Enzymatic Synthesis of Chiral 1-Phenyl-1,2- and 1,3-diols *via* Chiral Epoxy Alcohols

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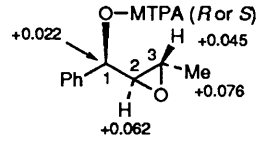
Chiral epoxy alcohols have been prepared by asymmetric reduction of 1-phenyl-2,3-epoxybutan-1-one with baker's yeast, or by enantioselective esterification of racemic 1-phenyl-2,3-epoxybutan-1-ol with lipase PS. The epoxy alcohols obtained were reduced with lithium aluminium hydride to afford chiral 1-phenylbutane-1,2- and 1,3-diols. The absolute configurations of the epoxy alcohols and diols were determined by use of modified Mosher's method or by the comparison with the diols, which were prepared from benzoylacetone *via* chiral enols by use of baker's yeast and lipase PS.

Asymmetric synthesis using enzymes in organic chemistry has been widely recognized as a useful tool for the preparation of chiral synthons in the synthesis of natural products. In particular, baker's yeast[1] has been most popularly used because of its cheapness and ease of handling. In addition, kinetic resolution by lipase-catalyzed esterification of racemic compounds has also been performed in organic solvents with high stereoselectivity.[2] In a previous paper,[3] we reported the enantioselective synthesis of chiral phenylglycidols (whose configurations were also determined by conversion into known chiral compounds), which are valuable chiral building blocks for the synthesis of biologically active compounds such as β-blockers,[4] by reduction of epoxy ketones with baker's yeast, or lipase-catalyzed esterification of racemic phenylglycidols. In a further extension of this series of work, we have investigated the asymmetric synthesis of 1,2- and 1,3-diols, for use as chiral auxiliaries *via* chiral phenylglycidoles from phenyl propenyl ketone with the aid of baker's yeast or lipase.

As shown in Scheme 1, when the *trans*-epoxy ketone **2** (prepared from phenyl propenyl ketone **1** using 30% H_2O_2 at −30 °C) was fermented with baker's yeast for 84 h at 30 °C, two *trans*-epoxy alcohols (−)-**3a** and (−)-**3b** were isolated in 77 and 98% e.e., respectively. The absolute configuration at C-1 in (−)-**3b** was deduced as *R* from the difference in chemical shifts (in the ^{1}H NMR spectrum) of the corresponding (*R*)-(+)- and (*S*)-(−)-methoxy(trifluoromethyl)phenylacetic acid (MTPA) esters

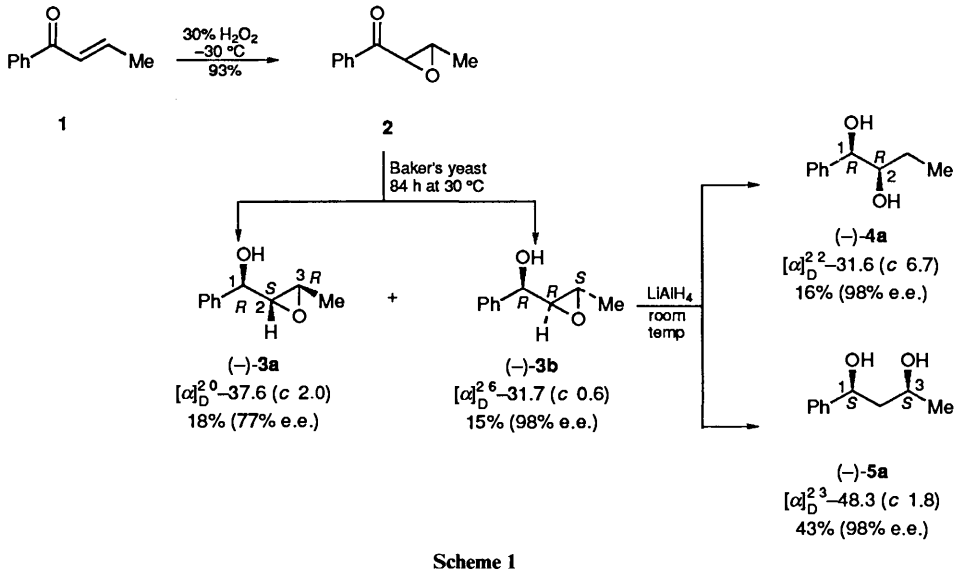


Δδ(ppm) = δ[(*R*)-MTPA ester **6a**] − δ[(*S*)-MTPA ester **6b**]

