the mixture was filtered, and the ether was distilled off using a rotary evaporator, yielding a dark red oil. The oil was analyzed by gas chromatography, showing the same four products that had been found in the pyrolysis of tosylhydrazone lithium salt **26**, but in totally different yields: 5,5-diphenyl-1,3-cyclohexadiene, **28** (2.0%), 1-methylene-6,6-diphenyl-2-cyclohexene, **30** (1.5%), 1-methylene-4,4-diphenyl-2-cyclohexene, **29** (0.5%), and 4,4-diphenyl-2-cyclohexenone, **6** (45.1%).

Determination of k_1. Since eq 8 is a symmetrical equation it was necessary to determine k_1 in an independent manner. This was accomplished by measurement of the loss of starting tosylhydrazone salt with an HPLC analysis. To a 25-mL round-bottom flask fitted with a rubber septum and an outlet connected to a measuring burette were added constant amounts (0.45 g, 0.0011 mol) of the tosylhydrazone lithium salt and of the internal standard *N,N*-dimethyl-*p*-tolylsulfonamide (0.22 g, 0.0011 mol) dissolved in 5.00 mL of freshly distilled DMSO. The mixture was heated at 125 °C, and five 0.5-mL aliquots were taken at different time intervals. The aliquots were quenched in cold empty test tubes set in an ice bath (the test tubes were not left in the ice bath too long since DMSO freezes at about 20 °C). Then 0.5 mL of 10% acetic acid in DMSO was added in order to convert the tosylhydrazone lithium salt back to its tosylhydrazone, since the latter is much easier to analyze on the HPLC.

The five aliquots were analyzed with HPLC and a reverse-phase column (Zorbax) and the following conditions: eluting solvent 60% CH_3CN and 40% H_2O; UV 250 and 260 nm for tosylhydrazones corresponding to **26** and **32**, respectively. The following retention times were obtained: internal standard 3 min, tosylhydrazone corresponding to **26** 10 min, and tosylhydrazone corresponding to **32**, 8 min. The rate constant, k_1, for decomposition of **26** is 5.0 h^{-1} at 125 °C, which compares well with the slow step k_1 from the curve fitting analysis (k_1 = 3.85 h^{-1} at 125 °C), while the rate constant k_1 for the decomposition of **32** is 6.50 h^{-1}, which compares well with the slow step k_1 from the curve fitting analysis (k_1 = 6.39 h^{-1} at 125 °C).

Nucleophilic Ring-Opening Reactions of Morpholin-2-ones. A Resolution of *dl*-(Secondary-alkyl)amines

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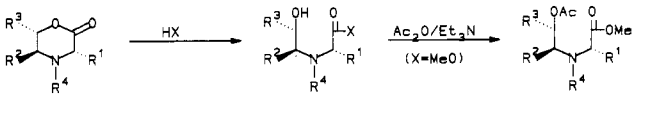
The alcoholysis of morpholin-2-ones yielded an equilibrium mixture of morpholin-2-one and the corresponding hydroxy ester. The equilibrium constants for the methanolysis of several substituted morpholin-2-ones were determined. Treatment of optically active morpholin-2-ones with (secondary-alkyl)amines resulted in stereoselective ring opening to afford hydroxy amides with up to 30% de. Hydrolysis of one such hydroxy amide regenerated the optically active (secondary-alkyl)amine and the morpholin-2-one.

Introduction

In our investigations of stereoselective reactions of amides, we have reported on the asymmetrically induced reduction of α-keto amides.[1] Although the aminolysis of α-amino acid esters seems to be an important methodology for the formation of amide bonds in peptide synthesis, there are few reports on the stereoselective aminolysis of esters. The reaction conditions generally employed in the aminolysis of esters are sufficiently severe to racemize the optically active α carbon of α-amino acid derivatives. Acyclic α-amino acid esters are sterically labile and should be less effective in asymmetric induction than their conformationally more stable cyclic analogues.

