Pergamon

Tetrahedron Vol. 51, No. 8, pp. 2403-2416, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01105-2

Synthesis of Chiral α-Aryl-α-Hydroxyacetic Acids: Substituent Effects in Pig Liver Acetone Powder (PLAP) Induced Enantioselective Hydrolysis

Deevi Basavaiah* **and Peddinti Rama Krishna**

School of Chemistry, University of Hyderabad
Hyderabad 500 134, India

Abstract: Pig liver acetone powder (PLAP) catalyzed hydrolysis of alkyl α-acetoxy-α-arylacetates produces alkyl (S)-α-aryl-α-hydroxyacetates in 23-80% enantiomeric purities. Enantioselectivity is dependent on the ester group of O-acetylmandelates. Substitution on the aromatic ring results in inferior selectivities. Only acetate group is hydrolyzed by PLAP while the ester functionality is found to be completely intact.

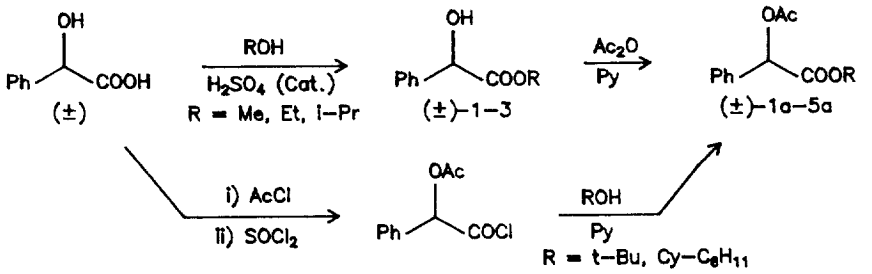
Enantiomerically pure α-aryl-α-hydroxyacetic acid derivatives are synthetically useful molecules and have been extensively utilized in a number of stereoselective processes.[1] Because of high synthetic potential of these fascinating molecules, a variety of synthetic methodologies have been developed for obtaining enantiomerically pure α-aryl-α-hydroxyacetic acid derivatives.[2] In recent years chemico-enzymatic methodology has gained much importance for producing a variety of enantiomerically pure molecules.[3] α-Aryl-α-hydroxyacetic acids have been synthesized in enantiomerically enriched form using purified enzymes[4] and whole cells[5].

Recently we[6] and others[7] have shown that certain crude enzyme preparations are as efficient as purified enzymes in a number of enantioselective syntheses. In continuation of our interest on applications of pig liver acetone powder (PLAP),[6a,b] we herein, report the enantioselective synthesis of α-aryl-α-hydroxyacetic acid derivatives using PLAP as a biocatalyst.

We have first selected methyl O-acetylmandelate (1a) as substrate

for enantioselective hydrolysis using PLAP as a biocatalyst. The required ester was prepared according to Scheme 1. Hydrolysis of the

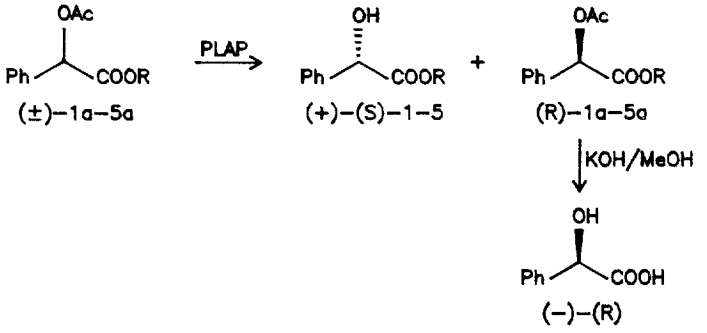
SCHEME 1:



R = Me (1a), Et (2a), *i*-Pr (3a), *t*-Bu (4a), Cy-C_6H_{11} (5a)

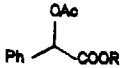
acetate **1a** was carried out in a variety of conditions and best results were obtained when the hydrolysis was carried out in a two phase medium producing the desired (+)-hydroxy ester **1** in 75% ee as determined by comparing its optical rotation with the literature value[4c] (Scheme 2). We also noticed that methyl ester functionality was completely intact.

SCHEME 2:



The recovered acetate on saponification produced (R)-mandelic acid in 70% enantiomeric purity. It occurred to us that the variation of ester group might provide better enantioselectivities in PLAP catalyzed hydrolysis of alkyl O-acetylmandelates. We, therefore, prepared representative O-acetylmandelic acid esters **2a-5a** according to Scheme 1. Hydrolysis of racemic acetates **2a-5a** was carried out in biphasic medium which produced the (+)-alcohols **2-5** in 47, 55, 80 and 23% optical purities respectively (Table 1).

Table 1: Enantioselective hydrolysis of alkyl O-acetylmandelates 1a-5a with PLAP.[a]

Substrate  (±)-1a-5a R =	Hydrolysis time (h)	Conversion[b] ratio	(+)-Alcohol (1-5) Yield[c] (%)	$[\alpha]_D^{24}$	ee[d] (%)	Conf.	Recovered diester Yield[c] (%)	ee[e] (%)
Me(1a)	5	48:52	83	+ 87.0(c 1.05, Acetone)	75	S	96	70
Et(2a)	8	41:59	65	+ 59.3(c 1.91, $CHCl_3$)	47	S	67	35
^{i}Pr(3a)	17	47:53	71	+ 62.6(c 1.01, $CHCl_3$)	55	S	95	50
^{t}Bu(4a)	17	34:66	66	+103.8(c 1.10, CCl_4)	80	S	80	49
Cyclohexyl (5a)	60	31:69	74	+ 16.8(c 1.13,EtOH)	23	S	71	15

a) All reactions were carried out in 5 mM scale with 2 g PLAP.

b) Conversion ratio was determined by HPLC.

