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Lipase-catalyzed separation of the enantiomers of 1-substituted-3-arylthio-2-propanols

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Abstract—Optically active (*R*)- and (*S*)-1-substituted-3-(arylthio)propan-2-ols have been prepared in the reaction of the appropriate 2-(arylthiomethyl)oxiranes with chloride and azide anions followed by a lipase-catalyzed transesterification. The effects of the enzyme preparation as well as of the reaction conditions have been compared in terms of the enantiomeric excess of the obtained acetate and unreacted alcohol.
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1. Introduction

The opening of the oxirane ring with various nucleophiles (e.g., halogen ions, CN^-, N_3^-, OH^-) is a very important synthetic transformation. It leads to racemic mixtures of 1,3-disubstituted secondary propanols, known as useful building blocks in the synthesis of many biologically active compounds. Having two reactive substituents, these compounds can be easily transformed into many new structures. The hydroxy group on the stereogenic carbon at the 2-position of the propane chain makes them very interesting models for the investigation of the hydrolase-catalyzed reactions capable of yielding pure enantiomers. For example, enantiomerically pure (*S*)-1-azido-3-aryloxypropanols are convenient intermediates in the preparation of several β-blockers and antidepressant drugs. The lipase-catalyzed reactions described to date have been successfully carried out with 1-substituted-3-aryloxy-2-propanols; which means that the aryloxy substituent is always present at the 3-position of the propane chain.

To the best of our knowledge, similar 1-substituted-3-arylthiopropan-2-ols have not been investigated as substrates in hydrolase-catalyzed reactions. Continuing our interest in the lipase-catalyzed transesterifications of the racemic 1,3-disubstituted-2-propanols[1–3] we recently focused our attention on 1-azido- and 1-chloro-3-arylthiopropan-2-ols, **2** and **3**, respectively, which can be easily prepared from 2-arylthiomethyloxiranes. Their optically active forms may be interesting as sulfur analogues of the intermediates leading to β-blockers.

2. Results and discussion

2.1. Synthesis of 1-azido- and 1-chloro-3-thioaryloxy-2-propanols

2-Arylthiomethyloxiranes **1a–c** were prepared in high yields (80–85%) from the corresponding thiophenols and epichlorohydrin in a NaOH/THF suspension according to the method described.[4] 1-Chloro-3-arylthiopropan-2-ol (±)-**3a–c** was the primary product of the reaction. It was subsequently converted into the appropriate 2-arylthiomethyloxirane **1a–c** by the NaOH excess present in the reaction mixture. The opening of the oxirane ring of **1a–c** by chloride or azide anions leads to racemic mixtures of 1-chloro- and 1-azido-3-arylthiopropan-2-ol, (±)-**3a–c** or (±)-**2a–c**, respectively. The reactions were carried out with potassium chloride or sodium azide in the presence of ammonium chloride in a methanol–water (8:1 v/v) solution (Scheme 1).

2.2. Kinetic resolution of (±)-2a–c and (±)-3a–c

The conditions of the lipase-catalyzed acetylation of racemic alcohols (±)-**2a–c** and (±)-**3a–c** were optimized according to the conventional methods[5] (Scheme 2). The effects of the lipase type, solvent and acyl donor

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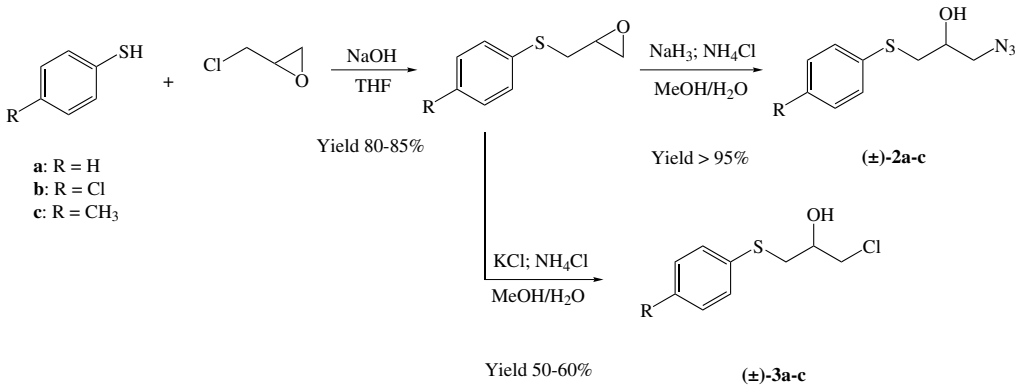
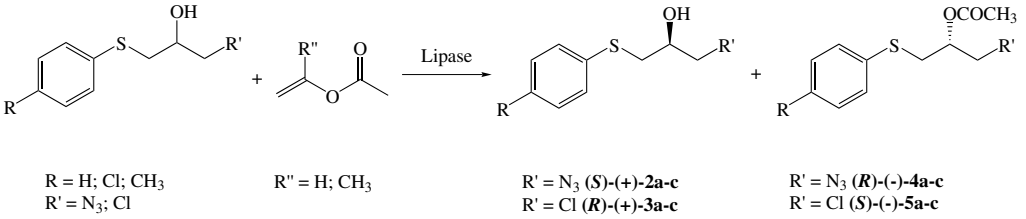


Scheme 1. Synthesis of (±)-**2a**–**c** and (±)-**3a**–**c**.



