The First Synthesis of the Pentacyclic Pyridoacridine Marine Alkaloids: Arnoamines A and B

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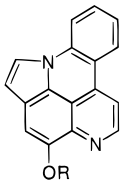
The synthesis of the marine pyridoacridine alkaloids arnoamines A and B has been accomplished in six and seven steps from 4-chloro-8-methoxy-5-nitroquinoline in 13% and 4% overall yield, respectively.

The search for new pharmaceuticals from marine environment has resulted in the isolation of an ever-increasing number of alkaloids.[1] Among them, the largest group to have been characterized so far is based on the pyrido[2,3,4-*kl*] acridine skeleton.[2] These structurally related polycyclic aromatic alkaloids show a broad range of biological properties including tumor toxicity and fungal growth inhibition.[3]

In 1998, Plubrukarn and Davidson[4] reported the isolation and structure elucidation of two new cytotoxic metabolites: arnoamines A (**1**) and B (**2**) isolated from the brownish purple ascidian *Cystodytes* sp. collected near Arno Atoll (Republic of the Marshall Islands). These are the first members of a new family of pentacyclic pyridoacridine alkaloids that possess a pyrrole ring fused to the pyridoacridine ring system.

In continuation of our work in this area,[5] we now report the first synthesis of the compounds (**1**) and (**2**).

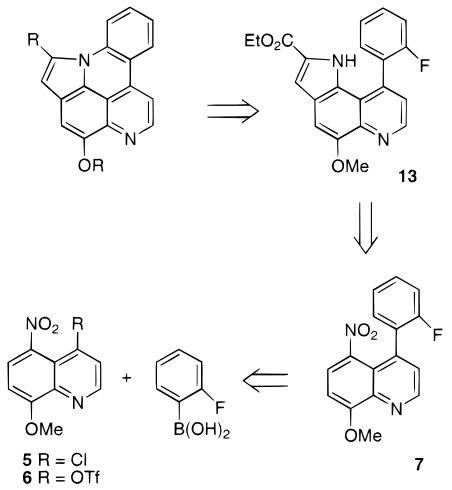


1 R = H
2 R = Me

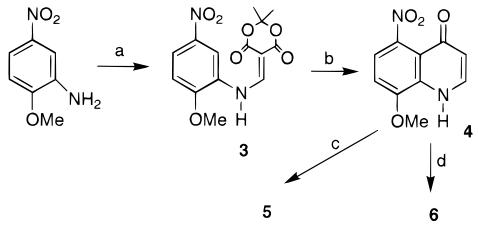
The retrosynthetic analysis shown in Scheme 1 is derived from that developed by Dunn and McKillop for the synthesis of norsegoline.[6]

The heart of our plan was the coupling of the quinoline halide **5** with 2-fluorobenzene boronic acid via the Suzuki reaction.[7] The indole moiety was introduced by the Fischer method,[8] the last cycle being formed according to the procedure previously described by Smith and Sawyer for the N-arylation of indoles.[9]

Scheme 1



Scheme 2[a]



[a] Key: (a) Meldrum acid, $HC(OEt)_3$; (b) PhOPh, N_2, reflux 40 min; (c) $POCl_3$, PCl_5, 85 °C, 1 h; (d) Tf_2O, DMAP, 2,6-lutidine, 0 °C, 2 h.

As starting material, the chloroquinoline **5** was obtained in a three-step procedure from 2-methoxy-5-nitroaniline via the Meldrum derivative **3** and the quinolinone **4** with 52% overall yield. This new pathway to obtain **5** constitutes an improvement of the synthesis of this compound reported in the literature.[10] The triflate

