SYNTHESIS OF POLYPYRROLINONES ON SOLID-SUPPORT

(SUPPORTING INFORMATION)

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MATERIALS AND METHODS

All reactions were carried out in oven-dried or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent or high performance liquid chromatography (HPLC) grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon prior to use. Dichloromethane was freshly distilled from calcium hydride before use. HPLC grade benzene was purchased from J.T. Baker and stored over 4 Å molecular sieves. Anhydrous dimethylformamide and dimethyl sulfoxide were purchased from Aldrich and used without purification. Wang resin (100-200 mesh, 1% DVB cross linked) was purchased from Novabiochem, the loading level is 0.83 mmol/g.

Unless otherwise stated, solid support reactions were vortexed using a Mistral multi-mixer; solution phase reactions were magnetically stirred and monitored by thin layer chromatography using 0.25 mm E. Merck pre-coated silica gel plates. Flash column chromatography was performed with the indicated solvents using silica gel-60 (particle size 0.040-0.062 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

All melting points were determined on a Bristoline heated-stage microscope or a Thomas-Hoover apparatus and are corrected. The IR and NMR spectra were obtained for $CHCl_3$ and $CDCl_3$ solutions respectively unless otherwise noted. Infrared spectra were recorded with a Perkin-Elmer Model 283B spectrometer using polystyrene as an external standard. Proton and carbon-13 NMR spectra were recorded on a Bruker AM-500 spectrometer and obtained at 305 K unless otherwise noted. Chemical shifts are reported relative to chloroform (δ 7.24 for proton and δ 77.0 for carbon-13). Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter in the solvent indicated. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on either a VG micromass 70/70H high resolution double-focusing electron impact/chemical ionization spectrometer or a VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories, Madison, New Jersey.

Preparation of Teoc-protected amino acid (+)-3. To a rt solution of (-)-**12** (1.69 g, 7.94 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (4.02 g, 5.53 mL, 39.7 mmol). The mixture was stirred for 5 min, and then Teoc-*O*-succinimidyl (2.06 g, 7.94 mmol) was added in one portion. The reaction was stirred for 14 h, diluted with

EtOAc (100 mL), washed with 2 N aqueous HCl (2 x 15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was separated, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (EtOAc/hexanes, 20:80) to afford the corresponding Teoc-protected amino ester (2.5 g, 88% yield) as a oil: $[\alpha]_D^{23}$ +38.7° (*c* 0.46, $CHCl_3$); IR (neat) 3425, 1714, 1503, 1444 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1 H), 4.88 (t, 1H, *J* = 7.0 Hz), 4.09 (t, 2H, *J* = 8.4 Hz), 3.70 (s, 3H), 2.99 (dd, 1H, *J* = 6.9, 14.0 Hz), 2.40-2.36 (m, 2H), 1.69-1.63 (m, 1H), 1.60-1.51 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 0.98-0.93 (m, 2H), 0.88 (d, 3H, *J* = 6.7 Hz), 0.75 (d, 3H, *J* = 6.6 Hz), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 154.4, 135.4, 117.8, 63.5, 62.4, 52.3, 43.8, 35.4, 25.9, 24.6, 23.8, 22.5, 17.8, 17.7, -1.5; high-resolution mass spectrum (CI, NH_3) *m/z* 358.2406 $[(M + H)^+]$, calcd for $C_{18}H_{36}NO_4Si$ 358.2414.

Anal. Calcd for $C_{18}H_{35}NO_4Si$: C, 60.46; H, 9.87. Found: C, 60.82; H, 9.72.

