# Concise Synthesis of TAN1251C

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**EXPERIMENTAL**

Optical rotations were measured on a JASCO P-1030 polarimeter in 10 cm cells at 25 °C.

Nuclear magnetic resonance [$^1$H NMR (500 MHz), $^{13}$C NMR (125 MHz)] spectra were determined on JEOL ECA-500 and JEOL α-500 instrument. Chemical shifts for $^1$H NMR were reported in parts per million downfields from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for $^{13}$C NMR were reported in ppm relative to the centerline of a triplet at 77.0 ppm for deuteriochloroform.

High-resolution mass spectra (HRMS) were obtained on a BRUKER DALTONICS micrOTOF (ESI).

Infrared (IR) spectra were recorded on a SHIMADZU IRPrestige-21.

Optical rotations were measured on a JASCO P-1030 Polarimeter at rt using the sodium D line.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Preparative TLC separations were made on 7 x 20 cm plates prepared with a 0.50 mm layer of Merck silica gel 60 F254. Compounds were eluted from the adsorbent with 10% MeOH in $CHCl_3$. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical) 40–50 μm, Silica Gel 60 (spherical) 63–210 μm, Silica Gel 60 N (spherical, neutral) 63–210 μm or Silica Gel 60 (spherical, NH) 40– 50 μm. Reagents and solvents were commercial grades and were used as supplied with following exceptions: $CH_2Cl_2$, $Et_2O$, *n*-hexane, THF, toluene: dried over molecular sieves 4A: MeOH, EtOH, MeCN : dried over molecular sieves 3A. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

**Ugi Product 26d.** To a solution of amine **23** (16.8 g, 33.9 mmol, 1.01 eq.) in toluene (285 mL) were added 1,4-cyclohexanedione monoethylene ketal (**9**) (5.25 g, 33.6 mmol, 1.00 eq.) and MS 4A (16.8 g). The solution was stirred at 80 ºC for 3 h. Then the solution was cooled to room temperature and carboxylic acid **11d** (4.47 g, 33.6 mmol, 1.00 eq.) and isonitrile **21** (6.43 g, 33.6 mmol, 1.00 eq.) were added. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. Then the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1) to afford pure **26d** (28.1 g, 80%) as a white amorphous solid. $[\alpha]_D^{27}$ –2.49 (*c* 1.00, $CHCl_3$); IR (film) 3393, 2955, 1763, 1724,

1678, 1656, 1510, 1240, 1215, 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, mixture of rotamers) δ 1.03 (s, 2.5H), 1.07 (s, 6.5H),.1.50–1.62 (m, 4H), 1.89–2.11 (m, 3H), 2.25 (d, *J* = 14.7, 1H), 2.80–2.98 (m, 2H), 3.16–3.37 (m, 2H), 3.58 (s, 1H), 3.61 (s, 2H), 3.76–4.31 (m, 12H), 5.03–5.09 (m, 2H), 5.44 (s, 0.3H), 5.69 (s, 0.2H), 6.10 (s, 0.5H), 6.87–6.97 (m, 1H), 6.94 (d, *J* = 8.5, 1H), 7.06 (d, *J* = 8.5, 1H), 7.14–7.24 (m, 3H), 7.29–7.44 (m, 14H), 7.44–7.54 (d, *J* = 7.37, 0.5H), 7.60–7.63 (m, 3.5H); $^{13}C$ NMR ($CDCl_3$, mixture of rotamers) δ 14.0, 19.1, 19.2, 27.0, 27.1, 31.6, 31.8, 38.2, 38.5, 44.5, 45.0, 52.1, 52.2, 64.0, 64.1, 64.4, 64.5, 65.4 (2C), 66.6, 67.0, 67.1, 70.0, 107.5, 108.0, 115.4, 115.5, 120.9, 121.0, 126.0, 127.4, 127.9, 128.0 (2C), 128.6, 129.4 (2C),125.9, 129.6 (2C), 130.0 (2C), 130.2, 132.6, 132.9, 135.3, 135.4 (2C), 136.8, 151.1, 153.3, 157.7, 174.5; HRMS-ESI: calcd for $C_{54}H_{63}N_3O_{11}SiNa$ 980.4124 $(M+Na)^+$; found 980.4093.

**Methyl Ester 31.** To a solution of **26d** (15.0 g, 15.7 mmol, 1.00 eq.) in MeOH (104 mL) and trimethyl orthoformate (104 mL) was added CSA (10.9 g, 47.0 mmol, 3.00 eq.) at room temperature. After stirring for 13 h, the reaction mixture was added $Et_3N$ and concentrated under reduced pressure. Then the residue was diluted with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Then the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 7:3 to 3:7) to afford pure **31** (7.60 g, 60%) as a white amorphous solid. $[\alpha]_D^{22}$ –0.64 (*c* 1.00, $CHCl_3$). IR (film) 2953, 1730, 1648, 1512, 1241, 1218, 1107, 1055 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, mixture of rotamers) δ 0.99 (s, 4.5H), 1.05 (s, 4.5H), 1.17–1.23 (td, *J* = 13.8, 2.86, 0.5H), 1.62–1.80 (m, 2.5H), 1.90–2.06 (m, 3H), 2.17–2.22(m, 1H), 2.51–2.54 (m, 0.5H), 2.83 (dd, *J* =13.8, 8.59, 0.5H), 2.99–3.20 (m, 7H), 3.58–4.17 (m, 11H), 5.04 (s, 1.5H), 5.05 (s, 0.5H), 5.49 (s, 0.4H), 5.60 (s, 0.6H), 6.84–6.90 (m, 2H), 6.97–7.06 (m, 2H), 7.26–7.28 (m, 1H), 7.25–7.48 (m, 11H), 7.58–7.64 (m, 3H); $^1H$ NMR

