Assembly of the nosiheptide A-Ring: A fruitful lesson

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Additional Experimental Section

All solvents, if not purchased in suitable purity or dryness, were distilled. Deionized water was used for all experiments. Thin Layer Chromatography (TLC) was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm or the KMnO\textsubscript{4} solution (KMnO\textsubscript{4} 1 g, K\textsubscript{2}CO\textsubscript{3} 6.6 g, 5\% NaOH solution 1.7 mL, H\textsubscript{2}O 100 mL) as staining reagent. Silica gel chromatography was performed using silica gel from J. T. Baker or Merck (particle size 40-60\,\mu m) under approximately 0.5 bar pressure.

IRAffinity 1. The following notations indicate the intensity of the absorption bands: s = strong, m = middle, w = weak, b = broad. Melting points were determined in a Büchi melting point B-540 apparatus in open capillaries (uncorrected). Electro-spray mass spectrometric analyses (ESI-MS) were performed on an Agilent 1100 HPLC system. Fast atom bombardment (FAB) mass spectra were recorded on a Finnigan LCQ spectrometer coupled to an Agilent 1100 HPLC system. System temperature. I\textsubscript{2} (4.05 g, 16.0 mmol) in DMF (30 mL) under Ar and stirred for 15 min at room temperature. I\textsubscript{2} (4.05 g, 16.0 mmol) was added dropwise and the reaction mixture was stirred until gas evolution ceased. The cooling bath was removed and the reaction mixture was then stirred at 40 °C (TLC control). The solvent was removed and the resulting residue was purified by column chromatography (silica gel) to give the thiazoline.

General procedure for oxidation with DBU/BrCCl\textsubscript{3} (GP 3):

Thiazoline was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (50 mmol) and cooled to -20 °C. DBU (2.1 eq.) was added and stirred for 5 min. BrCCl\textsubscript{3} (1.05 eq.) was added dropwise and cooled to -20 °C, slowly warmed to room temperature (TLC control). Aqueous HCl (0.1 N, 10 mL) was added and the azeotropic layer was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried with MgSO\textsubscript{4} and concentrated. Purification by column chromatography (silica gel) furnished the azole.

Ethyl 3-iodo-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-indole-2-carboxylate (9)

Indole 8 (4.40 g, 14.5 mmol) and anhydrous K\textsubscript{2}CO\textsubscript{3} (5.51 g, 39.9 mmol) were suspended in anhydrous DMF (70 mL) under Ar and stirred for 15 min at room temperature. I\textsubscript{2} (4.05 g, 16.0 mmol) in DMF (30 mL) was added dropwise and stirred for 5 h (TLC control). The reaction was quenched with aqueous NH\textsubscript{4}Cl (100 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 75 mL). The resulting organic layer was washed with aqueous Na\textsubscript{2}SO\textsubscript{4} (50 mL) and water (50 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated to dryness. Purification by column chromatography (silica gel, 400 g, light petroleum–ethyl acetate, 2:1) gave 5.49 g (12.9 mmol, 89\%) of indole 8 as a yellow solid.

Mp 120–121 °C; R\textsubscript{f} = 0.36 (cyclohexane–ethyl acetate, 2:1).

IR (KBr): \texttilde{v} = 3286 (m), 2939 (w), 1674 (s), 1267 (m), 770 (m), 746 (m) cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta = 1.46 (t, J = 7.1 Hz, 3H, CH\textsubscript{2}CH\textsubscript{2}), 1.95-1.52 (m, 6H, THP), 3.61-3.57 (m, 1H, THP), 4.01-3.96 (m, 1H, THP), 4.46 (q, J = 7.1 Hz, CH\textsubscript{2}CH\textsubscript{2}), 4.91 (t, J = 3.2 Hz, 1H, 2'-H), 5.34 (d, J = 12.5 Hz, 1H, PhCH\textsubscript{2}), 5.43 (d, J = 12.6 Hz, 1H, PhCH\textsubscript{2}), 7.40-7.57 (m, 2H, 5-H, 6-H, 7-H), 9.23 (bs, 1H, NH).
Ethyl 3-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-indole-2-carboxylate (10)

Iodoindole 9 (3.42 g, 8.0 mmol) and Pd(dpdpf)Cl₂ (98 mg, 1.5 mol%) were suspended in anhydrous 1,4-dioxane (100 mL) at room temperature, Me₂-Zn (1.2 M in Toluene, 13.2 mL, 15.9 mmol) was added dropwise with stirring, and the resulting mixture was heated to reflux for 16 h. The reaction mixture was cooled to room temperature, acidified with citric acid to pH 3 and stirred for 8 h at room temperature. The resulting residue was redissolved in AcOH (70%, 50 mL) and extracted with ethyl acetate (4 × 100 mL). The organic layer was washed with 1M HCl (100 mL) and water (100 mL), dried with Na₂SO₄ and concentrated. Aqueous NaOH (10%, 5 mL) was added to the suspension of indole 10 (1.21 g, 3.8 mmol) in H₂O/EtOH (1:1, 40 mL), and heated to reflux for 30 min. The reaction mixture was cooled to room temperature, acidified with citric acid to pH 3 and extracted with ethyl acetate (4 × 100 mL). The resulting residue was redissolved in AcOH (70%, 50 mL) and stirred for 8 h at room temperature. The reaction mixture was co-evaporated with toluene (2 × 25 mL). The crude product was dissolved in hot i-PrOH and cooled down to 0 °C. Addition of n-pentane initiated crystallization to give indolic acid 11 (0.57 g, 2.8 mmol, 73%) as fine needles.

Mp 236 °C (decomp.); Rf = 0.20 (CH₂Cl₂-MeOH, 10:1).

IR (KBr): \( \tilde{\nu} = 3472 \) (m), 3234 (bs), 2878 (m), 1638 (s), 1538 (m), 1477 (m), 1344 (m), 1246 (m), 994 (m), 956 (s), 905 (s), 873 (s), 785 (s), 750 (s) cm⁻¹.

HRMS (EI): m/z [M⁺] calcd for C₁₁H₁₁NO₃: 205.0739; found: 205.0741.

(4-Hydroxymethyl)-3-methyl-1H-indole-2-carboxylic acid diphenylmethyl ester (3)

Diphenyl diazomethane (1.58 g, 8.1 mmol) was prepared according to a published procedure, then dissolved in THF (3 mL) and added to a stirred solution of indolic acid 11 (557 mg, 2.7 mmol) in anhydrous THF (12 mL). A catalytic amount of TFA (0.1 mL) was added and the reaction mixture was heated to 60 °C for 3.5 h. Ethyl acetate (150 mL) was added. The organic layer was washed with 5% citric acid (30 mL), saturated NaHCO₃ (30 mL), saturated NaCl (30 mL), dried with MgSO₄ and concentrated. Purification by column chromatography (silica gel, 150 g, light petroleum–ethyl acetate, 4:1) gave 686 mg (1.9 mmol, 68%) of ester 3 as a light yellow solid.

Mp 157–158 °C; Rf = 0.20 (dichloromethane–MeOH, 10:1).

[α] 0 20 = −82.2 (c 1.0, CHCl 3); R f = 0.32 (light petroleum–methyl tert-butyl ether, 4:1).

IR (KBr): 3451 (m), 2979 (m), 2935 (m), 2128 (s), 1757 (s), 1688 (s), 1505 (s), 1298 (m), 1155 (m), 915 (s), 863 (m) cm⁻¹.

1H NMR (400 MHz, CDCl 3): δ = 1.09 (s, 9H, OC(CH 3) 3), 1.19 (d, J = 6.2 Hz, 3H, CH(CH 3) 2), 1.49 (s, 9H, CO 2C(CH 3) 3), 3.11 (dd, J = 8.2, 13.8 Hz, 1H, CH(CH 3) 2), 3.31 (dd, J = 5.8, 13.8 Hz, 1H, CH(CH 3) 2), 4.01 (dd, J = 5.8, 8.2 Hz, 1H, CH(CH 3) 2), 4.14 (dd, J = 1.4, 9.3 Hz, 1H, CH(CH 3) 2), 4.27 (qd, J = 1.3, 6.2 Hz, 1H, CH(CH 3) 2), 4.77–4.63 (m, 2H, CH 2CHCH–CH 2), 5.41–5.26 (m, 2H, CH=CH 2), 5.47 (d, J = 9.2 Hz, 1H, NH), 5.93 (dtd, J = 5.8, 10.4, 17.2 Hz, 1H, CH=CH 2).

13C NMR (100.6 MHz, CDCl 3): δ = 21.3, 28.6, 28.7, 30.3, 61.5, 66.3, 66.9, 76.3, 80.6, 119.6, 131.3, 156.1, 168.6, 202.0.


The above prepared triester (263 mg, 0.66 mmol) was transformed following GP 2 for theaza-Wittig reaction and GP 3 for the oxidation, giving 208 mg (5.0 mmol, 96%) of thiazoie 14 as a colorless solid after column chromatography purification (silica gel, 25 g, light petroleum–ethyl acetate, 4:1).

