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Bio-inspired Step-Economical, Redox-Economical and Protecting-Group-Free Enantioselective Total Syntheses of (–)-Chaetominine and Analogues†

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Full details of the enantioselective four-step and five-step total syntheses of (–)-chaetominine from D-Trp and L-Trp are described. Featuring an oxidative double cyclization reaction, and tandem C14 epimerization-lactamization reactions as key steps, the method provides a rapid access to (–)-chaetominine (**6a**) and analogues. The total syntheses of (–)-chaetominine (**6a**) are so far the most concise and efficient. Through comprehensive investigation, the stereochemical requirements for the double cyclization reaction were revealed, and the confusion regarding physicochemical properties of this natural product was clarified. Moreover, short pathways to complexity generation, a scenarios revealed for the biosynthesis of fungal peptidyl alkaloid multi-cyclic scaffolds, have been validated through the chemical synthesis. On the basis of these findings, a plausible biosynthetic pathway for (–)-chaetominine (**6a**) was suggested.

Keywords total synthesis, step economy, redox economy, double cyclization, alkaloids, bio-inspired synthesis

Introduction

In the late 1940s, anti-malaria alkaloids febrifugine (**1**) (Figure 1) and isofebrifugine were isolated from traditional Chinese medicinal plants *Dichroa febrifuga* Lour. (Chang Shan),[1] which opened up chemical and medicinal studies towards quinazolinone alkaloids.[2] The related studies have led to the discovery of synthetic quinazolinone drugs such as methaqualone[3] and halofuginone (**2**).[4] Up to 2006, more than 150 quinazolinone alkaloids have been isolated from natural sources,[2c] which include anti-fungal fumiquinazoline I (**3**), asperlicin (**4**), an antagonist of the peptide hormone CCK, and fiscalin C (**5**). In 2006, (–)-chaetominine (**6a**), a hexacyclic quinazolinone alkaloid, was isolated from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.[5a] Later on, the same alkaloid was isolated from the metabolites of *Aspergillus* sp. HT-2 collected from Guizhou province, China.[5b] Structurally and biosynthetically, this quinazolinone alkaloid also belongs to fungal peptidyl indole alkaloids.[6] The characteristic tetracyclic core structure of (–)-chaetominine (**6a**), with different stereochemical patterns, is also found in kapakahines (*e.g.* **7** and **8** in

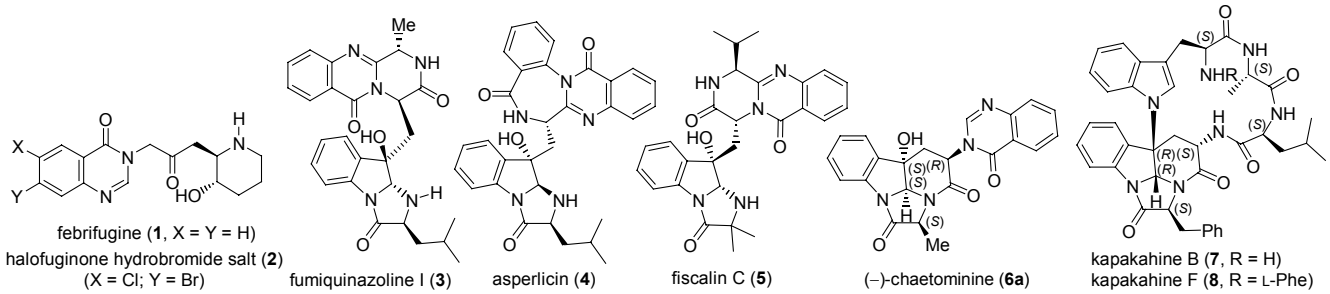

Figure 1 Some quinazolinone alkaloids and synthetic drugs.

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Figure 1), a group of seven cyclic peptides isolated from the marine sponge *Cribrochalina olemda*.[7] Unlike kapakahines, (−)-chaetominine contains a non-proteinogenic D-tryptophan (Trp) residue.

The unique yet diverse structural features of the fungal peptidyl alkaloids and the reported important biological activities[7] have attracted the attention of many chemists and biochemists. On one hand, a number of elegant enantioselective total syntheses have been reported.[8,9] On the other hand, biosynthetic pathways of several fungal peptidyl alkaloids have been revealed.[6]

As part of our continuous efforts in the synthesis of bioactive natural products and analogues[10] and the development of step-economical synthetic methodologies,[11] we embarked on the total synthesis of (−)-chaetominine (**6a**). The preliminary results, including a four-step and a five-step syntheses of (−)-chaetominine from D-Trp[8c,8f] and L-Trp,[8g] respectively, have been communicated recently. Herein we report full accounts of these studies, which include the syntheses of five analogues of (−)-chaetominine, the clarification on the physicochemical properties of (−)-chaetominine (**6a**), and a plausible biosynthetic pathway of (−)-chaetominine (**6a**).

Strategy for the total synthesis of (−)-chaetominine

In view of developing a concise total synthesis of (−)-chaetominine (**6a**), a biomimetic synthesis[12] was initially envisaged. Two plausible biosynthesis pathways have been suggested by Tan *et al.* (a in Scheme 1)[5a] and Walsh/Tang (b in Scheme 1),[6a] which feature D-Trp as the starting material, and the nine-membered bis-lactam ring-systems **A**[5a] or **D**/**E**[6a] as the key intermediates. They also mentioned that D-Trp is likely formed from L-Trp *via* inversion of configuration. In the extensive studies on the biosynthesis of fungal peptidyl alkaloids by Tang/Walsh and co-workers,[6] eleven-membered and ten-membered ring systems were suggested as the key intermediates in the biosyntheses of asperlicins **C**, **D**, and **E**,[6c] and fumiquinazolines **C** and **F**,[6c] respectively. Moreover, they also revealed short pathways to complexity generation in the biosynthesis of those polycyclic peptidyl alkaloids.[6a-6c]

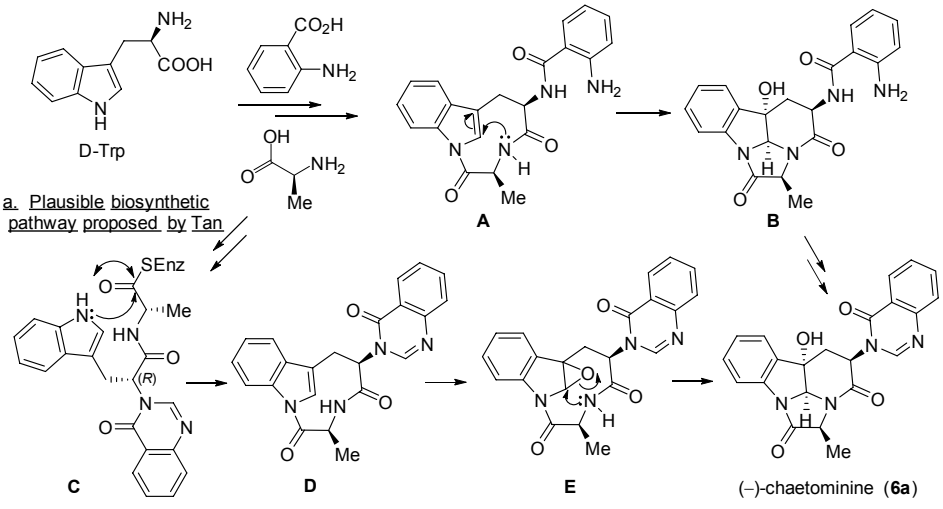
It is well known that direct formation of medium-sized rings (8 to 11 atoms) is challenging in organic synthesis due to unfavorable ring strain.[13] It is thus risky to plan a total synthesis based on a multiply functionalized key intermediate such as **A** or **D**. Thus, a bio-inspired but non-biomimetic approach to (−)-chaetominine (**6a**) from D-Trp bypassing any nine-membered ring was envisioned. To develop a protecting-group-free total synthesis,[14] we opted for a nitro group as a latent amino group. Thus, our retrosynthetic analysis of (−)-chaetominine (**6a**) is outlined in Scheme 2, which features the one-pot transformation of intermediate **10a** into (−)-chaetominine (**6a**) via an ambitious indole epoxidation – amidative cyclization – lactamization cascade process as the key step and the use of *o*-nitrobenzamide derivative **11a** as a precursor of the quinazolinone ring system. According to this analysis, no extra protection-deprotection steps are required.

Experimental

General methods

Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in ppm downfield from TMS. Silica gel (300−400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60−90 ℃) mixture. DMSO was pre-dried over calcium hydride. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium

Scheme 1 Plausible biosynthetic pathways to (−)-chaetominine (**6a**) suggested by Tan (a) and Walsh/Tang (b)



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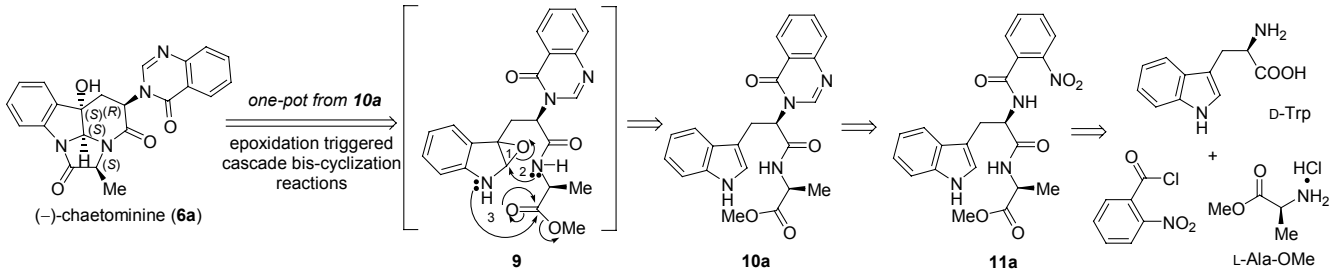
Scheme 2 Retrosynthetic analysis of (−)-chaetominine (**6a**)



hydride under N_2.

