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Kinetic resolution of 1-(benzofuran-2-yl)ethanols by lipase-catalyzed enantiomer selective reactions

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Abstract—Kinetic resolution of racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d** was performed by lipase-catalyzed enantiomer selective acylation ($E \gg 100$) yielding (1*R*)-1-acetoxy-1-(benzofuran-2-yl)ethanes (*R*)-**2a**–**d** and (1*S*)-1-(benzofuran-2-yl)ethanols (*S*)-**1a**–**d** in highly enantiopure form. The degree of enantiomer selectivity for enzymatic alcoholysis/hydrolysis processes starting from racemic 1-acetoxy-1-(benzofuran-2-yl)ethane *rac*-**2** was also tested under various conditions including supercritical CO_2 medium. Racemization-free lipase-catalyzed ethanolysis of the (1*R*)-1-acetoxy-1-(benzofuran-2-yl)ethanes (*R*)-**2a**–**d** yielded almost quantitatively the enantiopure (1*R*)-1-(benzofuran-2-yl)ethanols (*R*)-**1a**–**d**.

1. Introduction

Benzofuran-based structures are important units for the synthesis of various kinds of biologically active molecules. (Benzofuran-2-yl)carbinols exhibit various biological activities. Such derivatives were investigated as antibacterial[1] or antifungal agents.[1,2] Moreover, optically active 2-(2-*tert*-butylamino-1-hydroxyethyl)-benzofurans were investigated as β-blockers.[3] There are 2-substituted benzofuran drugs such as Amiodarone (cardiac anti-arrythmic)[4,5] and Benziodarone (coronary vasodilator).[6] 2-Substituted benzofuranes can also inhibit the HIV-1 reverse transcriptase[7] or act as anti-aging compounds.[8]

Since for discovery of novel biological activities chiral compounds as single enantiomers are required, appropriate methods providing enantiopure compounds are essential. Thus, biocatalysts where the homochirality of an enzyme is the source of the stereoselectivity, are becoming increasingly attractive tools for synthetic chemistry.[9,10]

Recently, we have investigated the baker's yeast reduction of 1-(benzofuran-2-yl)ethanones, -2-hydroxyethanones and -2-acetoxyethanones for the preparation of optically active (benzofuran-2-yl)carbinols.[13] By this method, both enantiomeric forms of 1-(benzofuran-2-yl)ethane-1,2-diols were obtained in acceptable enantiomeric purities (84–93% ee).[13] Baker's yeast reduction of the 1-(benzofuran-2-yl)ethanones, however, resulted in the formation of only the (*S*)-enantiomers of 1-(benzofuran-2-yl)ethanols in moderate enantiomeric purities (55–88% ee).[13]

Since for the baker's yeast reduction study methods for preparation of the racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d** from the 1-(benzofuran-2-yl)ethanones **3a**–**d** were also developed[13] (Fig. 1) and we have recently isolated a range of novel hydrolases from thermophilic filamentous fungi exhibiting high enantiomer selectivity towards aryl methyl carbinols,[14] it seemed worthwhile to investigate the enzyme-catalyzed kinetic resolution of the racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d** by lipase-catalyzed acylation (Fig. 1).

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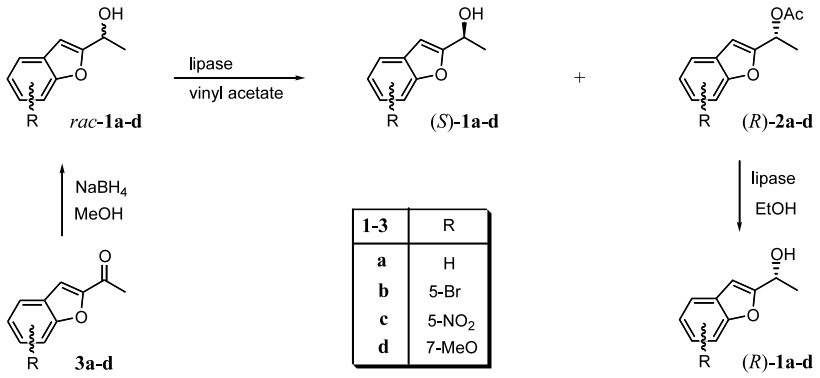

Figure 1. Preparation and lipase-mediated enantiomer separation of racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d**.

