A Reinvestigation of the Synthesis of *trans*-(±)-1,2,3,4,4a,10a-Hexahydro[1,4]benzodioxino[2,3-*c*]pyridine

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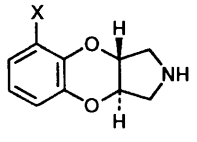
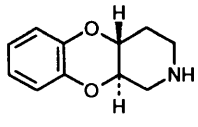
A reinvestigation of the reaction of *threo*-(±)-2,3-dibromopentane-1,5-diol **5** with the disodium salt of catechol has shown that the product is (±)-1-(2,3-dihydro[1,4]benzodioxin-2-yl)propane-1,3-diol **20** and not *trans*-(±)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-2,3-dihydro[1,4]benzodioxin **12**, as assumed previously. Consequently *trans*-(±)-1,2,3,4,4a,10a-hexahydro[1,4]benzodioxino-[2,3-*c*] pyridine **3** could not have been isolated earlier, and we now report its unambiguous synthesis *via* the epoxide **8** as well as the crystal structure of the diol **20**.

Recently (±)-*trans*-2,3,3a,9a-tetrahydro[1,4]benzodioxino-[2,3-*c*]pyrrole **1** was reported as a potent and selective α_2-antagonist, the 5-fluoro analogue **2** (fluparoxan) of which has been considered for use in the treatment of depression and male sexual dysfunction.[1] Because of the close similarity between compounds **1** and **3** we were interested in preparing the latter and comparing the pharmacological properties of the two. The corresponding *cis*-isomer **4** was originally described by Coulson,[2] followed by Berthold[3] and finally by Finch[4] who demonstrated that the synthesis as described by the first two groups gave a mixture of two compounds, one of which was compound **4**. A synthesis of the *trans*-isomer **3** was reported by Berthold[3] starting from racemic *threo*-2,3-dibromopentane-1,5-diol **5** and the disodium salt of catechol. The use of unprotected 2,3-dibromopentane-1,5-diol under basic conditions seemed perilous to us and so it was decided to use the longer but unambiguous route shown in Scheme 1, which was originally developed for the synthesis of the analogous [1,4]benzodioxinopyrrole derivatives **1** and **2**.[5]

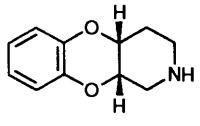


(±)

