Pergamon

Tetrahedron Vol. 50, No. 35, pp. 10521-10530, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00626-1

Pig Liver Acetone Powder (PLAP) as Biocatalyst: Enantioselective Synthesis of *trans*-2-Alkoxycyclohexan-1-ols†

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Abstract: Pig liver acetone powder (PLAP) enantioselectively hydrolyzes *trans*-1-acetoxy-2-alkoxycyclohexanes **1a-6a** in biphasic medium (ether and phosphate buffer) to provide the required (1R,2R)-2-alkoxycyclohexan-1-ols in 61-82% enantiomeric purities.

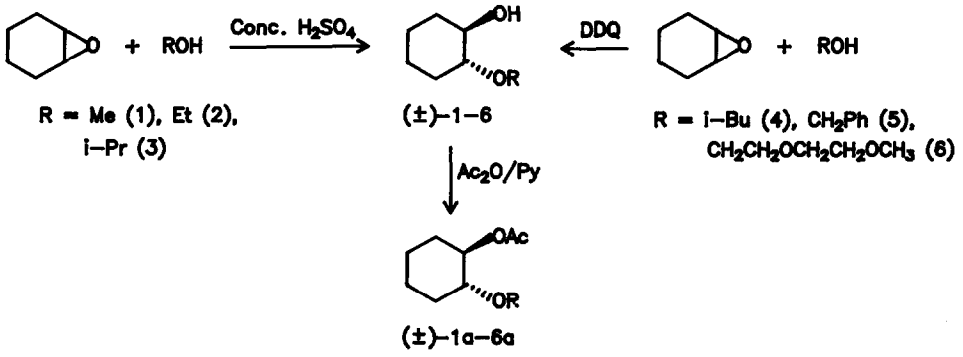
Enantioselectivity plays an important role in the present day organic synthesis particularly in the synthesis of medicinally important molecules.[1-3] A number of synthetic methodologies and reagents have been developed to achieve the synthesis of enantiomerically enriched molecules.[4] In recent years chemico-enzymatic methodology has proven to be more effective for obtaining optically active molecules[5-7] and therefore interest in the use of enzyme for the preparation of optically pure molecules has been growing continuously. Recent work of Klibanov on asymmetric transformations catalyzed by enzymes in organic solvents has made enzymes more popular among organic chemists.[8] Since cyclohexane ring constitutes a central structural moiety in a number of naturally occurring biologically active molecules and chiral auxiliries, there has been increasing interest in the synthesis of 2-substituted cyclohexan-1-ols in enantiomerically pure form using chemico-enzymatic methodology.[9-11] In continuation of our interest[12-14] on chemico-enzymatic methodology, we herein report enantioselective synthesis of 2-alkoxycyclohexan-1-ols using pig liver acetone powder (PLAP) as a biocatalyst.

In recent years applications of crude enzymes have become increasingly important for obtaining enantiomerically enriched molecules, because these enzymes are cheap, easy to prepare and handle.[12-17] Recently, we have successfully employed PLAP for the preparation of a variety of enantiomerically enriched molecules.[12-14] With a view to

expand the scope of PLAP in organic synthesis, we have undertaken the hydrolysis of racemic *trans*-2-alkoxycyclohex-1-yl acetates enantioselectively with PLAP to produce the corresponding alcohols in optically active form.

We have first selected racemic *trans*-1-acetoxy-2-methoxycyclohexane (1a) as a substrate for the enantioselective hydrolysis with PLAP. The desired racemic acetate 1a was prepared according to Scheme 1. We have

SCHEME 1:



examined the possible enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-methoxycyclohexane with PLAP under a variety of conditions. The best results were obtained when the hydrolysis was carried out in a two phase medium (ether: phosphate buffer). The resulting (-)-*trans*-2-methoxycyclohexan-1-ol was obtained in 80% enantiomeric excess with (R,R) configuration as determined by comparing the sign of optical rotation with that of literature value.[11] Encouraged by this result we have prepared a representative class of *trans*-1-acetoxy-2-alkoxycyclohexanes 2a-6a according to Scheme 1. These substrates were subjected to PLAP hydrolysis to provide the desired (-)-2-alkoxycyclohexan-1-ols 2-6 in 61-82% enantiomeric purities (Scheme 2) (Table).

