Electronic Supplementary Information

Conformational studies of Ant-Pro motif-incorporated cyclic peptides: Gramicidin S and Avellanin

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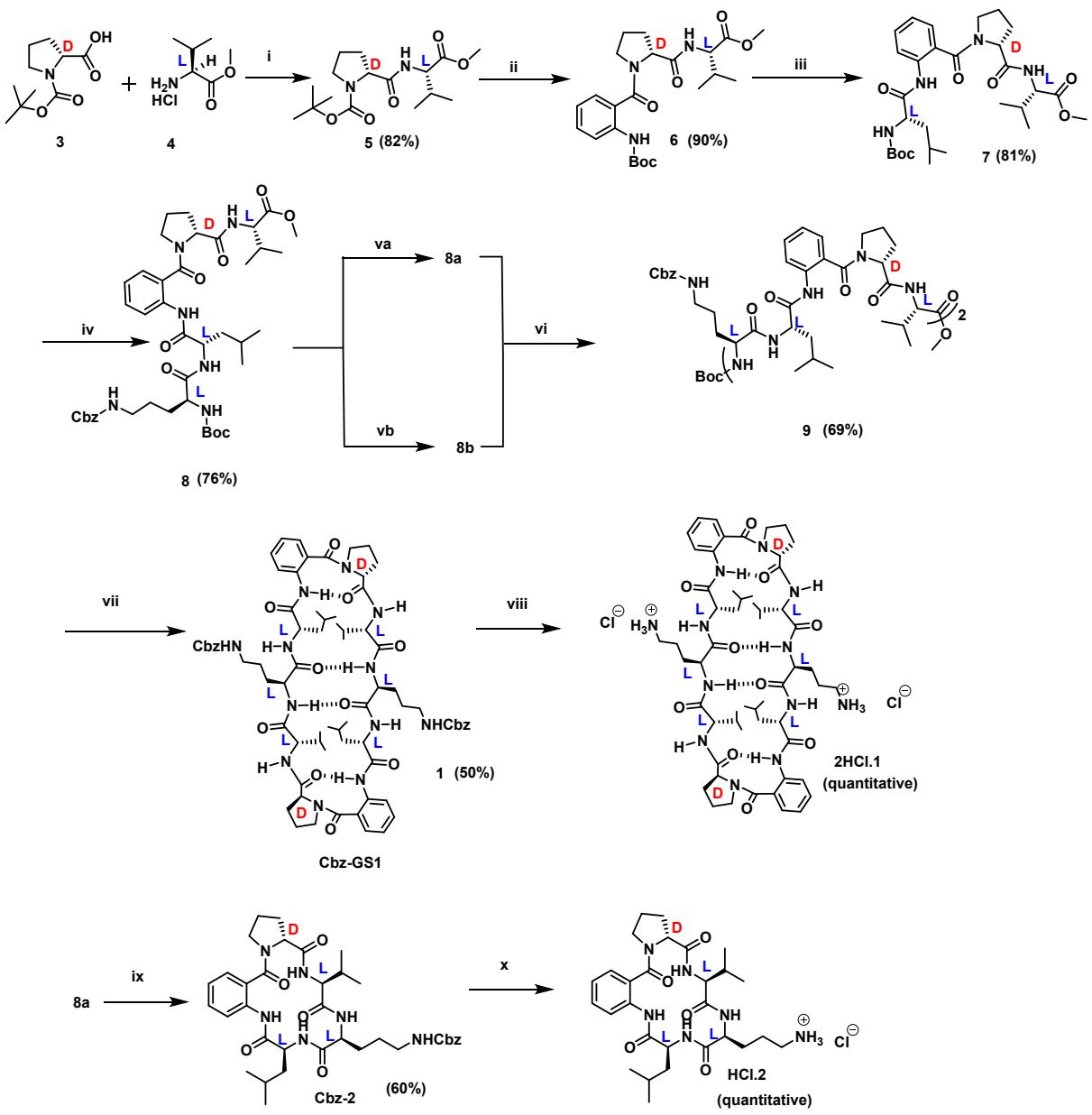
General Methods

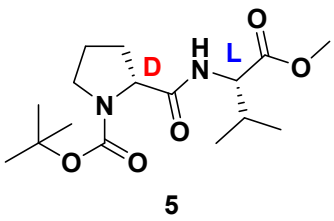
Unless otherwise stated, all the chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical Thin Layer Chromatography was done on precoated silica gel plates (Kieselgel $60F_{254}$, Merck). Column chromatographic purifications were done with 230-400 and 100-200 mesh silica gel. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on AV 400 MHz, AV 500 MHz and AV 700 MHz Bruker NMR spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), broad singlet (bs), and multiplet (m). The variable temperature experiment was done in DMSO-d_6. Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded in $CHCl_3$ using Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi Melting Point B-540. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Circular dichroism (CD) was performed using a cell of 2 mm path length. Spectra were recorded as an accumulation of 3 scans using a scan speed of 100nm/min, with resolution of 1.0 nm, band-width 1.0 nm and a response of 1 sec. Spectra were smoothened (5) and plotted using Origin Pro 6.0 software. Instrument used JASCO 2000 CD spectrometer.

Synthetic Scheme 1:



Reagents and conditions: (i) EDC.HCl, DIEA, HOBt, DCM, RT, 8 h; (ii) a) TFA:DCM; b)Boc-Ant-OH, HBTU, DIEA, ACN, RT, 6 h; (iii) a) TFA:DCM; b) Boc-Leu-OH, EDC.HCl, HOBt, DCM, RT, 8 h; (iv) a) TFA:DCM; b) Boc-(Cbz)-Orn-OH, HBTU, DIEA, ACN, RT, 12 h; (v) a) LiOH:H_2O; b) TFA:DCM; (vi) HBTU, DIEA, ACN, RT, 12 h; (vii) a) LiOH : H_2O; b) TFA:DCM; c) HBTU, DCM, RT, 12 h; (viii) H_2, 10 mol% Pd/C, 0.02 M HCl in MeOH, 12 h; (ix) a)TFA:DCM; b) HBTU, DIEA, DCM, RT, 12 h, x) H_2, 10 mol% Pd/C, 0.01 M HCl in MeOH, 12 h.

Compound 5 (Boc-^{D}Pro^{L}Val-OMe): To a solution of HCl.^{L}Val-OMe **4** (6.523 g, 34.88 mmol, 1.5 equiv.) in DCM (60 mL) at 0°C, DIEA (12.12 mL, 69.75 mmol, 3 equiv.) was added slowly and the reaction mixture stirred for 5 minutes. Later Boc-^{D}Pro-OH **3** (5g, 23.25 mmol,, 1 equiv.), EDC.HCl (8.88 g, 46.5 mmol, 2 equiv.) & HOBt (catalytic amount) were added sequentially and the reaction mixture was stirred, at room temperature. After 8 h, the reaction mixture was diluted with DCM and washed sequentially with solutions of $KHSO_4$, $NaHCO_3$ and brine. The organic layer dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography (eluent: 20% AcOEt/Pet. ether, R_f: 0.3) to afford **5** (6.25 g, 82%) as a white fluffy solid material. Mp: 102-104 °C; $[\alpha]^{25.97}_{D}$: 105.39° (*c* = 0.122, $CHCl_3$; IR ($CHCl_3$) *v* (cm^{-1}): 3294, 2967, 2358, 1741, 1691, 1658, 1442, 1209, 766; ^{1}H NMR (400MHz, $CDCl_3$) δ: 6.51 (bs, 1H), 4.54 (bs, 1H), 4.34 (bs, 1H), 3.72 (s, 3H), 3.60 (m, 1H), 3.44-3.27 (m, 1H), 3.49 (bs, 2H), 2.31 (bs, 1H), 2.26-2.11 (m, 2H), 1.89 (t, *J* = 6.6 Hz, 2H), 1.48 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 155.5, 80.5, 61.3, 60.0, 56.9, 52.1, 47.1, 31.2, 28.3, 24.3, 23.6, 19.0, 17.5; HRMS (ESI) $C_{16}H_{30}N_2O_5$ calculated $[M+H]^+$: 329.1998, found 329.2061, $C_{16}H_{28}N_2NaO_5$ calculated $[M+Na]^+$ 351.1896, found 351.1880.



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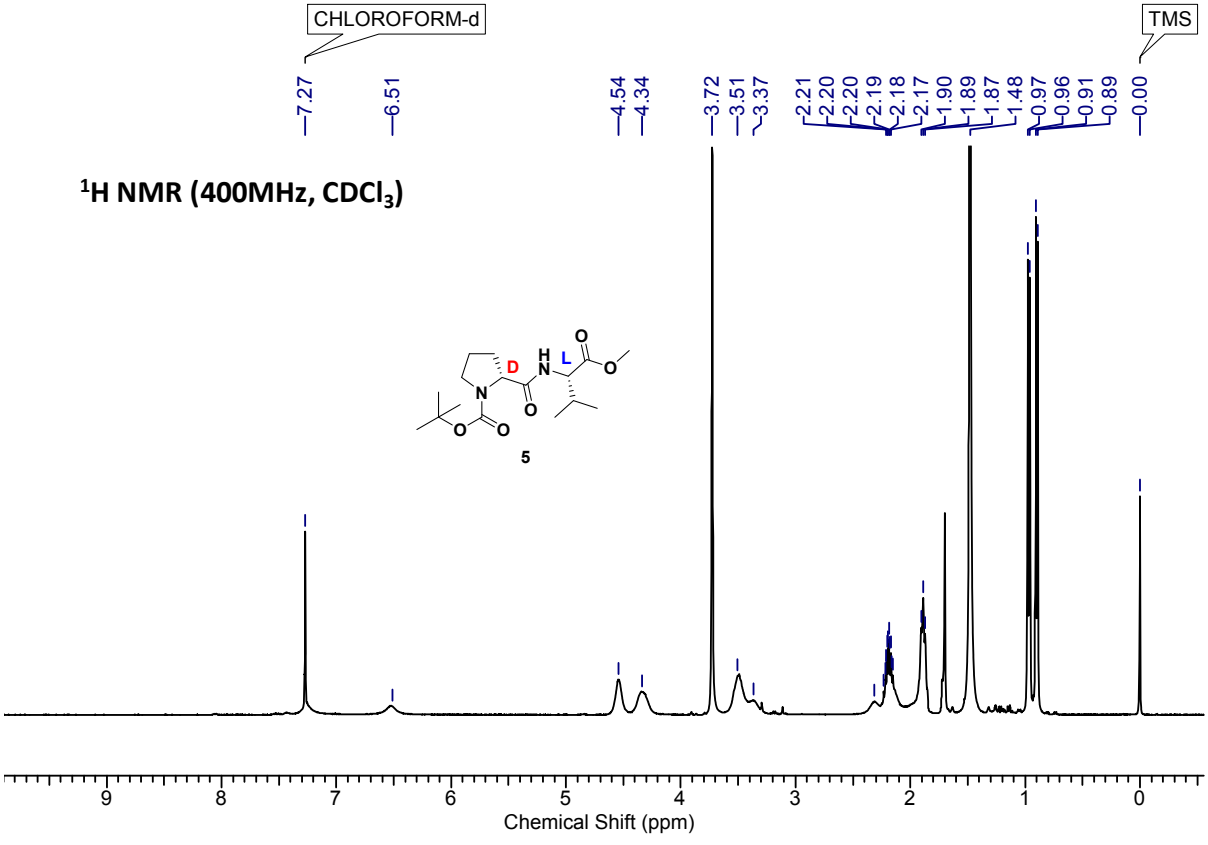
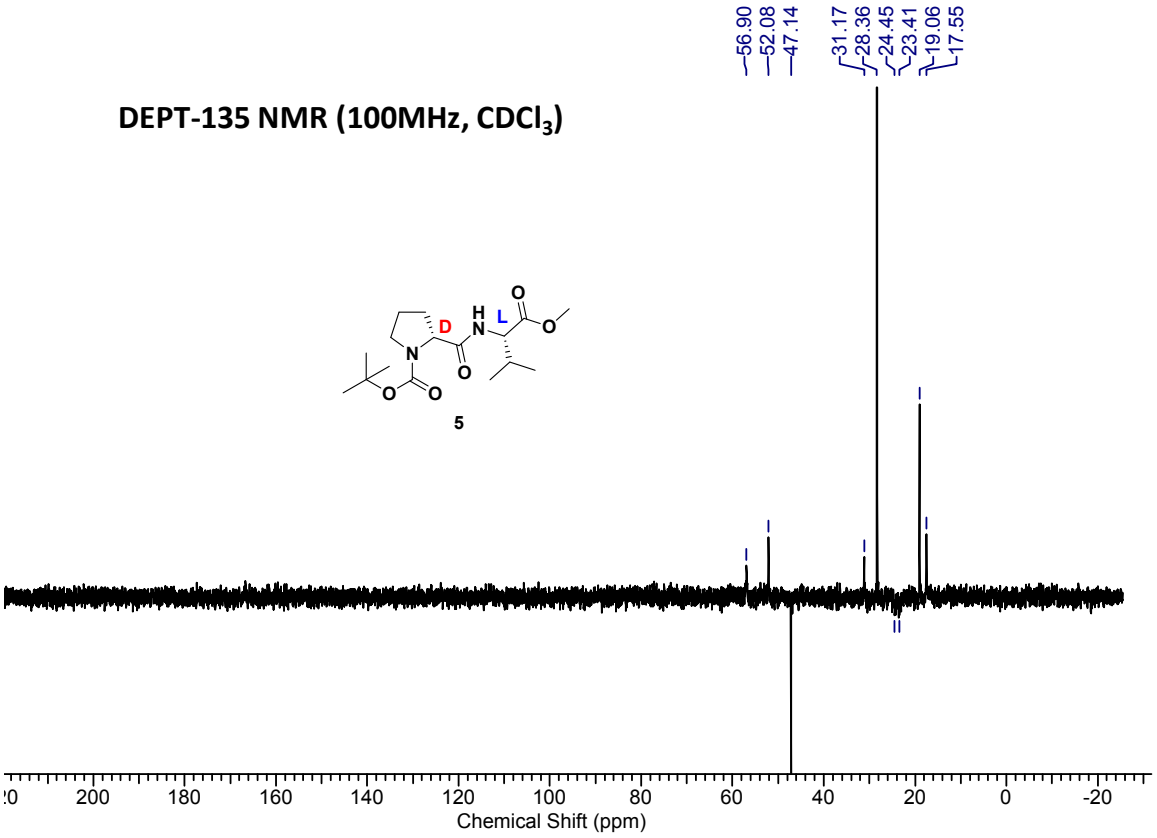


DEPT-135 NMR (100MHz, $CDCl_3$)



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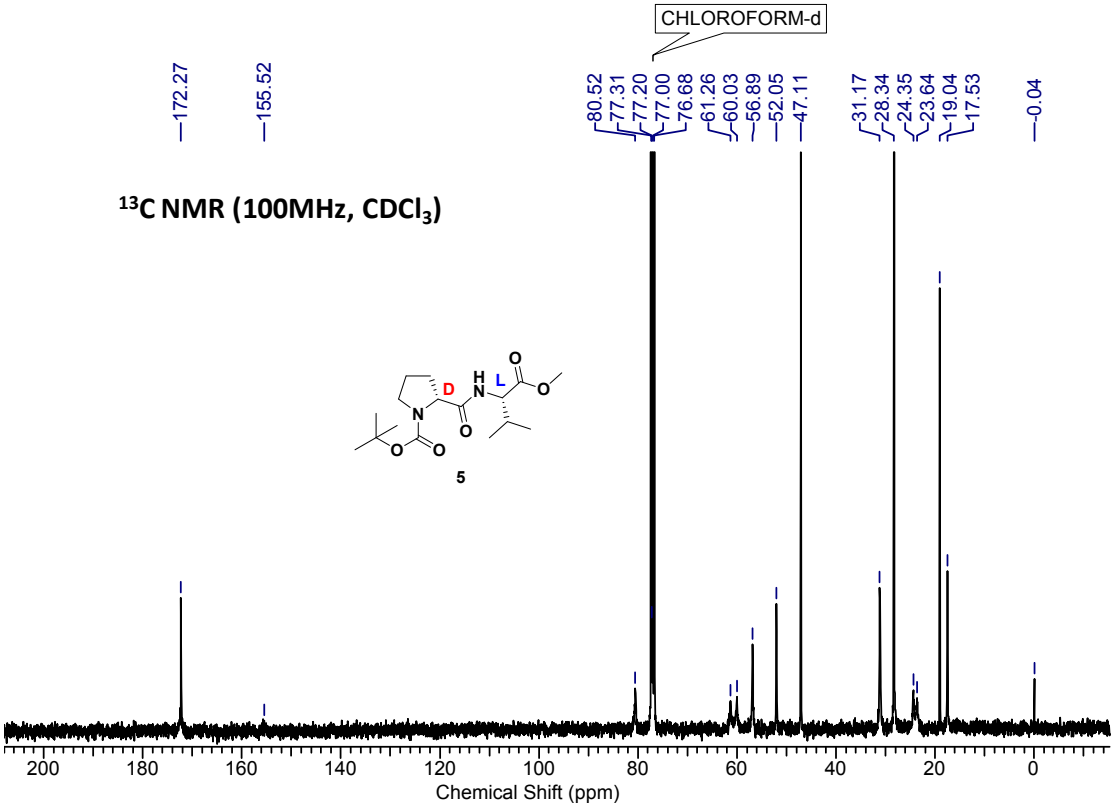
^{13}C NMR (100MHz, $CDCl_3$)



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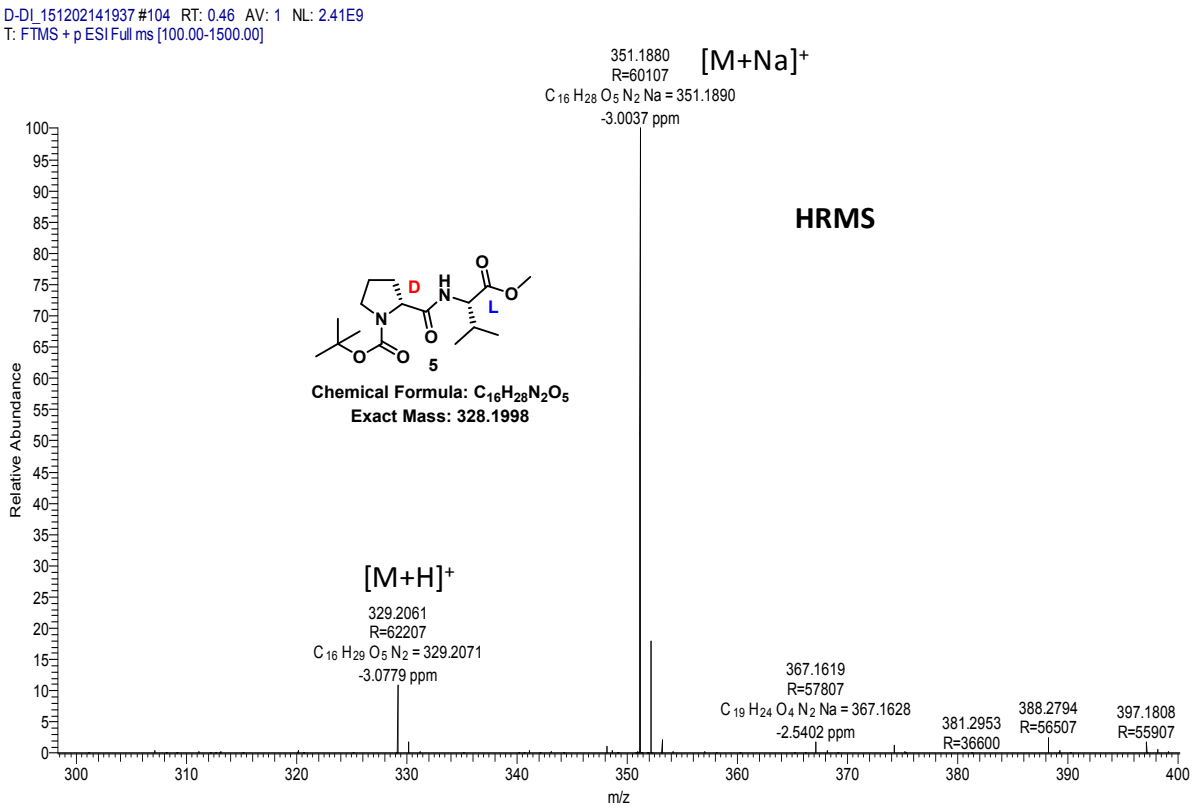
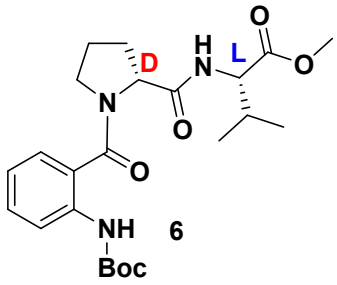
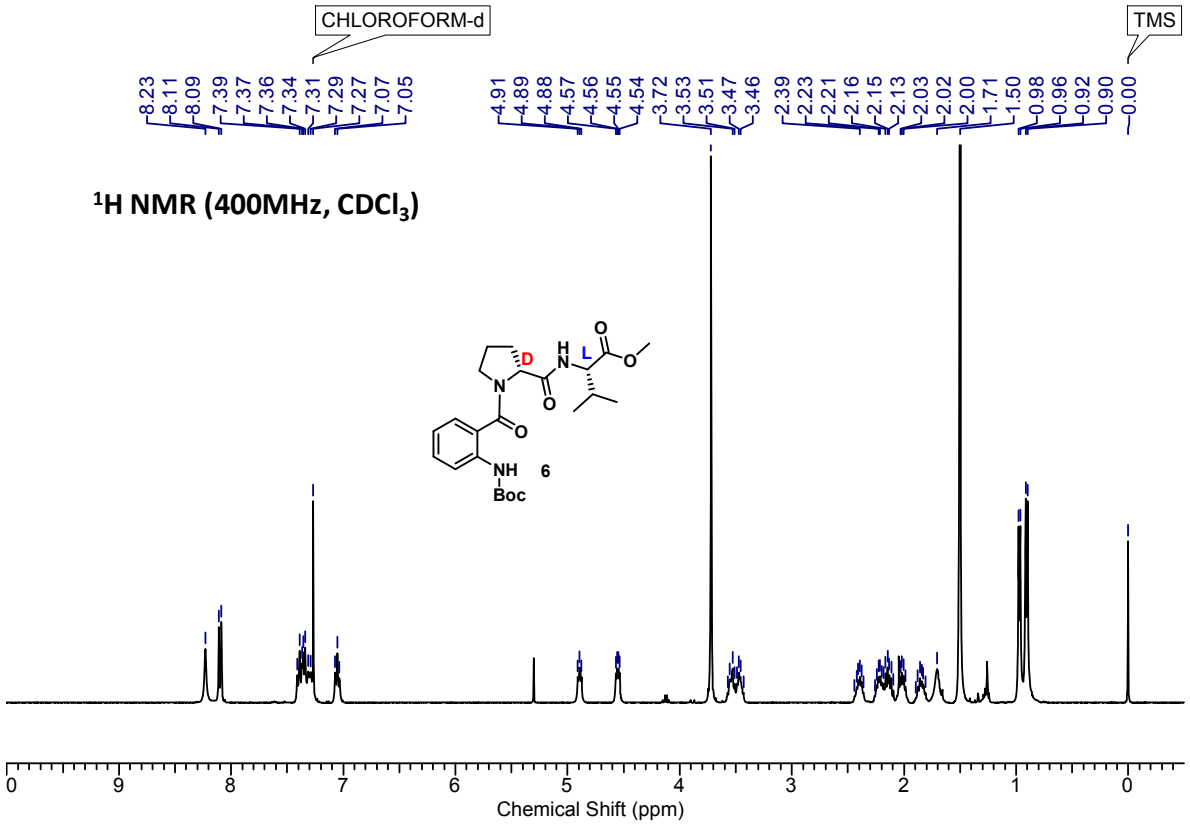


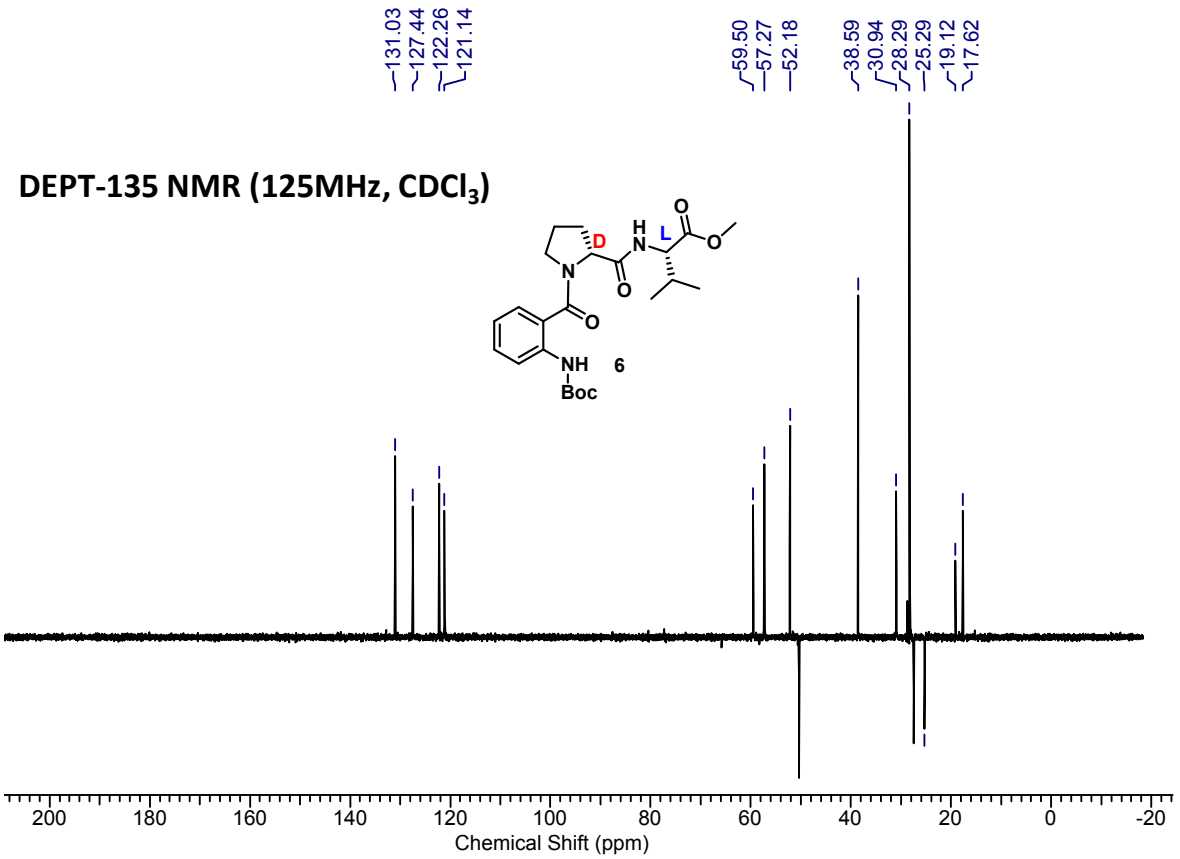
General procedure for Boc-deprotection: Boc protected compound was stirred in TFA:DCM (1:1) solution for 30 min at room temperature. After deprotection, solution was evaporated under vacuum, the TFA salt was neutralized by $NaHCO_3$ solution and compound was extracted with ethyl acetate. The resulting ethyl acetate solution dried over Na_2SO_4 and evaporated under vacuum. The crude product (free amine) was used for next reaction without further purification.

Compound 6 (Boc-Ant ^{D}Pro^{L}Val-OMe): To a solution of BocAnt-OH (2.495 g, 10.52 mmol, 1.2 equiv.) and DIEA (4.57 mL, 26.31 mmol, 3 equiv.) in 30mL of ACN, the amine (H-ProVal-OMe) (2 g, 8.77 mmol, 1 equiv.), HBTU (6.653 g, 17.54 mmol, 2 equiv.) and catalytic amount of HOBt were added sequentially at 0 °C. This reaction mixture was stirred at room temperature. After 6 h, ACN was removed under reduced pressure and the compound was taken into ethyl acetate. The combined organic layers were washed sequentially with saturated solutions of $KHSO_4$, $NaHCO_3$ and brine. Organic layer was then dried over Na_2SO_4 and was evaporated under vacuum. The crude product was purified by column chromatography (eluent 40% AcOEt/pet. Ether, R_f: 0.3) to furnish compound **6** (3.51



g, 90%) as a white solid. Mp: 144-146°C; $[\alpha]^{25.97}_{D}$:156.08° (*c* = 0.11, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3315, 2971, 2358, 1731, 1676, 1525, 1160, 761; ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.23 (bs, 3H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.40 (m, 1H), 7.37 - 7.28 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.90 (d, *J* = 5.6 Hz, 1H), 4.66 - 4.45 (m, 1H), 3.72 (s, 3H), 3.60 - 3.39 (m, 2H), 2.48 - 2.32 (m, 1H), 2.29 - 2.18 (m, 1H), 2.18 - 2.08 (m, 1H), 2.04 - 1.93 (m, 1H), 1.91 - 1.78 (m, 1H), 1.50 (s, 9H), 0.98 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H) ^{13}C NMR (125MHz , $CDCl_3$) δ = 172.3, 171.1, 170.2, 153.1, 137.0, 131.0, 127.4, 124.4, 122.3, 121.1, 80.4, 59.5, 57.3, 50.3, 38.6, 30.9, 28.3, 27.4, 25.3, 19.1, 17.6; HRMS (ESI) $C_{23}H_{34}N_3O_6$ calculated $[M+H]^+$: 448.2369, found 448.2431, $C_{23}H_{33}N_3NaO_6$ calculated $[M+Na]^+$ 470.2267, found 470.2249.

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121.14
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57.27
52.18
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28.29
25.29
19.12
17.62
DEPT-135 NMR (125MHz, CDCl3)
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NH
Boc
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140
120
100
80
60
40
20
0
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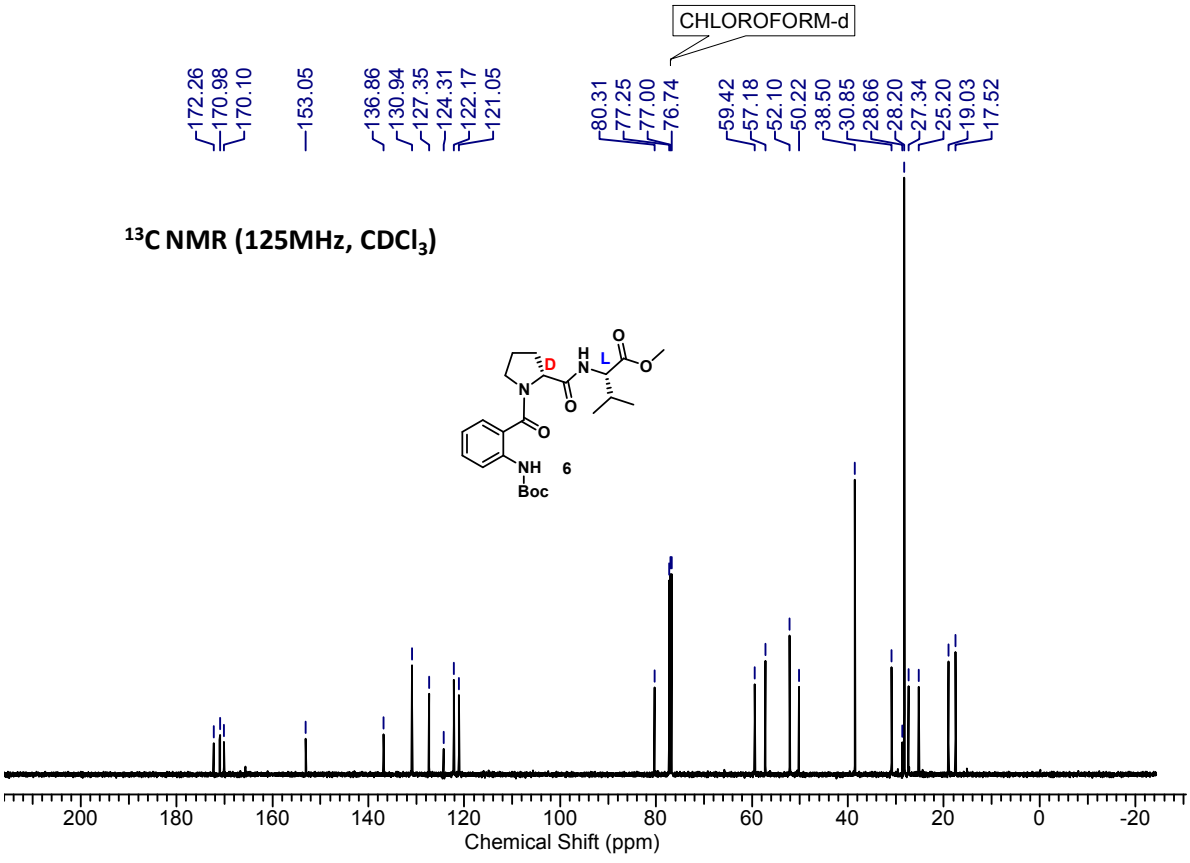
Chemical Shift (ppm)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170.10
153.05
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130.94
127.35
124.31
122.17
121.05
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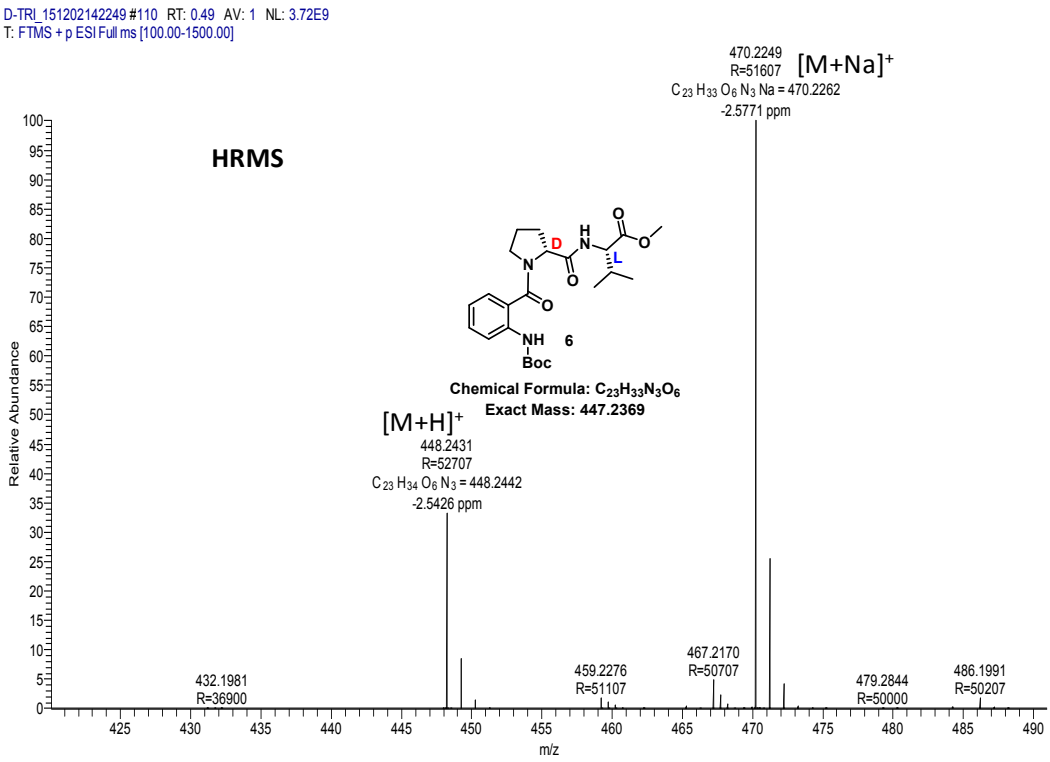
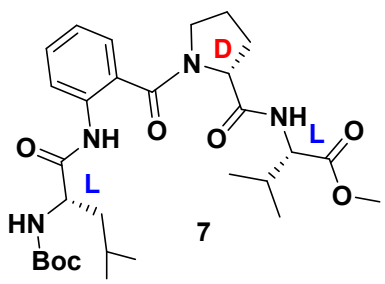
77.25
77.00
76.74
59.42
57.18
52.10
50.22
38.50
30.85
28.66
28.20
27.34
25.20
19.03
17.52
13C NMR (125MHz, CDCl3)
D
L
NH
Boc
6
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

