Practical Synthesis of Polyamine Succinamides and Branched Polyamines

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(N¹,N⁴,N⁸-Tri-tert-butoxycarbonyl)-1,11-diamino-4,8-diazaundecane 7

A solution of norspermine (thermine) 1 (2.00 g, 10.6 mmol) in methanol (150 mL), at -78 °C under nitrogen, was treated with ethyl trifluoroacetate (1.51 g, 10.6 mmol, 1 equiv.) dropwise over 15 min. Stirring was continued for a further 45 min, then the temperature was increased to 20 °C for 18 h to afford the mono-trifluoroacetamide 3. Without purification, the remaining amino functional groups were protected using di-tert-butyldicarbonate (6.95 g, 31.8 mmol, 3.0 equiv.) in methanol (20 ml) at 0 °C over 10 min. The reaction was then warmed to 20 °C and stirred for a further 18 h to afford the fully protected polyamine 5. The trifluoroacetate protecting group was then removed by increasing the pH of the solution to above 11 with conc. aq. ammonia (32%) and then stirring at 20 °C for 18 h. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography with DCM in MeOH (9.5:0.5 v/v). After combining fractions and concentrating them, the desired product 7 was obtained as a colourless oil (2.50 g, 48%). TLC analysis showed one spot (Rf = 0.5, DCM: MeOH: aq. ammonia (32%), 70:10:1 v/v/v). HRMS: Found 489.3641 (m/z), C24H49N4O6 requires 489.3573 (m/z) [M + H]+; IR (film); 1689 (C=O) cm⁻¹; ¹H NMR, 500 MHz (CDCl3): 1.37-1.51 (m, 27H, 9 x CH₃ Boc), 1.66-1.78 (m, 4H, 2-CH₂, 6-CH₂, overlapping), 1.88-193 (m, 2H, 10-CH₂), 2.91-2.98 (t, J = 6.4 Hz, 2H, 11-CH₂), 3.05-3.38 (m, 10H, 1-CH₂, 3-CH₂, 5-CH₂, 7-CH₂, 9-CH₂), 36.5 (11-CH₂), 40.6, 40.9, 46.1, 46.4 (1-CH₂, 3-CH₂, 5-CH₂, 7-CH₂, 9-CH₂), 79.9-80.8 (3 x Cq Boc), 156.5-158.0 (3 x C=O Boc).

(N¹,N⁴,N⁸-Tri-tert-butoxycarbonyl)-1,12-diamino-4,9-diazadodecane 8

A solution of spermine 2 (0.50 g, 2.47 mmol) in methanol (100 ml), at -78 °C under nitrogen, was treated with ethyl trifluoroacetate (0.35 g, 2.47 mmol, 1 equiv.). The ethyl trifluoroacetate was added dropwise over 20 min. Stirring was continued for a further 30 min, then the temperature was increased to 20 °C to afford predominantly the mono-trifluoroacetamide 4. Without purification, the remaining amino functional groups were protected using di-tert-butyldicarbonate (1.61 g, 7.41 mmol, 3.0 equiv.) in methanol (15 ml) over 10 min. The reaction was then warmed to 20 °C and stirred for a further 18 h.
to afford the fully protected polyamine 6. The trifluoroacetate protecting group was then removed by increasing the pH of the solution to above 11 with conc. aq. ammonia (32%) and then stirring at 20 °C for 18 h. The solution was concentrated under reduced pressure. The column chromatography was elution with DCM in MeOH (9.5:0.5 v/v). After combining fractions and concentrating them, the desired product 8 was obtained as a colourless oil (0.57 g, 46%). TLC analysis showed one spot (Rf = 0.6, DCM:MeOH: aq. ammonia (32%), 50:10:1 v/v/v). HRMS: Found 503.3728 (m/z), C25H51N4O6 requires 503.3730 (m/z) [M + H]+; IR (film); 1692 (C=O) cm⁻¹; 1H NMR, 500 MHz (CDCl3): 1.41-1.53 (m, 31H, 9 x CH₃Boc, 6-CH₂, 7-CH₂, overlapping), 1.60-1.65 (m, 4H, 2-CH₂, 11-CH₂), 2.70 (t, J = 6.7 Hz, 2H, 12-CH₂), 3.04-3.29 (m, 10H, 1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, overlapping); 13C NMR, 125.77 MHz (CDCl3): 25.5, 25.8 (6-CH₂, 7-CH₂), 28.4, 29.0, 34.0 (9 x CH₃Boc, 2-CH₂, 11-CH₂, overlapping), 37.3 (12-CH₂), 42.0, 42.2, 43.9, 44.1 (1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, overlapping), 79.2-81.4 (3 x Cq Boc), 156.1-157.9 (3 x C=O Boc).

