SUPPORTING INFORMATION I

For

Total synthesis of the proposed structure of cyclic hexadepsipeptide Veraguamide A

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Experimental section

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General considerations

All reactions were performed in glassware containing a Teflon-coated stir bar. CH_2Cl_2 and THF were purified and dried according to the standard methods prior to use. All reagents were obtained from commercial sources and used without further purifications. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal reference. Low- and high resolution mass spectra were obtained in the ESI mode. Flash column chromatography on silica gel (200-300 mesh) was used for the routine purification of reaction products, and a mixture of EtOAc and petroleum ether was used as the eluent. The column output was monitored by TLC on silica gel (100-200 mesh) precoated on glass plates (10 cm x 50 cm), and spots were visualized by UV light at 254 nM or by Potassium permanganate show color agent.

1. Preparation of 2-hydroxy-3-methyl-pentanoic acid allyl ester (2)

Isoleucine (32.75g, 250 mmol) was dissolved in 1.25M H_2SO_4 (175 mL) and cooled to 0 ^oC. A solution of $NaNO_2$ (25.9g, 375 mmol) in H_2O (125 mL) was added dropwise over 1 h and the obtained reaction mixture was stirred for 2 h at 0 ^oC and then over night at room temperature. The mixture was extracted with diethyl ether (3×300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. 2-Hydroxy-3-methyl-pentanoic acid was obtained as a colorless oil, which was then dissolved in DMF (60 mL). To the solution, K_2CO_3 (31.05 g, 225 mmol), allylbromide (26 ml, 49.2 mmol) and TBAB (9.67g, 30 mmol) were added. The obtained reaction mixture was stirred for 16 h at room temperature, and then diluted with 200 mL of H_2O. The mixture was extracted with diethyl ether (2×300 mL), washed with brine, dried over Na_2SO_4 and then concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/ethyl acetate, 30/1) provided **2** as a colorless oil (25.8 g, 60% in two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 6.06–5.88 (m, 1H), 5.31 (dd, *J* = 32.7, 13.8 Hz, 2H), 4.65 (d, *J* = 5.7 Hz, 2H), 4.03 (d, *J* = 4.9 Hz, 1H), 1.80 (m, 1H), 1.59 – 1.40 (m, 1H), 1.35 – 1.14 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).

2. Preparation of (2S,3S)-Allyl-2-((S)-2-(tert-butoxycarbonyl(methyl)amino)-3-methylbut-anoyloxy)-3-methylpentanoate (3)

To a solution of alcohol **2** (5 g, 29 mmol) and *N*-methyl-*N*-BOC valine (10.05 g, 43.5 mmol) in anhydrous CH_2Cl_2 (250 mL), were added DCC (11.95 g, 58 mmol) and 4-PPy (8.58g, 58 mmol).

The mixture was stirred for 24 h at room temperature (reaction complete by TLC). The mixture was cooled to 0 ^{o}C, diluted with H_2O, and extracted with CH_2Cl_2. The combined CH_2Cl_2 phase was washed with brine and dried with Na_2SO_4. Removal of solvents followed by flash chromatography (petroleum ether/ethyl acetate, 30/1) provided **3** as a colorless oil (10.21 g, 91%). ^{1}H NMR (300 MHz, CD_3OD): δ = 6.03–5.85 (m, 1H, CH allyl), 5.38–5.23 (dd, 2H, CH_2 allyl),4.89 (d, 1H), 4.65 (d, 2H, CH_2, allyl), 4.20-4.38 (dd, 1H), 2.83 (s, 1H), 2.22 (m, 1H), 2.01 (m, 1H) , 1.46 (s, 9H), 1.3 (m, 2H), 1.05-0.95 (m, 6H), 0.95-0.85 (m, 6H).

