Electronic Supplementary Material (ESI) for New Journal of Chemistry.

<Supporting Information>

Cis-2-Aminocyclohex-4-enecarboxylic Acid as a New Building Block of Helical Foldamers

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Synthetic procedures

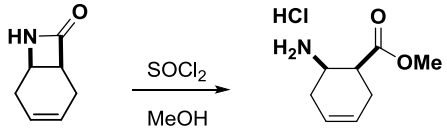
General

α-Amino acids and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI) were purchased from Chem-Impex International. Other reagents were purchased from Sigma-Aldrich, Alfa Aesar, Samchun Chemical, and TCI. Analytical thin-layer chromatography (TLC) was carried out on Pre-coated silica gel glass plate (Merck silica gel 60, F254, 0.25 mm). Silica gel 60 (230~240 mesh, Merck) was used for flash column chromatography. RP-HPLC analysis was performed on the Agilent 1260 infinity series with a UV detector and a C18 column. FT-IR spectra were recorded on Bruker Vertex 70 FT-IR spectrometer at 4000 cm^{-1} ~ 400 cm^{-1} of wave numbers. Mass spectra (MS) were acquired using an LTQ Orbitrap Spectrometer (ThermoFisher scientific Inc.).

β-Lactam (±)-4

β-Lactam **(±)-4** was synthesized by a method analogous to those reported previously.[S1-2] 1,3-Cyclohexadiene (8.8 mL, 93.5 mmol), and anhydrous Na_2CO_3 (1.35 g, 12.75 mmol) and CH_2Cl_2 (20 mL) were added to round-bottom flask and cooled to 0℃ with stirring under nitrogen gas. Chlorosulfonyl isocyanate (7.4 mL, 85 mmol) was added dropwisely to the reaction mixture with stirring over 30 min, and the mixture was stirred at 45 °C for 2 days. The resulting solution was diluted with CH_2Cl_2 (25 mL) and then added to a two-phased mixture of Na_2CO_3 (50 g) and Na_2HPO_4 (47.42 g) in H_2O (200 mL) with vigorous stirring. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash column chromatography (R_f 0.37, 1:1 EtOAc: hexanes). The isolated product was recrystallized from a mixture of n-pentane and ethyl acetate (white solid, 2.45 g, 22%).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.00-2.60 (m, 4H), 3.45 (t, 1H), 4.00 (t, 1H), 5.65-6.00 (m, 2H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.83, 126.05, 124.29, 48.00, 47.00, 27.06, 21.34.

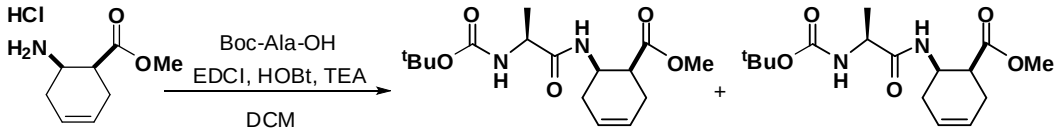
Methyl 6-aminocyclohex-3-ene carboxylate hydrochloride (±)- 10



(±)-4 (±)-10

β-Lactam **(±)-4** (1.00 g, 8.12 mmol) was stirred in methanol (15 mL) containing thionyl chloride (0.85 mL, 12.18 mmol, 1.5 eq) at rt for 24 h. The solvent was completely evaporated and concentrated in vacuo to give **(±)-10** as a yellowish oil (1.73 g, Quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.33-2.65 (m, 4H), 3.16 (s, 1H), 3.70 (s, 3H), 3.78 (s, 1H), 5.52-5.66 (m, 2H) 8.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 125.35, 122.93, 52.60, 47.46, 39.77, 27.62, 25.68.

Boc-Ala-*cis*-ACHE-OMe (5 + 6)

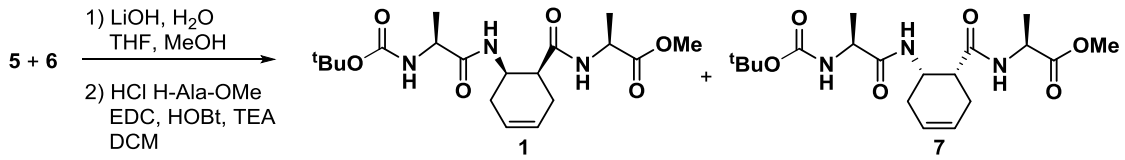


(±)-10 5 6

To a mixture of β-Amino ester **(±)-10** (1.6 g, 8.34 mmol), EDCI (2.40 g, 12.52 mmol), HOBt (1.47 g, 12.52 mmol), triethyl amine (1.29 mL, 9.18 mmol) in dichloromethane (30 mL), Boc-Ala-OH (1.58 g, 8.34 mmol) was added. The reaction mixture was stirred for a day at rt. The mixture was diluted with ethyl acetate (100 mL), washed with 10% citric acid, brine, Na_2CO_3 and brine successively. The organic layer was dried over

$MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by flash column chromatography (R_f 0.5, 1:1 EtOAc: hexanes) to give the mixture of **5** and **6** as a white solid (2.4 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.35 (d, 3H), 1.45 (s, 9H), 2.00-2.60 (m, 4H), 2.80 (t, 1H), 3.71 (s, 3H), 4.49 (m, 1H), 4.97 (d, 1H), 5.65-6.00 (m, 2H), 6.80 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.69, 172.13, 155.43, 124.94, 124.50, 79.81, 51.01, 50.08, 44.57, 41.58, 25.14, 17.99.

Boc-Ala-*cis*-(1S,2R)-ACHE-Ala-OMe (1) and Boc-Ala-*cis*-(1R,2S)-ACHE-Ala-OMe (7)

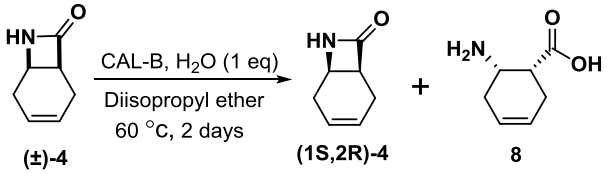


To a mixture of dimers **5** and **6** (2.32 g, 7.11 mmol) in methanol (40 mL) and THF (80 mL), a solution of LiOH (1.78 g, 42.65 mmol, 6 eq) in H_2O (15 mL) was added with stirring at 0 ℃. The mixture was stirred at 0 °C overnight. The solvent was evaporated off, and the mixture was acidified with 1 *N* HCl to pH 1. The turbid mixture was extracted with ethyl acetate. The combined organic layer was washed brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the corresponding acid mixture as a yellowish oil (2.6 g, Quant.), which was directly coupled with alanine methyl ester hydrochloride by a method described above. The yield of the amide coupling was not optimized. A crude mixture of **1** (R_f 0.25, 1:1 EtOAc:hexanes) and **7** (R_f 0.18, 1:1 EtOAc:hexanes) was separated by flash column chromatography to give isolated products **1** and **7**.

Tripeptide **1**: $[\alpha]_D^{20}$ = 59.0, *c* 0.1 $CHCl_3$; mp 62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.36 (d, 3H), 1.42 (s, 9), 1.44 (d, 3H), 2.0-2.25 (m, 4H), 2.75 (q, 1H), 3.76 (s, 3H), 3.91 (m, 1H), 4.39 (m, 1H), 4.68 (m, 1H), 4.98 (d, 1H), 5.60-5.73 (m, 2H), 7.43 (d, 1H), 7.49 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.79, 173.61, 172.93, 172.92, 169.91, 155.91, 123.34, 124.00, 79.96, 41.48, 52.49, 52.25, 51.19, 48.21, 47.89, 45.13, 42.50, 26.66, 22.80, 18.03, 17.63, 17.27, 16.31; HRMS (ESI) *m/z* Calcd for $C_{19}H_{31}N_3O_6$ $[M + H]^+$ 398.57, found 398.23.

Tripeptide **7**: $[\alpha]_D^{20}$ = -39.70, *c* 0.1 $CHCl_3$; mp 68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 (d, 3H), 1.32 (d, 3H) 1.34 (d, 9H), 2.00-2.55 (m, 4H), 2.67 (m, 1H), 3.68 (s, 1H), 4.03 (b, 1H), 4.39 (m, 1H), 4.46 (q, 1H), 4.94 (d, 1H), 5.65-6.00 (m, 2H), 6.65 (d, 1H), 6.76 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.40, 172.64, 172.43, 155.33, 125.01, 79.67, 52.26, 47.93, 44.56, 42.44, 30.47, 28.22, 25.05, 18.58, 17.70.

(1S,6R)-7-Azabicyclo[4.2.0]oct-3-en-8-one ((1S,2R)-4)and (1R, 6S)-6-aminocyclohex-3-enecarboxylic acid (8)



The chiral resolution of β-lactam **(±)-4** was carried out by a method reported previously.[S1-2]

β-lactam **(±)-4** (2.00 g, 16.24 mmol) and water (0.3 mL, 13.8 mmol) were added to a mixture of lipase CAL-B (Lipase from *Candida Aantarctica*) (2.3 g) in diisopropyl ether. The reaction mixture was stirred at 60 ℃ for 48 h, filtered, and rinsed with diisopropyl ether. The filtrate was concentrated in vacuo, and was recrystallized in ethyl acetate and hexane to yield chiral **(1S,2R)-4** as a white solid (0.61 g, 30%). The precipitate was rinsed with water and then filtered. The filtrate was concentrated in vacuo, and was recrystallized in water and acetone to yield chiral β-amino acid **8** as a white solid (1.06 g, 46%).

β-Lactam **(1S,2R)-4**: $[\alpha]_D^{20}$ = -45.33, *c* 0.1 $CHCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.00-2.60 (m, 4H), 3.45 (t, 1H), 4.00 (t, 1H), 5.65-6.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 126.13, 124.24, 47.03,

27.10, 21.36.

β-Amino acid **8**: ^{1}H NMR (400 MHz, D_2O) δ = 2.00-2.5 (m, 4H), 2.74-2.78 (m, 1H), 3.78 (q, 1H), 5.65-6.82 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ = 180.99, 126.28, 126.15, 47.02, 27.41, 27.74.

Boc-Ala-(1S,2R)-ACHE-OMe (5)

Chiral dipeptide **(5)** was synthesized from **(1S,2R)-4** and Boc-Ala-OH by a method described above.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.35 (d, 3H), 1.45 (s, 9H), 2.00-2.60 (m, 4H), 2.80 (t, 1H), 3.71 (s, 3H), 4.49 (m, 1H), 4.97 (d, 1H), 5.65-6.00 (m, 2H), 6.80 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.79, 171.99, 124.99, 124.60, 51.91, 50.17, 44.63, 41.67, 30.15, 28.29, 25.29, 18.11.

Boc-[Ala-(1*S*, 2*R*)-ACHE-Ala]$_2$-Ala-OMe (2) and Boc-[Ala-(1*S*, 2*R*)-ACHE-Ala]$_3$-Ala-OMe (3)

α/β-Peptide oligomers **2** and **3** were synthesized from (**5)** and **1** by a conventional fragment coupling strategy. Yields were not optimized.

Pentamer **2**: white solid; R_f 0.22, 1:1 EtOAc:hexanes, $[\alpha]_D^{20}$ = 33.3, *c* 0.1 $CHCl_3$; mp 73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.4-1.3 (m, 9H), 1.42 (s, 9H), 1.87-2.00 (m, 8H), 2.67 -2.70 (m, 2H), 3.74 (s, 3H), 4.02 (t, 1H), 4.13 (t, 1H), 4.27 (m, 1H), 4.39 (m, 1H), 5.00 (d, 1H), 5.56-5.72 (m, 4H), 7.56 (d, 1H), 7.76 (d, 1H), 7.92-7.95 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.40, 175.32, 174.24, 173.08, 172.74, 155.90, 125.53, 125.16, 123.82, 123.78, 80.12, 52.54, 51.98, 51.50, 48.38, 46.04, 46.03, 42.47, 42.24, 28.07, 27.66, 26.73, 17.40, 16.50, 15.90 ; HRMS (ESI) *m/z* Calcd for $C_{29}H_{45}N_5O_8$ $[M + H]^+$ 592.70, found 592.33.

Heptamer **3**: white solid; R_f 0.13, 1:1 EtOAc:hexanes, $[\alpha]_D^{20}$= 167.33, *c* 0.1 $CHCl_3$, mp 90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.41-1.37 (m, 12H), 1.42 (s, 9H), 1.87-2.00 (m, 12H), 2.67 -2.70 (m, 2H), 2.76 (t, 1H), 3.74 (s, 3H), 4.02 (t, 1H), 4.10 (t, 1H), 4.20-4.44 (m, 4H), 4.63 (m, 1H), 4.99 (d, 1H), 5.84-5.71 (m, 6H), 7.56 (d, 1H), 7.88 (d, 1H), 7.91 (d, 1H), 8.04-8.10 (m, 2H), 8.44 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.40, 175.72, 175.42, 174.20, 173.89, 173.04, 172.74, 155.87, 125.53, 125.20, 125.17, 123.91, 123.84, 123.64, 80.14, 52.55, 52.18, 51.51, 48.39, 46.06, 42.47, 42.29, 42.13, 28.28, 28.00, 27.64, 27.03, 26.90, 26.77, 17.48, 16.59, 16.30, 15.87 ; HRMS (ESI) *m/z* Calcd for $C_{39}H_{59}N_7O_{10}$ $[M + H]^+$ 786.93, found 786.44.