Mp 118–119 ºC; [α] 0 20 = −6.3 (c 1.0, CHCl 3); R f = 0.43 (light petroleum–methyl tert-butyl ether, 1:1).

IR (KBr): 3403 (bm), 3319 (bm), 2977 (s), 1718 (s), 1496 (s), 1451 (m), 1211 (s), 935 (s), 799 (s), cm⁻¹.

1H NMR (400 MHz, CDCl 3): δ = 0.96 (d, J = 6.3 Hz, 3H, 4'–CH 3), 1.28 (bs, 12H, 3'–H, OC(CH 3) 3), 3.22–2.65 (bs, 1H, OH), 4.26–4.14 (m, 2H, Fmoc, 3'–H), 4.32 (bs, 1H, 2'–H), 4.40 (d, J = 6.8 Hz, 2H, Fmoc), 4.67 (m, 1H, 2'–H), 4.83 (d, J = 3.8 Hz, 2H, CH 2CHCH=CH 2), 5.19 (d, J = 8.7 Hz, 1H, 1'–H), 5.30 (d, J = 10.2 Hz, 1H, CH=CH–Fmoc), 5.41 (d, J = 17.2 Hz, 1H, CH=CF–Fmoc), 6.12–5.91 (m, 2H, NH, CH=CH 2), 7.35 (dt, J = 7.1, 35.8 Hz, 4H, Fmoc), 7.60 (d, J = 7.1 Hz, 2H, Fmoc), 7.76 (d, J = 7.2 Hz, 2H, Fmoc), 8.24–8.09 (m, 2H, NH, 5–H).

HRMS (ESI): m/z [M + H] + calcd for C 33 H 40 N 5 O 7 S: 622.2587; found: 622.2577.

N-Boc-5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptane (20)

N-Boc-trans-L-Hydroxyproline 19 (5.30 g, 22.9 mmol) and PPh 3 (6.3 g, 24.1 mmol) were dissolved in THF and cooled to 0 ºC. DIAD (4.7 mL, 24.1 mmol) was added dropwise while keeping the temperature below 4 ºC. The reaction mixture was kept at 0ºC for 30 min and then at room temperature for 16 h. The reaction mixture was concentrated, then dissolved in EtO/light petroleum (500 mL, 9:1) at 0ºC. The precipitated triphenylphosphinoxide was removed by filtration and the filtrate was concentrated. Purification by column chromatography (silica gel, 200 g, light petroleum–ethyl acetate, 2:1) and recrystallization from light petroleum/ethyl acetate (4:1) gave 3.04 g (14.3 mmol, 62%) of lactone 18 as a colorless solid.

Mp 108–110 ºC; [α] 0 20 = +46.3 (c 1.0, CHCl 3); R f = 0.43 (cyclohexane–ethyl acetate, 1:1).

IR (KBr): 3401 (bm), 3319 (bm), 2977 (s), 1718 (s), 1496 (s), 1451 (m), 1211 (s), 935 (s), 799 (s), cm⁻¹.

1H NMR (400 MHz, CDCl 3): δ = 1.40 (s, 1H, C(CH 3) 3), 1.96 (d, J = 10.5 Hz, 1H, 7–H), 2.16 (dt, J = 1.2, 10.7 Hz, 1H, 7–H), 3.37 (d, J = 11.2 Hz, 1H, 6–H), 3.47 (dd, J = 1.2, 11.0 Hz, 1H, 6–H), 4.47 (bs, 1H, 1–H), 5.02 (m, 1H, 1–H).

13C NMR (100.6 MHz, CDCl 3): δ = 21.8, 28.1, 38.9, 49.6, 78.2, 81.1, 153.7, 170.8.


Pyrrolidinone 21

2,2,2-Trichlorethanol (10.2 mL, 106.7 mmol) was added to a suspension of NaH (2.13 g, 60% in mineral
oil, 53.4 mmol) in THF (200 mL) at 0 °C. The reaction mixture was cooled to -78 °C after H2-generation ceased. Lactone 20 (5.69 g, 26.7 mmol) dissolved in THF (40 mL) was added slowly and stirred at -78 °C for 30 min. HOAc (4.6 mL, 80 mmol) was added and the mixture was warmed to room temperature, diluted with H2O (400 mL) and extracted with CH2Cl2 (4 × 200 mL). The combined organic layer was dried with MgSO4, concentrated and purified by column chromatography (silica gel, 200 g, light petroleum ether, 5:1). The product was dissolved in DMF (50 mL) and cooled to -78 °C after H2-evolution ceased. The mixture was diluted with H2O (200 mL) and extracted with CH2Cl2 (3 × 100 mL). The combined organic extracts were washed with saturated NaCl (40 mL) by column chromatography (silica gel, 400 g, light petroleum – methyl tert-butyl ether, 9:1) gave 8.80 g (18.5 mmol, 69%) of pyrrolidine TBS-ether as a colorless solid.

Mp 69–71 °C; [α]D20 = -30.3 (c 1.0, CHCl3); Rf = 0.47 (light petroleum – methyl tert-butyl ether, 5:1).

IR (KBr): ν = 3392 (m), 3098 (m), 2955 (s), 2544 (m), 2044 (m), 1712 (s), 1470 (s), 1148 (s), 903 (s), 868 (bm), 741 (s), cm⁻1.

1H NMR (400 MHz, CDCl3): δ = 0.02, 0.03, 0.04, 0.05 (s, 3H, Si(CH3)2), 0.85, 0.84 (9H, SiC(C2H5)3), 1.46, 1.41 (s, 9H, CO2C(CH3)3), 2.20-2.13 (m, 1H, 5-H), 4.29 (dd, J = 7.8, 4.3 Hz, 1H, 4-H), 4.40-4.34 (m, 1H, 2-H), 4.54-4.43 (m, 1H, 3-H), 4.82-4.58 (m, 2H, CH2CCl3) (rotamers).

13C NMR (100.6 MHz, CDCl3): δ = -4.9, 17.9, 18.0, 25.6, 25.7, 28.3, 28.4, 38.7, 39.5, 54.3, 54.7, 57.2, 57.5, 69.8, 70.7, 74.3, 74.6, 80.2, 80.3, 95.4, 153.7, 170.4 (rotamers).

HRMS (FAB): m/z [M + H]+ calcd for C18H33NO5Cl3Si: 490.0986; found: 490.0965.

4-Hydroxyglutamate 22a

Pyrrolidinone 21 (6.10 g, 12.4 mmol) was dissolved in THF (100 mL) and cooled to -78 °C. In parallel, benzyl alcohol (1.28 mL, 12.4 mmol) was added to a suspension of NaH (0.52 g, 60% in mineral oil, 13.1 mmol) in THF (50 mL) at 0 °C. The mixture was cooled to -78 °C after H2-evolution ceased. The obtained alcoholate solution was added slowly to the pyrrolidinone solution by a double tipped needle and stirred for 30 min at -78 °C. AcOH (5 mL) was added, followed by H2O (500 mL), and the mixture was warmed to room temperature, diluted with H2O (200 mL) and extracted with CH2Cl2 (3 × 250 mL). The organic layer was dried with MgSO4 and concentrated. Purification by column chromatography (silica gel, 500 g, light petroleum – ethyl acetate, 7:1) gave 4.68 g (7.8 mmol, 63%; 87% based on recovered 21) of diester 22a as a colorless oil.

[a]D20 = -29.2 (c 0.9, CHCl3); Rf = 0.32 (light petroleum – methyl tert-butyl ether, 5:1).

IR (KBr): ν = 3757 (m), 3374 (s), 3158 (s), 2920 (s), 1952 (m), 1764 (s), 1628 (s), 1268 (s), 822 (s), 708 (s), cm⁻1.

1H NMR (400 MHz, CDCl3): δ = 0.01, 0.03 (s, 3H, Si(CH3)2), 0.89 (s, 9H, SiC(CH3)3), 1.41 (s, 9H, CO2C(CH3)3), 2.20-2.07 (m, 1H, 1-H), 3.37-3.28 (m, 1H, 3-H), 3.68-3.57 (m, 1H, 5-H), 4.40-4.34 (m, 1H, 4-H), 4.54-4.43 (m, 1H, 2-H), 4.82-4.58 (m, 2H, CH2CCl3) (rotamers).

HRMS (FAB): m/z [M + H]+ calcd for C18H31NO5Cl3Si: 476.1188; found: 476.1221.

RuO4 (540 mg, 4.1 mmol) was added to a solution of NaIO4 (10.85 g, 50.7 mmol) in H2O (150 mL) and stirred for 5 min at room temperature. Pyrrolidine TBS-ether (9.68 g, 20.3 mmol) in MeCN/CCl4 (100 mL, 9:1) was added to this yellow solution and stirred for 13 h. The reaction mixture was filtered through a pad of silica gel and washed with ethyl acetate (3 × 50 mL). The resulting mixture was washed with 30% NaHSO3 solution (100 mL) and brine (50 mL), dried with MgSO4 and concentrated. Purification by column chromatography (silica gel, 400 g, light petroleum – methyl tert-butyl ether, 4:1) gave 7.57 g (15.4 mmol, 76%) of pyrrolidinone 21 as a colorless solid.

