Pergamon

Tetrahedron Vol. 51, No. 44, pp. 12169-12178, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00771-7

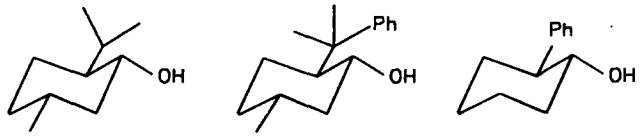
New Cyclohexyl-Based Chiral Auxiliaries: Enantioselective Synthesis of α-Hydroxy Acids†

Deevi Basavaiah* and Peddinti Rama Krishna

School of Chemistry, University of Hyderabad
Hyderabad 500 046, India

ABSTRACT: (1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohexan-1-ol (**5**) and (1R,2R)-2-(4-phenylphenoxy)cyclohexan-1-ol (**6**) have been used for the first time as chiral auxiliaries. Addition of alkylzinc chlorides to the corresponding glyoxylates **5a**, **6a**, after hydrolysis, provided (R)-α-hydroxy acids in high optical purities.

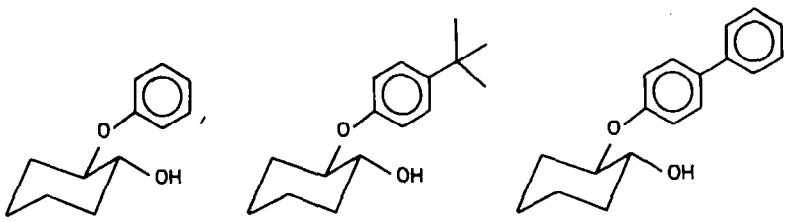
The exponential growth of asymmetric synthesis in the last two decades resulted mainly from the rational design of a large number of chiral auxiliaries and their applications in a large number of stereoselective processes.[1-5] Practical application of asymmetric synthesis requires that the chiral auxiliaries not only be recoverable in reusable form but they can also be readily obtained in the first place. Among the various chiral auxiliaries, the molecules based on cyclohexane frame[5] such as menthol[6] (**1**), Corey's 8-phenylmenthol[7] (**2**) and Whitesell's *trans*-2-phenylcyclohexanol[8] (**3**) occupy a special place because of high potential they offer in a variety of enantioselective processes. With a



1 **2** **3**

view that structurally similar cyclohexane frame based molecules, *trans*-2-aryloxycyclohexan-1-ols **4-6**, would be of interest as chiral auxiliaries, we have developed a convenient simple methodology for obtaining these chiral *trans*-2-aryloxycyclohexan-1-ols in high enantiomeric purities *via* enantioselective hydrolysis of the corresponding racemic acetates using pig liver acetone powder (PLAP) as a biocatalyst.[9,10]

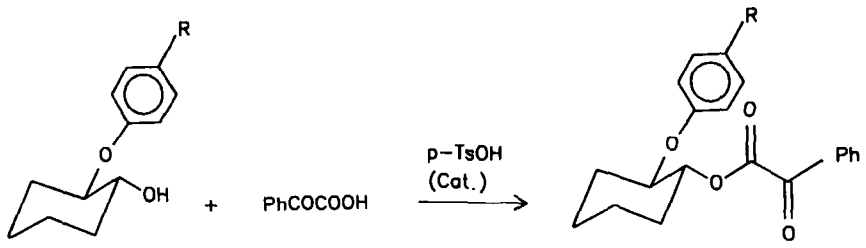
† Dedicated to Professor Gurbakhsh Singh on the occasion of his 75th birthday



4 5 6

Chiral α-hydroxy acids and their derivatives possessing tertiary hydroxy.stereogenic centre, are important synthons for the synthesis of biologically active molecules.[11-13] Recently menthol[6] (1) and 8-phenylmenthol[12] (2) have been used as chiral auxiliaries for the synthesis of α-hydroxy acids containing tertiary hydroxy stereogenic centre. We have recently examined the applicability of (1R,2S)-2-phenylcyclohexanol[14] (3) and (1R,2R)-2-phenoxycyclohexan-1-ol[15] (4) as chiral auxiliaries for obtaining α-hydroxy acids in high enantiomeric purities. With a view to examine the effect of sterically more demanding group on the phenyl ring of 2-phenoxycyclohexanol, we have selected the alcohols 5 and 6 as chiral auxiliaries.

