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Chemoenzymatic approach to optically active phenylglycidates: resolution of bromo- and iodohydrins

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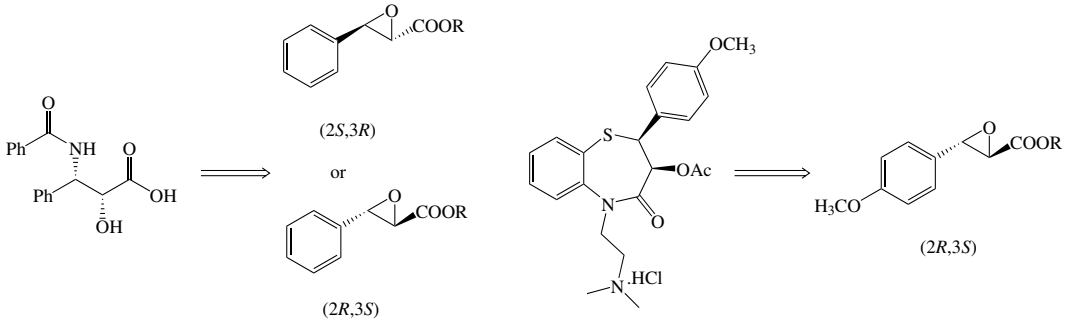
Abstract—Enantiomerically enriched phenylglycidates, precursors of the taxol C-13 phenylisoserine side chain and diltiazem, were prepared by kinetic resolution of *anti*-2-bromo-3-hydroxy- and *anti*-3-hydroxy-2-iodophenylpropanoates to provide enantioriched (2*R*,3*R*)- and (2*S*,3*S*)-halohydrins. The bulkiness and inflexibility of bromo and iodo groups in halohydrins have made them inaccessible to the active site of most of the lipases utilized for the hydrolysis of their acyloxy derivatives. In a set of 22 hydrolases screened herein, including native as well as commercial enzymes, only *Aspergillus niger* (Lipase AS, AMANO) could catalyze the hydrolysis with high enantioselectivity ($E = 176$). The resolved halohydrins easily underwent transformation to the corresponding (2*S*,3*R*)- and (2*R*,3*S*)-phenylglycidates.

1. Introduction

Enantiomerically enriched phenylglycidates, important intermediates of the phenylisoserine side chain in the anti-cancer drug taxol[1] and anti-anginal drug diltiazem,[2,3] (Scheme 1) have reportedly been prepared by kinetic resolution of chlorohydrins as they are easily accepted by lipases/esterases.[4a,b] However, both bromo- and iodohydrins are much less studied as substrates for hydrolases. The larger atomic sizes of both bromine and iodine make them better leaving groups, hence both bromo- and iodohydrins are ideal precursors of the corresponding glycidates. On the other hand, larger atomic size and rigidity of bromine/iodine in these substrates may also be a limiting factor in the approach and fitting into the active sites of most of the hydrolases.[5] The bulkiness and steric effects of the substituents may cause obstruction in the interactions with the enzyme, which in turn may not allow the reaction to take off.[6] In view of this, it would be interesting to investigate lipase catalyzed hydrolysis of α-halo-β-hydroxyphenylpropionates in presence of bromo or iodo groups.



Scheme 1.

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During our research programme on the kinetic resolution of chiral drugs/drug intermediates and chiral synthons/auxiliaries,[7] we envisaged the preparation of optically active phenylglycidates through kinetic resolution of *anti*-bromo- and iodohydrins as both the resolved enantiomers can easily be converted (via *syn*-glycidates) to the isoserine side chain of taxol by different synthetic routes[8] whereas *p*-methoxyphenylglycidate can be converted to diltiazem.[2] Furthermore, both bromo- and iodohydrin analogues are easy to handle as they are more stable and crystalline in nature and, unlike chlorohydrins, these compounds can be obtained exclusively as *anti*-isomers. Moreover we were also interested in studying the effect of higher molecular weight halohydrins on the kinetics as well as enantioselectivity.

A detailed survey of the literature revealed that not many attempts have been made in the past to prepare phenylglycidates through kinetic resolution of halohydrins, though there is a report, which describes the resolution of a chlorohydrin[4a] (comprising both *syn* and *anti* or mixture) in order to synthesize enantiomerically pure precursors of the C-13 side chain of taxol.

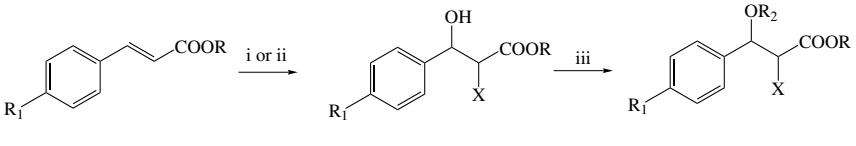
2. Results and discussion

Herein we report the preparation of *anti*-2-bromo-3-hydroxyphenylpropanoate and *anti*-3-hydroxy-2-iodophenylpropanoate and the application of lipases for their resolution and further conversion to (2*R*,3*S*)- and (2*S*,3*R*)-phenylglycidates **6** and **7**, respectively. In the proposed reaction in Scheme 2, unsubstituted and substituted cinnamates **1** were subjected to a cohalogenation reaction using potassium bromate or periodic acid[9] to exclusively generate *anti*-α-halo-β-hydroxyphenylpropionates **2a**–**h** in 65–77% yields.

