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Lipase-catalyzed enantiomeric separation of 1-aryloxy-3-thiocyanatopropan-2-ols: an attempt to prepare optically active thiiranes

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Abstract—Opening of the epoxide ring of several arylglycidyl ethers with thiocyanato anion followed by acetylation yielded racemic mixtures of 1-aryloxy-3-thiocyanato-propan-2-yl acetates. A lipase-catalyzed hydrolysis of the acetates resulted in the separation of the enantiomers. The unstable, optically active (*S*)-1-aryloxy-3-thiocyanatopropan-2-ols, were converted into the corresponding 2-aryloxymethyl thiiranes, which instantly polymerized to yield the optically active oligomers.

1. Introduction

Thiiranes, the simplest sulfur heterocycles, exist in nature mostly in plants. For example, terpene episulfides were found in the essential oil of hop.[1] Other thiiranes can be found in the hydrolysis products of rapeseed glucosinolates and in seeds of other species of the *Cruciferae* family.[2] Several synthetic racemic thiiranes have been used in the pharmaceutical, pesticide, and polymer industries.[3–8] For example, epithioandrostanol derivatives, Mepitiostane and Epitiostanol, are anti-tumor drugs[4] effective against breast cancer, while others show insecticidal, herbicidal, and juvenile hormone activity. Synthetic optically active thiiranes have recently gained considerable attention as useful building blocks in the synthesis of carboxypeptidase A and peptidic cysteine protease inhibitors[9,10] or as thiirane-containing glycomimetics inhibiting activity of other enzymes.[11] The known methods for the preparation of optically active thiiranes involve the use of enantiomerically enriched oxiranes as the substrates. A prolonged, even several-days-long, stirring at room temperature of the appropriate oxirane with thiourea in a methanol solution gave the expected thiirane in an almost quantitative yield. The procedure employed did not affect the chirality of the stereogenic center and no epimerization was observed.[12] Another employed procedure was a Ru(III) catalyzed[13] conversion of epoxides into the corresponding thiiranes in the presence of ammonium thiocyanate. In this case, a stereoselective conversion of (*R*)-(+)-styrene oxide to (*S*)-(−)-styrene sulfide was achieved in high enantiomeric excess and in excellent yield.

2. Results and discussion

It is well known that a nucleophilic attack of the thiocyanate anion on the epoxide ring results in the formation of a β-hydroxythiocyanato derivative, which is usually unstable spontaneously eliminating cyanic acid to leave the desired thiirane.[14–17] According to previous papers,[13,18–20] the attack of the thiocyanate anion on the oxirane ring is not always completely regioselective, since two isomeric β-thiocyanatohydrins can form with a strong preference toward the secondary alcohol. Two other compounds were also detected in the reaction mixture: the appropriate thiirane and a 1-(5-(substituted)-1,3-oxathiolan-2-ylidene)urea derivative.

In the search for a preparative method leading from racemic oxiranes to optically active thiiranes our attention was focused on the possibility of using β-thiocyanatohydrins in the mixed chemo-enzymatic procedure involving lipases as the chiral catalysts for the enantiomer separation. When the known reaction

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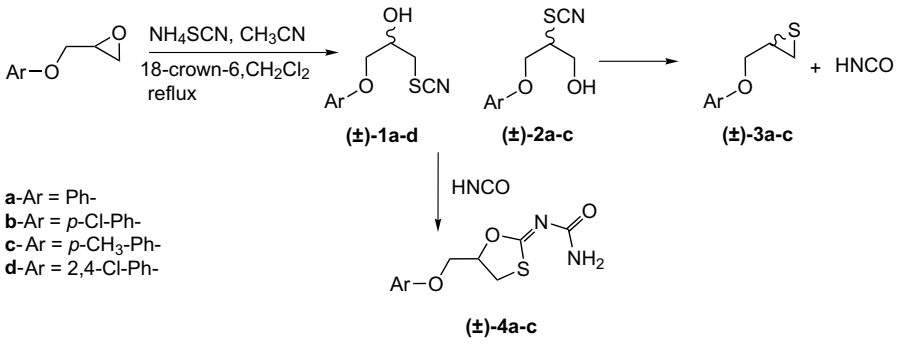


Scheme 1.

of phenylglycidyl ether with ammonium thiocyanate was presently carried out with other oxiranes, we were able to isolate and characterize all of the expected products (Scheme 1).

In contrast to the literature data[21] describing the reaction of phenylglycidyl ether with ammonium thiocyanate, not one but two isomeric β-thiocyanatohydrins **1** and **2** were formed with a marked preference of the secondary 1-aryloxy-3-thiocyanatopropan-2-ols **1**. Both **1** and **2** were stable enough to make their isolation possible. Two other compounds, namely 2-(aryloxymethyl) thiirane (±)-**3** and 1-(5-(aryloxymethyl)-1,3-oxathiolan-2-ylidene)urea (±)-**4**, were also detected in the reaction mixture. They were formed by the decomposition of β-hydroxythiocyanates and subsequent reaction of the liberated isocyanic acid with (±)-**1** or (±)-**2**. The apparent stability of the prepared 1-aryloxy-3-thiocyanatopropan-2-ols prompted us to use them as the substrates in the lipase-catalyzed acetylation reaction, which was expected to result in the separation of the secondary alcohol enantiomers as shown in the Scheme 2, and thus allow the preparation of the enantiomerically enriched thiiranes.

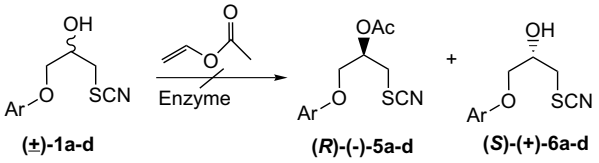
Unfortunately, under the conditions required for carrying on the enzyme-catalyzed acetylation, **1a**–**d** were not stable enough since decomposition was faster than the acetylation. This suggested reversing the reaction order and, instead of acetylation, trying to effect the enantiomer separation in a lipase-catalyzed hydrolysis of the corresponding acetates (±)-**7a**–**d**.

