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TOTAL SYNTHESIS OF STYELSAMINE C, AND FORMAL SYNTHESIS OF NORSEGOLINE

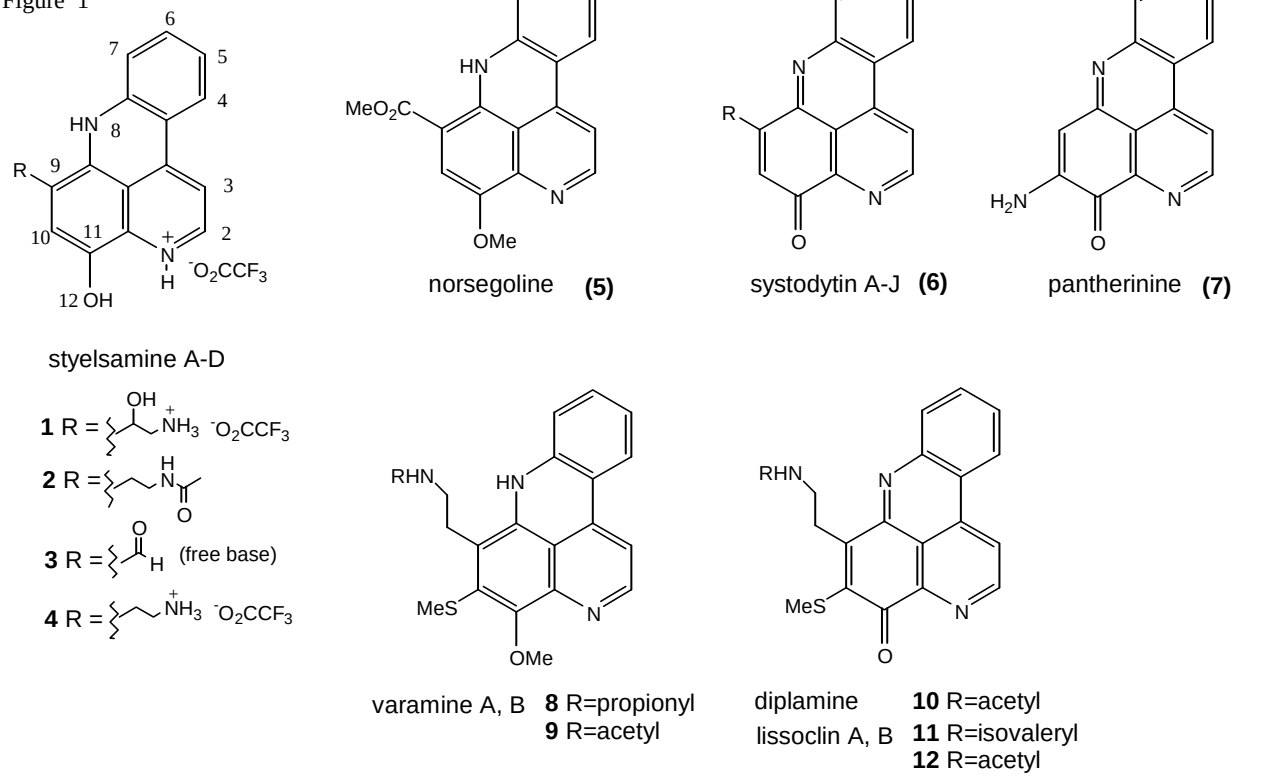
Shinsuke Nakahara* and Akinori Kubo

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

Abstract - Two fused tetracyclic aromatic alkaloids, styelsamine C (**3**) from the ascidian *Eusynstyela latericius*, and norsegoline (**5**) from the marine tunicate *Eudistoma* sp., were synthesized using a biaryl cross-coupling reaction.

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]

Figure 1



Systodytin A~J (**6**), isolated from *Cystodytes* dellechiaje,[2] pantherinine (**7**), isolated from the ascidian *Aplidium pantherinum*,[3] diplamine (**10**), isolated from *Diplosoma* sp.,[4] and lissoclin A, B (**11**, **12**) isolated from ascidian *Lissoclinum* sp.[5] contained an iminoquinolinequinone skeleton. Pantherinine (**7**) contains amino group and bromine, while alkaloid (**10**~**12**) and varamines A, B (**8**, **9**) isolated from the tunicate *Lissoclinum vareau*[6] contain a methylthioether group. Styelsamines A~D (**1**)~(**4**), which exhibit