Initially racemic substrates **2a**–**h** were subjected to kinetic resolution studies through stereoselective hydrolysis using native as well as commercial hydrolases[10] so as to obtain enantiomerically enriched 2-halo-3-hydroxyphenylpropanoic acid and their carboxylate esters. Not surprisingly, none of the hydrolases used (22 in total) could facilitate (Scheme 3) the hydrolysis of the substrates. It clearly highlights the influence of bulkier atoms, such as bromine and iodine in halohydrin esters, in causing steric hindrance during hydrolysis, even though many of the enzymes used in the present study (e.g., PSL, PPL, CCL, AK, MAP 10) have reportedly been successfully used in hydrolyzing the corresponding chlorohydrin propionates.[4a]

It is well known that alkyl acyloxy esters can be easily hydrolyzed by lipases, therefore **2a**–**h** were converted to the corresponding acyloxy esters **3a**–**h** in almost quantitative yields (Scheme 2). It was expected that most of the lipases would be able to stereoselectively hydrolyze the acyloxy ester group in substrates **3a**–**h** (Scheme 4).

Hence, we undertook the kinetic resolution of **3a**–**h**; this time only *Aspergillus niger* (Lipase AS, Amano) could effect the hydrolysis of acetoxy ester in aqueous buffer, furnishing (2*R*,3*R*)-2-halo-3-hydroxyphenylpropanoates **4a**–**h** in reasonable yield. All other lipases used earlier,



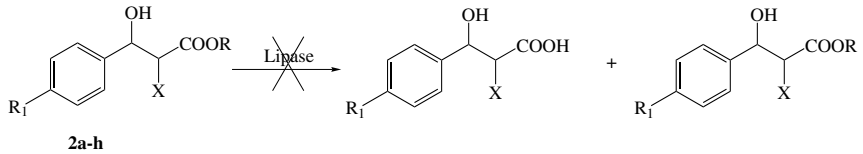
2a-h

(a) R = Me; R_1= H; X = Br
(b) R = Et; R_1= H; X = Br
(c) R = Me; R_1= H; X = I
(d) R = Et; R_1= H; X = I
(e) R = Me; R_1= OMe; X = Br
(f) R = Et; R_1= OMe; X = Br
(g) R = Me; R_1= OMe; X = I
(h) R = Et; R_1= OMe; X = I

3a-h

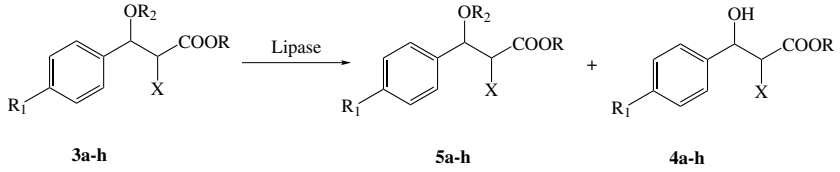
(a) R = Me; R_1= H; R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = Br
(b) R = Et; R_1= H; R_2= $COCH_3$, COC_2H_5, COC_3H_7; X= Br
(c) R = Me, R_1= H, R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = I
(d) R = Et, R_1= H, R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = I
(e) R = Me, R_1= OMe, R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = Br
(f) R = Et, R_1= OMe, R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = Br
(g) R = Me, R_1= OMe, R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = I
(h) R = Et, R_1= OMe, R_2= $COCH_3$, COC_2H_5, COC_3H_7; X = I

Scheme 2. Reagents and conditions: (i) $KBrO_3/NaHSO_3$; (ii) $HIO_4/NaHSO_3$; (iii) alkanoic acid anhydride/DMAP.



X = Br, I: R = Me, Et; R_1 = H, OMe

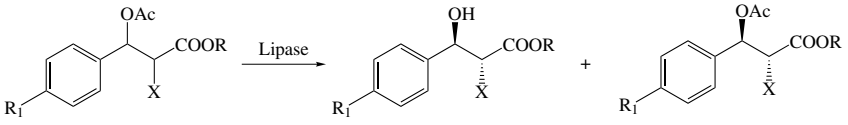
Scheme 3.



3a-h **5a-h** **4a-h**

X = Br, I; R = Me, Et; R_1 = H, OMe, R_2 = $COCH_3$, COC_2H_5, COC_3H_7

Scheme 4.



(2*R*,3*R*) **4** (2*S*,3*S*) **5**

X = Br, I; R = Me, Et; R_1 = H, OMe

Scheme 5.

again completely failed to hydrolyze these substrates, even in the presence of organic co-solvents or in ionic liquids. These observations support the results of some previous studies carried out on the steric requirements of lipases[11] where it had been specified that lipases such as those belonging to genus *Pseudomonas*, *Candida*, *Mucor*, etc. are capable of accepting only small to medium sized groups, while lipase from *A. niger* can accommodate comparatively larger groups. Previously Itoh et al.[12] had also carried out some experiments to study the behaviour of lipase A6 (*Aspergillus* sp.) on the acylates of α-alkylthio-β-hydroxyphenyl derivatives and observed that *anti*-isomers were more compatible for hydrolysis in comparison to *syn*-isomer. An increase in the size of the acyl alkyl group (at C-3) to either propyl or methylthiomethyl was also well accepted by the A6 lipase. However, the effect of neighbouring large atoms such as bromine or iodine at C-2 on hydrolytic behaviour has not been studied. However, our studies clearly showed that *A. niger* lipase was able to hydrolyze only the acetates ($R_2 = COCH_3$) in (±)-**3a**–**h** (Scheme 5), whereas higher alkyl homologues such as propionates ($R_2 = COC_2H_5$) and butyrates ($R_2 = COC_3H_7$) failed to hydrolyze. These experiments also provide some indications about the size and width of the cavity at the active site of lipase from *A. niger*.

