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Total Syntheses of Anti-HIV Cyclodepsipeptides Aetheramides A and B

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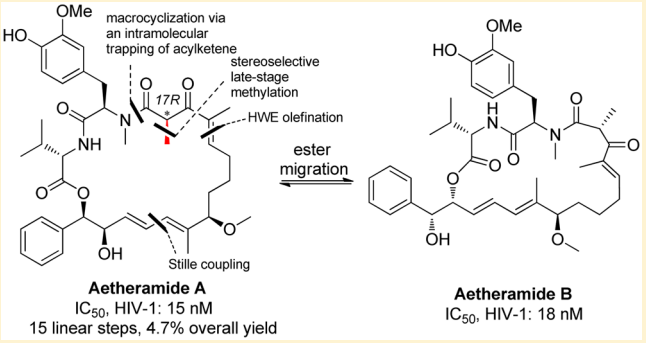
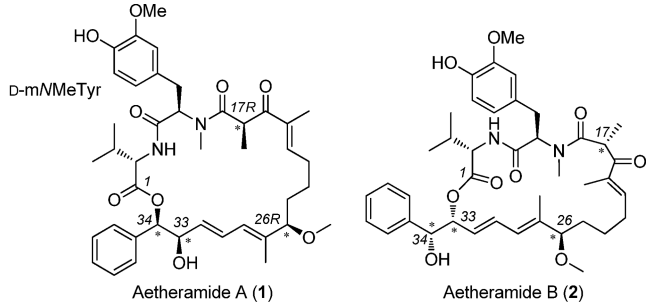
Supporting Information

ABSTRACT: A concise total synthesis of aetheramide A in an overall yield of 4.7% with a longest linear sequence of 15 steps is described. This synthetic strategy features macrocyclization via an intramolecular trapping of acylketene generated from dioxinone precursor, and stereoselective late-stage methylation of β-ketoamide. Aetheramide B could be synthesized via the ester migration of aetheramide A.



Aetheramides A and B (**1** and **2**, Figure 1) were isolated from a novel myxobacterial genus, named *Aetherobacter*, by



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

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

Müller's group in 2012.[1] Aetheramides A and B inhibited HIV-1 infection with IC_{50} values of 15 and 18 nM, respectively, showed cytostatic activity against human colon carcinoma (HCT-116) cells with IC_{50} values of 110 nM and exhibited moderate antifungal activity against *Candida albicans* at loads of 20 μg/disk. Aetheramides A and B are structurally distinctive 22/21-membered cyclodepsipeptides, which comprise a unique polyketide moiety and two amino acid residues, including rare D-3-(4-hydroxy-3-methoxyphenyl)-2(methylamino)propanoic acid (D-mNMeTyr). Since the structures of aetheramides are different from all reported HIV inhibitors, their potent anti-HIV activity might be associated with novel mechanisms of action. However, their scarce availability from natural sources prevented further studies of this promising class of compounds.

The syntheses of aetheramides were challenging because of the labile moieties in their skeletons. The ester migration between the adjacent hydroxyl groups at C-33 and C-34 could take place spontaneously in MeOH, and aetheramides A and B could reach a 1:1 equilibrium in 24 h. Moreover, the labile β-ketoamide moiety aggravates the synthetic difficulties. Inspired by the unique structures and promising activity, several research groups have made great efforts on the total syntheses of aetheramides and the establishment of previously undetermined stereochemistries.[2−5] In 2016, Kalesse's group reported the first synthesis of aetheramide A applying an ingenious dioxinone strategy in 18 linear steps and an overall yield of 0.2%, and established one undetermined stereochemistry (C-26).[4] However, several key steps in the synthesis provided the desired products in low yields of about 30%. Moreover, the hydroxyl groups at C-33 and C-34 were not protected in the late-stage transformations, which led to uncontrolled ester migrations and complicated reaction systems. In the last step, 0.5 mg of aetheramide A was afforded in 15% yield with HPLC purification. At almost the same time, our group independently developed efficient total syntheses of aetheramides A and B, and established both previously unassigned stereochemistries (C-17 and C-26).[5]

During the syntheses of aetheramide analogues and the relevant structure−activity relationship (SAR) studies, it was found that C-17 could tolerate certain modifications, which provided an opportunity to improve the biological activity of aetheramides. Herein, we disclose a concise and efficient synthesis of aetheramide A (**1**), which could allow the rapid

