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Efficient, scalable kinetic resolution of *cis*-4-benzyloxy-2,3-epoxybutanol

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Abstract—A new enzyme catalysed kinetic resolution of *cis*-4-benzyloxy-2,3-epoxybutanol has been reported. Efficient, scalable separation of the optically active alcohol from its ester derivative has been solved with liquid–liquid and solid–liquid extraction methods using commercial organic solvents and supercritical carbon dioxide. *cis*-4-Benzyloxy-2,3-epoxy-1-butanol enantiomers were applied for the enantioselective synthesis of (2*S*,3*S*,1′*S*)- and (2*R*,3*R*,1′*R*)-3-[2′-(dibenzylamino)-1′-hydroxyethyl]-2-phenyloxetane.

1. Introduction

Optically active oxiranes are useful intermediates in the synthesis of biologically active compounds. Regio- and stereoselective ring opening or rearrangement of chiral 2,3-disubstituted oxiranes are known routes to optically active alcohols, oxetanes and *cis*-but-2-ene-1,4-diol derivatives.[1–3] The oxetanes, for example, can be used as building blocks in the synthesis of oxetanocin A.[4] Different routes are known for the preparation of nonracemic chiral oxiranes. Allylic alcohols can be oxidised enantioselectively with *tert*-butyl hydroperoxide, titanium isopropoxide and a chiral catalyst.[5] Recently we reported the resolution of two amino group-containing oxiranyl ethers by preparing their diastereomeric salts.[6] The disadvantage of this resolution is that we have to find special conditions for each amino derivative.

The kinetic resolution of *cis*-4-benzyloxy-2,3-epoxybutanol **1** by enzyme catalysed enantiomer selective acylation would solve this problem and make possible the preparation of a large variety of enantiomerically pure oxiranyl ethers. Efficient and scalable separation of the acylated alcohol from the unreacted enantiomer is a key step of such protocols. The usual isolation method is column chromatography but it can be tedious on a multigram scale. Therefore, during development of a new enzyme catalysed kinetic resolution process for compound **1**, different methods were also investigated in our laboratories to find the optimum solution for the separation of the unreacted enantiomer of **1** from the reaction product.

2. Results and discussion

Synthesis of racemic **1** from the commercially available *cis*-2-buten-1,4-diol via monobenzylation and epoxidation was performed according to the literature procedure.[2] The enantiomer selectivity of the enzyme catalysed esterification of racemic **1** was screened with a wide selection of enzymes [AK, AY, F, M, Ps and R lipases from Amano; Novozym 435, Lipase IM 20 and Lipase TL IM from Novozymes; porcine liver esterase (liver acetone powder), *Candida rugosa* and *Pseudomonas fluorescens* lipases from Fluka; α-chymotripsin, papain, *Candida cylindracae* and porcine pancreatic lipases from Sigma]. Vinyl acetate was used as an acylating reagent and the esterification was carried out in hexane in these test reactions. Gas chromatographic

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analyses performed on a chiral stationary phase containing capillary column helped us in monitoring the enzymatic reactions. Comparison of the yields of the produced acetate **2a** and the residual alcohol **1** and ee values of **1** led us to conclude that the porcine pancreatic lipase (PPL) was one of the most active and enantioselective catalysts. Therefore all the further optimization reactions were carried out with PPL (Scheme 1) which accelerates esterification of the (−)-(2*S*,3*R*)-**1** enantiomer, thus an excess of (+)-(2*R*,3*S*)-**1** remained unreacted in the reaction mixture. The absolute configuration of optically active **1** is known.[5]

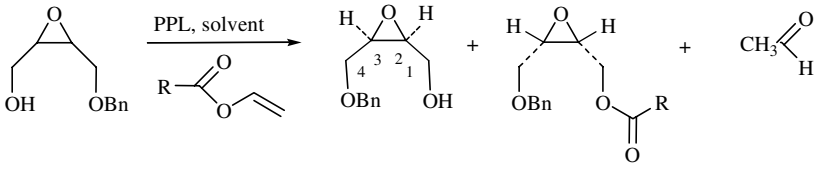
In order to find the optimum reaction conditions, the influence of the solvent, the acylating reagent (vinyl acetate, propionate and butyrate) and the epoxy alcohol/PPL ratio on the result of the kinetic resolution was investigated.

