Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Asymmetric Synthesis of Furo-Pyrrolo-Isoquinoline and Furo-Indolizino-Indole Derivatives Via A Diastereoselective N-Acyliminium ion Cyclization

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Published online: 22 Aug 2006.

To cite this article: Yong Sup Lee , Jae Yeol Lee & Hokoon Park (1997) Asymmetric Synthesis of Furo-Pyrrolo-Isoquinoline and Furo-Indolizino-Indole Derivatives Via A Diastereoselective N-Acyliminium ion Cyclization, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:16, 2799-2812

To link to this article: http://dx.doi.org/10.1080/00397919708004155

SYNTHETIC COMMUNICATIONS, 27(16), 2799-2812 (1997)

ASYMMETRIC SYNTHESIS OF FURO-PYRROLO-ISOQUINOLINE AND FURO-INDOLIZINO-INDOLE DERIVATIVES *VIA* A DIASTEREOSELECTIVE *N*-ACYLIMINIUM ION CYCLIZATION

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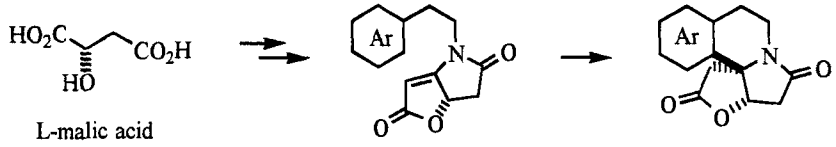
ABSTRACT Asymmetric synthesis of furo-pyrrolo-isoquinoline and furo-indolizino-indole derivatives *via* a diastereoselective *N*-acyliminium ion cyclization of chiral enamides is described. The requisite chiral enamides were prepared from readily available L-malic acid.

The isoquinoline and indole alkaloids are abundant in plant products[1] and many display a large spectrum of biological activity.[2] Heterocyclizations involving *N*-acyliminium ion cyclization, although well known, have only recently been examined for their usefulness in asymmetric synthesis. From the previous work of Speckamp,[3] and others,[4,6] such cyclizations have been found to achieve remarkable stereocontrol between proximate and remote chiral centers. Chiral hydroxy acids such as L-malic acid (**1**) have been widely used in conjunction with *N*-acyliminium ion chemistry for the synthesis of enantiomerically pure pyrrolidine and indolizidine alkaloids.[5] However, there is no application of *N*-acyliminium ion cyclizations to

the asymmetric synthesis of isoquinoline or indole alkaloids by the employment of chiral enamide **2**, derived from chiral hydroxy acids such as L-malic acid (**1**).

Scheme 1.

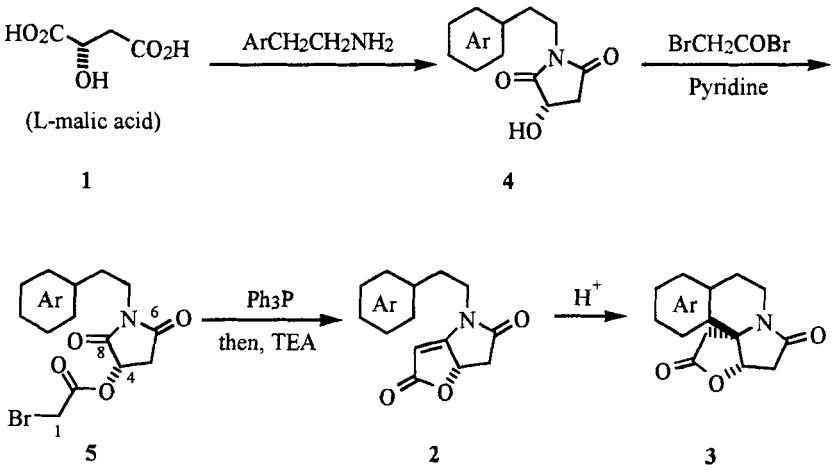


1 **2** **3**

Taking these facts into consideration, we were interested in developing a new asymmetric route to heterocyclic system **3** in optically pure form by the extension of our preceding strategy.[6] Herein we wish to report the asymmetric synthesis of novel furo-pyrrolo-isoquinoline and furo-indolizino-indole derivatives by using *N*-acyliminium ion cyclizations starting from L-malic acid. The key feature is the intramolecular diastereoselective *N*-acyliminium ion cyclization of chiral enamide **2** (Scheme 1). To prove the versatility of this strategy we used several aromatic rings as π-nucleophiles.