Mp 86–87 °C; [α]D20 = -39.6 (c 0.8, CHCl3); Rf = 0.36 (light petroleum – methyl tert-butyl ether, 5:1).

IR (KBr): ν = 3502 (m), 3372 (m), 2960 (s), 1768 (bs), 1725 (s), 1323 (s), 1148 (s), 1088 (s), 967 (s), 792 (s), cm⁻1.

1H NMR (400 MHz, CDCl3): δ = 0.10, 0.14 (s, 3H, Si(CH3)2), 0.86 (s, 9H, SiC(CH3)3), 1.49 (s, 9H, CO2C(CH3)3), 2.05 (dt, J = 4.7, 16.0 Hz, 1H, 3-H), 2.68-2.57 (m, 1H, 3-H), 4.29 (dd, J = 6.7, 7.4 Hz, 1H, 4-H), 4.59 (dd, J = 6.6, 8.1 Hz, 1H, 2-H), 4.67 (d, J = 11.9 Hz, 1H, CH2HCCl3).

13C NMR (100.6 MHz, CDCl3): δ = 5.3, -4.6, 18.1, 25.6, 27.9, 32.0, 55.4, 70.5, 74.5, 84.2, 94.4, 149.6, 169.0, 170.9.

HRMS (FAB): m/z [M + H]+ calcd for C18H31NO5Cl3Si: 490.0986; found: 490.0965.

Anal. Calcd for C18H31NO5Cl3Si: C 44.0; H 6.2; N 2.6.

4-Hydroxyglutamate 22b

By using 4-methoxybenzylalcohol (1.28 mL, 12.4 mmol), pyrrolidinone 21 was transformed to the PMB ester 22b and purified by column chromatography (silica gel, 200 g, light
petroleum–ethyl acetate, 8:1) yielding 1.76 g, (2.8 mmol, 90%) of diester as a colorless oil.

\[[\alpha]_D^{20} = -25.0 \ (c \ 1.0, \ \text{CHCl}_3) \]

\( R_f = 0.42 \) (light petroleum–ethyl acetate, 4:1).

IR (KBr): \( \tilde{\nu} = 3377 \) (m), 2957 (s), 2932 (s), 1758 (s), 1516 (m), 1368 (m), 1249 (s), 1174 (s), 812 (s), 572 (w) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.00, 0.03 \) (s, 3H, Si(CH\(_3\))\(_3\)), 0.88 (s, 9H, Si(CH\(_3\))\(_3\)), 1.41 (s, 9H, CO\(_2\)C(CH\(_3\))\(_3\)), 2.02-2.17 (m, 1H, 3-H), 2.20-2.34 (m, 1H, 3-H), 3.79 (s, 3H, PMB-OCH\(_3\)), 4.33 (dd, \( J = 3.0, 9.1 \) Hz, 1H, 4-H), 4.49 (bs, 1H, 2-H), 4.58 (d, \( J = 11.8 \) Hz, 1H, CHHCCl\(_3\)), 4.90 (d, \( J = 11.8 \) Hz, 1H, CHHCCl\(_3\)), 5.06 (d, \( J = 2.1 \) Hz, 2H, PMB-CH\(_3\)), 5.38 (d, \( J = 8.4 \) Hz, 1H, NH), 6.79-6.92 (m, 2H, PMB), 7.24-7.28 (m, 2H, PMB).

\(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \( \delta = -53.3, -4.7, 18.3, 25.9, 28.5, 36.1, 51.5, 55.5, 67.1, 69.8, 74.6, 80.3, 94.8, 114.2, 127.6, 130.6, 155.6, 160.1, 171.1, 172.7.

HRMS (ESI): \( m/z \ [M + H]^+ \) calcd for C\(_{26}\)H\(_{41}\)NO\(_8\)Cl\(_3\)Si\([\text{M}+\text{H}]^+\) : 684.3; found: 683.8.

**Azido-thioester 22b**

Transformation of diester 22b (77 mg, 0.12 mmol) according to the procedure for 22a, gave 51 mg (0.11 mmol, 84%) of glutamic acid after column chromatography (silica gel, 15 g, CHCl\(_3\)–MeOH, 12:1) as a colorless resin.

\([\alpha]_D^{20} = -23.8 \ (c \ 1.0, \ \text{CHCl}_3) \]

\( R_f = 0.21 \) (CHCl\(_3\)/MeOH, 12:1).

IR (KBr): \( \tilde{\nu} = 3376 \) (bw), 2956 (m), 2932 (m), 1715 (s), 1516 (m), 1506 (m), 1394 (m), 1249 (s), 1174 (s), 841 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.00, 0.02 \) (s, 3H, Si(CH\(_3\))\(_3\)), 0.88 (s, 9H, Si(CH\(_3\))\(_3\)), 1.42 (s, 9H, CO\(_2\)C(CH\(_3\))\(_3\)), 2.13 (bs, 1H, 3-H), 2.25 (bs, 1H, 3-H), 3.80 (s, 3H, PMB-OCH\(_3\)), 4.32 (bs, 1H, 2-H), 4.38 (bs, 1H, 4-H), 5.08 (s, 2H, PMB-CH\(_3\)), 5.51 (bs, 1H, NH), 6.87 (d, \( J = 8.6 \) Hz, 2H, PMB), 7.28 (d, \( J = 8.6 \) Hz, 2H, PMB).

**Thiazole 24b**

The crude thiazoline was obtained by GP 2 from thioester 23b (48 mg, 0.07 mmol) and PPh\(_3\) (28 mg, 0.1 mmol). After removal of the volatiles, the residue was oxidized with DBU (30 \( \mu \)L, 0.3 mmol) and BrC\(_6\)H\(_5\) (10 \( \mu \)L, 0.15 mmol) following GP 3. Purification by column chromatography (silica gel, 10 g, light petroleum–ethyl acetate, 6:1) gave 44 mg (0.07 mmol, 99%) of thiazole 24b as a colorless oil.

\([\alpha]_D^{20} = -31.5 \ (c \ 1.0, \ \text{CHCl}_3) \]

\( R_f = 0.46 \) (light petroleum–ethyl acetate, 2:1).

IR (KBr): \( \tilde{\nu} = 3353 \) (bw), 2953 (m), 2857 (m), 1715 (s), 1614 (m), 1515 (m), 1248 (s), 1203 (m), 1174 (s), 784 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = -0.02, 0.00 \) (both s, 3H, Si(CH\(_3\))\(_3\)), 0.89 (s, 9H, Si(CH\(_3\))\(_3\)), 1.43 (s, 9H, CO\(_2\)C(CH\(_3\))\(_3\)), 2.42 (dd, \( J = 4.7, 8.4 \) Hz, 2H, 2'-H2), 3.80 (s, 3H, PMB-OCH\(_3\)), 4.39 (dd, \( J = 4.0, 8.3 \) Hz, 1H, 3'-H), 4.83 (dt, \( J = 1.3, 5.7 \) Hz, 2H, CH\(_2\)CH=C(CH\(_3\))) 5.04 (d, \( J = 11.8 \) Hz, 1H, PMB-CH\(_2\)), 5.09 (d, \( J = 11.8 \) Hz, 1H, PMB-CH\(_2\)), 5.17 (bd, \( J = 4.4 \) Hz, 1H, 1'-H), 5.28 (dd, \( J = 1.3, 10.4 \) Hz, 1H, CH=CH\(_2\)), 5.40 (dq, \( J = 1.5, 17.2 \) Hz, 1H, CH=CH\(_2\)), 5.80 (d, \( J = 7.1 \) Hz, 1H, NH), 6.02 (ddt, \( J = 5.8, 10.4, 16.2 \) Hz, 1H, CH=CH\(_2\)), 6.87 (d, \( J = 8.7 \) Hz, 2H, PMB), 7.29 (d, \( J = 8.7 \) Hz, 2H, PMB), 8.09 (s, 1H, 5-H).

**Bis-thiazole 4b**

Glutamate 24b (10 mg, 16.1 \( \mu \)mol) and 2,6-lutidine (40 \( \mu \)L, 0.34 mmol) were dissolved in dichloromethane (1 mL) and cooled to 0°C. TBSOTf (40 \( \mu \)L, 0.17 mmol) was added dropwise. The reaction mixture was stirred for 12 h ( TLC control). The solvent and the volatiles were removed under high
vacuum. The crude product was dissolved in THF (1 mL) under argon at 0 °C, and acid 18 (8 mg, 14.2 μmol), HOAt (7.7 mg, 56.6 μmol), HATU (13.5 mg, 35.5 μmol) were added to the reaction mixture. NaHCO₃ (3.6 mg, 42.9 μmol) was added after 15 min. The reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was diluted with phosphate buffer (pH 2.5, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 9 mg (8.4 μmol, 59%) of the thiazolyl dipeptide 4b as colorless foam.

