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An Enantioselective Synthesis of a MEM-Protected Aetheramide A Derivative

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Abstract

Aetheramides A and B are very potent anti-HIV agents. An enantioselective synthesis of a MEM-protected aetheramide A derivative is described. The synthesis was accomplished in a convergent and stereoselective manner. The key reactions involved asymmetric dihydroxylation, asymmetric allylation, asymmetric *syn*-aldol reactions and asymmetric hydrogenation.

Keywords

Anti-HIV; Anticancer; Natural product; Asymmetric synthesis; Aetheramides

Natural products are traditionally an excellent source of bioactive compounds including a variety of anti-HIV agents.^{1,2} While anti-HIV drugs developed through drug-design have greatly improved mortality and morbidity of HIV/AIDS patients, there has been a great deal of interest in natural product derived lead structures.^{3,4} Aetheramides A and B (**1** and **2**, Figure 1) are unsaturated cyclic depsipeptides isolated from a novel myxobacterial genus *Aetherobacter* in 2012 by Müller and co-workers.^{5,6} Both aetheramides A and B contain a unique polyketide segment and a depsipeptide unit. Both these natural products exhibited potent anti-HIV activity with antiviral IC₅₀ values around 15 nM, however, the mechanism of action has not yet been reported.⁶ Aetheramides also displayed cytostatic activity against human colon carcinoma cell lines with IC₅₀ values of 110 nM. Furthermore, they have shown moderate antifungal activity against *Candida albicans* at loads of 20 µg/disk. Initial structures of aetheramides were elucidated by extensive NMR and mass spectral analysis, as well as chemical derivatizations and quantum mechanical calculations. The assignment of absolute stereochemistry of four of the six asymmetric centers has been reported. However, the stereochemistry of the C17 and C26 asymmetric centers has not yet been assigned. The potent anti-HIV activity of aetheramides and their unique structural features attracted our

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Supplementary Data

Supplementary data associated with this article can be found in the online version.

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interest in their synthesis for structure-activity studies, investigation of mode of action, and design of novel structural variants. Herein, we report our preliminary synthetic efforts leading to an enantioselective synthesis of a protected aetheramide A derivative.

As depicted in Figure 2, aetheramide A features a number of sensitive functionalities that are prone to elimination or epimerization. Particularly, the allylic ether at C26 and the methyl group at C17, both with unknown stereochemistry. As shown, our initial synthetic plan relied upon a cycloamidation reaction to construct the 22-membered macrocycle. Disconnection of the amino acid unit leads to polyketide unit **3**, valine, and tyrosine derivative **4**. The polyketide segment **3** can be assembled from α,β -unsaturated aldehyde **5** by an Evans aldol reaction. The C26-methyl ether stereochemistry is unassigned, however, we planned to synthesize the 26-(*S*)-isomer as a starting point using an asymmetric allylation reaction of the corresponding **6**-derived aldehyde. This unsaturated ester can be constructed from optically active diol **7** which would be obtained by Sharpless asymmetric dihydroxylation of *trans*-ethyl cinnamate **8**.

The synthesis of homoallylic alcohol **11** is shown in Scheme 1. Optically active *syn*-diol **7** was prepared in multigram quantities by asymmetric dihydroxylation of ethyl cinnamate using a known procedure.⁷ Treatment of diol **7** with TBSCl in the presence of pyridine resulted in selective protection of the benzylic alcohol in 50% yield.⁸ Reaction of the resulting alcohol with MEMCl in the presence of diisopropylethylamine (DIPEA) afforded MEM derivative **9** in 85% yield. Reduction of ester **9** with DIBAL-H provided the corresponding alcohol which was subjected to Swern oxidation to give an aldehyde. Wittig reaction of the aldehyde provided Weinreb amide **10** in 76% yield over 3 steps.⁹ Reaction of Weinreb amide **10** with DIBAL-H followed by Wittig reaction of the resulting aldehyde afforded unsaturated ester **6** in 83% yield over two steps. Reaction of compound **6** with DIBAL-H followed by Swern oxidation of the resulting alcohol provided the corresponding aldehyde in 88% yield over two steps. Asymmetric allylation of the resulting aldehyde with allyltributylstannane in the presence of a catalytic amount of (*S*)-BINAP (30 mol%) and AgOTf (30 mol%) afforded (*S*)-homoallylic alcohol **11** as the only diastereomer in 63% yield (87% BRSM).¹⁰

