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

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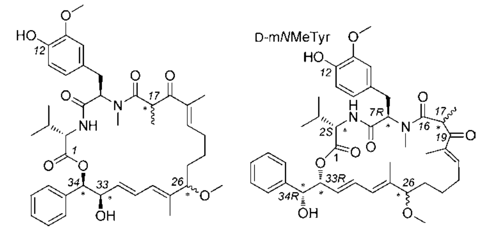
*Supporting Information*

**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 $IC_{50}$ values of 15 and 18 nM, respectively, and showed cytostatic activity against human colon carcinoma (HCT-116) cells with $IC_{50}$ 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-m*N*Me-Tyr) had not been previously reported in natural products. Aetheramides are structurally distinct from all reported HIV inhibitors[4] and may be associated with novel mechanisms of action. Despite vigorous efforts, the absolute stereochemistries at

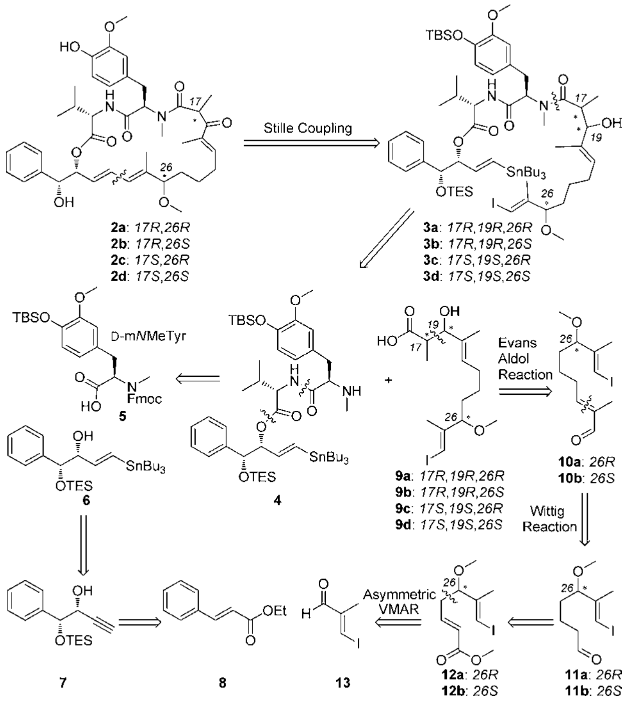


Aetheramide A | Aetheramide B

|  | Aetheramide A | Aetheramide B |
|---|---|---|
| $IC_{50}$, HIV-1 | 15 nM | 18 nM |
| $IC_{50}$, HCT-116 | 110 nM | 110 nM |
| MIC, *Candida albicans* | 20 μg/disk | 20 μg/disk |
|  | **1a**: *17R,26R*<br>or **1b**: *17R,26S*<br>or **1c**: *17S,26R*<br>or **1d**: *17S,26S* | **2a**: *17R,26R*<br>or **2b**: *17R,26S*<br>or **2c**: *17S,26R*<br>or **2d**: *17S,26S* |

**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**



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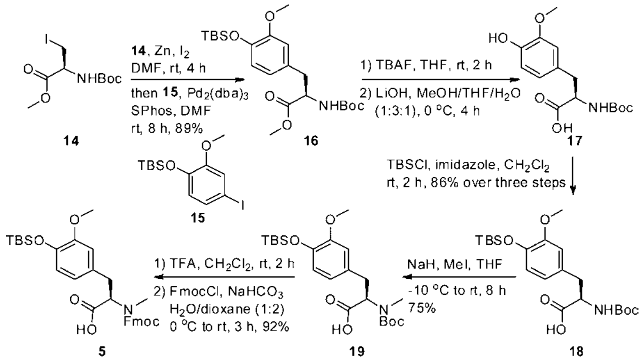
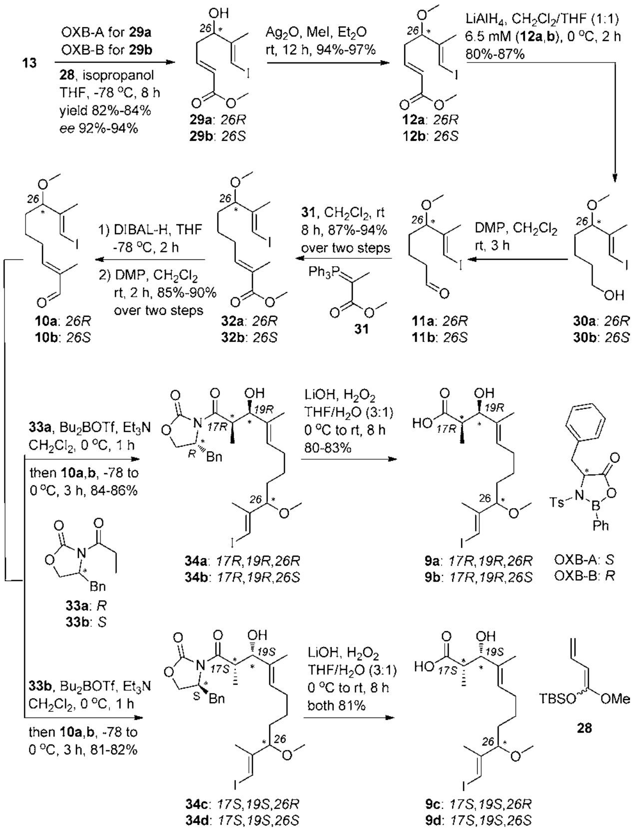
**Scheme 2. Synthesis of D-Fmoc-m*N*MeTyr 5**



