Tetrahedron: *Asymmetry* 22 (2011) 675–683

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Sequential use of regio- and stereoselective lipases for the efficient kinetic resolution of racemic 1-(5-phenylfuran-2-yl)ethane-1,2-diols

László Csaba Bencze, Csaba Paizs, Monica Ioana Toşa, Florin Dan Irimie *

Department of Biochemistry and Biochemical Engineering, Babeş-Bolyai University, Arany János str. 11, 400028 -Cluj Napoca, Romania

ARTICLE INFO

Article history:
Received 23 February 2011
Accepted 18 March 2011
Available online 7 May 2011

ABSTRACT

Possible routes for the enzymatic transformation of various substituted 1-(5-phenylfuran-2-yl)ethane-1,2-diols and their mono- and diacetylated counterparts were studied. Combining the regioselectivity of LPS mediated acylation of the starting racemic diols, the stereoselectivity of LAK shown in the enantiomer selective transformation of the previously formed racemic primary acetates and the LPS mediated mild hydrolysis–alcoholysis of the resolution products, an efficient preparative scale procedure for the synthesis of various highly enantiomerically enriched (*R*)- and (*S*)-phenylfuran-2-yl-ethane-1,2-diols has been developed.

1. Introduction

Phenylfuran based structures are important structural subunits in various biologically active compounds. Recently some phenylfuranyl derivatives have exhibited cytoprotective effects against neurotoxin- and LPS-induced cell death,[1] while others have proven to be efficient inhibitors of the methionine aminopeptidase (MetAP), which is a promising target for the development of novel antibacterial, antifungal, and anticancer agents.[2] Accordingly there is an increasing interest for the synthesis of novel phenylfuran based compounds with potential application in the pharmaceutical industry.

1,2-Ethanediols are important chiral intermediates in asymmetric synthesis, frequently used for the synthesis of pharmaceuticals.[3] Our previous work[4] devoted to the chemo-enzymatic synthesis of both enantiomeric forms of phenylfuran-2-yl-ethane-1,2-diols via Baker's yeast mediated biotransformation of α-acetoxymethyl-5-phenylfurane-2-yl-ethanones and of α-hydroxymethyl-5-phenylfuran-2-yl-ethanones did not give the expected results. Due to the observed strong substituent effect, in some cases no biotransformation occurred, or products with low enantiomeric excess were formed; the method proved to be unsatisfactory as a general synthetic procedure for the synthesis of both enantiomers of phenylfuran-2-yl-ethane-1,2-diols.

Therefore, we turned our interest to lipase mediated kinetic resolution, as an alternative procedure for the synthesis of highly enantiomerically enriched forms of phenylfuran-2-yl-ethane-1,2-diols.

Lipase mediated biotransformations of arylethane-1,2-diols have been studied extensively.[5–12] Enzymatic acylation of racemic 1,2-diols,[5–9,11,12] of primary[9–11] and secondary[9,11] acetates of 1,2-diols, as well as the hydrolysis[5,9,11] or alcoholysis[5,11] of primary and secondary monoacetates or 1,2-diol diacetates have all been investigated. Significant differences were found between the enzymatic transformations of 1,2-diols and their acylated derivatives. Lipases showed the highest activity and enantioselectivity for the kinetic resolution of various primary esters of the 1,2-diols.[5–12] LPS (formerly the lipase from *Pseudomonas cepacia*, now lipase from *Burkholderia cepacia*) was found to be a proper regio- and enantioselective catalyst. Thus, in the transformation of racemic 1,2-diols in the first acylation step, the racemic primary monoacetates of the 1,2-diols were formed, followed by a second highly enantioselective acylation step yielding both enantiomerically enriched diacetylated 1,2-diols and primary monoacetates. An efficient LAK (lipase AK from *Pseudomonas fluorescens*) mediated acylation of the secondary monoacetate of 1-phenylethane-1,2-diol was also reported.[9]

With the exception of the CaLB (lipase B from *Candida antarctica*) mediated one-pot methanolysis of the diacetate of 1-phenyl-ethane-1,2-diol,[11] which allows the preparation of the (*S*)-1-phenylethane-1,2-diol and the (*R*)-1-acetoxy-1-phenylethanol with high ee, enzymatic alcoholysis or hydrolysis generally shows lower regioselectivity and enantioselectivity.

In contrast to the numerous lipase mediated kinetic resolutions of arylethane-1,2-diols, except for the LPS mediated enzymatic resolution of racemic 2-(2-furyl)-2-hydroxyethyl acetate,[10] enzymatic resolution of heteroarylethane-1,2-diols has not been reported.

The significant differences observed in the regio- and stereoselectivity of various enzymatic transformations, prompted us to

* Corresponding author. Tel.: +40 264 593 833; fax: +40 264 593 818.
E-mail address: irimie@chem.ubbcluj.ro (F.D. Irimie).

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doi:10.1016/j.tetasy.2011.03.006

investigate all the possible enzymatic reactions of phenylfuran-2-yl-ethane-1,2-diols and their primary or secondary monoacylated or diacylated counterparts in order to develop an efficient enzymatic procedure for the synthesis of both enantiomers of various phenylfuran-2-yl-ethane-1,2-diols.

2. Results and discussion

2.1. Preparation of the racemic substrates by chemo-enzymatic methods

Racemic 1-(5-phenylfuran-2-yl)ethane-1,2-diols *rac*-**5a–d** were prepared by the chemoenzymatic method described earlier by us.[4] These were transformed by chemical acylation into racemic diacetates *rac*-**7a–d** (Scheme 1).

In order to avoid the usual drawbacks of the protecting groups employed for the regioselective acylation of *rac*-**5a–d** and because the chemical synthesis of racemic 2-hydroxy-1-(5-phenylfuran-2-yl)ethyl acetates *rac*-**6a–d** and 2-hydroxy-2-(5-phenylfuran-2-yl)ethyl acetates *rac*-**8a–d** by the previously described methods[11] were unsuccessful, we turned our attention toward highly regioselective, but non-stereoselective enzymatic methods.

In the enzymatic acylation of racemic 1,2-ethanediols *rac*-**5a–d** it was observed that LPS acts in a highly regioselective manner, yielding only *rac*-**6a–d** (Scheme 1). LPS was also found to be an appropriate biocatalyst for the synthesis of racemic 2-hydroxy-2-(5-phenylfuran-2-yl)ethyl acetates *rac*-**8a–d**. Thus, by the LPS mediated hydrolysis of the racemic diacetates *rac*-**7a–d** in THF–water mixture (1:1, v/v) *rac*-**8a–d** were quantitatively obtained.

The gram-scale procedures were carried out in a similar way; the isolation and the purification of the target compounds was easy and simple to carry out thus providing an accessible synthetic route to both monoacetylated phenylfuran-2-yl-ethane-1,2-diols *rac*-**6**,**8a–d**. In this manner the use of difficult chemical methods,[9,11,13] requiring special reagents or experimental conditions, was avoided.

In order to synthesize enantiomerically pure 1-(5-phenylfuran-2-yl)ethane-1,2-diols, the enzymatic kinetic resolution of authentic racemic compounds *rac*-**5–8a–d** was further investigated.

