Chiral Synthesis of *trans*-1-Aminoindolo[2,3-*a*]quinolizidine and *trans*-1-Aminobenzo[*a*]quinolizidine Derivatives from L-Pyroglutamic Acid

Yong Sup Lee,*,† Dae Joo Cho,† Sun Nam Kim,† Jung Hoon Choi,‡ and Hokoon Park†

Medicinal Chemistry Research Center, Korea Institute of Science & Technology, P.O. Box 131 Cheongryang, Seoul 130-650, Korea, and Department of Chemistry, Hanyang University, Seoul 133-791, Korea

Received July 27, 1999

Benzo[*a*]quinolizidine and indolo[2,3-*a*]quinolizidine ring systems are key subunits of naturally occurring isoquinoline and indole alkaloids.[1] 1-Aminoindolo[2,3-*a*]-quinolizidines have been used as intermediates in the synthesis of the pharmacologically interesting pentacyclic compound **6**[2] and (*E*)-azaeburnane derivatives.[3] Benzo-[*a*]quinolizidines, including 1-aminobenzo[*a*]quinolizidines, have also served as intermediates in the synthesis of the *Ipecac* alkaloid emetine[4] and an azasteroid.[5] Although the racemic syntheses of **1**−**3** have appeared in the literature,[3−5] methods for their chiral synthesis are scarce, and the chiral synthesis of **1** by the employment of a stereoselective Pictet−Spengler cyclocondensation starting from L-glutamic acid has only recently been reported.[3c]

Generally, racemic 1-aminoindolo[2,3-*a*]quinolizidine and 1-aminobenzo[*a*]quinolizidine were synthesized by introduction of the C-1 amino group via reduction of an oxime.[3b,5] Alternatively, racemic *cis*-1-aminoindolo[2,3-*a*]quinolizidine **1** was synthesized through the Bischler−Napieralski (B−N) reaction[3a] of a chiral amide, which was prepared from L-pyroglutamic acid. In this case, the chiral center coming from L-pyroglutamic acid was racemized under the cyclization conditions. The first chiral synthesis of *cis*-1-aminoindolo[2,3-*a*]quinolizidine **1** was achieved by the stereoselective Pictet−Spengler (P−S) cyclocondensation of tryptamine with a chiral α-amino-aldehyde, derived from L-glutamic acid.[3c] Although the *cis*−*trans* relative stereochemistry in 1-aminobenzo[*a*]-quinolizidine and 1-aminoindolo[2,3-*a*]quinolizidine rings is expected to be very important for their biological activity, there is no report on the chiral synthesis of

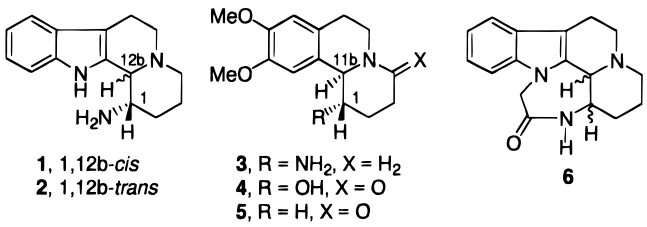


Figure 1.

trans-1-aminobenzo[*a*]quinolizidines and *trans*-1-aminoindolo[2,3-*a*]quinolizidines. In connection with our research on the synthesis of alkaloids from a chirality pool,[6−8] we investigated the chiral synthesis of *trans*-1-aminoindolo[2,3-*a*]quinolizidine **2** and *trans*-1-aminobenzo[*a*]quinolizidine **3** from a natural amino acid.

N-Acyliminium ion cyclization is a powerful tool in the synthesis of several types of alkaloids.[9,10] We have recently shown that the ring juncture stereochemistry in benzo[*a*]quinolizidine (**4** and **5**)[6] and pyrrolidinoiso-quinoline derivatives[7] could be controlled by the proximate chiral center during the *N*-acyliminium ion cyclization of a chiral lactam derived from our chirality pool. Although the previous results using the B−N reaction[3a] and the P−S reaction[3c] gave racemic or chiral *cis*-1-aminoaminoindolo[2,3-*a*]quinolizidine **1**, we envisioned that *trans*-1-aminoindolo[2,3-*a*]quinolizidine **2** and *trans*-1-aminobenzo[*a*]quinolizidine **3** could be synthesized from the same chiral source, L-pyroglutamic acid, through our *N*-acyliminium ion cyclization strategy (Scheme 1).

As illustrated in Scheme 2, it was believed that the aromatic ring would attack *N*-acyliminium ion **8** *anti* to the NHCbz group, leading to *trans*-substituted quinolizidine ring **9**. We expected that the chiral hydroxylactams **7**, *N*-acyliminium ion precursors for the cyclization, would be prepared from readily available L-pyroglutamic acid.

