ALTERNATIVE APPROACHES FOR THE ENANTIOSELECTIVE SYNTHESIS OF (*R*)- AND (*S*)-BUFURALOL

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INTRODUCTION

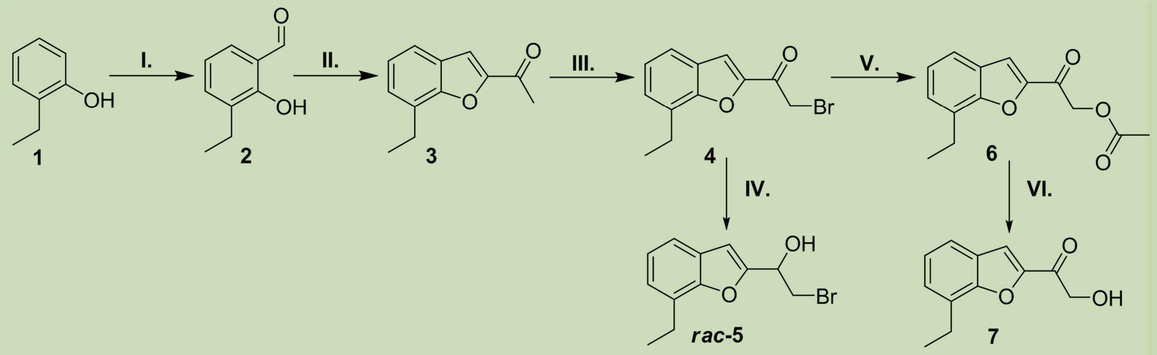
Bufuralol is a widely studied, potent, nonselective, β-adrenergic receptor antagonist. It is proved effective for the treatment of hypertension[1], it's an inhibitor of testosterone 6β-hydroxylase[2]. It is also used in studies of cytochrome P450 and undergoes enantioselective and regioselective oxidations in liver[3]. The β-blocking potency resides mainly in (S)-bufuralol, whereas the(*R*)-bufuralol is a commonly used marker of hepatic CYP 2D6 activity. Herein we present two alternative approaches for the synthesis of optically pure bufuralol: a baker's yeast-mediated reduction of prochiral 1-(7-ethylbenzofuran-2-yl)-2-oxoethyl-acetate **6** and 1-(7-ethylbenzofuran-2-yl)-2-hydroxyethanone **7** into 1,2-diols, and a procedure via lipase-mediated enantioselective acylation of racemic 2-bromo-1-(7-ethylbenzofuran-2-yl)ethanol ***rac*-5**.

RESULTS AND DISCUSSION

Firstly, the chemical synthesis of the corresponding substrates was performed starting from 2-ethylphenol **1** (**Scheme 1.**).

Baker's yeast mediated biotransformations are based on the activity of hydrolases and YADHs from *Saccharomyces cerevisiae.* Based on our previous results[4], we carried out the transformation of compound **6** and **7** under fermenting and non-fermenting conditions. The influence of various additives was also investigated, in order to enhance the enantiopurity of the product **(Table 1**.). The enantiopure diols **(*R*)-** and **(*S*)-11** were transformed into **(*R*)-** and **(*S*)-bufuralol** by standard chemical methods (**Scheme 2.**).

Scheme 1. Chemical synthesis of the substrates used in the biotransformations



I. Paraformaldehyde, Et_3N, $MgCl_2$, CH_3CN, reflux; **II.** Chloroacetone, K_2SO_4,CH_3CN, reflux; **III.** $PyrBr_3$, CH_3COOH, reflux; **IV.** $NaBH_4$, CH_3COONa, CH_3OH, r.t; **V.** CH_3COONa, 18-C-6/ 1,4-dioxane, reflux; **VI.** Cal-B/ EtOH, 300 rpm, r.t;

