Convenient Syntheses of Optically Active β-Lactams by Enzymatic Resolution

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Optically active β-lactams were synthesized by lipase-catalyzed kinetic resolution using the enantioselective hydrolysis of *N*-acyloxymethyl β-lactams (3) in an organic solvent and the transesterification of *N*-hydroxymethyl β-lactams (2) with vinyl acetate. A variety of highly optically pure β-lactams (2 and 3) possessing some substituents at the 3, 4, or both positions were obtained and the optically active *N*-hydroxymethyl β-lactams prepared were converted into useful *N*-unsubstituted ones without racemization.

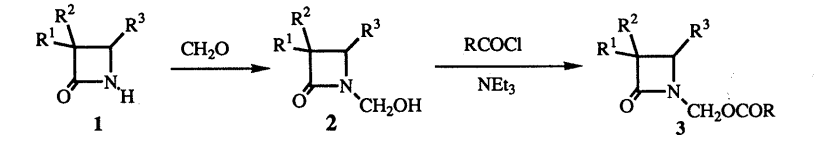
Keywords lipase; kinetic resolution; β-lactam; hydrolysis; transesterification

In the syntheses of β-lactam antibiotics, the presence of asymmetric carbons at the 3 and 4-positions constitutes a serious difficulty, and hence much labour has been expended for the creation of optically active β-lactams.[1] Enzymatic asymmetric synthesis has been developed in past 20 years, and in particular, lipase has come to be used routinely as a chemical reagent.[2] In the course of our investigation on lipase-catalyzed asymmetric syntheses,[3] we succeeded in the syntheses of optically active β-lactams by lipase-catalyzed resolution of *N*-acyloxymethyl or *N*-hydroxymethyl β-lactams. The details of these new methods are presented here.[4]

Our strategy for the enzymatic preparation is based on employment of *N*-acyloxymethyl β-lactam, which is not only suitable for lipase-catalyzed hydrolysis, but also convertible easily to *N*-unsubstituted β-lactam, a useful building block for synthesis of β-lactam antibiotics. The substrates, *N*-acyloxymethyl β-lactams, were synthesized by esterification of *N*-hydroxymethyl β-lactams, which were prepared easily from *N*-unsubstituted β-lactams and formaldehyde. The *N*-hydroxymethyl β-lactam was also used as a substrate for lipase-catalyzed transesterification in this study (Charts 1 and 2). Characteristic data of β-lactams prepared are given in the experimental section.

Since several preliminary experiments have indicated that lipase B and lipase PS[5] are well suited for enantioselective hydrolysis, we used mainly those two lipases, and examined their enantioselectivity by using 1-(acetoxymethyl)-3,3-dimethyl-4-phenyl-2-azetidinone (**3a-A**) as a representative substrate. Figure 1 shows the time course of the lipase-catalyzed hydrolysis of (±)-**3a-A**. Surprisingly, almost perfect enantioselectivity was observed in spite of the relatively large distance between the reaction site and the asymmetric center (three atoms). The (*R*)-ester was almost completely hydrolyzed after 8 h, although none of the (*S*)-ester reacted. As a result, the product, (*R*)-2-hydroxymethyl-3,3-dimethyl-4-phenyl-2-azetidinone (*R*-**2a**), and the recovered (*S*)-ester (*S*-**3a-A**) were obtained in high chemical and optical yields after usual chromatographic separation.

The above result encouraged us to apply this method to optical resolution of various β-lactams. First, the effects of



	R^1	R^2	R^3
a	CH_3	CH_3	C_6H_5
b	CH_3	CH_3	PhCH=CH
c	CH_3	CH_3	$PhCH_2CH_2$
d	CH_3	CH_3	cyclo-C_6H_{11}
e	CH_3	CH_3	$C_6H_4OCH_3$-*p*
f	H	H	C_6H_5
g	*n*-C_4H_9	H	C_6H_5
h			PhCH=CH