3. Preparation of (2S,3S)-allyl-2-((S)-2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-N,3-dimethylbutanamido)-3-methylbutanoyloxy)-3-methylpentanoate (P1)

To a stirred solution of **3** (10.21 g, 26.5 mmol) in CH_2Cl_2 (200 mL) at 0 ^{o}C was added TFA (39.2 ml) and the resulting solution was stirred at 0 ^{o}C for 6h. The reaction mixture was concentrated in vacuo to give the crude residue. To the solution of *N*-Fmoc valine (13.5 g, 39.8 mmol) in CH_2Cl_2 (200 mL) was added HATU (15.1 g, 39.8 mmol), HOAt (5.4 g, 39.8 mmol) followed by addition of the crude residue prepared above and DIPEA (13.8 mL, 79.5 mmol). The reaction mixture was allowed to stir for 10 h, and then diluted with H_2O. After extraction with CH_2Cl_2, the combined organic phase was washed with brine and dried with Na_2SO_4. Removal of solvent followed by flash chromatography (petroleum ether/ethyl acetate, 7/1) provided **P1** as a colorless oil (10.61 g, 66% in two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 6.8 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 2H), 5.87 (dq, *J* = 11.1, 5.8 Hz, 1H), 5.25 (dd, *J* = 30.3, 13.8 Hz, 2H), 4.90 (d, *J* = 9.9 Hz, 2H), 4.59 (d, *J* = 5.5 Hz, 2H), 4.40 (d, *J* = 8.0 Hz, 1H), 4.34 – 4.26 (m, 2H), 4.14 (t, *J* = 6.4 Hz, 1H), 3.08 (s, 3H), 2.29 – 2.13 (m, 1H), 2.04 (dd, *J* = 13.4, 6.7 Hz, 1H), 1.92 (s, 1H), 1.43 (dd, *J* = 13.3, 6.4 Hz, 1H), 1.30 – 1.14 (m, 1H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.97 – 0.82 (m, 12H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 171.3, 170.1, 158.3, 145.1, 145.0, 142.4, 132.9, 128.7, 128.1, 128.0, 126.2, 126.1, 120.9, 119.1, 78.0, 67.8, 66.6, 63.4, 57.7, 48.3, 37. 7, 32.7, 31.7, 28.4, 25.5, 20.3, 19.8, 19.2, 18.6, 15.8, 11.9; ESI-MS m/z 629.4 $(M+Na)^+$; HRMS Calcd for $C_{35}H_{46}N_2NaO_7$ $(M + Na)^+$: 629.3203, found 629.3201.

4. Preparation of (S)-allyl 2-(tert-butoxycarbonyl(methyl)amino)-3-methylbutanoate (4) and (R)-allyl 2-(tert-butoxycarbonyl(methyl)amino)-3-methylbutanoate (4')

NaH (60% in mineral oil, 4.91 g, 122.7 mmol) was added to a solution of L-*N*-Boc-valine

(5.29g, 24.3 mmol) and MeI (12.1 mL,184 mmol) in THF (100 mL) at 0 ^{o}C. After the reaction mixture had been stirred at room temperature for 18h, it was poured into saturated NH_4Cl solution (500 mL), extracted with EtOAc (3×150 mL) and dried over Na_2SO_4. After evaporation of the solvents, the obtained *N*-methyl-*N*-Boc-valine was mixture with K_2CO_3 (6.7 g, 48.6 mmol) and allyl bromide (3.15 mL, 36.5 mmol) in DMSO (80 mL). After stirring at room temperature for 12 h, the reaction mixture was partitioned between EtOAc (150 mL) and brine (150 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2×100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 15/1) gave **4** (5.9 g, 90% in two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 6.03 – 5.84 (m, 1H), 5.28 (dd, *J* = 28.9, 13.8 Hz, 2H), 4.66 – 4.58 (m, 2H), 4.21 (dd, *J* = 68.6, 10.2 Hz, 1H), 2.83 (s, 3H), 2.22 (s, 1H), 1.45 (s, 9H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 171.3, 170.8, 156.2, 155.6, 132.0, 131.8, 118.4, 118.1, 80.3, 80.0, 65.2, 65.1, 63.2, 30.6, 30. 5, 28.4, 27.8, 27.7, 20.0, 19.8, 19.0, 18.8.

Diastereomer **4'** was prepared following the same procedure starting from D-*N*-Boc-valine in 88% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 5.97 – 5.82 (m, 1H), 5.38 – 5.13 (m, 2H), 4.60 (d, *J* = 5.5 Hz, 2H), 4.29 (dd, *J* = 104.1, 10.4 Hz, 1H), 2.83 (d, *J* = 11.0 Hz, 3H), 2.19 (s, 1H), 1.45 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

5. Preparation of (S)-*tert*-Butyl-2-(((S)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl) carbamoyl)pyrrolidine-1-carboxylate (P2) and (S)-tert-butyl-2-(((R)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrrolidine-1-carboxylate (P2')

The fragments **P2** and **P2'** were obtained from **4** and **4'** following a similar procedure as that for the preparation of the fragment **P1**.