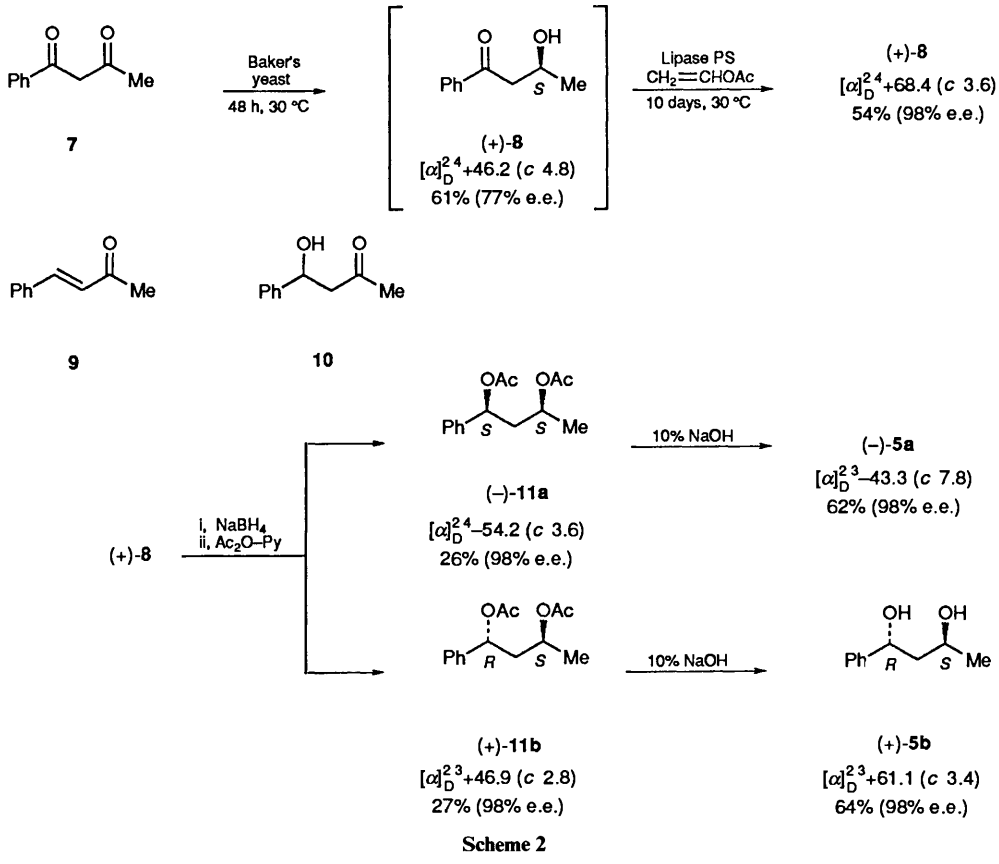
Fig. 1 The chemical shift differences of (*R*)-(+)-MTPA ester **6a** and (*S*)-(−)-MTPA ester **6b**

6a and **6b** by a modified Mosher's method (Fig. 1).[5] The absolute configuration at C-2 and C-3 of (−)-**3b** was determined as *R* and *S*, respectively, by its conversion with lithium aluminium hydride into the corresponding (1*S*,3*S*)-1,3-diol (−)-**5a** (98% e.e.),[6] which was also prepared *via* the ketone (*S*)-(+)-**8**[7] from benzoylacetone **7** by use of baker's yeast and lipase PS. In the reduction of (−)-**3b**, the (1*R*,2*R*)-diol (−)-**4a** (98%, e.e.) was also isolated and its absolute configuration was confirmed from that of the epoxy alcohol (−)-**3b**.

The synthesis of the chiral diols, (1*S*,3*S*)-(−)-**5a** and (1*R*,3*S*)-(+)-**5b** from benzoylacetone **7** was carried out by the following procedure. When the diketone **7** was treated with baker's yeast for 48 h at 30 °C, 3-hydroxy 1-phenylbutan-1-one (+)-**8**[7] 61%, 77% e.e.) was obtained, together with the racemic 1,3-diol derivatives **5** (< 1%) and 4-phenylbut-3-en-2-one **9** (3%) (which was assumed to be the dehydrated product of the



Scheme 1



Scheme 2

ketol **10**, reduced regioselectively at C-1 ketone of compound **7**) (Scheme 2).

In order to improve the optical yield of the ketone (+)-**8**, we investigated lipase-catalysed optical resolution. Namely, by treatment of (+)-**8** with lipase PS for 10 days in the presence of vinyl acetate, kinetically resolved (*S*)-(+)-**8** was afforded in excellent optical yield (98% e.e.). After the conversion of (+)-**8** with sodium borohydride into (1*S*,3*S*)-(−)-**5a** and (1*R*,3*S*)-(+)-**5b** as an inseparable diastereoisomeric mixture (1:1) and subsequent acetylation with acetic anhydride–pyridine, two diacetates (1*S*,2*S*)- and (1*R*,3*S*)-(−)-**11a** and (+)-**11b** were isolated by column chromatography (26 and 27%, respectively). Following hydrolysis of both (−)-**11a** and (+)-**11b** with 10% NaOH, the corresponding 1,3-diols (−)-**5a**[7] (62%, 98% e.e.) and (+)-**5b** (64%, 98% e.e.) were prepared.

