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A convergent total synthesis of the marine sponge alkaloid ageladine A via a strategic 6π-2-azatriene electrocyclization

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Abstract—A second generation total synthesis of the marine sponge metabolite ageladine A utilizing a biogenetically inspired 6π-2-aza-electrocyclization of triene **34** as the key step is performed to construct the imidazopyridine core of the metabolite.

1. Introduction

In 2003, Fusetani and co-workers reported the isolation of ageladine A (**1**) from the hydrophilic extract of the marine sponge *Agelas nakamurai* Hoshino, which was collected off the coast of Kuchinoerabu-jima Island in Southern Japan (Fig. 1).[1] The structure of this fluorescent marine alkaloid was elucidated using a series of NMR studies, including HMBC data for various *N*-methylated derivatives. Interestingly, ageladine A (**1**) is the first and, to date, only isolated metabolite of this family to possess a 2-aminoimidazopyridine core.

Ageladine A (**1**) displays inhibitory activity against matrix metalloproteinases (MMPs), particularly MMP-2 at micromolar levels. MMPs are a family of over two dozen zinc-dependent enzymes that regulate multiple steps of tumor angiogenesis.[2] One role of MMPs is to mediate the breakdown of connective tissue, allowing tumor growth. In addition to being involved in angiogenesis, MMP-2 is known to complex with other MMPs at the tumor migration front.[1,3] Thus, MMP-2 inhibitors are presumed to be both antiangiogenic and antimetastatic, making them potential cancer chemotherapeutic agents.

MMP inhibitors usually act by chelation of the catalytic zinc(II) ion within the active site of the enzymes. Interestingly, studies have shown that ageladine A (**1**) is not capable of zinc(II) binding and that the inhibition of MMP-2 is not competitive by kinetic analysis.[1] Thus, ageladine A is believed to have an atypical and as yet unknown mode of MMP inhibition.

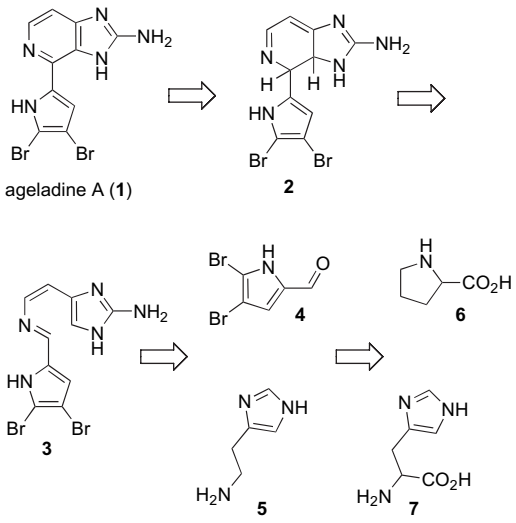

Figure 1. Postulated biosynthesis of ageladine A.

We reported the first total synthesis of ageladine A in 2006, which featured a 6π-1-azatriene electrocyclization and a Suzuki–Miyaura coupling of a 2-chloropyridine derivative as key steps.[3] Shengule and Karuso later described a second synthesis of the marine metabolite in which an efficient Pictet–Spengler reaction, followed by an oxidation, furnished the natural product.[4] Earlier this year we described a biogenetically inspired total synthesis highlighted by a 6π-2-azatriene electrocyclization to construct the imidazopyridine skeleton of ageladine A.[5,6] Herein, we provide a detailed account of our second generation total synthesis of ageladine A (**1**).

Keywords: Ageladine A; Electrocyclization; Natural product; Imidazole; Pyrrole.
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2. Synthetic plan

Marine sponges of the genus *Agelas* have been reported to contain numerous bioactive pyrrole–imidazole alkaloids, with most being derivatives of the oroidin class of natural products.[7] Kerr and co-workers have demonstrated through feeding studies of radio-labeled amino acids that the biogenetic precursors of one such metabolite, stevensine, are proline and histidine.[8,9] Based on these experimental results, Fusetani and co-workers proposed a biosynthesis for ageladine A (**1**) involving either an intramolecular 6π-2-azatriene electrocyclization of *N*-vinyl imine **3** or a Mannich-like ring closure of this same intermediate, followed by dehydrogenation of the resulting dihydropyridine **2** (Fig. 1). Formation of imine **3** could be envisioned from the precursors dibromopyrrole aldehyde **4** and histamine (**5**), which could be derived from proline (**6**) and histidine (**7**), respectively.[1]

We decided to explore a 6π-1-azatriene cyclization to produce the pyridine core and thus required a key 2-azatriene like **9** (Fig. 2). This intermediate is similar to that proposed by Fusetani, except that **9** is in a higher oxidation state than imine **3** (cf. Fig. 1). As a result, the cyclized product **8** could provide the fully aromatic imidazopyridine core of ageladine A simply via loss of H–X. Imidate derivative **9** should be available from the corresponding enamide **10**, which would be obtained from the coupling of (*Z*)-vinyl iodide **11** and dibromopyrrole amide **12**. We also planned to incorporate the pyrrole bromine atoms into intermediate **10**, which would avoid the inefficient late stage pyrrole halogenation step that was used in our first generation total synthesis of ageladine A.[3]

