Total Synthesis of TMC-95A and B via a New Reaction Leading to Z-Enamides. Some Preliminary Findings as to SAR

Songnian Lin[†], Zhi-Qiang Yang[†], Benjamin H. B. Kwok[¶], Michael Koldobskiy[¶],

Craig M. Crews^{¶,§,||}, and Samuel J. Danishefsky^{*,†,‡}

*Contribution from Laboratory for Bioorganic Chemistry, Sloan Kettering Institute for Cancer Research,
1275 York Avenue, New York, New York 10021, Department of Chemistry, Columbia University,
Havemayer Hall, 3000 Broadway, New York, New York 10027, and Department of Molecular, Cellular and
Developmental Biology, Pharmacology, and Chemistry, Yale University, 219 Prospect Street, New Haven,
CT 06520-8103*

Supporting Information Available: Experimental procedure and/or physical data for all new compounds (PDF). This material is available free of charge via the internet at <http://pubs.acs.org>.

Supplementary Material

General Methods: Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. THF, toluene, and methylene chloride was obtained from a dry solvent system (passed through a prepacked column of alumina) and used without further drying. All air and water sensitive reactions were performed in oven or flame-dried glassware. NMR (^1H and ^{13}C) spectra were recorded on Bruker AMX-400 MHz or Bruker Advance DRX-500 MHz as noted individually, referenced to CDCl_3 (7.27 ppm for ^1H and 77.23 ppm for ^{13}C). Optical rotations were obtained on a JASCO model DIP-370 digital polarimeter. Low resolution mass spectra (ESI) were determined with a PESCiex AP 130 spectrometer. High resolution mass spectra (FAB) were determined at University of Illinois at Urbana-Champaign, Mass Spectrometry Laboratory. Flash chromatography was performed with silica gel (230-400 mesh) from EM Science as the stationary phase. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Compounds which were not UV active were visualized by dipping the plates in phosphomolybdic acid solution and heating. Preparative thin layer chromatography was performed using the indicated solvent on Whatman® (LK6F Silica gel 60 Å 250 μM or Pk6F Silica Gel 60 Å 1000 μM) TLC plate.

^1H NMR (400 MHz, CDCl_3) (a mixture of two rotamers): δ 7.57-7.48 (m, 3H), 7.01 (bs, 1H), 6.91 (dd, $J = 15.1, 7.4$ Hz, 1H), 6.24 (d, $J = 14.7$ Hz, 0.4H), 6.13 (d, $J = 14.8$ Hz,

1H), 4.59 (bs, 0.4H), 4.45 (bs, 0.6H), 4.10 (d, $J = 7.1$ Hz, 1H), 1.65-1.44 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.0, 151.9, 151.6, 144.2, 143.8, 134.6, 134.5, 132.2, 129.6, 123.8, 123.6, 94.5, 94.1, 80.7, 80.2, 67.2, 58.1, 28.3, 27.3, 26.3, 24.4, 23.6, 14.1; ESIMS m/z 524.8 ($[\text{M} + \text{Na}^+]$, $\text{C}_{19}\text{H}_{24}\text{Br}_2\text{N}_2\text{NaO}_4$ requires 525.0).

^1H NMR (400 MHz, CDCl_3) (a mixture of two rotamers): δ 7.77 (bs, 0.5H), 7.65 (bs, 0.5H), 7.41-7.32 (m, 2H), 7.04-6.93 (m, 2H), 5.27 (m, 0.4H), 5.17 (m, 0.6H), 4.31 (t, $J = 8.6$ Hz, 1H), 3.87 (dd, $J = 9.1, 3.7$ Hz, 1H), 1.58-1.46 (m, 15H); ESIMS m/z 444.9 ($[\text{M} + \text{Na}^+]$, $\text{C}_{19}\text{H}_{23}\text{BrN}_2\text{NaO}_4$ requires 445.1).

^1H NMR (400 MHz, CDCl_3): δ 9.65 (s, 1H), 5.39 (d, $J = 5.8$ Hz, 1H), 4.27-4.24 (m, 2H), 3.94 (dd, $J = 10.0, 3.9$ Hz, 1H), 1.41 (s, 9H), 1.02 (m, 21 H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.4, 155.5, 80.0, 61.9, 61.8, 28.3, 17.8, 11.7; ESIMS m/z 367.9 ($[\text{M} + \text{Na}^+]$, $\text{C}_{17}\text{H}_{35}\text{NNaO}_4\text{Si}$ requires 368.2); HRMS (ESI) m/z 346.2425 ($[\text{M} + \text{H}]^+$, $\text{C}_{17}\text{H}_{36}\text{NO}_4\text{Si}$ requires 346.2414).

^1H NMR (400 MHz, CDCl_3): δ 7.54 (d, $J = 2.1$ Hz, 1H), 7.54-7.27 (m, 5H), 7.05 (dd, $J = 8.3, 1.9$ Hz), 6.71 (d, $J = 8.4$ Hz, 1H), 5.40 (d, $J = 8.1$ Hz, 1H), 5.14-5.07 (m, 2H), 4.61 (dt, $J = 8.0, 6.0$ Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.05 (dd, $J = 14.0, 5.6$ Hz, 1H), 2.97 (dd, $J = 14.0, 6.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 163.8, 156.1, 138.0, 136.7, 133.6, 128.9, 128.5, 128.4, 127.3, 111.0, 83.9, 67.3, 56.2, 55.4, 52.6, 37.7, 25.2, 14.6; ESIMS m/z 491.9 ($[\text{M} + \text{Na}^+]$, $\text{C}_{19}\text{H}_{20}\text{INNaO}_5$ requires 492.0); HRMS (EI^+) m/z 487.0721 ($[\text{M} + \text{NH}_4]^+$, $\text{C}_{19}\text{H}_{24}\text{IN}_2\text{O}_5$ requires 487.0730).

^1H NMR (400 MHz, CDCl_3): δ 7.42 (d, $J = 2.2$ Hz, 1H), 7.37-7.27 (m, 5H), 7.13 (dd, $J = 8.4, 2.3$ Hz), 6.76 (d, $J = 8.5$ Hz, 1H), 5.24 (d, $J = 8.1$ Hz, 1H), 5.10 (s, 2H), 4.61 (dd, $J = 13.8, 6.0$ Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.06 (m, 2H), 1.34 (s, 12H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 163.8, 156.1, 138.0, 136.7, 133.6, 128.9, 128.5, 128.4, 127.3, 111.0, 83.9, 67.3, 56.2, 55.4, 52.6, 37.7, 25.2, 14.6; ESIMS m/z 491.9 ($[\text{M} + \text{Na}^+]$, $\text{C}_{25}\text{H}_{32}\text{BNNaO}_7$ requires 492.2); HRMS (EI^+) m/z 487.2595 ($[\text{M} + \text{NH}_4]^+$, $\text{C}_{31}\text{H}_{40}\text{BN}_2\text{O}_7$ requires 487.2616).

E-isomer: ^1H NMR (400 MHz, CDCl_3) δ 8.27 (bs, 1H), 7.58 (d, $J = 6.2$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 6.94 (d, $J = 8.9$ Hz, 1H), 6.77 (t, $J = 7.9$ Hz, 1H), 5.17 (bs, 1H), 5.04 (bs, 1H), 3.94 (dd, $J = 9.8, 4.4$ Hz, 1H), 3.87 (dd, $J = 9.8, 4.3$ Hz, 1H), 1.45 (s, 9H), 1.04 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 155.3, 143.9, 140.1, 137.8, 124.1, 123.9, 122.3, 79.9, 74.9, 65.0, 50.5, 28.3, 17.9, 11.8; ESIMS m/z 608.9 ($[\text{M} + \text{Na}]^+$, $\text{C}_{25}\text{H}_{39}\text{IN}_2\text{NaO}_4\text{Si}$ requires 609.2); HRMS (EI^+) m/z 609.1597 ($[\text{M} + \text{Na}]^+$, $\text{C}_{25}\text{H}_{39}\text{IN}_2\text{NaO}_4\text{Si}$ requires 609.1622). *Z*-isomer: ^1H NMR (400 MHz, CDCl_3) δ 8.23 (bs, 1H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.31 (d, $J = 7.4$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 6.77 (t, $J = 7.3$ Hz, 1H), 5.66 (bs, 1H), 5.61 (bs, 1H), 4.02 (dd, $J = 9.8, 3.9$ Hz, 1H), 3.94 (m, 1H), 1.44 (s, 9H), 1.04 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 155.5, 142.8, 137.4, 123.7, 123.6, 119.4, 65.9, 50.1, 28.3, 17.9, 11.8; ESIMS m/z 627.2 ($[\text{M} + \text{Na}]^+$, $\text{C}_{25}\text{H}_{41}\text{IN}_2\text{NaO}_5\text{Si}$ requires 627.2); HRMS (ESI) m/z 1090.5188 ($[\text{M} + \text{Na}]^+$, $\text{C}_{57}\text{H}_{77}\text{N}_5\text{NaO}_{13}\text{Si}$ requires 1090.5185).