We have recently prepared optically active morpholin-2-ones **1** either from 2-amino alcohols and α-bromo esters or from α-amino acids and 1,2-dibromoethane.[2] In general, these cyclic esters are about 100 times more reactive than acyclic esters in such nucleophilic substitution reactions as alcoholysis and aminolysis.[3] We wished to compare nucleophilic ring-opening reactions such as hydrolysis, alcoholysis, and aminolysis of these cyclic α-amino acid esters with the same reactions of a carbocyclic lactone. Furthermore, we wished to investigate **1** as a model for asymmetric induction on amide bond formation from α-amino acid esters by aminolysis. Since α-lactones form equilibrium mixtures with their ring-opening products on hydrolysis and alcoholysis,[4] 2-[(2-hydroxyethyl)amino]-acetic acid and its homologues should be easily cyclized into morpholin-2-ones. Accordingly, the aminolysis of **1** followed by hydrolysis should provide a kinetic resolution of amines. There have been a few reports on the kinetic resolution of amino acids by (*S*)-α-amino acid esters in the presence of condensing agents,[5] with moderate stereose-

Scheme I



(1) (3) X=OH (4) X=OMe (5) (6) X=NHCHPh Me (7) X=NHCHEt Me

a: R^1=R^2=R^3=H, R^4=$PhCH_2$
b: R^1=R^2=R^3=H, R^4=Me
c: R^1=Me, R^2=R^3=H, R^4=$PhCH_2$
d: R^1=R^3=H, R^2=Me, R^4=$PhCH_2$
e: R^1=R^2=H, R^3=Me, R^4=$PhCH_2$
f: R^1=i-Bu, R^2=R^3=H, R^4=$PhCH_2$
g: R^1=i-Pr, R^2=R^3=H, R^4=$PhCH_2$

Table I. pH Dependence of the Hydrolysis of 4-Benzylmorpholin-2-one (1a) (25 °C)

	pH[a]					
	4.3	5.2	6.5	7.3	8.3	9.4
k ($\times 10^{-4}$ s^{-1})	4.9	1.8	0.98	0.79	1.6	3.0

[a] Represents the initial pH of the reaction mixture.

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Table II. Equilibrium Constants and ΔH in the Methanolysis of Morpholin-2-ones 1a–e and δ-Valerolactone (2)

compd	R^1	R^2	R^3	R^4	convn (%)[a]	K[b]	ΔH^{25} (kJ/mol)
1a	H	H	H	CH_2Ph	44	1.26	14.4
1b	H	H	H	Me	66	0.52	11.9
1c	Me	H	H	CH_2Ph	41	1.45	10.2
1d	H	Me	H	CH_2Ph	23	3.41	13.5
1e	H	H	Me	CH_2Ph	28	2.57	c
2	H	H	H		>95	<0.05	20.8

[a] Represents the amount of hydroxy ester at equilibrium at 60.9 °C. [b] Equilibrium constants at 60.9 °C. [c] Not determined.

lectivity. We report here on the hydrolysis and alcoholysis of morpholin-2-ones, the enantioselective aminolysis of 1 with racemic amines, and the kinetic resolution of amines (Scheme I).

Results and Discussion

The rate constants for the hydrolysis of 4-benzylmorpholin-2-one (**1a**) to the corresponding hydroxy carboxylic acid **3a** are shown in Table I. Hydrolysis occurred quite rapidly and was accelerated by the presence of an acid or a base. Under the same conditions, the hydrolysis of δ-valerolactone (**2**) was too fast to be evaluated.

In the methanolysis of **1a** with a large excess of methanol, hydroxy ester **4a** was detected spectroscopically but could not be isolated; most of the starting material was recovered. However, when the methanolysis mixture was treated immediately with acetyl chloride, the ring-opened *O*-acetate **5a** was isolated in 27% yield along with **1a** (36% recovery). Reaction of *N*-benzyl-2-aminoethanol with methyl bromoacetate followed by quenching with acetyl chloride gave *O*-acetate **5a** in 10% yield along with **1a** (69%). The reaction of **1** with CD_3OD was monitored by ^1H NMR, and a decrease in **1** with time was indicated by a decrease in the proton signal of the 6-position at 4.32 ppm. However, after a span of time there was not change in the ratio of **1** to **4**. Thus we conclude that **1** and the hydroxy ester **4** exist as an equilibrium mixture in methanol.

