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# Lipase-catalyzed remote kinetic resolution of arylic nitriles with adjacent quaternary chiral center and the determination of their absolute configuration

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**Abstract**

Enzymatic resolution of tertiary arylic nitrile alcohols (**1**–**8**) by lipases from *Pseudomonas cepacia* (PCL), *Pseudomonas flurescens* (LAK, made by Amano Enzyme Co. Ltd.), *Pseudomonas fluorescens* (PFL) and *Candida rugosa* (CRL) were described, and the absolute configuration of the resolved chiral alcohols (**1**–**8**) were determined by chemical transformations to the compounds with known configuration.


*Keywords:* Lipase; Arylic nitrile; Resolution; Biocatalyst

## 1. Introduction

Arylic nitriles [1] are very valuable intermediates for the organic synthesis as building blocks in biologically active substances [2–5] and pharmaceuticals [6,7] containing quaternary center. One of the chirotechnology for the construction of these quaternary chiral centers is chemo-enzymatic synthesis [8]. Both whole-cell catalytic systems and isolated enzymes from those cell are widely used as biocatalyst in construction of chirality. Among them, a pioneering work in Eisai Co. disclosed a lipase-catalyzed kinetic resolution of 4-cyano-4-phenyl-5-methyl-1-hexanol [9]. Surprisingly, the recognition of remote quaternary chiral center is accomplished.

In this study, to investigate regio- and stereoselectivities of various lipases from *Pseudomonas* sp. (PCL, PFL and LAK) and *Candida rugosa* (CRL) toward these structurally similar primary alcohols (**1**–**8**), enzymatic stereoselective transesterification of racemic primary alcohols (**1**–**8**) using vinyl acetate as an acyl donor and hydrolysis of their acetate esters were attempted.

Chemical modification of the enantiopure primary alcohols (**1**–**8**) would give biologically active compounds containing quaternary chiral center as shown in Fig. 1 and be used as precursor of bicyclic amidines [2], lactones [3], primary amines [4], aldehydes [5], amides [10], carboxylic acid [11], pyridine [12] and various intermediates.

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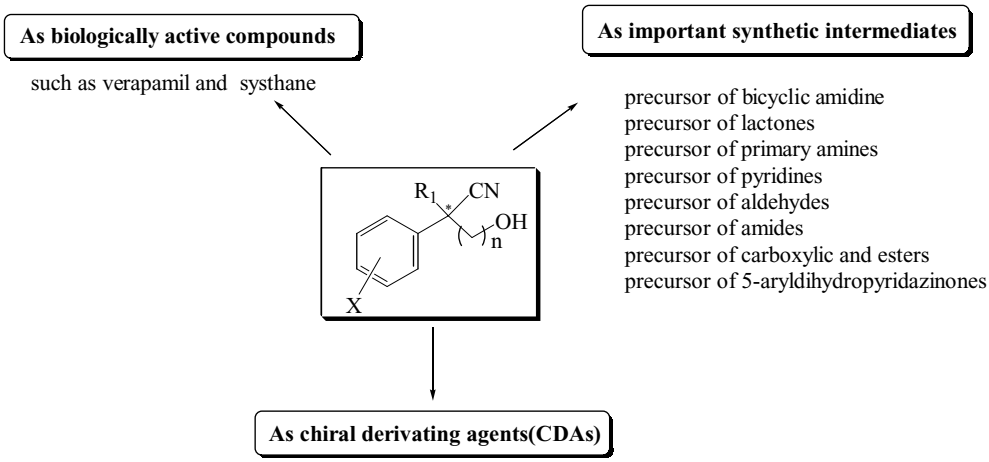



Fig. 1. Possible application of tertiary arylic alcohol.

## 2. Experimental

### 2.1. General

$^{1}$H NMR (300 MHz) and $^{13}$C NMR spectra (75 MHz) were recorded on a Varian Gemini 300 MHz spectrometer with TMS as an internal reference. pH-Stat (Metrohm 718 Stat, Tritino Ltd.) was used for lipase-catalyzed hydrolysis and optical rotation was measured on Autopol® III polarimeter (Rudolph Research Co.). Low EI resolution mass spectra were determined on HP GC 5972 (column: HP-5 cross-linked 5% phenyl methyl silicone, column ID 0.20 mm, film thickness: 0.11 μm, length: 25 m, detector: mass selective detector, 280 °C, injector 280 °C, program: initial temperature 70 °C (2 min), 20 °C/min, final temperature 300 °C) and HP MS 5988A system at 70 eV. Analytical HPLC works with chiral stationary phase were carried out on Varian 9010 solvent delivery system, Varian 9050 variable wavelength UV-Vis detector, and Varian 4400 integrator using a chiral column such as Chiralcel OD, Chiralcel OJ, Chiralpak AD and OB (250 mm × 4.6 mm, Daicel) for the substrate alcohols (**1**–**8**).

### 2.2. Materials

Column chromatography was performed on Merck silica gel 60 (230–400 mesh). TLC was carried out using glass sheets precoated with silica gel 60 $F_{254}$ prepared by E. Merck. All the commercially available reagents were obtained from Aldrich, Fluka and Tokyo Kasei Chemical and generally used without further purification. Solvents were distilled over appropriate drying materials before use. PCL (lipase from *Pseudomonas cepacia* lipase, 30,000 unit/g) and lipase AK (*Pseudomonas fluorescens* lipase, >20,000 unit/g) were obtained from Amano enzyme co. Ltd. CRL (*Candida rugosa* lipase, 860 unit/mg) and PFL (*Pseudomonas fluorescens* lipase, 42.5 u/mg) were obtained from Sigma and Aldrich, respectively.

### 2.3. Syntheses of substrates

#### 2.3.1. Syntheses of (±)-2-cyano-2-phenyl-1-propanol (*1*) [13]

To a stirred suspension of 60% sodium hydride (1.4 g, 35.1 mmol) in dry DMF (60 ml) was added dropwise 2-phenylpropionitrile (3.84 g, 29.2 mmol) for 30 min at 0 °C. After the mixture was stirred for 30 min, paraformaldehyde (1.1 g, 35.1 mmol) was added and the mixtures further stirred at 15 °C for 12 h. The reaction medium was quenched with cold ice water (50 ml) and extracted with diethyl ether (100 ml). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated to furnish the cyanide **1**. Compound **1** was purified by column

chromatography (*n*-hexane/ethyl acetate = 4/1 (v/v)).

Yield (3.6 g) 77%; GC/MSD retention time (min) 7.63, *m*/*z* 51, 55, 63, 77, 89, 104, 116, 131 (100), 140, 145, 161 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.75 (s, 3H), 2.59 (s, 1H), 3.77–3.90 (m, 2H), 7.35–7.50 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.9, 45.4, 70.2, 123.0, 126.4, 128.7, 129.5, 137.5; GC analysis (CP-Chirasil-DexCB column, 120 °C isothermal), retention time (min) 30.88 (*S*) and 32.53 (*R*).

### 2.3.2. Syntheses of (±)-2-(4-chlorophenyl)-2-cyano-2-phenyl-1-hexanol (**3**) and its ester (**3b**)

*2.3.2.1. (±)-2-(4-Chlorophenyl)hexanenitrile.* To a stirred suspension of 60% sodium hydride (2.2 g, 55.0 mmol) in dry DMF (80 ml) was added dropwise 4-chlorobenzyl cyanide (7.8 g, 50.0 mmol) for 30 min at 0 °C. After the mixture was stirred for 30 min, 1-bromobutane (6.4 g, 47.0 mmol) was added and the mixtures further stirred for 12 h at 15 °C. The reaction medium was quenched with cold ice water (50 ml) and extracted with diethyl ether (2 × 100 ml). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated to furnish the cyanide. The cyanide was purified by column chromatography (*n*-hexane/ethyl acetate = 10/1 (v/v)).

