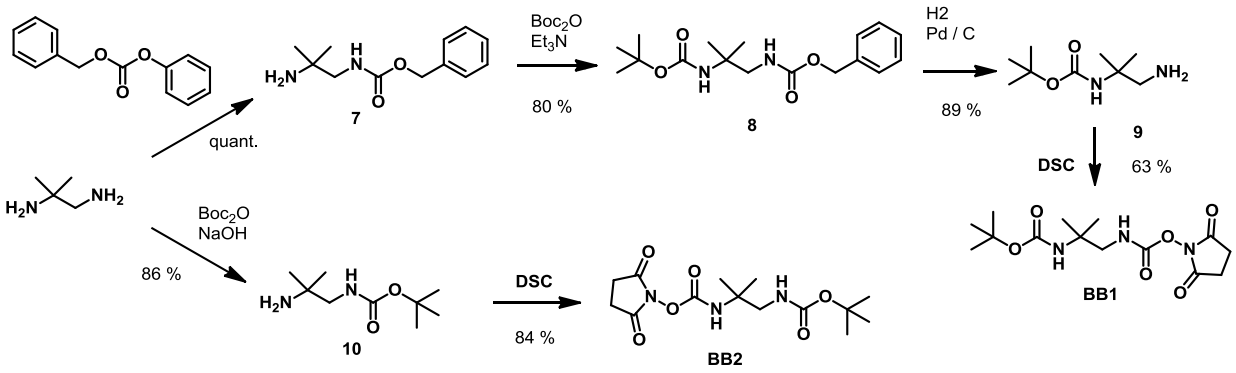
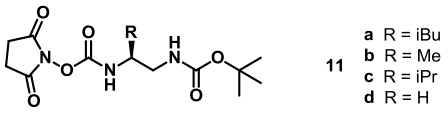
Supporting information

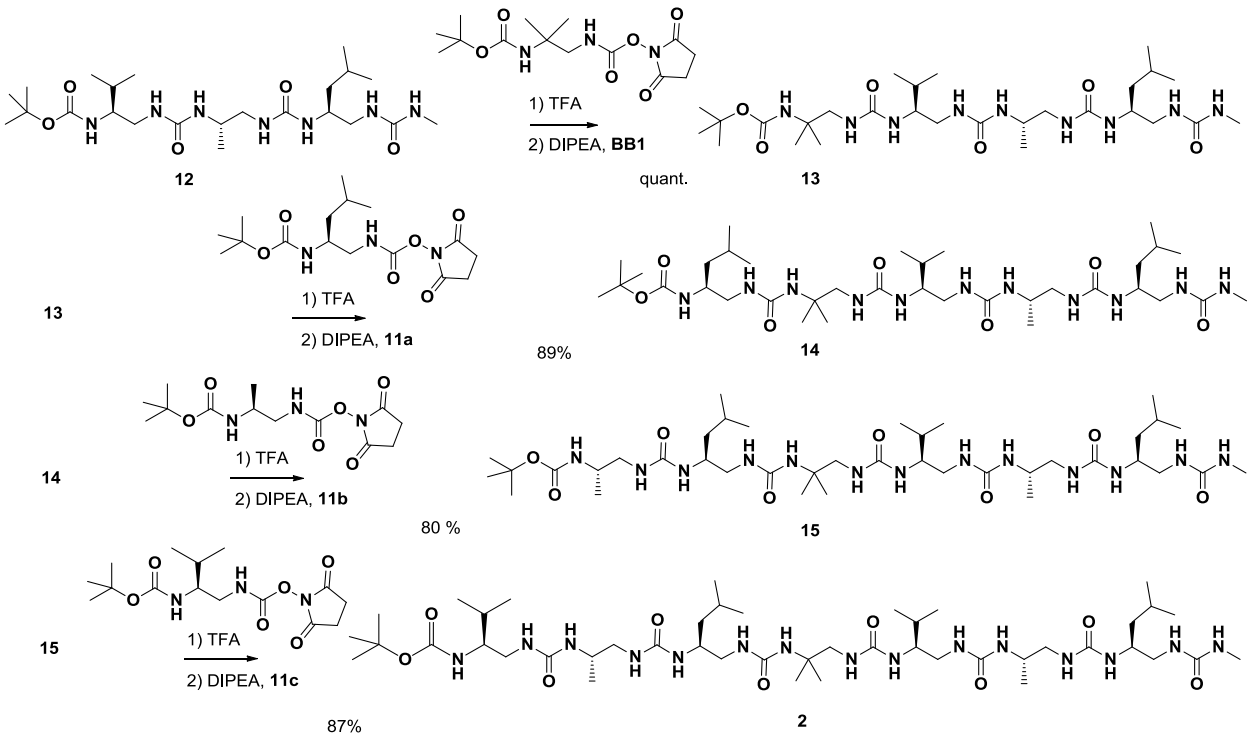
Synthesis of oligoureas



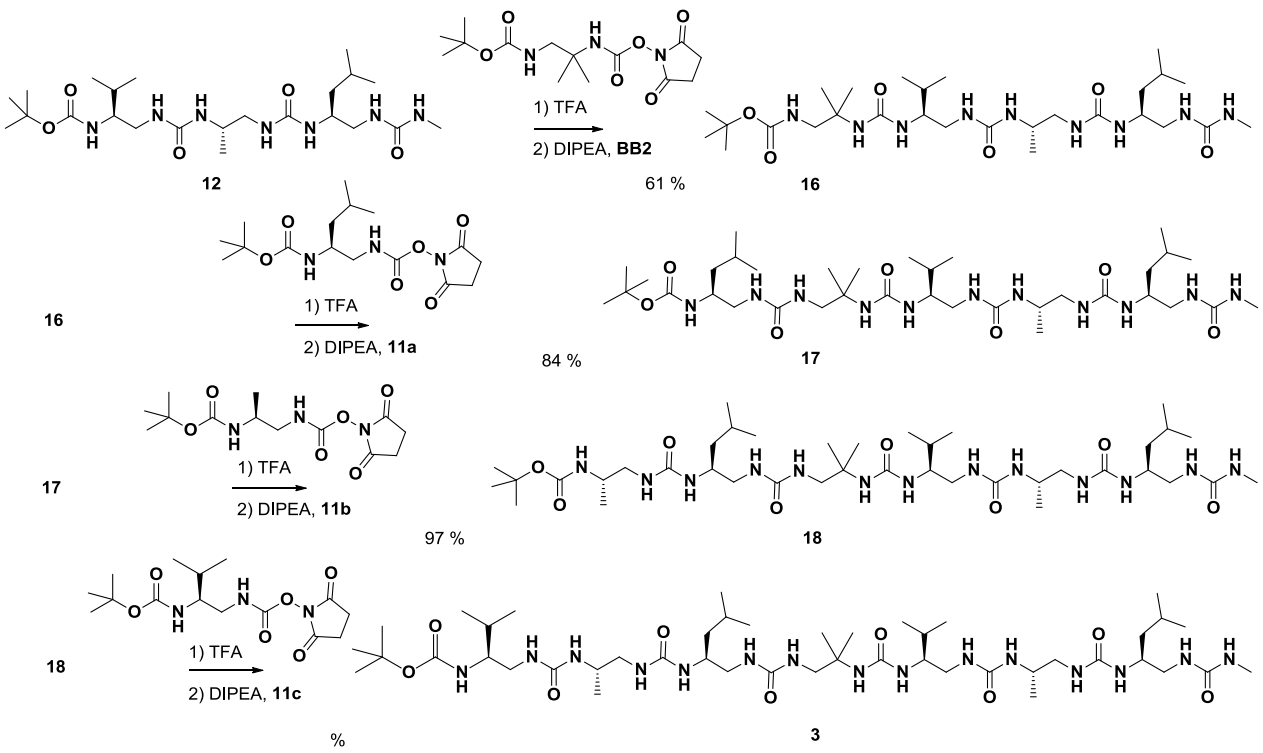
Scheme S1: Synthesis of activated monomers **BB1** and **BB2**



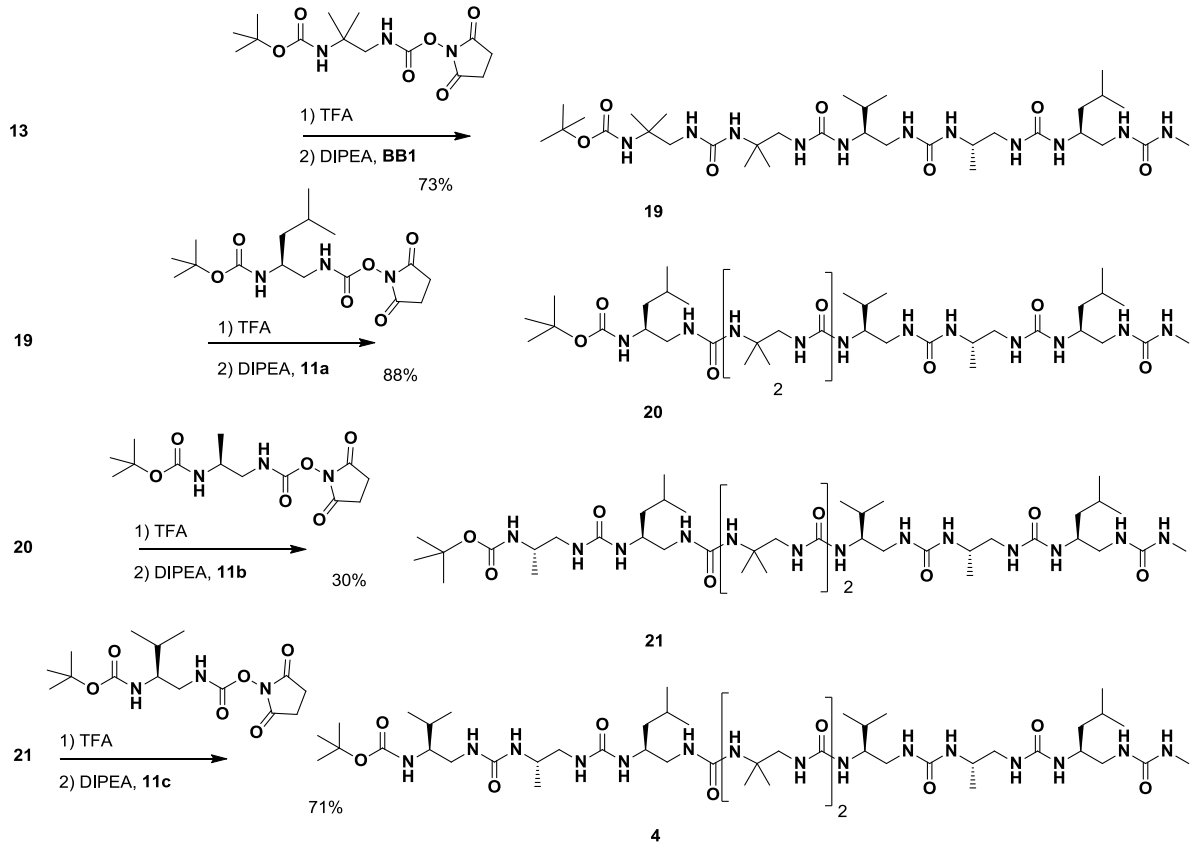
Scheme S2: Activated monomers **11a**, **11b, 11c** and **11d**