All kinetic resolution reactions were carried out in an aqueous phosphate buffer where the rate of hydrolysis was slow and enantioselectivity was also poor (Table 1). In some substrates, even after 100 h of reaction time, conversions beyond 26% could not be achieved. All attempts to achieve hydrolysis at C-1 including the attempts of transesterification (organic solvents/ionic liquids) proved unsuccessful.

With the aim to improve the rate of hydrolysis as well as the enantioselectivity, use of a co-solvents[14] was envisaged as a practical option. A biphasic system using an organic solvent proved to be advantageous. Both non-polar as well as polar solvents in the ratio of 5–30% v/v buffer were used in the resolution studies and finally toluene found to be the co-solvent of choice in terms of conversion rates as well as enantioselectivity, as depicted in Table 2 for substrate **3c**. Addition of toluene as the co-solvent (10% v/v) in buffer reduced the reaction time significantly (18 h, conversion ~ 44%) and also contributed to improving the ee (93–97.4%). Furthermore, the addition of acetonitrile (10% v/v) also proved to be beneficial (12 h, conversion ~ 40%, ee ~ 97%) however, it had its limitations as a co-solvent as the reaction proceeded well only with liquid substrates and became slow in presence of insoluble solids substrates.

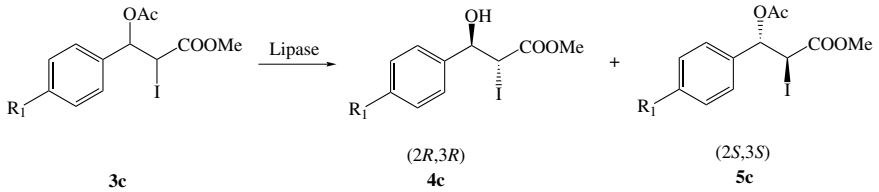
Any further increase in the ratio of the acetonitrile in the buffer had a detrimental effect on the lipase activity as well as the rate of hydrolysis. Therefore, toluene was selected as the co-solvent for detailed kinetic resolution studies of other substrates. In general, kinetic resolution studies of compounds **3a**–**f** (where $R_2 = COCH_3$) using toluene as the co-solvent displayed comparatively faster

Table 1. Lipase AS catalyzed hydrolysis of (±)-acetoxy ester **3a**–**h** in aqueous buffer phase

Substrate	Time (h)	Alcohol (**4a**–**h**)		Ester (**5a**–**h**)		Conv. (%)	E[c]
		Ee%	$[\alpha]_D^{25}$[a]	Ee%	$[\alpha]_D^{25}$[a]		
3a	96	60	−13.0	18	+9.9	23	5
3b	24	77	−13.1	56	+27.6	42	13
3c	96	93	0.0[b]	17	+10.3	15	32
3d	100	71	−7.0	19	+11.6	26	8
3e	96	85	−3.9	66	+27.5	43	24
3f	24	59	−10.9	48	+35.2	45	6
3g	24	13	−1.4	26	+17.5	33	1
3h	98	72	−3.4	19	+12.0	24	8

[a] The specific rotations were determined in $CHCl_3$ with $c = 1$.
[b] $[\alpha]_D^{25} = -3.5$ (c 1, CH_3OH).
[c] Calculated according to Chen et al.[13]

Table 2. Effect of co-solvents on Amano AS catalyzed hydrolysis of (±)-acetoxy ester **3c**



3c (2*R*,3*R*) **4c** (2*S*,3*S*) **5c**

Organic co-solvent	Time (h)	Ee_S (%) **4c**	Ee_P (%) **5c**	Conv. (%)	E[a]
None	144	15	93	14	32
Toluene	18	76	97.4	44	176
Acetone	22	81	82	49	24
Acetonitrile	12	63	97	40	128
Hexane	76	78	85	47	28

[a] Calculated according to Chen et al.[13]

Table 3. Lipase AS catalyzed hydrolysis of (±)-acetoxy ester **3a–h** with toluene as co-solvent

Substrate	Time (h)	Alcohol (**4a–h**)			Ester (**5a–h**)			Conv. (%)	E[c]
		Ee%	$[\alpha]_D^{25}$[a]	Yield (%)	Ee%	$[\alpha]_D^{25}$[a]	Yield (%)		
3a	24	94	−19.9	42	70	+41.3	42	43	69
3b	24	89	−15.5	43	73	+37.5	41	45	37
3c	18	97.4	0.0[b]	46	76	+48.0	44	44	176
3d	20	96	−9.5	45	60	+36.0	44	40	95
3e	48	93	−4.3	44	77	+32.4	45	49	84
3f	50	88	−16.9	42	63	+44.5	40	46	35
3g	45	97.3	−10.2	41	75	+50.5	44	43	162
3h	42	89	−4.4	42	77	+49.0	43	47	41

[a] The specific rotations were measured in $CHCl_3$ with $c = 1$.
[b] $[\alpha]_D^{25} = -3.8$ (c 1, CH_3OH).
[c] Calculated according to Chen et al.[13]

conversion rates as well as improved enantioselectivity. The results of these experiments are presented in Table 3.

As both (2*R*,3*S*)- and (2*S*,3*R*)-phenylglycidate enantiomers can easily be utilized for their conversion to the required isoserine side chain, hence further enrichment of the partially enriched (2*S*,3*S*)-esters **5a–f** ($R_2 = COCH_3$) was envisaged through double kinetic resolution. Through these experiments, the enantiomeric excess of acetoxy esters could be further improved from ee ~ 60% to ee ~ 96–99% as shown in Table 4.