Scheme 2. Acylation reaction of (±)-**2a**–**c** and (±)-**3a**–**c**.

as well as of the substituent in the aromatic ring on the enantioselectivity of the reaction were estimated by determining the reaction enantioselectivity.

2.2.1. Screening of different lipases. The catalytic efficiencies of the different commercially available lipases in the acylation reaction of the title alcohols were investigated. For this purpose, **2a**, used as a model substrate, was allowed to react at 20 °C in a *tert*-butyl methyl ether (TBME) solution with 3 equiv of vinyl acetate in the presence of the tested lipase. Control experiments revealed that the reaction failed to proceed in the absence of an enzyme. The transesterification reactions were monitored by thin layer chromatography and were arrested once the conversion reached 30–50%. The enzyme was then removed by filtration and the resulting solution of enantiomerically enriched acetate **4a** and unchanged alcohol **2a** was used for an exact determination of the conversion degree and enantiomeric excesses. The results are summarized in Table 1.

The absolute configurations of the products, that is, alcohol **2a** and acetate **4a**, were determined by the modified Mosher's method as described by Riguera and coworkers.[7] The method depends on comparing the difference between the ^{1}H NMR chemical shifts recorded for the diastereomeric ester prepared from a separated enantiomer of a given alcohol and the (*R*)- and (*S*)-enantiomers of methoxyphenylacetic acid. Our investigation has shown that the unchanged alcohol **2a** and its acetate **4a** have the (*S*)-(+)- and (*R*)-(−)-configurations, respectively. This assignment is in good agreement with the Kazlauskas' rule.[8] The results presented in Table 1 show that the (*S*)-(+)-alcohol **2a** reacts with the tested lipases considerably slower than the (*R*)-(−) enantiomer and that the reactions show poor-to-good enantioselectivities (E = 2–56). Among the tested enzymes, only lipase preparations from *Candida antarctica*-B (Novozym SP 435; Chirazyme L-2, c-f, lyo and Chirazyme L-2, c-f, C2, lyo) exhibited promising catalytic activity and enantioselectivity with this substrate.

Table 1. Results of the lipase-catalyzed kinetic resolution of (±)-**2a** by transesterification[a]

Entry	Enzyme	Time (h)	c[b] (%)	Ee_{sub}[d] (%)	Ee_{prod}[c] (%)	E[b]
1	Amano AK (*Pseudomonas fluorescens*)	30	32	12	25	2
2	Amano PS (*Pseudomonas cepacia*)	110	17	17	79	9
3	Novozym SP 435 (*Candida antarctica*-B (10 kU/g))	24	57	>99	77	56
4	Chirazyme L-1, c-f, lyo (*Pseudomonas cepacia*)	25	36	25	45	3
5	Chirazyme L-2, c-f, lyo (*Candida antarctica*-B (200 U/g))	25	24	29	93	37
6	Chirazyme L-2, c-f, C2, lyo (*Candida antarctica*-B (10 kU/g))	26	48	82	90	51

[a] Conditions: 1 mmol of (±)-**2a**, 3 mmol of vinyl acetate, 100 mg of the appropriate lipase and 12 mL of TBME at rt.
[b] Conversions and E-values were calculated[6] from the enantiomeric excess of substrate **2a** (ee_s) and product **4a** (ee_p) using the known formula: $E = \mathrm{Ln}[(1 - ee_s)(ee_p/(ee_s + ee_p))]/\mathrm{Ln}[(1 + ee_s)(ee_p/(ee_s + ee_p))]$, conversion $c = ee_s/(ee_s + ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.
[d] Determined by ^{1}H NMR spectra taken with the shift reagent Eu(tfc)$_3$ added.

Table 2. Results of the *Candida antarctica*-catalyzed acetylation of (±)-**2a** by vinyl acetate in TBME and toluene solutions[a]

Entry	Enzyme	Solvent	Log *P*	Time (h)	c[b] (%)	Ee_{sub}[d] (%)	Ee_{prod}[c] (%)	E[b]
1	Novozym SP 435	TBME	1.3	24	57	>99	77	56
2	Novozym SP 435	Toluene	2.5	24	45	75	94	68
3	Novozym SP 435	Hexane	3.5	23	54	>99	77	54
4	Novozym SP 435	*i*-Pr2O	1.1	23	55	96	77	30
5	Novozym SP 435	THF	0.49	64	19	22	94	43
6	Chirazyme L-2, c-f, c-2, lyo	TBME	1.3	25	24	29	93	37
7	Chirazyme L-2, c-f, c-2, lyo	Toluene	2.5	72	42	70	96	>100

[a] Conditions: 1 mmol of (±)-**2a**, 3 mmol of vinyl acetate, 100 mg of the appropriate lipase and 12 mL of TBME at rt.
[b] Conversions and *E*-values were calculated[6] from the enantiomeric excess of substrate **2a** (ee_s) and product **4a** (ee_p) using the known formula: $E = \mathrm{Ln}[(1 - ee_s)(ee_p/(ee_s + ee_p))]/\mathrm{Ln}[(1 + ee_s)(ee_p/(ee_s + ee_p))]$, conversion $c = ee_s/(ee_s + ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.
[d] Determined by ^{1}H NMR spectra taken with the shift reagent $Eu(tfc)_3$ added.

