A New Synthesis of N^{α},N^{δ}-Protected N^{δ}-Hydroxycycloornithine and Its Homologue from an L-Glutamic Acid Derivative†

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Recently, hydroxamic acid-based siderophores have received much attention, and considerable effort has been devoted to efficient chemical synthesis of these compounds.[1] The key to the synthesis of most of the hydroxamate-containing siderophores is the preparation of the constituent ω-*N*-hydroxy-α-amino acids in optically pure form. Syntheses of optically active δ-*N*-hydroxycycloornithines were reported by several groups.[2]

We now report an alternate approach to the synthesis of δ-*N*-hydroxycycloornithine, the key steps of which relied on new methods developed in our laboratory including (1) selective conversion of *O*-alkyl hydroxamic acid to *O*-alkyl aldoxime *via* hydrogenation of the corresponding *N*-alkoxyimidoyl halide,[3] (2) selective reduction of the oxime to the corresponding hydroxylamine with pyridine–borane,[4] and (3) use of the 2-(trimethylsilyl)ethyl group,[5,6] which is stable to catalytic hydrogenation and readily removed by boron trifluoride etherate or a fluoride ion, as a protective group.

An L-glutamic acid derivative was chosen as the starting material, since it is a commercially available chiral compound and contains the appropriate carbon framework. Previously, we demonstrated the conversion of carboxylic acids to the *O*-methylaldoximes *via* hydrogenation of *N*-methoxyimidoyl halides, which are readily synthesized from the corresponding carboxylic acids.[3,7] This methodology was successfully applied to the synthesis of the functionalized oxime **8**, the key intermediate for the synthesis of **1**, by use of *O*-[2-(trimethylsilyl)ethyl]-hydroxylamine[6] instead of methoxyamine to avoid formation of glutamate semialdehyde derivatives. The successful synthesis of hydroxamates is shown in Scheme 1.

Commercially available **3** was converted to **5** by the standard method in satisfactory yield. Treatment of **5** with *O*-[2-(trimethylsilyl)ethyl]hydroxylamine and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC·HCl) in dichloroethane afforded the amide **6** (95%) which was converted to the corresponding imidoyl bromide **7** (88%) with triphenylphosphine–carbon tetrabromide in acetonitrile. Hydrogenation of **7** produced **8**. Transformation of **8** into the corresponding *N*-hydroxysuccinimide ester and the reduction of the oxime double bond with pyridine–borane[4] in ethanol–10% HCl (5:1) resulted in direct cyclization to the desired δ-*N*-hydroxycycloornithine derivative **1** in 79% yield. The optical purity of **1** was determined by derivatization with dibenzoyl-L-(natural) and D-tartaric acids, following the literature method.[8] The NMR spectra of the dibenzoyltartarimide (DBT) derivatives, L-**11** and the corresponding diastereomer L-**12**, displayed each single sharp singlet at 6.36 and 6.31 ppm corresponding to the two methine protons of the DBT residue, respectively, which indicates that **1** was essentially optically pure. In addition, these diastereomers have different R_f values on TLC.

On the other hand, pyridine–borane reduction and subsequent acetylation of the benzyl ester **9** with acetic anhydride in pyridine gave the straight-chain δ-hydroxy α-amino acid derivative **2** in 80% yield. The 2-(trimethylsilyl)ethyl group which was selectively removed with boron trifluoride etherate in acetonitrile in good yield is a suitable protective group for a hydroxyl group especially for the synthesis of ω-*N*-hydroxy compounds bearing hydrogenolizable groups on nitrogen.[9]

The present method will be applicable to syntheses of other ω-*N*-hydroxy-α-amino acid derivatives as a general method.

Experimental Section

All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 270 MHz on a JEOL JNM-EX270 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. ^{1}H NMR spectral data are reported in parts per million (δ) relative to Me_4Si. Infrared (IR) spectra were recorded on a JASCO IR 810 spectrometer. Electron-impact mass spectra, chemical ionization mass spectra, and fast atom bombardment mass spectra were obtained with a JEOL JMX-DX 300 spectrometer. Optical rotations were taken on a JASCO DIP-181 digital polarimeter. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Materials. *O*-[2-(Trimethylsilyl)ethyl]hydroxylamine hydrochloride[6] and pyridine–borane[10] were prepared according to the published procedures. Compound **3** and other reagents were purchased from Peptide Institute, Inc. (Osaka), and Tokyo Kasei Co. Ltd., respectively.