Mixtures of 1-aryloxy-3-thiocyanatopropan-2-ols (±)-**1a**–**d** and 3-aryloxy-2-thiocyanato-propanols (±)-**2a**–**c** were prepared according to the earlier reported procedure[21] in the crown ether-catalyzed reaction of the appropriate aryglycidyl ethers with ammonium thiocyanate (Scheme 3).

In our experiments, (±)-**1a**–**d** and (±)-**2a**–**c** were not isolated as free alcohols because of their low stability. To the reaction mixture containing crude β-thiocyanatohydrins (±)-**1a**–**d** and (±)-**2a**–**c**, an excess of acetyl chloride was added and the mixture refluxed for approximately 2.5 h. The resulting stable acetates (±)-**7a**–**d** and (±)-**8a**–**c** were separated and purified. We also checked the earlier[21] suggestion that the addition of a trace amount of hydroquinone to the reaction mixture acts to stabilize the β-thiocyanatohydrins **1** and **2**. Data produced in Table 1 verified this suggestion.

The acetates of secondary and primary alcohols, (±)-**7a**–**d** and (±)-**8a**–**c**, respectively, were separated and characterized by IR, ^{1}H, and ^{13}C NMR spectra and elemental analysis.

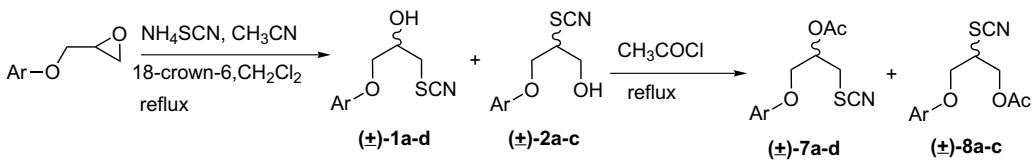
Racemic mixtures of 1-aryloxy-3-thiocyanatopropan-2-ol acetates **7a**–**d** were subjected to the lipase-catalyzed



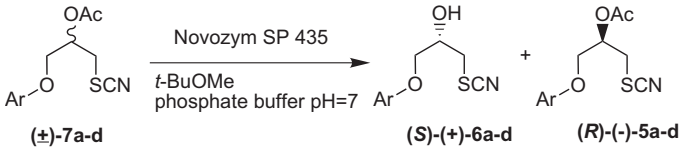
Scheme 2.

Table 1. A comparison of the yields of acetates (±)-**7a**–**d** and (±)-**8a**–**c** obtained with or without added hydroquinone

Substrate	Ar	Yield (%)	Yield (%) with hydroquinone	Product ratio (**7**:**8**)
1a, **2a**	C_6H_5–	34	56	14:1
1b, **2b**	4-Cl–C_6H_4–	43	58	12:1
1c, **2c**	4-CH_3–C_6H_4–	55	70	8.5:1
1d	2,4-Cl–C_6H_3–	56	70	1:0



Scheme 3.



Scheme 4.

Table 2. Hydrolysis[a] of the esters (±)-**7a**–**d** catalyzed by Novozym SP 435

Substrate	Ar	Time (h)	c[b] (%)	ee_s[c] (%)	ee_p[c] (%)	E[b]	$[\alpha]^{20}_{D\,substr}$	$[\alpha]^{20}_{D\,prod}$
7a	C_6H_5–	63	53	99	88	82	−50.75	+5.6
7b	4-Cl–C_6H_4–	69	48	90	>99	>100	−37.5	+0.45
7c	4-CH_3–C_6H_4–	53	39	61	95	73	−45	+1.9
7d	2,4-Cl–C_6H_3–	72	50	>99	>99	>100	−22.4	+0.7

[a] Conditions: 7 mmol of (±)-**7a**–**d**, 40 mL of TBME (*tert*-butyl methyl ether), 200 mL of 0.1 M phosphate buffer (pH = 7) and 800 mg Novozym SP 435 (*Candida antarctica*-B), room temperature.

[b] Conversion and E values were calculated from the enantiomeric excess of substrate (−)-**5a**–**d** (ee_s) and product (+)-**6a**-=**d** (ee_p) using the formula: $E = \mathrm{Ln}[(1 - ee_s)(ee_p/(ee_s + ee_p))]\mathrm{Ln}[(1 + ee_s)/(ee_s + ee_p)]$, conv. = $ee_s/(ee_s+ee_p)$.

[c] Determined by HPLC analysis using Chiralcel OD-H column.

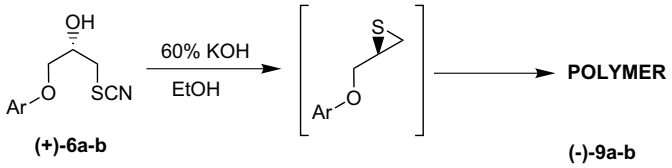
hydrolysis in a two-phase *tert*-butyl methyl ether–phosphate buffer system. From among several lipases tested (PPL, Amano AK, Amano PS, Lipozyme IM, Chirazyme L-2, Novozym SP 435, and a protease α-chymotrypsin), only Novozym (a *Candida antarctica* lipase) was able to efficiently hydrolyze acetates (±)-**7a**–**d** in good stereoselectivity. The preparative reactions were carried out at room temperature in a buffer solution of pH = 7 (Scheme 4). The hydrolysis of the esters was monitored by TLC and stopped when the conversion was approximately 50%. As shown in Table 2, the enantiomeric excesses of the remaining acetates (−)-**5a**–**c** and of the formed alcohols (+)-**6a**–**c** were sufficiently high and the compounds obtained almost enantiomerically pure. The (*R*)-configuration of the separated pure enantiomer of 1-(2,4-dichlorophenoxy)-3-thiocyanatopropan-2-yl acetate (−)-**5d** was determined by X-ray crystallography.