The trimethylaluminum-promoted aminolysis of *N*-Cbz-protected pyrrolidone **10**,[11] derived from L-pyroglutamic acid in two steps, with tryptamine or 3,4-dimethoxyphenethylamine afforded amidoesters **11a** and

† Korea Institute of Science & Technology.

‡ Hanyang University.

(1) (a) For a review of isoquinoline alkaloids, see: Kametani, T. The Total Syntheses of Isoquinoline Alkaloids. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1977; Vol. 3, pp 1−272. (b) For a review of indole alkaloids, see: Kutney, J. P. The Synthesis of Indole Alkaloids. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1977; Vol. 3, pp 273−438. (c) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701 and references therein.

(2) (a) López, I. L.; Diez, A.; Rubiralta, M. *Tetrahedron* **1996**, *52*, 8581. (b) Hammer, H.; Winterfeldt, E. *Tetrahedron* **1981**, *37*, 3609.

(3) (a) Melnyk, P.; Ducrot, P.; Demuynck, L.; Thal, C. *Tetrahedron Lett.* **1993**, *34*, 5085. (b) Schmitt, P.; Melnyk, P.; Bourde, O.; Demuynck, L.; Pujol, J.-F.; Thal, C. *Med. Chem. Res.* **1993**, *3*, 24. (c) Melnyk, P.; Ducrot, P.; Thal, C. *Tetrahedron* **1993**, *49*, 8589.

(4) (a) Ihara, M.; Yaui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469. (b) Kametani, T.; Surgenor, S. A.; Fukumoto, K. *Heterocycles* **1980**, *14*, 303.

(5) Brown, R. E.; Hansen, V.; Lustgarten, D. M.; Stanaback, R. J.; Meltzer, R. I. *J. Org. Chem.* **1968**, *33*, 4180.

(6) Lee, Y. S.; Kang, S. S.; Choi, J. H.; Park, H. *Tetrahedron* **1997**, *53*, 3045.

(7) (a) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149. (b) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449.

(8) (a) Lee, Y. S.; Kim, D. W.; Lee, J. Y.; Jeong, K. S.; Park, H. *Bull. Korean Chem. Soc.* **1998**, *19*, 814. (b) Lee, Y. S.; Lee, J. Y.; Kim, D. W.; Park, H. *Tetrahedron* **1999**, *55*, 4631.

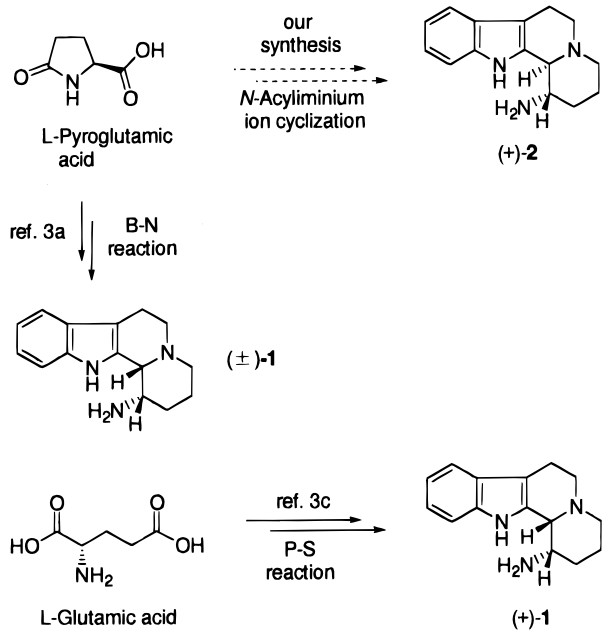
(9) For reviews, see: (a) Hiemstra, H.; Speckamp, W. N. Addition to *N*-Acyliminium Ions. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1047−1082. (b) Speckamp W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(10) For some recent examples, see: (a) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080. (b) Durand, J.-O.; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1998**, *39*, 5743. (c) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **1998**, *39*, 3341. (d) Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914. (e) Kim, J. H.; Lee, Y. S.; Park, H.; Kim, C. S. *Tetrahedron* **1998**, *54*, 7395. (f) Hucher, N.; Daïch, A.; Netchitaïlo, P.; Decroix, B. *Tetrahedron Lett.* **1999**, *40*, 3363. (g) Lee, Y. S.; Min, B. J.; Park, Y. K.; Lee, J. Y.; Lee, S. J.; Park, H. *Tetrahedron Lett.* **1999**, *40*, 5569.

