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Chemo-enzymatic synthesis of (*R*)-(+)-aminoglutethimide by kinetic resolution of (±)-4-cyano-4-phenyl-1-hexanol

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Dedicated to Prof. Joon Shick Rhee on occasion of his retirement

Abstract

Chemo-enzymatic approaches for the synthesis of the family of aromatase inhibitory drug via lipase-catalyzed kinetic resolution of (±)-4-cyano-4-phenyl-1-hexanol (**2**) as appropriate precursors were described. Enzymatic transesterification of primary alcohol (±)-**2** using *Pseudomonas cepacia* (Amano PS, PCL) provided the enantiopure alcohol (*R*)-(−)-**2** with 99% ee at conversion of 86%, while that of (±)-**2** using *Pseudomonas fluorescens* (Amano AK, LAK) provided the (*S*)-(+)-**2** with 96% ee at conversion of 86%. Chemical transformation of substrate (*R*)-(−)-**2** gave (*R*)-(+)-aminoglutethimide (**1**) in enantioselectively high yield.

Keywords: Aminoglutethimide; Tertiary benzylic center; Enzymatic resolution; Transesterification; Enantioselective

1. Introduction

Chiral tertiary benzylic centers are present in the family of aromatase inhibitory drugs such as (*R*)-(+)-aminoglutethimide (**1**) [1–6], (*S*)-(+)-3-(4-aminophenyl)-3-cyclohexylpiperidine-2,6-dione [2,7], (*R*)-(+)-rogletimide [8,9], (3*R*, 5*S*)-(+)-3-ethyl-5-octyl-3-(4-pyridyl)piperidine-2,6-dione [9], and (1*R*, 5*S*)-1-(4-aminophenyl)-3-azabicyclo[3,1,0]-hexane-2,4-dione. Convenient methods of enantioselective construction for these biologically active compounds have been investigated very much [1–9].

The aminoglutethimide (**1**) which was originally developed as an anticonvulsant is commercial aromatase inhibitor, and 3-(4-aminophenyl)-3-cyclohexyl-piperidine-2,6-dione, rogletimide derivatives, and azabicyclo derivative are known as effective drugs against breast cancer for postmenopausal patients [5,10].

The replacement of the 4-aminophenyl substituent of aminoglutethimide **1** by a 4-pyridyl group results in a decrease of inhibitory potency toward aromatase but in an increase of selectivity in that pyridoglutetimide exhibits a strongly reduced inhibitory potency toward the cholesterol side chain cleavage enzyme (desmolase), the first and rate-limiting enzyme in the overall steroidogensis [6]. Enlargement of 3-ethyl side chain

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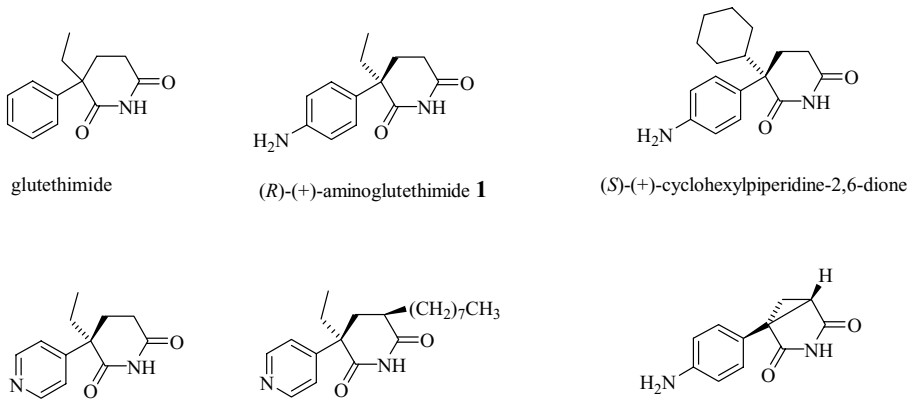


Fig. 1. Various aromatase inhibitor drugs.

of aminoglutethimide **1** by various straight, branched and cycloalkyl groups leads to a dramatic increase in aromatase inhibition without notably influencing desmolase inhibition (Fig. 1).

