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Total syntheses of isonaamine C and isonaamidine E

Heather M. Lima, Beatriz J. Garcia-Barboza [†], Nicole N. Khatibi [†], Carl J. Lovely *

Department of Chemistry & Biochemistry, University of Texas at Arlington, Arlington, TX 76019, United States

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ABSTRACT

The total syntheses of two alkaloids isolated from a marine sponge of the *Leucetta* sp. have been accomplished in 6 and 7 steps starting from a 4,5-diiodoimidazole derivative. Grignard mediated halogen–metal exchange was used to install the benzyl side chain. C2 substitution was accomplished via lithiation followed by quenching with trisyl azide which provided isonaamine C after hydrogenation. Isonaamidine E was then prepared from isonaamine C via introduction of the hydantoin ring by reaction with an activated parabanic acid derivative.

Marine sponges of the *Leucetta* and *Clathrina* genera produce a number of imidazole-containing alkaloids that are characterized by a 2-amino or *N*-imidazolidinedionyl group at C2, and varying benzyl substitution at C4 and C5 on the imidazole.[1,2] Isonaamine C (**1**)[3] and isonaamidine E (**2**) isolated by Wright in 2002,[4] among others, are representative examples of this class of natural products (Fig. 1).[5] Calcaridine A (**5**)[6,7] is an example of the more highly oxidized members of this family. Many of these alkaloids have been reported to exhibit varying biological activities including those of interest in this manuscript. Both isonaamine C (**1**) and isonaamidine E (**2**) were found to be cytotoxic against stomach (HM02) and liver (HepG2 and Huh7) cancer cell lines with GI_{50} values in the range of 1.3–7.0 μg/mL.[4]

A robust, efficient, and adaptable synthetic strategy was developed by our lab to access this family of natural products centers around the functionalization of 4,5-diiodoimidazoles via halogen-metal exchange of Grignard reagents to prepare the benzyl substituted framework.[2] C2 substitution using *n*-BuLi and TsN_3 or $TrisN_3$ to ultimately lead to the 2-amino substituted target following reduction has been a very effective method as evidenced by the successes in our own lab[7–9] and in numerous other examples. This manuscript will detail the application of this approach in the total syntheses of isonaamine C (**1**) and isonaamidine E (**2**).

The sequential functionalization of 4,5-dihaloimidazoles with Grignard reagents has been well documented, and follows the order of C5, then C4.[10–12] However, C4 functionalization of *N*-benzyl substituted derivatives leading to C4 benzyl substitution has not

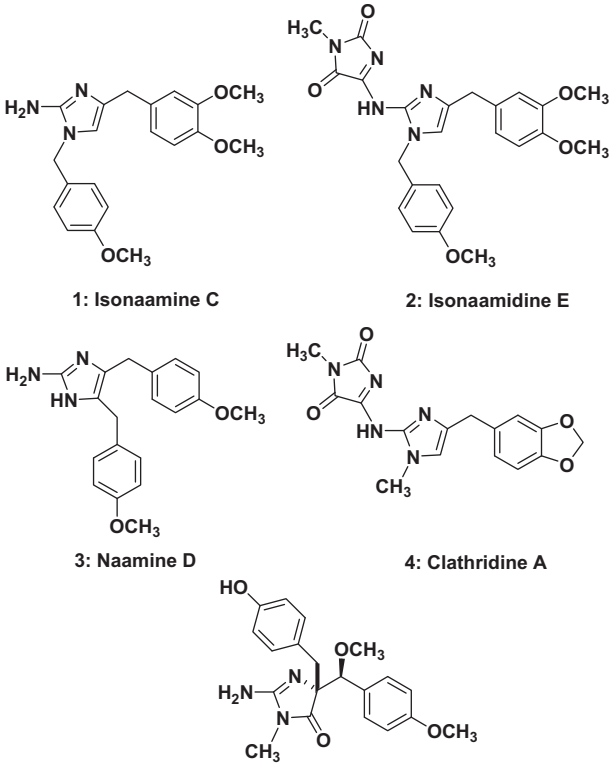

Figure 1. Examples of *Leucetta* alkaloids.