For the experimental procedures, spectral data, and ^{1}H and ^{13}C NMR spectra regarding compounds **6a**, **10a**, **11a**, (*R*)-**12**, **17a**, **18a** and **19**, and cif files regarding the single crystal X-ray diffraction analyses of compounds **6a**, **16**, **18a** and **19** (deposited to the Cambridge Crystallographic Data Centre: CCDC 791762; CDCC 791763; CCDC 791764; CCDC 884128), please see the electronic supplementary information (ESI) of reference 8f. For the experimental procedures regarding compounds (*S*)-**12**, **20**, **21**, **22** and **23**, and spectral data, ^{1}H and ^{13}C NMR spectra of compounds (*S*)-**12**, **20**, **21**, and **22**, please see the electronic supplementary information (ESI) of reference 8g.

Methyl (*S*)-[(*R*)-2-(2-aminobenzamido)-3-(1*H*-indol-3-yl)propanamido]propanoate (13)

To a suspension of Pd/C (0.260 g, 10% Pd) in ethanol (10 mL) was added a solution of **11a** (1.29 g, 2.94 mmol) in methanol (20 mL). The mixture was stirred at r.t. under an atmosphere of H_2 for 12 h. The resulting mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc∶PE＝1∶1) to provide compound **13** (1.16 g, 2.85 mmol, yield: 97%) as a white solid. M.p. 172－173 ℃ (EtOAc); $[\alpha]_D^{20}$ ＋36.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3349, 1738, 1633, 1513, 1454, 1217, 1159, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (br s, 1H), 7.73 (m, 1H), 7.36 (m, 1H), 7.23－7.08 (m, 5H), 6.84 (d, *J*＝7.2 Hz, 1H), 6.65 (m, 1H), 6.57 (m, 1H), 6.28 (d, *J*＝7.3 Hz, 1H), 5.52 (br s, 2H), 4.91 (m, 1H), 4.46 (dq, *J*＝7.3, 7.2 Hz, 1H), 3.65 (s, 3H), 3.45 (dd, *J*＝14.6, 5.6 Hz, 1H), 3.24 (dd, *J*＝14.6, 8.0 Hz, 1H), 1.11 (d, *J*＝7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.9, 170.9, 169.1, 148.9, 136.2, 132.6, 127.53, 127.46, 123.1, 122.4, 119.9, 118.9, 117.3, 116.7, 115.2, 111.3, 110.8, 53.9, 52.4, 48.0, 28.1, 17.8; MS (ESI) *m/z*: 431 (M＋Na$^+$, 100%), 409 (M＋H$^+$, 17%), 477 (M＋K$^+$, 7%). Anal. calcd for $C_{22}H_{24}N_4O_4$: C 64.69, H 5.92, N 13.72; found C 64.55, H 5.95, N 13.32.

General procedure for the synthesis of (−)-chaetominine (6a)

To a solution of compound **10a** (200 mg, 0.48 mmol) in anhydrous acetone (2 mL) was added a solution of 0.05 mol/L dimethyldioxirane (DMDO) in acetone (17 mL, 0.85 mmol) at −78 ℃. After being stirred for 1 h, K_2CO_3/MeOH (94 mg/10 mL) was added and the mixture was warmed up to −10 ℃ over 30 min. To the resulting mixture was added 10 mL of NH_4Cl (sat.). After removal of the solvent under reduced pressure, to the residue was added H_2O (100 mL), and the resulting mixture was extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc∶PE＝3∶2 then CH_2Cl_2∶CH_3OH＝30∶1) to give chaetominine (**6a**)[8f] (73 mg, yield: 38%) and compound **17a**[8f] (98 mg, yield: 47%).

Methyl (*S*)-2-((*R*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-4-methylpentanoate (11b)

To a solution of compound (*R*)-**12** (1.97 g, 5.58 mmol) in THF (20 mL) at −20 ℃ were added successively *N*-methylmorpholine (NMM, 0.74 mL, 6.69 mmol) and ^{t}BuOCOC1 (0.80 mL, 6.13 mmol). After being stirred at −20 ℃ under N_2 for 15 min, the resultant suspension was added dropwise to a solution of L-leucine methyl ester hydrochloride (2.02 g, 11.16 mmol) and *N*-methylmorpholine (1.84 mL, 16.74 mmol) in THF (36 mL) at −20 ℃, and the reaction mixture was stirred at −20 ℃ for 12 h. The reaction was quenched with a saturated aqueous NH_4Cl (20 mL) and diluted with water (100 mL). The aqueous phase was separated and extracted with EtOAc (20 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc∶PE＝3∶2) to give compound **11b** in 91% yield as a yellow solid. M.p. 73－75 ℃ (EtOAc); $[\alpha]_D^{20}$ −42.3 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3294, 2957, 1738, 1646, 1531, 1457, 1349, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 7.98－7.95 (m, 1H), 7.68－7.63 (m, 1H), 7.53－7.46 (m, 2H), 7.35－7.31 (m, 1H), 7.18－7.13 (m, 2H), 7.10－7.05 (m, 2H), 6.68 (d, *J*＝8.0 Hz, 1H), 6.58 (d, *J*＝7.8 Hz, 1H), 5.05 (ddd, *J*＝7.8, 7.1, 6.5 Hz, 1H), 4.53－4.47 (m, 1H), 3.66 (s, 3H), 3.44 (dd, *J*＝14.8, 6.5 Hz, 1H), 3.32 (dd, *J*＝14.8, 7.1 Hz, 1H), 1.50－1.36 (m, 3H), 0.84 (d, *J*＝6.3 Hz, 3H), 0.82 (d, *J*＝6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 170.7, 166.4, 146.2, 136.1, 133.7, 132.2, 130.5, 128.5, 127.5, 124.5, 123.2, 122.2,

119.7, 118.5, 111.3, 110.2, 54.2, 52.2, 51.0, 40.7, 27.3, 24.5, 22.6, 21.6; MS (ESI) *m/z*: 481 ($M+H^+$, 100%). Anal. calcd for $C_{25}H_{28}N_4O_6$: C 62.49, H 5.87, N 11.66; found C 62.58, H 5.95, N 11.58.

Methyl (*S*)-2-((*R*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-phenylpropanoate (11c)

Following the procedure described for the synthesis of compound **11b**, except for using L-phenylalanine methyl ester hydrochloride salt (2.40 g, 11.16 mmol) other than L-alanine methyl ester hydrochloride salt, compound **11c** was synthesized in 85% yield as a yellow solid. M.p. 176—179 ℃ (EtOAc); $[\alpha]_D^{20}$ –42.3 (*c* 1.0, THF); IR (film) ν_{max}: 3291, 2959, 1742, 1654, 1531, 1456, 1349, 1214, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.85—10.82 (m, 1H), 8.88 (d, J=8.4 Hz, 1H), 8.61 (d, J=8.0 Hz, 1H), 8.02—7.98 (m, 1H), 7.77—7.64 (m, 2H), 7.59 (d, J=7.8 Hz, 1H), 7.40—7.32 (m, 2H), 7.29—7.20 (m, 5H), 7.12—7.05 (m, 2H), 7.03—6.98 (m, 1H), 4.77 (m, 1H), 4.55 (m, 1H), 3.65 (s, 3H), 3.05 (dd, J=13.6, 5.4 Hz, 1H) 2.95 (dd, J=14.8, 5.0 Hz, 1H), 2.91—2.82 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.3, 171.6, 165.5, 147.6, 137.6, 136.5, 133.7, 132.5, 131.2, 129.7 (2C), 129.6, 128.7 (2C), 127.8, 127.1, 124.4, 124.0, 121.3, 118.9, 118.7, 111.7, 110.4, 54.01, 53.96, 52.4, 37.4, 28.2; MS (ESI) *m/z*: 537 ($M+Na^+$, 100%); HRMS-ESI calcd for $C_{28}H_{26}N_4O_6$: $(M+Na)^+$ 537.1750, found 537.1734.

Methyl (*R*)-2-(3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)-propanamido)-2-methylpropanoate (11d)

According to procedure for the synthesis of compound **11b**, except for the use of 2,2-dimythylalanine methyl ester hydrochloride (1.31 g, 11.16 mmol), compound **11d** was synthesized in 91% yield as a yellow solid. M.p. 91—93 ℃ (EtOAc); $[\alpha]_D^{20}$ –30.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3319, 2959, 1737, 1651, 1530, 1349, 1285, 1152, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67—8.64 (m, 1H), 7.95—7.91 (m, 1H), 7.67 (d, J=8.0 Hz, 1H), 7.49—7.42 (m, 2H), 7.32 (d, J=8.0 Hz, 1H), 7.16—7.02 (m, 4H), 6.81 (d, J=7.6 Hz, 1H), 6.65 (s, 1H), 4.93 (ddd, J=7.6, 6.8. 6.0 Hz, 1H), 3.66 (s, 3H), 3.37 (dd, J=14.8, 6.0 Hz, 1H), 3.24 (dd, J=14.8, 6.8 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 169.9, 166.3, 146.2, 136.1, 133.7, 132.1, 130.5, 128.5, 127.4, 124.4, 123.5, 122.0, 119.5, 118.6, 111.4, 110.1, 56.3, 54.0, 52.4, 27.1, 24.7, 24.5; MS (ESI) *m/z*: 475 ($M+Na^+$, 100%); HRMS-ESI calcd for $C_{23}H_{24}N_4O_6$: $(M+Na)^+$ 475.1594, found 475.1587.

Methyl (*R*)-2-(3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)acetate (11e)

Following the procedure described for the synthesis of compound **11b**, except for using glycine methyl ester hydrochloride salt (2.40 g, 11.16 mmol) other than L-alanine methyl ester hydrochloride salt, compound **11e** was synthesized in 87% yield as a yellow solid. M.p. 193—195 ℃ (EtOAc); $[\alpha]_D^{20}$ –9.0 (*c* 1.0, THF); IR (film) ν_{max}: 3292, 1747, 1649, 1530, 1348, 1213, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (s, 1H), 7.93—7.87 (m, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.47—7.39 (m, 2H), 7.29—7.24 (m, 1H), 7.17—7.07 (m, 5H), 6.81 (dd, J=5.3, 5.3 Hz, 1H), 4.97 (ddd, J=7.0, 6.8, 6.3 Hz, 1H), 3.89 (dd, J=17.9, 5.3 Hz, 1H), 3.89 (dd, J=17.9, 5.3 Hz, 1H), 3.62 (s, 3H), 3.37 (dd, J=14.7, 6.3 Hz, 1H), 3.28 (dd, J=14.7, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 169.8, 166.4, 146.2, 136.1, 133.6, 132.1, 130.5, 128.6, 127.5, 124.3, 123.5, 122.0, 119.5, 118.5, 111.3, 110.0, 54.1, 52.2, 41.2, 27.5; MS (ESI) *m/z*: 447 ($M+Na^+$, 100%); HRMS-ESI calcd for $C_{21}H_{20}N_4O_6$: $(M+Na)^+$ 447.1281, found 447.1271.