Synthesis of compound 9

A solution of the tri-Boc protected norspermine (thermine) 7 (0.35 g, 0.71 mmol) in anhydrous pyridine (5 mL) under nitrogen was treated with succinic anhydride (0.07 g, 0.71 mmol, 1 equiv.) at 20 °C. The solution was stirred for a further 18 h. The solution was then concentrated in vacuo, and the crude material was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The desired product 9 was obtained as a colourless oil (0.31 g, 75%). TLC analysis showed one spot (Rf = 0.3 (EtOAc: ethanol: aq. ammonia (32%); 7:2:1 v/v/v). HRMS: Found 587.3730 (m/z), C28H51N4O9 requires 587.3734 (m/z) [M - H]-; IR (film); 3746-3074 (COOH) and 1629 (C=O), cm⁻¹; 1H NMR, 500 MHz (CD3OD): 1.42-1.48 (m, 27H, 9 x CH₃Boc), 1.64-1.80 (m, 6H, 2-CH₂, 6-CH₂, 10-CH₂, overlapping), 2.51 (t, J = 7.0 Hz, 2H, CH₂), 2.68 (t, J = 7.0 Hz, 2H, CH₂), 3.03-3.24 (m, 12H, 1-CH₂, 3-CH₂, 5-CH₂, 7-CH₂, 9-CH₂, 11-CH₂, overlapping); 13C NMR, 125.77 MHz (CD3OD): 25.5, 25.8 (6-CH₂, 7-CH₂), 28.4, 29.0, 34.0 (9 x CH₃Boc, 2-CH₂, 11-CH₂, overlapping), 37.3 (12-CH₂), 42.0, 42.2, 43.9, 44.1 (1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, overlapping), 79.2-80.9 (3 x Cq Boc), 155.2-157.4 (3 x C=O Boc), 171.2 (CONH), 173.9 (COOH).
**Synthesis of compound 10**

A solution of the tri-Boc protected spermine 8 (0.61 g, 1.21 mmol) in anhydrous pyridine (5 mL) under nitrogen was treated with succinic anhydride (0.12 g, 1.21 mmol, 1 equiv.) at 20 °C. The solution was stirred for a further 18 h. The solution was then concentrated in vacuo. The crude material was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The desired product 10 was obtained as a colourless oil (0.63 g, 86%). TLC analysis showed one spot (Rₛ = 0.4 (EtOAc: ethanol: aq. ammonia (32%); 7:2:1 v/v/v). HRMS: Found 601.3867 (m/z), C₂₉H₅₃N₄O₉ requires 601.3860 (m/z) [M - H]⁻; IR (film); 2948-3536 (COOH) and 1686 (C=O) cm⁻¹; ¹H NMR, 500 MHz (CD₃OD): 1.41-1.49 (m, 27H, 9 x CH₃Boc) 1.48-1.53 (m, 4H, 6-CH₂, 7-CH₂), 1.64-1.74 (m, 4H, 2-CH₂, 11-CH₂), 2.45 (t, J = 7.0 Hz, 2H, CH₂), 2.58 (t, J = 7.0 Hz, 2H, CH₂), 3.03-3.24 (m, 12H, 1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, 12-CH₂, overlapping); ¹³C NMR, 125.77 MHz (CD₃OD): 25.5, 26.8 (6-CH₂, 7-CH₂), 27.5 (9 x CH₃ Boc), 26.9 (2-CH₂, 10-CH₂), 28.8 (CH₂), 30.2 (CH₂), 36.3, 36.7, 39.9, 44.1 (1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, 12-CH₂, overlapping), 79.5-81.0 (3 x Cq Boc), 156.1-157.5 (3 x C=O Boc), 173.4 (CONH), 174.8 (COOH).

