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Synthesis of Pantherinine, a Cytotoxic Fused Tetracyclic Aromatic Alkaloid

Shinsuke Nakahara, Junya Matsui, and Akinori Kubo*

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

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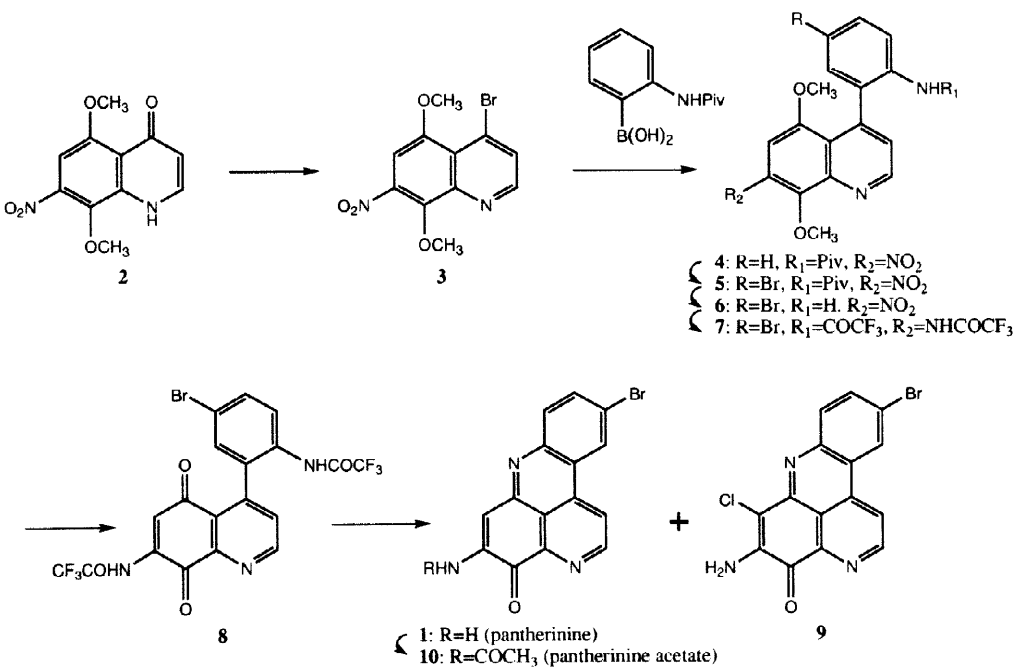
Abstract : A cytotoxic fused tetracyclic aromatic alkaloid, pantherinine (**1**) from the ascidian *aplidium pantherinum*, was synthesized using biaryl cross-coupling reaction.

During the last decade a series of structurally fascinating and biologically active fused polycyclic aromatic alkaloids have been isolated from marine sources.[1] In 1993, Schmitz and his colleagues reported the isolation and structural determination of a new tetracyclic aromatic alkaloid, pantherinine (**1**).[2] We report the first total synthesis of **1** using biaryl cross-coupling reaction.[3]

Treatment of the 5,8-dimethoxy-7-nitro-4-quinolone (**2**)[3c] with $POBr_3$ under reflux for 15 min afforded the 4-bromoquinoline (**3**) in 84 % yield. Suzuki reaction[4] between **3** and 2-pivaloyl(amino)benzeneboronic acid in benzene containing Na_2CO_3 and catalytic amounts of tetrakis(triphenylphosphine)palladium under reflux for 48 h gave the 4-phenylquinoline (**4**)[5] in 86% yield. Selective bromination of **4** with bromine in CH_2Cl_2 at 15°C for 10 min gave **5** in 97% yield.



Hydrolysis of **5** in 20% aqueous H_2SO_4 solution under reflux for 1 h gave amino compound (**6**) in 87% yield. Reduction of **6** with $Na_2S_2O_4$ in aqueous THF at 25°C for 30 min followed by trifluoroacetylation with $(CF_3CO)_2O$ in THF containing K_2CO_3 at 15°C for 15 min afforded the trifluoroacetate (**7**) in 38% yield. Direct oxidative demethylation of **7** with ceric ammonium nitrate (CAN) in aqueous CH_3CN at 0°C for 15 min,

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afforded the quinone (**8**) in 45% yield.

