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Expedient total syntheses of preclathridine A and clathridine A

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ABSTRACT

A short and operationally simple total synthesis of two *Leucetta*-derived marine alkaloids has been developed, which rely on position specific halogen–metal exchange to introduce the benzyl-substituted side chain. Introduction of the C2 amine group by lithiation and trapping with tosyl azide provides preclathridine A on catalytic hydrogenation, which can be converted to clathridine A by a procedure described in the literature.

2-Aminoimidazole alkaloids have recently attracted the attention of the synthetic community, in particular several members of the oroidin family of alkaloids.[1,2] A less well explored group of 2-aminoimidazole-containing natural products is found in sponges of the *Leucettidae* family. The *Leucetta* family of alkaloids are characterized by the presence of a 2-aminoimidazole moiety which is substituted at various positions around the heterocycle and contains at least one, but more commonly two benzylic fragments. They range in complexity from the fairly simple clathridine A (**1**),[3] preclathridine A (**2**),[4] and naamidine type systems (e.g., naamidine A (**3**))[5,6] to the more elaborate and highly oxygenated members such as calcaridine A (**4**),[7] spiroleucettadine (**5**),[7] and kealiiquinone (**6**).[8] From a biological perspective, some of these alkaloids have been reported to exhibit activities as antibiotics,[9] nitric oxide synthase inhibitors,[9] and are cytotoxic,[10] but in general their broad scale pharmacological evaluation has not been addressed. While in some cases these molecules are, relatively speaking, simple targets for total synthesis, they are attractive scaffolds for evaluation in high throughput screening programs, providing flexible and efficient synthetic approaches (Fig. 1).

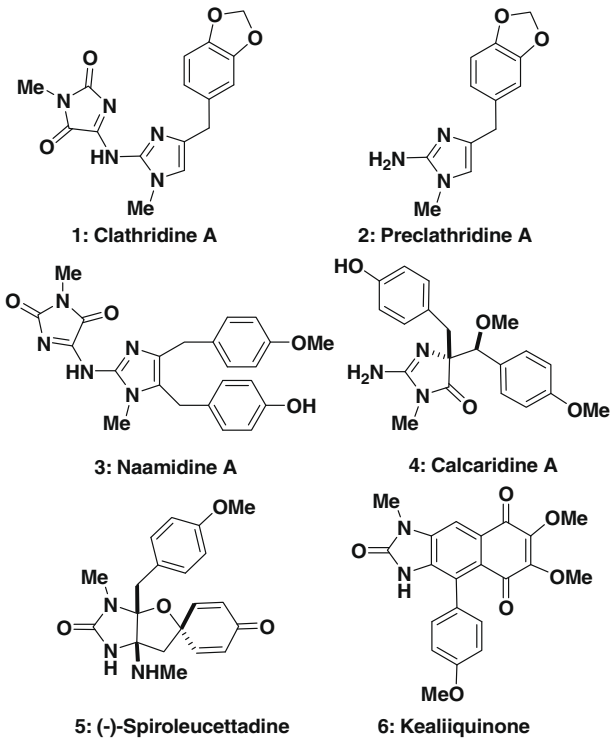

Figure 1. Selected *Leucetta* alkaloids.

In principle two general approaches to these molecules might be envisioned, one in which the imidazole ring is constructed in a de novo fashion, or a second in which a pre-existing imidazole is elaborated. While both strategies have different strengths and weaknesses, our laboratory has followed the latter approach using polyhaloimidazoles as the starting point and used this en route to the total synthesis of members of both the oroidin and the *Leucetta* families of alkaloids.[2] Following important precedents,[11] we and others have demonstrated that 4,5-dihaloimidazoles can be functionalized in a sequential and controlled manner in the order C5→C4→C2 using Grignard reagents (for the 4- and 5-positions) and *n*-BuLi (for C2).[12–15] The fact that functionalization of C2 can be accomplished late in a sequence, particularly the incorporation of an amino group, has practical advantages in approaches to the *Leucetta* and the oroidin alkaloids. This type of strategy has been used by us in a total synthesis of calcaridine A (**4**)[14] and the reported structure of nagelamide D.[15] The current report describes the extension of this strategy in the total syntheses of clathridine A and preclathridine A.

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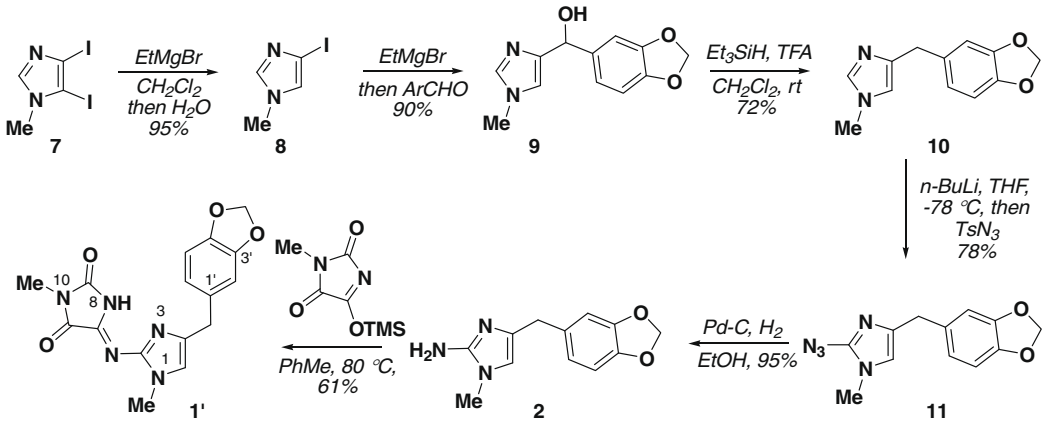

Scheme 1.

