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A Convenient Enantioselective Synthesis of *trans*-2-Aryloxycyclohexan-1-ols Using Pig Liver Acetone Powder (PLAP) as Biocatalyst†

Deevi Basavaiah*, Peddinti Rama Krishna and Tirumala K. Bharathi

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

ABSTRACT: Pig liver acetone powder (PLAP) has been used as a biocatalyst for enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-aryloxycyclohexanes to produce the resulting (R,R)-2-aryloxycyclohexan-1-ols upto >99% enantiomeric purities. (R,R)-Selectivity in this hydrolysis of racemic *trans*-2-aryloxycyclohexyl acetates was explained on the basis of Jones' three dimensional active site-model.

The development of convenient methods for obtaining enantiomerically pure molecules has become one of the most important goals in the fields of organic and bioorganic chemistry.[1] The importance of enantiomerically pure molecules stems from the central role of enantiomer recognition in biological activity.[2-4] The dependence of biological activity of several chemical products on the enantiomeric purity of these molecules has led to the development of a number of chiral reagents, chiral catalysts and synthetic strategies for synthesis of optically active molecules. Now the arsenal of synthetic organic chemists has become impressively very rich in methods for the preparation of enantiomerically enriched molecules.[1]

The application of biocatalysis to a variety of organic transformations has become increasingly important in recent years and the synthesis of enantiomerically pure molecules using chemico-enzymatic methodology is at present a well defined area of research.[5-9] Recent work of Klibanov on asymmetric transformations catalyzed by enzymes in organic solvents has made enzymes more popular among organic chemists.[9] However, there exists an apprehension amongst organic chemists with respect to the handling and purification of enzymes. Also the use of purified enzymes on a regular basis could be very expensive. This problem can possibly be overcome by using a crude preparation of certain enzymes in a projected reaction if

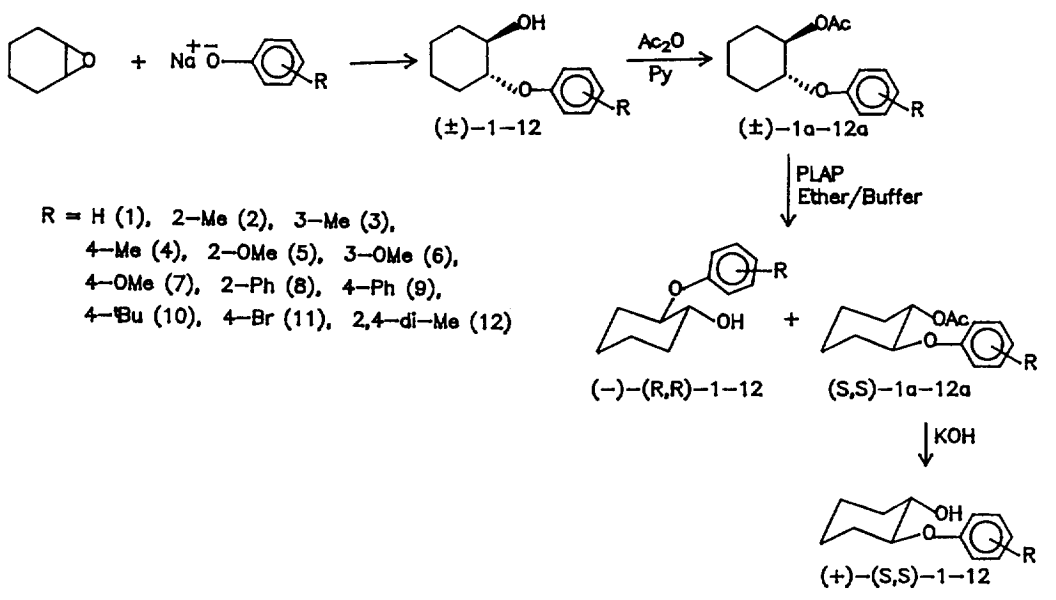
the other enzymes present in the crude preparation do not interfere. However, the literature survey reveals that crude enzyme preparations are relatively less exploited for organic transformations compared to the purified enzymes.[10-12] We herein report our work on the enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-aryloxycyclohexanes (**1a-12a**) using Pig liver acetone powder (PLAP), a crude preparation of Pig liver esterase (PLE) to produce the required (-)-(R,R)-*trans*-2-aryloxycyclohexan-1-ols in high enantiomeric purities.

RESULTS AND DISCUSSION

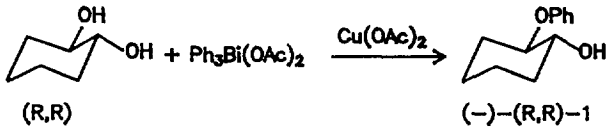
Recent efforts directed towards the synthesis of biologically active molecules have pointed out the need for a variety of chiral auxiliaries that are easy to synthesize. Among the various chiral auxiliaries, the cyclohexyl-based chiral auxiliaries[13] such as (+)/(-)-menthol,[14] (-)-8-phenylmenthol,[15] (+)/(-)-*trans*-2-phenylcyclohexanol[16,17] are some of the commonly used chiral auxiliaries for asymmetric transformations. With a view that structurally related *trans*-2-aryloxycyclohexan-1-ol derivatives would be of interest as chiral auxiliaries in organic synthesis, we have undertaken the synthesis of enantiomerically pure *trans*-2-aryloxycyclohexanols.