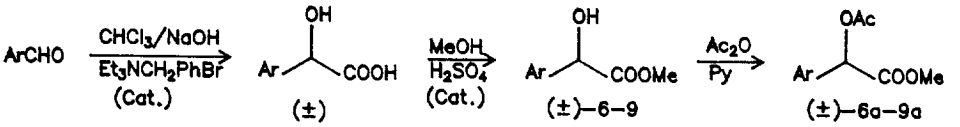
c) Yields of pure isolated products and are based on conversion ratio.

d) Enantiomeric purities were determined based on optical rotations reported in literature: **1**: $[\alpha]_D^{25}$ -115.4 (c 1.0, Acetone), ee >99%, Conf. (R), (Ref. 4c); **2**: $[\alpha]_D^{25}$ -126.2 (c 2.01, $CHCl_3$), Conf. (R), (Ref. 8); **3**: $[\alpha]_D^{25}$ -98.9 (c 1.00, $CHCl_3$), ee 88%, Conf. (R), (Ref. 2a); **4**: $[\alpha]_D^{27}$ -119.1 (c 1.05, CCl_4), ee 92%, Conf. (R), (Ref. 2a); **5**: $[\alpha]_D^{20}$ +71.97 (c 2.04, EtOH), ee 98%, Conf. (S), (Ref. 9).

e) Enantiomeric purities were determined after KOH/MeOH hydrolysis to (R)-mandelic acid.

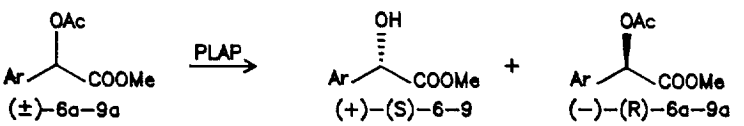
From Table 1 it is clear that methyl and *tert*-butyl esters of mandelic acid provide better selectivities compared to the other three ester groups in biocatalytic hydrolysis using PLAP. Also methyl O-acetylmandelate (1a) is hydrolyzed faster with PLAP compared to other alkyl derivatives (2a-5a). With a view to provide a general synthesis of chiral α-aryl-α-hydroxyacetic acids and to examine the effect of substitution on aromatic ring on enantioselectivity, we have directed our studies toward PLAP catalyzed hydrolysis of a representative class of methyl O-acetylarylacetates. The desired acids were prepared according to known procedure[10] and converted into the corresponding diesters 6a-9a (Scheme 3).

SCHEME 3:



Ar = 2-OMeC$_6$H$_4$ (6), 4-MeC$_6$H$_4$ (7), 4-OMeC$_6$H$_4$ (8), 1-Np (9)

We have examined the hydrolysis of acetate 6a with PLAP which produced the resulting (+)-alcohol 6 in 55% ee (Eq.1). The enantiomeric purity of the alcohol (+)-6 was determined by HPLC analysis using chiral column (CHIRALCEL OD) with racemic molecule 6 as reference. Similar HPLC



(Eq.1)

analysis of recovered diester (-)-6a with reference to racemic diester 6a showed that its optical purity is 43%. The absolute configuration of (+)-6 was found to be (S) and that of (-)-6a to be (R) by comparing the sign of optical rotation of the corresponding hydroxy acids with the literature value.[11] Then racemic acetates 7a-9a were also subjected to the enzymatic hydrolysis to produce (+)-alcohols 7-9 in 26, 57 and 30% enantiomeric purities respectively (Eq.1) (Table 2). The enantiomeric purities of alcohols (+)-7 and (+)-8 were determined by HPLC analysis as described for (+)-6. HPLC analysis of alcohol (±)-9 did not give any indication for separation of (R) & (S) enantiomers. However racemic

Table 2: Enantioselective hydrolysis of methyl α-acetoxy-α-arylacetates 6a-9a with PLAP.[a]

Substrate (±)-6a-9a, Ar =	Hydrolysis time (h)	Conversion ratio[b]	Product	Yield[c] (%)	$[\alpha]_D^{24}$	ee[d] (%)	Conf.
2-OMeC$_6$H$_4$ (6a)	2	43:57	(+)-6	84	+ 70.6 (c 0.98, EtOH)	55	S[e]
			(-)-6a	80	- 75.2 (c 0.61, EtOH)	43	R[e]
4-MeC$_6$H$_4$ (7a)	4	45:55	(+)-7	65	+ 29.3 (c 0.85, EtOH)	26	S[e]
			(-)-7a	70	- 50.8 (c 0.75, EtOH)	20[f]	R[e]
4-OMeC$_6$H$_4$ (8a)	3	44:56	(+)-8	78	+ 80.7 (c 1.02, EtOH)	57	S[g]
			(-)-8a	87	-117.1 (c 0.91, EtOH)	44[f]	R[e]
1-Np (9a)	4	57:43	(+)-9	64	+ 56.1 (c 0.75, EtOH)	30[h]	S[i]
			(-)-9a	67	-153.3 (c 0.89, EtOH)	53	R[i]

a) All reactions were carried out in 5 mM scale with 2 g of PLAP.

