Chemoenzymatic synthesis of *trans*-dihydrodiol derivatives of monosubstituted benzenes from the corresponding *cis*-dihydrodiol isomers†

Derek R. Boyd,*[a,b] Narain D. Sharma,[a,b] Nuria M. Llamas,[a] Gerard P. Coen,[a] Peter K. M. McGeehin[a] and Christopher C. R. Allen[c]

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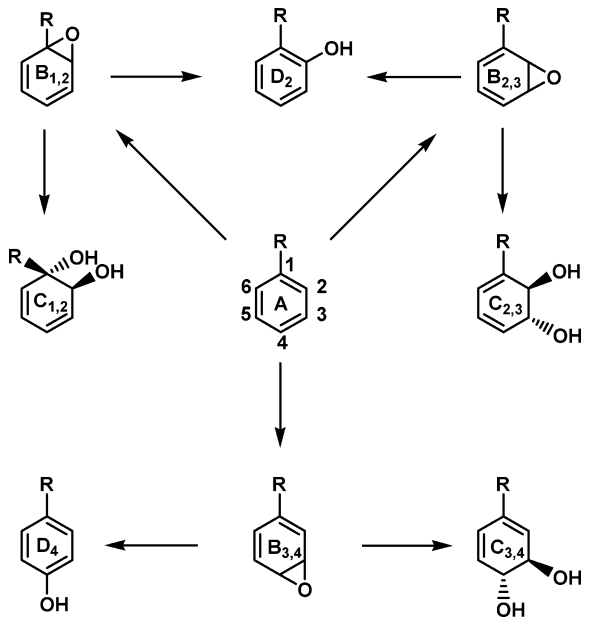
Enantiopure *trans*-dihydrodiols have been obtained by a chemoenzymatic synthesis from the corresponding *cis*-dihydrodiol metabolites, obtained by dioxygenase-catalysed arene *cis*-dihydroxylation at the 2,3-bond of monosubstituted benzene substrates. This generally applicable, seven-step synthetic route to *trans*-dihydrodiols involves a regioselective hydrogenation and a Mitsunobu inversion of configuration at C-2, followed by benzylic bromination and dehydrobromination steps. The method has also been extended to the synthesis of both enantiomers of the *trans*-dihydrodiol derivatives of toluene, through substitution of a vinyl bromine atom of the corresponding *trans*-dihydrodiol enantiomers derived from bromobenzene. Through incorporation of hydrogenolysis and diMTPA ester diastereoisomer resolution steps into the synthetic route, both *trans*-dihydrodiol enantiomers of monohalobenzenes were obtained from the *cis*-dihydrodiols of 4-haloiodobenzenes.

Introduction

Mammalian metabolism of arenes **A**, in common with fungal biodegradation, often involves monooxygenase-catalysed oxidation to yield phenols. The corresponding arene oxides $\mathbf{B}_{1,2}$, $\mathbf{B}_{2,3}$ and $\mathbf{B}_{3,4}$ have been proposed as initial metabolites on the basis of their detection or isolation, *e.g.* from benzene[1] (**A**, R = H) to yield benzene oxide ($\mathbf{B}_{1,2} = \mathbf{B}_{2,3} = \mathbf{B}_{3,4}$, R = H) or from methyl benzoate[2] (**A**, R = CO_2Me), to give the 1,2-oxide $\mathbf{B}_{1,2}$ (R = CO_2Me, Scheme 1). Substituted benzene oxide intermediates, *e.g.* $\mathbf{B}_{2,3}$ (R = Br), synthesised from enantiopure *cis*-dihydrodiol precursors, were found to spontaneously racemise *via* the corresponding oxepin valence tautomers.[3] Further examples of arene oxide intermediates have been isolated from mammalian liver metabolism of polycyclic arenes, *e.g.* naphthalene[4] and quinoline,[5] but these arene oxides do not equilibrate with the corresponding oxepins and are generally more stable. Arene oxide intermediates $\mathbf{B}_{1,2}$, $\mathbf{B}_{2,3}$ and $\mathbf{B}_{3,4}$, derived from substituted monocylic arenes **A**, are often unstable, and thus difficult to isolate, due to their rapid isomerisation to phenols. However, further evidence for the intermediacy of arene oxides can be obtained from their epoxide hydrolase-catalysed hydrolysis, to yield the corresponding *trans*-dihydrodiols $\mathbf{C}_{1,2}$, $\mathbf{C}_{2,3}$ and $\mathbf{C}_{3,4}$. A relatively small number of *trans*-dihydrodiol metabolites have been isolated from benzene ($\mathbf{C}_{1,2} = \mathbf{C}_{2,3} = \mathbf{C}_{3,4}$ where R = H) and from other monosubstituted benzene substrates ($\mathbf{C}_{3,4}$ where R = Cl, Br) as well as non-aromatic precursors ($\mathbf{C}_{2,3}$ where R = CO_2H).[6–10] *trans*-Dihydrodiols are commonly found as metabolites of polycyclic arenes, *e.g.* benzo[*a*]pyrene, and these have been extensively studied, in order to elucidate their role in carcinogenesis induced by polycyclic aromatic hydrocarbons.[11]



Scheme 1

Comprehensive studies of the alternative dioxygenase-catalysed metabolism pathway of mono- and poly-cyclic arenes in bacteria, have been carried out in these and other laboratories and, as a result, several hundred examples of *cis*-dihydrodiol metabolites are now available as synthetic precursors.[12–22] The corresponding range of *trans*-dihydrodiols, however, cannot yet be obtained in significant yields by direct biotransformation methods (excluding the *trans*-dihydrodiols from benzoic acid).[7,8] We have been interested in exploring potential methods for the synthesis of *trans*-dihydrodiols, from the readily available corresponding *cis*-dihydrodiols.[23] This has resulted in the development of a generally

[a]*School of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast, UK BT9 5AG. E-mail: dr.boyd@qub.ac.uk; Fax: 02890 323321; Tel: 02890 974421*
[b]*CenTACat, Queen's University Belfast, Belfast, UK BT9 5AG*
[c]*School of Biological Sciences, Queen's University Belfast, Belfast, UK BT9 5AG*

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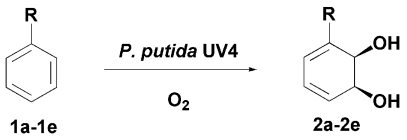
applicable synthetic route from *cis*-dihydrodiol metabolites **2a–2e** (Scheme 2) to the corresponding regioisomeric *trans*-dihydrodiols $\mathbf{C_{3,4}}$ (R = Cl, Br, I, Scheme 3).[24] A similar approach was also applied to the synthesis of an alternative *trans*-dihydrodiol regioisomer $\mathbf{C_{1,2}}$ (R = Me) but could not be used to synthesise any member of the regioisomeric *trans*-dihydrodiol series $\mathbf{C_{2,3}}$.[24] The present study, based on an earlier preliminary communication,[3] provides an alternative complementary chemoenzymatic route to the *trans*-dihydrodiols $\mathbf{C_{2,3}}$, from the corresponding *cis*-dihydrodiol precursors (Scheme 2). The chemoenzymatic routes reported in this and the earlier paper[3] provide access to all the possible types of *trans*-dihydrodiol regioisomers ($\mathbf{C_{1,2}}$, $\mathbf{C_{2,3}}$, $\mathbf{C_{3,4}}$) from monosubstituted benzenes which are required in our laboratories as (i) synthetic precursors, (ii) substrates for biological screening programmes and (iii) subjects for comparative aromatisation studies.