A: R=CH_3 B: R=CH_2CH_3 C: R=*n*-C_4H_9 D: R=Ph E: R=$C(CH_3)_3$

Chart 1

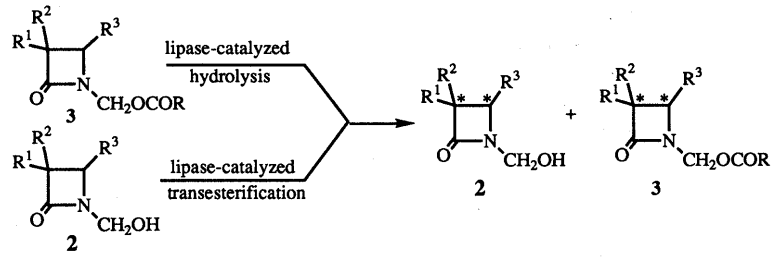


Chart 2

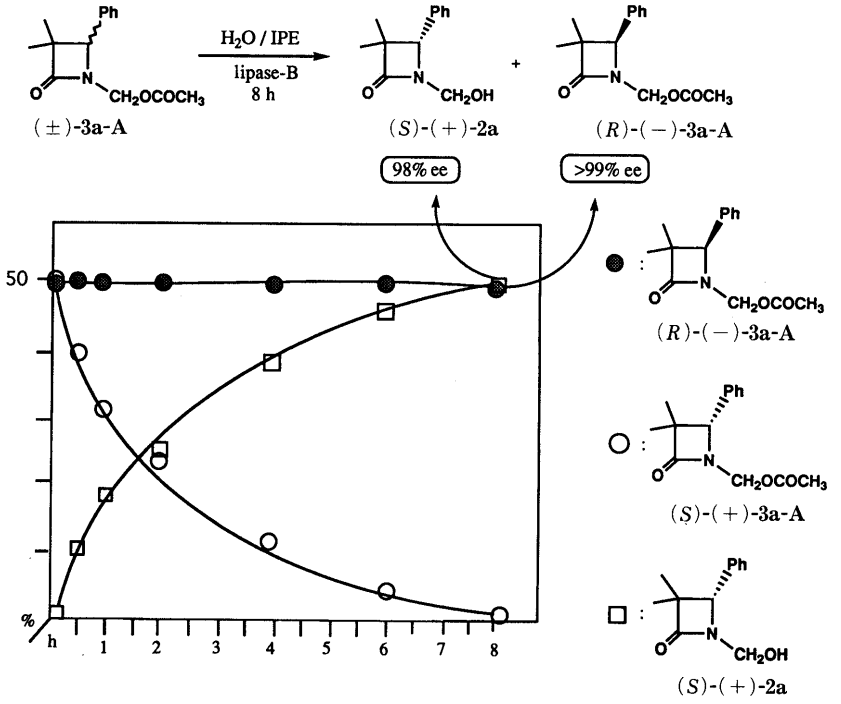


Fig. 1. Time Course of the Lipase-Catalyzed Hydrolysis

TABLE I. Lipase-Catalyzed Enantioselective Hydrolysis of 1-Acyloxymethyl-2-azetidinones

Entry	Comp. No.	Lipase	Time (h)	Product **2**		$[\alpha]_D^{21}$ (MeOH)	Recovery **3**		$[\alpha]_D^{21}$ (MeOH)
				C.Y. (%)[a]	O.Y. (% ee)[b]		C.Y. (%)[a]	O.Y. (% ee)[b]	
1	**3a-A**	Lipase B	8	49	98 (*S*)	+180.8° (*c*=0.8)	46	>99 (*R*)	−91.0° (*c*=0.8)
2	**3a-B**	Lipase B	5	45	>99 (*S*)	—	47	98 (*R*)	—
3	**3a-B**	Lipase PS	50	48	98 (*S*)	—	46	>99 (*R*)	—
4	**3a-C**	Lipase B	2	50	98 (*S*)	—	47	>99 (*R*)	—
5	**3a-D**	Lipase B	10 d	44	>99 (*S*)	—	52	89 (*R*)	—
6	**3a-E**	Lipase B	>10 d	—	—	—	—	—	—
7	**3b-B**	Lipase B	1	47	>99	+4.9° (*c*=1.0)	50	98	−12.0° (*c*=1.2)
8	**3b-B**	Lipase PS	11	35	>99	—	42	88	—
9	**3c-B**	Lipase B	6.5	47	89	+4.2° (*c*=1.0)	46	>99	+24.7° (*c*=1.0)
10	**3d-B**	Lipase B	72	43	97	+30.4° (*c*=0.74)	52	82	+3.4° (*c*=1.14)
11	**3e-B**	Lipase B	5	39	97	+147.6° (*c*=1.0)	42	99	−97.4° (*c*=1.02)
12	**3f-B**	Lipase B	2	47	>98 (*R*)	+161.2° (*c*=1.02)	50	93 (*S*)	−72.5° (*c*=1.02)
13	**3f-E**	Lipase B	216	41	91 (*R*)	—	50	95 (*S*)	—
14	**3g-B** (*cis*)	Lipase B	13	39	88	+166.6° (*c*=1.14)	32	78	−97.7° (*c*=1.14)
15	**3g-B** (*cis*)	Lipase PS	10 d	39	74	—	45	89	—
16	**3g-B** (*trans*)	Lipase B	1.5	37	98	+61.9° (*c*=0.28)	43	>99	−19.6° (*c*=0.3)
17	**3h-B** (*cis*)	Lipase B	76	41	95	+1.8° (*c*=1.42)	46	92	+44.5° (*c*=0.86)

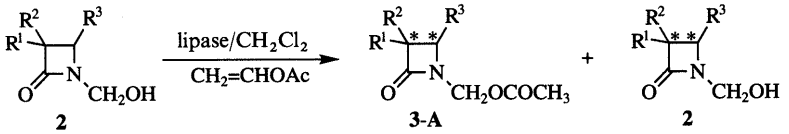
a) Isolated yield. *b*) Optical yields were determined by HPLC analyses (Chiralpak AS, isopropyl alcohol (IPA)–hexane).

N-acyloxymethyl moieties on the rate and enantioselectivity of this reaction were investigated. As shown in entries 1—6 (Table I), the chain length and bulkiness of the acyloxy moiety significantly affected the reaction rate but had little influence on the selectivity. Lipase B appeared to be more suitable than lipase PS for this reaction. 1-Pentanoyloxymethyl-3,3-dimethyl-4-phenyl-2-azetidinone (**3a-C**, entry 4) was hydrolyzed about 4 times as fast as the 1-acetoxymethyl compound (**3a-A**, entry 1). However, in the case of bulky *N*-acyloxymethyl moiety such as *N*-benzoyloxymethyl or *N*-pivaloyloxymethyl, the reaction required a long period or did not proceed (entries 5 and 6). The experimental results on the effects of some other substituents at the 3 or 4-position are shown in entries 7—12.