First we have selected chiral *trans*-2-phenoxycyclohexan-1-ol (**1**) as a target molecule. We planned to synthesize *trans*-2-phenoxycyclohexan-1-ol (**1**) in optically pure form *via* enantioselective hydrolysis of racemic

SCHEME 1



trans-2-phenoxycyclohexyl acetate (1a) with PLAP. The required racemic alcohol **1** was prepared by the opening of cyclohexene oxide with sodium phenoxide. This racemic alcohol was converted into the corresponding acetate by the action of acetic anhydride in the presence of pyridine (Scheme 1). Hydrolysis was carried out 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) thus producing the desired (-)-*trans*-2-phenoxycyclohexan-1-ol in 98% enantiomeric excess as determined by ^{1}H NMR analysis of the (-)-*trans*-1-acetoxy-2-phenoxycyclohexane using Eu(hfc)$_3$. The enantiomeric purity was further confirmed by HPLC analysis of (-)-alcohol with CHIRALCEL OD column using (±)-alcohol as reference. The absolute configuration of (-)-*trans*-2-phenoxycyclohexan-1-ol was determined to be (R,R) by synthesizing the same molecule *via* monophenylation of (1R,2R)-cyclohexanediol[18] with triphenylbismuth diacetate (eq 1) following the literature method.[19]



(Eq.1)

We have then prepared a variety of racemic *trans*-2-aryloxycyclohexan-1-ols (Scheme 1) and converted them into the corresponding acetates. Enantioselective hydrolysis of these racemic acetates with PLAP in two phase medium (ether : phosphate buffer) provided the desired (-)-*trans*-2-aryloxycyclohexan-1-ols in 13->99% optical purities (Table 1).

In our laboratory (R,R)-2-phenoxycyclohexan-1-ol was used as chiral auxiliary[20] for the preparation of (R)-α-hydroxy acids in 80-93% ee *via* alkylzinc chloride addition to the [(R,R)-2-phenoxycyclohex-1-yl] phenylglyoxylate (Scheme 2). Similar studies[21] using (-)-*trans*-2-(4-phenyl-

SCHEME 2

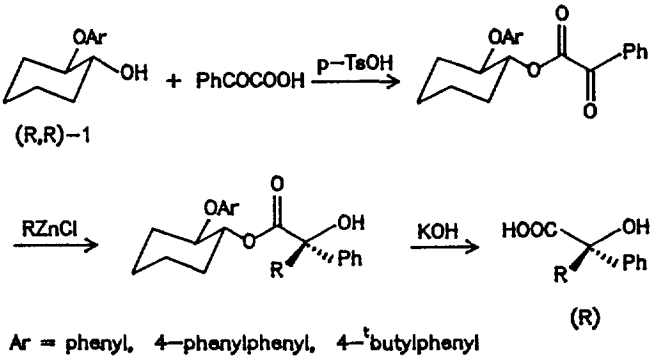
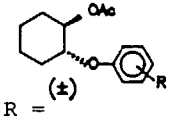


Table 1: Enantioselective hydrolysis of *trans*-2-aryloxycyclohex-1-yl acetates 1a-12a with PLAP.[a]

Substrate R = 		Hydrolysis time (h)	Conversion ratio[b]	(-)-Alcohol (1-12) Yield[c] (%)	$[\alpha]_D^{20}$	ee[d] (%)	Conf.	Recovered acetate Yield[c] (%)	ee[e] (%)	E[f]
H	1a	22	44:56	32	-79.1(c 0.86, MeOH)	98[g]	(R,R)	42	85	232
2-Me	2a	60	40:60	29	-44.3(c 1.67, Acetone)	71	(R,R)	55	48	9
3-Me	3a	45	41:59	32	-48.2(c 1.39, Acetone)	90	(R,R)	54	53	36
4-Me	4a	40	41:59	30	-57.1(c 1.54, Acetone)	>99[g]	(R,R)	41	70	>412
2-OMe	5a	96	45:55	34	-50.2(c 1.35, MeOH)	92	(R,R)	41	77	54
3-OMe	6a	23	49:51	47	-69.7(c 1.29, MeOH)	94	(R,R)	45	90	101
4-OMe	7a	11	48:52	44	-58.7(c 1.29, MeOH)	95	(R,R)	50	83	113
2-Ph	8a	96	37:63	35	- 8.3(c 0.48, Acetone)	13	(R,R)	59	4[h]	1
4-Ph	9a	96	47:53	34	-28.6(c 1.05, Acetone)	>99[g]	(R,R)	37	88	>581
4-^{t}Bu	10a	84	47:53	33	-45.3(c 1.06, Acetone)	>99[g]	(R,R)	36	90	>581
4-Br	11a	36	48:52	43	-29.5(c 1.35, Acetone)	96	(R,R)	46	89	146
2,4-di-Me	12a	50	37:63	24	-44.2(c 1.22, Acetone)	90[i]	(R,R)	38	60[i]	32

a) All reactions were carried out in 30 mM scale with 6 g of PLAP. b) Conversion ratio was determined by HPLC. c) Yields of pure isolated products. d) Determined by ^{1}H NMR analysis of corresponding acetate in the presence of Eu(hfc)$_3$ unless otherwise noted. e) Determined by ^{1}H NMR analysis in the presence of Eu(hfc)$_3$. f) Calculated according to the Sih equation[22] g) Also confirmed by HPLC analysis with chiral column, CHIRALCEL OD. h) Comparing the optical rotation of (+)-alcohol with that of (-)-alcohol. i) Determined by ^{1}H NMR analysis of corresponding (+)-MTPA derivative in the presence of Eu(hfc)$_3$.

