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A Concise Total Synthesis of Naamidine A

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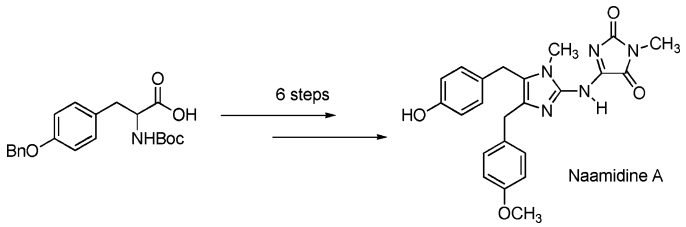
ABSTRACT



A total synthesis of naamidine A is reported. Key benefits of the described pathway include its brevity, its synthetic ease, and its flexibility with respect to the preparation of analogues. Formation of the 2-aminoimidazole core is achieved by condensation of the appropriate α-aminoketone with cyanamide.

Since the late 1980s, a range of 2-aminoimidazole alkaloids have been isolated from sponges of the genus *Leucetta* (Figure 1),[1] with naamidine A (**1**) being one of the more prominent members of the family. After being isolated by Carmely and Kashman in 1987,[2] naamidine A received little attention until initial reports of its biological activity were made by Ireland over a decade later.[3] Early studies showed the unusual tetrasubstituted 2-aminoimidazole alkaloid to be an antagonist of the epidermal growth factor receptor (EGFR) signaling pathway, overexpression of which has been implicated in a wide variety of human cancers and is typically associated with poor prognosis.[4] In vivo assays of **1**, featuring implanted tumors in athymic mice, demonstrated 85% tumor growth inhibition at the highest tolerated dose of 25 mg/kg.

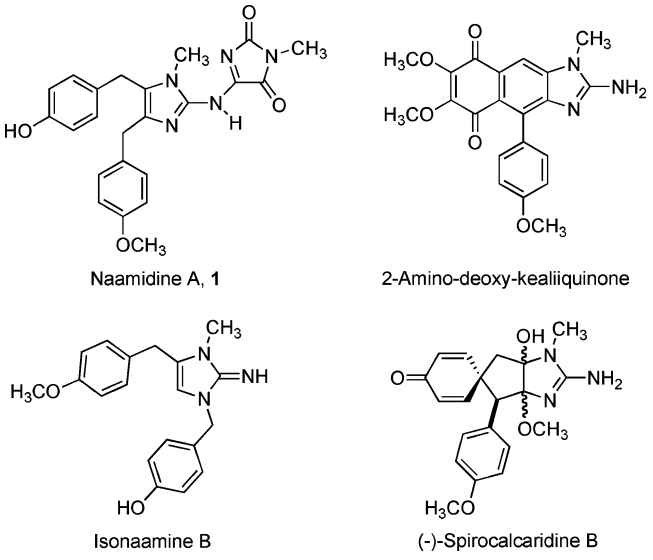


Figure 1. Examples of 2-aminoimidazoles from genus *Leucetta*.

Subsequent analysis revealed total abrogation of DNA synthesis at ∼1 μM with corresponding cell cycle arrest in

(1) (a) Ralifo, P.; Crews, P. *J. Org. Chem.* **2004**, *69*, 9025. (b) Edrada, R. A.; Stessman, C. C.; Crews, P. *J. Nat. Prod.* **2003**, *66*, 939. (c) Crews, P.; Clark, D. P.; Tenney, K. *J. Nat. Prod.* **2003**, *66*, 177. (d) Gross, H.; Kehraus, S.; Konig, G. M.; Woerheide, G.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1190. (e) Fu, X.; Schmitz, F. J.; Tanner, R. S.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 384. (f) Plubrukarn, A.; Smith, D. W.; Cramer, R. E.; Davidson, B. S. *J. Nat. Prod.* **1997**, *60*, 712.

(2) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 3003.

(3) Copp, B. R.; Fairchild, C. R.; Cornell, L.; Casazza, A. M.; Robinson, S.; Ireland, C. M. *J. Med. Chem.* **1998**, *41*, 3909.

(4) For example: (a) Laskin, J. J.; Sandler, A. B. *Cancer Treat. Rev.* **2004**, *30*, 1. (b) Nicholson, R. I.; Gee, J. M. W.; Harper, M. E. *Eur. J. Cancer* **2001**, *37*, S9. (c) Baselga, J. *Oncologist* **2002**, *7*, 2.