Scheme 2:

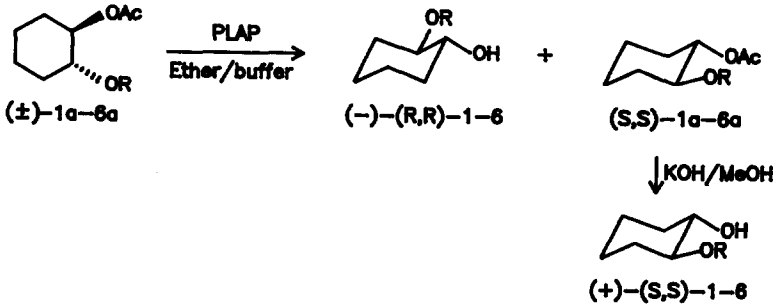


Table : Enantioselective hydrolysis of *trans*-2-alkoxycyclohex-1-yl acetates 1a-6a using PLAP.[a]

Substrate (±)-1a-6a, R =		Hydrolysis time (h)	Conversion[b] ratio	(-)-Alcohol (1-6) Yield[c] (%)	$[\alpha]_D^{24}$	ee[d] (%)	Conf.	Recovered acetate Yield[c] (%)	ee[e] (%)
Me	1a	8	47:53	57	-56.5(c 1.34, CH_2Cl_2)	80	(R,R)	79	75
Et	2a	26	46:54	73	-61.1(c 1.93, CH_2Cl_2)	76	(R,R)	90	60
i-Pr	3a	70	39:61	56	-68.8(c 1.60, CH_2Cl_2)	79	(R,R)	73	39
i-Bu	4a	24	44:56	58	-40.7(c 1.37, CH_2Cl_2)	61[f]	(R,R)	50	52
CH_2Ph	5a	17	44:56	90	-68.7(c 1.76, CH_2Cl_2)	79[g]	(R,R)	83	69
$CH_2CH_2OCH_2$ CH_2OCH_3	6a	16	48:52	63	-39.3(c 1.52, CH_2Cl_2)	82[f]	(R,R)	71	75

a) All reactions were carried out in 20 mM scale with 3 g of PLAP.

b) Conversion ratio was determined by GC.

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

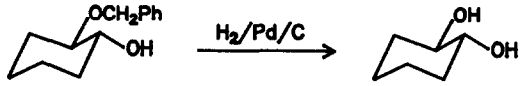
d) Comparing the optical rotation with the literature values unless otherwise noted: 1 : $[\alpha]_D^{20}$ -69.3 (c 2.0, CH_2Cl_2), ee 98%, Conf. (R,R), (Ref. 11); 2 : $[\alpha]_D^{20}$ -75.3 (c 2.0, CH_2Cl_2), ee 94%, Conf. (R,R), (Ref. 11); 3 : $[\alpha]_D^{20}$ -85.6 (c 2.0, CH_2Cl_2), ee 98%, Conf. (R,R), (Ref. 11).

e) Comparing the optical rotation of (+)-alcohol with that of corresponding (-)-alcohol.

f) Determined by ^1H NMR analysis of corresponding acetate in the presence of $Eu(hfc)_3$.

g) Comparing the optical rotation of diol (obtained after ether cleavage) with literature value.

The absolute configurations of (-)-*trans*-2-ethoxycyclohexan-1-ol and (-)-*trans*-2-(*iso*-propyloxy)cyclohexan-1-ol were found to be (R,R) by comparing the sign of optical rotations with literature values.[11] Chemical degradation of (-)-*trans*-2-benzyloxycyclohexan-1-ol (5) to (-)-(R,R)-cyclohexane-1,2-diol revealed that former is possessing (R,R) configuration (eq. 1). In analogy, the absolute configurations of optically active *trans*-2-alkoxycyclohexan-1-ols (-)-4 and (-)-6 can be tentatively assigned as (R,R).



