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Chemo-enzymatic preparation of optically active thiiranes

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Abstract—A simple method for the preparation of optically active 2-(arylsulfanylmethyl)thiiranes and 2-(aryloxymethyl)thiiranes from the corresponding 3-thiocyanatopropan-2-ols and their acetates was developed. The starting enantiomerically enriched β-thiocyanato-alcohols and the acetates were obtained by a lipase-catalyzed hydrolysis of the appropriate racemic acetates.
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1. Introduction

Several methods of thiirane preparation have been reported in the literature. The most efficient route consists of the conversion of oxiranes into the corresponding thiiranes by an oxygen–sulfur exchange reaction. Various sulfur reagents such as inorganic thiocyanates,[1–3] thiourea,[3,4] phosphine sulfide,[5] potassium thiocyanate[6] supported on silica gel or dimethylthioformamide[7] were used to this end. However, all these methods lead to the preparation of racemic mixtures. Optically active thiiranes were obtained almost quantitatively in a similar reaction of enantiomerically enriched oxiranes with thiourea in methanol solution at room temperature. This procedure does not affect the chirality of the stereogenic center since no epimerization is observed.[8] Another known procedure involves the Ru(III)-catalyzed[9] conversion of optically active oxiranes into the corresponding thiiranes in the presence of ammonium thiocyanate. In this case, (*S*)-(−)-styrene sulfide was obtained from (*R*)-(+)-styrene oxide in high enantiomeric excess and excellent yield.

2. Results and discussion

In recent work,[10] we have described an attempt to prepare optically active thiiranes from enantiomerically enriched 1-aryloxy-3-thiocyanatopropan-2-ols. In our studies, however, only optically active polymers were obtained instead of the expected monomeric thiiranes. Nevertheless, the mixed chemo-enzymatic procedure seems to be a promising route to optically active thiiranes.

Herein, new acetates of 1-arylsulfanyl-3-thiocyanatopropan-2-ols were used as starting compounds. It was supposed that the intermediate 1-arylsulfanyl-3-thiocyanatopropan-2-ols **1** as well as acetates **2** might turn out to be better substrates in lipase-catalyzed racemate separations and thus ensure better overall results and higher enzyme enantioselectivity.

1-Arylsulfanyl-3-thiocyanatopropan-2-ols **1** were prepared according to a two-step procedure reported[10,11] previously for the preparation of 1-aryloxy-3-thiocyanatopropan-2-ols. It consisted in the crown ether-catalyzed reaction of the appropriate 2-(arylsulfanylmethyl)oxiranes with ammonium thiocyanate in an acetonitrile solution (Scheme 1).

Because of low stability (±)-**1a**–**d** were not isolated. Instead they were converted in situ into the corresponding acetates (±)-**2a**–**d** by reaction with acetyl chloride. As could be expected, addition of trace amounts of hydroquinone stabilized[11] (±)-**1a**–**d** in the reaction medium and increased the yields of (±)-**2a**–**d.** The latter were stable enough to be separated and purified.

According to the literature data,[12] Selectfluor can be used to replace the crown ether as the catalyst in the epoxide cleavage reaction. In our experiments, Selectfluor was used in the ring opening reactions of 2-(arylsulfanylmethyl)oxiranes by ammonium thiocyanate with no hydroquinone added. The reactions were carried out at reflux since at room temperature the reaction rate was very low and some substrate was still present in the mixture even after 48 h.

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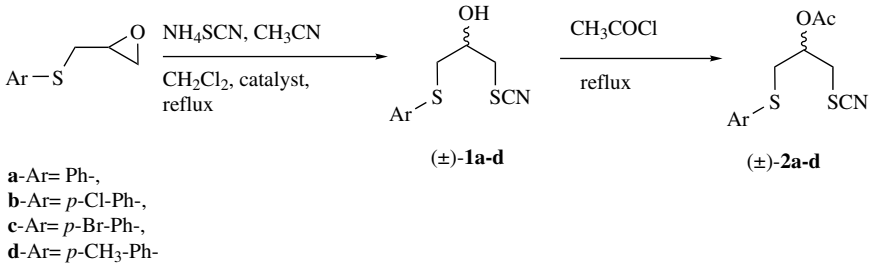


Scheme 1.

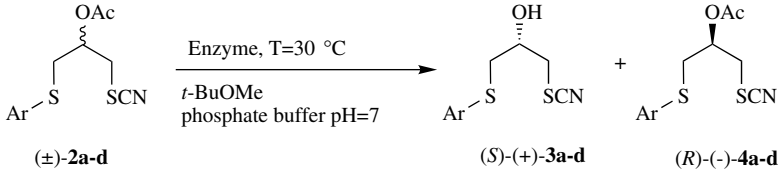
Table 1. The yields of acetates (±)-**2a**–**d** obtained with or without the addition of hydroquinone in the presence of a crown ether or Selectfluor catalyst

Entry	Ar–	Catalyst		
		18-Crown-6		Selectfluor
		Yield (%)	Yield (%) with hydroquinone	Yield (%)
a	Ph–	30	83	80
b	*p*-Cl–Ph–	36	69	68
c	*p*-Br–Ph–	64	80	65
d	*p*-CH_3–Ph–	40	68	70.5

Also in this case, (±)-**1a**–**d** were not isolated but converted in situ into (±)-**2a**–**d**. The yields were satisfactory and comparable with those obtained in the presence of 18-crown-6 with added hydroquinone. The relevant data are presented in Table 1.

