Stereoselective Access to Tubuphenylalanine and Tubuvaline: Improved Mn-Mediated Radical Additions and Assembly of A Tubulysin Tetrapeptide Analog

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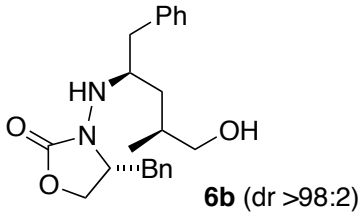
Supporting Information

Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. Toluene and CH_2Cl_2 were purchased inhibitor-free, sparged with argon, and passed through columns of activated alumina under argon atmosphere prior to use. Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230–400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient as indicated. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed with a Chromatotron using commercially supplied rotors. Nuclear magnetic resonance (NMR) data were obtained at

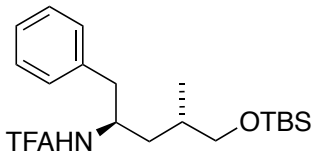
operating frequencies indicated in the text and are reported in units of ppm. Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission method. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low and high resolution mass spectra (TOF) were obtained from local instrumentation facilities services.



6b (dr >98:2)

Mn-Mediated Radical Addition: Hydrazino alcohol 6b. A solution of hydrazone **4**[1] (360 mg, 1.22 mmol) in CH_2Cl_2 (30 mL) was added to $InCl_3$ (541 mg, 2.45 mmol, dried under vacuum for ca. 12 h) in a pyrex Schlenk tube. The mixture was stirred for 2 h at room temperature. Then iodide **5b**[2] (degassed by bubbling argon for 15 min, 856 mg, 4.28 mmol) was added followed by addition of $Mn_2(CO)_{10}$ (524 mg, 1.35 mmol) as a solid. The reaction mixture was degassed by bubbling argon for 15 min, then irradiated for 15 h using a Rayonet photochemical reactor (300 nm, pyrex glassware); the ambient temperature inside the irradiation chamber reached ca 35 °C. The reaction mixture was diluted with diethyl ether, then triethylamine (2.0 mL, 16 mmol) was added. After stirring 1 h, concentration and flash chromatography (petroleum ether/ethyl acetate, 3:1 → 1:2) afforded hydrazino alcohol **6b** (357 mg, 79% yield, dr >98:2) as a colorless oil; $[\alpha]_D^{24}$ – 26.6; IR (NaCl, film) 3441, 2925, 1754, 1745, 1730, 1494, 1452, 1401, 1239, 1093, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.16 (m, 8H), 7.08-7.03 (m, 2H), 3.96-3.90 (m, 2H), 3.69-3.58 (m, 1H), 3.56-3.48 (m, 3H), 3.03 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.80 (m, apparent d, *J* = 6.8 Hz, 2H), 2.45 (dd, *J* = 13.3, 10.1 Hz, 1H), 1.99-1.88 (m apparent octet, 1H), 1.58 (ddd, *J* = 14.3, 7.2, 5.5 Hz, 1H), 1.43 (ddd, *J* = 14.2, 6.5, 6.5 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 139.0, 135.6, 129.1, 129.1, 128.8, 128.5, 127.0, 126.4, 68.0, 65.7, 58.8, 58.5, 40.2, 37.3, 36.7, 32.5, 17.6; MS

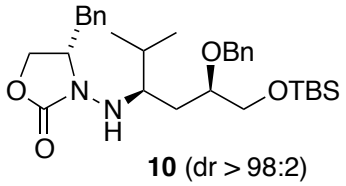
(ESI) m/e (rel. intensity) 391 ([M+Na]$^+$, 100), 369 ([M + H]$^+$, 57); Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.06; H, 7.47; N, 7.48.