(S)-*tert*-Butyl-2-(((S)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrrolidine-1-carboxylate (P2): 72% yield in two steps, ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 5.93 – 5.77 (m, 1H), 5.23 (dd, *J* = 23.8, 13.8 Hz, 2H), 4.91 (d, *J* = 10.4 Hz, 1H), 4.68 – 4.52 (m, 3H), 3.64 – 3.30 (m, 2H), 3.00 (d, *J* = 27.3 Hz, 3H), 2.23 – 1.78 (m, 5H), 1.38 (d, *J* = 7.7 Hz, 9H), 0.99 (dd, *J* = 11.4, 6.6 Hz, 3H), 0.89 (dd, *J* = 6.7, 2.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 173.5, 173.3, 169.5, 169.3, 153.8, 153.7, 131.3, 131.2, 116.9, 116.6, 79.1, 78.8, 64.4, 64.3, 61.7, 56. 7, 56.0, 46.0, 45.7, 29. 9, 29.6, 28.9, 28.2, 26.6, 26.3, 26.0, 23.0,

21.7, 18.2, 17.9; ESIMS m/z 391.1 $(M + Na)^+$; HRMS Calcd for $C_{19}H_{32}N_2NaO_5$ (M + Na): 391.2209, found 391.2192.

(S)-*tert*-Butyl-2-(((S)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrrolidine-1-carboxylate (P2'): 70% yield in two steps, ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 5.87 (m, 1H), 5.26 (dd, *J* = 27.6, 13.8 Hz, 2H), 4.89 (d, *J* = 10.5 Hz, 1H), 4.70 – 4.46 (m, 3H), 3.65 – 3.34 (m, 2H), 3.05 (d, *J* = 12.8 Hz, 3H), 2.33 – 1.75 (m, 5H), 1.38 (d, *J* = 21.2 Hz, 9H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 176.2, 175.8, 172.0, 171.9, 156.5, 156.2, 133.9, 133. 7, 119.8, 119.1, 81.7, 81.5, 67.1, 66.9, 64.4, 59.1, 58.9, 48.5, 48.2, 34.0, 32.9, 31.8, 30.9, 29.7, 29.2, 29.2, 25.6, 24.9, 20. 7, 19.7.

6. Preparation of (4S,2'S,3'R)-3-(3'-Hydroxy-2'-methyl-7'-octynoyl)-4-(phenylmethyl)-2-oxazolidinone (5).

To a stirred solution of *N*-propionyloxazolidinone (8.54 g, 36.7 mmol) in dry dichloromethane (40 mL) at 0 °C, dibutylborontriflate (1.0 M, 51.4 mL, 51.4 mmol in dichloromethane was added dropwise followed by triethylamine (9 mL, 62.4 mmol). The mixture was cooled to -78 °C, and a solution of hex-5-ynal (3.52 g) in dichloromethane (10 mL) was added dropwise via syringe. The reaction mixture was stirred at -78°C for 20 min and then for one hour at 0 °C. The mixture was then quenched by aqueous phosphate buffered solution (pH 7, 50 mL) and methanol (40 mL). A mixture of methanol and 30% H_2O_2 (1:1, 130 mL) was added, and the resulting solution was stirred for 45 min at room temperature. The solvents were evaporated under reduced pressure, the residue was redissolved in water (100 mL), and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield viscous yellow oil. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 4/1) to give aldol **5** as a colorless viscous oil (7.5 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 3H), 7.19 (dd, *J* = 7.4, 5.7 Hz, 2H), 4.72 – 4.63 (m, 1H), 4.26 – 4.12 (m, 2H), 3.95 (dd, *J* = 7.0, 3.9 Hz, 1H), 3.74 (qd, *J* = 7.0, 2.8 Hz, 1H), 3.22 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.01 (d, *J* = 3.0 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.3 Hz,1H), 2.26 – 2.17 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.80 – 1.48 (m, 4H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 153.0, 135.0, 129. 4, 129.0, 127.5, 84.2, 71.0, 68.7, 66.2, 55.1, 42.2, 37.8, 32.7, 25.0, 18.3, 10.4.

