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Asymmetric Total Syntheses of Aetheramides and Their Stereoisomers: Stereochemical Assignment of Aetheramides

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(5) Supporting Information

ABSTRACT: The concise total syntheses of the potent HIV inhibitors aetheramides A and B (IC_{50} values of 15 and 18 nM), as well as three pairs of their stereoisomers, were achieved, which allowed the complete stereochemical assignment of aetheramides for the first time. With a longest linear sequence of 15 steps, the convergent, fully stereocontrolled route provided aetheramides A and B in 5.3% and 3.6% yields, respectively. The synthetic strategy features efficient Stille coupling for macrocyclization, asymmetric aldol reactions to



establish the ambiguous stereochemistries at C-17 and C-26, and implementation of mild conditions to avoid the epimerization of the sensitive polyketide moiety and the migration of the labile lactone.

Myxobacteria is known as a famous natural product producer, and many of its second metabolites feature unique structures and novel mechanisms of action.¹ Aetherobacter is a new myxobacterial genus discovered by Müller's group in 2010.² Aetheramides A and B (Figure 1) were isolated from A. rufus (SBSr003), the first stain of Aetherobacter, in 2012. Aetheramides A and B potently inhibited HIV-1 infection with IC₅₀ values of 15 and 18 nM, respectively, and showed cytostatic activity against human colon carcinoma (HCT-116) cells with IC₅₀ values of 110 nM. They also exhibited moderate antifungal activity against Candida albicans.³

Aetheramides A and B possess structurally distinctive cyclic depsipeptide with six chiral centers, a unique polyketide moiety and two amino acid residues, in which D-3-(4-hydroxy-3-methoxyphenyl)-2(methylamino)propanoic acid (D-mNMe-Tyr) had not been previously reported in natural products.



Figure 1. Structures and activities of aetheramides A and B.

Scheme 1. Retrosynthetic Analysis of Aetheramide B and Its C-17 and C-26 Stereoisomers 2a-d



Aetheramides are structurally distinct from all reported HIV inhibitors⁴ and may be associated with novel mechanisms of action. Despite vigorous efforts, the absolute stereochemistries at

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Scheme 2. Synthesis of D-Fmoc-mNMeTyr 5



C-17 and C-26 remained undetermined.³ Moreover, aetheramides were isolated in small amounts, and their further studies were hampered.

The syntheses of aetheramides were expected to be challenging. The ester migration between the two adjacent hydroxyl groups at C-33 and C-34 was reported, and aetheramides A and B reached a 1:1 equilibrium in MeOH within 24 h.³ In addition, the epimerization at C-17 could be easily triggered under either basic or acidic conditions. Therefore, their syntheses require carefully planned transformations under mild conditions. Due to the unique structures and promising biological activities, several groups have focused on the syntheses of aetheramides.⁵ Herein, we disclose concise and efficient asymmetric syntheses of aetheramides, as well as three pairs of their stereoisomers. The undetermined absolute stereochemistries of aetheramides were completely established for the first time.

Aetheramide B was chosen as the first target. Since the stereochemistries of C-17 and C-26 were undetermined, the syntheses of all possible structures (2a-d) of aetheramide B were planned. As shown in the retrosynthetic analysis (Scheme 1), the 21-membered macrocycle core could be constructed via the intramolecular Stille coupling⁶ of vinylstannane–vinyl iodide precursors 3a-d, which could be assembled through the condensations of vinyl iodo acids 9a-d and vinylstannane amine 4, respectively. Vinyl iodo acids 9a-d could in turn be derived from esters 12a,b, which were planned to arise from aldehyde 13^7 through asymmetric vinylogous Mukaiyama aldol reaction (VMAR). Vinylstannane amine 4 could be prepared from the sequential condensations of (*E*)-vinylstannane alcohol 6, Fmoc-L-valine and the novel D-mNMeTyr fragment 5. The vinylstannane group in 6 could be generated from the terminal

Scheme 3. Synthesis of Vinylstannane Amine 4

Scheme 4. Syntheses of Vinyl Iodo Acids 9a-d



alkyne in 7, which could be readily accessed from *trans*-ethyl cinnamate 8.

