



Communication

Synthetic studies towards atkamine

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ARTICLE INFO

Article history:

Received 6 May 2020

Received in revised form 20 May 2020

Accepted 5 June 2020

Available online 6 June 2020

Keywords:

Atkamine

Total synthesis

Alkaloid

[5 + 2] annulation

Michael addition

ABSTRACT

Atkamine is a complex marine pyrroloiminoquinone alkaloid that comprises a heptacyclic scaffold bearing five different heterocycles and four contiguous stereocenters, and therefore it is a highly challenging target for synthetic chemists. We herein reported a modular synthetic strategy toward this alkaloid, featuring a formal [5 + 2] annulation and an asymmetric Michael addition. The efficient synthesis of the long-chain aliphatic aldehyde and chiral amino acetal fragments have been achieved. A simplified tetracyclic intermediate bearing the core structure of atkamine has been successfully constructed through the formal [5 + 2] annulation.

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Since the discovery of discorhabdin C (**1**, Fig. 1) by Blunt and Muro and coworkers in 1986, more than 100 pyrroloiminoquinone (PIQ)-related alkaloids have been identified, and most of them were isolated from marine sponges, and a few were collected from terrestrial organisms [1]. The majority of these alkaloids displayed prominent biological activities, including antitumor [2], antimicrobial [3], antiviral [3a], antimalarial [3a,4], immunomodulatory [5], and anti-feeding activities [6]. Besides the characteristic core PIQ ring, this group of natural products usually possess additional fused, spiro, or bridged carbocycles or heterocycles (**1-5**, Fig. 1) [1b,7]. The challenging structures and remarkable biological activities of these alkaloids have garnered intense interests from synthetic chemists [8]. Although many methods for the synthesis of PIQ units have been developed [9], the strategies for the construction of other attached ring systems are rather underdeveloped.

Atkamine (**6**, Fig. 1) is a brominated PIQ alkaloid isolated from the cold, deep water Alaskan sponge *Latrunculia* sp. by Zou and Hamann in 2013 [10]. Structurally, atkamine features an unprecedented heptacyclic scaffold containing a PIQ, a dihydrobenzothiophene, a bridged azepane ((8-oxa-2-azabicyclo[3.2.1]oct-3-ene), a long (*Z*)-olefin sidechain, and four contiguous stereocenters. Of particular note is a diverse array of heteroatoms within the molecule, including nitrogen, sulfur, oxygen, and bromine. The absolute configuration of atkamine was determined by electronic circular dichroism (ECD) experiments and density functional

theory (DFT) calculation. Furthermore, Hamman *et al.* proposed a biosynthetic pathway of atkamine in which two amino acids (tryptophan and tyrosine) and (*Z*)-15-docosenoic acid are involved, though several key steps have not yet been clarified. The bioactivity of atkamine was not reported, probably due to the low natural abundance (0.000125% isolation yield). The unique polycyclic structure and unknown bioactivity make atkamine an attractive and challenging target for synthetic chemists. To date, there was only one synthetic study toward **6** despite its intriguing structure [11]. As part of our continuing interest in developing novel synthetic strategies toward the halogenated marine natural products [12], we herein report our synthetic progress toward this complex brominated PIQ alkaloid.

The unprecedented structure and preliminary biosynthetic proposal of atkamine inspired us to pursue a modular synthetic strategy. As depicted in Scheme 1, we envisioned that atkamine (**6**) could arise from epoxide precursor **7** through intramolecular epoxide opening by benzenethiol to generate the dihydrothiophene ring (F ring) and subsequent oxidative tetrahydrofuran (D ring) formation. Then **7** could be obtained from olefin **8** by epoxidation. The azepene D ring in **8** could be forged by a formal [5 + 2] annulation of methoxy pyrroloiminoquinone (PIQ-OMe) (**9**) and amino acetal **10** (forming C9–C24 and C10–N13 bonds, highlighted with red lines). Several synthetic approaches to **9** have been reported [9]. **10** could be obtained from **11** by acetalization of the aldehyde group and reduction of the nitro group. The retrosynthetic scission of the C15–C23 bond of **11** led to β -nitrostyrene **12** and aldehyde **13**, which could be connected by an asymmetric Michael addition reaction [13]. As a whole, similar to Hamman's biosynthetic proposal, we anticipated atkamine could

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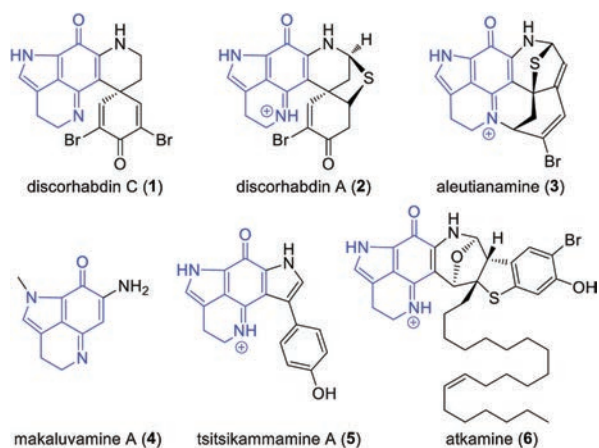


Fig. 1. Selected PIQ alkaloids.

be assembled with three fragments, PIQ-OMe **9**, nitrostyrene **12**, and aldehyde **13** in a convergent manner.