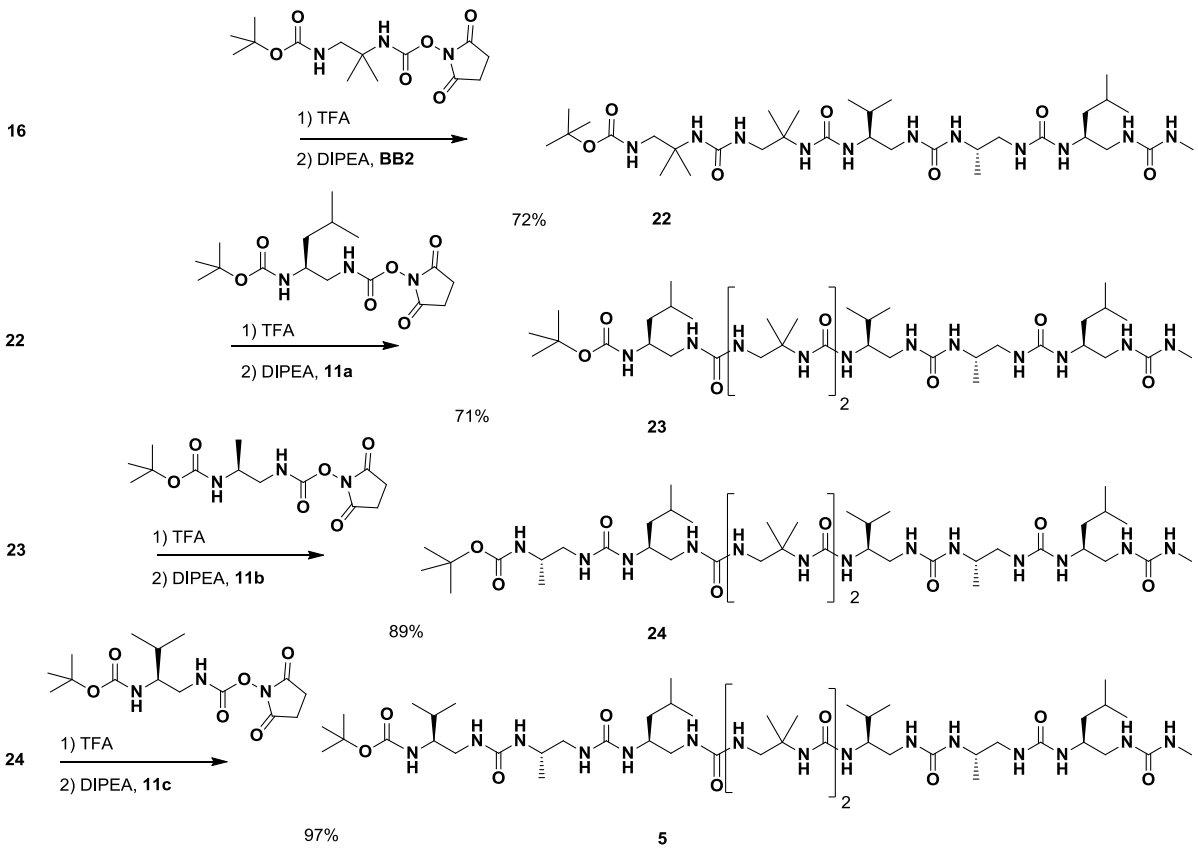
Scheme S3: Synthesis of oligomer **2**



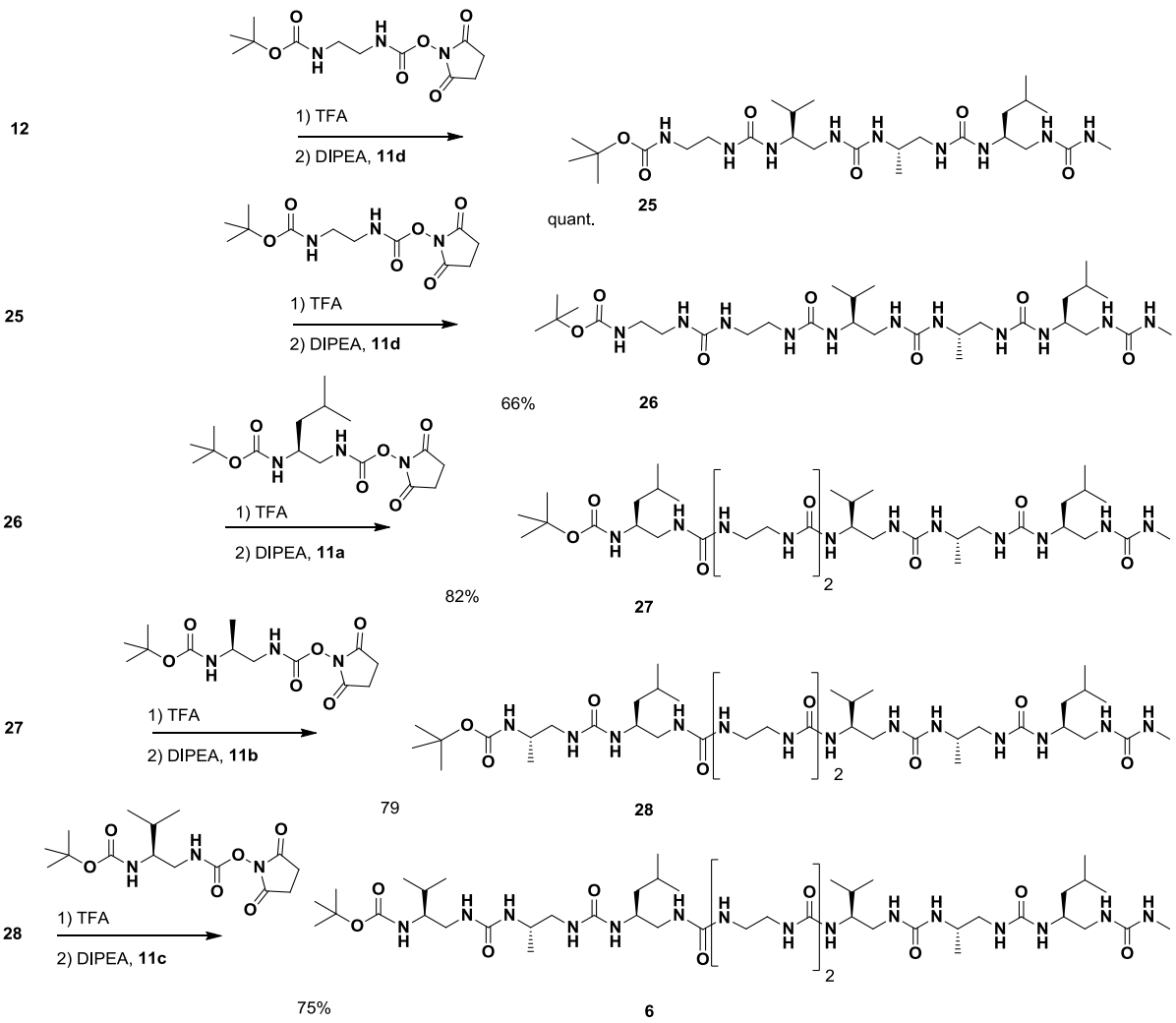
Scheme S4: Synthesis of oligomer **3**



Scheme S5: Synthesis of oligomer **4**



Scheme S6: Synthesis of oligomer **5**



Scheme S7: Synthesis of oligomer **6**

General. Thin layer chromatography (TLC) was performed on silica gel 60 F254 (Merk) with detection by UV light and charring with 1% w/w ninhydrin in ethanol followed by heating. Flash column chromatography was carried out on silica gel (40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance II NMR spectrometer (Bruker Biospin) with a vertical 7.05T narrow-bore/ultrashield magnet operating at 300 MHz for 1H observation and 75 MHz for 13C observation by means of a 5-mm direct BBO 1H/19F_XBB_H probe with Z gradient capabilities. Chemical shifts are reported in parts per million (ppm) relative to the 1H residual signal of the deuterated solvent used. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Coupling constants (*J*) are reported in hertz. ESI-MS analyses were carried out on a ThermoElectron LCQ Advantage spectrometer equipped with an ion trap mass analyzer and coupled with a ThermoElectron Surveyor HPLC system.

Compound **7**[1], activated monomers **11** (**a** R = *i*Bu; **b** R = Me; **c** R = *i*Pr; **d** R= H)[2] and oligomer **1** and **12**[3, 4] were prepared using a previously described procedure.

(2-Benzyloxycarbonylamino-1,1-dimethyl-ethyl)-carbamic acid *tert*-butyl ester, (8)

To a stirred solution of **7** (3 g, 13.5 mmol) in CH_2Cl_2 (25 mL), triethylamine (2.3 mL, 16.2 mmol) and di-*tert*-butyl dicarbonate (3.54 g, 16.2 mmol) were successively added and the reaction mixture was allowed to stir at room temperature overnight. CH_2Cl_2 was concentrated under reduced pressure and the resulting crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2-MeOH (v/v), 95:5). Compound **7** was obtained as a colorless oil (4.03 g, 92% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.25 (s, 6H), 1.42 (s, 9H), 3.40 (d, *J* = 6.4 Hz, 2H), 4.57 (br s, 1H), 5.11 (s, 2H), 5.36 (br s, 1H), 7.30-7.40 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 24.8, 28.1, 49.3, 53.0, 66.4, 78.8, 127.7, 128.1, 136.3, 154.6, 156.8 **ESI-MS** (MW 322.19): *m/z* 345.1 $[M + Na]^+$

(2-Amino-1,1-dimethyl-ethyl)-carbamic acid *tert*-butyl ester, (9)

To a stirred solution of **8** (3.88 g, 12.0 mmol) in EtOH (30 mL) at room temperature, 10% Pd/C (390 mg) was added and the reaction mixture was stirred under H_2 gas atmosphere for 20 h. The reaction mixture was then filtered over glass microfiber filter, the filtrate was concentrated under reduced pressure and dried under vacuum to afford amine **9** as a colorless oil (2.02 g, 89% yield), which was used for the next step without further purification. **^{1}H NMR**: (300 MHz, $CDCl_3$): δ = 1.24 (s, 6H), 1.42 (s, 9H), 1.53 (s, 2H), 2.74 (s, 2H), 4.79 (br

[1] M. Pittelkow, R. Lewinsky, J. B. Christensen, *Synthesis* **2002**, 2195-2202.
[2] G. Guichard, V. Semetey, C. Didierjean, A. Aubry, J.-P. Briand, M. Rodriguez, *J. Org. Chem.* **1999**, *64*, 8702.
[3] L.Fischer, P. Claudon, N. Pendem, E. Miclet, C. Didierjean, E. Ennifar, G. Guichard, *Angew. Chem. Int.Ed.* **2010**, *49*, 1067
[4] J.Fremaux, L. Fischer, T. Arbogast, B. Kauffmann, G. Guichard, *Angew. Chem. Int.Ed.* **2011**, *50*, 11382.

s, 1H). **^{13}C NMR**: (75 MHz, $CDCl_3$): δ = 24.6, 28.0, 49.6, 52.4, 78.6, 154.7 **ESI-MS** (Mw 188.15): m/z 188.9 $[M+H]^+$

(2-*tert*-Butoxycarbonylamino-2-methyl-propyl)-carbamic acid 2,5-dioxo-pyrrolidin-1-yl ester (BB1)

To a stirred solution of **9** (1.8 g, 9.6 mmol) in dry CH_2Cl_2 (30 mL), a solution of *N,N'*-disuccinimidyl carbonate (2.94 g, 11.5 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise and the reaction mixture was stirred at room temperature overnight. CH_2Cl_2 was removed under reduced pressure, the residue was dissolved in EtOAc (50 mL) and washed with an aqueous solution of 1M $KHSO_4$ (3 × 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum to afford compound **BB1** as a white solid (2.1 g, 67% yield). **^{1}H NMR:** (300 MHz, $CDCl_3$): δ = 1.27 (s, 6H), 1.43 (s, 9H), 2.81 (s, 4H), 3.46 (d, *J* = 6.1 Hz, 2H), 4.52 (br s, 1H), 6.50 (br s, 1H). **^{13}C NMR**: (75 MHz, $CDCl_3$): δ = 25.4, 25.6, 28.3, 50.3, 53.0, 79.9, 151.9, 155.2, 169.8 **HRMS** calcd. for $C_{14}H_{23}N_3O_6$ Na 352.1479 $[M+Na]^+$, found 352.1477, $[2M+Na]^+$, found 681.3060

(2-Amino-2-methyl-propyl)-carbamic acid *tert*-butyl ester, (10)

To a solution of 1,2-diamino-2-methylpropane (1 eq) and sodium hydroxide (0.8 eq) in dioxane/water (1:1 v/v) at 0°C was added a solution of di-*tert*-butyl dicarbonate (1 eq) in dioxane dropwise. The reaction was stirred at 0°C for 3.5 h and at room temperature for 2.5 h. The reaction was concentrated under reduced pressure then water added. The product was extracted into CH_2Cl_2, the organic layers combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. This afforded **6** as a white solid (77%).**^{1}H NMR**: (500 MHz, $CDCl_3$) δ = 4.95 (br s, 1H, NH), 3.00 (d, *J* = 6.3 Hz, 2H, CH_2N), 1.44 (s, 9H, Boc), 1.12 (br s, 2H, NH_2), 1.08 (s, 6H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 156.5, 79.1, 52.2, 50.1, 28.4, 28.2 **ESI-MS** (Mw 189.15): *m/z* 189.16 $[M + Na]^+$

(2-*tert*-Butoxycarbonylamino-1,1-dimethyl-ethyl)-carbamic acid 2,5-dioxo-pyrrolidin-1-yl ester, (BB2)

To a suspension of disuccinimidyl carbonate (1.2 eq) in CH_2Cl_2 was added **10** (1 eq). The reaction was stirred at room temperature overnight. A small quantity of white solid was removed by filtration. The organic phase was washed with aqueous 1M $KHSO_4$ solution and water, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was re-dissolved in CH_2Cl_2 and diethyl ether added. The solid precipitate formed was isolated by filtration and dried under vacuum to afford **BB2** as a white crystalline solid (56%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ= 6.23 (br s, 1H, NH), 4.98 (br s, 1H, NH), 3.26 (d, *J* = 6.8 Hz, 2H, CH_2N), 2.81 (s, 4H, CH_2), 1.46 (s, 9H, Boc), 1.35 (s, 6H, CH_3) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.96, 157.33, 149.72, 80.23, 77.25, 56.00, 49.37, 28.33, 25.49, 24.06. **ESI-MS** (Mw

329.16): *m/z* 347 $[M + Na]^+$ **HRMS** calcd. for $C_{14}H_{23}N_3O_6$ Na 352.1479 $[M+Na]^+$, found 352.1475, $[2M+Na]^+$, found 681.3057

General procedure for oligourea coupling.

Boc-protected oligourea (1.0 eq) was dissolved in TFA (3 ml / g) and stirred for 45 min. The reaction mixture was then concentrated under reduced pressure and coevaporated 3 times with cyclohexane. The crude product was then dissolved in CH_3CN (5 ml / g). DIPEA (3.0 eq) was then added and the mixture was cooled to 0°C prior to the dropwise addition of the desired carbamate, **BB1**, **BB2**, **11a**, **11b**, **11c** or **11d** dissolved in CH_3CN**.** The completion of reaction was controlled by TLC.

Boc-Aib^u-Val^u-Ala^u-Leu^u-NHMe, (13)

13 was prepared from **B**B1 (125 mg, 0.378 mmol) and **12** (200 mg, 0.398 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **13** as a white product. (>99%) **^{1}H NMR** : (300MHz, CD_3OH) δ = 6.32 (m, 1H, NH), 6.25 (m, 1H, NH),6.17-5.99 (m, 4H, NH), 5.98-5.79 (m, 3H, NH), 4.03-3.80 (m, 2H, CHN), 3.77-3.63 (m, 1H, CHN), 3.59-3.37 (m, 4H, CH_2N), 2.30-2.21 (m, 1H, CH_2N), 2.81-2.75 (m, 1H, CH_2N), 2.72 (d, J = 4.7 Hz, 1H, CH_3N), 2.60-2.48 (m, 1H, CH_2N), 1.77-1.62 (m,2H, CH), 1.45 (s, 9H, Boc), 1.35-1.28 (m, 2H, CH_2), 1.27-1.21 (m, 6H, CH_3), 1.06 (d, J = 6.8 Hz, 3H, CH_3), 0.97-0.89 (m, 12H, CH_3) **ESI-MS** (Mw 615.81): *m/z* 616.2 $[M+H]^+$, 638.3 $[M + Na]^+$, 1253.0 $[2M+Na]^+$

Boc-Leu^u-Aib^u-Val^u-Ala^u-Leu^u-NHMe, (14)

14 was prepared from **10a** (55 mg, 0.154 mmol) and **13** (100 mg, 0.162 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **14** as a white product. (116 mg, 89%) **^{1}H NMR** : (300MHz, CD_3CN) δ = 6.16 (m, 1H, NH), 5.98 (m, 1H, NH), 5.83 (m, 2H, NH), 5.65 (m, 1H, NH), 5.59 (m, 1H, NH), 5.52-5.38 (m, 4H, NH), 5.34 (m,1H,NH), 44.02-3.92 (m, 1H, CHN), 3.86-3.68 (m, 2H, CHN), 3.68-3.49 (m, 7H, CHN-CH_2N), 3.38-3.27 (1H, CH_2N), 2.64 (d, J = 4.7 Hz, 3H, CH_3N), 2.56-2.43 (m, 2H, CH_3N), 1.71-1.56 (m, 3H, CH), 1.45 (s, 9H, Boc), 1.35 (s, 3H, CH_3), 1.29-1.15 (m, 4H, CH_2), 1.13 (s, 3H, CH_3), 1.02-0.97 (m, 3H, CH_3), 0.94-0.80 (m, 18H, CH_3).**^{1}H NMR** : (300MHz, CD_3OH) δ = 66.47 (d, J = 9.3 Hz, 1H, NH), 6.37 (m, 1H, NH), 6.21-6.12 (m, 2H, NH), 6.09-6.00 (m,

2H, NH), 5.97-5.81 (m, 5H, NH), 4.04-3.93 (m, 1H, CHN), 3.92-.379 (m, 1H, CHN), 3.78-3.62 (m, 2H, CHN), 3.61-3.40 (m, 5H, CH_2N), 3.28-3.10 (m, 2H, CH_2N), 2.84-2.75 (m, 1H, CH_2N), 2.72 (d, J = 4.7 Hz, 3H, CH_3N), 2.70-2.58 (m, 1H, CH_2N), 2.55-2.41 (m, 1H, CH_2N), 1.78-1.57 (m, 3H, CH), 1.48 (s, 9H, CH_3), 1.31 (s, 3H, CH_3), 1.28-1.22 (m, 4H, CH_2), 1.19 (s, 3H, CH_3), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 0.97-0.89 (m, 18H, CH_3). **ESI-MS** (Mw 758.01): *m/z* 780 $[M + Na]^+$

Boc-Ala^u-Leu^u-Aib^u-Val^u-Ala^u-Leu^u-NHMe, (15)

15 was prepared from **11b** (27 mg, 0.077 mmol) and **14** (50 mg, 0.081 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **15** as a white product (56 mg, 80%). **^{1}H NMR** : (400MHz, CD_3CN) δ= 6.21 (d, J = 8.0 Hz, 1H, NH), 6.11 (m, 1H, NH), 5.99-5.90 (m, 2H, NH), 5.85-5.77 (m, 2H, NH), 5.66 (m, 1H, NH), 5.62-5.56 (m, 2H, NH), 5.52 (d, J = 9.7 Hz, 1H, NH), 5.48 (d, J = 8.0 Hz, 1H, NH), 5.46 (d, J = 9.4 Hz, 1H, NH), 5.12 (d, J = 9.8 Hz, 1H, NH), 3.95-3.84 (m, 1H, CHN), 3.84-3.67 (m, 3H, CHN), 3.64 (dd, J = 12.0, 2.8 Hz, 1H, CHN), 3.57-3.36 (m, 5H, CH_2N), 3.29-3.19 (m, 1H, CH_2N), 2.82-2.74 (m, 1H, CH_2N), 2.55 (d, J = 4.7 Hz, 3H, CH_3N), 2.46-2.36 (m, 1H, CH_2N), 2.34-2.26 (m, 1H, CH_2N), 2.24-2.15 (m, 1H, CH_2N), 1.62-1.49 (m, 2H, CH), 1.47-1.37 (m, 1H, CH), 1.36 (s, 9H, Boc), 1.28 (s, 3H, CH_3), 1.14-1.04 (m, 4H, CH_2), 0.99 (s, 3H, CH_3), 0.97 (d, J = 7.0 Hz, 3H, CH_3), 0.92 (d, J = 6.8 Hz, 3H, CH_3), 0.83-0.73 (m, 18H, CH_3). **ESI-MS** (Mw 857,62): *m/z* 880 $[M + Na]^+$

Boc-Val^u-Ala^u-Leu^u-Aib^u-Val^u-Ala^u-Leu^u-NHMe, (2)