(-)-5 (R,R) (Eq.1)

Though the chiral *trans*-2-alkoxycyclohexan-1-ols were not obtained in optically pure form, this study demonstrates the applicability of easily, abundantly available and cheap enzyme PLAP in organic synthesis. Further work in the application of PLAP in organic transformations is in progress.

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 (100 or 200 MHz) and ^{13}C NMR spectra (25 or 50 MHz) were recorded on JEOL-FX-100 or BRUKER-AC-200 spectrometers using Me_4Si (δ=0 ppm) as internal standard in $CDCl_3$. Mass spectra were recorded on finnigon MAT instrument (70 eV, 100A, 180°C). Elemental analysis was performed on a Perkin-Elmer 240C-CHN analyser. Optical rotations were measured on a Rudolph Polarimeter Autopol II. Gas chromatography analysis was performed on a CHEMITO Gas chromatograph equipped with a flame ionization detector on SE-30 column using nitrogen as carrier gas.

PLAP was prepared according to literature procedure.[12] 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 (+)-alcohols are based on recovered acetates. $Eu(hfc)_3$ {Tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium-(III) derivative} was used as a chiral shift reagent for ee

determination.

(±)-*trans*-2-Alkoxycyclohexan-1-ols (1-6):

(±)-*trans*-2-Alkoxycyclohexan-1-ols 1, 2, 3 were prepared by conc. H_2SO_4[18] catalyzed opening of cyclohexene oxide with the corresponding alcohols. The remaining alcohols 4, 5, 6 were prepared by DDQ[19] catalyzed opening of epoxide with the respective alcohols.

(±)-*trans*-2-Methoxycyclohexan-1-ol (1): To a stirred solution of cyclohexene oxide (5.0 mL, 50 mM) in methanol (25 mL), 2 drops of conc sulfuric acid was added at room temperature and then refluxed gently for 4 h. The excess methanol was distilled off. The residue was taken in ether (30 mL), washed with aqueous K_2CO_3 solution followed by brine. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. Distillation under reduced pressure afforded racemic alcohol 1 as a colorless liquid. yield: 5.86 g (90%); bp: 118-20°C/40 mm {Lit.[18] bp: 72.5-73.2°C/10 mm); IR(neat): 3400 cm^{-1}; ^1H NMR: δ 0.96-2.21(m, 8H), 2.84-3.42(m, 6H, 1H D_2O washable); ^{13}C NMR: δ 23.35, 27.83, 31.76, 55.76, 72.71, 84.36; MS (m/e): 130(M^+).

(±)-*trans*-2-Ethoxycyclohexan-1-ol (2): yield: 76%; bp: 98-100°C/10 mm (Lit.[11] bp: 78-79°C/13 mm); IR(neat): 3450 cm^{-1}; ^1H NMR: δ 1.00-2.18(m, 11H), 2.76-3.12(m, 2H, 1H D_2O washable), 3.20-3.84(m, 3H); ^{13}C NMR: δ 15.17, 23.59, 23.76, 29.00, 32.00, 63.71, 72.88, 82.94.

(±)-*trans*-2-(*iso*-Propyloxy)cyclohexan-1-ol (3): yield: 75%; bp: 104-6°C/16 mm (Lit.[11] bp: 81-83 °C/12 mm); IR (neat): 3400 cm^{-1}; ^1H NMR: δ 1.00-2.20(m, 14H), 2.68(s, 1H, D_2O washable), 2.88-3.48(m, 2H), 3.80(m, 1H); ^{13}C NMR: δ 21.88, 23.35, 23.64, 24.00, 30.06, 31.88, 69.18, 73.18, 80.83; MS (m/e): 158(M^+).

(±)-*trans*-2-(*iso*-Butyloxy)cyclohexan-1-ol (4): A mixture of cyclohexene oxide (5.0 mL, 50 mM), *iso*-butanol (30 mL, 320 mM) and DDQ (0.113 g, 0.5 mM, 1 mole %) was refluxed for 12 h. The excess *iso*-butanol was distilled off under reduced pressure. Thus obtained residue was fractionally distilled to afford the racemic alcohol 4 as a colorless liquid. yield: 5.25 g (61%); bp: 56-58°C/0.8 mm; IR(neat): 3400 cm^{-1}; ^1H NMR: δ 0.75-2.19(m, 15H), 2.74(s, 1H, D_2O washable), 2.68-3.58(m, 4H); ^{13}C NMR: δ 18.88, 23.47, 23.70, 28.35, 28.65, 31.65, 73.18, 75.30, 83.18; MS (m/e): 178(M^+).