We have first studied the applications of (1R,2R)-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (5) as chiral auxiliary for the synthesis of chiral α-hydroxy acids. The required [(1R,2R)-2-(4-*tert*-butylphenoxy)-cyclohex-1-yl] phenylglyoxylate (5a) was prepared by treating the alcohol 5 with benzoylformic acid in the presence of *p*-TsOH (eq 1).



(1)

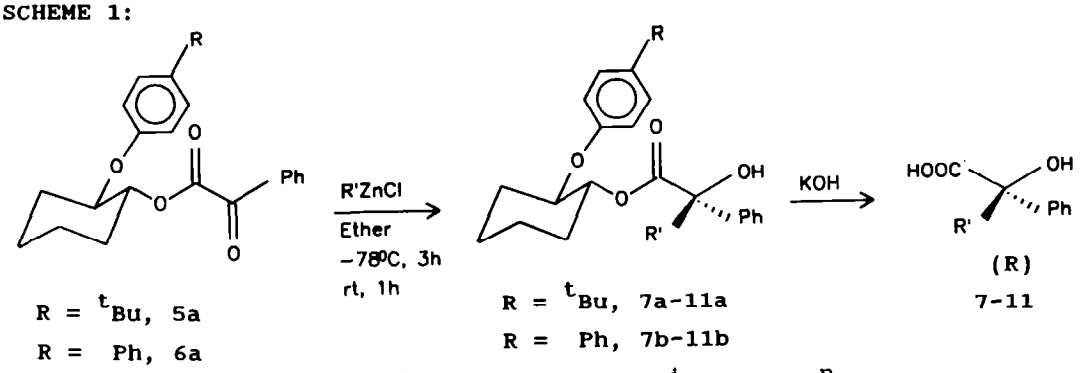
R = ^{t}Bu, 5
R = Ph, 6

R = ^{t}Bu, 5a
R = Ph, 6a

Reaction of keto ester **5a** with a variety of alkylzinc chlorides afforded chiral α-hydroxy esters **7a-11a**. Subsequent saponification provided (R)-2-hydroxy-2-phenylalkanoic acids **7-11** in 86-97% enantiomeric purities (Scheme 1, Table 1).

Similarly, alcohol **6** was converted into the glyoxylate **6a** (eq 1). Subsequent reaction with alkylzinc chlorides provided, after hydrolysis, the desired (R)-α-hydroxy acids **7-11** in 83-89% optical purities (Scheme

SCHEME 1:



R = ^{t}Bu, 5a
R = Ph, 6a

R = ^{t}Bu, 7a-11a
R = Ph, 7b-11b

(R)
7-11

R' = Et (7), ^{i}Pr (8), ^{n}Bu (9), ^{i}Bu (10), ^{n}Hex (11)

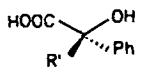
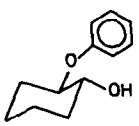
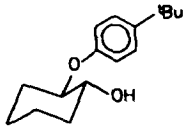
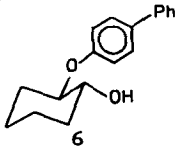
Table 1: Preparation of chiral α-hydroxy acids **7-11** from glyoxylates **5a** and **6a** and R'ZnCl.[a]

R' in R'ZnCl	Glyoxylate	Product	Over-all yield[b] (%)	$[\alpha]_D^{24}$ (c, EtOH)	ee[c] (%)	Abs Conf.
Et	**5a**	**7**	74	-32.3 (1.77)	97	R
Et	**6a**	**7**	77	-29.3 (1.75)	88	R
^{i}Pr	**5a**	**8**	76	-29.0 (2.05)	89	R
^{i}Pr	**6a**	**8**	72	-28.4 (2.01)	87	R
^{n}Bu	**5a**	**9**	73	-20.5 (1.98)	88	R
^{n}Bu	**6a**	**9**	74	-19.3 (2.18)	83	R
^{i}Bu	**5a**	**10**	75	-17.2 (1.90)	86	R
^{i}Bu	**6a**	**10**	71	-17.8 (1.97)	89	R
^{n}Hex	**5a**	**11**	74	-18.2 (2.04)	94	R
^{n}Hex	**6a**	**11**	73	-17.2 (1.82)	89	R

