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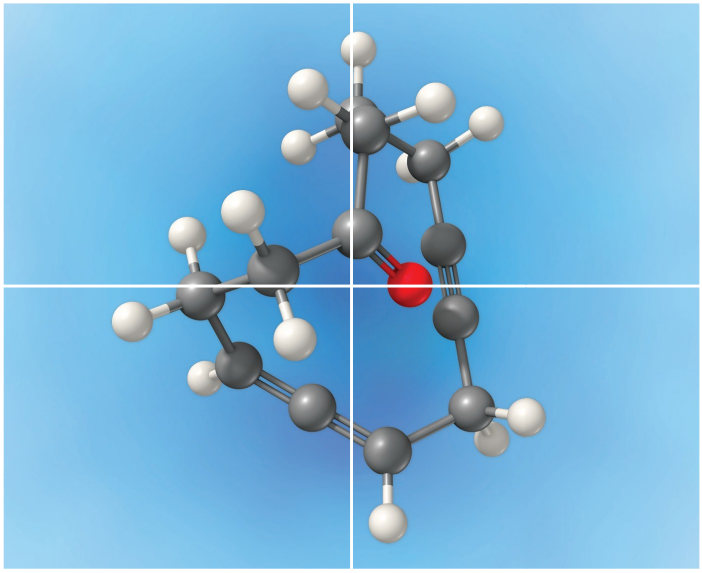

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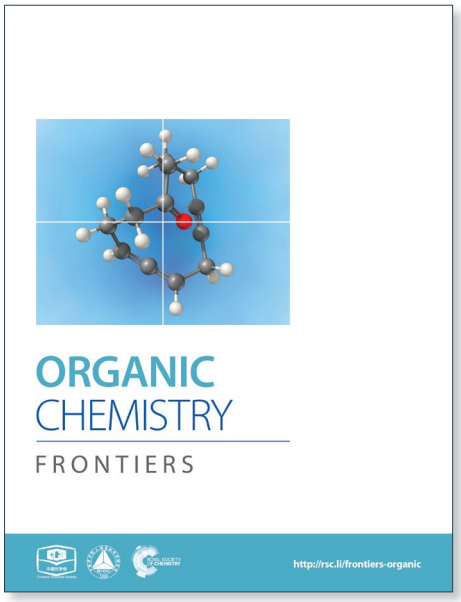

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ARTICLE TYPE

Stereodivergent and Enantioselective Total Syntheses of Isochaetominines A–C and Four Pairs of Isochaetominine C Enantiomers: A Six-Step Approach

Zhong-Yi Mao,[a] Hui Geng,[a] Tian-Tian Zhang,[a] Yuan-Ping Ruan,[a] Jian-Liang Ye,[a] and Pei-Qiang Huang*[a,b]

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The first enantioselective and stereodivergent total syntheses of (–)-isochaetominines A–C and all eight 2,3-*cis*-stereoisomers of (–)-isochaetominine C, including the natural (+)-14-*epi*-isochaetominine C, and the proposed structures of (–)-pseudofischerine (**2**) and (–)-aniquinazoline D (**3**), have been achieved. The stereodivergent approach relies on the DMDO-initiated divergent tandem reaction to give a separable mixture of two products, a monocyclization product and a diastereomer of isochaetominine C (or a homologue) as a result of double cyclization. An epimerization-free two-step protocol has been developed for the highly diastereoselective transformation of the former product into isochaetominine-type compound with characteristic 3,14-*cis*-stereochemistry. As a result of our synthetic efforts, the structures of the natural (–)-pseudofischerine and (–)-aniquinazoline D have been revised both as (–)-isochaetominine C (**6**).

Introduction

The traditional total synthesis of natural products is target-oriented synthesis (TOS).[1] In this context, a synthetic route is designed for a specific target molecule with defined skeleton, functionality and stereochemistry.[2] Many natural products co-exist with their diastereomers.[3] Under this circumstance, the total synthesis becomes the construction of multiple diastereomeric targets (MDTS). The efficient access to different diastereomers of a natural product and/or bioactive molecule possessing multi-stereocenters is imperative for both structure confirmation[4] and the study of structure-activity-relationship.[5] Traditional approaches to synthesize different enantioenriched diastereomers of a natural product frequently require the use of different starting materials and/or synthetic routes.[6] In addition, not all diastereomers are accessible by a certain method.[6] The stereodivergent synthesis[7] have been evolved as an efficient approach to access different naturally occurring diastereomers of natural products.[8] Among many approaches[4-9] that have been developed for the stereodivergent synthesis, the strategy based on the non-selective reactions has attracted less attention.[9]

Non-selective reactions that produce two or more isomeric products in about equal amounts are generally considered to be useless in organic synthesis. However, by carefully planning, the employment of a non-selective reaction in a synthetic route may lead to an efficient stereodivergent approach for the multiple diastereomeric targets synthesis (MDTS). For example, if the isomers produced in a non-selective reaction can all be used for the synthesis of different diastereomers of a target, a non-selective reaction becomes advantageous for stereodivergent synthesis. However, the success of such a strategy depends on the efficient separation of the isomers, which is also true for other stereodivergent strategies. It is desirable that a non-selective reaction produces quasi-equal amount of isomers, which is important for both the determination of stereochemistry of natural products[4] and the synthesis of stereodiversified libraries.[5]

Endophytic fungi have emerged as a rich source of bioactive natural products.[10] As a typical example, chaetominine-type alkaloids shows interesting stereochemical and substituent diversity. The first member, (–)-chaetominine[11] (**1**, Fig. 1) was first isolated from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves,[11a] and then from different endophytic fungi.[11b-c] After the first isolation by Tan *et al.* in 2006,[11a] several homologues and diastereomers of (–)-chaetominine have been isolated from different fungi, and

[a] *Department of Chemistry, Fujian Provincial Key Laboratory of Chemical Biology, iChEM (Collaborative Innovation Center of Chemistry for Energy Materials), College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China*
[b] *State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China*
E-mail: pqhuang@xmu.edu.cn

† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra of all reduction products^{1}H and ^{13}C NMR spectra of all new products, Chiral HPLC diagrams of compounds **3**, **6**, **7**, **8**, *ent*-**3**, *ent*-**6**, *ent*-**7** and *ent*-**8**, Crystallographic structure files for **3** and **7** (CIF). This material is available free of charge via xxx. See DOI: 10.1039/b000000x/

characterized as (–)-pseudofischerine (**2**),[12] (–)-aniquinazoline D (**3**),[13] (–)-isochaetominines A–C (**4**–**6**),[14] and (+)-14-*epi*-isochaetominine C (**7**),[14] respectively. Thus, except 11-*epi*-isochaetominine C (**8**), all other 2,3-*cis*-diastereomers of isochaetominine C (**6**) have been reported to be natural products, each as an enantiomer. Moreover, the key structural feature of 14-*epi*-isochaetominine C (**7**) is also found in kapakahines [e.g. kapakahines B, F (**9**, **10**)], a group of cyclic peptides isolated from the marine sponge *Cribrochalina olemda*.[15]

This group of quinazolinone alkaloids[16] feature the same singular hexacyclic structure and differ from each other on the stereochemistry and/or the substituent at C-11. The unprecedented framework makes chaetominine an idea target for exploring novel synthetic strategies,[17] which has resulted in several elegant approaches.[18] However, up to date, only the total syntheses of (–)-chaetominine (**1**) have been reported[18] and synthetic studies on other members of isochaetominine-type alkaloids (**2**–**7**) have not appeared.

In connection with our longstanding interests in the development of procedure-economical methodologies for the synthesis of bioactive alkaloids,[19] we have disclosed recently a four-step enantioselective total synthesis of (–)-chaetominine (**1**).[18c,f-h] We report herein the stereodivergent total synthesis of all of the eight

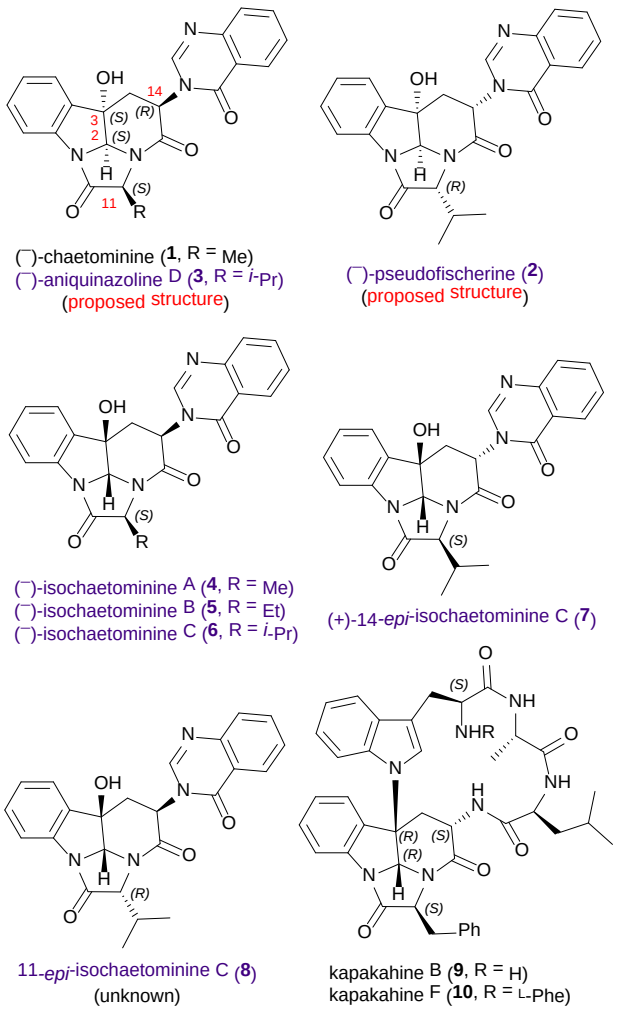


Fig.1 Structures of isochaetominine-type alkaloids and related compounds

2,3-*cis*-diastereoisomers/ enantiomers of isochaetominine C (**6**), and its congeners isochaetominines A and B (**4** and **5**).

