# A Short New Route to the Pyrido[2,3,4-*kl*]acridine Subunit Common to Pyridoacridine Alkaloids of Marine Origin

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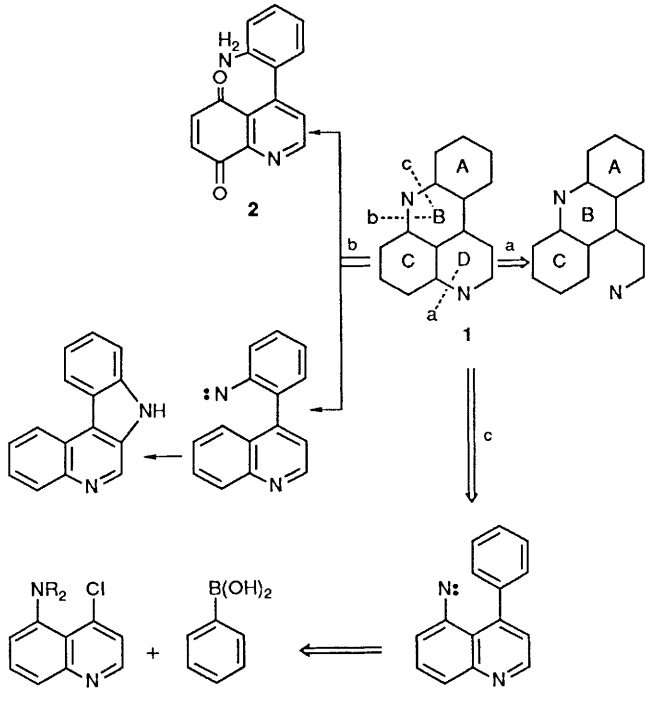
A short new route to the pyrido[2,3,4-*kl*]acridine ring system has been developed from readily available quinoline precursors involving two key steps: (*i*) a palladium(0)-catalysed Suzuki cross-coupling reaction of 4-chloroquinolines with arylboronic acids, and (*ii*) an intramolecular nitrene insertion reaction of the nitrenes derived from 4-phenyl-5-azidoquinolines.

During the last ten years a wide range of polycyclic alkaloids that contain a common pyrido[2,3,4-*kl*]acridine subunit have been isolated from marine sources, and many of them show interesting biological activity ranging from antineoplastic and antibacterial activity to topoisomerase inactivation.[1] Few of the natural products have been synthesised so far,[2–6] and examination of published work reveals that two general approaches have been used for construction of the key pyrido[2,3,4-*kl*]acridine system **1**. These are summarised in Scheme 1.

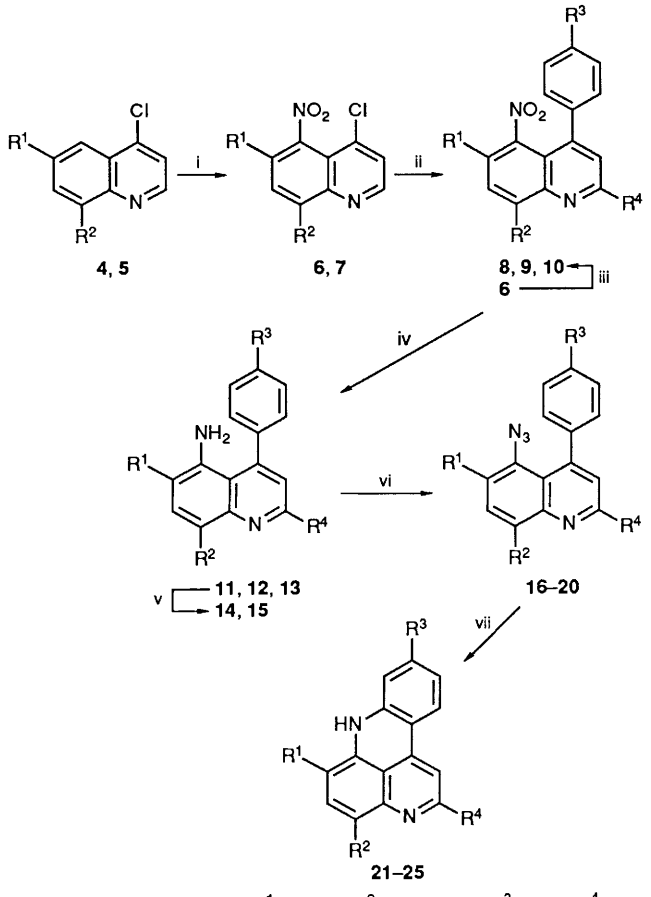
In the acridine approach (ABC → ABCD, disconnection a, Scheme 1) regioselective formation of the D ring proved to be problematic,[7] while in the two possible approaches contained within disconnection b success has largely been restricted to cyclocondensations of quinoline quinones of type **2**.[4] Attempts to construct the B ring through nitrene insertion into the quinoline 5-position (disconnection b) were unsuccessful, and led instead to carbolines **3**.[5,8] We have explored the alternative nitrene insertion route outlined in disconnection c and now report the successful application of this approach for the preparation of a number of pyrido[2,3,4-*kl*]acridine derivatives suitably functionalised for marine alkaloid synthesis.