(±)-*trans*-2-Benzyloxycyclohexan-1-ol (5): yield 64%; bp: 118-20°C/1 mm (Lit.[20] bp: 110-12°C/0.3 mm); IR(neat): 3400 cm^{-1}; ^1H NMR (200 MHz): δ 1.05-1.42 (m, 4H), 1.61-1.80 (m, 2H), 1.92-2.22 (m, 2H), 2.67 (s, 1H, D_2O washable), 3.18 (m, 1H), 3.49 (m, 1H), 4.46 & 4.69 (AB quartet 2H, J=11.5Hz), 7.35 (m, 5H); ^{13}C NMR (50 MHz): δ 23.93, 24.22, 29.26, 32.13, 70.84, 73.77, 83.47, 127.63, 127.68, 128.42, 138.76.

(±)-*trans*-2-[2-(2-Methoxyethoxy)ethoxy]cyclohexan-1-ol (6) : yield: 62%; bp: 108-10°C/2 mm; IR(neat): 3450 cm^{-1}; ^1H NMR: δ 0.84-2.16(m, 8H), 2.72-3.92(m, 14H, 1H D_2O washable); ^{13}C NMR: δ 23.53, 23.88, 29.35, 31.88, 58.41, 68.06, 69.94, 70.35, 71.47, 73.29, 84.06; MS (m/e): 218(M^+); Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.15. Found: C, 60.45; H, 10.11.

(±)-*trans*-1-Acetoxy-2-methyoxycyclohexane (1a): To a stirred solution of racemic *trans*-2-methoxycyclohexan-1-ol (1) (5.20 g, 40 mM) in dry CH_2Cl_2 (40 mL) were added pyridine (6.9 mL, 85 mM) and DMAP (0.060 g, 0.5 mM)at room temperature. To this mixture acetic anhydride (7.5 mL, 80 mM) was added dropwise. After 2 h stirring at room temperature the reaction mixture was poured into cold 2 N HCl solution (60 mL) and extracted with ether (3 x 40 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 as a colorless liquid. yield: 6.20 g (90%); bp: 94-96°C/10 mm; IR (neat): 1740 cm^{-1}; ^1H NMR: δ 1.08-2.04(m, 11H), 3.11(m, 1H), 3.14(s, 3H), 4.70 (m, 1H); ^{13}C NMR: δ 20.99, 22.87, 22.97, 28.85, 29.43, 56.70, 74.55, 80.12, 170.05.

(±)-*trans*-1-Acetoxy-2-ethoxycyclohexane (2a): yield: 92%; bp: 120-22°C/20 mm; IR (neat): 1740 cm^{-1}; ^1H NMR: δ 1.00-2.16(m, 14H) 3.14-3.80(m, 3H), 4.68(m, 1H); ^{13}C NMR: δ 15.17, 20.70, 22.82, 29.29, 29.53, 64.47, 74.59, 78.47, 170.00.

(±)-*trans*-1-Acetoxy-2-(*iso*-propyloxy)cyclohexane (3a): yield: 91%; bp: 112-14°C/10 mm; IR(neat): 1740 cm^{-1}; ^1H NMR: δ 0.98-2.12(m, 17H), 3.20(m, 1H), 3.64(m, 1H), 4.62(m, 1H); ^{13}C NMR: δ 20.70, 22.23, 22.70, 22.94, 29.53, 30.94, 70.89, 75.06, 76.83, 170.00.

(±)-*trans*-1-Acetoxy-2-(*iso*-butyloxy)cyclohexane (4a): yield: 95%; bp: 84-86°C/3 mm; IR(neat): 1740 cm^{-1}; ^1H NMR: δ 0.88 (d, 6H, J=6 Hz),

1.06-2.06 (m, 12H), 3.24(m, 3H), 4.68 (m, 1H); ^{13}C NMR (50 MHz): δ 18.91, 20.78, 22.86, 22.93, 28.47, 29.37, 74.37, 76.01, 78.84, 169.66.

