Asymmetric Synthesis of Both Enantiomers of Pyrrolidinoisoquinoline Derivatives from L-Malic Acid and L-Tartaric Acid

Yong Sup Lee,*,† Dong Wook Kang,‡ Sook Ja Lee,‡ and Hokoon Park*,†

Organic Chemistry Laboratory (I), Korea Institute of Science & Technology, P. O. Box 131 Cheongryang, Seoul 130-650, Korea and Department of Chemistry, Hankook University of Foreign Studies, Yong-in 449-791, Korea

Received May 31, 1995®

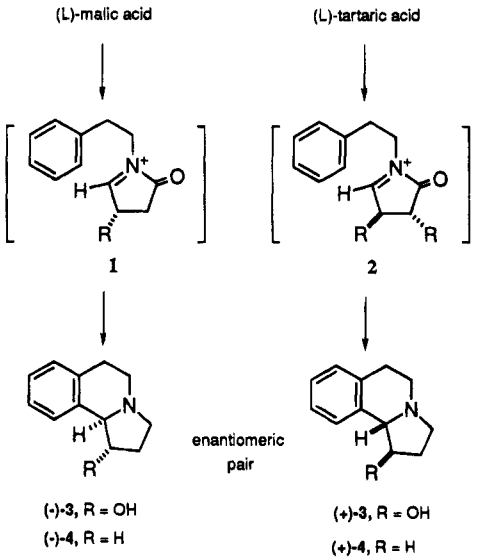
The pyrrolidinoisoquinoline derivatives ((−)-**3**, (−)-**4**) and their antipodes ((+)-**3**, (+)-**4**) were prepared by reductive deoxygenation and reduction from the intermediates **9** and **10**. The key intermediates **9** and **10** were prepared by a diastereoselective *N*-acyliminium ion cyclization of chiral lactams, which derived from L-malic acid and L-tartaric acid, respectively.

Introduction

Pyrrolidinoisoquinoline alkaloids are abundant in plant products and many exhibit interesting biological activity.[1] Accordingly, much attention has focused on the development of general approaches to these alkaloids.[2] Syntheses of the pyrrolidinoisoquinoline ring subunit have also appeared in the literature.[3] Boekelheide *et al.* synthesized racemic pyrrolidinoisoquinoline by the Bischler-Napieralski reaction of 1-(2-phenylethyl)-2-oxopyrroline.[3e] Optically active (+)-pyrrolidinoisoquinoline was first obtained by the degradative reduction of the alkaloid, norsecurinine, during its structural elucidation.[3b] However, it is surprising that only a few examples of asymmetric synthesis of the pyrrolidinoisoquinoline skeleton have been demonstrated.[4]

Synthesis of enantiomerically pure alkaloids is of widespread interest to both organic and medicinal chemists. A popular method for the synthesis of alkaloids involves *N*-acyliminium ion cyclizations.[5] The use of a chiral hydroxy lactam in an acyliminium ion cyclization can result in a stereoselective preparation of alkaloids. We herein describe an asymmetric synthesis of pyrrolidinoisoquinoline derivatives **3** and **4** and their antipodes (*ent*-**3**, *ent*-**4**) by using a diastereoselective *N*-acyliminium ion cyclization.[6] The synthetic strategy for the pyrrolidinoisoquinoline derivatives and their enantiomers starting from L-malic acid and L-tartaric acid is illustrated in Scheme 1. The synthesis involves the preparation of the required chiral *N*-acyliminium ions **1** and **2** from commonly available L-malic acid and L-tartaric acid. In many cases, enantiomerically pure compounds have been prepared from the natural L-series and also the unnatural D-series of a chiral synthons.[7] The synthesis of both enantiomers of the pyrrolidinoisoquinoline derivatives from the same inexpensive L-series of hydroxy acids is notable.

Scheme 1



Results

Chiral acyliminium ions **1** and **2** were targeted as synthetic intermediates since it was believed that the free or protected hydroxyl groups in the lactam would control the stereochemical outcome of the cyclization step and could be removed by a reductive deoxygenation later in the synthesis. The pyrrolidinoisoquinone derivatives **9**

† Korea Institute of Science & Technology.
‡ Hankook University of Foreign Studies.
® Abstract published in *Advance ACS Abstracts,* October 1, 1995.

(1) (a) Boekelheide, V. *Alkaloids* **1960**, *7*, 201. (b) Hill, R. K. *Alkaloids* **1967**, *9*, 483.

