Antibiotics

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Total Synthesis and Structural Reassignment of Aspergillomarasmine A

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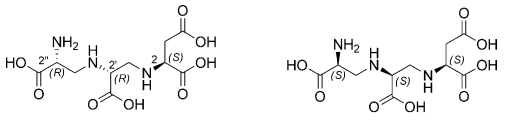
Abstract: *The increase and spread of Gram-negative bacteria that resistant are to almost all currently available β-lactam antibiotics is a major global health problem. The primary cause for drug resistance is the acquisition of metallo-β-lactamases such as metallo-β-lactamase-1 (NDM-1). The fungal natural product aspergillomarasmine A (AMA), a fungal natural product, is an inhibitor of NDM-1 and has shown promising in vivo therapeutic potential in a mouse model infected with NDM-1-expressing Gram-negative bacteria. The first total synthesis and stereochemical configuration reassignment of aspergillomarasmine A is reported. The synthesis highlights a flexible route and an effective strategy to achieve the required oxidation state at a late stage. This modular route is amenable to the efficient preparation of analogues for the development of metallo-β-lactamase inhibitors to potentiate β-lactam antibiotics.*

Since the landmark discovery of penicillin in 1928, antibiotics have become one of the most successful forms of chemotherapy in the history of human medicine.[1] However, the increase and spread of antibiotic resistance has become a severe global public health problem in the past two decades.[2] Among the most important and widely used classes of antibiotics, the β-lactams, which include penicillins, cephalosporins, and carbapenems, account for about half of all antibacterial drugs prescribed, and are essential for the treatment of serious infections caused by Gram-negative bacteria.[3] However, bacteria have developed a number of mechanisms to generate significant resistance against β-lactams, such as the acquisition of β-lactamases, enzymes that hydrolyze the β-lactam ring.[4] There are two major types of β-lactamase. The first class comprises serine-dependent enzymes, such as extended-spectrum β-lactamase (ESBL).[5] Several effective small-molecule inhibitors of serine-lactamases are clinically available, such as clavulanic acid and sulbactam, and these are used in combination with β-lactam antibiotics.[6] The second class is metallo-β-lactamases (MBLs), such as New Delhi metallo-β-lactamase-1 (NDM-1),[7] which are Zn^{II}-dependent enzymes. Unfortunately, no corresponding inhibitors for MBLs have so far been developed for clinical use.[8] Given the recent emergence of MBLs as a major driving force for the rapid spread of resistance in Gram-negative bacteria, which is significant clinical threat,[9] there is a pressing need for the development of potent and safe small-molecule inhibitors of MBLs.

Natural products have played a central role in antibiotic drug discovery,[10] which is further emphasized by the identification of the fungal natural product aspergillomarasmine A (AMA) as a potent inhibitor of NDM-1.[11] In 2014, Wright and co-workers reported that AMA could overcome metallo-β-lactamase antibiotic resistance by inhibiting NDM-1 ($IC_{50} = 4.0 \pm 1.0$ μM).[11a] AMA also showed good selectivity for MBLs over serine β-lactamases. Moreover, AMA has shown promising in vivo therapeutic potential in a mouse model infected with NDM-1-expressing Gram-negative bacteria.[11a]

AMA was originally identified and characterized in the early 1960s.[12] The molecule was first evaluated for its inhibitory effect against human angiotensin-converting enzyme (ACE).[13] Notably, the three stereogenic centers of the original structure **1**, proposed by Lederer and co-workers, were determined to be (2″*R*,2′*R*,2*S*) on the basis of degradation studies, as well as the fact that both the 2′ and 2″ amino groups of AMA are unreactive to *Crotalus adamantus* L-amino acid oxidase and are therefore derived from D-amino acids (Figure 1).[12] All of the following studies on this natural product adopted this originally proposed structure (**1**). Møller and co-workers have since suggested that AMA might have (2″*S*,2′*S*) configurations at C2′ and C2“ based on their biosynthetic studies.[14] However, no direct and conclusive evidence supported their hypothesis. Therefore, total synthesis represents the only practical means by which the



1: (*R*,*R*,*S*)-aspergillomarasmine A (proposed structure)

2: (*S*,*S*,*S*)-aspergillomarasmine A (revised structure)

Figure 1. Proposed (**1**) and revised (**2**) structures of aspergillomarasmine A.