The enriched (2*R*,3*R*)-halohydrins **4** could easily be converted to (2*S*,3*R*)-phenylglycidates **6** in quantitative yield, while the enriched (2*S*,3*S*)-acetoxy esters **5** were first hydrolyzed to the corresponding (2*S*,3*S*)-halohydrins in 2 M HCl/MeOH and then finally converted to (2*R*,3*S*) phenylglycidates **7** (Scheme 6) in the presence of DBU/CH_2Cl_2 without effecting the enantiomeric excess. Typically the reaction was over within 20–30 min.

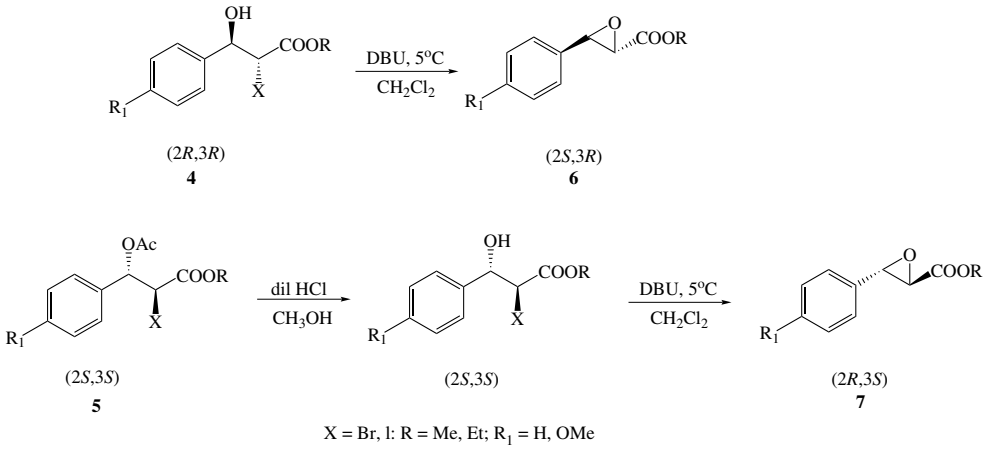
Table 4. Double kinetic resolution of enantiomerically enriched acetoxy esters **5a–f**

Substrate	Ee% subs.	Time (h)	Conv. (%)	Ee% DK[a]	$[\alpha]_D^{25}$
5a	70	36	15	99	+51.2
5b	73	42	18	98.8	+51.5
5c	76	38	13	97	+60.5
5d	60	36	22	96.3	+53.5
5e	77	33	13	96.7	+40.6
5f	83	28	10	96.5	+53.2

[a] DK = double kinetic resolution; the specific rotations were measured in $CHCl_3$ with $c = 1$.

3. Conclusions

The influence of the bulkiness and rigidity of the bromine and iodine atoms in *anti*-2-bromo-3-hydroxy- and *anti*-3-hydroxy-2-iodophenylpropanoates and the intermediates of (2*S*,3*R*)- and (2*R*,3*S*)-phenylglycidates was apparent when all the lipases except *A. niger* (lipase AS, Amano) completely failed to hydrolyze the carboxylates and/or acyloxy esters. Only *A. niger* could easily resolve their acetates in high enantiopurity. The use of toluene and acetonitrile further improved the rate of hydrolysis as well as enantioselectivity. Double kinetic resolution studies also improved the enantiopurity of the optically enriched unhydrolyzed acetoxy esters. Resolved bromo- and iodohydrins underwent facile conversion to the corresponding glycidates in almost quantitative yields with no change in enantiopurity.



Scheme 6.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR were recorded on a Bruker (200 and 50 MHz) spectrometer in $CDCl_3$ using TMS as the internal standard. IR was recorded on a FT-IR Bruker (270-30) spectrophotometer. Elemental analysis was performed on an Elementar CHNS analyzer. Mass spectra were recorded on LC–MS Bruker and Shimadzu GC–MSQP2000. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in the indicated solvents and concentrations. TLC was performed on Silica gel 60 F_{254} (Merck). The enantiomeric excesses (ee) were measured by chiral HPLC (Shimadzu) on (*R*,*R*)-Whelk-01 and Chiralcel OD-H chiral columns using hexane/isopropyl alcohol/acetic acid in 97:3:0.1. Melting points were determined on Buchi B-542 apparatus by open capillary method and are uncorrected. Lipase AS 'Amano' batch no LAY0651455S was a gift from Amano Enzyme Inc., Japan. All the reagents and enzymes were used directly without further purification.

4.2. Preparation of methyl (±)-*anti*-2-bromo-3-hydroxy-3-phenylpropanoate 2a

Potassium bromate (4.00 g, 24.0 mmol) was dissolved in water (40 mL) and adjusted to pH <3 with dil H_2SO_4. To the resultant solution was added methyl cinnamate (3.24 g, 20.0 mmol) dissolved in acetonitrile (40 mL) followed by 1 M sodium bisulfate solution (5.20 g in 50 mL water) added over a period of 3 h with stirring at 40 °C. The reaction mixture was further stirred for 36 h until the reaction was complete. The resulting solution was extracted with ethyl acetate (3×50 mL), and the combined organic layers were washed with aqueous sodium sulfite and dried over anhydrous sodium sulfate. The contents were concentrated in vacuo to give the crude material, which on crystallization (benzene–hexane 1:1) furnished **2a**, (3.50 g, 70%), mp 63 °C. IR (KBr): 3506, 2952, 1729, 1436, 1377, 1286, 1206, 1176, 1145, 1006, 920, 773, 722, 700, 651, 597 cm^{-1}. ^{1}H NMR (200 MHz): δ 3.80 (3H, s, –COOCH_3), 4.38 (1H, d, $J = 8.2$ Hz, C*H*–Br), 5.07 (1H, d, $J = 8.2$ Hz, C*H*–OH), 7.38 (5H, s, Ar–*H*). ^{13}C NMR (50 MHz): δ 47.4, 53.2, 75.3, 127.0, 128.6, 128.8, 139.0, 171.9. MS (*m*/*z*): (M+1) 260, 258, 243, 199, 162, 98. Anal. Calcd for $C_{10}H_{11}BrO_3$: C, 46.36; H, 4.28. Found: C, 46.52; H, 4.30.