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(5) (a) Bontemps, N.; Bonnard, I.; Banaigs, B.; Combaut, G.; Francisco, C. *Tetrahedron Lett.* **1994**, *35*, 7023. (b) Bonnard, I.; Bontemps, N.; Lahmy, S.; Banaigs, B.; Combaut, G.; Francisco, C.; Colson, P.; Houssier, C.; Bailly, C.; Waring, M. J. *Anticancer Drug Design* **1995**, *10*, 333. (c) Bontemps, N.; Delfourne, E.; Bastide, J.; Francisco, C.; Bracher, F. *Tetrahedron* **1997**, *53*, 1743.
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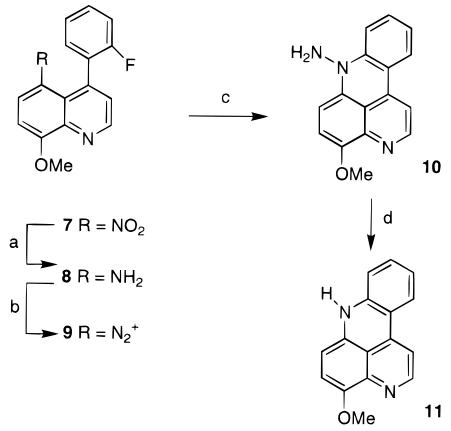
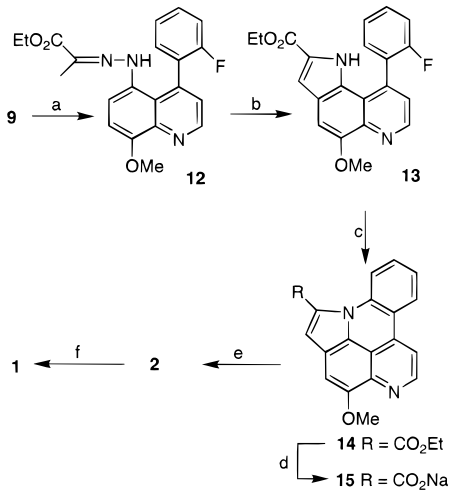
Scheme 3[a]



[a] Key: (a) 10% Pd/C, cyclohexene, EtOH, reflux, 15 min; (b) $NaNO_2$, 36% HCl, 0 °C, 15 min; (c) $Na_2S_2O_4$, H_2O/Et_2O 1:1; (d) methyl pyruvate, EtOH, 130 °C, 1 h.

Scheme 4[a]



[a] Key: (a) ethyl-2-methyl-3-oxobutyrate, KOH, EtOH, H_2O, 0 °C, overnight; (b) polyphosphoric acid, 100 °C, 6 h; (c) 37% KF/Al_2O_3, cat. 18-crown-6, DMSO, 120 °C, 2 h; (d) 2 M NaOH, H_2O, EtOH, 2 h; (e) copper chromite, quinoline, 200 °C, 1 h; (f) BBr_3, CH_2Cl_2.

6 was obtained from the quinolinone **4**. The Suzuki reaction, which is formally a palladium-catalyzed cross-coupling of organoboranes with organic electrophiles in the presence of base, was applied both on the triflate **6** and the chloride **5** to produce the expected adduct **7** with 47 and 78% yield, respectively. This nitro compound **7** was reduced by catalytic hydrogenation (the hydrogen donor being cyclohexene) to afford the amino derivative **8**, which was transformed into its diazonium salt **9**. Since the Fisher indole synthesis involved the formation of an arylhydrazone, we tried to reduce compound **9** into its hydrazine derivative. However, when **9** was treated with sodium dithionite, the tetracyclic hydrazine **10**, which corresponds to the cyclization of the expected hydrazine, was obtained. Unfortunately, attempts to form the five-membered ring by reaction of methyl pyruvate with compound **10** failed. In that case, the sole product isolated was the deaminated product **11**. An alternative was the conversion in 86% yield of the amino compound **8**, via its diazonium salt, into the hydrazone **12** by Japp–Klingemann reaction.[11] The cyclization of **12** to the indole **13** was accomplished in polyphosphoric acid. The formation of the last pyridine ring was performed in the presence of 37% KF/Al_2O_3 and catalytic 18-crown-6 in DMSO at 120 °C as previously described by Smith and Sawyer in 57% yield.[9] The ester **14** was hydrolyzed in 2 N sodium hydroxide at reflux. The sodium salt obtained was then decarboxylated by copper chromite in quinoline to give quantitatively arnoamine B. This alkaloid was finally demethylated by boron tribromide to yield the second natural product arnoamine A.