The racemic mixtures of **2a**–**d** were then used as the substrates in a lipase-catalyzed hydrolysis, which was carried out at 30 °C in a two-phase *tert*-butyl methyl ether-phosphate buffer of pH 7 system, as shown in Scheme 2 (Table 2).

Three lipase preparations were tested in the reactions: Amano AK from *Pseudomonas sp*., Amano PS from *Pseudomonas cepacia*, and Novozym SP 435 from *Candida antarctica*. Only the last enzyme was capable of hydrolyzing (±)-**2a**–**d** with high stereoselectivity. In the case of (±)-**2c**, a satisfactory enantiomeric excess was also obtained with the Amano PS lipase. The progress of the reactions was monitored on TLC plates and the reactions were stopped at a conversion level of approximately 50%. In these reactions alcohols and esters of high enantiomeric purity were obtained. The (*R*)-configuration of the separated enantiomer of 1-phenylsulfanyl-3-thiocyanatopropan-2-yl acetate (−)-**4a** was determined by X-ray crystallography (Fig. 1).



Scheme 2.

Table 2. Results of lipase-catalyzed hydrolysis[a] of esters (±)-**2a**–**d**

Entry	Ar–	Enzyme	Time (h)	*c*[b] (%)	ee_s[c] (%)	ee_p[c] (%)	*E*[b]
a	Ph–	Novozym SP 435	116	48	90	96	>100
b	*p*-Cl–Ph–		72	37.5	58	98	>100
c	*p*-Br–Ph–		165	42	61	85	23
d	*p*-CH_3–Ph–		91	—	ND[d]	80	—
a	Ph–	Amano AK	96	44	21	27	2
b	*p*-Cl–Ph–		120	43	24	32	2
c	*p*-Br–Ph–		73	20	95	38	2
d	*p*-CH_3–Ph–		120	—	ND[d]	90	—
a	Ph–	Amano PS	96	71	94	38	7
b	*p*-Cl–Ph–		96	71.5	95	38	7
c	*p*-Br–Ph–		48	40	58	85	22
d	*p*-CH_3–Ph–		89	—	ND[d]	95	—

[a] Conditions: 1 g of (±)-**2a**–**d**, 40 mL of TBME (*tert*-butyl methyl ether), 200 mL of 0.1 M phosphate buffer KH_2PO_4–K_2HPO_4 (pH 7), 1 g of enzyme (Novozym SP 435, Amano AK or Amano PS lipase), temperature 30 °C.

[b] Conversion (*c*) and *E* values were calculated from the enantiomeric excess of substrate (acetate) (−)-**3a**–**d** (ee_s) and product (alcohol) (+)-**4a**–**d** (ee_p) using the formula: $E = \mathrm{Ln}[(1 - ee_s) * (ee_p/(ee_s + ee_p))]/\mathrm{Ln}[(1 + ee_s) * (ee_p/(ee_s + ee_p))]$, conv. $= ee_s/(ee_s + ee_p)$.

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

[d] ND—not determined.

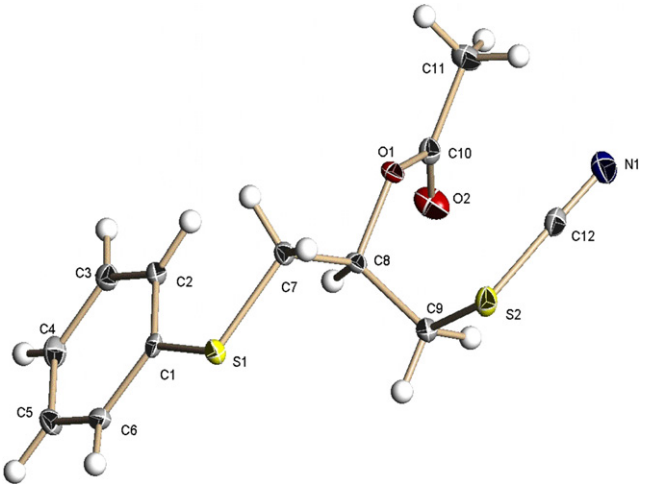
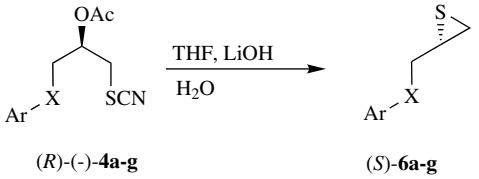


Figure 1. An ORTEP plot of (*R*)-(−)-1-phenylsulfanyl-3-thiocyanatopropan-2-yl acetate **4a** with thermal ellipsoids drawn at 50% probability level.

