Synthesis of Mauritiamine†

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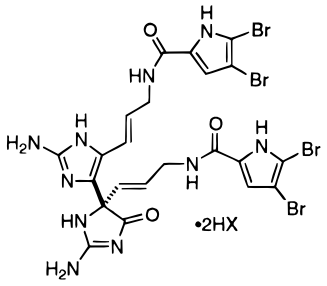
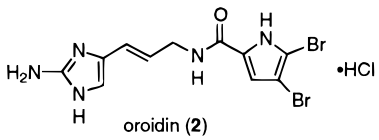
Herein, we describe a synthesis of the marine alkaloid mauritiamine (**1**) in which the key step centers on the oxidative dimerization of a pivotal 2-aminoimidazole derivative in a manner that may prove relevant to its biosynthesis.

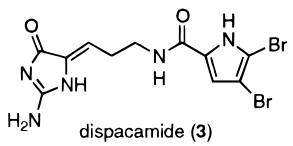
Marine sponges produce a broad spectrum of structurally diverse and pharmacologically interesting class of $C_{11}N_5$ and dimerically related, secondary metabolites.[1] Mauritiamine (**1**), isolated as a racemate from *Agelas mauritiana*, is a recently discovered member of this alkaloid group that possesses potent antifouling activity.[2] The structure of **1** was determined by spectral analysis. Closely related to **1** are the sponge metabolites oroidin (**2**)[3] and dispacamide (**3**).[4] Both oroidin (**2**) and dispacamide (**3**) have been isolated from a number of different *Agelas* species, including *A. mauritiana*. These metabolites can be considered hypothetical progenitors in the biosynthesis of **1**.



mauritiamine (**1**)

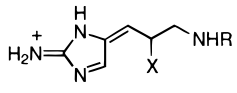


oroidin (**2**)

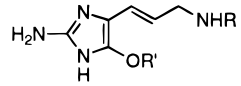


dispacamide (**3**)

Synthetically, the creation of the α,α-disubstituted 2-aminoimidazolinone unit **1** bearing the two different sp^2 carbon appendages is certainly the most challenging aspect of the research. The most efficient approach to this construction was envisaged to follow a biomimetic pathway involving the heterodimerization of intermediates **A** and **B**. In principle, these intermediates could



A



B

be derived from oroidin (**2**). The latter derivative, **B** (R′ = H), is simply the enol tautomer of dispacamide (**3**). From previous work in our laboratory on the synthesis of hymenin, stevensine, and hymenialdisines,[5] the glycocyamidine functionality found in secondary metabolites such as **3** can be derived readily from 2-aminoimidazoles. Therefore, the initial phase of the synthesis focused on the preparation of olefin **7** (3-amino-1-(2-aminoimidazol-4-yl)prop-1-ene) from its dihydro derivative **5** (Scheme 1).

Starting with ornithine methyl ester (**4**), transformation to the corresponding AI derivative **5**·2HCl was accomplished using the method of Lancini et al.[6] While side chain oxidations of alkyl derivatives of heteroaromatic compounds by halogens are known in aprotic solvents,[7] AI derivatives, however, are generally insoluble in such solvents. The development of an alternative approach to install the olefin functionality found in aminoimidazoles **1** and **2** was required. When **5** was treated with *N*-chlorosuccinimide (1 equiv) in methanol (23 °C, 1 h), conversion to the imidazoline adduct, **6**·2HCl, was achieved in 83% yield.[8,9] This dialkoxy cyclic guanidine adduct[10] was anticipated to serve as a useful precursor for the introduction of the alkene functionality upon rearrangement. Few, related examples in the literature involving the addition to the 4,5-double bond of AIs can be seen in the intramolecular oxidative cycloaddition used for the biomimetic synthesis of dibromophakellin[11] and the intermolecular [2 + 4] cycloaddition to afford tetrahydropurine derivatives[12] that we have reported previously. The trans stereochemical assign-

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† Dedicated to Professor Gilbert Stork on the occasion of his 75th birthday.

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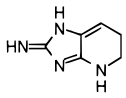
(8) In previous unpublished investigations from the Büchi group on the synthesis of saxitoxin, 4,5-dimethoxyimidazolines were obtained from the reaction of 4-acyl-2-aminoimidazoles with NBS in methanol. Dupriest, M. Ph.D. Thesis, Massachusetts Institute of Technology, 1982.

