Asymmetric Synthesis of 2-Substituted-3-aminocarbonyl Propionic Acid

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An asymmetric synthetic route to 2-substituted-3-aminocarbonyl propionic acid, which is the significant component of low-molecular-weight renin inhibitors, is described. The key step of this synthesis is diastereoselective alkylation by using chiral oxazolidinone and benzyl bromoacetate.

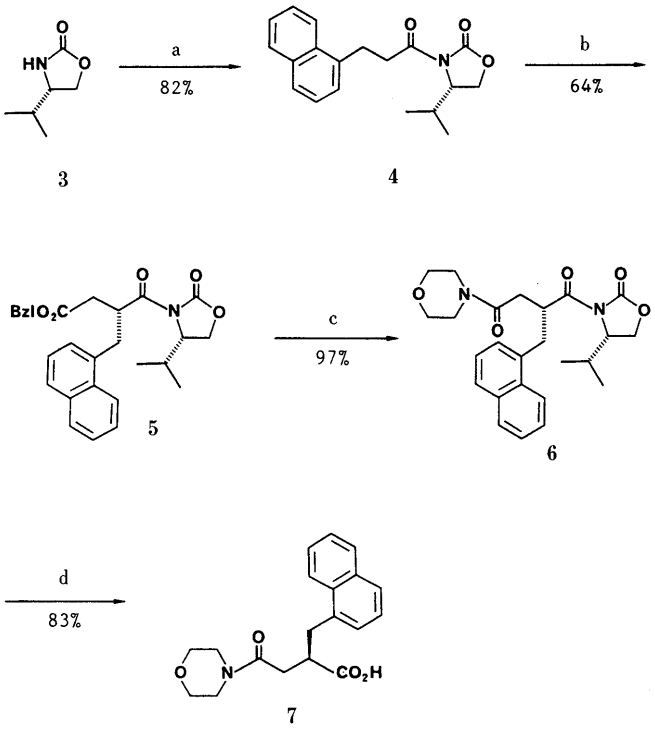
Keywords 2-substituted-3-aminocarbonyl propionic acid; N-terminal element; renin inhibitor; oxazolidinone; diastereoselective alkylation

The renin–angiotensin system plays an important role in the regulation of blood pressure.[1] Renin is an aspartic proteinase responsible for cleaving a decapeptide fragment from angiotensinogen, to generate angiotensin I.[2] Angiotensin I has no known biological activity, but it is converted to the octapeptide angiotensin II, which is a very potent vasoconstrictor and stimulates the release of aldosterone. The N-terminal sequence of human angiotensinogen is shown in Fig. 1. Renin cleaves the Leu–Val peptidic bond in angiotensinogen. Furthermore, renin has a high substrate specificity, and so an inhibitor of renin is expected to be an effective antihypertensive agent. Many peptide-like renin inhibitors based upon the substrate peptide sequence have been developed in several laboratories.[3] Recently, we reported orally active dipeptide renin inhibitors which contain 2-(*R*)-substituted-3-aminocarbonyl propionic acid as the N-terminal element.[4] These acids involve a retro-inverso amide bond and are considered to substitute for the Pro–Phe moiety (P_3–P_4 site). 2-(*R*)-(1-Naphthyl)methyl-3-morpholinocarbonyl propionic acid was first synthesized as the racemate by the Kissei group.[5]

The stereochemistry of the asymmetric carbon in the propionyl group is very significant and (*R*)-absolute configuration is necessary for renin inhibitory effect. Therefore we intended to develop an asymmetric synthetic method for 2-substituted-3-aminocarbonyl propionic acids. We wish to report here a facile asymmetric synthesis by using Evans's methodology.[6] This synthetic route involves diastereoselective alkylation using an optically active oxazolidinone and benzyl bromoacetate. A typical procedure is as follows (Chart 1).