Finally, hydrolysis of **8** in 10% HCl-MeOH at 25°C for 5 days gave pantherinine (**1**)[6] and 10-chloropantherinine (**9**) in 33% and 58% yields, respectively. Acetylation of **1** with CH_3COCl in pyridine at 25°C for 10 min afforded the pantherinine acetate (**10**)[7] in 60% yield.

The spectroscopic data (IR, ^1H- and ^{13}C-NMR) of pantherinine (**1**) and pantherinine acetate (**10**) thus obtained match those of authentic samples in all respects.

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5. **4**: mp 140-142°C (yellow needles from hexane-$CHCl_3$). MS m/z (%): 409(M^+, 100), 379 (86), 246 (64), 57 (61). Anal. Calcd $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.50; H, 5.72; N, 10.23. ^1H-NMR ($CDCl_3$) δ: 0.81 (9H, s, *t*-Bu) , 3.54 (3H, s, C_5-OCH_3) , 4.29 (3H, s, C_8-OCH_3) , 6.70 (1H, br, NH) , 7.14 (1H, s, C_6-H) , 7.18 (1H, dd, *J*=6.92, 1.65 Hz, C_6'-H) , 7.23 (1H, t, *J*=6.92 Hz, C_5'-H) 7.41 (1H, dd, *J*=4.29, 0.66 Hz, C_3-H) , 7.44 (1H, td, *J*=6.92, 1.65 Hz, C_4'-H) , 8.03 (1H, d, *J*=6.92 Hz, C_3'-H) , 9.11 (1H, d, *J*=4.29 Hz, C_2-H).
6. **1**: mp >300°C (purple powder from $CHCl_3$). MS m/z (%): 327(M^++2, 99), 325 (M^+, 100), 300 (73), 298 (75). HRMS Calcd $C_{15}H_8Br_{81}N_3O$: 326.9830. Found: 326.9824. Calcd $C_{15}H_8Br_{79}N_3O$: 324.9851. Found: 324.9849. ^1H-NMR (500 MHz, DMSO-d_6) δ: 6.57, 8.30 (2H,br, s, NH_2), 6.58 (1H, s, C_{10}-H), 7.87 (1H, d, *J*=8.85 Hz, C_1-H), 7.94 (1H, dd, *J*=8.85, 1.83 Hz, C_2-H), 8.97 (1H, d, *J*=5.19 Hz, C_5-H), 8.97 (1H, d, *J*=1.83 Hz, C_4-H), 9.17 (1H, d, *J*=5.19 Hz, C_6-H) . ^{13}C-NMR (DMSO-d_6) δ: 105.7 (C_{10}), 115.7, 119.7, 121.1(C_5), 121.9, 126.5 (C_4), 131.1(C_1), 134.3(C_2), 135.3, 145.4, 145.6, 146.5, 149.8 (C_6), 153.2 (C_9), 179.4.
7. **10**: mp >300°C (red glass from CH_3OH). MS m/z (%): 369(M^++2, 38), 367 (M^+, 39), 327 (100), 325 (97), 300 (56), 298 (59). HRMS Calcd $C_{17}H_{10}Br_{81}N_3O_2$: 368.9935. Found: 368.9924. Calcd $C_{17}H_{10}Br_{79}N_3O_2$: 366.9956. Found: 366.9961. ^1H-NMR ($CDCl_3$) δ: 3.49 (3H, s, N-Ac), 7.98 (1H, dd, *J*=8.58, 1.98 Hz, C_2-H), 8.12 (1H, d, *J*=8.58 Hz, C_1-H), 8.50 (1H, br, NH), 8.54 (1H, d, *J*=5.61 Hz, C_5-H), 8.66 (1H, d, *J*=1.98 Hz, C_4-H), 8.81 (1H, s, C_{10}-H), 9.29 (1H, d, *J*=5.61 Hz, C_6-H) . ^{13}C-NMR ($CDCl_3$) δ: 25.03 (-CO<u>C</u>H_3), 116.66 (C_{10b}), 120.45 (C_5), 122.04 (C_{10}), 122.56 (C_3), 123.41 (C_{4a}), 125.88 (C_4), 132.93 (C_1), 135.24 (C_2), 136.00 (C_{4b}), 137.06 (C_{10a}), 145.33 (C_{7a}), 145.45 (C_{11a}), 150.51 (C_6), 151.62 (C_9), 169.31 (-<u>C</u>OCH_3), 178.79 (C_8).