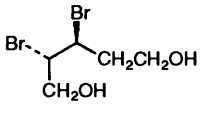
1 X = H
2 X = F



(±) **3**

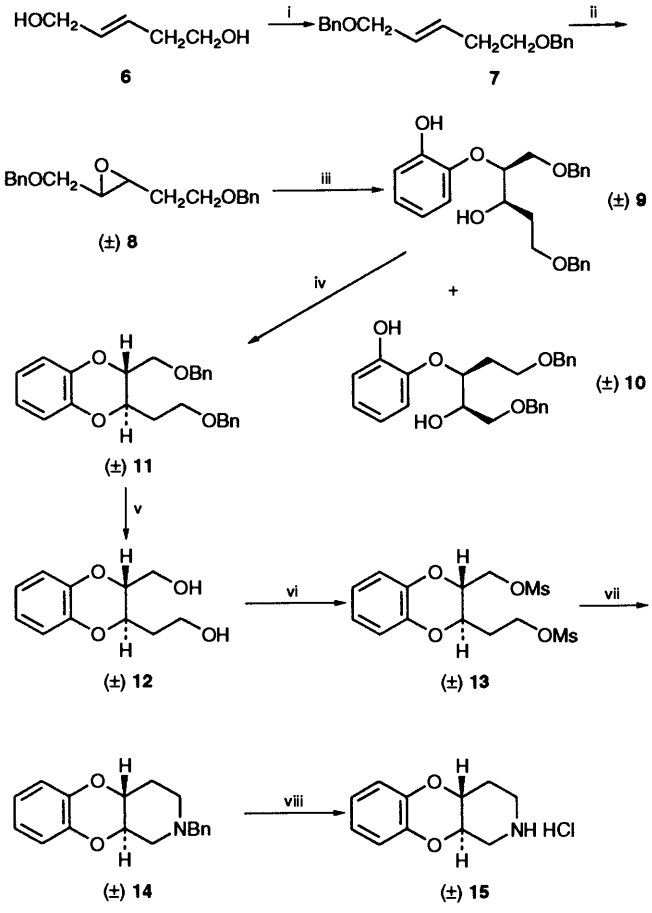


(±) **4**



(±) **5**

trans-Pent-2-ene-1,5-diol[6] **6** was first converted into the dibenzyl ether **7** and then into the epoxide **8**, which was then treated with catechol in the presence of sodium ethoxide in ethanol to give a mixture of the regioisomeric hydroxy phenols **9** and **10**. Cyclisation of the mixture of the hydroxy phenols **9** and **10** with triphenylphosphine–carbon tetrachloride–triethylamine in refluxing acetonitrile[7] gave the benzodioxane **11**. Hydrogenolysis of the benzyl ethers of compound **11** over 10% Pd–C gave the benzodioxane diol **12** (m.p. 80–81 °C). By contrast the previous workers[3] reported a lower melting point (48–50 °C) for the diol **12** and no further data. Reaction of the diol **12** with methanesulfonyl chloride (2 equiv.) in the presence of triethylamine gave the dimesylate **13**. The ^{1}H NMR spectrum of the dimesylate as previously reported[3] showed an unexpected resonance appearing as a quintuplet at δ 5.1, which had been assigned as the benzodioxane C-2 proton. The shift of the C-2 proton, however, should not be too different from that of the benzodioxane C-3 proton; in our sample, both protons appeared as a multiplet at δ 4.2–4.4. Treatment of the dimesylate **13** with benzylamine gave compound **14**. The previous workers[3] reported only a boiling point, and a TLC R_f value for their 'cyclised' compound **14**. Hydrogenolysis of compound **14** gave the required hexahydro[1,4]benzodioxino[2,3-*c*]pyridine hydrochloride **15** in 9% overall yield for the eight steps starting from the *trans*-pentenediol **6**. The 200 MHz NMR



Scheme 1 *Reagents:* i, NaH, DMF, BnBr, 73%; ii, MCPBA, CH_2Cl_2, 95%; iii, NaH, EtOH, catechol, 52%; iv, PPh_3, CCl_4, Et_3N, MeCN, 72%; v, H_2–Pd–C, MeOH, 88%; vi, MsCl, Et_3N, CH_2Cl_2, 78%; vii, $BnNH_2$, 67%; viii, HCl, H_2–Pd–C, MeOH, 77%

