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The four-step total synthesis of (−)-chaetominine†

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The total synthesis of the alkaloid (−)-chaetominine (1) has been achieved in four steps with an overall yield of 33.4%. Key features of our strategy include a one-pot cascade indole epoxidation – epoxide ring-opening cyclization – lactamization reaction sequence, and the use of a nitro group as a latent amino group for the one-pot construction of the quinazolinone ring. This constitutes a step economical, redox economical and protecting group-free total synthesis.

Efficiency is a major pursuit in organic synthesis, which is of particular importance in the field of the total synthesis of complex natural products.[1] With this end in view, the concepts of step economy,[2] pot economy,[3] redox economy,[4] and protecting group-free synthesis[5] have been introduced. Recently, a number of quite concise total syntheses have been achieved.[6]

In 2006, Tan and co-workers reported the isolation of a new alkaloid (−)-chaetominine (**1** in Fig. 1) from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.[7] The intriguing structural feature in combination with the reported potent activity against human leukemia K562 (21 nM) and colon cancer SW1116 (28 nM) cell lines[7] made (−)-chaetominine an attractive synthetic target.[8] Snider and co-workers reported the first total synthesis of (−)-chaetominine soon after its isolation.[8a] Later on, Evano and Papeo reported the second[8b] and the third approaches.[8c] Papeo's work also clarified that (−)-chaetominine (**1**) showed a negligible inhibitory activity on several cancer cell lines.[8c] The fourth one disclosed by Evano *et al.* has so far been the most efficient with nine steps and 14% overall yield from D-tryptophan.[8d]

With our interest in the asymmetric synthesis of bioactive natural products[9] and the development of step economical synthetic methodologies,[10] we envisaged that (−)-chaetominine (**1**) is an ideal molecule for demonstrating the concepts of step economy, pot economy, redox economy, and protecting group-free synthesis. We report herein a four-step total synthesis of (−)-chaetominine (**1**) starting from D-tryptophan.[11]

Our retrosynthetic analysis of (−)-chaetominine (**1**) is depicted in Scheme 1. The key feature of our approach resides in the ambitious one-pot formation of (−)-chaetominine (**1**) from

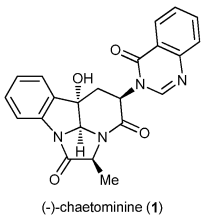

Fig. 1 Structure of (−)-chaetominine (**1**).

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† Electronic supplementary information (ESI) available: X-ray structures, experimental procedures and compound characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds. CCDC 791762–791764 and 884128. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc48833k

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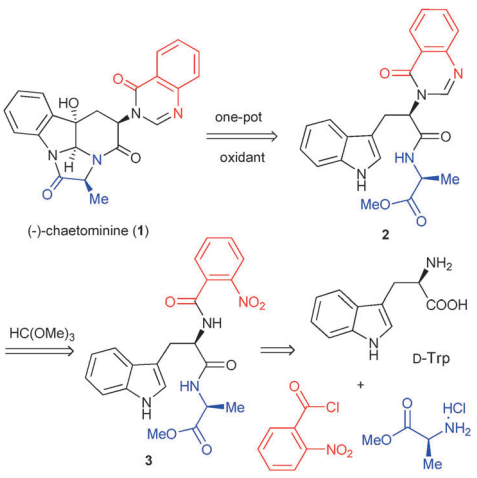


Scheme 1 Retrosynthetic analysis of (−)-chaetominine (**1**).