The novel D-Fmoc-mNMeTyr fragment **5** is an important component of vinylstannane amine **4**, whose synthesis is shown in Scheme 2. Iodo-D-serine 14^8 was allowed to react with aryl iodide 15^9 under Negishi conditions. The best result was achieved by applying the combination of Pd₂(dba)₃ and Sphos,¹⁰ furnishing compound **16** in 89% yield. The removal of the TBS group with TBAF, followed by the hydrolysis of the ester with lithium hydroxide, provided acid **17**, which was again protected with a TBS group to afford acid **18** in excellent yield. The *N*-methylation of **18** with NaH/MeI/THF provided optically pure **19** in 75% yield.¹¹ The Boc group in **19** was removed with TFA, followed by the treatment with FmocCl to yield Fmoc-protected fragment **5** in 92% yield.



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Scheme 5. Syntheses of Aetheramide A (1a), Aetheramide B (2a), and Their C-17 and C-26 Stereoisomers 1b-d and 2b-d

Scheme 6. Direct Synthesis of Aetheramide A



The synthesis of vinylstannane amine 4 started from transethyl cinnamate 8 (Scheme 3), which was subjected to the standard Sharpless asymmetrical dihydroxylation to provide optically pure diol **20** in 90% yield and 99% ee.¹² The diol was then protected with acetonide, and the ethyl ester was reduced to aldehyde and subsequently converted into terminal alkyne by Ohira-Bestmann reagent.¹³ The acetonide group was then removed using Amberlyst 15, and the resulting diol 23 was monoprotected with TES group to afford 24 and 7 in 50% and 46% yields, respectively, when the reaction was carried out at room temperature for an extended period of time. Silyl ether 24 could be obtained in 70% yield when the reaction was conducted at 0 $^\circ C$ for 3 h. Silyl ethers 7 and 24 could be used for the syntheses of the 21-membered macrocycles 2a-d and the 22membered macrocycles 1a-d, respectively, or easily recycled via diol 23.

Hydrostannation of alkyne 7 with Bu₃SnH and Pd(PPh₃)₂Cl₂ led to (*E*)-vinylstannane alcohol **6**.¹⁴ The ester-coupling reaction of **6** with Fmoc-L-valine in the presence of DCC/DMAP provided the desired ester **25** in 80% yield. The removal of the Fmoc group in **25** was found to be a bit complicated. The classical condition using piperidine led to unidentified products. Amine **26** could finally be obtained in excellent yield using DBU/ HOBt/DMF,¹⁵ and its coupling with the D-Fmoc-m/MeTyr fragment **5** and subsequent deprotection of the Fmoc group in **27** with piperidine led to key vinylstannane amine **4** smoothly.

The syntheses of vinyl iodo acids 9a-d were a challenge due to the difficulty in constructing the stereocenter of the isolated methoxyl group at C-26 and the adjacent (E)-1-iodo-2-methyl olefin. A number of synthetic strategies were examined, and an efficient route was developed as shown in Scheme 4. With tryptophane-based B-phenyloxazaborolidinone OXB-A¹⁶ as chiral Lewis acid and THF as solvent, alcohol 29a was obtained in 84% yield and 94% ee from aldehyde 13 under an optimized condition. Alcohol 29b could also be prepared with chiral Lewis acid OXB-B in good vield and ee value following a similar procedure. Alcohols 29a,b were then methylated. The transformation from the unsaturated esters 12a,b to alcohols 30a,b were found to be quite challenging due to the sensitivity of the iodo olefin moiety to most reducing conditions. Eventually, the combination of LiAlH₄ and proper solvents (CH_2Cl_2/THF , 1:1) provided 30a,b in excellent yields. Oxidation of alcohols 30a,b into aldehydes 11a,b followed by Wittig reaction with 31 led to esters 32a,b. After DIBAL-H reduction and DMP oxidation, the resulting aldehydes 10a,b were subjected to Evans aldol reactions with chiral auxiliaries 33a,b followed by the hydrolysis of the amides to provide key vinyl iodo acids 9a-d.