In view of the diastereo- and substituent-diversity of the isochaetominine-type alkaloids, it is highly desirable to develop a unified strategy that is accessible to all the eight 2,3-*cis*-diastereomers/ enantiomers. In our previous approach to (–)-chaetominine (**1**),[18c,f-h] the key epoxidation-triggered tandem cyclization reaction yielded two products as a result of non-stereoselective epoxidation. Although the non-selective reaction is unfavorable for the purpose of the TOS of **1**, it offers an opportunity to develop an efficient diastereodivergent approach to all the reported 2,3-*cis*-diastereomers of isochaetominine-type alkaloids (**2**–**7**).

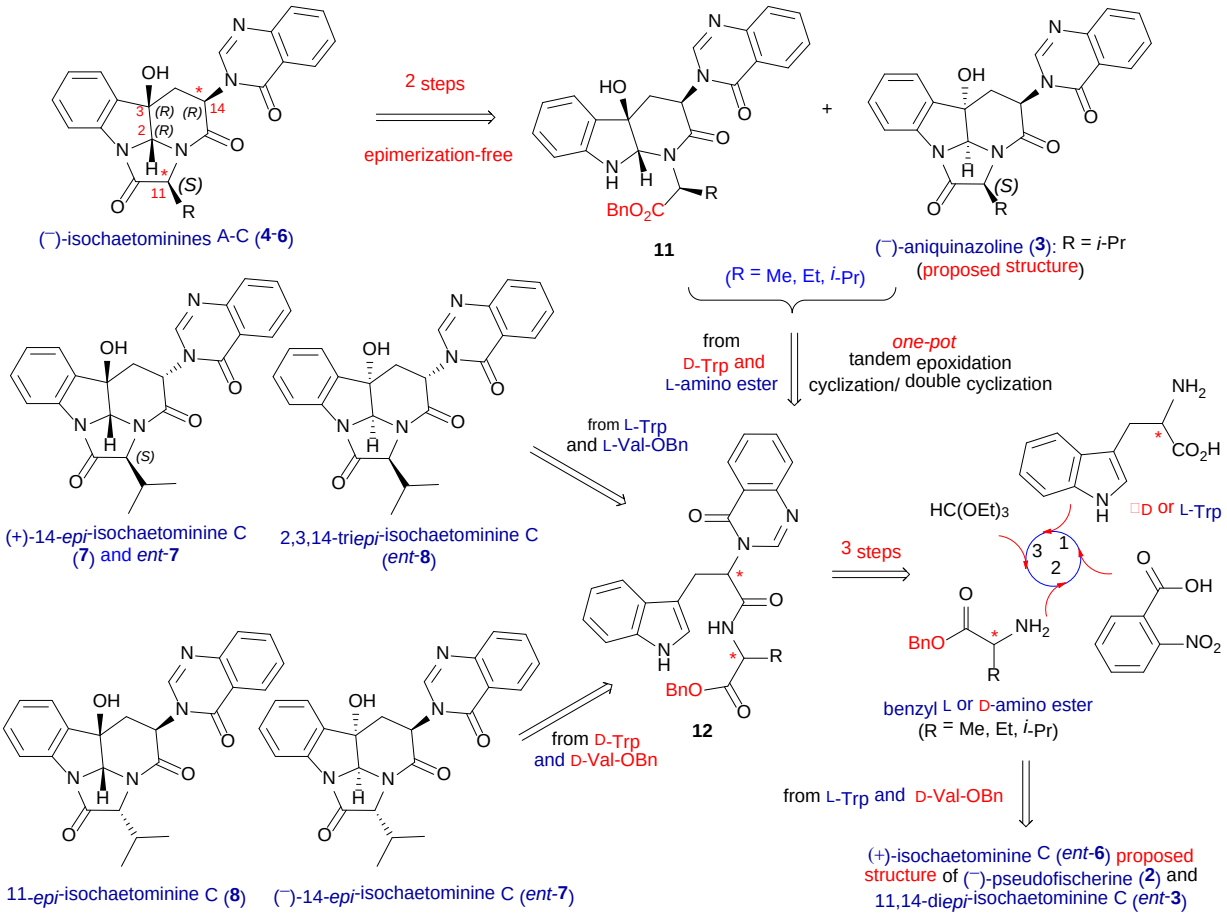
Results and discussion

On the basis of our previous strategy for the synthesis of (–)-chaetominine (**1**),[18c,f-h] the retrosynthetic analysis of isochaetominine-type alkaloids (**2**–**7**) is proposed and shown in Scheme 1. The key element of our strategy resided in the non-diastereoselective epoxidation of the easily available quinazolinonyl dipeptide **12** (from D-Trp and L-Ala) to give two diastereomeric epoxides (no shown). The α-epoxide is expected to convert spontaneously to the proposed structure of aniquinazoline D (**3**) when R is the isopropyl group, while the β-epoxide will form the monocyclization product **11**. Compound **11** is an ideal precursor for isochaetominines A–C (**4**–**6**). A similar route may be employed for the synthesis of (–)-pseudofischerine (**2**) from L-Trp and D-Ala. Finally, the syntheses of (+)-14-*epi*-isochaetominine C (**7**) would be realizable by the combination of L-Trp with L-Val or L-Ala. It is worth noting that the syntheses of (–)-pseudofischerine and (+)-14-*epi*-isochaetominine C will also afford other diastereomers 2,3,14-tri*epi*-isochaetominine C (*ent*-**8**) and 11,14-di*epi*-isochaetominine C (*ent*-**3**). In addition, the D-Trp and D-Ala combination would provide an access to the hitherto unknown enantiomers (–)-14-*epi*-isochaetominine C (*ent*-**7**) and 11-*epi*-isochaetominine C (**8**).

Previous results gained from our synthesis of (–)-chaetominine (**1**) revealed that only when the hydroxyl group at C-3 and the quinazolinonyl group at C-14 are *anti*-disposed can the final lactamization occur spontaneously. In addition, the stereocenter at C-14 is prone to epimerization.[18f-h] In a related work, Roche and Tréguier observed during the synthesis of *N*-Phth-Trp-Phe-OC_6F_5 that racemization/epimerization was unavoidable.[18i] Because of this problem, they had to use a 1:1 epimeric mixture of *N*-Phth-Trp-Phe-OC_6F_5 in their synthetic efforts to 2-fluoro-chaetominine. The subsequent Selectfluor-triggered double annulative cascade reaction resulted in the formation of the tetracyclic core as a mixture of four diastereomers in a ratio of 2:1:1:4 (combined yield: 42%), from which the overall C3-C14 *cis*/*trans* ratio was 5:3.[18i] Hence, the epimerization-free stereoselective formation of the 3,14-*cis*-stereochemistry found in (–)-pseudofischerine (**2**) and (–)-isochaetominines A–C (**4**–**6**) is challenging. To tackle the epimerization problem, the imidazolinone ring was envisioned to be formed from the corresponding carboxylic acid under mild conditions using a racemization-free peptide coupling reagent.[20,21] Thus benzyl valinate was selected as an amino acid component on hoping to cleave the benzyl group under epimerization-free conditions at a

later stage.

We started our investigation by developing a diastereodivergent synthesis of the proposed structure of (–)-aniquinazoline D (**3**) and (–)-isochaetominine C (**6**). (–)-Aniquinazoline D (**3**) was isolated by Wang *et al* from the culture of *Aspergillus nidulans* MA-143, an endophytic fungus obtained from the leaves of marine mangrove plant *Rhizophora stylosa*.[13] The relative stereochemistry was determined by NOESY technique, while the absolute configuration of C-11 was elucidated by Marfey's method, which led them to assume the absolute configuration of (–)-aniquinazoline D (**3**) as 2*S*,3*S*,11*S*,14*R*. The authors also showed that aniquinazoline D exhibited potent lethality against brine shrimp (LD_{50} = 3.42 μM), much more effective than the positive control colchicine (LD_{50} = 88.4 μM). (–)-Isochaetominines A–C (**4**–**6**) and (+)-14-*epi*-isochaetominine C (**7**) were isolated very recently by Oh, Shin and co-workers from the solid-substrate culture of an *Aspergillus* sp. fungus collected from marine-submerged decaying wood from Korea.[14] These alkaloids showed weak inhibition against Na^+/K^+-ATPase (IC_{50} = 78, 20, 38, and 57 μM, respectively).