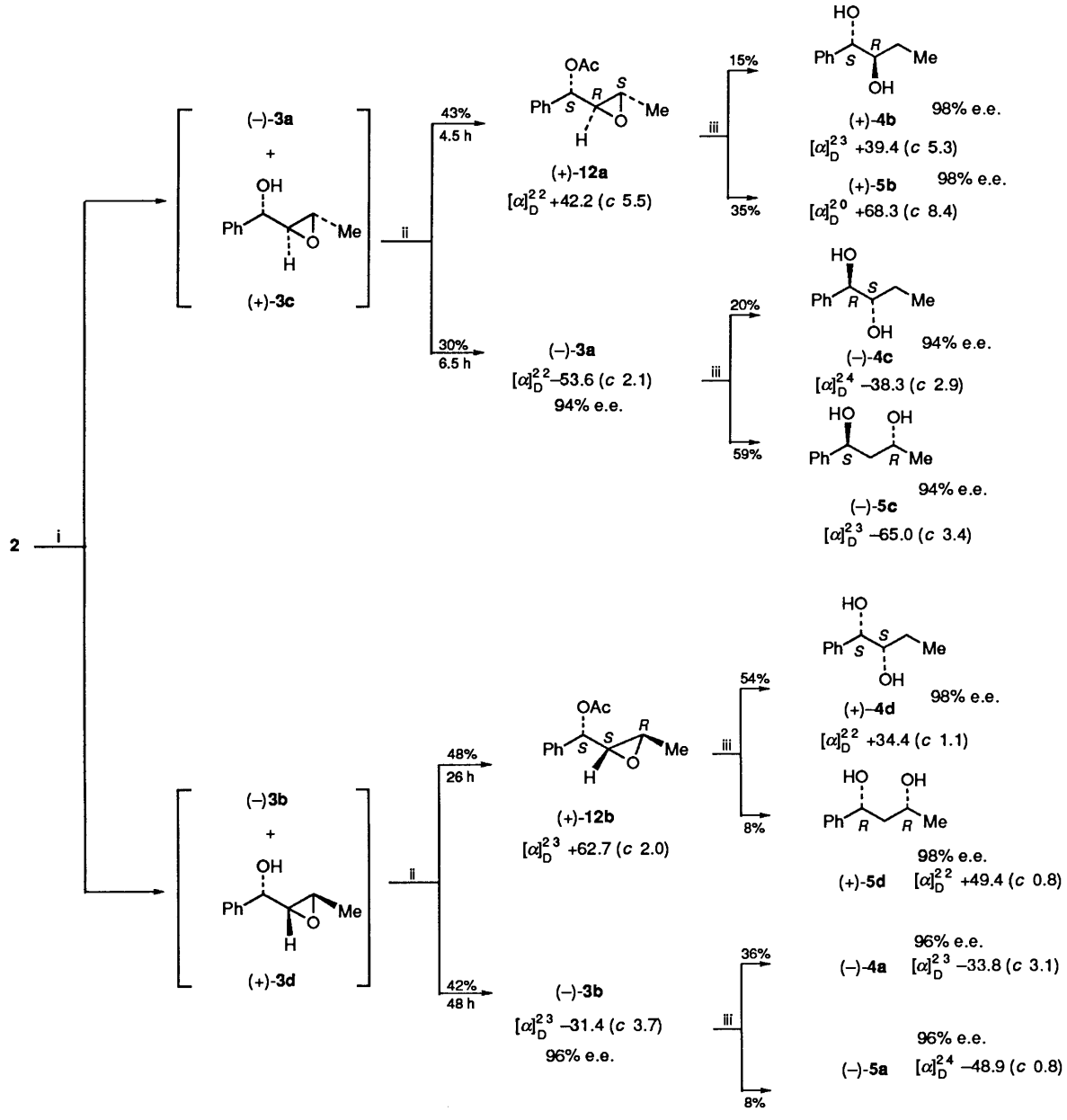
Furthermore, we have investigated the syntheses of chiral epoxy alcohols by kinetic resolution or asymmetric esterification of the racemic epoxy alcohols **3a**, **c** and **3b**, **d**, which were obtained by sodium borohydride reduction of the epoxy ketone **2**, by use of lipase PS. When a mixture of the alcohols **3a**, **c** was treated with lipase PS in the presence of vinyl acetate for 4.5 h at 30 °C (extract of esterification > 50%), the (1*S*,2*R*,3*S*)-acetate (+)-**12a** was isolated (43%), and successive reduction with lithium aluminium hydride afforded the two diols, (+)-**5b** (35%, 98% e.e.) and (+)-**4b** (15%, 98% e.e.). However, when the mixture **3a**, **c** was treated with lipase PS for 6.4 h at 30 °C (extract of esterification > 50%), in this time, the chiral epoxy alcohol (−)-**3a** was isolated (30%, 94% e.e.) upon lithium aluminium hydride reduction gave the corresponding diols (1*S*,3*R*)-(−)-**5c**[6] (59%, 94% e.e.) and (1*R*,2*S*)-(−)-**4c** (20%, 94% e.e.). The same reaction sequence was also performed for the mixture of alcohols **3b**, **d**. By treatment of the mixture **3b**, **d** with lipase PS for 26 h (extent of esterification > 50%) and 48 h (extent of esterification > 50%) at 30 °C, (1*S*,2*S*,3*R*)-acetate (+)-**12b** (48%) and (1*R*,2*R*,3*S*)-(−)-**3b** (42%, 96%, e.e.) were obtained, respectively. Reduction of the epoxides (+)-**12b** and (−)-**3b** with lithium aluminium hydride gave both the 1,3- and 1,2-diols, (1*R*,3*R*)-(+)-**5d**(8%, 98% e.e.), (1*S*,2*S*)-(+)-**4d** (54%, 98% e.e.) and (1*S*,3*S*)-(−)-**5a** (8% , 96% e.e.), (1*R*,2*R*)-(−)-**4a** (36%, 96%, e.e.), respectively.