Benzyl Ester of α-*N*-(9-Fluorenylmethoxycarbonyl)-γ-*tert*-butyl Ester of L-Glutamic Acid (4). DCC (4.86 g, 23.5 mmol) was added to a mixture of **3** (9.48 g, 21.4 mmol), benzyl alcohol (2.21 mL, 21.4 mmol), 4-(dimethylamino)pyridine (261 mg, 2.14 mmol), and CH_2Cl_2 (100 mL) with stirring at room temperature. After the solution was stirred overnight, CH_3COOH (1 mL) was added to decompose excess DCC, and the reaction mixture was stirred for an additional 30 min. The dicyclohex-

† This paper is dedicated to Professor Yoshifumi Maki on the occasion of his retirement from Gifu Pharmaceutical University in March 1994.

(1) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563. Gould, S. J.; Ju, S. *J. Am. Chem. Soc.* **1989**, *111*, 2329. Dolence, E. K.; Minnick, A. A.; Miller, M. J. *J. Med. Chem.* **1990**, *33*, 461. Leeson, P. D.; Williams, B. J.; Baker, R.; Ladduwahetty, T.; Moore, K. W.; Rowley, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1578. Dolence, E. K.; Lin, C.-E.; Miller, M. J.; Payne, S. M. *J. Med. Chem.* **1991**, *34*, 956. Dolence, E. K.; Minnick, A. A.; Lin, C.-E.; Miller, M. J.; Payne, S. M. *Ibid.* **1991**, *34*, 968. Dolence, E. K.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 492. Rowley, M.; Leeson, P. D.; Williams, B. J.; Moore, K. W.; Baker, R. *Tetrahedron* **1992**, *48*, 3557. Genet, J.-P.; Thorimbert, S.; Mallart, S.; Kardos, N. *Synthesis* **1993**, 321. Genet, J.-P.; Thorimbert, S.; Touzin, A.-M. *Tetrahedron Lett.* **1993**, *34*, 1159.

(2) Emery, T. F. *Biochemistry* **1966**, *5*, 3694. Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1464. Akers, H. A.; Neilands, J. B. *Biochemistry* **1973**, *12*, 1006. Kolasa, T.; Miller, M. J. *J. Org Chem.* **1990**, *55*, 1711.

(3) Sakamoto, T.; Okamura, K.; Kikugawa, Y. *J. Org. Chem.* **1992**, *57*, 3245.

(4) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1977**, 1279. Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 643.

(5) Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469. Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 4332. Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1986**, *27*, 753. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp 41, 242.

(6) Henmi, T.; Sakamoto, T.; Kikugawa, Y. *Org. Prep. Proced. Int.* **1994**, *26*, 101.

(7) Kikugawa, Y.; Fu, L. H.; Sakamoto, T. *Synth. Commun.* **1993**, *23*, 1061. Sakamoto, T.; Kikugawa, Y. *Synthesis* **1993**, 563.

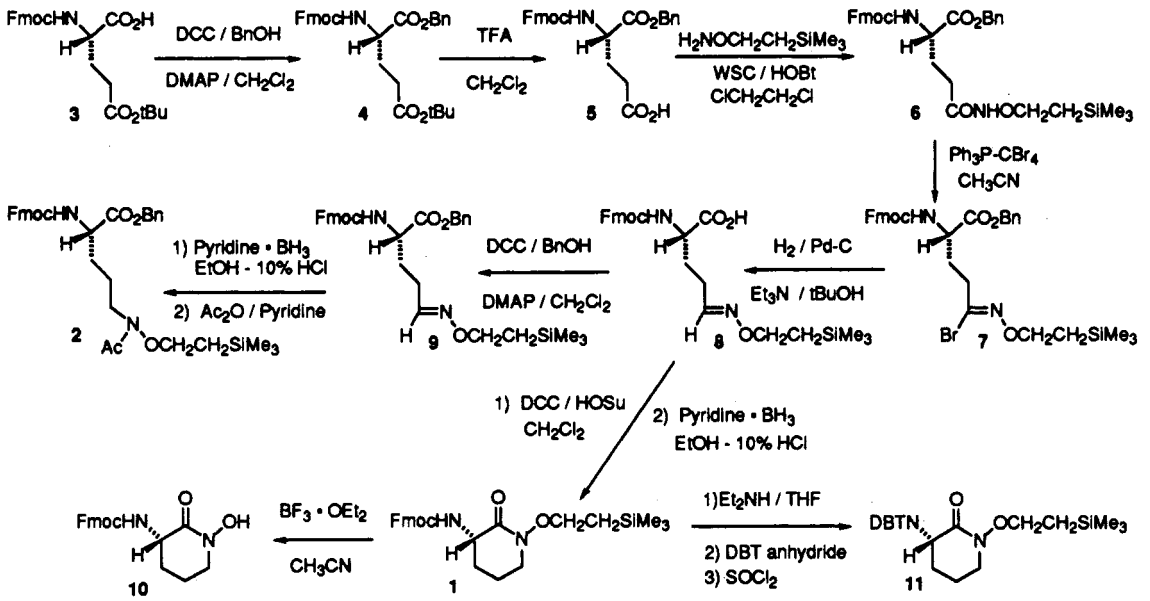
(8) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 3055.

