General Approach to the Synthesis of Marine Bryozoan *Flustra foliacea* Alkaloids: Total Syntheses of Debromoflustramines A and B

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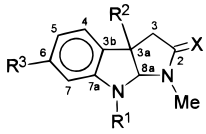
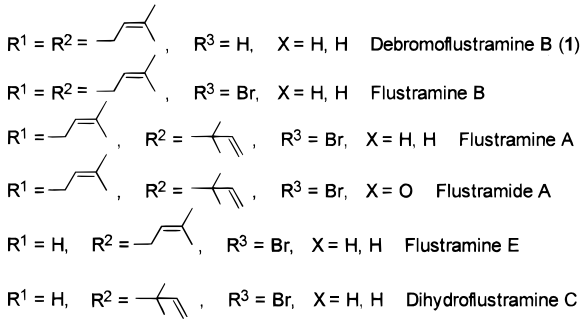
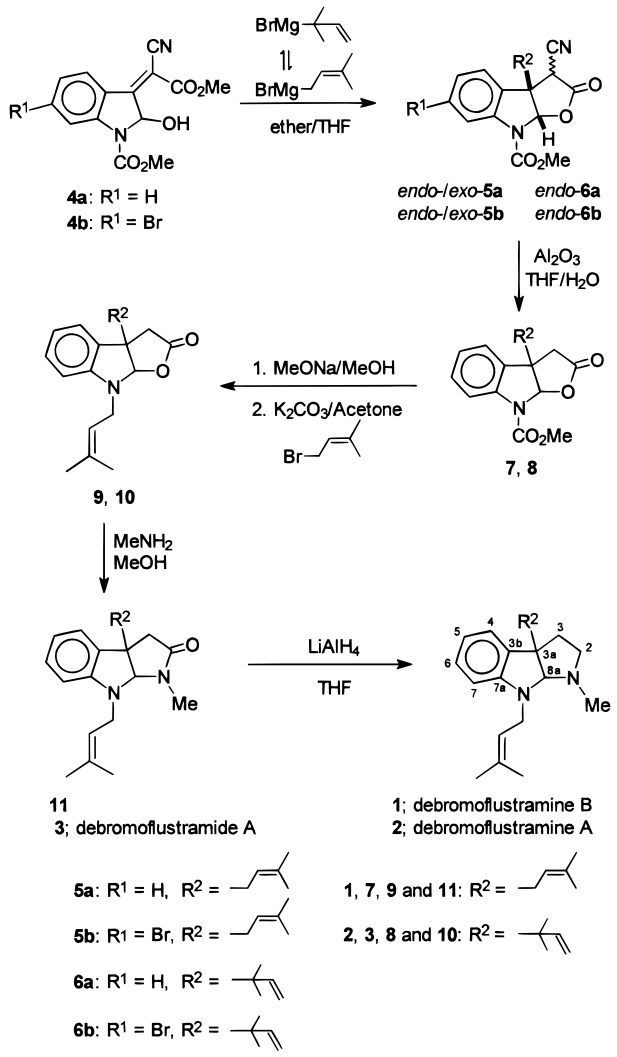
Debromoflustramine B (**1**) is an indole alkaloid isolated from the marine bryozoan *Flustra foliacea* together with a closely related group of brominated indoles, most of which display interesting biological activity.[1] These alkaloids have in common the basic physostigmine skeleton known from the minor group of terrestrial alkaloids from Calabar bean (*Physostigma venenosum* Balf), and some of them have one or two prenyl or inverted prenyl units at the 8 and/or 3a positions as shown below.