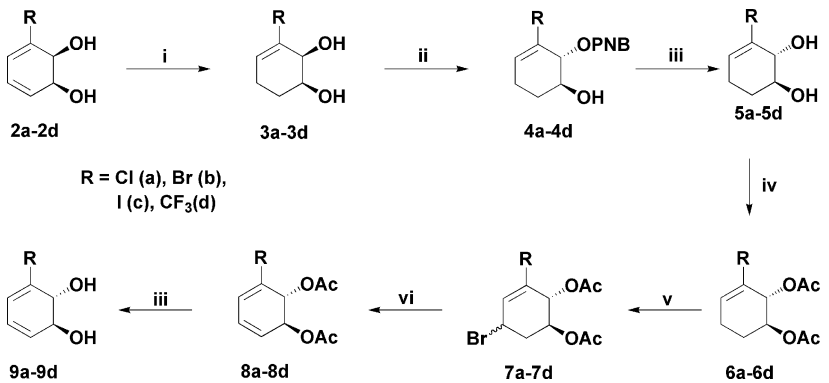
Scheme 2

Results and discussion

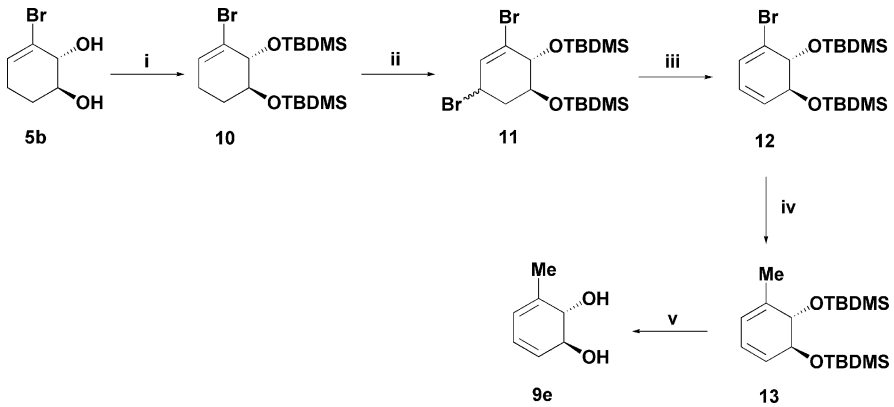
The enantiopure (>98% ee) *cis*-dihydrodiol metabolites **2a–2e**, derived from biotransformation of the monosubstituted benzene substrates, chlorobenzene (**1a**), bromobenzene (**1b**), iodobenzene (**1c**), 1,1,1-trifluorotoluene (**1d**) and toluene (**1e**) were available from earlier studies, using toluene dioxygenase (TDO) present in whole cells of *Pseudomonas putida* UV4 (Scheme 2).[25]

A generally applicable seven-step synthetic sequence, from *cis*-dihydrodiols **2a–2d** to the corresponding *trans*-dihydrodiols of type $\mathbf{C_{2,3}}$, has been developed (Scheme 3). The steps involve selective hydrogenation at the less substituted alkene bond (**2** → **3**), a regioselective Mitsunobu inversion at an allylic centre (**3** → **4**), hydrolysis (**4** → **5**), protection (**5** → **6**), allylic bromination (**6** → **7**), dehydrobromination (**7** → **8**) and deprotection (**8** → **9**).

Regioselective catalytic hydrogenation (H_2, 5% Rh–Al_2O_3) of *cis*-dihydrodiols **2a–2d**, under pressure in THF solution, yielded the corresponding *cis*-tetrahydrodiols **3a–3d**, generally, in high yield (80–90%). The partial hydrogenation of *cis*-dihydrodiol metabolite **2c** of iodobenzene proved difficult. It required careful monitoring of the progress of the reaction, to minimise the competing aromatization to *ortho*-iodophenol. *cis*-Tetrahydrodiol **3c** could only be obtained in *ca.* 50% yield. The selective hydrogenation of *cis*-dihydrodiol metabolite **2e** of toluene also proved to be more difficult and an alternative approach was adopted for the synthesis of *trans*-dihydrodiol **9e** of toluene (Scheme 4).



Scheme 3 *Reagents:* i H_2, Rh–Al_2O_3; ii PPh_3, DEAD, 4-NO_2·C_6H_4·CO_2H; iii K_2CO_3, H_2O, MeOH; iv Ac_2O, pyridine; v NBS, CCl_4; vi LiCl, Li_2CO_3, HMPA.



Scheme 4 *Reagents:* i TBDMSTf, Et_3N, DCM; ii NBS, AIBN, CCl_4; iii Li_2CO_3, LiCl, HMPA; iv MeMgBr, $Ni(acac)_2$, Et_2O; v TBAF, THF.

Due to the general instability of *cis*-dihydrodiols **2a–2d**, attempts to carry out the Mitsunobu inversion reaction on these parent diols did not succeed; the corresponding phenols were the only products formed. However, using standard conditions, their stable *cis*-tetrahydrodiol derivatives **3a–3d** were found to undergo inversion of the hydroxyl group at the allylic carbon centre. Thus, reaction of tetrahydrodiols **3a–3d**, with a mixture of triphenylphosphine, diethyldiazodicarboxylate (DEAD) and *para*-nitrobenzoic acid (*p*-NBA), in benzene, resulted in the exclusive inversion of configuration at C-2 to yield the monoesters **4a–4d**. The progress of the reaction was monitored by TLC and the identification of compounds **4a–4d** was carried out by ^{1}H-NMR spectroscopic analyses of small samples, after workup. The major portion of each of the crude reaction mixtures was hydrolysed, *in situ*, using K_2CO_3 in aq. MeOH, to give *trans*-tetrahydrodiols **5a–5d** in an overall yield of 58–64% from the corresponding *cis*-tetrahydrodiol precursors **3a–3d**.

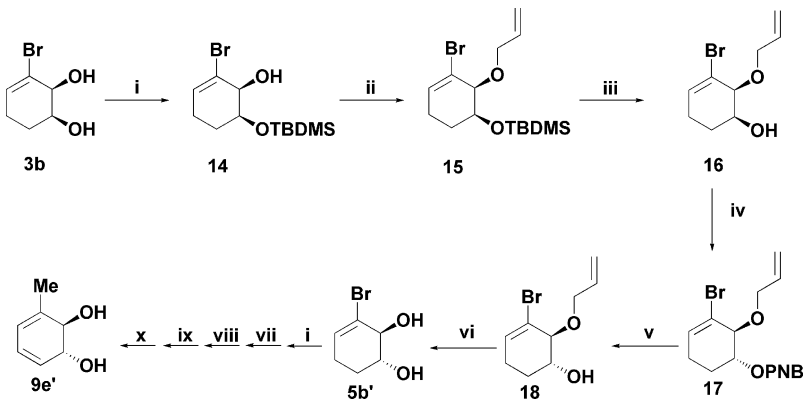
trans-Tetrahydrodiols **5a–5d** were protected, as diacetates **6a–6d** (Ac_2O–pyridine) in 93–96% yield prior to allylic bromination, using *N*-bromosuccinimide in CCl_4, to give the corresponding bromides **7a–7d**. The latter compounds were found to exist as isomeric mixtures that showed evidence of decomposition, during attempted purification by chromatography. These relatively unstable bromides **7a–7d** were, therefore, used without purification in the next dehydrobromination step (Li_2CO_3 and LiCl in HMPA) which gave the corresponding *trans*-dihydrodiol diacetates **8a–8d** (74–93% yields from the diacetate precursors **6a–6d**). The final hydrolysis step of diacetates **8a–8d** with K_2CO_3 in aq. MeOH yielded the target molecules, *trans*-dihydrodiols **9a–9d** (94–98%). The versatility of this synthetic route, from *cis*-dihydrodiol precursors **2a–2d** to the corresponding *trans*-dihydrodiols **9a–9d**, is demonstrated by its application to other members of the substituted benzene *cis*-dihydrodiol series and also to the opposite enantiomers, after suitable modification (Schemes 4–6).

The original synthetic sequence (Scheme 3) shows the conversion of the *trans*-tetrahydrodiol of bromobenzene **5b** to the corresponding *trans*-dihydrodiol **9b** in four steps, using acetate protecting groups (**6b**, **7b** and **8b**). *trans*-Tetrahydrodiol **5b** was also converted to the *trans*-dihydrodiol **9b** using a similar synthetic sequence but using diTBDMS protecting groups (**10**, **11** and **12** respectively, Scheme 4). This approach allowed the bromine atom in compound **12** to be replaced with a methyl group (to give intermediate **13** using a Grignard reagent), before deprotection to yield the *trans*-dihydrodiol of toluene **9e**, in a total of eight steps from *cis*-dihydrodiol **2b**.