(9) Maehr, H. *Pure Appl. Chem.* **1971**, *28*, 603. Kunze, B.; Trowitzsch-Kienast, W.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1992**, *45*, 147. Bergeron, R. J.; Phanstiel IV, O. *J. Org. Chem.* **1992**, *57*, 7140.

(10) Taylor, M. D.; Grant, L. R.; Sands, C. A. *J. Am. Chem. Soc.* **1955**, *77*, 1506.

0022-3263/94/1959-0929$04.50/0

Scheme 1



ylurea was filtered off and washed with CH_2Cl_2 (15 mL). The filtrate was concentrated under reduced pressure, and the residue was recrystallized from AcOEt–hexanes to give 4 (9.46 g, 86%): mp 98–100 °C. The mother solution was concentrated under reduced pressure, and the residue was chromatographed on a column of silica gel with benzene–AcOEt (20:1) as the eluent to give additional 4 (848 mg, total yield, 94%): colorless crystals; mp 101–102 °C (AcOEt–hexanes); $[\alpha]^{25}_D$ –1.6° (*c* 5, CH_2Cl_2); IR (KBr) 3360, 1740, 1720, 1700 cm^{-1}; NMR δ 1.43 (s, 9 H), 1.86–2.05 (m, 1 H), 2.08–2.44 (m, 3 H), 4.29 (t, 1 H, *J* = 7 Hz), 4.27–4.50 (m, 3 H), 5.18 (s, 2 H), 5.50 (br d, 1 H, *J* = 8 Hz), 7.30 (t, 2 H, *J* = 7 Hz), 7.34 (s, 5 H), 7.39 (t, 2 H, *J* = 7 Hz), 7.57 (d, 2 H, *J* = 7 Hz), 7.75 (d, 2 H, *J* = 7 Hz); MS (CI, isobutane) *m/z* 516 (M^+ + 1), 460, 238, 178, 165. Anal. Calcd for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.15; H, 6.50; N, 2.58.

Benzyl Ester of α-*N*-(9-Fluorenylmethoxycarbonyl)-L-glutamic Acid (5). A solution of 4 (3.77 g, 7.31 mmol), CF_3COOH (10 mL), and CH_2Cl_2 (10 mL) was stirred for 3.5 h with ice cooling. The solvents were removed under reduced pressure below 40 °C, and the residue was diluted with CH_2Cl_2 (60 mL). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was recrystallized from AcOEt–hexanes to give 5 (2.60 g, 77%): mp 117–118 °C. The mother solution was concentrated, and the residue was chromatographed on a column of silica gel with AcOEt–$CHCl_3$ (10:1) as the eluent to give additional 5 (444 mg, total yield, 91%): colorless crystals; mp 116–118 °C (AcOEt–hexanes); $[\alpha]^{24}_D$ –6.2° (*c* 8, THF); IR (KBr) 3320, 1740, 1695 cm^{-1}; NMR δ 1.88–2.04 (m, 1 H), 2.13–2.49 (m, 3 H), 4.19 (t, 1 H, *J* = 7 Hz), 4.39 (d, 2 H, *J* = 7 Hz), 4.36–4.52 (m, 1 H), 5.17 (s, 2 H), 5.49 (br d, 1 H, *J* = 8 Hz), 6.08 (br s, 1H), 7.29 (t, 2 H, *J* = 7 Hz), 7.33 (s, 5 H), 7.38 (t, 2 H, *J* = 7 Hz), 7.57 (d, 2 H, *J* = 7 Hz), 7.74 (d, 2 H, *J* = 7 Hz); MS (CI, isobutane) *m/z* 460 (M^+ + 1), 441, 238, 220, 179, 178, 91. Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.30; H, 5,75; N, 3.09.