4.3. Preparation of ethyl (±)-*anti*-2-bromo-3-hydroxy-3-phenylpropanoate 2b

Compound **2b** was prepared from ethyl cinnamate (3.52 g, 20.0 mmol) following the procedure described in Section 4.2 (3.80 g, 70%), mp 76–77 °C. IR (KBr): 3446, 2993, 1720, 1376, 1285, 1185, 1152, 1016, 871, 770, 700 cm^{-1}. ^{1}H NMR (200 MHz): δ 1.27 (3H, t, $J = 7.1$ Hz, –COOCH$_2$CH_3), 4.25 (2H, q, $J = 7.1$ Hz, –COOCH_2), 4.36 (1H, d, $J = 8.1$ Hz, C*H*–Br), 5.08 (1H, d, $J = 8.1$ Hz, C*H*–OH), 7.38 (5H, s, Ar–*H*). ^{13}C NMR (50 MHz): δ 14.0, 47.8, 62.5, 75.3, 127.1, 128.7, 128.9, 140.4, 169.6. MS (*m*/*z*): (M+1) 274, 272, 229, 193, 166, 148, 81. Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 48.41; H, 4.80. Found: C, 48.16; H, 4.80.

4.4. Preparation of methyl (±)-*anti*-3-hydroxy-2-iodo-3-phenylpropanoate 2c

In a stirred solution comprising of methyl cinnamate (3.26 g, 20.0 mmol) and $HIO_4 \cdot 2H_2O$ (5.20 g, 24.0 mmol) in acetonitrile (40 mL) at 25 °C, a solution of 1 M sodium bisulfate (5.50 g in 50 mL water) was added over a period of 3 h. The reaction mixture was further stirred for 48 h at 25 °C until the reaction was complete. Usual work-up and purification as described for **2a** afforded **2c** (4.50 g, 73%), mp 63 °C. IR (KBr): 3434, 2925, 1735, 1437, 1284, 1203, 999, 766 cm^{-1}. ^{1}H NMR (200 MHz): δ 3.76 (3H, s, –COOCH_3), 4.57 (1H, d, $J = 8.5$ Hz, C*H*–I), 5.06 (1H, d, $J = 8.5$ Hz, C*H*–OH), 7.37 (5H, s, Ar–*H*). ^{13}C NMR (50 MHz): δ 24.5, 53.1, 76.2, 127, 128.6, 128.8, 139.4, 171.7. MS (*m*/*z*): 306, 291, 275, 187, 186, 162, 119. Anal. Calcd for $C_{10}H_{11}IO_3$: C, 39.24; H, 3.62. Found: C, 39.34; H, 3.57.

4.5. Preparation of ethyl (±)-*anti*-3-hydroxy-2-iodo-3-phenylpropanoate 2d

Compound **2d** was prepared from ethyl cinnamate (3.52 g, 20.0 mmol) following the procedure as described for **2c** (4.80 g, 75%), mp 79 °C. IR (KBr): 3436, 2993, 1719, 1376, 1286, 1185, 1152, 1015, 871, 772, 700 cm^{-1}. ^1H NMR (200 MHz): δ 1.28 (3H, t, $J = 7.1$ Hz, $-COOCH_2CH_3$), 4.24 (2H, q, $J = 7.1$ Hz, $-COOCH_2$), 4.58 (1H, d, $J = 8.3$ Hz, C*H*–I), 5.08 (1H, d, $J = 8.3$ Hz, C*H*–OH), 7.38 (5H, s, Ar–*H*). ^{13}C NMR (50 MHz): δ 13.7, 25.1, 62.1, 76.2, 126.9, 128.5, 128.6, 139.4, 171.2. MS (*m*/*z*): 320, 275, 229, 193, 166. Anal. Calcd for $C_{11}H_{13}IO_3$: C, 41.27; H, 4.09. Found: C, 41.67; H, 4.02.

4.6. Preparation of methyl (±)-*anti*-2-bromo-3-hydroxy-3-(4-methoxyphenyl)-propanoate 2e

Compound **2e** was prepared from 4-methoxy methyl cinnamate (3.84 g, 20.0 mmol) following the procedure as described for **2a** (3.80 g, 66%), mp 59–60 °C. IR (KBr): 3300, 1734, 1612, 1517, 1167, 834 cm^{-1}. ^1H NMR (200 MHz): δ 3.81 (6H, s, $-COOCH_3$ and $-OCH_3$), 4.35 (1H, d, $J = 8.6$ Hz, C*H*–Br), 5.04 (1H, d, $J = 8.6$ Hz, C*H*–OH), 6.91 (2H, d, $J = 8.7$ Hz, Ar–*H*), 7.32 (2H, d, $J = 8.7$ Hz, Ar–*H*). ^{13}C NMR (50 MHz): δ 47.6, 53.0, 55.2, 74.7, 113.8, 128.1, 131.1, 159.7, 169.8. MS (*m*/*z*): (M+1) 290, 288, 209, 203, 175, 119, 109, 107. Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45.73; H, 4.54. Found: C, 46.27; H, 4.56.