The equilibrium constants and ΔH for the methanolysis of **1** and δ-valerolactone (**2**) in CD_3OD are listed in Table II. The equilibrium constants increase in the order **2** < **1b** < **1a** < **1c** < **1e** < **1d**, the highly substituted compounds being more resistant to nucleophilic attack. Thus the equilibrium constants depend mostly on steric factors rather than on the effect of the nitrogen atom.

The reaction of (*S*)-**1c** with 10 molar equiv of *dl*-1-phenylethylamine at 100 °C gave the corresponding hydroxy amide **6c** in 95% yield. There are several reports on GLC separations of amines on optically inactive stationary phases via their diastereomeric amides,[6] and we were able to separate the diastereomeric hydroxy amides **6c** by capillary GC. Comparison of the peaks in their ^1H NMR spectra indicated the formation of (3*S*,1′*S*)-**6c** with 18% de. Similar reactions of (*S*)-**1d** and (*S*)-**1e** were also examined, and from the former we obtained (5*S*,1′*R*)-**6d** with 5% de. The diastereomers from the reaction of (*S*)-**1e** could not be separated, and the de could not be determined (Table III).

By comparison, the reaction of *N*-benzyl-*N*-methylvaline methyl ester (**9**), the acyclic analogue of **1g**, with *dl*-1-phenylethylamine was sluggish, and the corresponding amide was not obtained. This result indicates that the reactivity of the ester moiety toward nucleophiles is enhanced by the lactone-like structure of the morpholin-2-one.

Table III. Aminolysis of 1 with (Secondary-alkyl)amines

morpholin-2-one	amine	product	yield (%)	de (%)	conf
(*S*)-**1c**	*dl*-PhCHMeNH$_2$	**4c**	97	18	3*S*,1′*S*
(*S*)-**1d**	*dl*-PhCHMeNH$_2$	**4d**	66	5	5*S*,1′*R*
(*S*)-**1e**	*dl*-PhCHMeNH$_2$	**4e**	75		
(*S*)-**1f**	*dl*-PhCHMeNH$_2$	**4f**	70	20	3*S*,1′*S*
(*S*)-**1g**	*dl*-PhCHMeNH$_2$	**4g**	66	30	3*S*,1′*S*
dl-**1g**	(*S*)-PhCHMeNH$_2$	**4g**	96	5	3*S*,1′*S*
(*S*)-**1g**	*dl*-EtCHMeNH$_2$	**5g**	49	27	*a*

[a] The configuration was not determined.

Table IV. Aminolysis of 1g with *dl*-1-Phenylethylamine

solvent[a]	catalyst	time (h)	yield of **6g** (%)	de (%)	conf
none	none	24	66	30	3*S*,1′*S*
MeCN	none	24	4	32	3*S*,1′*S*
DMF	none	24	4	20	3*S*,1′*S*
THF	none	24	4	26	3*S*,1′*S*
C_6H_6	none	24	5	30	3*S*,1′*S*
CH_2Cl_2	none	24	5	75	3*S*,1′*S*
$CHCl_3$	none	24	5	29	3*S*,1′*S*
CCl_4	none	24	6	43	3*S*,1′*S*
EtOH	none	24	6	15	3*S*,1′*S*
MeOH	none	24	6	1	3*S*,1′*S*
none	BF_3·Et_2O	12	11	34	3*S*,1′*S*
none	TsOH	24	19	31	3*S*,1′*S*
none	DABCO	24	6	29	3*S*,1′*S*
THF	LAH	24	20	0	
MeOH	NaCN[b]	84	3	34	3*S*,1′*R*

[a] 0.2 M solutions were employed. [b] 1.0 M solution of NaCN was employed.

