Tetrahedron xxx (2014) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

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ARTICLE INFO

Article history:
Received 30 July 2014
Received in revised form 4 September 2014
Accepted 9 September 2014
Available online xxx

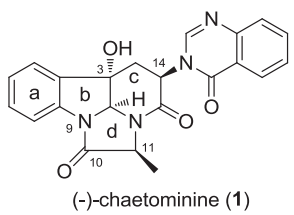
Keywords:
Indole alkaloids
(−)-Chaetominine
Total synthesis
Copper-catalyzed
Cyclization

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]



(-)-chaetominine (**1**)

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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http://dx.doi.org/10.1016/j.tet.2014.09.029
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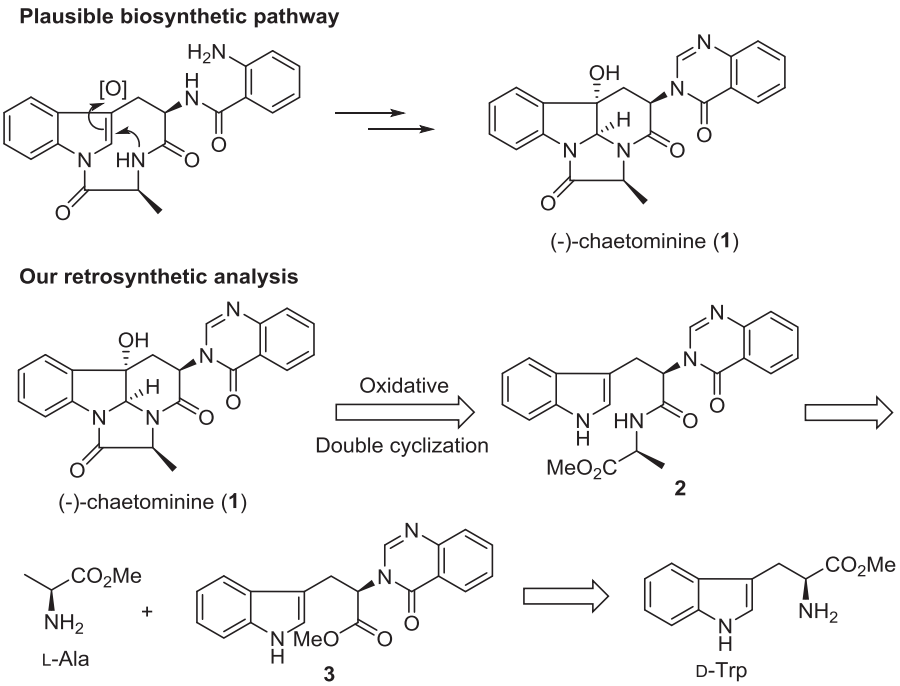
copper-catalyzed radical cyclization and the rapid access to (+)-2,3,14-*epi*-chaetominine **5** and (−)-11-*epi*-chaetominine **11**.

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] 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 dif-



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 ficult 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**.