2 was prepared from **11c** (19 mg, 0.055 mmol) and **15** (50 mg, 0.058 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **2** as a white product (50mg, 87%).**^{1}H NMR** : (400MHz, CD_3OH) δ= 6.65 (d, *J* = 10.6 Hz, 1H, NH), 6.53 (dd, J = 10.3, 2.9 Hz, 1H, NH), 6.45 (dd, 1H, NH), 6.37 (s, 1H, NH), 6.34 (dd, J = 9.9, 3.8 Hz, 1H, NH), 6.29 (d, J = 9.9 Hz, 1H, NH), 6.20 (m, 1H, NH), 6.17 (d, J = 10.5 Hz, 1H, NH), 6.03-5.98 (m, 3H, NH), 5.97 (d, J = 11.0 Hz, 1H, NH), 5.90 (dd, J = 8.6, 4.5 Hz, 1H, NH), 5.86 (d, J = 10.3 Hz, 1H, NH), 5.83 (dd, J = 9.9, 3.6 Hz, 1H, NH), 4.10-3.95 (m, 3H, CHN), 3.92-3.79 (m, 1H,CHN), 3.75-3.41 (m, 9H, 2 CHN-7 CH_2N), 3.19 (dd, J = 12.8, 9.3 Hz, 1H, CH_2N), 2.70 (d, J = 4.8 Hz, 3H, CH_3N), 2.67-2.24 (m, 6H, CH_2N), 1.76-1.57 (m, 4H, CH), 1.48 (s, 9H, Boc), 1.33 (s, 3H, CH_3 (Aib)), 1.31-1.14 (m, 4H, CH_2), 1.12 (s, 3H, CH_3 (Aib)), 1.07-1.01 (m, 6H, CH_3), 0.98-0.88 (m, 24H, CH_3). **^{13}C NMR** (400 MHz, CD_3OH) δ = 162.84, 162.26, 161.13, 160.66, 160.64, 160.00, 159.91, 158.76, 79.39, 56.88, 55.51, 52.52, 47.11,

46.05, 45.72, 45.31, 45.24, 43.94, 43.16, 42.94, 41.95, 31.12, 31.09, 27.85, 26.52, 25.94, 25.28, 25.06, 24.90, 22.79, 22.70, 21.50, 21.21, 19.21, 19.18, 18.10, 17.76, 17.72, 17.47.**ESI-MS** (Mw 985,71): *m/z* 1009 $[M + Na]^+$

Boc- $(Aib^u)_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (16)

16 was prepared from **BB2** (197 mg, 0.598 mmol) and **12** (300 mg, 0.598 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **16** as a white product (225 mg, 61%). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.88 (m, 1H, NH), 6.41 (m, 1H, NH), 6.29 (m, 1H, NH), 6.23-6.11 (m, 2H, NH), 5.94 (m, 1H, NH), 5.86-5.75 (m, 2H, NH), 5.63 (d, J = 9.8 Hz, 1H, NH), 4.10-3.95 (m, 1H, CHN), 3.94-3.83 (m, 1H, CHN), 3.77 (dd, J = 13.7, 7.9 Hz, 1H, CHN), 3.69-3.45 (m, 4H, CH_2N), 2.85 (dd, J = 14.0, 5.3 Hz, 1H, CH_2N), 2.73 (d, J = 4.6 Hz, 3H, CH_3N), 2.70-2.63 (m, 1H, CH_2N), 2.56-2.34 (m, 2H, CH_2N), 1.78-1.56 (m, 2H, CH), 1.49 (s, 9H, Boc), 1.38 (s, 3H, CH_3(Aib)), 1.32-1.20 (m, 2H, CH_2), 1.16 (s, 3H, CH_3(Aib)), 1.06 (d, J = 6.8 Hz, 2H, CH_3), 0.97-0.86 (m, 12H, CH_3) **ESI-MS** (Mw 615.81): *m/z* 616.2 $[M + H]^+$, 639.3 $[M + Na]^+$, 1230.8 $[2M + H]^+$, 1256.0 $[2M + Na]^+$

Boc- Leu^u-$(Aib^u)_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (17)

17 was prepared **11a** (34 mg, 0.097 mmol) and **16** (60 mg, 0.097 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **16** as a white product (62 mg, 84%). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.51 (d, J = 9.4 Hz, 1H, NH), 6.47-6.38 (m, 2H, NH), 6.31-6.10 (m, 5H, NH), 5.96 (d, J = 9.9 Hz, 1H, NH), 5.76 (d, J = 10.0 Hz, 1H, NH), 5.42 (s, 1H, NH), 4.05-3.78 (m, 3H, CHN), 3.79-3.66 (m, 2H, CHN), 3.64-3.49 (m, 4H, CH_2N), 3.42-3.35 (m, 1H, CH_2N), 3.28-3.16 (m, 1H, CH_2N), 2.71 (d, J = 4.0 Hz, 3H, CH_3N), 2.68-2.57 (m, 2H, CH_2N), 2.56-2.45 (m, 1H, CH_2N), 2.43-2.31 (m, 1H, CH_2N), 1.75-1.50 (m, 3H, CH), 1.45 (s, 9H, CH_3), 1.42 (s, 3H, CH_3), 1.35-1.17 (m, 4H, CH_2), 1.047 (s, 3H, CH_3), 1.04 (d, J = 6.8 Hz, 3H, CH_3), 0.95-0.83 (m, 18H, CH_3). **ESI-MS** (MW 758.01): *m/z* 758.3 $[M + H]^+$, 781.4 $[M + Na]^+$, 1514.9 $[2M + H]^+$, 1538.9 $[2M + Na]^+$

Boc- Ala^u-Leu^u-$(Aib^u)_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (18)

18 was prepared from **11b** (24 mg, 0.077 mmol) and **17** (62 mg, 0.081 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous

solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **18** as a white product (84 mg, 97%). **^{1}H NMR** : (400MHz, CD_3OH) δ = 6.59 (d, J = 8.8 Hz, 1H, NH), 6.51-6.41 (m, 2H, NH), 6.36-6.28 (m, 2H, NH), 6.27-6.10 (m, 3H, NH), 6.07 (d, J = 10.1 Hz, 1H, NH), 6.00 (t, J = 6.1 Hz, 1H, NH), 5.89 (d, J = 10.0 Hz, 1H, NH), 5.83 (d, J = 9.5 Hz, 1H, NH), 5.75 (s, 1H, NH), 4.07-3.94 (m, 2H, CHN), 3.94-3.78 (m, 4H, CHN), 3.71-3.46 (m, 8H, CH_2N), 2.91-2.77 (m, 1H, CH_2N), 2.74 (d, J = 4.7 Hz, 3H, CH_3N), 2.71-2.33 (m, 5H, CH_2N), 1.80-1.62 (m, 4H, CH), 1.47 (s, 9H, Boc), 1.46 (s, 3H, CH_3), 1.32-1.21 (m, 4H, CH_2), 1.14 (s, 3H, CH_3), 1.12-1.03 (m, 6H, CH_3), 0.99-0.87 (m, 24H, CH_3)

Boc-Val^u-Ala^u-Leu^u-(Aib^u)$_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (3)

3 was prepared from **11c** (32 mg, 0.093 mmol) and **18** (84 mg, 0.097 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) over silica gel gave **3** as a white product (75 mg, 78%). **^{1}H NMR** : (400MHz, CD_3OH) δ = 6.71 (m, 1H, NH), 6.61 (d, *J* = 10.4 Hz, 1H, NH), 6.53-6.45 (m, 2H, NH), 6.37-6.20 (m, 4H, NH), 6.05 (d, J = 10.3 Hz, 1H, NH), 6.02-5.97 (m, 2H, NH), 5.95 (d, J = 10.7 Hz, 1H, NH), 5.88 (d, J = 9.8 Hz, 1H, NH), 5.77 (m, 1H, NH), 5.68 (s, 1H, NH), 4.18-3.97 (m, 2H, CHN), 3.93-3.81 (m, 2H, CHN), 3.70-3.46 (m, 9H, CH_2N), 2.72 (d, J = 4.6 Hz, 3H, NH), 2.69-2.53 (m, 2H, CH_2N), 2.55-2.31 (m, 1H, CH_2N), 1.76-1.52 (m, 4H, CH), 1.49 (s, 9H, CH_3), 1.27-1.17 (m, 4H, CH_2), 1.14 (m, 3H, CH_3), 1.08-1.01 (m, 6H, CH_3), 0.99-0.82 (m, 24H, CH_3). **^{13}C NMR** (400 MHz, CD_3OH) δ 161.23, 161.12, 160.67, 160.48, 160.38, 159.97, 159.89, 158.68, 79.31, 56.65, 54.85, 53.40, 46.29, 45.60, 45.38, 45.32, 43.73, 43.16, 42.85, 42.32, 31.23, 31.06, 27.86, 26.23, 25.94, 25.29, 24.95, 24.88, 22.78, 22.73, 21.86, 21.52, 19.14, 19.12, 18.01, 17.62, 17.43. **ESI-MS** (Mw 985,71): *m/z* 1008.7 $[M + Na]^+$

Boc-Aib^u-Aib^u-Val^u-Ala^u-Leu^u-NHMe, (19)

19 was prepared from **BB1** (50 mg, 0.154 mmol) and **13** (100 mg, 0.162 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2 -MeOH (v/v), 95:5) over silica gel gave **19** as a white product (90 mg, 73%). **^{1}H NMR** : (300MHz, DMSO d_6) δ = 6.46 (s, 1H, NH), 6.10 (m, 1H, NH), 6.02-5.86 (m, 8H, NH), 5.82 (m, 1H, NH), 3.75-3.65 (m, 1H, CHN), 3.64-3.57 (m, 1H, CHN), 3.57-3.46 (m, 1H, CHN), 3.28-3.15 (m, 6H, CH_2N), 3.09-3.04 (m, 2H, CH_2N), 2.71-2.60 (m, 2H, CH_2N), 2.54 (d, J = 4.5 Hz, 3H, CH_3N), 1.67-1.54 (m, 2H, CH), 1.36 (s, 9H, Boc), 1.21-1.15 (m, 2H, CH_2), 1.17-1.07 (m, 12H, CH_3), 0.93 (d, J = 6.6 Hz, 3H, CH_3), 0.88-0.75 (m, 12H, CH_3). **ESI-MS** (Mw 729,95): *m/z* 752 $[M + Na]^+$

Boc-Leu^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe, (20

20 was prepared from **11a** (27 mg, 0.078 mmol) and **19** (60 mg, 0.082 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **20** as a white product (63 mg, 88%). **^{1}H NMR** : (400MHz, CD_3CN) δ= 6.05 (m, 1H, NH), 5.86-5.78 (m, 2H, NH), 5.74-5.54 (m, 4H, NH), 5.52-5.38 (m, 5H, NH), 5.33 (m, 1H, NH), 3.97-3.87 (m, 1H, CHN), 3.85-3.74 (m, 1H, CHN), 3.69-3.50 (m, 5H, CHN-CH_2N), 3.46-3.34 (m, 1H, CH_2N), 3.27-2.98 (m, 2H, CH_2N), 2.65 (d, J = 4.7 Hz, 3H, CH_3N), 2.59-2.48 (m, 1H, CH_2N), 1.70-1.56 (m, 3H, CH), 1.43 (s, 9H, Boc), 1.36-1.14 (m, 16H, CH_2-CH_3), 1.01 (d, J = 6.8 Hz, 3H, CH_3), 0.94-0.85 (m, 18H, CH_3). **ESI-MS** (Mw 872,15): *m/z* 894 $[M + Na]^+$

Boc-Ala^{u}-Leu^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe, (21)

21 was prepared **11b** (10 mg, 0.032 mmol) and **20** (30 mg, 0.034 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **21** as a white product (10 mg, 30%). **^{1}H NMR** : (400MHz, CD_3CN) δ= 6.13 (m, 1H, NH), 6.02 (m, 1H, NH), 5.96 (m, 1H, NH), 5.87 (m, 1H, NH), 5.83-5.65 (m, 4H, NH), 5.63-5.47 (m, 1H, NH), 5.37 (m, 1H, NH), 5.23 (m, 1H, NH), 4.99 (m, 1H, NH), 3.99-3.75 (m, 4H, CHN), 3.71-3.33 (m, 10H, CHN-CH_2N), 3.15-3.01 (m, 2H, CH_2N), 2.65 (s, 3H, CH_3N), 2.63-2.42 (m, 2H, CH_2N), 1.73-1.55 (m, 3H, CH), 1.47 (s, 9H, Boc), 1.35-1.27 (m, 6H, CH_3), 1.26-1.17 (m, 4H, CH_2), 1.16-1.07 (m, 6H, CH_3), 1.06-0.97 (m, 6H, CH_3), 0.96-0.84 (m, 18H, CH_3). **ESI-MS** (Mw 972,27): *m/z* 994 $[M + Na]^+$

Boc-Val^{u}-Ala^{u}-Leu^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe, (4)

4 was prepared from **11c** (3 mg, 0.009 mmol) and **21** (10 mg, 0.010 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 95:5) over silica gel gave **4** as a white product (8 mg, 71%) . **^{1}H NMR** : (400MHz, CD_3OH) δ= 6.57 (d, J = 11.6 Hz, 1H, NH), 6.39 (m, 1H, NH), 6.28 (m, 1H, NH), 6.25-6.17 (m, 2H, NH), 6.15-6.02 (m, 5H, NH), 5.93 (m, 1H, NH), 5.86-5.68 (m, 6H, NH), 3.97-3.83 (m, 3H, CHN), 3.76 (m, 1H, CHN), 3.65-3.32 (m, 10H, CHN-CH_2N), 3.23-3.08 (m, 2H, CH_2N), 2.61 (d, J = 4.5 Hz, 3H, CH_3), 2.59-2.03 (m, 6H, CH_2N), 1.67-1.46 (m, 4H, CH), 1.37 (s, 9H, Boc), 1.21 (s, 3H, CH_3), 1.19 (s, 6H, CH_3), 1.11

(s, 3H, CH_3), 0.99-0.91 (m, 6H, CH_3), 0.88-0.76 (m, 24H, CH_3). **ESI-MS** (Mw 1099,79): *m/z* 573 $[M/2 + Na]^+$, 1122 $[M + Na]^+$

Boc-(Aib^u)$_{rev}$-(Aib^u)$_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (22)

22 was prepared from **BB2** (63 mg, 0.193 mmol) and **16**(125 mg, 0.203 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) over silica gel gave **22** as a white product (110 mg, 72 %). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.74 (m, 1H, NH), 6.58-6.45 (m, 2H, NH), 6.33 (m, 1H, NH), 6.27-6.19 (m, 2H, NH), 6.07-5.98 (m, 2H, NH), 5.88 (s, 1H, NH), 5.72 (d, J = 10.0 Hz, 1H, NH), 5.65 (s, 1H, NH), 4.09-3.95 (m, 1H, CHN), 3.94-3.81 (m, 2H, CHN), 3.68-3.49 (m, 4H, CH_2N), 3.36-3.32 (m, 2H, CH_2N), 3.09-3.00 (m, 1H, CH_2N), 2.74 (d, J = 3.8 Hz, 3H, CH_3N), 2.73-2.62 (m, 1H, CH_2N), 2.59-2.39 (m, 2H, CH_2N), 1.79-1.55 (m, 2H, CH), 1.48 (s, 9H, CH_3), 1.42 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.29-1.23 (m, 2H, CH_2), 1.22 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.06 (d, J = 6.8 Hz, 3H, CH_3), 0.97-0.87 (m, 12H, CH_3). **ESI-MS** (Mw 729.95): *m/z* 730.3 $[M + H]^+$, 753.4 $[M + Na]^+$, 1459.9 $[2M + H]^+$, 1484.1 $[2M + Na]^+$

Boc-Leu^u-(Aib^u)$_{rev}$-(Aib^u)$_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (23)

23 was prepared from **11a** (51 mg, 0.144 mmol) and **22** (100 mg, 0.137 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) over silica gel gave **22** as a white product (85 mg, 71 %). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.49 (m, 1H, NH), 6.40 (m, 2H, NH), 6.33 (m, 1H, NH), 6.27-6.16 (m, 3H, NH), 6.13-6.02 (m, 3H, NH), 5.90-5.83 (m, 2H, NH), 5.79 (d, J = 10.0 Hz, 1H, NH), 4.05-3.94 (m, 1H, CHN), 3.94-3.80 (m, 2H, CHN), 3.76-3.66 (m, 1H, CHN), 6.65-3.48 (m, 5H, CH_2N), 3.33-3.21 (m, 1H, CH_2N), 3.07-2.96 (m, 2H, CH_2N), 2.74 (d, J = 3.8 Hz, 3H, CH_3N), 2.72-2.65 (m, 2H, CH_2N), 2.59-2.37 (m, 2H, CH_2N), 1.77-1.56 (m, 3H, CH), 1.47 (s, 9H, CH_3), 1.42 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31-1.25 (m, 4H, CH_2), 1.23 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.06 (d, J = 6.8 Hz, 3H, CH_3), 0.99-0.88 (m, 18H, CH_3).

