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SYNTHESIS OF ARNOAMINE B

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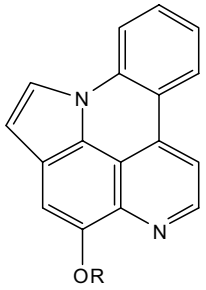
Abstract – The synthesis of arnoamine B (**2**), which inhibits the catalytic activity of topoisomerase II and exhibits selective cytotoxicity against human tumor cell lines, was achieved in six steps from 5-methoxy-6-nitroindole (**3**) in 33 % overall yield.

Over the last decade, a series of structurally interesting and biologically active fused polycyclic aromatic alkaloids containing a pyrido[2,3,4-*kl*]acridine subunit has been isolated from marine sources.[1] The pyridoacridine system is of interest, as the skeleton contains an indole ring.[2]



1 R = H
2 R =Me

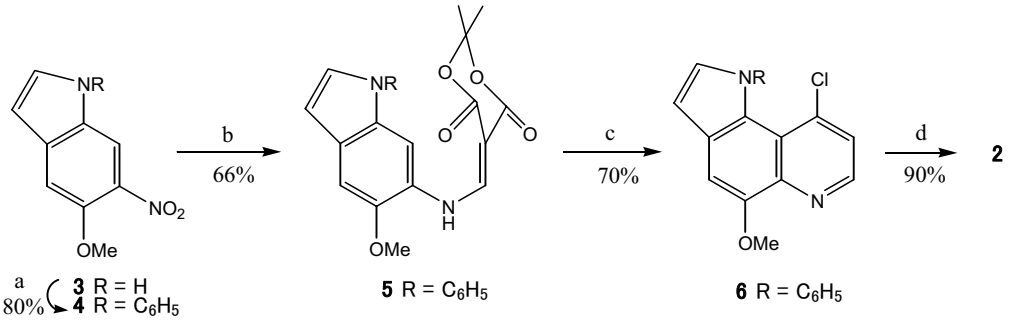
Arnoamine A (**1**) and B (**2**),[2a] which have relatively simple structures, were obtained in 1998 from the brownish-purple ascidian *Cystodytes* sp., collected near Arno Atoll in the Republic of the Marshall Islands. The structures of **1** and **2** were proposed on the basis of spectroscopic data, particularly those obtained from HMBC and NOE NMR experiments.

In 2000, the first synthesis of arnoamines A (**1**) and B (**2**) was accomplished by Delfourne and co-workers using thermolysis of arylaminomethylene Meldrum's acid derivative, biaryl cross coupling reaction, and the Fisher indole synthesis. Starting from commercially available 2-methoxy-5-nitroaniline, arnoamine B (**2**) was obtained in 12 steps with a 5% overall yield.[3] In 2006, Radchenko and co-workers reported a simple and effective approach to the synthesis of the pyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine skeleton of the arnoamines starting from a known indole.[4] In 2007, we reported the synthesis of arnoamine B (**2**) from 4-bromo-8-methoxy-6-methyl-5-nitroquinoline in four steps *via* biaryl cross coupling reaction. The indole moiety of **2** was introduced by the Leimgruber-Batcho indole synthesis.[5] The yield of the pyrrole ring was low, and the overall yield was 12% from 4-bromo-8-methoxy-6-methyl-5-nitroquinoline.

In this study we report a simple and convenient synthesis of arnoamine B (**2**) using *N*-arylation, thermolysis of arylaminomethylene Meldrum's acid derivative and intramolecular radical cyclization.

N-Arylation of 5-methyl-6-nitroindole (**3**)[6] with iodobenzene in toluene gave the 5-methyl-6-nitro-1-phenylindole (**4**) in 80% yield.[7] Enamine (**5**) was prepared by catalytic hydrogenation of **4** over 10% Pd-C in methanol, followed by reaction with Meldrum's acid in trimethyl orthoformate in 66% yield.[8] *N*-Phenylpyrrolo[2,3-*f*]quinoline (**6**) was prepared in 68% yield by cyclization of **5** *via* unstable

aminoketene in refluxing diphenyl ether for 20 min, followed by reaction with phosphorus oxychloride at 75 °C for 3.5 h. Compound **6** was also prepared in 70% yield under microwave irradiation[9] of **5** at 45 °C for 20 min. In the reaction with phosphorus oxybromide, monobromoquinoline was not prepared but tribromoquinoline[10] was obtained under microwave irradiation. Finally, intramolecular radical cyclization[11] of **6** with tri-*n*-butyltin hydride (30 equiv) and azobisisobutyronitrile (AIBN: 15 equiv) in toluene at 115 °C for 2.5 h afforded arnoamine B (**2**) in 90% yield, but the reaction did not go to completion with tri-*n*-butyltin hydride (4 equiv) and AIBN (2 equiv). The spectroscopic data of synthetic **2** matched those of authentic samples in all respects.



