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Total Synthesis of Originally Proposed and Revised Structure of Hetiamacin A

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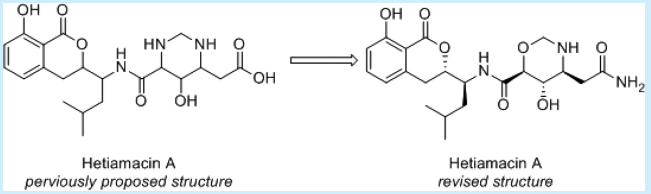
Supporting Information

ABSTRACT: The first total synthesis of the originally proposed and correct structures of hetiamacin A has been accomplished via Wittig olefination and Sharpless asymmetric dihydroxylation reaction. These total syntheses culminated in the stereostructural confirmation of the reassignment of hetiamacin A.



Hetiamacins A−D are new members of the amicoumacin group antibiotics isolated from the cultured broth of *Bacillus subtilis* PJS by our group recently.[1] Its homologue (AI-77-A, **2a**) is a new translation inhibitor that is distinct from the other known antibiotic targeting protein synthesis in chemical scaffold, and it binds to the ribosome in a unique way and inhibits translation by an unusual mechanism.[2] Preliminary bioassays of hetiamacin A have displayed in vitro antibacterial activity (MIC, 2 μg/mL, oxacillin-resistant *Staphylococcus aureus*). The structure of hetiamacin A (Figure 1) was elucidated by spectroscopic methods; however, the stereochemistry of all five chiral centers on hetiamacin A was not determined. As part of our continued interest in these natural products, we herein report the first total synthesis, the revised structure and absolute configuration of hetiamacin A.

The structure of hetiamacin A is similar to that of AI-77-B (**2b**), which is a potent gastroprotective agent.[3] Hetiamacin A could arise from a biogenetic process related to that for AI-77-B (Figure 1). Thus, we hypothesized that all five chiral centers on hetiamacin A preserved the (*S*)-configurations as AI-77-B. Our

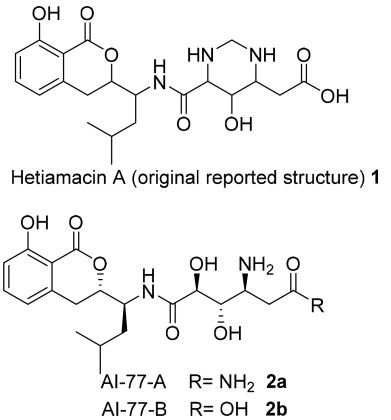


Figure 1. Structures of hetiamacins A, AI-77-A, and AI-77-B.

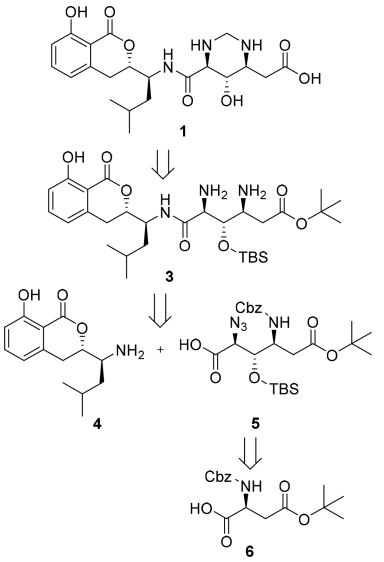


Figure 2. Retrosynthetic analysis of compound **1**.

retrosynthetic analysis of the proposed structure of hetiamacin A is outlined in Figure 2. We planned to introduce hexahydropyrimidine in a late stage from compound **3** by reaction with formaldehyde. Compound **3** would be available by coupling the known isocoumarin **4** and acid **5**. The key intermediate acid **5** could be derived from the commercially available, protected aspartic acid derivative **6** by a route featuring DIBAL-H reduction, Wittig reaction, and Sharpless asymmetric dihydroxylation.

