Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Table of Contents

Synthesis and Characterization Data

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. *trans*-2-Aminocyclopenatanecarboxylic acid (*trans*-ACPC) was prepared by the method reported previously.[S1] 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. Mass spectra (MS) were acquired using an LTQ Orbitrap Spectrometer (ThermoFisher scientific Inc.). Yields for general procedures were not optimized..

General procedure for peptide coupling I

To a 0.1 M solution of an amine (1 equiv) and an acid (1 equiv) in DCM(or DMF), EDCI (1.5 equiv), HOBt(1.3equiv) and TEA (1.1 equiv) are added, and the reaction mixture is stirred at rt for 2-3 days. The reaction mixture is diluted with EtOAc and then washed with 10% aqueous citric acid, aqueous saturated $NaHCO_3$, and brine. The organic layer is then dried over $MgSO_4$, filtered and concentrated to give a crude product, which is purified by flash column chromatography.

General procedure for peptide coupling II

To a 0.1 M solution of an amine (1 equiv) and an acid (1 equiv) in DCM(or DMF), EDCI (1.5 equiv), DMAP(0.3equiv) are added, and the reaction mixture is stirred at rt for 1-2 days. The reaction mixture is diluted with EtOAc and then washed with 10% aqueous citric acid, aqueous saturated $NaHCO_3$, and brine. The organic layer is then dried over $MgSO_4$, filtered and concentrated to give a crude product, which is purified by flash column chromatography.

General procedure for deprotection of the Boc group

An *N*-Boc protected oligomer is treated with TFA in DCM (1:1) for 30 min with stirring, and the mixture is then concentrated under a nitrogen gas stream. The concentrated mixture is used without purification to next step.

General procedure for saponification.

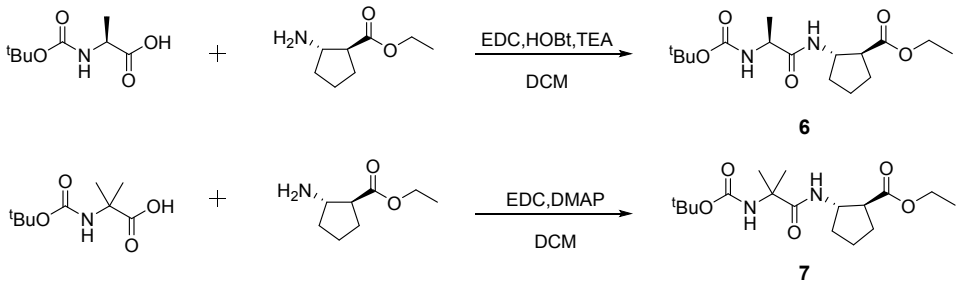
To a solution of an amino ester in MeOH/H_2O(2:1) or THF:MeOH:H_2O (3:1:1) at 0℃ was added LiOH·H_2O (5.0eq). The resulting mixture was stirred at 0℃ for 12h. The pH of the mixture is adjusted to 1.0 by addition of aqueous 1M HCl solution. The resulting mixture is then extracted with EtOAc four times. The combined organic fractions are dried over magnesium sulfate, filtered, and concentrated by rotary evaporation under reduced pressure to give a white solid.

General procedure for catalytic hydrogenolysis of C-terminal benzyl ester group.

An oligomer with C-terminal benzyl ester and 10% palladium on activated carbon (20% wt) are added to a two-necked round-bottomed flask charged with nitrogen gas. MeOH is slowly added to the flask under a nitrogen gas stream. A neck is fitted with a hydrogen gas balloon and the other neck is capped with a rubber septum. The mixture is stirred at rt for 2h and then filtered through Celite pad. The filtrate is concentrated under reduced pressure to give a crude product, which is used for the next step without purification.

Synthesis of peptide oligomers

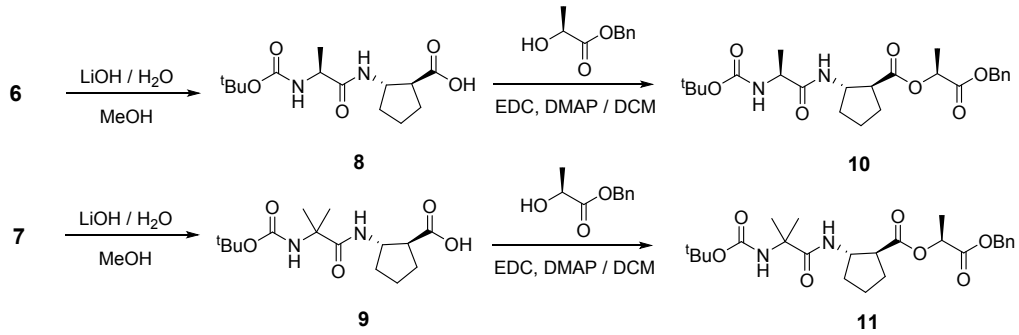
Dipeptide **6** and **7** were synthesized by the general procedures for peptide coupling analogous to the method reported previously.[S1]



Boc-Ala-ACPC-OEt (6) ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.53 (s, 1H), 5.16 (s, 1H), 4.36 (m, 1H), 4.12 (m, 2H), 3.7 (s, 2H), 2.61(quintet, *J* = 8Hz, 1H),2.15-2.07 (m, 1H), 2.04-1.87 (m,3H),1.81-1.68 (m, 2H), 1.43 (s, 1H), 1.33-1.32 (m, 3H), 1.27-1.22(m, 1H)

Boc-Aib-ACPC-OEt (7) ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.67 (s, 1H), 4.83 (s, 1H), 4.38-4.30 (m, 1H), 4.18-4.07 (m, 1H), 3.67 (s, 1H), 2.62(quintet, *J* = 8Hz, 1H),2.17-2.08 (m, 1H), 2.04-1.84 (m, 2H),1.81-1.67 (m, 1H), 1.59-1.37 (m, 16H), 1.30-1.22 (m, 2H)

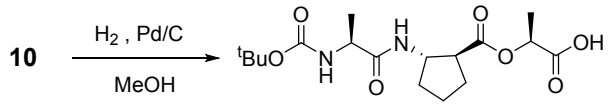
Tridepsipeptides **10** and **11** were synthesized by the general procedure of saponification followed by the general procedure for peptide coupling II from **6** and **7**, respectively.



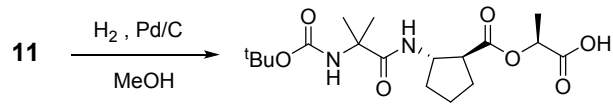
Boc-Ala-ACPC-Lac-OBn (10) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.33-7.28 (m, 5H), 6.58 (s, 1H), 5.24 (m, 1H), 5.13 (m, 2H), 4.32(m, 1H), 4.10 (s, 1H), 2.79(m, 1H), 2.1-1.8 (m, 4H), 1.8-1.62 (m, 3H),1.52 (m, 3H), 1.49(s, 9H), 1.31 (m, 3H)^{13}C NMR (100MHz, $CDCl_3$) δ 173.6, 172.4, 170.59, 155.5, 135.3, 128.4, 128.3, 128.1, 79.8, 68.6, 66.9, 60.3, 54.8, 50.0, 32.3, 28.23(3C), 27.9, 22.9, 21.0, 18.4, 16.8, 14.1

Boc-Aib-ACPC-Lac-OBn (11) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.37-7.28 (m, 5H), 6.64 (s, 1H), 5.21-5.09 (m, 2H), 4.88 (m, 2H), 4.38(m, 1H), 2.73 (s, 1H), 1.16-1.89 (m, 3H), 1.79-1.67 (m, 2H),1.66-1.48 (m, 20H)^{13}C NMR (100MHz, $CDCl_3$) δ 174.2, 173.7, 170.6, 154.8, 135.3, 128.5, 128.3, 128.1, 68.6, 66.9, 56.7, 55.0, 50.0, 32.2, 28.23(3C), 27.9, 25.3, 23.0, 16.8

Tridepsipeptide acids **12** and **13** were prepared by the general procedure for catalytic hydrogenolysis from **10** and **11**, respectively.



12

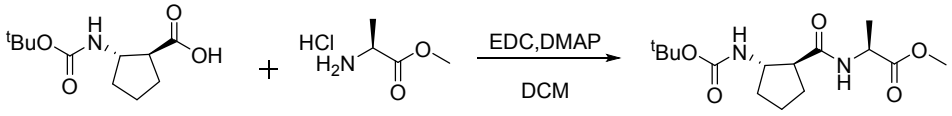


13

Boc-Ala-ACPC-Lac-OH (12) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.10 (s, 1H), 5.62 (s, 1H), 5.11 (quintet, *J* =6.8Hz, 1H), 4.37(m, 1H), 4.15 (s, 1H), 2.76(m, 1H), 2.1(m, 1H), 2.02 (m, 1H),1.96-1.71 (m, 3H), 1.58(m, 1H), 1.52 (m, 3H), 1.42 (m, 9H) 1.2 (m, 3H)

Boc-Aib-ACPC-Lac-OH (13) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.05 (s, 1H), 5.15 (s, 2H), 4.30 (s, 1H), 2.73(m, 1H), 2.18 (s, 1H), 2.06(m, 1H), 1.95(m, 1H), 1.76 (m, 1H),1.59 (m, 1H), 1.50(m, 3H), 1.45-1.44 (m, 16H)

Dipeptide **14** and **15** were synthesized by the general procedure for peptide coupling II.



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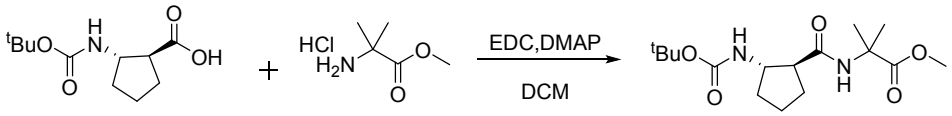
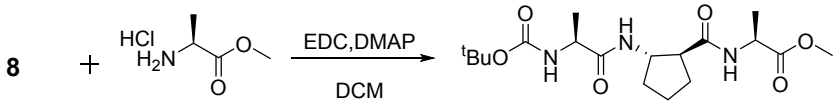


15

Boc-ACPC-Ala-OMe (14) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.88 (s, 1H),4.65 (s, 1H), 4.54 (quintet, *J* =8.Hz 1H), 4.07 (quintet, *J* =6.4.Hz 1H), 3.7(s, 3H), 2.6(s, 1H), 2.17-1.98(m, 2H), 1.89-1.81(m, 1H), 1.76-1.65 (m, 1H),1.61 (s, 1H), 1.47-1.37(m, 12H)

Boc-ACPC-Aib-OMe (15) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.91 (s, 1H), 4.65 (s, 1H), 4.54 (quintet, *J* =8.Hz 1H), 3.7(s, 3H), 2.66(s, 1H), 2.17-1.98(m, 1H), 1.89-1.81(m, 1H), 1.76-1.65 (m, 1H),1.61 (s, 1H), 1.5-1.37(m, 15H)

Tripeptides **16** and **17** were prepared by the general procedure for peptide coupling II from **8**.



