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Optically active 1-(benzofuran-2-yl)ethanols and ethane-1,2-diols by enantiotopic selective bioreductions

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Abstract—Enantiotopic selective reduction of 1-(benzofuran-2-yl)ethanones **1a–d**, 1-(benzofuran-2-yl)-2-hydroxyethanones **4a–c** and 2-acetoxy-1-(benzofuran-2-yl)ethanones **3a–c** was performed by baker's yeast for preparation of optically active (benzofuran-2-yl)carbinols [(*S*)-**5a–d**, (*S*)-**6a–c** and (*R*)-**6a–c**, enantiomeric excess from 55 to 93% ee].

1. Introduction

(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] 2-Substituted benzofurans can inhibit the HIV-1 reverse transcriptase[4] or act as antiaging compounds.[5]

Baker's yeast reduction of hydroxymethyl ketones[6–16] and acetoxymethyl ketones[10,11,14,16] proved to be useful for production of opposite enantiomeric forms of 1,2-diols (Fig. 1). Ketones with a relatively small and hydrophilic hydroxymethyl group were all reduced from the same face, whereas the acetoxymethyl ketones were reduced with the opposite enantiotopic preference. This inversion in the sense of enantiomeric preference (Fig. 1) was demonstrated by baker's yeast reductions of phenacyl alcohols and their acetates[11,15] or of 3-*O*-protected dihydroxyacetone derivatives.[16]

Recently, we developed a method for the preparation of similar hydroxymethyl and acetoxymethyl ketones bearing benzofuran-2-yl substituents.[17]

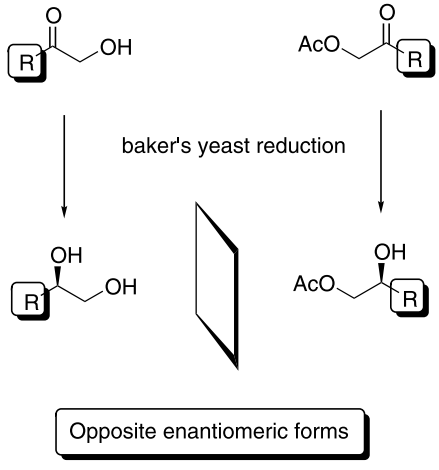

Figure 1. Yeast reduction of hydroxymethyl and acetoxymethyl ketones.

Thus, 1-(benzofuran-2-yl)-2-hydroxyethanones **4a–c** were obtained from methyl ketones **1a–c** via their transformation into bromomethyl ketones **2a–c** and subsequent conversion into acetoxymethyl ketones **3a–c** followed by a mild enzymatic ethanolysis (Fig. 2).

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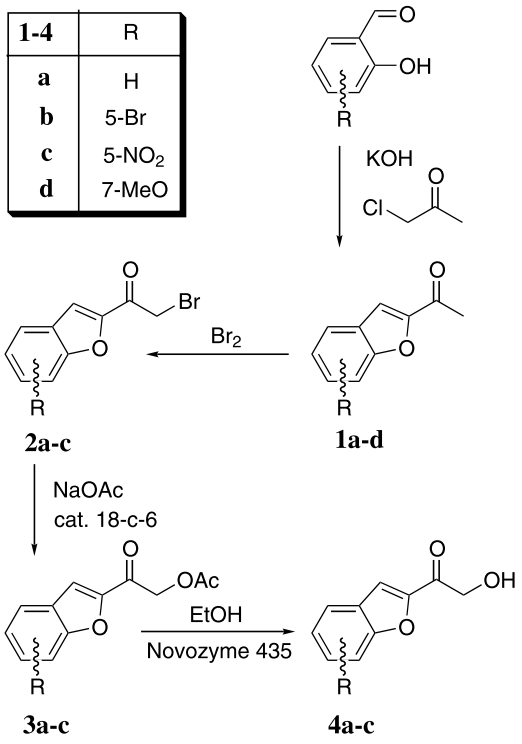

Figure 2. Preparation of the benzofuranyl ketones (**1**,**2**,**3**,**4a–d**).

