SUPPORTING INFORMATION

Homooligomers of substituted proline and β-prolines: syntheses and secondary structure investigation.

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1. Contents

1. General information

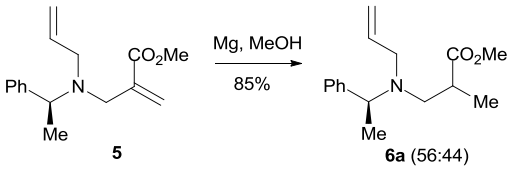
Experiments involving organometallic compounds were carried out in dried glassware under a positive pressure of dry N_2 or Ar and liquid nitrogen was used as a cryoscopic fluid. A three-necked, round-bottomed flask equipped with an internal thermometer, a septum cap and a nitrogen or Ar inlet was used. Anhydrous solvents were distilled to remove stabilizers and dried with a double column purification system. $ZnBr_2$ (98%) was melted under dry N_2 or Ar and, cooled to room temperature under vacuum, and immediately dissolved in anhydrous Et_2O or THF. All other reagents and solvents were of commercial quality and were used without further purification. All compounds were homogeneous by TLC analysis and had spectral properties consistent with their assigned structures. Column chromatography was performed on Silica Gel 60 (E. Merck).

^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer fitted with a BBFO probe or with a Bruker ARX 200 spectrometer fitted with a dual probe ($^{13}C/^1H$). Chemical shifts are reported in ppm units relative to an internal standard of residual chloroform (δ= 7.27 ppm for ^1H NMR spectra and δ = 77.16 ppm for ^{13}C NMR spectra). The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, and (br) broad. IR spectra were recorded with a diamond ATR spectrometer. High-resolution mass spectra (HRMS) were obtained with a Finnigan MAT 95 instrument. Optical rotations were measured with a Perkin–Elmer Model 241 digital polarimeter at 22 ± 3 °C. Peptides were characterized by MALDI-TOF MS (DE-Pro, ABI) in positive ion reflector mode using the matrix CHCA.

RP-HPLC was performed using a Waters setup, comprised of a Waters 1525 binary pump system with a Waters 2487 dual wavelength absorbance detector and using Breeze software. Analytical RP-HPLC was performed using an ACE reversed-phase C8 or C18 column (4.6 × 100 mm), using Solvent A: 0.1% TFA in water and solvent B: 0.1% TFA in CH_3CN, at a flow rate of 1.0 mL min^{-1} and UV detection at 220 nm. Semi-preparative RP-HPLC was performed using an ACE 5 Å C8 or C18 column (250 × 100 mm) with a flow rate of 5 mL min^{-1} using the appropriate gradient.

2. Monomer synthesis

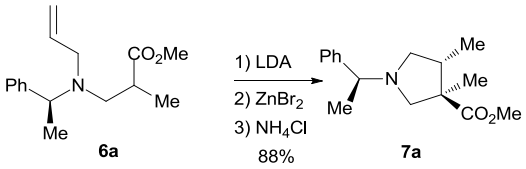
(2S,3R)-prolinovaline **1** was synthesized as previously described using (*S*)-phenylethylamine as chiral inducer and benzyl ester as carbonyl protecting group.[1, 2]



5 **6a** (56:44)

Methyl 3-(*N*-allyl-*N*-((*S*)-1-phenylethyl)amino)-2-methylpropanoate (6a):

To a MeOH (280 mL) solution of (1'*S*)-2-{[(allyl)-(1'-phenyl-ethyl)-amino]-methyl}-acrylic acid methyl ester **5** (11.2 g, 43.02 mmol) was added magnesium (3.1 g, 129.00 mmol). The mixture was stirred at RT for 21h and an aqueous solution of NH_4Cl/NH_4OH (2:1) was added. The aqueous layer was extracted with EtOAc (53). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford amino enoate **6a** (9.6 g, 85 %, d.r. = 56:44) as a colourless oil that was used without further purification. The analytical data were in agreement with those reported previously.[3]

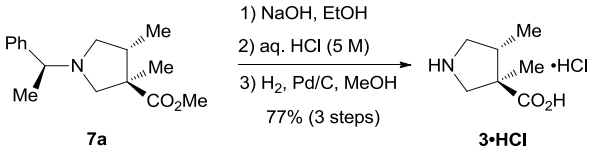


6a **7a**

(3*R*,4*R*)-methyl 3,4-dimethyl-1-((*S*)-1-phenylethyl)pyrrolidine-3-carboxylate (7a):

Under a nitrogen atmosphere, diisopropylamine (2.27 mL, 15.84 mmol) was added to *n*-BuLi (6.48 mL, 2.2 M in hexanes, 14.25 mmol) placed in a 4-necked round-bottom flask. After the gummy mixture had been formed, Et_2O (30 mL) was added and the resulting solution was cooled to –70 °C. A solution of ester **6a** (1.38 g, 5.28 mmol) in Et_2O (20 mL) was added drop-wise and the mixture was stirred for 2 h keeping the temperature below –20 °C before being cooled down to –70 °C. $ZnBr_2$ (15.84 mL, 15.84 mmoL, 1M in Et_2O) was added drop-wise at this temperature. The cold bath was removed and the turbid mixture was stirred at

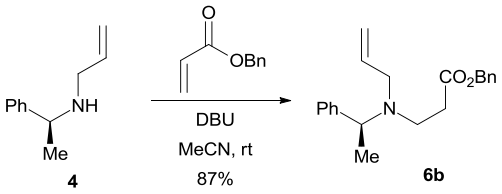
room temperature for 3 hours. An aqueous solution of NH_4Cl/ NH_4OH (2/1) (50 mL) and Et_2O (80 mL) were added. The layers were separated, the aqueous one being extracted with Et_2O (3550 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate = 90:10) afforded **7a** (1,240 g, 88%) as colourless oil. The spectral data were in agreement with those reported previously.[3]



7a **3•HCl**

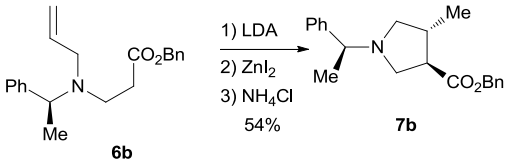
(3*R*,4*R*)-3,4-dimethylpyrrolidine-3-carboxylic acid hydrochloride (3•HCl):

NaOH (12 M, 1.5 mL, 19.06 mmol) was added to a solution of pyrrolidine **7a** (1.66 g, 6.35 mmol) in EtOH (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 h. HCl (5 M) was added until the pH remained acid (pH ≤ 3) and the reaction mixture was stirred at rt for 10 min. The layers were separated and the aqueous one was extracted with CH_2Cl_2 (2520 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (29 mL) and Pd/C (10 wt. %, 246.5 mg, 0.231 mmol) was added. The reaction mixture was stirred at room temperature for 14 h under H_2 atmosphere. The mixture was then filtered over celite and the solvents evaporated under reduced pressure to give pure **3** (865 mg, 77%) that was used without further purification. $[\alpha]^{23}_D$ = +2.4 (c = 1.0, MeOH). IR (neat): 3375, 1570, 1460, 1410, 750 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ 3.78 (d, J = 12.0 Hz, 1H), 3.51 (dd, J = 11.5, 7.5 Hz, 1H), 3.22 (d, J = 12.0 Hz, 1H), 3.04 (m, 1H), 2.67 (m, 1H), 1.29 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD): δ 180.4, 53.4, 50.9, 50.2, 39.5, 15.6, 10.9. HRMS (ESI) calcd for $C_7H_{14}NO_2$ [M^+] 144.1019, found 144.1024.



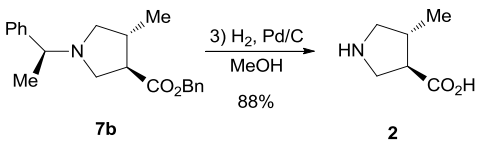
Benzyl 3-(*N*-allyl-*N*-((*S*)-1-phenylethyl)amino)propanoate (6b):

To a stirred solution of *N*-((*S*)-1-phenylethyl)prop-2-en-1-amine (**4**) (4.9 g, 30.4 mmol) in CH_3CN (30 mL) were added DBU (4.6 g, 30.4 mmol) and benzyl acrylate (7.39 g, 45.6 mmol) at room temperature. The solution was stirred at room temperature until completion (72 h). The reaction was quenched with NH_4Cl. Et_2O was added and the layers were separated, the aqueous one being extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification by flash chromatography (cyclohexane / ethyl acetate = 97:3 to 90:10) afforded amino enoate **6b** (8.5 g, 87%) as a colourless oil. IR (neat): 2972, 1735, 1451, 1175, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.27 (m, 10H), 5.82 (m, 1H), 5.22-5.09 (m, 2H), 5.14 (s, 2H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.15 (dd, *J* = 14.5 (AB system), 6.4 Hz, 1H), 3.04 (dd, *J* = 14.5 (AB system), 6.3 Hz, 1H), 2.93 (m, 1H), 2.84 (m, 1H), 2.53 (t, *J* = 7.2 Hz, 2H), 1.38 (d, *J*= 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 172.6, 143.8, 136.7, 136.1, 128.6, 128.3, 128.2, 128.1, 127.7, 126.8, 116.8, 66.2, 59.0, 53.3, 45.5, 33.4, 16.9. HRMS (ESI) calcd for $C_{21}H_{26}NO_2$ $[MH^+]$ 324.1958, found 324.1963.