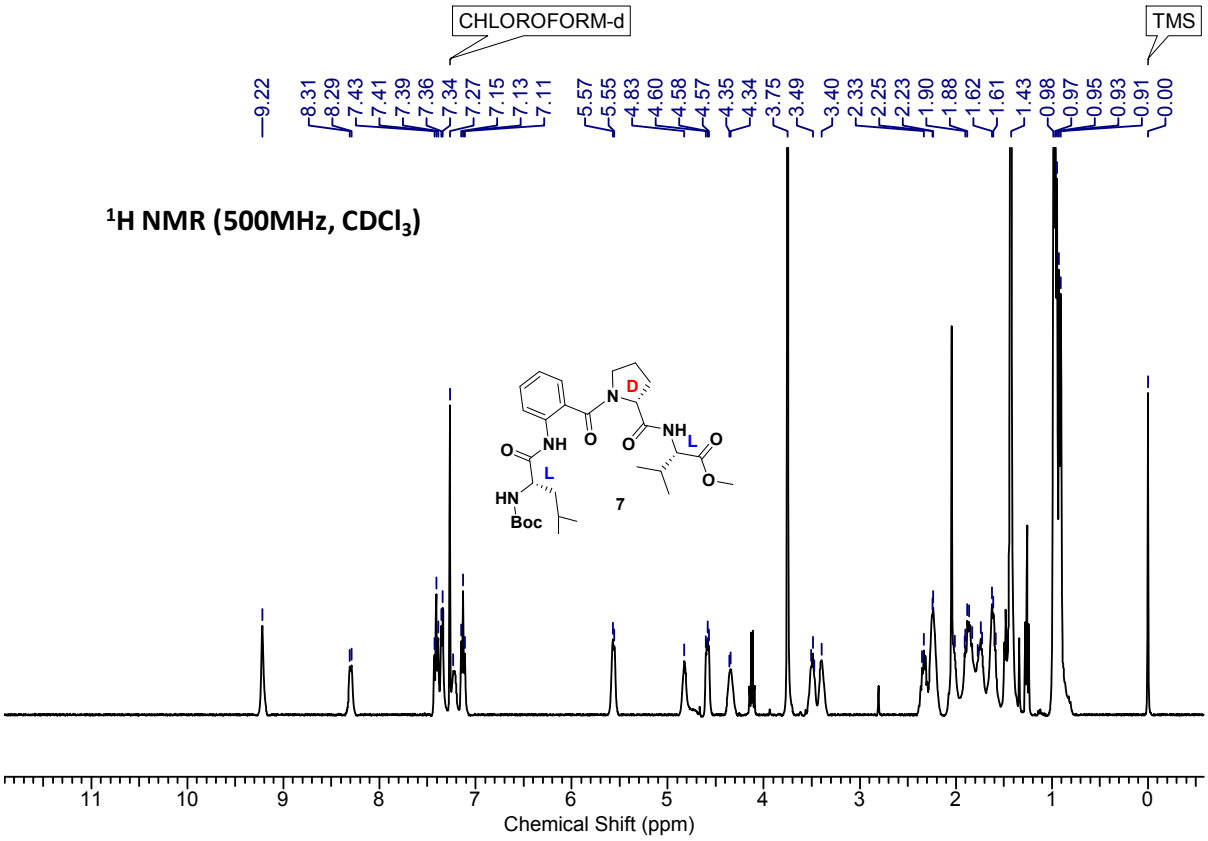


Compound 7 (Boc ^{L}LeuAnt ^{D}Pro^{L}Val-OMe):

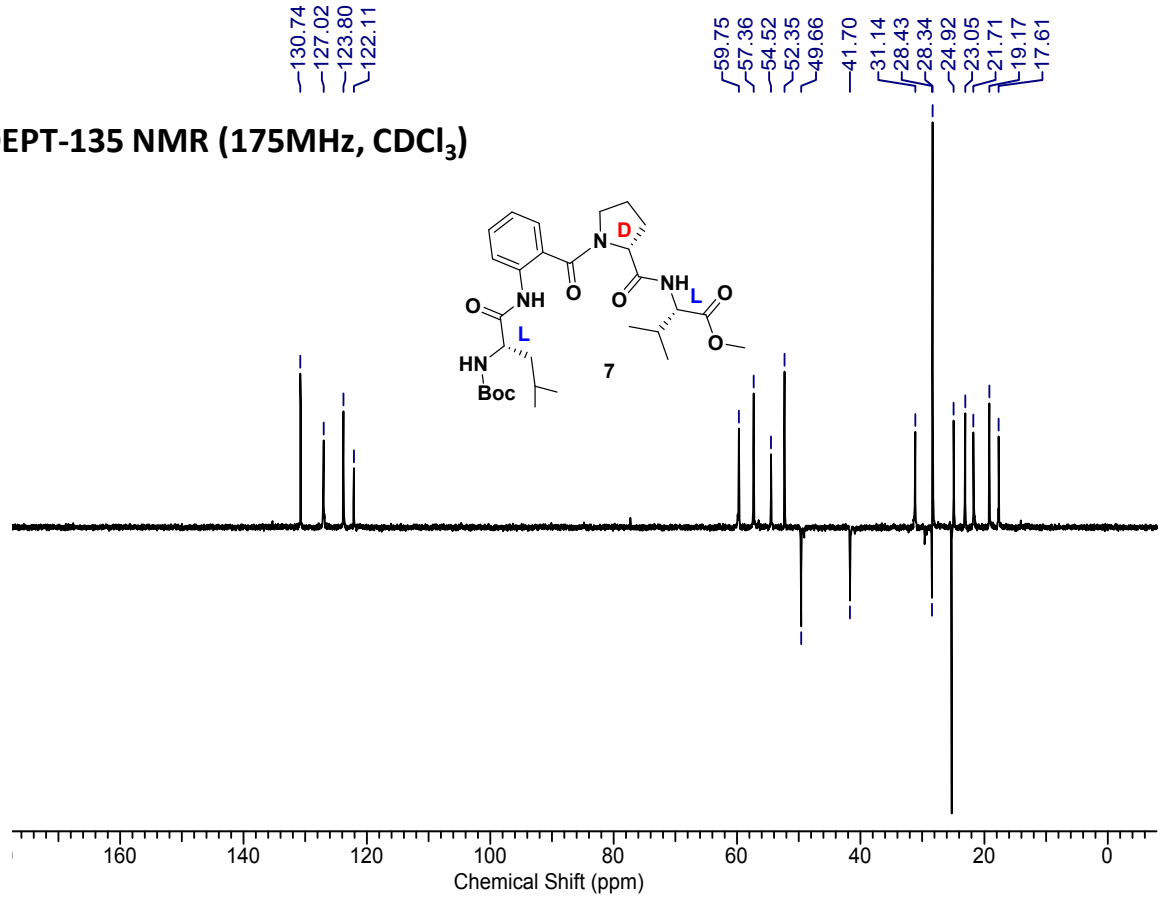


To a solution of Boc-^{L}Leu-OH (1.33 g, 5.76 mmol, 2 equiv.) in 20 mL DCM, EDC.HCl(1.1 g, 5.763 mmol, 2 equiv.) & catalytic amount of HOBt were added and reaction mixture was stirred at 0 °C for 30 min., the solution of amine (H-Ant^{D}Pro^{L}Val-OMe) (1 g, 2.88 mmol, 1equiv.) in 10mL DCM was added slowly to the reaction mixture at 0 °C. This reaction mixture was then stirred for 4 h at room temperature. After completion of reaction, solution was diluted with DCM. The organic layer was washed sequentially with saturated solutions of $KHSO_4$, $NaHCO_3$ and brine. Organic layer was then dried over Na_2SO_4 and was evaporated under vacuum. The crude product was purified by column chromatography (eluent 50% AcOEt/pet. Ether, R_f: 0.3) afforded **7** (1.3 g, 81%) as a white fluffy solid. Mp: 82-84°C; $[\alpha]^{25.97}_{D}$: 84.44° (*c* = 0.046, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3343, 3020, 2970, 2357, 1674, 1590, 1217, 764; ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 9.22 (bs, 1H), 8.30 (d, *J* = 6.6 Hz, 1H), 7.41 (t, *J* = 7.3 Hz 1H), 7.34 (d., *J* = 7.3 Hz, 1H), 7.23 (bs, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 5.56 (d, *J* = 7.1 Hz, 1H), 4.83 (m., 1H), 4.60 (m, 1H), 4.42 - 4.25 (m, 1H), 3.75 (s, 3H), 3.49 (m, 1H), 3.40 (m, 1H), 2.30 (m, 3H), 2.01 (m, 1H), 1.94 - 1.69 (m, 3H), 1.67 - 1.56 (m, 1H), 1.43 (s, 9H), 1.00 - 0.94 (m, 9H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz , $CDCl_3$) δ

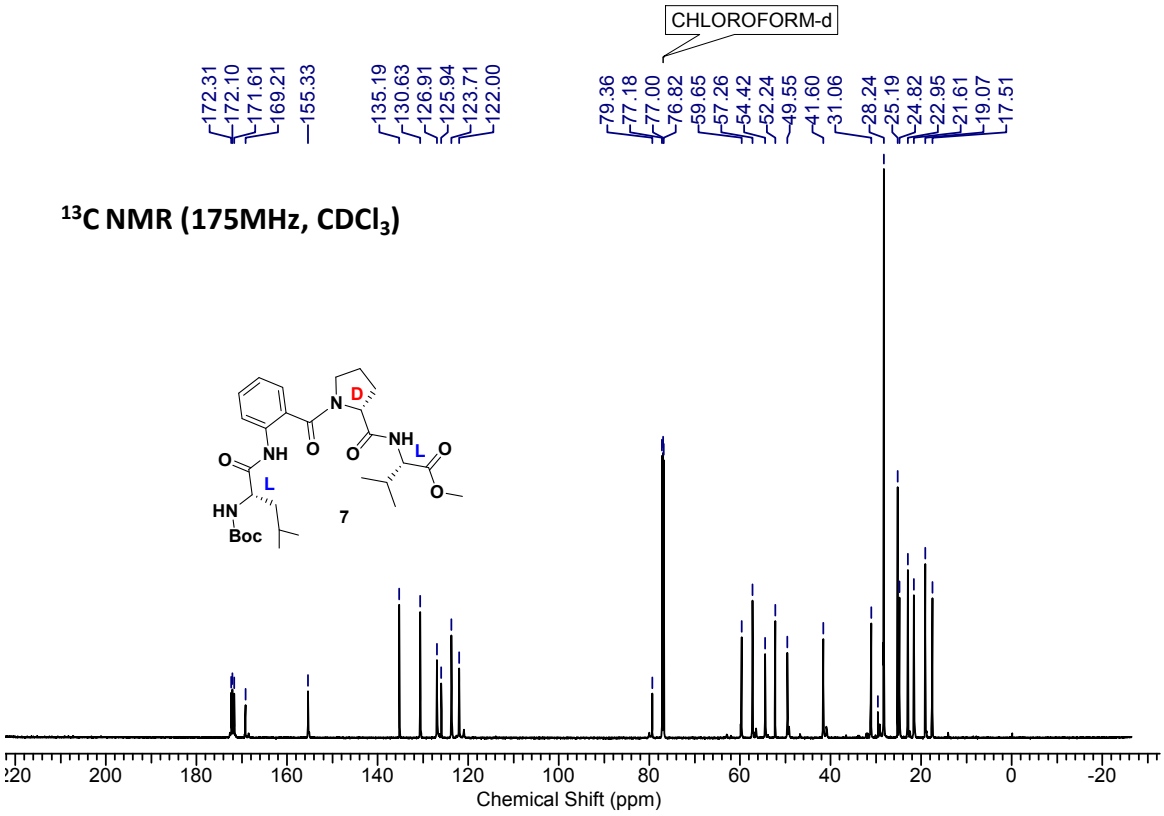
ppm 172.3, 172.1, 171.6, 169.2, 155.3, 135.2, 130.6, 126.9, 125.9, 123.7, 79.4, 59.6, 57.3, 54.4, 52.2, 49.6, 41.6, 31.1, 28.2, 25.2, 24.8, 23.0, 21.6, 21.6, 19.1, 17.5; HRMS (ESI) $C_{29}H_{45}N_4O_7$ calculated $[M+H]^+$: 561.3210, found 560.3273, $C_{29}H_{44}N_4NaO_7$ calculated $[M+Na]^+$ 583.3108, found 583.3091.

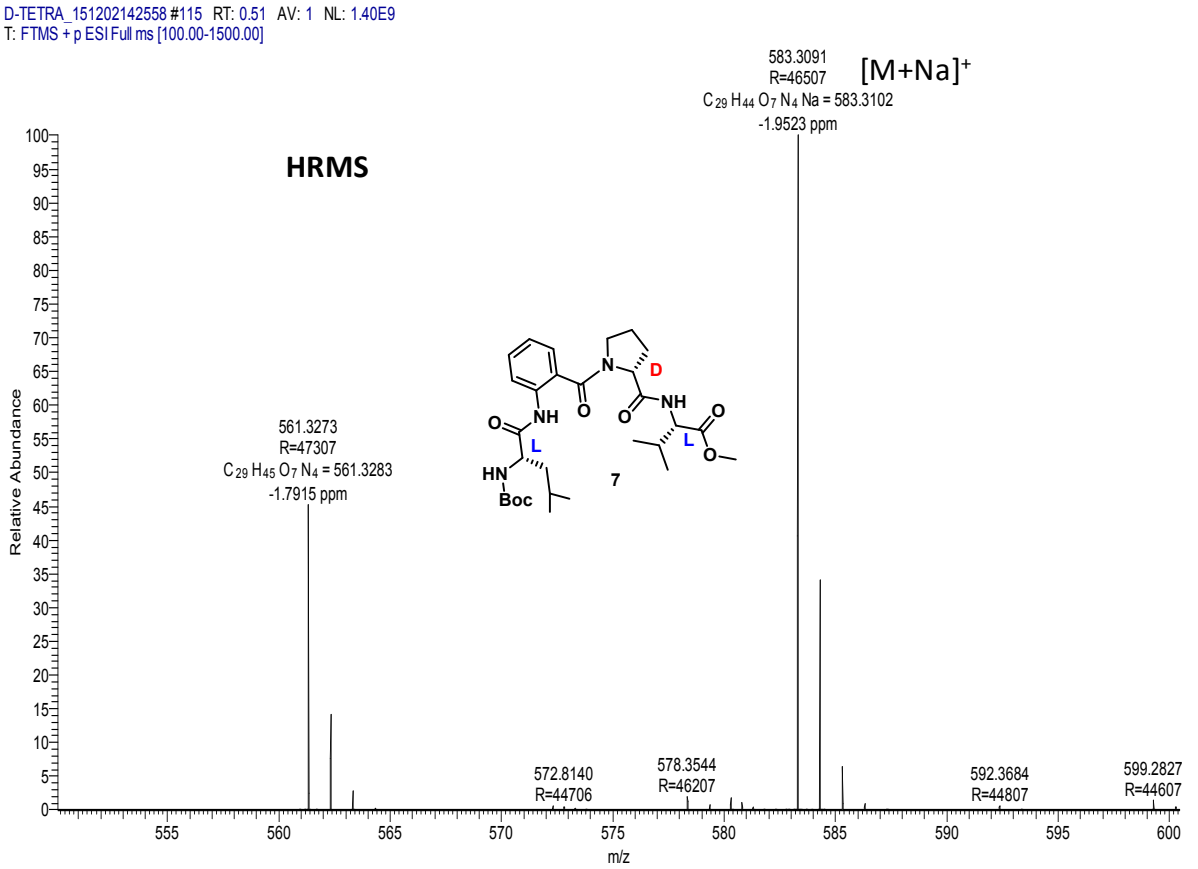


DEPT-135 NMR (175MHz, $CDCl_3$)

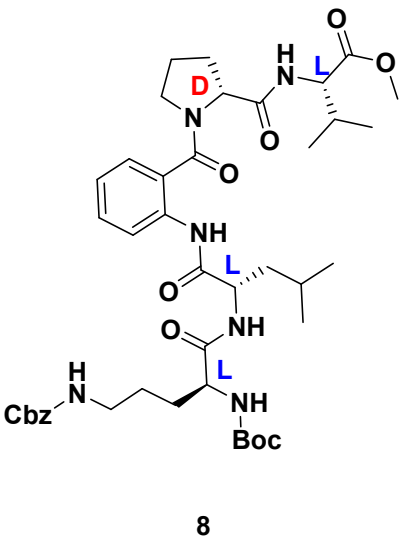


^{13}C NMR (175MHz, $CDCl_3$)



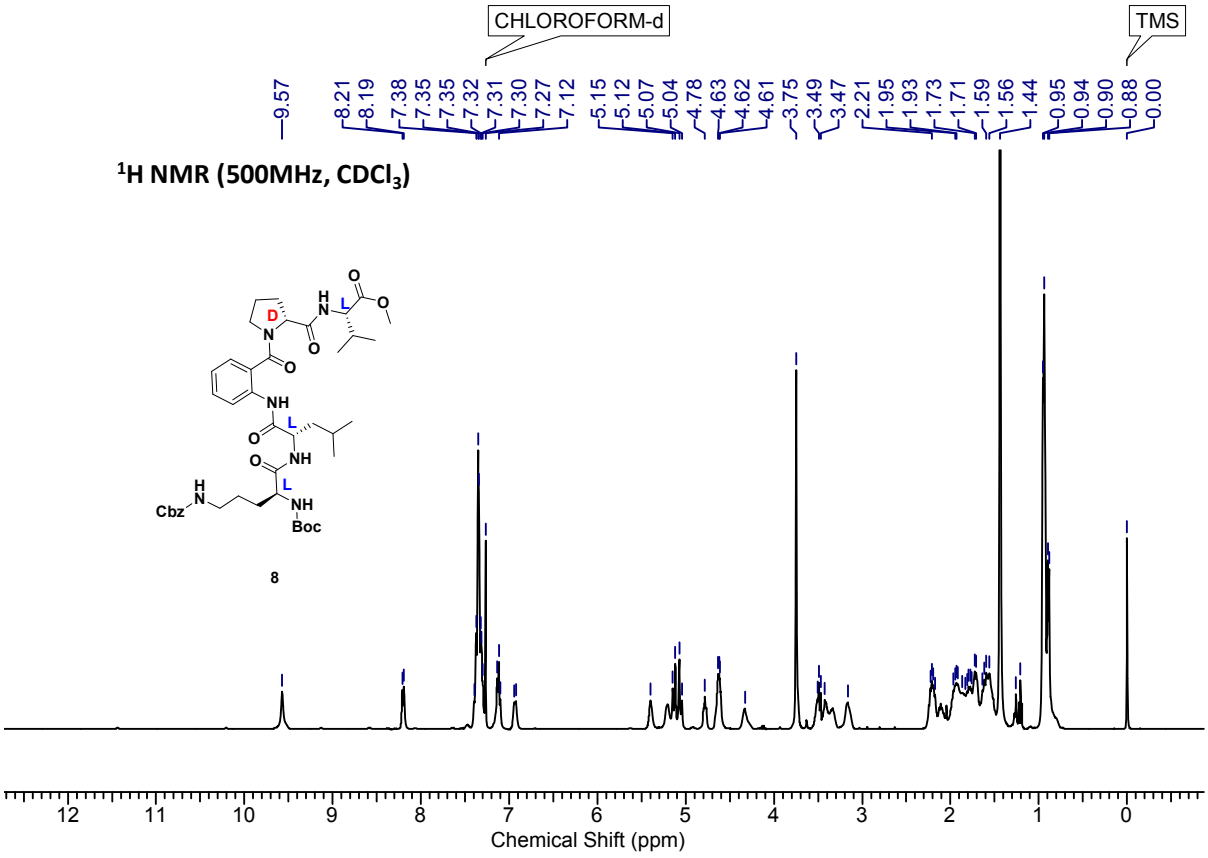


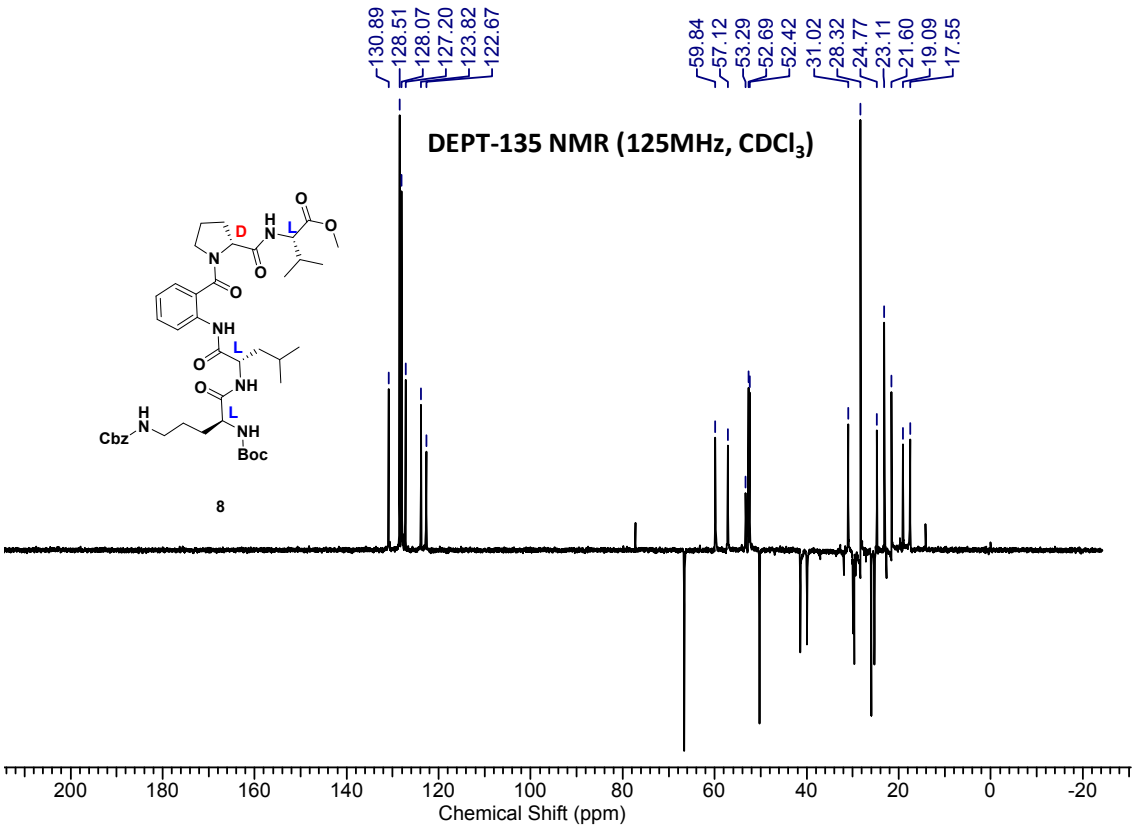
Compound 8 (Boc-(z)^{L}Orni^{L}LeuAnt^{D}ProVal-OMe):



To a stirred solution of tetra-amine (H-^{L}LeuAnt^{D}ProVal-OMe) (1 g, 2.17 mmol, 1equiv.), and DIEA (1.33 mL, 4.34 mmol, 3 equiv.) in 20mL ACN, Boc-(z)^{L}Orn-OH (0.96 g, 2.60 mmol, 1.2 equiv.) HBTU (1.643 g, 4.34 mmol, 2 equiv.) & catalytic amount of HOBt were added sequentially at 0 °C. This reaction mixture was then stirred, at room temperature. After 8 h, ACN was removed under reduced pressure and then the mixture was taken into ethyl acetate. The organic layer was washed sequentially with saturated solutions of $KHSO_4$, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and was evaporated under vacuum. The crude product was purified by column chromatography (eluent 60% AcOEt/pet. Ether, Rf: 0.3) to furnish **9** (1.33 g, 76%) as a white fluffy solid. Mp: 90-92°C; $[\alpha]^{25.60}_{D}$: 52.59° (*c* = 0.043, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 3331, 3020, 2970, 2405, 2357, 1679, 1217, 764; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm 9.57 (bs, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.43 - 7.28 (m, 8H), 7.17 - 7.07 (m, 2H), 6.93 (d, *J* = 6.4 Hz, 1H), 5.40 (bs, 1H), 5.20 (bs, 1H), 5.16 - 5.01 (dd,

11.90 Hz, 2H), 4.78 (m., 1H), 4.65 (m, 2H), 4.33 (m., 1H), 3.75 (s, 3H), 3.58 - 3.38 (m, 2H), 3.37 - 3.28 (m, 1 H), 3.16 (m., 1 H), 2.31 - 2.15 (m, 3 H), 2.11 (m, 1 H), 2.02 - 1.67 (m, 3 H), 1.67 - 1.55 (m, 3H), 1.44 (s, 9H), 0.95 (m, 9H), 0.89 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ ppm 172.6, 172.1, 171.5, 171.1, 169.6, 156.9, 155.7, 136.6, 135.6, 130.8, 128.4, 128.0, 127.1, 125.6, 123.8, 122.6, 79.8, 66.6, 59.8, 57.1, 53.3, 52.6, 52.3, 50.2, 41.3, 39.9, 31.0, 29.8, 29.6, 28.3, 26.0, 25.2, 24.7, 23.1, 21.6, 19.0, 17.5; HRMS (ESI) $C_{42}H_{60}N_6O_{10}$ calculated $[M+H]^+$: 809.4371, found 809.4429, $C_{42}H_{60}N_6NaO_{10}$ calculated $[M+Na]^+$ 831.4269, found 831.4244.

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127.20
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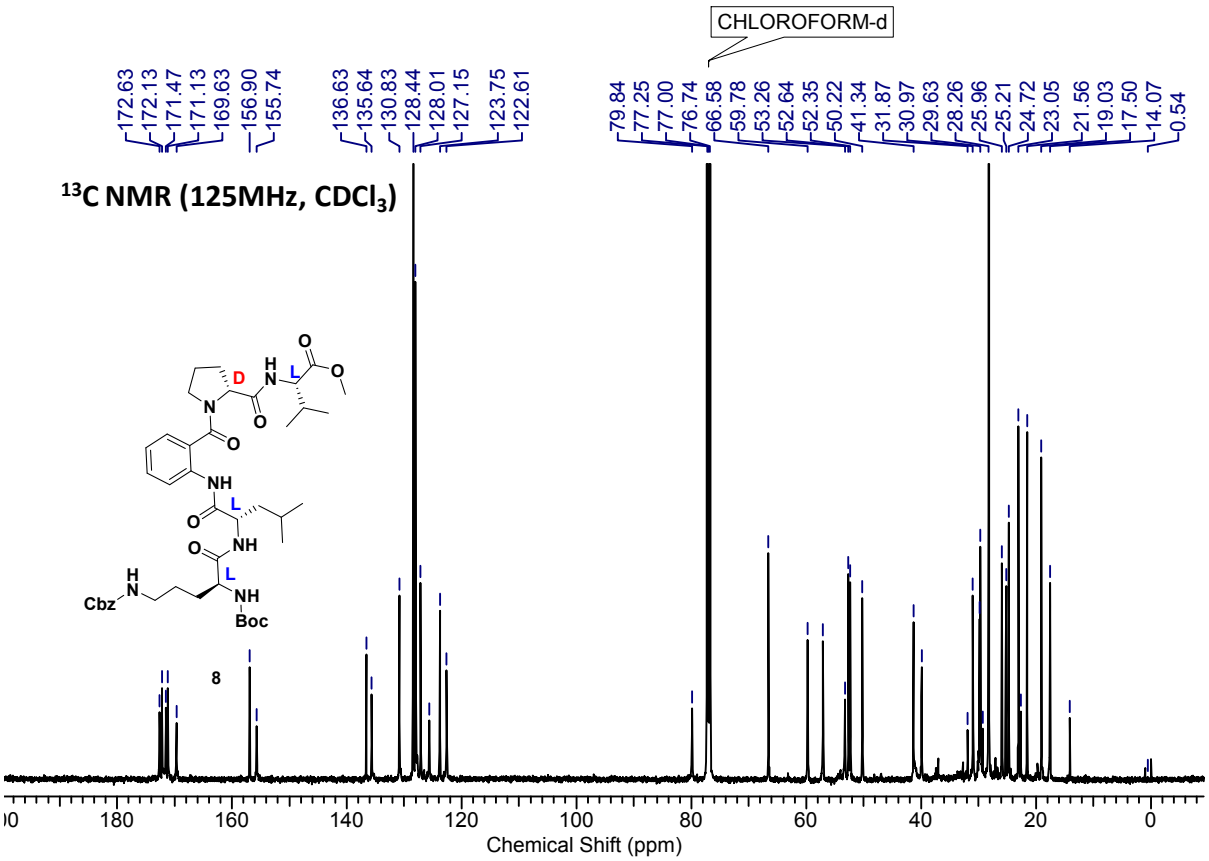
122.67
59.84
57.12
53.29
52.69
52.42
31.02
28.32
24.77
23.11
21.60
19.09
17.55
DEPT-135 NMR (125MHz, CDCl3)
8
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)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136.63
135.64
130.83
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128.01
127.15
123.75
122.61
79.84
77.25
77.00
76.74
66.58
59.78
53.26
52.64
52.35
50.22
41.34
31.87
30.97
29.63
28.26
25.96
25.21
24.72
23.05
21.56
19.03
17.50
14.07
0.54
13C NMR (125MHz, CDCl3)
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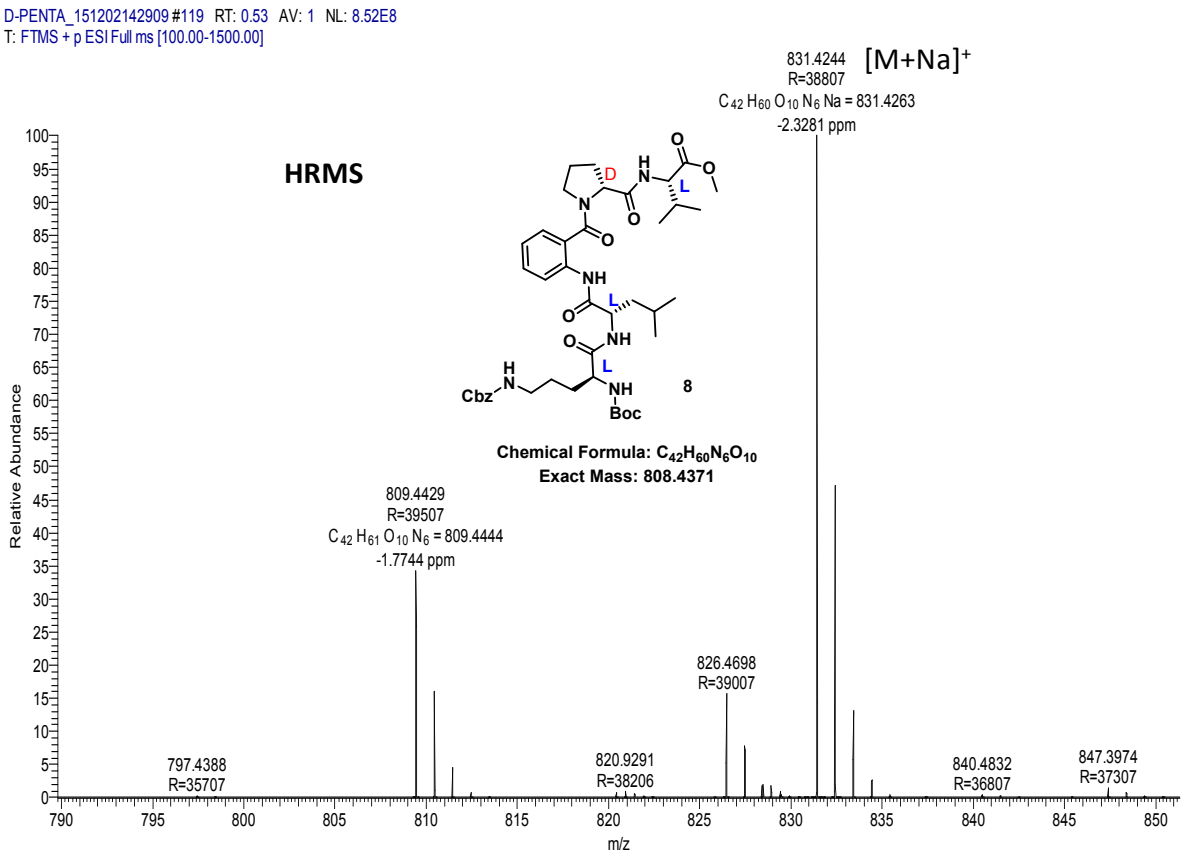
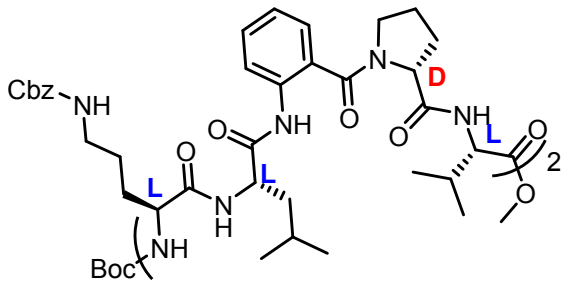
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



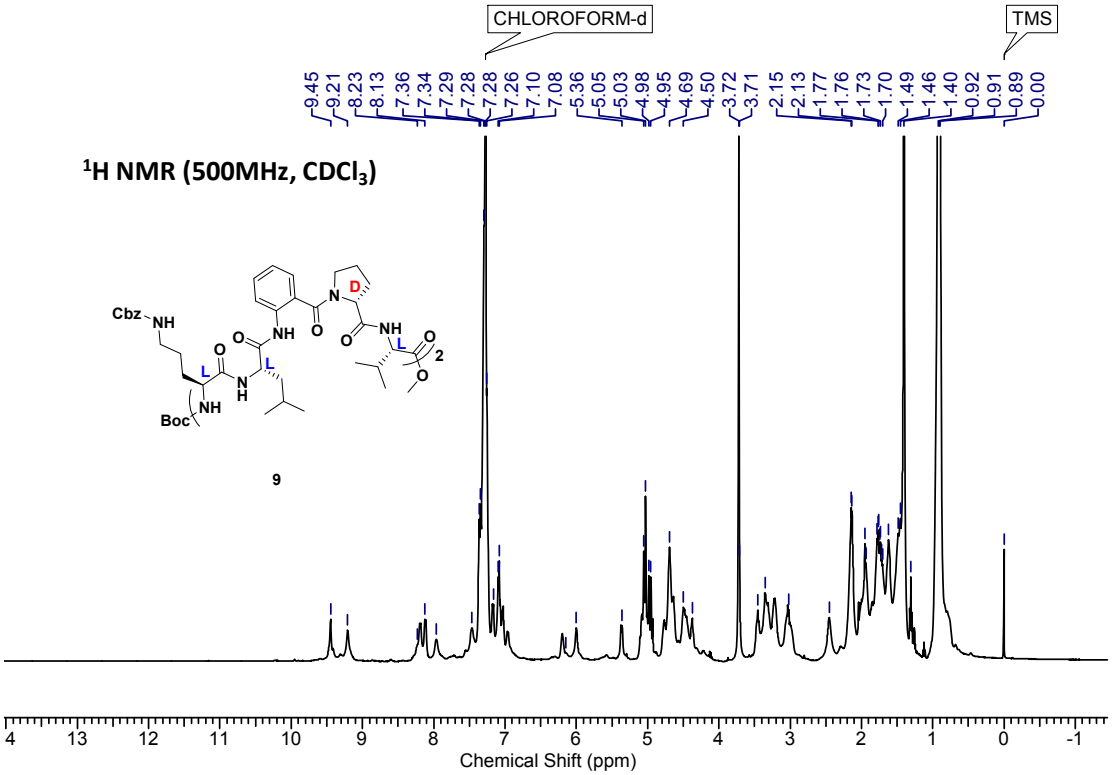
Hydrolysis of 8: To a stirred solution of **8** in MeOH, aq. LiOH:H_2O (2 equiv.) was added and reaction mixture was kept for 8h. After complete consumption of starting material, MeOH was evaporated under vacuum and then mixture was acidified with $KHSO_4$ solution. The compound was extracted with ethyl acetate and washed with water and brine. The ethyl acetate layer was dried over Na_2SO_4 and evaporated *in vacuo*. The solid, penta-peptide acid (Boc-(z)^{L}Orni^{L}LeuAnt^{D}ProVal-OH) **8a**, was used for next reaction without further purification.