Clathridine A (**1**) (from the sponge *Clathrina clathrus*) and preclathridine A (**2**) (from the nudibranch *Notodoris gardineri*) were isolated and reported by the Fattoruso and Crews laboratories, respectively, almost 20 years ago.[3,4] Little in terms of biological activity of these natural products has been reported, although it is mentioned that **1** is antimycotic.[3a] Three total syntheses of these molecules have been described in the literature. The first report by Ohta's laboratory employs the sequential metalation (Br→Li) of an imidazole derivative, but requires blocking groups (thiophenyl groups) to prevent unwanted metalation at the 2- and 5-positions.[16,19] Both the Molina[17] and the van der Eycken[18] groups have utilized methods that involve the de novo synthesis of the aminoimidazole system via iminophosphoranes and masked guanidine derivatives, respectively. While strategically our approach is closely related to that reported by the Ohta's laboratory,[16] as indicated above, we have developed methodology based on the elaboration of haloimidazoles via Grignard reagents which does not require protection (and subsequent deprotection) of the more reactive 2- and 5-positions which is necessary using deprotonation strategies or halogen–lithium exchange.

Our synthetic studies commenced with the conversion of diiodo-l-methylimidazole (**7**) to 4-iodoimidazole (**8**) by treatment with EtMgBr, followed by water (Scheme 1).[13] The resulting 4-iodoimidazole was reacted with EtMgBr to effect formation of imidazol-4-yl Grignard which was treated with piperonal to provide the alcohol **9**.[16] Removal of the doubly benzylic alcohol was accomplished by reduction with Et_3SiH and TFA at room temperature affording **10**. Lithiation at C2 was accomplished with *n*-BuLi and the resulting species was treated with TsN_3 to install an azide moiety. The synthesis of preclathridine A (**2**) was completed by reduction of the azide to the amine on catalytic hydrogenation. Preclathridine A was converted to clathridine A (**1**) using the procedure reported by Watson and co-workers with TMS-activated methyl parabanic acid.[6b] The two synthetic compounds displayed spectroscopic data generally consistent with the structures of the natural product. The ^1H NMR data were in excellent agreement, the ^{13}C NMR data were generally in good agreement but we noted small differences in the ^{13}C NMR spectrum to that reported in both the isolation papers and in synthetic material.[3,4,19] All three sets of reported data were acquired in different solvents, but there is apparently little solvent dependence on the chemical shifts, and so we do not believe that this is the cause of the discrepancies. Fortunately, our synthetic material provided a nicely crystalline product, which was subjected to X-ray crystallography, and this provided confirmation of the connectivity (Fig. 2). We also observed, that in the crystalline state, (**1**) exists as the N(8)H tautomer (cf **1'** in Scheme 1).

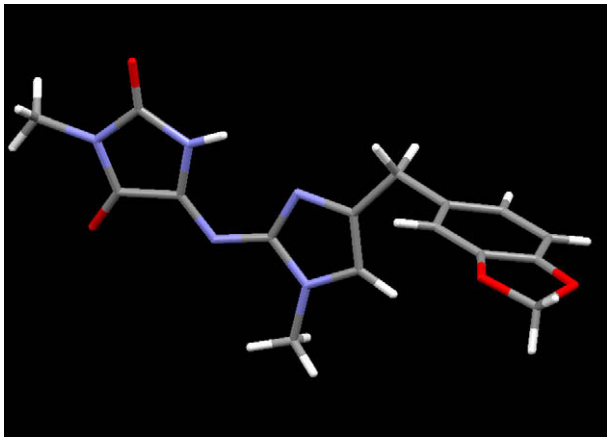

Figure 2. X-ray structure of synthetic clathridine A.

In summary, we have developed high yielding five- and six-step syntheses of the *Leucetta* alkaloids preclathridine A (**2**) and clathridine A (**1**), respectively. The syntheses rely on chemoselective halogen–magnesium exchange, permitting the selective installation of the C4-benzyl group without protection of the more acidic C2-and C5-positions. Subsequent lithiation at C2 and electrophilic trapping lead to introduction of 2-amino moiety. This chemistry is very easy to perform and leads to the preparation of these natural products on the gram-scale. This chemistry can be used for the synthesis of other members of the *Leucetta* family of alkaloids, and it is also amenable for the synthesis of analogs for medicinal chemistry programs. We are actively exploring these areas.

Acknowledgments

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