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Diastereoselective Synthesis of β-Hydroxy Sulfoxides: Enzymatic and Biomimetic Approaches

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Stereoselectivities of up to 98 % have been found in the enzymatic synthesis of β-hydroxy sulfoxides catalyzed by cyclohexanone monooxygenase (CHMO). The diastereoselectivity of the "one-pot" preparation of the title compounds in the presence of bovine serum albumin has also been investigated.

Introduction

Chiral β-hydroxy sulfoxides are well known for their usefulness as chiral auxiliaries in asymmetric synthesis either as ligands[1] or as building blocks for the preparation of a great variety of compounds such as cyclic sulfides,[2] benzoxathiepines,[3] benzothiazepines,[4] allylic alcohols,[5] macrolides[6] and leukotrienes.[7]

So far, optically active β-hydroxy sulfoxides have been obtained either by aldol-type reactions of α-sulfinyl anions with carbonyl compounds[8] or by reduction of β-keto sulfoxides with various hydride transfer agents.[9] Another procedure involves optically active β-hydroxy sulfides, obtained by addition of thiolates to enantiomerically pure epoxides,[10] followed by chemical oxidation with *t*BuOOH. A more direct approach is the asymmetric oxidation of racemic β-hydroxy sulfides; Modena and Kagan and their co-workers used systems based on titanium(IV), diethyl tartrate and an alkyl hydroperoxide as oxidizing agent and obtained fairly good enantiomeric excesses (20–80%).[11]

In view of the synthetic importance of optically pure β-hydroxy sulfoxides we have investigated the possibility of the asymmetric oxidation of β-hydroxy sulfides with cyclohexanone monooxygenase (CHMO) from *Acinetobacter calcoaceticus*. CHMO is a bacterial Baeyer–Villigerase that converts cyclic ketones into the corresponding lactones.[12] CHMO also catalyzes the oxygenation of boronic acids as well as cyclic and aryl alkyl sulfides, selenides and tertiary alkylamines.[13] What makes CHMO attractive for synthetic purposes is the fact that these reactions can proceed with exquisite selectivity with a wide variety of natural and synthetic substrates. Furthermore these biocatalytic oxidation reactions are less hazardous and polluting than conventional chemistry-based methodologies. Thus this enzyme has been used as a chemoenzymatic reagent for the large-scale synthesis of a variety of key chiral products.[14]

With the same purpose in mind, the asymmetric oxidation of β-hydroxy sulfides in the presence of bovine serum albumin (BSA) in a one-pot procedure was investigated (BSA/*t*BuOOH). BSA is an abundant carrier protein with no known catalytic function that possesses well-defined hydrophobic binding sites for a variety of hydrophobic substrates.[15] This makes such a readily available and inexpensive protein an attractive template for asymmetric oxidation. Indeed, BSA, like other carrier proteins, specifically binds and transfers a solute molecule across lipid membranes similarly to a specialized membrane-bound enzyme. In the last few years our research group has investigated some enantioselective reactions with BSA in water as solvent, in particular, the oxidation of sulfides to sulfoxides,[16] the catalytic asymmetric Weitz–Scheffer epoxidation of 1,4-naphthoquinones[17] and the kinetic dynamic resolution of tertiary amines to amine *N*-oxides.[18] The choice of water as solvent presents several advantages: water is cheap, readily available and nontoxic. The resulting process is economic and clearly constitutes an environmentally friendly solvent-alternative in organic synthesis.

Results and Discussion

The oxidation of different β-hydroxy sulfides was investigated using cyclohexanone monooxygenase as the catalyst or under biomimetic conditions. All the *trans* β-hydroxy sulfides were easily synthesized according to a standard procedure.[19]

