Chemoenzymatic synthesis of enantiopure dihydroxy-1,2,3,4-tetrahydronaphthalenes from naphthalene and dihydronaphthalene precursors

Derek R. Boyd,[a]* Narain D. Sharma,[a] Nuala A. Kerley,[a] Gareth McConville,[a] Christopher C. R. Allen,[b] and A. John Blacker[c]

[a] School of Chemistry and [b] The QUESTOR Centre, The Queen's University of Belfast, Belfast BT9 5AG, UK

[c] Avecia Fine Chemicals, PO Box 21, Huddersfield, West Yorkshire, UK

E-mail: dr.boyd@qub.ac.uk

Dedicated to Professor Tony McKervey on his 65th birthday

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Abstract

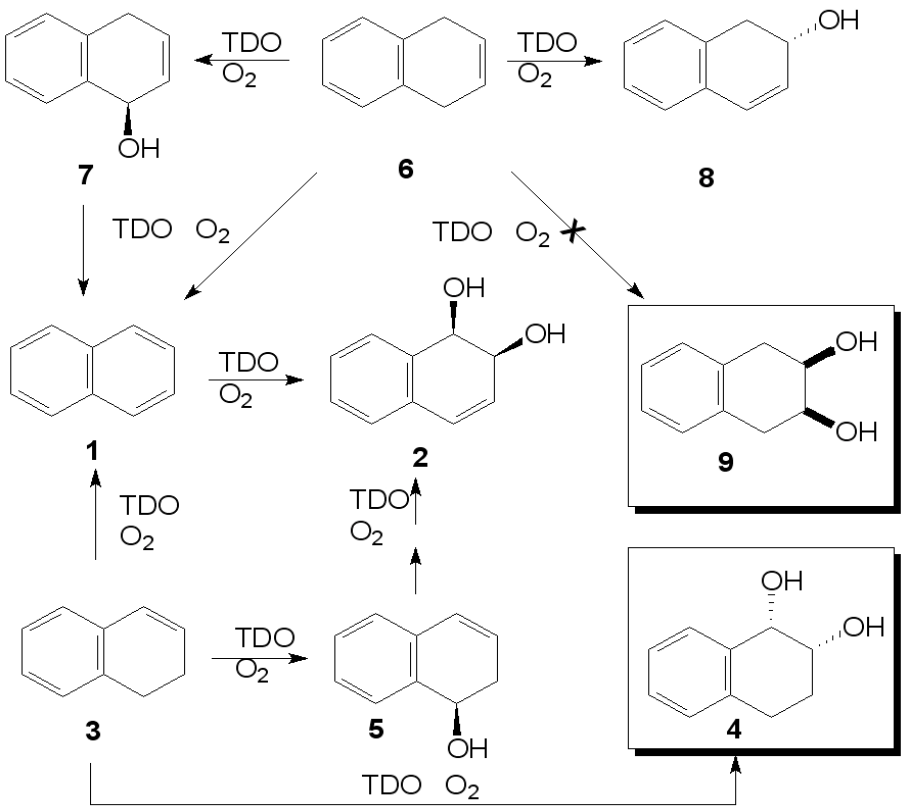
cis-Dihydrodiol, *cis*-tetrahydrodiol and arene hydrate bacterial metabolites, of naphthalene and 1,2-dihydronaphthalene, have been used as synthetic precursors; chemoenzymatic and enzyme-catalysed syntheses have been used to obtain all possible enantiopure samples of dihydroxy-1,2,3,4-tetrahydronaphthalene stereoisomers.

Keywords: Enantiopure, *cis*-dihydrodiols, *cis* and *trans*-tetrahydrodiols, arene hydrates, stereoinversion

Introduction

Bacterial, ring-hydroxylating dioxygenase enzymes have been used extensively in the production of enantiomerically pure *cis*-1,2-dihydrodiol derivatives of arene substrates.[1-5] These prokaryotic (*cis*-diol) metabolites of monosubstituted benzenes, have been widely utilised in the synthesis of a range of alkaloids, sugars and eucaryotic metabolites. [1-5] The first reported polycyclic arene *cis*-dihydrodiol derivative was *cis*-1,2-dihydroxy-1,2-dihydronaphthalene **2**, formed by dioxygenase-catalysed (*Pseudomonas putida*) asymmetric dihydroxylation of naphthalene **1**.[6] A constitutive mutant strain (UV4), of *P. putida*, containing toluene dioxygenase (TDO), but without the toluene *cis*-dihydrodiol dehydrogenase enzyme normally found in wild-type strains, was later used to produce enantiopure (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene **2** from naphthalene

substrate **1** (Scheme 1). [7] Using this strain, with improved biotransformation and down-stream processing facilities, we have recently isolated multi-gram quantities (>100g per biotransformation) of bioproduct **2**. Although *cis*-dihydrodiol **2** is now commercially available, to date, there have been few examples of its use as a synthetic precursor in chemoenzymatic synthesis. [2,3,8-10]



Scheme 1. TDO-catalysed biotransformation products from arene **1** and dihydroarene substrates **3** and **6.**

Asymmetric TDO-catalysed (*P. putida* UV4) dihydroxylation of the conjugated alkene 1,2-dihydronaphthalene **3**, gave enantiopure *cis*-tetrahydrodiol **4** and *cis*-dihydrodiol **2** metabolites of opposite absolute configuration.[7] Biotransformation studies, using deuterium labelled alkene **3**, showed that *cis*-dihydrodiol metabolite **2** was mainly formed by TDO-catalysed dehydrogenation of alkene **3** to yield naphthalene **1** followed by its *cis*-dihydroxylation (Scheme 1).[7] By contrast, no evidence was found for the TDO-catalysed dihydroxyation of non-conjugated alkene, 1,4-dihydronaphthalene **6**, to yield *cis*-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **9**.

Metabolites, resulting from TDO-catalysed (*P. putida* UV4) benzylic or allylic monohydroxylation of alkenes **3** and **6**, were also obtained (Scheme 1).[7] The isolated monols **5** (from alkene **3**), **7** and **8** (from alkene **6**), are among the first members of the arene hydrate

family of metabolites to have been isolated. With the exception of naphthalene hydrate **8**, the other naphthalene hydrates (**5** and **7**) and *cis*-diols (**2** and **4**) were found to be enantiopure.[7] This report describes the synthesis of all possible enantiopure diols of 1,2,3,4-tetrahydronaphthalene, starting from the readily available metabolites *cis*-dihydrodiol (**2**) and arene hydrate (**5**) and from the *meso cis*-diol (**9**).