Scheme 2. Synthesis of bufuralol by baker's yeast mediated biotransformations

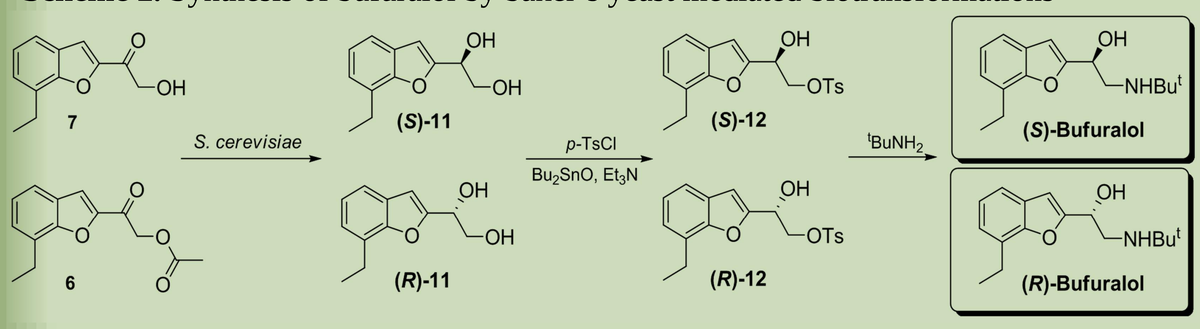


Table 1. Baker's yeast mediated biotransformations of **6** and **7** after 40 h

Entry	Additives	Fermenting				Non-fermenting			
		OAc		OH		OAc		OH	
		ee(%)	*c* (%)	*ee*(%)	*c* (%)	*ee*(%)	*c* (%)	*ee*(%)	*c* (%)
1	Without additive	92	90	86	91	90	84	87	88
2	Allyl alcohol	96	76	80	89	96[b]	89	80	89
3	*n*-Hexane	98	97	50	74	95[b]	74	78	90
4	L-Cysteine	96	83	96	94	95	94	76	86
5	Ethyl bromoacetate	-	-	-	-	-	-	-	-
6	$MgCl_2$	96[b]	93	62	81	92	81	50	74
7	DMSO	95	79	76	88	94	88	77	89

Figure 1. Chromatographic separations of the enantiomers of **11**

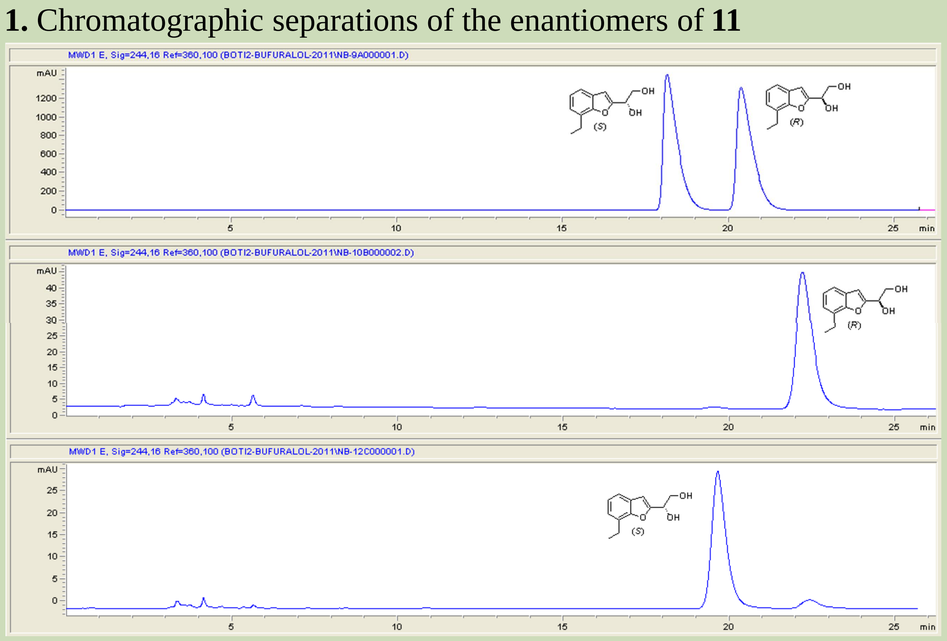
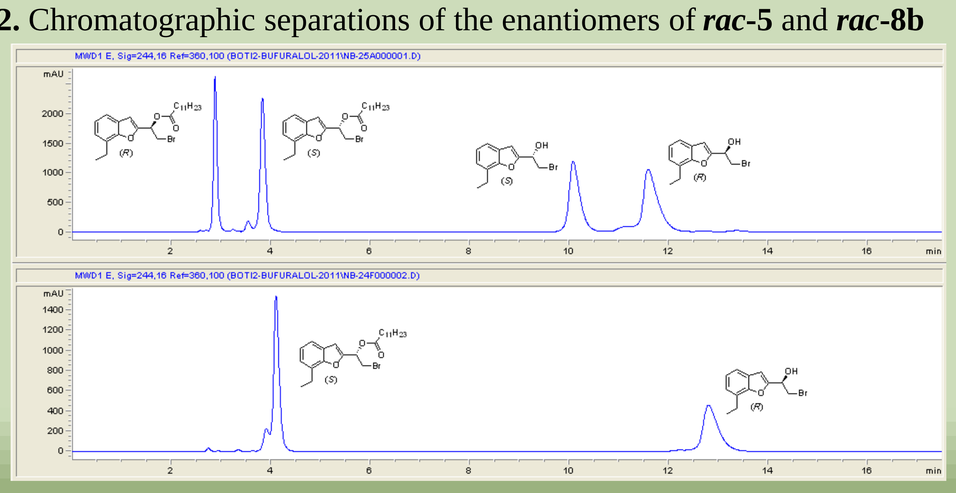


