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Chemoenzymatic synthesis of enantiomerically pure terminal 1,2-diols

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Abstract—A new practical method for the enzymatic synthesis of 1,2-diols has been developed by employing a lipase catalyzed one-pot transesterification protocol. A series of substituted α-acetoxyphenylethanones **3a**–**g** have been reduced to the corresponding alcohols under mild conditions employing sodium borohydride and moist neutral alumina, and further subjected for lipase catalyzed irreversible transesterification in the same pot to give mono- and diacetate diols (*R*)-**4** and (*S*)-**5**, which on hydrolysis afforded terminal 1,2-diols, (*R*)- and (*S*)-**6** in high enantiomeric excess.

1. Introduction

Enantiomerically pure 1,2-diols are valuable intermediates in organic synthesis of biologically active compounds and natural products.[1] They are readily transformed into chiral epoxides,[2a] aziridines and amino alcohols.[2b,c] Moreover, the 1,2-diol functionality is found in a number of synthetic[3a] and pharmaceutical intermediates.[3b] The necessity of preparing such chiral entities has triggered modern researchers to investigate various synthetic methods such as chemical asymmetric induction and enzymatic or biocatalytic transformations. Foremost among these methods are the catalytic asymmetric dihydroxylation of olefins,[3] oxazaborolidine-catalyzed asymmetric reduction[4] of α-hydroxy ketones. Biocatalytic methods such as hydrolysis of epoxides with epoxide hydrolases,[5] lipase mediated kinetic resolution of vicinal diols,[6] and microbial reduction of α-hydroxy ketones and α-acetoxy ketones[7] have been applied for the synthesis of enantiomerically pure 1,2-diols. Direct lipase catalyzed transesterification of 1,2-diols[6a] is less effective in most organic solvents and gives the corresponding monoacetate with poor enantioselectivity with a number of lipases. However, acetylation of the monoacetyl derivatives affords the corresponding diacetate in high enantiomeric excess but this sequential transesterification requires longer reaction time (1–4 days). Recently *Geotrichum* sp. was found to catalyze stereoselective reductions of α-acetoxy- and α-hydroxy-phenylethanones to the corresponding monoacetate and 1,2-diols, respectively.[7b] Reduction of α-acetoxyphenylethanone gives monoacetates in very low yields (3–25%) and corresponding 1,2-diol of the same configuration with moderate yields and enantioselectivity (36–92% e.e.). Moreover different substituents on the phenyl ring provide 1,2-diol of the opposite configuration and this method enables the synthesis of 1,2-diols in only one enantiomeric form. In order to overcome such limitations, herein we have investigated a one-pot lipase catalyzed reductive resolution protocol for the synthesis of 1,2-diols in both enantiomeric forms in high enantiomeric excess. Recently, we have reported the synthesis of enantiopure 1,4- and 1,5-diols by one-pot reduction of corresponding lactones and ketoesters to the racemic diols followed by their lipase-mediated kinetic resolution.[8] We have also synthesized chiral secondary alcohols, chiral allylic alcohols and biologically important intermediate employing this one-pot reductive resolution protocol.[9]

2. Result and discussion

The substituted α-acetoxyphenylethanones **3a**–**g** were prepared by Friedel–Craft's acylation[10] of substituted benzene with chloroacetyl chloride in presence of anhydrous aluminium chloride followed by nucleophilic sub-

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stitution of chloride with glacial acetic acid[11] in acetonitrile under reflux condition (Scheme 1). All the substituted α-acetoxyphenylethanones **3** have been reduced to the corresponding racemic alcohols **4** by alumina-assisted sodium borohydride under mild conditions. The one-pot reduction was carried in toluene at room temperature. *Pseudomonas cepacia* lipase immobilized on ceramic (Amano PS-C) enables the resolution of the racemic monoacetae **4** effectively through irreversible transesterification in the same pot (Scheme 2).