With acids 9a-d and amine 4 in hand, the synthesis of aetheramide B was embarked (Scheme 5). Under an optimized coupling condition, the coupling between 9a-d and 4 afforded vinylstannane-vinyl iodide precursors 3a-d in 55%-64% yields using HATU/DIPEA/DMF. The moderate yields were the consequence of the instability of acids 9a-d under amidecoupling conditions. The intramolecular Stille coupling of 3a-dwas critical in the total synthesis. With precursor 3a, many catalytic systems were screened. $Pd_2(dba)_3/AsPh_3/DIPEA^{17}$ was found to be the most efficient, and the cyclization of 3a was completed in 1 h at room temperature in 82% yield. The other three macrocycles 35b-d were also obtained in good yields under the same reaction conditions. Subsequently, the oxidation of the hydroxyl group at C-19 with DMP produced compounds 36a-d in excellent yields. Fortunately, the configuration of C-17 was not influenced under these oxidation conditions, and 36a-d were obtained as optically pure products.

The final deprotection of the silyl groups in **36a**–**d** was also crucial. To remove the TES and TBS in **36a**–**d**, a large number of

deprotection conditions were examined. Conditions with acid reagents (such as CSA) always provided a significant amount of unidentified polar byproducts. To our pleasure, the deprotection of 36a was efficient with TBAF/AcOH (molar ratio 1:1, 0.02 M in THF), providing 2a in 61% yield and its 22-membered isomer 1a from ester migration in 30% yield. Following the same reaction conditions, compounds 2b-d and 1b-d were obtained in combined yields of 66%-70%: 28%-42% for 2b-d and 28%-38% for 1b-d. The concentration of TBAF/AcOH was important for this deprotection, as more concentrated TBAF/ AcOH resulted in messy products. Fortunately, the stereocenter at C-17 in la-d and 2a-d was not impacted under the optimized conditions. Compound 1c could migrate to 2c spontaneously even in solvents other than MeOH and reach a ratio of 3.5/1 (1c/2c) rapidly; however, pure 1a,b, 1d, and 2a-d remained unchanged for at least 2 months at 4 °C.

The ¹H NMR and ¹³C NMR of 1a-d and 2a-d were compared with those of natural aetheramides A and B.³ The ¹H NMR and ¹³C NMR of 1a (17*R*,26*R*) and 2a (17*R*,26*R*), as well as their 2D spectra (COSY, HSQC, and HMBC), matched the reported spectra and/or data nicely.¹⁸ On the other hand, the spectra of 1b-d and 2b-d exhibited significant differences from the reported data. Thus, the two undetermined stereochemistries at C-17 and C-26 in aetheramides A and B were assigned as 17*R* and 26*R*.

Aetheramide A (1a) could be synthesized more directly from silyl ether 24, following a similar reaction sequence (Scheme 6; see the Supporting Information for details). The final deprotection of the silyl groups again proved to be sensitive. The use of TBAF/AcOH led to a complex mixture. After careful screening of reaction conditions, 0.05 M CSA in MeOH was found to be effective for the deprotection, affording 1a in 89% yield. Aetheramide B (2a) from ester migration was not observed under this deprotection condition. The overall yield for aetheramide A was 5.3% with 15 linear steps. Aetheramide B (2a) could be obtained from aetheramide A (1a) via ester migration.

In summary, a concise and efficient asymmetric route was developed to synthesize aetheramides A and B, as well as three pairs of their stereoisomers. Aetheramides A and B were synthesized in a longest linear sequence of 15 steps with overall yields of 5.3% and 3.6%, respectively, starting from commercially available *trans*-ethyl cinnamate **8**. The ambiguous stereo-chemistries at C-17 and C-26 were assigned as 17*R* and 26*R*, respectively, by comparing the NMR data of the synthetic samples with the reported. This is the first time the absolute stereochemistries of aetheramides have been fully established. The syntheses of more aetheramide analogues and their biological evaluations are underway, and the results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02371.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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