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# 1-Alkylthio-3-aryloxypropan-2-ols: synthesis and enantiomer separation by lipase-catalyzed transesterification

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**Abstract**—The optically active (*R*)- and (*S*)-1-alkylthio-3-aryloxypropan-2-ols were prepared in the reaction of the appropriate arylglycidyl ethers and alkyl thiols followed by lipase-catalyzed transesterification. The effect of aryl and alkyl substituents, the enzyme preparation as well as the reaction conditions have been compared in terms of enantiomeric excess of the obtained acetate and the unreacted alcohol.


## 1. Introduction

The oxirane ring opening with various nucleophiles (e.g. halogen ions, $CN^-$, $N_3^-$, $OH^-$, etc.) is an important synthetic transformation which provides an easy access to a large number of functionalized intermediates in the synthesis of natural and synthetic products. Continuing our interest in the lipase-catalyzed resolutions of the racemic mixtures of 1,3-disubstituted secondary propanols[1] we recently focused our attention on 1-alkylthio-3-aryloxypropan-2-ols **1** which can be easily prepared from arylglycidyl ethers and aliphatic thiols. Their optically active forms are expected to be convenient substrates for the preparation of chiral sulfoxides, which further may be used for the synthesis of chiral catalysts and chiral pharmaceuticals.

The known methods of the synthesis of **1** depend mostly on two reactions: alkylation of the appropriate thiols with 1-chloro-3-aryloxypropan-2-ols;[2] and epoxide ring opening of alkylsulfanylmethyloxiranes with the appropriate aryloxy anion.[3] In either case, the yields do not exceed 70%. There are also reports on epoxide ring opening with thiolate anions as the nucleophiles, they concern, however, mostly aryl thiolates;[4] the reactions of aliphatic thiols with epoxides have been investigated rarely.[5] In our search for a simple method for the synthesis of **1**, the reaction of arylglycidyl ethers with appropriate alkyl thiolates in a two-phase catalytic system (PTC conditions) was considered to be most effective.

## 2. Results and discussion

### 2.1. Synthesis of 1-alkylthio-3-aryloxypropan-2-ols (±)-1a–h

The starting aryl glycidyl ethers were prepared in high yields by the Williamson reaction from the corresponding phenols and epichlorhydrin in a 10% sodium hydroxide solution. The yields of the reaction depended on the substituent in the phenyl ring and varied from 75 to 90%. The epoxide ring opening reaction with thiolate anion as the nucleophile is well known and various bases were used for the generation of the anion. Also aryl glycidyl ethers were used as the substrates to yield the appropriate **1**, the yields were, however, moderate.[4c,e,5a,c] In our procedure, the reaction conditions have been adjusted to meet the two-phase (aqueous KOH/diethyl ether) system conditions with *tetra-n*-butylammonium bromide as the phase transfer catalyst. The yields of **1** were nearly quantitative, much higher than those reported earlier[5] (Scheme 1).

### 2.2. Kinetic resolution of (±)-1a–h by lipase-catalyzed transesterification

The conditions for the lipase-catalyzed acetylation of racemic alkylthio alcohols (±)-**1** were optimised according to the conventional method described earlier[6] (Scheme 2). The effects of lipase, solvent, acyl donor, temperature, and substituent in the aromatic ring on the enantioselectivity of enzymatic acetylation were

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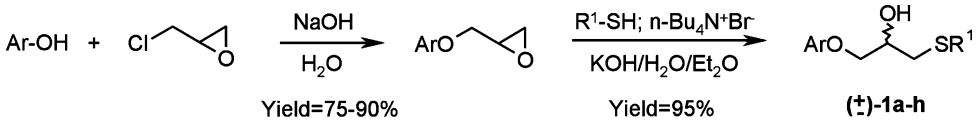
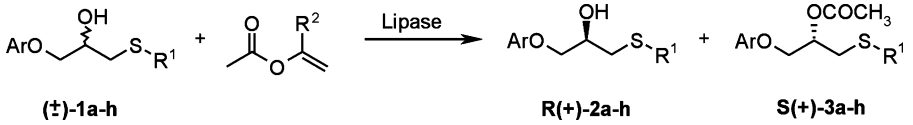



**Scheme 1.**




**Scheme 2.**

evaluated by determination of the reaction enantioselectivity ($E$).

The catalytic efficacy of different commercially available lipases in the acylation reaction was investigated. For this purpose, (±)-**1a**, used as a model substrate, was allowed to react at 20°C in *tert*-butyl methyl ether with two equivalents of vinyl acetate in the presence of different lipases. In control experiments, the reaction did not proceed in the absence of an enzyme. Generally, the transesterifications were monitored by thin layer chromatography and the reactions were arrested when the conversion reached 30–50%. The enzyme was then removed by filtration and the resulting solution of enantiomerically enriched acetate **3a** and unchanged alcohol **2a** was used for an exact determination of the conversion degree and enantiomeric excesses. The investigations were done by HPLC analyses with a chiral column. The results are summarized in Table 1.

The absolute configurations of the products, i.e. the alcohol **2a** and the acetate **3a**, were determined by the modified Mosher's method as described by Riguera et al.[7a] The method depends on comparing the differences of $^1$H NMR chemical shifts recorded for the diastereomeric esters prepared from a separated enantiomer of the alcohol and (*R*)- and (*S*)-enantiomers of methoxyphenylacetic acid. The utility of the method has been confirmed by several authors.[7b–i] According to our investigation, the unchanged alcohol **2a** and its acetate **3a** have the (*R*)-(+) and (*S*)-(+) configurations, respectively. This assignment is in good agreement with the Kazlauskas rule.[8] The results presented in Table 1 show that with the tested lipases the (*R*)-(+) alcohol **2a** reacts slower than the (*S*)-(−)-enantiomer and that the reactions show poor-to-moderate enantio-selectivities ($E=1$–27). It is also evident how the results depend on the kind of used enzyme preparation. Novozym SP-435, Chirazyme L-2 c-f lyo, and Chirazyme L-2 c-f c-2 are the same lipases produced by *Candida antarctica*, but their catalytic properties are substantially different. The same relates to Amano PS and Chirazyme L-1 c-f lyo lipase preparations. Among the tested lipase preparations only Amano AK (*Pseudomonas fluorescens*) and Chirazyme L-1 c-f lyo (*Pseudomonas cepacia*) exhibited promising catalytic activities and enantioselectivities with this substrate.