(Pyridine-$d_5$, mixture of rotamers) δ 1.07 (s, 4H), 1.14 (s, 5H), 1.51 (td, *J* = 13.17, 4.01, 0.5H), 1.79–2.15 (m, 5H), 2.24–2.41 (m, 2.5H), 2.92–2.95 (m, 0.5H), 3.06–3.17 (m, 6H), 3.28–3.31 (m, 0.5H), 3.52–3.42 (m, 1H), 3.56–3.61 (m, 6H), 4.09–4.12 (m, 0.5H), 4.44 – 4.21 (m, 3H), 4.61 – 4.50 (m, 1.5H), 4.96 (brs, 1H), 5.10 (s, 2H), 7.04 (d, *J* = 8.59, 1H), 7.11 (d, *J* = 8.59, 1H), 7.52 – 7.26 (m, 12H), 7.71 (d, *J* = 6.87, 1H), 7.81–7.83 (m, 1H), 7.85–7.89 (m, 2H), 8.08–8.09 (m, 0.5H), 8.44 (t, *J* = 5.44, 0.5H); $^{13}$C NMR ($CDCl_3$, mixture of rotamer) δ 19.0, 19.1, 26.7, 26.8, 27.9, 28.7, 28.8, 29.2, 29.5, 37.5, 38.4, 43.8, 45.1, 47.3 (2C), 47.8, 47.9, 51.9, 52.0, 52.1, 52.2, 63.2, 65.2, 66.2, 70.0, 98.6, 98.9, 115.1, 115.3, 127.4, 127.8, 127.9, 128.6 (2C), 129.7, 129.8, 130.0, 130.9 (2C), 132.7, 135.2, 135.5 (2C), 135.6, 137.0, 156.5, 156.8, 157.6, 169.6, 173.4, 173.6; HRMS-ESI: calcd for $C_{46}H_{58}N_2O_9SiNa$ 833.3803 $(M+Na)^+$; found 833.3791.

**Spiro Lactam 32.** To a solution of **31** (6.31 g, 7.78 mmol, 1.00 eq.) in THF (77.8 mL) was added LiHMDS (1.00 M in THF) (38.9 mL, 38.9 mmol, 5.00 eq.) at -78 ºC under an argon atmosphere, and the reaction mixture was warmed up to room temperature. After stirring for 30 minutes, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ at 0 ºC, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 4:1 to 7:3) to afford pure **32** (3.39 g, 56%) as a white amorphous solid. $[\alpha]_D^{26}$ –56.6 (*c* 1.00, $CHCl_3$); IR (film) 2951, 1654, 1510, 1439, 1427, 1352, 1273, 1116, 1057 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.48 (d, *J* =13.6, 1H), 1.07 (s, 9H), 1.14 (dt, *J* = 13.6, 4.53, 1H), 1.30 (d, *J* = 13.6, 1H), 1.60 (d, *J* =12.5, 1H), 1.77–1.83 (m, 2H), 1.91 (dt, *J* = 13.6, 4.53, 1H), 1.97–2.02 (m, 1H), 3.07 (s, 3H), 3.11 (dd, *J* = 12.5, 4.0, 1H), 3.17 (s, 3H), 3.26–3.37 (m, 2H), 3.76 (s, 3H), 3.87–3.90 (m, 1H), 4.04–4.07 (m, 1H), 5.03–5.07 (m, 2H), 6.73 (br s, 1H), 6.84 (d, *J* = 8.50, 2H), 7.02 (d, *J* = 8.50, 2H), 7.30–7.43 (m, 11H), 7.63–7.64 (m, 4H), 10.5 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 19.2, 26.9, 27.7, 27.8, 27.9, 29.6, 34.2, 47.3, 47.8, 53.5, 57.6, 61.3,

64.3, 69.9, 98.7, 100.9, 114.8, 127.3, 127.7, 127.8, 128.5, 129.6, 130.5, 131.9, 133.3, 133.4, 135.5, 137.1, 156.6, 157.2, 157.4, 165.6; HRMS-ESI : calcd for $C_{45}H_{54}N_2O_7SiNa$ 801.3542 $(M+Na)^+$; found 801.3546.

**Ketone 35.** To a solution of **32** (3.25g, 4.18mmol) in MeOH (20.9 mL) was added $NaBH_4$ (474 mg, 12.6 mmol, 3.00 eq.) at 0 ºC and stirred for 1 h at the same temperature. Then the reaction mixture was quenched with saturated aqueous $NH_4Cl$ at 0 ºC and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was used in the next reaction without further purification. To the solution of crude material (4.18 mmol) in $CH_2Cl_2$ (20.9 mL) were added $Et_3N$ (1.64 mL, 11.7 mmol, 2.8 eq.) and methanesulfonyl chloride (776 μL, 10.0 mmol, 2.4 eq.) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 3.5 h. Then the reaction mixture was added DBU (3.12 mL, 20.9 mmol, 5.0 eq.). After stirring for 4.5 h, the reaction mixture was diluted with EtOAc, acidified with 1 M HCl and the aqueous layer was extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product **34**, which was used in the next reaction without further purification. The solution of crude material including **34** (4.18 mmol) was dissolved in AcOH (7.00 mL), THF (7.00 mL) and water (7.00 mL) and stirred at 50 °C for 20.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then, the resulting residue was diluted with $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (*n*-hexane : EtOAc = 4:1 to 2:1) to afford pure **35** (2.11 g, 70%, 3 steps) as a white amorphous solid. $[\alpha]_D^{27}$ –68.1 (*c* 1.00, $CHCl_3$); IR (film) 1736, 1719, 1678, 1545, 1510, 1425, 1337, 1223, 1111 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.29–0.33 (m, 1H), 1.07 (s, 9H), 1.17–1.25 (m, 2H), 1.43 (td, *J* = 13.6,