(9) In the presence of base, **5** (free base) produced compound I as the major product.



I

(10) A limited number of related dihydroxy adducts has been reported from the reaction of guanidines with glyoxal and α-diketones: (a) Nishimura, T.; Nakano, K.; Shibamoto, S.; Kitajima, K. *J. Heterocycl. Chem.* **1975**, *12*, 471. (b) Nishimura, T.; Kitajima, K. *J. Org. Chem.* **1976**, *41*, 1590. (c) Nishimura, T.; Kitajima, K. *J. Org. Chem.* **1979**, *44*, 818. (d) McClelland, R. A.; Panicucci, R.; Rauth, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 4308.

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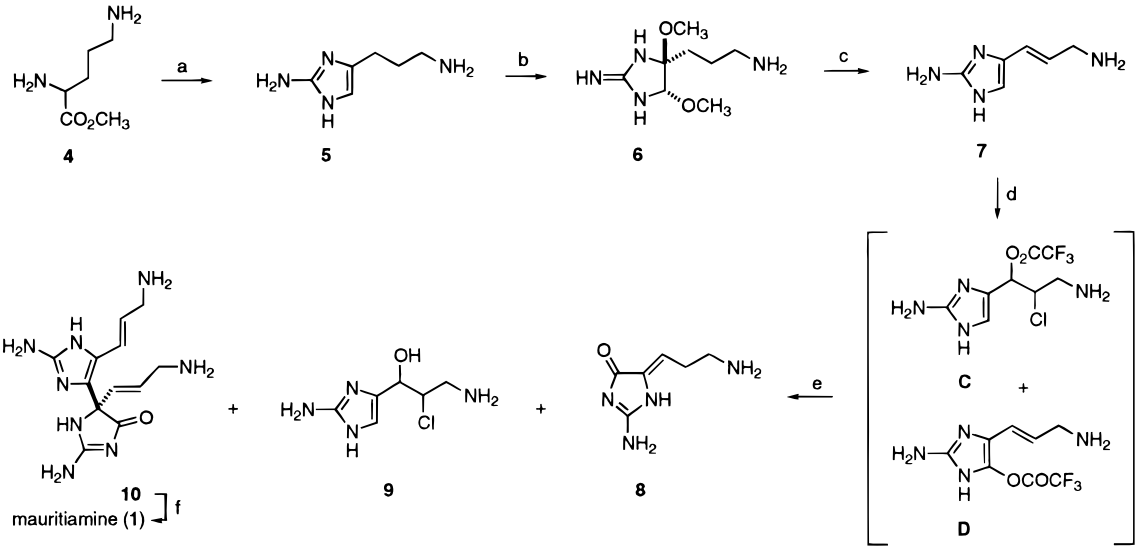
Scheme 1[a]



[a] Key: (a) Na/Hg, H_2NCN, 70%; (b) NCS, MeOH, 83%; (c) MeOH/xylene, 135 °C, **7** (60%); (d) NCS, TFA, rt; (e) MeOH/xylene, 135 °C, **8** (42%), **9** (12%), **10** (23%); (f) 4,5-dibromo-2-(trichloroacetyl)pyrrole, DMF, rt, 65%.

ment of the methoxyl groups of **6** was made based on 1-D selective NOESY analysis.[13]

Rearrangement of **6**·2HCl was investigated thermally by heating in a 1:1 mixture of methanol/*m*-xylene. After 3 h at 135 °C (during which MeOH was allowed to evaporate), **6** was converted to vinyl derivative **7** in 60% yield.[14,15] Olefin **7** is also a sponge metabolite isolated from *Axinellidae* sp.[16] Next, the oxidative dimerization of this metabolite was examined. Initially, olefin **7**·2HCl was exposed to NCS (1 equiv, 23 °C, 30 min) in TFA. Removal of TFA afforded a residue that was heated in a solution of MeOH/*m*-xylene while allowing MeOH to evaporate. This afforded imidazolinone **8** (42%), chlorohydrin **9** (12%), and dimer **10** (23%) after chromatography over silica.[17] Acylation of **10** with 4,5-dibromo-2-trichloroacetylpyrrole[18] produced mauritiamine (**1**). The spectral data for synthetic **1** were in satisfactory agreement with those reported for the natural material.[2,19]

