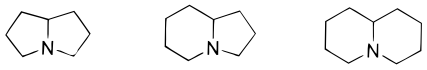
Samarium Diiodide-Promoted Cyclization of *N*-(ω-Iodoalkyl)imides to Polyhydroxylated Indolizidinones and Pyrrolizidinones: Synthesis of (+)-Lentiginosine

Deok-Chan Ha,* Chang-Soo Yun, and Yeonbae Lee

Department of Chemistry, Korea University, 5−1−2 Anam-dong, Seoul 136-701, Korea

Received August 31, 1999

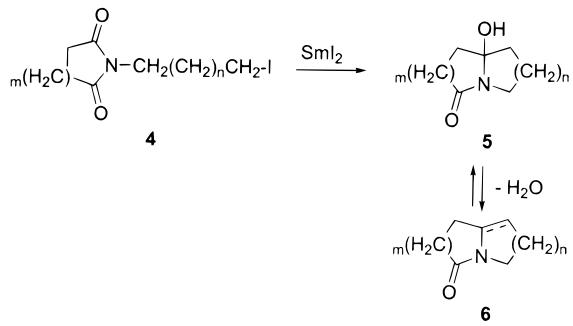
Nitrogen-fused bicyclic alkaloids, having pyrrolizidine (**1**), indolizidine (**2**), and quinolizidine (**3**) ring systems, have been the targets of many synthetic efforts due to their interesting and potent biological activities including antiviral, antitumor, and glucosidase inhibitions.[1] Many synthetic methodologies have been developed for the efficient construction of these bicyclic structures, including acyliminium ion and α-acylamino radical cyclizations from 2-pyrrolidinone intermediates.[2,3] Recently, Heck-type cyclization of iodovinyl-substituted cyclic enamides and titanium-mediated cyclization of ω-vinyl imides were also reported.[4] In this paper, we would like to add a new cyclization method, SmI_2-mediated cyclization of *N*-ω-iodoalkyl cyclic imides, to the synthetic arsenal for these alkaloids.



1 **2** **3**

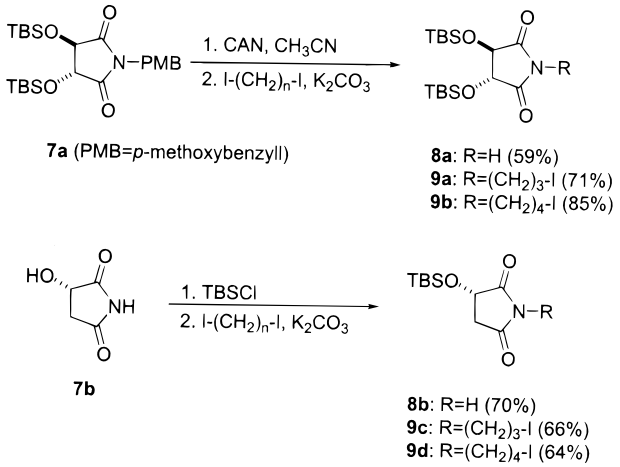
Samarium diiodide has been extensively used in the reduction of aldehydes and ketones designed to undergo elimination, cyclization, and coupling reactions.[5,6] More recent studies about intramolecular acyl substitution reactions of halo-substituted esters and lactones further proved the efficacy of these SmI_2-promoted reactions.[7] In our previous study, we reported our preliminary results on SmI_2-promoted cyclization of *N*-(iodoalkyl)-substituted cyclic imides of the type **4** to construct pyrrolizidinone, indolizidinone, and quinolizidinone ring systems of type **5** and **6** (Scheme 1).[8]

Scheme 1



4 **5** **6**

Scheme 2



7a (PMB=*p*-methoxybenzyll) **8a**: R=H (59%) **9a**: R=$(CH_2)_3$-I (71%) **9b**: R=$(CH_2)_4$-I (85%)

7b **8b**: R=H (70%) **9c**: R=$(CH_2)_3$-I (66%) **9d**: R=$(CH_2)_4$-I (64%)

The *N*-ω-iodoalkyl cyclic imides **9a**−**d** for the reductive cyclization were prepared from the imide **7a** derived from L-tartaric acid and the imide **7b** from L-malic acid (Scheme 2).[9,10] Oxidative removal of the 4-methoxybenzyl group from **7a** followed by the introduction of the iodoalkyl groups provided **9a** and **9b**. Also, imide **7b** was converted to **9c** and **9d** after the silylation and *N*-iodoalkylation.