In order to prepare thiiranes, the obtained optically active 1-aryloxy-3-thiocyanatopropan-2-ols (+)-**6a** and **b** were dissolved in ethanol and the solutions treated at room temperature with a few drops of 60% potassium hydroxide/water solution (Scheme 5). The expected 2-aryloxymethylthiiranes were separated by carefully evaporating the alcohol under reduced pressure, dissolving the residue in ethyl ether, washing the etherate with water, drying, and evaporating the solvent. The crude products revealed, however, to be not thiirane monomers but levorotatory oligomers (−)-**9a** and **9b**. Their ^{1}H and ^{13}C NMR spectra were very complicated. The instability of thiiranes in the presence of acids or bases is well documented.[16] They are highly reactive, even more so than oxiranes, to nucleophilic compounds[22] and ring opening at either the primary or the secondary carbon atom leads to a mixture of polymer isomers. This explains why closing the thiirane ring with a strong base resulted in a polymeric material, while a weaker base caused a multidirectional decomposition of 3-aryloxy-2-thiocyanatopropan-2-ols, and also accounts for the complexity of the NMR spectra of the oligomers obtained by us. Optical activity of the polymers obtained from optically active thiiranes was also mentioned.[22] Molecular weights of the oligomers prepared by us were measured by GPC in THF with the reported values given relative to the polystyrene standard. For **9a**: M_n = 891, M_w = 1189. For **9b**: M_n = 763, M_w = 1053.

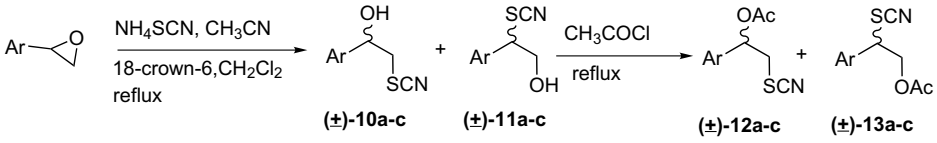
When the reaction of styrene oxide or its phenyl-ring substituted derivatives with ammonium thiocyanate followed by acetylation was carried out as previously described in the case of glycidyl ethers, nonequimolar mixtures of isomeric β-acetoxythiocyanates (±)-**12a**–**c** and (±)-**13a**–**c** were prepared (Scheme 6).

The aryl substituents are indicated in Table 3. Our attempts to separate the isomeric acetoxy derivatives **12** and **13** by silica-gel column chromatography proved unsuccessful. The ratios of the isomers were determined therefore on the basis of the ^{1}H NMR spectra of the mixtures.

We found, however, that the acetate hydrolysis catalyzed by Novozym SP 435 proceeds regioselectively.



Scheme 5.



Scheme 6.

Table 3. The total yields and the ratios of the two isomers of β-acetoxythiocyanates (±)-**12a–c** and (±)-**13a–c**

Substrate	Ar	Ratios of products **12**:**13**	Yield (%)
10a, **11a**	C_6H_5–	1:2.8	47
10b, **11b**	4-Cl–C_6H_4–	1:1.3	44
10c, **11c**	4-CH_3–C_6H_4–	1:2	45

Thus, it affects only the esters of the primary alcohols (±)-**13a–c**, while the acetates of the secondary alcohols were left unchanged (Scheme 7). Separation of the hydrolysis products was easily effected by a column chromatography on silica gel.

The properties of the primary alcohols **11a–c** and the acetates of secondary alcohols **12a–c** are reported in Section 3.

3. Experimental

3.1. General

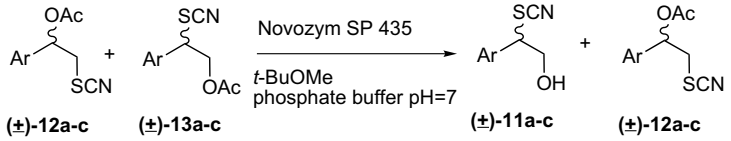
^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian Mercury 400 MHz spectrometer in $CDCl_3$ or CD_3COCD_3 solution; chemical shifts (δ) are reported in ppm. IR spectra were taken on a Carl Zeiss Specord M80 instrument. Ee's of the alcohols and esters were determined on a Thermo-Separation Products P-100 HPLC apparatus with Chiralcel OD-H column (in hexane–*iso*-propanol, 9:1; 0.8 mL/min) using racemic compounds as references. Optical rotations were measured in $CDCl_3$ solution with PolAAr 32 polarimeter. Elemental analyses were performed on CHNSCl/O Perkin–Elmer type 2400 instrument. The reactions were monitored by TLC on silica gel 60 (230–400 mesh). The arylglycidyl ethers were prepared[23] by the Williamson reaction from the appropriate phenols and epichlorohydrin in an aqueous NaOH solution. 2-(4-Chlorophenyl)oxirane and 2-*p*-tolyloxirane were prepared[24] from the appropriate benzaldehyde and trimethylsulfonium bromide in CH_3CN/H_2O solution with KOH at 60 °C. Novozym SP 435 (immobilized *C. antarctica*-B lipase) was kindly granted by Novo-Nordisk.

3.2. General procedure for the conversion of epoxides to β-hydroxy thiocyanates

To the mixture of an epoxide (10 mmol) and NH_4SCN (10 mmol, 0.76 g) in acetonitrile (30 mL), a solution of 18-crown-6 ether (0.1 mmol, 0.0264 g) in CH_2Cl_2 (5 mL) was added, and the mixture stirred under reflux conditions. The progress of the reaction was monitored by TLC, using *n*-hexane–ethyl acetate (3:1 v/v) as the eluent. After completion of the reaction, the solid was filtered off and the solvent evaporated. The resulting crude mixture of products was used as the substrate in the synthesis of acetates by adding an excess of acetyl chloride (25 mL) and stirring the mixture for 2.5 h at reflux. After cooling to room temperature, traces of the solid material were filtered off and the filtrate cooled in an ice bath and neutralized to pH = 7 with a K_2CO_3 solution. The products were extracted with CH_2Cl_2 (5 × 30 mL), and the organic layer washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated. The mixture of products was separated by column chromatography on a silica gel with *n*-hexane–ethyl acetate (7:1 v/v) as the eluent. ^{1}H, ^{13}C NMR spectra, IR data, and elemental analyses of the prepared esters are reported below.