These results suggested that lipase B favored substrates possessing aromatic or unsaturated groups. From a practical point of view, we also examined the reaction of 3,4-disubstituted 2-azetidinones, and obtained satisfactory results (entries 13 and 14). It is noteworthy that optically active *cis*-3-phthalimido-4-*β*-styryl-2-azetidinones (**2h** and **3h-B**, entry 17), which have two useful moieties, were obtained in high optical yields.

One of the most important aspects of this method is the possibility of conversion of *N*-hydroxymethyl *β*-lactam to *N*-unsubstituted form without racemization. After several trials, we succeeded in dehydroxymethylation of (+)-**2a** and (+)-**2f** by treatment with ammonia in methanol at room temperature. Both products [(+)-**1a** and (+)-**1f**] obtained

TABLE II. Lipase-Catalyzed Enantioselective Transesterification of 1-Hydroxymethyl-2-azetidinones



2 3-A 2

Entry	Comp. No.	Lipase	Time (h)	Product 3-A		[α]$_D^{20}$ (MeOH)	Recovery 2		[α]$_D^{20}$ (MeOH)
				C.Y. (%)[a]	O.Y. (% ee)[b]		C.Y. (%)[a]	O.Y. (% ee)[b]	
1	**2a**	Lipase PS	9	48	98 (*S*)	+93.0° (*c*=1.04)	46	>99 (*R*)	−179.3° (*c*=1.04)
2	**2a**	Lipase B	24	47	96 (*S*)	—	42	88 (*R*)	—
3	**2d**	Lipase PS	84	40	93	−1.6° (*c*=0.8)	53	74	−30.7° (*c*=0.6)
4	**2f**	Lipase PS	15	51	92	+69.2° (*c*=0.6)	43	>99	−160.9° (*c*=0.98)
5	**2g** (*cis*)	Lipase PS	72	39	76	+88.8° (*c*=0.68)	69	>99	−170.9° (*c*=0.8)

a) Isolated yield. *b*) Optical yields were determined by HPLC analyses (Chiralpak AS, IPA–hexane).

were optically pure on the basis of high performance liquid chromatographic (HPLC) analysis on a chiral column. The specific optical rotation of (+)-**1f** is +132.0° (*c*= 1.0, MeOH), which suggested *R* configuration at the 4 position by comparison with the reported value.[6] The absolute configuration of (+)-**2a** was also determined by comparing the result of HPLC analysis of *N-tert*-butyldimethylsilyl (TBDMS)-**1a** derived from (+)-**2a** on a chiral column with that of the same compound prepared from (*R*)-(+)-**1f** *via* methylation. The absolute configurations of the other chiral β-lactams are unknown.

In further investigation, we found that *N*-hydroxymethyl β-lactam was well suited for lipase-catalyzed transesterification with vinyl acetate. The experimental results are summarized in Table II. When this transesterification was compared with the hydrolysis described above, the acetate produced was revealed to have the opposite configuration to that of the corresponding recovered ester in the hydrolysis. It is of interest that lipase PS gave better results than lipase B, which was favorable in the hydrolysis. Although the reaction proceeded enantioselectively, the reaction time required is, generally, a little longer. Because the substrate can be prepared easily in one step, this transesterification method is suitable for synthetic purposes.

Advantages of the present methods are as follows: 1) the reaction proceeds enantioselectively under mild conditions, 2) the lipase can be removed by routine filtration because of the use of an organic solvent and each enantiomer is separable by usual column chromatography, 3) optically active *N*-hydroxymethyl β-lactams and their esters can be converted easily into *N*-unsubstituted form without racemization.

Experimental

Melting points were taken on a Yazawa micro melting point (BY-1) apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX270 or GSX500 spectrometer and are reported in parts per million (ppm) from internal tetramethylsilane. Coupling constants (*J* values) are given in hertz (Hz) and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br= broad. Positive fast atom bombardment mass (FAB-MS) spectra were recorded on a JEOL JMS-AX505W instrument. Column chromatography was performed over Merck silica gel (70—230 mesh). The optical yields were determined by HPLC analyses using a Shimadzu LC-10A equipped with Daicel Chiralpak AS column.

Preparation of 3,4-Substituted 2-Azetidinones Various 3-, 4-, or 3,4-substituted 2-azetidinones were synthesized by methods similar to those reported by Hart *et al.*[7] (**1a—e, g**), Loewe *et al.*[8] (**1f**), and Kronenthal *et al.*[9] (**1h**).

1a: mp 102—104 °C (lit.,[7] mp 103—104.5 °C). IR (KBr): 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, s, CH_3), 1.47 (3H, s, CH_3), 4.5 (1H, s, CH), 6.1 (1H, br s, NH), 7.2 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 18.20, 22.58, 57.06, 63.26, 126.07, 127.86, 128.57, 137.86, 174.88.

1b: mp 101.5—103.5 °C (lit.,[7] mp 102—104 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, s, CH_3), 1.4 (3H, s, CH_3), 4.0 (1H, dd, *J*=1.0, 7.3, CH), 5.8 (1H, br s, NH), 6.2 (1H, dd, *J*=7.3, 16.1 CH=), 6.6 (1H, d, *J*=16.1 CH=), 7.3 (5H, m, Ar-H).