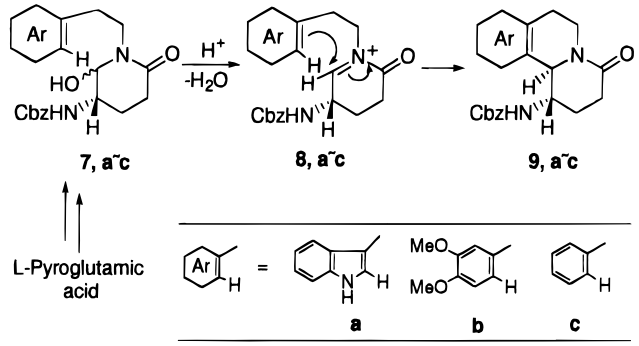
(11) (a) Sajio, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1449. (b) Chiesa, M. V.; Manzoni, L. Scolastico, C. *Synlett* **1996**, 441.

10.1021/jo9911950 CCC: $18.00
Published on Web 11/25/1999

Scheme 1



Scheme 2



11b in 80% and 85% yields, respectively (Scheme 3). To examine the scope and limitation of this procedure, phenethylamine was also used in the aminolysis to give **11c** in 84% yield. The partial reduction of the methyl ester group in **11a**−**c** to the aldehyde was achieved by treatment with DIBALH.[12] During the reduction, the intermediate aldehydes were trapped intramolecularly by the amide groups, resulting in the formation of hydroxylactams **7a**−**c** in 56−85% yields.

The hydroxylactams **7a**−**c** were subjected to *N*-acyliminium ion cyclization conditions. The treatment of **7a** and **7b** with $BF_3 \cdot Et_2O$ at −78 °C afforded cyclized products **9a** and **9b** in 94% and 66% yields, respectively.[10] As we observed previously,[7] the cyclization produced **9a** or **9b** as a single diastereomer resulting from a diastereoselective attack of the large indole or 3,4-dimethoxyphenyl ring on the more accessible side opposite the NHCbz group of *N*-acyliminium ion **8** (Scheme 2). The enantiomeric purities of **9a** and **9b** were >95% on the basis of the chiral phase HPLC analysis, demonstrating that no racemization occurred during the reaction sequence. The *trans*-stereochemistry was confirmed by comparing the $^1H-^1H$ coupling constants ($^3J_{H1-H12b}$ = 5.2 Hz for **9a**; $^3J_{H1-H11b}$ = 7.4 Hz for **9b**) with that of the *cis* isomer ($^3J_{H1-H12b} \cong 0$ Hz) of **9a** reported in the literature.[3c] It was found, however, that the cyclization of hydroxylactam **7c** did not take place under the same reaction conditions even though the starting material was consumed. This may be due to the decreased nucleophilicity of a phenyl ring relative to 3,4-dimethoxyphenyl and indole rings in the cyclization reaction. A number of different conditions were tried without success, indicating that the activation of the phenyl group is necessary for cyclization to proceed, in accordance with our previous results.[7]

The Cbz protecting group in **9a** and **9b** was removed by catalytic hydrogenolysis over palladium charcoal in methanol to furnish *trans*-1-aminoindolo[2,3-*a*]quinolizidine **12a** and *trans*-1-aminobenzo[*a*]quinolizidine **12b** in quantitative and 78% yield, respectively. Finally, reduction of the lactam carbonyl group in **12a** and **12b** with $LiAlH_4$ in the presence of $AlCl_3$[13] proceeded cleanly to provide *trans*-1-aminoindolo[2,3-*a*]quinolizidine **2** and *trans*-1-aminobenzo[*a*]quinolizidine **3** in 74% and 75% yields, respectively.

In conclusion, we have accomplished a chiral synthesis of *trans*-1-aminoindolo[2,3-*a*]quinolizidine **2** and *trans*-1-aminobenzo[*a*]quinolizidines **3** from L-pyroglutamic acid through a stereoselective *N*-acyliminium ion cyclization. This result is quite interesting in that the Pictet−Spengler reaction of tryptamine with an α-aminoaldehye, which was derived from L-glutamic acid, gave predominantly *cis*-1-aminoindolo[2,3-*a*]quinolizidine **1**,[5c] whereas *trans*-1-aminoindolo[2,3-*a*]quinolizidine **2** could be synthesized through *N*-acyliminium ion cyclization of a hydroxylactam derived from the same chiral starting material, L-pyroglutamic acid.