A substantial difference in the reaction rates of the two enantiomers was obtained only with the Amano AK lipase catalyst (a marked decrease of the reaction rate was observed after a 50% conversion).

A proper choice of the solvent used in enzymatic reactions is known to be a very important factor.[9] It is well-documented that, generally speaking, lipases show a higher activity in hydrophobic solvents of low polarity,[6] but they do work in polar solvents and there are examples of kinetic resolutions in dioxane,[10a,b] THF,[10a,b] chloroform,[10c] acetone,[10d] *tert*-butanol,[10d] pyridine,[10e] and ionic liquid.[10f] Therefore, we have investigated the *trans*-esterification of (±)-**1a** with vinyl acetate catalyzed by Amano AK in various solvents at room temperature. The reaction conditions were the same as given in the footnote to Table 1. The results are presented in Table 2.

**Table 1.** Kinetic resolution of (±)-**1a** by lipase-catalyzed acetylation[a] with vinyl acetate in *tert*-butyl methyl ether

| Lipase | Time (h) | Conv. (%)[b] | $Ee_{substr}$ (%)[c] | $Ee_{prod.}$ (%)[c] | $E$[b] |
|---|---|---|---|---|---|
| Amano AK (*Psaeudomonas fluorescens*) | 48 | 45 | 69 | 86 | 27 |
| Amano PS (*Pseudomonas cepacia*) | 193 | 36 | 44 | 78 | 12 |
| Novozym SP 435 (*Candida antarctica*-B) | 33 | 27 | 4 | 10 | 1 |
| Chirazyme L-2; c-f; lyo (*Candida antarctica*-B) | 75 | 31 | 4 | 9 | 1 |
| Chirazyme L-1; c-f; lyo (*Pseudomonas cepacia*) | 48 | 40 | 57 | 87 | 26 |
| Chirazyme L-2; c-f; c-2; lyo (*Candida antarctica*-B) | 48 | 44 | 4 | 5 | 1 |

[a] Conditions: 1 mmol of (±)-**1a**, 2 mmol of vinyl acetate, 120 mg of lipase and 12 mL of *tert*-butyl methyl ether at 20°C.
[b] Conversion and $E$ values were calculated from the enantiomeric excess of substrate **2a** ($ee_s$) and product **3a** ($ee_p$) using the usual formula: $E=\mathrm{Ln}[(1-ee_s)(ee_p/(ee_s+ee_p))]/\mathrm{Ln}[(1+ee_s)(ee_p/(ee_s+ee_p))]$, $\mathrm{Conv.}=ee_s/(ee_s+ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.

**Table 2.** Transesterification of (±)-**1a** with vinyl acetate catalyzed by Amano AK lipase[a] in various solvents

| Entry | Solvent | Log *P* | Time (h) | *C* (%)[b] | $Ee_s$ (%)[c] | $Ee_p$ (%)[c] | *E*[b] |
|---|---|---|---|---|---|---|---|
| 1 | TBME | 1.3 | 48 | 45 | 69 | 86 | 27 |
| 2 | *i*-$Pr_2O$ | 1.1 | 44 | 41 | 59 | 83 | 19 |
| 3 | Hexane | 3.5 | 44 | 45 | 67 | 82 | 20 |
| 4 | Benzene | 2.0 | 92 | 35 | 48 | 89 | 28 |
| 5 | Toluene | 2.5 | 92 | 34 | 46 | 90 | 29 |
| 6 | THF | 0.49 | 166 | 22 | 25 | 89 | 25 |

[a] Conditions: 1 mmol of (±)-**1a**, 2 mmol of vinyl acetate, 120 mg of lipase and 12 mL of *tert*-butyl methyl ether at 20°C.
[b] Conversion and *E* values were calculated from the enantiomeric excess of substrate **2a** ($ee_s$) and product **3a** ($ee_p$) using the usual formula: $E = \mathrm{Ln}[(1-ee_s)(ee_p/(ee_s+ee_p))]/\mathrm{Ln}[(1+ee_s)(ee_p/(ee_s+ee_p))]$, $\mathrm{Conv.} = ee_s/(ee_s+ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.

The enantioselectivities *E* of the reactions were highest with low polar aromatic hydrocarbons (Table 2, items 4 and 5). However, the reaction carried out in *tert*-butyl methyl ether (item 1) was twice as fast with only a slightly diminished *E* value. Another interesting observation is the lack of correlation between the solvent polarity and the reaction rate.

The next parameter tested during this investigation was the influence of the structure (especially the nature and position of the substituents in the aromatic ring) of 1-alkylthio-3-aryloxypropan-2-ols (±)-**1a**–**h** on the rate and enantioselectivity of the transesterification reaction. For this purpose several alcohols were acetylated with vinyl acetate in the presence of Amano AK lipase in a TBME solution. The results are presented in Table 3.

