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Synthesis of Optically Active 4-Hydroxyalkanenitriles via an Enzymatic Reaction

Yumiko TAKAGI and Toshiyuki ITOH*
Department of Chemistry, Faculty of Education, Okayama University, Okayama 700

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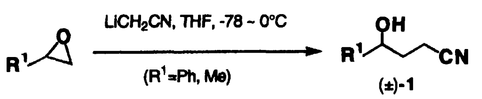
Lipase-catalyzed enantioselective hydrolysis of esters of 4-hydroxyalkanenitriles was demonstrated for the first time. Efficient optical resolution was achieved when (±)-3-cyano-1-phenylpropyl 2-(phenylthio)acetate was hydrolyzed by lipase PS (*Pseudomonas* sp.).

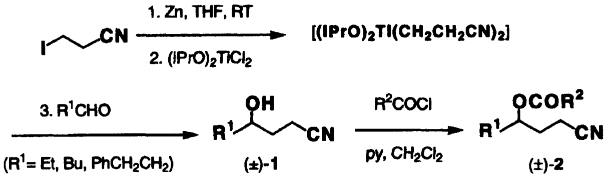
Optically active 4-hydroxyalkanenitriles (**1**) are thought to be useful building blocks for asymmetric synthesis because the cyano group is a functional precursor group of the amino and carbonyl groups.[1)] There has been only limited work reported on a method applicable to the preparation of chiral 4-hydroxyalkanenitriles.[2)] Enzymatic reaction is well recognized as an easy and dependable means of obtaining enantiomerically pure products.[3,4)] In this report, we describe the first use of a lipase to effect kinetic resolution of 4-hydroxyalkanenitriles.

Results and Discussion

This project was based on the use of an enzymatic hydrolysis of the racemic esters of **1**. The racemic hydroxy nitriles **1** were prepared as shown in Eq. 1 or Eq. 2. The subsequent reaction of an oxirane with the lithiated acetonitrile gave 4-hydroxyalkanenitriles **1** (Eq. 1). Hydroxy nitriles **1a** and **1d** were obtained by this method. Since commercially available oxiranes were limited, it was noted that an additional reaction of 2-cyanoethyltitanium reagent, which was derived from 2-cyanoethylzinc iodide, with an aldehyde was also a method conveniently furnishing 4-hydroxyalkanenitriles (Eq. 2).[5)] Hydroxy nitriles **1b**, **1c**, and **1e** were thus obtained by this latter means. Hydroxy nitriles **1** were then acylated by treatment of acyl chlorides to provide the corresponding esters, **2**, which were treated by the lipase-catalyzed hydrolysis.



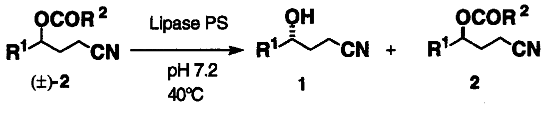
(1)



(2)

1a ($R^1 = Me$)
1b ($R^1 = Et$)
1c ($R^1 = Bu$)
1d ($R^1 = Ph$)
1e ($R^1 = PhCH_2CH_2$)
2aa ($R^1 = Me, R^2 = Me$)
2ab ($R^1 = Me, R^2 = CH_2SMe$)
2ac ($R^1 = Me, R^2 = CH_2SPh$)
2ad ($R^1 = Me, R^2 = CH_2OMe$)
2ae ($R^1 = Me, R^2 = CH_2OPh$)
2ba ($R^1 = Et, R^2 = Me$)
2bb ($R^1 = Et, R^2 = CH_2SMe$)
2ca ($R^1 = Bu, R^2 = Me$)
2cb ($R^1 = Bu, R^2 = CH_2SMe$)
2da ($R^1 = Bu, R^2 = Me$)
2db ($R^1 = Ph, R^2 = CH_2SPh$)
2ea ($R^1 = Ph, R^2 = Me$)
2eb ($R^1 = Ph, R^2 = CH_2SPh$)