4.7. Preparation of ethyl (±)-*anti*-2-bromo-3-hydroxy-3-(4-methoxyphenyl)-propanoate 2f

Compound **2f** was prepared from 4-methoxy ethyl cinnamate (4.12 g, 20.0 mmol) following the procedure as described for **2a** (4.20 g, 70%), mp 70–72 °C. IR (KBr): 3443, 1742, 1611, 1514, 1251, 1149, 838 cm^{-1}. ^1H NMR (200 MHz): δ 1.26 (3H, t, $J = 7.1$ Hz, $-COOCH_2CH_3$), 3.80 (3H, s, $-OCH_3$), 4.16 (2H, q, $J = 7.1$ Hz, $-COOCH_2$), 4.25 (1H, d, $J = 8.6$ Hz, C*H*–Br), 5.04 (1H, d, $J = 8.6$ Hz, C*H*–OH), 6.90 (2H, d, $J = 8.7$ Hz, Ar–*H*), 7.35 (2H, d, $J = 8.7$ Hz, Ar–*H*). ^{13}C NMR (50 MHz): δ 13.8, 48.0, 55.3, 62.3, 74.8, 113.9, 128.2, 131.3, 159.8, 169.5. MS (*m*/*z*): (M+1) 304, 302, 259, 257, 207, 178, 177, 161, 138, 137, 135, 121, 107, 94. Anal. Calcd for $C_{12}H_{15}BrO_4$: C, 47.54; H, 4.99. Found: C, 47.39; H, 5.06.

4.8. Preparation of methyl (±)-*anti*-3-hydroxy-2-iodo-3-(4-methoxyphenyl)-propanoate 2g

Compound **2g** was prepared from 4-methoxy methyl cinnamate (3.84 g, 20.0 mmol) following the procedure as described for **2c** (4.30 g, 65%), mp 86–87 °C. IR (KBr): 3300, 1734, 1612, 1517, 1167, 834 cm^{-1}. ^1H NMR (200 MHz): δ 3.78 (3H, s, $-COOCH_3$), 3.82 (3H, s, $-OCH_3$), 4.55 (1H, d, $J = 8.5$ Hz, C*H*–I), 5.05 (1H, d, $J = 8.5$ Hz, C*H*–OH), 6.90 (2H, d, $J = 8.7$ Hz, Ar–*H*), 7.30 (2H, d, $J = 8.7$ Hz, Ar–*H*). ^{13}C NMR (50 MHz): δ 25.4, 53.1, 55.4, 75.8, 114.3, 128.2, 131.6, 160.2, 171.7. MS (*m*/*z*): (M+1) 337, 192, 161, 138, 137, 109. Anal. Calcd for $C_{11}H_{13}IO_4$: C, 39.31; H, 3.90. Found: C, 39.48; H, 3.92.

4.9. Preparation of ethyl (±)-*anti*-3-hydroxy-2-iodo-3-(4-methoxyphenyl)propanoate 2h

Compound **2h** was prepared from 4-methoxy ethyl cinnamate (4.12 g, 20.0 mmol) following the procedure as described for **2c** to give **2h** (4.50 g, 65%), mp 108–109 °C. IR (KBr): 3436, 1736, 1610, 1513, 1253, 1118, 838 cm^{-1}. ^1H NMR (200 MHz): δ 1.28 (3H, t, $J = 7.1$ Hz, $-COOCH_2CH_3$), 3.82 (3H, s, $-OCH_3$), 4.25 (2H, q, $J = 7.1$ Hz, $-COOCH_2$), 4.54 (1H, d, $J = 8.5$ Hz, C*H*–I), 5.04 (1H, d, $J = 8.5$ Hz, C*H*–OH), 6.91 (2H, d, $J = 8.7$ Hz, Ar–*H*), 7.31 (2H, d, $J = 8.7$ Hz, Ar–*H*). ^{13}C NMR (50 MHz): δ 14.1, 25.7, 55.7, 62.5, 76.2, 114.3, 128.6, 132.0, 160.1, 171.6. MS (*m*/*z*): 350, 223, 206, 177, 161, 109. Anal. Calcd for $C_{12}H_{15}IO_4$: C, 41.16; H, 4.32. Found: C, 41.48; H, 4.40.

4.10. Preparation of methyl (±)-*anti*-3-acetoxy-2-bromo-3-phenylpropanoate 3a

A solution of **2a** (2.59 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) in dichloromethane (10 mL) was kept overnight at room temperature. After completion of the reaction, the contents were poured into ice-cold water and extracted with dichloromethane (3×50 mL). The organic layer was washed, dried and evaporated to furnish the crude product, which on purification by column chromatography over silica gel with ethyl acetate–*n*-hexane (3:97) as eluent gave **3a** (2.86 g, 95%), mp 56 °C. IR (KBr): 3006, 1732, 1436, 1372, 1234, 1130, 1013, 926, 768 cm^{-1}. ^1H NMR (200 MHz): δ 1.99 (3H, s, $-OCOCH_3$), 3.80 (3H, s, $-COOCH_3$), 4.64 (1H, d, $J = 10.7$ Hz, C*H*–Br), 6.15 (1H, d, $J = 10.7$ Hz, C*H*–OAc), 7.38 (5H, s, Ar–*H*). ^{13}C NMR (50 MHz): δ 20.6, 22.4, 53.1, 76.7, 128.0, 128.5, 129.2, 136.6, 168.7, 169.8. MS (*m*/*z*): (M+1) 302, 243, 221, 189, 179, 161, 149, 131. Anal. Calcd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.84; H, 4.27.

