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# Studies on the enzymatic kinetic resolution of β-hydroxy ketones

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**Abstract**

Kinetic resolution of aldol products using enzymatic transesterification and hydrolysis are described. The effect of structure of aldols on the enantioselectivity have also been studied in detail.


*Keywords:* β-Hydroxy ketones; Kinetic resolution; Candida cylindracea lipase; Enantioselectivity

## 1. Introduction

The aldol functionality is an important structural feature often encountered in many biologically active compounds, especially in macrolide and ionophore antibiotics [1]. Chiral β-hydroxy ketones can serve as versatile and useful building blocks for the synthesis of polyfunctional compounds and natural products. The chirality at the hydroxyl center can also be used to generate/control the stereochemistry at other sites. An excellent example of this type of chiral induction is illustrated in the synthesis of Lonomycin A, a polyether antibiotic reported by Evans et al. [2]. Chiral β-hydroxy carbonyl compounds can be readily converted to 1,3-*syn* [3a,b] and anti-diols [3c] and amino alcohols [4] and these units are present in many natural products such as antibiotics, pheromones and in many biologically active compounds. It is also worth mentioning that 1,5-diastereoselective aldol reactions are possible with chiral acetone aldol products leading to 1,5-diols [5].

Considerable efforts have been made over the years to develop synthetic strategies for the stereoselective synthesis of β-hydroxy ketones (aldols). Of the chemical methods known in literature for the stereoselective synthesis of these compounds, the most important are catalytic asymmetric aldol reactions and direct asymmetric aldol reactions [6,7]. Alternatively, they can be prepared by biochemical methods, viz: (i) use of aldolase enzymes [8]; (ii) use of aldolase antibodies [9]; (iii) through Baker's yeast-mediated reduction of 1,3-diketones [10];[1] and (iv) by simple kinetic resolution of racemic aldol product using enzymes [11].[2] However, there are only few reports on the use of enzymes for kinetic resolution of aldol products. Xu and coworkers [11a] used enzyme catalyzed resolution of the aldol products in the synthesis of (+)-calonolide, an anti-HIV agent. Kinetic resolution of trifluorinated derivatives of aldols has been reported by Kitazume and coworkers [11b].

Lipases are highly useful in the resolution of primary and secondary alcohols. The use of hydrolytic

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[1] For asymmetric biotransformation of 4-phenyl-3-buten-2-one to give **1** using rat liver see [10d].
[2] For enantioselective hydrolysis of (±)-**1a** using lyophilized Baker's yeast see [11b].

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enzymes such as lipases in organic solvents as well as in aqueous solution is well recognized [10a,12]. Enzymatic transesterification has been successfully used for the resolution of α-hydroxy and γ-hydroxy ketones [13]. Recently, we have reported the synthesis of optically active aryl β-hydroxy ketones by enzymatic transesterification [14]. In this paper, we further extend the use of lipases for the synthesis of different substituted aldols and for the hydrolysis of racemic acetates of aldol products. Since the outcome of enzyme catalyzed reactions depend largely on the structure of substrate, an in-depth study of the effect of structure of aldols on enantioselectivity has been carried out.

## 2. Experimental

*Candida cylindracea lipase* (CCL, Type VII, Aldrich, 700–1200 U/mg) was used as supplied. Other reagents were obtained from commercial suppliers and used without further purification. Analytical TLC was performed on silica gel $GF_{257}$ coated glass plates. Purification by gravity column chromatography was carried out using silica gel (100–200 mesh). Mixtures of ethyl acetate and petroleum ether were used as eluent. IR spectra were recorded either on Nicolet (Impact 400D FT-IR) or Bomem MB series FT-IR spectrophotometers. The NMR spectra were recorded on Bruker 300 MHz spectrometer. Chemical shifts are given in δ-scale with TMS as internal reference. Melting points were recorded on Aldrich Meltemp-II melting point apparatus and are uncorrected. The GC mass spectra were recorded on a Hewlett-Packard mass spectrometer model 5791. FAB mass was recorded on Hewlett-Packard series II mass spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 series II CHNS analyzer. Optical rotations were measured using Jasco DIP-370 digital polarimeter at ambient temperature (27 °C) using chloroform as the solvent.

### 2.1. Standard procedure for enzymatic resolution of aldols

To a solution of racemic **1** (150 mg, 0.92 mmol) in vinyl acetate (5 ml) was added CCL (225 mg) and stirred at room temperature for 28 h. The enzyme was then filtered off and the solvent was evaporated. The crude product thus obtained was subjected to column chromatography (petroleum ether:EtOAc 10–20%) to afford the acetate (+)-**1a** (60 mg, 33%) and alcohol (−)-**1** (97 mg, 65%).

#### 2.1.1. 4-(S)-(−)-Hydroxy-4-phenyl-2-butanone, *1* [15]

Colorless oily liquid; $[\alpha]_D^{27}$ −36.1 (c, 1.7, $CHCl_3$), ee 50%; IR ($CCl_4$) ($cm^{-1}$): 3424, 3031, 1720; $^1H$ NMR ($CDCl_3$) $\delta$: 2.15 (s, 3H), 2.75 (dd, 1H, $J = 3.3$, 17.3 Hz), 2.86 (dd, 1H, $J = 9.1$, 17.3 Hz), 3.60 (br s, 1H), 5.11 (dd, 1H, $J = 3.3$, 5.8 Hz), 7.25–7.33 (m, 5H); MS *m/z*: 164 ($M^+$, 48), 146 (74), 131 (46), 105 (100), 91 (8), 77 (92), 51 (22).