In an attempt to prepare 2-(arylsulfanylmethyl)thiiranes the solutions of optically active alcohols (*S*)-(+)-**3a** and (*S*)-(+)-**3b** were treated in ethanol with a few drops of a 60% aqueous solution of potassium hydroxide at room temperature. Upon a routine workup, optically active polymers (*S*)-(−)-**5a** and (*S*)-(−)-**5b** were isolated as the products (Scheme 3). The result is similar to that described earlier in our attempts to prepare 2-(aryloxymethyl)thiiranes from 1-aryloxy-3-thiocyanatopropan-2-ols.[10] Polymerization proceeds very fast under this condition, meaning that we were not able to isolate thiirane monomers. The results are in accordance with literature[1] data reporting the instability of thiiranes in the presence of both acids and bases. With nucleophiles, thiiranes are even more reactive than oxiranes[13] while ring opening at either the primary or the secondary carbon atom leads to a mixture of polymer isomers.

The following values of specific rotation were measured for **5a**: $[\alpha]_D^{24} = -8.7$ (*c* 1.61, $CHCl_3$), for **5b**: $[\alpha]_D^{24.6} = -7.5$ (*c* 2, $CHCl_3$). Molecular weights of the polymers measured by GPC in THF and referred to the polystyrene standard were $M_n = 1905.65$ and $M_w = 2701.50$ for **5a**; $M_n = 1139.22$ and $M_w = 2083.04$ for **5b**.

In order to avoid the thiirane polymerization, we changed the procedure and made the base react not with the alcohols (*S*)-(+)-**3a**–**d** but with their more stable acetates (*R*)-(−)-**4a**–**d**. Moreover, considering relatively small volume of the lithium cation, we used a solution of lithium hydroxide instead of potassium hydroxide. The reaction was carried out in a two-phase aqueous LiOH/THF system, thus the contact time of the formed thiirane and the base was considerably reduced. With those changes in procedure we were able to prepare the requested monomeric optically active 2-(arylsulfanylmethyl)thiiranes in good yields. Also, optically active 2-(aryloxymethyl)thiiranes **6e**–**g** were obtained from the previously described[10] 1-aryloxy-3-thiocyanatopropan-2-yl acetates (*R*)-(−)-**4e**–**g** by the same procedure (Scheme 4).



(*R*)-(-)-**4a-g** (*S*)-**6a-g**

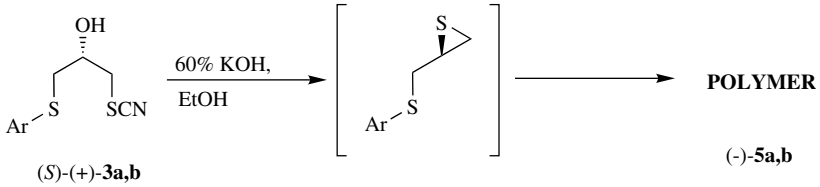
e-Ar-X= Ph-O-,
f-Ar-X= *p*-Cl-Ph-O-,
g-Ar-X= *p*-CH_3-Ph-O-

Scheme 4.

On the basis of the reaction mechanism proposed by Price and Kirk[14] (Scheme 5), it seems reasonable to assume that the optically active thiiranes prepared possess the opposite configuration to the starting 1-aryloxy- and 1-arylsulfanyl-3-thiocyanatopropan-2-ols or the corresponding acetates.

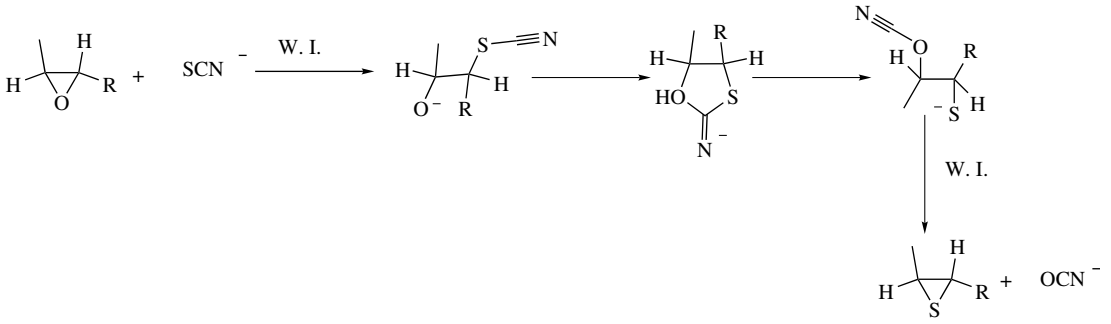
Determination of the enantiomeric excesses of the prepared thiiranes (*S*)-**6e**–**g** indicated that the conversion of acetates (*R*)-(−)-**4e**–**g** into the corresponding thiiranes did not affect the compounds enantiomeric purity; and no trace amounts of racemization were observed (Table 3). On the contrary, conversion of acetates (*R*)-(−)-**4a**–**d** into thiiranes **6a**–**d** is not so selective and some racemization was observed in the reaction (Table 3). The yields of the final step of thiiranes preparation ranged from 67% to 87% depending on the substrate used.

