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Stereoselective bioreduction of 1-(5-phenylfuran-2-yl)-ethanones mediated by baker's yeast

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Abstract

Baker's yeast mediated reduction of various phenylfuran-2-yl-ethanones has been studied. The influence of the reaction conditions, the type and position of the substituents, as well the presence of various additives on the enantiomeric composition of the products and the reaction yield are discussed. The absolute configuration of the reaction products was established using a retrosynthetic procedure.

Keywords: *phenylfuran-2-yl-ethanols, baker's yeast, stereoselective, bioreduction, cellular biotransformation*

Introduction

Enantiopure heteroaryl secondary alcohols are versatile chiral intermediates and building blocks in the synthesis of more complex structures (Farina et al. 2006). Phenylfuran derivatives are also important structural subunits in various biologically active compounds. It was recently found that some phenylfuranyl derivatives exhibit cytoprotective effects against neurotoxin- and l**ipopolysaccharide**-induced cell death (Nishio et al. 2008), while others proved to be efficient inhibitors of the methionine aminopeptidase (MetAP), which is a promising target for the development of novel antibacterial, antifungal and anticancer agents (Huang et al. 2005). Accordingly, there is an increasing interest in the synthesis of novel phenylfuran-based compounds with potential applications in the pharmaceutical industry.

The bioreduction of ketones is one of the most important and practical reactions for producing enantiomerically enriched alcohols (Matsuda et al. 2009, Toşa et al. 2002a, 2002b). For this purpose, numerous efficient biocatalysts have been developed over the last decades. Among them, 38 various types of oxidoreductase have been commercialised by Daicel (http://daicelchiral.com/en/contents/chiralscreen/oh/index.html). Codexis also commercialises various enzyme screening kits for the reduction of ketones (http://www.codexis.com/pdf/Product_List.pdf). However, due to its ready availability and low cost, baker's yeast remains widely used for asymmetric reductions.

Several baker's yeast mediated enantioselective syntheses of various heteroarylethanols have been described. Highly enantiomerically enriched benzofuranyl-, benzo[*b*]thiophenyl-, pyridinyl- and furanyl-ethanols have been synthesised in high yield by whole cell reduction (Toşa et al. 2008, Paizs et al. 2003, Busto et al. 2006, Takeshita et al. 1987). Due to its high substrate specificity, only 1-substituted ethanones are accepted as substrates by yeast alcohol dehydrogenase (YADH), the main oxidoreductase from yeast. However, whole cells of baker's yeast are able to stereoselectively reduce a large variety of ketones, indicating that other oxidoreductases are also involved in the cellular biotransformation. These oxidoreductases, both (*R*)- and (*S*)-specific enzymes, may also display nearly equal activities towards substrates. Therefore, a drawback of baker's yeast bioreduction is that the isolated products may have low enantiopurity. Several procedures can be used to improve the stereoselectivity of the reduction, such as modification of

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the biocatalyst (Nakamura et al. 1995, Kaluzna et al. 2002) or of the reaction conditions by the addition of specific enzyme inhibitors (Yang et al. 2004, Meth-Cohn et al. 1994) or modifying the substrate (Dao et al. 1998).

The stereochemical outcome of baker's yeast mediated bioreduction of ketones is predictable, generally following Prelog's rule (Prelog 1964), which states that the hydride anion of the cofactor is delivered from the back face of the ketone, with the small group positioned on the right, thus generally producing the (*S*)-alcohol. Bioreductions that are not governed by Prelog's rule have also been reported, confirming the involvement of various oxidoreductases present in the baker's yeast cells (Ushio et al. 1993). Recently, an unexpected behaviour of baker's yeast cells was noticed concerning the stereoselective synthesis of various phenylfuran-2-yl-ethane-1,2-diols by biotransformation of the corresponding prochiral α-acetoxy- and α-hydroxymethylketones, with substituent effects on the reactivity and stereochemical outcome of the products being very diverse (Bencze et al. 2010). Here, we extend the investigation of baker's yeast mediated biotransformation of phenylfuran-2-yl derivatives, describing the bioreduction of phenylfuran-2-yl-ethanones **1a-e** into the corresponding (*S*)-ethanols. Moreover, using a retrosynthetic procedure, the absolute configuration of these novel enantiomerically enriched phenylfuran-2-yl-ethanols was also determined.