Since **1c**, with a methyl group in the 3-position, showed greater asymmetric induction than 3-unsubstituted **1d**, we examined the reactions of other chiral 3-substituted morpholin-2-ones. The reaction of (*S*)-**1f** (3-*i*-Bu) with *dl*-1-phenylethylamine resulted in the formation of (3*S*,1′*S*)-**6f** with 20% de, while the same reaction of (*S*)-**1g** (3-*i*-Pr) gave (3*S*,1′*S*)-**6g** with 30% de (Table III). The reaction product of **1g** with 2-butylamine had a 28% excess of either 3*S*,1′*R* or 3*S*,1′*S* hydroxy amide **7g**; the configuration was not determined.

On the other hand, treatment of *dl*-**1c** with 0.5 equiv of (*S*)-1-phenylethylamine for 20 h at 100 °C gave the hydroxy amide **6c** in 96% yield based on the amine and containing a 5% de of the 3*S*,1′*S* isomer. The unreacted **1c** was recovered in 46% yield and showed an 11% op of its *R* isomer, suggesting that morpholin-2-ones can also be resolved with an optically active amine.

The de of **6c** obtained from the reaction of **1c** with *dl*-1-phenylethylamine was not changed by using different

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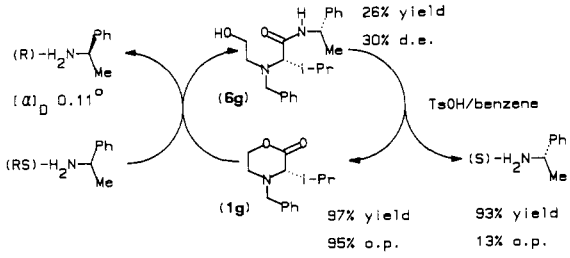
Scheme II



reaction times or different reaction temperatures between −78 °C and room temperature. On increasing the amount of 1-phenylethylamine from 1 to 8 equiv, a gradual increase in the rate of reaction was observed. Therefore, all subsequent experiments were carried out with 10 molar equiv of amine.

The same reaction was carried out in various solvents (Table IV). No change in stereoselectivity was observed in the aprotic solvents acetonitrile, dimethylformamide, tetrahydrofuran, and benzene. Although the de increased significantly in dichloromethane and carbon tetrachloride (but not in chloroform), large amounts of byproducts were formed, probably reflecting reaction of the amine with the solvent. On the other hand, a decrease in de was observed in the protic solvents ethanol and methanol, especially in the latter. In addition, the chemical yields of **6g** were low in all solvents, and we conclude that the aminolysis of 1 should be carried out without solvent.

Acid or base catalysts have been investigated to accelerate the aminolysis of esters,[7] and we explored the effect of typical catalysts on the reaction of **1g** with 1-phenylethylamine. No amide was detected when strong bases such as sodium methoxide[8] and sodium hydride[9] were employed. The acidic catalysts *p*-toluenesulfonic acid and BF_3·OEt_2 gave substantially lower yields of **6g** than were obtained in the neat reaction, with no increase in stereoselectivity (Table IV). Activation of 1-phenylethylamine with lithium aluminum hydride[10] gave a moderate yield of **6g** but no stereoselectivity. The use of potassium iodide, an effective catalyst for aminolysis of esters,[11] did not yield any **6g**.

Sodium cyanide is an effective catalyst for the aminolysis of esters,[12] the acceleration of the reaction being attributed to the formation of an intermediate acyl cyanide. In the reaction of (*S*)-**1g** with *dl*-1-phenylethylamine in the presence of sodium cyanide, the *R* amine reacted preferentially to yield (3*S*,1′*R*)-**6g** with a de of 34% but with a chemical yield of only 3% (Table IV).

