Enzymatic and chemoenzymatic synthesis and stereochemical assignment of *cis*-dihydrodiol derivatives of monosubstituted benzenes

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Toluene dioxygenase-catalysed oxidation of mono-substituted benzene substrates (R = F, Cl, Br, I, Me, Et, CH_2OAc, $CH{=}CH_2$, $C{\equiv}CH$, CF_3, CN, OMe, OEt, SMe) in growing cultures of *Pseudomonas putida* UV4 yielded the corresponding *cis*-dihydrodiol metabolites. Palladium-catalysed cross-coupling of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene with a range of tributyltin compounds provided a chemoenzymatic route to a further series of *cis*-dihydrodiol derivatives of monosubstituted benzenes (R = D, $CH_2CH{=}CH_2$, Bu^n, SEt, SPr^i, SBu^t, SPh, SC_6H_4Me-4). The enantiopurities and absolute configurations of the *cis*-dihydrodiols, obtained by both enzymatic and chemoenzymatic routes, were determined by several new methods including ^1H NMR spectroscopic analysis of the bis-MTPA esters of the 4-phenyl-1,2,4-triazoline-3,5-dione cycloadducts, X-ray crystallography, circular dichroism spectroscopy and stereochemical correlation.

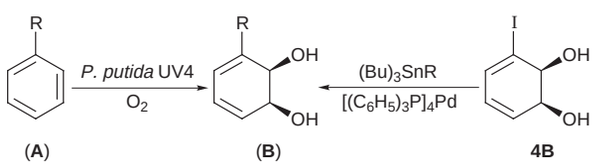
Introduction

Dioxygenase-catalysed oxidation of aromatic rings to yield *cis*-dihydrodiol derivatives is an important initial step in the bacterial biodegradation of arenes in the environment.[1] The production of mutant strains of the bacterium *Pseudomonas putida* (*e.g.* 39-D[1] and UV4[2]) has allowed the *cis*-dihydrodiols to be isolated in sufficient quantities for use as chiral precursors in synthesis.[3–8] As a prelude to a comprehensive study of the metabolism of monocyclic arenes in these laboratories, it was considered necessary to devise generally applicable methods for: (i) the determination of enantiomeric excess (% ee) and absolute configuration and (ii) the chemoenzymatic synthesis of *cis*-dihydrodiols which are not readily available by direct arene biotransformation.

In the preliminary reports of this work[9,10] we have shown that the % ee values and absolute configurations of *cis*-dihydrodiols may be determined using ^1H NMR spectroscopy, X-ray crystallographic and stereochemical correlation methods. The present comprehensive study demonstrates the general applicability of the enzyme-catalysed *cis*-dihydrodiol synthesis,[9,10] and evaluates alternative approaches to their stereochemical assignment. The chemoenzymatic synthesis of *cis*-dihydrodiol derivatives of alkyl aryl sulfides which are difficult to obtain directly by the biotransformation route is one of the important aspects of this study.

Results and discussion

The synthesis of *cis*-dihydrodiol metabolites, using mutant strains of the bacterium *P. putida* UV4 (a source of toluene dioxygenase, TDO) and a range of substituted benzene substrates, has been reported.[9] During the current programme *cis*-dihydrodiols **1B**–**14B** were isolated from the corresponding substituted benzene substrates **1A**–**14A** (Scheme 1). However, in some cases the yields of *cis*-dihydrodiols, obtained by this direct asymmetric dihydroxylation procedure, were extremely poor *e.g.* diols **9B** and **14B** (≤10%). The variable yields of *cis*-dihydrodiols, obtained from the biotransformations, may be due to several factors including substrate volatility and solubility, substrate and bioproduct toxicity, and growth conditions *e.g.* cell density and biotransformation time; bioproduct stability may be an additional factor. In general, *cis*-dihydrodiol metabolites of substituted benzene substrates were found to dehydrate (aromatise) under strongly acidic or basic conditions and at elevated temperatures. Kinetic studies on a series of *cis*-dihydrodiols, having strong electron withdrawing groups, *e.g.* diols **10B** and **11B**, have shown them to be more stable under weakly acidic conditions while those with electron donating groups, *e.g.* diols **5B**, **6B**, **12B**–**14B**, readily aromatised.[11]



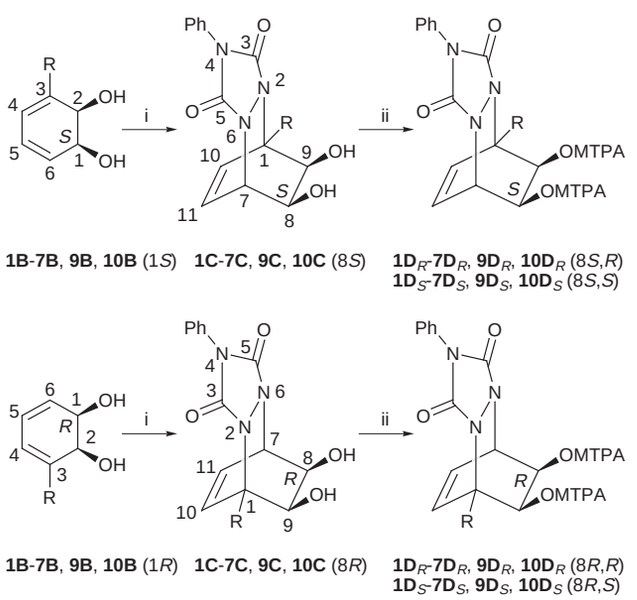
R		R	
1	F	**12**	OMe
2	Cl	**13**	OEt
3	Br	**14**	SMe
4	I	**15**	D
5	Me	**16**	$CH_2HC{=}CH_2$
6	Et	**17**	Bu^n
7	CH_2OAc	**18**	SEt
8	$HC{=}CH_2$	**19**	SPr^i
9	$C{\equiv}CH$	**20**	SBu^t
10	CF_3	**21**	SPh
11	CN	**22**	SC_6H_4Me-4

Scheme 1

All attempts to form diastereoisomeric bis[2-methoxy-2-(trifluoromethyl)phenylacetate] (bisMTPA) ester derivatives, directly from the *cis*-dihydrodiols **1B**–**14B**, using a number of solvents over a wide range of temperatures, as an indirect measure of enantiopurity, resulted in aromatisation. In most cases this problem could be circumvented when the *cis*-dihydrodiol metabolite, isolated by PLC purification without recourse to crystallisation, was treated at ambient temperature with the dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to yield stable cycloadducts. *cis*-Dihydrodiol metabolites (**1B**–**7B**, **9B**, **10B**) were found to give the corresponding PTAD cycloadducts

(**1C**–**7C**, **9C**, **10C**) in good yields (Scheme 2). Diels–Alder cycloaddition of the monosubstituted benzene *cis*-dihydrodiols with PTAD could, in principle, yield *syn*- and *anti*-addition products relative to the hydroxy groups. ^{1}H NMR spectroscopic analysis of the crude mixture containing the PTAD cycloadducts, however, showed essentially a single diastereoisomer (>97%) to be present. The bisMTPA esters (**1D**–**7D**, **9D**, **10D**), formed from the corresponding cycloadducts (**1C**–**7C**, **9C**, **10C**), were isolated after ^{1}H NMR spectroscopic analysis had shown that the reaction had gone to completion. The bisMTPA esters were then carefully purified ensuring that no separation of diastereoisomers should occur. In a few cases, the PTAD cycloadducts, *e.g.* **11C**–**14C**, proved to be less stable and consequently the corresponding bisMTPA esters (**11D**–**14D**) were not isolated.

^{1}H NMR spectroscopic analysis of the cycloadduct bisMTPA esters (**1D**–**7D**, **9D**, **10D**) provided a good method for enantiopurity determination. The stereochemical relationship between a single (1*S*)-enantiomer † of the *cis*-dihydrodiols **B**, the (8*S*) †-PTAD cycloadducts **C**, and the bis-(*R*)-MTPA(8*S*,*R*) or bis-(*S*)-MTPA (8*S*,*S*) † esters **D** (formed using the acid chloride derivative of (*R*)- or (*S*)-MTPA respectively), is shown in Scheme 2. The two diastereoisomeric bisMTPA pairs (8*S*,*R*) and



Scheme 2 *Reagents*: i PTAD, ii (*R*)-MTPA-Cl or (*S*)-MTPA-Cl

(8*R*,*R*) derived from the corresponding (1*S*) and (1*R*) enantiomers of *cis*-dihydrodiol **1B** were shown to be distinguishable by both ^{1}H NMR (-OMe) and ^{19}F NMR (-CF_3) spectroscopic analysis. The enantiopurity of the *cis*-dihydrodiol **1B** was found to vary from *ca*. 60–72% ee among different samples. Fractional recrystallization from chloroform–hexane did however provide a single enantiomer ([*a*]$_D$ −39, $CHCl_3$; ≥98% ee). The application of *cis*-diol **1B** in natural product synthesis, *e.g.* enantiopure conduritol C,[4] thus requires that the initially isolated metabolite be multiply recrystallized and checked for % ee prior to use.

The *cis*-dihydrodiols **2B**–**7B**, **9B** and **10B**, were converted to the corresponding bis-(*R*)-MTPA ester derivatives **2D**$_R$–**7D**$_R$, **9D**$_R$ and **10D**$_R$ (8*S*,*R*). ^{1}H NMR and ^{19}F NMR spectroscopic analyses appeared to indicate that only a single diastereoisomer, in each case, was present and thus diols **2B**–**7B**, **9B** and **10B** were assumed to be enantiopure. This conclusion was confirmed when single diastereoisomers of the bis-(*S*)-MTPA ester derivatives **2D**$_S$–**7D**$_S$, **9D**$_S$ and **10D**$_S$ (8*S*,*S*) again were formed and were clearly distinguishable from those obtained using (*R*)-MTPA. The latter (8*S*,*S*) diastereoisomers have an enantiomeric relationship with, and are thus spectrally indistinguishable from, the (8*R*,*R*) diastereoisomers which would have been formed using (*R*)-MTPA and the undetected (1*R*) enantiomers of *cis*-diols **2B**–**10B**. The % ee values for most of the *cis*-dihydrodiols *e.g.* **1B**–**7B**, **9B** and **10B** have also recently been confirmed by direct chiral stationary phase HPLC analysis (CSP HPLC),[12] and by indirect formation of the boronate derivatives obtained using (+)- and (−)-2-(1-methoxyethyl)-benzeneboronic acid (MBBA) followed by ^{1}H NMR spectroscopic analysis.[13] The CSP HPLC and boronate methods of enantiopurity determination of *cis*-dihydrodiols have the advantage of convenience and of smaller samples being required. However, while the CSP HPLC approach is very useful for a number of *cis*-dihydrodiols of monosubstituted benzenes, that are available in either enantiomeric form by enzymatic and/or chemoenzymatic methods,[14,15] (*e.g.* **1B**–**5B**), it is difficult to judge the applicability of this method when only one enantiomer is available. The MBBA method, which was found to be particularly useful in the determination of enantiopurity of *cis*-diol metabolites from polycyclic arenes,[16] proved to be of less value for monocyclic *cis*-diols due to poor resolution of diastereotopic ^{1}H NMR signals. The indirect bisMTPA method, described above, has the advantages of well resolved diastereotopic ^{1}H NMR signals and crystallinity of the products, facilitating X-ray crystallographic analysis. In view of the particular advantages in each case, all three methods have been used for the determination of enantiopurity of *cis*-diol metabolites.