Experimental

General.—Baker's yeast (*Saccharomyces cerevisiae*) and Lipase PS (*Saccharomyces sp*) were purchased from Oriental Yeast Co. and Amano Pharm. Co., Ltd., respectively. ^{1}H NMR Spectra were recorded on JEOL JNM-PMX-60, JNM-EX 270 or JNM-GSX 400 spectrometers with tetramethylsilane as an internal standard. *J*-Values are given in Hz. Optical rotations were recorded on JASCO DIP-360 polarimeter. The optical purities (% e.e.) were calculated from the ^{1}H NMR spectrum of the (−)-or(+)-MTPA ester, or by HPLC analysis [column: Chiralcel OD (Daicel Chemical Industries, Ltd), solvent hexane–propan-2-ol (95:5)]. For column chromatography, silica gel (Wacogel C-200, from Wako Pure Chemical Industries, Ltd.) was used.

1-*Phenyl*-2,3-*epoxybutan*-1-*one* **2**.—To a solution of phenyl propenyl ketone **1** (3 g, 20.5 mmol) in MeOH (78 cm^3), 30% H_2O_2 (18 cm^3) and 10% NaOH (6 cm^3) were added at −30 °C and stirred at this temperature for 1.5 h. After extraction of the solution with $CHCl_3$, the extracts were washed with saturated brine, (Na_2SO_4) and evaporated under reduced pressure to give the epoxy ketone **2** (3 g, 93%) as an oil; δ_H(270 MHz;$CDCl_3$) 1.51 (3 H, d, *J* 5.3, CH_3), 3.21 (1 H, dq, *J* 2.0, 5.3, C*H*CH_3), 3.99 (1 H, d, *J* 2.0, ArCOCH) and 7.45–7.64 and 7.99–8.03 (5 H, m, ArH).

Asymmetric Reduction of 1-*Phenyl*-2,3-*epoxybutan*-1-*one* **2** *with Baker's Yeast.*—A mixture of the epoxy ketone **2** (3 g, 18.5 mmol) and baker's yeast (500 g) in distilled water (300 cm^3) was incubated for 84 h at 30 °C. After extraction of the mixture with



Scheme 3 *Reagents and conditions:* i, $NaBH_4$; ii, Lipase PS, CH_2=$CHOH_2$, 30 °C; iii, $LiAlH_4$, reflux, 30 min.

$CHCl_3$ using a Soxlet apparatus, the extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g) using CH_2Cl_2 as eluent to give (1R,2S,3R)-1-*phenyl*-2,3-*epoxybutan*-1-*ol* (−)-**3a** (0.52 g, 18%, 77% e.e.) as an oil, $[\alpha]_D^{20}$ −37.6 (*c* 2.0, $CHCl_3$), and (1*R*,2*R*,3*S*)-1-*phenyl*-2,3-*epoxybutan*-1-*ol* (−)-**3b** (0.45 g, 15%, 98% e.e.) as an oil, $[\alpha]_D^{26}$ −31.7 (*c* 0.6, $CHCl_3$); δ_H(270 MHz;$CDCl_3$) 1.31 (3 H, d, *J* 5.3, CH_3), 2.96 (1 H, dd, *J* 2.0 and 5.3, PhC*H*O), 3.13 (1 H, dq, *J* 2.3 and 5.3, CHOC*H*CH_3), 4.50 [1H, bs, C*H*(OH)CH_3] and 7.26–7.42 (5 H, m, ArH).

Lithium Aluminum Hydride Reduction of the Epoxy Alcohol (−)-**3b**.—To a stirred suspension of $LiAlH_4$ (0.1 g, 2.63 mmol) in tetrahydrofuran (THF) (50 cm^3), a solution of the epoxyalcohol (−)-**3b** (0.15 g, 0.91 mmol) in THF (5 cm^3) was added dropwise at 0 °C under a nitrogen atmosphere, and the reaction mixture was refluxed for 30 min. 10% Aqueous NaOH (6 cm^3) was added very slowly to the mixture at 0 °C, and the precipitated solid was filtered off. The THF extracts were dried (Na_2SO_4) and evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (8 g) using CH_2Cl_2–MeOH (99.5:0.5) as eluent to give (1*R*,2*R*)-1-phenylbutane-1,2-diol (−)-**4a** (0.065 g, 16%, 98% e.e.) as an oil, $[\alpha]_D^{20}$ −31.6 (*c* 6.7, $CHCl_3$); δ_H(400 MHz;$CDCl_3$) 0.94 (3 H, t, *J* 7.3, CH_3), 1.32–1.43 (2 H, m, CH_2), 3.57–3.64 (1 H, m, C*H*CH_2CH_3), 4.44 (1 H, d, *J* 6.6, PhC*H*OH) and 7.26–7.38 (5 H, m, ArH). Further elution [CH_2Cl_2–MeOH (99:1)] afforded a colourless oil, whose ^1H NMR spectrum was identical with that of (1*S*,3*S*)-(−)-**5a** (0.0024 g, 43%, 98% e.e.) $[\alpha]_D^{23}$ −48.3 (*c* 1.8, $CHCl_3$).