Several kinds of lipases were tested using 4-hydroxyalkanenitriles, **1**, as substrates to find the best combination of ester and lipase, thus ensuring high enantioselection (Eq. 3). The reaction was done using the following procedure. To a suspension of (±)-3-cyanopropyl acetate (**2**) in 0.1 M phosphate buffer (pH 7.2) (1 M=1 mol dm^{-3}) was added the lipase (50 wt% of the ester) and the mixture was stirred at 40 °C. Progress of the reaction was monitored by silica-gel thin layer chromatography (TLC) and the reaction was stopped when the spots due to the ester and the produced alcohol became the same size. The reaction mixture was extracted with ethyl acetate and separated by silica-gel flash column chromatography after the conversion ratio was measured by ^{1}H NMR analysis of the crude product. Optical purity of the produced alcohol, **1**, was determined by ^{1}H NMR or ^{19}F NMR analysis of the corresponding (+)-3,3,3-trifluoro-2-methoxy-2-phenylacetate (MTPA ester).[6)] The results are summarized in Table 1. Preliminary experiments involving the hydrolysis of 3-cyano-1-methylpropyl acetate (**2aa**) showed that lipase PS (Amano, *Pseudomonas* sp.) was more promising than any other of the nine enzymes tested, though the (E)[7)] value of the reaction was only 2 (Entry 1). In these reactions, lipases from *Aspergillus* sp. (A and A6), *Candida* sp. (MY and M10), *Rhizopus* sp. (F-AP15 and Newlase F), porcine pancreatin (PPL), and hog pancreatin (F) were not stereo-specific. As can be seen in Table 1, the enantioselectivity was strongly dependent



(3)

Table 1. Kinetic Resolution of Various 3-Cyanopropyl Esters **2**

Entry	R^1	R^2	Time h	%ee of **1** (conv, %)	$[\alpha]^{23}_D$ in EtOH c=ca. 1	E[7]
1	CH_3	CH_3	28	22 (31)	−3.0° (S)	2
2	CH_3	CH_2SMe	15	40 (48)	−5.8° (S)	3
3	CH_3	CH_2SPh	20	33 (40)	−4.5° (S)	1
4	CH_3	CH_2OMe	35	16 (45)	−3.8° (S)	2
5	CH_3	CH_2OPh	35	9 (60)	−2.4° (S)	1
6	CH_3CH_2	CH_3	19	52 (48)	−8.6° (S)	5
7	CH_3CH_2	CH_2SMe	15	60 (45)	−21.8° (S)	7
8	n-C_4H_9	CH_3	24	13 (62)	+37.9° (R)	2
9	n-C_4H_9	CH_2SMe	24	26 (66)	+46.2° (R)	3
10	Ph	CH_3	94	90 (35)	+8.0° (R)	29
11	Ph	CH_2SPh	150	97 (47)	+15.6° (R)	214
12	$PhCH_2CH_2$	CH_3	19	49 (37)	−0.3° (R)	4
13	$PhCH_2CH_2$	CH_2SPh	19	76 (39)	−2.2° (R)	12