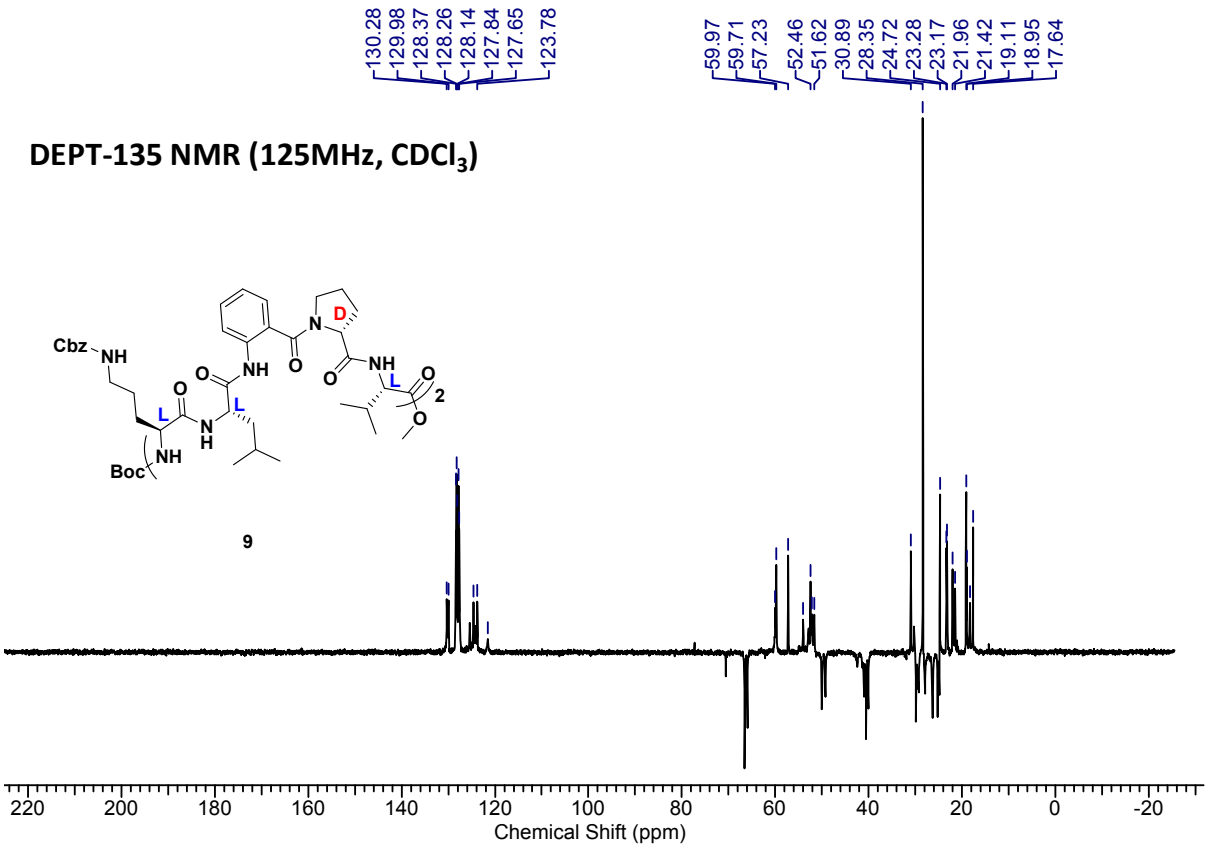
Compound 9 Boc-((z)^{L}Orni^{L}LeuAnt^{D}ProVal)$_2$-OMe (Deca-peptide): The deca-peptide **9** was synthesized by segment doubling strategy from penta-peptide. To a stirred solution of **8a** (0.41 g, 0.56 mmol, 1 equiv.) and **8b** (0.4 g, 0.56 mmol, 1 equiv.) in 15 mL of ACN, HBTU (0.43 g, 1.16 mmol, 2 equiv.) and DIEA (0.3 mL, 1.6 mmol, 3 equiv.) were added at 0 °C. The reaction mixture was then stirred at room temperature. After 8 h, ACN was removed under reduced pressure and then the mixture was taken into ethyl acetate. The organic layer

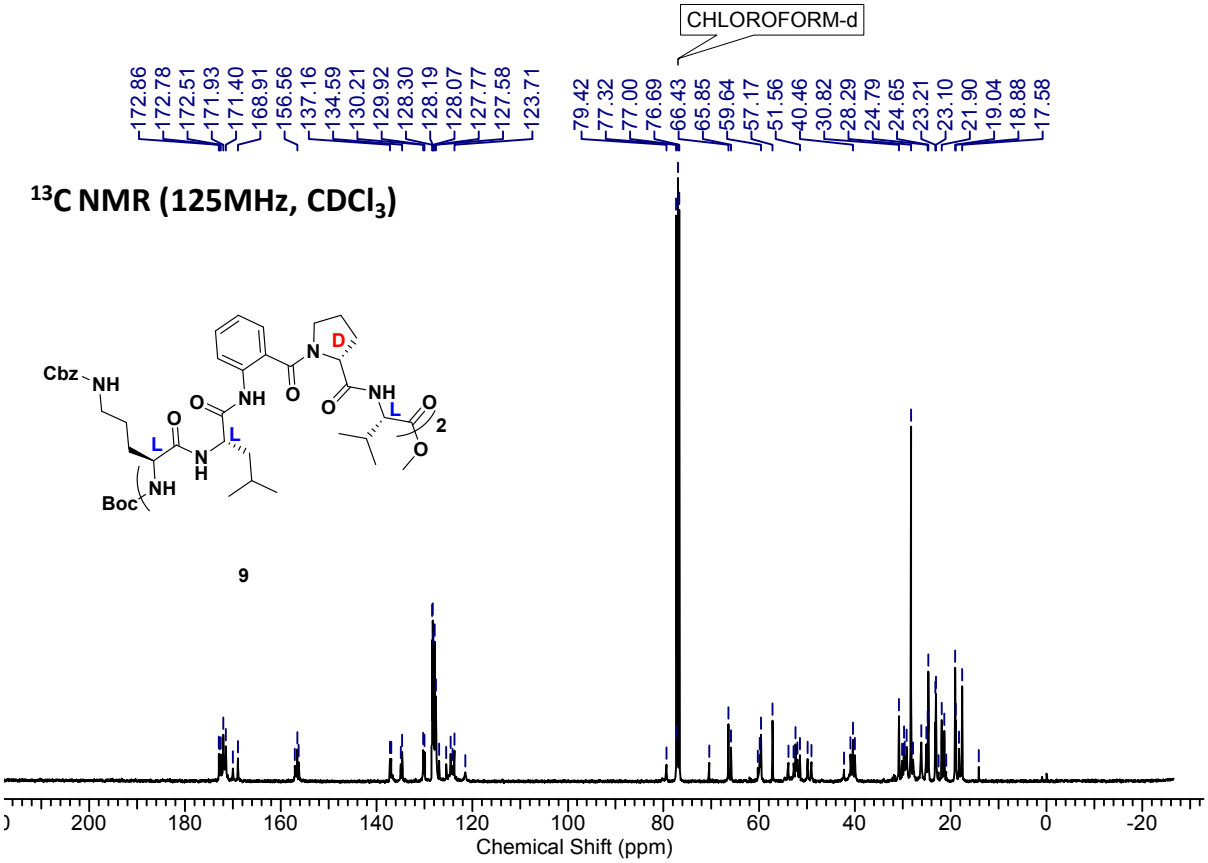


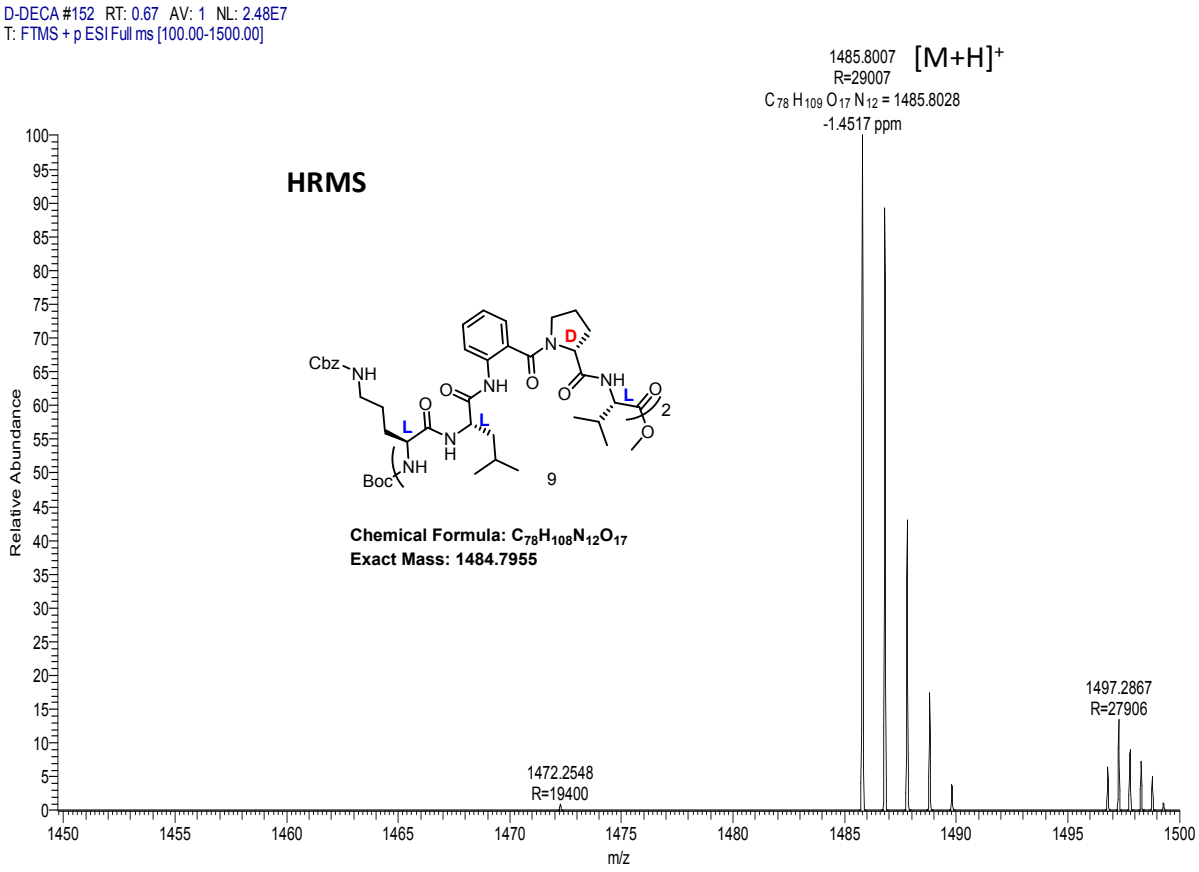
9

was washed sequentially with saturated solutions of $KHSO_4$, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and was evaporated under vacuum. The crude product was purified by column chromatography (eluent 70% AcOEt/pet. Ether, Rf: 0.3) to furnish **9** (0.57 g, 69%) as a white fluffy solid. mp: 126-128°C; $[\alpha]^{25.64}_D$ = 33.4824° (*c* = 0.012, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3297, 3071, 2962, 2357, 1646, 1538, 1252, 1160, 761; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.45 (bs, 1H), 9.21 (bs, 1H), 8.19 (d, *J* = 6.7 Hz, 1H), 8.13 (d, *J* = 7.6 Hz., 1H), 7.96 (bs, 1H), 7.46 (t, *J* = 6.7 Hz, 1H), 7.41 - 7.19 (m, 14H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.12 - 7.05 (m, 2H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 6.1 Hz, 1H), 6.20 (bs, 1H), 6.00 (bs, 1H), 5.36 (dd, *J* = 8.54 Hz, 1H), 5.16 - 4.90 (m, 5H), 4.77 (m., 1H), 4.72 - 4.60 (m, 3H), 4.48 (m, 2H), 4.37 (m, 1H), 3.71 (s, 3H), 3.45 (m, 1H), 3.35 (m, 3H), 3.22 (m, 2H), 3.02 (m, 2H), 2.45 (bs, 2H), 2.14 (m, 5H), 2.03 - 1.88 (m, 8H), 1.62 (m, 4H), 1.49-1.46(m, 5H), 1.43 (S, 9H), 0.97 - 0.84 (m, 24H). ^{13}C NMR (101 MHz , $CDCl_3$) δ ppm 172.9, 172.8, 172.5, 171.9, 171.5, 171.4, 170.0, 168.9, 157.0, 156.6, 156.2, 137.2, 136.9, 135.0, 134.6, 130.2, 129.9, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 126.8, 125.4, 124.5, 124.1, 123.7, 121.4, 79.4, 70.5, 66.4, 65.8, 60.3, 59.9, 59.6, 53.9, 52.8, 52.2, 51.8, 51.6, 50.0, 49.1, 42.3, 40.9, 40.5, 40.0, 30.8, 30.2, 29.7, 29.2, 28.3, 27.8, 26.3, 26.2, 25.1, 24.8, 24.7, 23.2, 23.1, 21.9, 21.4, 19.0, 18.9, 18.3, 17.6. HRMS (ESI) $C_{78}H_{108}N_{12}O_{17}$ calculated $[M+H]^+$: 1485.7955, found 1485.8007.



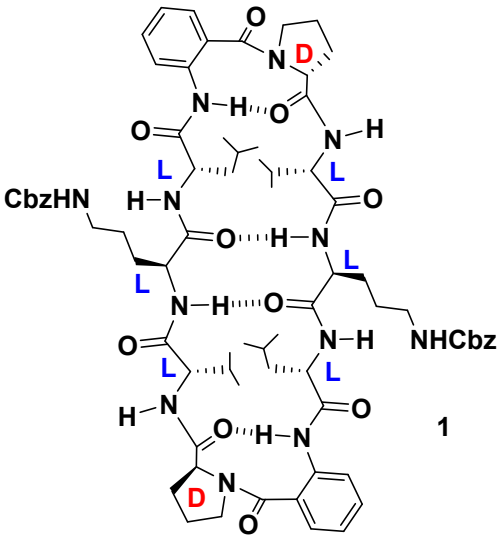

130.28
129.98
128.37
128.26
128.14
127.84
127.65
123.78
59.97
59.71
57.23
52.46
51.62
30.89
28.35
24.72
23.28
23.17
21.96
21.42
19.11
18.95
17.64
DEPT-135 NMR (125MHz, CDCl3)
Cbz
NH
Boc
NH
9
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


CHLOROFORM-d
172.86
172.78
172.51
171.93
171.40
168.91
156.56
137.16
134.59
130.21
129.92
128.30
128.19
128.07
127.77
127.58
123.71
79.42
77.32
77.00
76.69
66.43
65.85
59.64
57.17
51.56
40.46
30.82
28.29
24.79
24.65
23.21
23.10
21.90
19.04
18.88
17.58
13C NMR (125MHz, CDCl3)
Cbz
NH
Boc
NH
9
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

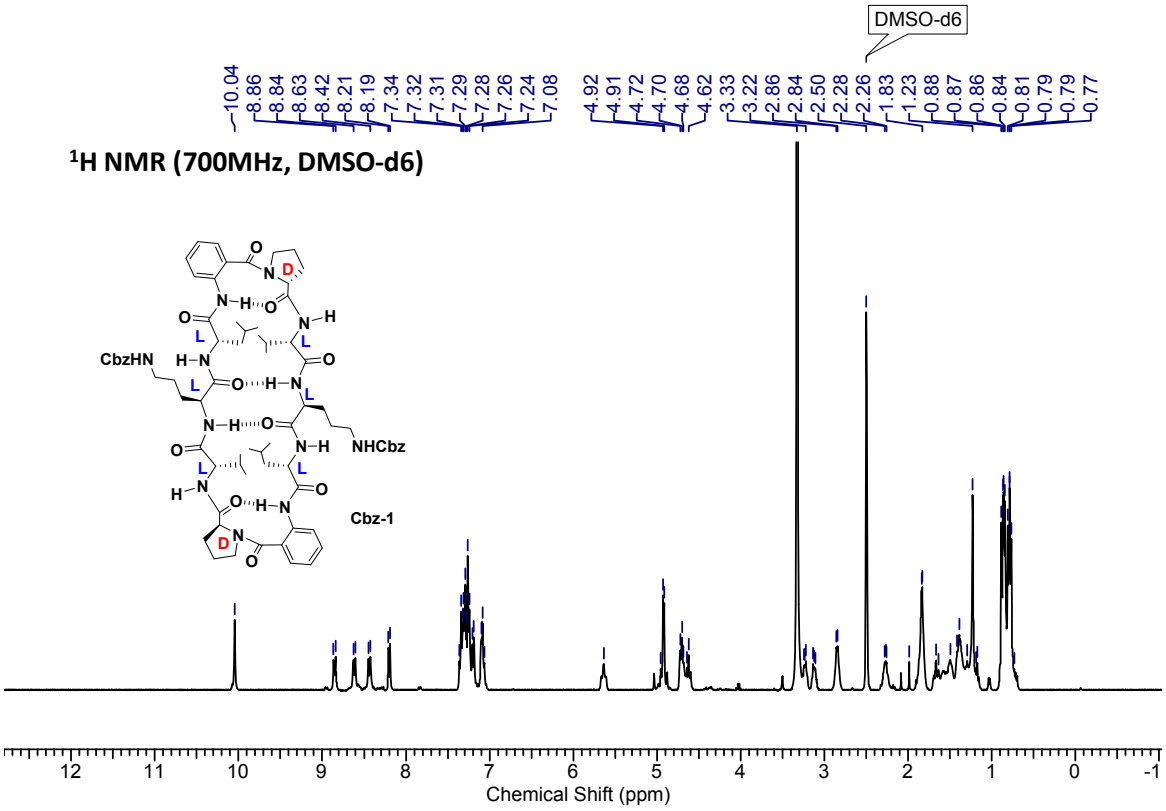


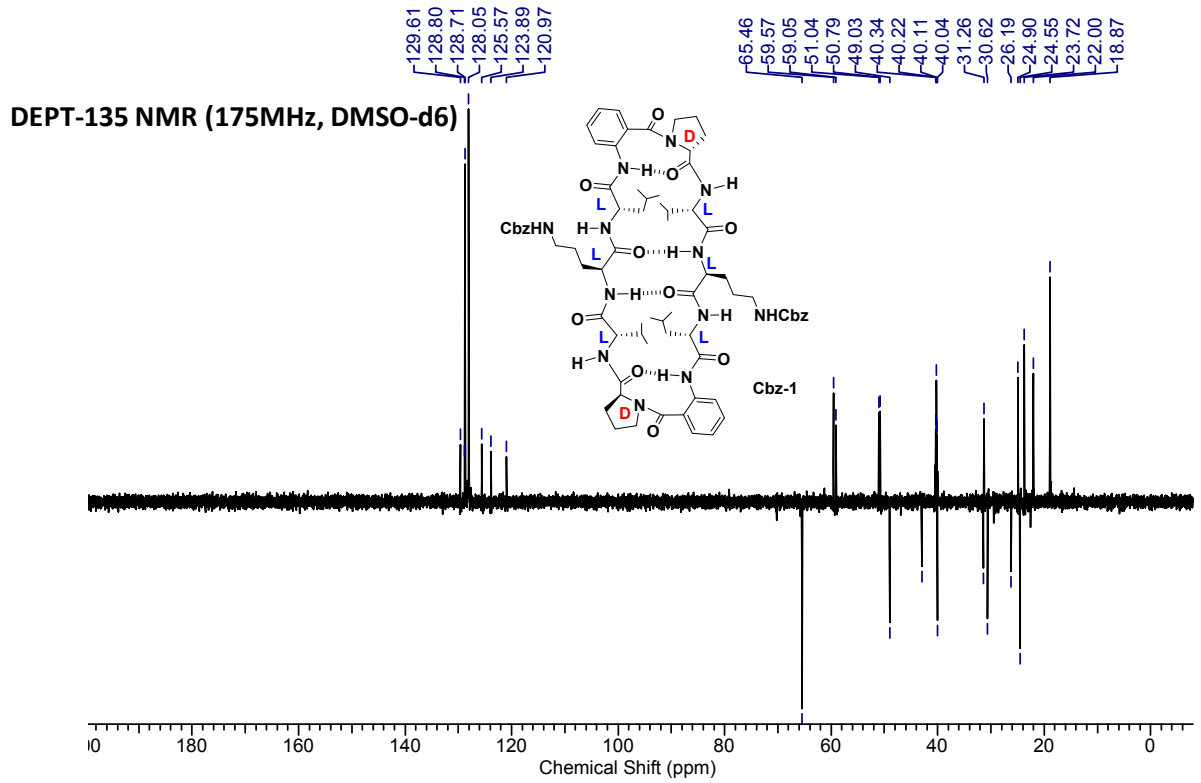
Hydrolysis of 9: Following the hydrolysis procedure of **8**, compound **9** was hydrolized to Boc-Deca-OH i.e. Boc-((z)^{L}Orni^{L}LeuAnt^{D}ProVal)$_2$-OH.

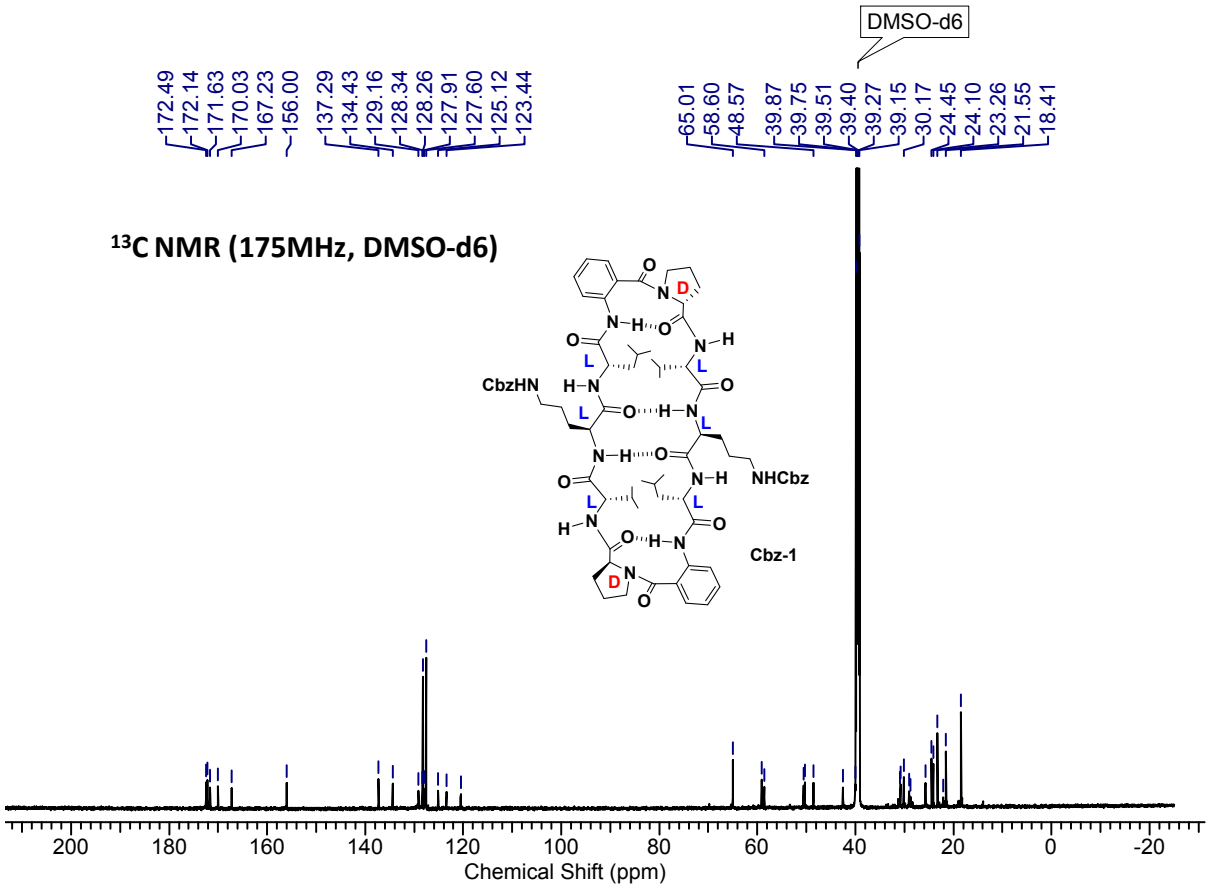
Compound 1 (Cbz-1): Cyclo-((z)^{L}Orn^{L}LeuAnt^{D}ProVal)-$_2$; The acid i.e. Boc-Deca-OH was stirred in TFA:DCM (1:1) solution for 30 minutes. Then solution was evaporated under reduced vacuum and it resulted to solid TFA salt of H-Deca-OH. This TFA salt of H-Deca-OH (0.08 g, 0.055 mmol, 1 equiv.) was taken in 10 mL DCM and DIEA (0.04mL, 0.033 mmol, 4 equiv.) was slowly added, this mixture was stirred for 5 min at 0°C. Later HBTU (0.042 g, 0.011, 2 equiv.) and HOBt (catalytic amount) were added into the reaction mixture and reaction was stirred for overnight at room temperature. The reaction mixture was diluted with DCM and washed with saturated solutions of $KHSO_4$, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified

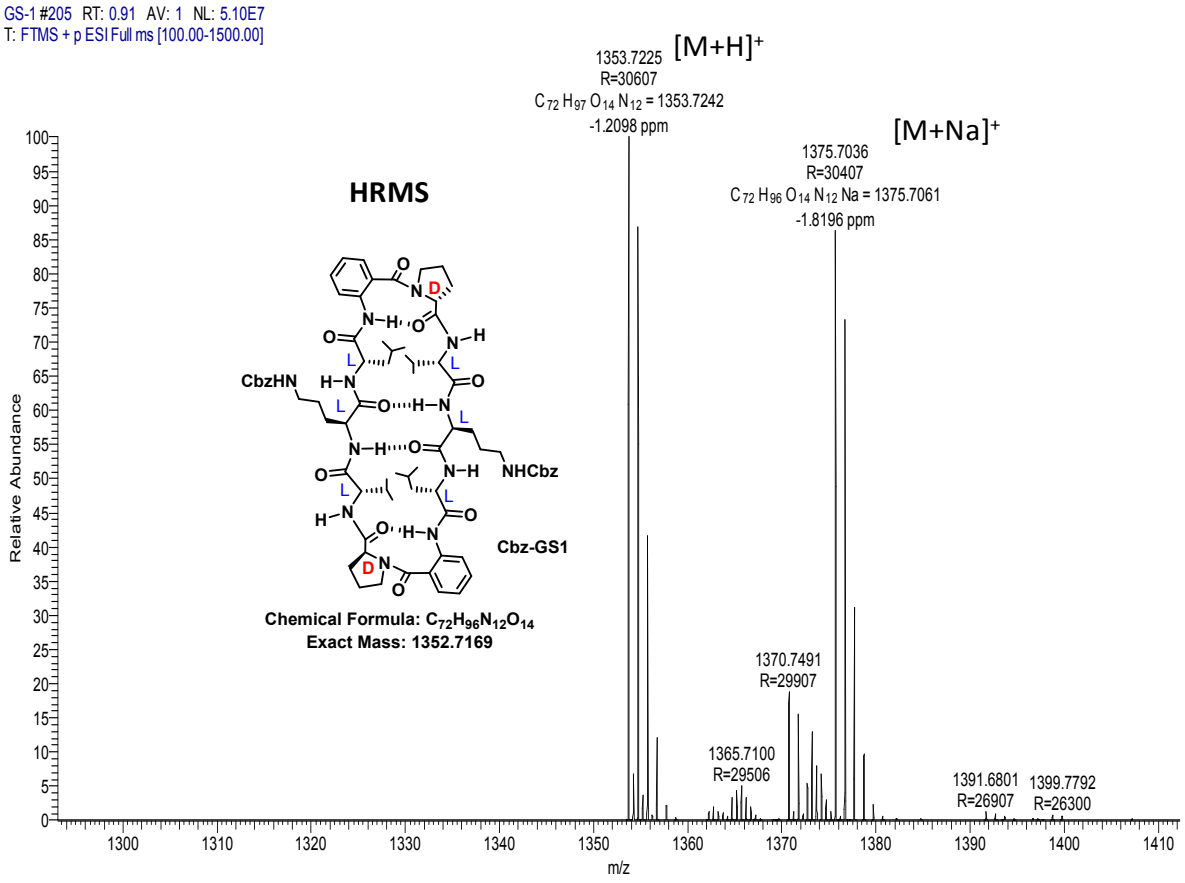


by column chromatography (eluent 2% methanol/DCM, R_f: 0.3) to furnish compound **1** (0.037 g, 50%) as a white fluffy solid. Mp: 284-286°C; $[\alpha]^{25.64}_{D}$: 87.08° (*c* =0.007, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3418, 3022, 2966, 2930, 2869, 2405, 2357, 1641, 1544, 1421, 1216, 765, 670; ^{1}H NMR (700 MHz, DMSO-d_6) δ ppm: 10.04 (s, 2H), 8.85 (d, *J* = 9.3 Hz, 2H), 8.62 (d, *J* = 9.5 Hz, 2H), 8.44 (d, *J* = 9.5 Hz, 2H), 8.20 (d, *J* = 8.3 Hz, 2H), 7.38 - 7.22 (m, 14H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.12 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 2H), 5.70 (m, 2H), 5.01 (m, 2H), 4.75 - 4.66 (m, 4H), 4.62 (m, 2H), 3.23(m, 2H), 3.17(m, 2H), 2.85 (m, 4H), 2.35 (m, 2H), 1.90-1.80(m, 8H), 1.72 (m, 2H), 1.60- 1.45 (m., 5H), 1.44-1.33 (m, 5H), 1.29 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.85 (d, *J* = 6.6 Hz, 6H), 0.80 (d, *J* = 7.3 Hz, 6 H), 0.78 (d, *J* = 7.3 Hz, 6H); ^{13}C NMR (175 MHz, DMSO-d_6) δ ppm: 172.5, 172.2, 171.6, 170.0, 167.23, 156.0, 137.2, 134.4, 129.2, 128.3, 128.2, 127.9, 127.6, 125.1, 123.4, 120.5, 65.0, 59.3, 58.6, 50.6, 50.3, 48.6, 42.5, 31.3, 31.0, 30.8, 30.2, 29.0, 25.7, 24.4, 24.1, 23.3, 21.5, 18.41; HRMS (ESI) $C_{72}H_{96}N_{12}O_{14}$ calculated $[M+H]^+$ 1353.7169 found 1353.7225, $C_{72}H_{96}N_{12}NaO_{14}$ calculated $[M+Na]^+$ 1375.7067, found 1375.7036.

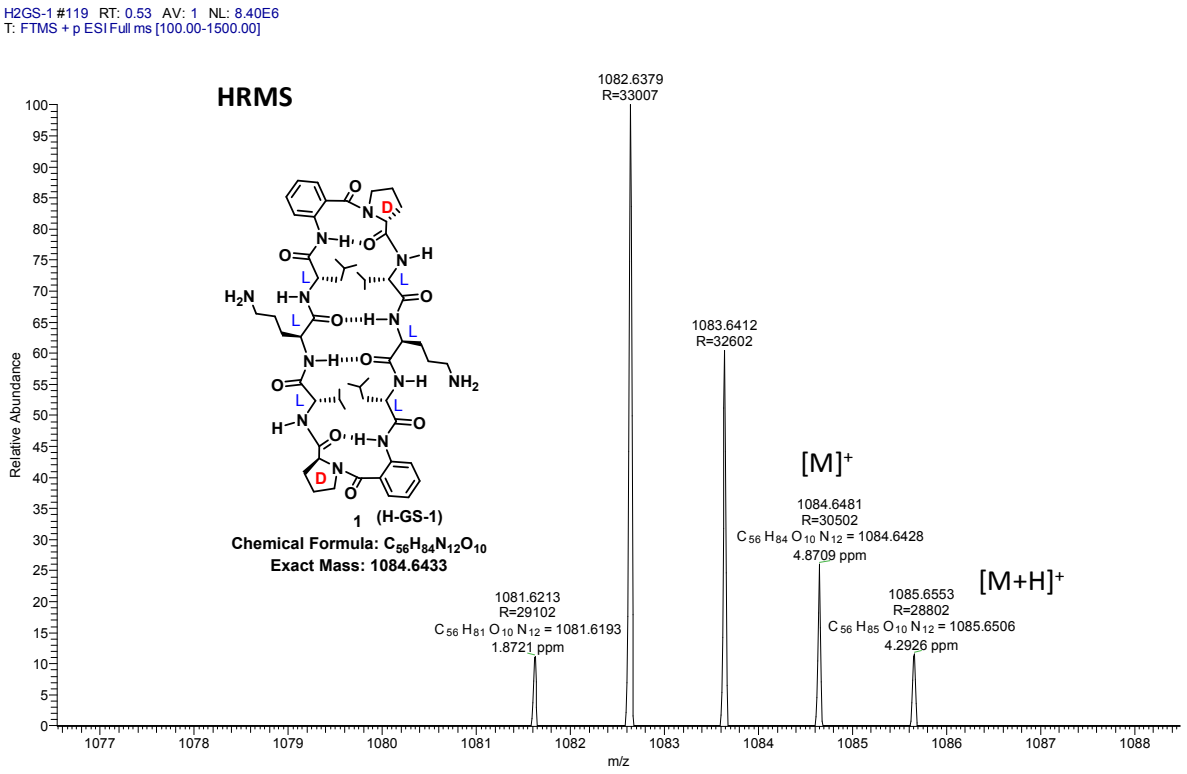



DEPT-135 NMR (175MHz, DMSO-d6)
129.61
128.80
128.71
128.05
125.57
123.89
120.97
65.46
59.57
59.05
51.04
50.79
49.03
40.34
40.22
40.11
40.04
31.26
30.62
26.19
24.90
24.55
23.72
22.00
18.87
CbzHN
NHCbz
Cbz-1
Chemical Shift (ppm)

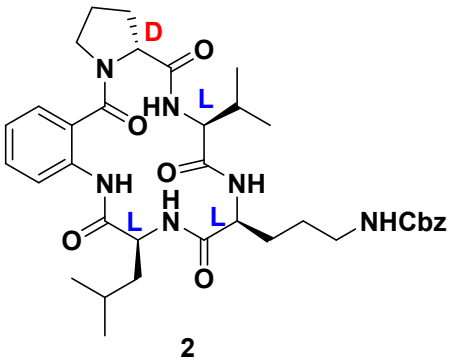

DMSO-d6
172.49
172.14
171.63
170.03
167.23
156.00
137.29
134.43
129.16
128.34
128.26
127.91
127.60
125.12
123.44
65.01
58.60
48.57
39.87
39.75
39.51
39.40
39.27
39.15
30.17
24.45
24.10
23.26
21.55
18.41
13C NMR (175MHz, DMSO-d6)
CbzHN
NHCbz
Cbz-1
Chemical Shift (ppm)



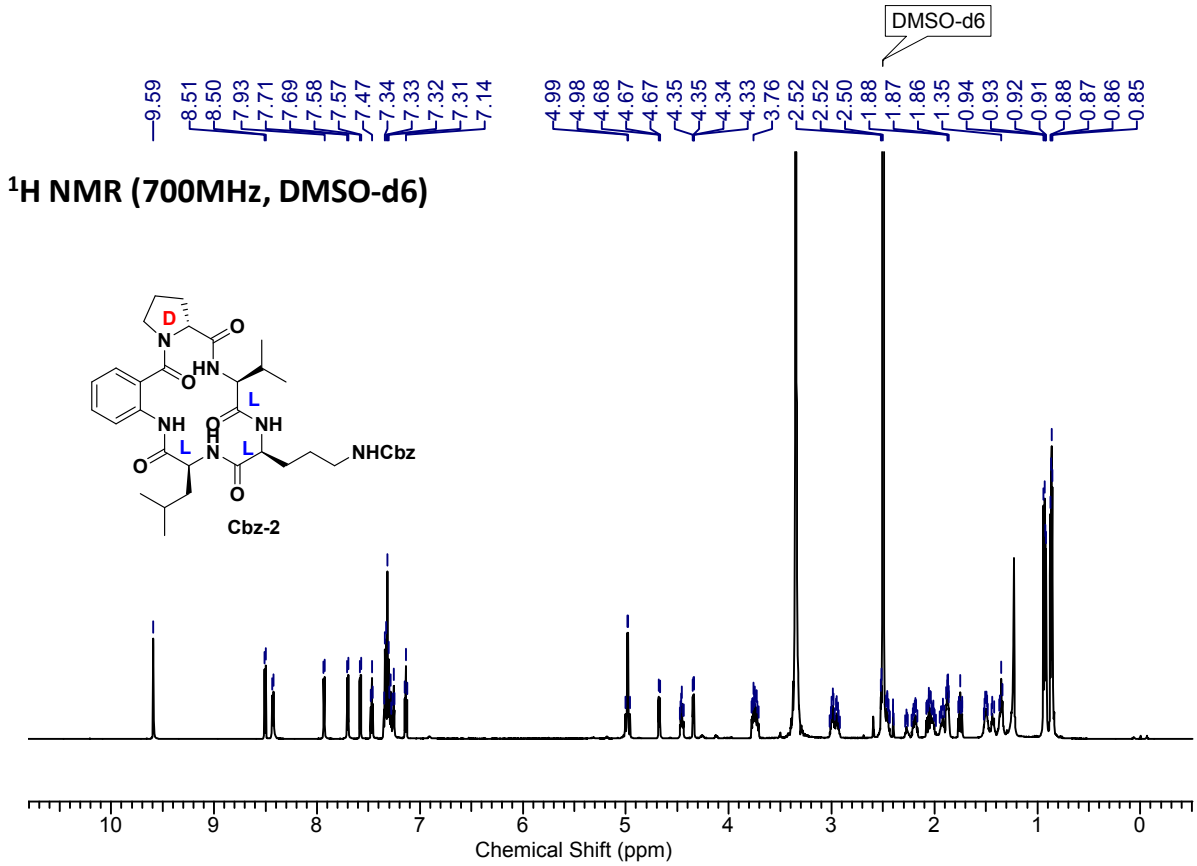
Procedure for Cbz deprotection and HCl salt formation of 1: The Cbz protecting groups in **Cbz-1** were successfully removed by hydrogenolysis in the presence of H_2, 10% Pd/C in a 0.02 M HCl/MeOH solution. After 12 h, reaction mixture was filtered through celite pad and then filtrate was evaporated under vacuum which resulted to a colorless solid; HRMS (ESI) $C_{72}H_{96}N_{12}O_{14}$ calculated $[M]^+$ 1084.6433 found 1084.6481, $C_{72}H_{97}N_{12}O_{14}$ calculated $[M+H]^+$ 1085.6433, found 1085.6553.