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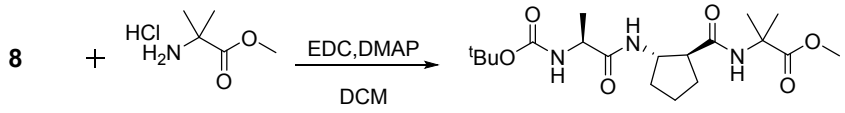
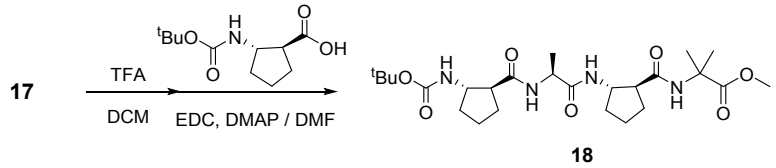


17

Boc-Ala-ACPC-Ala-OMe (16) ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.00 (s, 1H), 6.79 (s, 1H), 5.2 (d, *J* = 4Hz 1H), 4.21-4.09 (m, 3H), 3.69 (s, 3H), 2.64-2.59 (m, 1H), 2.15-2.08(m, 1H), 2.02-1.93 (m, 1H), 1.81-1.60 (m, 3H), 1.56-1.32 (m, 16H)

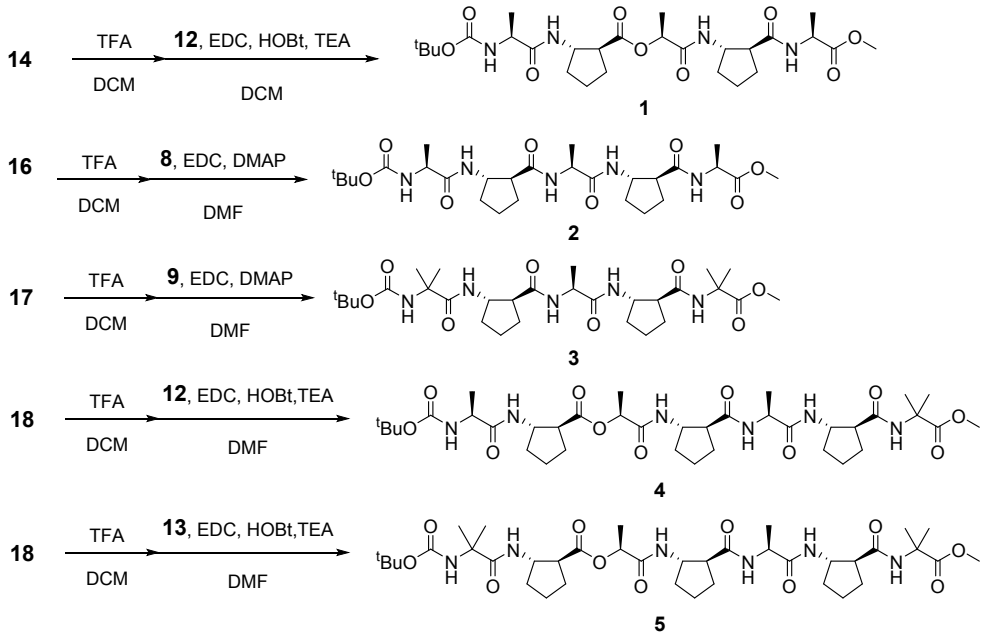
Boc-Ala-ACPC-Aib-OMe (17) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.97 (s, 1H), 6.66 (s, 1H), 5.07 (d, *J* = 8Hz 1H), 4.19-4.09 (m,3H), 2.63-2.58 (m,1H), 2.14-2.09 (m,1H), 2.04-1.93 (m,2H), 1.79-1.62(m, 4H), 1.54-1.48 (m, 7H), 1.44(s, 9H), 1.36(s, 3H)

Tetrapeptide **18** was synthesized by the general procedures for Boc deprotection and peptide coupling II from **17**



Boc-ACPC-Ala-ACPC-Aib-OMe (18) ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.84(s,1H), 7.41 (d, *J* = 7.2Hz 1H), 6.78(d, *J* = 5.6Hz 1H), 5.01 (d, *J* = 6.8Hz, 1H), 4.36 (m, 1H), 4.25 (m, 1H), 4.25 (m, 1H), 3.97 (quintet, *J* = 6.4Hz, 1H), 3.67 (s, 3H), 2.62 (m, 1H), 2.53 (m, 1H), 2.17-1.85(m, 6H), 1.81-1.55 (m, 6H), 1.52(s, 6H), 1.44 (s, 9H), 1.41(m, 3H)

Peptide oligomers **1-5** were synthesized from the smaller peptide fragments by the general procedures.



Boc-Ala-ACPC-Lac-ACPC-Ala-OMe (1) $[\alpha]_D^{20}$ = -20 (*c* 1, $CHCl_3$) ; ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.85 (d, *J* = 4Hz, 1H), 7.91 (d, *J* = 4Hz, 1H), 6.72 (s, 1H), 5.18 (d, *J* = 4Hz 1H), 4.87 (d, *J* = 4Hz, 1H), 4.52 (quintet, *J* = 5.7Hz, 1H), 4.38 (quintet, *J* = 5.5Hz, 1H), 4.23 (quintet, *J* = 4.9Hz, 1H), 4.13 (s, 1H), 3.72 (s, 3H), 2.72 (quartet, *J* = 4.5Hz, 1H), 2.67 (s, 1H), 2.1 (m, 2H), 2.0 (m, 2H), 1.9 (m, 1H), 1.8 (m, 3H), 1.7 – 1.6 (m, 5H), 1.55 – 1.13 (m, 17H), ^{13}C NMR (100MHz, $CDCl_3$) δ 174.9, 173.7, 173.5, 173.3, 171.6, 155.6, 80.4, 70.9, 55.2, 55.1, 52.1, 51.5(2C), 50.2, 48.2, 33.3, 32.4, 29.9, 28.2(3C), 27.1, 25.0, 23.8, 18, 17.8, 17.5; High-resolution MS m/z calculated for $C_{27}H_{44}N_4O_9$ $[M+H]^+$ 569.3181, found 569.3165.

Boc-Ala-ACPC-Ala-ACPC-Ala-OMe (2) ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.20 (d, *J* = 5.9Hz, 1H), 7.67 (d, *J* = 6.5Hz, 1H), 6.92 (d, *J* = 5.9Hz, 1H),), 6.55 (d, *J* = 7.4Hz, 1H), 5.061 (d, *J* = 3.8Hz, 1H), 4.53 (quintet, *J* = 7.3Hz, 1H), 4.35 (m, 1H), 4.28 (m, 1H), 4.20 (m, 1H), 4.03 (m, 1H), 3.72 (s, 3H), 2.77 (quartet, *J* = 6.0Hz, 1H), 2.35 (m, 1H), 2.10 (m, 1H),1.93 (m, 2H),1.81 (m, 3H),1.69 (m, 3H), 1.52 (m, 1H),1.44 (m, 3H), 1.42 (m, 2H), 1.37 (m, 3H); 1.25(s,1H)^{13}C NMR (100MHz, $CDCl_3$) δ 174.3, 173.8, 175.7, 173.5, 155.9, 81.0, 81, 56, 55.8, 53.3, 52.1, 51.9, 51.3, 50.3, 48.3, 33.6, 33.5, 32.3, 28.5, 28.3, 26.9, 24.7, 24.3, 24.4, 17.6, 17.5; MALDI-TOF m/z calculated for $C_{27}H_{45}N_5O_8$ $[M+Na]^+$ 590.32, found 590.01.

Boc-Aib-ACPC-Ala-ACPC-Aib-OMe (3) $[\alpha]_D^{20}$ = +69 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz), $CDCl_3$) δ 7.75 – 7.72 (m, 2H), 7.16 (d, *J* = 4Hz, 1H), 6.36 (d, *J* = 8Hz, 1H), 4.45 (s, 1H), 4.29 (m, 2H), 4.23 (quintet, *J* = 5.1Hz, 1H), 3.70 (s, 3H), 2.70 (quartet, *J* = 5.6Hz, 1H), 2.27-2.19 (m, 1H), 2.11 (m, 3H), 1.98-1.90 (m, 1H), 1.71 (m, 9H), 1.53 – 1.4 (m, 23H); ^{13}C NMR (100MHz, $CDCl_3$) δ 175.5, 174.6, 174, 173.4, 173.3, 154.9, 81.2, 56.9, 55.8, 55.5, 55.1, 53.1, 52.1, 51.8, 51.3, 33.8, 32.5, 28.2(3C), 27.8, 27.5, 26.7, 25.2(2C), 24.7, 24.4, 24, 17.7; High-resolution MS m/z calculated for $C_{29}H_{49}N_5O_8$ $[M+H]^+$ 596.3654, found 596.3639.

Boc-Ala-ACPC-Lac-ACPC-Ala-ACPC-Aib-OMe (4) $[\alpha]_D^{20}$ = -18 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz), $CDCl_3$) δ 7.78 (s, 2H), 7.52 (s, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 4.91 (quartet, *J* = 5.2Hz, 1H), 4.82 (s, 1H), 4.38-4.31 (m, 1H), 4.31-4.25 (m, 2H), 4.25-4.19 (m, 1H), 4.14-4.09(m, 1H) 3.69 (s, 3H), 2.70 (quartet, *J* = 5.4Hz, 1H), 2.64-2.60 (m, 1H), 2.57 (quartet, *J* = 5.4Hz, 1H); 2.21-2.15 (m, 1H); 2.13-2.0 (m, 5H); 1.98-1.76 (m, 10H); 1.74 – 1.6 (m, 6H), 1.56 – 1.13 (m, 29H); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.6, 175.5, 174.6, 173.8, 173.1, 171.6,155.6, 80.5, 72.5, 55.8, 55.3, 54.8, 52.1, 51.58(2C), 51.5, 51.0, 50.8, 33.0, 32.5, 32.4,30.9, 29.6, 28.2(3C), 27.8, 26.9, 25.3, 24.6, 24.5, 24, 23.6, 17.9, 17.7(2C); High-resolution MS m/z calculated for $C_{37}H_{60}N_6O_{11}$ $[M+H]^+$ 765.4393, found 765.4376.

Boc-Aib-ACPC-Lac-ACPC-Ala-ACPC-Aib-OMe (5) $[\alpha]_D^{20}$ = +20 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz), $CDCl_3$) δ 7.72 (s, 2H), 7.28 (s, 2H), 6.93 (d, *J* = 8Hz, 1H), 6.80 (s, 1H), 5.36 (s, 1H), 4.84 (quartet, *J* = 6.8Hz, 1H), 4.45 (quintet, *J* = 8.3Hz, 1H), 4.31 (m, 2H), 4.22 (m, 1H), 3.69 (s, 3H), 2.71-2.62 (m, 3H), 2.19-1.19 (m, 6H), 1.79-1.62 (m, 10H); 1.62-1.36 (m, 28H); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.9, 175.5, 175.4, 174.6, 173.5, 173.1,171.5, 154.6, 80.3, 72.6, 56.4, 55.7, 55.4, 55.3, 54.7, 52.1, 51.4, 51.2(3C), 51.1, 33.4, 32.6, 32.4,31.1, 29.6, 28.3(3C), 27.6, 26.9, 26.2, 25.3, 24.8(2C), 24.5, 24, 23.3, 17.9, 17.7;High-resolution MS m/z calculated for $C_{38}H_{62}N_6O_{11}$ $[M+H]^+$ 779.4549 found 779.4533.