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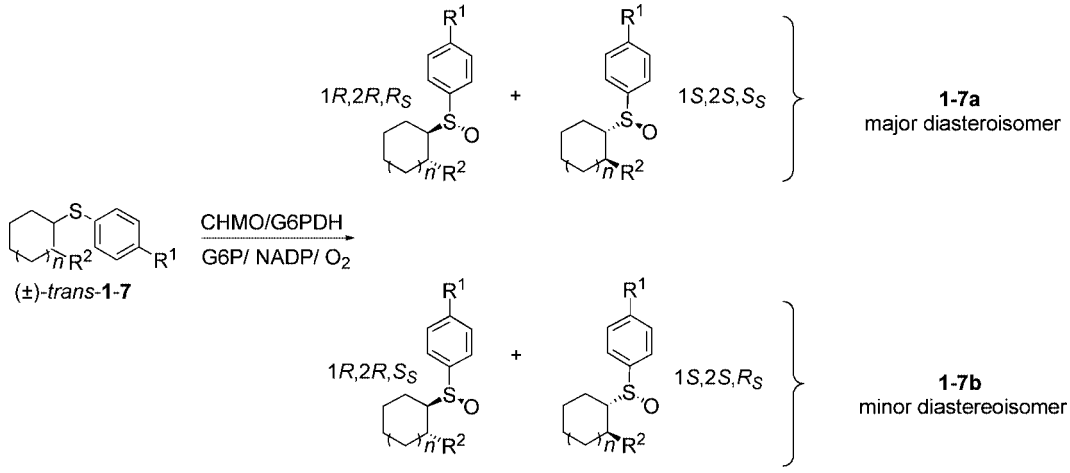
The asymmetric sulfoxidation of racemic *trans* β-hydroxy sulfides (±)-**1**–**7** catalyzed by CHMO led to kinetic resolution (see Scheme 1). The diastereomeric ratios were determined by comparison of the NMR spectra with those reported in literature.[20]

Excellent results were obtained in the oxidation of sulfide (±)-**2** (Table 1); the enzyme-catalyzed oxidation in fact showed remarkable enantio- and diastereoselectivity. The enantiomeric ratio *E*, calculated according to Chen et al.,[21] was about 299, which implies that the sulfide enantiomer (1*S*,2*S*) was almost exclusively recognised and transformed. Similarly, the high diastereomeric ratio of up to 99:1 indicates that oxygen was introduced almost solely in the *pro*-*S* position of the sulfur atom to give the sulfoxide with the absolute configuration (1*S*,2*S*,S_S). Note that the optical purities of both the major **2a** (*ee* ≥ 98%) and the minor **2b** (*ee* ≥ 95%) diastereomers were very high (Table 1). The unreacted sulfide **2** was recovered with a good *ee* and its absolute configuration was identified as (1*R*,2*R*) by comparison of its optical rotation value with that reported in the literature: *ee* = 47%, $[a]_D$ = –31.3 (*c* = 0.5, $CHCl_3$) (see the Exp. Sect.).[22] The absolute configurations of the two products **2a** and **2b** were established by comparison of the order of elution of appropriate samples synthesized according to a well-known procedure.

CHMO discriminated poorly the enantiomeric substrates of the sulfides (±)-**1** and (±)-**3** ($1.6 < E < 4.3$) (Table 1); with these substrates the diastereomeric ratios were also



Scheme 1. Oxidation of β-hydroxy sulfides (±)-*trans*-**1**–**7** to β-hydroxy sulfoxides catalyzed by CHMO.

Table 1. Oxidation of β-hydroxy sulfides (±)-*trans*-**1**–**7** to β-hydroxy sulfoxides catalyzed by CHMO.

Sulfides		Time [h]	*C* [%][a]	*ee* Sulfides [%][a]	Diastereomeric ratio[a] major/minor	ee_{major} [%][a]	ee_{minor} [%][a]
(±)-**1**	*n* = 0	24	97	69 (1.6)[b]	83:17	53	91
	R^1 = H,						
	R^2 = OH						
(±)-**2**	*n* = 1	1	36	47 (261)[b]	>99:1	≥98	–
	R^1 = H,	5	47	87 (299)[b]	99:1	≥98	≥95
	R^2 = OH					(1*S*,2*S*,S_S)	(1*R*,2*R*,S_S)
(±)-**3**	*n* = 2	1	52	50 (4.3)[b]	89:11	63	56
	R^1 = H,	3	78	79 (3.3)[b]	82:18	45	78
	R^2 = OH						
(±)-**4**	*n* = 1	5	21	8 (2.0)[b]		3 peaks 4:1.5:1 ratio[c]	
	R^1 = OCH_3	48	95	13 (1.1)[b]		3 peaks 8:3:1 ratio[c]	
	R^2 = OH						
(±)-**5**	*n* = 1	48	n.r.[d]				
	R^1 = H						
	R^2 = OCH_3						
(±)-**6**	*n* = 1	48	n.r.[d]				
	R^1 = H						
	R^2 = OC-OCH_3						
(±)-**7**	*n* = 1	48	n.r.[d]				
	R^1 = NO_2						
	R^2 = OH						

[a] The conversions, *C*, diastereomeric ratios and enantiomeric excesses were determined by HPLC analysis using an OD CHIRALCEL column. [b] Enantiomeric ratio, *E*. [c] Configuration not assignable. [d] n.r.: no reaction.

rather modest, but the enantiomeric excesses fairly good (45–91%). These results show that for enzymatic sulfoxidation mediated by CHMO the presence of a six-membered ring is essential for obtaining optically pure β-hydroxy sulfoxides.