#### 2.1.2. 4-(R)-(+)-Acetoxy-4-phenyl-2-butanone, *1a*

White solid; mp: 41–43 °C; $[\alpha]_D^{27}$ 64.6 (c, 0.71, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 3031, 1720 (br); $^1H$ NMR ($CDCl_3$) $\delta$: 2.04 (s, 3H), 2.16 (s, 3H), 2.83 (dd, 1H, $J = 4.9$, 16.7 Hz), 3.12 (dd, 1H, $J = 8.7$, 16.7 Hz), 6.19 (dd, 1H, $J = 4.9$, 8.7 Hz), 7.28–7.41 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 21.0, 30.3, 49.9, 71.6, 126.4, 128.2, 128.6, 139.7, 169.5, 204.1; GC–MS *m/z*: 206 ($M^+$, 3), 163 (100), 146 (24), 131 (27), 105 (100), 77 (19); Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; Found: C, 69.80; H, 6.79.

### 2.2. Resolution of 4-hydroxy-4-(4′-methyl phenyl)-2-butanone

The racemic **2** (45 mg, 0.25 mmol) was resolved according to standard procedure. After reaction for 27 h, the crude product was chromatographed with 10–20% petroleum ether:EtOAc to afford the acetate (+)-**2a** (21 mg, 38%) and alcohol (−)-**2** (27 mg, 60%).

#### 2.2.1. 4-(S)-(−)-Hydroxy-4-(4′-methyl phenyl)-2-butanone, *2*

Colorless oily liquid; $[\alpha]_D^{27}$ −27.0 (c, 0.3, $CHCl_3$), ee 68%; IR ($CCl_4$) ($cm^{-1}$): 3437, 3012, 1707; $^1H$ NMR ($CDCl_3$) $\delta$: 2.19 (s, 3H), 2.34 (s, 3H), 2.79 (dd, 1H, $J = 3.4$, 17.5 Hz), 2.89 (dd, 1H, $J = 8.9$, 17.5 Hz), 3.22 (br s, 1H), 5.12 (dd, 1H, $J = 3.4$, 5.6 Hz), 7.16 (d, 2H, $J = 7.9$ Hz), 7.24 (d, 2H, $J = 8.4$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$: 20.9, 30.5, 51.9, 69.5, 125.4, 128.9, 136.9, 139.7, 208.5; MS *m/z*: 178 ($M^+$, 6), 177 ($M^+ - 1$, 40), 160 (28), 144 (87), 121 (97), 119 (100), 105 (15), 91 (100), 77 (22); Anal. Calcd.

for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; Found: C, 74.07; H, 7.98.

*2.2.2. 4-(R)-(+)-Acetoxy-4-(4′-methyl phenyl)-2-butanone, **2a***

Colorless solid; mp: 35–36 °C; $[\alpha]_D^{27}$ 82.4 (c, 0.3, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 2924, 1739, 1720; $^1H$ NMR ($CDCl_3$) $\delta$: 2.02 (s, 3H), 2.14 (s, 3H), 2.33 (s, 3H), 2.77 (dd, 1H, $J$ = 5.1, 16.5 Hz), 3.09 (dd, 1H, $J$ = 8.6, 16.5 Hz), 6.13 (dd, 1H, $J$ = 5.1, 8.5 Hz), 7.13 (d, 2H, $J$ = 7.9 Hz), 7.23 (d, 2H, $J$ = 8.1 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$: 20.9, 21.1, 30.3, 49.8, 71.5, 126.4, 129.2, 136.7, 137.9, 169.5, 204.2; MS *m/z*: 219 ($M^+ - 1$, 7), 176 (64), 160 (14), 144 (50), 119 (100), 91 (18), 77 (3); Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; Found: C, 70.95; H, 7.18.

*2.3. Resolution of 4-hydroxy-4-(4′-chlorophenyl)-2-butanone*

The racemic **3** (180 mg, 0.91 mmol) was resolved according to standard procedure. After reaction for 29 h the crude product was chromatographed with 10–25% petroleum ether:EtOAc to afford the acetate (+)-**3a** (95 mg, 44%) and alcohol (−)-**3** (99 mg, 55%).

*2.3.1. 4-(S)-(−)-Hydroxy-4-(4′-chlorophenyl)-2-butanone, **3** [16]*

White solid; mp: 46–48 °C; $[\alpha]_D^{27}$ −40.9 (c, 1.17, $CHCl_3$), ee 70%; IR ($CCl_4$) ($cm^{-1}$): 3436, 2883, 1701; $^1H$ NMR ($CDCl_3$) $\delta$: 2.28 (s, 3H), 2.85–2.92 (m, 2H), 3.42 (d, 1H, $J$ = 2.9 Hz), 5.20–5.22 (m, 1H), 7.34–7.42 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 30.5, 51.7, 68.9, 126.9, 128.4, 129.3, 141.4, 208.6; MS *m/z*: 179 ($M^+ - 1 - H_2O$, 41), 164 (100), 140 (79), 138 (86), 110 (35), 75 (29).