Thus, *N*-(3-iodopropyl) and *N*-(4-iodobutyl)imide derivatives **9a**−**d** were subjected under the SmI_2-promoted reductive cyclization conditions in the presence of catalytic amounts of tris(dibenzoylmethido)iron(III)[$Fe(DBM)_3$] in THF (Table 1). Imide **9a** provided pyrrolizidinone **10a** as a single isomer in 77% yield. The stereochemistry of

* To whom correspondence should be addressed. Phone: 82-2-3290-3131. Fax: 82-2-3290-3121 E-mail: dechha@kuccnx.korea.ac.kr.

(1) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465−1487. Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413−418. Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187−194. Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619−636.

(2) Himstra, H.; Speckamp. W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 2, pp 1047−1082.

(3) Hart, D. J.; Choi, J.-K.; Burnett. D. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201−8209.

(4) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398−404. Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127−8128.

(5) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698. Molander, G. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 1, pp 251−282. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. Imamoto, T. In *Lanthanides in Organic Synthsis*; Academic Press: London, 1994; Chapter 4, pp 21−65. Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943−961. Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345−347. Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609.

(6) Inanaga, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 1737−1740. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132−3139. Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058. Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1994**, *35*, 1627−1628. Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110−1111. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(7) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216−7227. Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1994**, *59*, 3445−3452.

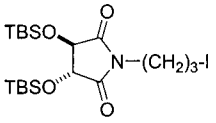
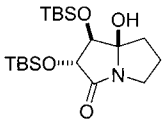
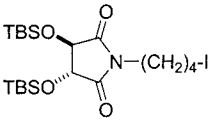
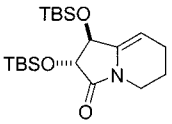
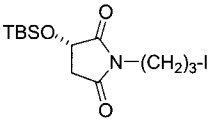
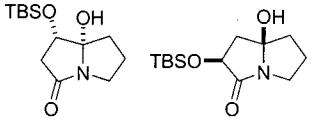
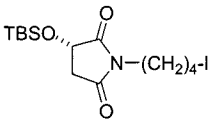
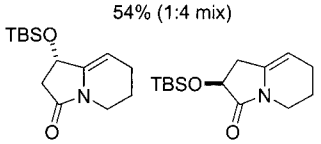
(8) Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577−2580. Ha, D.-C.; Yun, C.-S. *Bull. Kor. Chem. Soc.* **1997**, *18*, 1039−1041.

(9) Yoda, H.; Shirakawa, K.; Takabe, K. *Chem. Lett.* **1991**, 489−490. Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 3401−3404. Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455−1456.

(10) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653−3656.

10.1021/jo9913762 CCC: $19.00
Published on Web 12/31/1999

Table 1. SmI_2-Promoted Cyclizations of *N*-(ω-Iodoalkyl)succinimides

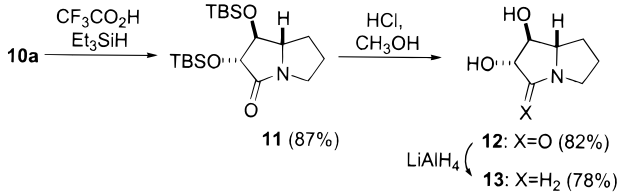
imides	products (yield)
 **9a**	 **10a** (77%)
 **9b**	 **10b** (82%)
 **9c**	 **10c** **10d** 54% (1:4 mix)
 **9d**	 **10e** (75%) **10f** (10%)

the hydroxy group at the ring junction of **10a** was tentatively assigned, and the assignment was based on the results of the NOE study of the reduction product from **10a** (vide infra). The 4-iodobutyl derivative **9b** was cyclized to the corresponding hydroxy indolizidinone which was slowly dehydrated to enamide **10b** during the purification by SiO_2 chromatography.[8] Thus, for the best result, the crude cyclization product from **9b** was directly subjected to the dehydration conditions (4 Å powdered molecular sieves, cat. *p*-TsOH, CH_2Cl_2), and the enamide **10b** was isolated in 82% yield. Imide **9c** gave a 1:4 mixture of **10c** and **10d** in 54% yield, while cyclization and dehydration of the 4-iodobutyl derivative **9d** gave 75% of **10e** and 10% of **10f**. The stereochemistry of **10c** and **10d** was not confirmed and tentatively assigned. The regioselectivities in the cyclizations of **9c** and **9d** were quite contrasting. The selectivity of **10e** over **10f** can be easily understood in terms of the well-known antiperiplanar electronic effect of an α-substituent of the imide carbonyl group.[11] The reason for the reversed selectivity in the cyclization of **9c** is not clear at this stage, but the increased angle strain during the second five-membered ring formation together with the probable steric effect by Sm(III) Lewis acid chelated to the imide carbonyl may play a significant role in the reversed regioselectivity.