Absolute Configuration at C-1 *in the Epoxy Alcohol* (-)-**3b**.—The absolute configuration at C-1 in (−)-**3b** was determined by a modified Mosher method, in which the epoxy alcohol (−)-**3b** was converted into the corresponding esters of (*R*)-(+)- and (*S*)-(−)-methoxy(trifluoromethyl)phenylacetic acid, (*R*)-(+)-MTPA ester **6a** (*S*)-(−)-MTPA ester **6b**, respectively. The absolute configuration at C-1 was determined from the chemical shift-differences of Δδ-values ($\Delta\delta = \delta$**6a** − δ**6b**) of 1-H and 3-H of compounds **6a** and **6b** in the ^1H NMR spectrum as shown in Fig. 1.

Asymmetric Reduction of 1-*Phenylbutane*-1,3-*dione* **7** *with Baker's Yeast*.—A mixture of 1-phenylbutane-1,3-dione **7** (2.4 g, 14.8 mmol) and baker's yeast (500 g) in distilled water (300 cm^3) was incubated for 48 h at 30 °C. The mixture was then extracted with $CHCl_3$ using a Soxlet apparatus and the $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g) using CH_2Cl_2 as eluent to give (+)-3-*hydroxy*-1-*phenylbutan*-1-*one* (+)-**8** (1.4 g, 61%, 77% e.e.) as an oil, $[\alpha]_D^{24}$ +46.2 (*c* 4.8, $CHCl_3$); δ_H(270 MHz;$CDCl_3$) 1.3 (3 H, d, *J* 6.3, CH_3), 3.1 (2 H, m, CH_2), 4.4 (1 H, dd, *J* 3.0 and 6.3, C*H*OH) and 7.7 (5 H, m, ArH). In addition, 1-phenylbutane-1,3-diol **5** (1% >, 46% e.e.) and the enone **9** (3%) were isolated.

(S)-(+)-3-*Hydroxy*-1-*phenylbutan*-1-*one* (+)-**8**.—To a solution of 3-hydroxy-1-phenylbutan-1-one (+)-**8** (77% e.e., prepared by use of baker's yeast) (0.4 g, 2.4 mmol), vinyl acetate (1 5 g, 17.4 mmol) and *tert*-butyl methyl ether (100 cm^3), lipase PS (Amano) (400 mg) was added and the mixture stirred for 10 days at 30 °C. Esterification was monitored by ^1H NMR (60 MHz). The lipase PS was then filtered off, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (13 g) using hexane–CH_2Cl_2(1:1) as eluent to give the hydroxy ketone (*S*)-(+)-**8** (0.11 g, 54%, 98% e.e.) as an oil, $[\alpha]_D^{24}$ +68.4 (*c* 3.6, $CHCl_3$) [lit.,[7] $[\alpha]_D^{25}$ +66 (*c* 0.04, $CHCl_3$) for *S*]; δ_H(270 MHz; $CDCl_3$) 1.3 (3 H, d, *J* 6.3, CH_3), 3.1 (2 H, m, CH_2), 4.4 (1 H, dd, *J* 3.0 and 6.3, C*H*OH) and 7.7 (5 H, m, ArH).

(1S,3S)- *and* (1R,3S)-1-*Phenylbutane*-1,3-*diyl Diacetates* (−)-**11a** and (+)-**11b**.—The ketol (+)-**8** (98% e.e., 0.294 g, 1.79 mmol) was allowed to react with sodium borohydride (0.15 g, 3.7 mmol) in methanol (20 cm^3) at 0 °C for 1 h to give a mixture of (1S,3S)- and (1R,3S)-1-*phenylbutane*-1,3-*diols* (−)-**5a** and (+)-**5b** (0.287 g, 97%). Without further purification, the mixture was treated with acetic anhydride (2 cm^3) in pyridine (3 cm^3) at room temp. for 15 h. The mixture was extracted with $CHCl_3$, and the extracts were washed sequentially with saturated aqueous $NaHCO_3$, 10% HCl and saturated brines dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g) using hexane–CH_2Cl_2(1:1) as eluent to give the (1*S*,3*S*)-1,3-diacetate (−)-**11a** (0.092 g, 26%, 98% e.e.) as an oil, $[\alpha]_D^{24}$ −54.2 (*c* 3.6, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 6.3, CH_3), 1.99 (3 H, s, OAc), 2.06 (3 H, s, OAc), 1.89–1.97 and 2.24–2.35 (each 1 H, m, CH_2), 4.80 (1 H, dq, *J* 6.3, 6.9, C*H*CH_3), 5.81 (1 H, t, *J* 6.9, ArC*H*) and 7.26–7.37 (5 H, m, Ar). Further elution afforded the (1*R*,3*S*)-1,3-diacetate (+)-**11b** (0.095 g, 27%, 98% e.e.) as an oil, $[\alpha]_D^{23}$ +46.9 (*c* 2.8, $CHCl_3$); δ_H(400 MHz;$CDCl_3$) 1.25 (3 H, d, *J* 6.3, CH_3), 2.00 (3 H, s, OAc), 2.04 (3 H, s, OAc), 1.98–2.09 (2 H, m, CH_2), 5.01–5.08 (1 H, m, C*H*CH_3), 5.83 (1 H, dd, *J* 4.6, 9.6, ArC*H*) and 7.25–7.34 (5 H, m, ArH).

