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Asymmetric total synthesis of *ent*-cyclooroidin

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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 C2-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 monomeric, 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 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 oxocyclostylidol¹¹ and potentially members of the agelastatin family e.g. (**4**)¹² for which the formation of just one additional carbon-carbon bond provides the appropriate framework.¹³ The isolation of cyclooroidin from a Mediterranean sponge *Agelas oroides* was reported in 2000, but only limited biological investigations in screens related to the peripheral nervous system 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

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Supporting Information Available Detailed experimental procedures and copies of ¹H and ¹³C NMR spectra for all new compounds, and crystallographic data and parameters (cif) for compound **18**. These materials are available free of charge via the internet at <http://pubs.acs.org>.

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**) which results in the total synthesis of the enantiopode of the naturally occurring material.

With the notable exception of the Lindel synthesis, all of the reported approaches to cyclooroidin have relied upon the *de novo* assembly of the 2-aminoimidazole core,¹⁴ 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 pyrroloperazinone 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 proceeded uneventfully via a Mitsunobu reaction with **8**, however, attempts to effect formation of the second CN 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 dimers, specifically nagelamide R and T,¹⁹ it proved to be a dead-end as far as cyclooroidin (**3**) 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.

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 could be effected in modest yield with Cs₂CO₃ 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 reaction with the NaN₃ provided the corresponding azide **16**. Reduction of the azide with Pd/H₂ gave the corresponding amine, which on 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 TsN₃ or TrisN₃, followed by reduction.^{21–23} Accordingly, treatment of **18** with LDA and introduction of TrisN₃ 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 towards a total synthesis of the reported structure of nagelamide D24 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Oroidin (1)

Massadine (2)

Styllisidine A (3)

Figure 1.
Several oroidin-derived alkaloids

Figure 2.
Retrosynthetic analysis of cyclooroidin (5)

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

Scheme 1.

Scheme 2.