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Total Synthesis of Ageladine A, an Angiogenesis Inhibitor from the Marine Sponge *Agelas nakamurai*

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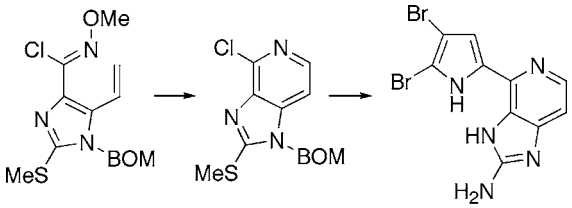
ABSTRACT



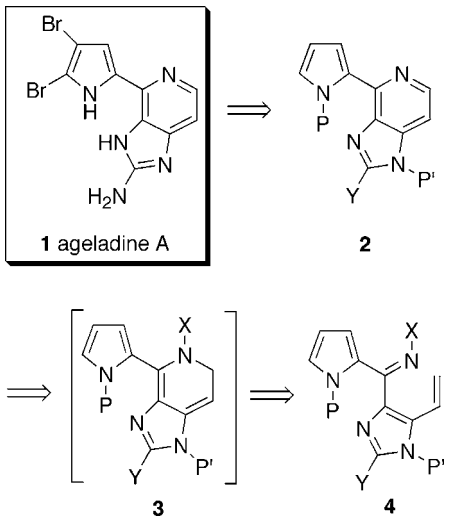
ageladine A

A 12-step total synthesis of the tricyclic heteroaromatic marine metabolite ageladine A has been achieved using a 6π-azaelectrocyclization and a Suzuki–Miyaura coupling of *N*-Boc-pyrrole-2-boronic acid with a chloropyridine as key steps.

In 2003, Fusetani and co-workers described the isolation of ageladine A (**1**) by bioassay-guided fractionation of the marine sponge *Agelas nakamurai* Hoshino collected near Kuchinoerabu-jima Island in southern Japan.[1] The structure of this metabolite was established primarily by 2D NMR analysis. Ageladine A shows activity at micromolar levels as an inhibitor of matrixmetalloproteinases (MMPs) which are involved in regulation of angiogenesis. Such inhibitors have promise as antimetastatic agents, and some are currently in clinical trials.[2] It is believed that ageladine A inhibits MMP-2 via a mechanism of action different from that of other inhibitors. This metabolite thus provides a novel structural and biological lead in this field and spurred our interest as a worthwhile target for total synthesis. In this communication, we describe the first total synthesis of ageladine A.

Our basic strategy for the synthesis of ageladine A is outlined in Scheme 1. The initial plan was to prepare a tricyclic intermediate **2** via a 6π-azaelectrocyclization of a vinylimidazole system such as **4**. This process would proceed through a dihydropyridine **3**, which would then aromatize

Scheme 1



(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) (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.

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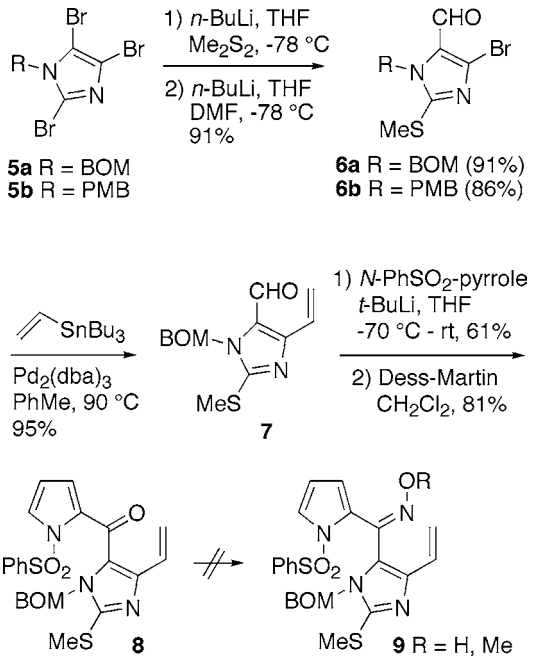
by elimination of HX. Such electrocyclizations of 1-azatrienes have been known for a number of years, although this reaction has not been widely utilized in natural product synthesis.[3,4] Moreover, there was good precedent for our strategy in the nice work of Hibino et al. who used electrocyclizations of 1-azatrienes for the preparation of various imidazopyridines.[5]

To prepare the requisite substrates for the ageladine A project, we chose to make use of the fact that trihaloimidazoles can be sequentially and predictably metalated.[6] We have explored two series of N-protected imidazoles in this work, one involving benzyloxymethyl (BOM) protection and the other utilizing a *p*-methoxybenzyl (PMB) group. Thus, readily available BOM-protected tribromo compound **5a**[7] was first metalated with *n*-butyllithium at C(2), and a thiomethyl group was introduced using dimethyl disulfide (Scheme 2).

