JOC Article

Application of a 6π-1-Azatriene Electrocyclization Strategy to the Total Synthesis of the Marine Sponge Metabolite Ageladine A and Biological Evaluation of Synthetic Analogues

Matthew L. Meketa,[†] Steven M. Weinreb,*[,†] Yoichi Nakao,[‡] and Nobuhiro Fusetani[§]

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, School of Advanced Science and Engineering, Waseda University, 3-4-1, Okubo, Shinjuku-ku, Tokyo, 169-8555, Japan, and Graduate School of Fisheries Sciences, Hokkaido University, 3-1-1, Minato-cho, Hakodate, 041-8611, Japan

smw@chem.psu.edu

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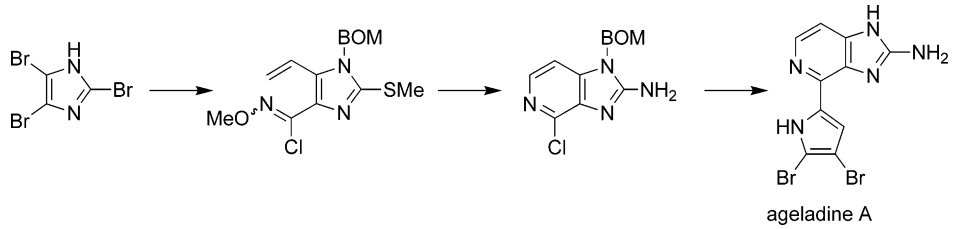

A 12-step synthesis of the angiogenesis inhibitory marine metabolite ageladine A is reported. The key steps include a 6π-1-azatriene electrocyclization for formation of the pyridine ring and a Suzuki−Miyaura coupling of *N*-Boc-pyrrole-2-boronic acid with a chloroimidazopyridine. In addition, an assessment of the biological activity of a variety of synthetic analogues of ageladine A prepared during this synthesis is described.

Introduction

Ageladine A (**1**) was isolated in 2003 by Fusetani, Nakao, and co-workers by bioassay-guided extraction and repetitive reverse-phase HPLC purification of the hydrophilic extract from the marine sponge *Agelas nakamurai*, which was obtained off the coast of Kuchinoerabu-jima Island in southern Japan (Scheme 1).[1] Marine sponges of the genus *Agelas* have been reported to contain many bioactive polycyclic pyrrole-imidazole alkaloids. Interestingly, ageladine A, whose structure was established primarily by 2D NMR studies, is the first example of this family to contain a 2-aminoimidazopyridine core.[2] Ageladine A is an inhibitor of matrix metalloproteinases at micromolar levels (MMPs), a family of enzymes involved in metastasis and tumor angiogenesis (vide infra).[3] Unlike other MMP inhibitors, kinetic analysis showed that the compound does not inhibit MMP-2 in a competitive manner.

To date, three total syntheses of ageladine A have been reported. In 2006, we described the first synthesis of this marine metabolite using a 6π-1-azatriene electrocyclization and a Suzuki−Miyaura coupling involving a 2-chloropyridine derivative as key steps.[4] Shortly afterward an alternative route to ageladine A was completed by Shengule and Karuso, in which a pivotal Pictet−Spengler reaction between 2-aminohistamine and 4,5-dibromo-2-formylpyrrole was used, ultimately leading to the natural product.[5] Recently, we described a second generation synthesis of **1** using a biomimetically inspired 6π-2-azatriene electrocyclization as the key step for construction of the imidazopyridine core.[6,7] In this paper we describe the full details of our first total synthesis of ageladine A, along with an assessment of the biological activity of a variety of synthetic analogues of **1**.

[†] The Pennsylvania State University.
[‡] Waseda University.
[§] Hokkaido University.

(1) (a) 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. (b) Nakao, Y.; Fusetani, N. *J. Nat. Prod.* **2007**, *70*, 689.

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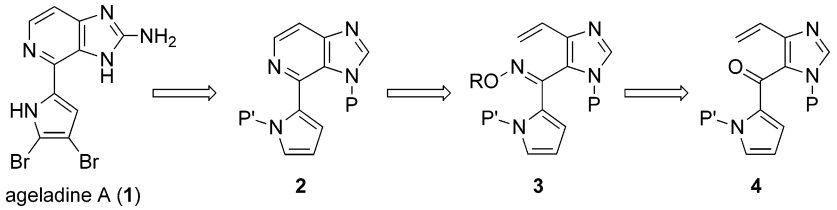
SCHEME 1



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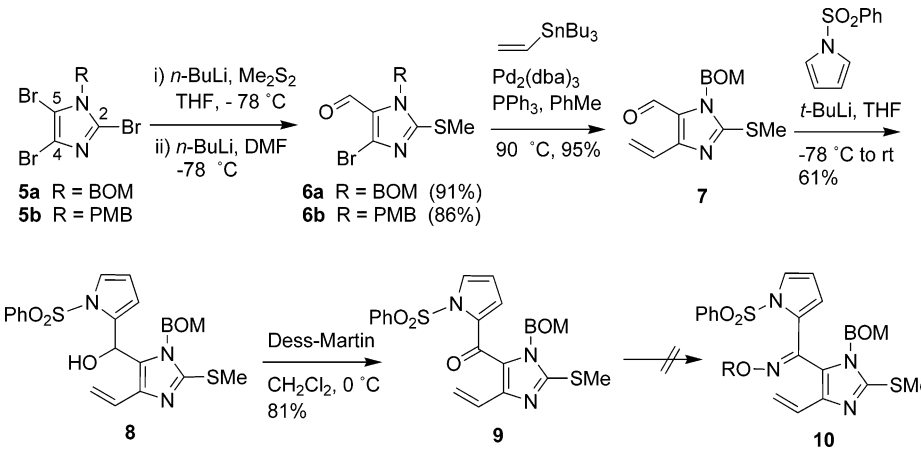

