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Efficient synthesis of the pyrido[2,3,4-*kl*]acridin-4-one system common to several cytotoxic marine alkaloids

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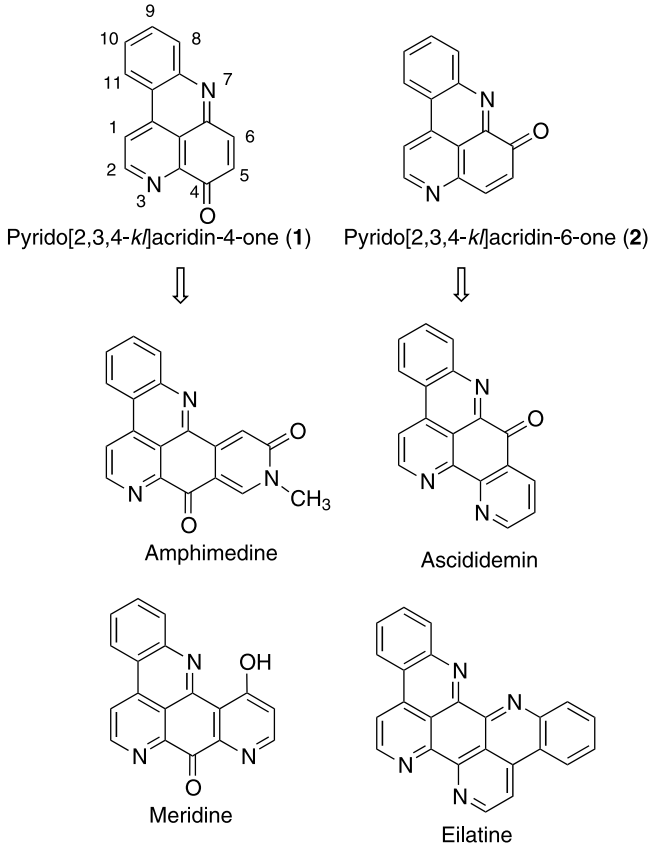
Abstract—An efficient, four-step synthesis of the pyrido[2,3,4-*kl*]acridin-4-one system is described, using a Suzuki coupling of a 4-iodoquinoline and a oxidative demethylation of a dimethoxyquinoline containing an anilino unit with cobalt trifluoride as the key steps.

Marine organisms are an increasingly important source of bioactive natural products. Starting in 1983, a wide range of polycyclic aromatic alkaloids have been isolated from marine sources.[1] Most of them can be grouped into three categories, namely derivatives of the pyrido[2,3,4-*kl*]acridine system with an additional ring fused at the 5–6 bond, at the 4–5 bond or at both. As a consequence, most of these compounds can be considered as derivatives of the structures **1** or **2**. For instance, amphimedine[2] and meridine,[3] among others,[4] contain a common pyrido[2,3,4-*kl*]acridin-4-one substructure **1**, while ascididemin[5] and eilatine,[6] among others,[7] have a pyrido[2,3,4-*kl*]acridin-6-one moiety **2** or related substructures.

Most of these 'sea alkaloids' show interesting biological properties, including very potent antitumour activities,[8] but their study is hampered by the difficulties found in isolating sufficient material from their natural sources. This fact, together with the need to obtain analogs in order to establish structure–activity relationships, has prompted extensive synthetic work in the field.[9] Regarding the parent structures, compound **2** has been recently prepared in eight steps from commercially available starting materials, as an intermediate in the synthesis of a regioisomer of ascididemin.[10] On the other hand, only one synthesis of the unsubstituted parent system **1** has been published, to our knowledge. It was based on the intramolecular condensation of a suitable 4-acetyl-5-formyl-benzonaphthyrydine derivative, which was constructed from 2-chloro-3-iodopyridine in a four-step route involving two palladium-catalyzed cross coupling reactions, but, unfortunately, the final oxidation–cyclization step of the synthesis proceeded in only 11% yield.[11]