The spectroscopic data obtained in the same solvent conditions for **1** and **2** were identical to the values reported for the natural products arnoamines A and B.

Experimental Section

General Procedures. All commercial chemicals were used without further purification. Flash chromatography was performed on flash silica gel 60 (Merck 0.015–0.040 mm). Nuclear magnetic resonance spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C.

5-[(2′-Methoxy-5′-nitrophenylamino)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane (3). A solution of 2,2-dimethyl-4,6-dioxo-1,3-dioxane (10.4 g, 72.2 mmol) in triethyl orthoformate (91 mL) was refluxed for 2 h, and 2-methoxy-5-nitroaniline (10 g, 59.5 mmol) was added. Filtration of the reaction mixture afforded a yellow solid: mp 230 °C (17 g, 89% yield); ^1H NMR ($CDCl_3$) 1.75 (6H, s), 4.09 (3H, s), 7.01 (1H, d, J = 8.8 Hz), 8.09 (1H, dd, J = 8.8, 2.4 Hz), 8,19 (1H, d, J = 2.4 Hz), 8.66 (1H, d, J = 14.4 Hz), 11.55 (1H, d, J = 14.4 Hz), ^{13}C NMR ($CDCl_3$) 27.13, 57.05, 89.25, 105.42, 110.83, 111.07, 122.45, 127.82, 141.79, 150.88, 153.77, 163.15, 165.15, IR ($CHCl_3$) 3300, 1729, 1684 cm^{-1}.

8-Methoxy-5-nitroquinolin-4-one (4). The Meldrum derivative **3** (10 g, 31.1 mmol) in diphenyl ether (500 mL) was refluxed under nitrogen for 40 min. After the mixture was cooled to room temperature, petroleum ether (700 mL) was added. Filtration of the reaction mixture afforded the expected quinolone as a green brown solid: mp 212 °C (5.9 g, 86% yield); ^1H NMR (DMSO-d_6) 4.06 (3H, s), 6.13 (1H, d, J = 7.4 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.84 (1H, d, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) 56.86, 109.66, 110.81, 116.95, 117.90, 131.28, 139.32, 141.29, 149.98, 173.57.

4-Chloro-8-methoxy-5-nitroquinoline (5). To a solution of phosphorus pentachloride (176 mg, 0.8 mmol) in phosphorus oxychloride (32 mL) was added the quinolinone **4** (8 g, 36.4 mmol), and the resulting mixture was warmed at 85 °C for 1 h. After cooling to room temperature and evaporation under reduced pressure to remove $POCl_3$, a saturated sodium carbonate solution was added. The reaction mixture was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated. Purification of the crude product on a silica gel chromatography column (CH_2Cl_2) afforded **5** as a clear brown solid: mp 191 °C (lit.[10] mp 189–191 °C) (3.5 g, 68% yield); ^1H NMR (DMSO-d_6) 4.16 (3H, s), 7.05 (1H, d, J = 8.8 Hz), 7.68 (1H, d, J = 4.4 Hz), 7.87 (1H, d, J = 8.8 Hz), 8.88 (1H, d, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$) 57.26, 106.26, 120.16, 125.59, 126.05, 140.00, 140.26, 140.43, 150.04, 158.69; IR (KBr) 1531, 1500, 1360 cm^{-1}.