b) Conversion ratio was determined by HPLC.

c) Yields of pure isolated products and are based on conversion ratio.

d) Determined by HPLC analysis using chiral column, CHIRALCEL OD unless otherwise noted.

e) Absolute configuration was assigned by comparing the sign of optical rotation of the corresponding α-hydroxy acid obtained after KOH/MeOH hydrolysis with that of reported one (Ref. 11 or 12).

f) Determined by comparing the optical rotation of α-hydroxy acid (after KOH/MeOH hydrolysis) with that of literature value.

g) Absolute configuration was assigned by comparing the sign of optical rotation with that of literature value (ref.13).

h) Determined by HPLC analysis of its acetate using chiral column, CHIRALCEL OD.

i) Tentatively assigned.

acetate **9a**, on HPLC analysis, showed two peaks arising from both the enantiomers. Similar HPLC analysis of acetate of (+)-**9** and (-)-**9a** showed that their optical purities are 30 & 53% respectively. These results clearly show that the substitution on the aromatic ring increases the rate of hydrolysis but results in inferior enantioselectivity.

In conclusion, we have shown that enantioselectivity in the PLAP mediated hydrolysis of alkyl O-acetylmandelates depends considerably on the ester grouping of the mandelate and that substitution on the aromatic ring leads to inferior selectivities. Further applications of PLAP in organic transformations are in progress in our laboratory.

EXPERIMENTAL

The boiling points and melting points were uncorrected. IR spectra were recorded on Perkin-Elmer model 1310 or 297 spectrophotometers, using samples as neat liquid or KBr disks. ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (25 or 50 MHz) were recorded on BRUKER-AC-200 or JEOL-FX-100 spectrometers using Me_4Si (δ=0 ppm) as internal standard in $CDCl_3$. Elemental analyses were performed on a Perkin-Elmer model 240C-CHN analyzer. Optical rotations were measured on a Rudolph Polarimeter Autopol II. HPLC analysis was performed on Shimadzu LC-10AD equipped with SPD-10A UV-VIS detector. PLAP was prepared according to literature procedure.[7a] Column chromatography was carried out on a silica gel (100-200 mesh) column. The yields of products of enzymatic hydrolysis are based on conversion ratio. Yields of (+)-hydroxy acids are based on (+)-α-hydroxy esters. Yields of (-)-hydroxy acids are based on recovered diesters.

Methyl (±)-mandelate (1): To a stirred solution of mandelic acid (4.56 g, 30 mM) in methanol (30 mL) 2 drops of conc. H_2SO_4 were added and refluxed for 3 h. Methanol was distilled off and the crude ester was taken in ether (25 mL), washed with aqueous K_2CO_3 solution followed by brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated and distilled under reduced pressure. Yield: 4.44 g (89%); bp: 86-88^{o}C/5 mm (Lit.[14] 135^{o}C/12 mm); IR (neat) ν_{max}: 3350, 1740 cm^{-1}; ^{1}H NMR: δ 3.48 (d, 1H, J = 6 Hz, D_2O washable), 3.75 (s, 3H), 5.17 (d, 1H, J = 6 Hz), 7.36 (m, 5H); ^{13}C NMR: δ 52.41, 72.77, 126.48, 128.21, 128.36, 138.30, 173.89.

Methyl (±)-O-acetylmandelate (1a): To a stirred solution of racemic

methyl mandelate (1) (1.66 g, 10 mM), pyridine (1.7 mL, 20 mM) and DMAP (0.015 g) in dry dichloromethane (10 mL) at room temperature was added acetic anhydride (1.6 mL, 20 mM) dropwise. After stirring 2 h, the reaction mixture was poured into cold 2 N HCl solution (15 mL) and extracted with ether (3 x 10 mL). The organic layer was washed successively with 2 N HCl, saturated K_2CO_3 solution and brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by distillation under reduced pressure furnished pure acetate 1a as a colorless oil. Yield: 2.0 g (96%); bp: 74-76°C/1 mm; IR (neat) ν_{max}: 1740 cm^{-1}; ^1H NMR: δ 2.18 (s, 3H), 3.70 (s, 3H), 5.93 (s, 1H), 7.38 (m, 5H); ^{13}C NMR: δ 20.23, 52.24, 74.29, 127.54, 128.71, 129.12, 133.77, 169.24, 170.13.

Ethyl (±)-mandelate (2): Reaction time: 3 h; Yield: 87%; bp: 96°C/5 mm (Lit.[14] 150°C/21 mm); IR (neat) ν_{max}: 3420, 1730 cm^{-1}; ^1H NMR: δ 1.18 (t, 3H, J = 6 Hz), 3.72 (br, 1H, D_2O washable), 4.18 (m, 2H), 5.14 (d, 1H, J = 6 Hz), 7.33 (m, 5H); ^{13}C NMR: 18.64, 61.77, 72.77, 126.48, 128.36, 128.77, 138.48, 173.53.

