Directed epoxidation of cyclohexa-1,4-dienes–stereoselective formation of up to six contiguous stereogenic centres†

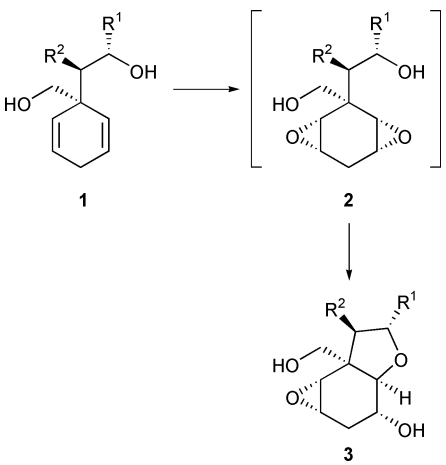
Michael Butters,[b] Dirk J. Beetstra,[a] Mark C. Elliott,*[a] Joseph Hill-Cousins[a] and Benson M. Kariuki[a]

Received 13th August 2008, Accepted 29th August 2008
First published as an Advance Article on the web 20th October 2008
DOI: 10.1039/b814131m

Epoxidation/cyclisation of cyclohexa-1,4-dienes containing pendant hydroxyl groups provides stereocontrolled access to highly-functionalised reduced benzol[*b*]furan derivatives.

Introduction

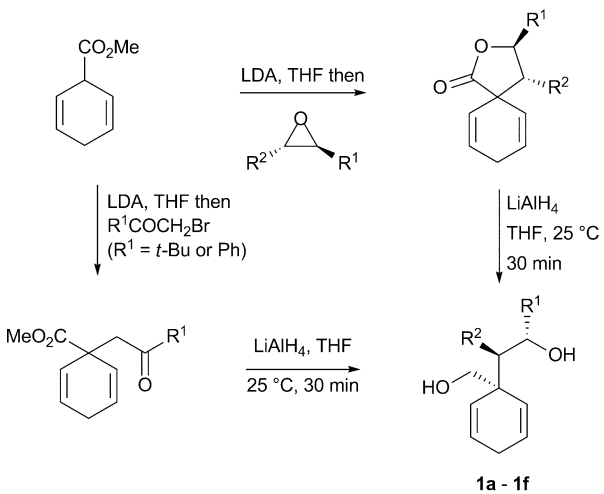
Desymmetrisation reactions of cyclohexa-1,4-dienes have considerable synthetic potential for the preparation of fused carbocyclic and heterocyclic systems.[1,2] Landais *et al.* have reported extensively on the use of asymmetric dihydroxylation reactions for the selective oxidation of such systems,[3] and these reactions have been used for the preparation of a number of biologically important carbocyclic sugar analogues.[4] We have demonstrated that conformational control can be used to impart high levels of diastereocontrol in the free-radical,[5] Prins[6] and iodocyclisation reactions[7] onto cyclohexa-1,4-dienes. The substrates that we used in the latter study generally contain two hydroxy groups as a result of the Birch reduction–alkylation reaction[8] used in their preparation. We reasoned that the homoallylic alcohol in compound **1** could be used to direct the facial selectivity in the epoxidation of the cyclohexa-1,4-diene ring, and that conformational control could then be used to direct the ring-opening of the resulting bis-epoxide **2** (Scheme 1) in order to prepare highly functionalised carbocyclic sugar analogues **3** containing five new contiguous stereogenic centres. We know from our previous work that the ring-opening of epoxides **2** should proceed with high levels of diastereocontrol.[7] Furthermore, the reaction also has the potential for "stereochemical proof-reading" since epoxidation of the upper face (as drawn) will not lead to the formation of a cyclised product. Epoxidation has previously been used to directly desymmetrise cyclohexa-1,4-dienes.[9]



Scheme 1 Direct epoxidation and cyclisation of cyclohexa-1,4-dienes.

Results and discussion

Substrates **1a–1f** were prepared as previously described (Scheme 2).[7] Epoxidation of these compounds was investigated with a range of oxidants, of which *m*-CPBA proved optimal. Cyclisation onto the epoxide is spontaneous and highly diastereoselective under the epoxidation conditions, resulting in the formation of a single diastereoisomer of products containing five new contiguous stereogenic centres! The results are summarised in Table 1.



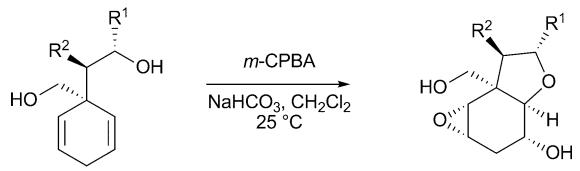
a, R^1 = *n*-Bu, R^2 = H; **b**, R^1 = *t*-Bu, R^2 = H; **c**, R^1 = *n*-C_6H_{13}, R^2 = H
d, R^1 = Ph, R^2 = H; **e**, R^1 = H, R^2 = Ph; **f**, R^1 = R^2 = -$(CH_2)_4$-

Scheme 2 Synthesis of substrates **1a–1f**.

The reaction yields are moderate to good, and NMR spectra of crude reaction mixtures show no other diastereoisomers. The reason for the lower yields (entries 1 and 3) is not readily apparent, since no other compounds were isolated, and the products **3a** and **3c** are stable to chromatography. Entry 4 shows a key limitation

[a]*School of Chemistry, Cardiff University, Park Place, Cardiff, UK, CF10 3AT. E-mail: elliottmc@cardiff.ac.uk; Fax: +44 (0)29 20874030; Tel: +44 (0)29 20874686*
[b]*AstraZeneca Process R & D Avlon/Charnwood, Avlon Works, Severn Road, Hallen, Bristol, UK, BS10 7ZE*
† CCDC reference numbers 694523 and 694524. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b814131m

Table 1 Cyclisation of compounds **1a–1f**



1a - 1f **3a - 3f**

Entry	Product	R_1	R_2	Yield (%)
1	**3a**	*n*-Bu	H	40
2	**3b**	*t*-Bu	H	75
3	**3c**	*n*-C_6H_{13}	H	36
4	—	Ph	H	0
5	**3e**	H	Ph	55
6	**3f**	-$(CH_2)_4$-		52

of the method. The presence of a benzylic alcohol in the substrate led to no identifiable products. The stereochemistry of compound **3e** was confirmed by NOESY NMR spectroscopy as described in the Experimental section. Compound **3b** was characterised crystallographically (Fig. 1).[10] The stereochemistry of the other compounds was assigned by analogy with these results, which are in line with the results obtained in the iodocyclisation reactions of compounds **1**.[7]

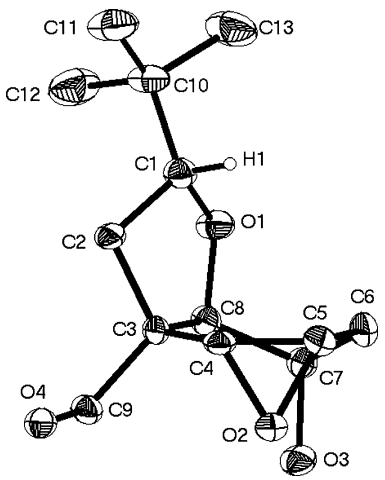
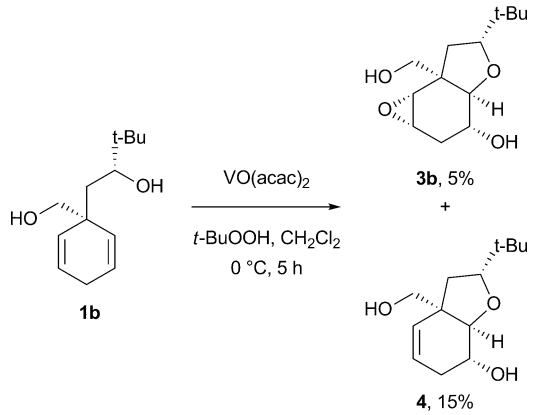


Fig. 1 Structure of compound **3b** from single crystal X-ray diffraction data. Thermal ellipsoids are shown at the 50% probability level. The unit cell contains both enantiomers. The enantiomer shown has been chosen for consistency with reaction schemes.

