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Kinetic resolution of heteroaryl β-hydroxy sulfides catalyzed by *Humicola lanuginosa* lipase

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Abstract—*Humicola lanuginosa* lipase-catalyzed resolution of heteroaryl substituted β-hydroxy sulfides by irreversible transesterification using vinyl acetate as acylating agent is discussed. The ee of the resolved alcohols was determined from the ^{1}H NMR of their corresponding (*S*)-(+)-*O*-acetylmandelic acid esters.

1. Introduction

The use of enzymes as chiral catalysts for the preparation of chiral non-racemic compounds has become an increasingly attractive alternative to conventional chemical methods. Lipases, have been shown to be versatile enzymes for kinetic resolution and desymmetrization of prostereogenic substrates in organic media.[1] However, it cannot be expected that every lipase always transforms a non-natural substrate in an optimal manner. Hence screening of all available lipases is required in hope of finding the most enantioselective one for a particular class of compound. Of all the commercially available lipases *Humicola lanuginosa lipase* (HLL), a fungal lipase, has not been extensively studied. Our recent studies[2] on HLL have shown that it has good potential as a chiral catalyst for the resolution of secondary alcohols in organic medium.

HLL (recently renamed *Thermomyces lanuginosa* lipase) is a 1,3 specific lipase, mainly used as a component in detergent formulations and is similar in structure to *Rhizomucor meihei* lipase. It has a molecular weight of 30 kDa and its X-ray structure[3] shows a helix, covering the superficial active site of the lipase in its closed conformation. According to the crystal structure of an HLL-inhibitor complex, the lipase has a hydrophobic crevice, which extends from the active site serine and accommodates the acyl chain. Tryptophan 89 (Trp 89) in the lid of the lipase plays an important role in positioning a substrate optimally in the active site for enantioselective acylation reaction.[4]

The synthetic utility of enantiomerically pure secondary alcohols is well documented.[5,6] Chiral hydroxy sulfides serve as intermediates in the synthesis of chiral oxiranes,[7] thiiranes,[8] tetrahydrofurans,[9] spiroketal pheromones,[10] and 4-acetoxyazetidinones.[11] The presence of an additional heteroatom in the molecule, placed at an appropriate position from the hydroxy group can provide additional versatility to chiral alcohols. Also, chiral alcohols appended to heterocycles are important synthons for the synthesis of biologically active compounds and can be used as chiral ligands in homogeneous asymmetric catalysis. Recently the synthesis of thioalkylpyridines and their potential as pyridine sp^2-nitrogen donor ligands for palladium-catalyzed allylic substitution have been reported by Chelucci[12] and Kellogg.[13] Similarly, enantiomerically pure 2-(1-hydroxyalkyl)pyridines have been found to be effective catalysts for the addition of diethylzinc to benzaldehyde.[14] Keeping in mind these literature reports, we planned to synthesize hydroxy sulfides linked to heterocycles including pyridine. In continuation of our interest in the application of HLL for the resolution of racemic secondary alcohols,[15] we report herein our studies on the effect of the presence of a heteroatom in the aromatic binding group on the rate of conversion and enantioselectivity.

2. Results and discussion

The enzymatic resolution of (±)-**1a** (Scheme 1) was carried out using two mass equivalent of lipase with vinyl acetate (10 equiv.) as acyl donor and as solvent at 24±1°C. In the preliminary experiments the catalytic efficiencies of HLL and CRL were evaluated and com-

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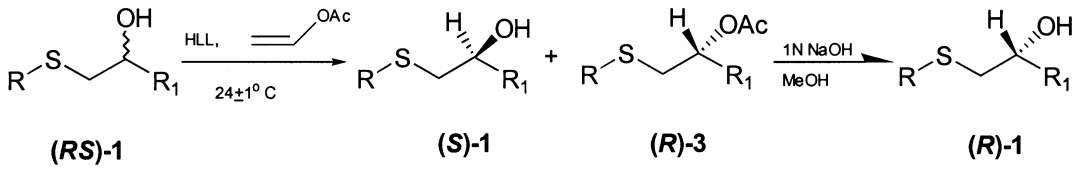


Scheme 1. HLL-catalyzed acylation of racemic alcohols (±)-**1a–e**.