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 0.1 nm data interval, 1.0 nm bandwidth, and 100 nm/min scanning speed. CD data were acquired in methanol by the background from the sample spectrum Peptide concentrations were 0.5 mM. The final spectra were normalized for the number of residues, path length, and peptide concentration.

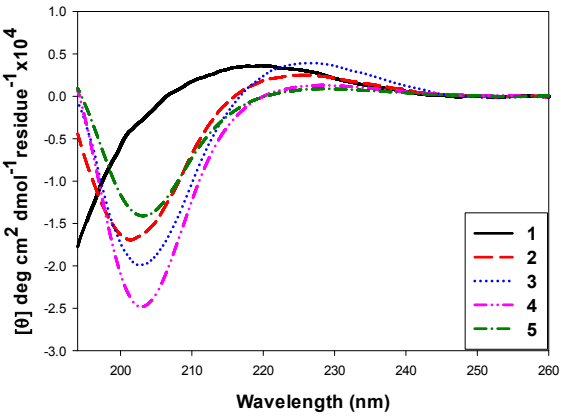


Figure S1. CD spectra of **1-5** in acetonitirile.

Backbone Proton Chemical Shifts (ppm, in $CDCl_3$)

α/β-Depsipeptide **1** :

	Boc	Hα	Hβ	HN	OMe
N-term	1.46	-	-	-	-
Ala1	-	4.13	-	4.86	
ACPC2	-	2.67	4.20	6.72	-
Lac3	-	5.17	-	-	-
ACPC4	-	2.78	4.38	7.91	-
Ala5	-	4.52	-	8.05	-
C-term	-	-	-	-	3.72

α/β-Pentapeptide **3** :

	Boc	Hα	Hβ	HN	OMe
N-term	1.46	-	-	-	-
Aib1	-	-	-	4.97	-
ACPC2	-	2.24	4.34	6.36	-
Ala3	-	4.22	-	7.21	-
ACPC4		2.67	4.30	7.75	-
Aib5	-	-	-	7.77	-
C-term	-	-	-	-	3.70

α/β-Depsipeptide **4** :

	Boc	Hα	Hβ	HN	OMe
N-term	1.46	-	-	-	-
Ala1	-	4.10	-	4.82	-
ACPC2	-	2.63	4.21	6.73	-
Lac3	-	4.89	-	-	-
ACPC4	-	2.55	4.35	7.78	-
Ala5	-	4.27	-	6.61	-
ACPC6	-	2.69	4.27	7.52	-
Aib7	-	-	-	7.78	-
C-term	-	-	-	-	3.69

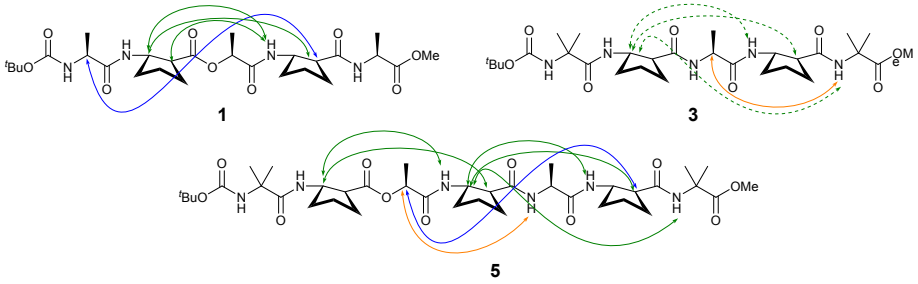
α/β-Depsipeptide **5** :

	Boc	Hα	Hβ	HN	OMe
N-term	1.45	-	-	-	-
Aib1	-	-	-	4.83	-
ACPC2	-	2.64	4.24	6.80	-
Lac3	-	4.86	-	-	-
ACPC4	-	2.59	4.38	7.80	-
Ala5	-	4.27	-	6.63	-
ACPC6	-	2.69	4.38	7.44	-
Aib7	-	-	-	7.77	-
C-term	-	-	-	-	3.70

Two-dimensional NMR Experiments

Two-dimensional NMR spectra, Total Correlation Spectroscopy (TOCSY) and Rotating frame Overhauser Effect Spectroscopy (ROESY), were recorded with Bruker DRX-500 (500 MHz) spectrometer equipped with cryogenic probe at 278 K in $CDCl_3$. The TOCSY experiments were performed with mixing time of 80 ms. The NOESY and ROESY experiments were performed with mixing time of 400 ms.

Table S1. Interproton distances measured from the crystal structures corresponding to medium-range NOEs.



Peptide	Observed NOE	NOE type	H-H distance (Å)
1	Hα(1) — Hα(4)	14/15-helix only	4.8
	Hβ(2) — NH(4)	Both helices	3.8
	Hβ(2) — Hα(4)	Both helices	4.7
	Hα(2) — NH(4)	Both helices	3.9
2	Hβ(2) — NH(4)*	Both helices	2.9
	Hβ(2) — Hα(4)*	Both helices	2.8
	Hβ(2) — Hβ(5)*	Both helices	2.9
	Hα(3) — NH(5)	11-helix only	4.8
5	Hβ(2) — NH(4)	Both helices	3.8
	Hβ(2) — Hα(4)	Both helices	4.4
	Hβ(4) — NH(6)	Both helices	3.4
	Hβ(4) — Hα(6)	Both helices	3.6
	Hβ(4) — Hβ(7)	Both helices	2.9
	Hα(3) — Hα(6)	14/15-helix only	2.9
	Hα(3) — NH(5)	11-helix only	5.0