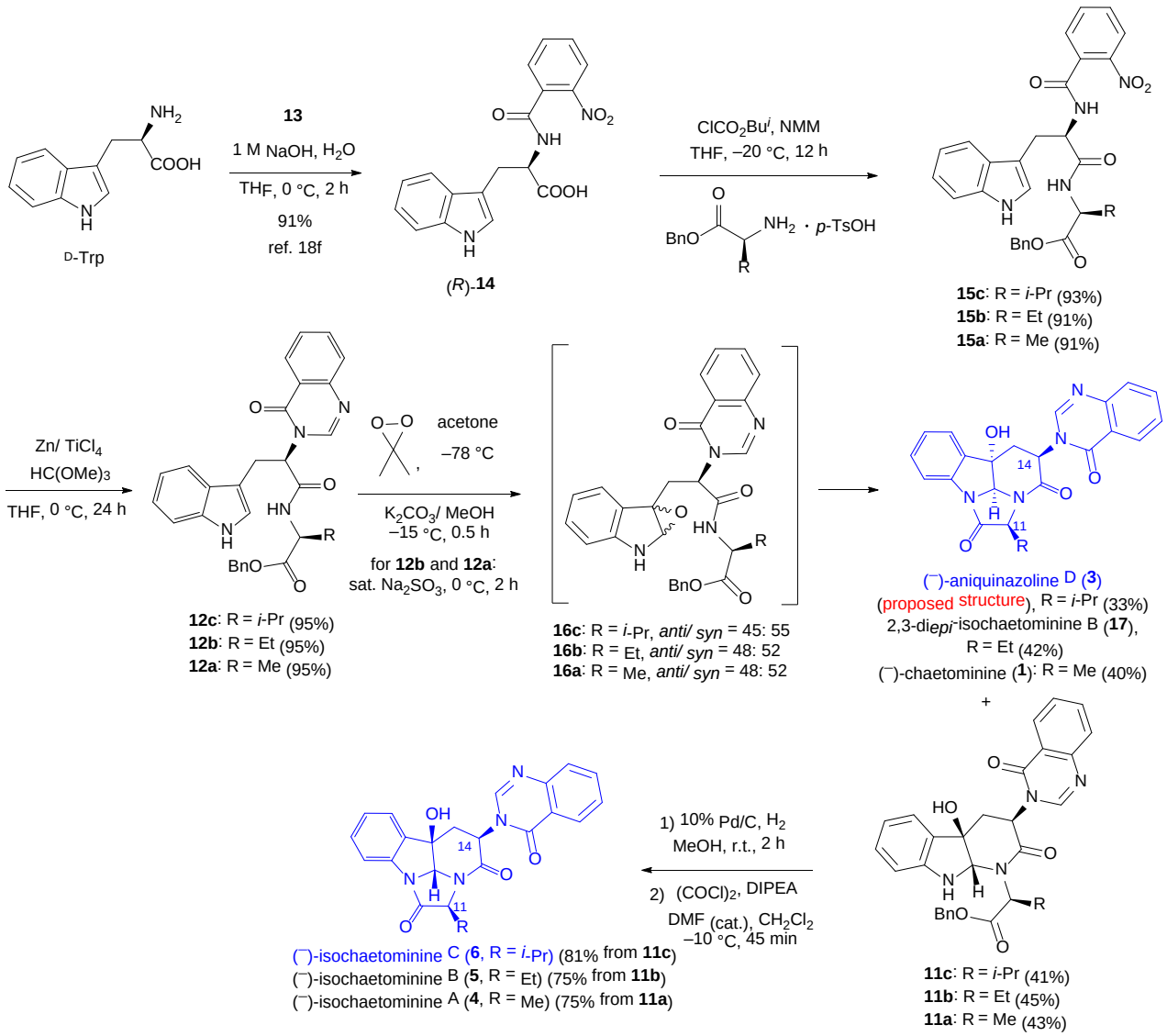
Scheme 1 Retrosynthetic analysis of all eight 2,3-*cis*-stereoisomers of (–)-isochaetominine C and (–)-isochaetominines A, B.

The synthesis started from *N*-aroylation of D-tryptophan (Trp) (o-nitrobenzoyl chloride, THF, 1 M NaOH, 0 °C, 2 h)[18f] (Scheme 2). Coupling of the resulting (*R*)-**14** with benzyl L-valinate *p*-toluenesulfonic acid salt [*i*-BuOCOCl/*N*-methylmorpholine (NMM), THF, 20 °C, 12 h] produced the dipeptide derivative **15c** in 93% yield. Treatment of **15c** with Zn/$TiCl_4$ and trimethyl orthoformate in THF[22] at 0 °C[18f] afforded quinazolinone derivative **12c** in 95% yield. We next carried out the key oxidative cyclization of **12c**. Thus, epoxidation of **12c** with dimethyldioxirane (DMDO)[23] in acetone at –78 °C, followed by treatment of the resulting sensitive epoxide intermediates *anti*-**16c** and *syn*-**16c** with K_2CO_3 in MeOH at –15 °C, produced the proposed structure of (–)-aniquinazoline D (**3**) in 33% yield and the monocyclization product **11c** in 41% yield. With **11c** in hand, we were in a position to close the last ring to form **6**. Since **11c** is prone to epimerization because of the *cis*-stereochemistry of the OH group at C-3 and the quinazolinonyl group at C-14, a careful selection of reaction conditions for the subsequent transformations is required.[18f-h] Pleasingly, removal of the benzyl group of **11c** under catalytic hydrogenation conditions (H_2, 10% Pd/ C, MeOH, r.t., 2 h) and subsequent lactam formation using Ye's coupling reagent (DEPBT)[21] led to the formation of isochaetominine C (**6**) in 77% yield without noticeable epimerization. Interestingly, the cyclization could also be promoted using oxalyl chloride-Hünig base (DIPEA) and a catalytic amount of DMF[24] (CH_2Cl_2, –10 °C). The spectral data (^1H and ^{13}C NMR) and the sign of the optical rotation of our synthetic product are in full agreement with those reported for the natural product. However, our product, obtained in high purity as colorless crystals (m.p. 166-168 °C), displayed a lower value of

specific rotation {$[\alpha]_D^{25}$ –71.0 (*c* 1.0, MeOH)} compared with that reported for the natural product {$[\alpha]_D^{25}$ –90 (*c* 0.6, MeOH)[14]}. These differences could be attributed to the minute quantities isolated from the natural source (pale yellow amorphous solid, no m.p. data reported) and relatively low purity of the isolated sample as indicated by the reported ^{1}H and ^{13}C NMR spectra.[14]

A careful comparison of the ^{1}H and ^{13}C NMR data of our synthetic **3** with those reported for the natural (–)-aniquinazoline D showed that they are different. The structure of our synthetic product **3** {colorless crystals, m.p. 302–303 °C; $[\alpha]_D^{25}$ –50.7 (*c* 0.5, MeOH)} was confirmed by single-crystal X-ray diffraction analysis (Figure 2). Thus, the structure assigned by Wang *et al*[13] for natural (–)-aniquinazoline D is incorrect. Interestingly, the ^{1}H and ^{13}C NMR data of natural (–)-aniquinazoline D fully matched those of both natural[14] and our synthetic (–)-isochaetominine C (**6**) although the value of specific rotation are different {(–)-aniquinazoline D: yellowish solid, $[\alpha]_D^{20}$ –33 (*c* 0.37, MeOH);[13] (–)-isochaetominine C (**6**): $[\alpha]_D^{25}$ –90 (*c* 0.6, MeOH)[14]}. *Based on these results, we concluded that the structure of the natural (–)-aniquinazoline D should be revised as that shown for (–)-isochaetominine C (**6**).*

With the mild epimerization-free route established for the synthesis of isochaetominine C (**6**), we finished the syntheses of isochaetominines B and A (**4** and **5**) by following a similar five-step synthetic sequence (Scheme 2). Thus, by substituting the benzyl L-valinate *p*-toluenesulfonic acid salt with its ethyl or methyl homologue, 2,3-di*epi*-isochaetominine B (**17**), isochaetominine B (**5**), chaetominine (**1**), and isochaetominine A (**4**) were obtained without incidents as colorless crystals (m.p., **17**: 302–304 °C; **5**: 173–175 °C; **1**: 301–302 °C; **4**: 184–186 °C). The spectral data (^{1}H and ^{13}C NMR) and the sign of the specific rotation of our synthetic products fully matched those reported for the natural products. As in the cases of isochaetominine C, our synthetic product **5** {$[\alpha]_D^{25}$ –49.0 (*c* 1.0, MeOH)} and **4** {$[\alpha]_D^{25}$ –23.0 (*c* 1.0, MeOH)} displayed a lower value of specific rotation compared with the corresponding value reported for the natural isochaetominine B (**5**) {$[\alpha]_D^{25}$ –73 (*c* 0.6, MeOH)[14]} and isochaetominine A (**4**) {$[\alpha]_D^{25}$ –63 (*c* 0.5, MeOH)[14]}, respectively. Once again, such differences are probably caused by the relatively low purity of the isolated samples.



Scheme 2 Diastereodivergent syntheses of (–)-isochaetominines A–C (**4**–**6**) and the proposed structure of (–)-aniquinazoline D (**2**).

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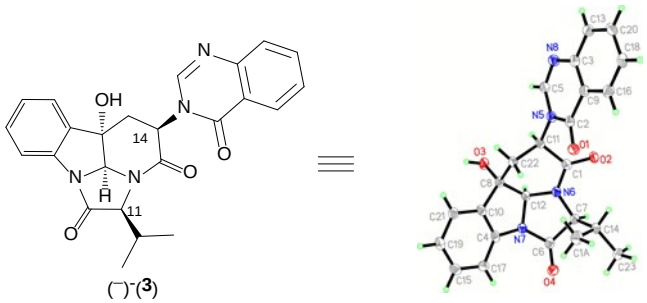
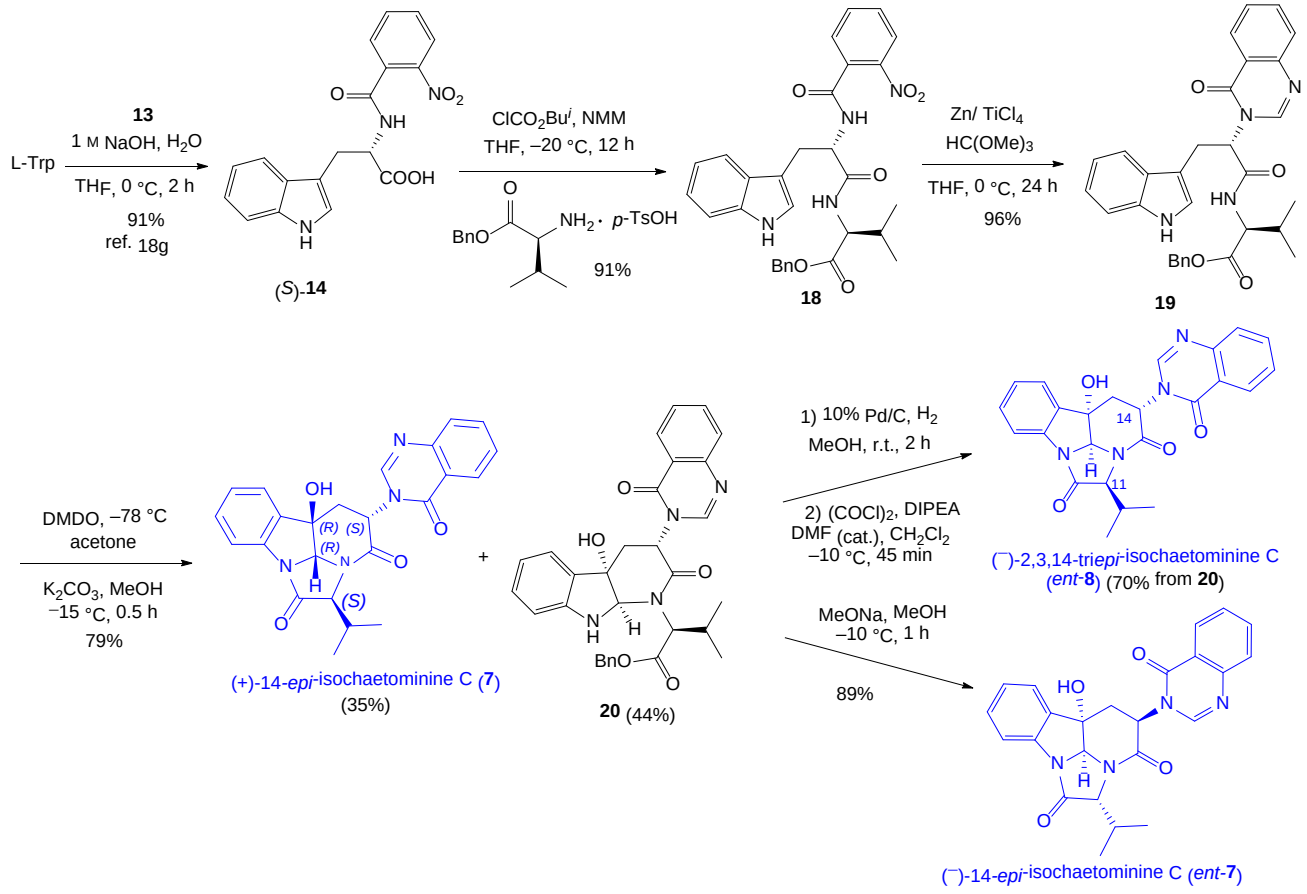