1c: mp 81.5—82.0 °C (EtOAc–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.72—1.95 (2H, m, CH_2), 2.62—2.71 (2H, m, CH_2), 3.33 (1H, dd, *J*=4.9, 8.8, CH), 5.49 (1H, br s, NH), 7.16—7.33 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 16.78, 22.65, 33.04, 33.48, 53.77, 60.33, 126.38, 128.35, 128.69, 141.00, 174.90.

1d: mp 125—126 °C (EtOAc–hexane). IR (KBr): 3200 (NH), 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.83 (11H, m, cyclo-C_6H_{11}), 1.23 and 1.29 (6H, each s, 2×CH_3), 2.94 (1H, d, *J*=10.7, CH), 6.34 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 17.16, 22.98, 25.32, 25.55, 26.24, 29.99, 30.15, 38.84, 53.29, 65.72, 175.55. *Anal.* Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 6.16; N, 9.52. Found: C, 73.27; H, 6.15; N, 9.28.

1e: mp 102—103 °C (EtOAc–hexane). IR (KBr): 3200 (NH), 1750 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, s, CH_3), 1.44 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.45 (1H, s, CH), 6.26 (1H, br s, NH), 6.92 (2H, d, *J*=8.3, Ar-H), 7.16 (2H, d, *J*=8.3, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 18.15, 22.49, 55.30, 56.86, 62.91, 113.94, 127.27, 129.85, 159.29, 175.17. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.92; H, 7.28; N, 6.65.

1f: mp 108—109 °C (EtOAc–hexane). IR (KBr): 3200 (NH), 1735 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (1H, ddd, *J*=1, 2.3, 15.1, CH_AH), 3.44 (1H, ddd, *J*=2.3, 5.4, 15.1, CH_BH), 4.72 (1H, dd, *J*=2.3, 5.4, CH), 6.45 (1H, br s, NH), 7.35 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 47.98, 50.37, 128.23, 128.65, 128.86, 140.21, 168.19. *Anal.* Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.36; H, 6,15; N, 9.28.

1g (*cis*): mp 81—82 °C (EtOAc–hexane). IR (KBr): 3200 (NH), 1735 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, t, *J*=7.0, CH_3), 1.07—1.30 (6H, m, $CH_2CH_2CH_2$), 3.45 (1H, m, CH), 4.86 (1H, d, *J*=5.4, CH), 6.1 (1H, br, NH), 7.35 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 13.65, 22.37, 25.27, 29.12, 54.96, 56.26, 126.82, 128.03, 128.44, 137.46, 171.50. *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.08; H, 8.33; N, 6.78.

1g (*trans*): mp 71—73 °C (EtOAc–hexane). IR (KBr): 3200 (NH), 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, *J*=7.0, CH_3), 1.40—1.87 (6H, m, $CH_2CH_2CH_2$), 3.00 (1H, m, CH), 4.37 (1H, d, *J*=2.0, CH), 6.60 (1H, br, NH), 7.32 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 13.29, 22.03, 27.92, 28.79, 57.13, 61.27, 125.03, 127.46, 128.26, 139.76, 171.09. *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.08; H, 8.38; N, 6.80.

1h: mp 167—168 °C (EtOAc–hexane). ^{1}H-NMR ($CDCl_3$) δ: 4.71 (1H, dd, *J*=5.4, 8.3, CH), 5.60 (1H, d, *J*=5.4, COCH), 6.28 (1H, dd, *J*=8.3, 16.1, =CH), 6.36 (1H, br, NH), 6.64 (1H, d, *J*=16.1, =CH), 7.24 (5H, m, Ar-H), 7.71 (2H, dd, *J*=3.0, 5.9, Ar-H), 7.85 (2H, dd, *J*=3.0, 5.9, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 57.50, 59.30, 123.77, 124.01, 126.67, 128.32, 128.61, 131.53, 134.46, 135.64, 136.27, 137.28, 164.78.

General Procedure for Syntheses of 1-Hydroxymethyl-2-azetidinones (2)

TABLE III. Spectral and Analytical Data for 1-Hydroxymethyl-2-azetidinones[a)]