With the 1-(benzofuran-2-yl)ethanones **1a–d**, 1-(benzofuran-2-yl)-2-hydroxyethanones **4a–c** and 2-acetoxy-1-(benzofuran-2-yl)-ethanones **3a–c** in our hands, we thought it worthwhile investigating their enantiotopic selective reduction by baker's yeast for the preparation of optically active (benzofuran-2-yl)carbinols.

2. Results and discussion

First, reduction of 1-(benzofuran-2-yl)etanone **1a** was studied under fermenting and non-fermenting conditions. Reduction of the **1a** with the fermenting system (80% yield, 2 days, 20% ee) was faster but less selective. Therefore, the non-fermenting system (60% yield, 7 days, 55% ee) was applied for reduction of the further (benzofuran-2-yl)ethanones **1b–d** as well (Fig. 3, Table 1). The enantiomeric composition of the products were precisely determined by GC and HPLC on chiral columns (see Sections 3.5 and 3.6). Comparison of the specific rotation of our sample {**5a**: $[\alpha]_D = -9.1$ (*c* 1, $CHCl_3$)} to the rotation value of (1*R*)-1-(benzofuran-2-yl)ethanol {(*R*)-**5a**: $[\alpha]_D = +19.9$ (*c* 1.21, $CHCl_3$)[18]} established its (*S*)-configuration. This (*S*)-configuration was also expected on the basis of the Prelog's rule.

Table 1. Baker's yeast reduction of 1-(benzofuran-2-yl)ethanones **1a–d**

Product	Time[a] (days)	Yield[a] (%)	$[\alpha]_D$[b]	E.e. (%)
(*S*)-**5a**	7	60	−9.1[c]	55
(*S*)-**5b**	7	74	−9.4	65
(*S*)-**5c**	7	61	−16.8	88
(*S*)-**5d**	7	66	−10.2	68

[a] Non-fermenting system (without saccharose) (see Section 3.6).
[b] temp. = 20°C, (*c* 1.00, $CHCl_3$).
[c] Lit. $[\alpha]_D = +19.9$ (*c* 1.21, $CHCl_3$) for (*R*)-**5a**.[18]

Although only the absolute configuration of the enantiomers of 1-(benzofuran-2-yl)ethanol (*S*)-**5a**[19] and (*R*)-**5a**[18,19] were known, configurations of all the products (**5a–d**) were assigned as (*S*) on the basis of the same sign of their specific rotation and also in accordance with Prelog's rule.

Next, several conditions were tested for the yeast reduction of 2-hydroxy-1-(benzofuran-2-yl)ethanone **4a** (Table 2).

It was found that the various additives significantly influenced the selectivity of the reduction. The moderate 42% ee enantiomeric excess observed with the fermenting system (entry 1) has been increased to 80% ee when the fermentation was performed in a hexane-water two-phase system (entry 4) or to 82% ee by