^1H NMR (400 MHz, CDCl_3) δ 9.63 (bs, 1H), 7.59 (d, $J = 6.8$, 1H), 7.35-7.28 (m, 6H), 7.26 (s, 1H), 7.18 (d, $J = 7.6$ Hz, 1H), 7.07 (bs, 1H), 7.06 (d, $J = 7.6$ Hz, 1H), 6.90 (d, $J = 8.1$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.51 (bs, 1H), 5.96 (bd, $J = 6.3$ Hz, 1H), 5.75 (bs, 1H), 5.19 (d, $J = 7.3$ Hz, 1H), 5.10 (bs, 3H), 4.71 (m, 1H), 4.45 (m, 1H), 3.99 (dd, $J = 9.8, 4.0$ Hz, 1H), 3.90 (dd, $J = 9.8, 4.2$ Hz, 1H), 3.75 (s, 3H), 3.33 (dd, $J = 10.0, 4.5$ Hz, 1H),

2.86 (m, 2H), 2.36 (dd, $J = 16.6, 3.3$ Hz, 1H), 1.45 (s, 9H), 1.37 (s, 9H), 1.08 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 170.1, 170.0, 168.4, 155.8, 155.6, 155.3, 140.7, 137.7, 136.4, 132.5, 130.8, 129.9, 128.4, 128.3, 128.0, 127.9, 126.2, 123.3, 122.0, 121.3, 111.3, 81.9, 79.6, 77.2, 66.7, 65.1, 56.0, 55.6, 50.7, 48.5, 38.9, 36.1, 28.3, 27.7, 17.9, 11.8; ESIMS m/z 824.4 ($[\text{M} + \text{Na}]^+$, $\text{C}_{44}\text{H}_{59}\text{N}_3\text{NaO}_9\text{Si}$ requires 824.4); HRMS (ESI) m/z 824.3916 ($[\text{M} + \text{Na}]^+$, $\text{C}_{44}\text{H}_{59}\text{N}_3\text{NaO}_9\text{Si}$ requires 824.3918).

^1H NMR (400 MHz, CDCl_3) δ 9.78 (bs, 1H), 7.57 (d, $J = 6.8$ Hz, 1H), 7.37-7.29 (m, 7H), 7.22 (d, $J = 7.6$ Hz, 1H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.10 (bs, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.25 (bs, 1H), 5.97 (d, $J = 5.9$ Hz, 1H), 5.55 (bs, 1H), 5.10 (s, 3H), 4.68 (m, 1H), 4.39 (bs, 1H), 4.25 (s, 1H), 4.19 (s, 1H), 4.01 (s, 1H), 3.96 (bs, 1H), 3.87 (bs, 1H), 3.82 (bs, 1H), 3.78 (s, 3H), 3.36 (bs, 1H), 2.85-2.81 (m, 2H), 2.33 (d, $J = 15.5$ Hz, 1H), 1.43 (s, 9H), 1.36 (s, 9H), 1.05 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 171.5, 170.0, 156.8, 156.6, 156.0, 137.2, 132.0, 129.2, 128.7, 126.7, 125.0, 123.4, 122.4, 111.9, 82.8, 67.2, 56.3, 55.9, 49.4, 39.1, 36.6, 28.4, 27.9, 24.9, 18.0, 17.9, 11.8; ESIMS m/z 1014.6 ($[\text{M} + \text{Na}]^+$, $\text{C}_{51}\text{H}_{73}\text{N}_5\text{NaO}_{13}$ requires 1014.5); HRMS (EI^+) m/z 1014.4893 ($[\text{M} + \text{Na}]^+$, $\text{C}_{51}\text{H}_{73}\text{N}_5\text{NaO}_{13}$ requires 1014.4872).

^1H NMR (400 MHz, CDCl_3) δ 9.81 (bs, 1H), 7.56 (d, $J = 7.0$ Hz, 1H), 7.36-7.28 (m, 7H), 7.22 (d, $J = 7.7$ Hz, 1H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.10 (bs, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.23 (bs, 1H), 5.97 (d, $J = 6.6$ Hz, 1H), 5.52 (bs, 1H), 5.11 (bs, 3H), 4.68 (m, 1H), 4.39 (m, 1H), 4.25 (s, 1H), 4.15 (bs, 1H), 4.01 (bs, 1H), 3.96 (m, 1H), 3.88 (d, $J = 10.0$ Hz, 1H), 3.84 (d, $J = 10.0$ Hz, 1H), 3.74 (s, 3H), 3.36 (bs, 1H), 2.83 (m, 1H), 2.32 (bd, $J = 15.9$ Hz, 1H), 1.43 (s, 9H), 1.04 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 170.0, 168.2, 156.0, 155.8, 155.6, 140.1, 136.4, 133.6, 133.5, 130.7, 130.4, 128.5, 128.2, 128.1, 128.0, 126.2, 124.6, 123.1, 121.9, 111.2, 82.0, 79.5, 78.7, 77.2, 74.3, 66.8, 65.4, 60.5, 56.2, 55.4, 51.2, 48.3, 39.1, 36.1, 28.3, 27.8, 17.9, 11.7; ESIMS m/z 1014.6 ($[\text{M} + \text{Na}^+]$, $\text{C}_{51}\text{H}_{73}\text{N}_5\text{NaO}_{13}$ requires 1014.5); HRMS (EI^+) m/z 1014.4911 ($[\text{M} + \text{Na}]^+$, $\text{C}_{51}\text{H}_{73}\text{N}_5\text{NaO}_{13}$ requires 1014.4872).

^1H NMR (400 MHz, $\text{acetone-}d_6$) δ 8.30 (d, $J = 8.0$ Hz, 1H), 8.13 (s, 1H), 7.52 (s, 1H), 7.45-7.31 (m, 7H), 7.27 (d, $J = 9.7$ Hz, 1H), 7.22 (dd, $J = 7.9, 1.2$ Hz, 1H), 6.96 (bs, 1H), 6.94 (t, $J = 7.6$ Hz, 1H), 6.90 (s, 1H), 5.43 (d, $J = 7.6$ Hz, 1H), 5.17 (d, $J = 12.6$ Hz, 1H), 5.12 (s, 1H), 5.06 (d, $J = 12.6$ Hz, 1H), 4.87 (ddd, $J = 10.5, 8.4, 5.3$ Hz, 1H), 4.66 (m, 1H),

4.58 (d, $J = 3.8$ Hz, 1H), 4.17 (dd, $J = 10.4, 3.8$ Hz, 1H), 3.95 (dd, $J = 9.6, 5.5$ Hz, 1H), 3.75 (s, 3H), 3.72 (dd, $J = 9.6, 3.2$ Hz, 1H), 3.65 (tt, $J = 10.3, 4.3$ Hz, 1H), 3.15 (dd, $J = 13.7, 2.4$ Hz, 1H), 3.07 (dd, $J = 13.7, 4.7$, 1H), 2.80 (dd, $J = 16.0, 5.5$, 1H), 2.58 (dd, 16.0, 8.7, 1H), 1.05-1.10 (m, 21H); ^{13}C NMR (125Hz, acetone- d_6) δ 181.1, 178.7, 172.0, 171.9, 171.5, 156.4, 155.9, 141.8, 138.3, 134.7, 132.1, 131.4, 130.1, 129.2, 128.7, 128.2, 126.1, 125.6, 121.7, 121.6, 121.3, 111.5, 79.1, 76.6, 76.5, 66.8, 64.7, 55.7, 54.9, 51.7, 51.0, 50.9, 38.8, 38.7, 38.1, 18.5, 12.7; ESIMS m/z 840.4 ($[\text{M} + \text{Na}]^+$, $\text{C}_{42}\text{H}_{55}\text{N}_5\text{NaO}_{10}\text{Si}$ requires 840.4); HRMS (EI^+) m/z 840.3638 ($[\text{M} + \text{Na}]^+$, $\text{C}_{42}\text{H}_{55}\text{N}_5\text{NaO}_{10}\text{Si}$ requires 840.3616).

7-iodooxindole 16. 7-iodoisatin **15** (4.2 g, 13.5 mmol) was mixed with hydrazine hydrate (13.5 mL), and heated to 125 °C for 1 h. The mixture was cooled, diluted with water. The product crystallized out from the solution, and was isolated by filtration as pale yellow solid (3.0 g). The aqueous filtrate was extracted with EtOAc (1x), and the organic layer was washed with water, brine, dried (MgSO_4) and concentrated to provide additional 0.15 g of the product as a yellow solid.

The combined above solid product (3.15 g) was dissolved in 22 mL of 6 N HCl, and heated to 60 °C for 2 hrs. The mixture was cooled in an ice bath, neutralized with 44 mL of 3 N NaOH, filtered, and the solid product was collected by filtration. The aqueous filtrate was extracted with EtOAc, and the organic layer was dried (MgSO_4), and concentrated to isolate additional amount of the product. The combined product was dried under high vacuum in the presence of P_2O_5 to give 7-iodooxindole **16** as a light

pink solid (total 2.8 g, 80%). ^1H NMR (400 MHz, CDCl_3): δ 7.82 (bs, 1H), 7.53 (dd, $J = 8.0, 0.73$ Hz, 1H), 7.17 (d, $J = 7.4$ Hz, 1H), 6.80 (dd, $J = 7.8, 7.6$ Hz, 1H), 3.68 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): 175.0, 145.1, 136.4, 125.5, 124.3, 124.0, 73.9, 37.8; ESIMS m/z 282 ($[\text{M} + \text{Na}^+]$, $\text{C}_8\text{H}_6\text{INO}$ requires 282); HRMS (EI) m/z 258.9500 (M^+ , $\text{C}_8\text{H}_6\text{INO}$ requires 258.9494).