* ambiguous NOEs

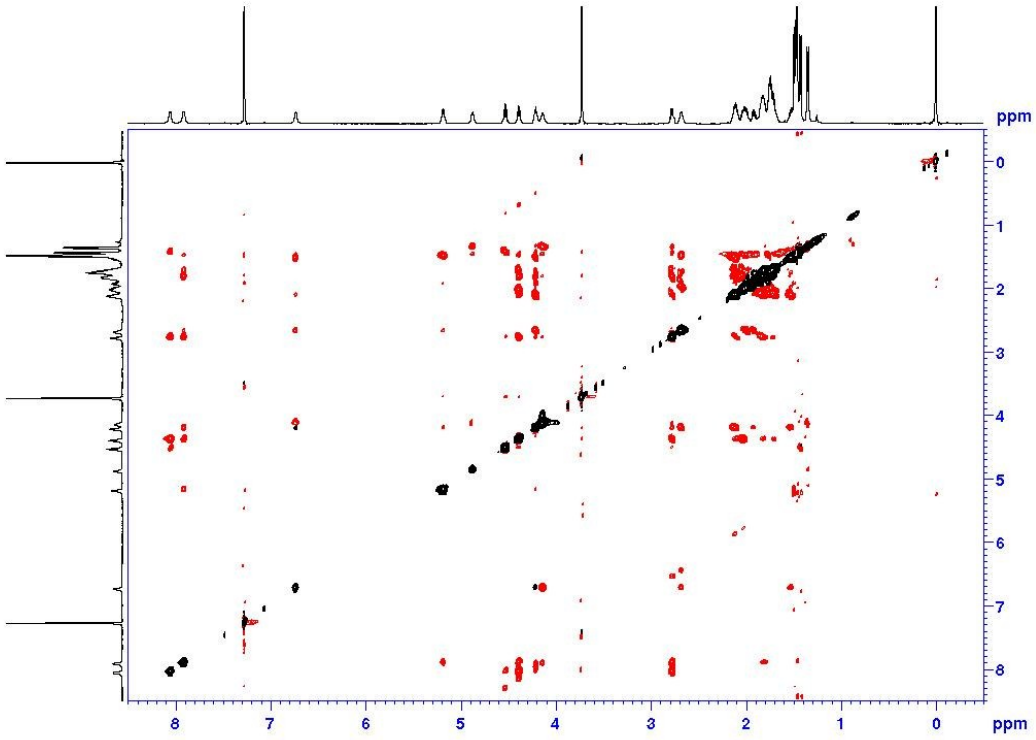


Figure S2. ROESY spectrum for **1** in $CDCl_3$

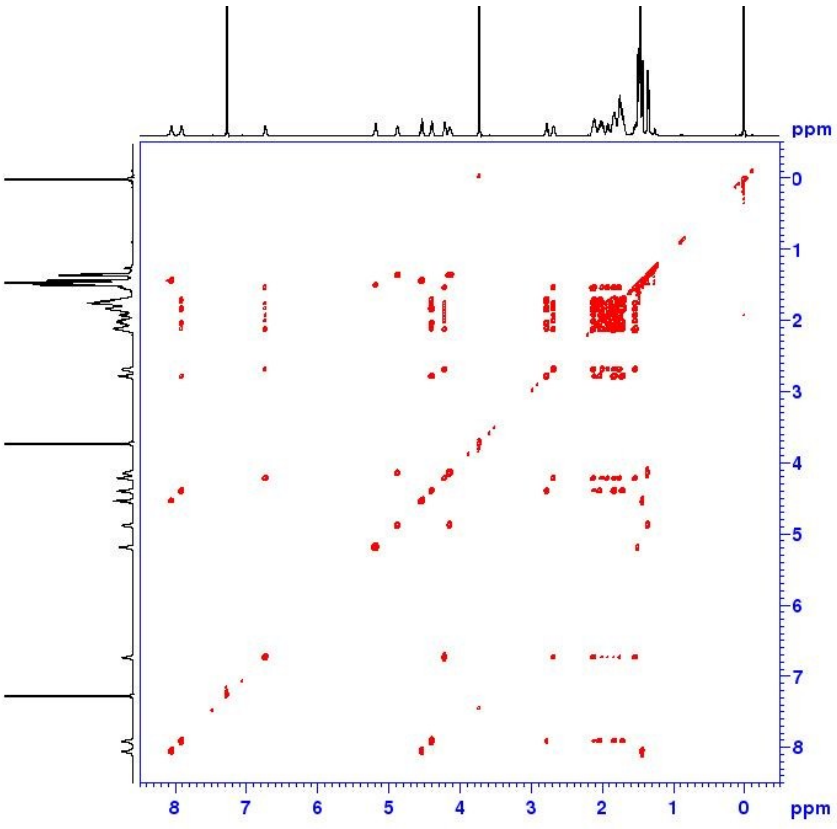


Figure S3. TOCSY spectrum for **1** in $CDCl_3$

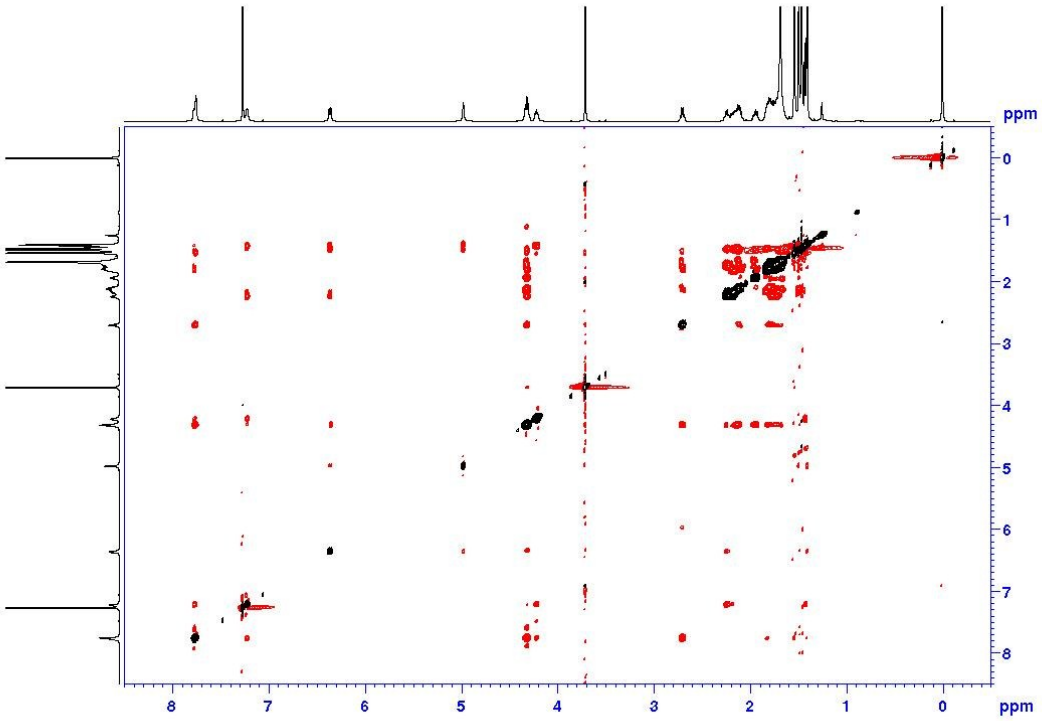


Figure S4. ROESY spectrum for **3** in $CDCl_3$

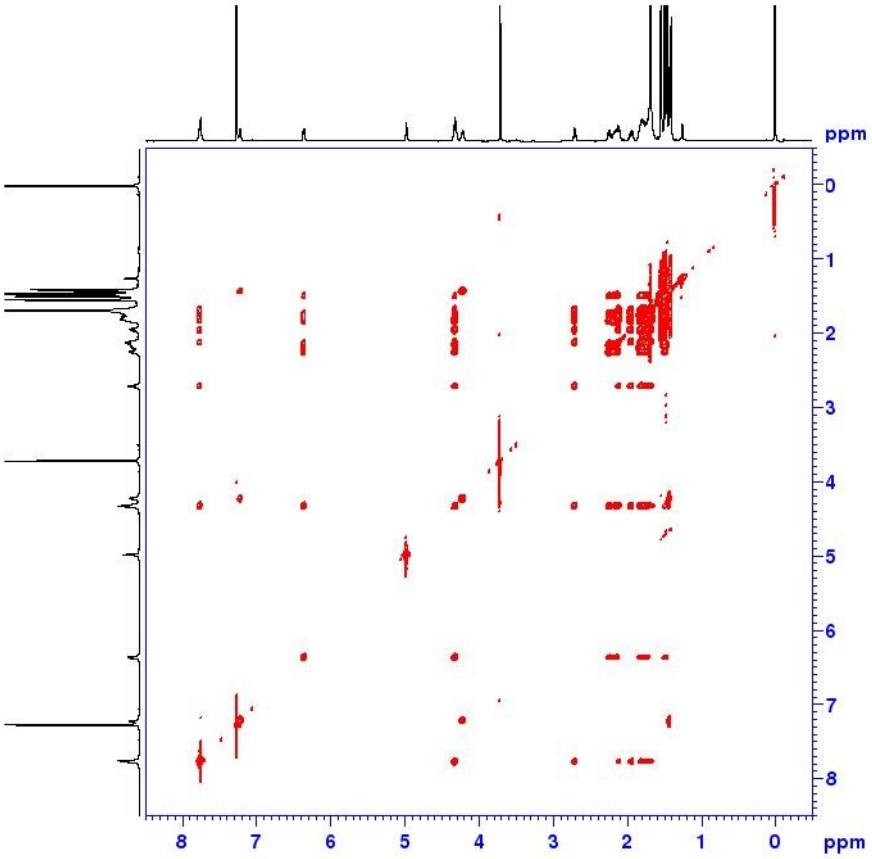


Figure S5. TOCSY spectrum for **3** in $CDCl_3$

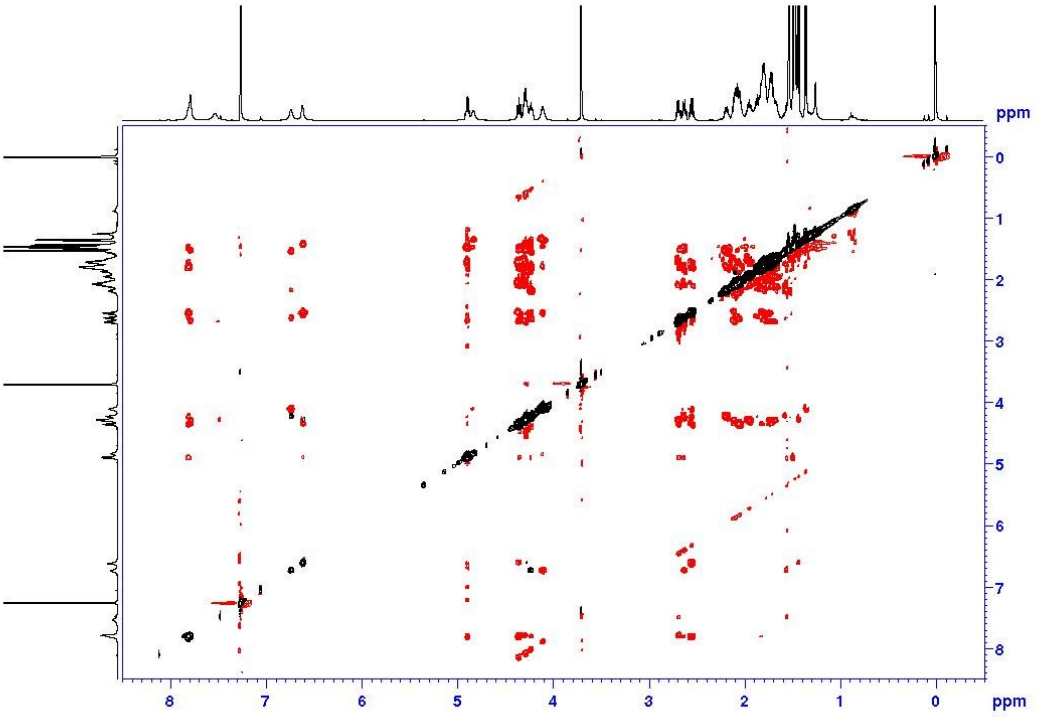


Figure S6. ROESY spectrum for heptapeptide **4** in $CDCl_3$