*2.3.2. 4-(R)-(+)-Acetoxy-4-(4′-chlorophenyl)-2-butanone, **3a***

Low melting solid; $[\alpha]_D^{27}$ 68.1 (c, 1.07, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 2931, 1745, 1720; $^1H$ NMR ($CDCl_3$) $\delta$: 2.04 (s, 3H), 2.15 (s, 3H), 2.80 (dd, 1H, $J$ = 5.3, 16.9 Hz), 3.10 (dd, 1H, $J$ = 8.3, 16.9 Hz), 6.14 (dd, 1H, $J$ = 5.3, 8.3 Hz), 7.26–7.31 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 20.9, 30.3, 49.5, 70.8, 127.9, 128.8, 134.1, 138.2, 169.4, 203.6; MS *m/z*: 239 ($M^+ - 1$, 5), 196 (70), 179 (12), 164 (27), 138 (100), 110 (7), 77 (7); FAB MS Calcd. for $C_{12}H_{13}ClO_3$: 240; Found: 240; Anal. Calcd. for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44; Found: C, 60.08; H, 5.40.

*2.4. Resolution of 4-hydroxy-4-(4′-methoxyphenyl)-2-butanone*

The racemic **4** (180 mg, 0.93 mmol) was resolved according to standard procedure. After reaction for 28 h the crude product was chromatographed with 10–20% petroleum ether:EtOAc to afford the acetate (+)-**4a** (88 mg, 40%) and alcohol (−)-**4** (106 mg, 59%).

*2.4.1. 4-(S)-(−)-Hydroxy-4-(4′-methoxyphenyl)-2-butanone, **4** [15]*

White solid, mp: 36–38 °C; $[\alpha]_D^{27}$ −33.5 (c, 1.04, $CHCl_3$), ee 65%; IR ($CCl_4$) ($cm^{-1}$): 3443, 2843, 1714; $^1H$ NMR ($CDCl_3$) $\delta$: 2.19 (s, 3H), 2.78 (dd, 1H, $J$ = 3.4, 17.4 Hz), 2.82 (dd, 1H, $J$ = 9.0, 17.4 Hz), 3.19 (br s, 1H), 3.80 (s, 3H), 5.10 (m, 1H), 6.88 (d, 2H, $J$ = 8.7 Hz), 7.28 (d, 2H, $J$ = 8.7 Hz); MS *m/z*: 176 ($M^+ - H_2O$, 48), 161 (100), 133 (27), 77 (10).

*2.4.2. 4-(R)-(+)-Acetoxy-4-(4′-methoxyphenyl)-2-butanone, **4a***

White solid, mp: 66–68 °C; $[\alpha]_D^{27}$ 79.5 (c, 0.76, $CHCl_3$), ee >96%; IR (KBr) ($cm^{-1}$): 2937, 1726, 1714; $^1H$ NMR ($CDCl_3$) $\delta$: 2.02 (s, 3H), 2.15 (s, 3H), 2.82 (dd, 1H, $J$ = 5.3, 16.5 Hz), 3.12 (dd, 1H, $J$ = 8.5, 16.5 Hz), 3.79 (s, 3H), 6.14 (dd, 1H, $J$ = 5.3, 8.3 Hz), 6.87 (d, 2H, $J$ = 8.6 Hz), 7.29 (d, 2H, $J$ = 8.6 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$: 21.1, 30.3, 49.7, 55.1, 71.3, 113.9, 127.9, 131.6, 159.5, 169.6, 204.3; MS *m/z*: 236 ($M^+$, 9), 193 (44), 176 (46), 161 (75), 135 (100), 91 (9), 77 (12); Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; Found: C, 66.02; H, 6.84.

*2.5. Resolution of 4-hydroxy-4-(4′-nitrophenyl)-2-butanone*

The racemic **5** (102 mg, 0.49 mmol) was resolved according to standard procedure. After reaction for 36 h the crude product was chromatographed with 20–40% petroleum ether:EtOAc to afford the acetate (+)-**5a** (38 mg, 31%) and alcohol (−)-**5** (70 mg, 67%).

*2.5.1. 4-(S)-(−)-Hydroxy-4-(4′-nitrophenyl)-2-butanone, **5** [17]*

Pale yellow solid; mp: 55–57 °C; $[\alpha]_D^{27}$ −15.6 (c, 1.19, $CHCl_3$), ee 30%; IR (KBr) ($cm^{-1}$): 3437, 2906, 1714, 1527; $^1H$ NMR ($CDCl_3$) $\delta$: 2.22 (s, 3H), 2.84 (m, 2H), 3.56 (d, 1H, $J = 2.9$ Hz), 5.24–5.26 (m, 1H), 7.53 (d, 2H, $J = 8.7$ Hz), 8.21 (d, 2H, $J = 8.7$ Hz).

*2.5.2. 4-(R)-(+)-Acetoxy-4-(4′-nitrophenyl)-2-butanone, **5a***

Low melting pale yellow solid; $[\alpha]_D^{27}$ 54.5 (c, 0.69, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 3081, 1745, 1720, 1520; $^1H$ NMR ($CDCl_3$) $\delta$: 2.07 (s, 3H), 2.17 (s, 3H), 2.83 (dd, 1H, $J = 5.4$, 17.2 Hz), 3.13 (dd, 1H, $J = 7.8$, 17.2 Hz), 6.21 (dd, 1H, $J = 5.5$, 7.7 Hz), 7.53 (d, 2H, $J = 8.6$ Hz), 8.21 (d, 2H, $J = 8.8$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$: 20.9, 30.4, 49.3, 70.5, 123.9, 127.3, 128.8, 146.9, 169.4, 203.3; Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58; Found: C, 57.56; H, 5.10; N, 5.53.