Our synthesis commenced with the synthesis of the long-chain aliphatic enaldehyde **13** from macrolide **14** (Scheme 2). The lactone ring was opened to form a Weinreb amide intermediate, which was further oxidized to generate aldehyde **15** in 79% overall yield. Then the *Z*-olefine **16** was smoothly constructed *via* Wittig reaction, which underwent reduction with DIBAL-H to afford the desired aldehyde **13** in high yield.

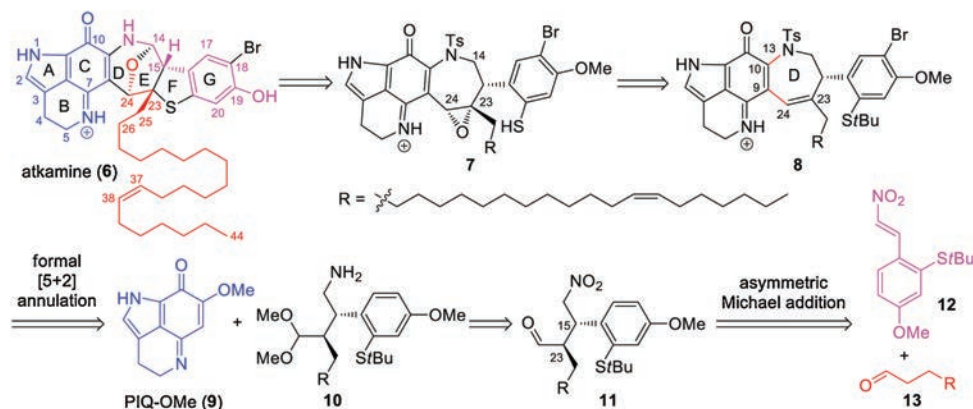
Then we focused on the synthesis of the amino acetal fragment. To supply a large amount of substrate for a thorough exploration of the formal [5 + 2] annulation reaction, a simplified amino acetal **21** was used (Scheme 3). To begin, β -nitrostyrene **18** was prepared from *p*-anisaldehyde **17** and nitromethane through Henry condensation [14]. After a brief survey of reaction conditions, we were delighted to find that when β -nitrostyrene **18** and aldehyde **13** were treated with *L*-proline lithium salt in *t*BuOMe at -20°C , the nitroaldehyde **19** was obtained in 87% yield and 93% *ee* [13c]. Then **19** was converted to the corresponding acetal **20** by treatment with *p*TSA and trimethylorthoformate. Finally, the nitro group in **20** was smoothly reduced to an amino group by LiAlH_4 to deliver the desired amino acetal **21** in 62% yield. Interestingly, when **20** was treated with NaBH_4 in the presence of NiCl_2 , the double bond in the aliphatic chain was saturated while the nitro group was also

reduced to generate an HCl salt (**22**) of the corresponding amino acetal [15]. Fortunately, we got a single crystal structure of **22** (CCDC No. 2001009), which confirmed the absolute configuration of the C15 and C23 stereocenters.

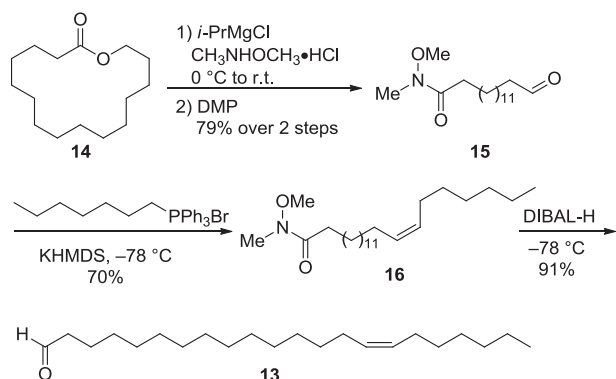
With the amino acetal **21** and PIQ-OMe **9** in hand, our investigation was then focused on the key formal [5 + 2] annulation (Scheme 4). We anticipated that the amino group of **21** would first undergo a Michael addition-elimination cascade with PIQ-OMe **9** to generate the coupling intermediate **24**, which could undergo an intramolecular aldol condensation between the enamine group and the acetal group to form the azepene D ring. To our delight, the coupling reaction of **21** and **9** proceeded smoothly in MeOH at room temperature; however, further treatment of the crude coupling product with TFA only gave dihydropyrrol compound **25** as the sole product. Although DFT calculations showed that the conversion of **25** to the desired azepene product **23** was a thermodynamically viable process ($\Delta G = -1.23$ kcal/mol) (Supporting information for details), we tried many Bronsted acids or Lewis acids at room temperature or upon heating and none of them worked [16]. To evaluate the influence of the steric hindrance of the substrate, we also synthesized the amino acetals devoid of either PMP group or long aliphatic side chain (Supporting information for details). Unfortunately, in these cases, only a tiny amount of the desired azepene products were observed under the above conditions.

