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Asymmetric Synthesis of Ageliferin

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Supporting Information

ABSTRACT: We describe herein an asymmetric synthesis of ageliferin. A Mn(III)-mediated oxidative radical cyclization reaction was used as the key step to construct the core skeleton of this pyrrole−imidazole dimer. This approach resembles the biogenic [4 + 2] dimerization in an intramolecular fashion.

Pyrrole−imidazole alkaloids are a family of highly nitrogenated and halogenated natural products that possess unique molecular skeletons and significant biological activities.[1] Ageliferin (**1**) is a dimeric member found in many *Agelas* and *Stylissa* sponges.[2] Conceptually, it is a [4 + 2] dimer of two molecules of hymenidin (**2**) (Figure 1). Together with the [2 + 2] and [3 + 2] congeners, these alkaloids provide valuable opportunities for studying chemistry. Over the past decades, chemists have developed various strategies to address the issues associated with their laboratory synthesis.[3] Notably, the synthesis of the [2 + 2] dimer sceptrin has been achieved by Baran[4] and Birman,[5] and the [4 + 2] and [3 + 2] dimers ageliferin (**1**),[6] axinellamine,[7] massadine,[8] and palau′amine[9] by Baran. Ohta has also reported a synthesis of 12,12′-dimethylageliferin.[10] Complementary to these elegant approaches, we seek to examine the potential of radical addition reactions in mimicking the putative [4 + 2] biosynthesis pathway. We further wish to use laboratory synthesis to support the viability of the biosynthetic hypotheses. We report herein the successful implementation of such an approach in the synthesis of **1**.

One prevailing biosynthesis proposal for these alkaloids is that the [2 + 2] and [4 + 2] dimers are generated by direct dimerization[11] while the [3 + 2] dimers are derived from the [4 + 2] dimers through an oxidative ring-contraction reaction.[12] We therefore sought to explore the hypothetical central role of **1** in the biosynthesis of this family of natural products. This direction of research has also been pursued by Romo, Lovely, and Baran.[13] Regarding the [4 + 2] dimerization, a Diels−Alder reaction has been used by Romo, Lovely, and Ohta in their biomimetic synthesis.[14] We envisioned that oxidation of β-ketoester **3** would initiate a radical tandem cyclization reaction affording **4** after removing the tether (Figure 1). We anticipated that mimicking this dimerization in an intramolecular way would allow for better efficiency and stereochemical controls. In addition, an asymmetric synthesis can be achieved with a chiral R* group. This transformation resembles the biogenic formation of the C9−C9′ and C10−C15′ bonds in producing **1**.

We have recently demonstrated that oxidation of an allylic γ-imidazolinoyl-β-ketoester (**3**, X = O) with $Mn(OAc)_3$ readily provides the core skeleton of **1**,[15,16] which can further be transformed to 13,13′-dioxoageliferin. However, all attempts to convert the imidazolinone groups to aminoimidazole groups failed. We therefore redesigned our route and introduced the 13- and 13′-amino groups at an early stage. An allylic γ-imidazolyl-β-ketoester (**3**, X = N) was employed despite the difficulty of radical addition to imidazole.[17]

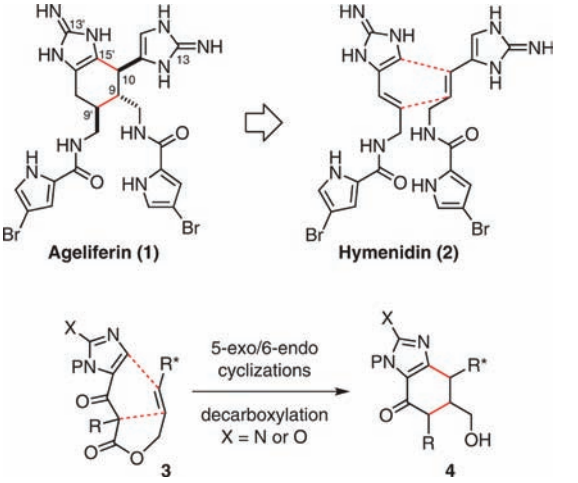
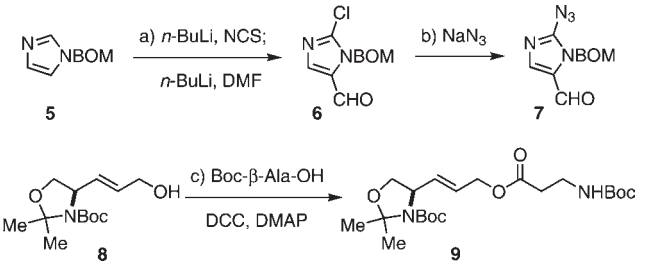


