Novel cyclodehydration reaction of hydroxyphenols. An alternative to the Mitsunobu reaction

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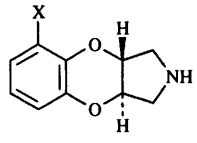
A mild, efficient and stereospecific intramolecular process for converting hydroxyphenols into benzodioxanes, dihydrobenzopyrans and dihydrobenzofurans *via* imidate esters is described. The only by-products are *N,N*-dimethylformamide and triethylamine hydrochloride which are removed by aqueous work-up making this process highly amenable to large scale operation.

Recently (±)-*trans*-2,3,3a,9a-tetrahydro-1*H*-[1,4]benzodioxino[2,3-*c*]pyrrole **1** was reported as a potent and selective α_2-



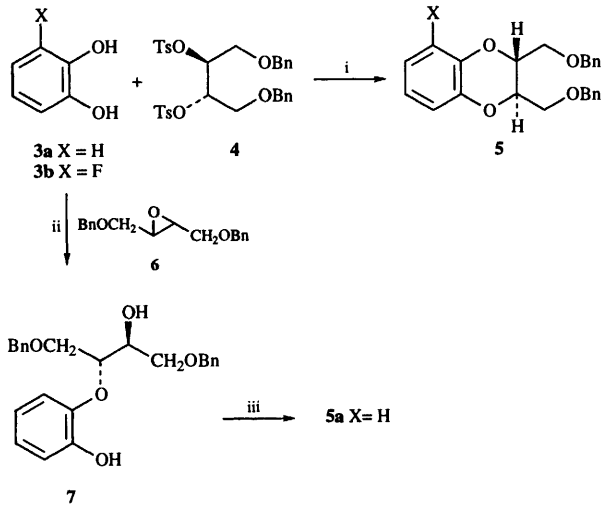
(±)

1 X = H
2 X = F

adrenoceptor antagonist, the 5-fluoro analogue **2** (fluparoxan) of which has been considered for use in the treatment of depression and male sexual dysfunction.[1,2] Compound **1** was first made as a racemic mixture by an 11 step linear synthesis in 14% overall yield.[2] In this first synthetic route there were a number of difficult steps and an epimerisation reaction that required separation of diastereoisomers by chromatography. Clearly this linear synthetic route was unacceptable for large scale preparation. New synthetic routes were designed, therefore, to overcome the practical problems and allow the convergent synthesis of either enantiomer of **1** and a variety of analogues for biological evaluation.

One synthetic route for the preparation of **1**, **2** and their analogues involved the condensation of catechols **3** with the threitol bis-toluene-*p*-sulfonate **4** derived from tartaric acid, one of the least expensive enantiomerically pure compounds possessing the correct configuration and right number of carbon atoms for building the pyrrolidine ring of **1**. The condensation of **4** with catechols was catalysed with caesium carbonate or caesium fluoride as base and provided benzodioxanes **5** in modest yield (30–39%) with complete inversion of both chiral centres.[2] A number of analogues were synthesised using this route and their pharmacological properties have been reported.[2] Although this route satisfied most of the requirements listed above it still required expensive and inconvenient chromatographic separation steps.

An alternative convergent synthesis of **1** involved the condensation of catechol **3a** (X = H) with the *trans*-substituted epoxide[3] **6** under basic conditions (sodium ethoxide in refluxing ethanol) to give the hydroxyphenol **7** in good yield (71%) (Scheme 1). Cyclodehydration of **7** using the Mitsunobu reaction,[4–7] triphenylphosphine–diethyl azodicarboxylate in refluxing acetonitrile or tetrahydrofuran, or using triphenylphosphine–carbon tetrachloride–triethylamine in refluxing acetonitrile, a variant of the Mitsunobu reaction which

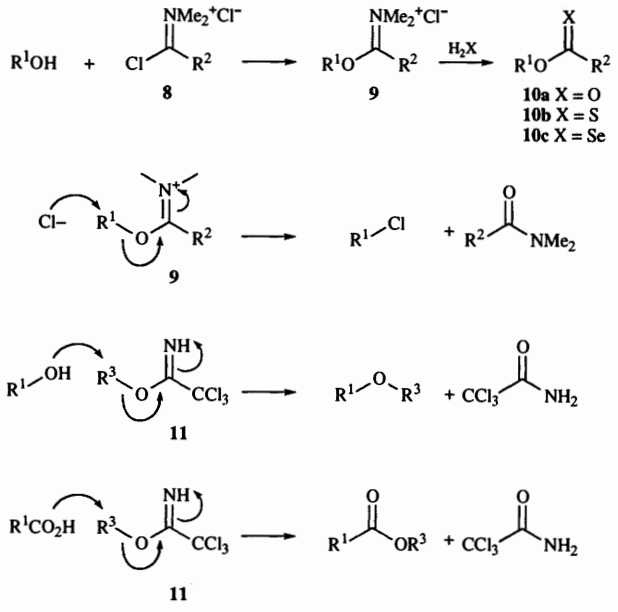


3a X = H
3b X = F

Scheme 1 *Reagents:* i, CsF or Cs_2CO_3, CH_3CN, reflux, 30–39%; ii, NaH, EtOH, reflux, 71%; iii, PPh_3, $EtO_2CN{=}NCO_2Et$ or PPh_3, CCl_4, Et_3N, CH_3CN, 90%

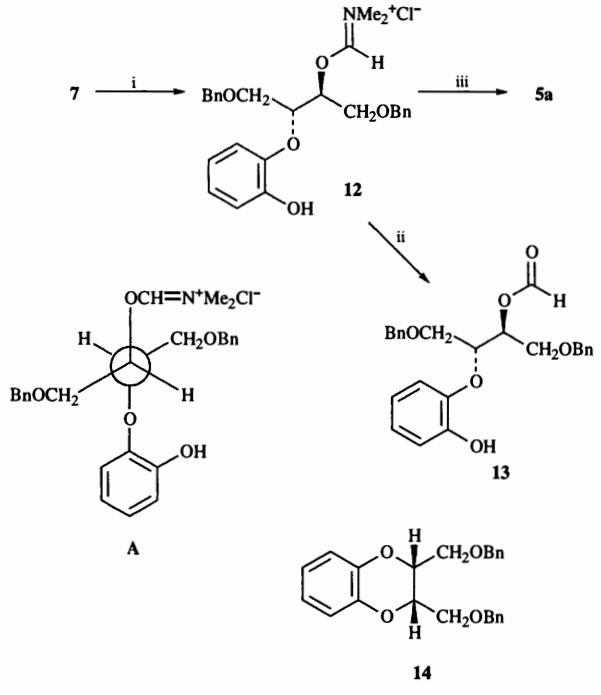
has been used[8] for the cyclodehydration of simple alkyl 1,4-diols, provided the benzodioxane **5a** (X = H) in 90% yield. Diethyl azodicarboxylate is, however, unstable and potentially explosive and carbon tetrachloride is extremely toxic; furthermore, chromatographic separation of the by-products, triphenylphosphine oxide and diethyl hydrazinedicarboxylate, was necessary which made both of these reactions totally unsuitable for large scale preparations. Another reagent was therefore sought that could effect the cyclisation of **7** efficiently, with complete inversion of configuration and without the disadvantages mentioned above. In preliminary investigations no cyclisation had taken place when polyphosphoric acid trimethylsilyl ester[9] or toluene-*p*-sulfonyl chloride in 2,6-dimethylpyridine[10] were used.

Reaction between Vilsmeier reagents **8** and alcohols provides imidate esters **9** which can be converted into carboxylic esters **10a**, carbothioic esters **10b** or carboselenoic esters **10c** upon treatment with water, hydrogen sulfide[11] or hydrogen selenide[12] respectively (Scheme 2). Imidate esters **9** are also known to produce alkyl halides[13] and this reaction has been reported as a synthetically useful method for the preparation of chlorides and bromides.[14] More recently alkyl trichloroacetimidates **11** have found synthetic utility as etherifying[15,16] or esterifying agents.[16] Schmidt[17] has also used carbohydrate trichloroacetimidate esters as leaving groups in the preparation of glycosides.