Ethyl (±)-O-acetylmandelate (2a): Yield: 92%; bp: 118-20°C/6.5 mm; IR (neat) ν_{max}: 1740 cm^{-1}; ^1H NMR: δ 1.21 (t, 3H, J = 6 Hz), 2.18 (s, 3H), 4.22 (m, 2H), 5.90 (s, 1H), 7.46 (m, 5H); ^{13}C NMR: δ 13.47, 20.06, 61.18, 74.29, 127.42, 128.48, 128.89, 133.77, 168.54, 169.89.

***iso*-Propyl (±)-mandelate (3):** Reaction time: 4 h; Yield: 88%; bp: 96-98°C/5 mm; IR (neat) ν_{max}: 1720, 3430 cm^{-1}; ^1H NMR: δ 1.09 (d, 3H, J = 6 Hz), 1.26 (d, 3H, J = 6 Hz), 3.72 (d, 1H, J = 4 Hz, D_2O washable), 4.92-5.19 (m, 2H), 7.24-7.50 (m, 5H); ^{13}C NMR: 20.94, 21.23, 69.35, 72.77, 126.30, 127.94, 128.18, 138.59, 172.95.

***iso*-Propyl (±)-O-acetylmandelate (3a):** Yield: 90% ; bp: 110-12°C/4.5 mm; IR (neat) ν_{max}: 1740 cm^{-1}; ^1H NMR: δ 1.05 (d, 3H, J = 6 Hz), 1.26 (d, 3H, J = 6 Hz), 2.17 (s, 3H), 5.03 (m, 1H), 5.86 (s, 1H), 7.39-7.52 (m, 5H); ^{13}C NMR: 20.29, 21.06, 21.29, 69.06, 74.59, 127.48, 128.59, 128.95, 133.95, 168.24, 170.06; Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; Found: C, 66.15; H, 6.86.

O-Acetylmandelic acid: This was prepared according to the literature procedure.[15] Acetyl chloride (15 mL, 210 mM) was added to mandelic acid (10.5 g, 70 mM) at room temperature with stirring. After the formation of clear solution (15 min), the excess acetyl chloride was distilled off. Traces of acetyl chloride were removed under reduced pressure. Thus, formed, O-acetylmandelic acid was used for the next reaction without further purification. Yield: 12.92 g (95%).

α-Acetoxy-α-phenylacetyl chloride: O-Acetylmandelic acid (12.62 g, 65 mM) was taken in thionyl chloride (30 mL) and refluxed for 4 h. The excess thionyl chloride was distilled off and the residue was distilled under reduced pressure, to produce α-acetoxy-α-phenylacetyl chloride. Yield: 11.19 g (81%); bp: 116-18°C/6.5 mm [Lit.[15] bp 125-30°C/10 mm]; IR (neat) ν_{max}: 1740, 1800 cm^{-1}.

***tert*-Butyl (±)-O-acetylmandelate (4a):** To a stirred solution of pyridine (1.6 mL, 20 mM) in *tert*-butanol (15 mL) α-acetoxy-α-phenylacetyl chloride (4.25 g, 20 mM) was added at room temperature and stirred over night. The reaction mixture was diluted with ether (15 mL), washed successively with dil. HCl, aqueous K_2CO_3 solution and brine. The organic phase was dried over anhydrous Na_2SO_4, solvent was evaporated and the crude ester was recrystallized from hexane to provide **4a** as colorless solid. Yield: 3.86 g (77%); mp: 60-61°C; IR (neat) ν_{max}: 1740 cm^{-1}; ^1H NMR: δ 1.40 (s, 9H), 2.18 (s, 3H), 5.79 (s, 1H), 7.38 (m, 5H); ^{13}C NMR: 20.47, 27.59, 74.88, 82.24, 127.47, 128.59, 128.89, 134.36, 167.83, 170.24; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; Found: C, 67.17; H, 7.28.

Cyclohexyl (±)-O-acetylmandelate (5a): This was prepared following the similar procedure as described for **4a**. Reaction time: 4 h; Yield: 69%; IR (neat) ν_{max}: 1740 cm^{-1}; ^1H NMR: δ 1.18-1.92 (m, 10H), 2.18 (s, 3H), 4.75 (br, 1H), 5.88 (s, 1H), 7.36 (m, 5H); ^{13}C NMR: δ 20.26, 22.88, 23.00, 24.94, 30.65, 30.88, 73.59, 74.53, 127.36, 128.48, 128.89, 134.01, 168.07, 170.06; Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29; Found: C, 69.65; H, 7.28.

General procedure for enzymatic hydrolysis of (±)-O-acetylmandelic acid esters:

To 0.5 M, pH 8.0, KH_2PO_4/K_2HPO_4 buffer (40 mL), racemic acetate (5 mM) in ether (10 mL) was added with rapid stirring at room temperature. After 5 minutes, 2 g of PLAP was added and the stirring was continued. The progress of the hydrolysis was monitored by HPLC. When an appropriate degree of hydrolysis was accomplished the reaction was quenched by acidification to pH 4.0 with 2N HCl. Then sodium chloride (5 g) and dichloromethane (15 mL) were added and the mixture was stirred for 30 minutes. The PLAP residue was removed by filtration with suction and the layers were separated. The aqueous layer was extracted with dichloromethane (3x10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude liquid was subjected to column chromatography (silica gel, 10% ethyl acetate in

hexane) to furnish optically active alcohol and unhydrolyzed diester. Optical purities of (+)-alcohols were determined based on optical rotations reported in literature. Optically active diesters were hydrolyzed with KOH/MeOH to provide (-)-mandelic acid.