Benzyl Ester of α-*N*-(9-Fluorenylmethoxycarbonyl)-γ-*N*-[2-(trimethylsilyl)ethoxy]amide of L-Glutamic Acid (6). To a mixture of 5 (2.71 g, 5.89 mmol), $Me_3SiCH_2CH_2ONH_2$·HCl (1.0 g, 5.89 mmol), Et_3N (1.63 mL, 11.8 mmol), 1-hydroxy-1*H*-benzotriazole monohydrate (876 mg, 6.48 mmol), and $ClCH_2CH_2Cl$ (60 mL) was added WSC·HCl (1.24 g, 6.48 mmol) with stirring, and the reaction mixture was left overnight. The solution was washed with 10% HCl (20 mL) and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with AcOEt–hexanes (1:1) as the eluent to give 6 (2.57 g, 95%): colorless crystals; mp 123–124 °C (AcOEt–hexanes); $[\alpha]^{24}_D$ –1.3° (*c* 3, CH_2Cl_2); IR (KBr) 3310, 3225, 1730, 1700, 1655 cm^{-1}; NMR δ 0.01 (s, 9 H), 1.01 (t, 2 H, *J* = 8 Hz), 1.83–2.34 (m, 3 H), 2.36-2.60 (m, 1 H), 3.94 (t, 2 H, *J* = 8 Hz), 4.20 (t, 1 H, *J* = 7 Hz), 4.41 (t, 3 H, *J* = 7 Hz), 5.14 (s, 2H), 5.67 (br d, 1 H, *J* = 7 Hz), 7.30 (t, 2 H, *J* = 7 Hz), 7.32 (s, 5 H), 7.40 (t, 2 H, *J* = 7 Hz), 7.58 (d, 2 H, *J* = 7 Hz), 7.76 (d, 2 H, *J* = 7 Hz), 8.76 (br s, 1 H); MS (CI, isobutane) *m/z* 531 (M^+ – 43), 513, 464, 439, 335, 220, 179. Anal. Calcd for $C_{32}H_{38}N_2O_6Si$: C, 66.87; H, 6.66; N, 4.87. Found: C, 67.00; H, 6.61; N, 4.87.

Benzyl Ester of α-*N*-(9-Fluorenylmethoxycarbonyl)-γ-*N*-[2-(trimethylsilyl)ethoxy]imidoyl Bromide of L-Glutamic Acid (7). CBr_4 (2.23 g, 6.18 mmol) was added to a mixture of 6 (2.37 g, 4.12 mmol), PPh_3 (1.62 g, 6.18 mmol), and CH_3CN (20 mL) with stirring at room temperature. The mixture was refluxed for 2.5 h. The solvent was concentrated under reduced pressure, and the residue was chromatographed on a column of silica gel with AcOEt–hexanes (1:7) as the eluent to give 7 (2.31 g, 88%): colorless oil; $[\alpha]^{25}_D$ +6.7° (*c* 4.18, CH_2Cl_2); IR (neat) 3325, 1725, 1250, cm^{-1}; NMR δ 0.03 (s, 9 H), 1.02 (t, 2 H, *J* = 8 Hz), 1.91–2.10 (m, 1 H), 2.13–2.33 (m, 1 H), 2.41–2.72 (m, 2 H), 4.18 (t, 3 H, *J* = 8 Hz), 4.38 (d, 2 H, *J* = 7 Hz), 4.42–4.50 (m, 1 H), 5.30 (s, 2 H), 5.33 (br d, 1 H, *J* = 8 Hz), 7.27 (t, 2 H, *J* = 7 Hz), 7.32 (s, 5 H), 7.37 (t, 2 H, *J* = 7 Hz), 7.51 (d, 2 H, *J* = 7 Hz), 7.73 (d, 2 H, *J* = 7 Hz); MS (EI) *m/z* 557 (M^+ – 79), 196, 178, 165; HRMS *m/z* calcd for $C_{32}H_{37}N_2O_5Si$ (M^+ - 79) 557.2472, found 557.2476.