In the first run, the effect of the solvent was studied at ambient temperature. The alcohol **1**/vinyl acetate/PPL/solvent ratios were kept constant in these experiments (Table 1) and after 2 h of shaking the reactions were stopped by filtration from the enzyme. The yields of the acetate **2a** and the residual (+)-**1** and (−)-**1** alcohols were determined by gas chromatography.

Surprisingly, the reaction was slower in tetrahydrofuran or in hexane than in their mixture. The selectivity (*E*) increased in that mixture, compared to the selectivity observed in hexane but remained lower than that in tetrahydrofuran (Table 1). The reaction was a bit slower but the enantioselectivity significantly increased ($E \sim 23$), probably due to the smaller water content of the more concentrated reaction system and larger substrate/enzyme ratio, in gram scale experiments (cf. Section 4.2). In that case, the reaction was interrupted at about 58% conversion to yield the unreacted (+)-**1** isomer in 97% ee.

In order to determine the dependence of the results on the type of the acyl group, the esterification process was investigated under the same reaction conditions as described above using vinyl acetate, propionate and butyrate, respectively (Scheme 1). The highest reaction rate was observed with vinyl butyrate, while approximately the same rates were detected with vinyl acetate and propionate (Table 2). The type of the acyl group did not significantly influence the enantiomer selectivity of the reaction. At about 62–65% conversion (calculated to the racemic **1**) 96–97% ee of the residual alcohol **1** was detected in each case.

The (−)-**1** enantiomer was prepared in ethanol via PPL catalysed alcoholysis of (−)-**2a** and (−)-**2b**, respectively (Scheme 2, Table 3). In spite of the increased amount of the enzyme, the reactions in ethanol were much slower than the acylation of (±)-**1** with vinyl esters



Scheme 1. PPL catalysed kinetic resolution of **1**.

Table 1. Results of the enzymatic resolution of **1** in different solvents after 2 h reaction[a]

Solvent	(+)-**1** (%)	(−)-**1** (%)	(−)-**2a** (%)	ee **1** (%)	*E*[b]
Chloroform	50.9	42.4	2.9	9.1	[b]
Dichloromethane	50.4	37.1	8.8	15.2	[b]
Acetone	49.1	33.5	14.0	18.9	[b]
Hexane	37.6	12.8	47.5	49.2	5.4
Vinyl acetate	33.6	1.9	63.1	89.3	9.0
THF–hexane 1:1[c]	36.2	2.1	60.1	89.0	11.1
Cyclohexane	45.4	19.3	32.6	40.3	16.4
Toluene	44.6	11.7	41.4	58.4	19.0
Ethyl acetate	45.8	15.7	35.9	48.9	24.1
Acetonitrile	45.7	12.6	39.3	56.8	27.0
Tetrahydrofuran	45.3	10.2	42.2	63.2	26.7
Diethyl ether	47.0	24.3	25.8	31.8	31.0

[a] Starting amounts of racemic **1**/vinyl acetate/PPL/solvent: 20 mg/200 μL/20 mg/1800 μL, in all cases. The amounts of the formed **2a** and the residual (+)-**1** and (−)-**1** are given in mol %, on the basis of GC measurements.

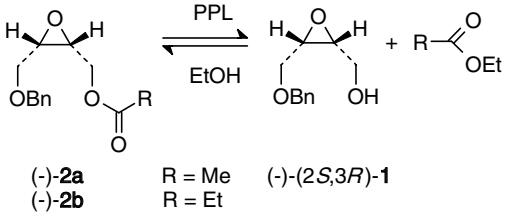
[b] Degree of the enantiomer selectivity (*E*) was calculated from the conversion and ee of **1**.[8] Due to extreme sensitivity to experimental errors at small conversions, no *E* values were calculated for conversion <15%.

[c] THF: tetrahydrofuran.

Table 2. Enzymatic resolution of **1** in the presence of different acyl group donating agents[a]

Reaction time (min)	Amount of the ester		
	2a[b] with vinyl acetate (%)	**2b**[b] with vinyl propionate (%)	**2c**[b] with vinyl butyrate (%)
30	11.8	8.6	19.1
60	22.0	18.5	32.4
90	31.8	26.8	45.2
120	40.3	37.1	53.5
150	45.5	42.8	60.5
180	50.2	53.6	64.9

[a] All reactions were accomplished using 0.29 g PPL for 1.0 g of racemic **1**.
[b] Data are given in mol %, related to the amount of the starting alcohol **1**.



Scheme 2. Alcoholysis of (−)-**2a** and (−)-**2b**.