The formation of both enantiomers of *cis*-dihydrodiol **1B**, during biotransformation, is consistent with a lower degree of facial selectivity during oxidation and may be steric in origin. A fluorine atom (r_v = 147 pm) is almost isosteric to a hydrogen atom (r_v = 120 pm) and this may result in a greater degree of flexibility in binding of the substrate **1A** within the active site of the enzyme compared with larger substrates *e.g.* **2A**–**10A** and **14A**. All other reported *cis*-dihydrodiol metabolites of monosubstituted arenes except compound **1B** were enantiopure.[8]

The absolute configurations of the *cis*-dihydrodiol metabolites **2B**, **5B** and **6B**, consistently found to be of (1*S*)-configuration, have been assigned using circular dichroism methods.[17,18] The absolute configurations of the enantiomers of *cis*-diols **1B**–**10B**, were found to be identical although the stereodescriptors changed from (2*R*) to (2*S*) according to the substituent priority in accordance with the *Sequence Rules*. In order to avoid ambiguity the absolute configurations of compounds **1B**–**10B** thus refer only to C–1 where the stereodescriptor remains constant for all C–3 substituents.

X-Ray crystallographic analysis was carried out on compounds **1D**$_R$, **5D**$_S$ and **10D**$_S$ derived from the corresponding enantiopure *cis*-dihydrodiol metabolites **1B**, **5B** and **10B** and the appropriate (*R* for **1D**$_R$) or (*S* for **5D**$_S$, **10D**$_S$) form of MTPA.‡ The structures of the parent diols **1B**, **5B** and **10B**, the *cis*-configuration between the hydroxy groups, and the absolute configuration in each case, was confirmed by crystal structure analysis of the bisMTPA esters **1D**$_R$, **5D**$_S$ and **10D**$_S$. Compounds **5D**$_S$ and **10D**$_S$ are isostructural and all three compounds show a similarity in the preferred conformation of the triazoline dione cycloadduct portion (Fig. 1–3). In each phenyltriazoline dione group the phenyl ring is twisted with respect to the triazoline ring. Torsions between the rings are

† The configuration at C–9 (**C** and **D**) and C–2 (**B**) are unspecified due to *Sequence Rule* priority changes associated with different *R* substituents.

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/213.

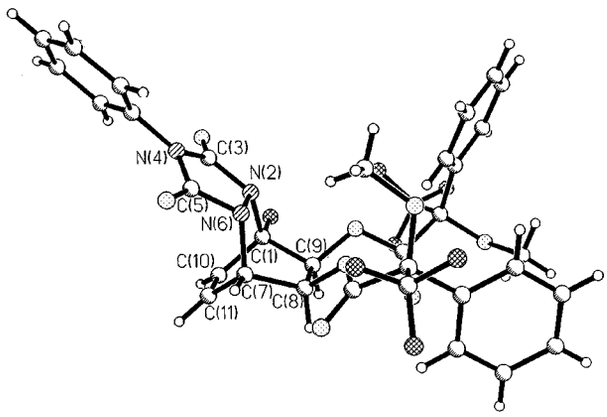


Fig. 1 A projection of molecule $\mathbf{1D}_R$

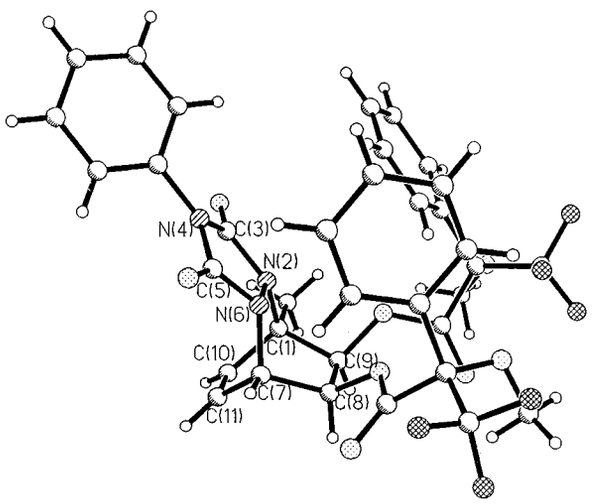


Fig. 2 A projection of molecule $\mathbf{5D}_S$

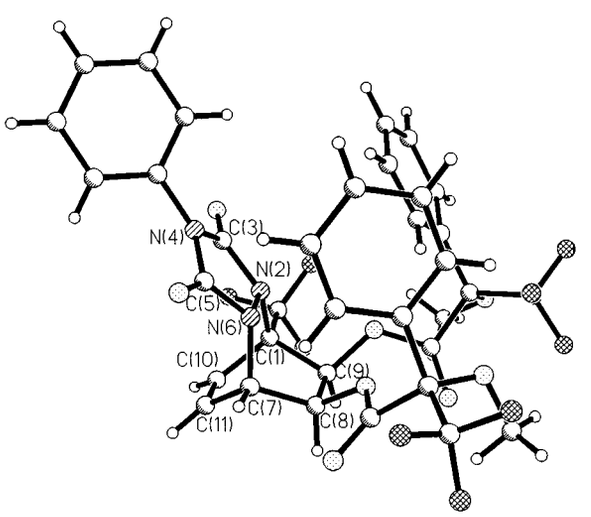


Fig. 3 A projection of molecule $\mathbf{10D}_S$

+37.7° ($\mathbf{1D}_R$), −49.1° ($\mathbf{5D}_S$), −55.5° ($\mathbf{10D}_S$). The structures also confirm that reaction between the *cis*-dihydrodiols **1B**–**10B** and PTAD occurred by *syn*-cycloaddition to the sterically more hindered face *i.e.* the face having the *cis*-hydroxy groups uppermost. The projections also show that the ring junction nitrogen atoms are pyramidal rather than planar in the solid state, with the nitrogen lone pairs *cis* to the OMTPA groups. The dihedral angles between the planes C1–N2–N6–C7 and the triazoline planes are 46.5° ($\mathbf{1D}_R$), 34.5° ($\mathbf{5D}_S$) and 35.5° ($\mathbf{10D}_S$). The absolute configuration at the chiral centre C–8 ($\mathbf{1D}_R$, $\mathbf{5D}_S$, $\mathbf{10D}_S$) was directly correlated with the known configurations of the MTPA groups, and thus allowed the (1*S*) configuration of the corresponding centre (C–1) to be unequivocally established in the parent *cis*-dihydrodiols (**1B**, **5B**, **10B**).

The absolute configurations of *cis*-dihydrodiols **1B**, **5B** and **10B**, having been rigorously established as (1*S*) by X-ray crystallography, were used to devise an empirical method for absolute configuration determination based upon diagnostic features in the ^{1}H and ^{19}F NMR spectra of the bisMTPA esters (**1D**–**7D**, **9D**, **10D**). Thus for *cis*-dihydrodiols having a (1*S*)-configuration (i) the more downfield MeO ^{1}H signal will have a larger δ value for esters obtained using (*R*)-MTPA (δ 3.65–3.59) compared with (*S*)-MTPA (δ 3.55–3.21); (ii) an aromatic signal (2H, doublet) was found downfield (δ 7.56–7.68) from the main aromatic signals only when (*S*)-MTPA was used; (iii) the more downfield CF_3 signal in the ^{19}F spectrum showed a smaller negative δ_F value (−7.49 to −8.39 ppm) using (*R*)-MTPA and larger negative δ_F value (−8.68 to −9.29 ppm) using (*S*)-MTPA. The formation of bisMTPA derivatives of the PTAD cycloadducts has also proved applicable for the determination of both enantiopurity and absolute configuration of a wide range of *cis*-dihydrodiol derivatives of disubstituted benzene substrates.[14] The chiral boronate derivatives of the parent *cis*-diol and the corresponding PTAD adducts have also been used to provide an empirical method[13] for absolute configuration determination and complements the bisMTPA method.

Although *cis*-dihydrodiol metabolites **1B**–**14B** were obtained by TDO-catalysed oxidation of the corresponding arenes, **1A**–**14A**, the isolated yields in some cases *e.g.* diols **9B** and **14B** were very low. Furthermore some of the PTAD-cycloadducts were unstable *e.g.* diols **8B**, **11B**–**14B** and alternative methods for the determination of enantiopurity and absolute configuration were required.

In an earlier communication from these laboratories,[10] it has been shown that the iodine atom in *cis*-diol **4B**, or bromine atom in *cis*-diol **3B**, can be replaced in a single-step reaction using organotin reagents. This method provides entry into a wider range of *cis*-dihydrodiols as chiral precursors and also a stereochemical correlation approach to the absolute configuration determination. The present study includes a much wider range of tributyltin reagents than reported earlier[10] using *cis*-dihydrodiols **3B** and **4B**.

Replacement of the iodine atom in *cis*-dihydrodiol **4B** with a hydrogen atom by treatment with tributyltin hydride gave the achiral *cis*-dihydrodiol of benzene (benzene *cis*-glycol). Utilisation of tributyltin deuteride in toluene solvent provided a single enantiomer of 3-deuteriobenzene-*cis*-dihydrodiol (**158**, 25% yield, $[a]_D$ −9). Palladium-catalysed cross-coupling has been reported between vinyl halides and organotin reagents[18,19] and it has been observed that activated groups *e.g.* allyl, alkenyl, alkynyl are transferred more readily than simple alkyl groups. One advantage of the palladium-catalysed cross-coupling of *cis*-dihydrodiols, containing a vinylic halide group with tributyltin reagents, is the ability to effect direct substitution without recourse to protection–deprotection procedures for the diol moiety.