3.2.1. (±)-1-Phenoxy-3-thiocyanatopropan-2-yl acetate 7a. Oil. ^{1}H NMR ($CDCl_3$): δ ppm: 2.16 (s, 3H (CH_3)); 3.34 (dd, 1H (CHCH_aH$_b$S); J_{HaCH} = 6.8 Hz; J_{HaHb} = 14Hz); 3.43 (dd, 1H (CHCH$_a$$H_b$S); J_{HbCH} = 4.4 Hz); 4.17 (m, 2H (OCH_2CH)); 5.43 (m, 1H (CH)); 6.89–7.30 (m, 5H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.39; 33.95; 66.08; 69.76; 111.56; 114.19; 121.32; 129.31; 157.52; 169.70. IR (film, cm^{-1}) 2150 (CN); 1740 (CO). Anal. Calcd for $C_{12}H_{13}NSO_3$: C, 57.37; H, 5.18; N, 5.58; S, 12.75. Found: C, 57.37; H, 5.11; N, 5.61; S, 12.20.

3.2.2. (±)-1-(4-Chlorophenoxy)-3-thiocyanatopropan-2-yl acetate 7b. Colorless crystals; mp 43–44 °C. ^{1}H NMR ($CDCl_3$): δ ppm: 2.16 (s, 3H (CH_3)); 3.32 (dd, 1H (CHCH_aH$_b$S); J_{HaCH} = 6.4 Hz; J_{HaHb} = 14 Hz); 3.42 (dd, 1H (CHCH$_a$$H_b$S); J_{HbCH} = 4.4 Hz); 4.12 (dd, (OCH_cH$_d$CH); J_{HcCH} = 5.6 Hz; J_{HcHd} = 10.4 Hz); 4.17 (dd, 1H (OCH$_c$$H_d$CH); J_{HdCH} = 4.4 Hz); 5.41 (m, 1H (CH)); 6.81–7.26 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ



Scheme 7.

ppm: 20.67; 34.17; 66.57; 69.86; 111.55; 115.74; 126.59; 129.45; 156.31; 169.97. IR (Nujol, cm^{-1}) 2150 (CN); 1742 (CO). Anal. Calcd for $C_{12}H_{12}NClSO_3$: C, 50.43; H, 4.20; N, 4.90; S, 11.20. Found: C, 50.46; H, 4.10; N, 4.75; S, 11.21.

3.2.3. (±)-3-Thiocyanato-1-(*p*-tolyloxy)propan-2-yl acetate 7c. Colorless crystals; mp 27–28 °C. ^{1}H NMR ($CDCl_3$): δ ppm: 2.16 (s, 1H ($CO\mathit{CH}_3$)); 2.29 (s, 3H ($\mathit{CH}_3C_6H_5$)); 3.32 (dd, 1H ($CHC\mathit{H}_aH_bS$); J_{HaCH} = 6.8 Hz; J_{HaHb} = 14 Hz); 3.42 (dd, 1H ($CHCH_a\mathit{H}_bS$); J_{HbCH} = 4.4 Hz); 4.11 (dd, 1H ($OC\mathit{H}_cH_dCH$); J_{HcCH} = 4.4 Hz; J_{HcHd} = 10 Hz); 4.17 (dd, 1H ($OCH_c\mathit{H}_dCH$); J_{HdCH} = 6 Hz); 5.41 (m, 1H (CH)); 6.80–7.09 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.61; 34.21; 66.36; 69.98; 111.67; 114.22; 129.92; 130.86; 155.58; 169.94. IR (Nujol, cm^{-1}) 2140 (CN); 1730 (CO). Anal. Calcd for $C_{13}H_{15}NSO_3$: C, 58.86; H, 5.66; N, 5.28; S, 12.08. Found: C, 58.72; H, 5.71; N, 5.24; S, 12.43.

3.2.4. (±)-1-(2,4-Dichlorophenoxy)-3-thiocyanatopropan-2-yl acetate 7d. Colorless crystals; mp 83–84 °C. ^{1}H NMR ($CDCl_3$): δ ppm: 2.16 (s, 3H (CH_3)); 3.38 (dd, 1H ($CHC\mathit{H}_aH_bS$); J_{HaCH} = 6.4 Hz; J_{HaHb} = 14.4 Hz); 3.47 (dd, 1H ($CHCH_a\mathit{H}_bS$); J_{HbCH} = 4.8 Hz); 4.20 (dd, 1H ($OC\mathit{H}_cH_dCH$); J_{HcCH} = 6 Hz; J_{HcHd} = 10 Hz); 4.25 (dd, 1H ($OCH_c\mathit{H}_dCH$); J_{HdCH} = 4.8 Hz); 5.44 (m, 1H (CH)); 6.87–7.37 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.70; 34.04; 67.63; 69.82; 111.52; 114.61; 124.10; 127.10; 127.76; 140.19; 152.18; 170.01. IR (Nujol, cm^{-1}) 2158 (CN); 1742 (CO). Anal. Calcd for $C_{12}H_{11}NCl_2SO_3$: C, 45; H, 3.43; N, 4.37; Cl, 22.19; S, 10. Found: C, 45.11; H, 3.58; N, 4.33; Cl, 22.15; S, 9.84.

3.2.5. (±)-3-(4-Chlorophenoxy)-2-thiocyanatopropyl acetate 8b. Oil. ^{1}H NMR ($CDCl_3$): δ ppm: 2.28 (s, 3H (CH_3)); 3.39 (dd, 1H ($C_6H_4OC\mathit{H}_aH_bCH$); J_{HaCH} = 6.8 Hz; J_{HaHb} = 14.4 Hz); 3.53 (dd, 1H ($C_6H_4OCH_a\mathit{H}_bCH$); J_{HbCH} = 6.4 Hz); 4.18 (m, 2H ($CH\mathit{CH}_2OCOCH_3$)); 4.35 (m, 1H (CH)); 6.83–7.26 (m, 4H (Ph)).