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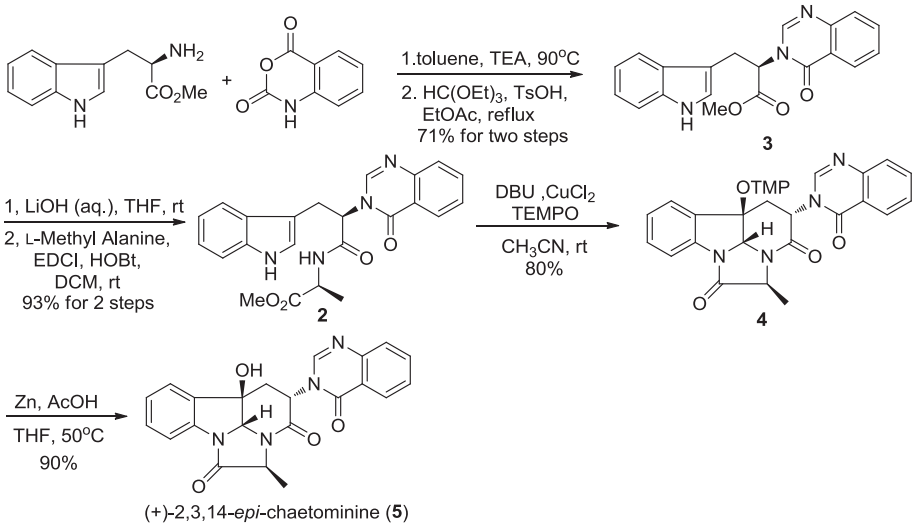
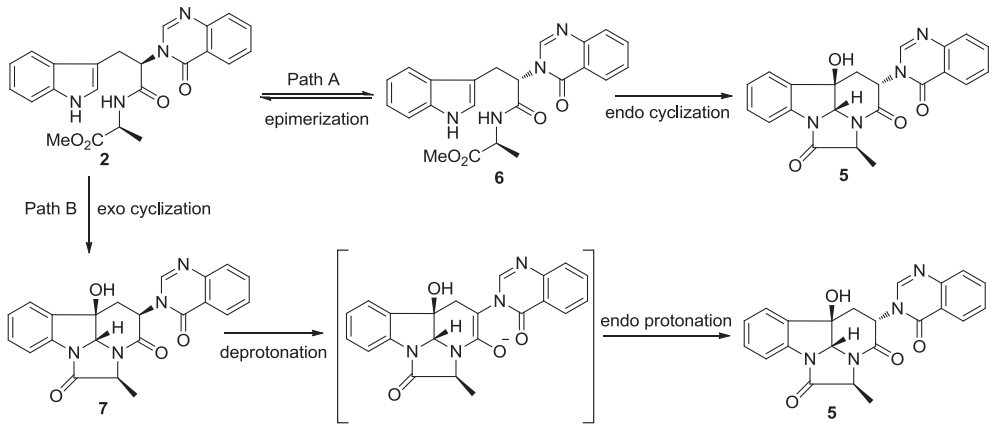


Scheme 2. TEMPO-mediated double cyclization to access (+)-2,3,14-*epi*-chaetominine.

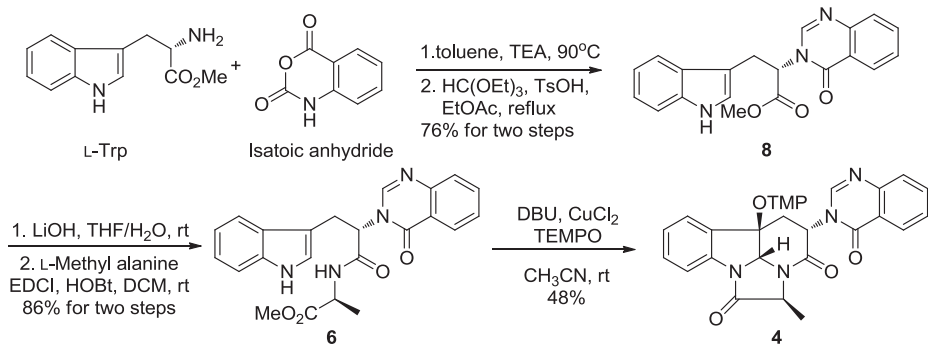


Scheme 3. Possible mechanism for the diastereo outcome of the double cyclization.

To investigate whether the substrate epimerized completely before the cyclization, we performed a control experiment. The tripeptide **2** was stirred with DBU under argon at room temperature, followed by analysis of the isolated tripeptide with ^{1}H NMR. It was revealed that tripeptide **2** epimerized in a time dependent manner (the epimerization ratio was 20% after 1.0 h and 32% after 12 h, respectively). It is likely that there is equilibration between two diastereoisomers (Scheme 3).

To determine the cyclization favors the *anti*–*cis* product or the *syn*–*cis* product, we prepared the 14-*epi*-tripeptide **6** starting from L-tryptophan methyl ester according to the above-mentioned route. Interestingly, compound **6** was not epimerized even by treating with DBU for several days.

When the tripeptide **6** was subjected to the cyclization condition, the same product **4** was obtained (Scheme 4), which indicated that the cyclization favors *anti*–*cis* product. No epimerization was detected during this process. We reasoned that the C11 methyl group plays a critical role in the epimerization of C14 stereocenter, whereas the C14 quinazolinone moiety is not the dominant controlling factor in cyclization.