(3R,4R)-benzyl 4-methyl-1-((S)-1-phenylethyl)pyrrolidine-3-carboxylate (7b):

Under a nitrogen atmosphere, diisopropylamine (1.96 mL, 13.93 mmol) was added to *n*-BuLi (6.02 mL, 2.1 M in hexanes, 12.53 mmol) placed in a 4-necked round-bottom flask. After the gummy mixture had been formed, Et_2O (25 mL) was added and the resulting solution was cooled to –78 °C. (*S*)-benzyl 3-(allyl(1-phenylethyl)amino)propanoate **6b** (1.5 g, 4.64 mmol) in Et_2O (25 mL) was then added, and the reaction mixture was stirred for 2 h keeping the temperature below –35 °C. The cold mixture was added via canula to an etheral solution of ZnI_2 (32.5 mL, 1M in Et_2O, 32.5 mmol) kept at –10 °C. The resulting biphasic mixture was next allowed to warm to room temperature and was stirred for 14 h. An aqueous solution of NH_4Cl/NH_3 (2:1) was then added. The layers were separated, and the aqueous one was extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography (cyclohexane / ethyl acetate = 96:04 to 90:10) afforded pyrrolidine **7b** (804 mg, 54%) as a pale yellow oil. $[\alpha]^{26}_D$ = – 8.5 (c = 1.0, $CHCl_3$). IR (neat): 2954, 1729, 1427, 1246, 835 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 5.17 (d(AB system), *J* = 12.6 Hz, 1H), 5.13 (d(AB system), *J* = 12.6 Hz, 1H), 3.23 (q, *J* = 6.6 Hz, 1H), 2.98 (dd, *J*= 13.8, 7.0 Hz, 1H), 2.72 (m, 2H), 2.65-2.42 (m, 2H), 2.23 (m, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H). ^{13}C RMN (75 MHz, CDCl3) δ 174.7, 145.5, 136.2, 128.6, 128.4, 128.2, 128.1, 127.3, 127.0, 66.4, 65.5, 60.6, 55.6, 50.5, 36.8, 23.1, 19.7. HRMS (ESI) calcd for $C_{21}H_{26}NO_2$ $[MH^+]$ 324.1958, found 324.1965.



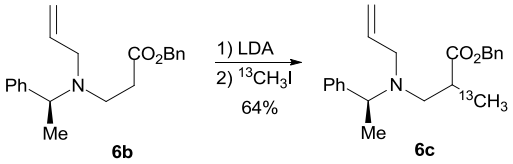
7b **2**

(3R,4R)-4-methylpyrrolidine-3-carboxylic acid (2):

To a solution of pyrrolidine **7b** (930 mg, 2.78 mmol) in MeOH (28 mL) was added Pd/C (10 wt. %, 915 mg, 0.83 mmol). The reaction mixture was stirred at room temperature for 14 h

under H_2 atmosphere. The mixture was then filtered over celite and the solvents evaporated under reduced pressure to give cyclic amino acid **2** (315 mg, 88%).

$[\alpha]^{23}_D$ = +13.5 (c = 1.0, MeOH). IR (neat) : 3300, 1590, 1395, 1020, 750 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 3.44 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.41 (d, *J* = 7.8 Hz, 2H), 3.27 (m, NH), 2.76 (dd, *J* = 11.4, 8.8 Hz, 1H), 2.51 (q, *J* = 8.0 Hz, 1H), 2.49-2.40 (m, 1H), 1.14 (d, *J* = 6.5 Hz, 3H). ^{13}C RMN (101 MHz, MeOD): δ 177.2, 52.8, 51.3, 48.3, 37.7, 15.8. HRMS (ESI) calcd for $C_6H_{11}NO_2Na$ [MNa^+] 152.0682, found 152.0681.

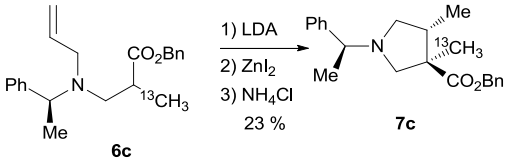


6b **6c**

Benzyl 3-(N-allyl-N-((S)-1-phenylethyl)amino)-2-(^{13}C)methylpropanoate (6c):

Under a nitrogen atmosphere, diisopropylamine (1.07 mL, 7.65 mmol) was added to *n*-BuLi (3.02 mL, 2.3 M in hexanes, 6.96 mmol) placed in a round-bottom flask. After the gummy mixture had been formed, THF (10 mL) was added and the resulting solution was cooled to – 78 °C. A solution of *(S)*-benzyl 3-(allyl(1-phenylethyl)amino)propanoate (**6b**) (1.5 g, 4.64 mmol) in THF (10 mL) was added drop wise. The solution was stirred for 1.5 h keeping the temperature below – 50 °C. The mixture was cooled to – 78°C and a solution of iodomethane-^{13}C (1.32 g, 9.28 mmol) in THF (3 mL) was added slowly. The solution was stirred at – 78 °C for 1 h and then the cold bath was removed and the reaction mixture was stirred at room temperature overnight. A NH_4Cl/NH_3 (2/1) solution (30 mL) and Et_2O (20 mL) were added and the layers were separated. The aqueous one was extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane / ethyl acetate = 95:5) afforded amino enoate **6c** (1.0 g, 64%, d.r. = 62:38) as a colorless oil.

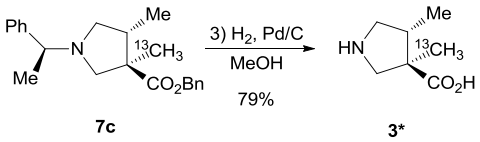
IR (neat): 3029, 1732, 1275, 1176, 750 cm^{-1}. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 10H), 5.85-5.72 (m, 1H), 5.23-5.02 (m, 4H), 3.98-3.87 (m, 1H), 3.14-3.06 (m, 1H), 3.05-2.97 (m, 1H), 2.92-2.81 (m, 1H), 2.80-2.69 (m, 1H), 2.57 (m, 1H-minor), 2.35 (ddd, *J* = 12.8, 6.3, 2.6 Hz, 1H-major), 1.34 (d, *J* = 6.9 Hz, 3H), 1.15 (dd, *J* = 128.2, 6.7 Hz, 3H-minor), 1.09 (dd, *J* = 128.3, 6.9 Hz, 3H-major). ^{13}C RMN (100 MHz, $CDCl_3$) Major isomer : δ 176.2, 143.1, 137.2, 136.4, 128.6, 128.2, 128.1, 128.0, 127.9, 126.8, 116.6, 66.1, 58.9, 53.9, 53.7, 39.6 (d, *J* = 34.0 Hz), 31.8, 16.1, 15.4. Minor isomer : δ 176.0, 143.7, 137.0, 136.3, 128.6, 128.1, 128.0, 127.9, 126.8, 116.6, 58.6, 58.2, 53.8, 53.4, 39.3 (d, *J* = 34.0 Hz), 31.9, 15.6, 15.3. HRMS (ESI) calcd. for $C_{21}H_{27}{}^{13}CNO_2Na$ [MNa^+] 361.1968, found 361.1957.



(3R,4R)-benzyl-3-(^{13}C),4-dimethyl-1-((S)-1-phenylethyl)pyrrolidine-3-carboxylate (7c):

Under a nitrogen atmosphere, diisopropylamine (1.21 mL, 5.61 mmol) was added to *n*-BuLi (2.19 mL, 2.3 M in hexanes, 5.05 mmol) placed in a 4-neck mechanically stirred round-bottom flask. After the gummy mixture had been formed, Et_2O (20 mL) was added and the resulting solution was cooled to –78 °C. A solution of enoate **6c** (1.5 g, 4.64 mmol) in Et_2O (25 mL) was added drop wise, and the solution was stirred for 1.5 h keeping the temperature below – 35 °C. The mixture was cooled to – 60 °C and an ethereal solution of zinc bromide (5.6 mL, 1 M in Et_2O, 5.6 mmol) was added. The cooling bath was removed at the end of the addition. The turbid mixture was stirred at room temperature for 14 h and then hydrolyzed with an aqueous solution of NH_4Cl/NH_3 (2:1). The layers were separated, and the aqueous one was extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (cyclohexane/AcOEt = 85:15) afforded pyrrolidine **7c** (343 mg, 23%) as a yellow oil.

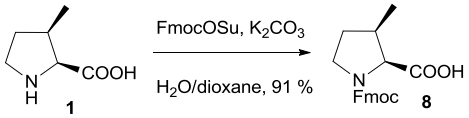
$[\alpha]^{23}_D$ = –12.4 (c = 1.0, $CHCl_3$). IR (neat): 2980, 1740, 1460, 1300, 760, 680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 10H), 5.16 (d(AB system), *J* = 12.6 Hz, 1H), 5.14 (d(AB system), *J* = 12.6 Hz, 1H), 3.41 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.26-3.23 (m, 1H), 2.79 (t, *J* = 8.3 Hz, 1H), 2.64 (ddt, *J* = 10.9, 7.5, 3.5 Hz, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.16 (d, *J* = 128.3 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 145.6, 136.4, 128.6, 128.4, 128.1, 127.8, 127.3, 127.0, 66.4, 66.0, 65.4, 59.7, 50.4 (d, *J* = 36.1 Hz), 38.6, 19.2, 18.9, 18.2. HRMS (ESI) calcd. for $C_{21}H_{27}{}^{13}CNO_2Na$ $[MNa^+]$ 361.1968, found 361.1982.