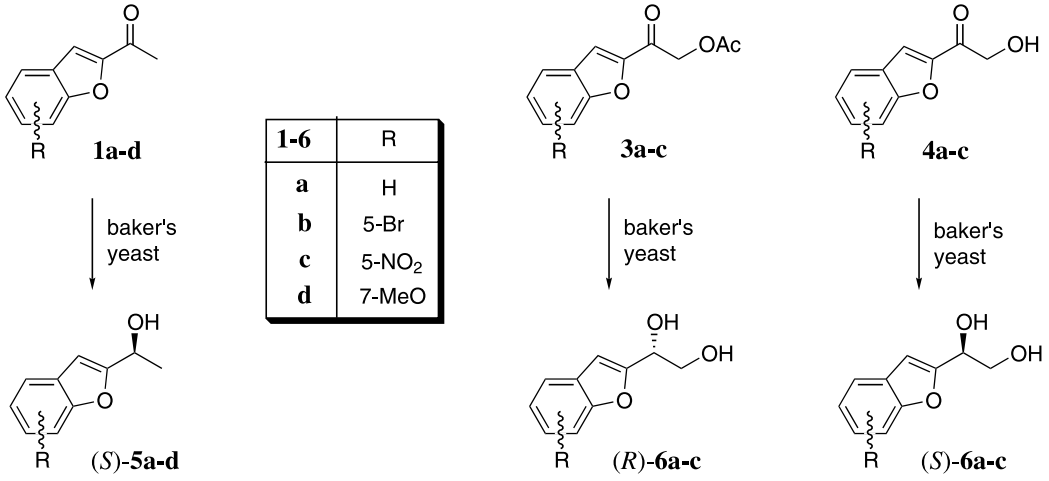

Figure 3. Asymmetric baker's yeast reduction of benzofuranyl ketones **1a–d**, **3a–c** and **4a–c**.

Table 2. Influence of the conditions on the selectivity of asymmetric reduction of 2-hydroxy-1-(benzofuran-2-yl)ethanone **4a**

Entry	Additive(s)[a] (amount)	Time (h)	Yield (%)	Config.[b] **6a**	E.e.[c] (%)
1	–	24	75	*S*	42
2	Ethyl chloroacetate (0.5%)	24	36	*S*	54
3	Allyl alcohol (0.5%)	24	46	*S*	61
4	Hexane (1:1, v:v)	24	56	*S*	80
5	L-Cysteine (0.5%)	24	80	*S*	82
6	–[d]	24	60	*S*	87

[a] A fermenting system (see Section 3.6) containing 25 g saccharose and the additive(s).
[b] Determined by chemical derivatization (see Section 3.7).
[c] Determined by HPLC (see Sections 3.4 and 3.6).
[d] Non-fermenting system (without saccharose).

Table 3. Baker's yeast reduction of 1-(benzofuran-2-yl) ketones **3a–c** and **4a–c**

Ketone	Product[a]	Time[b] (h)	Yield[b] (%)	$[\alpha]_D$[c]	E.e.[a] (%)
3a	(*R*)-**6a**	72	75	+24.1	84
3b	(*R*)-**6b**	72	82	+21.7	91
3c	(*R*)-**6c**	72	80	+19.0	91
4a	(*S*)-**6a**	24	60	−25.3	87
4b	(*S*)-**6b**	24	74	−22.1	92
4c	(*S*)-**6c**	24	61	−19.4	93

[a] Configuration and enantiomeric excess were determined by chemical derivatization (see Section 3.6).
[b] Non-fermenting system (without sucrose) (see Section 3.6).
[c] At 20°C, (*c* 1, $CHCl_3$).

adding L-cysteine (entry 5). The highest ee of the produced diol [(*S*)-**6a**, 87% ee); however, was achieved when the fermentation was carried out under non-fermenting conditions (entry 6).

Because non-fermenting conditions proved to be the most selective for reduction of the test hydroxymethyl ketone **4a**—similarly as for the simple ketones **1a–d** (Table 1)—reduction of the other hydroxymethyl ketones **4a–c** and acetoxymethyl ketones **3a–c** were also performed in this way (Table 3).

Interestingly, from the reduction of the acetoxymethyl ketones **3a–c** alcohols (−)-**6a–c** were exclusively isolated indicating that the benzofuran-2-yl derivatives are good substrates of the hydrolases also present in the baker's yeast cells. According to our expectations, these alcohols (−)-**6a–c** had the opposite sign of specific rotation than those (+)-**6a–c** obtained from the reduction of the hydroxymethyl ketones **4a–c**. The presence of a substituent at position 5 increased the selectivity of the reduction (in the acetoxymethyl series, **3a–c**, from 84 to 91% ee; or in the hydroxymethyl series, **4a–c**, from 87 to 92 and 93% ee).