(1S,3S)-1-*Phenylbutane*-1,3-*diol* (−)-**5a**.—To a solution of the diacetate (1*S*,3*S*)-(−)-**11a** (0.092 g, 0.37 mmol) in MeOH (10 cm^3), was added 10% NaOH (5 cm^3) and the mixture stirred for 5 h at room temperature. The solution was extracted with $CHCl_3$ and the extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (−)-**5a** (0.039 g, 62%) as an oil, $[\alpha]_D^{23}$ −43.3 (*c* 7.8, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 1.22 (3 H, d, *J* 6.3, CH_3), 1.71–1.92 (2 H, m, CH_2), 4.14 (1 H, m, C*H*CH_3), 4.94 (1 H, dd, *J* 3.3, 9.6, PhC*H*) and 7.26–7.36 (5 H, m, ArH). The ^1H NMR spectrum was identical with that reported.[6]

(1R,3S)-1-*Phenylbutane*-1,3-*diol* (+)-**5b**.—Following the above procedure, the diacetate gave the diol (+)-**5b** (0.039 g, 64%) as an oil $[\alpha]_D^{23}$ +61.1 (*c* 3.4, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 1.24 (3 H, d, *J* 6.3, CH_3), 1.79–1.96 (2 H, m, CH_2), 4.06 (1 H, m, C*H*OH), 5.05 (1 H, dd, *J* 4.0 and 7.6, PhC*H*) and 7.26–7.36 (5 H, m, ArH).

Sodium Borohydride Reduction of 1-*Phenyl*-2,3-*epoxybutan*-1-*one* **2**.—To a solution of the epoxy ketone **2** (3 g, 18.5 mmol) in MeOH (60 cm^3), $NaBH_4$ (1.8 g, 47.6 mmol) was added at 0 °C and the mixture stirred for 1 h. The mixture was then extracted with $CHCl_3$ and the extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (140 g) using CH_2Cl_2 as eluent to give the epoxy alcohols as an inseparable diastereoisomeric mixture (−)-**3a** and (+)-**3c** (1.31 g, 44%); and (−)-**3b** and (+)-**3d** (1.15 g, 39%).

Kinetic Resolution of the Diastereoisomeric Mixture (−)-**3a**, (+)-**3c** *with Lipase PS*.—*General Procedure*. (a) *Synthesis of* (1S,2R,3S)-1-*phenyl*-2,3-*epoxybutyl acetate* (+)-**12a**. To a solution of a mixture of the epoxy alcohols (−)-**3a** and (+)-**3c** (0.3 g, 1.82 mmol), vinyl acetate (1.5 g, 17.4 mmol) and *tert*-butyl methyl ether (100 cm^3), lipase PS (Amano) (300 mg) were added and the mixture was stirred for 4.5 h at 30 °C. Esterification was monitored by ^1H NMR (60 MHz). The lipase PS was then filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (12 g) using hexane–CH_2Cl_2(1:1) as eluent to give (1*S*,2*R*,3*S*)-(+)-**12a** (0.129 g, 43%) as an oil, $[\alpha]_D^{22}$ +42.2 (*c* 5.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.30 (3 H, d, *J* 5.3, CH_3), 2.10 (3 H, s, $COCH_3$), 2.94–3.00 [2 H, m, CH(OAc)-C*H*C*H*CH_3], 5.80 (1 H, d, *J* 4.3, PhC*H*OAc) and 7.25–7.65 (5 H, m, ArH). Further elution afforded the epoxy alcohols (−)-**3a** but in low optical yield. The synthesis of (−)-**3a** of high optical activity is described in the following experiment.