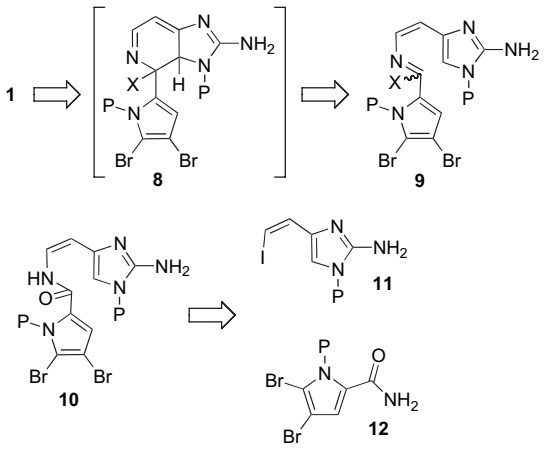
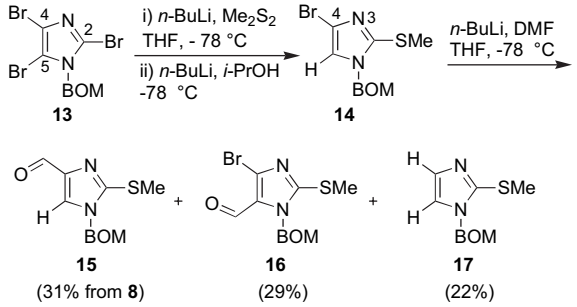


Figure 2. Retrosynthesis of ageladine A.

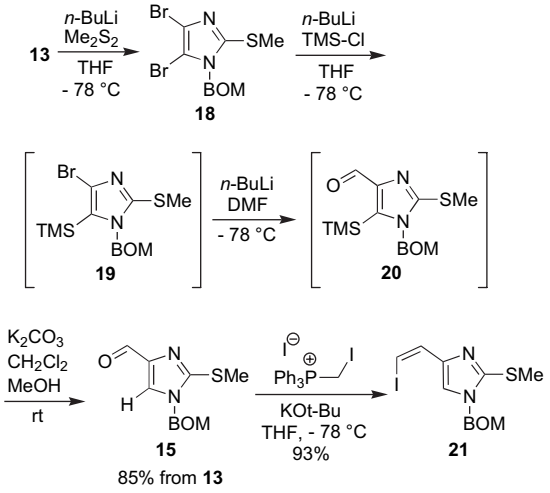
3. Results and discussion

Our initial synthetic efforts focused on a model study of the pivotal 6π-2-azatriene electrocyclization where the dibromopyrrole fragment of the natural product was replaced by a phenyl group. The synthesis began with BOM-protected tribromoimidazole (**13**), which can be sequentially and predictably metallated.[10] Thus, in a one-pot procedure, tribromoimidazole **13** was first metallated with *n*-butyllithium at C(2), and subsequent addition of dimethyl disulfide introduced a thiomethyl moiety. Without workup, addition of another equivalent *n*-butyllithium to the reaction mixture metallated C(5) and subsequent protonation of the lithiated species using isopropanol gave 4-bromoimidazole **14** (Scheme 1). Metallation of crude 4-bromoimidazole **14**, followed by addition of DMF gave the desired imidazole aldehyde **15** in 31% overall yield, along with 4-bromo-5-carboxaldehyde imidazole **16** and 4,5-unsubstituted imidazole **17** as significant by-products. Due to the formation of these unwanted compounds in the formylation of **14**, an alternative more efficient route to aldehyde **15** was devised.



Scheme 1.

The formation of significant amounts of the undesired regioisomeric aldehyde **16** can be rationalized by invoking the well documented adjacent lone pair effect (ALP effect),[11] where the carbanion resulting from halogen–metal exchange of imidazole **14** at C(4) is destabilized by the lone pair on the N(3) nitrogen. However, we believed that placing a C(5) protecting group on the imidazole should obviate this problem. Thus, tribromoimidazole **13** was selectively metallated, followed by addition of dimethyl disulfide to afford sulfide **18** (Scheme 2). In a one-pot process based upon the methodology of Begtrup and co-workers,[12] dibromoimidazole **18** was then lithiated at C(5) and subsequent addition of trimethylsilyl chloride resulted in the 4-bromo-5-silylimidazole **19**. Without isolation, this compound was immediately metallated and formylated with DMF to yield the functionalized aldehyde **20**. Without purification, TMS-imidazole **20** was desilylated using potassium

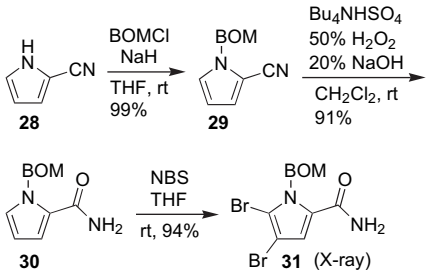


Scheme 2.

carbonate in methanol to afford the desired imidazole aldehyde **15** in 85% overall yield from tribromoimidazole **13**. Utilizing the procedure of Stork and Zhao,[13] aldehyde **15** was then smoothly converted to the requisite (*Z*)-vinyl iodide **21** using (iodomethyl)triphenylphosphonium iodide[14] and potassium *tert*-butoxide.