4.53, 1H), 2.06 (dt, *J* = 15.3, 2.27, 1H), 2.14 (dt, *J* = 15.3, 2.27, 1H), 2.25 (td, *J* = 14.7, 6.24, 1H), 2.34 (td, *J* = 14.7, 6.24, 1H), 3.12–3.19(m, 2H), 3.45–3.50 (dd, *J* = 14.7, 11.9, 1H), 3.74–3.76 (m, 1H), 3.78 (s, 3H), 4.19 (dd, *J* = 10.8, 8.50, 1H), 5.02 (s, 2H), 6.82 (d, *J* = 8.50, 2H), 6.98 (d, *J* = 8.50, 2H), 7.02 (br s, 1H), 7.07 (br s, 1H), 7.30–7.46 (m, 11H), 7.62–7.67 (m, 4H); $^{13}$C NMR ($CDCl_3$) δ 19.1, 26.9, 31.6, 32.9, 33.4, 38.6, 38.7, 52.7, 58.2, 63.7, 63.9, 69.9, 114.9, 118.8, 127.3, 127.8, 127.9, 128.5, 129.9, 130.1, 130.4, 130.8, 131.4, 132.8, 133.3, 135.5, 135.7, 136.9, 153.9, 157.3, 165.0, 208.3; HRMS-ESI : calcd for $C_{43}H_{48}N_2O_6SiNa$ 739.3174 $(M+Na)^+$; found 739.3176.

**Ketal 36.** To a solution of the ketone **35** (1.30 g, 1.81 mmol, 1.00 eq.) in 13.5 mL of $CH_2Cl_2$ at -78 °C was added 1,2-bis(trimethylsilyloxy)ethane (490 µL, 1.99 mmol, 1.10 eq.) followed by trimethylsilyl trifluoromethanesulfonate (64.0 µL, 0.36 mmol, 0.20 eq.). The reaction mixture was warmed up to -40 °C and stirred for 15.5 h. The mixture was quenched with a solution of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1 to EtOAc:MeOH = 10:1) to afford pure **36** (1.19 g, 86%) as a white amorphous solid. $[\alpha]_D^{26}$ –50.9 (*c* 1.00, $CHCl_3$); IR (film) 1676, 1545, 1510, 1427, 1222, 1111 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.14–0.17 (m, 1H), 1.04–1.07 (m, 1H), 1.07(s, 9H), 1.36 (td, *J* = 13.6, 3.97, 1H), 1.47 (d, *J* = 10.8, 1H), 1.54–1.67 (m, 3H), 1.83 (td, *J* = 13.0, 5.10, 1H), 3.15 (dd, *J* = 10.2, 18.1, 1H), 3.40–3.46 (m, 2H), 3.76 (s, 3H), 3.85–3.94 (m, 5H), 4.11 (dd, *J* = 10.2, 6.80, 1H), 5.01 (d, *J* = 12.5, 1H), 5.03 (d, *J* = 12.5, 1H), 6.82 (d, *J* = 8.50, 2H), 6.95 (br s, 1H), 7.02 (d, *J* = 8.50, 2H), 7.04 (br s, 1H), 7.29–7.44 (m, 11H), 7.64–7.69 (m, 4H); $^{13}$C NMR ($CDCl_3$) δ 165.2, 157.2, 153.9, 137.1, 135.6, 135.5, 133.4, 133.2, 131.6, 130.6, 129.8, 129.7, 129.6, 128.5, 127.8, 127.7 (2C), 127.4, 120.3, 114.8, 107.3, 69.9, 64.9, 64.4,

64.3, 63.8, 57.8, 52.6, 33.5, 32.6 (2C), 31.9, 29.9, 26.9, 19.2; HRMS-ESI: calcd for $C_{45}H_{52}N_2O_7SiNa$ 783.3466 $(M+Na)^+$; found 783.3457.