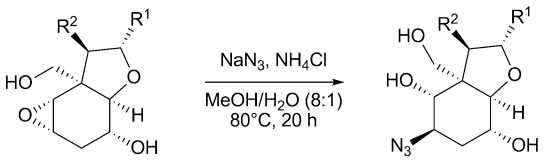
Other oxidation conditions were evaluated. Very slow epoxidation was observed under Payne conditions (H_2O_2/CH_3CN) such that no products were characterised. With vanadyl acetylacetonate and *tert*-butyl hydroperoxide, a mixture of compounds **3b** and **4** was obtained from compound **1b** (Scheme 3). Compound **4** (stereochemistry confirmed by NOESY NMR spectroscopy) is produced by cyclisation of a mono-epoxide, although the low yield makes it difficult to determine whether the actual epoxidation step is diastereoselective.

Compounds **3** are ripe for further elaboration. For example, the epoxides can be regiospecifically opened at the less hindered end using sodium azide,[11] giving azides **5** in moderate to excellent yield (Table 2). In fact, regioselective opening of the epoxide at the more



Scheme 3 Epoxidation of compound **1b** mediated by vanadyl acetylacetonate.

Table 2 Azide ring-opening of epoxides **3**



3 **5**

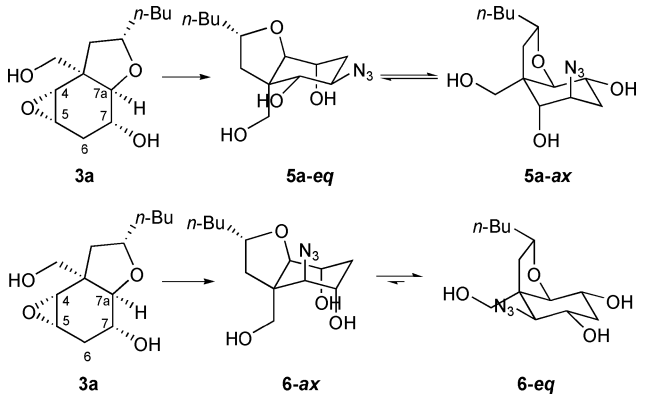
Entry	Product	R_1	R_2	Yield (%)
1	**5a**	*n*-Bu	H	36
2	**5b**	*t*-Bu	H	67
3	**5c**	*n*-C_6H_{13}	H	96
4	**5e**	H	Ph	67
5	**5f**	-$(CH_2)_4$-		46

hindered C4 end (Fig. 1) is predicted by the Fürst–Plattner rule.[12] However, this attack would lead to significant steric interactions between the incoming nucleophile and the tetrahydrofuran ring, so attack at C5 (crystallographic numbering) is preferred.

Assignment of the regiochemistry of epoxide-opening

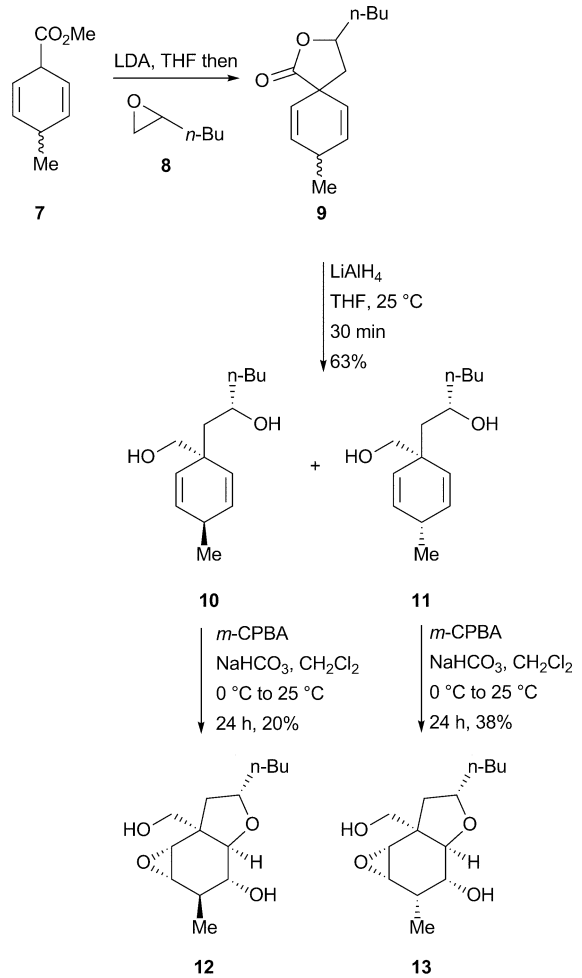
There are two possible outcomes for the epoxide-opening reaction of compounds **3**, each product potentially existing in one (or both) of two chair conformations. In the case of ring-opening of compound **3a** at C-5, the two conformations **5a-eq** and **5a-ax** each have three axial substituents and three equatorial substituents. Conformer **5a-ax** is presumably slightly more stable due to the small azide group being axial. Ring-opening at C-4 would presumably favour conformer **6-eq** almost exclusively (Scheme 4).

The methylene protons at C-6 are distinct in all of the compounds. In each case, one of these protons shows a single *trans*-diaxial coupling. For conformers **6-ax** and **6-eq** arising by C-4 epoxide-opening we would expect zero or two *trans*-diaxial couplings to this hydrogen, whereas with either of conformers **5a-eq** or **5a-ax** we would expect one, as observed. We can therefore conclude that epoxide-opening has taken place at C-5. This conclusion is further supported by the coupling constants of H-4 and H-7a in the azides **5**. In each case, one of these protons is axial while the other is equatorial, a situation that would not occur had epoxide opening taken place at C-4.



Scheme 4 Regioselectivity of the epoxide-opening of compound **3a**.

We have recently reported a synthesis of the tricyclic core of lycoposerramine S, which begins with methyl 4-methylcyclohexa-2,5-diene-1-carboxylate **7**.[13] In the present work, compound **7** was deprotonated and reacted with epoxide **8** to give lactone **9** as a 1:1 mixture of diastereoisomers. This mixture was then reduced to give a mixture of isomers **10** and **11** in good overall yield (Scheme 5). The individual isomers were separated by extensive chromatography on silica gel. Epoxidation of these compounds gave in each case a single isomer of epoxides, **12** and **13**, albeit in modest yield. The stereochemistry of compounds **10** and **11** was assigned retrospectively by single-crystal X-ray diffraction of compound **13** (Fig. 2),[10] which also confirmed the stereochemistry of that compound. The synthesis of compounds **12** and **13** feature the formation of six new contiguous stereogenic centres, one of them being quaternary, in a single synthetic step.[14] This therefore represents a substantial increase in molecular and stereochemical complexity.



Scheme 5 Synthesis and oxidative cyclisation of compounds **10** and **11**.