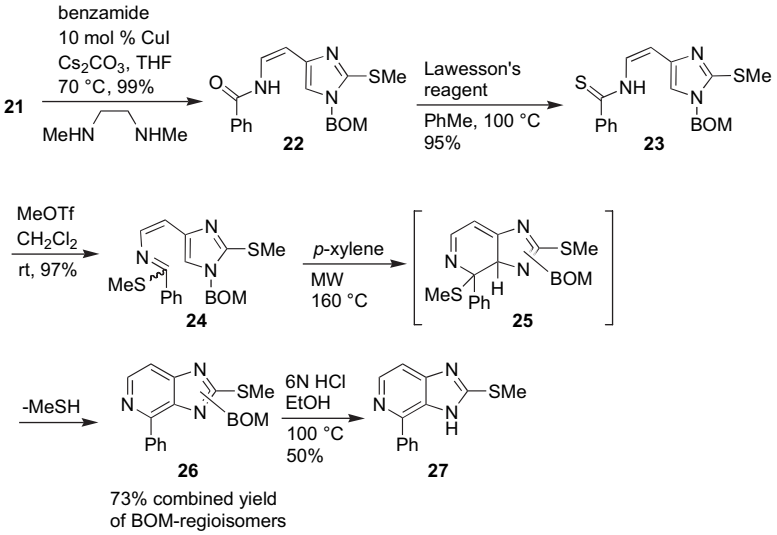
Continuing with the model study, an imidate substrate for the 6π-2-azatriene electrocyclization was fashioned.[15] Thus, the procedure of Buchwald and co-workers was used to couple (*Z*)-vinyl iodide **21** with benzamide to afford enamide **22** in high yield and with complete retention of the olefin geometry (Scheme 3).[16] Unfortunately, enamide **22** could not be directly converted to an imidate under a variety of conditions, including Meerwein's salt, triflic anhydride, trifluoroacetic anhydride, and several different silylating/base combinations. In all cases only starting imidate **22** was recovered. However, it was finally found that treatment of **22** with Lawesson's reagent gave the corresponding thioenamide **23** in 95% yield. Conversion of thioenamide **23** to the desired thioimidate **24** proceeded smoothly using methyl triflate.[17] We were pleased to find that subjecting a dilute solution of thioimidate **24** in *p*-xylene to microwave irradiation at 160 °C gave the desired imidazopyridine **26** as a separable mixture of BOM-regioisomers in 73% combined yield.[18] Heating enamide **24** as a dilute solution in refluxing xylene produced cyclization products **26** in significantly lower yield. Refluxing a solution of BOM-protected imidazopyridine regioisomers **26** in 6 N HCl in ethanol produced *N*–H imidazopyridine **27**. It might be noted that facile BOM migration has been noted in other imidazole systems.[19]

With the model system successfully tested, we addressed the synthesis of ageladine A by preparing the requisite dibromopyrrole amide substrate. Thus, commercially available 2-cyanopyrrole (**28**) was first BOM-protected to afford **29** in high yield (Scheme 4). Initial bromination attempts with unprotected nitrile **28** or BOM-protected nitrile **29** using a variety of brominating reagents led to complex mixtures of starting pyrrole, as well as mono-, di-, and tribrominated products in poor yields. Thus, basic hydrogen peroxide was utilized to convert the nitrile functionality of pyrrole **29** to the corresponding amide **30**.[20] Fortunately, bromination of pyrrole amide **30** with NBS gave the required 4,5-dibromopyrrole amide **31** in high yield. X-ray crystallography was used to confirm that the pyrrole had the desired bromine regiochemistry required for the natural product.



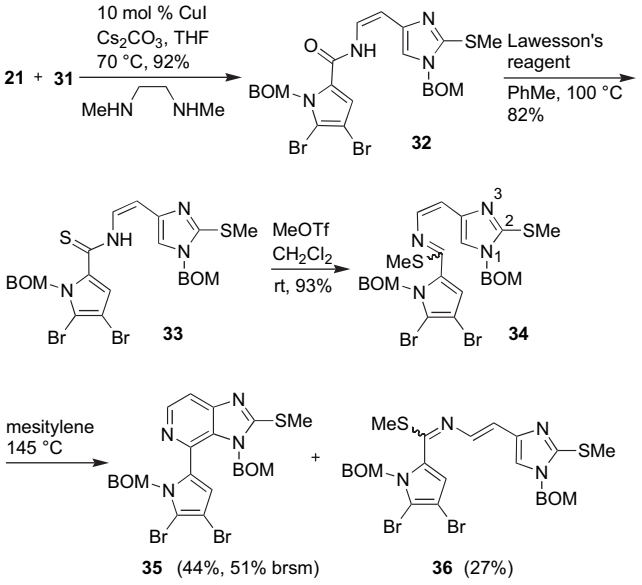
Scheme 4.

With both necessary substrates in hand, (*Z*)-vinyl iodide **21** and dibromopyrrole amide **31** were coupled using the Buchwald conditions to give (*Z*)-enamide **32** stereoselectively in 92% yield (Scheme 5). In addition, the copper-catalyzed coupling reaction was completely chemoselective, with the pyrrole bromine atoms being unaffected.[21] Following the protocol developed in the above model study, enamide **32** was first converted to the corresponding thioenamide **33** using Lawesson's reagent and treatment with methyl triflate then produced thioimidate **34** in good overall yield. However, attempts at the 6π-2-azatriene electrocyclization of thiomethyl imidate **34** in *p*-xylene using microwave irradiation at 160 °C gave complex mixtures of starting (*Z*)-vinyl thioimidate **34**, isomerized (*E*)-vinyl imidate **36**, and both BOM-regioisomers of imidazopyridine **35**. On the other hand, when the cyclization was performed by heating a dilute solution of **34** in mesitylene at 145 °C, BOM-regioisomer **29** was produced in 44% isolated yield (51% based on recovered starting material). The major byproduct in this 6π-2-azaelectrocyclization was the isomerized (*E*)-vinyl imidate **36** (27%). A range of reaction temperatures and solvent



Scheme 3.

