Pergamon

Tetrahedron, Vol. 53, No. 7, pp. 2449-2458, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01179-9

Asymmetric Synthesis of Both Enantiomers of Novel Tetracyclic Heterocycle, Furo[3',2':2,3]pyrrolo[2,1-*a*]isoquinoline Derivative *via* a Diastereoselective *N*-Acyliminium Ion Cyclization

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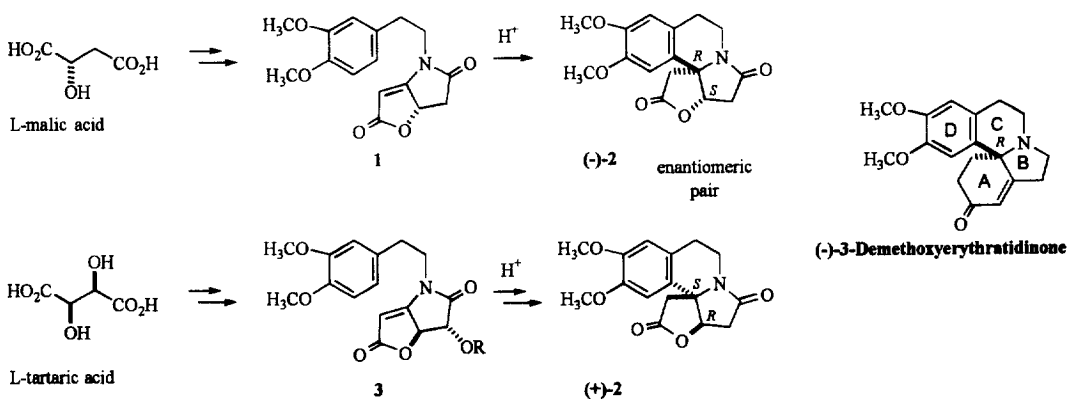
Abstract : An efficient synthesis of both enantiomers of tetracyclic isoquinoline derivative (-)-**2** and (+)-**2** was accomplished starting from L-malic acid and L-tartaric acid, respectively. The key step is the stereoselective introduction of quaternary carbon-center in ring juncture using a diastereoselective *N*-acyliminium ion cyclization of chiral enamides (**1, 3**).

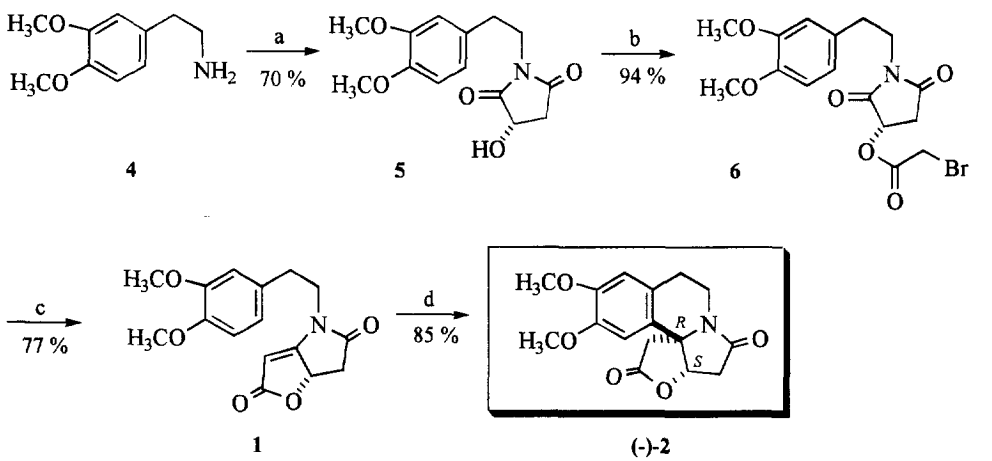
Chiral hydroxy acids such as L-malic acid and L-tartaric acid have been widely used in conjunction with *N*-acyliminium ion chemistry for the synthesis of enantiomerically pure pyrrolidine and indolizidine alkaloids.[1] However, it is surprising that the employment of chiral hydroxy acids in *N*-acyliminium ion cyclization for the chiral synthesis of pyrrolidinoisoquinoline alkaloids is scarce. Recently, we have shown that pyrrolidinoisoquinoline derivatives can be achieved by a diastereoselective *N*-acyliminium ion cyclization of chiral lactams derived from L-malic acid and L-tartaric acid as chiral sources.[2]



Scheme 1

A pyrrolidinoisoquinoline ring is a key sub-unit of naturally occurring *Erythrina* alkaloids. In many cases, pyrrolidinoisoquinoline derivatives containing quaternary carbon-center in ring juncture have been synthesized in a racemic form except some few cases[3] since their approach was focused on the formation of pyrrolidinoisoquinoline framework.[4] In connection with our research on the chiral synthesis of pyrrolidiniosoquinoline alkaloids,[2] we investigated the efficient introduction of quaternary carbon-center in ring juncture in both enantiomeric forms during the construction of pyrrolidinoisoquinoline ring.