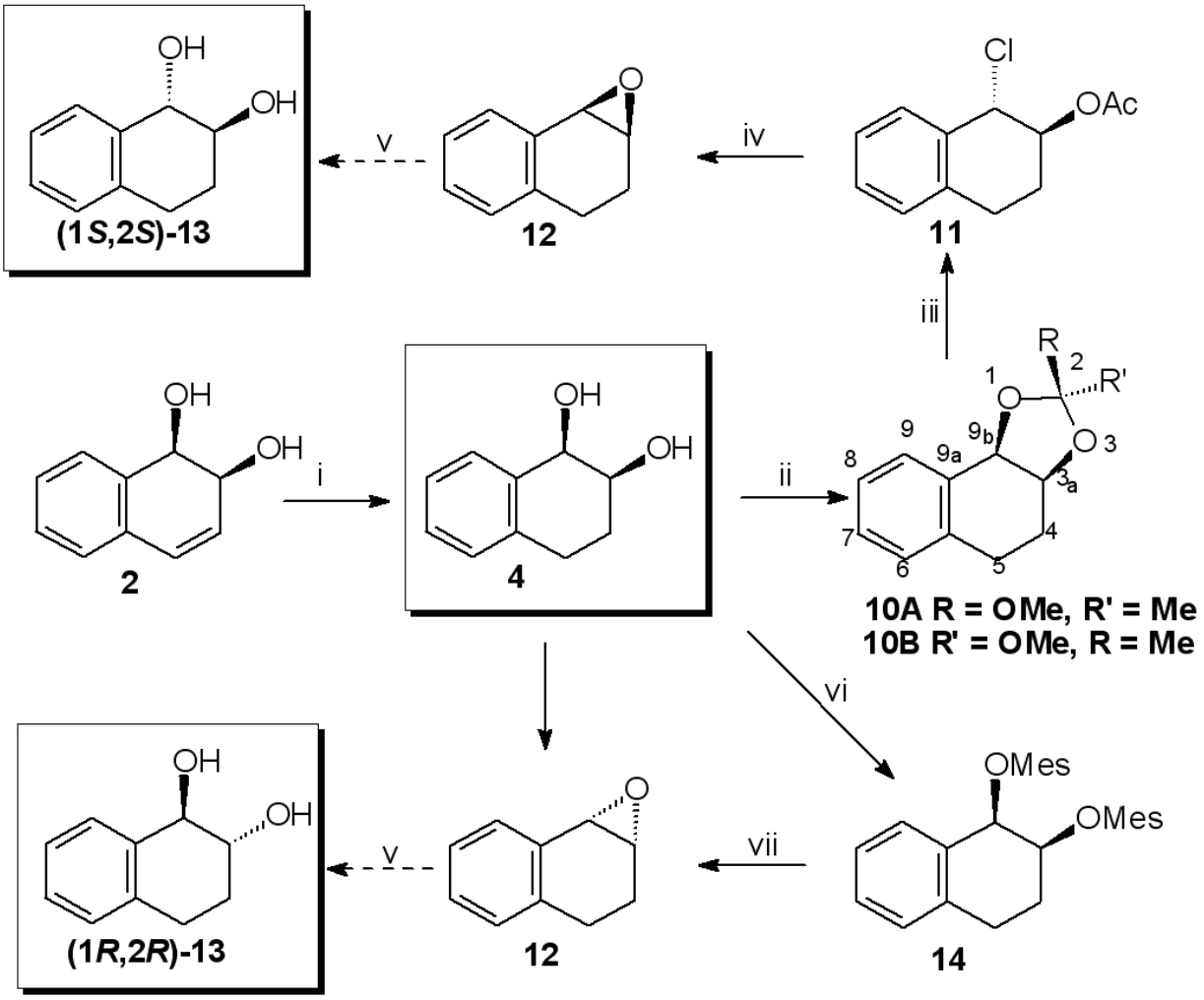
Results and Discussion

The reported[7] metabolites of naphthalene **1**, 1,2-dihydronaphthalene **3** and 1,4-dihydronaphthalene **6**, obtained using *P. putida* UV4, are shown in Scheme 1. TDO-catalysed dihydroxylation, of arene **1** and alkene **3**, thus, yielded (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene **2** and (1*S*,2*R*)-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene **4** respectively. The (1*R*,2*S*) enantiomer, of *cis*-dihydrodiol **2**, was also formed (*via* naphthalene **1**) from TDO-catalysed dehydrogenation of 1,2- dihydronaphthalene **3** and 1,4-dihydronaphthalene **6**, followed by TDO-catalysed *cis*-dihydroxylation. Addition of the corresponding arene hydrate metabolites **5** and **7**, as substrates, also gave (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydro-naphthalene **2** *via* (i) dihydroxylation followed by dehydration (**5** $\rightarrow\rightarrow$ **2**) and (ii) dehydration followed by dihydroxylation (**7** $\rightarrow$**1** $\rightarrow$**2**).[7]

Catalytic hydrogenation (H_2, Pd/C) of (1*R*,2*S*)-dihydrodiol **2** ($[\alpha]_D$ +244, $CHCl_3$) gave (1*R*,2*S*)-tetrahydrodiol **4** ($[\alpha]_D$ - 39, 95% yield) (Scheme 2). Reaction of (1*R*,2*S*)-tetrahydrodiol **4** with trimethylorthoacetate in the presence of a catalytic amount of benzoic acid yielded a mixture of dioxolane stereoisomers **10A** and **10B** (40:60, 82% crude yield). The structure of each of the isomers, in the mixture **10A** and **10B**, was investigated by ^{1}H-NMR and MS analysis. The major isomer **10B** was identified by ^{1}H-NMR spectroscopy, where an nOe (1%) was recorded between the bridgehead protons H-9b, H-3a and the MeO group. An nOe (3%) was also observed between the bridgehead protons H-9b and H-3a and the Me group of isomer **10A**. Due to instability, and the formation of a single product at the next step (**10A** and **10B** $\rightarrow$ **11**), no attempts were made to separate dioxolane isomers **10A** and **10B**. The crude isomeric mixture **10A** / **10B** was reacted with chlorotrimethylsilane at 0 ºC in dichloromethane to yield the stable (1*S*,2*S*)-chloroacetate derivative **11** ($[\alpha]_D$ -30; 72% yield); it was cyclised (NaOMe in THF) to give the corresponding (1*R*,2*S*)-epoxide **12** ($[\alpha]_D$ + 133; 58% yield). We had earlier reported the synthesis of (+)-(1*R*,2*S*)-epoxide **12** *via* resolution of racemic *trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydro-naphthalene, its cyclisation and base-catalysed hydrolysis (^{t}BuOH- KOH) of the epoxide to yield (-)-(1*S*,2*S*)-tetrahydrodiol **13**.[11]

(1*S*,2*R*)-Tetrahydrodiol **4**, of opposite configuration ($[\alpha]_D$ + 39), was isolated as a minor metabolite, from biotransformation (*P. putida* UV4) of 1,2-dihydronaphthalene **3** (Scheme 1). When the synthetic sequence **4** $\rightarrow$ **10A** and **10B** $\rightarrow$ **11** $\rightarrow$ **12** was repeated using (1*S*,2*R*)

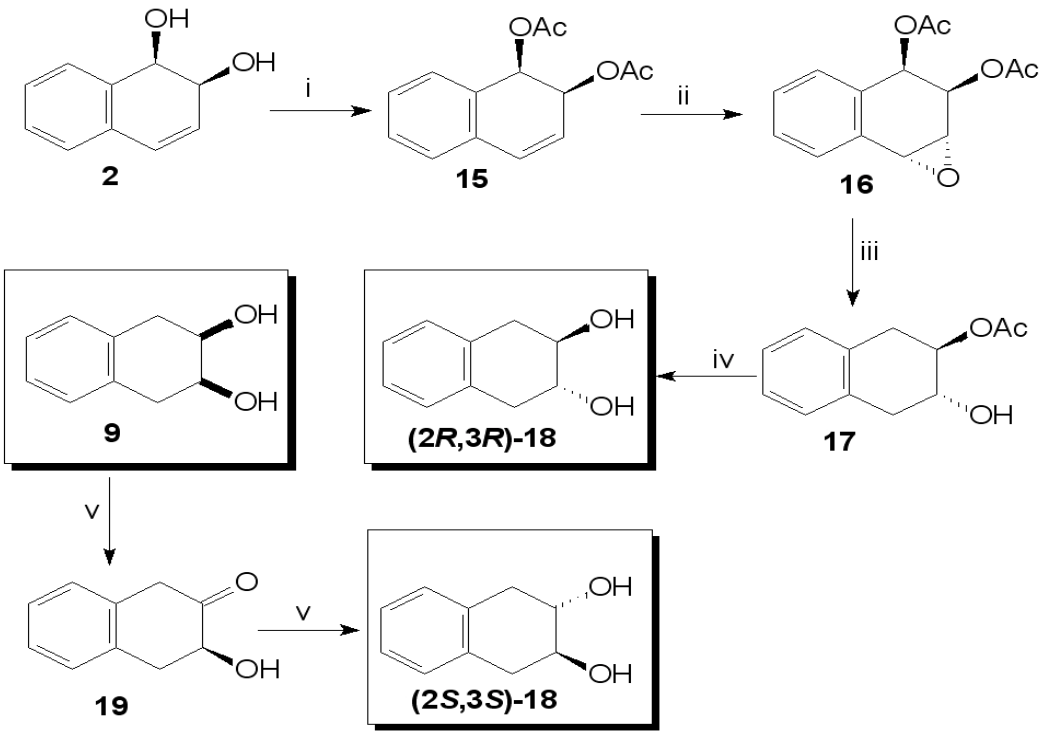
enantiomer of tetrahydrodiol **4**, the (1*S*,2*R*)-epoxide **12** ([α]$_D$ - 132), precursor of (+)-(1*R*,2*R*)-dihydrodiol **13**, was obtained. An alternative approach, involved treatment of (1*R*,2*S*)-tetrahydrodiol **4** with methanesulfonyl chloride and triethylamine at -20°C to yield (1*R*,2*S*)-dimesylate intermediate **14** (Scheme 2). Due to the limited stability of dimesylate **14**, during attempted chromatographic purification, it was characterised by spectral methods only (^{1}H-NMR and MS); the crude sample ([α]$_D$ - 21; 89% yield) was used in the next step. A solution of (1*R*,2*S*)-dimesylate **14**, in toluene, was reacted with aqueous potassium hydroxide, in the presence of a phase transfer catalyst (tetrabutylammonium bromide), to yield (1*S*,2*R*)-epoxide **12**([α]$_D$ - 130). This reaction was assumed to proceed by a two-step process involving: (i) regioselective nucleophilic substitution of the benzylic mesylate group by hydroxide and complete inversion of configuration at C-1 followed by (ii) base-catalysed cyclisation resulting in substitution of the remaining mesylate group with inversion of configuration at C-2.