The synthesis begins with the imide **4**, readily available in 82% yield from the (−)-oxazolidinone **3**. Treatment with lithium diisopropylamide followed by benzyl bromoacetate afforded **5** and its diastereomer (95 : 5).[7] The benzyl group of **5** was removed by hydrogenolysis using 10% Pd–C to give the carboxylic acid, and then treatment with morpholine, diethylphosphoryl cyanide,[8] and triethylamine afforded **6** in good yield. The stereochemistry of **6** was confirmed by X-ray analysis as shown in Fig. 2. Hydrolysis of **6** gave enantiomerically pure 2-(*R*)-(1-naphthyl)methyl-3-morpholinocarbonyl propionic acid **7** in 83% yield.[9]

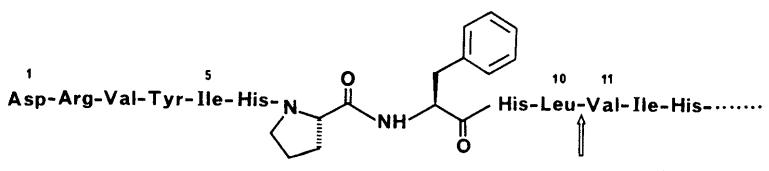
Some optically active propionic acids were synthesized in the same manner, and the results are shown in Table I.



3 4 5 6 7

a) i) *n*-BuLi, ii) (1-naphthyl)propionyl chloride, THF, −78 °C
b) i) LDA, ii) benzyl 2-bromoacetate, THF, −78→0 °C
c) i) H_2/Pd–C, EtOH, ii) morpholine, DEPC, NEt_3, THF, 0 °C
d) LiOH, aqueous THF, 0 °C

Chart 1



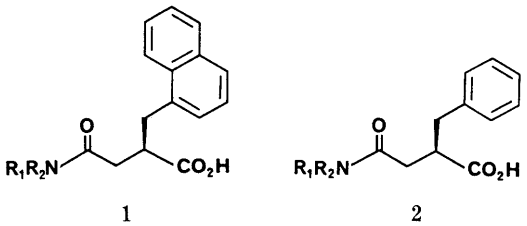
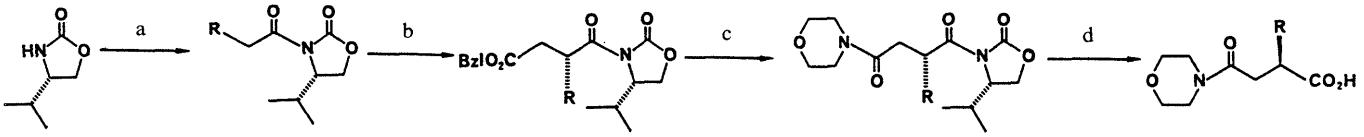


Fig. 1

TABLE I



3 **8a**: R = benzyl **8b**: R = 4-methoxybenzyl **9a, b** **10a, b** **11a, b**

a) i) *n*-BuLi, ii) acyl halide, THF, −78 °C
b) i) LDA, ii) benzyl 2-bromoacetate, THF, −78→0 °C
c) i) H_2/Pd–C, EtOH, ii) morpholine, DEPC, NEt_3, THF, 0 °C
d) LiOH, aqueous THF, 0 °C

	R	Yield (%)[a]				Diastereomer ratio of 9[b] 2(*R*):2(*S*)
		8	9	10	11	
a	Benzyl	85	74	99	76	95:5
b	4-Methoxybenzyl	80	72	93	84	97:3

a) Isolated yield. *b*) Determined by HPLC analyses.

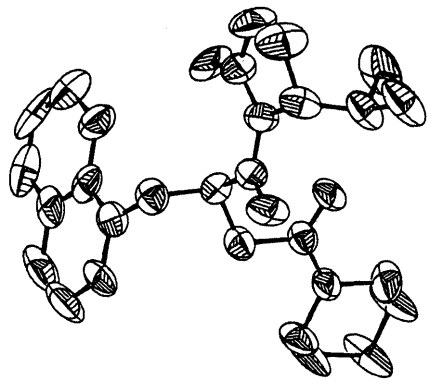


Fig. 2. Molecular Structure of **6**

We synthesized dipeptide renin inhibitors containing these propionic acids and evaluated their inhibitory activities. Among them, the inhibitors having the 2-(*R*)-(1-naphthyl)methyl-3-morpholinocarbonyl propionyl group, such as ES 6864, showed potent inhibitory effects against human renin.[4] Details of these biological activities will be reported elsewhere.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-102 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a JEOL JNM-GX 270 FT NMR spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. Mass spectra (MS) were obtained with a JEOL JMS-01SG or JMS D300 mass spectrometer. Column chromatography was done on Kieselgel 60 F_{254} (Merck, 70—230 mesh). In general, reactions were carried out under a nitrogen stream.

