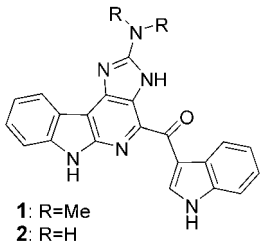
Biomimetic Synthesis

Biomimetic Synthesis of Grossularines-1**

*Fumiko Y. Miyake, Kenichi Yakushijin, and David A. Horne**

Dedicated to Professor Peter B. Dervan on the occasion of his 60th birthday

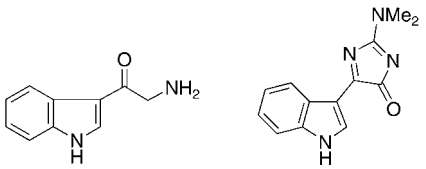
Isolated in only small amounts from the Britannia marine tunicate *Dendrodoa grossularia* (Styelidae), grossularine-1 (**1**) represents one of the more structurally intriguing members of a relatively small but potent class of α-carboline metabolites that exhibit pronounced effects against solid human tumor cell lines.[1] The limited material available from nature as well as synthetic sources, however, have hampered further investigations in vivo. Closely related to **1** is *N,N*-didesmethylgrossularine-1 (**2**) (from the Chuuk Atoll tunicate *Polycarpa aurata*) whose structure was established by X-ray crystallographic analysis.[2]



1: R=Me
2: R=H

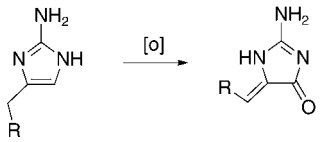
In contrast to the well-known class of β-carboline-derived natural products, grossularines represent the first examples of naturally occurring α-carbolines. Despite the promising biological activity of **1**, only one total synthesis has been completed.[3] In the approach of Hibino and co-workers, the construction of the tetracyclic pyrido[2,3-*b*]indole ring system proceeded in a linear manner through the use of Pd-catalyzed cross-coupling reactions of halogenated indoles and metallated imidazoles. A formal synthesis of **1** has been reported by Molina et al.[4] that intersects the key intermediate reported by Hibino and co-workers. Herein we describe a remarkably concise biomimetic synthesis of **1** and **2** that is based on a novel oxidative dimerization–electrocyclization sequence of 2-amino-4-(3-indolyl)imidazoles **5** and **6** derived from oxotryptamine (**3**).

Oxotryptamine (**3**) continues to serve as an important cornerstone in indole heterocyclic construction. In previous work reported by our research group, a practical procedure for the preparation of **3** was developed that avoids the use of protecting groups and DDQ oxidation, and was applied to the synthesis of various bis-indole marine natural products.[5] In a formal sense, grossularine **1** and its didesmethyl congener **2** consist of two oxotryptamine units that are linked by an oxidative coupling between the two carbon centers of the amino-bearing termini. Although such a mode of dimerization is difficult to envisage with oxotryptamine per se, the use of an electron-rich aromatic surrogate based on 2-aminoimidazoles **5** and **6** seemed plausible, particularly in view of the oxidized analogue, 2-dimethylamino-5-(3-indolyl)imidazol-4-one (**4**).[6] This derivative was co-isolated with **1** from the same tunicate. The presence of this oxidized metabolite



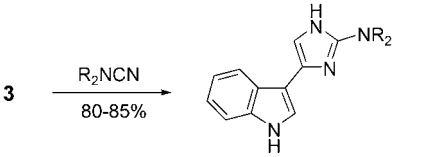
3 **4**

along with the fact that 2-aminoimidazoles are readily converted into imidazolones through oxidation [Eq. (1)],[7] suggests that 2-aminoimidazoles **5** and **6** could serve as potential biosynthetic forerunners.



(1)

The synthesis begins with the preparation of 2-aminoimidazoles **5** and **6** by using the classical cyclocondensation of α-amino carbonyl compounds and cyanamide (Scheme 1).[8] Condensation of oxotryptamine (**3**) and dimethylcyanamide in the absence of air produced 2-dimethylamino-4-(3-indolyl)imidazole (**5**).[9,10] Attempts to purify **5** as the free base by flash chromatography were unsuccessful owing to its instability; however, **5** can be obtained in relatively pure form



5: R=Me (as HCl salt)
6: R=H

Scheme 1. Preparation of 2-amino-4-(3-indolyl)imidazoles (**5**) and (**6**).

[*] F. Y. Miyake, Dr. K. Yakushijin, Dr. D. A. Horne
Department of Chemistry, Oregon State University
Corvallis, OR 97331 (USA)
Fax: (+1) 541-737-2062
E-mail: horned@onid.orst.edu