Because the absolute configurations of the produced diols were not known, the diols (−)-**6a–c** prepared by whole-cell biotransformation with *S. cerevisiae* from hydroxymethyl ketones **4a–c** were converted to (1*S*)-1-(benzofuran-2-yl)ethanols (*S*)-**5a–c** (Fig. 3). Thus, from the (−)-diols (−)-**6a–c** (1*S*)-ethanols (*S*)-**5a–c** were obtained via selective mesylation and $LiAlH_4$ reduction of the resulting mesylates (*S*)-**8a–c** (Fig. 4), proving the (*S*)-configuration of diols (−)-**6a–c**. Moreover, the 1-(benzofuran-2-yl)ethanols (*S*)-**5a–c** were converted into

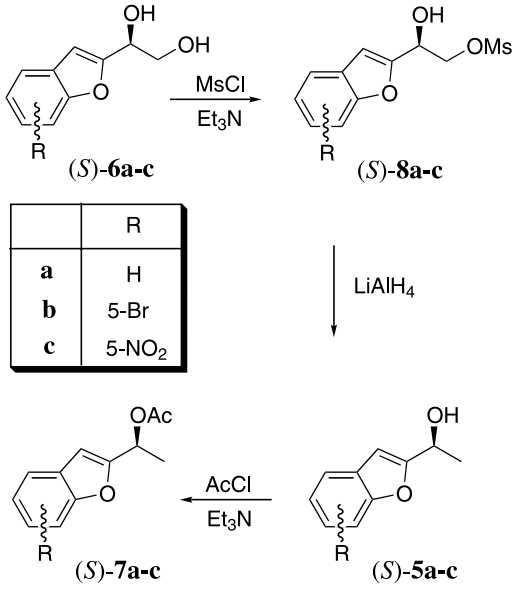

Figure 4. Chemical transformation of 1-(benzofuran-2-yl)ethane-1,2-diols **6a–c** into 1-(benzofuran-2-yl)ethanols **5a–c** and their acetates **7a–c**.

their acetates (*S*)-**7a–c** for determination of their enantiomeric composition by GC on chiral phase.

3. Experimental

3.1. Materials and methods

3.1.1. Analytical methods. The ^{1}H 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. In ^{1}H NMR measurements, long relaxation time ($D_1 = 20$ s) was applied for enhancing the accuracy of the integration. 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). HPLC determinations were made by a HP Series 1100 chromatograph equipped with isocratic pump, manual injector (20 μl) and DAD detector (detection at 254 nm) on (*S*,*S*)-Whelk-O1 (250×4 mm×5 μm; Merck) or (*R*,*R*)-Whelk-O1 (250×4 mm×5 μm; Merck) columns using hexane-*i*-PrOH (98:2, v/v) as eluant. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Melting points were determined by hot plate method and are uncorrected. TLC were made on Kieselgel 60 F_{254} aluminium sheets (Merck 1.05554). The spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution followed by heating. Preparative chromatography was performed using vacuum chromatography[20] on Merck Kieselgel 60 (0.063–0.200 μm).

3.1.2. Reagents and solvents. Salicylaldehydes, chloroacetone and the other commercial chemicals and solvents were products of Aldrich or Fluka. All solvents were purified and dried by standard methods. The bromomethyl ketones **2a**,[21] **2b**,[22] **2b**;[17] the hydroxymethyl ketones **3a–c**[17] and the acetoxymethyl ketones **3a–c**[17] were prepared according to the published procedures.

3.1.3. Biocatalyst. Baker's yeast produced as wet cakes by Budafok Ltd., Hungary, was from a local store.

3.2. Synthesis of 1-(benzofuran-2-yl)ethanones 1a–d

The corresponding salicylaldehydes (100 mmol) were added to a refluxing solution of KOH (5.6 g, 100 mmol) in methanol (250 ml). After cooling, chloroacetone (11.1 g, 120 mmol, 9.82 ml) was added dropwise at 0–10°C. The reactions were stirred under reflux for 2 h (or 48 h for **1c**). The solvent was distilled off in vacuum and the residue was extracted with CH_2Cl_2 and water (50 ml, each). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The product was obtained from the residue by recrystallization from ethanol.