Methyl (*S*)-2-((*R*)-3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido)-4-methylpentanoate (10b)

To a suspension of zinc powder (200 mg, 3.05 mmol) in THF (5 mL) was added $TiCl_4$ (0.22 mL, 2.59 mmol). The resulting mixture was stirred at 50 ℃ for 1 h. After being cooled to 0 ℃, a solution of compound **11b** (186 mg, 0.42 mmol) in THF (2 mL) and trimethyl orthoformate (0.20 mL, 1.82 mmol) were added dropwise. The reaction mixture was stirred at 0 ℃ for 24 h and then quenched with brine (5 mL) and stirred for another 2 h. The phases were separated, and the aqueous phase was extracted with EtOAc (2 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc∶PE=3∶2) to give compound **10b** in 99% yield as a white solid. M.p. 201—203 ℃ (EtOAc); $[\alpha]_D^{20}$+52.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3315, 2956, 1744, 1661, 1610, 1476, 1241, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 8.28 (br s, 1H), 8.21—8.17 (m, 1H), 7.72—7.63 (m, 3H), 7.45—7.39 (m, 1H), 7.32—7.28 (m, 1H), 7.17—7.12 (m, 1H), 7.08—7.01 (m, 2H), 6.90 (d, J=8.1 Hz, 1H), 5.94 (dd, J=8.9, 6.8 Hz, 1H), 4.50 (td, J=8.1, 5.4 Hz, 1H), 3.73 (dd, J=14.4, 8.9 Hz, 1H), 3.54 (s, 3H), 3.41 (dd, J=14.4, 6.8 Hz, 1H), 1.51—1.43 (m, 1H), 1.38—1.29 (m, 2H), 0.78 (d, J=6.3 Hz, 3H), 0.77 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 168.7, 161.2, 147.4, 144.2, 136.2, 134.5, 127.4, 127.2, 126.9, 126.8, 123.3, 122.3, 121.3, 119.8, 118.4, 111.3, 109.5, 56.2, 52.2, 51.1, 40.8, 27.3, 24.5, 22.6, 21.6; MS (ESI) *m/z*: 461 ($M+H^+$, 100%); HRMS-ESI calcd for $C_{26}H_{28}N_4O_4$: $(M+H)^+$ 461.2189, found 461.2172.

Methyl (*S*)-2-((*R*)-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-3,4-dihydro-2*H*-pyrido[2,3]indol-1(9*H*)-yl)-3-phenylpropanoate (10c)

Following the procedure described for the synthesis of compound **10b**, compound **10c** was synthesized in 93% yield as a white solid. M.p. 172—174 ℃ (EtOAc); $[\alpha]_D^{20}$ –10.5 (*c* 1.0, THF); IR (film) ν_{max}: 3306, 2950, 1743, 1671, 1608, 1475, 1217, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.38 (s, 1H), 8.32 (br s, 1H), 8.21—8.17 (m, 1H), 7. 73—7.63 (m, 3H), 7.44—7.38 (m, 1H),

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7.31 (d, J=8.0 Hz, 1H), 7.21−7.16 (m, 1H), 7.15−7.03 (m, 4H), 6.94−6.88 (m, 2H), 6.77−6.73 (m, 2H), 5.84 (dd, J=8.8, 7.0 Hz, 1H), 4,81 (dt, J=7.6, 6.0 Hz, 1H), 3.67 (dd, J=14.5, 8.8 Hz, 1H), 3.55 (s, 3H), 3.37 (dd, J=14.5, 7.0 Hz, 1H), 2.9 (d, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 168.4, 161.0, 147.4, 144.2, 136.2, 135.4, 134.5, 129.0 (2C), 128.4 (2C), 127.4, 127.2, 127.0, 126.9, 126.8, 123.2, 122.4, 121.4, 119.9, 118.4, 111.3, 109.4, 56.4, 53.4, 52.3, 37.4, 27.3; MS (ESI) *m/z*: 495 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{29}H_{26}N_4O_4$: (M+H)$^+$ 495.2032, found 495.2026.

Methyl (*R*)-2-(3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido)-2-methylpropanoate (10d)

Following the procedure described for the synthesis of compound **10b**, compound **10d** was synthesized in 96% yield as a white solid. M.p. 145−147 ℃ (EtOAc); $[\alpha]_D^{20}$ −66.1 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3324, 3011, 1740, 1659, 1610, 1547, 1475, 1286, 1157, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 8.52 (s, 1H), 8.20 (d, J=7.6 Hz, 1H), 7.72−7.60 (m, 2H), 7.50 (d, J=7.6 Hz, 1H), 7.46 (s, 1H), 7.38−7.32 (m, 1H), 7.21 (d, J=8.0 Hz, 1H), 7.07−6.98 (m, 2H), 6.88 (t, J=7.6 Hz, 1H), 5.88 (dd, J=8.4, 7.2 Hz, 1H), 3.68 (dd, J=14.4, 8.4 Hz, 1H), 3.60 (s, 3H), 3.37 (dd, J=14.4, 7.2 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.2, 168.2, 160.9, 146.9, 145.0, 136.1, 134.6, 127.2, 127.1, 126.8, 126.5, 123.7, 122.0, 121.1, 119.4, 118.2, 111.3, 109.0, 56.6, 56.4, 52.4, 27.1, 24.7, 24.5; MS (ESI) *m/z*: 433 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{24}H_{25}N_4O_4$: (M+H)$^+$ 433.1876, found 433.1867.

(*R*)-Methyl 2-(3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido) acetate (10e)

Following the procedure described for the synthesis of compound **10b**, compound **10e** was synthesized in 91% yield as a white solid. M.p. 142−145 ℃ (EtOAc); $[\alpha]_D^{20}$ −58.7 (*c* 1.0, MeOH); IR (film) ν_{max}: 3395, 1737, 1666, 1611, 1220, 1097, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 8.32 (br s, 1H), 8.20−8.15 (m, 1H), 7.73−7.63 (m, 2H), 7.61−7.56 (m, 1H), 7.45−7.40 (m, 1H), 7.29−7.25 (m, 1H), 7.15−7.01 (m, 3H), 7.00−6.97 (m, 1H), 5.87 (dd, J=8.2, 7.4 Hz, 1H), 3.96 (dd, J=18.2, 5.5 Hz, 1H), 3.91 (dd, J=18.2, 5.5 Hz, 1H), 3.73 (dd, J=14.7, 8.2 Hz, 1H), 3.62 (s, 3H), 3.45 (dd, J=14.7, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 169.3, 161.2, 147.4, 144.4, 136.2, 134.5, 127.4, 127.2, 126.84, 126.78, 123.3, 122.3, 121.4, 119.7, 118.3, 111.3, 109.4, 56.5, 52.3, 41.4, 27.0; MS (ESI) *m/z*: 405 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{22}H_{20}N_4O_4$: (M+H)$^+$ 405.1563, found 405.1562.

(2*S*,4*R*,5a*S*,9c*S*)-4,5,5a,9c-Tetrahydro-5a-hydroxy-2-isobutyl-4-(4-oxo-3(4*H*)-quinazolinyl)-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (6b) and methyl (α*S*,3*S*,4a*R*,9a*S*)-2,3,4,4a,9,9a-hexahydro-4a-hydroxy-*α*-methyl-2-oxo-3-(4-oxo-3(4*H*)-quinazolinyl)-1*H*-pyrido[2,3]indole-1-ethanoate (17b)

Following the *General Procedure*, the tandem reaction of compound **10b** (200 mg, 0.43 mmol) produced, after column chromatographic purification on silica gel (eluent: EtOA∶PE=1∶1 to EtOAc∶PE=3∶1), compound **6b** (60 mg, yield: 31%) and compound **17b** (93 mg, yield: 45%).

Compound **6b**: White solid, m.p. 171−175 ℃ (EtOAc); $[\alpha]_D^{20}$ −52.2 (*c* 0.9, $CHCl_3$); IR (film) ν_{max}: 3371, 2926, 1737, 1682, 1610, 1479, 1292, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17−8.15 (m, 1H), 7.81 (s, 1H), 7.76−7.71 (m, 1H), 7.49 (d, J=8.1 Hz, 1H), 7.61−7.57 (m, 1H), 7.48−7.43 (m, 1H), 7.41−7.36 (m, 2H), 7.20−7.16 (m, 1H), 5.80 (br s, 1H), 5.46 (s, 1H), 4.61 (br s, 1H), 4.34 (dd, J=5.5, 4.2 Hz, 1H), 2.83−2.48 (m, 2H), 2.22−2.13 (m, 1H), 2.05−1.95 (m, 2H), 0.89 (d, J=6.5 Hz, 3H), 0.77 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 165.5, 161.1, 147.5, 144.9, 139.7, 134.7, 134.3, 131.1, 127.6, 127.5, 126.9, 125.9, 124.3, 121.7, 115.4, 83.0, 77.6, 62.8, 39.2, 35.8, 25.3, 22.9, 22.2 (one amide carbonyl carbon was not observed due to slow rotation at the C9−N bond);[8a] MS (ESI) *m/z*: 445 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{25}H_{24}N_4O_4$: (M+H)$^+$ 445.1876, found 445.1870.