2.2.2. Solvent effect. As it is well known, changing the solvent almost always affects the enantiomeric selectivity and the reaction rate of the lipase-catalyzed kinetic resolutions. In this research, the acetylation of (±)-**2a** with vinyl acetate at room temperature in the presence of Novozym SP 435 or Chirazyme L-2, c-f, lyo was carried out in five different solvents. According to the literature,[2,9] toluene and hexane are the solvents of choice in the transesterification reactions catalyzed by lipases from *C. antarctica*. Our results reported in Table 2 confirm this statement showing the highest enantioselectivity of the enzymes in these solvents. However, the activities were a little lower than in TBME and ethyl ether.

2.2.3. Acyl donor effect. The effect of the structure of the acyl donor on the enantioselectivity of a lipase-catalyzed transesterification reaction has been well documented by Ema et al.[10] In general, among the various types of acyl donors they had examined, enol esters, owing to their high reactivity and irreversibility of the reaction, have been considered as the most suitable for the kinetic resolution by transesterification. As it is known, vinyl acetate is the ester of choice, although *iso*-propenyl acetate is also frequently used in these reactions. Usually, the reaction with *iso*-propenyl acetate is slower than that with vinyl acetate but the enantioselectivity is sometimes higher. The most important results of enzyme-catalyzed transesterifications of (±)-**2a**–**c** and (±)-**3a**–**c** are presented in Tables 3 and 4.

With 1-azido-3-thiophenoxy-propan-2-ol (±)-**2a**, the highest enantioselectivities were obtained with vinyl

Table 3. Selected results obtained in the enzyme-catalyzed transesterifications of (±)-**2a**–**c** in toluene solution at room temperature[a]

Entry	Substrate	Acyl donor	Enzyme	Time (h)	c[b] (%)	Ee_{sub}[c] (%)	Ee_{prod}[c](%)	E[b]
1	**2a**	Vinyl acetate	Chirazyme L-2, c-f, lyo	24	44	75	94	68
2	**2a**	Vinyl acetate	Novozym SP 435	72	42	70	96	>100
3	**2a**	*iso*-Propenyl acetate	Novozym SP 435	50	33	47	94	48
4	**2b**	Vinyl acetate	Novozym SP 435	24	40	61	92	45
5	**2b**	*iso*-Propenyl acetate	Chirazyme L-2, c-f, lyo	52	44	75	94	75
6	**2b**	*iso*-Propenyl acetate	Novozym SP 435	69	37	56	96	87
7	**2c**	Vinyl acetate	Novozym SP 435	24	45	73	90	43
8	**2c**	*iso*-Propenyl acetate	Novozym SP 435	52	35	50	93	47

[a] Conditions: 1 mmol of (±)-**2a**, 3 mmol of vinyl acetate, 100 mg of the appropriate lipase and 12 mL of TBME at rt.
[b] Conversions and *E*-values were calculated[6] from the enantiomeric excess of substrate **2a** (ee_s) and product **4a** (ee_p) using the known formula: $E = \mathrm{Ln}[(1 - ee_s)(ee_p/(ee_s + ee_p))]/\mathrm{Ln}[(1 + ee_s)(ee_p/(ee_s + ee_p))]$, conversion $c = ee_s/(ee_s + ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.

Table 4. Selected results obtained in the enzyme-catalyzed transesterifications of (±)-**3a**–**c** in a toluene solution at room temperature[a]

Entry	Substrate	Acyl donor	Enzyme	Time (h)	c[b] (%)	Ee_{sub} (%)	Ee_{prod} (%)	E
1	**3a**	Vinyl acetate	Novozym SP 435	23	27	35[c]	95	57[e]
2	**3a**	Vinyl acetate	Chirazyme L-2, c-f, lyo	192	43	72[c]	93	63[e]
3	**3a**	*iso*-Propenyl acetate	Novozym SP 435	72	40	61[c]	90	37[e]
4	**3b**	Vinyl acetate	Novozym SP 435	45	55	93	77[d]	25[f]
5	**3b**	Vinyl acetate	Amano AK	24	39	54	83[d]	19[f]
6	**3c**	Vinyl acetate	Novozym SP 435	24	19	22	92	30[a]
7	**3c**	Vinyl acetate	Chirazyme L-2, c-2, c-f, lyo	43	25	30	91	28[a]
8	**3c**	*iso*-Propenyl acetate	Chirazyme L-2, c-2, c-f, lyo	168	23	27	92	30[a]