3.2.1. 1-(Benzofuran-2-yl)ethanone 1a. Yield: 78%. Mp: 76°C (lit.[23] 75°C); ^{1}H NMR: 2.60 (3H, s), 7.29–7.33 (1H, m), 7.45–7.50 (2H, m), 7.57 (1H, d), 7.70 (1H, d); ^{13}C NMR: 26.83, 112.84, 113.44, 123.69, 124.30, 127.46, 128.66, 153.05, 156.06, 188.98; IR: 1676, 1552, 1448, 1368, 1320, 1296, 1176, 1080, 928, 848, 756. Anal. calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.86; H, 5.12%.

3.2.2. 1-(5-Bromo-benzofuran-2-yl)ethanone 1b. Yield: 85%. Mp: 110°C (lit.[24] 109–111°C); ^{1}H NMR: 2.62 (3H, s), 7.43 (1H, s), 7.47 (1H, d), 7.57 (1H, dd), 7.85 (1H, s); ^{13}C NMR: 26.93, 112.23, 114.38, 117.38, 126.16, 129.35, 131.63, 153.96, 154.66, 188.83; IR: 1668, 1544, 1368, 1324, 1304, 1284, 1176, 1084, 928, 804. Anal. calcd for $C_{10}H_7BrO_2$: C, 50.24; H, 2.95; Br, 33.42. Found: C, 50.29; H, 2.92; Br, 33.38%.

3.2.3. 1-(5-Nitrobenzofuran-2-yl)ethanone 1c. Yield: 65%. Mp: 175°C (lit.[25] 175–7°C); ^{1}H NMR: 2.66 (3H, s), 7.62 (1H, s), 7.69 (1H, d), 8.38 (1H, d), 8.66 (1H, s); ^{13}C NMR: 26.67, 112.86, 113.13, 119.99, 123.46, 127.38, 144.86, 155.13, 157.92, 188.13; IR: 1688, 1560, 1524, 1348, 1312, 1272, 1168, 1064, 928, 832. Anal. calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.49; H, 3.45; N, 6.87%.

3.2.4. 1-(7-Methoxybenzofuran-2-yl)ethanone 1d. Yield: 82%. Mp: 91°C (lit.[26] 92°C); ^{1}H NMR: 2.64 (3H, s), 4.04 (3H, s), 6.96 (1H, d), 7.19–7.22 (1H, m), 7.27–7.29 (1H, m), 7.49 (1H, s); ^{13}C NMR: 26.61, 56.09, 109.42, 112.67, 115.07, 124.57, 128.75, 145.35, 146.05, 153.06, 188.76; IR: 1680, 1568, 1356, 1320, 1264, 1168, 1092, 968, 912, 824. Anal. calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.52; H, 5.32%.

3.3. Preparation of racemic 1-(benzofuran-2-yl)ethanols *rac*-5a–d

The ketone **1a–d**, (1000 mg) was dissolved in methanol (50 ml) and $NaBH_4$ (400 mg) was added portionwise over 30 min at rt. After the reaction was completed (checked by TLC), a solution of 2N HCl (5 ml) was added. The solvent was distilled off in vacuo and the residue was extracted with CH_2Cl_2 (20 ml, twice). The resulting organic solution was dried over $MgSO_4$ and the solvent was removed by vacuum evaporation. The residue was purified by preparative vacuum-chromatography (silica gel, CH_2Cl_2–acetone, 10:1, v:v) to yield the racemic alcohol *rac*-**5a–d**.

3.3.1. 1-(Benzofuran-2-yl)ethanol *rac*-5a. Yield: 83%. Mp: 41°C (lit.[27] 40–41°C); ^{1}H 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%.

3.3.2. 1-(5-Bromobenzofuran-2-yl)ethanol *rac*-5b. Yield: 83%. Mp: 50°C; ^{1}H 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%.

3.3.3. 1-(5-Nitrobenzofuran-2-yl)ethanol *rac*-5c. Yield: 83%. Mp: 75°C (lit.[25] 73–76°C); ^{1}H 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%.