phenoxy)cyclohexan-1-ol (9) and (-)-*trans*-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (10) as chiral auxiliaries provided the resulting 2-hydroxy-2-phenylalkanoic acids in high optical purities with (R)-configuration (Scheme 2). On the basis of sense of asymmetric induction (in comparison with (R,R)-2-phenoxycyclohexan-1-ol (1)) obtained by the auxiliaries (-)-9, (-)-10 in this reaction, the absolute configurations of (-)-*trans*-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol and (-)-*trans*-2-(4-phenylphenoxy)-cyclohexan-1-ol were assigned as (R,R). In analogy, absolute configuration of all other (-)-*trans*-2-aryloxycyclohexan-1-ols can be tentatively assigned as (R,R).

Effect of the substitution on phenyl ring in enzymatic hydrolysis of acetates 1a-12a:

Examination of Table 1 led to the following conclusions in the hydrolysis of racemic *trans*-2-aryloxycyclohexyl acetates with PLAP.

1. The (R,R)-enantiomer is hydrolyzed faster.
2. The hydrolysis of *ortho/meta*-substituted compounds is slower than that of *para*-substituted ones.
3. The alcohol with phenyl substitution in *para*-position of the phenoxy group was obtained in >99% enantiomeric purity, whereas the phenyl substitution in *ortho*-position of phenoxy group reduced the optical purity to 13%.

Possible explanation for the results:

These results can possibly be explained on the basis of three dimensional (cubic) active site-model of PLE proposed by Jones and co-workers.[23] The enzyme responsible for the enantioselective hydrolysis of *trans*-2-aryloxycyclohexyl acetates is PLE present in PLAP. Since all isozymes present in PLE act in a more or less equivalent manner, PLE can be used as a single species for preparative purposes.[24]

The top perspective view of the model is shown in Fig.A. The catalytically more important region which is denoted by a circle, contains a serine moiety which initiates the hydrolysis by attacking the carbonyl group of the acetate to be hydrolyzed. This model has four binding

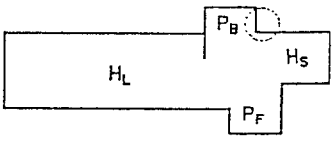


Fig.A: Top perspective view of active-site model

regions one large (H_L) and one small (H_S) hydrophobic pockets and two polar cavities on the front (P_F) and back (P_B) of the active-site.

Jones' active-site model is successfully utilized for explaining the results in the hydrolysis of bicyclic esters[25] with PLE; and the hydrolysis of *trans*-2-*tert*-butylcyclohexyl acetate[26] with PLAP which produced (1R,2S)-2-*tert*-butylcyclohexan-1-ol in 99% optical purity.

Tamm's original active-site model[27] and Jones' work[28] unequivocally established that the ester functions at equatorial position in cyclohexyl derivatives are preferentially hydrolyzed with PLE. Hydrolysis of an ester group can only occur when it is in proximity with the catalytically active serine function. Top perspective view of the active-site model is used to illustrate the binding mode selections for *trans*-2-aryloxy-cyclohexyl acetates. The binding depicted in Fig.B shows the preferred enzyme-substrate complex (ES complex) for hydrolysis of the (R,R)-ester to produce the (R,R)-alcohol. In this case aryloxy group fits comfortably in H_L pocket. The hydrolysis of (S,S)-ester would require the orientation

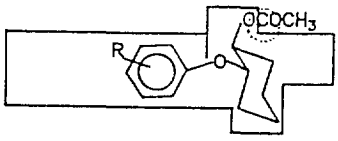


Fig.B: Binding mode for (R,R)-acetate (Favourable binding mode)

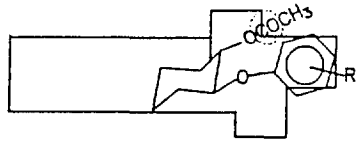


Fig.C: Binding mode for (S,S)-acetate (Unfavourable binding mode)

shown in Fig.C. This is clearly precluded since the H_S pocket is too small to accommodate aryloxy group.

The hydrolysis of *ortho/meta*-substituted aryloxycyclohexyl acetates is slower than that of *para*-substituted (or unsubstituted) ones probably due to better accommodation for *para*-substituted (or unsubstituted) aryloxy moiety in H_L pocket than the corresponding *ortho/meta*-substituted ones. The bulky phenyl substitution in *ortho*-position of phenoxy group cannot be accommodated in the enzyme pocket, thus resulting in slow hydrolysis and low selectivity (13% ee).

In conclusion, crude pig liver acetone powder (PLAP) is a suitable enzyme for the resolution of *trans*-2-aryloxycyclohexan-1-ols. Work towards the utility of PLAP in organic transformations is underway 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 (100 or 200 MHz) and ^{13}C NMR spectra (25 or 50 MHz) were recorded either on JEOL-FX-100 or BRUKER-AC-200 spectrometer using Me_4Si (δ = 0 ppm) as internal standard in $CDCl_3$. Mass spectra were recorded on finnigon MAT instrument. Optical rotations were measured on a Rudolph Polarimeter Autopol II. HPLC analysis was performed on Waters Associates Liquid Chromatograph equipped with model 440 absorbance detector (for conversion ratio determination) or Shimadzu LC-10AD equipped with SPD-10A UV-VIS detector (for ee determinations). Ee determinations were carried out using chiral column, CHIRALCEL OD (Diacel, Jpn.).

