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Efficient access to both enantiomers of 3-(1-hydroxyethyl) phenol by regioselective and enantioselective *CAL-B*–catalyzed hydrolysis of diacetate in organic media by sodium carbonate

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Abstract

In the present paper, we describe several pathways employing immobilized lipase from *Candida antarctica* B (*CAL-B*) as biocatalyst to prepare easily both enantiomers of 3-(1-hydroxyethyl)phenol. We have applied hydrolysis with Na_2CO_3 in organic media under mild conditions. The reaction parameters solvent effect, amount of lipase, and Na_2CO_3 were examined with 3-(1-acetoxyethyl)phenyl acetate as substrate. In alkaline hydrolysis, (*R*)-3-(1-hydroxyethyl)phenol was obtained with ee = 99% and (*S*)-(−)-3-(1-acetoxyethyl)phenol with ee = 98% at optimal conversion (c = 50%) and high selectivity (E > 200). Two other deacylation reactions were compared: alcoholysis with MeOH and with NEt_3. The acylation of 3-(1-hydroxyethyl)phenol with vinyl acetate was also examined. Alkaline hydrolysis gave the best results, while good regioselectivity and enantioselectivity were observed in alcoholysis and acylation reactions. Finally, (*S*)- and (*R*)-3-(1-hydroxyethyl)phenol (ee > 98%), key intermediates for the synthesis of important drugs, were prepared from the corresponding racemic diacetate through alkaline hydrolysis.

KEYWORDS

alkaline hydrolysis, *Candida antarctica* Lipase B, carbonate salts, diol, enzymatic resolution, nonaqueous media

1 | INTRODUCTION

The use of lipases in organic synthesis makes it possible to obtain enantiopure building blocks under mild, ecological, and environmentally friendly conditions.[1,2] Enzymatic kinetic resolution is one of the most potent and important method to access enantiopure compounds[3,4] and is widely used for the synthesis of chiral intermediates for pharmaceutical chemistry[5,6] where approximately 80% of the drugs currently under development are chiral.[7,8] Lipases (EC 3.1.1.3) are the most widely employed biocatalysts and have high industrial potential for the synthesis of enantiomerically pure compounds especially by transesterification in organic solvents or by hydrolysis in aqueous or biphasic media.[9,10] Enantiopure (hydroxyalkyl)phenols and their derivatives are important synthetic intermediates to develop drugs,[11,12] thus highlighting the industrial interest.[13-16] Enantiomers of 3-(1-hydroxy-ethyl)phenol and its derivatives are important synthetic intermediates for preparing drugs such as (*S*)-(−)-Rivastigmine, an acetylcholinesterase inhibitor that is prescribed for the treatment of mild to moderate dementia in patients with Alzheimer's disease and Parkinson's disease,[17,18] and (*R*)-(−)-Phenylephrine, a

potent adrenergic agent and β-receptor sympathomimetic drug, exclusively commercialized in the optically active form (Figure 1).

Chemoenzymatic synthesis of enantiopure (*S*)-(−)-Rivastigmine[19-23] or (*R*)-(−)-Phenylephrine[24-27] has been performed with multipathway processes involving asymmetric transformations of 3-hydroxyacetophenone to optically active corresponding esters. Lipase-catalyzed kinetic resolution for the production of enantiomerically pure alcohols precursors is a less described path.[28,29]

The development of procedures to obtain chemoselectively monoacetylated compounds from molecules containing phenolic and aliphatic hydroxyl groups is a challenge.[30,31] *Candida antarctica* Lipase B as a robust and environmentally benign biocatalyst with high stereoselectivity is attractive for a wide range of applications.[32-35] It catalyzes specifically regioselective and enantioselective acylations of polyfunctional compounds in mild conditions.[36,37] This lipase was described as the best catalyst for the regioselective monoacetylation of various diols that are important structural subunits in biologically active compounds[38,39] and was applied to chemoselective acylation of 4-(2-hydroxyethyl)phenol.[40]