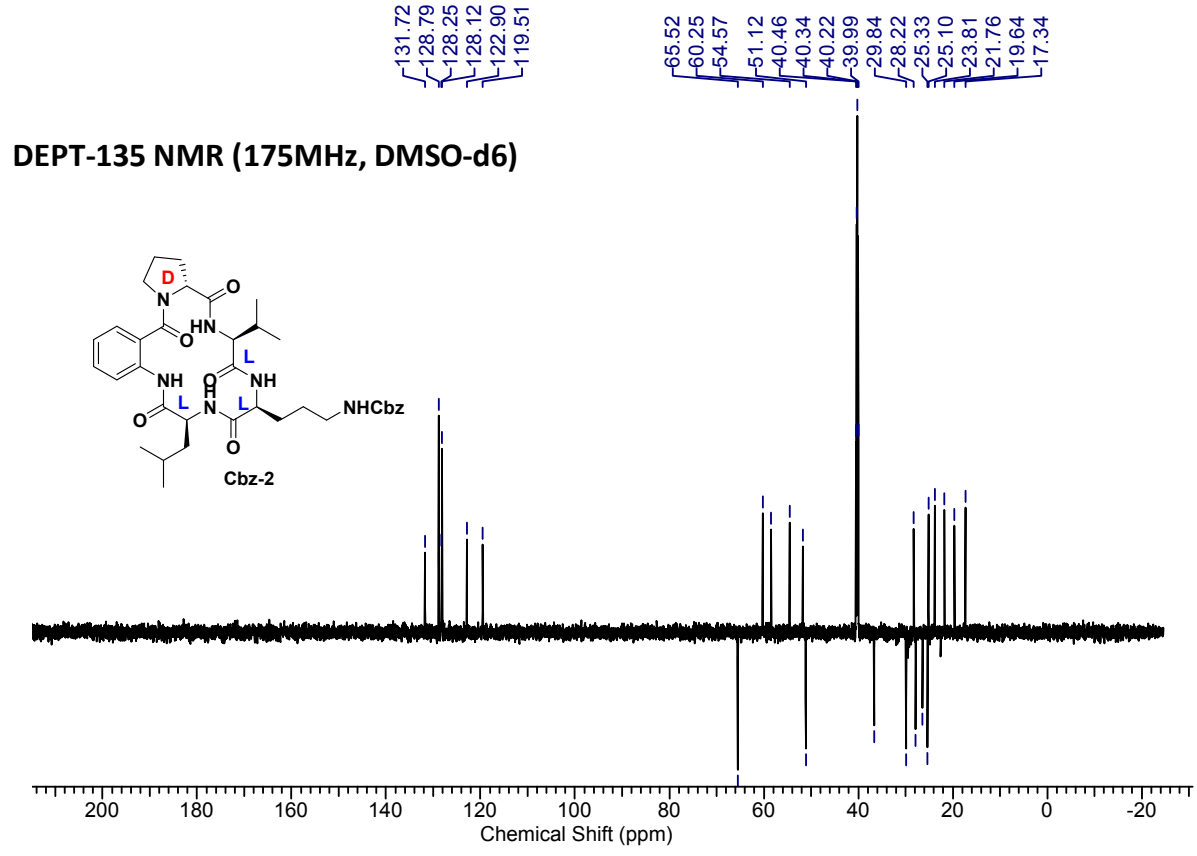
Compound 2 Cyclo-((z)^{L}Orni^{L}LeuAnt^{D}ProVal); Cyclic compound **2** was prepared using same synthetic procedure of **1**, which was purified by column chromatography (eluent 60% AcOEt/pet. Ether, R_f: 0.3) to furnish compound **2** (60%) as a white fluffy solid. Mp: 138-140°C; $[\alpha]^{25.64}_{D}$ – 162.6° (*c* =0.01, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3331, 2959, 2874, 2357, 1668, 1591, 1532, 1421, 763; ^{1}H NMR (700 MHz, DMSO-d_6) δ ppm 9.59 (s, 1H), 8.52 (d, *J* = 7.9 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 9.5 Hz, 1H), 7.58 (dd, *J* = 1.4, 7.6 Hz, 1H), 7.47 (dt, *J* = 1.1, 8.6 Hz, 1H), 7.36 - 7.27 (m, 3H), 7.26 (t, *J* = 5.7 Hz, 1H), 7.14 (dt, *J* = 1.1, 7.5 Hz, 1H), 4.91 (m, 2H), 4.67 (m, 1H), 4.46 (m, 2H), 4.34 (dd, *J* = 3.7 Hz, 8.4 Hz, 1H), 3.79 (m, 2H), 3.06 (m, 2H), 2.48 (m, 1H), 2.30 - 2.15 (m, 2H), 2.10 - 1.98 (m, 2H), 1.95 (m, 1H), 1.90 - 1.85 (m, 2H), 1.75 (m, 1H), 1.56 (m, 2H), 1.47 (m, 1H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (175MHz, DMSO-d_6) δ ppm 173.5, 170.8, 170.5, 169.8, 167.6, 156.1, 137.3, 136.9, 131.3, 128.3, 127.8, 127.7, 127.7, 122.5, 122.4, 119.1, 65.1, 59.9, 58.0, 54.1, 51.3, 50.7, 36.2, 29.4, 29.0, 27.8, 27.4, 25.9, 24.9, 23.3, 21.3, 19.2, 16.9; HRMS (ESI) $C_{36}H_{48}N_6O_7$ calculated $[M+H]^+$ 676.3584, found 676.3647, $C_{36}H_{48}N_6NaO_7$ calculated $[M+Na]^+$ 699.3482, found 699.3450.



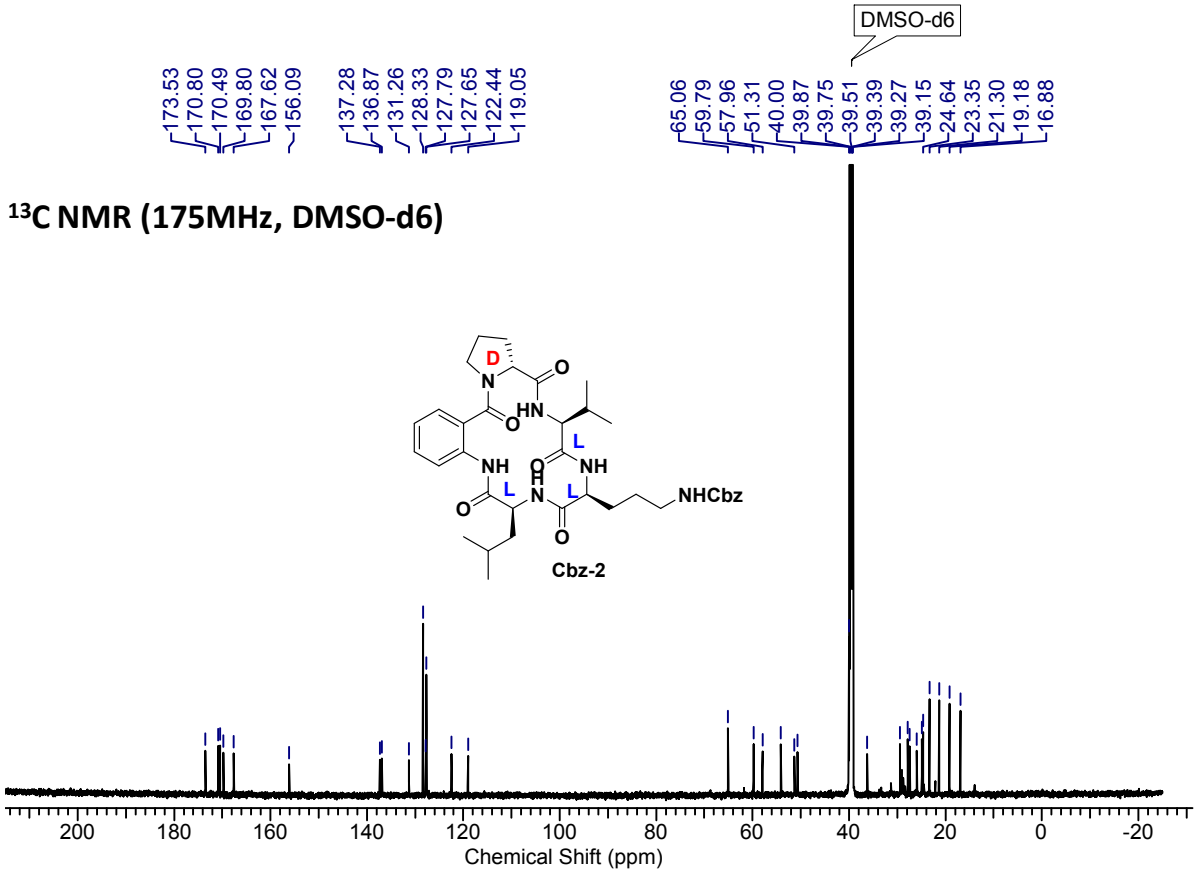
2

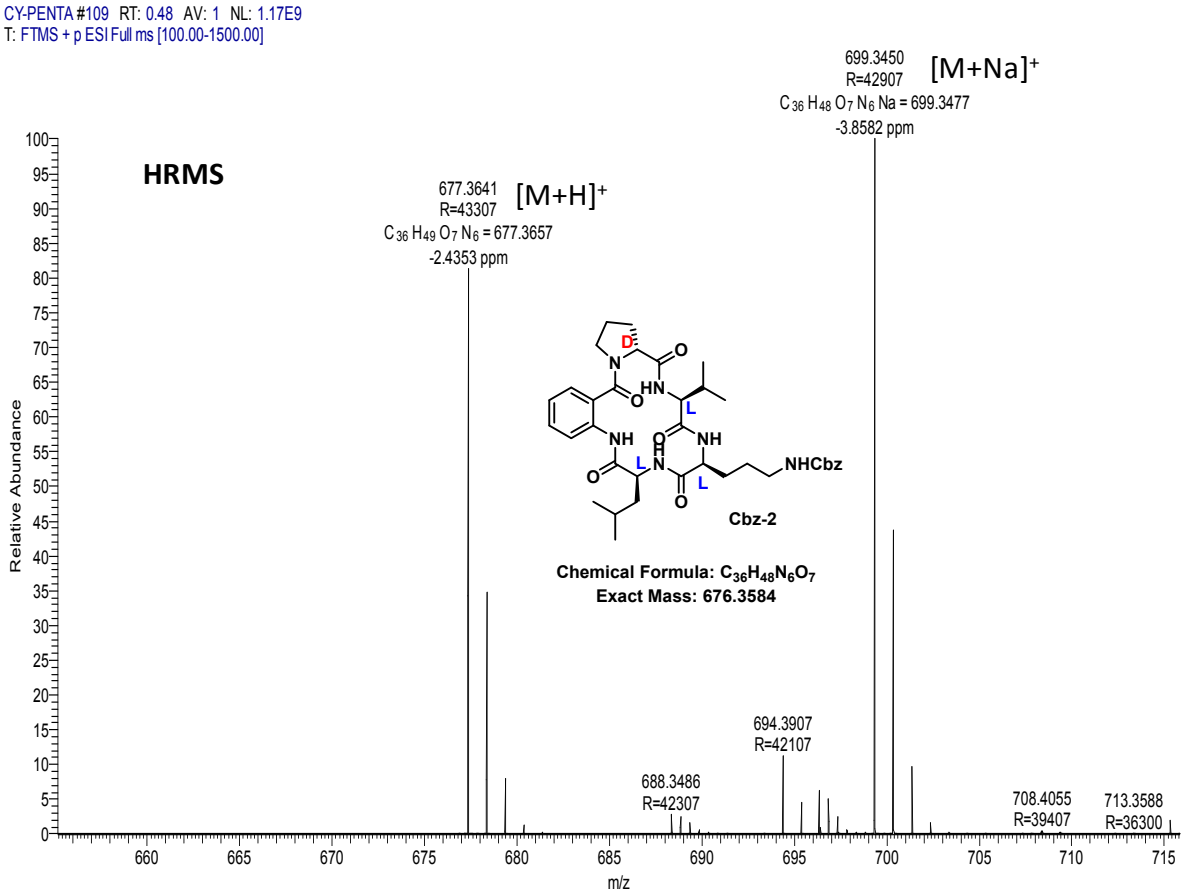


^{1}H NMR (700MHz, DMSO-d6)

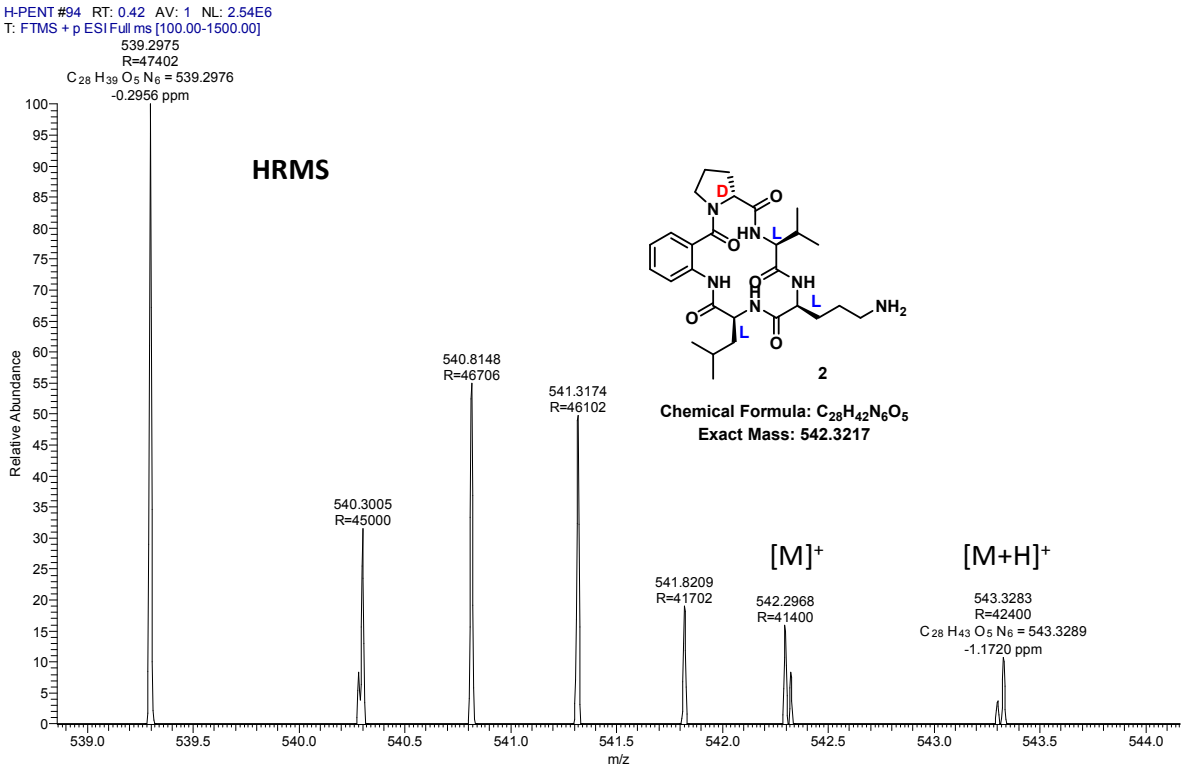


DEPT-135 NMR (175MHz, DMSO-d6)

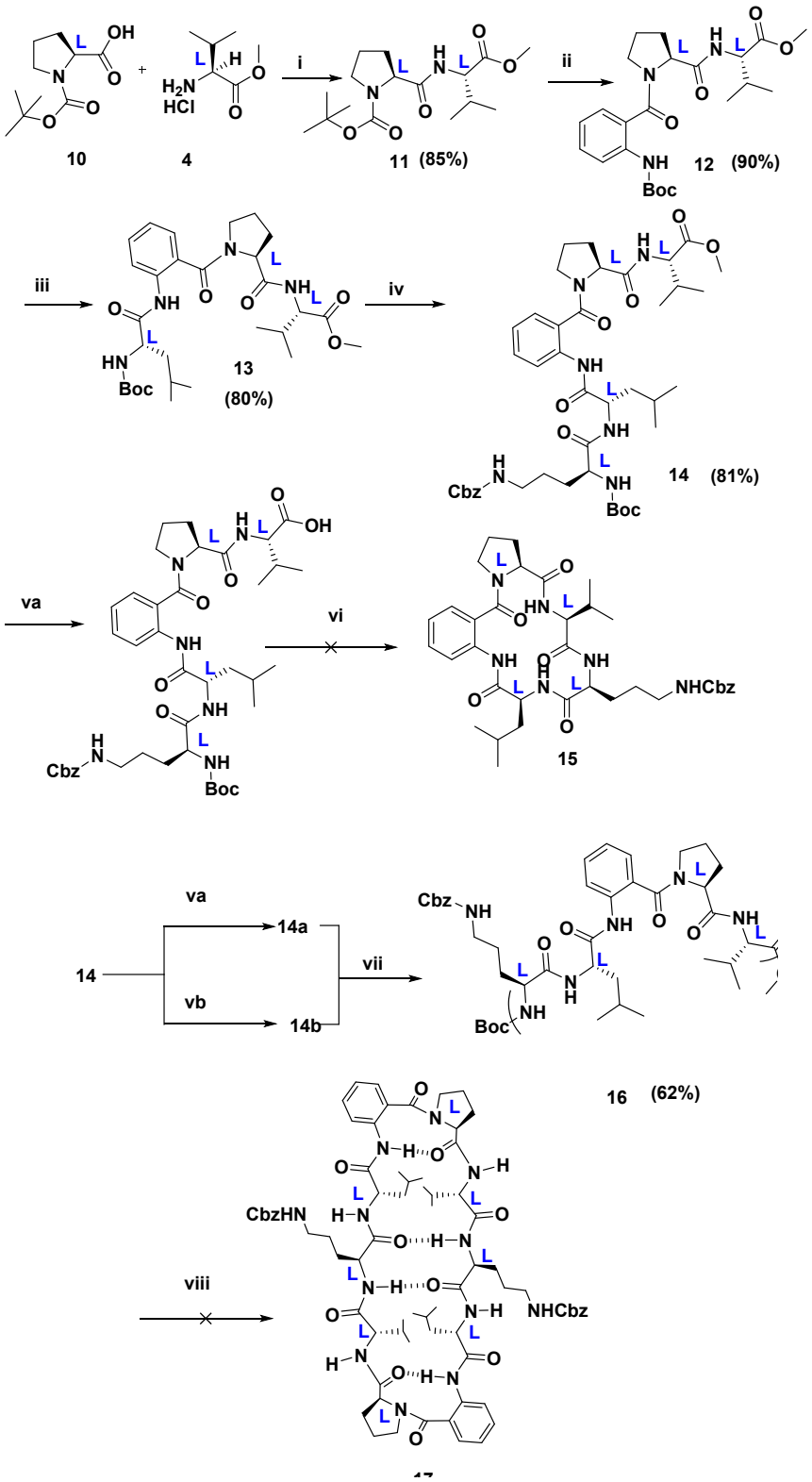

DMSO-d6
173.53
170.80
170.49
169.80
167.62
156.09
137.28
136.87
131.26
128.33
127.79
127.65
122.44
119.05
65.06
59.79
57.96
51.31
40.00
39.87
39.75
39.51
39.39
39.27
39.15
24.64
23.35
21.30
19.18
16.88
13C NMR (175MHz, DMSO-d6)
Cbz-2
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


CY-PENTA #109 RT: 0.48 AV: 1 NL: 1.17E9
T: FTMS + p ESI Full ms [100.00-1500.00]
HRMS
699.3450
R=42907
[M+Na]+
C36 H48 O7 N6 Na = 699.3477
-3.8582 ppm
677.3641
R=43307
[M+H]+
C36 H49 O7 N6 = 677.3657
-2.4353 ppm
Cbz-2
Chemical Formula: C36H48N6O7
Exact Mass: 676.3584
694.3907
R=42107
688.3486
R=42307
708.4055
R=39407
713.3588
R=36300
Relative Abundance
m/z

Cbz deprotection procedure and HCl salt formation of 2: Following the same procedure Cbz deprotection of **1,** compound **2** was deprotected and HCl salt of **2** was formed as a colorless solid; HRMS (ESI) $C_{28}H_{42}N_6O_5$ calculated $[M]^+$ 542.3217 found 542.2968, $C_{28}H_{43}N_6O_5$ calculated $[M+H]^+$ 542.3217, found 542.3283.



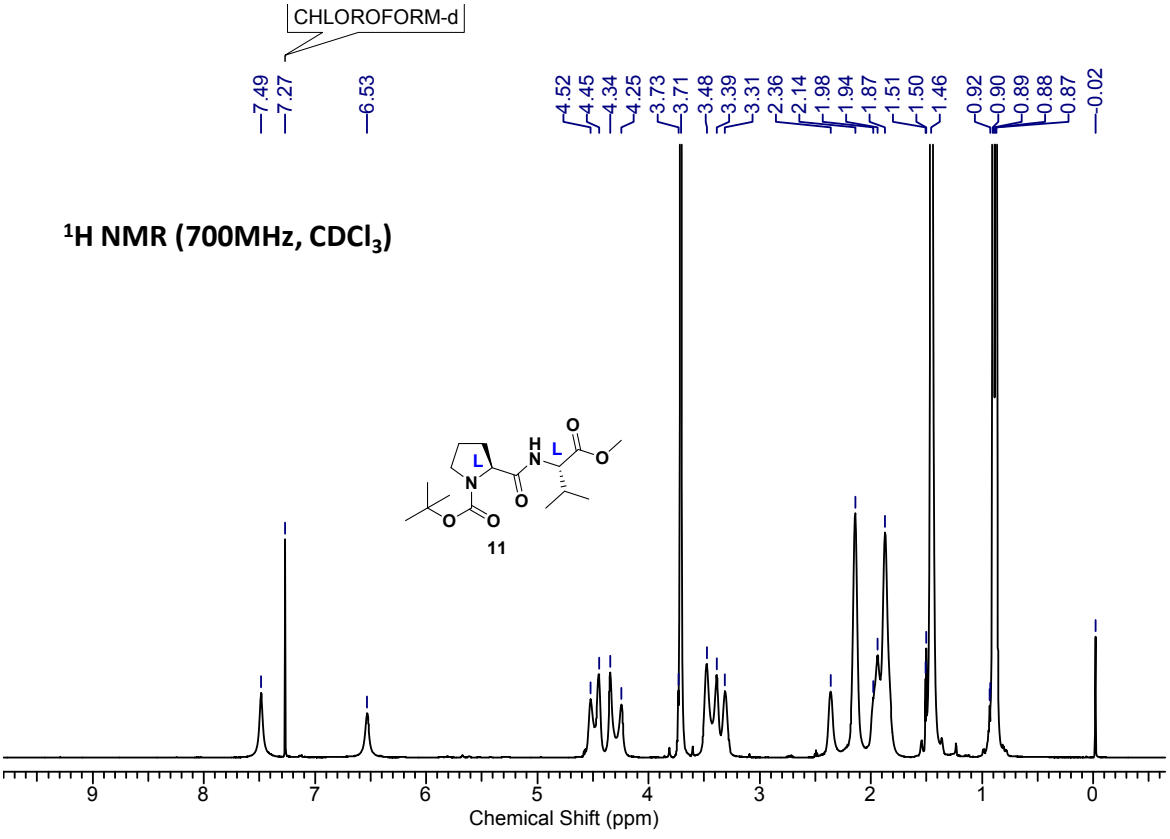
Scheme 2:

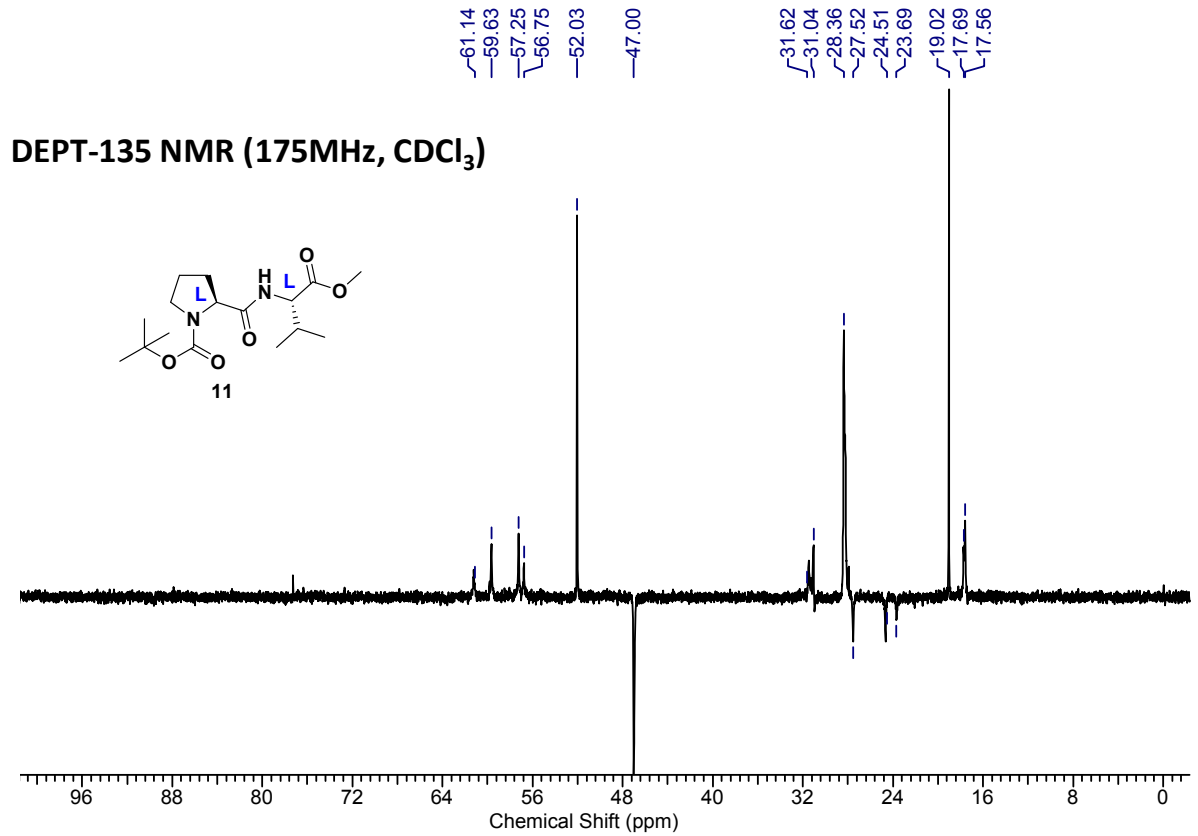


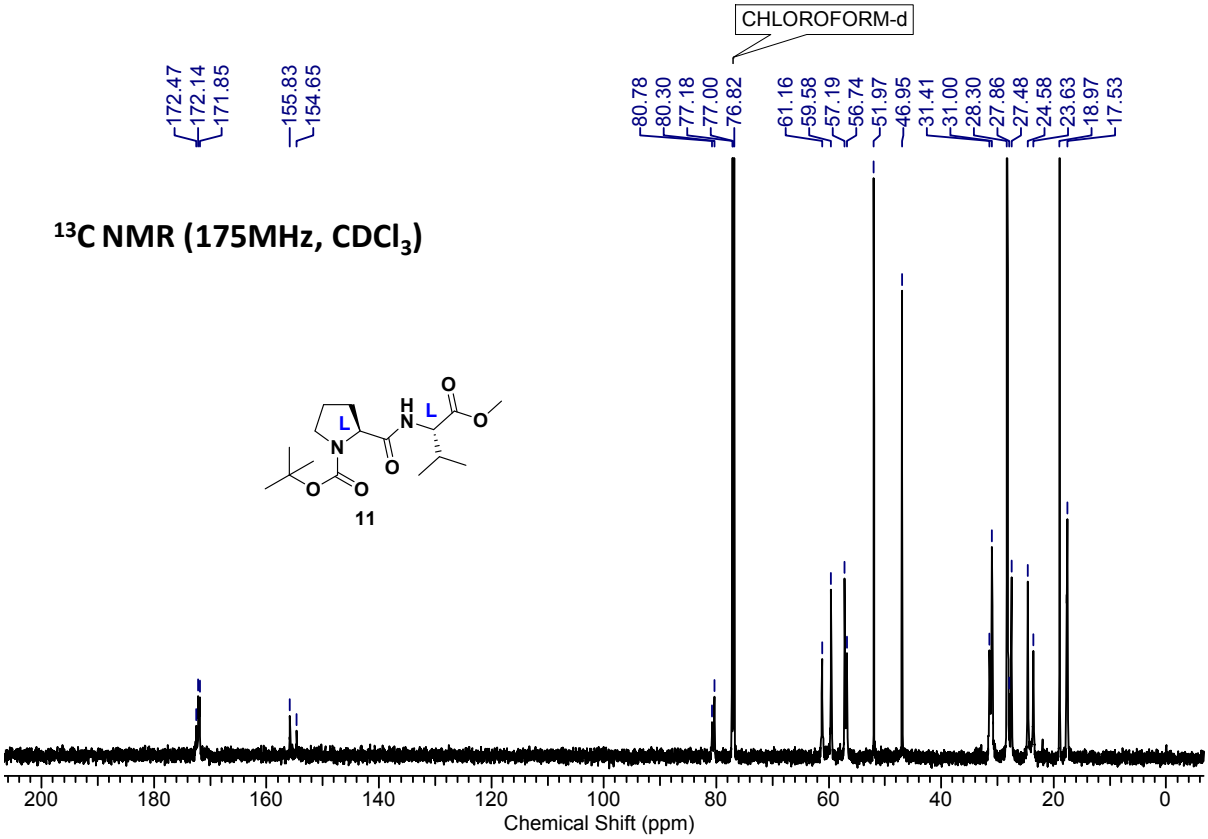
Reagents and Conditions: (i) EDC.HCl, DIEA, HOBt, DCM, RT, 8 h; (ii) a) TFA:DCM; b) Boc-Ant-OH, HBTU, DIEA, ACN, RT, 6h; (iii) a) TFA:DCM; b) Boc-Leu-OH, EDC.HCl, HOBt, DCM, RT, 8h; (iv) a) TFA:DCM; b) Boc-(Cbz)-Orn-OH, HBTU, DIEA, ACN, RT,

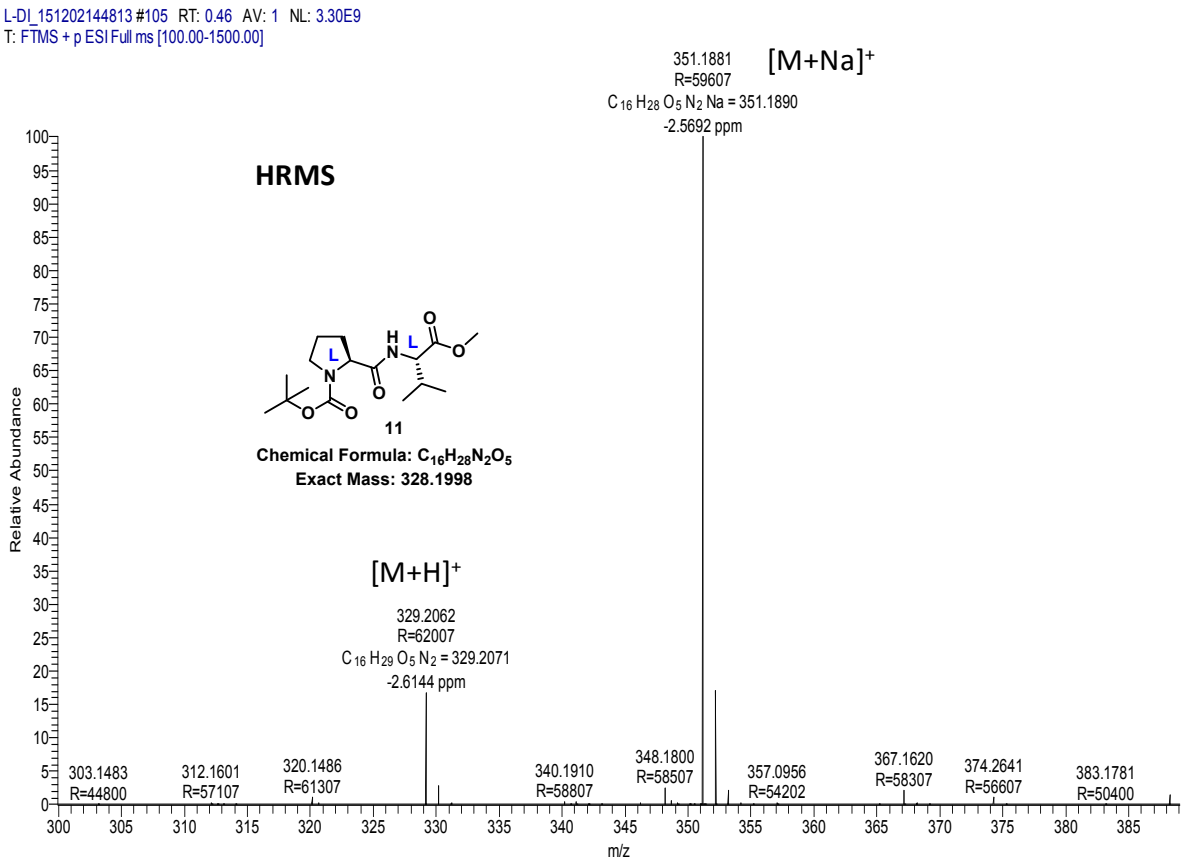
12h; (va) LiOH:H_2O; (vb) TFA:DCM; (vi) a) TFA:DCM; b) HBTU, DIEA, ACN, RT, 12h. (vii) HBTU, DIEA, ACN, RT, 12h, (vii) a) LiOH:H_2O b) TFA:DCM; b) HBTU, DIEA, ACN, RT, 12h.

