Chinese Chemical Letters 31 (2020) 61–63

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Communication

Concise, enantioselective total syntheses of both the proposed and revised structures of (−)-versiquinazoline H

Jiang-Feng Wu, Pei-Qiang Huang*

Department of Chemistry, Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

ARTICLE INFO

Article history:
Received 22 May 2019
Received in revised form 15 June 2019
Accepted 24 June 2019
Available online 3 July 2019

Keywords:
Alkaloids
Total synthesis
Tandem reaction
Structural revision
Protecting group-free

ABSTRACT

The enantioselective total synthesis of the putative structure of versiquinazoline H and three diastereomers has been achieved, which allowed the revision of the stereochemistry of this natural product. This six-step total synthesis relied on the evolution of the strategy that we previously developed, which features a DMDO-triggered tandem reaction. The modification of the lactamization step resulted in a significant improvement of yield that ensured the efficient total synthesis.

Efficiency is the major concern of contemporary organic synthesis [1]. Tandem/cascade/domino reaction [2] is an effective strategy to achieve high efficiency. (−)-Chaetominine (**1** in Fig. 1) is a hexacyclic fungal tripeptidal alkaloid isolated from endophytes of different origins. Following the isolation of chaetominine [3], its homologues and diastereomers (−)-isochaetominines A–C (**2**–**4**) and (+)-14-*epi*-isochaetominine C (**5**) were isolated from the solid-substrate culture of an *Aspergillus* sp. Fungus [4]. In 2016, Lin and coworkers reported that during a screening of their marine microorganism library, the gorgonian (*Pseudopterogorgia* sp.)-derived fungus *Aspergillus versicolor* LZD-14-1 was found to possess inhibitory effects against thioredoxin reductase (TrxR), a potential target for the treatment of cancer, AIDS and autoimmune diseases. The investigation led to the isolation of eleven new fumiquinazoline-type alkaloids named versiquinazolines A–K [5]. Among them, (−)-versiquinazoline H (**6**, the structure displayed in the original paper [5]) also belongs to the chaetominine family. Its relative stereochemistry was determined by 2D NMR techniques, and the absolute configuration was determined to be 14*S*,16*S*,17*S*,26*R* (referring to 2*S*,3*S*,11*R*,14*S* according to the numbering system used for compounds **1**–**4**) based on the comparison with the known compound (−)-isochaetominine C (**4**) [6], and on a comparison of the experimental ECD data with those of calculated for **6** and its enantiomer. On the other hand, the configuration of the isoleucine (Ile) unit was determined to be L by analysis of the degradation product.

The enantioselective total synthesis of (−)-chaetominine has been reported by several groups [7], and the diastereodivergent synthesis of this family of alkaloids has been achieved by the Huang group [6,8]. We have developed three enantioselective approaches to the chaetominine-family alkaloids. The first-generation approach is the four-step total synthesis of (−)-chaetominine from D-tryptophan (Trp) [7c,f,i,8a]. The second approach involves the first total synthesis of (−)-chaetominine from L-Trp [7g]. The third-generation method resides in using amino acid benzyl esters as components that allows accessing C_2/C_{14} *cis*-stereochemistry of the isochaetominine series of alkaloids [8b]. On the basis of these precedents, we report herein the fourth-generation total synthesis. Through this improved approach, we have achieved the first total synthesis of (−)-versiquinazoline H (**7**) and the proposed structure (**6**) as well as their diastereomers. The puzzle about the stereochemistry of (−)-versiquinazoline H has been clarified.

We opted for the total synthesis of the displayed structure (2*S*,3*S*,11*R*,12*S*,14*S*)-versiquinazoline H (**6**, Fig. 1) as the first objective of this investigation. For this purpose, Huang's third generation approach was adopted [8b]. Thus, the synthesis commenced with the known *N*-aroyl-L-tryptophan **8** [7g], prepared by aroylation of L-tryptophan (L-Trp) with *o*-nitrobenzoyl chloride (Scheme 1). The coupling of the mixed anhydride, generated *in situ* from **8** and *i*-BuOCOCl/*N*-methylmorpholine (NMM), with benzyl D-*allo*-isoleucinate *p*-toluenesulfonic acid salt

* Corresponding author.
E-mail address: pqhuang@xmu.edu.cn (P.-Q. Huang).

https://doi.org/10.1016/j.cclet.2019.06.043
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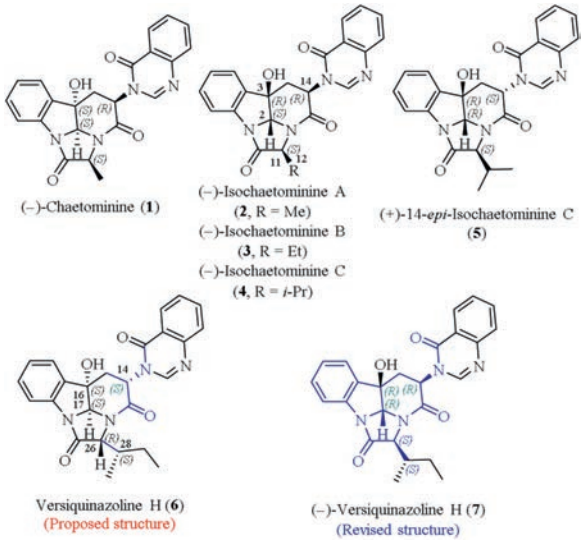