Table 3. Rates of the PPL catalysed alcoholysis[a] of **2a** and **2b**

Reaction time (h)	Alcoholysis of **2a**		Alcoholysis of **2b**	
	2a[b] (%)	(−)-**1**[b] (%)	**2b**[b] (%)	(−)-**1**[b] (%)
0	100.0	0.0	100.0	0.0
1	93.2	6.8	93.8	6.2
24	41.8	58.2	42.2	57.8
49	24.4	75.6	28.8	71.2

[a] Reactions in the presence of 1.35 g of PPL for 1.0 g of substrate **2**.
[b] Relative amounts (mol %) of **2a** or **2b** and (−)-**1** were calculated from GC data.

and there were no significant differences between the ethanolysis rates of **2a** and **2b**. The PPL enzyme facilitate the reactions of the same enantiomeric form of **1** in both directions (esterification and alcoholysis), therefore virtually enantiopure (−)-**1** (ee >99%) could be obtained from (±)-**1** by a combined acylation–ethanolysis sequence.

Due to the difference in their polarity, alcohol **1** and esters **2a**–**c** could be separated by column chromatography on silica gel using hexane/ethyl acetate 2:1 (v:v) mixture as eluent. Multigram scale separation of optically active **1** from the esters **2a**,**b** or **2c** is quite tedious using this method. In order to find out more efficient, scalable procedure for separation of compounds **1** and **2**, alternative (liquid–liquid and liquid–solid) extractive methods were investigated. First, selectivities of hexane/aqueous methanol two-phases systems were studied in separation of the free alcohol **1** and the acetate **2a** as a function of the methanol content of the polar liquid phase. A mixture of **1** and **2a** was distributed between equal volumes of hexane and aqueous methanol by shaking the mixture for 20 min. Then the phases were separated and the distributions of **1** and **2a** were monitored by gas chromatography. The experimental details and results are summarised in Table 4.

The best selectivity was achieved with a methanol/water 1:9 (v:v) mixture. According to these results, on a gram scale, a mixture of **1** and **2a** was dissolved in aqueous methanol and the solution was extracted five times with hexane. The hexane solutions contained a 95:5 mixture of **2a** and **1**. Pure **2a** could be obtained in 57% yield when this mixture was extracted twice two times with a methanol/water 1:9 mixture. The original aqueous methanol solution contained chemically pure alcohol **1**. It could be isolated from the solution in 75% yield by evaporation of the solvents. However, this extraction method requires large amounts of solvents relative to the amounts of the separated compounds **1** and **2a**.

Next, the amounts of solvents used in liquid–liquid extraction were decreased by application of solid carriers for selective adsorption of one between the polar alcohol **1** and apolar ester **2b**. Thus, the enzyme was filtered off from the reaction mixture of the kinetic resolutions and different carriers (Perfil, Silica gel 60, Celite 545 or Florisil) were suspended in the filtrates, respectively. Then the mixture of (+)-**1** and (−)-**2b** was adsorbed on the carriers by evaporation of the solvents and the solid residue was stirred with hexane and filtered again. Ester **2b** was isolated from the hexane filtrate,

Table 4. Liquid–liquid extractive separation of **1** and **2a** from their mixture using different hexane/aqueous methanol systems

Solvent compositions (mL)			Amounts of **2a** (mg) and **1** (mg)[a]				Selectivity[c]
			In hexane[b]		In aqueous methanol[b]		
Methanol	Water	Hexane	**2a**	**1**	**2a**	**1**	
1	9	10	9.50	0.2	6.47	6.83	50.14
3	7	10	6.09	0.10	9.89	6.92	42.61
4	6	10	1.63	0.02	14.35	7.00	39.76
5	5	10	0.59	0.01	15.38	7.02	26.93
9	1	10	0.10	0.01	15.87	7.02	4.42

[a] Composition of the starting mixture: 7.2 mg of **1** + 16.0 mg of **2a**.
[b] Determined by GC using undecene as internal standard.
[c] Selectivity was calculated as the ratio of the hexane/aqueous methanol distribution of **2a** and **1**.