Herein we wish to report an efficient synthesis of enantiomerically pure pyrrolidinoisoquinoline derivatives (-)-**2,** having a quaternary carbon-center and its antipode (+)-**2** (Scheme I). Our synthetic plan focused on the diastereoselective cyclization of chiral enamides (**1, 3**), which would permit complete stereocontrol of quaternary carbon-center in cyclization step by the approach of aromatic ring at the side opposite to lactone substituent to provide a novel heterocyclic system, furo-pyrrolo-isoquinoline derivative. While the *N*-acyliminium ion cyclization reactions of several racemic or chiral enamides have been reported by Tsuda group[3,5] and others[6] for the synthesis of polycyclic compounds including *Erythrina* alkaloids, there appeared no asymmetric route to the furo-pyrrolo-isoquinoline derivatives using enamides **1** and **3** derived from L-malic acid and L-tartaric acid. The tetracyclic compound **(-)-2** and **(+)-2** can be potential intermediates for the chiral synthesis of *Erythrina* alkaloids including (-)-3-demethoxyerythratidinone since they already possess a requisite quaternary carbon-center and a B/C/D ring system of *Erythrina* alkaloids. The tetracyclic pyrrolidinoisoquinoline derivatives (-)-**2** was prepared in an enantiomerically pure form from L-malic acid as shown in Scheme 2.



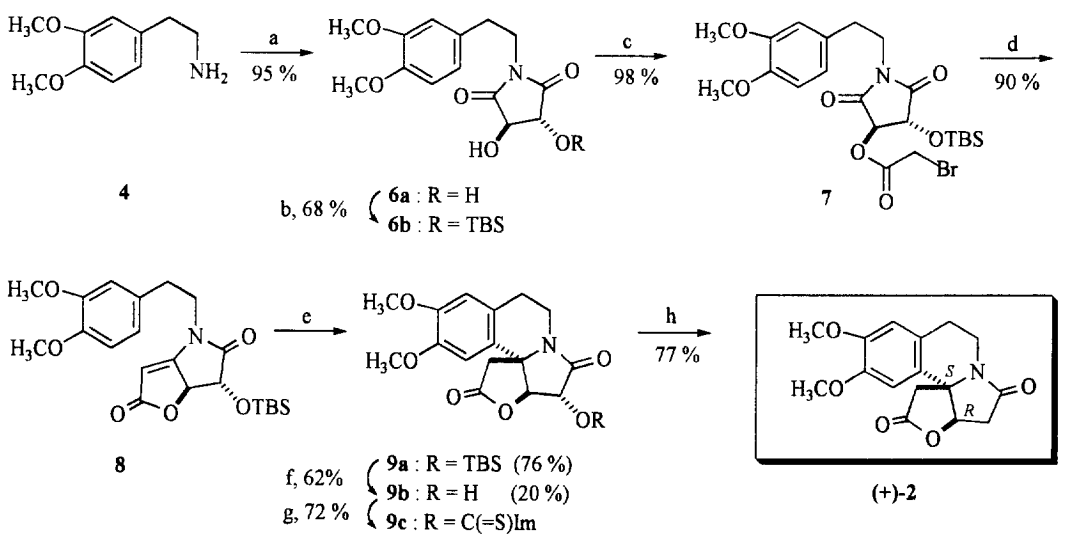
(a) L-malic acid, xylene, reflux, 4 h (b) bromoacetyl bromide, pyridine, CH_2Cl_2, 0 °C - rt., 30 min (c) Ph_3P, acetonitrile, 50 °C, 2 h then NEt_3, 50 °C, 16 h (d) *p*-TsOH, toluene, reflux, 1 h.

Scheme 2

L-Malic acid was condensed with 2-(3,4-dimethoxyphenyl)ethylamine **4** in refluxing xylene to afford 3-

hydroxy imide[2b] **5**. The 3-hydroxy imide **5** was bromoacetylated in methylene chloride to afford 3-bromoacetoxy imide **6** (94 %). The construction of new carbon-carbon bond in imide **6** was achieved by the intramolecular Wittig reaction in one-pot procedure.[7] The reaction of 3-bromoacetoxy imide **6** with triphenylphosphine in acetonitrile gave the phosphonium salt, which was subsequently treated with triethylamine to furnish the enamide **1** (77 %). *N*-Acyliminium ion cyclization of enamide **1** with *p*-toluenesulfonic acid in refluxing toluene proceeded cleanly to provide a tetracyclic isoquinoline derivative (-)-**2** {$[\alpha]^{25}_{D}$ = -145.2 (*c* 5.0, $CHCl_3$)} as a single diastereomer, the presence of which was identified with spectroscopic data (^{13}C NMR, ^{1}H NMR, GC-mass) and chiral phase HPLC analysis (*d.e.* >99.9 %).[8] The high stereoselectivity of *N*-acyliminium ion cyclization can be rationalized by the fact that the nucleophilic attack of the aromatic ring to the less hindered β-face occurs to give the less-strained *cis*-fused tetracyclic compound.[9]