PLAP was prepared according to literature procedure.[10] Column chromatography was carried out on a silica gel (100-200 mesh) column. 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 in ^{1}H NMR studies for ee determinations.

(±)-*trans*-2-Aryloxycyclohexan-1-ols (1-12):

(±)-*trans*-2-Aryloxycyclohexan-1-ols were prepared according to literature procedure[29] described for 2-(2-naphthyloxy)cyclohexan-1-ol. The following procedure for preparation of (±)-*trans*-2-phenoxycyclohexan-1-ol is representative.

(±)-*trans*-2-Phenoxycyclohexan-1-ol (1): To a solution of sodium phenoxide (150 mM) in water (40 mL) [prepared from sodium hydroxide (6 g, 150 mM) and phenol (14.11 g, 150 mM)] cyclohexene oxide (5.0 mL, 50 mM) was added dropwise with stirring at reflux temperature. After refluxing for 2 h the mixture was cooled to room temperature. Thus obtained solid was filtered, washed thoroughly with water. The dried product was crystallized from hexane as a white crystalline solid, 7.59 g (79% yield); mp 81-82^{o}C (Lit.[30] mp 82^{o}C); IR (KBr) 3400 cm^{-1}; ^{1}H NMR δ 1.00-2.28(m, 8H), 2.56(s, 1H, D_2O washable), 3.68(m, 1H), 3.96(m, 1H), 6.81-7.40(m, 5H); ^{13}C NMR δ 23.94, 29.17, 32.06, 73.41, 82.24, 116.48, 121.36, 129.65, 158.00; MS(m/e) 192(M^{+}).

(±)-*trans*-2-(2-Methylphenoxy)cyclohexan-1-ol (2): 2 h; 76% yield; bp 112-14^{o}C/ 2 mm, IR(neat) 3405 cm^{-1}; ^{1}H NMR δ 1.08-2.32(m, 11H), 2.56(s, 1H, D_2O washable), 3.84(m, 2H), 6.81-7.23(m, 4H); ^{13}C NMR δ 16.41, 23.82, 29.35, 32.00, 73.24, 82.24, 114.12, 121.06, 126.88, 128.12, 131.06, 156.12; Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.50; H, 8.78.

(±)-*trans*-2-(3-Methylphenoxy)cyclohexan-1-ol (3): 2 h; 75% yield; mp 62-63°C; IR(KBr) 3415 cm^{-1}; ^1H NMR δ 1.04-2.28(m, 11H), 2.52(s, 1H, D_2O washable), 3.81(m, 2H), 6.60-7.18(m, 4H); ^{13}C NMR δ 21.41, 23.94, 29.23, 32.06, 73.35, 82.18, 113.42, 117.42, 122.18, 129.36, 139.71, 158.06; Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69: H, 8.79. Found: C, 75.55; H, 8.80.

(±)-*trans*-2-(4-Methylphenoxy)cyclohexan-1-ol (4): 2 h; 80% yield; mp 82-83°C; IR(KBr) 3450 cm^{-1}; ^1H NMR δ 1.04-2.36(m, 11H), 2.68(br s, 1H D_2O washable), 3.44-4.04(m, 2H), 6.84(d, 2H, J=8Hz), 7.04(d, 2H, J= 8 Hz); ^{13}C NMR δ 20.41, 23.88, 29.18, 32.00, 73.36, 82.53, 116.60, 130.06, 130.65, 155.83; MS(m/e) 206(M^+); Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.89; H, 8.83.

(±)-*trans*-2-(2-Methoxyphenoxy)cyclohexan-1-ol (5) : 4 h; 72% yield; bp 130-32°C/0.9 mm; IR(neat) 3500 cm^{-1}; ^1H NMR δ 1.04-2.28(m, 8H), 3.48-3.80(m, 6H, 1H D_2O washable), 6.72-7.12(m, 4H); ^{13}C NMR δ 23.76, 24.12, 30.41, 32.17, 55.65, 73.53, 86.94, 112.12, 119.89, 121.12, 123.34, 147.77, 151.12; MS(m/e) 222(M^+); Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.11; H, 8.12.

(±)-*trans*-2-(3-Methoxyphenoxy)cyclohexan-1-ol (6) : 4 h; 70% yield; mp 72-73°C; IR(KBr) 3415 cm^{-1}; ^1H NMR δ 1.00-2.20(m, 8H), 2.64(s, 1H, D_2O washable), 3.24-4.08(m, 5H), 6.58(m, 3H), 7.12(m, 1H); ^{13}C NMR δ 23.70, 29.00, 31.94, 55.12, 73.12, 82.00, 102.77, 106.65, 108.41, 129.89, 159.18, 160.88; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.42; H, 8.14.

(±)-*trans*-2-(4-Methoxyphenoxy)cyclohexan-1-ol (7): 4 h; 77% yield; mp 75-76°C; IR(KBr) 3400 cm^{-1}; ^1H NMR (200 MHz) δ 1.12-1.48(m, 4H), 1.60-1.84(m, 2H), 1.96-2.22(m, 2H), 2.62(br, 1H, D_2O washable), 3.61-3.96(m, 5H), 6.88(m, 4H); ^{13}C NMR δ 23.82, 29.17, 32.00, 55.59, 73.01, 83.59, 114.65, 118.18, 151.83, 154.47; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.45; H, 8.18.