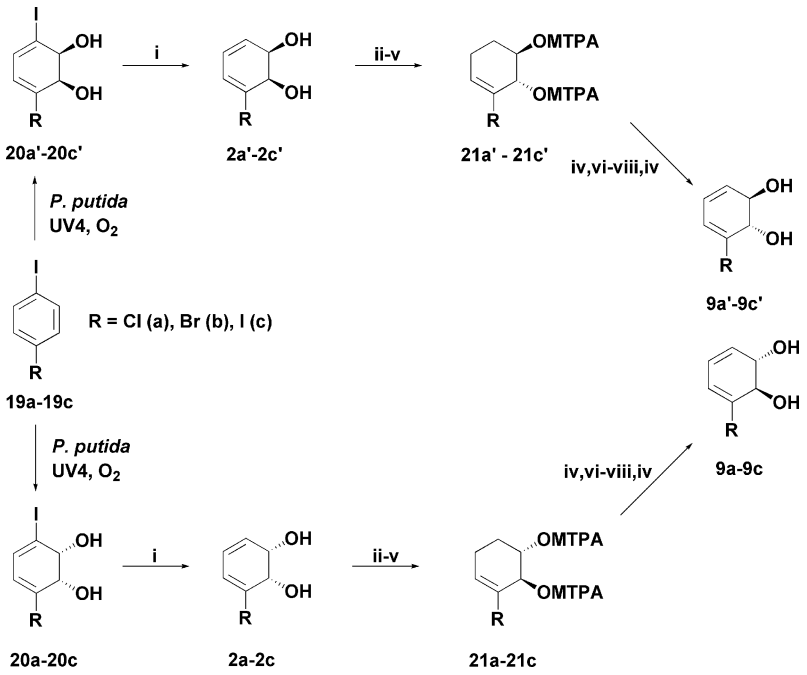
All of the *trans*-dihydrodiols **9a–9e**, obtained using the method shown in Schemes 3 and 4, were single enantiomers having (1*S*) absolute configurations. The synthesis of *trans*-dihydrodiol enantiomers **9a′**–**9c′** and **9e′** of (1*R*) configuration, was also carried out using two different methods.

The first synthetic approach was based on the Mitsunobu inversion of the non-allylic (C-1) chiral centre in a *cis*-tetrahydrodiol, using a suitably protected derivative. The *cis*-tetrahydrodiol of bromobenzene **3b** was thus selectively protected as a monoTBDMS derivative **14**, taking advantage of the less sterically hindered position of the C-1 hydroxyl group (Scheme 5). The remaining hydroxyl group at C-2 was then protected as the less sterically demanding allyl ether **15**. Removal of the TBDMS group yielded the required non-allylic alcohol **16** which was easily converted into *para*-nitrobenzoate **17** *via* a Mitsunobu inversion process. Alkaline hydrolysis of ester **17** gave alcohol **18** which on deprotection ($RhCl(Ph_3P)_3$, DABCO, EtOH, H_2O) yielded the (1*R*)-*trans*-1,2-tetrahydrodiol **5b′**. The remaining steps in the synthesis of (1*R*) enantiomer **9e′** were identical to those used for (1*S*)-*trans*-1,2-dihydrodiol **9e** (Scheme 4). The latter method requires a twelve step synthesis from *cis*-1,2-dihydrodiol **2b**.

A shorter alternative synthetic approach to enantiomers **9a′**–**9c′** was also examined (Scheme 6). In contrast to the enantiopure *cis*-dihydrodiol metabolites **2a–2e**, derived from the corresponding monosubstituted benzene substrates **1a–1e**, *para*-substituted iodobenzenes **19a–19c** on biotransformation (*P. putida* UV4) gave mixtures of *cis*-dihydrodiol enantiomers **20a**/**20a′** (from **19a**)[26] and **20b**/**20b′** (from **19b**)[26] and an achiral *cis*-dihydrodiol **20c** = **20c′** (from **19c**) (Scheme 6). Controlled hydrogenolysis to remove only an iodine atom, in each case, produced an enantiomeric mixture of monosubstituted benzene *cis*-dihydrodiols **2a**/**2a′** (35 : 60), **2b**/**2b′** (39 : 61), **2c**/**2c′** (50 : 50) in 40–70% yields. The partial hydrogenolysis of achiral *cis*-dihydrodiol **20c** = **20c′** required careful monitoring of the progress of the reaction, to minimise the loss of both iodine atoms. Partial hydrogenation of the enantiomeric mixtures of *cis*-dihydrodiols **2a–2c**/**2a′**–**2c′**, to yield the corresponding *cis*-tetrahydrodiols **3a–3c**/**3a′**–**3c′** and their



Scheme 5 *Reagents:* i TBDMSTf, Et_3N, DCM; ii $BrCH_2CH{=}CH_2$, BaO, DMF, H_2O; iii TBAF, THF; iv Ph_3P, DEAD, 4-$NO_2{\cdot}C_6H_4{\cdot}CO_2H$, THF; v K_2CO_3, MeOH; vi $RhCl(Ph_3P)_3$, DABCO, H_2O, EtOH; vii NBS, CCl_4; viii Li_2CO_3, LiCl, HMPA; ix MeMgBr, Et_2O; x TBAF, THF.



Scheme 6 *Reagents:* i H_2, Pd–C; ii H_2, Rh–Al_2O_3; iii PPh_3, DEAD, 4-NO_2·C_6H_4·CO_2H; iv NaOH, H_2O,MeOH; v (−)-MTPACl, pyridine; vi Ac_2O, pyridine; vii NBS, CCl_4; viii LiCl, Li_2CO_3, HMPA.

conversion to the corresponding *trans*-tetrahydrodiols **5a–5c/5a′–5c′**, was carried out as described (Scheme 3).

Earlier studies from these laboratories have shown that the *abnormal* (1*R*)-*cis*-dihydrodiol enantiomers **2a′–2c′** can be obtained *via* a second biotransformation, using an enzyme-catalysed kinetic resolution method.[27] In this further biotransformation, with naphthalene diol dehydrogenase enzymes present in whole cells of wild type (*e.g. P. putida* NCIMB 8859) or recombinant (*e.g. E. coli nar* B) strains,[27,28] only the *normal* (1*S*)-*cis*-dihydrodiol enantiomers **2a–2c** were found to be the substrates and were converted to the corresponding catechols. The residual *abnormal* (1*R*)-*cis*-dihydrodiol enantiomers **2a′–2c′** were then separated from the catechols by chromatography. An alternative method to the second biotransformation procedure, using a chemical resolution process, is also presented in this study.

The enantiomeric mixtures of *trans*-tetrahydrodiol enantiomers **5a/5a′–5c/5c′** were treated with (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride in pyridine solution, to yield the corresponding diMTPA diastereoisomers **21a/21a′–21c/21c′** which were separated by preparative layer chromatography (PLC) (Scheme 6). Hydrolysis of the separated diMTPA ester diastereoisomers under alkaline conditions, produced single enantiomers of the corresponding *trans*-tetrahydrodiol enantiomers **5a–5c** and **5a′–5c′** which were, in turn, converted in four steps to the corresponding *trans*-dihydrodiols **9a–9c** and **9a′–9c′**, using the method discussed earlier (Schemes 3 and 6). This route, to the synthesis of *trans*-1,2-dihydrodiol enantiomers **9a′–9c′**, from *cis*-1,2-dihydrodiol precursors **20a′–20c′**, is slightly shorter than the one used for *trans*-dihydrodiol **9e′** (Schemes 4 and 5). Furthermore, both *trans*-(1*S*,2*R*)-(**9a–9c**) and *trans*-(1*R*,2*S*)-dihydrodiols (**9a′–9c′**) were synthesised from metabolites produced by a single biotransformation.