General procedure for hydrolysis of recovered diesters:

To a solution of 85% KOH (0.30 g, 5 mM) in MeOH (4 mL), recovered diester (2 mM) was added and stirred for 3 h at room temperature. Then methanol was distilled off under reduced pressure. The residue was diluted with water (4 mL), acidified with dil.HCl and extracted with ether (3 x 5 mL). The ethereal solution was dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded (-)-acid as white solid.

Enzymatic hydrolysis of methyl (±)-O-acetylmandelate (1a): Hydrolysis of racemic diester (1.04 g, 5 mM) with PLAP (2 g) afforded (+)-methyl mandelate and unhydrolyzed diester in 48:52 ratio. Reaction time: 5 h; Yield of (+)-alcohol: 0.331 g (83%); Optical rotation: $[\alpha]_D^{24}$ + 87.0(c 1.05, acetone),75% ee, Conf. (S); (Lit.[4c] $[\alpha]_D^{25}$ -115.4 (c 1, acetone), >99% ee, Conf. (R)); Yield of recovered diester: 0.520 g (96%). Yield of (-)-mandelic acid: 0.342 g (90%); mp: 130°C (Lit.[14] mp: 133°C); Optical rotation: $[\alpha]_D^{24}$ -108.0(c 0.54, acetone), 70% ee, Conf. (R); (Lit.[4b] $[\alpha]_D^{25}$ -154.3(c 2.1, acetone), Conf (R)).

Enzymatic hydrolysis of ethyl (±)-O-acetylmandelate (2a): Hydrolysis time: 8 h; Conversion ratio: 41:59; **(+)-alcohol:** yield: 65%; Optical rotation: $[\alpha]_D^{24}$ +59.3(c 1.91, $CHCl_3$), 47% ee, Conf. (S); (Lit.[8] $[\alpha]_D^{25}$ -126.2(c 2.01, $CHCl_3$), Conf. (R)). **Recovered diester:** yield: 67%; **(-)-mandelic acid:** yield: 91%; mp: 126-27°C (Lit.[14] mp: 133°C); Optical rotation: $[\alpha]_D^{24}$ -54.3(c 0.99, acetone), 35% ee, Conf. (R); (Lit.[4b] $[\alpha]_D^{25}$ -154.3(c 2.1, acetone), Conf. (R)).

Enzymatic hydrolysis of *iso*-propyl (±)-O-acetylmandelate (3a): Hydrolysis time: 17 h; Conversion ratio: 47:53; **(+)-alcohol:** yield: 71%; Optical rotation: $[\alpha]_D^{24}$ +62.6(c 1.01, $CHCl_3$), 55% ee, Conf. (S); (Lit.[2a] $[\alpha]_D^{25}$ -98.9 (c 1.00, $CHCl_3$), 88% ee, Conf. (R)). **Recovered diester:** yield: 95%; **(-)-mandelic acid:** yield: 89%; mp: 128-29°C (Lit.[14] mp: 133°C); Optical rotation: $[\alpha]_D^{24}$ -76.9 (c 0.6, acetone), 50% ee, Conf. (R); (Lit.[4b] $[\alpha]_D^{25}$ -154.3(c 2.1, acetone), Conf. (R)).

Enzymatic hydrolysis of *tert*-butyl (±)-O-acetylmandelate (4a): Hydrolysis time: 17 h; Conversion ratio: 34:66; **(+)-alcohol:** yield: 66%; mp: 71-72°C (Lit.[2a] mp 73-75°C for 92% optically pure alcohol); Optical rotation: $[\alpha]_D^{24}$ +103.8(c 1.10, CCl_4), 80% ee, Conf. (S); (Lit.[2a] $[\alpha]_D^{27}$

-119.1 (c 1.05, CCl_4), 92% ee, Conf. (R)}; IR(KBr) ν_{max}: 3420, 1720 cm^{-1}; ^1H NMR: δ 1.42 (s, 9H), 3.50 (d, 1H, J = 5 Hz, D_2O washable), 5.01 (d, 1H, J = 4 Hz), 7.38 (m, 5H); ^{13}C NMR: δ 27.76, 73.06, 83.00, 126.48, 128.18, 128.48 139.12, 173.06; **Recovered diester: yield: 80%; (-)-mandelic acid:** yield: 90%; mp: 128-29°C {Lit.[14] mp: 133°C}; Optical rotation: $[\alpha]_D^{24}$ -75.7(c 1.00, acetone), 49% ee, Conf. (R); {Lit.[4b] $[\alpha]_D^{25}$ -154.3(c 2.1, acetone), Conf. (R)}.

Enzymatic hydrolysis of cyclohexyl (±)-O-acetylmandelate (5a): Hydrolysis time: 60 h; Conversion ratio: 31:69; **(+)-alcohol:** yield: 74%; Optical rotation: $[\alpha]_D^{24}$ + 16.8 (c 1.13, EtOH), 23% ee, Conf. (S); {Lit.[9] $[\alpha]_D^{20}$ +71.97 (c 2.04, EtOH) 98.% ee, Conf. (S)}; IR(neat)ν_{max}: 3400, 1720 cm^{-1}; ^1H NMR: δ 1.18-1.94 (m, 10H), 3.50 (d, 1H, J = 4 Hz, D_2O washable), 4.84 (m, 1H), 5.12 (d, 1H, J = 4 Hz) 7.34 (m, 5H); ^{13}C NMR: δ 23.06, 23.29, 25.12, 30.94, 31.29, 72.94, 74.65, 126.53, 128.30, 128.53, 138.89, 173.36; **Recovered diester:** yield: 71%; **(-)-mandelic acid:** yield: 88%; mp: 124-25°C {Lit.[14] mp: 133°C}; Optical rotation: $[\alpha]_D^{24}$ -24.0(c 1.00, acetone), 15% ee, Conf. (R); {Lit.[4b] $[\alpha]_D^{25}$ -154.3(c 2.1, acetone), Conf. (R)}.