Compound **17b**: White solid, m.p. 175−177 ℃ (EtOAc); $[\alpha]_D^{20}$ −125.2 (*c* 1.0, THF); IR (film) ν_{max}: 3391, 2956, 1738, 1681, 1612, 1471, 1322, 1227, 1176, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.22−8.18 (m, 1H), 7.74−7.69 (m, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.60 (br s, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.29 (d, J=7.4 Hz, 1H), 7.21−7.16 (m, 1H), 6.82 (t, J=7.4 Hz, 1H), 6.78 (d, J=8.0 Hz, 1H), 5.39 (dd, J=10.6, 5.2 Hz, 1H), 5.37 (d, J=4.0 Hz, 1H), 5.36 (br s, 1H), 5.33 (d, J=4.0 Hz, 1H), 3.75 (s, 3H), 3.33 (br s, 1H), 2.85 (br s, 1H), 2.50 (dd, J=12.1, 4.0 Hz, 1H), 1.92−1.78 (m, 2H), 1.77−1.70 (m, 1H), 1.01 (d, J=6.5 Hz, 3H), 1.00 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.0, 170.3, 160.5, 148.3, 147.3, 145.2, 134.4, 130.9, 129.0, 127.23, 127.19, 127.0, 123.6, 121.8, 120.1, 110.1, 80.0, 79.6, 53.4, 52.5, 51.7, 41.2, 39.2, 24.4, 23.1, 21.2; MS (ESI) *m/z*: 499 (M+Na$^+$, 100%); HRMS-ESI calcd for $C_{26}H_{28}N_4O_5$: (M+H)$^+$ 476.2138, found 476.2143.

(2*S*,4*R*,5a*S*,9c*S*)-4,5,5a,9c-Tetrahydro-5a-hydroxy-2-benzyl-4-(4-oxo-3(4*H*)-quinazolinyl)-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (6c) and methyl (α*S*,3*S*,4a*R*,9a*S*)-2,3,4,4a,9,9a-hexahydro-4a-hydroxy-*α*-methyl-2-oxo-3-(4-oxo-3(4*H*)-quinazolinyl)-1*H*-pyrido[2,3]indole-1-ethanoate (17c)

Following the *General Procedure*, the tandem reaction of compound **10c** (200 mg, 0.40 mmol) produced, after column chromatographic purification on silica gel (eluent: EtOAc∶PE=1∶1 to EtOAc∶PE=3∶1), compound **6c** (62 mg, yield: 32%) and compound **17c** (105 mg, yield: 51%).

Compound **6c**: White solid, m.p. 155−157 ℃ (EtOAc); $[\alpha]_D^{20}$ −70.0 (*c* 0.4, $CHCl_3$); IR (film) ν_{max}: 3370, 2925, 1736, 1677, 1610, 1478, 1286, 760 cm^{-1};

^{1}H NMR (400 MHz, acetone-d_6) δ: 8.13－8.09 (m, 1H), 7.74－7.70 (m, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.46－7.42 (m, 1H), 7.38－7.32 (m, 1H), 7.31－7.24 (m, 2H), 7.12－7.08 (m, 1H), 6.99－6.95 (m, 1H), 6.91－6.83 (m, 4H), 5.87－5.76 (m, 1H), 5.57 (s, 1H), 5.56 (br s, 1H), 4.73 (dd, J=6.2, 2.2 Hz, 1H), 3.55 (dd, J=14.6, 6.2 Hz, 1H), 3.37 (dd, J=14.6, 2.2 Hz, 1H), 2.66 (br s, 1H), 2.40 (dd, J=12.5, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 166.2, 161.2, 147.6, 144.0, 140.5, 135.5, 134.7, 133.8, 131.1, 130.0 (2C), 127.8 (2C), 127.6, 127.5, 127.2, 127.0, 126.0, 124.1, 121.4, 115.2, 83.3, 78.2, 63.2, 51.0, 38.8, 33.7; MS (ESI) *m/z*: 479 ($M+H^+$, 100%); HRMS-ESI calcd for $C_{28}H_{22}N_4O_4$: $(M+K)^+$ 479.1719, found 479.1716.

Compound **17c**: Colorless crystal, m.p. 251－253 ℃ (EtOAc); $[\alpha]_D^{20}$ –210.5 (*c* 1.0, THF); IR (film) ν_{max}: 3374, 2954, 1740, 1679, 1612, 1473, 1234, 745 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.04 (dd, J=8.0, 1.2 Hz, 1H), 7.85－7.81 (m, 1H), 7.67 (d, J=7.9 Hz, 1H), 7.57－7.50 (m, 2H), 7.42－7.23 (m, 6H), 7.17－1.12 (m, 1H), 6.79－6.74 (m, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.22 (s, 1H), 5.86 (d, J=4.0 Hz, 1H), 5.33 (d, J=4.0 Hz, 1H), 5.27 (dd, J=8.9, 6.4 Hz, 1H), 5.25－5.17 (m, 1H), 3.73 (s, 3H), 3.37 (dd, J=14.0, 6.4 Hz, 1H), 3.04 (dd, J=14.0, 8.9 Hz, 1H), 2.53 (br s, 1H), 2.44 (dd, J=11.9, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 171.3, 169.8, 160.1, 149.4, 147.6, 145.8, 137.6, 135.1, 130.7, 130.1 (3C), 128.6 (2C), 127.7, 127.6, 127.1, 126.8, 124.3, 121.4, 119.3, 110.4, 81.2, 79.1, 58.2, 52.9, 50.0, 40.3, 36.0; MS (ESI) *m/z*: 533 ($M+Na^+$, 100%); HRMS-ESI calcd for $C_{29}H_{26}N_4O_5$: $(M+H)^+$ 511.1981, found 511.1975.

Methyl (α*S*,3*S*,4a*R*,9a*S*)-2,3,4,4a,9,9a-hexahydro-4a-hydroxy-*α*,*α*-dimethyl-2-*oxo*-3-(4-*oxo*-3(4*H*)-quinazolinyl)-1*H*-pyrido[*2,3-b*]indole-1-ethanoate (17d)

Following the *General Procedure*, the tandem reaction of compound **10d** (200 mg, 0.44 mmol) produced, after column chromatographic purification on silica gel (eluent: EtOAc∶PE＝1∶1), compound **17d** (93 mg, 0.21 mmol, yield: 45%) as a white solid. M.p. 164－166 ℃ (EtOAc); $[\alpha]_D^{20}$ –195.0 (*c* 1.0, THF); IR (film) ν_{max}: 3340, 2955, 1740, 1678, 1611, 1474, 1244, 1157, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18－8.15 (m, 1H), 7.73－7.68 (m, 1H), 7.63－7.60 (m, 1H), 7.46－7.42 (m, 1H), 7.31－7.28 (m, 1H), 7.18－7.13 (m, 1H), 6.85－6.81 (m, 1H), 6.67 (d, J=7.9 Hz, 1H), 5.33 (s, 1H), 5.00 (br s, 1H), 4.90 (s, 1H), 4.24 (br s, 1H), 3.69 (s, 3H), 2.99 (br s, 1H), 2.45 (dd, J=12.0, 3.6 Hz, 1H), 1.49 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.9, 170.0, 160.4, 148.6, 147.2, 145.7, 134.5, 131.0, 129.0, 127.3, 127.1, 126.9, 123.8, 121.8, 120.6, 110.4, 79.8, 79.7, 61.6, 52.7 (2C), 39.6, 24.43, 24.39; MS (ESI) *m/z*: 471 ($M+Na^+$, 100%); HRMS-ESI calcd for $C_{24}H_{25}N_4O_4$: $(M+K)^+$ 487.1384, found 487.1378.

Methyl (α*S*,3*S*,4a*R*,9a*S*)-2,3,4,4a,9,9a-hexahydro-4a-hydroxy-2-*oxo*-3-(4-*oxo*-3(4*H*)-quinazolinyl)-1*H*-pyrido[2,3-*b*]indole-1-ethanoate (16a and 17e)

Following the *General Procedure*, the tandem reaction of compound **10e** (200 mg, 0.49 mmol) (EtOAc∶PE＝3∶1) gave two inseparable compound **17e** and compound **16a** as a mixture of two inseparable diastereomers (168 mg, 0.40 mmol, yield: 81%, ratio＝2∶1) as a white solid. IR (film) ν_{max}: 3341, 2949, 1741, 1678, 1610, 1476, 1241, 1158, 756 cm^{-1}; minor∶major＝1∶2. ^{1}H NMR (500 MHz, CD_3CN): major isomer δ: 8.15－8.12 (m, 1H), 2.93 (s, 1H), 7.82－7.76 (m, 1H), 7.67－7.63 (m, 1H), 7.54－7.46 (m, 1H), 7.31(d, J=7.4 Hz, 1H), 7.24－7.13 (m, 1H), 6.87－6.79 (m, 1H), 6.74 (d, J=7.9 Hz, 1H), 5.53 (d, J=3.3 Hz, 1H), 5.22 (br s, 1H), 5.14 (d, J=3.3 Hz, 1H), 4.33 (s, 1H), 4.24 (d, J=17.4 Hz, 1H), 4.20 (d, J=17.4 Hz, 1H), 3.72 (s, 3H), 3.01－2.92 (m, 1H), 2.68 (dd, J=12.3, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ: 170.4, 169.5, 161.1, 150.1, 148.4, 146.6, 135.2, 133.0, 131.3, 130.2, 128.1, 127.2, 124.5, 122.3, 120.3, 111.0, 84.7, 79.6, 52.6, 51.7, 48.5, 38.9; minor isomer δ: 8.20－8.12 (m, 1H), 7.97 (s, 1H), 7.82－7.76 (m, 1H), 7.67－7.63 (m, 1H), 7.54－7.46 (m, 1H), 7.24－7.19 (m, 1H), 7.17－7.13 (m, 1H), 6.87－6.79 (m, 1H), 6.71 (d, J=7.9 Hz, 1H), 5.43 (d, J=4.8 Hz, 1H), 5.22 (br s, 1H), 5.13 (d, J=4.8 Hz, 1H), 4.51 (br s, 1H), 4.45 (d, J=17.4 Hz, 1H), 4.41 (d, J=17.4 Hz, 1H), 3.69 (s, 1H), 2.73－2.66 (m, 1H), 2.46－2.37 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ: 170.0, 168.2, 161.2, 148.6, 147.8, 147.3, 135.2, 133.0, 131.2, 130.5, 127.9, 127.1, 123.5, 122.7, 120.8, 111.6, 83.1, 78.4, 52.5, 49.6, 46.4, 36.6; MS (ESI) *m/z*: 443 ($M+Na^+$, 100%); HRMS-ESI calcd for $C_{22}H_{20}N_4O_5$: $(M+Na)^+$ 443.1331, found 443.1334.