Using palladium(II) acetate and triphenylphosphine as catalyst at relatively low temperatures (25–40 °C), *cis*-dihydrodiols **8B**, **9B** and **17B** were isolated (11–35% yield). With tetrakis(triphenylphosphine)palladium(0) as catalyst at higher temperatures (35–90 °C) the *cis*-dihydrodiols **11B**, **16B**, **18B**–**22B** were obtained (31–75%). The *cis*-dihydrodiol derivative of bromobenzene **3B**, on similar palladium-catalysed coupling reactions with tributyltin reagents yielded compounds **8B** (23% yield) and **14B** (14%). Due to the instability of many of the *cis*-dihydrodiol products and the necessity to carry out chromatographic purification to remove organotin residues, the isolated yields of the *cis*-dihydrodiols were variable (11–75%).

Despite the modest yields recorded in some cases, the ability to substitute an iodine atom in compound **4B** provides a direct route to a series of enantiopure *cis*-dihydrodiol derivatives of

alkyl aryl (**14B**, **18B**–**20B**) and diaryl sulfides (**21B**, **22B**) of known absolute configuration that are generally unavailable *via* toluene dioxygenase-catalysed oxidation since sulfoxidation occurs preferentially.[20]

Substitution of the iodine atom in compound **4B** by vinyl (**8B**), ethynyl (**9B**), allyl (**16B**) and cyano (**11B**) groups occurred in the expected manner using the appropriate palladium catalyst and tributyltin reagent. Surprisingly, when tributyltin methoxide was used the iodine atom in compound **4B** was replaced by an *n*-butyl group rather than by a methoxy group yielding *cis*-dihydrodiol **17B**. While the transfer of an alkyl group from a trialkyltin reagent during palladium catalysed coupling reactions is normally a very slow reaction, the presence of an alkoxide group (OMe, OEt) appeared to weaken the tin–carbon bond thus facilitating transfer of a *n*-butyl group.

The palladium-catalysed cross coupling reaction between the (1*S*) enantiomer of *cis*-dihydrodiol **4B** and the appropriate tributyltin reagent yielded the (1*S*) enantiomer of *cis*-dihydrodiols **8B**, **9B**, **14B**, **17B**–**22B**. Thus, although the bisMTPA cycloadducts of diols **8B**, **11B**, and **13B** could not be obtained, confirmation of their % ee values and absolute configurations was provided by the stereochemical correlation.

cis-Dihydrodiols **12B** and **13B** remained as the only *cis*-dihydrodiols, from the total series **1B**–**22B**, whose enantiopurities and absolute configurations could not be determined by the bisMTPA ester method or by stereochemical correlation based on the palladium-catalysed cross-coupling of compound **4B** with tributyltin reagents.

The absolute configuration of *cis*-dihydrodiol **12B** had been independently assigned as (1*S*) by reaction with diiron nonacarbonyl to give the corresponding tricarbonyl iron η^4-cyclohexadiene iron(0) complex and correlation with the CD spectra of the corresponding complexes of *cis*-dihydrodiols **2B** and **5B**.[21] The close similarity in the CD spectra of the series of *cis*-dihydrodiols containing both an alkoxy group (**12B**, **13B**) and a thioalkyl group (**14B**, **18B**–**22B**), obtained during the present study, provided further confirmation of a (1*S*) configuration in each case.

During the course of the biotransformation studies of some alkyl aryl and diaryl sulfides,[20] sulfoxides were found to be the major or only identified metabolites. Occasionally these sulfoxides were found to be accompanied, in very low yields, by *cis*-dihydrodiols derived from the corresponding sulfides and sulfoxides. *cis*-Diol sulfoxides of sulfides **14A**, **19A** and **21A** were thus detected as minor metabolites. Chemical oxidation of the relatively unstable thioether *cis*-dihydrodiols **14B**, **18B**–**22B** has been found to give the corresponding diol sulfoxides and diol sulfones in good yields. These diol sulfoxides and sulfones appear to be among the most stable *cis*-dihydrodiol derivatives of substituted benzenes.[11] The results of the enzymatic and non-enzymatic sulfur oxidation studies on *cis*-dihydrodiols will be reported elsewhere.

The concept of direct replacement of an iodine atom by a hydrogen (or a deuterium atom *e.g.* **4B** ⟶ **15B**) in the *cis*-dihydrodiol series discussed herein, has also recently been applied to the synthesis of *cis*-dihydrodiols of both enantiomers and regioisomers of either absolute configuration.[14,15] A full discussion of this approach to the chemoenzymatic synthesis of unnatural stereo- and regio-isomers of *cis*-dihydrodiols will be reported in subsequent papers.

Experimental

^{1}H NMR spectra were recorded at 300 MHz and 500 MHz using General Electric QE300 and GNΩ-500 instruments. Tetramethylsilane was used as an internal reference and $CDCl_3$ as solvent, unless stated otherwise. ^{19}F NMR spectra were recorded at 470.49 MHz in $CDCl_3$ using the GNΩ-500 instrument and α,α,α-trifluorotoluene as internal reference. Coupling constants, *J*, are given in Hz. Mass spectra were run at 70 eV on an AEI-MS902 instrument updated by VG Autospec and accurate molecular weights were determined by the peak-matching method ($\pm 6 \times 10^{-6}$ a.m.u.).

Optical rotations $[\alpha]_D$ were measured on a Perkin-Elmer polarimeter (Model 241), in the specified solvent and concentration, at 589 nm and ambient temperature. Electronic circular dichroism (CD) spectra were recorded using a JASCO J-720 instrument in acetonitrile solvent.

Tributyltin deuteride, vinyltributyltin, ethynyltributyltin, allyltributyltin, tributyltin methoxide and tributyltin cyanide were available from commercial sources. Methyl, ethyl, isopropyl, *tert*-butyl and *p*-tolyl tributyltin sulfides were obtained by reaction of the corresponding thiol with tributyltin chloride according to the literature procedures. *cis*-Diol **1B** was supplied by Zeneca FCMOPT.

Isolation and characterisation of *cis*-dihydrodiol § metabolites 1B-14B

The *cis*-dihydrodiol metabolites **1B**–**14B** were obtained using *P. putida* UV4 under the biotransformation conditions reported.[22,23]

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-fluorocyclohexa-3,5-diene 1B.** Mp 69–71 °C (From dichloromethane–hexane); $[\alpha]_D$ −39 (*c* 0.7, $CHCl_3$, ⩾98% ee); δ_H(300 MHz), 4.27 (1H, dd, $J_{2,1}$ 6.6, $J_{2,F}$ 6.6, 2-H), 4.53 (1H, m, 1-H), 5.60 (1H, dd, $J_{4,F}$ 11.0, $J_{4,5}$ 6.1, 4-H), 5.70 (1H, dd, $J_{6,1}$ 3.1, $J_{6,5}$ 9.6, 6-H), 5.86 (1H, m, 5-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-chlorocyclohexa-3,5-diene 2B.** (*ca*. 80%), mp 81–83 °C (from ethyl acetate–hexane (*lit*.,[24] 82–84 °C); $[\alpha]_D$ +36 (*c* 0.7, $CHCl_3$); δ_H(300 MHz), 4.22 (1H, d, $J_{2,1}$ 6.4, 2-H), 4.51 (1H, dd, $J_{1,2}$ 6.4, $J_{1,6}$ 1.7, 1-H), 5.92 (2H, m, 5-H, 6-H), 6.14 (1H, m, 4-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-bromocyclohexa-3,5-diene 3B.** (*ca*. 85%), mp 91–94 °C (from ethyl acetate); $[\alpha]_D$ +20 (*c* 0.6, MeOH) (Found: C, 38.1; H, 3.6. $C_6H_7BrO_2$ requires C, 37.7; H, 3.7%); δ_H(300 MHz), 4.29 (1H, d, $J_{2,1}$ 6.4, 2-H), 4.49 (1H, m, 1-H), 5.85 (1H, m, 5-H), 5.97 (1H, dd, $J_{6,1}$ 3.5, $J_{6,5}$ 9.4, 6H), 6.38 (1H, d, $J_{4,5}$ 5.7, 4-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-iodocyclohexa-3,5-diene 4B.** (*ca*. 80%), mp 64–81 °C (decomp.) (from ethyl acetate); $[\alpha]_D$ +41 (*c* 0.5 MeOH) (Found: C, 30.5; H, 3.0. $C_6H_7IO_2$ requires C, 30.25; H, 2.9%); δ_H(300 MHz), 4.28 (1H, d, $J_{2,1}$ 6.1, 2-H), 4.43 (1H, m, 1-H), 5.72 (1H, m, 5-H), 6.03 (1H, dd, $J_{6,1}$ 4.2, $J_{6,5}$ 9.4, 6-H), 6.69 (1H, d, $J_{4,5}$ 5.5, 4-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-methylcyclohexa-3,5-diene 5B.** (*ca*. 60%), mp 56–58 °C (from ethyl acetate–hexane (*lit*.,[25] 59 °C); $[\alpha]_D$ +26 (*c* 1.76, MeOH) (*lit*.,[25] $[\alpha]_D$ +25); δ_H(300 MHz), 1.93 (3H, s, Me), 4.03 (1H, d, $J_{2,1}$ 6.0, 2-H), 4.29 (1H, m, 1-H), 5.72 (1H, d, $J_{4,5}$ 4.7, 4-H), 5.79 (1H, dd, $J_{6,1}$ 3.4, $J_{6,5}$ 9.5, 6-H), 5.91 (1H, m, 5-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-ethylcyclohexa-3,5-diene 6B.** (*ca*. 60%), mp 37–38 °C (from hexane) (*lit*.,[26] 38 °C); $[\alpha]_D$ +40 (*c* 1.3, MeOH); (*lit*.,[26] $[\alpha]_D$ +42, MeOH); δ_H(300 MHz), 1.09 (3H, m, CH_2CH_3), 2.29 (2H, q, J_{CH_3,CH_2} 7.4, CH_2CH_3), 4.00 (1H, d, $J_{2,1}$ 5.9, 2-H), 4.31 (1H, m, 1-H), 5.73 (2H, m, 4-H, 6-H), 5.93 (1H, m, 5-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-acetoxymethylcyclohexa-3,5-diene 7B.** (*ca*. 20%), mp 67–69 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +59 (*c* 1.1, $CHCl_3$), $[\alpha]_D$ +102 (*c* 0.92, MeOH) (Found: C, 58.5; H, 6.2. $C_9H_{12}O_4$ requires C, 58.7; H, 6.5%); δ_H(300 MHz), 2.10 (3H, s, CH_2OAc), 4.19 (1H, d, $J_{2,1}$ 6.3, 2-H), 4.35 (1H, m, 1-H), 4.69 (1H, d, J_{AB} 13.5, CH_AH_BOAc), 4.80 (1H, d, J_{AB} 13.4, CH_AH_BOAc), 5.97 (3H, m, 4-H, 5-H, 6-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-vinylcyclohexa-3,5-diene 8B.** (*ca*. 30%), mp 54–55 °C ($CHCl_3$–diethyl ether) (*lit*.,[27] 57–58 °C; $[\alpha]_D$ +115 (*c* 0.5, MeOH) (Found: M^+ 138.068 84. $C_8H_{10}O_2$ requires 138.068 07); δ_H(300 MHz), 1.69 (1H, d, $J_{OH,2}$ 7.9, OH), 2.62 (1H, d, $J_{OH,1}$ 9.5, OH), 4.37 (1H, dd, $J_{2,OH}$ 7.9, $J_{2,1}$ 5.4, 2-H), 4.46

§ Throughout the Experimental section, *cis* refers to the *cis* arrangement of the hydroxy groups in the compounds made.