Fig. 2 X-ray crystal structure of synthetic (–)-**3**.

To further demonstrate the versatility of our stereodivergent strategy, we turned to investigate the enantiodivergent synthesis of 14-*epi*-isochaetominine C **7** and *ent*-**7**, as well as 2,3,14-tri*epi*-isochaetominine C (*ent*-**8**). To this end, natural L-Trp was *o*-nitrobenzoylated[18g] and the resulting L-Trp-derivative (*S*)-**14** was coupled with benzyl L-valinate *p*-toluenesulfonic acid salt to give **18** in 91% yield (Scheme 3). The LVT-promoted reductive condensation of **18** with trimethyl orthoformate in THF at 0 °C provided quinazolinone **19** in 96% yield. Epoxidation of **19** with DMDO followed by work-up with K_2CO_3/MeOH at –15 °C afforded the double cyclization product (+)-14-*epi*-isochaetominine C (**7**) in 35% yield along with the monocyclization product **20** in 44% yield. The structure of our synthetic product **7** {colorless crystals, m.p. 323-325 °C; $[\alpha]_D^{25}$ +48.0 (*c* 1.0, MeOH); Lit.[14] $[\alpha]_D^{25}$ +33 (*c* 0.7, MeOH)} was confirmed by single-crystal X-ray diffraction analysis (Fig. 3). The spectral (^{1}H and ^{13}C NMR) data and the sign of specific rotation of our synthetic product matched those reported for the natural product.

Debenzylation of **20** followed by cyclization led to 2,3,14-tri*epi*-isochaetominine C (*ent*-**8**) in 70% yield over two steps. On the other hand, treatment of **20** with MeONa / MeOH at –10 °C for 1 h led to bis-epimerization at C-11 and C-14 and cyclization affording *ent*-**7** in 89% yield. This approach thus constitutes an enantio- and diastereo-divergent synthesis of three diastereomers/enantiomers of isochaetominine C.



Scheme 3 Enantio- and diastereo-divergent synthesis of (+)-14-*epi*-isochaetominine (**7**), *ent*-**7**, and 2,3,14-tri*epi*-isochaetominine C (*ent*-**8**).

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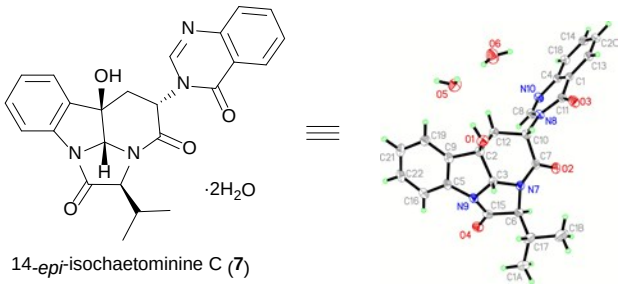


14-*epi*-isochaetominine C (**7**)

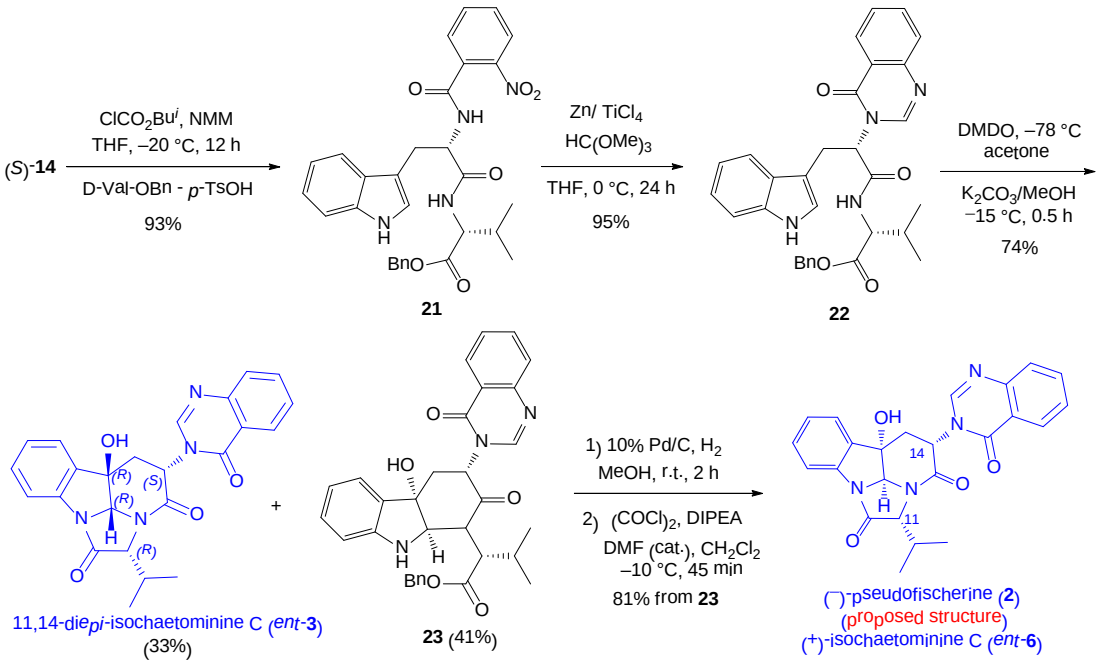
Figure 3 X-ray crystal structure of synthetic (+)-14-*epi*-isochaetominine C·2H_2O.

We next turned out attention to (–)-pseudofischerine (**2**), which was isolated from a culture of the fungus *Neosartorya pseudofischeri* S. W. Peterson obtained from agricultural soil collected in Thailand.[12] Although the absolute configuration has not been determined experimentally, the authors suggested that it was the one shown in Figure 1 and proposed that **2** was biosynthesized from L-tryptophan, anthranilic acid, and D-valine. The synthesis commenced with the preparation of dipeptide derivative **22** from L-Trp and D-Val-OBn (Scheme 4). The DMDO-initiated tandem reaction of **22** produced 11,14-di*epi*-isochaetominine C (*ent*-**3**) in 33% yield, along with **23** in 41% yield. Successive debenzylation and cyclization of **23** yielded the structure proposed for (–)-pseudofischerine (**2**), namely, the antipode of the alkaloid isochaetominine C (*ent*-**6**), in 81% yield.

