIBN (0.01 g) was then added to the mixture and heating continued for 10 h. Further tributyltin hydride (0.06 cm^3, 0.2 mmol) and AIBN (0.01 g) were added to the mixture and heating continued for a further 10 h. After this the solvent was removed from the mixture by distillation under reduced pressure and the residue dissolved in acetonitrile (50 cm^3). The resulting solution was washed with hexane (5 × 50 cm^3) which was subsequently backwashed with acetonitrile (50 cm^3). The combined acetonitrile fractions were dried ($MgSO_4$) and solvent was removed by distillation under reduced pressure. The products were isolated by chromatography over silica with ethyl acetate–light petroleum (1:15) as eluent to yield the title compound **10** as a white solid which was recrystalised from light petroleum (0.02 g, 33%), mp 147–148 °C, $[\alpha]_D^{27}$ −64.7 (*c* 1.5, $CHCl_3$). Later fractions yielded the bicyclooctanone **8** as a white solid (0.02 g, 29%).

(1*R*,2*S*,6*S*,7*S*)-4,4-Dimethyl-3,5,8-trioxatricyclo[5.2.2.0^{2,6}]-undec-10-en-9-one 13

To a stirred solution of the enol ether (−)-**10** (0.12 g, 0.3 mmol) in dichloromethane (2 cm^3) at 0 °C was added *m*-chloroperbenzoic acid (0.46 g, 3.0 mmol). The reaction mixture was stirred for 1 h and then diluted with dichloromethane (15 cm^3) and washed with a 1:1 mixture of saturated aqueous sodium metabisulfite and aqueous sodium hydrogencarbonate (2 × 20 cm^3). The aqueous layer was back-washed with dichloromethane (2 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with ethyl acetate–light petroleum (1:4) as eluent to give the title compound **13** as a white solid (0.05 g, 70%), mp 157–159 °C (from light petroleum), $[\alpha]_D^{25}$ −15.1 (*c* 0.7, $CHCl_3$), R_f 0.17 (ethyl acetate–light petroleum, 1:4); ν_{max}(KBr)/cm^{-1} 2995 (CH_{str}), 2935 (CH_{str}), 1765 (C=O_{str}), 1471 (CH_{def}) and 1063 (C–O_{str}); δ_H(250 MHz; $CDCl_3$) 6.42 (2 H, m, 10-H and 11-H), 5.22 (1 H, ddd, *J* 5, 4, and 2, 7-H), 4.66 (1 H, dd, *J* 7 and 5, 6-H), 4.60 (1 H, dd, *J* 7 and 4, 2-H), 3.84 (1 H, ddd, *J* 6, 4 and 2, 1-H and 1.32 (6 H, 2 × s, 2 × CH_3); δ_C(63 MHz; $CDCl_3$) 170.2 (CO), 130.2 (CH), 129.6 (CH), 113.5 (C), 75.7 (CH), 74.3 (CH), 72.6 (CH), 46.5 (CH), 25.4 (CH_3) and 25.3 (CH_3) (Found: M$^+$, 196.0728. $C_{10}H_{12}O_4$ requires *M*, 196.0736).

Methyl (4*SR*,5*RS*,6*SR*)-4,5,6-trihydroxycyclohex-1-ene-carboxylate 14

Toluene-*p*-sulfonic acid (0.01 g) was added to the lactone **13** (0.04 g, 0.22 mmol) in methanol (5 cm^3) and the mixture stirred vigorously for 20 h at room temp. The reaction was quenched with triethylamine (0.5 cm^3) and the mixture stirred overnight. The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate as eluent to yield the title compound **14** as a white solid, (0.04 g, 91%), mp 151–152 °C (from chloroform), R_f 0.09 (ethyl acetate, anisaldehyde); ν_{max}(KBr)/cm^{-1} 3324 (OH_{str}), 2925 (CH_{str}), 1706 (C=O_{str}), 1228 (C–O_{str}) and 1083 (C–O_{str}); δ_H(250 MHz; CD_3OD) 6.93 (1 H, dd, *J* 5 and 3, 2-H), 4.60 (1 H, d, *J* 4, 6-H), 3.90 (1 H, ddd, *J* 10, 9 and 6, 4-H), 3.76 (3 H, s, OCH_3), 3.43 (1 H, dd, *J* 10 and 4, 5-H), 2.71 (1 H, ddd, *J* 20, 6 and 5, 3-H) and 2.16 (1 H, dddd, *J* 20, 9, 3 and 1, 3-H); δ_C(62.7 MHz; CD_3OD) 168.0 (CO), 141.4 (CH), 132.5 (C), 75.0 (CH), 67.2 (CH), 66.9 (CH), 52.3 (CH_3) and 35.1 (CH_2) (Found: [M − OCH_3]$^+$, 157.0508. $C_7H_9O_4$ requires [*M* − OCH_3] 157.0501).