Experimental Section

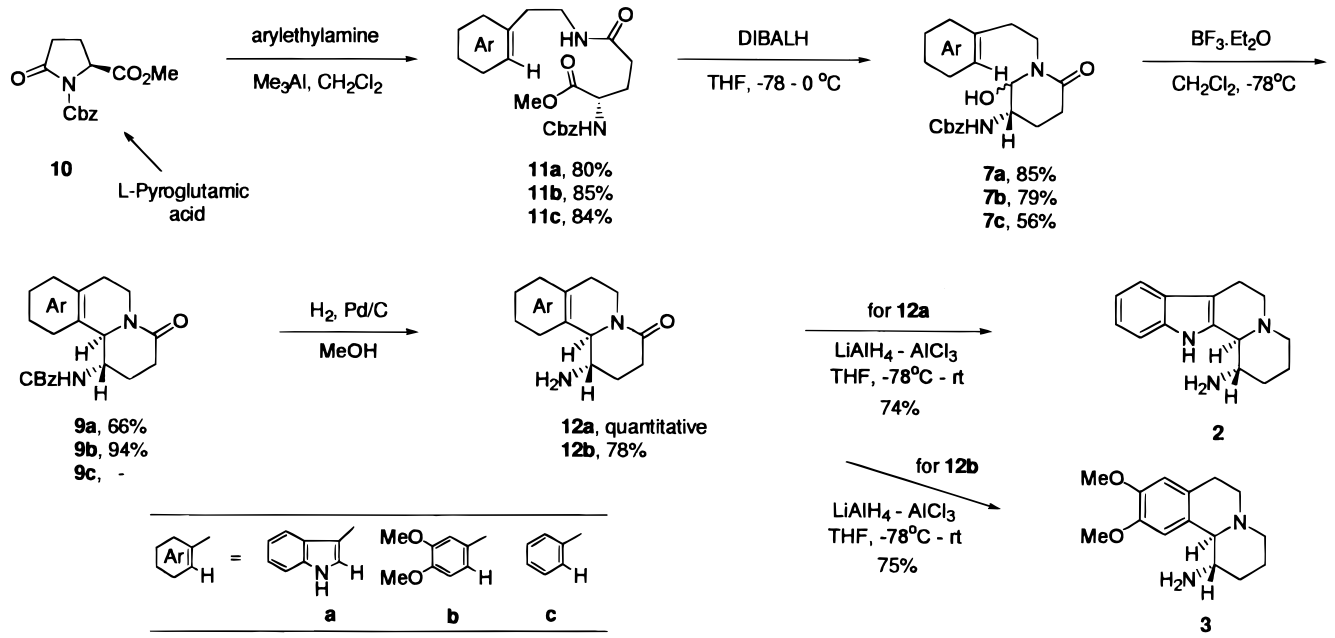
Melting points (mp) are uncorrected. ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. Infrared (IR) spectra were obtained using a potassium bromide pellet or sodium chloride cell. Optical rotations were determined using the sodium D line (λ = 589 nm). High (EI) resolution mass spectra were measured by using the electron impact method at 70 eV. Elemental analyses were performed by Elementar Analysensysteme GmbH Vario EL. Analytical thin layer chromatographies (TLC) were carried out by precoated silica gel (E. Merck Kiesegel $60F_{254}$, layer thickness 0.25 mm). Flash column chromatographies were performed with Merck Kiesegel 60 Art 9385 (230−400 mesh). All solvents used were purified according to standard procedures.

(5*S*)-*N*-(Benzyloxycarbonyl)-5-methoxycarbonyl-2-pyrrolidinone (10). To a stirred solution of L-pyroglutamic acid (25 g, 194 mmol) in MeOH (200 mL) was added $SOCl_2$ (15.2 mL, 213 mmol) dropwise at −20 °C over 10 min. The mixture was stirred at 0 °C for 2.5 h and further stirred at room temperature for 3 h. The mixture was concentrated in vacuo and diluted with THF (100 mL). This solution was added dropwise to a solution of 60% NaH (9.30 g, 232 mmol) in THF (700 mL) at 0 °C over 30 min and stirred for 30 min. The mixture was treated with a solution of benzyl chloroformate (35.3 mL, 232 mmol) in THF (50 mL) dropwise over 30 min. The reaction mixture was further stirred at 0 °C for 3 h and poured into a vigorously stirred solution of EtOAc (200 mL) and ice−water (300 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:1) to afford **10** (29.1 g, 59% for two steps) as an oil: $[\alpha]^{22}_D$ −41.5° (*c* 1.0, EtOH), lit.[11] $[\alpha]^{21}_D$ −41.3° (*c* 1.0, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.32 (5H, m), 5.13 and 5.24 (2H, ABq, J = 12.4 Hz), 4.62 (1H, dd, J = 10.2, 1.0 Hz), 3.61 (3H, s), 2.20−2.62 (3H,

(12) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051.

(13) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656.

Scheme 3



m), 1.95−2.03 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 171.6, 150.9, 135.1, 128.6 (2C), 128.4, 128.1 (2C), 68.2, 58.7, 52.6, 31.0, 21.7.