Yield (8.5 g) 82%; $R_f$ 0.59 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 8.82, *m*/*z* 51, 63, 75, 89, 101, 115, 137, 164, 192, 207 (100), 237 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (t, $J$ = 8.4 Hz, 3H), 1.31–1.49 (m, 4H), 1.84–1.91 (m, 2H), 3.75 (t, $J$ = 8.8 Hz, 2H), 7.24–7.37 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.7, 22.0, 28.9, 35.4, 36.7, 120.4, 128.5, 129.2, 133.9, 134.5.

*2.3.2.2. (±)-2-Cyano-2-(4-chlorophenyl)-1-hexanol (**3**).* Compound **3** was synthesized by the same method as compound **1**, and (±)-2-(4-chlorophenyl)-hexanenitrile (8.5 g, 40.9 mmol) and paraformaldehyde (2.2 g, 54.0 mmol) were used for reaction.

Yield (8.9) 92%; $R_f$ 0.56 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 10.00, *m*/*z* 51, 63, 75, 89, 101, 115, 137, 164, 192, 207 (100), 237 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (t, $J$ = 8.5 Hz, 3H), 1.07–1.22 (m, 1H), 1.08–1.54 (m, 3H) 1.84–1.91 (m, 1H), 2.02–2.14 (m, 1H), 2.07 (s, 1H), 3.81 (s, 2H), 7.38 (s, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 22.9, 27.4, 35.6, 51.1, 69.6, 121.6, 128.2, 129.6, 134.6, 134.9; GC analysis (CP-Chirasil-DexCB column, initial temperature 140 °C (20 min), 2 °C/min, final temperature 190 °C (10 min), retention time (min)) 47.51 (*R*) and 48.46 (*S*); HPLC analysis (Chiralcel OD column, *n*-hexane/IPA, 93/7 (v/v)), retention time (min) 15.00 (*S*) and 16.10 (*R*).

*2.3.2.3. (±)-2-(4-Chlorophenyl)-2-cyanohexyl acetate (**3b**).* To a solution of (±)-**3** (2.4 g, 10.0 mmol) was added 4-(dimethylamino)pyridine (10 mg), $Et_3N$ (4.2 ml, 30.0 mmol) and acetic anhydride (1.8 ml, 20.0 mmol) in $CH_2Cl_2$ (80 ml). The mixture was stirred at 25 °C for 5 h. The reaction mixture was neutralized with 2% aqueous HCl solution and extracted with $CH_2Cl_2$ (100 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated to afford (±)-**3b**. Compound (±)-**3b** was purified by column chromatography (*n*-hexane/ethyl acetate, 10/1 (v/v)).

Yield (2.65 g) 95%; $R_f$ 0.37 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 10.23, *m*/*z* 51, 73, 101, 115, 137, 150, 164, 180, 207 (100), 249, 279 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (t, $J$ = 7.2 Hz, 3H), 1.13–1.45 (m, 4H), 1.82–2.09 (m, 2H), 2.03 (s, 3H), 4.38 (s, 2H), 7.38 (s, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0, 20.9, 22.8, 27.2, 36.5, 48.0, 68.7, 120.6, 128.0, 129.6, 134.4, 134.8, 170.5; HPLC analysis (Chiralcel OD column, *n*-hexane/IPA, 93/7 (v/v)), retention time (min) 15.65 (*R*) and 16.26 (*S*).

### 2.3.3. Syntheses of (±)-2-cyano-2-(3,4-dimethoxyphenyl)-3-methyl-1-butanol (**4**) and its ester (**4b**)

*2.3.3.1. (±)-2-(3,4-Dimethoxyphenyl)-3-methylbutyronitrile.* (±)-2-(3,4-Dimethoxyphenyl)-3-methylbutyronitrile was synthesized by the same method as (±)-2-(4-chlorophenyl)hexanenitrile, and (3,4-dimethoxyphenyl)acetonitrile (9.16 g, 51.7 mmol) and 2-bromopropane (5.78 g, 47.0 mmol) were used for reaction.

Yield (7.1 g) 69%; $R_f$ 0.59 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 9.12, *m*/*z* 51, 63,

90, 103, 115, 131, 146, 162, 176 (100), 188, 203, 219 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.04 (d, $J$ = 6.7 Hz, 6H), 2.07–2.14 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 6.79–6.84 (m, 3H).

*2.3.3.2. (±)-2-Cyano-2-(3,4-dimethoxyphenyl)-3-methyl-1-butanol (**4**).* Compound **4** was synthesized by the same method as compound **1**, and (±)-2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile (2.2 g, 10.0 mmol) and paraformaldehyde (0.5 g, 1.6 eq.) were used for reaction.

Yield (2.3 g) 93%; $R_f$ 0.42 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 10.63, *m*/*z* 51, 65, 77, 91, 103, 123, 138, 151, 160, 179, 189, 206, 218 (100), 232, 249 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.79 (d, $J$ = 6.7 Hz, 3H), 1.14 (d, $J$ = 6.7 Hz, 3H), 2.15–2.24 (m, 1H), 2.37 (s, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.95 (dd, $J$ = 11.1, 41.1Hz, 2H), 6.82–6.97 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.8, 19.1, 34.1, 56.23, 56.27, 56.3, 67.4, 110.3, 111.6, 119.4, 120.9, 128.8, 149.0, 149.4; HPLC analysis (Chiralpak AD column, *n*-hexane/IPA, 9/1 (v/v)), retention time (min) 21.98 (*R*) and 23.60 (*S*).

*2.3.3.3. (±)-2-Cyano-2-(3,4-dimethoxyphenyl)-3-methylbutyl acetate (**4b**).* Compound **4b** was synthesized by the same method as compound **3b**.Yield (2.65 g) 91%; $R_f$ 0.35 (*n*-hexane/EtOAc, 4/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.78 (d, $J$ = 6.7 Hz, 3H), 1.12 (d, $J$ = 6.7 Hz, 3H), 1.88 (s, 3H), 2.15–2.24 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 4.44 (dd, $J$ = 11.1, 29.9 Hz, 2H), 6.78–6.92 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.91, 18.93, 35.1, 53.2, 56.1, 56.3, 67.2, 110.0, 111.3, 119.3, 120.0, 128.3, 149.0, 149.2, 170.5; HPLC analysis (Chiralpak AD column, *n*-hexane/IPA, 9/1 (v/v)), retention time (min) 11.95 (*R*) and 13.32 (*S*).

*2.3.4. Synthesis of (±)-3-cyano-3-phenyl-1-heptanol (**5**)*

*2.3.4.1. (±)-2-Phenyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]hexanenitrile.* (±)-2-Phenyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]hexanenitrile was synthesized by the same method as (±)-2-(4-chlorophenyl)-hexanenitrile [12], and (±)-2-phenylhexanenitrile (1.6 g, 9.6 mmol) and tetrahydropyranyloxyethyl bromide (2.0 g, 9.6 mmol) were used for reaction.

Yield (2.43 g) 84%; $R_f$ 0.34 (*n*-hexane/EtOAc, 4/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.85 (t, $J$ = 7.2 Hz, 3H), 1.01–1.12 (m, 1H), 1.20–1.36 (m, 2H), 1.43–1.65 (m, 6H), 1.68–1.79 (m, 1H), 1.81–1.92 (m, 1H), 1.95–2.07 (m, 1H), 2.13–2.23 (m, 1H), 2.30–2.39 (m, 1H), 3.22–3.43 (m, 2H), 3.56–3.83 (m, 2H), 4.45 (m, 2H), 7.35 (s, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 19.7, 22.8, 25.7, 27.5, 30.8, 40.6, 41.6, 46.0, 62.6, 64.2, 99.5, 122.1, 126.67, 127.4, 129.0, 137.4.