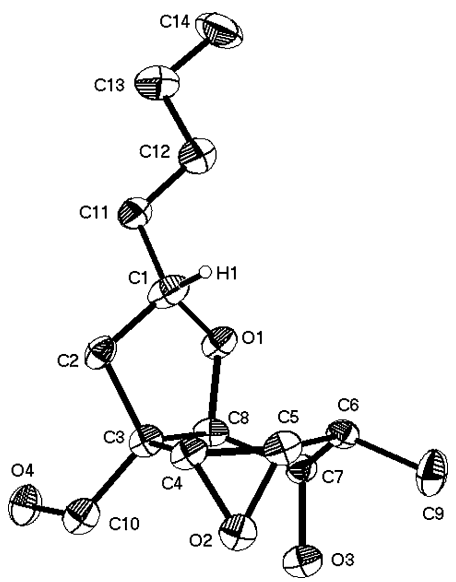


Fig. 2 Structure of compound **13** from single crystal X-ray diffraction data. Thermal ellipsoids are shown at the 50% probability level. Only one of the two independent molecules in the unit cell is shown.

Experimental section

General Experimental Points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Multiplicity in ^{1}H-NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in ^{13}C-NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 micron. Crystallographic data for compounds **3b** and **13** were recorded on a Nonius KappaCCD diffractometer equipped with an Oxford Cryosystem cryostat. The structures were solved by direct methods with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters

were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 or 1.5 times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. Compounds **1a-b**, **1d-f** were prepared as previously described.[7]

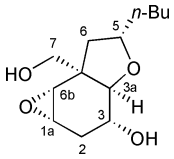
(±)-1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)octan-2-ol (1c)

n-Butyllithium (8.79 ml of a 1.6 M solution in hexanes, 14.1 mmol) was added to a solution of diisopropylamine (1.97 ml, 14.1 mmol) in dry THF (20 ml) at 0 °C, and the resulting solution was allowed to stir at 0 °C for 15 minutes. The reaction mixture was then cooled to −78 °C and the ester (1.74 g, 12.6 mmol) added dropwise. After stirring at −78 °C for 30 minutes, *n*-hexyloxirane (1.8 g, 14.1 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with diethyl ether, the combined extracts being dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O/petroleum ether 1:19) afforded the intermediate lactone (1.64 g, 56%) as a colourless oil. This lactone (1.64 g, 7.01 mmol) was immediately re-dissolved in dry THF (10 ml) and added dropwise to a suspension of $LiAlH_4$ (266 mg, 7.01 mmol) in dry THF (20 ml). The resulting suspension was allowed to stir for 15 minutes before the reaction was quenched with 2 M NaOH. The solution was filtered and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (eluent 2:1 hexane:ethyl acetate) afforded the diol **1c** (1.33 g, 80%) as a colourless oil (found: $M^+ - H_2O$, 220.1837. $C_{15}H_{24}O$ requires M, 220.1827); $\nu_{max.}$ (neat) 3354, 3017, 2930, 2882, 2856, 1615, 1516, 1458, 1377, 1244, 1040, 947, 877, 823 and 711 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.00–5.93 (2 H, m, alkene CH), 5.63 (1 H, app. dq, *J* 10.2, 2.0, alkene CH), 5.37 (1 H, app. dq, *J* 10.9, 2.1, alkene CH), 3.77–3.71 (1 H, m, C*H*OH), 3.30 (2 H, app. s, CH_2OH), 2.68–2.66 (2 H, m, ring CH_2), 1.67 (2 H, broad s, 2 × OH), 1.43 (1 H, dd, *J* 14.2, 9.0, one of CH_2CHOH), 1.36 (1 H, dd, *J* 14.2, 2.3, one of CH_2CHOH), 1.33–1.27 (2 H, m, CH_2), 1.26–1.16 (8 H, m, $(CH_2)_4$) and 0.81 (3 H, t, *J* 6.8, CH_3); δ_C (100 MHz; $CDCl_3$) 130.6 (CH), 129.7 (CH), 128.0 (CH), 127.4 (CH), 70.4 (CH_2), 69.4 (CH), 44.9 (CH_2), 42.3 (C), 38.0 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 26.6 CH_2), 25.6 (CH_2), 22.6 (CH_2) and 14.1 (CH_3); *m*/*z* (TOF EI^+) 220 ($M - H_2O$, 13%), 202 (98), 190 (90), 131 (93), 117 (97) and 104 (100).

General procedure for epoxidation reactions

50% *m*-CPBA (1.04 g, 3.01 mmol) and solid $NaHCO_3$ (379 mg, 4.51 mmol) were added to a solution of cyclohexadiene **1a-1f**, **10**, **11** (1.50 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The solution was stirred for 24 hours, after which an additional 0.1 equivalents of *m*-CPBA was added every hour until complete consumption of the starting material (TLC; typically 2.4 equivalents of *m*-CPBA was required). The reaction was quenched with saturated aqueous sodium thiosulfate solution and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (50 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel to give the pure epoxide.

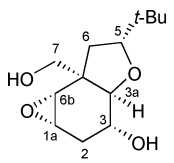
(1*aSR*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Butyl-octahydro-6*a*-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (3a)



3a

Epoxide **3a** was prepared from diene **1a** (316 mg, 1.50 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 1:1 ethyl acetate:hexane) afforded the *title compound* (144 mg, 40%) as a colourless oil (found: M^+, 242.1519. $C_{13}H_{22}O_4$ requires M, 242.1518); $\nu_{max.}$ (neat) 3415, 2922, 2862, 1466, 1426, 1381, 1259, 1127, 1058 and 838 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.88–3.81 (1 H, m, H-5), 3.82 (1 H, d, *J* 10.9, one of H-7), 3.79–3.74 (1 H, m, H-3), 3.74–3.72 (1 H, d, *J* 5.3, H-3a), 3.67 (1 H, d, *J* 10.9, one of H-7), 3.39–3.38 (1 H, m, H-1a), 3.30 (1 H, broad s, OH), 3.16 (1 H, app. dd, *J* 4.1, 1.2, H-6b), 2.60 (1 H, broad s, OH), 2.24–2.17 (1 H, m, one of H-2), 2.13 (1 H, ddd, *J* 15.8, 3.8, 1.3, one of H-2), 2.02 (1 H, dd, J 12.8, 5.3, one of H-6), 1.76 (1 H, dd, *J* 12.8, 9.9, one of H-6), 1.60–1.51 (1 H, m, one of C$H_2$$(CH_2)_2CH_3$), 1.43–1.35 (1 H, m, one of C$H_2$$(CH_2)_2CH_3$), 1.32–1.19 (4 H, m, $(CH_2)_2$) and 0.83 (3 H, t, *J* 7.0, CH_3); δ_C (100 MHz; $CDCl_3$) 78.6 (CH), 78.1 (CH), 67.6 (CH_2), 67.0 (CH), 56.6 (CH), 53.5 (CH), 46.5 (C), 41.8 (CH_2), 35.3 (CH_2), 28.2 (CH_2), 25.7 (CH_2), 22.7 (CH_2) and 14.1 (CH_3); *m*/*z* (TOF EI^+) 242 (M, 1%), 211 (100), 149 (80) and 95 (94).

