Lipase-Catalyzed Practical Synthesis of (*R*)-1-Benzyl-3-hydroxy-2,5-pyrrolidinedione and Its Related Compounds

Hiroshi Tomori,† Kuniko Shibutani,†† and Katsuyuki Ogura*

Department of Applied Chemistry, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263

†Graduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263

††Process Development Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140

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A practical method for preparing (*R*)-1-benzyl-3-hydroxy-2,5-pyrrolidinedione (**1**) was investigated by the use of the enzymatic hydrolysis of its acetate (**2a**). Among several hydrolases examined here, lipase PS from *Pseudomonas cepacia* gave the best result: In a mixed solvent (1 : 1 v/v) of dioxane and a phosphate buffer (pH 7), the hydrolysis took place smoothly with a high enantioselectivity ($E > 3000$). Several 3-alkanoyl derivatives of **1** were subjected to the lipase PS-catalyzed hydrolysis. The chain length of the alkanoyl does not noticeably influence the reaction rate or the enantioselectivity. In contrast, the hydrolysis of the 1-benzoyl derivative proceeded slowly with a low enantioselectivity ($E = 19$). The syntheses of optically active 3-hydroxypyrrolidines and 3-hydroxypiperidines were also achieved under the reaction conditions similar to the lipase PS-catalyzed hydrolysis of **2a**.

Optically active 1-benzyl-3-hydroxy-2,5-pyrrolidinedione (**1**) and its acetate (**2a**) have proven to be versatile synthetic intermediates of various useful organic molecules. Various groups, starting from **1** and **2a**, have synthesized enantiomerically pure β-hydroxy-γ-amino acids,[1] β-substituted γ-lactones,[2] and 3-hydroxypyrrolidines[3—5] that serve as synthetic precursors of biologically active compounds such as κ-opioid receptor agonists,[4,6] calcium antagonist,[5] muscarin receptor antagonists,[7] antibiotic agents,[8] antihistamine,[9] and prolyl depsipeptides.[10] Many methods have thus been reported for the preparation of optically active **1** and **2a**. During our survey of these synthetic methods, we noticed that no practical method has been reported for preparing the (*R*)-enantiomers of **1** and **2a**, although their (*S*)-enantiomers are synthesized from easily available (*S*)-malic acid.[1—5] Since (*R*)-**1** and (*R*)-**2a** can be used in the pharmaceutical industry, our interest lay in the development of a convenient synthesis for them. Hence we initiated our study on the enzyme-catalyzed hydrolysis of racemic **2a**, which can be easily obtained from readily available, cheap racemic malic acid.[11] Here we report a practical preparation of (*R*)-**1** by an enzymatic hydrolysis of **2a** with lipase PS, where (*R*)-**1** and (*S*)-**2a** were simultaneously given in almost enantiomerically pure forms. We also examined whether this lipase PS-catalyzed hydrolysis is applicable to the synthesis of various derivatives of 3-hydroxypyrrolidine and 3-hydroxypiperidine.

Results and Discussion

For a lipase-catalyzed hydrolysis of the esters derived from secondary alcohols, an empirical rule was well established for their asymmetric induction:[12] The enantiomer depicted in Fig. 1, in which "M" represents a medium substituent and "L" represents a large substituent, undergoes hydrolysis predominantly. If this empirical rule is applied to the hydrolysis of 3-acetoxy-1-benzyl-2,5-pyrrolidinedione (**2a**), the large substituent (L) is $-C(=O)N(CH_2Ph)-$ and the medium substituent (M) is $-CH_2C(=O)-$, predicting the preferable production of the desired (*R*)-enantiomer of **1**.

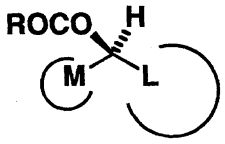


Fig. 1. Empirical rule that predicts which enantiomer reacts faster in the hydrolysis of the ester of a secondary alcohol with most hydrolases. This schematic, where "M" represents a medium substituent and "L" represents a large substituent, shows the favored enantiomer for esters.[24]

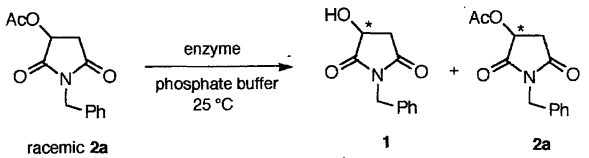
First the enzymatic hydrolysis of racemic **2a** was carried out with several lipases and a protease. To a solution of **2a** (0.40 mmol) in a phosphate buffer (2 ml) of pH 7 was added lipase PS from *Pseudomonas cepacia* (200 mg), and the resulting mixture was stirred at 25 °C. Removal of the enzyme, evaporation, and preparative TLC gave (*R*)-**1** together with (*S*)-**2a**. The enantiomeric excesses of **1** and **2a** were determined by the HPLC equipped with a chiral column. The conversion (*Conv*) of the reaction was calculated using the equation $Conv = ee_s/(ee_s + ee_p)$, and the enantioselectivity (E) was given by the equation $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$.[13] In a similar manner, we also examined the catalytic activity of six enzymes [lipase A from *Aspergillus niger*, pancreatin F from fog pancreas, lipase M from *Mucor javanicus*, newlase F form *Rhizopus*

niveus, CRL from *Candida rugosa* (Sigma Type VII), and PPL from porcine pancreas (Sigma Type II)] for hydrolysis of **2a**. The results are summarized in Table 1. Among the seven enzymes, lipase PS, CRL, and PPL gave (*R*)-**1** with good to high enantioselectivities ($E = 8$—560). In contrast, lipase A gave rise to favorable hydrolysis of the (*S*)-**2a**, but the enantioselectivity was poor ($E = 2$). These results indicated clearly that lipase PS is the most suitable enzyme for our purpose. The enantiopreference of lipase PS, CRL, and PPL for hydrolysis of **2a** is in accordance with the empirical rule mentioned above.

Next, we investigated an enantioselective transesterification of racemic **1** by the use of lipase PS and isopropenyl acetate as an enzyme and an acylating reagent, respectively. To a solution of racemic **1** (0.5 mmol) and isopropenyl acetate (2 mmol) in acetonitrile (2 ml) was added lipase PS (500 mg). Stirring of the resulting reaction mixture for 20 h at 25 °C produced (*S*)-**1** (49% yield) with 77.7% ee and (*R*)-**2a** (45% yield) with $> 99.5\%$ ee ($E > 940$). This reaction occurred efficiently in various aprotic solvents to give almost the same *E* value as summarized in Table 2. The enantioselectivities in all the cases were always high ($E > 450$). However, the reaction was so slow that a large amount of the lipase was required to increase the reaction rate up to a level for practical use. From an economical point of view, lipase PS-catalyzed hydrolysis of racemic **2a** is superior to the corresponding transesterification of racemic **1**. Therefore we investigated the lipase PS-catalyzed hydrolysis of racemic **2a** in detail.