A diastereoselective synthesis of debromoflustramine B (**1**) starting from a cyclic tautomer of L-tryptophan has appeared previously.[2] Racemic syntheses of **1** have also been reported involving alkylation at C3 of tryptamine derivatives.[3] Another approach to **1** involves a six-step sequence starting from 1-methoxyindole-3-carbaldehyde, in an overall yield of 4.4%.[4] Despite the above synthetic methods, there exists a need to develop more efficient and versatile procedures to this and other related compounds. Recently, we have shown the Grignard reagent addition to 2-hydroxyindolenines as a useful method for introducing an alkyl group at the C3 position of the indole nucleus.[5] In this paper, we describe our preliminary results regarding the synthesis of debromoflustramine B (**1**), which also resulted in the syntheses of related derivatives debromoflustramine A (**2**) and debromoflustramide A (**3**) via the conjugated addition of the Grignard reagent derived from prenyl bromide to 2-hydroxyindolenines. This method represents a new and general approach for the synthesis of 3a-alkylhexahydropyrrolo[2,3-*b*]indole-type alkaloids according to the strategy outlined in Scheme 1.

Scheme 1



In the first step (Scheme 1), the Grignard reagent addition to 2-hydroxyindolenines **4**[6] provides ready access to a range of functionalized 2-oxofuro[2,3-*b*]indoles **5** and **6**. Of the different reaction conditions examined, the highest yield for compounds **5** and **6** was obtained at low temperature (−78 °C, Table 1). Typically, when the 2-hydroxyindolenine **4a** was stirred with an excess (4 equiv) of an equilibrating mixture[7] of prenylmagnesium bromide (3-methyl-2-butenylmagnesium bromide) and its 1,1-dimethylallyl isomer (2-methyl-3-buten-2-yl) at −78 °C in anhydrous THF/ether, the products of the 1,4-addition, the prenylated 2-oxofuro[2,3-*b*]indole **5a** (mixture of endo/exo isomers as determined by

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(6) Compounds **4** were prepared in good overall yields by treatment of the appropriately substituted 3-acetonitrilindole with an alkyl carbonate in basic medium, followed by oxidation with either HNO_3/AcOH or CrO_3/AcOH. See: (a) Reference 5. (b) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *J. Heterocycl. Chem.* **1993**, *30*, 953−956.

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Table 1. Regioselectivity and Yields for the Formation of 2-Oxofuro[2,3-*b*]indoles 5 and 6[a]

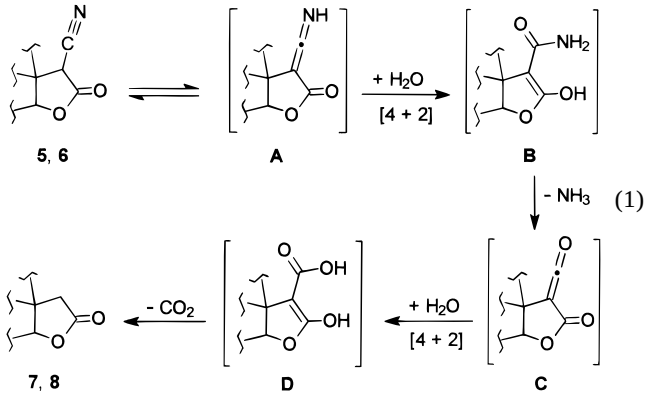
Entry	Substrate	Temp. °C	Products	Yield %
1.	R^1 = H, **4a**	0	R^2 =  , **5a**	21[b]
			R^2 =  , **6a**	26[c]
2.	R^1 = H, **4a**	-78	R^2 =  , **5a**	32[b]
			R^2 =  , **6a**	48[c]
3.	R^1 = Br, **4b**	0	R^2 =  , **5b**	23[b]
			R^2 =  , **6b**	40[c]
4.	R^1 = Br, **4b**	-78	R^2 =  , **5b**	24[b]
			R^2 =  , **6b**	44[c]

[a] Reactions were carried out on a 3.5 mmol scale. [b] Mixture of endo/exo isomers by ^{1}H NMR. [c] Only endo isomer.