8-Methoxy-5-nitro-4-quinolinyl Trifluoromethanesulfonate (6). To a solution of quinolone **4** (9.71 g, 44.1 mmol) in CH_2Cl_2 (466 mL) were successively added, at 0 °C under nitrogen atmosphere, 4-(dimethylamino)pyridine (0.81 g, 6.7 mmol), 2,6-lutidine (5.8 mL, 54.2 mmol) and trifluoromethane sulfonic anhydride (8.2 mL, 46.1 mmol). After being stirred for 2 h at 0 °C and then 1 h at room temperature, the reaction mixture was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2) gave the expected triflate as a brown oil (1.6 g, 50% yield): ^1H NMR ($CDCl_3$)

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4.12 (3H, s), 7.12 (1H, d, $J = 8.8$ Hz), 7.68 (1H, d, $J = 5.2$ Hz), 8.03 (1H, d, $J = 8.8$ Hz), 9.08 (1H, d, $J = 5.2$ Hz); ^{13}C NMR ($CDCl_3$) 57.10, 106.72, 114.60, 114.87, 118.29 (q, $J = 320$ Hz), 126.54, 137.97, 141.92, 150.12, 150.85, 158.56; IR (KBr) 1601, 1534, 1346 cm^{-1}.

8-Methoxy-5-nitro-4-(2′-fluorophenyl)quinoline (7). To a solution of 2 M K_2CO_3 (14 mL), EtOH (7 mL), and deoxygenated toluene (135 mL) were added chloride **5** (3.2 g, 13.4 mL) and 2-fluorobenzene boronic acid (1.9 g, 13.4 mmol). The mixture was stirred under nitrogen pressure, at room temperature, for 30 min, and tetrakis(triphenylphosphine)palladium (471 mg, 0.402 mmol) was added. The reaction mixture was refluxed overnight. After cooling, the precipitate was washed with toluene. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to give **7** as a yellow-orange solid: mp 215 °C (3.1 g, 78% yield); ^{1}H NMR ($CDCl_3$) 4.15 (3H, s), 7.04 (1H, d, $J = 8.8$ Hz), 7.18 (3H, m), 7.40 (1H, m), 7.57 (1H, d, $J = 4.4$ Hz), 7.99 (1H, d, $J = 8.8$ Hz), 9.05 (1H, d, $J = 4.4$ Hz); ^{13}C NMR ($CDCl_3$) 56.84, 105.07, 115.97 (d, $J = 21.4$ Hz), 120.71, 124.34, 125.88, 126.21 (d, $J = 16$ Hz), 126.84, 129.50, 130.75, 140.29, 140.60, 141.05, 149.56, 158.53 (d, $J = 245$ Hz),159.22; IR (KBr) 1614, 1517, 1342 cm^{-1}; EIMS *m*/*z* (relative intensity) 298 (19), 297 (16), 252 (68), 251 (80), 222 (83), 221 (100). Anal. Calcd for $C_{16}H_{11}FN_2O_3$: C, 64.43; H, 3.69; N, 9.40. Found: C, 64.19; H, 3.60; N, 9.36.

8-Methoxy-5-amino-4-(2′-fluorophenyl)quinoline (8). To a suspension of the nitro derivative **7** (1.45 g, 4.87 mmol) and 10% Pd/C (2.68 g) in absolute EtOH (67 mL) was added cyclohexene (3 mL). The reaction mixture was refluxed for 45 min. After evaporation, the crude product was purified by flash chromatography to yield the amino derivative as a yellow-brown solid: mp 191 °C (0.85 g, 65% yield); ^{1}H NMR ($CDCl_3$) 4.04 (3H, s), 6.66 (1H, d $J = 8.2$ Hz), 6.95 (1H, *d* = 8.2 Hz), 7.17 (1H, d, $J = 4.2$ Hz), 7.20 (1H, dd, $J = 8.8$ Hz; 0.7 Hz), 7.26 (1H, dd, $J = 7.4$, 1.1 Hz), 7.38 (1H, dd, $J = 7.4$ Hz; 1.8 Hz), 7.48 (1H, m), 8.9 (1H, d, $J = 4.2$ Hz); ^{13}C NMR ($CDCl_3$) 56.20, 108.79, 111.52, 115.9 (d, $J = 21.4$ Hz), 118.13, 123.30, 124.11, 128.40 (d, $J = 18$ Hz), 130.36, 130.67, 136.32, 140.41, 141, 147.94, 148.94, 159.2 (d, $J = 240$ Hz); IR ($CHCl_3$) 3468, 3362, 1611, 1474, 1277 cm^{-1}; EIMS *m*/*z* (relative intensity) 268 (100), 267 (91), 239 (26), 218 (38). Anal. Calcd for $C_{16}H_{13}FN_2O$: C,71.64; H,4.85; N,10.45. Found: C, 71.85; H, 5.09; N, 10.47.