The first enzymatic attempt to construct asymmetric quaternary carbon of (*R*)-(+)-**1** has already been undertaken. Fadel and Garcia-Argote reported [2] that (*R*)-(+)- and (*S*)-(−)-aminoglutethimide were synthesized in 97% ee via enzymatic hydrolysis of malonate followed by chemical modification. Although the enzymatic desymmetrization of prochiral diols has been extensively reported [11], the enzymatic resolution of the primary alcohol with quaternary chiral center appears only slightly in the literature [12].

Herein we report a convenient method for the improving enantioselective synthesis of (*R*)-(+)-aminoglutethimide (**1**) via lipase-catalyzed transesterification of (±)-4-cyano-4-phenyl-1-hexanol (**2**) as appropriate precursors possessing an asymmetric quaternary carbon.

2. Experimental

2.1. General

^{1}H NMR (250 or 300 MHz) and ^{13}C NMR spectra (63 or 75 MHz) were recorded on a Varian 300 MHz spectrometer with TMS as an internal reference. 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 i.d.: 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 were carried out on Varian 9010 solvent delivery system, Varian 9050 variable wavelength UV-Vis detector, and Varian 4400 integrator using a chiral column Chiralcel OD and OB (250 mm × 4.6 mm, Daicel) for substrate alcohol (**2**).

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 u/g) and Lipase AK (*Pseudomonas fluorescens* lipase, >20,000 u/g) were obtained from Amano Enzyme Co. Ltd. CRL (*Candida rugosa* lipase, 860 u/mg) and PFL (*Pseudomonas fluorescens* lipase, 42.5 u/mg) were obtained from Sigma and Aldrich, respectively.

2.3. Synthesis of (±)-4-cyano-4-phenyl-1-hexanol (**2**) and (±)-4-cyano-4-phenylhexyl acetate (**3**)

2.3.1. Synthesis of (±)-2-ethyl-2-phenyl-5-(tetrahydropyran-2-yloxy)pentanenitrile (**5**)

To a stirred suspension of 60% sodium hydride (0.46 g, 11.6 mmol) in dry DMF (50 ml) was added dropwise 2-phenylbutyronitrile (1.4 g, 9.7 mmol) for 30 min at 0 °C. After the mixture was stirred for 30 min, 3-tetrahydropyranyloxypropyl bromide (2.1 g, 9.7 mmol) was added at 15 °C and stirred for 12 h at 25 °C. The reaction medium was quenched with cold ice water (50 ml) and extracted with diethyl ether (2 × 50 ml). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated to furnish the crude **5**. Compound **5** was purified by column chromatography (*n*-hexane/ethyl acetate = 6/1 (v/v)).

Yield (2.6 g) 94%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 4.51–4.46 (m, 1H), 3.80–3.77 (m, 1H), 3.68–3.65 (m, 1H), 3.47–3.42 (m, 1H), 3.38–3.30 (m, 1H), 2.18–1.90 (m, 4H), 1.81–1.65 (m, 3H), 1.55–1.50 (m, 5H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 129.2, 128.0, 126.4, 122.6, 99.1, 67.0, 62.8, 49.2, 37.8, 34.6, 31.0, 26.0, 25.8, 20.0, 10.0; GC/MSD retention time (min) 10.9, *m*/*z* 287 (M^+), 261, 217, 204, 172, 159 (100), 145, 117, 91, 51.

2.3.2. Synthesis of (±)-4-cyano-4-phenyl-1-hexanol (**2**)

To a solution of compound **5** (2.6 g, 9.1 mmol) in methanol (40 ml) was added 1 M methanolic HCl (20 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 (100 ml) to afford chromatographically pure **2**.

Yield (1.3 g) 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 3.53 (t, J = 6.3 Hz, 2H), 2.26 (s, 1H), 2.16–1.87 (m, 4H), 1.72–1.59 (m, 1H), 1.48–1.31 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.9, 127.7, 126.0, 122.3, 61.9, 48.8, 37.0, 34.4, 28.6, 9.6; HPLC analysis (Column: Chiralcel OD, eluent: *n*-hexane/*iso*-PrOH (9/1), flow rate: 1.0 ml/min, detector: UV 254 nm), retention time (min) 11.29 (*S*) and 12.46 (*R*); (*S*)-(+)-**2** (96% ee) $[\alpha]_D^{25}$ + 7.70 (c = 0.53, methanol), (*R*)-(−)-**2** (99% ee) $[\alpha]_D^{25}$ − 9.20 (c = 0.72, methanol); Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89, Found: C, 76.9; H, 8.54; N, 7.00.