(1*aSR*,3*RS*,3*aRS*,5*RS*,6*aRS*,6*bRS*)-5-*tert*-Butyl-octahydro-6*a*-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (3b)

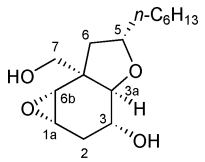


3b

Epoxide **3b** was prepared from diene **1b** (161 mg, 0.77 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 3:1 ethyl acetate:hexane) gave the *title compound* (139 mg, 75%) as a colourless solid, m.p. 86–87 °C (found: $M^+ - H_2O$, 224.1413. $C_{13}H_{20}O_3$ requires M, 224.1412); $\nu_{max.}$ (Nujol) 3388, 2923, 2853, 1259 and 1059 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.89 (1 H, d, *J* 10.9, one of H-7), 3.87–3.85 (1 H, m, H-3), 3.74–3.72 (1 H, m, H-3a), 3.72 (1 H, d, *J* 10.9, one of H-7), 3.60 (1 H, dd, *J* 10.8, 5.8, H-5), 3.46–3.43 (1 H, m, H-1a), 3.17 (1 H, app. dd, *J* 4.0, 1.2, H-6b), 2.75 (2 H, broad s, 2 × OH), 2.25 (1 H, app. dt, *J* 15.8, 2.4, one of H-2), 2.18 (1 H, ddd, *J* 15.8, 3.8, 1.3, one of H-2), 1.93 (1 H, dd, *J* 12.8, 10.8, one of H-6), 1.88 (1 H, dd, *J* 12.8, 5.8, one of H-6) and 0.86 (9 H, s, *t*-Bu); δ_C (100 MHz; $CDCl_3$) 85.8 (CH), 79.3 (CH), 67.9 (CH_2), 67.0 (CH), 56.7 (CH), 53.7 (CH), 46.4 (C), 37.2 (CH_2), 33.6 (C), 25.7 (CH_2) and 25.6 (3 × CH_3); *m*/*z* (TOF MS EI^+) 224 ($M - H_2O$, 3%), 185 (100), 149 (33), 121 (44) and 95 (39).

Crystallographic data for compound 3b. $C_{13}H_{22}O_4$, FW = 242.31, T = 150(2) K, λ = 0.71073 Å, monoclinic, $P2_1/a$, a = 11.8532(3) Å, b = 7.1565(2) Å, c = 16.0428(4), β = 102.4210(10), V = 1329.02(6) Å^3, Z = 4, ρ(calc) = 1.211 Mg/m^3, crystal size = 0.38 × 0.25 × 0.10 mm^3, reflections collected = 20521, independent reflections = 3023, R(int)= 0.109, parameters = 160, R1 [I>2σ(I)]= 0.075, wR2 [I>2σ(I)] = 0.19, R1 (all data) = 0.10, wR2 (all data) = 0.21, Flack parameter = 0.056(10).

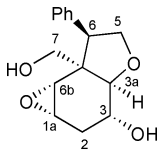
(1*aSR*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Hexyl-octahydro-6*a*-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (3c)



3c

Epoxide **3c** was prepared from diene **1c** (509 mg, 2.14 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (209 mg, 36%) as a colourless solid, m.p. 72–73 °C (found: M$^+$ – H_2O, 252.1725. $C_{15}H_{24}O_3$ requires M, 252.1725); $\nu_{max.}$ (Nujol) 3406, 2922, 2854, 1249, 1130, 1075, 1057, 1021, 932, 840, 721 and 668 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.89–3.84 (1 H, m, H-5), 3.85 (1 H, d, *J* 10.8, one of H-7), 3.82–3.77 (1 H, m, H-3), 3.75 (1 H, d, *J* 3.9, H-3a), 3.69 (1 H, d, *J* 10.8, one of H-7), 3.40–3.37 (1 H, m, H-1a), 3.26 (1 H, app. dd, *J* 4.0, 1.2, H-6b), 2.22 (1 H, app. dt, *J* 15.8, 2.5, one of H-2), 2.13 (1 H, ddd, *J* 15.8, 3.8, 1.4, one of H-2), 2.03 (1 H, dd, *J* 12.8, 5.3, one of H-6), 1.75 (1 H, dd, *J* 12.8, 9.9, one of H-6), 1.58–1.50 (2 H, m, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.43–1.14 (10 H, m, (CH$_2$)$_4$ and 2 × OH) and 0.81 (3 H, t, *J* 6.8, CH$_3$); δ_C (100 MHz; $CDCl_3$) 78.8 (CH), 78.1 (CH), 68.0 (CH$_2$), 67.0 (CH), 56.6 (CH), 53.5 (CH), 46.5 (C), 41.9 (CH$_2$), 35.7 (CH$_2$), 31.8 (CH$_2$), 29.3 (CH$_2$), 26.0 (CH$_2$), 25.8 (CH$_2$) 22.6 (CH$_2$) and 14.1 (CH$_3$); *m/z* (TOF ES$^+$) 252 (M – H_2O, 40%), 185 (100), 123 (98) and 95 (88).

(1*aSR*,3*RS*,3*aRS*,6*RS*,6*aRS*,6*bRS*)-Octahydro-6*a*-(hydroxymethyl)-6-phenyl-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (3e)

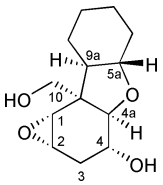


3e

Epoxide **3e** was prepared from diene **1e** (136 mg, 0.59 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 3:2 hexane:ethyl acetate) afforded the *title compound* (85 mg, 55%) as a colourless solid, m.p. 89–90 °C (found: M$^+$ – H_2O, 244.1091. $C_{15}H_{16}O_3$ requires M, 244.1099); $\nu_{max.}$ (Nujol) 3488, 3335, 2923, 2851, 1076, 1059 and 1040 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39–7.25 (5 H, m, Ph), 4.20 (1 H, dd, *J* 9.1, 5.0, one of H-5), 4.10 (1 H, dd, *J* 9.1, 6.8, one of H-5), 4.03–3.98 (1 H, m, H-3), 3.92 (1 H, d, *J* 11.0, one of H-7), 3.90 (1 H, d, *J* 11.0, one of H-7), 3.86–3.83 (1 H, m, H-3a), 3.71 (1 H, dd, *J* 6.8, 5.0, H-6), 3.50 (1 H, broad s, OH), 3.15–3.11 (1 H, m, H-1a), 2.77 (1 H, app. dd, *J* 4.2, 1.5, H-6b), 2.34–2.23 (2 H, m, H-2) and 1.65 (1 H, broad s, OH); δ_C (100 MHz; $CDCl_3$) 139.1 (C), 128.6 (2 × CH), 128.5 (2 × CH), 127.2 (CH), 80.6 (CH), 72.5 (CH$_2$), 66.7 (CH$_2$), 66.3 (CH), 55.4 (CH), 53.6 (CH), 51.5 (CH), 48.5 (C) and 25.7 (CH$_2$); *m/z* (TOF ES$^+$) 244 (M – H_2O, 9%), 214 (100), 171 (21) and 104 (85).

Stereochemistry was confirmed by nOe enhancement between H-3a and H-6 and between H-6b and phenyl.