Scheme 4. TEMPO-mediated double cyclization to access compound **4**.

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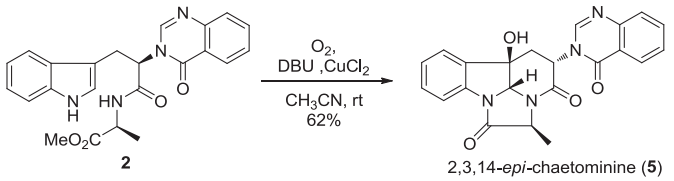
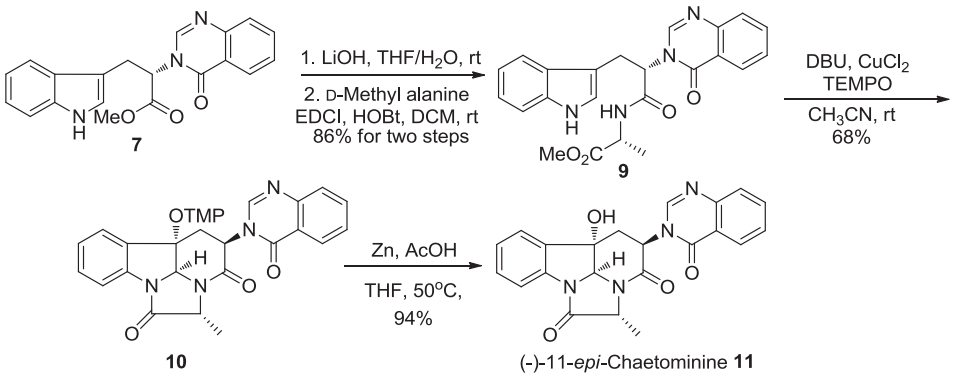
The isomerization of C14 might be due to the existence of bulky TMP group. In our previous report, we also noticed that different radical trapping reagents gave different stereoselectivities.[12] We proposed that switch the trapping reagent from TEMPO to dioxygen might enable the desired configuration. To test this hypothesis, a dioxygen-mediated oxidative cyclization reaction was conducted using dipeptide **2** as the substrate. However, only the same (+)-2,3,14-epimer **5** was isolated (Scheme 5). The high diastereoselectivity control of the cyclization is probably due to the chiral center forming event takes places during the amide addition and is nearby the chiral quinazolinone moiety. This is different from the previous reports that the chiral center forming at the dearomative step is far from the chiral quinazolinone moiety.[8,9,11]



Scheme 5. O_2-Mediated double cyclization to access (+)-2,3,14-*epi*-chaetominine.

2.3. Synthesis of (−)-11-*epi*-chaetominine

On basis of the above experimental results, we noticed that the C2–H and C3–OH were in the cis-position with the C11 methyl group, while the C14 quinazolinone in the *anti*-position of C11. We postulated that if a D-alanine instead of L-alanine was incorporated into the tripeptide, all of the C2, C3, C14 chiral configurations would be same as (−)-chaetominine (**1**) after copper-catalyzed cyclization. Then isomerization of the C11 methyl group with base would afford (−)-chaetominine (**1**). Thus we prepared the C11(*R*),C14(*S*) substrate **9** using L-tryptophan methyl ester and D-alanine methyl ester as the starting material. Subsequently, applying the substrate **9** to the standard cyclization reaction condition produced product **10** with the requisite stereochemistry at C2,C3,C14 as expected. Reductive removal of TMP moiety delivered (−)-11-*epi*-chaetominine **11** in good yield, which is characterized as an enantiomer of (+)-2,3,14-*epi*-chaetominine **5** by full match of spectra data to that of the previous report.[9] Subsequently, extensive efforts have been directed to epimerize the C11 stereocenter, such as deprotonation of H11 by LHMDS followed by trapping with *t*-BuOH, whereas no desired isomerization occurred (Scheme 6).



Scheme 6. TEMPO-mediated double cyclization to access (−)-11-*epi*-chaetominine **11**.