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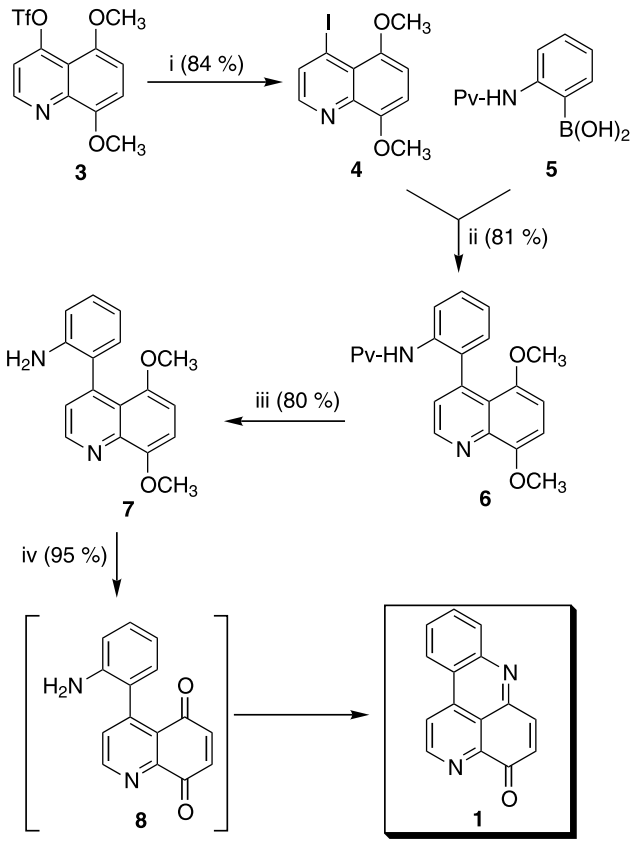
One possible route to compound **1** could be based on the creation of the 11a–11b bond using a palladium-catalyzed cross coupling reaction. Previous attempts at the preparation of derivatives of **1** using a Stille coupling of the 6-vinyl derivative of triflate **3** as the key step had to be abandoned due to poor yields in the cross-coupling step,[9b] and for this reason we decided to examine the use of the less studied Suzuki reaction of 4-halogenoquinolines as an alternative.

As shown in Scheme 1, iodide **4** was prepared by treatment of triflate **3**, available in three steps and 67% overall yield from commercially available starting materials,[12] with potassium iodide under solvent-free conditions, since all attempts to prepare **4** in solution from **3** or from the corresponding bromide were unsuccessful. Compound **4** gave smoothly the desired Suzuki coupling with boronic acid **5**[13] in the presence of $(Ph_3P)_4Pd$ and potassium carbonate, and afforded compound **6** in 81% yield.[14] Attempted oxidative demethylation of **6** with cerium ammonium nitrate in aqueous acetonitrile gave an intractable mixture, a result that was attributed to competing oxidation of the aniline ring. Instead of replacing the pivaloyl group by the more electron-withdrawing trifluoroacetyl unit, as proposed by other authors in a related situation,[12] we decided at this point to attempt the search for a milder oxidant. Hydrolysis of the pivaloyl group afforded amine **7** in 80% yield and, after some experimentation with other reagents, we found that cobalt trifluoride in dioxane[15] was suitable for our purposes, since, gratifyingly, it led to the transformation of compound **7** into the non-isolated intermediate aminoquinone **8** which cyclized[16] to the target compound **1**[17] in 95% combined yield.



Scheme 1. *Reagents and conditions*: (i) KI, 80°C, 2.5 days; (ii) K_2CO_3, EtOH–H_2O, $(Ph_3P)_4Pd$ deoxygenated toluene, reflux, 24 h; (iii) 3 M HCl in 1:1 water–dioxane, reflux, 18 h; (iv) CoF_3, water, dioxane, rt, 1 h.