*2.3.4.2. (±)-3-Cyano-3-phenyl-1-heptanol (**5**).* To a solution of (±)-2-phenyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]hexanenitrile (2.43 g, 8.1 mmol) in methanol (20 ml) was added 1N-methanolic HCl (5 ml), and stirred for 10 h at 25 °C. The reaction mixture was neutralized with cold saturated $NaHCO_3$ solution and extracted with diethyl ether (70 ml) to afford chromatographically pure **5**.

Yield (1.73 g) 83%; $R_f$ 0.34 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 9.42, *m*/*z* 51, 57, 77, 91, 103, 116, 130, 143 (100), 161, 173, 186, 199, 217 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.85 (t, $J$ = 7.2 Hz, 3H), 1.09–1.18 (m, 1H), 1.24–1.32 (m, 2H), 1.33–1.43 (m, 1H), 1.80–2.13 (m, 2H), 2.19–2.35 (m, 2H), 3.52–3.73 (m, 2H), 7.29–7.66 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 23.2, 27.5, 39.3, 43.4, 59.6, 65.5, 122.7, 126.7, 127.7, 129.4, 138.4; HPLC analysis (Chiralpak AD column, *n*-hexane/IPA, 96/4 (v/v)), retention time (min) 21.60 (*S*) and 23.09 (*R*).

*2.3.5. Synthesis of (±)-3-(4-chlorophenyl)-3-cyano-1-heptanol (**6**)*

*2.3.5.1. (±)-2-(4-Chlorophenyl)-2-[2-(tetrahydropyran-2-yloxy)ethyl]hexanenitrile.* (±)-2-(4-Chlorophenyl)-2-[2-(tetrahydropyran-2-yloxy)ethyl]hexanenitrile was synthesized by the same method as (±)-2-(4-chlorophenyl)hexanenitrile, and (±)-2-(4-chlorophenyl)hexanenitrile (3.12 g, 15.0 mmol) and tetrahydropyranyloxyethyl bromide (3.14 g, 15.0 mmol) were used for reaction.

Yield (4.65 g) 92%; $R_f$ 0.37 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 12.35, *m*/*z* 55, 67, 76, 85 (100), 101, 115, 125, 142, 151, 164, 177, 195, 206, 223, 235, 251, 262, 279, 292, 306, 335 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.84 (t, $J$ =

7.2 Hz, 3H), 1.02–1.13 (m, 1H), 1.20–1.36 (m, 2H), 1.43–1.65 (m, 6H), 1.68–1.79 (m, 1H), 1.81–1.92 (m, 1H), 1.95–2.07 (m, 1H), 2.13–2.23 (m, 1H), 2.30–2.39 (m, 1H), 3.22–3.43 (m, 2H), 3.56–3.83 (m, 2H), 4.45 (q, $J = 3.3$ Hz, 2H), 7.35 (s, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 19.7, 22.8, 25.7, 27.5, 30.8, 40.6, 41.6, 46.0, 62.6, 64.2, 99.5, 122.1, 127.7, 129.4, 134.0, 137.3.

*2.3.5.2. (±)-3-(4-Chlorophenyl)-3-cyano-1-heptanol (**6**).* Compound **6** was synthesized by the same method as compound **5**.

Yield (3.0 g) 95%; mp 40–42 °C; $R_f$ 0.15 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 10.15, *m/z* 51, 60, 73, 89, 101, 115, 125, 137, 144, 151, 159, 166, 177, 186, 195 (100), 208, 222, 251 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.85 (t, $J = 7.2$ Hz, 3H), 0.97–1.11 (m, 1H), 1.20–1.42 (m, 3H), 1.74 (s, 1H), 1.80–1.90 (m, 1H), 1.91–2.03 (m, 1H), 2.05–2.20 (m, 1H), 2.22–2.36 (m, 1H), 3.48–3.59 (m, 1H), 3.63–3.76 (m, 1H), 7.35 (s, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 22.8, 27.4, 41.5, 43.3, 45.8, 59.5, 122.3, 127.6, 129.6, 134.2, 136.9; HPLC analysis (Chiralcel OJ column, *n*-hexane/IPA, 95/5 (v/v)), retention time (min) 36.38 (*S*) and 38.67 (*R*).

*2.3.6. Synthesis of (±)-3-cyano-3-(3,4-dimethoxyphenyl)-4-methyl-1-pentanol (**7**)*

Compound 7 was synthesized by the same method as (±)-2-(4-chlorophenyl)hexanenitrile, and (±)-2-(3,4-dimethoxyphenyl)-3-methyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]butyronitrile (1.2 g, 3.46 mmol) was used for reaction.

Yield (1.67 g) 90%; $R_f$ 0.15 (*n*-hexane/EtOAc, 4:1 (v/v)); GC/MSD retention time (min) 10.91, *m/z* 51, 65, 77, 91, 119, 132, 163, 175, 190 (100), 203, 220, 232, 248, 263 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.76 (d, $J = 6.7$ Hz, 3H), 1.18 (d, $J = 6.7$ Hz, 3H), 1.92 (s, 1H), 2.04–2.13 (m, 2H), 2.33–2.47 (m, 1H), 3.32–3.43 (m, 1H), 3.58–3.69 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 6.82–6.95 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.8, 18.9, 38.5, 40.5, 51.1, 56.2, 56.3, 60.1, 109.4, 111.4, 118.9, 121.5, 130.2, 148.7, 149.4; HPLC analysis (Chiralpak AD column, *n*-hexane/IPA, 9/1 (v/v)), retention time (min) 21.98 (*S*) and 25.50 (*R*).

*2.3.7. Synthesis of (±)-4-cyano-4-phenyl-1-pentanol (**8**)*

*2.3.7.1. (±)-2-Methyl-2-phenyl-5-(tetrahydropyran-2-yloxy)pentanenitrile.* (±)-2-Methyl-2-phenyl-5-(tetrahydropyran-2-yloxy)pentanenitrile was synthesized by the same method as (±)-2-(4-chlorophenyl)-hexanenitrile, and (±)-2-phenylpropionitrile (1.23 g, 9.38 mmol) and tetrahydropyranyloxypropyl bromide (2.1 g, 9.39 mmol) were used for reaction.

Yield (2.5 g) 95%; $R_f$ 0.44 (*n*-hexane/EtOAc, 4/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.42–1.45 (m, 5H), 1.68 (m, 3H), 1.64–1.77 (m, 3H), 1.97–2.02 (m, 2H), 3.32–3.44 (m, 2H), 3.65–3.78 (m, 2H), 4.46–4.50 (m, 1H), 7.27–7.44 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 19.6, 25.3, 25.8, 27.7, 28.1, 38.8, 42.3, 62.4, 66.6, 98.5, 122.8, 125.4, 127.7, 128.9, 140.

*2.3.7.2. (±)-4-Cyano-4-phenyl-1-pentanol (**8**).* Compound **8** was synthesized by the same method as compound **5**.

Yield (1.3 g) 80%; $R_f$ 0.30 (*n*-hexane/EtOAc, 4/1 (v/v)); GC/MSD retention time (min) 8.55, *m/z* 51, 77, 104, 131 (100), 156, 189 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.46–1.50 (m, 1H), 1.65–1.71 (m, 1H), 1.68 (s, 3H), 1.98–2.02 (m, 2H), 2.18 (s, 1H), 3.56 (t, $J = 6.21$ Hz, 2H), 7.29–7.44 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.9, 28.8, 38.4, 42.3, 51.8, 123.4, 125.4, 127.8, 128.9, 140.0; HPLC analysis (Chiralcel OD column, *n*-hexane/IPA, 9/1 (v/v)), retention time (min) 16.30 (*S*) and 19.34 (*R*).