Conclusion

The syntheses of *trans*-(1*S*,2*R*)-dihydrodiols (**9a–9c**) and *trans*-(1*S*,2*S*)-dihydrodiol (**9d**) enantiomers from enantiopure *cis*-dihydrodiol precursors have been carried out through a generally applicable chemoenzymatic method. A modification of this route has been used in the synthesis of both *trans*-(1*S*,2*R*)-(**9a–9c**) and the reverse *trans*-(1*R*,2*S*)-dihydrodiol enantiomers (**9a′–9c′**). Thus, *cis*-dihydrodiol metabolites of 4-substituted iodobenzenes containing both enantiomers (**20a/20a′–20c/20c′**) were converted to the corresponding *trans*-tetrahydrodiols (**5a/5a′–5c/5c′**) and resolved *via* their diMTPA esters (**21a/21a′–21c/21c′**). Replacement of a bromine atom with a methyl group in the diTBDMS derivatives of *trans*-tetrahydrodiol enantiomers **5b** and **5b′** provided a synthetic route to the corresponding *trans*-dihydrodiols enantiomers **9e** and **9e′**.

Expermental

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 chromatography and 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. *cis*-Dihydrodiols (1*S*,2*S*)-**2a–2c** (>98% ee), (1*S*,2*R*)-**2d** and **2e** (>98% ee), (1*R*,2*S*)-**20a**/(1*S*,2*R*)-**20a′** (*ca.* 25% ee),

(1*R*,2*S*)-**20b**/(1*S*,2*R*)-**20b′** (*ca.* 22% ee) and the achiral *cis*-dihydrodiol **20c** were available from earlier work,[25,26] were used for this study.

Hydrogenolysis of *cis*-dihydrodiols 20a–20c/20a′–20c′ to yield the corresponding *cis*-dihydrodiols 2a–2c/2a′–2c′

A solution of *cis*-1,2-dihydroxycyclohexa-3,5-diene enantiomers **20a–20c/20a′–20c′** (3.0 mmol), in MeOH (20 cm^3) containing $NaOAc{\cdot}3H_2O$ (0.272 g, 6.0 mmol) and quinoline (50 μl), was stirred, at room temperature under H_2 (1 atm.) in the presence of Pd/C (3%, 0.1 g) until the hydrogenolysis was complete (2–4 h). Removal of the catalyst by filtration and concentration of the filtrate yielded the crude mixture of enantiomers **2a–2c/2a′–2c′** that was purified (40–70% yield) by PLC (R_f 0.3 to 0.5, 50% EtOAc in hexane).

Partial hydrogenation of *cis*-dihydrodiols 2a–2d/2a′–2c′ to yield *cis*-tetrahydrodiols 3a–3c/3a′–3c′

Typical procedure: cis-1,2-Dihydroxycyclohexa-3,5-diene **2a–2d/2a′–2c′** (5 mmol) was dissolved in THF (15 cm^3) and the solution poured into a hydrogenation bottle containing catalyst (0.5 g) Rh–Al_2O_3 (5%). The bottle filled with H_2 [25 psi (**2a/2a′**), 40 psi (**2b/2b′**), 75 psi (**2c/2c′**), 20 psi (**2d**)] was mechanically shaken until hydrogenation was complete [*ca.* 3 h (**2a/2a′**), 6 h (**2b/2b′**), 16 h (**2c/2c′**), 2 h (**2d**)]. The catalyst was removed by filtration, the filtrate concentrated, and the crude hydrogenated compound purified by flash chromatography (5% MeOH in $CHCl_3$ or 40% EtOAc in hexane) to give *cis*-tetrahydrodiol **3a–3d/3a′–3c′**.

***cis*-(1*S*,2*S*)- 3a and *cis*-(1*R*,2*R*)-1,2-Dihydroxy-3-chlorocyclohex-3-ene 3a′.** Enantiomer **3a**, white crystalline solid (0.64 g, 86%); mp 111–112 °C ($CHCl_3$–hexane); $[\alpha]_D$ −158 (*c* 1.06, MeOH); (Found: C, 48.5; H, 5.9. $C_6H_9ClO_2$ requires C 48.5; H, 6.1%); δ_H (500 MHz, $CDCl_3$) 1.79 (2 H, m, 6-H, 6′-H), 2.14 (1 H, m, 5-H), 2.30 (1 H, m, 5′-H), 3.93 (1 H, m, 1-H), 4.16 (1 H, d, $J_{2,1}$ 3.5, 2-H), 5.99 (1 H, dd, $J_{4,5} = J_{4,5'}$ 4.1, 4-H); *m/z* (EI) 150 (M^+, 1%), 148 (4), 106 (30), 104 (100), 95 (7), 69 (16), 65 (18). Enantiomer **3a′**: $[\alpha]_D$ +154 (*c* 1.11, MeOH).

For compounds **3b**, **3b′**, **3c**, **3c′** and **3d** see ESI.†

Mitsunobu inversion reaction with *cis*-tetrahydrodiols 3a–3d/3a′–3c′ to yield the 4-nitrobenzoates of *trans*-tetrahydrodiol 4a–4d/4a′–4c′ and their hydrolysis to produce *trans*-tetrahydrodiols 5a–5d/5a′–5c′

Typical procedure: To a stirring solution of *cis*-tetrahydrodiols **3a–3d/3a′–3c′** (5.5 mmol) and Ph_3P (6 mmol), in anhydrous benzene (20 cm^3) containing dry 3 Å molecular sieves (1 g), DEAD (6 mmol) was added drop-wise, at room temperature. After stirring the reaction mixture for 30 min, *p*-nitrobenzoic acid (5.4 mmol) was added, the mixture was stirred for a further 30 min, and then refluxed at 90 °C until the reaction was complete (*ca.* 3 h, by TLC). The mixture was filtered, the filtrate concentrated under reduced pressure, and the concentrate dissolved in MeOH (15 cm^3). Water (1 cm^3) and K_2CO_3 (15 mmol) were added, and the reaction mixture stirred at room temperature. When the hydrolysis was complete (*ca.* 3 h), the inorganic material was filtered off, and the filtrate concentrated under reduced pressure. The residue was partitioned by extraction, with a mixture of ethyl acetate (50 cm^3) and saturated aq. NaCl solution (30 cm^3). The EtOAc layer was separated, dried (Na_2SO_4), and concentrated. Further purification of the product, by flash chromatography (15% → 50% EtOAc in hexane) yielded *trans*-tetrahydrodiol **5a–5d/5a′–5c′**.

***trans*-(1*S*,2*R*)- 5a and *trans*-(1*R*,2*S*)-1,2-Dihydroxy-3-chlorocyclohex-3-ene 5a′.** Enantiomer **5a**, white crystals (0.53 g, 65%); mp 69–70 °C ($CHCl_3$–hexane), $[\alpha]_D$ +79 (*c* 1.77, MeOH); (Found: C, 48.5; H, 6.1. $C_6H_9ClO_2$ requires C 48.5; H, 6.1%); δ_H (500 MHz, $CDCl_3$) 1.74 (1 H, m, 6-H), 1.95 (1 H, m, 6′-H), 2.20 (2 H, m, 5-H, 5′-H), 3.85 (1 H, m, 1-H), 4.07 (1 H, d, $J_{2,1}$ 6.5, 2-H), 5.92 (1 H, dd, $J_{4,5} = J_{4,5'}$ 4.0, 4-H); *m/z* (EI) 150 (M^+, 1%), 148 (3), 132 (1), 132 (3), 106 (36), 104 (100), 95 (5), 69 (7), 65 (5), 41 (18). Enantiomer **5a′**: $[\alpha]_D$ −72 (*c* 1.62, MeOH).