IR (KBr): v = 3398 (w), 3316 (w), 2929 (s), 2856 (w), 1725 (s), 1696 (s), 1246 (s), 814 (s) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = -0.03 (3H, s, TBS), 0.86 (9H, s, TBS), 1.21 (s, 9H, s, CH₂), 1.26 (3H, d, J = 6.2 Hz, CH₃), 1.33 (9H, s, tBu), 1.86 (3H, d, J = 7.3 Hz, CH₂), 2.58-2.70 (2H, m, CH₂), 3.79 (3H, s, CH₃), 4.23 (1H, t, J = 6.8 Hz, CH), 4.29 (1H, t, J = 4.6 Hz, Fmoc), 4.43 (3H, t, J = 5.5 Hz, CH, Fmoc), 4.83 (2H, d, J = 5.9 Hz, CH₂Ph), 5.03 (2H, dd, J = 6.0 Hz, CH₂=CH₂), 5.28 (1H, d, J = 10.6 Hz, CH₂=CH₂), 5.39 (1H, dd, J = 17.2, 1.3 Hz, CH₂=CH₂), 5.69-5.75 (1H, m, CH), 5.96-6.06 (2H, m, CH₂=CH₂), Fmoc-NH), 6.69 (1H, dd, J = 7.2 Hz, CH₂CH₂), 8.62 (2H, d, J = 8.6 Hz, Fmoc), 7.30 (4H, dd, J = 8.6, 1.3 Hz, Fmoc), 7.39 (2H, t, J = 7.6 Hz, Fmoc), 7.60 (2H, d, J = 7.5 Hz, PMB), 7.76 (2H, d, J = 7.4 Hz, PMB), 7.92 (1H, d, J = 8.8 Hz, NH), 8.03 (1H, s, CH), 8.09 (1H, s, CH), 8.65 (1H, s, NH).

13C NMR (100.6 MHz, CDCl₃): δ = -5.4, -5.0, 14.1, 17.0, 18.2, 25.7, 28.3, 29.7, 39.0, 47.2, 47.7, 55.3, 58.9, 65.9, 66.7, 66.8, 67.0, 69.3, 76.2, 77.3, 113.9, 118.8, 120.0, 123.5, 125.1, 126.4, 127.1, 127.5, 127.7, 127.8, 128.0, 130.5, 131.9, 141.3, 143.1, 143.6, 143.8, 146.8, 149.5, 156.0, 159.8, 160.6, 160.9, 167.0, 167.9, 168.2, 171.7, 172.8, 178.7.

HRMS (ESI): m/z [M + H]^+ calc for C₉₃H₆₅N₅O₁₀S₂Si: 2083.6389; found: 2083.6389.

Peptidic bis-thiazole amine 26a

DBU (40 μL) and piperidine (40 μL) were added to a mixture of peptide 4b (24 mg, 22.5 μmol) in dichloromethane (4 mL) at room temperature. The reaction mixture was stirred for 20 min (TLC control) and concentrated under high vacuum. The residue was purified by column chromatography (silica gel, 20 g, dichloromethane/Methanol = 30:1) to give 16.8 mg (19.9 μmol, 88%) of free amine 26b as a colorless resin.

Rᶠ = 0.47 (dichloromethane–MeOH, 10:1).

HRMS (ESI): m/z [M + H]^+ calc for Ca₁₁H₁₇N₅NaO₃S₂Si: 866.3259; found: 866.3257.

Methyl bromopyruvate (29)

Preparation by analogy to Kruse et al.: To a solution of commercially available methyl L-lactate (15 g, 0.144 mol) in CCl₄ (260 mL) was added NBS (48.7 g, 0.27 mol). The reaction mixture was heated to reflux for 6 h and cooled to rt. The precipitate was filtered off and washed with small amount of CCl₄. The solvent was removed under reduced pressure and distillation of the residue gave 15.9 g (87.9 mmol, 61%) of α-bromo ketone 29 as yellowish oil.

Bp.: 65 °C (4 mbar).

IR (film): v = 3008 (w), 1736 (s), 1435 (w), 1226 (m), 1049 (s), 671 (w) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = -0.03 (d, J = 8.5 Hz, 6H, Si(CH₃)₃), 0.86 (s, 9H, Si(CH₃)₂), 1.21 (s, 9H, O(CH₂)₃), 1.27 (d, J = 6.3 Hz, 3H, 4°-CH₃), 1.85 (d, J = 7.2 Hz, 3H, 3°-CH₃), 2.66 (m, 2H, 2'-H), 3.62 (bs, 1H, 2°-H), 4.33-4.42 (m, 1H, 3°-H), 4.52-4.40 (m, 1H, 3'-H), 4.82 (dt, J = 1.3, 5.8 Hz, 2H, CH₂CH=CH₂), 5.06 (d, J = 12.1 Hz, 1H, CH=CHPh), 5.10 (d, J = 12.1 Hz, 1H, CH=CHH), 5.39 (dq, J = 1.5, 17.2 Hz, 1H, CH=CHH), 5.70 (dd, J = 8.4, 14.6 Hz, 1H, 1°-H), 6.01 (ddt, J = 5.8, 10.4, 17.2 Hz, 1H, CH=CH₂), 6.60 (q, J = 7.1 Hz, 1H, 2°-H), 7.39-7.28 (m, 5H, Ph), 7.98 (s, 1H, 5°-H), 8.08 (s, 1H, 5-H), 8.11 (d, J = 7.9 Hz, 1H, 1°-NH), 9.35 (s, 1H, 1°'-NH).

13C NMR (100.6 MHz, CDCl₃): δ = -5.2, -4.8, 14.5, 18.4, 19.9, 25.9, 28.9, 39.5, 48.0, 60.0, 66.2, 67.2, 67.6, 69.6, 75.0, 119.1, 123.5, 126.5, 128.3, 128.6, 128.7, 128.8, 132.1, 135.5, 146.8, 149.6, 161.0, 161.2, 167.3, 172.1, 173.2.

HRMS (ESI): m/z [M + H]^+ calc for C₁₉H₁₇N₅NaO₇S₂Si: 914.3050; found: 914.3053.

Methyl 2-aminothiazole-4-carboxylate (30)

Thiourea (4.42 g, 58 mmol) was added to a solution of methyl bromopyruvate (10 g, 55.3 mmol) in dry MeOH (100 mL) and the mixture was heated to reflux for 2 h. After cooling the solvent was removed under
reduced pressure. The residue was dissolved in ice-water (150 mL) and the pH was brought to 8 by addition of solid K₂CO₃. The precipitate was filtered, washed several times with water and dried under vacuum to give 8.13 g (51.4 mmol, 93%) of the title compound as a yellow powder.

Mpf: 174 ºC.

IR: v =3402 (w), 3105 (w), 1624 (w), 1693 (m), 1539 (m), 1346 (m), 1234 (s), 987 (m), 732 (m) cm⁻¹.

¹H NMR (250 MHz, DMSO-d₆): δ = 7.33 (s, 3H, CH₃), 7.24 (bs, 2H, NH₂), 7.48 (s, 1H, CH).

¹³C NMR (63 MHz, DMSO-d₆): δ = 153.9 (m), 134.8 (m), 123.4 (s), 98.7 (m), 73.2 (m) cm⁻¹.

IR (KBr): v = 3445 (w), 3060 (w), 2116 (s), 1730 cm⁻¹.

Methyl 2-iodothiazole-4-carboxylate (31)

7.48 g (47.3 mmol) 2-Aminothiazole (30) were dissolved in THF (95 mL), cooled to 0 ºC and CH₂Cl₂ (19.1 mL, 237 mmol) was added. Then tert-butyl nitrite (23.7 mL, 199 mmol) was added dropwise over a period of 75 min. The resulting thick slurry was stirred for another 15 min at 0 ºC and taken out of the cooling bath. After 5-10 min the solution became clear and gas evolution started. The mixture was cooled immediately with cold water and stirred for another 2 h. The reaction was diluted with EtOAc (500 mL), washed with sat. NaHCO₃ (2 × 150 mL), brine (150 mL), dried with Na₂SO₄ and concentrated. Purification by column chromatography (silica gel, 80 g, ethyl acetate/light petroleum 1:12 to dichloromethane) yielded 9.54 g (35.5 mmol, 75%) of the iodothiazole 31 as a yellowish solid.

Mpf 133 ºC; [α]Dₙ = +25.1 (c 1.0, CHCl₃); Rf = 0.50 (dichloromethane–MeOH, 10:1).

¹H NMR (400 MHz, CDCl₃): δ = 52.7, 101.3, 133.5, 148.9, 160.3.