The data presented below indicate that only the *m*-

**Table 3.** Transesterification of (±)-**1a**–**h** with vinyl acetate catalyzed by Amano AK lipase[a]

| Entry | Substrate | Ar | $R^1$ | Time (h) | *C* (%)[b] | $Ee_s$ (%)[c] | $Ee_p$ (%)[c] | *E*[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $C_6H_5$- | *n*-Bu | 48 | 45 | 69 | 86 | 27 |
| 2 | **1b** | 4-$CH_3$-$C_6H_4$- | *n*-Bu | 48 | 62 | 85 | 53 | 8 |
| 3 | **1c** | 3-$CH_3$-$C_6H_4$- | *n*-Bu | 48 | 49 | 83 | 86 | 34 |
| 4 | **1d** | 2-$CH_3$-$C_6H_4$- | *n*-Bu | 90 | 27 | 31 | 83 | 15 |
| 5 | **1e** | 4-Cl-$C_6H_4$- | *n*-Bu | 27 | 34 | 38 | 74 | 10 |
| 6 | **1f** | $C_6H_5$- | Et | 47 | 21 | 19 | 72 | 7 |
| 7 | **1g** | 4-$CH_3$-$C_6H_4$- | Et | 48 | 57 | 32 | 24 | 2 |
| 8 | **1h** | $C_6H_5$- | *tert*-Bu | 240 | 35 | 24 | 69 | 7 |

[a] Conditions: 1 mmol of (±)-**1a**, 2 mmol of vinyl acetate, 120 mg of lipase and 12 mL of *tert*-butyl methyl ether at 20°C.
[b] Conversion and *E* values were calculated from the enantiomeric excess of substrate **2a** ($ee_s$) and product **3a** ($ee_p$) using the usual formula: $E = \mathrm{Ln}[(1-ee_s)(ee_p/(ee_s+ee_p))]/\mathrm{Ln}[(1+ee_s)(ee_p/(ee_s+ee_p))]$, $\mathrm{Conv.} = ee_s/(ee_s+ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.

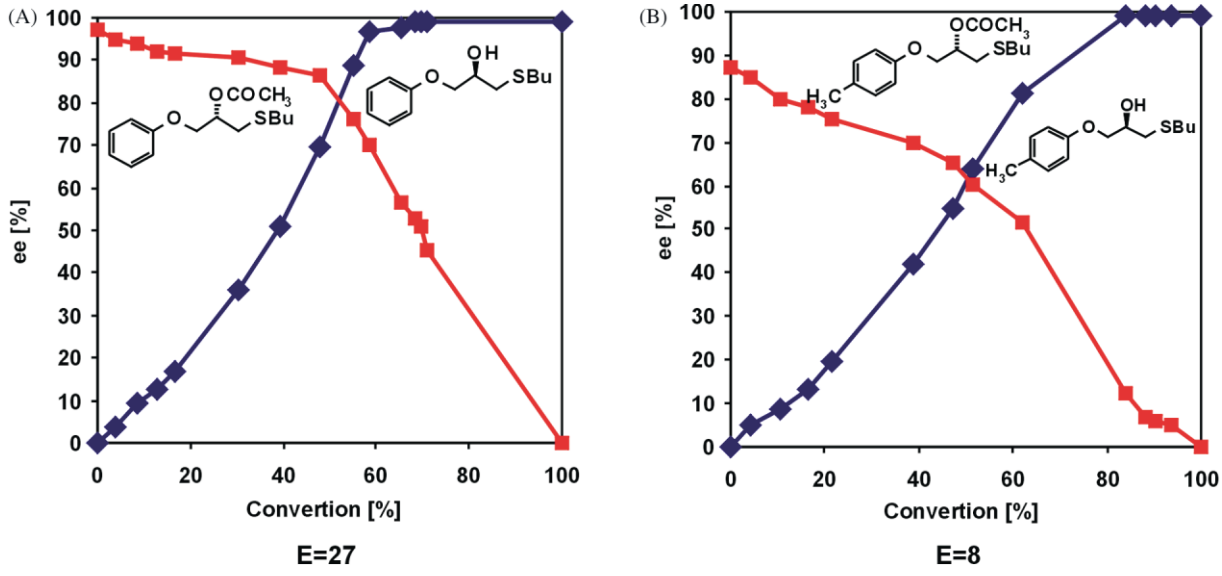



**Figure 1.** Dependence of enantiomeric purities ee [%] of (*R*)-(+)-**2a** and (*S*)-(+)-**3a** (Fig. 1A) and (*R*)-(+)-**2b** and (*S*)-(+)-**3b** (Fig. 1B) on the convertion of (±)-**1a** and (±)-**1b** in Amano AK lipase-catalyzed acetylation with vinyl acetate in TBME at 20°C.

**Table 4.** Transesterification of (±)-**1a**–**c**,**f** with *iso*-propenyl acetate in TBME solution at room temperature[a]

| Entry | Substrate | Lipase | Time (h) | $C$ (%)[b] | $Ee_s$ (%)[c] | $Ee_p$ (%)[c] | $E$[b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Amano AK | 96 | 35 | 49 | 91 | 34 |
| 2 | **1b** | Amano AK | 96 | 30 | 34 | 81 | 13 |
| 3 | **1c** | Amano AK | 96 | 41 | 64 | 91 | 41 |
| 4 | **1f** | Amano AK | 208 | 36 | 38 | 67 | 7 |
| 5 | **1a** | Amano PS | 287 | 23 | 25 | 86 | 17 |

[a] Conditions: 1 mmol of (±)-**1a**, 2 mmol of vinyl acetate, 120 mg of lipase and 12 mL of *tert*-butyl methyl ether at 20°C.
[b] Conversion and $E$ values were calculated from the enantiomeric excess of substrate **2a** ($ee_s$) and product **3a** ($ee_p$) using the usual formula: $E = \mathrm{Ln}[(1-ee_s)(ee_p/(ee_s+ee_p))]/\mathrm{Ln}[(1+ee_s)(ee_p/(ee_s+ee_p))]$, $\mathrm{Conv.} = ee_s/(ee_s+ee_p)$.
[c] Determined by HPLC analysis using Chiralcel OD-H column.

methyl substituent improved the enantioselectivity of the reaction (items 1 and 3). In comparison with the *n*-butyl substituent, both the smaller ethyl group and the bulkier *tert*-butyl one diminished the enantioselectivity of the reaction $E$ (item 1 versus 6 and 8).