2.2. The enzymatic acylation of racemic diols *rac*-5a–d

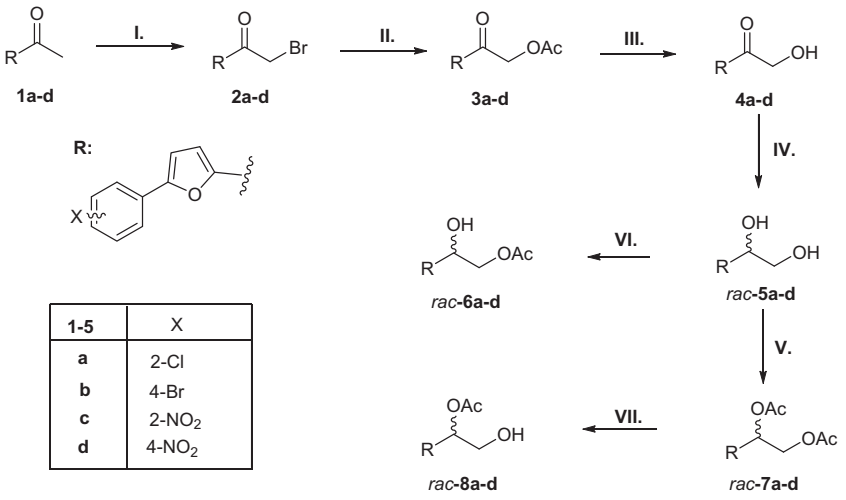
In our first approach we focused on the enzymatic acylation of the racemic 1,2-ethanediols *rac*-**5a–d**. Using various solvents as reaction media and vinyl acetate as the acyl donor, most of the lipases tested showed little to no activity. Only the highly active LPS and PPL (porcine pancreatic lipase) with moderate activity catalyzed regioselectively the acylation of the *rac*-**5a–d**, yielding the racemic 2-hydroxy-2-(5-phenylfuran-2-yl)ethyl acetates *rac*-**6a–d**. CaLA (lipase A from *C. antarctica*) catalyzed in the first step with poor regioselectivity; the acylation of *rac*-**5a–d** yielding both *rac*-**6a–d** and *rac*-**8a–d** with an approximate 4:1 ratio. In the second step, the monoacylated compounds formed were further acylated by CaLA. As described in the next paragraph, while the acetylation of *rac*-**6a–d** proceeded stereoselectively, *rac*-**8a–d** was transformed rapidly with low stereoselectivity, lowering the ee of (*R*)-**7a–d** produced in the reaction mixture (Scheme 2). Thus the use of the racemic heteroaryl-ethane-1,2-diols *rac*-**5a–d** as substrates for an efficient enzymatic enantiomer selective resolution was ruled out.

2.3. The enzymatic kinetic resolution of *rac*-6,8a–d

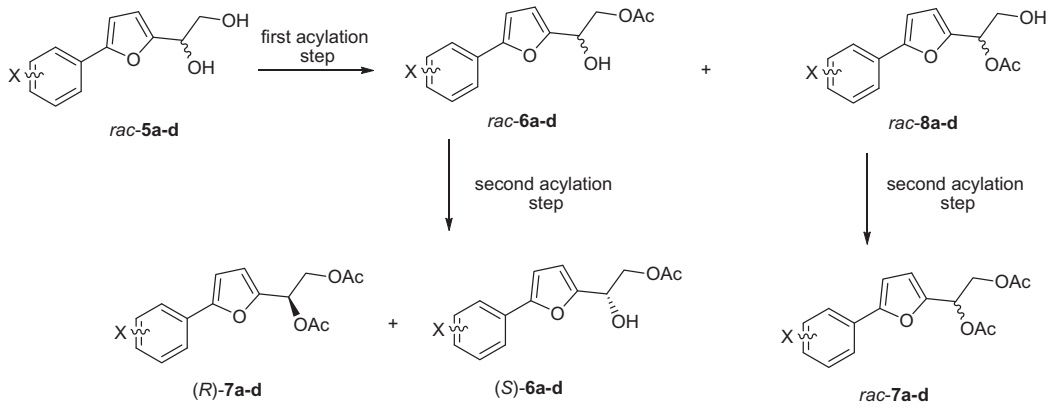
It is known that lipases catalyze in their biological function the 1,3-regioselective hydrolysis of triacylglycerols at water–lipid interfaces. Consequently, we decided to investigate the enzymatic kinetic resolution of racemic 2-hydroxy-2-(5-phenylfuran-2-yl)ethyl acetates *rac*-**8a–d**, since the enzymatic acylation of the primary hydroxyl group should be favoured.

Using racemic 1-(5-(4-bromophenyl)furan-2-yl)2-hydroxyethyl acetate *rac*-**8b** as a model compound, potentially useful lipases were screened for enantiomeric selective acylation with vinyl acetate (8 equiv) in various organic solvents. Most of the lipases showed high activity and low enantioselectivity in all tested solvents. The best results were obtained in diisopropyl ether (DIPE), however, the obtained results were unsatisfactory (E <7, Scheme 3a), as shown in Table 1. These results can be explained by the fact that the reacting hydroxyl group is near to the asymmetric center, thus the steric recognition between the catalytic center of the enzyme and the enantiomers of the substrate is poor.

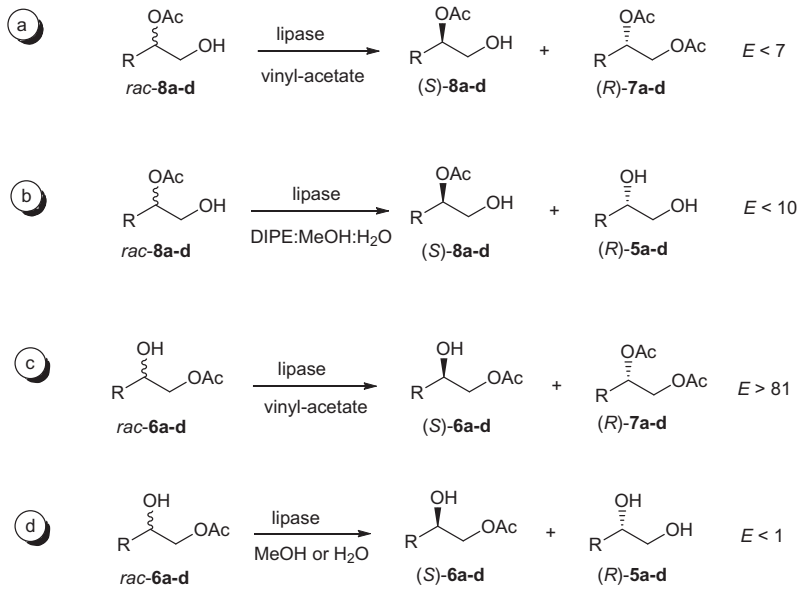
The enzymatic alcoholysis or hydrolysis of the racemic secondary monoacetate *rac*-**8b** also gave unsatisfactory results. Most of the lipases and other hydrolases like PLE, Acylase I and esterase from *Rhizopus oryzae* were catalytically inactive in neat alcohols such as methanol, ethanol, propanol, and butanol as well as in various organic solvents with a content of 8 equiv of the previously mentioned nucleophiles. The enzymatic hydrolysis performed in water or in THF–water (1:1, v/v) mixture also unsuccessful. A mixed enzymatic alcoholysis–hydrolysis process, with moderate



Scheme 1. Chemo-enzymatic synthesis of racemic *rac*-**5–8a–d**. Reagents and conditions: (I) pyridinium tribromide/CH_3COOH, 90 °C; (II) NaOAc, 18C6/1,4-dioxane, reflux ; (III) Novozyme 435/MeOH; (IV) $NaBH_4$ /MeOH; (V) AcCl, DMAP/Py. in CH_2Cl_2; (VI) LPS, vinyl acetate; (VII) LPS/H_2O–THF (1:1, v/v)



Scheme 2. CaLA mediated acylation of racemic phenylfuran-2-yl-ethane-1,2-diols *rac*-**5a**–**d**.



Scheme 3. Enzymatic kinetic resolution of the racemic monoacylated diols.

Table 1
Enzymatic acylation with vinyl acetate of *rac*-**8b** in DIPE

Entry	Enzyme	Time	*c* (%)	ee_P (%)	ee_S (%)	*E*
1	CaLA	2 h	29.5	31	13	2
2	LPS	2 h	61	52	81	7
3	CaLB*	2 h	61	46	72	6
4	CrL	16 h	54	49	58	5

* Anti-Kazlauskas type.