Since the coexistence of a water-miscible organic solvent was reported[14] to accelerate the lipase-catalyzed hydrolysis and to enhance the enantioselectivity in some cases, we investigated the hydrolysis reaction in a 1 : 1 v/v mixture of the phosphate buffer (pH 7) and a water-miscible organic solvent. Among the examined cosolvents (Table 3), dioxane exhibited the most significant effect not only on the reaction rate but also on the enantioselectivity ($E > 3000$). On the contrary, other cosolvents examined herein reduced the

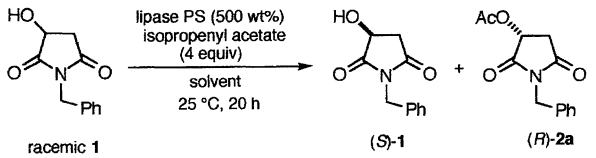
Table 1. Enantioselective Hydrolysis of **2a** Using Various Enzymes



Enzyme		Reaction	*Conv*[b]	% ee (config)		*E*
	wt%[a]	time/h	%	**1**	**2a**	
Lipase PS	200	5.5	51.7	93.4 (*R*)	100 (*S*)	560
CRL	100	5.5	48.3	78.3 (*R*)	73.1 (*S*)	18
PPL	100	2.5	18.1	74.4 (*R*)	16.4 (*S*)	8
Lipase A	100	5.5	52.1	29.6 (*S*)	32.2 (*R*)	2
Pancreatin F	100	2.0	No reaction			
Lipase M	100	2.0	No reaction			
Newlase F	100	19.0	No reaction			

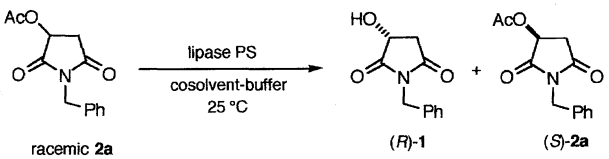
a) Percentage of enzyme by weight based on the substrate (**2a**).
b) Calculated by $Conv = ee_s/(ee_s + ee_p)$.[13]

Table 2. Lipase PS-Catalyzed Transesterification of Racemic **1** in Organic Solvents



Solvent	*Conv*	ee (%)		*E*
	%	(*S*)-**1**	(*R*)-**2a**	
Acetonitrile	43.8	77.7	>99.5	>940
IPE	43.6	77.0	>99.5	>930
Acetone	39.4	64.8	>99.5	>780
Toluene	34.7	52.8	>99.5	>670
THF	30.3	43.2	>99.5	>610
Dioxane	28.8	40.2	>99.5	>590
Chloroform	11.2	12.6	>99.5	>450

Table 3. Lipase PS-Catalyzed Hydrolysis of Racemic **2a** in Aqueous Media in the Presence of Organic Cosolvents



Cosolvent	Lipase PS	Reaction	*Conv*	ee (%)		*E*
	wt%	time/h	%	(*R*)-**1**	(*S*)-**2a**	
Dioxane	5	10.5	49.9	99.7	99.1	3380
Acetone	50	3.0	47.6	98.1	89.2	320
THF	50	2.0	47.1	98.0	87.1	280
Methanol	50	5.0	46.6	96.8	84.5	170
Acetonitrile	50	43.5	40.0	97.6	65.0	160
none	200	5.5	51.7	93.4	100	560

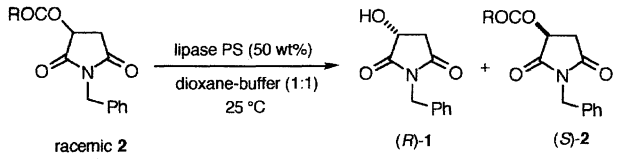
enantioselectivity (*E*).

Besides **2a** which has an acetoxyl group at the 3-position, we prepared various 3-acyloxyl derivatives (**2b**—**f**) of racemic **1** and subjected them to the lipase PS-catalyzed hydrolysis in order to evaluate the structural effect of 3-acyloxyl group. The results are listed in Table 4. In the cases of R = alkyl (**2b**—**e**), the chain length and the size of acyloxyl group had no noticeable effect on the enantioselectivity, whereas the reactivity (**2b** vs. **2c**) was influenced by the size to some extent. In the case of R = phenyl (**2f**), the hydrolysis reaction was very slow and the enantioselectivity was relatively low.

Judging from the data described above, we recommend these conditions for the enzymatic production of (*R*)-**1**: Racemic **2a** (2.0 g, 8.1 mmol) was treated with lipase PS (0.1 g) in a phosphate buffer (pH 7)–dioxane (1 : 1, 20 ml) at 25 °C for 10.5 h to give (*R*)-**1** (45% yield; 99.7% ee) and (*S*)-**2a** (47% yield; 99.1% ee). By crystallization, (*R*)-**1** could be easily isolated from the crude mixture in good yield. This implies that the present method is entirely practical.

The high enantioselectivity in the lipase PS-catalyzed hydrolysis of **2a** encouraged us to apply this method to preparing chiral derivatives of 3-hydroxypyrrolidine (**5**, X = H) and

Table 4. Lipase PS-Catalyzed Hydrolysis of Racemic **2b—f**



racemic **2** (*R*)-**1** (*S*)-**2**

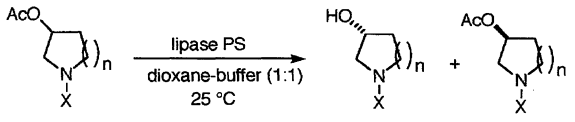
Substrate R	Reaction time/h	*Conv* %	ee (%) (*R*)-**1**	ee (%) (*S*)-**2**	*E*
C_2H_5 (**2b**)	2.5	49.8	98.2	97.5	490
i-C_3H_7 (**2c**)	8.0	46.9	>99.5	87.8	>1100
n-C_5H_{11} (**2d**)	2.0	47.2	>99.5	89.0	>1200
n-$C_{11}H_{23}$ (**2e**)	2.0	50.0	>99.5	>99.5	>2300
C_6H_5 (**2f**)	140	10.8	88.9	10.8	19

3-hydroxypiperidine (**6**, X = H), useful intermediates for the synthesis of several biologically active molecules.[15] Compounds **3a—c** and **4a—c** in Table 5 were subjected to the lipase PS-catalyzed hydrolysis.[16] All the formed alcohols (**5a—c**, **6a**, and **6b**) have *R* configuration with more than 96% enantiomeric excess. The enantioselectivity was high ($E > 200$) in the reactions of **3a**, **3b**, **4a**, and **4b**, but somewhat low in the reaction of **3c**. This is probably because, in the latter case, a nonenzymatic hydrolysis reaction occurred during the prolonged reaction (140 h). These results demonstrate that the present method using lipase PS is also effective for the kinetic resolution of **3a**, **3b**, **4a**, and **4b**. It is apparent from Table 5 that the five-membered ring compounds are more reactive than the corresponding compounds with six-membered ring (**3a** vs. **4a**, **3b** vs. **4b**, and **3c** vs. **4c**). In the literature,[16c] an enzymatic hydrolysis of 3-acyloxy-1-benzylpyrrolidines by lipoprotein lipase (LPL Amano 3) was described. The examination of the data reported therein showed that the lipoprotein lipase exhibits higher activity (a smaller amount of the enzyme) and somewhat lower enantioselectivity (98% ee of (*R*)-**5a**) for **3a** than the present lipase PS.

The data shown in Table 5 suggested that the reactivities of **3** and **4** were mainly influenced by the ability of the *N*-substituent to form a hydrogen bond. Recently, the detailed mechanisms for lipase-catalyzed reactions to predict their chiral preferences were clarified by high-resolution X-ray analyses for the crystal structures of several hydrolases[17—23] and the covalent complex of CRL[24] that is a transition-state analog of the hydrolysis reaction. In the lipase, the carbonyl group of the substrate (esters) is activated by hydrogen bonding with the amide NH of an oxyanion hole to facilitate the neucleophilic attack by the OH group of serine in the neighborhood. This mechanism may be applicable to the present hydrolysis reaction. If the *N*-substituent of **3** or **4** forms hydrogen bonding in the oxyanion hole of lipase PS, two different complexes **A** and **B** may coexist in equilibrium as depicted in Scheme 1. In the complex **B**, the acetoxyl group is too far from the serine OH group to be hydrolyzed. In case of **3a** with *N*-benzyl group, the acetoxyl group binds preferably with the oxyanion hole of lipase PS to be hydrolyzed. In the reaction of **3c**, the *N*-benzoyl group forms a hydrogen bond more tightly than the acetoxyl group to decrease the reaction rate. A similar tendency was observed for 3-hydroxypiperidine derivatives (**4a—4c**). It is worth noting that lipase PS-catalyzed hydrolysis of 4-acetoxy-1-benzyl-2-pyrrolidone (**7**),[25] where the amide carbonyl group was expected to form a strong hydrogen bond, did not take place. This is probably attributable to the predominant hydrogen bonding of the amide carbonyl with the oxyanion hole of lipase PS so as to locate the acetoxyl group far from the serine OH group. The structure-reactivity relationship revealed in this study will help to design substrates that are suitable for the lipase-catalyzed reactions.