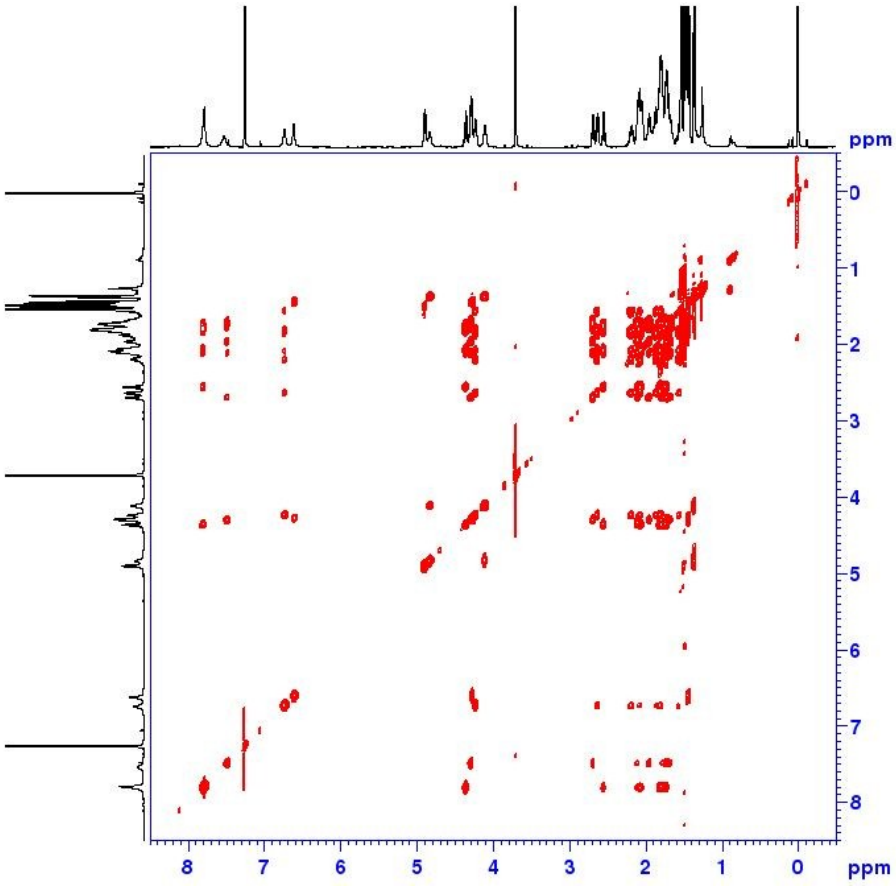


Figure S7. TOCSY spectrum for **4** in $CDCl_3$

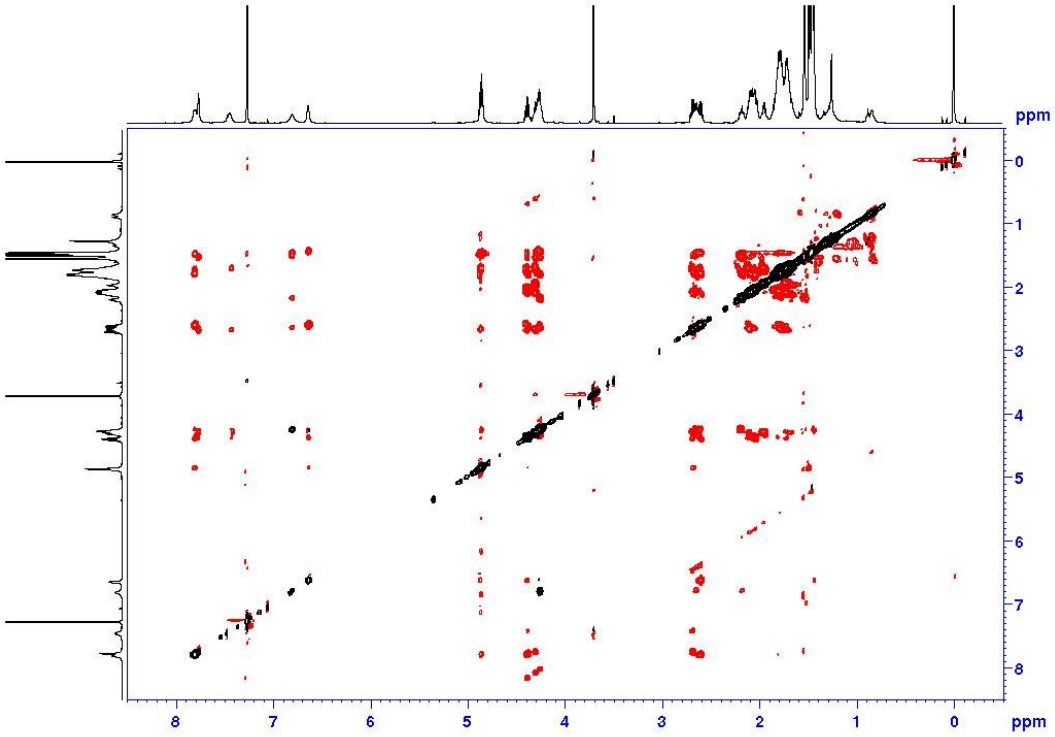


Figure S8. ROESY spectrum for heptapeptide **5** in $CDCl_3$

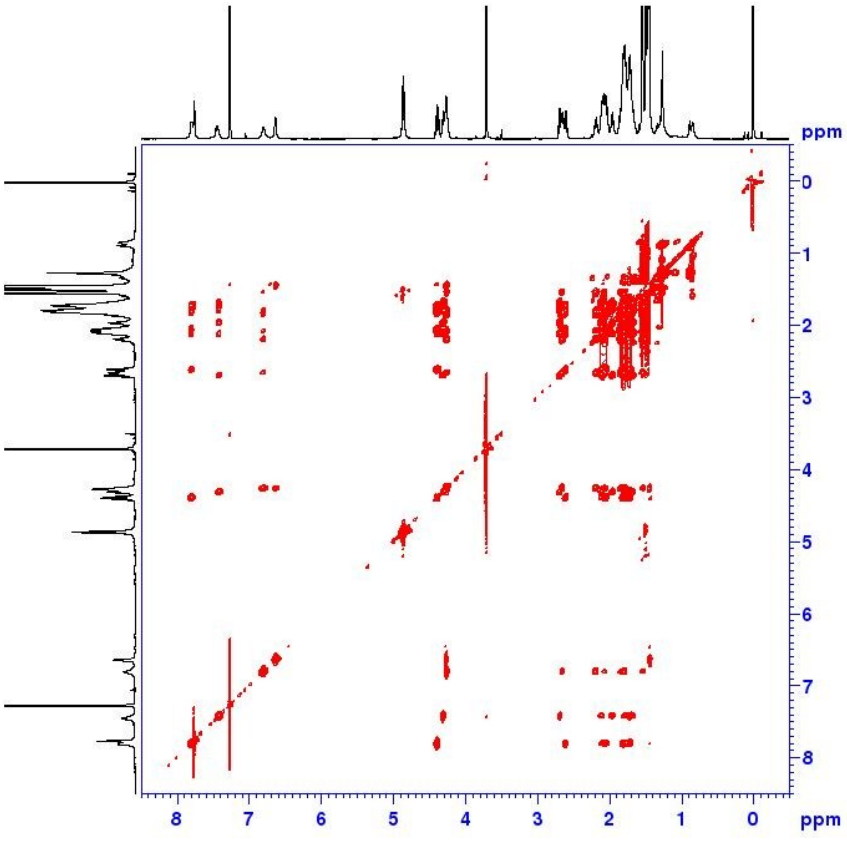


Figure S9. TOCSY spectrum for **5** in $CDCl_3$

Copies of H-NMR and C-NMR spectra

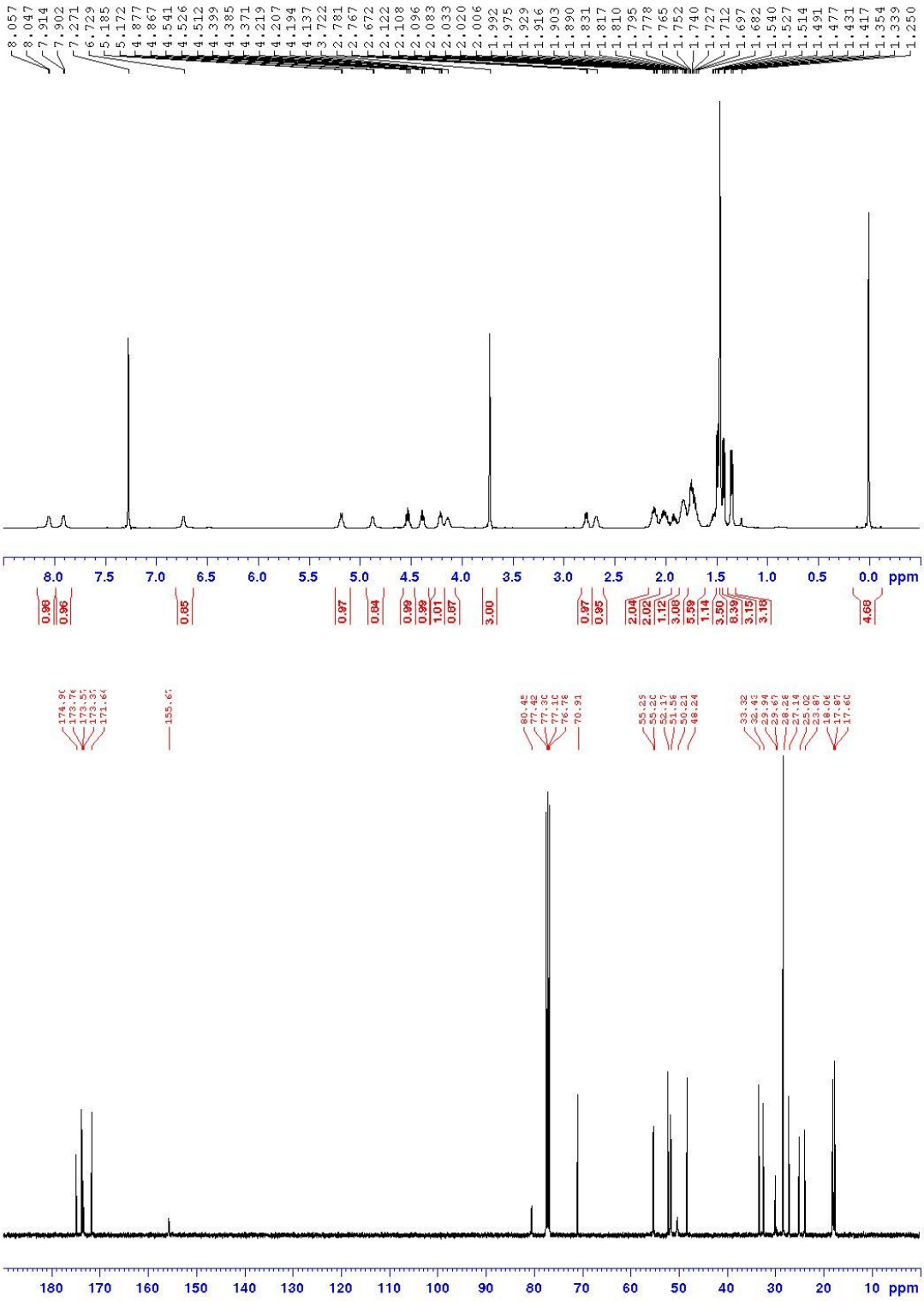


Figure S10. H-NMR and C-NMR spectra for **1** in CDCl3.

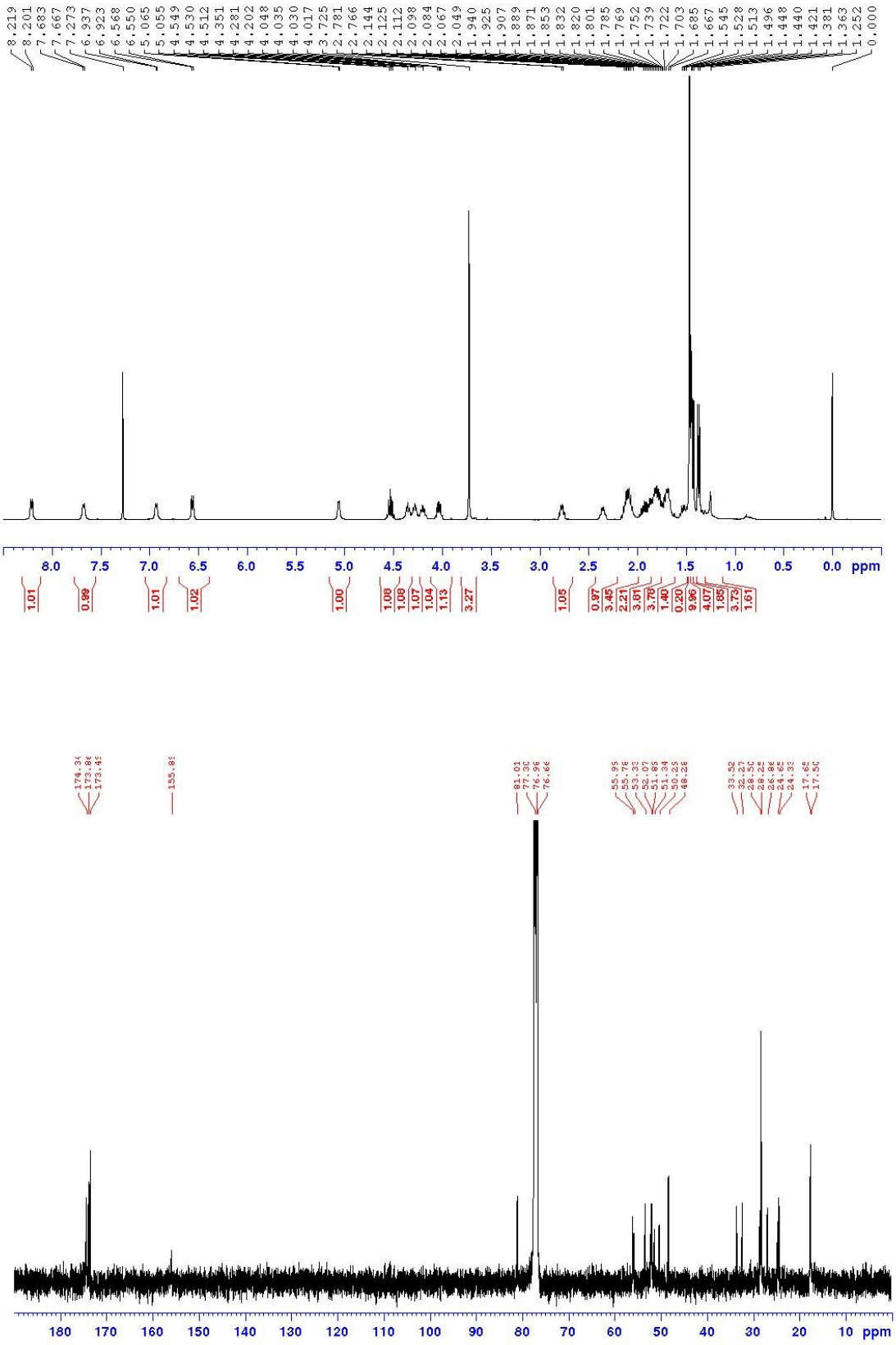


Figure S11. H-NMR and C-NMR spectra for **2** in CDCl3.