Aldol product 2c. To 30 mL of anhydrous THF a dry 250 mL round-bottom flask at -15 °C under Argon was added diisopropylamine (3.2 mL, 22.8 mmol) and a solution of *n*-butyl lithium (15.2 mL of 1.5 M solution in hexane, 22.8 mmol) sequentially. After 20 min at 15 °C, the reaction was cooled to -78 °C, and a solution of 7-iodooxindole **16** (2.95 g, 11.4 mmol) in THF (80 mL) was added dropwise. The stirring was continued for 20 min, and a solution of Garner aldehyde **26** (2.87 g, 12.5 mmol) in THF (40 mL) was added dropwise. After 2 hrs at -78 °C, the reaction was quenched by addition of 50 mL sat. aqueous NH_4Cl , followed by diluting with CH_2Cl_2 . The layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 x). The combined organic layers were dried (MgSO_4), filtered and concentrated. The brown solid isolated (6.21 g) was dissolved in CH_2Cl_2 and cooled to -70 °C. To this solution was added Et_3N (4.0 mL, 28.5 mmol) and MsCl (1.2 mL, 14.2 mmol). The resulting mixture was stirred for 80 min, during which period the temperature was controlled at -75 to -50 °C. The reaction was quenched by addition of sat. aqueous NaHCO_3 . The layers were separated, and the

aqueous layer was extracted with CH₂Cl₂ (2 x). The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (silica, 4:1 to 2:1 to 1:1 to 1:2 hexane/EtOAc) to give the aldol product **2** as two fractions: *Z*-isomer (1st fraction, 1.92 g, 36%) and *E*-isomer (2.4 g, 45%). *E*-isomer: ¹H NMR (500 MHz, CDCl₃): δ 8.10 (bs, 0.5H), 8.00 (bs, 0.5H), 7.56 (d, *J* = 7.8, 0.5H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.43-7.40 (m, 1H), 6.96-6.91 (m, 1H), 6.82-6.71 (m, 1H), 5.26 (m, 0.5H), 5.17 (m, 0.5 H), 4.30 (m, 1H), 3.87-3.85 (m, 1H), 1.69 (s, 1.5H), 1.66 (s, 1.5H), 1.61 (s, 1.5H), 1.57 (s, 1.5H), 1.48 (s, 4.5H), 1.28 (s, 4.5H); ¹³C NMR (100 MHz, CDCl₃) δ 167.7, 167.6, 152.0, 151.3, 143.9, 142.5, 137.9, 137.6, 128.8, 128.2, 123.5, 123.3, 122.1, 122.0, 94.8, 94.2, 80.8, 80.4, 75.1, 74.8, 55.5, 55.1, 28.2, 28.1, 17.1, 16.1, 14.9, 24.0; ESIMS *m/z* 493.1 ([M + Na⁺], C₁₉H₂₃IN₂NaO₄ requires 493.1); HRMS (ESI) *m/z* 493.0600 ([M+Na]⁺, C₁₉H₂₃IN₂NaO₄ requires 493.0600). *Z*-isomer: ¹H NMR (400 MHz, CDCl₃): δ 8.80 (bs, 1H), 7.50-7.26 (m, 2H), 6.82-6.61 (m, 2H), 5.84-5.75 (m, 1H), 4.37-4.28 (m, 1H), 3.83-3.80 (m, 1H), 1.68, 1.63 (2s, 3H), 1.53, 1.51 (2s, 3H), 1.47, 1.27 (2s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 167.2, 152.2, 151.2, 144.7, 143.6, 143.1, 142.9, 137.5, 137.3, 128.2, 127.7, 123.5, 123.3, 123.1, 119.6, 119.2, 94.4, 93.9, 80.5, 79.9, 74.5, 74.2, 69.0, 68.5, 55.6, 54.2, 28.3, 28.2, 28.1, 27.4, 26.5, 24.6, 23.6; ESIMS *m/z* 493 ([M + Na⁺], C₁₉H₂₃IN₂NaO₄ requires 493); HRMS (ESI) *m/z* 493.0600 ([M+Na]⁺, C₁₉H₂₃IN₂NaO₄ requires 493.0600).

Converting (*Z*)-**2c** to (*E*)-**2c**. To a solution of (*Z*)-**2c** (4.0 g, 8.5 mmol) in dry toluene (150 mL) was added a solution of I₂ (65 mg, 0.26 mmol) in toluene (5 mL). The resulting solution was heated to 120 °C for 12 hrs, and solid NaS₂O₃ (excess) was added at room temperature. The solvent was removed under reduced pressure. The residue was purified

by flash chromatography (silica, 4:1 to 3:1 to 2:1 hexane/EtOAc) to give (*E*)-**2c** (1.4 g), together with recovered *Z*-isomer (1.5 g).

N-Cbz Protected tyrosine methyl ester **27**. L-Tyrosine was first protected as its methyl ester. Thionyl chloride (4.6 mL) was added dropwise to dry methanol (65 mL) at -15 °C, following by addition of L -tyrosine (5.7 g, 31.5 mmol). The resulting mixture was warmed to room temperature for 21 hrs. The solvent was removed under reduced pressure, and the residue was further dried under high vacuum to provide the methyl ester as a white solid.

The above methyl ester and Na₂CO₃ (4.4 g, 31.5 mmol) was dissolved in 1:1 mixture 126 mL of acetone/H₂O. Benzyl chloroformate (CbzCl) (4.7 mL, 34.7 mmol) was added dropwise. After 2 hrs at room temperature, the reaction solution was diluted with EtOAc (350 mL). The layers were separated, and the organic layer was washed with H₂O (100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 3:1 to 1:1 hexane/EtOAc) to give *N*-Cbz protected tyrosine methyl ester (10.7 g, 100%). ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.27 (m, 5H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 6.13 (bs, 1H), 5.32 (d, *J* = 7.3 Hz, 1H), 5.13-5.02 (m, 2H), 4.66-4.61 (m, 1H), 3.73 (s, 3H), 3.09-2.93 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 155.8, 155.1, 136.0, 130.3, 128.5, 128.2, 128.0, 127.1, 115.5, 67.1, 54.9, 52.4, 37.4; ESIMS

Fully protected tyrosine **27**. N-Cbz protected tyrosine methyl ester (10.7 g, 32.5 mmol) and CsCO₃ (11.1 g, 34.1 mmol) were suspended in acetone, followed by addition of benzyl bromide (4.3 mL, 35.8 mmol). The resulted mixture was heated to 80 °C for 4 hrs, cooled to room temperature, filtered through celite, and washed with EtOAc. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica, 3:1 to 2:1 hexane/EtOAc) gave the product as a white solid (13.3 g, 100%). ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.31 (m, 10H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.24 (d, *J* = 8.1 Hz, 1H), 5.12-5.08 (m, 2H), 5.04 (s, 2H), 4.67-4.62 (m, 1H), 3.73 (s, 3H), 3.12-3.02 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 157.9, 155.6, 136.9, 136.2, 130.3, 128.6, 128.5, 128.1, 127.9, 127.8, 127.5, 114.9, 69.9, 66.9, 54.8, 52.3, 37.3; ESIMS *m/z* 442 ([M + Na]⁺, C₂₅H₂₅NNaO₅ requires 442); HRMS (ESI) *m/z* 442.1629 ([M+Na]⁺, C₂₅H₂₄INNaO₅ requires 442.1630).

Tyrosine iodide **28**. Protected tyrosine **27** (13.3 g, 31.7 mmol), I₂ (8.9 g, 34.9 mmol) and AgSO₄ (10.9 g, 34.9 mmol) were suspended in MeOH. The resulted mixture was stirred at room temperature for 2 hrs, and Na₂S₂SO₃ (excess) was added to quench the reaction, followed by filtration and elution with EtOAc. The filtrate was concentrated under reduced pressure. Purification of the residue gave iodide **28** (17.3 mmol, 100%). ¹H NMR (500 MHz, CDCl₃): δ 7.58 (d, *J* = 1.7 Hz, 1H), 7.51-7.49 (m, 2H), 7.45-7.33 (m,

8H), 7.03 (dd, $J = 1.4, 8.3$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 2H), 5.31 (d, $J = 8.0$ Hz, 1H), 5.20-5.09 (m, 4H), 4.65-4.61 (m, 1H), 3.74 (s, 3H), 3.07 (dd, $J = 14.1, 5.6$ Hz, 1H), 2.99 (dd, $J = 14.0, 5.9$ Hz, 1H), ^{13}C NMR (125 MHz, CDCl_3): δ 171.7, 156.4, 155.5, 140.1, 136.4, 136.2, 130.2, 130.1, 128.5, 128.1, 128.0, 127.8, 126.9, 112.5, 86.8, 70.8, 67.0, 54.8, 52.3, 36.8; ESIMS m/z 568 ($[\text{M} + \text{Na}^+]$, $\text{C}_{25}\text{H}_{24}\text{INNaO}_5$ requires 568); HRMS (ESI) m/z 568.0595 ($[\text{M} + \text{Na}]^+$, $\text{C}_{25}\text{H}_{24}\text{INNaO}_5$ requires 568.0597).