2.3.3. Synthesis of (±)-4-cyano-4-phenylhexyl acetate (**3**)

To a solution of (±)-**2** (896 mg, 4.42 mmol) was added 4-(dimethylamino)pyridine (10 mg), Et_3N (1.85 ml, 13.26 mmol) and acetic anhydride (0.83 ml, 8.8 mmol) in CH_2Cl_2 (35 ml). The mixture was stirred at 25 °C for 5 h. The reaction mixture was neutralized with 2% HCl solution and extracted with CH_2Cl_2 (40 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated to afford (±)-**3**. Compound (±)-**3** was purified by column chromatography (*n*-hexane/ethyl acetate, 10/1 (v/v)).

Yield (1.0 g) 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 3.53 (t, J = 6.3 Hz),1.98 (s, 3H), 2.12–1.88 (m, 4H) 1.85–1.68 (m, 1H), 1.48–1.33 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 138.1, 129.3, 128.2, 126.3, 122.3, 63.9, 49.1, 37.5, 34.6, 25.1, 21.2, 10.0; HPLC analysis (Chiralcel OB column, *n*-hexane/*iso*-PrOH, 92/8 (v/v)), retention time (min) 14.78 (*S*) and 17.84 (*R*).

2.4. General procedure for the enzymatic kinetic transesterification of (±)-4-cyano-4-phenyl-1-hexanol (**2**) using several lipases

To a stirred solution of (±)-**2** (1.0 mmol) in appropriate solvent (10 ml) 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 to give the reacted acetate of each alcohol and unreacted alcohol. The isolated acetate was hydrolyzed with 1.2 M methanolic KOH solution to afford the corresponding alcohol.

2.4.1. Enzymatic acylation of (±)-**2** using lipase from Pseudomonas cepacia (PCL)

According to the general procedure 203 mg (1.0 mmol) of (±)-**2** are treated with 101 mg of PCL.

After 3 h, HPLC analysis shows a conversion of 53% and the compounds are separated by silica gel column chromatography.

Reacted (*S*)-(+)-4-cyano-4-phenylhexyl acetate ((*S*)-(+)-3).

Yield 110 mg (45%); $[\alpha]_D^{25}$ + 6.68 (c = 0.5, methanol), 76% ee [Chiralcel OB, *n*-hexane/*iso*-PrOH (92/8)], retention time (min) 14.78 (*R*) and 17.84 (*S*).

Remaining (*R*)-(−)-4-cyano-4-phenyl-1-hexanol ((*R*)-(−)-**2**).

Yield 103 mg (45%); $[\alpha]_D^{25}$ − 7.9 (c = 0.5, methanol), 86% ee [Chiralcel OD, *n*-hexane/*iso*-PrOH (9/1)], retention time (min) 11.29 (*S*) and 12.46 (*R*).

2.4.2. Enzymatic acylation of (±)-*2* using lipase from Pseudomonas fluorescens (PFL)

According to the general procedure 203 mg (1.0 mmol) of (±)-**2** are treated with 20 mg of PFL. After 1 h, HPLC analysis shows a conversion of 39%.

Reacted (*S*)-(+)-**3** yield 110 mg (45%); $[\alpha]_D^{25}$ +5.63 (c = 0.5, methanol), 70% ee.

Remaining (*R*)-(−)-**2** yield 118 mg (45%); $[\alpha]_D^{25}$ − 3.6 (c = 0.5, methanol), 44% ee.

2.4.3. Enzymatic acylation of (±)-*2* using lipase from Pseudomonas fluorescens (LAK)

According to the general procedure 203 mg (1.0 mmol) of (±)-**2** are treated with 101 mg of LAK. After 1.5 h, HPLC analysis shows a conversion of 14%.

Reacted (*R*)-(−)-**3** yield 27 mg (11%); 96% ee.

Remaining (*S*)-(+)-**2** yield 166 mg (82%); 16% ee.

2.4.4. Enzymatic acylation of (±)-*2* using lipase from Candida rugosa (CRL)

According to the general procedure 203 mg (1.0 mmol) of (±)-**2** are treated with 203 mg of CRL. After 2.5 h, HPLC analysis shows a conversion of 1%.