*2.6. Resolution of 4-hydroxy-4-(3′,4′-dichlorophenyl)-2-butanone*

The racemic **9** (130 mg, 0.56 mmol) was resolved according to standard procedure. After reaction for 3 days the crude product was chromatographed with 15–30% petroleum ether:EtOAc to afford the acetate (+)-**9a** (50 mg, 33%) and alcohol (−)-**9** (76 mg, 58%).

*2.6.1. 4-(S)-(−)-Hydroxy-4-(3′,4′-dichlorophenyl)-2-butanone, **9***

White solid; mp: 37–38 °C; $[\alpha]_D^{27}$ −25.8 (c, 2.01, $CHCl_3$), ee 55%; IR ($CCl_4$) ($cm^{-1}$): 3441, 2909, 1713; $^1H$ NMR ($CDCl_3$) $\delta$: 2.20 (s, 3H), 2.79 (d, 2H, $J = 6.1$ Hz), 3.42 (br s, 1H), 5.09 (m, 1H), 7.16–7.19 (m, 1H), 7.39–7.46 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 30.6, 51.5, 68.4, 124.9, 127.6, 130.3, 131.2, 132.3, 140.5, 208.5; Anal. Calcd. for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; Found: C, 51.97; H, 4.26.

*2.6.2. 4-(R)-(+)-Acetoxy-4-(3′,4′-dichlorophenyl)-2-butanone, **9a***

Colorless viscous liquid; $[\alpha]_D^{27}$ 53.5 (c, 0.88, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 2928, 1744, 1721; $^1H$ NMR ($CDCl_3$) $\delta$: 2.05 (s, 3H), 2.16 (s, 3H), 2.79 (dd, 1H, $J = 5.3$, 17.1 Hz), 3.09 (dd, 1H, $J = 8.2$, 17.1 Hz), 6.09 (dd, 1H, $J = 5.4$, 7.8 Hz), 7.18–7.21 (m, 1H), 7.39–7.44 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 20.9, 30.4, 49.4, 70.3, 126.1, 128.5, 130.6, 132.4, 132.9, 140.0, 169.3, 203.3; MS *m/z*: 276 ($M^+ + 2$, 3), 274 ($M^+$, 6), 231 (94), 214 (16), 199 (39), 173 (100), 145 (25), 137 (28), 111 (34), 102 (37), 75 (69); FAB MS Calcd. for $C_{12}H_{12}Cl_2O_3$ + H: 275; Found: 275 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{12}Cl_2O_3$: C, 52.39; H, 4.40; Found: C, 52.42; H, 4.44.

*2.7. Resolution of 4-hydroxy-4-(3′,4′-methylenedioxyphenyl)-2-butanone*

The racemic **10** (111 mg, 0.54 mmol) was resolved according to standard procedure. After reaction for 27 h the crude product was chromatographed with 10–25% petroleum ether:EtOAc to afford the acetate (+)-**10a** (48 mg, 36%) and alcohol (−)-**10** (81 mg, 73%).

*2.7.1. 4-(S)-(−)-Hydroxy-4-(3′,4′-methylenedioxyphenyl)-2-butanone, **10***

White solid; mp: 48–50 °C; $[\alpha]_D^{27}$ −16.5 (c, 0.87, $CHCl_3$), ee 36%; IR ($CCl_4$) ($cm^{-1}$): 3337, 2912, 1707; $^1H$ NMR ($CDCl_3$) $\delta$: 2.18 (s, 3H), 2.76 (two dd, $J = 3.1$, 17.4 and 9.0, 17.4 Hz, 2H), 3.31 (s, 1H), 5.03 (m, 1H), 5.93 (s, 2H), 6.72–6.84 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 30.7, 52.1, 69.7, 100.9, 106.3, 108.2, 118.9, 136.9, 147.0, 147.8, 208.6; MS *m/z*: 208 ($M^+$, 6), 190 ($M^+ - H_2O$, 100), 175 (82), 149 (44), 145 (72), 117 (28), 89 (30), 73 (6), 63 (16); Anal. Calcd. for $C_{11}H_{12}O_3$: C, 63.45, H, 5.80; Found: C, 63.35, H, 5.68.

*2.7.2. 4-(R)-(+)-Acetoxy-4-(3′,4′-methylenedioxyphenyl)-2-butanone, **10a***

Colorless liquid; $[\alpha]_D^{27}$ 72.7 (c, 0.51, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 2906, 1745, 1714; $^1H$ NMR ($CDCl_3$) $\delta$: 2.02 (s, 3H), 2.14 (s, 3H), 2.77 (dd, 1H, $J = 5.2$, 16.6 Hz), 3.06 (dd, 1H, $J = 8.4$, 16.6 Hz), 5.95 (s, 2H), 6.07 (dd, 1H, $J = 5.2$, 8.4 Hz), 6.73–6.76 (m, 1H), 6.81–6.84 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 21.0, 30.4, 49.7, 71.4, 101.1, 106.9, 108.2, 120.2, 133.4, 147.4, 147.7, 169.8, 204.6; MS *m/z*: 250 ($M^+$, 47), 207 (27), 190 (47), 175 (38), 149 (100), 117 (11), 89 (18), 63 (9); FAB MS Calcd. for $C_{13}H_{14}O_5$ + Na: 273; Found: 273 $[M + Na]^+$; Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64; Found: C, 62.34; H, 5.62.