Aryl borate **3b**. Iodide **28** (2.1 g, 3.9 mmol), bis(pinacolato)diboron (1.1 g, 4.2 mmol), KOAc (1.2 g, 12.1 mmol) and Pd catalyst (330 mg, 0.403 mmol) were suspended in dry 1,2-dimethoxyethane (24 mL, degassed by sparging with N_2), and heated to 80 °C for 12 hrs. Water and EtOAc were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (MgSO_4), filtered, and concentrated in vacuum. Purification by flash chromatography (silica, 4:1 to 2:1 hexane/EtOAc) provided borate **3b** (1.9 g, 91%). ^1H NMR (400 MHz, CDCl_3): δ 7.63 (d, $J = 7.7$ Hz, 2H), 7.49 (s, 1H), 7.41-7.28 (m, 8H), 7.16 (dd, $J = 8.3, 1.1$ Hz), 6.86 (d, $J = 8.4$ Hz, 1H), 5.30 (d, $J = 8.1$ Hz, 1H), 5.12-5.11 (m, 4H), 4.69-4.62 (m, 1H), 3.73 (s, 3H), 3.12-3.03 (m, 2H), 1.38 (s, 12H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.1, 162.4, 155.6, 137.4, 136.2, 133.1, 128.4, 128.0, 127.9, 127.4, 127.2, 126.6, 112.0, 83.4, 69.8, 66.8, 54.9, 52.1, 37.2, 24.9, 24.8; ESIMS m/z 568 ($[\text{M} + \text{Na}^+]$, $\text{C}_{31}\text{H}_{36}\text{BNNaO}_7$ requires 568); HRMS (ESI) m/z 568.2484 ($[\text{M} + \text{Na}]^+$, $\text{C}_{31}\text{H}_{36}\text{BNNaO}_7$ requires 568.2483).

Suzuki coupling product **29**. Borate **3b** (740 mg, 1.36 mmol), iodide **2c** (580 mg, 1.23 mmol), K₂CO₃ (grinded powder, 682 mg, 4.93 mmol) and Pd catalyst (196 mg, 0.240 mmol) were suspended in dry 1,2-dimethoxyethane (15 mL, degassed by sparging with N₂), and heated to 80 °C for 5 hrs. At room temperature, EtOAc and H₂O were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification of the residue (silica, 3:1 to 2:1 to 1:1 to 1:2 hexane/EtOAc) afforded coupling product **29** (612 mg, 65%). ¹H NMR (400 MHz, CDCl₃): δ 8.14 (bs, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.31-7.24 (m, 10H) 7.07-6.86 (m, 5H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.35 (m, 0.5H), 5.25 (m, 0.5H), 5.09-5.04 (m, 4H), 4.74-4.69 (m, 1H), 4.34 (dd, *J* = 8.7, 7.0 Hz, 1H), 3.92-3.89 (m, 1H), 3.73 (s, 3H), 3.17 (d, *J* = 13.4 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.7 Hz, 1H), 1.72, 1.69 (2s, 3H), 1.64, 1.60 (2s, 3H), 1.51, 1.28 (2s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 168.3, 155.6, 154.4, 152.1, 151.6, 140.8, 140.4, 139.7, 136.3, 136.0, 131.9, 131.2, 130.5, 128.7, 128.6, 128.4, 128.0, 127.8, 127.0, 126.4, 123.0, 122.9, 121.6, 120.9, 120.7, 113.5, 113.3, 94.4, 94.2, 80.7, 80.4, 77.2, 74.9, 70.6, 67.4, 66.9, 55.9, 55.4, 54.7, 52.4, 37.7, 28.3, 28.2, 27.2, 26.1, 25.0, 24.1; ESIMS *m/z* 784 ([M + Na]⁺, C₄₄H₄₇N₃NaO₉ requires 784); HRMS (ESI) *m/z* 784.3208 ([M+Na]⁺, C₄₄H₄₇N₃NaO₉ requires 784.3210).

To a solution of compound **29** (500 mg, 0.656 mmol) in THF (5.8 mL) at 0 °C was added 2.6 mL of 0.5 M LiOH (1.31 mmol). After 2.5 hrs at 0 °C, 3 mL of water was added, followed by addition of 0.01 M HCl to adjust pH as 2~3. The mixture was extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuum. The crude residue (500 mg), *O*-*t*-butyl ester of asparagines (161 mg, 0.853 mmol) and HOAt (179 mg, 1.31 mmol) were dissolved in THF (12 mL), and cooled to 0 °C. EDC was added, and the resulted mixture was stirred at room temperature for 2.5 h, followed by diluting with water, and extracting with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuum. Purification of the residue by flash chromatography (silica, 1:2 to 1:3 hexane/EtOAc) provided product **30** (510 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.13 (m, 13H), 7.04 (t, *J* = 7.1, 1H), 6.92-6.77 (m, 3H), 5.32-5.26 (m, 2H), 5.08 (s, 2H), 5.01 (s, 2H), 4.67 (m, 1H), 4.52 (m, 1H), 4.34 (bs, 1H), 3.89 (bs, 1H), 3.24 (bs, 1H), 2.92 (bs, 1H), 2.83 (d, *J* = 15.3 Hz, 1H), 2.41 (d, *J* = 15.3 Hz, 1H), 1.72, 1.68 (2s, 3H), 1.643, 1.60 (2s, 3H), 1.49, 1.32 (2s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 170.3, 170.2, 169.6, 168.4, 155.7, 154.8, 152.1, 151.5, 140.8, 140.5, 140.2, 136.8, 136.2, 130.8, 128.9, 128.3, 128.2, 127.9, 127.8, 127.5, 122.8, 122.7, 121.5, 121.1, 120.9, 113.1, 94.7, 92.2, 81.8, 80.6, 80.4, 77.2, 70.3, 67.6, 66.6, 56.1, 55.9, 55.7, 55.4, 48.6, 38.9, 38.7, 35.9, 28.3, 27.1, 26.2, 24.9, 24.0; ESIMS

m/z 940 ($[M + Na]^+$, $C_{51}H_{59}N_5NaO_{11}$ requires 940); HRMS (ESI) m/z 940.4109 ($[M+Na]^+$, $C_{51}H_{59}N_5NaO_{11}$ requires 940.4109).

Compound **30** (450 mg, 0.490 mmol), (DHQD)₂PHAL (153 mg, 0.196 mmol), and N-methyl morpholine N-oxide (69 mg, 0.588 mmol) were dissolved in 33 mL of 2:1 *t*BuOH : H₂O. A solution of OsO₄ (2.5 wt% in *t*BuOH, 0.615 mL, 0.588 mmol) was added dropwise at room temperature. After 14 hours, sat. aqueous NH₄Cl (10 mL), EtOAc (20 mL) and sat. aqueous Na₂S₂O₃ (10 mL) were added sequentially, and stirring was continued for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated. Purification of the residue by flash chromatography (silica, 25:1 to 15:1 CH₂Cl₂/MeOH) gave diol **31** (412 mg, 88%, dr = 4:1). ¹H NMR (400 MHz, CDCl₃) δ 9.23 (bs, 1H), 7.460-7.11 (m, 14H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.50-6.01 (m, 2H), 5.10-4.95 (m, 4H), 4.69-4.48 (m, 3H), 4.25-3.81 (m, 2H), 3.51-3.30 (m, 2H), 3.02 (bs, 1H), 2.75 (d, *J* = 15.0 Hz, 1H), 2.39 (d, *J* = 15.0 Hz, 1H), 1.60-1.19 (m, 15H); ¹³C NMR (100 MHz, CDCl₃) δ 179.1, 173.5, 170.9, 169.5, 156.0, 154.5, 152.3, 151.6, 139.7, 136.5, 136.2, 132.1, 131.5, 130.7, 129.2, 128.4, 128.3, 127.8, 127.7, 127.0, 126.0, 124.4, 122.3, 121.5, 112.8, 112.5, 93.2, 93.0, 82.2, 80.3, 80.0, 77.8, 77.2, 74.8, 74.0, 70.1, 66.6, 62.7, 62.3, 57.2, 56.8, 49.3, 38.5, 36.3, 28.3, 17.6, 26.1, 25.7, 24.8, 23.3;

C₅₇H₇₇N₅NaO₁₃Si requires 1090.5); HRMS (ESI) *m/z* 1090.5188 ([M+Na]⁺, C₅₇H₇₇N₅NaO₁₃Si requires 1090.5185).

Compound **33** (60 mg, 0.056 mmol) was dissolved in CH₂Cl₂ (0.5 mL), and TFA (2 mL) was added. The resulting solution was stirred at room temperature for 1 hr and 40 min. The solvents were removed under reduced pressure, and the residual TFA was removed by co-evaporation with CH₂Cl₂ (4x), followed by drying under high vacuum. The crude residue was dissolved in CH₂Cl₂ (56 mL), and DIEA (26 mL, 0.15 mmol), HOAT (13 mg, 0.095 mmol) and EDC (16 mg, 0.084 mmol) were added sequentially. The mixture was stirred at room temperature for 4 hrs, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (4:1 hexane/EtOAc, then 20:1 to 15:1 CH₂Cl₂/MeOH) and PTLC (15:1 CH₂Cl₂/MeOH) provided desired lactam **6b** (18 mg, 36%). ¹H NMR (400 MHz, acetone-*d*₆) δ 8.28 (d, *J* = 7.9 Hz, 1H), 8.19 (s, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.44-7.26 (m, 13H), 7.00-6.85 (m, 4H), 6.51 (bs, 1H), 5.44 (d, *J* = 7.7 Hz, 1H), 5.20 (s, 1H), 5.19-5.16 (m, 2H), 5.07-5.01 (m, 2H), 4.93-4.87 (m, 1H), 4.69-4.63 (m, 1H), 4.56 (d, *J* = 2.8 Hz, 1H), 4.18 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.94 (dd, *J* = 9.6, 4.7 Hz, 1H), 3.73 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.70-3.60 (m, 1H), 3.16 (d, *J* = 13.6 Hz, 1H), 3.09 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.62-2.56 (m, 1H), 2.59 (dd, *J* = 15.9, 8.9 Hz, 1H), 1.13-1.05 (m, 21H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 178.8, 172.1, 172.0, 171.6, 155.9, 155.5, 141.8, 138.5, 138.3, 134.8, 132.2, 131.5, 130.2,

129.3, 129.2, 128.8, 128.7, 128.5, 128.3, 126.5, 125.7, 121.6, 121.2, 113.1, 79.1, 76.6, 70.8, 66.8, 64.7, 54.9, 51.7, 51.0, 38.8, 38.1, 18.5, 12.7. ESIMS m/z 916.4 ($[M + Na]^+$, $C_{48}H_{59}N_5NaO_{10}Si$ requires 916.4); HRMS (ESI) m/z 916.3929 ($[M+Na]^+$, $C_{48}H_{59}N_5NaO_{10}Si$ requires 916.3929).