2. Results and discussion

With the racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d**[13] and with a wide selection of commercial and prepared enzymes[14] in hand, firstly enantiomer selectivity of the enzyme-catalyzed acylations of the unsubstituted racemic 1-(benzofuran-2-yl)ethanol *rac*-**1a** was screened with different lipases (Fig. 1, Table 1).

As a result of the screen performed with about three dozen different enzymes, a number of highly enantiomer selective lipases for the acylation of 1-(benzofuran-2-yl)ethanol *rac*-**1a** were found. As expected from the earlier results,[9–12] lipases from *Pseudomonas* strains (lipase PS, lipase AK) were quite enantiomer selective ($E \gg 100$). In addition, several fungal lipases (Lipozyme TL IM, and a number of our novel preparations from thermophilic fungi[14]) also exhibited excellent selectivities ($E \gg 100$). Almost all of these lipases had an enantiomeric preference towards the (*R*)-enantiomer of the racemic alcohol, thus yielding a mixture of (*R*)-acetate (*R*)-**2a** and unreacted (*S*)-alcohol (*S*)-**1a**.

This stereochemical preference of lipase PS following the so called Kazlauskas rule[15]—which is derived from an empirical active site model consisting of two pockets of different sizes which distinguish between the two enantiomers of the secondary alcohols due to the size and steric arrangement of their substituents—seems to be more general for secondary alcohols.

Interestingly, lipases from *Rhizomucor* species (lipase from *Rhizomucor javanicus* and lipase F) exhibited opposite enantiomer preference and resulted in the formation of the (*S*)-acetate (*S*)-**2a**.

The two enzymes from the screen of the racemic 1-(benzofuran-2-yl)ethanol *rac*-**1a** which exhibited the highest

Table 1. Enantiomer selective enzymatic acylation of racemic 1-(benzofuran-2-yl)ethanol *rac*-**1a**[a]

Lipase	Time (h)	c[b] (%)	Ee (%)		E[c]
			(*R*)-**2a**[c]	(*S*)-**1a**[c]	
Lipase TUB 3b	24	50	>99	>99	≫100
Lipase AK	14	50	99	99	≫100
Lipozyme TL IM	14	35	99	52	≫100
Lipase PS	14	45	98	82	≫100
PPL	48	16	99	18	≫100
Novozyme 435	14	52	96	>98	>100
Lipase TUB 16b	48	10	98	11	90
Lipase TUB 7b	48	3	98	2	83
Lipase TUB 4a	48	7	97	7	77
Lipase TUB 19b	48	3	94	3	31
Lipase TUB 18a	48	3	89	3	18
Lipase TUB 20b	48	12	86	11	15
CrL	72	12	83	11	12
CcL	48	22	80	22	11
Lipase AY	48	8	79	7	9
Lipase F	72	11	88[d]	11[e]	18
Lipase *Rh. javanicus*	72	3	47[d]	1[e]	3

[a] Reactions with c >3% within 72 h. For details, see Section 4.2.
[b] Determined from GC on HP Chiral column.
[c] Calculated from c and ee_{2a}.
[d] (*S*)-**2a** was produced.
[e] (*R*)-**1a** was produced.

