

[C0020]

Synthesis of the pyrido[2,3,4-*kl*]acridine ring system common to several cytotoxic marine alkaloids

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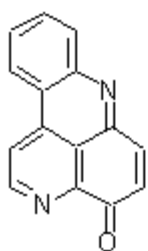
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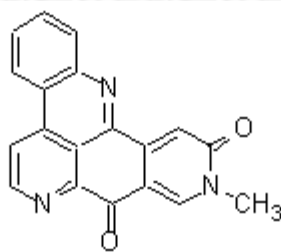
Received: 7 August 2000 / Uploaded: 10 August

Abstract. - An efficient five-step synthesis of the pyrido[2,3,4-*kl*]acridin-8-one system is described, using a Suzuki coupling of a 4-iodoquinoline and a oxidative demethylation with cobalt trifluoride as the key steps.

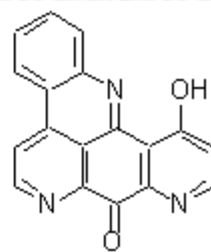
Marine organisms are an increasingly important source of bioactive natural products. During the last 15 years, a wide range of polycyclic aromatic alkaloids [1] that contain a common pyrido[2,3,4-*kl*]acridine substructure **1** (e.g. the cystoditins [2], amphimedine [3], meridine [4] and eilatine [5]) have been isolated. Many of them show interesting biological properties, including antitumour activity, 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 [6,7,8]. However, to our knowledge, an efficient synthesis of the unsubstituted parent system **1** has not yet been published.



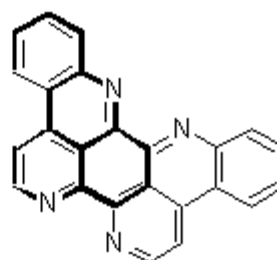
Pyrido[2,3,4-*kl*]acridine (**1**)



Amphimedine

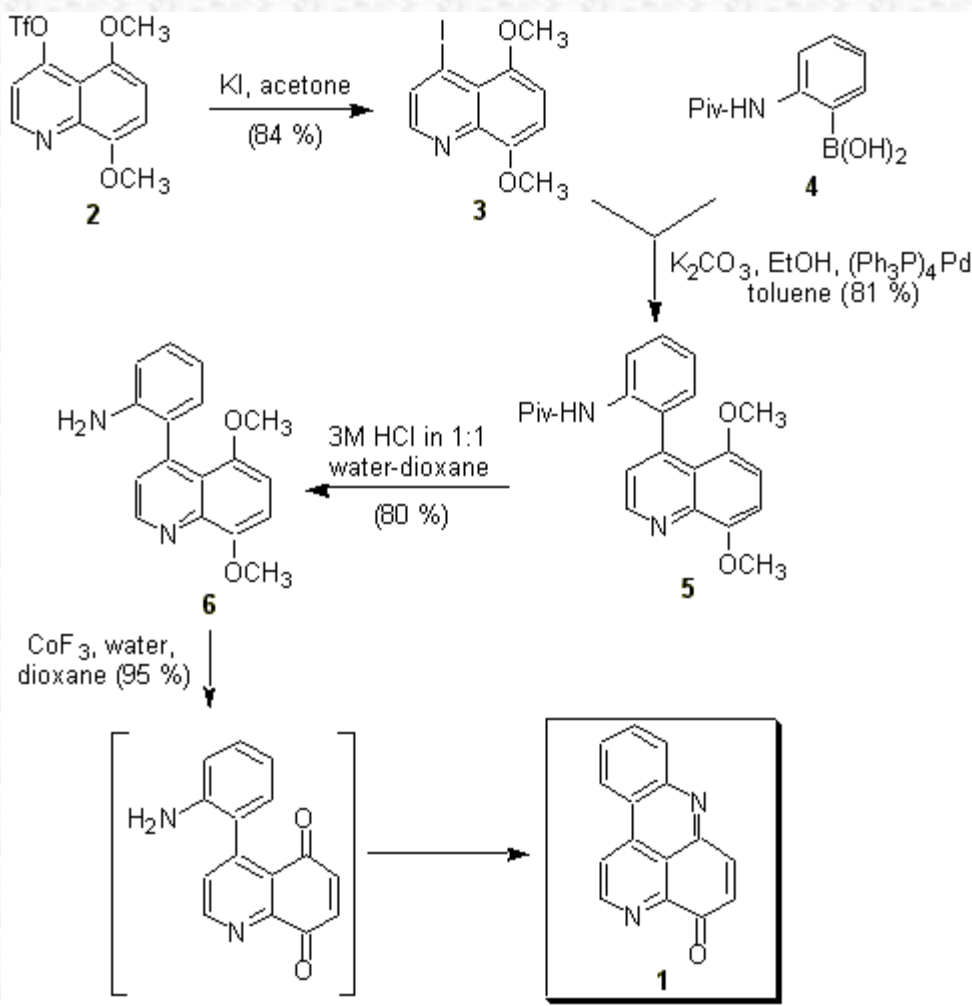


Meridine



Eilatine

Our route to **1** is summarized in Scheme 1. Iodide **3**, obtained from the known [9] triflate **2**, gave smoothly the key Suzuki coupling with boronic acid **4** [10] and afforded compound **5** in 81% yield (a synthetic intermediate of amphimedine similar to **5** has been previously prepared using a Stille coupling of **2** [9]). Attempted oxidative demethylation of **5** with cerium ammonium nitrate in aqueous acetonitrile gave an intractable mixture. Rather than attempting an exchange of the protective group [9], we decided to hydrolyze the pivaloyl group, obtaining amine **6**. This compound was transformed into the target **1** under mild conditions and in 95% yield by treatment with cobalt trifluoride in dioxane [11].



Scheme 1

Application of this chemistry to the preparation of compounds related to the cystodytins and meridine is currently in progress.

Acknowledgements

Financial support from CICYT (grant PTR-95-0230) is gratefully acknowledged.

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