(2*S*)-4-[2-(Indol-3-yl)ethylcarbamoyl]-2-(benzyloxycarbonyl)aminobutyric Acid Methyl Ester (11a). To a solution of **10** (2.88 g, 10.4 mmol) and tryptamine (2.03 g, 12.5 mmol) in CH_2Cl_2 (25 mL) was added Me_3Al (4.2 mL, 8.3 mmol) at −78 °C. The mixture was slowly warmed to room temperature and stirred for 30 min. The reaction mixture was cooled to 0 °C and quenched by addition of 1 N HCl (10 mL) and extracted with CH_2Cl_2. The organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (EtOAc/*n*-hexane = 2:1) to afford **11a** (3.60 g, 80%) as an oil: $[\alpha]^{24}_D$ −15.2° (*c* 1.25, MeOH); IR (neat) 3316, 1752, 1716, 1652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (1H, s), 7.58 (1H, d, J = 7.7 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.32 (5H, s), 7.05 (1H, t, J = 7.5 Hz), 7.16 (H, t, J = 7.5 Hz), 6.95 (1H, s), 6.27−6.33 (2H, m), 5.11 (2H, s), 4.33 (1H, br s), 3.64 (3H, s), 3.53 (2H, m), 2.92 (2H, t, J = 6.3 Hz), 2.17 (2H, br s), 1.97−2.02 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.3, 156.7, 136.6, 136.4, 128.6 (2C), 128.3, 128.1 (2C), 127.5, 121.9, 122.6, 119.2, 118.6, 112.5, 111.6, 67.1, 53.9, 40.2, 32.4, 27.9, 25.3. Anal. Calcd for $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.57; H, 6.29; N, 9.47.

(2*S*)-4-[2-(3,4-Dimethoxyphenyl)ethylcarbamoyl]-2-(benzyloxycarbonyl)aminobutyric Acid Methyl Ester (11b). Compound **11b** was prepared from pyrrolidone **10** (3.90 g, 14 mmol), 3,4-dimethoxyphenethylamine (7.5 mL, 43.3 mmol), and Me_3Al (13 mL, 43.3 mmol) following a procedure similar to that of **11a** in 85% yield (5.49 g) as a white solid: mp 115−117 °C; $[\alpha]^{24}_D$ −14.4° (*c* 0.9, MeOH); IR (KBr) 3300, 1732, 1682, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (5H, m), 6.58−6.67 (3H, m), 6.51 (1H, br s), 6.24 (1H, d, J = 7.6 Hz), 4.96 (2H, s), 4.18 (1H, br s), 3.70 (6H, s), 3.56 (3H, s), 3.32 (2H, m), 2.62 (2H, t, J = 6.8 Hz), 2.14 (2H, t, J = 6.3 Hz), 1.86−2.09 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 172.1, 156.4, 148.9, 147.6, 136.3, 131.5, 128.4 (2C), 128.1, 127.9 (2C), 120.6, 112.0, 111.4, 66.8, 55.8 (2C), 53.7, 52.3, 40.9, 35.1, 32.6, 27.9. Anal. Calcd for $C_{24}H_{30}N_2O_7$: C, 62.87; H, 6.59; N, 6.11. Found: C, 62.90; H, 6.66; N, 6.11.

(2*S*)-4-[2-(Phenyl)ethylcarbamoyl]-2-(benzyloxycarbonyl)-aminobutyric Acid Methyl Ester (11c). Compound **11c** was prepared from pyrrolidone **10** (2.0 g, 7.2 mmol), phenethylamine (1.1 mL, 8.7 mmol), and Me_3Al (3.6 mL, 7.2 mmol) following a procedure similar to that of **11a** in 84% yield (2.4 g) as a white solid: mp 112−115 °C; $[\alpha]^{24}_D$ −16.0° (*c* 0.85, MeOH); IR (KBr) 3304, 1740, 1694, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16−7.32 (10H, m), 6.23 (1H, br s), 6.04 (1H, d, J = 7.8 Hz), 5.08 (2H, s), 4.29 (1H, br s), 3.69 (3H, s), 3.44 (2H, m), 2.78 (2H, t, J = 7.0 Hz), 2.17 (1H, br s), 1.95−2.19 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 172.0, 156.4, 139.0, 136.3, 128.8 (2C), 128.6 (2C), 128.6 (2C), 128.2 (2C), 128.1, 126.5, 67.0, 53.7, 52.5, 40.8, 35.6, 32.4, 28.2. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.30; H, 6.60; N, 7.01.