The opposite (*R*)-enantiomers of thiiranes **6a**–**g** are also directly available from alcohols (*S*)-(+)-**3a**–**g** obtained from a lipase-catalyzed hydrolyses of racemic thiocyanatoacetates **4a**–**g** (Scheme 6), or through the intermediate acetates. For example, (*S*)-(+)-**3a** (ee = 96%) reacted with lithium hydroxide, as described earlier gave the appropriate thiirane (*R*)-(−)-**6a** of 86% enantiomeric excess in 70% yield. Acetylation of the optically active alcohol (*S*)-(+)-**3a** (ee = 96%) with acetyl chloride gave the corresponding acetate (*S*)-(+)-**4a** in 81% yield with no change of enantiomeric excess; and the further reaction of (*S*)-(+)-**4a** with lithium hydroxide afforded thiirane (*R*)-(−)-**6a** in 65% yield and enantiomeric excess 82%.



(*S*)-(+)-**3a,b** (-)-**5a,b**

Scheme 3.

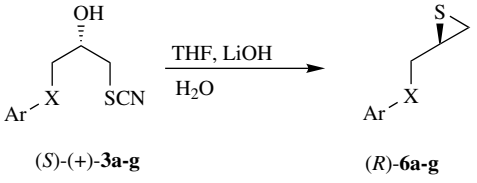


Scheme 5.

Table 3. Yields and properties of thiiranes (*S*)-**6a–g**

Entry	Ar–X–	ee_s (%)	ee_p (%)	$[\alpha]^{23}_{D\,s}$	$[\alpha]^{24}_{D\,p}$	Yield (%)
a	Ph–S–	90	86	−8.4	+71.4	79
b	*p*-Cl–Ph–S–	58	53	−0.65	+35.2	67
c	*p*-Br–Ph–S–	61	59	0	+33.0	84
d	*p*-CH_3–Ph–S–	ND[a]	32	−1.9	+24.2	71
e	Ph–O–	97	97	−49.3	−13.6	87
f	*p*-Cl–Ph–O–	90	90	−37.5	−12.5	83
g	*p*-CH_3–Ph–O–	86	86	−63.4	−10.7	76

[a] ND—not determined.



Scheme 6.

3. Conclusions

Lipase catalyzed enantiomer separation of 1-arylsulfanyl-3-thiocyanatopropan-2-yl acetates yields alcohols and esters of high enantiomeric purity. The highest enantioselectivities of the reaction ($E > 20$) were obtained with Novozym SP 435 from *C. antarctica*. Transformations of the optically active β-hydroxythiocyanatopropane derivatives into the corresponding enantiomerically enriched thiiranes were carried out in two phase aqueous LiOH/THF system.

4. Experimental

4.1. General

^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Mercury 400 MHz spectrometer in $CDCl_3$ solution; IR spectra were taken on a Carl Zeiss Specord M80 instrument. Ee's of the alcohols, esters, and thiiranes **6e–g** 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 for esters and alcohols and 95:5; 98:2; 99:1; 0.8 mL/min for thiiranes **6e–g**) using the corresponding racemic compounds as references. Ee's of thiiranes **6a–d** were determined on chromatograph fitted with the diode array detector (DAD) and Chiralpak AD-H column (in hexane:*iso*-propanol 95:5). Optical rotations were measured in a $CDCl_3$ solution with PolAAr 32 polarimeter. Elemental analyses were performed on a CHNSCl/O Perkin Elmer type 2400 instrument. The reactions were monitored by TLC on silica gel 60 (230–400 mesh). The arylsulfanylglycidyl ethers were prepared in high yields (80–85%) from the corresponding thiophenols and epichlorohydrin in a NaOH/THF suspension according to the described[15] method. The optically active 1-aryloxy-3-thiocyanatopropan-2-yl acetates (−)-**4f–g** were prepared by the lipase-catalyzed hydrolysis in a two-phase *tert*-butyl methyl ether-phosphate buffer system from the racemic mixtures.[10] Amano AK, Amano PS, and Novozym SP 435 (immobilized *C. antarctica*-B lipase) were kindly granted by Novo-Nordisk.

4.2. Preparation of 1-arylsulfanyl-3-thiocyanatopropan-2-yl acetates (±)-2a–d. General procedure

To the mixture of 2-(arylsulfanylmethyl)oxiranes (10 mmol) and NH_4SCN (10 mmol, 1.52 g) in acetonitrile (30 mL) a solution of 18-crown-6 ether in CH_2Cl_2 (0.1 mmol, 0.0264 g in 5 mL and traces of hydroquinone) or selectfluor (1 mmol, 0.39 g) 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 precipitate was filtered off and the solvent evaporated. The resulting crude mixture of β-hydroxythiocyanates 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, the traces of solid material were filtered off, the filtrate cooled in an ice bath and neutralized to pH 7 with 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 oily residue was purified by column chromatography on a silica gel with *n*-hexane–ethyl acetate (7:1 v/v) as the eluent. ^1H, ^{13}C NMR spectra, IR data, and elemental analyses of the prepared esters are reported below.

4.2.1. (±)-1-Phenylsulfanyl-3-thiocyanatopropan-2-yl acetate 2a. Colorless crystals, mp 50–51 °C. ^1H NMR ($CDCl_3$) δ ppm: 2.03 (s; 3H (CH_3)); 3.11–3.41 (m; 4H (CH_2SPh, CH_2SCN)); 5.18 (m; 1H (CH)); 7.22–7.42 (m; 5H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 20.57; 35.60; 35.83; 70.44; 111.65; 127.17; 129.26; 130.20; 134.00; 169.98. IR (Nujol, cm^{-1}) 2150 (CN); 1740 (CO). Anal. Calcd for $C_{12}H_{13}NS_2O_2$: C, 53.91; H, 4.90; N, 5.24; S, 23.98. Found: C, 53.95; H, 5.00; N, 5.16; S, 23.89.