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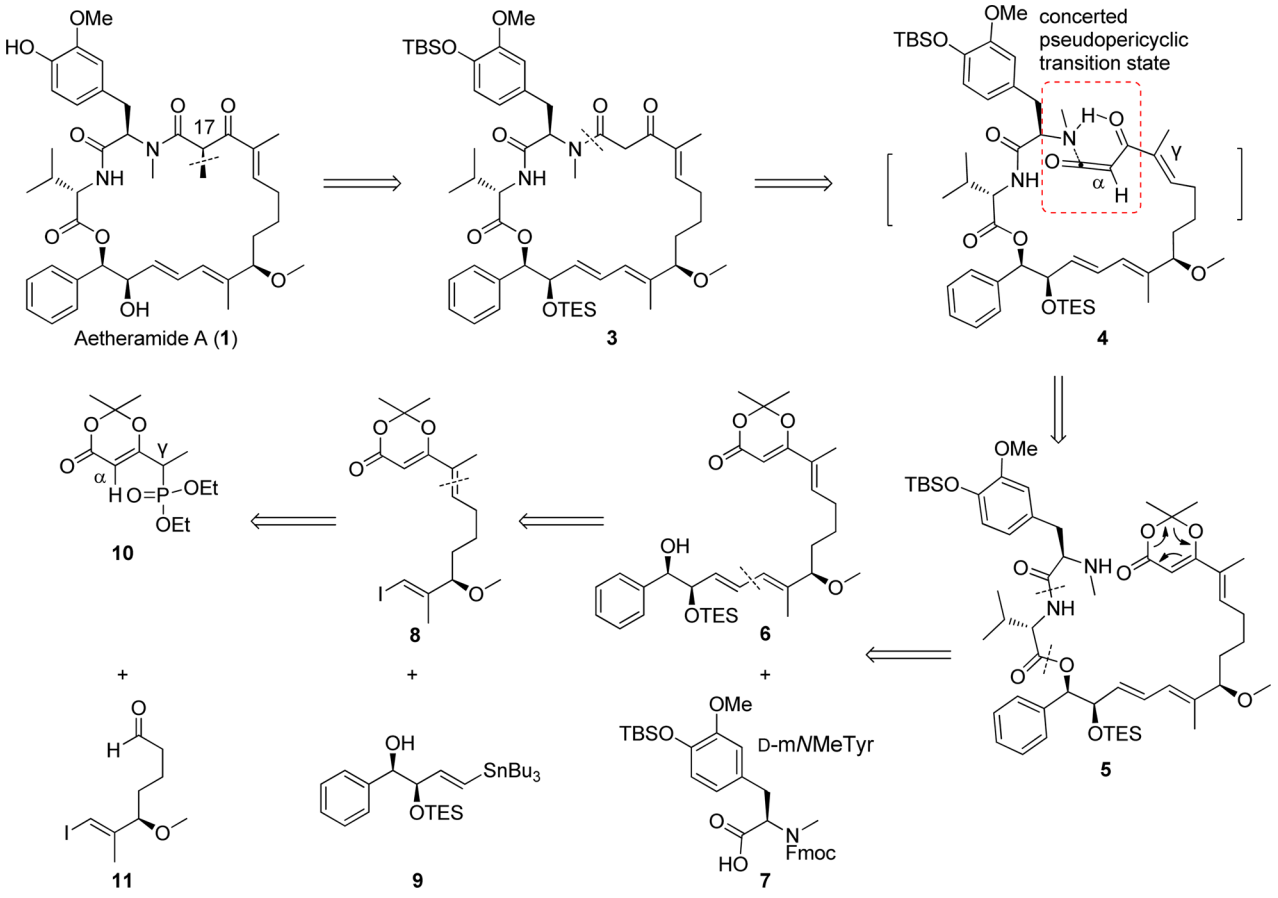
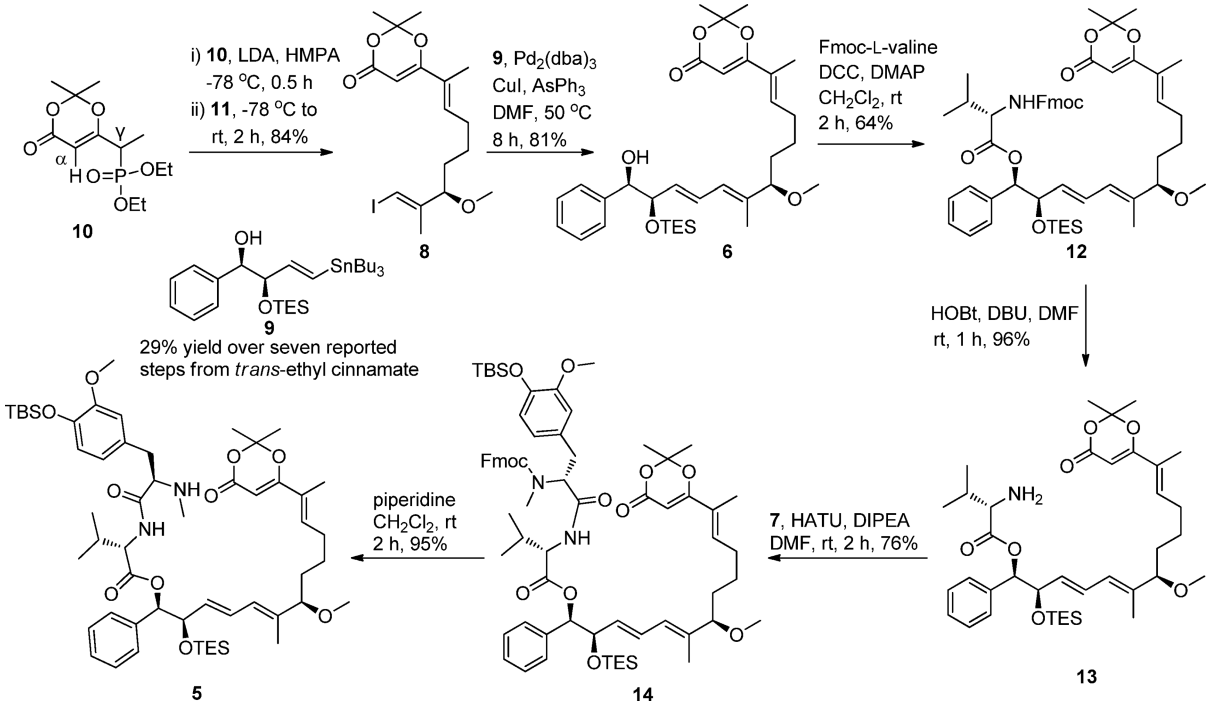
Scheme 1. Retrosynthesis of Aetheramide A



Scheme 2. Synthesis of Cyclization Precursor 5



preparations of analogues with modifications at C-17 during the late stage of the synthesis. Aetheramide B (**2**) could be synthesized via the ester migration of aetheramide A (**1**).

