Chemoenzymatic synthesis of the *trans*-dihydrodiol isomers of monosubstituted benzenes *via anti*-benzene dioxides

Derek R. Boyd,*[a,b] Narain D. Sharma,[a,b] Nuria M. Llamas,[a] Colin R. O'Dowd[a] and Christopher C. R. Allen[c]

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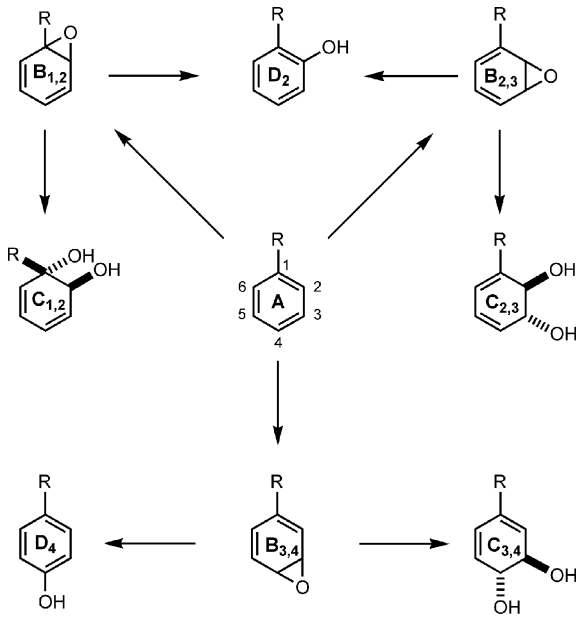
Enantiopure *cis*-2,3-dihydrodiols, available from dioxygenase-catalysed *cis*-dihydroxylation of monosubstituted benzene substrates, have been used as synthetic precursors of the corresponding *trans*-3,4-dihydrodiols. The six-step chemoenzymatic route from *cis*-dihydrodiol precursors, involving acetonide, tetraol, dibromodiacetate and diepoxide intermediates, and substitution of vinyl bromide and iodide atoms, has been used in the synthesis of ten *trans*-dihydrododiol derivatives of substituted benzenes. The general applicability of the method has been demonstrated by its use in the synthesis of both enantiomers of the *trans*-1,2-and 3,4-dihydrodiol derivatives of toluene.

Introduction

The dioxygenase-catalysed metabolism of mono- and poly-cyclic arenes, in prokaryotic (bacterial) cells, has been widely studied. Since the first report by Gibson *et al.*,[1] several hundred examples of *cis*-dihydrodiol metabolites have been reported to date, and in many cases the bioproducts have been used as synthetic precursors.[2–12] Alternative metabolic pathways for arenes **A** have been adopted in eukaryotic (animal, plant and fungal) cells involving monooxygenase enzymes to yield the corresponding arene oxides $\mathbf{B}_{1,2}$, $\mathbf{B}_{2,3}$ and $\mathbf{B}_{3,4}$ as initial metabolites (Scheme 1). Arene oxide intermediates are often unstable and rapidly isomerise to phenols (mainly $\mathbf{D}_2$ and $\mathbf{D}_4$) or undergo epoxide hydrolase-catalysed hydrolysis to yield the corresponding *trans*-dihydrodiols $\mathbf{C}_{1,2}$, $\mathbf{C}_{2,3}$ and $\mathbf{C}_{3,4}$. The small number of arene oxide metabolites that have been isolated (or detected) to date include the monocyclic arene oxide derivatives ($\mathbf{B}_{1,2} = \mathbf{B}_{2,3} = \mathbf{B}_{3,4}$ where R = H and $\mathbf{B}_{1,2}$ where R = CO_2Me) from benzene[13] (**A**, R = H) and methyl benzoate[14] (**A**, R = CO_2Me) respectively (Scheme 1). Arene oxide intermediates have also been isolated from polycyclic aromatic hydrocarbon (PAH) metabolism, *e.g.* naphthalene[15] and polycyclic azaarene metabolism *e.g.* quinoline.[16] Similarly, only a few *trans*-dihydrodiol metabolites have been isolated from monocyclic arenes *e.g.* benzene ($\mathbf{C}_{1,2} = \mathbf{C}_{2,3} = \mathbf{C}_{3,4}$ where R = H)[17] and monosubstituted benzene substrates ($\mathbf{C}_{2,3}$ where R = CO_2H)[18,19] and ($\mathbf{C}_{3,4}$ where R = Cl, Br, CO_2H).[18,20,21] In contrast, *trans*-dihydrodiols are generally the major mammalian metabolites from PAHs including potent carcinogens such as benzo[*a*]pyrene.[22]

trans-Dihydrodiols have been found to be much more stable than the corresponding *cis*-dihydrodiols and thus could, in principle, be more useful as synthetic precursors.[23] However, at present only *trans*-dihydrodiols $\mathbf{C}_{2,3}$ and $\mathbf{C}_{3,4}$ (R = CO_2H) of benzoic acid are available in significant quantities from arene biotransformations,[18,19] and have proved to be versatile starting compounds for the synthesis of natural products.[24] *trans*-Dihydrodiols **C** containing substituents other than a carboxylic group are not yet available as direct bacterial biotransformation products. To address this issue a limited range of *trans*-3,4-dihydrodiols of type $\mathbf{C}_{3,4}$ (Scheme 1), were earlier obtained using a novel chemoenzymatic route from the corresponding *cis*-dihydrodiol precursors. Thus, in a preliminary communication we reported that *trans*-diols $\mathbf{C}_{3,4}$ (R = Cl, Br, I) can be produced *via* the corresponding *anti*-benzene dioxide intermediates.[25] This route has now been adopted for a wider range of both *trans*-dihydrodiol regioisomers and enantiomers.



Scheme 1

In the Results and discussion section, the term *cis*-2,3-dihydrodiol has been used to describe bioproducts obtained *via cis*-dihydroxylation at the 2,3-bond of a monosubstituted

[a]*School of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast, UK BT9 5AG. E-mail: dr.boyd@qub.ac.uk; Fax: +44 2890 323321; Tel: +44 2897 274421*
[b]*CenTACatQueen's University Belfast, Belfast, UK BT9 5AG*
[c]*School of Biological Sciences, Queen's University Belfast, Belfast, UK BT9 5AG*

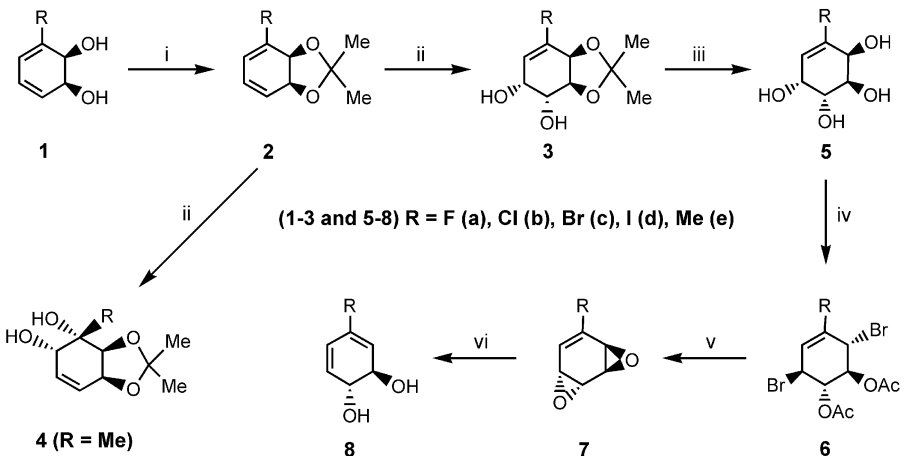
benzene. Similarly, the terms *trans*-1,2-dihydrodiol and *trans*-3,4-dihydrodiol have been used to describe derivatives formed by epoxidation/hydrolysis at the 1,2- and 3,4-bonds of monosubstituted benzenes. However, it should be noted that the correct systematic nomenclature used in the Experimental section describes each of these 2,3-*cis*-, 1,2-*trans*- and 3,4-*trans*-dihydrodiols as 1,2-diols.

Results and discussion

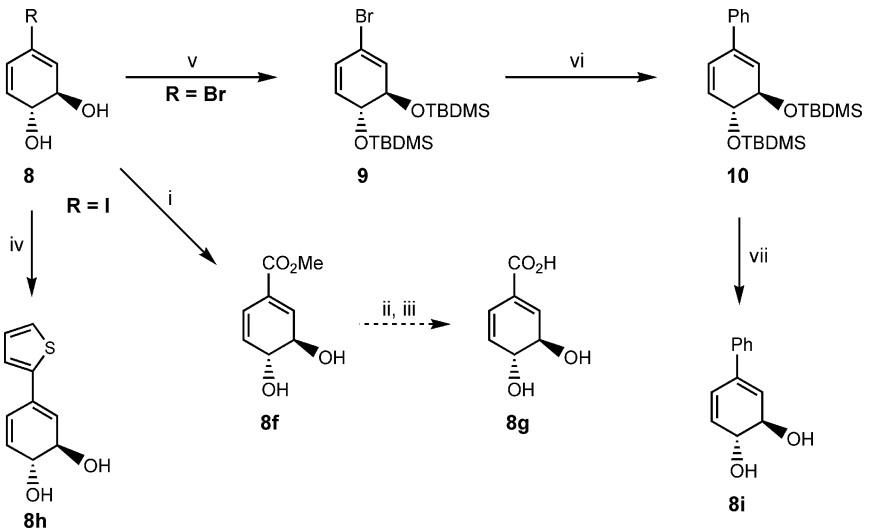
The *cis*-dihydrodiol metabolites of fluorobenzene (**1a**), chlorobenzene (**1b**), bromobenzene (**1c**), iodobenzene (**1d**), and toluene (**1e**) are readily available in good quantities through large-scale biotransformations, using the UV4 constitutive mutant strain of the soil bacterium *Pseudomonas putida*.[26] With the exception of the *cis*-dihydrodiol of fluorobenzene **1a** (*ca.* 60% ee), the other diols **1b–1e** were enantiopure (>98% ee).

A six-step synthetic sequence, involving acetonide formation (**1** → **2**), *cis*-dihydroxylation (**2** → **3** or **2** → **4**), deprotection (**3** → **5**), dibromodiacetylation (**5** → **6**), benzene dioxide formation (**6** → **7**) and reduction (**7** → **8**), was used to form the corresponding halogenated *trans*-dihydrodiols **8a–8d** (Scheme 2). The bromine and iodine atoms present in *trans*-dihydrodiols **8c** and **8d** were, in turn, found to be readily substituted yielding additional *trans*-dihydrodiols **8f**, **8h** and **8i** (Scheme 3). Minor modification of the procedure, involving separation of the isomeric *cis*-diols **3e** and **4**, *via* dibenzoates $\mathbf{3e}_{Bz}$ and $\mathbf{4}_{Bz}$ (Scheme 4), were required for the synthesis of the corresponding toluene *trans*-dihydrodiol **8e** and **14** (Schemes 2 and 4).