General procedure for preparation of (±)-α-hydroxy-α-arylacetic acid methyl esters:

α-Hydroxy acids were prepared according to literature procedure.[10]

To a stirred solution of aromatic aldehyde (20 mM) and triethylbenzylammonium chloride (0.228 g, 1 mM) in chloroform (3.5 mL), 50% NaOH solution (5 mL) was added dropwise at 55°C. After stirring 1 h at the same temperature the reaction mixture was cooled to room temperature and acidified with 50% H_2SO_4 (10 mL). Then the reaction mixture was extracted with ether (3 x 10 mL) and the combined ether extract was dried over anhydrous Na_2SO_4. Etheral layer was concentrated to provide α-hydroxy acid. Thus obtained crude α-hydroxy acids were esterified in methanol in presence of conc. H_2SO_4 (cat.) as described for the preparation of **1**. These methyl esters were converted into the corresponding O-acetyl derivatives by treating with acetic anhydride in the presence of pyridine. Yields of methyl esters (±)-**6-9** are based on the corresponding aldehydes.

Methyl (±)-α-hydroxy-α-(2-methoxyphenyl)acetate (6): Yield: 72%; IR (neat) ν_{max}: 3420, 1730 cm^{-1}; ^1H NMR: δ 3.57 (d, 1H, J = 6 Hz, D_2O Washable), 3.73 (s, 3H), 3.84 (s, 3H), 5.28 (d, 1H, J = 6 Hz), 6.95 (m,2H), 7.32 (m, 2H); ^{13}C NMR: δ 52.53, 55.53, 69.94, 111.24, 120.89,

127.12, 129.36, 129.94, 157.18, 174.34; Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17; Found: C, 61.25; H, 6.19.

Methyl (±)-α-acetoxy-α-(2-methoxyphenyl)acetate (6a): Yield: 93%; mp: 67-69°C; IR (KBr) ν_{max}: 1735 cm^{-1}; ^1H NMR: δ 2.15 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 6.44 (s, 1H), 6.96 (m, 2H), 7.36 (m, 2H); ^{13}C NMR: δ 20.29, 52.00, 55.47, 68.47, 112.12, 120.59, 122.48, 129.18, 130.59, 157.18, 169.59, 170.13.

Methyl (±)-α-hydroxy-α-(4-methylphenyl)acetate (7): Yield: 71%; IR (neat) ν_{max}: 3420, 1735 cm^{-1}; ^1H NMR: δ 2.32 (s, 3H), 3.6 (br, 1H, D_2O washable), 3.71 (s, 3H), 5.12 (d, 1H, J = 5 Hz), 7.14 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz); ^{13}C NMR: δ 20.88, 52.59, 72.71, 126.53, 129.24, 135.47, 138.18, 174.18; Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; Found: C, 66.90; H, 6.69.

Methyl (±)-α-acetoxy-α-(4-methylphenyl)acetate (7a): Yield: 92%; mp: 66-68°C; IR (KBr) ν_{max}: 1740 cm^{-1}; ^1H NMR: δ 2.18 (s, 3H), 2.35 (s, 3H), 3.71 (s, 3H), 5.90 (s, 1H), 7.18 (d, 2H, J = 8 Hz), 7.35 (d, 2H, J = 8 Hz); ^{13}C NMR: δ 20.29, 20.88, 52.18, 74.18, 127.59, 129.42, 130.89, 139.12, 169.35, 170.18.

Methyl (±)-α-hydroxy-α-(4-methoxyphenyl)acetate (8): Yield: 70%; IR (neat) ν_{max}: 3340, 1718 cm^{-1}; ^1H NMR: δ 3.55 (br, 1H, D_2O washable), 3.72 (s, 3H), 3.78 (s, 3H), 5.10 (d, 1H, J = 5 Hz), 6.87 (m, 2H), 7.31 (m, 2H); ^{13}C NMR (50 MHz): δ 52.53, 55.00, 72.41, 113.88, 127.89, 130.59, 159.65, 174.18; Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17; Found: C, 61.25; H, 6.14.

Methyl (±)-α-acetoxy-α-(4-methoxyphenyl)acetate (8a): Yield: 95%; IR (neat) ν_{max}: 1725 cm^{-1}; ^1H NMR: δ 2.17 (s, 3H), 3.71 (s, 3H), 3.80 (s, 3H), 5.87 (s, 1H), 6.90 (m, 2H), 7.37 (m, 2H); ^{13}C NMR: δ 20.59, 52.40, 55.21, 74.08, 114.18, 125.85, 129.08, 160.33, 169.49, 170.27.