(5*S*)-5-(Benzyloxycarbonyl)amino-6-hydroxy-1-[2-(indol-3-yl)ethyl]piperidin-2-one (7a). To a solution of amidoester **11a** (1.60 g, 3.66 mmol) in CH_2Cl_2 (20 mL) was added dropwise DIBALH (4 mL, 1 M in toluene) through syringe pump under an argon atmosphere at −78 °C. The mixture was slowly warmed to room temperature and further stirred for 2 h. This procedure was repeated twice with 2 mL and 1.5 mL of DIBALH (1 M in toluene), respectively. After cooling to 0 °C the reaction mixture was quenched by slow addition of MeOH (5 mL) and 1 N HCl (5 mL) and extracted with CH_2Cl_2. The combined organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (EtOAc/*n*-hexane = 2:1) to afford hydroxylactam **7a** (1.27 g, 85%) as an oil (ca. 94:6 mixture of epimers based on ^{1}H NMR and GC/MS analysis): IR (neat) 3306, 1694, 1633 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, s), 7.57 (1H, d, J = 7.4 Hz), 7.26−7.32 (5H, m), 7.02−7.19 (3H, m), 6.82 (1H, s), 4.95−5.42 (4H, m), 4.56 (1H, m), 3.91 (1H, m), 3.82 (1H, m), 3.42 (1H, m), 2.96−3.01 (2H, m), 2.16−2.34 (3H, m), 1.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 156.2, 136.3, 136.2, 128.7 (2C), 128.5, 128.3 (2C), 127.2, 122.3, 122.2, 119.5, 118.7, 112.8, 111.5, 83.1, 67.1, 50.3, 46.4, 27.8, 23.7, 20.7. Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 67.82; H, 6.21; N, 10.26.

(5*S*)-5-(Benzyloxycarbonyl)amino-1-[2-(3,4-dimethoxyphenyl)ethyl]-6-hydroxypiperidin-2-one (7b). Hydroxylactam **7b** was prepared from amidoester **11b** (1.0 g, 2.2 mmol) following a procedure similar to that of **7a** in 79% yield (0.74 g) as a white solid (ca. 93:2 mixture of epimers based on ^{1}H NMR and GC/MS analysis): mp 144−146 °C; IR (KBr) 3330, 1694, 1614 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.32 (5H, m), 6.68−6.76 (3H, m), 5.36 (1H, d, J = 8.8 Hz), 5.03 (2H, m), 4.66 (1H, s), 3.79 (6H, s), 3.71 (1H, s), 3.52 (1H, m), 3.23−3.46 (2H, m), 2.78 (2H, br s), 2.34−2.44 (2H, m), 1.72−2.02 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 155.7, 149.1, 147.7, 136.2, 131.5, 128.6 (2C), 128.7, 128.0 (2C), 120.8, 112.1, 111.5, 80.4, 67.0, 55.9 (2C), 49.8, 48.1, 33.9, 30.8, 21.7. Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.20; H, 6.56; N, 6.44.

(5*S*)-5-(Benzyloxycarbonyl)amino-6-hydroxy-1-(2-phenethyl)piperidin-2-one (7c). Hydroxylactam **7c** was prepared from amidoester **11c** (1.1 g, 2.8 mmol) following a procedure similar to that of **7a** in 56% yield (0.52 g) as a white solid: mp 174−175 °C; IR (KBr) 3314, 1682, 1614 cm^{-1}; ^{1}H NMR (300

MHz, CD_3OD) δ 7.15−7.31 (10H, m), 5.02 (2H, s), 4.40 (1H, m), 3.90 (1H, m), 3.78 (1H, m), 3.25 (1H, m), 2.79−2.88 (2H, m), 2.40−2.46 (2H, m), 2.07 (1H, m), 1.75 (1H, s); ^{13}C NMR (75 MHz, CD_3OD) δ 171.8, 157.9, 140.3, 137.9, 130.0 (2C), 129.7 (2C), 129.6 (2C), 129.3, 129.1 (2C), 127.6, 81.0, 67.9, 51.1, 49.1, 35.3, 31.9, 22.4. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.50; H, 6.57; N, 7.64.