Table 2
Lipase catalyzed acylation of the primary monoacetate *rac*-**6c**

Entry	Enzyme	Time (h)	*c* (%)	ee_P (%)	ee_S (%)	*E*
1	CaLA	6	47	91	76	49
2	CLEA	4	40	85	56	22
3	IMMCaLA T2–150	4	34	73	37	9
4	LAK	24	43	94	71	69
5	CaLB	16	4	50	2	3
6	CrL	16	21	53	14	4

enantioselectivity (*E* <10), yielding the (*R*)-**5b** (ee: 65%) and the (*S*)-**8b** (ee: 35%), occurred when the reaction was performed in a DIPE–MeOH–water (1:1:2, v/v) mixture in the presence of LPS (Scheme 3b). Similar results were found also for the LPS mediated mixed alcoholysis–hydrolysis for the rest of the substrates *rac*-**8a**,**c**,**d**.

The enzymatic acylation of primary monoacetate derivatives *rac*-**6a**–**d** was also performed (Scheme 3c). 2-Hydroxy-2-(5-(2-nitrophenyl)furan-2-yl)ethyl acetate *rac*-**6c** was used as the model compound for the screening of potentially useful lipases. All screening procedures were performed in DIPE in the presence of vinyl acetate (8 equiv) as reactant. Among the lipases tested, only CaLA (Table 2, entries 1–3), and LAK (Table 2, entry 4) proved to be efficient catalysts. CaLA showed higher activity than LAK, but the latest enzyme displayed a higher selectivity. In addition to CaLA, which is a Celite supported enzyme (Table 2, entry 1), other immobilized lipases A from *C. antarctica* such as CLEA (enzyme reticulated with glutaraldehyde, Table 2, entry 2) or IMMCALA T2–150 (covalently immobilized enzyme, Table 2, entry 3) were tested and it was found that with regard to stereoselectivity they are inefficient biocatalysts.

This behavior of CaLA is in accordance with the S_N2 preference showed by the enzyme toward triacylglycerols, however, CaLA was rarely used in enantioselective reactions[14], in many cases being reported to be highly active in a nonselective manner, as in the case of the kinetic resolution of phenylfuran based cyanohydrins[15] or β-hydroxynitriles.[16]

More surprising is the contrary behavior of the LAK compared to previously reported observations, when it was found as a highly selective biocatalyst for the acylation of the secondary monoacetate of several 1,2-ethanediols, while in the case of acylation of the primary monoacetate it showed significantly lower activity and selectivity.[9]

Using the most efficient enzymes (CaLA, LAK) solvents effects on the selectivity of the enzymatic acylation was next tested.

A strong solvent influence upon the reaction rate and selectivity was observed. In addition to various organic solvents, ionic liquids, previously found as appropriate media for the LPS-catalyzed enzymatic acylation of different substituted 1-phenylethane-1,2-diols,[12] were also used (Table 3, entries 7 and 14) with unsatisfactory results in the present case (Table 3, entries 7 and 14). The best results for the LAK mediated reaction were obtained in DIPE (Table 3, entry 8).

The same screening procedure was performed for the rest of the substrates and in all cases the optimal transformation was identical to that found in case of *rac*-**6c** (Table 4, entries 2, 4, 6, and 8). It is important to note that the CaLA mediated transformation of *rac*-**6a–d** in neat vinyl acetate was also satisfactory in most cases (Table 4, entries 1, 3, and 5), excepting the enzymatic transformation of *rac*-**6d** (Table 4, entry 7).

The enzymatic hydrolysis or alcoholysis of *rac*-**6a–d** was also tested (Scheme 3d). Using the methodology previously described for *rac*-**8a–d** it was found that most of the tested hydrolases (CaLA, LAK, LPS, PLE, CrL, lipase from *Mucor javanicus*, PLE, Acylase I) were useless. Only LPS and CaLB transformed in a totally nonselective manner, all the substrates into the corresponding racemic diols *rac*-**5a–d**, when the reactions were performed in a mixture of diisopropyl ether–methanol–water (1:1:2, v/v).

2.4. Kinetic resolution of the racemic diacetylated derivatives *rac*-7a–d

Finally the same hydrolases were tested as potential catalysts for methanolysis of the racemic diacetylated derivatives *rac*-**7a–d**. The reactions were performed in various solvents containing 8 equiv of nucleophile, as well as in neat methanol. While most of the lipases were catalytically inactive, CaLB was able to transform *rac*-**7a–d** into the (*R*)-diacetate and the (*S*)-secondary monoacetate as expected,[11] but surprisingly, in an *anti*-Kazlauskas manner.[17] However, the ee of the reaction products were only moderate [e.g., ee 82% for (*R*)-**7d** and ee 51% for (*S*)-**8d**] and at higher conversions the presence of a slight amount of the diol (5–10%) was also observed.

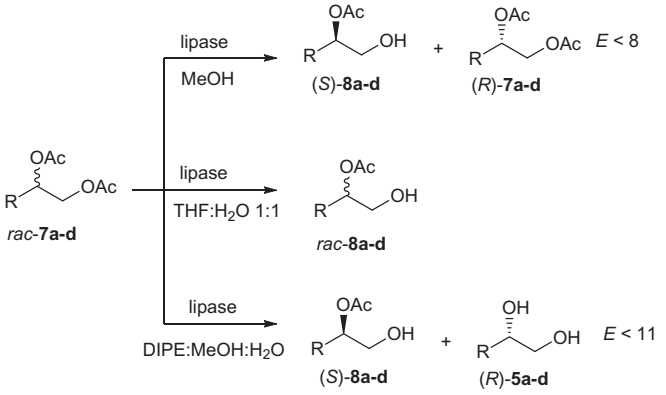
When the reactions were performed in a mixture of THF–H_2O (1:1, v/v), CaLB and LPS were able to regioselectively hydrolyze *rac*-**7a–d** into *rac*-**8a–d**. Using a mixture of DIPE–MeOH–H_2O as the reaction media LPS rapidly catalyzed the transformation of *rac*-**7a–d** into *rac*-**8a–d**, followed by the stereoselective lysis of the latest racemates, yielding (*R*)-**5a–d** and (*S*)-**8a–d** with moderate enantioselectivity (ee 65–71% for (*R*)-**5a–d** and 59–67% for (*S*)-**8a–d**). The possible routes are depicted in Scheme 4.

2.5. Preparative scale synthesis of enantiomerically pure (*R*)- and (*S*)-5a–d

Using racemic 1,2-diols *rac*-**5a–d** as starting materials, their regioselective LPS mediated enzymatic acylations were carried out to quantitatively yield *rac*-**6a–d** (Scheme 5). Further, the LAK mediated enantioselective enzymatic acylation of *rac*-**6a–d** was also performed, obtaining (*S*)-**6a–d** and (*R*)-**7a–d** in highly enantiomerically enriched forms by stopping the reactions at an approx. 50% conversion (monitored with HPLC) by removing the enzyme by filtration (Scheme 5). All dilutions, substrate-biocatalyst ratios and reaction conditions were the same as in the analytical scale reactions. Data on yields, enantiomeric excesses, and specific rotations of the enantiomers obtained are presented in Table 5. The isolated (*S*)-**6a–d** and (*R*)-**7a–d** were quantitatively transformed into the corresponding diols (*S*)- and (*R*)-**5a–b** without any loss of enantiopurity, by the LPS catalyzed mixed alcoholysis–hydrolysis procedure (Scheme 5). The chemical hydrolysis[18] and alcoholysis[11,12]

Table 3
The influence of the nature of solvent upon the CaLA and LAK mediated acylation of *rac*-**6c**