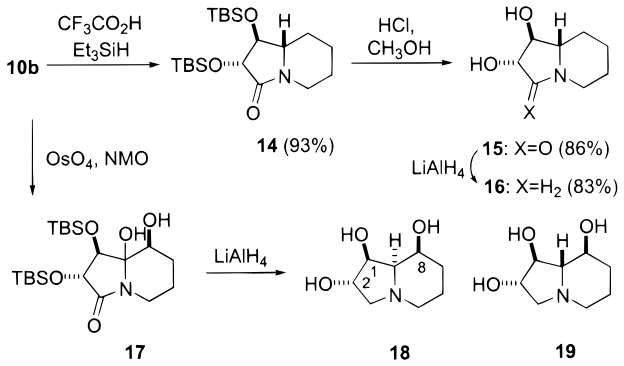
Hydroxylactam **10a** was easily converted to 1,2-dihydroxypyrrolizidine **13** through the stereoselective reduction to **11** with Et_3SiH/CF_3COOH and desilylation in methanolic hydrochloride followed by LAH reduction (Scheme 3).

The same approach was also applied to **10b** to provide the least hydroxylated indolizidine alkaloid, (+)-lentigi-

Scheme 3



Scheme 4



nosine (**16**). The spectroscopic data of **16** were compared and found to be identical with those reported.[12] Dihydroxylation of enamide **10b** with cat. OsO_4−NMO provided **17** as an inseparable epimeric mixture (Scheme 4), and the other two possible stereoisomers were not observed. Attempt to reduce **17** with CF_3CO_2H/Et_3SiH resulted in an unidentifiable complex mixture. But reduction of the crude **17** with LAH in THF heated at reflux directly provided the desilylated 1,2,8-trihydroxyindolizidinones **18** and **19** with 30% and 9% overall yields, respectively, from **10b**. The stereochemistry of C(8) and C(8a) **18** and **19** were assigned based on the results of the NOE experiments.

In summary, we have shown that SmI_2-promoted reductive cyclization of *N*-(ω-iodoalkyl) cyclic imide provides an expedient approach to pyrrolizidine and indolizidine ring systems. The synthesis of polyhydroxylated indolizidines and pyrrolizidines, including (+)-lentiginosine, from readily available imides demonstrate the synthetic utility of this approach for diverse nitrogen-fused bicyclic alkaloids and their analogues.

Experimental Section

General Procedures. Reagents obtained from commercial sources were used as received, and solvents were dried prior to use. All reactions, unless otherwise noted, were performed in flame-dried glassware under an atmosphere of dry argon. Column chromatography was performed on silica gel. Melting points are uncorrected. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz. Infrared spectra were recorded in the FT mode. Data for high-resolution mass spectra and elemental analyses were obtained from Organic Chemistry Research Center, Sogang University at Seoul, Korea.

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-2,5-pyrrolidindione (8a). To a solution of **7a** (6.30 g, 13.2 mmol) in 126 mL of acetonitrile cooled at 0 °C was added ceric ammonium nitrate (28.9 g, 52.8 mmol) in 63 mL of water in several portions over 20 min. The mixture was stirred at 0 °C for 5 h, diluted with 200 mL of water, and extracted three times with 200-mL portions of EtOAc. The organic extracts were washed with

(11) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192−1198. Kayser, M. M.; Salvador, J.; Morand, P.; Krishnamurty, H. G. *Can. J. Chem.* **1982**, *60*, 1199−1206. Kayser, M. M.; Salvador, J. Morand, P. *Can. J. Chem.* **1983**, *61*, 439−441. Vijin, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019−5030.

(12) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886−1891. Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949−952.

saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:8, EtOAc/hexanes) gave **8a** (2.79 g, 59%) as a colorless oil. R_f = 0.31 (1:6, EtOAc/hexanes); $[\alpha]^{21}_D$ +134.7° (*c* 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1 H), 4.52 (s, 2H), 0.84 (s, 18H), 0.22 (s, 6H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 77.4, 25.6, 18.2, −4.5, −5.1; IR (CH_2Cl_2, cm^{-1}) 1750, 1468, 1323, 1252; MS (EI) *m*/*z* (relative intensity) 302 (M^+ - 57, 26.3). Anal. Calcd for $C_{16}H_{33}NO_4Si_2$: C, 53.44; H, 9.25; N, 3.89. Found: C, 53.44; H, 9.47; N, 3.75.