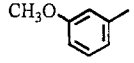
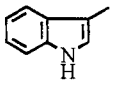
The synthetic route to optically pure furo-pyrrolo-isoquinoline and furo-indolizino-indole derivatives **3** is shown in Scheme 2. L-malic acid was condensed with 2-(3-methoxyphenyl)ethylamine (1.1 equiv) in refluxing xylene[6a] to afford chiral imide **4a** (81%). Other 2-arylethylamines similarly gave the chiral imides (**4b**, **4c**), which were recrystallized with EtOH to afford crystalline solids. The yields in each step were listed in Table 1.

Scheme 2.



The chiral 3-hydroxy imides (**4a - 4c**) were bromoacetylated [$BrCH_2COBr$ (1.1 equiv), pyridine (1.2 equiv), 0 °C - rt, 30 min] to afford bromoacetoxy imides (**5a - 5c**) in high yields. The construction of the carbon-carbon bond between C-1 and C-8 (pyrrolizine numbering) in the compounds **5** was achieved by the intramolecular Wittig reaction in one-pot procedure[7]: the reaction of **5a** with triphenylphosphine (1.2 equiv) in acetonitrile gave the phosphonium salt, which was subsequently treated with triethylamine (1.1 equiv) and heated again at 50 °C for 15 hr to furnish the chiral enamide **2a** {$[\alpha]^{30}_D$ -58.40 (*c* 2.30, $CHCl_3$)} (81 %). Other compounds (**5b, 5c**) were also transformed to chiral enamides **2b** and **2c** by the similar procedure. The chiral enamides (**2a, 2b, 2c**) were subjected to the *N*-acyliminium ion cyclization to provide optically pure furo-pyrrolo-isoquinoline and furo-indolizino-indole derivatives **3**.

Table 1 : Yields (%) [a] of each step of Scheme 2.

	Ar	4	5	2	3[a]
a		81[b]	70	81	53
b		76	98	77	50[b] (43 [c])
c		60	69	61	79

Note : [a] *p*-TsOH was used as an activating agent in CH_2Cl_2. [b] toluene was used as a solvent instead of CH_2Cl_2. [c] excess of PPA was used as an activating agent.

Cyclization of enamide **2a** with *p*-TsOH at reflux temperature in methylene chloride proceeded smoothly to afford a furo-pyrrolo-isoquinoline **3a** in 53 % yield. The cyclized compound **3a** {$[\alpha]^{30}_D$ -109.5 (*c* 2.60, $CHCl_3$)} was obtained as a single diastereomer and confirmed based on the ^1H NMR, ^{13}C NMR spectroscopy and capillary gas chromatography analysis.

The stereoselectivity of *N*-acyliminium ion cyclization of enamide **2a** can be rationalized by the fact that the electrophilic attack of the aromatic ring occurred on the less hindered β-face to give the less-strained *cis*-fused tetracyclic heterocycle **3a**. The cyclization of enamide **2c**, possessing an indole ring as the π-nucleophile, with *p*-TsOH at reflux temperature in methylene chloride also proceeded cleanly to give the pentacyclic heterocycle, furo-indolizino-indole derivative **3** in 79 % yield. In the case of compound **2b**, the selection of the solvent or activating agent was very important: when methylene chloride was used as the

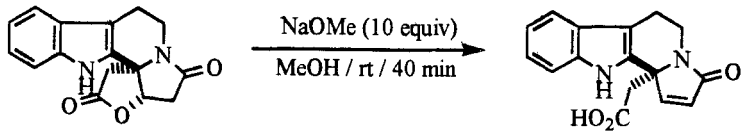
the solvent, the major product was an unidentified side-product, which was not a cyclization product on the basis of the interpretation of ^{1}H NMR and ^{13}C NMR. When toluene was used as the solvent or excess of PPA (polyphosphoric acid) was used as activating agent, the desired product **3b** was obtained in 50 and 43 % yield, respectively.

