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First total synthesis and stereochemical revision of okaramine M

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ABSTRACT

We describe the first total synthesis of the reported and revised structures of okaramine M (**1** and **7**) through the Ugi three-component reaction of pyrroloindole imine **10** with *p*-methoxyphenyl isonitrile and *N*-Boc-L-tryptophan, followed by cyclization and epimerization.

The okaramines are a family of dimeric tryptophane alkaloids isolated from the fermentation broth of *Penicillium simplicissimum* ATCC 90288, AHU 8402, and *Aspergillus aculeatus* KF-428 by Hayashi and co-workers.[1] Most okaramines are constructed of a hexahydropyrrolo[2,3-*b*]indole-diketopiperazine ring system with a hydroxy group at the C10b quaternary center. Among the okaramines, okaramine M (**1**) is distinguished by a reverse-prenyl group at the C10b quaternary carbon center of the ring system,[1c] which represents the key structural subunit in a number of biologically important natural products such as fructigenine A (**2**),[2] verrucofortine (**3**),[3] roquefortine D (**4**),[4] brevicompanine B (**5**),[5] and amauromine (**6**)[6] (Fig. 1). However, the absolute configuration at C10b in the proposed structure **1** is opposite to that in related natural products **2**–**6**. Although okaramine M has not yet demonstrated any remarkable bioactivity, its potential ability, like that of **2**–**6**, is still attractive. The absolute stereochemistry and the prospective bioactivity of okaramine M prompted us to undertake the synthesis of **1** and its diastereomers. Some approaches to the related alkaloids **4**–**6** according to Takase's[7] and Danishefsky's methodologies[8] are known, but to the best of our knowledge, there is no report on the total synthesis of okaramine M. Recently, we developed a concise and efficient synthetic methodology using domino reactions and multi-component reactions for the related pyrroloindole alkaloids.[9] Herein, we describe the first total synthesis of okaramine M and in turn clarify its absolute configuration on the basis of the synthetic evidence that natural okaramine M does not correspond to the proposed structure **1**, but rather to its diastereomer **7**.

For syntheses of **1** and three diastereomers including **7**, we have chosen to use a racemic imine **10** in a three-component reaction followed by cyclization and epimerization. As described previously,[9] hexahydropyroroindole (±)-**9** was prepared through a reductive cyclization of (±)-**8**[10] followed by Boc-protection, acetylation, and Boc-deprotection (Scheme 1). Instead of the TPAP/NMO-oxidation previously used,[9c] oxidation of (±)-**9** with NCS and DBU[11] improved the yield of (±)-**10** and the handling during workup. Next, the Ugi three-component reaction[12] of (±)-**10**, *p*-methoxyphenyl (PMP) isonitrile, and *N*-Boc-L-tryptophan afforded two diastereomeric

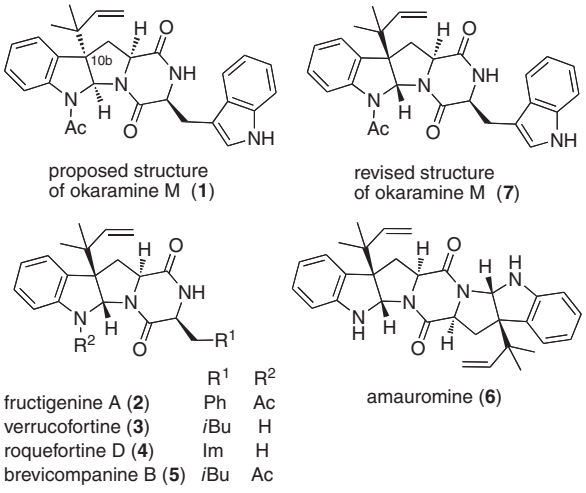

Figure 1. Okaramine M and related alkaloids; Im = 4-imydazoyl.