7

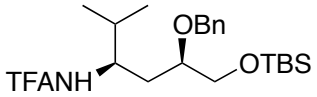
Trifluoroacetamide 7. To a solution of hydrazino alcohol **6b** (130 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added Et_3N (0.098 mL, 0.71 mmol) and DMAP (4 mg, 0.04 mmol), followed by tert-butyldimethylsilyl chloride (58 mg, 0.39 mmol). The mixture was stirred overnight while allowing to warm to room temperature. After dilution with petroleum ether and filtration, concentration and flash chromatography (petroleum ether → 3/1 petroleum ether/ethyl acetate) afforded silyl ether **6a** (167 mg, 98% yield). Analytical data for this material were consistent with the prior report.[5] A solution of **6a** (407 mg, 0.84 mmol) in THF (13 mL) was cooled to –78 °C and a freshly titrated solution of *n*-BuLi (1.32M in hexanes, 0.77 mL, 1.01 mmol) was introduced dropwise. After 50 min at –78 °C, trifluoroacetic anhydride (freshly distilled from P_2O_5, 0.24 mL, 1.7 mmol) was added dropwise. After 1 h at –78 °C, the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by addition of 4:1 ether/triethylamine (5 mL), partitioned between ether and saturated aqueous $NaHCO_3$, washed with brine, and dried over anhydrous $MgSO_4$. After concentration, the crude product mixture was subjected to the next step without further purification. To a solution of this product (≤0.84 mmol) in THF (1 mL) and MeOH (1.5 mL) was added a freshly prepared solution of SmI_2 (ca. 0.3 M in THF) until the blue color persisted (22 mL, ca. 6.6 mmol). The reaction mixture was quenched by opening to air. Filtration through silica gel (Et_2O eluent), concentration, and flash chromatography (petroleum ether/ethyl acetate) afforded unreacted silyl ether **6a** (27 mg, 7% recovery) and trifluoroacetamide **7**

(302 mg, 89% yield for 2 steps). Analytical data for this material were consistent with the prior report.[5]



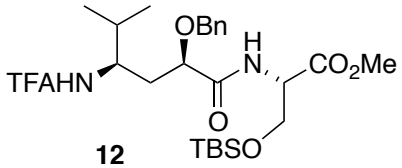
10 (dr > 98:2)

Mn-Mediated Radical Addition with Slow Addition: Hydrazine 10. To a solution of hydrazone **9**[1] (300 mg, 0.62 mmol) in CH_2Cl_2 (31 mL) was added $InCl_3$ (275 mg, 1.24 mmol dried under vacuum for ca. 12 h), followed by isopropyl iodide (0.25 mL, 2.49 mmol, filtered through basic alumina). The mixture was stirred for 15 min at room temperature. Using a syringe pump, a solution of $Mn_2(CO)_{10}$ in CH_2Cl_2 (10 mL) was added over 10 h at a rate of 1 mL/h while the mixture was irradiated using a Rayonet photochemical reactor (254 nm[3], pyrex glassware). After the addition was complete, irradiation was continued for another 5 h; the ambient temperature inside the irradiation chamber reached ca 35 °C. Concentration and flash chromatography (hexanes → 3:1 hexanes/EtOAc) afforded hydrazine **10** as a colorless oil (276 mg, 84% yield, dr >98:2). Analytical data for this material were consistent with the prior report.[1]



11

Trifluoroacetamide 11. Following the procedure described above for preparation of trifluoroacetamide **7**, the hydrazine **10** (34 mg, 0.065 mmol) was subjected to acylation (*n*-BuLi, TFAA, –78 °C to rt) and N–N bond cleavage (SmI_2, MeOH, THF) to afford trifluoroacetamide **11** (28 mg, 97% for two steps). Analytical data for this material were consistent with the prior report.[1]

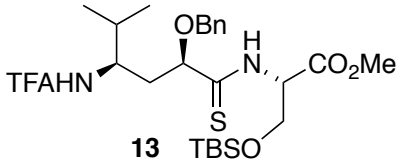


12

Depeptide 12. Trifluoroacetamide **11** was converted to the carboxylic acid **A** as previously described (i. TBAF; ii. $PhI(OAc)_2$, TEMPO, 96% for 2 steps).[1] To a solution of acid **A** (104 mg, 0.29 mmol) in DMF was added *i*-Pr_2NEt (0.208 mL, 1.19 mmol), L-serine methyl ester hydrochloride (56 mg, 0.35 mmol) and diethyl cyanophosphate (DECP, 0.054 mL, 0.35 mmol) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature. After 20 h, the reaction was partitioned between saturated $NaHCO_3$ and extracted using ethyl acetate. The organic phase was washed with brine followed by drying using Na_2SO_4 and then concentrated. Flash chromatography (1:1 petroleum ether/ethyl acetate → 1:2 petroleum ether/ethyl acetate) afforded the dipeptide (134 mg, >99%) as a pale yellow oil; $[\alpha]_D^{25}$ +29.1 (*c* 0.50, $CHCl_3$); IR (NaCl, film) 3410, 3276, 2963, 2881, 1747, 1718, 1666, 1526, 1210, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.42-7.31 (m, 5H), 6.91 (d, *J* = 9.5 Hz, 1H), 4.62-4.57 (m, 1H), 4.55 (ABq, *J* = 9.5 Hz, Δν = 14 Hz, 2H), 4.16-4.06 (m, 1H), 3.99 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.88 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.84 (dd, *J* = 11.3, 3.5 Hz, 1H), 3.77 (s, 3H), 2.59-2.20 (broad s, 1H), 2.00-1.84 (m, 2H), 1.84-1.74 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0, 170.3, 157.33 (q, *J* = 36 Hz), 136.4, 128.81, 128.76, 128.6, 116.0 (q, *J* = 288 Hz), 77.7, 74.3, 63.0, 54.3, 52.8, 52.2, 35.1, 32.0, 18.8, 18.0; MS (ESI) *m/e* (rel. intensity) 471 ($[M+Na]^+$, 100), 449 ($[M+H]^+$, 16); HRMS (ESI) Calcd. for $C_{20}H_{27}F_3N_2O_6Na$ $[M+Na]^+$: 471.1719, found: 471.1731.