4-(*S*)-Isopropyl-3-[3-(1-naphthyl)-1-oxopropyl]-2-oxazolidinone (4) A solution of 4-(*S*)-isopropyl-2-oxazolidinone **3** (10.75 g, 83.2 mmol) in dry tetrahydrofuran (THF) (200 ml) was added dropwise to *n*-BuLi (1.6 M solution in *n*-hexane, 62.4 ml) at −78 °C under nitrogen. The mixture was stirred for 30 min, then a solution of 3-(1-naphthyl)propionyl chloride (21.82 g, 99.9 mmol) in dry THF (100 ml) was added dropwise over a period of 10 min. This reaction mixture was stirred for 1 h, then the reaction was quenched by the addition of 1 N HCl (100 ml) and brine (100 ml). This solution was extracted with AcOEt and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 10—20% AcOEt in *n*-hexane (v/v) afforded **4** (23.19 g, 82%) as crystals. Recrystallization from isopropyl ether gave an analytical sample, mp 80—82 °C, $[\alpha]_D^{20}$ +61.3° (*c* = 1, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.28; H, 6.74; N, 4.47. IR (Nujol): 1770, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 and 0.90 (d, each 3H, *J* = 7 Hz, $-CH(C\underline{H}_3)_2$), 2.39 (m, 1H, $-C\underline{H}(CH_3)_2$), 3.3—3.6 (m, 4H, $-C\underline{H}_2-$), 4.20 (m, 2H, $-C\underline{H}_2O-$), 4.43 (m, 1H, $-NC\underline{H}-$), 7.3—8.2 (m, 5H, Ar$\underline{H}$). MS *m/z*: 311 (M^+), 154, 141.

3-[3-Benzyloxycarbonyl-2-(*R*)-(1-naphthyl)methyl-1-oxopropyl]-4-(*S*)-isopropyl-2-oxazolidinone (5) A solution of **4** (10.00 g, 32.1 mmol) in dry THF (50 ml) was added to a stirred solution of lithium diisopropylamide (LDA) (prepared from diisopropylamine (5.4 ml) and *n*-BuLi (1.6 M solution in *n*-hexane, 22.06 ml)) at −78 °C. The mixture was stirred for 1 h, and then a solution of benzyl bromoacetate (15.26 ml, 96.3 mmol) in dry THF (50 ml) was added. The reaction mixture was stirred for 5 h at −78°→0 °C. After neutralization with 1 N HCl and brine, this solution was extracted with AcOEt and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 10—20% AcOEt in *n*-hexane (v/v) afforded **5** (9.45 g, 64%) as crystals. Recrystallization from ethyl ether gave an analytical sample, mp 145—146 °C, $[\alpha]_D^{20}$ +79.8° (*c* = 1, $CHCl_3$). *Anal.* Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 72.77; H, 6.06; N, 3.04. IR (Nujol): 1770, 1730, 1700 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 0.83 and 0.85 (d, each 3H, *J* = 7 Hz, $-CH(C\underline{H}_3)_2$), 2.27 (m, 1H, $-C\underline{H}(CH_3)_2$), 2.40 (dd, 1H, *J* = 16.9, 4.6 Hz, $-C\underline{H}_2Ar$), 3.02 (dd, 1H, *J* = 16.9, 10.3 Hz, $-C\underline{H}_2Ar$), 3.15 (dd, 1H, *J* = 13.5, 8.6 Hz, $-C\underline{H}_2CO_2-$), 3.51 (dd, 1H, *J* = 13.5, 7.3 Hz, $-C\underline{H}_2CO_2-$), 3.82 (dd, 1H, *J* = 8.8, 8.8 Hz, $-C\underline{H}_2O-$), 4.05 (dd, 1H, *J* = 8.8, 2.4 Hz, $-C\underline{H}_2O-$), 4.20 (m, 1H, $-C\underline{H}N-$), 4.79 (m, 1H, $-C\underline{H}CO-$), 5.03 (ABq, 2H, *J* = 12.5 Hz, $\Delta\delta$ = 0.06 ppm, $-OC\underline{H}_2Ph$), 7.2—8.3 (m, 12H, Ar$\underline{H}$). MS *m/z*: 459 (M^+), 368, 221, 130, 91.