We previously developed a simple and practical enzymatic hydrolysis method with sodium carbonate in organic medium catalyzed by *CAL-B*.[41] This alkaline hydrolysis has been successfully applied to arylalkylcarbinol acetates,[42] *N*,*O*-protected amino alcohols,[43] and 2-aryl-1-cyclohexyl acetates.[44] In all cases, *CAL-B* showed high enantioselectivity and broad substrate specificity simultaneously after adjusting reactions parameters. In this context, and in the continuity of our investigations, we studied the regioselectivity and enantioselectivity of the lipase *CAL-B* in kinetic resolution of (*R*,*S*)-3-(1-hydroxy-ethyl)phenol and its diacetates by deacylation/acylation paths in organic medium. The goal can be achieved by two routes, one by the selective removal of a single acyl group from the diacetylated compounds and the other by the selective monoacylation of the dihydroxy compounds. The first method of deacylation (path A) was *CAL-B*–catalyzed alkaline hydrolysis in organic media via sodium carbonate. In path B, MeOH was used as the nucleophile of alcoholysis, and for path C, the deacylation was carried out in the presence of NEt_3 as additive. The acylation of the (*R*,*S*)-3-(1-hydroxy-ethyl)phenol is also examined (path D) (Figure 2). Up to now, there are no examples of the resolution of the racemic diacetate **1** by classic enzymatic hydrolysis.

2 | MATERIALS AND METHODS

2.1 | General information

All reagents purchased from Aldrich were used as received. The *C antarctica* Lipase B immobilized on acrylic resin (*CAL-B*) was purchased from Aldrich. Specific activity >10 000 U/g used without any pre-treatment. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel $60F_{254}$ plates type MERCK 5179, 250 mesh, using UV light (254 nm) as the visualizing agent. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker spectrometers (300 MHz for ^1H and 75 MHz for ^{13}C) instrument and calibrated using residual deuterated solvent as an internal reference (peak at 7.26 ppm in ^1H NMR and three peaks at 77 ppm in ^{13}C NMR in the case of $CDCl_3$ and DMSO). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and dd = double doublet. Chemical shifts were expressed in parts per million and coupling constant (*J*) in hertz. The enantiomeric excesses were measured by a chiral stationary phase High-Performance Liquid Chromatography (HPLC): Chiralpak OD-H column (4.6 × 250 mm) and Chiralpak IA column (4.6 × 250 mm); retention times

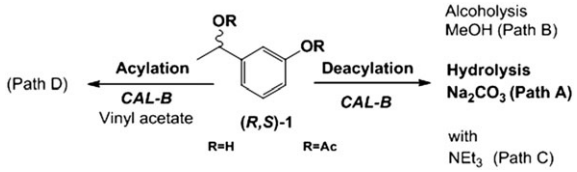


FIGURE 2 Different routes for enzymatic kinetic resolution

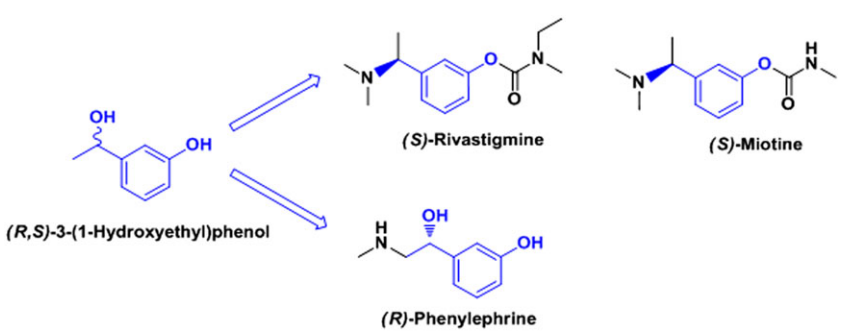


FIGURE 1 Biological interest of both enantiomers of diol

are reported in minutes. Optical rotations were determined using a Perkin-Elmer 341 Polarimeter at room temperature using a cell of 1-dm length and $\lambda = 589$ nm. The absolute configurations of all chiral compounds were determined by polarimetry by comparison with literature data.