Boc-Ala^u-Leu^u-(Aib^u)$_{rev}$- (Aib^u)$_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (24)

24 was prepared from **11b** (30 mg, 0.096 mmol) and **23** (80 mg, 0.091 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) over silica gel gave **24** as a white

product (80 mg, 89 %). **^{1}H NMR** : (300MHz, CD_3OH) δ = 6.60 (d, J = 9.1 Hz, 1H, NH), 6.53 (m, 1H, NH), 6.50-6.41 (m, 2H, NH), 6.36 (m, 1H, NH), 6.29 (d, J = 9.1 Hz, 1H, NH), 6.26-6.19 (m, 2H, NH), 6.16-6.00 (m, 3H, NH), 5.95 (s, 1H, NH), 5.88 (s, 1H, NH), 5.83 (m, 2H, NH), 4.07-3.79 (m, 4H, CHN), 3.78-3.65 (m, 1H, CHN), 3.64-6.40 (m, 5H, CH_2N), 3.33-3.21 (m, 2H, CH_2N), 2.97-2.84 (m, 1H, CH_2N),2.83-2.76 (m, 1H, CH_2N), 2.75 (d, J = 3.9 Hz, 3H, CH_3N), 2.71-2.40 (m, 4H, CH_2N), 1.79-1.54 (m, 3H, CH), 1.47 (s, 9H, CH_3), 1.43 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.35-1.25 (m, 4H, CH_2), 1.23 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.09-1.04 (m, 6H, CH_3), 0.98-0.88 (m, 18H, CH_3). **ESI-MS** (Mw 972.27): *m/z* 973.4 $[M + H]^+$, 995.5 $[M + Na]^+$, 1102.0 $[M + K]^+$

Boc-Val^u-Ala^u-Leu^u-(Aib^u)$_{rev}$- (Aib^u)$_{rev}$-Val^u-Ala^u-Leu^u-NHMe, (5)

5 was prepared from **11c** (29 mg, 0.086 mmol) and **24** (80 mg, 0.082 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) over silica gel gave **5** as a white product (88 mg, 97 %). **^{1}H NMR** : (300MHz, CD_3OH) δ = 6.66 (m, 1H, NH), 6.61 (d, J = 10.1 Hz, 1H, NH), 6.57-6.51 (m, 2H, NH), 6.50-6.43 (m, 2H, NH), 6.35 (m, 1H, NH), 6.30 (d, J = 9.1 Hz, 1H, NH), 6.24 (m, 1H, NH), 6.15 (d, J = 10.0 Hz, 1H, NH), 6.01-5.93 (m, 2H, NH), 5.92-5.92 (m, 2H, NH), 5.88 (m, 1H, NH), 5.85 (m, NH), 5.82 (m, 1H, NH), 4.17-3.82 (m, 4H, CHN), 3.81-3.71 (m, 1H, CHN), 3.70-3.46 (m, 9H, CHN-CH_2N), 2.91-2.82 (m, 1H, CH_2N), 2.79-2.69 (m, 1H, CH_2N), 2.75 (d, J = 3.8 Hz, 3H, CH_3N), 2.68-2.42 (m, 5H, CH_2N), 2.42-2.29 (m, 1H, CH_2N), 1.79-1.56 (m, 4H, CH), 1.50 (s, 9H, CH_3), 1.43 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.31-1.25 (m, 4H, CH_2), 1.24 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.08-1.01 (m, 6H, CH_3), 0.98-0.88 (m, 24H, CH_3). **^{13}C NMR** (300 MHz, CD_3OH) δ 160.68, 160.64, 160.21, 160.02, 159.66, 159.45, 159.20, 158.32, 78.93, 56.23, 56.13, 54.56, 54.46, 52.99, 52.89, 52.54, 52.45, 46.62, 46.34, 45.49, 45.25, 44.96, 44.78, 43.15, 42.82, 42.72, 42.29, 42.18, 30.68, 30.42, 27.50, 25.98, 25.93, 25.63, 25.50, 25.07, 24.72, 24.57, 24.48, 24.44, 22.39, 21.14, 21.12, 18.85, 18.78, 17.60, 17.50, 17.28, 17.18. **ESI-MS** (Mw 1100.44): *m/z* 1100.5 $[M + H]^+$, 1122.6 $[M + Na]^+$

Boc Gly^u-Val^u-Ala^u-Leu^u-NHMe, (25)

25 was prepared from **11d** (171 mg, 0.568 mmol) and **12**(300 mg, 0.598 mmol) as described in the general procedure. After completion (12h), the desired compound **25** was precipitated upon addition of water and washed with 1M $KHSO_4$ aqueous solution and water. Finally **25** was dried over vacuum. (360 mg, quantitative). **^{1}H NMR** : (300MHz, CD_3OH) δ = 6.72 (m, 1H,NH), 6.36 (m, 1H, NH), 6.27 (m, 1H, NH), 6.17 (m, 1H, NH), 6.09 (m, 1H, NH), 5.99 (d, J = 9.4 Hz, 1H, NH), 5.91-5.79 (m, 3H, NH), 4.08-3.96 (m, 1H, CHN), 3.94-3.83 (m, 1H, CHN), 3.69-3.44 (m, 4H, CHN- CH_2N), 3.11-2.94 (m, 2H, CH_2N), 2.73 (d, J = 4.1 Hz, 3H, CH_3N), 2.70-2.42 (m, 5H, CH_2N), 1.78-1.58 (m, 2H, CH), 1.48 (s, 9H, Boc), 1.37-1.21 (m,

2H, CH_2), 1.06 (d, J = 6.8 Hz, 3H, CH_3), 0.99-0.89 (m, 12H, CH_3). **ESI-MS** (Mw 587.76) : *m/z* 588.3 $[M+H]^+$, 611.4 $[M+Na]^+$

Boc Gly^u-Gly^u-Val^u-Ala^u-Leu^u-NHMe, (26)

26 was prepared from **11d** (112 mg, 0.371 mmol) and **25** (230 mg, 0.391 mmol) as described in the general procedure. After completion (12h), the desired compound **26** was precipitated upon addition of water and washed with 1M $KHSO_4$ aqueous solution and water. Finally **26** was dried over vacuum. (175 mg, 66 %). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.70 (m, 1H,NH), 6.40 (m, 1H, NH), 6.32 (m, 1H, NH), 6.28-6.14 (m, 3H, NH), 6.12-5.95 (m, 4H, NH), 5.87 (d, J = 9.8 Hz, 1H, NH), 4.08-3.96 (m, 1H, CHN), 3.95-3.84 (m, 1H, CHN), 3.68-3.43 (m, 7H, CHN-CH_2N), 3.30-2.80 (m, 6H, CH_2N), 2.73 (d, J = 4.3 Hz, 3H, CH_3N), 2.65-2.54 (m, 1H, CH_2N), 2.51-2.40 (m, 1H, CH_2N), 1.78-1.58 (m, 2H, CH), 1.48 (s, 9H, Boc), 1.34-1.22 (m, 2H, CH_2), 1.06 (d, J = 6.8 Hz, 3H, CH_3), 1.00-0.86 (m, 12H, CH_3). **ESI-MS** (Mw 673.85) : *m/z* 674.3 $[M+H]^+$, 697.4 $[M+Na]^+$

Boc Leu^u-Gly^u-Gly^u-Val^u-Ala^u-Leu^u-NHMe, (27)

27 was prepared from **11a** (80 mg, 0.225 mmol) and **26** (160 mg, 0.237 mmol) as described in the general procedure. After completion (12h), the desired compound **27** was precipitated upon addition of water and washed with 1M $KHSO_4$ aqueous solution and water. Finally **27** was dried over vacuum. (160 mg, 82 %). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.52 (d, J = 9.3 Hz, 1H, NH), 6.46-6.35 (m, 3H, NH), 6.31 (m, 1H, NH), 6.22 (m, 1H, NH), 6.20-6.00 (m, 6H, NH), 5.97(m, 1H, NH), 4.13-3.98 (m, 1H, CHN), 3.95-3.85 (m, 1H, CHN), 3.84-3.75 (m, 1H, CHN), 3.71-3.38 (m, 9H, CHN-CH_2N), 3.01-2.77 (m, 4H, CH_2N), 2.74 (d, J = 4.1 Hz, 3H, CH_3N), 2.71-2.62 (m, 2H, CH_2N), 2.60-2.49 (m, 1H, CH_2N), 2.48-2.37 (m, 1H, CH_2N), 1.79-1.57 (m, 3H, CH), 1.49 (s, 9H, Boc), 1.37-1.19 (m, 4H, CH_2), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 1.00-0.86 (m, 18H, CH_3). **ESI-MS** (Mw 816.5) : *m/z* 817.5 $[M+H]^+$, 839.5 $[M+Na]^+$

Boc Ala^u-Leu^u-Gly^u-Gly^u-Val^u-Ala^u-Leu^u-NHMe, (28)

28 was prepared from **11b** (51 mg, 0.163 mmol) and **27** (140 mg, 0.172 mmol) as described in the general procedure. After completion (12h), the desired compound **28** was precipitated upon addition of water and washed with 1M $KHSO_4$ aqueous solution and water. Finally **28** was dried over vacuum. (125 mg, 79 %). **^{1}H NMR** : (300MHz, CD_3OH) δ= 6.70-6.57 (m, 2H, NH), 6.49-6.34 (m, 5H, NH), 6.26-6.19 (m, 2H, NH), 6.16-5.98 (m, 6H, NH), 4.14-3.98 (m, 1H, CHN), 3.96-3.85 (m, 1H, CHN), 3.83-3.73 (m, 1H, CHN), 3.70-3.38 (m, 10H, CHN-CH_2N), 3.14-2.77 (m, 4H, CH_2N), 2.74 (d, J = 4.5 Hz, 3H, CH_3N), 2.72-2.62 (m, 2H, CH_2N), 2.59-2.35 (m, 4H, CH_2N), 1.80-1.55 (m, 3H, CH), 1.49 (s, 9H, Boc), 1.36-1.20 (m, 4H, CH_2), 1.14-1.04 (m, 6H, CH_3), 1.00-0.86 (m, 18H, CH_3). **ESI-MS** (Mw 916.17): *m/z* 918.5 $[M+H]^+$, 940.7 $[M+Na]^+$

Boc Val^{u}-Ala^{u}-Leu^{u}-Gly^{u}-Gly^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe, (6)

6 was prepared from **11c** (35 mg, 0.104 mmol) and **28** (100 mg, 0.109 mmol) as described in the general procedure. After completion (12h), the reaction mixture was evaporated, dissolved in ethyl acetate and treated with saturated $NaHCO_3$ aqueous solution, 1M $KHSO_4$ aqueous solution and brine. The organic layer was then dried over $MgSO_4$ and evaporated. Flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) over silica gel gave **6** as a white product (85 mg, 75 %). **^{1}H NMR** : (300MHz, CD_3OH) δ = 6.73-6.62 (m, 3H, NH), 6.53 (m, 1H, NH), 6.50-6.39 (m, 3H, NH), 6.30-6.20 (m, 3H, NH), 6.18-5.96 (m, 5H, NH), 5.92 (d, J = 9.7 Hz, 1H, NH), 5.84 (m, 1H, NH), 4.15-3.84 (m, 4H, CHN), 3.80-3.46 (m, 12H, CHN-CH_2N), 2.93-2.79 (m, 3H, CH_2N), 2.74 (d, J = 4.0 Hz, 3H, CH_3N), 2.71-2.31 (m, 7H, CH_2N), 1.81-1.57 (m, 4H, CH), 1.50 (s, 9H, Boc), 1.35-1.21 (m, 4H, CH_2), 1.11-1.04 (m, 6H, CH_3), 1.01-0.87 (m, 24H, CH_3). **^{13}C NMR**: (101 MHz, CD_3OH) δ 161.39, 161.24, 161.12, 161.03, 160.71, 160.58, 159.92, 158.72, 79.36, 56.81, 55.37, 46.40, 45.83, 45.36, 45.31, 43.74, 43.19, 42.90, 42.09, 41.59, 41.36, 39.64, 39.59, 31.07, 30.96, 27.86, 25.96, 25.29, 24.91, 24.29, 22.67, 21.72, 21.51, 19.16, 18.10, 17.83, 17.57, 17.31**. ESI-MS** (Mw 1044.34) : *m/z* 1044.7 $[M+H]^+$, 1066.7 $[M+Na]^+$

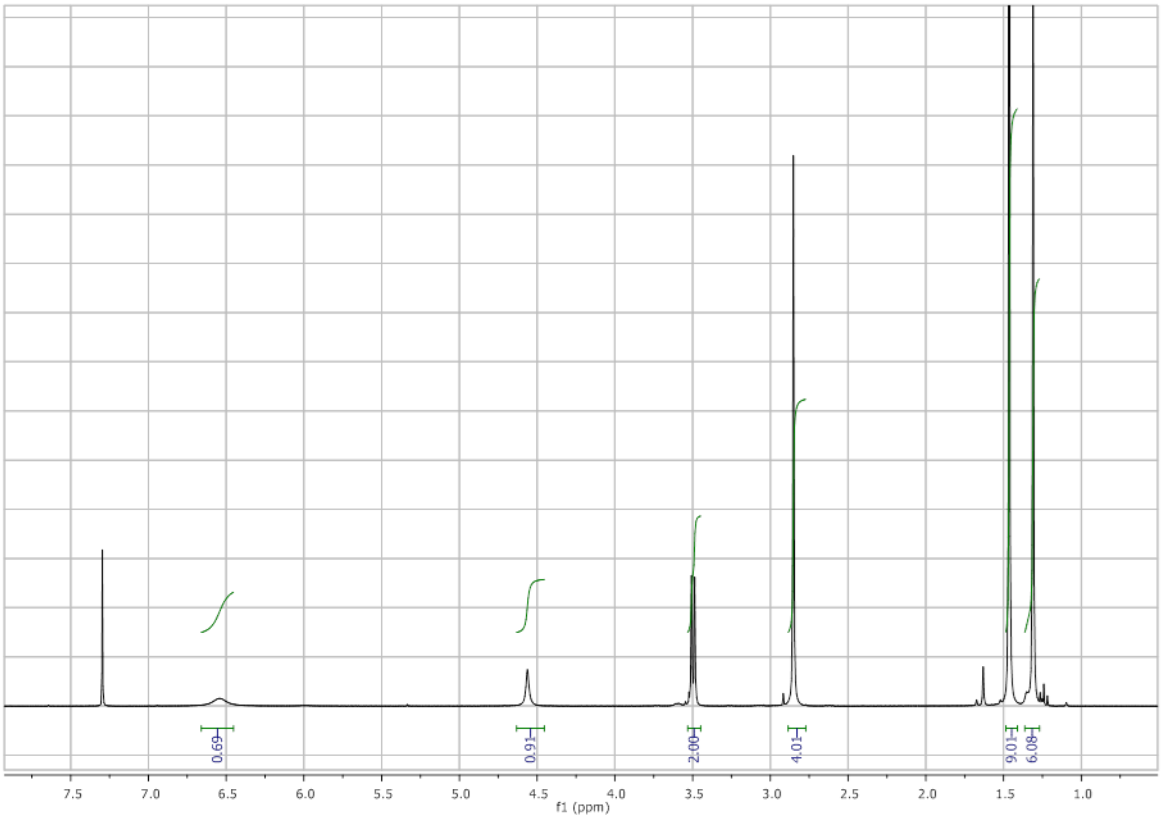


Figure S1: ^{1}H NMR spectra of carbamate **BB1**, recording in $CDCl_3$, (300MHz)