3.3.4. 1-(7-Methoxybenzofuran-2-yl)ethanol *rac*-5c. Semisolid. Yield: 83%; ^{1}H 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%.

3.4. Preparation of racemic 1-(benzofuran-2-yl)ethane-1,2-diols *rac*-6a-c

Chemical reduction of hydroxymethyl ketones **3a**–**c** (100 mg) by $NaBH_4$ in methanol was performed as described in Section 3.3.

3.4.1. 1-(Benzofuran-2-yl)ethane-1,2-diol *rac*-6a. Yield: 75%. Mp: 85°C (lit.[28] 87–88); ^{1}H NMR (MeOH-d_4): 3.82–3.93 (2H, m), 4.81–4.83 (1H, m), 6.73 (1H, s), 7.18 (1H, t), 7.16–7.26 (1H, m), 7.43 (1H, d), 7.53 (1H, d); ^{13}C NMR (MeOH-d_4): 65.87, 70.19, 104.59, 112.05, 122.12, 123.88, 125.21, 129.78, 156.40, 159.30; IR: 3272, 2984, 1960, 1712, 1672, 1576, 1484, 1392, 1280, 1192, 1152, 1136, 1128, 1084, 996, 984, 956, 920, 912, 808, 764, 736; HPLC ((*S*,*S*)-Whelk-O1, 1.5 ml/min) $R_{T(S)}$: 15.28 min, $R_{T(R)}$: 20.37 min. Anal. calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.45; H, 5.58%.

3.4.2. 1-(5-Bromobenzofuran-2-yl)ethane-1,2-diol *rac*-6b. Yield: 79%. Mp: 135°C; ^{1}H NMR (DMSO-d_6): 3.87–3.97 (2H, m), 4.82–4.84 (1H, m), 6.97 (1H, s), 7.64 (1H, d), 8.20 (1H, d), 8.51 (1H, s); ^{13}C NMR (DMSO-d_6): 65.37, 69.98, 105.53, 112.67, 118.51, 120.96, 130.38, 145.63, 159.17, 163.41; IR: 3268, 2988, 1962, 1718, 1662, 1556, 1464, 1388, 1282, 1190, 1154, 1132, 1124, 1080, 992, 948, 924, 916, 818, 756; HPLC ((*S*,*S*)-Whelk-O1, 1.5 ml/min) $R_{T(S)}$: 33.77 min, $R_{T(R)}$: 36.37 min. Anal. calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53; Br, 31.08. Found: C, 46.65; H, 3.58; Br, 31.15%.

3.4.3. 1-(5-Nitrobenzofuran-2-yl)ethane-1,2-diol *rac*-6c. Yield: 74%. Mp: 113°C; ^{1}H NMR (DMSO-d_6): 3.97–3.87 (2H, m), 4.89 (1H, m), 6.97 (1H, s), 7.64 (1H, d), 8.20 (1H, d), 8.51 (1H, s); ^{13}C NMR (DMSO-d_6): 65.37, 69.98, 105.53, 112.67, 118.51, 120.96, 130.38, 145.63, 159.17, 163.41; IR: 3232, 2992, 1960, 1624, 1616, 1592, 1572, 1480, 1396, 1284, 1192, 1176, 1132, 1080, 1040, 1000, 984, 964, 948, 912, 856, 796, 764, 700. Anal. calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.82; H, 4.12; N, 6.33%.

3.5. Preparation of racemic 1-acetoxy-1-(benzofuran-2-yl)ethanes *rac*-7a–d

To a solution of alcohol *rac*-**5a**–**d**, (0.3 mmol) and triethylamine (33.5 mg, 46 μl, 0.33 mmol) in CH_2Cl_2 (2 ml) acetylchloride (26 mg, 24 μl, 0.33 mmol) was added and the mixture was stirred at rt for 2 h. The reaction mixture was poured in water (10 ml) and extracted with CH_2Cl_2 (20 ml, twice). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified by vacuum-chromatography (eluent: CH_2Cl_2–acetone 9:1, v:v) yielding the racemic acetates (*rac*-**7a**–**d**) as colorless semisolids.