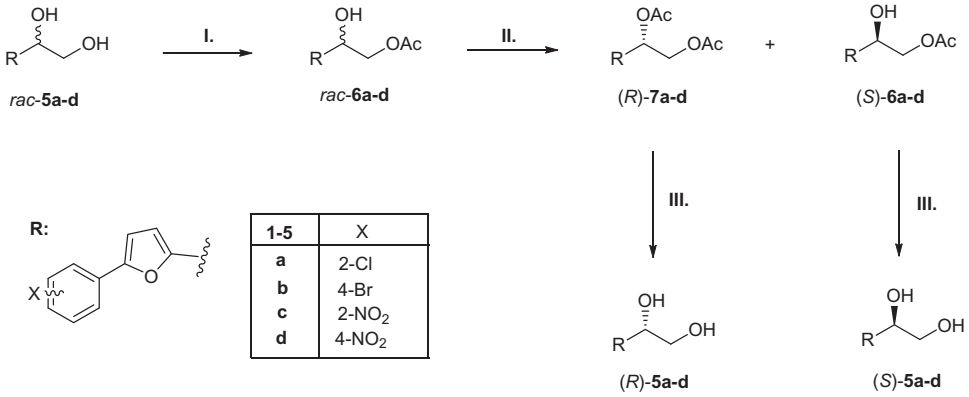
Entry	Enzyme	Solvent	Time (h)	*c* (%)	ee_P (%)	ee_S (%)	*E*
1	CaLA	DIPE	6	50	89	91	54
2	CaLA	*t*BME	6	41	81	56	16
3	CaLA	CH_2Cl_2	4	6	85	5	13
4	CaLA	Acetonitrile	4	16	70	13	6
5	CaLA	Toluene	4	34	88	45	24
6	CaLA	Vinyl acetate	6	50	89	92	56
7	CaLA	[bmim]PF_6	6	30	88	37	22
8	LAK	DIPE	24	43	95	71	83
9	LAK	*t*BME	24	35	90	48	31
10	LAK	Toluene	24	34	93	47	44
11	LAK	Vinyl acetate	24	16	89	17	20
12	LAK	CH_2Cl_2	24	17	93	19	33
13	LAK	Acetonitrile	24	12	91	13	24
14	LAK	[bmim]PF_6	24	20	91	23	27



Scheme 4. Lipase catalyzed reactions of the racemic diacylated diols.

Table 4
Comparison of the CaLA and LAK mediated acylation of *rac*-**6a–d**

Entry	Substrate	Enzyme	Solvent	Time (h)	*c* (%)	ee_p (%)	ee_s (%)	*E*
1	*rac*-**6a**	CaLA	Vinyl acetate	6	48	95	83	133
2	*rac*-**6a**	LAK	DIPE	13	50	97	97	>200
3	*rac*-**6b**	CaLA	Vinyl acetate	9	50	92	91	76
4	*rac*-**6b**	LAK	DIPE	9	50	97	96	>200
5	*rac*-**6c**	CaLA	Vinyl acetate	6	50	89	92	56
6	*rac*-**6c**	LAK	DIPE	30	50	93	95	102
7	*rac*-**6d**	CaLA	Vinyl acetate	12	55	46	56	5
8	*rac*-**6d**	LAK	DIPE	22	50	92	93	81



Scheme 5. Enzyme catalyzed preparative scale synthesis of (*R*)- and (*S*)-**5a–d**. Reagents and conditions: (I) LPS/vinyl acetate; (II) LAK, vinyl acetate/DIPE; III. LPS/MeOH–DIPE–H_2O (1:1:2, v/v).

Table 5
Yields, ee and specific rotations for products of the preparative scale procedure

Entry	Product	Yield[a] (%)	ee (%)	$[\alpha]_D25$[b]	Product	Yield[a] (%)	ee (%)	$[\alpha]_D^{25}$[b]
1	(*S*)-**6a**	49	97	−6.7	(*R*)-**7a**	49	97	+33.1
2	(*S*)-**6b**	48	96	−10.4	(*R*)-**7b**	49	97	+42.7
3	(*S*)-**6c**	49	95	−23.8	(*R*)-**7c**	47	93	+82.3
4	(*S*)-**6d**	48	93	−18.7	(*R*)-**7d**	47	92	+65.5
5	(*S*)-**5a**	47	97	−24.5	(*R*)-**5a**	47	97	+24.3
6	(*S*)-**5b**	46	96	−21.2	(*R*)-**5b**	48	96	+21.9
7	(*S*)-**5c**	48	95	−33.9	(*R*)-**5c**	46	93	+31.4
8	(*S*)-**5d**	46	93	−25.8	(*R*)-**5d**	46	92	+25.1

[a] Calculated for *rac*-**5a–d**.
[b] *c* 0.5, $CHCl_3$.

of (*S*)-**6a–d** and (*R*)-**7a–d** were also tested, but due to the structural instability of the diols in acidic or basic media, in most of the cases, the appearance of several by-products and partial racemization of the produced diols was observed.

The absolute configurations of the produced enantiomerically enriched 1,2-diols were established by comparing the chromatographic retention times of the enantiomers and the signs of the specific rotations for the produced enantiomerically enriched diols with previously reported data.[4]

3. Conclusion

All possible routes of enzymatic transformations of phenyl-furane-ethane-1,2-diols *rac*-**5a–d** and their mono- and diacetylated counterparts *rac*-**6**,**7**,**8a–d** have been studied. Except for CaLB, which displayed anti-Kazlauskas selectivity in the acylation of the secondary monoacetate *rac*-**8a–d**, and during alcoholysis of diacetate derivatives *rac*-**7a–d**, all other enzymes involved in the stereoselective reactions acted in accordance with the Kazlauskas rule.[17] For the investigated structures, the behavior of the lipases significantly differed from those previously reported in the field of kinetic resolutions of the arylethane-1,2-diols and their acylated analogues.

Out of all of the possible kinetic resolutions the most efficient, in terms of stereoselectivity and activity, proved to be LAK mediated acylation of racemic primary monoacetates *rac*-**6a–d**. Combining the regioselectivity of LPS mediated acylation of the starting racemic diols, the stereoselectivity of LAK showed in the enantiomer selective transformation of the previously formed racemic primary acetates and the LPS mediated mild hydrolysis–alcoholysis of the resolution products, an efficient preparative scale procedure was developed for the synthesis of various highly enantiomerically enriched (*R*)- and (*S*)-phenylfuran-2-yl-ethane-1,2-diols.

4. Experimental

4.1. Analytical methods

The ^1H- and ^{13}C- NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz and 75 MHz, respectively. Spectra were recorded at 25 °C in $CDCl_3$ or acetone-d_6. ^1H- 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 AS-H column (4.6 × 250 mm) and a mixture of *n*-hexane and 2-propanol 90:10, 85:15, and 78.5:21.5 (v/v) as eluent for the enantiomeric separation of *rac*-**5**–**8a**,**5c**, *rac*-**5**–**8b,** and *rac*-**5**–**8c**, respectively, and Chiralpak IB column and a mixture of *n*-hexane and 2-propanol 80:20 and 87:13 (v/v) as eluent for the enantiomeric separation of *rac*-**5d** and *rac*-**6**–**8d**, respectively (Table 6). Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60F254 sheets. Spots were visualized 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. Optical rotations were determined on a Perkin–Elmer 201 polarimeter and α_D^{25} values are given in units of 10^{-1} deg cm^2 g^{-1}.

4.2. Reagents and solvents

Pyridinium tribromide, sodium acetate, phase transfer catalyst 18C6 and all inorganic and organic reagents and solvents were products of Aldrich or Fluka. All solvents were dried and purified by standard methods as required. The racemic 1,2-ethanediols **5a–d** were prepared as previously reported by us.[4] LAK from *P. flu-*

Table 6
Chromatographic retention times of the enantiomers of *rac*-**5**–**8a**–**d**

Compound	t_R (min)	Compound	t_R (min)
(*R*)-**5a**	16.2	(*S*)-**5a**	14.9
(*R*)-**5b**	13.9	(*S*)-**5b**	12.9
(*R*)-**5c**	24.1	(*S*)-**5c**	25.5
(*R*)-**5c**	15.8	(*S*)-**5c**	17.2
(*R*)-**6a**	15.3	(*S*)-**6a**	17.5
(*R*)-**6b**	10.7	(*S*)-**6b**	12.1
(*R*)-**6c**	15.9	(*S*)-**6c**	20.3
(*R*)-**6d**	15.2	(*S*)-**6d**	15.9
(*R*)-**7a**	7.7	(*S*)-7**a**	9.1
(*R*)-**7b**	9.1	(*S*)-**7b**	8.6
(*R*)-**7c**	14.5	(*S*)-**7c**	17.7
(*R*)-**7d**	11.4	(*S*)-**7d**	9.9
(*R*)-**8a**	15.9	(*S*)-**8a**	18.3
(*R*)-**8b**	12.2	(*S*)-**8b**	9.9
(*R*)-**8c**	18.1	(*S*)-**8c**	16.1
(*R*)-**8d**	16.3	(*S*)-**8d**	17

orescens, LPS from *B. cepacia* (previously *P. cepacia*) were from Amano Europe, England. Lipase B from *C. antarctica* (CaLB, Novozyme 435) was purchased from Novozymes, Denmark. Lipase A from *C. antarctica* immobilized on celite (CaLA) was a generous gift from the research group of Dr. Liisa Kanerva. Lipase A from *C. antarctica* reticulated with glutaraldehyde (CLEA) or covalently immobilized (IMMCaLA T2-150) were purchased from Fluka and Chiralvision, respectively. CrL, PPL, PLE, Acylase I, lipase from *M. javanicus*, esterase from *R. oryzae* were purchased from Sigma–Aldrich and Fluka.