3.2.6. (±)-2-Thiocyanato-3-(*p*-tolyloxy)propyl acetate 8c. Oil. ^{1}H NMR ($CDCl_3$): δ ppm: 2.28 (s, 3H(CH_3)); 3.39 (dd, 1H ($CH_3C_4H_4OC\mathit{H}_aH_bCH$); J_{HaCH} = 6.8 Hz; J_{HaHb} = 14 Hz); 3.56 (dd, 1H ($CH_3C_4H_4OCH_a\mathit{H}_bCH$); J_{HbCH} = 6 Hz); 4.16 (dd, 1H ($CHC\mathit{H}_cH_dCH_2OCO$); J_{HcCH} = 5.6 Hz; J_{HcHd} = 10.4 Hz); 4.23 (dd, 1H ($CHCH_c\mathit{H}_dCH_2OCO$); J_{HdCH} = 5.2 Hz); 4.34 (m, 1H (CH)); 6.80–7.09 (m, 4H (Ph)).

3.2.7. (±)-2-(Phenoxymethyl)thiirane 3a. Oil. ^{1}H NMR ($CDCl_3$): δ ppm: 2.33–2.63 (m, 2H ($CH\mathit{CH}_2S$)); 3.28 (m, 1H (CH)); 3.91 (dd, 1H ($OC\mathit{H}_aH_bCH$); J_{HaCH} = 7.2 Hz; J_{HaHb} = 10 Hz); 4.22 (dd, 1H ($OCH_a\mathit{H}_bCH$); J_{HbCH} = 5.2 Hz); 6.91–7.32 (m, 5H (Ph)). ^{13}C NMR ($CDCl_3$) ppm: 24.00; 31.37; 72.53; 114.62; 121.21; 129.53; 158.20. Anal. Calcd for $C_9H_{10}SO$: C, 65.06; H, 6.02; S, 19.27. Found: C, 64.98; H, 5.87; S, 19.01. ^{1}H NMR and ^{13}C NMR spectra are identical with those given in the literature.[25]

3.2.8. (±)-2-((4-Chlorophenoxy)methyl)thiirane 3b. Oil. ^{1}H NMR ($CDCl_3$): δ ppm: 2.31–2.61 (m, 2H ($CH\mathit{CH}_2S$)); 3.25 (m, 1H ($OCH_2\mathit{CH}CH_2S$)); 3.87–4.16 (m, 2H ($O\mathit{CH}_2CH$)); 6.82–7.24 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 24.01; 31.40; 72.62; 114.92; 126.59; 129.50; 156.45. Anal Calcd for C_9H_9ClSO: C, 53.86; H, 4.48; Cl, 17.70; S, 15.9; Found: C, 53.36; H, 4.41; Cl, 17.38; S, 15.38.

3.2.9. (±)-2-(*p*-Tolyloxymethyl)thiirane 3c. Oil. ^{1}H NMR ($CDCl_3$): δ ppm: 2.29 (s, 3H (CH_3)); 2.32–2.61 (dd, 2H ($CH\mathit{CH}_2S$)); 3.26 (m, 1H ($CH_a\mathit{H}_b\mathit{CH}CH_2$)); 3.86 (dd, 1H ($OC\mathit{H}_aH_bCH$); J_{HaHb} = 10 Hz); 4.19 (dd, 1H ($OCH_a\mathit{H}_bCH$)); 6.80–7.10 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.46; 24.02; 31.45; 72.76; 114.57; 129.95; 130.51; 156.27. Anal. Calcd for $C_{10}H_{12}SO$: C, 66.66; H, 6.66; S, 17.77. Found: C, 66.01; H, 6.23; S, 17.55.

3.2.10. (±)-1-(5-(Phenoxymethyl)-1,3-oxathiolan-2-ylidene)urea 4a. White crystals, mp 164.5–166 °C. ^{1}H NMR (CD_3COCD_3): δ ppm: 3.37 (dd, 1H ($CHC\mathit{H}_aH_bS$); J_{HaCH} = 8.4 Hz; J_{HaHb} = 11.2 Hz); 3.52 (dd, 1H ($CHCH_a\mathit{H}_bS$); J_{HbCH} = 7.2 Hz); 4.29 (dd, 1H ($OC\mathit{H}_cH_dCH$); J_{HcCH} = 5.6; J_{HcHd} = 10.8 Hz); 4.37 (dd, 1H ($OCH_c\mathit{H}_dCH$); J_{HdCH} = 3.6 Hz); 5.04 (m, 1H (CH)); 6.10 (s, 1H (NH_2)); 6.32 (s, 1H (NH_2)); 6.98–7.30 (m, 5H (Ph)).^{13}C NMR (CD_3COCD_3): δ ppm: 31.97; 68.14; 80.04; 115.40; 122.02; 130.35; 159.34; 163.59; 177.11. IR (Nujol, cm^{-1}) 3360, 3180 (NH_2); 1693 (CO). Anal. Calcd for $C_{11}H_{12}N_2SO_3$: C, 52.38; H, 4.76; N, 11.12; S, 12.69. Found: C, 51.99; H, 4.73; 11.05; S, 12.47.