(2*R*,4*R*,5a*S*,9c*R*)-4,5,5a,9c-Tetrahydro-5a-hydroxy-2-isobutyl-4-(4-oxo-3(4*H*)-quinazolinyl)-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (18b)

To a solution of compound **17b** (48 mg, 0.1 mmol) in MeOH (1 mL) was added a solution of freshly prepared CH_3ONa (14 mg, 0.254 mmol) in CH_3OH (3.5 mL) at –10 ℃. After being stirred for 24 h, the reaction mixture was acidified with 10% HCOOH until pH 7. The solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (2 mL×3). The combined organic layers were washed with brine (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc∶PE＝3∶2) to give compound **18b** (39 mg, yield: 88%) as a white solid. M.p. 192－195 ℃ (EtOAc); $[\alpha]_D^{20}$＋89.9 (*c* 1.0, THF); IR (film) ν_{max}: 3363, 2956, 1682, 1611, 1481, 1326, 1293, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19－8.16 (m, 1H), 7.77 (s, 1H), 7.76－7.72 (m, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H), 7.48－7.44 (m, 1H), 7.41－7.37 (m, 1H), 7.34－7.30 (m, 1H), 7.14 (t, J=7.6 Hz, 1H), 5.95 (br s, 1H), 5.77 (s, 1H), 4.86 (dd, J=10.2, 4.5 Hz, 1H), 4.79 (br s,

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1H), 2.63 (dd, J=13.1, 3.5 Hz, 1H), 2.60−2.50 (m, 1H), 1.82−1.76 (m, 2H), 1.74−1.67 (m, 1H), 1.03 (d, J=6.3 Hz, 3H), 0.9 (d, J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4, 166.2, 160.9, 147.1, 144.9, 137.4, 135.8, 134.7, 130.6, 127.5, 127.2, 126.9, 126.0, 124.1, 121.4, 115.5, 83.8, 77.5, 63.1, 50.9, 39.4, 38.8, 25.2, 23.0, 21.5; MS (ESI) *m/z*: 445 ($M+H^+$, 100); HRMS-ESI calcd for $C_{25}H_{24}N_4O_4$: $(M+H)^+$ 445.1876, found 445.1879.

(2*S*,4*S*,5a*R*,9c*R*)-4,5,5a,9c-Tetrahydro-5a-hydroxy-2-benzyl-4-(4-oxo-3(4*H*)-quinazolinyl)-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (18c)

Following the procedure described for the synthesis of compound **18b**, reaction of **17c** (51 mg, 0.10 mmol) gave compound **18c** (31 mg, yield: 60%) as a white solid, and 15 mg of recovered **17c**. Compound **18c**: M.p. 150−152 ℃ (EtOAc); $[\alpha]_D^{20}$+122.0 (c 0.2, $CHCl_3$); IR (film) ν_{max}: 3357, 2925, 1679, 1611, 1480, 1327, 1293, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16−8.13 (m, 1H), 7.76−7.70 (m, 2H), 7.61 (d, J=7.9 Hz, 1H), 7.58−7.54 (m, 1H), 7.48−7.44 (m, 1H), 7.34−7.30 (m, 2H), 7.29−7.25 (m, 2H), 7.23−7.28 (m, 2H), 7.15−7.09 (m, 2H), 5.9 (br s, 1H), 5.04 (dd, J=5.6, 4.5 Hz, 1H), 4.82 (s, 1H), 4.5 (s, 1H), 3.29 (dd, J=14.1, 4.5 Hz, 1H), 3.23 (dd, J=14.1, 5.6 Hz, 1H), 2.57 (dd, J=12.0, 3.6 Hz, 1H), 2.54−2.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.8, 166.3, 160.9, 147.2, 144.8, 137.8, 135.3, 135.2, 134.7, 130.8, 129.6 (2C), 128.8 (2C), 127.5, 127.39, 127.35, 126.9, 126.2, 124.1, 121.5, 115.6, 85.0, 77.5, 65.6, 50.8, 39.5, 36.5; MS (ESI) *m/z*: 479 ($M+H^+$, 100%); HRMS-ESI calcd for $C_{28}H_{22}N_4O_4$: $(M+H)^+$ 479.1719, found 479.1713.

(4*S*,5a*R*,9c*R*)-4,5,5a,9c-Tetrahydro-5a-hydroxy-2,2-dimethyl-4-(4-oxo-3(4*H*)-quinazolinyl)-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (18d)

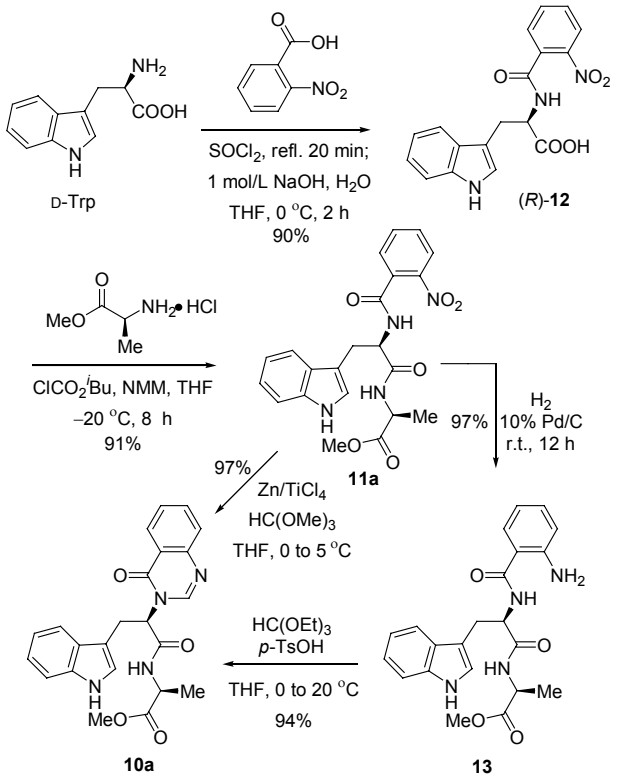
Following the procedure described for the synthesis of compound **18b**, reaction of **17d** (47 mg, 0.1 mmol) gave compound **18d** (38 mg, 0.092 mmol, yield: 92%) as a white solid. M.p. 164−167 ℃ (EtOAc); $[\alpha]_D^{20}$ +121.0 (c 1.0, THF); IR (film) ν_{max}: 3450, 2976, 1734, 1681, 1610, 1478, 1325, 1292, 1050, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16−8.11 (m, 1H), 7.77 (s, 1H), 7.75−7.69 (m, 1H), 7.65−7.60 (m, 1H), 7.57−7.53 (m, 1H), 7.47−7.42 (m, 1H), 7.38−7.33 (m, 2H), 7.17−7.12 (m, 1H), 5.50 (s, 1H), 4.99 (br s, 1H), 2.85−2.40 (m, 2H), 1.68 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.2, 165.0, 161.0, 147.3, 145.1, 139.0, 134.8, 134.7, 130.9, 127.6, 127.3, 126.8, 126.0, 124.3, 121.7, 115.6, 81.6, 77.5, 67.7, 38.8, 22.5, 21.1; MS (ESI) *m/z*: 455 ($M+K^+$, 100%). HRMS-ESI calcd for $C_{23}H_{21}N_4O_4$: $(M+H)^+$ 417.1563, found 417.1563.

Results and Discussion

Total synthesis of (−)-chaetominine (6a) from D-Trp

We first investigated the synthesis of (−)-chaetominine (**6a**) from D-Trp. The synthesis started with the aroylation of D-Trp with *o*-nitrobenzoyl chloride (THF, 0.4 N $NaHCO_3$, 0 ℃, 4 h), prepared *in situ* from *o*-nitrobenzoic acid ($SOCl_2$, reflux, 20 min), to give the aroylated product (*R*)-**12** {$[\alpha]_D^{20}$ −7.8 (c 1.1, CH_3OH)} in 80% yield (Scheme 3). The yield of (*R*)-**12** {$[\alpha]_D^{20}$ −7.7 (c 1.1, CH_3OH)} was improved to 90% by the use of 1 N NaOH (H_2O, THF, 0 ℃, 2 h). Successive treatment of compound (*R*)-**12** with *i*-BuOCOCl/*N*-methylmorpholine (NMM, THF, −20 ℃, 15 min), and L-Ala methyl ester hydrochloride salt (THF, NMM, −20 ℃, 8 h) produced the desired dipeptide derivative **11a** in 91% yield.

Scheme 3 Synthesis of quinazolinone derivative **10a**



To construct the quinazolinone ring system,[15] a two-step procedure was first investigated. The nitro group in **11a** was first reduced by catalytic hydrogenation (H_2, 1 atm, 10% Pd/C, EtOH, r.t., 12 h) to give aniline derivative **13** in 97% yield. The latter was then treated with $HC(OEt)_3$ in the presence of *p*-TsOH in THF[16] at 40 ℃ to yield the desired quinazolinone **10a**. However, partial epimerization was observed. To our delight, when the reaction was run at 0−20 ℃, epimerization could be avoided and quinazolinone **10a** was obtained in 94% yield. With the aim to develop a redox-economical total synthesis,[17] we next examined the possibility to undertake a direct synthesis of **10a** from **11a**. A one-pot reductive cyclization of *o*-nitrobenzamide and triethyl orthoformate to construct the quinazolinone ring has been developed by Shi and co-workers.[18] Following Shi's procedure, the mixture of **11a** and $HC(OMe)_3$ was treated with low-valent titanium,[19] generated *in situ* from $TiCl_4$ and Zn powder, in