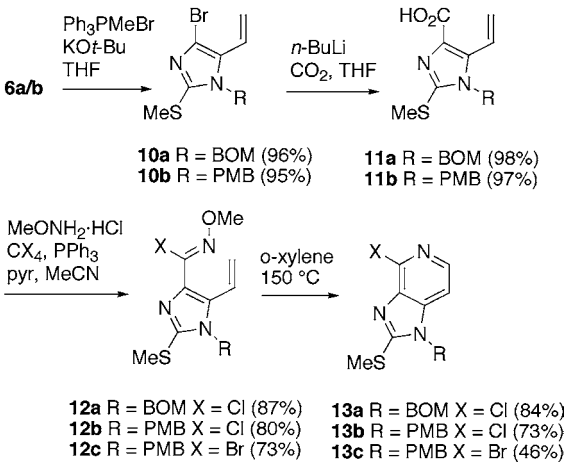
Scheme 2



Without workup, a second equivalent of *n*-butyllithium was then added to the reaction mixture to effect metalation at C(5), followed by introduction of DMF, leading to aldehyde **6a** in 91% overall yield for the one-pot operation. Similarly, known PMB-protected imidazole **5b**[8] could be transformed to bromo aldehyde **6b** in high yield. Continuing with the BOM-protected bromo aldehyde **6a**, it was possible to effect a Stille coupling with vinyltributylstannane to generate vinylimidazole aldehyde **7**. Addition of 2-lithio-*N*-benzenesulfonylpyrrole[9] to this aldehyde, followed by oxidation of the resulting alcohol with the Dess−Martin periodinane, yielded ketone **8**. However, despite considerable effort, we were unable to convert the ketone to the corresponding oxime or *O*-methyloxime **9**. Moreover, ketone **8** was unreactive toward any substituted hydrazines or semicarbazide. In view of these failures, it became necessary to modify the synthetic strategy.

Using Wittig chemistry, we converted imidazole aldehydes **6a** and **6b** to bromo vinylimidazoles **10a** and **10b**, respectively (Scheme 3). These bromides could then be lithiated,

Scheme 3



and upon treatment with carbon dioxide, they produced carboxylic acids **11a** and **11b**. Applying the methodology of Kikugawa, we transformed BOM-protected compound **11a** directly into *N*-methoxy imidoyl chloride **12a** in good yield.[10] Similarly, the PMB-protected acid **11b** was converted into both the *N*-methoxy imidoyl chloride **12b** and the corresponding bromo compound **12c**.

Inspired by the publication of Kim and co-workers,[11] we decided at this point to convert imidoyl bromide **12c** directly into oxime derivative **16** (eq 1). Unfortunately, attempts at coupling **12c** with either commercially available *N*-Boc-pyrrole boronic acid **14** or the stannane **15** were uniformly unsuccessful. In general, the only product which could be

(3) For a review, 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, 1991; Vol. 5, pp 699−750.

(4) (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763. (b) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099. (c) Tanaka, K.; Kobayashi, T.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 5906.

(5) (a) Yoshioka, H.; Choshi, T.; Sugino, E.; Hibino, S. *Heterocycles* **1995**, *41*, 161. (b) Yoshioka, H.; Matsuya, Y.; Choshi, T.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1996**, *44*, 709. (c) Kumemura, T.; Choshi, T.; Yukawa, J.; Hirose, A.; Nobuhiro, J.; Hibino, S. *Heterocycles* **2005**, *66*, 87.

(6) (a) Iddon, B.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1445. (b) Lipshutz, B. H.; Hagen, W. *Tetrahedron Lett.* **1992**, *33*, 5865. (c) Groziak, M. P.; Wei, L. *J. Org. Chem.* **1991**, *56*, 4296. (d) Chen, Y.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2003**, *44*, 1379. (e) Carver, D. S.; Lindell, S. D.; Saville-Stones, E. A. *Tetrahedron* **1997**, *53*, 14481.

(7) Preparation of **5a** from commercially available 2,4,5-tribromoimidazole: Schumacher, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935.