3.2.11. (±)-1-(5-((4-Chlorophenoxy)methyl)-1,3-oxathiolan-2-ylidene)urea 4b. White crystals, mp 179.5–181.5 °C. ^{1}H NMR (CD_3COCD_3): δ ppm: 3.35 (dd, 1H ($CHC\mathit{H}_aH_bCH$); J_{HaCH} = 8.8 Hz; J_{HaHb} = 10.8 Hz); 3.52 (dd, 1H ($CHCH_a\mathit{H}_bS$); J_{HbCH} = 6.8 Hz); 4.30 (dd, 1H ($OC\mathit{H}_cH_dCH$); J_{HcCH} = 5.6 Hz; J_{HcHd} = 10.6 Hz); 4.36 (dd, 1H ($OCH_c\mathit{H}_dCH$); J_{HdCH} = 3.6 Hz); 5.04 (m, 1H (CH)); 6.11 (s, 1H (NH_2)); 6.33 (s, 1H (NH_2)); 7.01–7.32 (m, 4H (Ph)). ^{13}C NMR (CD_3COCD_3): δ ppm: 31.90; 68.64; 79.91; 117.12; 126.45; 130.18; 158.18; 153.58; 177.10. IR (Nujol, cm^{-1}): 3360, 3180 (NH_2)1692 (CO). Anal. Calcd for $C_{11}H_{11}N_2ClSO_3$:C, 46.07; H, 3.83; N; 9.77; Cl, 12.39; S, 11.16. Found: C, 46.53; H, 3.54; N, 9.27; Cl, 12.47; S, 11.02.

3.2.12. (±)-1-(5-(*p*-Tolyloxymethyl)-1,3-oxathiolan-2-ylidene)urea 4c. White crystals, mp 176.5–179 °C. ^{1}H NMR (CD_3COCD_3): δ ppm: 2.24 (s, 3H (CH_3)); 3.35 (dd, 1H ($CHC\mathit{H}_aH_bS$); J_{HaCH} = 8.8 Hz; J_{HaHb} = 11.2 Hz); 3.51 (dd, 1H ($CHCH_a\mathit{H}_bS$); J_{HbCH} = 6.8 Hz); 4.24 (dd, 1H ($OC\mathit{H}_cH_dCH$); J_{HcCH} = 5.6 Hz; J_{HcHd} = 10.8 Hz); 4.32 (9dd, 1H ($OCH_c\mathit{H}_dCH$); J_{HdCH} = 4 Hz); 5.02 (m, 1H (CH)); 6.09 (s, 1H (NH_2)); 6.31 (s, 1H (NH_2)); 6.87–7.11 (m, 4H (Ph)). ^{13}C NMR (CD_3COCD_3): δ ppm: 20.42; 31.99; 68.33; 80.10; 115.32; 129.92; 130.74; 158.15; 163.40; 177.11. IR (Nujol, cm^{-1}): 3360, 3180 (NH_2); 1694 (CO). Anal. Calcd for $C_{12}H_{14}N_2SO_3$: C, 54.13; H, 5.26; N, 10.52; S, 12.03. Found: C, 54.11; H, 5.13; N, 10.21; S, 11.91.

3.3. General procedure for the enzyme-catalyzed hydrolysis of acetates (±)-7a–d

In a typical experiment, acetate (±)–**7a**–**c** (7 mmol) was dissolved in 40 mL of TBME (*tert*-butyl methyl ether). The solution was mixed with 0.1 M phosphate buffer (200 mL, pH = 7) and 800 mg of Novozym SP 435 (*C. antarctica*-B lipase) then added. The mixture was stirred at room temperature (17–20 °C) and the conversion monitored by TLC using *n*-hexane–ethyl acetate (3:1 v/v) as the eluent. After an appropriate time the reaction was stopped by filtering off the enzyme and the products extracted with diethyl ether (5 × 30 mL). The organic layers were combined, washed with water (3 × 50mL), and dried over anhydrous $MgSO_4$, whereupon the solvent was evaporated. The crude mixture was purified by chromatography on a silica-gel column with *n*-hexane–ethyl acetate (5:1 v/v). NMR spectra of the enantiomerically enriched acetates (−)-(*R*)-**5a**–**d** were identical with those of (±)-**7a**–**d**. The optical rotations measured in $CHCl_3$ solution for the prepared enantiomerically enriched acetates are as follows:

(*R*)-(−)-**5a**: $[\alpha]_D^{20} = -50.75$ (*c* 2, $CHCl_3$), ee = 99%.

(*R*)-(−)-**5b**: $[\alpha]_D^{20} = -37.5$ (*c* 2, $CHCl_3$), ee = 90%.

(*R*)-(−)-**5c**: $[\alpha]_D^{20} = -45$ (*c* 2, $CHCl_3$), ee = 61%.

(*R*)-(−)-**5d**: $[\alpha]_D^{20} = -22.4$ (*c* 5, $CHCl_3$), ee >99%.

^1H and ^{13}C NMR spectra, as well as IR data and elemental analyses of the prepared alcohols (+)-**6a**–**d** are reported below.

3.3.1. (*S*)-(+)-1-Phenoxy-3-thiocyanatopropan-2-ol 6a. Oil, yield 19%. ^1H NMR ($CDCl_3$): δ ppm: 2.52 (s, 1H (OH)); 3.19 (dd, 1H ($CHCH_aH_bS$); J_{HaCH} = 7.2 Hz; J_{HaHb} = 13.6 Hz); 3.31 (dd, 1H ($CHCH_aH_bS$); J_{HbCH} = 4.8 Hz); 4.10 (m, 2H (OCH_2CH)); 4.34 (m, 1H (CH)); 6.90–7.33 (m, 5H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 37.08; 68.78; 69.27; 112.37; 114.43; 121.63; 129.60; 157.83. IR (film, cm^{-1}) 3450 (OH); 2150 (CN). $[\alpha]_D^{20} = +5.6$ ($CHCl_3$, *c* 1.96, ee 88%). Anal. Calcd for $C_{10}H_{11}NSO_2$: C, 57.41; H, 5.26; N, 6.69; S, 15.31. Found: C, 57.59; H, 5.24; N, 6.70; S, 15.10.