Alkynylthiazole 33

To a dry Schlenk flask Pd(PPh₃)₂Cl₂ (240 mg, 0.34 mmol), Cul (130 mg, 0.68 mmol) and freshly distilled DMF (87 mL) were added under nitrogen, then iodo-thiazole 31 (9.52 g, 34.15 mmol), 3-butyne-2-ol (32) (3.7 mL, 50.9 mmol) and Et₃N (9.7 mL, 69.4 mmol) were introduced. The mixture was heated to 50 ºC for 2 h (TLC control). During this time the solution turned dark brown. The mixture was cooled to room temperature, diluted with dichloromethane (250 mL) and filtered through Celite. The pad of Celite was washed with dichloromethane (3 × 75 mL). The combined filtrates were concentrated in vacuum and purified by column chromatography (silica gel, 500 g, light petroleum/acetone = 2:1) to give 6.35 g (30.09 mmol, 88%) of alcohol 33 as a yellowish solid.

Analytical data were consistent with the previously reported data.⁶

(R)-2-Azido-3-(tritylthio)propanoic acid (35)

Trifluoromethanesulfonic anhydride (15.1 mL, 90.7 mmol) was added dropwise to a mixture of sodium azide (11.8 g, 181.5 mmol) in dichloromethane (30 mL) and water (30 mL) at 0 ºC with stirring. The reaction mixture was stirred for 2 h at this temperature, then saturated NaHCO₃ solution (25 mL) was added dropwise (gas evolution). The layers were separated and the aqueous layer was re-extracted with dichloromethane (2 × 15 mL), and the combined organic extracts were washed with saturated NaHCO₃ solution (2 × 15 mL). This freshly prepared solution of trifluoromethanesulfonyl azide in dichloromethane was added to a suspension of trityl-cysteine (10.9 g, 30.1 mmol) in MeOH (240 mL) and water (75 mL), followed by triethylamine (16.9 mL, 120.5 mmol) and CuSO₄ × 5 H₂O (0.36 g, 1.4 mmol). The reaction mixture became homogenous and was stirred at room temperature for 12 h. The volatiles were removed behind a blast shield. The aqueous phase was acidified to pH 1 with 0.2 M HCl solution and extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 80 g, ethyl acetate/light petroleum 1:2) to dichloromethane–MeOH, 40:1) gave 10.5 g (27.0 mmol, 90%) of azide 35 as a yellow sticky oil.

IR (KBr): v = 3344 (w), 3060 (w), 2116 (s), 1730 (m), 743 (s) cm⁻¹.

- CH3), 5.14 (s, 2H, PhCH3), 5.79 (d, J = 8.1 Hz, 1H, NH), 7.36 (m, 5H, Ph).

13C NMR (100.6 MHz, CDCl3): δ = -5.6, 18.2, 25.7, 55.6, 63.3, 67.2, 128.1, 128.2, 128.5, 136.1, 156.1, 174.7.

ESI-MS: m/z [M + H]+ calcd for C17H29N2O4Si: 352.2; found: 354.0.

S)-2-(Benzylxycarbonylamino)-3-(triisopropylsilyl)propanoic acid (36b)
The same procedure as the preparation of acid 36a was used. Cbz-serine (34.17 g, 42.6 mmol), and TIPSCI (8.21 g, 42.6 mmol) was added HOSu (5.07 g, 37 mmol) in THF (40 mL) was added. The reaction mixture was stirred at 0 °C. The residue was taken up in ethyl acetate (150 mL) and cooled to 0 °C, then aqueous NaHCO3 solution (25%, 3.7 mL) was added dropwise. The reaction mixture was stirred for 1 hour (TLC control), filtered, and the filter cake was rinsed with dichloromethane (3 × 10 mL), the combined filtrates were concentrated and purified by column chromatography (silica gel, 40 g, ethyl acetate–light petroleum, 1:1). The resulting residue (14.2 g) yield 6.77 g (31 mmol, 85% over two steps) of amine 37a as a light yellow sticky oil.

IR (KBr): ν = 3317 (bs), 2929 (s), 2858 (s), 1505 (s), 1256 (s), 1099 (s), 837 (s), 780 (s) cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.00-1.04 (21H, TIPS), 3.94 (1H, t, J = 5.8, 3.5 Hz, -CH3), 4.46 (1H, d, J = 9.4 Hz, -CH2-), 5.13 (2H, s, Cbz), 5.61 (1H, d, J = 7.6 Hz, NH), 7.36 (5H, s, Ph).

13C NMR (100.6 MHz, CDCl3): δ = 11.8, 17.8, 55.5, 63.7, 67.2, 128.1, 128.2, 128.5, 136.1, 156.0, 174.5.

HRMS (ESI): m/z [M + H]+ calcd for C20H34NO5Si: 396.2201; found: 396.2193.

Step 1:
To a stirred solution of TBS-serine (37a) (12.9 g, 37 mmol) in THF (40 mL) was added HOSu (5.07 g, 44 mmol) and DCC (9.06 g, 44 mmol) at 0 °C. The reaction mixture was stirred for 16 hours, then filtered to remove the resulting colorless precipitate (N,N'-dicyclohexylurea), and concentrated. The residue was taken up in ethyl acetate (150 mL) and cooled to 0 °C, then aqueous NH4OH solution (25%, 3.7 mL) was added dropwise. The reaction mixture was stirred for 1 hour (TLC control), filtered, and the filter cake was rinsed with ethyl acetate (3 × 50 mL). The organic filtrate was washed with saturated aqueous NaHCO3 solution (2 × 100 mL), brine (100 mL), dried with Na2SO4 and concentrated. The resulting residue (11.0 g, 27.9 mmol) was used. Serine amide (37a) was used. Cbz-serine (30.9 mmol) yielded 12.2 g (30.9 mmol, 73%) of acid 36b as a colorless glass.

IR (KBr): ν = 3335 (bs), 2929 (s), 2858 (s), 1505 (s), 1256 (s), 1099 (s), 837 (s), 780 (s) cm−1.

1H NMR (400 MHz, CDCl3): δ = 0.08, 0.88 (s, 15H, TBS), 3.66 (dd, J = 9.8 Hz, 1H, -CH2-), 4.04 (dd, J = 9.5 Hz, 1H, -CH2-), 4.21 (br, 1H, CH3), 5.11 (s, 2H, PhCH3), 5.73 (d, J = 4.8 Hz, 1H, NH), 5.96 (s, 1H, CONH2), 6.51 (s, 1H, CONH2), 7.35 (s, 5H, Ph).

13C NMR (100.6 MHz, CDCl3): δ = -5.5, 18.1, 25.7, 55.6, 63.0, 67.1, 128.1, 128.2, 128.5, 136.0, 156.0, 172.7.

ESI-MS: m/z [M + H]+ calcd for C17H29N2O4Si: 352.2; found: 353.0.

Step 2:
The crude propanamide (14.2 g) was dissolved in dry methanol (200 mL) under argon and Pd/C (0.39 g, 3.7 mmol) was added. The reaction vessel was purged three times with H2 to remove argon, and the flask was connected to hydrogen balloon. The reaction mixture was stirred for 12 hours (TLC control), and then filtered through Celite. The pad was washed with dichloromethane (3 × 10 mL), the combined filtrates were concentrated and purified by column chromatography (silica gel, 40 g, ethyl acetate–light petroleum, 1:1) to yield 6.77 g (31 mmol, 85% over two steps) of amine 37a as a light yellow sticky oil.

IR (KBr): ν = 3317 (bs), 2929 (s), 2858 (s), 1627 (s), 1668 (s), 1539 (s), 1128 (s), 883 (s), 680 (s) cm−1.

1H NMR (400 MHz, CDCl3): δ = 0.061, 0.88 (s, 15H, TBS), 2.11 (br, 2H, NH2), 3.45 (d, J = 4.8 Hz, 1H, -CH2-), 4.79 (d, J = 5.4 Hz, 2H, -CH2-), 5.91 (s, 1H, CONH2), 7.20 (2H, 1H, CONH2).


(S)-2-Amino-3-((tert-butyl(dimethyl)silyloxy)-propanamide (37b)
The same procedure as the preparation of amide “Step 1” was used. Serine acid (37b) (12.2 g, 30.9 mmol) was used. Serine amide (37a) was used. Cbz-serine (30.9 mmol) yielded 9.52 g (24.2 mmol, 78%) of propanamide as a colorless glass.

IR (KBr): ν = 3437 (s), 3294 (b), 2942 (b), 2865 (s), 1695 (s), 1668 (s), 1539 (s), 1128 (s), 883 (s), 680 (s) cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.06 (21H, TIPS), 3.73 (1H, t, J = 7.8, 9.2 Hz, -CH2-), 4.14 (1H, d, J = 6.2 Hz, -CH2-), 4.24 (1H, b, -CH2-), 5.12 (2H, s, Cbz), 5.74 (1H, s, NH), 5.91 (1H, s, NH), 6.58 (1H, s, NH), 7.30-7.35 (5H, s, Ph).

13C NMR (100.6 MHz, CDCl3): δ = 11.7, 17.8, 55.5, 63.4, 67.0, 128.1, 128.2, 128.5, 136.1, 156.0, 172.6.