(1H, m, 1-H), 5.22 (1H, d, J_{cis} 10.8, CH=CH_2), 5.53 (1H, d, J_{trans} 17.6, CH=CH_2), 5.86 (1H, d, $J_{4,5}$ 8.7, 4-H), 5.99 (2H, m, 5-H, 6-H), 6.41 (1H, dd, J_{cis} 10.8, J_{trans} 17.5, C*H*=CH_2).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-ethynylcyclohexa-3,5-diene 9B.** (*ca*. 10%), mp 51–52 °C (from ethyl acetate–hexane); $[\alpha]_D$ +194 (*c* 0.4, MeOH) (Found: M^+ 136.052 45. $C_8H_8O_2$ requires 136.051 66); δ_H(300 MHz), 2.34 (1H, br s, OH), 2.44 (1H, br s, OH), 3.27 (1H, s, ≡C-H), 4.23 (1H, d, $J_{2,1}$ 5.6, 2-H), 4.36 (1H, m, 1-H), 6.06 (2H, m, 5-H, 6-H), 6.38 (1H, m, 4-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-trifluoromethylcyclohexa-3,5-diene 10B.** (*ca*. 65%), mp 87–89 °C (from dichloromethane–hexane) (*lit*.,[28] 90–92 °C); $[\alpha]_D$ −63 (*c* 0.9, $CHCl_3$); δ_H(300 MHz), 4.30 (1H, d, $J_{2,1}$ 6.0, 2-H), 4.52 (1H, m, 1-H), 6.07 (2H, m, 5-H, 6-H), 6.58 (1H, m, 4-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-cyanocyclohexa-3,5-diene 11B.** (*ca*. 56%), mp 78–80 °C ($CHCl_3$); $[\alpha]_D$ +187 (*c* 0.6, MeOH) (Found: M^+ 137.099 32. $C_7H_7NO_2$ requires 137.047 67); δ_H(300 MHz; [$^2H_4$]MeOH), 4.20 (1H, dd, $J_{2,6}$ 0.6, $J_{2,1}$ 6.6, 2-H), 4.29 (1H, m, 1-H), 6.10 (1H, m, 5-H), 6.24 (1H, m, 6-H), 6.80 (1H, dd, $J_{4,5}$ 6.1, $J_{4,6}$ 0.8, 4-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-methoxycyclohexa-3,5-diene 12B.** (*ca*. 10%), unstable oil, $[\alpha]_D$ +44 (*c* 0.9, $CHCl_3$) (Found: M^+ 142.062 91. $C_7H_{10}O_3$ requires 142.062 99); δ_H(300 MHz), 3.67 (3H, s, OMe), 4.22 (1H, d, $J_{2,1}$ 5.9, 2-H), 4.36 (1H, m, 1-H), 5.00 (1H, d, $J_{4,5}$ 6.1, 4-H), 5.61 (1-H, dd, $J_{6,1}$ 4.1, $J_{6,5}$ 9.5, 6-H), 5.92 (1H, m, 5-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-ethoxycyclohexa-3,5-diene 13B.** (*ca*. 10%), unstable oil, $[\alpha]_D$ +51 (*c* 2.0, $CHCl_3$) (Found: M^+ 156.078 51. $C_8H_{12}O_3$ requires 156.078 64); δ_H(300 MHz) 1.35 (3H, t, *J* 7.0, OCH_2CH_3), 3.81 (2H, q, *J* 7.0, OCH_2CH_3), 4.12 (1H, d, $J_{2,1}$ 6.0, 2-H), 4.39 (1H, m, 1-H), 4.96 (1H, d, $J_{4,5}$ 6.1, 4-H), 5.53 (1H, dd, $J_{6,1}$ 3.5, $J_{6,5}$ 9.6, 6-H), 5.93 (1H, m, 5-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-methylsulfanylcyclohexa-3,5-diene 14B.** (*ca*. 1%), mp 57–61 °C, $[\alpha]_D$ +37 (*c* 0.7, MeOH); δ_H(300 MHz), 2.20 (3H, s, CH_3), 2.60 (1H, d, $J_{OH,2}$ 8.2, OH), 2.99 (1H, d, $J_{OH,1}$ 8.5, OH), 4.12 (1H, d, $J_{2,1}$ 5.7, 2-H), 4.21 (1H, m, 1-H), 5.44 (1H, d, $J_{4,5}$ 5.7, 4-H), 5.73 (1H, dd, $J_{6,1}$ 4.0, $J_{6,5}$ 9.4, 6-H), 5.94 (1H, dd, $J_{5,6}$ 9.5, $J_{5,4}$ 5.7, 5-H).

Formation of cycloadducts between *cis*-dihydrodiols and 4-phenyl-1,2,4-triazoline-3,5-dione

General procedure. A solution of freshly sublimed 4-phenyl-1,2,4-triazoline-3,5-dione (2 mmol) in dichloromethane (10 cm^3) was added dropwise with stirring to the *cis*-dihydrodiol (2.1 mmol) in dichloromethane (20 cm^3) at room temperature until the reaction was complete *i.e.* the pink colour of the reagent persisted (*ca*. 1 h). Removal of the solvent under reduced pressure yielded the cycloadduct which was purified by PLC or flash chromatography (75–95% ethyl acetate–hexane).

***cis*-(1*S*,8*S*,9*S*)-8,9-Dihydroxy-1-fluoro-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 1C.** Yield 73%; mp 231–233 °C (from MeOH); $[\alpha]_D$ −24 (*c* 0.7 in pyridine, after recrystallization to 100% ee) (Found: C, 54.9; H, 4.0; N, 13.3. $C_{14}H_{12}FN_3O_4$ requires C, 55.1; H, 4.0; N, 13.8%); δ_H(300 MHz; [$^2H_5$]pyridine), 4.32 (1H, m, 8-H), 4.43 (1H, dd, $J_{9,F}$ 6.4, $J_{9,8}$ 8.5, 9-H), 5.28 (1H, m, 7-H), 6.52 (1H, m, 11-H), 6.69 (1H, m, 10-H), 7.24–7.67 (5H, m, Ar-H).

***cis*-(1*S*,8*S*,9*S*)-8,9-Dihydroxy-1-chloro-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 2C.** Yield 50%; mp 216–218 °C (from MeOH); $[\alpha]_D$ −22 (*c* 1.1 in pyridine) (Found: C, 52.1; H, 3.8; N, 12.6. $C_{14}H_{12}ClN_3O_4$ requires C, 52.3; H, 3.8; N, 13.1%); δ_H(300 MHz), 3.96 (1H, d, $J_{9,8}$ 8.3, 9-H), 4.07 (1H, m, 8-H), 5.02 (1H, m, 7-H), 6.56 (2H, m, 10-H, 11-H), 7.29–7.49 (5H, m, Ar-H).

***cis*-(1*S*,8*S*,9*S*)-8,9-Dihydroxy-1-bromo-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 3C.** Yield 95%; mp 184–186 °C (from MeOH); $[\alpha]_D$ −5 (*c* 0.8 in acetone) (Found: C, 46.1; H, 3.6; N, 11.4. $C_{14}H_{12}BrN_3O_4$ requires C, 45.9; H, 3.3; N, 11.5%); δ_H(300 MHz; [$^2H_6$]acetone) 2.83 (2H, br s, 2 × OH), 4.08 (1H, d, $J_{9,8}$ 8.4, 9-H), 4.13 (1H, dd, $J_{8,7}$ 2.4, $J_{8,9}$ 8.4, 8-H), 4.94 (1H, m, 7-H), 6.63 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.6, 11-H), 6.70 (1H, dd, $J_{10,7}$ 1.6, $J_{10,11}$ 8.6, 10-H), 7.39–7.52 (5H, m, Ar-H).

***cis*-(1*S*,8*S*,9*S*)-8,9-Dihydroxy-1-iodo-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 4C.** Yield 93%; mp 186–194 °C (decomp.) (from MeOH); $[\alpha]_D$ −6 (*c* 0.7 in acetone) (Found: C, 40.7; H, 2.9; N, 10.2. $C_{14}H_{12}IN_3O_4$ requires C, 40.7; H, 2.9; N, 10.2%); δ_H(300 MHz; [$^2H_6$]acetone), 4.05 (1H, dd, $J_{8,7}$ 2.6, $J_{8,7}$ 8.4, 8-H), 4.11 (1H, d, $J_{9,8}$ 8.4, 9-H), 4.96 (1H, m, 7-H), 6.49 (1H, dd, $J_{11,7}$ 6.2, $J_{11,10}$ 8.5, 11-H), 6.92 (1H, dd, $J_{10,7}$ 1.3, $J_{10,11}$ 8.5, 10-H), 7.36–7.52 (5H, m, Ar-H).

***cis*-(1*R*,8*S*,9*R*)-8,9-Dihydroxy-1-methyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 5C.** Yield 76%; mp 180–183 °C (decomp.) (from MeOH); $[\alpha]_D$ +10 (*c* 0.8 in pyridine) (Found: C, 59.7; H, 5.1; N, 13.9. $C_{15}H_{15}N_3O_4$ requires C, 59.8; H, 5.0; N, 13.9%); δ_H(300 MHz), 2.01 (3H, s, Me), 3.58 (1H, d, $J_{9,8}$ 8.3, 9-H), 3.94 (1H, dd, $J_{8,7}$ 2.7, $J_{8,9}$ 8.3, 8-H), 4.96 (1H, m, 7-H), 6.28 (1H, dd, $J_{10,7}$ 1.4, $J_{10,11}$ 8.2, 10-H), 6.46 (1H, dd, $J_{11,7}$ 6.0, $J_{11,10}$ 8.2, 11-H), 7.28–7.48 (5H, m, Ar-H).