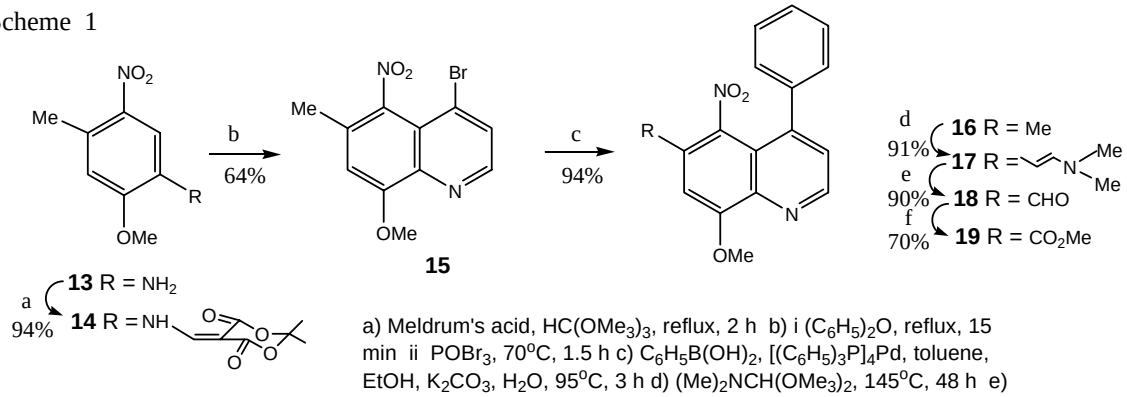
mild cytotoxicity toward the human colon tumor cell line HCT-116, were obtained from the marine ascidian *Eusynstyela latericius*;[7] the structures were confirmed by MS spectrometry and NMR spectral data. Norsegoline (**5**) was obtained from a marine tunicate *Eudistoma* sp.[8] and its structure was confirmed on the basis of spectroscopic data.

Styelsamine C (**3**) and norsegoline (**5**) are the simplest compounds of the group and are important as precursors in the synthesis of a variety of complex marine alkaloids.

Previously we reported the first synthesis of pantherinine (**7**)[9] and norsegoline (**5**)[10] utilizing a biaryl cross-coupling reaction.[11] Here, we report the synthetic detail of **3**[12] and formal synthesis of **5**.

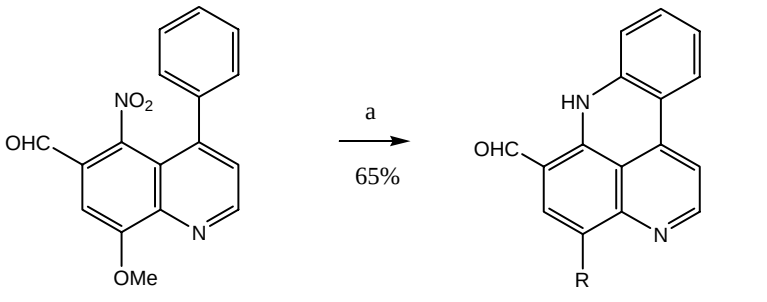
The bromoquinoline (**15**) was obtained from 2-methoxy-4-methyl-5-nitroaniline (**13**) *via* thermolysis of arylaminomethylene Meldrum's acid derivative (**14**).

Scheme 1



Nitroaniline (**13**) was treated with 5-methoxymethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione[13] under reflux for 2 h to give the enaminone (**14**) in 94% yield. Cyclization of **14** in refluxing diphenyl ether for 15 min followed by bromination with $POBr_3$ at 70℃ for 1.5 h afforded the 4-bromoquinoline (**15**) in 64% yield. Palladium(0)-catalyzed cross coupling reaction of **15** with phenylboronic acid gave the 4-phenylquinoline (**16**) in excellent yield. The 6-methyl group of **16** can be functionalized by condensation with *N,N*-dimethylformamide dimethyl acetal to provide the corresponding aminoalkene (**17**) in 91% yield and oxidation of **17** was accomplished with sodium periodate in 50% aqueous THF to provide the *o*-nitro aldehyde (**18**) in 90% yield.[14] Oxidation of **18** with potassium permanganate in 50% aqueous acetone followed by *O*-methylation with excess diazomethane in ether for 4 h, afforded the ester (**19**) in 70% yield. The synthesis of norsegoline (**5**) from **19** has been reported.[10]

Scheme 2



The intramolecular nitrene insertion reaction[15] of **18** with triethyl phosphite under reflux for 2 h gave the tetracyclic compound (**20**) in 65% yield. Finally, demethylation of **20** with BBr_3 in CH_2Cl_2 at room temperature furnished styelsamine C (**3**) in 86% yield. The spectroscopic data of synthetic **3** and **19** matched those of the authentic samples in all respects.

In summary, two fused tetracyclic aromatic alkaloids, styelsamine C (**3**) and norsegoline (**5**), were synthesized *via* three key reactions, thermolysis of arylaminomethylene Meldrum's acid derivative, biaryl cross coupling of a 4-bromoquinoline with phenylboronic acid, and pyridoacridine ring formation by intramolecular nitrene insertion.