In conclusion, an efficient kinetic resolution of racemic **2a** was achieved by lipase PS-catalyzed hydrolysis reaction to provide a practical synthetic method of (*R*)-**1**. This methodology is applicable to the synthesis of optically active 3-hydroxypyrrolidines and 3-hydroxypiperidines.

Table 5. Lipase PS-Catalyzed Hydrolysis of **3a—c** and **4a—c**

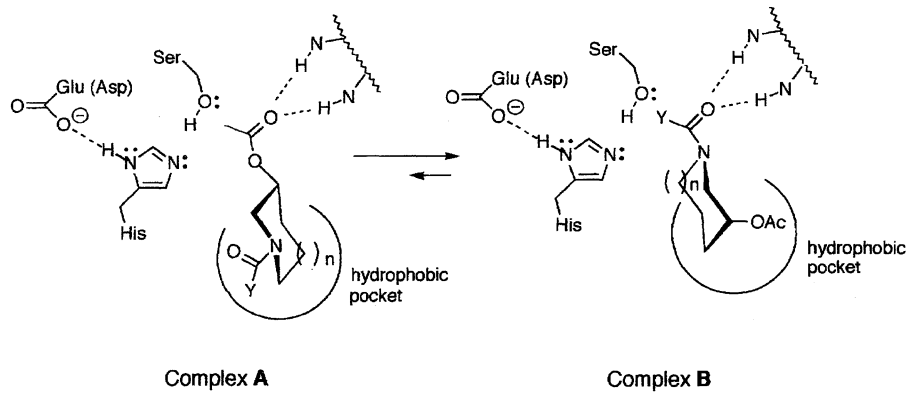


3: n = 1 **4**: n = 2 (*R*)-**5**: n = 1 (*R*)-**6**: n = 2 (*S*)-**3** (*S*)-**4**

a: $X=CH_2Ph$ b: $X=CO_2CH_2Ph$ c: X=COPh

Acetate	Lipase wt%	Reaction time/h	*Conv* %	(*R*)-**5,6** % Yield[a]	(*R*)-**5,6** % ee	(*R*)-**5,6** % Yield[a]	(*R*)-**5,6** % ee	*E*
3a	50	24	50.0	40	>99.5	45	>99.5	>2390
3b	50	24	48.7	44	97.4	46	92.4	260
3c	100	144	26.9	22	96.1	69	35.3	70
4a	50	74	46.6	47	98.2	43	85.6	300
4b	100	90	48.2	50	98.6	49	91.9	470
4c	100	7	No reaction					

a) Isolated yield.



Complex **A** Complex **B**

Scheme 1. Binding model of (*R*)-**3b**, **3c**, **4b**, or **4c** in the active site of lipase PS.

Experimental

Melting points were determined with a Yamato MP-21 melting point apparatus or a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined with a Horiba SEPA-300 polarimeter or a JASCO DIP-370 polarimeter. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX 400 (400 MHz) spectrometer, and chemical shifts were reported in ppm relative to tetramethylsilane as an internal standard. Infrared spectra were run on a JASCO IR-810 or JASCO FT/IR-8900 spectrometer. Column chromatography was performed on a pre-packed glass column (Merck, LiChroprep Si 60, ϕ 25×310 mm), unless otherwise noted. Preparative thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F_{254}, 2 mm). Reactions were monitored by HPLC equipped with a reversed-phase column, Shiseido Capcell Pak C18 SG 120 (ϕ 4.6×250 mm). Lipase PS from *Pseudomonas cepacia*, lipase A from *Aspergillus niger*, pancreatin F from fog pancreas, lipase M from *Mucor javanicus*, and newlase F from *Rhizopus niveus* were provided by Amano Pharmaceutical Co. CRL from *Candida rugosa* (Sigma Type VII) and PPL from porcine pancreas (Sigma Type II) were purchased from Sigma Chemical Co. All chemicals used were reagent grade.

Preparation of 3-Acetoxy-1-benzyl-2,5-pyrrolidinedione (2a). A suspension of (±)-malic acid (20.0 g, 0.149 mol) and acetyl chloride (60 ml) was refluxed for 2 h. The resulting clear solution was concentrated in vacuo to give crude *O*-acetyl malic anhydride. The anhydride was dissolved in CH_3CN (50 ml), and a solution of benzylamine (16.2 g, 0.151 mol) in CH_3CN (20 ml) was added dropwise at from 0 to 10 °C. Then the mixture was warmed up to room temperature and stirred for 1 h. After concentration, the residue was refluxed again with acetyl chloride (12 ml) for 2.5 h. Excess acetyl chloride was removed by evaporation, and the residue was dissolved in toluene (236 ml). The toluene layer was washed with 5% aqueous $NaHCO_3$ (100 ml) and water (50 ml), dried over Na_2SO_4, and evaporated to give 37.3 g (quantitative) of **2a** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ = 2.16 (s, 3H, CH_3), 2.67 (dd, J = 5.0 and 18.3 Hz, 1H, $CH_2C(=O)N$), 3.17 (dd, J = 8.8 and 18.3 Hz, 1H, $CH_2C(=O)N$), 4.69 (d, J = 14.1 Hz, 1H, NCH_2Ph), 4.72 (d, J = 14.1 Hz, 1H, NCH_2Ph), 5.45 (dd, J = 5.0 and 8.8 Hz, 1H, *CH*(OAc)), 7.26—7.40 (m, 5H, Ar*H*); IR (neat) 1750, 1720, 1400, 1250, 1225 cm^{-1}. These spectral data were in agreement with those reported for the (*S*)-enantiomer.[2a)]

Preparation of 1-Benzyl-3-hydroxy-2,5-pyrrolidinedione (1). A suspension of (±)-malic acid (50.0 g, 0.373 mol) and benzylamine (39.6 g, 0.370 mol) in ethanol (150 ml) was heated for 3 h in an oil bath (160—170 °C), while gradually removing the ethanol and the formed water by distillation. This mixture was cooled to room temperature. After the residue was dissolved in CH_2Cl_2 (400 ml), the resulting solution was washed successively with 3% aqueous $NaHCO_3$, with water, with dil hydrochloric acid, and with water. Evaporation followed by recrystallization from toluene afforded **1** (38.9 g; 51% yield) as colorless crystals: Mp 113—114 °C (toluene) (lit,[26)] mp 113—114 °C); ^{1}H NMR ($CDCl_3$) δ = 2.68 (dd, J = 4.9 and 18.2 Hz, 1H, $CH_2C(=O)N$), 3.07 (dd, J = 8.5 and 18.2 Hz, 1H, $CH_2C(=O)N$), 3.19 (br d, J = 2.8 Hz, 1H, O*H*), 4.60—4.64 (m, 1H, *CH*(OH)), 4.66 (s, 2H, NCH_2Ph), 7.26—7.38 (m, 5H, Ar*H*); IR (KBr) 3367, 1687, 1434, 1344, 1179 cm^{-1}. These physical data for this compound agreed with those reported.[26)]