pared (Table 1). The reactions were monitored by TLC and ^{1}H NMR to observe the degree of conversion. It was observed that although the reaction is faster with CRL as compared to HLL, the latter shows better enantiodiscrimination. So, all further reactions have been performed with HLL. It was also observed that when the extent of conversion reaches near 50% or more, the ee of the resolved acetate decreases and that of the unreacted alcohol increases. Thus, by controlling the extent of conversion both the enantiomers can be obtained in high enantiomeric purities (Table 2, entries 1 and 2). The exact degree of conversion was determined from the ^{1}H NMR of the crude reaction mixture. Column chromatography was used to separate the acetate from the unreactive alcohol. The absolute configuration and enantiomeric excess (ee) of the separated acetate and unreacted alcohol was determined by hydrolysis of the acetate and conversion of the resulting alcohols to the respective diastereomeric (*S*)-*O*-acetylmandelate ester derivatives. The enantiomeric ratio was calculated using the equations given by Chen et al.[16] According to Kazlauskas' rule for resolution of secondary alcohols with lipases,[17] which holds for *Rhizomucor meihei* lipase,[18] a lipase structurally similar to HLL,[19] transesterification should provide the acetates having (*R*)-configuration. So, the resolved acetates can be assigned (*R*)-configuration and the unreacted alcohol (*S*)-configuration. Also, in a homologous series the sign of the optical rotation remains the same for enantiomers so by comparison with the literature report[20] on 1-phenylthio-2-propanol, the (*S*)-alcohol is dextrorotatory. In the case of 1-(3-pyridylthio)propan-2-ol the unreactive enantiomer is dextrorotatory and the enantiomer kinetically acylated by lipase is levorotatory,

Table 1. Percentage conversion and $[\alpha]_D^{27}$ of **1a** with HLL and CRL at 24±1°C

S. No.	Lipase	Reaction time (h)	Conv. (%)	(*S*)-alcohol			(*R*)-alcohol		
				Yield	$[\alpha]_D^{27}$	ee (%)	Yield	$[\alpha]_D^{27}$	ee (%)
1	HLL	20	50	45	+28.8	65	42	−26.0	58
2	HLL	17	45	52	+29.5	66	44	−32.6	81
3	CRL	20	52	40	+17.3	39	49	−20.9	47
4	CRL	22	57	43	+26.1	52	52	−21.6	48

Table 2. Enantioselective acylation of **1a–e** by HLL[a] at 24±1°C

Entry	Substrate	R	R_1	Time (h)	Conv.[b] (%)	Yield[c] (*S*)-alc.	ee[d]-(*S*)-alc.	Yield[c] (*R*)-alc.	ee[d](*R*)-alc.	*E*[f]
1	1a		CH_3	12	33	62	38	31	96	71
2	1a			76	60	40	93	54	68	17
3	1b		CH_3	12	33	64	36	30	95	56
4	1c		CH_3	12	34	62	34	31	96	68
5	1d		CH_3	16	43	52	76	40	92	56
6	1e	CH_3CH_2		9 days	25	75	32	23	82	14
7	2	C_3H_7		11 days			No reaction			

[a] The substrate: enzyme ratio is 1: 2 w/w. [b] Percentage conversion was calculated with the help of ^{1}H NMR. [c] Yields refer to pure isolated products after column chromatography. [d] Enantiomeric excess calculated by ^{1}HNMR analysis of the corresponding acetylmandelic acid ester of the alcohol. [e] Overall yield of alcohol derived from hydrolysis of the initially formed chiral acetate. [f] Enantiomeric ratio (*E*) values were determined from the ee of residual substrate and extent of conversion. (Chen, Ch-Sh; Fujimoto, Y.; Girdaukas, G. and Sih, J. C. *J. Am. Chem. Soc.* **1982**, 104, 7294).

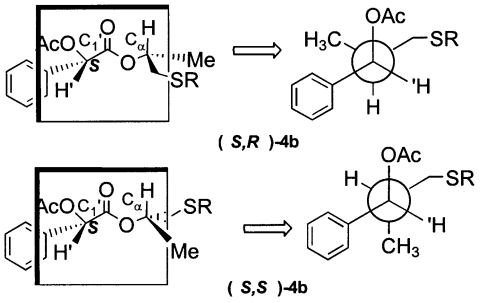


Figure 1. (*S*)-*O*-Acetylmandelic esters of **1b**.

which is in agreement with that predicted by Kazlauskas' rule.

Another important observation made in comparison with our earlier results[15] on the enzymatic resolution of 1-phenylthio-2-propanol (HLL, conv. = 46%, 36 h; CRL, conv. = 35%, 76 h) was that the time taken by **1a** to achieve approximately 50% conversion (24±1°C) was less in the cases of both CRL and HLL (Table 1). This effect may be attributed to the involvement of the pyridine nitrogen (a) in modulation of the general acid–base behavior of the lipase through changes in the protonation state of protein groups at the catalytic site of the enzyme, which enhances the catalytic activity of the lipase or (b) interaction with the α-helix forming the lid or flap covering the active site in such a way that it leads to opening of the lid, thus exposing the active site. The ability of organic bases like Et_3N and pyridine to enhance the activity of lipases in organic medium has been reported,[21] but their mode of action is not known. Since similar enhancement of the reaction was observed in the reaction of 3- and 4-pyridyl derivatives **1b**, **1c** and **1d**, so the increase in rate of reaction can be attributed to the π–π interactions between the electron deficient heterocyclic ring with the electron rich aromatic ring of the α-helix forming the lid. This results in opening of the lid, exposing the catalytic site of the lipase and hence giving the higher rate of reaction. Similar enantioselection ($E = 56$) was observed in the case of 1-(2-furylmethylthio)-2-propanol **1d**.