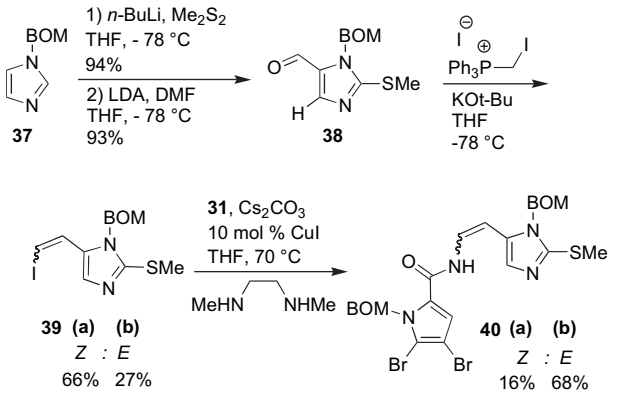
systems were examined for the electrocyclization, as well as the addition of various Lewis acids and buffers. However, the partial (*E*)/(*Z*) isomerization of the vinyl thioimidate could not be suppressed. Interestingly, this thermal (*E*)/(*Z*) isomerization was not observed in the model system **24**. Unfortunately, (*E*)-isomer **36** did not undergo cyclization either thermally or via microwave irradiation to give the desired imidazopyridine **35**. It should also be noted that attempts to photochemically effect the cyclization of thioenamide **33** or thioimidate **34** failed to give any pyridine products, with only starting material or isomerized (*E*)-vinyl imidate **36** being recovered.[22]



Scheme 5.

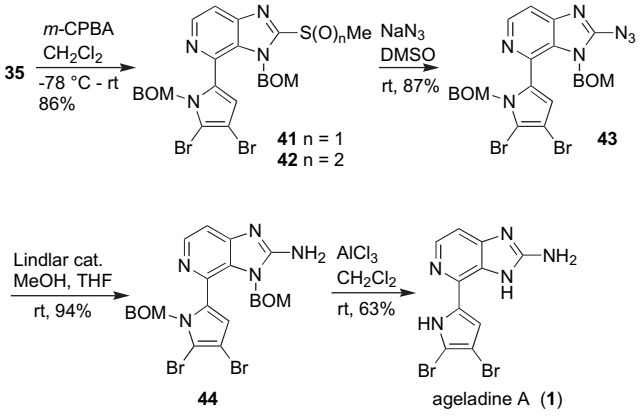
At this point, we decided to examine an alternative system to possibly improve the yield of the 6π-2-azaelectrocyclization product **35**. We chose to examine the imidazole N(3) BOM-regioisomer of **34** where the protecting group is adjacent to the vinyl substituent, perhaps relieving steric strain during the 6π-2-azaelectrocyclization. Thus, BOM-protected imidazole (**37**)[23] was selectively metallated at C(2) using *n*-butyllithium and converted to the corresponding sulfide with dimethyl disulfide. The 2-methylthioimidazole was then selectively metallated at C(5) with lithium diisopropylamide and the resulting carbanion was formylated to afford aldehyde imidazole **38** in high yield (Scheme 6). Stork–Zhao Wittig reaction of aldehyde **38** was found to be non-stereoselective giving a separable mixture of (*Z*)- and (*E*)-vinyl iodides **39a** and **39b** in 66% and 27% yields, respectively.[24] Interestingly, the undesired (*E*)-vinyl iodide **39b** had not been observed in the other BOM-regioisomeric series (cf. Scheme 2). When (*Z*)-vinyl iodide **39a** and pyrrole amide **31** were subjected to the Buchwald copper-catalyzed coupling conditions, the reaction produced (*E*)-enamide **40b** as the major product (68%) and the requisite (*Z*)-enamide **40a** in only 16% yield. Due to the poor overall yield of the (*Z*)-enamide **40a**, this route was abandoned.

Continuing the synthesis from sulfide imidazopyridine **35**, it was necessary at this point to install the 2-amino moiety of



Scheme 6.

ageladine A (**1**). Initial attempts to oxidize sulfide **35** using Oxone in a methanol/H_2O solvent system gave an inseparable 1:2 mixture of sulfoxide **41** and the corresponding 2-imidazolone derivative, respectively (Scheme 7). The use of hydrogen peroxide with a variety of molybdenum and vanadium catalysts to oxidize sulfide **35** produced a complex mixture of products. However, we were pleased to find that treatment of sulfide **35** with *m*-CPBA produced mainly sulfoxide **41** (76%) along with a small amount of the corresponding sulfone **42** (10%). The reaction temperature in this step had to be carefully controlled to optimize the sulfoxide/sulfone yield. This sulfoxide/sulfone mixture was subsequently treated with sodium azide in DMSO at rt to provide 2-azidoimidazopyridine **43** in 87% yield. When DMF was used as the solvent in this displacement as was done in our previous synthesis,[3] the reaction time was significantly longer and a substantial decrease in product yield was observed. The azide functionality was then reduced to amine **44** in high yield using Lindlar catalyst. It should be noted that attempts at direct displacement of sulfone **42** with methanolic ammonia did not afford the desired amine **44**, but rather gave a complex mixture of products.[25]



Scheme 7.