Copies of ^{1}H NMR and ^{13}C NMR spectra

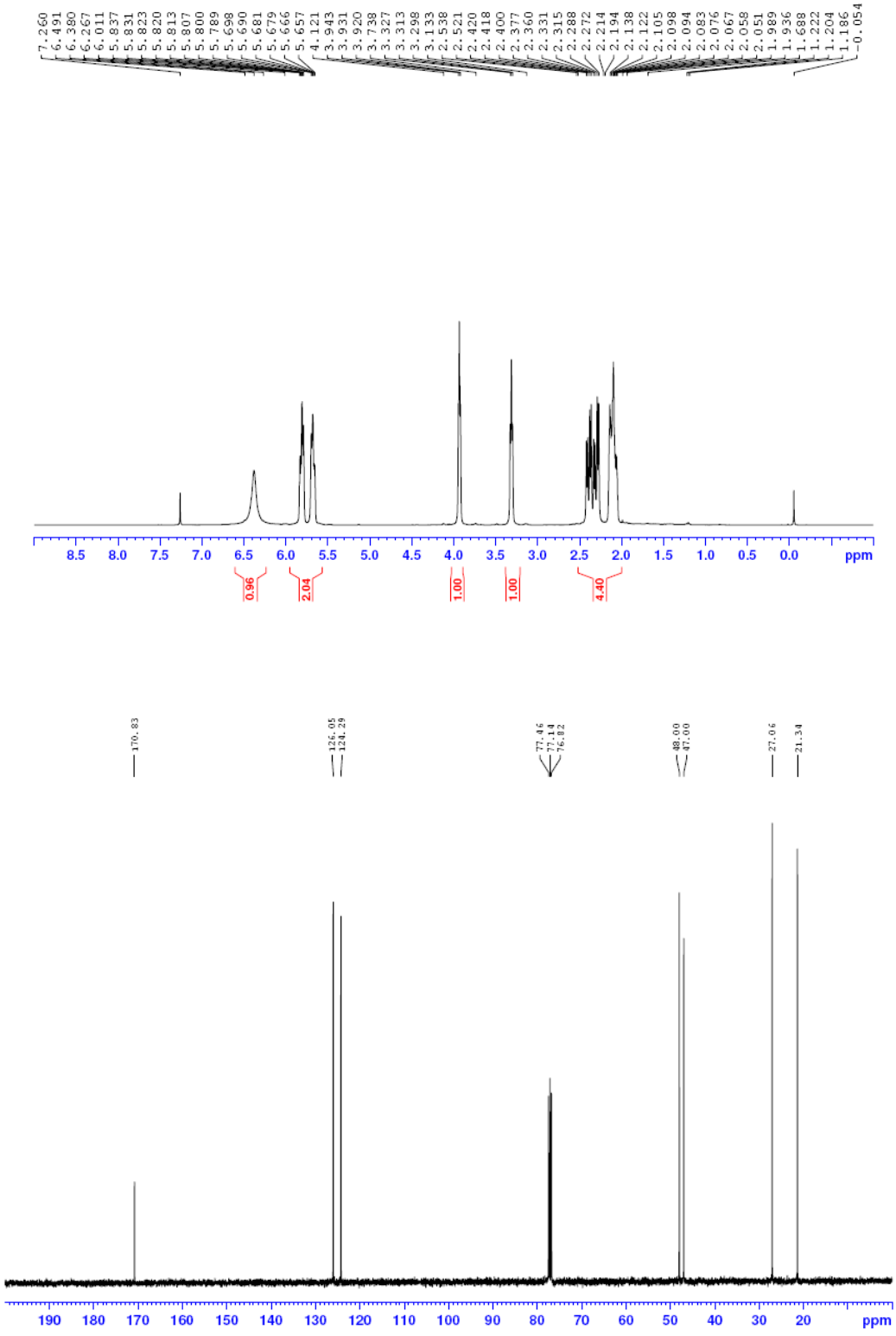


Figure S1. ^{1}H and ^{13}C NMR spectra for **(±)-4**

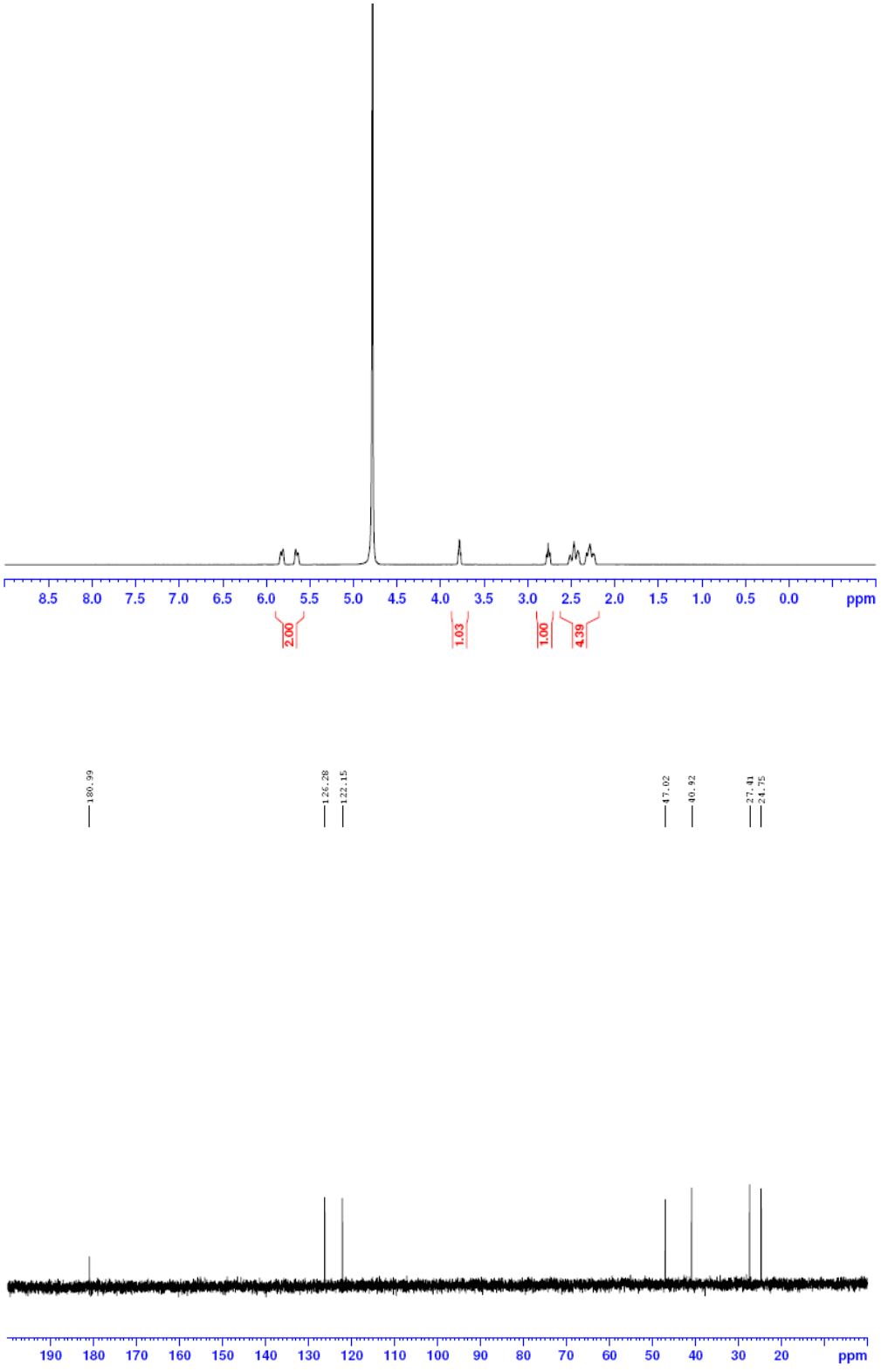


Figure S2. ^{1}H and ^{13}C NMR spectra for **8**

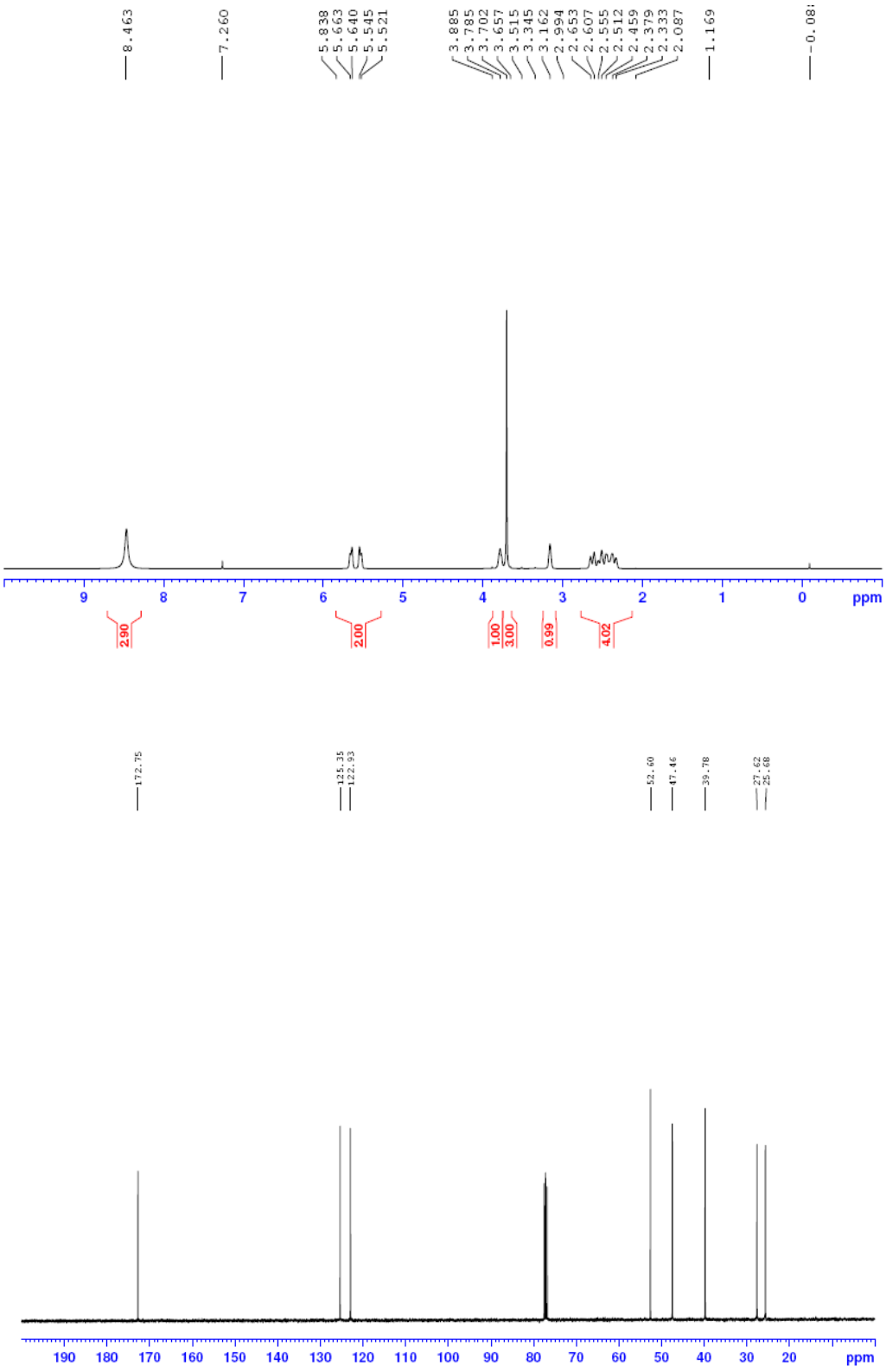


Figure S3. ^{1}H and ^{13}C NMR spectra for **(±)-10**

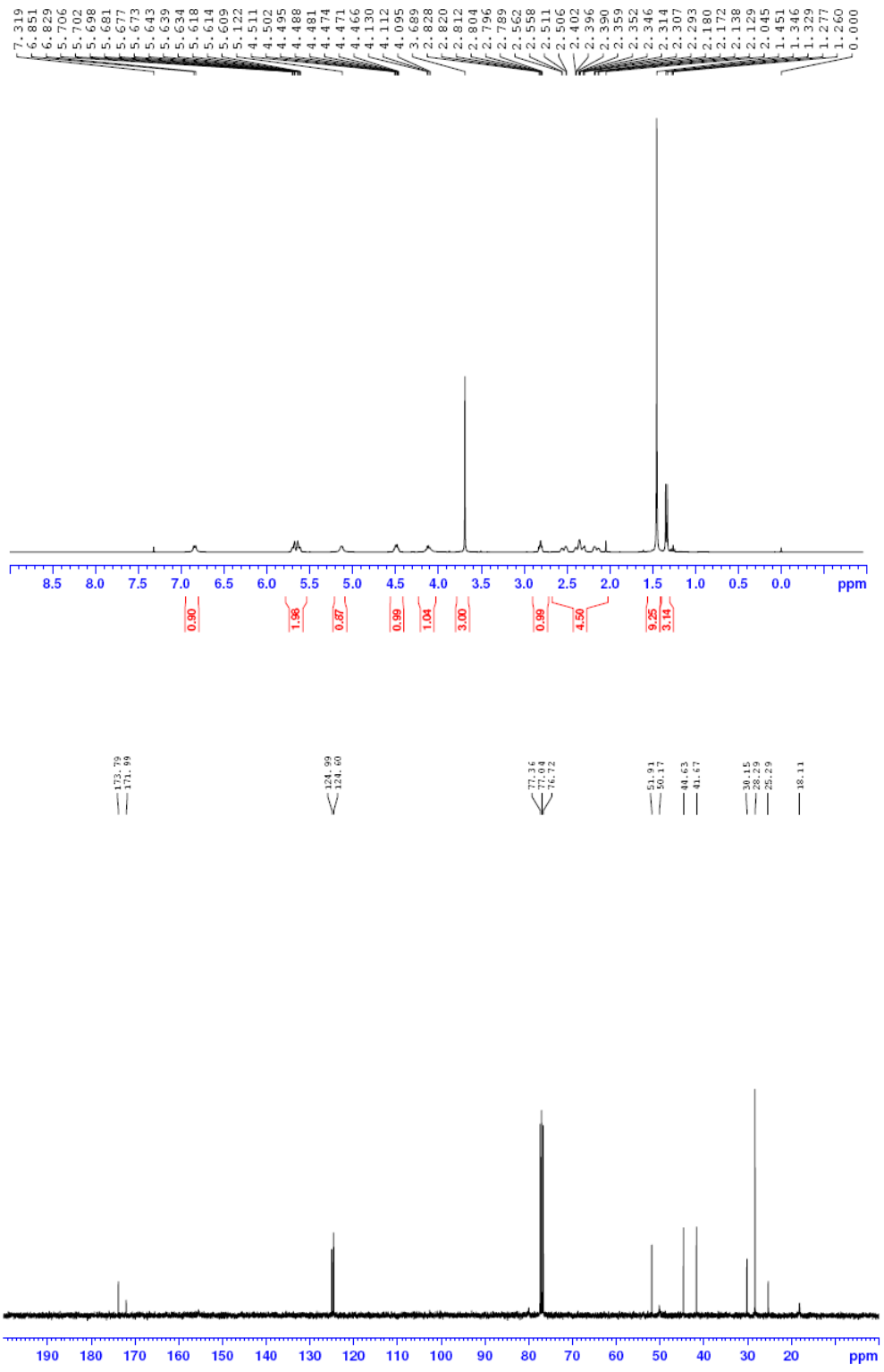


Figure S4. ^{1}H and ^{13}C NMR spectra for a diastereomeric mixture of **5** and **6**