In the above examples the heterocyclic ring is separated from the stereogenic carbon center by a two-atom spacer. So as to assess the scope of HLL in catalyzing the acylation of secondary alcohols with stereogenic carbons directly attached to heterocyclic ring, resolution of **1e** was carried out. The reaction of **1e** under similar conditions was allowed to run for nine days to achieve 25% conversion and an enantioselectivity ratio (E) value of 14. But, a similar reaction with a phenyl ring attached directly to the stereogenic carbon showed no conversion even after 11 days. Naemura et al.[22] have observed similar inertness with *Pseudomonas fluorescence* lipase. Thus, the presence of a heteroatom (N or O) in the aromatic binding group modulates the enzymatic activity of HLL in such a way so as to enhance its activity.

3. Determination of enantiomeric excess (ee)

The enantiomeric excess of the resolved alcohols were determined using ^{1}H NMR. Chiral shift reagents like $Pr(tfc)_3$ and $Eu(hfc)_3$ were not effective in resolving the methyl and methine signals in the enantiomers, which is required for enantiomeric excess determination. To overcome this, diastereomeric *S*-(+)-*O*-acetylmandelate esters of the resolved (*R*)- and (*S*)-**1b** were prepared with *S*-(+)-*O*-acetylmandelic acid. The enantiomeric excess of the resolved alcohols could be calculated via integration of the signal for the methine protons of the mandelate ester in the ^{1}H NMR spectra of the respective (*S*)-(+)-*O*-acetylmandelic acid ester. Proton NMR has since been used to determine the absolute configuration of secondary alcohols, by correlating the NMR spectra of mandelic acid esters with absolute configuration.[23] Similarly, from the observed chemical shift of methyl and methine protons, a correlation of the chemical shift with absolute configuration at the carbinol carbon (Cα) can be developed (Fig. 1). In the ^{1}H NMR (Table 3) of the *S*-(+)-*O*-acetylmandelic esters of the (*S*)-alcohols, methyl (CH_3) and methine proton (H′) are observed downfield, while for (*R*)-alcohols the signals are upfield. The ^{1}H NMR showed separate signals for these protons in all the diastereomeric esters except **4a**, where the methine signal at δ 5.87 ppm was not resolvable initially. This signal was resolved by titrating with 0.1 M $Pr(tfc)_3$ to give two signals at δ 5.88 and 5.85 ppm for (*S*,*S*)-**4a** and (*S*,*R*)-**4a** diastereomers, respectively (Fig. 2).

Further, we performed energy minimization[24] studies on (*S*,*S*)-**4b** and (*S*,*R*)-**4b** diastereomers using augumented MM3, followed by an optimized geometry cal-

Table 3. Chemical shift values of methine ($\delta_{H'}$) and methyl protons(δ_{CH3}) of the (*S*,*S*)-**4** and (*S*,*R*)-**4** diastereomers

Substrate	Chemical shifts (ppm)					
	$\delta_{H'(S,S)}$	$\delta_{H'(S,R)}$	$\Delta\delta_{H'}$	$\delta_{CH3(S,S)}$	$\delta_{CH3(S,R)}$	$\Delta\delta_{CH3}$
4a	5.88[a]	5.85[a]	0.03[a]	1.38	1.18	0.20
4b	5.88	5.84	0.04	1.26	1.13	0.13
4c	5.82	5.80	0.02	1.37	1.20	0.17
4d	5.86	5.83	0.03	1.19	1.01	0.18
4e	5.98	5.96	0.02	–	–	–

[a] The initial overlapping signal at δ 5.87 ppm due to both of the diastereomers were resolved by addition of Lanthanide shift reagent $Pr(tfc)_3$.