Compd. No.	mp (°C)	^{1}H-NMR ($CDCl_3$) δ: ^{13}C-NMR ($CDCl_3$) δ	Formula	Analysis (%) Calcd (Found)		
				C	H	N
2a	106—107	0.80 (3H, s, CH_3), 1.44 (3H, s, CH_3), 3.26 (1H, dd, J=5.9, 9.3, OH), 4.40 (1H, dd, J=9.3, 11.7, NC$\underline{H}_A$HO), 4.64 (1H, s, CH), 5.13 (1H, dd, J=5.9, 11.7, NC$\underline{H}_B$HO), 7.29 (5H, m, Ar-H): 17.76, 22.00, 56.35, 63.80, 65.61, 126.73, 128.06, 128.67, 136.00, 175.25	$C_{12}H_{15}NO_2$	69.53 (69.86	7.29 7.44	6.76 6.85)
2b	—	1.19 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.45 (1H, br, OH), 4.12 (1H, d, J=8.3 Hz, CH), 4.43 (1H, dd, J=8.3, 11.7, NC$\underline{H}_A$HO), 4.94 (1H, dd, J=5.9, 11.7, NC$\underline{H}_B$HO), 6.14 (1H, dd, J=8.3, 16.1, =CH), 6.69 (1H, d, J=16.1, =CH), 7.33 (5H, m, Ar-H): 17.69, 21.77, 55.82, 63.56, 64.63, 124.50, 126.62, 128.27, 128.72, 135.69, 136.05, 174.44	$C_{14}H_{17}NO_2$	72.70 (72.79	7.40 7.47	6.06 5.82)
2c	—	1.17 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.95 (2H, m, CH_2), 2.70 (2H, m, CH_2), 3.48 (1H, dd, J=6.3, 7.3, CH), 4.60—4.90 (3H, m, NC$\underline{H}_2$O$\underline{H}$), 7.24 (5H, m, Ar-H): 16.65, 22.14, 31.78, 33.12, 52.82, 62.68, 63.70, 126.21, 128.35, 128.56, 141.15, 175.13	$C_{14}H_{19}NO_2$	72.07 (72.30	8.20 8.15	6.00 5.71)
2d	70—71	0.90—2.00 (11H, m, C_6H_{11}), 1.24 (3H, s, CH_3), 1.26 (3H, s, CH_3), 3.15 (1H, d, J=9.8, CH), 3.85 (1H, br, OH), 4.64 (1H, dd, J=7.8, 11.2, NC$\underline{H}_A$HO), 4.75 (1H, dd, J=6.8, 11.2, NC$\underline{H}_B$HO): 17.19, 22.38, 25.39, 25.59, 26.14, 30.20, 30.40, 39.10, 52.51, 65.74, 68.60, 176.45	$C_{12}H_{21}NO_2$	68.21 (67.75	10.02 9.92	6.63 6.57)
2e	126—127	0.80 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 4.38 (1H, br t, OH), 4.58 (1H, s, CH), 5.09 (2H, dd, J=5.4, 11.2, NCH_2O), 6.92 (2H, d, J=8.8, Ar-H), 7.15 (2H, d, J=8.8, Ar-H): 17.73, 21.96, 55.31, 56.26, 63.69, 65.38, 114.10, 127.82, 128.02, 159.49, 175.31	$C_{13}H_{17}NO_3$	66.36 (66.11	7.28 7.42	5.95 5.61)
2f	84—85	2.88 (1H, dd, J=2.4, 15.1, C$\underline{H}_A$H), 3.38 (1H, dd, J=5.4, 15.1, C$\underline{H}_B$H), 4.20 (2H, br s, NC$\underline{H}_A$HO, OH), 4.85 (1H, dd, J=2.4, 5.4, CH), 5.03 (1H, br d, NC$\underline{H}_B$HO), 7.36 (5H, m, Ar-H): 47.03, 53.02, 63.81, 126.44, 128.61, 129.02, 137.98, 168.23	$C_{10}H_{11}NO_2$	67.79 (67.55	6.26 6.30	7.80 7.89)
2g (*cis*)	—	0.68 (3H, t, J=6.8, CH_3), 1.02—1.40 (6H, m, $CH_2CH_2CH_2$), 3.38 (1H, dt, J=5.4, 7.8, CH), 4.28 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.03 (1H, d, J=5.4, CH), 5.07 (1H, d, J=11.2, NC$\underline{H}_B$HO), 7.34 (5H, m, Ar-H): 13.48, 22.16, 24.68, 25.09, 28.94, 29.09, 55.44, 55.66, 57.25, 63.34, 127.33, 128.03, 128.37, 135.32, 171.81	$C_{16}H_{21}NO_2$	74.01 (73.88	8.16 8.01	5.40 5.55)
2g (*trans*)	—	0.89 (3H, t, J=7.1, CH_3), 1.37 (4H, m, CH_2CH_2), 1.80 (2H, m, CH_2), 3.02 (1H, ddd, J=2.4, 6.4, 8.8, CH), 4.21 (2H, m, NC$\underline{H}_A$HO, OH), 4.50 (1H, d, J=2.4, CH), 5.05 (1H, d, J=8.8, NC$\underline{H}_B$HO), 7.34 (5H, m, Ar-H): 13.84, 22.55, 27.99, 29.35, 60.10, 60.72, 63.53, 126.39, 128.40, 128.99, 138.07, 171.62				
2h (*cis*)	101—102	3.30 (1H, dd, J=6.8, 7.8, OH), 4.71 (1H, dd, J=7.8, 11.7, NC$\underline{H}_A$HO), 4.84 (1H, dd, J=5.4, 8.8, CH), 5.03 (1H, dd, J=6.8, 11.7, NC$\underline{H}_B$HO), 5.61 (1H, d, J=5.4, CH), 6.23 (1H, dd, J=8.8, 16.1, =CH), 6.70 (1H, d, J=16.1, =CH), 7.24 (5H, m, Ar-H), 7.72 (2H, dd, J=2.9, 5.9, Ar-H), 7.85 (2H, dd, J=2.9, 5.9, Ar-H): 58.55, 60.62, 64.19, 122.32, 123.83, 126.75, 128.47, 128.61, 131.54, 134.54, 135.55, 137.92, 164.26, 167.33	$C_{20}H_{16}N_2O_4$	68.95 (68.97	4.63 4.84	8.04 7.92)

a) In the IR spectra of all compounds, absorption bands due to OH and CO were observed at 3200 and 1745—1750 cm^{-1}, respectively.