α-*N*-(9-Fluorenylmethoxycarbonyl)-γ-*O*-[2-(trimethylsilyl)ethyl]oxime of L-Glutamic Acid Semialdehyde (8). Compound 7 (1.36 g, 2.14 mmol) and Et_3N (0.59 mL, 4.28 mmol) in *t*-BuOH (21 mL) containing 136 mg of 10% Pd–C were hydrogenated at atmospheric pressure for 1.5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with AcOEt (60 mL). The solution was washed with 10% HCl (30 mL) and brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–hexanes (1:2) and then AcOEt–$CHCl_3$ (10:1) as the eluent to give 8 (646 mg, 80%) as a mixture of *E* and *Z* isomers (7:3): colorless oil; $[\alpha]^{24}_D$ +3.85° (*c* 4.9, CH_2Cl_2); IR (neat) 3450, 1720 cm^{-1}; NMR δ 0.01 (s, 9 H), 0.91–1.7 (m, 2 H), 1.81–1.98 (m, 1 H), 1.99–2.19 (m, 1 H), 2.20–2.45 (m, 2 H), 4.03–4.16 (m, 2 H), 4.20 (t, 1 H, *J* = 6 Hz), 4.38 (d, 2 H, *J* = 6 Hz), 4.44–4.38 (m, 1 H), 4.84 (br s, 1 H), 5.52 and 5.65 (2 br s, 1 H), 6.68 (t, 0.3 H, *J* = 6 Hz), 7.28 (t, 2 H, *J* = 7 Hz), 7.38 (t, 2 H, *J* = 7 Hz), 7.47–7.62 (m, 2.7 H), 7.74 (d, 2 H, *J* = 7 Hz); MS (CI, isobutane) *m/z* 469 (M^+ + 1), 451, 439, 408, 336, 245, 179.

Benzyl Ester of α-*N*-(9-Fluorenylmethoxycarbonyl)-γ-*O*-[2-(trimethylsilyl)ethyl]oxime of L-Glutamic Acid Semialdehyde (9). This compound was prepared as a mixture of *E* and *Z* isomers (3:2) from 8, analogous to 4 described above (85%): colorless oil; $[\alpha]^{24}_D$ +1.43° (*c* 2.8, CH_2Cl_2); IR (neat) 3400, 1720 cm^{-1}; NMR δ 0.01 and 0.02 (2 s, 9 H), 0.92–1.03 (m, 2 H), 1.81–1.98 (m, 1 H), 1.99–2.28 (m, 2 H), 2.34 (dd, 1 H, *J* = 12 Hz, 8 Hz), 4.03–4.16 (m, 2 H), 4.20 (t, 1 H, *J* = 7 Hz), 4.39 (d, 2 H, *J* = 7 Hz), 4.40–4.51 (m, 1 H), 5.18 (s, 2 H), 5.46 (br d, 1 H, *J* =

8 Hz), 6.60 (t, 0.4 H, J = 6 Hz), 7.29 (t, 2 H, J = 7 Hz), 7.33 (s, 5.6 H), 7.39 (t, 2 H, J = 7 Hz), 7.58 (d, 2 H, J = 7 Hz), 7.75 (d, 2 H, J = 7 Hz); MS (CI, isobutane) m/z 559 (M^+ + 1), 468, 426, 204, 179; HRMS m/z calcd for $C_{30}H_{34}N_2O_5Si$ ($M^+ - CH_2CH_2$) 530.2237, found 530.2238.