Table 2. Enantiomer selective acylation of racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a–d** mediated by Lipase TUB 3b and Lipase F

Products **1**,**2**	Lipase	Time (h)	c[a] (%)	**2**		**1**		E[c]
				Config.[b]	Ee (%)[a]	Config.[b]	Ee (%)[c]	
a	TUB 3b	24	50	*R*	>99	*S*	>99	≫100
b	TUB 3b	168	49	*R*	97	*S*	99	≫100
c	TUB 3b	24	50	*R*	>99	*S*	>99	≫100
d	TUB 3b	168	51	*R*	98	*S*	>99	≫100
a	F	72	11	*S*	88	*R*	11	18
b	F	168	13	*S*	95	*R*	15	44
c	F	168	12	*S*	89	*R*	12	20
d	F	168	5	*S*	99	*R*	6	>100

[a] Determined from GC on HP Chiral column.
[b] Determined by comparison with samples of known configuration.
[c] Calculated from c and $ee_{\mathbf{2}}$.

Table 3. Preparative scale enantiomer selective acylation of racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a–d** mediated by Lipase AK

Products **1**,**2**	Time (h)	(*S*)-**1**[a]		(*R*)-**2**[a]		E
		Yield (%)	Ee[b] (%)	Yield (%)	Ee[c] (%)	
a	14	49	98.6	48	99.1	≫100
b	18	48	97.5	47	98.6	≫100
c	72	51	81.0	44	>99.8	≫100
d	72	51	81.0	43	99.1	≫100

[a] Configurations were determined by comparison with literature data.[13]
[b] Determined by GC on HP Chiral column.
[c] Determined after chemical acylation by GC on HP Chiral column.

enantiomer selectivities towards the (*R*)- and (*S*)-enantiomers of the racemic alcohol, were further tested for the acylation of substituted racemic 1-(benzofuran-2-yl)ethanols *rac*-**1b–d** (Table 2). As expected, the enzymes which performed the acylation of the unsubstituted racemic alcohol *rac*-**1a** with the highest selectivities were also quite selective towards the substituted ones *rac*-**1b–d**.

In the reactions with the best performing enzyme exhibiting (*R*)-enantiomeric preference, lipase TUB 3b (isolated during our screen for lipases from thermophilic filamentous fungi[14]), the high degree of selectivity remained unaltered and the quality and/or position of the substituents effected only the rate of the reaction (entries 1–4 in Table 2). Compared to the unsubstituted derivative (entry 1, **1a**), electron withdrawing substituent at position 5 (entry 3, **1c**, R = 5-NO_2) had no strong influence on the rate of acylation, whereas substituents with +M effects at positions 5 and 7 (entries 2 and 4, **1b**, R = 5-Br and **1d**, 7-MeO, respectively) significantly lowered the rate of the reaction.

On the contrary, with lipase F which showed the highest degree of (*S*)-enantiomeric preference not only the rate but the selectivity of the acylation reaction was dependent on the substitution pattern. In this case, the electron withdrawing substituent at position 5 (entry 7, **1c**, R = 5-NO_2) had no significant effect on the selectivity but lowered the rate of reaction, whereas substituents with +M effects at positions 5 and 7 (entries 6 and 8, **1b**, R = 5-Br and **1d**, 7-MeO, respectively) enhanced the degree of enantiomer selectivity. The cost of this enhancement in selectivity towards the (*S*)-enantiomer of the 7-methoxy-substituted alcohol (*S*)-**1d**, however, was a drop in the rate of the reaction.

Next, for full characterization of the products kinetic resolutions were performed on the racemic 1-(benzofuran-2-yl)ethanols (*rac*-**1a–d**, 200 mg, each) with the most selective commercial enzyme, lipase AK (Table 3).

In the reactions with lipase AK—as with lipase TUB 3b—the degree of the selectivity remained high and unaltered regardless of the quality and/or position of the substituents which affected only the rate of the reaction. Interestingly, in acylations performed with lipase AK—in contrast to lipase TUB 3b acylations—the 5-bromo substitution (entry 2, **1b**) did not have any influence but the 5-nitro substitution (entry 3, **1c**) lowered the rate of the reaction.