7c **3***

(3R,4R)-3-(^{13}C),4-dimethylpyrrolidine-3-carboxylic acid (3*):

To a solution of pyrrolidine **7c** (300 mg, 0.89 mmol) in MeOH (9 mL), Pd/C (10 wt. %, 823 mg, 0.267 mmol) was added. The reaction mixture was stirred at room temperature for 14 h under H_2 atmosphere. The mixture was then filtered and the solvents evaporated under reduced pressure to give ^{13}C-labelled cyclic amino acid **3*** (101 mg, 79%) as a yellow solid. $[\alpha]^{23}_D$ = –11.0 (c = 1.0, MeOH). IR (neat): 3375, 1570, 1460, 1410, 750 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ 3.75 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.49 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.06 (d, *J* = 11.4, 4.3 Hz, 1H), 2.95 (dd, *J* = 11.5, 8.2 Hz, 1H), 2.67 (m, 1H), 1.23 (d, *J* = 127.4 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, MeOD): δ 180.4, 54.4, 52.5 (d, *J* = 36.6 Hz) 50.9, 39.9, 16.6, 15.2. HRMS (ESI) calcd for $C_6{}^{13}CH_{14}NO_2$ $[MH^+]$ 145.1053, found 145.1057.

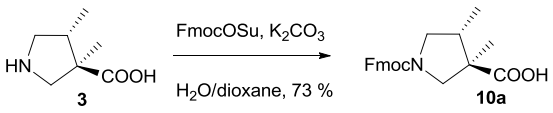


1 **8**

_N_-Fmoc (2S,3R)-prolinovaline 8:

To a solution of (2S,3R)-prolinovaline **1** (0.57 g, 4.43 mmol, 1 eq.) in H_2O/dioxane 1:1 (100 mL) were added FmocOSu (1.57 g, 4.65 mmol, 1.05 eq.) and K_2CO_3 (1.29 g, 9.30 mmol, 2.1 eq.). The reaction mixture was stirred at RT for 3 hours then concentrated under reduced pressure. The residue was diluted with water (50 mL), acidified to pH=1 by adding HCl 1N and then extracted with EtOAc (3*30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate + 0.1% AcOH 1:1 to 3:7) afforded **8** (1.42 g, 4.04 mmol, 88%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.68 (m, 2H), 7.65-7.50 (m, 2H), 7.45-7.26 (m, 4H), 4.53-4.08 (m, 4H), 3.74 (dd, J = 19.7, 9.7 Hz, 1H), 3.53-3.33 (m, 1H), 2.66-2.45 (m, 1H), 2.09-1.92 (m, 1H), 1.92-1.58 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5, 176.1, 155.0, 154.4, 144.0, 143.8, 143.7, 141.2, 127.6, 127.6, 127.0, 125.1, 125.0, 124.9, 119.9, 119.9, 67.6, 63.1, 62.7, 47.1, 46.5, 46.1, 37.2, 36.1, 31.9, 30.9, 14.7, 14.7.

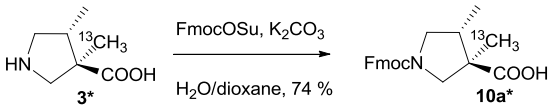


_N_-Fmoc (3R,4S)-dimethyl-β-proline 10a:

To a solution of (3R,4S)-3,4-dimethyl-β-prolinovaline **3** (508 mg, 3.55 mmol, 1 eq.) in H_2O/MeCN 1:1 (26 mL) were added FmocOSu (1.19 g, 3.55 mmol, 1 eq.) and K_2CO_3 (490 mg, 3.55 mmol, 1 eq.). The reaction mixture was stirred at RT for 5 hours then MeCN was removed under reduced pressure. The solution was acidified to pH=2 by adding HCl 1N and then extracted with DCM (3*15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography on

silica gel (cyclohexane/ethyl acetate/AcOH 85:14:1 v:v:v) afforded **10a** (832 mg, 2.27 mmol, 64 %) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 7.4 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.31 (tt, J = 6.3, 3.2 Hz, 2H), 4.39 (m, 2H), 4.25 (t, J = 7.1 Hz, 1H), 3.84 (t, J = 11.2 Hz, 1H), 3.76-3.61 (m, 1H), 3.45 (dd, J = 21.5, 10.9 Hz, 1H), 3.08 (dd, J = 21.5, 10.9 Hz, 1H), 2.78-2.58 (m, 1H), 1.25 (d, J = 3.5 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 154.8, 143.8, 141.2, 127.6, 127.0, 124.9, 119.9, 67.3, 67.3, 55.7, 55.4, 51.5, 51.2, 50.5, 49.6, 47.1, 47.1, 39.3, 38.6, 25.3, 16.1, 16.0, 12.3, 12.2.

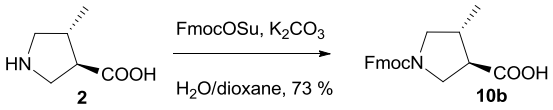


_N_-Fmoc (3R,4R)-3-(^{13}C),4-dimethyl-β-proline 10a*:

To a solution of (3R,4R)-3,4-dimethyl-β-prolinovaline **3*** (89 mg, 0.62 mmol, 1 eq.) in H_2O/dioxane 1:1 (22 mL) were added FmocOSu (219 mg, 0.65 mmol, 1.05 eq.) and K_2CO_3 (180 mg, 1.80 mmol, 2.1 eq.). The reaction mixture was stirred at RT overnight then dioxane was removed under reduced pressure. The solution was acidified to pH=2 by adding HCl 1N and then extracted with EtOAc (3*15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate/AcOH 70:30:1 v:v:v to 50:50:1) afforded **10a*** (168 mg, 0.46 mmol, 74 %) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 7.4 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.36-7.28 (m, 2H), 4.44-4.36 (m, 2H), 4.24 (t, J = 7.1 Hz, 1H), 3.84 (td, J = 11.2, 5.1 Hz, 1H), 3.76-3.62 (m, 1H), 3.45 (ddd, J = 21.8, 10.9, 4.7 Hz, 1H), 3.08 (dd, J = 21.3, 10.8 Hz, 1H), 2.78-2.58 (m, 1H), 1.25 (dd, J = 128.4, 3.5 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 180.5, 154.8, 144.0, 141.3, 127.7, 127.0, 125.0, 120.0, 67.3, 55.8, 55.4, 51.7, 51.3, 47.2, 39.4, 38.7, 16.2 (d, J = 9.6 Hz), 14.8, 14.6, 12.4.



***N*-Fmoc (3R,4R)-β-prolinovaline 10b:**

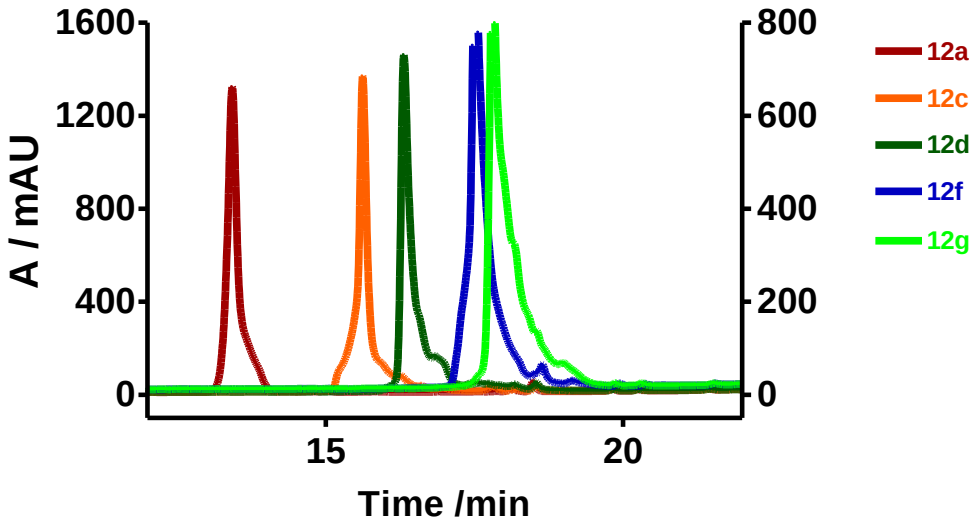
To a solution of (3R,4S)-β-prolinovaline **2** (269 mg, 2.08 mmol, 1 eq.) in H_2O/dioxane 1:1 (100 mL) were added FmocOSu (732 mg, 2.17 mmol, 1.05 eq.) and K_2CO_3 (604 mg, 2.10 mmol, 2.1 eq.). The reaction mixture was stirred at RT for 3 hours then concentrated under reduced pressure. The residue was diluted with water (50 mL), acidified to pH=1 by adding HCl 1N, and then extracted with EtOAc (3*15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate + 0.1% AcOH 1:1 to 3:7) afforded **10a** (536 mg, 1.54 mmol, 73%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 7.4 Hz, 2H), 7.60 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 4.49-4.31 (m, 2H), 4.31-4.19 (m, 1H), 3.90-3.60 (m, 3H), 3.14-2.97 (m, 1H), 2.85-2.64 (m, 1H), 2.64-2.45 (m, 1H), 1.19 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6, 177.5, 154.7, 154.7, 143.9, 143.8, 141.2, 127.7, 127.0, 125.0, 119.9, 67.5, 67.4, 52.9, 52.5, 50.1, 49.3, 48.4, 48.0, 47.2, 37.2, 36.5, 17.0, 16.9.