The same procedure as the preparation of amide 37a (Step 2) was used. Serine amide (11.0 g, 27.9 mmol) yielded 7.25 g (27.9 mmol, 99%) of amide 37b as colorless sticky oil.
[α]D20 = −7.3 (c 1.1, CHCl3). Rf = 0.09 (CH2Cl2–MeOH, 10:1).

IR (KBr): ν = 3388 (s), 3183 (b), 2943 (b), 2866 (s), 1681 (s), 1591 (s), 1463(s), 1112 (s), 882 (s), 680 (s) cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 1.02 (21H, TIPS), 3.44 (1H, t, J = 5.7 Hz, -CH2-), 3.84 (2H, dd, J = 2.5, 3.5 Hz, -CH2-), 6.34 (1H, s, NH), 7.19 (1H, s, NH)

13C NMR (100.6 MHz, CDCl3): δ = 11.8, 17.8, 56.6, 65.5, 176.2.


Azido dipeptide 38a

N-Methyl morpholine (7.9 mL, 71.9 mmol) was added to azido-cysteine 35 (14 g, 36.0 mmol) in THF (300 mL) at -20 °C, then isobutyl chloroformate (300 mL) at -20 °C, then isobutyl chloroformate (7.9 g, 36.2 mmol) was added, stirred at this temperature for another 2 hours, then slowly warm to room temperature, the resulting reaction mixture was stirred for 5 minutes (TLC control). The reaction mixture was diluted with phosphate buffer (pH 2, 0.5 M, 20 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were dried with Na2SO4 and concentrated. Purification by column chromatography (silica gel, ethyl acetate–light petroleum, 1:1) yielded 0.195 g (17.8 mmol, 49%) of the dipeptide 38a as a colorless foam.

[α]D20 = +50.2 (c 0.4, CDCl3); Rf = 0.37 (ethyl acetate–light petroleum, 1:1).

IR (KBr): ν = 3400 (bw), 3060 (m), 2929 (s), 1733 (s), 1673 (s), 1506 (s), 882 (s) cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.04-1.07 (21H, TIPS), 2.71 (1H, dd, J = 7.2 Hz, -CH2-), 2.81 (1H, dd, J = 5.4 Hz, -CH2-), 3.09 (1H, dd, J = 5.5 Hz, CH), 3.65 (1H, dd, J = 8.0 Hz, CH2OTIPS), 4.10 (1H, dd, J = 3.9 Hz, CH2OTIPS), 4.33-4.38 (1H, m, CHCONH2), 5.59 (1H, s, CONH2), 6.51 (1H, s, CONH2), 6.95 (1H, d, J = 6.7 Hz, NH), 7.21-7.46 (15H, m, trityl).


3-Hydroxypyridine 2-carboxylic acid 39

Step 1:

Procedure A: To a solution of triflate 5 (0.24 g, 0.331 mmol) in 1,4-dioxane (30 mL) was added 10% aqueous Bu4NOH solution (1.68 mL, 0.6 mmol) dropwise at room temperature, and the resulting reaction mixture was stirred for 5 minutes (TLC control). The reaction mixture was diluted with phosphate buffer (pH 2, 0.5 M, 20 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were dried with Na2SO4 and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate–light petroleum, 1:1) yielded 0.195 g (0.329 mmol, 99%) of the free 3-hydroxypyridine as a light yellow foam.

Procedure B: To a solution of triflate 5 (0.24 g, 0.33 mmol) in methanol (30 mL) was added NaOMe (36 mg, 0.6 mmol) at room temperature and the reaction mixture was stirred for 30 min (TLC control). The reaction mixture was diluted with phosphate buffer (pH 2, 0.5 M, 20 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were dried with Na2SO4 and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate–light petroleum, 1:1) gave 0.195 g (0.329 mmol, 99%) of the free 3-hydroxypyridine as a light yellow foam.

Rf = 0.08 (ethyl acetate–cyclohexane, 1:2).

IR (KBr): ν = 3481 (s), 3199 (b), 2977 (s), 2933 (s), 1695 (s), 1590 (s), 1357 (s), 1170 (s), 1072 (s), 773 (s) cm⁻¹.

1H NMR (400 MHz, CD2CD2): δ = 1.23 (s, 9H, t-Bu), 1.77 (s, 3H, CH3), 1.87 (s, 3H, CH3), 2.77, 2.80 (d, J = 12.1 Hz, 1H, CH2), 3.37-3.42 (dd, J = 6.0 Hz, 1H, CH2), 3.86 (s, 3H, COOCH3), 4.02 (s, 3H, COOCH3), 5.47 (br, 1H, CH), 7.69 (s, 1H, CH), 7.82 (s, 1H, CH), 8.29 (s, 1H, CH), 10.65 (s, 1H, OH).

13C NMR (100.6 MHz, CD2CD2): δ = 14.3, 23.3, 24.3, 28.4, 30.3, 32.6, 52.8, 53.9, 121.1, 128.0, 131.4, 134.8, 144.2, 147.6, 158.2, 162.3, 165.0, 170.2 (not all the carbon signals could be observed).
HRMS (FAB): m/z [M + H]^+ calcd for C_{23}H_{22}N_{4}O_{4}S_{3}: 593.1193; found: 593.1180.

**Step 2:**
A solution of above prepared 3-hydroxypyridine (0.16 g, 0.27 mmol) and Sc(OTf)_{3} (6.4 mg, 0.01 mmol) in 1,4-dioxane (36 mL) and water (12 mL) was titrated to pH 8.5 with saturated NaHCO_{3} aqueous solution (approximately 1 mL), and then heated to 60 °C for 8.5 hours (HPLC control). The reaction mixture was diluted by phosphate buffer (pH 2, 0.5 M, 30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried with Na_{2}SO_{4} and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane–MeOH, 15:1) yielded 0.14 g (0.24 mmol, 90%) of hydroxypyridine acid 39 as a light yellow solid.

Mp 239 °C (foaming); [α]_{D}^{20} = +125.8 (c 0.67, CHCl_{3}); R_{f} = 0.43 (dichloromethane–MeOH, 10:1).

IR (KBr): ν = 3445 (w), 3111 (b), 2978 (s), 1842 (s), 1769 (s),1660 (s), 1651 (s), 1347 (s), 1240 (s), 1168 (s), 798 (s), cm⁻¹.

1H NMR (400 MHz, CD_{3}OD): δ = 1.11 (s, 9H,t-Bu), 1.66 (s, 3H, CH_{3}), 1.80 (s, 3H, CH_{3}), 3.10 (d, J = 11.9 Hz, 1H, -CH_{2}-), 3.63 (d, J = 9.1 Hz, 1H, -CH_{2}-), 3.98 (s, 3H, COOCH_{3}), 5.94 (d, J = 5.5 Hz, 1H, -CH), 6.74 (s, 1H, CH), 7.61 (s, 1H, CH), 8.71 (s, 1H, CH).

HSRM (ESI): m/z [M + H]^+ calcd for C_{23}H_{22}N_{4}O_{4}S_{3}: 579.1036; found: 579.1033.

**Tris-thiazolyl pyridine 42**
Phosgene (240 μL, 20% in toluene) was added dropwise to a mixture of hydroxypyridine acid 39 (0.23 g, 0.40 mmol) and triethylamine (127 μL, 0.91 mmol) in THF (40 mL) under argon at -40 °C. The reaction mixture was stirred for 2 hours at -40 °C and filtered under argon. The resulting solution was cooled to -40 °C, and the excess of phosgene was removed under vacuum (20 mbar), to give a solution of a mixed-anhydride.

Trifluoroacetic acid (0.2 mL) and triethylsilane (0.1 mL) were added dropwise to a stirred solution of dipeptide 32a (0.36 g, 0.61 mmol) in dichloromethane (4 mL) at room temperature under argon, the reaction mixture was stirred for 30 minutes (TLC control). Toluene (4 mL) was added to the reaction mixture, and solvents and volatiles were removed under high vacuum. The resulting residue containing free thiol 6a was directly used in the next transformation.

The free thiol 6a in THF (4 mL) was added dropwise to the solution of mixed-anhydride at -40 °C, DMAP (4.9 mg, 0.04 mmol) was added to the reaction mixture. The reaction mixture was slowly warmed to room temperature and stirred for 48 hours, diluted with phosphate buffer (pH 2.5, 60 mL) and extracted with dichloromethane (3 × 30 mL). The combined extracts were dried with sodium sulfate and concentrated. The thioester 41 obtained was found to be unstable to silica gel, therefore, it was used directly in the next step.

The crude thioester 41 was dissolved in THF (30 mL) and cooled to -20 °C. PPh_{3} (162 mg, 0.62 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 hour at this temperature, slowly warmed to room temperature in 1 hour and to 40 °C for 20 hours (TLC control). The reaction mixture was concentrated and purified by column chromatography (silica gel, 10 g, dichloromethane–EtOH, 1:0 → 20:1) to give the crude thiazoline (containing still some PPh_{3}=O).