Scheme 2. Reagents: I h_2, Pd/C, EtOH ii M eC(OMe)$_3$, C_6H_6, $PhCO_2H$ iii Me_3Si Cl, CH_2 Cl_2

iv NaOMe, THF v TBuOH, KOH vi $MeSO_2Cl$, CH_2Cl_2, Et_3N
vii KOH, MeC_6H_5, Bu_4NBr.

The dimesylate (**4** → **14** → **12**) and chloroacetate routes (**4** → **10A / 10B** → **11** →**12**) provide enantiocomplementary approaches to the synthesis of the (1*S*,2*R*)- and (1*R*,2*S*)-epoxides **12** from a common precursor(*cis*-dihydrodiol **2)**. Conversion of each epoxide enantiomer of compound **12**, to the corresponding enantiomer of *trans*-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene **13**, using KOH in aqueous ^tBuOH, had been reported earlier.[11]



Scheme 3. Reagents: i Ac_2O, C_6H_5N ii MCPBA, CH_2Cl_2 iii H_2, Pd/C, EtOAc iv NH_3/MeOH v P. putida ML2, O_2.

(1*R*,2*S*)-1,2-Dihydroxy-1,2-dihydronaphthalene **2** was also found to be a suitable precursor for the synthesis of *trans*-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **18** (Scheme 3). Protection of (1*R*,2*S*)-dihydrodiol **2** as (1*R*,2*S*) diacetate derivative **15** ($[\alpha]_D$ + 96, 73% yield) was carried out, using acetic anhydride, in pyridine solution. Formation of the diacetate **15** ensured that epoxidation using *m*-chloroperoxybenzoic acid (MCPBA) was directed exclusively *trans* to the acetate groups giving (1*R*,2*S*,3*R*,4*R*)-epoxide **16** ($[\alpha]_D$ + 92; 95% yield). Catalytic hydrogenolysis (H_2, Pd/C, EtOH, 24 h), of the diacetate epoxide **16**, was used to cleave both the benzylic acetate group and the benzylic C-O bond of the epoxide ring stereoselectively, to give

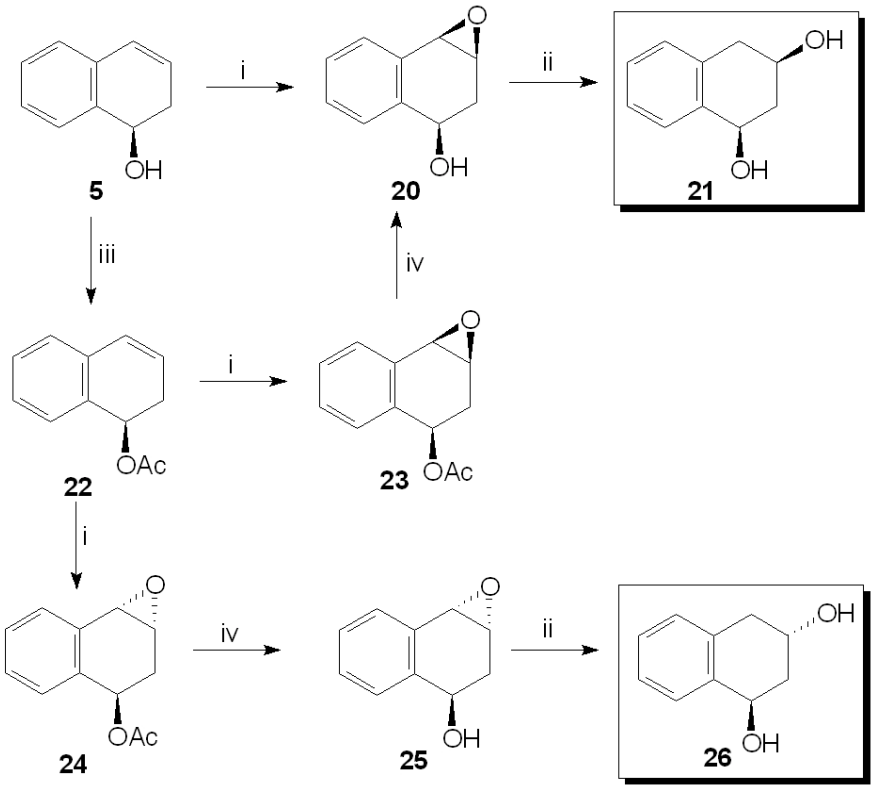
(2*R*,3*R*)-2-acetoxy-3-hydroxy-1,2,3,4-tetrahydronaphthalene **17** ($[\alpha]_D$ - 90; 80% yield). Similar treatment, of epoxide **16**, under milder conditions (H_2, Pd/C, EtOAc, 4 h), resulted in hydrogenolysis of the benzylic epoxide C-O bond only, to give a hydroxy diacetate product. Base-catalysed hydrolysis of (2*R*,3*R*)-monoacetate **17** (NH_3, MeOH) gave (2*R*,3*R*)-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **18** ($[\alpha]_D$ - 90, EtOH; 86% yield). Formation of the acetonide derivative of (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene **2** followed by epoxidation and hydrogenolysis has also been reported[9] to form a separable mixture of (2*R*,3*R*)-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **18** and a hydroxy acetonide derivative. (2*R*,3*R*)-Diol **18** has, in turn, been used as a precursor of both (2*R*,3*S*)-3-hydroxy-2-amino-1,2,3,4-tetrahydronaphthalene and (2*S*,3*S*)-2,3-diamino-1,2,3,4-tetrahydronaphthalene.[10]

In contrast with the UV4 mutant strain of *P. putida*, a source of TDO, the wild-type bacterium *P. putida* ML2 was found to have both a dioxygenase (benzene dioxygenase) and the corresponding *cis*-diol dehydrogenase (benzene *cis*-diol dehydrogenase) enzyme present. [12-14] GC-MS analysis had earlier confirmed that, in the presence of *P. putida* ML2, a series of acyclic and cyclic *vic*. diol substrates were oxidized to the corresponding ketoalcohols (ketols).[12-14] These were in turn found to be reduced enzymatically to yield both acyclic vic-diols[12] and monocyclic *trans*-diols[14] using *P. putida* ML2; thus, the *meso* substrate *cis*-1,2-dihydroxycyclohex-4-ene gave the corresponding ketoalcohol and enantiopure *trans*-diol.[14] A similar type of whole cell biotransformation has been reported,[15] using *cis*-1,2-dihydroxycyclohexane as substrate and the fungus *Corynesporia cassiicola*, to yield the corresponding *trans*-diol (>99% *ee*).

As part of a programme to evaluate the wider potential of enzymes from *P. putida* ML2, in the production of enantiopure *trans*-dihydrodiols from *meso cis*-dihydrodiol substrates,[14] a preliminary small-scale experiment was carried out with *cis*-diol substrate **9** (concentration 2 g/L, 5 h). GC-MS analysis, of the crude mixture of bioproducts, showed, that *cis*-diol substrate **9** (35%), ketoalcohol **19** (15%), *trans* diol **18** (35%), and a further unidentified bioproduct (15%) were present. When the biotransformation was repeated, on a larger scale, using a higher substrate concentration (4 g /L) and an extended biotransformation period (24 h), only the unreacted *cis*-diol substrate **9** and *trans*-diol bioproduct **18,** in equal ratio, were detected and isolated. Separation of *trans*-diol **18** was achieved by conversion of the residual *cis*-diol **9**, present in the *cis* / *trans* mixture, to the corresponding acetonide derivative followed by separation of the reaction mixture by flash chromatography. These biotransformations indicated that ketol **19** was a better substrate than *cis*-diol **9**; it was completely reduced to *trans*-diol **18** ($[\alpha]_D$ + 90, EtOH; 30% isolated yield) after being in contact with the enzyme system for the longer period. Formation of the di-2-methoxy-2-trifluoromethyl-2-phenylacetate (diMTPA) derivative of diol **18** confirmed that it was enantiopure (>98%) and of the (2*S*,3*S*) absolute configuration. A similar stereoselective (>98% *ee*) *cis* / *trans* stereoinversion process has, thus, been observed with the *meso cis*-diol substrates derived from cyclohexene (with *C. cassiicola*),[15]

1,4-cyclohexadiene (with *P. putida* ML2),[14] and now 1,4-dihydronaphthalene (with *P. putida* ML2). The latter single-step enzyme-catalysed asymmetric synthesis of (2*S*,2*S*)-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **18**, from achiral *cis*-diol substrate **9** (**Scheme 3**), provides a more convenient alternative approach to the multistep chemoenzymatic routes to the (2*R*,3*R*) enantiomer reported earlier[9] or shown in **Scheme 3** (**2→15→16→17→18**).