4.2.2. (±)-1-(4-Chlorophenylsulfanyl)-3-thiocyanatopropan-2-yl acetate 2b. Oil, ^1H NMR ($CDCl_3$) δ ppm: 2.05 (s; 3H (CH_3)); 3.08–3.40 (m; 4H (CH_2SPh, CH_2SCN)); 5.16 (m; 1H (CH)); 7.26–7.35 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 20.57; 35.82; 35.89; 70.76; 111.53; 129.40; 131.54; 132.53; 133.31; 169.96. IR (film, cm^{-1}) 2150 (CN); 1740 (CO). Anal. Calcd for $C_{12}H_{12}NClS_2O_2$: C, 47.76; H, 4.01; N, 4.64; S, 21.25. Found: C, 47.83; H, 4.10; N, 4.75; S, 21.21.

4.2.3. (±)-1-(4-Bromophenylsulfanyl)-3-thiocyanatopropan-2-yl acetate 2c. Oil, ^1H NMR ($CDCl_3$) δ ppm: 2.06 (s; 3H (CH_3)); 3.08–3.41 (m; 4H (CH_2SPh, CH_2SCN)); 5.17 (m; 1H (CH)); 7.26–7.45 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 20.62; 35.69; 35.83; 70.76; 111.55; 121.24; 131.66; 132.35; 133.21; 170.00. IR (film, cm^{-1}) 2140 (CN); 1735 (CO). Anal. Calcd for $C_{12}H_{12}NBrS_2O_2$: C, 41.63; H, 3.49; N, 4.05; S, 18.52; Br, 23.08. Found: C, 41.65; H, 3.70; N, 4.11; S, 18.20; Br, 22.98.

4.2.4. (±)-3-Thiocyanato-1-(*p*-tolylsulfanyl)propan-2-yl acetate 2d. Oil, ^1H NMR ($CDCl_3$) δ ppm: 2.04 (s; 3H ($CO\mathit{CH}_3$)); 2.32 (s; 3H ($\mathit{CH}_3C_6H_4$)); 3.05–3.41 (m; 4H (CH_2SPh, CH_2SCN)); 5.15 (m; 1H (CH)); 7.11–7.32 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 20.57; 20.97; 35.82; 36.23; 70.94; 111.71; 123.89; 130.01; 130.20; 134.09; 169.96. IR (Nujol, cm^{-1}) 2140 (CN); 1730 (CO). Anal. Calcd for $C_{13}H_{15}NS_2O_2$: C, 55.49; H, 5.37; N, 4.98; S, 22.79. Found: C, 55.60; H, 5.51; N, 4.93; S, 22.71.

4.3. General procedure for enzyme-catalyzed hydrolysis of acetates (±)-2a–d

In a typical experiment, acetate (±)-**2a–d** (1 g) was dissolved in 40 mL of TBME (*tert*-butyl methyl ether). The solution was mixed with 0.1 M phosphate buffer KH_2PO_4–K_2HPO_4 (200 mL, pH 7), and 1 g of enzyme (Novozym SP 435, Amano AK or Amano PS lipase) was added. The mixture was stirred at 30 °C, and the conversion was monitored by TLC with *n*-hexane–ethyl acetate (3:1 v/v) as the eluent. After an appropriate time, the reaction was arrested by filtering off the enzyme and the products were extracted with diethyl ether (5×30 mL). The organic layers were combined, washed with water (3×50 mL), and dried over anhydrous $MgSO_4$, whereupon the solvent was evaporated. The mixture was separated by chromatography on a silica-gel column with *n*-hexane–ethyl acetate (5:1 v/v). NMR spectra of the enantiomerically enriched acetates (*R*)-(−)-**4a–d** were identical with those of (±)-**2a–d**. The specific rotations measured in $CHCl_3$ solution for the prepared enantiomerically enriched acetates are as follows:

(*R*)-(−)-**4a**: $[\alpha]_D^{28} = -8.4$ (c 5, $CHCl_3$) ee = 90%

(*R*)-(−)-**4b**: $[\alpha]_D^{23} = -0.65$ (c 9.21, $CHCl_3$) ee = 58%

(*R*)-**4c**: $[\alpha]_D^{23.5} = 0$ (c 4.30, $CHCl_3$) ee = 61%

(*R*)-(−)-**4d**: $[\alpha]_D^{23} = -1.9$ (c 5.14, $CHCl_3$) ee = ND

^1H and ^{13}C NMR spectra, as well as IR data and elemental analyses of the prepared optically active alcohols (+)-**3a–d** are reported below.