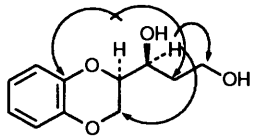


Fig. 1 H–C Three bond correlations

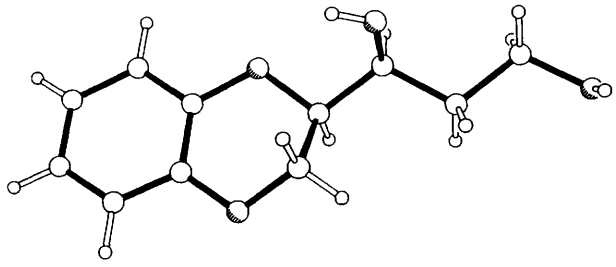


Fig. 2

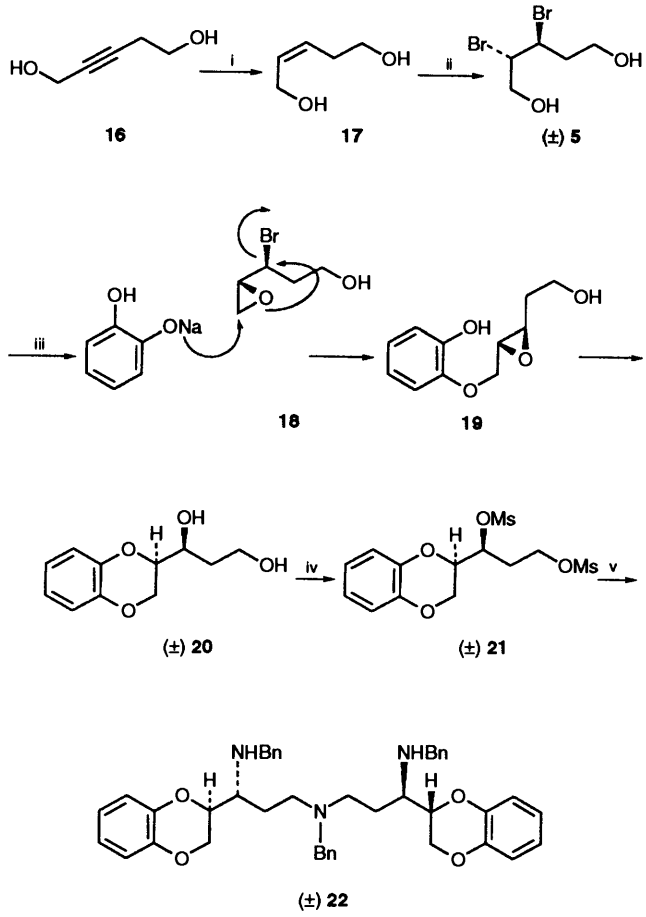
spectrum of the salt **15** was different from that previously reported.[3] At this stage we concluded that the earlier workers[3] must have isolated a regioisomer of compound **15** and that their synthesis must have gone wrong at an early step, either at the preparation of the dibromide **5** or, more likely, at the condensation of catechol with the dibromide **5**. In order to identify the products obtained by the previous workers[3] it was decided to repeat their work. Partial hydrogenation of the acetylenic diol[8] **16** over 5% Pd on $BaSO_4$, poisoned with chloroform, gave the *cis*-diol **17** which was brominated in chloroform to give the dibromide **5**. Reaction of compound **5** with the disodium salt of catechol as previously reported[3] gave, in our hands, the benzodioxane **20** as the only product, instead of its regioisomer **12**. The structure of **20** was unambiguously obtained by spectroscopic methods and, in particular, by long-range ^1H–^{13}C correlation NMR experiments (HMBC), which are shown diagrammatically in Fig. 1. In addition the structure and relative configuration of **20** were confirmed by X-ray crystallography (Fig. 2).*

The formation of compound **20** is rationalised as follows: base-catalysed elimination of HBr from the dibromide **5** would give the bromo epoxide **18** prior to reaction with catechol at the less hindered terminus of the epoxide. The generated alkoxide would then cause an intramolecular displacement of bromide to give the phenolic epoxide **19**, which, when followed by the intramolecular attack by the phenolic group onto the epoxide, as shown in Scheme 2, would then produce the [1,4]benzodioxane **20**.

Reaction of the diol **20** with methanesulfonyl chloride (2 equiv.) in the presence of triethylamine gave the dimesylate **21**, whose spectroscopic data are identical with those reported previously.[3] We were interested in identifying the product of the reaction between the dimesylate **21** and benzylamine since the previous workers provided no spectroscopic data for their products. In our hands, extensive decomposition occurred and the only identifiable product isolated from this reaction was a small quantity of the benzylamine derivative **22**.

Compound **3** was found to be a much weaker α_2-adrenoreceptor antagonist than compound **1** *in vitro*. Thus the pA_2 value for the restoration of the clonidine-induced inhibition of the twitch in the field stimulated rat vas deferens[1] was 6.5 for compound **3** and 8.0 for compound **1**. Furthermore, compound **3** was inactive *in vivo* in reversing the hypothermia induced in mice by clonidine.[1]

* Tables of atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme, please refer to 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.



Scheme 2 *Reagents:* i, 5% Pd–$BaSO_4$, EtOAc, $CHCl_3$, 53%; ii, Br_2, $CHCl_3$, 100%; iii, catechol, NaH, EtOH, 32%; iv, MsCl, Et_3N, CH_2Cl_2, 94%; v, $BnNH_2$, 2%

In conclusion, we have shown that compound **3** was not prepared by earlier workers because the condensation of catechol with the dibromide **5** provided the regioisomeric benzodioxane intermediate **20** and we are reporting the first unambiguous synthesis of compound **3**.

Experimental

Light petroleum refers to the fraction boiling at 60–80 °C. Organic solutions were dried over $MgSO_4$. Solvents were removed by rotary evaporation at or below 40 °C. TLC was conducted on Merck 0.25 mm Kieselgel F_{254} plates. Column chromatography was carried out on Merck Kieselgel 60 (Art 7734) and flash column chromatography on Merck Kieselgel 60 (Art 9385). Analytical HPLC was conducted on Inertsil (15 cm × 0.4 cm column) eluting with 0.1% aqueous H_3PO_4–MeCN using a gradient (0 ⟶ 95% MeCN over 40 min) with a flow rate of 1 cm^3 min^{-1} and detecting at λ 215 nm. NMR spectra were recorded on a Bruker AM500, AM250, Varian VXR400, XL200, JEOL MH100, Perkin-Elmer R32 or R24B. All NMR spectra were recorded with TMS as internal standard. All *J* values are in Hz. IR spectra were recorded in a Nicolet 5SXC FTIR or a Perkin-Elmer 257 spectrometer. UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer. Electron-impact mass spectrometry (EI 70 eV) was performed on a Finnigan MAT 8400, filament assisted thermospray positive ion (TSP +ve) on a HP Engine 5989A and field-desorption (FD), chemical-ionisation (CI) or fast-atom-bombardment (FAB) on a VG Autospec spectrometer. High resolution mass spectrometry was conducted on a VG Autospec