Hydrolysis of 2a by Lipase PS. To a solution of **2a** (100 mg, 0.404 mmol) in a phosphate buffer (1/15 M (1 M = 1 mol dm^{-3}), pH 7.0, 2 ml) was added lipase PS (200 mg). After the mixture was stirred at 25 °C for 5.5 h, insoluble materials were filtered off through a Celite pad and washed with acetone. The filtrate and the washing were combined and concentrated in vacuo. After ethyl acetate (10 ml) and water (5 ml) were added, the organic layer was separated, evaporated in vacuo, and separated by preparative TLC (CH_2Cl_2/ethyl acetate, 10 : 1) to give (*R*)-**1** with 93.4% ee (33 mg; 40% yield) and (*S*)-**2a** with 100% ee (34 mg; 34% yield). The enantioselectivity (*E*) and the conversion (*Conv*) were calculated to be 560 and 51.7%, respectively. The enantiomeric excesses of **1** and **2a** were measured by HPLC.

1: Column, Daicel Chiralpak AS (ϕ 4.6×250 mm); eluent, isopropyl alcohol (IPA)/hexane (1 : 6); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**1** 31.1 min, (*S*)-**1** 27.7 min.

2a: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 2); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**2a** 38.4 min, t_R of (*S*)-**2a** 40.7 min.

In a similar manner, **2a** was treated with CRL, PPL, and lipase A. The results are summarized in Table 1.

Hydrolysis of **2a** by pancreatin F, lipase M, or newlase F was carried out in a similar manner, but no hydrolyzed product was detected by HPLC analysis, as shown in Table 1.

Lipase PS-Catalyzed Transesterification of 1. To a solution of **1** (103 mg, 0.502 mmol) and isopropenyl acetate (0.22 ml, 2.0 mmol) in acetonitrile (2 ml) was added lipase PS (500 mg). After the mixture was stirred for 20 h at 25 °C, insoluble materials were filtered off through a Celite pad and washed with CH_2Cl_2. The filtrate and the washing were combined, concentrated in vacuo, and subjected to preparative TLC (CH_2Cl_2/ethyl acetate, 10 : 1) to give (*S*)-**1** with 77.8% ee (51 mg; 49% yield) and (*R*)-**2a** with > 99.5% ee (55 mg; 45% yield) (*Conv* = 43.8%, *E* > 940).

In a similar manner, transesterification of **1** (103 mg, 0.502 mmol) was carried out in various solvents (2 ml) to afford (*S*)-**1** and (*R*)-**2a**. The enantiomeric excesses of these products are given in Table 2, which also shows the *E* values and the conversions of the reaction.

Lipase PS-Catalyzed Hydrolysis of 2a in Aqueous Media Containing a Cosolvent. To a solution of **2a** (100 mg, 0.404 mmol) in a 1 : 1 mixture (2 ml) of a phosphate buffer (pH 7.0, 1/15 M)–acetone was added lipase PS (50 mg). After the mixture was stirred at 25 °C for 3 h, insoluble materials were filtered off through a Celite pad and washed with acetone. The filtrate and the washing were combined and concentrated in vacuo. After ethyl acetate (10 ml) and water (5 ml) were added, the organic layer was separated, evaporated in vacuo, and subjected to preparative TLC (CH_2Cl_2/ethyl acetate, 10 : 1) to give (*R*)-**1** with 98.1% ee (31 mg; 40% yield) and (*S*)-**2a** with 89.2% ee (44 mg; 44% yield) (*Conv* = 47.6%, *E* = 320).

Similarly, **2a** (100 mg, 0.404 mmol) was treated with lipase PS (50 mg) in a 1 : 1 mixture (2 ml) of a phosphate buffer (1/15 M, pH 7.0) and other cosolvent to afford (*R*)-**1** and (*S*)-**2a**. The results of the reaction are given in Table 3.

Optimal Conditions for Lipase PS-Catalyzed Hydrolysis of 2a. A solution of **2a** (2.00 g, 8.09 mmol) and lipase PS (100 mg) in a 1 : 1 mixture (20 ml) of a phosphate buffer (1/15 M, pH 7.0) and dioxane was stirred for 10.5 h at 25 °C. Insoluble materials were filtered off through a Celite pad and washed with acetone. After the filtrate and the washing were combined and concentrated in vacuo to ca. 7 ml, water (10 ml) was added. The resulting solution was extracted with ethyl acetate (45 ml) and the organic extract was washed with water (10 ml), dried (Na_2SO_4), and evaporated in vacuo. The residue was dissolved in toluene (5 ml) and allowed to stand at room temperature. The precipitates were collected by filtration, washed with a small amount of toluene, and dried to give 0.53 g (32%) of (*R*)-**1** with 99.8% ee. The filtrate was evaporated and the residue was purified by column chromatography (ethyl acetate/hexane, 1 : 2 and then 1 : 1) to afford (*S*)-**2a** with 99.1% ee (0.94 g; 47% yield) and (*R*)-**1** with 99.4% ee (0.22 g; 13% yield) (*Conv* = 49.9%, *E* = 3380).

(*S*)-2a: Mp 59—60 °C; $[\alpha]_D^{20}$ −42.4° (*c* 0.50, methanol) [lit,[1b] mp 58—60 °C; $[\alpha]_D^{20}$ −42° (*c* 1.18, methanol)]; IR (Nujol) 1760, 1705, 1430, 1405, 1225 cm^{-1}. The ^1H NMR spectrum was identical with that of racemic **2a**.

(*R*)-1: Mp 106—107 °C; $[\alpha]_D^{20}$ +62.7° (*c* 0.50, methanol) [lit,[5] mp 99—101 °C; $[\alpha]_D^{20}$ of (*S*)-**1**: −51.1° (*c* 1, methanol); 80% ee]. The ^1H NMR and IR spectra of this compound were in accordance with those of racemic **1**.

Acylation of 1 with Propionic Anhydride. To a mixture of **1** (0.41 g, 2.0 mmol), pyridine (0.21 ml, 2.6 mmol), and DMAP (4-dimethylaminopyridine) (12 mg, 0.10 mmol) in CH_2Cl_2 (4 ml) was added propionic anhydride (0.30 ml, 2.4 mmol) under ice-cooling. After stirring over night at room temperature and addition of CH_2Cl_2 (4 ml), the solution was successively washed with 1 M hydrochloric acid, with 1% aqueous $NaHCO_3$, and with water. Then the solution was dried (Na_2SO_4) and concentrated in vacuo to yield 0.48 g (92%) of 1-benzyl-3-propionyloxy-2,5-pyrrolidinedione (**2b**) as a colorless oil: ^1H NMR ($CDCl_3$) δ = 1.17 (t, *J* = 7.4 Hz, 3H, CH_3), 2.41 (dq, *J* = 16.9 and 7.4 Hz, 1H, CH_2CH_3), 2.45 (dq, *J* = 16.9 and 7.4 Hz, 1H, CH_2CH_3), 2.66 (dd, *J* = 4.6 and 18.4 Hz, 1H, $CH_2C(=O)N$), 3.16 (dd, *J* = 8.7 and 18.4 Hz, 1H, $CH_2C(=O)N$), 4.69 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 4.72 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 5.47 (dd, *J* = 4.6 and 8.7 Hz, 1H, $CH(OCOC_2H_5)$), 7.26—7.41 (m, 5H, Ar*H*); IR (neat) 1747, 1715, 1400, 1340, 1165 cm^{-1}. Found: C, 64.42; H, 5.91; N, 5.31%. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36%.