### 2.8. Resolution of 4-hydroxy-4-(2-naphthyl)-2-butanone

The racemic **13** (158 mg, 0.74 mmol) was resolved according to standard procedure. After reaction for 27 h, 50 mg of enzyme was added and stirred for an additional 7 h and the crude product was chromatographed with 10–20% petroleum ether:EtOAc to afford the acetate (+)-**13a** (45 mg, 24%) and alcohol (−)-**13** (108 mg, 68%).

#### 2.8.1. 4-(S)-(−)-Hydroxy-4-(2-naphthyl)-2-butanone, ***13*** [7h]

White solid, mp: 58–60 °C; $[\alpha]_D^{27}$ −15.9 (c, 0.78, $CHCl_3$), ee 33%; IR (KBr) ($cm^{-1}$): 3418, 2912, 1707; $^1H$ NMR ($CDCl_3$) $\delta$: 2.18 (s, 3H), 2.89 (two dd, 2H, $J$ = 3.6, 17.6 and 8.8, 17.5 Hz), 3.46 (br s, 1H), 5.27–5.30 (d, 1H, $J$ = 7.3 Hz), 7.41–7.46 (m, 3H), 7.78–7.81 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 30.7, 51.9, 69.8, 123.7, 124.3, 125.8, 126.1, 127.6, 127.9, 128.2, 132.9, 133.2, 140.2, 208.6; MS *m/z*: 196 ($M^+ - H_2O$, 13), 195 (96), 180 (100), 155 (44), 152 (76), 127 (49), 98 (7), 76 (22), 63 (9).

#### 2.8.2. 4-(R)-(+)-Acetoxy-4-(2-naphthyl)-2-butanone, ***13a***

White solid, mp: 66–68 °C; $[\alpha]_D^{27}$ 63.5 (c, 0.34, $CHCl_3$), ee >96%; IR (KBr) ($cm^{-1}$): 2931, 1745, 1720; $^1H$ NMR ($CDCl_3$) $\delta$: 2.06 (s, 3H), 2.16 (s, 3H), 2.89 (dd, 1H, $J$ = 5.0, 16.6 Hz), 3.19 (dd, 1H, $J$ = 8.5, 16.6 Hz), 6.33 (dd, 1H, $J$ = 5.0, 8.5 Hz), 7.43–7.48 (m, 3H), 7.80–7.83 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 21.0, 30.3, 49.8, 71.7, 124.0, 125.7, 126.2, 126.3, 127.6, 128.1, 128.5, 133.1, 136.9, 169.5, 204.0; MS *m/z*: 256 ($M^+$, 8), 255 ($M^+ - 1$, 42), 213 (42), 194 (36), 180 (36), 154 (100), 127 (22), 76 (7); Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.01; H, 6.25; Found: C, 75.50, H, 6.48.

### 2.9. Resolution of 4-hydroxy-5-phenyl-2-pentanone

The racemic **14** (106 mg, 0.59 mmol) was resolved according to standard procedure. After reaction for 21 h the crude product was chromatographed with 10–20% petroleum ether:EtOAc to afford the acetate (+)-**14a** (43 mg, 33%) and alcohol (−)-**14** (46 mg, 43%).

#### 2.9.1. (+)-4-Hydroxy-5-phenyl-2-pentanone, ***14***

Colorless oily liquid; $[\alpha]_D^{27}$ 2.3 (c, 1.42, $CHCl_3$), ee 28%; IR ($CCl_4$) ($cm^{-1}$): 3430, 2918, 1709; $^1H$ NMR ($CDCl_3$) $\delta$: 2.15 (s, 3H), 2.51–2.57 (m, 2H), 2.71 (dd, 1H, $J$ = 6.4, 13.5 Hz), 2.85 (dd, 1H, $J$ = 7.0, 13.5 Hz), 2.97 (br s, 1H), 4.27 (m, 1H), 7.18–7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 30.7, 42.9, 49.0, 68.6, 126.5, 128.5, 129.4, 137.8, 209.0; MS *m/z* 178 ($M^+$, 3), 160 ($M^+ - H_2O$, 8), 117 (8), 103 (4), 91 (100), 87 (44), 65 (64); Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; Found: C, 74.18; H, 7.53.

#### 2.9.2. (+)-4-Acetoxy-5-phenyl-2-pentanone, ***14a***

Colorless liquid; $[\alpha]_D^{27}$ 10.5 (c, 1.2, $CHCl_3$), ee 47%; IR ($CCl_4$) ($cm^{-1}$): 2925, 1737, 1717; $^1H$ NMR ($CDCl_3$) $\delta$: 2.00 (s, 3H), 2.11 (s, 3H), 2.55 (dd, 1H, $J$ = 5.2, 16.6 Hz), 2.69 (dd, 1H, $J$ = 7.4, 16.6 Hz), 2.84 (dd, 1H, $J$ = 6.5, 13.6 Hz), 2.95 (dd, 1H, $J$ = 6.1, 13.6 Hz), 5.41 (pentet, 1H, $J$ = 6.4 Hz), 7.17–7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 21.0, 30.3, 40.0, 46.7, 70.7, 126.8, 128.5, 129.5, 136.7, 169.9, 204.9; MS *m/z*: 160 ($M^+ - CH_3COOH$, 60), 145 (2), 120 (23), 117 (100), 91 (56), 77 (5); Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; Found: C, 70.53; H, 7.56.

### 2.10. Resolution of 4-hydroxy-6-phenyl-5-hexen-2-one

The racemic **16** (75 mg, 0.39 mmol) was resolved according to standard procedure. After reaction for 5 days the crude product was chromatographed with 10–25% petroleum ether:EtOAc to afford the acetate (+)-**16a** (25 mg, 27%) and alcohol (−)-**16** (48 mg, 64%).