Compound 11 (Boc-^{L}Pro^{L}Val-OMe): Following the same procedure for synthesis of **5**, compound **11** was synthesized. Purification was done by column chromatography (eluent 20% AcOEt/Pet. Ether, R_f: 0.3) afforded **11** (6.4 g, 85%) as a white fluffy solid material; Mp: 66-68°C $[\alpha]^{25.97}_{D}$: -85.09° (*c* = 0.09, $CHCl_3$; IR ($CHCl_3$) *v* (cm^{-1}): 3324, 2970, 2884, 2357, 1743, 1689, 1534, 1398, 1166, 761; ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm 7.49 (bs, rota. NH), 6.53 (bs, rota. NH), 4.60 (m, 1 H), 4.37 (m, 1 H), 3.71 (s, 3H), 3.52 - 3.24 (m, 2H), 2.36 (bs, rota. H), 2.14 (bs, rota. 2H), 2.02 - 1.75 (m, 3H), 1.46 (bs, 9H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm 172.5 (rota), 172.0, 172.1 (rota), 171.8, 155.8, 154.6 (rota), 80.8 (rota), 80.3, 61.2 (rota), 59.6, 57.2, 56.7 (rota), 52.0, 46.9 (rota),31.4 (rota), 31.2, 28.3, 27.5 (rota), 24.6, 23.6 (rota), 19.0, 17.6 (rota), 17.5. HRMS (ESI) $C_{16}H_{30}N_2O_5$ calculated $[M+H]^+$: 329.1998, found 329.2062, $C_{16}H_{28}N_2NaO_5$ calculated $[M+Na]^+$ 351.1896, found 351.1881.

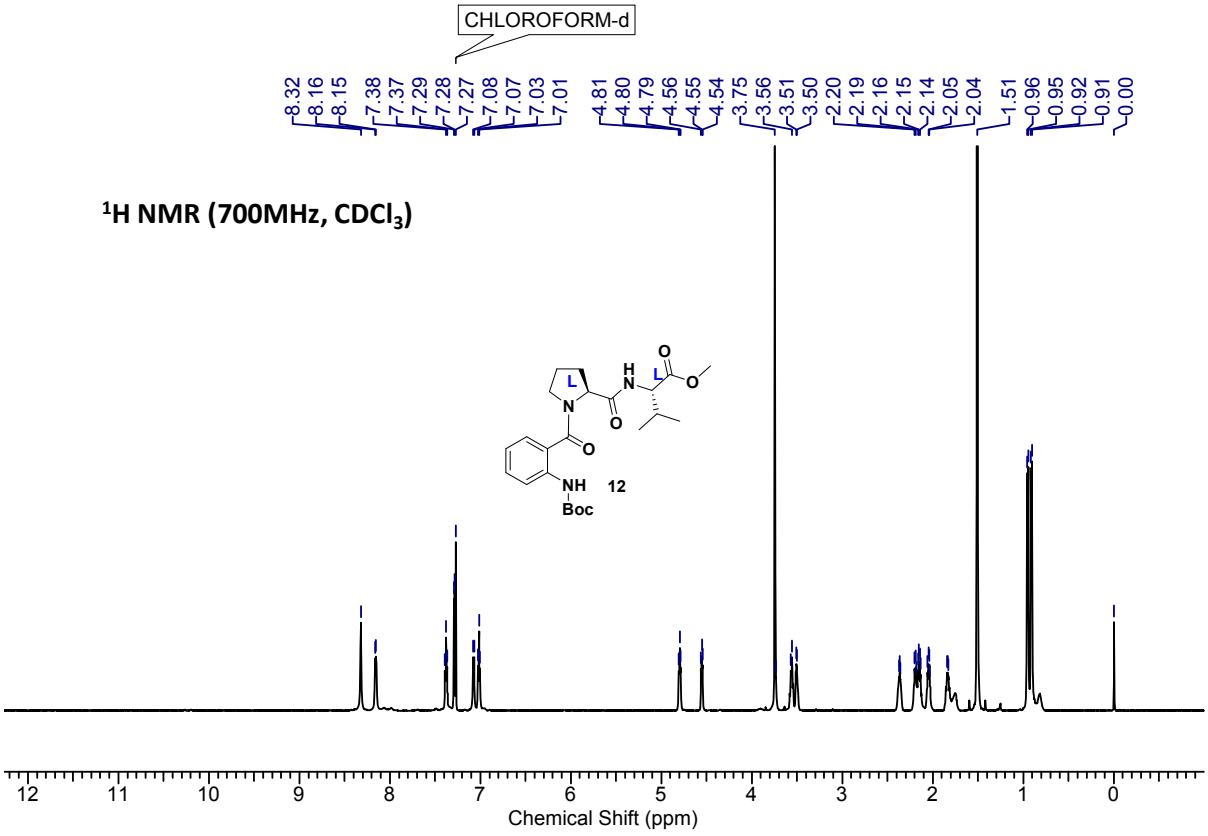



61.14
59.63
57.25
56.75
52.03
47.00
31.62
31.04
28.36
27.52
24.51
23.69
19.02
17.69
17.56
DEPT-135 NMR (175MHz, CDCl3)
11
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

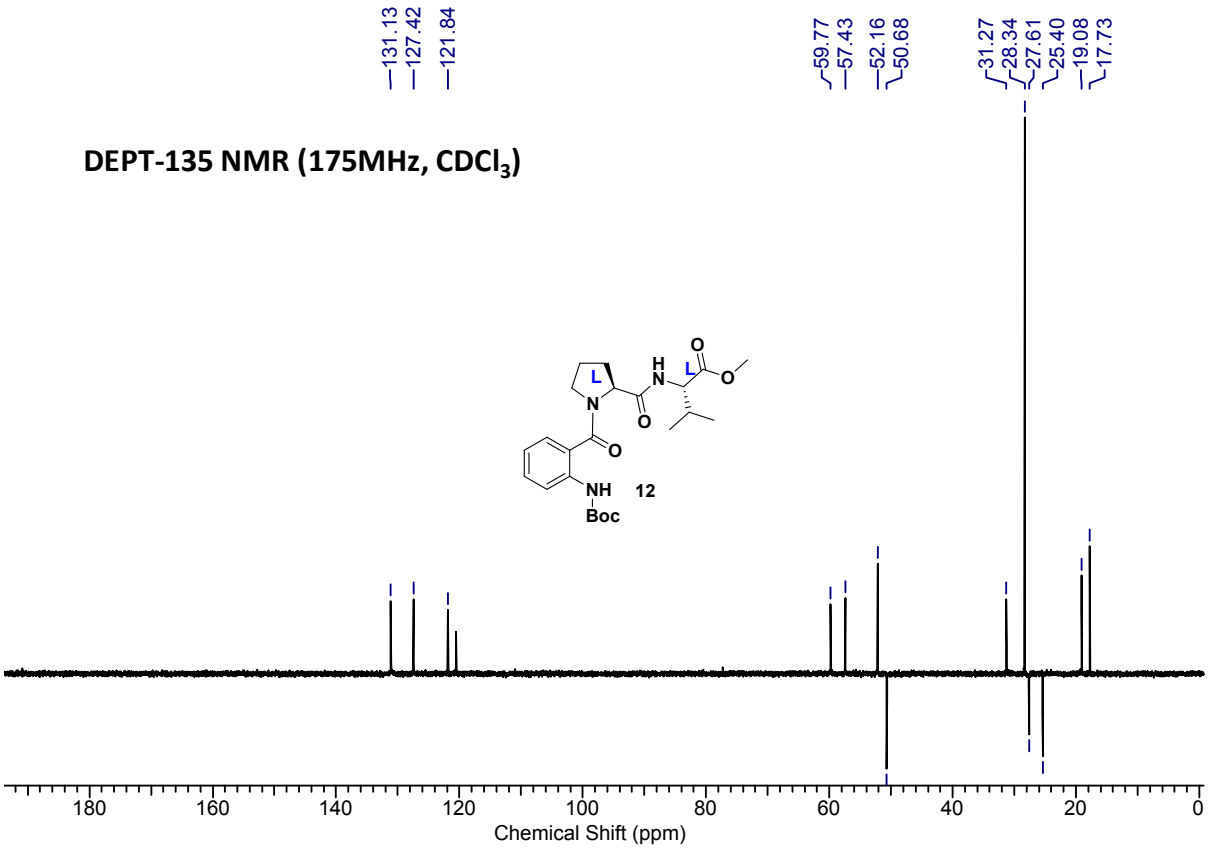

CHLOROFORM-d
172.47
172.14
171.85
155.83
154.65
80.78
80.30
77.18
77.00
76.82
61.16
59.58
57.19
56.74
51.97
46.95
31.41
31.00
28.30
27.86
27.48
24.58
23.63
18.97
17.53
13C NMR (175MHz, CDCl3)
11
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



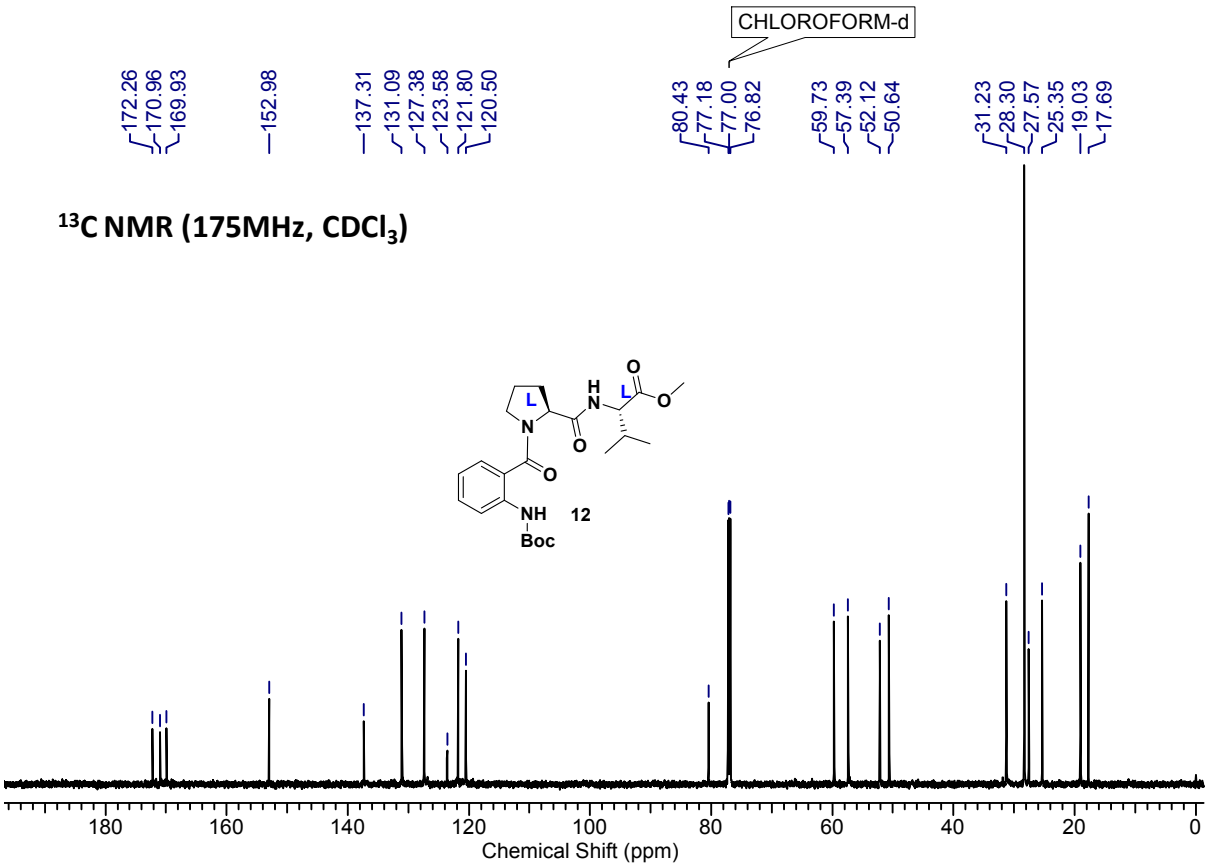
Compound 12 (Boc-Ant ^{L}Pro^{L}Val-OMe): Following the same synthetic procedure of **6**, compound **12** was synthesized and purification was done by column chromatography (eluent 15-20% AcOEt/Pet. Ether, R_f: 0.3) afforded **12** (3.5 g, 90%) as a white fluffy solid material; Mp: 110-112°C $[\alpha]^{25.95}_{D}$: -106.1° (*c* = 0.03, $CHCl_3$; IR ($CHCl_3$) *v* (cm^{-1}): 3331, 2971, 2888, 2357, 1820, 1728, 1675, 1623, 1595, 1160, 779; ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm: 8.32 (bs, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.3 Hz, 1 H), 4.80 (t, *J* = 6.6 Hz, 1 H), 4.55 (dd, *J* = 5.2, 7.7 Hz, 1 H), 3.75 (s, 3 H), 3.56 (m, 1H), 3.51 (m, 1H), 2.44 (m, 1H), 2.20 (m, 1H), 2.17 (m, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.51 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm 172.3, 171.0, 169.9, 153.0, 137.3, 131.1, 127.4, 123.6, 121.8, 120.5, 80.4, 59.7, 57.4, 52.1, 50.6, 31.2, 28.3, 27.6, 25.4, 19.0, 17.7; HRMS (ESI) $C_{23}H_{33}N_3O_6$ calculated $[M+H]^+$: 448.2369, found 448.2433, $C_{23}H_{33}N_3NaO_6$ calculated $[M+Na]^+$ 470.2267, found 470.2252.

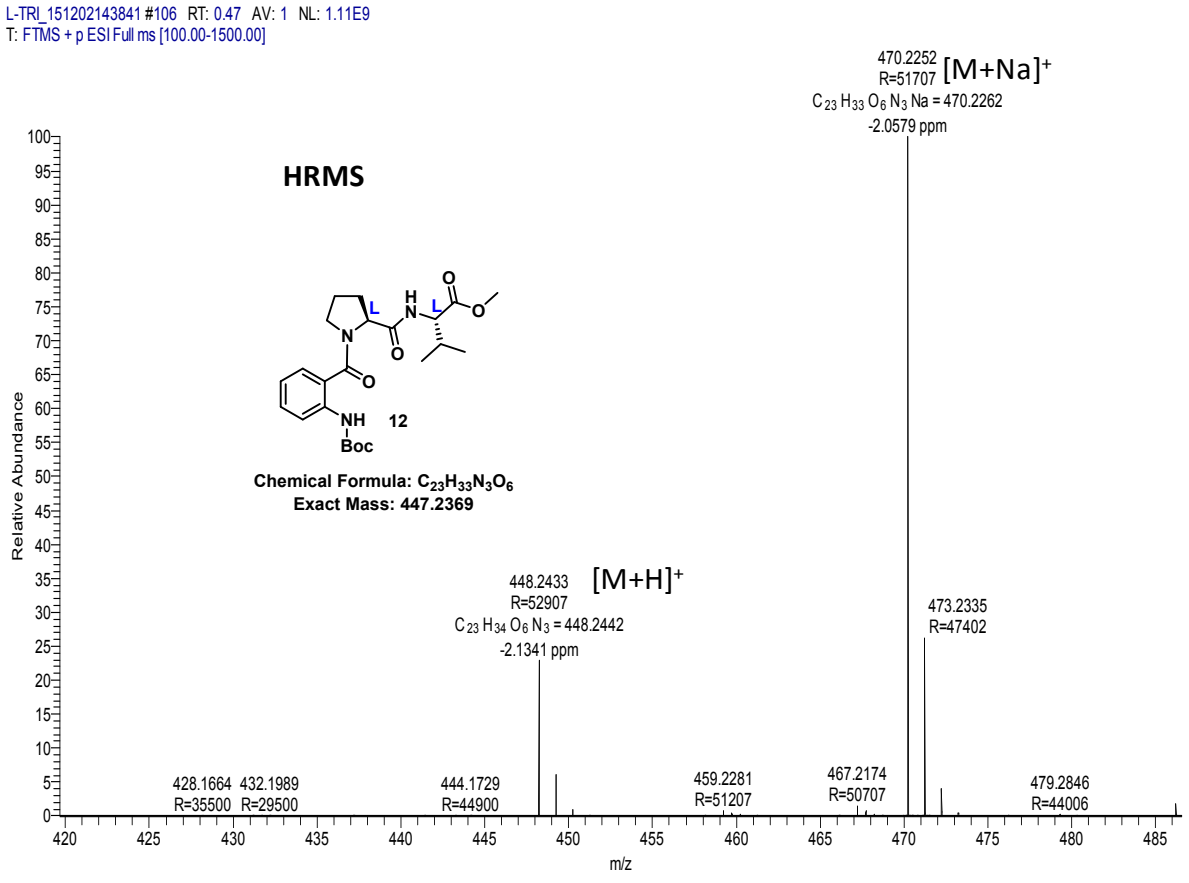


^{1}H NMR (700MHz, $CDCl_3$)

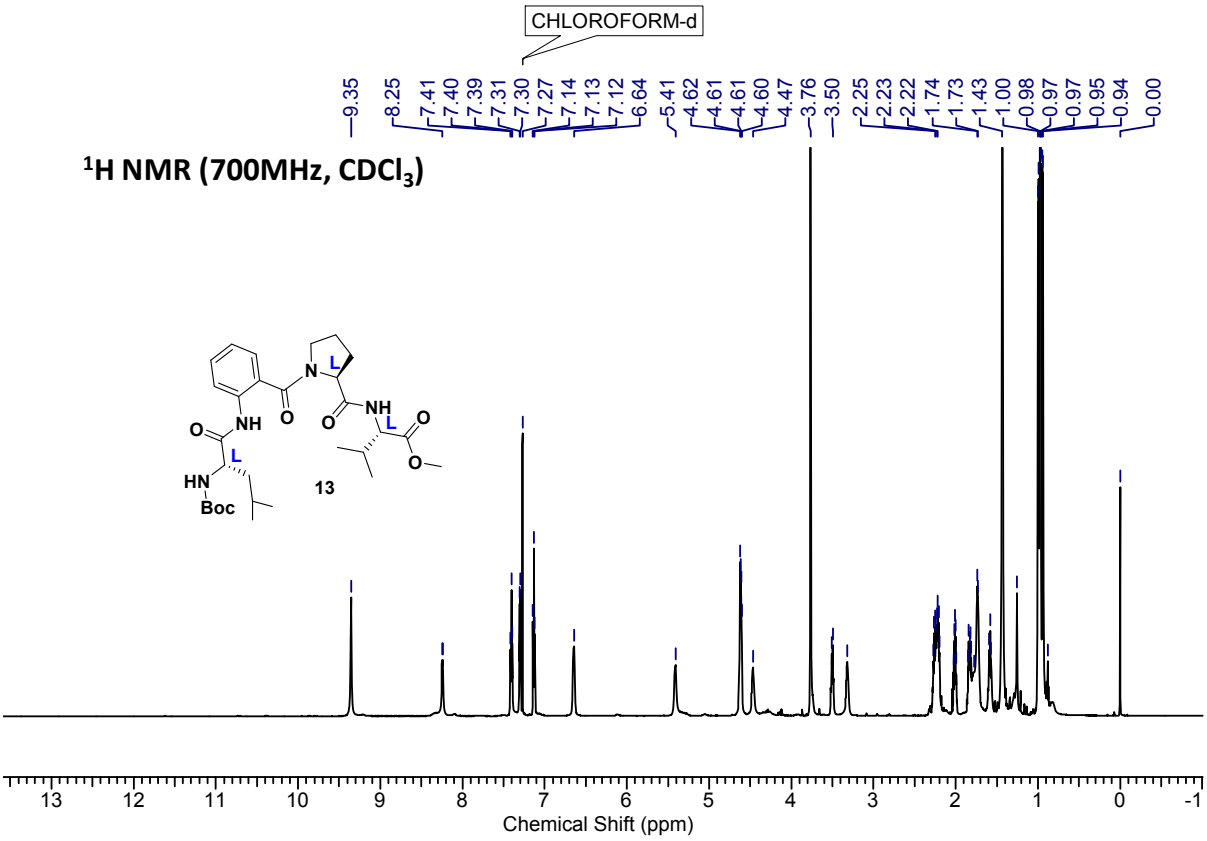


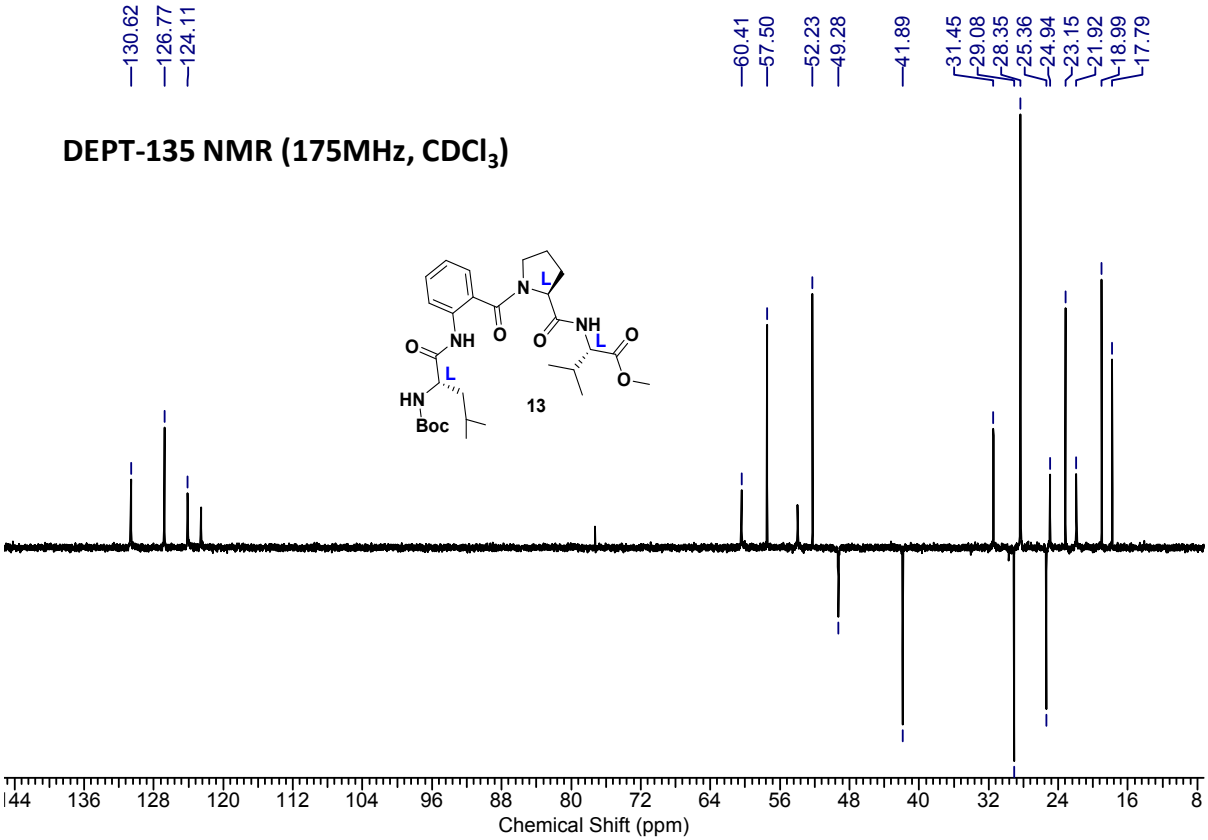
DEPT-135 NMR (175MHz, $CDCl_3$)

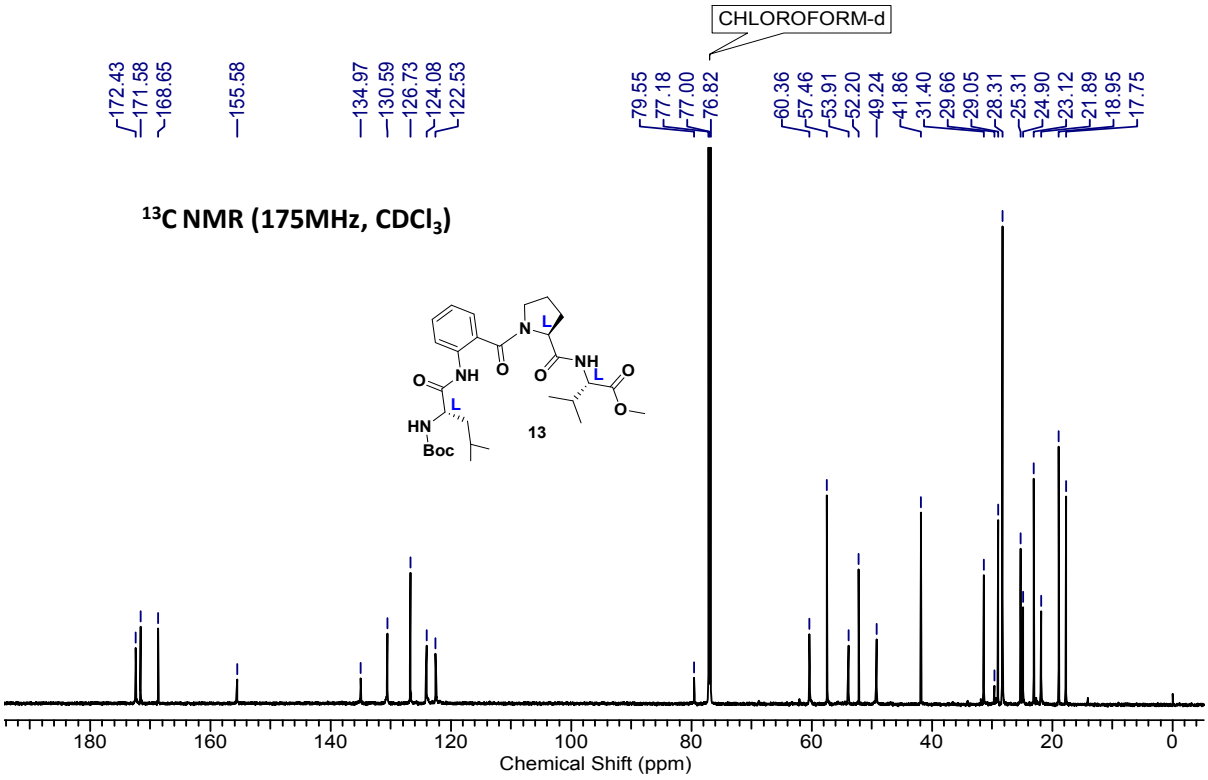

CHLOROFORM-d
172.26
170.96
169.93
152.98
137.31
131.09
127.38
123.58
121.80
120.50
80.43
77.18
77.00
76.82
59.73
57.39
52.12
50.64
31.23
28.30
27.57
25.35
19.03
17.69
13C NMR (175MHz, CDCl3)
NH
Boc
12
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

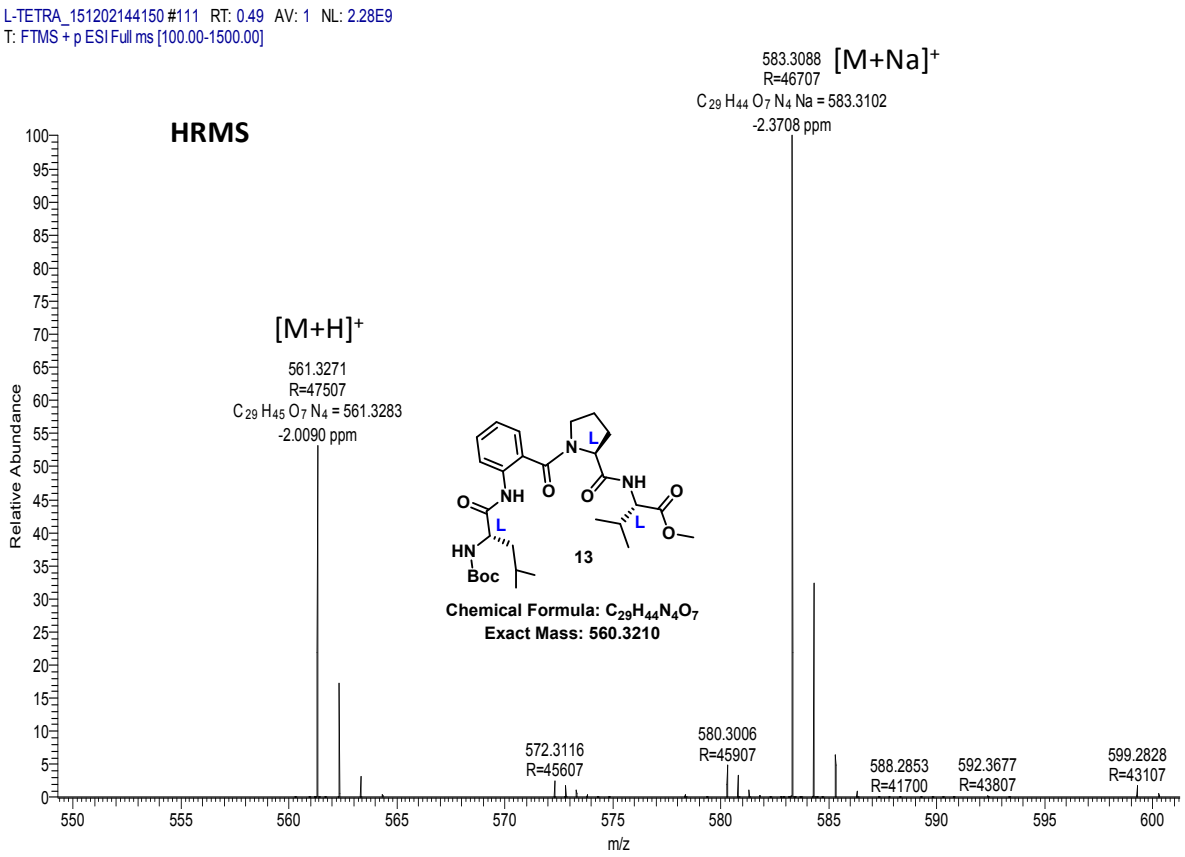

L-TRI_151202143841 #106 RT: 0.47 AV: 1 NL: 1.11E9
T: FTMS + p ESI Full ms [100.00-1500.00]
HRMS
470.2252
R=51707
[M+Na]+
C23 H33 O6 N3 Na = 470.2262
-2.0579 ppm
NH
Boc
12
Chemical Formula: C23H33N3O6
Exact Mass: 447.2369
448.2433
R=52907
[M+H]+
C23 H34 O6 N3 = 448.2442
-2.1341 ppm
473.2335
R=47402
428.1664
R=35500
432.1989
R=29500
444.1729
R=44900
459.2281
R=51207
467.2174
R=50707
479.2846
R=44006
Relative Abundance
m/z

Compound 13 (Boc ^{L}LeuAnt ^{L}Pro^{L}Val-OMe): Following the same synthetic procedure of **7**, compound **13** was synthesized. The crude product was purified by column chromatography (eluent 50% AcOEt/pet. Ether, R_f: 0.3) afforded **7** (1.03 g, 80%) as a white fluffy solid. Mp: 83-85°C; $[\alpha]^{25.87}_{D}$:-84.10° (*c* = 0.035, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3318, 2966, 2357, 1670, 1625, 1535, 1455, 1166, 760; ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm: 9.35 (bs, 1H), 8.24 (d, *J* = 7.1 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 4.5 Hz, 1H), 5.41 (bs, 1H), 4.67 (m, 2H), 4.47 (bs, 1H), 3.76 (s, 3H), 3.50 (m, 1H), 3.32 (m, 1H), 2.34 (m, 3H), 2.01 (m, 1H), 1.78 (m, 1H), 1.73 (m, 2H), 1.62 (m, 1H), 1.43 (s, 9H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.97 (dd, *J* = 5.8 Hz, 6H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (175MHz , $CDCl_3$) δ = 172.5, 172.4, 171.6, 168.6, 155.6, 135.0, 130.6, 126.7, 124.1, 122.5, 79.5, 60.4, 57.5, 53.9, 52.2, 49.2, 41.9, 31.4, 29.0, 28.3, 25.3, 24.9, 23.1, 21.9, 19.0, 17.7; HRMS (ESI) $C_{29}H_{45}N_4O_7$ calculated $[M+H]^+$: 561.3210, found 561.3271, $C_{29}H_{44}N_4NaO_7$ calculated $[M+Na]^+$ 583.3108, found 583.3088.