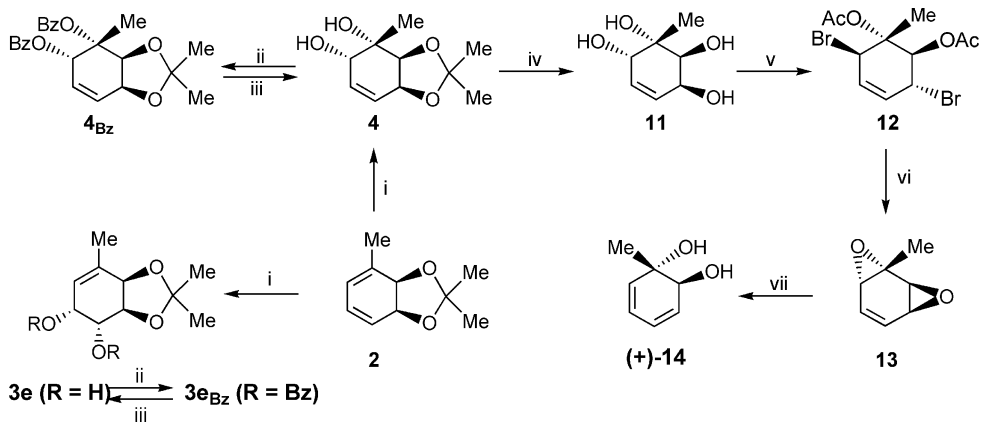
Protection of *cis*-dihydrodiols **1a–1e**, as acetonides **2a–2e**, was achieved in high yield (93–97%) using a mixture of acetone and dimethoxypropane. The acetonide derivatives **2a–2e** have been widely used in synthesis, since they are less likely to aromatise than the corresponding *cis*-dihydrodiols.[27–31] The acetonide group present in compounds **2a–2e** was used to stereodirect further oxidation. Thus, the steric requirements of the acetonide group ensured that catalytic *cis*-dihydroxylation of acetonides **2a–2d**, using osmium tetroxide and 4-methylmorpholine-*N*-oxide (NMNO), yielded the diol acetonide derivatives **3a–3d** (70–87% yield) exclusively (Scheme 2). *cis*-Dihydroxylation of acetonide **2e** proved to be exceptional; it gave a 60 : 40 mixture of regioisomers



Scheme 2 *Reagents*: i 2,2-DMP; ii NMNO, OsO_4, Me_2CO, H_2O; iii THF, TFA, H_2O; iv $AcOCMe_2COBr$, MeCN; v NaOMe, Et_2O; vi $Pd(OAc)_2$, CO, K_2CO_3, THF, H_2O.



Scheme 3 *Reagents*: i $Pd(OAc)_2$, CO, NaOAc, MeOH; ii KOH, H_2O; iii H^+; iv $(Ph_3P)_4Pd$, $Bu_3SnC_4H_3S$; v TBDMSOTf, CH_2Cl_2, Et_3N; vi PhMgBr, $Ni(ac)_2$, EtO_2; vii Bu_4NF, THF.



Scheme 4 *Reagents*: i OsO_4, NMNO, Me_2CO, H_2O; ii BzCl, pyridine; iii NaOH, MeOH; iv THF, TFA, H_2O; v $AcOCMe_2COBr$, MeCN; vi NaOMe, Et_2O; vii $Pd(OAc)_2$, CO, K_2CO_3, THF, H_2O.

3e and **4** in which the diol moiety was *anti* to the acetonide group in each case. This mixture was separated, by flash chromatography (25% EtOAc in hexane), as dibenzoates $\mathbf{3e}_{Bz}$ and $\mathbf{4}_{Bz}$. Base-catalysed hydrolysis of dibenzoate $\mathbf{3e}_{Bz}$ regenerated a pure sample of the required diol acetonide **3e** (Scheme 4).

Hydrolysis of the diol acetonides **3a–3e**, under acidic conditions (TFA or HCl) yielded (90–96%) the corresponding tetraols **5a–5e** (Scheme 2). Treatment of each of the tetraols **5a–5e**, with 2-acetoxyisobutyryl bromide (2.5 mol equiv.), then afforded (70–88%) bis-*trans*-bromoacetates **6a–6e**. The latter isomers were formed, exclusively, *via* nucleophilic attack of bromide at the allylic positions of the transient 1,3-dioxolane intermediates.

Treatment of bis-*trans*-bromoacetates **6a–6e** with sodium methoxide gave *anti*-benzene dioxides **7a–7e** (68–82% yield, Scheme 2). Dioxides **7a–7e** proved to be configurationally stable at elevated temperatures, in contrast to the corresponding *syn*-benzene dioxides which were found to racemize, at *ca.* 85 °C, *via* an electrocyclic rearrangement through the valence tautomeric 1,4-dioxocins.[25]

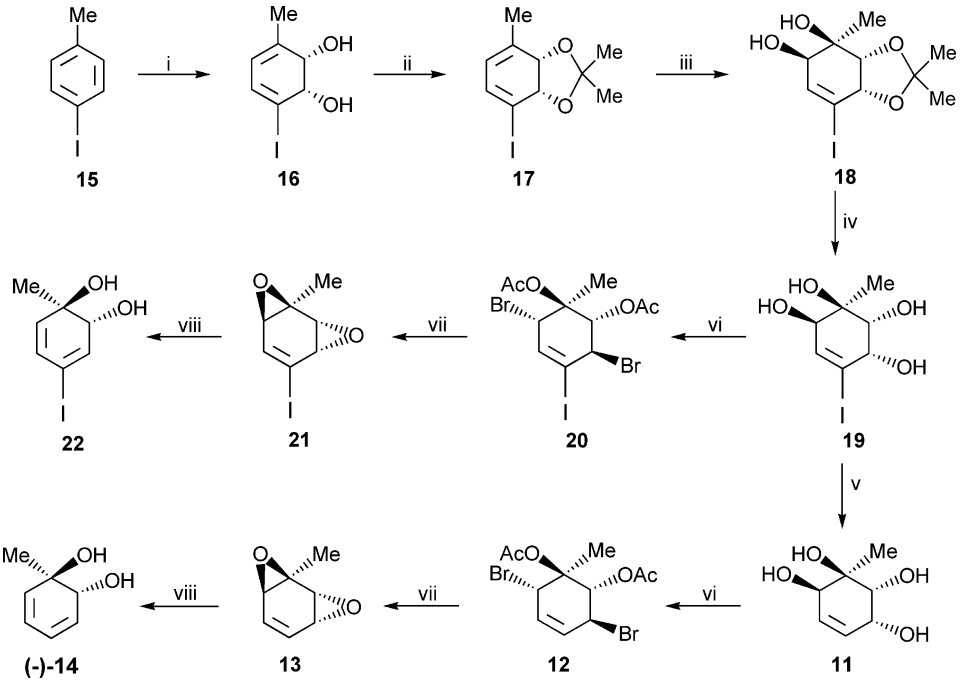
The final stage of the six-step synthesis, from *cis*-2,3-dihydrodiols **1a–1e**, involved a novel palladium catalysed reduction reaction (Scheme 2). Aryl iodides can be substituted with a carboxy group, on treatment with catalytic quantities of $Pd(OAc)_2$ in a mixture of K_2CO_3, THF, H_2O under CO atmosphere.[32] When these conditions were applied to the *anti*-benzene dioxide **7d**, substitution of the vinylic iodine atom did not occur; instead reduction to the corresponding *trans*-3,4-dihydrodiol **8d** (90% yield) was observed. Similar conditions were then employed to convert the other *anti*-benzene dioxides **7a–7c**, **7e** to the corresponding *trans*-dihydrodiols **8a–8c**, **8e** (68–86% yield). While the mechanism of this catalytic redox reaction has not been elucidated yet, it is assumed that it proceeds through the reduction of Pd(II) diacetate to Pd(0) with concomitant oxidation of CO to CO_2. The assumption was supported by the observation that the *anti*-benzene dioxides **7** were also reduced, in lower yields, to the corresponding *trans*-dihydrodiols **8**, with $(PPh_3)_4Pd$ in a mixture of K_2CO_3, THF, H_2O without the CO atmosphere.

Substitution of the vinylic halogen atoms of *trans*-3,4-dihydrodiols **8** (**8c** where R = Br; **8d** R = I), prepared by the Pd(0) catalysed reduction method, provided additional members of this series (Scheme 3). Thus, the iodine atom in *trans*-dihydrodiol **8d** was directly replaced by a carbomethoxy group using similar conditions to those used for the reduction of the *anti*-benzene dioxides **7a–7e** (Scheme 2), *i.e.* Pd-catalysed carbonylation in MeOH containing sodium acetate to yield (80%) *trans*-3,4-dihydrodiol **8f** (Scheme 3). The alkaline hydrolysis of the methyl ester group in a racemic sample of compound **8f** has been reported to gave racemic carboxylic acid **8g** (KOH, H_2O; 74% yield).[33] Both *trans*-2,3- and 3,4-dihydrodiol derivatives of benzoic acid have also been reported as enantiopure secondary metabolites of the shikimate pathways using recombinant cells of *Escherichia coli*[18] and *Klebsiella pneumoniae*.[19] *trans*-3,4-Dihydrodiol **8g** is now available by a direct biotransformation procedure,[18] chemical synthesis[33] or by our chemoenzymatic method. Palladium-catalysed cross-coupling, using $(PPh_3)_4Pd$ and 2-(tributylstannyl)thiophene and *trans*-dihydrodiol **8d** as starting material, resulted in the direct replacement of the iodine atom by a 2-thienyl group to give *trans*-dihydrodiol **8h** (83% yield, Scheme 3).

Protection of the *trans*-dihydrodiol **8c** by reaction with TBDMSOTf yielded di-TBDMS derivative **9** (92%) and facilitated the indirect cross-coupling of the vinyl bromide with phenylmagnesium bromide in the presence of nickel(II) acetylacetonate. The phenyl di-TBDMS derivative **10** (52% yield) on deprotection yielded (89%) the *trans*-3,4-dihydrodiol derivative of biphenyl **8i** (Scheme 3).

Diol acetonide **4**, obtained in high yield (87%) by hydrolysis of the corresponding dibenzoate derivative $\mathbf{4}_{Bz}$, was used as a precursor in the synthesis of the (+)-*trans*-1,2-dihydrodiol **14** (Scheme 4). The sequence used for the chemoenzymatic synthesis of diol **14** (70% yield from dioxide **13**) was similar to that used in Scheme 1 and involved tetraol (**11**, 82% yield), bis-bromoacetate (**12**, 79% yield), *anti*-benzene dioxide (**13**, 68% yield) intermediates. The versatility of this method is shown by the synthesis of both *trans*-1,2- (**14**) and *trans*-3,4-dihydrodiols (**8e**) from the corresponding *cis*-2,3-dihydrodiol precursor (**1e**).

The present method also appears to be applicable to a relatively wide range of *trans*-3,4-dihydrodiol derivatives (*e.g.* **8a–8h**, Schemes 2 and 3) that could be synthesised from monosubstituted benzene *cis*-2,3-dihydrodiol precursors (*e.g.* **1a–1e**). Unfortunately, only *trans*-1,2-dihydrodiol derivatives of monosubstituted benzene rings (*ipso-trans*-dihydrodiols) bearing an alkyl (*e.g.* **14**) or aryl group are likely to be sufficiently stable to permit their



Scheme 5 *Reagents*: i *P. putida* UV4/O_2; ii 2,2-DMP; iii OsO_4, NMNO, Me_2CO, H_2O; iv THF, TFA, H_2O; v H_2, Pd–C, NaOAc, MeOH; vi $AcOCMe_2COBr$, MeCN; vii NaOMe, Et_2O; viii $Pd(OAc)_2$, CO, K_2CO_3, THF, H_2O.

synthesis and isolation. Thus, no attempts were made to synthesise the *trans*-1,2-dihydrodiols from the corresponding halobenzene *cis*-dihydrodiols (**1a–1d**).