* Corresponding author. Tel.: +1 817 272 5446; fax: +1 817 272 3808.
E-mail address: lovely@uta.edu (C.J. Lovely).
† Undergraduate coworkers.

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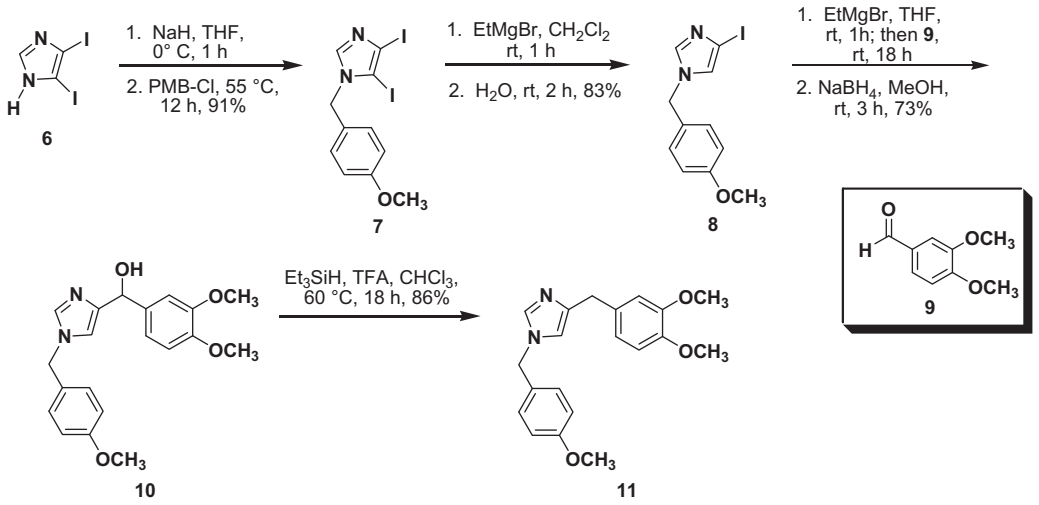
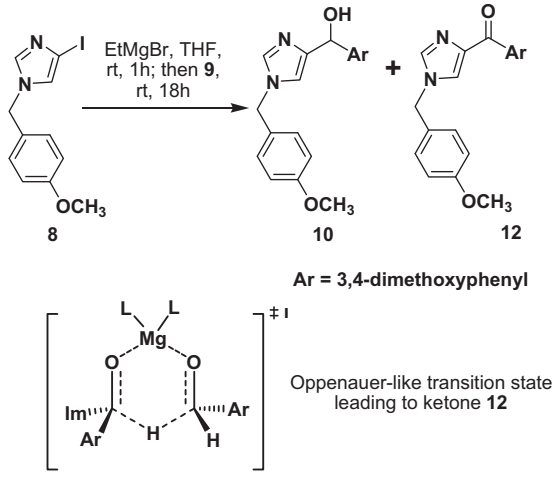
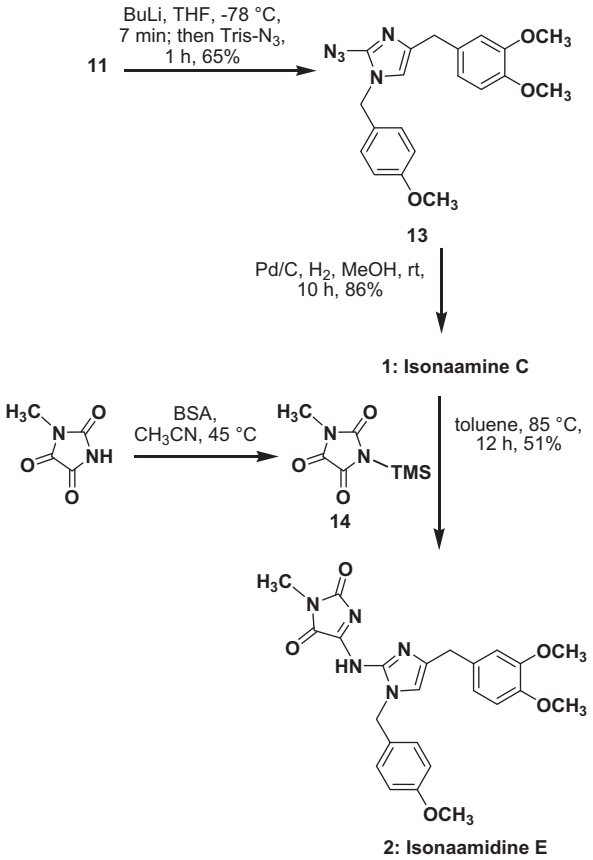