Reacted (*S*)-(+)-**3** yield 49 mg (20%); 0% ee.

Remaining (*R*)-(−)-**2** yield 154 mg (76%); 6% ee.

2.5. Synthesis of (R)-(+)-aminoglutethimide (*1*)

2.5.1. Synthesis of (R)-4-cyano-4-phenylhexanoic acid ((R)-(−)-*6*)

A solution of Jones reagent (1 ml) is added for 10 min to a stirred solution of (*R*)-**2** (230 mg, 1.13 mmol, 99% ee) in 5 ml of acetone at 0 °C. After being stirred for an additional 1 h, the reaction medium was quenched with cold ice water (10 ml) and extracted with diethyl ether (2 × 10 ml). The organic extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated to furnish the corresponding acid (**6**) as a white solid.

mp 114 °C ($CHCl_3$); yield (0.24 g) 88%; $[\alpha]_D^{20}$ − 9.30 (c = 1, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 1H), 7.44–7.33 (m, 5H), 3.92 (q, J = 7.28 Hz, 1H), 2.27–2.04 (m, 2H), 2.04–1.74 (m, 4H), 1.64 (d, J = 7.28 Hz, 3H), 0.73 (t, J = 7.5 Hz, 3H); GC/MSD retention time (min) 9.94 (m/z) 51, 63, 77, 91, 102, 115, 129, 142 (100), 157, 171, 190, 199, 218 (M^+).

2.5.2. Synthesis of (R)-3-phenyl-3-ethylpiperidine-2,6-dione ((R)-*7*)

To a solution of (*R*)-**6** (240 mg, 1.1 mmol) in acetic acid (2.5 ml) was concentrated sulfuric acid (0.5 ml) and the mixture was heated to 95 °C for 30 min. The reaction mixture was cooled and poured into cold ice water (10 ml) and after 1 h, the precipitate was filtered off, washed with water and dried to give compound **7**.

mp 94–94.5 °C (methanol); yield (0.22 g) 88%; $[\alpha]_D^{20}$ + 178 (c=1, methanol), lit. $[\alpha]_D^{20}$ + 181 (c=1, methanol) [4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.36–7.25 (m, 5H), 2.63–2.55 (m, 1H), 2.40–2.33 (m, 2H), 2.26–2.19 (m, 1H), 2.05–2.01 (m, 1H), 1.93–1.82 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 173.7, 139.2, 129.3, 127.9, 126.5, 51.4, 33.2, 29.6, 27.4, 9.4; GC/MSD retention time (min) 10.14 (m/z) 51, 64, 77, 91, 115, 117, 132, 146, 160, 172, 189 (100), 202, 217 (M^+).

2.5.3. Synthesis of (R)-(+)-3-ethyl-3-(4-nitrophenyl)piperidine-2,6-dione ((R)-*8*)

mp 129–129.5 °C (ethanol); $[\alpha]_D^{20}$ + 129.3 (c = 1, methanol), lit. $[\alpha]_D^{20}$ +136.6 (c = 1, methanol) [4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.18 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H), 2.72–2.67 (m, 1H), 2.46–2.32 (m, 3H), 2.10–2.02 (m, 1H), 1.99–1.92 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 172.5, 146.8, 127.9, 124.5, 51.6, 33.1, 29.4, 27.3, 9.3; GC/MSD retention time (min) 12.58, (m/z) 51, 55, 63, 77, 91, 102, 116, 130, 145, 160, 177, 191, 205, 219, 234 (100), 247, 262 (M^+).

*2.5.4. Synthesis of 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione ((R)-**1**)*

mp 111–112 °C (ethanol); $[\alpha]_D^{25}$ + 160.0 (c = 2, methanol) lit. $[\alpha]_D^{25}$ + 163 (c = 1, methanol) [4].

3. Results and discussion

The racemic alcohol **2** which is substrate for enzymatic transesterification is obtained from the reaction of 2-phenylbutyronitrile (**4**) with 3-tetrahydropyranyloxypropyl bromide, and then by acidic hydrolysis of compound **5** (Scheme 1).

The enzymatic transesterifications of racemic alcohol **2** using PCL, PFL, LAK, and CRL provided enantiopure corresponding esters and unreacted alcohols (Scheme 2).