2.2 | General procedure of preparation of racemic substrates

2.2.1 | Preparation of *rac*-3-(1-hydroxyethyl) phenol 3

The racemic diol **3** was prepared by the reduction of 3-hydroxyacetophenone (0.136 g, 1 mmol) with sodium borohydride (0.228 g, 6 mmol) in tetrahydrofuran (THF)/H_2O (80/20) mL. The reaction mixture was stirred under at 0°C. The evolution of the reactions was monitored by TLC. After 2 hours, the crude reaction mixture was quenched by adding a 10% (*v*/v) hydrochloric acid solution, after which the solvent was evaporated in vacuum and the mixture extracted with ethyl acetate. The organic layer was concentrated in vacuum followed by purification with silica gel chromatography using ethyl acetate as the mobile phase to produce *rac*-**3**. Yield = 80%. ^{1}H NMR (300 MHz, DMSO) δ = 1.28 (d, J = 6.5 Hz, 3H), 4.62 (q, J = 6.5 Hz, 1H) 5.08 (d, 1H, OH), 6.57-6.61 (dd, 1H), 6.71-6.76 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 9.26 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO) δ = 26, 68.1, 112.2, 113.4, 116, 128.9, 149, 157.1.

2.2.2 | Synthesis of *rac*-3-(1-acetoxyethyl) phenyl acetate 1

The diacetate **1** was synthesized by classical chemical acetylation of the *rac*-1-(3-hydroxyphenyl)-ethanol **3** (1 equiv), using 3 equiv of acetic anhydride, 2.4 equiv of Et_3N, and catalytic amount of 4-dimethylaminopyridine (0.2 equiv) in 4 mL of CH_2Cl_2. The acetates are obtained pure after standard workup. Yield = 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.52 (d, J = 6.6 Hz, 3H), 2 (s, 3H), 2.29 (s, 3H), 5.86 (q, J = 6.5 Hz, 1H), 7 (dd, 2H), 7.08 (s, 1H), 7.19 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.2, 22.2, 71.7, 119.3, 121.1, 123.6, 129.5, 143.4, 150.8, 169.4, 170.2.

2.3 | General procedure for the enzymatic kinetic resolution pathways

2.3.1 | Alkaline hydrolysis of *rac*-diacetate 1 with *CAL-B*

To 1 mmol (m = 0.222 g) of the racemic diacetate **1** dissolved in organic solvent are added an appropriate amount of sodium carbonate and *CAL-B* lipase. The suspension was stirred at 40°C for the indicated time. The reaction mixture was filtered on celite and concentrated in vacuo. The obtained product and the remaining substrate were separated by flash chromatography on silica gel (petroleum ether/ethyl acetate: 80/20) and analyzed by chiral HPLC. (*S*)-(−)-3-(1-acetoxyethyl) phenol 2: yield = 44%. Chiral HPLC: Chiralpak IA column, t_R = 26.05 minutes, t_S = 28.50 minutes. Eluant (v,v): hexane/iPrOH: 97/03; flow rate: 1 mL/min. ee = 98%. (*S*)-**2** $[\alpha]^{20}_D$ = −109.3 (*c* 0.1, MeOH). [Lit. $[\alpha]^{20}_D$ = +108.2 (*c* 1, MeOH), 98% ee (*R*)].[23] (*R*)-(+)-3-(1-hydroxyethyl)phenol **3**: yield = 40%. Chiral HPLC: Chiralpak OD-H column, t_R = 14.52 minutes, t_S = 16.48 minutes. Eluant (v,v): heptane/iPrOH: 92/08; flow rate: 1 mL/min. ee > 99%. (*R*)-**3** $[\alpha]_D$ = +33.83 (*c* 0.1, MeOH). [Lit. (*R*)-**3a**: $[\alpha]^{20}_D$ = +32 (*c* 1, MeOH), 99% ee].[45]