With the sulfide (±)-**2**, the crucial role, in terms of reactivity, played by the hydroxy group in the β position and the hydrogen atom in the *para* position must be stressed. Indeed, when the hydroxy group was replaced by a methoxy [(±)-**5**] or an acetoxy group [(±)-**6**], the sulfides were not transformed by the enzyme. When the hydrogen atom in the *para* position was replaced by a methoxy group [(±)-**4**] the diastereomeric ratio decreased noticeably whereas the nitro compound (±)-**7** did not act as a substrate at all with CHMO.

The same β-hydroxy sulfides (±)-**1**–**4** and (±)-**7** were also studied by a biomimetic approach based on a one-pot in situ thiolysis of the parent epoxides according to known methods,[20] followed by BSA/*t*BuOOH oxidation. The thiolysis of the epoxides was a stereospecific process that proceeded in an *anti* fashion and led to (±)-*trans*-β-hydroxy sulfides as the only products.[20] This reaction was carried out in a water/buffer solution at pH 9.0 and then a BSA/*t*BuOOH solution was added. Ring-opening of cyclopentene oxide with thiophenol gave the β-hydroxy sulfoxides **1a** and **1b** with high conversion and low *ee* (Table 2).

The control reactions carried out without BSA gave diastereomeric ratios lower than those obtained in the biomimetic reactions with the exception of the cyclopentenyl derivative **1** for which the diastereomeric ratio was higher (78:22) than that obtained with BSA (Table 2).

When cyclohexene oxide and thiophenol were used as the starting materials in the one-pot procedure the diastereomeric ratio of the β-hydroxy sulfoxides **2a/2b** was 72:28, similar to that reported by Fringuelli et al.[20] Note that the same reaction performed in the presence of BSA as chiral auxiliary was almost completely diastereoselective (95:5). However the prevailing diastereoisomer was obtained in a racemic form.

Replacement of thiophenol by *p*-methoxythiophenol again provided the corresponding β-hydroxy sulfoxides (**4a**, **4b**) with a very high diastereomeric ratio and low *ee*. When *p*-nitrothiophenol was used the reaction proceeded with low diastereoselectivity and the products obtained (**7a**, **7b**) were in a racemic form.

Cycloheptene oxide was not reactive enough and so we decided to use a different strategy involving the introduction of a Lewis acid such as $ZnCl_2$ into the reaction mixture in order to promote the formation of the β-hydroxy sulfide (±)-**3**, in accord with a well-known procedure.[23] $ZnCl_2$ increased the rate of epoxide opening, the yield and the conversion of the one-pot procedure. It had however detrimental effects on the diastereoselectivity of the reaction when carried out in the presence of BSA. This is possibly due to conformational changes to the protein induced by the chelation of Zn^{2+} ions to the external histidine group of the polypeptide.[24]

Also, for the BSA-mediated oxidation reactions, the role of the hydroxy group in the β position was significant. Indeed, the reactions of sulfides (±)-**5** and **8** with BSA/*t*BuOOH gave higher conversions but lower diastereoselectivities in the case of **5a**,**5b** (Table 3) with respect to sulfoxides **2a**,**2b**. Furthermore, in contrast with the enzyme-catalyzed reaction, racemic products were obtained.

The thiolysis of styrene oxide by thiophenol was also investigated in a one-pot reaction as an example of an α-substituted 1,2-epoxide. Nucleophilic attack occurred predominantly at the benzylic position due to electronic effects and the primary alcohol (±)-**10** was obtained in a 2:1 ratio with respect to the secondary alcohol (±)-**9** (Scheme 2). Subsequent sulfoxidation to give compounds **9a**,**b** and **10a**,**b** occurred again with low enantioselectivity.