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-[[(2'-Methoxy-4'-methyl-5'-nitrophenyl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (14). A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (4.18 g, 29 mmol) in methyl orthoformate (38 mL) was refluxed for 2 h, and 2-methoxy-4-methyl-5-nitroaniline (**13**) (4.39 g, 24 mmol) was immediately added. The mixture was refluxed for another 2 h. After the reaction mixture was cooled, the precipitated crystals were collected by filtration and recrystallized from $CHCl_3$-MeOH to give **14** (7.59 g, 94%) as yellow powder. mp 229-230°C. *Anal.* Calcd for $C_{15}H_{16}N_2O_7$: C, 53.57 ; H, 4.80 ; N, 8.33. Found: C, 53.31 ; H, 4.83 ; N, 8.03. IR(KBr) cm^{-1}: 1726, 1684, 1616, 1580, 1442, 1278, 1226, 1202. ^{1}H-NMR ($CDCl_3$) δ: 1.76(6H, s), 2.69(3H, s), 4.07(3H, s), 6.87(1H, s), 8.14(1H, s), 8.68(1H, d, *J*=14.2 Hz), 11.48(1H, br d, *J*=14.2 Hz). Ms *m/z* (%): 336(M^+, 48), 278(100), 175(50).

4-Bromo-8-methoxy-6-methyl-5-nitroquinoline (15). A mixture of **14** (336 mg, 1 mmol) and diphenyl ether (13 mL) was refluxed for 15 min. The reaction mixture was cooled, and diluted with hexane (18 mL). The precipitated crystals were collected by filtration, and washed with hexane (3 x 5 mL). A mixture of crude crystals and $POBr_3$ (1.4 g) was stirred at 70°C for 1.5 h, poured onto ice (3 g), diluted with water (7 mL), adjusted to pH 7 with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 7 mL). The extract was washed with brine, dried, and concentrated. The residue was chromatographed (eluting with hexane-ethyl acetate 1 : 1) to afford **15**(190 mg, 64%). mp 149-150°C (yellow crystals from $CHCl_3$-hexane). *Anal.* Calcd for $C_{11}H_9N_2O_3Br$: C, 44.47 ; H, 3.05 ; N, 9.43. Found: C, 44.60 ; H, 3.14 ; N, 9.25. IR(KBr) cm^{-1}: 1524, 1492, 1352. ^{1}H-NMR ($CDCl_3$) δ: 2.49(3H, s), 4.13(3H, s), 6.92(1H, s), 7.84(1H, d, *J*=4.6 Hz), 8.65(1H, d, *J*=4.6 Hz). Ms *m/z* (%): 298(M^++2, 18), 296(M^+, 18), 217(90), 187(100).

8-Methoxy-6-methyl-5-nitro-4-phenylquinoline (16). 2 M Aqueous K_2CO_3 (1 mL, 2 mmol) was added to a mixture of **15** (297 mg, 1 mmol) and phenylboronic acid (146 mg, 1.2 mmol) in toluene (10 mL) and EtOH (0.52 mL) under argon. Tetrakis(triphenylphosphine)palladium(0)(35 mg, 0.03 mmol) was added to the vigorously stirred two-phase mixture, and the resulting mixture was refluxed for 3 h.

The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 15 mL). The extract was washed with brine, dried, and concentrated. The residue was chromatographed (eluting with hexane-ethyl acetate 1 : 2) to afford **16**(279 mg, 94%). mp 140-141℃ (light yellow prisms from $CHCl_3$-hexane). HRMS Calcd for $C_{17}H_{14}N_2O_3$: 294.1005, Found: 294.1002. Ms *m/z* (%): 294(M^+, 66), 248(100), 218(40), 204(28). IR(KBr) cm^{-1}: 1502, 1464, 1342, 1240, 1114. ^{1}H-NMR（$CDCl_3$）δ: 2.46(3H, s), 4.17 (3H, s), 6.90 (1H, s), 7.27-7.33(2H, m), 7.36-7.46(4H, m), 8.96(1H, d, *J*=4.3 Hz).

8-Methoxy-6-[β-*trans*-(*N*,*N*-dimethylamino)ethenyl]-5-nitro-4-phenylquinoline (17). A solution of **16** (177 mg, 0.6 mmol) and N,N-dimethylformamide dimethyl acetal (3 mL) containing triethylamine (1 drop) was heated at 145℃ in sealed tube for 48 h. The solvent was evaporated, and the residue was chromatographed (eluting with ethyl acetate) to afford **17**(190 mg, 91%) mp 219-220℃ (red needles from $CHCl_3$-hexane). HRMS Calcd for $C_{20}H_{19}N_3O_3$: 349.1426, Found: 349.1424. Ms *m/z* (%): 349(M^+, 16), 332(100), 247(42), 218(46). IR(KBr) cm^{-1}: 1632, 1604, 1498, 1390, 1298, 1242, 1118. ^{1}H-NMR（$CDCl_3$）δ: 2.87(3H, s), 4.14(3H, s), 5.31(1H, d, *J*=13.2 Hz), 6.97 (1H, s), 7.02(1H, d, *J*=13.2 Hz), 7.28-7.54(4H, m), 7.63-7.71(2H, m), 8.76(1H, d, *J*=4.3 Hz).