Using 4-iodotoluene **15** as substrate, the corresponding *cis*-dihydrodiol metabolite **16** had earlier been isolated as a bioproduct from whole cells of *P. putida* UV4 (65% yield).[34] Conversion of the available *cis*-dihydrodiol **16** (*ca.* 80% ee) to (−)-*trans*-dihydrodiol **14** ($[\alpha]_D$ −37, 82% ee, Scheme 5), was carried out by employing a synthetic sequence similar to that used earlier to convert the *cis*-dihydrodiol **1e** (>98% ee) precursor into (+)-*trans*-dihydrodiol **14** ($[\alpha]_D$ +45, >98% ee, Schemes 2 and 4). The only significant difference was the inclusion of a catalytic hydrogenolysis step (**19** → **11**). The synthetic sequence again involved the formation of acetonide **17**, diol acetonide **18**, tetraols **19** and **11**, bis-bromoacetate **12**, and *anti*-benzene dioxide **13** intermediates, in similar yields to those previously reported, followed by the reduction step to give the (−)-*trans*-dihydrodiol **14** (Scheme 5). Iodotetraol intermediate **19** was also converted to *trans*-dihydrodiol **22**, *via* dibromodiacetate **20** and dioxide **21** intermediates, to provide a further example of this novel type of *ipso*-*trans*-dihydrodiol. Direct substitution of the iodine atom in compound **22**, using methods already described (Scheme 3) could, in principle, yield a further range of *ipso*-*trans*-dihydrodiol derivatives of disubstituted benzene substrates.

In a similar manner, hydrogenolysis of the *cis*-dihydrodiol metabolite **16** (82% ee) derived from 4-iodotoluene **15** yielded the *abnormal* (−)-*cis*-dihydrodiol enantiomer of toluene **1e** which was converted to the corresponding (+)-*trans*-3,4-dihydrodiol **8e** (*ca.* 80% ee) using the route shown in Scheme 2.

Conclusion

A generally applicable route to the synthesis of a series of *trans*-3,4- and -1,2-dihydrodiols of either absolute configuration, from the corresponding *cis*-2,3-dihydrodiol metabolites, *via* the formation and reduction of the corresponding *anti*-benzene dioxide intermediates, has been devised. A minor modification of this method has allowed the synthesis of both enantiomers of the 1,2- and 3,4-*trans*-dihydrodiols (**14** and **8e**) of toluene.

Experimental

NMR (^1H and ^{13}C) spectra were recorded on Bruker Avance DPX-300 and DPX-500 instruments and mass spectra were run at 70 eV, on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method, with perfluorokerosene as the standard. Elemental microanalyses were carried out on a PerkinElmer 2400 CHN microanalyser. For optical rotation ($[\alpha]_D$) measurements (*ca.* 20 °C, 10^{-1} deg cm^2 g^{-1}), a PerkinElmer 341 polarimeter was used. Flash column chromatography and preparative layer chromatography (PLC) were performed on Merck Kieselgel type 60 (250–400 mesh) and $PF_{254/366}$ respectively. Merck Kieselgel type $60F_{254}$ analytical plates were used for TLC. Compounds (1*S*,2*S*)-**1a** (*ca.* 60% ee), (1*S*,2*S*)-**1b–1d**, (1*S*,2*R*)-**1e**, **2d–6d** (*ca.* 98% ee) and (1*R*,2*R*)-**16** (*ca.* 80% ee), available from earlier work,[26,34,35] were used for this study.

Syntheses of acetonide derivatives 2a–2c, 2e and 17

To an ice cooled solution of *cis*-dihydrodiol (2.5–10 mmol), in a mixture of acetone (5 cm^3) and 2,2-DMP (10 cm^3), *p*-toluenesulfonic acid (0.05 g) was added. The reaction mixture was stirred in an ice bath (15 min) and then at room temperature until the diol had reacted completely (TLC analysis). The solvents were removed under reduced pressure and the residue extracted with a mixture of water (25 cm^3) and diethyl ether (2 × 30 cm^3). The diethyl ether extract was washed with water (20 cm^3), dried

(Na_2SO_4), concentrated, and the crude acetonide obtained was purified by flash column chromatography (20% EtOAc in hexane). Acetonides **2a–2c** and **2e** were found to be spectrally identical to those reported.[27–31]

(3a*S*,7a*S*)-4-Fluoro-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole 2a[27]. Colourless oil (1.6 g, 95%); $[\alpha]_D$ +2 (*c* 1.4, $CHCl_3$); δ_H(500 MHz, $CHCl_3$) 1.43, 1.46 [3 H × 2, s, $C(Me)_2$], 4.72 (1 H, dd, $J_{3a,F}$ 9.3, $J_{3a,7a}$ 3.5, 3a-H), 4.87 (1 H, dd, $J_{7a,7}$ 6.0, $J_{7a,3a}$ 3.5, 7a-H), 5.59 (1 H, dd, $J_{7,6}$ 9.7, $J_{7,7a}$ 6.0, 7-H), 5.74 (1 H, dd, $J_{6,7}$ 9.7, $J_{6,5}$ 3.8, 6-H), 5.91 (1 H, dd, $J_{5,F}$ 10.9, $J_{5,6}$ 3.8, 5-H); *m*/*z* (EI) 155 (M^+ − Me, 3%), 128 (3), 113 (31), 112 (100), 100 (15), 97 (4), 84 (17), 73 (6), 57 (34), 53 (8), 43 (29), 39 (15) and 31 (7).

(3a*S*,7a*S*)-4-Chloro-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole 2b[28]. Colourless oil (0.6 g, 94%); $[\alpha]_D$ +43 (*c* 0.67, $CHCl_3$); (lit.[28] $[\alpha]_D$ +45); δ_H(300 MHz, $CDCl_3$) 1.42, 1.43 [3 H × 2, s, $C(Me)_2$], 4.68 (1 H, d, $J_{3a,7a}$ 5.3, 3a-H), 4.78 (1 H, dd, $J_{7a,3a}$ 5.3, $J_{7a,7}$ 4.1, 7a-H), 5.92 (2 H, m, $J_{6,5}$ 4.1, 6-H, 7-H), 6.12 (1 H, d, $J_{5,6}$ 4.1, 5-H).

(3a*S*,7a*S*)-4-Bromo-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole 2c[29]. Colourless oil (0.57 g, 95%); $[\alpha]_D$ +45 (*c* 0.70, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 1.43, 1.44 [3 H × 2, s, $C(Me)_2$], 4.73 (2 H, m, 3a-H, 7a-H), 5.88 (1 H, $J_{6,7}$ 9.6, $J_{6,5}$ 6.0, 6-H), 5.96 (1 H, m, 7-H), 6.35 (1 H, d, $J_{5,6}$ 6.0, 5-H).

(3a*R*,7a*S*)- and (3a*S*,7a*R*)-2,2,4-Trimethyl-3a,7a-dihydro-1,3-benzodioxole 2e[31]. Colourless oil (1.3 g, 97%); $[\alpha]_D$ +98 (*c* 0.65, $CHCl_3$); (lit.[31] $[\alpha]_D$ +95); δ_H(500 MHz, $CDCl_3$) 1.27, 1.43 [3 H × 2, s, $C(Me)_2$], 1.89 (3 H, s, Me), 4.40 (1 H, s, $J_{3a,7a}$ 8.7, 3a-H), 4.63 (1 H, dd, $J_{7a,3a}$ 8.7, $J_{7a,7}$ 4.2, 7a-H), 5.77 (1 H, $J_{5,6}$ 6.2, 5-H), 5.83 (1 H, dd, $J_{7,6}$ 9.7, $J_{7,7a}$ 4.2, 7-H), 5.97 (1 H, dd, $J_{6,7}$ 9.7, $J_{6,5}$ 6.2, 6-H).

(3a*S*,7a*R*) Enantiomer, colourless oil, $[\alpha]_D$ −89 (*c* 0.53, $CHCl_3$).

(3a*S*,7a*S*)-4-Iodo-2,2,7-trimethyl-3a,7a-dihydro-1,3-benzodioxole 17. Colourless viscous oil (1.07 g, 93%); R_f 0.53 (10% Et_2O in hexane); $[\alpha]_D$ +69 (*c* 0.77, $CHCl_3$); (Found: M^+, 291.9949. $C_{10}H_{13}O_2I$ requires 291.9960); δ_H(500 MHz, $CDCl_3$) 1.43, 1.44 [3 H × 2, s, $C(Me)_2$], 1.88 (3 H, s, Me), 4.46 (1 H, d, $J_{7a,3a}$ 8.4, 7a-H), 4.74 (1 H, d, $J_{3a,7a}$ 8.4, 3a-H), 5.50 (1 H, d, $J_{6,5}$ 6.2, 6-H) 6.55 (1 H, d, $J_{5,6}$ 6.2, 5-H); δ_C(125 MHz, $CDCl_3$) 20.29, 25.39, 26.90, 76.03, 78.82, 96.27, 106.33, 120.54, 134.30, 134.91; *m*/*z* (EI) 292 (M^+, 78%), 277 (84), 235 (80), 165 (24), 150 (87), 127 (86), 109 (90), 77 (77), 65 (87), 59 (84), 41 (93), 38 (85) and 29 (100).

Syntheses of diol acetonides 3a–3c and 18

To a solution of acetonides **2a–2c** or **17** (1.5–3.0 mmol), in a mixture of acetone–water (5 : 1; 15 cm^3), was added NMNO (2.3 mol equiv.) and a catalytic amount of osmium tetroxide (*ca.* 0.002 g). The reaction mixture was stirred at room temperature until the dihydroxylation was completed (TLC analysis). A saturated solution of sodium metabisulfite (1 cm^3) was added and the reaction mixture stirred at room temperature (30 min). The solvents were removed *in vacuo*, a saturated solution of NaCl was added (30 cm^3), and the mixture extracted with EtOAc (2 × 35 cm^3). The organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and the crude diol acetonides **3a–3c** or **18** purified by flash column chromatography (50% EtOAc in hexane).

(3a*S*,4*R*,5*R*,7a*S*)-7-Fluoro-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol 3a. Viscous oil which solidified on standing to give an off-white crystalline solid (0.27 g, 89%); mp 48–50 °C; $[\alpha]_D$ −46 (*c* 0.77, $CHCl_3$); (Found: M^+ − Me 189.0566. $C_8H_{10}FO_4$ requires 189.0563); δ_H(500 MHz, $CDCl_3$) 1.39, 1.47 [3 H × 2, s, $C(Me)_2$], 4.01 (1 H, dd, $J_{4,3a}$ 6.3, $J_{4,5}$ 3.7, 4-H), 4.45 (1 H, dd, $J_{5,4}$ 4.8, $J_{5,6}$ 4.4, 5-H), 4.48 (1 H, dd, $J_{3a,7a}$ 7.7, $J_{3a,4}$ 6.3, 3a-H), 4.71 (1 H, dd, $J_{7a,F}$ 4.8, $J_{7a,3a}$ 3.4, 7a-H), 5.43 (1 H, dd, $J_{6,F}$ 14.7, $J_{6,5}$ 4.4, 6-H); δ_C(125 MHz, $CDCl_3$) 26.02, 27.86, 65.59, 70.40, 70.90, 76.19, 106.00, 111.04, 157.60; *m*/*z* (EI) 189 (M^+ − Me, 74%), 129 (19), 117 (12), 111 (25), 101 (100), 99 (18), 83 (17), 73 (12), 59 (33) and 55 (29).

(3a*S*,4*R*,5*R*,7a*S*)-7-Chloro-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol 3b. Colourless oil (0.50 g, 72%); $[\alpha]_D$ −8 (*c* 0.67, $CHCl_3$) (lit.[36] $[\alpha]_D$ −8.1); δ_H(300 MHz, $CDCl_3$) 1.41, 1.44 [3 H × 2, s, $C(Me)_2$], 2.78 (1 H, br s, OH), 2.83 (1 H, br s, OH), 4.16 (1 H, m, 4-H), 4.41 (1 H, br s, 5-H), 4.46 (1 H, m, $J_{3a,7a}$ 5.6, 3a-H), 4.60 (1 H, d, $J_{7a,3a}$ 5.6, 7a-H), 5.93 (1 H, d, $J_{6,5}$ 3.4, 6-H).