3.3.2. (*S*)-(+)-1-(4-Chlorophenoxy)-3-thiocyanatopropan-2-ol 6b. Oil, yield 24%. ^1H NMR ($CDCl_3$): δ ppm: 3.18 (dd, 1H ($CHCH_aH_bS$); J_{HaCH} = 7.6 Hz; J_{HaHb} = 13.2 Hz); 3.30 (dd, 1H ($CHCH_aH_bS$); J_{HbCH} = 4.4 Hz); 4.06 (m, 2H (OCH_2CH)); 4.33 (m, 1H (CH)); 6.83–7.26 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 36.98; 68.75; 69.65; 112.18; 115.75; 126.59; 129.50; 156.45. IR (film, cm^{-1}) 3440 (OH); 2150 (CN). $[\alpha]_D^{20} = +0.4$ ($CHCl_3$, *c* 4.50, ee >99%). Anal. Calcd for $C_{10}H_{10}NClSO_2$: C, 49.28; H, 4.10; N, 5.75; S, 13.14; Cl, 14.57. Found: C, 49.33; H, 4.12; N, 5.77; S, 12.98; Cl, 14.41.

3.3.3. (*S*)-(+)-1-Thiocyanato-3-(*p*-tolyloxy)propan-2-ol 6c. Oil, yield 18%. ^1H NMR ($CDCl_3$): δ ppm: 2.29 (s, 1H (CH_3)); 2.72 (s, 1H (OH)); 3.24 (m, 2H ($CHCH_2S$)); 4.07 (m, 2H (OCH_2CH)); 4.31 (m, 1H (CH)); 6.79–7.11 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.42; 37.08; 68.84; 69.48; 112.34; 114.32; 130.02; 130.98; 155.75. IR (film, cm^{-1}): 3440 (OH); 2150 (CN). $[\alpha]_D^{20} = +1.9$ ($CHCl_3$, *c* 1.80, ee 95%). Anal. Calcd for $C_{11}H_{13}NSO_2$: C, 59.19; H, 5.83; N, 6.27; S, 14.35. Found: C, 59.21; H, 5.83; N, 6.18; S, 14.36.

3.3.4. (*S*)-(+)-1-(2,4-Dichlorophenoxy)-3-thiocyanatopropan-2-ol 6d. Oil, yield 21%. ^1HNM ($CDCl_3$): δ ppm: 3.20 (dd, 1H ($CHCH_aH_bS$); J_{HaCH} = 7.2 Hz; J_{HaHb} = 13.6 Hz); 3.33 (dd, 1H ($CHCH_aH_bS$); J_{HbCH} = 4.4 Hz); 4.09 (m, 2H (OCH_2CH)); 4.34 (m, 1H (CH)); 6.83–7.34 (m, 3H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 36.84; 68.59; 70.76; 112.36; 114.62; 123.82; 126.81; 127.72; 129.97; 152.22. $[\alpha]_D^{20} = +0.7$ (*c* 8.82, $CHCl_3$, ee >99%). Anal. Calcd for $C_{10}H_9Cl_2NSO_2$: C, 43.18; H, 3.26; Cl, 25.49; N, 5.04; S, 11.53. Found: C, 43.31; H, 3.06; Cl, 25.61; N, 4.97; S, 11.63.

3.4. General procedure for separation of the acetates (±)-12a–c and (±)-13a–c

In a typical experiment, the mixture of isomeric acetates (±)-**12** and (±)-**13** (1.6 g) was dissolved in 30 mL of TBME, mixed with 0.1 M phosphate buffer (155 mL, pH = 7) and 620 mg of Novozym SP 435 added. The mixture was stirred at room temperature (17–20 °C) and the conversion monitored by TLC, using *n*-hexane–ethyl acetate (3:1 v/v) as the eluent. After the appropriate time, the reaction was arrested by filtering off the enzyme and the residue was extracted with diethyl ether (5 × 50 mL). The organic layers were combined, washed with water (3 × 50mL), and dried over anhydrous $MgSO_4$. Upon evaporation of the solvent, the crude mixture was separated by chromatography on a silica-gel column with *n*-hexane–ethyl acetate (5:1 v/v) as the eluent. ^1H, ^{13}C NMR spectra, IR data, and elemental analyses of the prepared primary alcohols (±)-**11a**–**c** and pure acetates of the secondary alcohols (±)-**12a**–**c** are reported below:

3.4.1. (±)-2-Phenyl-2-thiocyanatoethanol 11a. ^1H NMR ($CDCl_3$): δ ppm: 4.17 (m, 2H (CH_2)); 4.51 (m, 1H (CH)); 7.38–7.40 (m, 5H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 54.79; 64.70; 111.44; 127.83; 129.20; 129.30; 135.34. IR (film, cm^{-1}): 3450 (OH); 2150 (CN).

3.4.2. (±)-2-Thiocyanato-2-*p*-tolylethanol 11c. ^1H NMR ($CDCl_3$): δ ppm: 2.36 (s, 3H (CH_3)); 4.13 (m, 2H (CH_2)); 4.48 (m, 1H (CH)); 7.20–7.27 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 21.15; 54.66; 64.88; 111.39; 127.74; 129.93; 132.22; 139.43. IR (film, cm^{-1}): 3450 (OH); 2160 (CN).

3.4.3. (±)-1-Phenyl-2-thiocyanatoethyl acetate 12a. ^1H NMR ($CDCl_3$): δ ppm: 2.17 (s, 3H (CH_3)); 3.29 (dd, 1H (CH_aH_b); J_{HaCH} = 4.4 Hz; J_{HaHb} = 14 Hz); 3.37 (dd, 1H (CH_aH_b); J_{HbCH} = 8 Hz); 6.03 (m, 1H (CH)); 7.35–7.40 (m, 5H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.84; 39.02; 73.75; 111.59; 126.34; 128.92; 129.11; 137.07; 169.68. IR (film, cm^{-1}): 2150 (CN); 1745 (CO). Anal. Calcd for $C_{11}H_{11}NSO_2$: C, 59.71; H, 5.01; N,

6.33; S, 14.49. Found: C, 60.08; H, 4.95; N, 6.35; S, 14.47.