The synthesis of acid **5** is shown in Scheme 1. Aspartic acid derivative **6** was converted to Weinreb amide **7** in the presence of EDCI and NMM at room temperature in 94% yield. Reduction of **7** with DIBAL-H in toluene at −78 °C, followed

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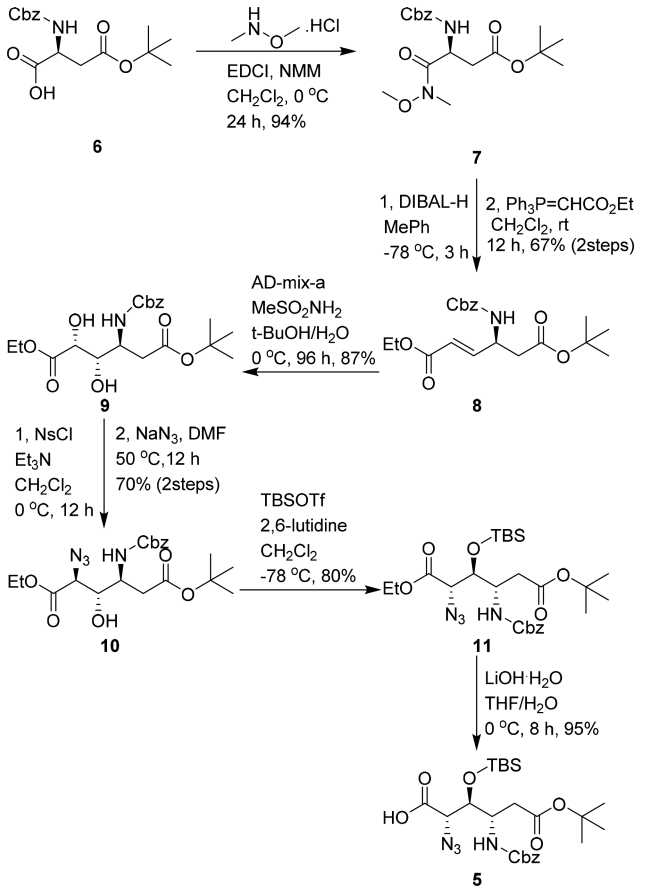
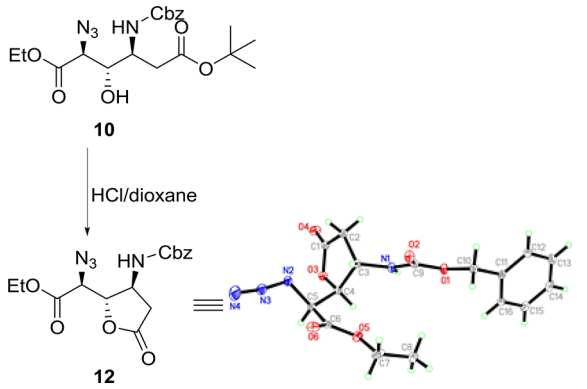
Scheme 1. Synthesis of Amino Acid Fragment



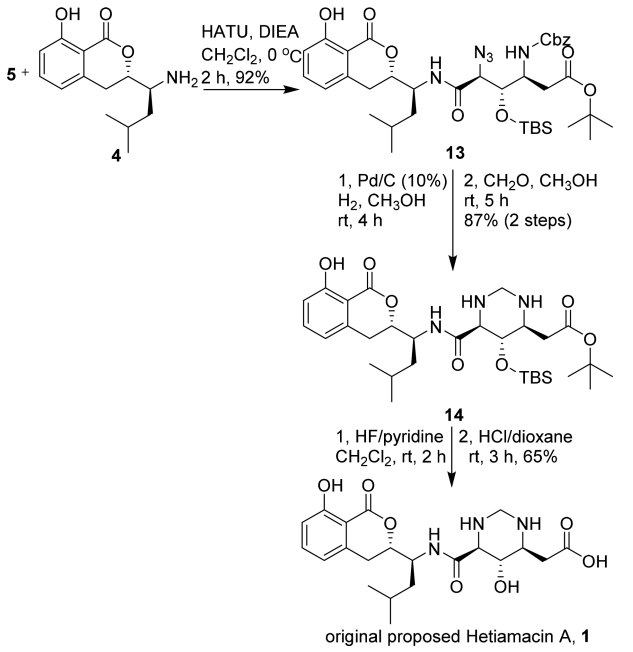
Scheme 2. Synthesis and Crystal Structure of Compound 12