(3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol 3c. Colourless crystals (0.4 g, 70%); mp 114 °C (lit.[36] mp 113–114 °C); $[\alpha]_D$ −11 (*c* 0.57, $CHCl_3$), (lit.[35] $[\alpha]_D$ −11.6); δ_H(500 MHz, $CHCl_3$) 1.41, 1.44 [3 H × 2, s, $C(Me)_2$], 2.52 (2 H, br s, OH), 4.19 (1 H, t, $J_{4,3a} = J_{4,5}$ 5.4, 4-H), 4.37 (1 H, br s, 5-H), 4.45 (1 H, m, 7a,-H), 4.66 (1 H, dd, $J_{3a,4}$ 5.4, $J_{3a,2}$ 1.4, 3a-H), 6.16 (1 H, dd, $J_{6,5}$ 3.2, $J_{6,2}$ 0.9, 6-H).

(3a*R*,4*R*,5*R*,7a*S*)-7-Iodo-2,2,4-trimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol 18. Colourless crystals (0.9 g, 91%); mp 149 °C (EtOAc–hexane); R_f 0.47 (50% EtOAc in hexane); $[\alpha]_D$ +34 (*c* 0.46, $CHCl_3$); (Found: C 36.45, H 4.4; $C_{10}H_{15}IO_4$ requires C 36.8, H 4.6%); δ_H(500 MHz, $CDCl_3$) 1.39 (3 H, s, Me), 1.39, 1.46 [3 H × 2, s, $C(Me)_2$], 4.10 (1 H, d, $J_{3a,7a}$ 4.8, 3a-H), 4.11 (1 H, d, $J_{5,6}$ 2.1, 5-H), 4.61 (1 H, d, $J_{7a,3a}$ 4.8, 7a-H), 6.32 (1 H, d, $J_{6,5}$ 2.1, 6-H); δ_C(125 MHz, $CDCl_3$) 24.30, 27.01, 27.99, 71.70, 72.94, 79.45, 81.10, 101.93, 110.89, 139.79; *m*/*z* (EI) 326 (M^+, 2%), 311 (30), 283 (27), 253 (5), 251 (12), 225 (22), 223 (10), 207 (9), 195 (12), 167 (11), 141 (7), 126 (15), 124 (100), 115 (89), 95 (33), 81 (16), 74 (27), 68 (31), 65 (8) and 59 (88).

Syntheses of diol acetonides 3e and 4

Catalytic *cis*-dihydroxylation (OsO_4) of acetonide **2e** (1.0 g, 6.0 mmol) gave a mixture, of diastereoisomeric diols **3e** and **4**, which was converted into the corresponding benzoate derivatives (benzoyl chloride/pyridine). The mixture was separated by flash column chromatography (25% EtOAc in hexane) to provide pure samples of dibenzoates $\mathbf{3e}_{Bz}$ and $\mathbf{4}_{Bz}$.

(3a*R*,4*S*,5*R*,7a*R*)-4-(Benzyloxy)-2,2,7-trimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl benzoate $\mathbf{3e}_{Bz}$. Colourless viscous oil (1.38 g, 56%); R_f 0.48 (25% EtOAc in hexane); $[\alpha]_D$ −252 (*c* 0.72, $CHCl_3$); (Found: M^+ − Me, 393.1323. $C_{23}H_{21}O_6$ requires 393. 1338); δ_H(500 MHz, $CDCl_3$) 1.43, 1.51 [3 H × 2, s, $C(Me)_2$], 1.96 (3 H, s, Me), 4.66 (1 H, d, $J_{7a,3a}$ 6.1, 7a-H), 4.75 (1 H, dd, $J_{3a,4}$ 8.2, $J_{3a,7a}$ 6.1, 3a-H), 5.52 (1 H, dd, $J_{4,5}$ 3.9, $J_{4,3a}$ 8.2, 4-H), 5.75 (1 H, dd, $J_{5,6}$ 4.1, $J_{5,4}$ 3.9, 5-H), 5.85 (1 H, d, $J_{6,5}$ 4.1, 6-H), 7.35–7.42 (4 H, m, Ar-H), 7.50–7.55 (2 H, m, Ar-H), 7.96–7.99 (4 H, m, Ar-H); *m*/*z* (EI) 393 (M^+ − Me, 17%), 366 (14), 245 (54), 228 (62), 147 (23), 106 (90), 95 (15), 77 (61), 51 (100), 43 (85) and 39 (32).

(3a*S*,4*R*,5*R*,7a*S*) - 4 - (Benzyloxy) - 2,2,4 - trimethyl - 3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl benzoate 4_{Bz}. White crystalline solid (1.0 g, 41%); mp 111–112 °C (from hexane); R_f 0.29 (25% EtOAc in hexane); $[\alpha]_D$ +146 (*c* 0.99, $CHCl_3$); (Found: C 70.45, H 5.6; $C_{24}H_{24}O_6$ requires C 70.6, H 5.9%); δ_H(500 MHz, $CDCl_3$) 1.36, 1.38 [3 H × 2, s, $C(Me)_2$], 1.42 (3 H, s, Me), 4.23 (1 H, d, $J_{3a,7a}$ 5.2, 3a-H), 4.73 (1 H, dd, $J_{7a,3a}$ 5.2, $J_{7a,7}$ 3.9, 7a-H), 5.65 (1 H, d, $J_{5,6}$ 3.9, 5-H), 5.70 (1 H, m, $J_{7,6}$ 10.3, $J_{7,7a}$ 3.9, 7-H), 5.99 (1 H, dd, $J_{6,7}$ 10.3, $J_{6,5}$ 3.9, 6-H), 7.46–7.49 (4 H, m, Ar-H), 7.60–7.62 (2 H, m, Ar-H), 8.07–8.13 (4 H, m, Ar-H); *m*/*z* (EI) 409 [(M + H)$^+$, 0.2%], 289 (12), 231 (5), 203 (6), 125 (11), 115 (19), 105 (100), 86 (22), 84 (35) and 77 (24).

(3a*S*,4*R*,5*R*,7a*R*)- and (3a*R*,4*S*,5*S*,7a*S*)-2,2,7-Trimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol 3e. A solution of dibenzoate $3e_{Bz}$ (1.5 g, 3.7 mmol) in MeOH (30 cm^3) was treated with aqueous NaOH (5%, 15 cm^3) and the mixture stirred at room temperature until the starting material had reacted completely (TLC analysis). A saturated aqueous solution of NH_4Cl (5 cm^3) was then added and the mixture heated (15 min) on a water bath (60 °C). The solvents were removed under reduced pressure and the residue obtained was purified by flash column chromatography (50% EtOAc in hexane). Diol acetonide **3e** was obtained as a white crystalline solid (0.7 g, 95%); mp 90 °C; $[\alpha]_D$ −96 (*c* 0.58, $CHCl_3$); (Found: M$^+$, 200.1042. $C_{10}H_{16}O_4$ requires 200.1048); δ_H(500 MHz, $CDCl_3$) 1.39, 1.44 [3 H × 2, s, $C(Me)_2$], 1.87 (3 H, s, Me), 3.89 (1 H, dd, $J_{4,5}$ 3.7, $J_{4,3a}$ 7.1, 4-H), 4.26 (1 H, dd, $J_{5,4}$ 3.7 $J_{5,6}$ 3.2, 5-H), 4.34 (1 H, dd, $J_{3a,4}$ 7.1, $J_{3a,7a}$ 6.0, 3a-H), 4.48 (1 H, d, $J_{7a,3a}$ 6.0, 7a-H), 5.63 (1 H, d, $J_{6,5}$ 3.2, 6-H); δ_C(125 MHz, $CDCl_3$) 20.39, 25.99, 27.95, 66.41, 71.20, 75.42, 75.91, 109.45, 124.29, 136.04; *m*/*z* (EI) 200 (M$^+$, 18%), 185 (90), 167 (61), 125 (91), 112 (27), 109 (38), 107 (90), 100 (93), 86 (32), 84 (100), 82 (89), 77 (93), 73 (95), 66 (92), 60 (87), 57 (93), 50 (87), 44 (72), 42 (95), 39 (93), 30 (47) and 27 (86).

(3a*R*,4*S*,5*S*,7a*S*) Enantiomer, mp 85 °C, $[\alpha]_D$ +76.0 (*c* 0.51, $CHCl_3$).

(3a*S*,4*S*,5*S*,7a*S*) - 2,2,4 - Trimethyl - 3a,4,5,7a - tetrahydro - 1,3-benzodioxole-4,5-diol 4. Alkaline hydrolysis of the dibenzoate 4_{Bz} (0.9 g, 2.2 mmol) under similar conditions, yielded diol acetonide **4** as white crystalline solid (0.4 g, 91%); mp 59–60 °C (from EtOAc–hexane); $[\alpha]_D$ +79 (*c* 0.62, $CHCl_3$); (Found: M$^+$ − Me, 184.9923. $C_9H_{13}O_4$ requires 184.9937); δ_H(500 MHz, $CDCl_3$) 1.36 (3 H, s, Me), 1.36, 1.46 [3 H × 2, s, $C(Me)_2$], 2.63 (1 H, br s, OH), 2.87 (1 H, br s, OH), 4.13 (1 H, s, 5-H), 4.18 (1 H, d, $J_{3a,7a}$ 5.0, 3a-H), 4.64 (1 H, dd, $J_{7a,3a}$ 5.0, $J_{7a,7}$ 2.7, 7a-H), 5.67 (1 H, m, $J_{7,6}$ 10.3, 7-H), 5.75 (1 H, d, $J_{6,7}$ 10.3, 6-H); δ_C(125 MHz, $CDCl_3$) 23.82, 26.57, 27.78, 69.29, 72.50, 73.31, 79.82, 109.59, 127.67, 129.62; *m*/*z* (EI) 185 (M$^+$ − Me, 39%), 157 (7), 127 (31), 125 (54), 115 (98), 107 (27), 100 (7), 97 (66), 87 (12), 83 (24), 81 (62), 74 (33), 69 (28), 59 (62), 53 (25), 45 (17), 43 (98), 41 (68), 32 (100) and 28 (90).

Syntheses of tetraols 5a–5c, 5e, 11 and 19

Method (a): a solution of the diol acetonide (1.5–5.0 mmol) in MeOH (25 cm^3) was treated with aqueous HCl solution (1.5 M, 10 cm^3) and the mixture heated at 50 °C until the starting material had reacted completely (TLC analysis). The crude tetraol, obtained after removal of the solvents, was purified either by chromatography or by crystallization. Method (b): alternatively, a solution of the diol acetonide (1 mmol), in a mixture of THF (4 cm^3), water (1 cm^3) and TFA (0.5 cm^3), was heated at 50 °C until the starting material had reacted completely.

(1*R*,2*R*,3*S*,4*S*)-5-Fluoro-5-cyclohexene-1,2,3,4-tetraol 5a. Removal of the acetonide group of diol **3a** (method a) gave tetraol **5a** as colourless crystals (0.7 g, 90%); mp 152–155 °C (from MeOH–acetone); $[\alpha]_D$ −3.0 (*c* 0.5, MeOH); (Found: C 43.6, H 5.5; $C_6H_9FO_4$ requires C 43.9, H 5.5%); δ_H(500 MHz, CD_3OD) 3.54 (1 H, dd, $J_{3,2}$ 10.3, $J_{3,4}$ 4.4, 3-H), 3.68 (1 H, dd, $J_{2,3}$ 10.3, $J_{2,1}$ 4.7, 2-H), 4.07 (1 H, dd, $J_{1,6}$ 5.3, $J_{1,2}$ 4.7, 1-H), 4.12 (1 H, dd, $J_{4,F}$ 8.0, $J_{4,3}$ 4.4, 4-H), 5.25 (1 H, dd, $J_{6,F}$ 13.8, $J_{6,1}$ 5.3, 6-H); δ_C(125 MHz, CD_3OD) 64.88, 66.80, 68.23, 68.56, 106.38, 160.99; *m*/*z* (EI) 164 (M$^+$, 2%), 146 (2), 128 (4), 129 (33), 117 (8), 113 (12), 111 (21), 104 (43), 85 (31), 71 (74), 57 (79), 43 (100), 39 (17), 32 (13) and 29 (27).