Scheme 2

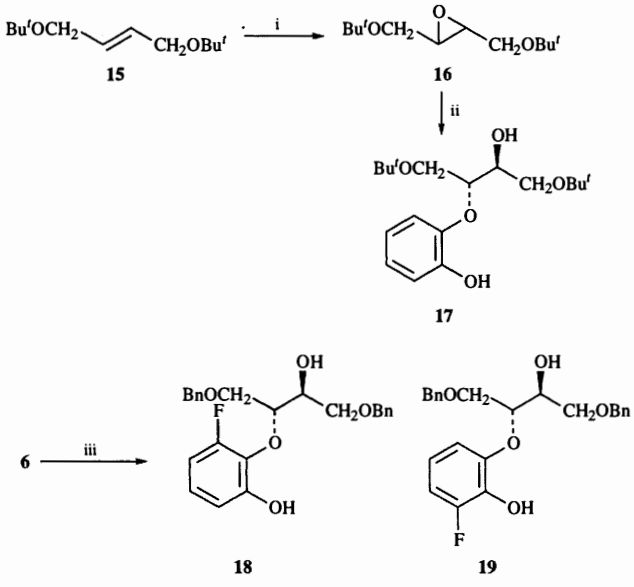
We envisaged[18] that reaction between the Vilsmeier reagent (chloromethylene)dimethylammonium chloride **8** (R^2 = H) and hydroxyphenol **7** would provide the alkyl imidate **12** selectively (Scheme 3) (pK_a of phenol 10, pK_a of propan-2-ol,



Scheme 3 *Reagents and conditions:* i, $ClCH{=}N^+Me_2Cl^-$, CH_2Cl_2; ii, HCl, H_2O, 100%; iii, Et_3N, CH_2Cl_2, reflux, 72%

18). The phenolic hydroxy group would then be set up for an intramolecular nucleophilic displacement of *N*,*N*-dimethylformamide (DMF) in preference to the intermolecular chloride displacement (structure **A**). Thus, reaction of **7** with one equivalent of **8** (R^2 = H), readily prepared from DMF and oxalyl chloride in dichloromethane at 0 °C, gave exclusively **12** whose structure was confirmed by isolation of the formate ester **13** following hydrolysis with dilute aqueous hydrochloric acid. Addition of 2.4 equiv. of triethylamine to a dichloromethane solution of the imidate **12**, followed by reaction at room temperature overnight or gentle reflux provided the *trans*-benzodioxane **5a** (X = H) in 78% yield. This product was identical to the product derived by the Mitsunobu procedure or the double S_N2 displacement of the bis-toluene-*p*-sulfonate **4**. The absence of the *cis*-benzodioxane[2] **14** (NMR, GC, HPLC) indicated that the reaction proceeded with complete inversion of configuration. When the reaction was performed on a small scale (less than 1 mmol), a small amount of the *O*-alkyl formate ester (*e.g.* **13**) with retention of configuration was detected. This is consistent with the S_N2 displacement of the imidate salt being incomplete and with fast hydrolysis of any remaining imidate by adventitious water or on work-up. As the only by-products from this reaction were DMF and triethylamine hydrochloride, which were removed by aqueous work-up, and the product was crystalline which facilitated its isolation in pure form, the reaction was readily scaled up. Our Process Research Department have successfully repeated it on multi-kilogram quantities in pilot plant operations to provide **5a** in yields of 72–78%.

The potential of this novel cyclisation procedure was investigated further by its application to a number of other hydroxyphenols and the results are summarised in Table 1. The hydroxyphenol substrates listed in Table 1 were prepared by the methods outlined in Schemes 4 and 5. Epoxidation of (*E*)-1,4-di-*tert*-butoxybut-2-ene **15** with *m*-chloroperbenzoic acid (MCPBA) gave the *trans*-epoxide **16** which on treatment with catechol **3a** provided the hydroxyphenol **17** (Scheme 4),

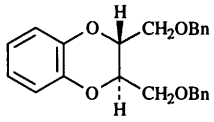
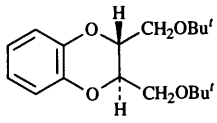
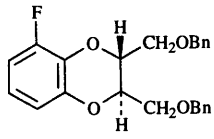
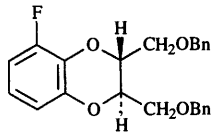
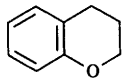
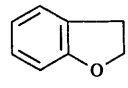
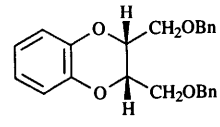


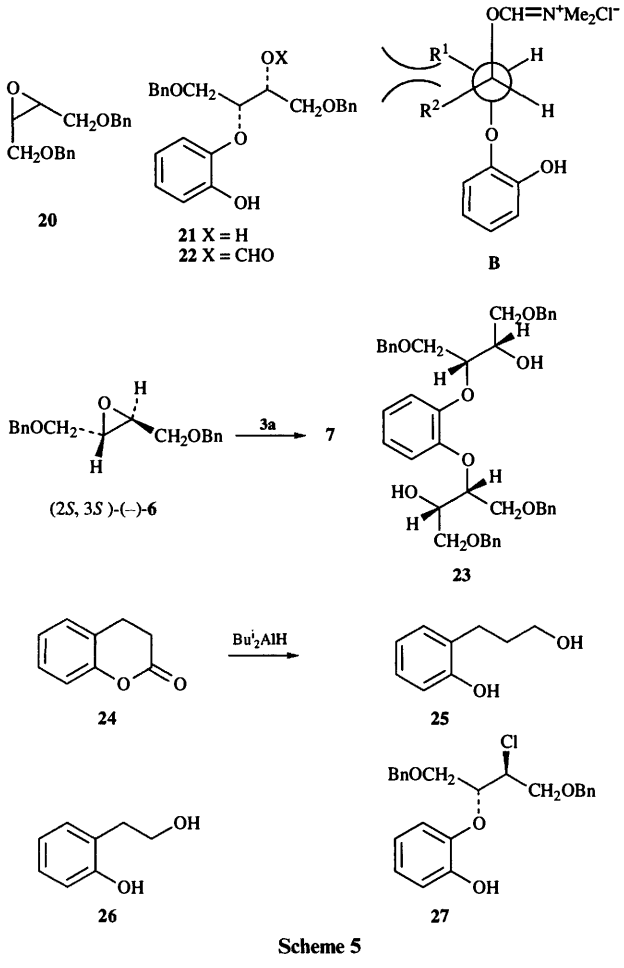
Scheme 4 *Reagents and conditions:* i, MCPBA, CH_2Cl_2, 82%; ii, **3a**, NaOEt, EtOH, 56%; iii, **3b**, K_2CO_3, DMF, 62%

whereas reaction of **3b** with *trans*-epoxide **6** gave the two regioisomeric phenols **18** and **19** in a ratio of 4:1. The regioisomers **18** and **19** were separated by chromatography and were distinguished by NMR experiments. In particular the observation of an NOE effect on the proton *ortho* to the phenolic hydroxyl upon irradiation of the latter proton established the structure of **18**. Condensation of catechol with *cis*-epoxide[3] **20** gave the *threo*-hydroxyphenol **21**, whereas condensation of catechol with the (2*S*,3*S*)-epoxide[19] **6** gave the expected (2*S*,3*R*)-*erythro*-hydroxyphenol **7** together with a small amount of the bis-alkylated catechol derivative **23** (Scheme 5). Diisobutylaluminium hydride reduction of dihydrocoumarin **24** gave 3-(2-hydroxyphenyl)propanol[20] **25**.

