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Hydrogenation Catalyst Generates Cyclic Peptide Stereocenters in Sequence

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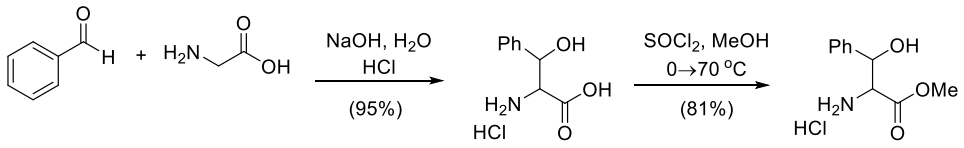
1. General considerations

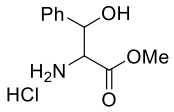
Commercial reagents were purchased from Sigma Aldrich, Strem, Acros Organics, ChemImpex, TCI and/or Alfa Aesar and used without further purification. Reaction progresses were monitored using a combination of LC/MS analysis[1] and thin-layer chromatography (TLC) on EMD Silica Gel 60 F254 plates. Visualization of the developed plates was performed under UV light (254 nm) and with $KMnO_4$ stain. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. ^{1}H, ^{13}C, and ^{19}F spectra were recorded on a Bruker DRX400, Bruker DRX500, Bruker DRX500 with TCI (three channel inverse) cryoprobe or a Bruker AVANCE600 with BBFO (broadband fluorine observe) cryoprobe spectrometer. ^{1}H NMR spectra were internally referenced to the residual solvent signal or TMS. ^{13}C NMR spectra were internally referenced to the residual solvent signal. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). High resolution mass spectra (HRMS) were obtained on a Waters LCT Premier spectrometer (using ESI-TOF). Infrared (IR) spectra were obtained on a Nicolet iS5 FT-IR spectrometer with an iD5 ATR, and are reported in terms of frequency of absorption (cm^{-1}). Column chromatography was performed with Silicycle Silia-P Flash Silica Gel, using either glass columns or a Teledyne Isco Combiflash Rf 200 automated purification system. Preparative reverse phase HPLC (RP-HPLC) was performed on a Beckman (Agilent Zorbax 80 SB C_{18} column, 50 x 4.6 mm; solvent A: H_2O/0.1% TFA, solvent B: CH_3CN/0.1% TFA). Enantiomeric excesses were determined by chiral SFC analysis using an Agilent Technologies HPLC (1200 series) system and Aurora A5 Fusion. Solvents were purchased from Fisher Chemical and were purified according to standard procedures.[2]

2. Typical procedures for synthesis of cyclic pentapeptides

i) Synthesis of pentapeptide **5a**

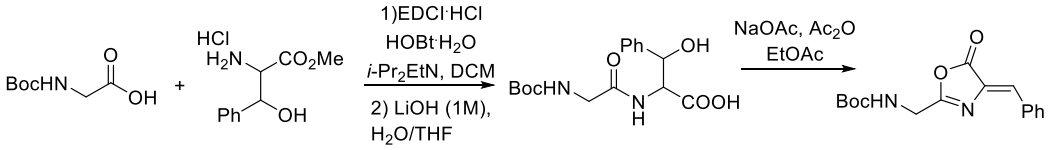


Methyl 2-amino-3-hydroxy-3-phenylpropanoate (S1)

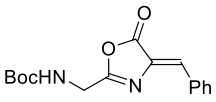


To a stirring solution of NaOH (60 g, 1.5 mol) in water (250 mL) at rt was added glycine (75 g, 1 mol). The solution was stirred for 10 min and benzaldehyde (215 mL, 2.1 mol) was added and the solution was stirred for 20 min. The solution became a beige emulsion and the solid was broken apart. Concentrated HCl (aq) (130 mL) was added slowly and the mixture stirred until the beige solid was consumed to give a clear yellow solution. Shortly, beige precipitates were observed and the mixture was cooled to 0 °C. The beige solid was collected via vacuum filtration and the solid was washed with Et_2O. The solid was dried *in vacuo* to give the (±)-β-phenylserine an off-white solid (172 g, 95%). Characterization data was consistent with those previously reported.[3]