7-Amino-4-methoxy-7*H*-pyrido[2,3,4-*kl*]acridine (10). To a solution of amino derivative **8** (100 mg, 0.4 mmol) in water (1 mL) were added, at 0 °C, 36% HCl (51 μL) and a solution of sodium nitrite (27 mg, 0.4 mmol) in water (70 μL). The reaction mixture was stirred for 15 min and then was added to a solution of $Na_2S_2O_4$ in water/ether (2 mL/2 mL) before being stirred for an additional 30 min. NaOH (1 N) was added until basic pH and the etheral phase was decanted. The aqueous phase was extracted with CH_2Cl_2, and the organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash chromatography gave compound **10** as an orange solid: mp 244 °C (35 mg, 33% yield); ^{1}H NMR (DMSO-d_6) 3.88 (3H, s), 5.74 (2H, s), 6.98 (1H, dd, $J = 7.8$, 7.8 Hz), 7.04 (1H, d, $J = 8.4$ Hz), 7.21 (1H, d, $J = 8.4$ Hz), 7.45 (1H, dd, $J = 7.8$, 7.8 Hz), 7.56 (1H, d, $J = 5.2$ Hz), 7.74 (1H, d, $J = 7.8$ Hz), 8.04 (1H, d, $J = 7.8$ Hz), 8.55 (1H, d, $J = 5.2$ Hz); ^{13}C NMR (DMSO-d_6) 56.05, 101.15, 107.60, 111.39, 114.26, 115.88, 119.30, 119.97, 123.82, 131.80, 134.91, 138.36, 140.70, 143.14, 146.30, 150.25; IR (KBr) 3418, 3299, 3138, 1534, 1359 cm^{-1}; EIMS *m*/*z* (relative intensity) 263 (71), 247 (100), 218 (61). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 73.00; H, 4.94; N, 15.97. Found: C, 72.92; H, 4.87; N, 15.92.

4-Methoxy-7*H*-pyrido[2,3,4-*kl*]acridine (11). Hydrazine derivative **10** (263 mg, 1 mmol) was dissolved in ethanol (5 mL). Methyl pyruvate (110 mg, 1.07 mmol) was added, and the resulting solution was stirred for 1 h. The solution was concentrated under reduced pressure. The crude product was heated at 130 °C under reduced pressure (20 mmHg) for 1 h. Purification by flash chromatography (CH_2Cl_2/MeOH 95:5) gave **11**: mp > 260 °C (65 mg, 26%); ^{1}H NMR (DMSO-d_6) 3.84 (s, 3H), 6.58 (1H, d, $J = 8.4$ Hz), 6.91 (1H, dd, $J = 7.8$, 7.8 Hz), 6.94 (1H, d, $J = 8.4$ Hz), 7.10 (1H, d, $J = 8.8$ Hz), 7.33 (1H, ddd, $J = 7$, 7, 1.5 Hz), 7.42 (1H, d, $J = 5$ Hz), 7.93 (1H, d, $J = 7.4$ Hz), 8.48 (1H, d, $J = 5.$ Hz); ^{13}C NMR (DMSO-d_6) 56.25, 101.87, 107.09, 112.67, 115.06, 115.42, 119.30, 120.04, 124.22, 132.06, 132.13, 140.13, 140.29, 140.44, 145.10, 150.42; IR (KBr) 3336, 1628, 1591, 1457, 1358 cm^{-1}; EIMS *m*/*z* (relative intensity) 248 (81), 247 (100), 233 (38), 219 (33). Anal. Calcd for $C_{16}H_{12}N_2O$, 1 CH_2Cl_2: C, 61.26; H, 4.20; N, 8.41. Found: C, 61.03; H, 4.20; N, 8.21.