A solution of Teoc-protected amino ester (1.22 g, 3.42 mmol) in MeOH (20 mL) and 3 N aqueous NaOH (10 mL) was heated to reflux for 20 h. The mixture was cooled to rt and concentrated in *vacuo*; the resultant mixture was then acidified with saturated aqueous $NaHSO_4$ to pH 2 and then extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with brine (15 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and azeotroped with toluene (3 x 15 mL). This procedure gave (+)-**3** (1.12 g, 96% yield) as a colorless oil that was used without further purification. Analytical sample: $[\alpha]_D^{23}$ +21.0° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3421, 1707, 1505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1 H), 4.95 (t, 1H, *J* = 6.8 Hz), 4.15-4.09 (m, 2H), 3.04-2.98 (m, 1H), 2.46 (dd, 1H, *J* = 7.4, 14.4 Hz), 2.37 (dd, 1H, *J* = 4.8, 14.3 Hz), 1.78-1.70 (m, 1H), 1.67 (s, 3H), 1.66-1.60 (m, 1H), 1.58 (s, 3H), 1.02-0.95 (m, 2H), 0.91 (d, 3H, *J* = 6.6 Hz), 0.83 (d, 3H, *J* = 6.6 Hz), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 154.6, 135.7, 117.5, 63.2, 62.6, 43.6, 35.3, 25.9, 24.7, 23.7, 22.7, 17.8, 17.6, -1.6; high-resolution mass spectrum (ES, Na^+) *m/z* 344.2251 $[(M + H)^+]$, calcd for $C_{17}H_{34}NO_4Si$ 344.2257.

Anal. Calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68. Found: C, 59.22; H, 9.48.

Preparation of resin bound Teoc-protected amino acid 4. To a suspension of Wang resin (3.52 g, 2.92 mmol, 1.0 equiv), PPh_3 (0.84 g, 3.21 mmol, 1.1 equiv), and (+)-**3** (1.10 g, 3.21 mmol, 1.1 equiv) in THF (55 mL) at 0 °C was added diethyl azodicarboxylate (0.51 mL, 0.56 g, 3.21 mmol, 1.1 equiv). The mixture was warmed to rt, shaken for 14 h, after which the resin was filtered, washed successively with THF (3 x 50 mL), Et_2O (3 x 50 mL) and dried under high vacuum to a constant weight of 4.63 g. The resin was then re-subjected to the same reaction conditions to afford **4** (4.64 g): IR (KBr) 3429, 1717 cm^{-1}.

Preparation of resin bound free amino acid 5. Typical procedure for Teoc deprotection with TBAF. To a suspension of resin bound Teoc-protected amino acid **4** (0.36 g, *ca*. 0.24 mmol, 1.0 equiv) in THF (8 mL) was added *n*-Bu_4NF (1.18 mL, 1.18 mmol, 1.0 M in THF, 5.0 equiv). The reaction was shaken for 12 h, after which the resin was filtered, washed successively with THF/H_2O (1:1, 3 x 20 mL), DMSO (3 x 15 mL), THF (3 x 20 mL), Et_2O (3 x 20 mL) and dried under high vacuum to afford **5** (0.33 g): IR (KBr) 1722 cm^{-1}.

Preparation of resin bound imine 6. Typical procedure for imine formation with hydrocinnamaldehyde. To a suspension of resin bound free amino acid **5** (60 mg, *ca*. 0.043 mmol, 1.0 equiv) in THF (3 mL) and $(MeO)_3CH$ (3 mL) was added hydrocinnamaldehyde (0.06 mL, 58 mg, 0.429 mmol, 10.0 equiv). The reaction was shaken for 12 h, after which the resin was filtered, washed successively with anhydrous THF (4 x 6 mL) under an argon atmosphere, and then dried under high vacuum. The resin was then re-subjected to the same reaction conditions to afford **6** which was taken immediately on to next step.

Synthesis of monopyrrolinone (-)-7. Typical procedure for the cleavage of substrate from the resin. To a suspension of resin bound imine **6** (*ca*. 0.043 mmol, 1.0 equiv) in THF (5 mL) was added KHMDS (1.28 mL, 0.64 mmol, 0.5 M in toluene, 15.0 equiv). The reaction was shaken for 3 h, cooled to 0 ^oC, and quenched by addition of 5% aqueous $NaHSO_4$ (3 mL). The resin was then filtered, washed successively with THF (2 x 10 mL), EtOAc (2 x 10 mL), Et_2O (2 x 10 mL). The filtrate and the washes were combined, washed with saturated aqueous $NaHCO_3$ and brine (15 mL each), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash

chromatography (EtOAc/hexanes 20:80) afforded (-)-**7** (7.9 mg, 62% yield) as a yellow solid: (-)-**7** has physical and spectroscopic properties identical to literature values.[1d].