**Alcohol 37.** To a solution of the ketal **36** (500 mg, 0.65 mmol, 1.00 eq.) in THF (13 mL) was added TBAF (1.0 M in THF, 0.65 mL, 0.65 mmol, 1.5 eq.) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 4.0 h. Then, the reaction mixture was added TBAF (1.0 M in THF, 0.65 mL, 0.65 mmol, 1.5 eq.) at 0 °C and warmed up to room temperature and stirred for 4.0 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$. The aqueous layers was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1 to 0:1 to EtOAc:MeOH = 10:1) to afford pure **37** (333 mg, 98%) as a white amorphous solid. $[\alpha]_D^{27}$ –27.7 (*c* 1.00, $CHCl_3$); IR (film) 1740, 1665, 1545, 1510, 1439, 1221, 1109 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.81 (d, *J* = 9.64, 1H), 1.31 (dd, *J* = 12.47, 2.27, 1H), 1.67–1.80 (m, 5H), 2.05 (dd, *J* = 21.5, 9.07, 1H), 3.06 (dd, *J* = 13.6, 7.37, 1H), 3.32–3.37 (m, 1H), 3.49 (br s, 1H), 3.76–3.86 (m, 5H), 3.90–3.97 (m, 4H), 4.34 (d, *J* = 7.94, 1H), 5.04 (s, 2H), 6.89 (d, *J* = 7.94, 2H), 7.07 (br s, 1H), 7.12 (br s, 1H), 7.17 (d, *J* = 7.94, 2H), 7.30–7.42 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 30.2, 31.7, 32.6 (2C), 33.4, 52.7, 57.1, 64.3, 64.5, 64.7, 65.8, 69.9, 107.1, 114.9, 121.2, 127.4, 127.9, 128.5, 129.8, 130.5, 130.7, 137.0, 153.9, 157.5, 166.7; HRMS-ESI: calcd for $C_{29}H_{34}N_2O_7SiNa$ 545.2258 $(M+Na)^+$; found 545.2248.

**Prenyl Ether 40.** To a solution of **37** (270 mg, 0.51 mmol) in MeOH (6.80 mL) was added $PtO_2$ (270 mg, 2.4 eq.) at room temperature. The resulting mixture was stirred at room temperature for 37 h under $H_2$ atmosphere (balloon). Then the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was used in the next reaction without further purification. To the solution of crude material including **39a** (0.51 mmol) and $Cs_2CO_3$ (335 mg, 1.03

mmol, 2.0 eq.) in acetone (5.1 mL) was added 3, 3-dimethylallyl bromide (127 μL, 1.03 mmol, 2.0 eq.) at room temperature. Then the reaction mixture was warmed up to 50 ºC, and stirred for 4 h. Then the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 3:7 to 0:1) to afford the inseparable mixture (194 mg, 77% for 2 steps) **40** and its diastereomer (4:1 determined by $^1$H NMR) as a white amorphous solid. $[\alpha]_D^{26}$ –43.5 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2885, 1724, 1672, 1510, 1443, 1238, 1108 cm$^{-1}$; $^1$H NMR ($CDCl_3$, mixture of diastereomers) δ 0.84 (br s, 1H), 1.74 (s, 3H), 1.79 (s, 3H), 1.49–1.98 (m, 7H), 2.78–2.90 (m, 1H), 3.00–3.04 (m, 1H), 3.13–3.38 (m, 2H), 3.71 (s, 3H), 3.71–3.87 (m, 2H), 3.86–3.95 (m, 6H), 4.13–4.31 (m, 1H), 4.48 (d, *J* = 6.80, 2H), 5.24 (br s, 0.8H), 5.35 (br s, 0.2H), 5.48 (t, *J* = 6.80, 1H), 6.84 (d, *J* = 7.94, 2H), 7.14 (d, *J* = 7.94, 2H); $^{13}$C NMR ($CDCl_3$) δ 18.1, 25.8, 30.6, 31.1, 32.1, 33.5, 34.0, 37.0, 51.1, 52.4, 57.4, 61.9, 64.0, 64.2, 64.4, 64.7, 106.9, 114.6 (2C), 119.6, 130.3, 130.5 (2C), 138.0, 157.0, 157.5, 173.7; HRMS-ESI: calcd for $C_{27}H_{38}N_2O_7Na$ 525.2571 $(M+Na)^+$; found 525.2571.

**The Ketal of TAN1251C 42 (via hydrogenation with $PtO_2$).** To a solution of **40** (96.2 mg, 0.19 mmol) in THF (3.80 mL) was added $LiAlH_4$ (0.14mg, 3.8 mmol) at 0 °C under an argon atmosphere. After stirring 50 °C for 8 h, sufficient amount of $Et_2O$, $H_2O$ (0.14 mL), 15% aqueous NaOH (0.14 mL) and $H_2O$ (0.14 mL) was added at 0 °C successively. After stirring at room temperature for 30 min, the mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was used in the next reaction without further purification. To a stirred solution of DMSO (0.20 mL, 2.85 mmol) in $CH_2Cl_2$ (2.0 mL) at –78 ºC was added TFAA (0.17 mL, 1.23 mmol) and the resulting mixture was stirred at this temperature under an argon atmosphere for 30 min. A crude material including **41** (0.19 mmol) in $CH_2Cl_2$ (2.75 mL) was added to the mixture and stirred for 90 min. $Et_3N$ (0.32 mL,