Benzyl Ester of α-*N*-(9-Fluorenylmethoxycarbonyl)-δ-*N*-acetyl-δ-*N*-[2-(trimethylsilyl)ethoxy]-L-ornithine (2). Pyridine–borane (163 mg, 1.76 mmol) was added to a solution of **9** (491 mg, 0.88 mmol) in 14 mL of EtOH–10% HCl (6:1) with ice cooling. After being stirred for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with AcOEt (50 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. To the crude reduced **9** was added CH_2Cl_2 (5 mL), pyridine (0.14 mL, 1.76 mmol), and Ac_2O (0.13 mL, 1.76 mmol), and the whole was stirred for 2 h at room temperature. HCl (10%, 15 mL) was added to the solution with ice cooling, and the aqueous layer was extracted with CH_2Cl_2 (25 mL × 2). The combined organic layer was washed with 10% Na_2CO_3 (25 mL) and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel. Elution with AcOEt–hexanes (1:3) afforded **2** (424 mg, 80%): colorless oil; $[\alpha]^{24}_D$ +0.94° (c 4.9, CH_2Cl_2); IR (neat) 3300, 1740, 1720, 1650 cm^{-1}; NMR δ 0.03 (s, 9 H), 0.94 (t, 2 H, J = 8 Hz), 1.55–1.79 (m, 2 H), 1.81–1.87 (m, 1 H), 2.00–2.16 (m, 1 H), 2.12 (s, 3 H), 3.54–3.64 (m, 2 H), 3.83 (t, 2 H, J = 8 Hz), 4.22 (t, 1 H, J = 7 Hz), 4.27–4.50 (m, 3 H), 5.18 (s, 2 H), 5.50 (br d, 1 H, J = 7 Hz), 7.31 (t, 2 H, J = 7 Hz), 7.34 (s, 5H), 7.40 (t, 2 H, J = 7 Hz), 7.60 (d, 2 H, J = 7 Hz), 7.62 (d, 2 H, J = 7 Hz); MS (CI, isobutane) m/z 603 (M^+ + 1), 559, 381, 179; HRMS m/z calcd for $C_{32}H_{38}O_6N_2Si$ ($M^+ - CH_2CH_2$) 574.2499, found 574.2497.

α-*N*-(9-Fluorenylmethoxycarbonyl)-δ-*N*-[2-(trimethylsilyl)ethoxy]-L-cycloornithine (1). To a solution of **9** (637 mg, 1.36 mmol), *N*-hydroxysuccinimide (188 mg, 1.63 mmol), and CH_2Cl_2 (15 mL) with ice cooling was added DCC (364 mg, 1.63 mmol) in CH_2Cl_2 (15 mL), and the reaction mixture was stirred at room temperature for 6 h. The dicyclohexylurea was filtered off. The filtrate was concentrated under reduced pressure and was redissolved in 12 mL of EtOH–10% HCl (5:1). To this solution was added pyridine–borane (274 mg, 2.95 mmol) with ice cooling, and the reaction mixture was stirred at room temperature for 1.5 h and was concentrated under reduced pressure. The residue was diluted with AcOEt (50 mL). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on a column of silica gel with benzene–AcOEt (10:1) as the eluent to give **1** (483 mg, 79%): colorless crystals; mp 79–81 °C (pentane); $[\alpha]^{24}_D$ +32.5° (c 2.0, CH_2Cl_2); IR (KBr) 3320, 1720, 1670 cm^{-1}; NMR δ 0.04 (s, 9 H), 0.92–1.04 (m, 2 H), 1.38–1.66 (m, 1 H), 1.80–2.07 (m, 2 H), 2.35–2.56 (m, 1 H), 3.40–3.66 (m, 2 H), 3.82–4.03 (m, 2 H), 4.06–4.23 (m, 1 H), 4.19 (t, 1 H, J = 7 Hz), 4.32 (d, 2 H, J = 7 Hz), 5.71 (br s, 1 H), 7.27 (t, 2 H, J = 7 Hz), 7.36 (t, 2 H, J = 7 Hz), 7.57 (d, 2 H, J = 7 Hz), 7.72 (d, 2 H, J = 7 Hz); MS (CI, isobutane) m/z 453 (M^+ + 1), 231, 178. Anal. Calcd for $C_{25}H_{32}N_2O_4Si·H_2O$: C, 63.80; H, 7.28; N, 5.95. Found: C, 63.86; H, 7.33; N, 6.10.