(b) *Synthesis of* (1R,2S,3R)-1-*phenyl*-2,3-*epoxybutan*-1-*ol* (−)-**3a**. To a solution of racemic mixture of the epoxy alcohols (−)-**3a** and (+)-**3c** (0.3 g, 1.82 mmol), vinyl acetate (1.5 g, 17.4 mmol) and *tert*-butyl methyl ether (100 cm^3), lipase PS (Amano) (300 mg) were added and the mixture was stirred for 6.5 h at 30 °C. Work-up as in (a) gave (1*R*,2*S*,3*R*)-(−)-**3a** (0.090 g, 30%) as an oil, $[\alpha]_D^{22}$ −53.6 (*c*. 2.1, $CHCl_3$), δ_H (270 MHz; $CDCl_3$) 1.29 (3 H, d, *J* 5.3, CH_3), 2.93–2.95 [1H, m, PhCH(OH)C*H*(O)], 3.23 (1 H, dq, *J* 2.3, 3.0, C*H*CH_3), 4.81 (1 H, br s, *J* 4.3, PhC*H*) and 7.25–7.38 (5 H, m, ArH). In addition, the acetate (+)-**12a** was also isolated but in low optical yield.

Kinetic Resolution of the Diastereoisomeric Mixture (−)-**3b** *and* (+)-**3d** *with Lipase PS*.—(a) (1S,2S,3R)-1-*Phenyl*-2,3-*epoxybutyl* 1-*acetate* (+)-**12b**. To a solution of racemic mixture of the epoxy alcohols (−)-**3b** and (+)-**3d** (0.3 g, 1.82 mmol), vinyl acetate (1.5 g, 17.4 mmol) and *tert*-butyl methyl ether (100 cm^3), lipase PS (Amano) (300 mg) were added and the mixture was stirred for 26 h at 30 °C. Work-up as described gave the acetate (1*S*,2*S*,3*R*)-(+)-**12b** (0.144 g, 48%) as an oil, $[\alpha]_D^{23}$ +62.7 (*c* 2.0, $CHCl_3$); δ_H(270 MHz;$CDCl_3$) 1.28 (3 H, d, *J* 5.3, CH_3), 2.12 (3 H, s, $COCH_3$), 2.97–3.06 (2 H, m, CHOCH), 5.54 (1 H, d, *J* 6.6, PhC*H*OAc) and 7.32–7.37 (5 H, m, ArH). In addition, the epoxy alcohol (−)-**3b** was recovered but in low optical yield.

(b) *Synthesis of* (1R,2R,3S-)-1-*phenyl*-2,3-*epoxybutan*-1-*ol* (−)-**3b**. To a solution of a racemic mixture of the epoxy alcohols (−)-**3b** and (+)-**3d** (0.26 g, 15.8 mmol), vinyl acetate (1.5 g, 17.4 mmol) and *tert*-butyl methyl ether (100 cm^3), lipase PS (Amano) (300 mg) were added and the mixture was stirred for 48 h at 30 °C work-up as described gave (1*R*,2*R*,3*S*)-(−)-**3b** (0.110 g, 42%, 96% e.e.) as an oil, $[\alpha]_D^{23}$ −31.4 (*c* 3.7, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.31 (3 H, d, *J* 5.3, CH_3), 2.95 (1 H, dd, *J* 2.3 and 5.6, OC*H*CH_3), 3.12 [1 H, dd, *J* 2.3 and 5.3,

CH(OH)C*H*O], 4.49 (1 H, d, *J* 5.3 PhC*H*OH), 7.26–7.42 (5 H, m, ArH). In addition, the acetate (+)-**12b** was also isolated, but in low optical yield.

Reduction of (1S,2R,3S)-1-*Phenyl*-2,3-*epoxybutyl Acetate* (+)-**12a** *with* $LiAlH_4$. *General Procedure.*—To a stirred suspension of $LiAlH_4$ (0.15 g, 3.98 mmol) in THF (50 cm^3), a solution of the epoxy acetate (+)-**12a** (0.156 g, 0.86 mmol) in THF (50 cm^3) was added dropwise at 0 °C under a nitrogen atmosphere, and the reaction mixture was refluxed for 30 min. 10% Aqueous NaOH was added very slowly to the mixture at 0 °C, and the precipitated solid was filtered off. The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (8 g) using CH_2Cl_2–MeOH (99.5:0.5) as the eluent to give (1S,2R)-1-*phenylbutane*-1,2-*diol* (+)-**4b** (0.024 g, 15%, 98% e.e.) as an oil $[\alpha]_D^{23}$ + 39.4 (*c* 5.3, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.3, CH_3), 1.21–1.37 (2 H, m, CH_2), 3.73–3.76 (1 H, m, C*H*CH_2CH_3), 4.68 (1 H, d, *J* 4.3, PhC*H*OH) and 7.26–7.37 (5 H, m, ArH). Further elution [CH_2Cl_2–MeOH (99:1)] afforded (1*R*,3*S*)-1-phenylbutane-1,3-diol (+)-**5b**[6] (0.055 g, 35%, 98% e.e.) as an oil, $[\alpha]_D^{20}$ + 68.3 (*c* 8.4, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.3, CH_3), 1.74–1.92 (2 H, m, CH_2), 4.03 (1 H, m, C*H*CH_3), 5.00 (1 H, dd, *J* 3.3, 7.6, PhC*H*) and 7.21–7.33 (5 H, m, ArH). The ^1H NMR spectrum was identical with that reported.[6]