2.28 mmol) was added and the mixture was allow to warm to 0 ºC, stirred for 1 h and was taken up in $CH_2Cl_2$, which was washed with $H_2O$ and brine and dried over anhydrous $Na_2SO_4$.The solvent was concentrated under reduced pressure to give the crude material. To the crude material (0.19 mmol) in 3:2 MeOH / $H_2O$ (12.6 mL) was added $K_2CO_3$ (210 mg, 1.52 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 4 h. The solvent was concentrated under reduced pressure and the residue was taken up in $CH_2Cl_2$, which was washed with $H_2O$ and brine and dried over anhydrous $Na_2SO_4$. The residue was concentrated under reduced pressure and purified by preparative TLC ($CH_2Cl_2$:EtOAc = 1:1) to afford pure **42** (14.3 mg, 17% for 3 steps) as yellow oil. $[\alpha]_D^{24}$ +56.5 (*c* 0.70, $CHCl_3$); IR (film) 3368, 2941, 2880, 1672, 1641, 1611, 1582, 1508, 1466, 1445, 1371, 1296, 1234, 1173, 1157, 1107, 1022 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.44–1.53 (m, 1H), 1.59–1.81 (m, 6H), 1.73 (s, 3H), 1.79 (s, 3H), 1.85–1.91 (m, 1H), 2.01–2.13 (m, 2H), 2.45 (s, 3H), 2.72 (dd, *J* = 11.5, 1.7 Hz, 1H), 3.15 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.21 (s, 2H), 3.30 (dd, *J* = 5.7, 2.3 Hz, 1H), 3.92 – 3.99 (m, 4H), 4.47 (d, *J* = 6.3 Hz, 2H), 5.09 (d, *J* = 1.2 Hz, 1H), 5.46–5.52 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) δ 18.3, 26.0, 31.8, 32.6, 33.6, 35.0, 40.6, 41.6, 42.6, 51.7, 59.2, 64.4, 64.8, 72.1, 108.6, 114.4, 120.0, 127.3, 129.3, 130.2, 132.2, 138.1, 157.2; HRMS-ESI calcd for $C_{26}H_{37}N_2O_3$ 425.2799 $(M+H)^+$, found 425.2805.

**Ugi Product 44a. 44a** (5.16 g) was prepared in 75% yield as a yellow amorphous according to the same procedure as **26d** by using carboxylic acid **11c** (1.60 g, 8.38 mmol) as the carboxylic acid and isonitrile **43** (1.24 g, 6.78 mmol) as the isonitrile. $[\alpha]_D^{31}$ –56.8 (*c* 2.27, $CHCl_3$); IR (film) 3374, 3069, 3049, 3032, 2955, 2932, 2887, 2859, 1711, 1694, 1659, 1611, 1584, 1564, 1510, 1503, 1485, 1431, 1402, 1383, 1371, 1298, 1240, 1227, 1179, 1157, 1105, 1040, 1028, 1011, 986, 972, 947, 935, 905, 824, 789, 770, 739, 702, 675, 658, 613, 584, 501; $^1H$ NMR ($CDCl_3$, mixture of rotamers) δ 1.06 (s, 9H), 1.36–1.76 (m, 3H), 1.86–

2.19 (m, 2H), 2.21–2.54 (m, 2H), 2.62–3.07 (m, 4.5H), 3.11–3.34 (m, 0.5H), 3.58–4.24(m, 8.5H), 4.27–4.47 (m, 0.5H), 4.81–5.24 (4H), 6.78–7.01 (m, 3H), 7.02–7.13 (m, 1.6H), 7.14–7.52 (m, 18H), 7.53–7.82 (m, 3.4H), 7.94–8.22 (m, 1H), 8.38–8.69 (m, 1H); $^{13}$C NMR ($CDCl_3$, mixture of rotamers) δ 19.0, 19.2, 27.0, 30.5, 30.8, 31.3, 31.5, 31.8, 35.3, 36.0, 36.4, 37.1, 38.5, 51.8, 52.2, 52.9, 53.3, 60.1, 63.3, 63.9, 64.1, 64.4, 64.5, 65.5, 65.7, 66.1, 66.2, 66.8, 66.9, 67.1, 67.2, 69.9, 70.0, 107.4, 107.6, 107.9, 108.0, 112.5, 112.6, 112.8, 115.5, 115.7 (2C), 122.7, 122.9, 123.3, 127.2, 127.5, 127.8, 128.3, 128.4, 129.8, 132.4, 132.5, 135.1, 135.6 (2C), 136.6, 138.8, 139.0, 139.1, 139.8, 140.0, 140.1, 151.3, 151.6, 151.9, 152.2, 156.1, 156.8, 157.5, 157.6, 170.6, 170.8, 171.5, 171.7, 172.1, 172.3; HRMS (ESI): calcd for $C_{57}H_{63}BrN_4O_8SiNa$ 1063.3486 $(M+Na)^+$, found 1063.3481.

**Triflate 46.** To a solution of **44a** (307 mg, 0.295 mmol) in MeOH (1.5 mL) was added NaOMe (5.0 M in MeOH, 590 μL, 2.95 mmol) at room temperature. The reaction mixture was heated at 50 ºC in a sealed tube and stirred for 2.5 h. Then the reaction mixture was quenched with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 2 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product **45**, which was used in the next reaction without further purification.