α-*N*-(9-Fluorenylmethoxycarbonyl)-δ-*N*-hydroxy-L-cycloornithine (10). Boron trifluoride etherate (0.052 mL, 0.42 mmol) was added to a solution of **1** (94 mg, 0.21 mmol) and CH_3CN (3 mL) with stirring at room temperature. After the mixture was stirred for 0.5 h, the solvent was removed under reduced pressure and the residue was diluted with AcOEt (40 mL). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product (73 mg, 99%, mp 155–158 °C) was recrystallized from MeOH to give pure **10** (63 mg, 79%): colorless crystals; mp 157–158 °C (MeOH); $[\alpha]^{24}_D$ +12.7° (c 3.6, $CHCl_3$); IR (KBr) 3400, 3325, 1700, 1650 cm^{-1}; NMR δ 1.46–1.84 (m, 2 H), 1.82 (m, 2 H), 2.29–2.54 (m, 1 H), 3.50 (s, 3 H), 3.54–3.79 (m, 2 H), 4.13–4.33 (m, 1 H), 4.23 (t, 1 H, J = 7 Hz), 4.35–4.52 (m, 2 H), 5.72 (br s, 1 H), 7.32 (t, 2 H, J = 7 Hz), 7.40 (t, 2 H, J = 7 Hz), 7.57 (d, 2 H, J = 7 Hz), 7.75 (d, 2 H, J = 7 Hz), 8.54 (s, 1 H); MS (positive ion FAB, *m*-nitrobenzyl alchohol matrix) m/z 353 (M^+ + 1). Anal. Calcd for $C_{20}H_{20}N_2O_4·CH_3OH$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.71; H, 6.03; N, 7.30.

α-*N*-[Bis(benzoyloxy)succinyl]-δ-*N*-[2-(trimethylsilyl)-ethoxy]-L-cycloornithine (11). The (9-fluorenyloxy)methoxycarbonyl group of **1** (168 mg, 0.37 mmol) was deprotected by use of $HNEt_2$ (0.38 mL, 3.71 mmol) in THF (4 mL) with ice cooling for 3 h. The solvent was removed under reduced pressure. The residue was diluted with 10% HCl (5 mL), and the solution was washed with Et_2O (8 mL). The aqueous layer was concentrated to dryness under reduced pressure. The residual glassy oil (94 mg, 95%) was submitted without further purification to derivatization with dibenzoyl-L-tartaric acid to formation the DBT derivative following the literature method.[8] Compound L-**12** was prepared similarly using dibenzoyl-D-tartaric acid instead of the L-tartaric acid.

L-**11**: colorless crystals; R_f 0.45 (AcOEt/hexanes (1:2)); mp 192–193 °C (MeOH); $[\alpha]^{25}_D$ +100° (c 1, CH_2Cl_2); IR (KBr) 1730, 1680 cm^{-1}; NMR (CD_3COCD_3) δ 0.04 (s, 9 H), 1.00 (dd, 2H, J = 10, 6.5 Hz), 2.02–2.20 (m, 3 H), 2.25–2.42 (m, 1 H), 3.64–3.81 (m, 2 H), 3.96–4.15 (m, 2 H), 4.82 (dd, 1 H, J = 12, 6 Hz), 6.36 (s, 2 H), 7.58 (t, 4 H, J = 7.5 Hz), 7.72 (t, 2 H, J = 7.5 Hz), 8.11 (d, 4 H, J = 7.5 Hz); MS (CI, isobutane) m/z 553 (M^+ + 1), 525, 509, 123, 105. Anal. Calcd for $C_{28}H_{32}N_2O_8Si$: C, 60.85; H, 5.84; N, 5.07. Found: C, 60.73; H, 6.06; N, 4.81.

L-**12**: colorless crystals; R_f 0.51 (AcOEt/hexanes (1:2)); mp 133–136 °C (*i*-Pr_2O); $[\alpha]^{23}_D$ −93.3° (c 0.98, CH_2Cl_2); IR 1740, 1720, 1680 cm^{-1}; NMR (CD_3COCD_3) δ 0.04 (s, 9 H), 0.09 (dd, 2 H, J = 9.5, 7.5 Hz), 2.08–2.14 (m, 3 H), 2.20–2.36 (m, 1 H), 3.63–3.84 (m, 2 H), 3.98–4.18 (m, 2 H), 4.87 (dd, 1 H, J = 11, 6 Hz), 6.31 (s, 2 H), 7.58 (t, 4 H, J = 7.5 Hz), 7.72 (t, 2 H, J = 7.5 Hz), 8.12 (d, 4 H, J = 7.5 Hz); MS (CI, isobutane) m/z 553 (M^+ + 1), 525, 509, 123, 105. Anal. Calcd for $C_{28}H_{32}N_2O_8Si$: C, 60.85; H, 5.84; N, 5.07. Found: C, 60.96; H, 6.01; N, 4.91.

Supplementary Material Available: ^{1}H NMR spectra of the mixture of L-**11** and L-**12** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.