To a dry round-bottom flask under argon were added anhydrous THF (30 mL) and allyl alcohol **37** (0.68 mL, 10 mmol). After cooled to $-78\text{ }^{\circ}\text{C}$, *n*-BuLi (7.0 mL, 1.5 M in hexane, 10.5 mmol) was added dropwise. After 15 min, TESC1 (1.76 mL, 10.5 mmol) was added rapidly at $-78\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then stirred at room temperature another 30 min. After re-cooled to $-78\text{ }^{\circ}\text{C}$, *s*-BuLi (1.28 M in pentane, 9.38 mL, 12 mmol) was added dropwise. The resulting solution was stirred for 80 min, and MsCl (0.95 mL, 12 mmol) was then added rapidly at $-78\text{ }^{\circ}\text{C}$. The reaction solution was allowed to gradually warm to room temperature over 60 min. Water was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (silica, 8:1 to 4:1 hexanes/EtOAc) to give the product as clear oil (1.6 g, 60%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, $J = 17.2, 10.6, 7.9$ Hz, 1H), 5.25 (dt, $J = 17.2, 1.2$ Hz, 1H), 5.18 (dt, $J = 10.6, 1.1$ Hz, 1H), 5.08 (dt, $J = 7.9, 1.2$ Hz, 1H), 2.95 (s, 3H), 0.99 (t, $J = 8.0$ Hz, 9H), 0.69 (q, $J = 7.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 114.9, 78.6, 39.2, 7.0, 1.3; ESIMS m/z 273 ($[M + Na]^+$,

C₁₀H₂₂NaO₃SSi requires 273); HRMS (EI⁺) *m/z* 268.1411 (M + NH₄)⁺, C₁₀H₂₆NO₃SSi requires 268.1403).

Mesylate **38** (917 mg, 3.66 mmol) was dissolved in anhydrous methanol (18 mL) in a tube that can be sealed. At 0 °C, ammonia gas was bubbled through the solution for 1.5 hours. The reaction vessel was then sealed and heated to 40 °C and stirred for 21 hours. After cooled to 0 °C, the reaction vessel was carefully opened. The reaction solution was diluted with CH₂Cl₂ (30 mL), and a solution of NaOH (1N, 10 mL) was added. The two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (15 mL x 3). The combined organic layers were dried (MgSO₄), filtered and concentrated. After purification by flash chromatography (silica, 30:1 to 20:1 to 15:1 CH₂Cl₂/MeOH), the product **39** was obtained as a light yellow oil (169 mg, 27%). ¹H NMR (400 MHz, CDCl₃) δ 6.04 (ddd, *J* = 17.0, 10.5, 5.9 Hz, 1H), 5.02 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.95 (dt, *J* = 10.5, 1.5 Hz, 1H), 3.18 (dt, *J* = 5.9, 1.7 Hz, 1H), 1.94 (bs, 1H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 133.2, 114.5, 43.9, 7.2, 1.3.

NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 7.1 Hz, 2H), 7.53-7.43 (m, 3H), 6.15 (d, *J* = 8.8 Hz, 1H), 5.97 (ddd, *J* = 16.7, 10.7, 5.30 Hz, 1H), 5.02-4.98 (m, 2H), 4.61-4.57 (m, 1H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.68 (q, *J* = 8.0 Hz, 6H); ESIMS *m/z* 298.0 ([M + Na]⁺),

C₁₆H₂₅NNaOSi requires 298.2); HRMS (EI⁺) *m/z* 276.1775 ([M+H]⁺, C₁₆H₂₆NOSi requires 276.1784).

¹H NMR (400 MHz, CDCl₃): δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.61 (bs, 1H), 7.57-7.53 (m, 1H), 7.49-7.46 (m, 2H), 6.96 (dt, *J* = 9.0, 1.7 Hz, 1H), 4.99-4.92 (m, 1H), 1.73 (dd, *J* = 7.1, 1.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 134.0, 131.9, 128.8, 127.0, 122.2, 106.1, 11.0; ESIMS *m/z* 183.8 ([M + Na]⁺, C₁₀H₁₁NNaO requires 184.1); HRMS (EI⁺) *m/z* 162.0919 ([M+H]⁺, C₁₆H₂₆NOSi requires 162.0919).

¹H NMR (400 MHz, CDCl₃): δ 7.757.72 (m, 2H), 6.95-6.91 (m, 2H), 6.08 (d, *J* = 9.1 Hz, 1H), 5.95 (ddd, *J* = 16.9, 10.6, 5.3 Hz, 1H), 5.01-4.96 (m, 2H), 4.58-4.54 (m, 1H), 3.84 (s, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 162.0, 136.7, 128.4, 127.2, 113.7, 110.1, 55.3, 42.5, 7.4, 2.0; ESIMS *m/z* 328.1 ([M + Na]⁺, C₁₇H₂₇NNaO₂Si requires 328.2); HRMS (EI⁺) *m/z* 306.1888 ([M+H]⁺, C₁₇H₂₈NO₂Si requires 306.1889).

^1H NMR (400 MHz, CDCl_3): δ 7.79 (dd, $J = 7.0, 1.9$ Hz, 2H), 7.54 (bs, 1H), 6.96 (d, $J = 9.7$ Hz, 1H), 6.94 (t, $J = 8.9$ Hz, 1H), 4.95-4.88 (m, 1H), 3.87 (s, 3H), 1.71 (dd, $J = 7.1, 1.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 162.5, 128.9, 126.1, 122.4, 113.9, 105.4, 55.4, 10.9; ESIMS m/z 214.1 ($[\text{M} + \text{Na}^+]$, $\text{C}_{11}\text{H}_{13}\text{NNaO}_2$ requires 214.1); HRMS (EI^+) m/z 192.1027 ($[\text{M} + \text{H}]^+$, $\text{C}_{11}\text{H}_{14}\text{NO}_2$ requires 192.1025).

^1H NMR (400 MHz, CDCl_3): δ 7.45 (dd, $J = 1.7, 0.8$ Hz, 1H), 7.10 (dd, $J = 3.5, 0.8$ Hz, 1H), 6.50 (dd, $J = 3.5, 1.8$ Hz, 1H), 6.38 (d, $J = 9.3$ Hz, 1H), 5.93 (ddd, $J = 17.1, 10.6, 5.3$ Hz, 1H), 5.02-4.96 (m, 2H), 4.53-4.49 (m, 2H), 1.00 (t, $J = 8.1$ Hz, 9H), 0.65 (q, $J = 8.2$ Hz, 6H); ESIMS m/z 288.1 ($[\text{M} + \text{Na}^+]$, $\text{C}_{14}\text{H}_{23}\text{NNaO}_2\text{Si}$ requires 288.1); HRMS (EI^+) m/z 266.1576 ($[\text{M} + \text{H}]^+$, $\text{C}_{14}\text{H}_{24}\text{NO}_2\text{Si}$ requires 266.1576).

^1H NMR (400 MHz, CDCl_3): δ 7.84 (bs, 1H), 7.50 (d, $J = 0.9$ Hz, 1H), 7.21 (d, $J = 3.6$ Hz, 1H), 6.88 (dt, $J = 9.0, 1.8$ Hz, 1H), 6.55 (dd, $J = 3.5, 1.7$ Hz, 1H), 4.98-4.91 (m, 1H), 1.73 (dd, $J = 7.1, 1.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.0, 151.0, 144.2, 121.1, 115.3, 112.6, 106.3, 10.9; ESIMS m/z 174.1 ($[\text{M} + \text{Na}^+]$, $\text{C}_8\text{H}_9\text{NNaO}_2$ requires 174.1); HRMS (EI^+) m/z 152.0714 ($[\text{M} + \text{H}]^+$, $\text{C}_8\text{H}_{10}\text{NO}_2$ requires 152.0712).