7. Preparation of (2S,3R)-3-*(tert*-butyldimethylsilyloxy)-N-methoxy-N,2-dimethyloct-7-ynamide (6)

To a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (6.23 g, 63.84 mmol) in dichloromethane (60 mL) at 0°C, was added dropwise a solution of trimethylaluminum in n-heptane (1.0 M, 63.84 mL, 63.84 mmol). The resulting solution was stirred at 0 °C for 10 min and at room temperature for 1h. The mixture was re-cooled to 0 °C, and a solution of **5** (7.0 g, 21.28 mmol) in 40 mL of dichloromethane was added. The resulting mixture was stirred for 3 h, then quenched by addition of H_2O at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 1 h and extracted with CH_2Cl_2. The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 4/1) to afford amide **5** (3.1 g, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 – 3.78 (m, 2H), 3.69 – 3.66 (m, 3H), 3.16 (s, 3H), 2.84 (d, *J* = 5.0 Hz, 1H), 2.24 – 2.15 (m, 2H), 1.92 (q, *J* = 2.4 Hz, 1H), 1.75 – 1.41 (m, 4H), 1.13 (t, *J* = 5.8 Hz, 3H).

To a stirred solution of **5** (2.94 g, 13.8 mmol) and imidazole (9.38 g, 138 mmol) in DMF (100 mL), was added tertbutyldimethylsilyl chloride (10.38 g, 69.0 mmol) at 0 ^{o}C and the resulting solution was stirred at room temperature overnight. The mixture was cooled to 0 ^{o}C, quenched with H_2O, and then extracted with Et_2O. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and then concentrated. The residual oil was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 15/1) to yield **6** (4.15 g, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (d, *J* = 8.0 Hz, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 2.96 (s, 1H), 2.17 – 2.09 (m, 2H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.57 (s, 4H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

8. Preparation of (2S,3R)-8-bromo-3-(tert-butyldimethylsilyloxy)-N-methoxy-N,2-dimethyloct-7-ynamide (7)

To a stirred solution of **6** (110 mg, 0.336 mmol) in acetone (5 mL) were added NBS (120 mg, 0.672 mmol) and silver (I) nitrate (5.7 mg, 0.034 mmol). The resulting solution was stirred for 2h at room temperature. After completion of the reaction (monitored by TLC), the solution was diluted with diethyl ether, and washed with H_2O and brine. The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure to give **7** (125 mg, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (d, *J* = 8.2 Hz, 1H), 3.69 (s, 3H), 3.17 (s, 3H), 2.97 (s, 1H),

2.17 (s, 2H), 1.56 (s, 4H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 80.1, 73.0, 61.4, 40.3, 37.8, 34.6, 32.0, 25.9, 22.9, 19.9, 18.0, 14.8, -4.3, -4.6. ESI-MS *m/z* 408.2 (M + H); HRMS Calcd for $C_{17}H_{32}BrNO_3SiNa$ (M + Na) : 428.1233, found 428.1219.

9. Preparation of (2S,3R)-allyl 8-bromo-3-(tert-butyldimethylsilyloxy)-2-methyloct-7-ynoate (P3)

To a stirred solution of **7** (1.4 g, 3.44 mmol) in THF (30 mL) at -78 °C, was added dropwise a 1.0 M solution of diisobutylaluminum hydride in toluene (10.0 mL,10.0 mmol). The mixture was stirred at -78 ^{o}C for 2 h, and then quenched by addition of saturated aqueous NH_4Cl and saturated aqueous tartaric acid. The resulting two-phase mixture was stirred at room temperature for 10 min. The solution was diluted with EtOAc and concentrated under reduced pressure, then extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20/1) to give **7** (1.0 g, 83%) as a yellow oil.