by Wittig olefination of the resulting aldehyde with commercially available ethyl (triphenylphosphoranylidene) acetate, gave **8** in 67% yield for two steps.[4] Sharpless asymmetric dihydroxylation of acrylate **8** using AD-mix-α gave diol **9** in 87% yield as a single diastereomer by ^{1}H NMR analysis.[5] Selective protection of diol **9** with *O*-*p*-nitrobenzenesulfonate (NsCl) in DCM at 0 °C provided the corresponding sulfonate, which was subjected to S_N2 displacement with sodium azide in DMF at 50 °C yielded azide **10** in 70% yield for two steps.[6] TBS protection of **10** using the standard procedure followed by LiOH-mediated hydrolysis provided the acid **5**.[7]

In order to ascertain the absolute stereochemistry of *tert*-butyl ester **9**, single-crystal X-ray crystallization of lactone **12** derived from **9** was carried out.[8] It was revealed that compound **9** conserves the 2*S*,3*S*,4*S* stereochemistry, as shown in Scheme 2.

Scheme 3. Synthesis of Original Proposed Hetiamacin A



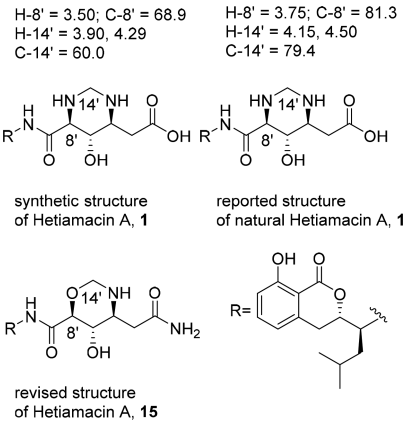


Figure 3. ^{1}H and ^{13}C NMR data of the synthetic and natural hetiamacin A and the revised structure **15**.

With the acid segment **5** in hand, we proceeded to the final stage of the synthesis of compound **1**. Coupling of segment **5** with the known compound **4** in the presence of HATU and DIEA yielded compound **13** in 92% yield.[9] Reduction of the azide moiety and deprotection of the Cbz group simultaneously over palladium on activated carbon (10%) under hydrogen yielded the corresponding diamine compound, which was cyclized by formaldehyde to provide hexahydropyridine **14** in 87% yield over two steps.[10] Removal of the TBS group with HF in pyridine afforded the corresponding alcohol, which upon hydrolysis using HCl in dioxane (1 N) gave the originally proposed hetiamacin A (Scheme 3).[11]

The structure of compound **1** was confirmed by HRMS, ^{1}H NMR, ^{13}C NMR, COSY, HMQC, and HMBC (available in the Supporting Information). Unexpectedly, the ^{1}H and ^{13}C NMR data of the synthetic compound **1** did not match the literature values of naturally occurring hetiamacin A (Figure 3). In

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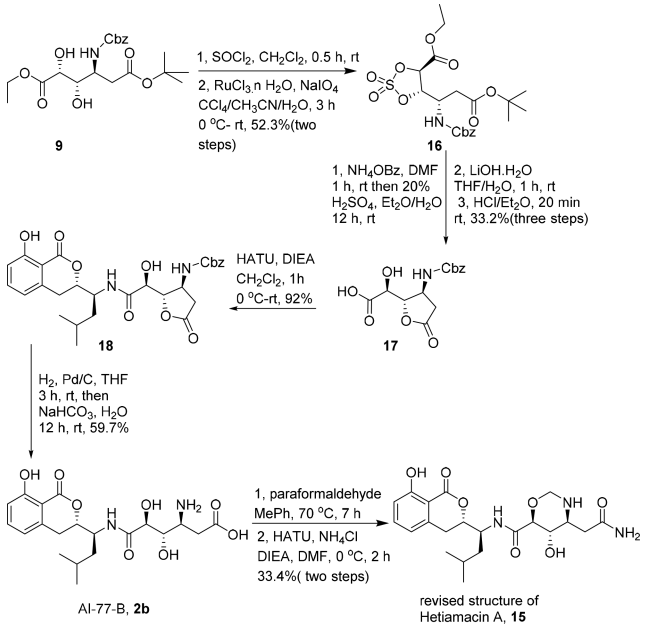
Scheme 4. Synthesis of the Predicted Structure 15 of Hetiamacin A



