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Asymmetric Total Synthesis of *ent*-Cyclooroidin

Sabuj Mukherjee, Rasapalli Sivappa,† Muhammed Yousufuddin, and Carl J. Lovely*

Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States

lovely@uta.edu

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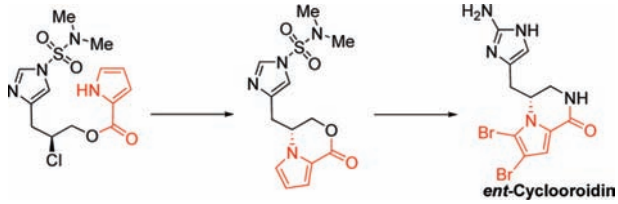
ABSTRACT



An enantiospecific total synthesis of the pyrrole−imidazole natural product cyclooroidin from histidine is described. The key N1−C9 bond is constructed through an intramolecular SN2-type of reaction of a chloro ester. Subsequent imidazole azidation at the 2-position, pyrrole bromination, azide reduction, and deprotection leads to the completion of the synthesis.

The oroidin alkaloids are a growing family of natural products isolated from marine sponges belonging to the *Agelasidae*, *Axinellidae*, *Dyctionellidae*, and *Hymeniacidonidae* families, which contain both a pyrrole and an imidazole moiety, the latter generally as a 2-aminoimidazole (Figure 1).[1] This family of natural products ranges in complexity from the parent molecule oroidin (**1**)[2] through to the tetrameric stylissidine A (**3**),[3] which itself appears to be a dimer of massadine (**2**).[4] Although little is known regarding the biosynthesis of these alkaloids,[5] they are frequently characterized according to the number of oroidin-like fragments that can be identified within the molecular framework. As a result of isolation efforts, several mono-

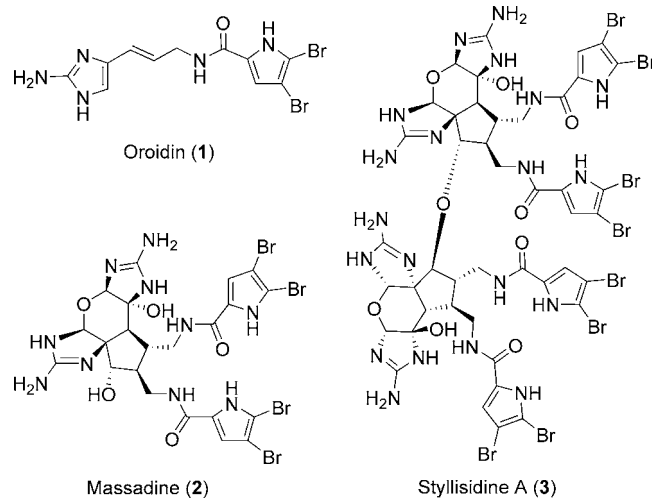


Figure 1. Several oroidin-derived alkaloids.

meric, dimeric, and tetrameric derivatives have been described as well as a number of synthetic efforts to several of these targets.[1] Our group's synthetic efforts have focused

† Current address: Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, MA 02747-2300.

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largely on the dimeric congeners,[6] and in the course of this program, we have investigated routes for the large scale preparation of urocanic acid derivatives from histidine that has led to the studies reported in this manuscript.[7] This chemistry involved the preparation of the α-chloro ester via diazonium chemistry,[8] and it occurred to us that this material might serve as an intermediate en route to several oroidin monomers, including cyclooroidin (**5**),[9] agesamides A and B,[10] oxocyclostylidol,[11] and potentially members of the agelastatin family, for example, (**4**)[12] for which the formation of just one additional carbon−carbon bond provides the appropriate framework.[13] The isolation of cyclooroidin from a Mediteranean sponge *Agelas oroides* was reported in 2000, but only limited biological investigations were reported.[9] Structurally, cyclooroidin possesses a relatively rare N1−C9 bond and a single stereocenter at C9. The absolute configuration was determined to be S through application of chiroptical methods, which was subsequently confirmed through synthesis. Four total syntheses have been reported, including one asymmetric total synthesis and a formal asymmetric synthesis.[14−17] In this paper, we describe an approach to cyclooroidin (**5**) that results in the total synthesis of the enantiopode of the naturally occurring material.

With the notable exception of the Lindel synthesis,[15] all of the reported approaches to cyclooroidin have relied upon the *de novo* assembly of the 2-aminoimidazole core,[14,16,17] whereas in the synthesis described herein the imidazole is present from the outset and thus represents a completely different strategy. Retrosynthetically we initially envisioned the construction of the two carbon−nitrogen bonds to assemble the pyrrolopiperazinone moiety, one of which needs to be performed in a stereodefined fashion. We anticipated that this could be accomplished through the formation of the N7−C8 bond (**7** + **8** → **9**, Figure 2) followed by an intramolecular displacement of the halogen with the pyrrole nitrogen, forming the N1−C9 bond (**9** → **5**, Figure 2). When we attempted to apply this strategy, the formation of the N7−C8 bond proceeded uneventfully via a Mitsunobu reaction with **8**, however, attempts to effect formation of the second C−N bond were unsuccessful with cyclization occurring exclusively through the amide oxygen leading to oxazoline **11**.[18] While this chemistry may prove useful en route to other oroidin derivatives, specifically nagelamide R and T,[19] it proved to be a dead-end as far as cyclooroidin (**5**) was concerned. A number of solutions to this issue were envisioned, including the simple expedient of protecting the amide nitrogen; however, we decided to pursue an approach in which the order of the C−N bond formations is interchanged. Specifically, we adopted a strategy in which the amide was replaced with an ester in the cyclization precursor.