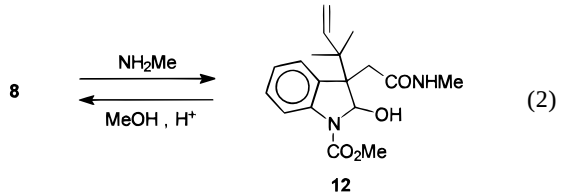
^{1}H NMR) and the 1,1-dimethylallyl isomer **6a** (only endo isomer), were obtained in a combined yield of 77% in a ratio of 40 (**5a**):60 (**6a**). The dependence of the C3/C3a endo/exo ratios on the alkyl group at C3a, observed in the reaction products, evidence that the lactone stereochemistry is set upon ring closure of the initially alkylated γ-hydroxy esters, whereas the preferred cis-5,5-fused system formation depends on the ring-chain tautomeric equilibrium of the hemiaminal group.[8,9]

To further illustrate the viability of this reaction as a practical strategy for the synthesis of brominated indole alkaloids, we have explored the reaction of the brominated 2-hydroxyindolenine **4b** with prenylmagnesium bromide. Our best results to date afforded the C3a-alkylated 2-oxofuroindoles **5b** (mixture of endo/exo isomers) and **6b** (endo isomer) in a combined yield of 68% in a ratio of 35 (**5b**):65 (**6b**) (Table 1).

Hydrolytic decyanation of the α-cyano γ-lactones **5a** and **6a** was conducted in refluxing THF, in the presence of wet alumina, to afford the corresponding γ-lactones **7** and **8** in 86% and 95% yield, respectively. No intermediates were detected during the reactions. Taking into account the high effectivity and the operationally simple procedure of this transformation, we propose a mechanism involving two successive pseudopericyclic [4 + 2] hydration processes,[10,11] as shown below. The initially produced tautomeric α-ketenimine-γ-lactone **A** can be hydrated to form amide **B** via a planar [4 + 2] pseudopericyclic transition structure. The facile loss of ammonia from **B** to give α-ketone γ-lactone **C** is in line with theoretical studies of a reverse transformation, namely the addition of ammonia to formylketene.[12] The reactive intermediate[13] **C** may undergo a further [4 + 2] hydration[14] to afford the corresponding carboxylic acid **D**, which after subsequent decarboxylation leads cleanly γ-lactones **7** and **8**.



Treatment of γ-lactone **8** with methylamine at room temperature afforded the γ-hydroxyamide **12**,



which by heating in methanol to reflux gave back γ-lactone **8**.[15] To overcome this difficulty, we examined the possibility of introducing the N_8 prenyl group in the synthetic sequence before transforming the lactone into the lactam. Thus, the electron-withdrawing substituent *N*-CO_2Me in compounds **7** and **8** was replaced by an *N*-prenyl group by treatment with MeONa/MeOH and concomitant alkylation with prenyl bromide. Under these conditions, the N-prenylated 2-oxofuroindoles **9** and **10** were obtained in 70% and 60% overall yield, respectively. As expected, the addition of methylamine to **9** in MeOH gave the desired lactam **11** in 92% isolated yield. Similar results were obtained upon addition of methylamine to **10**. Debromoflustramide A (**3**) was isolated in 98% yield and further reduced with $LiAlH_4$ in refluxing THF to give debromoflustramine A (**2**) in 98% isolated yield. Reaction of **11** with $LiAlH_4$ under similar conditions gave debromoflustramine B (**1**) in 98% isolated yield. The spectral properties of **1** are identical (IR, ^{1}H and ^{13}C NMR, EIMS) to those reported for the marine natural product debromoflustramine B except for the optical activity.[1b,2]

In summary, the steps described in Scheme 1 allow a straightforward synthesis of debromoflustramine B (**1**) and provide a widely potential route to a variety of marine *F. foliacea* alkaloids carrying the basic physostigmine skeleton.

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Supporting Information Available: Detailed experimental procedures and ^{1}H and ^{13}C NMR spectra for compound characterization.

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(8) Compounds **5** and **6** undergo a markedly fast deuterium exchange at C3 when treated with D_2O.

(9) The relative stereochemistry was evidenced by an NOE experiment in which enhancements of the H3 and H8a signals were observed when the methyl groups of the bulky 2-methyl-3-buten-2-yl substituent at C3a were irradiated.

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