The dependence of the enantiomeric excesses of the substrate (alcohol) and the product (acetate) on the conversion of (±)-1-butylthio-3-phenoxypropan-2-ol and (±)-1-butylthio-3-(4-methylphenoxy)-propan-2-ol is presented in Figure 1(A) and (B), respectively, together with the calculated enantioselectivities $E$ of the reactions. The plots (Fig. 1(A) and (B)) substantiate the data presented earlier indicating that the enantioselectivity of the Amano AK lipase catalyzed acetylation of *p*-methyl substituted **1** is much lower than that of the parent compound.

The effect of the acyl donor structure on the enantioselectivity of the lipase-catalyzed transesterification reaction has been well documented by Ema et al.[11] In general, among the various types of acyl donors they examined, enol esters, because of high reactivity and irreversibility of the reaction, have been considered as most suitable for the kinetic resolution by *trans*-esterification. As it is known, *iso*-propenyl acetate is also frequently used as an acyl donor in the enzyme-catalyzed acetylation reactions. Usually, the reaction with *iso*-propenyl acetate is slower than that with vinyl acetate but enantioselectivities are sometimes higher. Thus, in order to enhance the enantioselectivity of lipase-catalyzed acetylation of few (±)-**1**, propenyl acetate was examined as the acyl donor. The obtained results are presented in Table 4. The rates of all investigated reactions were much lower when *iso*-propenyl acetate was used instead of vinyl acetate. However, a considerable improvement of the reaction enantioselectivity for three of the investigated compounds (**1a**, **1b** and **1c**) was achieved. The obtained optical purities of the acetates **3a** and **3c** (>90%) suggest that the described method may be used for practical purposes.

## 3. Conclusion

In summary, we have presented a general method for enantioselective acetylation of 1-alkylthio-3-aryloxypropan-2-ols with various aromatic substituents. Highest enantioselectivities ($E = 34$–$41$) were obtained for two of the investigated alcohols with the use of Amano AK lipase and *iso*-propenyl acetate in *tetra*-butyl methyl ether solution at 20°C. In general, the obtained enantio-selectivities in the realized acetylation reactions of 1-alkylthio-3-aryloxypropan-2-ols were a little lower than for 1-azido- and 1-nitrato-3-aryloxypropan-2-ols investigated earlier.[1] This may be explained by larger volume and lower polarity of the substituent (thioalkyl versus azido or nitrato group).

## 4. Experimental

### 4.1. General

$^1$H (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on Varian Mercury 400 MHz spectrometer in $CDCl_3$ solution, and chemical shifts ($\delta$) are reported in ppm. IR spectra were taken on a Carl Zeiss Specord M80 instrument. Optical purities of alcohols (*R*)-(+)-**2a**–**h** and esters (*S*)-(+)-**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 *n*-hexane:*iso*-propanol, 99:1; 0.4 mL/min for esters) using racemic compounds as references. Optical rotation was measured in $CHCl_3$ with PolAAr 32 polarimeter. Elemental analyses were performed on CHNS/O Perkin Elmer type 2400 instrument. The reactions were monitored by TLC on silica gel 60 $F_{254}$ plates and by column chromatography on silica gel 60 (230–400 mesh). The arylglycidyl ethers were prepared by the Williamson reaction from the appropriate phenols and epichlorohydrin in an aqueous NaOH solution. Lipases Amano AK, and Amano PS 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 alcohols (±)-1a–h

The thiol (50 mmol) was dissolved in a warm solution of KOH (20 g) in water (35 mL) and then the appropriate aryl glycidyl ether (33 mmol) in diethyl ether (50 mL) and *tert*-butylammonium bromide (TBAB; 1 g) were added. The mixture was stirred vigorously under reflux for 2 h. Then the layers were separated and the aqueous layer was extracted with 20 mL of TBME. The organic layers were connected and washed with 20 mL

of water, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude mixture was purified by chromatography on a short silica gel column with hexane:ethyl acetate (10:1 v/v) as the eluent. $^1H$ and $^{13}C$ NMR spectra, IR data, and elemental analyses of the prepared alcohols (±)-**1a**–**h** are reported below:

**4.2.1. (±)-1-Butylthio-3-phenoxypropan-2-ol 1a**. Yield 93%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.91 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.6$ Hz); 1.40 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.57 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.57 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.72 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.6$ Hz; $J_{ac}=7.2$ Hz); 2.85 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=5.2$ Hz); 4.05 (m; 2H ($OCH_2CH_c$)); 4.11 (m; 1H ($CH_c$)); 6.90–7.30 (m; 5H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 21.8; 31.7; 32.2; 35.8; 68.6; 70.3; 114.5; 121.1; 129.4; 158.4; IR (film, $cm^{-1}$) 3420; 2920; 1590; 1470; 1235; 1030; 740; 680. Anal. calcd for $C_{13}H_{20}SO_2$: C, 64.96%; H, 8.39%. Found: C, 64.94%; H, 8.28%.

**4.2.2. (±)-1-Butylthio-3-(4-methylphenoxy)propan-2-ol 1b**. Yield 95%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.92 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 1.41 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.59 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.29 (s; 3H ($CH_3$)); 2.57 (t; 2H ($CH_3CH_2CH_2CH_2$) $J=7.6$ Hz); 2.72 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.7$ Hz; $J_{ac}=7$ Hz); 2.78 (s; 1H ($OH$)); 2.85 (dd; 1H ($CH_cCH_aH_bS$); $J_{ac}=5.2$ Hz); 4.02 (m; 2H ($OCH_2CH$)); 4.07 (m; 1H ($CH_c$)); 6.80–7.10 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 20.4; 21.9; 31.7; 32.2; 35.8; 68.6; 70.5; 114.4; 129.9; 130.4; 156.3. IR (film; $cm^{-1}$) 3440; 2920; 1610; 1500; 1235; 1030; 810. Anal. calcd for $C_{14}H_{22}SO_2$: C, 66.10%; H, 8.72%. Found: C; 66.20%; H, 8.54%.