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-*N*-(4-iodobutyl)-2,5-pyrrolidindione (9b). To a mixture of **8a** (0.92 g, 2.56 mmol), potassium carbonate (3.54 g, 25.6 mmol), and tetra-*n*-butylammonium bromide (0.25 g, 0.77 mmol) in 30 mL of acetone was added 1,4-diiodobutane (0.68 mL, 5.12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h, diluted with 150 mL of distilled water, and extracted twice with 150-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:1, CH_2Cl_2/hexanes) gave **9b** (1.18 g, 85%) as a colorless oil. R_f = 0.55 (1:6, EtOAc/hexanes); $[\alpha]^{21}_D$ +90.6° (*c* 2.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 2H), 3.47 (m, 2H), 3.17 (t, *J* = 7 Hz, 2H), 1.70−1.79 (m, 4H), 0.93 (s, 18H), 0.21 (s, 6H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 76.7, 37.3, 30.4, 28.4, 25.6, 18.1, 5.2, −4.5, −5.1; IR (CH_2Cl_2, cm^{-1}) 1723, 1467, 1362, 1252, 1135; MS (EI) *m*/*z* (relative intensity) 484 (M^+ - 57, 100). Anal. Calcd for $C_{20}H_{40}NO_4Si_2I$: C, 44.35; H, 7.44; N, 2.59. Found: C, 44.34; H, 7.71; N, 2.62.

(1*S*,2*R*)-1,2-Bis[(*tert*-butyldimethylsilyl)oxy]pyrrolizidin-8-ene-3-one (10b). To a solution of SmI_2 (9.36 mmol) in 63 mL of THF cooled at 0 °C was added 65 mg (0.09 mmol) of $Fe(DBM)_3$ in 10 mL of THF via cannula followed by stirring for 2 h at 0 °C. A solution of imide **7b** (1.69 g, 3.12 mmol) in 10 mL of THF was added via cannula, and the resulting mixture was stirred for 2 h at 0 °C. The mixture was quenched by Ruchelle's salt and extracted three times with 50-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was dissolved in 20 mL of CH_2Cl_2, and 4 Å powered molecular sieves (1.2 g) and *p*-TsOH (60 mg, 0.31 mmol) were added. The mixture was stirred for 3 h at room temperature and filtered over Celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:8, EtOAc/hexanes) gave **10b** (970 mg, 78%) as a colorless oil. R_f = 0.50 (1:6, EtOAc/hexanes); $[\alpha]^{24}_D$ +111.1° (*c* 6.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (m, 1H), 4.43 (m, 1H), 4.11 (d, *J* = 6 Hz, 1H), 3.60 (m, 1H), 3.04 (m, 1H), 1.99 (m, 1H), 1.57−1.67 (m, 2H), 0.78 (s, 18H), 0.06 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 137.6, 98.8, 77.9, 75.9, 38.2, 25.8, 25.7, 21.3, 20.4, 18.2, 17.9, −4.2, −4.3, −4.6, −4.7; IR (CH_2Cl_2, cm^{-1}) 2911, 1710, 1467, 1382, 1251; MS (EI) *m*/*z* (relative intensity) 397 (M^+, 0.01), 340 (M^+ - 57, 51.2). Anal. Calcd for $C_{20}H_{39}NO_3Si_2$: C, 60.40; H, 9.88; N, 3.52. Found: C, 60.49; H, 10.07; N, 3.35.

(1*S*,2*R*,8a*S*)-1,2-Bis[(*tert*-butyldimethylsilyl)oxy]-3-indolizidinone (14). To a solution of **10b** (420 mg, 1.06 mmol) in 5 mL of CH_2Cl_2 were added trifluoroacetic acid (0.15 mL, 1.94 mmol) and triethylsilane (0.50 mL, 3.13 mmol). The reaction mixture was stirred for 3 h at room temperature, diluted with 100 mL of saturated aqueous $NaHCO_3$, and extracted twice with 100-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:7, EtOAc/hexanes) gave **14** (395 mg, 93%) as a colorless oil. R_f = 0.41 (1:6, EtOAc/hexanes); $[\alpha]^{20}_D$ +47.7° (*c* 1.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (d, *J* = 6 Hz, 1H), 4.07 (s, 1H), 3.81 (t, *J* = 6 Hz, 1H), 3.0−3.07 (m, 1H), 2.59 (m, 1H), 2.02−2.06 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.37 (m, 2H), 1.16 (m, 1H), 0.94 (s, 9H), 0.90 (s, 9H), 0.09−0.22 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 80.7, 78.0, 59.4, 39.3, 30.4, 25.8, 25.6, 23.9, 23.2, 18.1, 17.7; IR (CH_2Cl_2, cm^{-1}) 2909, 1714, 1419, 1253, 1137; MS (EI) *m*/*z* (relative intensity) 342 (M^+-57, 100). Anal. Calcd for $C_{20}H_{41}NO_3Si_2$: C, 60.09; H, 10.34; N, 3.50. Found: C, 60.04; H, 10.46; N, 3.61.