a) C_6H_5I, CuI, $(CH_2NHMe)_2$, K_3PO_4, toluene, 115℃, 48 h b) i Pd-C, H_2, MeOH, 1h ii Meldrum's acid, $HC(OMe_3)_3$, 100℃, 2 h
c) i $(C_6H_5)_2O$, reflux, 20 min ii $POCl_3$, MW, 45℃, 20 min d) AIBN, Bu_3SnH, toluene, 115℃, 2.5 h

In summary, arnoamine B (**2**) was synthesized in six steps from a known compound in 33% overall yield. Microwave irradiation was useful at the chlorination step.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra at 270 MHz were measured in $CDCl_3$ with tetramethylsilane as an internal standard. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column chromatography (flash chromatography) was performed with silica gel 60 (Merck, 230-400 mesh).

5-Methoxy-6-nitro-1-phenylindole (4). To a solution of 5-methoxy-6-nitroindole (**3**) (231 mg, 1.2 mmol) in toluene (2.2 mL) were added iodobenzene (612 mg, 3 mmol), capper (I) iodide (28.5 mg, 15 mol %), *N,N'*-dimethylethylenediamine (52.8 mg, 60 mol %), and K_3PO_4 (679 mg, 3.2 mmol) and were heated at 115 ℃ in sealed tube for 2 days. The reaction mixture was cooled and diluted with $CHCl_3$ (5 mL), and filtered through a plug of silica gel, eluting with EtOAc (20 mL). The filtrate was concentrated. The residue was chromatographed (eluting with hexane-EtOAc 5 : 1) to afford **4** (257 mg, 80%). mp 107-108 ℃ (light yellow needles from $CHCl_3$-hexane). HRMS Calcd for $C_{15}H_{12}N_2O_5$: 268.0848, Found: 268.0854. Ms *m/z* (%): 268(M^+, 100), 253(9), 221(15), 192(30), 191(28). IR(KBr) cm^{-1}: 1594, 1504, 1469, 1266, 1162.

^{1}H-NMR ($CDCl_3$) δ : 3.99(3H, s), 6.65(1H, dd, *J*=3.3, 0.7 Hz), 7.25(1H, s), 7.38-7.46(3H, m,), 7.50-7.57(3H, m), 8.11(1H, d, *J*=0.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 57.02, 103.42, 104.06, 109.22, 124.26, 127.46, 129.04, 130.01, 133.37, 136.55, 138.56, 148.28.

5-[(5-Methoxy-1-phenylindol-6-ylamino)methylene]-2,2-dimethyl-4,6-dione-1,3-dioxane (5).

5-Methoxy-6-nitro-1-phenylindole (**4**) (616 mg, 2.3 mmol) in MeOH (100 mL) was hydrogenated for 1 h using 10% Pd-C (330 mg) as a catalyst under H_2 atomsphere. The catalyst was filtered off and the solvent was removed. A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (346 mg, 2.4 mmol) in methyl orthoformate (5 mL) was refluxed for 2 h and the crude aminoindole was immediately added. The mixture was stirred at 100 ℃ for another 2 h. After the reaction mixture was cooled, the precipitated crystals were collected by filtration and recrystallized from $CHCl_3$-hexane to give **5** (596 mg, 66%) as yellow needles. mp 216-217 ℃. HRMS Calcd for $C_{22}H_{20}N_2O_5$: 392.1372, Found: 392.1368. Ms *m/z* (%): 392(M^+, 23), 290(22), 275(11), 259(100). IR(KBr) cm^{-1}: 1719, 1673, 1612, 1449, 1318, 1279. ^{1}H-NMR ($CDCl_3$) δ : 1.74(6H, s), 4.00(3H, s), 6.62(1H, dd, *J*=3.3, 0.7 Hz), 7.20(1H, s), 7.33(1H, d, *J*=3.3 Hz), 7.40-7.47(4H, m,), 7.54-7.61(2H, m), 8.59(1H, d, *J*=14.5 Hz), 11.77(1H,br d, *J*=14.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 26.97, 56.43, 86.72, 97.77, 102.46, 103.24, 104.83, 124.06, 124.53, 127.26, 127.51, 129.63, 130.08, 130.60, 139.16, 145.23, 150.62, 164.11, 165.37.

9-Chloro-5-methoxy-1-phenylpyrrolo[2,3-*f*]quinoline (6).