(±)-*trans*-2-(2-Phenylphenoxy)cyclohexan-1-ol (8): 4 h; 62% yield; mp 70-71°C; IR(KBr) 3455 cm^{-1}; ^1H NMR δ 1.00-2.36(m, 9H, 1H D_2O washable), 3.54(m, 1H), 3.81(m, 1H), 6.82-7.58(m, 9H); ^{13}C NMR δ 23.83, 24.01, 29.64, 31.93, 73.33, 84.01, 116.01, 121.82, 126.98, 128.04, 128.63, 129.63, 131.04, 132.95, 138.53, 154.89; Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.45; H, 7.50.

(±)-*trans*-2-(4-Phenylphenoxy)cyclohexan-1-ol (9): 2 h; 63% yield; mp

115-16°C; IR(KBr) 3420 cm^{-1}; ^1H NMR δ 1.08-2.32(m, 8H), 2.64(s, 1H, D_2O washable), 3.76(m, 1H), 4.04(m, 1H), 6.92-7.62(m, 9H); ^{13}C NMR (50 MHz) δ 24.01, 29.38, 32.27, 73.35, 82.39, 116.80, 126.81, 128.28, 128.82, 134.39, 140.85, 157.64; MS(m/e) 268(M^+); Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.62; H, 7.55.

(±)-*trans*-2-[4-(*tert*-Butylphenoxy)cyclohexan-1-ol (10): 2 h; 64% yield; mp 91-92°C; IR(KBr) 3350 cm^{-1}; ^1H NMR δ 1.00-2.20(m, 17H), 2.56(s, 1H, D_2O washable), 3.44-4.08(m, 2H), 6.84(d, 2H, J=8Hz), 7.24(d, 2H, J=8Hz); ^{13}C NMR δ 23.88, 29.23, 31.47, 32.00, 34.00, 73.35, 82.29, 115.84, 126.36, 144.01, 155.71; MS(m/e) 248(M^+); Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.21; H, 9.69.

(±)-*trans*-2-(4-Bromophenoxy)cyclohexan-1-ol (11): 3 h; 68% yield; mp 87-88°C; IR(KBr) 3450 cm^{-1}; ^1H NMR (200 MHz) δ 1.14-1.90(m, 6H), 1.98-2.22(m, 2H), 2.54(s, 1H, D_2O washable), 3.71(m, 1H), 3.92(m, 1H), 6.81(m, 2H),7.37(m, 2H); ^{13}C NMR (50 MHz) δ 23.76, 29.00, 32.09, 73.03, 82.42, 113.23, 118.14, 132.23, 156.96; MS(m/e) 270 and 272(M^+); Anal. Calcd for $C_{12}H_{15}BrO_2$: C, 53.13; H, 5.57. Found: C, 53.15; H, 5.62.

(±)-*trans*-2-(2,4-Dimethylphenoxy)cyclohexan-1-ol (12): 5 h; 63% yield; bp 126-28°C/4 mm; IR(neat) 3400 cm^{-1}; ^1H NMR δ 1.04-2.28(m, 14H), 2.60(br, 1H, D_2O washable), 3.60-4.01(m, 2H), 6.84(m, 3H); ^{13}C NMR δ 16.30, 20.41, 23.87, 29.34, 31.93, 73.48, 82.81, 114.45, 127.15, 127.97, 130.41, 131.83, 157.80; MS(m/e) 220(M^+); Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.25; H, 9.11.

(±)-*trans*-1-Acetoxy-2-phenoxycyclohexane (1a): To a stirred solution of racemic *trans*-2-phenoxycyclohexan-1-ol (7.68 g, 40 mM) in dry CH_2Cl_2 (40 mL) consisting of pyridine (6.9 mL, 85 mM) and DMAP (0.061 g, 0.5 mM), 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 oil, 8.9 g (95% yield); bp 126-28°C /1.5 mm; IR(neat) 1740 cm^{-1}; ^1H NMR δ 1.08-2.26(m, 11H), 4.18(m, 1H), 4.96(m, 1H), 6.92(m, 3H), 7.20(m, 2H); ^{13}C NMR δ 21.06, 23.00, 29.70, 74.24, 77.70, 116.41, 121.12, 129.53, 158.47, 170.50.

(±)-*trans*-1-Acetoxy-2-(2-methylphenoxy)cyclohexane (2a): 91% yield; bp

112-14°C/2 mm; IR(neat) 1740 cm^{-1}; ^{1}H NMR δ 1.16-2.20(m, 14H), 4.22(m, 1H), 5.02(m, 1H), 6.78-7.18(m, 4H); ^{13}C NMR δ 15.76, 20.35, 22.41, 22.53, 29.06, 29.17, 73.35, 76.71, 112.83, 120.24, 126.30, 127.18, 130.48, 156.01, 169.66.

(±)-*trans*-1-Acetoxy-2-(3-methylphenoxy)cyclohexane (3a): 92% yield; bp 130-32°C/3 mm; IR(neat) 1735 cm^{-1}; ^{1}H NMR δ 1.08-2.28(m, 14H), 4.12(m, 1H), 4.88(m, 1H), 6.68(m, 3H), 7.08(m, 1H); ^{13}C NMR δ 20.47, 20.94, 22.41, 22.59, 29.17, 73.53, 76.82, 112.77, 116.83, 121.53, 128.83, 138.95, 158.06, 169.88.