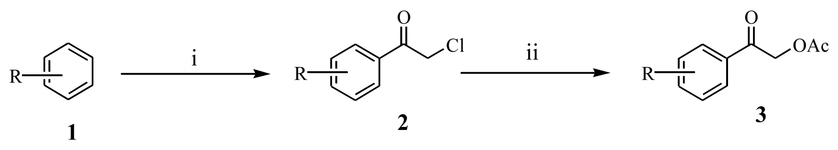
The one-pot reduction of α-acetoxyphenylethanone **3** and the subsequent resolution of the alcohol **4** have been carried out using Amano PS-C lipase in various solvents such as *n*-hexane, diisopropyl ether, ethyl acetate and toluene. Among these solvents the reduction and also the lipase mediated resolution proceeds efficiently in toluene at room temperature. Reduction of α-acetoxyphenylethanone **3** takes place in 3–6 h at room temperature. The racemic alcohol thus obtained is kinetically resolved by the lipase 'Amano' PS-C catalyzed transesterification at room temperature in the same pot (Scheme 2). The one-pot lipase catalyzed resolution of the racemic alcohol **4** takes 10–12 h for about 50% conversion as compared to the earlier reports.[6] The results of one-pot reduction of various substituted α-acetoxyphenylethanone and subsequent lipase catalyzed resolution of the corresponding racemic alcohol is summarized in Table 1.

It was interesting to note that various substituted α-acetoxyphenylethanone all gave diacetates of the (*S*)-configuration and the (*R*)-monoacetate indicating the consistency and applicability of the methodology. Diacetate (*S*)-**5** was obtained in high enantioselectivity for *p*-I, *p*-Br, *p*-OMe; *m*-Cl substituted α-acetoxyphenylethanone whereas *p*-Me, *p*-Cl afforded monoacetate (*R*)-**4** in >99% enantiomeric excess. These resolved compounds (*R*)-**4** and (*S*)-**5** were further hydrolyzed to the corresponding diols (*R*)-**6** and (*S*)-**6** quantitatively by using potassium carbonate in methanol (Scheme 2).

Configurations of resolved diols (*S*)-and (*R*)-**6** has been assigned by comparison of the sign of rotation obtained by the earlier methods. Various chiral 1,2-diols have been synthesized in high enantiopurity based on this one-pot reduction followed by resolution protocol. The results of enantioselectivity and optical rotation are summarized in Table 2.

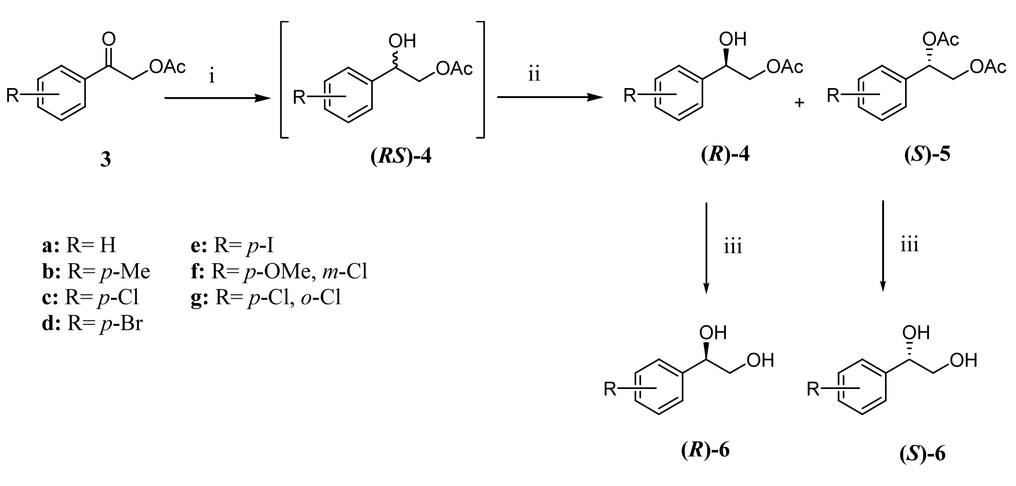
3. Conclusion

A new facile chemoenzymatic pathway has been developed for the synthesis of both (*R*) and (*S*) enantiopure terminal 1,2-diols from the corresponding α-acetoxyphenylethanone. The lipase from *Pseudomonas cepacia* (PS-C) catalyzes the kinetic resolution of monoacetate diol (*RS*)-**4** efficiently under one-pot con-