Method A) A mixture of **5** (346 mg, 0.8 mmol) and diphenyl ether (5 mL) was refluxed for 20 min. The reaction mixture was cooled and diluted with hexane (45 mL). The precipitated crystals were collected by filtration, washed with hexane (3 x 5 mL). A mixture of the crude pyrroloquinolone and $POCl_3$ (1.5 mL) was stirred at 75 ℃ for 3.5 h, poured into cold water (10 mL) and adjusted to pH 7 with saturated aqueous $NaHCO_3$ solution. The precipitated crystals were collected by filtration and chromatographed (eluting with hexane-EtOAc 5 : 1) to afford **6** (168 mg, 68%). mp 115.5-116.5 ℃ (yellow crystals from Et_2O-hexane). HRMS Calcd for $C_{18}H_{13}N_2ClO$: 308.0716, Found: 308.0717. Ms *m/z* (%): 310(M^++2, 34), 308(M^+, 100), 279(15), 271(38), 243(13). IR(KBr) cm^{-1}: 1601, 1499, 1460, 1390, 1274, 1240, 1193, 761. ^{1}H-NMR ($CDCl_3$) δ : 4.15(3H, s), 6.80(1H, d, *J*=3.3 Hz), 7.18-7.23(2H, m,), 7.26-7.42(6H, m), 8.69(1H, d, *J*=4.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 56.26, 102.68, 105.79, 118.10, 122.39, 122.52, 122.82, 126.24, 128.88, 129.60, 133.33, 137.47, 141.08, 144.69, 145.52, 150.82.

Method B) A mixture of **5** (157 mg, 0.4 mmol) and diphenyl ether (3 mL) was refluxed for 20 min. The reaction mixture was cooled and diluted with hexane (25 mL). The precipitated crystals were collected by filtration, washed with hexane (3 x 3 mL). A mixture of the crude pyrroloquinolone and $POCl_3$ (1.5 mL) was heated at 45 ℃ for 20 min in a sealed tube of microwave reactor, poured into cold water (10 mL) and adjusted to pH 7 with saturated aqueous $NaHCO_3$ solution. The precipitated crystals were collected by filtration and chromatographed (eluting with hexane- EtOAc 5 : 1) to afford **6** (86 mg, 70%).

Arnoamine B (**2**) 9-Chloro-5-methoxy-1-phenylpyrrolo[2,3-*f*]quinoline (**6**) (30.9 mg, 0.1 mmol) was

dissolved in deoxygenated toluene (3 mL), heated at 115 ℃ and tri-*n*-butyltin hydride (873 mg, 3 mmol) and AIBN (246 mg, 1.5 mmol) added in five portions over 2.5 h under N_2 with stirring. The resulting brown solution was cooled and chromatographed (eluting with EtOAc) to afford **2** (24.5 mg, 90%) mp 236-237 ℃ (yellow prisms from $CHCl_3$-hexane) HRMS Calcd for $C_{18}H_{12}N_2O$: 272.0949, Found: 272.0943. Ms *m/z* (%): 272(M^+, 100), 271(84), 257(10), 243(27), 242(31), 229(8). IR(KBr) cm^{-1}: 1610, 1474, 1389, 1361, 1284. ^{1}H-NMR ($CDCl_3$) δ : 4.20(3H, s), 7.10(1H, d, *J*=3.0 Hz), 7.43(1H, ddd, *J*=8.3, 7.3, 1.0 Hz), 7.51(1H, s), 7.68(1H, ddd, *J*=8.3, 7.3, 1.3 Hz), 7.91(1H, dd, *J*=8.0, 1.0 Hz), 7.96(1H, d, *J*=5.0 Hz), 8.04(1H, d, *J*=3.0 Hz), 8.40(1H, dd, *J*=8.3, 1.3 Hz), 9.09(1H, d, *J*=5.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 56.30, 102.41, 107.21, 110.67, 113.98, 115.08, 116.68, 116.96, 120.09, 121.51, 123.92, 125.57, 130.93, 132.56, 134.68, 138.81, 147.35, 150.35.

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10. Tribromoquinoline: mp 178-179 ℃ (light red needles from $CHCl_3$-hexane); HRMS Calcd for $C_{18}H_{11}N_2Br_3O$: 507.8421, Found: 507.8420. Ms *m/z* (%): 514(M^++6, 20), 512(M^++4, 62), 510(M^++2, 62), 508(M^+, 21), 431(59), 429(100), 427(47), 401(20), 322(16). ^{1}H-NMR ($CDCl_3$) δ : 4.19(3H, s), 7.11-7.21(2H, m,), 7.22(1H, s), 7.34-7.45(3H, m), 7.54(1H, d, *J*=4.6 Hz), 8.58(1H, d, *J*=4.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 56.53, 99.66, 100.31, 118.94, 119.25, 125.36, 126.74, 126.79, 127.26, 127.84, 128.14, 129.00, 141.20, 142.61, 146.04, 152.08.
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