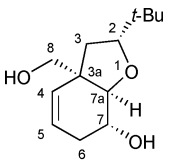
(1*RS*,2*SR*,4*RS*,4*aRS*,5*aSR*,9*aRS*,9*bSR*)-9*b*-(Hydroxymethyl)-1,2-epoxydodecahydrodibenzo[*b*,*d*]furan-4-ol (3f)



3f

Epoxide **3f** was prepared from diene **1f** (85 mg, 0.41 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 1:1 ethyl acetate:hexane) afforded the *title compound* (51 mg, 52%) as a colourless solid, m.p. 153–154 °C (found: M$^+$ – H_2O, 222.1253. $C_{13}H_{18}O_3$ requires M, 222.1256); $\nu_{max.}$ (Nujol) 3417, 2927, 2854, 1064, 1046 and 722 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.92–3.86 (2 H, m, H-4 and H-4a), 3.91 (1 H, d, *J* 11.0, one of H-10), 3.87 (1 H, d, *J* 11.0, one of H-10), 3.47–3.44 (1 H, m, H-2), 3.36–3.29 (2 H, m, H-1 and H-5a), 2.35 (1 H, app. broad d, *J* 16.0, one of H-3), 2.20–2.01 (4 H, m, one of H-3, H-9a and 2 × OH), 1.85–1.77 (2 H, m, cyclohexyl CH$_2$), 1.74–1.66 (2 H, m, cyclohexyl CH$_2$) and 1.39–1.13 (4 H, m, 2 × cyclohexyl CH$_2$); δ_C (100 MHz; $CDCl_3$) 81.1 (CH), 79.2 (CH), 67.7 (CH), 67.1 (CH$_2$), 53.8 (CH), 53.5 (CH), 52.3 (CH), 45.8 (C), 32.2 (CH$_2$), 25.7 (CH$_2$), 25.6 (CH$_2$), 25.2 (CH$_2$) and 23.9 (CH$_2$); *m/z* (TOF ES$^+$) 222 (M – H_2O, 1%), 192 (86) and 79 (100).

(2*RS*,3*aRS*,7*RS*,7*aRS*)-2-*tert*-Butyl-3*a*-(hydroxymethyl)-2,3,3a,6,7,7a-hexahydro-benzo[*b*]furan-7-ol (4)



4

Vanadyl acetylacetonate (73 mg, 0.276 mmol) and *tert*-butyl hydroperoxide (1.22 ml of 5.0–6.0 M solution in decane, 6.08 mmol) were added to a solution of diol **1b** (580 mg, 2.76 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (eluent hexane:ethyl acetate 2:1) afforded the *title compound* (93 mg, 15%) as a colourless solid, m.p. 83–85 °C (found: MH$^+$ – H_2O, 209.1532. $C_{13}H_{21}O_2$

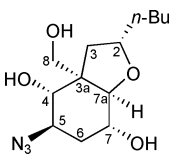
requires M, 209.1542); $\nu_{max.}$ (Nujol) 3186, 2922, 2856, 1205, 1171, 1131, 1043, 964, 910, 836, 776 and 746 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.83–5.79 (1 H, m, H-5), 5.43 (1 H, d, *J* 10.2, H-4), 4.22 (2 H, broad s, 2 × OH), 4.05–4.01 (1 H, m, H-7), 3.88 (1 H, d, *J* 3.9, H-7a), 3.62 (1 H, d, *J* 10.4, one of H-8), 3.55 (1 H, dd, *J* 10.5, 5.6, H-2), 3.46 (1 H, d, *J* 10.4, one of H-8), 2.36–2.31 (1 H, m, one of H-6), 2.04 (1 H, app. dd, *J* 17.9, 4.7, one of H-6), 1.52 (1 H, dd, *J* 12.1, 10.5, one of H-3), 1.48 (1 H, dd, *J* 12.1, 5.6, one of H-3) and 0.82 (9 H, d, $C(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 129.7 (CH), 126.5 (CH), 85.2 (CH), 83.5 (CH), 68.0 (CH_2), 64.7 (CH), 48.8 (C), 36.6 (CH_2), 33.5 (C), 28.2 (CH_2) and 25.7 (3 × CH_3); *m/z* (TOF AP$^+$) 209 ($MH^+ - H_2O$, 100%). In addition, compound **3b** (34 mg, 5%) was obtained.

Stereochemistry was confirmed by nOe enhancement between H-2 and one of H-6.

General procedure for azide ring-openings

Sodium azide (285 mg, 4.38 mmol) and ammonium chloride (117 mg, 2.19 mmol) were added portionwise to a solution of the epoxide **3a-3c**, **3e**, **3f** (0.44 mmol) in an 8:1 mixture of methanol/water (9 ml). The solution was stirred at 80 °C for 24 hours before being cooled to room temperature and quenched with water. The crude product was extracted into CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed *in vacuo.* The residue was purified by flash column chromatography on silica gel to give the pure azide **5**.

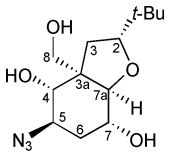
(2*SR*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-5-Azido-2-butyl-octahydro-3*a*-(hydroxymethyl)benzofuran-4,7-diol (5a)



5a

Azide **5a** was prepared from epoxide **3a** (106 mg, 0.44 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (45 mg, 36%) as a colourless solid, m.p. 107–108 °C (found: $M^+ - H_2O$, 267.1588. $C_{13}H_{21}N_3O_3$ requires M, 267.1583); $\nu_{max.}$ (Nujol) 3185, 2923, 2853, 2111, 1082, 721 and 668 cm^{-1}; δ_H (400 MHz; CD_3OD) 4.02 (1 H, app. tt, *J* 12.9, 6.5, H-2), 3.91 (1 H, ddd, *J* 12.3, 10.3, 4.3, H-5 or H-7), 3.89–3.85 (2 H, m, one of H-8 and H-5 or H-7), 3.69 (1 H, app. broad s, H-4 or H-7a), 3.48 (1 H, d, *J* 11.0, one of H-8), 3.40 (1 H, d, *J* 10.2, H-4 or H-7a), 2.18 (1 H, dd, *J* 12.7, 6.5, one of H-3), 1.88 (1 H, app. dt, *J* 13.8, 3.1, one of H-6), 1.65–1.49 (2 H, m, one of H-6 and butyl H), 1.44–1.18 (6 H, m, one of H-3 and butyl H) and 0.86 (3 H, t, *J* 6.8, CH_3); δ_C (100 MHz; CD_3OD) 85.1 (CH), 78.3 (CH), 76.5 (CH), 66.9 (CH), 65.0 (CH_2), 60.9 (CH), 53.9 (C), 41.3 (CH_2), 37.5 (CH_2), 34.6 (CH_2), 29.3 (CH_2), 23.8 (CH_2) and 14.5 (CH_3); *m/z* (TOF ES$^+$) 267 ($M - H_2O$, 26%), 208 (100), 181 (58), 155 (64) and 72 (81).

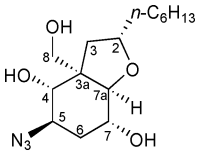
(2*RS*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-2-*tert*-Butyl-5-azido-octahydro-3*a*-(hydroxymethyl)benzofuran-4,7-diol (5b)



5b

Azide **5b** was prepared from epoxide **3b** (101 mg, 0.42 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (80 mg, 67%) as a colourless solid, m.p. 155–156 °C (found: $M^+ - H_2O$, 267.1581. $C_{13}H_{21}N_3O_3$ requires M, 267.1583); $\nu_{max.}$ (Nujol) 3192, 2920, 2853, 2113, 1258 and 1070 cm^{-1}; δ_H (400 MHz; CD_3OD) 4.03–3.92 (3 H, m, one of H-8, H-5 and H-7), 3.78 (1 H, dd, *J* 9.9, 6.6, H-2), 3.69 (1 H, app. broad s, H-4 or H-7a), 3.54 (1 H, d, *J* 11.0, one of H-8), 3.48 (1 H, d, *J* 10.3, H-4 or H-7a), 2.02 (1 H, app. dd, *J* 12.9, 6.6, one of H-3), 1.93 (1 H, app. broad d, *J* 13.4, one of H-6), 1.67 (1 H, ddd, *J* 13.4, 12.7, 3.0, one of H-6), 1.57 (1 H, app. dd, *J* 12.9, 9.9, one of H-3) and 0.88 (9 H, s, *t*-Bu); δ_C (100 MHz; CD_3OD) 86.5 (CH), 86.1 (CH), 76.5 (CH), 67.0 (CH), 65.0 (CH_2), 60.8 (CH), 53.9 (C), 35.9 (CH_2), 35.6 (C), 34.5 (CH_2) and 25.9 (3 × CH_3); *m/z* (TOF MS EI$^+$) 267 ($M - H_2O$, 34%), 240 (17), 182 (100), 137 (38), 111 (33) and 81 (28).