1-Benzyl-3-isobutyryloxy-2,5-pyrrolidinedione (2c): Colorless crystals; mp 76—77 °C (isopropyl ether–hexane); ^1H NMR ($CDCl_3$) δ = 1.20 (d, *J* = 6.9 Hz, 3H, CH_3), 1.21 (d, *J* = 6.9 Hz, 3H, CH_3), 2.64 (septet, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 2.64 (dd, *J* = 5.0 and 18.3 Hz, 1H, $CH_2C(=O)N$), 3.16 (dd, *J* = 8.7 and 18.3 Hz, 1H, $CH_2C(=O)N$), 4.69 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 4.73 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 5.45 (dd, *J* = 5.0 and 8.7 Hz, 1H, $CH(OCOCH)$), 7.26—7.41 (m, 5H, Ar*H*); IR (KBr) 1745, 1712, 1428, 1183, 1151 cm^{-1}. Found: C, 65.32; H, 6.24; N, 5.08%. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09%.

1-Benzyl-3-hexanoyloxy-2,5-pyrrolidinedione (2d): Colorless oil; ^1H NMR ($CDCl_3$) δ = 0.90 (t, *J* = 6.9 Hz, 3H, CH_3), 1.27—1.37 (m, 4H, $(CH_2)_2CH_3$), 1.65 (quintet, *J* = 7.4 Hz, 2H, $C(=O)CH_2CH_2$), 2.38 (dt, *J* = 18.0 and 7.4 Hz, 1H, $OC(=O)CH_2$), 2.41 (dt, *J* = 18.0 and 7.4 Hz, 1H, $OC(=O)CH_2$), 2.65 (dd, *J* = 4.7 and 18.3 Hz, 1H, $CH_2C(=O)N$), 3.16 (dd, *J* = 8.8 and 18.3 Hz, 1H, $CH_2C(=O)N$), 4.69 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 4.72 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 5.45 (dd, *J* = 4.7 and 8.8 Hz, 1H, $CH(OCOCH_2)$), 7.26—7.41 (m, 5H, Ar*H*); IR (neat) 1741, 1718, 1400, 1344, 1160 cm^{-1}. Found: C, 67.23; H, 7.11; N, 4.61%. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62%.

3-Benzoyloxy-1-benzyl-2,5-pyrrolidinedione (2f). In a similar manner, **2f** was obtained in 96% yield from **1** as colorless crystals: Mp 93—94 °C (toluene–isopropyl ether); ^1H NMR ($CDCl_3$) δ = 2.82 (dd, *J* = 4.7 and 18.4 Hz, 1H, $CH_2C(=O)N$), 3.28 (dd, *J* = 8.8 and 18.4 Hz, 1H, $CH_2C(=O)N$), 4.74 (d, *J* = 14.0 Hz, 1H, NCH_2Ph), 4.77 (d, *J* = 14.0 Hz, 1H, NCH_2Ph), 5.68 (dd, *J* = 4.7 and 8.8 Hz, 1H, $CH(OCOPh)$), 7.26—7.63 (m, 8H, Ar*H*), 8.04—8.06 (m, 2H, Ar*H*); IR (KBr) 1727, 1710, 1407, 1264, 1114 cm^{-1}. Found: C, 70.07; H, 5.14; N, 4.54%. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53%.

1-Benzyl-3-dodecanoyloxy-2,5-pyrrolidinedione (2e). Similarly **1** (0.82 g, 4.0 mmol) was subjected to the reaction with lauroyl chloride (1.02 ml, 4.41 mmol). After evaporation of the reaction mixture and addition of isopropyl ether and water, the organic layer was separated. Evaporation in vacuo and purification by column chromatography (ethyl acetate/hexane, 1 : 6) afforded **2e** (1.33 g; 86% yield) as a colorless solid: Mp 52—53 °C; ^1H NMR ($CDCl_3$) δ = 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.17—1.38 (m, 16H, $(CH_2)_8CH_3$), 1.64 (quintet, *J* = 7 Hz, 2H, $C(=O)CH_2CH_2$), 2.38 (dt, *J* = 16 and 7 Hz, 1H, $OC(=O)CH_2$), 2.41 (dt, *J* = 16 and 7 Hz, 1H, $OC(=O)CH_2$), 2.65 (dd, *J* = 4.6 and 18.3 Hz, 1H, $CH_2C(=O)N$), 3.16 (dd, *J* = 8.8 and 18.3 Hz, 1H, $CH_2C(=O)N$), 4.69 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 4.72 (d, *J* = 14.1 Hz, 1H, NCH_2Ph), 5.45 (dd, *J* = 4.6 and 8.8 Hz, 1H, $CH(OCOCH_2)$), 7.26—7.41 (m, 5H, Ar*H*); IR (KBr) 2920, 1754, 1745, 1717, 1159 cm^{-1}. Found: C, 71.26; H, 8.73; N, 3.61%. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61%.

Lipase PS-Catalyzed Hydrolysis of 2b. A solution of **2b** (100 mg, 0.383 mmol) and lipase PS (50 mg) in a 1 : 1 mixture (2 ml) of a phosphate buffer (1/15 M, pH 7.0) and dioxane was stirred for 2.5 h at 25 °C. Insoluble materials were removed by filtration through a Celite pad and washed with acetone. After the filtrate and the washing were combined and concentrated in vacuo, ethyl acetate (10 ml) and water (5 ml) were added. The organic layer was separated, evaporated in vacuo, and subjected to preparative TLC (CH_2Cl_2/ethyl acetate, 10 : 1) to give (*R*)-**1** with 98.2% ee (24 mg; 31% yield) and (*S*)-**2b** with 97.5% ee (34 mg; 34% yield) (*Conv* = 49.8%, *E* = 490).

(*S*)-2b:[27] Colorless oil; $[\alpha]_D^{20}$ −37.1° (*c* 0.19, methanol). The enantiomeric excess of **2b** was measured by HPLC: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 2);

flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**2b** 24.8 min, t_R of (*S*)-**2b** 27.3 min.

Similarly, **2c**, **2d**, **2e**, and **2f** were treated with lipase PS (50 mg) in a 1 : 1 mixture (2 ml) of a phosphate buffer (1/15 M, pH 7.0) and dioxane at 25 °C. The results are summarized in Table 4.

(*S*)-2c: Colorless solid; mp 79.5—81.5 °C; $[\alpha]_D^{20}$ −35.4° (*c* 0.13, methanol). After it was hydrolyzed with 1 M HCl in methanol to give (*S*)-**1**, the enantiomeric excess was determined.

(*S*)-2d:[27] Colorless oil; $[\alpha]_D^{20}$ −41.5° (*c* 0.22, methanol). Its enantiomeric excess was measured with HPLC: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 2); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**2** 27.1 min, t_R of (*S*)-**2d** 31.5 min.

(*S*)-2e:[27] Colorless solid; mp 45.5—46.5 °C; $[\alpha]_D^{20}$ −38.3° (*c* 0.22, methanol). The conditions for HPLC analysis of **2e**: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 30); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**2e** 18.7 min, t_R of (*S*)-**2e** 21.5 min.

(*S*)-2f:[27] Colorless oil; $[\alpha]_D^{20}$ −5.9° (*c* 0.24, methanol). The enantiomeric excess of **2f** was measured under the following HPLC conditions: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 2); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**2f** 47.4 min, t_R of (*S*)-**2f** 53.9 min.