*2.4. General procedure for the enzymatic kinetic transesterification of primary alcohols (**1**–**8**) using several lipases [6a,4]*

To a stirred solution of the primary racemic alcohols (**1**–**8**) (1.0 mmol) in anhydrous *n*-hexane (10 ml) or appropriate solvent was added any lipase in PCL (half mass), PFL (10% mass), LAK (half mass), and CRL (equivalent mass) and vinyl acetate (89 mg, 1.0 mmol) as an acyl donor at 32–34 °C and the progress of the reaction was monitored by chiral column of HPLC. The reaction mixture was diluted with diethyl ether and the enzyme was removed by filtration and the organic solvent was evaporated under reduced pressure. The reaction residue was

chromatographed on silica-gel column with the mixed solvent of *n*-hexane and ethyl acetate to give the reacted acetate of each alcohol and its unreacted alcohol. The isolated acetate was hydrolyzed with 1.2N methanolic KOH solution to afford the corresponding alcohol.

### 2.5. General procedure for the enzyme-catalyzed hydrolysis of primary alcohols (**1**–**8**) using several lipases

To a pH-Stat-attached reactor was added acetate ester (0.5 mmol) and phosphate buffer solution (8 ml). After any lipase (0.2–1.0 mass equivalent) in PCL, PFL, LAK and CRL was added to the reaction mixture, pH was adjusted to 7 by pH-Stat automatically and the reaction mixture was stirred for suitable period. Then, the reaction mixture was diluted with diethyl ether and the enzyme was removed by filtration and the organic solvent was evaporated under reduced pressure. The reaction residue was chromatographed on silica-gel column with the mixed solvent of *n*-hexane and ethyl acetate to give the reacted hydrolyzed alcohol and its unreacted ester. The isolated acetate was hydrolyzed with 1.2N methanolic KOH solution to afford the corresponding alcohol.

### 2.6. Syntheses of compounds for the determination of absolute configuration of chiral alcohols (**1**–**8**)

#### 2.6.1. Syntheses of compounds for the determination of absolute configuration of the resolved alcohol **1**

*2.6.1.1. (2S)-2-Methyl-2-phenyl-3-(tetrahydro-pyran-2-yloxy)propionitrile (**9**).* To stirred solution of the resolved alcohol (−)-**1** (0.1 g, 0.62 mmol, 100% e.e.) in methylene chloride (5 ml) was added pyridinium *p*-toluenesulfonate (10 mg) and stirred for 3 h. After the completion of reaction, to the reaction mixture was added water (30 ml) and methylene chloride (30 ml). The organic layer was separated, dried over anhydrous $MgSO_4$ and distilled. Chromatography of the crude mixture, eluting with the mixed solvent (*n*-hexane/EtOAc, 20/1 (v/v)) gave the pure (*S*)-**9**.

Yield (0.13 g) 82%; $R_f$ 0.44 (*n*-hexane/EtOAc, 3/1 (v/v)); GC/MSD retention time (min) 10.25, *m*/*z* 57, 67, 77, 85 (100), 91, 103, 116, 131, 144, 158, 167, 175, 186, 200, 215, 245 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.53–1.75 (m, 4H), 1.78 (s, 3H), 3.52–3.66 (m, 2H), 4.00–4.13 (m, 2H), 4.69–4.80 (m, 1H), 4.81 (s, 2H), 7.33–7.50 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.2, 25.7, 31.3, 43.4, 61.7, 63.7, 73.6, 98.9, 123.8, 126.4, 128.4, 129.1, 138.3.

*2.6.1.2. (2R)-(+)-α-methyltropic acid (**10**).* To a solution of (*S*)-**9** (0.1 g, 0.41 mmol) in ethanol (2 ml) was added 48% NaOH aqueous solution (0.2 ml) and 30% $H_2O_2$ (0.2 ml) and refluxed for 10 h. The reaction mixture was acidified by concentrated HCl (0.5 ml) and extracted by chloroform (10 ml), washed by brine, dried over $MgSO_4$ and distilled. The crude mixture product was purified by column chromatography (*n*-hexane/EtOAc, 1/2 (v/v)) to give the white solid **10**.

Yield (55 mg) 74%; mp 74–77 °C [literature [15] (*R*)-(+)-**10**: 77–79 °C], (*R*)-(+)-**10** (>99% e.e.) $[\alpha]_D^{24}$ + 21.29 (*c* 0.70, $CHCl_3$) literature [15b] $[\alpha]_D^{25}$ + 23.70 (*c* 2.00, $CHCl_3$).

#### 2.6.2. Syntheses of compounds for the determination of absolute configuration of the resolved alcohol **4**

*2.6.2.1. (S)-2-(3,4-dimethoxyphenyl)-2-formyl-3-methylbutyronitrile [(S)-**11**].* To a solution of (+)-**4** (0.15 g, 0.6 mmol) in methylene chloride (10 ml) was added PCC (0.16 g, 0.72 mmol) and stirred at rt for 5 h. The reaction mixture was concentrated and chromatography (*n*-hexane/EtOAc, 4/1 (v/v)) of the residue gave the pure (*S*)-**11**.

Yield (0.13 g) 88%; $R_f$ 0.30 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 9.61, (*m*/*e*) 51, 63, 77, 91, 103, 116, 123, 130, 146, 154, 162, 176, 190, 205, 218 (100), 232, 247 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.82 (d, $J$ = 6.7 Hz, 3H, CH3), 1.17 (d, $J$ = 6.7 Hz, 3H), 2.24–2.36 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 6.81–7.04 (m, 3H), 8.03 (s, 1H).

*2.6.2.2. trans-(S)-(−)-4-cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-2-enoic acid methyl ester [(S)-(−)-**12**].* To a solution of (*S*)-**11** (0.13 g, 0.53 mmol) in methylene chloride (10 ml) was added methyl (triphenylphosphoranylidene)acetate (0.18 g, 0.53 mmol) and stirred at rt for 2 h. The mixture was concentrated and chromatography (*n*-hexane/EtOAc, 10:1 (v/v)) of the residue gave the pure (*S*)-**12**.

Yield (0.14 g) 89%; $R_f$ 0.47 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 11.93, (*m*/*e*) 51, 59, 77, 89, 103, 115, 128, 140, 148, 158, 175, 186, 200, 215, 229, 246, 261 (100), 272, 288, 303 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.91 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H), 2.31–2.40 (m, 1H), 3.75 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 6.30 (d, $J = 15.5$ Hz, 1H), 6.94 (d, $J = 14.8$ Hz, 1H), 6.86–7.02 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.5, 18.9, 37.3, 52.3, 56.2, 56.3, 56.4, 109.5, 111.8, 118.7, 122.2, 129.7, 146.1, 149.3, 149.7, 166.5; (*S*)-(−)-**12** (90% e.e.) $[\alpha]_D^{24}$ − 19.29 (*c* 0.70, MeOH).

*2.6.2.3. (R)-(+)-4-cyano-4-(3,4-dimethoxyphenyl)-5-methylhexanoic acid methyl ester [(R)-(+)-**13**].* To a solution of (*S*)-**12** (0.14 g, 0.48 mmol) in methanol (5 ml) was added 10% Pd/C (10 mg) and charged with hydrogen by hydrogen-contained balloon. After 1 h, the reaction mixture was filtered by Celite 545 and the filtrate was concentrated. The crude mixture was purified by column chromatography (*n*-hexane/EtOAc, 10/1 (v/v)) to give (*R*)-**13**.

Yield (0.14 g) 95%; $R_f$ 0.45 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 11.64, (*m*/*e*) 51, 59, 77, 91, 103, 116, 128, 138, 146, 156, 171,189, 202 (100), 218, 230, 247, 262, 274, 290, 305 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.80 (d, $J = 6.7$ Hz, 3H), 1.22 (d, $J = 6.7$ Hz, 3H), 1.95–2.10 (m, 1H), 2.11–2.21 (m, 2H), 2.48–2.57 (m, 2H), 3.60 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.83–6.94 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.9, 19.4, 30.8, 33.2, 38.3, 52.1, 53.1, 56.2, 56.3, 109.6, 111.5, 119.1, 129.9, 148.8, 149.5, 173.4; (*R*)-(+)-**13** (90% e.e.) $[\alpha]_D^{24}$ + 23.5 (*c* 0.17, MeOH).