on the structure. The highest (E) value of the hydrolysis was obtained when 3-cyano-1-phenylpropyl 2-(phenylthio)actate **2db** was subjected to the reaction (Entry 11). We previously reported that the stereochemical behaviors of the *Pseudomonas* lipases are sensitive to the ester functionality, and that enantioselectivity of the lipase-catalyzed hydrolysis of esters of 3-hydroxyalkanenitriles could be enhanced by changing the acyl residue.[4a] With esters of 4-hydroxyalkanenitriles, this effect was not a drastic one. Lipase PS was not specific to any of the aliphatic 4-hydroxyalkanenitriles tested (Entries 1 to 9). The enantioselectivity was slightly enhanced when 3-cyano-1-methylpropyl 2-(methylthio)acetate (**2ab**) was reacted (Entry 2). Consequently, it seemed that this enzymatic hydrolysis promised satisfactory results only with 4-hydroxyalkanenitriles involving the aromatic group at the 4-position. To identify the absolute configuration of the produced alcohol, hydroxy nitrile **1d** (97%ee) was converted to the 4-phenyl-4-butanolide (**3**). Although partial racemization had occurred, optically active 4-butanolide **3** (76%ee) was obtained via hydrolysis of the cyano group of **1d** by treatment with 2 M NaOH aqueous solution under reflux conditions. Optical purity of the resulting lactone **3** was measured by the gas chromatography (GPC) analysis using a chiral capillary column (Chiraldex G-TA). After comparing the value of the optical rotation of the resulting lactone **3**, $[\alpha]^{18}_D$ +9.05° (c 1.01, EtOH), with the reported one, $[\alpha]^{21}_D$ +16.3° (R),[8] the configuration of the 4-position of lactone **3** was assigned as R. It was therefore confirmed that the starting hydroxy nitrile **1d** was the (R)-isomer. From the diastereomeric differences in chemical shifts made by the methoxyl group in (+)-MTPA esters, the configuration was theorized.[6] The absolute configuration assignment of **1a**, **1b**, and **1c** was done by ^{1}H NMR analysis of the corresponding (+)-MTPA esters using reference product (R)-**1d**.

This reaction allowed a simple preparation of optically active 4-hydroxyalkanenitriles, though only phenyl-substituted 4-hydroxyalkanenitriles were appropriate for the enantioselective reaction. This lipase resolution may be one of the most promising methods for preparing 4-aryl-4-hydroxyalkanenitriles in the optically active state.

Experimental

Instrument and Materials. NMR spectra were recorded on JEOL MH-100 and Varian VXR-200 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. IR spectra were obtained on a JASCO A-102 spectrometer. Optical rotations were measured with a JASCO DIP-181 digital polarimeter. Melting points are uncorrected. Reagents and solvents were purchased from a common commercial source and were used as received following purification by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Silica gel (Wako gel C-300) was used for column chromatography, and TLC analyses were done on Merck 60 F_{254} silica-gel plates and Wako gel B5F.

(±)-6-Phenyl-4-hydroxyhexanenitrile (1e).[5] The procedure was essentially that of Knochel et al.[5] A suspension of zinc (640 mg, 10.4 mmol) in a mixed solvent of tetrahydrofuran (THF) (2 mL) and 1,2-dibromoethane (76 mg, 0.4 mmol) was heated to gently reflux for 15 min. To this suspension was added 3 mL of THF solution of trimethylsilyl chloride (36 mg, 0.3 mmol) at room temperature. After being stirred for 15 min at r.t., a THF (5 mL) solution of 3-iodopropiononitrile (1.81 g, 10 mmol) was added dropwise using a syringe, and the mixture was stirred for 20 min at r.t. to form a dark brownish solution. To this solution was added a dichloromethane solution (5 mL) of $(i\text{-PrO})_2TiCl_2$ at −30 °C and allowed to warm to 0 °C. A dichloromethane solution (9 mL) of 3-phenylpropanal (1.03 g, 12 mmol) was added to the solution at 0 °C, then the mixture was stirred for 3 h at 0 °C and at 30 °C for another 3 h. The reaction was quenched by addition of 2 M HCl, and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to give a brownish oil. Purification by silica-gel flash column chromatography, (hexane : AcOEt=4 : 1), gave **1e** (1.591 g, 8.41 mmol) in 81% yield: Bp 150 °C/26.7 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt=2 : 1); ^{1}H NMR (100 MHz, $CDCl_3$) δ=1.8—2.0 (2H, m), 2.0—2.2 (2H, m), 3.5 (2H, s), 5.1—5.4 (1H, m), 5.8 (1H, dd, J_1=16.2 Hz, J_2=6.5 Hz), 6.5 (1H, dd, J=16.2 Hz), 7.0—7.4 (10H, m); IR (neat) 3050, 2940, 2250, 1580, 1480, 1440, 1260, 1120, 1020, 970, 740, and 690 cm^{-1}. Hydroxy nitriles **1b** and **1c** were prepared to 60—80% by the procedure described above.