**Synthesis of compound 11**

A solution of 9 (0.40 g, 0.67 mmol), HBTu (0.25 g, 0.67 mmol, 1 equiv.), and TEA (0.06 g, 0.67 mmol, 1 equiv.) in anhydrous DMF (10 mL) was treated with 7 (0.33 g, 0.67 mmol, 1 equiv.) in anhydrous DMF (3 mL) under nitrogen at 20 °C. The solution was stirred for a further 18 h. The solution was then concentrated in vacuo, and the crude material was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, concentrated in vacuo and purified over silica gel, (DCM: methanol; 9.5:0.5 to 9:1 v/v). After combining fractions and concentrating them, the desired product 11 was obtained as a pale yellow oil (0.47 g, 66%). TLC analysis showed one spot (Rₛ = 0.5 (DCM: methanol, 9:1 v/v). HRMS: Found 1059.7202 (m/z), C₅₂H₉₅N₈O₁₄ requires 1059.7224 (m/z) [M + H]⁺; IR (Film); 1693 (C=O) cm⁻¹; ¹H NMR, 500 MHz (CDCl₃): 1.40-1.48 (m, 54H, 18 x CH₃ Boc), 1.60-1.79 (m, 12H, 2-CH₂, 6-CH₂, 10-CH₂, overlapping), 2.52 (s, 4H, 14-CH₂), 3.06-3.35 (m, 24H, 1-CH₂, 3-CH₂, 5-CH₂, 7-CH₂, 9-CH₂, 11-CH₂); ¹³C NMR, 125.77 MHz (CDCl₃):
27.4, 28.3 (18 x CH₃ Boc, 2-CH₂, 6-CH₂, 10-CH₂, overlapping), 31.8 (14-CH₂), 35.9, 37.5, 43.7, 44.8 (1-CH₂, 3-CH₂, 5-CH₂, 7-CH₂, 9-CH₂, 11-CH₂), 79.3-79.8 (6 x Cq Boc), 155.3-157.7 (6 x C=O Boc), 172.6 (2 x NHCO).

**Synthesis of compound 12**

A solution of 10 (0.35 g, 0.58 mmol), HBTu (0.21 g, 0.58 mmol, 1 equiv.), and TEA (0.05 g, 0.58 mmol, 1 equiv.) in anhydrous DMF (10 mL) was treated with 8 (0.29 g, 0.58 mmol, 1 equiv.) in anhydrous DMF (3 mL) under nitrogen at 20 °C. The solution was stirred for a further 18 h. The solution was then concentrated in vacuo, and the crude material was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, concentrated in vacuo and purified over silica gel, (DCM: methanol; 9.5:0.5 to 9:1 v/v). After combining fractions and concentrating them, the desired product 12 was obtained as a pale yellow oil (0.37 g, 58%). TLC analysis showed one spot (Rₜ = 0.5 (DCM: methanol, 9: 1 v/v)). HRMS: Found 1087.7503 (m/z), Cₕ₄H₁ₐ₃Nₐ₈O₁₄ requires 1087.7516 (m/z) [M + H]+; IR (Film); 1673 (C=O) cm⁻¹; ¹H NMR, 500 MHz (CDCl₃): 1.40-1.52 (m, 62H, 18 x CH₃ Boc, 6-CH₂, 7-CH₂, overlapping), 1.61-1.71 (m, 8H, 2-CH₂, 11-CH₂, overlapping), 2.52 (s, 4H, 15-CH₂), 3.10-3.30 (m, 24H, 1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, 12-CH₂, overlapping); ¹³C NMR, 125.77 MHz (CDCl₃): 25.7 (6-CH₂, 7-CH₂), 28.8 (18 x CH₃ Boc, 2-CH₂, 11-CH₂, overlapping), 31.6 (15-CH₂), 36.4, 37.9, 43.4, 46.6 (1-CH₂, 3-CH₂, 5-CH₂, 8-CH₂, 10-CH₂, 12-CH₂, overlapping), 79.7 (6 x Cq Boc), 155.7-156.9 (6 x C=O Boc), 173.1 (2 x NHCO).