Table 2. One-pot synthesis of β-hydroxy sulfoxides **1**–**7a**,**b** by thiolysis of the corresponding epoxides and subsequent oxidation with BSA/*t*BuOOH.

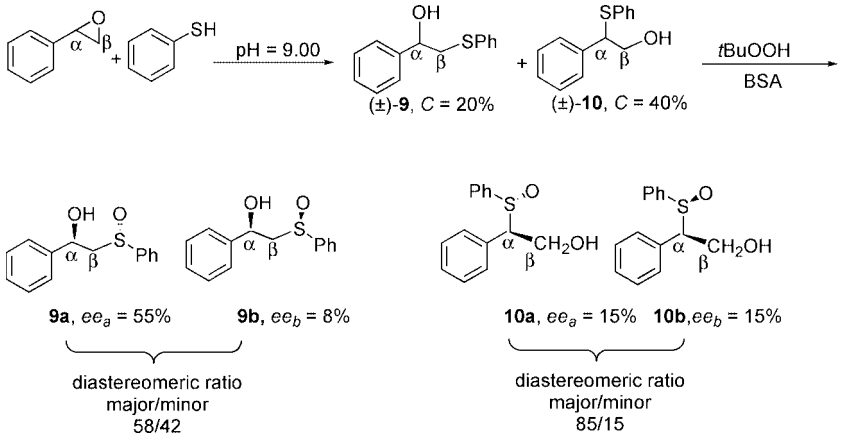
Sulfoxides	BSA [mol. equiv.]	$ZnCl_2$ [mol. equiv.]	*C* [%][a]	Diastereomeric ratio[b] major/minor	ee_{major} [%][a]	ee_{minor} [%][a]
1a,**b**	–	–	85	78:22	–	–
	0.025	–	95	69:31	15	10
2a,**b**	–	–	70	72:28	–	–
	0.025	–	45	95:5	<3	<3
	–	0.10	95	69:31	–	–
	0.025	0.10	65	74:26	<3	<3
3a,**b**	–	–	n.r.[c]	–	–	–
	0.025	–	n.r.[c]	–	–	–
	–	0.10	23	75:25	–	–
	0.025	0.10	43	85:15	<3	<3
4a,**b**	–	–	85	75:25	–	–
	0.025	–	95	>98:2	5	n.d.[d]
7a,**b**	–	–	35	63:37	–	–
	0.025	–	45	74:26	<3	<3

[a] Determined by ^1H NMR spectroscopy. [b] The diastereomeric ratios and the enantiomeric excesses were determined by HPLC analysis using an OD CHIRALCEL column. [c] n.r.: no reaction. [d] n.d.: not determined.

Table 3. Oxidation of sulfides (±)-**5** and **8** with BSA/*t*BuOOH.

Sulfide		BSA [mol. equiv.]	*C* [%][a]	Diastereomeric ratio[b] major/minor	ee_{major} [%][a]	ee_{minor} [%][a]
5	$n = 1$	–	15	57:43	–	–
	$R^1 = H$	0.025	52	68:32	<3	<3
	$R^2 = OCH_3$					
8	$n = 1$	–	34	n.a.[c]	–	–
	$R^1 = H$	0.025	59	n.a.[c]	<3	<3
	$R^2 = H$					

[a] Determined by ^{1}H NMR spectroscopy. [b] The diastereomeric ratios and the enantiomeric excesses were determined by HPLC analysis using an OD CHIRALCEL column. [c] n.a. = not applicable.



Scheme 2. One-pot sulfoxidation using styrene oxide and thiophenol as the starting materials.

Conclusions

The kinetic resolution of β-hydroxy sulfides mediated by CHMO provided an excellent result in the case of sulfide (±)-**2** and moderate results with (±)-**1** and (±)-**3**. Indeed, the enzyme-catalyzed oxidation to sulfoxide **2a** showed remarkable enantio- and diastereoselectivity with an enantiomeric ratio $E = 299$ and with an $ee \geq 98\%$ ($C = 47\%$). CHMO did not transform those substrates having a protected hydroxy group [(±)-**5**, (±)-**6**].

In the one-pot procedure, the presence of BSA as chiral auxiliary led to a substantial improvement in the diastereoselectivity of the β-hydroxy sulfoxides formed, but the products were practically racemic. Such results could possibly be a consequence of the poor immobilization of the β-hydroxy sulfides onto the binding site of BSA.