To a solution of the dipeptide obtained above (62 mg, 0.13 mmol) and imidazole (37 mg, 0.55 mmol) in DMF (0.33 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (62 mg, 0.071 mmol). After 4 h, the reaction mixture was diluted with diethyl ether, filtered through celite, washed sequentially with sat. $NaHCO_3$, water and brine, then dried

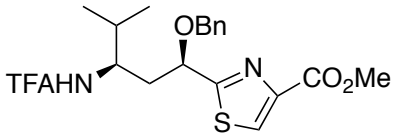
over anhydrous Na_2SO_4. Concentration and flash chromatography (petroleum ether → 1:2 petroleum ether/ethyl acetate) afforded *O*-silyl dipeptide **12** (77 mg, >99%) as a pale yellow oil; $[\alpha]_D^{25}$ +22.2 (*c* 0.49, $CHCl_3$); IR (NaCl, film) 3278, 2957, 2927, 2856, 1747, 1722, 1665, 1207, 1180, 1153; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.5 Hz, 1H), 7.42-7.30 (m, 5H), 7.05 (d, *J* = 9.0 Hz, 1H), 4.63 (dt, *J* = 8.6, 2.9 Hz, 1H), 4.53 (ABq, *J* = 10.7 Hz, Δν = 36 Hz, 2H), 4.12 (dd, *J* = 10.2, 2.7 Hz, 1H), 4.07-3.98 (m, 1H), 3.92-3.83 (m, 2H), 3.76 (s, 3H), 2.08-1.88 (m, 2H), 1.88-1.76 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.7, 170.6, 157.7 (q, *J* = 36 Hz), 136.6, 128.9, 128.8, 128.7, 116.1 (q, *J* = 287 Hz), 77.8, 74.1, 63.6, 54.2, 52.8, 52.7, 35.0, 32.0, 25.9, 19.1, 18.4 (2C), -5.3, -5.5; MS (ESI) *m/e* (rel. intensity) 585 ($[M+Na]^+$, 100), 563 ($[M+H]^+$, 46); HRMS (ESI) Calcd for $C_{26}H_{42}F_3N_2O_6Si$ $[M+H]^+$: 563.2764, found: 563.2767; Anal. Calcd for $C_{26}H_{41}F_3N_2O_6Si$: C, 55.50; H, 7.34; N, 4.98. Found: C, 55.60; H, 7.40; N, 4.94.



13

Thioamide 13. To a solution of dipeptide **12** (77 mg, 0.13 mmol) in THF (0.1 mL) at 60°C was added Belleau's reagent (58 mg, 0.10 mmol) dropwise as a solution in THF (0.15 mL). After 150 min at reflux, the reaction mixture was cooled to room temperature and concentrated. Flash chromatography (3:1 petroleum ether/ethyl acetate → 2:1 petroleum ether/ethyl acetate) afforded the corresponding thioamide (76 mg, 96% yield) as a pale yellow oil; $[\alpha]^{23}_D$ = + 54.0 (*c* = 0.53, $CHCl_3$); IR (neat) 3346, 1753, 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, *J* = 7.6 Hz, 1H), 7.39-7.32 (m, 5H), 6.62 (d, *J* = 9.1 Hz, 1H), 5.23 (dt, *J* = 7.9, 2.8 Hz, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 4.36 (dd, *J* = 9.8, 2.4 Hz, 1H), 4.17 (dd, *J* = 10.4, 2.7 Hz, 1H), 4.10 (dd, *J* = 10.4, 3.0 Hz, 1H), 4.05-3.99 (m, 1H), 3.79 (s, 3H), 2.26 (ddd, *J* = 14.9, 9.9, 2.5 Hz, 1H),