a: R= H **c:** R=*p*-Cl **e:** R=*p*-I **g:** R=*p*-Cl, *o*-Cl
b: R=*p*-Me **d:** R=*p*-Br **f:** R=*p*-OMe, *m*-Cl

Scheme 1. *Reagents and conditions*: (i) chloroacetyl chloride, aluminium chloride, dichloromethane (Ref. 10); (ii) glacial acetic acid, acetonitrile, reflux 3 h (Ref. 11).



a: R= H **e:** R=*p*-I
b: R=*p*-Me **f:** R=*p*-OMe, *m*-Cl
c: R=*p*-Cl **g:** R=*p*-Cl, *o*-Cl
d: R=*p*-Br

Scheme 2. *Reagents and conditions*: (i) $NaBH_4$, activated alumina, toluene; (ii) lipase PS-C, isopropenyl acetate; (iii) K_2CO_3, methanol.

Table 1. One-pot reduction of α-acetoxyphenylethanone **3** to the corresponding racemic alcohol **4** and its lipase-mediated transesterification by lipase (PS-C 'Amano' II)[a]

Entry	Substrate **3**	Time[b] (h)	Conv.[c] (%)	(*R*)-**4**		(*S*)-**5**		*E*[c]
				Yield[d] (%)	E.e.[e] (%)	Yield[d] (%)	E.e.[e] (%)	
1	**3a**	12	49	38	70	40	73	13
2	**3b**	12	56	42	>99	45	77	34
3	**3c**	10	58	36	>99	47	72	30
4	**3d**	10	47	46	98	39	91	52
5	**3e**	10	51	35	97	48	92	93
6	**3f**	12	42	39	69	40	96	101
7	**3g**	12	40	45	40	36	58	5

[a] Conditions: 1 mmol of **3**, 10 ml of toluene, 1 g activated alumina, 2 mmol $NaBH_4$; after 3–6 h lipase 1 equiv. w/w, 6 mmol isopropenyl acetate; room temperature.

[b] Time taken for transesterification.

[c] Conversion calculated from $e.e._s$ and $e.e._p$; $E=\{\ln[1-c(1+e.e._p)]\}/\{\ln[1-c(1-e.e._p)]\}$.

[d] Isolated yields after column chromatography.

[e] Determined by chiral HPLC analysis of the corresponding diol[13–15] (see Section 4).

Table 2. Hydrolysis of monoacetate **4** and diacetate **5** to their corresponding diols

Entry	Substrate **4**, **5**	(*R*)-**6**[a]		(*S*)-**6**[b]	
		E.e.[c] (%)	$[\alpha]_D$ (conc.)[d]	E.e.[c] (%)	$[\alpha]_D$ (conc.)[d]
1	**4a** or **5a**	70	−40.3 (0.74)	73	+45.8 (1.25)
2	**4b** or **5b**	>99	−65.2 (1.10)	77	+42.9 (1.45)
3	**4c** or **5c**	>99	−57.7 (0.51)	72	+38.0 (0.42)
4	**4d** or **5d**	98	−49.4 (0.90)	91	+44.2 (0.12)
5	**4e** or **5e**	97	−19.9 (1.24)[e]	92	+18.4 (1.92)[e]
6	**4f** or **5f**	69	−23.7 (0.81)	96	+32.8 (2.25)
7	**4g** or **5g**	40	−14.1 (0.99)	58	+31.8 (1.01)

[a] Obtained from hydrolysis of monoacetate **4a**–**g**.

[b] Obtained from hydrolysis of diacetate **5a**–**g**.