Results and Discussion

Our initial retrosynthetic analysis for ageladine A involved a pivotal 6π-1-azaelectrocyclization of vinylimidazole oxime derivative **3** to give key tricyclic intermediate **2** (Scheme 1).[8] Vinylimidazole oxime **3** would be derived from the corresponding ketone **4**. Hibino and co-workers have previously used 6π-azaelectrocyclizations of related 1-azatrienes in the synthesis of various imidazopyridines.[9] In addition, Trost and Gutierrez recently reported a novel route to pyridines utilizing a ruthenium-catalyzed cycloisomerization/6π-azaelectrocyclization sequence.[10] Although the basic pericyclic reaction has been known for a number of years,[11] few natural product syntheses have utilized 1-azaelectrocyclizations. One notable case is the recent biomimetically patterned synthesis of grossularine-1 by the Horne group.[12]

Our synthetic work initially focused on the formation of biaryl oxime **3**. Two different imidazole nitrogen protecting groups were investigated in these studies on ageladine A (**1**): benzyloxymethyl (BOM) and *p*-methoxybenzyl (PMB). Iddon and co-workers have shown that 2,4,5-tribromoimidazoles can be sequentially and predictably metalated, followed by trapping with various electrophiles.[13,14] Thus, using known BOM-protected tribromoimidazole (**5a**),[15] metalation with 1 equiv of *n*-butyllithium, followed by addition of dimethyl disulfide, selectively introduced a thiomethyl moiety at C(2) (Scheme 2). Without workup, the imidiazole was then lithiated at C(5) by using a second equivalent of *n*-butyllithium. Subsequent addition of DMF then afforded aldehyde **6a** in 91% overall yield. The corresponding PMB-protected imidazole aldehyde **6b** was generated in 86% yield by using an identical series of reactions.

Stille coupling of bromoimidazole **6a** and vinyltributylstannane proceeded smoothly to give vinylimidazole **7**. The highly functionalized vinylimidazole aldehyde **7** reacted with 2-lithio-*N*-benzenesulfonylpyrrole[16] to yield alcohol **8**, which was oxidized to the corresponding ketone **9** by using Dess−Martin periodinane. Interestingly, oxidation of alcohol **8** with manganese dioxide produced an inseparable 2:1 mixture of ketone **9** along with pyrrole aldehyde **11**, while PCC oxidation afforded exclusively pyrrole aldehyde **11** as the only isolable product (Scheme 3).

Unfortunately ketone **9** could not be converted to the desired oxime (**10**, R = H) or methoxime (**10**, R = Me). Moreover, formation of a hydrazone derivative with use of phenylhydrazine or semicarbazide could not be effected. Oxime formation from the analogous *N*-Boc-protected or *N*-H pyrrole ketone substrates

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(10) Trost, B. M.; Gutierrez, A. C. *Org. Lett.* **2007**, *9*, 1473.

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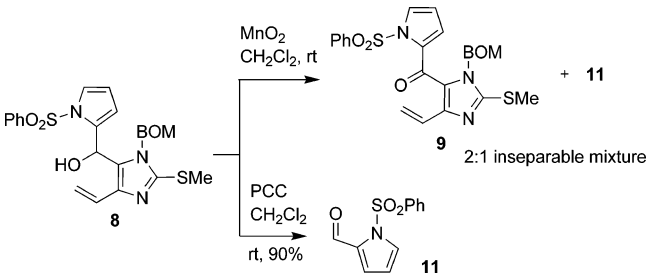
(14) Groziak, M. P.; Wei, L. *J. Org. Chem.* **1991**, *56*, 4296.

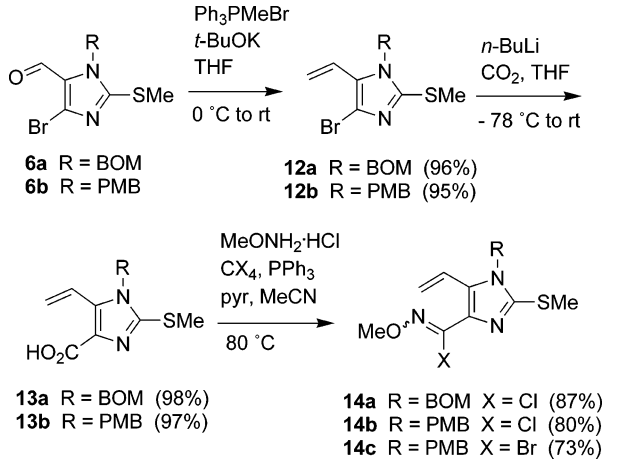
(15) (a) Preparation of **5a** from commercially available 2,4,5-tribromoimidazole: Schumacher, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935. (b) Preparation of **5b**: Iddon, B.; Khan, N.; Lim, B. L. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1437.

(16) (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.

SCHEME 3



SCHEME 4

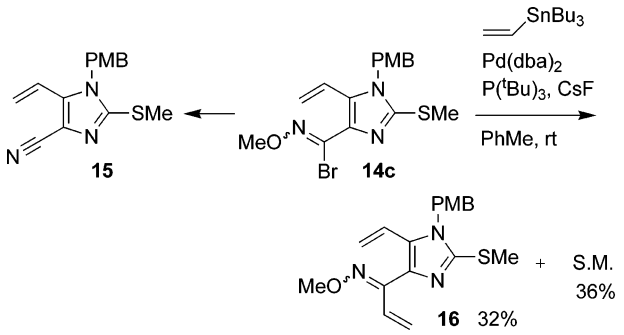


also failed. Only the starting ketone or the deprotected pyrrole was recovered in all of these reactions. These results are not too surprising since carbonyl compound **9** is hindered and is also a vinylogous amide. Due to the inability to form the requisite oxime, an alternative synthetic route was therefore devised.