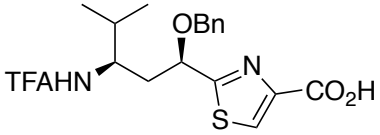
1.93 (ddd, J = 14.9, 9.8, 2.5 Hz, 1H), 1.74 (m, apparent octet, J = 6.8 Hz, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5, 169.4, 157.1 (q, J = 36 Hz), 136.1, 128.7, 128.6, 128.5, 118.6 (q, J = 289 Hz), 84.5, 73.5, 62.3, 58.9, 52.7, 52.6, 37.7, 31.6, 25.6, 18.9, 18.2, 18.1, -5.6, -5.8; MS (CI) *m/e* 579 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{41}F_3N_2O_5SiSNa$ $[M+Na]^+$: 601.2355, found 601.2355. On larger scales, diminished yields were obtained: from **12** (438 mg, 0.78 mmol) was obtained **13** (355 mg, 79% yield).



14

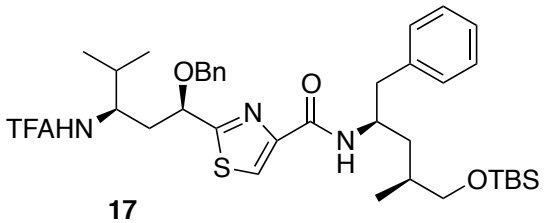
***N*-Trifluoroacetyl-*O*-benzyltubuvaline Methyl Ester (14).** To a solution of thioamide **13** (580 mg, 1.0 mmol) in THF (30 mL) at 0°C was added tetrabutylammonium fluoride (1M in THF, 1.5 mL, 1.5 mmol). After warming to room temperature over 30 min, the reaction mixture was partitioned between ethyl acetate and saturated aqueous NH_4Cl, washed with brine, and dried over anhydrous $MgSO_4$. Concentration and flash chromatography (1:1 → 2:1 petroleum ether/ethyl acetate) afforded the corresponding alcohol in semipure form (0.55 g) which was used without further purification. To a solution of this material in CH_2Cl_2 (5 mL) at –78 °C was added diethylaminosulfur trifluoride (DAST) (0.193 g, 1.2 mmol). After 2 h at –78 °C, the reaction was quenched by saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the cyclized thiazoline intermediate which was used without further purification. To a solution of the thiazoline in CH_2Cl_2 (20 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.61 g, 4.0 mmol) and $BrCCl_3$ (0.79 g, 4.0 mmol). After 3 h at 0 °C, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ethyl acetate. The organic phase was washed with brine, dried over anhydrous

Na_2SO_4 and concentrated. Flash chromatography (2:1 petroleum ether/ethyl acetate) afforded **14** (416 mg, 94% yield) as a colorless oil. $[\alpha]^{23}_D$ = +17.0 (*c* = 0.55, $CHCl_3$); IR (neat) 3318, 3091, 2963, 2929, 1737, 1725, 1710, 1692, 1549, 1456, 1326 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.30-7.40 (m, 5H), 6.62 (d, *J* = 9.7 Hz, 1H), 4.87 (dd, J = 9.5, 4.0 Hz, 1H), 4.54 (ABq, *J* = 10.6 Hz, Δν = 33.6 Hz, 2H), 4.18-4.21 (m, 1H), 3.96 (s, 3H), 1.99-2.11 (m, 2H), 1.78 (m, apparent octet, *J* = 6.7 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.9, 161.6, 157.1 (q, *J* = 36 Hz), 146.7, 136.4, 128.65, 128.62, 128.56, 128.3, 128.1, 116.1 (q, *J* = 289 Hz), 76.3, 73.2, 52.5, 52.0, 39.1, 31.7, 18.8, 18.0; MS (CI) *m/e* 445 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}F_3N_2O_4SNa$ $[M+Na]^+$: 467.1228, found 467.1226.



15

***N*-Trifluoroacetyl-*O*-benzyltubuvaline (15).** To a mixture of ester **14** (20 mg, 0.045 mmol) in MeOH/H_2O (0.6 mL, 2:1) was added LiOH•H_2O (2.8 mg, 0.06 mmol) at 0 °C. The reaction mixture was allowed to stir overnight at room temperature, then partitioned between saturated aqueous $NaHCO_3$ and ether. The aqueous phase was acidified with 2 N HCl, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford acid **15** (19 mg, 98% yield); $[\alpha]^{23}_D$ = +18.6 (*c* = 0.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 13.5-12.5 (br s, 1H), 8.31 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.36-7.40 (m, 5H), 5.19 (d, J = 9.8 Hz, 1H), 4.55 (ABq, J = 10.3 Hz, Δν = 31.5 Hz, 2H), 4.38-4.44 (m, 1H), 2.19-2.27 (m, 1H), 1.86-1.97 (m, 2H), 0.93 (d, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 182.0, 169.6, 160.2 (q, *J* = 36 Hz), 149.8, 138.9, 131.8, 131.6, 131.3, 131.2, 120.9 (q, *J* = 288 Hz), 78.4, 76.7, 53.8, 40.9, 34.9, 21.0, 20.6; IR (neat) 3337, 2964, 1723, 1703, 1230, 1208, 1181 cm^{-1}; MS (CI) *m/e* 431 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}F_3N_2O_4SNa$ $[M+Na]^+$: 453.1072, found 453.1069.

