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Original article

An attempted approach to the tricyclic core of haliclonin A: Structural elucidation of the final product by 2D NMR

Yan-Jiao Gao, Shi-Peng Luo, Jian-Liang Ye, Pei-Qiang Huang*

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 361005, China

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ABSTRACT

We describe the design and execution of a novel synthetic route to the tricyclic core of haliclonin A, a tetracyclic marine natural product. The approach features Bachi's thiol-medicated free radical cyclization of alkenyl isocyanide to build the bridged ring system, and ring-closing metathesis (RCM) reaction to form the macrocycle. Execution of the synthetic plan ultimately resulted in a diazatricyclic compound. By means of 2D NMR techniques, the structure of this compound was revealed to an unexpected product **8**. Analysis of the synthetic pathways allowed concluding that the unexpected product is a result of an "unexpected" migration of olefinic bond during dioxolanation of the 2-cyclohexenone derivative **7**. This investigation also resulted in a concise construction of the functionalized hexahydro-1*H*-isoindole-1,5(4*H*)-dione **12** and the macrocyclic tricyclic ring system **8**.

1. Introduction

In 2009, Oh, Shin, and co-workers reported the isolation of (−)-haliclonin A (**1**) (Fig. 1), a tetracyclic natural product, from a marine sponge *Haliclona* sp. collected from Korean waters [1]. In connection with our interest in the synthesis of bioactive natural products [2], we have embarked on the synthesis of (−)-haliclonin A. In 2013, we communicated a racemic synthesis of a tricyclic core of haliclonin A (**1**) [3]. Lately, we have disclosed the first enantioselective total synthesis of (−)-haliclonin A (**1**) [4].

In connection with our interest in the development of synthetic methodologies for the direct transformation of amides [5], we are interested in exploring an alternative approach for the efficient construction of the tricyclic core (**2**) of haliclonin A. The new approach is outlined retrosynthetically in Scheme 1. Inspired by Bachi's thiol-medicated free radical cyclization of alkenyl isocyanides [6] to give γ–lactams [6c–g], bridged-bicyclic intermediate **3** was envisioned to be accessible from isonitrile **4**. The latter in turn would be available from formamide **5** by dehydration [7]. Formamide **5** could be synthesized from nitro-enone **7** *via* its protected form, namely, acetal derivative **6**.

According to the retrosynthetic analysis, a synthetic route was planned and executed. However, after finishing the synthetic sequence, it appeared to us that the final product was not the desired tricyclic lactam **2**. To elucidate the structure of the final synthetic product, an investigation by means of various 2D NMR techniques [8] was undertaken, which revealed its structure to be that represented by **8** (Fig. 2). This result implicated that the acetal formed from 2-cyclohexenone **7** was **9** instead of **6**. These results allowed displaying a correct synthetic route. The results of this investigation are described in this report.

2. Results and discussion

2.1. Structural elucidation of the final synthetic product *8* by 2D NMR techniques

The absent of vinyl resonances in the low field zone of 4.80–6.60 ppm in the ^{1}H NMR spectrum of the RCM product, and the appearance of three more methylene resonances in the aliphatic region of ^{13}C NMR spectrum indicated that the expected macrocycle has been formed smoothly. The azabicyclononane core of the expected product **2** featured a CH_2-CH-CH-CH_2-CH_2 segment (C4-C3-C5-C10-C11) and two isolated methylenes (C7, C9). The resonances appeared at δ_H 2.76, 3.01 were assigned to the C9 methylene according to the observed correlations with lactam carbonyl (C2) at δ_C 174.0 in the HMBC spectrum. Likewise, HMBC correlation between ketone carbonyl (C6) at δ_C 211.7 and another lone methylene resonance at δ_H 2.19 allowed us to identify C7. The methylene at δ_H 3.09, 3.32 showed only two COSY cross peaks to

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

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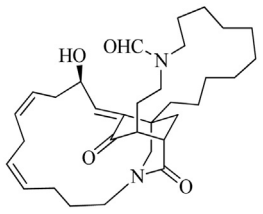
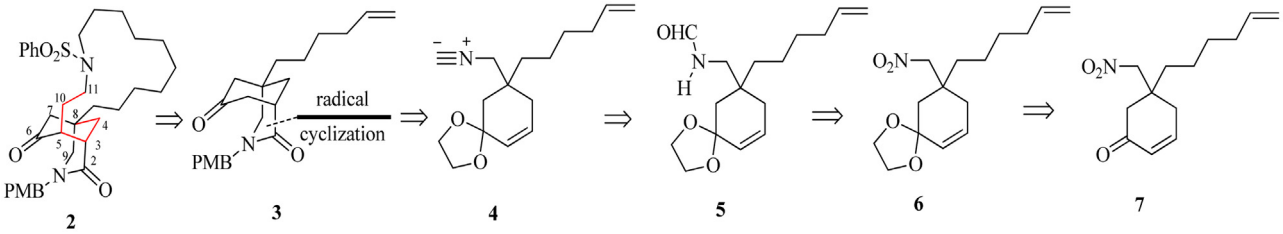


Fig. 1. Structure of (−)-haliclonin A.