(2) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Lete, E.; Egiarte, A.; Sotomayor, N.; Vicente, T.; Villa, M.-J. *Synlett* **1993**, 41. (c) Tsuda, Y.; Sakai, Y.; Kaneko, M.; Ishiguro, Y. *Heterocycles* **1981**, *15*, 431.

(3) (a) Morlacchi, F.; Losacco,V. *J. Heterocycl. Chem.* **1976**, *13*, 165. (b) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z-I; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1965**, *13*, 786. (c) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (d) Iketubosin, G. O.; Mathieson, D. W. *J. Pharm. and Pharmacol.* **1963**, *15*, 810. (e) Boekekheide, V.; Godfrey, J. C. *J. Am. Chem. Soc.* **1953**, *75*, 3679.

(4) (a) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567. (b) Maryanoff, B. E.; McComsey, D. F.; Mutter, M. S.; Sorgi, K. L., and Maryanoff, C. A. *Tetrahedron Lett.* **1988**, *29*, 5073. (c) Maryanoff B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911. (d) Maryanoff, B. E.; McComsey, D. F.; Almond, Jr., H. R.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *J. Org. Chem.* **1986**, *51*, 1341.

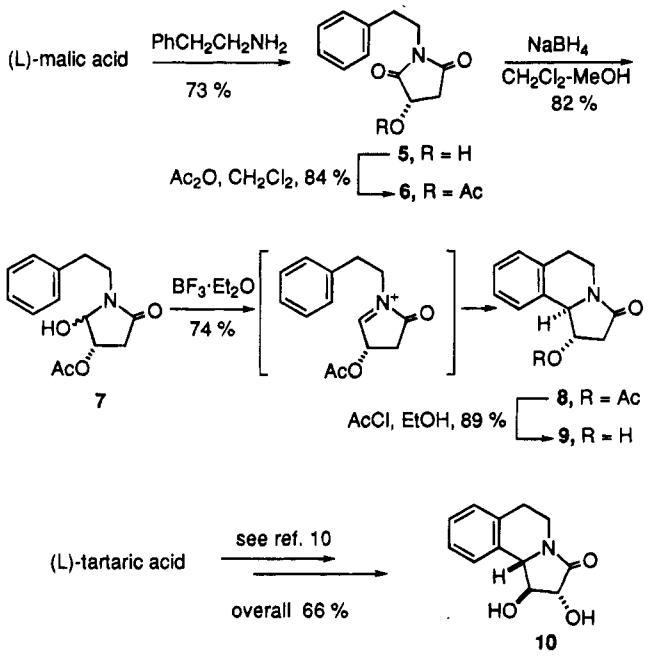
(5) (a) Hiemstra, H. and Speckamp, W. N. *Additions to N-Acyliminium Ions.* In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1047–1082. (b) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987. (d) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(6) (a) Lee, Y. S.; Kim, S. H.; Jung, S. H.; Lee, S. J.; Park, H. *Heterocycles* **1994**, *37*, 303. (b) Lee, Y. S.; Kim, C. S.; Park, H. *Heterocycles* **1994**, *38*, 2605.

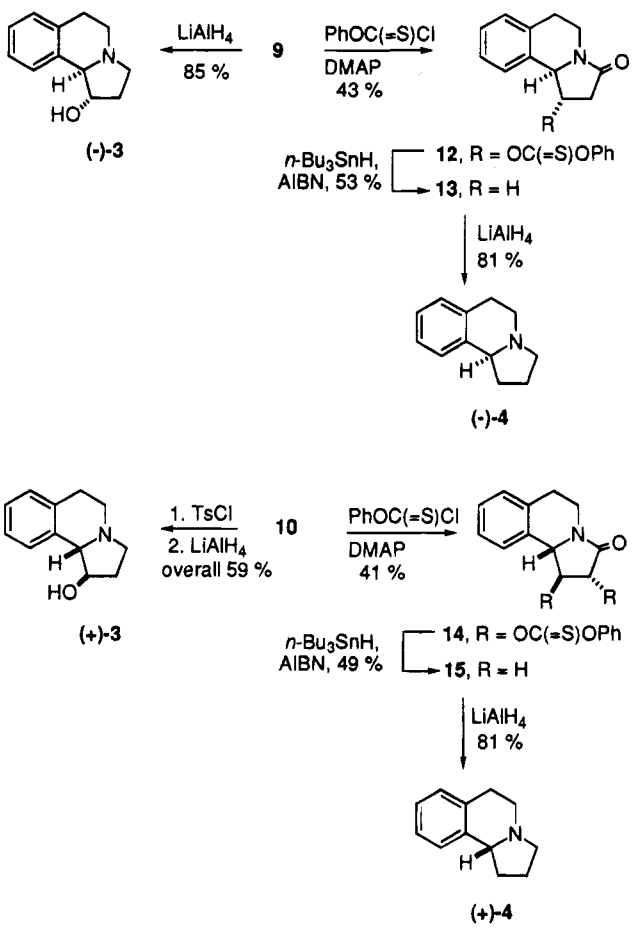
(7) (a) Fronza, G.; Fuganti, C.; Grasseli, P. *Tetrahedron Lett.* **1980**, *21*, 2999. (b) Bellamy, F. D.; Bondoux, M.; Dodey, P. *Tetrahedron Lett.* **1990**, *31*, 7323. (c) Mori, K.; Tamada, S. *Tetrahedron* **1979**, *35*, 1279.