To the solution of **7** (1.0 g, 2.88 mmol) in *tert*-butyl alcohol (30 mL) and 2-methyl-2-butene (16.6 mL), was added a solution of sodium chlorite (1.14g, 12.66 mmol) and NaH_2PO_4 (0.97g, 6.33 mmol) in 18 mL of water. The mixture was stirred for 6 h and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 5/1) to give acid **14** (0.9 g, 86%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (d, J = 4.7 Hz, 1H), 2.66 – 2.47 (m, 1H), 2.26 – 2.18 (m, 2H), 1.67 – 1.43 (m, 4H), 1.15 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.08 (d, J = 8.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 79.6, 72.9, 44.3, 38.3, 33.3, 25.7, 23.9, 19.7, 18.0, 11.1, -4.4, -4.8; ESI-MS *m/z* 363.1 (M - H).

To the solution of acid **14** (250 mg, 0.688 mmol) in DMF (20 mL), was added K_2CO_3 (380 mg, 2.75 mmol) and Allyl bromide (250 mg, 2.06 mmol). The resulting solution was stirred at room temperature over night, diluted with ethyl acetate and then washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 50/1) to give the fragment **P3** (247mg, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 – 5.83 (m, 1H), 5.28 (dd, *J* = 25.7, 13.8 Hz, 2H), 4.60 – 4.54 (m, 2H), 4.00 (q, *J* = 5.3 Hz, 1H), 2.62 – 2.49 (m, 1H), 2.21 (t, *J* = 6.4

Hz, 2H), 1.68 – 1.43 (m, 4H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.04 (d, *J* = 10.3 Hz, 6H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 174.5, 132.1, 118.3, 79.9, 72.7, 65.1, 44.6, 38.1, 34.1, 25.8, 23.6, 19.8, 18.0, 11.7, -4.3, -4.8; ESI-MS *m/z* 427.2 $(M + Na)^{+\cdot}$; HRMS Calcd for $C_{18}H_{31}BrNaO_3Si$ (M + Na): 427.1103, found 427.1096.

10. Preparation of (S)-allyl2-((S)-1-((5S, 8S, 11S)-11-sec-butyl-1-(9H-fluoren-9-yl)-5,8-di-isopropyl-7-methyl-3,6,9-trioxo-2,10-dioxa-4,7-diazadodecane)-N-methylpyrrolidine-2-carboxamido)-3-methylbutanoate (10)

To a solution of the fragment **P1** (0.6 g, 0.99 mmol) in CH_2Cl_2 (30 mL) at 0 °C, was added $[Pd(PPh_3)_4]$ (0.15 g, 0.13 mmol) and NMA (0.32 mL, 2.97 mmol). The reaction mixture had been stirred at room temperature for 6h. After evaporation in vacuo, the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3/1 to dichloromethane/MeOH 20:1) to afford acid **8** (0.5 g, 90%) as a yellow oil.

To a stirred solution of the fragment **P2** (20 mg, 0.054 mmol) in CH_2Cl_2 (1 mL) at 0 ^{o}C, was added TFA (0.08 mL). The resulting solution was stirred at 0 ^{o}C for 6 hand then concentrated in vacuo to give the crude dipeptide **9** in 95% yield. To the solution of **8** (30.6 mg, 0.054 mmol) in CH_2Cl_2 (2 mL) was added HATU (30.8 mg, 0.081 mmol), HOAt (11 mg, 0.081 mmol) followed by addition of the crude dipeptide **9** and DIPEA (0.03 mL, 0.162 mmol). The reaction mixture was allowed to stir for 10 h, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvents followed by flash chromatography (petroleum ether/ethyl acetate, 4/1) provided peptide **10** as a colorless oil (28 mg, 64% in two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.31 – 7.25 (m, 2H), 5.87 (ddt, *J* = 17.1, 11.4, 5.6 Hz, 1H), 5.57 (d, *J* = 9.0 Hz, 1H), 5.24 (dd, *J* = 22.9, 13.8 Hz, 2H), 4.92 (d, *J* = 10.3 Hz, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.79 (dd, *J* = 16.1, 8.9 Hz, 2H), 4.55 (dd, *J* = 13.7, 5.2 Hz, 3H), 4.34 (p, *J* = 10.3 Hz, 2H), 4.20 (t, *J* = 6.9 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.71 – 3.59 (m, 1H), 3.09 (d, *J* = 8.5 Hz, 6H), 2.35 – 1.77 (m, 9H), 1.56 (s, 1H), 1.29 – 0.77 (m, 24H).