[a] Conditions: 1 mmol of (±)-**2a**, 3 mmol of vinyl acetate, 100 mg of the appropriate lipase and 12 mL of TBME at rt.
[b] Conversion determined by GC.
[c] Enantiomeric excesses calculated from: $ee_{sub} = ee_{prod} * c/(1 - c)$.
[d] Enantiomeric excesses calculated from: $ee_{prod} = ee_{sub}(1 - c)/c$.
[e] *E*-values calculated[11] from the equation: $E = \mathrm{Ln}[1 - c*(1 + ee_{prod})]/\mathrm{Ln}[1 - c*(1 - ee_{prod})]$.
[f] *E*-values calculated[11] using the equation: $E = \mathrm{Ln}[(1 - c)(1 - ee_{sub})]/\mathrm{Ln}[(1 - c)(1 + ee_{sub})]$. Experimental ee values obtained according to 'c' in Table 1.

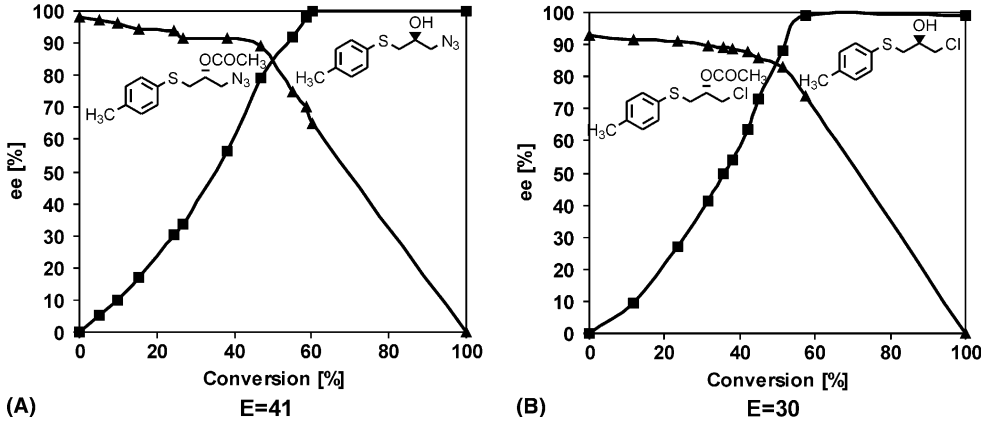


Figure 1. Dependence of the enantiomeric purities ee (%) of **2c** and **4c** (graph A) and **3c** and **5c** (graph B) on conversion of (±)-**2c** and (±)-**3c** in the Novozym SP 435-catalyzed acetylation with vinyl acetate in a toluene solution at 20 °C.

acetate acting as the acyl donor (E = 68–100). However, in the case of (±)-**2b** and (±)-**2c**, *iso*-propenyl acetate revealed a higher selectivity. With (±)-**3a**–**c**, the results of the reactions with both vinyl and *iso*-propenyl acetate were much worse than those obtained with (±)-**2a**–**c**. Also Amano AK lipase exhibited with these compounds a moderate enantioselectivity.

Analysis of the present results indicates that incorporation of a substituent into the phenyl ring of the substrate results in a decrease of the acetylation enantioselectivity (E) for all of the investigated alcohols. The effect was most pronounced with 1-chloro-3-(4-chlorophenylthio)-propan-2-ol (±)-**3b**.

Experimentally obtained dependence of the enantiomeric excess of the substrate (alcohol) and the product (acetate) on conversion of (±)-1-azido-3-(*p*-tolylthio)-propan-2-ol and (±)-1-chloro-3-(*p*-tolylthio)propan-2-ol is presented in Figure 1 graph A and graph B, respectively, together with the calculated enantioselectivity E of the reactions. The plots indicate good enantioselectivities of both reactions and only a slight influence of the substituent at the β-position.

3. Conclusions

A general and efficient method for a lipase-catalyzed kinetic resolution of the racemic mixtures of 3-thioaryloxy-propan-2-ols by their acetylation leading to the optically active compounds has been presented. The highest enantioselectivity values (E = 68–100) were obtained with 1-azido-3-arylthiopropan-2-ols when the *C. antarctica*-B lipase (Novozym SP 435 and two Chirazymes L-2) was used in a toluene solution at 20 °C.

4. Experimental

4.1. General

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Mercury 400 MHz spectrometer in a $CDCl_3$ solution, with chemical shifts (δ) reported in ppm. IR spectra were taken with a Carl Zeiss Specord M80 instrument. Enantiomeric purities of alcohols **2a**–**h** and esters **3a**–**h** were determined on a Thermo-Separation Products P-100 instrument and Chiralcel OD-H column (in *n*-hexane:*iso*-propanol 9:1; 0.8 mL/min for alcohols and in *n*-hexane:*iso*-propanol 99:1; 0.4 mL/min for esters) using the corresponding racemic compounds for reference. Optical rotations were measured in $CHCl_3$ with a PolAAr 32 polarimeter. Elemental analyses were performed with a CHNS/O Perkin–Elmer type 2400 instrument. The reactions were monitored by TLC on silica gel 60 F254 plates and by column chromatography on silica gel 60 (230–400 mesh). The arylthioglycidyl ethers were prepared from the appropriate thiophenols and epichlorohydrin according to the method described earlier.[4] Amano AK, and Amano PS lipases were generously provided by Amano Co (Japan). Novozym SP 435 was kindly granted by Novo-Nordisk. Chirazymes were supplied by Roche Molecular Biochemicals (Germany).