3.5.1. 1-Acetoxy-1-(benzofuran-2-yl)ethane *rac*-7a. Yield: 90%; ^{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; GC (165°C) $R_{T(R)}$: 3.75 min, $R_{T(S)}$: 3.84 min; HPLC ((*S*,*S*)-Whelk-O1, 1 ml/min) $R_{T(S)}$: 3.88 min, $R_{T(R)}$: 5.25 min, ((*R*,*R*)-Whelk-O1, 1 ml/min) $R_{T(R)}$: 4.4 min, $R_{T(S)}$: 6.37 min. Anal. calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.62; H, 5.95%.

3.5.2. 1-Acetoxy-1-(5-bromobenzofuran-2-yl)ethane *rac*-7b. Yield: 85%; ^{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; GC (120–170°C, 1°C/min) $R_{T(R)}$: 37.34 min, $R_{T(S)}$: 38.06 min; HPLC ((*S*,*S*)-Whelk-O1, 1 ml/min) $R_{T(S)}$: 4.07 min, $R_{T(R)}$: 5.45 min, ((*R*,*R*)-Whelk-O1, 1 ml/min) $R_{T(R)}$: 4.42 min, $R_{T(S)}$: 6.04 min. 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%.

3.5.3. 1-Acetoxy-1-(5-nitrobenzofuran-2-yl)ethane *rac*-7c. Yield: 93%; ^{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; GC (130–180°C, 1°C/min) $R_{T(R)}$: 46.94 min, $R_{T(S)}$: 47.56 min; HPLC ((*S*,*S*)-Whelk-O1, 2 ml/min) $R_{T(S)}$: 4.09 min, $R_{T(R)}$: 5.12 min, ((*R*,*R*)-Whelk-O1, 1 ml/min) $R_{T(R)}$: 4.75 min, $R_{T(S)}$: 6.03 min. 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%.

3.5.4. 1-Acetoxy-1-(7-methoxybenzofuran-2-yl)ethane *rac*-7d. Yield: 85%; ^{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; GC (120–170°C, 1°C/min) $R_{T(R)}$: 33.39 min, $R_{T(S)}$: 34.07 min; HPLC ((*S*,*S*)-Whelk-O1, 1 ml/min) $R_{T(S)}$: 7.70 min, $R_{T(R)}$: 11.56 min, ((*R*,*R*)-Whelk-O1, 1 ml/min) $R_{T(R)}$: 8.69 min, $R_{T(S)}$: 13.19 min. Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.62; H, 6.11%.

3.6. Asymmetric reduction of (1-benzofuran-2-yl) ketones 1a–d, 3a–c and 4a–c by baker's yeast

3.6.1. Non-fermenting reduction of (1-benzofuran-2-yl) ketones 1a–d, 3a-c and 4a-c by baker's yeast. Commercial baker's yeast (15 g) was suspended in water (250 ml). After stirring the resulting cell suspension for 15 min, the ketone **1a**–**d**, **3a**–**c** or **4a**–**c** (500 mg) dissolved in ethanol (5 ml) was added. The reaction mixture was stirred for the period indicated in Tables 1–3 and extracted with dichloromethane (2×250 ml). The combined organic layers were washed with saturated NaCl solution (50 ml), dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by vacuum-chromatography (CH_2Cl_2–acetone, 10:1, v:v) to give the corresponding alcohols [(*S*)-**5a**–**d**, yields are indicated in Table 1] or diols [(*R*)-**6a**–**c** or (*S*)-**6a**–**c**, yields are given in Tables 2 and 3].

The enantiomeric composition of the alcohols (*S*)-**5a**–**d** was determined after conversion into their acetates (*S*)-**7a**–**d** by GC and HPLC [for retention times, see Section 3.5].