4.3. Synthesis of rac-1-(heteroaryl)-ethane-1,2-diols *rac*-5a–d

The racemic 1,2-ethanediols **5a**–**d** were prepared by known methods, using as starting material the corresponding phenylfuran-2yl-ethanones **1a**–**d** as depicted in Scheme 1. By an α-bromination we obtained the corresponding bromo-derivatives **2a**–**d**, which were further transformed by NaOAc and 18C6 as catalyst into the acetoxymethyl ketones **3a**–**d**; these were then subjected to the CaLB mediated alcoholysis to obtain the α-hydromethyl ketone derivatives **4a**–**d**, followed by their chemical reduction with $NaBH_4$, yielding the racemic 1,2-ethanediols *rac*-**5a**–**d**. The yield values, ^{1}H-, ^{13}C- NMR data were in accordance with the data reported earlier.[4]

4.3.1. 1-(5-(2-Chlorophenyl)furan-2-yl)ethane-1,2-diol *rac*-5a

White semisolid; ^{1}H NMR (acetone-d_6): 3.72–3.88 (2H, m) 3.88–4.05 (1H, s, broad), 4.49–4.65 (1H, s, broad), 4.79 (1H, dd, J = 4.5 Hz, J = 5.4 Hz), 6.49 (1H, d, J = 3 Hz), 7.1 (1H, d, J = 3 Hz), 7.29 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.41 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.5 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 7.5 Hz); ^{13}C NMR (acetone-d_6): 66.8, 70.4, 110.3, 113.5, 129.1, 129.5, 130.9, 131.1, 132,5, 150.6, 157.9.

4.3.2. 1-(5-(4-Bromophenyl)furan-2-yl)ethane-1,2-diol *rac*-5b

White semisolid; ^{1}H NMR (acetone-d_6): 3.74–3.85 (2H, m), 3.9–4.01 (1H, s, broad), 4.5–4.6 (1H, s, broad), 4.71 (1H, dd, J = 4.5 Hz, J = 6.8 Hz), 6.39 (1H, d, J = 3.8 Hz), 6.8 (1H, d, J = 3.8 Hz), 7.5–7.65 (4H, m); ^{13}C NMR (acetone-d_6): 66.5, 70.1, 108.3, 110.2, 121.8, 126.7, 131.7, 133.3, 153.1, 153.8.

4.3.3. 1-(5-(2-Nitrophenyl)furan-2-yl)ethane-1,2-diol *rac*-5c

Yellow, semisolid; ^{1}H NMR (acetone-d_6): 3.65–3.85 (2H, ddd, J = 6.8 Hz, J = 4.5 Hz, J = 10.9 Hz), 3.89–4.11 (1H, s, broad), 4.53–4.71 (1H, s, broad), 4.7 (1H, dd, J = 4.5 Hz, J = 6.8 Hz), 6.44 (1H, d, J = 3.8 Hz), 6.71 (1H, d, J = 3.8 Hz), 7.5 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.64 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.74 (1H, d, J = 7.5 Hz), 7.79 (1H, d, J = 7.5 Hz); ^{13}C NMR (acetone-d_6): 66.6, 70.1, 110.2, 111.7, 124.9, 125.2, 129.9, 130.1, 133.5, 148.8, 159.1.

4.3.4. 1-(5-(4-Nitrophenyl)furan-2-yl)ethane-1,2-diol *rac*-5d

Yellow solid, mp: 98–99 °C; ^{1}H NMR (acetone-d_6): 3.8–3.95 (2H, ddd J = 6.8 Hz, J = 5.3 Hz, J = 11.5 Hz), 4.02–4.15 (1H, s, broad), 4.65–4.75 (1H, s, broad), 4.82 (1H, dd, J = 5.3 Hz, J = 6.8 Hz), 6.55 (1H, d, J = 3.8 Hz), 7.14 (1H, d, J = 3.8 Hz), 7.94 (2H, d, J = 9.1 Hz), 8.28 (2H, d, J = 9.1 Hz); ^{13}C NMR (acetone-d_6): 66.8, 70.4, 111.2, 112.2, 125.6, 126.1, 138.4, 148.1, 152.5, 160.1.

4.4. Synthesis of the primary monoacylated derivatives *rac*-6a–d

A mixture of the racemic 1,2-ethanediol *rac*-**5a**–**d** (100 mg), vinyl acetate (4 mL) and LPS (100 mg) was shaken at 300 rpm at room temperature. When the reaction was completed (checked by TLC, approx. 16 h) the enzyme was filtered off, and the solvent was removed in vacuo, to obtain the pure product *rac*-**6a**–**d** without further purification.

4.4.1. 2-(5-(2-Chlorophenyl)furan-2-yl)-2-hydroxyethyl acetate *rac*-6a

Yield: 97%; white oil; ^{1}H NMR ($CDCl_3$): 2.12 (3H, s), 4.45 (2H, m), 5.04 (1H, dd, J = 5.6 Hz, J = 5.3 Hz), 6.48 (1H, d, J = 3.8 Hz), 7.08 (1H, d, J = 3.8 Hz), 7.2 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.31 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.43 (1H, d, J = 7.5 Hz), 7.83 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$): 20.8, 65.9, 66.3, 111.5, 111.6, 126.7, 128.1, 128.6, 130.2, 130.7, 148.9, 150.6, 170.3; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}ClO_4$: 280.0502): 280.0511; MS: m/z (%) = 282 (M^+, ^{37}Cl, 3), 280 (M^+, ^{35}Cl, 9), 223 (^{37}Cl, 5), 222 (^{37}Cl, 31), 221 (^{35}Cl, 15), 220 (^{35}Cl, 100), 209 (^{37}Cl, 22), 207 (^{35}Cl, 91), 205 (32), 192 (7), 151 (8), 149 (26), 147 (8), 115 (13), 43 (16).

4.4.2. 2-(5-(4-Bromophenyl)furan-2-yl)-2-hydroxyethyl acetate *rac*-6b

Yield: 95%; white oil; ^{1}H NMR ($CDCl_3$): 2.12 (3H, s), 2.47–2.55 (1H, s, broad) 4.43 (2H, m), 5.02 (1H, dd, J = 5.3 Hz, J = 9.1 Hz), 6.42 (1H, d, J = 3.8 Hz), 6.62 (1H, d, J = 3.8 Hz),7.48–7.52 (4H, m); ^{13}C NMR ($CDCl_3$): 20.9, 66.4, 66.5, 106.2, 109.6, 121.4, 125.3, 131.8, 152.5, 152.9, 171.1; HRMS: M+ found (M^+ calculated for $C_{14}H_{13}BrO_4$: 323.9997): 323.9884; MS: m/z (%) = 308 (^{81}Br, 11), 306 (^{79}Br, 11), 266 (^{81}Br, 19), 264 (^{79}Br, 19), 258 (^{81}Br, 17), 256 (^{79}Br, 18), 222 (20), 220 (59), 200 (20), 185 (28), 151 (16), 149 (50), 125 (11), 111 (12), 97 (12), 83 (20), 71 (33), 69 (25), 57 (45), 43 (100).