4.2. Preparation of 3-substituted-1-arylthio-propan-2-ols (±)-2a–c and (±)-3a–c

The arylglycidyl thioether (0.01 mol), sodium azide or potassium chloride (0.05 mol), and ammonium chloride (1.28 g, 0.024 mol) were added to 30 mL of a methanol/water mixture. The reaction was carried out at 70 °C and the conversion monitored by TLC with hexane/ethyl acetate 5:1 (v/v). Upon completing the reaction, the methanol was evaporated, 30 mL of water was added to the residue and the product extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and dried over Na_2SO_4. The alcohols were purified by column chromatography using hexane/ethyl acetate 10:1 (v/v) for (±)-**2a**–**c** or hexane/CH_2Cl_2 1:4 (v/v) for (±)-**3a**–**c** as the eluents.

4.2.1. 1-Azido-3-phenylthiopropan-2-ol (±)-2a. ^{1}H NMR ($CDCl_3$) δ 2.67 (1; 1H; OH); 2.98 (dd; 1H; J_{gem} = 14 Hz; J = 7.8 Hz; SCH_aH_b); 3.10 (dd; 1H; J = 4.8 Hz; SCH_aH_b); 3.38 (dd; 1H; J_{gem} = 12.7 Hz; J = 6 Hz; $CH_cH_dN_3$); 3.45 (dd; 1H; J = 4 Hz;

$CH_cH_dN_3$); 2.84 (m; 1H; CH); 7.24–7.41 (m; 5H; aromat.); ^{13}C NMR ($CDCl_3$) δ 38.74; 54.97; 68.78; 127.03; 129.21; 130.30; 134.33; IR (film; cm^{-1}): 3440; 2100; 1480; 1440; 1280; 1080; 740; 690. Anal. Calcd for $C_9H_{11}N_3OS$: C, 51.66; H, 5.30; N, 20.08; S, 15.32. Found: C, 51.42; H, 5.39; N, 19.42; S, 15.42.

4.2.2. 1-Azido-3-(4-chlorophenylthio)propan-2-ol (±)-2b. ^1H NMR ($CDCl_3$) δ 2.79 (s; 1H; OH); 2.97 (dd; 1H; J_{gem} = 14 Hz; J = 7.6 Hz; SCH_aH_b); 3.06 (dd; 1H; J = 5.2 Hz; SCH_aH_b); 3.37 (dd; 1H; J_{gem} = 12.8 Hz; J = 6 Hz; $CH_cH_dN_3$); 3.44 (dd; 1H; J = 4 Hz; $CH_cH_dN_3$); 3.83 (m; 1H; CH); 7.25–7.28 (m; 2H; aromat.); 7.95–7.33 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 38.73; 54.92; 68.78; 129.25; 131.40; 132.95; 133.05; IR (film; cm^{-1}): 3420; 2110; 1475; 1285; 1100; 1015; 715. Anal. Calcd for $C_9H_{10}N_3ClOS$: C, 44.35; H, 4.13: N, 17.24. Found: C, 44.32; H, 3.94; N, 17.45.

4.2.3. 1-Azido-3-(4-methylphenylthio)propan-2-ol (±)-2c. ^1H NMR ($CDCl_3$) δ 2.33 (s; 3H; CH_3); 2.68 (d; 1H; J = 4 Hz; OH); 2.93 (dd; 1H; J_{gem} = 14 Hz; J = 8 Hz; SCH_aH_b); 3.04 (dd; 1H; J = 4.6 Hz; SCH_aH_b); 3.35 (dd; 1H; J_{gem} = 12.4 Hz; J = 6 Hz; $CH_cH_dN_3$); 3.43 (dd; 1H; J = 4 Hz; $CH_cH_dN_3$); 3.81 (m; 1H: CH); 7.11–7.14 (m; 2H; aromat.); 7.30–7.32 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 21.01; 39.52; 54.97; 68.73; 130.00; 130.44; 131.17; 137.43; IR (film; cm^{-1}): 3425; 2105; 1480; 1290; 1110; 1025; 815. Anal. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82. Found: C, 53.89; H, 5.62; N, 18.89.