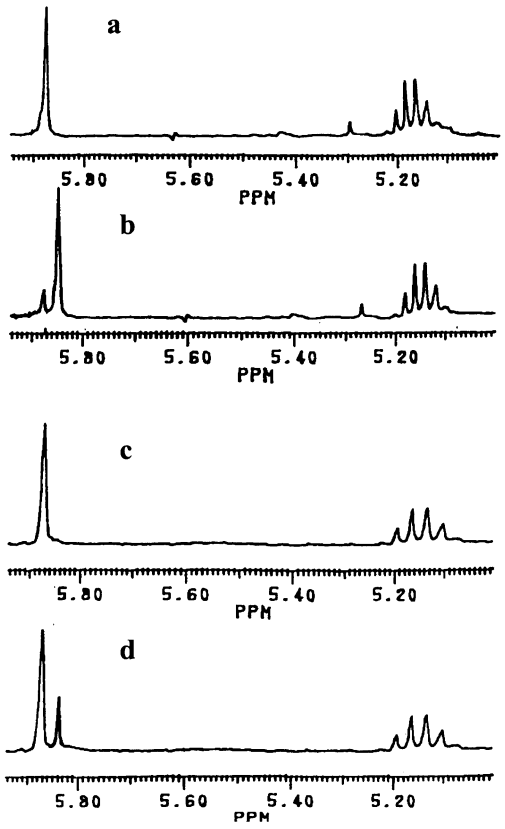


Figure 2. 200 MHz ^{1}H NMR spectrum (a) (*S*,*R*)-**4a**; (b) (*S*,*R*)-**4a**+0.1 M $Pr(tfc)_3$; (c) (*S*,*S*)-**4a**; (d) (*S*,*S*)-**4a**+0.1 M $Pr(tfc)_3$.

culations in MOPAC using PM3 parameters and have found that the (*S*,*R*)-diastereomer has approximately 1 kcal/mole lower energy than the (*S*,*S*)-diastereomer. Also, comparison of the energy minimized structures (Fig. 3), shows that the methine proton and the C=O group of the mandelate esters are *synperiplanar* (*sp*) to each other in the (*S*,*S*)-diastereomer ($\delta_{H'(S,S)}=5.88$ ppm) and *antiperiplanar* (*ap*) in (*S*,*R*)-diastereomer ($\delta_{H'(S,R)}=5.84$ ppm), indicating that the configuration at the carbinol carbon (C_α) controls the conformation around the C_1'–C=O bond, which gives rise to chemical shift differences of C_1'-H′ signal. The difference in chemical shifts of methyl protons of the esters is due to their different orientations in the anisotropic magnetic field around the phenyl ring (Table 3). Thus this difference in chemical shift ($\Delta\delta$) for the same proton in (*S*,*S*)- and (*S*,*R*)-diastereomers allows the determination of the absolute configuration of the chiral alcohols.

4. Conclusion

We have shown that heteroaryl β-hydroxy sulfides can be resolved with HLL, with enantiomeric ratios (*E*) ranging from 14 to 71. By hydrolysis of the optically active acetates **3a**–**e**, which are the products of the lipase-catalyzed acetylation, both enantiomers of these potentially useful building blocks are available. The utilization of *S*-(+)-*O*-acetylmandelic acid has allowed evaluation of enantiomeric purity and based on ^{1}H NMR and energy minimization studies, a correlation of chemical shift with absolute stereochemical assignment can be done. It is also concluded that Kazlauskas' rule, ^{1}H NMR of *S*-(+)-*O*-acetylmandelic acid esters and energy minimization studies are in close agreement.

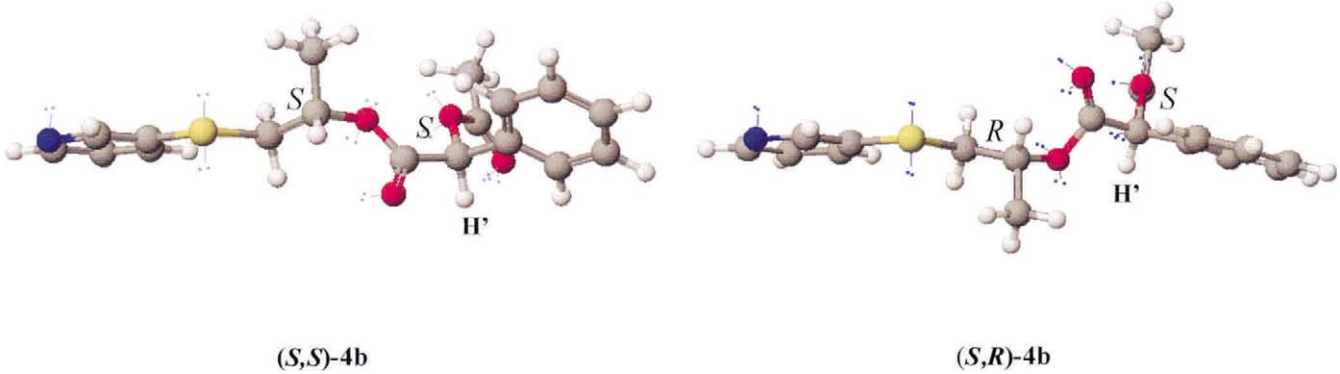
5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ containing 0.03% Me_4Si as internal standard on Bruker NMR spectrometers at 200 or 300 MHz. Chemical shifts are expressed as δ downfield from the TMS and *J* values are in Hz. When necessary, assignments were aided by DEPT-135 and decoupling experiments. IR spectra were obtained with Nicolet Avatar 320 FTIR. Mass spectra were recorded on GCMS-QP-2000 mass spectrometer by EI method. The specific rotation $[\alpha]_D^{27}$ was measured in CH_2Cl_2 with a Jasco DIP-360 digital polarimeter.