Table 5. Compositions[a] of the hexane filtrate and the dichloromethane extract of the hexane washed carriers supplemented with mixtures of **1** and **2b**

Carrier (1.0 g)		Perfil	Florisil	Celite	Silica gel
Starting composition	**1** (g)	0.1900	0.1900	0.1900	0.1900
	2b (g)	0.3100	0.3100	0.3100	0.3100
Hexane solution	**1** (g)	0.0662	0.0482	0.0687	—
	2b (g)	0.2638	0.2418	0.2954	0.2131
Dichloromethane solution	**1** (g)	0.1187	0.1057	0.1041	0.0754
	2b (g)	0.0313	0.0143	—	0.0780

[a] Determined by GC.

then alcohol **1** was recovered from the solid phase by washing it with dichloromethane (Table 5).

This new solid–liquid extraction method provided pure ester **2b** in 69% yield from the hexane filtrate when silica gel was the solid carrier and pure alcohol **1** was obtained from the dichloromethane solution in 55% yield when Celite was used as solid support.

It is known that supercritical carbon dioxide ($scCO_2$) acts as an apolar solvent like hexane. Application of $scCO_2$in the above mentioned solid–liquid extractive method could further decrease the amount of the organic solvents used. Thus, solvent free esters **2** can easily be obtained after evaporating the carbon dioxide from the $scCO_2$ extract. First, this idea was tested by the attempted separation of **1** and **2a** with supercritical fluid–solid extraction at 39 °C and different pressures (90, 160 bar) but insufficient separation was observed. Much better separation has been achieved when the difference between the polarities of alcohol **1** and ester **2** was increased by using the propionate **2b** instead of the acetate **2a**. Under these experiments, the crude reaction mixture [(+)-**1** and (−)-**2b**] obtained from the enzymatic reaction was mixed with silica gel and the solvents were evaporated. The residual solid was filled into the extractor tube and treated with $scCO_2$ at 33 °C, 100 bar. Three extract fractions were collected successively as separate samples. The ester **2b** was retrieved directly from the first fraction by decreasing the pressure. The second fraction contained about 8% of the mixture of **1** and **2b** in 4:1 ratio while the third fraction contained only a trace amount of these compounds. The alcohol **1** was isolated from the residual solid by extraction with methanol (Table 6). This method afforded good yields and sufficient purities (97% for **1**, 93% for **2b**) and, in addition, serves an environmentally begin process [7] for preparation of optically active **1** and **2**.

In order to demonstrate the synthetic usefulness of (2*R*,3*S*)-**1**, it was converted into a novel optically active dibenzylamino group containing oxiranyl ether **4** via the tosylate **3**. Then compound **4** was transformed into oxetane **5** by using potassium *tert*-butoxide activated lithium diisopropylamide (LiDA–KOR, Scheme 3), according to our previously reported rearrangement process.[3] The enantiomeric purity maintained throughout these reactions as well as during the formation of the new stereogenic centres in the oxetane ring of **5**. Configuration of C1′ did not change during these reactions. Starting from this fact, the absolute configurations of the new stereogenic centres of the oxetane ring in **5** have been determined on the basis of our earlier NMR investigations.[6] The opposite enantiomers of **4** and **5** were synthesised from (2*S*,3*R*)-**1** in the same way.

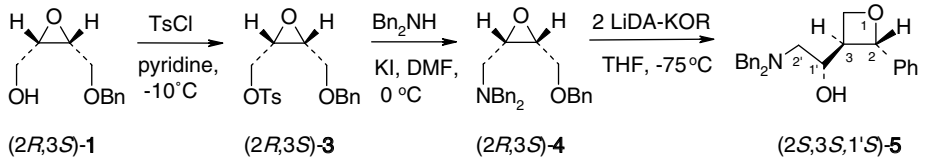
3. Conclusion

The experimental results allowed us to conclude that efficient kinetic resolution of 4-benzyloxy-2,3-epoxybutanol **1** can be accomplished by PPL catalysed acylation

Table 6. Supercritical fluid extraction of (−)-**2b** from its mixture with (+)-**1** at 100 bar, 33 °C

	Starting mixture[a]	First fraction[b]	Second fraction[b]	Residue[c]
Weight	2.13 g	1.01 g	0.17 g	0.81 g
(+)-**1** content[d]	0.81 g, 38%	0.07 g, 7%	0.03 g, 17%	0.79 g, 97%
(−)-**2b** content[d]	1.32 g, 62%	0.94 g, 93%	0.14 g, 83%	0.02 g, 3%

[a] On 4.26 g of silica gel (60 mesh).
[b] From the carbon dioxide extracts (18 g of $scCO_2$ eluent was used for each fraction).
[c] Recovered from silica gel with methanol.
[d] Determined by GC.



