HETEROCYCLES, Vol. 60, No. 9, 2003, pp. 2017 - 2018
Received, 17th June, 2003, Accepted, 1st August, 2003, Published online, 18th August, 2003

TOTAL SYNTHESIS OF STYELSAMINE C, A CYTOTOXIC FUSED TETRACYCLIC AROMATIC ALKALOID

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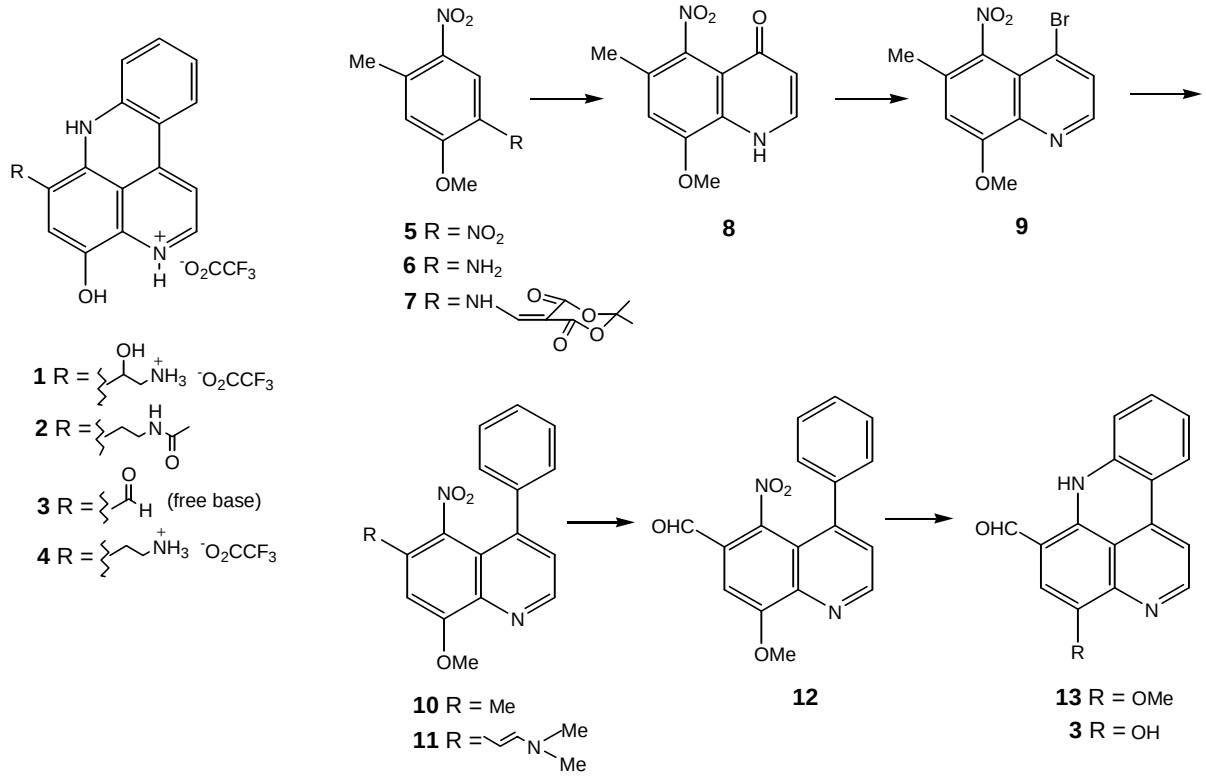
Abstract - A cytotoxic fused tetracyclic aromatic alkaloid, styelsamine C (**3**) from the ascidian *Eusynstyela latericius*, was synthesized utilizing biaryl cross-coupling reaction.

A series of structurally fascinating and biologically active fused polycyclic aromatic alkaloids containing pyrido[2,3,4-*kl*]acridine subunit have been isolated from marine sources during the last twenty years.[1] Styelsamines A~D (**1**)~(**4**) , structurally the most simple compound in the group and mild cytotoxicity toward the human colon tumor cell line HCT-116, was obtained in 1998 from the marine ascidian *Eusynstyela latericius.*[2] Previously we have achieved the synthesis of pantherinine, pyridoacridine ring system alkaloid.[3] We report herein the first total synthesis of **3** utilizing biaryl cross-coupling reaction.[4]



Selective transfer hydrogenation of 5-methoxy-2,4-dinitrotoluene (**5**) [5] with 10% Pd-C catalyst and cyclohexene in EtOH at 90°C for 15 min gave 4-amino compound (**6**) and 2-amino-4-nitro compound in 60% and 7% yield, respectively. **6** was treated with 5-methoxymethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione[6] under reflux for 2 h to give the enaminone (**7**) in 94% yield. The cyclization of **7** in refluxing diphenyl ether for 15 min afforded the 4-quinolinone (**8**) *via* unstable aminoketene in 83% yield. Treatment of **8** with $POBr_3$ at 70°C for 1.5 h afforded the 4-bromoquinoline (**9**) in 78% yield. Suzuki reaction between **9** and phenylboronic acid in EtOH/toluene containing K_2CO_3 and catalytic amounts of tetrakis(triphenylphosphine) palladium (0) at 95 °C for 3 h gave the 4-phenylquinoline (**10**) in 94% yield. Treatment of **10** and *N,N*-dimethylformamide at 170°C for 4 d afforded the aminoalkene (**11**) in 91% yield. Oxidation[7] of **11** was accomplished with $NaIO_4$ in THF/H_2O at room temperature for 2 h to provide the aldehyde (**12**) in 90% yield. The intramoleculer nitrene insertion reaction[8] of **12** with $(EtO)_3P$ at 180°C for 2 h gave the tetracyclic compound (**13**) in 65% yield. Finally, demethylation of **13** with BBr_3 in CH_2Cl_2 at room temperature for 2 h furnished styelsamine C (**3**)[9] in 86% yield. The spectral data of **3** obtained in the same solvent condition were identical with those of the natural product.[2] The synthesis of styelsamines A, B and D is currently in progress.

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9 Styelsamine C (**3**): orange solid, mp 270-272°C($CHCl_3$). HRFABMS(glycerol, MH^+) calcd for $C_{16}H_{11}N_2O_2$ 263.0821, found 263.0826. MS(FAB, glycerol) m/z(%) 263(100, MH^+). IR(KBr) ν_{max} 3296, 1648, 1620, 1514, 1248 cm^{-1}. NMR: δ_H (500 MHz, DMSO-d_6) 7.26(m, 1H), 7.34(s, 1H), 7.58(m, 2H), 7.91(d, 1H, J = 5.2 Hz), 8.30(d, 1H, J = 8.2 Hz), 8.81(d, 1H, J = 5.2 Hz), 9.91(s, 1H), 12.02(br s); δ_C (125 MHz, DMSO-d_6) 108.25, 109.32, 113.09; 116.77, 117.71, 117.78, 122.94, 124.27, 132.46, 134.79, 137.06, 140.42, 143.14, 143.92, 152.16, 191.76.