For compounds **5b**, **5b′**, **5c**, **5c′** and **5d** see ESI.†

Acetylation of *trans*-tetrahydrodiols 5a–5d/5a′–5c′ to yield *trans*-tetrahydrodiol diacetates 6a–6d/6a′–6c′

Typical procedure: A solution of *trans*-tetrahydrodiol **5a–5d/5a′–5c′** (3.5 mmol), in anhydrous pyridine (0.5 cm^3), was treated with Ac_2O (10 mmol), and the mixture heated at 50 °C for 4 h. The crude product obtained, after removal of excess of Ac_2O and pyridine under reduced pressure, was purified by flash chromatography (hexane → 30% Et_2O in hexane) to yield diacetate **6a–6d/6a′–6c′**.

***trans*-(1*S*,2*R*)- 6a and *trans*-(1*R*,2*S*)-1,2-Diacetoxy-3-chlorocyclohex-3-ene 6a′.** Enantiomer **6a**, white crystals (0.78 g, 96%); mp 43–45 °C ($CHCl_3$–hexane), $[\alpha]_D$ +97 (*c* 1.53, $CHCl_3$); (Found: C, 51.5; H, 5.6. $C_{10}H_{13}ClO_4$ requires C 51.6; H, 5.6%); δ_H (300 MHz, $CDCl_3$) 1.91 (2 H, m, 6-H, 6′-H), 2.06 (3 H, s, OCOMe), 2.12 (3 H, s, OCOMe), 2.25 (2 H, m, 5-H, 5′-H), 5.05 (1 H, m, H-1), 5.40 (1 H, d, $J_{2,1}$ 6.0, 2-H), 6.14 (1 H, dd, $J_{4,5} = J_{4,5'}$ 3.9, 4-H); *m/z* (EI) 234 (M^+, 1%), 232 (1), 197 (5), 174 (4), 172 (12), 132 (35), 130 (84), 112 (45), 95 (25), 77 (14), 43 (100). Enantiomer **6a′**: $[\alpha]_D$ −100 (*c* 1.40, $CHCl_3$).

For compounds **6b**, **6b′**, **6c**, **6c′** and **6d** see ESI.†

Benzylic bromination of the *trans*-tetrahydrodiol diacetates 6a–6d/6a′–6c′ to yield *trans*-tetrahydrodiol bromodiacetates 7a–7d/7a′–7c′

Typical procedure: Freshly crystallised *N*-bromosuccinimide (3.7 mmol) and α,α-azoisobisbutyronitrile (AIBN) (*ca.* 2 mg) were added to a solution of *trans*-tetrahydrodiol diacetate **6a–6d/6a′–6c′** (3.4 mmol) dissolved in carbon tetrachloride (10 cm^3). The reaction mixture was gently refluxed, under nitrogen, using a heat lamp. The reaction, monitored by TLC, was complete after 1.5 h of refluxing. The reaction mixture was cooled to room temperature, the precipitated succinimide filtered off, and the solvent removed *in vacuo.* The crude product **7a–7d/7a′–7c′**, identified as a diastereoisomeric mixture of bromides of tetrahydrodiol diacetate, by ^{1}H-NMR spectroscopy, was used immediately in the next step without purification due to its unstable nature.

***trans*-(1*S*,2*R*)- 7a and *trans*-(1*R*,2*S*)-1,2-Diacetoxy-3-chloro-5-bromocyclohex-3-ene 7a′.** Enantiomers **7a** and **7a′**, light yellow oil (1.01 g, 95%); δ_H (500 MHz, $CDCl_3$) 2.10 (3 H, s, OCOMe), 2.12 (3 H, s, OCOMe), 2.41 (1 H, m, 6-H), 2.51 (1 H, m, 6′-H), 4.78 (1 H, m, 5-H), 5.33 (1 H, m, 1-H), 5.55 (1 H, m, 2-H), 6.35 (1 H, m, 4-H).

For compounds **7b**, **7b′**, **7c**, **7c′** and **7d** see ESI.†

Dehydrobromination of *trans*-tetrahydrodiol bromodiacetates 7a–7d/7a′–7c′ to yield *trans*-dihydrodiol diacetates 8a–8d/8a′–8c′

Typical procedure: Anhydrous lithium chloride (8 mmol) and anhydrous lithium carbonate (7 mmol) were added with stirring to a solution of *trans*-tetrahydrodiol bromodiacetates **7a–7d/7a′–7c′** (2.9 mmol) in freshly distilled HMPA (2 cm^3). The reaction mixture was heated (2 h) at 95 °C under N_2 with stirring. The mixture was then cooled to 0 °C, diluted with Et_2O (25 cm^3), and aq. HCl solution (1 M, 15 cm^3) was added to it drop-wise. After shaking the mixture in a separating funnel, the Et_2O layer was separated and the aq. layer was again extracted with Et_2O (2 × 15 cm^3). The combined Et_2O extract was washed with aq. $NaHCO_3$ solution (2.5%, 20 cm^3), dried (Na_2SO_4), and concentrated *in vacuo.* Purification of the residue by PLC (50% Et_2O in hexane, R_f ~0.50,) yielded the *trans*-dihydrodioldiacetate **8a–8d/8a′–8c′**.

***trans*-(1*S*,2*R*)- 8a and *trans*-(1*R*,2*S*)-1,2-Diacetoxy-3-chloro-cyclohexa-3,5-diene 8a′.** Enantiomer **8a**, white crystals (0.63 g, 93%); mp 53–54 °C, (EtOAc–hexane); $[\alpha]_D$ +437 (*c* 1.03, $CHCl_3$); (Found: C, 51.9; H, 4.7. $C_{10}H_{11}ClO_4$ requires C 52.1; H, 4.8%); δ_H (500 MHz, $CDCl_3$) 2.08 (3 H, s, OCOMe), 2.13 (3 H, s, OCOMe), 5.34 (1 H, dd, $J_{1,2}$ 4.0, $J_{1,6}$ 4.6, 1-H), 5.66 (1 H, d, $J_{2,1}$ 4.0, 2-H), 5.90(1 H, dd, $J_{6,1}$ 4.6, $J_{6,5}$ 9.5, 6-H), 6.09 (1 H, dd, $J_{5,4}$ 6.2, $J_{5,6}$ 9.5, 5-H), 6.29 (1 H, d, $J_{4,5}$ 6.2, 4-H); *m/z* (EI) 232 (M^+, 3%), 230 (7), 195 (13), 130 (22), 128 (57), 43 (100). Enantiomer **8a′**: $[\alpha]_D$ −435 (*c* 0.75, $CHCl_3$).

For compounds **8b**, **8b′**, **8c**, **8c′** and **8d** see ESI.†

Hydrolysis of *trans*-dihydrodiol diacetates 8a–8d/8a′–8c′ to yield *trans*-dihydrodiols 9a–9d/9a′–9c′

Typical procedure: To a stirring solution of *trans*-dihydrodiol diacetate **8a–8d/8a′–8c′** (2.65 mmol) in MeOH (10 cm^3), was added water (1 cm^3) and K_2CO_3 (8 mmol). On completion of the hydrolysis (*ca.* 3 h, by TLC), the potassium salts were filtered off and the filtrate concentrated under reduced pressure. The crude product was dissolved in EtOAc (25 cm^3), the solution washed with brine solution (10 cm^3), dried (Na_2SO_4), and concentrated *in vacuo.* Purification of the residue by PLC (50% EtOAc in hexane) yielded *trans*-dihydrodiol **9a–9d/9a′–9c′**.

***trans*-(1*S*,2*R*)- 9a and *trans*-(1*R*,2*S*)-1,2-Dihydroxy-3-chloro-cyclohexa-3,5-diene 9a′.** Enantiomer **9a**, white crystals (0.38 g, 98%); mp 94–96 °C (MeOH–$CHCl_3$); $[\alpha]_D$ +504 (*c* 0.66, MeOH); (Found: M^+, 146.0138. $C_6H_7ClO_2$ requires 146.0135; δ_H (500 MHz, $CDCl_3$) 4.42 (1 H, dd, $J_{2,1}$ 9.1, $J_{2,6}$ 3.4, 2-H), 4.52 (1 H, m, 1-H), 5.92 (2 H, m, 5-H, 6-H), 6.12 (1 H, m, 4-H); *m/z* (EI) 146 (M^+, 54%), 130 (8), 128 (125), 117 (24), 111 (12), 100 (100), 93 (14), 81 (48), 65 (77), 53 (65). Enantiomer **9a′**: $[\alpha]_D$ −489 (*c* 0.59, MeOH).