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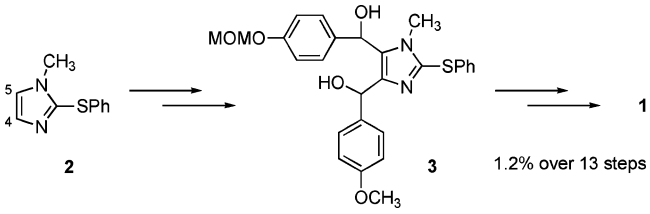
G_1, thought to be induced by enhanced phosphorylation of ERK1/2,[5] which are serine/threonine protein kinases of the MAPK signal transduction cascade and important anti-cancer targets.[6] The associated increase in phosphotransferase activity of ERK1/2 is a phenomenon unique among small molecules to naamidine A. This feature of its activity, along with its potential anti-tumor properties, make it an interesting target for further investigation.

The only previous total synthesis of naamidine A and its precursor naamine A was reported by Ohta and co-workers (Scheme 1).[7] A partially functionalized imidazole ring **2** was sequentially substituted at the 5- and 4-positions by a series of lithiation and alkylation steps. Several protections and deprotections were necessary to achieve the requisite intermediate **3**. Six further steps were required to eliminate the benzylic hydroxyl groups and to convert the 2-thiophenyl group to the primary amine. Introduction of the dehydrohydantoin unit was performed by an interesting regioselective condensation with 1-methyl-3-(trimethylsilyl)parabanic acid.[8]

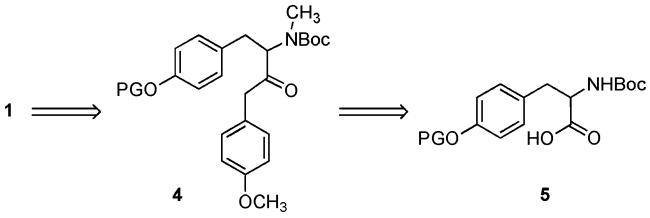
Scheme 1. Ohta Synthesis of Naamidine A



Our interest in an efficient total synthesis of naamidine A had two major goals: (i) to be able to easily produce sufficient quantities of the natural product for a range of biological analyses and (ii) for the synthesis to be amenable to the rapid preparation of a diverse set of analogues as part of our medicinal chemistry program. In assessing the fulfillment of these criteria, we considered that several improvements to the Ohta synthesis could be made.

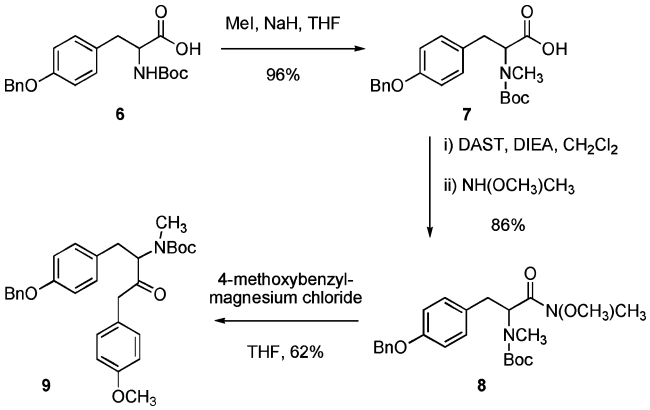
From a retrosynthetic perspective (Scheme 2), we intended to make use of the conditions developed by Ohta for the regioselective introduction of the dehydrohydantoin moiety. Rather than beginning with a preformed imidazole ring, we determined to create the 2-aminoimidazole via condensation of cyanamide with the appropriate α-amino ketone (**4**). This, in turn, we envisioned, could be easily obtained in several steps from a suitably protected tyrosine derivative (**5**), raising the possibility of a correlation between our approach and a potential biosynthetic pathway for these alkaloids.

Scheme 2. Retrosynthetic Analysis



To this end, we chose the relatively inexpensive, commercially available Boc-Tyr(Bzl)-OH (**6**) as our starting point (Scheme 3). Selective *N*-methylation of the Boc-protected amino acid was performed using the conditions of Benoiton,[9] proceeding in 96% yield (**7**) with no methyl ester formation observed. Methylation of this nitrogen at any early stage of the synthesis is essential to achieve the required regiospecificity in the formation of the imidazole ring. In situ formation of the acid fluoride was followed by reaction with *N*,*O*-dimethylhydroxylamine[10] to provide the Weinreb amide **8** (86%), existing as a mixture of four rotamers. This was then treated with the appropriate Grignard reagent to give the protected α-amino ketone **9** (62%).