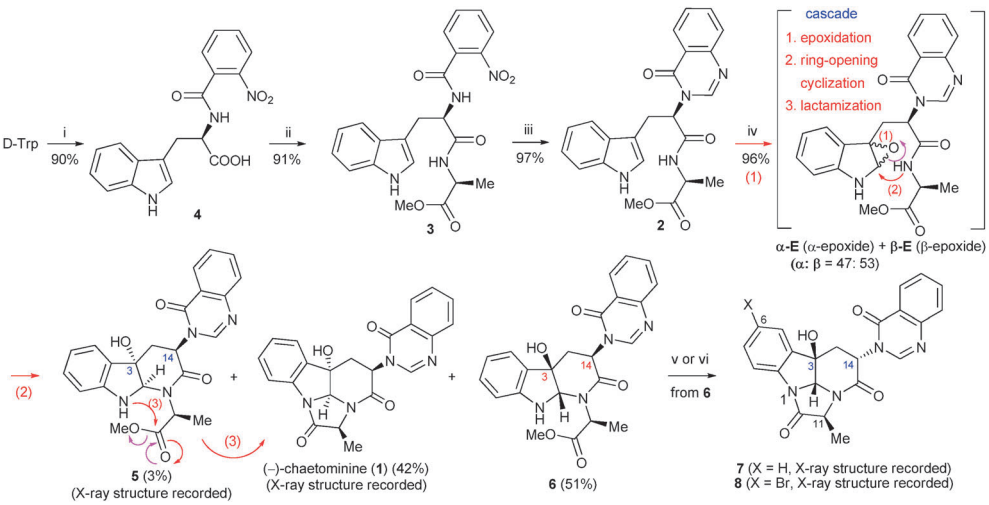
quinazolinonetripeptide **2** *via* a one-pot cascade indole epoxidation – epoxide ring-opening cyclization – lactamization reaction sequence. The formation of the pyrrolo[2,3-*b*]indole ring system through β-oxygenation of tryptophan derivatives followed by nucleophilic addition at the α-position has been known for a long time, which includes the photosensitized oxygenation,[12] and Witkop's stepwise oxidative transposition.[13] Recently, much attention has been paid to the oxidative cyclization of tryptophan derivatives,[14–16] due to the presence of the pyrrolo-[2,3-*b*]indole ring system in many bioactive alkaloids.[17] Nevertheless, to the best of our knowledge, no redox and protecting group-free oxidative cyclization leading to the fused six-membered ring system (piperidino[2,3-*b*]indole) has ever been reported.[12–17] Even in the cases where formation of both five or six-membered rings was possible, the five-membered ring product (pyrrolo[2,3-*b*]indole) always dominated over the six-membered ring.[14b,d] In the first total synthesis of kapakahines B and F,[14b,c] Baran and co-workers have developed an elegant method for the access to the tetrahydro-1*H*-pyrido[2,3-*b*]indole ring system of kapakahines by *in situ* kinetic trapping of a dynamic mixture.

Thus construction of the tricyclic core of (−)-chaetominine (**1**) from the tryptophan derived dipeptide **2** *via* epoxidative cyclization appeared to be quite challenging. Nevertheless, considering the high efficiency of this approach, it was worthwhile to be engaged in this adventure.

As regards the quinazolinone ring system, a number of methods have been reported.[18] In view of developing a protecting group-free total synthesis of (−)-chaetominine (**1**), the nitro group was envisioned as a latent amino group for the construction of the quinazolinone ring. Thus *o*-nitrobenzoyl dipeptide derivative **3** was envisaged as the intermediate of our synthesis, which is readily accessible from commercially available D-tryptophan, *o*-nitrobenzoyl chloride, and L-alanine methyl ester hydrochloride salt.

Our synthesis started with the aroylation of D-tryptophan with *o*-nitrobenzoyl chloride (THF, 1 M NaOH, 0 °C, 2 h), which gave the aroylated product **4** in 90% yield (Scheme 2). Successive treatment of compound **4** with i-BuOCOCl/*N*-methylmorpholine (NMM, THF, −20 °C, 15 min) and the L-alanine methyl ester hydrochloride salt (THF, NMM, −20 °C, 8 h) produced the desired dipeptide derivative **3** in 91% yield. The quinazolinone ring system[18] was constructed by a modification of Shi's method.[19] In the event, **3** was treated with $HC(OMe)_3$ and low valent titanium generated *in situ* from $TiCl_4$ and Zn powders in THF at 0–5 °C, which gave the desired quinazolinone **2** in 97% yield without observable epimerization. Higher temperature reported by Shi and co-workers[19] led to substantial epimerization.