**4.2.3. (±)-1-Butylthio-3-(3-methylphenoxy)propan-2-ol 1c**. Yield 96%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.92 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 1.41 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.59 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.33 (s; 3H ($CH_3$)); 2.57 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.72 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.6$ Hz; $J_{ac}=7.2$ Hz); 2.85 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=5.2$ Hz); 4.03 (m; 2H ($OCH_2CH_c$)); 4.10 (m; 1H ($CH_c$)); 6.70–7.20 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 21.4; 21.9; 31.7; 32.2; 35.8; 68.6; 70.2; 111.4; 115.3; 121.9; 129.2; 139.5; 158.4. IR (film; $cm^{-1}$) 3410; 2920; 1580; 1485; 1450; 1255; 1150; 1035; 770; 685. Anal. calcd for $C_{14}H_{22}SO_2$: C, 66.10%; H, 8.72%. Found: C, 66.18%; H, 8.60%.

**4.2.4. (±)-1-Butylthio-3-(2-methylphenoxy)propan-2-ol 1d**. Yield 93%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.92 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.6$ Hz); 1.42 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.60 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.24 (s; 3H ($CH_3$)); 2.58 (t, 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.75 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.8$ Hz; $J_{ac}=7$ Hz); 2.84 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=5$ Hz); 4.05 (m; 2H ($OCH_2CH_c$)); 4.15 (m; 1H ($CH_c$); 6.80–7.20 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 16.2; 21.9; 31.7; 32.2; 35.9; 68.7; 70.2; 111.1; 120.8; 126.6; 126.8; 130.7; 156.4. IR (film; $cm^{-1}$) 3420; 2940; 1600; 1490; 1460; 1240; 1115; 1025; 745. Anal. calcd for $C_{14}H_{22}SO_2$: C, 66.10; H, 8.72. Found: C, 66.19; H, 8.60.

**4.2.5. (±)-1-Butylthio-3-(4-chlorophenoxy)propan-2-ol 1e**. Yield 95%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.91 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 1.40 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.58 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.56 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.70 (dd; 1H ($CH_cCH_bH_a$); $J_{ab}=14$Hz; $J_{ac}=7.4$Hz); 2.80 (s; 1H ($OH$)); 2.84 (dd; 1H ($CH_cCH_bH_a$); $J_{bc}=5.2$ Hz); 4.01 (m; 2H ($OCH_2CH_c$)); 4.10 (m; 1H ($CH_c$)); 6.80–7.25 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 21.9; 31.7; 32.2; 35.8; 68.4; 70.7; 115.8; 126.0; 129.3; 157.0. IR (film; $cm^{-1}$) 3430; 2950; 1590; 1490; 1240; 1085; 1030; 820. Anal. calcd for $C_{13}H_{19}ClSO_2$: C, 56.82; H, 6.70. Found: C, 56.89; H, 6.90.

**4.2.6. (±)-1-Ethylthio-3-phenoxypropan-2-ol 1f**. Yield 99%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 1.28 (t; 3H ($CH_3CH_2$); $J=7.2$ Hz); 2.59 (q; 2H ($CH_3CH_2$)); 2.74 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.6$ Hz; $J_{ac}=7.2$ Hz); 2.87 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=5$ Hz); 4.04 (m; 2H ($OCH_2CH_c$)); 4.10 (m; 1H ($CH_c$)); 6.90–7.30 (m; 5H (aromatic H); $^{13}C$ NMR ($CDCl_3$); $\delta$ 14.8; 26.4; 35.4; 68.6; 70.3; 114.5; 121.2; 129.5; 158.4. IR (film; $cm^{-1}$) 3440; 2930; 1600; 1495; 1240; 1040; 750; 640. Anal. calcd for $C_{11}H_{16}SO_2$: C, 62.23; H, 7.60. Found: C, 62.30; H, 7.50.

**4.2.7. (±)-1-Ethylthio-3-(4-methylphenoxy)propan-2-ol 1g**. Yield 91%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 1.28 (t; 3H ($CH_3CH_2$); $J=7.2$ Hz); 2.29 (s; 3H ($CH_3$)); 2.60 (q; 2H ($CH_3CH_2$)); 2.73 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.8$ Hz; $J_{ac}=7$ Hz); 2.86 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=5.4$ Hz); 4.02 (m; 2H ($OCH_2CH_c$)); 4.08 (m; 1H ($CH_c$)); 6.80–7.10 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 14.8; 20.4; 26.4; 35.4; 68.6; 70.5; 114.4; 129.9; 130.4; 156.3. IR (film; $cm^{-1}$) 3450; 2930; 1610; 1510; 1240; 1040; 815. Anal. calcd for $C_{12}H_{18}SO_2$: C, 63.74%; H, 8.02%. Found: C, 63.74%; H, 7.94%.

**4.2.8. (±)-1-*tert*-Butylthio-3-phenoxypropan-2-ol 1h**. Yield 92%. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 1.35 (s, 9H ($3\times CH_3$)); 2.78 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=18.8$ Hz; $J_{ac}=6.6$ Hz); 2.78 (s; 1H (OH)); 2.88 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=6$ Hz); 4.0 (dd; 1H ($OCH_dH_eCH_c$); $J_{de}=9.2$ Hz; $J_{dc}=6.2$ Hz); 4.05 (dd; 1H ($OCH_dHeCH_c$); $J_{ec}=4.2$ Hz); 4.11 (m; 1H ($CH_c$)); 6.90–7.30 (m; 5H (aromatic H)) $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 30.9; 32.2; 42.5; 69.2; 70.5; 114.5; 121.1; 129.4; 158.4. IR (film; $cm^{-1}$) 3420; 2940; 1600; 1490; 1450; 1240; 1035; 750; 690. Anal. calcd for $C_{13}H_{20}SO_2$: C, 64.50%; H, 8.39%. Found: C, 64.86%; H, 8.31%.