2.3.2 | Alcoholysis of racemic diacetate 1 with *CAL-B*

To 1 mmol (m = 0.222 g) of the racemic diacetate **1** dissolved in 3 mL of THF are added 4 mmol of MeOH, 40 mg of *CAL-B*, and 60 mg of molecular sieves 4 Å. The suspension was stirred at 40°C for 72 hours. The reaction mixture was filtered on celite and concentrated in vacuo. The obtained product and the remaining substrate were separated by flash chromatography on silica gel (petroleum ether/ethyl acetate: 80/20) and analyzed by chiral HPLC. (*S*)-(−)-3-(1-acetoxyethyl) phenol **2**: yield = 40%. $[\alpha]^{20}_D$ = −56.2 (*c* 0.1, MeOH). (*R*)-(+)-3-(1-hydroxyethyl)phenol **3**: yield = 30%. $[\alpha]^{20}_D$ = +33.8 (*c* 0.1, MeOH).

2.3.3 | Deacylation of *rac*-diacetate 1 with *CAL-B* in the presence of Et_3N

To 1 mmol (m = 0.222 g) of racemic diacetate **1** dissolved in 3 mL of THF, 4 mmol (m = 0.404 g) of the triethylamine, 40 mg of *CAL-B*, and 60 mg of molecular sieves 4 Å were added. The suspension was stirred at 40°C for 72 hours. The outcome of the reaction was monitored by TLC. Only the monoacetate **2** was formed. The reaction mixture was filtered on celite and concentrated in vacuo. *Rac*-3-(1-acetoxyethyl)phenol **2**: Yield = 67%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.52 (d, J = 6.6 Hz, 3H), 2 (s, 3H), 5.84 (q, J = 6.5 Hz, 1H), 6.02 (br, 1H, OH), 6 (dd, J_1 = 7.9 Hz, J_2 = 2.5 Hz, 1H), 6.82 (s, 1H), 6.89 (d, J = 7.7 Hz, 1H), 7.2 (t, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.2, 22.2, 72.6, 113.2, 115, 118.1, 129.9, 143.4, 150, 171.2.

2.3.4 | Enzymatic acylation of 3-(1-hydroxyethyl)phenol 3

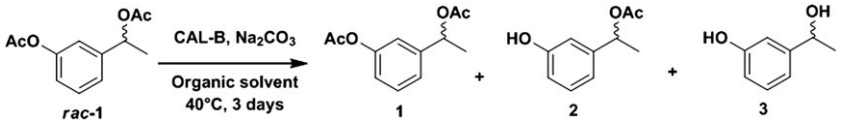
The enzymatic acetylation was performed using 1 equiv of 3-(1-hydroxyethyl)phenol (0.138 g, 1 mmol) and (0.258 g, 3 mmol) of the vinyl acetate dissolved in 3 mL of THF. Then, 40 mg of CAL-B was added and the resulting mixture was stirred at room temperature for 72 hours. After removal of the enzyme by filtration and evaporation of the solvent, the obtained product and the remaining substrate were separated by flash chromatography on silica gel (petroleum ether/ethyl acetate: 80/20) and analyzed by chiral HPLC. (*S*)-(−)-3-(1-hydroxyethyl)phenol **3**: yield = 37%. Chiral HPLC: Chiralpak OD-H column, t_R = 14.52 minutes, t_S = 16.48 minutes. Eluant (v,v): heptane/PrOH: 92/08; flow rate: 1 mL/min. ee = 87%. (*S*)-**3** $[\alpha]^{20}_D$ = −28 (*c* 0.1, MeOH). (*R*)-(+)-3-(1-acetoxyethyl) phenol **2**: Yield = 35%. Chiral HPLC: Chiralpak IA column; t_R = 26.05 minutes, t_S = 28.50 minutes. Eluant (v, v): hexane/iPrOH: 97/03; flow rate: 1 mL/min. ee = 94.2%. (*R*)-**2** $[\alpha]_D$ = +103.8 (*c* 0.11, MeOH).