a) All reactions were carried out with 2.5 mM of keto ester and 12.5 mM of R'ZnCl in dry ether for 3h at -78°C and 1h at room temperature. b) Over-all yields of the pure crystallized products based on the keto ester. c) Enantiomeric purities were based on the reported optical rotations (see experimental).

1, Table 1). Comparison of these results (**5**, **6** as chiral auxiliaries) with that of **4** as chiral auxiliary (Table 2) indicates that introduction of bulky groups in the *para*-position of the phenyl ring of 2-phenoxycyclohexan-1-ol does not have significant variation on the diastereoselectivity in the addition of alkylzinc chlorides to the corresponding glyoxylates.

Table 2: Comparison of enantioselectivity (ee values in %) achieved using chiral auxiliaries **4**,[a] **5** and **6** in the synthesis of (R)-α-hydroxy acids **7-11**.

	enantiomeric purities of α-hydroxy acids **7-11**		
 **7-11** R'	 **4**	 **5**	 **6**
Ethyl, **7**	80	97	88
i-Propyl, **8**	93	89	87
n-Butyl, **9**	82	88	83
i-Butyl, **10**	90	86	89
n-Hexyl, **11**	91	94	89

a) Values are taken from ref. 15.

Our study demonstrates the applicability of (1R,2R)-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (**5**) and (1R,2R)-2-(4-phenylphenoxy)cyclohexan-1-ol (**6**) as new chiral auxiliaries for the synthesis of (R)-α-hydroxy acids in high enantiomeric purities.

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 MHz) were recorded on JEOL-FX-100 spectrometer and ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (50 MHz) were recorded on BRUKER-AC-200 spectrometer using Me_4Si (δ = 0 ppm) as internal standard in $CDCl_3$. In ^{1}H NMR spectra, the underlined chemical shift values are due to minor diastereomer. Mass spectra were recorded on Finnegan MAT instrument. Optical rotations were measured on a Rudolph Polarimeter Autopol II. Column chromatography was carried out on a silica gel (100-200 mesh) column. NMR spectra for compounds **7a-11a** and **7b-11b** were taken after passing the samples through silica gel column (5% ethyl acetate in hexane). α-Hydroxy acids **7-11** were crystallized from hexane-ether (3:1) mixture.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] phenylglyoxylate (5a): A solution of (1R,2R)-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (**5**) (7.45 g, 30 mM), benzoylformic acid (4.95 g, 33 mM) and *p*-toluenesulfonic acid