(±)-*trans*-1-Acetoxy-2-(4-methylphenoxy)cyclohexane (4a): 96% yield; bp 112-14°C/2 mm; IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 1.20-2.28(m, 14H), 4.12(m, 1H), 4.92(m, 1H), 6.78(d, 2H, J=8Hz), 7.02(d, 2H, J=8Hz); ^{13}C NMR δ 20.12, 20.70, 22.64, 22.76, 29.29, 29.41, 73.83, 77.59, 116.18, 129.65, 130.06, 156.06, 170.13.

(±)-*trans*-1-Acetoxy-2-(2-methoxyphenoxy)cyclohexane (5a): 92% Yield; bp 150-52°C/3.5 mm; IR(neat) 1740 cm^{-1}; ^{1}H NMR δ 1.00-2.24(m, 11H), 3.80(s, 3H), 4.08(m, 1H), 4.96(m, 1H), 6.88 (m, 4H); ^{13}C NMR δ 21.07, 23.19, 29.82, 30.23, 55.95, 74.67, 79.85, 112.66, 118.06, 120.82, 122.17, 146.60, 150.82, 170.26.

(±)-*trans*-1-Acetoxy-2-(3-methoxyphenoxy)cyclohexane (6a): 93% yield; bp 142-44°C/3 mm; IR(neat) 1735 cm^{-1}; ^{1}H NMR δ 1.00-2.24(m, 11H), 3.76(s, 3H), 4.16(m, 1H), 4.98(m, 1H), 6.50(m, 3H), 7.18(m, 1H); ^{13}C NMR δ 20.17, 22.17, 22.29, 28.88, 54.35, 73.12, 76.53, 102.06, 106.12, 107.77, 129.30, 159.12, 160.54, 169.53.

(±)-*trans*-1-Acetoxy-2-(4-methoxyphenoxy)cyclohexane (7a): 96% yield; bp 126-28°C/1 mm; IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 1.06-2.24(m, 11H), 3.76(s, 3H), 4.04(m, 1H), 4.96(m, 1H), 6.82(m, 4H); ^{13}C NMR δ 21.12, 23.06, 29.65, 29.82, 55.65, 74.35, 79.06, 114.59, 118.01, 152.53, 154.36, 170.62.

(±)-*trans*-1-Acetoxy-2-(2-phenylphenoxy)cyclohexane (8a): 90% yield; mp 76-77°C; IR(KBr) 1735 cm^{-1}; ^{1}H NMR δ 1.12-2.08(m, 11H), 4.16(m, 1H), 4.84(m, 1H), 6.92-7.58(m, 9H); ^{13}C NMR δ 21.11, 22.63, 22.70, 29.24, 29.30, 73.68, 77.59, 114.86, 121.32, 126.80, 127.78, 128.46, 129.65, 131.01, 132.01, 138.63, 155.08, 170.30.

(±)-*trans*-1-Acetoxy-2-(4-phenylphenoxy)cyclohexane (9a): 94% yield; mp

76-77°C; IR (KBr) 1740 cm^{-1}; ^1H NMR δ 1.16-2.24(m, 11H), 4.20(m, 1H), 4.96(m, 1H), 6.92-7.62(m, 9H); ^{13}C NMR δ 21.06, 23.00, 29.65, 74.12, 77.65, 116.59, 126.71, 128.12, 128.77, 134.12, 140.83, 158.00, 170.53.

(±)-*trans*-1-Acetoxy-2-(4-*tert*-butylphenoxy)cyclohexane (10a): 92% yield; bp 136-38°C/1.5 mm; IR(neat) 1735 cm^{-1}; ^1H NMR δ 1.08-2.20(m, 20 H), 4.14(m, 1H), 4.96(m, 1H), 6.84(d, 2H, J=8Hz), 7.24(d, 2H, J=8Hz); ^{13}C NMR δ 20.59, 22.48, 22.64, 29.17, 31.18, 33.59, 73.59, 77.18, 115.53, 125.83, 143.30, 155.83, 169.95.

(±)-*trans*-1-Acetoxy-2-(4-bromophenoxy)cyclohexane (11a): 93% yield; bp 140-42°C/3 mm; IR (neat) 1740 cm^{-1}; ^1H NMR δ 1.04-2.24(m, 11H), 4.12(m, 1H), 4,88(m, 1H), 6.78(m, 2H), 7.32(m, 2H); ^{13}C NMR δ 20.29, 22.23, 28.88, 73.12, 77.00, 112.48, 117.59, 131.71, 157.01, 169.42.

(±)-*trans*-1-Acetoxy-2-(2,4-dimethylphenoxy)cyclohexane (12a): 89% yield; bp 118-20°C/0.5 mm; IR(neat) 1740 cm^{-1}; ^1H NMR δ 1.08-2.36(m, 17H), 4.12(m, 1H), 4.98(m, 1H), 6.84(m, 3H); ^{13}C NMR δ 15.88, 20.00, 20.47, 22.53, 22.64, 29.17, 29.35, 73.53, 77.12, 113.18, 126.71, 127.12, 129.42, 131.36, 154.01, 169.77.