3 | RESULTS AND DISCUSSION

3.1 | *CAL-B*–catalyzed alkaline hydrolysis of racemic diacetate 1 (path A)

The studies of the solvent effect have been firstly conducted on the alkaline hydrolysis of 3-(1-acetoxyethyl) phenyl acetate **1** catalyzed by *CAL-B* in the presence of sodium carbonates. Several organic solvents having diverse hydrophobicities were used: THF, toluene, acetone, heptane, and dichloromethane. The alkaline hydrolysis experiments were carried out using diacetate **1** (1 mmol), Na_2CO_3 (0.5 mmol), and 40 mg of *CAL-B* dissolved in 2 mL of the organic solvent.[41] The reaction was stirred for 72 hours at 40°C, and the evolution of the reaction was monitored by TLC (Scheme 1). Conversions and enantiomeric excesses were determined by chiral HPLC after separations by flash chromatography. The results are summarized in Table 1.

Results in Table 1 show an important influence of the solvent on the regioselectivity of *CAL-B* in alkaline hydrolysis of diacetate **1**. Moreover, selective hydrolysis of phenolic hydroxyl groups in the presence of aliphatic hydroxyl group was achieved. The fast regioselective cleavage of the acetyl moiety depends on the solvent hydrophobicity. The diol **3** and the monoacetate **2** were recovered only in THF and acetone as solvents (Table 1, entries 1-2). In both cases, enantiomer ratio is high (E > 200) and the diol **3** was recovered enantiopure (ee > 99%). More importantly, conversion was recorded in THF as solvent compared with acetone in which denaturation of enzyme could occur.[47] In toluene or in dichloromethane, monoacetate **2** and residual diacetate **1** are obtained both in racemic form (Table 1, entries 3-4). Surprisingly in heptane, hydrophobic solvent, only the cleavage of the aromatic acetyl was observed with total conversion in favor of the monoacetate **2** (Table 1, entry 5). The above results show that the THF is the



SCHEME 1 Lipase *CAL-B*–catalyzed hydrolysis of diacetate **1** in the presence of Na_2CO_3

TABLE 1 Solvent effect in *CAL-B*–catalyzed alkaline hydrolysis of diacetate **1**

		1	2	3		
Entry[a]	Solvent (LogP)	ee, %[b] Yield, %[c]	ee, %[b] Yield, %[c]	ee, %[b] Yield, %[c]	c, %[d]	E[e]
1	**THF (0.48)**	-	**31 (40)**	**>99% (21)**	**24**	**>200**
2	Acetone (−0.23)	-	4 (15)	>99 (trace)	4	>200
3	CH_2Cl_2 (1.01)	*6* (8)	*1.5* (40)	-	80	1
4	Toluene (2.5)	*5* (10)	*4* (50)	-	55.6	1
5	Heptane (4)	-	*4* (65)	-	100	-

Bold entries indicate the best result.

[a]Reaction conditions: 1 mmol of racemic diacetate, 0.5 mmol of Na_2CO_3, 40 mg of *CAL-B*, in 2 mL of organic solvent at 40°C for 72 hours.

[b]Enantiomeric excess of recovered products are measured by chiral high-performance liquid chromatography.

[c]Isolated yields.

[d]Conversion: $c = ee_S/ee_P + ee_s$.[46]

[e]Enantiomeric ratio: $E = \ln[(1-c)(1-ee_{(S)})]/\ln[(1-c)(1+ee_{(S)})$.

suitable organic media for the alkaline-enzymatic hydrolysis of diacetate **1**. In order to optimize the alkaline hydrolysis conditions, various parameters were examined such as the amount of lipase, the amount of Na_2CO_3, and the reaction time. Conversions and enantiomeric excesses were determined by chiral HPLC after separations by flash chromatography. The results are summarized in Table 2.