(130 mg) in 60 mL of dry benzene was refluxed for 3 h with azeotropic removal of water. The reaction mixture was cooled to room temperature, diluted with ether (40 mL) and washed with saturated K_2CO_3 solution followed by water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was passed through silica gel (5% ethyl acetate in hexane). Thus obtained material was crystallized from hexane-benzene (5:1) to get pure glyoxylate **5a**. Yield: 9.25 g (81%); mp: 61-62°C; Optical rotation: $[\alpha]_D^{24}$ -34.85 (c 1.01, acetone); IR (KBr) ν_{max}: 1747, 1685 cm^{-1}; ^1H NMR: δ 1.26 (s, 9H), 1.29-1.84 (m, 6H), 2.22 (m, 2H), 4.28 (m, 1H), 5.32 (m, 1H), 6.90 (m, 2H), 7.25 (m, 4H), 7.62 (m, 1H), 7.94 (m, 2H); ^{13}C NMR: δ 22.62, 22.98, 29.45, 31.11, 33.62, 76.03, 77.15, 115.28, 125.88, 128.34, 129.56, 131.90, 134.26, 143.54, 154.92, 163.34, 186.34; Mass (m/e): 380 (M^+); Analysis Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42; Found: C, 75.58; H, 7.39.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenylbutanoate (7a): To a stirred solution of ethylmagnesium bromide (12.5 mM) (prepared from bromoethane and magnesium) in dry ether (25 mL), anhydrous $ZnCl_2$ (1.7 g, 12.5 mM) was added at 0°C. After stirring for 2 h, it was cooled to -78°C. To this a solution of [(1R,2R)-2-(4-*tert*-butylphenoxy)cyclohex-1-yl] phenylglyoxylate (**5a**) (0.95 g, 2.5 mM) in ether (30 mL) was added dropwise at -78°C. After stirring for 3 h at the same temperature, the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride solution (15 mL) and extracted with ether (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to provide **7a** as colorless solid. Yield: 0.975 g, (95%); mp: 67-68°C; IR (KBr) ν_{max}: 3420, 1715 cm^{-1}; ^1H NMR: δ 0.80 & 0.90 (2 t in ≈ 2:98 ratio, 3H, diastereomeric CH_3, J = 8Hz), 1.29 (s, 9H), 1.34-2.28 (m, 10H), 3.65 (s, 1H, D_2O washable), 4.18 (m, 1H), 5.06 (m, 1H), 6.68 (m, 2H), 7.08-7.32 (m, 5H), 7.50 (m, 2H); ^{13}C NMR : δ 7.40, 22.03, 22.32, 28.70, 30.93, 32.14, 33.44, 75.38, 75.64, 78.16, 114.64, 124.86, 125.54, 126.78, 127.41, 141.21, 143.04, 154.58, 174.21.

(R)-2-Hydroxy-2-phenylbutanoic acid (7): To a stirred solution of KOH (0.255 g) in methanol (10 mL), the crude ester **7a** (0.903 g, 2.2 mM) was added at room temperature. After 2 h, methanol was removed and the residue was diluted with water (10 mL) and extracted with ether (3 x 10 mL) (to recover the chiral auxiliary). The aqueous layer was neutralized with 2N HCl and extracted with ether (3 x 10 mL). The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and recrystallized from

hexane-ether (3:1) mixture. Yield: 0.310 g (78%); mp: 123-24°C {Lit.[16] optically pure acid mp 124-25°C}; Optical rotation: $[\alpha]_D^{24}$ -32.3 (c 1.77, EtOH), 97% ee, Conf (R); {Lit.[16] $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH), >99% ee, Conf (S)}; IR (KBr) ν_{max}: 3400, 3190-2550, 1715 cm^{-1}; ^1H NMR (100 MHz): δ 0.94 (t, 3H, J = 6 Hz), 1.84-2.52 (m, 2H), 4.82-6.10 (br, 2H, D_2O washable), 7.23-7.76 (m, 5H); ^{13}C NMR: δ 7.94, 32.60, 78.74, 125.57, 128.00, 128.36, 140.84, 179.98.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-3-methyl-2-phenylbutanoate (8a): This was prepared from the keto ester **5a** and *iso*-propylzinc chloride. Yield: 94%; mp: 97-98°C; IR (KBr) ν_{max}: 3499, 1718 cm^{-1}; ^1H NMR: δ 0.65 & 0.68 (2d, 3H, J = 6 Hz), 0.88 & 1.02 (2 d in 7:93 ratio, 3H, diastereomeric CH_3, J = 6 Hz), 1.22-2.32 (m, 17H), 2.58 (m, 1H), 3.69 (s, 1H, D_2O washable), 4.18 (m, 1H), 5 02 (m, 1H), 6.62-7.68 (m, 9H). ^{13}C NMR (for major isomer): δ 15.87, 17.13, 22.51, 22.85, 29.08, 31.59, 34.09, 35.79, 75.84, 80.91, 115.15, 125.89, 126.16, 127.24, 127.91, 141.05, 143.62, 155.13, 175.22.