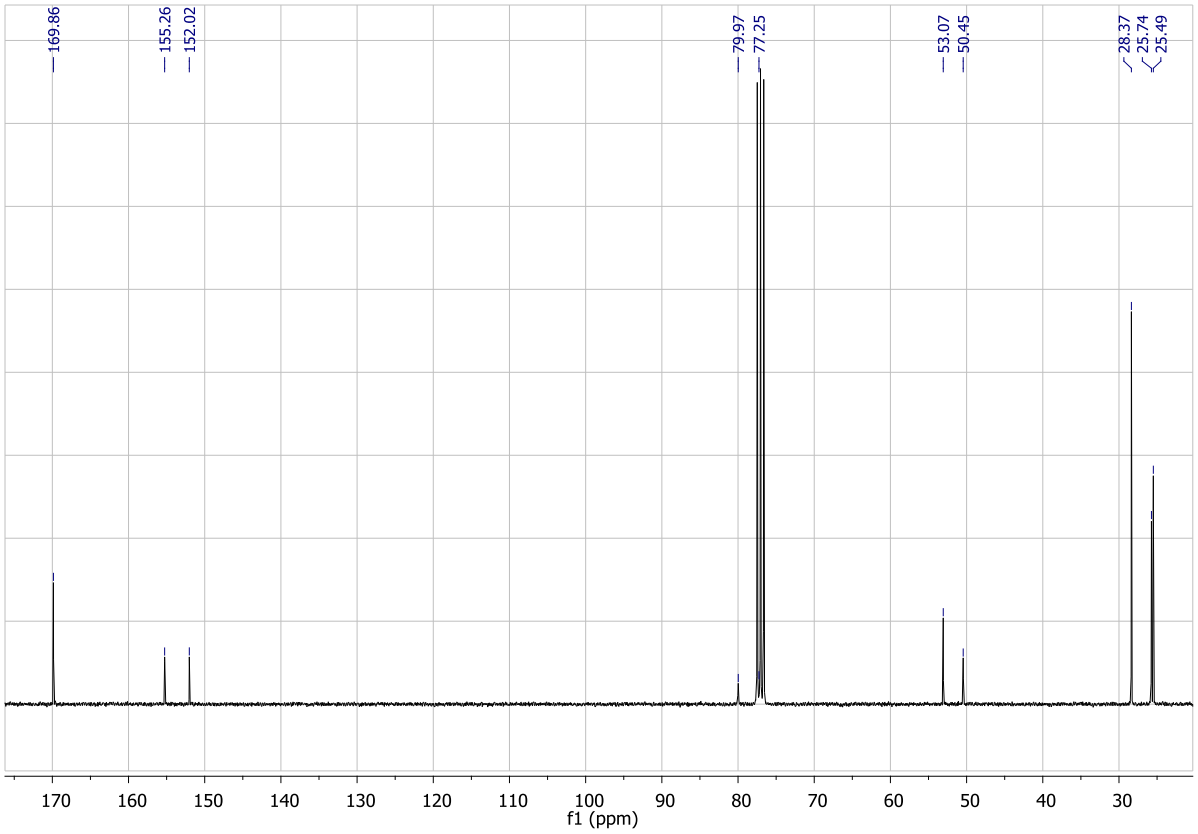


Figure S2: ^{13}C NMR spectra of carbamate **BB1**, recording in $CDCl_3$, (75MHz)

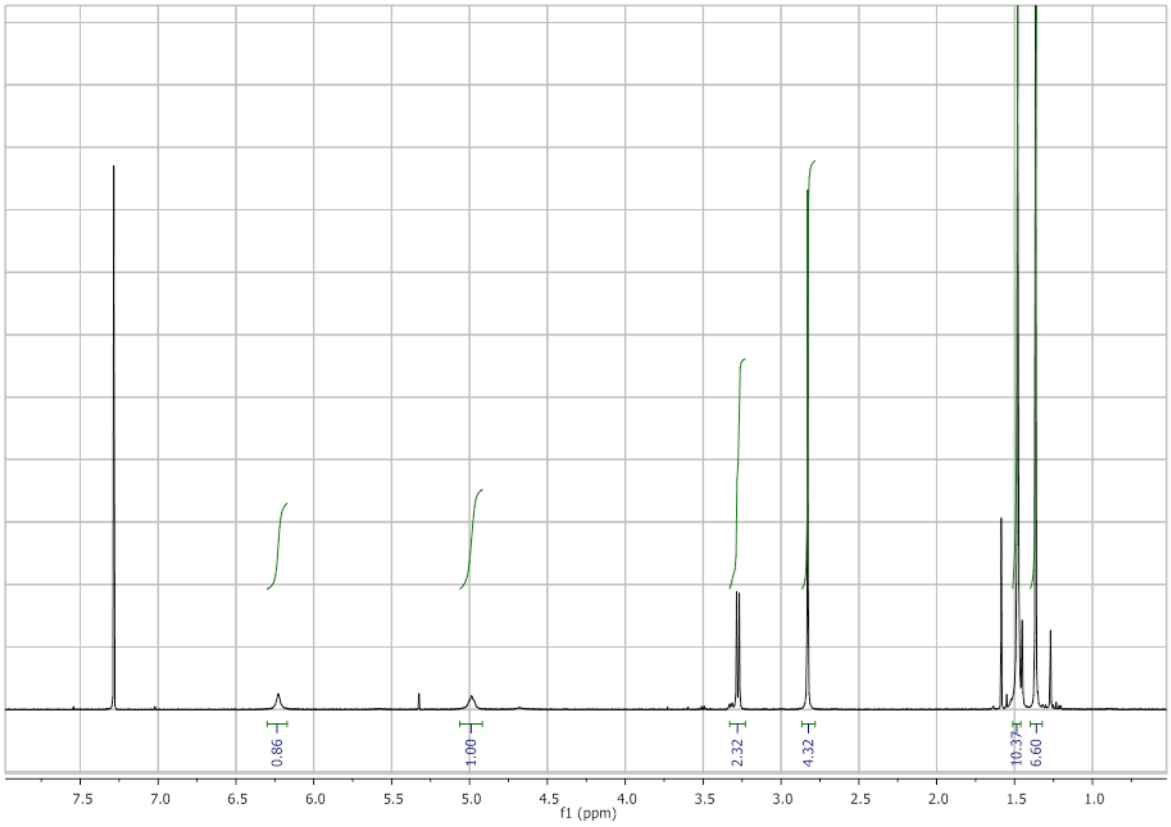


Figure S3: ^{1}H NMR spectra of carbamate **BB2**, recording in $CDCl_3$, (300MHz)

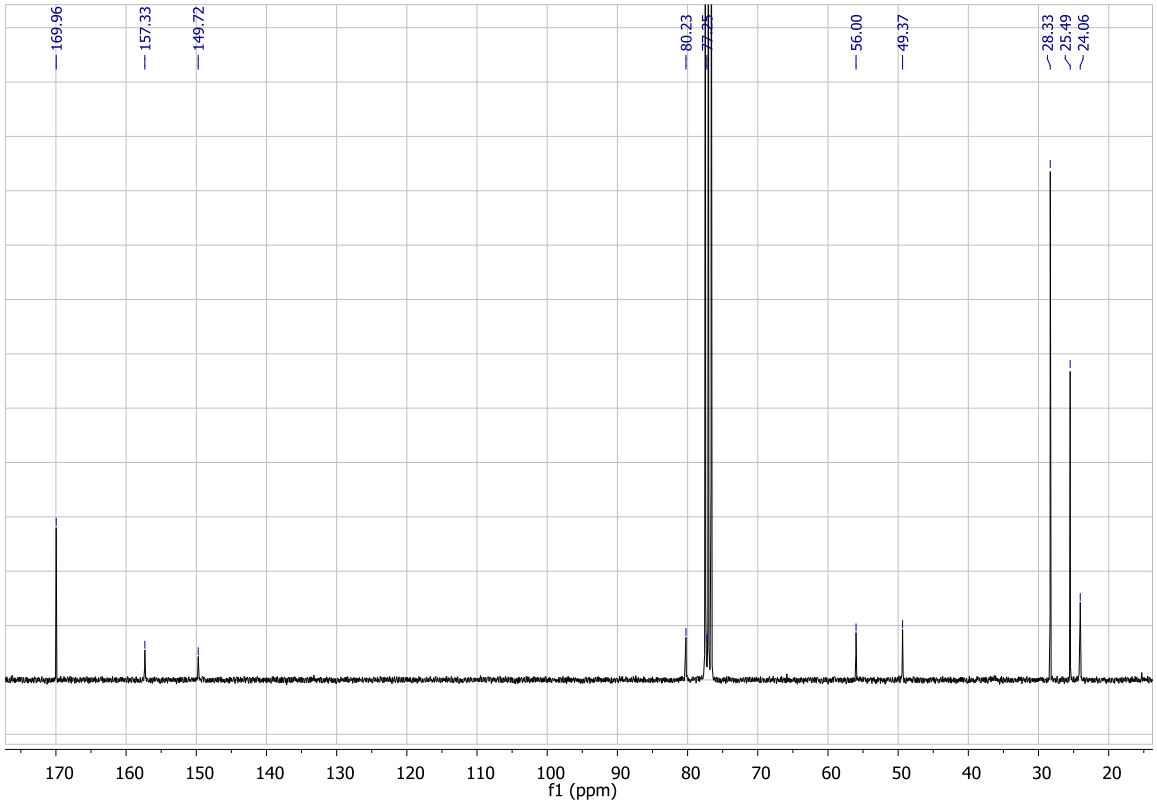


Figure S4: ^{13}C NMR spectra of compound **BB2**, recording in $CDCl_3$, (75MHz)

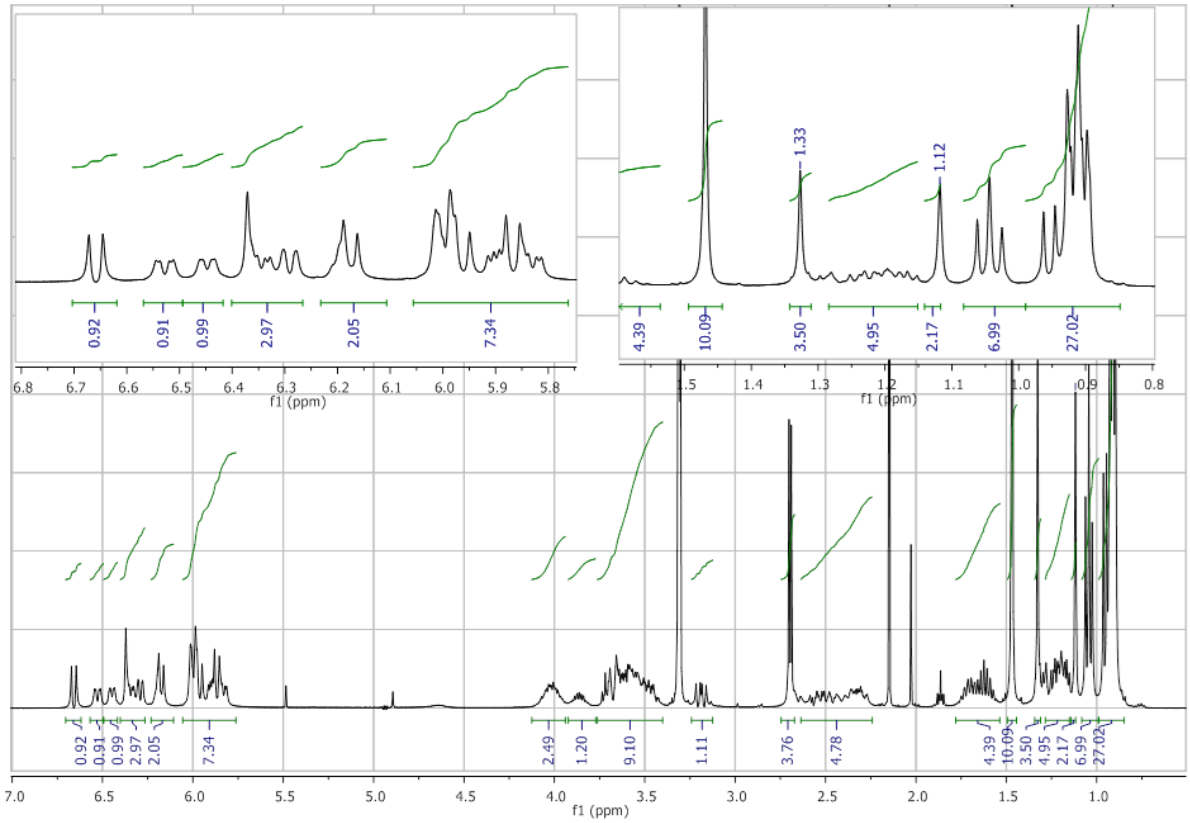


Figure S5: ^{1}H NMR spectra of compound **2**, recording in CD_3OH, (400MHz)

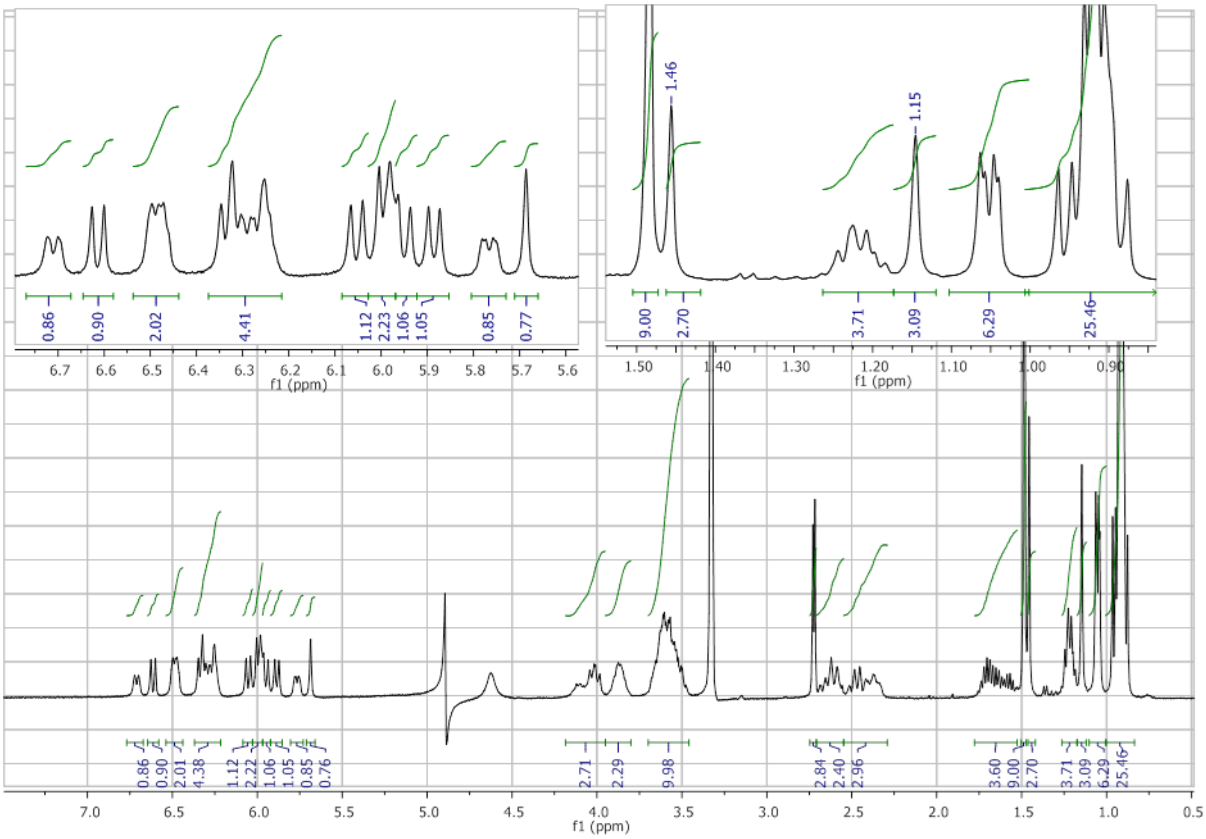


Figure S6: ^{1}H NMR spectra of compound **3**, recording in CD_3OH, (400MHz)