**Synthesis of compound 13**

A solution of 9 (0.30 g, 0.49 mmol), HBTu (0.18 g, 0.49 mmol, 1 equiv.), and TEA (0.04 g, 0.49 mmol, 1 equiv.) in anhydrous DMF (10 mL) was treated with 8 (0.24 g, 0.49 mmol, 1 equiv.) in anhydrous DMF (3 mL) under nitrogen at 20 °C. The solution was stirred for a further 18 h. The solution was then concentrated in vacuo, and the crude material was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, concentrated in vacuo and purified over silica gel, (DCM: methanol; 9.5:0.5 to 9:1 v/v). After combining fractions and concentrating them, the desired product 13 was obtained as a pale yellow oil (0.22 g, 41%). TLC analysis showed
one spot ($R_f = 0.5$ (DCM: methanol, 9:1 v/v)). HRMS: Found 1073.7359 (m/z), $C_{53}H_{101}N_{8}O_{14}$ requires 1073.7352 (m/z) [M + H]$^+$; IR (Film); 1693 (C=O) cm$^{-1}$; $^1$H NMR, 500 MHz (CDCl$_3$): 1.39-1.54 (m, 58H, 18x CH$_3$ Boc, 23-CH$_2$, 24-CH$_2$, overlapping), 1.58-1.78 (m, 10H, 2-CH$_2$, 6-CH$_2$, 10-CH$_2$, 19-CH$_2$, 28-CH$_2$, overlapping), 2.53 (s, 4H, 14-CH$_2$, 15-CH$_2$), 3.06-3.33 (m, 24H, 1-CH$_2$, 3-CH$_2$, 5-CH$_2$, 7-CH$_2$, 9-CH$_2$, 11-CH$_2$, 18-CH$_2$, 20-CH$_2$, 22-CH$_2$, 25-CH$_2$, 27-CH$_2$, 29-CH$_2$, overlapping); $^{13}$C NMR, 125.77 MHz (CDCl$_3$): 25.6 (23-CH$_2$, 24-CH$_2$), 28.4, 27.6, 28.9 (18x CH$_3$ Boc, 2-CH$_2$, 6-CH$_2$, 10-CH$_2$, 19-CH$_2$, 28-CH$_2$, overlapping), 31.9 (14-CH$_2$, 15-CH$_2$), 35.9, 37.2, 37.6, 43.4, 44.9, 46.6 (1-CH$_2$, 3-CH$_2$, 5-CH$_2$, 7-CH$_2$, 9-CH$_2$, 11-CH$_2$, 18-CH$_2$, 20-CH$_2$, 22-CH$_2$, 25-CH$_2$, 27-CH$_2$, 29-CH$_2$), 78.8, 79.9 (6 x Cq Boc), 155.0, 156.0 (6 x C=O Boc), 172.36 (2 x NHCO).

**Synthesis of compound 14**

Compound 11 (0.24 g, 0.22 mmol) was deprotected according to general procedure Boc removal to yield the desired product 14 as a white solid (0.24 g, 99 %). HRMS: Found 459.4058 (m/z), $C_{22}H_{51}N_{8}O_{2}$ requires 459.4057 (m/z) [M + H]$^+$; IR (KBr disc); 1695 (C=O) cm$^{-1}$; $^1$H NMR, 500 MHz (D$_2$O): 1.84-1.93 (m, 4H, 10-CH$_2$), 2.05-2.15 (m, 8H, 2-CH$_2$, 6-CH$_2$), 2.53 (s, 4H, 2 x CH$_2$), 3.04-3.21 (m, 20H, 1-CH$_2$, 3-CH$_2$, 5-CH$_2$, 7-CH$_2$, 9-CH$_2$, overlapping), 3.27 (t, $J = 7.4$ Hz, 4H, 11-CH$_2$); $^{13}$C NMR, 125.77 MHz (D$_2$O): 22.7, 23.7 (2-CH$_2$, 6-CH$_2$), 25.5 (10-CH$_2$), 30.7 (14-CH$_2$), 36.0 (11-CH$_2$), 36.4, 44.3, 44.5, 44.6, 45.2 (1-CH$_2$, 3-CH$_2$, 5-CH$_2$, 7-CH$_2$, 9-CH$_2$), 116.1 (q, $^1J = 291.3$ Hz, CF$_3$), 162.9 (q, $^2J = 37.6$ Hz, CO-CF$_3$), 175.3 (2 x NHCO).