To a solution of crude material including **45** and $PhNTf_2$ (211 mg, 0.59 mmol) in THF (3.0 mL) was added dropwise KHMDS (0.5 M in toluene, 2.24 mL, 1.12 mmol) over 1 min at -78 ºC under an argon atmosphere, then the reaction mixture was warmed up to room temperature. After stirring for 4 h, the reaction mixture was quenched with saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc= 19:1 to 7:3) to afford **46** (142 mg, 48% for 2 steps) as a white amorphous

solid. $[\alpha]_D^{31}$ –31.6 (*c* 1.26, $CHCl_3$); IR (film) 2957, 2936, 2886, 2860, 1728, 1697, 1510, 1472, 1425, 1389, 1362, 1306, 1225, 1134, 1113, 1082, 1055, 1028, 910, 824, 804, 781, 745, 702, 606, 590, 505 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, mixture of rotamers) δ 0.59 (t, *J* = 14.2 Hz, 1H), 1.03 (s, 3H), 1.07 (s, 6H), 1.12–1.32 (m, 2H), 1.37–1.49 (m, 2H), 1.51–1.76 (m, 3H), 1.94–2.15 (m, 1H), 2.98–3.13 (m, 1H), 3.16–3.27 (m, 3H), 3.29–3.53 (m, 2H), 3.83–4.15 (m, 6H), 4.87–4.95 (m, 0.8H), 4.96–5.08 (m, 1.9H), 5.11–5.22 (m, 1.3H), 6.67 (d, *J* = 8.5 Hz, 0.8H), 6.82–6.88 (m, 1.2H), 6.93–7.06 (m, 2H), 7.10–7.16 (m, 1.5H), 7.22–7.46 (m, 14.5H), 7.59–7.66 (m, 4H); $^{13}C$ NMR ($CDCl_3$, mixture of rotamers) δ 19.1, 19.2, 26.6, 26.9, 28.8, 29.2, 30.4, 30.6, 30.8, 33.7, 33.9, 34.3, 34.5, 34.7, 58.6, 58.7, 61.6, 61.8, 63.9, 64.3,64.4, 68.2, 68.4, 69.9, 70.0, 106.4, 106.6, 114.7, 114.9, 116.8, 119.4, 120.7, 120.8, 127.3, 127.6, 127.7, 127.9, 128.0, 128.3, 128.5, 129.7, 129.8, 130.6, 133.1, 133.2, 135.3, 135.5, 135.7, 137.0, 153.8, 154.0, 157.1, 157.2, 157.4 (2C), 164.0; HRMS (ESI): calcd for $C_{53}H_{59}F_3N_2O_{10}Si$ 999.3528 $(M+H)^+$, found 999.3511.

**Unsaturated Lactam 47.** To a solution of **46** (5.19 g, 5.19 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (848 mg, 1.04 mmol) in DMF (26 mL) was added $Et_3SiH$ (8.30 mL, 52.9 mmol) at room temperature under an argon atmosphere, and the reaction mixture was warmed up to 60 ºC. After stirring for 7.5 h, the reaction mixture was diluted with $Et_2O$ at 0 ºC. Then the mixture was filtered through a pad of Celite® and the filtrate was basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc= 9:1 to 2:1) to afford **47** (3.74 g, 85%) as a white amorphous solid. $[\alpha]_D^{26}$ –50.8 (*c* 0.375, $CHCl_3$); IR (film) 2936, 2886, 2859, 1713, 1686, 1659, 1512, 1450, 1427, 1389, 1323, 1300, 1238, 1150, 1111, 1030, 826, 741, 702, 613, 440 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.12 (dd, *J* = 12.5, 2.3 Hz, 1H), 1.07 (s, 9H), 1.01–1.10 (m, 1H), 1.23–1.63 (m, 5H), 1.82 (ddd, *J* = 13.6, 13.6, 4.5 Hz, 1H), 3.13 (dd, *J* = 13.3,

4.5 Hz, 1H), 3.30 (s, 3H), 3.32–3.40 (m, 1H), 3.47 (dd, *J* = 13.3, 10.2 Hz, 1H), 3.83–3.90 (m, 5H), 4.17 (dd, *J* = 9.6, 7.9 Hz, 1H), 4.99 (s, 2H), 5.15 (s, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.98 (br s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.25–7.33 (m, 6H), 7.34–7.44 (m, 10H), 7.63–7.68 (m, 4H); $^{13}$C NMR ($CDCl_3$) δ 19.2, 26.9 (4C), 29.4, 31.7, 32.5 (2C), 33.4, 35.0, 57.9, 63.1, 64.0, 64.3, 64.4, 67.7, 69.9, 107.1, 114.7 (2C), 127.3 (2C), 127.7 (4C), 127.8 (2C), 128.1, 128.5 (4C), 129.6, 129.7, 130.7 (2C), 131.8, 133.3, 133.5, 135.6 (4C), 135.8 (2C), 136.1, 137.1, 155.1, 157.2, 166.1; HRMS (ESI): calcd for $C_{52}H_{58}N_2O_7SiNa$ 873.3906 $(M+Na)^+$, found 873.3906.

**Oxime 48.** To a solution of **47** (695 mg, 0.82 mmol) in MeOH (16 mL) was added Pd/C (5% wet, 348 mg) and the mixture was stirred under 1 atm of hydrogen for 24 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to afford the crude product. To a solution of crude material in MeOH (8 mL) were added hydroxylamine hydrochloride (85.2 mg, 1.23 mmol) and pyridine (112 μL, 1.39 mmol). After stirring for 10 h, the reaction mixture was diluted with EtOAc, and the mixture was washed with 1 M HCl and saturated aqueous $NaHCO_3$, then dried over anhydrous $Na_2SO_4$. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc= 4:1 to 1:4) to afford **48** (438 mg, 86% for 2 steps) as a white amorphous. $[\alpha]_D^{25}$ –74.3 (*c* 0.710, $CHCl_3$); IR (film) 3304, 3292, 2957, 2934, 1692, 1647, 1516, 1441, 1429, 1265, 1254, 1132, 1113, 826, 737, 704, 503 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.19 (d, *J* = 11.9 Hz, 1H), 1.07 (s, 9H), 1.02–1.23 (m, 2H), 1.25–1.70 (m, 4H), 1.80 (ddd, *J* = 13.3, 12.8, 4.0 Hz, 1H), 2.45 (d, *J* = 19.3 Hz, 1H), 2.66 (d, *J* = 19.3 Hz, 1H), 3.09 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.35–3.44 (m, 1H), 3.50 (dd, *J* = 12.2, 10.8 Hz, 1H), 3.86–4.08 (m, 5H), 4.17 (dd, J = 17.0, 7.4 Hz, 1H), 5.10 (br s, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.35–7.49 (m, 6H), 7.62–7.76(m, 4H), 8.56 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 19.2, 26.9, 31.4, 31.5, 31.8, 32.2, 33.3, 33.7, 59.0, 61.2, 63.9,