(1*S*,12b*S*)-1-(Benzyloxycarbonyl)amino-1,2,3,6,7,12b-hexahydro-indolo[2,3-*a*]quinolizin-4-one (9a). To a solution of hydroxylactam **7a** (0.1 g, 0.25 mmol) in acetonitrile (4 mL) was added dropwise $BF_3{\cdot}Et_2O$ (0.1 mL, 0.7 mmol) at −78 °C, and the mixture was slowly warmed to −10 °C. After stirring for 5 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched by addition of aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (EtOAc/*n*-hexane/CH_2Cl_2 = 6:3:1) to afford hydroxylactam **9a** (63 mg, 66%) as a foam: $[\alpha]^{24}_D$ −28.8° (*c* 0.17, MeOH); IR ($CHCl_3$) 3270, 1694, 1634 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 9.30 (1H, br s), 7.48 (1H, d, *J* = 7.6 Hz), 7.37 (5H, s), 7.32 (1H, d, *J* = 7.9 Hz), 7.19 (1H, t, *J* = 6.7 Hz), 7.12 (1H, t, *J* = 7.7 Hz), 5.90 (1H, d, *J* = 8.0 Hz), 5.21 (2H, s), 5.02 (1H, dd, *J* = 11.5, 4.4 Hz), 4.68 (1H, d, *J* = 5.2 Hz), 4.19 (1H, br s), 2.76−2.92 (2H, m), 2.67 (1H, d, *J* = 13.7 Hz), 2.30−2.58 (2H, m), 1.85−2.09 (2H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 169.1, 156.7, 136.2, 136.0, 131.8, 128.8 (2C), 128.6 (2C), 128.2, 126.6, 122.3, 119.7, 118.3, 111.5, 110.1, 67.5, 59.9, 50.5, 41.9, 29.8, 25.9, 20.7. Anal. Calcd for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79. Found: C, 70.82; H, 6.04; N, 10.68. Chiral HPLC analysis: chiral column, ChiraSpher NT 250 mm × 4 mm i.d.; eluting solvents, MeOH/*i*-PrOH/*n*-hexane = 83:7.4:5.6; flow rate, 1.3 mL/min; detector, UV (280 nm), retention time, 11.6 min.

(1*S*,11b*R*)-1-(Benzyloxycarbonyl)amino-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (9b). Cyclized product **9b** was prepared from hydroxylactam **7b** (0.53 g, 1.3 mmol) following a procedure similar to that of **9a** in 94% yield (0.47 g) as a foam: $[\alpha]^{24}_D$ −42.6° (*c* 0.7, MeOH); IR ($CHCl_3$) 3270, 1716, 1632 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.26 (5H, m), 6.89 (1H, s), 6.69 (1H, s), 4.80 and 5.04 (2H, ABq, *J* = 12.4 Hz), 4.48 (1H, d, *J* = 7.4 Hz), 4.29 (1H, m), 4.04 (1H, m), 3.74 (3H, s), 3.55 (3H, s), 2.78−2.95 (2H,m), 2.53−2.70 (2H, m), 2.38 (1H, m), 1.86−2.01 (2H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 169.4, 156.9, 148.3, 147.6, 136.3, 128.6 (2C), 128.2 (2C), 127.0, 120.8, 111.8, 108.1, 67.0, 60.9, 55.9, 49.5, 42.1, 28.9, 28.0, 24.7, 17.4. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C 67.30; H 6.38; N 6.82. Found: C 67.18; H 6.41; N 6.75. Chiral HPLC analysis: chiral column, ChiraSpher NT 250 mm × 4 mm i.d.; eluting solvents, MeOH/*i*-PrOH/*n*-hexane = 83:7.4:5.6; flow rate, 1.3 mL/min; detector, UV (280 nm), retention time, 13.9 min.

(1*S*,12b*S*)-1-Amino-1,2,3,6,7,12b-hexahydro-indolo[2,3-*a*]-quinolizin-4-one (12a). A solution of **7a** (0.24 g, 0.6 mmol) in MeOH (10 mL) was stirred at room temperature under H_2 (1 atm) with a catalytic amount of 10% palladium on charcoal (0.02 g) for 3 h. The reaction mixture was filtered through Celite-545 and concentrated to give **12a** (0.16 g) in quantitative yield as a white foam: $[\alpha]^{25}_D$ −75.0° (*c* 1.1, MeOH); IR ($CHCl_3$) 3356, 2918, 1620, 1464, 1442 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (1H, s), 7.49 (1H, d, *J* = 7.7 Hz), 7.34 (1H, d, *J* = 7.9 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 7.09 (1H, t, *J* = 7.4 Hz), 5.10 (1H, m), 4.29 (1H, d, *J* = 10.0 Hz), 2.71−2.98 (4H, m), 2.61 (1H, m), 2.45 (1H, m), 1.90 (1H, m), 1.76 (1H, m), 1.64 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 135.9, 134.2, 126.8, 122.2, 119.7, 118.6, 111.5, 108.9, 59.6, 53.1, 41.1, 33.1, 31.8, 21.4; HRMS (EI) calcd for $C_{15}H_{17}N_3O$ *m*/*z* 255.1372, found 255.1371.