The exact process by which **7** undergoes oxidative dimerization is unclear at this time. In TFA, oxidation of **7** by NCS is believed to produce intermediates **C** and **D**. Intermediate **C** arises from 1,2-addition of Cl^+ and CF_3CO_2H while 1,4-addition followed by elimination of HCl affords **D**. Upon the addition of MeOH/*m*-xylene and heating, **C** is converted to intermediate **A** (R = H, X = Cl) by elimination of CF_3CO_2H and to chlorohydrin **9** by methanolysis of the trifluoroacetyl group. Nucleophilic addition to intermediate **A** upon methanolysis of the trifluoroacetyl moiety of **D** followed by elimination of HCl produces dimer **10**.

Starting from ornithine methyl ester (**4**), the synthesis of mauritiamine (**1**) required only five steps and no protecting groups. The key transformation is the oxidative dimerization of vinyl AI **7**, which notably lacks the pyrrole carboxamide group. Perhaps a similar pathway is operative in the biogenesis of **1**.

Acknowledgment. We are grateful to Professor Nobuhiro Fusetani and Dr. Sachiko Tsukamoto for sending us the ^1H and ^{13}C NMR spectra of **1** and for their correspondences. We thank Professors Koji Nakanishi and Gilbert Stork for helpful discussions. We also thank Dr. John Decatur for his assistance in performing the NOESY experiment. Financial support from the National Institutes of Health (R01-GM50929), National Science Foundation (Young Investigator Award to D.A.H.), American Chemical Society Petroleum Research Fund, and Kanagawa Academy of Science and Technology (KAST) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds **1** and **5**−**10** (7 pages).

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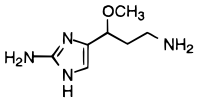
(13) Irradiation of the C5 ring proton singlet at 4.73 ppm showed NOE's to both methoxyl groups (3.35 and 3.15 ppm), whereas no enhancement was observed to the methylene protons of the aminopropyl side chain.

(14) Initially, the rearrangement was attempted in refluxing MeOH. The major product obtained under these conditions is compound II.



II

(15) All previously reported syntheses of vinyl AI derivatives related to **2** and **7** utilized Wittig chemistry in creating the olefinic double bond and relied heavily on the use of numerous protecting groups. See: (a) de Nanteuil, G.; Ahond, A.; Poupat, C.; Thoison, O.; Potier, P. *Bull. Soc. Chim. Fr.* **1986**, 813. (b) Daninos, S.; AlMourabit, A.; Ahond, A.; Zurita, M. B.; Poupat, C.; Potier, P. *Bull Soc. Chim. Fr.* **1994**, *131*, 590. (c) Webber, S. E.; Little, T. L. *J. Org. Chem.* **1994**, *59*, 7299.

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(17) Compound **9** was isolated as a 9:1 mixture of erythro:threo diastereomers. The threo isomer, (2*S*,3*S*)-2-chloro-3-hydroxy-3-(2-aminoimidazol-4-yl)propylamine, is known as girolline, a potent antitumor agent isolated from the marine sponge *Pseudaxinissa cantharella*. (a) Ahond, A.; Bedoya-Zurita, M.; Colin, M.; Fizames, C.; Laboute, P.; Lavelle, F.; Laurent, D.; Poupat, C.; Pusset, J.; Pusset, M.; Thoison, O.; Potier, P. *C. R. Seances Acad. Sci. Paris, Ser. 2* **1988**, *307*, 145. (b) Bedoya-Surita, M.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1989**, *45*, 6713. (c) Chiaroni, A.; Riche, C.; Ahond, A.; Poupat, C.; Pusset, M.; Potier, P. *C. R. Seances Acad. Sci. Paris Ser. 2* **1991**, *312*, 49.

(18) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300.

(19) The ^{13}C chemical shift values reported for mauritiamine (**1**) in ref 2 correspond to a neutral glycocyamidine species that was found to be unstable (Fusetani, N. Personal communication). We have observed significant differences in ^{13}C chemical shifts between neutral and protonated glycocyamidine derivatives, which will be the subject of a future publication.