Our revised strategy was to form the pyridine ring prior to introducing the pyrrole moiety. Synthetic routes were performed with both the BOM- and PMB-protected imidazoles, which gave comparable product yields for most steps. Bromo vinylimidazoles **12a** and **12b** were produced in high yields from aldehydes **6a** and **6b** via a Wittig reaction (Scheme 4). Bromides **12a** and **12b** were then lithiated with *n*-butyllithium, followed by treatment with carbon dioxide, to afford carboxylic acids **13a** and **13b**, respectively. The yields of the acids were significantly higher when freshly crushed dry ice was added directly to a solution of the lithiated imidazole, rather than by bubbling CO_2 into the reaction mixture. Carboxylic acids **13a** and **13b** were then converted into the corresponding halomethoximes **14a**−**c** in a single step by using the methodology of Kikugawa and co-workers.[17] Chloro- or bromomethoximes **14** could be produced in good yield by using either carbon tetrachloride or tetrabromide, respectively.

On the basis of the work of Kim et al., cross coupling of the halomethoximes **14b** and **14c** with a wide variety of stannanes, boronic acids, and organozinc halides was explored.[18] However, the only coupled product that could be isolated was vinylimidazole **16**, obtained in low yield from Stille reaction of **14c** with vinyltributylstannane (Scheme 5). In all other cases, the only detectable product was nitrile imidazole **15**, derived from reductive elimination of the halomethoxime starting material.[19,20] Interestingly, Kim and co-workers did not report observing such a nitrile product during their studies.

SCHEME 5



As a result of the failure of the halomethoxime cross-coupling reactions, we turned to 6π-1-azaelectrocyclizations related to those of Hibino.[9] Thus, heating dilute solutions of halomethoximes **14b** and **14c** in *o*-xylene at 150 °C gave cyclized haloimidazopyridines **17b** (73%) and **17c** (46%), respectively (Scheme 6). When the cyclization of **14b** was performed in a microwave reactor, the product yield increased slightly to 81%. However, due to scale-up problems associated with the microwave, this procedure was not routinely used. Similarly, thermal cyclization of chloromethoxime **14a** in *o*-xylene at reflux afforded chloro imidazopyridine **17a** in 84% yield.

With the halopyridines **17a**−**c** in hand, cross couplings with the pyrrole moiety were then explored. Initial attempts at both Suzuki−Miyaura and Stille couplings with *N*-Boc-pyrrole-2-boronic acid (**18**)[21] or the analogous 2-tributylstannylpyrrole, respectively, afforded only the starting halopyridines. Negishi cross couplings of *N*-benzenesulfonylpyrrole-2-zinc chloride with the halopyridines were also unsuccessful.[22] After extensive experimentation, it was discovered that a Suzuki−Miyaura cross coupling with Buchwald's 2-biphenyldicyclohexylphosphine ligand afforded the desired product.[23] Thus, refluxing bromopyridine **17c** with pyrrole boronic acid **18** in 1,4-dioxane for 20 h in the presence of 25% $Pd(dba)_2$, the Buchwald ligand, and potassium phosphate afforded tricycle **19** in 60% yield, along with 20% of recovered bromide (Scheme 6). Chloropyridine **17b** underwent cross coupling in higher yield (70%) along with 26% of recovered chloride. Interestingly, when the coupling of **17b** with boronic acid **18** was performed in a microwave reactor,[24] the yield of **19** increased to 91% with only 5% recovered starting material. It should be noted that the Lakshman

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

(19) The conversion of a halomethoxime to a nitrile has been performed under basic conditions,[20a,b] photolytically,[17a,20c] or with a zinc/acetic acid/DMF protocol.[17c]

(20) (a) Shustov, G. V.; Kachanov, A. V.; Kostyanovsky, R. G. *Izv. Akad. Nauk, Ser. Khim.* **1992**, *11*, 2584. (b) Nie, H.; Wu, Y.-W.; Mei, H.-S. *Zh. Yiyao Gongye Zazhi* **1999**, *30*, 469. (c) Sakamoto, T.; Okamoto, K.; Kikugawa, Y. *J. Org. Chem.* **1992**, *57*, 3245.

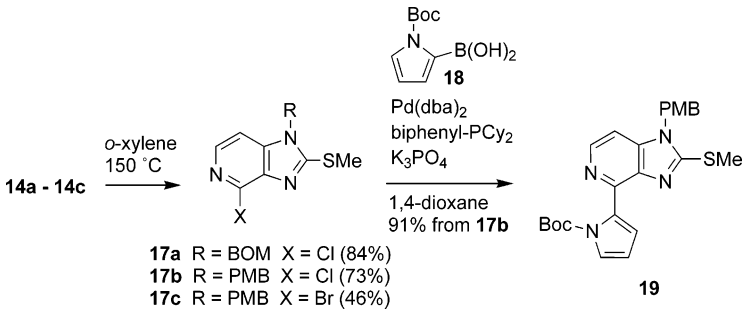
(21) Kelly, T. A.; Fuchs, V. U.; Perry, C. W.; Snow, R. J. *Tetrahedron* **1993**, *49*, 1009.