The retrosynthetic analysis of aetheramide A is outlined in Scheme 1. The methylation at C-17 was planned at late stage. Dioxinone is a stable equivalent of labile β-ketoamide. The

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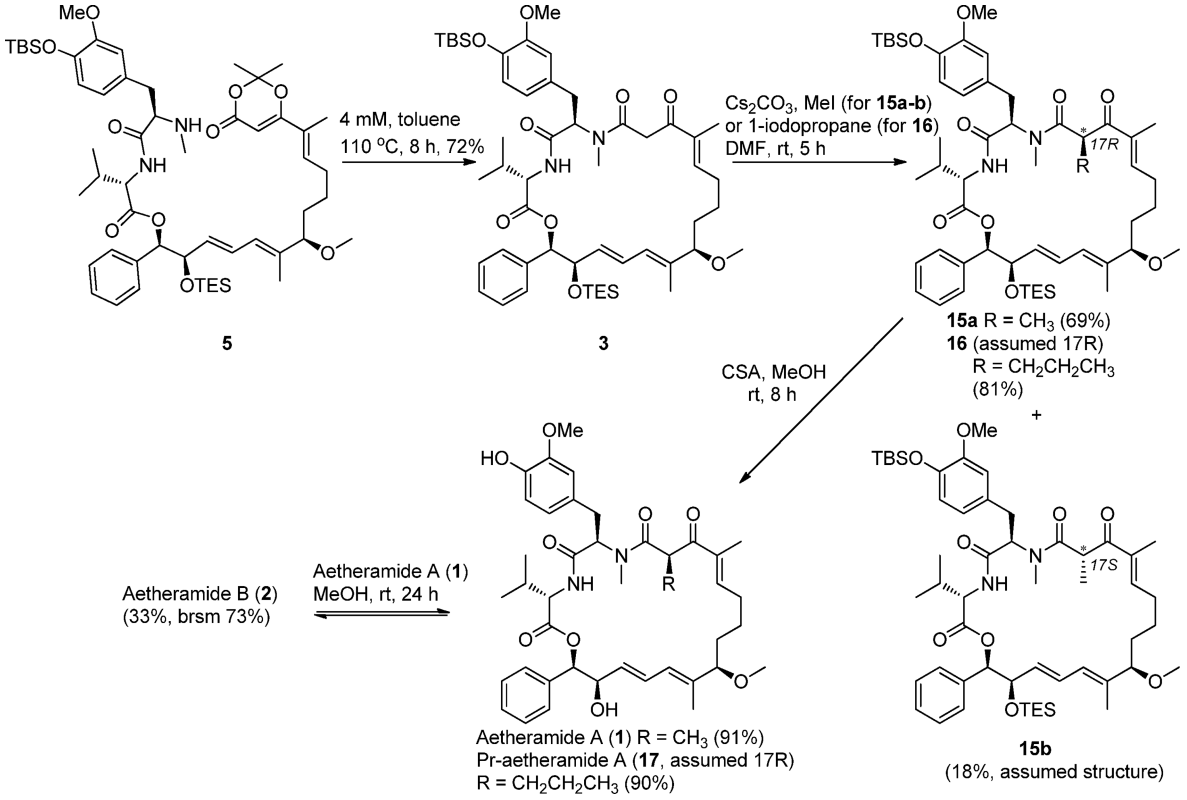
Scheme 3. Syntheses of Aetheramides A (1) and B (2) and Pr-aetheramide A (17)



dioxinone strategy for the macrocyclization of natural products has been proved to be efficient since it was introduced by Boeckman in 1989.[6] In order to bypass the labile β-ketoamide moiety in the synthesis of aetheramide A, the 22-membered macrocycle core was designed to be constructed through the intramolecular nucleophilic attack of *N*-Me to acylketene generated from dioxinone (Scheme 1, **4**) at late stage. However, differing from Kalesse's work,[4] the dioxinone without α-methyl group was adopted in our synthesis. When a nucleophile bearing a proton attacks acylketene intermediate, it is believed to form a concerted, pseudopericyclic transition state, so this requires the acylketene adopts an s-*cis* conformation (Scheme 1, **4**).[7] Therefore, the macrocyclization without α-methyl group (C-17 methyl group) should be favored by minimizing the unfavorable steric interaction between the α and γ positions. Cyclization precursor **5** could be assembled through the sequential condensations of alcohol **6**, Fmoc-L-valine and the rare D-mNMeTyr fragment **7**.[5] Alcohol **6** could be accessed from the Stille coupling of iodide **8** and vinylstannane alcohol **9**.[5] Iodide **8** could be prepared through the Horner–Wadsworth–Emmons (HWE) olefination of dioxinone phosphonate **10**[8] and iodo aldehyde **11**.[5]

The synthesis of aetheramide A started from the HWE olefination between **10** and **11** (Scheme 2), providing iodide **8** in 84% yield. The high efficiency of this reaction is likely due to the reduced steric interaction between the α and γ positions in **10**. Under the condition of $Pd_2(dba)_3/AsPh_3/CuI$,[9] the subsequent Stille coupling of **8** with vinylstannane alcohol **9** (synthesized from *trans*-ethyl cinnamate in 29% yield with seven reported steps) led to alcohol **6** in 81% yield. The coupling of **6** with Fmoc-L-valine, followed by the deprotection of Fmoc with HOBt/DBU/DMF[10] afforded amine **13**. Amine **13** was coupled with rare D-mNMeTyr **7**, followed by the deprotection of Fmoc with piperidine to furnish cyclization precursor **5**.

As expected, heating precursor **5** in toluene at 110 °C under diluted condition resulted in the smooth macrocyclization, affording the desired 22-membered macrocycle **3** in 72% yield, presumably as a mixture of two major conformers and other minor conformers/tautomer about the β-ketoamide functionality (Scheme 3). In Kalesse's work, the macrocyclization processing between *N*-Me and α-methyl dioxinone afforded the desired product in only 30% yield at 165 °C in mesitylene. The lower reaction temperature and much higher yield for the macrocyclization in our work suggested that the reduced steric hindrance of the dioxinone without α-methyl group facilitated the cyclization significantly.