Enzymatic hydrolysis of (±)-*trans*-1-Acetoxy-2-aryloxycyclohexanes: General procedure:

To 0.5 M, pH 8.0, KH_2PO_4/K_2HPO_4 buffer(240 mL), racemic acetate (30 mM) in ether (45 mL) was added with rapid stirring at room temperature. After 15 minutes, 6 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 (25 g) and dichloromethane (75 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 (3x30 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, 30 mM) in MeOH (20 mL), recovered acetate (10 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 (20 mL) and extracted with ether (3 x 20 mL). The

ethereal solution was dried over anhydrous Na_2SO_4 and concentrated. The crude material was purified by column chromatography (silica gel, 10% ethyl acetate in hexane) to afford (+)-alcohol.

Determination of enantiomeric purities of (-)-*trans*-2-aryloxycyclohexan-1-ols:

(-)-*trans*-2-Aryloxycyclohexan-1-ols were acylated with acetyl chloride in the presence of pyridine in benzene.

The enantiomeric purities of (-)-alcohols **1-11** were determined by examining the ^1H NMR spectra of their acetates (5 mg) in the presence of $Eu(hfc)_3$ (10-20 mg) with reference to ^1H NMR spectra of the corresponding racemic acetates (O-CO-$\underline{CH}_3$ signal separates). The ee of (-)-**12** was determined by examining the ^1H NMR spectra of MTPA esters of (-)-alcohol and (±)-alcohol in the presence of $Eu(hfc)_3$.

The enantiomeric purities of alcohols (-)-**1**, (-)-**4**, (-)-**9** and (-)-**10** were further confirmed by HPLC analysis of these molecules on chiral column, CHIRALCEL OD with reference to the corresponding racemic molecules.

Enzymatic hydrolysis of racemic acetate 1a:

Hydrolysis of this acetate (7.03 g, 30 mM) with PLAP (6 g) afforded (-)-alcohol and unhydrolyzed acetate in 44:56 ratio in 22 h. **(-)-alcohol:** 1.85 g 32% yield; mp 84-85°C; Optical rotation $[\alpha]_D^{20}$ -79.1 (c 0.86, MeOH), 98% ee; HPLC analysis: eluent:i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 18.91 min & 21.71 min for (±)-alcohol and 18.92 min for (-)-alcohol; enantiomeric purity: >99%; **Recovered acetate:** 2.95 g 42% yield; **(+)-alcohol:** 2.30 g 95% yield, mp 83-84°C; Optical rotation $[\alpha]_D^{20}$ +66.1 (c 1.26, MeOH).

Monophenylation of (-)-(1R,2R)-cyclohexanediol:

This was carried out according to known procedure reported for the preparation of racemic molecule.[30]

A mixture of $Ph_3Bi(OAc)_2$ (1.68 g, 3 mM), (-)-(1R,2R)-cyclohexanediol (70% ee)[18] (0.35 g, 3 mM) and $Cu(OAc)_2$ (0.016 g, 0.09 mM) was dissolved in 50 mL of dichloromethane and stirred for 5 h at room temperature. The reaction mixture was passed through silica gel column to afford pure (-)-*trans*-2-phenoxycyclohexan-1-ol, 0.476 g (82% yield); mp 82-83°C; Optical rotation: $[\alpha]_D^{20}$ -58.5 (c 0.34, MeOH), 72% ee. Thus the absolute configuration of (-)-*trans*-2-phenoxycyclohexan-1-ol is assigned as (1R,2R).

Enzymatic hydrolysis of racemic acetate 2a:

Hydrolysis time: 60 h; Conversion ratio: 40:60; **(-)-alcohol:** 29% yield;

Optical rotation: $[\alpha]_D^{20}$ -44.3 (c 1.67, acetone), 71% ee; **Recovered acetate:** 55% yield. **(+)-alcohol:** 90% yield; Optical rotation: $[\alpha]_D^{20}$ +30.9 (c 1.25, acetone).

Enzymatic hydrolysis of racemic acetate 3a:
Hydrolysis time: 45 h; Conversion ratio: 41:59; **(-)-alcohol:** 32% yield; mp 71-72°C; Optical rotation: $[\alpha]_D^{20}$ -48.2 (c 1.39, Acetone), 90% ee; **Recovered acetate:** 54% yield; **(+)-alcohol:** 91% yield; mp 68-69°C; Optical rotation: $[\alpha]_D^{20}$ +27.9 (c 1.28, Acetone).

Enzymatic hydrolysis of racemic acetate 4a:
Hydrolysis time: 40 h; Conversion ratio: 41:59; **(-)-alcohol:** 30% yield; mp 83-84°C; Optical rotation: $[\alpha]_D^{20}$ -57.1 (c 1.54, acetone), >99% ee; HPLC analysis: eluent: i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 18.13 min & 22.78 min for (±)-alcohol and 18.01 min for (-)-alcohol; enantiomeric purity: >99%; **Recovered acetate:** 41% yield; **(+)-alcohol:** 94% yield; mp 81-82°C; Optical rotation: $[\alpha]_D^{20}$ +40.9 (c 0.98, acetone).

Enzymatic hydrolysis of racemic acetate 5a:
Hydrolysis time: 96 h; Conversion ratio: 45:55; **(-)-alcohol:** 34% yield; Optical rotation: $[\alpha]_D^{20}$ -50.2 (c 1.35, MeOH), 92% ee; **Recovered acetate:** 41% yield; **(+)-alcohol:** 94% yield; Optical rotation: $[\alpha]_D^{20}$ +41.4 (c 1.11, MeOH).