The synthesis of antipode (+)-**2** can be achieved from unnatural D-malic acid by the same reaction sequence, carried out on the synthesis of (-)-**2** as usual manner.[10] However, natural L-tartaric acid can be used in replacement of expensive D-malic acid[2b] since two hydroxyl groups in L-tartaric acid have the same configuration as D-malic acid and can be differentiated upon functionalization. The synthesis of antipode (+)-**2**, starting from L-tartaric acid is illustrated in Scheme 3.



(a) L-tartaric acid, xylene, reflux, 4 h (b) TBSCl, imidazole, DMF, rt., 16 h (c) bromoacetyl bromide, pyridine, CH_2Cl_2, 0 °C - rt., 30 min (d) Ph_3P, acetonitrile, 50 °C, 2 h then NEt_3, 50 °C, 16 h (e) *p*-TsOH, CH_2Cl_2, reflux, 1 h (f) *n*-Bu_4NF, THF, 0 °C - rt., 2 h (g) TCDI, CH_2Cl_2, rt., 2 h (h) *n*-Bu_3SnH, toluene, reflux, 4 h.

Scheme 3

The condensation of L-tartaric acid with 2-(3,4-dimethoxyphenyl)ethylamine **4** in refluxing xylene afforded 3,4-dihydroxyimide **6a** (95 %). Attempted selective mono-acylation of **6a** was not satisfactory since 3,4-bis(bromoacetoxy)imide was obtained as a major product (41 %). Thus, one of two hydroxyl groups in imide

was protected selectively with TBS group (68 %) and the monosilylated imide **6b** was transformed into enamide **8** by the same sequence of reaction described for **1** (2 steps yield : 88 %). Cyclization of the enamide **8** with *p*-toluenesulfonic acid in methylene chloride proceeded cleanly to afford a cyclized product **9a** (76 %) and its desilylated derivative **9b** (20 %). The desilylation of **9a** with tetrabutylammmonium fluoride gave **9b** (62 %). The compound **9b** was also identified as a single diastereomer from analysis of 300 MHz ^{1}H NMR spectroscopy and capillary gas chromatography. The final synthesis of (+)-**2** was carried out by the deoxygenation of hydroxyl group in **9b**. The compound **9b** was treated with *N,N'*-thiocarbonyldiimidazole (TCDI) in methylene chloride to afford thiocarbonylimidazolide **9c** (72 %).[11] Reduction of **9c** with tributyltin hydride in refluxing toluene cleanly produced the deoxygenated product (+)-**2** (77 %). The spectral data (^{1}H NMR, ^{13}C NMR, IR, mass fragmentation) of (+)-**2** were identical with those of (-)-**2**, prepared from L-malic acid except the sign of the optical rotation {$[\alpha]^{25}_D$ = +145.1, (*c* 5.0, $CHCl_3$)}. The enantiomeric purities of (+)-**2** and (-)-**2** were >99.9 % based on the chiral phase HPLC analysis to demonstrate that no racemizations occurred during the reaction sequences.[8]

In conclusion, asymmetric synthesis of both enantiomers of novel tetracyclic isoquinoline derivatives ((-)-**2**, (+)-**2**) has been accomplished by the sterereoselective introduction of quaternary carbon-center in ring juncture using *N*-acyliminium ion cyclization strategy. Synthesis of both enantiomers was performed starting from the naturally available L-series of hydroxy acids, L-malic acid and L-tartaric acid. The low cost for the synthesis of both enanatiomers of tetracyclic isoquinoline derivatives makes this methodology synthetically attractive. These both enantiomers will be applicable to the asymmetric total synthesis of *Erythrina* alkaloids, in particular, (-)- and (+)-3-demethoxyerythratidinone.

EXPERIMENTAL

Melting points (mp) were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Gemini Varian-300 (75 MHz) spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer 16F-PC FT-IR and MIDAC 101025 using a potassium bromide pellet. Optical rotations were determined on a Autopol III automatic polarimeter (Rudolph Research Co.) using the sodium D line (λ = 589nm). Low (EI) resolution mass spectra were determined on HP GC 5972 and HP MS 5988A system at 70eV and High (EI) resolution mass spectra were determined on VG70-VSEQ (VG ANALITICAL, UK) at 70eV. Elemental analysis was performed by Elementar Analysensysteme GmbH Vario EL. High pressure liquid chromatography for the determination of optical purity was performed on Water pump model 510, UV detector (λ = 280nm) using a chiral phase (R, R) Whelk-01 column 25 cm x 4.6 mm i.d. 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 - 400mesh). All solvents used were

purified according to standard procedures.