(R)-2-Hydroxy-3-methyl-2-phenylbutanoic acid (8): The above α-hydroxy ester was hydrolyzed to furnish the chiral acid **8**. Yield: 81%; mp: 104°C {Lit.[16] optically pure acid mp 103-4°C}; Optical rotation: $[\alpha]_D^{24}$ -29.0 (c 2.05, EtOH), 89% ee, Conf. R; {Lit.[16] $[\alpha]_D^{25}$ +32.5 (c 2, EtOH), >99% ee, Conf. (S)}; IR (KBr) ν_{max}: 3475, 3300-2600, 1720 cm^{-1}; ^1H NMR: δ 0.72 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6 Hz), 2.66 (sept, 1H, J = 6 Hz), 3.28-5.26 (br, 2H, D_2O washable), 7.22-7.46 (m, 3H), 7.62- 7.75 (m, 2H); ^{13}C NMR: δ 15.77, 17.27, 35.92, 81.10, 125.98, 127.86, 128.30, 140.41, 180.58.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenylhexanoate (9a): This was prepared from α-keto ester **5a** and *n*-butylzinc chloride. Yield: 95%; IR (neat) ν_{max}: 3520, 1725 cm^{-1}; ^1H NMR: δ 0.72 & 0.90 (2 t in 5:95 ratio, 3H, diastereomeric $-CH_3$, J = 6.6 Hz), 1.24-2.28 (m, 23H), 3.68 (s, 1H, D_2O washable), 4.18 (m, 1H), 5.02 (m, 1H), 6.70-7.85 (m, 9H); ^{13}C NMR (for major isomer): δ 14.04, 22.69, 22.87, 22.98, 25.90, 29.33, 31.59, 34.09, 39.64, 76.00, 76.27, 78.52, 115.30, 125.47, 126.20, 127.40, 128.06, 142.11, 143.68, 155.28, 174.92.

(R)-2-Hydroxy-2-phenylhexanoic acid (9): Hydrolysis of the hydroxy ester **9a** afforded the chiral acid **9**; Yield: 77%; mp: 98-99°C; Optical rotation: $[\alpha]_D^{24}$ -20.5 (c 1.98, EtOH), 88% ee, Conf (R), {Lit.[6] $[\alpha]_D^{22}$ -19.00 (c 2.20, EtOH), 82% ee, Conf (R)}.; IR (KBr) ν_{max}: 3400,

3150-2500 (br), 1710 cm^{-1}; ^1H NMR (100 MHz): δ 0.91 (distorted t, 3H), 1.06-1.48 (m, 4H), 1.82-2.42 (m, 2H), 4.71-6.12 (br, 2H, D_2O washable), 7.23-7.68 (m, 5H); ^{13}C NMR: δ 13.95, 22.78, 25.77, 39.45, 78.48, 125.56, 128.02, 128.41, 141.11, 180.36.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-4-methyl-2-phenylpentanoate (10a): This compound was prepared from the glyoxylate **5a** and *iso*-butylzinc chloride; Yield: 93%; IR (neat) ν_{max}: 3350, 1745 cm^{-1}; ^1H NMR: δ 0.74 & 0.86 (2 m in 6:94 ratio, 6H, diastereomeric $(CH_3)_2$), 1.12-2.24 (m, 20H), 3.64 (s, 1H, D_2O washable), 4.02-4.18 (m, 1H), 4.84-5.02 (m, 1H), 6.54-7.80 (m, 9H); ^{13}C NMR (for major isomer): δ 22.62, 22.95, 23.65, 24.60, 24.76, 29.21, 31.59, 34.11, 47.86, 76.05, 78.52, 115.18, 125.38, 126.18, 127.34, 128.02, 142.75, 143.66, 155.17, 175.40.