The enantiomeric composition of the diols (*R*)-**6a**,**b** or (*S*)-**6a**,**b** was determined by HPLC on (*S*,*S*)-Whelk-O1 column [for HPLC retention times see Section 3.4]

3.6.2. Reduction of (1-benzofuran-2-yl) ketones 1a and 4a with fermenting baker's yeast. Fresh wet cake of baker's yeast (15 g) and sucrose (15 g) were added to water (250 ml) and the resulting suspension was stirred for 30 min. Then ethanolic solution of ketone **1a** and **4a** (500 mg/5 ml) was added and the reaction mixture was stirred for 48 h **1a** and 24 h **4a**, respectively. The further work up was performed as described in Section 3.6.1.

3.6.3. Baker's yeast mediated reduction of (1-benzofuran-2-yl) ketone 4a in the presence of additives. To a suspension of baker's yeast in water (15 g / 250 ml) additives (see Table 2; entries 2, 3 and 5; 1.25 g each), and after further 15 min. ethanolic solution of ketone **4a** (500 mg/5 ml) were added and the resulting mixture was stirred at rt for 24 h. For work up, see Section 3.6.1.

3.6.4. Non-fermenting reduction of (1-benzofuran-2-yl) ketone 4a by baker's yeast in water–hexane biphasic system. Baker's yeast (15 g) was suspended in water (250 ml) followed by addition of hexane (250 ml). After stirring the resulting cell suspension for 15 min, ethanolic solution of ketone **4a** (500 mg/5 ml) was added and the reaction mixture was stirred for 24 h. After separation, the aqueous phase was extracted with ethyl acetate (2×250 ml). The combined organic layers (hexane and ethyl acetate) were washed with saturated NaCl solution (50 ml), dried over $MgSO_4$. The further work up was performed as described in Section 3.6.1.

3.7. Configuration and enantiomeric composition of 1-(benzofuran-2-yl)ethane-1,2-diols (*R*)-6a–c or (*S*)-6a–c

Methanesulfonyl chloride (120 mmol, 120 mg, 116 μl) was added dropwise at −20°C into a solution of the corresponding 1-(benzofuran-2-yl)ethane-1,2-diol (*S*)-**6a**–**c** (112 mmol) and Et_3N (140 mmol, 141 mg, 181 μl) in CH_2Cl_2 (1 ml). After stirring the resulting mixture at rt for 30 min., it was washed with 2 M HCl (1 ml) and 10% $NaHCO_3$ (2 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuum. The residue was purified by vacuum-chromatography (silica gel, CH_2Cl_2). The resulting product (*S*)-**8a**–**c** was used in the next step immediately.

1 M $LiAlH_4$ solution in THF (25 mmol, 25 ml) was added dropwise into a solution of the corresponding mesylate (*S*)-**8a**–**c** in anhydrous THF (10 ml). The reaction mixture was stirred at rt for 1 h and under reflux for 3 h. After cooling, 5% HCl (10 ml) was added and the resulting mixture was evaporated to a final volume of about 10 ml. This residue was extracted with CH_2Cl_2 (15 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by vacuum-chromatography (CH_2Cl_2–acetone, 10:1, v:v) to yield the corresponding alcohol (*S*)-**5a**–**c**.

To determine the configuration and enantiomeric excess of the resulting alcohols (*S*)-**5a**–**c** by GC analysis on chiral column, they were transformed into their acetates (*S*)-**7a**–**c** as described in Section 3.5.

4. Conclusion

Baker's yeast mediated enantiotopic selective reduction of (benzofuran-2-yl)ketones proved to be a convenient method for preparation of optically active (benzofuran-2-yl)carbinols. Reduction of 1-(benzofuran-2-yl)ethanones **1a**–**d** yielded secondary alcohols (*S*)-**5a**–**d** with moderate to good enantiomeric excess [from 55 to 87% ee], whereas reduction of 1-(benzofuran-2-yl)-2-hydroxyethanones **4a**–**c** and 2-acetoxy-1-(benzofuran-2-yl)ethanones (**3a**–**c**) provided both enantiomeric forms of diols (*S*)-**6a**–**c** and (*R*)-**6a**–**c** in high enantiomeric purity [from 84 to 93% ee].

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