3.4.4. (±)-1-(4-Chlorophenyl)-2-thiocyanatoethyl acetate 12b. ^{1}H NMR ($CDCl_3$): δ ppm: 2.16 (s, 3H (CH_3)); 3.26 (dd, 1H (CH_aH_b); J_{HaCH} = 4.4 Hz; J_{HaHb} = 14 Hz); 3.33 (dd, 1H (CH_aH_b); J_{HbCH} = 8 Hz); 5.99 (m, 1H (CH)); 7.29–7.38 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.79; 38.77; 73.12; 111.38; 127.79; 129.77; 135.07; 135.55; 169.57. IR (film, cm^{-1}): 2150 (CN); 1750 (CO). Anal. Calcd for $C_{11}H_{10}ClNSO_2$: C, 51.67; H, 3.94; Cl, 13.86; N, 5.48; S, 12.54. Found: C, 51.61; H, 3.84; Cl, 13.70; N, 5.50; S, 12.60.

3.4.5. (±)-2-Thiocyanato-1-*p*-tolylethyl acetate 12c. ^{1}H NMR ($CDCl_3$): δ ppm: 2.32 (s, 3H (CH_3CO)); 2.35 (s, 3H ($CH_3C_6H_4$)); 3.27 (dd, 1H (CH_aH_b); J_{HaCH} = 4.4 Hz; J_{HaHb} = 14 Hz); 3.36 (dd, 1H (CH_aH_b); J_{HbCH} = 8.4 Hz); 5.99 (m, 1H (CH)); 7.15–7.26 (m, 4H (Ph)). ^{13}C NMR ($CDCl_3$): δ ppm: 20.89; 27.16; 39.03; 73.12; 11.68; 126.34; 129.60; 130.00; 139.71; 169.74. IR (film, cm^{-1}): 2150 (CN); 1740 (CO). Anal. Calcd for $C_{12}H_{13}NSO_2$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.15; H, 5.31; N, 5.86; S, 13.81.

3.5. Assignment of absolute configuration of 1-(2,4-dichlorophenoxy)-3-thiocyanatopropan-2-yl acetate 5d

Crystal data concerning the structure of (−)-1-(2,4-dichlorophenoxy)-3-thiocyanatopropan-2-yl acetate and the pertinent refinement details are given in Table 4. All measurements were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The crystal was positioned at 62.25 mm from the KM4CCD camera. As much as 1204 frames were measured at 1° intervals with a counting time of 15 s. The data were corrected for Lorentz and polarization effects. The numeric absorption correction was applied. Data collection, cell refinement, and data reduction were carried out with the Kuma Diffraction programs: CrysAlis CCD and CrysAlis RED.[26]

Table 4. Crystal data and structure refinement details

Empirical formula	$C_{12}H_{11}Cl_2NO_3S$
Formula weight	320.18
T/K	100(2)
λ/Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	7.107(2)
b/Å	8.957(1)
c/Å	11.137(2)
β/°	95.79(2)
V/Å^3	705.3(2)
Z	2
D_c/Mg m^{-3}	1.508
μ/mm^{-1}	0.610
F(000)	328
Crystal size/mm	0.25 × 0.25 × 0.15
Diffractometer	Kuma KM4CCD
θ range for data collection/°	3.21–24.99
Index ranges	$-8 \leqslant h \leqslant 8$, $-10 \leqslant k \leqslant 10$, $-13 \leqslant l \leqslant 13$
Reflections collected	10,766
Independent reflections	2473 [R(int) = 0.0985]
Max. and min. transmission	0.75566 and 0.49314
Data/parameters	2473/174
Goodness-of-fit (F^2)	1.104
Final R_1/wR_2 indices ($I > 2\sigma_I$)	R_1 = 0.0579, wR_2 = 0.1450
Absolute structure parameter	−0.03(10)
Extinction coefficient	0.000(6)
Largest diff. peak/hole/e Å^{-3}	0.791 and −0.679

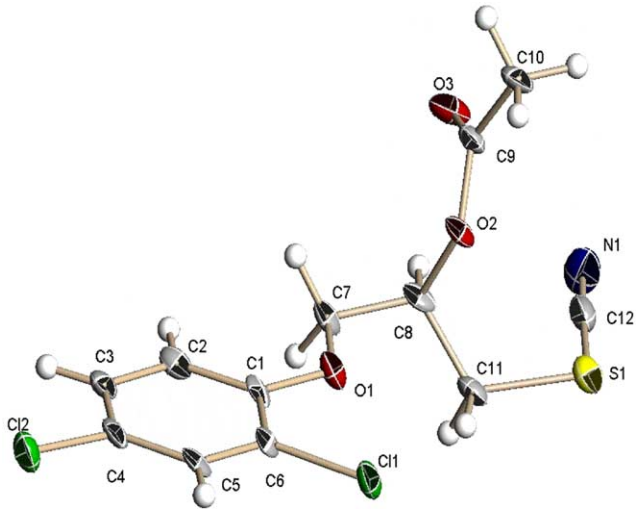


Figure 1. An ORTEP plot of (−)-(*R*)-1-(2,4-dichlorophenoxy)-3-thiocyanatopropan-2-yl acetate **5d** with thermal ellipsoids drawn at 50% probability level.

The structure was solved by direct methods[27] and refined using SHELXL (Fig. 1).[28] The refinement was based on F^2 for all reflections except those with very negative F^2. The weighted R factors wR and all goodness-of-fit S values are based on F^2. Conventional R factors are based on F with F set to zero for negative F^2. The Fo2 > 2s(Fo2) criterion was used only for calculating R factors and is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. All hydrogen atoms were located from a differential map and refined isotropically. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in Ref. 29. Final results give R_1 = 0.0579 and wR_2 = 0.1450 for 10766 reflections with $I > 2\sigma(I)$. The absolute structure was established based on anomalous dispersion using the Flack parameter x.[30] The x refined during the final structure factor evaluation of the model with the molecule of the R absolute configuration amounted to a value of −0.03(10). Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 268819. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).

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