Considering the above results, the enamide **2a**, possessing an electron-donating 3-methoxy group in the benzene ring and the enamide **2c**, having an electron-rich indole ring as π-nucleophiles were easily cyclized under mild conditions. On the other hand, the enamide **2b** which does not possess an electron-donating group in the benzene ring was found to be cyclized only under vigorous conditions (*i.e.* toluene reflux or excess of PPA) to provide a furo-pyrrolo-isoquinoline **3b**. These two products **3b, 3c** were also obtained as a single diastereomer respectively.

The cyclized products (**3a - 3c**) can be valuable intermediates for the synthesis of other heterocyclic compounds. To prove the synthetic utility of these compounds, furo-indolizino-indole derivative **3c** was converted to carboxymethyl-substituted indolizino-indole derivative **6** in 60 % yield by treatment with 10 equiv of NaOMe in methanol (Scheme 3). By functional group manipulation of the double bond and the carboxy group, compound **6** would be tranformated into various optically pure indole-type alkaloids.

In summary, the asymmetric synthesis of furo-pyrrolo-isoquinoline and furo-indolizino-indole derivatives (**3a - 3c**) was accomplished using an intramolecular diastereoselective *N*-acyliminium ion cyclization of the chiral enamides (**2a - 2c**).

Scheme 3.



3c **6**

The chiral enamides were prepared from cheap L-malic acid as a chiral synthon. The possibility of using various aromatic rings as a π-nucleophile enhances the synthetic versatility of this strategy. The furo-pyrrolo-isoquinoline derivatives (**3a, 3b**) will be applied to the chiral synthesis of erythrina alkaloids since they have a requisite quaternary carbon-center and a B/C/D ring skeleton of erythrina alkaloids.[8] Such synthetic applications are in progress in our laboratory.

EXPERIMENTAL SECTION

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 = 589 nm) at the temperature indicated. 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.

Synthesis of 1-(2-Arylethyl)-3-hydroxypyrrolidine-2,5-dione (4a - 4c).

General procedure. To a refluxed solution of L-malic acid (**1**) in 100 ml of xylene

was added dropwise 2-arylethylamine (1.1 equiv), 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 recrystallized with EtOH (for **4b** and **4c**) or purified by flash column chromatography (hexane : ethyl acetate = 1 : 5) (for **4a**) to give a product as a white solid.

***(3S)*-3-Hydroxy-1-[2-(3-methoxyphenyl)ethyl]pyrrolidine-2,5-dione (4a).** Yield : 81 %; mp 58 °C; $[\alpha]^{30}_D$ -72.7 (*c* 4.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ph-H), 6.80-6.75 (3H, m, Ph), 4.58 (1H, dd, *J* = 8.3, 4.7 Hz, C<u>H</u>-OH), 4.35 (1H, br s, -OH), 3.79 (3H, s, OCH_3), 3.74 (2H, t, *J* = 8.0, Hz, N-C<u>H</u>$_2$), 3.02 (1H, dd, *J* = 18.1, 8.3 Hz, NCO-C<u>H</u>), 2.86 (2H, t, *J* = 8.0 Hz, Ph-C<u>H</u>$_2$), 2.63 (1H, dd, *J* = 4.7, 18.1 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.66, 174.43, 159.74, 139.14, 129.63, 121.19, 114.48, 112.26, 66.81, 55.22, 39.85, 37.24, 33.43; IR (KBr) 3444, 2940, 1694 cm^{-1}; MS (EI), m/z (relative intensity, %) 249 (M^+, 12), 134 (100), 121 (13), 104 (4); Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.49; H, 6.20; N, 5.66.

***(3S)*-3-Hydroxy-1-(2-phenylethyl)pyrrolidine-2,5-dione (4b).** Yield: 76 %; mp 132 °C (EtOH); $[\alpha]^{27}_D$ -85.4 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.19 (5H, m, Ph), 4.56 (1H, dd, *J* = 8.4, 4.7 Hz, C<u>H</u>-OH), 4.07 (1H, br s, OH), 3.75 (2H, t, *J* = 7.6 Hz, N-C<u>H</u>$_2$), 3.02 (1H, dd, *J* = 18.1, 8.4 Hz, NCO-C<u>H</u>), 2.89 (2H, d, *J* = 7.6 Hz, PhC<u>H</u>$_2$), 2.63 (1H, dd, *J* = 18.1, 4.7 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.60, 174.12, 137.49, 128.88 (2), 128.65 (2), 126.86, 66.84, 40.05, 37.16, 33.46; IR (KBr) 3943, 1698 cm^{-1}; MS (EI), m/z (relative intensity, %) 219 (M^+, 10), 104 (100), 91 (25), 77 (4), 65 (7); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.75; H, 5.98; N, 6.41.