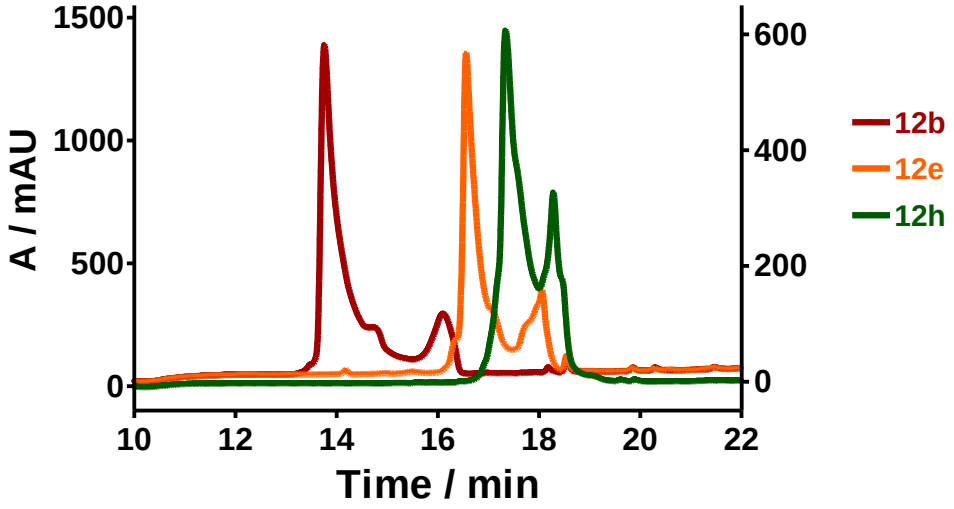
3. Characterization of oligomers

(2S,3R)-3-methyl-proline oligomers **12a-h**

Oligomer	Retention Time (min)	MW / g.mol^{-1}	MALDI-TOF $[M+Na]^+$ / g.mol^{-1}
12a dimer	13.4	281.35	304.16
12b trimer	13.8 (83%) 16.1 (17%)	392.49	415.23
12c tetramer	15.6	503.63	526.27
12d pentamer	16.3	614.78	637.37
12e hexamer	16.6 (77%) 18.1 (23%)	725.92	748.65
12f heptamer	17.5	837.06	859.28
12g octamer	17.8	948.20	970.35
12h nonamer	17.1 (67%) 18.0 (33%)	1059.34	1081.82

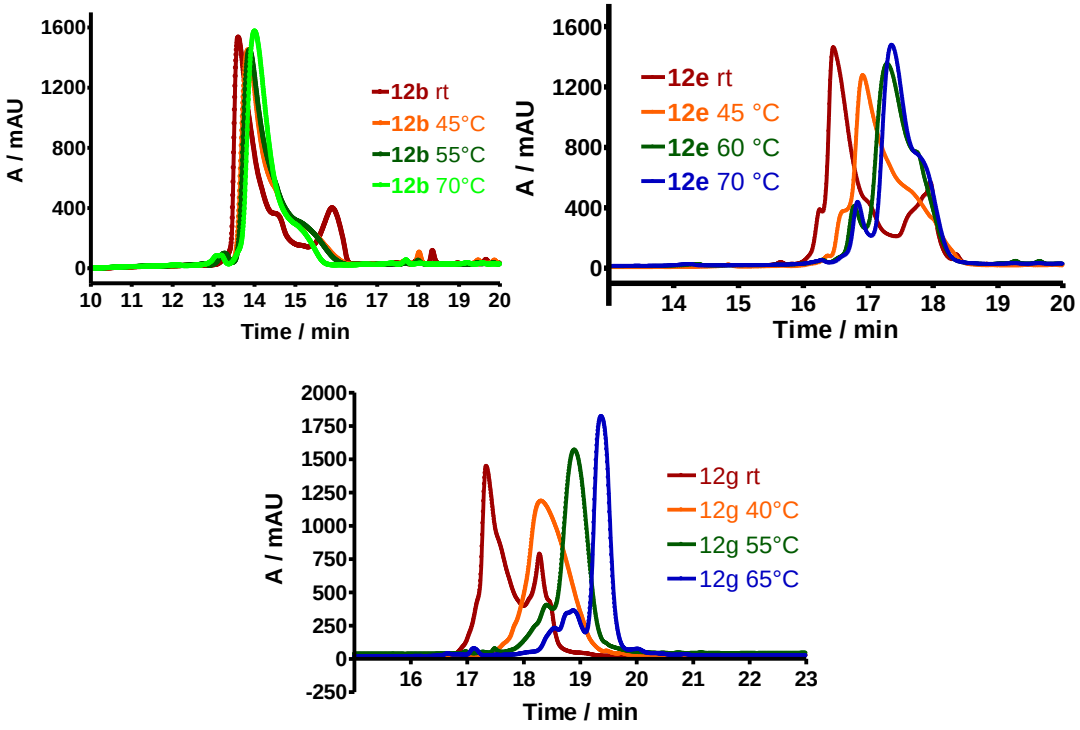


Overlap of HPLC traces of oligomers **12a**, **12c-d** and **12f-g**: elution through a Symmetry® C18 column (gradient from 5 to 100 % MeCN over 30 min).



Overlap of HPLC traces of oligomers trimer **12b**, hexamer **12e** and nonamer **12h**: elution through a Symmetry® C18 column (gradient from 5 to 100 % MeCN over 30 min).

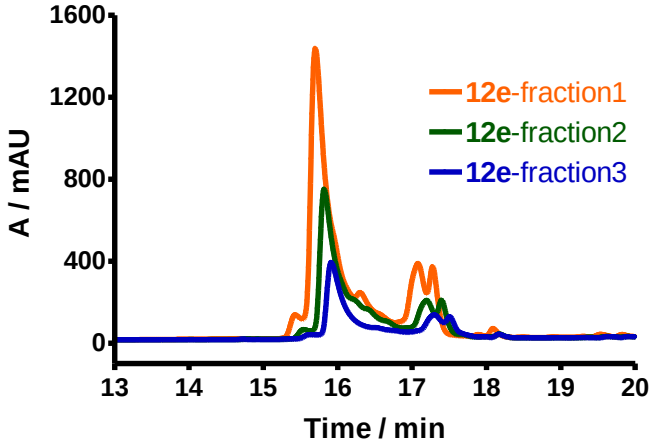
HPLC traces of oligomers **12b**, **12e** and **12h** show several peaks, all having the same molecular weight. The observed signal splitting corresponds to conformational equilibrium on the column. This was evidenced by temperature experiments: elutions throw a heated column increase the speed of exchange between conformers giving one major thinner peak.



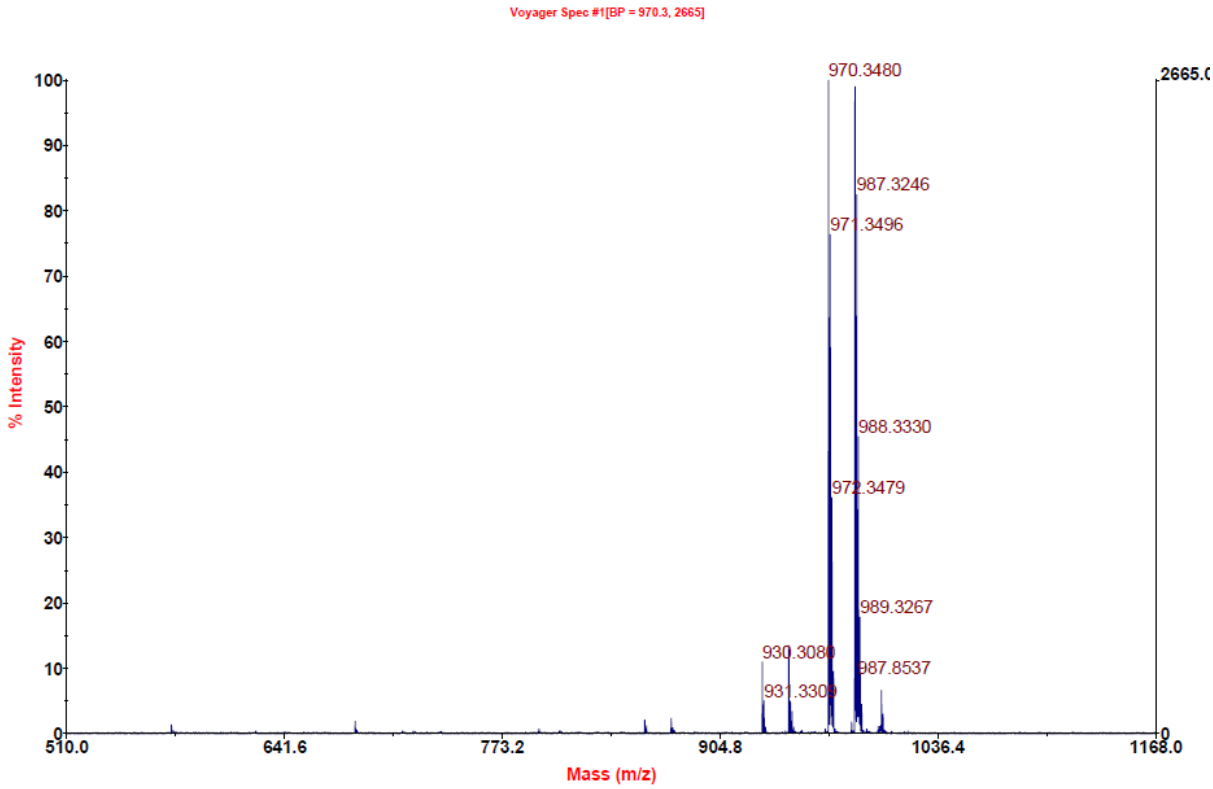
HPLC traces of **12b**, **12e** and **12h** at different temperature: elution through a Symmetry® C18 column (gradient from 5 to 100 % MeCN over 30 min) heated at the desired temperature.

Moreover, the distorted peaks were separated in three fractions (beginning, middle, end of the massif) by reverse phase HPLC then re-injected on analytical HPLC. Each fraction showed the same HPLC chromatograms, confirming that the distortion is more likely due to conformational equilibrium.

Example on the hexamer **12e**: elution through a Symmetry® C18 column (gradient from 5 to 100 % MeCN over 30 min).



HPLC traces of hexamer **12e** split in three fractions: elution through a Symmetry® C18 column (gradient from 5 to 100 % MeCN over 30 min).