*2.6.2.4. (R)-(+)-4-cyano-5-methyl-4-(3,4-dimethoxyphenyl)-1-hexanol (**14**) [6a].* To a solution of (*R*)-**13** (0.14 g, 0.45 mmol) in methanol (5 ml) was added $NaBH_4$ (0.17 g, 4.5 mmol) and refluxed for 5 h. The reaction mixture was quenched by 1N aqueous HCl solution in ice bath and extracted by diethyl ether (2 × 10 ml). The residue resulted from the concentrating organic layer was purified by column chromatography (*n*-hexane/EtOAc, 4/1 (v/v)) to give (*R*)-**14**.

Yield (0.1 g) 80%; $R_f$ 0.20 (*n*-hexane/EtOAc, 2/1 (v/v)); (*R*)-(+)-**14** (>99% e.e.) $[\alpha]_D^{30}$ + 16.92 (*c* 1.77, $CHCl_3$), literature [16] $[\alpha]_D^{22}$ + 12.7 (*c* 3.23, $CHCl_3$).

*2.6.3. Syntheses of compounds for the determination of absolute configuration of the resolved alcohol **5***

*2.6.3.1. (S)-2-formyl-2-phenylhexanenitrile [(S)-**15**].* Compound (*S*)-**15** was synthesized by the same method as compound (*S*)-**11**, and (*S*)-**2** (0.47 g, 2.32 mmol) and PCC (0.6 g, 2.78 mmol) were used for reaction.

Yield (0.4 g) 86%; $R_f$ 0.52 (*n*-hexane/EA, 4/1 (v/v)); GC/MSD retention time (min) 7.69, (*m*/*e*) 51, 63, 77, 89, 103 (100), 117, 130, 145, 158, 173, 201 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J = 7.3$ Hz, 3H), 1.18–1.45 (m, 4H), 1.87–2.11 (m, 2H), 7.35–7.47 (m, 5H), 8.03 (s, 1H).

*2.6.3.2. cis- and trans-(S)-2-butyl-4-methoxy-2-phenylbut-3-enenitrile [(S)-**16**].* To a solution of (methoxymethyl)triphenylphosphonium chloride (0.48 g, 1.39 mmol) in THF (5 ml) was added dropwise *n*-butyllithium (0.87 ml, 1.39 mmol, 1.6 M in *n*-hexane) at −78 °C and stirred for 10 min. An aldehyde (*S*)-**15** (0.3 g, 1.39 mmol) was added to reaction mixture dropwise at −78 °C at 30 min and the mixture was stirred for 10 h at rt. After the reaction mixture was quenched by ice water (5 ml) and extracted by diethyl ether (20 ml), the organic layer was concentrated and purified by column chromatography (*n*-hexane/EtOAc, 10/1 (v/v)) to give (*S*)-**16**.

Yield (0.26 g) 82%; *trans*-(*S*)-**16**: $R_f$ 0.32 (*n*-hexane/EtOAc, 10/1 (v/v)); GC/MSD retention time (min) 9.11, (*m*/*e*) 51, 63, 77, 91, 103, 115, 128, 134, 140, 156, 172 (100), 186, 197, 203, 214, 223, 229 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (t, $J = 6.7$ Hz, 3H), 1.22–1.39 (m, 4H), 1.95–2.10 (m, 2H), 3.59 (s, 3H), 4.96 (d, $J = 12.7$ Hz, 1H), 6.64 (d, $J = 12.7$ Hz, 1H), 7.31–7.48 (m, 5H). *cis*-(*S*)-**16**: $R_f$ 0.23 (*n*-hexane/EtOAc, 10/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J = 7.0$ Hz, 3H), 1.24–1.45 (m, 4H), 1.85–1.97 (m, 1H), 2.07–2.18 (m, 1H), 3.61 (s, 3H), 4.59 (d, $J = 6.3$ Hz, 1H), 6.07 (d, $J = 6.3$ Hz, 1H), 7.27–7.50 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 22.9, 27.7, 27.8, 42.5, 57.1, 106.2, 108.1, 126.3, 127.6, 128.8, 129.2, 150.2.

*2.6.3.3. (S)-2-(2-methoxyethyl)-2-phenylhexanenitrile [(S)-**17**].* Compound **17** was synthesized by the same method as compound (*R*)-**13**, and (*S*)-**16** (0.12 g, 0.50 mmol) and 10% Pd/C (10 mg) were used for reaction.

Yield (0.12 g) 95%; $R_f$ 0.17 (*n*-hexane/EtOAc, 10/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.83 (t, $J$ = 7.3 Hz, 3H), 1.03–1.17 (m, 1H), 1.23–1.35 (m, 1H), 1.37–1.50 (m, 1H), 1.85–2.08 (m, 2H), 2.12–2.22 (m, 1H), 2.27–2.38 (m, 1H), 3.16–3.26 (m, 1H), 3.21 (s, 3H), 3.41–3.49 (m, 1H), 7.27–7.43 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 22.9, 22.6, 27.3, 27.8, 42.5, 55.4, 57.1, 121.3, 127.6, 128.8, 129.2, 139.2; HPLC analysis (Chiralcel OJ, *n*-hexane/IPA, 97/3 (v/v)), retention time (min), 7.76 (*S*) and 8.98 (*R*); (*S*)-(−)-**17** (64% e.e.) $[\alpha]_D^{30}$ − 13.75 (*c* 0.24, $CHCl_3$).

*2.6.4. Syntheses of compounds for the determination of absolute configuration of resolved alcohol **6***

*(S)-2-(4-Chlorophenyl)-2-formylhexanenitrile [(S)-**18**]*

Compound **18** was synthesized by the same method as compound (*S*)-**11**, and (*S*)-**3** (0.15 g, 0.63 mmol, 95% e.e.) and PCC (0.27 g, 1.27 mmol) were used for reaction.

Yield (0.13 g) 87%; $R_f$ 0.26 (*n*-hexane/EtOAc, 4/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (t, $J$ = 7.3 Hz, 3H), 1.17–1.46 (m, 4H), 1.98–2.15 (m, 1H), 2.17–2.30 (m, 1H), 7.35–7.47 (m, 5H), 9.42 (s, 1H).

*2.6.4.1. (S)-2-(4-chlorophenyl)-2-(2-methoxyethyl)-hexanenitrile [(S)-**20**].* Compound **20** was synthesized by the same method as compound (*R*)-**13**, and (*S*)-**19** (0.13 g, 0.47 mmol) and Pd/C (10 mg) were used for reaction.

Yield (0.12 g) 96%; $R_f$ 0.58 (*n*-hexane/EtOAc, 4/1 (v/v)). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.83 (t, $J$ = 7.4 Hz, 3H), 0.97–1.12 (m, 1H), 1.20–1.37 (m, 2H), 1.38–1.50 (m, 1H), 1.80–1.93 (m, 1H), 1.95–2.17 (m, 2H), 2.27–2.38 (m, 1H), 3.16–3.30 (m, 1H), 3.21 (s, 3H), 3.38–3.50 (m, 1H), 7.37 (s, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.6, 23.0, 23.6, 27.3, 27.8, 42.5, 55.5, 57.3, 120.8, 127.7, 128.8, 129.5, 141.2; HPLC analysis (Chiralcel OD, *n*-hexane/IPA, 96/4 (v/v), flow rate 0.5 ml/min), retention time (min), 15.14 (*S*) and 13.61 (*R*).