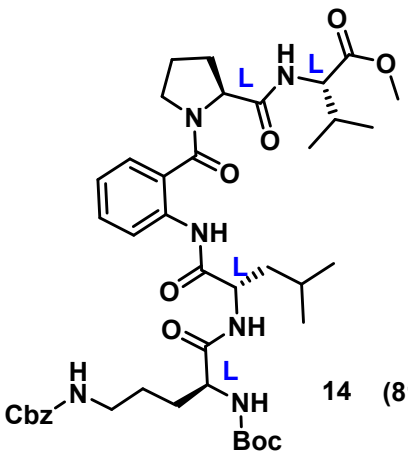



130.62
126.77
124.11
60.41
57.50
52.23
49.28
41.89
31.45
29.08
28.35
25.36
24.94
23.15
21.92
18.99
17.79
DEPT-135 NMR (175MHz, CDCl3)
13
Chemical Shift (ppm)


CHLOROFORM-d
172.43
171.58
168.65
155.58
134.97
130.59
126.73
124.08
122.53
79.55
77.18
77.00
76.82
60.36
57.46
53.91
52.20
49.24
41.86
31.40
29.66
29.05
28.31
25.31
24.90
23.12
21.89
18.95
17.75
13C NMR (175MHz, CDCl3)
13
Chemical Shift (ppm)

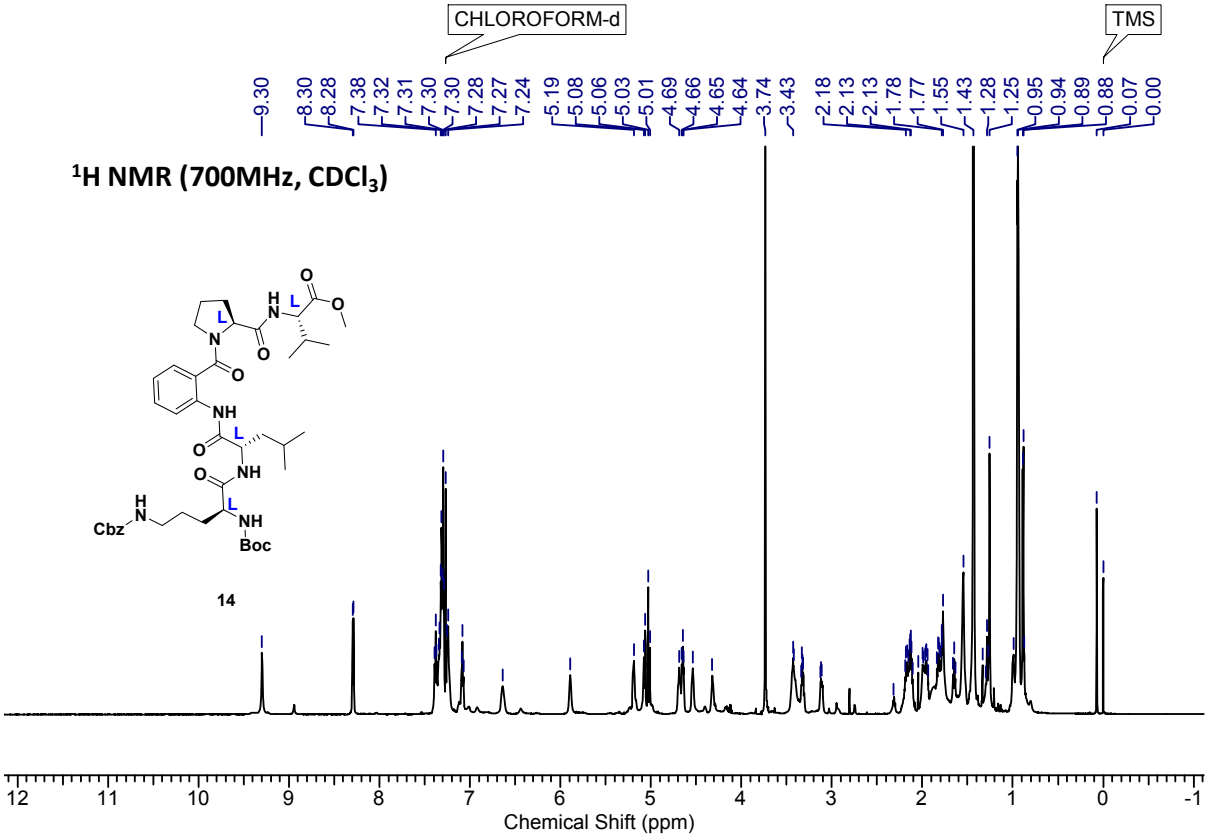


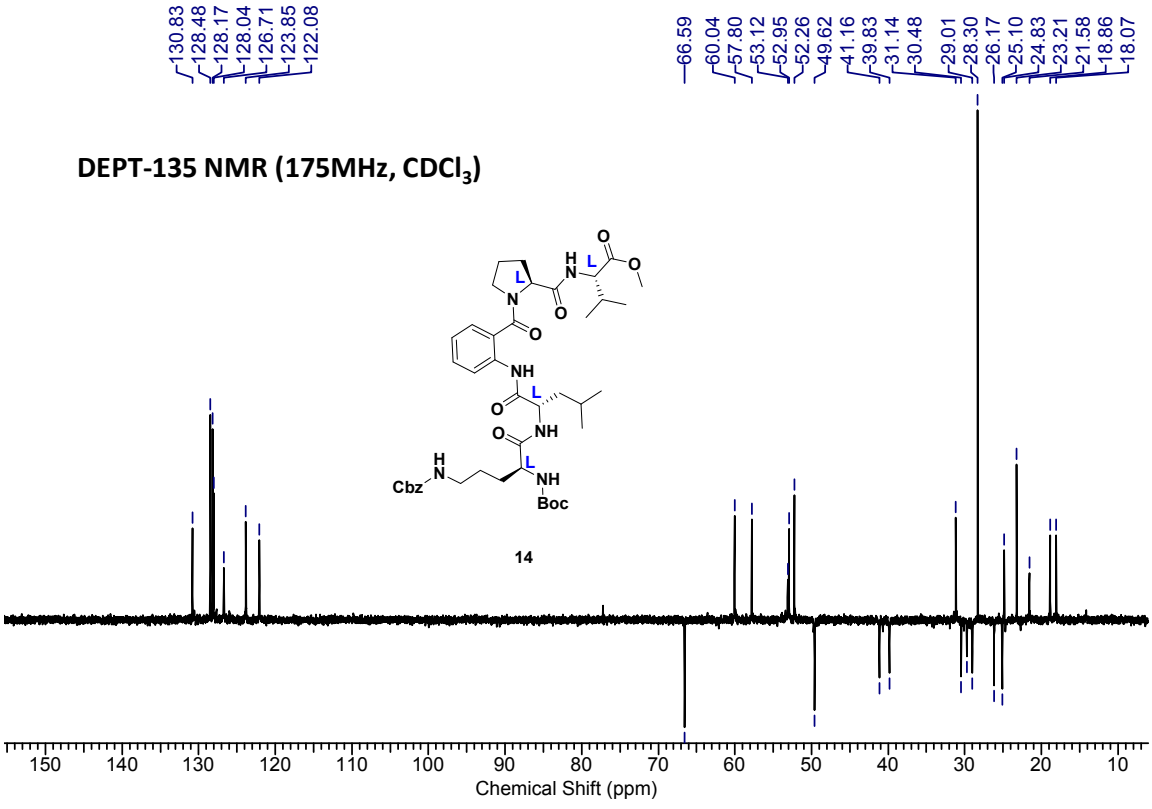
Compound 14 Boc-(z)^{L}Orni^{L}LeuAnt^{L}ProVal-OMe: (Penta-peptide): Following the same synthetic procedure of **8**, compound **14** was synthesized. The crude product was purified by column chromatography (eluent 60% AcOEt/Pet. Ether, R_f: 0.3) afforded **14** (0.71g, 81%) as a white fluffy hygroscopic solid. Mp: 74-78°C; $[\alpha]^{25.87}_{D}$:-52.26° (*c* = 0.03, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 3334, 3019, 2408, 1675, 1217, 763; ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm 9.30 (bs, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.36 - 7.27 (m, 6H), 7.25 (m, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.64 (bs, 1H), 5.89 (bs, 1H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 5.04 - 5.00 (m, 1H), 4.69 (bs, 1H), 4.65 (t, *J* = 6.7 Hz, 1H), 4.54 (bs, 1H), 4.32 (bs, 1H), 3.74 (s, 3H), 3.43 (m, 2H), 3.36 (m, 1H), 3.18 (m, 1H), 2.2 (m, 3H), 2.0 (m, 2H), 1.95 (m, 2H), 1.85 (m, 4H), 1.65 (m, 1H), 1.43 (s, 9H), 0.94 (m, 9H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (175MHz, $CDCl_3$) δ ppm 172.6, 172.5, 171.7, 171.5, 168.9, 157.2, 155.6, 136.7, 135.1, 130.8, 128.4, 128.1, 128.0, 126.7, 125.8, 123.8, 122.0, 79.6, 66.5, 60.0,

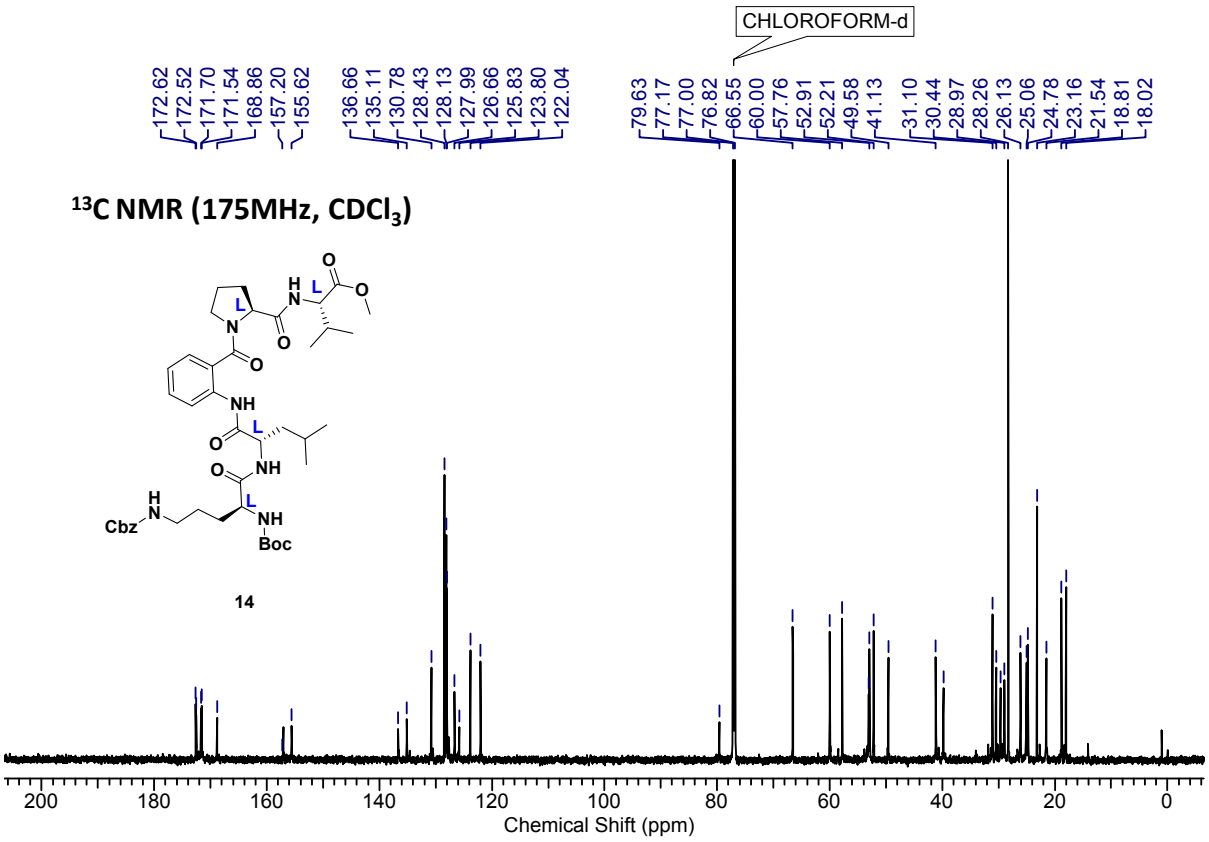


14 (81%)

57.8, 53.1, 52.9, 52.2, 49.6, 41.1, 39.8, 31.1, 30.4, 29.0, 28.3, 26.1, 25.1, 24.8, 23.2, 21.5, 18.8, 18.0; HRMS (ESI) C42H60N6O10 calculated $[M+H]^+$: 809.4371, found 809.4432, C42H60N6NaO10 calculated $[M+Na]^+$ 831.4269, found 831.4244.







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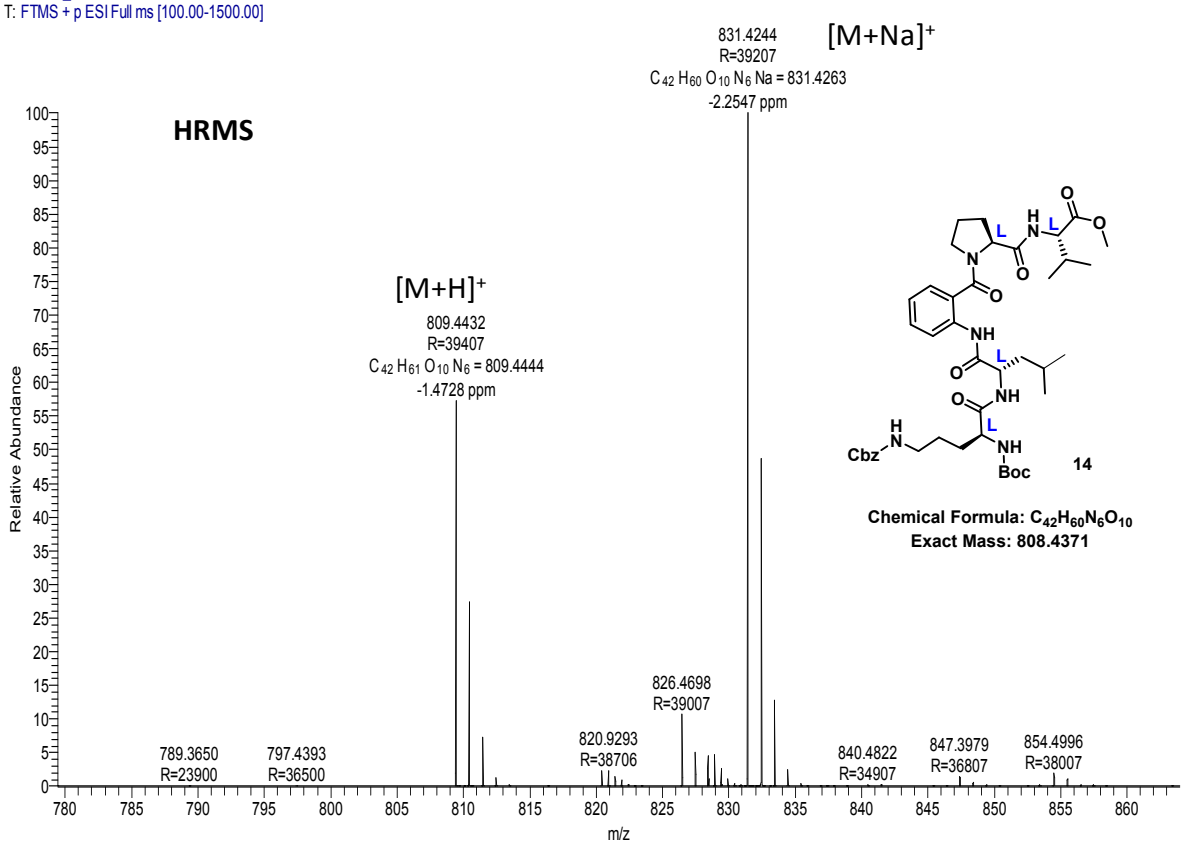
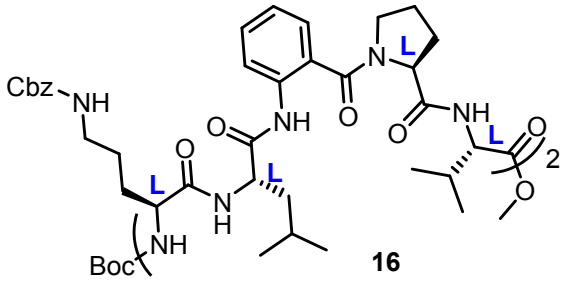
T: FTMS + p ESI Full ms [100.00-1500.00]

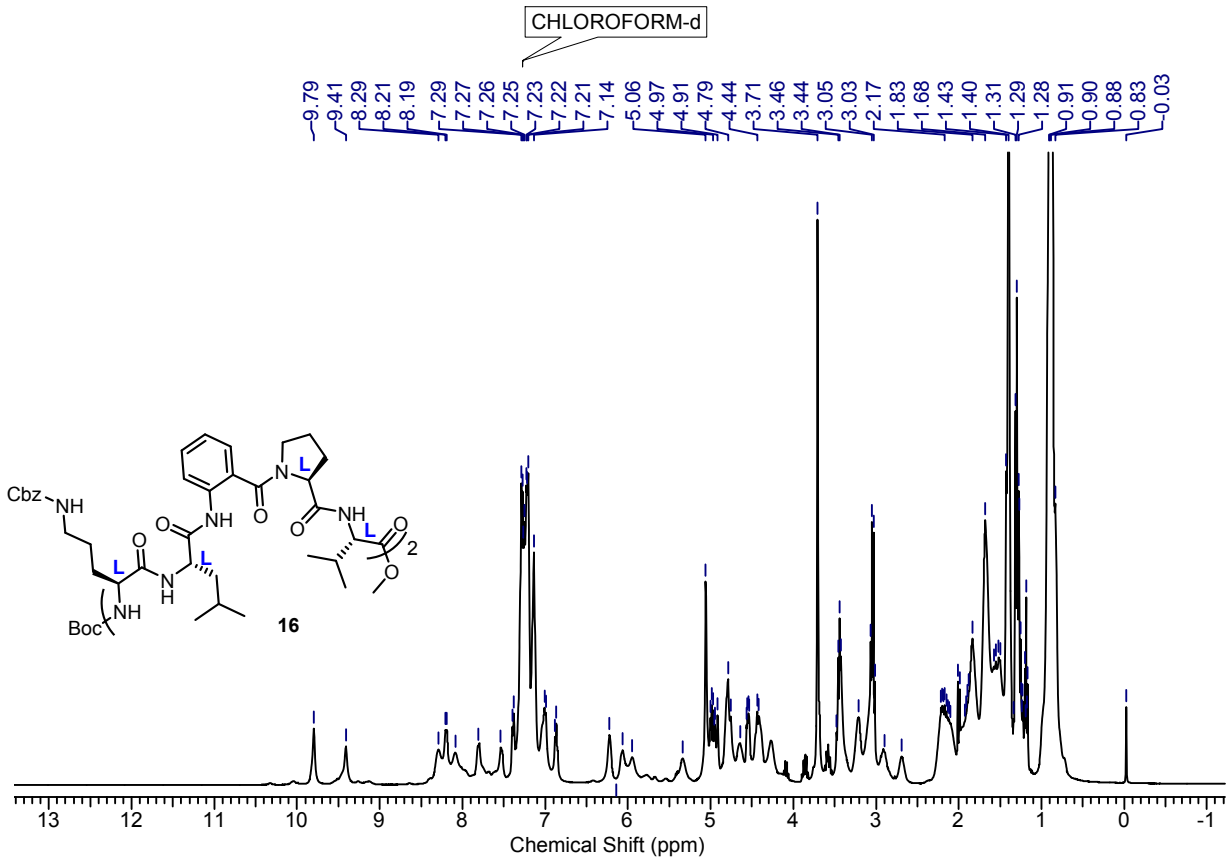


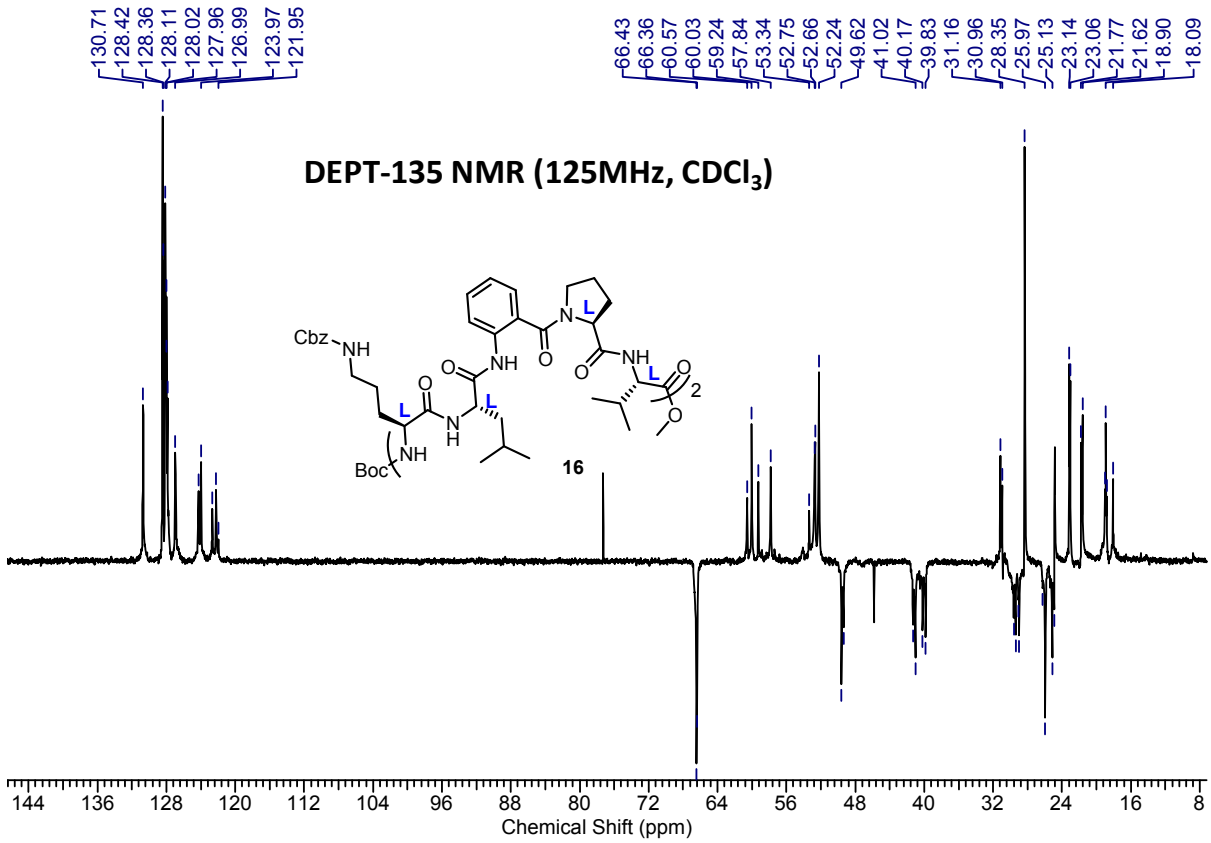
Compound 14a Boc-(z)^{L}Orni^{L}LeuAnt^{L}ProVal-OH: Following the same hydrolysis procedure of **8**, compound **14** was hydrolyzed to **14a (**Boc-(z)^{L}Orni^{L}LeuAnt^{L}ProVal-OH or Boc-Penta-OH).

Attempts for synthesis of cyclic compound 15: Initially, synthesis of cyclic compound **15** was attempted using same synthetic procedure of **2**, but reaction did not give the desired product **15**. Later, this reaction was tried using various coupling reagents but none of the reaction offered the cyclic compound **15.**

Compound 16 Boc-((z)^{L}Orni^{L}LeuAnt^{L}ProVal)$_2$-OMe (Deca-peptide): Following the same synthetic procedure of **9**, compound **16** was synthesized. The crude product was purified by column chromatography (eluent: 70% AcOEt/pet. Ether, R_f: 0.3) to furnish **16** (0.57 g, 62%) as a white fluffy solid. Mp: 128-130°C; $[\alpha]^{26}{}_{D}$: -755° (*c* = 0.014, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3324, 3021, 2969, 1674, 1519, 1422, 1217, 1039, 766, 670; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 9.82 (bs, 1H), 9.44 (bs, 1H), 8.39 (bs, 1H), 8.17 (d, *J* = 6.9 Hz, 1H), 7.84 (d. *J* = 5.9 Hz, 1H), 7.56 (bs, 1H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.31 (m., 3H), 7.29 (m, 7H), 7.16 (m., 3H), 7.03 (m, 2H), 6.96 (t, *J* = 6.9 Hz, 1H), 6.25 (bs, 1H), 6.09 (bs, 1H), 5.42 (m, 1H), 5.09 (m, 2H), 5.04 (m, 2H), 4.87 (m, 3H), 4.67 (m, 1H), 4.58 (dd, *J* = 4.4, 8.6 Hz, 1H), 4.45 (m, 2 H), 4.30 (m, 1H), 3.74 (s, 3H), 3.67 (m, 1H), 3.54 (m, 2H), 3.24 (m, 1H), 2.94 (m, 2H), 2.81 (m, 2H), 2.35 (m, 4H), 2.0 (m, 1H), 1.95 (m, 5H), 1.7(m, 4H) 1.64 (m, 6H), 1.43 (bs, 9H), 1.08 (m, 24H); ^{13}C NMR (125MHz , $CDCl_3$) δ ppm 172.6, 172.5, 171.9, 171.7, 171.6, 171.4, 171.3, 168.8, 168.8, 156.9, 156.9, 155.7, 136.8, 136.7, 135.1, 134.5, 130.6, 128.3, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 126.9, 126.8, 126.6, 126.1, 122.6, 122.1, 79.9, 66.4, 66.3, 60.5, 60.0, 57.8, 53.3, 52.7, 52.6, 52.2, 52.1, 49.6, 49.3, 45.8, 41.2, 40.1, 39.8, 31.1, 30.9, 30.8, 29.5, 29.3, 28.9, 28.3, 28.2, 25.9, 25.1, 24.8, 24.8, 23.1, 23.0, 21.7, 21.6, 18.9, 18.8, 18.7, 18.0; HRMS (ESI) $C_{78}H_{108}N_{12}O_{17}$ calculated $[M+H]^+$: 1485.7955, found 1485.8011.




CHLOROFORM-d
9.79
9.41
8.29
8.21
8.19
7.29
7.27
7.26
7.25
7.23
7.22
7.21
7.14
5.06
4.97
4.91
4.79
4.44
3.71
3.46
3.44
3.05
3.03
2.17
1.83
1.68
1.43
1.40
1.31
1.29
1.28
0.91
0.90
0.88
0.83
0.03
Cbz
NH
Boc
16
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)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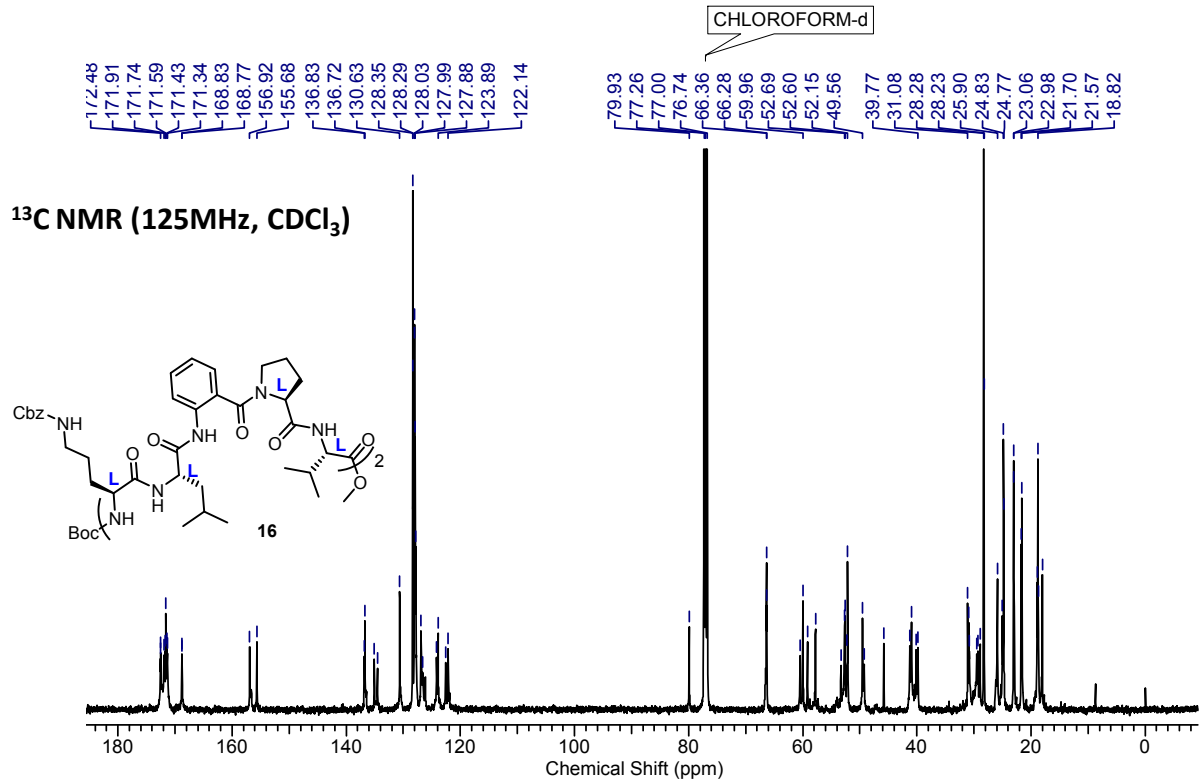
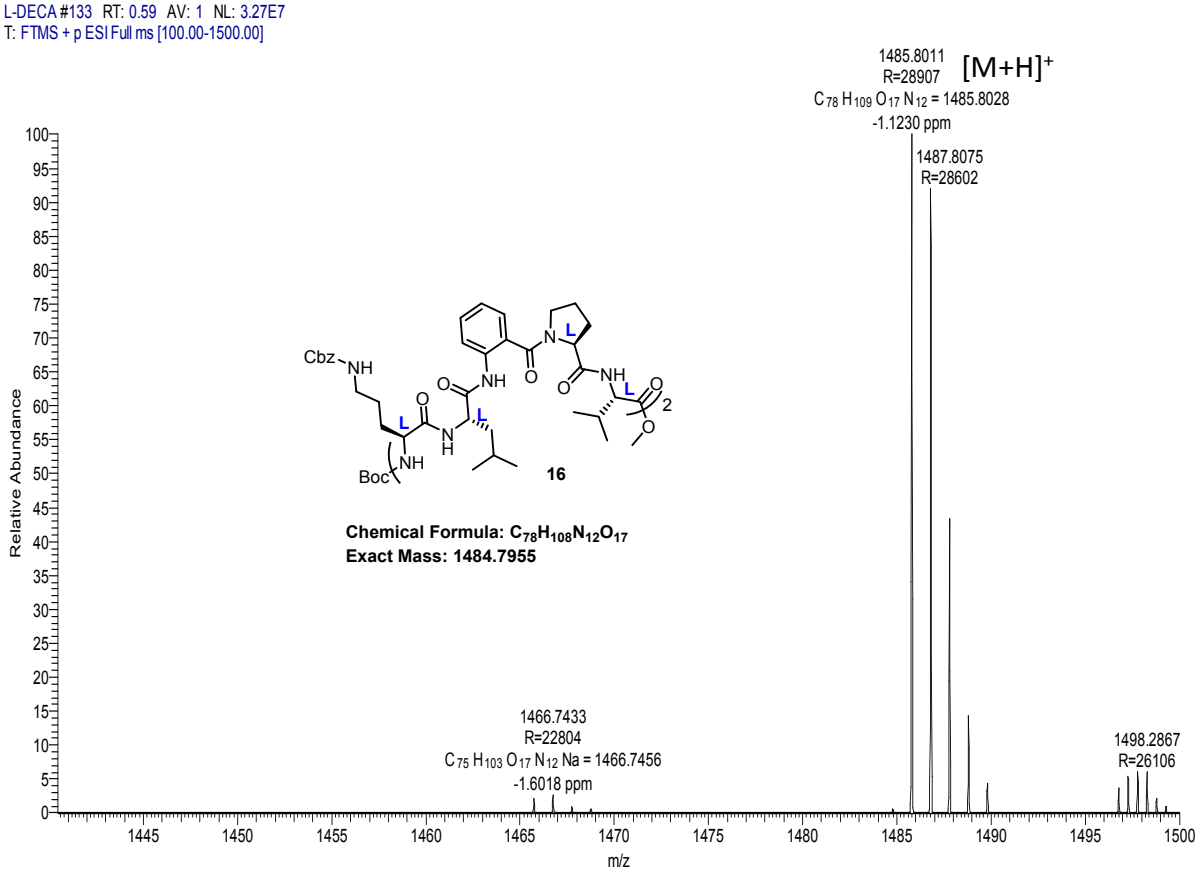
128.42
128.36
128.11
128.02
127.96
126.99
123.97
121.95
66.43
66.36
60.57
60.03
59.24
57.84
53.34
52.75
52.66
52.24
49.62
41.02
40.17
39.83
31.16
30.96
28.35
25.97
25.13
23.14
23.06
21.77
21.62
18.90
18.09
DEPT-135 NMR (125MHz, CDCl3)
Cbz
NH
Boc
16
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)





Attempt to synthesis of cyclic compound 17: Using the same synthetic procedure of **1**, for synthesis of compound **17** was attempted; but reaction did not give the desired cyclic product **17.**

Variable temperature studies

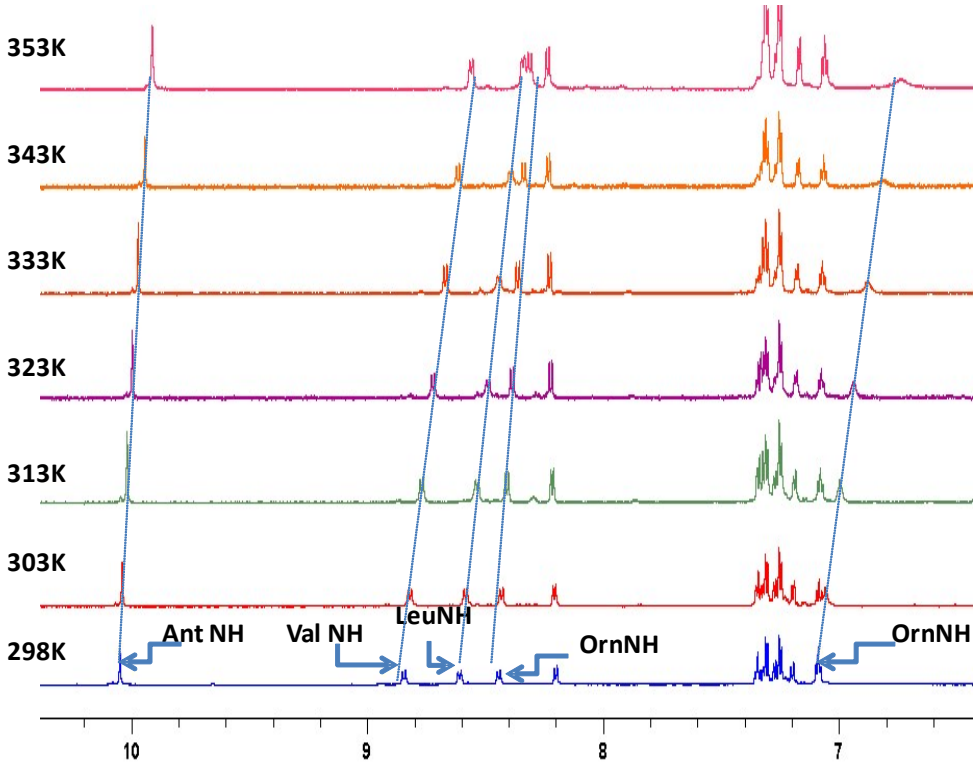
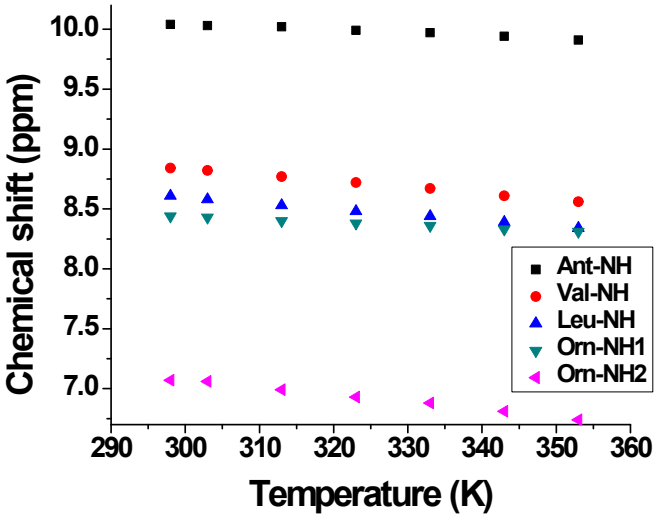
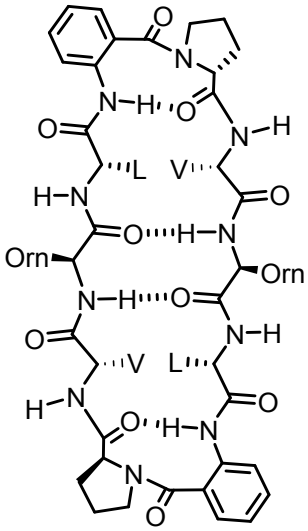


Figure S1. Stacked partial ^{1}H NMR spectra of **1** (2 mM, 700 MHz) in DMSO-d_6 at different temperatures.

Table S1a: Temperature variable study of **1** (2 mM, 700 MHz) in DMSO-d_6.