4.3.1. (*S*)-(+)-1-Phenylsulfanyl-3-thiocyanatopropan-2-ol 3a. Oil, yield 19%. ^1H NMR ($CDCl_3$) δ ppm: 2.96 (s; 1H (OH)); 3.02 (dd; 1H ($C\mathit{H}_aH_bSCN$); $J_{H_aCH} = 2.8$ Hz; $J_{H_aH_b} = 7.6$ Hz); 3.06 (dd; 1H ($CH_a\mathit{H}_bSCN$); $J_{H_bCH} = 2.4$ Hz); 3.17 (dd; 1H ($C\mathit{H}_cH_dSPh$) $J_{H_cCH} = 4.8$ Hz; $J_{H_cH_d} = 14$ Hz); 3.23 (dd; 1H ($CH_c\mathit{H}_dSPh$); $J_{H_dCH} = 4$ Hz); 3.99 (m; 1H (CH)); 7.30–7.42 (m; 5H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 39.08; 40.18; 68.38; 112.32; 127.38; 129.33; 130.64; 133.83. IR (film, cm^{-1}) 3450 (OH); 2150 (CN). $[\alpha]_D^{25} = +7.2$ (c 9.76, $CHCl_3$) ee 96%. Anal. Calcd for $C_{10}H_{11}NS_2O$: C, 53.30; H, 4.92; N, 6.22; S, 28.46. Found: C, 53.34; H, 5.22; N, 6.40; S, 28.23.

4.3.2. (*S*)-(+)-1-(4-Chlorophenylsulfanyl)-3-thiocyanatopropan-2-ol 3b. Colorless crystals; mp 52–53 °C, yield 15%. ^1H NMR ($CDCl_3$) δ ppm: 2.87 (s; 1H (OH)); 3.01 (dd; 1H ($C\mathit{H}_aH_bSCN$); $J_{H_aCH} = 6.4$ Hz; $J_{H_aH_b} = 7.6$ Hz); 3.05 (dd; 1H ($CH_a\mathit{H}_bSCN$); $J_{H_bCH} = 5.6$ Hz); 3.15 (dd; 1H ($C\mathit{H}_cCH_dSPh$); $J_{H_cCH} = 4.8$ Hz; $J_{H_cH_d} = 14$ Hz); 3.23 (dd; 1H ($CH_c\mathit{H}_dSPh$); $J_{H_dCH} = 4$ Hz); 3.99 (m; 1H (CH)); 7.26–7.35 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 39.05; 40.39; 68.41; 112.21; 129.47; 131.96; 132.46; 133.53. IR (film, cm^{-1}) 3445 (OH); 2150 (CN). $[\alpha]_D^{23} = +9.42$ ($CHCl_3$, c 4.67; ee 98%). Anal. Calcd for $C_{10}H_{10}NS_2ClO$: C, 46.24; H, 3.88; N, 5.39; S, 24.69; Cl, 13.65. Found: C, 46.04; H, 3.89; N, 5.30; S, 24.70; Cl, 13.57.

4.3.3. (*S*)-(+)-1-(4-Bromophenylsulfanyl)-3-thiocyanatopropan-2-ol 3c. Oil, yield 12%. ^1H NMR ($CDCl_3$) δ ppm: 2.99 (s; 1H (OH)); 3.02 (dd; 1H ($C\mathit{H}_aH_bSCN$); $J_{H_aCH} = 3.6$ Hz; $J_{H_aH_b} = 7.2$ Hz); 3.05 (dd; 1H ($CH_a\mathit{H}_bSCN$); $J_{H_bCH} = 3.2$ Hz); 3.15 (dd; 1H ($C\mathit{H}_cCH_dSPh$); $J_{H_cCH} = 5.2$ Hz; $J_{H_cH_d} = 13.6$ Hz); 3.24 (dd; 1H ($CH_c\mathit{H}_dSPh$); $J_{H_dCH} = 4$ Hz); 4.00 (m; 1H (CH)); 7.26–7.45 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 39.05; 40.09; 68.42; 112.26; 121.33; 131.98; 132.35; 133.24. IR (film, cm^{-1}) 3445 (OH); 2150 (CN). $[\alpha]_D^{23.5} = +6.4$ (c 1.71, $CHCl_3$) ee 85%. Anal. Calcd for $C_{10}H_{10}NS_2BrO$: C, 39.48; H, 3.31; N, 4.60; S, 21.08; Br, 26.26. Found: C, 39.60; H, 3.27; N, 4.58; S, 21.13; Br, 26.17.

4.3.4. (*S*)-(+)-1-Thiocyanato-3-(*p*-tolylsulfanyl)propan-2-ol 3d. Oil, yield 13%. ^1H NMR ($CDCl_3$) δ ppm: 2.33 (s; 3H (CH_3)); 2.86 (d; 1H (OH); $J_{OHCH} = 3.6$ Hz); 2.98 (dd;

1H (CH_aH_bSCN); $J_{H_aCH} = 7.6$ Hz; $J_{H_aH_b} = 13.2$ Hz); 3.03 (dd; 1H (CH_aH_bSCN); $J_{H_bCH} = 7.2$ Hz); 3.12 (dd; 1H (CH_cCH_dSPh); $J_{H_cCH} = 4.4$ Hz; $J_{H_cH_d} = 14$ Hz); 3.22 (dd; 1H (CH_cH_dSPh); $J_{H_dCH} = 4$ Hz); 3.96 (m; 1H (CH)); 7.13–7.33 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 21.05; 39.10; 41.04; 68.29; 112.30; 129.87; 130.16; 131.56; 137.91. IR (film, cm^{-1}) 3400 (OH); 2170 (CN). $[\alpha]_D^{27} = +5.7$ (c 0.87, $CHCl_3$) ee 80%. Anal. Calcd for $C_{11}H_{13}NS_2O$: C, 55.20; H, 5.47; N, 5.85; S, 26.79. Found: C, 55.48; H, 5.53; N, 5.68; S, 26.78.