Figure 1. Ageliferin and its hypothetical biosynthetic pathway.

Scheme 1. Preparation of 7 and 9[a]



[a] Conditions: (a) *n*-BuLi, NCS, THF, −78 °C; then *n*-BuLi, DMF, THF, −78 °C, 56% yield after recrystallization. (b) NaN_3, DMF, 50 °C, 92% crude yield. (c) Boc-β-Ala-OH, DCC, DMAP, CH_2Cl_2, 23 °C.

Starting from BOM-protected imidazole **5**,[18] chlorination at the 2-position and formylation at the 4-position can be carried out in one-pot to give **6** (Scheme 1). The BOM group serves as a good directing group for the second lithiation reaction providing good regioselectivity. The azido group can then be introduced easily by aromatic substitution to give **7**. Separately, allylic alcohol **8**,

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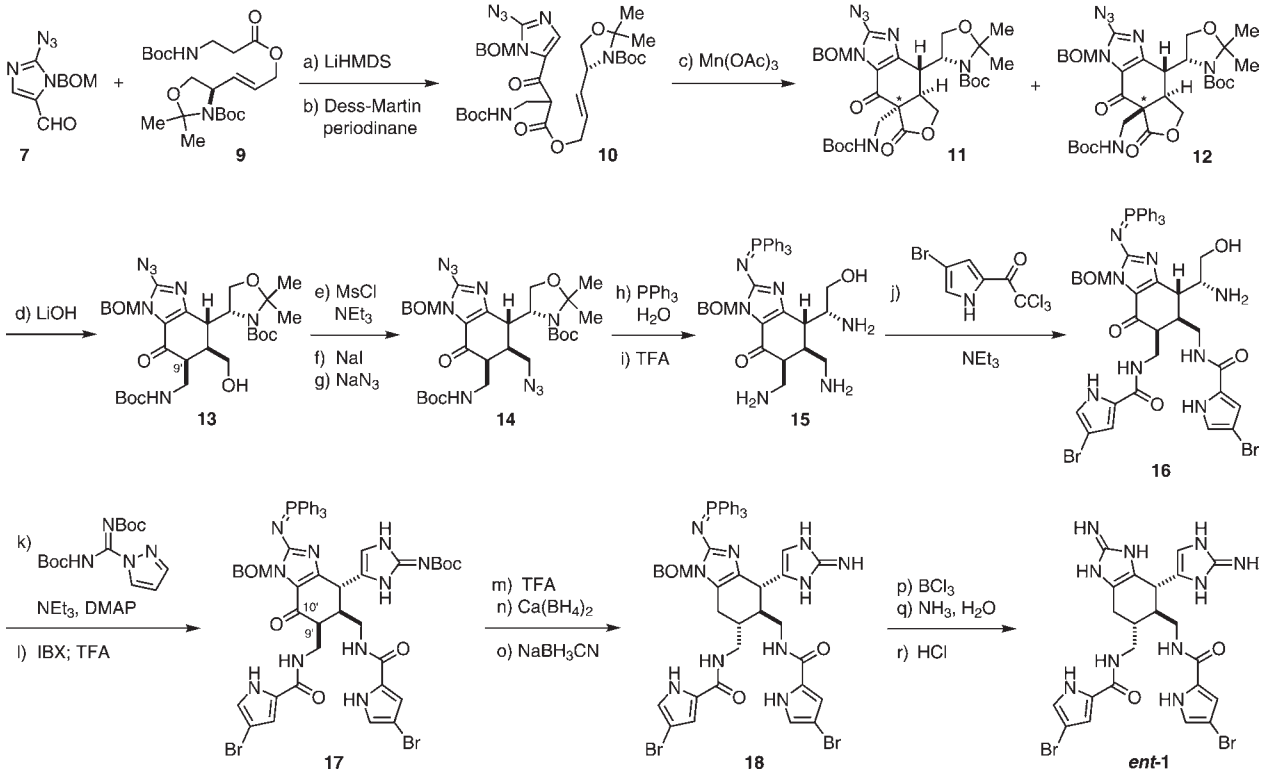
Scheme 2. Completion of the Synthesis of Ageliferin[a]