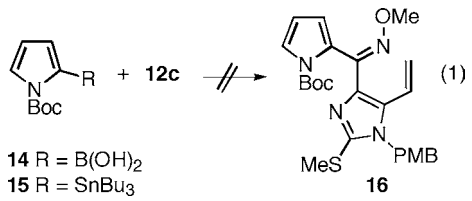
(8) Preparation of **5b**: Iddon, B.; Khan, N.; Lim, B. L. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1437.

(9) (a) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157. (b) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418.

(10) Kikugawa, Y.; Fu, L. H.; Sakamoto, T. *Synth. Commun.* **1993**, *23*, 1061.

(11) Chang, S.; Lee, M.; Kim, S. *Synlett* **2001**, 1557.

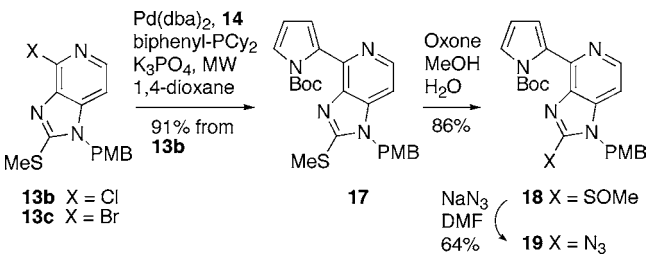
isolated from these reactions was the vinylimidazole nitrile derived from reductive elimination of the bromide **12c**.



At this stage, we returned to the *N*-methoxy imidoyl halides, and 6π-electrocyclizations of these systems were investigated based upon the results of Hibino.[5b] It was found that heating a dilute solution of imidoyl chloride **12b** in *o*-xylene indeed afforded the desired chloro imidazopyridine **13b** in 73% yield. The yield of **13b** could be improved slightly to 81% if the electrocyclization was run in a microwave reactor, but because of scale-up problems, this procedure was not normally used. In the case of imidoyl bromide **12c**, the electrocyclization afforded only a modest 46% yield of bromopyridine **13c**, along with about 13% of recovered starting material. With the BOM-protected imidoyl chloride **12a**, chloropyridine **13a** was obtained in 84% isolated yield upon heating in *o*-xylene.

We next turned to introduction of a pyrrole moiety into these halopyridines via a transition-metal-mediated coupling, and this transformation turned out to be surprisingly difficult to effect. In general, standard Suzuki−Miyaura couplings with pyrrole boronic acid **14** or Stille couplings with stannane **15** left the halopyridines unchanged. In addition, similar problems were found with Negishi couplings using known methodology.[12] After considerable experimentation, it was finally discovered that if Buchwald's 2-biphenyldicyclohexylphosphine ligand was used[13] Suzuki−Miyaura couplings of our halopyridines with boronic acid **14** could be achieved. Thus, heating chloropyridine **13b** in 1,4-dioxane at 80 °C for 20 h in the presence of the Buchwald ligand, $Pd(dba)_2$, and potassium phosphate afforded tricycle **17** in 70% yield, along with 25% of recovered starting chloride (Scheme 4). In the case of bromopyridine **13c**, the yield of