(1*RS*,2*SR*,5*RS*,6*SR*)-5-Hydroxymethyl-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]hept-3-ene-2-ol 15

Lithium aluminium hydride (0.09 g, 2.4 mmol) was added to lactone **13** (0.22 g, 1.1 mmol) in dry THF (8 cm^3) at −15 °C with vigorous stirring. After 1 h the reaction was quenched by dropwise addition of saturated aqueous sodium sulfite to the mixture until a precipitate formed. The solvent was removed from the mixture by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate–light petroleum (1:1) as eluent to yield the title compound **15** as a white solid (0.15 g, 69%), mp 68–70 °C (from diethyl ether). R_f 0.10 (ethyl acetate in light petroleum, 1:1); ν_{max}(KBr)/cm^{-1} 3316 (OH_{str}), 2908 (CH_{str}), 1385 (CH_{def}), 1265 (C–O_{str} or OH_{def}), 1205 and 1065 (C–O_{str}); δ_H(250 MHz; $CDCl_3$) 5.95 (1 H, ddd, *J* 10, 3 and 3, 3-H), 5.67 (1 H, ddd, *J* 10, 4 and 2, 4-H), 4.16 (3 H, m, 1-H, 2-H and 6-H), 3.60 (2 H, m, 2 × 10-H), 2.97 (1 H, br s, OH), 2.41 (2 H, br m, H-5 and OH), 1.46 (3 H, s, CH_3) and 1.36 (3 H, s, CH_3); δ_C(62.7 MHz; $CDCl_3$) 131.8 (CH), 127.1 (CH), 108.7 (C), 80.6 (CH), 75.3 (CH), 70.0 (CH), 64.1 CH_2), 42.5 (CH), 27.2 (CH_3) and 24.8 (CH_3) (Found: M$^+$, 200.1048. $C_{10}H_{16}O_4$ requires *M*, 200.1049).

(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*,6*SR*)-5-Hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol 16