(2*R*,3*S*)-**1** (2*R*,3*S*)-**3** (2*R*,3*S*)-**4** (2*S*,3*S*,1′*S*)-**5**

Scheme 3. Synthesis of (2*R*,3*S*)-**4** and (2*S*,3*S*,1′*S*)-**5**.

of (±)-**1** with vinyl esters in tetrahydrofuran–hexane mixture. The enantioselectivity did not significantly depend on the quality of the acyl moiety but the ease of separation of the formed new esters (−)-**2a**, (−)-**2b** and (−)-**2c** from the residual alcohol (+)-**1** depended on the polarity difference between the ester **2** and the alcohol **1**. Thus novel, solid–liquid extractive methods were developed for the separation of **1** and **2b** using different solid carriers and eluents as hexane or supercritical carbon dioxide. The PPL catalysed acylation of (±)-**1** with vinyl propionate and the PPL catalysed alcoholysis of (−)-**2b** combined with the above mentioned solid–liquid extractive separation method provide a novel, efficient and scalable process for the preparation of both enantiomers of **1** in 97–99% ee. Starting from (+)-**1** and (−)-**1**, new, optically active amino group containing oxirane **4** and oxetane **5** derivatives could also be synthesised.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker WM 250 or Bruker DRX 300 spectrometer using deuteriochloroform as solvent. Chemical shifts are given relative to the signal of tetramethylsilane ($\delta_{TMS} = 0.00$ ppm). Coupling constants are given in hertz. IR spectra were taken on a Perkin–Elmer 1600 FT spectrometer. Gas chromatography was carried out on Agilent 4890D instrument equipped with FID detector (nitrogen as carrier gas, injector 250 °C, detector 250 °C, head pressure: 15 psi, at 1:100 split ratio). GC–MS spectra were recorded on a Finnigan Mat/Automass II GC/MS. Optical rotations were determined on Perkin–Elmer 241 polarimeter. TLC was carried out on Kieselgel 60 F_{254} (Merck) sheets. Spots were visualised by UV and treatment with iodine or with an aqueous solution of $(NH_4)_6Mo_7O_{24}$, $Ce(SO_4)_2$ and sulfuric acid, followed by heating of the dried plates. Solvents were freshly distilled. Commercial starting materials and PPL enzyme were purchased from FLUKA AG and Sigma, respectively, and were used without further purification. Butyllithium in hexane solution was supplied by Chemetall AG. Racemic *cis*-4-benzyloxy-2,3-epoxybutan-1-ol **1** was prepared according to the literature procedure.[2]

4.2. Kinetic resolution of *cis*-4-benzyloxy-2,3-epoxybutanol 1, general procedure

The PPL enzyme (0.6 g) was added into a solution of racemic *cis*-4-benzyloxy-2,3-epoxybutan-1-ol **1** (10.7 mmol, 2.07 g) made in tetrahydrofuran (45 mL), hexane (45 mL) and vinyl ester (acetate, propionate or butyrate, respectively; 20 mL) mixture. The resulting suspension was stirred at room temperature and analysed by gas chromatography [HP-Chiral B233 capillary column (30 m × 0.25 mm, 0.25 μm film), 5 min at 180 °C, 4 °C/min to 200 °C, then kept at 200 °C; retention times: (+)-(2*R*,3*S*)-**1**: 18.49 min, (−)-(2*S*,3*R*)-**1**: 18.59 min; **2a** (sum of enantiomers): 21.12 min; **2b** (sum of enantiomers): 26.31 min; **2c** (sum of enantiomers): 33.98 min, respectively]. At about 58–65% conversion (according to GC) the enzyme was filtered off and washed with acetone. The filtrate was concentrated in vacuum and the residual oil was separated by column chromatography on silica gel (hexane/ethyl acetate 2:1 v:v) to yield optically active alcohol **1** and ester **2a**,**b** or **2c**.

4.2.1. (+)-(2*R*,3*S*)-4-Benzyloxy-2,3-epoxybutanol, (+)-1. Oil (40% of the starting racemate[2]), ^{1}H NMR (250 MHz): δ 2.30 (1H, br s, O*H*), 3.3 (2H, m, oxirane C*H*), 3.7 (4H, m, CH_2O), 4.46 (1H, d, *J* 11.8, CH_aH$_b$Ph), 4.61 (1H, d, *J* 11.8, CH_aH$_b$Ph), 7.3 (5H, m, Ph); $[\alpha]_D$ +23.0 (*c* 2.4, $CHCl_3$), ee 97%.