[a] Conditions: (a) LiHMDS, THF, −78 °C. (b) Dess-Martin periodinane, H_2O, CH_2Cl_2, 23 °C. (c) $Mn(OAc)_3 \cdot 2H_2O$, HOAc, 50−60 °C, **11**: 18−25%, **12**: ca. 9% yield for four steps. (d) LiOH, THF, H_2O, 23 °C. (e) MsCl, NEt_3, CH_2Cl_2, 23 °C. (f) NaI, acetone, 70 °C. (g) NaN_3, DMSO, 60 °C, 36% yield for four steps. (h) PPh_3, H_2O, THF, 70 °C. (i) TFA, CH_2Cl_2, 23 °C. (j) 4-Bromo-2-(trichloroacetyl)pyrrole, NEt_3, DMF, 0 °C, 66% yield for three steps. (k) 1-[*N*,*N*′-(di-Boc)amidino]pyrazole, NEt_3, DMAP, CH_3CN, 40 °C, 60% yield. (l) IBX, DMSO, 40 °C; then TFA 40 °C, 54% yield. (m) TFA, CH_2Cl_2, 23 °C. (n) $Ca(BH_4)_2 \cdot 2THF$, THF, 23 °C. (o) $NaBH_3CN$, HOAc, 50 °C, 38% yield for three steps. (p) BCl_3, CH_2Cl_2, −10 °C. (q) NH_4OH, H_2O, CH_3CN, 23 °C, 77% yield for two steps. (r) HCl, EtOH, H_2O, 60 °C, 88% yield.

obtained from Garner's aldehyde according to known procedures,[19] was coupled to Boc-β-Ala-OH to afford **9**. Both crude **7** and **9** were used directly in the subsequent reaction.

β-Ketoester **10** for the critical Mn-oxidation reaction was synthesized from **7** and **9** through an aldol reaction and Dess-Martin oxidation (Scheme 2). Treating **10** with $Mn(OAc)_3$ in acetic acid at 50−60 °C or $Mn(picolinate)_3$ in methanol at 90 °C gave **11** and **12** in a 2.5−3:1 ratio. The major product **11** was isolated in 18−25% yield and the minor product **12** in ca. 9% yield over four steps based on **8**.[20] Lactones **11** and **12** differ only in their C9′ stereochemistry as the two compounds gave rise to the same product **13** after decarboxylation. These results suggest that only one face of the olefin was accessible for the radical addition. However, the facial selectivity is opposite to that predicted based on the $A^{1,3}$ strain model,[21] giving *ent*-**1** at the end of the synthesis. The stereoselectivity for reactions of homologated Garner's aldehyde derivatives has been shown to be less predictable.[22]

Removal of the tether for the manganese oxidation reaction can be done under mild conditions. As previously described, decarboxylation of both **11** and **12** gave **13**. The initial trans decarboxylation product epimerized rapidly at the C9′ position to give *cis*-**13**. This rather unexpected stereochemical preference presumably helps release the unfavorable steric interactions among the three side chains while maintaining the carbonyl−imidazole conjugation on a flattened half-chair cyclohexenone ring.[23] Considering the propensity of this C9′ epimerization, we decided to correct this stereochemical issue at a late stage and focus on the installation of the remaining functional groups.