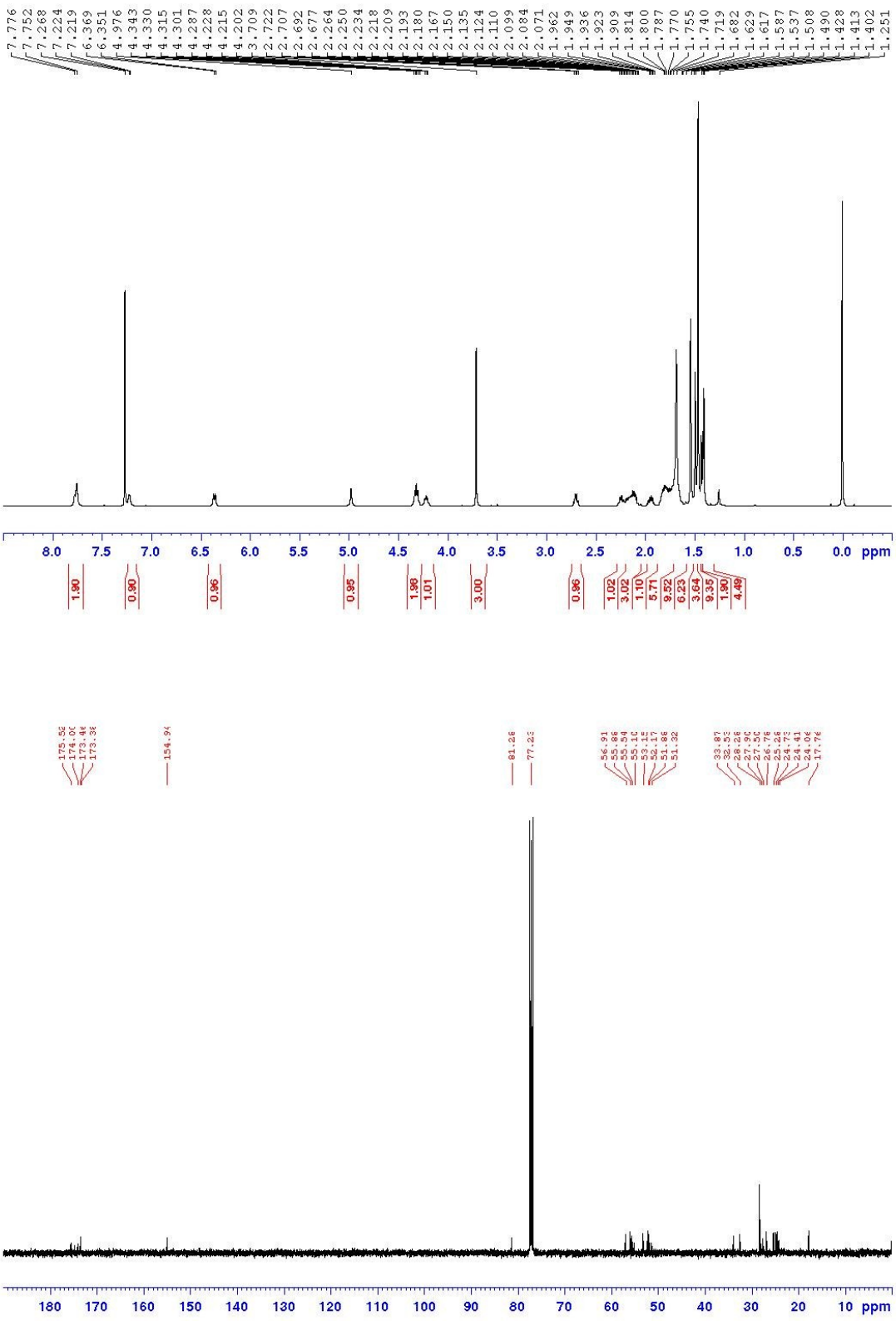


Figure S12. H-NMR and C-NMR spectra for **3** in CDCl3.

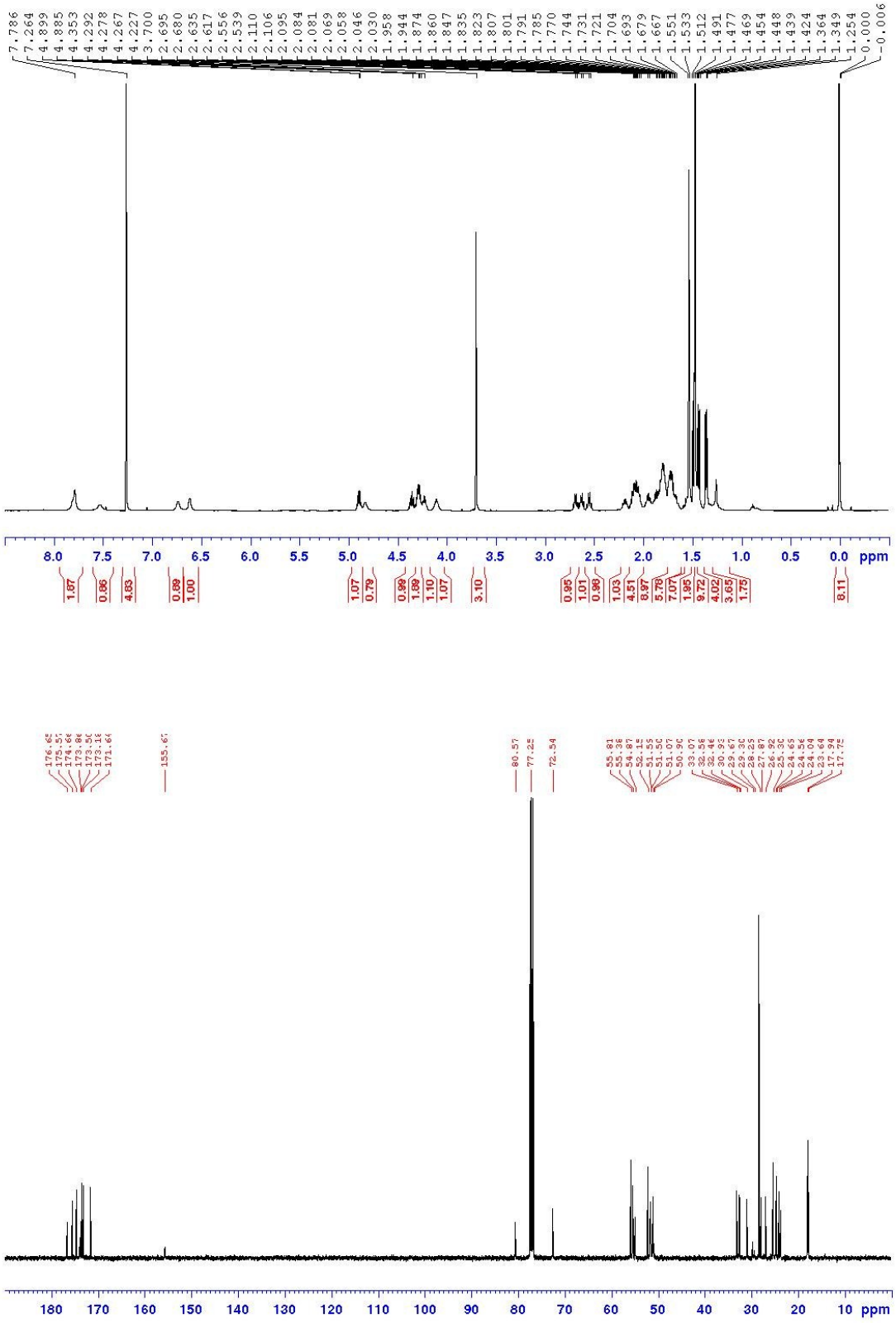


Figure S13. H-NMR and C-NMR spectra for **4** in CDCl3.

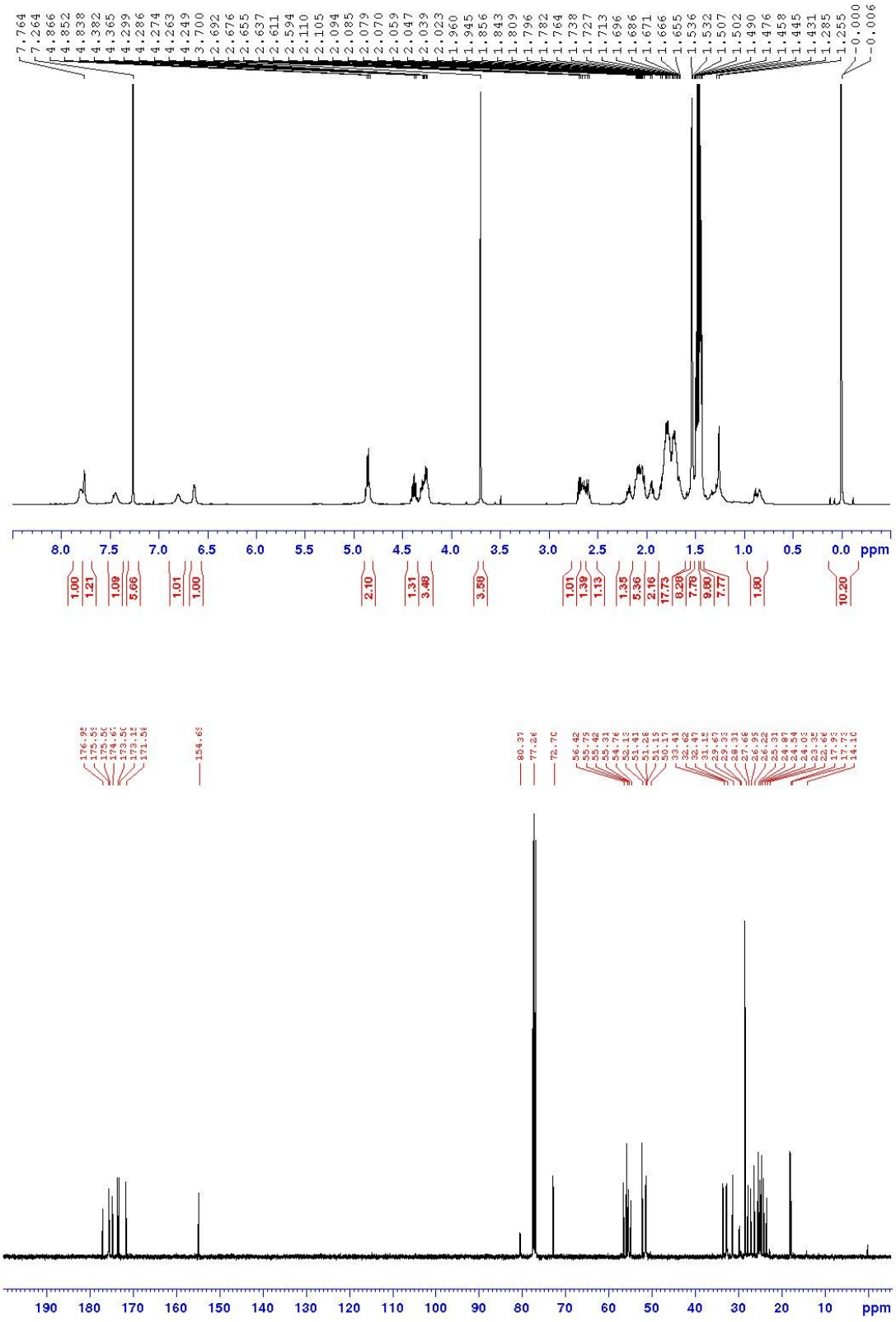


Figure S14. H-NMR and C-NMR spectra for **5** in CDCl3.