***(3S)*-1-[2-(3,4-Dimethoxyphenyl)ethyl]-3-hydroxypyrrolidine-2,5-dione (5):** To a refluxing solution of L-malic acid (5.0 g, 37.3 mmol) in 100 ml of xylene was added dropwise 2-(3,4-dimethoxyphenyl)ethylamine **4** (7.4 g, 41.0 mmol), and the reaction mixture was refluxed for 4 hr with the use of a Dean-Stark water separator. The mixture was cooled to room temperature and the resulting solid was filtered. The filtered solid was washed with xylene and recrystallized with EtOH to give 7.2 g (70 %) of **5** as a white solid. mp 125 °C (EtOH); $[\alpha]^{26}_{D}$ -67.2° (*c* 3.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78-6.70 (3H, m, Ph), 4.55 (1H, dd, *J*=8.3, 4.6 Hz, C<u>H</u>-OH), 3.85 & 3.83 (6H, two s, 2 x OCH_3), 3.71 (2H, t, *J*=7.2 Hz, N-C<u>H</u>$_2$), 3.00 (1H, dd, *J*=17.9, 8.3 Hz, NCO-C<u>H</u>), 2.82 (2H, d, *J*=7.2 Hz, Ph-C<u>H</u>$_2$), 2.61 (1H, dd, *J*=17.9, 4.6 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.99, 173.03, 148.99, 148.00, 129.97, 120.94, 112.09, 111.41, 66.83, 55.96, 55.92, 40.07, 37.17, 33.00; IR (KBr) 3410, 2940, 1696 cm^{-1}; MS (EI), m/z (relative intensity, %) 279 (M^+, 18), 164 (100), 151 (85); Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.02; H, 6.21; N, 4.85.

***(3S)*-3-Bromoacetoxy-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2,5-dione (6):** Bromoacetyl bromide (795 mg, 3.9 mmol) was added to a stirred solution of **5** (1.0 g, 3.6 mmol) and pyridine (339 mg, 4.3 mmol) in 30 ml of CH_2Cl_2 at 0 °C under nitrogen. The mixture was stirred at room temperature for 30 min, diluted with cold water (30 ml), and extracted with CH_2Cl_2 (30 ml x 2). The combined organic extracts were washed successively with saturated $CuSO_4$ solution, water, and saturated $NaHCO_3$, dried, and concentrated. The residue was purified by flash column chromatography (*n*-hexane : EtOAc = 1 : 1) to afford 1.3 g (94 %) of **6** as a colorless viscous oil which solidified on standing. mp 71-72 °C; $[\alpha]^{28}_{D}$ -15.2° (*c* 2.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 -6.65 (3H, m, Ph), 5.35 (1H, dd, *J*=8.6, 4.4 Hz, CO_2C<u>H</u>), 3.84 (2H, s, BrC<u>H</u>$_2$), 3.78 & 3.75 (6H, two s, 2 x OCH_3), 3.62 (2H, t, *J*=7.5 Hz, N-C<u>H</u>$_2$), 3.05 (1H, dd, *J*=17.2, 8.6 Hz, NCO-C<u>H</u>), 2.75 (2H, t, *J*=7.5 Hz, PhC<u>H</u>$_2$), 2.55 (1H, dd, *J*=17.2, 4.4 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.59, 172.50, 166.37, 148.93, 147.84, 129.82, 120.85, 111.99, 111.36, 68.66, 55.90 (2C), 40.27, 35.14, 32.80, 24.83; IR (KBr) 2940, 1751, 1701 cm^{-1}; MS (EI), m/z (relative intensity, %) 401 (M^+: Br^{81}, 4), 399 (M^+: Br^{79}, 4), 164 (100), 151 (71); Anal. Calcd for $C_{16}H_{18}BrNO_6$: C, 48.02; H, 4.53; N, 3.50. Found: C, 47.78; H, 4.64; N, 3.41.