(1*S*,2*R*,8a*S*)-1,2-Dihydroxy-3-indolizidinone (15). A solution of **14** (220 mg, 0.55 mmol) in 5 mL of 10% methanolic HCl was stirred for 3 h at room temperature. The reaction mixture was quenched by NH_3 solution, filtered over a Celite pad, and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (8:1, CH_2Cl_2/MeOH) to give **15** (81 mg, 86%) as a white solid: R_f = 0.38 (8:1, CH_2Cl_2/MeOH); mp 136−137 °C; $[\alpha]^{21}_D$ +52.3° (*c* 1.99, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 3.79−3.93 (m, 2H), 3.48 (t, *J* = 7 Hz, 1H), 2.90 (m, 1H), 2.47 (m, 1H), 1.92 (m, 1H), 1.67 (m, 1H), 1.52 (m, 1H), 1.11−1.13 (m, 2H), 0.94−1.08 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.8, 80.8, 77.4, 60.3, 40.6, 31.6, 25.2, 24.0; IR (KBr, cm^{-1}) 1683, 1451, 1370, 1280; MS (EI) *m*/*z* (relative intensity) 171 (M^+, 13.4). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.15; H, 7.64; N, 8.06; HRMS calcd for $C_8H_{13}NO_3$ (M^+) 171.0895, found 171.0897.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxyindolizidine [16, (+)-Lentiginosine]. To a solution of **15** (70 mg, 0.41 mmol) in 5 mL of THF was added $LiAlH_4$ (62 mg, 1.64 mmol), and the mixture was heated at reflux for 4 h. Under ice cooling, the mixture was quenched by careful addition of distilled water (0.5 mL) and 1 N NaOH (0.5 mL). The resulting mixture was filtered over Celite pad and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (41:8:1, CH_2Cl_2/MeOH/NH_3) to give **16** (53 mg, 83%) as a white solid: R_f = 0.33 (41:8:1, CH_2Cl_2/MeOH/NH_3); mp 106 °C; $[\alpha]^{20}_D$ +3.0° (*c* 0.70, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 3.95 (m, 1H), 3.60 (dd, *J* = 9, 3 Hz, 1H), 2.96 (d, *J* = 11 Hz, 1H), 2.86 (d, *J* = 11 Hz, 1H), 2.54 (dd, *J* = 11, 7 Hz, 1H), 2.00 (m, 2H), 1.83 (m, 2H), 1.61 (m, 2H), 1.30 (m, 2H); ^{1}H NMR (300 MHz, D_2O) δ 4.01 (m, 1H), 3.59 (dd, *J* = 9, 3 Hz, 1H), 2.89 (d, *J* = 11 Hz, 1H), 2.77 (d, *J* = 11 Hz, 1H), 2.58 (dd, *J* = 11, 7 Hz, 1H), 2.00 (m, 1H), 1.90 (m, 2H), 1.74 (m, 1H), 1.56 (m, 1H), 1.42 (m, 1H), 1.19 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 85.0, 77.5, 71.0, 62.8, 54.4, 29.3, 25.7, 24.9; ^{13}C NMR (75 MHz, D_2O) δ 86.0, 78.7, 71.6, 63.3, 55.7, 30.7, 27.1, 26.2; IR (KBr, cm^{-1}) 3402, 2817; MS (CI, CH_4) *m*/*z* (relative intensity) 158 [$(M + H)^+$, 100]. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.48; H, 9.43; N, 8.43; HRMS calcd for $C_8H_{15}NO_2$ (M^+) 157.1103, found 157.1101.

Acknowledgment. This work was financially supported by the Korea Research Foundation through the Basic Science Research Institute Program (BSRI-98-3406).

Supporting Information Available: Experimental procedures and compound characterization data for **8b**, **9a**, **9c**, **9d**, **10a**, **10c**−**f**, **11**−**13**, **18**, **19**, and NOE-difference of **11**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9913762