Methods

Analytical methods

^{1}H– and ^{13}C–NMR spectra were recorded on a Bruker spectrometer operating at 300 and 75 MHz, respectively. Spectra were recorded at 25°C in $CDCl_3$. ^{1}H– and ^{13}C–NMR spectra were referenced internally to the solvent signal. Electron impact mass spectra (EI-MS) were taken on a VG 7070E mass spectrometer operating at 70 eV. High performance liquid chromatography (HPLC) analyses were conducted with an Agilent 1200 instrument using a Chiralpak IA column (4.6 × 250 mm) and a mixture of *n*-hexane and 2-propanol (90: 10, v/v) as eluent for the enantiomeric separation of *rac*-**2a** and *rac*-**2d**, respectively; a Chiralcel AS-H column and a mixture of *n*-hexane and 2-propanol (90:10, v/v) as eluent for the enantiomeric separation of *rac*-**2b**; and a Chiralpak IC column and a mixture of *n*-hexane and 2-propanol (90:10, v/v) as eluent for the enantiomeric separation of *rac*-**2c,e**. Retention times for (*R*)- and (*S*)**-2a-e** are presented in Table IV. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60F^{254} sheets. Spots were visualised by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (63–200 μm). Melting points were determined by the hot plate method and are uncorrected. The optical rotatory powers were determined on a Perkin-Elmer 201 polarimeter and $[\alpha]_D^{25}$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Reagents and solvents

All organic and inorganic reagents and solvents were products of Aldrich or Fluka. All solvents were dried and purified by standard methods as required. Baker's yeast, produced as wet cakes by Budafok Ltd. (Hungary), was from a local store.

Synthesis of 1-(5-phenylfuran-2-yl)-ethanones 1a-e

2-Acetyl-furan (11.6 g, 0.105 mol) and cupric chloride (0.105 mol) were added at 0–5°C to a solution of one of the diazonium salts (0.1 mol) in water (100 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was extracted with dichloromethane (3 × 100 mL), the isolated organic layer was dried over anhydrous Na_2SO_4, filtered and the organic solvent was evaporated *in vacuo*. The crude product was purified by column chromatography using dichloromethane as eluent. Further purification of the products was performed by several recrystallisations from hexane.

The yield of the reaction and the analytical data – MS, NMR spectra and melting points – were identical to those reported earlier (Bencze et al. 2010).

Synthesis of racemic 1-(5-phenylfuran-2-yl) ethanols rac-2a-e

Small portions of sodium borohydride were added to the stirred mixture of 1-heteroaryl-ethanones **1a-e** (100 mg) in methanol (5 mL), until the entire amount of ketone was transformed (measured by TLC). Then, water (1 mL) was added gently to the mixture and the methanol removed *in vacuo*. The crude product was treated with CH_2Cl_2:water (1:1, v/v) (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography using *n*-hexane-ethylacetate: triethylamine (1:2:0.001, v/v) as eluent. The pure racemic 1-heteroarylethanols *rac*-**2a-e** were used as reference for the chiral HPLC separation.