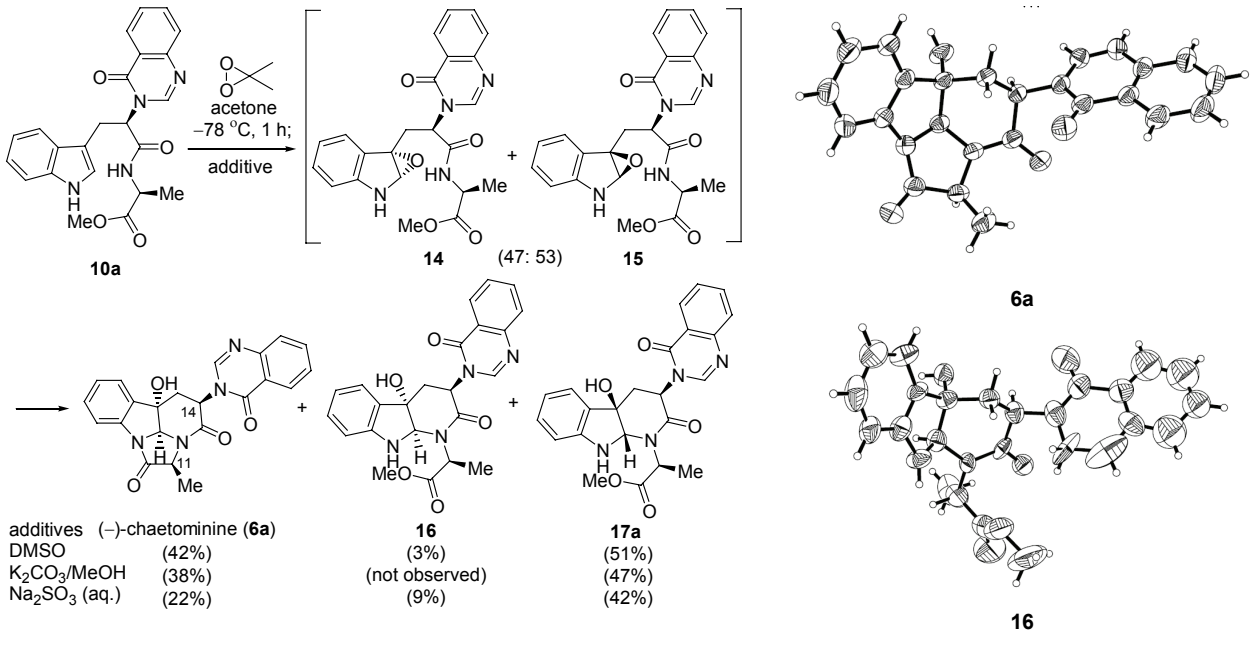
refluxing THF. The desired quinazolinone **10a** was formed, however, with considerable epimerization observed. The epimerization occurred even if the reaction temperature was lowered to r.t. Further studies showed that when running the reaction at 0—5 ℃, the desired product **10a** could be obtained in 97% yield without epimerization.

With compound **10a** in hand, we next investigated the key epoxidation-triggered tandem reaction to construct the tricyclic core of (−)-chaetominine (**6a**) (*cf.* Scheme 2). The oxidative cyclization of tryptophan derivatives leading to *β*-oxygenated pyrrolo[2,3-*b*]indole ring systems has been known for a long time.[20,21] This strategy has been used extensively in the total synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids.[22] However, to the best of our knowledge, no direct oxidative cyclization leading to the fused six-membered ring system (oxygenated piperidino[2,3-*b*]indoline) has ever been reported. Even when the formation of both five and six-membered rings were possible, five-membered ring product (pyrrolo[2,3-*b*]indole) always dominated over six-membered ring.[9,20k,23] The only solution was found in Baran's total synthesis of kapakahines,[9a,9b] where the piperidino[2,3-*b*]indoline ring system was formed ingeniously *via* a shift of topology by dynamic equilibration of the corresponding pyrroloindoline. In Rainier's total synthesis of kapakahines **E** and **F**,[9c,9d] the transformation of pyrroloindoline derivative to piperidino-[2,3-*b*]indoline ring system was proven to be much more challenging. In Evano's and Papeo's total syntheses of chaetominine,[8b,8d,8e] while piperidino[2,3-*b*]-indoline ring systems were built stereoselectively, several steps were required for further transform into the target molecules.

For the oxidation of indole,[20] the mild and green oxidant dimethyldioxirane (DMDO)[24] appeared to be promising and it was selected for the cascade reaction. Dipeptide **10a** was first treated with a freshly prepared solution of DMDO in acetone at −78 ℃ for up to 1 h (Scheme 4). However, no desired epoxidative cyclization product was obtained. It was recognized that basic conditions would be necessary to realize the tandem epoxidation-bis-cyclization reactions. In view of the easy epimerization of our substrates (*vide supra*), weakly basic conditions are preferred to avoid any epimerization during the cyclization. After considerable trials, it was found that a combination of DMDO with DMSO gave optimal results. In the event, dipeptide **10a** was treated with DMDO in acetone at −78 ℃ for 1 h, and then with CaH_2 dried DMSO, and the mixture was stirred at r.t. for 2 d to produce directly the desired (−)-chaetominine (**6a**) in 42% yield, along with a small amount of its precursor **16** (3 % yield) and an epimer of the latter (**17a**) in 51% yield.

Besides the DMDO-DMSO (CaH_2-dried) combination, many weak bases were examined. A combination of DMDO with K_2CO_3/MeOH was also effective for this tandem epoxidation-bis-cyclization reaction, which yielded (−)-chaetominine (**6a**) and compound **17a** in 38% and 47% yields, respectively. Moreover, treatment of the presumed epoxide intermediates with a saturated aqueous solution of Na_2SO_3 also yielded chaetominine (**6a**, 22% yield), its precursor **16** (9% yield) and **17a** (42% yield). The structures of (−)-chaetominine (**6a**) and its precursor **16** were confirmed by single crystal X-ray analyses (Scheme 4).[8f] The spectral data of our synthetic (−)-chaetominine (**6a**) are identical with those reported (*vide infra* for a discussion on the physical properties).[5a,8a] It is interesting that the two carbonyl groups have a *syn*-disposition in the single crystal of (−)-chaetominine (**6a**) we obtained, while they are in a *anti*-disposition in the single crystal of (−)-chaeto-

Scheme 4 Epoxidation-triggered cascade reaction leading to (−)-chaetominine (**6a**)



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minine•MeOH that Tan reported.

The formation of compound **17a** in substantial amount led us to carry out its cyclization for the synthesis of a diastereomer of (−)-chaetominine (**6a**). Compound **17a** was thus treated with NaOMe/MeOH at −10 ℃ to produce 2,3,14-tri*epi*-chaetominine **18a** in 90% yield (Scheme 5). The relative stereochemistry of **18a** was confirmed by X-ray analysis of a single crystal of **18a**•H_2O (Scheme 5, cf. Supporting Information, p. 22).[8f]

To determine the absolute stereochemistries of compounds **17a** and **18a**, compound **17a** was converted to its bromo derivative and further cyclized to give **19**. X-ray analysis of a single crystal of **19**•H_2O[8f] confirmed its absolute stereochemical structure as displayed in Scheme 5. In addition, using Marfey's method,[25,5a] the absolute configuration of the Ala residue in **17a** was determined to be *S*, identical to that in **10a**.

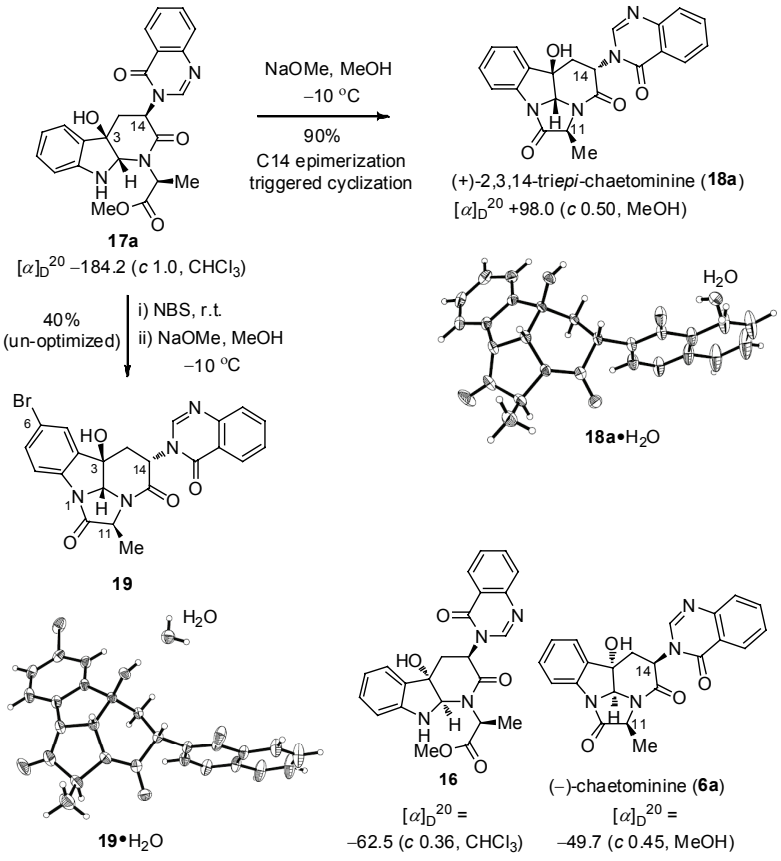
Moreover, the comparison of the optical rotation data of the precursor **16** and its lactamization product **6a** (minor difference) with those of **17a** and **18a** (significant difference in value with opposite sense) implicated that compound **18a** is a concomitantly epimerized lactamization product, instead of a simple lactamization product from **17a** (Scheme 5).

On the basis of these results, the absolute stereochemistry of **17a** was deduced as 2*R*,3*R*,11*S*,14*S*. The stereochemistries of the epoxide intermediates **14** and **15** were thus deduced as those shown in Scheme 4 and the diastereoselectivity in the epoxidation of **10a** with DMDO was determined to be 53∶47 in favor of *β*-epoxide. To improve the diastereoselectivity of the key tandem reaction, several other oxidants were examined, including Oxone, *m*CPBA, TBTH/$VO(acac)_2$,[26] NaClO,[27] as well as Salen (Mn)/DMDO[28] and Shi oxidation.[29] However, the starting material **10a** was either destroyed or remained intact in most cases. Only the latter two conditions gave **6a** and **17a** in disappointing 20%/25% yields, and 10%/13% yields, respectively.