m-Chloroperoxybenzoic acid (0.60 g, 3.82 mmol) was added to diol **15** (0.15 g, 0.75 mmol) in dichloromethane (5 cm^3) and the resultant mixture stirred at room temp. for 20 h. The solvent was removed from the mixture by distillation under reduced pressure and the residue purified by chromatography over silica with ethyl acetate–light petroleum (1:1) as eluent to yield (1*RS*,2*SR*,3*RS*,7*SR*,8*RS*,9*SR*)-8-hydroxymethyl-4,6,10-trioxatricyclo[7.1.0.0^{3,7}]decan-2-ol as a white solid (0.14 g, 85%), mp 83–84 °C (from diethyl ether). R_f 0.28 (ethyl acetate); ν_{max}($CHCl_3$)/cm^{-1} 3693 (OH_{str}), 3510 (OH_{str}), 2995 (CH_{str}), 2937 (CH_{str}) and 1051 (C–O_{str}); δ_H(300 MHz; [$^2H_6$]-DMSO) 5.52 (1 H, d, *J* 5, OH), 4.88 (1 H, dd, *J* 6 and 6, OH), 3.88 (3 H, m, 2-H, 3-H and 7-H), 3.67 (1 H, ddd, *J* 11, 6 and 4, 11-H), 3.50 (1 H, ddd, *J* 11, 8 and 6, 11-H), 3.29 (1 H, d, *J* 5, 9-H), 3.17 (1 H, d, *J* 5, 1-H), 1.96 (1 H, ddd, *J* 8, 8 and 4, 8-H), 1.35 (3 H, s, CH_3) and 1.21 (3 H, s, CH_3); δ_C(75.5 MHz; [$^2H_6$]-DMSO) 106.3 (C), 78.6 (CH), 72.1 (CH), 70.6 (CH), 61.5 (CH_2), 54.7 (CH), 51.7 (CH), 41.6 (CH), 27.1 (CH_3) and 24.0 (CH_3) (Found: [M − CH_3]$^+$, 201.0760. $C_9H_{13}O_5$ requires *M* − CH_3, 201.0763). Amberlyst 15(wet) ion-exchange resin (0.03 g) was added to the diol (0.03 g, 0.13 mmol) suspended in water (2 cm^3) and the mixture was stirred at room temp. for 20 h. It was then filtered, and the solvent removed by distillation under reduced pressure. The residue was purified by chromatography over silica with methanol–ethyl acetate (1:4) as eluent to yield the tetrol **16** as a clear colourless oil (0.02 g, 90%). R_f 0.20 (methanol in ethyl acetate, 1:4); ν_{max}/cm^{-1} 3378 (OH_{str}), 3009 (CH_{str}), 2915 (CH_{str}) and 1064 (C–O_{str}); δ_H(300 MHz; CD_3OD) 4.52 (1 H, s, OH), 4.08 (1 H, dd, *J* 7 and 3, 2-H), 3.70 (3 H, m, 4-H, and 2 × 8-H), 3.50 (1 H, dd, *J* 7 and 2, 3-H), 3.40 (1 H, dd, *J* 4 and 4, 6-H), 3.34 (1 H, dd, *J* 4 and 3, 1-H) and 2.28 (1 H, dddd, *J* 8, 4, 2 and 2, 5-H); δ_C(75.5 MHz; CD_3OD) 72.5 (CH), 70.6 (CH), 70.4 (CH), 61.9 (CH_2), 56.4 (CH), 55.9 (CH) and 43.7 (CH) (Found: [M + NH_4]$^+$, 194.1028. $C_7H_{16}NO_5$ requires *M* + NH_4, 194.1028).

Acknowledgements

We thank the BBSRC and Peboc for support of a research assistant (P. W. S.) and Dr Bryan Winchester (Great Ormond St. Hospital for Children NHS Trust) for biological testing.

References

1 K. Faber, 'Biotransformations in Organic Chemistry', Springer Verlag, Heidelberg, 1992, pp. 196–9; H. A. J. Carless, *Tetrahedron Asymmetry*, 1991, **3**, 797.

2 S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **28,** 225.
3 T. Hudlicky, M. Mandel, J. Rouden, R. S. Lee, B. Bachmann, T. Dudding, K. J. Yost and J. S. Merola, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1553; T. Hudlicky, J. Rouden, H. Luna and S. Allen, *J. Am. Chem. Soc.*, 1994, **116,** 5099; T. Hudlicky, H. F. Olivo and B. McKibben, *J. Am. Chem. Soc.*, 1994, **116,** 5108.
4 M. F. Mahon, K. Molloy, C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik, J. O. Williams and J. A. Winders, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1255.
5 C. A. Pittol, S. M. Roberts, P. W. Sutton and J. O. Williams, *J. Chem. Soc., Chem. Commun.*, 1994, 803.
6 I. E. Marko, P. Seres, T. M. Swarbrick, I. Staton and M. Adams, *Tetrahedron Lett.*, 1992, **33,** 5648.
7 G. H. Posner, T. D. Nelson, C. M. Kinter and N. Johnson, *J. Org. Chem.*, 1992, **57,** 4083; G. H. Posner, V. Vinader and K. Agarinkia, *J. Org. Chem.*, 1992, **57,** 4088.
8 T. K. M. Shing and V. W.-F. Tai, *J. Chem. Soc., Perkin Trans.1*, 1994, 2017.

Paper 5/00917K
Received 15*th February* 1995
Accepted 28*th February* 1995