3. Conclusion

In summary, copper-catalyzed cyclization was utilized for the biomimetic synthesis of (−)-chaetominine epimers. It is discovered that the newly formed stereo center is controlled by the chiral of alanine. Both of the C ring and D ring were formed in one-pot procedures. With this method, two of the (−)-chaetominine epimers **5** and **11** were efficiently generated. This is the first example of copper-catalyzed radical cyclization to rapid access tetrahydro-1*H*-pyrido[2,3,*b*]-indole skeleton.

4. Experimental section

4.1. General information

All reactions were performed under argon atmosphere using oven-dried glassware unless otherwise stated. Acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and *N*,*N*-dimethylformamide (DMF) were distilled over CaH_2 under N_2. Toluene and tetrahydrofuran were distilled over sodium benzophenone under N_2. All reagents were commercially available and used without further purification unless otherwise indicated. Thin layer chromatographies were carried out on GF_{254} plates (0.25 mm layer thickness). Flash chromatography was performed with 300–400 mesh silica gels. Visualization of the developed chromatogram was performed by fluorescence quenching or by ceric ammonium molybdate, or $KMnO_4$ stain. Yields reported were for isolated, spectroscopically pure compounds. Zinc powder was activated by washing sequentially with 3 M HCl, water, acetone, and ether and dried under reduced pressure.

^1H and ^{13}C NMR experiments were performed on a Bruker AM-400 and DRX-600 NMR spectrometers at ambient temperature. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in parts per million (ppm) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. Mass spectra (MS) and high-resolution mass spectra (HRMS) were taken on API STAR Pulsar.

4.2. *R*-3-(1*H*-Indol-3-yl)-2-(4-oxo-4*H*-quinazolin-3-yl)-propionic acid methyl ester (3)

To a solution of D-tryptophan methyl ester hydrochloride (1020 mg, 5.0 mmol) in dry toluene (100 mL) were added isatoic anhydride (1222 mg, 7.5 mmol) and Et_3N (5050 mg, 50 mmol) successively. The resulting suspension was heated to 90 °C for 24 h. Then the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography over silica gel (dichloromethane/methanol=30:1) to give the product as a yellow solid (1240 mg, 79%).

The crude product (674 mg, 2.0 mmol) was dissolved in AcOEt (20 mL) under argon. Then *p*-TsOH (69 mg, 0.4 mmol) and triethyl

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orthoformate (1480 mg, 10.0 mmol) were added to the mixture successively. The resulting mixture was heated to 50 °C overnight. The mixture was quenched with triethyl amine and then washed with water (50 mL×2), dried over Na_2SO_4, filtered and then concentrated in vacuo. The resulting crude product was purified by flash chromatography (petrol ether/ethyl acetate=3:1) to give compound **3** (617 mg, 89%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.58 (d, J=8.3 Hz, 1H), 8.38 (d, J=1.6 Hz, 1H), 8.32 (s, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.42 (dd, J=11.5, 4.1 Hz, 1H), 7.35 (d, J=8.1 Hz, 1H), 7.29 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.4 Hz, 1H), 7.09 (t, J=7.3 Hz, 1H), 7.02–6.97 (m, 2H), 6.81 (d, J=7.3 Hz, 1H), 5.06 (dd, J=12.9, 5.5 Hz, 1H), 3.76 (s, 3H), 3.44 (qd, J=14.8, 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 168.3, 159.6, 138.4, 136.2, 132.8, 127.4, 126.9, 123.4, 123.0, 122.4, 122.0, 119.9, 119.8, 118.4, 111.5, 109.5, 53.5, 52.6, 27.5; ESIMS (m/z): 370 $[M+Na]^+$.

4.3. *S*-3-(1*H*-Indol-3-yl)-2-(4-oxo-4*H*-quinazolin-3-yl)-propionic acid methyl ester (8)

The protocol for preparation of compound **8** follows that of compound **3** by using L-tryptophan methyl ester hydrochloride as the substrate instead. The optimized yield for compound **8** is 76%. The spectral data for compound **8** are the same to that of compound **3**.