***cis*-(1*R*,8*S*,9*R*)-8,9-Dihydroxy-1-ethyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 6C.** Yield 63%; mp 187–189 °C (from $CHCl_3$–diethyl ether); $[\alpha]_D$ −29 (*c* 0.5, $CHCl_3$) (Found: C, 60.4; H, 5.6; N, 13.1. $C_{16}H_{17}N_3O_4$ requires C, 60.9; H, 5.4; N, 13.3%); δ_H(300 MHz), 1.15 (3H, t, *J* 7.3, CH_2CH_3), 2.04 (1H, m, CH_2CH_3), 2.72 (1H, m, CH_2CH_3), 3.64 (1H, d, $J_{9,8}$ 8.3, 9-H), 3.82 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.3, 8-H), 4.89 (1H, m, 7-H), 6.29 (1H, dd, $J_{10,7}$ 0.8, $J_{10,11}$ 8.3, 10-H), 6.46 (1H, dd, $J_{11,7}$ 6.3, $J_{11,10}$ 8.3, 11-H), 7.33–7.44 (5H, m, Ar-H).

***cis*-(1*R*,8*S*,9*R*)-8,9-Dihydroxy-1-acetoxymethyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 7C.** Yield 43%; oil, $[\alpha]_D$ −6 (*c* 1.0 in $CHCl_3$) (Found: M^+ 359.111 26. $C_{17}H_{17}N_3O_6$ requires 359.111 72); δ_H(300 MHz), 2.11 (3H, s, CH_2OAc), 3.79 (1H, d, $J_{9,8}$ 8.4, 9-H), 3.91 (1H, dd, $J_{8,7}$ 2.1, $J_{8,9}$ 8.4, 8-H), 4.89 (1H, d, J_{AB} 11.9, CH_2OAc), 4.97 (1H, m, 7-H), 5.08 (1H, d, J_{AB} 11.9, CH_2OAc), 6.41 (1H, dd, $J_{10,7}$ 0.8, $J_{10,11}$ 8.2, 10-H), 6.50 (1H, dd, $J_{11,7}$ 6.4, $J_{11,10}$ 8.2, 11-H), 7.33–7.44 (5H, m, Ar-H).

***cis*-(1*R*,8*S*,9*R*)-8,9-Dihydroxy-1-ethynyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 9C.** Yield 63%; mp 200–202 °C (from MeOH); $[\alpha]_D$ +57 (*c* 1.2 in acetone) (Found: M^+ 311.091 30. $C_{16}H_{13}N_3O_4$ requires 311.090 57); δ_H(300 MHz; [$^2H_6$]acetone), 3.24 (1H, s, ≡C–H), 3.97 (1H, d, $J_{9,8}$ 8.4, 9-H), 4.05 (1H, dd, $J_{8,7}$ 2.5, $J_{8,9}$ 8.4, 8-H), 4.91 (1H, m, 7-H), 6.48 (1H, d, $J_{10,11}$ 8.3, 10-H), 6.65 (1H, dd, $J_{11,7}$ 6.0, $J_{11,10}$ 8.3, 11-H), 7.36–7.54 (5H, m, Ar-H).

***cis*-(1*R*,8*S*,9*R*)-8,9-Dihydroxy-1-trifluoromethyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 10C.** Yield 65%; mp 210–215 °C (decomp.) (from MeOH); $[\alpha]_D$ +12 (*c* 0.8 in pyridine) (Found: C, 50.6; H, 3.4; N, 11.8. $C_{15}H_{12}F_3N_3O_4$ requires C, 50.7; H, 3.4; N, 11.8%); δ_H(300 MHz), 4.03 (1H, m, 8-H), 4.19 (1H, dd, $J_{9,7}$ 6.4, $J_{9,8}$ 8.4, 9-H), 5.09 (1H, m, 7-H), 6.55 (1H, dd, $J_{10,7}$ 1.4, $J_{10,11}$ 8.3, 10-H), 6.65 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.3, 11-H), 7.24–7.43 (5H, m, Ar-H).

Preparation of bis-(*R*)-(+)- and bis-(*S*)-(−)-MTPA esters of cycloadducts derived from monosubstituted arene *cis*-dihydrodiols

General procedure. To a solution of the PTAD cycloadduct (0.1 mmol) in anhydrous pyridine (2 cm^3) was added (*S*)-(+)- or (*R*)-(−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride (0.22 mmol) and 4-dimethylaminopyridine (5 mg). The mixture was stirred at 60 °C until ^{1}H NMR spectroscopic analysis indicated that esterification had gone to completion (48 h). Purification by PLC (2% methanol–chloroform) afforded the respective (*R*)-(+) or (*S*)-(−)-bisMTPA esters in good yield (>90%). The diastereoisomeric composition of the bisMTPA esters (^{1}H NMR spectroscopy), *e.g.* **1D**, provided an indirect measure of the % ee of the corresponding *cis*-dihydrodiols, *e.g.* **1B**.

(1*S*,8*S*,9*R*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-fluoro-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 1D$_R$. Mp 177–178 °C (from acetone–diethyl

ether); $[\alpha]_D$ +10 (*c* 1.1, $CHCl_3$) (Found: C, 55.35; H, 3.55; N, 5.9. $C_{34}H_{26}F_7N_3O_8$ requires C, 55.4; H, 3.55; N, 5.7%); δ_H(500 MHz), 3.18 (3H, s, OMe), 3.63 (3H, s, OMe), 5.36 (3H, s, 7-H, 8-H, 9-H), 6.56 (1H, m, 11-H), 6.76 (1H, m, 10-H), 7.34–7.47 (15H, m, Ar-H); δ_F(470 MHz) −8.39 (CF_3), −10.07 (CF_3).

(1*S*,8*S*,9*R*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-fluoro-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 1D$_S$. Mp 201–203 °C (from MeOH–$CHCl_3$); $[\alpha]_D$ +23 (*c* 0.5, $CHCl_3$) (Found: C, 55.2; H, 3.6; N, 5.6 $C_{34}H_{26}F_7N_3O_8$ requires C, 55.4; H, 3.55; N, 5.7%); δ_H(500 MHz), 3.19 (3H, s, OMe), 3.55 (3H, s, OMe), 5.20 (2H, s, 7-H, 9-H), 5.58 (1H, dd, $J_{8,7}$ 5.3, $J_{8,9}$ 9.0, 8-H), 6.58 (1H, m, 11-H), 6.80 (1H, m, 10-H), 7.31–7.48 (13H, m, Ar-H), 7.56 (2H, d, *J* 7.3, Ar-H); δ_F(470 MHz) −9.27 (CF_3), −9.35 (CF_3).

Although this bisMTPA ester was initially obtained as a diastereomeric mixture (ratio *ca.* 4:1) of **1D**$_R$ (8*S*,*R*:8*R*,*R* using *R*-MTPA) or **1D**$_S$ (8*S*,*S*:8*R*,*S* using *S*-MTPA), the above physical data relates to the major diastereoisomer only which was obtained exclusively after recrystallisation.

X-Ray crystal structure analysis of compound 1D$_R$

Crystal data. $C_{34}H_{26}F_7N_3O_8$. M = 737.6. Orthorhombic, a = 11.927(9), b = 15.096(9), c = 18.284(14) Å, V = 3292(4) Å^3, λ = 0.710 73 Å, space group $P2_12_12_1$ (No. 19), Z = 4, D_x = 1.488 g cm^{-1}, colourless blocks, dimensions 0.56 × 0.46 × 0.25 mm, μ(Mo-Kα) = 1.32 cm^{-1}, F(000) = 1512.

Data collection and processing. Siemens P3 diffractometer, θ–2θ scan, θ scan width 1.2°, 3.5 < 2θ < 50°, h: 0→14, k: 0→17, l: 0→21; graphite monochromated Mo-Kα radiation; 3269 unique reflections measured giving 2278 with $F > 4\sigma(F)$; Lorentz and polarisation corrections applied.

Structure analysis and refinement. Direct methods (SHELXS-86);[29] full-matrix least squares refinement on F^2 (SHELXL-93)[30] with all non-hydrogen atoms anisotropic and hydrogens in calculated positions using the riding model with U_{iso}(H) = 1.2 U(eq) for the attached atom. (The calculated positions for methyl hydrogens were confirmed as corresponding to those located in an earlier difference Fourier map). Final R_1 = 0.046 (for 2278 data), wR_2 = 0.123 (all data), Goodness of Fit = 0.98, residual electron density: −0.24→0.20. A projection of the molecule is shown in Fig. 1.

(1*S*,8*S*,9*S*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-chloro-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 2D$_R$. Mp 95–98 °C (from MeOH); $[\alpha]_D$ +2 (*c* 0.5, $CHCl_3$) (Found: M$^+$ 753.132 17. $C_{34}H_{26}F_6{}^{35}ClN_3O_8$ requires 753.131 24); δ_H(500 MHz), 3.24 (3H, s, OMe), 3.63 (3H, s, OMe), 5.09 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.33 (1H, m, 7-H), 5.37 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 6.58 (1H, dd, $J_{11,7}$ 6.2, $J_{11,10}$ 8.8, 11-H), 6.64 (1H, dd, $J_{10,7}$ 1.5, $J_{10,11}$ 8.8, 10-H), 7.34–7.49 (15H, m, Ar-H); δ_F(470 MHz) −8.05 (CF_3), −9.85 (CF_3).

(1*S*,8*S*,9*S*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-chloro-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 2D$_S$. Mp 198–200 °C (from MeOH); $[\alpha]_D$ +36 (*c* 1.1, $CHCl_3$) (Found: C, 53.5; H, 3.5; N, 5.7. $C_{34}H_{26}F_6ClN_3O_8$ requires C, 54.1; H, 3.5; N, 5.6%); δ_H(500 MHz), 3.22 (3H, s, OMe), 3.42 (3H, s, OMe), 5.19 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 5.31 (1H, m, 7-H), 5.36 (1H, d, $J_{9,8}$ 8.8, 9-H), 6.59 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 6.69 (1H, dd, $J_{10,7}$ 1.1, $J_{10,11}$ 8.4, 10-H), 7.33–7.48 (13H, m, Ar-H), 7.61 (2H, d, *J* 7.3, Ar-H); δ_F(470 MHz) −9.09 (CF_3), −9.85 (CF_3).