Cyclodehydration of the *erythro*-hydroxyphenol **17** gave benzodioxane **28** (70%) (Table 1) indicating that *tert*-butyl and benzyl protecting groups are equally effective under the cyclisation conditions (Table 1, entries 1 and 2). Cyclisation of pure 2-fluoro-6-hydroxyphenol **18** or a mixture of **18** and **19** gave the 5-fluorobenzodioxane **29** (77%) (entries 3 and 4). Cyclodehydration of 3-(2-hydroxyphenyl)propanol **25** and 2-(2-hydroxyphenyl)ethanol **26** gave the chroman[21] **30** and the

Table 1

Entry	Substrate	Product		Yield (%)
1	(±)-**7**		**5a**	72
2	(±)-**17**		**28**	70
3	(±)-**18**		**29**	77
4	(±)-**18** (±)-**19**		**29**	77
5	**24**		**30**	78
6	**28**		**31**	80
7	(±)-**21**		**14**	35
8	(−)-**7**	(+)-**5a**		68

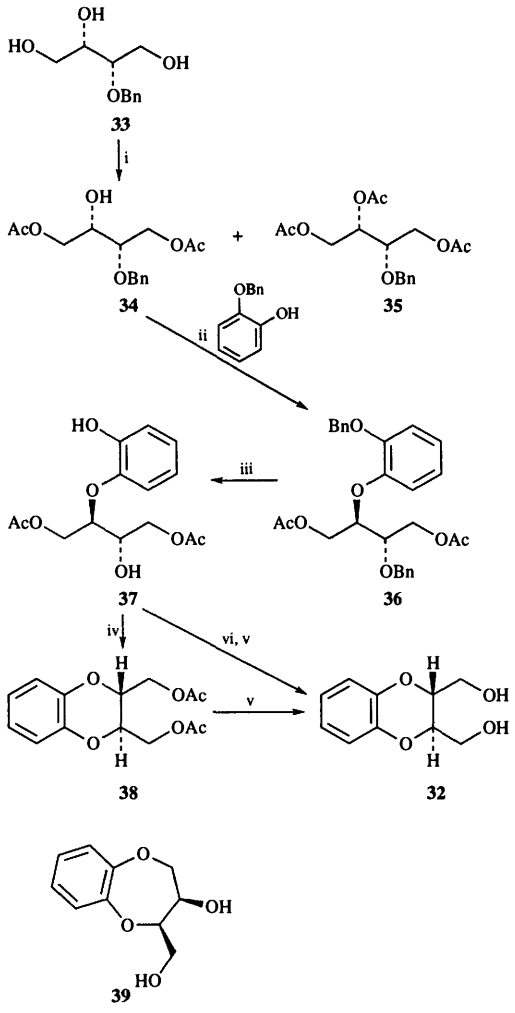


Scheme 5

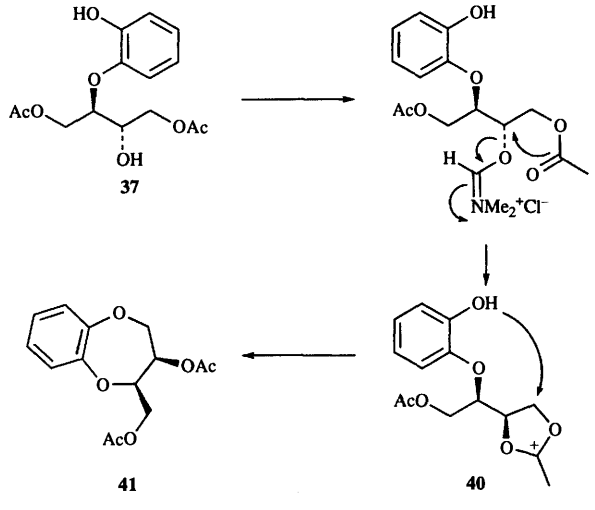
dihydrobenzofuran[22] **31** respectively in high yields (entries 5 and 6). Attempts to cyclise the *threo*-hydroxyphenol **21** at room temperature in dichloromethane were unsuccessful; however in refluxing chloroform the reaction proceeded slowly and while the intermediate imidate ester was still present after five days, work-up and chromatography provided the benzodioxanes **14** and **5** in 35% yield in the ratio of 6:1 respectively, recovered starting material **21** (25%) and the formate ester **22** (4%) derived from hydrolysis of unreacted imidate ester (entry 7). The antiperiplanar disposition of the nucleophile with the leaving group would place the substituents in a severely congested environment (structure **B**). Consequently the intermolecular chloride displacement starts to compete with the cyclisation and the derived chloride can then react further to provide the observed *trans*-benzodioxane **5**. Indeed the chloro derivative **27** is the only product formed when the same reaction is carried out in the absence of triethylamine. Subsequent treatment of the chloride **27** with base produced the *trans*-benzodioxane **5** (84%).[23] Finally the cyclodehydration reaction was applied to enantiomerically pure (2*S*,3*R*)-(−)-hydroxyphenol **7** to provide (2*R*,3*R*)-(+)-**5** (68%).

Removal of the two benzyl groups of (+)-**5** by catalytic hydrogenolysis provided the homochiral benzodioxane derivative (2*R*,3*R*)-(+)-**32** (90%) identical in all respects to authentic material and to material obtained by the route outlined in Scheme 6. Thus, acetylation of threitol derivative **33** with 2 equiv. of acetic anhydride provided the diacetate **34** (63%) accompanied by a small amount of the triacetate **35** (12%). Condensation of **34** with 2-benzyloxyphenol using the Mitsunobu conditions gave **36** (47%) which was deprotected by catalytic hydrogenolysis to give the (2*S*,3*R*)-hydroxyphenol derivative **37** in quantitative yield. A second Mitsunobu reaction provided the benzodioxane **38** (31%) which on hydrolysis gave the (2*R*,3*R*)-(+)-diol-**32** (42%) identical with the material obtained by our more efficient cyclodehydration reaction *via* the chiral epoxide **6**. It was interesting to investigate the cyclisation of **37** using our Vilsmeier methodology in order to explore the compatibility of the neighbouring acetate protecting group. Thus when **37** was treated with the Vilsmeier salt in refluxing dichloromethane no reaction took place. However, when the reaction was repeated using tetrahydrofuran as solvent and performed in a sealed vessel, partial reaction had taken place producing a mixture of regioisomeric diacetates (49%). Hydrolysis of the diacetates gave a 3:2 mixture of diols (73%) the minor component of which was diol **32** (NMR, HPLC, LCMS). The NMR data of the major component were compatible with those of diol **39**. A plausible mechanism for the formation of diol **39** is shown in Scheme 7. Formation of the acetoxonium ion **40** *via* neighbouring group participation of the acetate group, followed by phenoxide attack at the primary position would provide the benzodioxepine ring **41**. However, attack at the secondary position would be analogous to the difficult cyclisation observed for the *threo*-hydroxyphenol **21** and hence the lower yield of the benzodioxane product.

Following the publication of our initial communication describing this novel cyclodehydration reaction[18] another report has appeared in the literature[24] utilising this method for



Scheme 6 *Reagents and conditions:* i, Ac_2O, Et_3N, CH_2Cl_2, 63%; ii, PPh_3, DEAD, THF, N_2, 47%; iii, H_2, 10% Pd/C, EtOH, 100%; iv, PPh_3, DEAD, THF, 49%; v, K_2CO_3, H_2O, MeOH, 82%; vi, (a) $ClCH{=}NMe_2{}^+Cl^-$, CH_2Cl_2, (b) Et_3N, THF



Scheme 7

the cyclisation of highly and diversely substituted hydroxyphenols that were resisting cyclodehydration under the standard Mitsunobu conditions. Furthermore, this methodology has recently been extended by us to the synthesis of benzoate esters of secondary alcohols with inversion of configuration.[25] Eschenmoser's[26] esterification of carboxylic acids with dialkyl acetals of DMF is mechanistically similar to our own esterification procedure. Further exploration of the utility of the Vilsmeier methodology will form the basis of further publications.