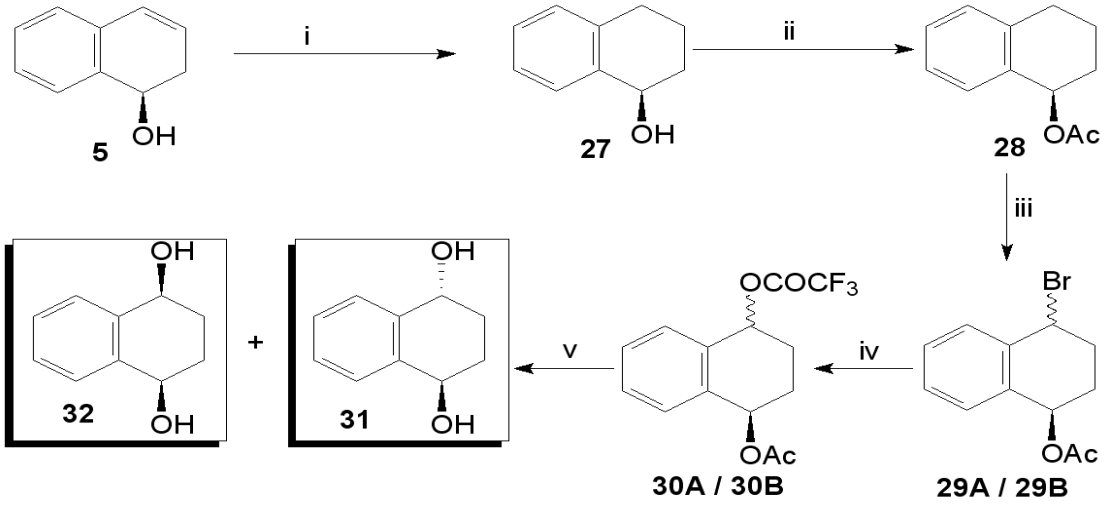
Arene hydrates of naphthalene (**5**, **7** and **8**), available from biotransformation (*P. putida* UV4) of 1,2- (**3**) and 1,4-dihydronaphthalene (**6**) (**Scheme 1**),[7] have not, to date, been used as chiral synthetic precursors. The tendency of arene hydrates to dehydrate under acidic conditions[16] must be avoided during their potential synthetic applications. Epoxidation of the enantiopure (1*R*)-1-hydroxy-1,2-dihydronaphthalene **5** ($[\alpha]_D$ + 52) was, thus, carried out using a two-phase system involving MCPBA in CH_2Cl_2 solution and an aqueous phosphate buffer (pH 8) (**Scheme 4**). The procedure ensured *cis*-epoxidation of the acid-sensitive arene hydrate **5**, without decomposition, yielding *syn*-(1*R*,2*S*,4*R*)-1,2-epoxy-4-hydroxy-1,2,3,4-tetrahydronaphthalene **20** ($[\alpha]_D$ + 95; 91% yield). Hydrogenolysis (H_2, Pd/C, EtOH) of (1*R*,2*S*,4*R*)-monol epoxide **20** resulted in exclusive cleavage of the benzylic epoxide C-O bond and formation of *cis*-(1*R*,3*R*)-1,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **21** ($[\alpha]_D$ - 58; 71% yield).



Scheme 4. Reagents: i MCPBA, CH_2Cl_2 ii H_2, Pd/C, EtOH iii Ac_2O, C_6H_5N iv NH_3, MeOH.

A similar MCPBA epoxidation, of (1*R*)-acetate derivative **22** ($[\alpha]_D$ +52) of arene hydrate **5**, gave a separable mixture (PLC) of acetate epoxides **23** / **24**, containing an excess of the *anti* (1*S*,2*R*,4*R*) isomer **24** ($[\alpha]_D$ - 73; 47% yield) over the *syn* (1*R*,2*S*,4*R*) isomer **23** ($[\alpha]_D$ +184; 35% yield, **Scheme 4**). Hydrolysis (NH_3, MeOH) of *syn* (1*R*,2*S*,4*R*)-acetate epoxide **23**, followed by hydrogenolysis, provided an alternative route to the *syn* monol epoxide **20** which was used to supplement material obtained from epoxidation of arene hydrate **5**. Hydrolysis of the *anti* (1*S*,2*R*,4*R*)-acetate epoxide **24**, under similar conditions, gave the *anti* (1*S*,2*R*,4*R*)-monol epoxide **25** ($[\alpha]_D$ -97; 80% yield); hydrogenolysis yielded (1*R*,3*S*)-diol **26** ($[\alpha]_D$ +43; 61% yield).

Earlier studies had shown that benzylic hydroxylation of 1,2,3,4-tetrahydronaphthalene, in the presence of *P. putida* UV4, yielded (1*R*)-tetralol **27** ($[\alpha]_D$ -32).[17] Hydrogenation of (1*R*)-1-hydroxy-1,2-dihydronaphthalene **5** also provided (1*R*)-tetralol **27**. Benzylic bromination (NBS, CCl_4), of (1*R*)-acetate derivative **28** ($[\alpha]_D$ + 98; 86% yield) of tetralol **27,** at C-4, yielded a mixture (1:1) of bromoacetate diastereoisomers **29A/29B**; a pure sample of one isomer of **29A/29B** was obtained by crystallization (**Scheme 5**). The diastereoisomeric mixture **29A/29B** was treated with silver trifluoroacetate, to yield the corresponding diesters **30A/30B**. This mixture showed evidence of instability during attempted chromatographic separation and was, therefore, characterised without further purification; hydrolysis gave a mixture of the corresponding chiral *trans*-diol **31** and *meso cis*-diol **32**. Separation of the stable *trans* (**31)** and *cis* isomers **(32**) was achieved by HPLC (Zorbax Sil, MeOH-CH_2Cl_2) with the *trans* isomer **31** ($[\alpha]_D$ –59, MeOH) being eluted early and the *cis* isomer **32** in later fractions.



Scheme 5. Reagents: i H_2, Pd/C, EtOH ii Ac_2O, C_6H_5N iii NBS, CCl4 iv AgO_2CF_3, C_6H_6 v Na_2CO_3, MeOH, H_2O.

Conclusions

The enantiopure (1*R*,2*S*) dihydrodiol **2** and (1*R*) arene hydrate **5** derivatives, readily available from biotransformation of naphthalene **1** and 1,2-dihydronaphthalene **3** respectively, have been used as precursors of chiral 1,2,3,4-tetrahydronaphthalene diols **4**, **13**, **18**, **21**, **26** and **31**. A useful example of enzyme-catalysed stereoinversion of a *meso cis*-diol **(9)** to yield an enantiopure *trans*-diol (**18**) has also been found. The absolute configurations and enantiomeric excess values (>98%) of the diols **4**, **13**, **18**, **21**, **26** and **31** have been determined by unequivocal methods. New routes to diol enantiomers **4**, **13** and **18**, of either absolute configuration, using enzymatic and chemoenzymatic methods, have been developed.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 300 MHz (Bruker Avance DPX-300) and 500 MHz (Bruker Avance DRX-500) in $CDCl_3$ solvent unless stated otherwise. Chemical shifts (δ) are reported in ppm relative to $SiMe_4$ and coupling constants (*J*) are given in Hz. Mass spectra were recorded at 70eV on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method with perfluorokerosene as standard. Elemental microanalyses were obtained on a Perkin-Elmer 2400 CHN microanalyser. HPLC analyses were carried out using a Perkin-Elmer Series 3B liquid chromatograph coupled to a Perkin-Elmer LC1-100 computing integrator. Analytical TLC was performed on Merck Kieselgel 60_{254} plastic sheets and preparative TLC (PLC) on glass plates (20 cm x 20 cm) coated with Merck Kieselgel PF $_{254+366}$.

The biotransformations of naphthalene **1** and 1,2-dihydronaphthalene **3**, using *P. putida* UV4, and isolation of enantiopure (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene **2** ($[\alpha]_D$ + 244, $CHCl_3$)**,** (1*S*,2*R*)-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene **4** ($[\alpha]_D$ + 39, $CHCl_3$) and (1*R*)-1-hydroxy-1,2-dihydronaphthalene **5** ($[\alpha]_D$ + 52, $CHCl_3$), was carried out as reported earlier.[7] Samples of substrate 1,4-dihydronaphthalene **6**, and synthetic precursors (+)-(1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene **2**, (+)-(1*S*,2*R*)-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene **4**, (+)-(1*R*)-1-hydroxy-l,2-dihydronaphthalene **5**, and (-)-(1*R*)-1-hydroxy-l,2,3,4-tetrahydronaphthalene **27** were available from earlier studies. The biotransformation conditions, used for *P. putida* ML2 and 1,4-dihydronaphthalene **6** were very similar to those reported.[12,13]

***cis*-2,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (9).** 1,4-Dihydronaphthalene **6** (9 g, 69 mmol) was added to a mixture of dichloromethane (500 cm^3) and water (8 cm^3) containing trimethylamine N-oxide (7.66 g, 69 mmol.). A catalytic amount of osmium tetroxide (0.01 g)

was added to the reaction mixture, which was allowed to stir overnight at room temperature. Saturated aqueous solution of sodium metabisulfite (1cm^3) was added and the reaction mixture stirred for another hour. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to yield a product, that was purified by column chromatography (4% methanol in chloroform) to yield *cis*-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **9** (8.61 g, 76%), mp 114-115 ºC (EtOAc / hexane) (lit.,[18] 110-112 ºC); δ_H (500 MHz, $CDCl_3$) 2.97-3.06 (4 H, m, 1-H), 4.13 (2 H, s, 2-H, 3-H), 7.08-7.15 (4 H, m, Ar-H); *m/z* 164 (M^+, 16%), 146 (100), 131 (52), 117 (74).

Synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-1,2-dihydroxy-1,2,3,4-tetrahydro-naphthalene (13)

(-)-(1*R*,2*S*)-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (4). (1*R*,2*S*)-1,2-Dihydroxy-1,2-dihydronaphthalene **2** (1.9 g, 12 mmol, $[\alpha]_D$ + 244, $CHCl_3$) was, catalytically, hydrogenated (10% Pd/C, H_2, EtOH, 4 h) at room temperature and atmospheric pressure. The catalyst was removed by filtration and the solvent evaporated under reduced pressure to yield (1*R*,2*S*)-tetrahydrodiol **4**, as a white crystalline solid (1.8 g, 95%), mp 130-131 ºC (from CH_2Cl_2/hexane) (lit.,[19] mp. 130-131 ºC); $[\alpha]_D$ -39 (*c* 0.8, $CHCl_3$) (lit.,[19] $[\alpha]_D$ –38) (Found: M^+ 164.0841. $C_{10}H_{10}O_2$ requires 164.0837); δ_H (300 MHz, $CDCl_3$) 1.99 (2 H, m, 3'-H, 3-H), 2.93 (2 H, m, 4'-H, 4-H), 4.03 (1 H, m, 2-H), 4.71 (1-H, d, $J_{1,2}$ 3.6, 1-H), 7.12-7.46 (4 H, m, Ar-H); *m/z* 164 (M^+, 5%), 146 (65), 120 (100).

2-Methoxy-2-methyl-3a,4,5,9b-tetrahydronaphtho[l,2-d] [l,3]dioxoles (10A and 10B). To a suspension of (1*R*,2*S*)-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene **4** (0.55 g 3.4 mmol, $[\alpha]_D$ – 39), in dry benzene (50 cm^3) containing a catalytic amount of benzoic acid, was added trimethylorthoacetate (1.2 cm^3, 9.48 mmol). The reaction mixture was refluxed (2 h), cooled, and dried over anhydrous sodium carbonate; the solvent was removed under reduced pressure to give an isomeric mixture of 2-methoxy-2-methyl-3a,4,5,9b-tetrahydronaphtho[l,2-d] [l,3]dioxoles **10A** (40 %) and **10B** (60 %) as a brown oil (0.61 g, 82%) (Found: M^+ 220.1097. $C_{13}H_{16}O_3$ requires 220.1099); δ_H (300 MHz, $CDCl_3$) 1.50 (3 H, s, Me_B), 1.60 (3 H, s, Me_A), 1.75-3.00 (8 H, m, 4-H_A, 4-H_B, 4'-H_A, 4'-H_B, 5-H_A, 5-H_B, 5'-H_A, 5'-H_B), 3.26 (3H, s, OMe_A), 3.37 (3 H, s, OMe_B , 4.60 (1 H, m, 3a-H_A), 4.72 (1 H, m, 3a-H_B). 5.15 (1 H, d, $J_{9b,3a}$ 6.8, 9b-H_A), 5.28 (1 H, d, $J_{9b,3a}$, 6.8, 9b-H_B), 7.09-7.44 (8 H, m, Ar-H); *m/z* 220 (M^+, 2%), 205 (3), 147 (100). Similar treatment of (*1S,2R*)-l,2-dihydroxy-l,2,3,4-tetrahydronaphthalene **4,** ($[\alpha]_D$ +37), yielded the opposite enantiomers of compounds **10A** and **10B** (0.20 g, 95%) with identical spectral data.

(-)-(1*S*,2*S*)- and (+)-(1*R*,2*R*)-2-Acetoxy-l-chloro-1,2,3,4-tetrahydro-naphthalene (11). A solution of dioxolane mixture **10A** and **10B** (0.61 g, 2.7 mmol, from 1*R*,2*S* diol **4**), at 0 °C in dichloromethane (20 cm^3), containing triethylamine (0.7 cm^3) and chlorotrimethylsilane (0.8 cm^3, 6.25 mmol), was stirred (20 min.) under nitrogen; the solvent was removed, from the reaction mixture, under reduced pressure to give a brown oil (0.6 g, 96%). Purification by PLC (20% diethyl ether in hexane) yielded (1*S*,2*S*)-2-acetoxy-l-chloro-l,2,3,4-tetrahydronaphthalene

11 as a white solid which, on crystallization (from $CHCl_3$/hexane), formed large colourless crystals, mp 45-46 ºC; $[\alpha]_D$ -30 (*c* 0.56, $CHCl_3$) (Found: C, 63.7; H, 5.8. $C_{12}H_{13}C1O_2$ requires C, 64.1; H, 5.8%); δ_H (300 MHz, $CDCl_3$) 1.99-2.15 (1 H, m, 3-H), 2.05 (3 H, s, OCOMe), 2.39 (1 H, m, 3'-H), 2.92 (2H, m, 4-H, 4'-H), 5.08 (1 H, d, $J_{1,2}$ 4.4, 1-H), 5.34 (1 H, m, 2-H), 7.13-7.42 (4 H, m, Ar-H); *m/z* 224 (M^+, 1%), 129 (100).

Similar treatment of dioxolane mixture **10A** and **10B** (from 1*S*,2*R* diol **4**), yielded (1*R*,2*R*)-2-acetoxy-l-chloro-l,2,3,4-tetrahydronaphthalene **11**
(72%), mp 45-46 ºC; $[\alpha]_D$ +26 (*c* 0.92, $CHCl_3$). The spectral data for the (+) and (-) enantiomers of the *trans*-chloroacetate **11** were identical.

(+)-(1*R*,2*S*) and (-)-(1*S*,2*R*)-1,2-Epoxy-l,2,3,4-tetrahydronaphthalene (12). Sodium methoxide (0.5 g, 13 mmol) was added, to a solution of (1*S*,2*S*)- 2-acetoxy-l-chloro-l,2,3,4-tetrahydronaphthalene **11** (0.4 g, 1.78 mmol, $[\alpha]_D$ -30) in dry THF (25 cm^3), at 0˚C. The reaction mixture was stirred for 2 h at 0 ºC and then for 1 h at ambient temperature. The salts were filtered off and the filtrate concentrated under reduced pressure; the brown oily residue was dissolved in diethyl ether (25 cm^3), the solution washed with water (10 cm^3), dried ($MgSO_4$), and concentrated, to give (1*R*,2*S*)-1,2-epoxy-l,2,3,4-tetrahydronaphthalene **12** as a colourless oil (0.14 g, 58%). Crystallization (from Et_2O/pentane) gave epoxide **12** as colourless crystals, mp 45-47 ºC (lit.,[11] 45-48 ºC), $[\alpha]_D$ +133 (*c* 0.4, $CHCl_3$) (lit.,[11] $[\alpha]_D$ +135) (Found: M^+, 146.0732. $C_{10}H_{10}O$ requires 146.0732); δ_H (300 MHz, $CDCl_3$) 1.77 (1 H, m, 3-H), 2.41 (1H, m, 3'-H), 2.54 (1 H, m, 4-H), 2.76 (1 H, m, 4'-H), 3.73 (1 H, m, 2-H), 3.84 (1 H, d, $J_{1,2}$ 4.2, 1-H), 7.07-7.40 (4 H, m, Ar-H); *m/z* 146 (M^+, 100%), 128 (20), 118 (62).

Similar treatment of (1*R*,2*R*)-2-acetoxy-l-chloro-l,2,3,4-tetrahydro-naphthalene **11** ($[\alpha]_D$ +26) yielded (1*S*,2*R*)-1,2-epoxy-l,2,3,4-tetrahydronaphthalene **12** (0.020 g. 51%); $[\alpha]_D$ -133 (*c* 0.4, $CHCl_3$). The spectral data for the (+) and (-) enantiomers of tetrahydroepoxide **12** were indistinguishable.