For compounds **9b**, **9b′**, **9c**, **9c′** and **9d** see ESI.†

(1*R*,6*S*)- 10 and [(1*S*,6*R*)-2-Bromo-6-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-cyclohexenyl)oxy] (*tert*-butyl)-dimethylsilane 10′

A stirring solution of *trans*-tetrahydrodiol **5b** (0.135 g, 0.7 mmol) and Et_3N (0.4 cm^3, 2.8 mmol) in dry CH_2Cl_2 (10 cm^3) was treated, under N_2 at 0 °C, with TBDMSTf (0.37 cm^3, 1.6 mmol), and the reaction mixture was allowed to come to room temperature. After stirring for 1 h, the reaction was quenched by the addition of 5% aq. $NaHCO_3$ solution. The organic layer was separated and the aq. layer extracted with CH_2Cl_2 (10 cm^3). The combined solution was dried (Na_2SO_4) and the solvent evaporated. Purification of the residue by flash chromatography (hexane) yielded pure diTBDMS derivative **10** as a colourless semisolid (0.28 g, 95%); $[\alpha]_D$ +76 (*c* 0.73, $CHCl_3$); (Found: M^+–C_4H_9, 363.0798. $C_{14}H_{28}BrO_2Si_2$ requires 363.0811); δ_H(500 MHz, $CDCl_3$) 0.06, 0.07, 0.13, 0.20 [3 H each, s, 2 × –$Si(Me)_2$], 0.87, 0.91 [9 H each, s, 2 × –$C(Me)_3$], 1.57–1.63 (1H, m, 5-H), 1.80–1.86 (1 H, m, 5′-H), 1.94–2.00 (1 H, m, 4-H), 2.24–2.31 (1 H, m, 4′-H), 3.84 (1 H, d, $J_{1,6}$ 2.9, 1-H), 3.89 (1 H, m, 6-H), 6.16 (1 H, dd, $J_{3,4}$ 2.5, $J_{3,4'}$ 5.5, 3-H); *m/z* (EI) 363 (M^+–C_4H_9, 27%), 263 (18), 233 (21), 205 (24), 189 (16), 147 (100), 79 (11) and 73 (62). Enantiomer **10′** was similarly prepared from *trans*-tetrahydrodiol **5b′** (0.220 g, 1.14 mmol), as a colourless semisolid (0.44 g, 92%); $[\alpha]_D$ −75 (*c* 0.87, $CHCl_3$).

(1*R*,6*S*)- 12 and [(1*S*,6*R*)-2-Bromo-6-[{1-(*tert*-butyl)-1,1-dimethylsilyl}oxy]-2,4-cyclohexenyl)oxy](*tert*-butyl)-dimethylsilane 12′

DiTBDMS derivative **10** (0.172 g, 0.41 mmol) was converted into the corresponding diastereomeric mixture of bromo compounds **11** with *N*-bromosuccinimide, using the typical procedure for bromination mentioned earlier. The crude brominated mixture (*ca.* 0.220 g) was dissolved in HMPA (0.5 cm^3), and treated with anhydrous Li_2CO_3 (0.06 g, 0.82 mmol) and LiCl (0.03 g, 0.82 mmol) according to the typical procedure mentioned earlier. Purification of the crude product by PLC (hexane) gave compound **12** as a colourless oil (0.07 g, 43%); $[\alpha]_D$ +303 (*c* 0.88, $CHCl_3$); (Found M^+, 418.1344. $C_{18}H_{35}BrO_2Si_2$ requires 418.1359); δ_H(500 MHz, $CDCl_3$) 0.07, 0.11, 0.17, 0.19, (3 H each, s, 2 × –$Si(Me)_2$) 0.88, 0.90 (9 H each, s, 2 × –$C(Me)_3$), 4.14 (1 H, dd, $J_{6,1}$ 2.5, $J_{6,5}$ 6.0, 6-H), 4.17 (1 H, d, $J_{1,6}$ 2.5, 1-H), 5.87 (1 H, dd, $J_{5,4}$ 9.3, $J_{5,6}$ 6.0, 5-H), 5.89 (1H, dd, $J_{4,5}$ 9.3, $J_{4,3}$ 5.3, 4-H), 6.34 (1 H, d, $J_{3,4}$ 4.5, 3-H); *m/z* (EI) 418 (M^+, 45%), 339 (47), 305 (8), 225 (15), 189 (18), 147 (100), 115 (6), 73 (84) and 59 (8).

Bromo diTBDMS derivative **12′** was similarly prepared from compound **10′** (0.2 g, 0.55 mmol), as a colourless semisolid (0.092 g, 40%); $[\alpha]_D$ +295 (*c* 0.68, $CHCl_3$).

tert-Butyl(1*R*,6*R*)- 13 and *tert*-butyl](1*S*,6*S*)-6-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-methyl-2,4-cyclohexadienyl)oxy] dimethylsilane 13′

A solution of compound **12** (0.34 g, 0.81 mmol) in dry THF (7 cm^3), containing nickel(II) acetylacetonate (0.01 g, 0.04 mmol), was treated drop-wise with a solution of MeMgBr (3 M in Et_2O, 2.0 mmol, 0.68 cm^3), under a N_2 atmosphere. The reaction mixture was refluxed at 60 °C (3 h), left stirring at room temperature

(10 h), cooled (0 °C), and then treated with aq. NH_4Cl solution to terminate the reaction. Ether (30 cm^3) was added to the mixture and the organic layer separated. The remaining aq. layer was extracted with Et_2O (2 × 10 cm^3). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by PLC (hexane). DiTBDMS derivative **13** was obtained as a colourless semisolid (0.245 g, 85%); $[\alpha]_D$ +275 (*c* 0.98, $CHCl_3$); (Found: M^+, 354.2400. $C_{19}H_{38}O_2Si_2$ requires 354.2410); δ_H(500 MHz, $CDCl_3$) 0.026, 0001, 0006, 0.024 [3 H each, s, 2 × –Si(Me)$_2$], 0.79, 0.80 [9 H each, s, 2 × –C(Me)$_3$], 1.75 (3 H, s, –Me), 3.94 (1 H, d, $J_{1,6}$ 5.5, 1-H), 4.01 (1 H, dd, $J_{6,1}$ 5.5, $J_{6,5}$ 5.0, 6-H), 5.59–5.62 (2 H, m, 4-H, 6-H), 5.78 (1 H, dd, $J_{4,5}$ 5.0, $J_{4,3}$ 3.2, 4-H); *m*/*z* (EI) 354 (M^+, 100%), 165 (13), 147 (46), 137 (20), 133 (8), 91 (13), 84 (35) and 73 (70).

Enantiomer **13′** was similarly obtained from compound **12′** (0.290 g, 0.7 mmol) as a colourless semisolid (0.17 g, 70%); $[\alpha]_D$ −270 (*c* 0.60, $CHCl_3$).