**Synthesis of compound 15**

Compound 12 (0.18 g, 0.17 mmol) was deprotected according to general procedure Boc removal to yield the desired product 15 as a white solid (0.18 g, 99 %). HRMS: Found 487.4372 (m/z), $C_{24}H_{55}N_{8}O_{2}$ requires 487.4370 (m/z) [M + H]$^+$; IR (KBr disc); 1688 (C=O) cm$^{-1}$; $^1$H NMR, 500 MHz (D$_2$O): 1.75-1.80 (m, 6-CH$_2$, 7-CH$_2$), 1.86-1.92 (m, 4H, 11-CH$_2$), 2.04-2.13 (m, 4H, 2-CH$_2$), 2.53 (s, 4H, 15-CH$_2$), 3.02-3.20 (m, 20H, 1-CH$_2$, 3-CH$_2$, 5-CH$_2$, 8-CH$_2$, 10-CH$_2$), 3.26 (t, $J = 7.0$ Hz, 4H, 12-CH$_2$); $^{13}$C NMR, 125.77 MHz (D$_2$O): 22.7 (6-CH$_2$, 7-CH$_2$), 23.7 (2-CH$_2$), 25.5 (11-CH$_2$), 30.7 (15-
CH\(_2\)), 36.0 (12-CH\(_2\)), 36.4, 44.4, 45.1, 46.7, 46.9 (1-CH\(_2\), 3-CH\(_2\), 5-CH\(_2\), 8-CH\(_2\), 10-CH\(_2\)), 116.3 (q, \(^1J = 292.0\) Hz, CF\(_3\)), 161.7 (q, \(^2J = 36.6\) Hz, CO-CF\(_3\)), 175.3 (2 x NHCO).

**Synthesis of compound 16**

Compound 13 (0.22 g, 0.20 mmol) was deprotected according to general procedure Boc removal to yield the desired product 16 as a white solid (0.22 g, 99%). HRMS: Found 473.4213 (m/z), C\(_{23}\)H\(_{53}\)N\(_8\)O\(_2\) requires 473.4212 (m/z) [M + H]\(^+\); IR (KBr disc); 1683 (C=O) cm\(^{-1}\); \(^1\)H NMR, 500 MHz (D\(_2\)O): 1.71-1.78 (m, 4H, 23-CH\(_2\), 24-CH\(_2\)), 1.83-1.91 (m, 4H, 10-CH\(_2\), 19-CH\(_2\)), 2.02-2.14 (m, 6H, 2-CH\(_2\), 6-CH\(_2\), 28-CH\(_2\)), 2.53 (s, 4H, 14-CH\(_2\), 15-CH\(_2\)), 2.85-3.13 (m, 20H, 1-CH\(_2\), 3-CH\(_2\), 5-CH\(_2\), 7-CH\(_2\), 9-CH\(_2\), 20-CH\(_2\), 22-CH\(_2\), 25-CH\(_2\), 27-CH\(_2\), 29-CH\(_2\)), 3.27 (t, \(^1J = 7.4\) Hz, 4H, 11-CH\(_2\), 18-CH\(_2\)), \(^{13}\)C NMR, 125.77 MHz (D\(_2\)O): 22.6, 22.7 (23-CH\(_2\), 24-CH\(_2\)), 23.5 (2-CH\(_2\), 6-CH\(_2\), 28-CH\(_2\)), 25.5 (10-CH\(_2\), 19-CH\(_2\)), 30.7 (14-CH\(_2\), 15-CH\(_2\)), 36.0 (11-CH\(_2\), 18-CH\(_2\)), 36.4, 44.3, 44.4, 44.5, 44.6, 45.0, 45.2, 46.8, 46.9 (1-CH\(_2\), 3-CH\(_2\), 5-CH\(_2\), 7-CH\(_2\), 9-CH\(_2\), 20-CH\(_2\), 22-CH\(_2\), 25-CH\(_2\), 27-CH\(_2\), 29-CH\(_2\)), 116.5 (q, \(^1J = 291.0\) Hz, CF\(_3\)), 163.1 (q, \(^2J = 38.0\) Hz, CO-CF\(_3\)), 175.3 (2 x NHCO).