***(6aS)*-4-[2-(3,4-Dimethoxyphenyl)ethyl]-6,6a-dihydro-*4H*-furo[3,2-*b*]pyrrole-2,5-dione (1):**

Triphenylphosphine (2.0 g, 7.5 mmol) was added in one portion to a stirred solution of **6** (3.2 g, 6.2 mmol) in 60 ml of CH_3CN under nitrogen. The mixture was stirred at 50 °C for 2 hr, and then triethylamine (690 mg, 6.8 mmol) was added. The mixture was further stirred at 50 °C for 16 hr, cooled to room temperature, and concentrated. The residue was purified by flash column chromatography (*n*-hexane : EtOAc = 1: 2) to give 1.4 g (77 %) of **1** as a white solid. mp 164 °C; $[\alpha]^{27}_{D}$ -58.7° (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 -

6.67 (3H, m, Ph), 5.04 (1H, dd, *J*=9.0, 7.7 Hz, $CO_2C\underline{H}$-), 5.01 (1H, s, $COC\underline{H}$-), 4.03 (1H, dt, *J*=13.8, 7.1 Hz, N-C$\underline{H}$), 3.86 & 3.85 (6H, two s, 2 x OCH_3), 3.66 (1H, dt, *J*=13.8, 7.1 Hz, N-C$\underline{H}$), 3.02 (1H, dd, *J*=16.0, 7.7 Hz, NCO-C$\underline{H}$), 2.91 (2H, t, *J*=7.1 Hz, Ph$C\underline{H}_2$), 2.61 (1H, dd, *J*=16.0, 9.0 Hz, NCO-C$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.63, 172.12, 170.35, 149.29, 148.31, 129.43, 120.86, 111.98, 111.62, 89.58, 75.23, 56.03, 55.98, 43.77, 38.47, 33.20; IR (KBr) 2947, 1761, 1645 cm^{-1}; MS (EI), m/z (relative intensity, %) 303 (M^+, 28), 164 (60), 151 (100), 107 (7), 91 (5); Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.20; H, 5.75; N, 4.44.

***(3aS,12bR)*-10,11-Dimethoxy-3a,4,7,8-tetrahydro-furo[3',2':2,3]pyrrolo[2,1-*a*]isoquinoline-2(*1H*),5-dione (-)-2:** *p*-Toluenesulfonic acid (209 mg, 1.1 mmol) was added to a suspension of **1** (330 mg, 1.1 mmol) in 10 ml of toluene. The reaction mixture was refluxed for 1 hr, cooled to room temperature, and diluted with 20ml of EtOAc. The mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (EtOAc : CH_2Cl_2 = 3:1) to afford 280 mg (85 %) of **(-)-2** as a white solid. mp 214-215 °C; $[\alpha]^{25}_D$ -145.2° (*c* 5.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (1H, s, Ph), 6.56 (1H, s, Ph), 5.20 (1H, dd, *J*=5.7, 2.1 Hz, $CO_2C\underline{H}$-), 4.35 (1H, m, N- C$\underline{H}$), 3.87 & 3.84 (6H, two s, 2 x OCH_3), 3.08 & 2.93 (2H, ABq, *J*=18.5 Hz, $C\underline{H}_2CO_2$), 3.07 - 2.65 (2H, m, PhC$\underline{H}$, and CON-C$\underline{H}$), 2.75 (2H, m, NCO-$C\underline{H}_2$), 2.60 (1H, m, Ph-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43, 171.32, 149.12, 148.67, 126.96, 126.24, 112.06, 107.37, 81.92, 68.08, 56.33, 56.00, 43.78, 37.25, 36.03, 26.76; IR (KBr) 1784, 1692 cm^{-1}; MS (EI), m/z (relative intensity, %) 303 (M^+, 60), 260 (100), 244 (48), 230 (41), 190 (27); HRMS (EI) Calcd for $C_{16}H_{17}NO_5$: (M^+) m/z 303.1107. Found: 303.1102.

***(3R,4R)*-3,4-Dihydroxy-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2,5-dione (6a):** By using a similar procedure to that described above for the preparation of **5**, L-tartaric acid (5.0 g, 3.3 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine **4** (6.6 g, 3.7 mmol) were reacted to afford 9.3 g (95 %) of **6a** as a white solid. mp 178 °C (EtOH); $[\alpha]^{28}_D$ +123.3° (*c* 1.74, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.84 (1H, d, *J*= 7.9 Hz, C_5-H of Ph), 6.74 (1H, s, C_2-H of Ph), 6.66 (1H, d, *J*=7.9 Hz, C_6-H of Ph), 6.29 (2H, br s, 2 x OH), 4.23 (2H, s, 2 x CO-C$\underline{H}$-OH), 3.73 & 3.70 (6H, two s, 2 x OCH_3), 3.56 (2H, t, *J*=6.7 Hz, N-$C\underline{H}_2$), 2.73 (2H, t, *J*=6.7 Hz, Ph-$C\underline{H}_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.43 (2C), 148.55, 147.39, 130.34, 120.55, 112.33, 111.72, 74.22, 55.34 (2C), 39.09, 32.32; IR (KBr) 3378, 2646, 1792, 1712 cm^{-1}; MS (EI), m/z (relative intensity, %) 295 (M^+, 24), 164 (100), 151 (98), 149 (15), 107 (10), 77 (8); Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.65; H, 5.80; N, 4.74. Found: C, 56.85; H, 5.96; N, 4.52.