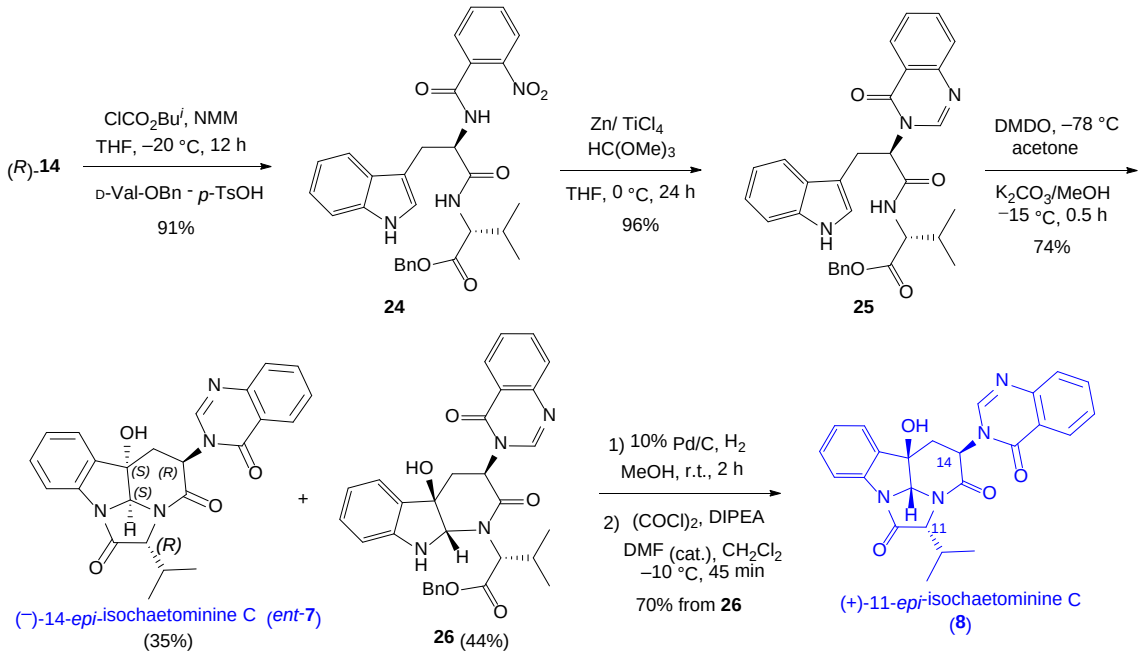
The ^{1}H and ^{13}C NMR data of our synthetic compound **2** are identical with those reported for (–)-pseudofischerine as well as isochaetominine C (**6**). However, the sign and magnitude of the specific rotation of our synthetic product {**2**: $[\alpha]_D^{20}$ +76.8 (*c* 1.0, $CHCl_3$)} are different from those reported for the natural (–)-pseudofischerine {$[\alpha]_D^{20}$ –16.9 (*c* 0.18, $CHCl_3$)}.[12] Because the reported optical rotation data of natural (–)-pseudofischerine and natural (–)-isochaetominine C (**6**) have been recorded in different solvents, which prevents a direct comparison of those data to determine their enantiomeric relationship. To clarify this issue, we measured the optical rotations of our two synthetic enantiomers **2** (*ent*-**6**) and **6** in both MeOH and $CHCl_3$ {**2**: {$[\alpha]_D^{25}$ +71.0 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ +76.8 (*c* 1.0, $CHCl_3$); **6**: $[\alpha]_D^{25}$ –71.0 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ –76.8 (*c* 1.0, $CHCl_3$); natural isochaetominine C (**6**): $[\alpha]_D^{25}$ –90 (*c* 0.6, MeOH)[14]}. *These results allowed us to conclude that natural (–)-pseudofischerine and (–)-isochaetominine C (6) are the same, namely, the structure of (–)-pseudofischerine should be revised to that shown for (–)-isochaetominine C (6).*

Finally, the D-Trp - D-Val-OBn combination was investigated leading to synthesis of (–)-14-*epi*-isochaetominine C (*ent*-**7**) and (+)-11-*epi*-isochaetominine C (**8**) in three and five steps respectively (Scheme 5) from the same tryptophan derivative (*R*)-**14**.

Since the magnitudes of specific rotation of all our synthetic



Scheme 4 Diastereodivergent synthesis of 11,14-di*epi*-isochaetominine C (*ent*-**3**) and the proposed structure of (–)-pseudofischerine (**2**).



Scheme 5 Diastereodivergent synthesis of (–)-14-*epi*-isochaetominine C (*ent*-**7**) and (+)-11-*epi*-isochaetominine C (**8**).

products are significant different from those reported for the natural products, it was necessary to determine the enantiopurities of the synthetic samples. HPLC analyses on a chiral stationary phase (see the Electronic Supplementary Information) of (–)-isochaetominine A (**6**), (+)-14-*epi*-isochaetominine C (**7**), the proposed structures of (–)-pseudofischerine (**2** = *ent*-**6**) and (–)-aniquinazoline D (**3**), unnatural diastereomer 11-*epi*-isochaetominine C (**8**), *ent*-**3**, *ent*-**7**, and *ent*-**8**, showed that the enantiomeric excesses of all compounds are >99%.

Conclusion

In summary, a unified strategy has been developed for the highly enantioselective total syntheses of the proposed structures of (–)-pseudofischerine (**2**) and (–)-aniquinazoline D (**3**), (–)-isochaetominines A–C (**4**–**6**), (+)-14-*epi*-isochaetominine C (**7**), as well as other four hitherto unknown stereoisomers of isochaetominine C. The non-diastereoselective epoxidation reaction led to the formation of two diastereomers for each of the six-step synthetic sequence. In addition, in combination with a regioselective epimerization reaction, three diastereomers were obtained in a seven-step route. All eight 2,3-*cis*-stereoisomers of (–)-isochaetominine C have been synthesized from the combination of four amino acids/ esters, D-Trp, L-Trp, L-Val-OBn, and D-Val-OBn. The sensitive 3,14-*cis*-stereochemistry of isochaetominines A–C has been established through the use of a mild and epimerization-free protocol involving the use of benzyl α-amino esters (e.g. Val-OBn) and a lactamization reaction. It is worth noting that Ye's peptide coupling reagent afforded advantages of operational simplicity in the lactamization step. Importantly, the structures of natural (–)-pseudofischerine (**2**) and (–)-aniquinazoline D (**3**) have been revised both to (–)-isochaetominine C (**6**) based on our synthetic efforts. Although neither (+)-11-*epi*-isochaetominine C (**8**) nor its antipode *ent*-**8** has been isolated from natural source, the ready availability of both **8** and *ent*-**8** by chemical synthesis allowed assuming that an enantiomer of 11-*epi*-isochaetominine C be a natural product. Finally, our strategy for the synthesis of 14-*epi*-isochaetominine C (**7**) could serve as inspiration for the development of efficient enantioselective synthesis of the structurally related natural products such as kapakahines B and F[25] (**9** and **10**).

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 or Bruker 500 (^{1}H/ 400 or 500 MHz, ^{13}C/ 100 or 125 MHz) spectrometer. Chemical shifts are expressed in parts per million (δ) relative to an internal standard of residual chloroform (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Data for ^{1}H NMR are reported as chemical shift (multiplicity, coupling constant, number of proton). ESI-Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter or an Anton Paar MCP 500 polarimeter. Melting points were determined on a Büchi M560 Automatic Melting Point apparatus. Infrared spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer using film or KBr pellet technique.

Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl-acetate/ petroleum ether (PE) (60-90 °C) mixture. THF was distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

General Procedure for the Step 1

The preparations of (*R*)-**14** from D-tryptophan,[18f] and (*S*)-**14** from L-tryptophan[18g] by *N*-aroylation have been described in our

previous reports.[18f-h]

General Procedure for the Step 2 (General Procedure 2)

To a stirring solution of **14** (5.09 mmol) in THF (20 mL) at –20 °C were added successively *N*-methylmorpholine (0.84 mL, 7.63 mmol) and ^{i}BuOCOC1 (0.74 mL, 5.60 mmol). After being stirred at –20 °C under N_2 for 15 min, the resulting mixture was added slowly to a solution of an amino acid benzyl ester *p*-toluenesulfonic acid salt (10.18 mmol) and *N*-methylmorpholine (1.68 mL, 15.28 mmol) in THF (36 mL) at –78 °C. The resulting mixture was stirred for 12 h at –20 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL). The resulting mixture was diluted with water (100 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 20 mL). 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 the corresponding dipeptide derivative.

General Procedure for the Step 3 (General Procedure 3)

To a suspension of zinc powder (776 mg, 11.94 mmol) in THF (50 mL) was added $TiCl_4$ (0.66 mL, 5.98 mmol). The resulting mixture was stirred for 1 h at 50 °C, and cooled to 0 °C. A THF (10 mL) solution of a tryptophan-derived dipeptide derivative (1.50 mmol) and trimethyl orthoformate (0.66 mL, 5.98 mmol) was added. The resulting mixture was stirred for 24 h at 0 °C. The reaction mixture was quenched with brine (10 mL) and the resulting mixture was stirred for 2 h. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). 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 = 1:3 to DCM: MeOH = 40:1) to give the corresponding quinazolinonyl dipeptide derivative.

General Procedure A for the Step 4 (General Procedure 4-A)

To a solution of quinazolinonyl dipeptide derivative (0.38 mmol) in anhydrous acetone (2 mL) was added a 0.04 M solution of DMDO in acetone (19 mL, 0.76 mmol) at –78 °C. After being stirred for 1 h, a saturated aqueous solution of Na_2SO_3 (10 mL) was added and the resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and concentrated under reduced pressure. To the resulting residue was added H_2O (50 mL), and the mixture was extracted with EtOAc (3 × 30 mL). 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 flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give a chaetominine/ isochaetominine-type compound and a monocylization product.

(–)-(2*S*,3*S*,11*S*,14*R*)-Chaetominine (1), and benzyl (*S*)-2-((3*R*,4a*R*,9a*S*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)propanoate (11a)

Following the general procedure 4-A, reaction of compound **12a** (188 mg, 0.38 mmol) gave (–)-chaetominine (**1**) (61 mg, yield: 40%) and compound **11a** (83 mg, yield: 43%) (eluent: EtOAc: PE = 1:1).

(–)-Chaetominine (**1**): colorless crystals, M.p. 301–302 °C (EtOAc) [lit. 161–163 °C;[11a] 288–290 °C (MeOH)[18f]]; $[\alpha]_D^{20}$ –49.7 (*c* 0.5, MeOH) {lit. $[\alpha]_D^{20}$ –70 (*c* 0.48, MeOH);[11a] $[\alpha]_D^{20}$ –49.4 (*c* 0.26, MeOH);[18a] $[\alpha]_D^{20}$ –49.7 (*c* 0.48, MeOH)[18f]}; The IR, ^{1}H NMR, ^{13}C NMR, and MS data are identical with those reported previously.[18f]

Compound **11a:** White solid, M.p. 154–156 °C (EtOAc); $[\alpha]_D^{20}$ –145.1 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3365, 2930, 1738, 1677, 1610, 1475, 1321, 1244, 1185, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.69 (td, *J* = 7.8, 1.2 Hz, 1H), 7.64–7.56 (m, 2H), 7.43 (ddd, *J* = 8.2, 7.8, 0.9 Hz, 1H) 7.38–7.26 (m, 6H), 7.13 (td, *J* = 7.8, 0.9 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.36–5.05 (m, 6H), 4.10 (s, 1H), 2.88 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.48 (dd, *J* = 12.5, 4.0 Hz, 1H), 1.53 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.5, 160.6, 148.2, 147.2, 145.4, 135.1, 134.4, 130.8, 129.1, 128.7 (2C), 128.6, 128.2 (2C), 127.3, 127.1, 126.9, 123.6, 121.8, 120.2, 110.2, 80.5, 79.3, 67.3, 52.2, 40.7, 16.3 (one carbon was not observed due to slow rotation at the C9-N bond);[18a] MS (ESI) *m/z* 533 (M+Na$^+$, 100%), HRMS (ESI, *m/z*) calcd for $C_{29}H_{26}N_4O_5Na$ [M+Na]$^+$: 533.1795, found: 533.1795.