[c] Determined from chiral HPLC (Chiracel OD, OJ and OB-H column, Daicel)[13–15] see Section 4.

[d] Specific rotation in $CHCl_3$.

[e] Specific rotation in methanol.

dition to afford monoacetate (*R*)-**4** and diacetate (*S*)-**5** in moderate to high enantiomeric excess. The kinetically resolved enantiomers was further hydrolyzed to their corresponding diols which are important and widely used chiral building blocks in organic synthesis for the preparation of biologically active molecules.

4. Experimental

4.1. General

Infrared spectra of neat sample are reported in wave numbers (cm^{-1}). Proton NMR spectra were recorded in $CDCl_3$ at 200 and 300 MHz on Varian VXR-Unity and Bruker UXNMR/XWIN-NMR instruments, respectively. Coupling constants (*J*) are reported in hertz (Hz). Low resolution mass spectra were recorded on VG 7070H Micromass mass spectrometer at 200°C, 70 eV with a trap current of 200 μA and 4 kV acceleration voltage. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-10AT system controller, SPD-10A fixed wavelength UV monitor as detector using chiracel OB-H, OD and OJ columns (Daicel) employing hexane and isopropanol. Specific rotations were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with sodium lamp of wavelength 589 nm. Melting points have been recorded on an Electrothermal melting point apparatus and are uncorrected.

4.2. Chemicals and enzymes

Sodium borohydride, neutral alumina and solvents were obtained commercially and used without purification. Activated neutral alumina was prepared by homogeneous addition of 1.1 ml water to 10 gram of neutral alumina (preheated in oven at 200°C).[9a] Lipase from *Pseudomonas cepacia* immobilized on ceramic particles (PS-C), was purchased from Amano (Nagoya, Japan).

4.3. Synthesis of α-acetoxyphenylethanone 3a–g

α-Acetoxyphenylethanones **3a**–**g** were prepared by Friedel–Craft's acylation of corresponding substituted benzene using chloroacetyl chloride and anhydrous aluminium chloride (see Ref. 10 for experimental details). α-Chlorophenylethanones **2a**–**g** on treatment with glacial acetic acid in acetonitrile at reflux condition resulted in the corresponding α-acetoxyphenylethanones **3a–g** (see Ref. 11 for experimental details). Racemic 1,2-diol (*RS*)-**6** were prepared by $NaBH_4$ reduction of corresponding α-acetoxyphenylethanone **3a–g** in methanol.

4.4. General procedure for one-pot reduction of α-acetoxyphenylethanone 3a–g and subsequent lipase (PS-C) catalyzed acetylation

To a solution of the α-acetoxyphenylethanone **3** (1 mmol) in toluene (10 mL) was added activated alumina (1.0 g) and $NaBH_4$ (2 mmol). The suspension was stirred vigorously at room temperature for 3–6 h and monitored by TLC for the complete reduction to racemic alcohol. Then lipase 'Amano' PS-C (1 equiv. w/w) and isopropenyl acetate (6 mmol) were added to the reaction mixture. The reaction was monitored by TLC until it reaches to 50% conversion (10–12 h). The reaction was filtered through pad of celite and the filtrate was washed with water, followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography.

4.4.1. (*R*)-2-Hydroxy-2-phenylethyl acetate[6b] 4a. Yield: 38%; $[\alpha]_D^{25}$ −28.2 (*c* 3.92, $CHCl_3$); IR (neat): 3450, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1 (3H, s), 4.0 (1H, dd, *J*=8.91, 11.89), 4.2 (1H, dd, *J*=3.71, 11.89), 4.9 (1H, dd, *J*=3.71, 8.91), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 120 (M^+−60). Anal. calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.25; H, 6.52%.

4.4.2. (*S*)-2-Methylcarbonyloxy-1-phenylethyl acetate[6b] 5a. Yield: 40%; $[\alpha]_D^{25}$ +46.5 (*c* 3.44, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.0–2.1 (3H, s), 2.1–2.2 (3H, s), 4.2 (1H, dd, *J*=8.17, 11.89), 4.3 (1H, dd, *J*=3.71, 11.89), 6.0 (1H, dd, *J*=3.71, 8.17), 7.3 (5H, s); EIMS (*m*/*z*): 162 (M^+−60). Anal. calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.28; H, 6.17%.