(-)-(1*R*,2*S*)-1,2-Dimesyloxy-l,2,3,4-tetrahydronaphthalene (14). To a cooled (-20 °C) stirring solution of (1*R*,2*S*)-1,2-dihydroxy-l,2,3,4-tetrahydronaphthalene **4** (0.7 g, 4.2 mmol, $[\alpha]_D$ –39), in dichloromethane (50 cm^3) containing triethylamine (2.4 cm^3, 17 mmol), was added, dropwise, methane sulfonyl chloride (1.65 cm^3, 17 mmol). The reaction mixture was allowed to warm to room temperature, washed successively with water (25 cm^3) and saturated solution of sodium bicarbonate (10 cm^3). After drying ($MgSO_4$), the organic layer was concentrated to give the dimesylate **14** as a pale yellow oil (1.2 g, 89%). Due to the instability, dimesylate **14** was characterized by spectral methods only and the crude product was used for the next step: $[\alpha]_D$ -21 (*c* 4.0, $CHCl_3$) (Found: M^+-OSO_2Me 225.0571, $C_{11}H_{13}O_3S$ requires 225.0585); δ_H (300 MHz, $CDCl_3$) 2.18 (1 H, m, 3-H), 2.43 (1 H, m, 3'-H), 3.10 (3 H, s, OSO_2Me), 3.14 (3 H, s, OSO_2Me), 3.40 (2 H, m, 4-H, 4'-H), 5.15 (1 H, m, 2-H), 5.91 (1 H, d, $J_{1,2}$ 3, 1-H), 7.16-7.48 (4 H, m, Ar-H); *m/z* 225 (M^+-OSO_2Me, 60%), 118 (100).

(-)-(1*S*,2*R*)-1,2-Epoxy-1,2,3,4-tetrahydronaphthalene (12). To a solution of dimesylate **14**

(1.34 g, 4.1 mmol, $[\alpha]_D$ –21), in toluene (120 cm^3), was added potassium hydroxide solution (10%, 20 cm^3) and the phase transfer catalyst tetrabutylammonium bromide (0.040 g); the reaction mixture was stirred vigorously (4 h) at room temperature. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to yield a brown oil. Purification by PLC (30% diethyl ether in hexane) yielded (1*S*,2*R*)-1,2-epoxy-l,2,3,4-tetrahydronaphthalene **12** as a colourless oil (0.20 g, 32%); $[\alpha]_D$ -130 (*c* 0.9, $CHCl_3$). The spectral data was identical to that of tetrahydroepoxide **12** formed *via trans*-chloroacetate **11**.

Synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-1,2-dihydroxy-1,2,3,4-tetrahydro-naphthalene (18)

(+)-(1*R*,2*S*)-1,2-Diacetoxy-1,2-dihydronaphthalene (15). *cis*-Dihydrodiol **2** (0.2 g, 1.2 mmol, $[\alpha]_D$ +244) was treated with an excess of acetic anhydride in pyridine (1 cm^3) and the mixture maintained at 45 °C for 4 h. Pyridine was removed under reduced pressure, water (20 cm^3) added to the residue and the reaction mixture extracted with diethyl ether (2 x 15 cm^3). The organic extract was dried ($MgSO_4$) and the solvent removed to give a colourless oil; purification by PLC (15% diethyl ether in hexane) yielded diacetate **15**, as a light yellow oil (0.22 g, 73%); $[\alpha]_D$ +96 (*c* 1.4, $CHCl_3$) (lit.,[6] $[\alpha]_D$ +94, $CHCl_3$) (Found: M^+ 246.0891, $C_{14}H_{14}O_4$ requires 246.0892); δ_H (300 MHz, $CDCl_3$) 2.05 (3 H, s, OCOMe), 2.11 (3 H, s, OCOMe), 5.69 (1 H, m, 2-H), 5.95 (1 H, dd, $J_{3,4}$ 9.7, $J_{3,2}$ 3.9, 3-H), 6.10 (1 H, d, $J_{1,2}$ 4.7, 1-H), 6.64 (1 H, d, $J_{4,3}$ 9.7, 4-H), 7.15-7.35 (4 H, m, Ar-H); *m/z* 246 (M^+, 8%), 186 (9), 144 (100).

(+)-(1*R*,2*S*,3*R*,4*R*)-1,2-Diacetoxy-3,4-epoxy-1,2,3,4-tetrahydro-naphthalene (16). To a vigorously stirred biphasic solution (0 °C), of (1*R*,2*S*)-1,2-diacetoxy-1,2-dihydronaphthalene **15** (0.22 g, 0.89 mmol, $[\alpha]_D$ +96) in dichloromethane (40 cm^3), and phosphate buffer (pH 8.0, 50 cm^3) was added, in small portions, MCPBA (0.210 g, 1.2 mmol). The reaction mixture was stirred at 0 °C for 2 h and then allowed to stir at room temperature overnight. The dichloromethane layer was separated, washed, successively, with sodium sulfite and sodium bicarbonate solutions, dried ($MgSO_4$), and concentrated to leave an oily residue. Purification by PLC (20% diethyl ether in hexane) afforded diacetate epoxide **16** as a white solid (0.21 g, 95%), mp 71-73 °C ($CHCl_3$/hexane); $[\alpha]_D$ +92 (*c* 1.6, $CHCl_3$) (Found: C, 64.1; H, 5.2 $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); δ_H (300 MHz, $CDCl_3$) 1.98 (3 H, s, OCOMe), 2.19 (3 H, s, OCOMe), 3.75 (1 H, m, 3-H), 3.99 (1 H, d, $J_{4,3}$ 3.7, 4-H), 6.01 (2 H, m, 1-H, 2-H), 7.26-7.53 (4 H, m, Ar-H); *m/z* 262 (M^+, 5%), 219 (15), 202 (100).

(-)-(2*R*,3R)-2-Acetoxy-3-hydroxy-l,2,3,4-tetrahydronaphthalene (17). (1*R*,2*S*,3*R*,4*R*)-1,2-diacetoxy-3,4-epoxy-1,2,3,4-tetrahydro-naphthalene **16** (0.80 g, 0.30 mmol, $[\alpha]_D$ +92) was catalytically hydrogenolysed (10% Pd/C, H_2, EtOH, 24 h) at room temperature and atmospheric pressure. Purification by PLC (50% diethyl ether in hexane) afforded (2*R*,3*R*)-2-acetoxy-3-hydroxy-l,2,3,4-tetrahydronaphthalene **17** (0.50 g, 80%), mp 116-117 °C (from Et_2O/hexane) (lit.,[20] mp 92 °C); $[\alpha]_D$ -90 (*c* 1.1, $CHCl_3$) (Found: C, 69.6; H, 6.9, $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%); δ_H (300 MHz, $CDCl_3$) 2.05 (3 H, s, OCOMe), 2.78 (2 H, m, 1-H, 4-H), 3.14 (1 H, dd, $J_{4',4}$

16.6, $J_{4',3}$ 5.8, 4'-H), 3.23 (1 H, dd, $J_{1,'1}$16.6, $J_{1',2}$ 5.8, 1'-H), 4.00 (IH, m, 3-H), 4.95 (1 H, m, 2-H), 6.99-7.18 (4 H, m, Ar-H); *m/z* 206 (M^+, 1%), 189 (2), 146 (100).

(-)-(2*R*,3*R*)-2,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (18). Ammonia gas was bubbled (1 h) through a solution of (2*R,*3*R*)-2-acetoxy-3-hydroxy-l,2,3,4-tetrahydronaphthalene **17** (0.030 g, 0.14 mmol), in methanol (5 cm^3) maintained at 0 °C. After leaving the reaction mixture, overnight at room temperature, the solvent was removed under reduced pressure to give *trans*-2,3-diol **18** as a white crystalline solid (0.02 g, 86%), mp 157-159 °C ($CHCl_3$/hexane) (lit.,[8] mp 158-160 °C); $[\alpha]_D$ - 90 (*c* 0.7, EtOH); (lit. [8,21], $[\alpha]_D$ -99 EtOH); δ_H (300 MHz, $CDCl_3$) 2.83 (2 H, m, 1-H, 4-H), 3.20 (2 H, m, 1'-H, 4'-H), 3.89 (2 H, m, 2-H, 3-H), 7.08-7.18 (4 H, m, Ar-H); *m/z* 164 (M^+, 85%), 146 (100).