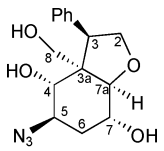
(2*SR*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-5-Azido-2-hexyl-octahydro-3*a*-(hydroxymethyl)benzofuran-4,7-diol (5c)



5c

Azide **5c** was prepared from epoxide **3c** (67 mg, 0.25 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (75 mg, 96%) as a colourless solid, m.p. 97–98 °C (found: $M^+ + NH_4^+$, 331.2359. $C_{15}H_{31}N_4O_4$ requires M, 331.2345); $\nu_{max.}$ (Nujol) 3199, 2927, 2853, 2114, 1256, 1183, 1068, 1037, 1009, 961, 921 and 802 cm^{-1}; δ_H (400 MHz; CD_3OD) 4.13–4.03 (1 H, m, H-2), 3.97 (1 H, ddd, *J* 12.2, 10.2, 4.3, H-5 or H-7), 3.95–3.91 (2 H, m, one of H-8 and H-5 or H-7), 3.76–3.74 (1 H, m, H-4 or H-7a), 3.55 (1 H, d, *J* 11.0, one of H-8), 3.46 (1 H, d, *J* 10.2, H-4 or H-7a), 2.24 (1 H, dd, *J* 12.7, 6.5, one of H-3), 1.94 (1 H, app. broad d, *J* 13.7, one of H-6), 1.67 (1 H, ddd, *J* 13.7, 12.4, 3.0, one of H-6), 1.62–1.48 (1 H, m, hexyl H), 1.49–1.24 (9 H, m, hexyl H), 1.37 (1 H, dd, *J* 12.7, 9.0, one of H-3) and 0.91 (3 H, t, *J* 6.8, CH_3); δ_C (100 MHz; CD_3OD) 85.1 (CH), 78.3 (CH), 76.5 (CH), 66.9 (CH), 65.0 (CH_2), 60.9 (CH), 53.9 (C), 41.3 (CH_2), 37.8 (CH_2), 34.6 (CH_2), 33.1 (CH_2), 30.5 (CH_2), 27.1 (CH_2), 23.7 (CH_2) and 14.5 (CH_3); *m/z* (TOF ES$^+$) 331 ($M + NH_4^+$, 67%), 287 (22), 286 (100), 268 (7), 252 (2) and 222 (1).

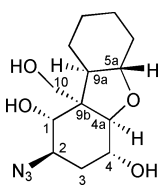
(3*RS*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-5-Azido-octahydro-3*a*-(hydroxymethyl)-3-phenylbenzofuran-4,7-diol (5e)



5e

Azide **5e** was prepared from epoxide **3e** (45 mg, 0.17 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 1:1 hexane:ethyl acetate) afforded the *title compound* (35 mg, 67%) as a colourless solid, m.p. 140–141 °C (found: $M^+ + NH_4^+$, 323.1734. $C_{15}H_{23}N_4O_4$ requires M, 323.1719); $\nu_{max.}$ (Nujol) 3260, 2924, 2854, 2100, 1246, 1158, 1061 and 722 cm^{-1}; δ_H (400 MHz; CD_3OD) 7.24–7.12 (5 H, m, Ph), 4.21 (1 H, dd, *J* 9.9, 8.9, one of H-2), 4.03 (1 H, app. t, *J* 8.7, one of H-2), 3.99 (1 H, d, *J* 10.9, one of H-8), 3.90 (1 H, app. q, *J* 3.1, H-5 or H-7), 3.86 (1 H, app. d, *J* 2.8, H-4 or H-7a), 3.84–3.78 (1 H, m, H-5 or H-7), 3.68 (1 H, d, *J* 9.9, H-4 or H-7a), 3.53 (1 H, d, *J* 10.9, one of H-8), 3.40 (1 H, app. t, *J* 9.5, H-3), 1.87 (1 H, app. dt, *J* 13.5, 3.9, one of H-6) and 1.71–1.64 (1 H, m, one of H-6); δ_C (100 MHz; CD_3OD) 136.7 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 126.8 (CH), 126.6 (CH), 85.9 (CH), 71.1 (CH), 69.1 (CH_2), 65.8 (CH), 62.7 (CH_2), 60.8 (CH), 53.9 (C), 51.0 (CH) and 32.5 (CH_2); *m*/*z* (TOF ES^+) 323 ($M + NH_4^+$, 100%), 278 (97), 260 (14) and 242 (1).

(1*RS*,2*RS*,4*RS*,4a*RS*,5a*SR*,9a*RS*,9b*SR*)-2-Azido-9*b*-(hydroxymethyl)dodecahydrodibenzo[*b*,*d*]furan-1,4-diol (5f)



5f

Azide **5f** was prepared from epoxide **3f** (78 mg, 0.33 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 1:1 hexane:ethyl acetate) afforded the *title compound* (42 mg, 46%) as a colourless solid, m.p. 156–157 °C; $\nu_{max.}$ (Nujol) 3418, 2922, 2103, 1303, 1064, 1036, 979, 826 and 722 cm^{-1}; δ_H (400 MHz; CD_3OD) 3.75 (1 H, d, *J* 11.1, one of H-10), 3.72 (1 H, app. broad d, *J* 3.6, H-1 or H-4a), 3.70–3.65 (1 H, broad m, H-2 or H-4), 3.60 (1 H, d, *J* 11.1, one of H-10), 3.33–3.26 (2 H, m, H-5a and H-2 or H-4), 3.18 (1 H, app. d, *J* 3.1, H-1 or H-4a), 2.15 (1 H, app. broad d, *J* 16.0, one of H-3), 2.04 (1 H, app. ddd, *J* 16.0, 3.7, 1.0, one of H-3), 2.00–1.91 (2 H, broad m, H-9a and one of CH_2), 1.70–1.62 (3 H, broad m, one of CH_2 and CH_2) and 1.33–1.10 (4 H, m, 2 × CH_2); δ_C (100 MHz; CD_3OD) 80.9 (CH), 78.9 (CH), 67.5 (CH), 65.0 (CH_2), 53.0 (CH), 52.8 (CH), 51.8 (CH), 45.5 (C), 32.1 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 24.7 (CH_2) and 23.6 (CH_2).