The following methylation was crucial for this strategy. To our delight, the methylation of macrocycle **3** with Cs_2CO_3 and MeI in DMF indeed afforded the methylated macrocycle **15a** with the desired configuration (17R) in 69% yield, which was confirmed by comparing with the previously reported ^1H NMR and ^{13}C NMR data of **15a**.[5] At the same time, a byproduct **15b**, presumably the C-17 diastereoisomer of compound **15a** was isolated in 18% yield. The final deprotection of silyl ethers in **15a** was easily achieved with CSA in MeOH to furnish aetheramide A in 91% yield. When aetheramide A (**1**) was dissolved in MeOH and stirred for 24 h at room temperature, aetheramide B (**2**) could be obtained in 33% yield (brsm 73%) through ester migration, and the remaining aetheramide A (**1**) was recovered. The ^1H NMR and ^{13}C NMR of the synthetic samples nicely matched the reported data for natural aetheramides A and B.[1,5]

To verify the feasibility of the modifications at C-17, the substitution of C-17 in macrocycle **3** with propyl group was attempted. With Cs_2CO_3 and 1-iodopropane in DMF, compound **16** (assumed 17R) with propyl group at C-17 was

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obtained in 81% yield, and a byproduct, presumably the C-17 diastereoisomer of **16** formed in very small amount. It was speculated that the increased bulkness of the propyl group enhanced the stereoselectivity in this step. Pr-aetheramide A (**17**, assumed 17R) was obtained in 90% yield after the deprotection of silyl ethers with CSA.

In order to understand the stereoselectivity of the alkylation at C-17, the optimized conformation of macrocycle **3** was constructed with Gaussian 09 package (Figure 2).[11] The results suggested that the alkylation from less hindered face would lead to the desired configuration (17R).

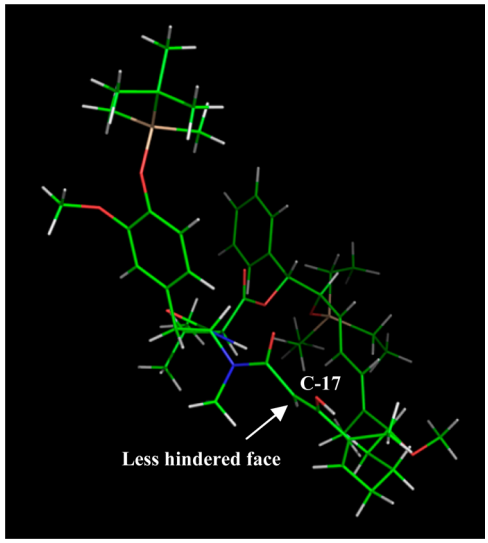

Figure 2. Optimized conformation of macrocycle **3** (green: C; white: H; red: O; blue: N; pale yellow: Si).

In conclusion, a concise asymmetric synthesis of aetheramide A has been accomplished with a longest linear sequence of 15 steps in an overall yield of 4.7% (calculated from *trans*-ethyl cinnamate, the commercially available starting material for alcohol **9**). Aetheramide B was obtained through the ester migration of aetheramide A. This synthetic strategy features stereoselective late-stage methylation, and could allow the rapid syntheses of analogues with modifications at C-17 for further SAR studies. Meanwhile, the strategy with late-stage methylation improved the overall yield significantly by minimizing the steric hindrance in the synthesis. Moreover, the application of dioxinone instead of labile β-ketoamide improved the compatibility of the synthetic route with varying reaction conditions, which would facilitate the preparations of diverse analogues.

EXPERIMENTAL SECTION

General. For product purification by column chromatography, silica gel (200−300 mesh) and petroleum ether (bp. 60−90 °C) were used unless otherwise indicated. All solvents were dried by standard techniques and distilled prior to use. All commercially available reagents were used as received without further purification unless otherwise indicated. All moisture-sensitive reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under vacuum. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with TMS as internal reference. Optical rotations were measured with a polarimeter at 589 nm. IR spectra were recorded on a FT-IR spectrometer. HRMS were obtained on a time-of-flight instrument using electrospray ionization (ESI).

Preparation of Compound 8. To a solution of diethyl (1-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl) ethyl)phosphonate **10** (800 mg, 2.74 mmol, 1.2 equiv) in THF (10 mL), was added LDA (2 M in THF, 2.28 mL, 4.56 mmol, 2.0 equiv) at −78 °C. The resulting mixture was warmed to rt and stirred for 20 min. The mixture was recooled to −78 °C and HMPA (1.63 g, 9.12 mmol, 4.0 equiv) was added. After stirring at −78 °C for another 0.5 h, a solution of iodo aldehyde **11** (644 mg, 2.28 mmol, 1 equiv) in THF (10 mL) was added slowly. The resulting mixture was warmed slowly to rt and stirred for another 2 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Compound **8** (804 mg, 84%) was obtained with silica gel column chromatography (PE/EtOAc 20/1, R_f = 0.25) as colorless oil. $[\alpha]_D^{27}$ + 2.6 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2931, 1728, 1639, 1595, 1375, 1278, 1206, 1096, 1011, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (t, *J* = 7.6 Hz, 1H), 6.19 (s, 1H), 5.40 (s, 1H), 3.61 (t, *J* = 6.4 Hz, 1H), 3.18 (s, 3H), 2.24−2.14 (m, 2H), 1.78 (s, 3H), 1.72 (s, 3H), 1.69 (s, 6H), 1.64−1.57 (m, 1H), 1.51−1.44 (m, 2H), 1.38−1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.5, 147.9, 137.3, 127.6, 106.1, 91.6, 86.1, 79.2, 56.5, 33.4, 28.6, 25.1, 25.1, 25.1, 18.7, 12.3; HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{17}H_{25}INaO_4^+$ 443.0690; Found 443.0682.