Finally, the degree of enantioselectivity was tested in alcoholysis/hydrolysis reactions of the racemic 1-acetoxy-1-(benzofuran-2-yl)ethane *rac*-**2a** with the most selective immobilized lipase (Lipozyme TL IM) (Table 4).

Table 4. Alcoholysis/hydrolysis of 1-acetoxy-1-(benzofuran-2-yl)ethane *rac*-**2a** mediated by Lipozyme TL IM[a]

Method[a]	Nucleophile	Time (h)	c[b] (%)	Ee (%)		E[c]
				(*S*)-**1a**[c]	(*R*)-**2a**[b]	
A	H_2O	24	40	34	50.0	11.4
B	H_2O	24	20	4	17.5	7.2
C	H_2O	4	9	7	6.7	5.2
A	MeOH	24	3	<1	0.7	1.5
B	MeOH	24	5	<1	3.7	8.8
C	MeOH	4	4	<1	1.3	2.1
A	EtOH	24	3	<1	2.1	12.8
B	EtOH	24	11	1	9.4	8.5
C	EtOH	4	11	<1	1.6	1.3
A	PrOH	24	7	<1	7.7	54.9
B	PrOH	24	25	8	24.2	8.2
C	PrOH	4	6	<1	3.2	3.3
A	BuOH	24	30	6	14.3	2.3
B	BuOH	24	41	41	58.2	19.6
C	BuOH	4	6	<1	1.0	1.4

[a] Method A: neat nucleophile, Method B: hexane containing nucleophile (10%), Method C: supercritical CO_2 containing nucleophile (1%). The reactions with Methods A and B were performed at room temperature, reactions with Method C were made at 38°C.
[b] Determined from GC on HP Chiral column.
[c] Calculated from c and ee_s.

For alcoholysis/hydrolysis of the racemic 1-acetoxy-1-(benzofuran-2-yl)ethane *rac*-**2a** three conditions were compared. The reactions were first performed in alcohol/water as solvent at room temperature (Method A). Then the alcoholysis/hydrolysis reactions were carried out at room temperature in hexane containing 10% of the different nucleophiles (Method B) and in supercritical CO_2 containing 1% of the nucleophile at 38°C (Method C).

The results indicated that any of the tested alcoholysis/hydrolysis reaction condition was significantly less enantiomer selective (Table 4: $E \sim 1.3$–54.9) than the corresponding acylation (entry 3, Table 1: $E \gg 100$). Interestingly, different nucleophiles exhibited the highest selectivities for the three different conditions. In reactions performed in the nucleophile as solvent (Method A) the highest selectivity was achieved with propanol (entry 10, Table 4: $E = 54.9$). In the reactions conducted in hexane as solvent (Method B) butanol provided the highest selectivity (entry 14, Table 4: $E = 19.6$), whereas among the reactions carried out in supercritical CO_2 water as nucleophile gave the highest selectivity (entry 3, Table 4: $E = 5.2$).

Although the low selectivities made alcoholysis/hydrolysis reactions unattractive as alternative for kinetic resolution purposes, this approach seemed to be ideal for racemization-free desacetylation of the produced highly enantiopure (*R*)-acetates (*R*)-**2a**–**d** (Table 5).

Although it seems to be simple, the racemization-free desacetylation of esters of aryl methyl carbinols is not a trivial task. It was observed by the hydrolysis of the enantiopure (1*R*)-1-phenylethyl acetate that desacetylation either with 5% aqueous NaOH or catalytical NaOMe/MeOH at room temperature resulted in about 5% racemization and thus ~90% ee for the product

Table 5. Lipase-catalyzed ethanolysis of (1*R*)-1-acetoxy-1-(benzofuran-2-yl)ethanes (*R*)-**2a**–**d**

Product **1**	Yield (%)	Ee[a] (%)	$[\alpha]_D^{20}$ (*c* 1.0, $CHCl_3$)
a	96	>99	+16.6
b	95	99	+14.5
c	97	>99	+18.9
d	96	>99	+14.8

[a] Determined by GC on HP Chiral column as acetate derivative.