4.2.4. 1-Chloro-3-phenylthiopropan-2-ol (±)-3a. ^1H NMR ($CDCl_3$) δ 2.65 (d; 1H; J = 4.8 Hz; OH); 3.08 (dd; 1H; J_{gem} = 14 Hz; J = 7 Hz; SCH_aH_b); 3.17 (dd; 1H; J = 5.6 Hz; SCH_aH_b); 3.66 (dd; 1H; J_{gem} = 11.2 Hz; J = 5.2 Hz; CH_cH_dCl); 3.70 (dd; 1H; J = 4.4 Hz; CH_cH_dCl); 3.93 (m; 1H; CH); 7.21–7.26 (m; 1H; aromat.); 7.29–7.33 (m; 2H; aromat.); 7.39–7.42 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 38.22; 47.95; 69.44; 126.92; 129.18; 130.11; 134.53; IR (film; cm^{-1}): Anal. Calcd for $C_9H_{11}ClOS$: C, 53.33; H, 5.47; S, 15.82; Cl, 17.49. Found: C, 53.08; H, 5.54; S, 15.75; Cl, 17.60.

4.2.5. 1-Chloro-3-(4-chlorophenylthio)propan-2-ol (±)-3b. ^1H NMR ($CDCl_3$) δ 2.68 (d; 1H; J = 4.8 Hz; OH); 3.05 (dd; 1H; J_{gem} = 14 Hz; J = 7.2 Hz; SCH_aH_b); 3.14 (dd; 1H; J = 5.6 Hz; SCH_aH_b); 3.65 (dd; 1H; J_{gem} = 11.2 Hz; J = 5.2 Hz; CH_cH_dCl); 3.68 (dd; 1H; J = 4.4 Hz; CH_cH_dCl); 3.92 (m; 1H; CH); 7.25–7.35 (m; 4H; aromat.); ^{13}C NMR ($CDCl_3$) δ 38.35; 47.88; 69.47; 129.27; 131.34; 132.94; 133.21; IR (film; cm^{-1}): 3410; 1495; 1425; 1210; 1190; 1145; 810. Anal. Calcd for $C_9H_{10}Cl_2OS$: C, 45.58; H, 4.25. Found: C, 45.69; H, 4.34.

4.2.6. 1-Chloro-3-(4-methylphenylthio)propan-2-ol (±)-3c. ^1H NMR ($CDCl_3$) δ 2.71 (d; 1H; J = 4.8 Hz; OH); 3.02 (dd; 1Ha; J_{gem} = 14 Hz; J = 7.2 Hz; SCH_aH_b); 3.12 (dd; 1Hb; J = 5.6 Hz; SCH_aH_b); 3.64 (dd; 1Hc; J_{gem} = 11.2 Hz; J = 5.2 Hz; CH_cH_dCl); 3.68 (dd; 1Hd; J = 4.4 Hz; CH_cH_dCl); 3.88 (m; 1H; CH); 7.11–7.13 (m; 2H; aromat.); 7.29–7.32 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 21.00; 38.98; 47.92; 69.41; 129.95; 130.30; 130.93; 137.26; IR (film; cm^{-1}): 3400; 1475; 1425; 1385; 1095; 1010; 810. Anal. Calcd for $C_{10}H_{13}ClOS$: C, 55.42; H, 6.04. Found: C, 55.44; H, 6.08.

4.3. Typical transesterification procedure for (±)-2a–c and (±)-3a–c

The appropriate alcohol (±)-**2a**–**c** or (±)-**3a**–**c** (1 mmol) was dissolved in 12 mL of TBME and vinyl acetate (3 mmol) and 100 mg of lipase were added. The mixture was stirred at room temperature (20–22 °C) and the conversion monitored by TLC. When the reaction was completed, the enzyme was filtered off and the solvent evaporated under reduced pressure. The mixture of acetate and unchanged alcohol was separated by column chromatography on silica gel with a hexane–ethyl acetate (5:1 v/v) mixture as the eluent. The enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column or ^1H NMR analysis with $Eu(tfc)_3$ as the shift reagent.

With the aim of defining the absolute configuration we prepared the alcohols in very high enantiomeric excess by extending conversions of the transesterifications up to 65%. NMR spectra of enantiomerically enriched alcohols (***S***)-(+)-**2a**–**c** and (***R***)-(+)-**3a**–**c** were identical with those of (±)-**2a**–**c** and (±)-**3a**–**c**. The optical rotations of enantiomerically enriched alcohols obtained in the Novozym 435 catalyzed reactions measured in $CHCl_3$ solutions are as follows:

(***S***)-(+)-**2a**: $[\alpha]_D^{22} = +27.3$ (*c* 0.99; ee = 99%)
(***S***)-(+)-**2b**: $[\alpha]_D^{22} = +16.8$ (*c* 1.07; ee = 95%)
(***S***)-(+)-**2c**: $[\alpha]_D^{22} = +30.8$ (*c* 1.03; ee = 99%)
(***R***)-(+)-**3a**: $[\alpha]_D^{22} = +5.7$ (*c* 1.05; ee = 89%)
(***R***)-(+)-**3b**: $[\alpha]_D^{22} = +6.8$ (*c* 1.03; ee = 93%)
(***R***)-(+)-**3c**: $[\alpha]_D^{22} = +27.8$ (*c* 0.99; ee = 99%)