Addition of $ZnCl_2$ to the one-pot procedure with the recalcitrant starting oxirane (cycloheptene oxide) had a positive effect on the reaction rates and chemical yields.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 300 or AC 200 instrument in $CDCl_3$ solutions and chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm). Low-resolution mass spectra were recorded with a Fisons MD 800 spectrometer using the EI method. Analytical HPLC analyses were performed with a Jasco HPLC instrument (model 980-PU pump, model 975-UV detector) on a chiral stationary phase using a Daicel Chiralcel OD column and hexane/2-propanol in various ratios as the mobile phase at a flow rate of 1 mL min^{-1}; readings were taken at 254 nm. Melting points were recorded with a Stuart Scientific apparatus. Infrared spectra were recorded with an FT-IR Perkin-Elmer SPECTRUM ONE spectrophotometer using thin films between NaCl plates in the cases of liquid samples and as KBr tablets for solid samples. Chemical reactions were monitored by analytical TLC performed with Merck silica gel 60 F_{254} plates and visualized by UV irradiation or by iodine. For column chromatography, columns were packed with Merck silica gel 60 (230–400 mesh) as the stationary phase and eluted using the flash chromatographic technique. All commercially available compounds were used without further purification. CHMO was obtained from *Acinetobacter calcoaceticus* as already described.[13b] β-Hydroxy sulfides **1**–**4** and **7** were synthesized according to known methods.[19]

Preparation of *trans*-2-Methoxycyclohexyl Phenyl Sulfide [(±)-5]: *n*BuLi (1.5 mmol, 1.6 M in hexane) was added under N_2 to a solution of the hydroxy sulfide (±)-**2** (1.5 mmol) in dry THF (20 mL) at –78 °C. The solution was stirred for 5 min and then iodomethane was added (1.5 mmol). The reaction mixture was stirred for 20 h at –78 °C and then allowed warm to room temperature. Then a mixture of 1:1 H_2O/Et_3N (5 mL) was added. The reaction mixture was extracted with diethyl ether (3 × 20 mL) and then washed with brine. The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure to provide the desired product. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 9:1) to give the product as a colourless oil. Yield 80 mg, 24%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.21–1.29 (m, 4 H, 3-H, 4-H), 1.72–1.80 (m, 2 H, 6-H), 1.95–2.02 (m, 2 H, 3-H), 2.10–2.20 (m, 1 H, 2-H), 3.13 (m, 1 H, 1-H), 3.38 (s, 3 H, CH_3), 7.25 (m, 3 H, Ar-H), 7.44 (m, 2 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 222 (100) $[M]^+$.

Preparation of *trans*-2-Acetoxycyclohexyl Phenyl Sulfide [(±)-6]: Acetic anhydride (1.5 mmol, 0.142 mL) was added to a stirred solu-

tion of **2** (312 mg, 1.5 mmol) in pyridine (5 mL). The reaction mixture was stirred overnight and then evaporated under reduced pressure. The crude was redissolved in diethyl ether (5 mL) and washed with a 1% HCl solution (2 mL) and brine (2 mL). The organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure to give the product **6** without the need of further purification. Yield 257 mg, 65%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.36–1.74 (m, 6 H, 4-H, 5-H, 6-H), 1.91 (s, 3 H, CH_3, 2.04–2.08 (m, 2 H, 3-H), 3.14 (m, 1 H, 2-H), 4.78 (m, 1 H, 1-H), 7.21–7.46 (m, 5 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 264 (100) $[M]^+$.

Analytical Biotransformations with CHMO: Sulfides (±)-**1**–**7** (1 mg mL^{-1}) were bio-oxidized, at 25 °C and under gentle stirring, in 50 mM Tris/HCl buffer (pH 8.6) containing 0.5 mM $NADP^+$, 50 mM glucose 6-phosphate, partially purified CHMO (1 U mL^{-1}) and glucose 6-phosphate dehydrogenase from *Leuconostoc mesenteroides* (G6PDH) (18 U mL^{-1}). The biotransformation process was monitored by withdrawing samples at different times from the reaction medium and extracting them with diethyl ether (1:1 volume). The degree of oxidation and the enantiomeric excesses of the products were determined on the extracts, evaporated and redissolved in propan-2-ol, by chiral HPLC on a Chiralcel OD column (Daicel, Illkirch, France) using the appropriate ratio of *n*-hexane/propan-2-ol as the mobile phase; readings were taken at 254 nm.

