

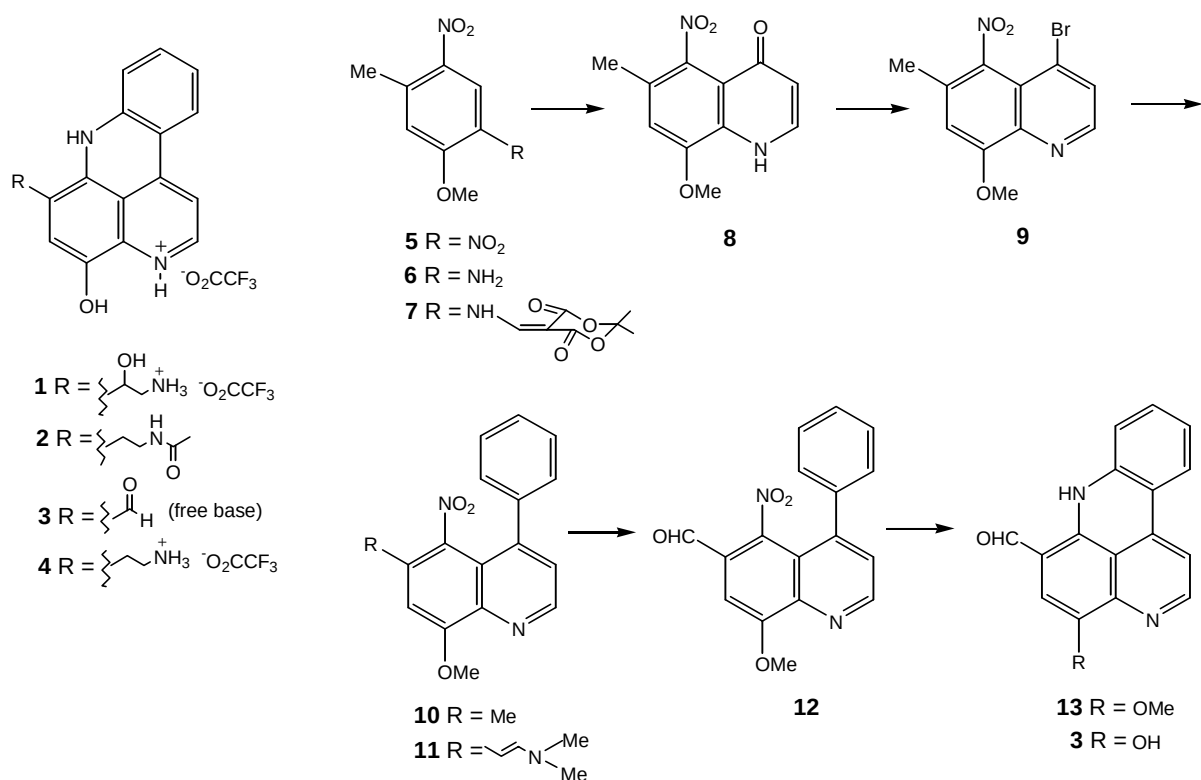
TOTAL SYNTHESIS OF STYELSAMINE C, A CYTOTOXIC FUSED TETRACYCLIC AROMATIC ALKALOID

Shinsuke Nakahara* and Akinori Kubo

Meiji Pharmaceutical University
2-552-1, Noshio, Kiyose, Tokyo 204-8588, Japan

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-*k*]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-dione⁶ 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 POBr₃ 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 K₂CO₃ 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. Oxidation⁷ of **11** was accomplished with NaIO₄ in THF/H₂O at room temperature for 2 h to provide the aldehyde (**12**) in 90% yield. The intramolecular nitrene insertion reaction⁸ of **12** with (EtO)₃P at 180°C for 2 h gave the tetracyclic compound (**13**) in 65% yield. Finally, demethylation of **13** with BBr₃ in CH₂Cl₂ 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.

REFERENCES AND NOTES

- (a) T. Ozturk, "The Alkaloid", Vol. 49, ed. by G. A. Cordell, Academic Press Inc., New York, **1997**, pp. 79-220. (b) D. Skyler and C. H. Heathcock, *J. Nat. Prod.*, 2002, **65**, 1573.
- B. R. Copp, J. Jompa, A. Tahir, and C. M. Ireland, *J. Org. Chem.*, 1998, **63**, 8024.
- S. Nakahara, J. Matsui, and A. Kubo, *Tetrahedron Lett.*, 1998, **39**, 5521.
- N. Miyaoura and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.
- S. S. Gitis and V. I. Trunov-Krasovskii, *Zhur. Obshchet. Khim.*, 1959, **29**, 2648.
- R. Cassis, R. Tapia, and J. A. Valderrama, *Synth. Commun.*, 1985, **15**, 125.
- E. C. Riesgo, X. Jin, and R. P. Thummel, *J. Org. Chem.*, 1996, **61**, 3017.
- R. J. Sundberg, B. P. Dass, and R. H. Smith, Jr., *J. Amer. Chem. Soc.*, 1969, **91**, 658.
- Styelsamine C (**3**): orange solid, mp 270-272°C(CHCl₃). HRFABMS(glycerol, MH⁺) calcd for C₁₆H₁₁N₂O₂ 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.