**Synthesis of compound 18**

To a solution of norspermidine 17 (0.50 g, 3.81 mmol) in ethanol (10 mL) was treated with acrylonitrile (0.60 g, 11.4 mmol, 3 equiv.) at 25 °C. The solution was stirred for a further 48 h. The solution was then concentrated in vacuo, and the crude material was purified over silica gel, (DCM: methanol; 9.9:0.1 to 9:1 v/v). After combining fractions and concentrating them, the desired product 18 was obtained as a yellow oil (0.331 g, 30%). TLC analysis showed one spot (R\(_f\) = 0.4 (DCM: methanol, 9:1 v/v). HRMS: Found 291.2342 (m/z), C\(_{15}\)H\(_{27}\)N\(_6\) requires 291.2292 (m/z) [M + H]\(^+\); IR (Film): 2250 (CN) cm\(^{-1}\); \(^1\)H NMR, 500 MHz (CDCl\(_3\)): 1.62-1.69 (m, 4H, 6-CH\(_2\)), 2.47-2.57 (m, 10H, 2 x 2-CH\(_2\), 2 x 7-CH\(_2\), 10-CH\(_2\)), 2.68-2.76 (m, 6H, 2 x 5-CH\(_2\), 9-CH\(_2\)), 2.92 (t, \(J = 6.5\) Hz, 4H, 2 x 3-CH\(_2\)); \(^{13}\)C NMR, 125.77 MHz (CDCl\(_3\)): 16.7 (10-CH\(_2\)), 18.7 (2 x 2-CH\(_2\)), 27.4 (2 x 6-CH\(_2\)), 45.1 (2 x 3-CH\(_2\)), 47.2 (2 x 5-CH\(_2\)), 49.5 (9-CH\(_2\)), 51.7 (2 x 7-CH\(_2\)), 118.9 (1-CN), 119.2 (2 x 11-CN).
Synthesis of compound 19

To a solution of norspermidine 17 (0.50 g, 3.81 mmol) in ethanol (10 mL) was treated with acrylonitrile (1.01 g, 19.0 mmol, 5 equiv.) at 20°C. The solution was stirred for a further 72 h. The solution was then concentrated in vacuo, and the crude material was purified over silica gel, (DCM: methanol; 10:0 to 9:1 v/v). After combining fractions and concentrating them, the desired product 19 was obtained as a yellow oil (0.60 g, 40%). TLC analysis showed one spot ($R_f = 0.6$ (DCM: methanol, 9:1 v/v)). HRMS: Found 397.2761 ($m/z$). C$_{21}$H$_{33}$N$_8$ requires 397.2750 ($m/z$) [M + H]$^+$; IR (Film) 2254 (CN) cm$^{-1}$; $^1$H NMR, 500 MHz (CDCl$_3$): 1.60-1.70 (m, 4H, 2x CH$_2$), 2.51 (t, $J = 6.9$ Hz, 10H, 4 x 2-CH$_2$, 10-CH$_2$), 2.56 (t, $J = 6.9$ Hz, 4H, 2 x 7-CH$_2$), 2.63 (t, $J = 6.9$ Hz, 4H, 2 x 5-CH$_2$), 2.74 (t, $J = 6.9$ Hz, 2H, 9-CH$_2$), 2.86 (t, $J = 6.9$ Hz, 8H, 4 x 3-CH$_2$); $^{13}$C NMR, 125.77 MHz (CDCl$_3$): 16.8 (10-CH$_2$), 16.9 (4x 2-CH$_2$), 25.3 (2x 6-CH$_2$), 49.2 (9-CH$_2$), 49.5 (4x 3-CH$_2$), 51.1 (2 x 5-CH$_2$), 51.2 (2x 7-CH$_2$), 118.8 (4x 1-CN), 119.5 (11-CN).

Synthesis of compound 22

To a solution of 18 (0.33 g, 1.14 mmol) and NaOH (0.13 g, 3.42 mmol, 3 equiv.) in ethanol (15 mL). Raney nickel (~ 0.5 g) was added to the mixture. The atmosphere over the solution was evacuated and replaced with N$_2$ gas three times, and then replaced with H$_2$. The solution was stirred under H$_2$ for a further 18 h at 20°C. The solution mixture was then filtered through Celite with ethanol. Without further purification, (Boc)$_2$O (2.48 g, 11.4 mmol, 10 equiv.) was added to the ethanolic solution. The solution was stirred for a further 2 h at 20°C. The solution was then concentrated in vacuo, and the crude material was extracted with chloroform (5 x 15 mL) in order to remove the NaOH. The combined organic extracts were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. The desired product 20 was obtained as a pale yellow oil. After combining fractions and concentrating them, the desired product 20, without further analysis, was deprotected according to general procedure Boc removal to yield the desired product 22 as a pale yellow oil (0.44 g, 40 %). HRMS: Found 303.3158 ($m/z$). C$_{15}$H$_{39}$N$_6$ requires 303.3098 ($m/z$) [M + H]$^+$; $^1$H NMR, 500 MHz (D$_2$O): 1.76-1.96 (m, 10H, 2 x 2-CH$_2$, 2 x 6-CH$_2$, 10-CH$_2$), 2.81 (t, $J = 8.0$ Hz, 6H, 2 x 7-CH$_2$, 9-CH$_2$), 2.85-2.94 (m, 8H, 2 x 3-CH$_2$, 2 x 5-CH$_2$), 3.02-3.10 (m, 6H, 2 x 1-CH$_2$, 11-CH$_2$); $^{13}$C NMR, 125.77 MHz (D$_2$O): 20.2, 23.5 (2 x 2-...
CH₂, 2 x 6-CH₃, 10-CH₃), 35.9, 36.1 (2 x 7-CH₂, 9-CH₂), 44.1, 44.5 (2 x 3-CH₂, 2 x 5-CH₂), 49.5 (2 x 1-CH₂, 11-CH₂), 115.0 (q, 1^J = 293.0 Hz, CF₃), 162.2 (q, 2^J = 36.4 Hz, CO-CF₃).