(–)-(2*S*,3*S*,11*S*,14*R*)-2,3-Di*epi*-isochaetominine B (17), and benzyl (*S*)-2-((3*R*,4a*R*,9a*S*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)butanoate (11b)

Following the general procedure 4-A, reaction of compound **12b** (193 mg, 0.38 mmol) gave compound **17** (66 mg, yield: 42%) and compound **11b** (90 mg, yield: 45%) (eluent: EtOAc:PE = 1:1).

2,3-Di*epi*-isochaetominine B (**17**): colorless crystals, M.p. 302–304 °C (EtOAc); $[\alpha]_D^{20}$ –47.7 (*c* 1.0, MeOH); IR (film) ν_{max}: 3443, 1732, 1656, 1476, 1277, 1191, 1137 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (br. s, 1H), 8.17 (d, *J* = 1.3 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.6, 1.5 Hz, 1H), 7.71 (d, *J* = 6.9 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.54–7.47 (m, 2H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 6.70 (br. s, 1H), 6.18–5.70 (br. s, 1H), 5.58 (s, 1H), 4.65 (t, *J* = 3.5 Hz, 1H), 2.90 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.63 (dd, *J* = 12.8, 3.0 Hz, 1H), 2.49–2.38 (m, 1H), 1.97–1.80 (m, 1H), 0.69 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.2, 165.5 (br.), 160.3, 147.6, 146.6 (br.), 139.1, 136.5, 134.9, 130.2, 127.5, 127.4, 126.5, 125.6, 125.2, 121.5, 114.4, 82.6, 76.7, 64.1, 50.8 (br.), 38.1, 20.0, 8.9 (br.); MS (ESI) *m/z* 439 (M+Na$^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{23}H_{20}N_4O_4Na$ [M+Na]$^+$: 439.1377, found: 439.1380.

Compound **11b**: white solid, M.p. 113–115 °C (EtOAc); $[\alpha]_D^{20}$ –146.7 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3442, 2932, 1733, 1671, 1612, 1470, 1321, 1238, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.68 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.50–7.39 (m, 2H), 7.38–7.30 (m, 5H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.10 (ddd, *J* = 8.2, 7.8, 1.1 Hz, 1H), 6.74 (dd, *J* = 7.4, 7.2 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 5.40–5.10 (m, 6H), 4.30 (s, 1H), 2.88 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.43 (dd, *J* = 12.5, 3.9 Hz, 1H), 2.10–1.98 (m, 1H), 1.85–1.71 (m, 1H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.4, 160.5, 148.2, 147.2, 145.3, 135.0, 134.3, 130.7, 129.3, 128.7 (2C), 128.6, 128.3 (2C), 127.2, 127.0, 127.0, 123.6, 121.8, 120.0, 110.0, 80.1, 79.5, 67.3, 57.1, 41.2, 23.6, 10.4 (one carbon was not observed due to slow rotation at the C9-N bond);[18a] MS

(ESI) *m/z* 547 (M+Na$^+$, 100%), HRMS (ESI, *m/z*) calcd for $C_{30}H_{28}N_4O_5Na$ [M+Na]$^+$: 547.1952, found: 547.1954.

General Procedure B for the Step 4 (General Procedure 4-B)

To a solution of a quinazolinonyl dipeptide derivative in anhydrous acetone (2 mL) was added a 0.04 M solution of DMDO in acetone (19 mL, 0.76 mmol) at –78 °C. After being stirred for 1 h, K_2CO_3/ MeOH (94 mg/ 10 mL) was added and the resulting mixture was warmed up to –15 °C over 30 minutes. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and the resulting mixture was concentrated under reduced pressure. To the resulting residue was added H_2O (50 mL), and the mixture was extracted with EtOAc (3 × 30 mL). 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 flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give an isochaetominine-type compound and a monocyclization product.

The proposed structure of (–)-aniquinazoline D [(2*S*,3*S*,11*S*,14*R*)-3], and benzyl (*S*)-2-((3*R*,4a*R*,9a*S*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (11c)

Following the general procedure 4-B, reaction of compound **12c** (200 mg, 0.38 mmol) gave compound **3** (53 mg, yield: 33%) and compound **11c** (82 mg, yield: 41%) (eluent: EtOAc:PE = 1:1).

Compound **3** [the proposed structure of (–)-aniquinazoline D[13]]: colorless crystals, M.p. 302–303 °C (EtOAc); $[\alpha]_D^{20}$ –50.7 (*c* 0.5, MeOH); IR (film) ν_{max}: 3446, 2965, 1738, 1642, 1610, 1475, 1275, 1192, 1137 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.30 (br. s, 1H), 8.16 (d, *J* = 1.3 Hz, 1H), 7.86 (ddd, *J* = 7.7, 7.6, 1.5 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.53–7.46 (m, 2H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (br. s, 1H), 6.16–5.68 (br. s, 1H), 5.52 (s, 1H), 4.56 (d, *J* = 2.8 Hz, 1H), 3.17 (m, 1H), 2.91 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.62 (dd, *J* = 12.8, 3.0 Hz, 1H), 1.13 (d, *J* = 7.3 Hz, 3H), 0.79 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 171.9, 166.3 (br.), 160.6, 147.9, 146.6 (br.), 139.5, 136.5, 135.1, 130.5, 127.8, 127.7, 126.8, 125.8, 125.4, 121.8, 114.6, 82.6, 77.0, 68.0, 51.2 (br.), 38.6, 25.8, 18.3, 16.6 (br.); MS (ESI) *m/z* 453 (M+Na$^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ [M+Na]$^+$: 453.1533, found: 453.1536; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 9.9 min, respectively. The enantiomeric excess was determined to be >99%.

Crystallographic data for compound **3**: $C_{24}N_4O_4H_{22}$, M = 430.46 g·mol^{-1}, crystal size 0.3 × 0.2 × 0.1 mm^3, orthorhombic, space group $P2_12_12_1$, *a* = 7.6889(2) Å, *b* = 15.5382(5) Å, *c* = 16.4272(6) Å, α = 90.00°, β = 90.00°, γ = 90.00°, *V* = 1962.58(11) Å^3, *Z* = 4, ρ_{calc} = 1.457 g·cm^{-3}, μ = 0.832 mm^{-1}, λ = 1.54184 Å, *T* = 99.8(5) K, θ range = 3.92−68.84°, reflections collected 4748, independent reflections 3186 (R_{int} = 0.0469, R_{sigma} = 0.0597), 292 parameters. The structure was solved by direct methods and refined by goodness-of-fit on F^2 (1.037); final *R* indices [I >2σ(I)] R_1 = 0.0413 and wR_2 = 0.0982; Largest diff. peak/hole 0.18/-0.23 e·Å^{-3}. CCDC-1423418 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compound **11c:** White solid, M.p. 296–298 °C (EtOAc); $[\alpha]_D^{20}$ –180.1 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3388, 2924, 1731, 1680, 1610, 1472, 1321, 1229, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.70 (ddd, *J* = 7.8, 7.6, 1.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.57 (br. s, 1H), 7.44 (ddd, *J* = 7.7, 7.5, 0.9 Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.15 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H), 6.79 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.47 (d, *J* = 4.4 Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 4.2 Hz, 1H), 3.66 (s, 1H), 2.89 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.47 (dd, *J* = 13.0, 3.7 Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 170.5, 160.5, 148.3, 147.2, 145.2, 134.9, 134.3, 130.8, 129.1, 128.7 (2C), 128.6, 128.5 (2C), 127.2, 127.1, 127.0, 123.7, 121.8, 120.2, 110.2, 80.1, 79.8, 67.2, 60.8, 41.2, 28.9, 19.4, 18.7 (one carbon was not observed due to slow rotation at the C9-N bond);[18a] MS (ESI) *m/z* 561 (M+Na$^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{31}H_{30}N_4O_5Na$ [M+Na]$^+$: 561.2108, found: 561.2115.

(+)-(2*R*,3*R*,11*S*,14*S*)-14-*epi*-Isochaetominine C (7), and benzyl (*S*)-2-((3*S*,4a*S*,9a*R*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (20)

Following the general procedure 4-B, reaction of compound **19** (183 mg，0.35 mmol) gave (+)-14-*epi*-isochaetominine C (**7**, 51 mg, yield: 35%) and compound **20** (83 mg, yield: 44%) (eluent: EtOAc:PE = 1:1).

(+)-14-*epi*-Isochaetominine C (**7**): white solid, M.p. 323–325 °C (EtOAc); $[\alpha]_D^{25}$ +48.0 (*c* 1.0, MeOH) {lit. $[\alpha]_D^{25}$ +33 (*c* 0.7, MeOH)[14]}; IR (film) ν_{max}: 3406, 1716, 1690, 1603, 1443, 1325, 1267, 1224 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.22 (br s, 1H), 8.19 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.87–7.83 (ddd, *J* = 7.8, 7.6, 1.2 Hz, 1H), 7.70 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.6, 0.9 Hz, 1H), 7.50 (dd, J = 7.8, 1.2 Hz, 1H), 7.47 (dd, J = 7.9, 0.9 Hz, 1H), 7.42 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 1H), 7.24 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H), 6.74 (br s, 1H), 5.99 (dd, *J* = 13.0, 2.9 Hz, 1H), 5.78 (s, 1H), 4.38 (d, *J* = 6.6 Hz, 1H), 2.94 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.49 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.30–2.21 (m, 1 H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 169.7, 167.2, 160.0, 147.3, 146.7, 137.6, 137.5, 134.7, 129.7, 127.2, 127.2, 126.4, 125.5, 124.5, 121.0, 114.7, 84.5, 76.7, 69.6, 49.1, 38.2, 30.3, 19.1, 19.0; MS (ESI) *m/z* 453 (M+Na$^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ [M+Na]$^+$: 453.1533, found: 453.1539; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 17.0 min, respectively. The enantiomeric excess was determined to be >99%.