0022-3263/95/1960-7149$09.00/0

Scheme 2



Scheme 3



and **10** were prepared in enantiomerically pure form from L-malic acid and L-tartaric acid, respectively, as shown in Scheme 2. L-Malic acid was condensed with phenethylamine in refluxing xylene to give imide **5** (73%). The hydroxyl group in imide **5** was acetylated and reduced with $NaBH_4$ in CH_2Cl_2/MeOH at −15 °C to afford the crude chiral hydroxy lactam **7** (69% over two steps).[8] The crude hydroxy lactam **7** was subjected to the *N*-acyliminium ion cyclization conditions to provide the pyrrolidinoisoquinolines.

The *N*-acyliminium ion cyclization of hydroxy lactam **7** with BF_3·OEt_2 at room temperature proceeded cleanly to provide pyrrolidinoisoquinolinone **8** (74%). The acetoxy group in **8** was cleaved (AcCl, EtOH) to afford 1-hydroxypyrrolidinoisoquinolinone **9** (89%).[10] From an analysis of **8** and **9** by 300 MHz ^1H NMR spectroscopy and capillary gas chromatography, it was concluded that the cyclization produced only a single diastereomer, resulting from a diastereospecific attack of the large benzene ring on the least hindered side opposite to the C-4 acetoxy group of the acyliminium ion.

Precursor **10** was prepared in enantiomerically pure form by a similar manner from L-tartaric acid in overall 66% yield.[10] As was observed in the cyclization of **7**, only a single diastereomer **10** was produced.

The enantiomerically pure pyrrolidinoisoquinoline derivatives (−)-**3** and (−)-**4** and their antipodes ((+)-**3**, (+)-**4**) were synthesized from **9** and **10**, respectively, as shown in Scheme 3. The reduction ($LiAlH_4$, THF) of **9** afforded 1-hydroxylated pyrrolidinoisoquinoline derivative **3** ($[\alpha]^{25}_D$ −10.3° (*c* 2, MeOH)), in 85% yield. The synthesis of (+)-**3** was carried out by the selective deoxygenation of C-2 hydroxyl group in **10**. Tosylation of **10** (TsCl, CH_2Cl_2) proceeded regioselectively at the less hindered C-2 hydroxyl group to afford 2-(tosyloxy)pyrrolidinoisoquinoline derivative **11** in 77% yield. The C-2 tosylated compound **11** was then converted to 1-hydroxylated pyrrolidinoisoquinoline (+)-**3** in 76% yield by the concomitant reductive deoxygenation of tosyloxy group and reduction of the lactam carbonyl group ($LiAlH_4$, THF). The 1-hydroxylated pyrrolidinoisoquinoline (+)-**3** exhibited spectroscopic properties (^{13}C NMR, ^1H NMR, IR, mass fragmentation) identical with those of the compound (−)-**3** except for optical rotation ($[\alpha]^{25}_D$ +9.8° (*c* 0.4, MeOH)). Accordingly, the synthesis of the enantiomerically pure 1-hydroxylated pyrrolidinoisoquinoline derivative (−)-**3** and its antipode (+)-**3** were accomplished by the diastereospecific *N*-acyliminium ion cyclization strategy starting with from L-malic acid and L-tartaric acid, respectively.