Preparation of Compound 6. To a solution of compound **8** (690 mg, 1.64 mmol, 1 equiv) and compound **9** (1.31 g, 2.30 mmol, 1.4 equiv) in DMF (10 mL), were added $Pd_2(dba)_3$ (300 mg, 0.33 mmol, 0.2 equiv), CuI (250 mg, 1.31 mmol, 0.8 equiv), and $AsPh_3$ (401 mg, 1.31 mmol, 0.8 equiv) at rt under a N_2 atmosphere. The reaction was stirred at 50 °C for 8 h under N_2. The reaction was concentrated *in vacuo* and purified with silica gel column chromatography (PE/EtOAc 6/1, R_f = 0.2) to afford compound **6** (760 mg, 81%) as colorless oil. $[\alpha]_D^{27}$ + 16.8 (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 2950, 2876, 1727, 1638, 1594, 1376, 1278, 1205, 1092, 1010, 743, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 6.38 (t, *J* = 7.6 Hz, 1H), 6.28 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.90 (d, *J* = 11.2 Hz, 1H), 5.59 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.40 (s, 1H), 4.48 (dd, *J* = 6.0, 3.6 Hz, 1H), 4.25−4.19 (m, 1H), 3.44 (t, *J* = 6.4 Hz, 1H), 3.19−3.10 (m, 4H), 2.25−2.15 (m, 2H), 1.78 (s, 3H), 1.69 (s, 6H), 1.65−1.60 (m, 1H), 1.57 (s, 3H), 1.54−1.42 (m, 2H), 1.39−1.31 (m, 1H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 162.5, 140.7, 137.7, 137.6, 132.5, 128.1, 127.8, 127.6, 127.4, 127.1, 127.0, 106.1, 91.5, 86.9, 78.5, 77.7, 56.1, 33.5, 28.7, 25.3, 25.1, 25.1, 12.3, 11.1, 6.8, 5.0; HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{33}H_{50}NaO_6Si^+$ 593.3269; Found 593.3274.

Preparation of Compound 12. To a solution of compound **6** (490 mg, 0.86 mmol, 1 equiv) and Fmoc-L-valine (437 mg, 1.29 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL), were added DCC (531 mg, 2.58 mmol, 3.0 equiv) and DMAP (11 mg, 0.09 mmol, 0.1 equiv) at rt. The reaction was stirred at rt for 2 h. The mixture was concentrated and purified with silica gel column chromatography (PE/EtOAc 6/1, R_f = 0.2) to afford compound **12** (490 mg, 64%) as colorless oil. $[\alpha]_D^{27}$ −21.7 (*c* 0.29, $CHCl_3$); IR (film) ν_{max} 2957, 2875, 1723, 1636, 1594, 1522, 1451, 1374, 1277, 1202, 1093, 1008, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.42−7.36 (m, 2H), 7.35−7.26 (m, 7H), 6.41−6.30 (m, 2H), 5.84 (d, *J* = 11.2 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 5.45−5.34 (m, 3H), 4.55−4.49 (m, 1H), 4.44 (dd, *J* = 9.2, 4.4 Hz, 1H), 4.41−4.34 (m, 2H), 4.24 (t, *J* = 7.2 Hz, 1H), 3.41 (t, *J* = 6.0 Hz, 1H), 3.12 (s, 3H), 2.26−2.13 (m, 3H), 1.77 (s, 3H), 1.69 (s, 6H), 1.63−1.59 (m, 1H), 1.58 (s, 3H), 1.48−1.41 (m, 2H), 1.35−1.28 (m, 1H), 0.97−0.86 (m, 12H), 0.73 (d, *J* = 6.8 Hz, 3H), 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 165.7, 162.5, 156.2, 144.0, 143.9, 141.4, 137.8, 137.6, 136.9, 131.3, 128.4, 128.2, 127.9, 127.8, 127.4, 127.2, 126.9, 125.2, 120.1, 106.0, 91.5, 86.9, 80.4, 74.9, 67.2, 58.9, 56.1, 47.3, 33.4, 31.6, 28.7, 25.2, 25.1, 25.0, 19.1, 17.2, 12.3, 11.1, 6.9, 5.0; HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{53}H_{69}NNaO_9Si^+$ 914.4634; Found 914.4644.

Preparation of Compound 13. To a solution of compound **12** (400 mg, 0.45 mmol, 1.0 equiv) in DMF (5 mL), were added HOBt (36 mg, 0.27 mmol, 0.6 equiv) and DBU (54 μL, 0.36 mmol, 0.8 equiv) at rt. The reaction was stirred at rt for 1 h. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified with silica gel column chromatography (PE/

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EtOAc 4/1, R_f = 0.2) to afford compound **13** (290 mg, 96%) as colorless oil. $[\alpha]_D^{27}$ −2.9 (*c* 0.17, MeOH); IR (film) ν_{max} 2956, 2876, 1731, 1639, 1595, 1375, 1278, 1205, 1095, 1008, 743, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5H), 6.38−6.29 (m, 2H), 5.84 (d, *J* = 11.2 Hz, 1H), 5.66 (d, *J* = 6.8 Hz, 1H), 5.45−5.37 (m, 2H), 4.53−4.48 (m, 1H), 3.41 (t, *J* = 6.4 Hz, 1H), 3.37 (d, *J* = 4.4 Hz, 1H), 3.13 (s, 3H), 2.23−2.15 (m, 2H), 2.11−2.04 (m, 1H), 1.78 (s, 3H), 1.69 (s, 6H), 1.63−1.58 (m, 4H), 1.48−1.42 (m, 2H), 1.37−1.31 (m, 1H), 0.97−0.89 (m, 12H), 0.72 (d, *J* = 7.2 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 165.8, 162.6, 137.6, 137.4, 131.7, 128.2, 128.2, 127.8, 127.5, 127.4, 127.0, 106.1, 91.5, 86.9, 79.6, 75.0, 59.9, 56.1, 33.5, 32.0, 28.8, 25.3, 25.1, 25.1, 19.6, 16.8, 12.3, 11.1, 6.9, 5.0; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{38}H_{60}NO_7Si^+$ 670.4134; Found 670.4113.