(±)-4-Hydroxyhexanenitrile (1b): Bp 96 °C/333 Pa (Kugelrohr); R_f 0.5 (Hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ=0.9 (3H, t, J=7.4 Hz), 1.4—1.6 (2H, m), 1.6—1.9 (2H, m), 2.0—2.1 (1H, brs, OH), 2.5 (2H, t,

J=7.2 Hz), 3.6—3.7 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=9.68, 13.62, 30.13, 31.97, 71.15, 119.96; IR (neat) 3400, 2950, 2900, 2230 (CN), 1420, 1300, 1110, 1070, and 860 cm^{-1}. Calcd for C$_6$H$_{11}$ON: C, 63.45; H, 9.94; N, 12.16%. Found: C, 63.69; H, 9.80; N, 12.38%.

(±)-4-Hydroxyoctanenitrile (1c): Bp 95 °C/333 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt=2 : 1); ^{1}H NMR (100 MHz, CDCl$_3$) δ=0.9 (3H, t, J=7.3 Hz), 1.3—1.5 (6H, m), 1.6—1.8 (2H, m), 2.0—2.1 (1H, brs, OH), 2.5 (2H, t, J=7.3 Hz), 3.6—3.7 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=13.58, 13.89, 32.48, 27.56, 32.41, 36.99, 69.80, 119.95; IR (neat) 3400, 2930, 2850, 2240 (CN), 1420, 1130, 1090, 1050, 940, 900, and 730 cm^{-1}; Calcd for C$_8$H$_{15}$ON: C, 68.04; H, 10.71; N, 9.92%. Found: C, 68.22; H, 10.69; N, 10.01%.

(±)-4-Hydroxy-4-phenylbutanenitrile (1d): To a solution of lithium diisopropylamide (LDA) (12 mmol) in THF (20 mL) was added a THF (5 mL) solution of acetonitrile (411 mg, 10 mmol) at −78 °C under argon and the mixture was stirred for 2 h at the same temperature to form a pale yellow solution. To this solution was added a THF (5 mL) solution of 1,2-epoxyethylbenzene (1.202 g, 10 mmol) dropwise at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was acidified by NH$_4$Cl and 2 M HCl, extracted with ether, dried over MgSO$_4$, and evaporated. Purification by silica-gel flash column chromatography, (hexane/AcOEt=7 : 1), gave **1d** (1.11 g, 6.9 mmol) in 69% yield as a yellow oil: Bp 150 °C/200 Pa (Kugelrohr); R_f 0.4 (hexane/AcOEt=2 : 1) ^{1}H NMR (100 MHz, CCl$_4$) δ=1.9 (2H, q, J=7.1 Hz), 2.3 (2H, t, J=6.3 Hz), 3.2 (1H, s), 4.6 (1H, t, J=6.8 Hz), 7.2 (5H, s); IR (neat) 3450, 3050, 2950, 2250 (CN), 1600, 1500, 1200, 1060, 920, 760 and 700 cm^{-1}. Calcd for C$_{10}$H$_{11}$ON: C, 74.51; H, 6.88; N, 8.69%. Found: C, 74.66; H, 6.79; N, 8.81%. Hydroxy nitrile **1a** was prepared from propylene oxide by the procedure described above.

(±)-4-Hydroxypentanenitrile (1a): Bp 70 °C/267 Pa (Kugelrohr); R_f 0.3 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=1.2 (3H, d, J=6.1 Hz), 1.6—1.9 (3H, m, 2H+OH), 2.5 (2H, t, J=7.3 Hz), 3.6—4.0 (1H, m); IR (neat) 3500, 2950, 2230 (CN), 1420, 1370, 1120, 1080, 950, 890, and 850 cm^{-1}; Calcd for C$_5$H$_9$ON: C, 60.58; H, 9.15; N, 14.13%. Found: C, 60.55; H, 9.09; N, 14.15%.