(1*S*,8*S*,9*S*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-bromo-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 3D$_R$. Mp 189–190 °C (from chloroform–diethyl ether); $[\alpha]_D$ −15 (*c* 0.5, $CHCl_3$) (Found: C, 51.0; H, 3.1; N, 5.5. $C_{34}H_{26}F_6BrN_3O_8$ requires C, 51.1; H, 3.3; N, 5.3%); δ_H(500 MHz), 3.31 (3H, s, OMe), 3.62 (3H, s, OMe), 5.11 (1H, d, $J_{9,8}$ 8.7, 9-H), 5.33 (1H, m, 7-H), 5.35 (1H, dd, $J_{8,7}$ 2.5, $J_{8,9}$ 8.7, 8-H), 6.52 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 6.74 (1H, dd, $J_{10,7}$ 1.2, $J_{10,11}$ 8.4, 10-H), 7.35–7.52 (15H, m, Ar-H); δ_F(470 MHz) −7.75 (CF_3), −9.47 (CF_3).

(1*S*,8*S*,9*S*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-bromo-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 3D$_S$. Mp 191–192 °C (from $CHCl_3$–diethyl ether); $[\alpha]_D$ +48 (*c* 0.8, $CHCl_3$) (Found: C, 51.1; H, 3.2; N, 5.1. $C_{34}H_{26}F_6BrN_3O_8$ requires C, 51.1; H, 3.3; N, 5.3%); δ_H(500 MHz), 3.23 (3H, s, OMe), 3.36 (3H, s, OMe), 5.18 (1H, dd, $J_{8,7}$ 2.2, $J_{8,9}$ 8.7, 8-H), 5.34 (1H, m, 7-H), 5.37 (1H, d, $J_{9,8}$ 8.7, 9-H), 6.53 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 6.80 (1H, dd, $J_{10,7}$ 1.2, $J_{10,11}$ 8.4, 10-H), 7.32–7.48 (13H, m, Ar-H), 7.63 (2H, d, *J* 7.4, Ar-H); δ_F(470 MHz) −8.79 (CF_3), −9.48 (CF_3).

(1*S*,8*S*,9*S*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-iodo-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 4D$_R$. Mp 200–220 °C (decomp.) (from $CHCl_3$–diethyl ether); $[\alpha]_D$ +18 (*c* 0.7, $CHCl_3$) (Found: C, 47.6; H, 3.0; N, 4.7. $C_{34}H_{26}F_6IN_3O_8$ requires C, 48.3; H, 3.1; N, 5.0%); δ_H(500 MHz), 3.41 (3H, s, OMe), 3.59 (3H, s, OMe), 5.07 (1H, d, $J_{9,8}$ 8.7, 9-H), 5.30 (1H, dd, $J_{8,7}$ 2.5, $J_{8,9}$ 8.7, 8-H), 5.34 (1H, m, 7-H), 6.37 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 6.89 (1H, dd, $J_{10,7}$ 1.2, $J_{10,11}$ 8.4, 10-H), 7.34–7.56 (15H, m, Ar-H); δ_F(470 MHz) −7.56 (CF_3), −9.15 (CF_3).

(1*S*,8*S*,9*S*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-iodo-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 4D$_S$. Mp 150–151 °C (from $CHCl_3$–diethyl ether); $[\alpha]_D$ +59 (*c* 0.6, $CHCl_3$) (Found: C, 48.2; H, 3.2; N, 4.9. $C_{34}H_{26}F_6IN_3O_8$ requires C, 48.3; H, 3.1; N, 5.0%); δ_H(500 MHz), 3.25 (3H, s, OMe), 3.30 (3H, s, OMe), 5.14 (1H, dd, $J_{8,7}$ 2.5, $J_{8,9}$ 8.7, 8-H), 5.33 (1H, d, $J_{9,8}$ 8.7, 9-H), 5.38 (1H, m, 7-H), 6.38 (1H, dd, $J_{11,7}$ 6.2, $J_{11,10}$ 8.4, 11-H), 6.97 (1H, dd, $J_{10,7}$ 1.2, $J_{10,11}$ 8.4, 10-H), 7.30–7.48 (13H, m, Ar-H), 7.65 (2H, d, *J* 7.8, Ar-H); δ_F(470 MHz), −8.66 (CF_3), −9.16 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-methyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 5D$_R$. Mp 171–173 °C (from MeOH); $[\alpha]_D$ −20 (*c* 0.5, $CHCl_3$) (Found: C, 57.0; H, 3.9; N, 5.7. $C_{35}H_{29}F_6N_3O_8$ requires C, 57.3; H, 4.0; N, 5.7%); δ_H(500 MHz), 1.50 (3H, s, Me), 3.15 (3H, s, OMe), 3.64 (3H, s, OMe), 4.63 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.33 (1H, m, 7-H), 5.37 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 6.34 (1H, dd, $J_{10,7}$ 1.5, $J_{10,11}$ 8.1, 10-H), 6.55 (1H, dd, $J_{11,7}$ 6.6, $J_{11,10}$ 8.1, 11-H), 7.32–7.47 (15H, m, Ar-H); δ_F(470 MHz), −7.86 (CF_3), −9.57 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-methyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 5D$_S$. Mp 203–204 °C (from MeOH); $[\alpha]_D$ +23 (*c* 0.5, $CHCl_3$) (Found: C, 57.4; H, 4.0; N, 6.0. $C_{35}H_{29}F_6N_3O_8$ requires C, 57.3; H, 4.0; N, 5.7%); δ_H(500 MHz), 1.92 (3H, s, Me), 3.21 (6H, s, 2 × OMe), 4.89 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.18 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 5.38 (1H, m, 7-H), 6.41 (1H, dd, $J_{10,7}$ 1.1, $J_{10,11}$ 8.1, 11-H), 6.57 (1H, dd, $J_{11,7}$ 6.2, $J_{11,10}$ 8.1, 11-H), 7.25–7.48 (13H, m, Ar-H), 7.65 (2H, d, *J* 7.3, Hz, Ar-H); δ_F(470 MHz), −9.00 (CF_3), −11.01 (CF_3).

X-Ray crystal structure analysis of compound 5D$_S$

Crystal data. $C_{35}H_{29}F_6N_3O_8$. M = 733.6. Orthorhombic, a = 11.593(16), b = 15.664(24), c = 18.655(19) Å, V = 3387(8) Å^3, λ = 0.710 73 Å, space group $P2_12_12_1$ (No. 19), Z = 4, D_x = 1.438 g cm^{-1}, colourless blocks, dimensions 0.84 × 0.38 × 0.36 mm, μ(Mo-Kα) = 1.24 cm^{-1}, F(000) = 1512.

Data collection and processing. Siemens P3 diffractometer, θ–2θ scan, θ scan width 1.2°, 5 < 2θ < 50°, h: 0→13, k: 0→18, l: 0→22; graphite monochromated Mo-Kα radiation; 3352 unique reflections measured giving 2301 with $F > 4\sigma(F)$; Lorentz and polarisation corrections applied.

Structure analysis and refinement. Direct methods (SHELXS-86);[29] full-matrix least squares refinement on F^2 (SHELXL-93)[30] with all non-hydrogen atoms anisotropic and hydrogens in calculated positions using the riding model with U_{iso}(H) = 1.2 U(eq) for the attached atom. (The calculated positions for methyl hydrogens were confirmed as corresponding to those located in an earlier difference Fourier map). Final R_1 = 0.065 (for 2301 data), wR_2 = 0.176 (all data), Goodness of Fit = 0.99,

residual electron density: −0.35→0.26. A projection of the molecule is shown in Fig. 2.