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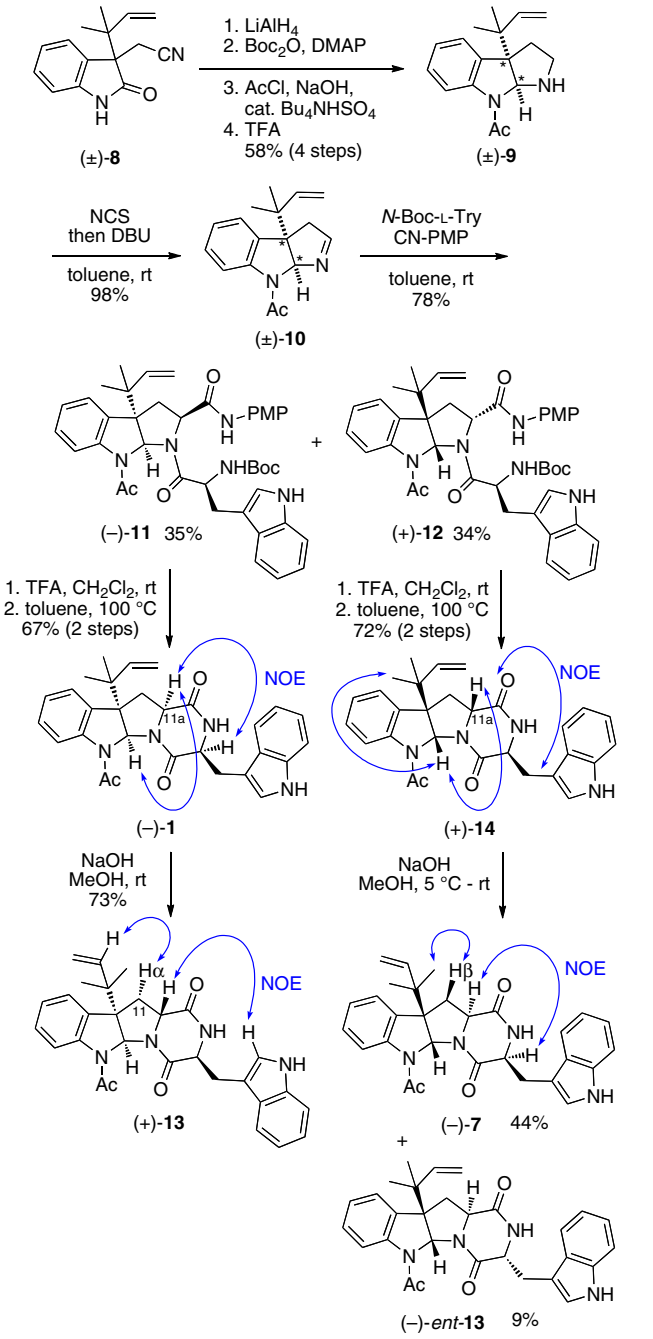
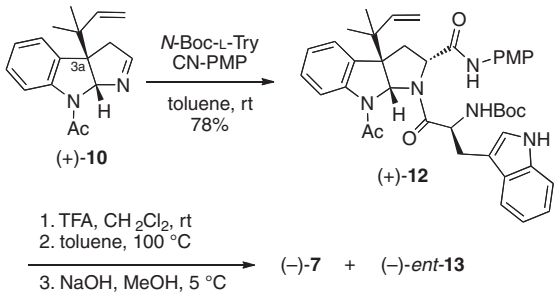


Scheme 1. Synthesis of okaramine M and its diastereomers through a racemic imine (±)-**10**.

dipeptides (−)-**11** and (+)-**12** in 35% and 34% yields, respectively.[13] Subsequent Boc-deprotection of (−)-**11** with TFA and cyclization on heating at 100 °C provided the proposed okaramine M (−)-**1** in 67% two-step yield as a single isomer, whose stereochemistry was confirmed by NOE experiments as shown. Unfortunately, the ^{1}H and ^{13}C NMR data of our synthetic compound **1** did not match with those of the reported natural compound.[1]

In order to confirm the stereochemistry of the natural compound, we synthesized its corresponding diastereomers **13**, **14**, and **7**, of which the spectral data were analyzed by comparison with the natural compound. On treatment of (−)-**1** with NaOH at room temperature, epimerization at C11a proceeded selectively to give the desired diastereomer (+)-**13** in 73% yield. The stereochemistry was assigned on the basis of the NOE correlation and



Scheme 2. Synthesis of okaramine M (**7**) from an optically pure imine (3a*R*)-(+)-**10**.

the coupling constants ($J_{11\alpha,11a}$ = 10.2 Hz; $J_{11\beta,11a}$ = 5.4 Hz). Treatment of another dipeptide (+)-**12** with TFA followed by heating at 100 °C produced a cyclic product (+)-**14** in 72% yield, of which the configuration was decided by NOE analysis as shown. The spectral data of (+)-**13** and (+)-**14** are incongruous with those of the natural product. The forth diastereomer (−)-**7** was obtained in 44% yield with a by-product (−)-*ent*-**13** (9%) by treatment of (+)-**14** with NaOH at 5–10 °C.[14] As predicted, the ^{1}H and ^{13}C NMR data of (−)-**7** were identical to those of the reported natural compound,[1] and both the coupling constants ($J_{11\alpha,11a}$ = 5.5 Hz; $J_{11\beta,11a}$ = 12.0 Hz) and the NOE correlation confirmed the stereochemistry of (−)-**7** as shown in Scheme 1. Consequently, we propose compound **7**, which is a diastereomer of **1** with different absolute configurations at the 5a and C10b chiral centers bearing a reverse-prenyl group, to be the structure of the isolated natural product, as well as the structures of the related natural products **2**–**6**.

Finally, we performed an asymmetric synthesis of revised okaramine M (**7**) from optically pure pyroroindole imine (3a*R*)-(+)-**10** (99% ee) (Scheme 2).[9c] As a result, the Ugi three-component reaction of (+)-**10**, PMP-isonitrile, and *N*-Boc-L-tryptophan took place stereoselectively to give (+)-**12** in 78% yield. In a similar way, okaramine M (−)-(**7**) was obtained through Boc-deprotection of (+)-**12**, cyclization, and epimerization.

In summary, we have successfully completed the first total synthesis of the proposed and revised structures **1** and **7** of okaramine M in a concise and efficient manner. The biological evaluation of okaramine M will be disclosed in due course.

Acknowledgments

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Supplementary data

Supplementary data (characterization data and ^{1}H and ^{13}C NMR spectra of synthetic okaramine M and its diastereomers) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.026.

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14. In this case, the starting compound **14** was recovered (33%). The prolonged reaction time or increased reaction temperature resulted in consumption of **14** and more formation of *ent*-**13** than **7**.