Crystallographic data for (+)-14-*epi*-isochaetominine C (**7**)·2H_2O: $C_{24}N_4O_6H_{26}$, M = 466.50 g·mol^{-1}, crystal size 0.2 × 0.1 × 0.05 mm^3, triclinic, space group P-1, *a* = 9.3200(6) Å, *b* = 10.5489(6) Å, *c* = 12.1772(7) Å, α = 95.818(5)°, β = 90.490(5)°, γ = 111.805(6)°, *V* = 1104.43(12) Å^3, *Z* = 2, ρ_{calc} = 1.4027 g·cm^{-3}, μ = 0.849 mm−1, λ = 1.54184 Å, *T* = 173.00(14) K, θ range = 3.65−60.18 °, reflections collected 5671, independent reflections 3246 (R_{int} = 0.0442, R_{sigma} = 0.0662), 315 parameters. The structure was solved by direct methods and refined by goodness-of-fit on F^2 (0.939); final *R* indices [I >2σ(I)] R_1 = 0.0380 and wR_2 = 0.0881; Largest diff. peak/hole 0.27/-0.27 e·Å^{-3}. CCDC-

1423426 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compound **20:** White solid, M.p. 121–122 °C (EtOAc); $[\alpha]_D^{20}$ +98.7 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3356, 2914, 2850, 1732, 1681, 1607, 1476, 1239, 1198, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.70 (ddd, *J* = 7.8, 7.6, 1.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.57 (br. s, 1H), 7.44 (ddd, *J* = 7.7, 7.5, 0.9 Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.15 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H), 6.79 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.47 (d, *J* = 4.4 Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 4.2 Hz, 1H), 3.66 (s, 1H), 2.89 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.47 (dd, *J* = 13.0, 3.7 Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.0, 160.1, 147.9, 147.3, 144.9, 135.0, 134.4, 130.8, 128.9, 128.7 (2C), 128.7, 128.6 (2C), 127.3, 127.2, 126.9, 123.8, 121.7, 120.9, 110.5, 82.4, 80.0, 67.6, 63.6, 41.9, 29.3, 20.1, 19.5 (one carbon was not observed due to slow rotation at the C9-N bond);[18a] MS(ESI) *m/z* 561 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{31}H_{30}N_4O_5Na$ $[M+Na]^+$: 561.2108, found: 561.2108.

(+)-(2*R*,3*R*,11*R*,14*S*)-11,14-Di*epi*-isochaetominine C (*ent*-3), and benzyl (*R*)-2-((3*S*,4a*S*,9a*R*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (23)

Following the general procedure 4-B, reaction of compound **22** (183 mg，0.35 mmol) gave compound *ent*-**3** (48 mg, yield: 33%) and compound **23** (77 mg, yield: 41%) (eluent: EtOAc: PE = 1:1).

11,14-Di*epi*-isochaetominine C (*ent*-**3**): colorless crystals, M.p. 302–303 °C (EtOAc); $[\alpha]_D^{20}$ +50.7 (*c* 0.5, MeOH); IR (film) ν_{max}: 3407, 2962, 1732, 1655, 1613, 1476, 1198, 1133, 1076 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.30 (br. s, 1H), 8.16 (d, *J* = 1.3 Hz, 1H), 7.86 (ddd, *J* = 7.7, 7.6, 1.5 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.53–7.46 (m, 2H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (br. s, 1H), 6.16–5.68 (br. s, 1H), 5.52 (s, 1H), 4.56 (d, *J* = 2.8 Hz, 1H), 3.17 (m, 1H), 2.91 (dd, *J* = 12.8, 12.8 Hz, 1H) 2.62 (dd, *J* = 12.8, 3.0 Hz, 1H), 1.13 (d, *J* = 7.3 Hz, 3H), 0.79 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.9, 166.3 (br.), 160.6, 147.9, 146.6 (br.), 139.5, 136.5, 135.1, 130.5, 127.8, 127.7, 126.8, 125.8, 125.4, 121.8, 114.6, 82.6, 77.0, 68.0, 51.2 (br.), 38.6, 25.8, 18.3, 16.6 (br.); MS (ESI) *m/z* 453 ($M+Na^+$, 100%), HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ $[M+Na]^+$: 453.1533, found: 453.1533; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 11.8 min, respectively. The enantiomeric excess was determined to be >99%.

Compound **23:** White solid, M.p. 296–298 °C (EtOAc); $[\alpha]_D^{20}$ +180.1 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3388, 2924, 1731, 1680, 1610, 1472, 1321, 1229, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 0.8 Hz, 1H),7.70 (ddd, *J* = 7.8, 7.6, 1.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.57 (br/ s, 1H), 7.44 (ddd, *J* = 7.7, 7.5, 0.9 Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.15 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H), 6.79 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.47 (d, *J* = 4.4 Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 4.2 Hz, 1H), 3.66 (s, 1H), 2.89 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.47 (dd, *J* = 13.0, 3.7 Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.5, 160.5, 148.3, 147.2, 145.2, 134.8, 134.4, 130.9, 129.0, 128.7 (2C), 128.6, 128.5 (2C), 127.3, 127.1, 127.0, 123.7, 121.8, 120.2, 110.2, 80.1, 79.8, 67.3, 60.7, 41.2, 28.9, 19.4, 18.7 (one carbon was not observed due to slow rotation at the C9-N bond);[18a] MS (ESI) *m/z* 561 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{31}H_{30}N_4O_5Na$ $[M+Na]^+$: 561.2108, found: 561.2110.

(–)-(2*S*,3*S*,11*R*,14*R*)-14-*epi*-Isochaetominine C (*ent*-7) and benzyl (*R*)-2-((3*R*,4a*R*,9a*S*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (26)

Following the general procedure 4-B, reaction of compound **25** (183 mg, 0.35 mmol) gave compound *ent*-**7** (51 mg, yield: 35%) and compound **26** (83 mg, yield: 44%)(eluent: EtOAc:PE = 1:1).

14-*epi*-Isochaetominine C (*ent*-**7**): white solid, M.p. 323–325 °C (EtOAc); $[\alpha]_D^{25}$ –48.0 (*c* 1.0, MeOH); IR (film) ν_{max}: 3406, 1716, 1690, 1603, 1443, 1325, 1267, 1224 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.22 (br s, 1H), 8.19 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.87–7.83 (ddd, *J* = 7.8, 7.6, 1.2 Hz, 1H), 7.70 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.6, 0.9 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.42 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 1H), 7.24 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H), 6.74 (br s, 1H), 5.99 (dd, *J* = 13.0, 2.9 Hz, 1H), 5.78 (s, 1H), 4.38 (d, *J* = 6.6 Hz, 1H), 2.94 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.49 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.30–2.21 (m, 1 H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.7, 167.2, 160.0, 147.3, 146.7, 137.6, 137.5, 134.7, 129.7, 127.2, 127.2, 126.4, 125.5, 124.5, 121.0, 114.7, 84.5, 76.7, 69.6, 49.1, 38.2, 30.3, 19.1, 19.0; MS (ESI) *m/z* 453 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4$ $[M+Na]^+$: 453.1533, found: 453.1535; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 28.7 min, respectively. The enantiomeric excess was determined to be >99%.

Compound **26**: White solid, M.p. 121–122 °C (EtOAc); $[\alpha]_D^{20}$ –98.**7** (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3356, 2914, 2850, 1732, 1681, 1607, 1476, 1239, 1198, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.70 (ddd, *J* = 7.8, 7.6, 1.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.57 (br s, 1H), 7.44 (ddd, *J* = 7.7, 7.5, 0.9 Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.15 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H), 6.79 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.47 (d, *J* = 4.4 Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 4.2 Hz, 1H), 3.66 (s, 1H), 2.89 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.47 (dd, *J* = 13.0, 3.7 Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.0, 160.1, 147.9, 147.3, 144.9, 135.0, 134.4, 130.8, 128.9, 128.7 (2C), 128.7, 128.6 (2C), 127.3, 127.2, 126.9, 123.8, 121.7, 120.9, 110.5, 82.4, 80.0, 67.6, 63.6, 41.9, 29.3, 20.1, 19.5 (one carbon was not observed due to slow rotation at the C9-N bond);[18a] MS(ESI) *m/z* 561 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{31}H_{30}N_4O_5Na$ $[M+Na]^+$: 561.2108, found: 561.2112.

General Procedure A for the Step 5 (General Procedure 5-A)

A suspension of a quinazolinonyl dipeptide derivative (0.10 mmol) and 10% Pd/C (8 mg) in methanol (2 mL) was stirred under an atmosphere of H_2 for 2 h at room temperature. The

reaction mixture was filtered through a Celite pad and the residue was washed with methanol. The filtrate was concentrated under reduced pressure. Without further purification, the residue was directly treated with Ye's reagent (DEPBT)[21] (63 mg, 0.21 mmol) and DIPEA (0.035 mL, 0.21 mmol) in anhydrous CH_2Cl_2 (3 mL) for 8 h at room temperature. The reaction was quenched with water (5 mL) at 0 °C, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). 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 flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give the corresponding isochaetominine-type compound.

General Procedure B for the Step 5 (General Procedure 5-B)

A suspension of a quinazolinonyl dipeptide derivative (0.10 mmol) and 10% Pd/C (8.00 mg) in methanol (2 mL) was stirred under an atmosphere of H_2 for 2 h at room temperature. The mixture was filtered through a Celite pad and the solid was washed with methanol. The filtrate was concentrated under reduced pressure. Without further purification, the residue was directly treated with $(COCl)_2$ (0.013 mL, 0.15 mmol) and a catalytic amount of DMF in anhydrous CH_2Cl_2 (3 mL) for 5 minutes at −10 °C. To the resulting mixture was added DIPEA (0.035 mL, 0.21 mmol) and the mixture was stirred for 45 min. The reaction was quenched with water (5 mL) at −10 °C, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). 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 flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give the corresponding isochaetominine-type compound.