Results in Table 2 show a high regioselectivity and enantioselectiviy of *CAL-B* in alkaline hydrolysis of diacetate **1** in the optimized experimental conditions. (*R*)-diol **3** was obtained enantiopure with a high selectivity (E > 200), but conversion depends on the other parameters of the reaction: catalytic charge, amount of Na_2CO_3, and reaction time. The use of 0.2 equiv of Na_2CO_3 in the presence of 40 mg of enzyme during 72 hours yielded the racemic monoacetate **2** (72% yield) (Table 2, entry 2). No reaction was occurred without Na_2CO_3 (Table 2, entry 1). Progressive increase of the amount of Na_2CO_3 from 0.3 to 1 equiv enhances significantly the conversion ratio of the alkaline hydrolysis (Table 2, entries 3-6). Prolongation of the reaction time to 96 hours improves the conversion rate up to c = 35% (Table 2, entry 8). Increasing the amount of Na_2CO_3 (2 equiv) with dilution of the reaction medium for a better solubility achieves 40% conversion, which does not change after a longer reaction time up to 96 hours (Table 2, entries 10-12). However, the increase of the lipase loading to 120 mg allows reaching the optimal resolution (c = 50% and E > 200). The enantiomers (*S*)-monoacetate **2** and (*R*)-diol **3** are recovered enantiopure (ee > 98%) (Table 1, entry 13). This result supports our hypothesis that the alkaline hydrolysis efficiency is due probably to the water provided by the enzyme itself.[41]

3.2 | *CAL-B*–catalyzed deacylation of racemic diacetate 1 and acylation of racemic diol 3 (paths B, C, and D): comparison of regioselectivity and enantioselectivity

Then, we intended to examine the regioselectivity and the enantioselectivity of the *CAL-B* in other kinetic resolution approaches of deacylation of diacetate **1** and in the

TABLE 2 *CAL-B*–catalyzed alkaline hydrolysis of diacetate **1**: study of several parameters

Entry	Na_2CO_3, Eq.	*CAL-B*, mg	Time, h	(*S*)-2		(*R*)-3		c, %[g]	E[h]
				ee_s, %[e]	Yield, %[f]	ee_p, %[e]	Yield, %[f]		
1[a]	-	40	72	-	-	-	-	NR	-
2[a]	0.2	40	72	0.1	72	-	-	-	-
3[a]	0.3	40	72	12	55	>99	8	10	>200
4[a]	0.4	40	72	17	50	>99	10	14	>200
5[a]	0.5	40	72	31	40	>99	21	23	>200
6[a]	1	40	72	33	44	>99	20	25	>200
7[b]	1	-	72	-	-	-	-	NR	-
8[a]	1	40	96	53	34	>99	30	35	>200
9[c]	1.5	40	96	55	36	>99	30	36	>200
10[c]	2	40	72	67	44	>99	36	40	>200
11[c]	2	40	96	67	37	>99	38	40	>200
12[c]	2	80	96	67	30	>99	28	40	>200
13[d]	**2**	**120**	**96**	**98**	**44**	**>99**	**40**	**50**	**>200**

Bold entries indicate the best result.

Abbreviation: NR, no reaction.

[a]1 mmol racemic diacetate an appropriate amount of Na_2CO_3, 40 mg of *CAL-B* in 2 mL of tetrahydrofuran (THF) at 40°C.

[b]Without lipase in presence of 0.02 mL of water.

[c]4 mL of THF.

[d]6 mL of THF.

[e]Enantiomeric excess of recovered alcohols and remaining acetates are measured by chiral high-performance liquid chromatography.

[f]Isolated yields.