(R)-2-Hydroxy-4-methyl-2-phenylpentanoic acid (10): This acid was obtained by the hydrolysis of above hydroxy ester; Yield: 81%; mp: 116-18°C {Lit.[16] optically pure acid mp 118-20°C}; Optical rotation: $[\alpha]_D^{24}$ -17.2(c 1.90, EtOH), 86% ee, Conf (R); {Lit.[16] $[\alpha]_D^{25}$ +20.0 (c 2.0, EtOH), >99% ee, Conf (S)}; IR (KBr) ν_{max}: 3400, 3140-2550, 1710 cm^{-1}; ^1H NMR (100 MHz): δ 0.92 (t, 6H, J = 5Hz), 1.65-2.21 (m, 3H), 4.82-6.02 (br, 2H, D_2O washable), 7.32-7.81 (m, 5H); ^{13}C NMR: δ 23.32, 24.40, 24.67, 47.84, 78.44, 125.55, 128.00, 128.42, 141.84, 180.92.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenyloctanoate (11a): This compound was prepared from the glyoxylate **5a** and *n*-hexylzinc chloride; Yield: 95%; mp: 64-66°C; IR (KBr) ν_{max}: 3475, 1720 cm^{-1}; ^1H NMR: δ 0.75-2.28 (m, 30H), 3.68 (s, 1H, OH), 4.12-4.28 (m, 1H), 4.92-5.08 (m, 1H), 6.62-7.68 (m, 9H); ^{13}C NMR (for major isomer): δ 14.20, 22.70, 23.02, 23.78, 29.34, 29.55, 31.69, 31.82, 34.13, 40.13, 75.91, 76.22, 78.62, 115.43, 125.58, 126.24, 127.43, 128.11, 142.34, 143.65, 155.41, 174.94.

(R)-2-Hydroxy-2-phenyloctanoic acid (11): The hydroxy ester **11a** was hydrolyzed to furnish chiral acid **11**; Yield: 78%; mp: 94-95°C; $[\alpha]_D^{24}$ -18.2 (c 2.04, EtOH), Conf. (R), 94% ee, {Lit.[6] $[\alpha]_D^{22}$ -17 (c 2.2, EtOH), Conf. (R), 88% ee}; IR (KBr) ν_{max}: 3426, 3180-2530, 1722 cm^{-1}; ^1H NMR: δ 0.86 (dist t, 3H, J = 6.6 Hz), 1.08-1.54 (m, 8H), 1.92-2.38 (m, 2H), 4.04-5.08 (br, 2H, D_2O washable), 7.22-7.46 (m, 3H), 7.52-7.65 (m, 2H); ^{13}C NMR: δ 14.07, 22.62, 23.59, 29.35, 31.66, 39.74, 78.53, 125.56, 128.02, 128.41, 141.11, 180.51.

(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl phenylglyoxylate (6a): This was prepared from the alcohol **6** and benzoylformic acid. Yield: 83%; mp: 105-6°C (hexane-benzene/5:1); Optical rotation: $[\alpha]_D^{24}$ -43.78 (c 0.98, acetone); IR (KBr) ν_{max}: 1722, 1685 cm^{-1}; ^1H NMR: δ 1.24-1.94 (m, 6H), 2.25 (m, 2H), 4.35 (m, 1H), 5.34 (m, 1H), 7.05 (m, 2H), 7.49 (m, 10H), 7.90 (m, 2H); ^{13}C NMR: δ 23.08, 23.41, 29.84, 29.93, 76.50, 77.65, 116.43, 126.70, 126.79, 128.22, 128.79, 129.96, 132.28, 134.34, 134.80, 140.62, 157.18, 163.81, 186.82; Mass (m/e): 400 (M^+); Analysis: Calcd. for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04; : Found: C, 78.25: H, 6.06.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenylbutanoate (7b): This was prepared from the glyoxylate **6a** and ethylmagnesium bromide; Yield: 95%; mp: 79-80°C; IR (KBr) ν_{max}: 3470, 1710 cm^{-1}; ^1H NMR: δ 0.85 & 0.92 (2 t in 7:93 ratio, 3H, diastereomeric $-CH_3$, J = 7.2 Hz), 1.21-2.36 (m, 10H), 3.71 (s, 1H, D_2O washable), 4.22 (m, 1H), 5.07 (m, 1H), 6.72-7.68 (m, 14H); ^{13}C NMR (for major isomer): δ 8.08, 22.79, 23.06, 29.33., 29.51, 32.79, 76.06, 76.65, 78.85, 116.11, 125.54, 126.77, 127.51, 128.14, 128.80, 134.21, 141.05, 142.00, 157.11, 175.02.