Pyrrolidinoisoquinoline derivative (−)-**4** and its antipode were also synthesized from **9** and **10** by the removal of the existing hydroxyl groups. Attempted reductive deoxygenation of C-1 hydroxyl group in **9** and **10** through tosylation followed by reduction were unsuccessful. Tosylation of **9** and **10** was found to be difficult due to the steric hindrance of the C-1 hydroxyl group. Accordingly, the hydroxyl groups in **9** and **10** were removed by thioacylation followed by radical cleavage of thio ester.[11] The reaction of **9** with phenyl chlorothionocarbonate afforded thio ester **12** in 43% yield. The thioester **12** was converted to pyrrolidinoisoquinoline derivative (−)-**4** ($[\alpha]^{23}_D$ −101.7°, (*c* 2.0, MeOH); lit.[3a] $[\alpha]_D$ −47.33°, optical purity 48.9%, (*c* 0.77, MeOH)) by a two-step sequence: radical cleavage of carbon-oxygen bond (*n*-Bu_3SnH, AIBN) and reduction of the lactam carbonyl group ($LiAlH_4$, THF)

(8) Shiokawa, S.; Ohta, T.; Nozoe, S. *Chem. Pharm. Bull.* **1992**, *40*, 1398.

(9) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941.

(10) The preliminary results for the synthesis of **10** from L-tartaric acid see: Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *Synth. Commun.* **1995**, *25*, 1947.

(11) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.

in 43% yield over two steps. The synthesis of (+)-**4** was accomplished by the similar reaction pathway from **10**. Pyrrolidinoisoquinone derivative **10** was converted to bis-thio ester **14** in 41% yield by the reaction with phenyl chlorothionocarbonate. Finally, the radical cleavage of carbon-oxygen bond followed by the reduction of the lactam carbonyl group in bis-thio ester **14** afforded (+)-**4** in 40% yield in over two steps. The spectral data (^{13}C NMR, ^{1}H NMR, IR, mass fragmentation) of (+)-**4** were identical with those of the compound (−)-**4** except the optical rotation ($[\alpha]^{22}_D$ +97.6°, (*c* 0.6, MeOH)).

In conclusion, an asymmetric synthesis of pyrrolidinoisoquinoline derivatives (−)-**3** and (−)-**4** and their antipodes have been accomplished using a diastereoselective *N*-acyliminium ion cyclization. The synthesis of both enantiomers of pyrrolidinoisoquinoline derivatives were carried out starting with the inexpensive same L-series of hydroxy acid, L-malic acid and L-tartaric acid. This methodology is valuable since L-tartaric acid can be used in replacement of unnatural D-malic acid for the synthesis of enantiomeric antipodes of pyrrolidinoisoquinoline derivatives. We are currently investigating transformations of the cyclized products **9** and **10** to other alkaloids since the existing hydroxyl groups in lactam ring are functionally differentiable.

Experimental Section

Melting points (mp) are uncorrected. The ^{1}H 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. High resolution mass spectra (HRMS) were measured by using the electron impact (EI) method at 70 eV. Flash column chromatography was carried out on Merck silica gel 60, 230−400 mesh ASTM; eluents are given in parentheses. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates.

Anhydrous THF was distilled from Na/benzophenone ketyl; CH_2Cl_2 and CH_3CN were distilled from CaH_2.

(3*S*)-3-Hydroxy-1-(2-phenylethyl)-2,5-pyrrolidinedione (5). L-Malic acid (22.1 g, 165 mmol) was added to xylene (100 mL) in a 1 L three-necked flask with a Dean−Stark trap and condenser. To the stirred and refluxing solution was added 2-phenethylamine (22 g, 181 mmol), and reflux was continued for 3.5 h. The solution was cooled in an ice bath, and crystalline product was filtered and washed with ether to afford imide **5** (26.5 g, 73%) as a white solid: mp 130−132 °C; $[\alpha]^{27}_D$ −71.7° (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (1H, dd, J = 18.1, 4.7 Hz), 2.88 (2H, t, J = 7.3 Hz), 3.01 (1H, dd, J = 18.1, 8.3 Hz), 3.75 (2H, t, J = 7.3 Hz), 4.56 (1H, dd, J = 8.3, 4.7 Hz), 7.18−7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 174.2, 137.5, 129.2, 128.9, 128.6, 126.9, 67.0, 40.1, 37.2, 33.5; IR (KBr) 3476, 1779, 1699 cm^{-1}; MS, *m*/*z* (relative intensity) 219 (M^+, 11), 105 (10), 104 (100), 91(25), 65(8), 43(9). Anal. Calcd for $C_{12}H_{13}NO_3$: C 65.74; H 5.98; N 6.39. Found: C 65.90; H 6.04; N 6.31.