instrument. Elemental microanalyses were determined with a Perkin-Elmer 240C or a Carlo–Erba 1106 elemental analyser.

(E)-1,5-*Bis(benzyloxy)pent-2-ene* **7**.—A mixture of sodium hydride (50% oil dispersion; 1.81 g, 76.4 mmol), in DMF (10 cm^3) was treated with a solution of *E*-pent-2-ene-1,5-diol **6** (2.5 g, 24.5 mmol) in DMF (6 cm^3) at 20 °C, followed by a solution of benzyl bromide (12.19 g, 76.9 mmol) in DMF (15 cm^3). After the mixture had been stirred at 20 °C for 18 h it was treated with glacial acetic acid and diluted with ethyl acetate. The solution was washed with aq. hydrochloric acid, aq. sodium hydrogen carbonate, dried and evaporated to dryness. Chromatography using ethyl acetate–light petroleum (1:15) as the eluent gave compound **7** (5.08 g, 73.5%) (Found: C, 80.75; H, 7.9. $C_{19}H_{22}O_2$ requires C, 81.1; H, 7.85%); $\nu_{max}(CS_2)/cm^{-1}$ 1102, 747 and 699; δ_H(90 MHz; $CDCl_3$) 2.2–2.6 (2 H, m, CH_2CH_2O), 3.53 (2 H, t, *J* 7, CH_2CH_2O), 4.0 (2 H, d, *J* 4, OCH_2CH), 4.5 (4 H, s, $PhCH_2O$), 5.65–5.9 (2 H, m, CH=CH) and 7.3 (10 H, s, Ph).

trans-(±)-1,5-*Bis(benzyloxy)-2,3-epoxypentane* **8**.—A mixture of *m*-chloroperbenzoic acid (85% pure; 3.3 g; 19.3 mmol) and the olefin **7** in dichloromethane (50 cm^3) was stirred at 20 °C for 16 h. The solid was filtered off and the filtrate was washed with aq. sodium metabisulfite, aq. sodium hydrogen carbonate and dried and evaporated to give compound **8** (5.02 g, 95%) (Found: C, 76.1; H, 7.5. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); $\nu_{max}(CHBr_3)/cm^{-1}$ 1605, 1500, 1082 and 742; δ_H(100 MHz; $CDCl_3$) 1.6–2.1 (2 H, m, CH_2CH_2O), 2.8–3.1 (2 H, m, CHCH), 3.3–3.8 (4 H, m, OCH_2), 5.46 and 5.51 (2 H each, 2 s, $PhCH_2O$) and 7.27 (10 H, s, Ph).

trans-(±)-2-[2-(*Benzyloxy)ethyl*]-3-(*benzyloxymethyl*)-2,3-*dihydro*[1,4]*benzodioxine* **11**.—A solution of the epoxide **8** (4.22 g, 14.1 mmol), in ethanol (15 cm^3) was added to a mixture of sodium hydride (50% oil dispersion; 0.3 g, 12.5 mmol) and catechol (1.56 g, 14.1 mmol) in ethanol (65 cm^3) and the mixture was heated to reflux for 90 h under nitrogen. After this it was diluted with diisopropyl ether and poured into water. The organic layer was separated, washed with aq. hydrochloric acid and brine, dried and then concentrated. Chromatography using ethyl acetate–light petroleum (1:5) as the eluent gave a mixture of compounds **9** and **10** (3.01 g, 52%); δ_H(60 MHz; $CDCl_3$) 1.7–2.2 (2 H, m, CH_2CH_2O), 3.4–4.7 (7 H, m), 4.5 (4 H, s, $PhCH_2O$), 6.5–7.1 (4 H, m, C_6H_4) and 7.3 (10 H, s, Ph). The above mixture of the hydroxyphenols **9** and **10** (2.6 g, 6.4 mmol), triphenylphosphine (1.9 g, 7.25 mmol), triethylamine (1.35 g, 13.4 mmol) and carbon tetrachloride (4.92 g, 32 mmol) in acetonitrile (30 cm^3) was heated to reflux, under nitrogen for 90 min and concentrated. Chromatography using ethyl acetate–light petroleum (1:15) as the eluent gave compound **11** (1.8 g, 72%) (Found: C, 76.8; H, 6.8. $C_{25}H_{26}O_4$ requires C, 76.9; H, 6.7%); $\nu_{max}(CHBr_3)/cm^{-1}$ 1598, 1493, 1270 and 752; δ_H(100 MHz; $CDCl_3$) 1.8–2.2 (2 H, m, CH_2CH_2O), 3.6–3.8 (4 H, m, CH_2O), 4.0–4.5 (2 H, m, CHO), 4.46 and 4.52 (2 H each, 2 s, OCH_2Ph), 6.78 (4 H, s, C_6H_4) and 7.25 (10 H, s, Ph).