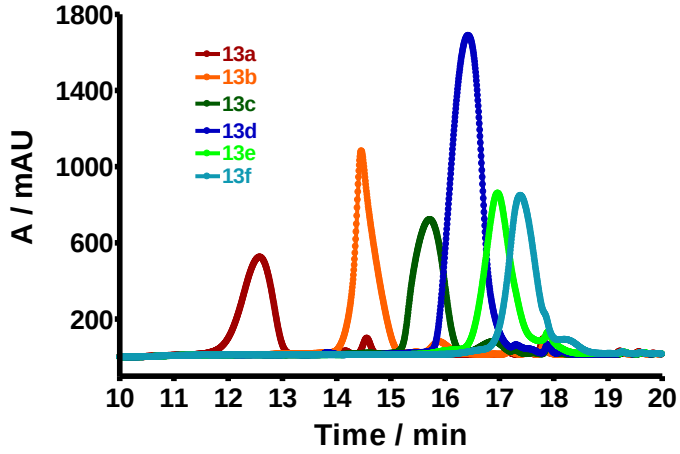


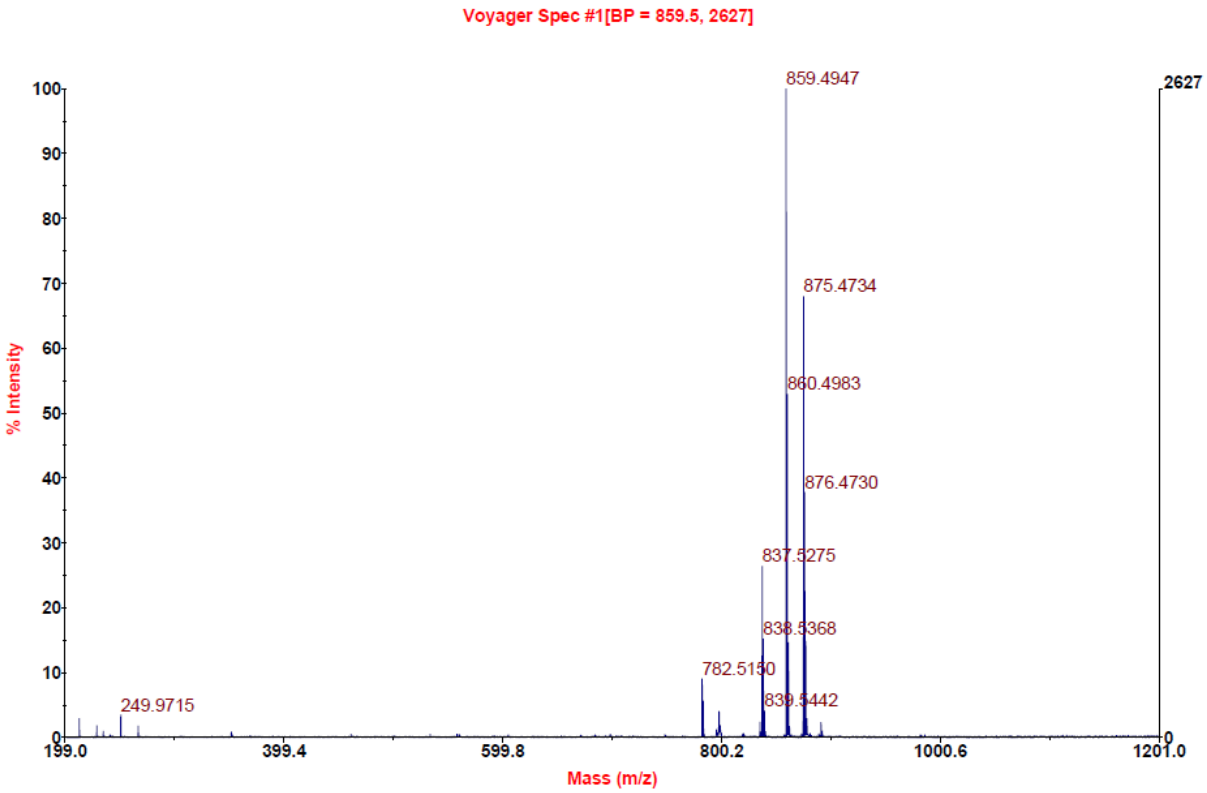
Maldi spectrum of octamer **12g**.

(3R,4R)-3-methyl-β-proline oligomers **13a-f**

Oligomer	Retention Time (min)	MW / g.mol^{-1}	MALDI-TOF $[M+Na]^+$ / g.mol^{-1}
13a dimer	12.6	281.35	304.16
13b trimer	14.5	392.49	415.21
13c tetramer	15.7	503.63	526.26
13d pentamer	16.4	614.78	637.35
13e hexamer	17.0	725.92	748.43
13f heptamer	17.4	837.06	859.50

Overlap of HPLC traces of oligomers **13a-f**: elution through a Symmetry® C8 column (gradient from 5 to 100 % MeCN over 30 min).



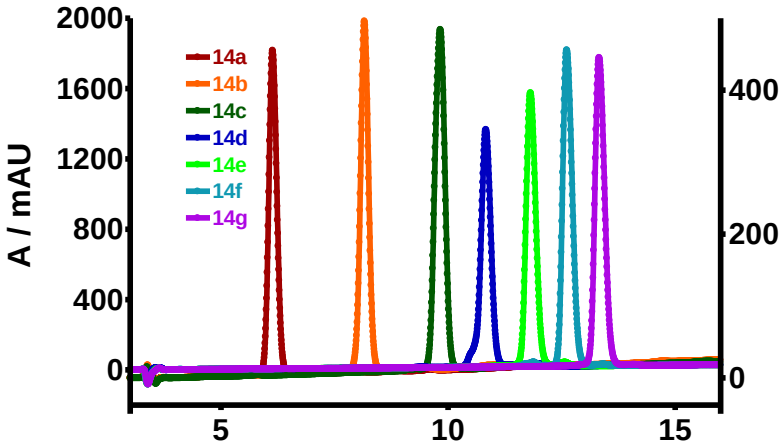


Maldi spectrum of heptamer **13f**.

(3R,4R)-3,4-dimethyl-β-proline oligomers **14a-g**

Oligomer	Retention Time (min)	MW / g.mol^{-1}	MALDI-TOF $[M+Na]^+$ / g.mol^{-1}
14a dimer	5.2	309.40	332.45
14b trimer	8.2	434.57	457.38
14c tetramer	9.7	559.37	582.39
14d pentamer	11.2	684.91	707.46
14e hexamer	12.1	810.08	832.90
14f heptamer	12.8	935.25	957.75
14g octamer	13.5	1060.41	1082.70

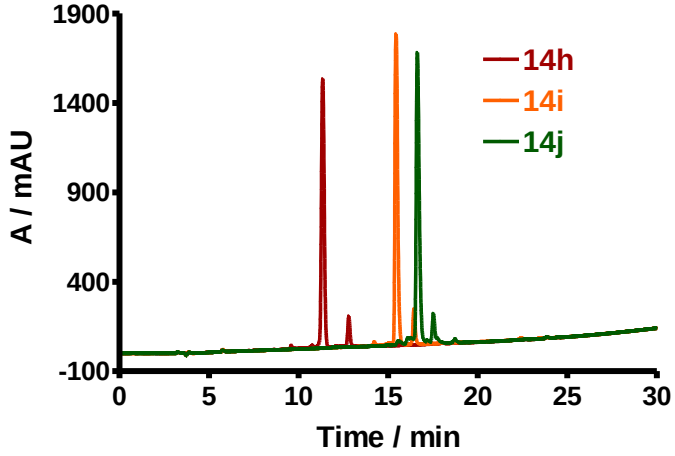
Overlap of HPLC traces of oligomers **14a-g**: elution through a Symmetry® C8 column (gradient from 5 to 100 % MeCN over 30 min).

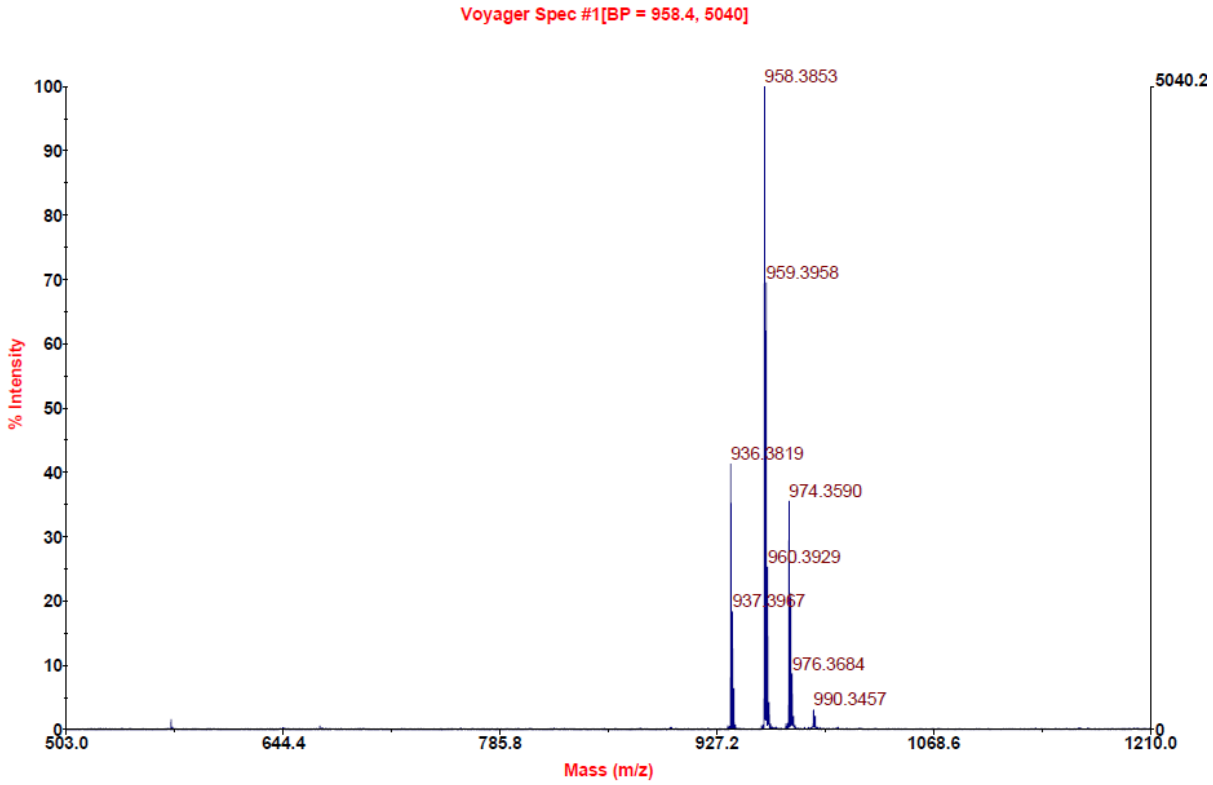


13C-labelled 3,4-dimethyl-β-proline oligomers **14h-j**

Oligomer	Retention Time (min)	MW / g.mol^{-1}	MALDI-TOF $[M+Na]^+$ / g.mol^{-1}
14h trimer	11.4	435.56	458.20
14i heptamer	15.4	935.63	958.39
14j nonamer	16.6	1185.59	1208.51