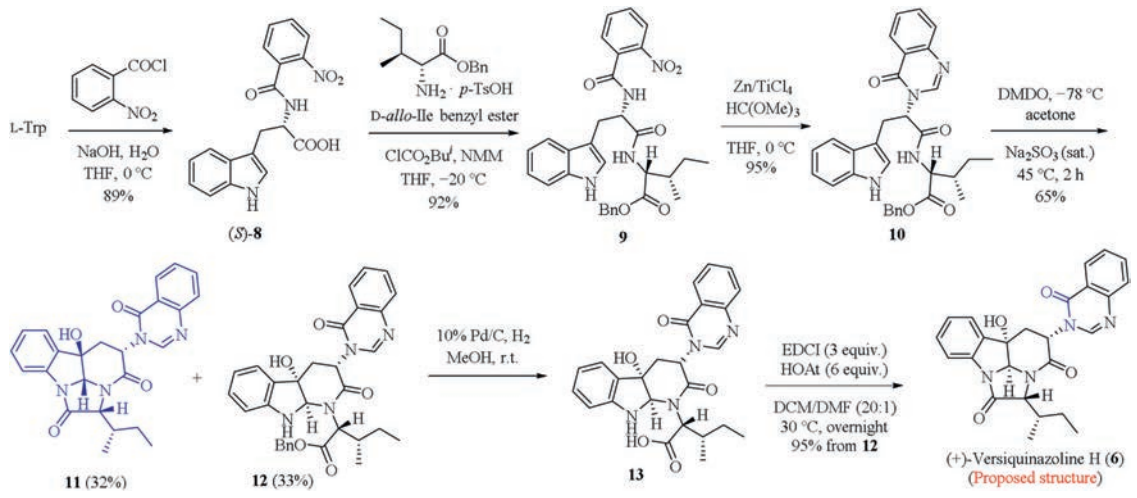
Fig. 1. Some chaetominine-family alkaloids.

(THF, −20 °C, 12 h) afforded **9** in 92% yield. The low-valent Ti-reagent mediated-quinazolinone formation [9] ($Zn/TiCl_4$ and trimethyl orthoformate, THF) [7c] proceeded smoothly at 0 °C to give **10** in 95% yield. Exposure of **10** to DMDO [8,10] at −78 °C followed by treating the resultant intermediates with an aqueous solution of Na_2SO_3 [8] at 45 °C for 2 h afforded, in one-pot, the double cyclization product **11** along with monocyclization product **12** in 32% and 33% yield, respectively. *O*-Debenzylation of **12** under catalytic hydrogenolytic conditions yielded the corresponding acid derivative **13**, which, without isolation, was subjected to lactamization conditions. However, under the previously used lactamization conditions [$(COCl)_2$ (1.5 equiv.), DIPEA (2.0 equiv.), cat. DMF, DCM (0.04 mol/L), −10 °C, 45 min], the desired product **6** was obtained in only 29% yield. Increasing $(COCl)_2$ from 1.5 equiv. to 3.0 equiv. led to an even lower yield (20%). Employing the Ye coupling reagent (DEPBT) [(2.0 equiv.) [11], DIPEA (2.0 equiv.), DCM (0.04 mol/L), 25 °C, 8 h] resulted in a higher yield of 54%. Finally, it was found that another coupling method employing HOAt (6.0 equiv.) and EDCI (3.0 equiv.) in dichloromethane (0.05 mol/L) (30 °C, 12 h) produced the proposed structure of versiquinazoline H (**6**) in 95% yield over two steps. The sense of optical rotation {$[\alpha]_D^{20}$ 69.6 (*c* 0.1, CH_3OH)} and spectral (^1H and ^{13}C NMR) data of our synthetic compound are different from those reported for the natural (−)-versiquinazoline H {$[\alpha]_D^{20}$ −100 (*c* 0.1, MeOH) [5]}, suggesting that the originally proposed stereochemistry (**6**) for (−)-versiquinazoline H was incorrect.