To complete the synthesis, both BOM protecting groups needed to be removed from tricycle **44**. Initial experimentation using refluxing 8 N HCl in ethanol led to complex mixtures that could not be separated. Attempts at using boron tribromide to partially cleave the BOM groups to the

corresponding hydroxymethyl compounds, followed by treatment with aqueous potassium carbonate, failed to give the desired deprotected compound. However, it was finally found that subjecting **44** to anhydrous aluminum chloride[26] in methylene chloride at rt provided ageladine A (**1**) in 63% yield. This material was identical to the alkaloid that we previously synthesized via our first-generation route.[3]

4. Conclusion

In conclusion, we have completed a convergent total synthesis of ageladine A (**1**) from commercially available tribromoimidazole and 2-cyanopyrrole in 12.5% overall yield for the longest linear sequence (11 operations). This second generation synthesis incorporates a novel 6π-2-azatriene electrocyclization to furnish the imidazopyridine core of the marine metabolite. Furthermore, synthetic structural analogues of ageladine A for biological testing should be available via this approach.

5. Experimental

5.1. General methods

All non-aqueous reactions were carried out under a positive atmosphere of nitrogen in flame-dried glassware unless otherwise noted. Air and moisture sensitive liquid reagents were added via a dry syringe. Anhydrous THF, CH_2Cl_2, and toluene were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Microwave irradiation reactions were performed on a CEM Discover microwave reactor. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300, CDPX-300, or DRX-400 MHz spectrometers. Chemical shifts of ^1H and ^{13}C NMR spectra were referenced to the solvent peaks: δ_H 3.30 and δ_C 49.0 for CD_3OD. Flash chromatography was performed using Sorbent Technologies silica gel 60 (230–400 mesh). Purification by preparative reverse phase HPLC employed an Agilent 1100 preparative pump/gradient extension instrument equipped with a Hamilton PRP-1 (polystyrene–divinylbenzene) reverse phase column (7 μm particle size, 21.5 mm×25 cm). The following two solvent systems were used: solvent system A (99.9% double deionized H_2O and 0.1% TFA) and solvent system B (99.9% acetonitrile and 0.1% TFA). The HPLC gradient for the purification of ageladine A (20 mL/min flow rate) was as follows: 99–70% A from 0 to 5 min and 70–60% A from 5 to 25 min; retention time of **1** was 10.2 min.

5.1.1. 1-Benzyloxymethyl-2-methylsulfanylimidazole-4-carbaldehyde (15). To a solution of BOM-protected 2,4,5-tribromoimidazole **13** (7.15 g, 16.83 mmol) in THF (100 mL) was added *n*-BuLi in hexanes (2.5 M, 6.73 mL, 16.83 mmol) at −78 °C and the reaction mixture was stirred for 10 min. Dimethyl disulfide (1.59 g, 16.83 mmol) was then added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 15 min and then warmed to rt. The mixture was diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude mixture was dissolved in THF (100 mL) and *n*-BuLi in hexanes (2.5 M, 6.73 mL, 16.83 mmol) was added at −78 °C. After the mixture was stirred for 10 min at −78 °C, TMSCl (1.83 g, 16.83 mmol) was added slowly. Afterwards, the reaction mixture was stirred at −78 °C for an additional 20 min, before *n*-BuLi in hexanes (2.5 M, 6.73 mL, 16.83 mmol) was added slowly. After the mixture was stirred for 10 min at −78 °C, DMF (3.69 g, 3.92 mL, 50.49 mmol) was added slowly. The reaction mixture was stirred at −78 °C for 1 h and then warmed to rt. The mixture was diluted with H_2O (50 mL) and was extracted with CH_2Cl_2 (3×10 mL).

MeOH (20 mL) and K_2CO_3 (4.65 g, 33.66 mmol) were added to the combined organic extracts, and the reaction mixture was stirred at rt for 3 h. The mixture was diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (3× 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 3:1) afforded aldehyde **15** (3.79 g, 85%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.45 (s, 1H), 7.00–7.45 (m, 5H), 5.04 (s, 2H), 4.23 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 148.6, 142.7, 136.7, 129.4, 129.2, 129.1, 128.7, 75.9, 71.6, 16.2; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_2S$, 263.0854; found 263.0863.

5.1.2. 1-Benzyloxymethyl-4-(2-iodovinyl)-2-methylsulfanylimidazole (21). To a solution of $Ph_3PCH_2I_2$ (8.08 g, 15.25 mmol) in THF (50 mL) was added *t*-BuOK (1.71 g, 15.25 mmol). The reaction mixture was stirred at rt for 5 min and cooled to −78 °C before a solution of aldehyde **15** (2.00 g, 7.62 mmol) in THF (10 mL) was added slowly. The reaction mixture was stirred at −78 °C for 30 min and then warmed to rt. The mixture was diluted with H_2O (30 mL) and was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 3:1) afforded vinylimidazole **21** (2.74 g, 93%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.31 (d, J=8.7 Hz, 1H), 7.18–7.22 (m, 5H), 6.26 (d, J=8.7 Hz, 1H), 5.18 (s, 2H), 4.37 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 140.0, 136.7, 133.3, 129.0, 128.7, 128.5, 120.5, 76.7, 75.1, 70.8, 16.7; ESI (+): $[M+H]^+$ calcd for $C_{14}H_{16}N_2OSI$, 387.0028; found 387.0023.