(±)-3-Cyano-1-phenylpropyl Acetate (2da): To a solution of **1d** (100 mg, 0.62 mmol) and pyridine (0.3 mL) in CH$_2$Cl$_2$ (1.0 mL) was added a CH$_2$Cl$_2$ (2 mL) solution of acetyl chloride (73 mg, 0.93 mmol) at 0 °C. After being stirred for 23 h at r.t., the mixture was added with a crushed ice and extracted with CH$_2$Cl$_2$. The combined organic layers were dried (MgSO$_4$) and evaporated. Purification by silica-gel TLC, (hexane/AcOEt=2 : 1), gave **2da** (120 mg, 0.59 mmol) in 95% yield: Bp 130 °C/267 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (100 MHz, CDCl$_3$) δ=2.0 (3H, s), 1.9—2.4 (4H, m), 5.7 (1H, t, J=6.8 Hz), 7.2 (5H, s); IR (neat) 3040, 2940, 2240 (CN), 1740 (CO), 1500, 1420, 1370, 1230, 950, 760, and 700 cm^{-1}. 3-Cyanopropyl esters were prepared using the same procedure.

(±)-3-Cyano-1-methylpropyl Acetate (2aa): Bp 100 °C/533 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (100 MHz, CCl$_4$) δ=1.2 (3H, d, J=6.6 Hz), 1.9 (2H, q, J=7.0 Hz), 2.0 (3H, s), 2.3 (2H, t, J=9.1 Hz), 4.8—5.0 (1H, m); IR (neat) 2950, 2240 (CN), 1740 (CO), 1380, 1240, 950, and 700 cm^{-1}.

(±)-3-Cyano-1-methylpropyl 2-(Methylthio)acetate (2ab): Bp 120 °C/533 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=1.3 (3H, d, J=6.4 Hz), 1.9 (2H, q, J=6.7 Hz), 2.1 (3H, s), 2.4 (3H, t, J=7.4 Hz), 3.2 (2H, s), 4.9—5.0 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=13.42, 16.24, 19.53, 35.74, 63.91, 118.96; IR (neat) 2950, 2240 (CN), 1740 (CO), 1380, 1250, 1030, and 900 cm^{-1}; Calcd for C$_8$H$_{13}$O$_2$NS: C, 51.31; H, 7.00; N, 7.48%. Found: C, 51.18; H, 7.22; N, 7.37%.

(±)-3-Cyano-1-methylpropyl 2-(Phenylthio)acetate (2ac): Bp 120 °C/533 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=1.2 (3H, d, J=6.3 Hz), 1.9 (2H, t, J=6.7 Hz), 2.2 (2H, t, J=7.1 Hz), 3.0 (2H, s), 4.9 (1H, m), 7.2—7.4 (5H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=13.19, 19.41, 31.30, 36.59, 70.30, 118.94, 127.15, 129.07, 130.00, 134.52, 169.01; IR (neat) 3050, 2960, 2910, 2220 (CN), 1720 (CO), 1580, 1480, 1440, 1270, 1130, 1020, 960, 740, and 690 cm^{-1}; Calcd for C$_{12}$H$_{15}$O$_2$NS: C, 60.73; H, 6.37; N, 5.92%. Found: C, 60.60; H, 6.22; N, 6.00%.

(±)-3-Cyano-1-methylpropyl 2-Methoxyacetate (2ad): Bp 90 °C/533 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=1.3 (3H, d, J=6.3 Hz), 1.9 (2H, q, J=6.9 Hz), 2.4 (2H, t, J=7.3 Hz), 3.4 (3H, s), 4.0 (2H, s), 5.1 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$) 13.43, 19.53, 31.22, 59.22, 69.65, 69.74, 118.89, 169.64; IR (neat) 2950, 2250 (CN), 1740 (CO), 1420, 1375, 1190, 1120, 1060, 850, and 720 cm^{-1}; Calcd for C$_8$H$_{13}$O$_3$N: C, 56.13; H, 7.65; N, 8.18%. Found: C, 55.51; H, 7.77; N, 7.41%.