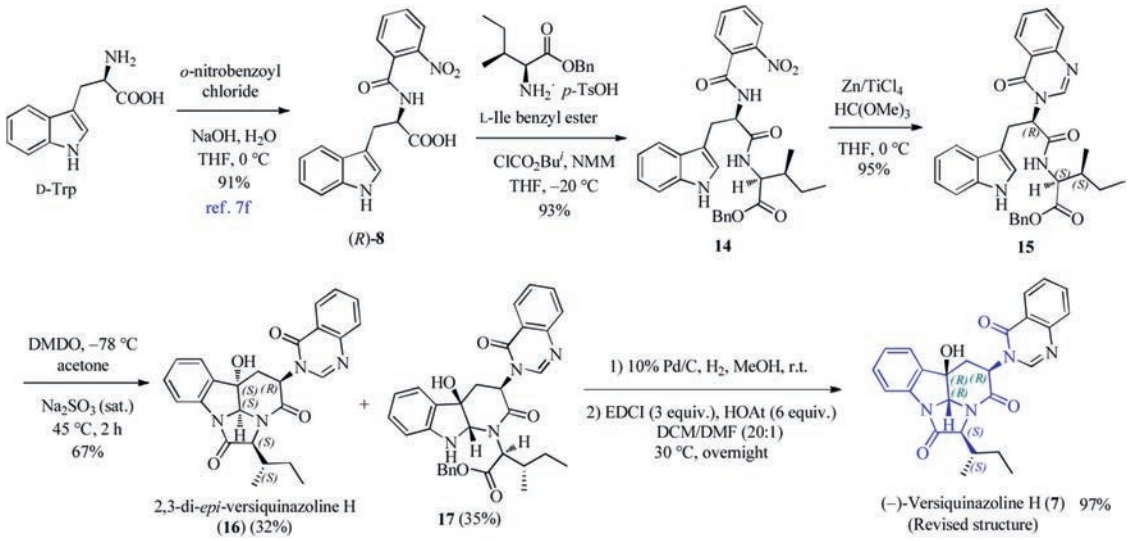
To address the enantioselective total synthesis of the natural (−)-versiquinazoline H, we commenced with the identification of the stereoisomers of the amino acids present in (−)-versiquinazoline H.

A closer inspection of the original paper [5] showed that the evidences provided and conclusion obtained about the stereochemistry of (−)-versiquinazoline H are contradictory. First, the authors stated: "the absolute configuration was determined to be 14*S*,16*S*,17*S*,26*R* based on the closely similar ECD and specific rotation data of (−)-versiquinazoline H and (−)-isochaetominine C (**4**)" [6]. However, as can be seen from Fig. 1, in terms of stereochemistry, the ring system of (−)-isochaetominine C (**4**) appears to be an "enantiomer" of the proposed structure of "(−)-versiquinazoline H" (**6**) for the on-ring stereogenic centers. Second, they described: "the configuration of the isoleucine unit has been determined to be L by the advanced Marfey's method". However, the proposed structure of "(−)-versiquinazoline H" (**6**) contains a D-*allo*-Ile instead of an L-Ile residue. This analysis allowed us to suggest stereoisomer **7** as the actual structure of the natural (−)-versiquinazoline H.

To further confirm the structure of the natural (−)-versiquinazoline H, we proceeded to synthesize the stereoisomer **7** containing D-Trp and L-Ile residues. Under the standard conditions [7f], the coupling of the known (*R*)-**8** with benzyl L-isoleucinate *p*-toluenesulfonic acid salt yielded compound **14** in 93% yield. The latter was converted to **15** in 95% yield. The DMDO oxidation of **15** followed by treating the resulting mixture with a saturated aqueous solution of Na_2SO_3 at 45 °C for 2 h produced the double cyclization product **16** and monocyclization product **17** in 32% and 35% yield, respectively. *O*-Debenzylation of **17** under catalytic hydrogenolytic conditions yielded the corresponding amino acid, which, without separation, was subjected to our newly established lactamization conditions [HOAt (6.0 equiv.), EDCI (3.0 equiv.), DCM (0.05 mol/L), 30 °C, 12 h], which produced compound **7** as a white solid in 97% yield over two steps. The sense of optical rotation and spectral (^1H and ^{13}C NMR) data of our synthetic compound fully matched those reported for the natural versiquinazoline H, but a



Scheme 1. The enantioselective total synthesis of the proposed structure of versiquinazoline H (**6**).



Scheme 2. The enantioselective total synthesis of (−)-versiquinazoline H (**7**).

difference exists for the values of specific rotation {synthetic **7**: $[\alpha]_D^{20}$ −74.6 (*c* 0.1, MeOH); natural product (colorless oil): $[\alpha]_D^{20}$ −100 (*c* 0.1, MeOH) [5]}. The results allowed us to conclude that the stereochemistry of the natural (−)-versiquinazoline H to be 2*R*,3*R*,11*S*,12*S*,14*R* as represented by **7**. It is worth noting that, H14, H19, H25, C13, C14, C17, C18, and C23 of compounds **11** and **16** are very broad, which are similar to the observations noted by Tan [3a], Snider [7a], and Huang for chaetominine [3a,7a,8b] (Scheme 2).

In summary, through evolution of our previously developed strategy, we have completed the first total synthesis of both the proposed and the revised structures of versiquinazoline H both in six steps with an overall yield of 24.4% and 27.3%, respectively. Through this fourth-generation strategy, the stereochemistry of this natural product has been revised to 2*R*,3*R*,11*S*,12*S*,14*R*. Work is in progress in our laboratories to further extend this efficient strategy [12], and results will be reported in due course.

Acknowledgments

This paper is dedicated to Professor Henry N.C. Wong for his significant contribution to the development of organic chemistry in China. The authors are grateful for the financial support from the National Natural Science Foundation of China (Nos. 21672176 and 21332007) and the National Key R&D Program of China (No. 2017YFA0207302). We thank Ms. Yan-Jiao Gao for assistance in the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.06.043.

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