***trans*-2-(Phenylsulfinyl)cyclopentan-1-ol (1a):** Major diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 2:8) to give the product as a white solid; m.p. 102 °C. IR (KBr): $\tilde{\nu}$ = 3390, 3058, 1651, 1085, 1028 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.62–1.83 (m, 5 H, 3′-H, 4-H, 5-H), 2.07 (m, 1 H, 3′′-H), 3.02 (m, 2 H, 2-H, OH), 4.64 (m, 1 H, 1-H), 7.50 (m, 3 H, Ar-H), 7.77 (2 H, m Ar-H) ppm. EI-MS: *m*/*z* (%) = 210 (100) $[M]^+$.

***trans*-2-(Phenylsulfinyl)cyclopentan-1-ol (1b):** Minor diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 2:8) to give the product as a white solid; m.p. 97 °C. IR (KBr): $\tilde{\nu}$ = 3295, 3058, 1637, 1085, 1012 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.53–1.71 (m, 4 H, 4-H, 5-H), 1.84–2.06 (m, 3 H, 3-H, OH), 3.03 (m, 1 H, 2-H), 4.56 (m, 1 H, 1-H), 7.85 (m, 5 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 210 (100) $[M]^+$.

***trans*-2-(Phenylsulfinyl)cyclohexan-1-ol (2a):** Major diastereoisomer (1*S*,2*S*,S_S). The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid; m.p. 156–157 °C. IR (KBr): $\tilde{\nu}$ = 3444, 2931, 1628, 1077, 1002 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.11–1.40 (m, 6 H, 4-H, 5-H, 6-H), 1.73 (m, 2 H, 3-H), 2.75 (m, 1 H, 2-H), 3.03 (m, 1 H, 1-H), 4.16 (br. s, 1 H, OH), 7.55 (m, 3 H, Ar-H), 7.74 (m, 2 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 224 (100) $[M]^+$. $[\alpha]_D^{20}$ = –134 (*c* = 1.5, $CHCl_3$).

***trans*-2-(Phenylsulfinyl)cyclohexan-1-ol (2b):** Minor diastereoisomer (1*R*,2*R*,S_S). The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid; m.p. 138–139 °C. IR (KBr): $\tilde{\nu}$ = 3450, 2931, 1648, 1077, 1012 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.09–1.71 (m, 7 H, 3′-H, 4-H, 5-H, 6-H), 2.11 (m, 1 H, 3′′-H), 2.66 (m, 1 H, 2-H), 3.93 (m, 1 H, 1-H), 4.01 (br. s, 1 H, OH), 7.58 (m, 5 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 224 (100) $[M]^+$. $[\alpha]_D^{20}$ = +100.9 (*c* = 1.5, $CHCl_3$).

***trans*-2-(Phenylsulfinyl)cycloheptan-1-ol (3a):** Major diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid; m.p. 148 °C. IR (KBr): $\tilde{\nu}$ = 3353, 3059, 1579, 1050, 1014 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.19–1.90 (m, 10 H, 3-H, 4-H, 5-H, 6-H, 7-H), 2.85 (br. s, 1 H, OH), 2.94 (m, 1 H, 2-H), 4.32 (m, 1 H, 1-H), 7.56 (m, 3 H, Ar-H), 7.76 (2 H, m, Ar-H) ppm. EI-MS: *m*/*z* (%) = 238 (100) $[M]^+$.

***trans*-2-(Phenylsulfinyl)cycloheptan-1-ol (3b):** Minor diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 2:8) to give the product as a white solid; m.p. 125 °C. IR (KBr): $\tilde{\nu}$ = 3358, 3057, 1638, 1050, 1014 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.24–1.89 (m, 10 H, 3-H, 4-H, 5-H, 6-H, 7-H), 2.16 (br. s, 1 H, OH), 2.99 (m, 1 H, 2-H), 4.16 (m, 1 H, 1-H), 7.53 (m, 3 H, Ar-H), 7.88 (2 H, m Ar-H) ppm. EI-MS: *m*/*z* (%) = 238 (100) $[M]^+$.

