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Total Synthesis of Debromoflustramine B via Biomimetic Alkylative Cyclization

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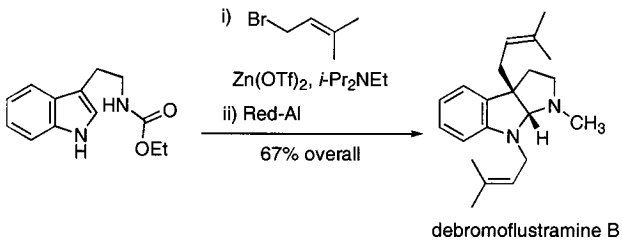
ABSTRACT



The hexahydropyrrolo[2,3-*b*]indoline skeleton is readily accessed by the zinc triflate-mediated alkylation of tryptamine derivatives. The methodology was employed in a three-step total synthesis of debromoflustramine B.

The hexahydropyrrolo[2,3-*b*]indoline ring system is present in numerous alkaloid natural products. Biogenetically, it can be perceived to arise via electrophilic attack on a tryptophan or tryptamine unit at the indole C-3 position, followed by capture of the resulting C-2 iminium ion by the side-chain nitrogen. Although this retrosynthetic disconnection has been realized in the laboratory, beginning with Hoshino's pioneering approach[1] to physostigmine, it is highly sensitive to the nature of the electrophile and the indole substrate. Yields are often poor, and many total syntheses have adopted less direct nonbiomimetic solutions for the construction of this skeleton.

A subset of the hexahydropyrrolo[2,3-*b*]indoline alkaloids feature a prenyl group as the electrophile. The simplest examples are the flustramines isolated from the marine byrozoan *Flustra foliacea*, as exemplified[2] by flustramines B and E, and debromoflustramine B (Figure 1). While debromoflustramine E has yet to be identified in *F. foliacea* extracts, it was recently detected[3] in trace amounts from the skin of the Australian frog *Pseudophyrne semimarmorata*

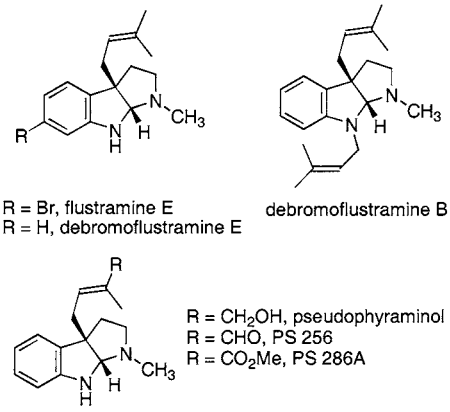


Figure 1. Examples of flustramines and pseudophyrnamines.

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raised in captivity. *Pseudophyrne* frogs are a rich source of related alkaloids, the pseudophyrnamines,[4] usually with an oxidized prenyl group and lacking aromatic halogenation, as in pseudophyrnaminol. Unlike most dendrobatid alkaloids that are sequestered from the diet, the pseudophyrnamines appear to be biosynthesized by the amphibian itself.

The scarcity of flustramines and pseudophyrnamines from natural sources, coupled with diverse biological activities such as muscle relaxant properties[2d,g] and antimicrobial[2e] and cytotoxic[2h] effects, has led to continued interest in total synthesis of these alkaloids via either biomimetic[5] or nonbiomimetic[6] approaches. Recently, we reported[7] the regioselective C-3 alkylation of indoles promoted by zinc triflate under mild conditions. Here, we demonstrate the potential of this methodology for hexahydropyrrolo[2,3-*b*]-indoline synthesis, as illustrated by a facile route to debromoflustramine B.