To further examine the feasibility of such a challenging formal [5 + 2] annulation strategy, we investigated this transformation with PIQ-OMe **9** and 4,4-diethoxybutanamine **26**, an amino acetal without any extra substituent (Scheme 5). To our great delight, when the above conditions were employed, the azepene ring was successfully constructed to deliver tetracyclic compound **27** in 97% overall yield.

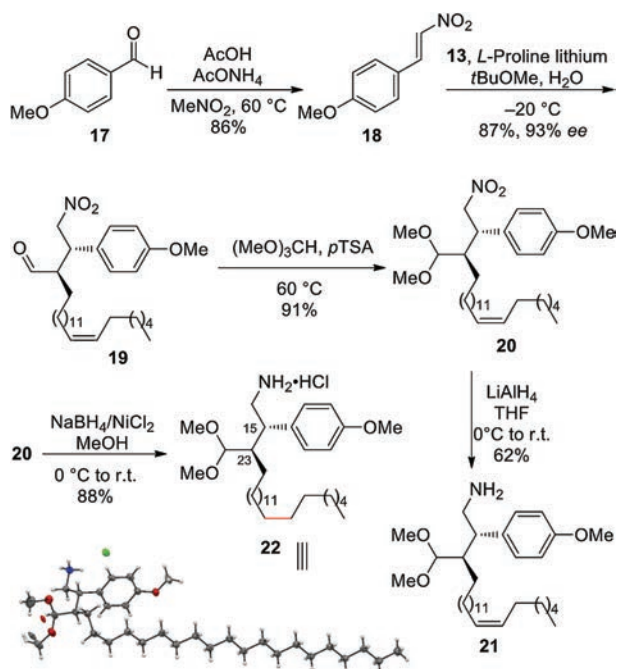
In summary, we have developed a modular strategy towards the complex marine pyrroloiminoquinone alkaloid atkamine, featuring a formal [5 + 2] annulation for the construction of the central azepene D ring and an asymmetric Michael addition to couple the long-chain aldehyde fragment and β -nitrostyrene fragment. The efficient synthesis of the long-chain aliphatic aldehyde **13** and chiral amino acetal **21** have been achieved. A simplified tetracyclic intermediate **27** bearing the core structure of atkamine has been constructed through the formal [5 + 2] annulation. More exploration of the key [5 + 2] annulation in the complex substrate system and the further elaboration of the advance intermediate **27** to atkamine are currently undergoing in our laboratory.



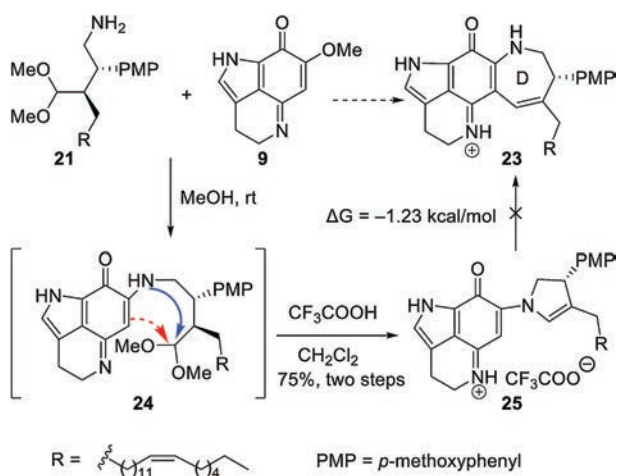
Scheme 1. Retrosynthetic analysis of atkamine (**6**).



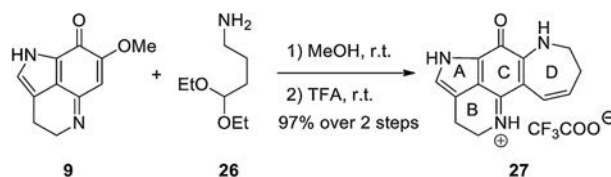
Scheme 2. Synthesis of aldehyde 13.



Scheme 3. Synthesis of aminoacetal 21.



Scheme 4. Attempts for the formal [5 + 2] annulation. DFT calculation was carried out on a model substrate (R = Et) for simplicity.



Scheme 5. A successful model for the formal [5 + 2] annulation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We gratefully acknowledge the National Natural Science Foundation of China for financial support of this work by grants (Nos. 21772164 and 21572187). We thank the National Found for Fostering Talents of Basic Science (NFFTBS, No. J1310024), New Century Excellent Talents in University of Fujian Province (NECTFJ) and Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT) for support.

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.ccl.2020.06.008>.

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