### 4.3. Typical transesterification procedure for (±)-1a–h by using Amano AK lipase in TBME solution at 20°C

Alcohol (±)-**1a**–**h** (1 mmol) was dissolved in 12 mL of TBME (*tert*-butyl methyl ether) and vinyl acetate (2 mmol) and 125 mg of Amano AK lipase were added. The mixture was stirred at 20°C and the conversion was monitored by TLC. After the appropriate time, the reaction was stopped by filtering off the enzyme and the solvent was evaporated under reduced pressure. The

crude mixture of acetate (*S*)-(+)-**3a**–**h** and unchanged alcohol (*R*)-(+)-**2a**–**h** was separated by column chromatography on silica gel with a hexane:ethyl acetate (5:1) mixture as the eluent. Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column, but in the case of (*S*)-(+)-**3c** and (*S*)-(+)-**3d** it was necessary to hydrolyze the acetates to the corresponding alcohols. NMR spectra of enantiomerically enriched alcohols (*R*)-(+)-**2a**–**h** were identical with those of (±)-**1a**–**h**. The optical rotations measured in $CHCl_3$ solutions for prepared enantiomerically enriched alcohols are as follows:

(*R*)-(+)-**2a**: $[\alpha]_D^{22}=+4.5$ (*c* 1.76; ee = 99%)
(*R*)-(+)-**2b**: $[\alpha]_D^{22}=+4.9$ (*c* 1; ee = 85%)
(*R*)-(+)-**2c**: $[\alpha]_D^{22}=+5.8$ (*c* 1.98; ee = 86%)
(*R*)-(+)-**2d**: $[\alpha]_D^{22}=+1.6$ (*c* 0.54; ee = 43%)
(*R*)-(+)-**2e**: $[\alpha]_D^{22}=+3.6$ (*c* 2.95; ee = 38%)
(*R*)-(+)-**2f**: $[\alpha]_D^{22}=+2.9$ (*c* 2.09; ee = 47%)
(*R*)-(+)-**2g**: $[\alpha]_D^{22}=+1.6$ (*c* 1.82; ee = 22%)
(*R*)-(+)-**2h**: $[\alpha]_D^{22}=+1.6$ (*c* 1.90; ee = 24%)

$^1H$ and $^{13}C$ NMR spectra, IR data, elemental analyses and optical rotations of obtained acetates (*S*)-(+)-**3a**–**h** are reported below.

**4.3.1. (*S*)-(+)-1-Butylthio-3-phenoxypropan-2-ol acetate 3a**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.90 (t; 3H ($CH_3CH_2$-$CH_2CH_2$); $J=7.4$ Hz); 1.38 (m; 2H ($CH_3CH_2CH_2$-$CH_2$)); 1.57 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.09 (s; 3H ($CH_3CO$)); 2.57 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.80 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14$ Hz; $J_{ac}=6$ Hz); 2.89 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=7$ Hz); 4.18 (d, 2H ($OCH_2CH_c$); $J=4.8$ Hz); 5.25 (m; 1H ($CH_c$)); 6.90–7.30 (m; 5H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 21.1; 21.9; 31.6; 32.0; 32.4; 67.2; 71.5; 114.6; 121.2; 129.5; 158.4; 170.5. IR (film; $cm^{-1}$): 2920; 1730; 1585; 1480; 1355; 1215; 1020; 735; 675; $[\alpha]_D^{22}=+6.4$ ($CHCl_3$, *c* 1.72; ee = 91%). Anal. calcd for $C_{15}H_{22}SO_3$: C, 63.80%; H, 7.85%. Found: C, 63.80%; H, 7.73%.

**4.3.2. (*S*)-(+)-1-Butylthio-3-(4-methylphenoxy)propan-2-ol acetate 3b**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.80 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 1.28 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.46 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.97 (s; 3H ($CH_3CO$)); 2.18 (s; 3H ($CH_3$)); 2.46 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.69 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14$ Hz; $J_{ac}=6$ Hz); 2.78 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=7$ Hz); 4.04 (d; 2H ($OCH_2CH_c$); $J=4.8$ Hz); 5.13 (m; 1H ($CH_c$)); 6.65–7.00 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 20.4; 21.1; 21.8; 31.6; 32.0; 32.4; 67.4; 71.5; 114.4; 129.9; 130.4; 156.3; 170.5. IR (film; $cm^{-1}$): 2940; 1735; 1505; 1365; 1220; 1040; 810; $[\alpha]_D^{22}=+5.0$ ($CHCl_3$, *c* 1.79; ee = 67%). Anal. calcd for $C_{16}H_{24}SO_3$: C, 64.83%; H, 8.16%. Found: C, 64.95%, H, 8.07%.