Preparation of 3-Acetoxy-1-benzylpyrrolidine (3a). To a mixture of commercially available 1-benzyl-3-hydroxypyrrolidine (**5a**) (1.772 g, 10.00 mmol), pyridine (1.21 ml, 15.0 mmol), and DMAP (37 mg, 0.30 mmol) in CH_2Cl_2 (18 ml) was added acetic anhydride (1.32 ml, 14.0 mmol). The resulting mixture was stirred for 3 h at room temperature, and then CH_2Cl_2 (18 ml) was added. After washing with 5% aqueous Na_2CO_3 (15 ml) and with water (2×10 ml), the solution was dried (Na_2SO_4) and evaporated in vacuo to give **3a** (2.11 g; 96% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ = 1.80—1.90 (m, 1H, CH(OAc)C*H*$_2$), 2.03 (s, 3H, OCOC*H*$_3$), 2.20—2.32 (m, 1H, CH(OAc)C*H*$_2$), 2.38—2.48 (m, 1H, C*H*$_2$N(Bn)C*H*$_2$), 2.62—2.68 (m, 1H, C*H*$_2$N(Bn)C*H*$_2$), 2.73—2.85 (m, 2H, C*H*$_2$N(Bn)C*H*$_2$), 3.58 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$Ph), 3.68 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$Ph), 5.14—5.21 (m, 1H, C*H*(OAc)), 7.21—7.40 (m, 5H, Ar*H*); IR (neat) 2793, 1739, 1373, 1246, 700 cm^{-1}. These data were identical with those reported in the literature.[16a]

Preparation of 3-Acetoxy-1-(benzyloxycarbonyl)pyrrolidine (3b). A solution of benzyl chloroformate (1.96 g, 11.5 mmol) in THF (2 ml) was added to a stirred mixture of commercially available 3-hydroxypyrrolidine (1.00 g, 11.5 mmol) and $NaHCO_3$ (1.25 g, 14.9 mmol) in THF–water (1 : 1, 10 ml). The solution was further stirred for 2 h at room temperature, then CH_2Cl_2 (20 ml) and 5% aqueous Na_2CO_3 (5 ml) were added. The organic layer was separated, washed with water (5 ml), dried (Na_2SO_4), and concentrated in vacuo to afford crude 1-benzyloxycarbonyl-3-hydroxypyrrolidine (**5b**) as a colorless oil (2.26 g). Thus, a mixture of the crude **5b** (1.50 g), pyridine (0.95 ml, 12 mmol), DMAP (29 mg, 0.24 mmol), and acetic anhydride (0.89 ml, 9.4 mmol) in CH_2Cl_2 (15 ml) was stirred for 4 h at ambient temperature. The solution was diluted with CH_2Cl_2 (15 ml), washed with 5% aqueous Na_2CO_3 (15 ml) and water (10 ml), dried (Na_2SO_4), and concentrated to dryness. Column chromatography (ethyl acetate/hexane, 1 : 2) of the residue gave 1.57 g (88% overall yield in two steps) of **3b** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ = 2.05 (s, 3H, OCOC*H*$_3$), 1.98—2.18 (m, 2H, CH(OAc)C*H*$_2$), 3.43—3.71 (m, 4H, C*H*$_2$NC*H*$_2$), 5.13 (d, *J* = 13.1 Hz, 1H, OC*H*$_2$Ph), 5.17 (d, *J* = 13.1 Hz, 1H, OC*H*$_2$Ph), 5.29 (br m, 1H, C*H*(OAc)), 7.28—7.48 (m, 5H, Ar*H*); IR (neat) 1740, 1706, 1421, 1245, 1226 cm^{-1}. Found: C, 63.87; H, 6.54; N, 5.32%. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32%.

Preparation of 3-Acetoxy-1-benzoylpyrrolidine (3c). To a solution of 3-hydroxypyrrolidine (1.00 g, 11.5 mmol) and pyridine (1.36 g, 17.2 mmol) in CH_2Cl_2 (10 ml) was added benzoic anhydride (2.60 g, 11.5 mmol) under ice-cooling. After being stirred for 4 h at room temperature, the mixture was diluted with CH_2Cl_2 (10 ml) and washed successively with water (10 ml), with 5% aqueous Na_2CO_3 (15 ml), and with water (5 ml). The resulting solution was dried (Na_2SO_4) and evaporated in vacuo to give 1.54 g of crude 1-benzoyl-3-hydroxypyrrolidine (**5c**). A mixture of the crude **5c** (1.30 g), pyridine (0.83 ml, 10 mmol), DMAP (25 mg, 0.20 mmol), and acetic anhydride (0.77 ml, 8.2 mmol) in CH_2Cl_2 (15 ml) was stirred for 4 h at an ambient temperature. The solution was diluted with CH_2Cl_2 (10 ml), washed with 5% aqueous Na_2CO_3 (15 ml) and water (10 ml), dried (Na_2SO_4), and concentrated to dryness. Column chromatography (ethyl acetate/hexane, 1 : 1) of the residue gave **3c** (1.57 g; 88% overall yield in two steps) as a colorless oil which consisted of two conformers in a ratio of 1 : 1: ^{1}H NMR ($CDCl_3$) δ = 2.03 (s, 3H×0.5, OCOC*H*$_3$), 2.10 (s, 3H×0.5, OCOC*H*$_3$), 2.00—2.25 (m, 2H, CH(OAc)C*H*$_2$), 2.47—3.93 (m, 4H, C*H*$_2$NC*H*$_2$), 5.25 (br m, 1H×0.5, C*H*(OAc)), 5.41 (br m, 1H×0.5, C*H*(OAc)), 7.40—7.56 (m, 5H, Ar*H*); IR (neat) 1738, 1731, 1622, 1427, 1241 cm^{-1}. Found: C, 66.81; H, 6.38; N, 6.19%. Calcd for $C_{13}H_{15}NO_4$: C, 66.94; H, 6.48; N, 6.01%.

Lipase PS-Catalyzed Hydrolysis of 3a. A solution of **3a** (1.500 g, 6.841 mmol) and lipase PS (0.75 g) in a 1 : 1 mixture (15 ml) of a phosphate buffer (1/15 M, pH 7.0) and dioxane was stirred at 25 °C for 24 h. After insoluble materials were filtered off through a Celite pad and washed with acetone, the filtrate and the washing were combined and concentrated in vacuo. A 5% aqueous $NaHCO_3$ (20 ml) was added and the resulting solution was extracted with ethyl acetate (2×30 ml). The combined organic extracts were washed with 20% aqueous NaCl (10 ml), dried (Na_2SO_4), and evaporated in vacuo. Column chromatography of the residue using ethyl acetate–hexane (1 : 2) and ethyl acetate–methanol (4 : 1) as eluents afforded (*S*)-**3a** with > 99.5% ee (0.680 g; 45% yield) and (*R*)-**5a** with > 99.5% ee (0.485 g; 40% yield) (*Conv* = 50.0%, *E* > 2390). The enantiomeric excesses of **3a** and **5a** were measured by HPLC equipped with Daicel Chiralcel OJ (ϕ 4.6×250 mm): eluent, IPA/hexane (1 : 50); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**3a** 18.4 min, t_R of (*S*)-**3a** 16.5 min, t_R of (*R*)-**5a** 37.1 min, t_R of (*S*)-**5a** 33.1 min.

(*S*)-3a: Colorless oil; $[\alpha]_D^{20}$ −23.0° (*c* 1.00, methanol) [lit,[16b] $[\alpha]_D^{20}$ of (*R*)-**3a**: +20.0° (*c* 5.3, methanol)].