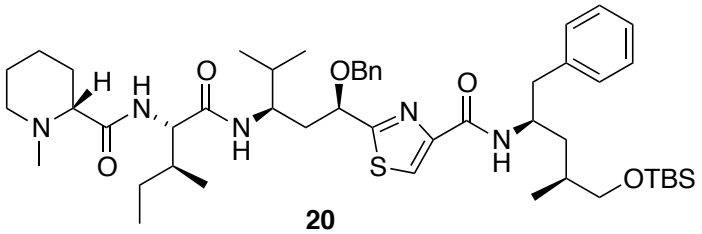


17

Tuv-Tup Dipeptide 17. To a solution of trifluoroacetamide **7** (50 mg, 0.12 mmol) in MeOH (4 mL) at 0 °C was added $Ba(OH)_2 \bullet 8H_2O$ (313 mg, 0.99 mmol). The reaction mixture was warmed to 40 °C for 2 h, then at room temperature overnight. The reaction was incomplete, as judged by TLC, and was heated at reflux for 1 h, whereupon TLC showed complete conversion. Filtration through celite and concentration afforded amine **16** (37 mg, 97% yield), which was used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.07 (m, 5H), 3.43 (m, apparent dd, J = 5.9, 0.9 Hz, 2H), 3.18-3.09 (m, 1H), 2.82 (dd, J = 13.3, 4.1 Hz, 1H), 2.39 (dd, J = 13.3, 8.9 Hz, 1H), 1.80 (m, apparent octet, J = 6.7 Hz, 1H), 1.80-1.65 (br s, 2H), 1.58-1.49 (m, 1H), 1.25-1.16 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 139.5, 129.3, 128.4, 126.2, 68.1, 50.5, 44.5, 41.9, 32.7, 25.9, 18.3, 17.7, -5.4 (2C).

To a solution of acid **15** (35 mg, 0.081 mmol) in DMF (1.5 mL) at 0 °C were sequentially added *i*-Pr_2NEt (0.021 mL, 012 mmol), amine **16** (37 mg, 0.12 mmol) and DECP (0.015 mL, 0.10 mmol). The reaction mixture was allowed to stir at room temperature overnight. The mixture was diluted with EtOAc, washed successively with brine, saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. Concentration and flash chromatography (3:1 petroleum ether/ethyl acetate) afforded the dipeptide **17** (54 mg, 93%) as a colorless oil; IR (neat) 3301, 2957, 2927, 2855, 1721, 1658, 1547, 1461, 1371, 1157, 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.38-7.33 (m, 5H), 7.26-7.22 (m, 5H), 7.09 (d, J = 9.0 Hz, 1H), 6.66 (d, J = 9.8 Hz, 1H), 4.77 (dd, J = 9.7, 3.5 Hz, 1H), 4.53 (ABq, J = 10.7 Hz, Δν = 43.8 Hz, 2H), 4.48-4.44 (m, 1H), 4.19-4.09 (m, 1H), 3.47 (ABX, J_{AB} = 9.5 Hz, J_{AX} = 5.3 Hz, J_{BX} = 4.5 Hz, Δν = 22.7

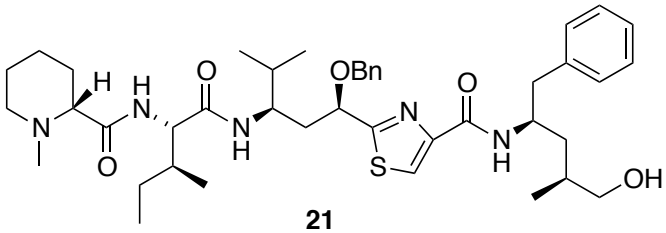
Hz, 2H), 2.94-2.90 (m, apparent d, J = 5.8 Hz, 2H), 2.13-1.95 (m, 2H), 1.85-1.70 (m, 2H), 1.35-1.20 (m, 2H), 0.98 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 160.2, 157.0 (q, J = 36 Hz), 150.3, 137.8, 136.4, 129.6, 128.63, 128.51, 128.42, 128.3, 126.3, 123.5, 76.0, 72.8, 66.9, 52.4, 48.2, 41.1, 39.1, 37.3, 32.6, 31.6, 25.9, 19.1, 18.3, 18.2, 17.5, -5.4, -5.5, CF_3 signal was below noise level in this spectrum; MS (CI) *m/e* 720 $[M+H]^+$; HRMS (ESI) calcd for $C_{37}H_{53}F_3N_3O_4SSi$ $[M+H]^+$: 720.3478, found 720.3491.