***(3S)*-3-Hydroxy-1-[2-(3-indolyl)ethyl]pyrrolidine-2,5-dione (4c).** Yield: 60 %. mp 168 - 170 °C (EtOH); $[\alpha]^{27}_D$ -31.4 (*c* 0.57, DMSO); ^1H NMR (300 MHz, DMSO-d_6) δ 10.87 (1H, br s, NH), 7.55 (1H, d, *J* = 7.6 Hz, Ph-H), 7.35 (1H, d, *J* = 7.8 Hz, Ph-H), 7.20 (1H, s, indole-H), 7.09 (1H, dd, *J* = 7.6, 7.3 Hz, Ph-H),

7.01 (1H, dd, J = 7.8, 7.3 Hz, Ph-H), 6.13 (1H, dd, J = 8.4, 4.4 Hz, C<u>H</u>-OH), 4.47 (1H, br s, OH), 3.64 (2H, t, J = 7.8 Hz, CON-C<u>H</u>$_2$), 3.00 (1H, dd, J = 17.7, 8.4 Hz, NCOC<u>H</u>), 2.90 (2H, t, J = 7.8 Hz, PhC<u>H</u>$_2$), 2.43 (1H, dd, J = 17.7, 4.4 Hz, NCOC<u>H</u>); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.08, 174.75, 136.21, 127.00, 122.90, 121.02, 118.39, 117.93, 111.45, 110.49, 66.17, 38.51, 37.76, 23.06; IR (KBr) 3472, 1696 cm^{-1}; MS (EI), m/z (relative intensity, %) 258 (M^+, 15), 143 (44), 130 (100), 77 (10); HRMS (EI) Calcd for $C_{14}H_{14}N_2O_3$: (M^+) m/z 258.1004. Found: 258.1001.

Synthesis of 1-(2-Arylethyl)-3-bromoacetoxypyrrolidin-2,5-dione (5a - 5c).

General procedure. Bromoacetyl bromide (1.1 equiv) was added to the stirred solution of **4** and pyridine (1.2 equiv) in 30 ml of CH_2Cl_2 at 0°C under nitrogen. The reaction 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 $NaHCO_3$ solution successively, dried, and concentrated. The residue was purified by flash column chromatography.

***(3S)*-3-(2-Bromoacetoxy)-1-[2-(3-methoxyphenyl)ethyl)]pyrrolidine-2,5-dione (5a).** Yield: 70 %; $[\alpha]^{27}_D$ -14.1 (*c* 2.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (1H, dd, J = 7.5, 7.8 Hz, Ph-H), 6.77-6.71 (2H, m, Ph-2H), 6.71 (1H, s, Ph-H), 5.41 (1H, dd, J = 4.8, 8.7 Hz, CO_2C<u>H</u>), 3.89 (2H, s, BrC<u>H</u>$_2$), 3.74 (3H, s, OCH_3), 3.72 (2H, t, J = 8.2 Hz, N-CH_2), 3.08 (1H, dd, J = 8.7, 18.3 Hz, NCO-C<u>H</u>), 2.83 (2H, t, J=8.2 Hz, PhC<u>H</u>$_2$), 2.59 (1H, dd, J = 4.8, 18.3 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.74, 172.59, 166.47, 159.78, 139.07, 129.67, 121.15, 114.47, 112.30, 68.76, 55.22, 40.10, 35.18, 33.28, 25.07; IR (KBr) 2957, 1761, 1719 cm^{-1}; MS (EI), m/z (relative intensity, %) 371(M^+: Br^{81}, 0.2), 369 (M^+: Br^{79}, 0.2), 231 (0.6), 134 (100), 121 (12), 91 (7), 78 (3), 55 (4); HRMS (EI) Calcd for $C_{15}H_{16}BrNO_5$: (M^+) m/z 371.0191 (Br^{81}), 369.0212 (Br^{79}). Found: 371.0188 (Br^{81}), 369.0215 (Br^{79}).