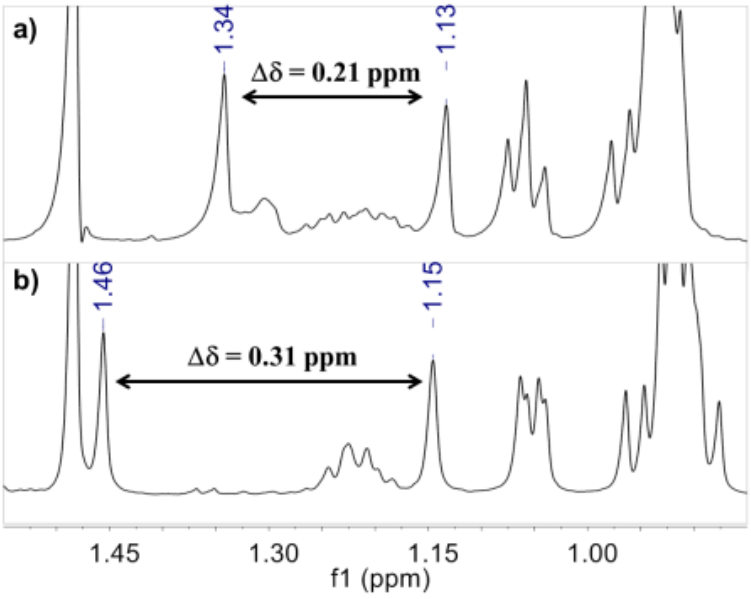


Figure S7: ^{1}H NMR region of methyl protons of DADME residues in a) oligourea **2** and b) oligourea **3**

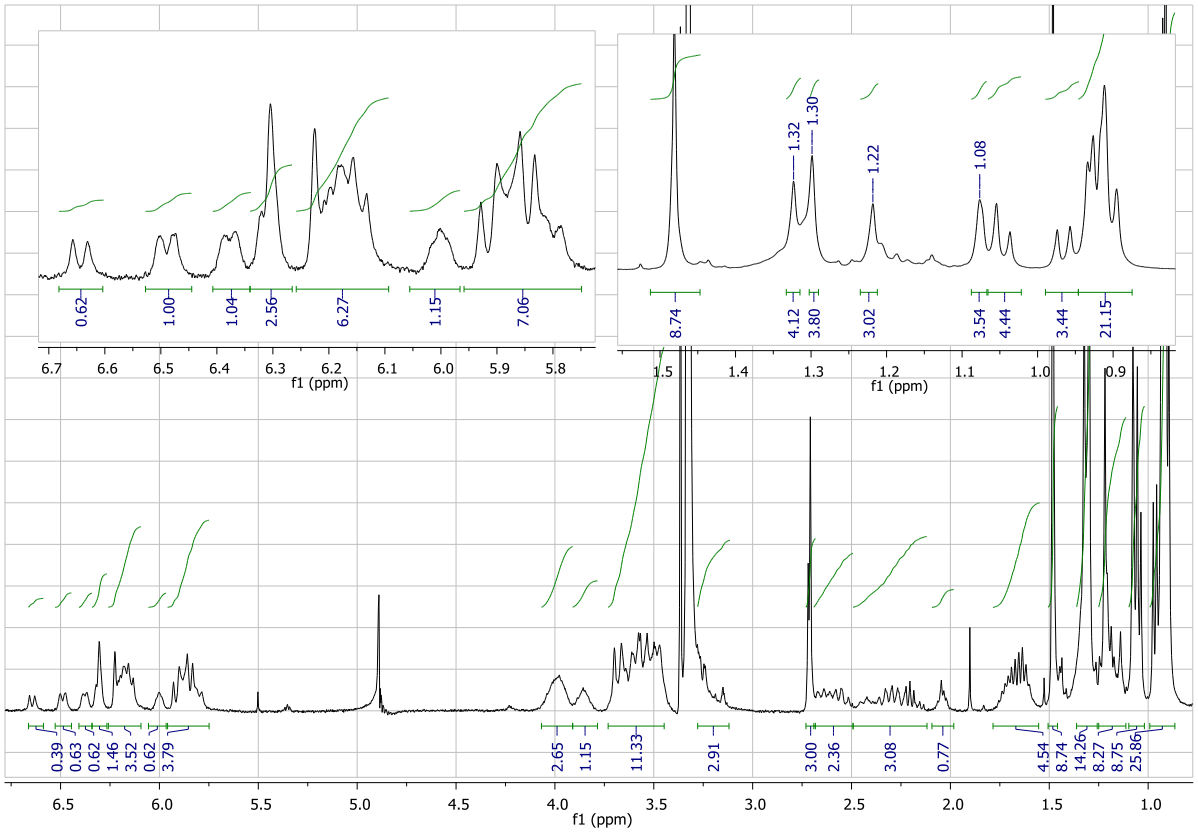


Figure S8: ^{1}H NMR spectra of compound **4** recording in CD_3OH (400MHz)

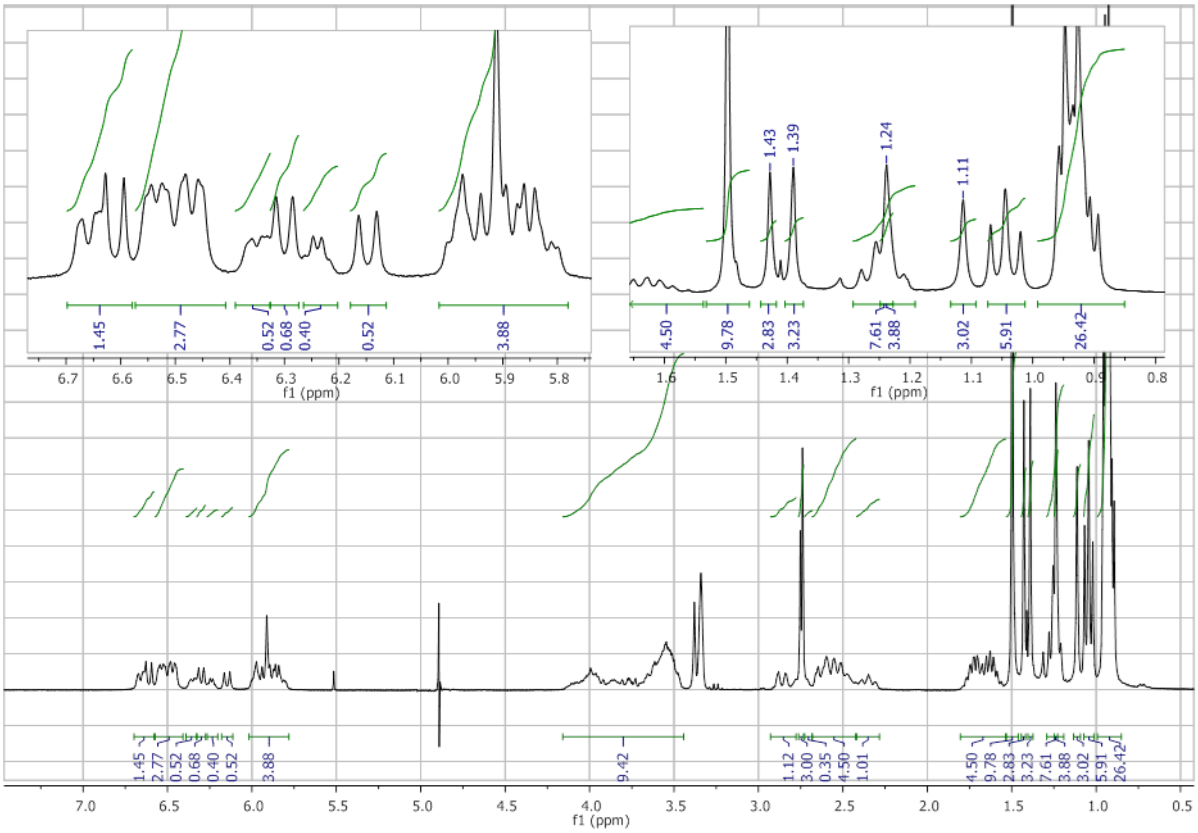


Figure S9: ^{1}H NMR spectra of compound **5**, recording in CD_3OH, (300MHz)

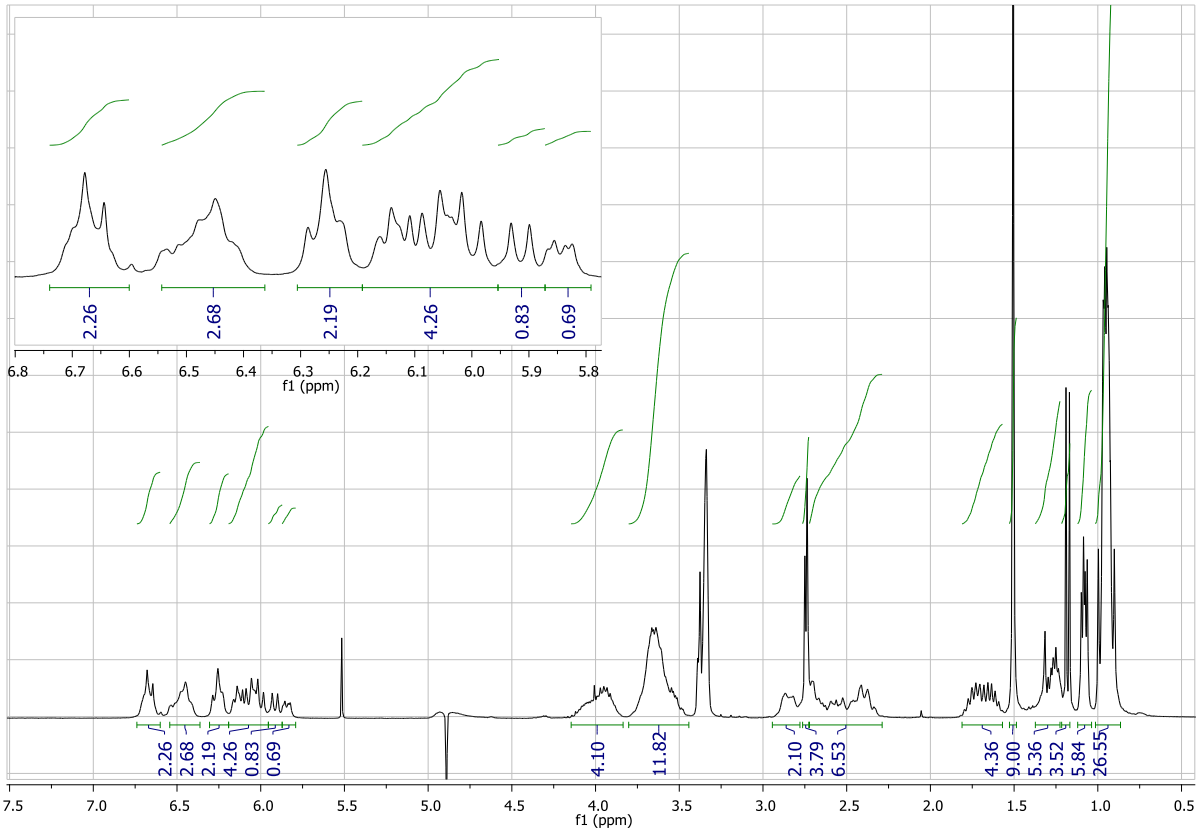
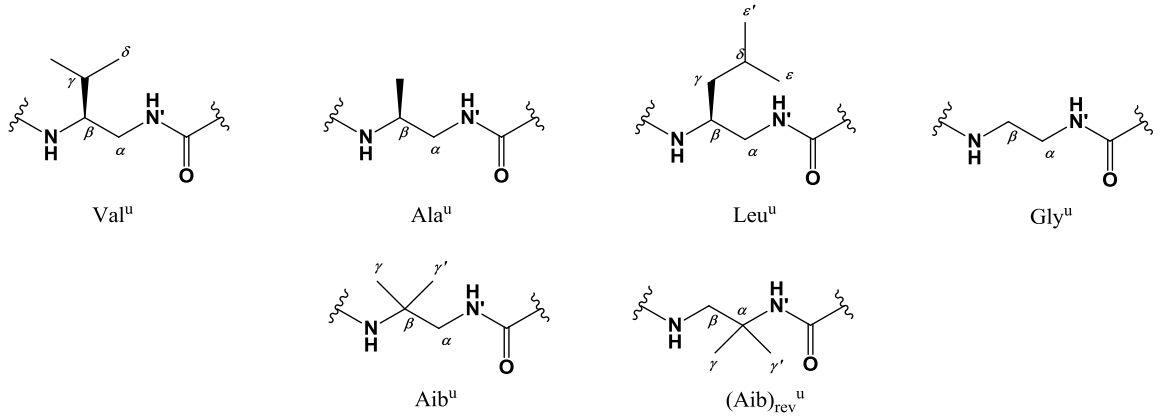


Figure S10: ^{1}H NMR spectra of compound **6**, recording in CD_3OH, (300MHz)

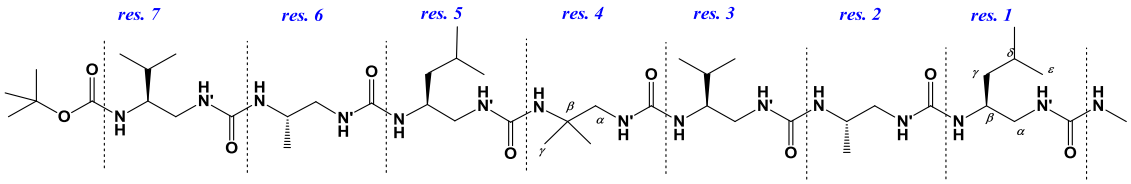
NMR Characterization

Experiments were recorded on a DPX-400 NMR spectrometer (Bruker Biospin) with a vertical 9.4T narrow-bore/ultrashield magnet operating at 400 MHz for ^{1}H observation by means of a 5-mm direct QNP 1H_13C/31P/19F_2H probe with Z gradient capabilities. The four oligomers were dissolved in CD_3OH at room temperature.



Scheme S8: Nomenclature used for the description of the various protons for each residue type

Table S1: ^{1}H NMR chemical shifts (in ppm) of **2** in CD_3OH (400 MHz)



Residue		N'H	NH	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	$^{\delta}CH$	$^{\varepsilon}CH$	term CH
	NH-Me		6,20							2,71
Leu^{u}	**U1**	6,44	5,99	3,58	2,66	3,88	1,23	1,70	0,93	
Ala^{u}	**U2**	6,34	6,00	3,51	2,40	4,01	1,06			
Val^{u}	**U3**	5,89	6,17	3,56	2,49	6,67	1,61	0,92		
Aib^{u}	**U4**	6,30	6,37	3,69	3,20		1,34 1,13			
Leu^{u}	**U5**	6,53	5,97	3,61	2,32	4,03	1,19	1,72	0,92	
Ala^{u}	**U6**	5,83	5,87	3,59	2,34	4,05	1,04			
Val^{u}	**U7**	6,00	6,65	3,47	2,56	3,63	1,64	0,94		
	Boc									1,48