Methyl (±)-α-hydroxy-α-(1-naphthyl)acetate (9): Yield: 72%; IR (neat) ν_{max}: 3425, 1728 cm^{-1}; ^1H NMR: δ 3.52 (d, 1H, J = 4 Hz, D_2O Washable), 3.71 (s, 3H), 5.80 (d, 1H, J = 4 Hz), 7.49 (m, 4H), 7.81 (m, 2H), 8.14 (m, 1H); ^{13}C NMR: δ 52.71, 71.29, 123.71, 125.18, 125.83, 126.53, 128.77, 129.36, 131.00, 134.01, 134.12, 174.53; Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59; Found: C, 72.31; H, 5.61.

Methyl (±)-α-acetoxy-α-(1-naphthyl)acetate (9a): Yield: 95% ; IR (neat) ν_{max}: 1735 cm^{-1}; ^1H NMR: δ 2.20 (s, 3H), 3.69 (s, 3H), 6.7 (s, 1H), 7.58 (m, 4H), 7.81 (m, 2H), 8.18 (m, 1H); ^{13}C NMR: δ 20.47, 52.47, 72.35,

123.71, 125.18, 126.06, 126.95, 127.47, 128.83, 130.01, 131.06, 133.95, 169.66, 170.30.

General procedure for enzymatic hydrolysis of methyl (±)-α-acetoxy-α-aryl-acetates:

Hydrolysis of methyl α-acetoxy-α-arylacetates was carried out in 5 mM scale with phosphate buffer (0.5 M, pH 8.0, 40 mL), ether (10 mL) and PLAP (2 g). Conversion ratio was determined by HPLC. Chiral column, CHIRALCEL OD was used for the determination of enantiomeric purities. Optically active hydroxy esters and diesters were hydrolyzed with KOH/MeOH to provide the corresponding hydroxy acids.

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(2-methoxyphenyl)acetate (6a): Hydrolysis time: 2 h; Conversion ratio: 43:57, **(+)-alcohol:** yield: 84%; Optical rotation: $[\alpha]_D^{24}$ +70.6 (c 0.98, EtOH), 55% ee; **Recovered ester:** yield: 80%; Optical rotation: $[\alpha]_D^{24}$ -75.2 (c 0.61, EtOH).

Determination of enantiomeric excess:

HPLC analysis of racemic alcohol 6 showed two peaks in 1:1 ratio (eluent: i-PrOH/Hexane: 5:95; flow rate: 0.5 mL/min; retention times: 46.75 and 54.20 min) due to (S) & (R) enantiomers. Similar analysis of optically active alcohol (+)-6 showed two peaks in 7.77:2.23 ratio (retention times: 47.30 and 55.61 min respectively) indicating that its optical purity is 55% ee.

Similarly racemic acetate 6a showed two peaks in 1:1 ratio (retention times: 19.92 and 22.78 min) due to (S) & (R) enantiomers under the same conditions. The recovered ester (-)-6a showed two peaks in 2.82:7.17 ratio (retention times: 19.13 and 21.72 min respectively) indicating that its optical purity is 43%.

Assignment of absolute configuration:

The alcohol (+)-6 was saponified with KOH/MeOH to afford (+)-α-hydroxy-α-(2-methoxyphenyl)acetic acid. Optical rotation: $[\alpha]_D^{24}$ +89.15 (c 1.0, MeOH), Conf. (S), (Lit.[11] *levo* rotation in MeOH for (R)-acid at 589 nm).

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(4-methylphenyl)acetate (7a): Hydrolysis time: 4 h; Conversion ratio: 45:55; **(+)-alcohol:** Yield: 65%; Optical rotation: $[\alpha]_D^{24}$ +29.3 (c 0.85, EtOH); HPLC analysis (eluent: i-PrOH/Hexane: 5:95; flow rate: 0.5 mL/min) of (+)-7 using chiral column (CHIRALCEL OD) with reference to (±)-7 showed that the enantiomeric purity of (+)-7 to be 26% (retention times 23.74 & 31.44 min for S & R isomers). **(+)-hydroxy acid:** Yield: 93%; mp: 136-37°C

(Lit.[10] mp: 144°C for (±)-hydroxy acid); Optical rotation: $[\alpha]_D^{24}$ +41.0 (c 0.3, EtOH), 27% ee, Conf. (S); (Lit.[12] $[\alpha]_D^{25}$ -153 (c 0.3, EtOH), Conf. (R)); **Recovered ester:** Yield: 70%; Optical rotation: $[\alpha]_D^{24}$ -50.8 (c 0.75, EtOH); **(-)-hydroxy acid:** Yield: 90%; mp: 136-37°C (Lit.[12] mp: 132-4°C); optical rotation: $[\alpha]_D^{24}$ -30.8 (c 0.29, EtOH), 20% ee, Conf. (R).