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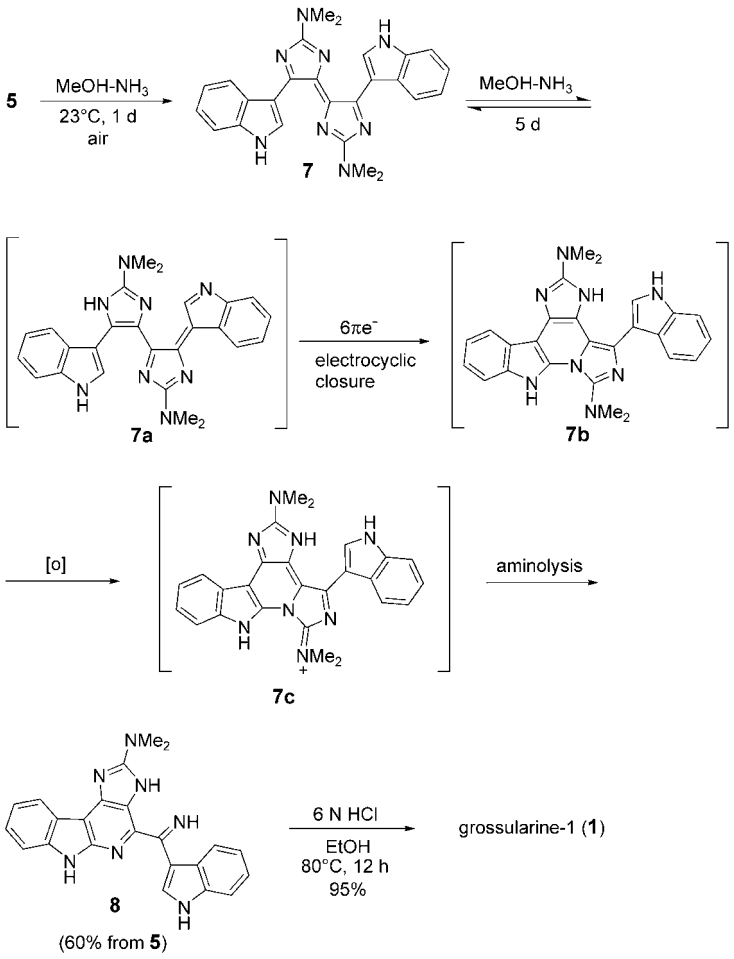
as the hydrochloride salt. On the other hand, 2-amino-4-(3-indolyl)imidazole (**6**), which lacks the dimethyl substituent, can be secured as the free base by the condensation of **3** with cyanamide followed by chromatographic purification over silica. These findings are consistent with observations made by Snyder and co-workers during their investigations of Diels–Alder reactions of 2-aminoimidazoles, in which greater thermal and air sensitivity of 2-dimethylaminoimidazole was observed.[11]

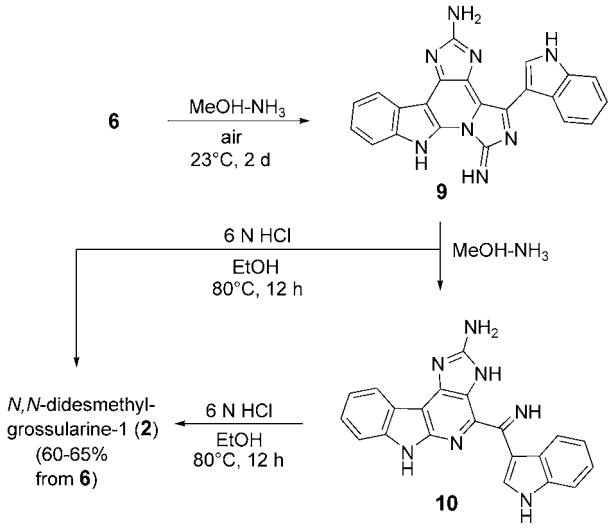
The instability of **5** normally would not be judged very significant on its own; however, further investigation was inspired by the fact that this 2-aminoimidazole derivative is quite sensitive to air and that an oxidative coupling event could, in principle, deliver conjoined indole units as a means to potentially access the α-carboline core. We were quite surprised to find that upon exposure of **5**·HCl to a methanol solution saturated with ammonia, α-carboline **8** was produced (Scheme 2).[12] During the course of the reaction, dimer **7** partially precipitated from solution after 1 day as a dark violet solid. Collection and resubjection of **7** to the reaction conditions afforded **8**. To explain these results, one mechanistic pathway might involve initial oxidative dimerization of **5** to yield dimer **7**. Upon standing in a methanol-saturated ammonia solution, **7** undergoes an electrocyclization–aromatization event via tautomer **7a**. Oxidation of the resulting intermediate **7b** to **7c** followed by facile aminolysis results in the loss of dimethylguanidine and the formation of α-carboline **8**. The sequence is remarkably efficient, delivering **8** directly in one pot and good overall yield from **5**. Aromatic imine **8** was found to be quite stable and required fairly rigorous hydrolysis conditions to yield grossularine-1 (**1**) as a yellow solid. All spectral data of synthetic **1** were in excellent agreement with data reported for the natural product.[1]

Similarly, treatment of **6** under analogous MeOH–NH_3 conditions produced fused pentacyclic dimer **9** as a dark violet to black solid (Scheme 3). Upon further standing in MeOH–NH_3, **9** underwent aminolysis to afford imine **10**. Hydrolysis of the imine functionality of **10** gave *N*,*N*-didesmethylgrossularine-1 (**2**). Alternatively, **2** can be obtained directly from the hydrolysis of **9**. All spectral data of synthetic **2** were in excellent agreement with those reported for the natural product.[2] In noting differences between dimethylaminoimidazole **5** and its didesmethylamino analogue **6**, the precyclized desmethylamino dimer corresponding to **7** was not obtained in the case of **6**. This outcome is attributed to the greater solubility of the putative desmethyl intermediate in methanolic ammonia. In the case of **5**, the *N*,*N*-dimethylamino analogue **7c** corresponding to **9** also was not obtained. The greater propensity toward aminolysis of this putative guanidinium ion intermediate explains this result.

Although electron-rich aromatic heterocycles such as indoles are known to undergo autoxidative coupling,[13] the oxidative dimerization of 2-aminoimidazoles under simple aerobic conditions is unprecedented. The structurally and biologically significant α-carboline natural products **1** and **2** were produced in excellent overall yields with an operationally simple, three-pot sequence starting from oxotryptamine. The chemistry and brevity of this novel sequence support a plausible biogenetic con-



Scheme 2. Synthesis of grossularine-1 (**1**).



Scheme 3. Synthesis of *N*,*N*-didesmethylgrossularine-1 (**2**).

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nection that explains these and several other structurally related members this α-carboline family.

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