11. Preparation of (2S,3R)-allyl8-bromo-3-((S)-2-((S)-1-((5S,8S,11S)-11-*sec*-butyl-1-(9H-fluoren-9-yl)-5,8-diisopropyl-7-methyl-3,6,9-trioxo-2,10-dioxa-4,7-diazadodecane)-N-methylpyrrolidine-2-carboxamido)-3-methylbutanoyloxy)-2-methyloct-7-ynoate (11)

The fragment **P3** (100 mg, 0.25 mmol) was dissolved in 10 mL of THF, TBAF (1.0 M in THF,

0.5 mL, 0.5 mmol) was added. The solution was stirred overnight, and then concentrated in vacuo. After dilution with H_2O, the mixture was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried with Na_2SO_4 and them evaporated. The residue was subjected to flash chromatography (petroleum ether/ethyl acetate, 8/1) to provide the desilylated alcohol intermediate as a colorless oil (68 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 – 5.75 (m, 1H), 5.29 (dd, *J* = 21.6, 13.8 Hz, 2H), 4.61 (d, *J* = 5.7 Hz, 2H), 3.91 (td, *J* = 8.2, 4.6 Hz, 1H), 2.61 – 2.49 (m, 2H), 2.25 (t, *J* = 6.4 Hz, 2H), 1.83 – 1.40 (m, 4H), 1.21 (d, *J* = 7.2 Hz, 3H).

To the solution of the desilylated alcohol intermediate (65 mg, 0.225 mmol) prepared above, was added the des-allyl acid intermediate that was prepared in 85% yield by treating ester **10** with $Pd(PPh_3)_4$ by following a similar procedure as preparation of **8**. EDC (0.129 g, 0.675 mmol) was then added, and the reaction was stirred at room temperature for 16 h. After evaporation in vacuo, the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3/1) to provide ester **11** (152 mg, 55%) as clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 2H), 5.99 – 5.82 (m, 1H), 5.59 – 5.51 (m, 1H), 5.37 – 5.32 (m, 1H), 5.31 – 5.15 (m, 2H), 4.96 – 4.85 (m, 1H), 4.84 – 4.76 (m, 2H), 4.71 – 4.61 (m, 1H), 4.56 (d, *J* = 5.3 Hz, 3H), 4.35 (s, 2H), 4.25 – 4.17 (m, 1H), 3.99 – 3.78 (m, 1H), 3.71 – 3.58 (m, 1H), 3.14 – 2.79 (m, 6H), 2.78 – 2.62 (m, 1H), 2.57 – 2.42 (m, 1H), 2.13 (m, 8H), 1.59 (s, 7H), 1.34 – 0.73 (m, 27H).

12. Preparation of (5S,6S,9S,12S)-((2S,3S)-1-(allyloxy)-3-methyl-1-oxopentan-2-yl)5-(5-bromopent-4-ynyl)-9,12-diisopropyl-2,2,3,3,6,11-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (15)

To a solution of the fragment **P1** (200 mg, 0.33 mmol) in CH_3CN (5 mL), diethylamine (1.7 mL) was added. The mixture was stirred for 15 min at 0 ^oC and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), to which was added **14** (120 mg,0.33 mmol), HATU (188 mg, 0.5mmol), HOAt (68 mg, 0.5mmol) and DIPEA (0.17 mL, 0.99 mmol) at 0^oC under nitrogen. The mixture was stirred overnight and concentrated in vacuo. The residue was purified by chromatography (petroleum ether/ethyl acetate, 5/1) to give amide **15** (120 mg) in 50% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.9 Hz, 1H), 5.87 (dq, *J* = 11.1, 5.8 Hz, 1H), 5.27 (dd, *J* = 23.4, 13.8 Hz, 2H), 5.12 (d, *J* = 10.3 Hz, 1H), 4.88 (d, *J* = 4.4 Hz, 1H), 4.70 (t, *J* = 8.5 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 2H), 3.73 (s, 1H), 3.02 (d, *J* = 58.7 Hz, 3H), 2.50 (dd, *J* = 7.0, 4.9 Hz,

1H), 2.31 – 1.90 (m, 5H), 1.44 (ddd, *J* = 40.3, 32.9, 16.6 Hz, 6H), 1.08 (dd, *J* = 15.4, 6.8 Hz, 6H), 0.93 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 15H), 0.10 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 168.3, 166.0, 164.2, 126.8, 114.3, 75.2, 72.3, 69.9, 61.1, 56.3, 49.2, 41.1, 33.3, 31.8, 27.0, 26.8, 26.7, 22.8, 19.8, 19.8, 15.0, 15.0, 14.6, 14.2, 13.7, 13.3, 10.7, 9.2, 6.8, -9.1, -9.2; ESI-MS *m/z* 751 (M + Na); HRMS Calcd for $C_{35}H_{61}BrN_2NaO_7Si$ (M + Na) : 751.3329, found 751.3348.