[g]Conversion: $c = ee_S/ee_P + ee_s$.[46]

[h]Enantiomeric ratio: $E = \ln [(1 - c)(1 - ee_{(S)})]/\ln [(1 - c)(1 + ee_{(S)})]$.[46]

TABLE 3 Comparison *CAL-B*–catalyzed acylation/deacylation approaches

Entry	Approach	Nucleophile	[(*S*)-substrate] ee_s, %[e] Yield, %[f]	[(*R*)-product] ee_p, %[e] Yield, %[f]	c, %[g]	E[h]
1[a]	**Deacylation**	**Na_2CO_3**	**[2] 98 (44)**	**[3] 99 (40)**	**50**	**>200**
2[b]		MeOH	[2] 51 (40)	[3] 99 (30)	34	>200
3[c]		Et_3N	[2] 1.5 (67)	-	100	-
4[d]	Acylation		[3] 87 (37)	[2] 94.2 (35)	48	70

Bold entries indicate the best result.

[a]1 mmol racemic diacetate, 2 mmol Na_2CO_3, and 120 mg *CAL-B* in 6 mL of tetrahydrofuran (THF) at 40°C for 96 hours.

[b]1 mmol racemic diacetate, 4 mmol of MeOH, and 40 mg *CAL-B* in 3 mL of THF at 40°C for 72 hours.

[c]1 mmol racemic diacetate, 4 mmol of Et_3N, and 40 mg *CAL-B* in 3 mL of THF at 40°C for 72 hours.

[d]1 mmol racemic diol, 3 mmol vinyl acetate, and 40 mg *CAL-B* in 3 mL of THF at room temperature for 72 hours.

[e]Enantiomeric excess of recovered alcohols and remaining acetates are measured by chiral high-performance liquid chromatography.

[f]Isolated yields.

[g]Conversion: $c = ee_S/ee_P + ee_s$.[46]

[h]Enantiomeric ratio: $E = \ln[(1 - C)(1 - ee_{(S)})]/\ln[(1 - C)(1 + ee_{(S)})]$.[46]

acylation of diol **3** using enol ester as an acylating agent (path D). Two deacylation routes were studied: alcoholysis using methanol as acetyl acceptor[48] (path B) and with the Et_3N as basic additive[49] (path C) according to previous works (Figure 2). The alcoholysis was carried out on 1 mmol of diacetate **1** and 4 equiv of MeOH in the presence of 40 mg of *CAL-B* and 60 mg of molecular sieves 4 Å in 3 ml THF. The deacylation using triethylamine was performed under the same conditions using 4 equiv of tertiary amine. The acylation of diol **3** was performed using 3 equiv of vinyl acetate in the same solvent. All kinetic resolution reactions were stirred at 40°C during 72 hours. The evolution of the reaction was monitored by TLC. The conversions and the enantiomeric excesses of products were quantified by chiral HPLC after separations by flash chromatography. Results of comparison *CAL-B*–catalyzed acylation/deacylation approaches are summarized in Table 3.

The kinetic resolution of racemic diacetate **1** via *CAL-B*–catalyzed alcoholysis (path B) shows a high enantioselectivity and furnishes the enantiopure (*R*)-**3** diol (ee > 99%) at conversion rate of c = 34%. The deacylation using triethylamine leads only to racemic monoacetate **2** (path C). The acylation of racemic diol **3** gives (*R*)-monoacetate **2** with ee = 94.2% and the (*S*)-diol **3** with ee = 87% and selectivity E = 70 at 48% conversion rate (path D). The results of the different pathways (Table 3) show clearly that the best results in terms of reactivity and enantioselectivity were afforded by *CAL-B*–catalyzed alkaline hydrolysis reaction (path A) (Figure 3).

Lipase was highly regioselective and enantioselective; the (*S*)-monoacetate **2** and (*R*)-diol **3** enantiomers