4.4.3. (*R*)-2-Hydroxy-2-(4-methylphenyl)ethyl acetate 4b. Yield: 42%; $[\alpha]_D^{25}$ −46.4 (*c* 1.74, $CHCl_3$); IR (neat): 3450, 1730, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (3H, s), 2.4 (3H, s), 4.1 (1H, dd, *J*=8.30, 11.70), 4.2 (1H, dd, *J*=3.39, 11.70), 4.9 (1H, dd, *J*=3.39, 8.30), 7.1 (1H, d, *J*=7.93), 7.2 (1H, d, *J*=7.93); EIMS (*m*/*z*): 194 (M^+). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.95; H, 7.15%.

4.4.4. (*S*)-2-Methylcarbonyloxy-1-(4-methylphenyl)ethyl acetate 5b. Yield: 45%; $[\alpha]_D^{25}$ +55.3 (*c* 3.25, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.0 (3H, s), 2.1 (3H, s), 2.4 (3H, s), 4.2 (1H, dd, *J*=11.70, 7.93), 4.3 (1H, dd, *J*=3.77, 11.70), 5.9 (1H, dd, *J*=3.77, 7.93), 7.1 (2H, d, *J*=7.93), 7.2 (2H, d, *J*=7.93 Hz); EIMS (*m*/*z*): 236 (M^+). Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.92; H, 6.55%.

4.4.5. (*R*)-2-Hydroxy-2-(4-chlorophenyl)ethyl acetate 4c. Yield: 36%; $[\alpha]_D^{25}$ −36.6 (*c* 0.92, $CHCl_3$); IR (neat): 3400, 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1 (3H, s), 4.0–4.4 (2H, m), 4.9 (1H, dd, *J*=8.75, 3.74), 7.2–7.4 (4H, m); EIMS (*m*/*z*): 154 (M^+−60), 141 (M^+−73). Anal. calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17; Cl, 16.52. Found: C, 55.75; H, 5.03; Cl, 16.25%.

4.4.6. (*S*)-2-Methylcarbonyloxy-1-(4-chlorophenyl)ethyl acetate 5c. Yield: 47%; $[\alpha]_D^{25}$ +44.7 (*c* 2.08, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.0 (3H, s), 2.1 (3H, s), 4.2 (1H, dd, *J*=11.89, 7.43), 4.3 (1H, dd, *J*=3.71, 11.89), 5.9 (1H, dd, *J*=3.71, 7.43), 7.2–7.4 (4H, m); EIMS (*m*/*z*): 256 (M^+), 196 (M^+−60). Anal. calcd for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.10; Cl, 13.81. Found: C, 56.09; H, 5.02; Cl, 13%.

4.4.7. (*R*)-2-Hydroxy-2-(4-bromophenyl)ethyl acetate 4d. Yield: 46%; $[\alpha]_D^{25}$ −25.8 (*c* 1.69, $CHCl_3$); IR (neat): 3440, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (3H, s), 4.1 (1H, dd, *J*=8.17, 11.89), 4.3 (1H, dd, *J*=3.71, 11.89), 4.9 (1H, m), 7.2 (2H, d, *J*=8.17), 7.5 (2H, d, *J*=8.17); EIMS (*m*/*z*): 200 (M^+−59), 198 (M^+−61). Anal. calcd for $C_{10}H_{11}BrO_3$: C, 46.36; H, 4.28; Br, 30.84. Found: C, 46.25; H, 4.18; Br, 30.59%.