Overlap of HPLC traces of oligomers **14h-j**: elution through a Symmetry® C8 column (gradient from 5 to 100 % MeCN over 30 min).





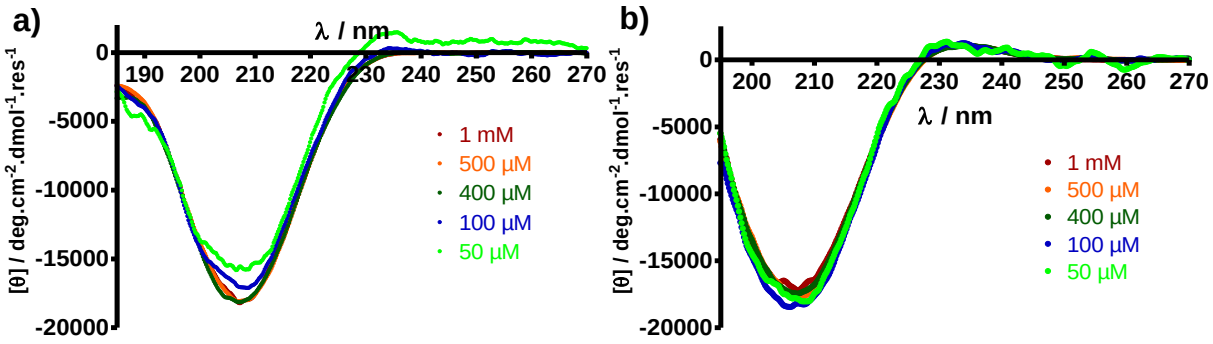
Maldi spectrum of heptamer **14i**.

4. NMR titration of oligomers

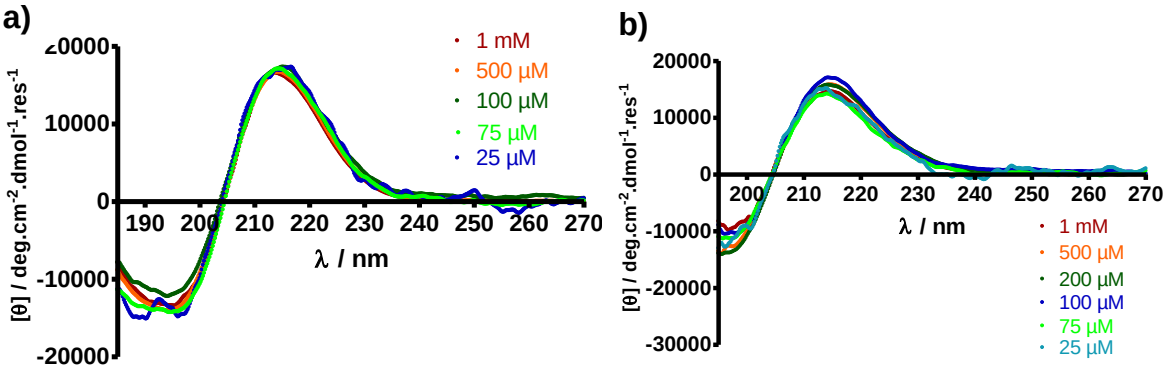
Stock solutions of each peptide were prepared in deionised H_2O and were in the millimolar range. The peptide concentration of each stock solution was determined by NMR using deuterated 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) as an internal reference compound. Typically, 50 µL of peptide stock solution was diluted with 120 µL of D_2O and 2 µL of DSS (11.1 mM in D_2O) were added. Peptide concentration was assessed by relative integration of methyl or acetyl groups to DSS signal on ^1H spectrum acquired using Watergate sequence in 3 mm NMR tube.

5. Additional CD spectra

5.1 Concentration influence

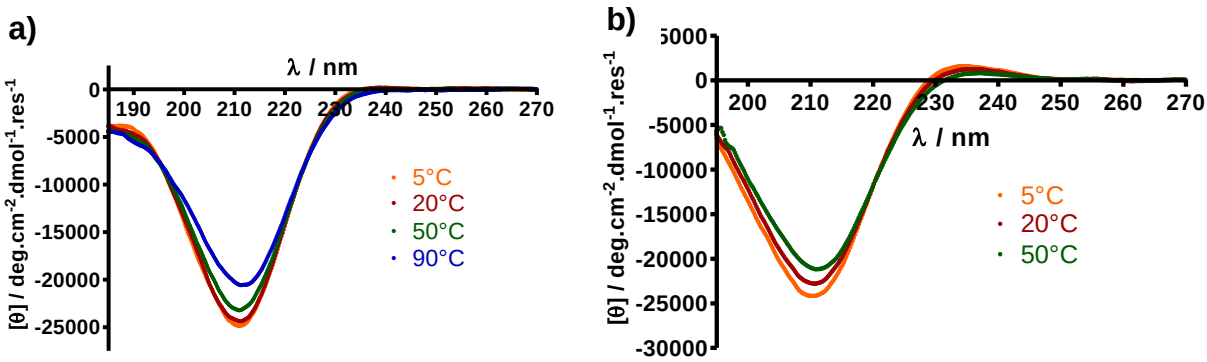


CD spectra of **12c** recorded at different concentrations at 20°C using a 0.1 cm cell length a) in H_2O. b) in MeOH.

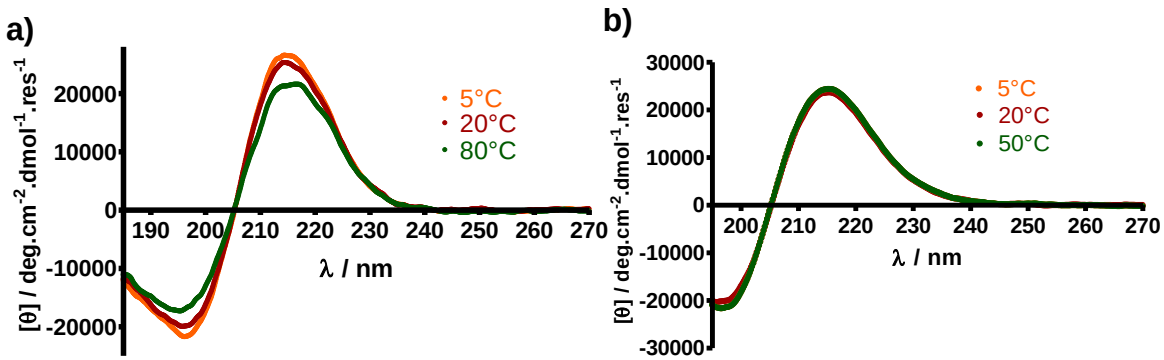


CD spectra of **13c** recorded at different concentrations at 20°C using a 0.1 cm cell length. a) In H_2O. b) In MeOH.

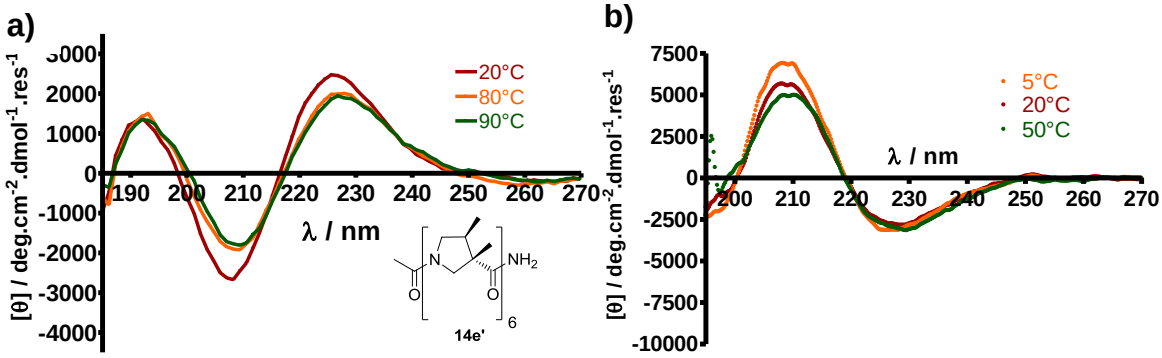
5.2 Temperature influence



CD spectra of octamer **12g** at 200 µM recorded at different temperatures using a 0.1 cm cell length. a) In H_2O. b) In MeOH.