4.4.3. 2-Hydroxy-2-(5-(2-nitrophenyl)furan-2-yl)ethyl acetate *rac*-6c

Yield: 97%; yellow semisolid; ^{1}H NMR ($CDCl_3$): 2.1 (3H, s), 2.73–2.84 (1H, s, broad), 4.34–4.41 (2H, m), 4.97 (1H, dd, J = 5.3 Hz, J = 10.9 Hz), 6.45 (1H, d, J = 3 Hz), 6.62 (1H, d, J = 3 Hz), 7.42 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.57 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.69 (2H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) : 20.8, 66.3, 66.4, 109.4, 110.4, 123.8, 123.9, 128.4, 128.8, 131.9, 147.4, 148.2, 154.2, 171.2; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}NO_6$: 291.0743): 291.0746; MS: m/z (%) = 291 (M^+, 9), 231 (20), 218 (84), 188 (100), 172 (25), 144 (16), 117 (27), 116 (58), 115 (29), 97 (93), 77 (14), 43 (60).

4.4.4. 2-Hydroxy-2-(5-(4-nitrophenyl)furan-2-yl)ethyl acetate *rac*-6d

Yield: 96%; yellow semisolid; ^{1}H NMR ($CDCl_3$): 2.12 (3H, s), 2.73–2.95 (1H, s, broad), 4.43–4.45 (2H, m), 5.05 (1H, dd, J = 5.3 Hz, J = 5.7 Hz), 6.45(1H, d, J = 3 Hz), 6.83 (1H, d, J = 3 Hz), 7.76(2H, d, J = 9.1 Hz), 8.22 (2H, d, J = 9.1 Hz); ^{13}C NMR ($CDCl_3$):

20.8, 66.4, 66.5, 109.7, 110.1, 123.9, 124.3, 136, 146.5, 151.5, 154.6, 171.1; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}NO_6$: 291.0743): 291.0733; MS: *m*/*z* (%) = 291 (M+, 1) 285 (7), 229 (20), 160 (7), 159 (100), 158 (9), 140 (7), 71 (8), 57 (10), 43 (10).

4.5. Synthesis of 1,2-diacetoxy-derivatives *rac*-7a–d

To a solution of one of the racemic 1,2-ethanediols *rac*-**5a**–**d** (1 mmol) in dichloromethane (10 mL), acetyl chloride (4 mmol, 290 μL), and a catalytic amount of 4-*N*,*N*-dimethylamino-pyridine in pyridine (290 μL, 1% solution) were added. After stirring for 30 min at room temperature, the solvent was evaporated in vacuo and the crude product was purified by column chromatography using dichloromethane as eluent.

4.5.1. 1-(5-(2-Chlorophenyl)furan-2-yl)ethane-1,2-diyl diacetate *rac*-7a

Yield: 93%; white oil; ^{1}H NMR ($CDCl_3$): 2.07 (3H, s), 2.11 (3H, s), 4.48 (1H, dd, *J* = 7.5 Hz, *J* = 12.1 Hz), 4.56 (1H, dd, *J* = 4.5 Hz, *J* = 12.1 Hz), 6.2 (1H, dd, *J* = 7.5 Hz, *J* = 4.3 Hz), 6.53 (1H, d, *J* = 3 Hz), 7.08 (1H, d, *J* = 3 Hz), 7.2 (1H, dd, *J* = 7.5 Hz, *J* = 6.1 Hz), 7.31 (1H, dd, *J* = 7.5 Hz, *J* = 6.1 Hz), 7.42 (1H, d, *J* = 7.5 Hz), 7.83 (1H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$): 20.8, 21, 63.3, 66.3, 111.5, 111.6, 126.9, 128, 128.5, 128.6, 130.2, 130.7, 148.6, 150.5, 169.9, 170.5; HRMS: M^+ found (M^+ calculated for $C_{16}H_{15}ClO_5$: 322.0608): 322.0787; MS: *m*/*z* (%) = 324 (M+, ^{37}Cl, 4), 323 (M+1, ^{35}Cl, 2), 322 (M^+, ^{35}Cl, 13), 264 (^{37}Cl, 14), 262 (^{35}Cl, 35), 223 (^{37}Cl, 6), 222 (^{37}Cl, 33), 221 (^{35}Cl, 21), 220 (^{35}Cl, 100), 209 (^{37}Cl, 15), 207 (^{35}Cl, 49), 123 (24), 107 (8), 43 (10).

4.5.2. 1-(5-(4-Bromophenyl)furan-2-yl)ethane-1,2-diyl diacetate *rac*-7b

Yield: 93%, white oil; ^{1}H NMR ($CDCl_3$): 2.08 (3H, s), 2.11 (3H, s), 4.51 (2H, ddd, *J* = 4.5 Hz, *J* = 7.5 Hz, *J* = 12.1 Hz), 6.13 (1H, dd, *J* = 4.5, *J* = 7.5 Hz), 6.48 (1H, dd, *J* = 3.8 Hz), 6.61 (1H, *J* = 3.8 Hz), 7.48–7.54 (4H, m); ^{13}C NMR($CDCl_3$): 20.8, 21, 63.2, 66.3, 106.2, 111.8, 121.6, 125.4, 131.8, 149, 152.8, 153.3, 170, 170.6; HRMS: M^+ found (M^+ calculated for $C_{16}H_{15}BrO_5$: 366.0103): 366.0095; MS: *m*/*z* (%) = 268 (M^+, ^{81}Br, 8), 266 (M^+, ^{79}Br, 8), 308 (^{81}Br, 27), 306 (^{79}Br, 27), 267 (^{81}Br, 21), 266 (^{81}Br, 51), 265 (^{79}Br, 22), 264 (^{79}Br, 50), 253 (^{81}Br, 29), 252 (^{81}Br, 10), 251 (^{79}Br, 36), 250 (^{79}Br, 12), 242 (^{81}Br,10), 240 (^{79}Br,11), 220 (25), 187 (17), 186 (11), 185 (49), 183 (29), 149 (16), 115 (11), 87 (13), 43 (100).

4.5.3. 1-(5-(2-Nitrophenyl)furan-2-yl)ethane-1,2-diyl diacetate *rac*-7c

Yield: 91%; yellow semisolid; ^{1}H NMR ($CDCl_3$): 2.1 (3H, s), 2.13 (3H, s), 4.43 (1H, dd, *J* = 7.5 Hz, *J* = 12.1 Hz), 4.53 (1H, dd, *J* = 4.5 Hz, *J* = 12.1 Hz), 6.11 (1H, dd, *J* = 7.5 Hz, *J* = 4.5 Hz), 6.52 (1H, d, *J* = 3.8 Hz), 6.64 (1H, d, *J* = 3.8 Hz), 7.43 (1H, dd, *J* = 7.5 Hz, *J* = 6.8 Hz), 7.61 (1H, dd, *J* = 7.5 Hz, *J* = 7.1 Hz) 7.68–7.71 (2H, m); ^{13}C NMR ($CDCl_3$): 20.8, 20.9, 63.1, 66.2, 109.6, 110.3, 111.7, 123.7, 124, 128.7, 129, 132, 147.6, 148.7, 150.6, 170, 170.6; HRMS: M^+ found (M^+ calculated for $C_{16}H_{15}NO_7$: 333.0849): 333.0931; MS: *m*/*z* (%) = 333.1 (M+, 5), 273 (11), 218 (52), 189 (10), 188 (80), 172 (19), 149 (11), 144 (11), 117 (13), 116 (32), 115 (12), 97 (100), 57 (10), 43 (78).

4.5.4. 1-(5-(4-Nitrophenyl)furan-2-yl)ethane-1,2-diyl diacetate *rac*-7d

Yield: 91%; yellow semisolid; ^{1}H NMR ($CDCl_3$): 2.09 (3H, s), 2.14 (3H, s), 4.47–4.62 (2H, m), 6.17 (1H, dd, *J* = 4.5 Hz, *J* = 6.8 Hz), 6.57 (1H, d, *J* = 3.3 Hz), 6.86 (1H, d, *J* = 3.3 Hz), 7.79 (2H, d, *J* = 9.1 Hz) 8.26 (2H, d, *J* = 9.1 Hz); ^{13}C NMR ($CDCl_3$): 20.8, 21, 63.1, 66.2, 109.6, 112.3, 124.2, 124.4, 135.8, 151, 152, 170, 170.5; HRMS: M^+ found (M^+ calculated for $C_{16}H_{15}NO_7$: 333.0849): 333.0911; MS: *m*/*z* (%) = 333.1 (M^+, 1), 231 (20), 222 (10), 220 (25), 218 (10), 207 (18), 205 (15), 204 (16), 167 (12), 161 (13), 159 (14), 149 (29), 147 (12), 115 (11), 57 (13), 45 (34), 43 (100).