4.2.2. (−)-(2*S*,3*R*)-1-Benzyloxy-2,3-epoxybutyl acetate, (−)-2a. Oil, ^{1}H NMR (300 MHz): δ 2.10 (3H, s, COCH_3), 3.3 (2H, m, oxirane C*H*), 3.59 (1H, dd, *J* 6.0, 11.4, CH_aH$_b$OBn), 3.71 (1H, dd, *J* 4.2, 11.4, CH$_a$$H_b$-OBn), 4.03 (1H, dd, *J* 6.9, 12.3, CH_aH$_b$O), 4.32 (1H, dd, *J* 3.9, 12.3, CH$_a$$H_b$O), 4.53 (1H, d, *J* 12.0, CH_aH$_b$Ph), 4.62 (1H, d, *J* 12.0, CH$_a$$H_b$Ph), 7.4 (5H, m, Ph); ^{13}C NMR (300 MHz): δ 170.93, 137.75, 128.69, 128.10, 128.01, 73.59, 68.01, 62.80, 54.91, 53.20, 20.95; GC–MS (EI, *m*/*z*): 237 ([M+H]$^+$), 173, 107, 91; HRMS (FAB): [M+H]$^+$ found 237.11202, $C_{13}H_{17}O_4$ requires 237.11268; $[\alpha]_D = -12.4$ (*c* 2.2, $CHCl_3$), ee 71% (at 58% conversion of the starting racemate).

4.2.3. (−)-(2*S*,3*R*)-1-Benzyloxy-2,3-epoxybutyl propionate, (−)-2b. Oil, ^{1}H NMR (300 MHz): δ 1.15 (3H, t, *J* 7.5, CH_3), 2.37 (2H, q, *J* 7.5, COCH_2), 3.3 (2H, m, oxirane C*H*), 3.59 (1H, dd, *J* 6.5, 11.1, CH_aH$_b$OBn), 3.72 (1H, dd, *J* 4.0, 11.0, CH$_a$$H_b$OBn), 4.04 (1H, dd, *J* 7.0, 12.5, CH_aH$_b$O), 4.33 (1H, dd, *J* 3.5, 12.5, CH$_a$$H_b$O), 4.54 (1H, d, *J* 12.0, CH_aH$_b$Ph), 4.62 (1H, d, *J* 12.0, CH$_a$$H_b$Ph), 7.3 (5H, m, Ph); ^{13}C NMR (300 MHz): δ 174.39, 137.77, 128.69, 128.10, 128.01, 73.59, 68.06, 62.65, 54.94, 53.26, 27.55, 9.21; GC–MS (EI, *m*/*z*): 251 ([M+H]$^+$), 175, 107, 91; HRMS (FAB): [M+H]$^+$ found 251.12937, $C_{14}H_{19}O_4$ requires 251.12833; $[\alpha]_D = -10.8$ (*c* 2.0, $CHCl_3$), ee 52% (at 65% conversion of the starting racemate).

4.2.4. (−)-(2*S*,3*R*)-1-Benzyloxy-2,3-epoxybutyl butyrate, (−)-2c. Oil, ^{1}H NMR (300 MHz): δ 0.95 (3H, t, *J* 7.5, CH_3), 1.7 (2H, m, CH_2), 2.33 (2H, t, *J* 7.5, COCH_2), 3.3 (2H, m, oxirane C*H*), 3.61 (1H, dd, *J* 6.0, 11.1, CH_aH$_b$OBn), 3.73 (1H, dd, *J* 4.2, 11.4, CH$_a$$H_b$OBn), 4.04 (1H, dd, *J* 6.9, 12.5, CH_aH$_b$O), 4.32 (1H, dd, *J* 3.9, 12.5, CH$_a$$H_b$O), 4.54 (1H, d, *J* 12.0, CH_aH$_b$Ph), 4.62 (1H, d, *J* 12.0, CH$_a$$H_b$Ph), 7.4 (5H, m, Ph); ^{13}C NMR (300 MHz): δ 173.58, 137.77, 128.70, 128.11, 128.02, 73.60, 68.07, 62.55, 54.95, 53.28, 36.13, 18.55, 13.85; GC–MS (EI, *m*/*z*): 265 ([M+H]$^+$), 107, 91; HRMS (FAB): [M$^+$] found 264.13699. $C_{15}H_{20}O_4$ requires 264.13616; $[\alpha]_D = -12.3$ (*c* 2.0, $CHCl_3$), ee 54% (at 65% conversion of the starting racemate).