The crude thiazoline was dissolved in dichloromethane (30 mL) and cooled to -20 °C. BrCCl_{3} (50 μL, 0.5 mmol) and DBU (124 μL, 0.8 mmol) were added dropwise. The reaction mixture was stirred for 1 hour at -20 °C and then slowly warm to room temperature in 1 hour, diluted with phosphate buffer (pH 2.5, 40 mL) and extracted with dichloromethane (3 × 30 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane–ethanol, 30:1) gave 250 mg (0.29 mmol, 74% over 4 steps) of tristhiazolylpyridine 42 as a yellow foam.

R_{f} = 0.44 (dichloromethane–methanol, 10:1).

1H NMR (400 MHz, CD_{3}CN): δ = 0.09 (s, 6H, TBS), 0.90 (s, 9H,t-Bu), 1.66 (s, 3H, CH_{3}), 1.88 (s, 3H, CH_{3}), 2.79 (d, J = 12.2 Hz, 1H, CH_{2}), 3.40 (dd, J = 6.2 Hz, 1H, CH_{2}), 3.87 (s, 3H, COOCH_{3}), 3.97 (dd, J = 5.5 Hz, 1H, CH_{2}), 4.07 (dd, J = 4.5 Hz, 1H, CH_{2}), 4.55 (dd, J = 7.3, 5.1 Hz, 1H, CH), 5.47 (br, 1H, CH), 6.06 (br, 1H, NH_{2}), 6.66 (br, 1H, NH_{2}), 7.79 (s, 1H, CH), 7.81 (s, 1H, CH), 7.84 (d, J = 7.6 Hz, 1H, NH), 8.26 (s, 1H, CH), 8.28 (s, 1H, CH), 10.80 (s, 1H, OH).

1C NMR (100.6 MHz, CDCl_{3}): δ = -5.6, -5.5, 4.2, 6.6, 13.5, 18.2, 23.9, 25.8, 28.3, 52.5, 54.1, 58.7, 62.5, 120.1, 126.0, 127.4, 129.4, 131.0, 134.6, 143.4, 146.7, 149.5, 151.4, 152.0, 160.1, 161.8, 165.2, 170.0, 172.1.

HRMS (FAB): m/z [M + H]^+ calcd for C_{36}H_{48}N_{7}O_{8}S_{4}Si: 862.2216; found: 862.2198.

**3-Toslyoxypyridine 43**
Tosyl chloride (53 mg, 0.28 mmol) was added to the mixture of hydroxypyridine 42 (200 mg, 0.23 mmol) and triethylamine (39 μL, 0.28 mmol) in dichloromethane (40 mL) at 0 °C, and DMAP (3 mg, 0.02 mmol) was added after 5 min. The reaction mixture was stirred for 90 min at 0 °C (TLC control), diluted with phosphate buffer (pH 2.5, 50 mL) and extracted with dichloromethane (3 × 40 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane–MeOH, 50:1) gave 172 mg (0.17 mmol, 73%) of pyridine tosylate 43 as a colorless resin.
HRMS (ESI): \[ m/z \] [M + Na]^+ caled for C_{13}H_{23}N_{2}NaO_{10}S_{2}Si: 1038.2119; found: 1038.2119.

Carboxylic acid 44

Trimethyltin hydroxide (174 mg, 0.96 mmol) was added to a mixture of pyridine tosylate 43 (117 mg, 0.11 mmol) in 1,2-dichloroethane (10 mL). The reaction mixture was heated to 80 °C for 4 hours (TLC control), cooled down to room temperature, diluted with phosphate buffer (pH 7.0, 20 mL) and extracted with ethyl acetate (3 × 40 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by C18 cartridge (CH3CN as eluent) gave 117 mg (0.11 mmol, quant.) of acid 44 as a yellow foam.

HRMS (ESI): \[ m/z \] [M + H]^+ caled for C_{14}H_{16}N_{2}O_{10}S_{2}Si: 1741.4673; found: 1741.4684.

MS data for the side product 46:

HRMS (ESI): \[ m/z \] [M + H]^+ caled for C_{8}H_{10}N_{2}O_{20}S_{2}Si-P: 1878.4996; found: 1878.4986.

3-Tosyloxypyridine 47

The free amine 26a (9 mg, 11 μmol) was added to a stirred solution of free acid 44 (13.3 mg, 13.3 μmol), DEPBPT (15 mg, 0.05 mmol) and NaHCO₃ (10 mg, 0.12 mmol) in anhydrous THF (0.3 mL). The reaction mixture was stirred for 16 h at room temperature (TLC control), then diluted with phosphate buffer (pH 7.0, 20 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane–MeOH, 40:1) gave 17.2 mg (10 μmol, 87%) of the coupling product 47 as a colorless glass.

R_{f} = 0.46 (dichloromethane–MeOH, 10:1).

HRMS (ESI): \[ m/z \] [M + H]^+ caled for C_{8}H_{10}N_{2}O_{20}S_{2}Si-P: 1878.4996, found: 1878.4986.

1H NMR (400 MHz, CD_2OD): \[ \delta = 0.03 \] (s, 3H, TBS), 0.01 (s, 3H, TBS), 0.14 (s, 3H, TBS), 0.15 (s, 3H, TBS), 0.87 (s, 9H, TBS), 0.93 (s, 9H, TBS), 1.25 (d, J = 3.3 Hz, 3H, CH₃), 1.32 (s, 9H, t-Bu), 1.76 (s, 3H, CH₃), 1.90 (s, 3H, CH₃), 1.91 (d, J = 7.0 Hz, 3H, CH₂), 2.15 (d, J = 7.4 Hz, 1H, CH₂), 2.32 (s, 3H, CH₃), 2.59-2.70 (m, 1H, CH₂), 2.79 (d, J = 12.3 Hz, 1H, CH), 3.38 (dd, J = 6.0 Hz, 1H, CH), 4.08 (dd, J = 5.5, 4.9 Hz, 1H, CH₂), 4.17 (dd, J = 4.7 Hz, 1H, CH₂), 4.30 (dd, J = 6.8, 2.9 Hz, 1H, CH), 4.39 (dd,
$J = 3.9$ Hz, 1H, CH), 4.53 (t, $J = 4.3$ Hz, 1H, CH), 4.69 (dt, $J = 4.7$, 3.9 Hz, 2H, CH$_2$CH=CH$_2$), 5.12 (s, 2H, CH$_3$Ph), 5.28 (d, $J = 10.6$ Hz, 1H, CH$_2$CH=CH$_2$), 5.41 (dd, $J = 17.2$, 1.4 Hz, 1H, CH$_2$CH=CH$_2$), 5.48 (b, 1H, CH), 5.70 (dd, $J = 4.7$ Hz, 1H, CH), 5.99-6.09 (m, 1H, CH$_2$CH=CH$_2$), 6.77 (dd, $J = 7.0$ Hz, 1H, CHCH$_3$), 7.26-7.37 (m, 7H, Ph, tosyl), 7.50 (s, 1H, CH), 8.09 (s, 1H, CH), 8.14 (s, 1H, CH), 8.36 (s, 1H, CH), 8.46 (s, 1H, CH).

ESI-MS: $m/z$ [M + H]$^+$ calcd for C$_{68}$H$_{105}$N$_{12}$O$_{17}$S$_7$Si$_2$: 1797.5; found: 1798.8.

**Carboxylic acid 48**

Allylester 47 (9.0 mg, 5.0 μmol) was dissolved in degassed CH$_2$Cl$_2$ (1 mL), Pd(PPh$_3$)$_4$ (50 μL, 0.01 M in CH$_2$Cl$_2$), and PhSiH$_3$ (100 μL, 0.1 M in CH$_2$Cl$_2$, 10 μmol) and the mixture was stirred for 15 min. The reaction mixture was quenched by addition of 5% citric acid (5 mL), and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated. Purification by column chromatography (silica gel, 1.5 g, CH$_2$Cl$_2$, 10:1) gave 4.7 mg (2.7 μmol, 54%) of the thioester 48 as a colorless resin.

$R_f = 0.09$ (dichloromethane–MeOH, 10:1).

ESI-MS: $m/z$ [M + H]$^+$ calcd for C$_{78}$H$_{100}$N$_{12}$O$_{17}$S$_7$Si$_2$: 1756.5; found: 1756.6.

**Thioester 49**

Carboxylic acid 48 (2.0 mg, 1.1 μmol) was dissolved in CH$_2$Cl$_2$ (0.6 mL), cooled to 0 °C, EDC·HCl (100 μL, 0.022M in DMF, 2.2 μmol) and DMAP (100 μL, 0.022M in DMF, 2.2 μmol) were added. After 15 min Methyl 3-mercaptopropionate (100 μL, 0.057M in CH$_2$Cl$_2$, 5.7 μmol) and PbU$_3$ (100 μL, 0.011M in CH$_2$Cl$_2$, 1.1 μmol) were added. The mixture was stirred for 13 h (0 °C–rt), quenched with 5% citric acid (5 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried with magnesium sulfate and concentrated. Purification by column chromatography (silica gel, 1.5 g, dichloromethane–MeOH, 30:1) gave 1.2 mg (0.6 μmol, 59%) of the thioester 49 as a colorless resin.