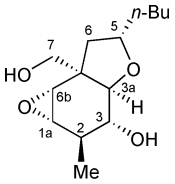
(±)-1-((1,4-*trans*)-1-(Hydroxymethyl)-4-methylcyclohexa-2,5-dienyl)hexan-2-ol (10) and (±)-1-((1,4-*cis*)-1-(hydroxymethyl)-4-methylcyclohexa-2,5-dienyl)hexan-2-ol (11)

n-Butyllithium (10.1 ml of a 2.5 M solution in hexanes, 25.3 mmol) was added to a solution of diisopropylamine (3.55 ml, 25.3 mmol) in dry THF (30 ml) at −78 °C and the resulting solution was allowed to warm to room temperature. After re-cooling to −78 °C, the ester **7** (3.50 g, 23.0 mmol) was added dropwise. After stirring for 30 minutes at −78 °C, *n*-butyloxirane **8** (3.61 ml, 29.9 mmol) was added and the reaction mixture allowed to warm to 5 °C over 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution (50 ml) and extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo* affording the crude intermediate lactones **9** (5.44 g) as a yellow oil. This lactone (3.99 g, 18.1 mmol) was redissolved in dry THF (20 ml) and added dropwise to a suspension of $LiAlH_4$ (688 mg, 18.1 mmol) in dry THF (30 ml). The resulting suspension was allowed to stir for 15 minutes before the reaction was quenched slowly with 2 M NaOH. The solution was filtered and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (eluent hexane:diethyl ether 2:1) afforded a 1:1 mixture of diols **10** and **11** (2.56 g, 63%) as a colourless oil. Further chromatography (eluent hexane:diethyl ether 4:1) provided pure samples of the individual diastereoisomers.

Data for compound 10. Found: $M^+ - H_2O$, 206.1668. $C_{14}H_{22}O$ requires M, 206.1671; $\nu_{max.}$ (neat) 3384, 3011, 2957, 2928, 2871, 1636, 1456, 1378, 1278, 1122, 1037, 918, 804 and 746 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.97–5.88 (2 H, m, alkene CH), 5.65 (1 H, app. dt, *J* 10.3, 2.3, alkene CH), 5.38 (1 H, app. dt, *J* 10.8, 2.1, alkene CH), 3.82–3.74 (1 H, broad m, C*H*OH), 3.35 (2 H, s, CH_2OH), 2.85–2.77 (1 H, broad m, C*H*CH_3), 1.99 (2 H, broad s, 2 × OH), 1.50 (1 H, dd, *J* 14.2, 9.1, one of CCH_2), 1.42 (1 H, dd, *J* 14.2, 2.1, one of CCH_2), 1.38–1.22 (6 H, broad m, $(CH_2)_3$), 1.06 (3 H, d, *J* 7.3, CH_3) and 0.88 (3 H, t, *J* 6.8, CH_3); δ_C (100 MHz; $CDCl_3$) 134.4 (CH), 133.7 (CH), 129.5 (CH), 128.4 (CH), 70.4 (CH_2), 69.2 (CH), 44.6 (CH_2), 42.7 (C), 37.6 (CH_2), 30.9 (CH), 27.8 (CH_2), 22.8 (CH_2), 22.1 (CH_3) and 14.1 (CH_3); *m*/*z* (TOF EI^+) 206 ($M - H_2O$, 32%), 188 (100), 176 (62), 159 (50), 145 (97) and 131 (99).

Data for compound 11. Found: $M^+ - H_2O$, 207.1757. $C_{14}H_{23}O$ requires M, 207.1749; $\nu_{max.}$ (Neat) 3355, 3012, 2957, 2928, 2871, 1457, 1124, 1038, 945, 899, 802 and 746 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.96–5.89 (2 H, m, alkene CH), 5.64 (1 H, app. dt, *J* 10.1, 2.0, alkene CH), 5.38 (1 H, app. dt, *J* 10.6, 2.0, alkene CH), 3.82–3.75 (1 H, broad m, C*H*OH), 3.34 (2 H, s, CH_2OH), 2.86–2.77 (1 H, broad m, C*H*CH_3), 1.82 (2 H, broad s, 2 × OH), 1.51 (1 H, dd, *J* 14.2, 9.0, one of CCH_2), 1.44 (1 H, dd, *J* 14.2, 2.3, one of CCH_2), 1.41–1.22 (6 H, broad m, $(CH_2)_3$), 1.11 (3 H, d, *J* 7.3, CH_3) and 0.89 (3 H, t, *J* 6.7, CH_3); δ_C (100 MHz; $CDCl_3$) 134.2 (CH), 133.7 (CH), 129.5 (CH), 128.5 (CH), 70.0 (CH_2), 69.3 (CH), 44.9 (CH_2), 42.7 (C), 37.7 (CH_2), 30.9 (CH), 27.8 (CH_2), 22.7 (CH_2), 22.4 (CH_3) and 14.1 (CH_3); *m*/*z* (TOF AP^+) 207 ($M - H_2O$, 30%), 189 (100), 146 (3), 118 (3) and 91 (1).

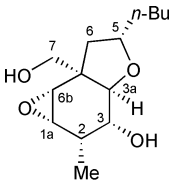
(1*aSR*,2*RS*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Butyl-octahydro-6*a*-(hydroxymethyl)-2-methyl-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (12)



12

Epoxide **12** was prepared from diol **10** (105 mg, 0.47 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 2:1 diethyl ether:hexane) afforded the *title compound* (24 mg, 20%) as a colourless oil (found: $M^+ - H_2O$, 238.1573. $C_{14}H_{22}O_3$ requires M, 238.1569); $\nu_{max.}$ (CH_2Cl_2) 3410, 2931, 1645, 1456, 1379, 1034, 899 and 837 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.95 (1 H, app. quintet, *J* 6.9, H-5), 3.76 (1 H, d, *J* 10.8, one of H-7), 3.69 (1 H, d, *J* 10.8, one of H-7), 3.65 (1 H, d, *J* 6.9, H-3a), 3.42 (1 H, app. dt, *J* 6.9, 4.8, H-3), 3.16 (1 H, d, *J* 3.8, H-1a), 3.00 (1 H, dd, *J* 3.8, 1.0, H-6b), 2.56 (2 H, broad s, 2 × OH), 2.09–2.02 (1 H, m, H-2), 1.97 (1 H, dd, *J* 13.1, 7.6, one of H-6), 1.71 (1 H, dd, *J* 13.1, 7.1, one of H-6), 1.61–1.52 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.45–1.36 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.30–1.22 (4 H, m, $(CH_2)_2$), 1.18 (3 H, d, *J* 7.5, CH_3) and 0.83 (3 H, t, *J* 7.0, CH_3); δ_C (100 MHz; $CDCl_3$) 81.5 (CH), 77.0 (CH), 70.7 (CH), 67.9 (CH_2), 57.5 (CH), 56.9 (CH), 47.2 (C), 38.6 (CH_2), 36.2 (CH_2), 34.6 (CH), 28.4 (CH_2), 22.7 (CH_2), 15.9 (CH_3) and 14.1 (CH_3); *m*/*z* (TOF EI^+) 238 ($M - H_2O$, 9%), 190 (75), 147 (100), 121 (82) and 91 (71).