1-(5-(2-chlorophenyl)furan-2-yl)ethanol rac-**2a**: Yield: 88%, white semisolid; HRMS: M+ found (M+ calculated for $C_{12}H_{11}ClO_2$: 222.0448): 222.1007; MS: *m/z* (%) = 225 (M + 1, ^{37}Cl, 2), 224 (M+, ^{37}Cl, 16), 223 (M + 1, ^{35}Cl, 7), 222 (M+, ^{35}Cl, 50), 210 (^{37}Cl, 3), 209 (^{37}Cl, 30), 208 (^{35}Cl, 12), 207 (^{35}Cl, 100), 179 (5), 151 (5), 149 (9), 144 (10), 141 (5), 139 (9), 116 (10), 115 (21), 114 (5), 113 (4), 111 (6), 83(5), 43 (13); ^{1}H-NMR ($CDCl_3$, 25°C): 1.56 (3H, d, J = 6.7 Hz), 2.00 (1H, s), 4.98 (1H, q, J = 6.6 Hz), 6.35 (1H, d, J = 3.3 Hz), 7.04 (1H, d, J = 3.3 Hz), 7.17–7.40 (2H, m), 7.46, 7.96 (1H, d, J = 7.5); ^{13}C-NMR ($CDCl_3$, 25°C): 19.7, 20.6, 21.3, 63.7, 68.2, 107.3, 108.7, 109.2, 111.5, 126.8, 127.8, 128.0.

1-(5-(4-bromophenyl)furan-2-yl)ethanol rac-**2b**: Yield: 91%, yellow semisolid; HRMS: M+ found (M+ calculated for $C_{12}H_{11}BrO_2$: 265.9942): 266.0152; MS: *m/z* (%) = 268 (M+, ^{81}Br, 97), 267 (M−1, ^{81}Br, 12), 266 (M+, ^{79}Br, 100), 265 (M−1, ^{79}Br, 18), 264 (94), 252 (^{81}Br, 19), 251 (^{81}Br, 93), 250 (^{79}Br, 24), 249 (^{79}Br, 96), 195 (^{81}Br, 65), 193 (^{79}Br, 77), 128 (12), 115 (^{81}Br, 11), 114 (42), 113 (^{79}Br, 15), 88 (16), 74 (17), 63 (12); ^{1}H-NMR ($CDCl_3$, 25°C): 1.61 (3H, d, J = 6.6 Hz), 2.21 (1H, s), 4.95 (1H, q, J = 6.5 Hz), 6.33 (1H, d, J = 3.2 Hz), 6.60 (1H, d, J = 3.2 Hz), 7.47–7.60 (4H, m); ^{13}C-NMR ($CDCl_3$, 25°C): 21.3, 63.7, 106.1, 107.5, 121.1, 125.2, 129.6, 131.7, 152.2, 157.5.

1-(5-(2-nitrophenyl)furan-2-yl)ethanol rac-**2c**: Yield: 89%, yellow semisolid; HRMS: M+ found (M+ calculated for $C_{12}H_{11}NO_4$: 233.0668): 223.0719; MS: *m/z* (%) = 234 (M + 1, 15), 233 (M+, 40.5), 231 (16), 218 (41), 202 (100), 189 (1.2), 117 (30), 111 (4.3), 109 (35), 97 (59), 83 (5.1), 71 (12), 69 (48), 57 (70), 43 (41); ^{1}H-NMR ($CDCl_3$, 25°C): 1.46 (3H, d, J = 6.6 Hz), 2.00 (1H, s, broad), 4.80 (1H, q, J = 6.6 Hz), 6.35 (1H, d, J = 3.0 Hz), 6.62 (1H, d, J = 3.2 Hz), 7.42 (1H, dd, J = 7.5 Hz, J = 7.7 Hz), 7.58 (1H, dd, J = 7.3 Hz, J = 7.5 Hz), 7.65 (1H, d, J = 8.1 Hz), 7.72 (1H, d, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 25°C): 21.8, 64.1, 108.2, 111.0, 122.2, 124.6, 124.8, 129.4, 129.5, 132.9, 148.6, 160.9.

1-(5-(4-nitrophenyl)furan-2-yl)ethanol rac-**2d**: Yield: 92%, brown semisolid; HRMS: M+ found (M+ calculated for $C_{12}H_{11}NO_4$: 233.0668): 233.0691; MS: *m/z* (%) = 233 (M+, 1.58), 232 (4.8), 231 (13.2), 218 (9.9), 217 (61.8), 216 (100), 203 (5.6), 202 (63), 186 (4.3), 170 (28), 158 (5), 141 (3.4), 43 (5); ^{1}H-NMR ($CDCl_3$, 25°C): 1.62 (3H, d, J = 6.7 Hz), 2.34 (1H, s), 4.92 (1H, q, J = 6.7 Hz), 6.31 (1H, d, J = 3.2 Hz), 6.69 (1H, d, J = 3.2 Hz), 7.23–7.57 (4H, m); ^{13}C-NMR ($CDCl_3$, 25°C): 21.3, 63.7, 11.2, 112.7, 122.2, 123.8, 123.9, 125.9, 134.9, 149, 154.4, 156.7.

