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Bioinspired Syntheses of the Pyridoacridine Marine Alkaloids Demethyldeoxyamphimedine, Deoxyamphimedine, and Amphimedine

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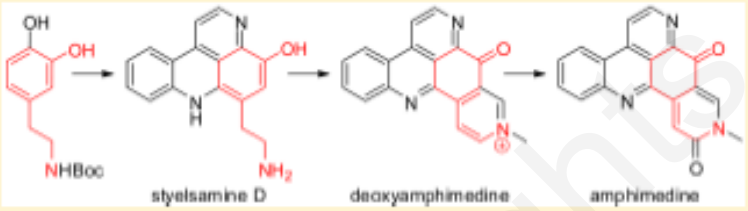
Supporting Information



ABSTRACT: Efficient bioinspired syntheses of the biologically active pyridoacridine marine alkaloids demethyldeoxyamphimedine, deoxyamphimedine, and amphimedine are reported. Reaction of styelsamine D, prepared via an optimized route starting from Boc-dopamine, with paraformaldehyde afforded demethyldeoxyamphimedine and deoxyamphimedine. Oxidation of the latter using either $K_3[Fe(CN)_6]$ or DMSO/conc. HCl gave amphimedine in 8 steps from tryptamine with an overall yield of 14%. The versatility of the method was demonstrated by the synthesis of non-natural ethyl and benzyl congeners of deoxyamphimedine and amphimedine.

Amphimedine (**1**), reported in 1983 from an *Amphimedon* sp. sponge, was the first example of a natural product bearing a new alkaloid skeleton.[1] Related dopamine-based pyridoacridines, encapsulating the 11*H*-pyrido[4,3,2-*mn*]-acridine skeleton, now number greater than 40.[2,3] Alkaloids belonging to this family typically exhibit significant biological activities, including cytotoxicity.[4] For example, of the pentacyclic pyridoacridine analogues amphimedine (**1**), neoamphimedine (**2**),[5] deoxyamphimedine (**3**),[6] and demethyldeoxyamphimedine (**4**)[7] (Figure 1), **1** induces specific developmental effects in zebrafish embryos,[8] **2** is cytotoxic and stimulates topoisomerase II to catenate DNA,[5,9,10] and **3** causes damage to DNA via the production of reactive oxygen species.[11] A number of syntheses of amphimedine (**1**)[12−15] and demethyldeoxyamphimedine (**4**)[16,17] have been reported, all relying upon either hetero-Diels−Alder or Pd- or Li-metalation reactions to construct the core skeleton. In the case of amphimedine, total syntheses have been reported that incorporate a longest linear sequence of up to 13 steps. Syntheses of demethyldeoxyamphimedine on the other hand are considerably shorter with the recent report by Bracher of a 4 step, 6.4% yield sequence being the most efficient to date.[17] None of the syntheses, however, can be considered bioinspired or biomimetic. Several groups have speculated that styelsamine D (**5**), itself a natural product isolated from the ascidian *Eusynstyela latericius*,[18] could be a biosynthetic intermediate to a large subset of pyridoacridine alkaloids, including **1**−**4**.[3,7] Preliminary experiments by Bry et al. observed that addition of formaldehyde to a marine organism extract that contains both styelsamine D (**5**) and demethyldeoxyamphimedine (**4**) led to the disappearance of the former with time and a concomitant increase in detectable quantities of the latter.[7]

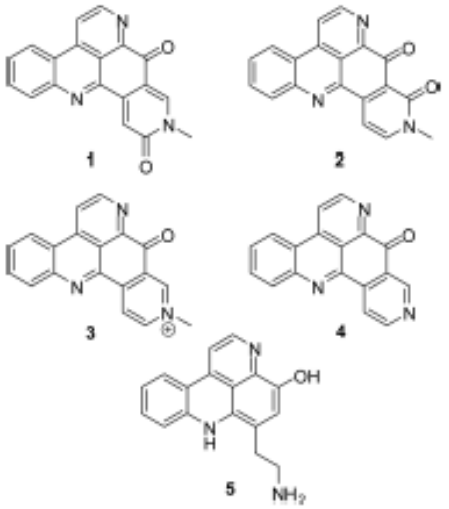


Figure 1. Structures of marine pyridoacridine alkaloids amphimedine (**1**), neoamphimedine (**2**), deoxyamphimedine (**3**), demethyldeoxyamphimedine (**4**), and styelsamine D (**5**).

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