(Poppe, L., unpublished). The enzymatic method, however, gave from the highly enantiopure (*R*)-acetates (*R*)-**2a**–**d** non-racemized alcohols (*R*)-**1a**–**d** almost quantitatively.

3. Conclusion

For kinetic resolution of racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d** by enantiomer selective acylation several highly selective ($E \gg 100$) bacterial and fungal lipases were positively tested. Most enzymes exhibited (*R*)-enantiomeric preference yielding (1*R*)-1-acetoxy-1-(benzo-furan-2-yl)-ethanes (*R*)-**2a**–**d** and (1*S*)-1-(benzofuran-2-yl)ethanols (*S*)-**1a**–**d** but a few lipases (e.g. lipase F) had opposite enantiopreference. The preparative scale reactions with lipase AK resulted in the acetates (*R*)-**2a**–**d** and alcohols (*S*)-**1a**–**d** in highly enantiopure form. The degree of enantiomer selectivity for enzymatic alcoholysis/hydrolysis processes starting from racemic 1-acetoxy-1-(benzofuran-2-yl)ethane *rac*-**2** was also tested under various conditions including supercritical CO_2 medium and found it significantly lower than that of the acylation process. Preparative scale lipase-catalyzed ethanolysis was used for racemization-free production of enantiopure (1*R*)-1-(benzofuran-2-yl)ethanols (*R*)-**1a**–**d** in almost quantitative yields.

4. Experimental

4.1. Materials and methods

4.1.1. Analytical methods. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Brucker DRX-500 spectrometer operating at 500 and 125 MHz, respectively. Chemical shifts are expressed in ppm values from TMS as internal standard. IR spectra were recorded in KBr on a Specord 2000 spectrometer and the wavenumbers are reported in cm^{-1}. GC analyses were made by an Agilent 4890D gas chromatograph (carrier gas H_2; head pressure: 12 psi, injector: 250°C; FID detector: 250°C) on a HP-Chiral column (30 m× 0.32 mm, 0. 25 μm 20% permethylated β-cyclodextrin, No. 19091G-B312). Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Preparative vacuum-chromatography[16] was performed on Merck Kieselgel 60 (0.063–0.200 μm).

4.1.2. Reagents and solvents. Vinyl acetate and the other commercial chemicals and solvents were products of Aldrich or Fluka. All solvents were purified and dried by standard methods. Racemic 1-(benzofuran-2-yl)ethanols *rac*-**1a**–**d** and 1-acetoxy-1-(benzofuran-2-yl)ethanes *rac*-**2a**–**d** were prepared from 2-acetylbenzofuranes **3a**–**d** according to the published procedures.[13]

4.1.3. Biocatalysts. Lipase A, lipase AK, lipase AY, lipase M, lipase PS and lipase R were obtained from Amano Europe. Lipozyme IM, Lipozyme IM 20, Lipozyme TL IM, Novozyme 435 and *Candida antarctica* lipase A were products of Novozymes, Denmark. Lipases from *Candida rugosa* and *Pseudomonas fluorescens* were purchased from Fluka. PPL and lipase from *Candida cylindracae* were obtained from Sigma. A selection of extracellular hydrolases from various thermophilic fungi (lipases TUB 1-52a,b) were isolated as acetone dried supernatants of shake flask fermentations.[14]

4.1.4. Reactor for SCF alcoholysis/hydrolysis tests. Reactions in supercritical CO_2 were performed in a thermostated (38°C) tube-reactor (reactor volume 5 ml). Supercritical CO_2 was filled in the system (total volume 20 ml) by an SFC 300 pump (Carlo Erba) and recycled through the reactor by a pump system. The CO_2 used in this study was 99.5% (w/w) pure and supplied by Messer Griesheim Hungaria Ltd. (Budapest).