Preparation of resin bound Teoc-protected amino aldehyde 8. A suspension of resin bound Teoc-protected amino acid **4** (1.74 g, *ca*. 1.14 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was cooled to -78 °C, and ozone bubbled into the mixture until a blue color persisted. The mixture was then stirred for another 20 min, and then the excess ozone purged with argon. To this suspension, PPh_3 (1.20 g, 4.55 mmol, 4.0 equiv) was added, and the reaction mixture was warmed to rt, shaken for 14 h, after which the resin was filtered, washed successively with CH_2Cl_2 (2 x 50 mL), THF (2 x 50 mL), Et_2O (2 x 50 mL) and dried under high vacuum to afford **8** (1.62 g): IR (KBr) 3422, 1720 cm^{-1}.

Preparation of resin bound monopyrrolinone 9. Typical procedure for pyrrolinone ring formation on solid support using amino ester (-)-12. To a suspension of resin bound amino aldehyde **8** (1.62 g, *ca*. 1.08 mmol, 1.0 equiv) in THF (15 mL) and $(MeO)_3CH$ (15 mL) was added amino ester (-)-**12** (0.58 g, 2.7 mmol, 2.5 equiv). The mixture was shaken for 12 h, after which the resin was filtered, washed successively with anhydrous THF (4 x 6 mL) under argon protection, and dried under high vacuum. The resin was then re-subjected to the same reaction conditions to afford the resin bound imine, which was immediately taken on to next step.

To a suspension of resin bound imine (*ca*. 1.08 mmol, 1.0 equiv) in THF (15 mL) was added KHMDS (21.6 mL, 10.8 mmol, 0.5 M in toluene, 10.0 equiv). The mixture was then shaken for 2 h, cooled to 0 ^oC, and quenched by addition of saturated aqueous NH_4Cl (5 mL). The resin was then filtered, washed successively with H_2O (3 x 15 mL), H_2O/THF (1:1, 2 x 20 mL), THF (2 x 30 mL), Et_2O (2 x 30 mL), dried under high vacuum to afford **9** (1.74 g).

Preparation of resin bound monopyrrolinone aldehyde 14. Typical procedure for solid support dimethyl acetal deprotection. To a suspension of resin bound monopyrrolinone **13** (0.48 g, *ca*. 0.29 mmol, 1.0 equiv) in THF (20 mL) and H_2O (4 mL) was added TsOH (0.35 g, 1.86 mmol, 6.5 equiv). The

reaction was stirred at 40 ^{o}C for 20 h, after which the resin was filtered, washed successively with H_2O (3 x 15 mL), H_2O/THF (1:1, 2 x 20 mL), THF (2 x 30 mL), Et_2O (2 x 30 mL), and dried under high vacuum to afford **14** (0.46 g).

Preparation of resin bound monopyrrolinone aldehyde 14. Typical procedure for two step oxidation on solid support. To a suspension of resin bound monopyrrolinone **9** (168 mg, *ca*. 0.10 mmol, 1.0 equiv) in acetone (4 mL) and H_2O (0.5 mL) was added OsO_4 (*ca*. 1 mg), followed by NMO (60 mg, 0.50 mmol, 5.0 equiv). The reaction mixture was shaken for 20 h, after which the resin was filtered, washed successively with acetone/H_2O (1:1, 3 x 5 mL), THF (4 x 5 mL), CH_2Cl_2 (3 x 5 mL), Et_2O (2 x 10 mL), and dried under high vacuum to afford **18** (172 mg).

To a suspension of **18** (80 mg, *ca*. 0.047 mmol, 1.0 equiv) in 1,4-dioxane (4 mL) and H_2O (0.5 mL) was added $NaIO_4$ (51 mg, 0.24 mmol, 5.0 equiv). The reaction mixture was shaken for 20 h, after which the resin was filtered, washed successively with 1,4-dioxane/H_2O (1:1, 3 x 5 mL), THF/H_2O (1:1, 3 x 5 mL), THF (4 x 5 mL), CH_2Cl_2 (3 x 5 mL), Et_2O (2 x 10 mL), and dried under high vacuum to afford **14** (73 mg).

