SUPPORTING INFORMATION I

For

Total synthesis of the proposed structure of cyclic hexadepsipeptide Veraguamide A

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General considerations

All reactions were performed in glassware containing a Teflon-coated stir bar. CH₂Cl₂ 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 ¹³C 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 (32.75 g, 250 mmol) was dissolved in 1.25 M H₂SO₄ (175 mL) and cooled to 0°C. A solution of NaNO₂ (25.9 g, 375 mmol) in H₂O (125 mL) was added dropwise over 1 h and the obtained reaction mixture was stirred for 2 h at 0°C 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 Na₂SO₄ 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, K₂CO₃ (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 H₂O. The mixture was extracted with diethyl ether (2 × 300 mL), washed with brine, dried over Na₂SO₄ 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, CDCl₃) 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-\textsuperscript{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 CH₂Cl₂ (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°C, diluted with H₂O, and extracted with CH₂Cl₂. The combined CH₂Cl₂ phase was washed with brine and dried with Na₂SO₄. Removal of solvents followed by flash chromatography (petroleum ether/ethyl acetate, 30/1) provided 3 as a colorless oil (10.21 g, 91%).

¹H NMR (300 MHz, CDCl₃): δ = 6.03–5.85 (m, 1H, CH allyl), 5.38–5.23 (dd, 2H, CH₂ allyl), 4.89 (d, 1H), 4.65 (d, 2H, CH₂ 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-(((9H-fluoren-9-yl)methoxy)carbonylamo)-N₃-3-methylbutanamido)-3-methylbutanoxyloxy)-3-methylpentanoate (P1)

To a stirred solution of 3 (10.21 g, 26.5 mmol) in CH₂Cl₂ (200 mL) at 0 °C was added TFA (39.2 ml) and the resulting solution was stirred at 0 °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 CH₂Cl₂ (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 H₂O. After extraction with CH₂Cl₂, the combined organic phase was washed with brine and dried with Na₂SO₄. 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).¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₃₅H₄₆N₃NaO₇ (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...
(5.29 g, 24.3 mmol) and MeI (12.1 mL, 184 mmol) in THF (100 mL) at 0°C. After the reaction mixture had been stirred at room temperature for 18 h, it was poured into saturated NH₄Cl solution (500 mL), extracted with EtOAc (3 × 150 mL) and dried over Na₂SO₄. After evaporation of the solvents, the obtained N-methyl-N-Boc-valine was mixed with K₂CO₃ (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 Na₂SO₄ and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 15/1) gave 4 (5.9 g, 90% in two steps) as a colorless oil. ¹H NMR (300 MHz, CDCl₃, 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); ¹³C NMR (126 MHz, CDCl₃, 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. ¹H NMR (300 MHz, CDCl₃, 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 fragment P1.

(S)-tert-Butyl-2-(((S)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrroldine-1-carboxylate (P2): 72% yield in two steps, ¹H NMR (300 MHz, CDCl₃, 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); ¹³C NMR (101 MHz, CDCl₃, 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_{22}N_{2}NaO_{3} (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) $\delta$ 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, $J = 2.6$ Hz, 3H), 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 (101 MHz, CDCl$_3$, mixture of rotamers) $\delta$ 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, 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, dibutylboron triflate (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$_2$O$_2$ (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$_2$SO$_4$, 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 aldo 5 as a colorless viscous oil (7.5 g, 62% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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-7ynamide (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 1 h. 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 H₂O at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 1 h and extracted with CH₂Cl₂. The combined extracts were washed with brine (50 mL), dried (Na₂SO₄), 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, CDCl₃) 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).

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

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 °C and the resulting solution was stirred at room temperature overnight. The mixture was cooled to 0 °C, quenched with H₂O, and then extracted with Et₂O. The combined extracts were washed with H₂O and brine, dried (Na₂SO₄), 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, CDCl₃) 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).
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$_3$SiNa (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 diisobutyaluminum hydride in toluene (10.0 mL, 10.0 mmol). The mixture was stirred at -78 °C for 2 h, and then quenched by addition of saturated aqueous NH$_4$Cl 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$_2$SO$_4$), 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 (1.14 g, 12.66 mmol) and NaH$_2$PO$_4$ (0.97 g, 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$_2$SO$_4$ 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$_2$CO$_3$ (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$_2$SO$_4$ 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 (247 mg, 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).
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)$^+$; HRMS Calcd for C$_{18}$H$_{31}$BrNaO$_3$Si (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-diisopropyl-7-methyl-3,6,9-triioxo-2,10-dioxo-4,7-diazadodecane)-N-methylpyrrolidine-2-ca rboxamido)-3-methylbutanoate (10)

To a solution of the fragment P1 (0.6 g, 0.99 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (1 mL) at 0 °C, was added TFA (0.08 mL). The resulting solution was stirred at 0 °C for 6 h and 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$_2$Cl$_2$ (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$_2$O, and extracted with CH$_2$Cl$_2$. The combined organic phase was washed with brine and dried over Na$_2$SO$_4$. 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 (dtt, 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).


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 H₂O, the mixture was extracted with CH₂Cl₂. The combined organic phase was washed with brine, dried with Na₂SO₄ and then 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%). ¹H NMR (300 MHz, CDCl₃) 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(PPh₃)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. ¹H NMR (300 MHz, CDCl₃) 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-si latridecan-13-oate (15)

To a solution of the fragment P1 (200 mg, 0.33 mmol) in CH₃CN (5 mL), diethylamine (1.7 mL) was added. The mixture was stirred for 15 min at 0 °C and then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (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°C 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. ¹H NMR (300 MHz, CDCl₃) 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); 13C NMR (101 MHz, CDCl3) 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 C38H56BrN3NaO2Si (M + Na): 751.3329, found 751.3348.

13. Preparation of (5R,6S,9S,12S)-((2S,3S)-1-((S)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxopentan-2-yl5-(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. 1H NMR (400 MHz, CDCl3) 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. 1H NMR (300 MHz, CDCl3, 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. 1H NMR (300 MHz, CDCl3, 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).

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, 172.6, 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, 54.2, 47.1, 46.4, 44.1, 43.7, 36.4, 31.6, 31.5, 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$_{48}$H$_{73}$BrN$_4$NaO$_{11}$ (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$_2$Cl$_2$ (7 mL) at 0 ºC, 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$_2$Cl$_2$ (6 mL). To the solution just obtained, TFA (0.13 mL) was added at 0 ºC. 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$_2$Cl$_2$ (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 ºC. The reaction mixture was allowed to stir at room temperature for 3 d, then diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The combined organic phase was washed with brine, dried over Na$_2$SO$_4$, 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. [α]$_{20}^{D}$ -33.0 (c
0.27, MeOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_{59}\)Br\(_4\)N\(_4\)O\(_8\) (M + Na): 789.3414, found 789.3411.