(3*S*)-3-(Acetyloxy)-1-(2-phenylethyl)-2,5-pyrrolidinedione (6). To a stirred solution of imide **5** (3.01 g, 13.7 mmol) in dry CH_2Cl_2 (20 mL) were added triethylamine (3.58 g, 35.3 mmol), acetic anhydride (3.01g, 29.5 mmol), and a catalytic amount of DMAP. After stirring at rt for 4 h the solution was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was dried ($MgSO_4$) and concentrated. Flash column chromatography (EtOAc−hexane = 1:3−1:1) gave 3-acetyloxy imide **6** (3.0 g, 84%) as a white solid: mp 97−99 °C; $[\alpha]^{25}_D$ −19.6° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (3H, s), 2.61 (1H, dd, J = 18.4, 4.5 Hz), 2.91 (2H, t, J = 7.8 Hz), 3.11 (1H, dd, J = 18.4, 9.0 Hz), 3.79 (2H, t, J = 7.8 Hz), 5.37 (1H, dd, J = 9.0, 4.5 Hz), 7.21−7.31 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3. 173.0, 169.8, 137.5, 128.9, 128.6, 126.8, 67.4, 40.2, 35.5, 33.4, 20.5; IR (KBr) 1714, 1414 cm^{-1}; MS *m*/*z* (relative intensity) 261 (M^+, 10), 105 (10), 104 (100), 43 (35). Anal. Calcd for $C_{14}H_{15}NO_4$: C 64.36; H 5.79; N 5.36. Found: C 64.36; H 5.82; N 5.52.

(3*S*)-4-(Acetyloxy)-5-hydroxy-1-(2-phenylethyl)-2-pyrrolidinone (7). To a stirred solution of 3-acetyloxy imide **6** (2.2 g, 8.42 mmol) in dry CH_2Cl_2 (10 mL) and MeOH (5 mL) was added $NaBH_4$ (320 mg, 8.46 mmol) at −40 °C. The solution was stirred at −10 °C for 5 h and quenched with H_2O (15 mL). The mixture was extracted with CH_2Cl_2 (25 mL × 2). The combined organic layer was dried ($MgSO_4$) and concentrated. Flash column chromatography (EtOAc-hexane = 2:1) gave hydroxy lactam **7** (1.8 g, 82%) as a white solid: mp 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (3H, s), 2.55 (1H, dd, J = 17.3, 5.7 Hz), 2.67 (1H, dd, J = 17.3, 7.4 Hz), 2.85−2.94 (2H, m), 3.46−3.74 (2H, m), 5.05−5.12 (2H, m), 7.21−7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.1, 138.7, 128.8, 128.6, 126.7, 82.2, 67.9, 42.0, 35.1, 34.1, 20.6; IR (KBr) 3216, 1740, 1658 cm^{-1}; MS *m*/*z* (relative intensity) 244 ($M^+ + 1 - H_2O$, 1), 202 ($M^+ - H_2O$ − acetyl, 7), 185 (100), 174 (12), 156 (49), 132 (45), 103 (8), 77 (8). Anal. Calcd for $C_{14}H_{17}NO_4$: C 63.87; H 6.51; N 5.32. Found: C 64.11; H 6.34; N 5.45.

(1*S*,10b*R*)-1-(Acetyloxy)-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-3-one (8). To a stirred solution of hydroxy lactam **7** (520 mg, 1.98 mmol) in dry CH_2Cl_2 (7 mL) was added $BF_3{\cdot}OEt_2$ (1.73g , 12.2 mmol) via syringe under nitrogen atmosphere in an ice bath. The solution was stirred at rt for 2 days and poured over saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was dried ($MgSO_4$) and concentrated. Flash column chromatography (EtOAc−hexane = 2:1−5:1) gave 1-(acetyloxy)isoquinolinopyrrolidinone **8** (360 mg, 74%): mp 100−102 °C; $[\alpha]^{25}_D$ −94.3° (*c* 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.52 (1H, dd, J = 7.3, 5.5 Hz), 2.69−3.12 (4H, m), 4.29−4.35 (1H, m), 4.80 (1H, d, J = 4.0 Hz), 5.20−5.26 (1H, m), 7.11−7.38 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.2, 134.2, 134.0, 129.4, 127.6, 127.1, 125.1, 73.9, 62.0, 38.1, 37.1, 28.1, 21.1; IR (KBr) 1706, 1436 cm^{-1}; MS, *m*/*z* (relative intensity) 203 (M^+ − acetyl, 19), 132 (2), 112 (26), 104 (100), 91 (15), 84 (31); Anal. Calcd for $C_{14}H_{15}NO_3$: C 68.56; H 6.16; N 5.71. Found: C 68.47; H 6.22; N 5.71.