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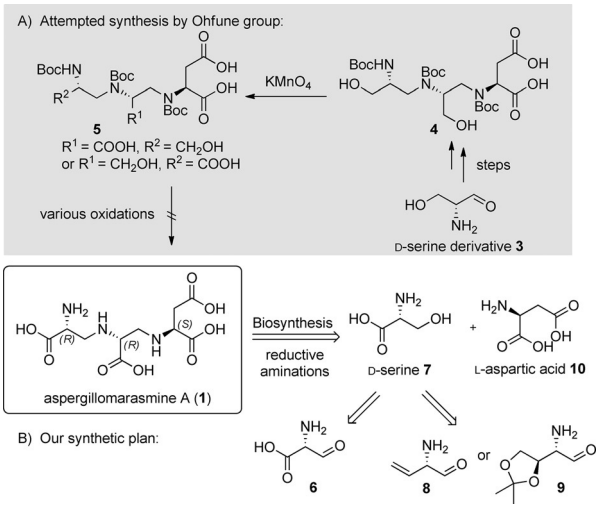
correct structure of AMA can be elucidated unambiguously.[15] Herein, we report the first total synthesis of AMA through a modular approach that is amenable to derivatization for analogue synthesis. Our synthetic studies also enabled us to revise the originally proposed structure of AMA (Figure 1).

The chemical syntheses of AMA and related natural products have proven to be challenging. The Ohfune group has investigated the total synthesis of this family of natural products.[16] Unfortunately, they failed to achieve the total synthesis of AMA.[16a] As depicted in Scheme 1 A, Ohfune

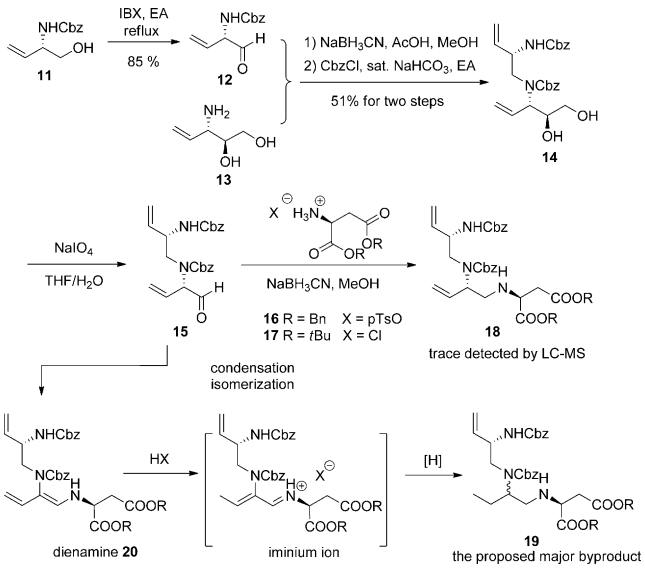


Scheme 1. Previous synthetic studies and our synthetic plan.

and co-workers successfully coupled three amino acid equivalent building blocks, including D-serine derivative **3** and an L-aspartic acid derivative to afford diol **4**, but they were unable to achieve the late-stage oxidation of both hydroxy groups of **4** and were only able to produce **5**, despite examination of various oxidation conditions.[16a]

We therefore recognized during our synthetic planning that the selection of suitable carboxylic acid precursors would be critical. The presence of a carboxylic acid group from an early stage was precluded by the expected racemization of compound **6** during oxidation from serine **7**. Consequently, we decided to use alkene **8** and protected diol **9** as carboxylic acid synthons to be unmasked after conjugation of the three amino acid derivatives (Scheme 1 B). The strategy for N-alkyl bond formation was also carefully considered: the presence of several nitrogen atoms in a target molecule is known to complicate total syntheses owing to the basicity of nitrogen atoms and their susceptibility to oxidation.[17] We envisaged that reductive amination would serve as the key conjugation reaction. The mild reaction conditions would prevent racemization and facilitate sequential transformations with minimal requirements for workup and purification. The selection of suitable protecting groups would be essential for the success of the synthesis, considering the presence of various polar and reactive functionalities.