1-(5-(4-chloro-2-nitrophenyl)furan-2-yl)ethanol rac-**2e**: Yield: 93%, yellow semisolid; HRMS: M+ found (M+ calculated for $C_{12}H_{10}ClNO_4$: 267.0298): 267.0191; MS: *m/z* (%) = 269 (M+, ^{37}Cl, 8), 268 (M + 1, ^{35}Cl, 3), 267 (M+, ^{35}Cl, 24), 225 (^{37}Cl, 3), 224 (^{37}Cl, 32), 223 (^{35}Cl, 11), 222 (^{35}Cl, 100), 206 (5), 205 (4), 195 (6), 180 (5), 179 (6), 178 (10), 153 (^{37}Cl, 9), 151 (^{35}Cl, 27), 150 (48), 140 (5), 139 (10), 138 (7), 115 (13), 113 (6), 58 (52), 55 (6), 43 (75); ^{1}H-NMR ($CDCl_3$, 25°C): 1.56 (3H, d, J = 6.6 Hz), 2.33 (1H, s, broad), 4.90 (1H, q, J = 6.5 Hz), 6.35 (1H, d, J = 3.3 Hz), 6.62 (1H, d, J = 3.3 Hz), 7.54 (1H, dd, J = 2.0 Hz, J = 8.4 Hz), 7.64–7.71 (2H, m); ^{13}C-NMR ($CDCl_3$, 25°C): 21.4, 63.6, 67.0, 107.6, 110.8, 122.4, 124.0, 129.6, 132.0, 133.7, 146.5, 159.4.

Cellular biotransformations of 1-(5-phenylfuran-2-yl)-ethanones 1a-e with baker's yeast

Analytical scale biotransformations of the prochiral ketones 1a-e

Non-fermenting biotransformations. Baker's yeast (2.5 g) was suspended in water (25 mL). After stirring for 15 min, the phenylfuran-2-yl-ethanones **1a-e** (10 mg) dissolved in DMSO (0.5 mL) were added to the resulting cell suspension. Samples (100 µL) were taken every 12 h over 48 h and were extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, the solvent was evaporated, the crude solid was redissolved in *n*-hexane-isopropanol (1:1, v/v) and analysed by HPLC.

Fermenting biotransformations. A fresh wet cake of baker's yeast (2.5 g) and sucrose (1 g) were added to water (25 mL). The resulting suspension was stirred for 30 min, followed by the addition of phenylfuran-2-yl-ethanones **1a-e** (10 mg) dissolved in DMSO (0.5 mL). Further experiments were performed as described in the previous section.

Biotransformations of ketones under fermenting conditions in the presence of additives. Experiments were conducted as previously described. *n*-Hexane (0.5 mL) or one of the other additives (15 mg) was introduced into the suspension together with the sucrose.

Preparative scale synthesis of (S)-heteroarylethanols 2a,c-e with baker's yeast

Sucrose (3 g) was added to a suspension of baker's yeast (15 g) in water (100 mL) and the mixture was

stirred for 30 min. For the biotransformation of **1c**, *n*-hexane (100 μL) was added to the reaction mixture. Subsequently, the solution of phenylfuran-2-yl-ethanones **1a-e** (100 mg) dissolved in DMSO (2 mL) was added to the fermenting suspension. The reaction mixture was stirred at room temperature until the transformation of the substrate was completed (checked by TLC: samples of 100 μL were taken and extracted with ethylacetate, then analysed with TLC). On completion of the reaction, the mixture was extracted with EtOAc (3 × 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo* and the crude product was purified by column chromatography using *n*-hexane-ethylacetate-triethylamine (1:2:0.001, v/v) as eluent.