Ethyl 2-[*N*-[8-Methoxy-4-(2′-fluorophenyl)quinolin-5-yl]hydrazono]propionate (12). To a well-stirred suspension of amino derivative **8** (0.5 g, 1.87 mmol) in 4 M HCl solution (2.5 mL, 9.35 mmol) was slowly added a solution of $NaNO_2$ (0.131 g, 1.87 mmol) in water (0.4 mL). After being stirred, at 0 °C, for 30 min, the resulting diazonium salt solution was added into a vigorously stirred mixture of ethyl-2-methyl-3-oxobutyrate (90%, 0.3 g, 1.87 mmol), EtOH (2.4 mL), KOH (0.56 g, 10.1 mmol), NaOAc (0.56 g), and H_2O (3.5 mL) maintained at 0 °C. The mixture was stirred continuously at 0 °C for 1 h. The precipitate was collected by filtration and washed with water to obtain **12** as a bright yellow solid: mp 64 °C (0.612 g, 86% yield); ^{1}H NMR ($CDCl_3$) 1.22 (3H, s), 1.34 (3H, t, $J = 7.3$ Hz), 4.11 (3H, s), 4.26 (2H, q, $J = 7.3$ Hz), 7.14 (1H, d, $J = 8.8$ Hz), 7.22 (1H, d, $J = 4.4$ Hz), 7.24 (1H, d, $J = 7.4$ Hz), 7.33 (1H, ddd, $J = 7.4$, 7.4, 1.1 Hz), 7.43 (1H, ddd, $J = 7.4$, 7.4, 1.8 Hz), 7.47 (1H, bs), 7.51 (2H, m), 7.71 (1H, d, $J = 8.8$ Hz); ^{13}C NMR ($CDCl_3$) 9.21, 14.31, 56.21, 61.18, 108.66, 113.25, 116.55 (d, $J = 21$ Hz), 117.80, 124.23, 124.98, 127, 130.64, 131.26, 132.55 (d, $J = 40$ Hz), 138.85, 140.63, 147.87, 151.32, 159.19 (d, $J = 227$ Hz), 165.38, 175.14; IR ($CHCl_3$) 3370, 1700, 1613, 1559, 1490 cm^{-1}; EIMS *m*/*z* (relative intensity) 381 (100), 247 (91), 218 (39). Anal. Calcd for $C_{21}H_{20}FN_3O_3$: C, 66.14; H, 5.25; N, 11.02. Found: C, 66.10; H, 5.45; N, 10.68.

Ethyl 9-(2′-Fluorophenyl)-5-methoxypyrrolo[2,3-*f*]quinoline-2-carboxylate (13). A mixture of ester derivative **12** (200 mg, 0.53 mmol) and polyphosphoric acid (1.3 g) in toluene (2.5 mL) was warmed at 100 °C for 6 h. After cooling, water was added until complete dissolution. The reaction mixture was extracted with CH_2Cl_2, and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2) afforded the indolic compound **13** as a yellow solid: mp 105 °C (110 mg, 58% yield); ^{1}H NMR ($CDCl_3$) 1.31 (3H, t, $J = 7.3$ Hz), 4.13 (3H, s), 4.23 (2H, q, $J = 7.3$ Hz), 7.16 (1H, d, $J = 2.2$ Hz), 7.25 (1H, s), 7.37 (1H, d, $J = 8.4$ Hz), 7.41 (1H, d, $J = 4.4$ Hz), 7.45 (1H, m), 7.47 (1H, ddd, $J = 7.7$, 7, 2.2 Hz), 7.67 (1H, m), 8.15 (1H, bs), 9.02 (1H, d, $J = 4.4$ Hz); ^{13}C NMR ($CDCl_3$) 14.19, 56.06, 60.65, 101.71, 108.46, 116.72 (d, $J = 15$ Hz), 117.02, 122.85, 124.25, 125.20 (d, $J = 3.8$ Hz), 125.63, 126.41, 126.58, 130.51, 132.16, 138.24, 141.28, 147.12, 150.80, 159.27 (d, $J = 300$ Hz), 160.25; IR ($CHCl_3$) 3449, 1700, 1613, 1330 cm^{-1}; EIMS *m*/*z* (relative intensity) 364 (100), 363 (95), 317 (62), 316 (61), 288 (25). Anal. Calcd for $C_{21}H_{17}FN_2O_3$: C, 69.23; H, 4.67; N, 7.69. Found: C, 69.13; H, 4.71; N, 7.77.