4.4. (*S*)-2-[(*R*)-3-(1*H*-Indol-3-yl)-2-(4-oxo-4*H*-quinazolin-3-yl)-propriony lamino]propionic acid methyl ester (2)

To a solution of compound **3** (155 mg, 0.447 mmol) dissolved in THF (4 mL) was added an aqueous solution of LiOH (2 N, 0.224 mL) dropwise. The mixture was stirred at room temperature for 2 h until the reaction was deemed complete by TLC. The mixture was neutralized by 1 N HCl aqueous solution and was extracted with EtOAc (20 mL×3). The combined the organic layers were washed with saturated $NaHCO_3$, and brine, followed by drying over Na_2SO_4. Filtration and concentration in vacuo yielded the crude product, which was used for the next step without further purifications.

The crude product (149 mg, 0.447 mmol) was dissolved in dry DMF (4 mL) at 0 °C. HOBT (102 mg, 0.67 mmol), DIPEA (213 mg, 1.34 mmol), and L-alanine (74 mg, 0.53 mmol) were subsequently added under argon atmosphere. EDC-HCl (128 mg, 0.67 mmol) was then added. After 24 h until no starting material was detected by TLC, the reaction mixture was poured into water and extracted with DCM (15 mL×3). The combined the organic layers were washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4, followed by filtration and concentration in vacuo to give the crude material, which was subjected to chromatography to afford compound **2** as white solid (petrol ether/acetone=3:1, 173 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.30 (s, 1H), 8.16 (dd, J=8.0, 1.0 Hz, 1H), 7.70–7.60 (m, 3H), 7.43–7.37 (m, 1H), 7.29 (d, J=8.1 Hz, 1H), 7.18–7.11 (m, 1H), 7.06 (dd, J=10.9, 3.9 Hz, 2H), 7.00 (d, J=2.3 Hz, 1H), 5.87 (dd, J=8.4, 7.2 Hz, 1H), 4.47 (t, J=7.2 Hz, 1H), 3.72 (dd, J=14.5, 8.7 Hz, 1H), 3.58 (s, 3H), 3.40 (dd, J=14.6, 6.9 Hz, 1H), 1.20 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.4, 161.1, 147.4, 144.3, 136.1, 134.5, 127.4, 127.2, 126.9, 126.8, 123.3, 122.3, 121.3, 119.8, 118.4, 111.3, 109.6, 56.3, 52.4, 48.4, 27.2, 17.5; ESIMS (m/z): 419 $[M+H]^+$.

4.5. (*S*)-2-[(*S*)-3-(1*H*-Indol-3-yl)-2-(4-oxo-4*H*-quinazolin-3-yl)-propriony lamino]propionic acid methyl ester (6)

The protocol for preparation of compound **6** follows that of compound **2** by using compound **8** as the substrate instead. The optimized yield for compound **6** is 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.44 (s, 1H), 8.20 (d, J=7.9 Hz, 1H), 7.84 (d, J=6.9 Hz, 1H), 7.74 (t, J=7.6 Hz, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.61 (d, J=7.9 Hz, 1H), 7.47 (t, J=7.5 Hz, 1H), 7.32 (d, J=12.8 Hz, 1H), 7.12 (t, J=7.5 Hz, 1H), 7.03 (d, J=8.8 Hz, 2H), 5.89 (t, J=7.8 Hz, 1H), 4.47 (p, J=7.0 Hz, 1H), 3.73 (d, J=7.5 Hz, 1H), 3.69 (s, 3H), 3.49–3.41 (m, 1H), 1.33 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 169.0, 161.1, 146.9, 144.9, 136.3, 134.6, 127.2, 126.8, 126.6, 123.5, 121.8, 121.1, 119.2, 117.9, 111.3, 108.4, 56.0, 52.2, 48.9, 27.4, 17.1; ESIMS (m/z): 419 $[M+H]^+$.