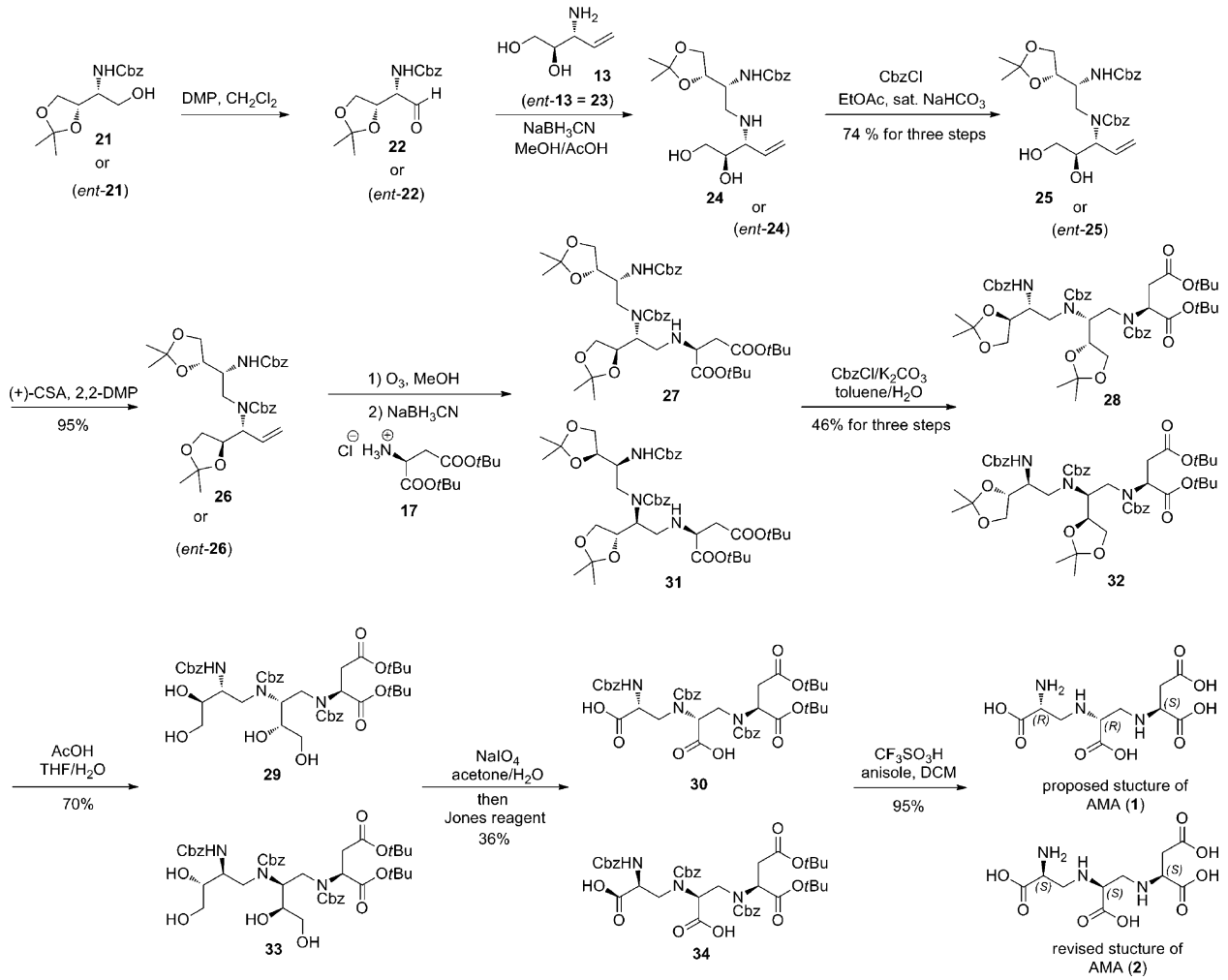
Our initial attempts began with IBX oxidation of the readily available chiral alcohol **11**, which was prepared from commercially available 2-butene-1,4-diol in 43 % yield over four steps,[18] to afford aldehyde **12** in 85 % yield with93 % *ee* (Scheme 2).[19] Reductive amination of aldehyde **12** with the