trans-(±)-3-(2-*Hydroxyethyl*)-2-(*hydroxymethyl*)-2,3-*dihydro*[1,4]*benzodioxine* **12**.—A solution of the dibenzyl ether **11** (1.85 g, 4.74 mmol) in methanol (20 cm^3) was hydrogenolysed over 10% Pd–C (185 mg) for 2.5 h after which the catalyst was filtered off and washed with methanol. The combined filtrate and washings were evaporated to dryness to give compound **12** as a white solid (0.88 g, 88%); m.p. 80–81 °C (Found: C, 62.9, H, 6.7. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%); $\nu_{max}(CHBr_3)/cm^{-1}$ 3600, 3450, 1599, 1497, 1271 and 753; δ_H(200 MHz; $CDCl_3$) 1.8–2.2 (2 H, m, CH_2CH_2O), 2.18 (2 H, br s, OH), 3.9–4.1 (5 H, m, CH_2OH and CHO), 4.29 (1 H, m, CHO) and 6.8–7.0 (4 H, m, C_6H_4); *m/z* (EI) 210 (M^+, 100%).

trans-(±)-2-[2-(*Mesyloxy)ethyl*]-3-(*mesyloxymethyl*)-2,3-*dihydro*[1,4]*benzodioxine* **13**.—Methanesulfonyl chloride (0.65 cm^3, 8.4 mmol) was added to a mixture of the diol **12** (0.88 g, 4.2 mmol) and triethylamine (1.75 cm^3, 12.6 mmol) in dichloromethane (30 cm^3) at 0 °C and the mixture was stirred for 0.5 h. The solution was poured into aq. hydrochloric acid and the organic layer was washed with aq. sodium hydrogen carbonate, dried and evaporated to dryness. Trituration in diethyl ether gave compound **13** as a white solid (1.2 g, 78%), m.p. 77–78 °C (Found: C, 42.7; H, 5.1; S, 17.5. $C_{13}H_{18}O_8S_2$ requires C, 42.6; H, 4.95; S, 17.5%); $\nu_{max}(CHBr_3)/cm^{-1}$ 1600, 1496, 1363, 1271 and 758; δ_H(200 MHz; $CDCl_3$) 2.0–2.4 (2 H, m, CH_2CH_2O), 3.05 and 3.09 (3 H each, 2 s, OSO_2Me), 4.2–4.4 (2 H, m, CHO), 4.4–4.6 (4 H, m, CH_2O) and 6.92 (4 H, m, C_6H_4).