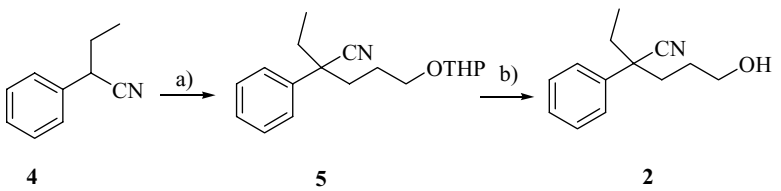
The results of enzymatic resolution of (±)-**2** by transesterification with vinyl acetate as an acyl donor using PCL, PFL, LAK and CRL are summarized in Table 1.

Absolute configuration of resolved alcohols **2** and **3** were confirmed by comparison of specific rotation values of chemically synthesized aromatase inhibitors from these alcohols with that reported in the literatures [4,7,9] and enantiomeric ratios were calculated using Selectivity-Win-1.0 [13] by the Sih's equation [14]. The progress of the reaction was monitored by chiral column of HPLC such as Chiralcel OJ and OB column.

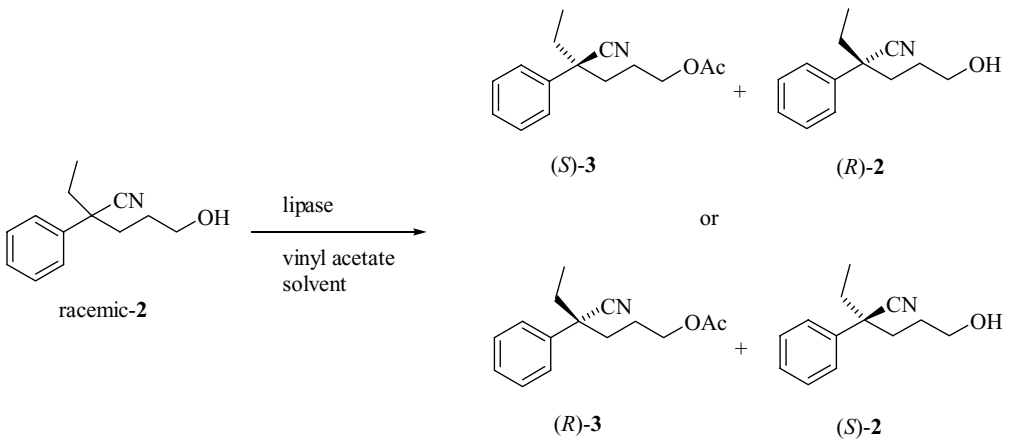
Table 1
Enzymatic transesterification of (±)-4-cyano-4-phenyl-1-hexanol (**2**) using some lipases in *n*-hexane

Lipase	Reaction time (h)	Conversion (%)[a]	Reacted acetate (ee_p)[b]	Residue alcohol (ee_s)	E[a]
PCL	1.5	25	96 (*S*)	32 (*R*)	66
	3	53	76 (*S*)	86 (*R*)	19
	8	66	52 (*S*)	99 (*R*)	15
PFL	1	39	70 (*S*)	44 (*R*)	8.7
LAK	1.5	14	96 (*R*)	16 (*S*)	57
CRL	2.5	1	0	6 (*R*)	–

[a] Calculated from $ee_{substrate\ alcohol}$ and $ee_{product\ acetate}$ using standard equation [14].
[b] Measured by chiral column of HPLC and compared by literatures [4,7,9].



Scheme 1. Synthetic method of racemic alcohol **2**: (a) NaH, $Br(CH_2)_3OTHP$ and (b) 1 M methanolic HCl.



Scheme 2. Enzymatic transesterification of racemic **2**.