5.2. General procedure for the synthesis of racemic 1a–e

The method given by Crumbie et al.[20] was used for the preparation of starting compounds **1a**–**e**. To a well stirred solution of the sodium thiolate, prepared from sodium ethoxide (0.11 moles) and the respective thiol (0.10 moles) was added dropwise, a solution of corre-



(*S*,*S*)-4b (*S*,*R*)-4b

Figure 3. Energy minimized conformations of (*S*,*S*) and (*S*,*R*)-**4b**.

sponding α-haloketone (0.12 moles) in absolute alcohol (10 mL) over 30 min. Stirring was further continued for 2 h before filtering off the precipitated sodium chloride. The filtrate was concentrated under reduced pressure and the resulting viscous oil was diluted with water (10 mL) and extracted with ethyl acetate (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude thioketone, which was reduced with $NaBH_4$ in ethanol. To a stirred solution of the parent ketone (0.1 moles) in ethanol (30 mL), $NaBH_4$ (1.85 g, 0.05 moles) was added in small portions. The mixture was stirred until the reduction was complete (TLC). The reaction mixture was extracted with ethyl acetate. The organic layer was dried and evaporated to yield the crude product, which was purified by column chromatography with 60–120 mesh silica gel using hexane–ethyl acetate (90:10) as eluent. All compounds have been completely characterized.

5.2.1. (*RS*)-1-(2-Pyridylthio)propan-2-ol 1a. Yellow liquid; yield = 80%; IR (Neat): 3391, 2972, 1579, 1351, 1043, 759, 722 cm^{-1}; MS (m/z): 169 (M^+), 151 (M−18), 124, 111, 94, 79, 71 (100); ^1H NMR ($CDCl_3$): δ 1.31 (d, 3H, J = 6.2 Hz, CH_3), 1.63 (bs, 1H, OH), 3.15 (dd, 1H, J = 14.7 and 6.8 Hz, CH_2), 3.35 (dd, 1H, J = 14.7 and 2.8 Hz, CH_2), 4.16 (d quartet, 1H, J = 6.4 and 2.8 Hz, CH), 7.01–7.07 (m, 1H, ArH), 7.28–7.33 (m, 1H, ArH), 7.48–7.52 (m, 1H, ArH), 8.35–8.38 (m, 1H, ArH); ^{13}C NMR/DEPT ($CDCl_3$): δ 21.51 (+ve, CH_3), 37.94 (-ve, CH_2), 66.05 (+ve, CH), 118.58 (+ve, C-Ar), 121.33 (+ve, C-Ar), 135.20 (+ve, C-Ar), 147.76 (+ve, C-Ar), 157.89 (C-Ar).

5.2.2. (*RS*)-1-(3-Pyridylthio)propan-2-ol 1b. Pale yellow liquid; yield = 75%; IR (Neat): 3310, 3023, 2967, 1404, 1272, 704 cm^{-1}; MS (m/z): 169 (M^+), 151 (M −18), 135, 124, 96, 78, 73, 71; ^1H NMR ($CDCl_3$): δ 1.31 (d, 3H, J = 6.2 Hz, CH_3), 2.99 (dd, 1H, J = 13.6 and 8.0 Hz, CH_2), 3.11 (dd, 2H, J = 13.6 and 4.2 Hz, 1H of CH_2 and 1H of OH), 3.85–3.94 (m, 1H, CH), 7.21–7.28 (m, 1H, ArH), 7.70–7.76 (m, 1H, ArH), 8.43–8.46 (m, 1H, ArH), 8.61–8.62 (d, 1H, J = 1.8 Hz); ^{13}C NMR/ ($CDCl_3$): δ 22.14 (CH_3), 42.64 (CH_2), 65.76 (CH), 123.62 (C-Ar), 133.84 (C-Ar), 137.26 (C-Ar), 146.43 (C-Ar), 149.48 (C-Ar).

5.2.3. (*RS*)-1-(4-Pyridylthio)propan-2-ol 1c. Light brown solid; yield = 83%; MP: 52°C (CH_2Cl_2/hexane); IR (KBr): 3380, 3020, 2971, 1550, 1030, 694 cm^{-1}; MS (m/z): 169 (M^+), 152, 151 (M−18), 124, 110, 92, 83, 77, 71, 58 (100); ^1H NMR ($CDCl_3$): δ 1.34 (d, 3H, J = 6.2 Hz, CH_3), 2.55 (brs, 1H, OH), 2.99 (dd, 1H, J = 13.6 and 7.3 Hz, CH_2), 3.11 (dd, 1H, J = 13.6 and 4.7 Hz, CH_2), 3.95–4.05 (m, 1H, CH), 7.13 (d, 2H, J = 6.2 Hz, ArH), 8.37 (d, 2H, J = 6.1 Hz, ArH); ^{13}C NMR/DEPT ($CDCl_3$): δ 22.51 (+ve, CH_3), 39.28 (-ve, CH_2), 65.48 (+ve, CH), 120.70 (+ve, C-Ar), 148.33 (+ve, C-Ar), 149.73 (C-Ar). Found C, 56.62; H, 6.43; N, 8.41; S, 18.86; $C_8H_{11}NOS$ requires C, 56.77; H, 6.55; N, 8.28 and S, 18.95%.