***(3S)*-3-(2-Bromoacetoxy)-1-(2-phenylethyl)pyrrolidine-2,5-dione (5b).**

Yield: 98 %; $[\alpha]^{27}_D$ -15.3 (*c* 3.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-

7.19 (5H, m, Ph), 5.43 (1H, dd, J = 8.7, 4.6 Hz, C<u>H</u>-OH), 3.90 (2H, s, Br-C<u>H</u>$_2$), 3.77 (2H, t, J = 7.7 Hz, N-C<u>H</u>$_2$), 3.11 (1H, dd, J = 18.3, 8.7 Hz, NCO-C<u>H</u>), 2.90 (2H, t, J = 7.7 Hz, PhC<u>H</u>$_2$), 2.63 (1H, dd, J = 18.3, 4.6 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.52, 172.42, 166.40, 137.37, 128.86 (2C), 128.67 (2C), 126.91, 68.63, 40.31, 35.23, 33.32, 24.77; IR (KBr) 2949, 1713 cm^{-1}; MS (EI), m/z (relative intensity, %) 341(M^+: Br^{81}, 2.8), 339 (M^+: Br^{79}, 2.8), 104 (100), 91 (15), 77 (2), 65 (4); HRMS (EI) Calcd for $C_{14}H_{14}BrNO_4$: (M^+) m/z 341.0086 (Br^{81}), 339.0106 (Br^{79}), Found: 341.0083 (Br^{81}), 339.0106 (Br^{79}).

***(3S)*-3-(2-Bromoacetoxy)-1-[2-(3-indolyl)ethyl]pyrrolidine-2,5-dione (5c).** Yield: 69 %; mp 98 - 100 °C; $[\alpha]^{27}_D$ -21.3 (*c* 1.05, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (1H, br s, NH), 7.64 (1H, d, J = 7.6 Hz, Ph-H), 7.32 (1H, d, J = 7.7 Hz, Ph-H), 7.20 (1H, dd, J = 7.7, 6.7 Hz, Ph-H), 7.12 (1H, dd, J = 7.6, 6.7 Hz, Ph-H), 5.29 (1H, dd, J = 8.7, 4.7 Hz, CO_2C<u>H</u>-), 3.83 (2H, s, BrC<u>H</u>$_2$), 3.31 (2H, t, J = 7.3 Hz, N-C<u>H</u>$_2$), 3.07 (2H, t, J = 7.3 Hz, Ph-C<u>H</u>$_2$), 2.97 (1H, dd, J = 18.3, 8.7 Hz, NCO-C<u>H</u>), 2.55 (1H, dd, J=18.3, 4.7 Hz, NCO-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.05, 172.90, 166.58, 136.27, 127.43, 122.63, 122.39, 122.16, 119.59, 118.53, 111.54, 68.76, 40.02, 35.17, 25.01, 23.18; IR (KBr) 3414, 1750, 1705 cm^{-1}; MS (EI), m/z (relative intensity, %) 240 [$(M\text{-}BrCH_2CO_2)^+$, 19], 143 (21), 130 (100), 103 (8), 77 (12); HRMS (EI) Calcd for $C_{16}H_{15}BrN_2O_4$: (M^+) m/z 380.0195 (Br^{81}), 378.0215 (Br^{79}). Found: 380.0200 (Br^{81}), 378.0219 (Br^{79}).

Synthesis of 4-(2-Arylethyl)-6,6a-dihydro-4*H*-furo[3,2-*b*]pyrrole-2,5-dione (2a - 2c).

General procedure. Triphenylphosphine (1.2 equiv) was added to the stirred solution of **5** (1 equiv) in 60 ml of CH_3CN under nitrogen. The mixture was stirred at 50 °C for 2 hr, and then triethylamine (1.1 equiv) 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.