(1*S*,11b*R*)-1-Amino-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (12b). A solution of **9b** (0.18 g, 0.4 mmol) in MeOH (10 mL) was stirred at room temperature under H_2 (1 atm) with a catalytic amount of 10% palladium on charcoal (0.02 g) for 2h. The reaction mixture was filtered through Celite-545, concentrated, and purified by flash column chromatography (MeOH/CH_2Cl_2 = 1:20) to give **12b** (0.09 g, 78%) as a white foam: $[\alpha]^{25}_D$ −34.2° (*c* 1.2, MeOH); IR ($CHCl_3$) 3422, 2938, 1616, 1518, 1466 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, s), 6.66 (1H, s), 4.63 (1H, m), 4.30 (1H, d, *J* = 7.3 Hz), 3.87 and 3.88 (6H, two s), 3.23 (1H, m), 2.86−2.93 (2H, m), 2.40−2.67 (3H, m), 2.00 (1H, m), 1.77 (1H, m) 1.59 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 148.5, 147.7, 129.1, 127.8, 112.1, 110.1, 63.2, 56.6, 56.3, 51.8, 41.4, 30.0, 29.4, 29.0; HRMS (EI) calcd for $C_{15}H_{20}N_2O_3$ *m*/*z* 276.1474, found 276.1472.

(1*S*,12b*S*)-1-Amino-1,2,3,4,6,7,12,12b-octahydro-indolo-[2,3-*a*]quinolizine (2). A solution of $AlCl_3$ (25.8 mg, 0.19 mmol) in THF (1 mL) was added dropwise to a solution of $LiAlH_4$ (44 mg, 1.16 mmol) in THF (1 mL) at −78 °C under argon atmosphere, and the mixture was slowly warmed to room temperature. After stirring for 30 min, this suspension was added to a solution of **12a** (49.7 mg, 0.19 mmol) in THF (2 mL) at −78 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and quenched by careful addition of ether (5 mL), $Na_2SO_4{\cdot}10H_2O$ (0.24 g), and Celite-545. The mixture was stirred at room temperature for 1 h and filtered through Celite-545. The filtrate was concentrated and purified by flash column chromatography (MeOH/CH_2Cl_2 = 1:20) to give **2** (35 mg, 74%) as a white solid: mp 132.5−135.0 °C (dec); $[\alpha]^{23}_D$ +3.64° (*c* 0.17, MeOH); IR (KBr) 3348, 3266, 2924, 2800, 2746, 1460, 1316 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (1H, s), 7.47 (1H, d, *J* = 7.6 Hz), 7.32 (1H, d, *J* = 7.8 Hz), 7.11 (1H, t, *J* = 7.1 Hz), 7.04 (1H, t, *J* = 7.1 Hz), 2.91−3.13 (4H, m), 2.82 (1H, td, *J* = 10.5, 4.1 Hz), 2.55−2.76 (2H, m), 2.34 (1H, td, *J* = 11.5, 3.2 Hz), 2.08 (1H, m), 1.66−1.90 (4H, m), 1.25 (1H, m); ^{13}C NMR(75 MHz, $CDCl_3$) δ 135.9, 135.8, 127.3, 121.3, 119.0, 118.3, 111.4, 107.8, 65.9, 55.7, 54.2, 53.3, 39.2, 25.1, 22.1; HRMS (EI) calcd for $C_{15}H_{19}N_3$ *m*/*z* 241.1579, found 241.1577. The ^{1}H NMR spectroscopic data of **2** was in accord with that described in the literature for racemic mixture.[3a]

(1*S*,11b*R*)-1-Amino-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizine (3). Compound **3** was prepared from hydroxylactam **12b** (52 mg, 0.2 mmol) following a procedure similar to that of **2** in 75% yield (37 mg) as a viscous oil: $[\alpha]^{25}_D$ +17.1° (*c* 1.4, MeOH); IR ($CHCl_3$) 3420, 2934, 1516, 1460, 1264, 1134 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (1H, s), 6.54 (1H, s), 3.78 (6H, s), 4.30 (1H, d, *J* = 7.9 Hz), 3.18 (1H, m), 3.09 (1H, m), 2.67−2.93 (5H, m), 2.02 (2H, br s), 1.64−1.88 (2H, m), 1.55 (1H, m),1.42 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 146.3, 128.3, 127.2, 112.4, 111.2, 65.9, 56.4, 56.1, 53.5, 48.8, 47.4, 33.9, 28.4, 21.4; HRMS (EI) calcd for $C_{15}H_{22}N_2O_2$ *m*/*z* 262.1681, found 262.1682.

Acknowledgment. Financial support from the Ministry of Science and Technology, Korea (2E14578) is gratefully acknowledged. Elemental analyses data were provided by Specific Analysis Center at Korea Institute of Science and Technology. High (EI) resolution mass spectra were obtained at Korea Basic Science Institute.

JO9911950