#### 2.10.1. 4-(S)-(−)-Hydroxy-6-phenyl-5-hexen-2-one, ***16***

Low melting pale yellow solid; $[\alpha]_D^{27}$ −10.1 (c, 0.96, $CHCl_3$), ee 53%; IR ($CCl_4$) ($cm^{-1}$): 3419, 3026, 1713; $^1H$ NMR ($CDCl_3$) $\delta$: 2.21 (s, 3H), 2.75 (d, 2H, $J$ = 5.9 Hz), 3.08 (br s, 1H), 4.73–4.75 (m, 1H), 6.18 (dd, 1H, $J$ = 6.0, 15.9 Hz), 6.62 (d, 1H, $J$ = 15.9 Hz), 7.22–7.37 (m, 5H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 30.8, 49.9, 68.4, 126.4, 127.2, 127.7, 128.5, 130.0, 136.4, 208.9; MS *m/z*: 190 ($M^+$, 11), 172 (51), 157 (47), 128 (100), 115 (81), 102 (23), 77 (34); Anal.

Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; Found: C, 75.36; H, 7.46.

*2.10.2. 4-(R)-(+)-Acetoxy-6-phenyl-5-hexen-2-one,* ***16a***

Yellow oily liquid; $[\alpha]_D^{27}$ 65.3 (c, 0.52, $CHCl_3$), ee >96%; IR ($CCl_4$) ($cm^{-1}$): 3031, 1738, 1712; $^1H$ NMR ($CDCl_3$) $\delta$: 2.06 (s, 3H), 2.19 (s, 3H), 2.76 (dd, 1H, $J$ = 5.5, 16.5 Hz), 2.93 (dd, 1H, $J$ = 7.6, 16.5 Hz), 5.81 (q, 1H, $J$ = 6.7 Hz), 6.14 (m, 1H), 6.64 (d, $J$ = 15.9 Hz, 1H), 7.23–7.37 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 21.1, 30.4, 48.1, 70.3, 126.1, 126.6, 128.1, 128.5, 132.9, 135.9, 169.6, 204.2; MS *m/z*: 232 ($M^+$, 12), 190 (41), 189 (100), 172 (87), 157 (69), 131 (100), 115 (93), 104 (100), 91 (50), 77 (97); FAB MS Calcd. for $C_{14}H_{16}O_3$ + H: 233, Found: 233 $[M+H]^+$; Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; Found: C, 72.59; H, 6.98.

*2.11. Resolution of 4-hydroxy-5-nonene-2-one*

The racemic **22** (117 mg, 0.75 mmol) was resolved according to standard procedure. After reaction for 40 h the crude product was chromatographed with 5–15% petroleum ether:EtOAc to afford the acetate (+)-**22a** (46 mg, 32%) and alcohol (−)-**22** (68 mg, 58%).

*2.11.1. (−)-4-Hydroxy-5-nonene-2-one,* ***22***

Colorless liquid; $[\alpha]_D^{27}$ −14.9 (c, 0.84, $CHCl_3$), ee 48%; IR ($CCl_4$) ($cm^{-1}$): 3420, 2930, 1712; $^1H$ NMR ($CDCl_3$) $\delta$: 0.89 (t, 3H, $J$ = 7.3 Hz), 1.39 (sextet, 2H, $J$ = 7.3 Hz), 1.97–2.04 (m, 2H), 2.18 (s, 3H), 2.63–2.65 (m, 2H), 2.98 (br s, 1H), 4.49–4.51 (m, 1H), 5.45 (dd, 1H, $J$ = 6.3, 15.4 Hz), 5.63–5.71 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 13.7, 22.2, 30.8, 34.2, 50.2, 68.5, 130.9, 131.9, 208.7; MS *m/z*: 155 ($M^+ - 1$, 3), 138 ($M^+ - H_2O$, 3), 113 (24), 100 (41), 57 (100); Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32; Found: C, 69.26; H, 10.41.

*2.11.2. (+)-4-Acetoxy-5-nonene-2-one,* ***22a***

Colorless liquid; $[\alpha]_D^{27}$ 34.6 (c, 0.80, $CHCl_3$); ee 80%; IR ($CCl_4$) ($cm^{-1}$): 2931, 1741, 1724; $^1H$ NMR ($CDCl_3$) $\delta$: 0.88 (t, 3H, $J$ = 7.3 Hz), 1.39 (sextet, 2H, $J$ = 7.3 Hz), 1.96–2.02 (s and m merged, 5H), 2.16 (s, 3H), 2.63 (dd, $J$ = 5.5, $J$ = 16.1 Hz, 1H), 2.81 (dd, 7.7, $J$ = 16.1 Hz, 1H), 5.40 (dd, $J$ = 7.1, $J$ = 15.4 Hz, 1H), 5.56–5.63 (m, 1H), 5.75 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 13.5, 20.9, 21.9, 30.2, 34.1, 48.1, 70.3, 127.1, 134.6, 169.5, 204.4; MS *m/z*: 198 ($M^+$, 3), 155 (94), 138 (28), 113 (56), 97 (100), 81 (100), 67 (100), 55 (100); FAB MS Calcd. for $C_{11}H_{18}O_3$ + Na: 221; Found: 221 $[M + Na]^+$; Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; Found: 66.60; H, 9.20.