(1*R*,8*S*,9*R*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-ethyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 6D$_R$. Mp 158–160 °C (from MeOH); $[\alpha]_D$ −29 (*c* 0.7, $CHCl_3$) (Found: C, 57.7; H, 4.3; N, 5.7. $C_{36}H_{31}F_6N_3O_8$ requires C, 57.8; H, 4.2; N, 5.6%); δ_H(500 MHz), 0.69 (3H, t, *J* 7.5, CH_2CH_3), 1.68 (1H, m, CH_2CH_3), 2.44 (1H, m, CH_2CH_3), 3.22 (3H, s, OMe), 3.61 (3H, s, OMe), 4.91 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.33 (2H, m, 7-H, 8-H), 6.42 (1H, dd, $J_{10,7}$ 1.1, $J_{10,11}$ 8.1, 10-H), 6.60 (1H, dd, $J_{11,7}$ 5.7, $J_{11,10}$ 8.1, 11-H), 7.33–7.52 (15H, m, Ar-H); δ_F(470 MHz), −7.74 (CF_3), −9.43 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-ethyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 6D$_S$. Mp 131–134 °C (from MeOH); $[\alpha]_D$ +29 (*c* 0.6, $CHCl_3$) (Found: C, 58.0; H, 4.3; N, 5.7. $C_{36}H_{31}F_6N_3O_8$ requires C, 57.8; H, 4.2; N, 5.6%); δ_H(500 MHz), 0.96 (3H, t, *J* 7.5, CH_2CH_3), 2.22 (1H, m, CH_2CH_3), 2.70 (1H, m, CH_2CH_3), 3.15 (3H, s, OMe), 3.21 (3H, s, OMe), 5.10 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.17 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 5.41 (1H, m, 7-H), 6.49 (1H, dd, $J_{10,7}$ 1.1, $J_{10,11}$ 8.4, 10-H), 6.62 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 7.24–7.47 (13H, m, Ar-H), 7.68 (2H, d, *J* 7.3, Ar-H); δ_F(470 MHz), −9.28 (CF_3), −9.38 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-acetoxymethyl-4-phenyl-2,4,6-triazatricyclo-[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 7D$_R$. Mp 197–198 °C (from MeOH); $[\alpha]_D$ +18 (*c* 0.6, $CHCl_3$) (Found: C, 55.6; H, 4.0; N, 5.5. $C_{37}H_{31}F_6N_3O_{10}$ requires C, 56.1; H, 3.95; N, 5.3%); δ_H(500 MHz), 2.02 (3H, s, CH_2OAc), 3.11 (3H, s, OMe), 3.65 (3H, s, OMe), 3.83 (1H, d, J_{AB} 11.7, CH_2OAc), 5.11 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.24 (1H, d, J_{AB} 11.7, CH_2OAc), 5.35 (1H, m, 7-H), 5.39 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 6.49 (1H, dd, $J_{10,7}$ 1.5, $J_{10,11}$ 8.4, 10-H), 6.60 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 7.30–7.47 (15H, m, Ar-H); δ_F(470 MHz), −7.79 (CF_3), −9.66 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-acetoxymethyl-4-phenyl-2,4,6-triazatricyclo-[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 7D$_S$. Mp 183–185 °C (from MeOH–$CHCl_3$); $[\alpha]_D$ +52 (*c* 0.6, $CHCl_3$) (Found: C, 56.0; H, 4.0; N, 5.5. $C_{37}H_{31}F_6N_3O_{10}$ requires C, 56.0; H, 3.95; N, 5.3%); δ_H(500 MHz), 2.07 (3H, s, CH_2OAc), 3.19 (3H, s, OMe), 3.22 (3H, s, OMe), 4.44 (1H, d, J_{AB} 12.1, CH_2OAc), 5.23 (2H, m, 8-H, 9-H), 5.36 (1H, d, J_{AB} 12.1, CH_2OAc), 5.44 (1H, m, 7-H), 6.58 (2H, m, 10-H, 11-H), 7.26–7.48 (13H, m, Ar-H), 7.66 (2H, d, *J* 7.3, Ar-H); δ_F(470 MHz), −8.33 (CF_3), −11.19 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-ethynyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]-undec-10-ene-3,5-dione 9D$_R$. Mp 89–91 °C (from $CHCl_3$–diethyl ether); $[\alpha]_D$ +23 (*c* 0.6, $CHCl_3$) (Found: M^+ 743.169 16. $C_{36}H_{27}F_6N_3O_8$ requires 743.170 23); δ_H(500 MHz), 2.13 (3H, s, ≡CH), 3.30 (3H, s, OMe), 3.62 (3H, s, OMe), 5.04 (1H, d, $J_{9,8}$ 8.9, 9-H), 5.35 (2H, m, 7-H, 8-H), 6.58 (2H, m, 10-H, 11-H), 7.34–7.53 (15H, m, Ar-H); δ_F(470 MHz); −7.79 (CF_3), −9.51 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-ethynyl-4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{2,6}]-undec-10-ene-3,5-dione 9D$_S$. Mp 164–165 °C (from $CHCl_3$–diethyl ether; $[\alpha]_D$ +67 (*c* 0.8, $CHCl_3$) (Found: M^+ 743.169 16. $C_{36}H_{27}F_6N_3O_8$ requires 743.170 23); δ_H(500 MHz), 2.74 (1H, s, ≡CH), 3.15 (3H, s, OMe), 3.49 (3H, s, OMe), 5.17 (1H, d, $J_{8,7}$ 2.8, $J_{8,9}$, 8-H), 5.27 (1H, m, 7-H), 5.43 (1H, d, $J_{9,8}$ 8.9, 9-H), 6.61 (2H, m, 10-H, 11-H), 7.32–7.50 (13H, m, Ar-H), 7.62 (2H, d, *J* 7.8, Ar-H); δ_F(470 MHz), −8.97 (CF_3), −9.14 (CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*R*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-trifluoromethyl-4-phenyl-2,4,6-triazatricyclo-[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 10D$_R$. Mp 157–158 °C (from MeOH); $[\alpha]_D$ −11 (*c* 0.5, $CHCl_3$) (Found: C, 53.2; H, 3.4; N, 5.5. $C_{35}H_{26}F_9N_3O_8$ requires C, 53.4; H, 3.3; N, 5.3%); δ_H(500 MHz), 3.35 (3H, s, OMe), 3.61 (3H, s, OMe), 5.21 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.39 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 5.43 (1H, m, 7-H), 6.60 (1H, d, $J_{10,11}$ 8.4, 10-H), 6.71 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.8, 11-H), 7.38–7.44 (15H, m, Ar-H); δ_F(470 MHz), −4.47 (1-CF_3); −7.66 (MTPA-CF_3), −9.92 (MTPA-CF_3).

(1*R*,8*S*,9*R*)-8,9-Bis[(*S*)-2-methoxy-2-phenyl-2-trifluoroacetoxy]-1-trifluoromethyl-4-phenyl-2,4,6-triazatricyclo-[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 10D$_S$. Mp 203–209 °C (from MeOH); $[\alpha]_D$ +16 (*c* 1.1, $CHCl_3$) (Found: C, 53.2; H, 3.4; N, 5.5. $C_{35}H_{26}F_9N_3O_8$ requires C, 53.4; H, 3.3; N, 5.3%); δ_H(500 MHz), 3.23 (6H, s, 2 × OMe), 5.22 (1H, dd, $J_{8,7}$ 2.6, $J_{8,9}$ 8.8, 8-H), 5.35 (1H, d, $J_{9,8}$ 8.8, 9-H), 5.51 (1H, m, 7-H), 6.68 (1H, dd, $J_{10,7}$ 1.1, $J_{10,11}$ 8.4, 10-H), 6.74 (1H, dd, $J_{11,7}$ 5.9, $J_{11,10}$ 8.4, 11-H), 7.28–7.49 (13H, m, Ar-H), 7.61 (2H, d, *J* 7.7, Ar-H); δ_F(470 MHz), −4.37 (1-CF_3), −8.72 (MTPA-CF_3), −11.01 (MTPA-CF_3).

X-Ray crystal structure analysis of compound 10D$_S$

Crystal data. $C_{35}H_{26}F_9N_3O_8$. M = 787.6 Orthorhombic, a = 11.588(5), b = 15.721(5), c = 18.926(6) Å, V = 3448(2) Å^3, λ = 0.710 73 Å, space group $P2_12_12_1$ (No. 19), Z = 4, D_x = 1.517 g cm^{-1}, colourless blocks, dimensions 1.00 × 0.57 × 0.50 mm, μ(Mo-Kα) = 1.39 cm^{-1}, F(000) = 1608.

Data collection and processing. Siemens P3 diffractometer, θ–2θ scan, θ scan width 1.2°, 3.3 < 2θ < 50°, h: 0→13, k: 0→18, l: 0→22; graphite monochromated Mo-Kα radiation; 3424 unique reflections measured giving 2621 with $F > 4\sigma(F)$; Lorentz and polarisation corrections applied.

Structure analysis and refinement. Direct methods (SHELXS-86);[29] full-matrix least squares refinement on F^2 (SHELXL-93)[30] with all non-hydrogen atoms anisotropic and hydrogens in calculated positions using the riding model with $U_{iso}(H)$ = 1.2 U(eq) for the attached atom. (The calculated positions for methyl hydrogens were confirmed as corresponding to those located in an earlier difference Fourier map). Final R_1 = 0.040 (for 2621 data), wR_2 = 0.129 (all data), Goodness of Fit = 0.76, residual electron density: −0.19→0.18. A projection of the molecule is shown in Fig. 3.

Substitution reactions of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene 4B using tributyltin reagents

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-deuteriocyclohexa-3,5-diene 15B.** To a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.9 g, 3.75 mmol) in anhydrous toluene (40 cm^3) was added tributyltin deuteride (1.0 g, 3.42 mmol) and azoisobutyronitrile (0.040 g, 0.24 mmol) and the resulting solution heated at 80 °C for five hours under an atmosphere of nitrogen. Extraction using ethyl acetate and purification by flash chromatography (hexane then 5% methanol–chloroform) followed by PLC (70% ethyl acetate–hexane then 5% MeOH–$CHCl_3$) furnished *cis*-(1*S*,2*R*)-1,2-dihydroxy-3-deuteriocyclohexa-3,5-diene **15B** as a yellow oil (0.080 g, 25%) (Found: M^+, 113.0589; $C_6H_8O_2$ requires 113.0587); $[\alpha]_D$ −9.3 (*c* 2.3, MeOH); δ_H(300 MHz), 2.24 (2H, br s, 2 × OH), 4.66 (2H, m, 1-H, 2-H), 5.96 (3H, m, 4-H, 5-H, 6-H).

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-vinylcyclohexa-3,5-diene 8B.** To a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.5 g, 2.1 mmol), palladium(II) acetate (0.047 g, 10 mol%) and triphenylphosphine (0.11 g, 20 mol%) in anhydrous THF (40 cm^3) was added vinyltributyltin (0.73 g, 2.3 mmol). The mixture was stirred at room temperature for 16 h under an atmosphere of nitrogen. The THF was removed under reduced pressure and the residue was stirred overnight at room temperature with saturated aqueous potassium fluoride (15 cm^3) and ethyl acetate (100 cm^3). The organic layer was separated and the aqueous phase re-extracted with ethyl acetate. The combined extracts were dried (anhydrous magnesium sulfate) and concentrated under reduced pressure to yield the crude product which on purification by flash chromatography (80% ethyl acetate–hexane) gave *cis*-(1*S*,2*R*)-1,2-dihydroxy-3-vinylcyclohexa-3,5-diene **8B** as a pale yellow solid (0.076 g, 26%); $[\alpha]_D$ +126 (*c* 0.5, MeOH). The synthetic sample of diol **8B** was found to be spectroscopically and stereochemically indistinguishable from the *cis*-dihydrodiol metabolite **8B**, isolated from the biotransform-

ation of styrene by *P. putida* UV4. *cis*-Dihydrodiols **9B** and **17B** were synthesised from *cis*-dihydrodiol **4B** using similar conditions.

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-ethynylcyclohexa-3,5-diene 9B.** Ethynyltributyltin (0.4 cm^3, 1.39 mmol) was added to a stirred mixture of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.3 g, 1.25 mmol), palladium(II) acetate (0.028 g, 10 mol%) and triphenylphosphine (0.066 g, 20 mol%) in anhydrous tetrahydrofuran (10 cm^3). The reaction mixture was stirred at room temperature for 16 h under nitrogen. Purification by PLC (70% ethyl acetate–hexane then 10% MeOH–methylene chloride) afforded *cis*-(1*S*,2*R*)-1,2-dihydroxy-3-ethynylcyclohexa-3,5-diene **9B** as an orange solid (0.060 g, 35%), mp 51–52 °C (ethyl acetate–hexane); $[a]_D$ +216 (*c* 0.4, MeOH). The synthetic product was found to be spectrally and stereochemically indistinguishable from the metabolite **9B** obtained from ethynylbenzene **9A**.