Synthesis of polyketide segment **3** is outlined in Scheme 2. Reaction of compound **11** with NaH and MeI followed by hydroboration-oxidation provided alcohol **12** in 71% yield over two steps. Alcohol **12** was treated with methanesulfonyl chloride in the presence of Et₃N to provide the corresponding mesylate. Reaction of the resulting mesylate with NaCN furnished nitrile **13** in 69% yield over two steps. Nitrile **13** was subjected to DIBAL-H reduction to provide the corresponding aldehyde. Wittig reaction of the resulting aldehyde afforded unsaturated aldehyde **5** in 65% yield over two steps. Aldol reaction of aldehyde **5** and chiral oxazolidinone **14** using Evans protocol afforded *syn*-aldol product **15** as a single isomer in 82% yield. The alcohol was protected as its TBS ether with TBSOTf in the presence of 2,6-lutidine. Hydrolysis of the oxazolidinone using LiOH-H₂O₂ provided acid **3** in 70% yield over two steps.

Synthesis of tyrosine derivative **4** is shown in Scheme 3. Acylamido cinnamate ester **16** was prepared as described in the literature.¹¹ Asymmetric hydrogenation of **16** was carried out

with chiral rhodium catalyst using conditions developed by Boaz *et al* to afford an optically active amino acid derivative.¹² Removal of the benzyl protecting group by catalytic hydrogenation furnished amino acid **18** in 75% yield (over two steps) with 98% *ee*. Deprotection of *N*-acetyl group of **18** by exposure to methanesulfonic acid followed by reaction of the resulting amine with benzylchloroformate resulted in Cbz-protection of amine as well as formation of *O*-carbobenzyloxy derivative. Selective hydrolysis of *O*-carbobenzyloxy group was achieved with K₂CO₃ in methanol to furnish Cbz-derivative **19** in 48% yield over three steps. Reaction of phenol **19** with MEM-Cl and DIPEA followed by *N*-methylation¹³ and subsequent removal of the *N*-Cbz protecting group afforded amino acid derivative **4** in 51% yield over 3 steps.

As shown in Scheme 4, coupling of acid **3** with amine **4** in the presence of BOPCl gave the corresponding amide **20** in 63% yield. The TBS ether of benzyl alcohol was selectively deprotected using TBAF-AcOH (1.6:1). The corresponding alcohol was obtained in 70% yield. Esterification of the resulting alcohol with F-Moc valine using EDC, DIPEA and DMAP afforded compound **21** in 70% (93% BRSM) yield. Hydrolysis of the methyl ester was accomplished using Me₃SnOH in refluxing CH₂Cl₂ to provide the corresponding acid in 82% yield.¹⁴ Fmoc deprotection followed by cycloamidation using BOPCl¹⁵ afforded compound **22** in 57% yield over two steps. Treatment of compound **22** with TBAF-AcOH (5:1) followed by oxidation of the resulting alcohol using DMP provided α -keto cycloamide **23** in 53% yield over two steps.¹⁶ To complete the synthesis of aetheramide or its stereoisomer, we require to deprotect two MEM-protecting groups. Our subsequent attempts to remove MEM groups from cycloamide **23** under acid-catalyzed conditions however, resulted in elimination of the methyl ether followed by decomposition to a mixture of unidentified products.

In conclusion, we have accomplished an enantioselective synthesis of MEM-protected aetheramide A derivative. The synthesis is convergent and features asymmetric dihydroxylation, asymmetric allylation, asymmetric *syn*-aldol reactions and asymmetric hydrogenation as the key reactions. Our attempted removal of MEM protecting groups resulted in decomposition of the product. Further investigation leading to the total synthesis of aetheramide A structure and structure-activity studies is in progress.

Supplementary Material

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Acknowledgments

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16. For more details, please see supporting information section.

Figure 1.
Structures of aetheramides A and B.

Figure 2.
Retrosynthesis of aetheramide A.

Scheme 1.
Synthesis of homoallylic alcohol **11**.

Scheme 2.
Synthesis of polyketide segment **3**.

Scheme 3.
Synthesis of optically active amino acid **4**.

Scheme 4.
Synthesis of cycloamide **23**