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A Simple Biomimetic Synthesis of Styelsamine B

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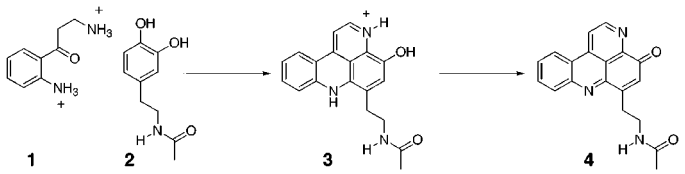
ABSTRACT



An extremely rapid, low cost, and environmentally friendly entry into the pyridoacridine family of alkaloids has been devised, as demonstrated here by the first total synthesis of styelsamine B (3) and its oxidation to the quinoneimine cystodytin J (4). The known reaction of cystodytin J with methanethiol makes this a formal synthesis of diplamine.

For all natural products, there exists a synthesis from ubiquitous biomolecules. The inherent interconnectivity of natural products implies that a truly biomimetic total synthesis represents a general solution not to the preparation of a compound but to the preparation of all similarly derived natural products (discovered and undiscovered). We herein report our preliminary work toward a general solution to pyridoacridine synthesis.

The pyridoacridines are representatives of a growing class of polycyclic aromatic alkaloid zoochromes isolated from marine invertebrates. Since the isolation and structural elucidation of the first members of this class of compounds in the 1980s, these redox active alkaloids have attracted a great deal of synthetic attention due to their cytotoxicity and the variety of biological activities they have been shown to exhibit.[1] In particular, cystodytin J (**4**) and diplamine are potent cytotoxins that disrupt the action of topoisomerase II by DNA intercalation.[2] Total syntheses of these natural products have previously been reported;[3] however, no biological or synthetic studies on styelsamine B appear to have been published as of yet.

It has previously been proposed that the pyridoacridine alkaloids eilatin and ascidemnin arise biosynthetically by the reaction of kynuramine/kynurenine with benzoquinone and a quinolinequinone, respectively. The plausibility of this proposal has been confirmed by the total synthesis of these natural products using a protected form of kynuramine.[4] Others have made the unsupported claim that the ethylamine side chain bearing pyridoacridines such as those synthesized here arise by oxidative merger of tyramine directly with the biosynthetic precursor of kynuramine (**1**).[3c]

These proposals claim the amine rather than the aniline as the initial reactive partner, whereas our work in this area implies that the Michael addition occurs in an environment where the amine is protonated (acidic) and therefore the less reactive nucleophilic center (Scheme 1). The rigidity of the aromatic ring separating the aniline and ketone functionalities appears to preorganize the system for the requisite cyclization, whereas no such bias exists in the cyclization of an aliphatic β-amino ketone.

(1) Related reviews: (a) Molinski, T. *Chem. Rev.* **1993**, *93*, 1825. (b) Bowden, B. *Stud. Nat. Prod. Chem.* **2000**, *23*, 233.

(2) Mcdonald, L.; Eldredge, G.; Barrows, L.; Ireland C. *J. Med. Chem.* **1994**, *37*, 3819.

(3) (a) Szczepankiewicz, B.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 3512. (b) Ciufolini, M.; Shen, Y. *Tetrahedron Lett.* **1995**, *36*, 4709. (c) Ciufolini, M.; Shen, Y.; Bishop, M. *J. Am. Chem. Soc.* **1995**, *117*, 12460.

(4) (a) Gellerman, G.; Rudi, A.; Kashman, Y. *Tetrahedron* **1994**, *50*, 12959. (b) Gellerman, G.; Rudi, A.; Kashman, Y. *Tetrahedron Lett.* **1993**, *34*, 1823. (c) Gellerman, G.; Babad, M.; Kashman, Y. *Tetrahedron Lett.* **1993**, *34*, 1827. (d) Gellerman, G.; Rudi, A.; Kashman, Y. *Synthesis* **1994**, 239.