4.6. Synthesis of secondary monoacetate derivatives *rac*-8a–d

Into a solution of the racemic diacetate derivative *rac*-**7a**–**d** (100 mg) in THF (4 mL), LPS (100 mg), and phosphate buffer (10 mM, pH 7.5, 4 mL) were added, and the resulting mixture was shaken at 300 rpm, until the reaction was complete (checked by TLC, approx. 16 h). The enzyme was filtered off, and the solvent was removed in vacuo, to obtain the pure product *rac*-**6a**–**d**. In some cases, supplementary column chromatography purification, using dichloromethane–methanol 95:5 (v/v) as eluent, was necessary.

4.6.1. 1-(5-(2-Chlorophenyl)furan-2-yl)-2-hydroxyethyl acetate *rac*-8a

Yield: 87%; white oil ^{1}H NMR ($CDCl_3$): 2.13 (3H, s), 4.03 (1H, dd, *J* = 4.5 Hz, *J* = 11.5 Hz), 4.11 (1H, dd, *J* = 7.5 Hz, *J* = 11.5 Hz), 5.99 (1H, dd, *J* = 4.5 Hz, *J* = 7.5 Hz), 6.54 (1H, d, *J* = 3.8 Hz), 7.07 (1H, d, *J* = 3.8 Hz), 7.21 (1H, ddd, *J* = 1.5 Hz, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.32 (1H, ddd, *J* = 1.5 Hz, *J* = 8.3 Hz, *J* = 7.5 Hz), 7.43 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz), 7.81 (1H, dd, *J* = 8.3 Hz, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$): 21.1, 63, 66.6, 111.5, 111.6, 126.8, 128, 128.4, 128.7, 130.2, 130.7, 149.4, 150.5, 170.5; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}ClO_4$: 280.0502): 280.0491; MS: *m*/*z* (%) = 282 (M^+, ^{37}Cl, 6), 280 (M^+, ^{35}Cl, 13), 264 (^{37}Cl, 4), 262 (^{35}Cl, 12), 223 (^{37}Cl, 5), 222 (^{37}Cl, 22), 221 (^{35}Cl, 15), 220 (^{35}Cl, 68), 209 (^{37}Cl, 30), 207 (^{35}Cl, 100), 205 (6), 151 (^{37}Cl, 5), 149 (^{35}Cl, 13), 144 (6), 115 (19), 77 (4), 43 (4).

4.6.2. 1-(5-(4-Bromophenyl)furan-2-yl)2-hydroxyethyl acetate *rac*-8b

Yield: 89%; white oil; ^{1}H NMR ($CDCl_3$): 2.13 (3H, s), 4.03 (1H, dd, *J* = 4.5 Hz, *J* = 12.1 Hz), 4.09 (1H, dd, *J* = 7.5 Hz, *J* = 12.1 Hz), 5.97 (1H, dd, *J* = 4.5 Hz, *J* = 7.5 Hz), 6.49 (1H, d, *J* = 3.8 Hz), 6.61 (1H, d, *J* = 3.8 Hz),7.48–7.52 (4H, m); ^{13}C NMR ($CDCl_3$): 21.1, 62.9, 69.6, 106.2, 111.8, 121.5, 125.3, 129.2, 131.8, 149.7, 153.1, 170.5; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}BrO_4$: 323.9997): 323.9913; MS: *m*/*z* (%) = 326 (M^+, ^{81}Br, 11), 324 (M^+, ^{79}Br, 11), 308 (^{81}Br, 31), 306 (^{79}Br, 29), 282 (^{81}Br, 16), 280 (^{79}Br, 17), 267 (^{81}Br, 60), 266 (^{81}Br, 61), 265 (^{79}Br, 64), 264 (^{79}Br, 56), 253 (^{81}Br, 85), 251 (^{79}Br, 100), 222 (15), 220 (31), 205 (27), 193 (20), 187 (24), 185 (61), 183 (31), 149 (32), 115 (30), 114 (18), 77 (12), 57 (12), 43 (83).

4.6.3. 2-Hydroxy-1-(5-(2-nitrophenyl)furan-2-yl)ethyl acetate *rac*-8c

Yield: 87%; yellow semisolid; ^{1}H NMR ($CDCl_3$): 2.12 (3H, s), 3.95–4.07 (2H, ddd, *J* = 5.3 Hz, *J* = 5.7 Hz, *J* = 12 Hz), 5.91 (1H, dd, *J* = 5.3 Hz, *J* = 5.7 Hz), 6.53 (1H, d, *J* = 3 Hz), 6.64 (1H, d, *J* = 3 Hz), 7.44 (1H, dd, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.59 (1H, dd, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.67 (1H, d, *J* = 7.5 Hz), 7.71 (1H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$): 21, 62.7, 69.3, 110.2, 111.8, 123.8, 124, 128.6, 128.9, 132, 151.3, 170.3; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}NO_6$: 291.0743): 291.0737; MS: *m*/*z* (%) = 291 (M+, 22), 219 (20), 218 (100), 188 (91), 172 (44), 171 (14), 149 (20), 145 (17), 144 (20), 128 (13), 117 (26), 116 (63), 115 (33), 97 (72), 77 (14), 43 (71).

4.6.4. 2-Hydroxy-1-(5-(4-nitrophenyl)furan-2-yl)ethyl acetate *rac*-8d

Yield: 90%; yellow semisolid; ^{1}H NMR ($CDCl_3$): 2.15 (3H, s), 4.04 (1H, dd, *J* = 4.5 Hz, *J* = 12.1 Hz), 4.11 (1H, dd, *J* = 6.8 Hz, *J* = 12.1 Hz), 5.98 (1H, dd, *J* = 4.53 Hz, *J* = 6.8 Hz), 6.57 (1H, d, *J* = 3.8 Hz), 6.84 (1H, d, *J* = 3.8 Hz), 7.78 (2H, d, *J* = 9.1 Hz), 8.24 (2H, d, *J* = 9.1 Hz);

^{13}C NMR ($CDCl_3$): 21, 62.9, 69.5, 109.5, 112.1, 124.1, 124.3, 135.9, 146.6, 151.8, 170.3; HRMS: M^+ found (M^+ calculated for $C_{14}H_{13}NO_6$: 291.0743): 291.07804; MS: *m*/*z* (%) = 291 (M^+, 2), 285 (8), 231 (10), 229 (21), 218 (13), 160 (11), 159 (100), 149 (37), 115 (11), 71 (14), 57 (19), 43 (29).

4.7. Analytical scale procedure

4.7.1. Analytical scale enzymatic acylation of racemic heteroaryl-1,2-ethadiols *rac*-5a–d

In a typical small scale experiment, one of the heteroaryl-1,2-ethanediols *rac*-**5a–d** (0.05 mmol) and vinyl acetate (0.1, 0.2, 0.25, and 0.4 mmol) were dissolved in a dry organic solvent (1 mL). Lipase preparation (10 mg) was added. The mixture was shaken at 300 rpm at room temperature. Samples (10 μL) were taken after different intervals of time, diluted with the same solvent (100 μL) as the mobile phase for HPLC and analyzed with HPLC.

4.7.2. Analytical scale enzymatic acylation of racemic heteroaryl-2-acetoxy-1-ethanol *rac*-6a–d

In a typical small scale experiment, one of the heteroaryl-2-acetoxy-1-ethanol *rac*-**6a–d** (0.05 mmol) and vinyl acetate (0.4 mmol) were dissolved in a dry organic solvent (1 mL). Lipase preparation (10 mg) was added. The mixture was shaken at 300 rpm at room temperature. Samples (10 μL) were taken after different intervals of time, diluted with the same solvent (100 μL) as the mobile phase for HPLC and analyzed with HPLC.