***trans*-2-[(4-Methoxyphenyl)sulfinyl]cyclohexan-1-ol (4a):** Major diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid; m.p. 166 °C. IR (KBr): $\tilde{\nu}$ = 3358, 2934, 1594, 1254, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.11–1.73 (m, 7 H, 3′-H, 4-H, 5-H, 6-H), 2.07 (m, 1 H, 3′′-H), 2.69 (m, 1 H, 2-H), 3.83 (s, 3 H, CH_3), 4.03 (m, 1 H, 1-H), 5.18 (br. s, 1 H, OH), 7.00 (d, $J_{H,H}$ = 8.8 Hz, 2 H, Ar-H), 7.62 (d, $J_{H,H}$ = 8.8 Hz, 2 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 254 (100) $[M]^+$.

***trans*-2-[(4-Methoxyphenyl)sulfinyl]cyclohexan-1-ol (4b):** Minor diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid; m.p. 152 °C. IR (KBr): $\tilde{\nu}$ = 3390, 2936, 1594, 1251, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.04–1.49 (m, 6 H, 4-H, 5-H, 6-H), 1.92–2.09 (m, 2 H, 3-H), 2.67 (m, 1 H, 2-H), 3.84 (s, 3 H, CH_3), 3.88 (m, 1 H, 1-H), 4.74 (br. s, 1 H, OH), 7.02 (d, $J_{H,H}$ = 9.7 Hz, 2 H, Ar-H), 7.51 (d, $J_{H,H}$ = 9.7 Hz, 2 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 254 (100) $[M]^+$.

Preparation of Enantiopure Sulfide (1*S*,2*S*)-2: A mixture of racemic sulfide **2** (0.5 mmol), isopropenyl acetate (1 mmol) and lipase PS (Amano) (250 mg) in diisopropyl ether was stirred at 23 °C overnight. When about half of the substrate had been acetylated, the mixture was filtered and the solvent evaporated. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 8:2) to give the product as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.79–1.84 (m, 6 H, 3-H, 4-H, 5-H), 2.00–2.31 (m, 2 H, 3-H), 3.40 (dt, $J_{H,H}$ = 7.1, 14.1 Hz, 1 H, 2-H, 4.10 (dt, $J_{H,H}$ = 7.0, 13.9 Hz, 1 H, 1-H), 7,17–7.44 (m, 5 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 208 (100) $[M]^+$. $[\alpha]_D^{20}$ = +69.0 (*c* = 1.5, $CHCl_3$) [ref.[22] $[\alpha]_D^{20}$ = +71.9 (*c* = 1.21, $CHCl_3$)].

Preparation of Enantiopure Sulfoxides (1*S*,2*S*,S_S)-2a and (1*S*,2*S*,R_S)-2b: The sulfide (1*S*,2*S*)-**2** (0.25 mmol) was dissolved in dichloromethane (2 mL) and then oxidized with MCPBA (0.25 mmol) at 0 °C for 1 h. The reaction mixture was washed with a saturated solution of Na_2SO_3 (1 mL) and brine. The recovered organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The sulfoxides (1*S*,2*S*,S_S)-**2a** and (1*S*,2*S*,R_S)-**2b** were characterized, giving the data as shown above.

Analytical HPLC analyses were performed on a chiral stationary phase using a Daicel Chiralcel OD column and hexane/2-propanol in a ratio of 95:5 as the mobile phase. Retention times: (1*R*,2*R*)-**2** 6.69 min, (1*S*,2*S*)-**2** 10.76 min, (1*S*,2*S*,R_S)-**2b** 12.10 min, (1*R*,2*R*,S_S)-**2b** 15.38 min, (1*R*,2*R*,R_S)-**2a** 19.03 min, (1*S*,2*S*,S_S)-**2a** 21.31 min.

General Procedure for the One-Pot Preparation of β-Hydroxy Sulfoxides 1–4, 7 and 9,10a,b: The appropriate thiol (1.0 mmol) was added at room temperature to a phosphate buffer (2 mL) at pH 9.00. The resulting pH was adjusted to 9.00 by adding an aqueous 5 M solution of NaOH (20 μL) and then the epoxide

(0.66 mmol) was added. During the reaction the pH was kept constant at 9.00 by adding a 1% aqueous H_2SO_4 solution. After 3–6 h BSA (0.025 mol. equiv.) was added. The reaction mixture was stirred magnetically for 2 h and then *t*BuOOH (6.0 mol. equiv.) was added. The mixture was stirred for 15 h, chloroform (20 mL) was then added and the mixture left to stand overnight. The resulting slurry was filtered through a cake of Celite, dried with $MgSO_4$ and the solvent evaporated. The organic phase was purified by flash chromatography using the appropriate eluent.