4.2.5. Alcoholysis of (−)-2, general procedure. The PPL enzyme (3.2 g) was added to a solution of (−)-**2a** or (−)-**2b** (10 mmol, 2.36 g or 2.50 g, ee 71%) in ethanol (60 mL) and the resulting suspension was stirred at room temperature for 48 h and analysed by GC (HP-Chiral B233 capillary column, for conditions, see

Section 4.2). The enzyme was filtered off, washed with acetone and the filtrate was concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate 2:1 v:v) to yield (−)-**1** (1.23 g, 63%); $[\alpha]_D = -23.8$ (*c* 2.2, $CHCl_3$); ee >99%.

4.3. Separation of 1 and 2 by liquid–liquid extraction, a typical procedure

The mixture of alcohol **1** (0.1022 g) and ester **2a** (0.1020 g) was dissolved in a mixture of water (45 mL) and methanol (5 mL), then extracted with hexane (5 × 20 mL). The hexane extracts were collected and concentrated to 25 mL volume in vacuum, then washed two times with a mixture of water (3.6 mL) and methanol (0.4 mL), dried and evaporated to give pure **2** (0.058 g, 57%, purity 99%, GC). After removal of methanol from the first aqueous methanol solution in vacuum, the aqueous phase was extracted with dichloromethane (25 mL). The dichloromethane solution was dried on sodium sulfate and concentrated in vacuum to yield **1** (0.077 g, 75%, purity 99%, GC).

4.4. Separation of (+)-1 and (−)-2b by solid–liquid extraction using different carriers

A mixture of (+)-**1** (0.98 mmol, 0.19 g) and (−)-**2b** (1.24 mmol, 0.31 g) was dissolved in dichloromethane (5 mL), then a solid carrier (Perfil, Silica gel 60, Celite 545 or Florisil, 1.0 g) was added and the suspension was evaporated in vacuum. The dry solid was stirred with hexane (15 mL) for an hour, then filtered off and washed with hexane (2 × 5 mL).

The filtrate was concentrated in vacuum. Using silica gel as carrier, pure propionate (−)-**2b** (0.22 g, 69% of the starting ester, $[\alpha]_D = -11.5$ (*c* 2.0, $CHCl_3$), ee 58%) was obtained from the hexane solution. The solid phase was suspended in dichloromethane (10 mL) and stirred for 30 min. The suspension was filtered off, then washed with dichloromethane (2 × 5 mL). The filtrate was concentrated in vacuum. Using Celite as carrier, pure alcohol (+)-**1** (0.10 g, 55% of the starting alcohol (+)-**1**, $[\alpha]_D = +23.4$ (*c* 2.1, $CHCl_3$), ee 98%) was obtained from the dichloromethane solution.

4.5. Separation of 1 and 2b by supercritical fluid extraction

A mixture of **1** (4.48 mmol, 0.87 g) and **2b** (5.03 mmol, 1.26 g) was dissolved in dichloromethane (10 mL), then silica gel (4.26 g) was added and the solvent was removed from the suspension by vacuum rotary evaporator. The solid residue was filled into an extractor tube and treated with supercritical carbon dioxide (3 × 18 g) at 100 bar, 33 °C. (A more detailed description of the equipment and the extraction is given elsewhere.[8]) From the first fraction 75% of the starting **2b** (1.01 g, 93% **2b** content, GC) was recovered. The second fraction contained a mixture of **1** and **2b** in approximately 1:5 ratio (0.17 g, Table 6) and the third fraction contained only trace amounts of **1** and **2b**. The residual solid was removed from the extractor, suspended in methanol (25 mL) and stirred at room temperature for 30 min. The silica gel was filtered off then the methanol solution was concentrated in vacuum to yield 90% of the starting alcohol **1** (0.81 g, 97% 1 content, GC).

4.6. Conversion of (+)-(2*R*,3*S*)-1 and (−)-(2*S*,3*R*)-1 into optically active *cis*-3-[2′-(dibenzylamino)-1′-hydroxyethyl]-2-phenyloxetane[2] (+)-5 and (−)-5

4.6.1. Optically active *cis*-4-benzyloxy-2,3-epoxybutyl tosylates, (2*R*,3*S*)-3 and (2*S*,3*R*)-3. Compounds (2*R*,3*S*)-**3** and (2*S*,3*R*)-**3** were synthesised from (+)-(2*R*,3*S*)-**1** and (−)-(2*S*,3*R*)-**1** according to the literature procedure for racemic **3**.[2] Tosylates **3** were used without further purification.