Scheme 3. Synthesis of α-Amino Ketone **9**

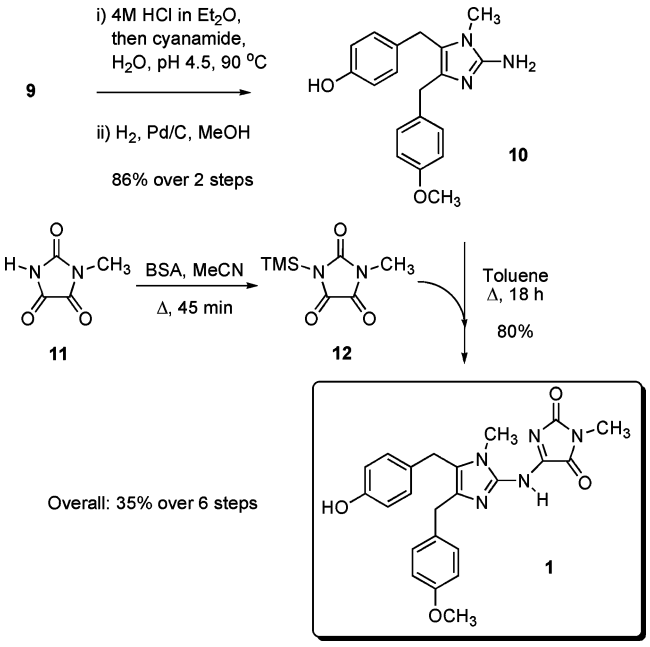


Removal of the Boc protecting group of **9** was best achieved using 4 M HCl in diethyl ether (Scheme 4), as an aqueous suspension of the resulting salt provided a pH ideal for the subsequent condensation with cyanamide,[11] ultimately affording the trisubstituted 2-aminoimidazole (86%). Cleavage of the benzyl group was effected in quantitative yield by standard catalytic hydrogenolysis conditions (10% Pd/C) to provide naamine A, **10**.

Applying the general concept of Ohta's introduction of the unique dehydrohydantoin moiety, 1-methylparabanic acid (**11**)[12] was silylated to **12** with *N*,*O*-bis(trimethylsilyl)-

(5) James, R. D.; Jones, D. A.; Aalbersberg, W.; Ireland, C. M. *Mol. Cancer Ther.* **2003**, *2*, 747.
(6) (a) Sebolt-Leopold, J. S.; Herrera, R. *Nat. Rev. Cancer* **2004**, *4*, 937. (b) English, J. M.; Cobb, M. H. *Trends Pharmacol. Sci.* **2002**, *23*, 40. (c) Sebolt-Leopold, J. S. *Oncogene* **2000**, *19*, 6594.
(7) Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. *Heterocycles* **2000**, *53*, 1939.
(8) The conditions used in the total synthesis were subsequently improved and applied to the total synthesis of related imidazole alkaloids: Nakamura, S.; Kawasaki, I.; Yamashita, M.; Ohta, S. *Heterocycles* **2003**, *60*, 583.
(9) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.
(10) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091.
(11) (a) Lancini, G. C.; Lazzari, E. *J. Heterocycl. Chem.* **1966**, *3*, 152. (b) Boehm, J. C.; Gleason, J. G.; Pendrak, I.; Sarau, H. M.; Schmidt, D. B.; Foley, J. J.; Kingsbury, W. D. *J. Med. Chem.* **1993**, *36*, 3333.
(12) Kolonko, K. J.; Shapiro, R. H.; Barkley, R. M.; Sievers, R. E. *J. Org. Chem.* **1979**, *44*, 3769.

Scheme 4. Synthesis of Naamidine A



acetamide (BSA) and then reacted with **10** (80%) to complete the second total synthesis of naamidine A, carried out in six linear steps with an overall yield of 35%. Spectral data (^{1}H and ^{13}C NMR) for the synthetic material matched that reported in the literature for the natural sample.[13] Preliminary biological assessment has confirmed that the synthetic **1** inhibits EGF- and IL3-stimulated DNA synthesis in BaF/ERX cells with an IC_{50} of 3 μM, consistent with the reported values.

We are now in a position to conduct an in depth analysis of naamidine A's biological activity and to prepare a range of analogues for structure−activity relationships in the quest for clinically relevant anti-cancer properties.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Carmely, S.; Ilan, M.; Kashman, Y. *Tetrahedron* **1989**, *45*, 2193.