MS and NMR spectra of the optically active products were indistinguishable from those of their racemates. Data on yield, the enantiomeric composition and the optical rotatory power of the products are presented in Table III.

Results and discussion

The prochiral heteroaryl-ethanones **1a-e** used as substrates were prepared by the Meerwein method (Meerwein et al. 1939) from the corresponding diazonium salts of various anilines and 2-acetyl-furan. Further, the racemic phenylfuran-2-yl-ethanols *rac*-**2a-e** were obtained by the chemical reduction of ketones **1a-e** (Scheme 1a). Due to the high instability of the phenylfuran-2-yl-ethanols *rac*-**2a-e** during their isolation and purification processes, the use of even weakly acidic media had to be avoided. The chromatographic enantiomeric separation of *rac*-**2-a-e** was further developed, which allowed us to investigate the stereochemical outcome of the baker's yeast mediated bioreductions (Table IV).

Initially, the analytical scale baker's yeast mediated transformation of **1a-e** was performed under fermenting (with sucrose) and non-fermenting (without sucrose) conditions (Table I). In all cases, the bioreduction in fermentative conditions resulted in higher stereoselectivity and conversion compared to the one performed in non-fermentative conditions.

As an example, while the fermenting bioreduction of **1c** occurred with a relatively high yield, the non-fermenting bioreduction of the same substrate failed (Table I, entry 3), as well as the biotransformation of **1b** under both conditions, almost quantitatively recovering the starting materials. This agrees with our earlier observation that both (5-(4-bromophenyl)furan-2-yl)-α-hydroxyethanone and (5-(4-bromophenyl)-furan-2-yl)-α-acetoxy-methylethanone are inadequate substrates for the baker's yeast enzymes (Bencze et al. 2010), probably due to the high steric demand of 1-(5-(4-bromophenyl)furan-2-yl)-ethanone preventing the interaction of these compounds with the catalytic site of cellular oxidoreductases.

The high enantiomeric excesses (ee) for (*S*)-**2d** and (*S*)-**2e** (Table I, entries 4 and 5) also accord with the previous good results for the synthesis of the corresponding 1,2-ethanediols by baker's yeast mediated biotransformation (Bencze et al. 2010). The difference between the ee values of the products obtained by bioreduction of **1c** and **1d** (Table I, entries 3 and 4) showed that the baker's yeast enzymes preferred the *para* substituted substrates over the *ortho* substituted ones.

Besides position, the electronic effects of the substituents could also influence the yields and enantiomeric composition of the obtained compounds. By selective reduction of **1c-e** with $SnCl_2$, the corresponding 1-(amino-5-phenyl-furan-2-yl)-ethanones were synthesised. Unfortunately, the bioreductions of these derivatives failed: as in the case of **1b**, no trace of product could be found in the reaction mixture. The absence of the cellular transformation of the amino ketones suggested a structural incompatibility between these substances and the enzymes in the baker's yeast cells, which could be explained by the different electronic distribution in the amino ketones compared to that of nitro ketones.

With the exception of the highly stereoselective bioreduction of **1d,e** (Table I, entries 4 and 5), the biotransformation of the other substrates **1a,c** yielded the corresponding (*S*)-phenylfuran-2-yl-ethanols (*S*)-**2a,c** with poor ee. These unsatisfactory results led us to perform the fermenting baker's yeast reductions of **1a,c** in the presence of various additives that could enhance the stereoselectivity of the enzymatic reductions. These compounds could act as specific inhibitors of (*S*)- or (*R*)-selective oxidoreductases. In most of the cases, their presence in the reaction mixture caused a variation (increase or decrease) of ee of the (*S*)-alcohols produced. The influence of the additives on the stereoselectivity of

Table I. Fermenting and non-fermenting biotransformation of **1a-e**.