Compound (2*R*,3*S*)-**3**: Oil (98%);^{1}H NMR (250 MHz): δ 2.44 (3H, s, Me–Ph), 3.24 (2H, m, oxirane C*H*), 3.53 (1H, dd, *J* 5.4, 11.4, CH_aH_bO), 3.58 (1H, d, *J* 3.6, 11.4, CH_aH_bO), 4.05 (1H, dd, *J* 6.6, 11.5, $CH_aH_bOSO_2$), 4.24 (1H, dd, *J* 3.8, 11.5, $CH_aH_bOSO_2$), 4.48 (1H, d, *J* 11.8, CH_aH_bPh), 4.54 (1H, d, *J* 11.8, CH_aH_bPh), 7.3 (7H, m, Ph), 7.78 (2H, d, *J* 8.3, Ph).

Compound (2*S*,3*R*)-**3**: ^{1}H NMR spectrum of (2*S*,3*R*)-**3** was indistinguishable from that of (2*R*,3*S*)-**3**.

4.6.2. Optically active *cis*-4-benzyloxy-1-dibenzylamino-2,3-epoxybutanes,[2] (−)-4 and (+)-4. Compounds (−)-**4** and (+)-**4** were synthesised from (2*R*,3*S*)-**3** and (2*S*,3*R*)-**3** by replacement of the tosyl group with dibenzylamine according to the literature procedure.[2]

Compound (−)-(2*R*,3*S*)-**4** (from (+)-(2*R*,3*S*)-**1**): Oil, (74%); ^{1}H NMR (250 MHz): δ 2.44 (1H, dd, *J* 4.0, 13.0, CH_aH_bN), 2.76 (1H, dd, *J* 4.0, 13.0, CH_aH_bN), 3.2 (2H, m, oxirane C*H*), 3.4 (1H, m, CH_aH_bO), 3.50 (2H, d, *J* 13.6, NCH_2Ph), 3.6 (1H, m, CH_aH_bO), 3.83 (2H, d, *J* 13.6, NCH_2Ph), 4.47 (1H, d, *J* 11.2, CH_aH_bPh), 4.59 (1H, d, *J* 11.2, CH_aH_bPh), 7.3 (15H, m, Ph).

$[\alpha]_D = -19.7$ (*c* 2.3, $CHCl_3$), ee 97%; (+)-(2*S*,3*R*)-**4** (from (−)-(2*S*,3*R*)-**1**): oil, (74%); The ^{1}H NMR spectrum was indistinguishable from that of (−)-(2*R*,3*S*)-**4**; $[\alpha]_D = +20.0$ (*c* 2.2, $CHCl_3$), ee >99%.

4.6.3. Optically active *cis*-3-[2′-(dibenzylamino)-1′-hydroxyethyl]-2-phenyloxetanes,[2] (+)-5 and (−)-5. Enantiomers of **5** were prepared via rearrangement of optically active **4**, induced by the superbasic mixture of potassium *tert*-butoxide and lithium diisopropylamide, according to the literature procedure.[2,6]

Compound (+)-(2*S*,3*S*,1′*S*)-**5** (from (−)-**4**): oil (47%); ^{1}H NMR (250 MHz): δ 1.60 (1H, br s, O*H*), 2.3 (2H, m, NCH_2), 2.8 (1H, m, oxetane C*H*), 3.34 (2H, d, *J* 13.2, NCH_2Ph), 3.89 (2H, d, *J* 13.2, NCH_2Ph), 4.1 (1H, m, C*H*OH), 4.61 (2H, d, *J* 8.0, oxetane CH_2O), 5.56 (1H, d, *J* 6.2, oxetane C*H*Ph), 7.3 (15H, m, Ph); $[\alpha]_D = -35.6$ (*c* 2.3, $CHCl_3$), ee 97%.

Compound (−)-(2*R*,3*R*,1′*R*)-**5** (from (+)-**4**): oil (47%); ^{1}H NMR spectrum was undistinguishable from that of (+)-(2*S*,3*S*,1′*S*)-**5**; $[\alpha]_D = +37.7$ (*c* 2.1, $CHCl_3$), ee > 99%.

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