To a round bottom flask equipped with a stir bar was added 2-amino-3-hydroxy-3-phenylpropanoic acid (25 g, 138 mmol) and anhydrous MeOH (190 mL) under N_2 and the mixture was cooled to 0 °C. Thionyl chloride (22.5 mL, 310 mmol) was subsequently added and the reaction stirred overnight for 16 h at 70 °C. The reaction mixture was concentrated under reduced pressure, redissolved in DCM, and subsequently concentrated again (2x). The resulting white solid was washed with Et_2O to afford DL-(β-OH)–Phe–OMe **S1** as an off-white solid (26.0 g, 81%). Characterization data was consistent with those previously reported.[4]



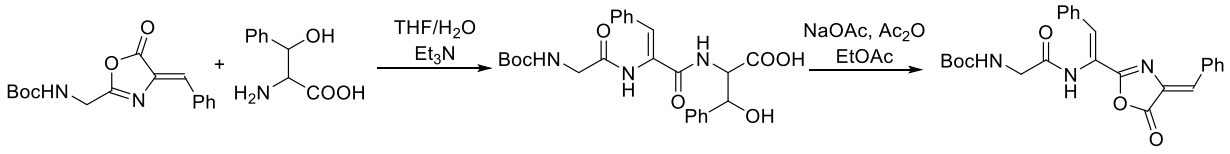
***tert*-butyl (*Z*)-((4-benzylidene-5-oxo-4,5-dihydrooxazol-2-yl)methyl)carbamate (1)**



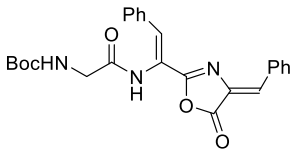
To a round bottom flask equipped with a stir bar was added Boc-Gly-OH (20 g, 114 mmol), DL-(β-OH)–Phe–OMe **S1** (29 g, 125 mmol), $HOBt{\cdot}H_2O$ (24 g, 125 mmol) and DCM (400 mL). The mixture was cooled to 0 °C and *i*-Pr_2EtN (50 mL, 285 mmol) was subsequently added. EDCI·HCl (24 g, 125 mmol) was added in portions and the reaction gradually warmed to rt and stirred for 16 h. The reaction mixture was transferred to a separatory funnel and washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), H_2O, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (eluting with 30:70 hexanes/EtOAc) and obtained as a white solid (21 g, 53% yield). Characterization data was consistent with those previously reported.[5]

To a round bottom flask equipped with a stir bar was added methyl ester (17.2 g, 48.8 mmol), THF (244 mL), and H_2O (185 mL). The mixture was cooled to 0 °C and 1 M LiOH (aq) (58.6 mL, 1.2 equiv) was subsequently added. The reaction gradually warmed to rt and stirred for 16 h. The reaction mixture was quenched with 10% $KHSO_4$ (aq) and the THF was concentrated under reduced pressure. The reaction mixture was transferred to a separatory funnel where it was extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired carboxylic acid, which was used without further purification.

To a round bottom flask equipped with a stir bar was added carboxylic acid (48.8 mmol) and EtOAc (98 mL). To this solution was added acetic anhydride (46 mL, 488 mmol) and sodium acetate (7.9 g, 96.7 mmol) and the mixture was stirred at rt for 16 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure to afford the product as a light yellow solid (11.5 g, 79% over two steps). Characterization data was consistent with those previously reported.[6]

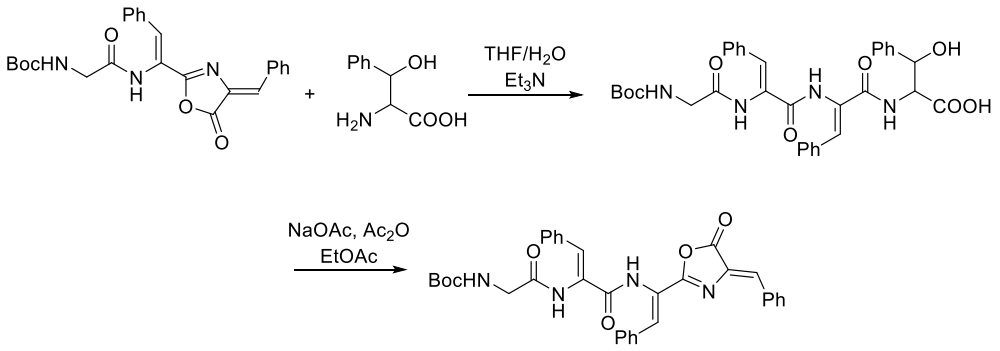


***tert*-butyl(2-(((*Z*)-1-(4-((*Z*)-benzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)-2-phenylvinyl)amino)-2-oxoethyl)carbamate (3)**