Copies of mass spectra

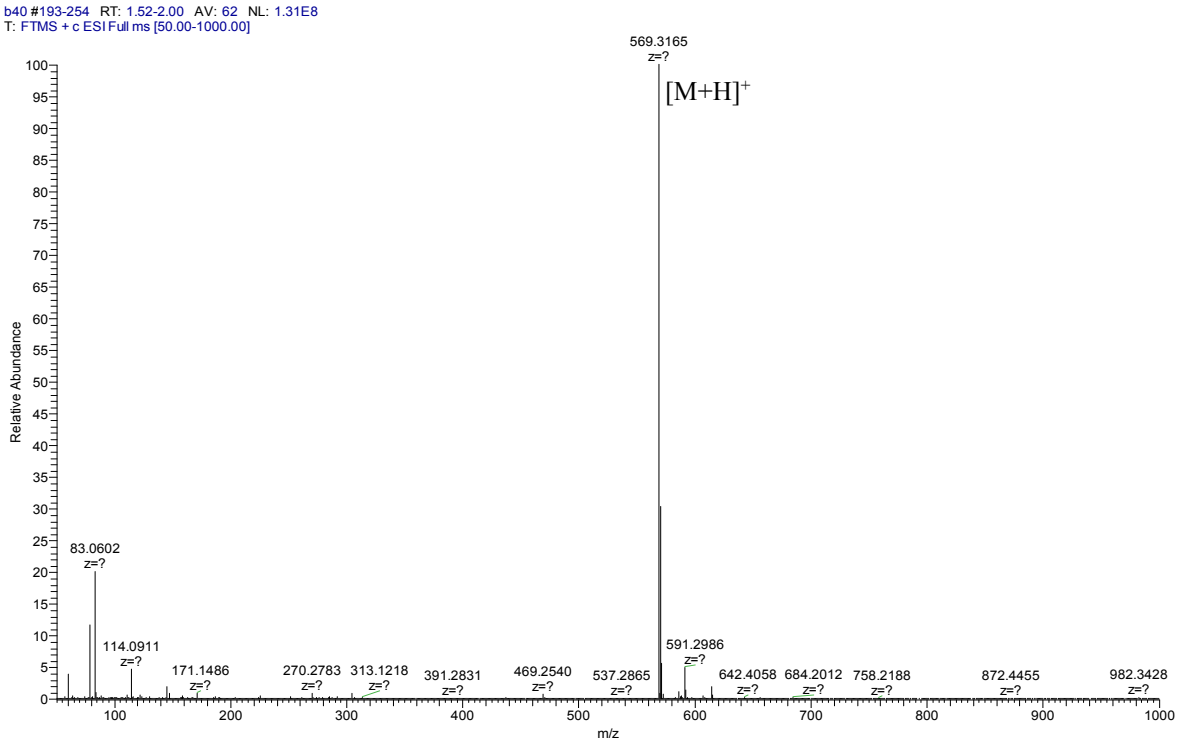


Figure S15. HRMS data for **1**.