(1*S*,2*S*)- 9e and (1*R*,2*R*)-3-Methyl-3,5-cyclohexadiene-1,2-diol 9e′

Tetrabutylammonium fluoride solution (1.0 M in THF, 1.7 cm^3) was added to a cooled (0 °C) solution of diTBDMS derivative **13** (0.17 g, 0.48 mmol) in THF (3 cm^3). After stirring the reaction mixture at 0 °C (10 min.) and then room temperature (3 h), the solvent was removed under reduced pressure and the residue purified by PLC (50% EtOAc in hexane). *trans*-Dihydrodiol **9e** was obtained as a white crystalline solid (0.04 g, 67%); R_f 0.26 (45% EtOAc in hexane); mp 90–92 °C (from EtOAc–hexane); $[\alpha]_D$ +310 (*c* 0.40, MeOH); (Found: M^+, 126.0679. $C_7H_{10}O_2$ requires 126.0681); δ_H(500 MHz, $CDCl_3$) 1.91 (3 H, s, –Me), 4.22 (1 H, d, $J_{1,2}$ 10.5, $J_{6,1}$ 1.5, 1-H), 4.37 (1 H, d, $J_{2,1}$ 10.5, 2-H), 5.70 (1 H, dd, $J_{6,5}$ 11.5, $J_{6,1}$ 1.5, 6-H), 5.80 (1 H, dd, $J_{4,5}$ 10.5, 4-H), 5.89 (1 H, ddd, $J_{5,6}$ 11.5, $J_{5,4}$ 3.0, $J_{5,1}$ 1.5, 5-H); δ_C(125 MHz, $CDCl_3$) 18.94, 73.76, 76.36, 119.85, 124.93, 126.57, 126.99; *m*/*z* (EI) 126 (M^+, 66%), 111 (22), 108 (63), 97 (41), 80 (100), 77 (36), 69 (27), 65 (56) and 55 (54). *trans*-Dihydrodiol **9e′** was similarly obtained from compound **13′** (0.17 g, 0.48 mmol) as a white solid (0.042 g, 70%); $[\alpha]_D$ −301 (*c* 0.47, MeOH).

(1*S*,6*S*)-2-Bromo-6-[{1-(*tert*-butyl)-1,1-dimethylsilyl}oxy]-2-cyclohexen-1-ol 14

To a solution of tetrahydrodiol **3b** (2 g, 10.4 mmol) in dry pyridine (4 cm^3), TBDMSCl (1.9 g, 12.6 mmol) and DMAP (5 mol%, 0.063 g) were added and the reaction mixture was stirred overnight at room temperature. Excess of pyridine was removed *in vacuo*, the residue extracted with EtOAc (50 cm^3), the extract washed with water (2 × 15 cm^3) and dried (Na_2SO_4). Removal of solvent under reduced pressure yielded crude monoTBDMS **14**. Purification by flash chromatography (10% EtOAc in hexane) gave monoTBDMS **14** as a colourless oil (2.94 g, 92%); (Found: M^+–C(Me)$_3$, 248.9944. $C_8H_{14}BrO_2Si$ requires 248.9947); $[\alpha]_D$ −51 (*c* 1.0, $CHCl_3$); δ_H(500 MHz, $CDCl_3$) 0.006, 0.008 [3 H each, s, –Si(Me)$_2$], 0.79 [9 H, s, –C(Me)$_3$], 1.49–1.53 (1 H, m, 5-H), 1.68–1.76 (1 H, m, 5′-H), 1.89–1.97 (1 H, m, 4-H), 2.07–2.14 (1 H, m, 4′-H), 2.66 (1 H, d, *J* 3.7, –OH), 3.83 (1 H, ddd, $J_{6,5}$ 10.5, $J_{6,5'}$ 4.0, $J_{6,1}$ 3.5, 6-H), 3.99 (1 H, d, $J_{1,6}$ 3.5, 1-H), 6.09 (1 H, dd, $J_{3,4}$ 4.9 $J_{3,4'}$ 3.4, 3-H); δ_C(125 MHz, $CDCl_3$) −4.84, −4.50, 17.28, 25.23, 25.45, 25.47, 25.80, 25.84, 70.80, 72.33, 121.84, 132.35; *m*/*z* (EI) 249 [M^+–C(Me)$_3$, 8%], 211 (15), 197 (94), 184 (100), 170 (7), 150 (3), 90 (10) and 43 (5).

(1*S*,2*S*)-2-[{(Allyloxy)-3-bromo-3-cyclohexenyl}oxy]-(*tert*-butyl)dimethylsilane 15

MonoTBDMS ether **14** (0.06 g, 0.2 mmol) was dissolved in DMF (0.5 cm^3) and BaO (0.06 g, 0.4 mmol), allyl bromide (0.045 cm^3, 0.52 mmol) and water (0.25 cm^3) were added to the solution. The reaction mixture was stirred at room temperature. When the starting material had been consumed (~48 h), the barium salts were filtered off and the filtrate concentrated *in vacuo*. Purification of the residue by flash chromatography (10% ether in hexane) gave the allyloxy TBDMS derivative **15** as a colourless oil (0.061 g, 90%); $[\alpha]_D$ −284 (*c* 0.40, $CHCl_3$); (Found: M^+–C(Me)$_3$, 289.9944. $C_{11}H_{18}BrO_2Si$ requires 289.9960); δ_H(500 MHz, $CDCl_3$) 0.07, 0.09 [3 H each, s, –Si(Me)$_2$], 0.91 [9 H, s, –C(Me)$_3$], 1.58–1.62 (1 H, m, 6-H), 1.91–1.98 (1 H, m, 6′-H), 2.00–2.09 (1 H, m, 5′-H), 2.17–2.23 (1 H, m, 5-H), 3.85–3.87 (1 H, m, 1-H), 3.90 (1 H, d, $J_{2,1}$ 3.5, 2-H), 4.23–4.27 (1 H, ddt, *J* 14, *J* 7.5, *J* 1.5, –OCH_2CHCH$_2$), 4.40–4.44 (1 H, ddt, *J* 14.0, *J* 7.5, *J* 1.5, –OCH_2CHCH$_2$), 5.15–5.18 (1 H, ddd, *J* 10.5, *J* 3.0, *J* 1.5, –OCH$_2$CHCH_2), 5.27–5.31 (1 H, ddd, *J* 17.5, *J* 5.0, *J* 1.5, –OCH$_2$CHCH_2), 5.98–6.06 (1 H, m, –OCH$_2$C*H*CH$_2$), 6.10 (1 H, dd, $J_{4,5}$ 5.0, $J_{4,5'}$ 2.5, 4-H); *m*/*z* (EI) 290 [M^+–C(Me)$_3$, 17%], 231 (28), 200 (13), 156 (34), 122 (43), 87 (21), 43 (100) and 23 (66).

(1*S*,2*S*)-2-(Allyloxy)-3-bromo-3-cyclohexen-1-ol 16

Allyloxy monoalcohol **16** was prepared from compound **15** (0.22 g, 0.63 mmol) using the procedure described for the synthesis of compound **9e**. Purification by flash chromatography (20% Et_2O in hexane) afforded allyloxy monoalcohol **16** as a colourless oil (0.125 g, 84%); $[\alpha]_D$ −235 (*c* 0.26, $CHCl_3$); (Found: M^+, 232.0097. $C_9H_{13}BrO_2$ requires 232.0099); δ_H(500 MHz, $CDCl_3$) 1.76–1.80 (2 H, m, 6-H), 2.02–2.08 (1 H, m, 5-H), 2.24–2.31 (1 H, m, 5′-H), 2.47 (1 H, d, *J* 8.0, –OH), 3.87–3.92 (1 H, m, 1-H), 3.95 (1 H, d, $J_{2,1}$ 4.5, 2-H), 4.26–4.29 (1 H, ddt, *J* 13.7, *J* 7.0, *J* 1.5, –OCH_2CHCH$_2$), 4.44–4.85 (1 H, ddt, *J* 13.7, *J* 7.0, *J* 1.5, –OCH_2CHCH$_2$), 5.22–5.25 (1 H, ddd, *J* 10.5, *J* 4.0, *J* 1.0, –OCH$_2$CHCH_2), 5.32–5.37 (1 H, ddd, *J* 17.5, *J* 4.0, *J* 1.0, –OCH$_2$CHCH_2), 5.96–6.03 (1 H, m, –OCH$_2$C*H*CH$_2$), 6.22 (1 H, t, $J_{4,5} = J_{4,5'}$ 4.0, 4-H); *m*/*z* (EI) 232 (M^+, 3%), 190 (98), 188 (100), 160 (22), 162 (24), 119 (13), 109 (25), 97 (43), 81 (61), 67 (58) and 55 (41).