*2.6.5. Syntheses of compounds for the determination of absolute configuration of the resolved alcohol **7***

*2.6.5.1. cis- and trans-(S)-2-(3,4-dimethoxyphenyl)-2-isopropyl-4-methoxybut-3-enenitrile [cis- and trans (S)-**21**].* Compound (*S*)-**21** was synthesized by the same method as compound (*S*)-**16** and (*S*)-**11** (0.18 g, 0.72 mmol) and (methoxymethyl)triphenylphosphonium chloride (0.25 g, 0.72 mmol) were used for reaction.

Yield *trans*-(*S*)-**21** (0.17 g) 84%; $R_f$ 0.60 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 10.93, (*m*/*e*) 51, 65, 77, 91, 103, 115, 128, 140, 148, 156, 171, 184, 192, 202, 229, 237, 244 (100), 258, 275 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (d, $J$ = 6.7 Hz, 3H), 1.23 (d, $J$ = 6.7 Hz, 3H), 2.21–2.32 (m, 1H), 3.61 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.95 (d, $J$ = 15.4 Hz, 1H), 6.67 (d, $J$ = 15.4 Hz, 1H), 6.81–6.97 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 19.3, 19.8, 21.1, 31.9, 45.1, 56.3, 56.5, 110.3, 111.4, 118.7, 120.5, 120.6, 123.0, 127.7, 149.0, 149.6.

*cis*-(*S*)-**21**: $R_f$ 0.58 (*n*-hexane/EtOAc, 2/1 (v/v)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (d, $J$ = 6.7 Hz, 3H), 1.12 (d, $J$ = 6.7 Hz, 3H), 2.65–2.77 (m, 1H), 3.61 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.62 (d, $J$ = 6.4 Hz, 1H), 6.07 (d, $J$ = 6.4 Hz, 1H), 6.81–7.00 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.7, 18.8, 22.1, 31.9, 55.1, 56.3, 56.5, 110.3, 111.4, 118.7, 120.5, 120.6, 123.0, 127.7, 148.6, 149.4.

*2.6.5.2. (S)-2-(3,4-dimethoxyphenyl)-2-(2-methoxyethyl)-3-methylbutyronitrile [(S)-**22**].* Compound (*S*)-**22** was synthesized by the same method as compound (*R*)-**13**, and (*S*)-**21** (0.17 g, 0.61 mmol) and Pd/C (10 mg) were used for reaction.

Yield (0.16 g) 92%; $R_f$ 0.43 (*n*-hexane/EtOAc, 2/1 (v/v)); GC/MSD retention time (min) 10.95, (*m*/*e*) 51, 65, 77, 91, 103, 119, 128, 138, 146, 156, 163, 172, 181, 189, 203, 218, 234 (100), 251, 262, 277 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.79 (d, $J$ = 6.7 Hz, 3H), 1.21 (d, $J$ = 6.7 Hz, 3H), 2.04–2.23 (m, 2H), 2.39–2.47 (m, 1H), 3.05–3.17 (m, 1H), 3.21 (s, 3H), 3.30–3.45 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 6.88–6.95 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.8, 18.9, 37.7, 38.6, 51.0, 56.2, 56.3, 59.1, 69.8, 109.5, 111.4, 118.8, 121.5, 130.2, 148.7, 149.4; HPLC analysis (Chiralpak AD, *n*-hexane/IPA, 95/5 (v/v)), retention time (min), 13.18 (*S*) and 14.80 (*R*).

*2.6.6. Syntheses of compounds for the determination of absolute configuration of the resolved alcohol **8***

*2.6.6.1. trans-(R)-4-cyano-4-methyl-4-phenylbut-2-enoic acid methyl ester [(R)-(+)-**24**].* Compound (*R*)-**24** was synthesized by the same method as compound (*S*)-**12**, and (*R*)-**23** (0.15 g, 0.91 mmol, 95% e.e.) and methyl (triphenylphosphoranylidene)acetate (0.3 g, 0.91 mmol) were used for reaction.

Yield (0.18 g) 92% $R_f$ 0.51 (benzene/EtOAc, 5/1 (v/v)); GC/MSD retention time (min) 9.34, (*m*/*e*) 51, 59, 77, 91, 103, 115, 129, 140 (100), 146, 156, 169, 183, 200, 215 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.90 (s, 3H), 3.78 (s, 3H), 6.29 (d, $J$ = 15.5 Hz, 1H), 6.93 (d, $J$ = 15.5 Hz, 1H), 7.34–7.46 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.6, 44.0, 52.4, 121.0, 121.9, 126.3, 129.0, 129.7, 138.0, 146.7, 166.3; (*R*)-(+)-**24** $[\alpha]_D^{24}$ + 22.9 (*c* 0.30, MeOH).

*2.6.6.2. (R)-(−)-4-cyano-4-methyl-4-phenylbutyric acid methyl ester [(R)-(−)-**25**].* Compound (*R*)-**25** was synthesized by the same method as compound (*R*)-**13**, and (*R*)-**24** (0.11 g, 0.51 mmol) and Pd/C (10 mg) were used for reaction.

Yield (0.11) 99%; $R_f$ 0.44 (benzene/EtOAc, 5/1 (v/v)); GC/MSD retention time (min) 9.05, (*m*/*e*) 51, 59, 77, 91, 103, 115, 130 (100), 143, 159, 170, 186, 202, 217 ($M^+$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.75 (s, 3H), 2.19–2.38 (m, 3H), 2.43–2.57 (m, 1H), 3.63 (s, 3H), 7.30–7.46 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.3, 30.7, 37.1, 42.3, 52.2, 122.3, 125.8, 128.5, 129.5, 139.3, 173.0; (*R*)-(−)-**25** $[\alpha]_D^{24}$ − 13.55 (*c* 1.10, MeOH).

*2.6.6.3. (R)-(−)-4-cyano-4-phenyl-1-pentanol [(R)-(−)-**8**].* Compound (*R*)-**8** was synthesized by the same method as compound (*R*)-**16**, and (*R*)-**25** (0.11 g, 0.50 mmol) and powdered $NaBH_4$ (0.19 g, 5.0 mmol) were used for reaction.

Yield (75 mg) 79%; $R_f$ 0.30 (*n*-hexane/EtOAc, 4/1 (v/v)); HPLC analysis (Chiralcel OD column, *n*-hexane/IPA, 9/1 (v/v)), retention time (min) 19.34 (*R*); (*R*)-(−)-**8** $[\alpha]_D^{20}$ − 5.09 (*c* 0.22, MeOH).

## 3. Results and discussion

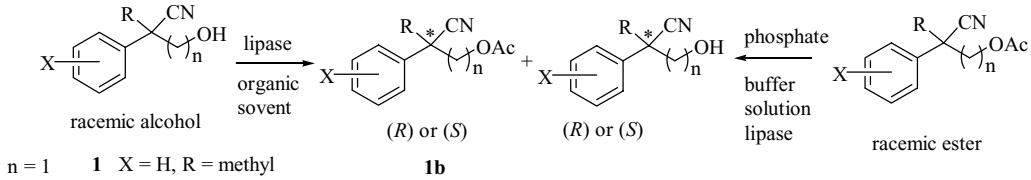
The enzymatic transesterification of racemic alcohols (**1**–**8**) using lipases such as PCL, PFL, LAK and CRL proceeded and the results of their enzymatic resolution of racemic alcohols (**1**–**8**) are summarized in Table 1 (Scheme 1).