(±)-*trans*-1-Acetoxy-2-benzyloxycyclohexane (5a): yield: 94%; bp: 138-40°C/12 mm; IR(neat): 1740 cm^{-1}; ^1H NMR: δ 1.04-2.20(m, 11H), 3.32(m, 1H), 4.51-4.98(m, 3H), 7.28(s, 5H); ^{13}C NMR (50 MHz): δ 21.26, 23.26, 29.86, 71.29, 75.09, 78.71, 127.34, 128.26, 139.03, 170.35.

(±)-*trans*-1-Acetoxy-2-[2-(2-methoxyethoxy)ethoxy]cyclohexane (6a): yield 96%; bp: 126-28°C/4 mm; IR(neat): 1740 cm^{-1}; ^1H NMR: δ 1.00-2.08(m, 11H), 3.08-3.76(m, 12H), 4.62(m, 1H); ^{13}C NMR (50 MHz): δ 20.96, 23.04, 29.56, 29.67, 58.63, 68.87, 70.27, 70.62, 71.70, 74.86, 79.41, 170.06.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-alkoxycyclohexanes:
General procedure:

To 0.5 M, pH 8.0, KH_2PO_4/K_2HPO_4 buffer(120 mL), racemic acetate (20 mM) in ether (20 mL) was added with rapid stirring at room temperature. After 15 minutes, 3 g of PLAP was added and the stirring was continued. The progress of the hydrolysis was monitored by GC. When an appropriate degree of hydrolysis was accomplished the reaction was quenched by acidification to pH 4.0 with 2N HCl. Then sodium chloride (15 g) and dichloromethane (40 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 (3x15 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 get optically active alcohol and unhydrolyzed acetate.

Hydrolysis of recovered acetates:

To a solution of 85% KOH (1.68 g, 15 mM) in MeOH (10 mL), recovered acetate (5 mM) was added and stirred for 3 h at room temperature. Then methanol was distilled off under reduced pressure and the residue was diluted with water (10 mL) and extracted with ether (3 x 10 mL). The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated. The crude liquid was purified by column chromatography (silica gel, 10% ethyl acetate in hexane) to afford (+)-alcohol.

Enzymatic hydrolysis of 1a:
Hydrolysis time: 8 h; Conversion ratio: 47:53; (-)-alcohol: yield: 57%;

Optical rotation: $[\alpha]_D^{24}$ -56.5(c 1.34, CH_2Cl_2), 80% ee, Conf. (R,R); (Lit.[11] $[\alpha]_D^{20}$ -69.3(c 2.0, CH_2Cl_2), 98% ee, Conf. (R,R)); Recovered acetate: yield: 79%; (+)-alcohol: yield: 90%; Optical rotation: $[\alpha]_D^{24}$ +53.0 (c 2.13, CH_2Cl_2), 75% ee.

Enzymatic hydrolysis of 2a:

Hydrolysis time: 26 h; Conversion ratio: 46:54; (-)-alcohol: yield: 73%; Optical rotation: $[\alpha]_D^{24}$ -61.1(c 1.93, CH_2Cl_2), 76% ee, Conf. (R,R); (Lit.[11] $[\alpha]_D^{20}$ -75.3 (c 2.0, CH_2Cl_2),94% ee, Conf. (R,R)); Recovered acetate: yield: 90%; (+)-alcohol: yield: 94%; Optical rotation: $[\alpha]_D^{24}$ +48.4 (c 0.93, CH_2Cl_2), 60% ee.

Enzymatic hydrolysis of 3a:

Hydrolysis time: 70 h; Conversion ratio: 39:61; (-)-alcohol: yield: 56%; Optical rotation: $[\alpha]_D^{24}$ -68.8 (c 1.6, CH_2Cl_2), 79% ee, Conf. (R,R); (Lit.[11] $[\alpha]_D^{20}$ -85.6 (c 2.0, CH_2Cl_2), 98% ee, Conf. (R,R)); Recovered acetate: yield: 73%; (+)-alcohol: yield: 92%; Optical rotation: $[\alpha]_D^{24}$ +33.8 (c 1.83, CH_2Cl_2), 39% ee.