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

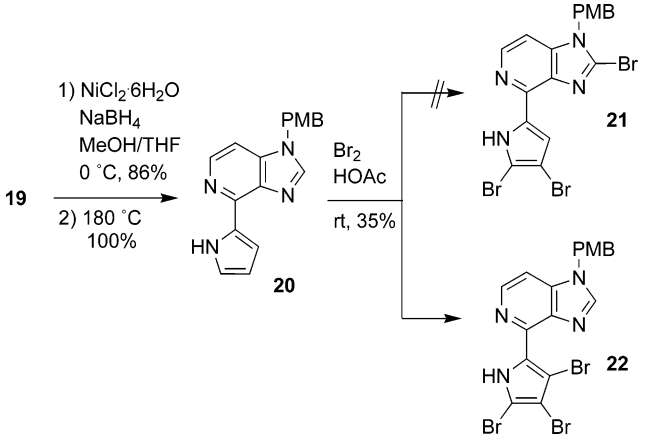
(23) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

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

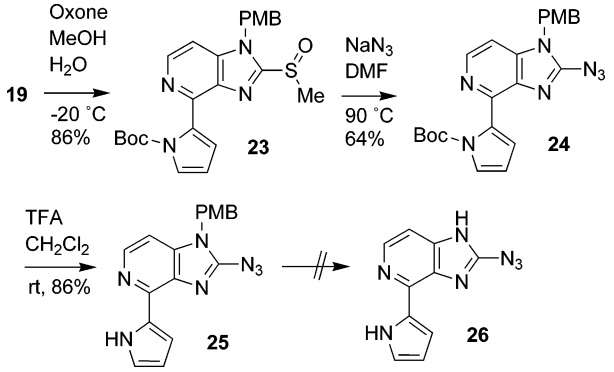
SCHEME 6



SCHEME 7



SCHEME 8



group has noted improved product yields for chloride over bromide substrates in purine derivatives when performing Suzuki−Miyaura cross couplings.[25] However, the reason for this trend is currently unclear.

To continue the synthesis, tricyclic sulfide **19** could be desulfurized with nickel boride[26] followed by thermolytic removal of the Boc protecting group to produce *N*-H pyrrole **20** (Scheme 7). We hoped it would then be possible to selectively tribrominate compound **20** to produce **21**. The bromine at the C(2) position of the imidazopyridine could subsequently serve as a handle for the introduction of the amino group of ageladine A (**1**). Unfortunately, with use of Br_2 in acetic acid, *N*-H pyrrole **20** underwent tribromination at the three pyrrole carbons to give tricycle **22**, with no bromination observed at the imidazopyridine C(2) position. Bromination attempts with NBS gave an inseparable mixture of di- and tribrominated products. As a result of the high reactivity of the pyrrole toward bromination, an alternative route had to be devised for the selective dibromination of the pyrrole and introduction of the imidazole amino moiety.

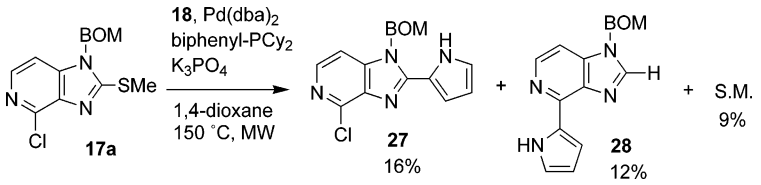
Toward this end, we hoped to initially introduce the amine moiety at C(2) of imidazopyridine via displacement of an appropriate thio derivative. Therefore, methyl sulfide **19** was oxidized to the corresponding sulfoxide **23** with Oxone in high yield (Scheme 8).[27] Attempts to further oxidize the sulfoxide to the corresponding sulfone with Oxone or *m*-CPBA failed, resulting only in decomposition. On the basis of the work of Jarosinski and Anderson, displacement of the sulfoxide moiety with sodium azide in DMF at 90 °C afforded the desired azide **24** in 64% yield.[28] Removal of the Boc protecting group of **24** under acidic conditions then generated *N*-H pyrrole **25**. Unfortunately, removal of the PMB protecting group of imidazopyridine **25** either by treatment with acid or by catalytic hydrogenation failed. Similar attempts to remove the PMB group from precursors **19** and **23** also failed. In light of these difficulties, the PMB series was abandoned in favor of the BOM-protected compounds.

However, it was found that all attempts to cross couple the BOM-protected chloropyridine **17a** with boronic acid **18** under microwave irradiation at 150 °C resulted in a complex mixture of products (Scheme 9). In addition to recovered starting material, 16% of the C(2) coupled product **27** and a desulfurized coupled product **28** (12%) were also isolated. Presumably these products result via initial BOM protecting group coordination with the palladium, placing the metal in close proximity to the C−S bond, thereby increasing the thiophilicity of the metal. In addition, the pyrrole Boc protecting group was also lost in both isolated products, probably due to the high temperature of the reaction. In light of these results, the synthetic strategy for ageladine A required further modification.