A mixture of 1-unsubstituted 2-azetidinones (4 mmol), 30% aqueous formaldehyde (780 mg, 10 mmol) and potassium carbonate (100 mg) in EtOH (10 ml) was refluxed for 1 h, and then the mixture was stirred overnight at room temperature. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. A CH_2Cl_2 solution of the residue was washed with brine and dried over $MgSO_4$. After removal of the CH_2Cl_2, the residue was chromatographed on a silica gel column with AcOEt–hexane to afford 2-hydroxymethyl-2-azetidinones (**2**). The yields were generally over 80% and the spectral data of the products are listed in Table III.

General Procedure for Syntheses of 1-Acyloxymethyl-2-azetidinones (3) Acyl chloride (2.4 mmol) was added dropwise to a cooled solution of 1-hydroxymethyl-2-azetidinone (**2**) (2 mmol) and triethylamine (300 mg, 3 mmol) in CH_2Cl_2 (50 ml) with stirring. After being stirred overnight at room temperature, the solution was washed with water and brine, and then dried over $MgSO_4$. The residue obtained by concentration was chromatographed on a silica gel column to afford the corresponding 1-acyloxymethyl-2-azetidinones (**3**) in 70—90% yields. The spectral data of the products are recorded in Table IV.

General Procedure for Lipase-Catalyzed Hydrolysis of 1-Acyloxymethyl-2-azetidinones (3) A mixture of 1-acyloxymethyl-2-azetidinones (**3**) (2 mmol) and lipase B (50 mg) or lipase PS (100 mg) in isopropyl ether saturated with water (10 ml) was stirred at room temperature. After consumption of a half of the substrate had been confirmed by HPLC analysis on a chiral column, the lipase was removed by filtration and washed with CH_2Cl_2. The combined organic layer was concentrated to afford a residue, which was chromatographed on a silica gel column to give the corresponding 1-hydroxymethyl-2-azetidinone (**2**) and its ester (**3**). The reaction times, yields and specific optical rotations are listed in Table I and characteristic data of the products were identical with those of the corresponding racemic compounds shown in Table III.

General Procedure for Lipase-Catalyzed Transesterification of 1-Hydroxymethyl-2-azetidinones (2) A mixture of a 1-hydroxymethyl-2-azetidinones (**2**) (2 mmol), lipase PS (100 mg) or lipase B (50 mg) and vinyl acetate (3 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature. After consumption of half of the 1-hydroxymethyl-2-azetidinone had been confirmed by HPLC analysis on a chiral column, the lipase was removed by filtration and washed with CH_2Cl_2. The combined organic layer was concentrated to afford a residue which was chromatographed on a silica gel column to give the corresponding 1-acetoxymethyl-2-azetidinone (**3-A**) and 1-hydroxymethyl-2-azetidinone (**2**). The reaction times and yields are listed in Table II. The spectral data of the products were identical with those of the corresponding racemic compounds shown in Table IV.

Dehydroxymethylation of (+)-2f A solution of (+)-**2f** (177 mg, 1 mmol) and 25% ammonium hydroxide (0.3 ml) in MeOH (2 ml) was stirred overnight at room temperature. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column to give (*R*)-(+)-**1f** (132 mg, 90.0%). The spectral data of the product were identical with those of (±)-**1f**. $[\alpha]_D^{21}$ +132.0° (c=1.0, MeOH) [lit.,[6] (*S*)-**1f**: $[\alpha]_D^{24}$ −128.0° (c=1.0, MeOH)].

Determination of Absolute Configuration of (+)-2a 1) Preparation of *N*-TBDMS-(*R*)-(+)-**1a** from (+)-**2a**: A solution of (+)-**2a** (205 mg,