20

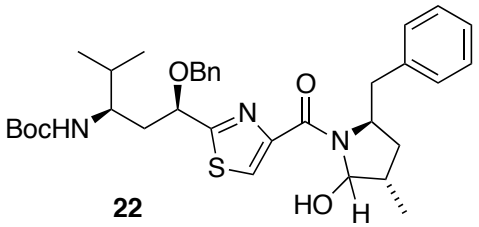
Tetrapeptide 20. Following the trifluoroacetamide methanolysis procedure described above (for **7** → **16**), trifluoroacetamide **17** (140 mg) was converted to the corresponding free amine **18** (114 mg, 94%), which was used without further purification. IR (neat) 3394, 3229, 2956, 2926, 2855, 1666, 1536, 1493, 1462, 1091 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.37-7.30 (m, 5H), 7.27-7.16 (m, 5H), 7.15 (d, J = 9.4 Hz, 1H), 4.97 (dd, J = 9.5, 3.0 Hz, 1H), 4.62 (ABq, J = 11.5 Hz, Δν = 70.4 Hz, 2H), 4.49-4.39 (m, 1H), 3.47 (ABX, J_{AB} = 9.8 Hz, J_{AX} = 5.0 Hz, J_{BX} = 4.4 Hz, Δν = 28.4 Hz, 2H), 2.92-2.81 (m, 3H), 1.96 (ddd, J = 14.2, 9.5, 2.4 Hz, 1H), 1.92 (br s, 1H), 1.80-1.58 (m, 5H), 1.31-1.25 (m, 1H), 0.95 (d, J = 6.3 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.5, 160.4, 150.2, 137.8, 137.2, 129.6, 128.5, 128.2, 128.12, 128.09, 126.3, 122.9, 76.4, 72.3, 66.8, 52.5, 48.2, 42.4, 41.2, 37.3, 33.8, 32.6, 25.9, 18.8, 18.2, 17.6, 17.3, -5.48, -5.50.

To a suspension of Mep-IleOH trifluoroacetate[4] (**19**, 18 mg, 0.048 mmol) in EtOAc (0.3 mL) was added *N*-methylmorpholine (NMM, 5 μL, 0.05 mmol). The mixture was cooled to ca. –10 °C (ice-salt bath), and isobutyl chloroformate (6 μL, 0.05 mmol) was introduced. After 5 min, a solution of amine **18** (15 mg, 0.024 mmol) in EtOAc (0.12 mL) was added. The mixture was allowed to warm slowly to room temperature. After 8 h, the mixture was partitioned between water and EtOAc. The organic phase was dried over anhydrous Na_2SO_4. Concentration and flash chromatography (1% MeOH/CH_2Cl_2 → 5% MeOH/CH_2Cl_2) furnished unreacted amine **18** (3 mg, 20% recovery) and tetrapeptide **20** (10 mg, 48% yield); IR (neat) 3287, 2957, 2931, 1658, 1649, 1546, 1371, 1249, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (s, 1H), 7.45-7.18 (m, 10H), 7.13 (d, J = 9.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.15 (d, J = 9.9 Hz, 1H), 4.70 (dd, J = 10.5, 2.4 Hz, 1H), 4.57 (ABq, J = 10.4 Hz, Δν = 13.3 Hz, 2H), 4.49-4.40 (m, 1H), 4.32-4.23 (m, 1H), 4.13 (dd, apparent t, J = 8.5 Hz, 1H), 3.47 (ABX, J_{AB} = 9.7 Hz, J_{AX} = 5.1 Hz, J_{BX} = 4.3 Hz, Δν = 25.8 Hz, 2H), 2.97-2.85 (m, 3H), 2.52 (dd, J = 11.0, 3.2 Hz, 1H), 2.23 (s, 3H), 2.08-1.85 (m, 4H), 1.83-1.46 (m, 8H), 1.44-1.15 (m, 4H), 0.97 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.93-0.89 (m, 9H), 0.85 (s, 9H), 0.003 (s, 3H), -0.004 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.0, 174.3, 170.8, 160.4, 150.3, 138.0, 137.1, 129.6, 128.52, 128.50, 128.3, 128.1, 126.3, 123.1, 76.8, 73.3, 69.6, 66.8, 57.8, 55.4, 50.7, 48.3, 44.9, 41.4, 40.5, 37.4, 35.2, 32.7, 32.1, 30.8, 25.9, 25.1, 24.9, 23.3, 19.1, 18.3, 17.7, 17.6, 16.1, 11.8, -5.46, -5.48; MS (ESI) 862 ($[M+H]^+$), 884 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{48}H_{76}N_5O_5SSi$ 862.5336 ($[M+H]^+$), found 862.5354.