With compound **2** in hand, we then focused on the key epoxidation-initiated cascade reaction to construct the tricyclic core of (−)-chaetominine (**1**). Although treatment of dipeptide **2** with a solution of DMDO in acetone at −78 °C for up to 1 h led to complex products, the results implied that the epoxidation might have occurred, but the unstable epoxide intermediate failed to cyclize to give the desired product **1**. So, basic conditions were envisaged to be necessary to realize the cascade epoxidation-bis-cyclization reactions (Scheme 2). In view of the easy epimerization of our substrate (*vide supra*), weak basic conditions are preferred to avoid any epimerization during the cyclization. After considerable experimentation, it was found that a combination of DMDO with DMSO gave optimal results. In the event, dipeptide **2** was first treated with DMDO in acetone at −78 °C for 1 h, and then DMSO (CaH_2 dried) was added, and the mixture was stirred at rt for 2 days to give the desired chaetominine (**1**) in 42% yield, along with a small portion of its lactamization precursor **5** (3% yield) and an epimer of the latter (**6**) in 51% yield. The structure of (−)-chaetominine (**1**) was confirmed by single crystal X-ray analysis.[20] The physical {$[\alpha]_D^{20}$ −49.7 (*c* 0.48, MeOH) lit. −48 (*c* 0.45, MeOH);[8a] −49.4 (*c* 0.26, MeOH);[8b,c] −47.9 (*c* 0.25, MeOH);[8d] −70 (*c* 0.48, MeOH)[7]} and spectral data of our synthetic (−)-chaetominine (**1**) are identical to those reported. The structure of compound **6** was tentatively deduced from its cyclized product **7** and the bromo derivative **8**, both determined



Scheme 2 *Reagents and conditions*: (i) *o*-nitrobenzoyl chloride, 1 M NaOH, THF, 0 °C, 2 h; (ii) H-L-Ala-OMe·HCl, $ClCO_2{}^iBu$, NMM, THF, −20 °C, 8 h; (iii) $HC(OMe)_3$, Zn/$TiCl_4$, THF, 0 °C, 1 day; (iv) DMDO, acetone, −78 °C, 1 h; then, DMSO (CaH_2 dried), rt, 48 h. Syntheses of compounds **7** and **8** for single crystal X-ray diffraction analysis: (v) NaOMe, MeOH, −10 °C, 90%; (vi) NBS, rt; NaOMe, MeOH, −10 °C, 40% (unoptimized).

by single crystal X-ray analysis.[20] The direct formation of chaetominine (**1**) from **2** implied that an *anti–cis* disposition between the hydroxyl group at C3 and the quinazolinonyl group favors the lactamization. For diastereomer **6**, the fact that only in the presence of a base can the lactamization occur implied a *syn*-disposition between the substituents at C3 and C14.

It is worth mentioning that although the yield of chaetominine (**1**) from **2** *via* the epoxidation-trigged cascade reaction was modest, the strategy is highly efficient. In this cascade reaction sequence, three reactions have been accomplished in one-pot, which also avoided the use of any protecting group. In the previous syntheses,[8a–d] the highest diastereoselectivity (95% de) has been achieved with DMDO in Evano's first generation total synthesis of (−)-chaetominine (**1**).[8b] However, five steps were required to build the tricyclic ring system, which let them to abandon that route and develop a more efficient one.[8d]

In summary, we have disclosed a very concise and efficient strategy for the total synthesis of (−)-chaetominine (**1**) starting from D-Trp. This four-step total synthesis of (−)-chaetominine (**1**) has so far been the shortest one, with the highest overall yield of 33.4%.

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