4.11. Preparation of ethyl (±)-*anti*-3-acetoxy-2-bromo-3-phenylpropanoate 3b

Compound **3b** was prepared from **2b** (2.73 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the procedure for **3a** (2.93 g, 93%). IR (neat): 2984, 1746, 1371, 1268, 1221, 1147, 1020, 763 cm^{-1}. ^1H NMR (200 MHz): δ 1.30 (3H, t, $J = 7.1$ Hz, $-COOCH_2CH_3$), 2.00 (3H, s, $-OCOCH_3$), 4.27 (2H, q, $J = 7.1$ Hz, $-COOCH_2$), 4.48 (1H, d, $J = 10.0$ Hz, C*H*–Br), 6.10 (1H, d, $J = 10.0$ Hz, C*H*–OAc), 7.40 (5H, s, Ar–*H*). ^{13}C NMR (50 MHz): δ 14.5, 21.3, 46.9, 62.9, 76.1, 128.5, 128.6, 129.8, 136.6, 168.2, 169.2. MS (*m*/*z*): 315, 301, 293, 277, 252, 236, 233, 217, 212, 211, 195, 196, 170, 154. Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.56; H, 4.80. Found: C, 50.04; H, 4.71.

4.12. Preparation of methyl (±)-*anti*-3-acetoxy-2-iodo-3-phenylpropanoate 3c

Compound **3c** was prepared from **2c** (3.06 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the procedure as described for **3a** (3.30 g, 95%), mp 57–58 °C. IR (KBr): 3006, 2953, 1732, 1436, 1375, 1234, 1130, 1013, 764 cm^{-1}. ^1H NMR (200 MHz): δ 2.01 (3H, s, –OCOCH_3), 3.81 (3H, s, –COOCH_3), 4.65 (1H, d, J = 10.7 Hz, CH–I), 6.15 (1H, d, J = 10.7 Hz, CH–OAc), 7.37 (5H, s, Ar–H). ^{13}C NMR (50 MHz): δ 20.7, 22.5, 53.1, 77.0, 128.0, 128.5, 129.2, 136.6, 168.7, 169.8. MS (*m*/*z*): 348, 273, 263, 220, 204, 198, 182, 167, 166, 151, 150, 140, 124, 108, 96, 80. Anal. Calcd for $C_{12}H_{13}IO_4$: C, 41.40; H, 3.76. Found: C, 41.03; H, 3.80.

4.13. Preparation of ethyl (±)-*anti*-3-acetoxy-2-iodo-3-phenylpropanoate 3d

Compound **3d** was prepared from **2d** (3.19 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the procedure as described for **3a** to furnish **3d** (3.28 g, 91%). IR (neat): 2982, 1738, 1371, 1263, 1222, 1017, 967, 699 cm^{-1}. ^1H NMR (200 MHz): δ 1.29 (3H, t, J = 7.1 Hz, –COOCH$_2$CH_3), 1.98 (3H, s, –OCOCH_3), 4.27 (2H, q, J = 7.1 Hz, –COOCH_2), 4.62 (1H, d, J = 10.8 Hz, CH–I), 6.15 (1H, d, J = 10.8 Hz, CH–OAc), 7.38 (5H, s, Ar–H). ^{13}C NMR (50 MHz): δ 13.8, 20.6, 23.1, 62.1, 76.7, 128.0, 128.4, 129.1, 136.6, 168.6, 169.2. MS (*m*/*z*): 362, 236, 215, 194, 177, 150, 147, 132, 108, 105, 91. Anal. Calcd for $C_{13}H_{15}IO_4$: C, 43.12; H, 4.18. Found: C, 43.23; H, 4.22.

4.14. Preparation of methyl (±)-*anti*-3-acetoxy-2-bromo-3-(4-methoxyphenyl)-propanoate 3e

Compound **3e** was prepared from **2e** (2.89 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the procedure as described for **3a** (3.11 g, 94%). IR (neat): 3004, 2956, 1748, 1612, 1516, 1371, 1022, 964, 832 cm^{-1}. ^1H NMR (200 MHz): δ 2.00 (3H, s, –OCOCH_3), 3.81 (3H, s, COOCH_3), 3.82 (3H, s, –OCH_3), 4.71 (1H, d, J = 10.2 Hz, CH–Br), 6.10 (1H, d, J = 10.2 Hz, CH–OAc), 6.90 (2H, d, J = 8.7 Hz, Ar–H), 7.32 (2H, d, J = 8.7 Hz, Ar–H). ^{13}C NMR (50 MHz): δ 20.6, 22.8, 53.3, 62.3, 75.3, 113.9, 128.1, 129.3, 160.1, 167.8, 168.8. MS (*m*/*z*): 331, 251, 209, 207, 177, 153, 136, 134. Anal. Calcd for $C_{13}H_{15}BrO_5$: C, 47.13; H, 4.53. Found: C, 47.41; H, 4.49.

4.15. Preparation of ethyl (±)-*anti*-3-acetoxy-2-bromo-3-(4-methoxyphenyl)-propanoate 3f

Compound **3f** was prepared from **2f** (3.03 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the procedure as described for **3a** (3.21 g, 93%), mp 54–55 °C. IR (neat): 2984, 1746, 1371, 1268, 1221, 1147, 1020, 763, 698, 611, 580, 541 cm^{-1}. ^1H NMR (200 MHz): δ 1.31 (3H, t, J = 7.1 Hz, –COOCH$_2$CH_3), 2.00 (3H, s, –OCOCH_3), 3.81 (3H, s, –OCH_3), 4.25 (2H, q, J = 7.1 Hz, –COOCH_2), 4.69 (1H, d, J = 10.1 Hz, CH–Br), 6.08 (1H, d, J = 10.1 Hz, CH–OAc), 6.90 (2H, d, J = 8.7 Hz, Ar-H), 7.32 (2H, d, J = 8.7 Hz, Ar–H). ^{13}C NMR (50 MHz): δ 14.0, 20.9, 46.7, 53.3, 62.3, 75.3, 113.9, 128.1, 129.3, 160.1, 167.8, 168.8. MS (*m*/*z*): 345, 265, 223, 222, 219, 177, 109, 91, 90, 89. Anal. Calcd for $C_{14}H_{17}BrO_5$: C, 48.71; H, 4.96. Found: C, 49.13; H, 5.08.