4.2. Lipase-catalyzed acylations of racemic 1-(benzofuran-2-yl)ethanol *rac*-1a

To a solution of racemic 1-(benzofuran-2-yl)ethanol (*rac*-**1a**, 20 mg) in vinyl acetate (0.5 ml) lipase (20 mg) was added and the mixture was shaken at room temperature and 1000 rpm for the time indicated in Table 1. Samples from the supernatant were analyzed by GC [R_t (HP Chiral; oven: 165°C)/min: 3.50 **1a**, 3.75 (*S*)-**2a**, 3.84 (*R*)-**2a**] according to the published procedure.[13] Conversion and enantiomeric composition data are presented in Table 1.

4.3. Preparative scale acylation of racemic 1-(benzofuran-2-yl)ethanols catalyzed by lipase AK

To a solution of racemic 1-(benzofuran-2-yl)ethanol (*rac*-**1a**–**d**, 200 mg, each) in vinyl acetate (6 ml) lipase AK (200 mg) was added and the mixture was stirred at rt for the time indicated in Table 2. Then the enzyme was filtered off and washed with acetone (2×5 ml). Solvents were distilled off from the combined filtrates and the residue was purified by column chromatography (silica gel, CH_2Cl_2) yielding the optically active alcohol (*S*)-**1a**–**d** and acetate (*R*)-**2a**–**d**.

4.3.1. (1*S*)-1-(Benzofuran-2-yl)ethanol, (*S*)-1a. Yield: 49%; ee: 98.6% (by GC after conversion to acetate); $[\alpha]_D^{20}$ −16.6 (*c* 1.0, $CHCl_3$); ^1H NMR: 1.66 (3H, d), 2.41 (1H, broad s), 5.04 (1H, q), 6.63 (1H, s), 7.23–7.26 (1H, m), 7.28–7.32 (1H, m), 7.49 (1H, d), 7.57 (1H, d); ^{13}C NMR: 21.47, 64.14, 101.36, 112.69, 115.84, 123.75, 127.11, 130.20, 153.58, 161.60; IR: 3384, 2984, 1456, 1376, 1304, 1256, 1152, 1076, 1008, 944, 808, 748. Anal calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.16; H, 6.25%.

4.3.2. (1*S*)-1-(5-Bromobenzofuran-2-yl)ethanol, (*S*)-1b. Yield: 48%; ee: 97.5% (by GC after conversion to acetate); $[\alpha]_D^{20}$ −14.5 (*c* 1.0, $CHCl_3$); ^1H NMR: 1.63 (3H, d), 2.26 (1H, broad s), 5.00 (1H, q), 6.55 (1H, s), 7.27–7.37 (2H, m), 7.66 (1H, s); ^{13}C NMR: 21.47, 64.14, 101.36, 112.69, 115.84, 123.75, 127.11, 130.20, 153.58, 161.69; IR: 3408, 2984, 1448, 1372, 1300, 1264, 1152, 1088, 1024, 936, 808. Anal calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.14. Found: C, 49.76; H, 3.65; Br, 33.05%.

4.3.3. (1*S*)-1-(5-Nitrobenzofuran-2-yl)ethanol, (*S*)-1c. Yield: 51%; ee: 81.0% (by GC after conversion to acetate); $[\alpha]_D^{20}$ −15.5 (*c* 1.0, $CHCl_3$); ^1H NMR: 1.66 (3H, d), 2.42 (1H, broad s), 5.06 (1H, q), 6.75 (1H, s), 7.51 (1H, d), 8.18 (1H, d), 8.43 (1H, s); ^{13}C NMR: 21.50, 64.06, 102.58, 111.54, 117.57, 120.94, 128.64, 144.16, 157.64, 163.91; IR: 3320, 1528, 1348, 1296, 1264, 1160, 1080, 1024, 884, 816, 736. Anal calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.92; H, 4.27; N, 6.77%.