64.2, 64.3, 106.9, 115.4, 127.7, 129.7 (2C), 130.5, 130.8, 133.2, 133.4, 135.6, 151.4, 154.5, 164.0; HRMS (ESI): calcd for $C_{36}H_{44}N_2O_6SiNa$ 651.2861 $(M+Na)^+$; found 651.2862.

**Prenyl Ether 53.** To a solution of **48** (1.29 g) in acetic acid (21 mL) at room temperature was added activated zinc dust (5.40 g, 82.5 mmol) and $NH_4Cl$ (2.20 g, 41.3 mmol), and the reaction mixture was stirred at 50 °C for 7 h. Then the mixture was filtered over a pad of Celite® and the filtrate was concentrated under reduced pressure to afford the crude product **49** as an acetic acid salt, which was used in the next reaction without further purification. To a solution of crude material including **49** in 1:1 THF / $H_2O$ (41 mL) at 0 °C was added $NaHCO_3$ (3.5 g, 41.3 mmol) and methyl chloroformate (0.79 mL, 10.3 mmol), and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was taken up in EtOAc, which was washed with brine and dried over anhydrous $MgSO_4$. The solvent was concentrated under reduced pressure to afford the crude product. To a solution of crude material in acetone (21 mL) at room temperature was added $Cs_2CO_3$ (1.34 g, 4.12 mmol) and prenyl bromide (0.48 mL, 4.12 mmol), and the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc= 4:1 to 1:1) to afford **53** (1.43 g, 94% for 3 steps) as a white amorphous solid. $[\alpha]_D^{25}$ –40.1 (*c* 0.275, $CHCl_3$); IR (film) 3302, 3051, 2936, 2889, 1728, 1686, 1674, 1612, 1512, 1443, 1373, 1238, 1196, 1169, 1111, 1011, 941, 891, 826, 741, 706, 667, 613 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, mixture of rotamers) δ 0.11 (d, *J* = 9.1 Hz, 0.8H), 0.36 (d, *J* = 9.1 Hz, 0.2H), 1.06 (s, 7.5H), 1.08 (s, 1.5H), 1.16–1.34 (m, 4H), 1.36–1.52 (m, 3H), 1.54–1.61 (m, 1H), 1.73 (s, 3H), 1.69–1.76 (m, 1H), 1.79 (s, 3H), 2.66–2.86 (m, 1H), 2.96 (ddd, *J* = 11.9, 4.0 Hz, 6.2 Hz, 0.9H), 3.10 (dd, *J* = 13.6, 5.1 Hz, 0.1H), 3.21–3.35 (m, 1.9H), 3.47 (dd, *J* = 13.0, 10.8 Hz, 0.1H), 3.67 (s, 0.4H), 3.69 (s, 2.6H), 3.81–3.96 (m, 4H), 3.99 (dd, *J* = 10.2, 6.2 Hz, 1H), 4.05 (dd, *J* = 10.2, 6.2 Hz, 1H), 4.04–

4.14 (m, 1H), 4.42–4.51 (m, 2H), 5.16 (br s, 0.2H), 5.28 (br s, 0.8H), 5.42–5.51 (m, 1H), 6.78 (d, $J$ = 8.5 Hz, 1.8H), 6.80 (d, $J$ = 8.5 Hz, 0.2H), 6.97 (d, $J$ = 8.5 Hz, 1.8H), 7.03 (d, $J$ = 8.5 Hz, 0.2H), 7.34–7.45 (m, 6H), 7.61–7.68 (m, 4H); $^{13}$C NMR ($CDCl_3$, mixture of rotamers) δ 18.2, 19.1, 19.2, 25.8, 26.9, 31.1, 31.2, 32.0, 33.3, 34.2, 35.0, 37.2, 51.1, 52.3, 57.9, 58.2, 63.1, 64.2, 64.3, 64.8, 107.0 (2C), 114.5, 114.6, 119.7, 127.7, 129.6 (2C), 130.5, 131.0, 133.3 (2C), 135.6, 137.9, 157.1, 157.4, 171.9; HRMS (ESI): calcd for $C_{43}H_{56}N_2O_7SiNa$ 763.3749 $(M+Na)^+$, found 763.3722.