(±)-3-Cyano-1-methylpropyl 2-Phenoxyacetate (2ae): Bp 140 °C/533 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=1.3 (3H, d, J=6.4 Hz), 1.9 (2H, q, J=7.0 Hz), 2.2 (2H, dt, J_1=7.3, J_2=1.6 Hz), 4.6 (2H, d, J=1.5 Hz), 5.0—5.1 (1H, m), 6.9—7.3 (5H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=13.22, 19.50, 31.21, 65.25, 70.41, 114.45, 118.88, 121.77, 129.56, 157.62, 168.51; IR (neat) 2980, 2240 (CN), 1750 (CO), 1600, 1495, 1440, 1380, 1200, 1190, 760, and 720 cm^{-1}; Calcd for C$_{13}$H$_{15}$O$_3$N: C, 66.94; H, 6.48; N, 6.00%. Found: C, 67.08; H, 6.57; N, 5.30%.

(±)-3-Cyano-1-ethylpropyl Acetate (2ba): 65 °C/267 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt=3 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=0.9 (3H, t, J=7.4 Hz), 1.5—1.7 (2H, m), 1.9—2.0 (2H, m), 2.1 (3H, s), 2.1 (2H, t, J=7.4 Hz), 4.8—4.9 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=9.38, 13.56, 21.00, 26.68, 29.29, 73.54, 119.20, 170.74; IR (neat) 2970, 2940, 2240 (CN), 1740 (CO), 1420, 1380, 1080, 1020, 950, 860, and 720 cm^{-1}; Calcd for C$_8$H$_{13}$O$_2$N: C, 61.91; H, 8.44; N, 9.03%. Found: C, 61.30; H, 8.53; N, 9.00%.

(±)-3-Cyano-1-ethylpropyl 2-(Methylthio)acetate (2bb): Bp 100 °C/267 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt=3 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=0.9 (3H, t, J=7.4 Hz), 1.6—1.7 (2H, m), 1.9—2.0 (2H, m), 2.2 (3H, t, J=1.3 Hz), 2.41 (2H, t, J=7.4 Hz), 3.12 (2H, s), 4.8—5.0 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ=9.31, 13.43, 16.30, 26.70, 29.36, 35.71, 74.36, 119.10, 169.90; IR (neat) 2960, 2920, 2230 (CN), 1720 (CO), 1420, 1020, 950, 890, and 790 cm^{-1}.

(±)-1-(2-Cyanoethyl)pentyl Acetate (2ca): Bp 80 °C/267 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, CDCl$_3$) δ=0.9 (3H, dt, J_1=5.3 Hz, J_2=3.0 Hz), 1.2—1.3 (4H, m), 1.8—2.0 (2H, brs), 2.1 (3H,

Table 2. Results of Lipase-Catalyzed Hydrolysis of **2**

Entry	Substrate	Time h	Yield of **1** (conv, %)	^{1}H NMR of **1** (OMe)$^{a)}$ L : H	Yield of **2**	$[\alpha]_D$ of **1** in EtOH c=ca. 1	$[\alpha]_D$ of **2** in EtOH c=ca. 1
1	**2aa**	28	19 (31)	39.0 : 61.0	67	−3.0°	+4.9°
2	**2ab**	15	39 (48)	30.0 : 70.0	44	−5.8°	+9.7°
3	**2ac**	20	22 (40)	33.5 : 66.5	50	−4.5°	+5.9°
4	**2ad**	35	30 (45)	42.0 : 58.0	30	−3.8°	+7.4°
5	**2ae**	35	35 (60)	45.5 : 54.5	20	−2.4°	+6.1°
6	**2ba**	19	32 (48)	24.0 : 76.0	35	−8.6°	+0.9°
7	**2bb**	15	21 (45)	20.0 : 80.0	34	−21.8°	+0.8°
8	**2bc**	24	54 (62)	56.5 : 43.5	33	−37.9°	−29.3°
9	**2bd**	24	51 (66)	63.0 : 37.0	32	+46.2°	−13.3°
10	**2da**	94	33 (35)	5.0 : 95.0	50	+8.0°	−28.8°
11	**2db**	150	44 (47)	1.5 : 98.5	46	+15.6°	−41.5°
12	**2ea**	19	35 (37)	74.5 : 25.2	52	−0.3°	+0.7°
13	**2eb**	19	36 (39)	88.0 : 12.0	51	−2.2°	+0.8°

