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Biomimetic synthesis of (−)-chaetominine epimers via copper-catalyzed radical cyclization

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ABSTRACT

Synthetic endeavors toward (−)-chaetominine via copper-catalyzed radical cyclization are reported. Both of the pyrido[2,3,*b*]-indole ring (C ring) and imidazolidinone (D ring) are efficiently constructed in one-pot manner. It's unveiled that the newly formed stereo center is controlled by the chiral of alanine, not by tryptophan. With these synthetic discoveries, highly efficient and diastereoselective synthesis of (+)-2,3,14-*epi*-chaetominine **5** and (−)-11-*epi*-chaetominine **11** is achieved.

1. Introduction

Endophytic fungi represent one of the most productive sources of secondary metabolites with novel architectures and/or broad biological profiles.[1] (−)-Chaetominine (**1**) (Fig. 1) was isolated from the solid culture of an endophytic fungus, *Chaetomium* sp. IFB-E015, and found on apparently healthy *Adenophora axilliflora* leaves.[2] Its structure was fully characterized by spectroscopic analysis and single crystal X-ray diffraction analysis. The absolute stereochemistry was assigned by Marfey's analysis. The intriguing structural features of (−)-chaetominine (**1**) include the strained tetracyclic core along with four stereogenic centers, and the unique quinazolinone moiety. (−)-Chaetominine (**1**) has been shown potent cytotoxicity against human leukemia K562 (21 nM) and colon cancer SW1116 (28 nM) cell lines.[2] However, Papeo's assays revealed that their synthetic (−)-chaetominine exhibited negligible inhibitory activities on several cancer cell lines.[3]

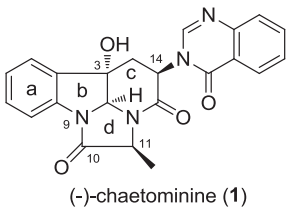

Fig. 1. Structure of (−)-chaetominine (**1**).

Given the unprecedented architecture and potential biological profiles, numerous synthetic efforts have been directed to the total synthesis of (−)-chaetominine (**1**).[3–9,11] Soon after its isolation, Snider and co-workers reported the first synthesis of (−)-chaetominine (**1**) with the Buchwald palladium-catalyzed cyclization as the key step.[4] Later, Evano described the first generation synthesis of (−)-chaetominine (**1**) through copper-mediated cyclization to install the ABC tricyclic core,[5,6] and the second-generation synthesis via an oxidative NCS-mediated cyclization.[7] Meanwhile, Papeo also reported a unique NCS-mediated *N*-acyl cyclization to construct ABC ring system.[3] Recently, Huang and co-workers disclosed the most efficient route with DMDO-mediated cyclization as the key transformation.[8–10] Moreover, Roche reported a fluorine-mediated cascade annulation of preactivated tryptophan dipeptide to construct tetracyclic α-carboline architectures.[11] As part of our ongoing efforts toward the rapid synthesis of pyrroloindoline alkaloids, we recently reported a method involving copper-catalyzed radical cyclization to access 3-hydroxypyrroloindoline skeleton.[12] This report details the synthetic endeavors toward (−)-chaetominine via

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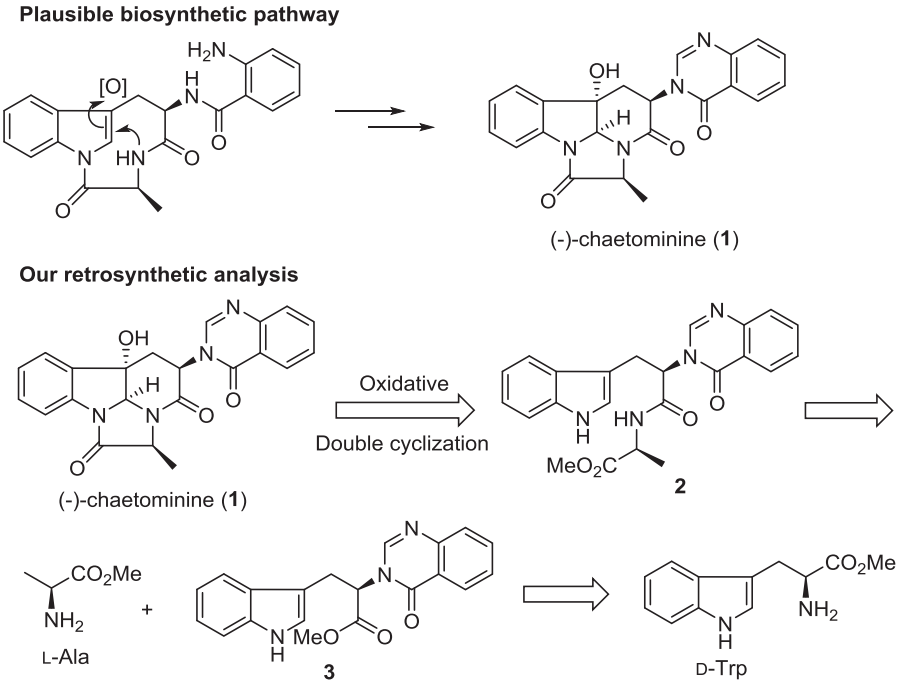
copper-catalyzed radical cyclization and the rapid access to (+)-2,3,14-*epi*-chaetominine **5** and (−)-11-*epi*-chaetominine **11**.