The enzymatic acylation of (±)-**1** by LAK gave (*R*)-**1** in 100% e.e. $[\alpha]_D^{23}$ + 13.95 (*c* 1.5, MeOH) and conversion of 76% and that of (±)-**2** by LAK gave acetate ester (*S*)-**2b** in 100% e.e. and conversion of 23%. The enzymatic reaction of (±)-**3** gave good enantioselectivity by CRL in 84% e.e. and that of (±)-**5** gave excellent enantioselectivity by LAK in 96% e.e., indicating good recognition. Also, the enzymatic acylation of (±)-**6** by PCL gave acetate ester of (*S*)-**6** in 100% e.e., while that of (±)-**6** by PFL gave (*R*)-**6** in 100%

Table 1
Results of lipase-catalyzed transesterification of racemic primary alcohols (**1–8**) using vinyl acetate as an acyl donor

| Substrate alcohol | Lipase amounts (mass eq.) | Time (h) | Solvent | Conversion (%)[a] | e.e. (%)[b] | | $E$[a] |
|---|---|---|---|---|---|---|---|
| | | | | | Reacted acetate | Residue alcohol | |
| **1** | LAK (0.5) | 42 | *n*-Hexane | 76 | 32 (*S*) | 100 (*R*) | 11 |
| **2** | LAK (0.5) | 48 | *n*-Hexane | 23 | 100 (*S*) | 30 (*R*)[c] | 200 |
| **3** | CRL (1) | 2 | *n*-Hexane | 28 | 84 (*S*) | 32 (*R*) | 15 |
| **4** | PCL (0.5) | 34 | *n*-Hexane/EtOAc (9/1) | 17 | 100 (*S*) | 20 (*R*) | 200 |
| **5** | LAK (0.5) | 2 | *n*-Hexane | 20 | 96 (*S*) | 24 (*R*) | 61 |
| **6** | PCL (1) | 52 | *n*-Hexane | 17 | 100 (*S*) | 20 (*R*) | 200 |
| **6** | PFL (0.2) | 24 | *n*-Hexane | 59 | 70 (*S*) | 100 (*R*) | 40 |
| **7** | LAK (0.5) | 24 | *n*-Hexane/EtOAc (9/1) | 29 | 48 (*R*) | 20 (*S*) | 3.4 |
| **8** | PCL (1) | 5 | *n*-Hexane | 83 | 10 (*R*) | 99 (*S*) | 4.1 |

[a] Conversion and $E$ were calculated from $e.e._{substrate\ alcohol}$ and $e.e._{product\ acetate}$ [17].
[b] Measured by chiral column of HPLC and GC, indicated in experiment part.
[c] Resolution data in literature [14].




| | | |
|---|---|---|
| n = 1 | **1** X = H, R = methyl | **1b** |
| | **2** X = H, R = butyl | **2b** |
| | **3** X = 4-Cl, R = butyl | **3b** |
| | **4** X = 3,4-dimethoxy, R = isopropyl | **4b** |
| n = 2 | **5** X = H, R = butyl | **5b** |
| | **6** X = 4-Cl, R = butyl | **6b** |
| | **7** X = 3,4-dimethoxy, R = isopropyl | **7b** |
| n = 3 | **8** X = H, R = methyl | **8b** |

Scheme 1. Lipase-catalyzed reaction of racemic alcohols (**1**–**8**).

e.e. and conversion of 59%. Most of the primary alcohol were resolved as optically pure states by lipases.

To know the possibility of resolution of ester (**2b**–**4b**) by lipase-catalyzed hydrolysis, the enzyme reaction attempted in phosphate buffer solution of pH 7 at 25 °C using pH-Stat. Resolution of compound **2b** by LAK gave the hydrolyzed alcohol (*S*)-**2** of 100% e.e. and residue acetate (*R*)-**2b** of 8% e.e. Resolution of compound **3b** by CRL gave the hydrolyzed alcohol (*S*)-**3** of 100% e.e. Resolution of compound **4b** by LAK gave the hydrolyzed (*S*)-**4** of 100% e.e. and residual acetate (*R*)-**4b** of 48% e.e. (Table 2).

The absolute configuration of the resolved alcohol **1** was confirmed by comparison of specific rotation value of (*R*)-(+)-α-methyltropic acid ($[\alpha]_D^{20}$ + 21.29) which was synthesized from resolved alcohol (−)-1 with that ($[\alpha]_D^{20}$ + 23.70) of (*R*)-(+)-α-methyltropic acid (**10**) reported in the literature [15] and *E* value and conversion yield were calculated by the Sih's equation [17]. (*R*)-(+)-α-methyltropic acid (**10**) was synthesized in two steps by the reaction of (−)-**1** with 3,4-dihydro-2H-pyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS), followed by hydrolysis as shown in Scheme 2.

The absolute configuration of the resolved alcohol **3** was determined by the result of reaction of (*S*)-**2** [12] with tin(IV) chloride in the presence of lead acetate. (*S*)-**2** reacted with tin(IV) chloride and lead acetate to give (*S*)-**3** in 57% yield. The absolute configuration of the resolved alcohol **4** was determined by chemical transformation of resolved alcohol **4** to enantiomerically enriched **14** whose absolute configuration was reported in the literature [6a]. The transformation of the resolved alcohol **4** to (*R*)-**14** was accomplished in four steps as shown in Scheme 3.

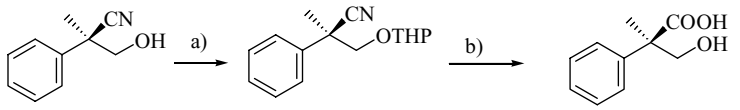
The absolute configuration of the resolved alcohol **5** was determined by chemical transformation of (*S*)-**2** to (*S*)-**17** and that of the resolved alcohol **5** to (*S*)-**17** by methyl iodide. The rotation value obtained by transformation of (*S*)-**2** to (*S*)-**17** was compared to that obtained by transformation of the resolved alcohol **5** to (*S*)-**17** as shown in Scheme 4.

Compound (*S*)-**3** was oxidized with pyridinium chlorochromate in methylene chloride to give

Table 2
Results of lipase-catalyzed hydrolysis of racemic primary alcohols (**2b**–**4b**) using phosphate buffer solution

| Substrate alcohol | Lipase (mass eq.) | ($R \times n$) time (h) | Conversion (%)[a] | e.e. (%)[b] | | $E$[a] |
|---|---|---|---|---|---|---|
| | | | | Hydrolyzed alcohol | Residue acetate | |
| **2b** | LAK (1) | 12 | 22 | 100 (*S*) | 8 (*R*) | 200 |
| **3b** | CRL (1) | 0.5 | 7 | 100 (*S*) | 8 (*R*) | 200 |
| **4b** | LAK (0.5) | 70 | 32 | 100 (*S*) | 48 (*R*) | 200 |

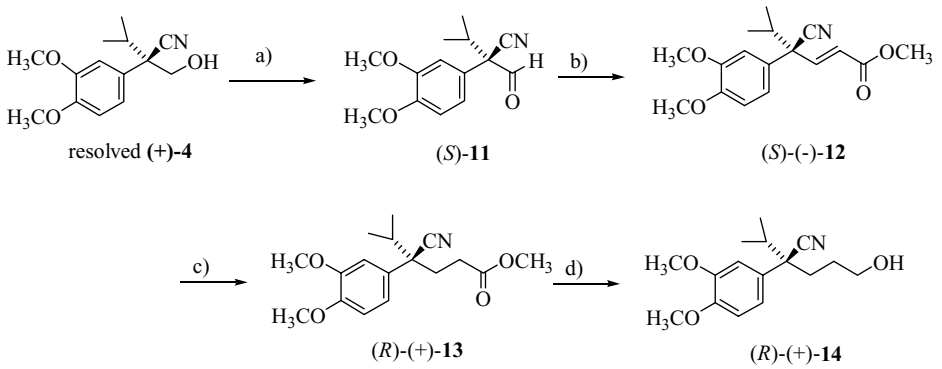
[a] Conversion and *E* were calculated from $e.e._{substrate\ acetate}$ and $e.e._{product\ alcohol}$ [17].
[b] Measured by chiral column of HPLC and GC, indicated in experiment part.




resolved **(-)-1** (*S*)-**9** (*R*)-(+)-**10**

a) DHP, PPTS, $CH_2Cl_2$, rt, 3 h, 89%, b) 30% aqu. $H_2O_2$, 48% aqu. NaOH, reflux, 10 h, conc. HCl, 74%