(−)-(2*R*,3*R*,11*S*,14*R*)-Isochaetominine A (4)

Following the general procedure 5-B, reaction of compound **11a** (51 mg, 0.10 mmol), gave compound **4** (30 mg, yield: 75%)(eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 184–186 °C (EtOAc); $[\alpha]_D^{25}$ –23.0 (*c* 1.0, MeOH) {lit.[14] $[\alpha]_D^{25}$ –63 (*c* 0.5, MeOH)}; IR (film) ν_{max}: 3410, 2925, 1728, 1674, 1608, 1477, 1383, 1327, 1290, 1136 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.18 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.87 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.9, 0.9 Hz, 1H), 7.51 (dd, *J* = 7.6, 0.9 Hz, 1H) , 7.44 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.42 (ddd, *J* = 7.6, 7.4, 1.0 Hz, 1H), 7.24 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.29 (br. s, 1H), 5.92 (s, 1H), 4.91 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.62 (q, *J* = 7.3 Hz, 1H), 2.98 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.73 (dd, *J* = 14.2, 5.2 Hz, 1H), 1.60 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 164.2, 159.9, 147.6, 146.7, 139.8, 135.8, 134.8, 130.1, 127.4, 127.2, 126.2, 125.3, 124.7, 121.5, 114.1, 82.9, 74.1, 59.7, 55.6, 34.7, 13.9; MS (ESI) *m/z* 425 ($M+Na^+$, 100%), HRMS (ESI, *m/z*) calcd for $C_{22}H_{18}N_4O_4Na$ $[M+Na]^+$: 425.1220, found: 425.1224.

(−)-(2*R*,3*R*,11*S*,14*R*)-Isochaetominine B (5)

Following the general procedure 5-B, reaction of compound **11b** (52 mg, 0.10 mmol) gave compound **5** (31 mg, yield: 75%)(eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 173–175 °C (EtOAc); $[\alpha]_D^{25}$ –49.0 (*c* 1.0, MeOH) {lit.[14] $[\alpha]_D^{25}$ –73 (*c* 0.6, MeOH)}; IR (film) ν_{max}: 3435, 2079, 1643, 1477, 1381, 1326, 1290, 1136 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.18 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.87 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.9, 0.9 Hz, 1H), 7.52 (dd, *J* = 7.6, 0.9 Hz, 1H) , 7.43 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.42 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 7.25 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.28 (br. s, 1H), 5.86 (s, 1H), 4.90 (dd, *J* = 7.3, 5.2 Hz, 1H), 4.47 (dd, *J* = 9.2, 5.9 Hz, 1H), 2.98 (dd, *J* = 14.2, 7.5 Hz, 1H), 2.73 (dd, *J* = 14.2, 5.3 Hz, 1H), 2.11–1.93 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 164.6, 159.8, 147.5, 146.7, 139.9, 135.4, 134.7, 130.0, 127.3, 127.2, 126.2, 125.2, 124.6, 121.4, 114.1, 83.3, 74.0, 65.3, 55.6, 34.4, 21.7, 10.9; MS (ESI) *m/z* 439 ($M+Na^+$, 100%), HRMS (ESI, *m/z*) calcd for $C_{23}H_{20}N_4O_4Na$ $[M+Na]^+$: 439.1377, found: 439.1381.

(−)-(2*R*,3*R*,11*S*,14*R*)-Isochaetominine C (6)

Following the general procedure 5-A, reaction of compound **11c** (54 mg, 0.10 mmol) gave compound **6** (32 mg, yield: 77%) (eluent: EtOAc: PE = 1:1).

Following the general procedure 5-B, reaction of compound **11c** (54 mg, 0.10 mmol) gave compound **6** (34 mg, yield: 81%) (eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 166−168 °C (EtOAc); $[\alpha]_D^{25}$ −71.0 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ −76.8 (*c* 1.0, $CHCl_3$) {lit. $[\alpha]_D^{20}$ −33 (*c* 0.37, MeOH);[13] $[\alpha]_D^{25}$ −90 (*c* 0.6, MeOH);[14] $[\alpha]_D^{20}$ −16.9 (*c* 0.18, $CHCl_3$);[12]}; IR (film) ν_{max}: 3404, 2962, 2917, 1732, 1684, 1607, 1476, 1325, 1197, 1181 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.18 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.5, 1.5 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.6, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.43 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 6.29 (br. s, 1H), 5.81 (s, 1H), 4.85 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.21 (d, *J* = 9.3 Hz, 1H), 3.00 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.77 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.43–2.46 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.9, 164.9, 159.8, 147.5, 146.9, 140.3, 134.9, 134.7, 130.1, 127.4, 127.2, 126.2, 125.2, 124.6, 121.5, 114.2, 83.7, 73.8, 69.4, 55.7, 34.1, 28.2, 20.2, 18.7; MS (ESI) *m/z* 453 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ $[M+Na]^+$: 453.1533, found:453.1535; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ isopropanol, 70:30), flow rate = 0.8 mL/min, R_t = 21.4 min, respectively. The enantiomeric excess was determined to be >99%.

(−)-(2*S*,3*S*,11*S*,14*S*)-2,3,14-tri*epi*-isochaetominine C (*ent*-8)

Following the general procedure 5-B, reaction of compound **20** (54 mg, 0.10 mmol) gave compound *ent*-**8** (29 mg, yield: 70%) (eluent: EtOAc: PE = 1:1) as a white solid. M.p. 179−181 °C (EtOAc); $[\alpha]_D^{20}$ −105.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3395, 2964, 1732, 1681, 1607, 1476, 1328, 1262, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.01 (s, 1H), 7.77 (ddd, *J* = 7.9, 7.7, 1.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H), 7.40–7.30 (m, 2H), 7.16 (ddd, *J* = 7.6, 7.5, 0.7 Hz, 1H), 5.80 (s, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 4.49 (d, *J* = 3.0 Hz, 1H), 4.21 (s, 1H), 3.33–3.20 (m, 1H), 2.87 (dd, *J* = 15.4, 1.3 Hz, 1H), 2.46 (dd, *J* = 15.4, 6.3 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.4, 162.1, 147.7, 145.5,

138.6, 135.9, 135.0, 130.7, 128.0, 127.5, 126.7, 125.7, 124.0, 121.7, 115.3, 84.2, 75.6, 68.6, 58.9, 39.2, 25.2, 17.8, 16.2; MS (ESI) *m/z* 453 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ $[M+Na]^+$: 453.1533, found: 453.1534; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 28.1 min, respectively. The enantiomeric excess was determined to be >99%.

(+)-(2*S*,3*S*,11*R*,14*S*)-Isochaetominine C (*ent*-6)

Following the general procedure 5-B, reaction of compound **23** (54 mg, 0.10 mmol) gave compound *ent*-**6** (34 mg, yield: 81%)(eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 166–168 °C (EtOAc); $[\alpha]_D^{25}$ +71.0 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ +76.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3404, 2962, 1732, 1684, 1607, 1476, 1198, 1181, 1076 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.18 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.5, 1.5 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.6, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.43 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 6.29 (br. s, 1H), 5.81 (s, 1H), 4.85 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.21 (d, *J* = 9.3 Hz, 1H), 3.00 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.77 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.43–2.46 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.9, 164.9, 159.8, 147.5, 146.9, 140.3, 134.9, 134.7, 130.1, 127.4, 127.2, 126.2, 125.2, 124.6, 121.5, 114.2, 83.7, 73.8, 69.4, 55.7, 34.1, 28.2, 20.2, 18.7; MS (ESI) *m/z* 453 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ $[M+Na]^+$: 453.1533, found: 453.1532; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ isopropanol, 70:30), flow rate = 0.8 mL/min, R_t = 14.2 min, respectively. The enantiomeric excess was determined to be >99%.

(+)-(2*R*,3*R*,11*R*,14*R*)-11-*epi*-Isochaetominine C (8)

Following the general procedure 5-B, reaction of compound **26** (54 mg, 0.10 mmol) gave compound **8** (29 mg, yield: 70%) (eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 179–181 °C (EtOAc); $[\alpha]_D^{20}$ +105.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3395, 2964, 1732, 1681, 1607, 1476, 1328, 1262, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.01 (s, 1H), 7.77 (ddd, *J* = 7.9, 7.7, 1.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H), 7.40–7.30 (m, 2H), 7.16 (ddd, *J* = 7.6, 7.5, 0.7 Hz, 1H), 5.80 (s, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 4.49 (d, *J* = 3.0 Hz, 1H), 4.21 (s, 1H), 3.33–3.20 (m, 1H), 2.87 (dd, *J* = 15.4, 1.3 Hz, 1H), 2.46 (dd, *J* = 15.4, 6.3 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.4, 162.1, 147.7, 145.5, 138.6, 135.9, 135.0, 130.7, 128.0, 127.5, 126.7, 125.7, 124.0, 121.7, 115.3, 84.2, 75.6, 68.6, 58.9, 39.2, 25.2, 17.8, 16.2; MS (ESI) *m/z* 453 ($M+Na^+$, 100%); HRMS (ESI, *m/z*) calcd for $C_{24}H_{22}N_4O_4Na$ $[M+Na]^+$: 453.1533, found: 453.1535; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 47.0 min, respectively. The enantiomeric excess was determined to be >99%.

(–)-(2*R*,3*R*,11*S*,14*S*)-14-*epi*-Isochaetominine C (from compound 20)

To a solution of compound **20** (54 mg, 0.1 mmol) in MeOH (1.5 mL) was added a solution of freshly prepared CH_3ONa (27 mg, 0.5 mmol) in CH_3OH (3.5 mL) at –10 °C. After being stirred for 1 h, the reaction mixture was acidified with 10% HCOOH to reach pH = 7. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give (–)-14-*epi*-isochaetominine C (*ent*-**7**) (38 mg, yield: 89%) as a white solid. The physical and spectral data of *ent*-**7** thus obtained are in full agreement with those of *ent*-**7** prepared from **25**.

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