Synthesis of Norsegoline

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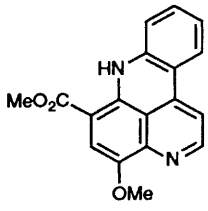
Intramolecular insertion of the nitrene derived from methyl 5-azido-8-methoxy-4-phenylquinoline-6-carboxylate into the 4-phenyl substituent gave the pyridoacridine alkaloid norsegoline **1** in good yield.

More than thirty marine alkaloids that contain a common pyrido[2,3,4-*kl*]acridine subunit have been isolated during the last ten years.[1] Most show interesting and potentially useful biological activity but few have been synthesised.[2–6] Norsegoline **1**, structurally the most simple compound in the



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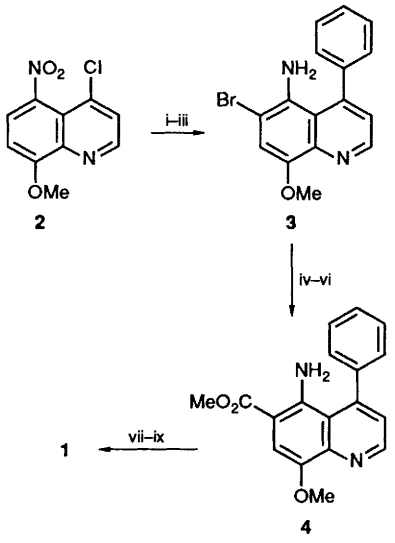
group, was obtained in 1988 from the marine tunicate *Eudistoma sp.*[7] It is an important synthetic target within this class of alkaloids as in principle it can serve as precursor to a variety of the more complex marine alkaloids, in particular the cystodytins, the varamines and diplamine. We recently described[8] a short and flexible new route to the pyrido[2,3,4-*kl*]acridine subunit central to these alkaloids based on two key reactions, *viz.* Suzuki cross-coupling of a 4-chloroquinoline with an arylboronic acid and pyridoacridine ring formation by intramolecular nitrene insertion. We now report the adaptation and application of this approach for the first synthesis of norsegoline (Scheme 1).

Palladium-catalysed cross-coupling of 4-chloro-8-methoxy-5-nitroquinoline **2** with phenylboronic acid gave 8-methoxy-5-nitro-4-phenylquinoline in almost quantitative yield.[9] Reduction of the 5-nitro group with iron–acetic acid–ethanol and bromination of the derived 5-aminoquinoline proceeded in excellent yield to give 6-bromo-8-methoxy-4-phenylquinoline-5-amine **3**. Cyanation of compound **3** proved unexpectedly difficult. All attempts to apply palladium-catalysed cyanation procedures were unsuccessful, and use of copper(I) cyanide in DMF or NMP (1-methylpyrrolidin-2-one) led to low and variable yields (5–25%) of the desired quinoline-6-carbonitrile together with much tar formation. DMPU [1,3-dimethyl-3,4,-5,6-tetrahydropyrimidin-2(1*H*)-one] was poorly effective as a solvent for cyanation, but recourse to HMPA (hexamethylphosphoramide) resulted in smooth reaction and formation of 5-amino-8-methoxy-4-phenylquinoline-6-carbonitrile in 65% yield. Hydrolysis of the nitrile to the carboxylic acid was straightforward, but conversion of the latter to the methyl ester **4** was troublesome. Standard procedures for the esterification of anthranilic acids, such as thionyl chloride–methanol, gave moderate yields at best (*ca.* 40%), but diazomethane was effective (75%). Conversion of **4** into norsegoline **1**, by contrast, was trouble free: diazotisation of the 5-amino group in **4** followed by conversion into the azide and thermolysis of the latter in xylene gave norsegoline **1** in 58% overall yield from **4**. The spectroscopic data for the synthetic



Scheme 1 *Reagents and conditions:* i, $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, EtOH, benzene, reflux, 95%; ii, Fe, AcOH, EtOH, reflux, 92%; iii, Br_2, AcOH, $CHCl_3$, 0 °C, 96%; iv, CuCN, HMPA, 140–150 °C, N_2, 65%; v, KOH, H_2O, EtOH, reflux, N_2, 89%; vi, CH_2N_2, ether, 75%; vii, $NaNO_2$, H_2O, HCl; viii, NaN_3; ix, xylene, reflux, N_2, 58% overall for steps vii–ix

material were in excellent agreement with those reported for the natural product.[7]

Experimental

Conversion of Methyl 5-Amino-8-methoxy-4-phenylquinoline-6-carboxylate **4** *into Norsegoline* **1**.—A mixture of the 5-aminoquinoline **4** (50 mg, 0.16 mmol) in water (2 cm^3) containing conc. hydrochloric acid (5–6 drops) was stirred at room temp. until all of the solid had dissolved, and then the solution was cooled in an ice bath. A solution of sodium nitrite (12 mg, 0.17 mmol) in water (0.1 cm^3) was added dropwise during 15 min and the mixture was stirred at 0 °C for a further 45 min. A solution of sodium azide (13 mg, 0.2 mmol) in water (0.1 cm^3) was then added to the vigorously stirred solution and stirring was continued for 40 min. The pH of the mixture was then adjusted to 9 by addition of satd. sodium hydrogen carbonate solution and the resulting mixture was extracted with dichloromethane (5 × 50 cm^3). The combined organic extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$) and filtered, and the filtrate was evaporated under reduced pressure to give the crude azide [$\nu_{max}(CDCl_3)/cm^{-1}$ 2110] which was not purified.

De-gassed xylene (30 cm^3) was added to the crude azidoquinoline and the solution was heated under reflux in a nitrogen atmosphere for 2 h. The xylene was then removed by distillation under reduced pressure and the residue was

chromatographed on silica using ethyl acetate as eluent. This gave 29 mg (58%) of norsegoline **1** as an orange–red powder, m.p. 187 °C; δ_H(400 MHz; $CDCl_3$) 3.95 (3 H, s), 4.01 (3 H, s), 7.02 (1 H, dd, *J* 8.3, 0.9), 7.09 (1 H, dt, *J* 8.1, 7.3, 1.1), 7.38 (1 H, s), 7.40 (1 H, ddd, *J* 7.7, 7.2, 1.5), 7.46 (1 H, d, *J* 5.1), 7.90 (1 H, br d, *J* 7.7), 8.77 (1 H, d, *J* 5.1) and 11.48 (1 H, br s, D_2O exch.); δ_C(100 MHz; $CDCl_3$) 51.73, 55.89, 97.98, 107.72, 108.99, 116.37, 116.77, 118.86, 121.97, 123.56, 131.92, 137.11, 137.48, 140.18, 144.81, 145.23, 152.11 and 168.62.

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