2. Results and discussion

2.1. Retrosynthetic analysis

Biosynthetically, (−)-chaetominine (**1**) is speculated to originate from D-tryptophan, L-alanine, and anthranilic acid via oxidative cyclization of the tripeptide precursor (Scheme 1).[2,13–15] Inspired by the biosynthetic pathway and in combination with our well-developed copper-catalyzed radical cyclization,[12] we envisaged a biomimetic strategy of (−)-chaetominine (**1**) as illustrated in Scheme 1. The key feature involves the expeditious copper-catalyzed radical cyclization to form tetrahydro-1*H*-pyrido[2,3,*b*]-indole moiety. The tripeptide **2** would be prepared by the coupling of L-alanine with the intermediate **3**, which could be obtained by acylation of D-tryptophan with isatoic anhydride and incorporation of a C-1 unit.[4]



Scheme 1. Key step of plausible biosynthetic pathways and our retrosynthetic analysis of (−)-chaetominine **1**.

As the abundant occurrence of C3-hydroxylpyrroloindoline alkaloids in nature,[16] plenty of efficient methods are available in our toolbox, including iodine(III)-mediated intramolecular annulation,[17,18] selenocyclization/oxidative deselenation sequence,[19,20] Danishefsky's DMDO oxidation,[21] and photosensitized oxygenation.[22–24] Whereas, the direct method leading to the fused tetrahydro-1*H*-pyrido[2,3,*b*]-indole ring system remains scarce.[8,9] We presumed that there are two main challenges during the total synthesis of (−)chaetominine (**1**): (1) whether the copper-catalyzed radical cyclization could access tetrahydro-1*H*-pyrido [2,3,*b*]-indole core, which has not been testified previously; (2) whether the diastereoselectivity would be correct and sufficiently high as expected. Thus it is worthwhile to engage in this adventure.

2.2. Synthesis of (+)-2,3,14-*epi*-chaetominine

Our first synthetic route to (−)-chaetominine (**1**) commenced with the installation of the exocyclic quinazolinone moiety (Scheme 2).[3,8,25] In this event, D-tryptophan methyl ester was heated with isatoic anhydride in the presence of Et_3N, followed by treatment with triethyl orthoformate in the presence of the catalytic TsOH to furnish the desired tryptophan-quinazolinone **3** in good overall yield.[3,5,26] Subsequently, hydrolysis of compound **3** followed by the coupling with L-alanine methyl ester using EDCI as the activation agent produced the tripeptide **2** in excellent yield. However, partial racemization of the quinazolinone-bearing stereo center was detected by ^1H NMR analysis (14%), possibly due to the LiOH-mediated hydrolysis of the methyl ester **3**, giving an inseparable mixture, which was used without further purifications. This was also observed by Papeo during the hydrolysis.[3]

With the tripeptide **2** in hand, we then turned to investigate the key copper-catalyzed radical cyclization. A base screen revealed that Et_3N was not competent, and NaH was capable to access the C ring but with only partial conversion. Upon considerable experiments, we were pleased to find that DBU was the optimal choice (Scheme 2). The double cyclization occurred smoothly and afforded product **4** in excellent diastereoselectivity.[12] At this stage, it's difficult to establish the configuration of the newly formed stereocenters. Further reductive removal of the 2,2,6,6-tetramethylpiperidinyl (TMP) moiety gave the product **5** in excellent yield, which was assigned to be (+)-2,3,14-*epi*-chaetominine by full matching the data with the reported.[8,9] This indicated that the quinazolinone-bearing stereocenter epimerized during the oxidative cyclization reaction, which has also been observed by Huang.[8,9] It was also observed that the C2−H and C3−OH were in the cis-position with the C11 methyl group of alanine.

There are two possible pathways for the diastereo outcome during the double cyclization (Scheme 3). In pathway A, the tripeptide **2** partially epimerizes at C14 in the presence of base to provide its epimer **6**. Subsequently, compound **6** undergoes thermodynamically favored *endo* cyclization to form (+)-2,3,14-*epi*-chaetominine **5**, which drives equilibrium from **2** to **6**. Alternatively, in pathway B, the tripeptide **2** proceeds kinetically *exo* cyclization first, giving 2,3-*epi*-chaetominine **7**. Then compound **7** was deprotonated followed by thermodynamically favored *endo* protonation to afford (+)-2,3,14-*epi*-chaetominine **5**.