The diastereomeric ratio was determined to be 95:5 by high performance liquid chromatography (HPLC) analysis (column, Senshu Pak ODS-1251-SH 4.6 i.d. × 250 mm; eluent, 65:35 CH_3CN–H_2O mixture; flow rate, 1.0 ml/min; t_R of **5**, 20.4 min; t_R of the 2-(*S*)-isomer, 23.3 min).

Independent Preparation and Separation of 5 and Its Diastereomer 1,5-Diazabicyclo[5.4.0]undecene-5 (DBU) (0.12 ml, 0.80 mmol) was added to a solution of **5** (180 mg, 0.39 mmol) in dry benzene (5 ml), and the mixture was refluxed for 6 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Separation of the two isomers was achieved by HPLC under the above conditions, and the ratio of **5** and its diastereomer was 3.3:1.

3-[1,4-Dioxo-4-morpholino-2-(*R*)-(1-naphthyl)methylbutyl]-4-(*S*)-isopropyl-2-oxazolidinone (6) The benzyl ester **5** (1.80 g, 3.92 mmol) in EtOH (180 ml) was hydrogenated with 10% Pd–C (500 mg) at room temperature under a hydrogen atmosphere overnight. Filtration and removal of the solvent gave the carboxylic acid. This product was dissolved in dry THF (100 ml). To this solution, morpholine (0.57 ml, 4.47 mmol), diethylphosphoryl cyanide (0.72 ml, 4.47 mmol), and triethylamine (0.66 ml, 4.73 mmol) were added dropwise under nitrogen at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. The solvent was removed *in vacuo*, and the residue was purified by silica gel column

chromatography. Elution with 20—30% AcOEt in *n*-hexane (v/v) afforded **6** (1.67 g, 97%) as crystals. Recrystallization from isopropyl ether gave an analytical sample, mp 127—129 °C, $[\alpha]_D^{20}$ +99.4° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.33; H, 6.70; N, 6.42. IR (Nujol): 1760, 1700, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 and 0.91 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.28 (dd, 1H, $J=16.2$, 4.4 Hz, $-CH_2Ar$), 2.34 (m, 1H, $-CH(CH_3)_2$), 2.94 (dd, 1H, $J=16.2$, 10.4 Hz, $-CH_2Ar$), 3.16 (dd, 1H, $J=13.4$, 9.0 Hz, $-CH_2CO-$), 3.1—3.7 (m, 9H, $-CH_2CO-$, morpholine-CH_2), 3.82 (dd, 1H, $J=9.0$, 9.0 Hz, $-CH_2O-$), 4.06 (dd, 1H, $J=9.0$, 2.6 Hz, $-CH_2O-$), 4.20 (m, 1H, $-CHN-$), 4.83 (m, 1H, $-CHCO-$), 7.3—8.3 (m, 7H, ArH). MS *m/z*: 438 (M^+), 310, 129.

X-Ray Crystallography of 6 A crystal with dimensions of $0.5\times0.3\times0.2$ mm, obtained from ethanol–hexane, was used for intensity measurement. Intensity data were obtained on a Rigaku AFC-5R diffractometer with graphite-monochromated Cu K_α radiation, and using the θ—2θ scan technique ($2\theta\leq128°$). During data collection three standard peaks, measured before every 200 reflections, showed no significant variation. The data were corrected for Lorentz and polarization effects but not for absorption. Among the 2288 unique reflections collected, 1629 were considered to be observed at the $2.0\sigma(F_o)$ level. Crystal data. $C_{25}H_{30}N_2O_5$, $M_r=438.5$. Orthorhombic, $P2_12_12_1$, $a=5.839(1)$, $b=22.117(4)$, $c=18.263(3)$ Å, $U=2358.5$ Å^3, $z=4$, $D_x=1.24$ g·cm^{-3}, $\mu(CuK_\alpha)=7.1$ cm^{-1}. The structure was solved by the direct method with MULTAIN[10] and refined by block-diagonal least-squares methods. The positions of the hydrogen atoms were estimated from standard geometry. Final refinements, with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for hydrogen atoms, lowered the *R* value to 0.062 ($Rw=0.078$, $w=1/\sigma^2(F_o)$).