^1H NMR (400 MHz, CDCl_3): δ 5.85 (ddd, $J = 17.5, 10.4, 5.4$ Hz, 1H), 5.40 (d, $J = 8.8$ Hz, 1H), 4.94-4.89 (m, 2H), 4.40-4.35 (m, 1H), 2.09 (s, 2H), 1.04 (s, 9H), 1.02 (t, $J = 8.1$ Hz, 9H), 0.60 (q, $J = 8.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 136.9, 110.0, 50.7, 41.9, 30.8, 29.8, 7.3, 1.9; ESIMS m/z 292.2 ($[\text{M} + \text{Na}^+]$, $\text{C}_{15}\text{H}_{31}\text{NNaOSi}$ requires 292.2); HRMS (EI^+) m/z 270.2256 ($[\text{M} + \text{H}]^+$, $\text{C}_{15}\text{H}_{32}\text{NOSi}$ requires 270.2253).

^1H NMR (400 MHz, CDCl_3): δ 6.76 (bs, 1H), 6.73 (t, $J = 9.1$ Hz, 1H), 4.82-4.73 (m, 1H), 2.15 (s, 2H), 1.60 (d, $J = 6.8$ Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 121.9, 104.6, 50.7, 31.0, 29.8, 10.8; ESIMS m/z 178.1 ($[\text{M} + \text{Na}^+]$, $\text{C}_9\text{H}_{17}\text{NNaO}$ requires 178.1); HRMS (ESI) m/z 178.1208 ($[\text{M} + \text{Na}]^+$, $\text{C}_9\text{H}_{17}\text{NNaO}$ requires 178.1208).

^1H NMR (400 MHz, CDCl_3): δ 6.59 (t, $J = 8.2$ Hz, 1H), 5.89-5.81 (m, 1H), 5.39 (bs, 1H), 5.02-4.90 (m, 2H), 4.38-4.35 (m, 1H), 4.22-4.12 (m, 2H), 3.84-3.77 (m, 1H), 1.45 (s, 9H), 1.03 (m, 21H), 0.96 (t, 9H), 0.63-.57 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.8, 169.6, 136.2, 110.3, 63.4, 42.1, 28.2, 17.9, 11.8, 7.3, 1.8; ESIMS m/z 537.4 ($[\text{M} + \text{Na}^+]$, $\text{C}_{26}\text{H}_{54}\text{N}_2\text{NaO}_4\text{Si}_2$ requires 537.4); HRMS (EI^+) m/z 515.3716 ($[\text{M} + \text{H}]^+$, $\text{C}_{26}\text{H}_{55}\text{N}_2\text{O}_4\text{Si}_2$ requires 515.3700).

^1H NMR (400 MHz, CDCl_3): δ 8.05 (bs, 1H), 6.71 (dt, $J = 9.3, 1.8$ Hz, 1H), 5.41 (bs, 1H), 4.89-4.84 (m, 1H), 4.21 (bs, 1H), 4.13 (dd, $J = 9.6, 4.0$ Hz, 1H), 3.78 (dd, $J = 9.6, 7.0$ Hz, 1H), 1.61 (d, $J = 7.0$ Hz, 3H), 1.47 (s, 9H), 1.07 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 121.5, 80.3, 63.5, 55.7, 28.3, 17.9, 11.8; ESIMS m/z 423.2 ($[\text{M} + \text{Na}]^+$, $\text{C}_{20}\text{H}_{40}\text{N}_2\text{NaO}_4\text{Si}$ requires 423.3); HRMS (ESI) m/z 423.2655 ($[\text{M} + \text{Na}]^+$, $\text{C}_{20}\text{H}_{40}\text{N}_2\text{NaO}_4\text{Si}$ requires 423.2655).

Pd-C (8 mg) in a flask was activated through 3 cycles of vacuum- H_2 flush. A solution of lactam **6b** (16 mg, 0.018 mmol) in EtOH (2.5 mL) was added, and the resulting suspension was stirred at room temperature under a H_2 balloon for 19 hrs. The catalyst was removed by filtration through celite. The filtrate was concentrated in vacuum. The crude residue was dissolved in 0.4 mL of 1:1 DMF/ CH_2Cl_2 . HOAT (2.9 mg, 0.021 mmol) was added, followed by addition of a solution of acid **5** (2.8 mg, 0.021 mmol) in CH_2Cl_2 (0.2 mL) and a solution of EDC (4.1 mg, 0.021 mmol) in CH_2Cl_2 (0.2 mL). The resulting mixture was stirred at room temperature for 90 min. The solvents were removed in vacuum. Purification of the residue by PTLC (15:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) gave products **40a,b**.

(11.9 mg, 85%). ^1H NMR (400 MHz, acetone- d_6) δ 8.37 (d, J = 7.8 Hz, 1H), 8.18-8.17 (m, 2H), 7.53 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 7.34-7.32 (m, 1H), 7.30 (dd, J = 7.9, 1.0 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.96 (bs, 1H), 6.85 (dd, J = 8.1, 4.9 Hz, 1H), 6.75 (ddd, J = 13.4, 8.2, 2.2 Hz, 1H), 6.55 (bs, 1H), 5.21 (d, J = 1.9 Hz, 1H), 4.98-4.90 (m, 1H), 4.86-4.84 (m, 1H), 4.59 (d, J = 3.0 Hz, 1H), 4.19 (dd, J = 10.5, 3.3 Hz, 1H), 3.94 (dd, J = 9.7, 4.8 Hz, 1H), 3.70-3.65 (m, 1H), 3.48-3.38 (m, 1H), 3.19 (dd, J = 13.8, 1.3 Hz, 1H), 3.09 (dt, J = 13.7, 4.7 Hz, 1H), 2.90-2.83 (m, 4H), 2.62 (dd, J = 14.9, 9.1 Hz, 1H), 1.79-1.65 (m, 1H), 1.49-1.30 (m, 1H), 1.11 (d, J = 7.0 Hz, 1.5H), 1.09 (d, J = 7.0 Hz, 1.5H), 1.06-1.05 (m, 21H), 0.91 (t, J = 7.5 Hz, 1.5H), 0.86 (t, J = 7.5 Hz, 1.5H); ^{13}C NMR (125Hz, acetone- d_6) δ 202.2, 178.6, 171.8, 171.4, 159.9, 154.1, 141.9, 134.7, 132.0, 131.1, 130.1, 127.0, 125.7, 124.6, 121.7, 121.4, 116.2, 79.1, 76.7, 64.7, 53.4, 51.8, 51.0, 41.3, 41.0, 38.8, 37.6, 37.5, 26.2, 25.9, 18.5, 15.5, 15.2, 12.7, 11.8, 11.7; ESIMS m/z 804.6 ($[\text{M} + \text{Na}]^+$, $\text{C}_{39}\text{H}_{55}\text{N}_5\text{NaO}_{10}\text{Si}$ requires 804.4); HRMS (ESI) m/z 804.3618 ($[\text{M} + \text{Na}]^+$, $\text{C}_{39}\text{H}_{55}\text{N}_5\text{NaO}_{10}\text{Si}$ requires 804.3616).

Compound **40a,b** (6.5 mg, 0.0083 mmol) was dissolved in THF (0.4 mL). Pyridine (0.15 mL) and HF/py (0.05 mL) was added, and the resulting mixture was stirred at room temperature for 22 hrs. TMSOMe (1 mL) was added, and stirring was continued for 30 min. The solvents were removed under reduced pressure. The residue was dissolved in

CH₂Cl₂ (0.6 mL), and 2,6-lutidine (0.074 mL, 0.62 mmol) was added. At 0 °C, TESOTf (0.048 mL, 0.21 mmol) was added, and the resulting mixture was stirred at room temperature for 24 hrs. The reaction was quenched by addition of sat. aqueous NaHCO₃ (1 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was dissolved in EtOAc (2 mL), and an aqueous solution of citric acid (0.01 M, 0.5 mL) was added. The resulting mixture was stirred at room temperature for 30 min. The layers were separated. The aqueous layer was extracted with EtOAc (2x), and the combined organic layers were washed with sat. aqueous NaHCO₃, dried (MgSO₄), filtered and concentrated. Purification of the residue by PTLC provided products **41a,b** (6.6 mg, 73%). ¹H NMR (400 MHz, acetone-*d*₆) δ 8.46 (s, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 7.60 (s, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.28 (m, 1H), 7.23 (d, *J* = 9.6 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.95 (bs, 1H), 6.87-6.79 (m, 2H), 6.40 (bs, 1H), 4.93-4.80 (m, 2H), 4.20 (d, *J* = 10.2 Hz, 1H), 3.72 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.62 (dd, *J* = 9.8, 3.1 Hz, 1H), 3.60-3.50 (m, 1H), 3.50-3.40 (m, 1H), 3.21-3.08 (m, 2H), 2.89 (dd, *J* = 15.8, 5.0 Hz, 1H), 2.60 (dd, *J* = 15.8, 9.3 Hz, 1H), 1.67-1.62 (m, 1H), 1.49-1.30 (m, 1H), 1.11-1.05 (m, 10H), 1.05-1.00 (m, 3H), 0.99-0.79 (m, 40H), 0.63-0.57 (m, 10H), 0.55-0.45 (m, 3H); ¹³C NMR (125Hz, acetone-*d*₆) δ 202.1, 178.4, 171.8, 171.7, 160.0, 152.7, 141.6, 134.6, 132.8, 131.3, 130.0, 128.9, 128.7, 126.5, 122.0, 121.3, 120.0, 90.1, 81.5, 79.3, 65.5, 64.3, 53.2, 52.5, 51.4, 44.9, 43.3, 41.3, 41.0, 38.6, 37.7, 37.5, 33.8, 32.7, 26.3, 26.0, 23.4, 15.7, 15.3, 11.8, 11.7, 7.7, 7.4, 7.3, 7.2, 7.1, 7.0, 6.7, 6.5, 6.4, 6.2, 6.1, 5.9, 5.4, 5.2, 5.0; ESIMS *m/z* 1104.6 ([M + Na⁺], C₅₄H₅₉N₅NaO₁₀Si₄ requires 1104.6);

TMC-95A and B (**1a** and **1b**). Compounds **41a,b** (30.7 mg, 0.0284 mmol) were dissolved in acetone (3.4 mL). At 0 °C, a solution of Jones reagent (2.6 M, 0.044 mL, 0.11 mmol) in acetone (1 mL) was added. After 2 hrs at 0 °C, the reaction was quenched by addition of isopropanol (0.6 mL), and stirring was continued for 5 min. The solvents were removed by a stream of N₂, followed by diluting with EtOAc (6 mL). The resulting solution was dried (MgSO₄), filtered and concentrated. The crude residue was dissolved in CH₂Cl₂ (1.7 mL) with HOAT (9.2 mg, 0.068 mmol), EDC (12.0 mg, 0.063 mmol) and DIEA (0.025 mL, 0.14 mmol). A solution of α-silyl allylamine **39** (14.5 mg, 0.085 mmol) in CH₂Cl₂ (0.8 mL) was added. After 13 hrs at room temperature, the solvent was removed under reduced pressure. The residue was purified by PTLC (15:1 CH₂Cl₂/MeOH) to provide intermediates **42** and **43** (10.2 mg).