4.6. (2*S*,4*S*,5a*R*,9c*R*)-4,5,5a,9c-Tetrahydro-2-methyl-4-(4-oxo-3(4*H*)-quinazolinyl)-5a-[(2,2,6,6-tetramethyl-1-piperidinyl) oxy]-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (4)

To a solution of compound **2** (104 mg, 0.25 mmol) in CH_3CN (2.5 mL) under argon was added DBU (114 mg 0.75 mmol). The mixture was stirred at room temperature for 0.5 h. Then TEMPO (117 mg, 0.75 mmol) and $CuCl_2$ (3.5 mg, 0.025 mmol) were added to the mixture successively. The resulting suspension was stirred at room temperature for 24 h until no starting material was detected by TLC. The reaction was quenched with HCl solution (2 N). The aqueous phase was extracted with EtOAc (25 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was subjected to flash chromatography on silica gel to afford compound **4** (petrol ether/acetone=6:1, 108 mg, 0.20 mmol, 80% yield). $[\alpha]_D^{25}$ +65.8 (c 0.27, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, J=7.8 Hz, 1H), 7.84 (s, 1H), 7.80–7.76 (m, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.52 (dd, J=13.0, 7.3 Hz, 2H), 7.38 (t, J=7.8 Hz, 1H), 7.15 (t, J=7.6 Hz, 1H), 6.12 (s, 1H), 4.86 (q, J=7.2 Hz, 1H), 3.15 (dd, J=13.6, 2.5 Hz, 1H), 1.65 (d, J=7.2 Hz, 3H), 1.63–1.56 (m, 3H), 1.54 (m, 2H), 1.42 (d, J=13.1 Hz, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 160.6, 147.4, 144.8, 139.8, 134.5, 133.4, 130.4, 128.4, 127.5, 127.3, 127.1, 124.7, 121.7, 115.0, 86.4, 82.5, 61.1, 59.9, 59.4, 40.9, 40.4, 35.6, 33.4, 29.6, 21.2, 21.2, 16.9, 15.3; HRESIMS (m/z): calcd for $C_{31}H_{35}N_5O_4Na$ $[M+Na]^+$, 564.2587, found 564.2588.

4.7. (2*R*,4*R*,5a*S*,9c*S*)-4,5,5a,9c-Tetrahydro-2-methyl-4-(4-oxo-3(4*H*)-quinazolinyl)-5a-[(2,2,6,6-tetramethyl-1-piperidinyl) oxy]-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (10)

The protocol for preparation of compound **10** follows that of compound **4** by using compound **6** as the substrate instead. The optimized yield for compound **10** is 68%. $[\alpha]_D^{25}$ −99.4 (c 0.69, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, J=7.9 Hz, 1H), 7.84 (s, 1H), 7.76 (t, J=7.6 Hz, 1H), 7.68 (d, J=8.1 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.50 (t, J=7.4 Hz, 2H), 7.35 (t, J=7.8 Hz, 1H), 7.13 (t, J=7.6 Hz, 1H), 6.10 (s, 1H), 4.81 (q, J=7.1 Hz, 1H), 4.09 (q, J=7.1 Hz, 1H), 1.62 (d, J=7.2 Hz, 3H), 1.52–1.57 (m, 2H), 1.40 (d, J=13.1 Hz, 1H), 1.29 (s, 3H), 1.24 (d, J=7.2 Hz, 2H), 1.20 (s, 3H), 1.12 (s, 3H), 0.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 165.6, 147.2, 147.1, 139.7, 134.7, 133.5, 130.4, 128.3, 127.5, 127.3, 127.1, 124.7, 115.0, 86.3, 82.4, 61.1, 60.4, 59.9, 59.5, 40.9, 40.4, 35.6, 33.4, 21.2, 21.1, 20.9, 16.9, 15.2, 14.1; HREIMS (m/z): calcd for $C_{31}H_{35}N_5O_4$ $[M]^+$, 541.2689, found 541.2691.