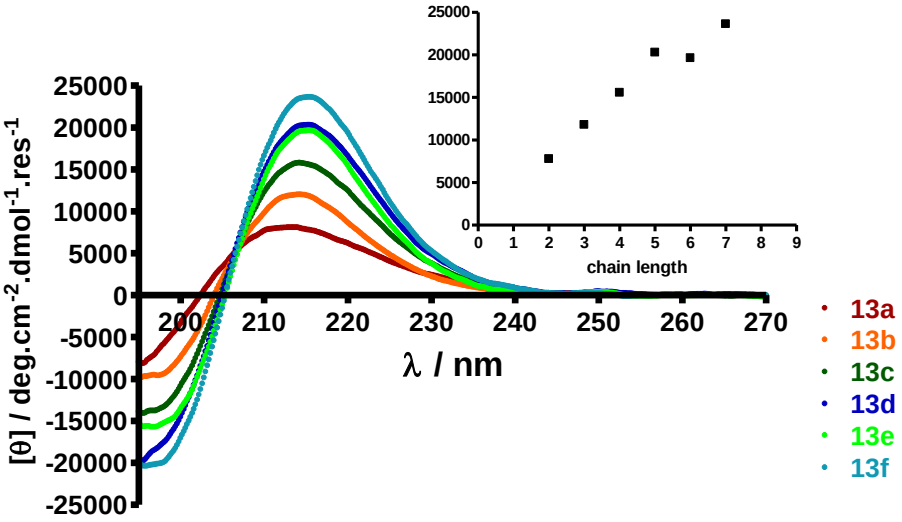


CD spectra of heptamer **13f** at 100 µM recorded at different temperatures using a 0.1 cm cell length. a) In H_2O. b) In MeOH

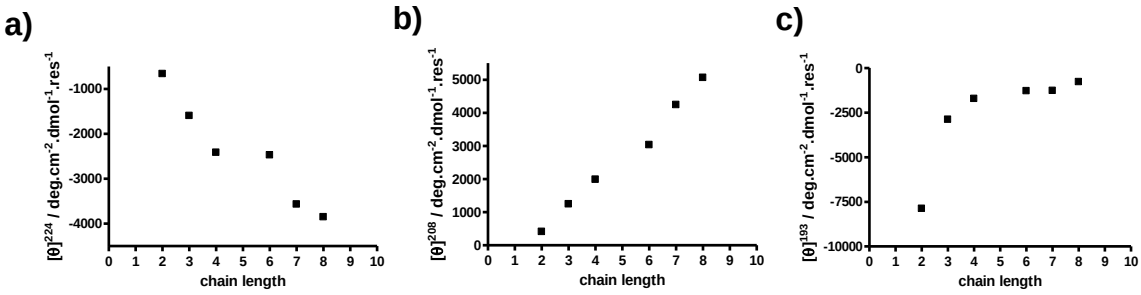


CD spectra at 100 µM recorded at different temperatures using a 0.1 cm cell length. a) of hexamer **14e** in H_2O. b) of heptamer **14g** in MeOH.

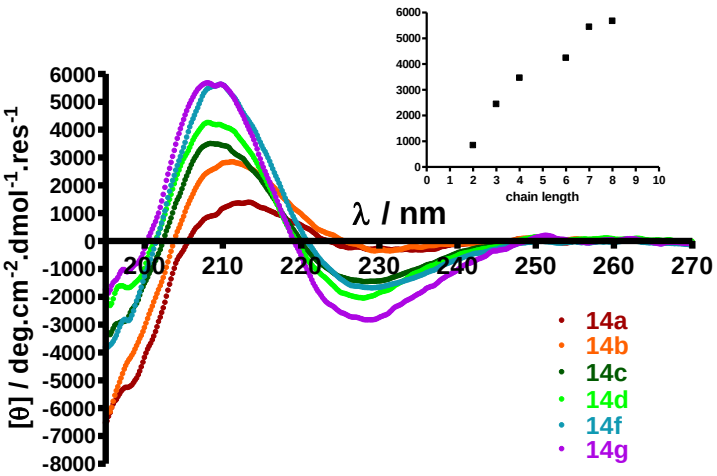
5.3 Length influence



CD spectra of **13a-f** in MeOH at 20°C using a 0.1 cm cell length. Inset: [θ] at 215 nm in function of chain length. Concentrations of **13a-b** are 400 µM, **13c** is 200 µM, **13d-f** are 100 µM.



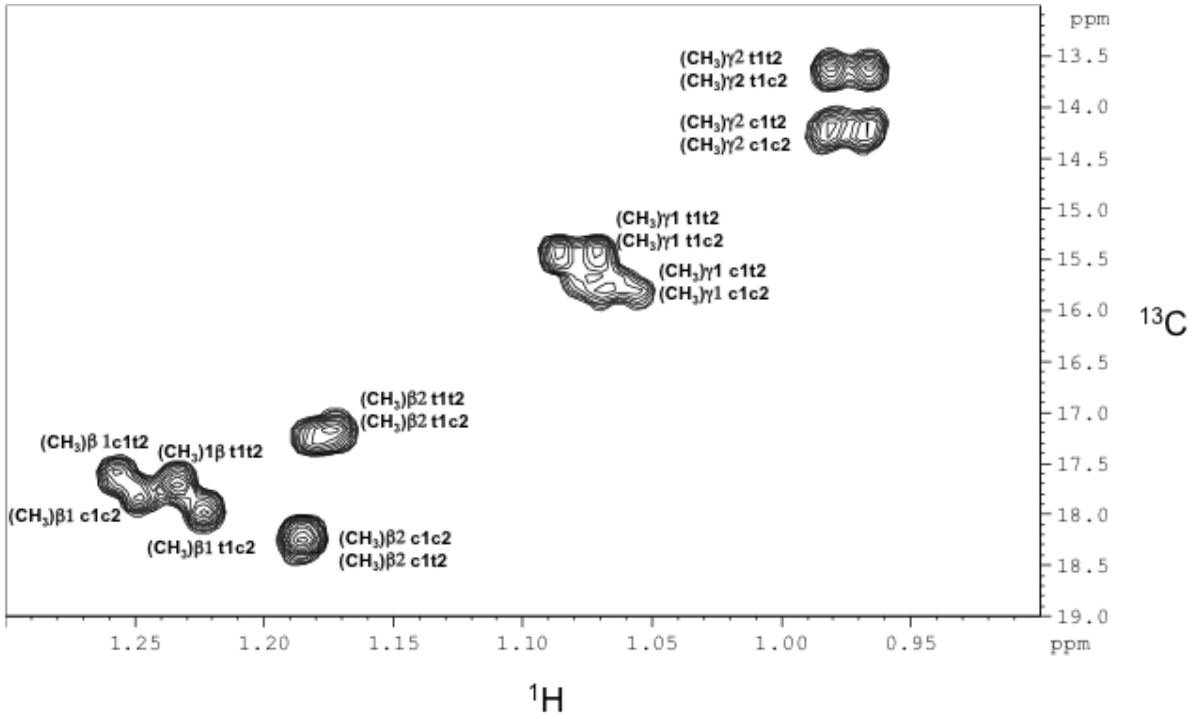
Evolution of [θ] in function of chain length for oligomers **14a-g** at different fixed wavelengths a) 224 nm, b) 208 nm, c)193 nm.



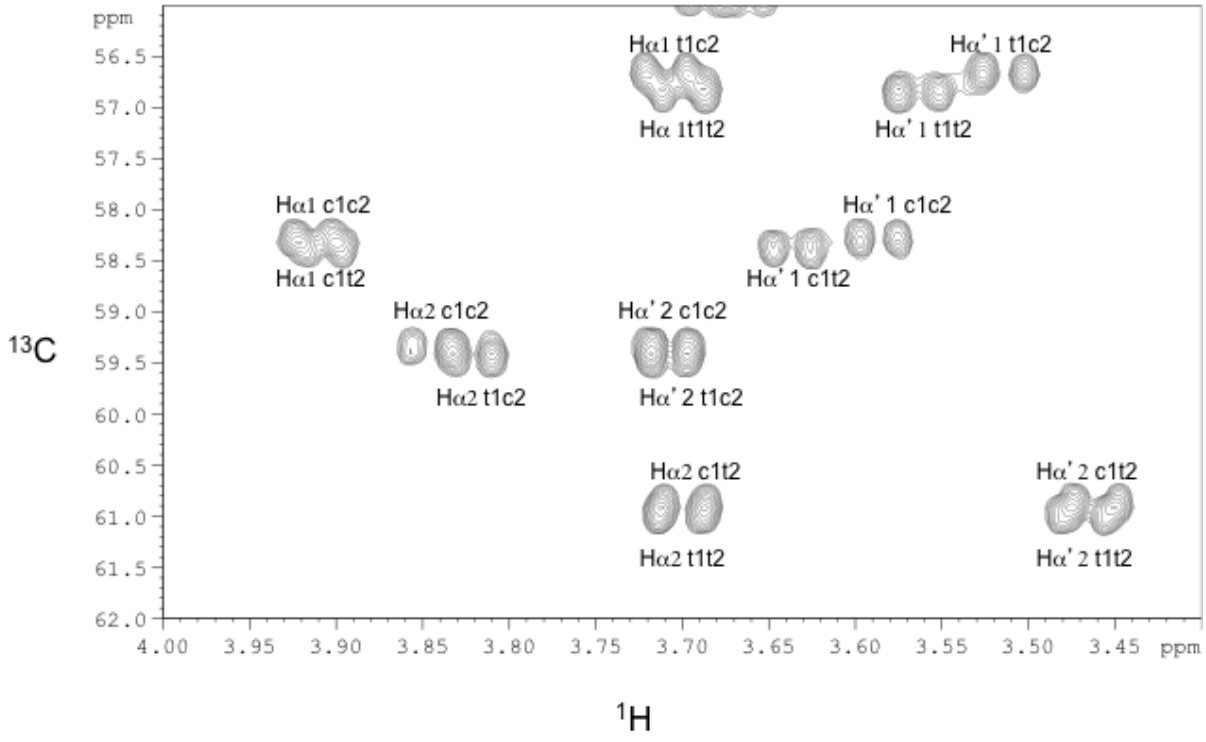
CD spectra of **14a-g** in MeOH at 20°C. Inset: [θ] at 208 nm in function of chain length. Concentrations of **14a-c** are 400 µM, **14c-f** are 200 µM, **14g** is 100 µM.