Scheme 4

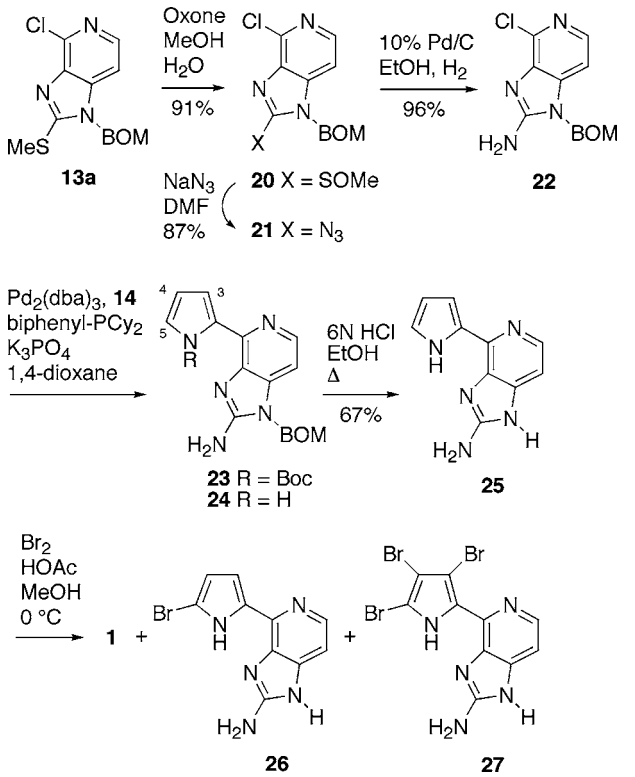


coupled product **17** was somewhat lower (60%), along with that of starting material (20%).[14] Because the yields for the synthesis of bromopyridine **13c** were lower than that for the chloro compound and because of the poorer coupling yields, we concentrated on optimizing the formation of **17** from chloropyridine **13b**. It was found that, if the coupling of **13b** with boronic acid **14** is conducted at 150 °C for 40 min in a microwave reactor,[15] tricycle **17** can be produced in 91% yield along with only 5% of recovered chloride.

To continue the synthesis, tricyclic sulfide **17** was oxidized to the corresponding sulfoxide **18**, and this functionality could be displaced by heating with sodium azide in DMF to afford 2-azidoimidazolopyridine **19**.[16] Unfortunately, we have been unable to remove the PMB protecting group from any of the intermediates **17**−**19** by either treatment with acid or catalytic hydrogenation. Because of these difficulties, we therefore returned to the BOM-protected series.

It was found, however, that Suzuki−Miyaura coupling of BOM-protected chloropyridine **13a** with boronic acid **14** could not be effected, once again requiring a modification of the strategy.[17] Thus, Oxone oxidation of sulfide **13a** led to the sulfoxide **20**, and displacement with sodium azide at room temperature afforded the azide **21** in good yield (Scheme 5). Catalytic hydrogenation of this azide then cleanly afforded 2-aminoimidazolopyridine **22**.

Scheme 5



Using the reaction conditions previously employed (cf. Scheme 4), we could couple chloride **22** with boronic acid

(12) Dinsmore, A.; Billing, D. G.; Mandy, K.; Michael, J. P.; Mogano, D.; Patil, S. *Org. Lett.* **2004**, *6*, 293.

(13) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779.

14 to afford a ~2:1 mixture of Boc-protected tricyclic pyrrole **23** and compound **24** where the Boc group has been lost. In this reaction, no coupling of the amino group of **22** with boronic acid **14** was observed.[18] The crude mixture of coupled products **23** and **24** was then hydrolyzed with 6 N HCl in ethanol to afford deprotected tricycle **25** in 67% overall yield from chloropyridine **22**.

Bromination of pyrrole **25** proved to be problematic and was quite difficult to control.[19] The best conditions found for the halogenation involved treating **25** with bromine in cold acetic acid/methanol which produced ageladine A (**1**) (17%), along with recovered starting material (29%), the 5-bromo compound **26** (50%), and a small amount of 3,4,5-tribromopyrrole **27** (2%).[20] These compounds were separable by reverse-phase HPLC. Both the monobromopyrrole **26** and the starting material could be recycled to the natural product. Synthetic ageladine A has proton and carbon NMR spectra, as well as UV and fluoresence maxima, identical to those reported for the natural material.[1]

Acknowledgment. We are grateful to the National Science Foundation (CHE-0404792) for financial support of this research. We also thank Professor Blake Peterson and Jocelyn Edathil for assistance with reverse-phase HPLC analysis and Dr. A. Ganesan (University of Southampton, U.K.) for helpful discussions.

Supporting Information Available: Experimental procedures for the preparation of new compounds including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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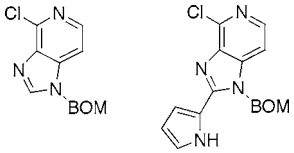
(14) It should be noted that, using similar reaction conditions in purine systems, Lakshman et al. found that chlorides generally undergo Suzuki–Miyaura couplings in higher yields than do the corresponding bromides.[13b]

(15) Song, Y. S.; Kim, B. T.; Heo, J.-N. *Tetrahedron Lett*. **2005**, *46*, 5987.

(16) Jarosinski, M. A.; Anderson, W. K. *J. Org. Chem*. **1991**, *56*, 4058.

(17) Only the compounds shown below could be isolated in low yields in these reactions. It appears that the BOM group directs metalation to the C(2) position of imidazolopyridine **13a**.



(18) For analogous chemoselectivity, see: Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem*. **2005**, *70*, 388.

(19) Although bromination of the Boc-protected pyrrole **23** was more controllable, to our surprise, the product in this case was the undesired 3,5-dibromo compound.

(20) Attempts to push the bromination of **25** to completion led to significant quantities of tribromopyrrole **27** which is difficult to separate from ageladine A (see Supporting Information).