particular, the chemical shifts of H-8′ and H-14′ were reported to be δ 3.75 and δ 4.15, 4.50, respectively. However, these protons for synthetic **1** were observed at δ 3.50 and δ 3.90, 4.29, respectively. Likewise, significant chemical shift differences for the corresponding C-8′ and C-14′ in the ^{13}C NMR spectra were also observed. For the natural product **1**, the chemical shifts for C-8′ and C-14′ were reported to be δ 81.3 and δ 79.4, whereas in our synthetic compound **1**, these carbon signals were found at δ 68.9 and δ 60.0.

Comparison of the ^{1}H and ^{13}C NMR data originally reported for the natural product **1** with the synthetic compound **1** established that the original structure assignment for hetaiamacin A was incorrect; this significant difference can not arise from the stereochemistry. It seemed more plausible that the actual structure of hetiamacin A should be revised to structure **15**. The revised structure **15** could be easily acquired from AI-77-B by cyclization the 8′-hydroxyl group and 10′-amine group. The total synthesis of AI-77-B was accomplished from diol **9** in 7 steps. Cyclic sulfite formation from **9** and subsequent oxidation with catalytic RuO_4 and stoichiometric $NaIO_4$ provided the cyclic sulfate **16** in 52.3% yield over two steps. The benzoate resulted from the regioselective nucleophilic ring opening of the cyclic sulfate **16** at the less hindered C-2 position giving rise to inversion of stereochemistry at C-2, formed under the acidic hydrolysis conditions. The benzoate group was removed by methanolysis, and subsequent treatment with HCl gave lactone **17** in 33.2% yield over three steps. Coupling of segment **5** with the known compound **4** in the presence of HATU and DIEA yielded compound **18** in 92% yield. Deprotection of the Cbz group simultaneously over palladium on activated carbon (10%) under hydrogen followed by with NaOH aqueous solution gave AI-77-B ($[\alpha]_D^{25}$ = −77.8 (*c* 0.08, MeOH); lit.[8,9b] $[\alpha]_D^{22}$ = −78.2 (*c* 0.08, MeOH); mp 138.5−140 °C; lit.[6] mp 139.5 °C). The absolute stereochemistry of AI-77-B was also ascertained by single-crystal X-ray crystallography. Treatment of AI-77-B with paraformaldehyde in toluene followed by amidation afforded the final product **15** (Scheme 4).[12] The ^{1}H, ^{13}C NMR data of **15** are identical with those of the naturally isolated hetiamacin A. Furthermore, the measured specific rotation of the synthesized **15** $[\alpha]_D^{25}$ = −140.0 (*c* 0.01, MeOH) was agreement with the data of the natural product, $[\alpha]_D^{25}$ = −140.0 (*c* 0.01, MeOH). Therefore, the structure of hetiamacin A was revised to compound **15**, and the absolute configuration of hetiamacin A was confirmed to be 3*S*,5′*S*,8′*S*,9′*S*,10′*S*.

In conclusion, we have achieved the first total synthesis of the originally proposed and corrected structures of hetiamacin A. The stereochemistry of all five chiral centers on hetiamacin A was also assigned to be 3*S*,5′*S*,8′*S*,9′*S*,10′*S* on the basis of our synthetic work. The synthesis features of the originally proposed hetiamacin A include a Sharpless asymmetric dihydroxylation reaction and a Wittig olefination. The synthesis features of revised hetiamacin A include a new way of total synthesis of AI-77-B.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01350.

Experimental procedures and characterization data of all new compounds; NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 1533092 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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