The above intermediates were dissolved in dry *o*-xylene (1.5 mL) and heated to 140 °C for 3 days. The solvent was removed under reduced pressure. The crude residue was dissolved in THF (3.2 mL). Pyridine (1.0 mL) and HF/pyridine complex (0.4 mL) was added. The resulting mixture was stirred at room temperature for 23 hrs. TMSOMe (8 mL) was added, and stirring was continued for 50 min. The solvents were removed under reduced pressure. Purification of the residue by PTLC (8:1 CH₂Cl₂/MeOH) to provide a mixture of TMC-95A and B (**1a,b**) (3.5 mg, 18% over 4 steps). Separation by HPLC (column = YMC-pack, ODS-AM, 150 x 10 mm; eluant: 25 MeCN in water; flow rate:

2.5 mL/min; t_R (**1a**) = 39.1 min, t_R (**1b**) = 36.0 min.) provided pure TMC-95A and TMC-95B. TMC-95A (**1a**): ^1H NMR (500 MHz, acetone- d_6) δ 8.99 (d, J = 10.1 Hz, 1H), 8.53 (bs, 1H), 8.28 (s, 1H), 8.12 (s, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.34-7.31 (m, 2H), 7.14 (bs, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.1, 2.3 Hz, 1H), 6.60 (dt, J = 9.0, 1.7 Hz, 1H), 6.38 (bs, 1H), 5.32 (s, 1H), 5.26 (s, 1H), 4.95-4.84 (m, 2H), 4.77-4.70 (m, 1H), 4.39 (dd, J = 10.9, 3.8 Hz, 1H), 4.21 (t, J = 10.1 Hz, 1H), 3.48 (q, J = 6.7 Hz, 1H), 3.22 (d, J = 14.1 Hz, 1H), 3.08 (dd, J = 14.1, 4.9 Hz, 1H), 2.75 (dd, J = 15.7, 4.8 Hz, 1H), 2.51 (dd, J = 15.7, 8.4 Hz, 1H), 1.82-1.67 (m, 1H), 1.61 (dd, J = 7.1, 1.7 Hz, 3H), 1.50-1.39 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone- d_6): δ 202.3, 170.7, 170.4, 170.2, 159.0, 153.1, 133.5, 131.2, 130.2, 128.9, 128.6, 126.1, 125.4, 123.5, 122.1, 120.8, 115.3, 103.6, 79.2, 78.9, 52.5, 40.1, 37.2, 36.6, 25.3, 14.3, 10.8, 10.4; ESIMS m/z 701.3 ($[\text{M} + \text{Na}^+]$, $\text{C}_{33}\text{H}_{38}\text{N}_6\text{NaO}_{10}$ requires 701.3); $[\alpha]_D^{22} + 89$ (c 0.13, MeOH).

TMC-95B: ^1H NMR (500 MHz, acetone- d_6) δ 8.97 (d, J = 10.1 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.29 (s, 1H), 8.16 (s, 1H), 7.57 (d, J = 9.8 Hz, 1H), 7.50-7.43 (m, 2H), 7.40 (d, J = 2.3 Hz, 1H), 7.31-7.25 (m, 2H), 7.16 (bs, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 8.2, 2.2 Hz, 1H), 6.60 (dt, J = 8.9, 1.6 Hz, 1H), 6.37 (bs, 1H), 5.31 (d, J = 3.5, 1H), 5.24 (s, 1H), 4.96-4.84 (m, 2H), 4.78-4.69 (m, 1H), 4.38 (dd, J = 10.5, 3.7 Hz, 1H), 4.21 (t, J = 10.2 Hz, 1H), 3.44 (q, J = 6.8 Hz, 1H), 3.21 (d, J = 13.8 Hz, 1H), 3.08 (dd, J = 13.6, 4.9 Hz, 1H), 2.72 (dd, J = 15.7, 4.9 Hz, 1H), 2.64 (dd, J = 15.7, 8.4 Hz, 1H), 1.73-1.62 (m, 1H), 1.59 (dd, J = 7.1, 1.7 Hz, 3H), 1.41-1.30 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone- d_6): δ 202.3, 171.7, 171.5, 160.0, 154.1, 149.2, 134.5, 132.2, 132.1, 131.3, 127.1, 126.4, 125.0, 124.5,

123.7, 121.8, 116.5 79.2, 78.9, 55.5, 54.0, 53.5, 51.2, 41.3, 40.4, 38.2, 37.7, 26.0, 15.6, 11.8, 11.4 ppm; ESIMS m/z 701.3 ($[M + Na]^+$, $C_{33}H_{38}N_6NaO_{10}$ requires 701.3). $[\alpha]_D^{22} + 75$ (c 0.12, MeOH).

Compound **6b** (26 mg, 0.029 mmol) and Pd-C (14 mg) were suspended in EtOH (4.2 mL). The resulting mixture was subjected to 3-cycle of vacuum- H_2 , and was stirred at room temperature under a H_2 balloon for 17 hours. The catalyst was removed by filtration through celite, and the filtrate was concentrated in vacuum. The crude residue and HOAt (5.9 mg, 0.044 mmol) were dissolved in 0.75 mL of 2:1 CH_2Cl_2 /DMF. A solution of acid **44** (6.8 mg, 0.058 mmol) in CH_2Cl_2 (0.5 mL) was added, following by addition of EDC (8.4 mg, 0.044 mmol) and DIEA (0.015 mL, 0.087 mmol). The resulting mixture was stirred at room temperature for 2 hrs. The solvents were removed under reduced pressure. Purification of the residue by PTLC (15:1 CH_2Cl_2 /MeOH) gave product **45** (14.3 mg, 63%). ^1H NMR (500 MHz, acetone- d_6) δ 8.52 (d, $J = 7.8$ Hz, 1H), 8.19 (s, 1H), 7.53 (d, $J = 2.2$ Hz, 1H), 7.47 (dd, $J = 7.4, 0.8$ Hz, 1H), 7.34-7.30 (m, 2H), 7.11 (bs, 1H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 6.77 (dd, $J = 8.1, 2.2$ Hz, 1H), 6.56 (bs, 1H), 4.94-4.87 (m, 2H), 4.66 (bs, 1H), 4.21 (d, $J = 12.5$ Hz, 1H), 3.94 (dd, $J = 9.7, 4.9$ Hz, 1H), 3.77 (dd, $J = 9.7, 3.3$ Hz, 1H), 3.72-3.66 (m, 2H), 3.55 (m, $J = 6.9$ Hz, 1H), 3.23 (dd, $J = 13.7, 2.0$ Hz, 1H), 3.20-3.16 (m, 1H), 3.08 (dd, $J = 13.8, 4.9$ Hz, 1H), 2.86 (dd, $J =$

15.6, 4.9 Hz, 1H), 1.14 (d, $J = 6.9$ Hz, 6H), 1.09-1.04 (m, 21H); ^{13}C NMR (125 MHz, acetone- d_6) δ 202.3, 179.0, 172.3, 171.6, 159.8, 154.2, 141.9, 134.6, 131.9, 131.2, 130.3, 127.0, 125.7, 124.6, 121.9, 121.6, 116.3, 79.3, 76.7, 64.8, 53.4, 51.9, 51.3, 38.9, 37.7, 34.8, 18.5, 18.2, 17.9, 12.8; ESIMS m/z 790.3 ($[\text{M} + \text{Na}^+]$, $\text{C}_{38}\text{H}_{53}\text{N}_5\text{NaO}_{10}\text{Si}$ requires 790.4).