Preparation of Compound 14. To a solution of compound **13** (250 mg, 0.37 mmol, 1.0 equiv) and compound **7** (314 mg, 0.56 mmol, 1.5 equiv) in DMF (5 mL), were added DIPEA (129 μL, 0.78 mmol, 2.1 equiv) and HATU (281 mg, 0.74 mmol, 2.0 equiv) at rt. The reaction was stirred at rt for 2 h. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified with silica gel column chromatography (PE/EtOAc 5/1, R_f = 0.3) to afford compound **14** (341 mg, 76%) as colorless oil. (2.6:1 mixture of rotamers; the major signals were given.) $[\alpha]_D^{27}$ + 22.0 (*c* 0.44, MeOH); IR (film) ν_{max} 2956, 2877, 1729, 1515, 1452, 1281, 1156, 905, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.42−7.34 (m, 2H), 7.30−7.18 (m, 7H), 6.76−6.59 (m, 4H), 6.40−6.30 (m, 2H), 5.84 (d, *J* = 10.8 Hz, 1H), 5.60 (d, *J* = 6.8 Hz, 1H), 5.44−5.35 (m, 2H), 5.05−4.97 (m, 1H), 4.65 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.53−4.47 (m, 1H), 4.30 (d, *J* = 7.6 Hz, 2H), 4.21−4.14 (m, 1H), 3.73 (s, 3H), 3.41 (t, *J* = 6.4 Hz, 1H), 3.32 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.12 (s, 3H), 2.95−2.85 (m, 4H), 2.26−2.14 (m, 3H), 1.77 (s, 3H), 1.69 (s, 6H), 1.62−1.55 (m, 4H), 1.49−1.40 (m, 2H), 1.35−1.29 (m, 1H), 1.02−0.88 (m, 18H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.67−0.50 (m, 9H), 0.12−0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.3, 165.8, 162.5, 157.3, 150.9, 144.0, 141.3, 137.6, 137.0, 131.4, 130.6, 128.4, 128.2, 127.8, 127.4, 127.2, 127.2, 127.0, 125.2, 121.4, 120.9, 120.1, 120.0, 112.9, 106.0, 91.5, 86.9, 80.5, 74.9, 68.2, 60.5, 56.9, 56.1, 55.5, 47.2, 33.9, 33.4, 31.3, 30.6, 28.7, 25.8, 25.3, 25.1, 25.1, 19.3, 18.5, 17.2, 12.3, 11.1, 6.9, 5.0, −4.5, −4.6; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{70}H_{96}N_2NaO_{12}Si_2^+$ 1235.6394; Found 1235.6381.

Preparation of Compound 5. To a solution of compound **14** (290 mg, 0.24 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL), was added piperidine (0.2 mL) at rt. After being stirred at rt for 2 h, the reaction was concentrated and purified with silica gel column chromatography (PE/EtOAc 2/1, R_f = 0.25) to afford compound **5** (225 mg, 95%) as colorless oil. $[\alpha]_D^{27}$ −12.0 (*c* 0.05, MeOH); IR (film) ν_{max} 2956, 2934, 2877, 1731, 1513, 1280, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.6 Hz, 1H), 7.34−7.27 (m, 5H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 1.6 Hz, 1H), 6.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.41−6.32 (m, 2H), 5.86 (d, *J* = 10.8 Hz, 1H), 5.66 (d, *J* = 6.4 Hz, 1H), 5.44 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.40 (s, 1H), 4.69 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.55−4.50 (m, 1H), 3.78 (s, 3H), 3.42 (t, *J* = 6.0 Hz, 1H), 3.21−3.07 (m, 5H), 2.50 (dd, *J* = 14.8, 11.6 Hz, 1H), 2.25 (s, 3H), 2.23−2.13 (m, 3H), 1.78 (s, 3H), 1.69 (s, 6H), 1.61−1.57 (m, 4H), 1.49−1.43 (m, 2H), 1.38−1.30 (m, 1H), 0.99 (s, 9H), 0.97−0.86 (m, 12H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.59 (q, *J* = 7.6 Hz, 6H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 171.2, 165.8, 162.6, 151.3, 144.0, 137.7, 137.6, 137.2, 131.6, 131.2, 128.4, 128.2, 127.9, 127.7, 127.4, 127.0, 121.3, 121.1, 112.7, 106.1, 91.5, 87.0, 80.4, 74.9, 66.8, 56.5, 56.2, 55.6, 39.4, 35.9, 33.5, 31.5, 28.8, 25.9, 25.3, 25.1, 25.1, 19.5, 18.6, 17.4, 12.3, 11.1, 7.0, 5.1, −4.5; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{55}H_{86}N_2NaO_{10}Si_2^+$ 1013.5713; Found 1013.5703.

Preparation of Compound 3. Compound **5** (200 mg, 0.20 mmol, 4 mM, 1.0 equiv) was dissolved in toluene (50 mL) in a sealed tube. The solution was stirred at 110 °C for 8 h. The reaction was concentrated and purified with silica gel column chromatography (PE/EtOAc 6/1, R_f = 0.30) to afford compound **3** (134 mg, 72%) as colorless oil. (A mixture of two major conformers and other minor conformers/tautomer, the major ^1H NMR and ^{13}C NMR signals were given.) $[\alpha]_D^{27}$ + 41.3 (*c* 0.15, MeOH); IR (film) ν_{max} 2932, 1738, 1647, 1514, 1464, 1281, 1250, 1158, 1127, 1005, 903, 840, 783, 700 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.32−7.20 (m, 5H), 6.87−6.62 (m, 5H), 6.41 (dd, *J* = 14.8, 11.4 Hz, 1H), 5.96−5.81 (m, 2H), 5.78−5.72 (m, 1H), 5.44−5.36 (m, 1H), 4.63−4.54 (m, 1H), 4.44−4.34 (m, 1H), 4.06 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H), 3.58−3.42 (m, 2H), 3.37 (d, *J* = 16.2 Hz, 1H), 3.17−3.07 (m, 3H), 2.92−2.83 (m, 1H), 2.81−2.68 (m, 3H), 2.38−2.23 (m, 3H), 1.84−1.74 (m, 3H), 1.66−1.59 (m, 1H), 1.58−1.51 (m, 3H), 1.50−1.44 (m, 2H), 1.40−1.36 (m, 1H), 1.08−0.70 (m, 24H), 0.53−0.33 (m, 6H), 0.16−0.06 (m, 6H); ^{13}C NMR (100 MHz, CD_3CN) δ 197.7, 171.5, 171.4, 170.0, 151.8, 146.3, 144.4, 138.8, 138.3, 137.4, 132.7, 132.4, 132.1, 128.8, 128.7, 128.6, 128.1, 127.6, 122.0, 121.5, 113.9, 86.1, 79.5, 74.7, 59.1, 59.1, 56.4, 56.1, 45.5, 34.8, 33.5, 33.3, 31.5, 28.9, 26.2, 24.3, 19.6, 19.1, 18.4, 12.0, 11.7, 7.2, 5.3, −4.4; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{52}H_{80}N_2O_9Si_2^+$ 955.5295; Found 955.5294.