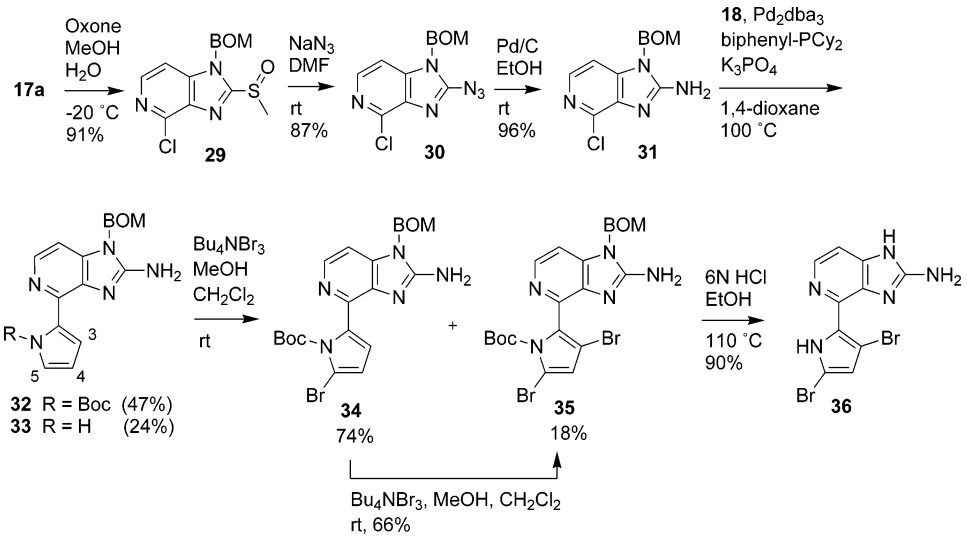
To circumvent the above problems, we decided to install the imidazopyridine C(2)-amino group prior to introducing the pyrrole fragment. Thus, Oxone oxidation of sulfide **17a** efficiently produced sulfoxide **29** (Scheme 10). Displacement of the sulfoxide moiety of **29** with sodium azide in DMF could be effected at room temperature in this case to afford azide **30**. A competing reaction at temperatures above 23 °C was hydrolysis of the imidazole sulfoxide by adventitious moisture to produce the corresponding 2-imidazolone. Interestingly, the analogous imidazolone byproduct had not been observed in the previous conversion of sulfoxide **23** to azide **24** (cf. Scheme 8). Catalytic

(25) 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.
(26) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407.
(27) Oxidation of methyl sulfide **19** with *m*-CPBA only led to decomposition.
(28) Jarosinski, M. A.; Anderson, W. K. *J. Org. Chem.* **1991**, *56*, 4058.

SCHEME 9



SCHEME 10

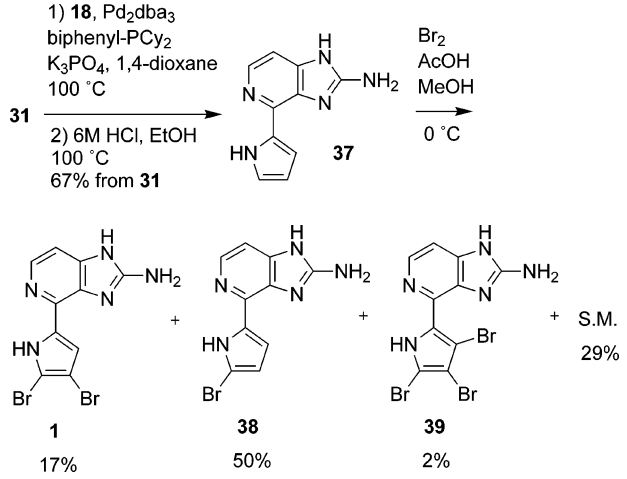


hydrogenation of azide **30** cleanly produced 2-amino-imidazopyridine **31**. With the amino group in place, Suzuki−Miyaura cross coupling with pyrrole boronic acid **18** then produced Boc-protected tricyclic pyrrole **32** and *N*-H compound **33** as a separable 2:1 mixture in good total yield. We were pleased to find that no arylation of the amino group of **31** with boronic acid **18** had occurred.[29]

Next, Boc-protected tricyclic pyrrole **32** was brominated with tetrabutylammonium tribromide (TBATB), which to our surprise gave the 3,5-dibromopyrrole **35** in 18% yield along with monobromopyrrole **34** as the major product (74%).[30] The monobromopyrrole **34** could be brominated to generate additional dibromopyrrole **35**. Bromination of tricyclic pyrrole **32** with Br_2 in carbon tetrachloride led to a mixture of starting material, along with the same mono- and dibrominated products but in poorer yields. The Boc protecting group of tricycle **35** was removed with refluxing 6 N HCl in ethanol to give the 3,5-dibromo regioisomer **36** of ageladine A. The positions of the bromines in bromopyrroles **34**, **35**, and **36** were established by using ^{1}H NMR chemical shift data and proton−proton coupling constants.[31] At this point, we do not have a good rationale for the observed regioselectivity in the bromination step since there is little literature precedent for dibromination of pyrrole derivatives bearing a C(2) aryl substituent.[32]

Since the Boc-protected pyrrole **32** led to the undesired dibromination product, we decided to investigate the bromination of the analogous unprotected system. Thus, the crude mixture of 2:1 Boc protected/*N*-H pyrrole tricycle products **32**/**33** was hydrolyzed to afford the fully deprotected tricycle **37** in 67% overall yield from chloropyridine **31** (Scheme 11). Bromination of the *N*-H pyrrole **37** with either TBATB or NBS resulted in complex mixtures of dibromo and tribrominated pyrrole products. After some experimentation, the optimal conditions found for halogenation were to treat pyrrole **37** with Br_2 in an acetic acid/methanol solvent mixture at 0 °C. These conditions produced ageladine A (**1**) in 17% yield, along with recovered starting material (29%), monobromopyrrole **38** (50%),

SCHEME 11



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and tribromopyrrole **39** (2%). Purification of this mixture was accomplished via reverse-phase HPLC. Ageladine A (**1**) and the tribrominated product **39** were very difficult to separate since they have similar retention times. Bromination conditions, therefore, had to be optimized such that the maximum amount of ageladine A was produced, while minimizing the formation of undesired tribromopyrrole **39**. Both the recovered starting material and monobromopyrrole **38** could be resubjected to the same bromination conditions to produce additional ageladine A. Synthetic ageladine A had proton and carbon NMR spectra, as well as UV and fluorescence maxima, identical with those reported for the natural product.[1]