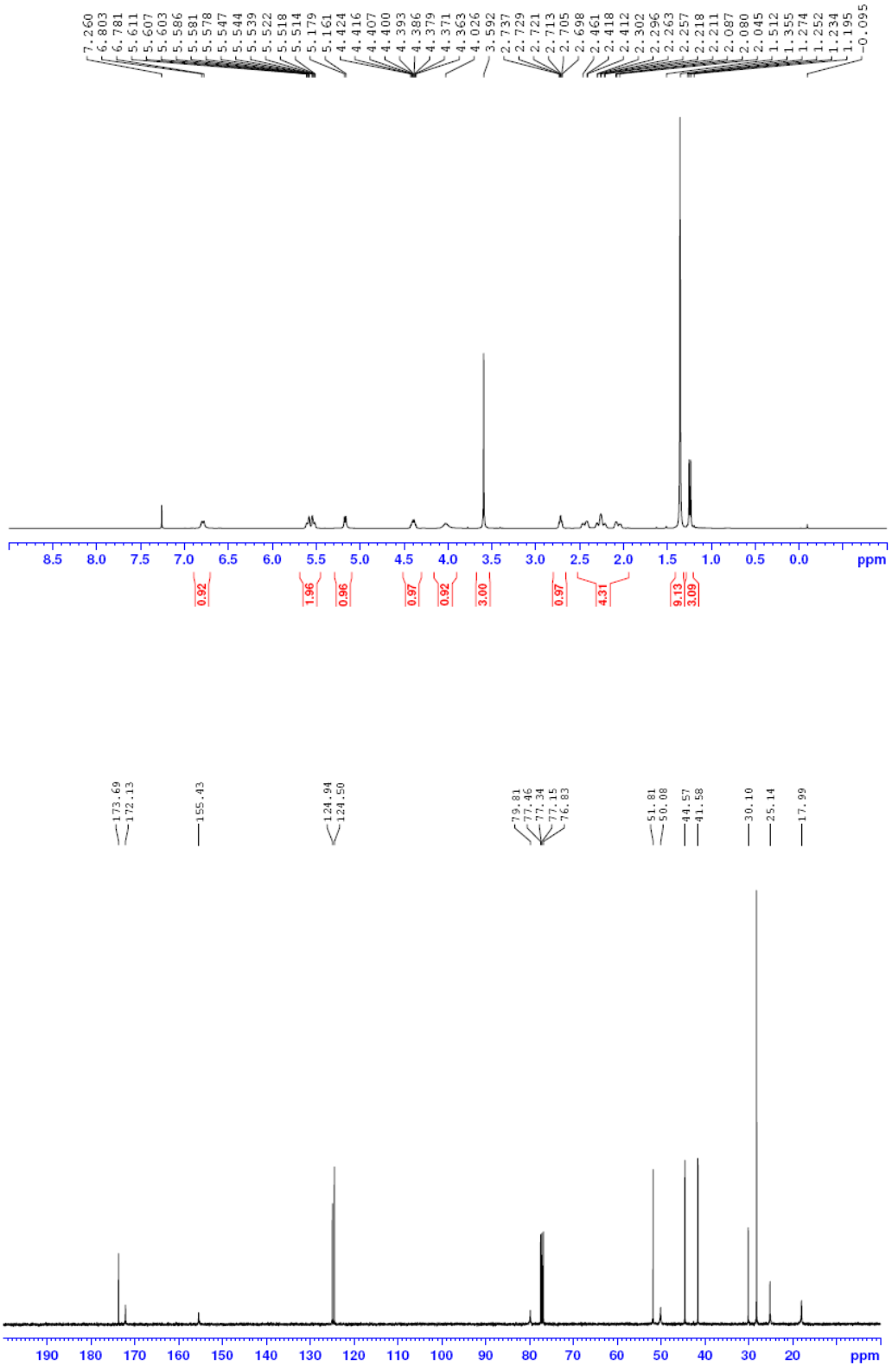


Figure S5. ^{1}H and ^{13}C NMR spectra for **5**

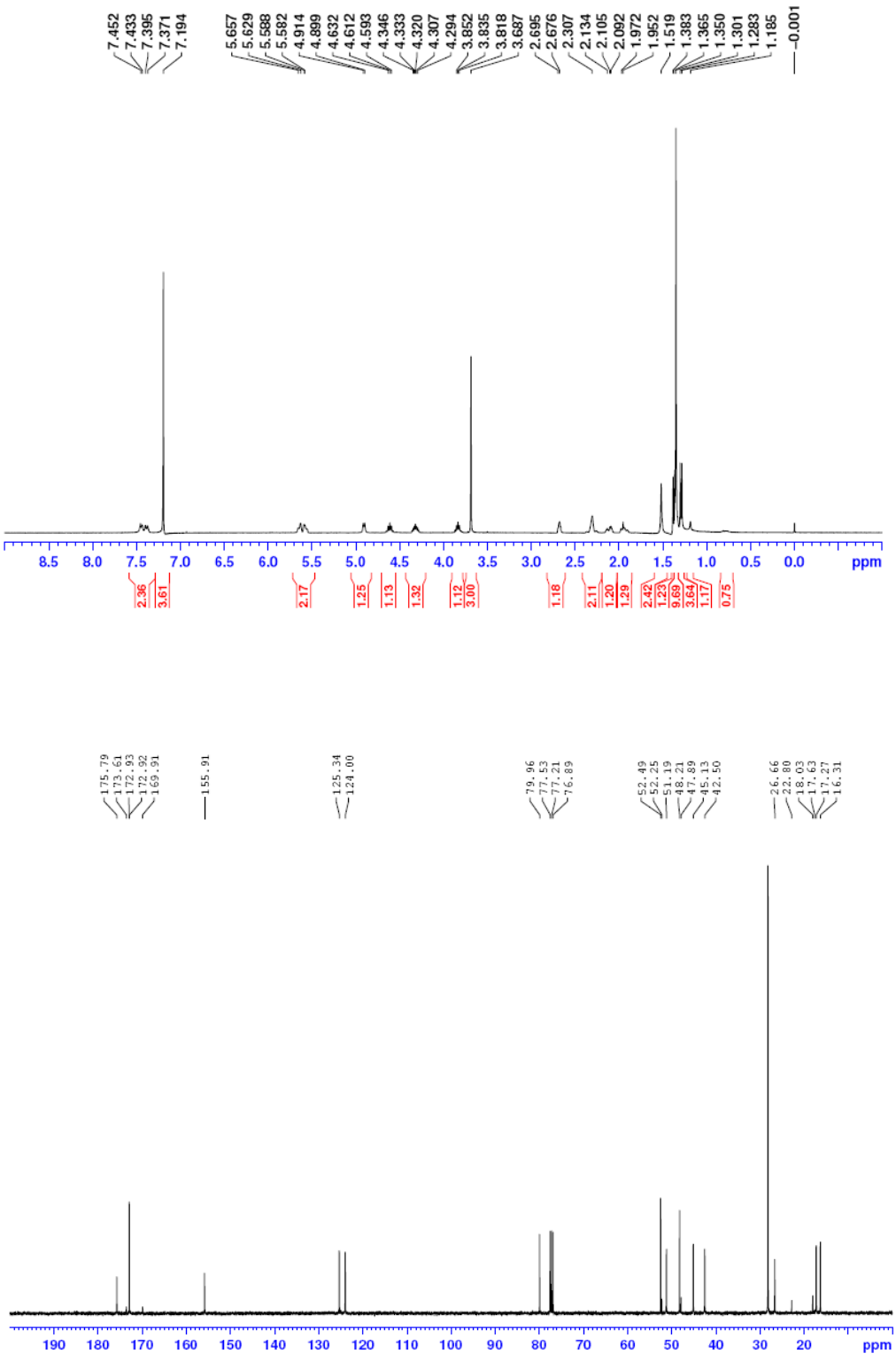


Figure S6. ^{1}H and ^{13}C NMR spectra for **1**

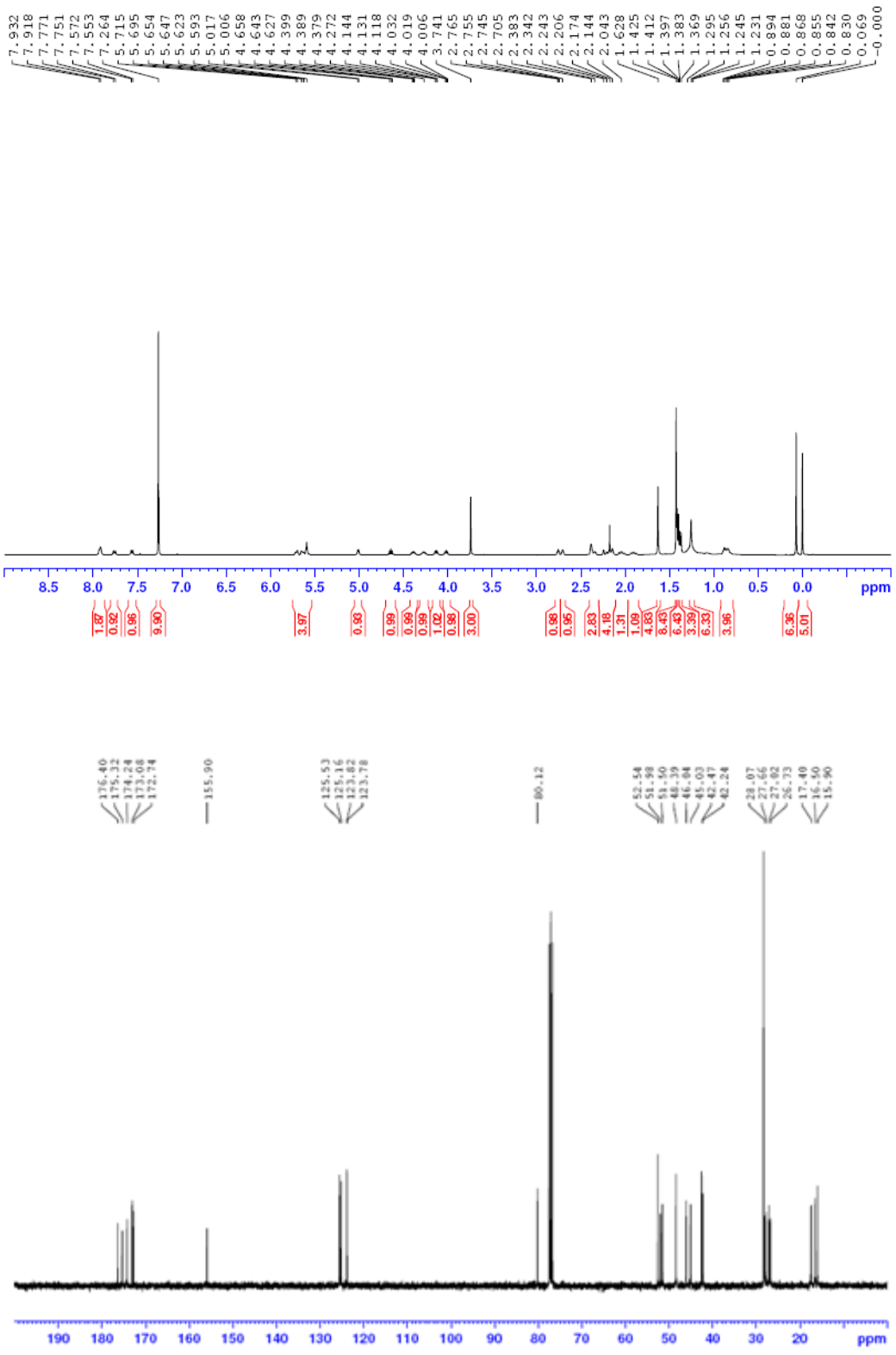


Figure S7. ^{1}H and ^{13}C NMR spectra for **2**

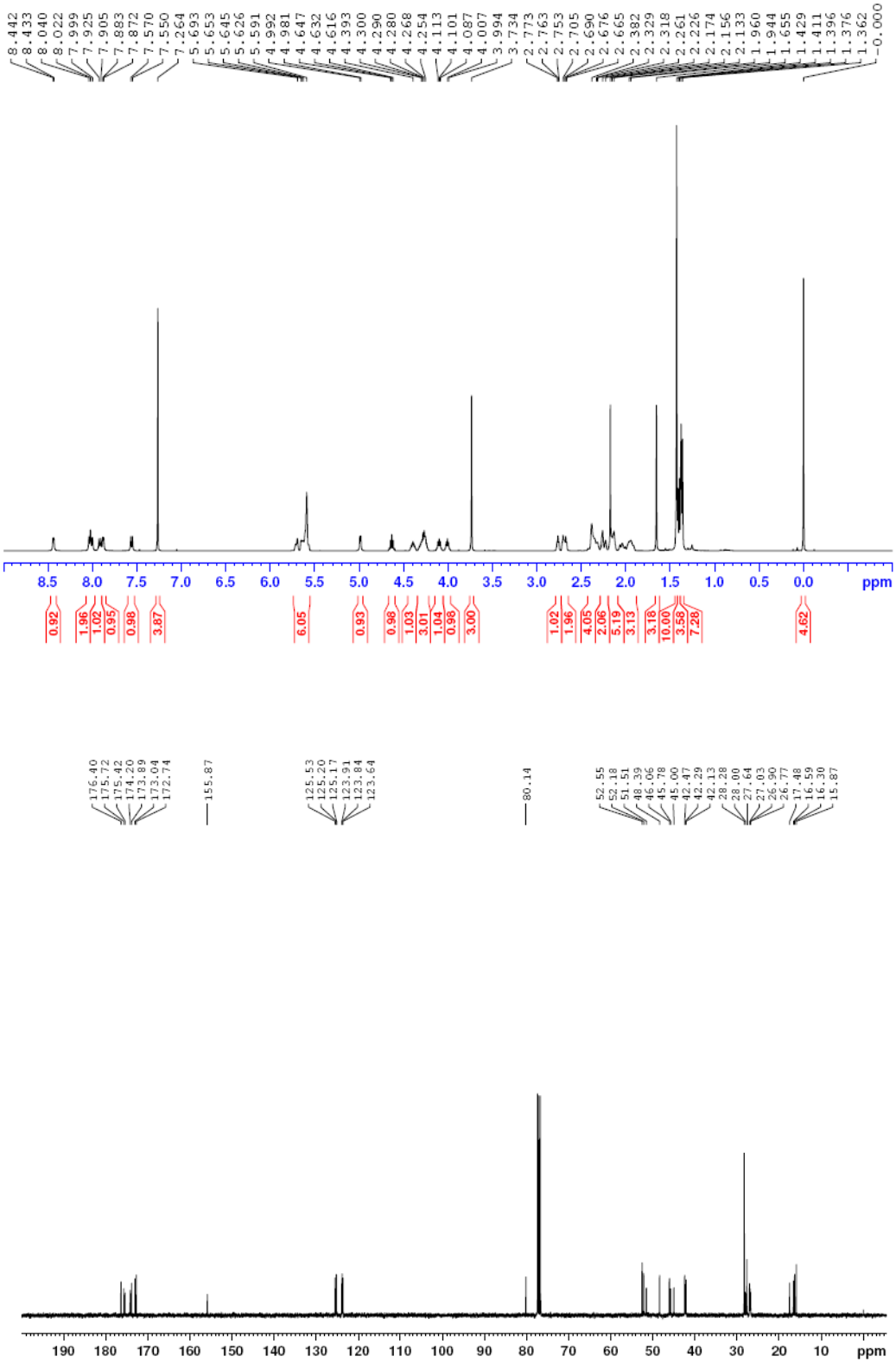


Figure S8. ^{1}H and ^{13}C NMR spectra for **3**

Two-dimensional NMR experiments

Two-dimensional NMR data were collected on an a Bruker Biospin DRX-500 spectrometer. NOESY (mixing time : 600 ms), ROESY (mixing time : 400 ms), and TOCSY (mixing time : 60 ms) were performed at 298K.