21

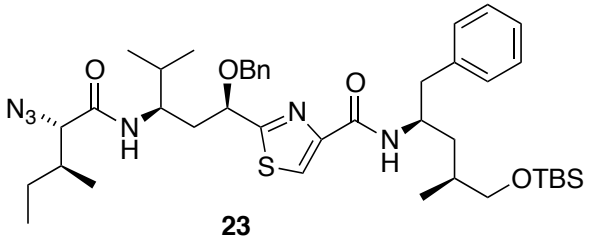
Alcohol 21. To a solution of silyl ether **20** (9 mg, 0.01 mmol) in THF (1 mL) at 0 °C was added tetrabutylammonium fluoride (1 M in THF, 15 μL, 0.015 mmol) and acetic acid (15 μL, 0.25 mmol). The mixture was allowed to warm to room temperature. After 5.5 h, concentration and flash chromatography (hexane → 5% MeOH/CH_2Cl_2) afforded alcohol **21** (8 mg, >99% yield) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.50-7.25 (m, 10H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.30 (d, *J* = 10.1 Hz, 1H), 4.68 (dd, *J* = 10.4, 3.5 Hz, 1H), 4.58 (ABq, *J* = 10.4 Hz, Δν = 11.1 Hz, 2H), 4.32-4.10 (m, 3H), 3.56 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.50 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.20 (br s, 1H), 3.02-2.88 (m, 2H), 2.53 (dd, *J* = 10.9, 2.7 Hz, 1H), 2.23 (s, 3H), 2.10-1.15 (m, 17H), 0.98-0.87 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.5, 174.5, 170.7, 160.9, 150.1, 138.2, 137.2, 129.4, 128.5 (2C), 128.4, 128.1, 126.4, 123.4, 76.1, 73.3, 69.6, 67.9, 57.9, 55.4, 50.8, 45.0, 41.3, 40.3, 38.9, 38.6, 35.0, 32.2, 32.1, 31.0, 25.1, 24.8, 23.3, 19.1, 18.1, 17.7, 16.1, 10.9; MS (ESI) 239 ([M–TuvTup(CH_2OH)]$^+$), 510 ([M+H–MepIle]$^+$), 748 ([M+H]$^+$), 771 ([M+Na]$^+$).



22

Hemiacetal 22. A solution of amine **18** (32 mg, 0.051 mmol), Boc-anhydride (13 μL, 0.059 mmol) and DMAP (<1 mg) in THF (0.5 mL) was heated at 45–50°C for 30 min. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and dichloromethane. The organic phase was washed with brine and dried over Na_2SO_4.