5.1.3. *N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)vinyl]benzamide (22). In an oven-dried Schlenk tube was placed (*Z*)-vinyliodide **21** (250 mg, 0.65 mmol), benzamide (94 mg, 0.78 mmol), CuI (12 mg, 0.07 mmol), Cs_2CO_3 (422 mg, 1.29 mmol), *N*,*N*′-dimethylethylenediamine (11 mg, 0.13 mmol), and THF (4 mL). The tube was flushed with nitrogen, sealed, and heated at 70 °C for 15 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc 2:1) affording the coupled (*Z*)-enamide **22** (243 mg, 99%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 11.88 (d, J=10.1 Hz, 1H), 7.91–7.94 (m, 2H), 7.34–7.44 (m, 3H), 7.19–7.28 (m, 5H), 7.07–7.16 (m, 1H), 6.86 (s, 1H), 5.49 (d, J=8.9 Hz, 1H), 5.18 (s, 2H), 4.39 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 142.9, 139.5, 135.2, 133.2,

130.7, 127.6, 127.5, 127.2, 126.9, 126.4, 121.4, 117.2, 99.2, 73.5, 69.4, 14.8; ESI (+): $[M+H]^+$ calcd for $C_{21}H_{22}N_3O_2S$, 380.1433; found 380.1425.

5.1.4. *N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]thiobenzamide (23). To a solution of enamide **22** (0.20 g, 0.53 mmol) in PhMe (20 mL) was added Lawesson's reagent (0.13 g, 0.32 mmol). The reaction mixture was heated at 100 °C for 3.5 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 1:1) afforded thioenamide **23** (0.20 g, 95%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.19 (d, J=9.6 Hz, 1H), 7.92–7.95 (m, 2H), 7.61–7.68 (m, 1H), 7.17–7.42 (m, 8H), 6.95 (s, 1H), 5.77 (d, J=8.9 Hz, 1H), 5.18 (s, 2H), 4.40 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 144.0, 140.7, 138.7, 135.1, 130.2, 127.6, 127.3, 126.9, 126.4, 124.8, 118.4, 104.2, 73.5, 69.5, 14.6; ESI (+): $[M+H]^+$ calcd for $C_{21}H_{22}N_3OS_2$, 396.1204; found 396.1198.

5.1.5. *N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]thiobenzimidic acid methyl ester (24). To a solution of thioenamide **23** (150 mg, 0.38 mmol) in CH_2Cl_2 (15 mL) was added MeOTf (68 mg, 0.42 mmol). The reaction mixture was stirred at rt for 45 min and then concentrated. The crude reaction mixture was partitioned between CH_2Cl_2 (15 mL) and NaOH (1 N, 20 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The reaction cleanly afforded thioimidate **24** (151 mg, 97%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.19–7.50 (m, 10H), 6.64 (br s, 1H), 6.03 (br s, 1H), 5.29 (s, 2H), 4.44 (s, 2H), 2.55 (s, 3H), 2.47 (br s, 3H); ESI (+): $[M+H]^+$ calcd for $C_{22}H_{24}N_3OS_2$, 410.1361; found 410.1365.

5.1.6. 3-Benzyloxymethyl-2-methylsulfanyl-4-phenylimidazopyridine (26). A solution of thioimidate **24** (55 mg, 0.13 mmol) in *p*-xylene (2.5 mL) was subjected to microwave irradiation at 160 °C for 1 h and then concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc 1:1) afforded imidazopyridine **26a** (19 mg, 40%) and BOM-regioisomeric imidazopyridine **26b** (16 mg, 33%) as clear oils. Imidazopyridine **26a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J=7.4 Hz, 2H), 8.39 (d, J=5.4 Hz, 1H), 7.43–7.47 (m, 2H), 7.36–7.38 (m, 1H), 7.18–7.28 (m, 5H), 7.14 (d, J=5.4 Hz, 1H), 5.46 (s, 2H), 4.45 (s, 2H), 2.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 147.3, 143.3, 141.7, 138.6, 137.5, 136.6, 129.7, 129.6, 129.0, 128.8, 128.7, 128.3, 104.3, 73.1, 71.3, 15.3. Imidazopyridine **26b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J=5.5 Hz, 1H), 7.53–7.55 (m, 2H), 7.49 (d, J=5.5 Hz, 1H), 7.40–7.42 (m, 3H), 7.18–7.21 (m, 3H), 7.04–7.07 (m, 2H), 5.09 (s, 2H), 4.09 (s, 2H), 2.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 150.3, 144.2, 142.3, 138.4, 136.9, 131.8, 129.6, 129.4, 129.0, 128.8, 128.4, 127.8, 112.6, 73.6, 71.0, 15.1; ESI (+): $[M+H]^+$ calcd for $C_{21}H_{20}N_3OS$, 362.1327; found 362.1310.

5.1.7. 2-Methylsulfanyl-4-phenylimidazopyridine (27). A solution of BOM-protected imidazopyridine **26** (5 mg, 0.01 mmol) in EtOH (2 mL) and 6 N HCl (1.5 mL) was heated at 100 °C for 1 h and then concentrated. Purification of the residue by preparative TLC (EtOAc) afforded *N*–H imidazopyridine **27** (1.5 mg, 50%) as a clear oil. ^{1}H NMR (300 MHz, MeOD) δ 8.23 (d, J=5.7 Hz, 1H), 8.18–8.21 (m, 2H), 7.46–7.55 (m, 3H), 7.42 (d, J=5.7 Hz, 1H), 2.78 (s, 3H); ESI (+): $[M+H]^+$ calcd for $C_{13}H_{12}N_3S$, 242.0752; found 242.0738.

