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A New Total Synthesis of the Zinc Matrixmetalloproteinase Inhibitor Ageladine A Featuring a Biogenetically Patterned 6π-2-Azatriene Electrocyclization

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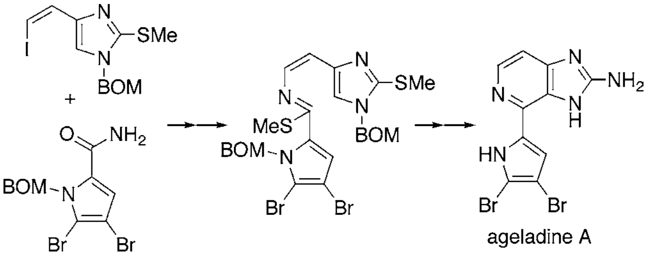
ABSTRACT



A convergent second generation total synthesis of the heterocyclic marine sponge metabolite ageladine A has been achieved by using a biomimetically inspired 6π-2-azatriene electrocyclization as the key step for formation of the imidazolopyridine moiety.

The Fusetani group recently described the isolation and characterization of ageladine A (**1**) from the marine sponge *Agelas nakamurai* Hoshino collected near Kuchinoerabujima Island in southern Japan.[1] Ageladine A was found to be active at micromolar levels as an inhibitor of various zinc matrixmetalloproteinases (MMPs) which, among other functions, are involved in the regulation of angiogenesis. Such inhibitors have shown potential as chemotherapeutic agents for the treatment of cancer, and some are presently being evaluated in clinical trials.[2] Earlier this year we reported the first total synthesis of this unique marine metabolite via a route that utilized a 6π-1-azatriene electrocyclization and a Suzuki−Miyaura coupling of *N*-Boc-pyrrole-2-boronic acid with a 2-chloropyridine derivative as key steps.[3] More recently, Shengule and Karuso have described a short synthesis of **1** using a Pictet−Spengler reaction of an imine derived from 2-aminohistamine and *N*-Boc-2-formyl-4,5-dibromopyrrole, followed by an oxidation, to generate the pyridine ring system.[4]

It was proposed by Fusetani and co-workers[1] that ageladine A (**1**) arises in nature from pyrrole aldehyde **2** (presumably derived from proline or arginine) and histamine (**3**) (Scheme 1).[5] These two fragments combine, eventually leading to *N*-vinylimine **4**, which then undergoes a 6π-2-azatriene electrocyclization to produce dihydropyridine **5**. Subsequent dehydrogenation of intermediate **5** affords the natural

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[1] Fujita, M.; Nakao, Y.; Matsunaga, S.; Seiki, M.; Itoh, Y.; Yamashita, J.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc*. **2003**, *125*, 15700.

[2] For reviews see: (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735. (b) Matter, A. *Drug Discovery Today* **2001**, *6*, 1005.

[3] Meketa, M. L.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1443.

[4] Shengule, S. R.; Karuso, P. *Org. Lett.* **2006**, *8*, 4083.

[5] For biosynthetic studies on pyrrole-imidazole alkaloids see: (a) Vergne, C.; Boury-Esnault, N.; Perez, T.; Martin, M.-T.; Adeline, M.-T.; Dau, E. T. H.; Al Mourabit, A. *Org. Lett.* **2006**, *8*, 2421 and references cited therein. (b) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

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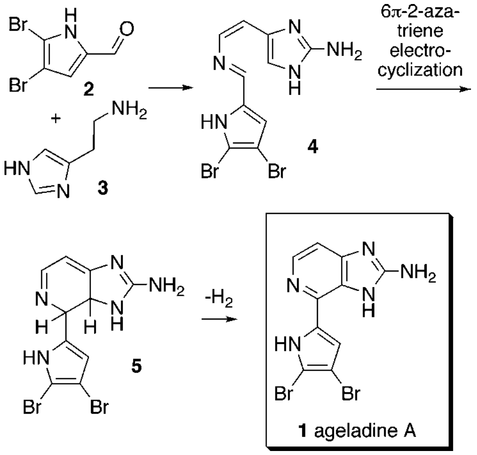
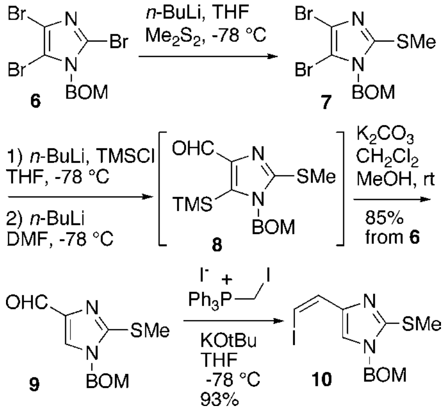
product. In this letter, we describe a new synthesis of ageladine A that features a biomimetically inspired 6π-2-azatriene electrocyclization as the pivotal step to construct the imidazolopyridine moiety.