(H5), 2.47(H3)/δ_C 47.2(C7); δ_H 2.47(H3), 2.19(H7)/δ_C 44.3(C8); δ_H 2.57(H4)/δ_C 211.7(C6, C=O) suggested a cyclohexanone moiety. The HMBC cross peaks at δ_H 2.57, 1.87(H4), 2.47(H3)/δ_C 174.0(C2); δ_H 3.01, 2.76(H9)/δ_C 44.3(C8), δ_C 47.2(C7); δ_H 2.19(H7)/δ_C 56.9(C9) implied a five-membered lactam ring fused with cyclohexanone ring at C3 and C8. The pended macrocycle linked at quaternary C8 was confirmed by the HMBC cross peaks at δ_H 3.01(H9), 2.47(H3), 2.19(H7)/δ_C 38.5(C22); δ_H 1.47, 1.35(H22)/δ_C 44.3(C8).

Finally, the relative configuration of **8** was deduced from the key correlations in its NOESY spectrum. The cross peaks at δ_{H3} 2.47/δ_{H22} 1.47, 1.35, $\delta_{\beta\text{-}H9}$ 3.01; $\delta_{\beta\text{-}H9}$/δ_{H22} 1.47, 1.35 suggested the proximity of H3, H22 and β-H6. The relative stereochemistry of C5



Scheme 1. Retrosynthetic analysis of 2.

the methylene at δ_H 1.82, furthermore, the HMBC correlation was observed between δ_H 1.82 and δ_C 211.7. Therefore, the resonances at δ_H 3.09, 3.32 and at δ_H 1.82 were assigned to H11(CH_2) and H10 (CH_2), respectively. The observed COSY cross peaks at δ_{H10} 1.82/δ_H 2.33(CH); δ_H 2.33/δ_H 1.87, 2.57(CH_2); δ_H 1.87, 2.57/δ_H 2.47(CH, triplet) allowed us to identify a CH-CH_2-CH-CH_2-CH_2 segment. However, this was not in agreement with the CH_2-CH-CH-CH_2-CH_2 segment of the expected product **2**. This evidence allowed concluding that the product did not possess an azabicyclononane core, *i.e.*, the final product was not the expected **2**.

Next we proceeded to assign the structure of the unexpected product. The HMBC cross peaks at δ_H 2.19(H7)/δ_C 43.0(C5); δ_H 2.33

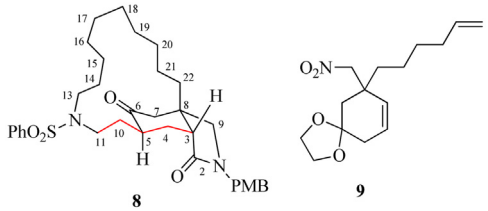


Fig. 2. Structures of compound **8** and **9**.

was determined by the NOESY correlations between δ_{H3} 2.47/$\delta_{\beta\text{-}H4}$ 1.87; $\delta_{\beta\text{-}H4}$ 1.87/δ_{H11} 3.09, 3.32; δ_{H5} 2.33/$\delta_{\alpha\text{-}H4}$ 2.57. Thus the structure of the unexpected di-aza-tricyclic product was elucidated to be **8** (Fig. 3).

2.2. Execution of the synthetic plan

The synthesis started from the known nitro-enone **7** [3,4] (Scheme 2). At the outset of our investigation the mild Hwu's protocol [9] that we have previously used for the synthesis of a tricyclic core of sarain A was adopted [2d]. However, when nitro-enone **7** was treated with 1,2-bis[(trimethylsilyl)oxy]ethane (BTSE) and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at −20 °C for 12 h, the starting material remained intact. To our delight, by running the reaction at room temperature for 12 h, a dioxolanation product was obtained in 80% yield. Alternatively, we also examined the simpler classical protocol. Thus, *p*-toluene sulfonic acid (PTSA, 0.25 equiv.) catalyzed condensation of **7** with ethylene glycol in refluxing toluene with removal of water formed with a Dean-Stark apparatus produced the same acetal in 90% yield. Interestingly, replacing PTSA by pyridinium *p*-toluenesulfonate (PPTS) afforded the same major product (78% yield), along with an isomer in 10% yield. The ^{1}H NMR

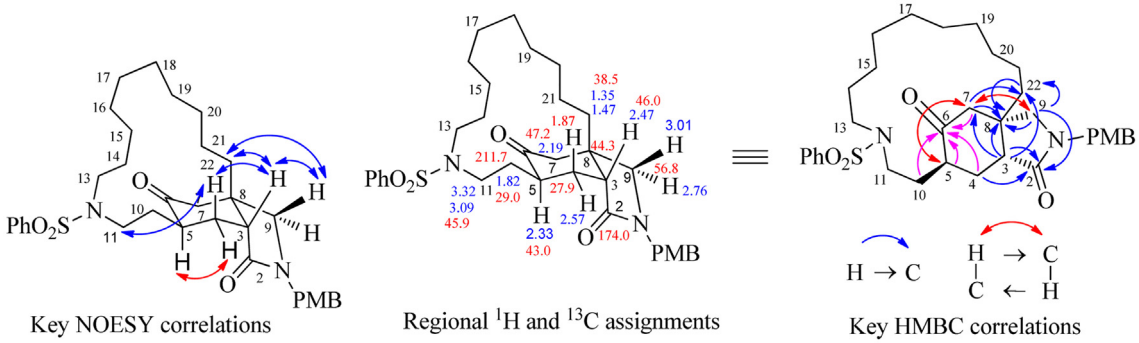


Fig. 3. Key ^{1}H and ^{13}C NMR data and key correlations in the NOESY and HMBC spectra of compound **8**.