trans-(±)-2-*Benzyl*-1,2,3,4,4a,10a-*hexahydro*[1,4]*benzodioxino*[2,3-c]*pyridine* **14**.—The dimesylate **13** (1.17 g, 3.2 mmol) was added to benzylamine (1.71 g, 16 mmol) at 120 °C and the mixture was stirred at 120 °C for 1 h. After this it was diluted with ethyl acetate, washed with aq. sodium hydroxide, concentrated, diluted with ethyl acetate–diethyl ether (1:1) and acidified with aq. hydrochloric acid. The precipitated white solid was filtered off and dried *in vacuo* to give the hydrochloride salt of the title compound (0.73 g, 72%). The solid was dissolved in aq. sodium hydroxide and extracted with ethyl acetate, dried and evaporated to give compound **14** as a white solid (606 mg, 67%), m.p. 95–96 °C (Found: C, 76.6; H, 6.8; N, 4.9. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); λ_{max}(EtOH)/nm 277.5 and 284 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 2740 and 2480) and inflexions at 229, 254 and 259 (3480, 445 and 780); ν_{max}(Nujol)/cm^{-1} 1590, 1492, 1275, 1262, 749 and 700; δ_H(200 MHz; $CDCl_3$) 1.7–2.3 (4 H, m, CH_2CH_2), 2.88 (1 H, br d, *J* 11, CH_2CH_2N), 3.29 (1 H, ddd, *J* 11, 4 and 2, CH_2CH_2N), 3.57 and 3.67 (2 H, ABq, *J* 14, NCH_2Ph), 3.68 (1 H, ddd, *J* 12, 8 and 5, CHO), 3.89 (1 H, ddd, *J* 10, 8 and 5, CHO), 6.82 (4 H, m, C_6H_4) and 7.31 (5 H, m, Ph).

trans-(±)-1,2,3,4,4a,10a-*Hexahydro*[1,4]*benzodioxino*-[2,3-c]*pyridine Hydrochloride* **15**.—A mixture of compound **14** (195 mg, 0.69 mmol), concentrated hydrochloric acid (0.08 cm^3) and methanol (20 cm^3) was hydrogenolysed over 10% Pd–C (20 mg). The catalyst was filtered off and washed with methanol and the filtrate and washings were evaporated to dryness. Crystallisation of the residue from methanol gave compound **15** (122 mg, 77%), m.p. 272–274 °C (sublim.) (Found: C, 57.8; H, 6.2; Cl, 15.5; N, 6.1. $C_{11}H_{13}NO_2$·HCl requires C, 58.0; H, 6.2; Cl, 15.6; N, 6.15%); λ_{max}(EtOH)/nm 276.5 ($\varepsilon/dm^3mol^{-1}\ cm^{-1}$ 2470) and inflexions at 228, 270 and 281 (2920, 1860 and 2230); ν_{max}(Nujol)/cm^{-1}, 2800–2300, 1610, 1598, 1503, 1278 and 775; δ_H(200 MHz; [$^2H_6$]DMSO) 1.98 and 2.38 (1 H each, m, CH_2CH_2N), 3.0–3.6 (3 H, m, CH_2N), 3.7 (1 H, m, CH_2N), 4.05–4.3 (2 H, m, CHO), 6.85–7.03 (4 H, m, C_6H_4) and 9.7 (2 H, br, NH HCl).

cis-*Pent-2-ene-1,5-diol* **17**.—A solution of pent-2-yne-1,5-diol **16** (2.48 g, 24.8 mmol) in ethyl acetate (100 cm^3) and chloroform (0.1 cm^3) was hydrogenated over 5% Pd–$BaSO_4$ at 20 °C. The catalyst was filtered off and the filtrate was concentrated and chromatographed, eluting with methanol–dichloromethane (1:49 to 1:19), to give compound **17** (1.35 g, 53%) as an oil [Found: (CI, CH_4) 103.0756 $(M + H)^+$. $C_5H_{11}O_2$ requires 103.0759]; $\nu_{max}(CHBr_3)/cm^{-1}$ 3600, 3430, 1658, 1651 and 1600; δ_H(250 MHz; $CDCl_3$) 2.36 (2 H, m, CH_2CH_2OH), 3.34 (2 H, br, OH), 3.65 (2 H, t, *J* 6, CH_2CH_2OH), 4.14 (2 H, d, *J* 7, $CHCH_2OH$) and 5.60 (1 H, dt, *J* 10 and 7, $CH{=}CHCH_2OH$), 5.84 (1 H, m, $CH{=}CHCH_2CH_2OH$); *m/z* (TSP +ve) 120 [$(M + NH_4)^+$, 100%] and 103 [$(M + H)^+$, 25].