**Synthesis of compound 23**

To a solution of 19 (0.60 g, 1.51 mmol) and NaOH (0.18 g, 4.54 mmol, 3 equiv.) in ethanol (15 mL) was added Raney nickel (~ 0.5 g). The atmosphere over the solution was evacuated and replaced with N₂ gas three times, and then replaced with H₂. The solution was stirred under H₂ for 18 h at 20°C. The mixture was then filtered through Celite with ethanol. Without further purification, (Boc)₂O (3.29 g, 15.1 mmol, 10 equiv.) was added to the ethanolic solution. The solution was stirred for a further 2 h at 20°C. The solution was then concentrated in vacuo, and the crude material was extracted with chloroform (5 x 15 mL) in order to remove the NaOH. The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The desired product 21 was obtained as a pale yellow oil. After combining fractions and concentrating them, the desired product 21, without further analysis, was deprotected according to general procedure Boc removal to yield the desired product 23 as a pale yellow oil (1.10 g, 55%). HRMS: Found 417.4357 (m/z), C₂₁H₅₃N₈ requires 417.4315 (m/z) [M + H]^+; ^1H NMR, 500 MHz (D₂O): 2.12-2.21 (m, 10H, 4 x 2-CH₂, 10-CH₂), 2.24-2.32 (m, 4H, 2 x 6-CH₂), 3.07-3.15 (m, 10H, 4 x 1-CH₂, 11-CH₂), 3.30-3.42 (m, 18H, 4 x 1-CH₂, 2 x 7-CH₂, 2 x 5-CH₂, 9-CH₂); ^13C NMR, 125.77 MHz (D₂O): 18.7 (2 x 6-CH₂), 21.4 (4 x 2-CH₂, 10-CH₂), 36.2 (4 x 1-CH₂, 11-CH₂), 49.9 (4 x 3-CH₂, 2 x 7-CH₂, 2 x 5-CH₂, 9-CH₂), 116.1 (q, 1^J = 290.5 Hz, CF₃), 163.0 (q, 2^J = 38.1 Hz, CO-CF₃).
Supplementary Figures

**Suppl Figure 1.** $^1$H-$^{13}$C HMBC NMR spectrum of compound 10 referenced to TMS in 99.8% CD$_3$OD at 25 °C.

**Suppl Figure 2.** The $^1$H NMR spectra of A 10 and B 12 referenced to TMS in 99.8% CD$_3$OD and CDCl$_3$, respectively, at 25 °C.
The $^{13}$C NMR spectrum of compound 14

The $^1$H-$^{13}$C HSQC NMR spectrum of compound 14
The $^1$H-$^{13}$C HMBC NMR spectrum of compound 14
The $^{13}$C NMR spectrum of compound 15

The $^1$H-$^{13}$C HSQC NMR spectrum of compound 15

The $^{13}$C NMR spectrum of compound 16
The $^1$H-$^{13}$C HSQC NMR spectrum of compound 16

The $^1$H-$^{13}$C HMBC NMR spectrum of compound 16
The $^1$H NMR spectrum of compound 18

The $^1$H-$^1$C HSQC NMR spectrum of compound 18
The $^1$H NMR spectrum of compound 19

The $^1$H-$^{13}$C HSQC NMR spectrum of compound 19
The $^1$H NMR spectrum of compound 22

The $^{13}$C NMR spectrum of compound 22
The $^1$H-$^1$C HSQC NMR spectrum of compound 22

The $^1$H NMR spectrum of compound 23
The $^{13}$C NMR spectrum of compound 23

The $^1$H-$^{13}$C HSQC NMR spectrum of compound 23