(1*S*,10b*R*)-1-Hydroxy-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-3-one (9). To a solution of 1-(acetyloxy)-isoquinolinopyrrolidinone **8** (2.83 g, 11.5 mmol) in absolute EtOH (20 mL) was added acetyl chloride (7 mL) and stirred at rt for 6 h. The solution was poured into saturated aqueous $NaHCO_3$ (50 mL) in an ice bath and extracted with CH_2Cl_2 (70 mL x 2). The combined organic layer was dried ($MgSO_4$) and concentrated. Flash column chromatography (EtOAc−hexane = 4:1) gave 1-hydroxyisoquinolinopyrrolidinone **9** (2.1 g, 89%) as a white solid: mp 161−163 °C; $[\alpha]^{25}_D$ −148.6° (*c* 0.2, CH_3OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.60−3.07 (5H, m), 4.26−4.36 (2H, m) 4.64 (1H, d, J = 6.3 Hz), 7.13−7.55 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 135.4, 133.5, 129.2, 127.3, 127.0, 125.2, 73.3, 63.7, 41.3, 36.7, 28.6; IR (KBr) 3336, 1664, 1462 cm^{-1}; MS *m*/*z* (relative intensity) 204 (M^+ + 1, 12), 203 (M^+, 97), 174 (77), 156 (13), 13(100), 13(88), 10(20), 10(21), 7 (20). Anal. Calcd for $C_{12}H_{13}NO_2$: C 70.90; H 6.45; N 6.89. Found: C 70.76; H 6.37; N 6.92.

(−)-(1*S*,10b*R*)-1-Hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline ((−)-3). To a stirred suspension of $LiAlH_4$ (710 mg, 18.8 mmol) in dry THF (30 mL) was added 1-hydroxyisoquinolinopyrrolidinone **9** (1.05 g, 5.17 mmol) in an ice bath and refluxed for 12 h. The solution was cooled in an ice bath and quenched by the successive addition of EtOAc (5 mL), MeOH (5 mL), and H_2O (20 mL) in an ice bath. The precipitate was filtered off through Celite 545 and washed with EtOH several times. The combined filtrate was concentrated and purified by flash column chromatography (EtOAc−MeOH = 3:1−1:1) giving 1-hydroxypyrrolidinoisoquinoline (−)-**3** (830 mg, 85%) as an oil: $[\alpha]^{25}_D$ −10.3° (*c* 2.0, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.74−2.27 (2H, m), 2.71−3.34 (6H, m), 4.05 (1H, d, J = 5.5 Hz), 4.31 (1H, m), 7.18−7.45 (4H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 137.5, 135.1, 129.6, 127.9, 127.4, 77.9, 70.3, 52.5, 49.6, 34.1, 28.7; IR (film) 3266, 2934, 1584

cm^{-1}; MS m/z (relative intensity) 189 (M^+, 23), 145 (100), 130 (24), 117 (100), 115 (37), 103 (16), 91 (15), 77 (24), 51 (13); HRMS (EI) calcd for $C_{12}H_{15}NO$ 189.115364, found 189.115609.