*2.12. Standard procedure for the enzymatic hydrolysis—hydrolysis of (±)-**1a***

Racemic **1a** (142 mg, 0.69 mmol) was dissolved in $CH_3CN$ (0.5 ml). To this was added 7 ml 0.1 M phosphate buffer (pH 7.0) and lipase CCL (215 mg). After stirring the reaction mixture for 19 h at room temperature, the reaction mixture was treated with 3 ml saturated brine and filtered through celite. The filtrate was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ solution, distilled water and brine and dried over $Na_2SO_4$ and concentrated in vacuo. The residue was subjected to column chromatography (petroleum ether:ethyl acetate 85:15–80:20) to get the product acetate (−)-**1a** (65 mg, 46%, 43% ee) and alcohol (+)-**1** (34 mg, 30%, 93% ee). The spectral characteristics of the acetate and alcohol were comparable to that given earlier.

*2.13. Determination of ee of **1a** and **1** using chiral shift reagent, Eu(hfc)$_3$*

Separation of the methyl signals of the two enantiomers were observed by the sequential addition of 5 mg of $Eu(hfc)_3$ to a solution of racemic (±)-**1a** (5 mg) in 0.5 ml $CDCl_3$. Finally, baseline separation of the methyl signals were obtained with 40 mg of shift reagent. The difference in chemical shifts of the two signals of (±)-**1a** was found to be 0.049 ppm. In the case of hydroxy compound (±)-**1**, the ee was determined by NMR as described above, where 30 mg shift reagent was required to get a baseline separation and difference in chemical shifts of the methyl signal of (±)-**1** was found to be 0.068 ppm.

## 3. Results and discussion

Various acetone aldol products (**1**–**22**, Fig. 1) were prepared using standard methods [14] and subjected

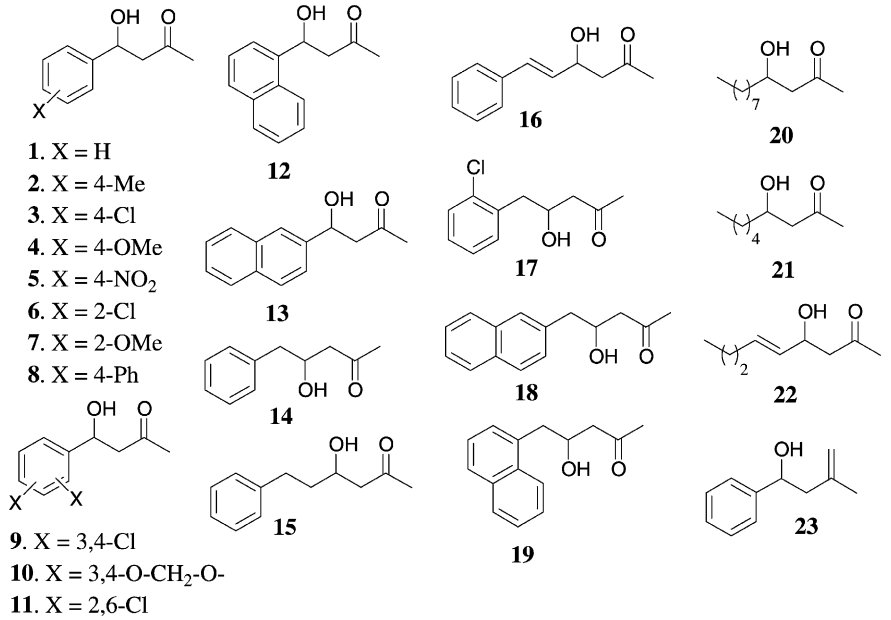
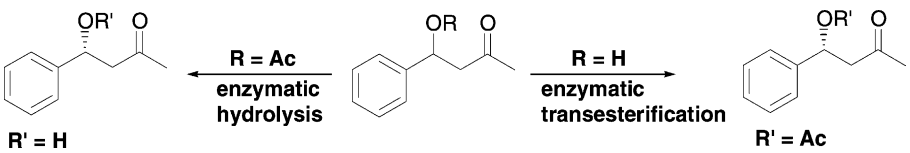



Fig. 1. Substrates used for enzymatic resolution.

to transesterification conditions using vinyl acetate as the acyl donor in the presence of *Candida cylindracea lipase* (Scheme 1). The reactions were done at room temperature (28–31 °C) and were followed by TLC analysis. The ee's of the products and substrates were determined using $^1$H NMR spectra of the Eu(hfc)$_3$ complex. The *E* values were determined using Sih and coworker's method [18].

With aryl-substituted β-hydroxy ketones, CCL showed higher enantioselectivity yielding the acetate with >96% ee (Table 1, entries 1–7). This high enantioselectivity observed in the transesterification reaction encouraged us to test other aldols. The enantioselectivity of the transformation depends significantly on the substituent position in the aryl ring. Unsubstituted (**1**) as well as derivatives with substituent in the 4- or 3-position of the aromatic ring (**2**–**5**, **9** and **10**) exhibited high enantioselectivity, whereas derivatives with substituent in the 2-position (**6**, **7** and **11**) reacted very sluggishly and led to <8% yield even after 6 days. When the substituent in the 4-position was a large group like phenyl as in **8**, the product was obtained in about 5% yield only after 6 days.

Insertion of one or two methylene groups between the chiral center and the phenyl ring resulted in a decrease in enantioselectivity, as seen in the case of **14** and **15**. In the case of **15**, the conversion was very low. However, excellent enantioselectivity was observed by the introduction of a double bond between chiral center and phenyl group as in **16** (Table 1, entry 10). Oehlschlager and coworkers earlier reported similar results in PPL catalyzed kinetic resolution of aryl alkanols [19]. Once again when an *ortho*-substituent was present on the phenyl ring and the chiral center was one carbon away, as




Scheme 1.