***(6aS)*-4-[2-(3-Methoxyphenyl)ethyl]-6,6a-dihydro-4*H*-furo[3,2-*b*]pyrrole-2,5-dione (2a).** Yield: 81 %; mp 109 -110 °C; $[\alpha]^{30}_D$ -58.4 (*c* 2.30, $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.22 (1H, dd, J = 7.5, 7.8 Hz, Ph-H), 6.08-6.73 (2H, m, Ph-2H), 6.70 (1H, s, Ph-H), 5.05 (1H, dd, J = 7.7, 8.9 Hz, CO_2CH), 5.00 (1H, s, $COCH$=C), 4.03 (1H, m, CON-CH), 3.79 (3H, s, OCH_3), 3.67 (1H, m, CON-CH), 3.02 (1H, dd, J = 7.7, 15.9 Hz, NCO-CH), 2.92 (2H, m, Ph-CH_2), 2.62 (1H, dd, J = 8.9, 15.9 Hz, NCO-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.74, 172.18, 170.40, 159.97, 138.71, 129.91, 121.00, 114.80, 112.19, 89.57, 75.22, 55.26, 43.81, 38.45, 33.70; IR (KBr) 2928, 1766, 1658, 1598 cm^{-1}; MS (EI), m/z (relative intensity, %) 273 (M^+, 9), 229 (0.4), 134 (100), 121 (21), 91 (10), 82 (11); Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.85; H, 5.65; N, 5.24.

***(6aS)*-4-[2-(Phenyl)ethyl]-6,6a-dihydro-4*H*-furo[3,2-*b*]pyrrole-2,5-dione (2b).** Yield: 77 %; mp 150 °C; $[\alpha]^{28}_D$ -89.9 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.14 (5H, m, Ph), 5.03 (1H, dd, J = 8.9, 7.7 Hz, $-CO_2CH$), 4.97 (1H, s, $COCH$=C), 4.02 (1H, m, CON-CH), 3.68 (1H, m, CON-CH), 2.98 (1H, dd, J = 15.8, 7.7 Hz, NCO-CH), 2.96 (2H, t, J = 7.2 Hz, Ph-CH_2), 2.59 (1H, dd, J = 15.8, 8.9 Hz, NCO-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.65, 172.13, 170.31, 137.13, 128.93 (2C), 128.74 (2C), 127.31, 89.65, 75.21, 44.00, 38.49, 33.75; IR (KBr) 2939, 1771, 1663 cm^{-1}; MS (EI), m/z (relative intensity, %) 243 (M^+, 8), 152 (5), 104 (100), 92 (25), 82 (14), 65 (5); Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.04; H, 5.40; N, 5.81.

***(6aS)*-4-[2-(1*H*-Indol-3-yl)ethyl]-6,6a-dihydro-4*H*-furo[3,2-*b*]pyrrole-2,5-dione (2d).** Yield: 61 %; mp 195 °C; $[\alpha]^{27}_D$ -49.3 (*c* 0.48, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (1H, br s, NH), 7.17 (1H, d, J = 7.7 Hz, Ph-H), 7.04 (1H, d, J = 7.9 Hz, Ph-H), 6.80 (1H, dd, J = 7.7, 7.0 Hz, Ph-H), 6.72 (1H, dd, J = 7.9, 7.0 Hz, Ph-H), 6.70 (1H, s, indole-H), 4.63 (1H, dd, J = 8.8, 7.8 Hz, CH-OH), 4.47 (1H, s, $COCH$=C), 3.74 (1H, m, CON-CH), 3.36 (1H, m, CON-CH), 2.85-2.68 (2H, m, Ph-CH_2), 2.64 (1H, dd, J = 15.5, 7.8 Hz, NCO-CH), 2.25 (1H, dd, J = 5.5, 8.8 Hz, NCO-CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.97, 172.86, 171.92, 136.02, 126.88, 123.11, 121.01, 118.52, 118.11, 111.36, 110.16, 88.12, 75.06, 42.49, 37.92, 22.88; IR (KBr) 3321, 1753, 1644 cm^{-1}; MS (EI), m/z (relative intensity, %) 282 (M^+, 12), 207 (10), 143 (22), 130 (100), 77 (9); HRMS (EI)

Calcd for $C_{16}H_{14}N_2O_3$: (M^+) m/z 282.1004. Found: 282.1005.

_N_-Acyliminium ion cyclization of enamides (2a-2c) to afford furo-pyrrolo-isoquinoline and furo-indolizino-indole derivatives (3a-3c).

General procedure. *p*-Toluenesulfonic acid [1 (for **3a** and **3b**) or 3 (for **3c**) equiv] or excess of PPA (for **3b**) was added to a suspension or solution of enamide **2** in 10 ml of toluene (for **3b**) or methylene chloride (for **3a** and **3c**). The reaction mixture was refluxed for 1 hr, cooled to room temperature, and diluted with 20 ml of ethyl acetate. The mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography.