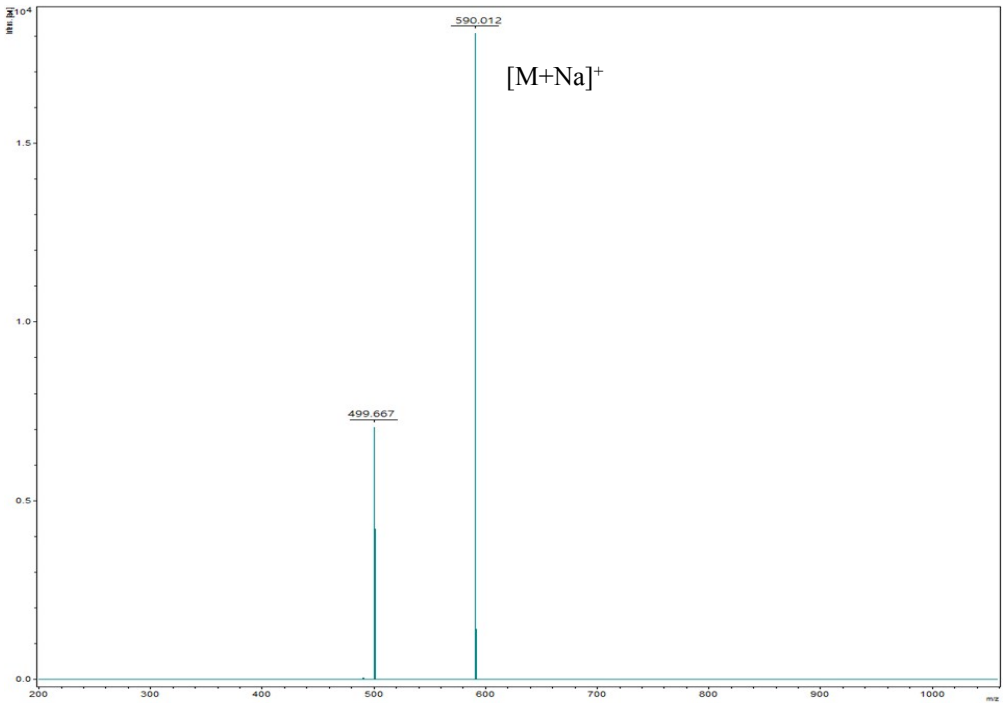


Figure S16. MALDI-TOF LRMS data for **2**

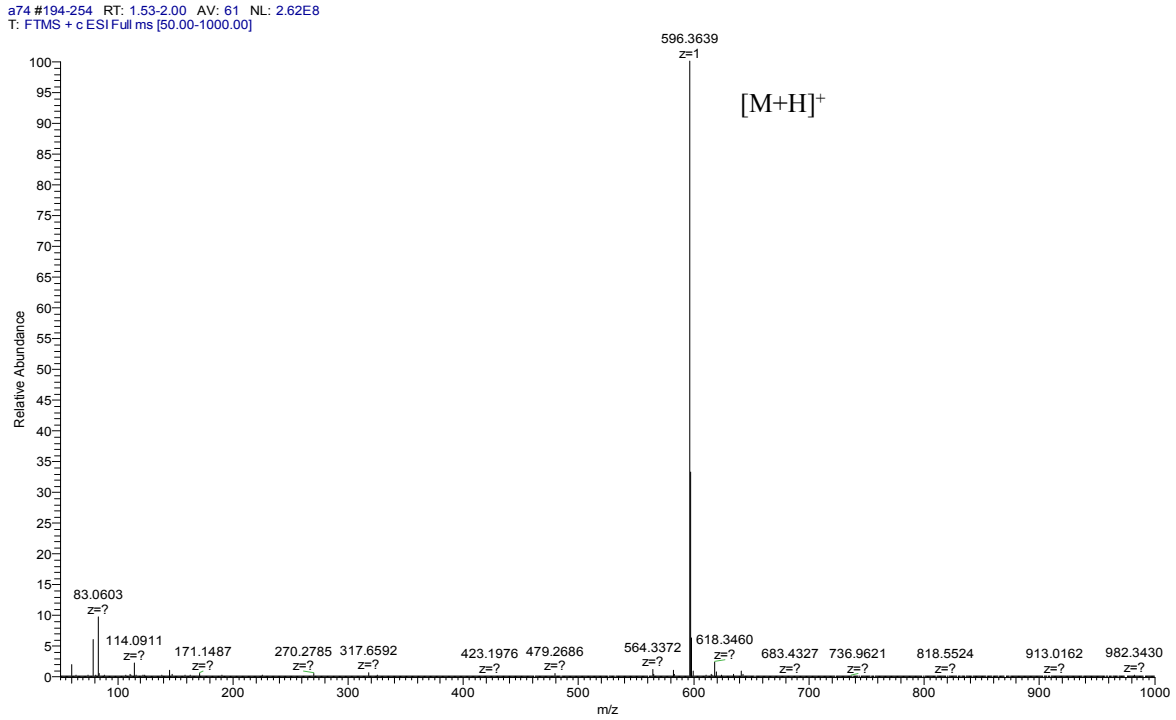


Figure S17. HRMS data for **3**

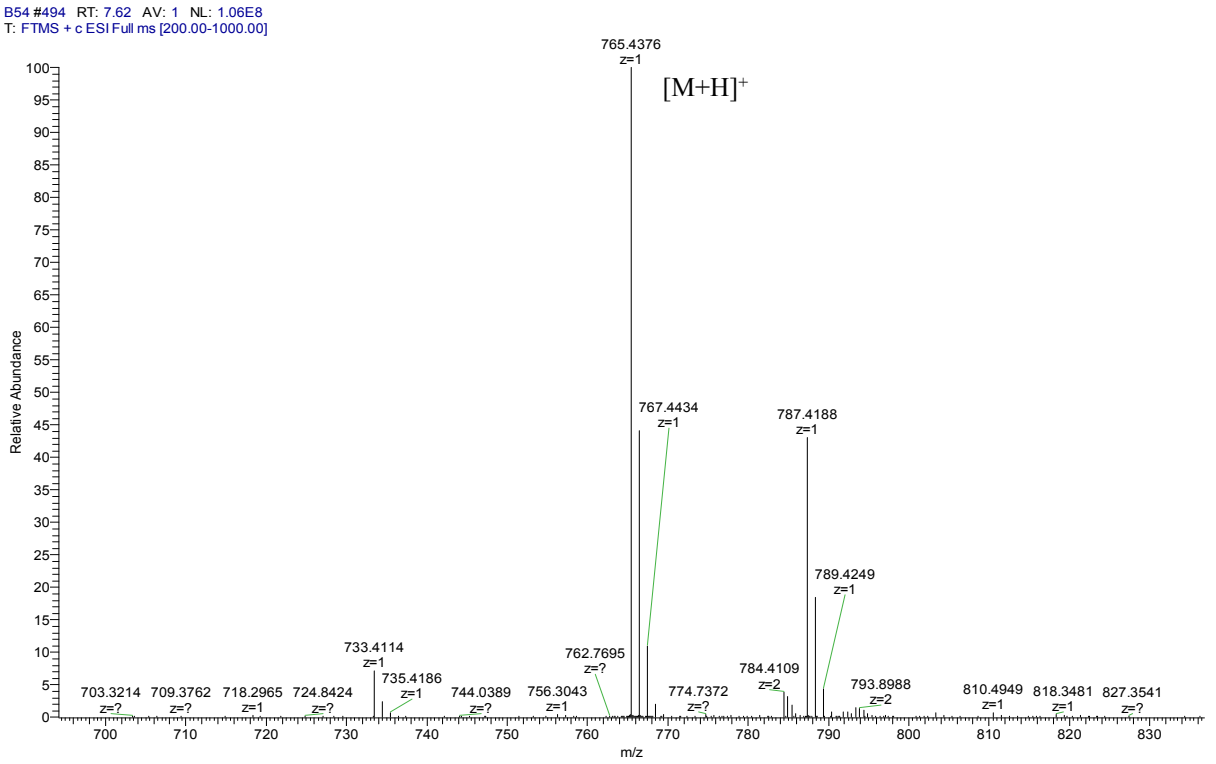


Figure S18. HRMS data for **4**

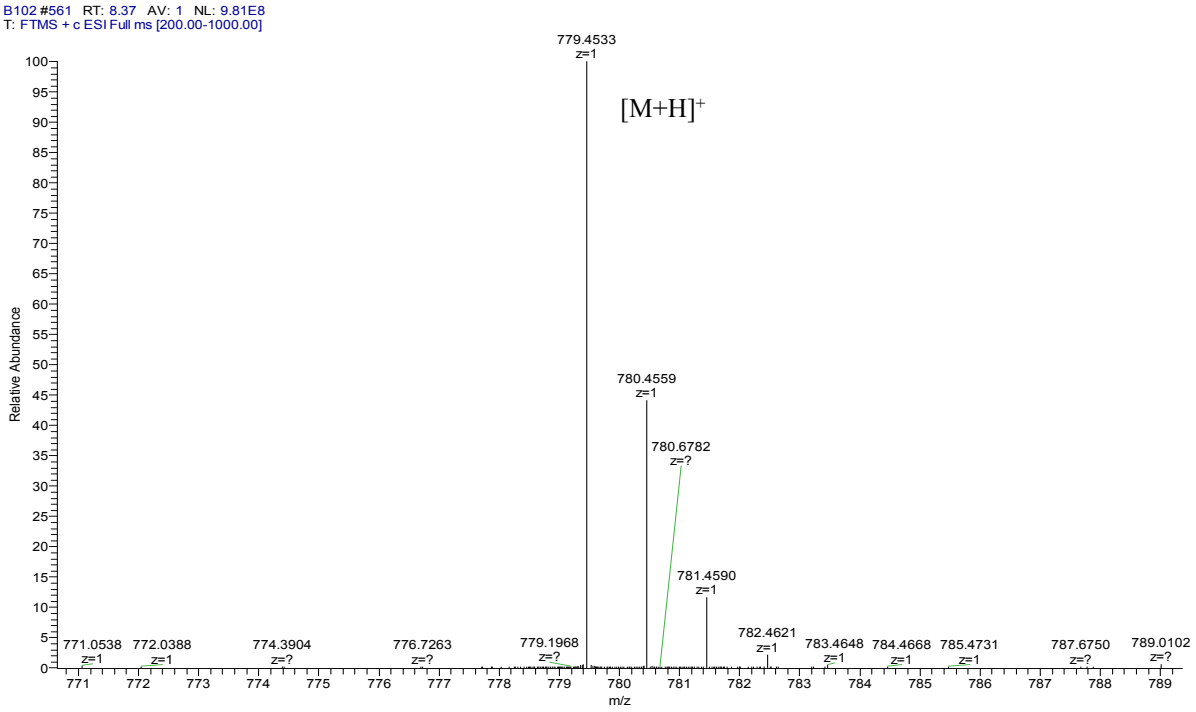


Figure S19. HRMS data for **5**

Crystallization and X-ray structural analysis

Crystallization

X-ray quality crystals of **1-3** were grown from chloroform/ether/n-pentane. The crystal structure data were deposited at the Cambridge Crystallographic Data Centre. CCDC numbers: **1** (964598), **3** (964594), **5** (1448856).

• **Boc-Ala-ACPC-Lac-ACPC-Ala-OMe (1)**

Data Collection

A colorless crystal with approximate dimensions 0.08 × 0.08 × 0.05 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 150 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 0.5º in 10-15º 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 9992 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 25847 data were harvested by collecting 7 sets of frames with 1º scans in ω and φ with an exposure time 10-20 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. [1]

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 [2-3].

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 369 parameters against 5656 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0351 and 0.0857, respectively. The final difference Fourier map was featureless.

Summary

Crystal Data for $C_{27}H_{44}N_4O_9$ (M =568.66): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 10.4185(4) Å, b = 15.6536(6) Å, c = 18.1560(8) Å, V = 2961.0(2) Å^3, Z = 4, T = 150.0 K, μ(CuKα) = 0.795 mm^{-1}, *Dcalc* = 1.276 g/mm^3, 25847 reflections measured (7.45 ≤ 2Θ ≤ 144.09), 5656 unique (R_{int} = 0.0410) which were used in all calculations. The final R_1 was 0.0351 (I > 2σ(I)) and wR_2 was 0.0857 (all data).

Table S2. Crystal data and structure refinement for **1**

Empirical formula	$C_{27}H_{44}N_4O_9$
Formula weight	568.66
Temperature/K	150.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.4185(4)
b/Å	15.6536(6)
c/Å	18.1560(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2961.0(2)
Z	4
ρ_{calc}mg/mm^3	1.276
m/mm^{-1}	0.795
F(000)	1224.0
Crystal size/mm^3	0.08 × 0.08 × 0.05
2Θ range for data collection	7.456 to 144.092°
Index ranges	-12 ≤ h ≤ 12, -18 ≤ k ≤ 18, -21 ≤ l ≤ 22
Reflections collected	25847
Independent reflections	5656[R(int) = 0.0410]
Data/restraints/parameters	5656/0/369
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0351, wR_2 = 0.0828
Final R indexes [all data]	R_1 = 0.0410, wR_2 = 0.0857
Largest diff. peak/hole / e Å^{-3}	0.20/-0.22
Flack parameter	-0.02(7)

• **Boc-Aib-ACPC-Ala-ACPC-Aib-OMe (3)**

Data Collection

A colorless crystal with approximate dimensions 0.1 × 0.1 × 0.07 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was at 304 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 0.5º in a 6º 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 9536 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 44095 data were harvested by collecting 3 sets of frames with 0.5º scans in ω and φ with an exposure time 5 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. [1]

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 [2-3].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The cyclopentanes were found to be disordered, and were modeled in two different orientations. 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 444 parameters against 7676 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0638 and 0.1974, respectively. The final difference Fourier map was featureless.

Summary

Crystal Data for $C_{30}H_{50}Cl_3N_5O_8$ (*M* =715.10): monoclinic, space group $P2_1$ (no. 4), *a* = 9.2919(4) Å, *b* = 11.0410(5) Å, *c* = 19.2470(10) Å, β = 100.1200(16)°, *V* = 1943.87(16) $Å^3$, *Z* = 2, *T* = 304.0 K, μ(MoKα) = 0.285 mm^{-1}, *Dcalc* = 1.222 g/mm^3, 44095 reflections measured ($4.27 \leq 2\Theta \leq 52.01$), 7676 unique ($R_{int}$ = 0.0588, R_{sigma} = 0.0412) which were used in all calculations. The final R_1 was 0.0638 ($I > 2\sigma(I)$) and wR_2 was 0.1975 (all data).

Table S3. Crystal data and structure refinement for **3**

Empirical formula	$C_{30}H_{50}Cl_3N_5O_8$
Formula weight	715.10
Temperature/K	304.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.2919(4)
b/Å	11.0410(5)
c/Å	19.2470(10)
α/°	90
β/°	100.1200(16)
γ/°	90
Volume/Å^3	1943.87(16)
Z	2
ρ_{calc}mg/mm^3	1.222
m/mm^{-1}	0.285
F(000)	760.0
Crystal size/mm^3	0.1 × 0.1 × 0.07
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.27 to 52.096°
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, -23 ≤ l ≤ 23
Reflections collected	44095
Independent reflections	7676 [R_{int} = 0.0588, R_{sigma} = 0.0412]
Data/restraints/parameters	7676/122/444
Goodness-of-fit on F^2	1.019
Final R indexes [I>=2σ (I)]	R_1 = 0.0638, wR_2 = 0.1690
Final R indexes [all data]	R_1 = 0.1096, wR_2 = 0.1975
Largest diff. peak/hole / e Å^{-3}	0.30/-0.42
Flack parameter	0.07(3)

• **Boc-Aib-ACPC-Lac-ACPC-Ala-ACPC-Aib-OMe (5)**

Data Collection

A colorless crystal with approximate dimensions 0.12 × 0.08 × 0.03 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was at 250 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 0.5º in a 6º range about ω with the exposure time of 20 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 2787 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 24592 data were harvested by collecting 2 sets of frames with 0.5º 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 [1].

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 [2-3].

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 Aib-ACPC-Lac-ACPC-Ala-ACPC-Aib was found to be highly disordered, and so the SQUEEZE procedure of the PLATON program was used [4].

The final least-squares refinement of 566 parameters against 9623 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0696 and 0.1673 respectively. The final difference Fourier map was featureless.

Summary

Crystal Data for $C_{38}H_{62}N_6O_{11}$ (M =778.93): monoclinic, space group $P2_1$ (no. 4), a = 10.7226(16) Å, b = 10.6558(17) Å, c = 21.682(3) Å, β = 91.429(5)°, V = 2476.6(7) $Å^3$, Z = 2, T = 250.1 K, μ(MoKα) = 0.077 mm^{-1}, *Dcalc* = 1.045 g/mm^3, 24592 reflections measured (1.87 ≤ 2Θ ≤ 52.09), 9623 unique (R_{int} = 0.1605, R_{sigma} = 0.1975) which were used in all calculations. The final R_1 was 0.0696 (I > 2σ(I)) and wR_2 was 0.1673 (all data).

Table S4. Crystal data and structure refinement for **5**

Empirical formula	$C_{38}H_{62}N_6O_{11}$
Formula weight	778.93
Temperature/K	250.1
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.7226(16)
b/Å	10.6558(17)
c/Å	21.682(3)
α/°	90
β/°	91.429(5)
γ/°	90
Volume/Å^3	2476.6(7)
Z	2
ρ_{calc}mg/mm^3	1.045
m/mm^{-1}	0.077
F(000)	840.0
Crystal size/mm^3	0.12 × 0.08 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	1.878 to 52.094°
Index ranges	$-12 \leq h \leq 13$, $-13 \leq k \leq 13$, $-26 \leq l \leq 26$
Reflections collected	24592
Independent reflections	9623 [R_{int} = 0.1605, R_{sigma} = 0.1975]
Data/restraints/parameters	9623/478/566
Goodness-of-fit on F^2	0.792
Final R indexes [I>=2σ (I)]	R_1 = 0.0696, wR_2 = 0.1443
Final R indexes [all data]	R_1 = 0.1625, wR_2 = 0.1673
Largest diff. peak/hole / e Å^{-3}	0.31/-0.20
Flack parameter	0.4(10)

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[S2] Bruker-AXS. (2007-2013) APEX2 (Ver. 2013.2-0), SADABS (2012-1), and SAINT+ (Ver. 8.30C) Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

[S3] G. M. Sheldrick, (2008) SHELXL. *Acta Cryst.* **A64**, 112-122.

[S4] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, "OLEX2: a complete structure solution, refinement and analysis program". *J. Appl. Cryst.* (2009) **42**, *339-341*.

[S5] P. v.d. Sluis and A.L. Spek, *Acta Crystallogr., C*, 1990, **A46**, 194