Table 1
Transesterification[a] of racemic aldol products

| Entry | Compound | Reaction time | Conversion ($c$, %)[b] | Alcohol | | Acetate | | $E$[c] |
|---|---|---|---|---|---|---|---|---|
| | | | | ee (%)[d] | Yield (%)[e] | ee (%)[d] | Yield (%)[e] | |
| 1 | **1** | 28 h | 34 | 50 | 65 | >96 | 33 | 80 |
| 2 | **2** | 27 h | 41 | 68 | 60 | >96 | 38 | 98 |
| 3 | **3** | 29 h | 42 | 70 | 55 | >96 | 44 | 102 |
| 4 | **4** | 28 h | 40 | 65 | 59 | >96 | 40 | 95 |
| 5 | **5** | 36 h | 24 | 30 | 67 | >96 | 31 | 66 |
| 6 | **9** | 3 days | 36 | 55 | 58 | >96 | 33 | 87 |
| 7 | **10** | 26 h | 27 | 36 | 73 | >96 | 36 | 69 |
| 8 | **13** | 34 h | 26 | 33 | 68 | >96 | 24 | 68 |
| 9 | **14** | 21 h | 37 | 28 | 43 | 47 | 33 | 5 |
| 10 | **16** | 5 days | 36 | 53 | 64 | >96 | 27 | 84 |
| 11 | **22** | 45 h | 37 | 48 | 58 | 80 | 31 | 14 |

[a] Reaction conditions: CCL, vinyl acetate, room temperature.
[b] $c = ee_s/(ee_s + ee_p)$.
[c] [18].
[d] Determined from $^1$H NMR spectra of the Eu(hfc)$_3$ complex.
[e] Isolated yield after column chromatography.

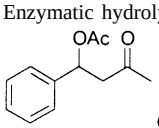
in **17**, negligible conversion was observed even after 7 days.

We had earlier found that in the case of naphthyl β-hydroxy ketones 1′- and 2′-isomers differ in their reactivity [14]. In order to find the influence of the naphthyl ring, we prepared aldols in which the naphthyl ring was one carbon away from the chiral center (**18** and **19**). Here both 1′- and 2′-isomers were inert even after 5 days.

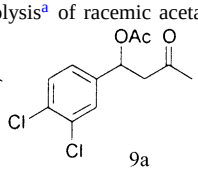
After studying aryl aldols, the effect of straight chain substituents were also examined (Fig. 1). For this, substrates **20**–**22** were selected and the enzyme was unable to resolve 4-hydroxy-2-dodecanone, **20**, and 4-hydroxy-2-nonanone, **21**. But *trans*-2-hexenal aldol, **22**, showed moderate selectivity. This selectivity may be due to the π–π interaction of the substrate with an aromatic residue present in the hydrophobic region of the enzyme [20].

In order to find the influence of a carbonyl group in these systems, resolution of the methallyl alcohol **23** was carried out. In this resolution process, <8% conversion was obtained, showing that the carbonyl group plays a major role in the rate and enantioselectivity exhibited by the lipase.

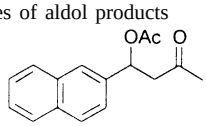
Table 2
Enzymatic hydrolysis[a] of racemic acetates of aldol products



1a



9a



13a

| Entry | Compound | Reaction time | Conversion ($c$, %) | Alcohol | | Acetate | | $E$ |
|---|---|---|---|---|---|---|---|---|
| | | | | ee (%) | Yield (%) | ee (%) | Yield (%) | |
| 1 | **1a** | 19 | 32 | 93 | 30 | 43 | 46 | 34 |
| 2 | **1a** | 29 | 60 | 64 | 45 | >96 | 27 | 17 |
| 3 | **9a** | 26 | 57 | 72 | 52 | >96 | 29 | 24 |
| 4 | **13a** | 24 | 55 | 79 | 42 | >96 | 31 | 34 |

[a] Reaction conditions: CCL, 0.1 M phosphate buffer, pH 7.0, room temperature.

In view of the well-known ability of lipases for ester hydrolysis, the enzymatic hydrolysis of the racemic acetates of aldols was carried out. The racemic acetates were prepared from the corresponding aldols using $Ac_2O$, $Et_3N$ and DMAP (Scheme 1). Enzymatic hydrolysis of the acetates was carried out in 0.1 M phosphate buffer. The hydrolysis was found to be faster compared to transesterification, but the selectivity was found to be low. The results are summarized in Table 2.

The stereochemistry of the products was also ascertained by synthesizing 4-(*R*)-acetoxy-4-phenyl-2-butanone and comparing the optical rotation values [14]. In the case of **16**, the recovered alcohol was hydrogenated using 10% palladium on charcoal under hydrogen atmosphere and the optical rotation values compared with literature data [21]. In the transesterification reaction and in hydrolysis *R*-acetates and *R*-alcohols, respectively, were obtained as products.

In conclusion, optically active aryl β-hydroxy ketones of complementary stereochemistry can be obtained by using both enzymatic methods—transesterification and hydrolysis. We have also observed that when there is an unsaturation near the chiral center, the aldols were resolved with high selectivity. We have carried out an in depth study pertaining to the effect of structure of the substrate on the enantioselectivity of the reaction.

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