Scheme 2. Attempted synthesis of AMA from alkenes. IBX = 2-iodoxy benzoic acid, CbzCl = benzyl carbonochloridate, EA = ethyl acetate.

known amine **13**, which was obtained from commercially available material in three steps with 65 % yield and 99 % *ee*,[20] and subsequent in situ Cbz protection of the newly formed secondary amine moiety smoothly generated diol **14** in 51 % yield over two steps. Oxidative cleavage of diol **14** with $NaIO_4$ in a mixture of THF and H_2O provided the crude aldehyde **15**, which was used directly in the next reductive amination step involving treatment with either Bn- or ^{t}Bu-protected aspartic acids **16** and **17**, respectively. Unfortunately, all of these attempts failed to deliver the desired product **18**. Instead, during the reductive amination process, we always observed a complex mixture of byproducts. Based on the preliminary NMR and LC–MS analysis, we postulated that the major byproduct might be **19**, which was presumably generated via dienamine **20** through migration of the terminal double bond under acidic conditions, followed by sequential 1,4- and 1,2-reductions of the iminum species.

In order to avoid the alkene isomerization problem, we proposed that diol **9** may be a better carboxylic acid synthon. Accordingly, the revised synthetic route commenced with Dess–Martin oxidation of the reported chiral alcohol **21**, which was obtained from commercially available 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane in four steps with 50 % yield and 99 % *ee*,[21] to afford the desired aldehyde **22** (Scheme 3). To our delight, the first reductive amination between aldehyde **22** and the readily available amine **13** proceeded smoothly to furnish the desired amine **24** without any racemization (within our limits of detection). Compound **24** was protected in situ with Cbz to afford **25** in 74 % yield over three steps. The free diol moiety of **25** was subsequently protected with 2,2-dimethoxylpropene to generate alkene **26** in 95 % yield. Ozonolysis of the alkene efficiently afforded



Scheme 3. Total synthesis and structural reassignment of aspergillomarasmine A. DMP = Dess–Martin periodinane, (+)-CSA = (+)-camphorsulfonic acid, 2,2-DMP = 2, 2-dimethoxylpropene, Jones reagent = a solution of chromium trioxide in dilute sulfuric acid and water.

the crude aldehyde, which was directly used for the following reductive amination with ^{t}Bu-protected aspartic acid **17** to generate amine **27**, followed by in situ Cbz protection to afford **28** in 46% yield over three steps. Selective removal of two acetonide groups with AcOH afforded tetraol **29** in 70% yield. Subsequent oxidative cleavage of the vicinal diol group with $NaIO_4$ in a mixture of acetone and H_2O furnished the crude aldehyde intermediate, which was oxidized using the Jones reagent to generate the desired di-acid **30** in 36% yield.

With compound **30** in hand, we were in a position to complete the synthesis after global deprotection to remove the three Cbz groups and two *tert*-butyl groups (Scheme 3). However, this process proved challenging. Initially, we sought to remove the *tert-butyl* groups with TFA to generate the desired tetra-acid first, followed by hydrogenolysis of the Cbz group with a Pd catalyst. A number of conditions (Pd black, Pd/C, $Pd(OH)_2/C$, etc.) were examined, yet few were successful. We then decided to explore the possibility of removing both the *tert-butyl* and Cbz groups under acidic conditions. A variety of acids, including CH_3SO_3H, HCl, CF_3COOH, CF_3SO_3H, and $AlCl_3$, were surveyed for their ability to promote the deprotection process. Ultimately it was discovered that treatment of **30** with CF_3SO_3H[22] and anisole in dichloromethane effected a clean and complete global deprotection in one vessel to afford the desired (*R*,*R*,*S*)-AMA (**1**) in 95% yield. We anticipate that this mild and robust global deprotection method will find further applications in peptide synthesis.