4.16. Preparation of methyl (±)-*anti*-3-acetoxy-2-iodo-3-(4-methoxyphenyl)-propanoate 3g

Compound **3g** was prepared from **2g** (3.36 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the procedure described for **3a** (3.40 g, 90%), mp 58 °C. IR (neat): 3451, 3005, 2951, 1735, 1611, 1435, 1375, 1022, 958, 830, 777 cm^{-1}. ^1H NMR (200 MHz): δ 1.99 (3H, s, –OCOCH_3), 3.80 (3H, s, –COOCH_3), 3.82 (3H, s, –OCH_3), 4.64 (1H, d, J = 10.8 Hz, CH–I), 6.12 (1H, d, J = 10.8 Hz, CH–OAc), 6.90 (2H, d, J = 8.7 Hz, Ar–H), 7.33 (2H, d, J = 8.7 Hz, Ar–H). ^{13}C NMR (50 MHz): δ 20.7, 22.9, 53.1, 55.7, 76.8, 113.8, 128.7, 129.3, 160.1, 168.7, 169.9. MS (*m*/*z*): 378, 335, 251, 208, 133, 108. Anal. Calcd for $C_{13}H_{15}IO_5$: C, 41.30; H, 4.00. Found: C, 41.80; H, 4.04.

4.17. Preparation of ethyl (±)-*anti*-3-acetoxy-2-iodo-3-(4-methoxyphenyl)-propanoate 3h

Compound **3h** was prepared from **2h** (3.50 g, 10.0 mmol), acetic anhydride (1.22 g, 12.0 mmol) and DMAP (5 mg) following the above procedure (3.56 g, 91%), mp 51–53 °C. IR (neat): 2981, 1739, 1612, 1516, 1371, 1252, 1224, 1177, 1019, 967, 832 cm^{-1}. ^1H NMR (200 MHz): δ 1.30 (3H, t, J = 7.1 Hz, –COOCH$_2$CH_3), 1.98 (3H, s, –OCOCH_3), 3.81 (3H, s, –OCH$_3$), 4.26 (2H, q, J = 7.1 Hz, –COOCH_2), 4.61 (1H, d, J = 10.9 Hz, CH–I), 6.12 (1H, d, J = 10.9 Hz, CH–OAc), 6.90 (2H, d, J = 8.7 Hz, Ar–H), 7.34 (2H, s, J = 8.7 Hz, Ar-H). ^{13}C NMR (50 MHz): δ 13.8, 20.7, 23.6, 55.2, 62.0, 76.4, 113.8, 128.7, 129.3, 160.1, 168.7, 169.4. MS (*m*/*z*): 392, 347, 333, 262, 222, 213, 206, 189, 179, 137, 132. Anal. Calcd for $C_{14}H_{17}IO_5$: C, 42.87; H, 4.37. Found: C, 43.33; H, 4.44.

4.18. General procedure of lipase catalyzed kinetic resolution of 3

In a typical experiment, a mixture of substrate **3a** (800 mg, 2.7 mmol), toluene (1.6 mL), crude powder of enzyme AS Amano (800 mg) in 14.4 mL phosphate buffer (pH 7.0, 0.1 M) was stirred at 30 ± 1 °C. The course of the reaction was monitored by chiral HPLC. After a certain degree of conversion, the reaction was terminated and contents extracted with ethyl acetate (3 × 50 mL), and organic phase washed with water, dried over sodium sulfate and concentrated in vacuo to give the crude product, which after column chromatography on silica gel with ethyl acetate–hexane (3:97) as eluent furnished (−)-**4a** (385 mg, 42%): ee 94%, $[\alpha]_D^{25}$ = −19.9 (*c* 1, $CHCl_3$) and (+)-**5a** (250 mg, 42%): ee 70%, $[\alpha]_D^{25}$ = +41.3 (*c* 1, $CHCl_3$).

4.19. General procedure for the preparation of 6 from 4

In a typical experiment, a mixture of alkyl (2*R*,3*R*)-2-halo-3-hydroxy-3-phenylpropanoate **4** (200 mg), DBU (200 μL) in dichloromethane (4 mL) was stirred at 5 °C for 5 min and gradually warmed to room temperature. Stirring was continued for another 30 min and monitored by TLC. After completion, the contents were diluted with dichloromethane (20 mL), and the organic phase washed with water, dried and chromatographed to give pure alkyl (2*S*,3*R*)-phenylglycidates **6**.

4.20. General procedure for the preparation of 7 from 5

In a typical experiment, alkyl (2*S*,3*S*)-3-acetoxy-2-halo-3-phenylpropanoate **5** (200 mg) was dissolved in methanol (4 mL). To this was added 2 M HCl (200 μL) and the reaction mixture stirred at room temperature for 24 h until the conversion was complete. Excess of solvent was evaporated and the reaction mixture diluted with water (10 mL) and extracted with ethyl acetate, dried and evaporated to give alkyl (2*S*,3*S*)-2-halo-3-hydroxy-3-phenylpropanoate, which was converted to **7** following the procedure as described for **6.**

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