			Fermenting system		Non-fermenting system	
Entry	Substrate	Product	ee (%)	Yield (%)	ee (%)	Yield (%)
1	**1a**	(*S*)-**2a**	64	70	52	49
2	**1b**	(*S*)-**2b**	–	–	–	–
3	**1c**	(*S*)-**2c**	41	85	–	–
4	**1d**	(*S*)-**2d**	98	80	80	57
5	**1e**	(*S*)-**2e**	99	87	27	61

Table II. The influence of various additives on the stereoselectivity of bioreduction of ketones **1a,c**.

Entry	Additives	ee (%)		Yield (%)		Time (h)
		(*S*)-**2a**	(*S*)-**2c**	(*S*)-**2a**	(*S*)-**2c**	
1	Fermenting	64	41	70	85	48
2	Non-fermenting	52	–	49	–	48
3	*n*-Hexane	46	58	40	79	48
4	L-Cysteine	53	56	45	70	48
5	$MgCl_2$	35	54	43	73	48
6	$MnCl_2$	41	49	51	81	48

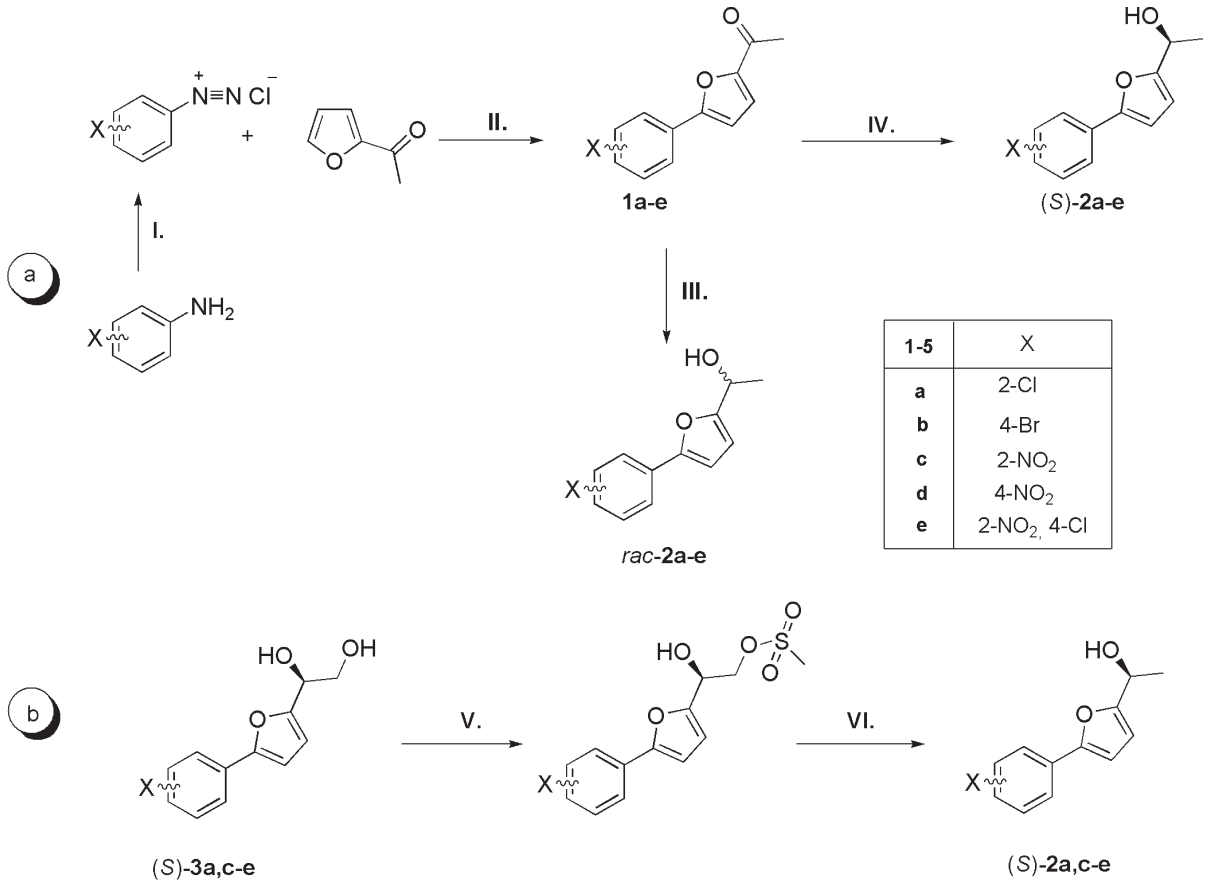
Table III. Baker's yeast mediated preparative scale synthesis of (*S*)-phenylfuran-2-yl-ethanols **2a,c-e**.