***(3R,4R)*-3-*t*-Butyldimethylsilyloxy-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxypyrrolidine-2,5-dione (6b):** To a stirred solution of **6a** (1.5 g, 5.1 mmol) and imidazole (1.1 g, 15.2 mmol) in 25 ml of DMF was added *t*-butyldimethylsilyl chloride (846 mg, 5.6 mmol) at room temperature. The reaction mixture was stirred

at room temperature for 16 hr and poured into a mixture of EtOAc (50 ml) and water (10 ml). The organic layer was washed with water and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (n-hexane : EtOAc = 3 : 2) to afford 1.42 g (68 %) of **6b** as a white solid and 236 mg (9 %) of bis-silyloxy compound **6b'** as an oil. **6b**: mp 94 °C; $[\alpha]^{28}_D$ +120.1° (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 - 6.67 (3H, m, Ph), 4.40 (2H, s, C<u>H</u>-OH and C<u>H</u>-OTBS), 3.85 & 3.83 (6H, two s, 2 x OCH_3), 3.80 - 3.60 (2H, m, N-CH_2), 2.83 (2H, t, *J*=7.4 Hz, Ph-CH_2), 0.93 (9H, s, *t*-butyl), 0.21 & 0.18 (6H, two s, 2 x CH_3-Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.80, 173.29, 148.96, 147.92, 129.81, 120.96, 112.04, 111.38, 75.83, 75.65, 55.89 (2C), 40.09, 32.96, 32.96, 25.64 (3C), 18.31, -5.02, -5.13; IR (KBr) 3506, 2940, 1722 cm^{-1}; MS (EI), m/z (relative intensity, %) 295 (M^+, 24), 164 (100), 151 (98), 149 (15), 107 (10), 77 (8); Anal. Calcd for $C_{26}H_{45}NO_6Si_2$: C, 58.65; H, 7.63; N, 3.42. Found: C, 58.62; H, 6.86; N, 3.35. **6b'**; ^1H NMR (300MHz, $CDCl_3$) δ 6.78 - 6.68 (3H, m, Ph), 4.34 (2H, s, 2 x C<u>H</u>-OTBS), 3.84 & 3.82 (6H, two s, 2 x OCH_3), 3.73-3.62 (2H, m, N-CH_2), 2.82 (2H, t, *J*=7.7 Hz, Ph-CH_2), 0.91 (9H, s, *t*-butyl), 0.18 & 0.13 (6H, two s, 2 x CH_3-Si); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.23, 148.95, 147.92, 129.95, 120.99, 112.18, 111.39, 76.74, 55.87, 55.80, 39.83, 32.98, 25.64 (6C), 18.22 (2C), -5.01 (2C), -5.08 (2C).

***(3R,4R)*-4-Bromoacetoxy-3-*t*-butyldimethylsilyloxy-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidin-2,5-dione (7):** By using a similar procedure to that described above for the preparation of **6**, bromoacetyl bromide (668 mg, 3.3 mmol), pyridine (285 mg, 3.6 mmol), and **6b** (1.2 g, 3.0 mmol) were reacted to provide 1.6 g (98 %) of 7 as an oil. $[\alpha]^{28}_D$ +79.1° (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.77-6.70 (3H, m, Ph), 5.37 (1H, d, *J*=4.4 Hz, -CO_2C<u>H</u>), 4.62 (1H, d, *J*=4.4 Hz -C<u>H</u>OTBS), 3.92 (2H, s, BrC<u>H</u>$_2$), 3.86 & 3.84 (6H, two s, 2 x OCH_3), 3.80-3.71 (2H, m, -NCH_2), 2.86 (2H, d, *J*=7.4 Hz, Ph-C<u>H</u>$_2$), 0.91(9H, s, *t*-butyl), 0.17 & 0.14 (6H, two s, 2 x CH_3-Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.06, 169.02, 166.34, 149.07, 148.02, 129.73, 120.98, 111.44, 77.31, 73.12, 55.95 (2C), 40.44, 32.93, 25.57 (3C), 24.34, 18.25, -4.71, -5.10; IR (neat) 2940, 1716 cm^{-1}; MS (EI), m/z (relative intensity, %) 472 [(M^+-*t*-butyl), 16], 352 (10), 334 (25), 264 (17), 165 (100), 151 (56), 121 (13), 75 (23); HRMS (EI) Calcd for $C_{22}H_{32}BrNO_7Si$: m/z 531.1111 (M^+: Br^{81}), 529.1131 (M^+: Br^{79}), Found: 531.1119 (M^+: Br^{81}), 529.1114 (M^+: Br^{79}).