Preparation of resin bound monohydroxy pyrrolinone 25. Typical procedure for pyrrolinone ring formation on solid support using amino lactone (-)-26. To a suspension of resin bound amino aldehyde **8** (590 mg, *ca*. 0.39 mmol, 1.0 equiv) in THF (5 mL) and $(MeO)_3CH$ (5 mL) was added amino lactone (-)-**26** (153 mg, 0.98 mmol, 2.5 equiv). The reaction was shaken for 12 h, after which the resin was filtered, washed successively with anhydrous THF (4 x 10 mL) under argon protection, and dried under high vacuum. The resin was then re-subjected to the same reaction conditions to afford the resin bound imine which was taken immediately on to next step.

To a 0 ^{o}C suspension of resin bound imine (*ca*. 0.39 mmol, 1.0 equiv) in THF (10 mL) was added a solution of KHMDS (6.28 mL, 3.14 mmol, 0.5 M in toluene, 8.0 equiv) and 18-c-6 (830 mg, 3.14 mmol, 8.0 equiv) in THF (6 mL) via cannula. The reaction was shaken at 0 ^{o}C for 2 h, at rt for 3h, then cooled to 0 ^{o}C, and quenched by addition of 5% aqueous $NaHSO_4$ (5 mL). The resin was then filtered, washed successively with H_2O (3

x 15 mL), H_2O/THF (1:1, 2 x 30 mL), DMSO (3 x 15 mL), THF (2 x 30 mL), Et_2O (2 x 30 mL), and dried under high vacuum to afford **25** (615 mg).

Preparation of resin bound monopyrrolinone aldehyde 14. Typical procedure for Swern Oxidation on solid support. To a -70 °C solution of $(COCl)_2$ (0.44 mL, 0.88 mmol, 2.0 M in CH_2Cl_2, 2.5 equiv) in CH_2Cl_2 (4 mL) was added DMSO (0.14 mL, 137 mg, 1.75 mmol, 5.0 equiv). The resulting solution was stirred for 5 min, and then added to a suspension of resin bound monohydroxy pyrrolinone **25** (575 mg, *ca*. 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) via cotton wrapped cannula at -78 °C. High vacuum was attached to the flask containing the resin to facilitate the addition process. The suspension was stirred for another 20 min at -78 °C and then DBU (0.39 mL, 399 mg, 2.62 mmol, 7.5 equiv) was added via syringe. The reaction was warmed to rt, stirred for 20 min, cooled back to 0 °C, and quenched by addition of water (5 mL). The resin was then filtered, washed successively with H_2O (3 x 15 mL), H_2O/THF (1:1, 2 x 30 mL), DMSO (3 x 15 mL), THF (2 x 30 mL), Et_2O (2 x 30 mL), and dried under high vacuum to afford **14** (560 mg).

Preparation of resin bound bispyrrolinone amine. Typical procedure for the Teoc deprotection with CsF/TBAF. To a suspension of resin bound bispyrrolinone **15** (110 mg, *ca*. 0.06 mmol, 1.0 equiv) in anhydrous DMF (3.5 mL) was added CsF (46 mg, 0.31 mmol, 5.0 equiv). The reaction was shaken for 12 h, after which the resin was filtered, washed successively with THF/H_2O (1:1, 3 x 10 mL), DMSO (3 x 10 mL), THF (3 x 10 mL), Et_2O (3 x 10 mL) and dried under high vacuum.

To this resin was added THF (4 mL), followed by *n*-Bu_4NF (0.31 mL, 0.31 mmol, 1.0 M in THF, 5.0 equiv). The reaction mixture was shaken for 4 h, after which the resin was filtered, washed successively with THF/H_2O (1:1, 3 x 20 mL), DMSO (3 x 15 mL), THF (3 x 20 mL), Et_2O (3 x 20 mL) and dried under high vacuum to afford bispyrrolinone amine (98 mg).