2-(*R*)-(1-Naphthyl)methyl-3-morpholinocarbonyl Propionic Acid (7) The amide **6** (3.87 g, 8.83 mmol) was dissolved in aqueous THF (20% H_2O in THF (v/v), 100 ml), then lithium hydroxide monohydrate (741 mg, 17.7 mmol) was added at 0 °C, and the mixture was stirred for 3 h. The solvent was removed *in vacuo* and the residue was dissolved in 10% NaOH. This solution was washed with CH_2Cl_2, and then the aqueous layer was acidified with ice-cold 1 N HCl. This solution was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 5—10% MeOH in CH_2Cl_2 (v/v) afforded **7** (2.40 g, 83%) as amorphous crystals. $[\alpha]_D^{20}$ −37.9° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.88; H, 6.41; N, 4.45. IR ($CHCl_3$): 1710, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34—2.71 (m, 2H, $-CH_2Ar$), 3.15—3.73 (m, 11H, $-CH_2CO-$, $-CHCO_2H$, morpholine-CH_2), 7.25—8.14 (m, 7H, ArH). MS *m/z*: 327 (M^+), 240, 141.

The enantiomeric excess of **7** was determined to be >98% by HPLC analysis of the corresponding methyl ester (column, CHIRALCEL OC (Daicel) 4.6 i.d. × 250 mm; eluent, 50 : 50 *n*-hexane–2-propanol mixture; flow rate, 1.5 ml/min; t_R of methyl ester of **7**, 13.1 min; t_R of the 2-(*S*)-isomer, 21.2 min).

The authentic enantioisomer of **7** was synthesized in the same manner starting from (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone as a chiral auxiliary.

4-(*S*)-Isopropyl-3-(1-oxo-3-phenylpropyl)-2-oxazolidinone (8a) This compound was obtained in 85% yield (20.12 g) from **3** (11.75 g, 91.0 mmol) by the same procedure as used for the synthesis of **4**. Recrystallization from isopropyl ether gave an analytical sample, mp 62—63 °C, $[\alpha]_D^{20}$ +71.4° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.12; N, 5.43. IR (Nujol): 1785, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 and 0.89 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.35 (m, 1H, $-CH(CH_3)_2$), 3.00 (m, 2H, $-CH_2Ar$), 3.28 (m, 2H, $-CH_2CO-$), 4.20 (m, 2H, $-CH_2O-$), 4.41 (m, 1H, $-CHN-$), 7.15—7.35 (m, 5H, ArH). MS *m/z*: 261 (M^+), 130, 104, 91.

4-(*S*)-Isopropyl-3-[1-oxo-3-(4-methoxyphenyl)propyl]-2-oxazolidinone (8b) This compound was obtained in 80% yield (5.63 g) from **3** (3.13 g, 24.2 mmol) by the same procedure as used for the synthesis of **4**. Recrystallization from isopropyl ether gave an analytical sample, mp 62—64 °C, $[\alpha]_D^{20}$ +60.4° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.98; H, 7.25; N, 4.75. IR (KBr): 1777, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 and 0.90 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.35 (m, 1H, $-CH(CH_3)_2$), 2.93 (m, 2H, $-CH_2Ar$), 3.23 (m, 2H, $-CH_2CO-$), 3.78 (s, 3H, $-OCH_3$), 4.22 (m, 2H, $-CH_2O-$), 4.41 (m, 1H, $-CHN-$), 6.82 and 7.16 (d, each 2H, ArH). MS *m/z*: 291 (M^+), 134, 121.

3-[2-(*R*)-Benzyl-3-(benzyloxycarbonyl)propionyl]-4-(*S*)-isopropyl-2-oxazolidinone (9a) This compound was obtained in 74% yield (9.05 g) from **8a** (7.84 g, 30.0 mmol) by the same procedure as used for the synthesis of **5**. Recrystallization from isopropyl ether gave an analytical sample, mp 118—120 °C, $[\alpha]_D^{20}$ +86.6° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.78; H, 6.71; N, 3.54. IR (Nujol): 1780, 1730, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 and 0.87 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.31 (m, 1H, $-CH(CH_3)_2$), 2.47 (dd, 1H, $J=17.2$, 4.0 Hz, $-CH_2-$), 2.61 (dd, 1H, $J=13.0$, 9.0 Hz, $-CH_2-$), 2.85—3.10 (m, 2H, $-CH_2-$), 4.02 (dd, 1H, $J=8.9$, 8.9 Hz, $-CH_2O-$), 4.13 (dd, 1H, $J=8.9$, 2.7 Hz, $-CH_2O-$), 4.30 (m, 1H, $-CHN-$), 4.57 (m, 1H, $-CHCO-$), 5.05 (ABq, 2H, $J=12.3$ Hz, $\Delta\delta=0.05$ ppm, $-OCH_2Ph$), 7.1—7.4 (m, 10H, ArH). MS *m/z*: 409 (M^+), 318, 130, 91.