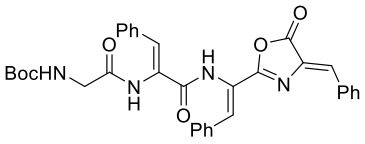


To a solution of (±)-β-phenylserine (7.41 g, 40.88 mmol) in THF/H_2O (1:1, 0.1 M) was added triethylamine (5.7 mL, 40.88 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **1** (10.3 g, 34.07 mmol) in THF (340 mL). The reaction was stirred at rt for 15 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used without further purification.

To a round bottom flask equipped with a stir bar was added the carboxylic acid (34.07 mmol) and EtOAc (68 mL). To this solution was added acetic anhydride (32 mL, 340.7 mmol) and sodium acetate (5.60 g, 68.14 mmol) and the mixture was stirred at rt for 24 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure. The oil was dissolved in a minimal amount of DCM and hexanes was added to precipitate the oxazolone **3**. The solvent was decanted and the solid was washed 2x with hexanes to afford the product as a yellow solid (12.5 g, 82% over two steps). ^{1}H NMR (400 MHz, DMSO) δ 9.78 (s, 1H), 8.31 – 8.19 (m, 2H), 7.92 – 7.76 (m, 2H), 7.56 – 7.50 (m, 4H), 7.49 – 7.39 (m, 3H), 7.33 (s, 1H), 7.19 (t, *J* = 5.8 Hz, 1H), 3.82 (d, *J* = 6.0 Hz, 2H), 1.41 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 167.1, 162.1, 156.5, 135.3, 133.5, 133.4, 133.0, 132.7, 132.5, 131.5, 130.4, 129.1, 128.9, 119.7, 110.1, 80.9, 45.2, 28.4. IR (ATR): 3268, 1784, 1689, 1650 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{25}H_{26}N_3O_5$ $[M+H]^+$: 448.1866, found 448.1851.



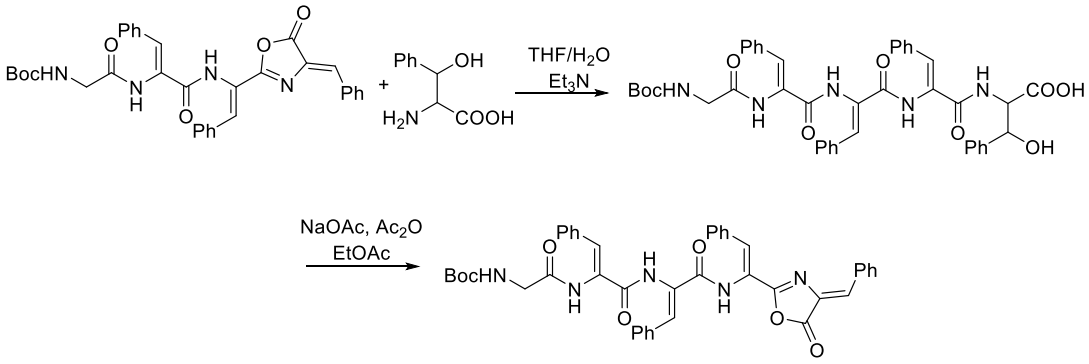
***tert*-butyl (2-(((*Z*)-3-(((*Z*)-1-(4-((*Z*)-benzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)-2-phenylvinyl)amino)-3-oxo-1-phenylprop-1-en-2-yl)amino)-2-oxoethyl)carbamate (S2)**



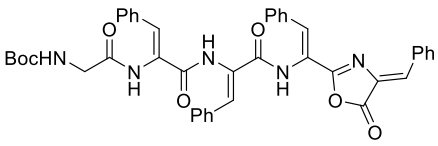
To a solution of (±)-β-phenylserine (6.0 g, 33.25 mmol) in THF/H_2O (1:1, 0.1 M) was added triethylamine (4.6 mL, 33.25 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **3** (12.4 g, 27.7 mmol) in THF (270 mL). The reaction was stirred at rt for 21 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used without further purification.