1-Phenyl-2-(phenylsulfinyl)ethanol (9a): Minor diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 2:8) to give the product as a white solid. Yield 8 mg, 5%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.95 (m, 1 H), 3.30 (m, 1 H), 3.43 (br. s, 1 H, OH), 5.37 (m, 1 H), 7.20–7.70 (m, 10 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 246 (100) $[M]^+$.

1-Phenyl-2-(phenylsulfinyl)ethanol (9b): Major diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 2:8) to give the product as a white solid. Yield 45 mg, 28%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.90 (m, 1 H), 3.20 (m, 1 H), 3.43 (br. s, 1 H, OH), 5.27 (m, 1 H), 7.20–7.70 (m, 10 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 246 (100) $[M]^+$.

2-Phenyl-2-(phenylsulfinyl)ethanol (10a): Major diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid. Yield 16 mg, 10%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.68 (br. s, 1 H, OH), 4.09 (m, 2 H), 5.25 (m, 1 H), 6.77–7.75 (m, 10 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 246 (100) $[M]^+$.

2-Phenyl-2-(phenylsulfinyl)ethanol (10b): Minor diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 4:6) to give the product as a white solid. Yield 13 mg, 8%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.68 (br. s, 1 H, OH), 3.92 (dd, $J_{H,H}$ = 3.7, 7.8 Hz, 1 H), 4.20 (dd, $J_{H,H}$ = 3.7, 12.3 Hz, 1 H), 4.60 (dd, $J_{H,H}$ = 7.8, 12.3 Hz, 1 H), 6.77–7.75 (m, 10 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 246 (100) $[M]^+$.

Oxidation of β-Hydroxy Sulfides (±)-5 and 8 in the Presence of BSA: The β-hydroxy sulfide (1.0 mmol) and *t*BuOOH (3 equiv. mol.) were added to a well stirred solution of BSA (0.025 mol. equiv.) in a buffer solution (3 mL) at pH 9.00. The mixture was stirred for 15 h and then stirred overnight with chloroform (20 mL). The resulting slurry was filtered through a cake of Celite, dried with $MgSO_4$ and the solvent evaporated. The organic phase was purified by flash chromatography using the appropriate eluent.

***trans*-[(2-Methoxycyclohexyl)sulfinyl]benzene (5a):** Major diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 9:1) to give the product as a white solid. Yield 33%; m.p. 136–137 °C. IR (KBr): $\tilde{\nu}$ = 3447, 2940, 1638, 1057, 1014 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.14–1.85 (m, 6 H, 4-H, 5-H, 6-H), 2.13–2.36 (m, 2 H, 3-H), 2.91 (m, 1 H, 2-H), 3.29 (s, 3 H, CH_3), 3.45 (m, 1 H, 1-H), 7.50 (m, 3 H, Ar-H), 7.86 (m, 2 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 238 (100) $[M]^+$.

***trans*-[(2-Methoxycyclohexyl)sulfinyl]benzene (5b):** Minor diastereoisomer. The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 9:1) to give the product as a white solid. Yield 15%; m.p. 129–130 °C. IR (KBr): $\tilde{\nu}$ = 3455, 2951, 1657, 1027, 1004 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.14–1.85 (m, 6 H, 4-H, 5-H, 6-H), 2.13–2.36 (m, 2 H, 3-H), 3.03 (m, 1 H, 2-H), 3.11 (s, 3 H, CH_3), 3.47 (m, 1 H, 1-H), 7.57 (m, 5 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 238 (100) $[M]^+$.

Cyclohexyl Phenyl Sulfoxide (8a): The crude product was purified by column chromatography (elution with hexane/ethyl acetate, 6:4) to give the product as a colourless oil. Yield 30%. IR (NaCl): $\tilde{\nu}$ = 3055, 2930, 1742, 1444, 1040 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.17–1.84 (m, 10 H), 2.60 (m, 1 H, 1-H), 7.47–7.61 (m, 5 H, Ar-H) ppm. EI-MS: *m*/*z* (%) = 208 (100) $[M]^+$.

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