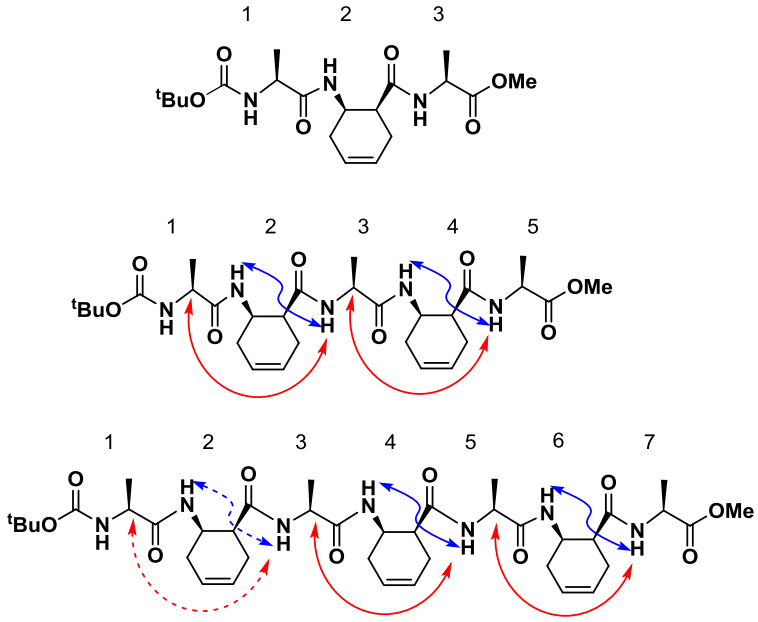


Figure S9. The characteristic NOEs for the 11/9-helix observed in $CDCl_3$. A dashed arrow indicates an ambiguous NOE because of signal overlap.