13. Preparation of (5R,6S,9S,12S)-((2S,3S)-1-((S)-2-(((S)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxopentan-2-yl)5-(5-bromopent-4-ynyl)-9,12-diisopropyl-2,2,3,3,6,11-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (16)

This compound was prepared deallylation of **15** followed by condensation with amine **9** by following a similar procedure as that for preparation of **16** in 48% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 9.0 Hz, 1H), 5.90 (ddd, *J* = 22.7, 10.8, 5.6 Hz, 1H), 5.27 (dd, *J* = 30.3, 13.8 Hz, 2H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 4.91 – 4.88 (m, 1H), 4.86 (d, *J* = 7.5 Hz, 1H), 4.77 – 4.72 (m, 1H), 4.61 (d, *J* = 5.4 Hz, 2H), 3.95 – 3.84 (m, 1H), 3.76 (s, 1H), 3.69 (dd, *J* = 14.8, 7.6 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 6H), 2.55 – 2.45 (m, 1H), 2.26 – 2.11 (m, 6H), 2.08 – 1.95 (m, 3H), 1.89 (ddd, *J* = 17.3, 8.6, 4.7 Hz, 1H), 1.50 (dddd, *J* = 63.3, 58.6, 16.3, 5.5 Hz, 6H), 1.13 (d, *J* = 7.1 Hz, 3H), 1.05 – 0.98 (m, 9H), 0.95 (s, 9H), 0.94 – 0.80 (m, 15H), 0.12 (s, 6H).

14. Preparation of (S)-*tert*-butyl2-(((S)-1-((2S,3R)-1-(allyloxy)-8-bromo-2-methyl-1-oxooct-7-yn-3-yloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrrolidine-1-carboxylate (19)

Acid **18** was obtained in 85% yield following a similar procedure as that for preparation of **8**. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 4.68 (dd, *J* = 26.6, 15.6 Hz, 1H), 4.50 – 4.03 (m, 1H), 3.66 – 3.41 (m, 2H), 3.17 – 2.75 (m, 3H), 2.06 (m, 5H), 1.44 (s, 9H), 1.13 – 1.02 (m, 3H), 0.89 (dd, *J* = 29.9, 6.6 Hz, 3H).

Ester **19** was obtained by reaction of acid **18** with desilylated intermediate of the fragment **P3** in 52% yield following a similar procedure as that for preparation of **11**. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 6.02 – 5.81 (m, 1H), 5.35 – 5.14 (m, 3H), 4.81 – 4.50 (m, 4H), 3.65 – 3.32 (m, 2H), 2.98 (t, *J* = 33.3 Hz, 3H), 2.77 – 2.63 (m, 1H), 2.31 – 1.63 (m, 11H), 1.41 (d, *J* = 8.3 Hz, 9H), 1.27 – 1.14 (m, 3H), 1.04 – 0.93 (m, 3H), 0.85 (dd, *J* = 9.0, 6.8 Hz, 3H).

15. Preparation of (S)-*tert*-butyl2-(((6S,9S,12S,15S,16R,19S)-16-(5-bromopent-4-ynyl)-6-*sec*-butyl-9,12-diisopropyl-10,15,20-trimethyl-5,8,11,14,18-pentaoxo-4,7,17-trioxa-10,13-diazahenicos-1-en-19-yl)(methyl)carbamoyl)pyrrolidine-1-carboxylate (20)--Path b