To a round bottom flask equipped with a stir bar was added the carboxylic acid (27.7 mmol) and EtOAc (55 mL). To this solution was added acetic anhydride (26 mL, 277 mmol) and sodium acetate (4.5 g, 55.4 mmol) and the mixture was stirred at rt for 16 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure. The oil was dissolved in a minimal amount of DCM and hexanes was added to precipitate the oxazolone. The solvent was decanted and the solid was washed 2x with hexanes to afford the product as a yellow solid (12.0 g, 73% over two steps). ^{1}H NMR (499 MHz, DMSO) δ 9.85 (s, 1H), 9.80 (s, 1H), 8.28 (d, *J* = 7.0 Hz, 2H), 7.92 (d, *J* = 5.0 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.58 (s, 1H), 7.53 – 7.36 (m, 9H), 7.35 (s, 1H), 7.27 (s, 1H), 7.11 (t, *J* = 5.7 Hz, 1H), 3.80 (d, *J* = 5.8 Hz, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 169.9, 166.7, 165.5, 162.4, 156.1, 135.0, 133.7, 133.3, 133.3, 133.0, 132.5, 131.3, 131.0, 130.9, 130.2, 129.9, 129.4, 129.3, 129.1, 128.9, 128.7, 128.6, 128.3, 121.9, 78.2, 43.6, 28.2.

IR (ATR): 3372, 3237, 2989, 1806, 1778, 1686, 1660 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{34}H_{33}N_4O_6$ $[M+H]^+$: 593.2394, found 593.2368.



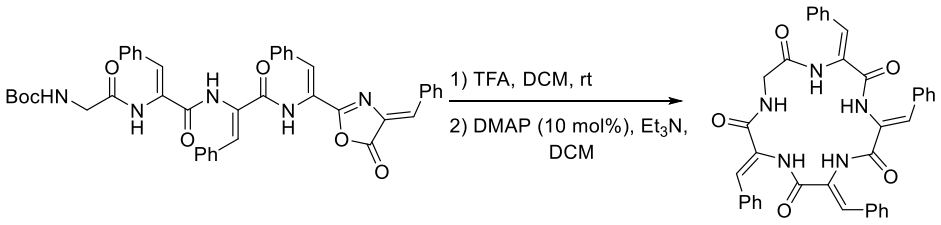
***tert*-butyl (2-(((*Z*)-3-(((Z)-3-(((*Z*)-1-(4-((*Z*)-benzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)-2-phenylvinyl)amino)-3-oxo-1-phenylprop-1-en-2-yl)amino)-3-oxo-1-phenylprop-1-en-2-yl)amino)-2-oxoethyl)carbamate (4)**



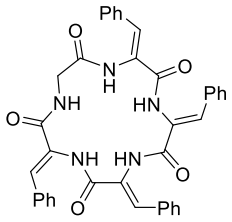
To a solution of (±)-β-phenylserine (114 mg, 0.628 mmol) in THF/H_2O (1:1, 0.1 M) was added triethylamine (88 µL, 0.628 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **S2** (310 mg, 0.523 mmol) in THF (10 mL). The reaction was stirred at rt for 15 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used without further purification.

To a round bottom flask equipped with a stir bar was added the carboxylic acid (0.523 mmol) and EtOAc (1 mL). To this solution was added acetic anhydride (0.5 mL, 5.23 mmol) and sodium acetate (86 mg, 1.05 mmol) and the mixture was stirred at rt for 26 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure. The oil was dissolved in a minimal amount of DCM and hexanes was added to precipitate the oxazolone. The solvent was decanted and the solid was washed 2x with hexanes to afford the product as a yellow solid (343 mg, 89% over two steps). ^{1}H NMR (600 MHz, DMF-d_7) δ 10.09 (s, 1H), 9.89 (s, 1H), 9.68 (s, 1H), 8.39-8.40 (m, 2H), 8.05 (d, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 7.5 Hz,