In order to investigate the possibility of resolving racemic amines with this reaction, (*S*)-**1g** was treated with 10 molar equiv of *dl*-1-phenylethylamine for 1 day at 100 °C to yield 26% of the 3*S*,1′*S*-enriched **6g**. The unreacted 1-phenylethylamine showed $[\alpha]^{31}_D$ +0.11° (neat), indicating about 11% optical resolution to the *R* isomer. Hydrolysis of the 3*S*,1′*S*-enriched **6g** with 2 molar equiv of *p*-toluenesulfonic acid in benzene gave 1-phenylethylamine (93%) enriched with the *S* isomer with an op of 13%. The (*S*)-**1g** was regenerated in 97% yield, thus retaining >95% of the chirality of **1g** (Scheme II).

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded on Hitachi R-24 (60 MHz) and JOEL-100 (100 MHz) spectrometers with tetramethylsilane as internal standard. HPLC was performed on a JASCO Familic-100 high pressure micro liquid chromatograph. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 230–400 mesh). Morpholin-2-ones **1a**,**c**–**g** and the hydroxy carboxylic acid **3a** were prepared as previously reported.[2] 4-Methylmorpholin-2-one (**1b**) was prepared by the method previously reported[2] from *N*-methylethanolamine and methyl bromoacetate and showed physical properties identical with those in the literature.[13] 4-Benzyl-3-isobutylmorpholin-2-one (**1f**) was prepared according to the above method from *N*-benzylleucine and ethylene bromide: 57% yield; bp 160 °C/5 mmHg; IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 0.92 (d, 3 H, *J* = 6.4 Hz), 0.94 (d, 3 H, *J* = 5.9 Hz), 1.7–2.1 (m, 3 H), 2.49 (dt, 1 H, *J* = 5.9 and 13.2 Hz), 3.32 (t, 1 H, *J* = 5.9 Hz), 3.36 (d, 1 H, *J* = 13.2 Hz), 3.95 (d, 1 H, *J* = 13.2 Hz), 4.35 (dd, 2 H, *J* = 4.0 and 5.9 Hz), 7.31 ppm (s, 5 H); ^{13}C NMR (δ, $CDCl_3$) 22.2 (q), 23.0 (q), 24.7 (d), 39.6 (t), 45.9 (t), 58.5 (t), 62.8 (d), 67.2 (t), 127.5 (d), 128.5 (d), 128.8 (d), 137.4 (s), 171.2 ppm (s). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.54; H, 8.62; N, 5.61.

Determination of the Rate of Hydrolysis of 1a. The hydrolysis of **1a** was carried out in the pH range 5 to 10 by using a Sorensen buffer (KH_2PO_4–Na_2HPO_4) at room temperature. A small portion was removed with time from the reaction mixture and subjected to liquid chromatography (Fine SIL C_{18}–10 column). The rate of hydrolysis of **1b** and **2** in deuterium oxide was too rapid to be measured.

Methanolysis of Morpholin-2-ones 1a–e and δ-Valerolactone (2) and Determination of Equilibrium Constants. A 1.0–1.5 M methanol solution of 4-benzylmorpholin-2-one was placed in a micro tube. The solution was heated at various temperatures (40 to 100 °C) and ^{1}H NMR measurements were carried out at certain time intervals. The reaction was monitored by the decrease of the C-6 protons of the morpholin-2-one or lactone, using 1,1,2,2-tetrachloroethane as an internal standard, until the reaction reached equilibrium. Acetylation of the newly formed hydroxy ester by the reaction of **1a** in methanol was performed by removal of the solvent by evaporation in vacuo, followed by treatment of the residue with acetyl chloride (a large excess) in dichloromethane in the presence of triethylamine to yield the *O*-acetate: IR ($CHCl_3$) 1740 and 1720 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 1.99 (s, 3 H), 2.93 (t, 2 H, *J* = 6 Hz), 3.40 (s, 2 H), 3.68 (s, 3 H), 3.87 (s, 2 H), 4.16 (t, 2 H, *J* = 6 Hz), and 7.34 ppm (s, 5 H) exact mass M^+ calcd for $C_{14}H_{19}NO_4$ 265.1309, found 265.1298.