threo-(±)-2,3-*Dibromopentane*-1,5-*diol* **5**.—A solution of *cis*-pent-2-ene-1,5-diol **17** (1.29 g, 12.6 mmol) in chloroform (10 cm^3) was treated with a solution of bromine (0.64 cm^3, 12.5 mmol) in chloroform (3 cm^3) at −10 °C. The mixture was stirred at 0 °C for 1 h, after which the solvent was removed under reduced pressure to give compound **5** (3.3 g, 100%) as a gum (Found: C, 22.8; H, 3.85. $C_5H_{10}Br_2O_2$ requires C, 22.9; H, 3.85%), ν_{max}(KBr)/cm^{-1} 3300 and 1044; δ_H(400 MHz; [$^2H_6$]DMSO) 2.0 (2 H, m, CH_2CH_2OH), 3.5–3.6 (2 H, m, CH_2CH_2OH), 3.68 (2 H, d, *J* 7, CH_2OH), 4.28 (1 H, m, $CHBrCH_2OH$) and 4.70 (1 H, m, $CHBrCH_2CH_2$); δ_C(100 MHz; [$^2H_6$]DMSO), 65.0, 61.1, 58.5, 55.0 and 41.0; *m*/*z* (FD) 265 (MH^+, 44%), 263 (MH^+, 100) and 261 (MH^+, 52).

(±)-(1S,2'R)-1-(2',3'-*Dihydro*[1,4]*benzodioxin*-2'-*yl*)*propane*-1,3-*diol* **20**.—A solution of catechol (2.75 g, 25 mmol) in ethanol (10 cm^3) was added to sodium ethoxide [generated from NaH (60% oil dispersion; 1 g, 25 mmol) in ethanol (25 cm^3)] followed by the dibromide **5** (3.25 g, 12.4 mmol) in ethanol (20 cm^3) under nitrogen. The mixture was heated to reflux for 24 h and then evaporated to dryness. The residue was dissolved in diethyl ether and the solution washed with aq. sodium hydroxide and brine, dried and chromatographed with methanol–dichloromethane as eluent (1 : 19) to give compound **20** (826 mg, 32%) as a white solid, analytical HPLC r_T = 16.24 min, 98.5% pure; m.p. 60–62 °C (from diethyl ether–cyclohexane) (Found: C, 62.7; H, 6.6. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%); ν_{max}(KBr)/cm^{-1} 3382, 1594, 1494, 1267, 1055 and 752; δ_H(500 MHz; $CDCl_3$) 1.82 (1 H, m, CH_2CH_2OH), 2.00 (1 H, m, CH_2CH_2OH), 2.8 (1 H, br s, OH), 3.65 (1 H, s, OH), 3.89 (1 H, m, CH_2CH_2OH), 3.96 (1 H, m, CH_2CH_2OH), 4.04 (1 H, m, 2-H), 4.07 (1 H, m, CHOH), 4.15 (1 H, dd, *J* 11 and 6, 3-H), 4.39 (1 H, dd, *J* 11 and 2, 3-H) and 6.81–6.91 (4 H, m, C_6H_4); δ_C(125 MHz; $CDCl_3$), 143.5, 143.1, 121.4, 117.1, 75.5, 70.3, 64.8, 61.2 and 34.2; *m*/*z* (TSP +ve) 228 [$(M + NH_4)^+$, 100%] and 211 [$(M + H)^+$, 35%].

A portion of this compound was recrystallised from diethyl ether–cyclohexane to give crystals which were suitable for X-ray diffraction experiments. The X-ray data suggested that the crystal was homochiral hence the enantiomeric purity of compound **20** was determined by ^1H NMR spectroscopy (400 MHz) using the chiral solvating agent (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (10 mol equiv.) in $CDCl_3$. The double doublets (dd) at δ 4.15 and 4.39 were resolved into two sets of dds of equal intensity confirming that compound **20** was indeed racemic, as expected.

Mesylation of the Diol **20**.—A solution of the diol **20** (730 mg, 3.5 mmol) in dichloromethane (10 cm^3) was treated with triethylamine (1.04 cm^3, 7.5 mmol) and methanesulfonyl chloride (0.55 cm^3, 7.1 mmol) at 0 °C and allowed to warm to room temp. The reaction was then diluted with dichloromethane and poured into cold dilute aq. hydrochloric acid. The organic solution was washed with water, dried and evaporated to dryness to give the dimesylate **21** as an oil (1.205 g, 94%); analytical HPLC r_T = 23.86 min, 92.5% pure [Found: (LSIMS +ve) 366.0447 (M^+). $C_{13}H_{18}O_8S_2$ requires 366.0443]; ν_{max}(KBr)/cm^{-1} 1601, 1495, 1351, 1268 and 1174; δ_H(250 MHz; $CDCl_3$) 2.13–2.4 (2 H, m, CH_2CH_2O), 3.07 and 3.15 (3 H each, 2 s, $MeSO_2$), 4.11 (1 H, dd, *J* 7 and 12), 4.28–4.5 (4 H, m), 5.10 (1 H, quint, *J* 4) and 6.90 (4 H, m, C_6H_4); *m*/*z* (FAB +ve) 366 (M^+, 85%), 271 (40) and 175 (100).