(R)-2-Hydroxy-2-phenylbutanoic acid (7): The hydroxy ester **7b** was hydrolyzed to produce acid **7**; Yield: 81%; mp: 121-23°C {Lit.[16] optically pure acid mp 124-25°C}; Optical rotation: $[\alpha]_D^{24}$ -29.3 (c 1.75, EtOH), 88% ee, Conf (R); {Lit[16] $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH), >99% ee, Conf (S)}.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-3-methyl-2-phenylbutanoate (8b): This was prepared from the keto ester **6a** and *iso*-propylzinc chloride. Yield: 93%; mp: 139-40°C; IR (KBr) ν_{max}: 3495, 1724 cm^{-1}; ^1H NMR: δ 0.64 & 0.72 (2d, 3H, J = 6 Hz), 0.92 & 1.04 (2 d in 5:95 ratio, 3H, diastereomeric CH_3, J = 6 Hz), 1.28-2.32 (m, 8H), 2.64 (sept, 1H, J = 6 Hz), 3.70 (s, 1H, OH), 4.18-4.32 (m, 1H), 4.98-5.12 (m, 1H), 6.74-7.68 (m, 14H); ^{13}C NMR (for major isomer): δ 15.95, 17.21, 22.69, 23.01, 29.17, 29.33, 35.85, 75.94, 76.29, 80.97, 115.98, 125,95, 126.79, 127.34, 128.01, 128.16, 128.84, 134.08, 140.93, 141.07, 157.04, 175.33.

(R)-2-Hydroxy-3-methyl-2-phenylbutanoic acid (8): The above hydroxy ester was hydrolyzed to furnish the chiral acid **8**. Yield: 78%; mp: 102-3°C {Lit.[16] optically pure acid mp 103-4°C}; Optical rotation: $[\alpha]_D^{24}$ -28.4 (c 2.01, EtOH), 87% ee, Conf. R; {Lit.[16] $[\alpha]_D^{25}$ +32.5 (c 2, EtOH), >99% ee, Conf. (S)}.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenylhexanoate (9b): This compound was prepared from [(1R,2R)-2-(4-phenylphenoxy)-cyclohex-1-yl] phenylglyoxylate **6a** and *n*-butylzinc chloride as a viscous liquid. Yield: 94%; IR (neat) ν_{max}: 3450, 1715 cm^{-1}; ^1H NMR: δ 0.72 & 0.87 (2 t in 9:91 ratio, 3H, diastereomeric $-CH_3$, J = 6Hz), 1.12-2.24 (m, 14H), 3.74 (s, 1H, D_2O washable), 4.25 (m, 1H), 5.06 (m, 1H), 6.82-7.65 (m, 14H); ^{13}C NMR (for major isomer): δ 13.40, 22.22, 22.44, 25.27, 28.70, 28.87, 38.94, 75.41, 75.99, 77.88, 115.43, 124.82, 126.13, 126.84, 127.49, 128.15, 133.50, 140.24, 141.38, 156.45, 174.37.

(R)-2-Hydroxy-2-phenylhexanoic acid (9): Hydrolysis of the above hydroxy ester **9b** afforded chiral acid **9** as crystalline solid; Yield: 79%; mp: 98-99°C; Optical rotation: $[\alpha]_D^{24}$ -19.3 (c 2.18, EtOH), 83% ee, Conf (R), {Lit[6] $[\alpha]_D^{22}$ -19.0 (c 2.20, EtOH), 82% ee, Conf (R)}.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-4-methyl-2-phenyl-pentanoate (10b): This was prepared from the glyoxylate **6a** and *iso*-butylzinc chloride. Yield: 96%; mp: 86-87°C; IR (KBr) ν_{max}: 3455, 1705 cm^{-1}; ^1H NMR: δ 0.79 & 0.90 (m & t in 6:94 ratio, 6H, diastereomeric $(CH_3)_2$, J = 7.2 Hz), 1.22-2.28 (m, 11H), 3.78 (s, 1H, D_2O washable), 4.24 (m, 1H), 5.08 (m, 1H), 6.74-7.62 (m, 14H); ^{13}C NMR (for major isomer): δ 22.02, 22.35, 22.98, 23.75, 24.09, 28.52, 28.69, 47.19, 75.35, 75.66, 77.81, 115.28, 124.69, 126.05, 126.70, 127.41, 128.10, 133.37, 140.17, 142.03, 156.31, 174.77.