(1*S*,2*R*,10b*S*)-1-Hydroxy-2-(*p*-toluenesulfonyloxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (11). To a stirred solution of dihydroxyisoquinolinopyrrolidinone **10**[10] (100 mg, 0.46 mmol) in dry CH_2Cl_2 (3 mL) were added triethylamine (350 mg, 3.46 mmol), a catalytic amount of DMAP, and tosyl chloride (320 mg, 1.67 mmol) in an ice bath. The reaction mixture was stirred at rt for 16 h, and stirring was continued at 40 °C for 1 h. The solution was poured into 10% aqueous $NaHCO_3$ (20 mL) in an ice bath and extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was dried ($MgSO_4$) and concentrated. Flash column chromatography (EtOAc-hexane = 1:3−1:1) gave 2-(tosyloxy) isoquinolinopyrrolidinone **11** (130 mg, 77%): $[\alpha]^{25}_D$ +47.0° (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (3H, s), 2.73−3.09 (3H, m), 2.75 (1H, m), 2.91 (1H, m), 4.22 (1H, m), 4.35 (1H, dd, *J* = 9.2, 7.1 Hz), 4.60 (1H, d, *J* = 7.1 Hz), 5.08 (1H, d, *J* = 9.2 Hz), 7.12−7.91(8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 145.6, 133.9, 133.0, 129.5, 129.1, 128.9, 128.8, 128.5, 127.6, 127.2, 125.5, 83.2, 78.9, 57.9, 37.0, 28.1, 21.7; IR (KBr) 3381, 1707, 1364 cm^{-1}; MS m/z (relative intensity) 202 (M^+ + 1 − TsOH, 11), 201 ((M^+ − TsOH, 100), 185 (19), 172 (23), 156 (18), 144 (8), 130 (73), 115 (32), 103 (16), 91 (9), 77 (15). Anal. Calcd for $C_{12}H_{13}NO_3$: C 61.11; H 5.13; N 3.75; S 8.59. Found: C 61.12; H 5.17; N 3.63; S 8.14.

(+)-(1*R*,10b*S*)-1-Hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (*ent*-3). To a stirred suspension of $LiAlH_4$ (0.62 g, 16.2 mmol) in dry THF (15 mL) was added 2-(tosyloxy)isoquinolinopyrrolidinone **11** (2.01 g, 5.38 mmol) and refluxed for 12 h. The solution was cooled in an ice bath and carefully quenched by successive addition of EtOAc (5 mL), MeOH (5 mL), and H_2O (5 mL). The precipitate was filtered off with Celite 545 and washed with EtOH several times. The filtrate was concentrated and purified by column chromatography on silica gel (EtOAc-MeOH = 5:1−3:1) to give 1-hydroxypyrrolidinoisoquinoline (+)-**3** (770 mg, 76%) as pale yellow oil: $[\alpha]^{25}_D$ +9.8° (*c* 0.4, CH_3OH). This sample was indistinguishable from (−)-**3** by ^{13}C NMR, ^1H NMR, IR, mass fragmentation analysis, and GC analysis.

(1*S*,10b*S*)-1-[[Phenoxy(thiocarbonyl)]oxy]-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (12). To a stirred solution of 1-hydroxyisoquinolinopyrrolidinone **9** (4.3 g, 21.2 mmol) and DMAP (5.1 g, 41.3 mmol) in dry CH_3CN (35 mL) was added phenyl chlorothionoformate (4.4 g, 25.8 mmol) for 10 min in an ice bath. The solution was stirred for 1 h in an ice bath and stirred at rt for 5 h. The reaction mixture was concentrated and purified by flash column chromatography (hexane−EtOAc = 2:1−1:2) gave 1-thio ester **12** (3.1 g, 43%). This compound is unstable on storage and used directly for next reaction: ^1H NMR (300 MHz, $CDCl_3$) δ 2.71−2.77 (2H, m), 3.00−3.19 (3H, m), 4.39 (1H, m), 5.07 (1H, d, *J* = 4.3 Hz), 5.75 (1H, m), 7.16−7.48 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 169.7, 153.4, 134.2, 133.2, 129.7, 129.6, 127.9, 127.2, 126.9, 125.2, 121.8, 82.2, 61.6, 37.7, 37.3, 28.1; IR (KBr) 1664, 1566, 1470 cm^{-1}.

(10b*S*)-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (13). To a stirred solution of 1-thio ester **12** (1.64 g, 4.83 mmol) and AIBN (130 mg) in dry toluene (25 mL) was added *n*-Bu_3SnH (14.2 g, 48.7 mmol) under nitrogen and refluxed for 5 h. The solution was concentrated and purified by flash column chromatography (hexane:EtOAc = 1:3−EtOAc only) to give isoquinolinopyrrolidinone **13** (480 mg, 53%) as an oil: $[\alpha]^{23}_D$ −223.6° (*c* 4.0, CH_3OH), ^1H NMR (300 MHz, CD_3OD) δ 1.81 (1H, m), 2.38 (1H, m), 2.52−2.89 (4H, m), 3.09 (1H, m), 4.11 (1H, m), 4.80 (1H, dd, *J* = 8.4, 4.7 Hz), 7.15−7.22 (4H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 138.9, 134.7, 130.0, 128.02, 127.99, 125.9, 58.4, 38.4, 32.7, 29.4, 28.5; MS m/z (relative intensity) 187 (M^+, 55), 186 (100), 130 (27), 115 (7), 103 (6), 91 (3), 77 (7); HRMS (EI) calcd for $C_{12}H_{13}NO$ 187.099714, found 187.099556.