Enantioselective syntheses of homologues and analogues of (−)-chaetominine from D-Trp

To demonstrate the flexibility of the method, the syntheses of homologues/analogues of (−)-chaetominine with different substituents at C-11 were envisioned, in view of the presence of different alkyl groups in structurally related quinazolinone-containing indole alkaloids.[2] The synthesis of (−)-chaetominine analogue incorporating an L-Leu, the residue presenting in both fumiquinazoline I (**3**) and asperlicin (**4**), was first undertaken. Following the procedures developed for the synthesis of (−)-chaetominine (**6a**), C11-*iso*-butyl analogue (**6b**) of (−)-chaetominine and its diastereomer **17b** were obtained in three and four steps, respectively, starting from D-Trp derivative (*R*)-**12** and L-leucine methyl ester hydrochloride salt (Scheme 6). The yield of each

Scheme 5 Syntheses of diastereomer and analogue of chaetominine and comparison of specific optical rotation values

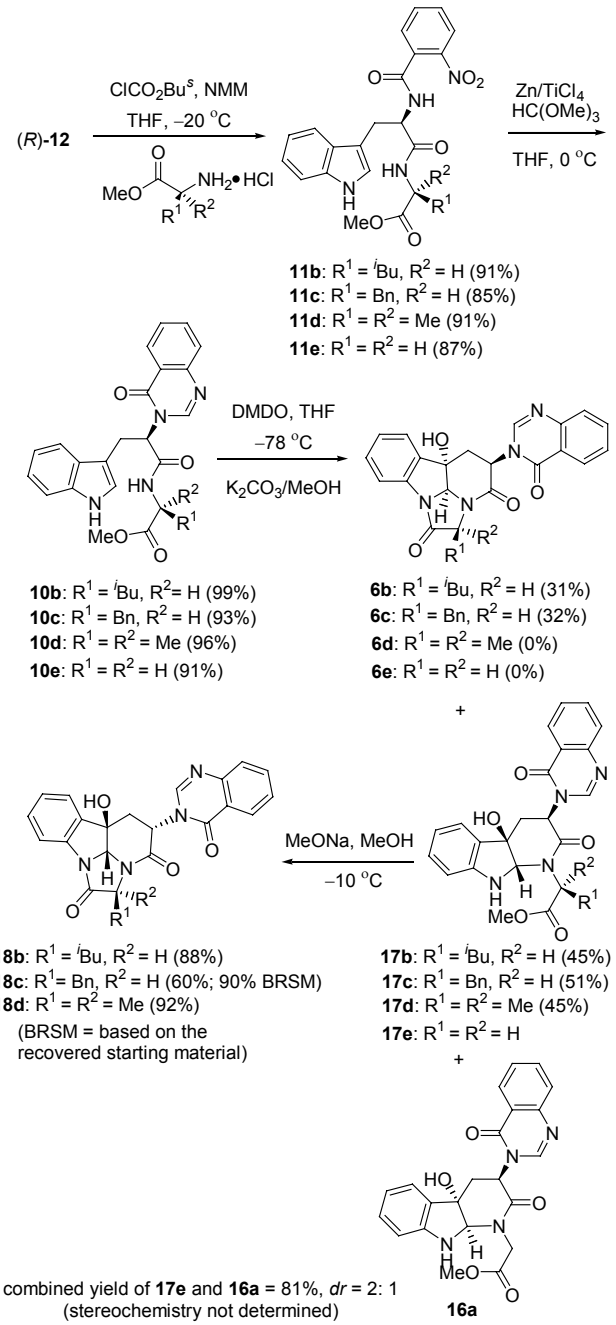


(carbon numbered according to the ring system of chaetominine)

step is comparable to that of (−)-chaetominine (**6a**) and its diastereomer **17a**. It is worth mentioning that DMDO-K_2CO_3/MeOH combination gave more reproducible results for the cascade reaction and it was used for the synthesis of (−)-chaetominine analogues. Treatment of **17b** with NaOMe led to **18b** in 88% yield.

Considering the presence of a benzyl group in kapakahines **B** and **F**,[7] the synthesis of C-11 benzyl analogue of (−)-chaetominine was next undertaken (Scheme 6). Starting from (*R*)-**12** and L-phenylalanine methyl ester hydrochloride salt, 11-benzyl analogue (**6c**) of (−)-chaetominine and its diastereomer **17c** were synthesized in four and five steps, respectively. The

Scheme 6 Syntheses of homologues/analogues of (−)-chaetominine (**6a**)



final NaOMe-mediated cyclization of **17c** afforded **18c** in 60% yield (90% based on the recovered **17c**).

The incorporation of non-proteinogenic amino acid as *gem*-dimethyl group in several quinazoline-containing indole alkaloids such as tryptoquialanine, deoxytryptoquivaline, and fiscalin C (**5**) prompted us to synthesize 11-methylchaetominine (**6d**) (Scheme 6). Starting from (*R*)-**12** and α-methylglycine methyl ester hydrochloride salt, compound **10d** was obtained in 87% overall yield over two steps. Treatment of **10d** with DMDO and K_2CO_3/MeOH produced only **17d** in 45% yield. The expected tandem cyclization product 11-methylchaetominine (**6d**) was not observed. Treatment of **17d** with NaOMe in MeOH afforded the lactamization product **18d** in 92% yield.

Enantioselective synthesis of (–)-chaetominine from L-Trp

During the synthesis of (−)-chaetominine from D-Trp, the β-epoxide **15** (and thus the diastereomer **17a**) was formed predominately from **10a** (Scheme 4). And the complete epimerization at C14 was observed during the transformations of compounds **17a** (Scheme 5) and **17b**−**17d** (Scheme 6) to **18a** and **18b**−**18d**. Taking advantages of these two results, we assumed that it is possible to develop a second generation total synthesis of (−)-chaetominine (**6a**) starting from L-Trp. To test the feasibility of our assumption, we needed to figure out which stereogenic center between C11 and C14 is determinant in the preferred β-epoxidation of **10a**. For this purpose, tripeptide derivative **10e** was synthesized (Scheme 6). Treatment of **10e** with DMDO and K_2CO_3/MeOH produced diastereomers **17e** and **16a** as an inseparable diastereomeric mixture (*dr* = 2 : 1, combined yield: 81%). Although the stereochemistries of **17e** and **16a** could not be determined, a comparison of this result with those from the epoxidation reactions of **10a**−**10d** (*dr* = 53 : 47) indicated that the asymmetric inductions of C14 and C11 are mismatch and the chirality at C14 is slightly dominant over C11 to give β-diastereoselective epoxidation products. The predominant asymmetric induction of C14 over C11 could be readily understood since the larger quinazolinonyl group at C14 situates closer to the indole ring than the methyl, isobutyl or benzyl group at C11.

In order to get further insight into the asymmetric induction of the C14, we next undertook a conformational analysis (Scheme 7). From the observed low diastereoselectivity in the epoxidation of **10x**, we assumed that the reaction passed through a product-like transition state to give the more stable β-epoxide **15x** as the major product. With the quinazolinonyl group at the axial position of the chair-like conformation, the α-epoxide **14x** is less stable, and formed as the minor product. Epoxides **15x** and **14x** are probably in equilibrium with their iminol tautomers **14xa** and **15xa**, which upon treatment with a weak base, yielded lactams **16x** and **17x**, respec-

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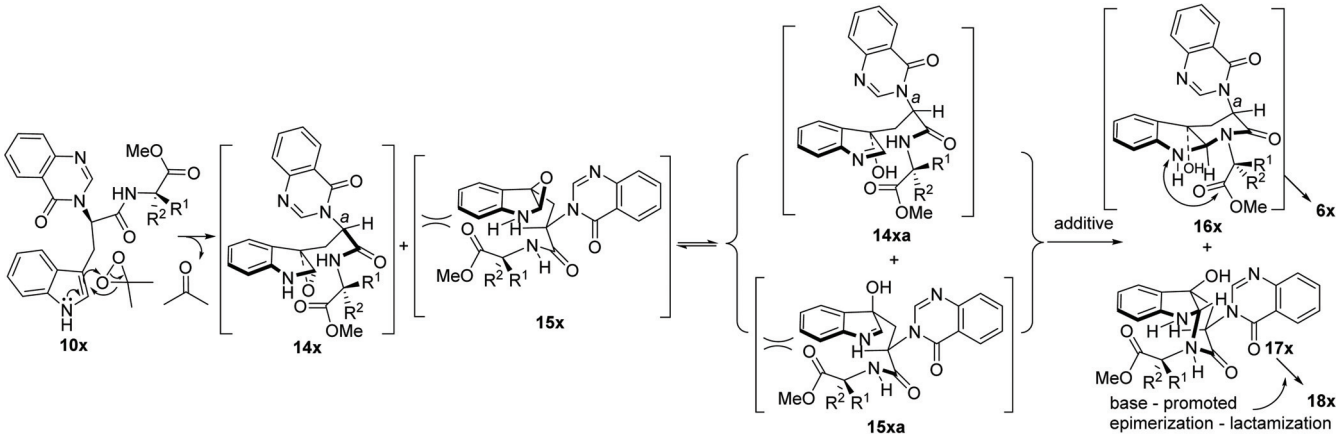
Scheme 7 Conformational analysis of the diastereoselective oxidative double cyclization of tripeptide derivative **10x**



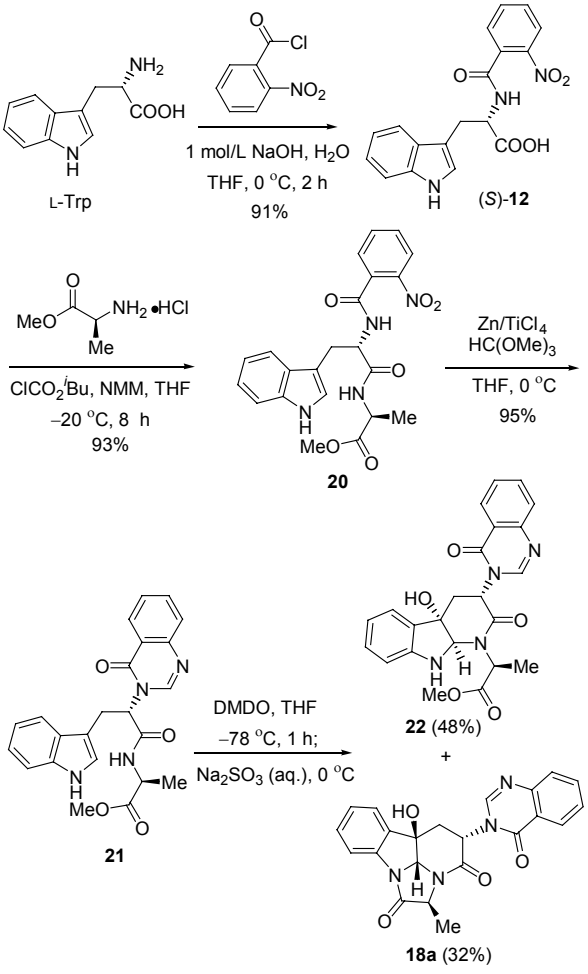
tively. Inspection of conformer **16x** and the single crystal structure of **16** (Scheme 4) revealed the indoline nitrogen is quite close to the ester carbonyl. This explains why the amino ester **16**, once formed, is prone to undergo second lactamization to give spontaneously (−)-chaetominine (**6a**). In fact, it is difficult to obtain amino ester **16** in a pure form. The equilibrium between amino ester **16** and its tautomer (−)-chaetominine (**6a**) has been investigated by Snider and Wu.[8a]

In contrast, the indoline nitrogen is far away from the ester carbonyl in **17x** (Scheme 7), which prevents a direct cyclization. A base-promoted epimerization at C14 is thus necessary for the next cyclization to **18x**.