Reaction of the Dimesylate **21** *with Benzylamine*.—The dimesylate **21** (1.19 g, 3.25 mmol) was treated with benzylamine (1.8 cm^3, 16.24 mmol) and the mixture was heated to 140 °C for 4 h. The mixture was allowed to cool to 20 °C and then diluted with diethyl ether and washed with aq. sodium hydroxide. The diethyl ether layer was diluted with ethyl acetate and acidified with aq. hydrochloric acid. The organic solution was evaporated to dryness and the residue was partitioned between diethyl ether and sodium hydroxide. The organic solution was dried, concentrated and purified by PLC (2 plates 20 cm × 20 cm eluting with ethyl acetate) to give compound **22** as a gum (20 mg, 2%), analytical HPLC r_T = 19.09 min, 84% pure [Found: (LSIMS +ve) 670.3644 $(M + H)^+$. $C_{43}H_{48}N_3O_4$ requires 670.3645]; ν_{max}(KBr)/cm^{-1} 3354, 3271, 1592, 1494, 1265, 737 and 699; δ_H(400 MHz; $CDCl_3$) 1.6–2.2 (6 H, m, 2 × CH_2CH_2N and 2 × NH), 2.6 (4 H, m, 2 × CH_2CH_2N), 2.92 (2 H, m, 2 × CHNH), 3.4–3.8 (6 H, m, 3 × $PhCH_2N$), 4.0–4.3 (3 H, m, $OCHCH_2O$), 6.7–6.9 (4 H, m, C_6H_4) and 7.1–7.4 (15 H, m, Ph), δ_C(100 MHz; $CDCl_3$), 143.6, 140.2, 129.0, 128.3, 128.1, 127.1, 121.3, 117.2, 117.0, 74.4, 66.0, 58.9, 56.4, 51.6, 51.2 and 27.3; *m*/*z* (FAB +ve) 670 [$(M + H)^+$, 10%], 91 (100); *m*/*z* (TSP +ve) 670 [$(M + H)^+$, 100%].

Crystal Structure Analysis of the Diol **20**.—Crystal Data $C_{11}H_{14}O_4$, *M* = 210.23, Monoclinic, *a* = 5.656(2), *b* = 6.949(3), *c* = 13.346(5) Å, β = 92.02(3)°, *V* = 524.2(6) $Å^3$ (by least-squares refinement on diffractometer angles for 12 automatically centred reflections, λ = 1.54178 Å). Space group $P2_1$ (No. 4), *Z* = 2, D_c = 1.33 g cm^{-3}, *F*(000) = 224, μ(Cu-Kα) = 0.80 mm^{-1}. The compound crystallised from ether–cyclohexane as thin colourless plates.

Data Collection and Processing.—Three-dimensional, room-temp. (295 K) X-ray data was collected on a Siemens R3m/V diffractometer with monochromatised Cu-Kα X-radiation. $2\theta/\omega$ mode with scan range (ω) 1.14° plus Kα separation and a variable scan speed (1.95–14.65° min^{-1}). 825 Reflections were measured ($3 < 2\theta < 115°$, min. *h*,*k*,*l* −7 0 0, max. *h*,*k*,*l* 7 8 15) of which 785 were unique [$R(\sigma)$ = 0.091, Friedel opposites merged] and 500 had $I > 2\sigma(I)$. Two control data monitored every 98 reflections showed no appreciable decay during 11.5 h of exposure of the crystal to X-rays.

Structure Analysis and Refinement.—Direct methods resulted in the location of all the non-hydrogen atoms. Full matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode. The crystal analysed unexpectedly solved in the chiral space group $P2_1$ even though a racemic sample was submitted, indicating that the enantiomers must have crystallised separately. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0010|F_o|^2]^{-1}$, refinement converged at *R* 0.055, R_w 0.052, goodness-of-fit = 1.18. Maximum and mean shift/error in final cycle of refinement was 0.187 and 0.009 respectively. The final electron density difference synthesis showed no peaks >0.26 or holes < −0.21 e $Å^{-3}$. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[9]

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