4.7.3. Analytical scale enzymatic acylation of racemic heteroaryl-1-acetoxy-1-ethanol *rac*-8a–d

In a typical small scale experiment, one of the heteroaryl-1-acetoxy-1-ethanol *rac*-**8a–d** (0.05 mmol) and vinyl acetate (0.4 mmol) were dissolved in a dry organic solvent (1 mL). Lipase preparation (10 mg) was added. The mixture was shaken at 300 rpm at room temperature. Samples (10 μL) were taken after different intervals of time, diluted with the same solvent (100 μL) as the mobile phase for HPLC and analyzed with HPLC.

4.7.4. Analytical scale enzymatic alcoholysis of racemic primary monoacetates, secondary monoacetates, and the diacetylated derivatives *rac*-6–8a–d

In a typical small scale experiment, the mixture of one of the 1-heteroarylethyl acetates *rac*-**6–8a–d** (0.05 mmol), lipase preparation (10 mg), and methanol (500 μL), was shaken at 300 rpm at room temperature. Samples were taken at different intervals of time, diluted with the same solvent (100 μL) as the mobile phase for HPLC (see Section 4.1.) and analyzed with HPLC.

4.7.5. Analytical scale enzymatic hydrolysis of racemic primary monoacetates, secondary monoacetates, and the diacetylated derivatives *rac*-6–8a–d

In a typical small scale experiment, the mixture of one of the 1-heteroarylethyl acetates *rac*-**6–8a–d** (0.05 mmol), lipase preparation (10 mg), and THF (500 μL) and phosphate buffer (500 μL, 10 mM, pH 7.5), was shaken at 300 rpm at room temperature. Samples were taken at different intervals of time and extracted with ethyl-acetate. The organic phase was dried over Na_2SO_4, the solvent was removed in vacuo, and the sample obtained was diluted with the same solvent (100 μL) as the mobile phase for HPLC (see Section 4.1.) and analyzed with HPLC.

4.7.6. Analytical scale mixed enzymatic alcoholysis-hydrolysis of racemic primary monoacetates, secondary monoacetates, and the diacetylated derivatives *rac*-6–8a–d

In a typical small scale experiment, the mixture of one of the 1-heteroarylethyl acetates *rac*-**6–8a–d** (0.05 mmol), lipase preparation (10 mg), diisopropyl ether (250 μL), methanol (250 μL) and phosphate buffer (500 μL, 10 mM, pH 7.5), was shaken at 300 rpm at room temperature. Samples were taken at different intervals of time and extracted with ethyl-acetate. The organic phase was dried over Na_2SO_4, the solvent was removed in vacuo, and the sample obtained was diluted with the same solvent (100 μL) as the mobile phase for HPLC (see Section 4.1.) and analyzed with HPLC.

4.8. Preparative scale procedure

4.8.1. Preparative scale enzymatic acylation of racemic 1,2-ethanediols *rac*-5a–d

The procedure described in Section 4.4. was used.

4.8.2. Preparative scale enzymatic acylation of racemic primary monoacetates *rac*-6a–d

A mixture of *rac*-**6a–d** (100 mg), vinyl acetate (2 mL) and LAK (50 mg) was shaken at 300 rpm at room temperature. Samples from the reaction mixture (20 μL) were diluted with *n*-hexane–2-propanol (8:2, 200 μL) and analyzed with HPLC. The reactions were stopped by filtering the enzyme at approximately 50% conversions. The solvent was removed in vacuo, and the crude product was purified by column chromatography using dichloromethane–methanol (95:5 v/v), resulting in the optically active primary monoacetates (*S*)-**6a–d** and the corresponding diacetylated products (*R*)-**7a–d**.

4.8.3. Preparative scale mixed enzymatic alcoholysis–hydrolysis of enantiomerically enriched primary monoacetates and diacetates (*S*)-6a–d and (*R*)-7a–d

The mixture of the enantiomerically enriched derivative *rac*-**6**,**7a–d** (100 mg), LPS (50 mg), diisopropyl ether (1 mL), MeOH (1 mL) and phosphate buffer (10 mM, pH 7.5, 2 mL) added was shaken at 300 rpm, until the reaction was complete (checked by TLC, approx. 12 h). The enzyme was filtered off, and the solvent was removed in vacuo, to give the pure enantiomerically enriched product (*S*)-**5a–d** and (*R*)-**5a–d**.

The MS, NMR spectra of the optically active products were indistinguishable from those of their racemates. Data on yield, enantiomeric composition, and specific rotation of the products are shown in Table 5.

Acknowledgment

The financial support to C.P. from the Romanian Ministry of Education and Research (CNCSIS No. 527/2461) is gratefully acknowledged.

References

1. Nishio, K.; Fukuhara, A.; Omata, Y.; Saito, Y.; Yamaguchi, S.; Kato, H.; Yoshida, Y.; Niki, E. *Bioorg. Med. Chem.* **2008**, *16*, 10332–10337.
2. Huang, Q.-Q.; Huang, M.; Nan, F.-J.; Ye, Q.-Z. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5386–5391.
3. (a) Nelson, W. L.; Wennerstrom, J. E.; Sankar, S. R. *J. Org. Chem.* **1977**, *42*, 1006–1012; (b) Bianchi, D.; Bosetti, A.; Cesti, P.; Golini, P. *Tetrahedron Lett.* **1992**, *33*, 3231–3234; (c) Pye, P. J.; Rossen, K.; Weissman, S. A.; Maliakal, A.; Reamer, R. A.; Ball, R.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *Chem. Eur. J.* **2002**, *8*, 1372–1376; (d) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
4. Bencze, L. C.; Paizs, C.; Tosa, M. I.; Irimie, F. D. *Tetrahedron: Asymmetry* **2010**, *21*, 356–364.
5. Bosetti, A.; Bianchi, D.; Cesti, P.; Golini, P.; Spezia, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2395–2398.
6. Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *Tetrahedron Lett.* **1993**, *34*, 305–306.
7. Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem.* **1994**, *59*, 388–393.

8. Lemke, K.; Theil, F.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1996**, *7*, 971–974.
9. Egri, G.; Baitz-Gacs, E.; Poppe, L. *Tetrahedron: Asymmetry* **1996**, *7*, 1437–1448.
10. Raminska, J. E.; Smigielski, K.; Lobodzinska, D.; Gora, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1211–1215.
11. Virsu, P.; Liljebad, A.; Kanerva, A.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2001**, *12*, 2447–2455.
12. Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2004**, *45*, 8801–8805.
13. Bianco, A.; Brufani, M.; Melchioni, C.; Romagnoli, P. *Tetrahedron Lett.* **1997**, *38*, 651–652.
14. (a) Paizs, C.; Toşa, M. I.; Majdik, C.; Tahtinen, P.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 619–627; (b) de Gonzalo, G.; Lavandera, I.; Brieva, R.; Gotor, V. *Tetrahedron* **2004**, *60*, 10525–10532; (c) Paizs, C.; Tahtinen, P.; Toşa, M. I.; Majdik, C.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron* **2004**, *60*, 10533–10540; (d) Bencze, L. C.; Paizs, C.; Toşa, M. I.; Trif, M.; Irimie, F. D. *Tetrahedron: Asymmetry* **2010**, *21*, 1999–2004.
15. Paizs, C.; Tahtinen, P.; Lundell, K.; Poppe, L.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 1895–1904.
16. Turcu, M. C.; Perkio, P.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2010**, *21*, 739–745.
17. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
18. (a) Hirose, K.; Aksharamandana, P.; Suzuki, M.; Wada, K.; Nameura, K.; Tobe, Y. *Heterocycles* **2005**, *66*, 405–431; (b) Singh, S.; Duffy, C. D.; Shal, S. T. A.; Guiry, P. J. *J. Org. Chem.* **2008**, *73*, 6429–6432.