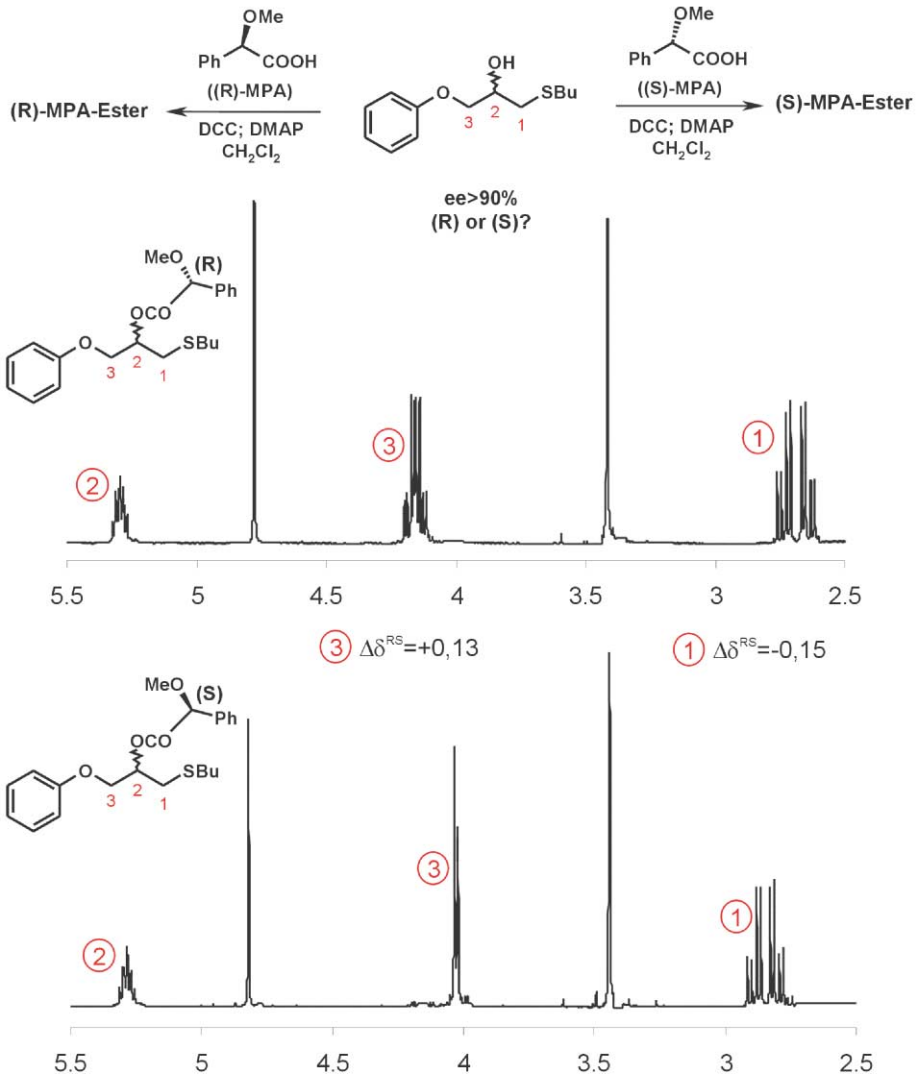
**4.3.3. (*S*)-(+)-1-Butylthio-3-(3-methylphenoxy)propan-2-ol acetate 3c**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.91 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.6$ Hz); 1.40 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.58 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.10 (s; 3H ($CH_3CO$)); 2.33 (s; 3H ($CH_3$)); 2.58 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 2.81 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14$ Hz; $J_{ac}=6$ Hz); 2.90 (dd, 1H ($CH_cCH_aH_bS$); $J_{bc}=7.2$ Hz) 4.17 (d; 2H ($OCH_2CH_c$); $J=4.8$ Hz); 5.25 (m; 1H ($CH_c$)); 6.70–7.20 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 21.1; 21.5; 21.9; 31.6; 32.0; 32.4; 67.1; 71.5; 111.4; 115.4; 121.9; 129.2; 139.5; 158.4; 170.5. IR (film; $cm^{-1}$): 2940; 1740; 1570; 1485; 1225; 1035; 815; 680; $[\alpha]_D^{22}=+6.1$ ($CHCl_3$, *c* 1.81; ee = 83%). Anal. calcd for $C_{16}H_{24}SO_3$: C, 64.83%; H, 8.16%. Found: C, 64.96%; H, 8.02%.

**4.3.4. (*S*)-(+)-1-Butylthio-3-(2-methylphenoxy)propan-2-ol acetate 3d**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.92 (t; 3H ($CH_3CH_2CH_2CH_2$); $J=7.6$ Hz); 1.42 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.59 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.10 (s; 3H ($CH_3CO$)); 2.23 (s; 3H ($CH_3$)); 2.59 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.6$ Hz); 2.83 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14$ Hz; $J_{ac}=6.4$ Hz); 2.94 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=6.8$ Hz); 4.18 (m; 2H ($OCH_2CH_c$)); 5.31 (m; 1H ($CH_c$)); 6.80–7.20 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 16.1; 21.0; 21.8; 31.6; 32.2; 32.4; 67.3; 71.4; 111.0; 120.8; 126.7; 126.8; 130.7; 156.4; 170.4. IR (film; $cm^{-1}$) 2940; 1740; 1490; 1365;1220; 1035; 745; $[\alpha]_D^{22}=+13.9$ ($CHCl_3$, *c* 0.54; ee = 82%). Anal. calcd for $C_{16}H_{24}SO_3$: C, 64.83; H, 8.16. Found: C, 64.95; H, 8.05.

**4.3.5. (*S*)-(+)-1-Butylthio-3-(4-chlorophenoxy)propan-2-ol acetate 3e**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 0.90 (t, 3H ($CH_3CH_2CH_2CH_2$); $J=7.2$ Hz); 1.38 (m; 2H ($CH_3CH_2CH_2CH_2$)); 1.56 (m; 2H ($CH_3CH_2CH_2CH_2$)); 2.09 (s; 3H (CH3CO)); 2.56 (t; 2H ($CH_3CH_2CH_2CH_2$); $J=7.4$ Hz); 2.79 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14$ Hz; $J_{ac}=5.6$ Hz); 2.87 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=7.4$ Hz); 4.15 (d; 2H ($OCH_2CH_c$); $=4.4$ Hz); 5.23 (m; 1H ($CH_c$)); 6.80–7.25 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 13.6; 21.0; 21.8; 31.6; 32.0; 32.4; 67.6; 71.3; 115.9; 126.1; 129.3; 157.0. IR (film; $cm^{-1}$) 2920; 1740; 1485; 1515; 1220; 1035; 820; $[\alpha]_D^{22}=+4.6$ ($CHCl_3$, *c* 1.83; ee = 73%). Anal. calcd for $C_{15}H_{21}ClSO_3$: C, 56.86%; H, 6.68%. Found: C, 56.80%; H, 6.50%.