Reaction of Morpholin-2-ones 1c–g and Ester 9. *N*-Benzyl-*N*-methyl-L-valine methyl ester (**9**) was obtained by esterification of (*S*)-*N*-benzyl-*N*-methylvaline[14] by using diazomethane: 71% yield; bp 140 °C/5 mmHg; IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 0.86 (d, 3 H, *J* = 6.3 Hz), 1.03 (d, 3 H, *J* = 6.8 Hz), 1.8–2.3 (m, 1 H), 2.20 (s, 3 H), 2.85 (d, 1 H, *J* = 11 Hz), 3.46 (d, 1 H, *J* = 13.7 Hz), 3.69 (s, 3 H), 3.74 (d, 1 H, *J* = 13.7 Hz), 7.27 ppm (s, 5 H); ^{13}C NMR (δ, $CDCl_3$) 19.3 (q), 19.8 (q), 27.3 (d), 37.6 (q), 50.3 (q), 58.5 (t), 72.9 (d), 126.7 (d), 128.0 (d), 128.4 (d), 139.5 (s), and 171.9 ppm (s). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 8.99; N, 5.95. Found: C, 71.57; H, 9.06; N, 5.96.

The reaction of 4-benzyl-3-methylmorpholin-2-one (**1c**) with various amounts of *dl*-1-phenylethylamine was carried out at 100 °C for 24 h, and the stereoselectivity of the reaction was determined by GC separation of the resulting diastereomers. The configurations of the diastereomers were determined by preparation of authentic samples. The stereoselectivity of the reaction reached a maximum when 10 molar equiv of amine was employed; therefore, all experiments were carried out by using 10 molar equiv of the amine. The reaction of **1c** with 1-phenylethylamine at various temperatures was monitored by GC with time using benzanilide as an internal standard. The reaction of morpholin-2-ones **1d**–**g** and ester **9** with 1-phenylethylamine and 2-bu-

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tylamine were carried out for 24 h. The reaction mixture was subjected to GC or worked up as described previously[2] to yield the pure hydroxy amides (**6** or **7**).

***N*-Benzyl-*N*-(2-hydroxyethyl)-*N'*-(1-phenylethyl)-(*S*)-alaninamide (6c)**: 97% yield; bp 190 °C/10^{-2} mmHg; IR ($CHCl_3$) 3330 and 1655 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 1.20 and 1.23 (a pair of d, 3 H, J = 7.3 and 6.8 Hz, respectively), 1.42 and 1.44 (d, 3 H, J = 6.8 Hz), 2.4–2.8 (m, 2 H), 2.95 (br s, 1 H), 3.2–4.3 (m, 5 H), 4.9–5.2 (m, 1 H), 7.0–7.4 (m, 10 H), and 8.00 and 8.20 ppm (a pair of br d, 1 H, J = 8.3 and 7.8 Hz, respectively); ^{13}C NMR (δ, $CDCl_3$) 8.6 and 9.0 (q), 21.8 and 22.2 (q), 48.4 and 48.7 (d), 52.1 (t), 55.3 (t), 58.6 and 58.9 (d), 59.7 (t), 125.9 (d), 126.3 (d), 126.9 (d), 127.1 (d), 127.2 (d), 128.5 (d), 139.1 and 139.2 (s), 143.9 (s), and 172.9 ppm (s). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.49; H, 8.11; N, 8.53.

***N*-Benzyl-*N*-[(*S*)-1-methyl-2-hydroxyethyl]-*N'*-(1-phenylethyl)glycinamide (6d)**: 66% yield; mp 130–132 °C; IR (KBr) 3320, 3250, and 1650 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.90 (d, 3 H, J = 6.8 Hz), 1.35 (d, 3 H, J = 6.8 Hz), 2.7–3.9 (m, 8 H), 4.96 (dq, 1 H, J = 6.8 and 7.8 Hz), 7.23 (s, 5 H), 7.24 (s, 5 H), and 8.09 ppm (d, 1 H, J = 7.8 Hz); ^{13}C NMR (δ, $CDCl_3$) 10.6 (q), 22.1 (q), 48.5 (d), 53.6 (t), 54.7 (t), 57.9 (d), 63.8 (t), 126.1 (d), 127.2 (d), 128.4 (d), 128.8 (d), 138.9 (s), 143.6 (s), and 171.1 ppm (s). Anal. Cald for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.76; H, 8.16; N, 8.37.