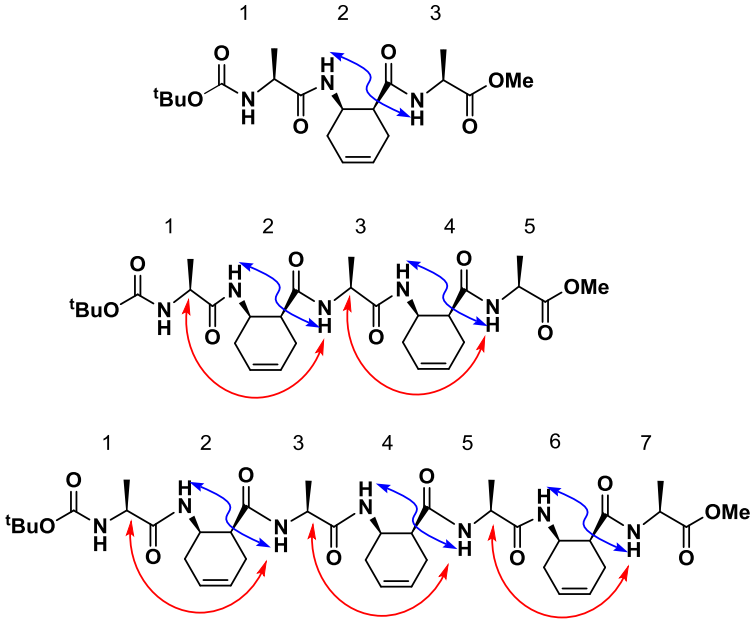


Figure S10. The characteristic NOEs for the 11/9-helix observed in CD_3OH

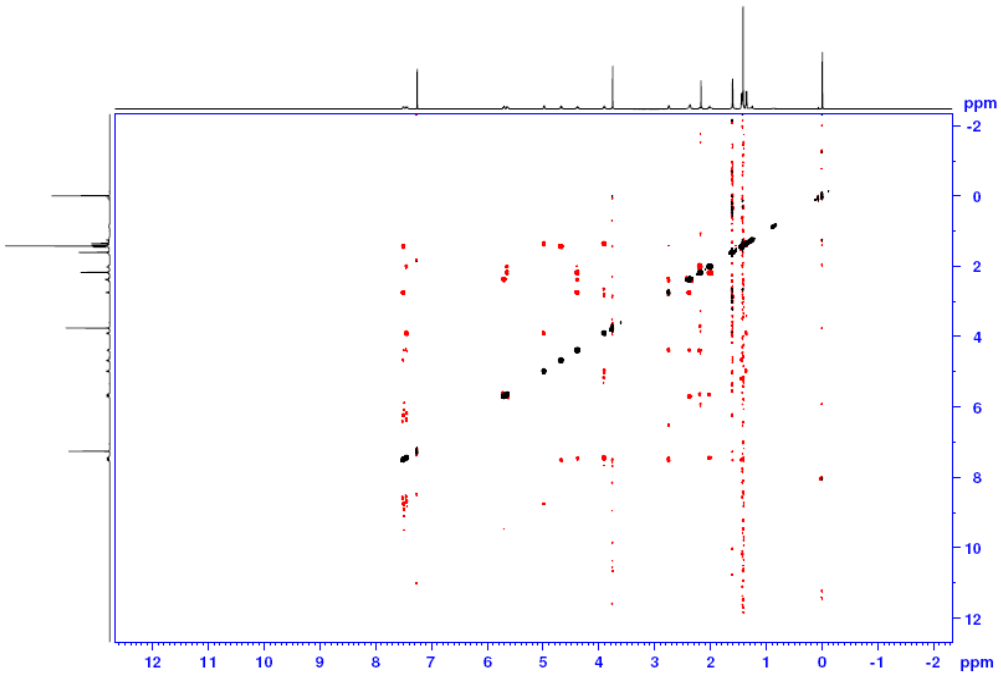


Figure S11. NOESY spectrum for **1** in $CDCl_3$

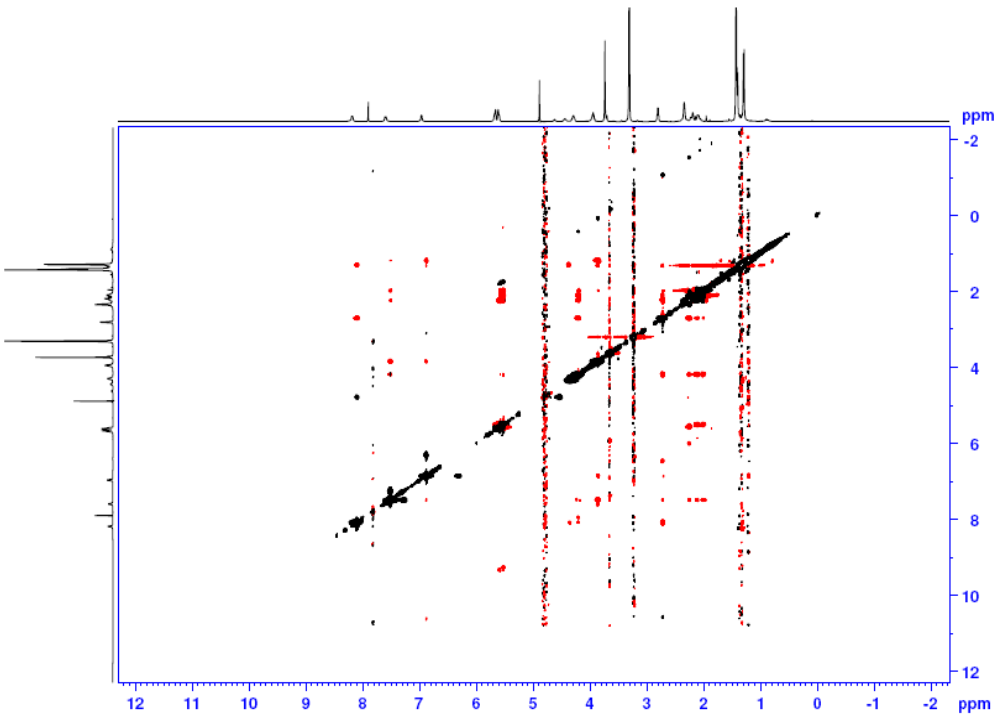


Figure S12. NOESY spectrum for **1** in CD_3OH

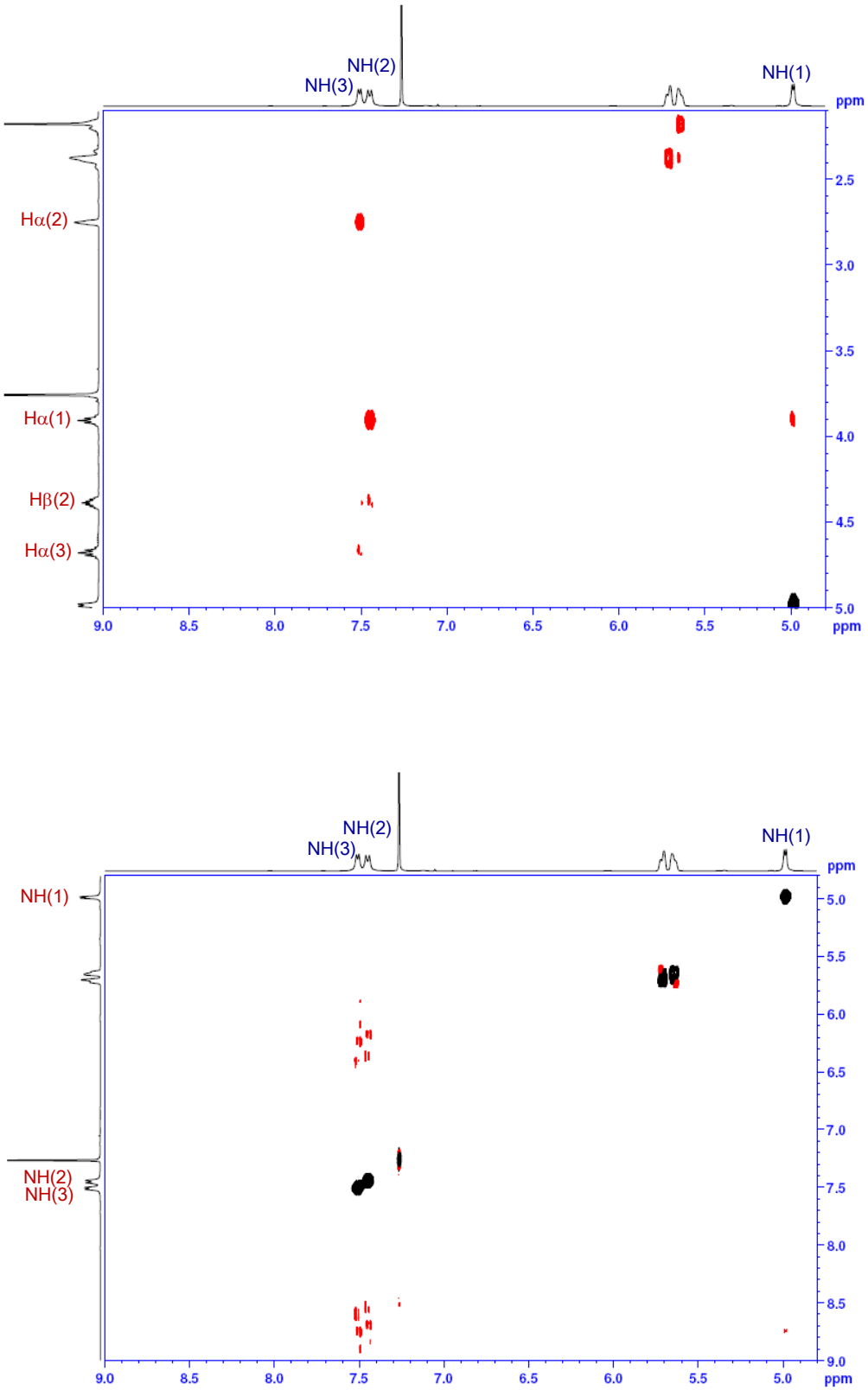


Figure S13. Partial NOESY spectra for **1** in $CDCl_3$

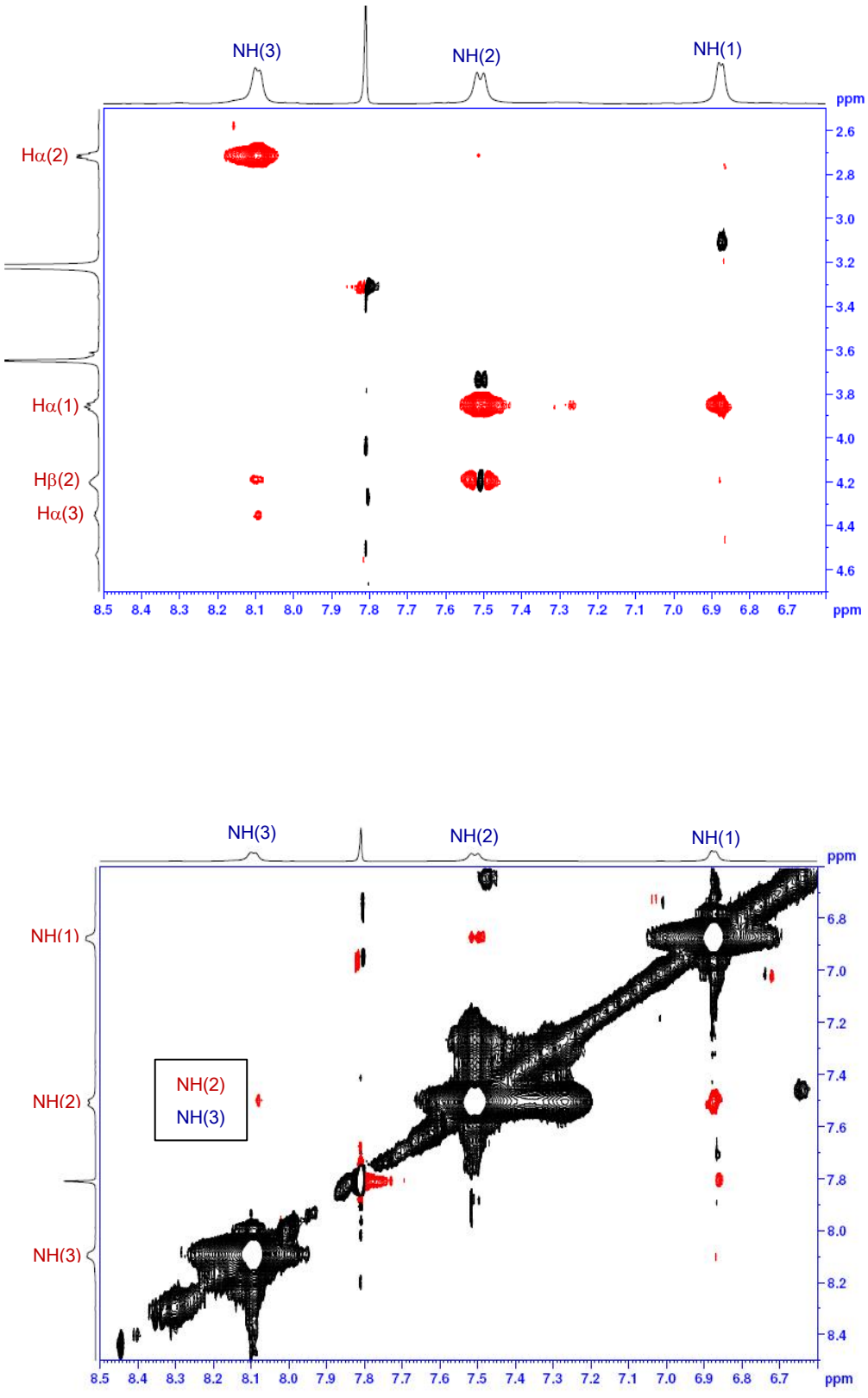


Figure S14. Partial NOESY spectra for **1** in CD_3OH

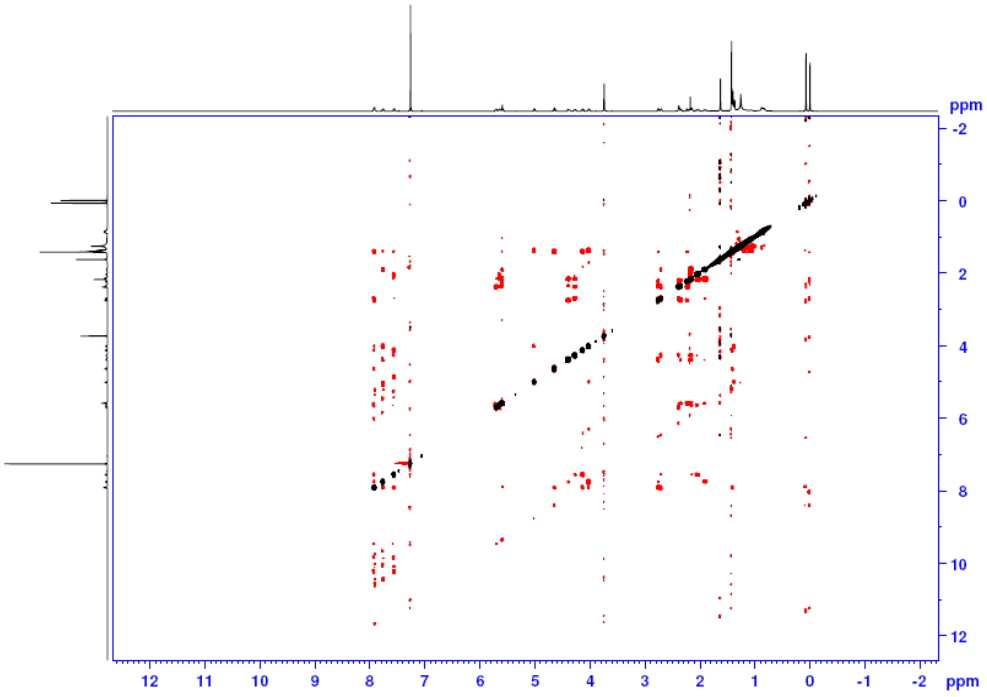


Figure S15. NOESY spectrum for **2** in $CDCl_3$

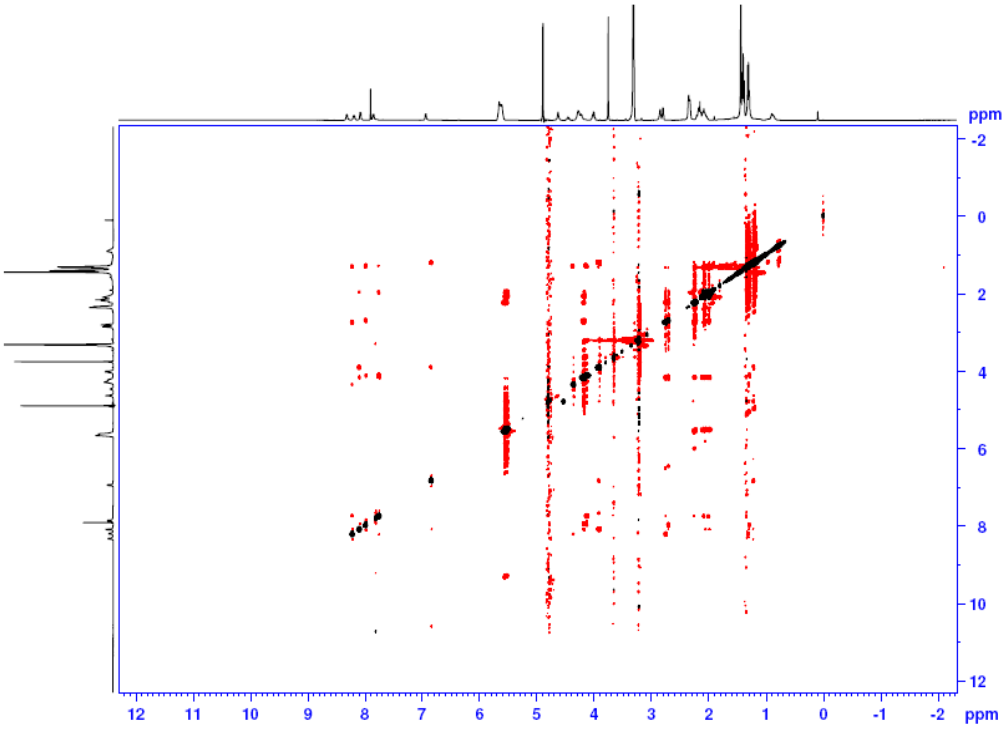


Figure S16. NOESY spectrum for **2** in CD_3OH

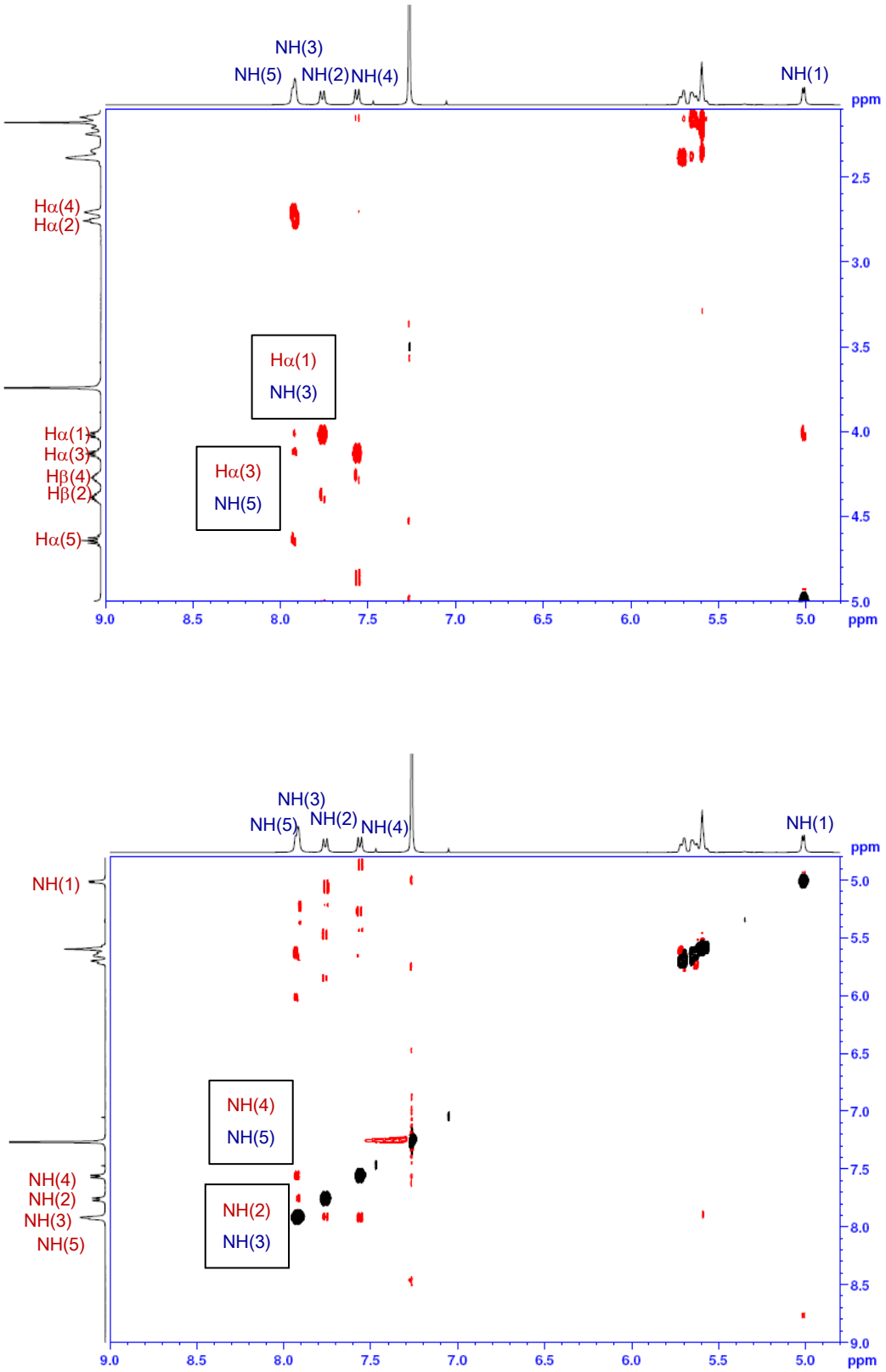


Figure S17. Partial NOESY spectra for **2** in $CDCl_3$

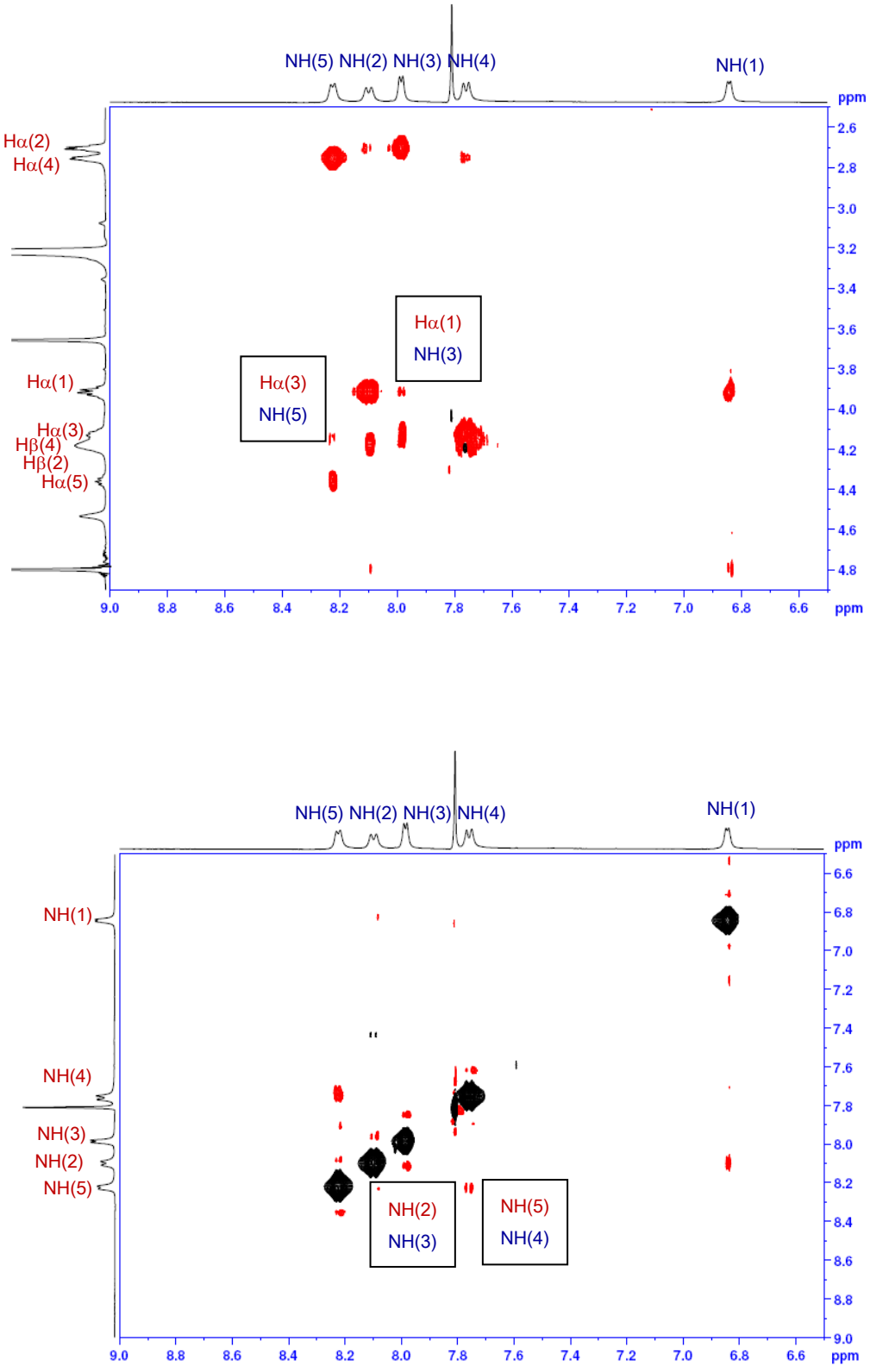


Figure S18. Partial NOESY spectra for **2** in CD_3OH

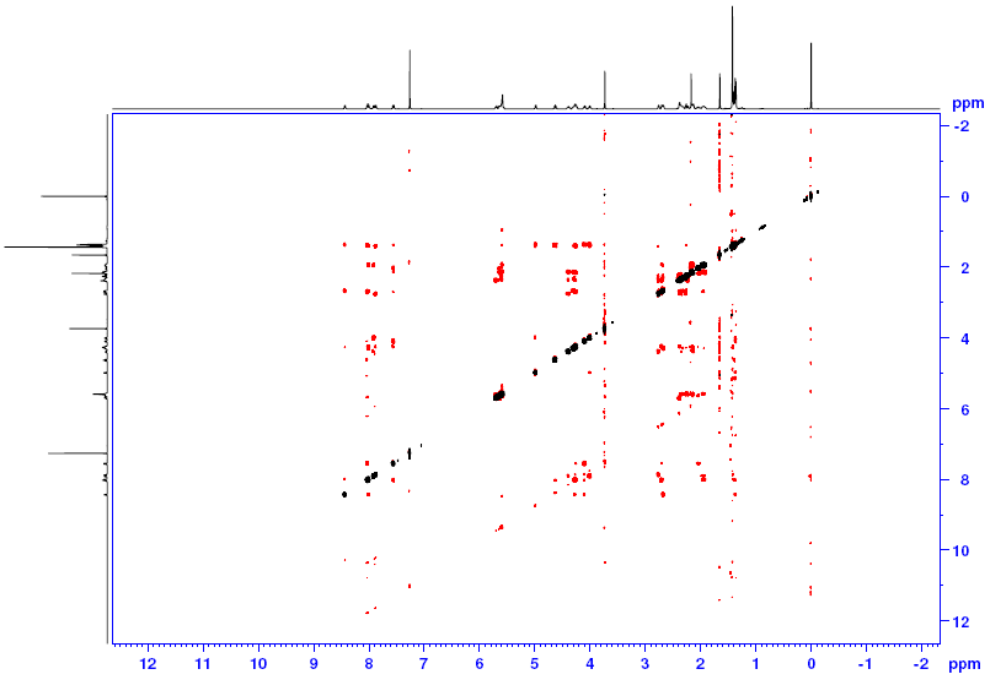


Figure S19. NOESY spectrum for **3** in $CDCl_3$

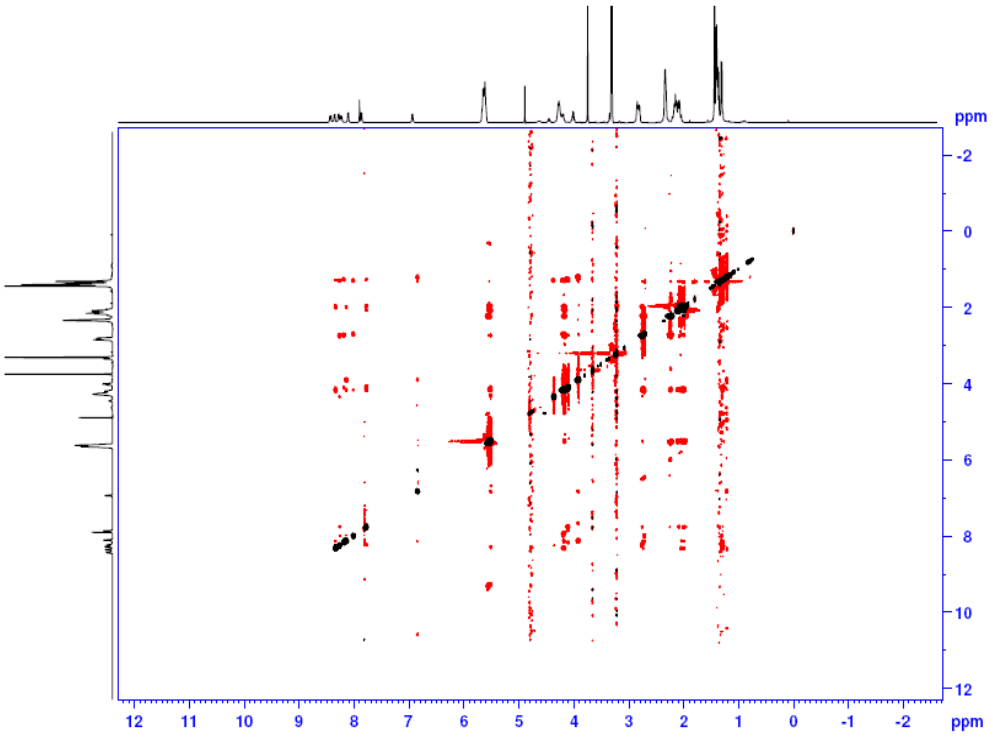


Figure S20. ROESY spectrum for **3** in CD_3OH

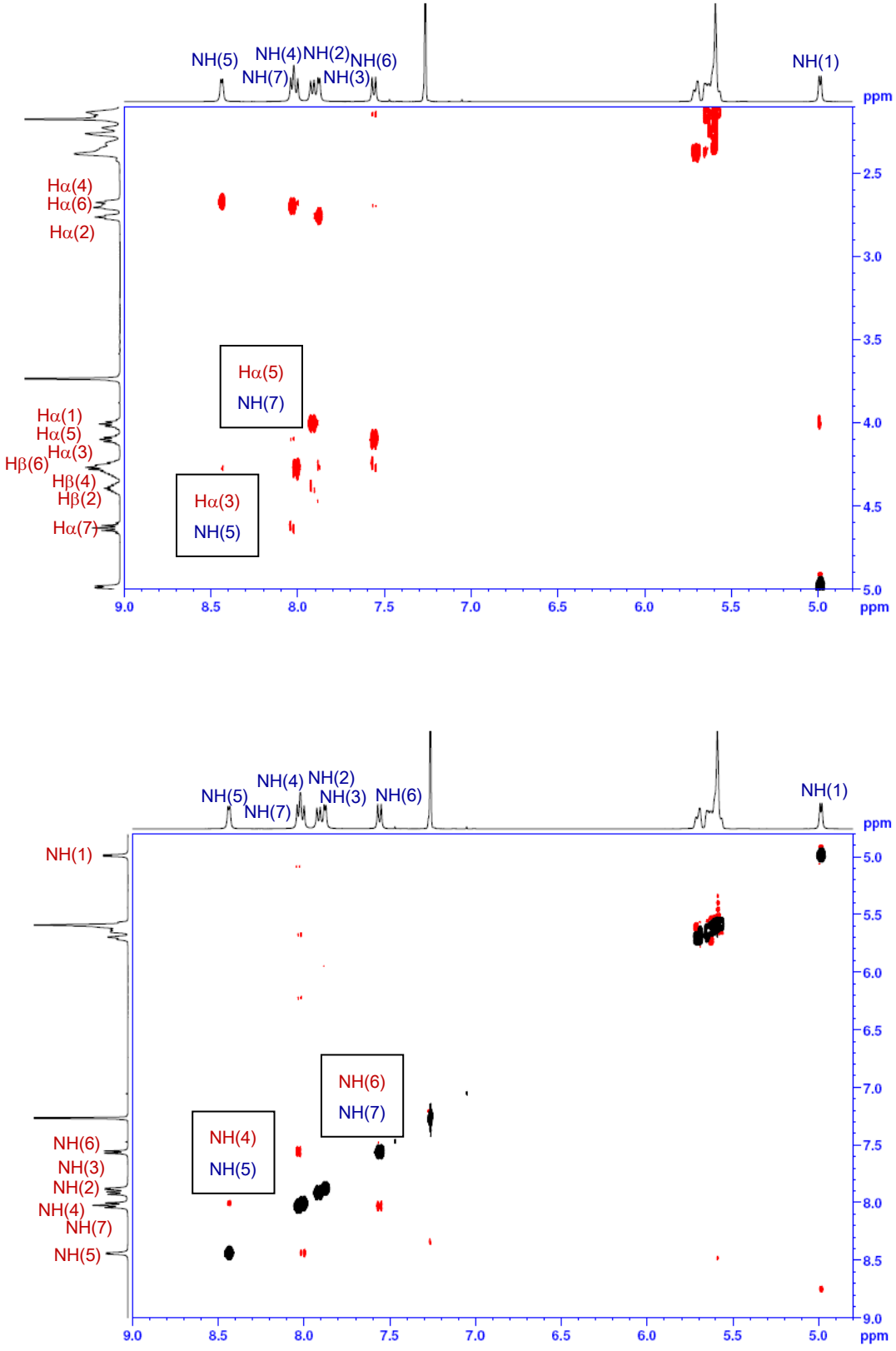


Figure S21. Partial NOESY spectra for **3** in $CDCl_3$

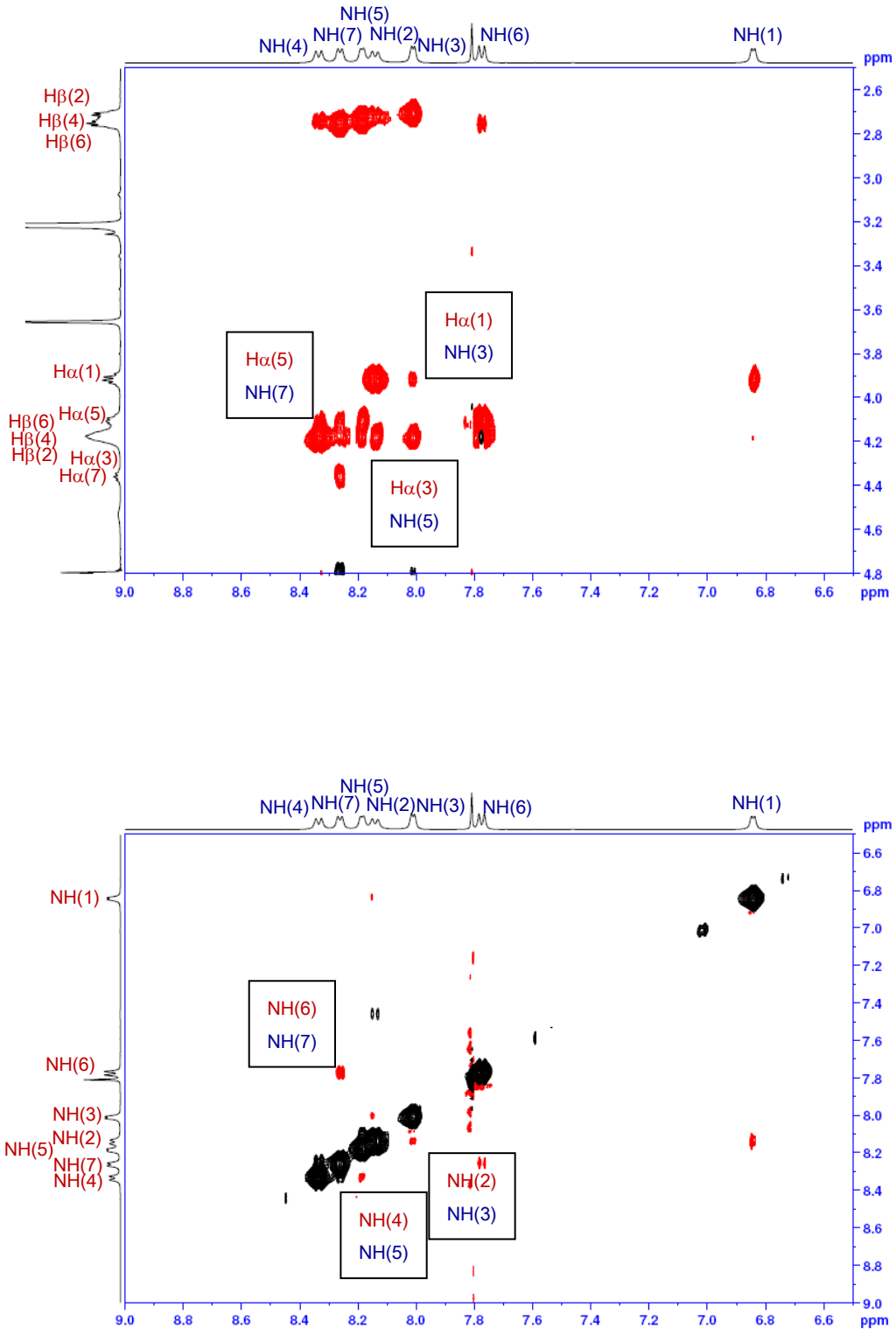


Figure S22. Partial ROESY spectra for **3** in CD_3OH