TABLE IV. Spectral Data for 1-Acyloxymethyl-2-azetidinones

Compd. No.	mp (°C)	FAB-MS m/z $(M+H)^+$	^{1}H-NMR ($CDCl_3$) δ
3a-A	—	247 (M^+)	0.80 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.04 (3H, s, $COCH_3$), 4.53 (1H, s, CH), 5.00 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.44 (1H, d, J=11.2, NC$\underline{H}_B$HO), 7.33 (5H, m, Ar-H)
3a-B	—	262	0.80 (3H, s, CH_3), 1.10 (3H, t, J=7.4, CH_3), 1.44 (3H, s, CH_3), 2.31 (2H, q, J=7.4, $COCH_2$), 4.53 (1H, s, CH), 5.31 (1H, d, J=11.1, NC$\underline{H}_A$HO), 5.45 (1H, d, J=11.1, NC$\underline{H}_B$HO), 7.31 (5H, m, Ar-H)
3a-C	—	290	0.80 (3H, s, CH_3), 0.89 (3H, t, J=6.8, CH_3), 1.29 (4H, m, CH_2CH_2), 1.44 (3H, s, CH_3), 2.29 (2H, t, J=7.3, $COCH_2$), 4.52 (1H, s, CH), 5.02 (1H, d, J=11.1, NC$\underline{H}_A$HO), 5.44 (1H, d, J=11.1, NC$\underline{H}_B$HO), 7.32 (5H, m, Ar-H)
3a-D	93—94	310	0.81 (3H, s, CH_3), 1.44 (3H, s, CH_3), 4.60 (1H, s, CH), 5.31 (1H, d, J=11.0, NC$\underline{H}_A$HO), 5.66 (1H, d, J=11.0, NC$\underline{H}_B$HO), 7.2—7.6, and 7.9—8.1 (10H, m, Ar-H)
3a-E	75—76	290	0.79 (3H, s, CH_3), 1.19 (9H, s, $C(CH_3)_3$), 1.23 (3H, s, CH_3), 4.49 (1H, s, CH), 5.05 (1H, d, J=11.0, NC$\underline{H}_A$HO), 5.42 (1H, d, J=11.0, NC$\underline{H}_B$HO), 7.36 (5H, m, Ar-H)
3b-B	—	287	1.11 (3H, t, J=7.3, CH_3), 1.19 (3H, s, CH_3), 1.37 (3H, s, CH_3), 2.33 (2H, q, J=7.3, CH_2), 4.04 (1H, d, J=8.8, CH), 5.04 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.27 (1H, d, J=11.2, NC$\underline{H}_B$HO), 6.11 (1H, dd, J=8.8, 16.1, =CH), 6.70 (1H, d, J=16.1, =CH), 7.40 (5H, m, Ar-H)
3c-B	—	290	1.14 (3H, t, J=7.3, CH_3), 1.21 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.85 (1H, m, C$\underline{H}_A$H), 2.12 (1H, m, C$\underline{H}_B$H), 2.35 (2H, q, J=7.3, $COCH_2$), 2.68 (2H, m, CH_2), 3.39 (1H, dd, J=5.5, 8.3, CH), 5.15 (2H, s, NCH_2O), 7.26 (5H, m, Ar-H)
3d-A	—	276	0.93—1.85 (11H, m, C_6H_{11}), 1.23 (3H, s, CH_3), 1.27 (3H, s, CH_3), 2.08 (3H, s, CH_3), 3.08 (1H, d, J=5.1, CH), 5.19 (1H, d, J=12.2, NC$\underline{H}_A$HO), 5.22 (1H, d, J=12.2, NC$\underline{H}_B$HO)
3d-B	—	268	0.90—1.90 (11H, m, C_6H_{11}), 1.15 (3H, t, J=7.3, CH_3), 1.25 and 1.27 (6H, each s, $CH_3 \times 2$), 2.36 (2H, q, J=7.3, $COCH_2$), 3.07 (1H, d, J=9.8, CH), 5.18 (1H, d, J=11.0, NC$\underline{H}_A$HO), 5.25 (1H, d, J=11.0, NC$\underline{H}_B$HO)
3f-A	—	220	1.99 (3H, s, CH_3), 2.95 (1H, dd, J=2.9, 15.1, C$\underline{H}_A$H), 3.44 (1H, dd, J=5.4, 15.1, C$\underline{H}_B$H), 4.73 (1H, dd, J=2.9, 5.4, CH), 4.83 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.32 (1H, d, J=11.2, NC$\underline{H}_B$HO), 7.33 (5H, m, Ar-H)
3e-B	76—77	292	0.81 (3H, s, CH_3), 1.11 (3H, t, J=7.3, CH_3), 1.41 (3H, s, CH_3), 2.32 (2H, q, J=7.3, CH_2), 3.82 (3H, s, OCH_3), 4.47 (1H, s, CH), 5.00 (1H, d, J=11.0, NC$\underline{H}_A$HO), 5.42 (1H, d, J=11.0, NC$\underline{H}_B$HO), 6.92 (2H, d, J=8.8, Ar-H), 7.13 (2H, d, J=8.8, Ar-H)
3f-B	—	234	1.07 (3H, t, J=7.8, CH_3), 2.26 and 2.27 (2H, each q, J=7.8, $COCH_2$), 2.95 (1H, dd, J=2.9, 15.1, C$\underline{H}_A$H), 3.44 (1H, dd, J=5.4, 15.1, C$\underline{H}_B$H), 4.73 (1H, dd, J=2.9, 5.4, CH), 4.85 (1H, d, J=11.5, NC$\underline{H}_A$HO), 5.32 (1H, d, J=11.5, NC$\underline{H}_B$HO), 7.37 (5H, m, Ar-H)
3g-A (*cis*)	—	276	0.66—1.43 (9H, m, C_4H_9), 2.01 (3H, s, $COCH_3$), 3.46 (1H, dt, J=5.8, 7.8, CH), 4.91 (1H, d, J=5.8, CH), 4.94 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.38 (1H, d, J=11.2, NC$\underline{H}_B$HO), 7.33 (5H, m, Ar-H)
3g-B (*cis*)	31—31.5	289 (M^+)	0.68 (3H, t, J=7.8, CH_3), 0.96—1.28 (6H, m, $CH_2CH_2CH_2$), 1.08 (3H, t, J=7.8, CH_3), 2.99 (2H, q, J=7.8, $COCH_2$), 3.46 (1H, dt, J=5.7, 7.8, CH), 4.92 (1H, d, J=5.7, CH), 4.97 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.40 (1H, d, J=11.2, NC$\underline{H}_B$HO), 7.30 (5H, m, Ar-H)
3g-B (*trans*)	—	289 (M^+)	0.89 (3H, t, J=7.3, CH_3), 1.07 (3H, t, J=7.3, CH_3), 1.35 (4H, m, CH_2CH_2), 1.81 (2H, m, CH_2), 2.26 (2H, q, J=7.3, CH_2), 3.08 (1H, m, CH), 4.38 (1H, d, J=2.4, CH), 4.86 (1H, d, J=11.2, NC$\underline{H}_A$HO), 5.34 (1H, d, J=11.2, NC$\underline{H}_B$HO), 7.35 (5H, m, Ar-H)
3h-B (*cis*)	71—72	405	1.14 (3H, t, J=7.3, CH_3), 2.38 (2H, q, J=7.3, $COCH_2$), 4.77 (1H, dd, J=5.0, 8.8, CH), 5.16 (1H, d, J=11.5, NC$\underline{H}_A$HO), 5.43 (1H, d, J=11.5, NC$\underline{H}_B$HO), 6.20 (1H, dd, J=8.8, 16.1, =CH), 6.74 (1H, d, J=16.1, =CH), 7.25 (5H, m, Ar-H), 7.74 (2H, dd, J=2.9, 5.4, Ar-H), 7.85 (2H, dd, J=2.9, 5.4, Ar-H)