Experimental

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. Products were visualised under UV light and/or by staining with aqueous 1% potassium permanganate solution. Benzodioxane derivatives were detected by their colour reactions obtained by treating the plates with 5% aqueous ceric sulfate in concentrated sulfuric acid. 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 S5 ODS-2 (15 cm × 0.46 cm column) eluting with aqueous 0.05 mol dm^{-3} $(NH_4)H_2PO_4$–CH_3CN isocratically with a flow rate of 2 cm^3 min^{-1} (column A), or on inertsil (15 cm × 0.46 cm column) eluting with 0.1% aqueous H_3PO_4–CH_3CN using a gradient (0 ⟶ 95% CH_3CN over 40 min) with a flow rate of 1 cm^3 min^{-1} and detecting at 215 nm (column B), or on a Phenomenex Prodigy ODS-2 (15 cm × 0.46 cm column) eluting with 0.05% aqueous trifluoroacetic acid–CH_3CN using a gradient (15 ⟶ 95% CH_3CN over 16 min) with a flow rate of 1.5 cm^3 min^{-1} (column C). GC analyses were performed on a Hewlett-Packard 5880A instrument on a Quadrex CPS-2 25 m × 0.25 mm id column using helium as carrier gas at a flow rate of 2 cm^3 min^{-1} at 200 °C. Melting points were recorded in open capillary tubes and are uncorrected. Optical rotations were measured with an Optical Activity AA100 digital polarimeter at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a Bruker, AM250, Varian VXR400, XL200, or JEOL MH100. All NMR spectra were recorded with tetramethylsilane (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. Electron-impact mass spectrometry (EI 70eV) was performed on a Finningan MAT 8400, filament assisted thermospray positive ion (TSP +ve) or negative ion (TSP −ve) on an HP Engine 5989A and electrospray positive ion (ES +ve) on a VG Autospec instrument. High resolution mass spectrometry was conducted on a VG Autospec instrument.

trans-1,4-Di-*tert*-butoxy-2,3-epoxybutane 16

A mixture of (*E*)-1,4-di-*tert*-butoxybut-2-ene[27] **15** (6.18 g, 30.9 mmol), *m*-chloroperbenzoic acid (85% pure, 7.22 g, 35.6 mmol) and dichloromethane (80 cm^3) was stirred at room temperature for 17 h. After filtration the solution was evaporated and diluted with ethyl acetate. The organic solution was washed with aqueous sodium hydrogen sulfite, aqueous sodium hydrogen carbonate, dried, concentrated and chromatographed eluting with ethyl acetate–petroleum (1 : 10) to give compound **16** (5.51 g, 82%) as a colourless liquid (Found: C, 67.0; H, 11.2. $C_{12}H_{24}O_3$ requires C, 67.25; H, 11.3%); $\nu_{max}(CHBr_3)$/cm^{-1} 1470, 1390, 1370 and 760; δ_H(250 MHz; $CDCl_3$) 1.2 (18 H, s), 3.0 (2 H, m), 3.4–3.5 (4 H, m); *m*/*z* (TSP +ve) 234 [$(M + NH_4)^+$].

erythro-(±)-1,4-Bis(benzyloxy)-3-(2-hydroxyphenoxy)butan-2-ol 7

Sodium hydride (50% oil dispersion; 1.63 g, 34 mmol) was reacted under nitrogen with ethanol (30 cm^3), followed by a solution of catechol (**3a**) (7.52 g, 68 mmol) in ethanol (10 cm^3) and after 5 min by a solution of epoxide **6** (9.72 g, 34 mmol) in ethanol (10 cm^3). The reaction mixture was heated to reflux for 24 h, allowed to cool to 20 °C, diluted with diethyl ether and poured into water. The organic solution was washed

thoroughly with aqueous sodium hydroxide, aqueous hydrochloric acid, brine, dried and chromatographed eluting with ethyl acetate–cyclohexane (1:4) to give compound **7** (9.52 g, 71%) as a colourless oil [Found: (ES +ve) $(M + H)^+$, 395.1856. $C_{24}H_{27}O_5$ requires $(M + H)^+$, 395.1858]; analytical HPLC t_r 3.47 min 95% pure (column A); t_r 31.66 min, 95% pure (column B); ν_{max}(KBr)/cm^{-1} 3330, 1594, 1496, 1455, 1264, 1102, 744 and 699; δ_H(250 MHz; $CDCl_3$) 2.87 (1 H, d, *J* 5, CHO*H*), 3.63–3.83 (4 H, m, OCHCH_2O), 4.10–4.20 (2 H, m, OC*H*CH$_2$O), 4.54 (2 H, s, OCH_2Ph), 4.58 (2 H, AB q, *J* 12, OCH_2Ph), 6.72–6.80 (1 H, m, C_6H_4), 6.90–7.00 (3 H, m, C_6H_4), 7.25–7.40 (10 H, m, Ph) and 7.45 (1 H, s, ArO*H*); *m/z* (TSP +ve) 412 [$(M + NH_4)^+$, 100%], 395 [$(M + H)^+$, 21%]; *m/z* (ES +ve) 395 [$(M + H)^+$, 100%].

erythro-(±)-1,4-Di-*tert*-butoxy-3-(2-hydroxyphenoxy)butan-2-ol 17

Compound **17** was prepared from epoxide **16** using a similar procedure to the above (Found: C, 64.5; H, 9.3. $C_{18}H_{30}O_5$·0.5H_2O requires C, 64.45; H, 9.3%) [Found: (ES +ve) $(M + H)^+$, 327.2181. $C_{18}H_{31}O_5$ requires $(M + H)^+$, 327.2171); analytical HPLC t_r 30.83 min, 97.7% pure (column B); ν_{max}(KBr)/cm^{-1} 3310, 1593, 1495, 1364, 1264, 1194 and 1084; δ_H(400 MHz; [$^2H_6$]DMSO) 1.10 and 1.15 (9 H each, s, Bu^{t}O) 3.38 (1 H, dd, *J* 9 and 6, 1-H), 3.44 (1 H, dd, *J* 9 and 5, 1-H), 3.58 (1 H, dd, *J* 9 and 6, 4-H) 3.65 (1 H, dd, *J* 9 and 4, 4-H), 3.83 (1 H, q, *J* 5, 2-H), 4.04 (1 H, dt, *J* 6 and 4, 3-H), 5.07 (1 H, br s, 2-OH), 6.70 (1 H, dt, *J* 7.5 and 1.5), 6.79 (1 H, dd, *J* 7.5 and 1.5), 6.82 (1 H, dt, *J* 7.5 and 1.5), 7.05 (1 H, dd, *J* 7.5 and 1.5), and 8.63 (1 H, br s, ArO*H*); *m/z* (TSP +ve) 344 [$(M + NH_4)^+$, 100%], 327 [$(M + H)^+$, 31%].

erythro-(±)-3-(3-Fluoro-2-hydroxyphenoxy)-1,4-bis(benzyloxy)-butan-2-ol 19 and *erythro*-(±)-3-(2-fluoro-6-hydroxyphenoxy)-1,4-bis(benzyloxy)butan-2-ol 18