4.4. General procedure for the conversion of acetates 4a–g to thiiranes 6a–g

In a typical experiment, optically active acetate **4a**–**d** (1 mmol) was dissolved in 17 mL of THF and a solution of $LiOH{\cdot}H_2O$ (4 mmol) in 5 mL H_2O was added. For compounds **4e**–**f**, 2 mmol of the acetate was dissolved in 28 mL of THF and a solution of $LiOH{\cdot}H_2O$ (4 mmol) in 5 mL H_2O was added. The mixture was stirred at room temperature and 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 (about 2 h), the organic layer was separated and the solvent was evaporated. The crude mixture was purified by chromatography on a short silica gel column with hexane–ethyl acetate (15:1 for thiiranes **6a**–**d** and 7:1 for thiiranes **6e**–**g**) as the eluent. ^{1}H, ^{13}C NMR spectra, and elemental analyses of the prepared thiiranes **6a**–**g** are reported below.

4.4.1. (*S*)-(+)-2-(Phenylsulfanylmethyl)thiirane 6a. Oil, yield 71%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.10 (dd; 1H ($CHCH_aH_bS$); $J_{H_aCH} = 1.6$ Hz; $J_{H_aH_b} = 5.2$ Hz); 2.48 (dd; 1H ($CHCH_aH_bS$); $J_{H_bCH} = 2.4$ Hz); 2.79 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_cCH} = 8.8$ Hz; $J_{H_cH_d} = 14$ Hz); 3.11 (m; 1H (CH)); 3.45 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_dCH} = 5.6$ Hz); 7.25–7.45 (m; 5H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 26.04; 33.57; 41.15; 127.07; 129.09; 131.05; 135.02. $[\alpha]_D^{24} = +71.4$ (c 6.78, $CHCl_3$) ee = 86%. Anal. Calcd for $C_9H_{10}S_2$: C, 59.30; H, 5.53; S, 35.18. Found: C, 59.55; H, 5.72; S, 34.98.

4.4.2. (*S*)-(+)-2-(4-Chlorophenylsulfanylmethyl)thiirane 6b. Oil, yield 67%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.10 (dd; 1H ($CHCH_aH_bS$); $J_{H_aCH} = 1.6$ Hz; $J_{H_aH_b} = 5.2$ Hz); 2.48 (dd; 1H ($CHCH_aH_bS$); $J_{H_bCH} = 2.4$ Hz); 2.80 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_cCH} = 8.4$ Hz; $J_{H_cH_d} = 13.6$ Hz); 3.07 (m; 1H (CH)); 3.39 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_dCH} = 4.8$ Hz); 7.26–7.38 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 25.91; 33.33; 41.30; 129.21; 132.36; 133.17; 133.54. $[\alpha]_D^{24} = +35.2$ (c 5.47, $CHCl_3$) ee = 53%. Anal. Calcd for $C_9H_9S_2Cl$: C, 49.87; H, 4.19; S, 29.59; Cl, 16.36. Found: C, 49.97; H, 4.23; S, 29.40.

4.4.3. (*S*)-(+)-2-(4-Bromophenylsulfanylmethyl)thiirane 6c. Oil, yield 84%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.11 (dd; 1H ($CHCH_aH_bS$); $J_{H_aCH} = 0.8$ Hz; $J_{H_aH_b} = 5.6$ Hz); 2.48 (dd; 1H ($CHCH_aH_bS$); $J_{H_bCH} = 1.2$ Hz); 2.81 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_cCH} = 8.4$ Hz; $J_{H_cH_d} = 13.6$ Hz); 3.07 (m; 1H (CH)); 3.39 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_dCH} = 4.8$ Hz); 7.28–7.45 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 25.92; 33.29; 41.08; 121.05; 132.12; 132.42; 134.26. $[\alpha]_D^{24} = +33.02$ (c 4.36, $CHCl_3$) ee = 59%. Anal. Calcd for $C_9H_9S_2Br$: C, 41.39; H, 43.47; S, 24.55; Br, 30.59. Found: C, 41.63; H, 3.26; S, 24.67; Br, 30.49.

4.4.4. (*S*)-(+)-2-(*p*-Tolylsulfanylmethyl)thiirane 6d. Oil, yield 71%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.06 (dd; 1H ($CHCH_aH_bS$); $J_{H_aCH} = 1.2$ Hz; $J_{H_aH_b} = 5.2$ Hz); 2.34 (s; 3H (CH_3)); 2.46 (dd; 1H ($CHCH_aH_bS$); $J_{H_bCH} = 2.4$ Hz); 2.73 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_cCH} = 8.8$ Hz; $J_{H_cH_d} = 13.6$ Hz); 3.09 (m; 1H (CH)); 3.40 (dd; 1H ($PhSCH_cH_dCH$); $J_{H_dCH} = 4.4$ Hz); 7.11–7.37 (m; 4H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 21.06; 26.06; 33.73; 41.81; 129.84; 131.17; 131.88; 137.38. $[\alpha]_D^{24} = +24.2$ (c 4.54, $CHCl_3$) ee = 32%. Anal. Calcd for $C_{10}H_{12}S_2$: C, 61.18; H, 6,16; S, 32.66. Found: C, 61.34; H, 6.20.