Scheme 1. Substitution of 4,5-diiodoimidazole.



Scheme 2. Grignard reaction leading to **10** and **12**.



Scheme 3. Total synthesis of isonaamine C and isonaamidine E.

been demonstrated before, and the occurrence of competitive lateral metalation of the *N*-benzyl side chain is a possible complication.[13,14] Therefore, the application of this synthetic strategy to isonaamine C provides the first example of selective C4 metalation in the presence of an *N*-benzyl substituent. Going forward, 4,5-diiodoimidazole (**6**) was treated with NaH, then 4-methoxybenzyl chloride to give the PMB-protected imidazole **7**. Treatment of **7** with EtMgBr induced a halogen–metal exchange at C5 selectively which when quenched with water resulted in an overall reduction leading to the 4-iodoimidazole intermediate **8** (Scheme 1).

Treatment of **8** with another round of EtMgBr followed by 3,4-dimethoxybenzaldehyde (**9**) led to a mixture of alcohol **10** and the corresponding ketone **12**, which is thought to form via an Oppenauer-type oxidation as a result of coordination through the magnesium alkoxide salt and the benzaldehyde **9** (Scheme 2).[15–17] However, it was found that the formation of the ketone by-product could be minimized by the addition of the prepared Grignard reagent to a dilute solution of the aldehyde at room temperature. In addition, the crude mixture of products isolated from the Grignard reaction could be treated with $NaBH_4$ in MeOH to provide **10** in 73% yield over the two steps.

Reduction of **10** with Et_3SiH and TFA[7–9] led to **11** allowing access to the necessary bis-benzyl substituted framework of isonaamine C and isonaamidine E (Scheme 1). The 2-amino substituent was introduced by treatment of **11** with *n*-BuLi and quenched with $TrisN_3$ to give **13** which was reduced via hydrogenation on Pd/C resulting in isonaamine C (**1**) in 86% yield. The hydantoin ring of isonaamidine E was introduced following the literature procedure involving the reaction of 1-methylparabanic acid and BSA leading to the activated acid **14**.[8,9,18,19] Upon treatment of **1** with **14**, isonaamidine E (**2**) was isolated in 51% yield from **1** (Scheme 3). In both cases, the spectroscopic data for compounds **1** and **2** agree with the reported values.[4]

In conclusion, isonaamine C (27% overall) and isonaamidine E (14% overall) have been synthesized in 6 and 7 steps, respectively,

from **7** following a general synthetic route developed by us to access this family of natural products. Central to this approach is the application of the chemoselective reactivity of 4,5-dihaloimidazole substitution that has allowed for the controlled elaboration of imidazoles, including those having *N*-benzyl substituents, leading to the desired benzyl substituted core of the target alkaloids. To date a number of bioactive *Leucetta* and *Clathrina* alkaloids have been synthesized following this strategy attesting not only to its versatile and efficient nature, but also to its potential applicability in medicinal chemistry projects.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and copies of ^{1}H and ^{13}C NMR data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.030.

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