Converting the hydroxyl group of **13** to an amino group was surprisingly difficult, due presumably to the congested steric environment. After extensive studies, we found that **13** can first be mesylated and then converted to an iodide. Reaction of this iodide with NaN_3 in warm DMSO gave **14** in moderate yields.

To install the pyrrole side chains, the azido groups were first reduced by a Staudinger reaction. Interestingly, we found the triphenylphosphine imide of aminoimidazole to be quite stable toward hydrolysis, rendering it a good protecting group for our synthesis. The acetonide and Boc groups can be removed selectively to yield triamine **15**, which was crashed out from the ether solution to remove the excess reagents and triphenylphosphine oxide. Installation of the pyrrole groups was done with good regioselectivity, giving a 3:1 ratio of **16** and the monopyrrole product, which can be resubjected to the reaction to improve the overall efficiency.

With the pyrrole side chains in place, our next task was to introduce the second aminoimidazole group. After evaluating several routes, we found the following one most efficient and reliable. A guanidine group was first introduced selectively to **16**. Oxidation of the hydroxyl group then gave an aldehyde that slowly cyclized with the guanidine to give aminoimidazole **17**. Addition of 0.5 equiv of TFA after oxidation facilitated this cyclization.

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At this stage, we found that the C9′ epimerization can be easily done to provide the correct C9′ configuration under acidic conditions. The C10′ carbonyl group was then removed with sequential reductions to afford **18**. The BOM protecting group was subsequently removed by a two-step process. The benzyl group was first cleaved by BCl_3. The resulting hydroxymethyl group was then removed by basic hydrolysis. Finally, the triphenylphosphine imide group was hydrolyzed by HCl at 60 °C to afford ageliferin, whose CD spectrum indicated that *ent*-**1** was obtained. The absolute configuration of **1** has been assigned by Baran.[6b]

In summary, utilizing an oxidative radical tandem cyclization reaction as the key step, we successfully synthesized *ent*-ageliferin (*ent*-**1**) in a biomimetic fashion. Our synthesis supports the possibility that a single-electron transfer (SET) reaction is used in nature to dimerize **2** to form **1**.[24] We are currently applying this strategy to the biomimetic synthesis of the [3 + 2] pyrrole–imidazole dimers.

■ ASSOCIATED CONTENT

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

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(12) (a) Ref 11d. (b) Ref 11e. (c) Ref 6d. (d) Ref 11i. (e) Ref 11j.

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(20) All the reaction products beyond this point in the synthesis were purified by reverse-phase column chromatography or HPLC to minimize material loss. Most HPLC purification was performed in the presence of TFA and all the basic products, including ageliferin (**1**), were

therefore isolated as TFA salts. The byproduct produced from IBX oxidation decomposed **17** upon concentration. While ageliferin (**1**) is generally stable toward acids, neutralization or direct concentration of the reaction mixture of the final step led to considerable decomposition. Therefore, **17** and **1** were purified directly by HPLC without workup.

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(23) Conformational analysis of an analogue of **13** having simplified substituent groups indicates that the *cis*- and *trans*-isomers are close in energy. Increasing the size of the side-chains led to the equatorial-axial-axial conformer of the *cis*-isomer being more stable than the all equatorial conformer of the *trans*-isomer. For an example of related conformational analysis, see:Todoroki, Y.; Hirai, N. *Tetrahedron* **2000**, *56*, 8095–8100.

(24) We thank a reviewer for suggesting this biosynthetic hypothesis. It should also be noted that failed attempts to directly dimerize oroidin (bromo-**2**) to form dibromo-**1** under thermal conditions have been reported: ref 11h.