^1H and ^{13}C NMR spectra, IR data, elemental analyses and optical rotations of obtained acetates (***R***)-(−)-**4a**–**c** and (***S***)-(−)-**5a**–**c** are reported below:

4.3.1. (*R*)-(−)-1-Azido-3-phenylthiopropan-2-ol acetate 4a. Yield: 94%; ^1H NMR ($CDCl_3$) δ 2.02 (s; 3H; CH_3); 3.09 (dd; $1H_a$; J_{gem} =14 Hz; J = 7.4 Hz; SCH_aH_b); 3.21 (dd; $1H_b$; J = 5.6 Hz; SCH_aH_b); 3.55 (m; 2H; CH_2N_3); 5.06 (m; 1H; CH); 7.20–7.33 (m; 3H; aromat.); 7.39–7.42 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 20.79; 34.35; 51.96; 71.59; 126.78; 129.12; 129.84; 134.73; 170.11; IR (film; cm^{-1}): 2110; 1745; 1445; 1375; 1225; 1040; 745; 700; $[\alpha]_D^{22} = -2.8$ (*c* 1.05; ee = 96%). Anal. Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.75; H, 5.08; N, 16.81.

4.3.2. (*R*)-(−)-1-Azido-3-(4-chlorophenylthio)propan-2-ol acetate 4b. ^1H NMR ($CDCl_3$) δ 2.04 (s; 3H; CH_3); 3.07 (dd; $1H_a$; J_{gem} = 14 Hz; J = 7.4 Hz; SCH_aH_b); 3.18 (dd; $1H_b$; J = 6 Hz; SCH_aH_b); 3.54 (m; 2H; CH_2N_3); 5.03 (m; 1H; CH); 7.26 (m; 2H; aromat.); 7.32–7.35 (m;

2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 20.82; 34.56; 51.94; 71.40; 129.28; 131.18; 132.91; 133.26; 170.11; IR (film; cm^{-1}): 2120; 1750; 1495; 1375; 1230; 1045; 810 $[\alpha]_D^{22} = -8.06$ (c 1.025; ee = 94%). Anal. Calcd for $C_{11}H_{12}N_3ClO_2S$: C, 46.24; H, 4.23; N, 14.71. Found: C, 46.31; H, 4.28; N, 14.66.

4.3.3. (*R*)-(−)-1-Azido-3-(4-methylophenylthio)propan-2-ol acetate 4c. ^{1}H NMR ($CDCl_3$) δ 2.03 (s; 3H; CH_3CO); 2.32 (s; 3H; CH_3); 3.04 (dd; 1H$_a$; J_{gem} = 14 Hz; J = 7.4 Hz; SCH_aH_b); 3.15 (dd; 1H$_b$; J = 5.8 Hz; SCH_aH_b); 3.53 (m; 2H; CH_2N_3); 5.03 (m; 1H; CH); 7.10–7.13 (m; 2H; aromat.); 7.30–7.32 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 20.84; 21.00; 35.98; 51.98; 71.65; 129.90; 130.68; 130.88; 137.11; 170.12; $[\alpha]_D^{22} = -5.7$ (c 1.10; ee = 96%). Anal. Calcd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.15; H, 5.55; N, 15.59.

4.3.4. (*S*)-(−)-1-Chloro-3-phenylthiopropan-2-ol acetate 5a. ^{1}H NMR ($CDCl_3$) δ 2.01 (s; 3H; CH_3); 3.20 (dd; 1H$_a$; J_{gem} = 14.4 Hz; J = 6.6 Hz; SCH_aH_b); 3.24 (dd; 1H$_b$; J = 6 Hz; SCH_aH_b); 3.77 (m; 2H; CH_2Cl); 5.12 (m; 1H; CH); 7.20–7.24 (m; 1H; aromat.); 7.28–7.33 (m; 2H; aromat.); 7.39–7.43 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 20.79; 34.61; 44.27; 71.60; 126.81; 129.13; 129.98; 134.76; 170.13; IR (film; cm^{-1}); $[\alpha]_D^{22} = -3.2$ (c 0.99; ee = 95%). Anal. Calcd for $C_{11}H_{13}ClO_2S$: C, 53.98, H, 5.35; Cl, 14.49; S, 13.10. Found: C, 54.16; H, 5.39; Cl, 14.38; S, 13.21.

4.3.5. (*S*)-(−)-1-Chloro-3-(4-chlorophenylthio)propan-2-ol acetate 5b. ^{1}H NMR ($CDCl_3$) δ 2.03 (s; 3H; CH_3); 3.17 (dd; 1H$_a$; J_{gem} = 14.2 Hz; J = 6.6 Hz; SCH_aH_b); 3.21 (dd; 1H$_b$; J = 6.2 Hz; SCH_aH_b); 3.75 (m; 2H; CH_2Cl); 5.10 (m; 1H; CH); 7.26–7.29 (m; 2H; aromat.); 7.33–7.36 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 20.77; 34.92; 44.17; 71.45; 129.27; 131.36; 133.32; 170.10; IR (film; cm^{-1}): 1745; 1480; 1425; 1370; 1230; 1095; 1030; 820; $[\alpha]_D^{22} = -8.5$ (c 1.08; ee = 83%). Anal. Calcd for $C_{11}H_{12}Cl_2O_2S$: C, 47.31; H, 4.33. Found: C, 47.18; H, 4.50.