(1*aSR*,2*SR*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Butyl-octahydro-6*a*-(hydroxymethyl)-2-methyl-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (13)



13

Epoxide **13** was prepared from diol **11** (278 mg, 1.24 mmol) according to the general procedure above. Purification by flash column chromatography (eluent 2:1 diethyl ether:hexane) afforded the *title compound* (120 mg, 38%) as a colourless solid, m.p. 66–68 °C (found: $M^+ - H_2O$, 238.1574. $C_{14}H_{22}O_3$ requires M, 238.1569); $\nu_{max.}$ (Nujol) 3394, 2926, 2853, 1644, 1152, 1053 and 834 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.86–3.77 (3 H, m, one of H-7, H-3a and H-5), 3.66 (1 H, d, *J* 10.9, one of H-7), 3.59 (1 H, app. broad s, H-3), 3.21 (1 H, d, *J* 4.2, H-1a), 3.17 (1 H, dd, *J* 4.2 1.5, H-6b), 2.94 (2 H, broad s, 2 × OH), 2.23 (1 H, app. qd, *J* 7.3, 3.3, H-2), 2.02 (1 H, dd, *J* 12.8, 5.1, one of H-6), 1.77 (1 H, dd, *J* 12.8, 10.2, one of H-6), 1.59–1.51 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.42–1.34 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.25 (3 H, d, *J* 7.3, CH_3) 1.25–1.20 (4 H, m, $(CH_2)_2$) and 0.83 (3 H, t, *J* 7.0, CH_3); δ_C (100 MHz; $CDCl_3$) 79.9 (CH), 78.3 (CH), 71.4 (CH), 67.9 (CH_2), 58.9 (CH), 58.0 (CH), 46.7 (C), 42.1 (CH_2), 35.3 (CH_2), 28.2 (CH_2), 27.9 (CH), 22.8 (CH_2), 14.4 (CH_3) and 14.1 (CH_3); *m*/*z* (TOF EI^+) 238 ($M - H_2O$, 12%), 190 (69), 147 (100) and 121 (86).

Crystallographic data for compound 13. $C_{14}H_{24}O_4$, FW = 256.33, T = 150(2) K, λ = 0.71073 Å, triclinic, P-1, a = 6.3080(2) Å, b = 13.5420(5) Å, c = 17.5900(7) Å, α = 73.293(2)°, β = 81.756(2)°, γ = 79.108(2)°, V = 1406.88(9) $Å^3$, Z = 4, ρ(calc) = 1.210 Mg/m^3, crystal size = 0.50 × 0.18 × 0.08 mm^3, reflections collected = 7267, independent reflections = 4761, R(int) = 0.079, parameters = 333, R1 [I>2σ(I)]= 0.14, wR2 [I>2σ(I)] = 0.34, R1 (all data) = 0.19, wR2 (all data) = 0.37. The asymmetric unit of compound **13** consists of two independent molecules. The higher R indices for **13** are due to the poor quality of the available sample and thus data were recorded using a twinned crystal.

Conclusion

In summary, cyclohexadiene-diols **1a-1f**, **10** and **11** undergo diastereoselective epoxidation followed by diastereoselective ring-opening to give highly functionalised benzo[*b*]furan derivatives **3**, **12** and **13** with excellent diastereocontrol.

Acknowledgements

We are extremely grateful to AstraZeneca and the EPSRC for financial support.

References

1 A. Studer and F. Schleth, *Synlett*, 2005, 3033.
2 F. Villar, T. Kolly-Kovac, O. Equey and P. Renaud, *Chem. Eur. J.*, 2003, **9**, 1566; F. Villar, O. Equey and P. Renaud, *Org. Lett.*, 2000, **2**, 1061; D. P. Curran, H. Qi and N. C. De Mello, *J. Am. Chem. Soc.*, 1994, **116**, 8430; D. P. Curran, S. J. Geib and C.-H. Lin, *Tetrahedron: Asymmetry*, 1994, **5**, 199; R. Lebeuf, F. Robert, K. Schenk and Y. Landais, *Org. Lett.*, 2006, **8**, 4755; A. Studer and F. Schleth, *Angew. Chem. Int. Ed.*, 2004, **43**, 313; F. Schleth, T. Vogler, K. Harms and A. Studer, *Chem. Eur. J.*, 2004, **10**, 4171; P. Wipf, S. R. Rector and H. Takahashi, *J. Am. Chem. Soc.*, 2002, **124**, 14848; T. M. Nguyen, R. J. Seifert, D. R. Mowrey and D. Lee, *Org. Lett.*, 2002, **4**, 3959; D. Bland, D. J. Hart and S. Lacoutiere, *Tetrahedron*, 1997, **53**, 8871; P. Wipf, Y. Kim and D. M. Goldstein, *J. Am. Chem. Soc.*, 1995, **117**, 11106; H. Fujioka, S. Kitagaki, N. Ono, H. Kitagawa, Y. Kita and K. Matsumoto, *Tetrahedron: Asymmetry*, 1994, **5**, 333; P. Wipf and Y. Kim, *Tetrahedron Lett.*, 1992, **33**, 5477; S. F. Martin and C. L. Campbell, *J. Org. Chem.*, 1988, **53**, 3184; S. F. Martin, S. K. Davidsen and T. A. Puckette, *J. Org. Chem.*, 1987, **52**, 1962; R. S. Grainger, T. Tisselli and J. W. Steed, *Org. Biomol. Chem.*, 2004, **2**, 151; M. C. Carreño, M. P. González and K. N. Houk, *J. Org. Chem.*, 1997, **62**, 9128.
3 R. Angelaud, O. Babot, T. Charvat and Y. Landais, *J. Org. Chem.*, 1999, **64**, 9613; Y. Landais and E. Zekri, *Eur. J. Org. Chem.*, 2002, 4037; Y. Landais and E. Zekri, *Tetrahedron Lett.*, 2001, **42**, 6547.
4 For a review see M. S. Gueltekin, M. Celik and M. Balci, *Curr. Org. Chem.*, 2004, **8**, 1159. For approaches featuring oxidation of cyclohexa-1,4-dienes see: N. Abd Rahman and Y. Landais, *Curr. Org. Chem.*, 2002, **6**, 1369; R. Angelaud, Y. Landais and L. Parra-Rapado, *Tetrahedron Lett.*, 1997, **38**, 8845; R. Angelaud and Y. Landais, *Tetrahedron Lett.*, 1997, **38**, 8841; R. Angelaud, Y. Landais and K. Schenk, *Tetrahedron Lett.*, 1997, **38**, 1407; R. Angelaud and Y. Landais, *J. Org. Chem.*, 1996, **61**, 5202.
5 M. C. Elliott and N. N. E. El Sayed, *Tetrahedron Lett.*, 2005, **46**, 2957.
6 M. C. Elliott, N. N. E. El Sayed and J. S. Paine, *Eur. J. Org. Chem.*, 2007, 792; M. Butters, M. C. Elliott, J. Hill-Cousins, J. S. Paine and A. W. J. Westwood, *Tetrahedron Lett.*, 2008, **49**, 4446.
7 M. Butters, M. C. Elliott, J. Hill-Cousins, J. S. Paine and J. K. E. Walker, *Org Lett.*, 2007, **9**, 3635.

8 G. Binmore, L. Cardellini and J. C. Walton, *J. Chem. Soc. Perkin Trans. 2*, 1997, 757.
9 J. C. Lorenz, M. Frohn, X. Zhou, J.-R. Zhang, Y. Tang, C. Burke and Y. Shi, *J. Org. Chem.*, 2005, **70**, 2904.
10 Crystallographic data for compounds **3b** and **13** have been deposited with the CCDC, reference numbers 694523 and 694524 respectively, and can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.
11 M. Egido-Gabás, P. Serrano, J. Casas, A. Liebaria and A. Delgado, *Org. Biomol. Chem.*, 2005, **3**, 1195.
12 A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, 1949, **32**, 275; J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 1961, 758.
13 M. C. Elliott, N. N. E. El Sayed and J. S. Paine, *Org. Biomol. Chem.*, 2008, **6**, 2611.
14 M. Koutsaplis, P. C. Andrews, S. D. Bull, P. J. Duggan, B. H. Fraser and P. Jensen, *Chem. Commun.*, 2007, 3580.