4.4.8. (*S*)-2-Methylcarbonyloxy-1-(4-bromophenyl)ethyl acetate 5d. Yield: 39%; $[\alpha]_D^{25}$ +44.1 (*c* 2.26, $CHCl_3$); IR (neat): 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (3H, s), 4.0–4.2 (1H, dd, *J*=12.08, 7.93), 4.2–4.4 (1H, dd, *J*=3.77, 12.08), 5.9 (1H, dd, *J*=3.77, 7.93), 7.2 (2H, d, *J*=8.30), 7.4 (2H, d, *J*=8.30); EIMS (*m*/*z*): 242 (M^+−59), 240 (M^+−61). Anal. calcd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35; Br, 26.53. Found: C, 47.69; H, 4.15; Br, 26.34%.

4.4.9. (*R*)-2-Hydroxy-2-(4-iodophenyl)ethyl acetate 4e. Yield: 35%; $[\alpha]_D^{25}$ −23.0 (*c* 1.92, $CHCl_3$); IR (neat): 3450, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (3H, s), 4.1 (1H, dd, *J*=8.17, 11.89), 4.3 (1H, dd, *J*=3.71, 11.89), 4.9 (1H, m), 7.2 (2H, d, *J*=8.17), 7.5 (2H, d, *J*=8.17); EIMS (*m*/*z*): 246 (M^+−60). Anal. calcd for $C_{10}H_{11}IO_3$: C, 39.24; H, 3.62; I, 41.46. Found: C, 39.15; H, 3.54; I, 41.35%.

4.4.10. (*S*)-2-Methylcarbonyloxy-1-(4-iodophenyl)ethyl acetate 5e. Yield: 48%; $[\alpha]_D^{25}$ +43.7 (*c* 3.60, $CHCl_3$); IR (neat): 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.0 (3H, s), 2.1 (3H, s), 4.2 (1H, dd, *J*=11.89, 7.43), 4.3 (1H, dd, *J*=3.71, 11.89), 5.9 (1H, d, *J*=7.43, 3.71), 7.0 (2H, d, *J*=8.17), 7.7 (2H, d, *J*=8.17); EIMS (*m*/*z*): 288 (M^+−60), 246 (M^+−102). Anal. calcd for $C_{12}H_{13}IO_4$: C, 41.4; H, 3.76; I, 36.45. Found: C, 41.28; H, 3.63; I, 36.35%.

4.4.11. (*R*)-2-(3-Chloro-4-methoxyphenyl)-2-hydroxyethyl acetate 4f. Yield: 39%; $[\alpha]_D^{25}$ −18.2 (*c* 3.58, $CHCl_3$); IR (neat): 3400, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (3H, s), 3.9 (3H, s), 4.1 (1H, dd, *J*=8.30, 11.70), 4.2 (1H, dd, *J*=3.39, 11.70), 4.8 (1H, dd, *J*=3.39, 8.30), 6.8 (1H, d, *J*=8.68), 7.2 (1H, dd, *J*=8.68, 2.26), 7.4 (1H, d, *J*=2.26); EIMS (*m*/*z*): 244 (M^+), 185 (M^+−59). Anal. calcd for $C_{11}H_{13}ClO_4$: C, 54.00; H, 5.36; Cl, 14.49. Found: C, 53.96; H, 5.29; Cl, 14.39%.

4.4.12. (*S*)-2-Methylcarbonyloxy-2-(3-chloro-4-methoxyphenyl)ethyl acetate 5f. Yield: 40%; $[\alpha]_D^{25}$ +47.8 (*c* 4.30, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (3H, s), 2.2 (3H, s), 3.9 (3H, s), 4.2 (1H, dd, *J*=7.93, 11.70), 4.3 (1H, dd, *J*=4.15, 11.70), 5.9 (1H, dd, *J*=4.15, 7.93), 6.8 (1H, d, *J*=8.68), 7.2 (1H, dd, *J*=8.68, 2.26), 7.4 (1H, d, *J*=2.26); EIMS (*m*/*z*): 226 (M$^+$–60). Anal. calcd for $C_{13}H_{15}ClO_5$: C, 54.46; H, 5.27; Cl, 12.37. Found: C, 54.39; H, 5.16; Cl, 12.26%.