(*R*)-5a: Pale yellow oil; $[\alpha]_D^{20}$ +3.87° (*c* 0.50, methanol) [lit,[5] $[\alpha]_D^{20}$ +3.76° (*c* 5, methanol)]. The ^{1}H NMR and IR spectra of these compounds were identical with those of the corresponding racemates.

In a similar manner, **3b** and **3c** were hydrolyzed with lipase PS. The results are given in Table 5. The enantiomeric excesses were measured by HPLC equipped with Daicel Chiralpak AS (ϕ 4.6×250 mm). **3b**: Eluent, IPA/hexane (1 : 20); flow rate, 0.8 ml min^{-1}; t_R of (*R*)-**3b** 53.6 min; t_R of (*S*)-**3b** 47.2 min. **5b**: Eluent, IPA/hexane (1 : 20); flow rate, 1.0 ml min^{-1}; t_R of (*R*)-**5b** 43.4 min, t_R of (*S*)-**5b** 35.5 min. **3c** and **5c**: Eluent, IPA/hexane (1 : 6); flow rate, 1.0 ml min^{-1}; t_R of (*R*)-**3c** 57.9 min, t_R of (*S*)-**3c** 74.4 min, t_R of (*R*)-**5c** 37.9 min, t_R of (*S*)-**5c** 47.0 min.

(*S*)-3b:[28] Colorless oil; $[\alpha]_D^{20}$ +16.1° (*c* 1.56, methanol). The ^{1}H NMR and IR spectra for this compound were in agreement with those of its racemate.

(*R*)-5b: Colorless solid; mp 77—79 °C; $[\alpha]_D^{20}$ −23.7° (*c* 1.24, methanol). [lit,[29] $[\alpha]_D^{20}$ of (*S*)-**5b**: +23.85° (*c* 0.85, methanol)]; ^{1}H NMR ($CDCl_3$) δ = 1.68 (br s, 1H, O*H*), 1.86—2.09 (m, 2H, CH(OH)C*H*$_2$), 3.38—3.67 (m, 4H, C*H*$_2$NC*H*$_2$), 4.48 (m, 1H,

CH(OH)), 5.14 (s, 2H, OCH_2Ph), 7.28—7.43 (m, 5H, ArH); IR (KBr) 3360, 1667, 1434, 1350, 1128 cm^{-1}. These spectral data for this compound were in good agreement with those reported in the literature.[29]

(*S*)-3c:[28] Colorless solid; mp 80—94 °C; $[\alpha]_D^{20}$ +26.0° (*c* 1.08, methanol). The ^{1}H NMR and IR spectra of this compound were in agreement with those of its racemate.

(*R*)-5c: That was shown by ^{1}H NMR to be a 1 : 1 mixture of two conformers: Colorless solid; mp 108—113 °C; $[\alpha]_D^{20}$ −84.6° (*c* 1.06, methanol); ^{1}H NMR ($CDCl_3$) δ = 1.85—2.37 (m, 3H, CH(OH)CH_2), 3.33—3.90 (m, 4H, CH_2NCH_2), 4.40 (br m, 1H×0.5, CH(OH)), 4.58 (br m, 1H×0.5, CH(OH)), 7.29—7.64 (m, 5H, ArH); IR (KBr) 3360, 1610, 1580, 1455, 1440 cm^{-1}. The ^{1}H NMR and IR spectra of this compound were in good agreement with those reported in the literature.[30] The absolute configuration was confirmed by comparison of its optical rotation with that of an authentic sample derived from (*R*)-3-hydroxypyrrolidine.

Preparation of 3-Acetoxy-1-benzylpiperidine (4a). To a solution of commercially available 3-hydroxypiperidine (5.06 g, 50.0 mmol) in methanol (50 ml) was dropwise added benzyl bromide (5.95 ml, 50.0 mmol) over 40 min. The resulting mixture was stirred for 1 h at 40 °C and then refluxed for 2 h. After concentration in vacuo and addition of 4 M aqueous NaOH (20 ml), the mixture was extracted with toluene (2×50 ml), dried (Na_2SO_4), and evaporated in vacuo to give crude 1-benzyl-3-hydroxypiperidine (**6a**) (7.51 g) as a yellow oil. A mixture of crude **6a** (1.91 g) and acetic anhydride (1.04 ml, 11.0 mmol) in toluene (15 ml) was heated at 90 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with toluene (25 ml), and washed with aqueous K_2CO_3 (1 M; 10 ml). The solution was evaporated and purified by chromatography on silica gel (Kieselgel 60, 70—270 mesh; ethyl acetate/hexane, 1 : 4) to afford **4a** (1.85 g; 62% overall yield in two steps) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ = 1.1—2.9 (m, 8H, CH_2N(CH_2)$_3$), 2.04 (s, 3H, OCOCH_3), 3.57 (s, 2H, NCH_2Ph), 4.88 (br m, 1H, CH(OAc)), 7.2—7.5 (m, 5H, ArH); IR (neat) 1735, 1370, 1240, 1044, 1033 cm^{-1}. Found: C, 72.04; H, 8.31; N, 6.04%. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%.

Preparation of 3-Acetoxy-1-(benzyloxycarbonyl)piperidine (4b). To a mixture of 3-hydroxypiperidine (0.506 g, 5.00 mmol) and $NaHCO_3$ (0.84 g, 10 mmol) in THF-water (1 : 1, 10 ml) was added a 30% toluene solution (2.84 g) of benzyl chloroformate (5.0 mmol) under ice-cooling. Then the solution was further stirred at room temperature overnight. After the addition of NaOH (0.24 g, 6.0 mmol) and water (5 ml), the reaction mixture was extracted with toluene (20 ml), and the organic extract was washed with 10% aqueous NaOH (5 ml), evaporated in vacuo, and separated by column chromatography (ethyl acetate/hexane, 1 : 1) to give 1-benzyloxycarbonyl-3-hydroxypiperidine (**6b**) (1.126 g; 96% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ = 1.40—2.00 (m, 4H, CH(OH)CH_2CH_2), 1.73 (br s, 1H, OH), 3.11—3.37 (m, 2H, CH_2NCH_2), 3.50—3.88 (m, 3H, CH_2NCH_2 and CH(OH)), 5.13 (s, 2H, OCH_2Ph), 7.29—7.44 (m, 5H, ArH); IR (neat) 3428, 1699, 1683, 1435, 1231 cm^{-1}. These spectral data were in agreement with those reported for the (*S*)-enantiomer.[15c]

A mixture of **6b** (0.952 g, 4.05 mmol) and acetic anhydride (0.46 ml, 4.9 mmol) in toluene (10 ml) was heated at 100 °C for 5.5 h and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 1 : 1) afforded **4b** (1.12 g; 99% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ = 1.42—2.19 (m, 4H, CH(OAc)CH_2CH_2), 1.99 (s, 3H, OCOCH_3), 3.28—3.79 (m, 4H, CH_2NCH_2), 4.73—4.92 (m, 1H, CH(OAc)), 5.10 (d, *J* = 14 Hz, 1H, OCH_2Ph), 5.17 (d, *J* = 14 Hz, 1H, OCH_2Ph), 7.24—7.41 (m, 5H, ArH); IR (neat) 1739, 1702, 1431, 1261, 1231 cm^{-1}. Found: C, 64.93; H, 6.96; N, 5.05%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05%.