Compound **45** (13.6 mg, 0.0177 mmol) was dissolved in THF (0.8 mL). Pyridine (0.3 mL) and HF/pyridine complex (0.1 mL) was added. The resulting mixture was stirred at room temperature for 24 hrs. TMSOMe (2 mL) was added, and stirring was continued for 40 min. The solvents were removed under reduced pressure. The crude residue was co-evaporated from dry toluene (2 mL x 2) and dried under high vacuum for 3 hours. Dried powdered 4 Å molecular sieves (20 mg) was added. The resulting mixture was suspended in CH_2Cl_2 (1.2 mL) and stirred for 40 min. 2,6-lutidine (0.15 mL, 1.33 mmol) was added, and the reaction mixture was then cooled to 0 °C. TESOTf (0.10 mL, 0.44 mmol) was added, and stirring was continued for 24 hours at room temperature. The reaction was quenched by addition of sat. aqueous NaHCO_3 (2 mL), followed by diluting with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layers were dried (MgSO_4), filtered and concentrated. The crude residue was dissolved in EtOAc (4 mL), and 1 mL of 1 mM aqueous citric acid was added. The resulting mixture was stirred at room temperature for 30 min. The layers

were separated, and the aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with sat. aqueous NaHCO₃ (1 mL), dried (MgSO₄), filtered and concentrated. Purification by PTLC (15:1 CH₂Cl₂/MeOH) provided product **46** (9 mg, 48%). ¹H NMR (500 MHz, acetone-*d*₆) δ 8.47 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.45-7.18 (m, 4H), 7.05-6.93 (m, 2H), 6.89-6.80 (m, 2H), 6.45 (bs, 1H), 4.95-4.83 (m, 2H), 4.20 (d, *J* = 10.3 Hz, 1H), 3.72 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.62 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.60-3.50 (m, 2H), 3.24 (dd, *J* = 13.7, 2.1 Hz, 1H), 3.11 (dd, *J* = 14.2, 6.5 Hz, 1H), 2.61 (dd, *J* = 15.8, 9.5 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 6H), 1.15-1.06 (m, 10H), 1.00-0.80 (m, 40H), 0.71-0.54 (m, 10H); ¹³C NMR (125 MHz, acetone-*d*₆) δ 202.5, 178.9, 172.4, 172.3, 172.2, 12.1, 160.3, 153.1, 141.9, 135.1, 129.3, 126.4, 121.7, 120.4, 79.6, 64.7, 53.5, 52.9, 51.8, 39.0, 38.1, 35.2, 18.6, 18.3, 8.1, 7.8, 7.4, 6.5, 6.1, 5.6; ESIMS *m/z* 1090.5 ([M + Na⁺], C₅₃H₈₉N₅NaO₁₀Si₄ requires 1090.6).

Compound **46** (6.1 mg, 0.0057 mmol) was dissolved in acetone (0.5 mL). At 0 °C, a solution of Jones reagent (2.6 M, 0.0088 mL, 0.023 mmol) in acetone (0.4 mL) was added. After 1.5 hrs at 0 °C, the reaction was quenched by addition of isopropanol (0.1 mL), and stirring was continued for 5 min. The solvents were removed by a stream of N₂, followed by diluting with EtOAc (2 mL). The resulting solution was dried (MgSO₄), filtered and concentrated. The crude residue was dissolved in CH₂Cl₂ (0.5 mL) with HOAT (2.4 mg,

0.018 mmol), EDC (2.7 mg, 0.063 mmol) and DIEA (0.0079 mL, 0.046 mmol). A solution of allylamine (0.018 mL, 0.024 mmol) in CH₂Cl₂ (0.1 mL) was added. After 4 hrs at room temperature, the solvent was removed under reduced pressure. The residue was purified by PTLC (15:1 CH₂Cl₂/MeOH) to provide protected allylamide derivative (2.3 mg).

This intermediate was then dissolved in THF (0.8 mL). Pyridine (0.26 mL) and HF/pyridine complex (0.1 mL) was added. The resulting mixture was stirred at room temperature for 26 hrs. TMSOMe (2 mL) was added, and stirring was continued for 45 min. The solvents were removed under reduced pressure. Purification of the residue by PTLC (8:1 CH₂Cl₂/MeOH) gave allylamide analogue **47** (1.5 mg, 40%). ¹H NMR (400 MHz, acetone-*d*₆) δ 8.47 (d, 1H, *J* = 8.3 Hz; NH-12), 8.22 (s, 1H; OH-19), 8.18 (s, 1H; NH-22), 7.72 (bs, 1H; NH-26), 7.58 (d, 1H, *J* = 9.8 Hz; NH-9), 7.51 (d, 1H, *J* = 7.4 Hz; H-4), 7.43 (d, 1H, *J* = 2.0 Hz; H-24), 7.33 (dd, 1H, *J* = 8.9, 1.0 Hz; H-2), 7.32 (d, 1H, *J* = 6.2 Hz; NH-33), 7.15 (s, 1H; NH-32), 7.00 (dd, 1H, *J* = 7.68, 7.59 Hz; H-3), 6.87 (d, 1H, *J* = 8.2 Hz; H-18), 6.80 (dd, 1H, *J* = 8.2, 2.2 Hz; H-17), 6.46 (s, 1H; NH-32), 5.85-5.75 (m, 1H; H-28), 5.67 (s, 1H; OH-6), 5.25 (s, 1H; OH-7), 5.15 (dq, 1H, *J* = 17.2, 1.7 Hz; H-29), 4.99 (dq, 1H, *J* = 10.4, 1.6 Hz; H-29), 4.97-4.90 (m, 2H; H-14, H-11), 4.43 (dd, 1H, *J* = 10.4, 3.1 Hz; H-7), 4.09 (t, *J* = 10.1 Hz; H-8), 3.81-3.77 (m, 2H; H-27), 3.54 (m, 1H, *J* = 7.0 Hz; H-36), 3.22 (dd, 1H, *J* = 13.9, 2.4 Hz; H-15), 3.08 (dd, 1H, *J* = 13.9, 4.9 Hz; H-15), 1.14 (d, 3H, *J* = 7.0 Hz, CH₃), 1.08 (d, 3H, *J* = 7.0 Hz, CH₃) ppm; ¹³C NMR (125 MHz, acetone-*d*₆): δ 202.7, 179.0, 172.5, 172.0, 171.7, 171.5, 160.2, 154.5, 142.0, 135.9, 134.8, 132.4, 131.6, 127.4, 126.7, 124.8, 122.2, 116.8, 115.9, 79.4, 77.8, 55.3, 53.9, 53.7,

51.6, 42.5, 38.6, 38.0, 35.2, 18.4, 18.2; ESIMS m/z 687.2 ($[M + Na]^+$, $C_{32}H_{36}N_6NaO_{10}$ requires 687.3).

Compound **46** (7.7 mg, 0.0072 mmol) was dissolved in acetone (0.6 mL). At 0 °C, a solution of Jones reagent (2.6 M, 0.011 mL, 0.029 mmol) in acetone (0.5 mL) was added. After 103 min at 0 °C, the reaction was quenched by addition of isopropanol (0.1 mL), and stirring was continued for 5 min. The solvents were removed by a stream of N_2 , followed by diluting with EtOAc (5 mL). The resulting solution was dried ($MgSO_4$), filtered and concentrated. The crude residue was dissolved in CH_2Cl_2 (0.5 mL) with HOAt (2.8 mg, 0.021 mmol), EDC (3.2 mg, 0.017 mmol) and DIEA (0.0076 mL, 0.044 mmol). A solution of n-propylamine (0.0012 mL, 0.014 mmol) in CH_2Cl_2 (0.1 mL) was added. After 2 hrs at room temperature, the solvent was removed under reduced pressure. The residue was purified by PTLC (15:1 CH_2Cl_2 /MeOH) to provide propylamide derivative (2.3 mg). This intermediate (2.3 mg) was then dissolved in THF (0.4 mL), pyridine (0.13 mL) and HF/pyridine complex (0.06 mL) was added. The resulting mixture was stirred at room temperature for 13 hrs and 20 min. TMSOMe (1 mL) was added, and stirring was continued for 30 min. The solvents were removed under reduced pressure. Purification of the residue by PTLC (8:1 CH_2Cl_2 /MeOH) gave propylamide analogue **48** (1.5 mg, 32%). ^1H NMR (500 MHz, acetone- d_6) δ 8.52 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H),

8.19 (s, 1H), 7.67 (bs, 1H), 7.60 (d, $J = 10.0$ Hz, 1H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.34 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.22 (bs, 1H), 7.00 (t, $J = 7.6$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.80 (dd, $J = 8.1, 2.2$ Hz, 1H), 5.74 (bs, 1H), 5.30 (bs, 1H), 4.96-4.92 (m, 2H), 4.55 (dd, $J = 10.5, 2.8$ Hz, 1H), 4.06-4.01 (m, 1H), 3.61 (d, $J = 2.3$ Hz, 1H), 3.60-3.51 (m, 1H), 3.54 (m, $J = 7.0$ Hz, 1H), 3.23 (dd, $J = 13.7, 2.2$ Hz, 1H), 3.15-3.10 (m, 2H), 3.07 (dd, $J = 13.6, 4.9$ Hz, 1H), 2.76 (m, 1H), 1.51-1.44 (m, $J = 7.2$ Hz, 2H), 1.14 (d, $J = 7.0$ Hz, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.4, 171.9, 171.7, 171.1, 154.2, 141.8, 134.5, 132.1, 131.2, 127.1, 126.4, 124.5, 121.9, 116.5, 79.2, 77.5, 53.4, 51.3, 41.8, 38.3, 37.7, 34.9, 23.2, 18.1, 17.9, 11.7, 1.5; ESIMS m/z 689.2 ($[\text{M} + \text{Na}]^+$, $\text{C}_{32}\text{H}_{38}\text{N}_6\text{NaO}_{10}$ requires 689.3).