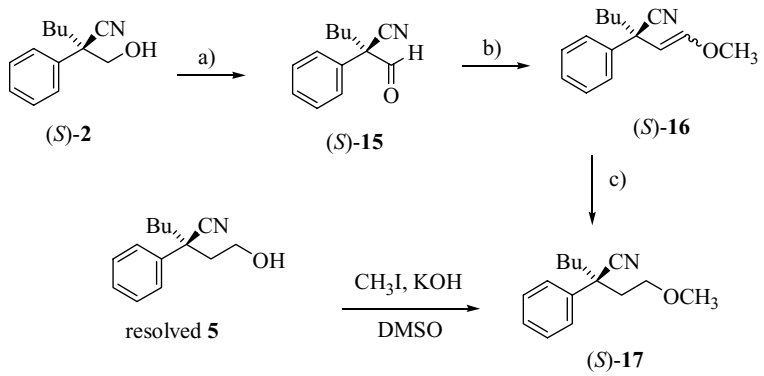
Scheme 2. The determination of absolute configuration of the resolved 1.




resolved **(+)-4** (*S*)-**11** (*S*)-(-)-**12** (*R*)-(+)-**13** (*R*)-(+)-**14**

a) PCC, $CH_2Cl_2$, rt, 5h, 88%, b) $Ph_3PCHCO_2CH_3$, $CH_2Cl_2$, rt 2h, 89%,
c) $H_2$, 10% Pd/C. $CH_3OH$, rt, 95%, d) $NaBH_4$, $CH_3OH$, reflux, 80%

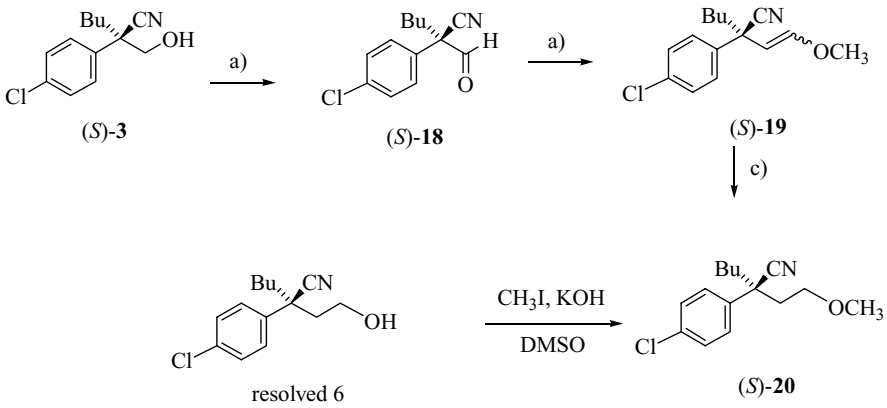
Scheme 3. The determination of absolute configuration of the resolved 4.




(*S*)-**2** (*S*)-**15** (*S*)-**16** resolved **5** (*S*)-**17**

a) PCC, $CH_2Cl_2$, rt, 3h, 86%, b) $Ph_3PCHOCH_3$, *n*-BuLi, -78 °C to rt, 10h, 82%,
c) $H_2$, 10% Pd/C. $CH_3OH$, rt, 1h, 95%

Scheme 4. The determination of absolute configuration of the resolved 5.

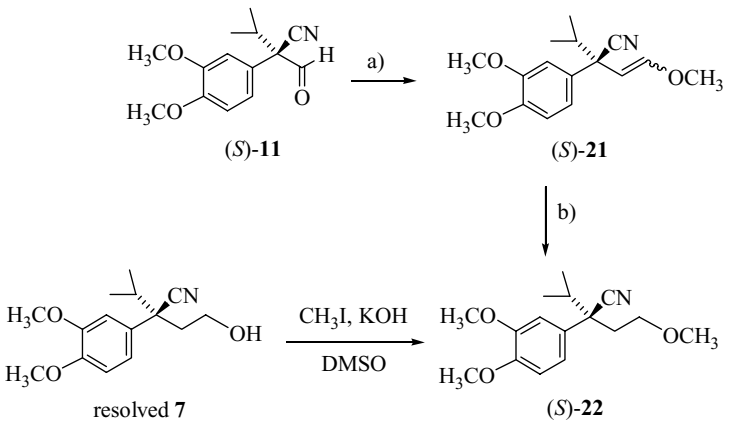



a) PCC, $CH_2Cl_2$, rt, 3h, 87%, b) $Ph_3PCHOCH_3Cl$, *n*-BuLi, -78 °C to rt, 10h, 86%, c) $H_2$, 10% Pd/C, $CH_3OH$, rt, 1h, 96%

Scheme 5. The determination of absolute configuration of the resolved 6.

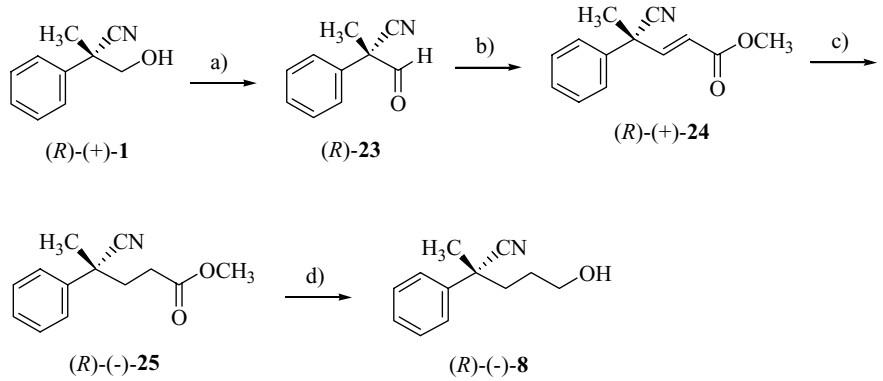
(*S*)-**18**, followed by the reaction of (*S*)-**18** with (methoxymethyl)triphenyphosphonium chloride to give (*S*)-**19**. This ether (*S*)-**19** was reduced with hydrogen in 10% Pd/C to give (*S*)-**20**. Also, the resolved alcohol **7** was treated with methyl iodide to give (*S*)-**20**. The absolute configuration of the resolved alcohol **6** was determined as shown in Scheme 5.

Then, (*S*)-**11** was treated with (methoxymethyl)triphenylphosphonium chloride in Wittig reaction to give (*S*)-**21**, which was reduced by 10% palladium on charcoal. The data such as rotation value and NMR of the synthesized (*S*)-**22** was compared to those of the compound obtained by the reaction of resolved alcohol **7** with methyl iodide. Moreover, (*R*)-**8** was obtained in high yield through the successive conversion of (*R*)-**1** to (*R*)-**23** by pyridinium chlorochromate in dichloromethane, Wittig reaction of the resulting aldehyde (*R*)-**23**, the reduction with 10% palladium on charcoal and another reduction by sodium borohydride. The absolute configuration of the resolved (*R*)-**7** and (*R*)-**8** were determined as shown in Schemes 6 and 7, respectively.




a) $Ph_3PCHOCH_3Cl$, *n*-BuLi, -78 °C to rt, 10h, 84%, b) $H_2$, 10% Pd/C, $CH_3OH$, rt, 1h, 92%

Scheme 6. The determination of absolute configuration of the resolved 7.




a) PCC, $CH_2Cl_2$, rt, 5h, 91%, b) $Ph_3PCHOCH_3Cl$, *n*-BuLi, -78 °C to rt, 5h, 92%,
c) $H_2$, 10% Pd/C, $CH_3OH$, rt, 1h, 99%, d) $NaBH_4$, $CH_3OH$, reflux, 5h, 79%

Scheme 7. The determination of absolute configuration of the resolved 8.

Chemical modification of each resolved enantiopure primary alcohols (**1**–**8**) can give biologically active compounds such as verapamil [6b], systhane [7b] and various compounds [18].

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