Preparation of 3-Acetoxy-1-benzoylpiperidine (4c). To a mixture of 3-hydroxypiperidine (0.506 g, 5.00 mmol) and pyridine (0.41 ml, 5.1 mmol) in CH_2Cl_2 (5 ml) was added benzoic anhydride (1.24 g, 5.48 mmol). The mixture was stirred for 4 h at room temperature and then evaporated. After aqueous NaOH (1 M; 6 ml) was added, the resulting mixture was extracted with toluene (20 ml) and with ethyl acetate (20 ml). The combined organic layers were evaporated to afford crude 1-benzoylpiperidine (**6c**) (0.721 g) as an oil. A mixture of the crude **6c** (0.349 g) and acetic anhydride (0.19 ml, 2.0 mmol) in toluene (3.5 ml) was heated at 100 °C for 5.5 h. After the addition of 5 M aqueous K_2CO_3 (5 ml), the mixture was extracted with toluene (2×15 ml). The combined organic extracts were washed with a brine, dried (Na_2SO_4), and evaporated in vacuo. Column chromatography (ethyl acetate/hexane, 2 : 3) of the residue gave **4c** (0.399 g; 80% overall yield in two steps) as a colorless oil, which was shown by ^{1}H NMR to consist of two conformers in a ratio of 1 : 1: ^{1}H NMR ($CDCl_3$) δ = 1.38—2.24 (m, 4H, CH(OAc)CH_2CH_2), 2.03 (s, 3H, OCOCH_3), 3.21—4.06 (m, 4H, CH_2NCH_2), 4.78 (br m, 1H×0.5, CH(OAc)), 4.94 (br m, 1H×0.5, CH(OAc)), 7.37—7.46 (m, 5H, ArH); IR (neat) 1732, 1635, 1432, 1280, 1233 cm^{-1}. Found: C, 67.21; H, 6.76; N, 5.65%. Calcd for $C_{14}H_{17}NO_3 \cdot 0.15H_2O$: C, 67.26; H, 6.98; N, 5.60%.

Preparation of 4-Acetoxy-1-benzyl-2-pyrrolidone (7). To a mixture of 4-acetoxy-2-pyrrolidone[31] (0.43 g, 3.0 mmol) and benzyl bromide (0.43 ml, 3.0 mmol) in *N*, *N*-dimethylacetamide (5 ml) was added NaH (63.3 wt% in an oil, 119 mg, 3.14 mmol) by portions at a temperature of −20 to −30 °C over 80 min, and the resulting mixture was stirred for 30 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 ml), and extracted with toluene (20 ml and 10 ml). The combined organic layers were dried (Na_2SO_4), evaporated, and subjected to column chromatography (ethyl acetate/hexane, 1 : 1) to afford 0.20 g (29%) of **7** as colorless crystals: Mp 100—102 °C; ^{1}H NMR ($CDCl_3$) δ = 2.03 (s, 3H, OC(=O)CH_3), 2.54 (dd, *J* = 2.5 and 17.8 Hz, 1H, NC(=O)CH_2), 2.82 (dd, *J* = 7.2 and 17.8 Hz, 1H, NC(=O)CH_2), 3.23 (dd, *J* = 2.1 and 11.6 Hz, 1H, CH_2NC(=O)), 3.61 (dd, *J* = 6.1 and 11.6 Hz, 1H, CH_2NC(=O)), 4.46 (d, *J* = 14.8 Hz, 1H, NCH_2Ph), 4.51 (d, *J* = 14.8 Hz, 1H, NCH_2Ph), 5.23—5.30 (m, 1H, CH(OAc)), 7.22—7.36 (m, 5H, ArH); IR (KBr) 1735, 1679, 1276, 1241, 1213 cm^{-1}. Found: C, 66.90; H, 6.41; N, 6.00%. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01%.

Lipase PS-Catalyzed Hydrolysis of 4a. A solution of **4a** (1.00 g, 4.29 mmol) and lipase PS (0.50 g) in a 1 : 1 mixture (15 ml) of a phosphate buffer (1/15 M, pH 7.0)–dioxane was stirred at 25 °C for 74 h. After insoluble materials were filtered off through a Celite pad and washed with acetone, the filtrate and the washing were combined and concentrated in vacuo. Then, aqueous $NaHCO_3$ (1 M; 10 ml) was added and the resulting solution was extracted with ethyl acetate (2×20 ml). The combined organic extracts were washed with 10% aqueous NaCl (10 ml), dried (Na_2SO_4), and evaporated in vacuo. Column chromatography of the residue using ethyl acetate–hexane (1 : 2) and chloroform–methanol (5 : 1) as eluents afforded (*S*)-**4a** with 85.6% ee (0.468 g; 43% yield) and (*R*)-**6a** with 98.2% ee (0.352 g; 47% yield) (*Conv* = 46.6%, *E* = 300). The enantiomeric excess of (*S*)-**6a** was measured after its conversion to (*S*)-**4a**. HPLC analysis conditions: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 50); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**4a** 12.1 min, t_R of (*S*)-**4a** 19.0 min.

(*S*)-4a:[28] Colorless oil; $[\alpha]_D^{20}$ −22.8° (*c* 0.54, methanol). The spectral data for this compound were in agreement with those of its racemate.

(*R*)-6a: Pale yellow oil; $[\alpha]_D^{20}$ −13.3° (*c* 0.22, methanol) [lit,[15a] $[\alpha]_D^{23}$ of (*S*)-**6a**: +11.9° (*c* 2.14, methanol)]. ^{1}H NMR ($CDCl_3$) δ = 1.50—1.93 (m, 4H, CH(OH)CH_2CH_2), 2.2—2.7 (m, 4H, CH_2NCH_2), 2.70 (br s, 1H, O*H*), 3.57 (s, 2H, NCH_2Ph), 3.86 (m, 1H, C*H*(OH)), 7.20—7.40 (m, 5H, Ar*H*); IR (neat) 3358, 2936, 2798, 1454, 1102 cm^{-1}. Found: C, 75.39; H, 9.23; N, 7.27%. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32%.

In a similar manner, **4b** (1.00 g, 3.61 mmol) was hydrolyzed with lipase PS to afford (*S*)-**4b** with 91.9% ee (0.493 g; 49% yield) and (*R*)-**6b** with 98.6% ee (0.427 g; 50% yield) (*Conv*=48.2%, *E*=470). The enantiomeric excesses of these products were obtained after conversion to the corresponding 1-benzyloxycarbonyl-3-(phenylcarbamoyloxy)piperidine (**8**). Analysis conditions using HPLC: Column, Daicel Chiralcel OD (ϕ 4.6×250 mm); eluent, IPA/hexane (1 : 6); flow rate, 0.6 ml min^{-1}; t_R of (*R*)-**8** 43.8 min, t_R of (*S*)-**8** 25.8 min.

(*S*)-4b:[28] Colorless oil; $[\alpha]_D^{20}$ −24.2° (*c* 1.07, methanol). The spectral data for this compound were identical with those of the racemate.

(*R*)-6b: Colorless oil; $[\alpha]_D^{20}$ −19.5° (*c* 0.21, methanol). The ^{1}H NMR and IR spectra of this compound were in good agreement with those of the racemate. The absolute configuration of (*R*)-**6b** was confirmed as follows: Hydrogenolysis of (*R*)-**6b** with 5% Pd on carbon and subsequent treatment with (*S*)-10-camphorsulfonic acid gave (*R*)-3-hydroxypiperidinium (*S*)-10-camphorsulfonate, which was identified by comparison of its physical properties with those reported:[32] Colorless solid (very hygroscopic); mp 134—135 °C (ethanol–ethyl ether) (lit, mp 134—135 °C); $[\alpha]_D^{20}$ +24.1° (*c* 0.73, 50% ethanol) [lit, $[\alpha]_D^{20}$ +23.0° (*c* 1.5, 50% ethanol)].

In a similar manner, **4c** and **7** were treated with lipase PS, but no hydrolyzed product was detected by HPLC analysis.

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