Reduction of (1R,2S,3R)-1-*phenyl*-2,3-*epoxybutan*-1-*ol* (−)-**3a** *with* $LiAlH_4$. To a stirred suspension of $LiAlH_4$ (0.2 g, 5.2 mmol) in THF (50 cm^3), a solution of the epoxy alcohol (−)-**3a** (0.21 g, 1.28 mmol) in THF (50cm^3) was added dropwise at 0 °C under nitrogen atmosphere. Reaction, work-up and purification as in the general procedure gave (1R,2S)-1-*phenylbutane*-1,2-*diol* (−)-**4c** (0.042 g, 20%, 98% e.e.) as an oil, $[\alpha]_D^{24}$ − 38.3 (*c* 2.9, $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.3, CH_3), 1.20–1.49 (2 H, m, CH_2), 3.71–3.77 (1 H, m, CHC*H*C_2H_5), 4.68 (1 H, d, *J* 4.6, PhC*H*) and 7.34 (5 H, s, ArH). Further elution [CH_2Cl_2–MeOH (99:1)] gave (1*S*,3*R*)-1-phenylbutane-1,3-diol (−)-**5c** (0.124 g, 59%, 98% e.e.) as an oil. The ^1H NMR spectrum was identical with that reported:[6] $[\alpha]_D^{23}$ − 65.0 (*c* 3.4, $CHCl_3$).

Reduction of (1S,2S,3R)-1-*phenyl*-2,3-*epoxybutyl acetate* (+)-**12b** *with* $LiAlH_4$. To a stirred suspension of $LiAlH_4$ (0.18 g, 4.73 mmol) in THF (50 cm^3), a solution of the acetate (+)-**12b** (0.175 g, 0.96 mmol) in THF (50 cm^3) was added dropwise at 0 °C under a nitrogen atmosphere. Reaction, work-up and purification as in the general procedure gave (1S,2S)-1-*phenylbutane*-1,2-*diol* (+)-**4d** (0.074 g, 54%, 98% e.e.) as an oil, which was characterized by comparison of its ^1H NMR spectrum with that of the (1*R*,2*R*)-isomer: $[\alpha]_D^{22}$ + 34.4 (*c* 1.1, $CHCl_3$). Further elution [CH_2Cl_2–MeOH (99:1)] gave (1R,3R)-1-*phenylbutane*-1,3-*diol* (+)-**5d** (0.018 g, 8%, 98% e.e) as an oil, which was characterized by comparison of its ^1H NMR spectrum with that of the (1*S*,3*S*)-isomer: $[\alpha]_D^{22}$ + 49.4 (*c* 0.8, $CHCl_3$).

Reduction of (1R,2R,3S)-1-*phenyl*-2,3-*epoxybutan*-1-*ol* (−)-**3b** *with* $LiAlH_4$. To a stirred suspension of $LiAlH_4$ (0.15 g, 3.95 mmol) in THF (50 cm^3), a solution of the epoxyalcohol (−)-**3b** (0.162 g, 0.99 mmol) in THF (50 cm^3) was added dropwise at 0 °C under a nitrogen atmosphere. Reaction, work-up and purification as in the general procedure gave an oil, which was identical with (1*R*,2*R*)-1-phenylbutane-1,2-diol (−)-**4a** (0.059 g, 36%, 96% e.e.), $[\alpha]_D^{23}$ − 33.8 (*c* 3.1, $CHCl_3$). Further elution [CH_2Cl_2–MeOH (99:1)] gave a colourless oil (0.013 g, 8%, 96% e.e.), which was identical with (1*S*,3*S*)-(−)-**5a**: $[\alpha]_D^{24}$ − 48.9 (*c* 0.8, $CHCl_3$).

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References

1 R. Csuk and B. I. Glanzer, *Chem. Rev.*, 1991, **91**, 49; J. B. Jones, *Tetrahedron*, 1986, **42**, 3351.
2 A. M. Klibanov, *Acc. Chem. Res.*, 1990, **23**, 114.
3 M. Takeshita, R. Yaguchi and N. Akutsu, *Tetrahedron Asymmetry*, 1992, **3**, 1369; M. Takeshita and N. Akutsu, *Tetrahedron Asymmetry*, 1992, **3**, 1381; M. Takeshita and T. Sato, *Chem. Pharm. Bull.*, 1989, **37**, 1085.
4 B. J. Price and S. M. Roberts, in *Medicinal Chemistry, The Role of Organic Chemistry In Drug Research*, Academic Press, 1985; Y. Terao, M. Murata and K. Achiwa, *Tetrahedron Lett.*, 1988, **29**, 5137.
5 T. Kusumi, Y. Fujita, I. Ohtani and H. Kawasaki, *Tetrahedron Lett.*, 1992, **32**, 2923; S. Takano, M. Takahashi, M. Yanase, Y. Sekuguchi, Y. Iwabuchi and K. Ogasawara, *Chem. Lett.*, 1988, 1827; H. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
6 M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 629 and supplementary material.
7 A. Fauve and H. Veshambre, *J. Org. Chem.*, 1988, **54**, 5215.

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