**4.3.6. (*S*)-(+)-1-Ethylthio-3-phenoxypropan-2-ol acetate 3f**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 1.27 (t; 3H ($CH_3CH_2$); $J=7.2$ Hz); 2.10 (s; 3H ($CH_3CO$)); 2.61 (q, 2H ($CH_3CH_2$)); 2.83 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14.4$ Hz; $J_{ac}=5.6$ Hz); 2.92 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=7.2$ Hz); 4.18 (d; 2H ($OCH_2CH_c$); $J=4.8$ Hz); 5.26 (m; 1H ($CH_c$)); 6.90–7.30 (m; 5H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 14.7; 21.1; 26.6; 31.6; 67.2; 71.5; 114.6; 121.2; 129.5; 158.4; 170.5. IR (film; $cm^{-1}$) 2940; 1745; 1600; 1495; 1370; 1230; 1045; 750; 690; $[\alpha]_D^{22}=+5.6$ ($CHCl_3$, *c* 1.70; ee+83%). Anal. calcd for $C_{13}H_{18}SO_3$: C, 61.39%; H, 7.13%. Found: C, 61%.45; H, 7.01%.

**4.3.7. (*S*)-(+)-1-Ethylthio-3-(4-methylphenoxy)propan-2-ol acetate 3g**. $^1H$ NMR ($CDCl_3$) $\delta$ ppm: 1.27 (t; 3H ($CH_3CH_2$); $J=7.2$ Hz); 2.10 (s; 3H ($CH_3CO$)); 2.29 (s; 3H ($CH_3$)); 2.60 (q; 2H ($CH_3CH_2$)); 2.82 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=14.2$ Hz; $J_{ac}=6.2$ Hz); 2.91 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=7$ Hz); 4.15 (d; 2H ($OCH_2CH_c$); $J=4.4$ Hz); 5.25 (m; 1H ($CH_c$)); 6.80–7.10 (m; 4H (aromatic H)); $^{13}C$ NMR ($CDCl_3$) $\delta$ ppm: 14.6; 20.4; 21.0; 26.5; 31.6; 67.4; 71.5; 114.4; 129.8; 130.3; 156.2; 170.4. IR (film; $cm^{-1}$) 2920; 1735; 1605; 1565;




**Scheme 3.**

1230; 1040; 810; $[\alpha]_D^{22}=+3.5$ ($CHCl_3$, *c* 1.70; ee = 24%). Anal. calcd for $C_{14}H_{20}SO_3$: C, 62.66%; H, 7.51%. Found: C, 62.75%; H, 7.40%.

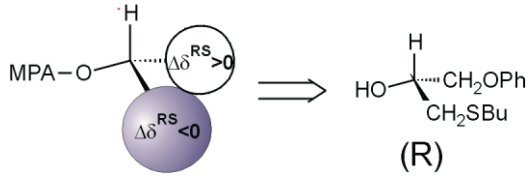
**4.3.8. (*S*)-(+)-1-*tert*-Butylthio-3-phenoxypropan-2-ol acetate 3h**. $^1$H NMR ($CDCl_3$) $\delta$ ppm: 1.33 (s; 9H (3× $CH_3$)); 2.09 (s; 3H ($CH_3CO$)); 2.85 (dd; 1H ($CH_cCH_aH_bS$); $J_{ab}=13.2$ Hz; $J_{ac}=5.8$ Hz); 2.92 (dd; 1H ($CH_cCH_aH_bS$); $J_{bc}=7.2$ Hz); 4.16 (m; 2H ($OCH_2CH_c$)); 5.23 (m; 1H ($CH_c$)); 6.90–7.30 (m; 5H (aromatic H)); $^{13}$C NMR ($CDCl_3$); $\delta$ ppm: 21.0; 28.5; 30.8; 42.7; 67.2; 72.1; 114.5; 121.0; 129.4; 158.3; 170.4. IR (film; $cm^{-1}$) 2960; 1740; 1600; 1495; 1360; 1225; 1045; 750; 640; $[\alpha]_D^{22}=+4.8$ ($CHCl_3$, *c* 1.60; ee = 67%). Anal. calcd for $C_{15}H_{22}SO_3$: C, 63.80%; H, 7.85%. Found: C, 63.78%; H, 7.75%.

### 4.4. Assignment of absolute configuration of 1-*n*-butylthio-3-phenoxypropan-2-ol 1a and its acetate 3a

The enantiomer of 1-*n*-butylthio-3-phenoxypropan-2-ol, isolated from the reaction of lipase catalyzed transesterification of the racemate, was made to react[7] with optically pure (*R*)- and (*S*)-enantiomers of methoxyphenylacetic acid (MPA) and $^1$H NMR spectra of the resulting esters were taken in a $CDCl_3$ solution (Scheme 3). 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 chirality center as shown by the following equations:

$$\Delta\delta^{RS}\ L_1=\delta^R L_1-\delta^S L_1=2.71-2.86=-0.15\ \text{ppm}$$

$$\Delta\delta^{RS}\ L_3=\delta^R L_3-\delta^S L_3=4.16-4.03=+0.13\ \text{ppm}$$




**Scheme 4.**

The negative value of $\Delta\delta^{RS}$, which corresponds to the signal of protons of the substituent $L_1$, and the opposite plus sign resulting for the protons $L_3$ determine the ***R*** configuration according to the drawing (Scheme 4).

The same procedure was applied to the second enantiomer of the alcohol isolated after hydrolysis of the acetate **3a.** As compared with (*R*)-(+)-**2a**, the respective $\Delta\delta^{RS}$ values are of opposite signs thus indicating the (*S*)-configuration.

$$\Delta\delta^{RS}L_1 = \delta^{R}L_1 - \delta^{S}L_1 = 2.85 - 2.70 = +0.15$$

$$\Delta\delta^{RS}L_3 = \delta^{R}L_3 - \delta^{S}L_3 = 4.06 - 4.19 = -0.13$$

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