1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.68 (s, 1H), 7.49-7.56 (m, 4H), 7.39-7.48 (m, 9H), 7.35 (s, 1H), 6.93 (br, 1H), 3.96 (d, *J* = 5.4 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 167.8, 164.9, 164.5, 162.6, 156.9, 135.1, 134.6, 133.7, 133.6, 133.1, 132.8, 131.7, 131.2, 131.1, 130.3, 130.1, 129.9, 129.7, 129.6, 129.5, 129.2, 129.0, 128.8, 128.7, 128.6, 127.7, 127.3, 120.7, 81.6, 45.2, 28.3. IR (ATR): 3253, 1779, 1670, 1640 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{43}H_{40}N_5O_7$ $[M+H]^+$: 738.2922, found 738.2886.



3,6,9,12-tetra((*Z*)-benzylidene)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (1')

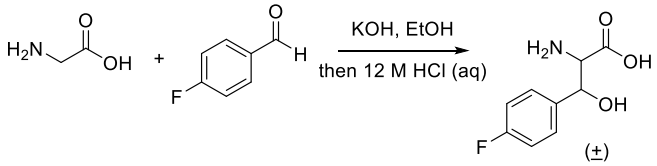


To a round bottom flask equipped with a stir bar under N_2 was added Boc-protected amine **4** (346 mg, 0.469 mmol) and anhydrous DCM (5.9 mL). The reaction mixture was cooled to 0 °C and TFA (0.897 mL, 11.7 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 2 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure. The crude reaction mixture was further dried on the high vacuum and subsequently triturated with Et_2O to afford TFA·amine salt and was immediately used in the next reaction without further purification.

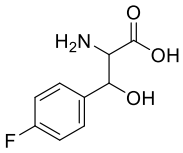
TFA·amine salt (0.469 mmol) was dissolved in anhydrous DCM (4.69 mL, 0.1 M) and to this yellow solution was added anhydrous Et_3N (0.131 mL, 0.938 mmol) and DMAP (5.7 mg, 0.0469 mmol). The reaction mixture was stirred at rt for 30 min. The solution was then diluted by addition of 150 mL of DCM. The organic phase was washed four times with 10 mL 1 M HCl. The organic phase was then dried with Na_2SO_4 and concentrated under reduced pressure to afford a light yellow solid. This solid was then triturated with Et_2O to afford cyclic pentapeptide **5a** as a light yellow solid (243 mg, 81% over 2 steps). ^{1}H NMR (499 MHz, DMSO, 373K, d1=5 s) δ 9.63 (s, 1H), 9.38 (s, 1H), 9.34 (s, 1H), 9.23 (s, 1H), 8.05 (t, *J* = 4.4 Hz, 1H), 7.63 – 7.52 (m, 8H), 7.46 – 7.32 (m,

12H), 7.28 (s, 1H), 7.20 (s, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 4.00 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO, 373 K, d1=25 s) δ 169.1, 165.4, 165.3, 164.8, 164.0, 133.9, 133.8, 133.5, 133.3, 131.8, 131.7, 129.3, 129.1, 129.0, 128.9, 128.7, 128.5, 128.44, 128.42, 128.40, 128.3, 128.2, 128.08, 128.06, 127.98, 127.96, 127.82, 127.79, 127.7, 127.40, 43.36. IR (ATR): 3272, 3050, 2927, 1634, 1500, 1490, 1447, 1363, 1256, 1203, 1075, 1029, 1001, 929 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{31}N_5O_5$ $[M+H]^+$: 638.2397, found 638.2379.