A mixture of 3-fluorocatechol **3b** (6 g, 46.8 mmol), *trans*-epoxide **6** (5.72 g, 20 mmol), anhydrous potassium carbonate (1.4 g, 10.1 mmol) and DMF (10 cm^3) was stirred at 142 °C for 2 h. The mixture was allowed to cool, diluted with toluene (100 cm^3) and poured into aqueous hydrochloric acid (50 cm^3). The aqueous layer was extracted with toluene (50 cm^3) and the combined organic layers were washed sequentially with aqueous hydrochloric acid, aqueous sodium hydrogen carbonate, aqueous sodium hydroxide, dried and then concentrated. Chromatography using ethyl acetate–dichloromethane (1:19) as eluent gave the 2-fluoro-regioisomer **18** as a colourless oil (4 g, 48%) [Found: (ES +ve) $(M + Na)^+$, 435.1576. $C_{24}H_{25}FO_5Na$ requires $(M + Na)^+$, 435.1584]; analytical HPLC t_r 33.11 min 99.6% pure (column B); ν_{max}(KBr)/cm^{-1} 3258, 1592, 1495, 1484, 1303, 1241, 1203, 1098, 1014, 737 and 698; δ_H(400 MHz; $CDCl_3$) 2.97 (1 H, d, *J* 5, OH), 3.65–3.77 (3 H, m), 3.88 (1 H, dd, *J* 10 and 5), 4.08 (1 H, q, *J* 4), 4.22 (1 H, quintet, *J* 5), 4.54 and 4.59 (2 H each, AB q, *J* 11, OCH_2Ph), 6.58 (1 H, t, *J* 9), 6.72 (1 H, d, *J* 8), 6.92 (1 H, ddd, *J* 9, 8 and 6), 7.28–7.4 (10 H, m, Ph), 8.17 (1 H, s, OH); an NOE effect was observed at 5′-H when the phenolic proton at 8.17 was irradiated; *m/z* (TSP +ve) 430 [$(M + NH_4)^+$, 100%], 413 [$(M + H)^+$, 22%] and the 3-fluoro-isomer **19** as a colourless oil (1.16 g, 14%) [Found: (ES +ve) $(M + Na)^+$, 435.1594. $C_{24}H_{25}FO_5Na$ requires $(M + Na)^+$, 435.1584]; analytical HPLC t_r 31.71 min 94.6% pure (column B); ν_{max}(KBr)/cm^{-1} 3320, 1593, 1504, 1495, 1479, 1360, 1290, 1228, 1099, 732 and 698; δ_H(400 MHz; $CDCl_3$) 2.82 (1 H, br d, OH), 3.64–3.82 (4 H, m, OCHCH_2O) 4.15 (2 H, m, OC*H*CH$_2$O), 4.55 (2 H, s, OCH_2Ph), 4.59 (2 H, d, AB q, *J* 11, OCH_2Ph), 6.67 (1 H, ddd, *J* 9, 8 and 5), 6.75 (1 H, dt, *J* 8 and 1), 6.84 (1 H, dt, *J* 9 and 1), 7.28–7.38 (10 H, m, Ph) and 7.66 (1 H, s, OH); no NOE effect was observed when the phenolic proton at 7.66 was irradiated; *m/z* (TSP +ve) 430 [$(M + NH_4)^+$, 100%], 413 [$(M + H)^+$, 24%].

threo-(±)-1,4-Bis(benzyloxy)-3-(2-hydroxyphenoxy)butan-2-ol 21

Compound **21** was prepared from epoxide **20** in a similar way (Found: C, 69.8; H, 6.8. $C_{24}H_{26}O_5$·H_2O requires C, 69.9; H, 6.8%); analytical HPLC t_r 31.52 min, 96.3% pure (column B); ν_{max}(KBr)/cm^{-1} 3400, 1594, 1498, 1265, 734 and 699; δ_H(250 MHz; $CDCl_3$) 3.18 (1 H, d, *J* 4, CHO*H*), 3.50–3.80 (4 H, m, OCHCH_2O), 4.12–4.23 (2 H, m, OC*H*CH$_2$O), 4.50 (2 H, s, OCH_2Ph) 4.54 (2 H, AB q, *J* 11, OCH_2Ph), 6.72–6.80 (1 H, m, C_6H_4), 6.90–7.00 (3 H, m, C_6H_4), 7.25–7.40 (10 H, m, Ph) and 7.66 (1 H, s, ArO*H*); *m/z* (ES +ve) 395 [$(M + H)^+$, 100%].

Reaction of catechol with (2*S*,3*S*)-1,4-di(benzyloxy)-2,3-epoxybutane 6

A mixture of the (2*S*,3*S*)-epoxide **6** (1.443 g, 5.07 mmol), catechol (1.12 g, 10.2 mmol) and potassium carbonate (2.1 g, 15.2 mmol) in DMF (5 cm^3) was heated under nitrogen to 142 °C for 4 h. The mixture was then allowed to cool, diluted with diethyl ether and washed with aqueous sodium hydroxide (×5). The organic solution was washed with dilute aqueous hydrochloric acid, brine, dried and chromatographed eluting with ethyl acetate–cyclohexane (1:3) to give **7** (1.3 g, 65%) as a colourless oil $[\alpha]_D$ −24.3 (*c* 1.58 in chloroform); analytical HPLC t_r 9.16 min 100% pure (column C) (Found: C, 72.3; H, 6.9. $C_{24}H_{26}O_5$·0.2H_2O) requires C, 72.4; H, 6.7%); ν_{max}-(KBr)/cm^{-1} 3335, 1593, 1495, 1454, 1264, 1102, 754, 734 and 698; δ_H(250 MHz; $CDCl_3$) 2.9 (1 H, br, CHO*H*), 3.6–3.84 (4 H, m, OCHCH_2O), 4.10–4.20 (2 H, m, OC*H*CH$_2$O), 4.54 (2 H, s, OCH_2Ph), 4.58 (2 H, AB q, *J* 12, OCH_2Ph), 6.7–6.8 (1 H, m, C_6H_4), 6.90–7.00 (3 H, m, C_6H_4), 7.25–7.40 (10 H, m, Ph) and 7.53 (1 H, s, ArO*H*); *m/z* (TSP +ve) 412 [$(M + NH_4)^+$, 100%], 395 [$(M + H)^+$, 35%] and 1,2-bis[(1*R*,2*S*)-3-benzyloxy-1-benzyloxymethyl-2-hydroxypropoxy]benzene **23** (301 mg, 17%) as a colourless oil $[\alpha]_D$ −26.6 (*c* 1.47 in chloroform) (Found: C, 73.4; H, 6.85. $C_{42}H_{46}O_8$·0.5H_2O requires C, 73.3; H, 6.9%); ν_{max}(KBr)/cm^{-1} 3461, 1601, 1495, 1454, 1256, 1110, 734 and 697; δ_H(250 MHz; $CDCl_3$) 3.31 (2 H, d, *J* 5, CHO*H*), 3.61 (4 H, d, *J* 5), 3.77 (4 H, m), 4.05 (2 H, m), 4.45 (2 H, m), 4.46 (4 H, s, OCH_2Ph), 4.50 (4 H, s, OCH_2Ph), 6.9–6.96 (2 H, m), 7.02–7.08 (2 H, m), and 7.2–7.36 (20 H, m, Ph)

Preparation of *trans*-(±)-2,3-bis(benzyloxymethyl)-2,3-dihydro-[1,4]benzodioxine 5

Method A. A mixture of **7** (395 mg, 1.05 mmol), triphenylphosphine (300 mg, 1.14 mmol) and triethylamine (0.3 cm^3, 2.1 mmol) in acetonitrile (5 cm^3) was treated with carbon tetrachloride (0.5 cm^3, 5.1 mmol) and the mixture was heated to reflux under nitrogen for 100 min. The mixture was concentrated under reduced pressure and chromatographed on silica gel eluting with ethyl acetate–light petroleum (1:4) to give compound **5** (341 mg, 90%) as a white solid mp 53–54 °C (from methanol) (Found: C, 76.5; H, 6.4. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%); analytical HPLC t_r 11.02 min, 98% pure (column A); t_r 36.9 min, 98% pure (column B); ν_{max}($CHBr_3$)/cm^{-1} 1600, 1500, 1270 and 750; δ_H(250 MHz; $CDCl_3$) 3.68–3.84 (4 H, m, CHCH_2O), 4.32 (2 H, m, OC*H*CH$_2$), 4.55 (4 H, AB q, *J* 10, OCH_2Ph), 6.80–6.95 (4 H, m, C_6H_4) and 7.25–7.40 (10 H, m, Ph); *m/z* (TSP +ve) 394 [$(M + NH_4)^+$].

Method B. A mixture of **7** (394 mg, 1.05 mmol), triphenylphosphine (300 mg, 1.14 mmol) and diethyl azodicarboxylate (0.23 cm^3, 1.5 mmol) in tetrahydrofuran (40 cm^3) was heated to reflux for 24 h under nitrogen. The mixture was concentrated under reduced pressure, the residue was triturated in diethyl ether, and filtered. The filtrate was chromatographed on silica gel eluting with ethyl acetate–light petroleum (1:4) to give compound **5** (341 mg, 90%) as a gum which crystallised on standing, identical to the material obtained by method A.