**Amine 41.** To a solution of **53** (103 mg, 0.14 mmol) in THF (3 mL) was added $LiAlH_4$ (106 mg, 2.80 mmol) at 0 °C under an argon atmosphere. After stirring 50 °C for 15 h, sufficient amount of $Et_2O$, $H_2O$ (106 μL), 4 M NaOH (106 μL) and $H_2O$ (318 μL) was added at 0 °C successively. After stirring at room temperature for 1 h, the mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1 to 0:1, then EtOAc:MeOH = 19:1) to afford pure **41** (33.6 mg, 54%) as a pale yellow oil. $[\alpha]_D^{24}$ +1.4 (*c* 0.515, $CHCl_3$); IR (film) 3348, 2932, 1612, 1510, 1438, 1371,1236, 1142, 1105, 1034, 943, 887 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.22–1.29 (m, 1H), 1.57 (dd, $J$ = 12.9, 7.5 Hz, 1H), 1.61–1.71 (m, 2H), 1.75 (s, 3H), 1.80 (s, 3H), 1.71–1.82 (m, 3H), 1.85–1.95 (m, 2H), 2.22 (dd, $J$ = 12.9, 8.6 Hz, 1H), 2.46 (s, 3H), 2.41–2.49 (m, 1H), 2.68 (t, $J$ = 8.0 Hz, 1H), 2.94 (dd, $J$ = 13.5, 2.9 Hz, 1H), 3.09–3.24 (m, 4H), 3.27–3.33 (m, 1H), 3.90–4.01 (m, 4H), 4.49 (d, $J$ = 6.9 Hz, 2H), 5.46–5.52 (m, 1H), 6.84 (d, $J$ = 8.6 Hz, 2H), 7.06 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ 18.2, 25.8, 31.5, 32.2, 33.0, 35.0, 35.3, 36.3, 41.8, 49.1, 56.0, 57.3, 60.5, 62.3, 64.2, 64.3, 64.7, 108.0, 114.6 (2C), 119.7, 129.7 (2C), 130.8, 138.1, 157.3; HRMS (ESI): calcd for $C_{26}H_{41}N_2O_4$ 445.3061 $(M+H)^+$, found 445.3058.

**The Ketal of TAN1251C 42 (via Zn reduction).** To a stirred solution of DMSO (0.18 mL, 2.50 mmol) in $CH_2Cl_2$ (2 mL) at -78 ºC was added TFAA (0.16 mL, 1.10 mmol) and the resulting mixture was stirred at

this temperature under an argon atmosphere for 50 min. A solution of **41** (75.0 mg, 0.17 mmol) in $CH_2Cl_2$ (2 mL) was added to the mixture and stirred for 40 min. $Et_3N$ (0.28 mL, 2.00 mmol) was added and the mixture was allow to warm to 0 ºC, stirred for 40 min and was taken up in $CHCl_3$, which was washed with $H_2O$ and brine and dried over anhydrous $Na_2SO_4$. The solvent was concentrated under reduced pressure to give the crude product. To a solution of the crude product in MeOH / $H_2O$ (5:2, 12.6 mL) was added $K_2CO_3$ (0.38 g, 2.70 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 2 h. The solvent was concentrated under reduced pressure and the residue was taken up in $CHCl_3$, which was washed with $H_2O$ and brine and dried over anhydrous $Na_2SO_4$. The residue was concentrated under reduced pressure and purified by preparative TLC ($CH_2Cl_2$:EtOAc = 1:1) to afford pure **42** (43 mg, 60% for 2 steps) as a yellow oil. $[\alpha]_D^{24}$ +71.1 (*c* 0.590, $CHCl_3$).

**TAN1251C (1c).** To a solution of **42** (20 mg, 47 μmol) in acetone (5.0 mL) was added aqueous 1 M HCl (1.5 mL), and the reaction mixture was stirred at room temperature for 22 h. Then the reaction mixture was neutralized with saturated aqueous $Na_2CO_3$. The acetone was concentrated under reduced pressure and the residue was taken up in $CHCl_3$ which was washed with saturated aqueous $Na_2CO_3$ and brine and dried over anhydrous $Na_2SO_4$. The residue was concentrated under reduced pressure and purified by preparative TLC ($CH_2Cl_2$:EtOAc= 1:1) to afford TAN1251C (**1c**) (12 mg, 65%) as a yellow oil. $[\alpha]_D^{25}$ +23.8 (*c* 0.37, MeOH); IR (film) 3408, 2926, 2853, 1713, 1672, 1641, 1611, 1505, 1445, 1427, 1371, 1335, 1298, 1234, 1172, 1124, 1107, 1055, 1007, 860, 839, 810, 789 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.74 (s, 3H), 1.80 (s, 3H), 1.82–1.91 (m, 3H), 1.97 (ddd, J = 13.8, 10.6, 4.6 Hz, 1H), 2.17–2.43 (m, 4H), 2.44–2.50 (m, 1H), 2.51 (s, 3H), 2.56–2.62 (m, 1H), 2.79 (dd, *J* = 11.7, 1.7 Hz, 1H), 3.18–3.24 (m, 3H), 3.38–3.42 (m, 1H), 4.48 (d, *J* = 6.9 Hz, 1H), 5.24 (d, *J* = 1.2 Hz, 1H), 5.48–5.53 (m, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) δ 18.2, 25.8, 34.6, 37.2, 37.8, 39.5, 40.3, 41.4, 42.8,

52.1, 59.0, 64.7, 71.4, 114.3 (2C), 119.8, 127.8, 128.2, 129.8 (2C), 131.9, 138.0, 157.1, 211.7; HRMS (ESI): calcd for $C_{24}H_{33}N_2O_2$ 381.2537 $(M+H)^+$, found 381.2547.