4.3.4. (1*S*)-1-(7-Methoxybenzofuran-2-yl)ethanol, (*S*)-1d. Yield: 51%; ee: 81.0% (by GC after conversion to acetate); $[\alpha]_D^{20}$ −12.1 (*c* 1.0, $CHCl_3$); ^1H NMR: 1.64 (3H, d), 2.46 (1H, broad s), 4.00 (3H, s), 5.03 (1H, q), 6.60 (1H, s), 6.76–6.80 (1H, m), 7.14 (2H, d); ^{13}C NMR: 21.41, 55.98, 64.08, 102.02, 106.29, 113.46, 123.46, 129.86, 143.96, 145.26, 160.64; IR: 3296, 2984, 1624, 1600, 1496, 1440, 1376, 1312, 1272, 1200, 1184, 1096, 1032, 936, 892, 836, 728. Anal calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.25%.

4.3.5. GC determination of the enantiomeric purity of 1-(benzofuran-2-yl)ethanols 1a–d. Alcohols **1a**–**d** were transformed to acetates **2a**–**d** according to the published procedure[13] [alcohol (**1a**–**d**, 0.3 mmol), triethylamine (33.5 mg, 46 μl, 0.33 mmol), CH_2Cl_2 (2 ml), acetyl chloride (26 mg, 24 μl, 0.33 mmol), stirring at room

temperature for 2 h] and analysed by GC on HP Chiral column [**2a**, GC (165°C) $R_{T(R)}$: 3.75 min, $R_{T(S)}$: 3.84 min; **2b**: GC (120–170°C, 1°C/min) $R_{T(R)}$: 37.34 min, $R_{T(S)}$: 38.06 min; **2c**: GC (130–180°C, 1°C/min) $R_{T(R)}$: 46.94 min, $R_{T(S)}$: 47.56 min; **2d**: GC (120–170°C, 1°C/min) $R_{T(R)}$: 33.39 min, $R_{T(S)}$: 34.07 min].

4.3.6. (1*R*)-1-Acetoxy-1-(benzofuran-2-yl)ethane, (*R*)-2a. Yield: 48%; ee: 99.1% (by GC); $[\alpha]_D^{20}$ +198.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR: 1.71 (3H, d), 2.13 (3H, s), 6.13 (1H, q), 6.72 (1H, s), 7.24–7.29 (1H, m), 7.31–7.34 (1H, m), 7.51 (1H, d), 7.58 (1H, d); ^{13}C NMR: 18.43, 21.16, 65.51, 104.24, 111.37, 121.24, 122.87, 124.56, 127.86, 154.86, 155.99, 170.12; IR: 1744, 1456, 1372, 1236, 1060, 1028, 752. Anal calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.62; H, 5.95%.

4.3.7. (1*R*)-1-Acetoxy-1-(5-bromobenzofuran-2-yl)-ethane, (*R*)-2b. Yield: 47%; ee: 98.6% (by GC); $[\alpha]_D^{20}$ +144.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR: 1.66 (3H, d), 2.11 (3H, s), 6.07 (1H, q), 6.63 (1H, s), 7.33–7.39 (2H, m), 7.67 (1H, s); ^{13}C NMR: 18.80, 21.52, 65.68, 104.05, 113.24, 116.30, 124.27, 127.87, 130.26, 153.99, 157.84, 170.44; IR: 1740, 1448, 1372, 1264, 1024, 800. Anal calcd for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92; Br, 28.22. Found: C, 50.82; H, 3.88; Br, 28.34%.