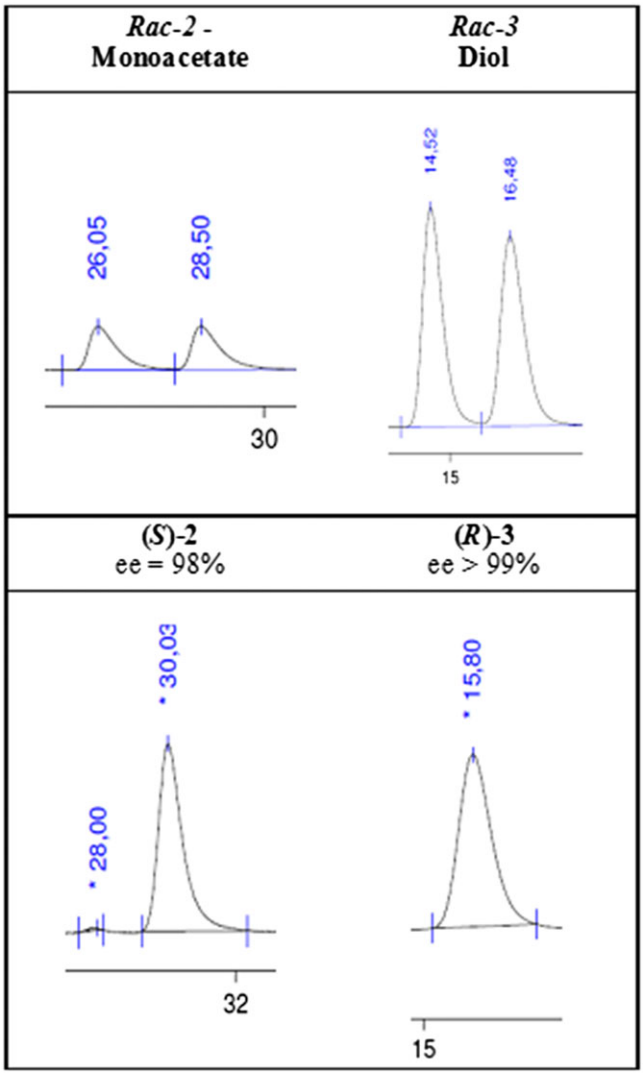


FIGURE 3 Chromatograms of enantiomers (path A)

were obtained enantiomerically pure in high yields. *CAL-B* lipase leads to selective hydrolysis of the phenolic hydroxyl group and (*R*)-enantioselection of the chiral hydroxyl. Furthermore, alkaline hydrolysis of diacetate **1** and acylation of diol **3** are selective and enantiocomplementary reactions. Alkali-mediated enzymatic hydrolysis in organic media gives access to (*S*)-monoacetate **2** and (*R*)-diol **3** enantiomers in a straightforward and practical manner. This approach that makes it possible to valorize both enantiomers of racemic 3-(1-hydroxyethyl)phenol is described for the first time.

4 | CONCLUSION

We developed a novel and efficient process to access (*S*) and (*R*) enantiomers of 3-(1-hydroxyethyl)phenol, which are key intermediates, respectively, for the synthesis (*S*)-Rivastigmine and (*R*)-Phenylephrine. We have applied alkaline hydrolysis in organic media under mild conditions with *CAL-B* and sodium carbonate on 3-(1-acetoxyethyl)phenyl acetate. High regioselectivity and enantioselectivity were observed: (*R*)-3-(1-hydroxyethyl)phenol was obtained with a 99% ee and (*S*)-3-(1-acetoxyethyl)phenol with a 98% ee with high selectivity $E > 200$ and optimal conversion $c = 50\%$. Two deacylation approaches are compared: alcoholysis with MeOH and in the presence of triethylamine. The *CAL-B*–catalyzed acylation of 3-(1-hydroxyethyl)phenol with vinyl acetate is also examined. The best results were obtained by alkaline hydrolysis, but good regioselectivity and enantioselectivity were also observed in alcoholysis and acylation reactions. With triethylamine, only the racemic monoacetate was obtained. In all cases, a selective hydrolysis of phenolic hydroxyl groups in the presence of aliphatic hydroxyl group was obtained. Finally, these enantiopure enantiomers, key intermediates for access to (*S*)-(−)-Rivastigmine and (*R*)-(−)-Phenylephrine, were obtained with high enantiopurity from the corresponding racemic diacetate through *CAL-B*–catalyzed hydrolysis by sodium carbonate in organic media.

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