5.2.4. (*RS*)-1-(Furan-2-ylmethylthio)propan-2-ol 1d. Brown oil; yield = 64%; IR (Neat): 3398, 2940, 1580, 1430, 730 cm^{-1}; MS (m/z): 172 (M^+), 129, 128, 127, 113, 112, 81, 71, 57 (100); ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, J = 6.2 Hz, CH_3), 2.39 (dd, 2H, J = 13.6 and 8.7 Hz, 1H of CH_2 and 1H of OH), 2.68 (dd, 1H, J = 13.8 and 3.5 Hz, CH_2), 3.65–3.82 (m, 3H, 2H of CH_2 and 1H of CH), 6.17 (d, 1H, J = 3.13 Hz, ArH), 6.31–6.35 (m, 1H, ArH), 7.35 (d, 1H, J = 1.27 Hz, ArH); ^{13}C NMR/DEPT ($CDCl_3$): δ 22.06 (+ve, CH_3), 28.33 (-ve, CH_2), 40.42 (-ve, CH_2), 65.98 (+ve, CH), 107.50 (+ve, C-Ar), 110.36 (+ve, C-Ar), 141.93 (+ve, C-Ar), 151.44 (C-Ar).

5.2.5. (*RS*)-2-Ethylthio-1-thiophen-2-yl-ethanol 1e. Yellow liquid; yield = 63%; IR (Neat): 3450, 2930, 2890, 1460, 1045, 715 cm^{-1}; MS (m/z): 188 (M^+), 187, 170, 149, 143, 125 (100), 83, 71; ^1H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.4 Hz, CH_3), 2.57 (q, 2H, J = 7.4 Hz, CH_2), 2.86 (dd, 1H, J = 13.8 and 8.5 Hz, CH_2), 3.02 (dd, 1H, J = 13.8 and 4.2 Hz, CH_2), 3.17 (d, 1H, J = 3.0 Hz, OH), 4.99–5.03 (m, 1H, CH), 6.95–7.01 (m, 2H, ArH), 7.24–7.27 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.76 (CH_3), 26.20 (CH_2), 41.44 (CH_2), 68.17 (CH), 123.84 (C-Ar), 124.69 (C-Ar), 126.62 (C-Ar), 146.26 (C-Ar).

5.2.6. (*RS*)-2-Propylthio-1-phenylethanol 2. Colorless liquid; yield = 74%; IR (Neat): 3482, 3029, 2960, 1087 cm^{-1}; MS (m/z): 197 (M^+), 182, 168, 154, 122, 77, 58 (100); ^1H NMR ($CDCl_3$): δ 1.00 (t, 3H, J = 7.3 Hz, CH_3), 1.63 (sextet, 2H, J = 7.3 Hz, CH_2), 2.53 (t, 2H, J = 7.3 Hz, CH_2), 2.70 (dd, 1H, J = 13.8 and 9.5 Hz, CH_2), 2.94 (dd, 1H, J = 13.8 and 3.6 Hz, CH_2), 3.02 (d, 1H, 2.4 Hz, OH), 4.70–4.77 (m, 1H, CH), 7.29–7.38 (m, 5H, ArH); ^{13}C NMR/ DEPT ($CDCl_3$): δ 13.25 (+ve, CH_3), 22.80 (-ve, CH_2), 34.06 (-ve, CH_2), 41.74 (-ve, CH_2), 71.66 (+ve, CH), 125.65 (+ve, C-Ar), 127.58 (+ve, C-Ar), 128.27 (+ve, C-Ar), 142.52 (C-Ar).

5.3. General procedure for resolution

To a solution of the (*RS*)-**1a** (338 mg, 2 mmol) and vinyl acetate (1.8 mL, 20 mmol) in a 25 mL round bottom flask, HLL (676 mg, 2 equiv. w/w) was added and the reaction mixture stirred at 24±1°C and monitored by taking ^1H NMR of aliquots taken at regular intervals. The reaction was stopped by filtering the enzyme on a sintered glass funnel. Concentration of the filtrate followed by column chromatography provided (*R*)-**3a** and (*S*)-**1a**.