4.4.13. (*R*)-2-(2,4-Dihlorophenyl)-2-hydroxyethyl acetate 4g. Yield: 45%; $[\alpha]_D^{25}$ –21.4 (*c* 1.40, $CHCl_3$); IR (neat): 3440, 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.0 (3H, s), 3.9 (3H, s), 4.1 (1H, dd, *J*=8.30, 11.70), 4.2 (1H, dd, *J*=3.39, 11.70), 4.8 (1H, dd, *J*=3.39, 8.30), 6.8 (1H, d, *J*=8.68), 7.2 (1H, dd, *J*=8.68, 2.26), 7.4 (1H, d, *J*=2.26). Anal. calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.22; H, 4.05; Cl, 28.47. Found: C, 48.14; H, 3.97; Cl, 28.39%.

4.4.14. (*S*)-2-Methylcarbonyloxy-1-(2,4-dichlorophenyl)-ethyl acetate 5g. Yield: 36%; $[\alpha]_D^{25}$ +22.7 (*c* 1.59, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.0 (3H, s), 2.1 (3H, s), 4.2–4.4 (2H, m), 6.3 (1H, dd, *J*=4.46, 6.69), 7.2 (1H, dd, *J*=8.91, 1.49), 7.3 (1H, d, *J*=8.91), 7.5 (1H, d, *J*=1.49). Anal. calcd for $C_{12}H_{12}Cl_2O_4$: C, 49.51; H, 4.15; Cl, 24.36. Found: C, 49.38; H, 4.05; Cl, 24.16%.

4.5. General procedure for ester hydrolysis reaction

To the solution of ester **4** and **5** (1 mmol) in 10 mL methanol was added K_2CO_3 (1.5 mmol) and (2.5 mmol), respectively. The mixture was stirred for 4 h, acidified with 1N HCl and extracted with ether, after evaporation of the methanol.

4.5.1. (*R*)-1-Phenyl-1,2-ethanediol[5a] 6a. Yield: 95%; mp 62–63°C; 70% e.e.;[14] $t_R(R)$ 14.74 min and $t_R(S)$ 18.83 min; IR (neat): 3330 cm^{-1} (broad); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.8 (1H, broad s), 3.2 (1H, broad s), 3.6 (1H, dd, *J*=11.33, 8.30), 3.7 (1H, dd, *J*=11.33, 3.39), 4.8 (1H, dd, *J*=3.39, 8.30), 7.3 (5H, m); EIMS (*m*/*z*): 138 (M$^+$), 121 (M$^+$–17), 107 (M$^+$–31). Anal. calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.29. Found: C, 69.35; H, 7.12%.

4.5.2. (*R*)-1-(4-Methylphenyl)-1,2-ethanediol[5a] 6b. Yield: 92%; mp 71–72°C [lit.[12] 76–76.5°C]; >99% e.e.;[13] $t_R(R)$ 18.86 min and $t_R(S)$ 19.50 min; IR (neat): 3330 cm^{-1} (broad); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.3 (3H, s), 3.6 (2H, m), 4.8 (1H, m), 7.0–7.4 (4H, m); EIMS (*m*/*z*): 152 (M$^+$), 121 (M$^+$–31). Anal. calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.95; H, 7.86%.

4.5.3. (*R*)-1-(4-Chlorophenyl)-1,2-ethanediol[5a] 6c. Yield: 94%; mp 81–82°C [lit.[12] 76.5–78°C]; >99% e.e.;[13] $t_R(R)$ 20.41 min and $t_R(S)$ 21.25 min; IR (neat): 3340 cm^{-1} (broad); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.2 (1H, broad s), 2.4–2.6 (1H, broad s), 3.5–3.6 (1H, dd, *J*=8.17, 11.15), 3.7 (1H, dd, *J*=3.71, 11.15), 4.8 (1H, dd, *J*=8.17, 3.71), 7.2–7.4 (4H, m); EIMS (*m*/*z*): 172 (M$^+$), 141 (M$^+$–31). Anal. calcd for $C_8H_9ClO_2$: C, 55.67; H, 5.26; Cl, 20.54. Found: C, 55.48; H, 5.13; Cl, 20.14%.