1 mmol) and 25% ammonium hydroxide (0.2 ml) in MeOH (5 ml) was treated in the same manner as described above to give (+)-**1a** (165 mg, 94%). The spectral data of the product were identical with those of (±)-**1a**, $[\alpha]_D^{21}$ +99.5° (c=1.0, MeOH).

A solution of *tert*-butyldimethylsilyl chloride (180 mg, 1.2 mmol), (+)-**1a** (157 mg, 0.9 mmol) and triethylamine (150 mg, 1.5 mmol) in CH_2Cl_2 (3 ml) was stirred overnight at room temperature, and the solution was washed with water and brine, and then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column to give *N*-TBDMS-(+)-**1a** (263 mg, 91%), $[\alpha]_D^{22}$ = +117.7° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: −0.14 (3H, s, CH_3), 0.33 (3H, s, CH_3), 0.73 (3H, s, CH_3), 0.98 (9H, s, $C(CH_3)_3$), 1.44 (3H, s, CH_3), 4.33 (1H, s, CH), 7.30 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: −5.80, −4.95, 17.76, 19.00, 24.04, 26.40, 56.84, 65.93, 126.93, 127.71, 128.23, 139.08, 180.12.

2) Preparation of *N*-TBDMS-(*R*)-(+)-**1a** from (+)-**1f**: A solution of *N*-*tert*-butyldimethylsilyl chloride (180 mg, 1.2 mmol), (+)-**1f** (147 mg, 1 mmol) and triethylamine (150 mg, 1.5 mmol) in CH_2Cl_2 (3 ml) was stirred overnight at room temperature, and then the solution was washed with water and brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column to give *N*-TBDMS-(+)-**1f** (227 mg, 87%). ^{1}H-NMR ($CDCl_3$) δ: −0.15 (3H, s, CH_3), 0.20 (3H, s, CH_3), 0.90 (9H, s, $C(CH_3)_3$), 2.93 (1H, dd, J=2.9, 15.6, C$\underline{H}_A$H), 3.50 (1H, dd, J=5.9, 15.6, C$\underline{H}_B$H), 4.52 (1H, dd, J=2.9, 5.9, CH), 7.32 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: −6.07, −5.45, 18.52, 26.17, 48.77, 52.38, 126.44, 128.20, 128.70, 141.64, 172.97.

A solution of *N*-TBDMS-(+)-**1f** (227 mg, 0.95 mmol) in tetrahydrofuran (THF) (3 mml) was added to lithium diisopropylamine (LDA) (2 eq) [prepared by addition of a 1.6 M solution of *n*-butyllithium in hexane (1.2 ml, 2 mmol) to a solution of diisopropylamine (200 mg, 2 mmol) in THF (3 ml) at 0 °C] at 0 °C with stirring. The mixture was stirred for 15 min, then iodomethane (426 mg, 3 mmol) was added and the whole was stirred for 2 h. The reaction mixture was diluted with ether (5 ml), and treated with potassium bisulfate (204 mg, 1.5 mmol). After being stirred at room temperature for 3 min, the mixture was washed with water and brine, and then dried over $MgSO_4$. The residue obtained by concentration was chromatographed on a silica gel column to give an oil (141 mg), which was assumed to be the *trans* monomethylated product on the basis of its ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$) δ: −0.19 and 0.22, (6H, each s, $Si(CH_3)_2$), 0.92 (9H, s, $C(CH_3)_3$), 1.38 (3H, d, J=7.3, CH_3), 3.08 (1H, dt, J=2.3, 7.3, CH), 4.09 (1H, d, J=2.3, CH), 7.29—7.40 (5H, m, Ar-H).

This oily product was treated as follows: A 1.3 M solution of *sec*-butyllithium in cyclohexane (0.8 ml, 1 mmol) was added to a solution of the oil described above in THF (5 mml) at −70 °C. The mixture was stirred for 5 min, then iodomethane (140 mg, 1 mmol) was added. The mixture was further stirred for 2 h, and potassium bisulfate (200 mg) was added. Insoluble materials were filtered off and the filtrate was concentrated to give an oily residue, which was subjected to preparative thin layer chromatography (THF–hexane) to afford an oil (60 mg). The ^{1}H-NMR spectrum of this product was identical with that of *N*-TBDMS-**1a**, and the retention time in HPLC analysis on a chiral column was agreed well

with that of *N*-TMDMS-(*R*)-(+)-**1a** prepared from (*R*)-(+)-**2a**.

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