Titration study of α/β-peptides (10 mmol) in $CDCl_3$ with DMSO-*d*$_6$

Chemical shifts of the amide protons (δNHs) were measured while up to 250 μL of DMSO-d_6 was added sequentially to 500 μL $CDCl_3$ solutions of α/β-peptides. The changes of δNHs suggest that all NHs except NH(1) are involved in intramolecular hydrogen bonds for **1-3**. These results are consistent with hydrogen bonding patterns for the 11/9-helix.

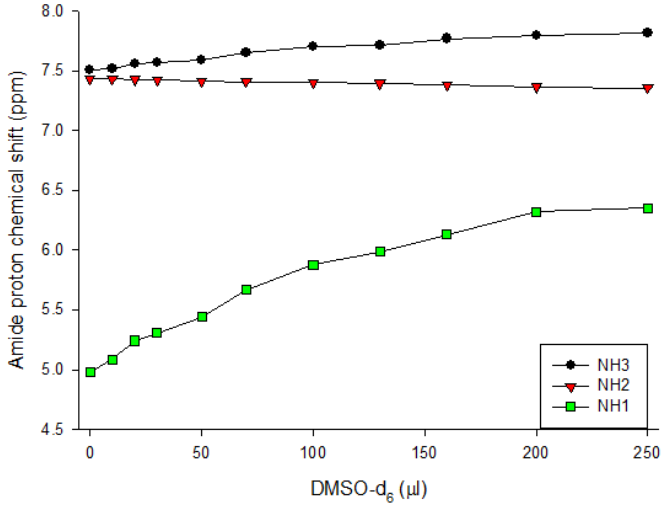


Figure S23. DMSO-d_6 Dependence of amide proton chemical shifts for **1** in $CDCl_3$

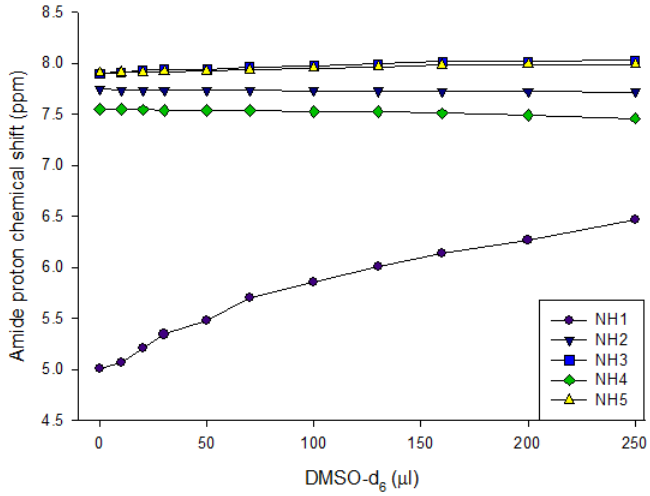


Figure S24. DMSO-d_6 Dependence of amide proton chemical shifts **2** in $CDCl_3$

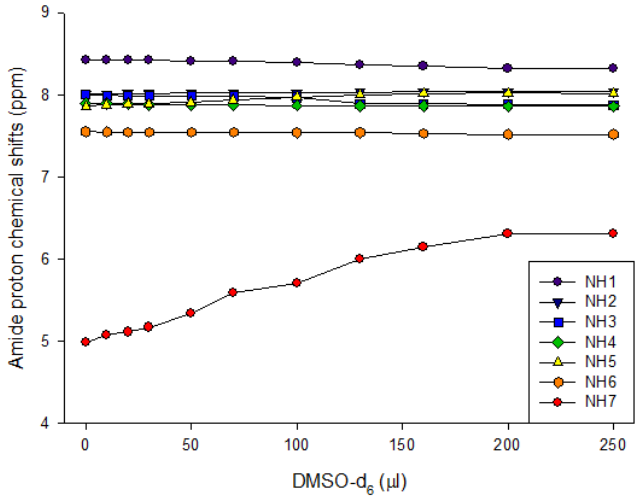


Figure S25. DMSO-d_6 Dependence of amide proton chemical shifts for **3** in $CDCl_3$

Circular dichroism experiments

Circular Dichroism spectra were measured by using JASCO-815 spectrometer at 298K. The spectra were obtained using 1-mm path length cell, wavelength range of 190 to 260 nm with 0.2 nm data interval, 1.0 nm bandwidth, and 200 nm/min scanning speed. CD data were acquired by the background from the sample spectrum and smoothened over 25 data points and then normalized for the number of residues. The final spectra were normalized for the number of residues, path length and concentration.