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(4-methoxyphenyl)acetate (8a): Hydrolysis time: 3 h; Conversion ratio: 44:56; **(+)-alcohol:** Yield: 78%; Optical rotation: $[\alpha]_D^{24}$ +80.7 (c 1.02, EtOH), 59% ee, Conf. (S); (Lit.[13] $[\alpha]_D^{18}$ +136.1 (c 2.4, EtOH), Conf. (S)); HPLC analysis (eluent: i-PrOH/Hexane: 10:90; flow rate: 0.5 mL/min) of (+)-**8** using chiral column (CHIRALCEL OD) with reference to (±)-**8** showed that the enantiomeric purity of (+)-**8** to be 57% (retention times 24.94 & 39.28 min for S & R isomers). **(+)-hydroxy acid:** Yield: 92%; mp: 101-2°C (Lit.[10] mp: 108°C for (±)-hydroxy acid); Optical rotation: $[\alpha]_D^{24}$+82.1 (c 0.27, H_2O), 58% ee, Conf. (S); (Lit.[12] $[\alpha]_D^{25}$ -141 (c 0.3, H_2O) Conf. (R)); **Recovered ester:** Yield: 87%; Optical rotation: $[\alpha]_D^{24}$ -117.1 (c 0.91, EtOH); **(-)-hydroxy acid:** Yield: 94%; mp: 102°C (Lit.[12] mp: 102-4°C); Optical rotation: $[\alpha]_D^{24}$ -62.1 (c 0.29, H_2O), 44% ee, Conf. (R).

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(1-naphthyl)acetate (9a): Hydrolysis time: 4 h; Conversion ratio: 57:43; **(+)-alcohol:** Yield: 64%; mp: 67-69°C; Optical rotation: $[\alpha]_D^{24}$ +56.1 (c 0.75, EtOH); HPLC analysis (eluent: i-PrOH/Hexane: 1:99; flow rate: 0.5 mL/min) of (+)-**9a** using chiral column (CHIRALCEL OD) with reference to (±)-**9a** showed that the enantiomeric purity of (+)-**9a** to be 30% (retention times 38.95 & 41.82 min for S & R isomers); **Recovered ester:** Yield: 67%; mp: 56-58°C; Optical rotation: $[\alpha]_D^{24}$ -153.3 (c 0.89, EtOH), 53% ee.

Acknowledgements: We thank DST (New Delhi) for funding this project. PRK thanks CSIR (New Delhi) for financial assistance. We also thank UGC (New Delhi) for Special Assistance and COSIST programs in Organic Synthesis in the School of Chemistry, University of Hyderabad.

REFERENCES

1. a) Whitesell, J.K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548-3551. b) Mashraqui, S.H.; Kellogg, R.M. *J. Org. Chem.* **1984**, *49*, 2513-2516.
2. a) Brown, H.C.; Pai, G.G. *J. Org. Chem.* **1985**, *50*, 1384-1394. b) Davies, F.A.; Vishwakarma, L.C. *Tetrahedron Lett.* **1985**, *26*, 3539-

3542. c) Burgess, V.A.; Davies, S.G.; Skerlj, R.T. *Tetrahedron: Asymmetry* **1991**, *2*, 299-328.

3. a) Jones, J.B. *Tetrahedron* **1986**, *42*, 3351-3403. b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-120. c) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071-1140.
4. a) Bevinakatti, H.S.; Banerji, A.A.; Newadkar, R.V. *J. Org. Chem.*, **1989**, *54*, 2453-2455. b) Chenevert, R.; Letourneau, M. *Can. J. Chem.* **1990**, *68*, 314-316. c) Miyazawa, T.; Kurita, S.; Ueji, S.; Yamada, T.; Kuwata, S.; *J. Chem. Soc., Perkin Trans.1* **1992**, 2253-2255.
5. Servi, S. *Synthesis*, **1990**, 1-25.
6. a) Basavaiah, D.; Rama Krishna, P.; Bharathi, T.K. *Tetrahedron Lett.* **1990**, *31*, 4347-4348. b) Basavaiah, D.; Rama Krishna, P. *Pure & Appl. Chem.* **1992**, *64*, 1067-1072 and references cited therein. c) Basavaiah, D.; Bhaskar Raju, S.; *Tetrahedron* **1994**, *50*, 4137-4148.
7. a) Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia* **1986**, *40*, 311-314. b) Whitesell, J.K.; Lawrence, R.M. *Chimia* **1986**, *40*, 318-321. c) Kazlauskas, R.J. *J. Am. Chem. Soc.* **1989**, *111*, 4953-4959. d) Esser, P.; Buschmann, H.; Meyer-Stork, M.; Scharf, H.-D.; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1190-1192.
8. Roger, R. *J. Chem. Soc.* **1932**, 2168-2180.
9. Ojima, I.; Kogure, T.; Kumagai, M. *J. Org. Chem.* **1977**, *42*, 1671-1679.
10. Merz, A.; *Synthesis* **1974**, 724-725.
11. Emerson, T.R.; Ewing, D.F.; Klyne, W.; Neilson, D.G.; Peters, D.A.V.; Roach, L.H.; Swan, R.J. *J. Chem. Soc.* **1965**, 4007-4014.
12. Hoover, J.R.E.; Dunn, G.L.; Jakas, D.R.; Lam, L.L.; Taggart, J.J.; Guarini, J.R.; Phillips, L. *J. Med. Chem.* **1974**, *17*, 34-41.
13. Pratesi, P.; La Manna, A.; Campiglio, A.; Ghislandi, V. *J. Org. Chem.* **1958**, 2069-2074.
14. *Dictionary of Organic Compounds*, Eyre & Spottiswoode publishers LTD; E. & F. N. Spon LTD (London), **1965**, *4*, 2052-2053.
15. Thayer, F.K.; *Org. Syntheses Coll. Vol.1* **1971**, 12-13.

(*Received in UK* 11 *October* 1994; *revised* 12 *December* 1994; *accepted* 16 *December* 1994)