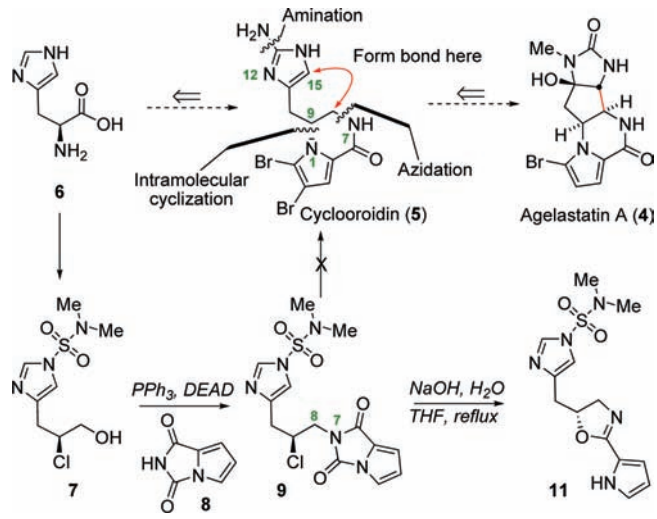

Figure 2. Retrosynthetic analysis of cyclooroidin (**5**).

Our synthesis began with the conversion of histidine (**6**) to the known chlorohydrin derivative **7**.[8,20] Acylation of **7** with the pyrrole carboxylic acid **12** provided the key ester **13** (Scheme 1). After some experimentation with various bases, we found that the intramolecular displacement reaction

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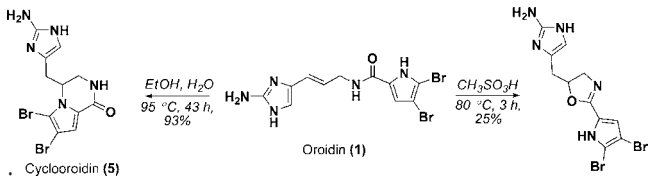
(13) After submission of this manuscript we became aware of a strategically similar approach to the agelestatin family of alkaloids, see Movassaghi, M.; Siegel, D. S.; Han, S. *Chem. Sci.* 2010, DOI: 10.1039/C0SC00351D.

(14) Papeo, G.; Frau, M. A. G.-Z.; Borghi, D.; Varasi, M. *Tetrahedron Lett.* **2005**, *46*, 8635–8638.

(15) (a) Poeverlein, C.; Breckle, G.; Lindel, T. *Org. Lett.* **2006**, *8*, 819–821. In this report the Lindel lab obtained racemic cyclooroidin on heating a solution of oroidin, as the formate salt, for 48 h at 95 °C in ethanol. Interestingly, and in contrast, Al-Mourabit found that heating oroidin in CH_3SO_3H for 3 h led to the formation of oxazoline related to **11** in Figure 2 in 25% yield. See: (b) Appenzeller, J.; Tilvi, S.; Martin, M.-T.; Gallard, J.-F.; El-bitar, H.; Dau, E. T. H.; Debitus, C.; Laurent, D.; Moriou, C.; Al-Mourabit, A. *Org. Lett.* **2009**, *11*, 4874–4877. These results presumably reflect the thermodynamic and kinetic preferences for the cyclization of oroidin.