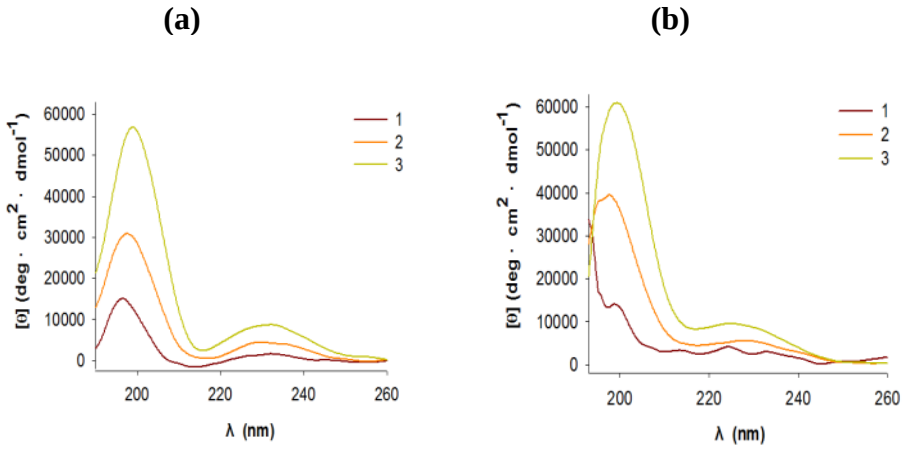


Figure S26. CD spectra for **1-3**: (a) in acetonitrile and (b) in methanol

IR spectra

IR spectra were recorded in the range between 8000 and 350 cm^{-1} with KBr beamsplitter by using Vertex 70 FT-IR spectrophotometer. The sample concentrations were 1 mM in DCM.

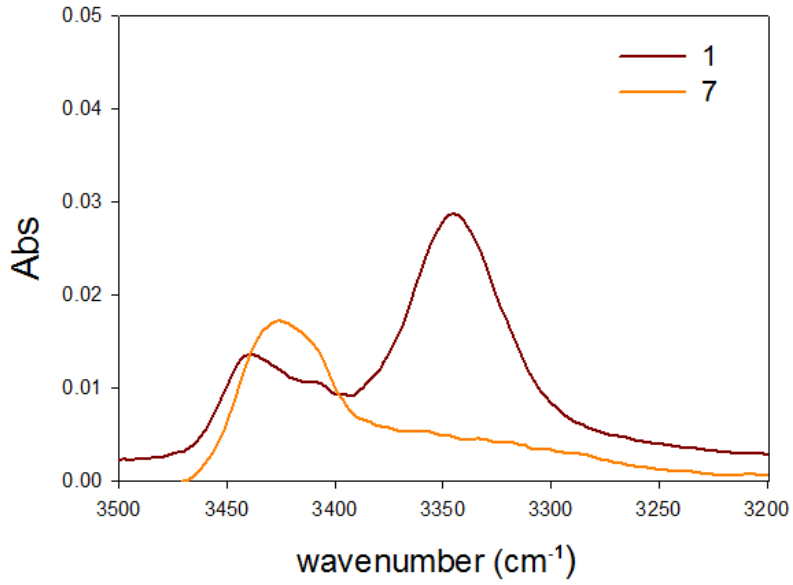


Figure S27. IR spectra for **1** and **7** in N-H band stretch region

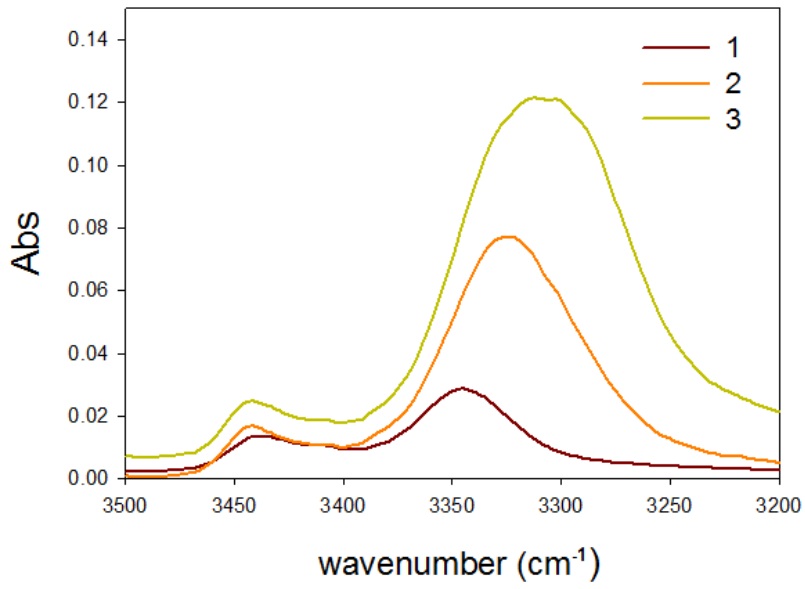


Figure S28. IR spectra for **1-3** in N-H band stretch region

Copies of high-resolution mass spectra

[M+Na⁺] = 349.1742 [349.1715-349.1750]

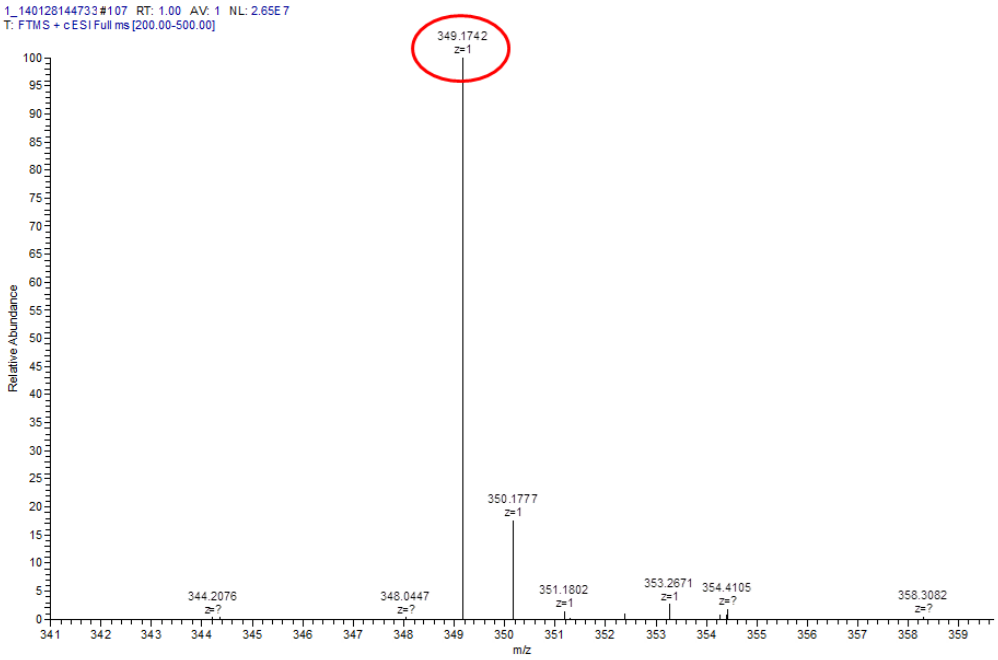


Figure S29. High-resolusion mass spectrum for **5**

[M+H⁺]= 398.2284 [398.2265-398.2304]

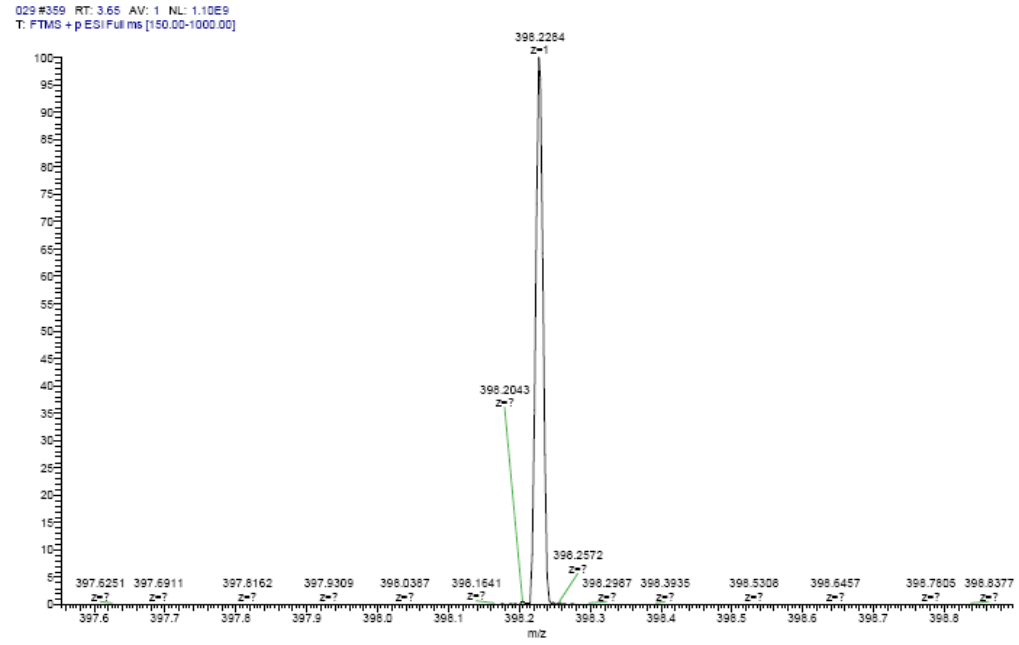


Figure S30. High-resolusion mass spectrum for **1**

[M+H⁺]= 592.3339 [592.3310-592.3369]

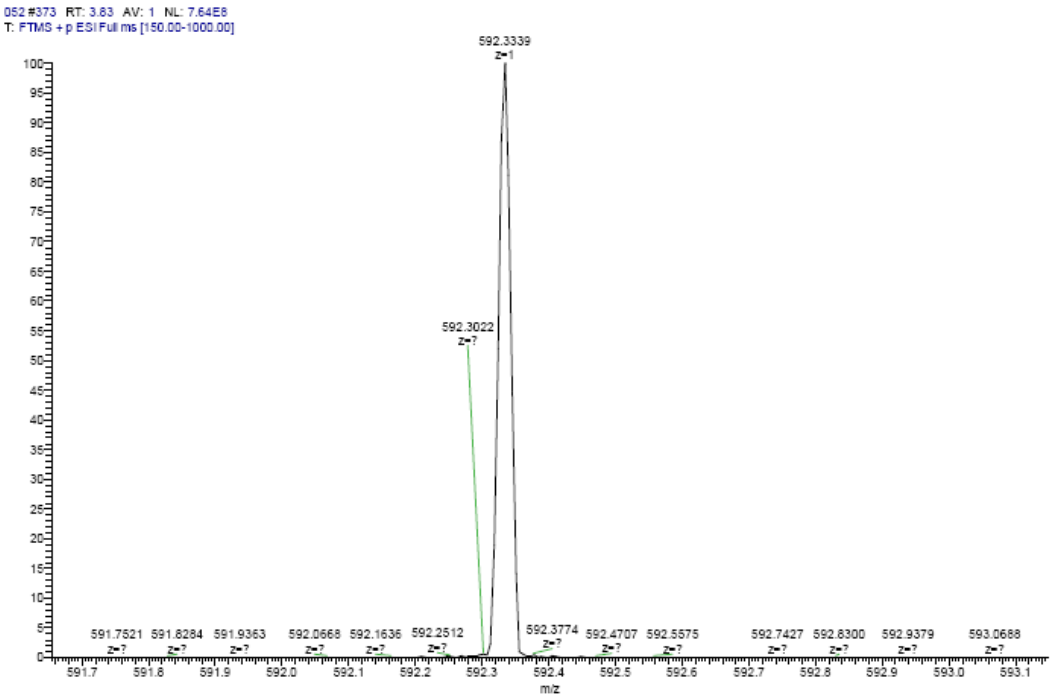


Figure S31. High-resolusion mass spectrum for **2**

[M+H⁺]= 786.4381 [786.4356-786.4435]

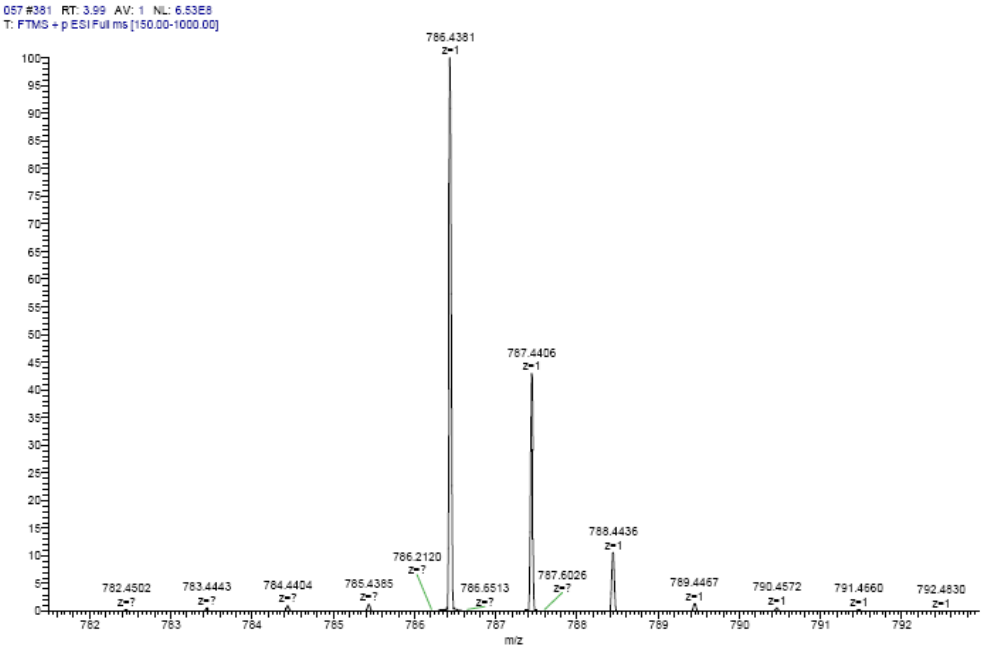


Figure S32. High-resolusion mass spectrum for **3**

X-ray crystallographic experiments

◇ 1:1 α/β-Peptide trimer 1

Data collection

A colorless crystal with approximate dimensions 0.26 × 0.105 × 0.097 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted at 300 K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker D8 Venture diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.00 cm. The initial cell constants were obtained from two series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in a 6° range about ω with the exposure time of 5 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9879 strong reflections from the actual data collection. The data were collected by using the half sphere data collection routine to survey the reciprocal space to the extent of a half sphere to a resolution of 0.81 Å. A total of 35606 data were harvested by collecting 6 sets of frames with 0.5° scans in ω and φ with an exposure time 10 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [3]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group $P2_1$ that yielded chemically reasonable and computationally stable results of refinement [4-5].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The final least-squares refinement of 276 parameters against 4284 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0319 and 0.0717, respectively. The final difference Fourier map was featureless.