Preparation of Compounds 15a and 15b. To a solution of **3** (20 mg, 21.4 μmol, 1 equiv) in DMF (2 mL), were added Cs_2CO_3 (21 mg, 64.2 μmol, 3 equiv) and MeI (13 μL, 0.21 mmol, 10 equiv) at 0 °C. The reaction was stirred at rt for 5 h. The mixture was diluted with saturated aqueous NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated and purified with preparative TLC (PE/EtOAc 2/1, R_f = 0.2) to afford compound **15a** (14 mg, 69%) as colorless oil. The byproduct **15b** (3.7 mg, 18%) was also isolated as colorless oil.

15a: $[\alpha]_D^{27}$ + 38.2 (*c* 0.1, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.26 (m, 5H), 6.76−6.66 (m, 3H), 6.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.52 (t, *J* = 7.2 Hz, 1H), 6.46 (dd, *J* = 15.2, 11.8 Hz, 1H), 5.85 (d, *J* = 11.2 Hz, 1H), 5.82−5.74 (m, 2H), 5.68 (dd, *J* = 15.2, 5.2 Hz, 1H), 4.54−4.45 (m, 2H), 4.02 (q, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.51−3.40 (m, 2H), 3.19 (s, 3H), 2.79 (dd, *J* = 15.2, 11.4 Hz, 1H), 2.70 (s, 3H), 2.40−2.30 (m, 2H), 2.26−2.18 (m, 1H), 1.86 (s, 3H), 1.77−1.70 (m, 1H), 1.64−1.54 (m, 5H), 1.37−1.30 (m, 1H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.05−0.87 (m, 15H), 0.79 (t, *J* = 8.0 Hz, 9H), 0.45−0.26 (m, 6H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 172.2, 170.7, 170.5, 151.0, 143.6, 143.1, 137.4, 137.2, 136.0, 131.7, 130.3, 127.9, 127.8, 127.7, 127.5, 127.2, 120.9, 120.8, 112.3, 85.7, 78.5, 73.8, 58.0, 56.4, 56.2, 55.5, 45.1, 34.6, 32.8, 31.5, 30.7, 28.3, 25.9, 23.5, 19.1, 18.6, 18.0, 14.2, 12.3, 11.1, 6.9, 4.7, −4.6, −4.6; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{53}H_{82}N_2NaO_9Si_2^+$ 969.5451; Found 969.5478. The data matched the reported.[5]

15b (1.3:1 mixture of conformers): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 6.81−6.56 (m, 5H), 6.52−6.34 (m, 1H), 6.06−5.18 (m, 2H), 5.87−5.67 (m, 2H), 4.60−4.50 (m, 1H), 4.45−4.27 (m, 2H), 3.79 and 3.76 (each s, 3H), 3.54−3.23 (m, 2H), 3.19 and 3.18 (each s, 3H), 2.96−2.77 (m, 1H), 2.93 and 2.70 (each s, 3H), 2.46−2.07 (m, 3H), 1.80−1.70 (m, 6H), 1.59−1.44 (m, 3H), 1.32 and 1.03 (each d, *J* = 7.2 Hz, 3H), 1.28−1.25 (m, 1H), 1.01−0.70 (m, 21H), 0.86 and 0.66 (each d, *J* = 7.2 Hz, 3H), 0.40−0.23 (m, 6H), 0.14−0.10 (m, 3H), 0.09−0.03 (m, 3H); (the major signals were given in ^{13}C NMR data) ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 172.0, 171.7, 169.8, 150.9, 144.0, 143.6, 138.4, 137.6, 136.6, 132.3, 130.7, 128.2, 128.1, 128.0, 127.4, 127.2, 121.6, 120.9, 113.1, 85.4, 78.9, 76.6, 57.8, 57.1, 56.4, 55.6, 45.8, 35.1, 33.9, 33.3, 31.1, 28.8, 25.9, 24.6, 19.3, 18.6, 17.6, 11.8, 11.6, 10.5, 6.8, 4.7, −4.6; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{53}H_{82}N_2NaO_9Si_2^+$ 969.5451; Found 969.5471.