Ethyl 4-Methoxypyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine-1-carboxylate (14). The indole derivative **13** (50 mg, 0.137 mmol) in DMSO (0.5 mL) was heated at 120 °C for 2 h, in the presence of 18-crown-6 (4 mg, 0.0137 mmol) and 37% potassium fluoride absorbed onto basic alumina (1 weight equivalent based on the indole, 50 mg). The reaction mixture was filtered and partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to give the pentacyclic derivative as a yellow solid: mp 179 °C (141 mg, 57% yield); ^{1}H NMR ($CDCl_3$) 1.50 (3H, t, $J = 7.3$ Hz), 4.19 (3H, s), 4.52 (2H, q, $J = 7.3$ Hz), 7.43 (1H, s), 7.56 (1H, dd, $J = 8.8$, 7 Hz), 7.75 (1H, dd, $J = 7$, 8.1 Hz), 7.91 (1H, s), 8.13 (1H, d, $J = 5.1$ Hz), 8.54 (1H, d, $J = 8.1$ Hz), 9.03 (1H, d, $J = 8.8$ Hz), 9.17 (1H, d, $J = 5.1$ Hz); ^{13}C NMR ($CDCl_3$) 14.41, 56.04, 61.26, 101.01, 110.92, 114.02, 115.15, 118.02, 120.21, 120.81, 124.61, 124.84, 125.10, 126.14, 130.49, 133.28, 135.40, 140.49, 148.17, 150.96, 162.11; IR ($CHCl_3$) 1700, 1507, 1428 cm^{-1}; EIMS *m*/*z* (relative intensity) 344 (56), 343 (100), 342 (72), 315 (14), 314 (17), 242 (10), 241

(15). Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.26; H, 4.65; N, 8.14. Found: C, 73.01; H, 4.29; N, 7.98.

4-Methoxypyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine-1-carboxylate, Sodium Salt (15). A suspension of ester **14** (17 mg, 0.049 mmol) in 2 M NaOH (0.12 mL), and MeOH (2 mL) was refluxed for 2 h. CH_2Cl_2 (20 mL) was added, and the mixture was filtered to yield the expected salt as a yellow solid: mp > 260 °C (14 mg, 91% yield); ^{1}H NMR (DMSO-d_6) 3.31 (3H, s), 7.19 (1H, s), 7.53 (1H, dd, J = 7, 8.1 Hz), 7.65 (1H, s), 7.73 (1H, dd, J = 7, 8.8 Hz), 8.34 (1H, d, J = 5.1 Hz), 8.72 (1H, d, J = 8.1 Hz), 8.98 (1H, d, J = 5.1 Hz), 9.41 (1H, d, J = 8.8 Hz); ^{13}C NMR (DMSO-d_6) 56.09, 103.55, 108.42, 110.51, 113.99, 115.66, 120.45, 120.95, 121.44, 123.73, 125.20, 130.33, 132.36, 135.84, 138.06, 139.45, 146.27, 149.62, 164.79; IR (KBr) 1582, 1502, 1435 cm^{-1}. Anal. Calcd for $C_{19}H_{11}N_2O_3Na$, (0.75 CH_2Cl_2), C, 58.99; H, 3.11; N, 6.97. Found: C, 59.02; H, 3.48; N, 7.24.