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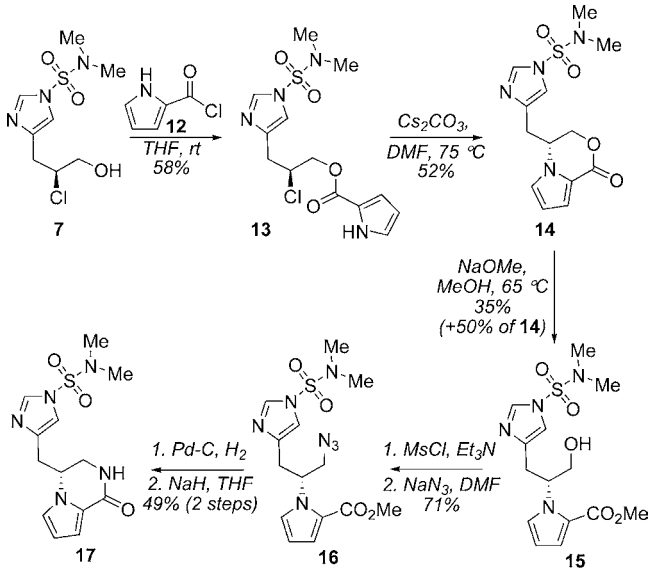
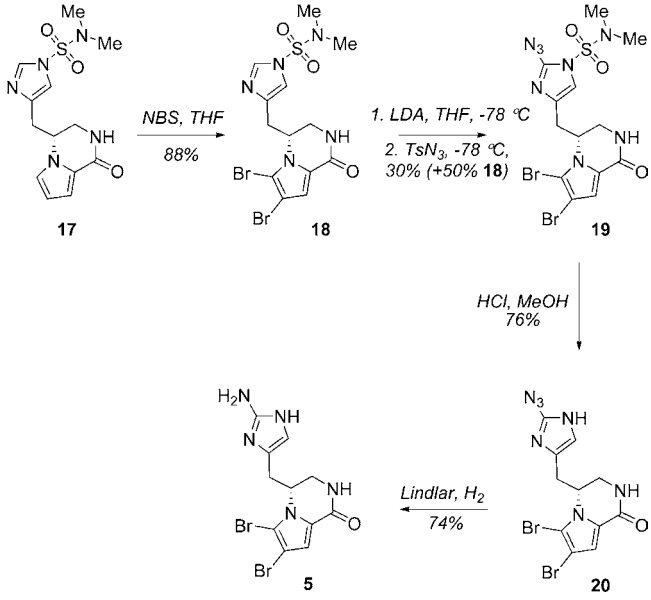
Scheme 1



Scheme 2



could be effected in modest yield with Cs_2CO_3 to provide **14**. We were unable to identify conditions in which there was not at least some competitive dehydrochlorination, which accounts for the modest yield in this reaction. Ring-opening of the lactone **14** was accomplished by *trans* esterification with NaOMe/MeOH leading to the formation of the hydroxy methyl ester **15** in 35% yield, with unreacted lactone **14** (50%) accounting for the material balance, which could be recycled. At this point, the primary hydroxyl group was activated by treatment with MsCl and then the reaction with NaN_3 provided the corresponding azide **16**. Reduction of the azide with Pd/H_2 gave the corresponding amine, which on

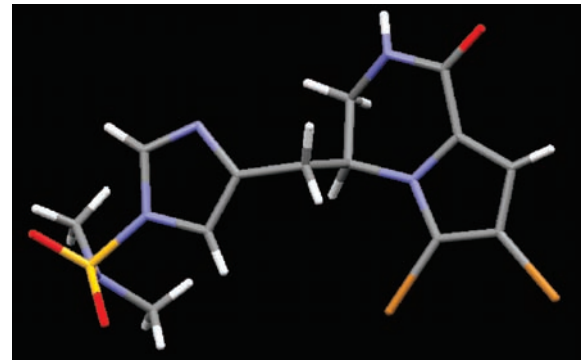


Figure 3. X-ray crystal structure of compound **18**.

deprotonation with NaH cyclized to provide the corresponding amide **17**.

Treatment of amide **17** with NBS at low temperature resulted in the efficient dibromination of the pyrrole moiety at C4 and C5 providing compound **18**. Dibromopyrrole **18** was highly crystalline and an X-ray crystal structure confirmed not only the location of the bromines but also connectivity between N1−C9. We and others have demonstrated that the C2-amine on the imidazole (C13 in cyclooroidin) can be introduced by C2-metalation and trapping with azide, either as TsN_3 or $TrisN_3$, followed by reduction.[21−23] Accordingly, treatment of **18** with LDA and introduction of $TrisN_3$ led to the formation of the corresponding 2-azido derivative and recovered **18**. Unfortunately, the chemical yield was rather low and we were not able to improve this situation through varying base equivalents, concentration, solvent, temperature, or order of addition. An earlier investigation in our lab toward a total synthesis of the reported structure of nagelamide D[24] indicated that deprotection could be achieved at the azide stage under relatively mild conditions with warm methanolic HCl. Thus, exposure of azide **19** to these conditions led to the formation of the free imidazole **20**, which upon hydrogenation in the presence of the Lindlar catalyst provided (+)-cyclooroidin in 56% yield for the two steps. The spectroscopic and other physical properties were in complete accord with those reported for the natural product with the exception of the specific rotation, which was of the opposite sign.

In summary, we have developed an ex-chiral pool asymmetric synthesis of the pyrrole−imidazole alkaloid cyclooroidin, providing the non-natural enantiomer. Key features of the route include an intramolecular nucleophilic substitution reaction to construct the N1−C9 bond. Azidation, bromination, reduction, and deprotection complete the synthesis. Cyclooroidin (and precursors from this synthetic

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approach) contain some of the structural features present in the agelastatin family of natural products and therefore may serve as intermediates en route to this group of alkaloids. Efforts toward this end are under investigation and will be reported in due course.

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Note Added after ASAP Publication. Schemes 1 and 2 contained errors in the version published ASAP October 7, 2010; the correct version reposted October 12, 2010.

Supporting Information Available: Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. and crystallographic data and paramaters (cif) for compound **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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