The diastereomeric ratio was determined to be 95 : 5 by HPLC analysis (column, Senshu Pak ODS-1251-SH 4.6 i.d. × 250 mm; eluent, 60 : 40 CH_3CN–H_2O mixture; flow rate, 1.0 ml/min; t_R of **9a**, 21.1 min; t_R of the 2-(*S*)-isomer, 23.9 min).

Independent Preparation and Separation of 9a and Its Diastereomer DBU (0.13 ml, 0.87 mmol) was added to a solution of **9a** (180 mg, 0.44 mmol) in dry benzene (5 ml). And this solution was refluxed for 6 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Separation of the two isomers was achieved by HPLC under the above conditions, and the ratio of **9a** and its diastereomer was 1.2 : 1.

3-[3-(Benzyloxycarbonyl)-2-(*R*)-(4-methoxybenzyl)propionyl]-4-(*S*)-isopropyl-2-oxazolidinone (9b) This compound was obtained in 72% yield (6.03 g) from **8b** (5.56 g, 19.1 mmol) by the same procedure as used for the synthesis of **5**. Recrystallization from isopropyl ether gave an analytical sample, mp 101—103 °C, $[\alpha]_D^{20}$ +82.4° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 67.94; H, 6.59; N, 3.38. IR (KBr): 1767, 1731, 1699 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 and 0.87 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.30 (m, 1H, $-CH(CH_3)_2$), 2.46 (dd, 1H, $J=17.2$, 4.0 Hz, $-CH_2-$), 2.54 (dd, 1H, $J=13.7$, 8.8 Hz, $-CH_2-$), 2.87—2.99 (m, 2H, $-CH_2-$), 3.77 (s, 3H, $-OCH_3$), 4.06 (dd, 1H, $J=8.8$, 8.8 Hz, $-CH_2O-$), 4.15 (dd, 1H, $J=8.8$, 2.8 Hz, $-CH_2O-$), 4.31 (m, 1H, $-CHN-$), 4.50 (m, 1H, $-CHCO-$), 5.05 (s, 2H, $-OCH_2Ph$), 6.81 and 7.16 (d, each 2H, ArH), 7.26—7.36 (m, 5H, ArH). MS *m/z*: 439 (M^+), 130, 121, 91.

The diastereomeric ratio was determined to be 97 : 3 by HPLC analysis (column, Senshu Pak ODS-1251-SH 4.6 i.d. × 250 mm; eluent, 55 : 45 CH_3CN–H_2O mixture; flow rate, 1.0 ml/min; t_R of **9b**, 30.6 min; t_R of the 2-(*S*)-isomer, 33.1 min).

Independent Preparation and Separation of 9b and Its Diastereomer DBU (0.68 ml, 4.55 mmol) was added to a solution of **9b** (1.00 g, 2.28 mmol) in dry benzene (20 ml), and the mixture was refluxed for 6 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Separation of the two isomers was achieved by HPLC under the above conditions, and the ratio of **9b** and its diastereomer was 2.9 : 1.

3-[2-(*R*)-Benzyl-1,4-dioxo-4-morpholinobutyl]-4-(*S*)-isopropyl-2-oxazolidinone (10a) This compound was obtained in 99% yield (2.41 g) from **9a** (2.56 g, 6.25 mmol) by the same procedure as used for the synthesis of **6**. Recrystallization from isopropyl ether gave an analytical sample, mp 139—141 °C, $[\alpha]_D^{20}$ +100.4° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 65.08; H, 7.26; N, 7.22. IR (Nujol): 1790, 1695, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 and 0.94 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.36 (dd, 1H, $J=16.1$, 3.7 Hz, $-CH_2Ph$), 2.37 (m, 1H, $-CH(CH_3)_2$), 2.62 (dd, 1H, $J=13.1$, 9.3 Hz, $-CH_2CO-$), 2.88 (dd, 1H, $J=16.1$, 11.0 Hz, $-CH_2Ph$), 3.01 (dd, 1H, $J=13.1$, 6.2 Hz, $-CH_2CO-$), 3.3—3.7 (m, 8H, morpholine-CH_2), 3.99 (dd, 1H, $J=8.9$, 8.9 Hz, $-CH_2O-$), 4.13 (dd, 1H, $J=8.9$, 2.6 Hz, $-CH_2O-$), 4.30 (m, 1H, $-CHN-$), 4.62 (m, 1H, $-CHCO-$), 7.2—7.4 (m, 5H, ArH). MS *m/z*: 388 (M^+), 260, 129.