(+)-(2*S*,3*S*)-2,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (18). Biotransformation (*P. Putida* ML2, OD=30, 4 g / L) of *cis*-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **9** (1 g, 6.1 mmol) was carried out at 30 °C for 24 h. The aqueous culture medium, containing the bioproducts, was concentrated, under reduced pressure, and the brown viscous concentrate extracted with hot (40 °C) ethyl acetate (3 x 75 cm^3). Solvent was removed, from the dried (Na_2SO_4) extract, and the residue dissolved in a (1:1) mixture of acetone and dimethoxypropane (15 cm^3) containing a catalytic amount of *p*-toluenesulfonic acid; the reaction mixture was stirred, overnight, at room temperature. The crude mixture, obtained after removal of solvents, was purified by column chromatography (CH_2Cl_2 → 20% acetone in CH_2Cl_2). The earlier dichloromethane column fractions gave the acetonide derivative of *cis*-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **9**, while the later eluting acetone-dichloromethane fractions yielded (2*S*,3*S*)-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **18** , as a white crystalline solid (0.30 g, 30%), mp 157-159 °C ($CHCl_3$/hexane); $[\alpha]_D$ + 90 (*c* 0.8, EtOH). The spectral data was identical to that of the (-) enantiomer **18**.

Synthesis of (1*R*,3*R*)-1,3-dihydroxy-1,2,3,4-tetrahydronaphthalene (21) and (1*R*,3*S*)-1,3-dihydroxy-1,2,3,4-tetrahydronaphthalene (26)

(+)-(1*R*,2*S*,4*R*)-1,2-Epoxy- 4-hydroxy-l,2,3,4-tetrahydronaphthalene (20). MCPBA (0.175 g, 1.0 mmol) was added, in small portions, to a vigorously stirred biphasic solution (0 °C), of (1*R*)-1-hydroxy-l,2-dihydronaphthalene **5** (0.10 g, 0.68 mmol, $[\alpha]_D$ +52) in dichloromethane (20 cm^3) and phosphate buffer (20 cm^3, pH 8). PLC purification (75% diethyl ether in hexane) gave (1*R*,2*S*,4*R*)-1,2-epoxy-4-hydroxy-1,2,3,4-tetrahydronaphthalene **20** as a colourless oil; (0.10 g, 91%) (Found: M^+ 162.0675. $C_{l0}H_{l0}O_2$ requires 162.0807); $[\alpha]_D$ +95 (*c* 1.4, MeOH); δ_H (300 MHz, $CDCl_3$) 1.98 (1 H, dd, $J_{3,4}$ 4.0, $J_{3,3'}$ 15.0, 3-H), 2.75 (1 H, d, $J_{3',3}$ 15Hz, 3'-H), 2.96 (1 H, d, $J_{4,OH}$ 11.6, OH), 3.94 (1 H, br s, 2-H), 4.08 (1 H, d, $J_{1,2}$ 4.0, 1-H), 4.65 (1 H, m, 4-H), 7.34- 7.53 (4 H, m, Ar-H); *m/z* 162 (M^+, 12%) 144 (36), 116 (100).

(-)-(1*R*,3*R*)-l,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (21). (1*R*,2*S*,4*R*)-1,2-Epoxy-4-hydroxy-l,2,3,4-tetrahydronaphthalene **20** (0.014 g, 0.086 mmol, $[\alpha]_D$ +95), on catalytic

hydrogenation (10% Pd/C, H_2, EtOAc) at room temperature and atmospheric pressure, yielded (1*R*,3*R*)-l,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **21** as transparent crystals (0.0l g, 71%), mp 114-115 °C ($CHCl_3$/hexane) (lit.[18] mp 81-82 °C) (Found: M^+ 164.0834, $C_{10}H_{12}O_2$ requires 164.0837); $[\alpha]_D$ -58 (*c* 0.9, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.11(1-H, m, 2-H), 2.31 (1 H, m, 2'-H), 3.03 (2 H, m, 4-H, 4'-H), 4.43 (1 H, br s, 3-H), 4.84 (1 H, br s, 1-H), 7.12-7.44 (4 H, m, Ar-H); *m/z* 164 (M^+, 33%), 146 (100).

(+)-(1*R*)-1-Acetoxy-l,2-dihydronaphthalene (22). A solution of (1*R*)-1-hydroxy-l,2-dihydronaphthalene **5** (0.190 g, 1.3 mmol, $[\alpha]_D$ +52), in pyridine (0.5 cm^3), was treated with an excess of acetic anhydride (1 cm^3). After leaving the reaction mixture overnight at 5 °C, it was worked up as described for diacetate **15**. (1*R*)-1-Acetoxy-l,2-dihydronaphthalene **22** (0.20 g, 80%) was obtained as a light yellow oil that was found to decompose during attempted purification by PLC; $[\alpha]_D$ +154 (*c* 0.38, $CHCl_3$) (Found: M^+ 188.0835, $C_{12}H_{12}O_2$ requires 188.0837); δ_H (300 MHz, $CDCl_3$) 1.98 (3 H, s, OCOMe) 2.58 (2 H, m, 2-H, 2'-H), 5.98 (2 H, m, 1-H, 3- H), 6.53 (1 H, d, $J_{4,3}$ 9.5, 4-H), 7.09-7.36 (4 H, m, Ar-H); *m/z* 188 (M^+, 2%), 128 (100).

(+)-(1*R*,2*S*,4*R*)- 23 and (-)-(1*S*,2*R*,4*R*)- 1,2-Epoxy-4-acetoxy-l,2,3,4-tetrahydro-naphthalene (24). (1*R*)-1-Acetoxy-l,2-dihydronaphthalene **22** (0.090 g, 0.48 mmol, $[\alpha]_D$ +154) was epoxidised, using MCPBA (0.105 g, 0.6 mmol), as described earlier, to give a mixture of two epoxides. PLC (60% diethyl ether in hexane) separation of the mixture afforded: (i) (1*R*,2*S*,4*R*)-1,2-epoxy-4-acetoxy-1,2,3,4-tetrahydro-naphthalene **23**, a viscous oil (0.034 g, 35%), R_f 0.38; mp 100-103 °C (CH_2C1_2/hexane); $[\alpha]_D$ +184 (*c* 0.8, $CHCl_3$) (Found: C, 70.9; H, 6.1, $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%); δ_H (300 MHz, $CDCl_3$) 2.03 (3 H, s, OCOMe), 2.13 (1 H, m, $J_{3,3'}$ 16.0, $J_{3,4}$ 5.0, 3-H), 2.67 (1 H, m, $J_{3',3}$ 16.0, 3'-H), 3.79 (1 H, m, 2-H), 3.96 (1 H, d, $J_{1,2}$ 3.9, 1-H), 6.09 (1 H, d, $J_{4,3}$ 5.0, 4-H), 7.25-7.53 (4 H, m, Ar-H); *m/z* 204 (M^+, 5%), 162 (43),144 (100) and (ii) (1*S*,2*R*,4*R*)-1,2-Epoxy-4-acetoxy-l,2,3,4-tetrahydronaphthalene **24**, viscous oil (0.048 g, 47%); R_f 0.49; $[\alpha]_D$ -73 (*c* 0.32, $CHCl_3$) (Found: M^+-HOAc 144.0579 $C_{l0}H_8O$ requires 144.0575); δ_H (300 MHz, $CDCl_3$) 1.77 (1 H, m, J $_{3,3'}$ 13.9, $J_{3,4}$ 10.8, 3-H), 2.21 (3 H, s, OCOMe) 2.92 (1 H, m, J $_{3',3}$ 13.9, 3'-H), 3.73 (1 H, m, 2-H), 3.91 (1 H, d, $J_{1,2}$ 4.0, 1-H), 5.93 (1 H, dd, $J_{4,3}$ 10.8, $J_{4,3'}$ 6.8, 4-H), 7.29-7.48 (4H, m, Ar-H); *m/z* 162 (M^{+1}-CH_3CO, 73%), 144 (100).

(-)-(1*S*,2*R*,4*R*)-1,2-Epoxy-4-hydroxy-1,2,3,4-tetrahydronaphthalene (25). Ammonia gas was bubbled (1 h) through a stirred solution (0 °C) of acetate epoxide **24** (0.07 g, 0.33 mmol, $[\alpha]_D$ -73) in methanol (5 cm^3). After keeping the reaction mixture at room temperature (3 h), the solvent was removed; purification, of the product by PLC (75% diethyl ether in hexane), gave (1*S*,2*R*,4*R*)-1,2-epoxy-4-hydroxy-1,2,3,4-tetrahydronaphthalene **25** as a white solid (0.045 g, 80%). mp 74-76 °C (CH_2Cl_2/hexane); $[\alpha]_D$ -97 (*c* 0.74, $CHCl_3$) (Found: C, 73.6; H, 6.5 $C_{10}H_{10}O_2$ requires C, 74.0; H, 6.2%); (Found: M^+ 162.0673 $C_{10}H_{10}O_2$ requires 162.0680); δ_H (300 MHz, $CDCl_3$) 1.64 (1H, m, $J_{3,3'}$ 13.9, 3-H), 2.78 (1 H, m, J $_{3,'3}$ 13.9, 3'-H), 3.64 (1 H, m, 2-H), 3.87 (1 H, d, $J_{1,2}$ 4.1, 1-H), 4.75 (1 H, m, 4-H), 7.25-7.62 (4 H, m, Ar-H); *m/z* 162 (M^+, 32%), 144 (26), 116 (55).