8-Methoxy-5-nitro-4-phenyl-6-quinolinecarbaldehyde (18). A solution of **17** (349 mg, 1 mmol) and sodium periodate (642 mg, 3 mmol) was stirred in 50% aqueous THF (15 mL) at rt for 1 h. The reaction mixture was poured into cold water (50 mL) and the precipitated crystals were collected by filtration, and recrystallized from $CHCl_3$-hexane to give **18**(277 mg, 90%) as light yellow prisms. mp 201-202℃. HRMS Calcd for $C_{17}H_{12}N_2O_4$: 308.0797, Found: 308.0802. Ms *m/z* (%): 308(M^+, 22), 262(100), 232(35), 204(35). IR(KBr) cm^{-1}: 1688, 1492, 1378, 1346, 1118. ^{1}H-NMR（$CDCl_3$）δ: 4.25(3H, s), 7.32-7.35(2H, m), 7.41-7.51(3H, m), 7.53(1H, s), 7.55(1H, d, *J*=4.3 Hz), 9.12(1H, d, *J*=4.3 Hz), 10.01(1H, s).

Methyl 8-methoxy-5-nitro-4-phenylquinoline-6-carboxylate (19). A solution of **18**(62 mg, 0.2 mmol) and potassium permanganate (44 mg, 0.28 mmol) was stirred in 50% aqueous acetone (8 mL) at rt for 3 h. The solution was concentrated under reduced pressure, and MeOH (6 mL) was added to the residue. The insoluble materials were filtered off, and the filtrate was added to an ether solution containing excess of CH_2N_2. The mixture was kept at rt for 4 h, then the water (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 x 20 mL). The extract was washed with brine, dried, and concentrated. The residue was recrystallized from $CHCl_3$-hexane to give (**19**)(48 mg, 70%) as colorless crystals. mp 156.5-157.5℃. HRMS Calcd for $C_{18}H_{14}N_2O_5$: 338.0903, Found: 338.0904. Ms *m/z* (%): 338(M^+, 19), 292(100), 232(36), 204(26). IR(KBr) cm^{-1}: 1726, 1548, 1374, 1260, 1232. ^{1}H-NMR（$CDCl_3$）δ: 3.86(3H, s), 4.22(3H, s), 7.22-7.50(6H, m), 7.45(1H, d, *J*=4.3 Hz), 9.06(1H, d, *J*=4.3 Hz).

12-Methylstyelsamine C (20). A solution of **18**(31 mg, 0.1 mmol) in triethyl phosphite (1 mL) was refluxed for 2 h, and evaporated. The residue was chromatographed (eluting with ethyl acetate) to afford **20**(18 mg, 65%). mp 225-226℃ (orange needles from $CHCl_3$-hexane). HRMS Calcd for $C_{17}H_{12}N_2O_2$: 276.0899, Found: 276.0905. Ms *m/z* (%): 276(M^+, 100), 261(48), 247(21), 233(14), 203(15). IR(KBr) cm^{-1}: 3272, 1642, 1618, 1598. ^{1}H-NMR（$CDCl_3$）δ: 4.08(3H, s), 7.10(1H, s), 7.22-7.28(2H, m), 7.54(1H, t, *J*=8.6 Hz), 7.64(1H, d, *J*=4.9 Hz), 8.07(1H, d, *J*=8.6 Hz), 8.91(1H, d, *J*=4.9 Hz), 9.83(1H, s), 12.44(1H, br s).

Styelsamine C (3). To 12-methylstyelsamine (**20**)(31 mg, 0.1 mmol) was added a solution of BBr_3 (1

M/CH_2Cl_2, 1 mL) under a dry nitrogen atmosphere. The solution was stirred at rt for 21 h, then poured into 1 M aqueous $NaHCO_3$ (10 mL), and extracted with $CHCl_3$ (3 x 5 mL). The extract was washed with brine, dried, and concentrated. The residue was recrystallized from $CHCl_3$ to give styelsamine (**3**) (6.8 mg, 86%) as orange solid. mp 270-272℃. 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)cm^{-1}: 3296, 1648, 1620, 1514, 1248. ^{1}H- NMR (500 MHz, DMSO-d_6) δ: 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); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 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.

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