With the asymmetric induction of the C14 confirmed, the total synthesis of (−)-chaetominine (**6a**) from L-Trp was conducted. Following the procedure described for the synthesis of quinazolinone **10a**, compound **21** was synthesized from L-Trp in three steps as shown in Scheme 8. Treatment of **21** with DMDO in THF at –78 ℃ followed by work-up with an aqueous solution of Na_2SO_3 produced the mono-cyclized product **22** in 48% yield, along with 2,3,14-tri*epi*-chaetominine (**18a**) in 32% yield.

Next the selective C14 epimerization-induced lactamization of compound **22** was conducted. To our disappointment, treatment of **22** with NaOMe in methanol at –10 ℃ yielded the bis-epimerized product (−)-11-*epi*-chaetominine **23**, the antipode of **18a**, in 82% yield (Scheme 9). Treatment of **22** with *t*-BuOK at –70 ℃ gave **23** in 50% yield. After tremendous trials, it was discovered that a 60% yield of (−)-chaetominine (together with 19% of **23**) could be obtained by treating **22** with 0.1 equiv. of DMAP in refluxing toluene for 168 h.

Scheme 8 Synthesis of compound **22** from L-Trp

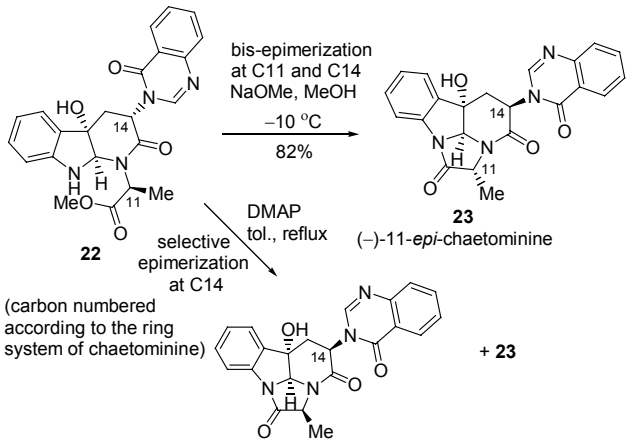


About the physical properties of (−)-chaetominine (6a)

With the rapid access to (−)-chaetominine (**6a**) secured, we were in a position to clarify the issues of its physical properties.

The optical rotation value of our synthetic (−)-chaetominine (**6a**) {$[\alpha]_D^{20}$ –49.7 (*c* 0.45, MeOH)} is in agreement with those of the synthetic ones {–49.4 (*c* 0.26, MeOH);[8a] –48 (*c* 0.45, MeOH);[8b,8e] –47.9 (*c* 0.25, MeOH)[8d]}. However all the optical rotation values of above-mentioned synthetic samples of (−)-chaetominine are different from that reported for the natural product {$[\alpha]_D^{20}$ –70 (*c* 0.48, MeOH)}.[5a] The higher optical rotation value of the natural product

Scheme 9 C14-Epimerization-triggered lactamization leading to (−)-chaetominine (**6a**) or (−)-11-*epi*-chaetominine (**23**)



	(−)-chaetominine (**6a**)	**23**
DMAP (1.0 equiv), 22 h	43% (81% BRSM)	10%
DMAP (0.5 equiv), 38.5 h	48% (63% BRSM)	28%
DMAP (0.1 equiv), 168 h	60%	19%

(BRSM = based on the recovered starting material)

might be ascribed to a contamination with some ring-opening product **16**. The interconversion between (−)-chaetominine (**6a**) and **16** in refluxing methanol has been described by Snider.[8a] To test this assumption, our synthetic (−)-chaetominine (**6a**) was dissolved in MeOH under ultrasonic conditions for 4 h then allowed standing at room temperature for 7 d. A 1.2∶1 mixture of **6a** and its ring-opening amino ester **16** is formed, which displayed an optical rotation of $\{[\alpha]_D^{20}$ −68.0 (*c* 0.45, MeOH)}, consisting with that reported for the natural product $\{[\alpha]_D^{20}$ −70 (*c* 0.48, MeOH)[5a]}. It is thus reasonable to assume that the reported higher optical rotation value for the natural (−)-chaetominine (**6a**) is caused by a contamination with the ring-opening methyl ester **16** formed during the isolation and purification.[5a]

On the other hand, our synthetic chaetominine, when collected from column chromatographic purification, exhibited a melting point of 165—167 ℃, which is comparable with those reported for the natural product (m.p.=161—163 ℃)[5a] and for the synthetic ones (162—165 ℃;[8a] 164 ℃;[8b,8e] 160—162 ℃[8d]). However, after recrystallization from EtOAc/hexane, a much higher melting point of 196—198 ℃ was recorded. More surprisingly, a sample recrystallized from MeOH gave an even higher melting point of 288—290 ℃.

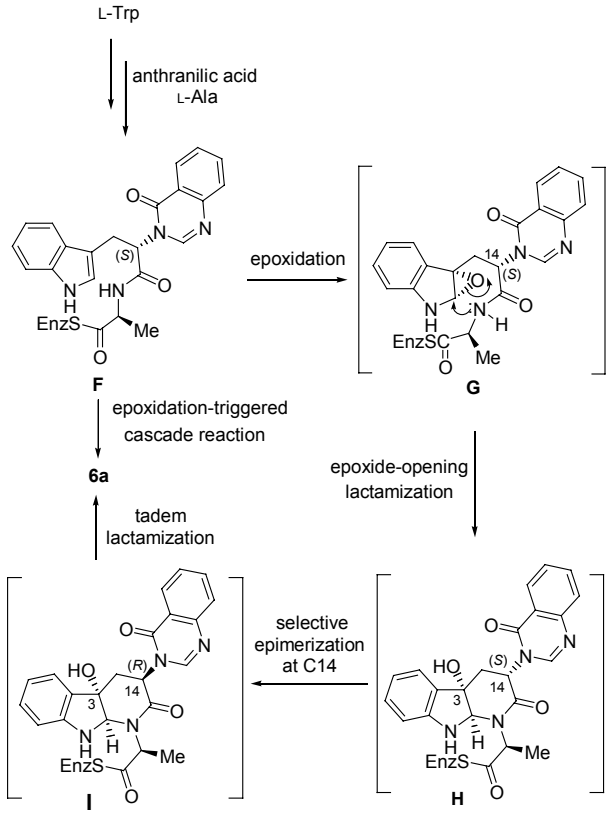
On the lactamization endgame of the total synthesis

As outlined in Schemes 4 and 8, only (−)-chaetominine (**6a**) and its diastereomer **18a** were formed from **10a** and **21** *via* the cascade reaction, while the spontaneous lactamization could not occur for **17a** and **22**, which, after epimerization at C14, could be lactamized to give (−)-chaetominine (**6a**) and its diastereomers **23** and **18a**, respectively (Schemes 9 and 5). All the synthetic (−)-chaetominine (**6a**), its diastereomers and analogues possess a *trans*-disposition between the hydroxyl group at C3 and the quinazolinonyl group at C14. It is clear that only such a *trans*-disposition favors the tandem lactamization of its precursor (*e.g.* **16**). For those having a *cis*-disposition between the substituents at C3 and C14 (*e.g.* **17a** and **22**), a base-promoted epimerization is necessary for establishing the required C3/C14 *trans*-disposition for the lactamization.

On the plausible biogenetic pathway of (−)-chaetominine (6a)

The successful syntheses of (−)-chaetominine (**6a**) from D-Trp and L-Trp in four and five steps, respectively, also chemically validate the short pathways to complexity generation revealed for the biosynthesis of fungal peptidyl alkaloids.[6a-6c] This led us to consider a plausible biosynthetic pathway of (−)-chaetominine (**6a**) on the basis of purely chemical principles. Our hypothesis is outlined in Scheme 10, which involves three key elements: (1) the direct use of L-Trp as a staring material for the formation of the tripeptide derivative **F**; (2) the epoxidation-triggered lactamization for the conversion of intermediate **F** to **G**, then to **H**; (3) the selective epimerization at C14 of the intermediate **H** for the subsequent tandem lactamization to produce (−)-chaetominine (**6a**). Although the epoxidation proceeded with low diastereoselectivity in our synthesis, it is reasonable to assume that this biogenetic route could run with high stereoselectivity with the sophisticated enzyme system.[30]

Scheme 10 A plausible biosynthetic pathway of (−)-chaetominine suggested on the basis of chemical syntheses



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Conclusions

In summary, we have disclosed two bio-inspired but non-biomimetic concise total syntheses of (−)-chaetominine (**6a**), its analogues and diastereomers. The first one, starting from D-Trp, L-alanine methyl ester and *o*-nitrobenzoic acid, has been achieved in four steps with an overall yield of 31.5%. The second approach used, for the first time, L-Trp as a starting material, which led to (−)-chaetominine (**6a**) with an overall yield of 23.2% in five steps. Using these efficient routes, several analogues and diastereomers of chaetominine have been synthesized. Through this work, the ambiguity about the optical rotation value and the melting point of (−)-chaetominine (**6a**) have been clarified. More importantly, our synthetic routes, which feature a cascade epoxidation-double cyclization reaction as the key step, provide a new example of step-economical, redox-economical and protecting-group-free syntheses of complex natural products. The synthesis also serves as a good example of complexity generation in short pathways by chemical synthesis. On the basis of chemical evidences gained during our investigations, a more plausible biosynthetic approach to (−)-chaetominine (**6a**) has been proposed, which is also significant for understanding the biosyntheses of other fungal peptidyl alkaloids.

Acknowledgement

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