***N*-Benzyl-*N*-(*S*)-(2-hydroxypropyl)-*N'*-(1-phenylethyl)-glycinamide (6e)**: 75% yield; bp 160 °C/10^{-2} mmHg; IR ($CDCl_3$) 3300 and 1655 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 1.08 (d, 3 H, J = 5.86 Hz), 1.43 (d, 3 H, J = 6.8 Hz), 2.4–2.6 (m, 1 H), 2.72 (br s, 1 H), 3.0–3.2 (m, 1 H), 3.3–4.0 (m, 3 H), 4.9–5.3 (m, 1 H), 7.0–7.5 (m, 10 H), and 7.7–8.0 ppm (br m, 1 H); ^{13}C NMR (δ, $CDCl_3$) 21.2 (q), 22. (q), 48.3 and 48.4 (d), 58.4 (t), 59.6 and 59.8 (t), 63.3 (t), 64.7 (d), 126.1 (d), 126.2 (d), 127.1 (d), 127.4 (d), 128.5 (d), 128.9 (d), 138.1 (s), 143.5 (s), and 170.2 ppm (s). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.50; H, 8.08; N, 8.54.

***N*-Benzyl-*N*-(2-hydroxyethyl)-*N'*-(1-phenylethyl)-(*S*)-leucinamide (6f)**: 70% yield; bp 190 °C/10^{-2} mmHg; IR ($CHCl_3$) 3420, 3320, and 1660 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.7–1.0 (m, 6 H), 1.43 and 1.46 (a pair of d, 3 H, J = 6.8 Hz), 1.3–2.0 (m, 3 H), 2.53 (br s, 1 H), 2.5–2.8 (m, 2 H), 3.1–3.3 (m, 1 H), 3.4–3.8 (m, 4 H), 4.9–5.2 (m, 1 H), 6.9–7.5 (m, 10 H), 7.71 ppm (d, 1 H, J = 8.3 Hz); ^{13}C NMR (δ, $CDCl_3$) 21.8 (q), 22.2 (q), 22.5 (q), 22.9 (q), 25.9 (d), 36.1 (t), 48.5 and 48.7 (d), 52.1 (t), 55.3 and 55.5 (t), 59.8 (t), 61.1 and 61.2 (d), 126.0 (d), 127.0 (d), 127.2 (d), 128.5 (d), 139.4 and 139.5 (s), 143.7 (s), and 172.7 ppm (s). Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.91; H, 8.83; N, 7.54.

***N*-Benzoyl-*N*-(2-hydroxyethyl)-*N'*-(1-phenylethyl)-(*S*)-valinamide (6g)**: 66% yield; bp 180° C/10^{-2} mmHg; IR ($CHCl_3$) 3420, 3320, and 1660 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.78 and 0.88 (a pair of d, 3 H, J = 6.4 Hz), 1.03 (d, 3 H, J = 6.8 Hz), 1.43 and 1.51 (a pair of d, 3 H, J = 7.4 Hz), 2.0–2.4 (m, 1 H), 2.5–3.1 (m, 3 H), 3.1–3.7 (m, 3 H), 3.8–4.2 (m, 1 H), 5.0–5.3 (m, 1 H), 6.48 and 6.68 (d, 1 H, J = 7.8 Hz), and 6.9–7.4 ppm (m, 10 H); ^{13}C NMR (δ, $CDCl_3$) 20.0 (q), 21.5 (q), 22.2 (q), 27.1 (d), 48.4 (d), 52.2 (t), 55.2 (t), 60.1 and 60.4 (t), 70.6 (d), 126.1 (d), 126.4 (d), 127.0 (d), 127.1 (d), 128.4 (d), 128.6 (d), 139.5 and 139.8 (s), 143.2 and 143.3 (s), and 170.6 and 170.9 ppm (s). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.47; H, 8.54; N, 7.95.