Ester **20** was obtained in 52% overall yield by reaction of the desilylated intermediate of **15** with acid **18** following a similar procedure as that for preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 6.92 (d, *J* = 8.3 Hz, 1H), 5.89 (dq, *J* = 10.6, 5.8 Hz, 1H), 5.30 (dd, *J* = 31.7, 13.8 Hz, 2H), 5.19 – 5.05 (m, 1H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.90 (d, *J* = 4.5 Hz, 1H), 4.84 – 4.58 (m, 4H), 4.19 (ddd, *J* = 28.8, 21.3, 8.7 Hz, 1H), 3.62 – 3.32 (m, 2H), 3.13 (dd, *J* = 12.9, 5.5 Hz, 6H), 2.65 – 2.52 (m, 1H), 2.41 – 2.11 (m, 5H), 2.04 – 1.78 (m, 7H), 1.76 – 1.47 (m, 4H), 1.43 (d, *J* = 7.1 Hz, 9H), 1.34 – 1.24 (m, 2H), 1.17 (dd, *J* = 14.9, 6.4 Hz, 3H), 1.09 – 1.01 (m, 6H), 0.91 (ddd, *J* = 13.4, 13.0, 8.5 Hz, 16H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 173.4, 173.1, 172.9, 172.8, 172.6, 172.5, 170.8, 170.7, 170.3, 168.9, 154.2, 153.6, 131.4, 119.0, 79.9, 79.5, 79.2, 76.9, 76.0, 75.6, 65.7, 61.2, 57.0, 56.5, 54.4, 54.2, 46.7, 46.4, 44.1, 43.7, 36.4, 31.6, 31.5, 31.0, 31.0, 30.0, 29.9, 29.7, 29.3, 28.6, 28.4, 28.3, 27.9, 27.8, 27.5, 27.4, 27.1, 24.7, 24.4, 24.1, 23.0, 21.1, 20.5, 19.7, 19.6, 19.3, 19.3, 19.0, 18.9, 18.2, 18.1, 15.3, 14.5, 14.0, 11.5; ESI-MS *m/z* 947 (M + Na); HRMS Calcd for $C_{45}H_{73}BrN_4NaO_{11}$ (M + Na): 947.4357, found 947.4349.

16. Preparation of natural product 1

To a solution of peptide **20** (125 mg, 0.135 mmol) in CH_2Cl_2 (7 mL) at 0 °C, was added $[Pd(PPh_3)_4]$ (31.2 mg, 0.027 mmol) and NMA (0.04 mL, 0.405 mmol). The reaction was stirred at room temperature for 10 h. After evaporation in vacuo, the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 2/1 to dichloromethane/MeOH 20:1) to give the carboxyl acid intermediate as yellow oil, which was then dissolved in CH_2Cl_2 (6 mL). To the solution just obtained, TFA (0.13 mL) was added at 0 ^{o}C. The resulting solution was stirred for 6 h, and then concentrated in vacuo to give the *N*-deprotected intermediate. To the solution of the *N*-deprotected intermediate in CH_2Cl_2 (100 mL), was added HATU (116 mg, 0.306 mmol), HOAt (42 mg, 0.306 mmol) and DIPEA (0.11 mL, 0.612 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 3 d, then diluted with H_2O and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2/1) to give cyclic peptide **1** (32.1 mg, 31% yield for 3 steps) as a colorless amorphous solid. $[\alpha]^{20}_{D}$ -33.0 (*c*

0.27, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, *J* = 9.8 Hz, 1H), 5.20 (d, *J* = 10.1 Hz, 1H), 5.05 (dd, *J* = 16.9, 8.7 Hz, 3H), 4.89 (d, *J* = 8.3 Hz, 1H), 4.80 (t, *J* = 8.6 Hz, 1H), 3.86 (m, 1H), 3.71 (m, 1H), 3.01 (s, 6H), 2.69 (s, 1H), 1.85-2.31 (m, 12H), 1.58 (m, 4H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.05 – 0.93 (m, 13H), 0.90 – 0.76 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 173.8, 172.6, 170.6, 170.2, 167.9, 80.2, 76.2, 75.7, 61.4, 60.8, 56.9, 53.1, 47.3, 44.6, 37.7, 36.6, 32.3, 32.0, 31.9, 31.7, 28.7, 27.9, 26.9, 25.1, 24.7, 24.0, 20.6, 20.4, 19.6, 19.5, 19.5, 18.3, 18.1, 16.4, 13.5, 10.7; ESI-MS *m/z* 789 (M + Na); HRMS Calcd for $C_{37}H_{59}BrN_4NaO_8$ (M + Na): 789.3414, found 789.3411.