(1*R*,2*R*,3*S*,4*S*)-5-Chloro-5-cyclohexene-1,2,3,4-tetraol 5b. Cleavage of acetonide group of diol **3b** (method b) yielded tetraol **5b**, a white solid, (0.56 g, 92%); mp 147–149 °C (from acetone); $[\alpha]_D$ −161 (*c* 0.47, MeOH); (Found: M$^+$ − H_2O, 162.0091. $C_6H_7ClO_3$ requires 162.0084); δ_H(500 MHz, D_2O) 4.01 (1 H, dd, $J_{3,2}$ 9.9, $J_{3,4}$ 4.4, 3-H), 4.14 (1 H, dd, $J_{2,3}$ 9.9, $J_{2,1}$ 5.1, 2-H), 4.44 (1 H, d, $J_{4,3}$ 4.4, 4-H), 4.47 (1 H, t, $J_{1,2} = J_{1,6}$ 5.1, 1-H), 6.19 (1 H, d, $J_{6,1}$ 5.1, 6-H); δ_H(75 MHz, D_2O) 66.73, 68.21, 68.99, 71.22, 127.37, 135.47; *m*/*z* (EI) 162 (M$^+$ − H_2O, 13%), 133 (22), 122 (75), 120 (100), 93 (42), 91 (82), 60 (40), 39 (36) and 29 (40).

(1*R*,2*R*,3*S*,4*S*)-5-Bromo-5-cyclohexene-1,2,3,4-tetraol 5c. Cleavage of acetonide group of diol **3c** (method b) gave tetraol **5c** as colourless crystals (0.32 g, 94%); mp 99–102 °C (from MeOH–acetone); $[\alpha]_D$ −74 (*c* 0.47, MeOH); (Found: C 32.3, H 3.9; $C_6H_9BrO_4$ requires C 32.1, H 4.0%); δ_H(500 MHz, D_2O) 3.95 (1 H, dd, $J_{3,2}$ 9.8, $J_{3,4}$ 4.3, 3-H), 4.09 (1 H, dd, $J_{2,3}$ 9.8, $J_{2,1}$ 4.4, 2-H), 4.36 (1 H, m, 1-H), 4.44 (1 H, d, $J_{4,3}$ 4.3, 4-H), 6.36 (1 H, d, $J_{6,1}$ 5.1, 6-H); δ_C(75 MHz, D_2O) 67.45, 68.28, 69.34, 72.70, 126.51, 131.76; *m*/*z* (EI) 206 (M$^+$ − H_2O, 4%), 177 (5), 164 (100), 135 (28), 127 (7), 109 (12), 81 (31), 69 (22), 60 (55).and 57 (26).

(1*R*,2*R*,3*R*,4*R*)- and (1*S*,2*S*,3*S*,4*R*)-5-Methyl-5-cyclohexene-1,2,3,4-tetraol 5e. Deprotection of the acetonide group of diol **3e** (method a) yielded tetraol **5e** (0.8 g, 80%), as a white crystalline solid, mp 176–178 °C (from MeOH); $[\alpha]_D$ −280 (*c* 0.86, H_2O) (lit.[37] $[\alpha]_D$ −272, H_2O); (Found: C 52.5, H 7.4; $C_7H_{12}O_4$ requires C 52.5, H 7.5%); δ_H(500 MHz, D_2O) 1.73 (3 H, s, Me), 3.76 (1 H, dd, $J_{2,3}$ 10.5, $J_{2,1}$ 4.0, 2-H), 3.80 (1 H, dd, $J_{3,2}$ 10.5, $J_{3,4}$ 3.9, 3-H), 4.02 (1 H, d, $J_{4,3}$ 3.9, 4-H), 4.15 (1 H, dd, $J_{1,6}$ 5.0, $J_{1,2}$ 4.0, 1-H), 5.55 (1 H, d, $J_{6,1}$ 5.0, 6-H); δ_C(125 MHz, D_2O) 20.06, 66.91, 68.69, 69.07, 70.82, 124.38, 138.77; *m*/*z* (EI) 142 (M$^+$ − H_2O, 10%), 124 (16), 133 (11), 100 (97), 96 (34), 81 (11), 71 (100), 69 (17), 60 (10), 57 (18), 55 (25), 43 (59), 41 (49), 39 (34) and 31 (15).

(1*S*,2*S*,3*S*,4*R*) Enantiomer, white solid, mp 178–180 °C, $[\alpha]_D$ −220 (*c* 0.89, H_2O).

(1*S*,2*S*,3*S*,4*S*)-2-Methyl-5-cyclohexene-1,2,3,4-tetraol 11. Deprotection of the acetonide group of diol **4** (method a) yielded tetraol **11** as colourless viscous oil (1.6 g, 82%); $[\alpha]_D$ +43 (*c* 0.58, MeOH); (Found: M$^+$ − H_2O, 142.0634. $C_7H_{10}O_3$ requires 142.0630); δ_H(500 MHz, D_2O) 1.21 (3 H, s, Me), 3.67 (1 H, d, $J_{3,4}$ 3.3, 3-H), 3.98 (1 H, d, $J_{1,6}$ 2.7, 1-H), 4.33 (1 H, dd, $J_{4,5} = J_{4,3}$ 3.3, 4-H), 5.52–5.54 (2 H, br s, 5-H, 6-H); δ_C(125 MHz, D_2O) 22.83,

66.85, 69.71, 74.97, 75.96, 129.38, 130.09; *m/z* (EI) 142 ($M^+ - H_2O$, 6%), 125 (20), 113 (13), 99 (90), 97 (33), 95 (24), 86 (82), 81 (50), 74 (88), 69 (36), 57 (85), 55 (68), 53 (44), 45 (25), 43 (83), 41 (71), 39 (66), 21 (50), 29 (100) and 27 (61).

(1*R*,2*R*,3*R*,4*S*)-5-Iodo-2-methyl-5-cyclohexene-1,2,3,4-tetraol 19. Deprotection of diol acetonide **18** (method a) furnished tetraol **19** as colourless glassy solid (0.8 g, 90%); mp 98–100 °C; R_f 0.27 (10% MeOH in $CHCl_3$); $[\alpha]_D$ −20 (*c* 1.1, MeOH); (Found: M^+, 285.9703. $C_7H_{11}IO_4$ requires 285.9702); δ_H(500 MHz, D_2O) 1.35 (3 H, s, Me), 3.80 (1 H, d, $J_{3,4}$ 3.8, 3-H), 4.05 (1 H, d, $J_{1,6}$ 4.2, 1-H), 4.30 (1 H, d, $J_{4,3}$ 3.8, 4-H), 6.39 (1 H, d, $J_{6,1}$ 4.2, 6-H); δ_C(125 MHz, D_2O) 22.15, 71.41, 71.61, 73.25, 75.25, 104.47, 140.73; *m/z* (EI) 286 (M^+, 28%), 268 (99), 250 (13), 212 (84), 123 (23), 85 (47), 74 (92), 57 (57), 43 (73), 31 (100) and 7 (21).

Hydrogenolysis of iodotetraol 19 to yield (−)-tetraol 11

A solution of the iodotetraol **19** (0.3 g, 1 mmol) in MeOH (10 cm^3) containing NaOAc·$3H_2O$ (2 mmol) and Pd/C (3%, 0.05 g) was stirred under hydrogen atmosphere, at atmospheric pressure. When the hydrogenolysis was complete (TLC analysis), the reaction mixture was filtered through a pad of celite and the filtrate concentrated under reduced pressure. The crude hydrogenolysed product was purified by charcoal–celite (1 : 1, w/w) column chromatography (water → 10% EtOH in water) to yield (1*R*,2*R*,3*R*,4*R*)-2-methyl-5-cyclohexene-1,2,3,4-tetraol **11** (0.16 g, 95%); $[\alpha]_D$ −34.4 (*c* 0.58, MeOH). The sample had identical spectral characteristics to (1*S*,2*S*,3*S*,4*S*)-tetraol **11**.

Syntheses of bis-bromoacetates 6a–6c, 6e, 12 and 20

To a stirred suspension of the tetraol (0.3–3.0 mmol) in dry acetonitrile (10 cm^3) at 0 °C under nitrogen atmosphere, 1-bromocarbonyl-1-methyl-ethylacetate (2.5 mol equiv.) was added dropwise. The reaction mixture was kept stirring at 0 °C (15 min) and then at room temperature (2 h). The solvent was removed under reduced pressure and the residue thoroughly extracted with a mixture of ether (50 cm^3) and 3% aqueous $NaHCO_3$ (30 cm^3). The ether extract was washed with water, dried (Na_2SO_4), and concentrated to afford the crude sample of bis-bromoacetate.

(1*S*,2*R*,5*S*,6*S*)-6-(Acetyloxy)-2,5-dibromo-3-fluoro-3-cyclohexenyl acetate 6a. Colourless crystals (1 g, 87%); mp 122–129 °C (from toluene–hexane); R_f 0.45 (25% EtOAc in hexane); $[\alpha]_D$ +35 (*c* 0.71, $CHCl_3$); (Found: M^+ − OAc, 312.8883. $C_8H_8Br_2FO_2$ requires 312.8875); δ_H(500 MHz, $CDCl_3$) 2.11, 2.13 (3 H each, s, 2 × OCOMe), 4.65 (1 H, dd, $J_{2,F}$ 8.2, $J_{2,1}$ 4.8, 2-H), 4.70 (1 H, dd, $J_{5,6}$ 5.1, $J_{5,4}$ 3.5, 5-H), 5.41 (1 H, dd, $J_{6,1}$ 7.2, $J_{6,5}$ 5.1, 6-H), 5.50 (1 H, dd, $J_{1,6}$ 7.2, $J_{1,2}$ 4.8, 1-H), 5.75 (1 H, dd, $J_{4,F}$ 12.2, $J_{4,5}$ 3.5, 4-H); δ_C(125 MHz, $CDCl_3$) 20.64, 20.65, 39.40, 40.80, 71.59, 72.52, 107.70, 154.48 ($J_{C3,F}$ 2.0), 169.03, 169.14; *m/z* (EI) 313 (M^+ − OAc, 33%), 295 (12), 233 (19), 193 (45), 129 (51), 112 (47), 101 (81), 70 (33), 59 (70) and 43 (100).

(1*S*,2*R*,5*S*,6*S*)-6-(Acetyloxy)-2,5-dibromo-3-chloro-3-cyclohexenyl acetate 6b. White crystals (0.55 g, 83%); mp 77–79 °C (from MeOH); $[\alpha]_D$ +276 (*c* 0.53, $CHCl_3$); (Found: C 30.8, H 2.9; $C_{10}H_{11}Br_2ClO_4$ requires C 30.8, H 2.8%); δ_H(500 MHz, $CDCl_3$) 2.11, 2.13 (3 H each, s, 2 × OCOMe), 4.66 (2 H, m, 2-H, 5-H), 5.41(1 H, dd, $J_{1,6}$ 6.8, $J_{1,2}$ 4.27, 1-H), 5.54 (1 H, dd, $J_{6,1}$ 6.8, $J_{6,5}$ 4.2, 6-H), 6.22 (1 H, d, $J_{4,5}$ 3.1, 4-H); δ_C(125 MHz, $CDCl_3$) 20.66, 20.67, 41.51, 46.17, 70.98, 72.49, 127.14, 132.61, 168.99, 169.10; *m/z* (EI) 391 (M^+, 10%), 389 (4), 311 (9), 309 (7), 251 (33), 249 (26), 209 (50), 207 (45) and 128 (50).