Furo-pyrrolo-isoquinoline (3a). Yield: 53 %; mp 140 °C; $[\alpha]^{30}_D$ -109.5 (*c* 2.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (1H, d, *J* = 8.7 Hz, Ph-H), 6.87 (1H, dd, *J* = 8.7, 2.7 Hz, Ph-H), 6.65 (1H, d, *J* = 2.4 Hz, Ph-H), 5.19 (1H, dd, *J* = 2.0, 6.2 Hz, $CO_2C\underline{H}$-), 4.37 (1H, m, CON-C<u>H</u>), 3.80 (3H, s, OCH_3), 3.11 & 3.01 (2H, ABq, *J* = 8.3 Hz, $C\underline{H}_2CO_2$), 3.09-2.97 (2H, m, Ph-C<u>H</u> & CON-C<u>H</u>), 2.79-2.75 (2H, m, NCO-C<u>H</u>$_2$), 2.69 (1H, m, Ph-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43, 171.43, 159.25, 136.04, 126.79, 125.97, 114.23, 113.98, 82.06, 68.00, 55.39, 44.02, 37.24, 35.84, 27.50; IR (KBr) 2940, 1792, 1696 cm^{-1}; MS (EI), m/z (relative intensity, %) 273 (M^+, 48), 231 (100), 230 (93), 214 (60), 202 (12), 186 (9), 160 (39); HRMS (EI) Calcd for $C_{15}H_{15}NO_4$: (M^+) m/z 273.1001. Found: 273.1007.

Furo-pyrrolo-isoquinoline (3b). Yield : 50 % (*p*-TsOH) , 43 % (PPA) ; an oil; $[\alpha]^{22}_D$ -140.3 (*c* 2.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.13 (4H, m, Ph), 5.24 (1H, br d, *J* = 6.5 Hz, CO_2-C*H*), 4.39 (1H, m, CON-C<u>H</u>), 3.16-3.06 (2H, m, Ph-C<u>H</u> & CON-C<u>H</u>), 3.13 & 2.94 (2H, ABq, *J* = 18.3 Hz, -$CO_2C\underline{H}_2$), 2.86-2.70 (3H, m, NCOC<u>H</u>$_2$ & Ph-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.22, 171.20, 134.99, 134.52, 130.02, 128.42, 127.56, 124.70, 82.14, 68.15, 44.22, 37.34, 35.92, 27.19; IR (KBr) 1776, 1648 cm^{-1}; MS (EI), m/z (relative intensity, %) 243 (M^+, 22), 201 (100), 184 (26), 172 (16), 156 (9), 130 (25), 103 (11), 77 (10); HRMS (EI), Calcd for $C_{14}H_{13}NO_3$: (M^+) m/z 243.0895. Found: 243.0894.

Furo-indolizino-indole (3c). Yield: 79 %; mp 184 °C (foamy solid); $[\alpha]^{27}_{D}$ -106.4 (*c* 2.60, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6 + CD_3OD) δ 7.36 (1H, d, *J* = 7.8 Hz, Ph-H), 7.32 (1H, d, *J* = 8.2 Hz, Ph-H), 7.09 (1H, dd, *J* = 7.8, 7.3 Hz, Ph-H), 7.00 (1H, dd, *J* = 8.2, 7.3 Hz, Ph-H), 5.36 (1H, br d, *J* = 6.2 Hz, $CO_2C\underline{H}$-), 4.21 (1H, m, CON-C<u>H</u>), 3.21-3.10 (3H, m, -CO-C<u>H</u>$_2$ & CON-C<u>H</u>) 2.81-2.58 (4H, m, Ph-C<u>H</u>$_2$ & NCO-C<u>H</u>$_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.68, 172.40, 136.16, 130.36, 126.05, 122.00, 118.98, 118.15, 111.48, 109.17, 78.91, 66.26, 40.58, 36.62, 36.22, 19.69; IR (KBr) 3180, 1786, 1704 cm^{-1}; MS (EI), m/z (relative intensity, %) 282 (M^+, 82), 240 (97), 239 (100), 223 (49), 207 (30), 169 (32), 154 (24), 128 (13), 115 (17), 77 (15); HRMS (EI) Calcd for $C_{16}H_{14}N_2O_3$: (M^+) m/z 282.1004. Found: 282.1000.