(1*R*,2*S*)-2-(Allyloxy)-3-bromo-3-cyclohexenyl (4-nitrophenyl) carbonate 17

Monoalcohol **16** (0.12 g, 0.52 mmol) was converted into *p*-nitrobenzoate derivative **17** using the typical procedure described earlier for the Mitsunobu reaction. Purification by flash chromatography (20% Et_2O in hexane) yielded *p*-nitrobenzoate **17** as white needles (0.128 g, 65%); R_f 0.38 (15% Et_2O in hexane); mp 104–105 °C (from hexane); $[\alpha]_D$ −137 (*c* 0.88, $CHCl_3$); (Found: M^+–C_3H_5, 339.9870. $C_{13}H_{11}BrNO_5$ requires 339.9821); δ_H(500 MHz, $CDCl_3$) 2.02–2.09 (2 H, m, 6-H), 2.21–2.26 (1 H, m, 5-H), 2.29–2.35 (1 H, m, 5′-H), 3.90 (1 H, d, $J_{2,1}$ 2.5, 2-H), 4.27–4.35 (2 H, m, –OCH_2CHCH$_2$), 5.23 (1 H, d, *J* 10.5, –OCH$_2$CHCH_2), 5.34–5.37 (1 H, m, –OCH$_2$CHCH_2), 5.41 (1 H, dt, $J_{1,2}$ 2.5, $J_{1,6} = J_{1,6'}$ 5.0, 1-H), 5.95–6.03 (1 H, m, –OCH$_2$C*H*CH$_2$), 6.38 (1 H, m,

$J_{4,6}$ 5.0, $J_{4,6'}$ 3.06, 4-H), 8.16–8.18 (2 H, d, *J* 8.5, Ar–H), 8.29–8.31 (2 H, d, *J* 8.5, Ar–H); *m/z* (EI) 340 (M^+–C_3H_5, 12%), 233 (8), 231 (9), 214 (22), 190 (39), 188 (42), 158 (53), 150 (100), 135 (30), 104 (56), 79 (29) and 65 (15).

(1*R*,2*S*)-2-(Allyloxy)-3-bromo-3-cyclohexen-1-ol 18

Allyloxy monoalcohol **18** was obtained by the hydrolysis of *p*-nitrobenzoate **17** (0.3 g, 0.78 mmol), using the procedure described earlier. Purification by flash chromatography (5% EtOAc in hexane) afforded alcohol **18** as an off-white semisolid (0.16 g, 87%); R_f 0.18 (20% Et_2O in hexane); $[\alpha]_D$ −66 (*c* 0.95, $CHCl_3$); (Found: M^+, 232.0090. $C_9H_{13}BrO_2$ requires 232.0099); δ_H(500 MHz, $CDCl_3$) 1.72–1.79 (1 H, m, 6-H), 1.92–1.97 (1 H, m, 6′-H), 2.09–2.24 (2 H, m, 5-H), 3.80 (1 H, d, $J_{2,1}$ 5.0, 2-H), 3.97–3.99 (1 H, m, 1-H), 4.18–4.22 (1 H, ddt, *J* 12.5, *J* 6.0, *J* 1.5, –OCH_2CHCH$_2$), 4.29–4.33 (1 H, ddt, *J* 12.5, *J* 6.0, *J* 1.5, –OCH_2CHCH$_2$), 5.15–5.24 (1 H, ddd, *J* 10.0, *J* 2.5, *J* 1.0, –OCH$_2$CHCH_2), 5.32–5.36 (1 H, ddd, *J* 17.5, *J* 3.0, *J* 1.5, –OCH$_2$CHCH_2), 5.96–6.04 (1 H, m, –OCH$_2$C*H*CH$_2$), 6.21 (1 H, t, $J_{4,5} = J_{4,5'}$ 4.0, 4-H); *m/z* (EI) 232 (M^+, 5%), 190 (97), 188 (100), 153 (15), 146 (22), 109 (29), 97 (40), 81 (68), 67 (61) and 55 (53).

(1*R*,2*S*)-3-Bromo-3-cyclohexene-1,2-diol 5b′

To a solution of compound **18** (0.12 g, 0.51 mmol) in a mixture of H$_2$O–EtOH (9 : 1, 5 cm^3), tris(triphenylphosphine)rhodium(I) chloride [RhCl(Ph$_3$P)$_3$] (0.034 g, 7 mol equv.) and 1,4-diazobicyclo[2.2.2]octane (0.015 g, 0.13 mmol) were added. After refluxing the reaction mixture (3 h), at 100 °C under N_2, 1 M aq. HCl solution (2 cm^3) was added to quench the reaction. The solvents were removed under reduced pressure and the residue purified by PLC (50% EtOAc in hexane), to yield pure *trans*-tetrahydrodiol **5b′** as colourless crystals (0.08 g, 80%); mp 98 °C (from $CHCl_3$); $[\alpha]_D$ −77 (*c* 0.97, MeOH).

DiMTPA esters 21a–21c/21a′–21c′ of *trans*-tetrahydrodiols 5a–5c/5a′–5c′

Typical procedure: A solution of the enantiomeric mixture of *trans*-tetrahydrodiol **5a–5c/5a′–5c′** (2.5 mmol) in dry pyridine (2 cm^3) was treated with (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride (1.40 g, 5.5 mmol) and the reaction mixture was stirred at 60 °C overnight. Excess of pyridine was removed *in vacuo* and the crude mixture of two diastereoisomers (>95% yield) was separated by multi-elution PLC (7% ether in hexane), after purifying the mixture by filtering its chloroform solution through a pad of silica gel.

(1*S*,2*R*)-Di-[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-3-chlorocyclohex-3-ene 21a. White solid, mp 125–127 °C; (Found: M^+, 580.1074. $C_{26}H_{23}{}^{35}ClF_6O_6$ requires 580.1087); $[\alpha]_D$ +40 (*c* 1.94, $CHCl_3$); δ_H(500 MHz, $CDCl_3$) 1.69 (1 H, m, 6-H), 1.93 (1 H, m, 6′-H), 2.18 (2 H, m, 5-H, 5′-H), 3.51 (3 H, s, OMe), 3.60 (3 H, s, OMe), 5.26 (1 H, m, 1-H), 5.48 (1 H, d, $J_{2,1}$ 2.9, 2-H), 6.18 (1 H, d, $J_{4,5}$ 4.0, 4-H), 7.41–7.59 (10 H, m, Ar–H).

(1*R*,2*S*)-Di-[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-3-chlorocyclohex-3-ene 21a′. White solid, mp 128–130 °C; (Found: M^+, 580.1077. $C_{26}H_{23}{}^{35}ClF_6O_6$ requires 580.1087); $[\alpha]_D$ −110 (*c* 1.81, $CHCl_3$); δ_H(500 MHz, $CDCl_3$) 1.88 (1 H, m, 6-H), 1.94 (1 H, m, 6′-H), 2.15 (1 H, m, 5-H), 2.17 (1 H, m, 5′-H), 3.54 (3 H, s, OMe), 3.56 (3 H, s, OMe), 5.36 (1 H, m, 1-H), 5.60 (1 H, d, $J_{2,1}$ 3.3, 2-H), 6.12 (1 H, m, 4-H), 7.40–7.58 (10 H, m, Ar–H).

For compounds **21b**, **21b′**, **21c** and **21c′** see ESI.†

Hydrolysis of diMTPA esters 21a–21c/21a′–21c′ to *trans*-tetrahydrodiols 5a–5c/5a′-5c′

Typical procedure: DiMTPA ester **21a–21c/21a′–21c′** (2 mmol) in THF (15 cm^3) was treated with a methanolic solution of NaOH (1 M, 3 cm^3) and the reaction mixture was stirred at ambient temperature (3 h). A saturated aq. solution of NH_4Cl (2 cm^3) was added and the solvents were distilled off at normal pressure. A solution of brine (20 cm^3) was added to the residue, the aq. mixture extracted with EtOAc (2 × 25 cm^3), the extract dried (Na_2SO_4) and concentrated *in vacuo* to give *trans*-tetrahydrodiol **5a–5c/5a′–5c′** (*ca.* 95% yield).

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