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Concise Total Synthesis of the Marine Natural Product Ageladine A

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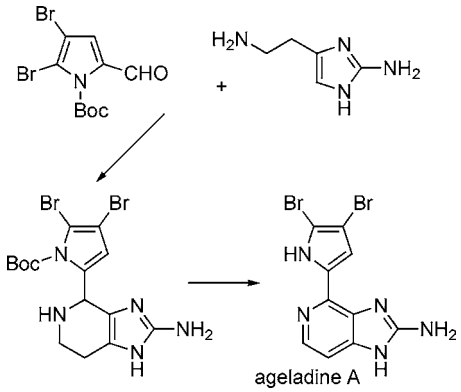
ABSTRACT



A total synthesis of ageladine A has been achieved by exploiting a Pictet–Spengler-type condensation between 2-aminohistamine and 4,5-dibromo-2-formylpyrrole as the key step.

The recent publication of a 12-step synthesis of the marine natural product ageladine A in this journal[1] by Weinreb and co-workers prompted us to consider a shorter synthesis based on biomimetic principles.

Ageladine A (**1**), first isolated from the marine sponge *Agelas nakamurai* by Fusetani, has important anti-angiogenic activity arising from its inhibition of matrix metalloproteases-2 (MMP-2).[2] The discovery of this novel compound is significant because it is believed to inhibit MMP-2 via a mechanism that does not involve zinc complexation as was found for other previous inhibitors.

The biogenesis of ageladine A as suggested by Fusetani[2] is likely to be from proline and histidine (Scheme 1), which could produce 4,5-dibromo-2-formylpyrrole and 2-aminohistamine (**2**).

Retrosynthetic analysis of this pathway suggested that an imine (**3**) between **2** and the 2-formylpyrrole could form, and if it was possible to effect an intramolecular cyclization between the imine and the imidazole, the requisite skeleton of the ageladine A could be synthesized in one step from readily available starting materials. Precedence for this type of condensation can be found in the chemistry of vitamin B_6, which is known to form tetrahydroimidazopyridine analogues through condensation with histidine (Scheme 2).[3]

If the skeleton of ageladine A could be constructed in a similar manner, the remaining step would only involve dehydrogenation of the tetrahydropyridine intermediate.

To prepare the starting materials for the total synthesis of ageladine A, we chose to use the putative biosynthetic precursors, 2-aminohistamine (**2**)[4] and *N*-Boc-4,5-dibromo-2-formylpyrrole (**4**).[5] Stirring a 1:1 mixture of **2** and **4** in

(1) Meketa, M. L.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1443.
(2) Fujita, M.; Nakao, Y.; Matsunaga, S.; Seiko, M.; Itoh, Y.; Yamashita, J.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2003**, *125*, 15700.
(3) Heyl, D.; Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 3429.
(4) Aminohistamine (**2**) is commercially available or can be prepared by several published routes. In this case, the preparation of **2** from Boc-guanidine and β-alanine was effected in six steps: (a) Jones, R. G.; Kornfeld, E. C.; McLaughlin, K. C. *J. Am. Chem. Soc.* **1950**, *72*, 4526. (b) Little, T. L.; Webber, S. E. *J. Org. Chem.* **1994**, *59*, 7299.

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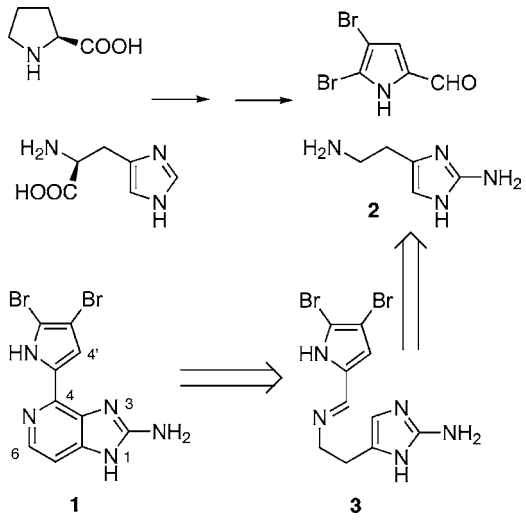
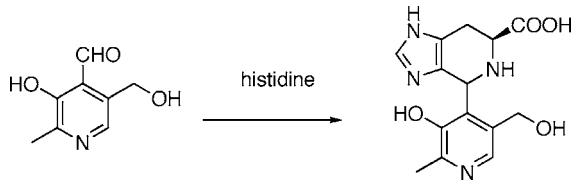
Scheme 1. Biogenesis and Retrosynthetic Analysis of Ageladine A



ethanol in the presence of scandium triflate led to the expected Boc-protected tetrahydroageladine A (**5**) in a

Scheme 2

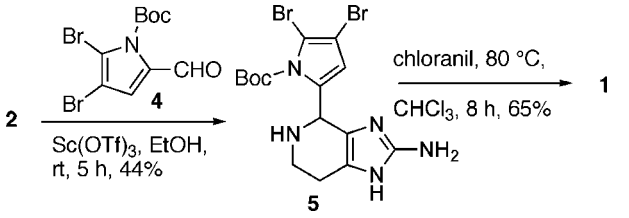


reasonable yield (Scheme 3). The reaction was found to proceed without a catalyst (overnight) but was considerably accelerated with Lewis acid catalysts such as $Sc(OTf)_3$, $In(OTf)_3$, or $La(OTf)_3$. Acceleration of Pictet−Spengler reactions with Lewis acid catalysts has been previously noted for tryptamines.[6] NMR analysis of **5** (Supporting Information) suggested that the compound existed as a mixture of

(5) 4,5-Dibromo-2-formylpyrrole is commercially available, but the preparation of **4** can be effected in near quantitative yield from 2-formylpyrrole in two steps: Handy, S. T.; Sabatini, J. J.; Zhang, Y.; Vulfova, I. *Tetrahedron Lett.* **2004**, *45*, 5057.

(6) Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, 916.

Scheme 3



diastereomers by virtue of the formation of a new chiral center and atropoisomerization. This led to two broad signals for H4′ (δ_H 5.88/5.97) of the pyrrole and H4 (δ_H 5.51/5.78) of the tetrahydroimidazo[4,5-*c*]pyridine in the ^1H NMR spectrum of **5**.

Dehydrogenation and deprotection of **5** were cleanly effected by refluxing with chloranil overnight to yield ageladine A as a fluorescent yellow solid, identical in all respects to the natural product.[2] Alternatively, the tetrahydroageladine A (**5**) can be dehydrogenated with chloranil ($CHCl_3$, 50 °C, 5 h) to yield Boc-protected ageladine A, which can be deprotected quantitatively by stirring with 50% TFA in dichloromethane.

Although the individual steps of the Weinreb synthesis[1] are high yielding (generally over 80%), it is not commercially attractive due to its length and the types of reagents used. A 29% yield for the final step, due to the facile over-bromination of the didebromoageladine A, can be avoided by bromination of 2-formylpyrrole at the beginning of the synthesis where dibromination can be quantitatively produced due to the deactivating effect of the formyl group.

The biomimetic synthesis reported here opens the door to further biological testing and clinical trials as well as to the easy synthesis of a range of analogues that will be reported in due course.

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Supporting Information Available: The experimental procedures and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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