(1*S*,2*R*,5*S*,6*S*)-6-(Acetyloxy)-2,3,5-tribromo-3-cyclohexenyl acetate 6c. White crystals (0.2 g, 80%); mp 88–90 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +189 (*c* 0.51, $CHCl_3$); (Found: C 27.55, H 2.5; $C_{10}H_{11}Br_3O_4$ requires C 27.6, H 2.55%); δ_H(500 MHz, $CDCl_3$) 2.11, 2.13 (3 H each, s, 2 × OCOMe), 4.60 (1 H, m, 5-H), 4.71 (1 H, m, 2-H), 5.42 (1 H, dd, $J_{1,6}$ 6.8, $J_{1,2}$ 4.9, 1-H), 5.55 (1 H, dd, $J_{6,1}$ 6.9, $J_{6,5}$ 4.8, 6-H), 6.43 (1 H, dd, $J_{4,5}$ 3.6, $J_{4,2}$ 1.1, 4-H); δ_C(125 MHz, $CDCl_3$) 20.66, 20.67, 42.07, 48.17, 70.89, 72.41, 123.10, 131.07, 168.97, 169.10; *m/z* (EI) 435 (M^+, 4%), 355 (25), 297 (31), 295 (49), 293 (32), 255 (50), 253 (65), 251 (52), 174 (57), 172 (58) and 43 (100).

(1*S*,2*S*,5*S*,6*S*)- and (1*R*,2*R*,5*R*,6*R*)-6-(Acetyloxy)-2,5-dibromo-3-methyl-3-cyclohexenyl acetate 6e. White crystalline solid (0.45 g, 88%); mp 80–82 °C; $[\alpha]_D$ +227 (*c* 0.99, $CHCl_3$); (Found: M + NH_4^+, 385.9593. $C_{11}H_{18}Br_2NO_4$ requires 385.9597); δ_H(500 MHz, $CDCl_3$) 1.98 (3 H, s, Me), 2.10 (6 H, s, 2 × OCOMe), 4.65 (1 H, d, $J_{2,1}$ 7.2, 2-H), 4.67 (1 H, dd, $J_{5,6}$ 7.1, $J_{5,4}$ 2.5, 5-H), 5.34 (1 H, dd, $J_{6,1}$ 9.3, $J_{6,5}$ 7.1, 6-H), 5.45 (1 H, dd, $J_{1,6}$ 9.3, $J_{1,2}$ 7.2, 1-H), 5.80 (1 H, d, $J_{4,5}$ 2.5, 4-H); δ_C(125 MHz, $CDCl_3$) 20.70, 20.75, 21.50, 43.9, 47.60, 71.70, 72.60, 128.00, 134.02, 169.58, 169.70; *m/z* (EI) 309 (M^+(^{79}Br) − OAc, 1%), 291 (5), 289 (5), 251 (7) 231 (13), 229 (13), 189 (78), 187 (79), 125 (29), 108 (97), 107 (39), 97 (15), 79 (17) and 43 (100).

(1*R*,2*R*,5*R*,6*R*) Enantiomer, light yellow oil, $[\alpha]_D$ −178 (*c* 0.65, $CHCl_3$).

(1*R*,2*R*,5*R*,6*R*) and (1*S*,2*S*,5*S*,6*S*)-6-(Acetyloxy)-2,5-dibromo-1-methyl-3-cyclohexenyl acetate 12. Colourless oil (0.26 g, 79%); R_f 0.53 (20% EtOAc in hexane); $[\alpha]_D$ −163 (*c* 0.81, $CHCl_3$); (Found: M^+, 367.9260. $C_{11}H_{14}{}^{79}Br_2O_4$ requires 367.9258); δ_H(500 MHz, $CDCl_3$) 1.43 (3 H, s, Me), 1.99, 2.16 (3 H each, s, 2 × -OCOMe), 4.57 (1 H, ddd, $J_{5,6}$ 8.0, $J_{5,2}$ 5.5, $J_{5,4}$ 2.5, 5-H), 5.78 (1 H, ddd, $J_{4,3}$ 10.5, $J_{4,5} = J_{4,2}$ 2.5, 4-H), 5.86 (1 H, dd, $J_{3,4}$ 10.5, $J_{3,2}$ 2.1, 3-H), 6.08 (1 H, d, $J_{6,5}$ 8.0, 6-H), 6.25 (1 H, dd, $J_{2,5}$ 5.5, $J_{2,4}$ 2.4, 2-H); δ_C(125 MHz, $CDCl_3$) 17.71, 20.66, 22.10, 47.00, 49.88, 74.64, 82.53, 127.42, 130.70, 169.27, 170.02; *m/z* (EI) 372 (M^+, 20%), 370 (10), 291 (6), 267 (32), 187 (60), 169 (21), 125 (29), 107 (83),77 (61), 51 (33) 43 and (100).

(1*S*,2*S*,5*S*,6*S*) Enantiomer of compound **12**, colourless oil $[\alpha]_D$ +101 (*c*, 0.74, $CHCl_3$).

(1*S*,2*S*,5*R*,6*S*)-6-(Acetyloxy)-2,5-dibromo-4-iodo-1-methyl-3-cyclohexenyl acetate 20. White crystalline solid (0.14 g, 84%); mp 91 °C (from Et_2O–hexane); R_f 0.64 (25% EtOAc in hexane); $[\alpha]_D$ +14 (*c* 0.72, $CHCl_3$); (Found: M + NH_4^+, 511.8565. $C_{11}H_{17}Br_2INO_4$ requires 511.8564); δ_H(500 MHz, $CDCl_3$) 1.58 (3 H, s, Me), 2.00, 2.17 (3 H each, s, 2 × OCOMe), 4.59 (1 H, dd, $J_{5,6}$ 6.1, $J_{5,3}$ 1.4, 5-H), 5.90 (1 H, d, $J_{2,3}$ 2.9, 2-H), 6.14 (1 H, d, $J_{6,5}$ 6.1, 6-H), 6.61 (1 H, dd, $J_{3,2}$ 2.9, $J_{3,5}$ 1.4, 3-H); δ_C(125 MHz, $CDCl_3$) 18.64, 20.68, 22.18, 48.84, 55.4, 73.38, 80.90, 96.98, 140.87, 168.93, 169.99; *m/z* (EI) 415 ($M^+ - {}^{79}Br$, 0.5%), 394 (4), 375 (3), 373 (3), 315 (10), 313 (10) 254 (6), 251 (13), 234 (13), 188 (16), 186 (18), 124 (44), 74 (14), and 43 (100).

Syntheses of *anti*-benzene dioxides 7a–7e, 13 and 21

To a solution of bis-bromoacetate (0.4–1.5 mmol) in dry ether (25 cm^3) at 0 °C, was added sodium methoxide (4 mol equiv.) and the mixture stirred (15 min) at 0 °C and then at room temperature (3 h). The reaction mixture was filtered through a pad of celite, the solid residue washed with ether (10 cm^3), and the combined filtrate concentrated at atmospheric pressure to yield the dioxide.

(1*R*,2*S*,4*S*,7*R*)-5-Fluoro-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene 7a. Light yellow oil (0.14 g, 71%); $[\alpha]_D$ −14 (*c* 0.50, $CHCl_3$); (Found: M^+, 128.0284. $C_6H_5FO_2$ requires 128.0273); δ_H(500 MHz, $CDCl_3$) 3.19 (2 H, m, 4-H, 7-H), 3.70 (1 H, dd, $J_{2,1}$ 4.0, $J_{2,4}$ 3.5, 2-H), 3.88 (1 H, dd, $J_{1,2}$ 4.0, $J_{1,7}$ 3.8, 1-H), 5.53 (1 H, dd, $J_{6,F}$ 9.7, $J_{6,7}$ 4.5, 6-H); δ_C(125 MHz, $CDCl_3$) 46.86, 46.96, 52.36, 54.77, 102.50, 161.92 ($J_{C2,F}$ 2.1); *m*/*z* (EI) 128 (M^+, 13%), 110 (74), 95 (66), 87 (60), 74 (72), 69 (76), 55 (100), 43 (93), 39 (30) and 29 (67).

(1*R*,2*S*,4*S*,7*R*)-5-Chloro-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene 7b. White solid (0.07 g, 78%); mp 42–44 °C (from ether–hexane); $[\alpha]_D$ −115 (*c* 0.40, $CHCl_3$); (Found: M^+, 143.9980. $C_6H_5ClO_2$ requires 143.9978); δ_H(500 MHz, $CDCl_3$) 3.15 (1 H, dd, $J_{7,1}$ 4.2, $J_{7,6}$ 4.3, 7-H), 3.20 (1 H, dd, $J_{4,2}$ 4.2, $J_{4,6}$ 2.2, 4-H), 3.72 (1 H, m, 1-H), 3.82 (1 H, m, 2-H), 6.12 (1 H, dd, $J_{6,7}$ 4.3, $J_{6,4}$ 2.2, 6-H); δ_C(125 MHz, $CDCl_3$) 47.26, 52.28, 52.70, 55.26, 124.11, 135.69; *m*/*z* (EI) 145 (M^+ + 1, 31%), 144 (27), 117 (52), 115 (69), 86 (55), 84 (58), 81 (61), 51 (100), 49 (96) and 43 (83).

(1*R*,2*S*,4*S*,7*R*)-5-Bromo-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene 7c. White crystalline solid (0.064 g, 82%); mp 52–54 °C (from $CHCl_3$–hexane); $[\alpha]_D$ −54 (*c* 0.30, $CHCl_3$); (Found: M^+, 187.9469. $C_6H_5BrO_2$ requires 187.9473); δ_H(500 MHz, $CDCl_3$), 3.10 (1 H, m, 7-H), 3.32 (1 H, m, 4-H), 3.75 (1 H, m, 1-H), 3.82 (1 H, m, 2-H), 6.39 (1 H, dd, $J_{6,7}$ 4.3, $J_{6,4}$ 2.2, 6-H); δ_C(125 MHz, $CDCl_3$), 47.85, 52.63, 53.70, 55.85, 125.02, 128.59; *m*/*z* (EI) 188 (M^+, 3%), 161 (85), 159 (86), 141 (43), 132 (51), 130 (49), 109 (52), 81 (94), 53 (94), 51 (100) and 29 (90).

(1*R*,2*S*,4*S*,7*R*)-5-Iodo-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene 7d. White crystalline solid (0.08 g, 81%); mp 68–70 °C (from $CHCl_3$–hexane); $[\alpha]_D$ −6.0 (*c* 0.50, $CHCl_3$); (Found: M^+, 235.9341. $C_6H_5IO_2$ requires 235.9334); δ_H(500 MHz, $CDCl_3$) 2.96 (1 H, dd, $J_{7,1} = J_{7,6}$ 4.1, 7-H), 3.44 (1 H, dd, $J_{4,2}$ 3.9, $J_{4,6}$ 2.0, 4-H), 3.77 (2 H, m, 1-H, 2-H), 6.73 (1 H, dd, $J_{6,7}$ 4.1, $J_{6,4}$ 2.0, 6-H); δ_C(125 MHz, $CDCl_3$) 48.48, 52.59, 56.52, 56.74, 98.97, 137.25; *m*/*z* (EI) 236 (M^+, 81%), 207 (89), 178 (23), 127 (29), 109 (29), 81 (77), 53 (100) and 51 (84).