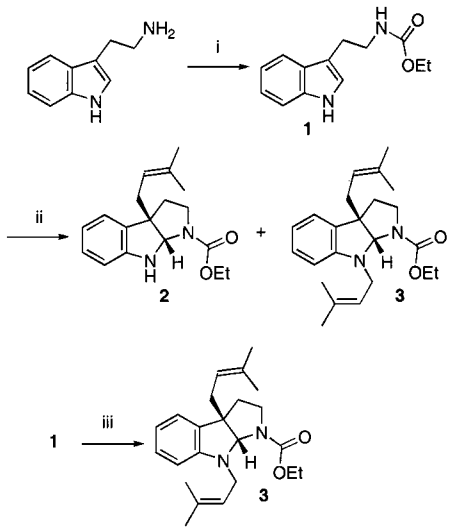
Our synthesis began with tryptamine, which was converted to the known[8] ethyl carbamate **1** (Scheme 1). The carbamate group was chosen to modulate the reactivity of the side-chain nitrogen such that it does not undergo direct alkylation in the next step but is sufficiently nucleophilic for the intramolecular iminium ion capture. In addition to this function, the carbamate serves as a latent methyl group upon reduction. Pleasingly, subjection of **1** to our zinc triflate-mediated prenylation conditions gave 42% of the desired hexahydropyrrolo[2,3-*b*]indoline **2**, accompanied by a small amount (~10%) of the dialkylated product **3**.

Hexahydropyrrolo[2,3-*b*]indoline **2** is a reasonable intermediate for the synthesis of debromoflustramine E. Indeed, **2** represents a formal total synthesis of pseudophyrnaminol, as it intersects the Mitchell route.[5c] Meanwhile, the isolation of **3** attracted us to the possibility of driving the reaction toward this product. Using an excess (4 equiv) of prenyl bromide afforded **3** in 70% yield.

For completion of the total synthesis, the carbamate needed to be reduced to a methyl group. This seemingly straightforward transformation is rendered nontrivial by the documented[5a] acid and base sensitivity of compounds such as **3**. In our hands, attempts at lithium aluminum hydride reduction were unsatisfactory. Success was achieved with the Nakagawa procedure[9] of Red-Al in refluxing toluene (Scheme 2). This gave a nearly quantitative yield of debromoflustramine B, provided that acidic conditions were avoided during the reaction workup. In the presence of acid, the alkaloid underwent partial rearrangement to the 2-prenyl methyltryptamine, as previously[5a] reported.

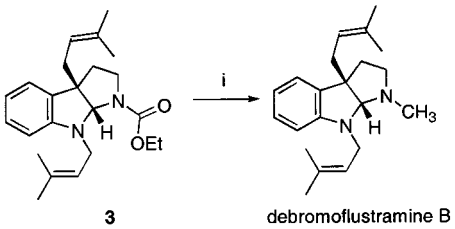
In summary, we have shown that hexahydropyrrolo[2,3-*b*]indolines can be obtained by zinc triflate-mediated indole alkylation. The present total synthesis of debromoflustramine

Scheme 1 [a]



[a] Reagents and conditions: (i) $ClCO_2Et$ (1.5 equiv), CH_2Cl_2/aqueous $NaHCO_3$, 0 °C, 3 h; 84%. (ii) Prenyl bromide, $Zn(OTf)_2$, Bu_4NI, *i*-Pr_2NEt (1 equiv each), toluene, rt, 3 h; 42% **2** + ca. 10% **3**. (iii) Prenyl bromide (4 equiv), $Zn(OTf)_2$ (1 equiv), Bu_4NI (2 equiv), *i*-Pr_2NEt (2.2 equiv), toluene, rt, 3 h; 70%.

Scheme 2 [a]



[a] Reagents and conditions: (i) Red-Al (10 equiv), toluene, reflux, 24 h; 96%.

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B is the shortest yet (three steps from tryptamine, 57% overall) reported for this alkaloid and scalable (we prepared 300 mg of debromoflustramine B). We are presently exploring the zinc triflate methodology for accessing more complex alkaloids as well as the parallel synthesis of hexahydropyrrolo[2,3-*b*]indolines by varying the indole, the nitrogen substituent, and the alkylating agent. In addition, we are investigating asymmetric variants of the cyclization.

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Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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