(+)-(1*R*,3*S*)-l,3-Dihydroxy-1,2,3,4-tetrahydronaphthalene (26). (1*S*,2*R*,4*R*)-1,2-Epoxy-4-hydroxy-1,2,3,4-tetrahydronaphthalene **25** (0.050 g, 0.3 mmol, $[\alpha]_D$ -97), on catalytic hydrogenation (10% Pd/C, H_2, EtOAc) at atmospheric pressure, yielded (+)-(1*R*,3*S*)-l,3-dihydroxy-1,2,3,4-tetrahydronaphthalene **26** (0.03 g, 61%), mp 92-94 °C ($CHCl_3$/hexane) (Found: M^+ 164.0839 $C_{10}H_{12}O_2$ requires 164.0837); $[\alpha]_D$ +43 (*c* 0.59, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.89 (1 H, m, 2-H), 2.17 (1 H, m, 2'-H), 2.69 (1 H, m, 4-H), 3.08 (1 H, m, 4'-H), 4.31 (1 H, m, 3-H), 4.90 (1 H, m, 1-H), 7.08-7.42 (4 H, m, Ar-H); *m/z* 164 (M^+, 5%), 146 (100).

Synthesis of (1*R*,4*R*)-1,4-dihydroxy-1,2,3,4-tetrahydronaphthalene (31)

(+)-(1*R*)-1-Acetoxy-1,2,3,4-tetrahydronaphthalene (28). (1*R*)-1-hydroxy-1,2,3,4-tetrahydronaphthalene **27** (0.50 g, 3.37 mmol, $[\alpha]_D$ -32) was converted (Ac_2O/pyridine) into the acetate derivative **28**, an oil (0.550 g, 86%), bp 84 °C at 0.4mmHg; $[\alpha]_D$ +98 (*c* 0.44, $CHCl_3$) (Found: M^+ 190.0997, $C_{12}H_{14}O_2$ requires 190.0994); δ_H (300 MHz, $CDCl_3$) 1.78-2.05 (4 H, m, 3-H, 3'-H, 2-H, 2'-H), 2.07 (3 H, s, OCOMe), 2.70-2.91 (2 H, m, 4-H, 4'-H), 5.99 (1 H, d, $J_{1,2}$ 3.8, 1-H), 7.11-7.28 (4 H, m, Ar-H); *m/z* 190 (M^+,7%), 130 (100),148 (22).

(1*R*,4*R*) / (1*R*,4*S*)-1-Acetoxy-4-bromo-1,2,3,4-tetrahydronaphthalene (29A/29B). A solution of (-)-(1*R*)-1-acetoxy-l,2,3,4-tetrahydronaphthalene **28** (0.50 g, 2.63 mmol), in carbon tetrachloride (20 cm^3), containing N-bromosuccinimide (0.6 g, 3.4 mmol) and a catalytic amount of 2,2'-azobis(isobutyronitrile), was heated under reflux (1.5 h). The reaction mixture was cooled, filtered, and the solvent removed under reduced pressure, to yield a mixture (1:1) of *cis* and *trans*-1-acetoxy-4-bromo-l,2,3,4-tetrahydronaphthalene **29A/29B**, as a yellow oil (0.6 g, 86%), $[\alpha]_D$ +49 (*c* 3.6, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.03 (3 H, s, $OCOMe_A$), 2.17 (3 H, s, $OCOMe_B$) 2.03-2.50 (8 H, m, 2-H_A, 2'-H_A, 2-H_B, 2'-H_B 3-H_A, 3'-H_A, 3-H_B, 3'-H_B), 5.50 (1 H, m, 4-H_B), 5.60 (1 H, m, 4-H_A), 6.05 (2 H, m, 1-H_A, 1-H_B) 7.22-7.43 (8 H, m, Ar-H); *m/z* 268 (M^+ ^{79}Br, 1%), 270 (M^+ ^{81}Br,1), 226 (60), 224 (57). A small sample, of the diastereoisomeric mixture **29A/29B**, on crystallization, afforded white needles of a single isomer, mp 86-88 °C (hexane); $[\alpha]_D$ +72 (*c* 0.58, $CHCl_3$) (Found: C, 53.6 H, 4.5 $C_{12}H_{13}O_2Br$ requires C, 52.5; H, 4.9%).

(1*R*,4*R*) / (1*R*,4*S*)-1-Acetoxy-4-trifluoroacetoxy-1,2,3,4-tetrahydro-naphthalene (30A/30B). A suspension of silver trifluoroacetate (0.58 g, 2.62 mmol), in benzene (4 cm^3), was added to a cooled solution (~ 10 °C) of (1*R*,4*R*) / (1*R* /4*S*)-1-acetoxy-4-bromo-1,2,3,4-tetrahydronaphthalene **29A/29B** (0.47 g, 1.74 mmol, $[\alpha]_D$ +49) in benzene (l0 cm^3) and the mixture stirred (5h) at room temperature. The reaction mixture was filtered and the filtrate concentrated under reduced pressure, to yield an isomeric mixture (1:1) of (1*R*,4*R*) / (1*R*,4*S*)-1-acetoxy-4-trifluoroacetoxy-1,2,3,4-tetrahydronaphthalene **30A/30B**, as an oil (0.4 g, 80%). Diastereoisomers **30A/30B** showed evidence of decomposition during attempted separation by PLC; (Found: M^+-HOAc 242.0554 $C_{12}H_9O_2F_3$ requires 242.0555); δ_H (300 MHz, $CDCl_3$) 2.07 (3 H, s, $OCOMe_A$), 2.15 (3 H, s, $OCOMe_B$), 2.09-2.41 (8 H, m, 2-H_A, 2'-H_A, 2-H_B, 2'-H_B 3-H_A, 3'-H_A, 3-H_B, 3'-H_B), 5.97-6.22 (4 H, m, 1-H_A, 1-H_B, 4-H_A, 4-H_B) 7.30-7.44 (8 H, m, Ar-H); *m/z* 242

(M^+ - HOAc, 54%), 146 (100), 129 (6).

(-)-(1*R*,4*R*)-1,4-Dihydroxy-1,2,3,4-tetrahydronaphthalene 31 and *cis*-1,4-dihydroxy-1,2,3,4-tetrahydronaphthalene (32). A solution of (1*R*,4*R*) / (1*R*,4*S*)-1-acetoxy-4-trifluoroacetoxy-l,2,3,4-tetrahydro-naphthalene **30A/30B** (0.30 g, 0.9 mmol) in methanol (20 cm^3) and aqueous Na_2CO_3 (l0 cm^3, 5%) was stirred (12 h) at room temperature. Methanol was removed under reduced pressure, and the residual aqueous reaction mixture extracted with EtOAc (2 x 15 cm^3). The extract was dried ($MgSO_4$) and then concentrated under reduced pressure to yield an isomeric mixture (1:1) of *cis* / *trans* diols **32** and **31** (0.15 g, 93%), mp 116-118 °C (CH_2Cl_2/hexane) (Found: C, 72.6; H, 7.5. $C_{10}H_{10}O_2$ requires C, 73.1; H, 7.4%); *m/z* 164 (M^+, 7%), 146 (100).

Small samples (*ca* 0.01 g), of *cis* / *trans* diols **32** and **31**, were separated, by HPLC, on a Zorbax Sil analytical column (1% MeOH/CH_2Cl_2, 1.5 cm^3/min). (1*R*,4*R*)-1,4-Dihydroxy-1,2,3,4-tetrahydronaphthalene **31** was the early eluting isomer, a white crystalline solid, mp 141-142 °C (lit.,[22] racemic mp 137-138 °C); $[\alpha]_D$ -59 (*c* 0.5, MeOH); δ_H (300 MHz, $CDCl_3$) 1.82 (2 H, m, 2-H, 3-H), 2.31 (2 H, m, 2'-H, 3'-H), 4.83 (2 H, m, 1-H, 4-H), 7.31-7.47 (4H, m, Ar-H). *cis*-1,4-Dihydroxy-1,2,3,4-tetrahydronaphthalene **32**, was the late eluting isomer, a white crystalline solid, mp 136-138 °C (lit.,[23] mp 138 °C); δ_H (300 MHz, $CDCl_3$) 2.04 (4 H, m, 2-H, 2'-H, 3-H, 3'-H), 4.75 (2 H, m, 1-H, 4-H) 7.31-7.47 (4 H, m, Ar-H).

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