Method C. A stirred and cooled (−5 °C) solution of DMF (5.2 dm^3, 67.15 mol) in dichloromethane (80 dm^3) was

cautiously reacted with a solution of oxalyl chloride (7.60 kg, 59.88 mol) in dichloromethane (3 dm^3) at −10 °C over 25 min. The white suspension formed was treated after 10 min with a solution of compound **7** (23.4 kg, 59.33 mol) in dichloromethane (75 dm^3) over 20 min, and stirred and cooled for 35 min. An aliquot was *hydrolysed* in dilute aqueous hydrochloric acid, dried and evaporated to dryness to give compound **13** as a colourless oil (Found: C, 70.8; H, 6.25. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.2%); $\nu_{max}(CHBr_3)/cm^{-1}$ 3320, 1728, 1594, 1496, 1263 and 750; δ_H(100 MHz; $CDCl_3$) 3.6–4.0 (4 H, m, $CHCH_2O$), 4.30 (1 H, m, ArOC*H*), 4.46 and 4.52 (2 H each, s, OCH_2Ph), 5.48 (1 H, m, HCO_2CH), 6.6–7.1 (4 H, m, C_6H_4), 7.25 (10 H, m, Ph) and 8.00 (1 H, s, HCO_2CH). The remainder of the reaction mixture was treated slowly with a solution of triethylamine (20 dm^3, 143 mol) in dichloromethane (20 dm^3) over 22 min (the temperature rose to 20 °C), and then the mixture was heated to reflux for 19 h. The cooled reaction mixture was washed with water (100 dm^3), the aqueous phase was back extracted with dichloromethane (15 dm^3). The organic phase was washed with dilute aqueous sulfuric acid (0.4 mol dm^{-3}; 100 dm^3), brine (50 dm^3), dried over sodium sulfate (10 kg), filtered and concentrated to a volume of about 23 dm^3. Methanol (80 dm^3) was added over 6 min, the mixture was stirred for 30 min, and then cooled to −18 °C overnight. The crystalline product was collected by filtration and dried to give compound **5** (16.005 kg, 71.6%) identical with the product obtained by methods A and B. GC **5a** t_r 69.4 min 99.9% pure; **14** t_r 68.1 min (none detected).

Method D. A solution of chlorophenol **27** (4.13 g, 10 mmol) in acetone (41 cm^3) was stirred and heated to reflux with potassium carbonate (4.14 g, 30 mmol) for 3 h. The mixture was cooled, the solids were collected by filtration and washed with acetone. The combined filtrate and washings were evaporated under reduced pressure, and the residue was dissolved in dichloromethane and chromatographed on sorbsil to give the benzodioxane **5** as a colourless gum (3.16 g, 84%), identical to material obtained by the methods above.

trans-(±)-2,3-Bis(*tert*-butoxymethyl)-2,3-dihydro[1,4]benzodioxine 28

Compound **28** was prepared according to procedure C from hydroxyphenol **17** (9.79 g, 30 mmol) and after chromatography on silica gel eluting with ethyl acetate–light petroleum (1:19, 1:4) was isolated as a colourless oil (6.477 g, 70%) (Found: C, 70.4; H, 9.3. $C_{18}H_{28}O_4$ requires C, 70.1; H, 9.15%); analytical HPLC t_r 37.0 min, 93% pure (column B); $\nu_{max}(CHBr_3)/cm^{-1}$ 1594, 1491, 1270 and 751; δ_H(250 MHz; $CDCl_3$) 1.20 (18 H, s, Bu^{t}O), 3.55–3.70 (4 H, m, $CHCH_2O$), 4.24 (2 H, m, $CHCH_2O$) and 6.70–6.95 (4 H, m, C_6H_4); *m/z* (TSP +ve) 326 [(M + NH_4)$^+$].

trans-(±)-2,3-Bis(benzyloxymethyl)-5-fluoro-2,3-dihydro[1,4]-benzodioxine 29

Compound **29** was prepared according to procedure C from hydroxyphenol **18** (3 g, 7.27 mmol) and after chromatography on sorbsil eluting with dichloromethane–light petroleum (1:9) was isolated **29** as a solid (2.2 g, 77%) mp 61.5–63 °C (from methanol) (Found: C, 73.2; H, 5.9; F, 4.9. $C_{24}H_{23}FO_4$ requires C, 73.1; H, 5.9; F, 4.8%); $\nu_{max}(CHBr_3)/cm^{-1}$ 1600, 1500, 1480, 1240 and 770; δ_H(200 MHz; $CDCl_3$) 3.7–3.9 (4 H, m, $CHCH_2O$), 4.35 (2 H, m, $CHCH_2O$), 4.58 (4 H, AB q, *J* 10 Hz, OCH_2Ph), 6.6–6.8 (3 H, m, C_6H_3) and 7.26–7.4 (10 H, m, Ph); *m/z* (TSP +ve) 412 [(M + NH_4)$^+$].

The above compound was also prepared in 77% yield from a mixture of the 2- and 3-fluoro-regioisomers **18** and **19** (1:9) (394 mg, 1 mmol).

3-(2-Hydroxyphenyl)propanol 25

A solution of dihydrocoumarin **24** (2.52 cm^3, 19.9 mmol) in toluene (20 cm^3) was treated with a solution of diisobutylaluminium hydride (1.5 mol dm^{-3}; 33 cm^3, 49.5 mmol) at 20 °C under nitrogen. After 20 min aqueous dilute hydrochloric acid was added cautiously with ice-cooling, followed by diethyl ether (50 cm^3). The mixture was stirred vigorously for 1 h, and then the two phases were separated. The organic layer was washed with aqueous dilute hydrochloric acid, brine, dried and evaporated to dryness to give compound[20] **25** (3 g, 99%) as a colourless oil which was used in the next stage without any further purification: $\nu_{max}(CHBr_3)/cm^{-1}$ 3587, 3324, 1570, 1488, 1243 and 757; δ_H(250 MHz; [$^2H_6$]DMSO) 1.69 (2 H, quintet, *J* 8, CH_2CH_2Ph), 2.55 (2 H, t, *J* 8, CH_2Ph), 3.42 (2 H, dt, *J* 8 and 5, CH_2CH_2OH), 4.46 (1 H, t, *J* 5, CH_2OH), 6.70 (1 H, t, *J* 8), 6.78 (1 H, d, *J* 8), 7.00 (1 H, t, *J* 8), 7.05 (1 H, d, *J* 8) and 9.2 (1 H, s, OH).

3,4-Dihydro-2*H*-1-benzopyran 30

Was prepared according to procedure C from 3-(2-hydroxyphenyl)propanol **25** (1.52 g, 10 mmol) to give chroman[21] **30** (1.048 g, 78%) as a colourless oil: δ_H(250 MHz; [$^2H_6$]DMSO) 1.90 (2 H, m, $CH_2CH_2CH_2O$), 2.72 (2 H, t, *J* 7, $CH_2CH_2CH_2O$), 4.10 (2 H, t, *J* 5, $CH_2CH_2CH_2O$), 6.71 (1 H, d, *J* 8), 6.79 (1 H, t, *J* 8) and 7.00–7.08 (2 H, m); *m/z* (EI) 134 ($M^{+\bullet}$, 100%).

2,3-Dihydro-1-benzofuran 31

Was prepared according to procedure C from 2-(2-hydroxyphenyl)ethanol **26** (1.38 g, 10 mmol) to give coumaran[22] **31** (961 mg, 80%) as a colourless oil: ν_{max}(KBr)/cm^{-1} 1596, 1482, 1461, 1228, 983 and 753; δ_H(250 MHz; $CDCl_3$) 3.20 (2 H, t, *J* 9, $ArCH_2CH_2O$), 4.56 (2 H, t, *J* 9, $ArCH_2CH_2O$), 6.80 (1 H, t, *J* 8), 6.87 (1 H, d, *J* 8), 7.10 (1 H, t, *J* 8) and 7.18 (1 H, d, *J* 8).