(R)-2-Hydroxy-4-methyl-2-phenylpentanoic acid (10): This acid was obtained by the hydrolysis of above hydroxy ester; Yield: 74%; mp: 116-18°C {Lit.[16] optically pure acid mp 118-20°C}; Optical rotation: $[\alpha]_D^{24}$ -17.8(c 1.97, EtOH), 89% ee, Conf (R); {Lit.[16] $[\alpha]_D^{25}$ +20.0 (c 2.0, EtOH), >99% ee, Conf (S)}.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenyloctanoate (11b): This compound was prepared from the glyoxylate **6a** and *n*-hexylzinc chloride; Yield: 95%; IR (neat) ν_{max}: 3480, 1715 cm^{-1}; ^1H NMR: δ 0.72-2.32 (m, 21H), 3.68 (s, 1H, OH), 4.14-4.38 (m, 1H), 4.92-5.18 (m, 1H), 6.74-7.72 (m, 14H); ^{13}C NMR (for major isomer): δ 14.23, 22.73, 23.12, 23.82, 29.40, 29.56, 31.85, 40.08, 76.03, 76.62, 78.66, 116.20, 125.60, 126.82, 127.55, 128.21, 128.88, 134.20, 140.94, 142.26, 157.23, 175.05.

(R)-2-Hydroxy-2-phenyloctanoic acid (11): Hydrolysis of the above hydroxy ester **9a** afforded chiral acid **11**; Yield: 77%; mp: 94°C; $[\alpha]_D^{24}$ -17.2 (c 1.82, EtOH), Conf. (R), 89% ee, {Lit.[6] $[\alpha]_D^{22}$ -17 (c 2.2, EtOH), Conf. (R), 88% ee}.

Acknowledgements: We thank Rajiv Gandhi foundation (JNCASR, IISc Campus, Bangalore) 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. Morrison, J.D. (Editor); *Asymmetric Synthesis*, Academic Press, New York, **1983-1985**, *Vol. 1-5*.
2. Oppolzer, W.; *Tetrahedron*, **1987**, *43*, 1969-2004.
3. ApSimon, J.W.; Collier, T.L.; *Tetrahedron*, **1986**, *42*, 5157-5254.
4. Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581-1590.
5. Whitesell, J.K. *Chem. Rev.* **1992**, *92*, 953-964.
6. Bireau, G.; Deberly, A.; Abenhaim, D.; *Tetrahedron Lett.*, **1988**, *29*, 2175-2176.
7. Corey, E.J.; Ensley, H.E.; *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.
8. Greene, A.E.; Charbonnier, F.; Luche, M.J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752-4753.
9. Basavaiah, D.; Rama Krishna, P.; Bharathi, T.K. *Tetrahedron Lett.* **1990**, *31*, 4347-4348.
10. Basavaiah, D.; Rama Krishna, P.; Bharathi, T.K. *Tetrahedron: Asymmetry* **1995**, *6*, 436-451.
11. Fujimoto, Y.; Yadav, J.S.; Sih, C.J. *Tetrahedron Lett.* **1980**, *21*, 2481-2482.
12. Whitesell, J.K.; Buchanan, C.M. *J. Org. Chem.* **1986**, *51*, 5443-5445.
13. Corey, P.F. *Tetrahedron Lett.* **1987**, 28, 2801-2804.
14. Basavaiah, D.; Bharathi, T.K.; *Tetrahedron Lett.* **1991**, *32*, 3417-3420.
15. Basavaiah, D.; Bharathi, T.K.; Rama Krishna, P. *Synth. Commun.* **1992**, *22*, 941-947.
16. Meyers, A.I.; Slade, J.; *J.Org.Chem.* **1980**, *45*, 2912-2914.

(*Received in UK* 30 *June* 1995; *revised* 12 *September* 1995; *accepted* 15 *September* 1995)