$R_f = 0.60$ (dichloromethane–MeOH, 10:1).

ESI-MS: $m/z$ [M + H]$^+$ calcd for C$_{82}$H$_{107}$N$_{12}$O$_{18}$S$_8$Si$_2$: 1859.5; found: 1859.7.

**Carboxylic acid 54**

TFA (13 mL) and triethysilane (1 mL) was added dropwise to a solution of hydroxypyridine acid 39 (480 mg, 0.8 mmol) in dichloromethane (13 mL) with stirring. The reaction mixture was stirred for 30 min (HPLC control). The solvent was removed under high vacuum and the residue was directly used in next step without purification.

The above residue was dissolved in DMF (20 mL), and triyl chloride (0.69 g, 2.5 mmol) was added. The reaction mixture was stirred for 14 hours (HPLC control). DMF was removed under reduced pressure. The residue was triturated with n-hexane (3 × 10 mL) to remove excess triyl chloride. The resulting amine was pure enough for the next step.

The amine was dissolved in THF (20 mL) and water (4 mL), the reaction mixture was cooled down to 0 °C, and NaHCO$_3$ (140 mg, 1.7 mmol) was added. Allyl chloroforomate (89 μL, 0.8 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1h. Another portion of NaHCO$_3$ (140 mg, 1.7 mmol) and allyl chloroforomate (89 μL, 0.8 mmol) was added. The reaction mixture was stirred for 1 hour (HPLC control). The reaction mixture was diluted with phosphate buffer (pH 2.5, 100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane–EtOH, 30:1) gave 634 mg (0.8 mmol, 82% over 3 steps) of hydroxypyridine acid 54 as a light yellow foam.

$[\alpha]_D^{26} = -26.3$ (c 0.08, CHCl$_3$); $R_f = 0.18$ (dichloromethane–MeOH, 10:1).

IR (KBr): $\tilde{\nu}$ = 3392 (b), 2958 (s), 2856 (s), 1729 (s), 1644 (s), 1441 (s), 1384 (s), 1245 (s), 751 (s) cm$^{-1}$.

$1^H$ NMR (400 MHz, DMSO): $\delta = 2.00$ (dd, $J = 7.9$ Hz, 1H, CH$_2$), 2.69 (t, $J = 9.5$ Hz, 1H, CH$_2$), 3.83 (s, 3H, COOCH$_3$), 4.32-4.39 (m, 1H, CH), 4.48 (d, $J = 3.8$ Hz, 2H, CH$_2$CH=CH$_2$), 5.17 (d, $J = 10.5$ Hz, 1H, CH=CH$_2$), 5.28 (d, $J = 17.4$ Hz, 1H, CH=CH$_2$), 5.85-5.95 (m, 1H, CH=CH$_2$), 7.22-7.32 (m, 15H, trityl), 7.45 (s, 1H, CH), 7.69 (s, 1H, CH), 8.03 (d, $J = 7.3$ Hz, 1H, NH), 8.22 (s, 1H, CH).


**Tris-thiazoyl 3-hydroxypyridine 55**

The same procedure as the preparation of hydroxypyridine 42 was used. Hydroxypyridine 54 (229 mg, 0.30 mmol) yielded 150 mg (0.14 mmol, 46%) of hydroxypyridine 55 as a light yellow foam.

$[\alpha]_D^{20} = +12.8$ (c 0.6, CHCl$_3$); $R_f = 0.54$ (dichloromethane–MeOH, 10:1).

IR (KBr): $\tilde{\nu}$ = 3421 (b), 3059 (w), 2927 (s), 2864 (s), 1724 (s), 1664 (s), 1492 (s), 1245 (s), 746 (s), 724 (s) cm$^{-1}$.

$1^H$ NMR (400 MHz, CDCl$_3$): $\delta = 1.09-1.26$ (21H, TIPS), 2.20 (dd, $J = 7.7$ Hz, 1H, CH$_2$), 2.61 (dd, $J = 5.7$ Hz, 1H, CH$_2$), 3.85 (t, $J = 8.2$ Hz, 1H, CH), 3.96 (s, 3H, COOCH$_3$), 4.34 (ddd, $J = 3.9$ Hz, 1H, CH), 4.53 (d, $J = 5.3$ Hz, 2H, CH$_2$OTIPS), 4.63-4.68 (m, 2H, CH$_2$CH=CH$_2$), 5.11 (dd, $J = 7.4$ Hz, 1H, CH=CH$_2$), 5.23 (d, $J = 10.4$ Hz, 1H, CH=CH$_2$), 5.56 (b, 1H, NH$_2$), 5.90 (dd, $J = 4.3$ Hz, 1H, CH=CH$_2$), 6.68 (b, 1H, NH$_2$), 7.19-7.37 (m, 15H, trityl), 7.72 (s,
The reaction mixture was stirred for 20 h at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (10 mL), then extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with sodium sulfate and concentrated. Purification by preparative HPLC gave 6 mg (2.9 mmol, 16%) of the coupling product \(57b\) as a colorless resin.

\[\alpha_{D}^{20} = -1.5 (c 0.2, \text{CHCl}_3); \quad R_{f} = 0.63 \text{ (dichloromethane–MeOH, 10:1)}.\]

IR (KBr): \(\bar{v} = 3446\) (b), 2925 (s), 2855 (s), 1716 (s), 1669 (s), 1471 (s), 1318 (s), 1250 (s), 1104 (b), 669 (s) cm\(^{-1}\).

\[^1\text{H} \text{NMR (400 MHz, CD}_2\text{CN):} \delta = 0.06 (3\text{H, s, TBS}), -0.04 (3\text{H, s, TBS}), 0.85 (9\text{H, s, TBS}), 1.09, 1.10 (21\text{H, TIPS}), 1.26 (3\text{H, d, } J = 4.5 \text{ Hz, CH}_3), 1.33 (9\text{H, s, t-Bu}), 1.90 (3\text{H, d, } J = 7.2 \text{ Hz, CH}_3), 2.14 (1\text{H, d, } J = 7.4 \text{ Hz, CH}), 2.29 (3\text{H, s, CH}_3), 2.61 (2\text{H, dd, } J = 8.0, 2.8 \text{ Hz, CH}_2), 2.72 (1\text{H, dd, } J = 6.5 \text{ Hz, CH}_5), 3.76 (3\text{H, s, OCH}_3), 4.16 (1\text{H, d, } J = 5.0 \text{ Hz, CH}_2), 4.25 (1\text{H, dd, } J = 4.6 \text{ Hz, CH}_2), 4.38 (1\text{H, dd, } J = 5.5 \text{ Hz, CH}_5), 4.50 (4\text{H, dd, } J = 5.3, 2.9 \text{ Hz, } 2 \times \text{CH}_2\text{CH=CH}_2), 4.69 (1\text{H, dd, } J = 4.6, 3.3 \text{ Hz, CH}_3), 4.75 (1\text{H, dd, } J = 3.3 \text{ Hz, CH}_5), 4.78-4.84 (2\text{H, } \text{m, CH}_2), 5.02 (2\text{H, s, CH}_2\text{Ph}), 5.18 (1\text{H, d, } J = 10.0 \text{ Hz, CH}_2\text{CH=CH}_2), 5.26 (1\text{H, d, } J = 10.3 \text{ Hz, CH}_2\text{CH=CH}_2), 5.30 (1\text{H, d, } J = 17.9 \text{ Hz, CH}_2\text{CH=CH}_2), 5.39 (1\text{H, d, } J = 17.2 \text{ Hz, CH}_2\text{CH=CH}_2), 5.68 (1\text{H, dd, } J = 9.4, 5.4 \text{ Hz, CH}_5), 5.86-5.95 (1\text{H, m, CH}_2\text{CH=CH}_2), 5.97-6.07 (1\text{H, m, } 2 \times \text{CH}_2\text{CH=CH}_2), 6.82 (1\text{H, dd, } J = 10.2, 8.6 \text{ Hz, CH}_3\text{CH}_3), 7.16-7.34 (22\text{H, m, trityl, Ph, tosyl}), 7.70 (2\text{H, d, } J = 8.0 \text{ Hz, tosyl}), 8.00 (1\text{H, s, CH}), 8.11 (1\text{H, s, CH}_5), 8.18 (1\text{H, s, CH}_5), 8.26 (1\text{H, s, CH}), 8.29 (1\text{H, s, CH}), 8.34 (1\text{H, s, CH}), 8.50 (1\text{H, d, } J = 8.2 \text{ Hz, NH}).\]

HRMS (ESI): \(m/z [\text{M} + \text{H}]^+\) celled for C\(_{160}\)H\(_{210}\)N\(_{20}\)O\(_{10}\)S\(_{10}\): 2079.3282; found: 2079.3219.

Supporting References

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