In conclusion, we have achieved a simple and efficient synthesis of pyrido[2,3,4-*kl*]acridin-4-one, the parent system of a family of marine alkaloids with potent cytotoxic activity, which proceeds in 52% overall yield from a known 4-quinolyl triflate. This synthesis highlights the use of a Suzuki coupling of a 4-iodoquinoline for the construction of the 11a–11b bond of the pyridoacridine system and demonstrates the usefulness of cobalt trifluoride in the oxidative demethylation of substrates containing anilino subunits, a transformation that has previously proved troublesome using alternative, better known methods.

Acknowledgements

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14. Iodide **4** (200 mg, 0.63 mmol) and boronic acid **5**[13] (140 mg, 0.63 mmol) were dissolved in toluene (6 mL), previously degassed by means of an argon stream (15 min). A solution of potassium carbonate (176 mg, 1.26 mmol) in water (0.6 mL) and ethanol (0.6 mL) was added, and the solution was stirred at room temperature for 30 min, under an argon atmosphere. Solid $(Ph_3P)_4Pd$ (22 mg, 0.017 mmol) was added, and the reacting mixture was refluxed for 24 h. After cooling, the suspension was filtered and the solid was washed with toluene (3×5 mL). The combined toluene layers were evaporated and the residue was chromatographed on silica gel, eluting with 2:1 petroleum ether–ethyl acetate, to give 150 mg (81%) of compound **6**. IR (NaCl): 3443 (NH), 1684 (C=O); 1262 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.95 (d, 1H, $J=4.3$ Hz, H-2); 8.10 (d, 1H, $J=8.1$ Hz, H-3′); 7.35 (td, 1H, $J=8.1$ and 2.9 Hz, H-4′); 7.23 (d, 1H, $J=4.3$ Hz, H-3); 7.17–7.10 (m, 2H, H-5′,6′); 6.99 (d, 1H, $J=8.6$ Hz, H-7); 6.85 (br. s, 1H, NH); 6.74 (d, 1H, $J=8.6$ Hz, H-6); 4.04 (s, 3H, C_8-OCH_3); 3.39 (s, 3H, C_5-OCH_3); 0.72 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.1 (C=O); 150.1 (C-8); 149.6 (C-5); 149.5 (C-2); 143.3 (C-4); 141.2 (C-8a); 135.2 (C-2′); 133.7 (C-1′); 128.3 (C-4′); 127.9 (C-6′); 124.5 (C-5′); 123.7 (C-2′); 120.8 (C-3); 107.6 (C-7); 106.4 (C-6); 119.7 (C-4a); 56.2 and 56.1 (2 OCH_3); 39.4 ($C(CH_3)_3$); 27.2 ($C(CH_3)_3$). Anal. calcd for $C_{22}H_{24}N_2O_3$, M = 364.3: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.25, H, 6.74; N, 7.44.
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17. To a solution of compound **7** (40 mg, 0.18 mmol) in dioxane (0.6 mL) was added cobalt trifluoride (83 mg, 0.71 mmol, 4 equiv.) and water (30 μL). The mixture was vigorously stirred for 1 h at room temperature and diluted with water (3 mL), which was extracted with ethyl acetate (4×5 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated. The residue was washed with ethyl ether and chromatographed on silica gel, eluting with ethyl acetate, to yield 40 mg (95%) of compound **1**, as yellow crystals. Mp 276°C (dec.), lit.[11a] 278°C (dec.). IR and ^1H NMR data were identical to those described in Ref. 11a. ^{13}C NMR (63 MHz, $CDCl_3$) δ 183.5 (C-4); 161,2 (C-6a); 151.3 (C-4a); 150.7 (C-7a); 150.2 (C-2); 142.5 (C-6); 137.1 (C-12b); 134.1 (C-5); 131.8 (C-9); 131.6 (C-8); 129.7 (C-11); 121.7 (C-11a); 122.9 (C-12); 119.5 (C-11); 117.9 (C-11c) ppm.