6. Additional NMR spectra

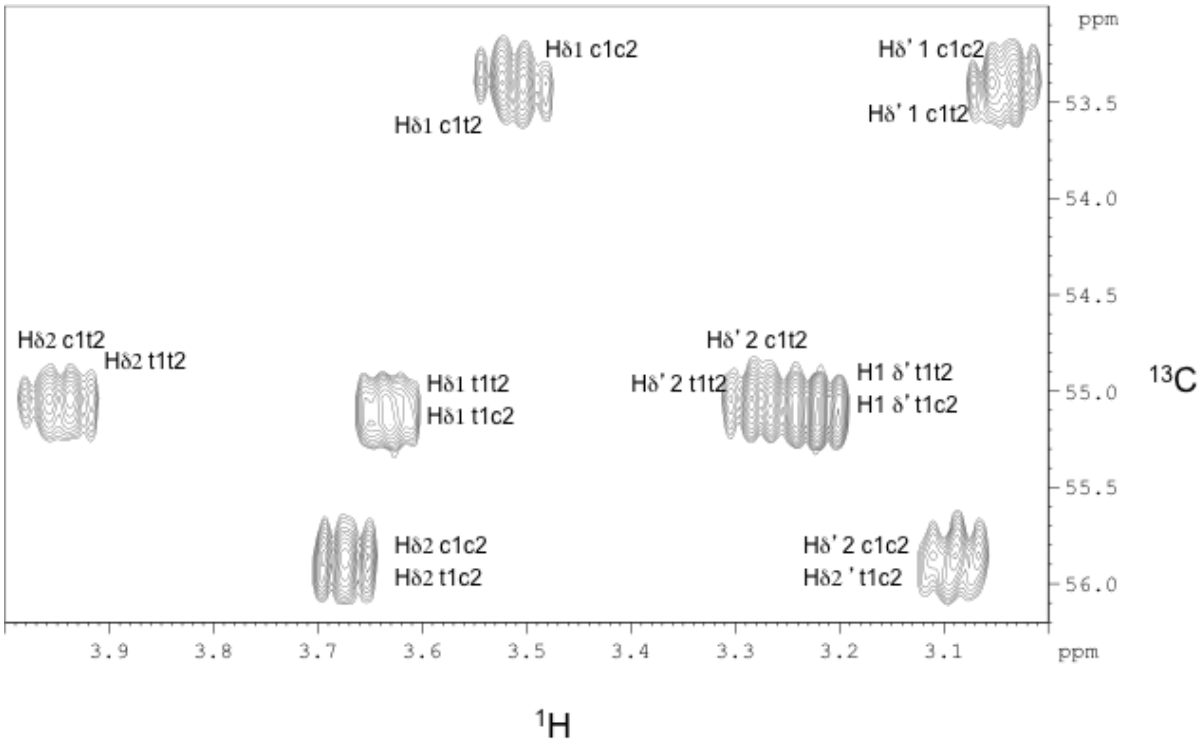
The four distinct isomers are labelled t1t2, t1c2, c1t2 and c1c2; c and t correspond to the *cis* and *trans* conformation of amide bonds; 1-2 labels correspond to the first and second amide bonds. The assignment of 2D ^{1}H-^{13}C HSQC spectrum is shown below.



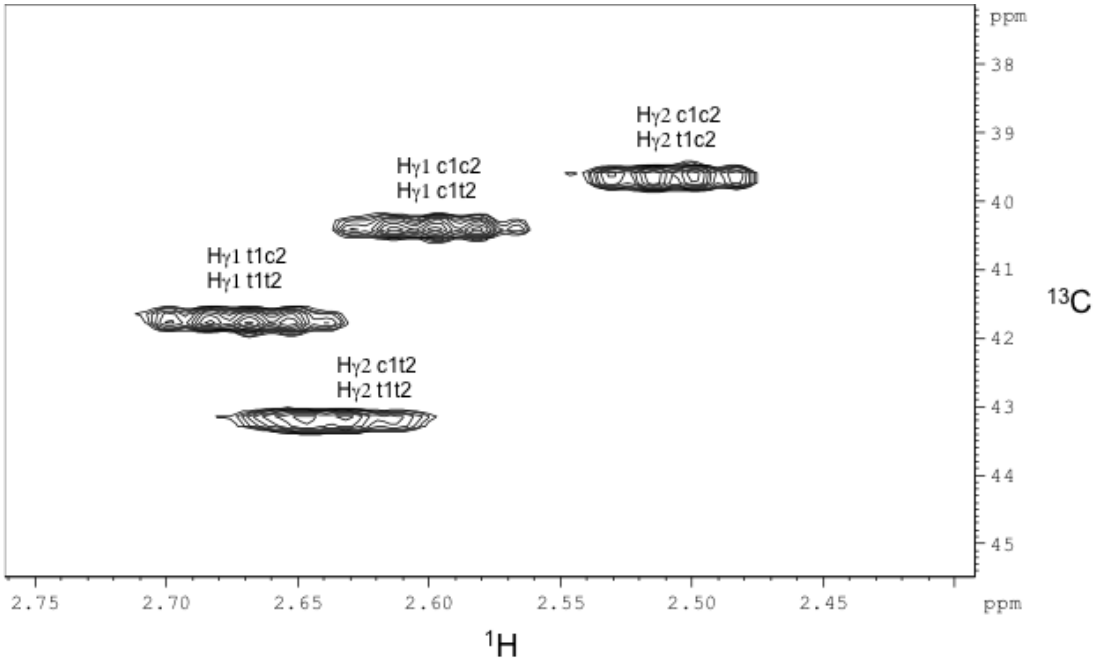
Assignment of methyl groups in β and γ positions



Assignment of α methylene groups



Assignment of δ methylene groups



Assignment of γ CH groups

^{1}H and ^{13}C chemical shifts of the dimer **14a** in D_2O at 296.4 K				
	Unit 1		Unit 2	
	δ ^{1}H (ppm)	δ ^{13}C (ppm)	δ ^{1}H (ppm)	δ ^{13}C (ppm)
α t_1t_2	3.70/3.57	56.7	3.70/3.47	60.8/60.9
α t_1c_2	3.71/3.51	56.6	3.82/3.71	59.3
α c_1t_2	3.906/3.64	58.3	3.70/3.47	60.9/60.8
α c_1c_2	3.91/3.59	58.2	3.85/3.71	59.3
β t_1t_2	-	51.8	-	54.3
β t_1c_2	-	51.8	-	54.3
β c_1t_2	-	53.2	-	50.9
β c_1c_2	-	53.2	-	50.9
γ t_1t_2	2.67	41.7	2.64	43.1
γ t_1c_2	2.67	41.7	2.51	39.6
γ c_1t_2	2.60	40.3	2.64	43.1
γ c_1c_2	2.59	40.3	2.51	39.6
δ t_1t_2	3.63/3.22	55.0	3.94/3.23	54.9
δ t_1c_2	3.63/3.22	55.0	3.68/3.09	55.8
δ c_1t_2	3.51/3.05	53.1	3.96/3.28	54.9
δ c_1c_2	3.51/3.03	53.1	3.68/3.09	55.8
CH_3 Ac t_1t_2	2.01	23.5	-	-
CH_3 Ac t_1c_2	2.01	23.5	-	-
CH_3 Ac c_1t_2	2.04	23.6	-	-
CH_3 Ac c_1c_2	2.04	23.6	-	-
CH_3 $^{\beta}$ t_1t_2	1.24	17.6	1.17	17.1
CH_3 $^{\beta}$ t_1c_2	1.23	17.9	1.18	17.2
CH_3 $^{\beta}$ c_1t_2	1.26	17.5	1.19	18.2
CH_3 $^{\beta}$ c_1c_2	1.25	17.8	1.19	18.2
CH_3 $^{\gamma}$ t_1t_2	1.08	15.4	0.98	13.5
CH_3 $^{\gamma}$ t_1c_2	1.08	15.4	0.98	13.5
CH_3 $^{\gamma}$ c_1t_2	1.07	15.6	0.98	14.1
CH_3 $^{\gamma}$ c_1c_2	1.06	15.6	0.98	14.1
CO Ac t_1t_2	-	175.1	-	-
CO Ac t_1c_2	-	175.1	-	-
CO Ac c_1t_2	-	175.0	-	-
CO Ac c_1c_2	-	175.0	-	-
CO t_1t_2	-	178.6	-	-
CO t_1c_2	-	178.6	-	-
CO c_1t_2	-	178.4	-	-
CO c_1c_2	-	178.4	-	-
CO NH_2 t_1t_2	-	-	-	183.2
CO NH_2 t_1c_2	-	-	-	182.2
CO NH_2 c_1t_2	-	-	-	183.2
CO NH_2 c_1c_2	-	-	-	182.3

1. P. Karoyan and G. Chassaing, *Tetrahedron: Asymmetry*, 1997, **8**, 2025-2032.

2. C. Mothes, S. Lavielle and P. Karoyan, *J. Org. Chem.*, 2008, **73**, 6706-6710.
3. F. Denes, A. Perez-Luna and F. Chemla, *J. Org. Chem.*, 2006, **72**, 398-406.