(1*R*,2*S*,4*S*,7*R*)- and (1*S*,2*R*,4*R*,7*S*)-5-Methyl-3,8-dioxa-tricyclo-[5.1.0.0^{2,4}]oct-5-ene 7e. Colourless oil (0.04 g, 68%); $[\alpha]_D$ −183 (*c* 0.53, $CHCl_3$); (Found: M^+, 124.0527, $C_7H_8O_2$ requires 124.0524); δ_H(500 MHz, $CDCl_3$) 1.91 (3 H, s, Me), 2.92 (1 H, dd, $J_{4,2}$ 4.0, $J_{4,6}$ 1.9, 4-H), 3.05 (1 H, dd, $J_{7,1}$ 4.1, $J_{7,6}$ 4.0, 7-H), 3.68 (1 H, dd, $J_{1,7}$ 4.1, $J_{1,2}$ 2.8, 1-H), 3.74 (1 H, dd, $J_{2,4}$ 4.0, $J_{2,1}$ 2.8, 2-H), 5.73 (1 H, dd, $J_{6,7}$ 4.0, $J_{6,4}$ 1.9, 6-H); δ_C(125 MHz, $CDCl_3$) 21.93, 47.31, 50.93, 53.09, 54.37, 122.04, 133.88; *m*/*z* (EI) 124 (M^+, 19%), 109 (11), 95 (81), 66 (22), 53 (66), 49 (100), 41 (96), 29 (41) and 27 (55).

(1*S*,2*R*,4*R*,7*S*) Enantiomer, colourless oil, $[\alpha]_D$ +143 (*c* 0.43, $CHCl_3$).

(1*S*,2*S*,4*S*,7*S*) and (1*R*,2*R*,4*R*,7*R*)-1-Methyl-3,8-dioxa-tricyclo-[5.1.0.0^{2,4}]oct-5-ene 13. Colourless viscous oil (0.04 g, 65%); $[\alpha]_D$ +35 (*c* 0.73, $CHCl_3$); (Found: M^+, 124.0527. $C_7H_8O_2$ requires 124.0524); δ_H(500 MHz, $CDCl_3$) 1.56 (3 H, s, Me), 2.95 (1 H, dd, $J_{4,5}$ 4.1, $J_{4,2}$ 2.5, 4-H), 3.15 (1 H, d, $J_{2,4}$ 2.5, 2-H), 3.61 (1 H, d, $J_{7,6}$ 4.1, 7-H), 6.08 (2 H, m, 5-H, 6-H); δ_C(125 MHz, $CDCl_3$), 20.47, 48.02, 53.37, 57.99, 65.85, 129.41, 130.53; *m*/*z* (EI) 124 (M^+, 5%), 109 (12), 107 (100), 95 (65), 66 (7), 53 (39), 43 (95), 39 (48) and 27 (30).

(1*R*,2*R*,4*R*,7*R*)-Enantiomer of compound **13**, light yellow viscous oil $[\alpha]_D$ −32 (*c* 0.72, $CHCl_3$).

(1*R*,2*R*,4*R*,7*R*)-5-Iodo-1-methyl-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene 21. Colourless crystalline solid (0.12 g, 62%); mp 80 °C (from $CHCl_3$); $[\alpha]_D$ +37 (*c* 0.77, $CHCl_3$); (Found: M^+, 249.9495. $C_7H_7IO_2$ requires 249.9491); δ_H(500 MHz, $CDCl_3$), 1.55 (3 H, s, Me), 2.81 (1 H, d, $J_{7,6}$ 4.3, 7-H), 3.50 (1 H, dd, $J_{4,2}$ 4.1, $J_{4,6}$ 1.9, 4-H), 3.63 (1 H, d, $J_{2,4}$ 4.1, 2-H), 6.74 (1 H, dd, $J_{6,7}$ 4.3, $J_{6,4}$ 1.9, 6-H); δ_C(125 MHz, $CDCl_3$), 20.20, 55.13, 57.98, 59.00, 60.60, 98.67, 138.13; *m*/*z* (EI) 250 (M^+, 98%), 235 (8), 227 (47), 222 (83), 207 (93), 179 (54), 178 (93), 165 (25), 140 (72), 123 (92), 108 (31), 94 (92), 80 (90), 77 (68), 65 (80), 50 (100), 39 (96) and 27 (78).

Syntheses of *trans*-dihydrodiols 8a–8f, 8h, 8i, 14 and 22

A mixture of dioxide (0.32–0.60 mmol), THF (1 cm^3), water (0.4 cm^3), K_2CO_3 (4 mol equiv.) were stirred in the presence of palladium(II) acetate (*ca.* 0.015 g) under an atmosphere of CO until the dioxide had reacted completely (TLC analysis). The catalyst was filtered off and saturated NaCl solution (6 cm^3) was added to the filtrate. The aqueous solution was extracted with EtOAc (3 × 10 cm^3), the extract dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by PLC (50% EtOAc in hexane) yielded the *trans*-dihydrodiol.

(1*R*,2*R*)-4-Fluoro-3,5-cyclohexadiene-1,2-diol 8a. White crystalline solid (0.05 g, 70%); mp 43–45 °C (from EtOAc–hexane); R_f 0.23 (50% EtOAc in hexane); $[\alpha]_D$ −38 (*c* 0.37, $CHCl_3$); (Found: M^+, 130.0432. $C_6H_7FO_2$ requires 130.0430); δ_H(500 MHz, $CDCl_3$) 4.42 (1 H, dd, $J_{2,1}$ 9.5, $J_{2,3}$ 2.9, 2-H), 4.54 (1 H, dd, $J_{1,2}$ 9.5, $J_{1,6}$ 3.6, 1-H), 5.35 (1 H, dd, $J_{6,5}$ 9.9, $J_{6,1}$ 3.6, 6-H), 5.91 (1 H, dd, $J_{5,F}$ 11.9, $J_{5,6}$ 9.9, 5-H), 6.04 (1 H, dd, $J_{3,F}$ 11.4, $J_{3,2}$ 2.9, 3-H); δ_C(125 MHz, $CDCl_3$) 67.86, 68.69, 121.91, 133.42, 133.56, 159.87 ($J_{C4,F}$ 2.0); *m*/*z* (EI) 130 (M^+, 82%), 117 (45), 113 (53), 99 (92), 87 (94), 81 (87), 73 (93), 59 (76), 55 (97), 47 (52), 39 (86), 31 (100) and 27 (84).

(1*R*,2*R*)-4-Chloro-3,5-cyclohexadiene-1,2-diol 8b. White crystalline solid (0.07 g, 88%); mp 114–116 °C (from EtOAc–hexane); R_f 0.30 (40% EtOAc in hexane); $[\alpha]_D$ −176 (*c* 0.38, MeOH); (Found: M^+, 146.0141. $C_6H_7ClO_2$ requires 146.0135); δ_H(500 MHz, acetone-d_6) 4.25–4.38 (4 H, m, 1-H, 2-H, 2 × OH), 5.78 (1H, dt, $J_{6,5}$ 10.0, $J_{6,1} = J_{6,2}$ 2.0, 6-H), 5.90 (1 H, t, $J_{3,2} = J_{3,5}$ 2.8, 3-H), 5.98 (1 H, dd, $J_{5,6}$ 10.0, $J_{5,3}$ 2.8, 5-H); δ_C(125 MHz, acetone-d_6) 72.99, 74.72, 126.10, 128.12, 128.17, 134.95; *m*/*z* (EI) 146 (M^+(^{35}Cl), 85), 128 (33), 117 (74), 102 (82), 100 (100), 81 (75) 65 (95), 53 (100), 39 (78) and 27 (54).

(1*R*,2*R*)-4-Bromo-3,5-cyclohexadiene-1,2-diol 8c. White crystalline solid (0.07 g, 87%); mp 128–130 °C (from $CHCl_3$); R_f 0.40 (50% EtOAc in hexane); $[\alpha]_D$ −253 (*c* 0.28, MeOH); (Found: M^+, 191.9623. $C_6H_7BrO_2$ requires 191.9609); δ_H(500 MHz, $CDCl_3$) 2.01 (2 H, br s, OH), 4.45 (2 H, m, 1-H, 2-H), 5.95 (2 H, m,

$J_{5,6}$ 10.5, $J_{5,3}$ 1.8, 5-H, 6-H), 6.21 (1 H, t, $J_{3,2} = J_{3,5}$ 1.8, 3-H); δ_C(125 MHz, $CDCl_3$) 72.79, 75.24, 125.90, 128.75, 131.80, 129.97; *m/z* (EI) 192 (M^+(^{81}Br), 46%), 190 (M^+(^{79}Br), 46), 174 (19), 172 (19), 163 (25), 161 (27), 146 (54), 144 (50), 111 (17), 93 (25), 83 (37), 82 (33) and 65 (100).

(1*R*,2*R*)-4-Iodo-3,5-cyclohexadiene-1,2-diol 8d. White crystalline solid (0.09 g, 90%); mp 113–115 °C; R_f 0.40 (50% EtOAc in hexane); $[\alpha]_D$ −145 (*c* 0.38, MeOH); (Found: M^+, 237.9485. $C_6H_7IO_2$ requires 237.9491); δ_H(500 MHz, $CDCl_3$) 2.03 (2 H, br s, OH), 4.42 (2 H, m, 1-H, 2-H), 5.74 (1 H, dd, $J_{6,5}$ 10, $J_{6,1}$ 2.4, 6-H), 6.06 (1 H, ddd, $J_{5,6}$ 10, $J_{5,3}$ 2.1, $J_{5,1}$ 1.9, 5-H), 6.52 (1 H, dd, $J_{3,5}$ 2.1, $J_{3,2}$ 2.0, 3-H); δ_C(75 MHz, $CDCl_3$) 72.67, 75.91, 89.15, 131.34, 132.39, 138.79; *m/z* (EI) 238 (M^+, 44%), 220 (10), 192 (10), 127 (42), 111 (43), 93 (37), 83 (74), 65 (100) and 55 (80).

(1*R*,2*R*)- and (1*S*,2*S*)-4-Methyl-3,5-cyclohexadiene-1,2-diol 8e. White crystalline solid (0.05 g, 68%); mp 69–70 °C (from EtOAc–hexane); R_f 0.34 (50% EtOAc in hexane); $[\alpha]_D$ −345 (*c* 0.85, MeOH); (Found: M^+, 126.0684. $C_7H_{10}O_2$ requires 126.0681); δ_H(500 MHz, $CDCl_3$) 1.75 (3 H, s, Me), 4.39 (2 H, m, 1-H, 2-H), 5.53 (1 H, b s, 3-H), 5.73 (1 H, d, $J_{6,5}$ 9.7, 6-H), 5.84 (1 H, d, $J_{5,6}$ 9.7, 5-H); δ_C(125 MHz, $CDCl_3$) 20.80, 74.38, 74.72, 124.70, 128.28, 130.19, 132.49; *m/z* (EI) 126 (M^+, 65%), 108 (18), 97 (38), 95 (22), 80 (100), 77 (32), 69 (14), 57 (8), 55 (24), 43 (35), 41 (43), 39 (34), 32 (10) and 28 (66).

(1*S*,2*S*) Enantiomer (*ca*: 80% ee), mp 66 °C, $[\alpha]_D$ +270 (*c* 0.70, MeOH).