4.3.8. (1*R*)-1-Acetoxy-1-(5-nitrobenzofuran-2-yl)ethane, (*R*)-2c. Yield: 44%; ee: >99.8% (by GC); $[\alpha]_D^{20}$ +139.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR: 1.70 (3H, d), 2.13 (3H, s), 6.10 (1H, q), 6.83 (1H, s), 7.55 (1H, d), 8.23 (1H, d), 8.48, (1H, s); ^{13}C NMR: 18.42, 21.08, 65.10, 104.85, 111.78, 117.8, 120.48, 128.34, 144.31, 157.61, 159.66, 169.70; IR: 1748, 1524, 1348, 1232, 1064, 1032, 952. Anal calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.75; H, 4.52; N, 5.68%.

4.3.9. (1*R*)-1-Acetoxy-1-(7-methoxybenzofuran-2-yl)-ethane, (*R*)-2c. Yield: 43%; ee: 99.1% (by GC); $[\alpha]_D^{20}$ +156.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR: 1.69 (3H, d), 2.09 (3H, s), 4.01 (3H, s), 6.08 (1H, q), 6.79–6.82 (1H, m), 6.69 (1H, s), 7.14–7.16 (2H, m); ^{13}C NMR: 18.93, 21.58, 56.41, 66.41, 105.01, 107.09, 113.93, 123.97, 129.95, 144.56, 145.78, 156.57, 170.50; IR: 1740, 1496, 1372, 1272, 1096, 1056, 1028, 852, 928, 732. Anal calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.62; H, 6.11%.

4.4. Alcoholysis/hydrolysis of racemic 1-acetoxy-1-(benzofuran-2-yl)ethane *rac*-2a

Method A: To a solution of racemic 1-acetoxy-(benzofuran-2-yl)ethane (*rac*-**2a**, 20 mg) in the nucleophile (500 μl, see Table 4) Lipozyme TL IM (20 mg) was added and the mixture was shaken at 1000 rpm and rt for the time indicated in Table 4.

Method B: To a solution of racemic 1-acetoxy-(benzofuran-2-yl)ethane (*rac*-**2a**, 20 mg) in hexane (450 μl) containing nucleophile (50 μl, see Table 4) Lipozyme TL IM (20 mg) was added and the mixture was shaken at 1000 rpm and rt for the time indicated in Table 4.

Method C: Racemic 1-acetoxy-1-(benzofuran-2-yl)ethane (*rac*-**2a**, 50 mg) was evaporated from CH_2Cl_2 (20 ml) onto Perfil 100™ (500 mg, expanded and milled perlite, Baumit Co., Budapest) and the resulted dry material was filled into the SCF reactor. Over this layer, immobilized enzyme (Lipozyme TL IM, 200 mg) and nucleophile (1 ml) were also added. After filling the reactor CO_2 was pumped in and the supercritical CO_2 was recycled through the so-prepared reactor at 38°C and 120 bar for 4 h. Work up of the reaction was performed by releasing the CO_2 into a dry-ice cooled trap. The trap, the adsorbent and the enzyme were washed with acetone (2×20 ml). The unified acetone solutions were evaporated and the residue was analysed by GC as described in Section 4.2.

Details for and results of the reactions with the three methods (kind of nucleophile, reaction time, *c*, ee and *E* values) are reported in Table 4.

4.5. Preparative scale ethanolysis of (1*R*)-1-acetoxy-1-(benzofuran-2-yl)ethanes (*R*)-2a–d

Lipozyme TL IM (100 mg) was added to an ethanolic solution of (1*R*)-1-acetoxy-1-(benzofuran-2-yl)ethanes (100 mg in 5 ml) obtained from the preparative acylations (Section 4.2). The reaction mixture was shaken at 1000 rpm and rt overnight until complete conversion (by TLC). Then the enzyme was filtered off and washed with ethanol (2×5 ml). The solvent was evaporated in vacuum and the crude product was purified by vacuum chromatography on silica gel with CH_2Cl_2 yielding the alcohols (*R*)-**1a–d** (for isolated yield, optical rotation and enantiomeric composition data, see Table 5).

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