**Scheme 4. Syntheses of Vinyl Iodo Acids 9a−d**



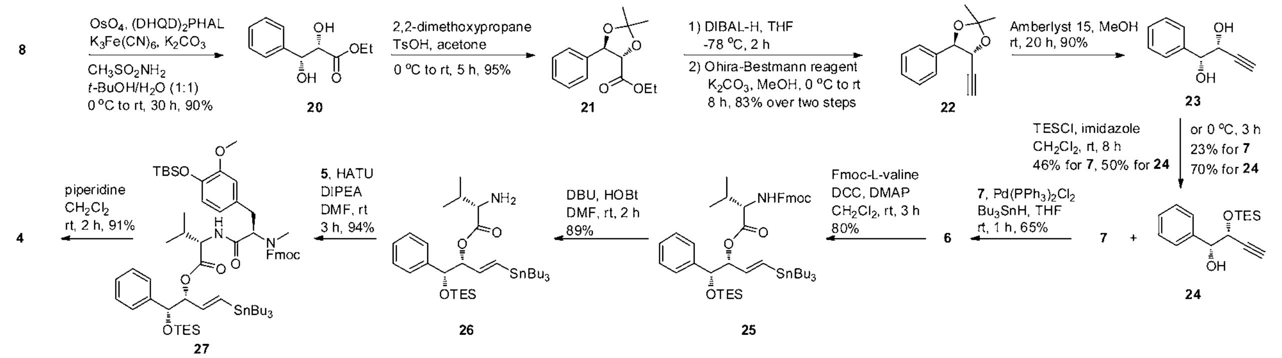
C-17 and C-26 remained undetermined.[3] Moreover, aetheramides were isolated in small amounts, and their further studies were hampered.

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 coupling[6] 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-m*N*MeTyr fragment **5**. The vinylstannane group in **6** could be generated from the terminal alkyne in **7**, which could be readily accessed from *trans*-ethyl cinnamate **8**.

The novel D-Fmoc-m*N*MeTyr 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 Pd$_2$(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.

**Scheme 3. Synthesis of Vinylstannane Amine 4**



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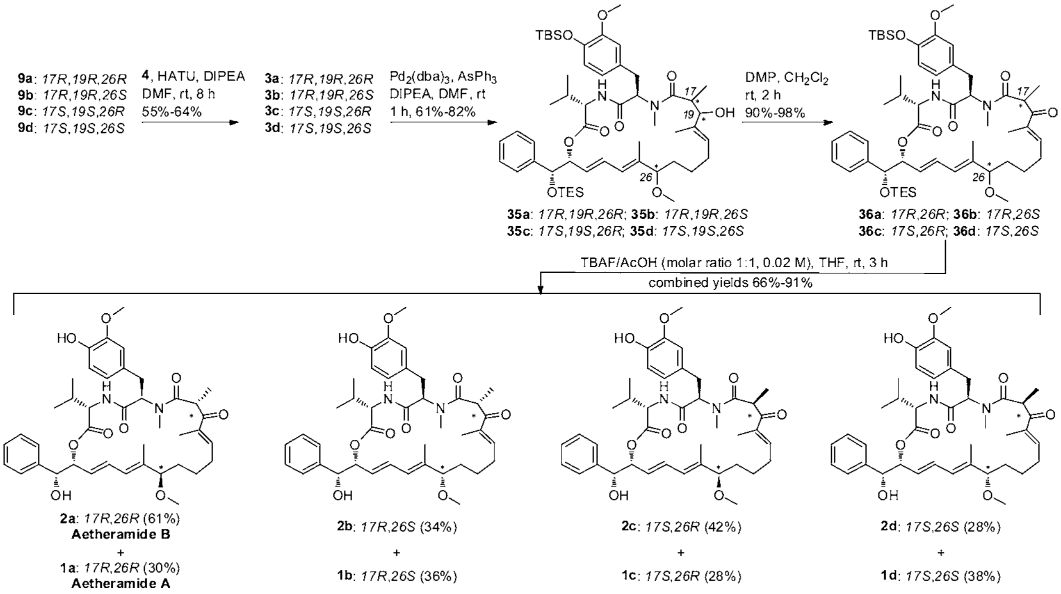
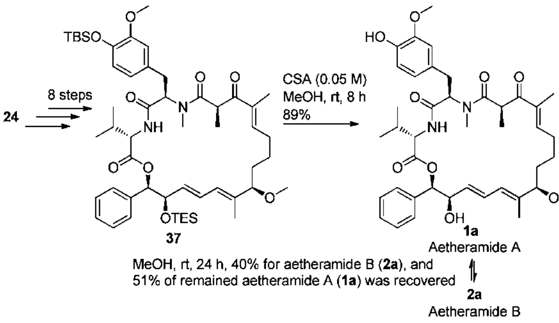
Scheme 5. Syntheses of Aetheramide A (1a), Aetheramide B (2a), and Their C-17 and C-26 Stereoisomers 1b–d and 2b–d