(3*R*,4*R*)-3,4-Dihydroxy-1,5-cyclohexadiene-1-carboxylic acid methyl ester 8f. A solution of (1*R*,2*R*)-4-iodo-3,5-cyclohexadiene-1,2-diol **8d** (0.03 g, 0.13 mmol) in dry MeOH (2 cm^3) containing NaOAc·$3H_2O$ (0.07 g, 0.49 mmol, 4 equiv.) and $Pd(OAc)_2$ (0.003 g) was stirred (18 h) at room temperature under an atmosphere of CO. The catalyst was removed by filtration, the filtrate concentrated under reduced pressure, and the residue purified by PLC (50% EtOAc in hexane), to give methyl ester **8f** as colourless oil (0.016 g, 78%); R_f 0.17 (50% EtOAc in hexane); $[\alpha]_D$ −94 (*c* 1.26, MeOH); (Found M^+, 170.0585. $C_8H_{10}O_4$ requires 170.0579); δ_H(500 MHz, $CDCl_3$) 3.78 (3 H, s, COOMe), 4.51–4.62 (2 H, m, 3-H, 4-H), 5.96 (1 H, dd, $J_{5,6}$ 10, $J_{5,4}$ 1.6, 5-H), 6.33 (1 H, dt, $J_{6,5}$ 10, $J_{6,2} = J_{6,4}$ 1.9, 6-H), 6.91 (1 H, m, 2-H); δ_C(125 MHz, $CDCl_3$) 52.14, 73.91, 74.92, 122.19, 128.20, 131.71, 139.50, 165.19; *m/z* (EI) 170 (M^+, 48%), 152 (51), 138 (77), 124 (55), 121 (60), 110 (88), 109 (66), 82 (79), 81 (97), 65 (76), 53 (92), 43 (100), 39 (83) and 29 (80).

(1*R*,2*R*)-4-(2′-Thienyl)-3,5-cyclohexadiene-1,2-diol 8h. To a solution of (1*R*,2*R*)-4-bromocyclohexa-3,5-diene-1,2-diol **8c** (0.06 g, 0.3 mmol) in dry THF (5 cm^3) was added tetrakis(triphenylphosphine)palladium(0) (5 mol%, 0.02 g) and 2-(tributylstannyl)thiophene (0.13 cm^3, 0.43 mmol). The reaction mixture was stirred (2 h) at 40 °C, cooled to room temperature, and quenched with a saturated solution of potassium fluoride (3 cm^3). The precipitates formed were filtered off, the filtrate extracted with EtOAc, and the extract concentrated. The crude product obtained was purified by PLC (50% EtOAc in hexane) to yield *trans*-dihydrodiol **8h** as light yellow oil (0.05 g, 83%); R_f 0.29 (50% EtOAc in hexane); $[\alpha]_D$ −136 (*c* 0.76, $CHCl_3$); (Found: M^+, 194.0408. $C_{10}H_{10}O_2S$ requires 194.0402); δ_H(500 MHz, $CDCl_3$) 4.50 (1 H, ddd, $J_{1,2}$ 10.5, $J_{1,6}$ 2.1, $J_{1,5}$ 1.8, 1-H), 4.59 (1 H, dd, $J_{2,1}$ 10.5, $J_{2,3}$ 3.0, 2-H), 6.07 (1 H, dd, $J_{5,6}$ 9.9, $J_{5,1}$ 1.8, 5-H), 6.16 (1 H, d, $J_{3,2}$ 3.0, 3-H), 6.31 (1 H, dd, $J_{6,5}$ 9.9, $J_{6,1}$ 2.1, 6-H), 6.99 (1 H, dd, $J_{4',5'}$ 5.1, $J_{4',3'}$ 3.6, 4′-H), 7.03 (1 H, d, $J_{3',4'}$ 3.6, 3′-H), 7.20 (1 H, dd, $J_{5',4'}$ 5.1, $J_{5',3'}$ 1.0, 5′-H); δ_C(125 MHz, $CDCl_3$) 74.54, 75.16, 123.80, 124.33, 125.04, 125.28, 129.04, 130.01, 132.00, 142.74; *m/z* (EI) 194 (M^+, 9%), 177 (18), 176 (100), 163 (9), 148 (98), 147 (49), 137 (10), 131 (13), 121 (16), 115 (41), 109 (11), 97 (19), 81 (16), 77 (32), 65 (28), 63 (19) and 57 (25)

(1*R*,2*R*)-1,2-Di-*tert*-butyldimethylsilyloxy-4-bromocyclohexa-3,5-diene 9. TBDMSTf (0.95 g, 0.36 mmol) was added dropwise, under nitrogen atmosphere at 0 °C, to a solution of (1*R*,2*R*)-4-bromocyclohexa-3,5-diene-1,2-diol **8c** (0.3 g, 0.15 mmol) in dry CH_2Cl_2 (10 cm^3) containing triethylamine (0.46 g, 0.46 mmol). The reaction mixture was stirred (1 h) before quenching with 5% aqueous $NaHCO_3$ (10 cm^3). The organic layer was separated, after diluting with CH_2Cl_2, washed with water and dried (Na_2SO_4). Removal of the solvent gave a crude product which on purification by PLC (ether) yielded di-TBDMS derivative **9** as a colourless viscous oil (0.48 g, 74%); R_f 0.35 (ether); $[\alpha]_D$ −138 (*c* 0.76, $CHCl_3$); (Found: M^+, 418.1354. $C_{18}H_{35}BrO_2Si_2$ requires 418.1357); δ_H(500 MHz, $CDCl_3$) 0.006 (12 H, s, 2 × $SiMe_3$), 0.81 (18 H, s, 2 × CMe_3), 4.32 (2 H, m, 1-H, 2-H), 5.66 (1 H, dd, $J_{6,5}$ 9.7, $J_{6,1}$ 1.8, 6-H), 5.75 (1 H, d, $J_{5,6}$ 9.7, 5-H), 5.93 (1 H, d, $J_{3,2}$ 1.8, 3-H); *m/z* (EI) 418 (M^+, 78%), 416 (65), 361 (7), 304 (14), 303 (7), 275 (20), 189 (27), 167 (56), 147 (87), 133 (46), 115 (57), 75 (100), 57 (67), 41 (56) and 32 (46).

(1*R*,2*R*)-1,2-Di-*tert*-butyldimethylsilyloxy-4-phenylcyclohexa-3,5-diene 10. To a stirred ether solution (20 cm^3, 0 °C, under nitrogen atmosphere) of di-TBDMS derivative **9** (0.40 g, 0.96 mmol) and nickel(II) acetylacetonate (0.01 g, 0.04 mmol), phenyl magnesium bromide solution (1 M in diethyl ether, 1.2 cm^3) was added drop-wise. The reaction mixture was stirred (3 h) at 0 °C and subsequently at room temperature (3 h). A saturated aqueous solution of NH_4Cl was added to terminate the reaction. The organic layer was separated, and the remaining aqueous layer extracted with ether. The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by PLC (hexane). (1*R*,2*R*)-1,2-Di-*tert*-butyldimethylsilyloxy-4-phenylcyclohexa-3,5-diene **10** was obtained as colourless viscous oil (0.1 g, 25%); $[\alpha]_D$ −81 (*c* 0.64, $CHCl_3$); (Found: M^+, 416.2579. $C_{24}H_{40}O_2Si_2$ requires 416.2567); δ_H(500 MHz, $CDCl_3$) −0.023, −0.002, 0.011, 0.012 [3 H each, s, 2 × $Si(Me)_2$], 0.80 [18 H, s, 2 × $C(Me)_3$], 4.42 (1 H, dd, $J_{1,2}$ 11.6, $J_{1,6}$ 2.2, 1-H), 4.51 (1 H, dd, $J_{2,1}$ 11.6, $J_{2,3}$ 2.6, 2-H), 5.80 (1 H, dd, $J_{6,5}$ 9.9, $J_{6,1}$ 2.2, 6-H), 5.84 (1 H, dd, $J_{3,2}$ 2.6, $J_{3,5}$ 2.0, 3-H), 6.08 (1 H, dd, $J_{5,6}$ 9.9, $J_{5,3}$ 2.0, 5-H); *m/z* (EI) 416 (M^+, 47%), 301 (22), 244 (13), 228 (87), 211 (95), 199 (54), 167 (56), 154 (98), 133 (56), 115 (93), 105 (72), 73 (64), 57 (92) and 41 (100).

(1*R*,2*R*)-4-Phenylcyclohexa-3,5-diene-1,2-diol 8i. A solution of Bu_4NF (0.8 cm^3, 1.0 M in THF) was added to a stirred solution of di-TBDMS **10** (0.1 g, 0.24 mmol) in THF (1 cm^3) at 0 °C. After stirring the mixture (3 h) at 0 °C, the solvent was removed under reduced pressure, and the crude product purified by PLC (50% EtOAc in hexane) to yield dihydrodiol **8i** as light yellow oil (0.02 g, 44%); $[\alpha]_D$ +34 (*c* 0.35, $CHCl_3$); (Found: M^+, 188.0856. $C_{12}H_{12}O_2$ requires 188.0837); δ_H(500 MHz, $CDCl_3$) 4.51 (1 H, dd, $J_{1,2}$ 12.0, $J_{1,6}$ 2.5, 1-H), 4.60 (1 H, dd, $J_{2,1}$ 12.0, $J_{2,3}$ 2.7, 2-H), 6.08 (1 H, dd,

$J_{6,5}$ 9.9, $J_{6,1}$ 2.5, 6-H), 6.12 (1 H, d, $J_{3,2}$ 2.7, 3-H), 6.32 (1 H, d, $J_{5,6}$ 9.9, 5-H), 7.31, 7.34, 7.37, 7.39, 7.41 (5 H, m, Ar-H); δ_C(125 MHz, $CDCl_3$) 76.40, 77.22, 126.32, 126.80, 127.24, 128.60, 128.67, 128.76, 129.50, 130.44, 137.22, 143.11; *m/z* (EI) 188 (M^+, 4%), 170 (56), 134 (7), 110 (32), 78 (56), 56 (87), 49 (12), 43 (100) and 25 (10).

(1*S*,2*S*)- and (1*R*,2*R*)-1-Methyl-3,5-cyclohexadiene-1,2-diol 14. Colourless crystalline solid (0.05 g, 70%); mp 202–204 °C (from $CHCl_3$–hexane); R_f 0.38 (50% EtOAc in hexane); $[\alpha]_D$ +45 (*c* 0.63, $CHCl_3$); (Found: M^+, 126.0676. $C_7H_{10}O_2$ requires 126.0681); δ_H(500 MHz, $CDCl_3$) 1.26 (3 H, s, Me), 4.49 (1 H, br s, 2-H), 5.79–5.88 (4 H, m, 3-H, 4-H, 5-H, 6-H); δ_C(125 MHz, $CDCl_3$) 19.00, 75.21, 76.48, 123.10, 123.61, 131.53, 135.81; *m/z* (EI) 126 (M^+, 6%), 108 (16%), 105 (90), 97 (29), 83 (53), 71 (61), 57 (100), 43 (89) and 28 (28).

(1*R*,2*R*) Enantiomer (*ca*: 80% ee), $[\alpha]_D$ −37 (*c* 0.74, $CHCl_3$).

(1*R*,2*R*)-4-Iodo-1-methyl-3,5-cyclohexadiene-1,2-diol 22. Colourless viscous oil (0.015 g, 20%); R_f 0.46 (50% EtOAc in hexane); $[\alpha]_D$ +11 (*c* 0.50, $CHCl_3$); (Found: M^+, 251.9646. $C_7H_9IO_2$ requires 251.9647); δ_H(500 MHz, $CDCl_3$), 1.27 (3 H, s, Me), 4.43 (1 H, d, $J_{2,3}$ 3.1, 2-H), 5.63 (1 H, d, $J_{6,5}$ 10.0, 6-H), 5.99 (1 H, d, $J_{5,6}$ 10.0, 5-H), 6.50 (1 H, d, $J_{3,2}$ 3.1, 3-H); δ_C(125 MHz, $CDCl_3$) 19.18, 71.50, 76.76, 89.90, 130.18, 136.90, 139.96; *m/z* (EI) 252 (M^+, 25%), 234 (8), 125 (25), 107 (10), 81 (5), 79 (12), 77 (15), 65 (6), 53 (7), 43 (100), 39 (10) and 27 (7).

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