5.4. (*R*)-(−)-1-(2-Pyridylthio)propan-2-yl acetate 3a

Pale yellow liquid; $[\alpha]_D^{27} = -42.2$ (c 0.62, CH_2Cl_2); IR: 3060, 2980, 2935, 1735, 1115, 758 cm^{-1}; MS (m/z): 211 (M^+), 196, 169 (100), 168, 136, 125, 111, 110, 71; ^1H NMR ($CDCl_3$): δ 1.35 (d, 3H, J = 6.3 Hz, CH_3), 1.98 (s, 3H, OAc), 3.31 (dd, 1H, J = 13.9 and 6.6 Hz, CH_2), 3.48 (dd, 1H, J = 13.9 and 5.4 Hz, CH_2), 5.11 (sextet, 1H, J = 6.0 Hz, CH), 6.93–6.99 (m, 1H, ArH), 7.15–7.27 (m, 1H, ArH), 7.41–7.50 (m, 1H, ArH), 8.40 (d, 1H, ArH, J = 4.7 Hz); ^{13}C NMR/DEPT ($CDCl_3$): δ 18.90 (+ve, CH_3), 20.74 (+ve, CH_3), 34.12 (-ve, CH_2), 69.37

(+ve, CH), 119.08 (+ve, C-Ar), 121.86 (+ve, C-Ar), 135.47 (+ve, C-Ar), 148.96 (+ve, C-Ar), 157.69 (ab, C-Ar), 169.44 (C=O).

5.4.1. (*S*)-(+)-1-(2-Pyridylthio)propan-2-ol (*S*)-(+)-1a. Yellow liquid; $[\alpha]_D^{27}=+15.8$ (*c* 0.85 CH_2Cl_2) for 38% ee.

5.4.2. (*R*)-(−)-1-(3-Pyridylthio)propan-2-yl acetate 3b. Colorless liquid; $[\alpha]_D^{27}=-1.2$ (*c* 0.50, CH_2Cl_2); IR (film): 3048, 2921, 1737, 1404, 1372, 1238 cm^{-1}; MS (*m*/*z*): 211 (M^+), 210, 196, 165, 149 (100), 124, 110, 78, 73; ^1H NMR ($CDCl_3$): 1.34 (d, 3H, $J=6.3$ Hz, CH_3), 1.98 (s, 3H, OAc), 3.00 (dd, 2H, $J=13.9$ and 5.9 Hz, 1H of CH_2), 3.16 (dd, 1H, $J=13.9$ and 6.3 Hz, CH_2), 4.98–5.08 (m, 1H, CH), 7.20–7.25 (m, 1H, ArH), 7.71–7.78 (m, 1H, ArH), 8.42–8.46 (m, 1H, ArH), 8.61–8.62 (d, 1H, $J=2.0$ Hz, ArH); ^{13}C NMR/($CDCl_3$): 19.13 (CH_3), 21.03 (CH_3), 39.16 (CH_2), 69.45 (CH), 123.67 (C-Ar), 137.47 (C-Ar), 147.44 (C-Ar), 150.67 (C-Ar), 170.39 (C=O).

5.4.3. (*S*)-(+)-1-(3-Pyridylthio)propan-2-ol[(*S*)-(+)-1b]. Pale yellow liquid; $[\alpha]_D^{27}=+18.6$ (*c* 0.62, CH_2Cl_2) for 36% ee.

5.4.4. (*R*)-(+)-1-(4-Pyridylthio)propan-2-yl acetate (3c). Colorless oil; $[\alpha]_D^{27}=+8.2$ (*c* 0.36, CH_2Cl_2); IR (film): 3052, 2970, 1732, 1450, 702 cm^{-1}; MS (*m*/*z*): 211 (M^+), 210, 196, 165, 149 (100), 124, 110, 78, 73; ^1H NMR ($CDCl_3$):1.38 (d, 3H, $J=6.3$ Hz, CH_3), 1.98 (s, 3H, OAc), 2.94 (dd, 1H, $J=13.8$ and 7.0 Hz, CH_2), 3.28 (dd, 1H, $J=13.8$ and 5.6 Hz, CH_2), 5.06 (sextet, 1H, $J=6.3$ Hz, CH), 7.20 (d, 2H, $J=6.1$ Hz, ArH), 8.40 (d, 2H, $J=5.6$ Hz, ArH); ^{13}C NMR/DEPT ($CDCl_3$): 19.20 (+ve, CH_3), 20.52 (+ve, CH_3), 36.44 (-ve, CH_2), 69.11 (+ve, CH), 120.52 (+ve, C-Ar), 149.55 (+ve, C-Ar), 148.65 (ab, C-Ar), 170.24 (ab, C=O).

5.4.5. (*S*)-(+)-1-(4-Pyridylthio)propan-2-ol (*S*)-(+)-1c. Colorless liquid; $[\alpha]_D^{27}=+10.2$ (*c* 0.56, CH_2Cl_2) for 34% ee.