Cyclisation of 21

A solution of the phenolic alcohol **21** (1.85 g, 4.69 mmol) in dichloromethane (5 cm^3) was added to the Vilsmeier reagent [prepared from DMF (0.47 cm^3, 6.10 mmol) and oxalyl chloride (0.45 cm^3, 5.1 mmol) in dichloromethane (30 cm^3)] at 3 °C. After 10 min triethylamine (5 cm^3, 36 mmol) was added and the mixture was heated to reflux for 24 h. The solvent was replaced with chloroform (30 cm^3) and the mixture was heated to reflux for a further 4 days. The reaction mixture was allowed to cool to 20 °C and poured into aqueous dilute hydrochloric acid. The organic phase was washed with water, dried and chromatographed on silica gel eluting with ethyl acetate–cyclohexane (1:19, 1:1) to give the cyclisation product (337 mg, 35%) as a mixture of the *cis*- and *trans*-benzodioxane[2] derivatives **14** and **5** in the ratio of 6:1; analytical HPLC t_r 36.64 min (*cis*), 36.93 min (*trans*) (column B); δ_H(250 MHz; $CDCl_3$) 3.62–3.70 (4 H, m, $CHCH_2O$), 4.45–4.61 (6 H, m, $CHCH_2O$, OCH_2Ph), 6.8–6.93 (4 H, m, C_6H_4), and 7.25–7.39 (10 H, m, Ph); *m/z* (TSP +ve) 394 [(M + NH_4)$^+$]; the formate ester **22** (47 mg, 4%) as a colourless oil $\nu_{max}(CHBr_3)/cm^{-1}$ 3350, 1720, 1595, 1500, 1260 and 697; δ_H(250 MHz; $CDCl_3$) 3.57–3.78 (4 H, m, $CHCH_2O$), 4.40–4.58 (5 H, m, $CHCH_2O$, OCH_2Ph), 5.50 (1 H, m, CHOCHO), 6.75–7.00 (4 H, m, C_6H_4), 7.2–7.4 (10 H, m, Ph) and 8.10 (1 H, s, OCHO); *m/z* (TSP −ve) 421 [(M − H)]$^-$ and recovered starting material **21** (253 mg, 25%).

Formation of *erythro*-(±)-1,4-bis(benzyloxy)-2-chloro-3-(2-hydroxyphenoxy)butane 27

Oxalyl chloride (3.45 cm^{-3}, 40 mmol) was added to a solution of DMF (3.45 cm^{-3}, 45 mmol) in dioxane (100 cm^{-3}) at 10 °C and after 10 min a solution of the hydroxyphenol **21** (9.86 g, 25 mmol) in dioxane (75 cm^{-3}) was added dropwise over 5 min. The mixture was heated to reflux for 3 h. The reaction mixture was evaporated to dryness under reduced pressure and then partitioned between diethyl ether and water. The organic phase was washed sequentially with aq. hydrochloric acid, aq. sodium hydroxide, water, brine, dried and chromatographed on sorbsil eluting with diethyl ether–light petroleum to give chloride **27**

(9.84 g, 95%) as a colourless oil (Found: C, 69.6; H, 6.1; Cl, 8.7. $C_{24}H_{25}ClO_4$ requires C, 69.8; H, 6.1; Cl, 8.6%); ν_{max}(CHBr$_3$)/cm^{-1} 3550–2600, 1600, 1495, 1270 and 760; δ_H(100 MHz; $CDCl_3$) 3.65–4.1 (4 H, m, CHCH_2O), 4.5 (2 H, m, OCHCH$_2$), 4.6 (4 H, s, OCH_2Ph), 6.7–7.2 (5 H, m) and 7.25–7.4 (10 H, m, Ph).

(2*R*,3*R*)-(+)-2,3-Bis(benzyloxymethyl)-2,3-dihydro[1,4]benzodioxine 5

Was prepared according to procedure C from hydroxyphenol (−)-**7** (541 mg, 1.37 mmol) to give after preparative thin layer chromatography (PLC) (ethyl acetate–cyclohexane, 1:3) (+)-**5** (351 mg, 68%) as a colourless gum: analytical HPLC t_r 11.89 min 100% pure (column C); $[\alpha]_D$ +44.6 (*c* 1.04 in chloroform) (Found: C, 76.8; H, 6.5. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%); ν_{max}(KBr)/cm^{-1} 1595, 1494, 1454, 1270, 746 and 698; δ_H(250 MHz; $CDCl_3$) 3.65–3.85 (4 H, m, CHCH_2O), 4.32 (2 H, m, OCHCH$_2$), 4.55 (4 H, AB q, *J* 12, OCH_2Ph), 6.80–7.00 (4 H, m, C_6H_4) and 7.28–7.40 (10 H, m, Ph); *m*/*z* (ES +ve) 377 [(M + H)$^+$].

Acetylation of (2*S*,3*S*)-(+)-3-benzyloxybutane-1,2,4-triol 33

Triol **33** (6.37 g, 30 mmol) in dichloromethane (80 cm^3) and triethylamine (8.4 cm^3, 60 mmol) was reacted with acetic anhydride (5.67 cm^3, 60 mmol) and the mixture was left to stand at 20 °C for 3 h. The solution was washed with aqueous hydrochloric acid, aqueous sodium hydrogen carbonate, dried and chromatographed on silica gel eluting with ethyl acetate–light petroleum (1:3, 1:1) to give 3-benzyloxybutane-1,2,4-triyl triacetate **35** (1.22 g, 12%) as an oil: $[\alpha]_D$ −4.3 (*c* 1.276 in $CHCl_3$) (Found: C, 60.6; H, 6.6. $C_{17}H_{22}O_7$ requires C, 60.3; H, 6.6%); ν_{max}(CHBr$_3$)/cm^{-1} 1738, 1600, 1497 and 752; δ_H(250 MHz; $CDCl_3$) 2.02, 2.06, 2.09 (3 H each, s, AcO), 3.83 (1 H, q, *J* 6, CHOBn), 4.1–4.2 (2 H, m), 4.22–4.37 (2 H, m), 4.67 (2 H, AB q, *J* 15, OCH_2Ph), 5.28 (1 H, m, CHOAc) and 7.35 (5 H, m, Ph); *m*/*z* (TSP +ve) 356 [(M + NH$_4$)$^+$] and 2-benzyloxy-3-hydroxybutane-1,4-diyl diacetate **34** (5.59 g, 63%), $[\alpha]_D$ +19.3 (*c* 1.060 in $CHCl_3$) (Found: C, 60.7; H, 6.8. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%); ν_{max}(KBr)/cm^{-1} 3488, 1745, 1738, 1731, 1234, 741 and 700; δ_H(250 MHz; $CDCl_3$) 2.05 and 2.07 (3 H each, s, AcO), 2.53 (1 H, d, *J* 7, OH), 3.67 (1 H, m), 3.90 (1 H, m), 4.1–4.4 (4 H, m), 4.57 and 4.75 (2 H, AB q, *J* 11 Hz, OCH_2Ph), and 7.35 (5 H, m, Ph); *m*/*z* (TSP +ve) 314 [(M + NH$_4$)$^+$].

(2*S*,3*R*)-(−)-2-Benzyloxy-3-(2-benzyloxyphenoxy)butane-1,4-diyl diacetate 36

A mixture of 2-benzyloxyphenol (3.4 g, 17 mmol), diacetate **34** (5.03 g, 17 mmol), triphenylphosphine (4.46 g, 17 mmol) and diethyl azodicarboxylate (2.67 cm^3, 17 mmol) was heated to reflux in tetrahydrofuran (70 cm^3) for 19 h under nitrogen. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with ethyl acetate–light petroleum (1:9, 1:4) to give **36** (3.84 g, 47%) as a colourless gum $[\alpha]_D$ −13.6 (*c* 1.249 in $CHCl_3$); analytical HPLC t_r 34.54 min 90% pure (column B) [Found: (ES +ve) 479.2071 (M + H)$^+$; $C_{28}H_{31}O_7$ requires (*M* + H)$^+$ 479.2070]; ν_{max}(KBr)/cm^{-1} 1739, 1600, 1502, 1230 and 746; δ_H(250 MHz; $CDCl_3$) 1.93 and 1.95 (3 H each, s, AcO), 3.95–4.73 (8 H, m) 5.08 (2 H, s), 6.85–7.05 (4 H, m, C_6H_4), and 7.25–7.45 (10 H, m, Ph); *m*/*z* (TSP +ve) 496 [(M + NH$_4$)$^+$].