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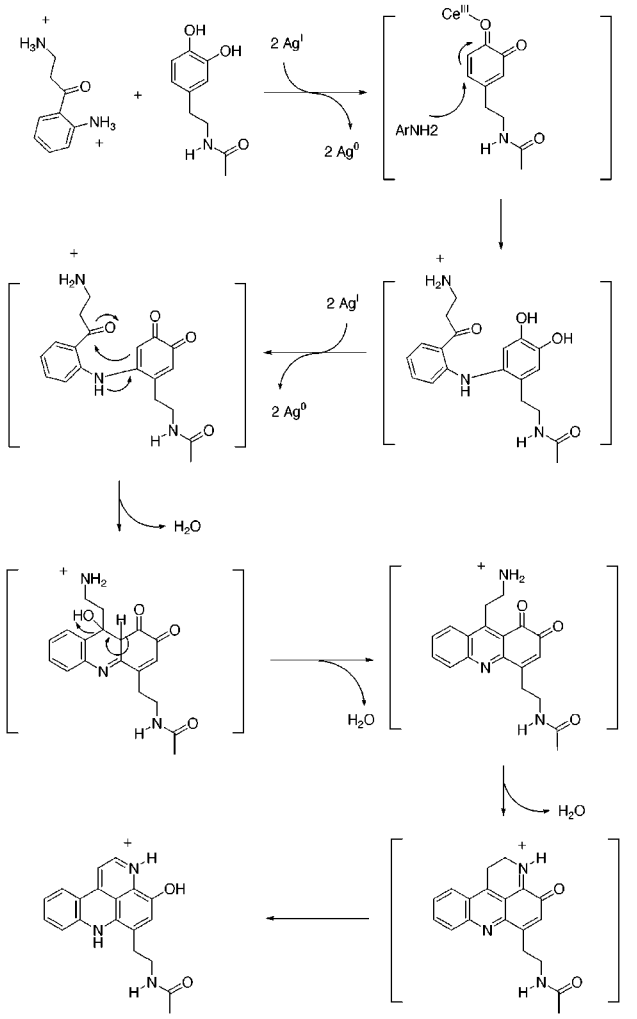
Scheme 1. Proposed Mechanism



The reaction conditions of the title synthesis (see Supporting Information) were developed over time by a combination of rational design and empirical experimentation. Reagents do not normally participate in only a single reaction type, and as the complexity of a reagent grows the likelihood of unexpected and undesired side reactions grows as well. We have attempted to maintain experimental simplicity as the guiding principle in synthetic design.

As a practical "oxidant in the raw" Ag^I has become our reagent of choice for catechol oxidation. The Lewis acidity of this reagent did not seem to be of particular concern since the Michael addition step is itself Lewis acid catalyzed. Ag^I has the advantage of having an oxidation potential strong enough for the initial dopamine oxidation but weak enough to avoid unselective oxidation (i.e., competitive oxidation of kynuramine (**1**)). The innocuous and easily separable byproduct (Ag^0) made this a particularly attractive choice. Silver oxide (Ag_2O) was chosen as a particularly inexpensive source of Ag^I.

The starting reaction solvent was chosen for its ability to dissolve essentially any desired catechol or catecholamine starting material, thereby eliminating this as a variable variable when switching between substrates. The choice of $CeCl_3$ as Lewis acid catalyst for the initial Michael addition was made empirically.

The solvent switch to 6 N HCl accelerates the final stages of the cascade. A similar rate enhancement appears to occur with the addition of trifluoroacetic acid. The choice of an aqueous acid has the important advantage of providing a medium in which the starting materials and intermediates are soluble but the reaction product is not. Although this may be applicable to several pyridoacridines, it is unlikely to be universal. Our further work in this area will be reported shortly.

The conversion of styelsamine B (**3**) to cystodytin J (**4**) has yet to be optimized but serves to illustrate the power of this approach. In summary, two natural products have been synthesized and one formally synthesized. This procedure is simple and delivers the natural products in a matter of hours.

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Supporting Information Available: Spectra for the reported compounds, a convenient multigram preparation of kynuramine dihydrobromide, and experimental details for the title synthesis. This material is available free of charge at http://pubs.acs.org.

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