5.4.6. (*R*)-(+)-1-(Furan-2-ylmethylthio)propan-2-yl acetate 3d. Brown oil; $[\alpha]_D^{27}=+20.4$ (*c* 0.76, CH_2Cl_2); IR (film): 3050, 2984, 2940, 1730, 760 cm^{-1}; MS (*m*/*z*): 214, 199, 169, 112, 71, 53, 51; ^1H NMR ($CDCl_3$): 1.29 (d, 3H, $J=6.3$ Hz, CH_3), 2.05 (s, 3H, OAc), 2.52 (dd, 1H, $J=13.9$ and 6.2 Hz, CH_2), 2.64 (dd, 1H, $J=13.9$ and 6.3 Hz, CH_2), 3.72 (s, 2H, CH_2), 4.97 (sextet, 1H, $J=6.2$ Hz, CH), 6.17–6.18 (m, 1H, ArH), 6.28–6.29 (m, 1H, ArH), 7.34 (m, 1H, ArH); ^{13}C NMR/DEPT ($CDCl_3$): 19.16 (+ve, CH_3), 21.07 (+ve, CH_3), 28.36 (-ve, CH_2), 36.51 (-ve, CH_2), 69.26 (+ve, CH), 107.69 (+ve, C-Ar), 110.31 (+ve, C-Ar), 141.99 (+ve, C-Ar), 151.22 (ab, C-Ar), 169.72 (ab, C=O).

5.4.7. (*S*)-(+)-1-(Furan-2-ylmethylthio)propan-2-ol (*S*)-(+)-1d. Pale yellow liquid; $[\alpha]_D^{27}=+52.8$ (1.03, CH_2Cl_2) for 76% ee.

5.4.8. (*R*)-(+)-2-Ethylthio-1-thiophen-2-yl-ethyl acetate 3e. Yellow liquid; $[\alpha]_D^{27}=+56.4$ (*c* 0.56, CH_2Cl_2); IR (film): 3052, 2942, 1731, 1238, 1050, 712 cm^{-1}; MS (*m*/*z*):230 (M^+), 201, 187, 169, 155; ^1H NMR ($CDCl_3$): 1.23 (t, 3H, $J=7.4$ Hz, CH_3), 2.10 (s, 3H, OAc), 2.52 (q, 2H, $J=7.3$ Hz, CH_2), 2.80 (dd, 1H, $J=13.5$ and 5.9 Hz, CH_2), 3.03 (dd, 1H, $J=13.8$ and 7.4 Hz, CH_2), 4.62–4.74 (m, 1H, CH), 6.97–7.00 (m, 2H, ArH), 7.26–7.29 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$): 14.71 (CH_3), 22.95 (CH_3), 23.75 (CH_2), 38.74 (CH_2), 67.73 (CH), 128.69 (C-Ar), 130.51 (C-Ar), 132.55 (C-Ar), 136.52 (C-Ar), 167.06 (C=O).

5.4.9. (*S*)-(+)-2-Ethylthio-1-thiophen-2-yl-ethanol (*S*)-(−)-1e. Brown liquid: $[\alpha]_D^{27}=-6.9$ (*c* 1.50, CH_2Cl_2) for 32% ee.

5.5. Chemical hydrolysis of the (*R*)-acetates 3a–e

To a solution of (*R*)-**3a**–**e** (2 mmol) in a solution of methanol and water (4:1, 8 mL), 1 N aqueous NaOH (2.0 mL, 2 mmol) was added. The solution was stirred at room temperature until the hydrolysis was complete (TLC). The solution was extracted with chloroform, dried with anhydrous Na_2SO_4 and evaporated to give (*R*)-**1a**–**e**.

5.5.1. (*R*)-(−)-1-(2-Pyridylthio)propan-2-ol (*R*)-(−)-1a. $[\alpha]_D^{27}=-37.4$ (*c* 0.40, CH_2Cl_2) for 96% ee.

5.5.2. (*R*)-(−)-1-(3-Pyridylthio)propan-2-ol (*R*)-(−)-1b. $[\alpha]_D^{27}=-49.2$ (*c* 0.44, CH_2Cl_2) for 95% ee.

5.5.3. (*R*)-(−)-1-(4-Pyridylthio)propan-2-ol (*R*)-(−)-1c. $[\alpha]_D^{27}=$-26.2 (*c* 0.22, CH_2Cl_2) for 96% ee.

5.5.4. (*R*)-(−)-1-(Furan-2-ylmethylthio)propan-2-ol (*R*)-(−)-1d. $[\alpha]_D^{27}=-67.9$ (*c* 0.47, CH_2Cl_2) for 92% ee.

5.5.5. (*R*)-(−)-2-Ethylthio-1-thiophen-2-yl-ethanol (*R*)-(+)-1e. $[\alpha]_D^{27}=+25.1$ (*c* 0.43, CH_2Cl_2) for 82% ee.

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