Enzymatic hydrolysis of racemic acetate 6a:
Hydrolysis time: 23 h; Conversion ratio: 49:51; **(-)-alcohol:** 47% yield; mp 99-100°C; Optical rotation: $[\alpha]_D^{20}$ -69.7 (c 1.29, MeOH), 94% ee; **Recovered acetate:** 45% yield; **(+)-alcohol:** 93% yield; mp 96-98°C; Optical rotation: $[\alpha]_D^{20}$ +67.9 (c 1.23, MeOH).

Enzymatic hydrolysis of racemic acetate 7a:
Hydrolysis time: 11 h; Conversion ratio: 48:52; **(-)-alcohol:** 44% yield; mp 89-90°C; Optical rotation: $[\alpha]_D^{20}$ -58.7 (c 1.29, MeOH), 95% ee; **Recovered acetate:** 50% yield; **(+)-alcohol:** 92% yield; mp 81-82°C; Optical rotation: $[\alpha]_D^{20}$ +50.1 (c 1.06, MeOH).

Enzymatic hydrolysis of racemic acetate 8a:
Hydrolysis time: 96 h; Conversion ratio: 37:63; **(-)-alcohol:** 35% yield; mp 78-79°C; Optical rotation: $[\alpha]_D^{20}$ -8.3 (c 0.48, acetone), 13% ee; **Recovered acetate:** 59% yield; **(+)-alcohol:** 93% yield; mp 77-78°C; Optical rotation: $[\alpha]^{20}$ +2.2 (c 2.24, acetone), 4 % ee.

Enzymatic hydrolysis of racemic acetate 9a:
Hydrolysis time: 96 h; Conversion ratio: 47:53; **(-)-alcohol:** 34% yield; mp 112-13°C; Optical rotation: $[\alpha]_D^{20}$ -28.6 (c 1.05, acetone), >99% ee; HPLC analysis: eluent:i-PrOH/hexane: 10:90; flow rate: 0.5 mL/min; retention times: 16.24 min & 19.66 min for (±)-alcohol and 19.54 min for (-)-alcohol; enantiomeric purity: >99%; **Recovered acetate:** 37% yield; **(+)-alcohol:** 96% yield; mp 110-11°C; Optical rotation: $[\alpha]_D^{20}$ +24.3 (c 1.23, acetone).

Enzymatic hydrolysis of racemic acetate 10a:
Hydrolysis time: 84 h; Conversion ratio: 47:53; **(-)-alcohol:** 33% yield; mp 96-98°C; Optical rotation: $[\alpha]_D^{20}$ -45.3 (c 1.06, acetone), >99% ee; HPLC analysis: eluent:i-PrOH/hexane: 2:98; flow rate: 0.5 mL/min; retention times: 18.77 min & 21.34 min for (±)-alcohol and 18.73 min for (-)-alcohol; enantiomeric purity: >99%; **Recovered acetate:** 36% yield; **(+)-alcohol:** 95% yield; mp 96-97°C; Optical rotation: $[\alpha]_D^{20}$ +41.3 (c 0.99, acetone).

Enzymatic hydrolysis of racemic acetate 11a:
Hydrolysis time: 36 h; Conversion ratio: 48:52; **(-)-alcohol:** 43% yield; mp 88-89°C; Optical rotation: $[\alpha]_D^{20}$ -29.5 (c 1.35, acetone), 96% ee; **Recovered acetate:** 46% yield; **(+)-alcohol:** 93% yield; mp 88-89°C; Optical rotation: $[\alpha]_D^{20}$ +26.4 (c 1.46, acetone).

Enzymatic hydrolysis of racemic acetate 12a:
Hydrolysis time: 50 h; Conversion ratio: 37:63; **(-)-alcohol:** 24% yield; Optical rotation: $[\alpha]_D^{20}$ -44.2 (c 1.22, acetone), 90% ee; **Recovered acetate:** 38% yield; **(+)-alcohol:** 90% yield; Optical rotation: $[\alpha]_D^{20}$ +30.1 (c 0.98, acetone).

Determination of enantiomeric excess:

Preparation of Mosher's ester[31]*:*

To a solution of (±)-alcohol (0.022 g) in pyridine (0.2 mL), 0.2 M solution of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPACl] in dichloromethane (1 mL) was added and stirred for 12 h at room temperature under nitrogen. Water (1 mL) and ether (15 mL) were added. Organic layer was separated, washed successively with dil. HCl, saturated K_2CO_3 solution and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated and passed through silica gel column (5% ethyl acetate in hexane) to provide Mosher's ester in 92% yield (0.040 g). ^{1}H NMR: δ 1.16-1.84 (m, 8H), 2.08 (s, 3H), 2.21 (s, 3H), 3.44 (m, 3H), 4.22 (m, 1H), 5.24 (m, 1H), 6.52-7.60 (m, 8H).

^{1}H NMR analysis of Mosher's ester in presence of Eu(hfc)$_3$:

In ^{1}H NMR spectrum of Mosher's ester in the presence of shift reagent [sample:Eu(hfc)$_3$ = 1:2], the peak originally at δ 3.44 due to -OMe group splits into two broad singlets of equal integration due to (R,R) & (S,S) enantiomers. ^{1}H NMR analysis of Mosher's ester from (-)-alcohol in the presence of Eu(hfc)$_3$ showed two broad singlets in 7.9:0.4 ratio, indicating the enantiomeric purity of (-)-alcohol to be 90%. Similar analysis of Mosher's ester of (+)-alcohol showed that the enantiomeric purity of (+)-alcohol is 60%.

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