Unfortunately, the ^{1}H and ^{13}C NMR spectra, as well as the optical rotation value of synthetic (*R*,*R*,*S*)-AMA (**1**) were not identical to those reported for the natural product,[11a,19] which suggested that structural reassignment is required. In agreement with Møller and co-workers' suggestion that C2′ and C2″ of aspergillomarasmine A have an *S* configuration, we postulated that AMA has the revised (*S*,*S*,*S*) structure **2**. Accordingly, we conducted the chemical synthesis of the proposed new structure for AMA by following our previously established synthetic route (Scheme 3). As a result, (*S*,*S*,*S*)-AMA (**2**) was efficiently generated from *ent*-**21**. To our delight, synthetic (*S*,*S*,*S*)-AMA (**2**) exhibited ^{1}H and ^{13}C NMR spectra indistinguishable from those reported for the natural isolate.[11a,19] In addition, the optical rotation value of **2**

($[\alpha]_D^{23} = -51.2$, $c = 0.8$, pH 7 phosphate buffer) was consistent with that of the natural product ($[\alpha]_D^{20} = -48$, $c = 1$, pH 7 phosphate buffer), which unambiguously establishes the absolute configurations of AMA. Moreover, we applied the same synthetic route to obtain the other two possible isomers (*R*,*S*,*S*)-AMA and (*S*,*R*,*S*)-AMA. The ^{1}H and ^{13}C NMR spectra of these two isomers did not fully match those of the natural isolate.[19] Collectively, the results unambiguously show that the configuration of AMA should be reassigned as (*S*,*S*,*S*).

Wright and co-workers have demonstrated that the natural product AMA has good in vitro dose-dependent inhibition against metallo-β-lactamase NDM-1 and related MBLs such as VIM-2.[11a] To validate the NDM-1 inhibition activity of our synthetic samples, we performed an enzyme inhibition assay with the purified NDM-1 protein and nitrocefin as a substrate (Figure 2).[19] As expected, the revised

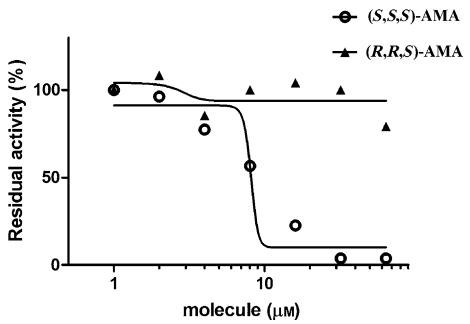


Figure 2. Inhibition of NDM-1 by (*S*,*S*,*S*)-AMA. (*S*,*S*,*S*)-AMA (white circles) inhibits NDM-1 with a half-maximal inhibitory concentration (IC_{50}) value of 8.1 μM, while (*R*,*R*,*S*)-AMA shows no inhibition activity against NDM-1.

structure (*S*,*S*,*S*)-AMA (**2**) showed significant in vitro dose-dependent inhibition of NDM-1. Interestingly, the originally proposed structure (*R*,*R*,*S*)-AMA (**1**) showed no inhibition of NDM-1 whatsoever. Thus, both our biological and chemical studies confirm that natural AMA should have the reassigned structure **2**. Furthermore, this interesting result provides initial leads for the development of more effective AMA-derived antibiotics.

In summary, we have accomplished the first total synthesis of the natural product aspergillomarasmine A, a potent and selective inhibitor of NDM-1. In the course of our synthetic studies, we reassigned the stereochemical configurations of the originally proposed structure of AMA. The structurally revised synthetic AMA was confirmed to have same inhibitory effect on NDM-1 as the naturally occurring AMA. We have also developed an effective late-stage oxidation strategy and a robust global deprotection method that might find further synthetic application in peptide natural product synthesis. Notably, our synthesis features a convergent, flexible, and stereocontrolled route that is amenable to the efficient preparation of analogues. Studies towards the development of more potent and selective metallo-β-lactamase inhibitors based on AMA are currently ongoing in our laboratory.

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Keywords: antibiotics · aspergillomarasmine A · metallo-β-lactamase · structural reassignment · total synthesis

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