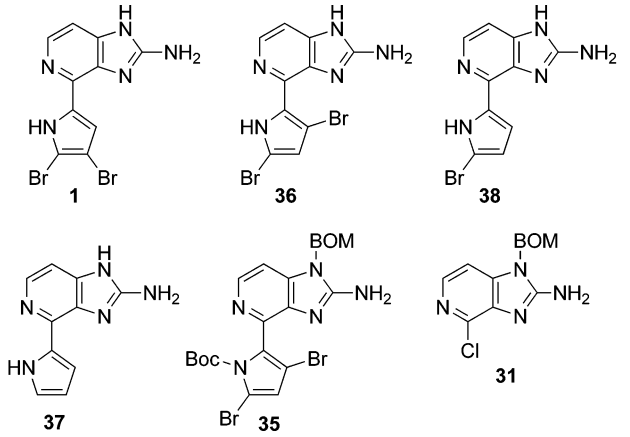
Biological Activity of Ageladine A and Analogues

Ageladine A (**1**) has been shown to be a unique inhibitor of matrix metalloproteinases (MMPs), particularly MMP-2.[1] In addition to significant inhibition of MMP-2 (2.0 μg/mL), natural ageladine A has been found to display inhibitory activity against MMP-1, -8, -9, -12, and -13 with IC_{50} values of 1.2, 0.39, 0.79, 0.33, and 0.47 μg/mL, respectively. Matrix metalloproteinases are a family of zinc-containing enzymes that regulate multiple steps of tumor metastasis and angiogenesis.[3] These enzymes are involved in degradation of most components of the extracellular matrix (ECM) including collagens, elastins, and fibronectins, thereby allowing for tumor growth and expansion. The entire family of MMPs in humans now includes over two dozen related enzymes that are commonly grouped as either collagenases, gelatinases, stromelysins, or membrane-type MMPs (MT-MMPs). One such gelatinase is MMP-2, which in addition to being involved in tumor metastasis and angiogenesis, is known to complex with MT1-MMP via TIMP at the migration front of tumor or endothelial cells.[1,3] In addition, the ratio of activated to total MMP levels, particularly MMP-2, can be correlated with tumor aggressiveness.[33] As a result, MMP-2 inhibitors are presumed to be both antiangiogenic and antimetastatic, making MMP-2 inhibition an important area of cancer research.

The vast majority of MMP inhibitors act by chelation of the enzyme active-site zinc(II) ion and such compounds usually contain chelating groups like carboxylates, hydroxamates, or thiols. Interestingly, studies have revealed that ageladine A is not capable of zinc binding and that its MMP-2 inhibition is noncompetitive by kinetic analysis.[1] Therefore ageladine A is believed to have a novel and as yet unknown mode of MMP inhibition.

Our total synthesis of ageladine A supplied us not only with samples of synthetic natural product, but also with several structural analogues that were screened for MMP inhibition using procedures previously described.[1] The compounds which were evaluated include synthetic ageladine A (**1**), 3,5-dibromo regioisomer **36**, monobromopyrrole **38**, its fully protected version **35**, tricyclic analogue **37**, and 2-chloropyridine **31** (Figure 1). The biological screening focused on MMP-2 and MT1-MMP.[1]

The synthetic ageladine A displayed the same level of inhibition as the isolated natural product against MMP-2 and MT1-MMP. However, as indicated from the testing results, none of our analogues was a more potent inhibitor than ageladine A (Figure 1). It appears that the quantity and location of the bromine atoms impacts on MMP inhibition. Both brominated analogues **36** and **38** inhibited MMP-2 and MT1-MMP, but with about a 5-fold decrease relative to **1**. The complete removal of bromine from the molecule (i.e., **37**) appeared to substantially decrease MMP inhibition. However, due to the strong fluorescence of **37**, which interferes with the inhibition assay, the data are not entirely reliable. The data also indicated that the presence of the nitrogen protecting groups in **35** negatively impacts MMP inhibition, as does removal of the pyrrole ring (cf. **31**).



	MMP-2 (μg/mL)	**MT1-MMP** (μg/mL)
ageladine A (**1**)	2	1.2
3,5-dibromo isomer **36**	10	5
debromoageladine A **38**	5.6	5
protected tricycle **35**	33% (@ 20 μg/mL)	20% (@ 20 μg/mL)
2-chloropyridine **31**	4% (@ 20 μg/mL)	0% (@ 20 μg/mL)

FIGURE 1. MMP inhibition results for synthetic analogues of ageladine A.

Conclusion

A 12-step total synthesis of the tricyclic marine metabolite ageladine A (**1**) has been developed starting from 2,4,5-tribromoimidazole, utilizing a 6π-1-azaelectrocyclization and a Suzuki−Miyaura coupling of *N*-Boc-pyrrole-2-boronic acid (**18**) with a chloro imidazopyridine as key steps. The synthesis has led to the production of several structural analogues of **1** that were subjected to MMP inhibition testing. Although none of the analogues prepared to date are as potent as the natural product, this route, along with our recently reported second generation synthesis of ageladine A,[6] allows for the facile synthesis of additional compounds for further biological testing.

Experimental Section

3-Benzyloxymethyl-5-bromo-2-methylsulfanylimidazole-4-carboxaldehyde (6a). To a solution of tribromoimidazole **5a** (6.00 g, 14.1 mmol) in THF (35 mL) was added *n*-BuLi in hexanes (2.4 M, 5.88 mL, 14.1 mmol) at −78 °C and the reaction mixture was stirred for 15 min.[34] Dimethyl disulfide (1.33 g, 14.1 mmol) was then added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 15 h, and *n*-BuLi in hexanes (2.4 M, 5.88 mL, 14.1 mmol) was added dropwise. After the mixture was stirred for 15 min at −78 °C, DMF (3.09 g, 3.29 mL, 42.4 mmol) was added slowly. The reaction mixture was stirred at −78 °C for 30 min and

(33) Zucker, S.; Cao, J.; Wen-Tien, C. *Oncogene* **2000**, *19*, 6642 and references cited therein.