4.3.6. (*S*)-(−)-1-Chloro-3-(4-methylphenylthio)propan-2-ol acetate 5c. ^{1}H NMR ($CDCl_3$) δ 2.02 (s; 3H; CH_3CO); 2.32 (s; 3H; CH_3); 3.14 (dd; 1H$_a$; J_{gem} = 14.4 Hz; J = 6.6 Hz; SCH_aH_b); 3.19 (dd; 1H$_b$; J = 6 Hz; SCH_aH_b); 3.76 (m; 2H; CH_2Cl); 5.10 (m; 1H; CH); 7.10–7.13 (m; 2H; aromat.); 7.30–7.33 (m; 2H; aromat.); ^{13}C NMR ($CDCl_3$) δ 20.79; 21.01; 35.41; 44.33; 71.66; 129.91; 130.84; 130.96; 137.11; 170.12; IR (film; cm^{-1}): 1740; 1490; 1370; 1225; 1030; 800; $[\alpha]_D^{22} = -11.1$ (c 1.08; ee = 92%). Anal. Calcd for $C_{12}H_{15}ClO_2S$: C, 55.70; H, 5.84. Found: C, 55.67; H, 6.01.

4.4. Assignment of absolute configuration

The enantiomers of (**+**)-**2a**, isolated from the reaction of the lipase-catalyzed transesterification of the racemates, were made to react[7] with optically pure (*R*)- and (*S*)-enantiomers of methoxyphenylacetic acid (MPA). Next, ^{1}H NMR spectra of the resulting esters were taken in a $CDCl_3$ solution and the differences in the chemical shifts ($\Delta\delta^{RS}$) observed in the esters prepared from the (*R*)- and (*S*)-acids, respectively, were calculated separately for the protons attached to one and the other carbon atom adjacent to the stereogenic center as shown by the following equations:

$$\Delta\delta^{RS}L_1 = \delta^R L_1 - \delta^S L_1 = 3.09 - 2.86 = +0.23 \text{ ppm}$$

$$\Delta\delta^{RS}L_2 = \delta^R L_2 - \delta^S L_2 = 3.42 - 3.50 = -0.08 \text{ ppm}$$

The negative value of $\Delta\delta^{RS}$, which corresponds to the signal of protons of the substituent L_2 (CH_2N_3), and the plus sign resulting for the L_1 (CH_2SPh) protons determine the (*S*)-configuration according to the drawing (Scheme 3). In the case of 1-chloro-3-phenylthiopropan-2-ol (±)-**3a** the values of $\Delta\delta^{RS}$ are similar, the minus sign corresponds to the signal of protons of the substituent L_2 (CH_2Cl) and the plus sign to the substituent L_1 (CH_2SPh). Following the equations, they suggest an (*R*)-configuration. The opposite configurations of (***S***)-(+)-**2a** and (***R***)-(**+**)-**3a** results from the substituents ranking in Cahn-Ingold-Prelog system.

$$\Delta\delta^{RS}L_1 = \delta^R L_1 - \delta^S L_1 = 3.14 - 2.96 = +0.18 \text{ ppm}$$

$$\Delta\delta^{RS}L_2 = \delta^R L_2 - \delta^S L_2 = 3.58 - 3.73 = -0.15 \text{ ppm}$$

The same procedure was applied to the enantiomers of the alcohols isolated after hydrolysis of the acetates (−)-**4a-c** and (−)-**5a**–**c**. As compared with (***S***)-(+)-**2a**–**c** and (***R***)-(+)-**3a**–**c**, the respective $\Delta\delta^{RS}$ values are of opposite signs thus indicating the (*R*)- and (*S*)-configuration.

$$\Delta\delta^{RS}L_1 = \delta^R L_1 - \delta^S L_1 = 2.90 - 3.09 = -0.19 \text{ ppm}$$

$$\Delta\delta^{RS}L_2 = \delta^R L_2 - \delta^S L_2 = 3.52 - 3.42 = +0.10 \text{ ppm}$$

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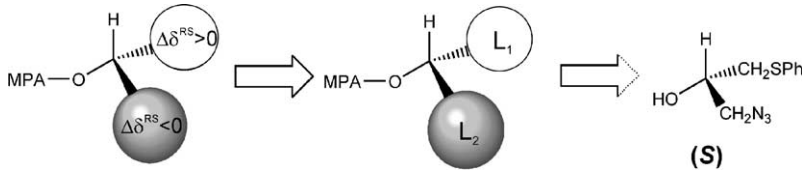

Scheme 3. Description of substituents for determination of the absolute configuration of (+)-**2a**.

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