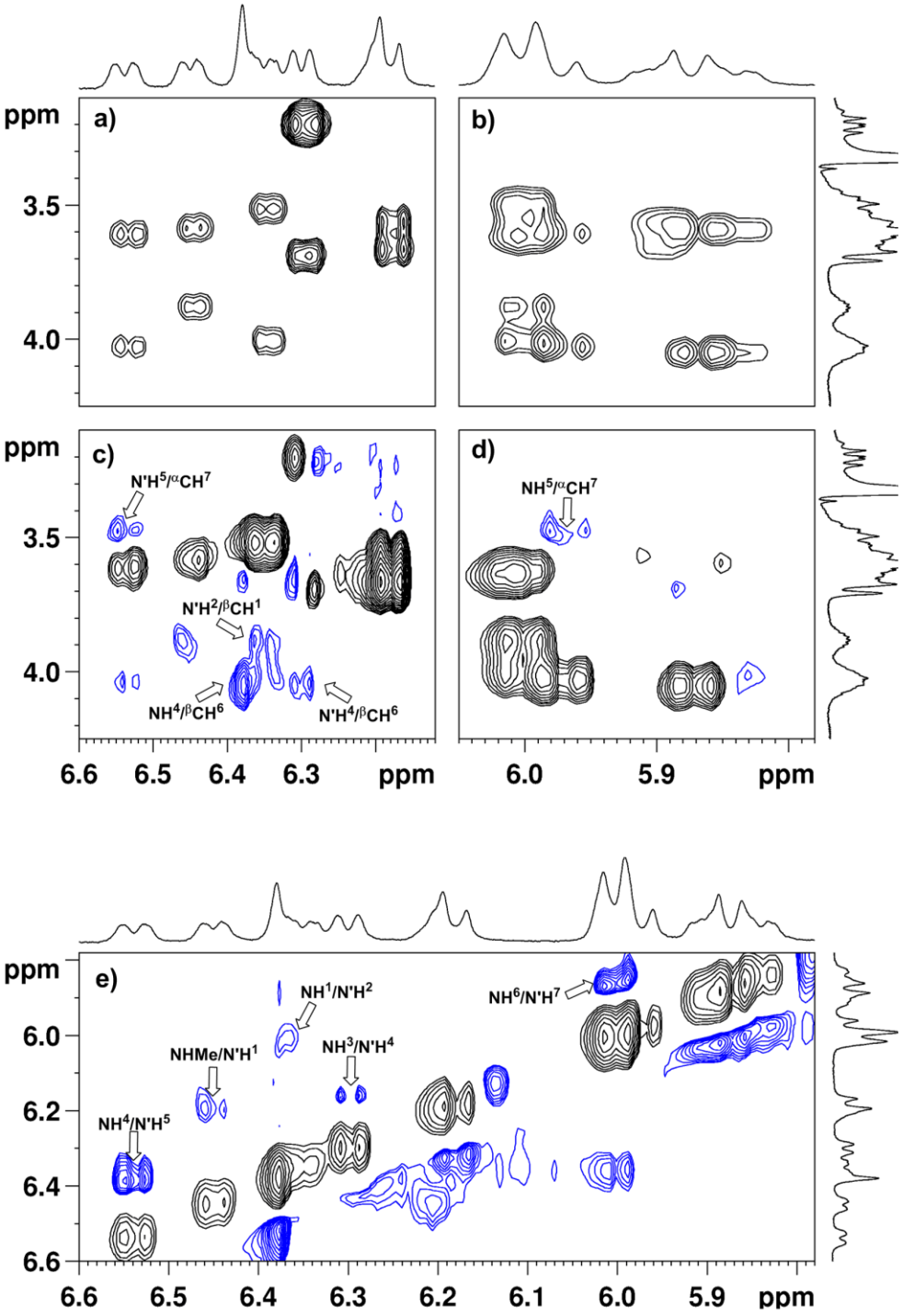
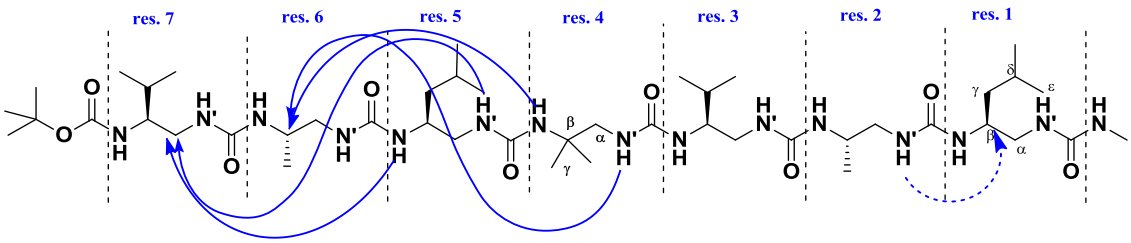
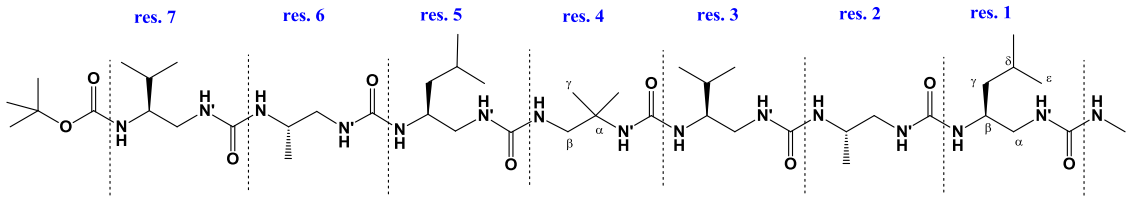


Figure S11: Representative sets of NOE connectivities observed for **2** in CD_3OH (400MHz). a) and b) part of the TOCSY plot shown for comparison c) and d) Part of the NH/CH region of the ROESY. e) Part of the NH/NH region of the ROESY plot of **2** in CD_3OH



Scheme S9: NOE connectivities observed for **2** in CD_3OH. N'H(i+1)/$^{\beta}$CH(i) represented in dashed arrows have been attributed previously as *Z-E* isomerization[5]

Table S2: ^{1}H NMR chemical shifts (in ppm) of **3** in CD_3OH (400 MHz)



Residue		N'H	NH	$^{\alpha}$CH^{1}	$^{\alpha}$CH^{2}	$^{\beta}$CH	$^{\gamma}$CH	$^{\delta}$CH	$^{\varepsilon}$CH	term CH
	NH-Me		6,25							2,73
Leu^{u}	**U1**	6,29	6,34	3,60	2,65	3,87	1,22	1,7	0,92	
Ala^{u}	**U2**	6,47	6,05	3,57	2,38	4,02	1,06			
Val^{u}	**U3**	6,49	5,95	3,55	2,45	3,62	1,58	0,90		
(Aib)$_{rev}^{u}$	**U4**	5,69	6,27			4,01 2,60	1,46 1,15			
Leu^{u}	**U5**	6,71	5,99	3,64	2,48	3,86	1,21	1,71	0,91	
Ala^{u}	**U6**	5,76	5,88	3,58	2,37	4,11	1,05			
Val^{u}	**U7**	5,98	6,61	3,51	2,59	3,59	1,64	0,93		
	Boc									

[5] A. Violette, M. C. Averlant-Petit, V. Semetey, C. Hemmerlin, R. Casimir, R. Graff, M. Marraud, J.-P. Briand, D. Rognan, G. Guichard, *JACS*, **2005**, *127*, 2156-2164.

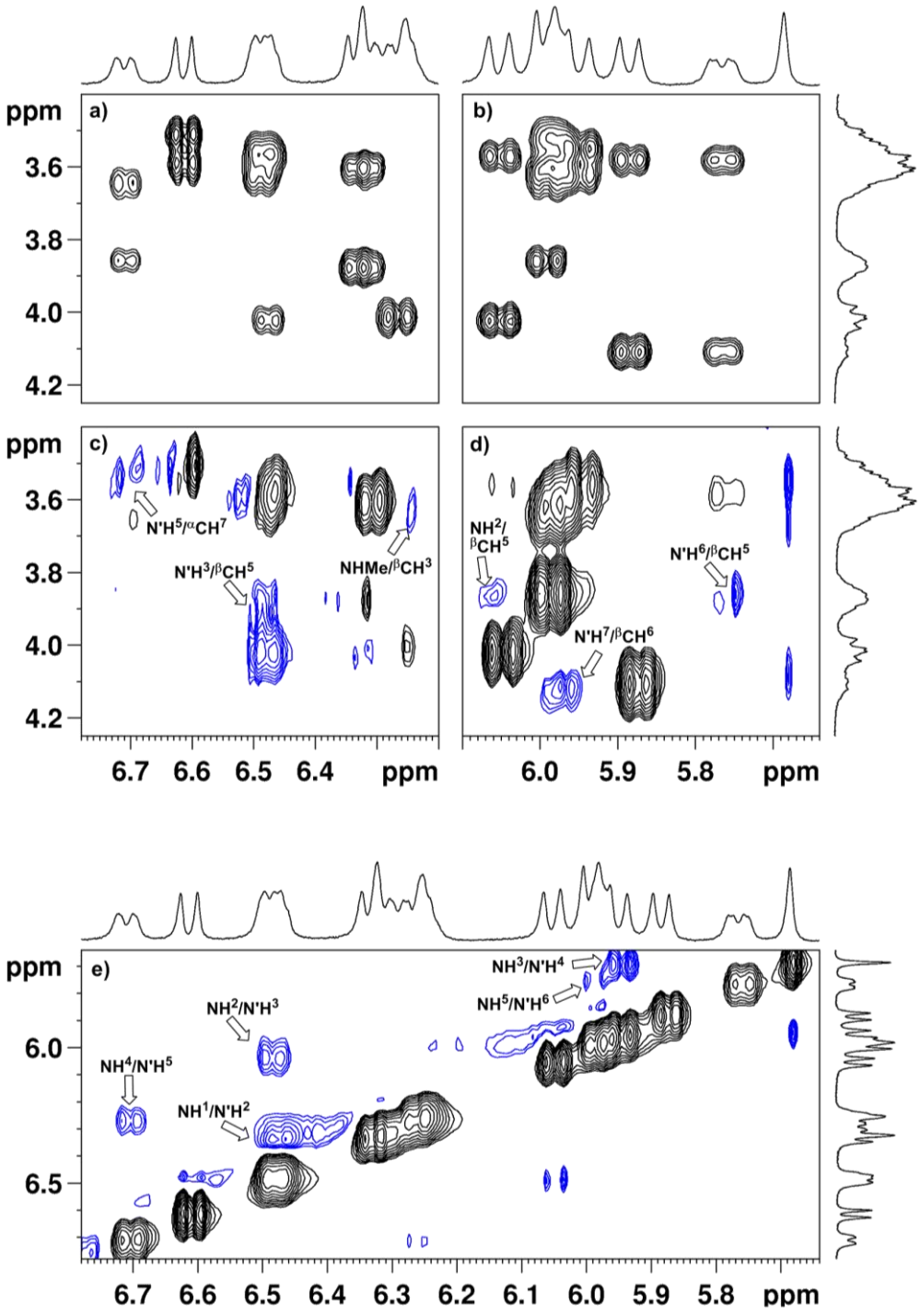
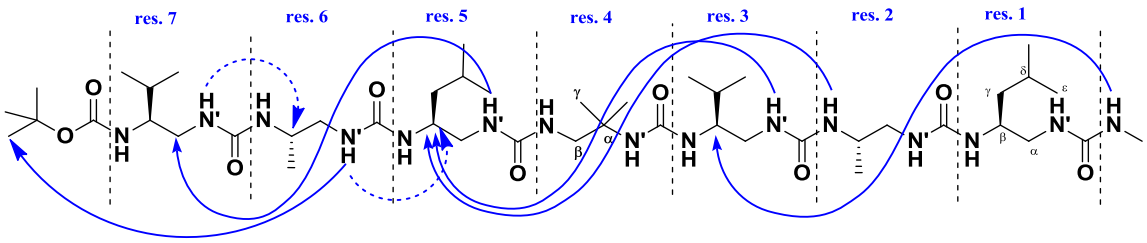
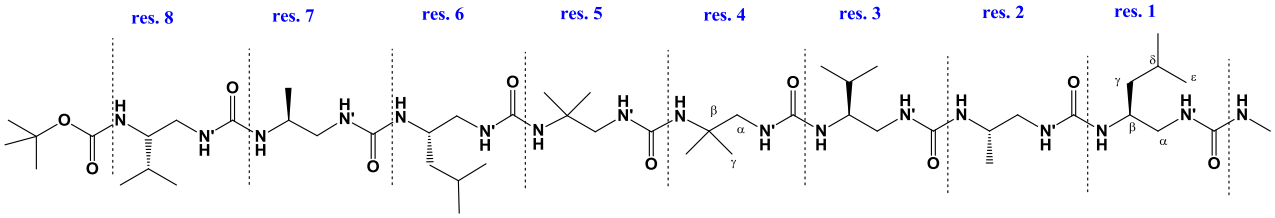


Figure S12: Representative sets of NOe connectivities observed for **3** in CD_3OH (400MHz). a) and b) part of the TOCSY plot shown for comparison c) and d) Part of the NH/CH region of the ROESY e) Part of the NH/NH region of the ROESY plot of **3.**



Scheme S10: NOE connectivities observed for **3** in CD_3OH. N'H(i+1)/$^{\beta}$CH(i) represented in dashed arrows have been attributed previously as *Z-E* isomerization[6]

Table S3: ^{1}H NMR chemical shifts (in ppm) of **4** in CD_3OH (400 MHz)



Residue		N'H	NH	$^{\alpha}$CH^{1}	$^{\alpha}$CH^{2}	$^{\beta}$CH	$^{\gamma}$CH	$^{\delta}$CH	$^{\varepsilon}$CH	term CH
	NH-Me		6,18							2,71
Leu^{u}	**U1**	6,37	6,14	3,56	2,67	3,85	1,68	1,20	0,90	
Ala^{u}	**U2**	6,20	5,84	3,49	2,41	3,96	1,04			
Val^{u}	**U3**	5,87	5,84	3,50	2,61	3,69	1,63	0,91		
Aib^{u}	**U4**	6,16	6,22	3,55	3,32		1,30 1,22			
Aib^{u}	**U5**	6,32	6,30	3,68	3,26		1,31 1,07			
Leu^{u}	**U6**	6,49	5,90	3,57	2,26	3,98	1,71	1,18	0,91	
Ala^{u}	**U7**	5,80	5,87	3,61	2,32	4,02	1,06			
Val^{u}	**U8**	5,99	6,64	3,47	2,55	3,63	1,64	0,93		
	Boc									1,47

[6] A. Violette, M. C. Averlant-Petit, V. Semetey, C. Hemmerlin, R. Casimir, R. Graff, M. Marraud, J.-P. Briand, D. Rognan, G. Guichard, *JACS*, **2005**, *127*, 2156-2164.

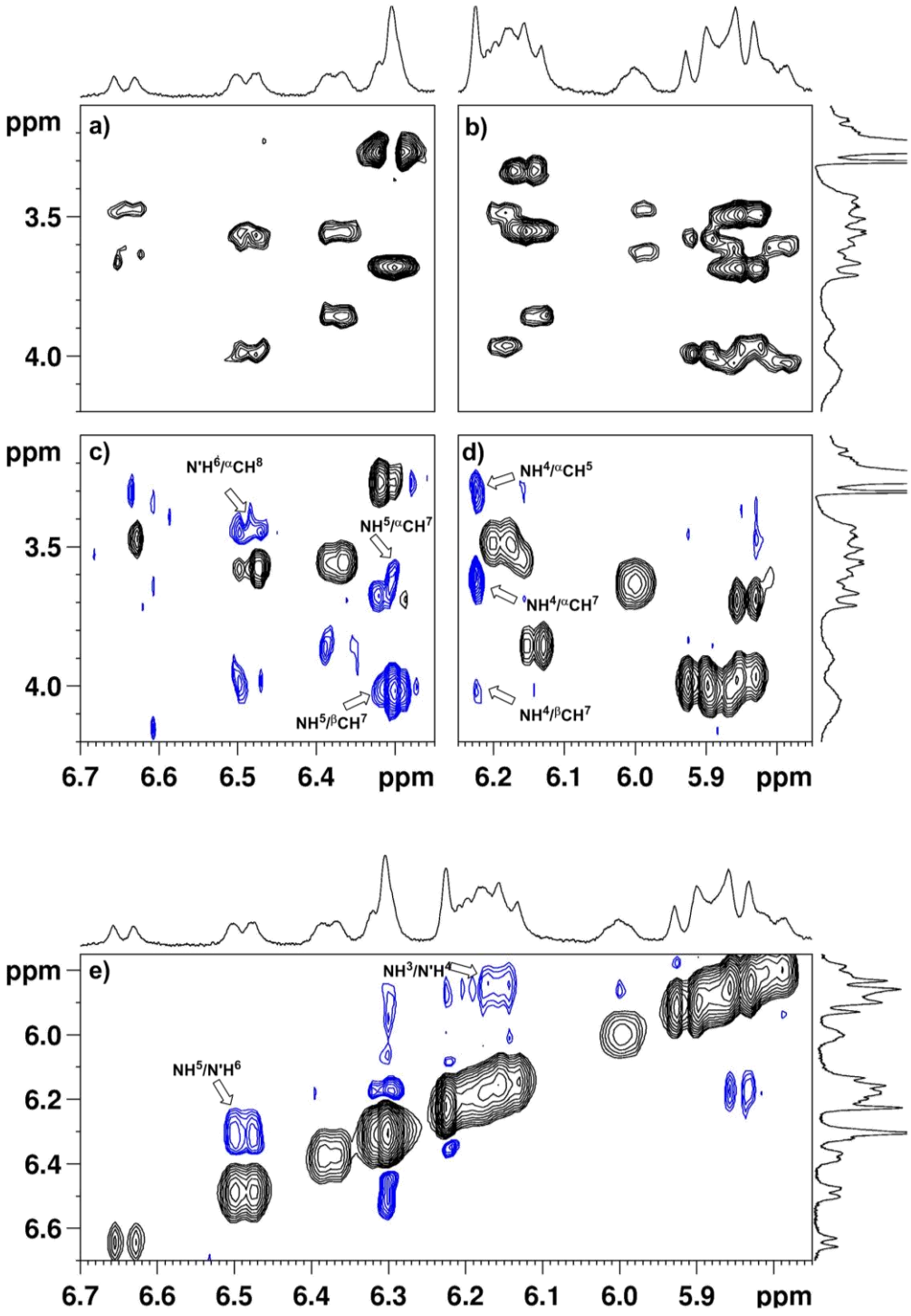
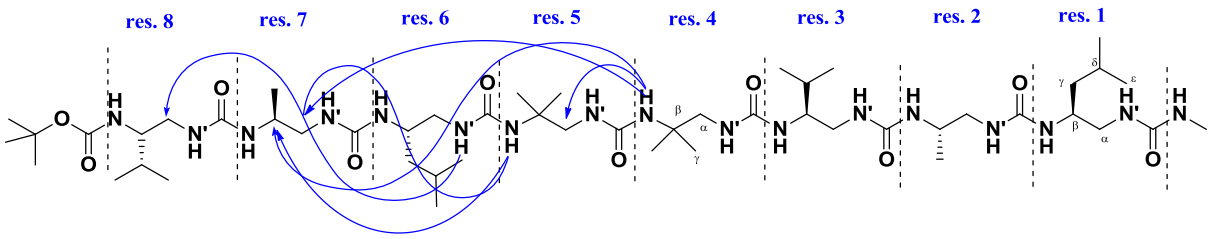
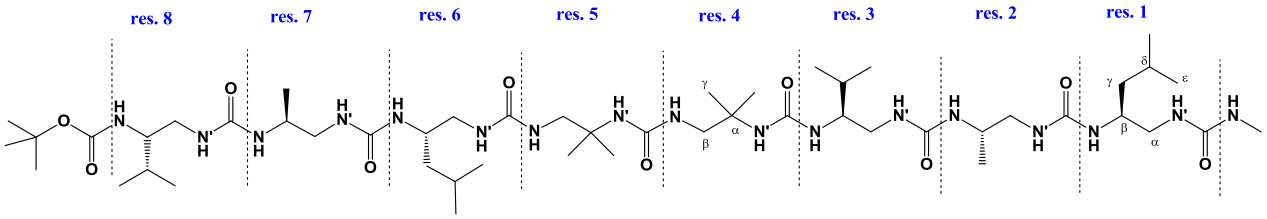