5.1.8. 1-Benzyloxymethylpyrrole-2-carboxylic acid amide (30). To a solution of nitrile **29** (1.00 g, 4.71 mmol) and Bu_4NHSO_4 (1.60 g, 4.71 mmol) in CH_2Cl_2 (15 mL) was added 50% H_2O_2 (3 mL), followed by 20% aq NaOH (3 mL). The reaction mixture was stirred at rt for 3 h, diluted with H_2O (100 mL), and was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 3:1) afforded amide **30** (0.99 g, 91%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.23 (m, 5H), 6.84 (dd, J=2.8, 1.7 Hz, 1H), 6.66 (dd, J=3.8, 1.7 Hz, 1H), 6.19 (br s, 2H), 6.07 (dd, J=3.8, 2.8 Hz, 1H), 5.64 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 139.1, 130.5, 129.9, 129.6, 127.6, 117.4, 110.6, 78.5, 72.1; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_2$, 231.1134; found 231.1120.

5.1.9. 1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic acid amide (31). To a solution of pyrrole amide **30** (1.00 g, 4.34 mmol) in THF (50 mL) was added NBS (1.62 g, 9.12 mmol). The reaction mixture was stirred at rt for 30 min and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 2:1) afforded dibromopyrrole **31** (1.58 g, 94%) as a white solid. X-ray crystal structure analysis[27] confirmed the assignment of dibromopyrrole **31** (recrystallized from CH_2Cl_2). Mp 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.25 (m, 5H), 6.71 (s, 1H), 5.82 (s, 2H), 4.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 135.9, 127.4, 126.9, 126.6, 126.5, 116.2, 111.0, 99.3, 74.5, 69.7; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{13}N_2O_2{}^{79}Br_2$, 386.9344; found 386.9381.

5.1.10. 1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic acid [2-(1-benzyloxymethyl-2-methylsulfanyl-imidazol-4-yl)-vinyl]amide (32). In an oven-dried Schlenk tube was placed imidazole vinyliodide **21** (0.50 g, 1.29 mmol), pyrrole amide **31** (0.55 g, 1.42 mmol), CuI (25 mg, 0.13 mmol), Cs_2CO_3 (0.84 g, 2.59 mmol), *N*,*N*′-dimethylethylenediamine (23 mg, 0.26 mmol), and THF (6 mL). The tube was flushed with nitrogen, sealed, and heated at 70 °C for 17 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc 4:1) affording the coupled (*Z*)-enamide **32** (0.77 g, 92%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (d, J=10.2 Hz, 1H), 7.11–7.23 (m, 10H), 6.93 (dd, J=10.2, 9.0 Hz, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 5.91 (s, 2H), 5.43 (d, J=8.9 Hz, 1H), 5.13 (s, 2H), 4.51 (s, 2H), 4.35 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 144.5, 140.8, 137.9, 136.6, 129.1, 128.8, 128.7, 128.6, 128.4, 128.1, 128.0, 121.9, 118.8, 116.3, 112.5, 100.7, 100.6, 75.9, 75.0, 71.2, 70.9, 16.4; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_3S^{79}Br_2$, 645.0171; found 645.0167.

5.1.11. 1-Benzyloxymethyl-4,5-dibromopyrrole-2-carbothioic acid [2-(1-benzyloxymethyl-2-methylsulfanylimid-

azol-4-yl)-vinyl]amide (33). To a solution of enamide **32** (0.60 g, 0.93 mmol) in PhMe (30 mL) was added Lawesson's reagent (0.56 g, 1.39 mmol). The reaction mixture was heated at 100 °C for 2 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 4:1) afforded thioenamide **33** (0.51 g, 82%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.00 (d, J=9.8 Hz, 1H), 7.49 (t, J=9.7 Hz, 1H), 7.18–7.26 (m, 5H), 7.08–7.11 (m, 5H), 6.90 (s, 1H), 6.64 (s, 1H), 6.13 (s, 2H), 5.71 (d, J=8.8 Hz, 1H), 5.13 (s, 2H), 4.41 (s, 2H), 4.37 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 145.8, 140.0, 137.6, 137.5, 136.6, 129.1, 128.8, 128.4, 128.2, 128.0, 124.8, 120.0, 114.5, 113.3, 105.7, 101.0, 75.5, 75.0, 71.2, 71.1, 16.0; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_2S_2{}^{79}Br_2$, 660.9942; found 660.9994.

5.1.12. 1-Benzyloxymethyl-*N*-[2-(1-benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]4,5-dibromopyrrole-2-carboximidothioic acid methyl ester (34). To a solution of thioenamide **33** (100 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) was added MeOTf (27 mg, 0.17 mmol). The reaction mixture was stirred at rt for 2 h and concentrated. The crude reaction mixture was partitioned between CH_2Cl_2 (5 mL) and NaOH (1 N, 10 mL), and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 3:1) afforded thioimidate **34** (95 mg, 93%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.14–7.23 (m, 11H), 6.49 (br s, 1H), 6.16 (br s, 1H), 5.21–5.70 (m, 4H), 4.39 (br s, 2H), 4.30 (s, 2H), 2.56 (s, 3H), 2.43 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 138.9, 137.2, 136.8, 133.0, 129.0, 128.8, 128.6, 128.3, 128.0, 123.1, 118.3, 101.3, 76.0, 75.0, 70.9, 70.7, 17.0; ESI (+): $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_2S_2{}^{79}Br_2$, 675.0099; found 675.0141.