Scheme 1



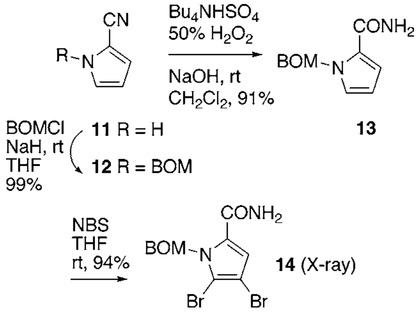
The synthesis commenced with tribromoimidazole **6**,[3] which was selectively transmetallated at C-2 with *n*-butyllithium and converted into sulfide **7** with dimethyl disulfide (Scheme 2). In a one-pot process based upon the methodology of Begtrup,[6] dibromide **7** was first selectively transmetallated at C-5 and the resulting carbanion was C-silylated. Without isolation the 4-bromosilylimidazole product was transmetallated and formylated to produce aldehyde **8**. The crude compound was then desilylated with potassium carbonate to afford the desired imidazole aldehyde **9** in good overall yield from tribromide **6**. Employing the procedure of Stork and Zhao,[7] aldehyde **9** could subsequently be converted cleanly into the (*Z*)-vinyl iodide **10**.

Scheme 2



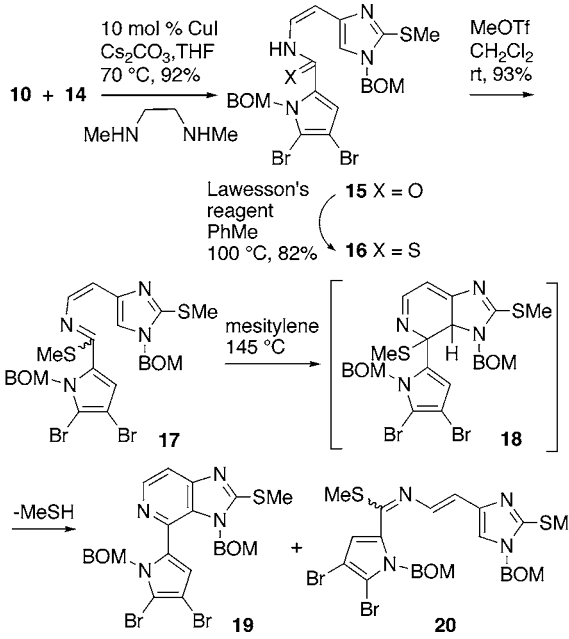
The requisite pyrrole fragment was prepared from commercially available 2-cyanopyrrole (**11**), which was first protected as its *N*-BOM derivative **12** (Scheme 3). The nitrile functionality was then transformed into amide **13** with basic hydrogen peroxide,[8] and bromination with NBS led to dibromopyrrole amide **14**. To ensure that the dibromination step had occurred with the desired regiochemistry, the structure of **14** was confirmed by X-ray crystallography.

Scheme 3



By using the protocol of Buchwald and co-workers,[9] it was possible to combine vinyl iodide **10** with amide **14** to produce (*Z*)-enamide **15** stereoselectively in high yield (Scheme 4). We were pleased to find that the bromine atoms in the pyrrole ring were fully compatible with this coupling process.[10] This enamide could be converted to the thioenamide **16** with Lawesson's reagent, and methyl triflate

Scheme 4



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(6) Eriksen, B. L.; Vedso, P.; Begtrup, M. *J. Org. Chem.* **2001**, *66*, 8344.

(7) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.

(8) Zlatopolskiy, B. D.; Kroll, H.-P.; Melotto, E.; de Meijere, A. *Eur. J. Org. Chem.* **2004**, 4492.