(34) For general procedures and HPLC conditions, see the Supporting Information.

then warmed to rt. The mixture was diluted with H_2O 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, 6/1) afforded aldehyde **6a** (4.39 g, 91%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 4.52 (s, 2H), 5.68 (s, 2H), 7.21−7.23 (m, 5H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 155.3, 137.1, 132.1, 128.8, 128.6, 128.4, 128.1, 74.3, 71.8, 15.1; ESI (+) $[M + Na]^+$ calcd for $C_{13}H_{13}N_2O_2BrSNa$ 362.9779, found 362.9775.

1-Benzyloxymethyl-4-bromo-2-methylsulfanyl-5-vinylimidazole (12a). To a solution of Ph_3PMeBr (6.54 g, 18.32 mmol) in THF (35 mL) was added *t*-BuOK (1.81 g, 16.12 mmol) in portions at 0 °C. The reaction mixture was stirred at rt for 30 min and cooled to 0 °C. A solution of aldehyde **6a** (2.50 g, 7.33 mmol) in THF (5 mL) was added slowly after which the reaction mixture was warmed to rt and stirred for 3.5 h. The reaction mixture was diluted with saturated NH_4Cl and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded vinylimidazole **12a** (2.39 g, 96%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) 2.56 (s, 3H), 4.47 (s, 2H), 5.28 (m, 3H), 5.87 (d, J = 17.9 Hz, 1H), 6.45 (dd, J = 17.9, 12.1 Hz, 1H), 7.18−7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 135.4, 128.0, 127.5, 127.1, 126.7, 120.9, 116.1, 115.0, 72.3, 69.6, 15.0; ESI (+) $[M + H]^+$ calcd for $C_{14}H_{16}N_2OSBr$ 339.0167, found 339.0153.

1-Benzyloxymethyl-2-methylsulfanyl-5-vinylimidazole-4-carboxylic Acid (13a). To a solution of bromoimidazole **12a** (3.50 g, 10.32 mmol) in THF (30 mL) was added *n*-BuLi in hexanes (2.4 M, 6.45 mL, 15.47 mmol) at −78 °C and the reaction mixture was stirred for 1.25 h. Excess freshly crushed dry ice was then added at −78 °C and the reaction mixture was slowly warmed to rt. The reaction mixture was quenched with H_2O and extracted with Et_2O. The aqueous layer was acidified to pH 3 with 1 M HCl and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated. Purification of the residue by recrystallization (hexanes/EtOAc) afforded acid **13a** (3.09 g, 98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 4.55 (s, 2H), 5.31 (s, 2H), 5.55 (dd, J = 12.2, 1.0 Hz, 1H), 6.08 (dd, J = 18.1, 0.9 Hz, 1H), 7.02 (dd, J = 18.1, 12.2 Hz, 1H), 7.19−7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 146.9, 138.2, 136.7, 129.9, 129.0, 128.7, 128.2, 123.0, 122.7, 74.0, 71.5, 15.9; ESI (+) $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3S$ 305.0960, found 305.0947.

1-Benzyloxymethyl-2-methylsulfanyl-4-(*N*-methoxyimino-1-chloromethyl)-5-vinylimidazole (14a). A solution of methoxylamine hydrochloride (82 mg, 0.99 mmol) and pyridine (78 mg, 0.08 mL, 0.99 mmol) in acetonitrile (15 mL) was stirred at rt for 10 min, and acid **13a** (250 mg, 0.82 mmol) and carbon tetrachloride (505 mg, 0.32 mL, 3.29 mmol) were added. The reaction mixture was stirred at rt for 10 min before the addition of triphenylphosphine (862 mg, 3.29 mmol). The mixture was refluxed at 80 °C for 4 h and then concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 6/1) affording chloromethoxime **14a** (251 mg, 87%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.97 (s, 3H), 4.51 (s, 2H), 5.28 (s, 2H), 5.36 (dd, J = 12.1, 1.0 Hz, 1H), 5.83 (dd, J = 18.0, 1.09 Hz, 1H), 6.77 (dd, J = 18.0, 12.1 Hz, 1H), 7.19−7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 137.0, 133.3, 133.1, 132.6, 128.9, 128.5, 128.1, 123.6, 119.9, 74.1, 71.2, 63.5, 16.5; ESI (+) $[M + H]^+$ calcd for $C_{16}H_{19}N_3O_2SCl$ 352.0887, found 352.0888.

1-Benzyloxymethyl-4-chloro-2-methylsulfanylimidazopyridine (17a). A solution of methoxime **14a** (0.50 g, 1.42 mmol) in *o*-xylene (50 mL) was refluxed at 145 °C for 17 h and concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 2/1) affording pyridine **17a** (0.38 g, 84%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (s, 3H), 4.43 (s, 2H), 5.43 (s, 2H), 7.12 (d, J = 5.5 Hz, 1H), 7.16−7.19 (m, 2H), 7.23−7.26 (m, 3H), 8.05 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 142.1, 140.6, 139.7, 137.2, 135.3, 128.1, 127.8, 127.3, 104.1, 72.5, 70.4, 14.3; ESI (+) $[M + H]^+$ calcd for $C_{15}H_{15}N_3OSCl$ 320.0624, found 320.0616.