4.5.4. (*R*)-1-(4-Bromophenyl)-1,2-ethanediol[5b] 6d. Yield: 92%; mp 103–104°C; 98% e.e.;[13] $t_R(R)$ 23.32 min and $t_R(S)$ 24.70 min; IR (neat): 3330 cm^{-1} (broad); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.0 (1H, broad s), 2.6 (1H, broad s), 3.5 (1H, dd, *J*=8.30, 11.33), 3.7 (1H, dd, *J*=11.33, 3.39), 4.8 (1H, dd, *J*=8.30, 3.39), 7.2 (2H, d, *J*=7.93), 7.5 (2H, d, *J*=7.93); EIMS (*m*/*z*): 218 (M$^+$+1), 216 (M$^+$–1). Anal. calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18; Br, 36.81. Found: C, 44.11; H, 4.04; Br, 36.63%.

4.5.5. (*R*)-1-(4-Iodophenyl)-1,2-ethanediol[5a] 6e. Yield: 96%; mp 118–120°C; 97% e.e.;[15] $t_R(R)$ 21.19 min and $t_R(S)$ 22.80 min; IR (neat): 3350 cm^{-1} (broad); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.4 (2H, m), 4.4 (1H, t, *J*=5.94), 4.6 (1H, m), 5.0 (1H, d, *J*=3.71), 7.2 (2H, d, *J*=8.17), 7.6 (2H, d, *J*=8.17); EIMS (*m*/*z*): 264 (M$^+$), 233 (M$^+$–31). Anal. calcd for $C_8H_9IO_2$: C, 36.39; H, 3.44; I, 48.06. Found: C, 36.26; H, 3.23; I, 47.96%.

4.5.6. (*R*)-1-(3-Chloro-4-methoxyphenyl)-1,2-ethanediol 6f. Yield: 96%; mp 94–95°C; 69% e.e.;[13] $t_R(R)$ 34.23 min and $t_R(S)$ 38.40 min; IR (neat): 3340 cm^{-1} (broad); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.0 (1H, broad s), 2.5 (1H, broad s), 3.6 (2H, m), 3.9 (3H, s), 4.7 (1H, dd, *J*=3.71, 8.17), 6.8 (1H, d, *J*=8.91), 7.2 (1H, dd, *J*=8.91, 2.23), 7.4 (1H, d, *J*=2.23); EIMS (*m*/*z*): 202 (M$^+$), 171 (M$^+$–31), 173 (M$^+$–29). Anal. calcd for $C_9H_{11}ClO_3$: C, 53.35; H, 5.47; Cl, 17.50. Found: C, 53.27; H, 5.39; Cl, 17.42%.

4.5.7. (*R*)-1-(2,4-Dihloroyphenyl)-1,2-ethanediol 6g. Yield: 90%; 40% e.e.;[14] $t_R(R)$ 10.55 min and $t_R(S)$ 11.42 min; IR (neat): 3330 cm^{-1} (broad); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.4 (1H, dd, *J*=11.15, 8.17), 3.8 (1H, d, *J*=11.15), 5.1 (1H, d, *J*=6.69), 7.2 (1H, dd, *J*=8.91, 1.49), 7.3 (1H, d, *J*=1.49), 7.5 (1H, d, *J*=8.17); EIMS (*m*/*z*): 202 (M$^+$), 171 (M$^+$–31), 173 (M$^+$–29). Anal. calcd for $C_8H_8Cl_2O_2$: C, 46.41; H, 3.89; Cl, 34.24. Found: C, 46.37; H, 3.82; Cl, 34.19%.

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15. Determined by chiral HPLC (Chiracel OJ column, Daicel) employing hexane–isopropanol (90:10) as mobile phase with 0.5 mL/min flow and monitored at 254 nm wavelength.