4-Methoxypyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine: Arnoamine B (2). A suspension of sodium salt **15** (5 mg, 0.015 mmol) and copper chromite (5 mg) in quinoline (0.5 mL) was heated at 200 °C for 1 h. Water (3 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to give quantitatively the expected alkaloid **2** as a yellow solid: mp 180 °C; ^{1}H NMR ($CDCl_3$) 4.20 (3H, s), 7.16 (1H, d, J = 2.9 Hz), 7.49 (1H, dd, J = 7.0, 7.3 Hz), 7.55 (s, 1H), 7.74 (1H, dd, J = 7.3, 8.0 Hz), 8.00 (1H, d, J = 8.0 Hz), 8.04 (1H, d, J = 4.8 Hz), 8.12 (1H, d, J = 2.9 Hz), 8.48 (1H, d, J = 7.0 Hz), 9.13 (1H, d, J = 4.8 Hz); ^{1}H NMR ($CDCl_3$ + TFA) 4.27 (3H, s), 7.59 (1H, d, J = 3.3 Hz), 7.83 (1H, dd, J = 8.1, 7.3 Hz), 8.14 (1H, dd, J = 7.3, 8.4 Hz), 8.16 (1H, s), 8.35 (1H, d, J = 8.4 Hz), 8.51 (1H, d, J = 6 Hz), 8.57 (1H, d, J = 3.3 Hz), 8.78 (1H, d, J = 8.1 Hz), 9.05 (bd, 1H); ^{13}C NMR ($CDCl_3$) 56.34, 102.52, 107.33, 110.79, 114.16, 115.24, 116.79, 117.11, 120.31, 121.75, 124.06, 125.75, 131.09, 132.85, 134.85, 138.96, 147.43, 150.53; IR (film) 1610, 1471, 1359 cm^{-1}; EIMS m/z (relative intensity) 272 (55), 271 (100), 270 (34), 242 (77), 229 (38). Anal. Calcd for $C_{18}H_{12}N_2O$ (1.25 CH_2Cl_2): C, 61.07; H, 3.83; N, 7.40. Found: C, 61.33; H, 3.70; N, 7.74.

4-Hydroxypyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine: Arnoamine A (1). To arnoamine B (**2**) (10 mg, 0.037 mmol) was added a solution of BBr_3 (1 M/CH_2Cl_2, 2 mL) under a dry nitrogen atmosphere. After 24 h, aqueous solution of $NaHCO_3$ (1 M, 5 mL) was added and extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography gave **1** as a yellow solid: mp 176 °C (3 mg, 0.012 mmol, 30%); ^{1}H NMR ($CDCl_3$) 7.21 (1H, d, J = 3 Hz), 7.52 (1H, ddd, J = 8.4, 7.0, 1.5 Hz), 7.72 (1H, s), 7.78 (1H, ddd, J = 8.4, 7.0, 1.5 Hz), 8.06 (1H, d, J = 5.1 Hz), 8.08 (1H, dd, J = 8.4, 1.5 Hz), 8.19 (1H, d, J = 3.0 Hz), 8.54 (1H, dd, J = 8.4, 1.5 Hz), 9.01 (1H, d, 5 Hz); ^{1}H NMR ($CDCl_3$ + TFA) 7.59 (1H, d, J = 3.3 Hz), 7.83 (1H, dd, J = 8.1, 7.0 Hz), 8.15 (1H, dd, J = 8.4, 7.0 Hz), 8.31 (1H, s), 8.36 (1H, d, J = 8.4 Hz), 8.42 (1H, d, J = 6.6 Hz), 8.57 (1H, d, J = 3.3 Hz), 8.75 (1H, d, J = 8.1 Hz), 8.93 (1H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 103.98, 108.01, 110.77, 113.04, 115.25, 115.65, 117.32, 119.12, 121.12, 123.93, 126.06, 126.1, 126.7, 130.86, 131.37, 146.44, 148.44; IR ($CHCl_3$) 1611, 1509, 1472, 1446, 1263 cm^{-1}; EIMS m/z (relative intensity) 258 (94), 229 (30), 202 (3). Anal. Calcd for $C_{17}H_{10}N_2O$ (0.5 CH_2Cl_2): C, 69.90; H, 3.66; N, 9.31. Found: C, 69.77; H, 3.84; N, 9.13.

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