Figure 2. Chromatographic separations of the enantiomers of ***rac*-5** and ***rac*-8b**



Commercially available immobilized lipases, such as lipase A and B from *Candida antarctica*, lipase from *Pseudomonas fluorescens* (AK), lipase LPS, and CRL were tested in various organic solvents for the enantioselective acylation of ***rac*-5** with vinyl acetate and vinyl laurate as the acyl donor. Cal-B was found to be the optimal biocatalyst in both cases (**Table 2,3.**).

Cromatographic separation of the enantiomers was established using various HPLC columns and hexane-2-propanol mixtures as eluent (**Figure 2.**). The products **(*R*)-5** and **(*S*)-8a,b** were further transformed by chemical methods.

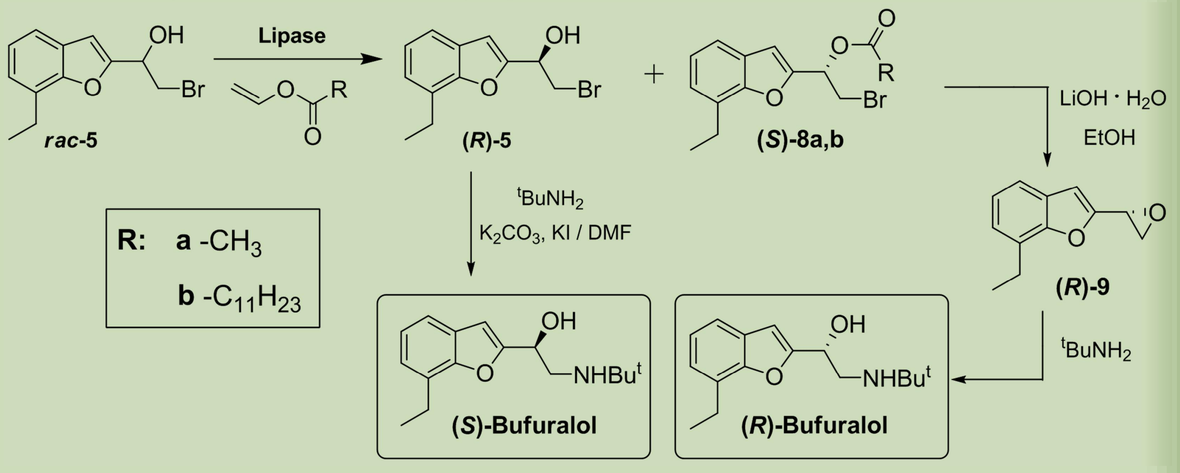
Table 2. Enantioselective acylation of ***rac*-5** with Cal-B and vinyl acetate after 24 hours

Entry	Solvent	ee_p (%)	ee_s (%)	*c* (%)	E
1	DIPE	44	85	66	6
2	n-Hexane	96	84	47	120
3	CH_3CN	92	84	48	61
4	Toluene	99	54	35	>>200
5	n-Octane	99	33	25	>>200

Table 3. Enantioselective acylation of ***rac*-5** with Cal-B and vinyl laurate after 24 hours

Entry	Solvent	ee_p (%)	ee_s (%)	*c* %	E
1	MTBE	99	99	50	>>200
2	DIPE	95	99	49	>>200
3	MeTHF	99	51	34	>200
4	n-Hexane	87	99	50	132
5	CH_3CN	99	45	31	>>200
6	Toluene	99	99	50	>>200
7	n-Octane	87	99	53	122

Scheme 3. Synthesis of bufuralol by lipase mediated kinetic resolution of ***rac*-5**



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