Table S1. Crystal data and structure refinement for trimer **1**

Empirical formula	$C_{19}H_{33}N_3O_7$
Formula weight	415.48
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.4237(6)
b/Å	11.6936(7)
c/Å	9.8675(7)
α/°	90
β/°	95.103(2)
γ/°	90
Volume/Å ^{3}	1083.06(12)
Z	2
ρ_{calc}mg/mm^3	1.274
m/mm^{-1}	0.097
F(000)	448.0
Crystal size/mm^3	0.26 × 0.105 × 0.097
2Θ range for data collection	4.144 to 52.166°
Index ranges	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-12 \leq l \leq 12$
Reflections collected	35606
Independent reflections	4284[R(int) = 0.0615]
Data/restraints/parameters	4284/68/276
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0319, wR_2 = 0.0680
Final R indexes [all data]	R_1 = 0.0404, wR_2 = 0.0717
Largest diff. peak/hole / e Å $^{-3}$	0.20/-0.18
Flack parameter	0.0(4)

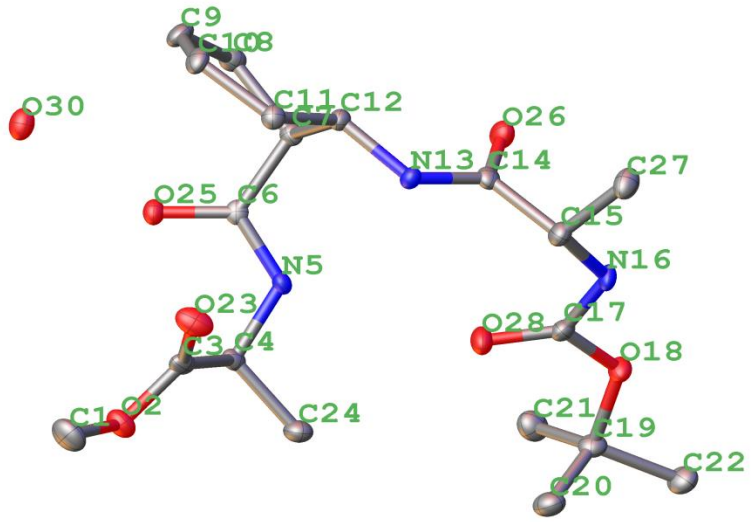


Figure S33. molecular drawing of trimer **1**

Summary

Crystal Data for $C_{19}H_{33}N_3O_7$ (M =415.48): monoclinic, space group $P2_1$ (no. 4), a = 9.4237(6) Å , b = 11.6936(7) Å , c = 9.8675(7) Å , β = 95.103(2)°, V = 1083.06(12) Å ^{3}, Z = 2, T = 300.0 K, μ(MoKα) = 0.097 mm^{-1}, Dcalc = 1.274 g/mm^3, 35606 reflections measured (4.144 ≤ 2Θ ≤ 52.166), 4284 unique (Rint = 0.0615) which were used in all calculations. The final R1 was 0.0319 (I > 2σ(I)) and wR2 was 0.0717 (all data).

◇ 1:1 α/β-Peptide pentamer 2·H_2O (co-crystallized with a water molecule)

Data collection

A colorless crystal with approximate dimensions 0.3 × 0.1 × 0.03 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted at 301(4) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker D8 Venture diffractometer with Cu K_α (λ = 1.54178 Å) radiation and the diffractometer to crystal distance of 4.00 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 20-30 frames collected at intervals of 0.5° in a 10-15° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of

7030 strong reflections from the actual data collection. The data were collected by using the half sphere data collection routine to survey the reciprocal space to the extent of a half sphere to a resolution of 0.81 Å. A total of 33557 data were harvested by collecting 20 sets of frames with 1º scans in ω and φ with an exposure time 20 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [3]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group $p2_1$ that yielded chemically reasonable and computationally stable results of refinement [4-5].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The final least-squares refinement of 403 parameters against 6447 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0475 and 0.1331, respectively. The final difference Fourier map was featureless.

Table S2. Crystal data and structure refinement for pentamer **2**·H_2O

Empirical formula	$C_{29}H_{47}N_5O_9$
Formula weight	609.71
Temperature/K	301.4
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.4408(3)
b/Å	11.5247(3)
c/Å	15.0540(4)
α/°	90
β/°	91.5670(15)
γ/°	90
Volume/Å ^{3}	1637.30(8)
Z	2
ρ_{calc}mg/mm^3	1.237
m/mm^{-1}	0.762
F(000)	656.0

Crystal size/mm^3	0.3 × 0.1 × 0.03
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection	5.872 to 145.112°
Index ranges	-11 ≤ h ≤ 9, -14 ≤ k ≤ 14, -18 ≤ l ≤ 18
Reflections collected	33557
Independent reflections	6447 [R_{int} = 0.0775, R_{sigma} = 0.0525]
Data/restraints/parameters	6447/1/399
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0475, wR_2 = 0.1181
Final R indexes [all data]	R_1 = 0.0727, wR_2 = 0.1331
Largest diff. peak/hole / e Å $^{-3}$	0.18/-0.27

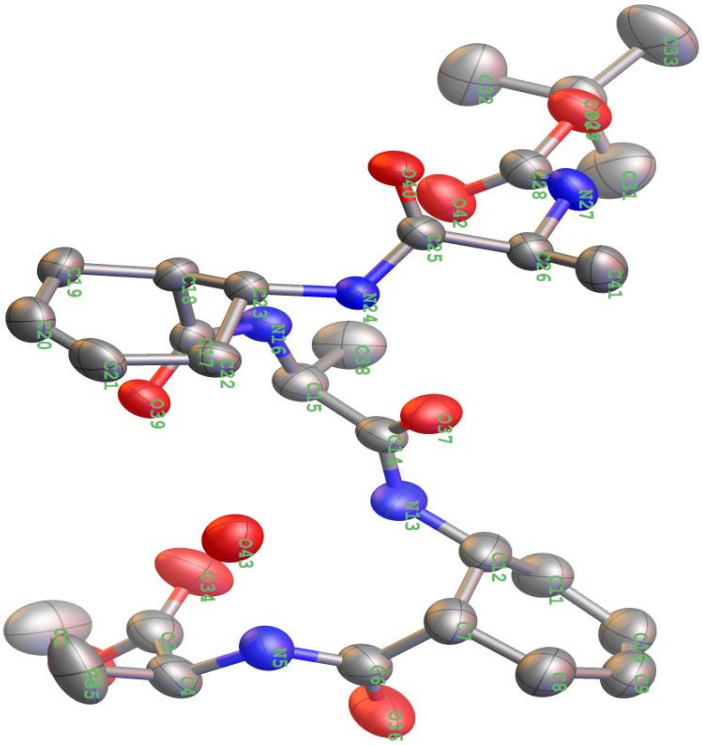


Figure S34. molecular drawing of pentamer **2**

Summary

Crystal Data for $C_{29}H_{47}N_5O_9$ (*M* =609.71): monoclinic, space group $P2_1$ (no. 4), *a* = 9.4408(3) Å, *b* = 11.5247(3) Å, *c* = 15.0540(4) Å, *β* = 91.5670(15)°, *V* = 1637.30(8) Å^3, *Z* = 2, *T* = 301.4 K, μ(CuKα) = 0.762 mm^{-1}, *Dcalc* = 1.237 g/mm^3, 33557 reflections measured (5.872 ≤ 2Θ ≤ 145.112), 6447 unique (R_{int} = 0.0775) which were used in all calculations. The final R_1 was 0.0475 (I > 2σ(I)) and wR_2 was 0.1331 (all data).

◇ 1:1 α/β-Peptide pentamer 2 (without water molecules)

Data Collection

A colorless crystal with approximate dimensions 0.2 × 0.1 × 0.1 mm^3 was selected under oil under ambient conditions and attached to the tip of a CryoLoop (Hampton Research). The crystal was mounted in a stream of cold nitrogen at 100 K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a Bruker D8 Venture diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.00 cm. The initial cell constants were obtained from two series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in a 6° range about ω with the exposure time of 5 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9709 strong reflections from the actual data collection. The data were collected by using the half sphere data collection routine to survey the reciprocal space to the extent of a half sphere to a resolution of 0.81 Å. A total of 130459 data were harvested by collecting 4 sets of frames with 0.5° scans in ω and φ with an exposure time 30 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[3]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group $P2_12_12_1$ that yielded chemically reasonable and computationally stable results of refinement.[4-5]

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The solvent present in the structure of Ala-ACHE_5mer was found to be highly disordered, and so the SQUEEZE procedure of the PLATON program was used.[6]

The final least-squares refinement of 386 parameters against 7600 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0470 and 0.1196, respectively. The

final difference Fourier map was featureless.

Table S3. Crystal data and structure refinement for pentamer **2**

Identification code	Ala-ACHE_5mer_moon234
Empirical formula	$C_{29}H_{45}N_5O_8$
Formula weight	591.70
Temperature/K	100.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.2829(8)
b/Å	17.955(2)
c/Å	23.143(3)
α/°	90
β/°	90
γ/°	90
Volume/Å ^{3}	3857.3(7)
Z	4
ρ_{calc}mg/mm^3	1.019
m/mm^{-1}	0.075
F(000)	1272.0
Crystal size/mm^3	0.2 × 0.2 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.538 to 52.144°
Index ranges	-10 ≤ h ≤ 11, -22 ≤ k ≤ 22, -28 ≤ l ≤ 28
Reflections collected	130459
Independent reflections	7600 [R_{int} = 0.0642, R_{sigma} = 0.0247]
Data/restraints/parameters	7600/309/386
Goodness-of-fit on F^2	1.079
Final R indexes [I>=2σ (I)]	R_1 = 0.0470, wR_2 = 0.1150
Final R indexes [all data]	R_1 = 0.0567, wR_2 = 0.1196
Largest diff. peak/hole / e Å $^{-3}$	0.25/-0.17
Flack parameter	0.1(3)

Summary

Crystal Data for $C_{29}H_{45}N_5O_8$ (*M* =591.70): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 9.2829(8) Å , *b* = 17.955(2) Å , *c* = 23.143(3) Å , *V* = 3857.3(7) Å ^{3}, *Z* = 4, *T* = 100.0 K, μ(MoKα) = 0.075 mm^{-1}, *Dcalc* = 1.019 g/mm^3, 130459 reflections measured (4.53 ≤ 2Θ ≤ 52.14), 7600 unique (R_{int} = 0.0642, R_{sigma} = 0.0247) which were used in all calculations. The final R_1 was 0.0470 (I > 2σ(I)) and wR_2 was 0.1196 (all data).

◇ 1:1 α/β-Peptide heptamer 3

Data collection

A colorless crystal with approximate dimensions 0.3 × 0.3 × 0.2 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 103(5) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a Bruker D8 Venture diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.00 cm. The initial cell constants were obtained from two series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in a 6° range about ω with the exposure time of 5 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9833 strong reflections from the actual data collection. The data were collected by using the half sphere data collection routine to survey the reciprocal space to the extent of a half sphere to a resolution of 0.81 Å. A total of 82006 data were harvested by collecting 13 sets of frames with 0.5° scans in ω and φ with an exposure time 8 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[3]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group *C*2 that yielded chemically reasonable and computationally stable results of refinement. [4-5]

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The final least-squares refinement of 596 parameters against 8983 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0774 and 0.2363, respectively. The final difference Fourier map was featureless.

Table S4. Crystal data and structure refinement for heptamer **3**

Empirical formula	$C_{39}H_{58}N_7O_{10}$
Formula weight	784.92
Temperature/K	103.5
Crystal system	monoclinic
Space group	C2
a/Å	31.232(8)
b/Å	8.842(2)
c/Å	18.831(5)
α/°	90
β/°	95.848(7)
γ/°	90
Volume/Å ^{3}	5173(2)
Z	4
ρ_{calc}mg/mm^3	1.008
m/mm^{-1}	0.073
F(000)	1684.0
Crystal size/mm^3	0.3 × 0.3 × 0.2
2Θ range for data collection	3.58 to 52.04°
Index ranges	$-38 \leq h \leq 38$, $-10 \leq k \leq 10$, $-23 \leq l \leq 23$
Reflections collected	10039
Independent reflections	8983[R(int) = 0.0000]
Data/restraints/parameters	8983/739/597
Goodness-of-fit on F^2	1.005
Final R indexes [I>=2σ (I)]	R_1 = 0.0689, wR_2 = 0.1919
Final R indexes [all data]	R_1 = 0.0932, wR_2 = 0.2068
Largest diff. peak/hole / e Å $^{-3}$	0.27/-0.26
Flack parameter	-0.2(5)

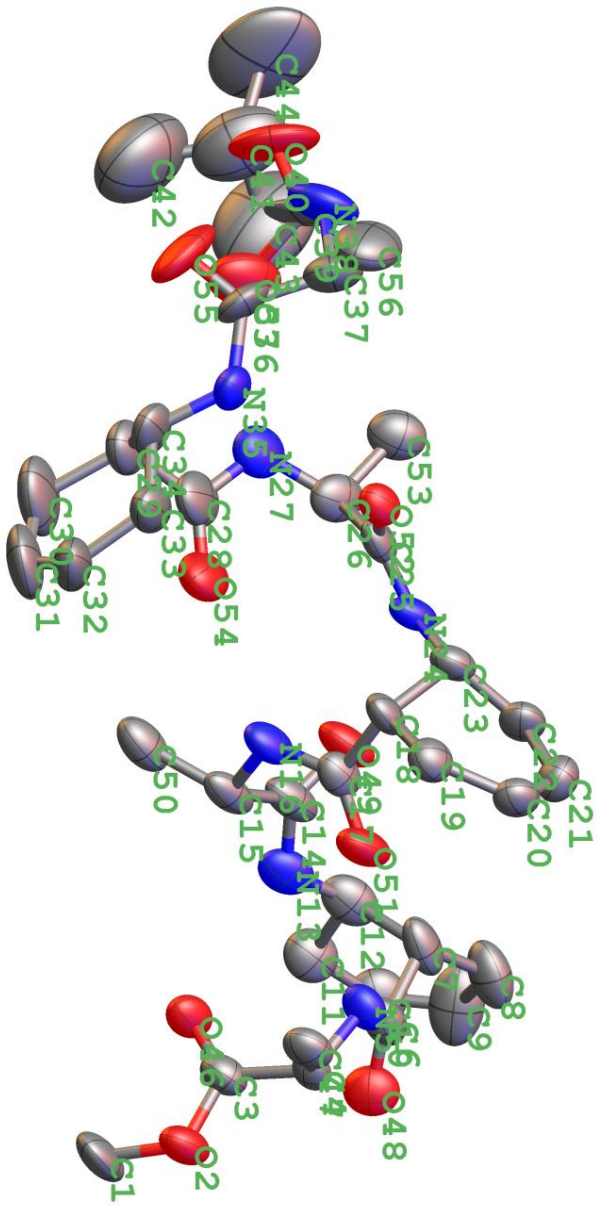


Figure S35. molecular drawing of heptamer **3**

Summary

Crystal Data for $C_{39}H_{58}N_7O_{10}$ (*M* =784.92): monoclinic, space group C2 (no. 5), *a* = 31.232(8) Å , *b* = 8.842(2) Å , *c* = 18.831(5) Å , *β* = 95.848(7)°, *V* = 5173(2) Å ^{3}, *Z* = 4, *T* = 103.5 K, μ(Mokα) = 0.073 mm^{-1}, *Dcalc* = 1.008 g/mm^3, 82006 reflections measured (3.58 ≤ 2Θ ≤ 52.42), 8983 unique (R_{int} = 0.0952) which were used in all calculations. The final R_1 was 0.0774 (I > 2σ(I)) and wR_2 was 0.2364 (all data).

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