***(11bS)*-11b-Carboxymethyl-3-oxo-5,6,11,11b-tetrahydro-*3H*-indolizino[8,7-*b*]indole (6).** To a stirred solution of 10 ml of MeOH was added a excess of sodium metal (299 mg, 13.0 mmol) at room temperature. After stirring for 5 min, furo-indolizino-indole (**3c**) (390 mg, 1.30 mmol) was added to the above solution and the reaction mixture was stirred at room temperature for 40 min. Saturated NH_4Cl solution was added and the reaction mixture was acidified to pH 4 with 1*N*-HCl. The product was extracted with ethyl acetate (20 ml x 2). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a solid, which was washed with ethyl ether and dried *in vacuo* to give 234 mg (60 %) of **6** as a pale yellowish solid. mp 280-290 °C (dec.); $[\alpha]^{17}_{D}$ -162.2 (*c* 1.0, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6 + CD_3OD) δ 8.03 (1H, d, *J* = 5.7 Hz, NCOCH=C<u>H</u>), 7.35 (1H, d, *J* = 7.7 Hz, Ph-H), 7.30 (1H, d, *J* = 7.9 Hz, Ph-H), 7.02 (1H, dd, *J* = 7.7, 7.4 Hz, Ph-H) 6.93 (1H, dd, *J* = 7.9, 7.4 Hz, Ph-H), 6.02 (1H, d, *J* = 5.6 Hz, NCOC<u>H</u>=C), 4.30 (1H, m, CON-C<u>H</u>), 3.18 (1H, m, CON-C<u>H</u>), 2.99 & 2.45 (2H, ABq, *J* = 15.4 Hz, C<u>H</u>$_2$CO$_2$H), 2.70-2.55 (2H, m, PhC<u>H</u>$_2$); ^{13}C NMR (75 MHz, DMSO-d_6 + CD_3OD) δ 174.62, 170.68, 152.94, 135.37, 134.09, 126.07, 124.47, 121.13, 118.44, 117.97, 111.04, 105.55, 65.18, 45.80, 35.17, 21.09; IR (KBr) 3482, 1661, 1566 cm^{-1}; MS (EI), m/z (relative intensity, %) 238 [$(M-CO_2)^+$, 100], 223 (85), 207 (63), 167 (7).

ACKNOWLEDGEMENTS

Financial support from the Korea Ministry of Science and Technology (2E1400I) is gratefully acknowledged.

REFERENCES AND NOTES

1. Hill, R. K. "The Alkaloids" Vol. 9, ed. by Manske, R. N. F. Academic Press, New York, **1967**, pp. 483.
2. a) Pelletier, S. W. "Chemistry of the Alkaloids," Van Nostrand Reinhold Co., New York, **1970**, pp. 77; b) Shamma, M. and Moniot, J. L. "Isoquinoline Alkaloids Research," Plenum press, New York, **1978**, pp. 57.
3. 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) Speckamp, W. N. *Recl. Trav. Chim., Pay-Bas* **1981**, 100, 345; c) Veenstra, S. J. and Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, 103, 4645; d) Wijnberg, B. P. and Speckamp, W. N. *Tetrahedron Lett.* **1981**, 22, 5079.
4. a) Li, T.-T.; Lesko, P.; Ellison, R. H.; Subramanian, N; Fried, J. H. *J. Org. Chem.* **1981**, 46, 111; b) Takano, S.; Takahashi, M.; Ogasawara, K. *J. Am. Chem. Soc.* **1980**, 102, 4282.
5. a) Wijnberg, B. P. and Speckamp, W. N. *Tetrahedron Lett.* **1980**, 21, 1987; b) Chamberlin, A. R. and Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, 105, 3653; c) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, 4, 1455.
6. a) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, 60, 7149; b) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *Synth. Commun.* **1995**, 25, 1947.
7. a) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, 52, 2941; b) Hart, D. J.; Sun, L.-Q.; Kozikowski, A. P.

Tetrahedron Lett. **1995**, 36, 7787.

8. Hosoi, S.; Ishida, K.; Sangai, M.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, 40, 3115.

(Received in The Netherlands 27 March 1997)