4.8. (+)-2,3,14-*epi*-Chaetominine (5)

To a solution of compound **4** (68 mg, 0.125 mmol) in THF (2.5 mL) under argon were added activated zinc dust (65 mg, 1.0 mmol) and HOAc (60 mg, 1.0 mmol) successively. The mixture was heated to 50 °C. When the reaction was complete as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted with DCM (15 mL×3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was subjected to flash chromatography on silica gel to afford 2,3,14-tri-*epi*-chaetominine **5** (petrol ether/acetone=3:1, 45 mg, 0.112 mmol, 90% yield). $[\alpha]_D^{25}$ +55.2 (c 1.08, $CHCl_3$) {lit. $[\alpha]_D^{20}$ +98.0 (c 0.5, MeOH)[8,9]}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.19 (d, J=7.2 Hz, 1H), 7.89–7.83 (m, 1H), 7.69 (d, J=8.0 Hz, 1H), 7.60–7.54 (m, 1H), 7.48–7.44 (m, 2H), 7.42–7.38 (m, 1H), 7.23 (td, J=7.5, 0.9 Hz, 1H),

Please cite this article in press as: Deng, X.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.09.029

6.76 (s, 1H), 5.90 (d, J=11.2 Hz, 1H), 5.84 (s, 1H), 4.63 (q, J=7.2 Hz, 1H), 3.43 (ddd, J=14.0, 7.0, 5.1 Hz, 1H), 2.91 (t, J=13.0 Hz, 1H), 2.46 (d, J=3.3 Hz, 1H), 1.48 (d, J=7.3 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.9, 166.2, 159.9, 147.3, 146.7, 137.7, 137.5, 134.7, 129.7, 127.3, 127.2, 126.4, 125.5, 124.6, 121.0, 114.5, 82.9, 82.5, 76.6, 59.7, 56.0, 38.3, 18.5, 15.1; HRESIMS (m/z): calcd for $C_{22}H_{18}N_4O_4Na$ $[M+Na]^+$, 425.1226, found 425.1222.

4.9. Alternative synthesis of (+)-2,3,14-*epi*-chaetominine (5)

To a solution of compound **2** (42 mg) in CH_3CN (1.0 mL) under argon was added DBU (76 mg) dropwise. The mixture was stirred at room temperature for 15 min. Then the atmosphere was replaced with O_2. And $CuCl_2$ (2 mg) was added to the mixture in one portion. The resulting mixture was stirred at room temperature. When the reaction was complete as indicated by TLC, the mixture was quenched with HCl solution (2 M). The aqueous phase was extracted with EtOAc (15 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was subjected to flash chromatography on silica gel to afford 2,3,14-tri-*epi*-chaetominine (**5**) (petrol ether/acetone=3:1, 25 mg, 62% yield).

4.10. 11-*epi*-Chaetominine (11)

The protocol for preparation of 11-*epi*-chaetominine **11** follows that of 2,3,14-tri-*epi*-chaetominine **5** by using compound **10** as the starting material instead. The optimized yield for 11-*epi*-chaetominine **11** is 94%. $[\alpha]_D^{25}$ −33.6 (c 0.57, $CHCl_3$); {lit. $[\alpha]_D^{20}$ −98.0 (c 0.5, MeOH)[8]}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.23 (s, 1H), 8.20 (d, J=7.3 Hz, 1H), 7.88 (d, J=7.2 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.59 (dd, J=11.6, 4.4 Hz, 1H), 7.48 (d, J=8.6 Hz, 2H), 7.42 (d, J=7.8 Hz, 1H), 7.25 (td, J=7.5, 0.9 Hz, 1H), 6.79 (s, 1H), 5.86 (s, 1H), 4.64 (q, J=7.2 Hz, 1H), 2.93 (t, J=13.0 Hz, 1H), 1.49 (d, J=7.3 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.3, 166.6, 160.4, 147.7, 147.1, 138.1, 138.0, 135.2, 130.2, 127.7, 127.7, 126.9, 125.9, 125.1, 121.4, 114.9, 83.3, 77.0, 60.1, 39.9, 15.5; HREIMS (m/z): calcd for $C_{22}H_{18}N_4O_4$ $[M]^+$, 402.1328, found 402.1318.

Acknowledgements

This work was financially supported by National Natural Science Foundation of China (21272242 and 21302193), Yunnan High-End Technology Professionals Introduction Program (2010CI117), the West Doctor Foundation of Chinese Academy of Sciences (292014312D11016), and National Basic Research Program of China (2011CB915500).

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra associated with this article. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.09.029.

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