The chloroquinolines **4** and **5** were readily accessible in bulk and in 62–69% overall yield in three and four steps, respectively, from *o*-anisidine and 2-nitro-4-methoxyaniline (condensation with Meldrum's acid and trimethyl orthoformate followed by cyclisation to 4-quinolones,[9] then treatment with $POCl_3$–$PCl_5$; for **5**: reductive acetylation).† Nitration of both **4** and **5** with mixed acid gave excellent yields (82–86%) of the 5-nitro derivatives **6** and **7** (Scheme 2), which could easily be separated from minor amounts of the isomeric 7-nitro compounds. We have recently described in detail the results of an extensive investigation of the palladium(0)-catalysed Suzuki cross-coupling reactions of a wide range of chloroazines with arylboronic acids,[10] and application of this chemistry to **6** and **7** gave the 4-arylquinolines **8–10** in 80–96% yield. Reduction of the nitro groups in compounds **8–10**




Scheme 1

† Satisfactory microanalytical and/or spectroscopic data were obtained for all new compounds.




| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **4, 6** | H | OMe | – | – |
| **5, 7** | OMe | NHCOMe | – | – |
| **8, 11, 16, 21** | H | OMe | H | H |
| **9, 12, 17, 22** | OMe | NHCOMe | H | H |
| **10, 13, 18, 23** | H | OMe | OMe | H |
| **14, 19, 24** | Br | OMe | H | H |
| **15, 20, 25** | OMe | H | H | OH |

**Scheme 2** *Reagents and conditions*: i, $HNO_3$–$H_2SO_4$, 4–25 °C, 4–5 h; ii, $PhB(OH)_2$–$Pd(Ph_3P)_4$–$Na_2CO_3$–benzene–ethanol, reflux, 36–48 h; iii, *p*-$MeOC_6H_4B(OH)_2$–$Pd(Ph_3P)_4$–$Na_2CO_3$–benzene–ethanol, reflux 48 h; iv, Fe–AcOH–ethanol–$N_2$ atmosphere, reflux, 4–6 h; v $Br_2$–AcOH–$CHCl_3$, 0 °C, 1 h; vi, $NaNO_2$–$H_2SO_4$, 0–5 °C, 1 h, $NaN_3$, 0 °C, 1 h, room temp. 30 min; vii, xylene, reflux, 1.5–2 h

(85–96%) was straightforward using iron/acetic acid and ethanol, and bromination of 5-amino-8-methoxy-4-phenylquinoline **11** gave the 6-bromo derivative **14**. The final 5-aminoquinoline derivative reported here, compound **15**, was prepared from *o*-anisidine by a different, classical route.

The viability of the key nitrene insertion reaction was then investigated with each of the five different 5-aminoquinoline derivatives **11–15**.‡ High yield conversion into the azides **16–20** was unexceptional, and heating of each of these in refluxing xylene led to smooth decomposition and formation of the pyrido[2,3,4-*kl*]acridines **21–25** in 57–90% yield. The products were obtained as deeply coloured, high-melting solids, which are poorly soluble in common organic solvents and which are characteristically intense red in acid media.

The simple route to the tetracycles **21–25** outlined in Scheme 2 is particularly attractive in that it is flexible with respect to the selective incorporation of substituent groups into either ring A, ring C or ring D of the pyridoacridine system. It should, thus, prove valuable not only for the preparation of representative marine alkaloids based on the pyridoacridine subunit, but also for the synthesis of analogues for biological evaluation. Work is currently in progress in these areas.

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‡ Attempts to convert the nitroquinoline **8** directly into the pyridoacridine **21** by treatment with triethyl phosphite were unsuccessful, and led only to formation of the 5-phosphoramidate in 60% yield.