Figure S13: Representative sets of NOe connectivities observed for **4** in CD_3OH (400MHz). a) and b) part of the TOCSY plot shown for comparison c) and d) Part of the NH/CH region of the ROESY e) Part of the NH/NH region of the ROESY plot of **4.**



Scheme S11: NOE connectivities observed for **4** in CD_3OH.

Table S4: ^{1}H NMR chemical shifts (in ppm) of **5** in CD_3OH (700 MHz)



Residue		N'H	NH	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	$^{\delta}CH$	$^{\varepsilon}CH$	term CH
	NH-Me		6,23							2,73
Leu^{u}	**U1**	6,34	6,29	3,57	2,73	3,85	1,71	1,25	0,93	
Ala^{u}	**U2**	6,526	6,14	3,55	2,45	4,00	1,05			
Val^{u}	**U3**	6,46	5,86	3,56	2,51	3,55	1,61	0,91		
(Aib)$_{rev}^{u}$	**U4**	5,904	6,53			3,96 2,63	1,41 1,08			
(Aib)$_{rev}^{u}$	**U5**	5,899	6,46			3,76 2,86	1,38 1,22			
Leu^{u}	**U6**	6,65	5,94	3,65	2,54	3,98	1,72	1,22	0,94	
Ala^{u}	**U7**	5,81	5,84	3,50	2,34	4,08	1,02			
Val^{u}	**U8**	5,96	6,61	3,53	2,58	3,53	1,63	0,93		
	Boc									1,48

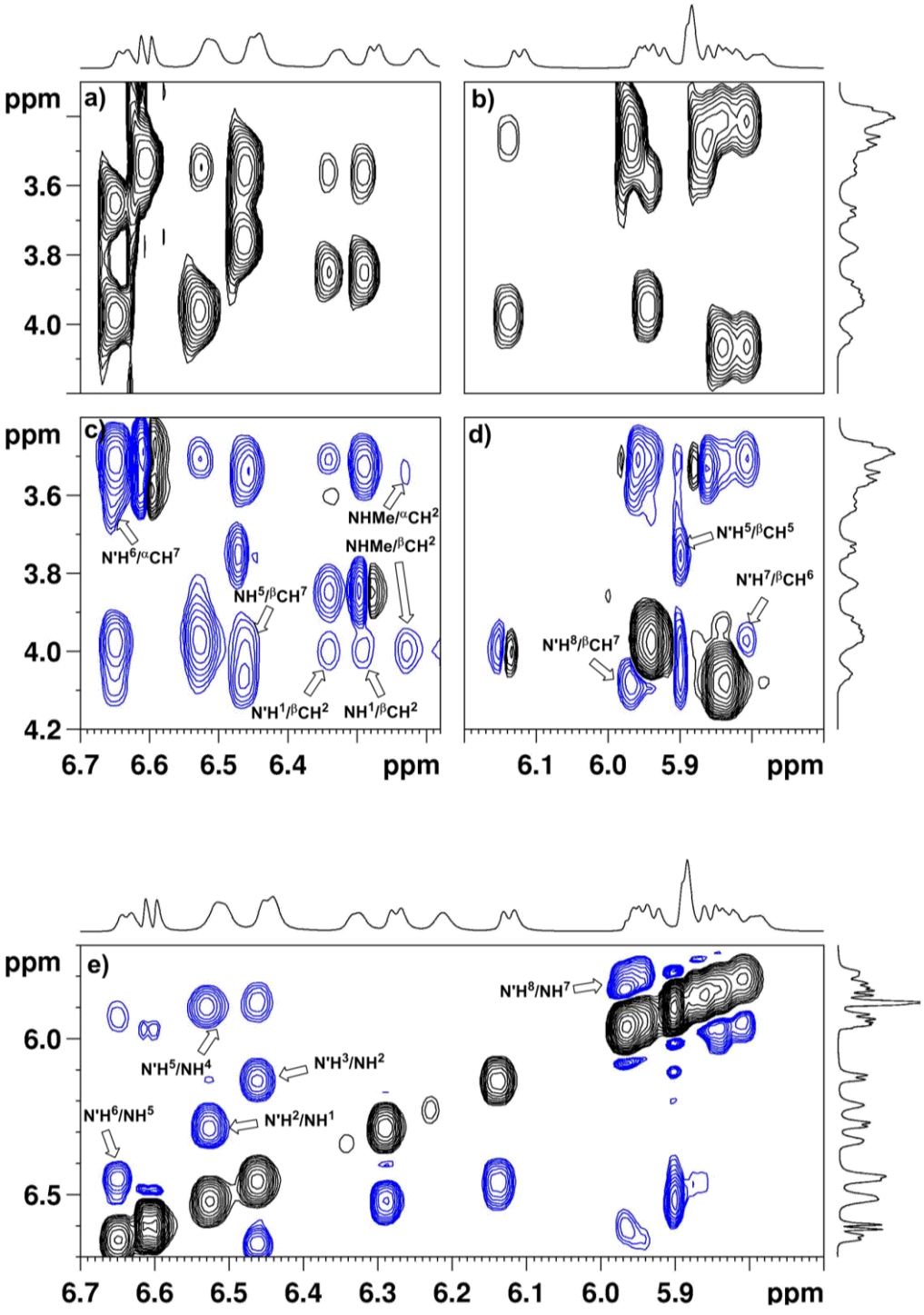
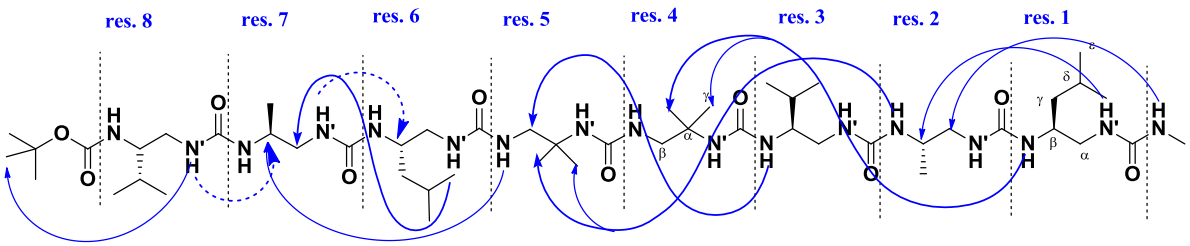
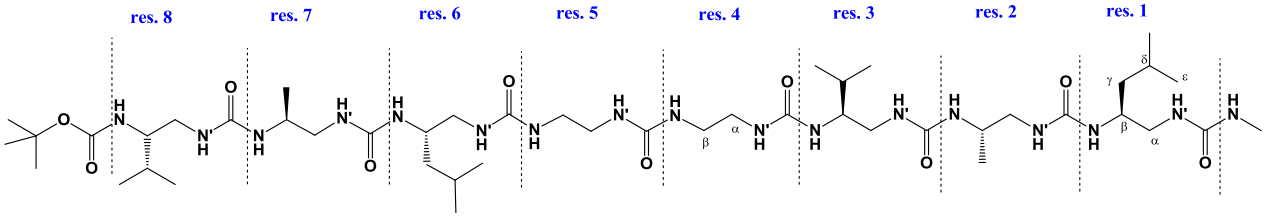


Figure S14: Representative sets of NOe connectivities observed for **5** in CD_3OH (700MHz). a) and b) part of the TOCSY plot shown for comparison c) and d) Part of the NH/CH region of the ROESY e) Part of the NH/NH region of the ROESY plot of **5.**



Scheme S12: NOE connectivities observed for **5** in CD_3OH. N'H(i+1)/$^{\beta}$CH(i) represented in dashed arrows have been attributed previously as *Z-E* isomerization[7]

Table S5: ^{1}H NMR chemical shifts (in ppm) of **6** in CD_3OH (600 MHz)



Residue		N'H	NH	$^{\alpha}$CH^{1}	$^{\alpha}$CH^{2}	$^{\beta}$CH	$^{\gamma}$CH	$^{\delta}$CH	$^{\varepsilon}$CH	term CH
	NH-Me		6.23							2.72
Leu^{u}	**U1**	6.44	6.05	3.57	2.68	3.89	1.70	1.24	0.93	
Ala^{u}	**U2**	6.45	6.10	3.55	2.40	4.03	1.04			
Val^{u}	**U3**	6.41	6.26	3.63	2.50	3.63	1.59	0.90		
Gly^{u}	**U4**	6.51	6.13	3.62	2.81	3.69 2.71				
Gly^{u}	**U5**	6.66	6.22	3.64	2.84	3.65 2.68				
Leu^{u}	**U6**	6.68	5.98	3.65	2.38	3.98	1.72	1.22	0.93	
Ala^{u}	**U7**	5.82	5.90	3.61	2.35	3.92	1.06			
Val^{u}	**U8**	6.02	6.65	3.51	2.57	3.63	1.65	0.95		
	Boc									1.48

Table S6: ^{1}H NMR anisochronicity (Δδ) values for main chain methylene protons in compounds **1**, **2** and **3**

Compound	P7	P6	P5	P4	P3	P2	P1
1	0,94	1,16	1,24	1,37	1,22	1,21	0,96
2	0,92	1,11	1,07	0,49	1,29	1,25	0,91
3	0,95	1,19	1,10	1,41	1,16	1,21	0,92

[7] A. Violette, M. C. Averlant-Petit, V. Semetey, C. Hemmerlin, R. Casimir, R. Graff, M. Marraud, J.-P. Briand, D. Rognan, G. Guichard, *JACS*, **2005**, *127*, 2156-2164.

Table S7: ^{1}H NMR anisochronicity (Δδ) values for main chain methylene protons in compounds **4**, **5** and **6**.

Compound	P8	P7	P6	P5	P4	P3	P2	P1
4	0,89	1,08	0,89	0,42	0,23	1,31	1,29	0,92
5	0,84	1,10	1,05	1,33	0,90	1,11	1,16	0,95
6	0,94	1,26	1,27	0.97-0.80	0.98-0.81	1,13	1,15	0,89

Circular dichroism (CD) measurements

All Circular dichroism (CD) spectra were recorded on a J-815 Jasco dichrographe (Jasco France, Nantes, France).
Spectra were acquired between 300 and 180 nm at a concentration of 0.2 mM in 2,2,2-trifluoroethanol (NMR grade, ≥99.5%) using a quartz cell with a path length of 1 mm (Hellma 110-QS 1mm, Paris, France).
Sample temperature was regulated at 20°C. Data were collected in continuous scan mode with a data pitch of 0.1 nm, a scanning speed of 50 nm.min^{-1}, 2 nm bandwith and 2 accumulations per sample. Sample Data were collected as raw ellipticity (ψ in mdeg) and converted to mean residue ellipticity (MRE or [θ]) in deg.cm^2.dmol^{-1}.residue^{-1} using the following equation:

$$[\theta] = \frac{\psi \times 10^{-3}}{res \times l \times c}$$

Where *res* is the number of residues in the oligomer, *l* is the pathlength in cm, and *c* is the Oligourea concentration in dmol.cm^{-3}.

X-Ray diffraction studies

Data collections were performed at the IECB X-ray facility at room temperature on rotating anode sources. Crystal structures of compounds **2** and **3** were solved from data collected on a Rigaku micromax MM07 equiped with a partial chi goniometer and a detector IP RAPID .The data for the crystal structure of compound **5** were collected on a Bruker microstar X8 PROTEUM with a classical kappa geometry and Platinum135 CCD camera. All the statistics are compiled in table S7. All structures were solved by the ab-initio method implemented in SHELXD and refined with SHELXL (Sheldrick, G.M. Acta Cryst. A64, 2008, 112-122). Full-matrix least-squares refinement was performed on F^2 for all unique reflections, minimizing $w(Fo^2- Fc^2)^2$, with anisotropic displacement parameters for non-hydrogen atoms. The positions of the H atoms were deduced from coordinates of the non-H atoms. The non-H atoms were refined with anisotropic temperature parameters. H atoms were included for structure factor calculations but not refined

CCDC 922576 (**2**), CCDC 922577 (**3**) and CCDC 922578 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S8: Crystallographic data for compounds **2**, **3** and **5**

Compound	**2**	**3**	**5**
CCDC code			
Formula	C23.50 H48.50 N7.50 O5 S0.50	C90 H183 N30 O19	C25 H50.50 N8.50 O6
M	532.23	1989.66	566.24
Crystal system	triclinic	monoclinic	monoclinic
Space group	P1	P2(1)	P2(1)
***a*/Å**	9.866(2)	14.2758(7)	10.658(2)
***b*/Å**	10.472(2)	10.5020(7)	18.807(4)
***c*/Å**	16.893(3)	39.927(3)	17.672(4)
α/o	96.60(3)	90.00	90.00
β/o	95.35(3)	90.983(6)	106.39(3)
γ/o	113.94(3)	90.00	90.00
***V*/Å^3**	1565.7(5)	5985.1(6)	3398.2(12)
T /K	293(2)	293(2)	293(2)
Z	2	2	4
ρ/g cm^{-1}	1.129	1.104	1.107
size (mm)	0.2x 0.02x 0.01	0.05x 0.05x 0.01	0.1x0.02x0.01
λ/ Å	1.54178	1.54178	1.54178
μ/mm^{-1}	0.951	0.641	0.656
Independent reflections	8949	9534	5521
measured reflections	18961	56320	13718
parameters/restraints	677/3	1284/1	708/4
***R*1, *wR*2**	0.1196/ 0.3192	0.0459/ 0.0833	0.0676/0.1834
goodness of fit	1.113	0.874	1.072