***(6R,6aR)*-6-(*tert*-Butyldimethylsilyloxy)-4-[2-(3,4-dimethoxyphenyl)ethyl]-6,6a-dihydro-4*H*-furo[3,2-*b*]-pyrrole-2,5-dione (8):** By using a similar procedure to that described above for the preparation of **1**, triphenylphosphine (866 mg, 3.3 mmol), **7** (1.46 mg, 2.8 mmol) and triethylamine (292 mg, 2.9 mmol) were reacted to give 1.1 g (90 %) of **8** as a white solid. mp 103-104 °C; $[\alpha]^{26}_D$ +147.6° (*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 - 6.64 (3H, m, Ph), 5.08 (1H, s, COC<u>H</u>=), 5.90 (1H, d, *J* = 7.7 Hz, CO_2-C<u>H</u>) 4.30 (1H, d, *J* = 7.7 Hz, C<u>H</u>-OTBS), 3.95 - 3.60 (2H, m, N-C<u>H</u>$_2$), 3.81 & 3.80 (6H, two s, 2 x OCH_3), 2.86 (2H, m, PhC<u>H</u>$_2$), 0.89 (9H, s, *t*-butyl), 0.13 & 0.11 (6H, two s, 2 x CH_3-Si); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 172.41, 172.18, 164.53, 149.24, 148.31, 129.19, 120.89, 111.95, 111.51, 90.44, 83.23, 76.82, 55.97 (2C), 44.37, 33.05,

25.58 (3C), 18.25, -4.86, -5.21; IR (KBr) 3112, 2934, 1764, 1652 cm^{-1} ; MS (EI), m/z (relative intensity, %) 376 [(M^+-*t*-butyl), 34], 207 (6), 165 (100), 151 (13), 73 (14); Anal. Calcd for $C_{22}H_{31}NO_6Si$: C, 60.94; H, 7.21; N, 3.23. Found: C, 60.79; H, 7.15; N, 3.21.

***(3aR,4R,12bS)*-4-(*tert*-Butyldimethylsilyoxy)-10,11-dimethoxy-3a,4,7,8-tetrahydro-furo[3',2':2,3]-pyrrolo[2,1-*a*]isoquinoline-2(*1H*),5-dione (9a):** *p*-Toluenesulfonic acid (444 mg, 2.4 mmol) was added to a solution of **8** (506 mg, 1.2 mmol) in 10 ml of CH_2Cl_2. The reaction mixture was refluxed for 2 hr and cooled to room temperature. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (*n*-hexane : EtOAc = 3 : 2) to afford 284 mg (76 %) of **9a** and 100 mg (20 %) of desilylated compound **9b**. **9a**: mp 69-70 °C; $[\alpha]^{26}_D$ +147.6°(*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, s, Ph), 6.47 (1H, s, Ph), 4.78 (1H, d, *J*=2.4 Hz, CO_2CH-), 4.32 (1H, d, *J*=2.4 Hz, CH-OTBS), 4.20 (1H, dd, *J*=12.8, 4.4 Hz, N-CH), 3.75 & 3.73 (6H, two s, 2 x OCH_3), 3.00 & 2.51 (2H, m, PhCH and N-CH), 2.94 & 2.86 (2H, ABq, *J*=18.4 Hz, CH_2CO_2), 2.54 (1H, m, PhCH), 0.67 (9H, s, *t*-butyl), 0.03 & 0.01 (6H, two s, 2 x CH_3-Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43, 169.88, 148.90, 148.71, 128.22, 125.75, 111.77, 106.72, 88.91, 75.38, 65.16, 56.20, 55.89, 43.70, 36.27, 26.88, 25.41 (3C), 17.98, -4.71, -5.30; IR (KBr) 2940, 1792, 1714 cm^{-1}; MS (EI), m/z (relative intensity, %) 418 [$(M-CH_3)^+$, 2], 376 [(M-*t*-butyl) $^+$, 100], 188 (11), 75 (22); Anal. Calcd for $C_{22}H_{31}NO_6Si$: C, 60.68; H, 7.21; N, 3.23. Found: C, 60.68; H, 7.49; N, 3.09. **9b** : mp 205 - 208 ° C; $[\alpha]^{25}_D$ +208.60 ° (*c* 5.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (1H, s, Ph), 6.49 (1H, s, Ph), 4.92 (1H, d, *J*=2.8 Hz, CO_2CH-), 4.35 (1H, d, *J*=2.8 Hz, CH-OH), 4.25 (1H, m, N-CH), 3.78 & 3.77 (6H, two s, 2 x OCH_3), 3.10 - 2.86 (2H, m, Ph-CH and N-CH), 2.98 & 2.89 (2H, ABq, *J*=18.5 Hz, CH_2CO_2-), 2.55 (1H, m, PhCH-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.73, 171.57, 148.96, 148.86, 128.32, 125.42, 111.69, 106.47, 88.61, 74.75, 65.47, 56.23, 55.95, 43.76, 35.59, 26.87; IR (KBr) 3342, 2930, 1784, 1692 cm^{-1}; MS (EI), m/z (relative intensity, %) 319 (M^+, 52), 277 (38), 260 (100), 248 (25), 231 (26), 220 (14), 176 (12), 77 (13); Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.71; H, 4.61; N, 4.34.