Concentration and flash chromatography (petroleum ether → 98:2 dichloromethane/methanol) afforded the *N*-Boc derivative (29 mg, 78% yield). To a solution of this compound in THF (3 mL) at 0°C was added tetrabutylammonium fluoride (1 M in THF, 50 μL, 0.050 mmol) and glacial acetic acid (17 μL, 0.28 mmol). After 24 h the reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. Concentration and flash chromatography (petroleum ether → 96:4 dichloromethane/methanol) afforded the corresponding desilylated alcohol (21 mg, 91% yield). To a solution of this alcohol in CH_2Cl_2 (0.4 mL) at 0°C was added water (0.05 mL), $PhI(OAc)_2$ (23 mg, 0.07 mmol) and TEMPO (0.2 mg, 0.001 mmol), and the mixture was allowed to warmed to room temperature overnight. The reaction mixture was then diluted with ether, quenched with aqueous $Na_2S_2O_3$, and extracted with CH_2Cl_2. Concentration and flash chromatography (petroleum ether → 96:4 dichloromethane/methanol) afforded hemiaminal **22** (16 mg, 52% over 3 steps) as a pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.60-7.09 (m, 10H), 5.94 (s, 1H), 5.17 (s, 1H), 4.83 (dd, *J* = 10.7, 2.8 Hz, 1H), 4.64 (ABq, *J* = 10.7 Hz, Δν = 42.8 Hz, 2H), 4.54-4.42 (m, 2H), 3.99-3.89 (m, 1H), 3.62 (dd, *J* = 12.8, 3.8 Hz, 1H), 2.63 (dd, *J* = 12.9, 10.1 Hz, 1H), 2.46-2.38 (m, 1H), 2.15–2.09 (m, 1H), 2.04-1.94 (m, 1H), 1.83-1.68 (m, 2H), 1.62-1.53 (m, 1H), 1.47 (s, 9H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 161.9, 155.8, 151.1, 139.0, 137.0, 129.4, 128.6, 128.5, 128.3, 128.1, 126.3, 126.2, 89.4, 79.2, 77.2, 73.5, 59.0, 51.9, 41.1, 40.4, 38.7, 34.8, 32.8, 28.4, 19.1, 17.7, 17.3; MS (ESI) *m/e* (rel. intensity) 630 ($[M+Na]^+$, 100); HRMS (ESI) Calcd. for $C_{34}H_{45}N_3O_5SNa$ ($[M+Na]^+$: 630.2978, Found: 630.2988.



23

Tripeptide 23. To a solution of 2-azidoisoleucine[5] (9.2 mg, 0.058 mmol) in 2.0 mL dry EtOAc at 0 °C was added NMM (6 mg, 0.058 mmol) and *i*-BuOCOCl (8 mg, 0.058 mmol). After 10 min, a solution of amine **18** (22 mg, 0.045 mmol) in 1 mL EtOAc was added. The reaction mixture was allowed to warm to room temperature. After 20 h, the mixture was partitioned between water and EtOAc. The organic phase was dried over anhydrous Na_2SO_4. Concentration and flash chromatography (4:1 petroleum ether/EtOAc) afforded **23** (27 mg, 79% yield) as a colorless oil. $[\alpha]^{23}_D$ = + 0.92 (*c* = 0.32, $CHCl_3$); IR (neat) 3394, 3317, 2959, 2927, 2108, 1665, 1658, 1546, 1494, 1251, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (s, 1H), 7.43-7.36 (m, 5H), 7.36-7.16 (m, 5H), 7.13 (d, J = 9.6 Hz, 1H), 6.48 (d, J = 9.6 Hz, 1H), 4.73 (dd, J = 10.0, 2.8 Hz, 1H), 4.56 (ABq, *J* = 10.7 Hz, Δν = 16.5 Hz, 2H), 4.52-4.37 (m, 1H), 4.24-4.14 (m, 1H), 3.87 (d, J = 4.2 Hz, 1H), 3.46 (ABX, J_{AB} = 9.8 Hz, J_{AX} = 5.0 Hz, J_{BX} = 4.4 Hz, Δν = 21.9 Hz, 2H), 2.96-2.84 (m, 2H), 2.12-2.00 (m, 2H), 1.92 (dd, J = 9.7, 2.9 Hz, 1H), 1.78-1.70 (m, 3H), 1.54-1.42 (m, 1H), 1.34-1.22 (m, 2H), 1.06 (d, J = 6.9, 3H), 0.96-0.88 (m, 12H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.8, 168.4, 160.3, 150.3, 137.9, 136.9, 129.6, 128.55, 128.52, 128.25, 128.17, 126.3, 123.3, 76.4, 72.9, 70.4, 66.9, 51.3, 48.3, 41.2, 40.0, 38.2, 37.3, 32.7, 31.8, 25.9, 24.3, 19.1, 18.3, 18.2, 17.6, 16.1, 11.6, -5.45, -5.47; MS (ESI) 763 ($[M+H]^+$, 785 ($[M+Na]^+$.

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1. Friestad, G. K.; Deveau, A. M.; Marié, J.-C. *Org. Lett.* **2004**, *6*, 3249-3252.

2. Chesis, P. L.; Hwang, D. R.; Welch, M. J. *J. Med. Chem.* **1990**, *33*, 1482-1490.

3. Control experiments confirmed that 254 nm and 300 nm bulbs could be used interchangeably (Rayonet reactor, pyrex glassware). Quartz glassware was not evaluated in these control experiments.

4. Patrick, K. S.; Singletary, J. L. *Chirality* **1991**, *3*, 208-211.

5. Kim, H.; Cho, J. K.; Aimoto, S.; Lee, Y.-S. *Org. Lett.* **2006**, *8*, 1149-1151.