Preparation of Compound 16. To a solution of **3** (20 mg, 21.4 μmol, 1 equiv) in DMF (2 mL), were added Cs_2CO_3 (21 mg, 64.2 μmol, 3 equiv) and 1-iodopropane (20 μL, 0.21 mmol, 10 equiv) at 0 °C. The reaction was stirred at rt for 5 h. The mixture was diluted with saturated aqueous NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified with preparative TLC (PE/EtOAc 2/1, R_f = 0.2) to afford compound **16** (16.8 mg, 81%) as colorless oil. $[\alpha]_D^{24}$ + 16.3 (*c* 0.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.23 (m, 5H), 6.75−6.67 (m, 3H), 6.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.54−6.48 (m, 1H), 6.42 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.84 (d, *J* = 10.8 Hz, 1H), 5.81−5.74 (m, 2H), 5.66 (dd, *J* = 15.2, 5.2 Hz, 1H), 4.51−4.47 (m, 2H), 3.94−3.87 (m, 1H), 3.75 (s, 3H), 3.54−3.49 (m, 1H), 3.45 (dd, *J* = 15.2, 5.6 Hz, 1H), 3.19 (s, 3H), 2.77 (dd, *J* = 15.2, 11.6 Hz, 1H), 2.69 (s, 3H), 2.40−2.30 (m, 2H), 2.26−2.19 (m, 1H), 1.86 (s, 3H), 1.68−1.61 (m, 4H), 1.57−1.49 (m, 2H), 1.36−1.30 (m, 1H), 1.14−1.06 (m, 2H),

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1.02−0.92 (m, 15H), 0.90−0.71 (m, 14H), 0.46−0.32 (m, 6H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 171.2, 170.7, 170.6, 151.0, 143.8, 142.8, 137.4, 137.2, 136.4, 131.8, 130.4, 127.9, 127.8, 127.5, 127.1, 120.9, 120.7, 112.4, 85.5, 78.7, 73.8, 58.2, 56.6, 56.3, 55.5, 51.1, 34.3, 32.7, 31.5, 31.2, 30.7, 28.2, 25.9, 23.6, 21.7, 19.3, 18.6, 18.0, 13.9, 12.4, 11.1, 6.9, 4.7, −4.5; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{55}H_{86}N_2NaO_9Si_2^+$ 997.5764; Found 997.5787.

Preparation of Aetheramide A (1). To a round-bottom flask containing compound **15a** (14 mg, 14.8 μmol, 1.0 equiv), was added a solution of CSA (0.05 M in MeOH, 1 mL) at rt. The resulting solution was stirred at rt for 8 h. After quenching with saturated aqueous $NaHCO_3$ (3 mL) at 0 °C, the reaction was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified with preparative TLC (CH_2Cl_2/MeOH, 30/1, R_f = 0.15) to afford aetheramide A (**1**) (9.7 mg, 91%) as an amorphous white solid. $[\alpha]_D^{28}$ + 7.9 (*c* 0.12, CH_3CN); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{41}H_{54}N_2NaO_9^+$ 741.3722; Found 741.3732; The ^{1}H NMR and ^{13}C NMR data for aetheramide A (**1**) (DMSO-d_6) is listed in the Supporting Information.

Preparation of Aetheramide B (2). Aetheramide A (**1**) (8.0 mg, 11.1 μmol, 1.0 equiv) was dissolved in MeOH (20 mL) and stirred at rt for 24 h. The solution was concentrated and purified with preparative TLC (CH_2Cl_2/MeOH, 30/1, R_f = 0.15) to afford aetheramide B (**2**) (2.6 mg, 33%, brsm 73%) as an amorphous white solid. The remaining aetheramide A (**1**) (4.4 mg, 55%) was recovered. $[\alpha]_D^{27}$ + 38.4 (*c* 0.04, CH_3CN); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{41}H_{54}N_2NaO_9^+$ 741.3722; Found 741.3720; The ^{1}H NMR and ^{13}C NMR data for aetheramide B (**2**) (DMSO-d_6) is listed in the Supporting Information.

Preparation of Pr-aetheramide A (17). To a round-bottom flask containing compound **16** (10 mg, 10.3 μmol, 1.0 equiv), was added a solution of CSA (0.05 M in MeOH, 1 mL) at rt. The resulting solution was stirred at rt for 8 h. After quenching with saturated aqueous $NaHCO_3$ (3 mL) at 0 °C, the reaction was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified with preparative TLC (CH_2Cl_2/MeOH, 30/1, R_f = 0.15) to afford **17** (6.9 mg, 90%) as an amorphous white solid. $[\alpha]_D^{27}$ + 37.3 (*c* 0.04, CH_3CN); ^{1}H NMR (400 MHz, CD_3CN) δ 7.42−7.29 (m, 5H), 6.82 (d, *J* = 0.8 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.68−6.64 (m, 2H), 6.62 (ddd, *J* = 15.2, 10.8, 1.6 Hz, 1H), 6.55−6.48 (m, 1H), 6.37 (br s, 1H), 5.97 (d, *J* = 10.8 Hz, 1H), 5.86 (d, *J* = 1.6 Hz, 1H), 5.81 (dd, *J* = 15.2, 4.4 Hz, 1H), 5.58 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.50 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.47−4.39 (m, 1H), 4.11 (t, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.52 (t, *J* = 6.4 Hz, 1H), 3.30 (dd, *J* = 15.6, 4.8 Hz, 1H), 3.18 (d, *J* = 7.2 Hz, 1H), 3.12 (s, 3H), 2.93−2.85 (m, 4H), 2.45−2.33 (m, 2H), 2.14−2.08 (m, 1H), 1.75 (s, 3H), 1.66 (s, 3H), 1.63−1.54 (m, 3H), 1.53−1.30 (m, 4H), 1.15−1.05 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 198.8, 172.7, 172.0, 171.8, 148.1, 145.9, 144.2, 139.2, 138.5, 137.8, 133.5, 129.9, 129.1, 128.8, 128.0, 127.5, 122.3, 115.4, 113.1, 86.3, 78.4, 74.2, 57.9, 57.5, 56.7, 56.2, 50.5, 35.7, 33.6, 32.6, 32.1, 31.5, 29.1, 24.5, 21.7, 19.7, 17.6, 14.3, 12.1, 11.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{43}H_{58}N_2NaO_9^+$ 769.4035; Found 769.4042.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02292.

Comparison of ^{1}H NMR and ^{13}C NMR of natural vs synthetic aetheramides A and B, the absolute calculation energy and atom coordinates of the optimized structure of macrocycle **3**, full authorship of Gaussian 09, and copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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