3-[1,4-Dioxo-2-(*R*)-(4-methoxybenzyl)-4-morpholinobutyl]-4-(*S*)-isopropyl-2-oxazolidinone (10b) This compound was obtained in 93% yield (5.11 g) from **9b** (5.75 g, 13.1 mmol) by the same procedure as used for the synthesis of **6**. Recrystallization from isopropyl ether gave an analytical sample, mp 119—121 °C, $[\alpha]_D^{20}$ +91.1° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.07; H, 7.27; N, 6.90. IR (KBr): 1762, 1697, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 and 0.94 (d, each 3H, $J=7$ Hz, $-CH(CH_3)_2$), 2.35 (m, 1H, $-CH(CH_3)_2$), 2.35 (dd, 1H, $J=16.1$, 3.7 Hz, $-CH_2-$), 2.55 (dd, 1H, $J=13.2$, 9.2 Hz, $-CH_2-$), 2.86 (dd, 1H, $J=16.1$, 11.0 Hz, $-CH_2-$), 2.95 (dd, 1H, $J=13.2$, 6.2 Hz, $-CH_2-$), 3.3—3.7 (m, 8H, morpholine-CH_2), 3.78 (s, 3H, $-OCH_3$), 4.03 (dd, 1H, $J=8.9$, 8.9 Hz, $-CH_2O-$), 4.15 (dd, 1H, $J=8.9$, 2.8 Hz, $-CH_2O-$), 4.30 (m, 1H, $-CHN-$), 4.57 (m, 1H, $-CHCO-$), 6.82 and 7.18 (d, each 2H, ArH). MS *m/z*: 418 (M^+), 290, 161, 121.

2-(*R*)-Benzyl-3-morpholinocarbonyl Propionic Acid (11a) This compound was obtained in 76% yield (1.09 g) from **10a** (2.00 g, 5.15 mmol) by the same procedure as used for the synthesis of **7**, $[\alpha]_D^{20}$ −15.8° ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C,

64.63; H, 7.16; N, 4.77. IR ($CHCl_3$): 1710, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.34—2.67 (m, 2H, $-CH_2Ph$), 2.77—3.78 (m, 11H, $-CH_2CO-$, $-CHCO_2H$, morpholine-CH_2), 7.17—7.34 (m, 5H, ArH). MS *m/z*: 277 (M^+), 129, 91.

The enantiomeric excess of **11a** was determined to be >98% by HPLC analysis of the corresponding methyl ester (column, CHIRALCEL OC (Daicel) 4.6 i.d. × 250 mm; eluent, 30:70 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of methyl ester of **11a**, 11.9 min; t_R of the 2-(*S*)-isomer, 15.6 min).

2-(*R*)-(4-Methoxybenzyl)-3-morpholinocarbonyl Propionic Acid (11b) This compound was obtained in 84% yield (2.16 g) from **10b** (3.50 g, 8.36 mmol) by the same procedure as used for the synthesis of **7**, $[\alpha]_D^{20}$ −12.1° (c=1, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.16; H, 6.89; N, 4.11. IR ($CHCl_3$): 1710, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.3—3.7 (m, 13H, $-CH_2Ar$, $-CH_2CO-$, $-CHCO_2H$, morpholine-CH_2), 3.78 (s, 3H, $-OCH_3$), 6.83 and 7.10 (d, each 2H, ArH). MS *m/z*: 307 (M^+), 220, 121.

The enantiomeric excess of **11b** was determined to be >98% by HPLC analysis of the corresponding methyl ester (column, CHIRALCEL OC (Daicel) 4.6 i.d. × 250 mm; eluent, 30:70 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of methyl ester of **11b**, 18.2 min; t_R of the 2-(*S*)-isomer, 25.9 min).

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