***(3aR,4R,12bS)*-10,11-Dimethoxy-4-hydroxy-3a,4,7,8-tetrahydro-furo[3',2':2,3]pyrrolo[2,1-*a*] isoquinoline-2(*1H*),5-dione (9b):** To a stirred solution of **9a** (272 mg, 0.6 mmol) in 15 ml of anhydrous THF was added a solution of *n*-Bu_4NF (0.63 ml, 1M solution) in THF at 0 °C. After stirring at room temperature for 2 hr, the reaction mixture was concentrated and purified by flash column chromatography (CH_2Cl_2 : EtOAc = 1: 3) to afford 124 mg (62 %) of **9b** as a white solid.

***(3aR,4R,12bS)*-10,11-Dimethoxy-4-[1-imidazololo)thiocarbonyloxy]-3a,4,7,8-tetrahydro-furo[3',2':2,3]-pyrrolo[2,1-*a*]isoquinoline-2(*1H*),5-dione (9c):** A solution of **9b** (100 mg, 0.3 mmol) and thiocarbonyl diimidazole (TCDI, 112 mg, 0.6 mmol) in 5 ml of CH_2Cl_2 was gently refluxed for 20 hr and concentrated. The

residue was purified by flash column chromatography (CH_2Cl_2 : EtOAc = 1: 3) to afford 96 mg (72 %) of **9c**. mp 115 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, s, imidazole), 7.38 (1H, s, imidazole), 6.90 (1H, s, imidazole), 6.57 (2H, s, Ph), 6.16 (1H, m, C<u>H</u>-OCS-), 5.23 (1H, br s, CO_2C<u>H</u>-), 4.35 (1H, m, N-C<u>H</u>), 3.81 & 3.78 (6H, two s, 2 x OCH_3), 3.20-3.05 (2H, m, Ph<u>CH</u> and N-C<u>H</u>), 3.11 (2H, ABq, *J*=18.7 Hz, <u>CH_2</u>CO_2-), 2.68 (1H, m, PhC<u>H</u>-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.75, 172.82, 164.79, 149.34, 149.09, 136.88, 131.16, 127.39, 125.51, 118.24, 111.77, 106.36, 85.41, 81.14, 65.83, 56.27, 55.99, 43.67, 36.99, 26.76; IR (KBr) 1784, 1692 cm^{-1}.

***(3aR,12bS)*-10,11-Dimethoxy-3a,4,7,8-tetrahydro-furo[3',2':2,3]pyrrolo[2,1-*a*]isoquinoline-2(1*H*),5-dione (+)-2:** To a solution of **9c** (96 mg, 0.2 mmol) in a mixture of toluene (5 ml) and dioxane (1 ml) was added tributyltin hydride (99 mg, 0.3 mmol) at room temperature, and then the reaction mixture was refluxed for 4 hr. After concentrating, the residue was purified by flash column chromatography (CH_2Cl_2 : EtOAc = 1: 3) to provide 52 mg (77 %) of **(+)-2** as a white solid. $[\alpha]^{25}_D$ +145.1° (*c* 5.00, $CHCl_3$); HRMS (EI) Calcd for $C_{16}H_{17}NO_5$: (M^+) m/z 303.1107. Found: 303.1108. This compound was indistinguishable from **(-)-2** by ^{1}H-NMR, ^{13}C-NMR, IR, mass fragmentation analysis, GC, and HPLC analysis.

ACKNOWLEDGEMENTS

The authors thank Dr. W. J. Lee (Lucky Co.) for help in the chiral phase HPLC analysis of compound **(-)-2** and **(+)-2**. This work was supported by the Korea Ministry of Science and Technology (2E1400I).

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8. Retention times of **(-)-2** and **(+)-2** were 14.92 min and 16.60 min, respectively. Conditions of separation : (a) chiral column; CSP (R, R) Whelk-01 25 cm x 4.6 mm i.d. (b) eluting solvents; EtOH/hexane : 6/4 (v/v) with 0.1% TEA. (c) flow rate = 1 ml/min. (d) detector : UV (280nm).
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(*Received in Japan* 18 *November* 1996; *accepted* 16 *December* 1996)