1-Benzyloxymethyl-4-chloro-2-methanesulfinylimidazopyridine (29). To a solution of sulfide **17a** (100 mg, 0.31 mmol) in MeOH (3 mL) at −20 °C was added Oxone (Aldrich, 577 mg, 0.19 mmol) in H_2O (3 mL). The mixture was stirred at −20 °C for 2.5 h, after which the MeOH was removed in vacuo. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded sulfoxide **29** (96 mg, 91%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 3H), 4.56 (s, 2H), 5.97 (s, 2H), 7.15−7.18 (m, 2H), 7.21−7.24 (m, 3H), 7.31 (d, J = 5.7 Hz, 1H), 8.21 (d, J = 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 143.1, 142.3, 141.5, 135.3, 135.1, 127.9, 127.7, 127.1, 105.3, 73.1, 70.8, 39.7; ESI (+) $[M + H]^+$ calcd for $C_{15}H_{15}N_3O_2SCl$ 336.0574, found 336.0575.

2-Azido-1-benzyloxymethyl-4-chloroimidazopyridine (30). To a solution of sulfoxide **29** (75 mg, 0.22 mmol) in DMF (5 mL) was added NaN_3 (73 mg, 1.12 mmol) at rt. The mixture was stirred at rt for 14 h, diluted with H_2O, 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 azide **30** (61 mg, 87%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 2H), 5.34 (s, 3H), 7.12−7.16 (m, 3H), 7.20−7.24 (m, 3H), 8.05 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 143.3, 142.4, 142.0, 137.6, 137.4, 130.3, 130.2, 129.5, 107.0, 74.1, 73.1; ESI (+) $[M + H]^+$ calcd for $C_{14}H_{12}N_6OCl$ 315.0761, found 315.0765.

1-Benzyloxymethyl-4-chloroimidazopyridin-2-ylamine (31). A solution of azide **30** (50 mg, 0.16 mmol) in EtOH (3 mL) was reduced with 10% Pd/C (16 mg) at rt under 1 atm of H_2 for 3.5 h. The mixture was then filtered through a Celite pad, which was washed with MeOH. The filtrate was concentrated to afford amine **31** (44 mg, 96%) as a white solid sufficiently pure for use in the next step. ^{1}H NMR (300 MHz, CD_3OD) δ 4.55 (s, 2H), 5.55 (s, 2H), 7.23−7.25 (m, 6H), 7.88 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.9, 141.5, 138.9, 137.1, 136.3, 136.0, 128.3, 127.9, 127.8, 104.4, 72.3, 71.0; ESI (+) $[M + H]^+$ calcd for $C_{14}H_{14}N_4OCl$ 289.0856, found 289.0866.

4-(1*H*-Pyrrol-2-yl)imidazopyridin-2-ylamine (37). In an oven-dried Schlenk tube were placed chloropyridine **31** (70 mg, 0.24 mmol), boronic acid **18** (205 mg, 0.97 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), (2-biphenyl)dicyclohexylphosphine (85 mg, 0.24 mmol), K_3PO_4 (206 mg, 0.97 mmol), and 1,4-dioxane (6 mL). The Schlenk tube was flushed with argon, sealed, and heated at 100 °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 crude coupled product mixture **32** and **33** (2:1 mixture of **32**:**33**) was dissolved in EtOH (7 mL) and 6 N HCl (4 mL). The mixture was heated at 100 °C for 12 h and then concentrated. The residue was redissolved in MeOH, neutralized with 1% KOH, and concentrated again. The residue was purified with use of a short silica plug (CH_2Cl_2/MeOH, 4/1) affording deprotected imidazole **37** (32 mg, 67%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 6.41 (dd, J = 3.9, 2.6 Hz, 1H), 7.17 (dd, J = 3.9, 1.3 Hz, 1H), 7.23 (dd, J = 2.6, 1.3 Hz, 1H), 7.33 (d, J = 6.5 Hz, 1H), 7.94 (d, J = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.3, 146.2, 136.5, 131.8, 131.5, 125.6, 123.5, 112.6, 112.0, 104.4; ESI (+) $[M + H]^+$ calcd for $C_{10}H_{10}N_5$ 200.0936, found 200.0923.

Ageladine A (1). To a solution of pyrrole **37** (20 mg, 0.1 mmol) in AcOH/MeOH (5 mL/1 mL) at 0 °C was slowly added Br_2 in glacial AcOH (20 mM, 0.36 mL, 0.07 mmol). The mixture was stirred at 0 °C for 20 min and then concentrated. Purification of the residue by reverse-phase HPLC[34] afforded ageladine A (**1**, 6 mg, 17%) as a yellow solid, along with starting pyrrole **37** (6 mg, 29%), monobromopyrrole **38** (14 mg, 50%), and tribromopyrrole

39 (1 mg, 2%). Ageladine A (**1**): ^{1}H NMR (300 MHz, CD_3OD) δ 7.17 (s, 1H), 7.41 (d, $J = 6.4$ Hz, 1H), 8.05 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.8, 147.1, 136.7, 133.0, 128.5, 125.7, 115.1, 107.7, 105.4, 102.3; ESI (+) $[M + H]^+$ calcd for $C_{10}H_8N_5{}^{79}Br_2$ 355.9146, found 355.9163. Monobromopyrrole **38**: ^{1}H NMR (400 MHz, CD_3OD) δ 6.34 (d, $J = 6.0$ Hz, 1H), 7.03 (d, $J = 6.0$ Hz, 1H), 7.30 (d, $J = 6.5$ Hz, 1H), 7.91 (d, $J = 6.5$ Hz, 1H); ESI (+) $[M + H]^+$ calcd for $C_{10}H_9N_5{}^{79}Br$ 277, found 278.0. Tribromopyrrole **39**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, $J = 6.4$ Hz, 1H), 8.15 (d, $J = 6.4$ Hz, 1H); ESI (+) $[M + H]^+$ calcd for $C_{10}H_7N_5{}^{79}Br_3$ 433, found 433.8.

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

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