5.1.13. 3-Benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)-2-methylsulfanyl-imidazopyridine (35). A solution of thioimidate **34** (75 mg, 0.11 mmol) in mesitylene (30 mL) was heated at 145 °C for 16 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 2:1) afforded pyridine **35** (31 mg, 44%, 51% brsm) as a clear oil, along with starting thioimidate **34** (9 mg, 12%) and isomerized (*E*)-thioimidate **36** (20 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J=5.4 Hz, 1H), 7.61 (d, J=5.4 Hz, 1H), 7.27–7.37 (m, 5H), 7.19–7.21 (m, 3H), 6.92–6.96 (m, 2H), 6.65 (s, 1H), 5.41 (s, 2H), 5.14 (s, 2H), 4.42 (s, 2H), 4.30 (s, 2H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 150.5, 142.3, 137.2, 136.7, 133.9, 133.5, 130.5, 129.0, 128.7, 128.6, 128.2, 128.1, 127.7, 115.1, 113.6, 107.1, 100.4, 75.5, 73.3, 71.5, 70.6, 15.1; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_2S^{79}Br_2$, 627.0065; found 627.0047.

5.1.14. 3-Benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)-2-methanesulfinyl-imidazopyridine (41). To a solution of sulfide **35** (40 mg, 0.06 mmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (29 mg, 0.13 mmol, dissolved in 1 mL of CH_2Cl_2) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, 0 °C for 1 h, and then at rt for 20 min. The reaction mixture was diluted with saturated Na_2SO_3 and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc 1:1) afforded sulfoxide **41** (31 mg, 76%) as a clear oil, along with the corresponding sulfone **42** (4 mg, 10%). Sulfoxide **41**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J=5.5 Hz, 1H), 7.66 (d, J=5.5 Hz, 1H), 7.22–7.25 (m, 3H), 7.14–7.19 (m, 2H), 7.09–7.11 (m, 3H), 6.84–6.87 (m, 2H), 6.58 (s, 1H), 5.46–5.58 (m, 2H), 5.36–5.37 (m, 2H), 4.35 (s, 2H), 4.24 (s, 2H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 148.7, 142.7, 137.0, 136.6, 136.3, 132.7, 129.8, 129.0, 128.7, 128.3, 128.2, 127.8, 127.7, 115.9, 115.6, 108.0, 100.6, 75.4, 73.4, 71.8, 70.8, 40.8; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_3S^{79}Br_2$, 643.0014; found 642.9984. Sulfone **42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J=5.2 Hz, 1H), 7.68 (d, J=5.3 Hz, 1H), 7.17–7.26 (m, 5H), 7.09–7.11 (m, 3H), 6.85–6.87 (m, 2H), 6.60 (s, 1H), 5.57 (s, 2H), 5.32 (s, 2H), 4.38 (s, 2H), 4.25 (s, 2H), 3.43 (s, 3H).

5.1.15. 2-Azido-3-benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)imidazopyridine (43). To a mixture of sulfoxide **41** (22 mg, 0.02 mmol) and sulfone **42** (3 mg, 3.0 μmol) in DMSO (0.5 mL) was added sodium azide (13 mg, 0.19 mmol). The reaction mixture was stirred at rt for 6 h, then directly purified by column chromatography (hexanes/EtOAc 1:1) to afford amide **43** (21 mg, 87%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J=5.5 Hz, 1H), 7.50 (d, J=5.5 Hz, 1H), 7.19–7.25 (m, 3H), 7.09–7.15 (m, 5H), 6.82–6.85 (m, 2H), 6.58 (s, 1H), 5.34 (s, 2H), 4.97 (s, 2H), 4.31 (s, 2H), 4.20 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 149.1, 142.8, 137.2, 136.7, 134.7, 131.5, 129.9, 129.0, 128.7, 128.6, 128.2, 127.9, 127.7, 115.3, 113.6, 107.4, 100.3, 75.5, 72.3, 71.7, 70.5; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{22}N_7O_2{}^{79}Br_2$, 622.0202; found 622.0239.

5.1.16. 3-Benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)imidazopyridin-2-ylamine (44). A solution of azide **43** (17 mg, 0.03 mmol) in MeOH (1 mL) and THF (1 mL) was reduced with Lindlar catalyst (4 mg) at rt under one atmosphere of H_2 for 17 h. The mixture was then filtered through a Celite pad, which was washed with MeOH. The filtrate was concentrated to afford amine **44** (16 mg, 94%) as a yellow solid sufficiently pure for use in the next step. ^{1}H NMR (300 MHz, CD_3OD) δ 8.16 (d, J=5.5 Hz, 1H), 7.23–7.28 (m, 4H), 7.17–7.21 (m, 2H), 7.13–7.15 (m, 3H), 6.85–6.88 (m, 2H), 6.55 (s, 1H), 5.14 (s, 2H), 5.00 (s, 2H), 4.30 (s, 2H), 4.21 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.1, 150.7, 141.9, 137.2, 131.6, 131.2, 130.7, 128.5, 128.3, 128.0, 127.8, 127.4, 114.4, 110.9, 106.1, 99.7, 75.0, 72.2, 70.5, 70.2; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{24}N_5O_2{}^{79}Br_2$, 596.0297; found 596.0313.

5.1.17. Ageladine A (1). To a solution of BOM-protected tricyclic compound **44** (15.1 mg, 25.2 μmol) in CH_2Cl_2 (6 mL) was added $AlCl_3$ (33.7 mg, 0.25 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt for 30 min. The mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3×5 mL). The aqueous layer was concentrated and purification of the residue by reverse phase HPLC afforded ageladine A (**1**, 5.7 mg, 63%) as a yellow solid, which was identical to previously prepared material.[3] ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (d, J=6.4 Hz, 1H), 7.42 (d, J=6.4 Hz, 1H), 7.17 (s, 1H); ESI (+): $[M+H]^+$ calcd for $C_{10}H_8N_5{}^{79}Br_2$, 355.9146; found 355.9146.

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