(−)-(10b*S*)-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinoline ((−)-4). To a stirred suspension of $LiAlH_4$ (190 mg, 5.0 mmol) in dry THF (7 mL) was added isoquinolinopyrrolidinone **13** (400 mg, 2.14 mmol) in dry THF (15 mL) and refluxed for 5 h. The solution was cooled to room temperature and quenched by successive addition of EtOAc (3 mL), MeOH (4 mL), and H_2O (5 mL). The resulting precipitate was filtered through Celite pad and washed several times with EtOH. The combined filtrate was concentrated and purified by flash column chromatography ($CHCl_3$:MeOH = 15:1−4:1) to give (−)-pyrrolidinoisoquinoline (−)-**4** (300 mg, 81%) as pale yellow oil: $[\alpha]^{23}_D$ −101.7° (*c* 2.0, CH_3OH), lit.[3a] $[\alpha]_D$ −47.33°, optical purity 48.9% (*c* 0.77, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 1.8 (1H, m), 1.85−2.00 (2H, m), 2.35 (1H, m), 2.58−3.17 (6H, m), 3.52 (1H, t, *J* = 7.8 Hz), 7.06−7.15 (4H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 139.2, 135.0, 129.5, 127.5, 127.2, 126.9, 64.5, 54.4, 49.2, 31.4, 29.3, 23.1; IR (film) 2952, 2784, 1492, 1454 cm^{-1}; MS, m/z (relative intensity) 173 (M^+, 43), 172 (100), 145 (50), 130 (13), 117 (35), 103 (7), 91 (6), 77 (8); HRMS (EI) calcd for $C_{12}H_{15}N$ 173.120450, found 173.120599.

(1*S*,2*R*,10b*S*)-1,2-Bis[[phenoxy(thiocarbonyl)]oxy]-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (14). To a stirred solution of dihydroxyisoquinolinopyrrolidinone **10** (390 mg, 1.78 mmol) and DMAP (2.2 g, 17.9 mmol) in dry CH_3CN (10 mL) was added phenyl chlorothionoformate (0.8 g, 4.7 mmol) via syringe under nitrogen atmosphere in an ice bath. After stirring at rt for 20 h the solution was concentrated and purified by flash column chromatography (EtOAc-hexane = 1:3−1:1) to afford bis-thio ester **14** (359 mg, 41%). This compound is unstable on storage and used directly for next reaction: ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (1H, m), 3.09 (1H, m), 3.24 (1H, m), 4.41 (1H, m), 5.12 (1H, d, *J* = 6.9 Hz), 6.37 (1H, t, *J* = 6.9, 9.8 Hz), 6.70 (1H, d, *J* = 9.8 Hz), 7.07−7.48 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3, 194.2, 163.7, 153.8, 153.6, 133.6, 132.7, 129.6, 128.2, 127.6, 127.0, 126.8, 124.7, 121.9, 86.1, 82.7, 56.4, 37.5, 28.1; IR (KBr) 1726, 1489, 1283 cm^{-1}.

(+)-(10b*R*)-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-a]isoquinoline (*ent*-4). By the similar method for the preparation of (−)-**4** from **12**, bis-thio ester **14** was converted to (+)-**4** through radical deoxygenation and subsequent reduction by $LiAlH_4$ in 40% yield over two steps: $[\alpha]^{22}_D$ +97.6° (*c* 0.6, CH_3OH). The IR spectroscopic data was in accord with that described in literature[3b] and this sample was indistinguishable from (−)-**4** by ^{13}C NMR, ^1H NMR, IR, mass fragmentation analysis, and GC analysis.

Acknowledgment. This work was supported by the Korea Institute of Science and Technology (2E-12970). We thank Dr. Sajan P. Joseph (North Carolina State University) for valuable help in preparation of the manuscript.

JO950996+