***N*-Benzyl-*N*-(2-hydroxyethyl)-*N'*-(2-butyl)-(*S*)-valinamide (7g)**: 49% yield; bp 160 °C/10^{-2} mmHg; IR ($CHCl_3$) 3430, 3300, and 1655 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.88 (d, 6 H, J = 6.3 Hz), 1.06 (d, 3 H, J = 6.4 Hz), 1.08 and 1.17 (a pair of d, 3 H, J = 6 Hz), 1.3–1.5 (m, 2 H), 1.9–2.4 (m, 1 H), 2.5–3.1 (m, 3 H), 3.2–3.7 (m, 3 H), 3.7–4.1 (m, 3 H), 6.59 (m, 1 H), and 7.27 ppm (s, 5 H); ^{13}C NMR (δ, $CDCl_3$) 10.5 and 10.8 (q), 20.1 (q), 20.5 and 21.1 (q), 26.9 and 27.1 (d), 29.5 and 29.7 (t), 46.4 (d), 52.3 (t), 55.1 (t), 60.4 and 60.6 (t), 70.8 and 71.0 (d), 126.9 (d), 128.4 (d), 140.1 (s), and 170.9 and 171.1 ppm (s). Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.26; H, 9.97; N, 9.06.

Hydrolysis of Hydroxy Amide 6g. Hydroxy amide **6g** (1 mmol) and *p*-toluenesulfonic acid (2.5 equiv) in benzene (40 mL) were heated at reflux for 90 h. The resulting solution was extracted with dilute hydrochloric acid. The acidic aqueous solution was extracted with dichloromethane (3 times), and the dichloromethane layer was combined with the original benzene solution, which was dried over anhydrous magnesium sulfate and evaporated to yield morpholin-2-one **1g** in 97% yield. The acidic aqueous solution was neutralized with dilute sodium hydroxide solution and extracted with dichloromethane (3 times). The dichloromethane layer was dried over anhydrous magnesium sulfate and evaporated to yield 1-phenylethylamine in 93% yield; $[\alpha]^{30}_D$ −5.30° (*c* 3.19, $CHCl_3$) (13% op) (lit.[15] $[\alpha]^{22}_D$ −40.3° (neat)).

Registry No. **1a**, 5453-99-6; **1b**, 18424-96-9; (*S*)-**1c**, 118460-10-9; *dl*-**1c**, 118493-34-8; (*S*)-**1d**, 118460-11-0; (*S*)-**1e**, 118460-12-1; (*S*)-**1f**, 118460-13-2; (*S*)-**1g**, 118460-14-3; *dl*-**1g**, 118493-35-9; **2**, 542-28-9; **4a**, 118460-24-5; **4a** (O-acetate), 118460-15-4; **4b**, 118460-25-6; **4c**, 118460-26-7; **4d**, 118460-27-8; **4e**, 118460-28-9; (3*S*,1′*S*)-**6c**, 118460-16-5; (5*S*,1′*S*)-**6d**, 118460-17-6; **6e**, 118460-18-7; (3*S*,1′*S*)-**6f**, 118460-19-8; (3*S*,1′*S*)-**6g**, 118460-20-1; (3*S*,1′*R*)-**6g**, 118460-21-2; **7g**, 118460-22-3; **9**, 118460-23-4; *dl*-$PhCHMeNH_2$, 618-36-0; (*S*)-$PhCHMeNH_2$, 2627-86-3; *dl*-$EtCHMeNH_2$, 33966-50-6; $MeNHCH_2CH_2OH$, 109-83-1; $BrCH_2COOMe$, 96-32-2; $PhCH_2$-Leu-OH, 2743-42-2; $BrCH_2CH_2Br$, 106-93-4; $HO(CH_2)_4COOMe$, 14273-92-8.

(15) Theilacker, W.; Winkler, H. G. *Chem. Ber.* **1954**, *87*, 690.