Synthesis of trispyrrolinone (-)-16. Following the procedure described above for (-)-**7**, condensation of resin bound bispyrrolinone amine (91 mg, *ca*. 0.055 mmol) with hydrocinnamaldehyde followed by

cyclization with KHMDS afforded (-)-**16** (4.2 mg, 13.4%) as a yellow solid after flash chromatography (EtOAc/hexanes, 50:50): mp 90-95 °C dec; $[\alpha]_D^{23}$ -164.5° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3448, 1522, 1424 cm-^{1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, 1H, *J* = 4.1 Hz), 8.16 (d, 1H, *J* = 4.2 Hz), 7.58 (d, 1H, *J* = 3.6 Hz), 7.38 (d, 1H, *J* = 3.9 Hz), 7.23-7.19 (m, 2H), 7.16-7.08 (m, 4 H), 5.26 (d, 1H, *J* = 3.9 Hz), 4.95 (t, 1H, *J* = 7.7 Hz), 3.47 (s, 2H), 2.31 (dd, 1H, *J* = 7.6, 14.1 Hz), 2.22 (dd, 1H, *J* = 7.0, 14.5 Hz), 1.82-1.75 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.65-1.38 (m, 7H), 0.82 (d, 3H, *J* = 6.7 Hz), 0.81 (d, 3H, *J* = 6.5 Hz), 0.80 (d, 3H, *J* = 6.8 Hz), 0.79 (d, 3H, *J* = 6.6 Hz), 0.72 (d, 3H, *J* = 6.4 Hz), 0.70 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.43, 203.16, 202.27, 162.51, 161.64, 159.80, 140.83, 136.05, 128.46, 128.31,125.83, 116.97, 112.45, 110.03, 108.65, 71.37, 68.68, 67.90, 47.98, 47.47, 44.78, 36.19, 28.46, 25.89, 24.83, 24.61, 24.52, 24.47, 24.36, 24.31, 23.81, 23.66, 23.40, 18.09; high-resolution mass spectrum (ES, Na^+) *m/z* 594.3681 [$(M + Na)^+$], calcd for $C_{36}H_{49}N_3O_3Na$ 594.3672.

Anal. Calcd for $C_{36}H_{49}N_3O_3$: C, 75.62; H, 8.64. Found: C, 75.42; H, 8.34.

Synthesis of tetrapyrrolinone (-)-21. Following the procedure described above for (-)-**7**, condensation of resin bound trispyrrolinone amine (282 mg, *ca*. 0.157 mmol) with hydrocinnamaldehyde followed by cyclization with KHMDS afforded (-)-**21** (2.8 mg, 2.5%) as a yellow solid after flash chromatography (EtOAc/hexanes, 50:50), along with (-)-**16** (2.6 mg, 2.9%); tetrapyrrolinone (-)-**21**: mp 90-92 °C dec; $[\alpha]_D^{23}$ -386.4° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3450, 1644, 1580, 1454 cm-^{1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, 1H, *J* = 4.1 Hz), 8.19 (d, 1H, *J* = 4.1 Hz), 8.18 (d, 1H, *J* = 4.2 Hz), 7.59 (d, 1H, *J* = 3.5 Hz), 7.45-7.42 (m, 2H), 7.24-7.21 (m, 2H), 7.19-7.13 (m, 4 H), 5.30 (d, 1H, *J* = 4.0 Hz), 4.96 (t, 1H, *J* = 7.6 Hz), 3.49 (s, 2H), 2.33 (dd, 1H, *J* = 7.8, 14.6 Hz), 2.24 (dd, 1H, *J* = 7.2, 14.6 Hz), 1.83-1.71 (m, 4H), 1.67 (s, 3H), 1.65-1.40 (m, 8H), 1.60 (s, 3H), 0.85-0.80 (series of doublet, 12H), 0.78 (d, 3H, *J* = 6.7 Hz), 0.76 (d, 3H, *J* = 6.2 Hz), 0.74 (d, 3H, *J* = 6.6 Hz), 0.71 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.35, 203.18, 202.37, 202.20, 162.51, 161.66, 161.03, 159.88, 140.82, 136.04, 128.45, 128.30, 125.82, 116.91, 112.26, 109.74, 108.68, 108.29, 71.38, 68.76, 68.47, 67.89, 48.03, 47.65, 47.56, 44.76, 36.17, 28.47, 25.88, 24.80, 24.64, 24.61, 24.46, 24.42, 24.41, 24.33, 24.31, 23.83, 23.61, 23.56, 23.52, 18.09; high-resolution mass spectrum (ES, Na^+) *m/z* 709.4678 [$(M + H)^+$], calcd for $C_{44}H_{61}N_4O_4$ 709.4693.