4.4.5. (*S*)-(−)-2-(Phenoxymethyl)thiirane 6e. Oil, yield 87%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.33–2.63 (m; 2H ($CHCH_2S$)); 3.28 (m; 1H (CH)); 3.91 (dd; 1H (OCH_aH_bCH); $J_{H_aCH} = 7.2$ Hz; $J_{H_aH_b} = 10$ Hz); 4.22 (dd; 1H (OCH_aH_bCH); $J_{H_bCH} = 5.2$ Hz); 6.91–7.32 (m; 5H (Ph)). ^{13}C NMR ($CDCl_3$) δ ppm: 24.00; 31.37; 72.53; 114.62; 121.21; 129.53; 158.20. $[\alpha]_D^{25} = -13.6$ (c 2.8, $CHCl_3$) ee = 97%. ^{1}H NMR and ^{13}C NMR spectra are identical with those given in the literature.[10]

4.4.6. (*S*)-(−)-2-(4-Chlorophenoxymethyl)thiirane 6f. Oil, yield 83%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.31–2.61 (m; 2H ($CHCH_2S$)); 3.25 (m; 1H (OCH_2CHCH_2S)); 3.89 (dd; 1H (OCH_aH_bCH); $J_{H_aCH} = 6.8$ Hz; $J_{H_aH_b} = 10$ Hz); 4.14 (dd; 1H (OCH_aH_bCH); $J_{H_bCH} = 5.6$ Hz); 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. $[\alpha]_D^{25} = -12.5$ (c 4.64, $CHCl_3$) ee = 90%. ^{1}H NMR and ^{13}C NMR spectra are identical with those given in the literature.[10]

4.4.7. (*S*)-(−)-2-(*p*-Tolyloxymethyl)thiirane 6g. Oil, yield 76%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.29 (s; 3H (CH_3)); 2.32–2.61 (m; 2H ($CHCH_2S$)); 3.26 (m; 1H ($CH_aH_bCHCH_2$)); 3.86 (dd; 1H (OCH_aH_bCH); $J_{H_aCH} = 7.2$ Hz; $J_{H_aH_b} = 10$ Hz); 4.19 (dd; 1H (OCH_aH_bCH); $J_{H_bCH} = 5.6$ Hz); 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. $[\alpha]_D^{25} = -10.7$ (c 4.48, $CHCl_3$) ee = 86%. ^{1}H NMR and ^{13}C NMR spectra are identical with those given in the literature.[10]

4.5. Assignment of absolute configuration of 1-phenylsulfanyl-3-thiocyanatopropan-2-yl acetate 4a

Crystal data concerning the structure of (−)-1-phenylsulfanyl-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. 512 frames were measured at 1.2° intervals with a counting time of 12 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction programs: CrysAlis CCD and CrysAlis RED.[16] The structure was solved by direct

Table 4. Crystal data and structure refinement details

Empirical formula	$C_{12}H_{13}NO_2S_2$
Formula weight	267.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorombic
Space group	*P*2(1)2(1)2(1)
Unit cell dimensions	$a = 7.9426(9)$ Å, $\alpha = 90°$ $b = 12.1238(16)$ Å, $\beta = 90°$ $c = 12.8644(15)$ Å, $\gamma = 90°$
Volume	1238.8(3) Å^3
Z	2
Calculated density	1.434 Mg/m^3
Absorption coefficient	0.418 mm^{-1}
F(000)	560
Crystal size	0.70 mm × 0.53 mm × 0.44 mm
Theta range for data collection	3.01–28.58°
Limiting indices	$-10 \leqslant h \leqslant 10$, $-16 \leqslant k \leqslant 12$, $-16 \leqslant l \leqslant 16$
Reflections collected/unique	11,354/2956 [R(int) = 0.0333]
Completeness to theta = 28.58	95.3%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2956/12/207
Goodness-of-fit on F^2	1.108
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0219$, $wR_2 = 0.0557$
R indices (all data)	$R_1 = 0.0227$, $wR_2 = 0.0565$
Absolute structure parameter	−0.05(5)
Extinction coefficient	0.0121(14)
Largest diff. peak and hole	0.195 and −0.219 e Å^{-3}

methods[17] and refined using SHELXL.[18] 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 $F_o^2 > 2\sigma(F_o^2)$ 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 and restraints on the C–H bond lengths were set for all hydrogen atoms. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in Ref. 19. Final results give $R_1 = 0.0219$ and $wR_2 = 0.557$ for 11,354 reflections with $I > 2\sigma(I)$. The absolute structure was established based on anomalous dispersion using the Flack parameter x.[20] 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 −0.05(5). Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 626648. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

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