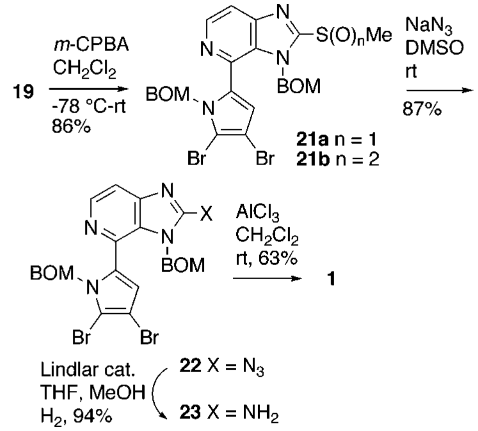
(9) Jieng, L.; Job, G. E.; Klapers, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

(10) Cf.: Sun, C.; Camp, J. E.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1779.

served to produce the thiomethyl imidate **17**.[11,12] To effect the key electrocyclization step,[13,14] heating *N*-vinyl imidate **17** in a dilute solution of mesitylene at 145 °C for 16 h afforded the desired imidazolopyridine **19** (44% isolated yield, 51% based on recovered starting material **17**). The major byproduct detected in this process appears to be the isomerized (*E*)-vinyl imidate **20** (27%).

To continue the synthesis, sulfide **19** was first treated with *m*-CPBA to produce mainly sulfoxide **21a** (76%) along with a smaller amount of the corresponding sulfone **21b** (10%) (Scheme 5). This mixture was subsequently treated with sodium azide in DMSO at room temperature to afford the 2-azidoimidazole **22** in good yield. The azide was then reduced by hydrogenation over Lindlar catalyst to afford amine **23** in 94% yield. After some experimentation, it was found that both BOM protecting groups can be removed by exposure of intermediate **23** to anhydrous aluminum trichloride[15] in methylene chloride at room temperature, affording ageladine A (**1**) identical with material that we have previously synthesized.[3]

Scheme 5



In conclusion, we have completed a biogenetically inspired total synthesis of the antiangiogenic marine metabolite ageladine A (**1**) that features as the key step a thermal 6π-2-azatriene electrocyclization for construction of the imidazolopyridine system. This new convergent synthesis requires only seven steps from easily prepared (*Z*)-vinyl iodide imidazole fragment **10** and dibromopyrrole amide **14**, and the approach would appear to be amenable to facile synthesis of structural analogues of the natural product.

Acknowledgment. We are grateful to the National Science Foundation (CHE-0404792) for financial support of this research and Dr. H. Yennawar (Penn State Small Molecule X-ray Crystallographic Facility) for the X-ray structure determination of dibromopyrrole **14**. We also thank Professor Blake Peterson and Jocelyn Edathil (Penn State University) for assistance with reverse phase HPLC analysis.

Supporting Information Available: Experimental procedures for preparation of new compounds including X-ray and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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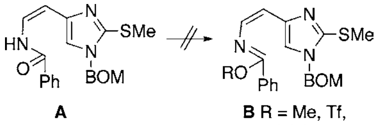
[11] In some extensive studies with model enamide **A** we were unable to directly form any imidate derivatives **B**



A

B R = Me, Tf, Ac, $COCF_3$, etc.

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[12] The NMR spectra of thioimidate **17** show broad peaks (see the Supporting Information) which might be due to rapid inversion of the imine nitrogen.

[13] Cf.: (a) Biere, H.; Russe, R.; Seelen, W. *Liebigs Ann. Chem*. **1986**, 1749. (b) Qiang, L. G.; Baine, N. H. *Tetrahedron Lett.* **1988**, *29*, 3517. (c) Palacios, F.; Gil, M. J.; Martinez de Marigorta, E.; Rodriguez, M. *Tetrahedron* **2000**, *56*, 6319. (d) Campos, P. J.; Caro, M.; Rodriguez, M. A. *Tetrahedron Lett.* **2001**, *42*, 3575.

[14] For a general review of triene electrocyclizations see: Okamura, W. H.; de Lera, A. R. 1,3-Cyclohexadiene Formation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, pp. 699−750.

[15] Groves, J. K.; Cundasawmy, N. E.; Anderson, H. J. *Can. J. Chem.* **1973**, *51*, 1089.