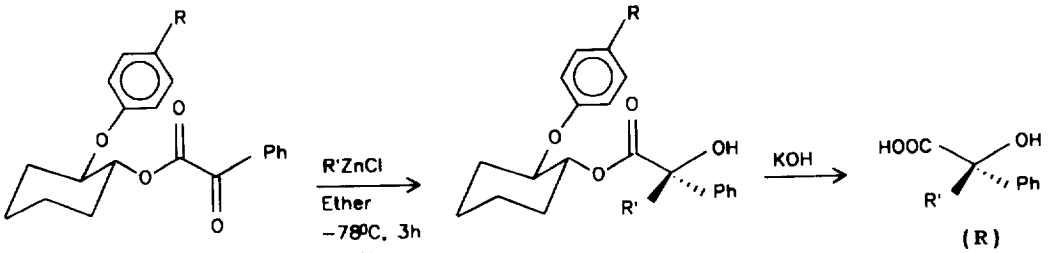
SCHEME 1:



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

R = ^{t}Bu, 7a-11a
R = Ph, 6b-11b

(R)
7-11

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

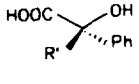
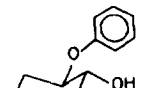
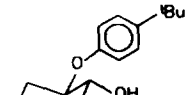
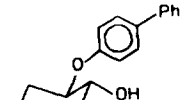
Table 1: Preparation of chiral α-hydroxy acids **7-11** from glyoxylates **5a** and **6a** and R'ZnCl.[a]

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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}.

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Selective Synthesis of 1-Indanones *via* Tandem Knoevenagel Condensation-Cycloalkylation of β-Dicarbonyl Compounds and Aldehydes

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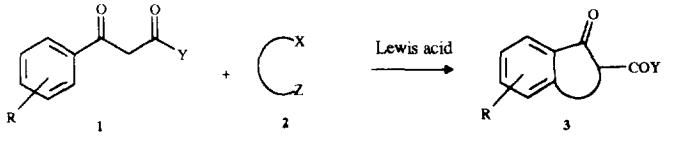
Abstract: Aromatic 1,3-dicarbonyl compounds react with not enolizable aldehydes in the presence of C_2H_5MgBr or $AlCl_3$ affording 2-carbethoxy- and 2-acetyl-1-indanones *via* tandem Knoevenagel condensation-cycloalkylation process.

Introduction

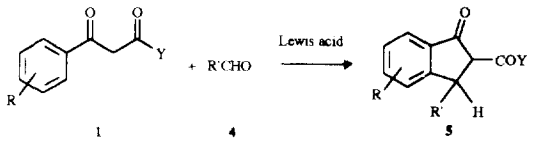
Aromatic 1,3-dicarbonyl compounds **1** constitute a family of useful reagents which possess three sites capable of reacting with electrophiles: namely the aromatic ring, the active methylene and the carbonyl oxygen. It is thus of considerable interest to find new practical methods for the regioselective functionalization of these compounds.

During the course of our studies aimed at achieving highly selective electrophilic substitution on ambidental substrates[1], we went to explore the potential of the reaction between convenient metal chelates of compounds **1** and multireactive electrophiles **2** towards the regioselective synthesis of bicyclic derivatives **3** (Scheme 1).



Scheme 1

As a result of these studies we reported the synthesis of indanediones[2] and hydroxynaphthoquinones[3] by regioselective bisacylation of dichloroaluminium chelates of substrates **1** with suitable acyl dichlorides. Following this strategy we decided to develop a one-step approach to 1-indanones **5** by a tandem Knoevenagel condensation-cycloalkylation process involving aromatic β-dicarbonyl compounds **1** and not enolizable aldehydes **4**, with the possibility to vary substituents R, R' and Y and control the regiochemistry of the entire reaction[4] (Scheme 2). 2-Carbethoxy- and 2-acetyl-1-indanones **5** are important building blocks in the synthesis of many natural products[5] and considerable efforts have been made to find selective routes to these compounds[6].



R=H, alkyl, OCH_3; R'=H, Ar, CH=CH-Ar; Y=OC_2H_5, CH_3

Scheme 2

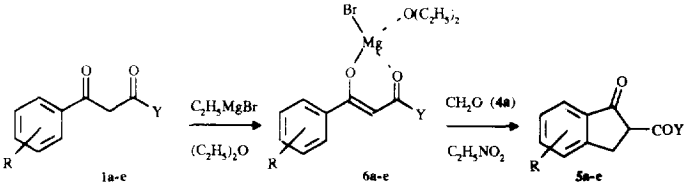
We now wish to present results from our investigations of this reaction.

Results and Discussion

The starting β-dicarbonyl compounds (**1a-e**) required for the present study were of commercial quality or were prepared as described in the literature from readily available acetophenones by condensation with diethyl carbonate[7].

The first reaction examined was the alkylation of the bromomagnesium chelate **6a** (R=H, Y=OC_2H_5) with formaldehyde since our previous studies on the reaction of phenols with aldehydes indicated that best yields were obtained with bromomagnesium phenolates[8] (Scheme 3).

The chelate **6a** was prepared from a rapid reaction of ethyl-3-oxo-3-phenylpropionate (**1a**) and C_2H_5MgBr in dry ether. After replacing nitroethane as the reaction solvent, addition of formaldehyde and heating at 110°C for 3 hours, product **5a** was obtained in 72% yield[9].



Scheme 3