(2*S*,3*R*)-(−)-2-Hydroxy-3-(2-hydroxyphenoxy)butane-1,4-diyl diacetate 37

A solution of the dibenzyl ether **36** (3.3 g, 6.9 mmol) in methanol (40 cm^3) was hydrogenolysed over 10% Pd/C (0.4 g) for 3 h. The catalyst was collected by filtration and washed with methanol. The combined washings and filtrate were evaporated to dryness to give the hydroxyphenol **37** (2.07 g, 100%) as a colourless gum: $[\alpha]_D$ −23.8 (*c* 2.665 in chloroform); analytical HPLC t_r 18.29 min 89.3% pure (column B) [(Found: C, 54.0; H, 6.1. $C_{14}H_{18}O_7$·0.75H_2O requires C, 53.9; H, 6.3%) and (ES +ve) (M + H)$^+$ 299.1129. $C_{14}H_{19}O_7$ requires (*M* + H)$^+$, 299.1131]; ν_{max}(CHBr$_3$)/cm^{-1} 3700–3200, 1740, 1599, 1498, 1230, 1049 and 750; δ_H(250 MHz; $CDCl_3$) 2.08 and 2.12 (3 H each, 2 s, AcO), 3.2 (1 H, br, OH), 4.06–4.55 (6 H, m), 6.55 (1 H, br, OH), and 6.80–7.05 (4 H, m, C_6H_4); *m*/*z* (TSP +ve) 316 [(M + NH$_4$)$^+$].

(2*R*,3*R*)-(+)-2,3-Bis(acetoxymethyl)-2,3-dihydro[1,4]benzodioxine 38

A mixture of phenolic alcohol **37** (2 g, 6.7 mmol), triphenylphosphine (1.76 g, 6.7 mmol) and diethyl azodicarboxylate (1.1 cm^3, 7 mmol) was heated to reflux in tetrahydrofuran (50 cm^3). After 5 h extra triphenylphosphine (1.76 g, 6.7 mmol) and diethyl azodicarboxylate (0.9 cm^3, 5.7 mmol) were added and the mixture was heated to reflux for 19 h. The solvent was removed under reduced pressure and the residue was triturated in diethyl ether. The solid was removed by filtration, and the filtrate was chromatographed on silica gel eluting with ethyl acetate–light petroleum (1:4) to give a gum (0.92 g) which was crystallised in diethyl ether to give dioxane **38** (0.59 g, 31%) as a white solid, mp 91–93 °C; $[\alpha]_D$ +66.4 (*c* 0.994 in $CHCl_3$) (Found: C, 59.7; H, 5.9. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.8%); ν_{max}(CHBr$_3$)/cm^{-1} 1741, 1599, 1502, 1231 and 749; δ_H(200 MHz; $CDCl_3$) 2.10 (6 H, s, AcO), 4.2–4.4 (6 H, m), and 6.8–7.0 (4 H, m, C_6H_4).

(2*R*,3*R*)-(+)-2,3-Dihydro[1,4]benzodioxine-2,3-dimethanol 32

Hydrolysis of diacetate 38. A solution of the diacetate **38** (0.56 g, 2 mmol) in methanol–tetrahydrofuran (1:1; 50 cm^3) was treated with potassium carbonate (0.69 g, 5 mmol) in water (25 cm^3) and the mixture was stirred for 3 h. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium hydrogen carbonate, brine, dried and evaporated to dryness. The residue was recrystallised twice from hot chloroform to give the diol **32** (165 mg, 42%) as white crystals mp 127–129 °C, $[\alpha]_D$ +54.2 (*c* 0.886 in ethanol) (Found: C, 61.0; H, 6.2. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.2%); ν_{max}(KBr)/cm^{-1} 3330, 1594, 1494, 1269, 1040 and 758; δ_H(200 MHz; [$^2H_6$]DMSO) 3.60–3.82 (4 H, m, CH_2OH), 4.00–4.13 (2 H, m, CHCH$_2$OH), 5.0 (2 H, t, *J* 5, CH$_2$OH) and 6.80–6.90 (4 H, m, C_6H_4).

Hydrogenolysis of 5. A solution of the dibenzyl ether (+)-**5** (175 mg, 0.46 mmol) in ethanol (50 cm^3) was hydrogenated over 10% Pd/C (100 mg) for 3 h. The catalyst was collected by filtration and washed with ethanol. The filtrate and washings were evaporated to dryness to give diol **32** (82 mg, 90%) as a white solid mp 128–129 °C; $[\alpha]_D$ +54.4 (*c* 1.015 in ethanol); analytical HPLC t_r 4.23 min 100% pure (column C); *m*/*z* (TSP +ve) 214 [(M + NH$_4$)$^+$] spectroscopic data identical to those of the product obtained by hydrolysis of the diacetate above.

Cyclisation of hydroxyphenol 37

The Vilsmeier salt was prepared from DMF (0.034 cm^3, 0.44 mmol) and oxalyl chloride (0.022 cm^3, 0.25 mmol) in dichloromethane (0.5 cm^3) at 0 °C. A solution of the diol **37** (66 mg, 0.22 mmol) in dichloromethane (0.5 cm^3) was added, the cooling bath was removed and the mixture was stirred for 50 min. Triethylamine (0.25 cm^3, 1.32 mmol) was added and the mixture was stirred at 20 °C for 3 days. TLC indicated that no reaction had occurred. The mixture was then heated in a closed vessel for 36 h, replacing the solvent with tetrahydrofuran (1.5 cm^3). TLC indicated that partial reaction had taken place, starting material was still present and a less polar product had formed. The reaction mixture was diluted with ethyl acetate and poured into dilute hydrochloric acid. The organic solution was washed with brine, dried and purified by PLC (ethyl acetate–cyclohexane 1:1) to give a colourless oil (30 mg, 49%): ν_{max}(KBr)/cm^{-1} 1747, 1596, 1495, 1222 and 751; δ_H(250 MHz; $CDCl_3$) 2.10 and 2.11 (6 H, 2s, AcO), 4.05 (0.6 H, dd, *J* 12 and

6), 4.2–4.4 (4.3 H, m), 4.56 (0.6 H, dd, *J* 12 and 2), 5.22 (0.6 H, m) and 6.8–7.0 (4 H, m, C_6H_4); *m/z* (ES +ve) 281 [$(M + H)^+$, 40%], 303 [$(M + Na)^+$, 100%].

The mixture of diacetates (20 mg, 0.07 mmol) in methanol (1 cm^3) and tetrahydrofuran (1 cm^3) was hydrolysed with potassium carbonate (25 mg, 0.18 mmol) in water (2 cm^3) at 20 °C for 18 h. The mixture was diluted with ethyl acetate and poured into dilute hydrochloric acid. The organic solution was washed with brine, dried and evaporated to give a mixture of two regioisomeric diols (10 mg, 73%) as a waxy solid: analytical HPLC t_r 4.25 min 44% (compound **32**), and 5.17 min 56% pure (column C); ν_{max}(KBr)/cm^{-1} 3327, 1594, 1494, 1269, 1041 and 758; δ_H(250 MHz; [$^2H_6$]DMSO) 3.45–3.8 (3.5 H, m), 4.00–4.13 (2 H, m), 4.3–4.4 (0.6 H, m), 4.71 (0.6 H, t, *J* 5, CH_2OH), 5.03 (0.75 H, t, *J* 5, CH_2OH), 5.18 (0.6 H, d, *J* 5, CHO*H*) and 6.77–6.90 (4 H, m, C_6H_4); *m/z* (ES +ve) 197 $(M + H)^+$; LCMS (ES +ve) t_r 3.30 min (*m/z* 214 [$(M + NH_4)^+$, 100%], 196 {[$(M + NH_4) - H_2O]^+$, 98%}) and t_r 3.54 min (*m/z* 214 [$(M + NH_4)^+$, 100%], 196 {[$(M + NH_4) - H_2O]^+$, 100%}).

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