Temperature (in K)	**Chemical shift (in ppm)**				
	$\delta_{Ant\text{-}NH}$	$\delta_{Val\text{-}NH}$	$\delta_{Leu\text{-}NH}$	$\delta_{Orn\text{-}NH1}$	$\delta_{Orn\text{-}NH2}$
298	10.04	8.84	8.61	8.44	7.07
303	10.03	8.82	8.58	8.43	7.06
313	10.02	8.77	8.53	8.4	6.99
323	9.99	8.72	8.48	8.38	6.93
333	9.97	8.67	8.44	8.36	6.88
343	9.94	8.61	8.39	8.33	6.81
353	9.91	8.56	8.34	8.31	6.74





Cbz-1

Table S1b: Temperature coefficient for each NH of **1**

NH of **1**	Temperature Coefficient in ppb/K
Ant-NH	**-2.36**
Val-NH	**-5.09**
Leu-NH	**-4.9**
Orn-NH	**-2.31**
Orn-NH	**-6.0**

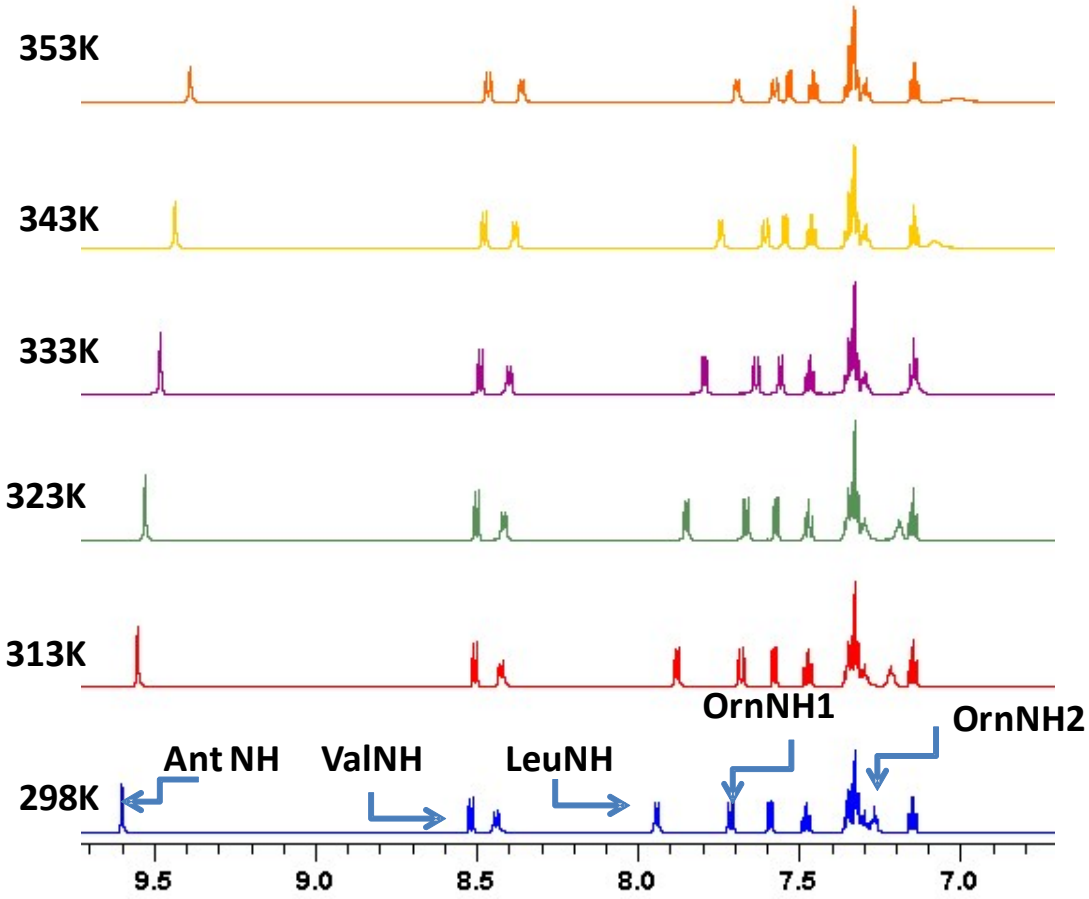


Figure S2. Stacked plot of partial ^{1}H NMR spectra of **2** (5 mM, 700 MHz) in DMSO-d_6 at different temperatures.

Table S2a: Temperature variation study of **2** (5 mM, 700 MHz) in DMSO-d_6

Temperature (K)	Chemical shift (in ppm)				
	$\delta_{Ant\text{-}NH}$	$\delta_{Val\text{-}NH}$	$\delta_{Leu\text{-}NH}$	$\delta_{Orn\text{-}NH1}$	$\delta_{Orn\text{-}NH2}$
298	9.59	8.43	7.93	7.71	7.26
303	9.57	8.43	7.91	7.69	7.24
308	9.54	8.42	7.87	7.67	7.21
313	9.52	8.41	7.84	7.66	7.18
323	9.47	8.39	7.79	7.63	7.12
333	9.43	8.37	7.73	7.6	7.07
343	9.38	8.35	7.69	7.57	7
353	9.34	8.33	7.64	7.54	6.93

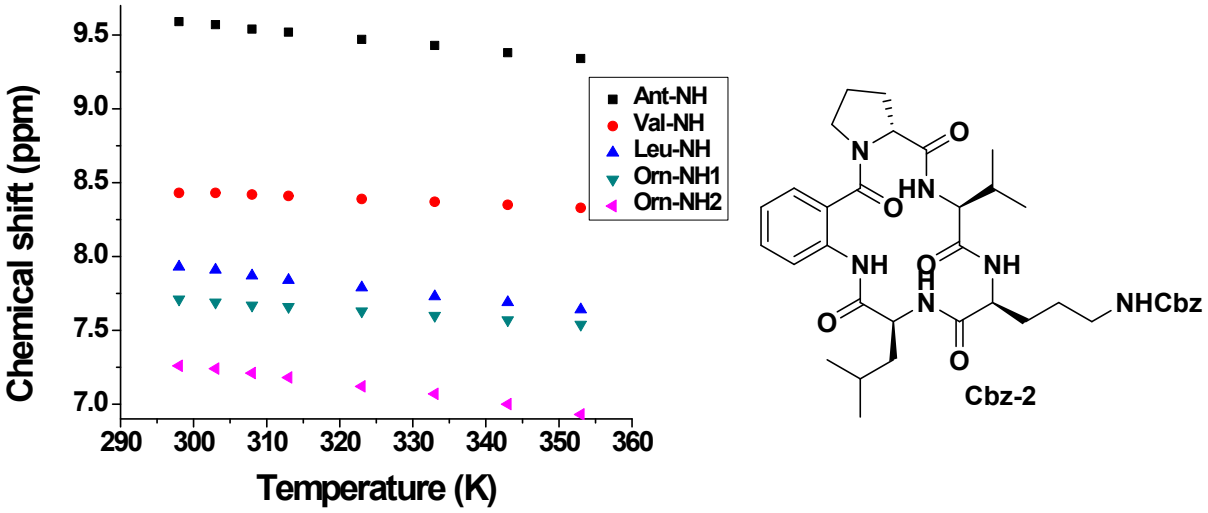


Table S2b: Temperature coefficient for each NH of **2**

NH of 2	Temperature Coefficient in ppb/K
Ant-NH	**-4.36**
Val-NH	**-1.81**
Leu-NH	**-5.27**
Orn-NH	**-3.09**
Orn-δNH2	**-6.0**

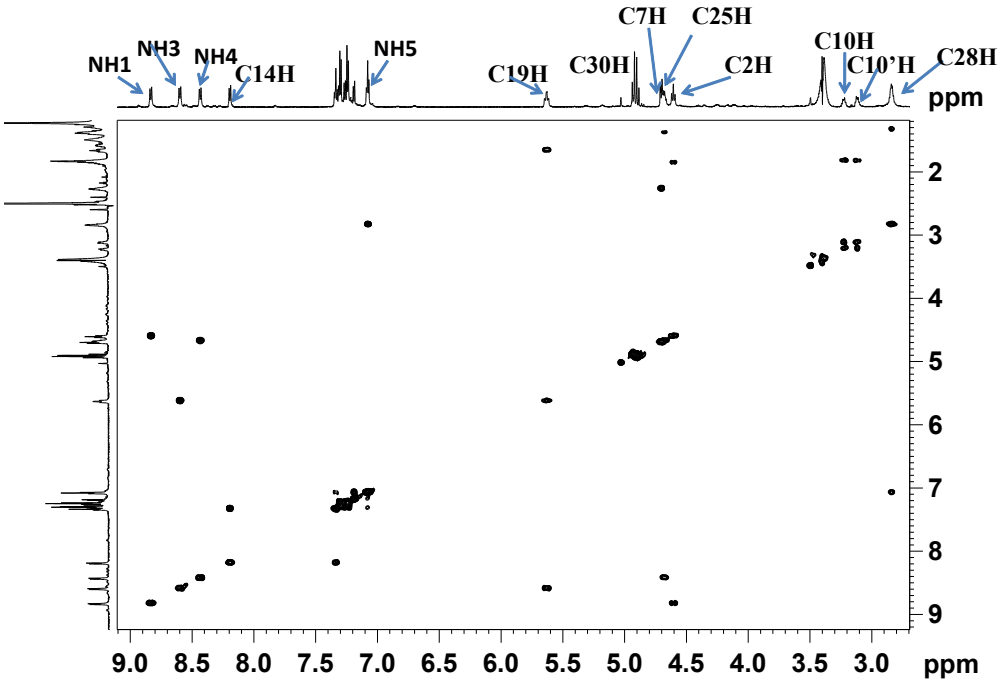
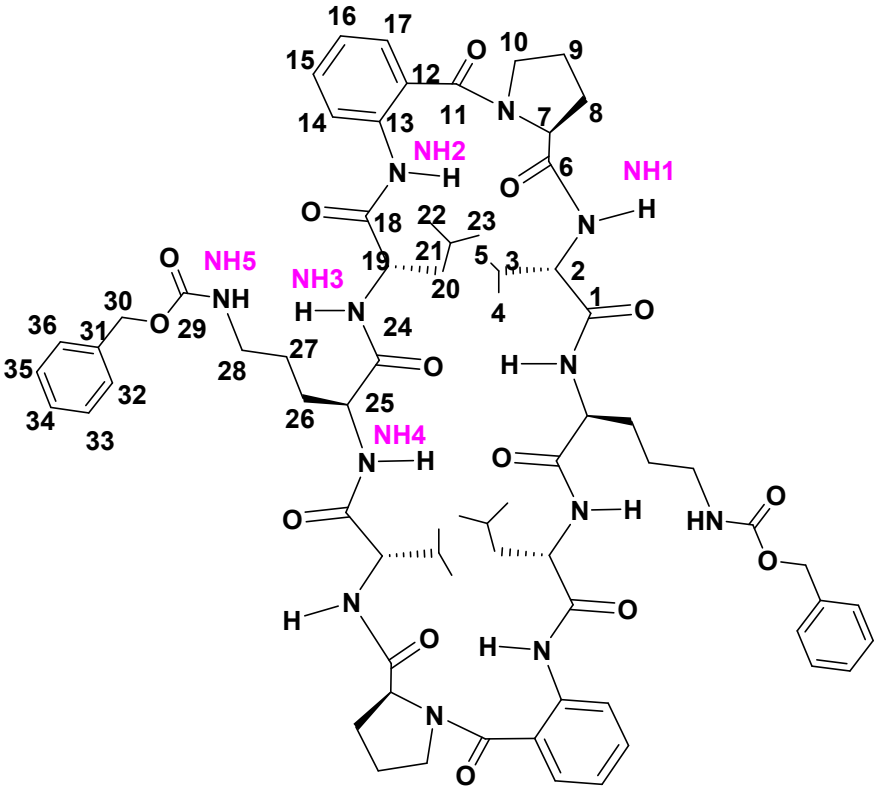


Figure S3. Partial COSY spectra of **1** (10 mM, 700 MHz) in DMSO-d_6



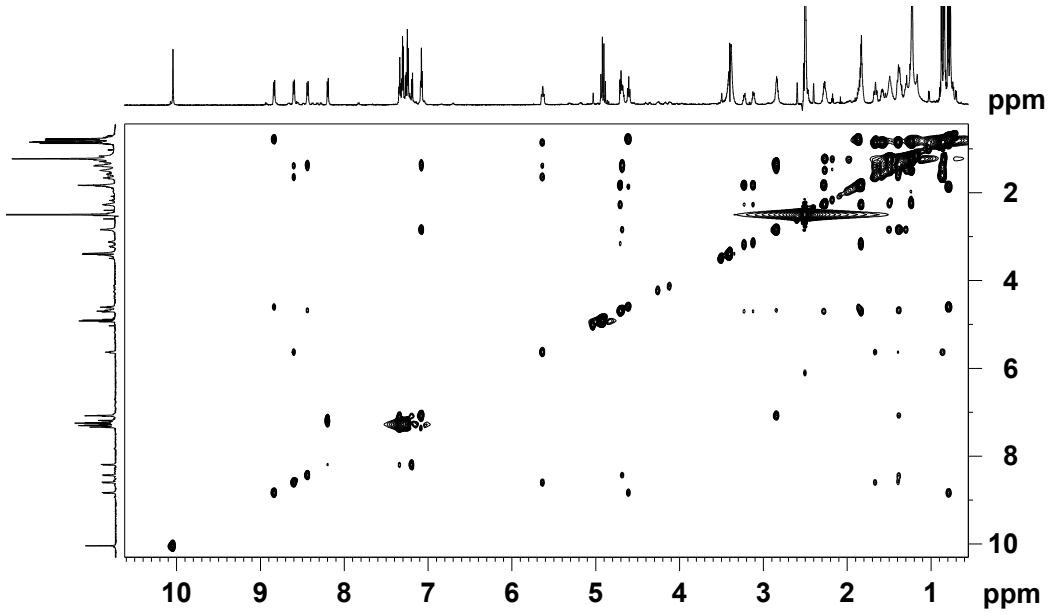


Figure S4. Full TOCSY spectra of **1** (10 mM, 700 MHz) in DMSO-d_6

Table S3: Signal assignment of **1** from TOCSY Spectra.

Proton Vs chemical shift	**NH1**	**αH/1H**	**βH/2H**	**γH/3H**	**δH/4H**	**NH2**
Val	8.86(d) NH1	4.61(t) C1H	1.86(m) C2H	0.77(d)C3H 0.79(d)C3'H		
Pro		4.70(dd) C7H	2.25(m) C8H	1.82(m) C9H	3.11(m)C10H 3.22(m)C10'H	
Ant	10.04(s) NH2	8.18(d) C14H	7.33(t) C15H	7.08(t) C16H	7.19(d) C17H	
Leu	8.58(d) NH3	5.63(t) C19H	1.65(m)C20H 1.38(m)C20'H	1.58(m) C21H	0.83(d)C22H 0.87(d)C23H	
Orn	8.43(d) NH4	4.66(m) C25H	1.66(m) C26H	1.37(m) C27H	2.85(m) 28CH	7.08(t) NH5

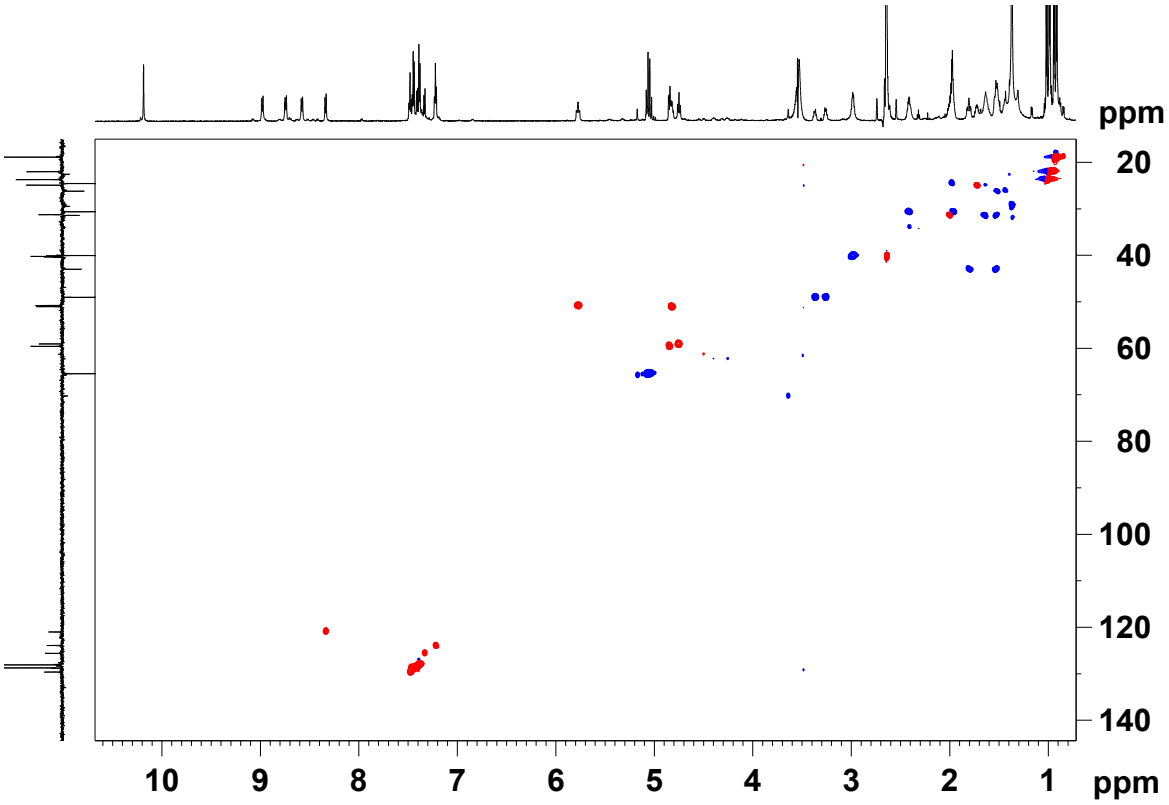


Figure S5. Full HSQC spectra of **1** (10 mM, 700 MHz) in DMSO-d_6

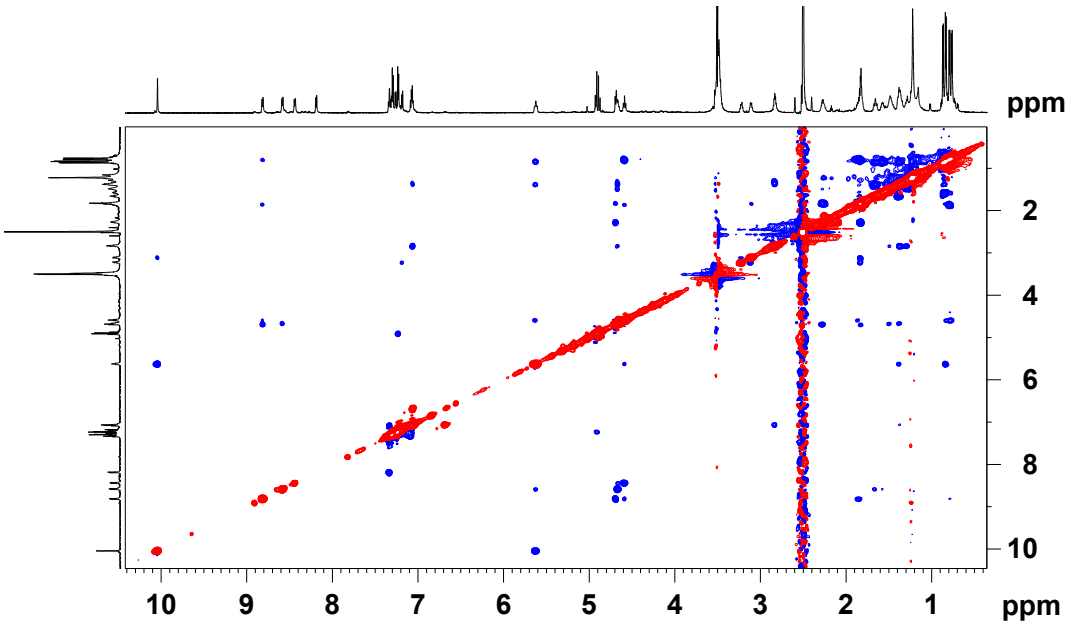


Figure S6 Full ROESY spectra of **1** (10 mM, 700 MHz) in DMSO-d_6

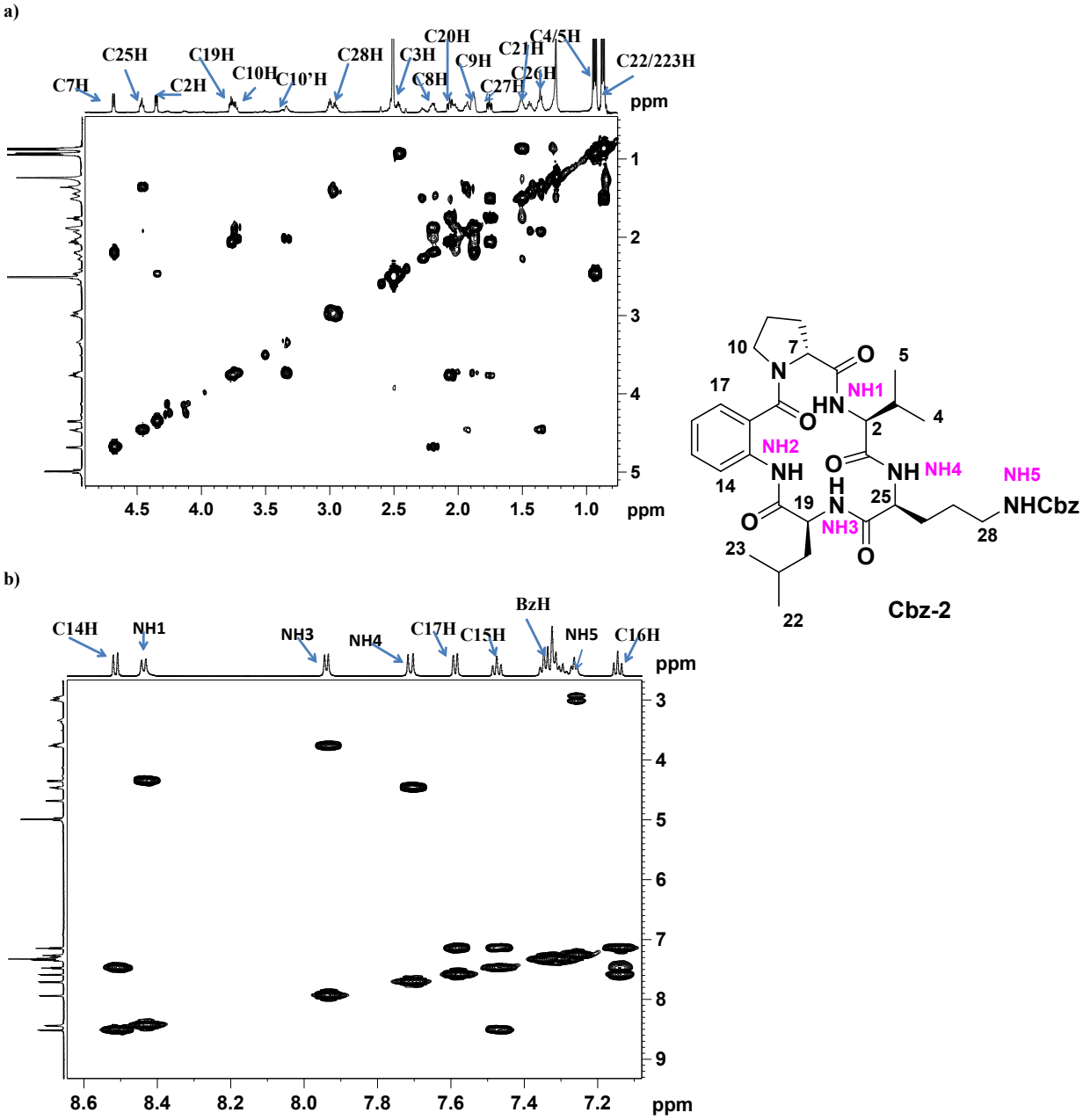


Figure S7 Partial COSY spectra of **2**, (10 mM, 700 MHz) in DMSO-d_6: aliphatic region (**a)**, aromatic region (**b)**.

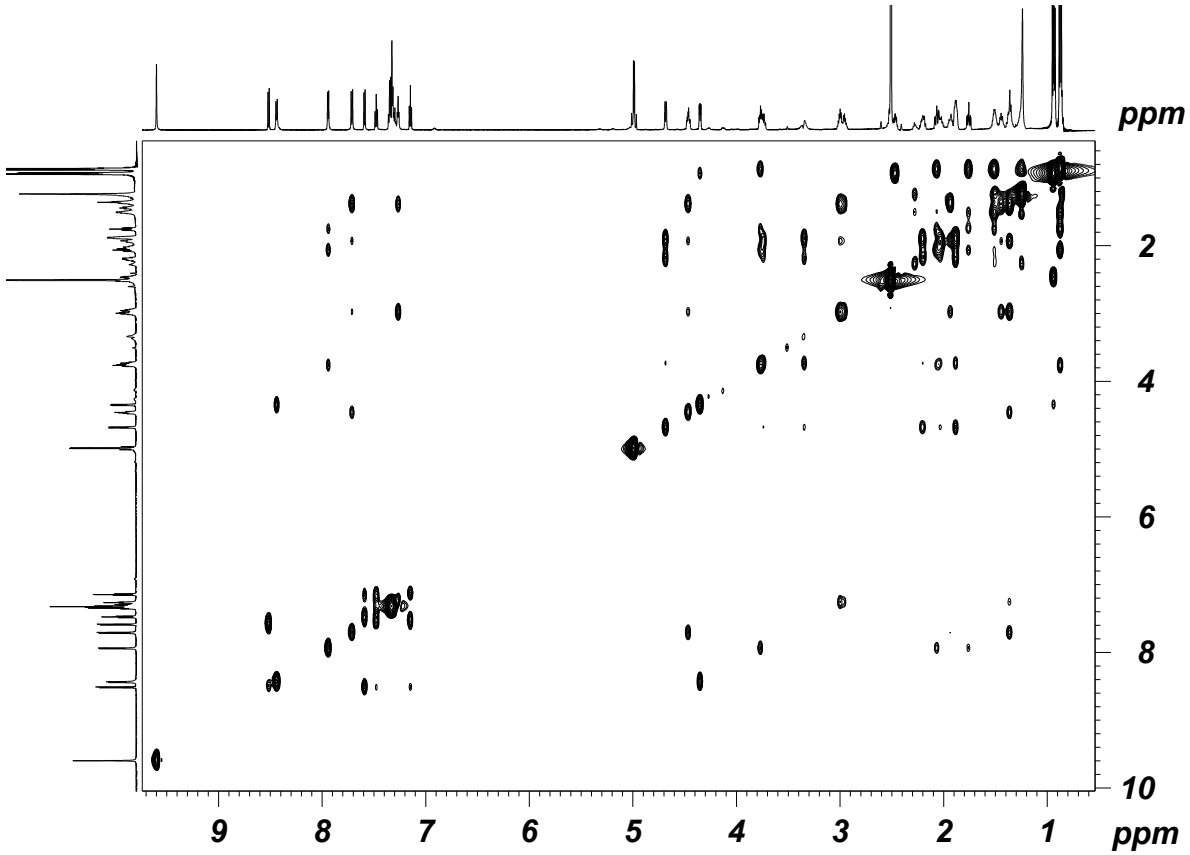


Figure S8 Full TOCSY spectra of **2** (10 mM, 700 MHz) in DMSO-d6

Table S4: Signal assignment of **2** from TOCSY Spectra.

Proton Vs chemical shift	**NH1**	**αH/1H**	**βH/2H**	**γH/3H**	**δH/4H**	**NH2**
Val	8.83(d) NH1	4.34(dd) C2H	2.47(m) C3H	0.94(d)C4H 0.93(d)C5H		
Pro		4.68(br. d) C7H	2.20(m) C8H	1.88(m) C9H	3.75(m)C10H 3.34(m)C10'H	
Ant	9.59(s) NH2	8.51(d) C14H	7.49(t) C15H	7.14(t) C16H	7.50(d) C17H	
Leu	7.94(d) NH3	3.76(m) C19H	2.07(m) C20H 1.92 (m) C20'H	1.51(m) C21H	0.88(d)C22H 0.86(d)C23H	
Orn	7.71(d) NH4	4.46(m) C25H	1.91(m) C26H	1.35(m) C27H	2.96(m) 28CH	7.26(t) NH5

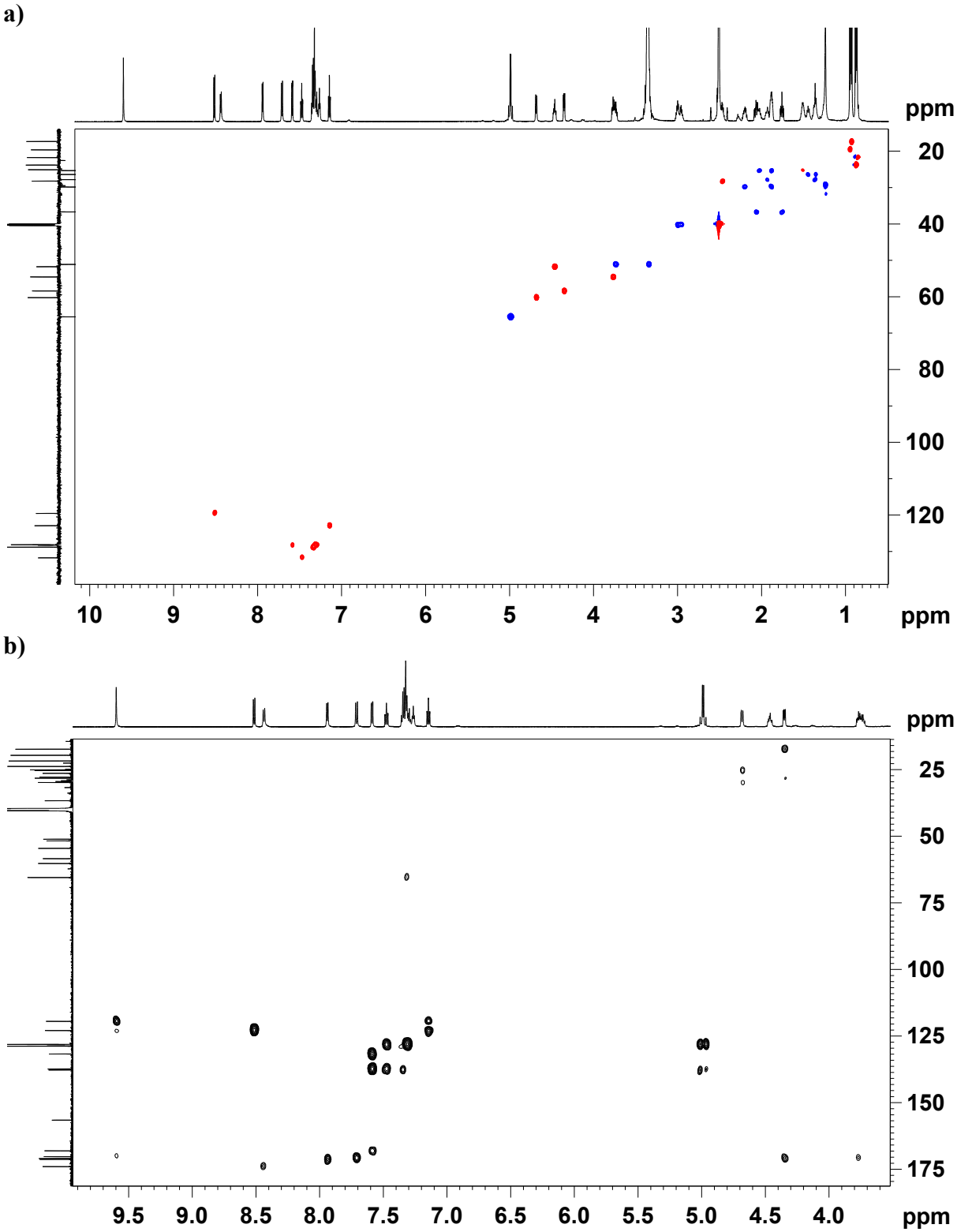


Figure S9 a) HSQC spectra, **b**) HMBC spectra of **2** (10 mM, 700 MHz) in DMSO-d_6

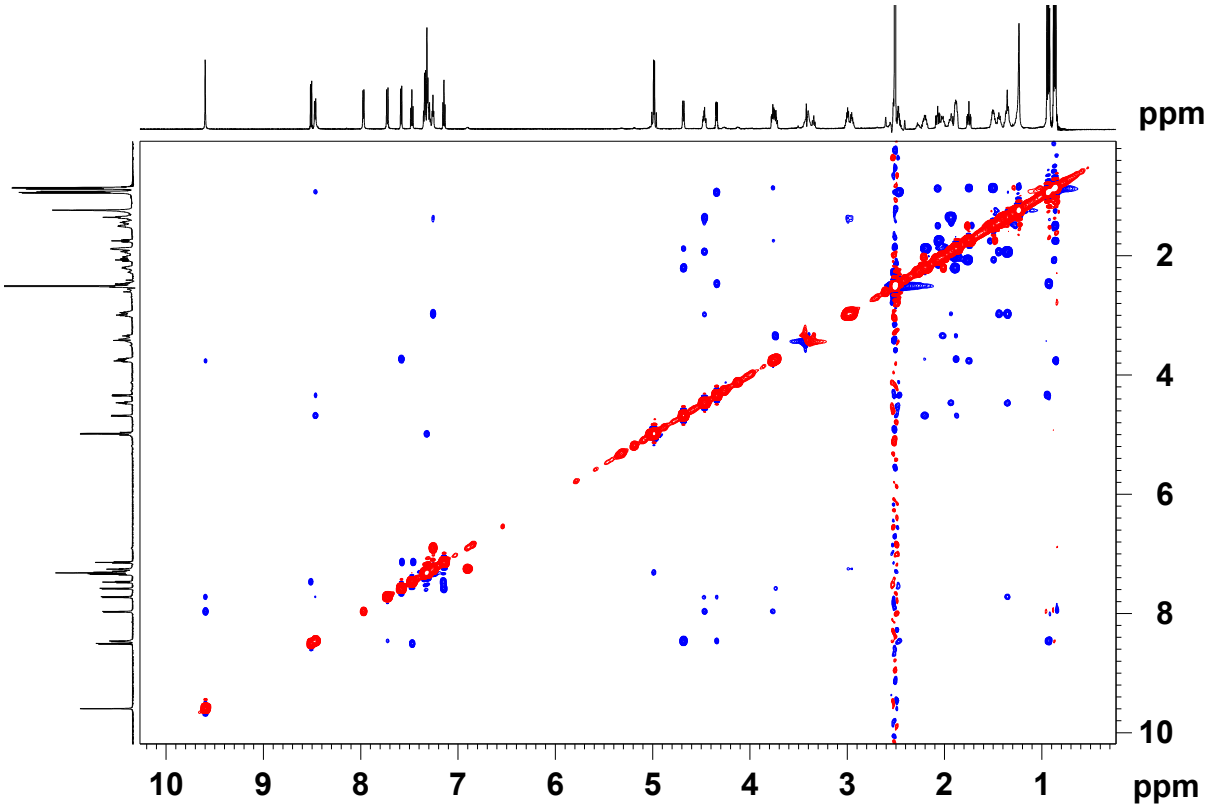


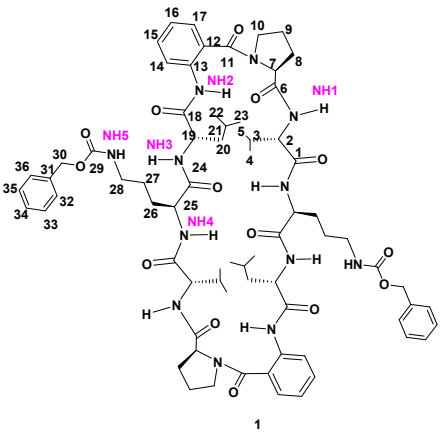
Figure S10 ROESY spectra of **2** (10 mM, 700 MHz) in DMSO-d_6

Molecular Dynamic Studies

The molecular dynamic study was carried out on MacroModel, version 10.8 program from Schrodinger software with OPLS_2005 Force Field, using the quantitative restraints obtained from the ROESY spectra calculating the relativity of cross-peak intensities of the volume integrals. The 20 superimposed minimum energy of **1** (RMSD <0.15Å) and **2** (RMSD <0.2 Å).