Enzymatic hydrolysis of 4a:

Hydrolysis time: 24 h; Conversion ratio: 44:56; (-)-alcohol: yield: 58%; Optical rotation: $[\alpha]_D^{24}$ -40.7 (c 1.37, CH_2Cl_2), 61% ee; Recovered acetate: yield: 50%; (+)-alcohol: yield: 91%; Optical rotation: $[\alpha]_D^{24}$ +34.6 (c 1.14, CH_2Cl_2) 52% ee.

Determination of enantiomeric purity of (-)-*trans*-2-alkoxycyclohexan-1-ol 4:

^1H NMR analysis of racemic acetate **4a** (5 mg) in the presence of shift reagent, $Eu(hfc)_3$ (30 mg) shows that the acetate ($-COCH_3$) signal shifts and splits into two distinct singlets of equal integrations due to (R,R) and (S,S) enantiomers. ^1H NMR analysis of acetate of optically active alcohol (-)-**4** in the presence of $Eu(hfc)_3$ showed two distinct singlets in the ratio 8:1.94 for $-COCH_3$ protons indicating that its optical purity is 61%.

Enzymatic hydrolysis of 5a:

Hydrolysis time: 17 h; Conversion ratio: 44:56; (-)-alcohol: yield: 90%; Optical rotation: $[\alpha]_D^{24}$ -68.7 (c 1.76, CH_2Cl_2),79% ee Conf. (R,R); Recovered acetate: yield: 83%; (+)-alcohol: yield: 95%; Optical rotation: $[\alpha]_D^{24}$ +60.6 (c 1.76, CH_2Cl_2), 69% ee.

Determination of enantiomeric excess and absolute configuration of (-)-5:

Chemical degradation of (-)-5 to (-)-(1R,2R)-cyclohexane-1,2-diol:

A solution of optically active alcohol (-)-5 (206 mg, 1 mM) in methanol (3 mL) was shaken with 10% palladium on charcoal (50 mg) at 35 lbs/sq. inch pressure at room temperature in a Parr hydrogenator for 3 h. Then the catalyst was filtered off. Removal of solvent afforded pure crystalline (-)-(R,R)-cyclohexane-1,2-diol. yield: 0.097 g (84%); mp: 109-110°C [Lit.[21] optically pure diol mp: 113-14°C]; IR (KBr): 3300 cm^{-1}; ^1H NMR (200 MHz): δ 1.26(m, 4H), 1.70(m, 2H), 1.96(m, 2H), 2.30(s, 2H, D_2O washable), 3.35(m, 2H); ^{13}C NMR: δ 24.35, 32.88, 75.71. Optical rotation : $[\alpha]_D^{24}$ -31.5 (c 0.58, $CHCl_3$), 79% ee, Conf. (R,R); {Lit.[21] $[\alpha]_D^{25}$ -40 (c 0.32, $CHCl_3$), Conf. (R,R)}.

Enzymatic hydrolysis of 6a:

Hydrolysis time: 16 h; Conversion ratio: 48:52; (-)-alcohol: yield: 63%; Optical rotation: $[\alpha]_D^{24}$ -39.3 (c 1.52, CH_2Cl_2), 82% ee; Recovered acetate: yield: 71%; (+)-alcohol: yield: 95%; Optical rotation: $[\alpha]_D^{24}$ +35.9 (c 1.57, CH_2Cl_2), 75% ee.

^1H NMR analysis of racemic acetate 6a (5 mg) in the presence of shift reagent, $Eu(hfc)_3$ (30 mg) shows that the signal of OCH_3 protons shifts and splits into two singlets of equal integrations due to both enantiomers. Similar ^1H NMR analysis of acetate of optically active alcohol (-)-6 in the presence of $Eu(hfc)_3$ showed two singlets for OCH_3 protons in the ratio of 91:9 indicates that its enantiomeric purity is 82%.

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.

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(*Received in UK* 2 *June* 1994; *revised* 12 *July* 1994; *accepted* 15 *July* 1994)