a) (+)-MTPA ester of **1**.

s), 2.4 (2H, t, J=7.4 Hz), 4.8—5.0 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ=13.51, 13.83, 21.00, 22.35, 27.20, 29.75, 33.40, 72.40, 119.19, 170.67; IR (neat) 2950, 2860, 2250 (CN), 1730 (CO), 1370, 1230, 1030, and 950 cm^{-1}; Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35; N, 7.64%. Found: C, 65.42; H, 9.34; N, 7.76%.

(±)-1-(2-Cyanoethyl)pentyl 2-(Methylthio)acetate (2cb): Bp 100 °C/200 Pa (Kugelrohr); R_f 0.6 (hexane/AcOEt=2 : 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ=0.9 (3H, t, J=6.5 Hz), 1.25—1.34 (4H, m), 1.5—1.7 (2H, m), 1.9—2.0 (3H, m), 2.2 (3H, s), 2.4 (2H, t, J=7.4 Hz), 3.2 (2H, s), 4.9—5.0 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ=13.43, 13.83, 16.32, 22.33, 27.12, 29.85, 33.42, 35.76, 73.24, 119.13, 169.89; IR (neat) 2960, 2940, 2780, 2250 (CN), 1720 (CO), 1420, 1270, 1080, 1130, 950, 780, 730, and 690 cm^{-1}; Calcd for $C_{11}H_{19}O_2NS$: C, 57.61; H, 8.35; N, 6.11%. Found: C, 57.62; H, 8.44; N, 6.37%.

(±)-3-Cyano-1-phenylpropyl 2-(Phenylthio)acetate (2db): Bp 150 °C/667 Pa (Kugelrohr); R_f 0.4 (hexane/AcOEt=3 : 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ=2.1 (3H, s), 2.1—2.3 (2H, s), 2.3—2.4 (2H, m), 5.8 (1H, dt, J_1=7.2 Hz, J_2=5.4 Hz), 7.3—7.4 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ=13.53, 20.97, 31.79, 73.92, 118.78, 126.09, 128.44, 128.71, 138.55, 169.89; IR (neat) 3040, 2950, 2250 (CN), 1730 (CO), 1150, 1430, 1370, 1220, 1040, 950, 890, 760, and 700 cm^{-1}.

(±)-3-Cyano-1-phenethylpropyl Acetate (2ea): Bp 150 °C/267 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt= 3 : 1); ^{1}H NMR (100 MHz, CCl_4) δ=1.7—2.0 (4H, m), 2.0 (3H, s), 2.2 (2H, t, J=6.8 Hz), 2.5 (2H, t, J=8.1 Hz), 4.7—5.0 (1H, m), 7.0 (5H, s); IR (neat) 3040, 2940, 2250 (CN), 1730 (CO), 1600, 1500, 1460, 1380, 1240, 1040, 790, 750, and 700 cm^{-1}.