Table 2
Optimization of PCL- and LAK-catalyzed transesterification of (±)-4-cyano-4-phenyl-1-hexanol **2**

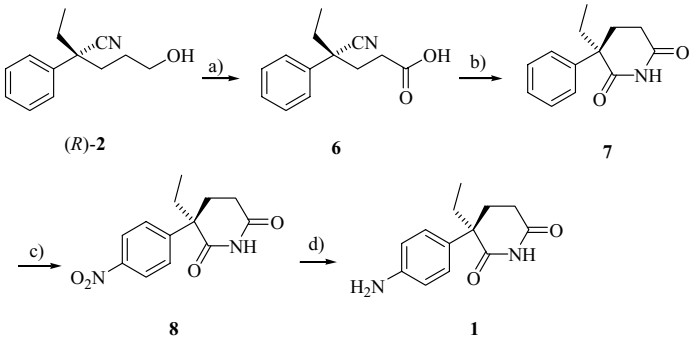
Lipase (mass equivalent)	Reaction solvent	Additives	Reaction time (h)	Conversion (%)[a]	Reacted acetate (ee_p)[b]	Residue alcohol (ee_s)	E[a]
PCL (0.5)	*n*-Hexane	Molecular sieve (4 Å)	0.5	14	38 (*S*)	6 (*R*)	2.4
			2.5	69	44 (*S*)	99 (*R*)	11
PCL (0.5)	*n*-Hexane/EtOAc (9/1)	None	8	64	52 (*S*)	86 (*R*)	8.3
LAK (0.5)	*n*-Hexane	Molecular sieve (4 Å)	0.5	43	53 (*R*)	40 (*S*)	4.8
			1.5	77	30 (*R*)	99 (*S*)	7.9
LAK (0.5)	*n*-Hexane/EtOAc (9/1)	None	1	21	82 (*R*)	22 (*S*)	12
LAK (0.5)	Benzene	None	1.5	17	96 (*R*)	20 (*S*)	59
LAK (0.5)	*iso*-Propyl ether	None	0.5	25	99 (*R*)	33 (*S*)	4.1
			6	86	16 (*R*)	96 (*S*)	200

[a] Calculated from $ee_{substrate\ alcohol}$ and $ee_{product\ acetate}$ using standard equation [14].
[b] Measured by chiral column of HPLC and compared by literatures [4,7,9].

The result of resolution by CRL showed very poor enantioselectivity toward primary alcohol (±)-**2**, but PCL and LAK showed better enantioselecivity toward (±)-**2** than PFL and CRL tested. The enzymatic acylation by PCL at reaction time of 1.5 h provided the (*S*)-(**3**) with 96% ee at conversion of 25%, while that by PCL at reaction time of 8 h, provided (*R*)-(**2**) with 99% ee at conversion of 66%. The special result is that in acylation reaction of (±)-**2** by PCL, the reacted acetate is (*S*) form, but in that by LAK, it is (*R*) form. Also, PFL and CRL did not show good enantioselectivity toward (±)-**2** (Table 2).

To optimize the enzymatic acylation by PCL and LAK, the enzyme screening by changing reaction solvent, additives and reaction time was progressed toward (±)-(**2**). In case of PCL, the use of another solvent and additives did not show better enantioselectivity toward (±)-(**2**) than the use of only *n*-hexane. However, in case of LAK, the use of *iso*-propyl ether showed better enantioselectivity than the use of only *n*-hexane.

Enantiopure alcohol (*R*)-**2** treats with Jones oxidant in acetone to give the cyanoacid **6** in 88% yield. Cyclization of the resulting (*R*)-**6** by acetic acid and concentrated H_2SO_4 yielded 3-ethyl-3-phenylpiperidine-2,6-dione (**7**) in 88% yield. Nitration of compound **7** was performed according to the method of Fuganti and coworkers [4] using concentrated sulphuric acid and nitric acid to give (*R*)-**8**.



Scheme 3. Synthesis of (*R*)-(+)-**1**: (a) Jones oxidant acetone, 88% yield, (b) conc. H_2SO_4/CH_3COOH (1/1), 88% yield, (c) conc. H_2SO_4/HNO_3 (1/1), 85% yield, and (d) 10% Pd/C, MeOH, 95% yield.

After the crystallization of the crude product from methanol, its reduction by palladium on charcoal gave (*R*)-(+)-**1** in 95% yield as shown in Scheme 3.

In conclusion, lipase-catalyzed kinetic resolution of (±)-**2** using PCL, PFL, LAK and CRL was described. Enzymatic acylation of (±)-**2** by PCL provided (*R*)-**2** with 99% ee at conversion of 66%, while that by LAK provided (*S*)-**3** with 96% ee at conversion of 86%. Chemical transformation of (*R*)-**2** gave (*R*)-**1** in up to 99% ee.

Acknowledgements

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