Entry	Substrate	Product	ee (%)	Yield (%)	$[\alpha_D^{25}]$
1	**1a**	(*S*)-**2a**[a]	64	65	−6.2
2	**1c**	(*S*)-**2c**[b]	58	81	−28
3	**1d**	(*S*)-**2d**[a]	98	76	+13
4	**1e**	(*S*)-**2e**[a]	99	80	−24

[a]Fermenting system, 48 h.
[b]Fermenting system with *n*-hexane 0.1% as additive, 48 h.

the bioreduction of **1a,c** differed for each substrate (Table II). However, none of the additives improved the ee of the produced (*S*)-phenylfuran-2-yl-ethanol (*S*)-**2a**, the best result remaining that obtained without additives in fermenting conditions (Table II, entry 1). The bioreduction of **1c** in the presence of 0.1% *n*-hexane showed the highest selectivity; however, a slight decrease in yield was observed (Table II, entry 3). As expected, the use of phenacyl-chloride, known to be an inhibitor of (*S*)-selective yeast oxidoreductases (Dao et al. 1998a, 1998b) impaired the cellular reduction of **1a,c**. Surprisingly, in the presence of allyl alcohol and ethyl bromoacetate, as inhibitors of (*R*)-selective yeast oxidoreductases (Shi et al. 2009, Cui et al. 1998, Forni et al. 1994, Nakamura et al. 1991), the bioreduction of **1a,c** failed.

Using the optimal conditions determined for the analytical scale reactions, preparative scale biore-



Scheme 1. (a) Chemical synthesis of phenylfuran-2-yl-compounds and baker's yeast mediated reduction of the ketones. (b) The synthetic route applied to determine the absolute configuration of the products.

Table IV. Retention times of the enantiomers of *rac*-**2a-e**.

Compound	t_R (min)	Compound	t_R (min)
(*S*)-**2a**	20.8	(*R*)-**2a**	22.3
(*S*)-**2b**	8.4	(*R*)-**2b**	9.7
(*S*)-**2c**	14.1	(*R*)-**2c**	15.9
(*S*)-**2d**	16.8	(*R*)-**2d**	17.7
(*S*)-**2e**	13.7	(*R*)-**2e**	17.1

ductions of **1a,c-e** were performed. In the scale-up procedure, no significant changes in yield, stereoselectivity and reaction time were observed, as compared to those found for the analytical scale procedures (Table III).

To determine the absolute configuration of the novel heteroarylethanols, a known retrosynthetic pathway was employed (Paizs et al. 2003). Thus, the known optically active diols (Bencze et al. 2010, 2011) (*S*)-**3a,c-e** were selectively mesylated at the primary hydroxyl group, followed by a reduction of the mesylated intermediates with $LiAlH_4$, yielding the corresponding optically active heteroarylethanols (*S*)-**2a,c-e** (Scheme 1b). The absolute configuration was established comparing the sign of the specific rotations and of the retention times of the heteroarylethanols obtained by the two different methods.

Conclusions

The baker's yeast mediated stereoselective synthesis of novel phenylfuran-2-yl-ethanols was developed. The procedure yielded the enantiomerically enriched (*S*)-alcohols with moderate to high yield and ee. A strong substituent effect was observed and investigated in comparison with our previous results obtained in the baker's yeast synthesis of novel phenylfuran-2-yl-ethanediols.

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