Scheme 6. Direct Synthesis of Aetheramide A



The synthesis of vinylstannane amine **4** started from *trans*-ethyl 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 °C for 3 h. Silyl ethers **7** and **24** could be used for the syntheses of the 21-membered macrocycles **2a–d** and the 22-membered macrocycles **1a–d**, respectively, or easily recycled via diol **23**.

Hydrostannation of alkyne **7** with $Bu_3SnH$ and $Pd(PPh_3)_2Cl_2$ 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*N*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-A[16] 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 yield 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 $LiAlH_4$ 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 amide-coupling conditions. The intramolecular Stille coupling of **3a–d** was 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 **1a**–**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 $^{1}$H NMR and $^{13}$C NMR of **1a**–**d** and **2a**–**d** were compared with those of natural aetheramides A and B.[3] The $^{1}$H NMR and $^{13}$C 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 stereochemistries 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.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) Weissman, K. J.; Müller, R. *Nat. Prod. Rep.* **2010**, *27*, 1276.

(2) Garcia, R.; Gerth, K.; Stadler, M.; Dogma, I. J., Jr.; Müller, R. *Mol. Phylogenet. Evol.* **2010**, *57*, 878.

(3) Plaza, A.; Garcia, R.; Bifulco, G.; Martinez, J. P.; Huttel, S.; Sasse, F.; Meyerhans, A.; Stadler, M.; Müller, R. *Org. Lett.* **2012**, *14*, 2854.

(4) Celebeside A, a 26-membered depsipeptide with a negative phosphate moiety, has some related structural features and weakly inhibits HIV-1 infection ($IC_{50}$, 2 $\mu$M). Plaza, A.; Bifulco, G.; Keffer, J. L.; Lloyd, J. R.; Baker, H. L.; Bewley, C. A. *J. Org. Chem.* **2009**, *74*, 504.

(5) (a) Ghosh, A. K.; Rao, K. V.; Akasapu, S. *Tetrahedron Lett.* **2014**, *55*, 5191. (b) Revu, O.; Prasad, K. R. *Synlett* **2014**, *25*, 2887. (c) Gerstmann, L.; Kalesse, M. During the submission of the manuscript, a total synthesis of aetheramide A in 18 linear steps with an overall yield of 0.2% appeared online. However, the stereochemistry of C-17 remained undetermined, and the $^{13}$C NMR spectrum of aetheramide A was not reported due to some difficulties. They attempted the total synthesis of aetheramide B but were not successful. *Chem. - Eur. J.* **2016**, *22*, 11210.

(6) For reviews of intramolecular Stille coupling, see: (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 1235. (b) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261. For representative examples of intramolecular Stille coupling, see: (c) Brodmann, T.; Janssen, D.; Kalesse, M. *J. Am. Chem. Soc.* **2010**, *132*, 13610. (d) Sato, E.; Tanabe, Y.; Nakajima, N.; Ohkubo, A.; Suenaga, K. *Org. Lett.* **2016**, *18*, 2047.

(7) Gieseler, M. T.; Kalesse, M. *Org. Lett.* **2011**, *13*, 2430.

(8) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599.

(9) Manda, S.; Nakanishi, I.; Ohkubo, K.; Uto, Y.; Kawashima, T.; Hori, H.; Fukuhara, K.; Okuda, H.; Ozawa, T.; Ikota, N.; Fukuzumi, S.; Anzai, K. *Chem. Commun.* **2008**, 626.

(10) Ross, A. J.; Lang, H. L.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 245.

(11) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.

(12) Kim, E. J.; An, K. M.; Ko, S. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 2019.

(13) (a) Gallant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521.

(14) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2007**, *72*, 3868.

(15) Bu, X.; Xie, G.; Law, C. W.; Guo, Z. *Tetrahedron Lett.* **2002**, *43*, 2419.

(16) Simsek, S.; Horzella, M.; Kalesse, M. *Org. Lett.* **2007**, *9*, 5637.

(17) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830.

(18) In the original paper, Müller's group reported $^{13}$C NMR data for aetheramides A and B; however, no $^{13}$C NMR spectra were provided. In Kalesse's paper on the total synthesis of aetheramide A, no $^{13}$C NMR data or spectrum was provided. Through our syntheses, large enough amounts of aetheramides A and B were obtained, and $^{13}$C NMR data and clean spectra are provided in the Supporting Information.