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-*n*-butylcyclohexa-3,5-diene 17B.** To a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.5 g, 2.1 mmol) in anhydrous THF (10 cm^3), was added palladium(II) acetate (0.047 g, 10 mol%), triphenylphosphine (0.11 g, 20 mol%), and tributyltin methoxide (0.74 g, 2.3 mmol). The reaction mixture was stirred at room temperature for 16 h. Purification of the crude product by flash chromatography (60% ethyl acetate–hexane) afforded *cis*-(1*S*,2*R*)-1,2-dihydroxy-3-*n*-butylcyclohexa-3,5-diene **17B** as a relatively unstable light brown oil (0.039 g, 11%); $[a]_D$ +77 (*c* 0.5, MeOH) (Found: M^+ 168.114 62. $C_{10}H_{16}O_2$ requires 168.115 02); δ_H(300 MHz) 0.93 [3H, t, *J* 7.1, $(CH_2)_3CH_3$], 1.30–1.59 (4H, m, $CH_2(CH_2)_2CH_3$), 1.60 (1H, br s, OH), 1.92 (1H, br s, OH), 2.21 [2H, m, $CH_2(CH_2)_2CH_3$], 4.01 (1H, d, $J_{2,1}$ 5.4, 2-H), 4.31 (1H, m, 1-H), 5.70 (1H, d, $J_{4,5}$ 5.2, 4-H), 5.77 (1H, dd, $J_{6,1}$ 3.3, $J_{6,5}$ 9.5, 6-H), 5.93 (1H, m, 5-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-methylsulfanylcyclohexa-3,5-diene 14B.** Methyl tributyltin sulfide (1 cm^3, 2.79 mmol) was added to a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.3 g, 1.26 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.030 g, 3 mol%) in anhydrous benzene (15 cm^3). The reaction mixture was stirred at 90 °C for 2.5 h under nitrogen and the solvent was removed under reduced pressure to yield the crude product. Purification by PLC (70% ethyl acetate–hexane then 10% MeOH–dichloromethane) gave *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-methylsulfanylcyclohexa-3,5-diene **14B** as an off-white solid (0.110 g, 55%), mp 57–61 °C (Found: M^+ 158.038 88. $C_7H_{10}SO_2$ requires 158.040 15) $[a]_D$ +36 (*c* 0.6, MeOH), which was found to be spectrally and stereochemically indistinguishable from the *cis*-dihydrodiol **14B** isolated earlier from the biotransformation of methyl phenyl sulfide by *P. putida* UV4. *cis*-Dihydrodiols **11B**, **16B**, **18B**–**22B**, were synthesised in a similar manner to *cis*-diol **14B** using compound **4B** and the appropriate tributyltin reagent.

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-cyanocyclohexa-3,5-diene 11B.** To a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.5 g, 2.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.32 mmol) in anhydrous THF (40 cm^3) was added tributyltin cyanide (0.73 g, 2.3 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen (4 h). Purification by flash chromatography (ethyl acetate) gave *cis*-(1*S*,2*R*)-1,2-dihydroxy-3-cyanocyclohexa-3,5-diene **11B** as a white solid (0.15 g, 52%); $[a]_D$ +188 °C (*c* 0.7, MeOH) which was found to be spectrally and stereochemically indistinguishable from the *cis*-dihydrodiol **11B** isolated earlier from the biotransformation of benzonitrile by *P. putida* UV4.

***cis*-(1*S*,2*R*)-1,2-Dihydroxy-3-allylcyclohexa-3,5-diene 16B.** To a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.25 g, 1.05 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.18 g, 0.155 mmol) in anhydrous THF (20 cm^3) was added allyltributyltin (0.37 g, 1.12 mmol). The mixture was stirred at 35 °C for 45 min under an atmosphere of nitrogen. Purification by flash chromatography (75% ethyl acetate–hexane) gave *cis*-(1*S*,2*R*)-1,2-dihydroxy-3-allylcyclohexa-3,5-diene **16B** as a low-melting unstable solid (0.049 g, 31%); $[a]_D$ +16 (*c* 0.5, MeOH) (Found: M^+ 152.083 52. $C_9H_{12}O_2$ requires 152.083 72); δ_H(300 MHz), 3.00 (2H, d, *J* 6.7, $CH_2CH{=}CH_2$), 4.05 (1H, d, $J_{2,1}$ 6.0, 2-H), 5.13 (2H, m, $CH_2CH{=}CH_2$), 5.74 (1H, d, $J_{4,5}$ 5.0, 4-H), 5.79–5.98 (3H, m, $CH_2CH{=}CH_2$, 5-H, 6-H).

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-ethylsulfanylcyclohexa-3,5-diene 18B.** To a solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **4B** (0.160 g, 0.67 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.013 g, 1 mol%) in anhydrous benzene (10 cm^3) under nitrogen was added ethyl tributyltin sulfide (0.23 g, 0.66 mmol) and the solution stirred at 90 °C for 4 h. Purification by PLC (70% ethyl acetate–hexane then 10% methanol–chloroform) furnished *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-ethylsulfanylcyclohexa-3,5-diene **18B** as a yellow solid (0.070 g, 61%), mp 71–73 °C (from ethyl acetate–hexane) (Found: C, 55.95; H, 7.1; $C_8H_{12}O_2S$ requires C, 55.8; H, 7.0%); $[a]_D$ +60 (*c* 1.0, $CHCl_3$); δ_H(300 MHz), 1.34 (3H, t, *J* 7.4, CH_2CH_3), 2.46 (1H, d, $J_{OH,2}$ 8.6, OH), 2.78 (2H, q, *J* 7.4, CH_2CH_3), 4.17 (1H, dd, $J_{2,1}$ 6, $J_{2,OH}$ 8, 2-H), 4.32 (1H, m, 1-H), 5.66 (1H, d, $J_{4,5}$ 5.7, 4-H), 5.81 (1H, dd, $J_{6,5}$ 9.6, $J_{6,1}$ 4.0, 6-H), 6.00 (1H, dd, $J_{5,4}$ 5.8, $J_{5,6}$ 9.6, 5-H). Electronic CD data 310.80 nm $\Delta\varepsilon$ 1.377, 209.30 nm $\Delta\varepsilon$ −7.797. A similar procedure was used for the synthesis of the *cis*-dihydrodiols **19B**–**22B**.

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-isopropylsulfanylcyclohexa-3,5-diene 19B.** (0.060 g, 31%), Mp 116–118 °C (from $CHCl_3$–hexane) (Found: M^+, 186.0711. $C_9H_{14}O_2S$ requires 186.0715); $[a]_D$ +50 (*c* 1.0, $CHCl_3$); δ_H(300 MHz), 1.33 (3H, d, J_{H,CH_3} 3.0, CH_3), 1.35 (3H, d, J_{H,CH_3} 3.0, CH_3), 2.21 (1H, d, $J_{OH,2}$ 8.5, OH), 2.45 (1H, d, $J_{OH,1}$ 7.8, OH), 3.29 [1H, septet, *J* 6.7, $CH(CH_3)_2$], 4.15 (1H, d, $J_{2,1}$ 7.0, 2-H), 4.34 (1H, m, 1-H), 5.85 (2H, m, 4-H, 6-H), 6.01 (1H, dd, $J_{5,4}$ 5.5, $J_{5,6}$ 9.6, 5-H). Electronic CD data 321.20 nm $\Delta\varepsilon$ 8.814×10^{-1}, 285.50 nm $\Delta\varepsilon$ 1.791, 209.00 nm $\Delta\varepsilon$ −7.535.

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-*tert*-butylsulfanylcyclohexa-3,5-diene 20B.** (0.190 g, 75%), Mp 91–93 °C (from hexane) (Found: M^+, 200.0881; $C_{10}H_{16}O_2S$ requires 200.0871); $[a]_D$ +160 (*c* 1.3, $CHCl_3$); δ_H(300 MHz), 1.38 [9H, s, $C(CH_3)_3$], 2.44 (1H, d, $J_{OH,1}$ 5.8, OH), 2.88 (1H, d, $J_{OH,2}$ 4.2, OH), 4.20 (1H, dd, $J_{2,OH}$ 4.2, $J_{2,1}$ 5.4, 2-H), 4.37 (1H, dd, $J_{1,2}$ 5.9, $J_{1,6}$ 3.4, 1-H), 6.10 (2H, m, 4-H, 6-H), 6.39 (1H, m, 5-H). Electronic CD data 330.90 nm $\Delta\varepsilon$ 1.145, 271.60 nm $\Delta\varepsilon$ 7.514.

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-phenylsulfanylcyclohexa-3,5-diene 21B.** (0.060 g, 43%), Mp 48–52 °C (from hexane) (Found: M^+, 220.0553; $C_{11}H_{11}O_2S$ requires 220.0558); $[a]_D$ +20 (*c* 1.0, $CHCl_3$); δ_H(500 MHz), 2.23 (1H, br s, OH), 2.37 (1H, br s, OH), 4.19 (1H, d, $J_{2,1}$ 5.9, 2-H), 4.38 (1H, m, 1-H), 5.79 (1H, d, $J_{4,5}$ 5.5, 4-H), 5.88 (1H, ddd, $J_{6,5}$ 9.5, $J_{6,1}$ 3.3, $J_{6,4}$ 0.9, 6-H), 5.94 (1H, ddd, $J_{5,4}$ 5.5, $J_{5,6}$ 9.5, $J_{5,1}$ 1.3, 5-H), 7.36 (3H, m, ArH), 7.48 (2H, m, ArH). Electronic CD data 307.20 nm $\Delta\varepsilon$ -6.29×10, 266.60 nm $\Delta\varepsilon$ 1.293×10, 200.70 nm $\Delta\varepsilon$ -2.530×10.

***cis*-(1*S*,2*S*)-1,2-Dihydroxy-3-*p*-tolylsulfanylcyclohexa-3,5-diene 22B.** (0.220 g, 75%), Mp 46–48 °C (from hexane) (Found: M^+, 234.0717. $C_{13}H_{14}O_2S$ requires 234.0715); $[a]_D$ −16 (*c* 1.8, $CHCl_3$); δ_H(500 MHz), 2.28 (3H, s, CH_3), 2.56 (1H, br s, OH), 2.67 (1H, br s, OH), 4.08 (1H, d, $J_{2,1}$ 6, 2-H), 4.27 (1H, m, 1-H), 5.58 (1H, d, $J_{4,5}$ 5.6, 4-H), 5.74 (1H, dd, $J_{6,5}$ 9.4, $J_{6,1}$ 3.4, 6-H), 5.81 (1H, ddd, $J_{5,4}$ 5.6, $J_{5,6}$ 9.4, $J_{5,1}$ 1.3, 5-H), 7.10 (2H, d, *J* 8.1, ArH), 7.29 (2H, d, *J* 8.2, ArH). Electronic CD data 307.40 nm $\Delta\varepsilon$ −3.585, 268.10 nm $\Delta\varepsilon$ 8.632, 201.00 nm $\Delta\varepsilon$ -1.384×10.

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