Table S5: ROESY restraints used for MD simulation studies of **1**

Atom1	Atom2	Upper Bound(Å)	Lower Bound(Å)
14H	15H	2.68	2.2
NH2	19H	2.43	1.99
NH2	10aH	3.75	3.07
NH1	4H/5H	3.79	3.1
NH1	3H	3.09	2.53
NH1	2H	3.48	2.85
NH1	7H	2.6	2.12
NH3	21H	3.57	2.92
NH3	20H	3.25	2.66
NH3	25H	2.49	2.03
NH3	19H	3.43	2.81
NH4	2H	2.5	2.05
NH4	25H	3.69	3.02
NH5	27aH	3.76	3.08
NH5	27bH	4.79	3.92
NH5	28H	2.83	2.31
30H	32H/36H	2.91	2.38
2H	19H	3.23	2.64
19H	22H/23H	2.75	2.25
19H	20H	3.06	2.5
19H	21H	3.62	2.97
2H	4H/5H	2.46	2.01
25H	27H	3.32	2.72
25H	26aH	2.95	2.41
25H	26bH	3.08	2.52
7H	9aH	3.2	2.62
2H	3H	3.2	2.61
7H	8H	2.63	2.15



1

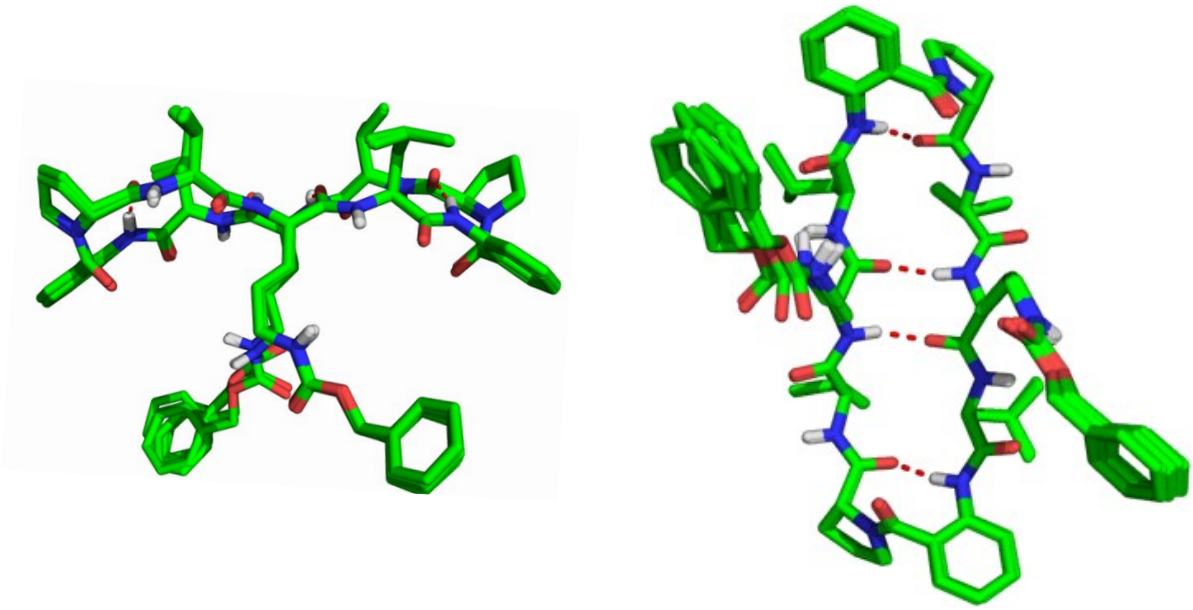
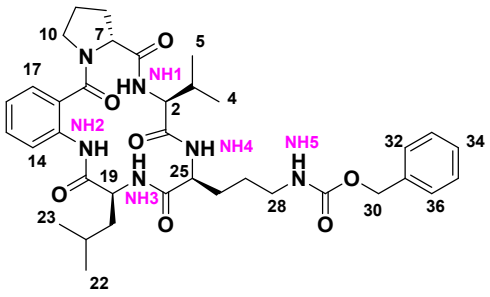


Figure S11 Different stereo views of 20 superimposed minimum energy structures for peptide **1**. Note-hydrogens, other than the polar amide hydrogens have been removed for clarity.

Table S6: ROESY restraints used for MD simulation studies of **2**

Atom I	Atom II	Upper Bound	Lower Bound
14H	15H	2.68	2.2
NH2	NH3	2.88	2.36
NH2	NH4	3.3	2.7
NH2	14H	4.32	3.54
NH2	19H	3.34	2.73
NH1	3H	3.78	3.09
NH1	2H	3.35	2.74
NH1	7H	2.41	1.97
NH1	NH4	2.88	2.36
NH3	21H	3.57	2.92
NH3	26aH	3.64	2.98
NH3	20AH	3.77	3.08
NH3	25H	3.07	2.51
NH3	2H	4.18	3.42
NH4	4H/5H	4.07	3.33
NH4	27aH	3.05	2.49
NH4	27bH	3.53	2.88
NH4	2H	3.43	2.81
NH4	25H	3.25	2.66
17H	10bH	3.44	2.82
17H	10aH	2.49	2.04
30H	32H/36H	2.88	2.36
NH5	28H	2.72	2.23



2

NH5	26aH	3.57	2.92
NH5	27aH	3.72	3.05
NH5	27bH	3.45	2.82
7H	9aH	3.11	2.54
7H	8aH	2.65	2.17
25H	28aH	3.12	2.56
2H	4H/5H	2.59	2.12
19H	22H/23H	2.64	2.16
19H	21H	3.26	2.67
NH1	4H/5H	2.65	2.17
NH3	22H/23H	3.64	2.98
7H	10aH	4	3.28
NH3	NH4	3.07	2.51
NH4	7H	4.08	3.34

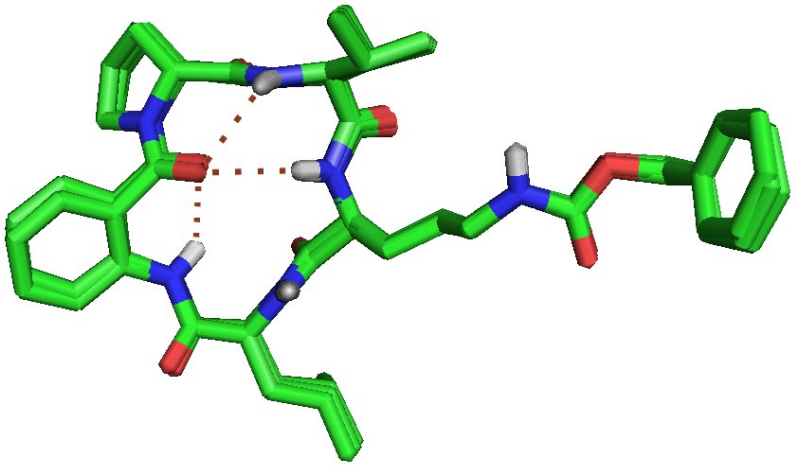


Figure S12 Stereo view of 10 superimposed minimum energy structures for peptide **2**. Note- hydrogens, other than the polar amide have been removed for clarity.

Table S7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **6**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5104(2)	7355(3)	5249(1)	24(1)
C(2)	7335(2)	8037(2)	5444(1)	22(1)
C(3)	8128(2)	7905(2)	5675(1)	20(1)
C(4)	9163(2)	8854(3)	5727(1)	24(1)
C(5)	9461(3)	9910(3)	5554(1)	27(1)
C(6)	8703(3)	10013(3)	5325(1)	28(1)
C(7)	7644(3)	9096(3)	5270(1)	26(1)
C(8)	7812(2)	6778(2)	5868(1)	20(1)
C(9)	7710(2)	4289(2)	5944(1)	19(1)
C(10)	8538(3)	3081(3)	5824(1)	26(1)
C(11)	9737(3)	3781(3)	5683(1)	29(1)
C(12)	9121(2)	5129(2)	5583(1)	23(1)
C(13)	6171(2)	4055(2)	5899(1)	19(1)
C(14)	4263(2)	2494(2)	5982(1)	22(1)
C(15)	4433(3)	1307(3)	5782(1)	29(1)
C(16)	3064(3)	857(3)	5665(1)	45(1)
C(17)	5225(3)	81(3)	5894(1)	39(1)
C(18)	3535(2)	2023(2)	6229(1)	23(1)
C(19)	1355(3)	1541(3)	6417(1)	41(1)
C(20)	2867(2)	6275(3)	5153(1)	23(1)
C(21)	2024(3)	7431(3)	5274(1)	29(1)
C(22)	2302(3)	4872(3)	5235(1)	30(1)
C(23)	2958(3)	6379(3)	4857(1)	32(1)
N(1)	6247(2)	7099(2)	5401(1)	24(1)
N(2)	8157(2)	5497(2)	5795(1)	19(1)
N(3)	5598(2)	3079(2)	6052(1)	22(1)
O(1)	4884(2)	8387(2)	5123(1)	32(1)
O(2)	7231(2)	7027(2)	6079(1)	24(1)
O(3)	5529(2)	4664(2)	5725(1)	24(1)
O(4)	4100(2)	1603(2)	6423(1)	30(1)
O(5)	2159(2)	2101(2)	6202(1)	33(1)
O(6)	4263(2)	6249(2)	5269(1)	26(1)

Table S8. Bond lengths [Å] and angles [°] for **6**.

C(1)-O(1)	1.210(3)
C(1)-O(6)	1.350(3)
C(1)-N(1)	1.373(3)
C(2)-C(7)	1.392(3)
C(2)-C(3)	1.411(3)
C(2)-N(1)	1.409(3)
C(3)-C(4)	1.386(3)
C(3)-C(8)	1.501(3)
C(4)-C(5)	1.383(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.384(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.386(3)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
C(8)-O(2)	1.243(3)
C(8)-N(2)	1.338(3)
C(9)-N(2)	1.461(3)
C(9)-C(13)	1.525(3)
C(9)-C(10)	1.543(3)
C(9)-H(9)	1.0000
C(10)-C(11)	1.526(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.523(3)
C(11)-H(11B)	0.9900
C(11)-H(11A)	0.9900
C(12)-N(2)	1.471(3)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-O(3)	1.233(3)
C(13)-N(3)	1.347(3)
C(14)-N(3)	1.456(3)
C(14)-C(18)	1.513(3)
C(14)-C(15)	1.550(3)
C(14)-H(14)	1.0000

C(15)-C(16)	1.518(4)
C(15)-C(17)	1.526(4)
C(15)-H(15)	1.0000
C(16)-H(16B)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(17)-H(17A)	0.9800
C(18)-O(4)	1.201(3)
C(18)-O(5)	1.343(3)
C(19)-O(5)	1.452(3)
C(19)-H(19B)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19C)	0.9800
C(20)-O(6)	1.476(3)
C(20)-C(21)	1.517(3)
C(20)-C(23)	1.521(3)
C(20)-C(22)	1.524(3)
C(21)-H(21A)	0.9800
C(21)-H(21C)	0.9800
C(21)-H(21B)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(22)-H(22A)	0.9800
C(23)-H(23C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
N(1)-H(1N)	0.8800
N(3)-H(3N)	0.8800

O(1)-C(1)-O(6)	126.2(2)
O(1)-C(1)-N(1)	126.3(2)
O(6)-C(1)-N(1)	107.49(19)
C(7)-C(2)-C(3)	119.0(2)
C(7)-C(2)-N(1)	122.3(2)
C(3)-C(2)-N(1)	118.7(2)
C(4)-C(3)-C(2)	119.6(2)

C(4)-C(3)-C(8)	120.2(2)
C(2)-C(3)-C(8)	120.2(2)
C(5)-C(4)-C(3)	121.2(2)
C(5)-C(4)-H(4)	119.4
C(3)-C(4)-H(4)	119.4
C(4)-C(5)-C(6)	118.9(2)
C(4)-C(5)-H(5)	120.6
C(6)-C(5)-H(5)	120.6
C(5)-C(6)-C(7)	121.2(2)
C(5)-C(6)-H(6)	119.4
C(7)-C(6)-H(6)	119.4
C(6)-C(7)-C(2)	120.1(2)
C(6)-C(7)-H(7)	120.0
C(2)-C(7)-H(7)	120.0
O(2)-C(8)-N(2)	122.3(2)
O(2)-C(8)-C(3)	121.4(2)
N(2)-C(8)-C(3)	116.18(18)
N(2)-C(9)-C(13)	109.26(18)
N(2)-C(9)-C(10)	104.33(17)
C(13)-C(9)-C(10)	109.60(19)
N(2)-C(9)-H(9)	111.1
C(13)-C(9)-H(9)	111.1
C(10)-C(9)-H(9)	111.1
C(11)-C(10)-C(9)	104.17(19)
C(11)-C(10)-H(10A)	110.9
C(9)-C(10)-H(10A)	110.9
C(11)-C(10)-H(10B)	110.9
C(9)-C(10)-H(10B)	110.9
H(10A)-C(10)-H(10B)	108.9
C(10)-C(11)-C(12)	103.94(19)
C(10)-C(11)-H(11B)	111.0
C(12)-C(11)-H(11B)	111.0
C(10)-C(11)-H(11A)	111.0
C(12)-C(11)-H(11A)	111.0
H(11B)-C(11)-H(11A)	109.0
N(2)-C(12)-C(11)	102.17(18)
N(2)-C(12)-H(12A)	111.3
C(11)-C(12)-H(12A)	111.3

N(2)-C(12)-H(12B)	111.3
C(11)-C(12)-H(12B)	111.3
H(12A)-C(12)-H(12B)	109.2
O(3)-C(13)-N(3)	123.0(2)
O(3)-C(13)-C(9)	122.1(2)
N(3)-C(13)-C(9)	114.81(19)
N(3)-C(14)-C(18)	109.17(18)
N(3)-C(14)-C(15)	110.8(2)
C(18)-C(14)-C(15)	112.1(2)
N(3)-C(14)-H(14)	108.2
C(18)-C(14)-H(14)	108.2
C(15)-C(14)-H(14)	108.2
C(16)-C(15)-C(17)	111.4(2)
C(16)-C(15)-C(14)	112.4(2)
C(17)-C(15)-C(14)	112.4(2)
C(16)-C(15)-H(15)	106.7
C(17)-C(15)-H(15)	106.7
C(14)-C(15)-H(15)	106.7
C(15)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16A)	109.5
H(16B)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(15)-C(17)-H(17A)	109.5
H(17B)-C(17)-H(17A)	109.5
H(17C)-C(17)-H(17A)	109.5
O(4)-C(18)-O(5)	123.8(2)
O(4)-C(18)-C(14)	125.1(2)
O(5)-C(18)-C(14)	111.04(19)
O(5)-C(19)-H(19B)	109.5
O(5)-C(19)-H(19A)	109.5
H(19B)-C(19)-H(19A)	109.5
O(5)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

H(19A)-C(19)-H(19C)	109.5
O(6)-C(20)-C(21)	109.98(19)
O(6)-C(20)-C(23)	110.35(19)
C(21)-C(20)-C(23)	112.9(2)
O(6)-C(20)-C(22)	101.73(19)
C(21)-C(20)-C(22)	110.7(2)
C(23)-C(20)-C(22)	110.7(2)
C(20)-C(21)-H(21A)	109.5
C(20)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
C(20)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
H(21C)-C(21)-H(21B)	109.5
C(20)-C(22)-H(22B)	109.5
C(20)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(20)-C(22)-H(22A)	109.5
H(22B)-C(22)-H(22A)	109.5
H(22C)-C(22)-H(22A)	109.5
C(20)-C(23)-H(23C)	109.5
C(20)-C(23)-H(23A)	109.5
H(23C)-C(23)-H(23A)	109.5
C(20)-C(23)-H(23B)	109.5
H(23C)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(1)-N(1)-C(2)	125.2(2)
C(1)-N(1)-H(1N)	117.4
C(2)-N(1)-H(1N)	117.4
C(8)-N(2)-C(9)	121.61(18)
C(8)-N(2)-C(12)	125.97(19)
C(9)-N(2)-C(12)	112.07(17)
C(13)-N(3)-C(14)	119.88(19)
C(13)-N(3)-H(3N)	120.1
C(14)-N(3)-H(3N)	120.1
C(18)-O(5)-C(19)	115.65(19)
C(1)-O(6)-C(20)	120.55(19)

Symmetry transformations used to generate equivalent atoms.

Table S9. Crystal data and structure refinement for **12**.

Identification code	mo_LLTRI_220816_0m	
Empirical formula	C23 H33 N3 O6	
Formula weight	447.52	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 13.3238(5) Å	α= 90°.
	b = 7.2153(3) Å	β= 114.1870(10)°.
	c = 13.5409(6) Å	γ = 90°.
Volume	1187.48(9) $Å^3$	
Z	2	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	480	
Crystal size	0.340 x 0.210 x 0.100 mm^3	
Theta range for data collection	2.791 to 30.531°.	
Index ranges	-18<=h<=19, -10<=k<=10, -19<=l<=19	
Reflections collected	41983	
Independent reflections	7203 [R(int) = 0.0621]	
Completeness to theta = 25.242°	99.1 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7203 / 1 / 295	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0861	
R indices (all data)	R1 = 0.0388, wR2 = 0.0878	
Absolute structure parameter	0.3(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.323 and -0.271 $e.Å^{-3}$	

Table S10. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **12**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7442(1)	3980(2)	2003(1)	17(1)
C(2)	7994(1)	2881(2)	3858(1)	12(1)
C(3)	7866(1)	3336(2)	4809(1)	11(1)
C(4)	8649(1)	2751(2)	5812(1)	16(1)
C(5)	9566(1)	1739(2)	5884(1)	18(1)
C(6)	9676(1)	1263(2)	4941(1)	17(1)
C(7)	8902(1)	1816(2)	3937(1)	15(1)
C(8)	6845(1)	4266(2)	4778(1)	12(1)
C(9)	5518(1)	6765(2)	4083(1)	14(1)
C(10)	5629(1)	8742(2)	3710(2)	23(1)
C(11)	6485(1)	8513(2)	3236(1)	21(1)
C(12)	7321(1)	7216(2)	4045(1)	13(1)
C(13)	4690(1)	5650(2)	3141(1)	12(1)
C(14)	2769(1)	5011(2)	2042(1)	11(1)
C(15)	2334(1)	3170(2)	2307(1)	14(1)
C(16)	1646(1)	3481(3)	2955(2)	23(1)
C(17)	3283(1)	1844(2)	2884(1)	19(1)
C(18)	1825(1)	6332(2)	1469(1)	13(1)
C(19)	218(1)	6668(3)	-150(2)	27(1)
C(20)	6586(2)	5442(3)	231(2)	27(1)
C(21)	5422(2)	6129(3)	-417(2)	29(1)
C(22)	6866(2)	3892(5)	-381(2)	52(1)
C(23)	7386(2)	7042(5)	530(2)	53(1)
N(1)	7187(1)	3435(2)	2841(1)	13(1)
N(2)	6620(1)	5991(2)	4373(1)	11(1)
N(3)	3625(1)	5886(2)	2971(1)	12(1)
O(1)	8341(1)	3874(3)	1985(1)	32(1)
O(2)	6230(1)	3427(2)	5103(1)	17(1)
O(3)	4978(1)	4674(2)	2559(1)	16(1)
O(4)	1661(1)	7781(2)	1812(1)	17(1)
O(5)	1179(1)	5606(2)	508(1)	19(1)
O(6)	6527(1)	4675(2)	1212(1)	18(1)

Table S11. Bond lengths [Å] and angles [°] for **12**

C(1)-O(1)	1.210(2)
C(1)-O(6)	1.3477(19)
C(1)-N(1)	1.370(2)
C(2)-C(7)	1.400(2)
C(2)-C(3)	1.404(2)
C(2)-N(1)	1.4136(18)
C(3)-C(4)	1.397(2)
C(3)-C(8)	1.5020(19)
C(4)-C(5)	1.391(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.387(2)
C(5)-H(5)	0.9500
C(6)-C(7)	1.386(2)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
C(8)-O(2)	1.2360(18)
C(8)-N(2)	1.344(2)
C(9)-N(2)	1.4664(18)
C(9)-C(13)	1.529(2)
C(9)-C(10)	1.540(2)
C(9)-H(9)	1.0000
C(10)-C(11)	1.529(3)
C(10)-H(10B)	0.9900
C(10)-H(10A)	0.9900
C(11)-C(12)	1.522(2)
C(11)-H(11B)	0.9900
C(11)-H(11A)	0.9900
C(12)-N(2)	1.4802(19)
C(12)-H(12B)	0.9900
C(12)-H(12A)	0.9900
C(13)-O(3)	1.2292(18)
C(13)-N(3)	1.3523(18)
C(14)-N(3)	1.4515(18)
C(14)-C(18)	1.514(2)
C(14)-C(15)	1.549(2)
C(14)-H(14)	1.0000

C(15)-C(17)	1.521(2)
C(15)-C(16)	1.523(2)
C(15)-H(15)	1.0000
C(16)-H(16B)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(17)-H(17A)	0.9800
C(18)-O(4)	1.200(2)
C(18)-O(5)	1.3387(18)
C(19)-O(5)	1.4433(19)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-O(6)	1.471(2)
C(20)-C(23)	1.510(4)
C(20)-C(21)	1.518(3)
C(20)-C(22)	1.526(3)
C(21)-H(21C)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(22)-H(22A)	0.9800
C(23)-H(23C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
N(1)-H(1N)	0.8800
N(3)-H(3N)	0.8800

O(1)-C(1)-O(6)	126.07(15)
O(1)-C(1)-N(1)	125.61(15)
O(6)-C(1)-N(1)	108.32(13)
C(7)-C(2)-C(3)	118.91(13)
C(7)-C(2)-N(1)	121.19(13)
C(3)-C(2)-N(1)	119.85(12)
C(4)-C(3)-C(2)	119.88(13)

C(4)-C(3)-C(8)	117.97(13)
C(2)-C(3)-C(8)	121.82(12)
C(5)-C(4)-C(3)	120.72(15)
C(5)-C(4)-H(4)	119.6
C(3)-C(4)-H(4)	119.6
C(6)-C(5)-C(4)	119.11(14)
C(6)-C(5)-H(5)	120.4
C(4)-C(5)-H(5)	120.4
C(7)-C(6)-C(5)	120.95(14)
C(7)-C(6)-H(6)	119.5
C(5)-C(6)-H(6)	119.5
C(6)-C(7)-C(2)	120.39(14)
C(6)-C(7)-H(7)	119.8
C(2)-C(7)-H(7)	119.8
O(2)-C(8)-N(2)	121.94(13)
O(2)-C(8)-C(3)	119.79(13)
N(2)-C(8)-C(3)	118.25(12)
N(2)-C(9)-C(13)	108.93(12)
N(2)-C(9)-C(10)	102.71(12)
C(13)-C(9)-C(10)	110.33(13)
N(2)-C(9)-H(9)	111.5
C(13)-C(9)-H(9)	111.5
C(10)-C(9)-H(9)	111.5
C(11)-C(10)-C(9)	103.05(13)
C(11)-C(10)-H(10B)	111.2
C(9)-C(10)-H(10B)	111.2
C(11)-C(10)-H(10A)	111.2
C(9)-C(10)-H(10A)	111.2
H(10B)-C(10)-H(10A)	109.1
C(12)-C(11)-C(10)	102.49(14)
C(12)-C(11)-H(11B)	111.3
C(10)-C(11)-H(11B)	111.3
C(12)-C(11)-H(11A)	111.3
C(10)-C(11)-H(11A)	111.3
H(11B)-C(11)-H(11A)	109.2
N(2)-C(12)-C(11)	102.54(11)
N(2)-C(12)-H(12B)	111.3
C(11)-C(12)-H(12B)	111.3

N(2)-C(12)-H(12A)	111.3
C(11)-C(12)-H(12A)	111.3
H(12B)-C(12)-H(12A)	109.2
O(3)-C(13)-N(3)	122.97(13)
O(3)-C(13)-C(9)	121.92(13)
N(3)-C(13)-C(9)	115.04(13)
N(3)-C(14)-C(18)	111.29(12)
N(3)-C(14)-C(15)	114.02(12)
C(18)-C(14)-C(15)	110.32(11)
N(3)-C(14)-H(14)	106.9
C(18)-C(14)-H(14)	106.9
C(15)-C(14)-H(14)	106.9
C(17)-C(15)-C(16)	111.52(14)
C(17)-C(15)-C(14)	110.32(12)
C(16)-C(15)-C(14)	112.20(13)
C(17)-C(15)-H(15)	107.5
C(16)-C(15)-H(15)	107.5
C(14)-C(15)-H(15)	107.5
C(15)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16A)	109.5
H(16B)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(15)-C(17)-H(17A)	109.5
H(17B)-C(17)-H(17A)	109.5
H(17C)-C(17)-H(17A)	109.5
O(4)-C(18)-O(5)	124.78(14)
O(4)-C(18)-C(14)	126.54(13)
O(5)-C(18)-C(14)	108.68(12)
O(5)-C(19)-H(19A)	109.5
O(5)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(5)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5

H(19B)-C(19)-H(19C)	109.5
O(6)-C(20)-C(23)	109.78(17)
O(6)-C(20)-C(21)	102.94(14)
C(23)-C(20)-C(21)	110.31(19)
O(6)-C(20)-C(22)	109.27(17)
C(23)-C(20)-C(22)	113.8(2)
C(21)-C(20)-C(22)	110.18(18)
C(20)-C(21)-H(21C)	109.5
C(20)-C(21)-H(21A)	109.5
H(21C)-C(21)-H(21A)	109.5
C(20)-C(21)-H(21B)	109.5
H(21C)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(20)-C(22)-H(22B)	109.5
C(20)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(20)-C(22)-H(22A)	109.5
H(22B)-C(22)-H(22A)	109.5
H(22C)-C(22)-H(22A)	109.5
C(20)-C(23)-H(23C)	109.5
C(20)-C(23)-H(23A)	109.5
H(23C)-C(23)-H(23A)	109.5
C(20)-C(23)-H(23B)	109.5
H(23C)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(1)-N(1)-C(2)	122.74(12)
C(1)-N(1)-H(1N)	118.6
C(2)-N(1)-H(1N)	118.6
C(8)-N(2)-C(9)	119.59(12)
C(8)-N(2)-C(12)	127.78(12)
C(9)-N(2)-C(12)	112.22(12)
C(13)-N(3)-C(14)	119.30(12)
C(13)-N(3)-H(3N)	120.4
C(14)-N(3)-H(3N)	120.4
C(18)-O(5)-C(19)	116.52(13)
C(1)-O(6)-C(20)	119.43(13)

Table S12.. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **12**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	16(1)	20(1)	15(1)	1(1)	7(1)	2(1)
C(2)	10(1)	11(1)	13(1)	0(1)	4(1)	0(1)
C(3)	10(1)	10(1)	14(1)	2(1)	5(1)	0(1)
C(4)	14(1)	18(1)	14(1)	4(1)	5(1)	-1(1)
C(5)	13(1)	20(1)	18(1)	7(1)	3(1)	2(1)
C(6)	12(1)	14(1)	25(1)	3(1)	7(1)	2(1)
C(7)	13(1)	14(1)	19(1)	-2(1)	8(1)	1(1)
C(8)	10(1)	15(1)	9(1)	-1(1)	3(1)	-1(1)
C(9)	8(1)	17(1)	14(1)	-5(1)	2(1)	2(1)
C(10)	14(1)	12(1)	38(1)	-4(1)	4(1)	3(1)
C(11)	17(1)	12(1)	28(1)	6(1)	3(1)	-1(1)
C(12)	11(1)	11(1)	16(1)	1(1)	5(1)	-1(1)
C(13)	10(1)	13(1)	12(1)	1(1)	3(1)	1(1)
C(14)	10(1)	13(1)	10(1)	0(1)	2(1)	1(1)
C(15)	13(1)	12(1)	13(1)	1(1)	3(1)	1(1)
C(16)	25(1)	21(1)	28(1)	2(1)	17(1)	0(1)
C(17)	20(1)	16(1)	17(1)	3(1)	3(1)	4(1)
C(18)	10(1)	14(1)	13(1)	2(1)	3(1)	0(1)
C(19)	18(1)	24(1)	25(1)	4(1)	-6(1)	5(1)
C(20)	29(1)	38(1)	18(1)	13(1)	14(1)	12(1)
C(21)	32(1)	35(1)	21(1)	11(1)	10(1)	13(1)
C(22)	63(2)	80(2)	22(1)	16(1)	26(1)	46(2)
C(23)	39(1)	66(2)	51(2)	36(1)	16(1)	-7(1)
N(1)	10(1)	16(1)	12(1)	0(1)	5(1)	2(1)
N(2)	8(1)	14(1)	12(1)	-1(1)	3(1)	0(1)
N(3)	8(1)	14(1)	12(1)	-4(1)	3(1)	1(1)
O(1)	19(1)	56(1)	26(1)	16(1)	15(1)	10(1)
O(2)	14(1)	20(1)	18(1)	0(1)	9(1)	-2(1)
O(3)	12(1)	21(1)	15(1)	-6(1)	5(1)	1(1)
O(4)	17(1)	15(1)	18(1)	1(1)	6(1)	4(1)
O(5)	14(1)	18(1)	15(1)	0(1)	-4(1)	3(1)
O(6)	17(1)	24(1)	13(1)	5(1)	7(1)	5(1)

Table S13. Torsion angles [°] for **12**.

C(7)-C(2)-C(3)-C(4)	1.0(2)
N(1)-C(2)-C(3)-C(4)	178.44(14)
C(7)-C(2)-C(3)-C(8)	-172.24(14)
N(1)-C(2)-C(3)-C(8)	5.2(2)
C(2)-C(3)-C(4)-C(5)	0.8(2)
C(8)-C(3)-C(4)-C(5)	174.37(15)
C(3)-C(4)-C(5)-C(6)	-2.1(2)
C(4)-C(5)-C(6)-C(7)	1.5(2)
C(5)-C(6)-C(7)-C(2)	0.4(2)
C(3)-C(2)-C(7)-C(6)	-1.6(2)
N(1)-C(2)-C(7)-C(6)	-179.01(14)
C(4)-C(3)-C(8)-O(2)	-59.66(19)
C(2)-C(3)-C(8)-O(2)	113.74(16)
C(4)-C(3)-C(8)-N(2)	121.62(15)
C(2)-C(3)-C(8)-N(2)	-64.98(19)
N(2)-C(9)-C(10)-C(11)	30.94(15)
C(13)-C(9)-C(10)-C(11)	-85.06(15)
C(9)-C(10)-C(11)-C(12)	-41.40(16)
C(10)-C(11)-C(12)-N(2)	35.15(15)
N(2)-C(9)-C(13)-O(3)	-19.1(2)
C(10)-C(9)-C(13)-O(3)	92.90(18)
N(2)-C(9)-C(13)-N(3)	163.62(13)
C(10)-C(9)-C(13)-N(3)	-84.34(16)
N(3)-C(14)-C(15)-C(17)	-53.82(16)
C(18)-C(14)-C(15)-C(17)	-179.91(13)
N(3)-C(14)-C(15)-C(16)	71.18(16)
C(18)-C(14)-C(15)-C(16)	-54.91(16)
N(3)-C(14)-C(18)-O(4)	-13.6(2)
C(15)-C(14)-C(18)-O(4)	113.97(16)
N(3)-C(14)-C(18)-O(5)	167.24(12)
C(15)-C(14)-C(18)-O(5)	-65.15(15)
O(1)-C(1)-N(1)-C(2)	8.2(3)
O(6)-C(1)-N(1)-C(2)	-171.01(14)
C(7)-C(2)-N(1)-C(1)	-39.0(2)
C(3)-C(2)-N(1)-C(1)	143.66(15)
O(2)-C(8)-N(2)-C(9)	-13.7(2)

C(3)-C(8)-N(2)-C(9)	165.01(12)
O(2)-C(8)-N(2)-C(12)	174.24(14)
C(3)-C(8)-N(2)-C(12)	-7.1(2)
C(13)-C(9)-N(2)-C(8)	-65.36(17)
C(10)-C(9)-N(2)-C(8)	177.64(13)
C(13)-C(9)-N(2)-C(12)	107.88(14)
C(10)-C(9)-N(2)-C(12)	-9.12(16)
C(11)-C(12)-N(2)-C(8)	156.14(14)
C(11)-C(12)-N(2)-C(9)	-16.43(16)
O(3)-C(13)-N(3)-C(14)	-2.3(2)
C(9)-C(13)-N(3)-C(14)	174.88(13)
C(18)-C(14)-N(3)-C(13)	-135.77(14)
C(15)-C(14)-N(3)-C(13)	98.66(16)
O(4)-C(18)-O(5)-C(19)	-0.2(2)
C(14)-C(18)-O(5)-C(19)	178.99(14)
O(1)-C(1)-O(6)-C(20)	-1.8(3)
N(1)-C(1)-O(6)-C(20)	177.33(15)
C(23)-C(20)-O(6)-C(1)	-60.4(2)
C(21)-C(20)-O(6)-C(1)	-177.87(15)
C(22)-C(20)-O(6)-C(1)	65.0(2)

CD spectra of protected and deprotected GS mimic 1:

(a) **(b)**

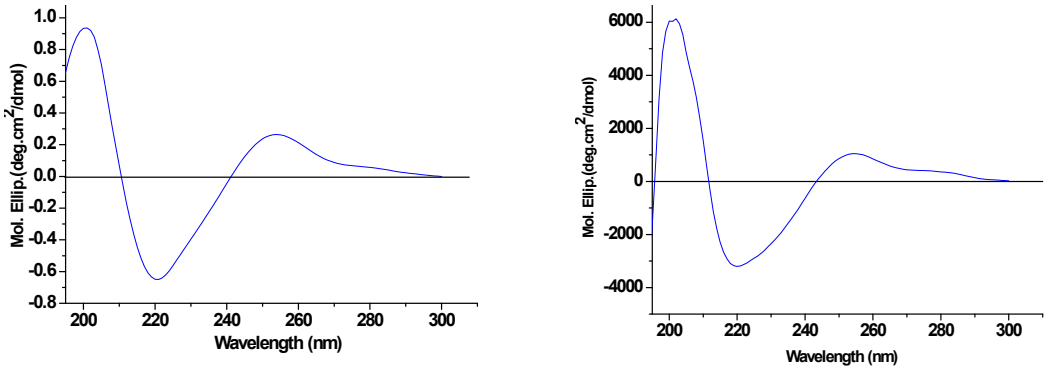


Figure S13. (a) CD spectra of Cbz GS-**1** (protected GS mimic) and (b) H-GS-**1** (free amine of GS mimic) at right, in methanol.

Details of antibacterial studies:

Bacterial strains *E. coli* (NCIM 2688), *P. aeruginosa* (NCIM 2036) as gram-negative and *B. S. aureus (NCIM 2010)*, *subtilus* (NCIM 2079) as gram-positive were obtained from NCIM (NCL, Pune) and were grown in Luria Burtony medium from Himedia, India. Once the culture reached 1 O.D 620, it was used for anti-bacterial assay. Briefly, 0.1 OD 620 bacterial culture was treated with synthesized compound at different concentration (0-100 µg/mL) and incubated for 8 h at 37 °C. The *in vitro* preliminary screening values (% inhibition) against microorganisms tested are summarized in Table S 13.

Table S14: *In vitro* antibacterial activity

Entry	***S. aureus***		***B. subtilus***		***E. coli***		***P. aeruginosa***	
	IC_{50}	***MIC***	IC_{50}	***MIC***	IC_{50}	***MIC***	IC_{50}	***MIC***
1	0.42	2.9	0.38	3.66	0.48	10.56	0.45	10.53
2	>100	-	>100	-	>100	-	>100	-

References:

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(3) L. J. Farrugia, *J. Appl. Cryst.* 1997, **30**, 565–565.