(±)-3-Cyano-1-phenethylpropyl 2-(Phenylthio)acetate (2eb): Bp 160 °C/267 Pa (Kugelrohr); R_f 0.5 (hexane/AcOEt=3 : 1); ^{1}H NMR (100 MHz, CCl_4) δ=1.6—1.9 (4H, m), 2.0 (2H, t, J=8.1 Hz), 3.4 (2H, s), 4.6—4.9 (1H, m), 6.8—7.2 (10H, m); IR (neat) 3030, 2940, 2250 (CN), 1730 (CO), 1580, 1485, 1440, 1270, 1140, 1025, 960, 890, 840, and 700 cm^{-1}.

Lipase-Catalyzed Hydrolysis. Ester **2db** (374 mg, 1.2 mmol) and lipase PS (180 mg, Amano Pharmaceutical Co., Ltd.,) in 0.1 M phosphate buffer (pH 7.2, 6.0 mL) was incubated at 40 °C for 150 h. The mixture was extracted with ethyl acetate and evaporated to give a crude product. The hydrolysis ratio was measured by ^{1}H NMR analysis as 47%. Separation by silica-gel flash column chromatography gave **1d**($[\alpha]_D^{25}$ +15.6° (c 1.09, EtOH); 85 mg, 0.53 mmol; 44%) and unreacted **2db**($[\alpha]_D^{25}$ −41.5° (c 0.80, EtOH); 172 mg, 0.55 mmol; 46%), respectively. The optical purity of the produced alcohol, **1d**, was measured by the ^{1}H NMR analysis of the corresponding (+)-MTPA ester. (+)-MTPA ester of **1d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ=2.1—2.3 (4H, m), 3.45 (q, J=1.25 Hz, OMe, H-signal, (R)-isomer), 3.51 (q, J=1.25 Hz, OMe, L-signal, (S)-isomer), 6.02 (1H, t, J=6.3 Hz), 7.3—7.5 (10H, m). Peak intensity ratio of the H-signal (δ=3.45) to the L-signal (δ=3.51) is 98.7 to 1.3; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6 as a internal reference) δ=90.42 (3F, s, H-signal, (S)-isomer), 90.52 (3F, s, L-signal, (R)-isomer); H-signal (δ=90.42): L-signal (δ=90.52)=1.5 : 98.5. Therefore, the %ee of **1d** was calculated as 97%ee. Since the hydrolysis ratio (% conversion) was 47%, the (E)$^{7)}$ value was calculated as 214. The results of chemical yield of the lipase-resolution, $[\alpha]_D$, and ^{1}H or ^{19}F NMR analysis of (+)-MTPA esters are summarized in Table 2.

(R)-4-Phenyl-4-butanolide (3).$^{8)}$ A suspension of 97%ee of (+)-**1d** (100 mg, 0.62 mmol) in 2 M NaOH (10 mL) was heated to reflux for 2 h. After being cooled to r.t., the reaction mixture was acidified by 2 M HCl and extracted with ether, dried ($MgSO_4$), and evaporated to dryness. The crude product (100 mg) was purified by silica-gel flash column chromatography to give **3** (61 mg, 0.376 mmol) in 61% yield as a colorless oil. Capillary GPC analysis using a chiral column (Chiraldex G-TA, ϕ 0.25 mm×20 m, He:70 mL min^{-1}, 130 °C) found that the optical purity of **3** was 76%ee. Retention time of (S)-isomer was 24.1 min, that of (R)-isomer was 27.7 min. When (+)-**1d** was treated with 2M HCl under reflux conditions for 2 h, the lactone **3** obtained was in a racemic state. (R)-**3** (76%ee): $[\alpha]_D^{18}$ +9.05° (c 1.01, EtOH), Lit,$^{8)}$ +16.3°(R); R_f 0.5 (hexane/AcOEt=2 : 1); ^{1}H NMR (100 MHz, CCl_4) δ=2.3—2.8 (4H, m), 5.4 (1H, m), 7.2 (5H, s); IR (neat) 3050, 2980, 1780 (CO), 1500, 1460, 1420, 1330, 1300, 1220, 1180, 1140, 1020, 990, 940, 900, 830, 760, and

700 cm^{-1}.

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