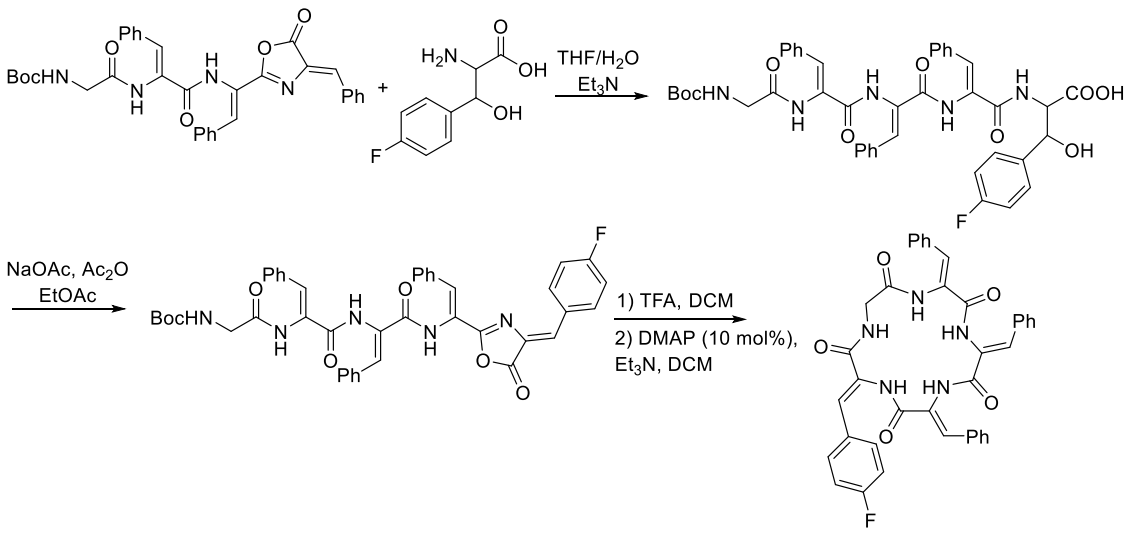
ii) Synthesis of pentapeptide **5a'**



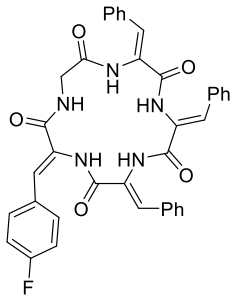
2-amino-3-(4-fluorophenyl)-3-hydroxypropanoic acid (S3)



To a 250 mL Erlenmeyer flask equipped with a stir bar was added EtOH (200 mL) and KOH (5.6 g, 100 mmol) and this mixture was stirred at rt until complete dissolution of the KOH was observed. Glycine (3.75 g, 50 mmol) was then added, and this mixture was again stirred until homogeneous. 4-fluorobenzaldehyde (10.7 mL, 100 mmol) was then added with stirring. After 2-4 h of stirring at rt, precipitate formed until the entire reaction mixture became a white solid. This solid was then broken up mechanically and 9 mL of 12 M HCl (aq.) was added with stirring. Any remaining large clumps were crushed using a glass rod. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. To the crude concentrate was added 50 mL of DCM and 80 mL of H_2O. The phases were separated and the aqueous phase was washed twice more with dichloromethane (2 x 50 mL) then concentrated under reduced pressure. The crude solid was then triturated with Et_2O to afford (±) fluoroserine **S3** derivative as a white solid (1.5 g, 17%). ^{1}H NMR (600 MHz, DMSO) δ 7.40 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.13 (t, *J* = 8.9 Hz, 2H), 5.04 (d, *J* = 4.3 Hz, 1H), 3.39 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 168.7, 161.5 (d, *J* = 242.1 Hz), 138.4 (d, *J* = 2.8 Hz), 128.5 (d, *J* = 8.2 Hz), 114.7 (d, *J* = 21.2 Hz), 70.3, 59.3. ^{19}F NMR (376 MHz, DMSO) δ -116.36. IR (ATR): 3133, 2915, 1635, 1596, 1506, 1484, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_9H_{10}FNO_3Na$ $[M+Na]^+$: 222.0542, found: 222.0542.



6,9,12-tri((*Z*)-benzylidene)-3-((*Z*)-4-fluorobenzylidene)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (5a')[a]



To a solution of fluoroserine **S3** (806 mg, 4.05 mmol) in THF/H_2O (1:1, 0.1 M) was added triethylamine (564 µL, 4.05 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **S2** (2.00 g, 3.37 mmol) in THF (34 mL). The reaction was stirred at rt for 15 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used without further purification.
To a round bottom flask equipped with a stir bar was added the carboxylic acid (3.37 mmol) and EtOAc (6.7 mL). To this solution was added acetic anhydride (3.18 mL, 33.7 mmol) and sodium acetate (552 mg, 6.74 mmol) and the mixture was stirred at rt for 26 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure. The oil was dissolved in a minimal amount of DCM and hexanes was

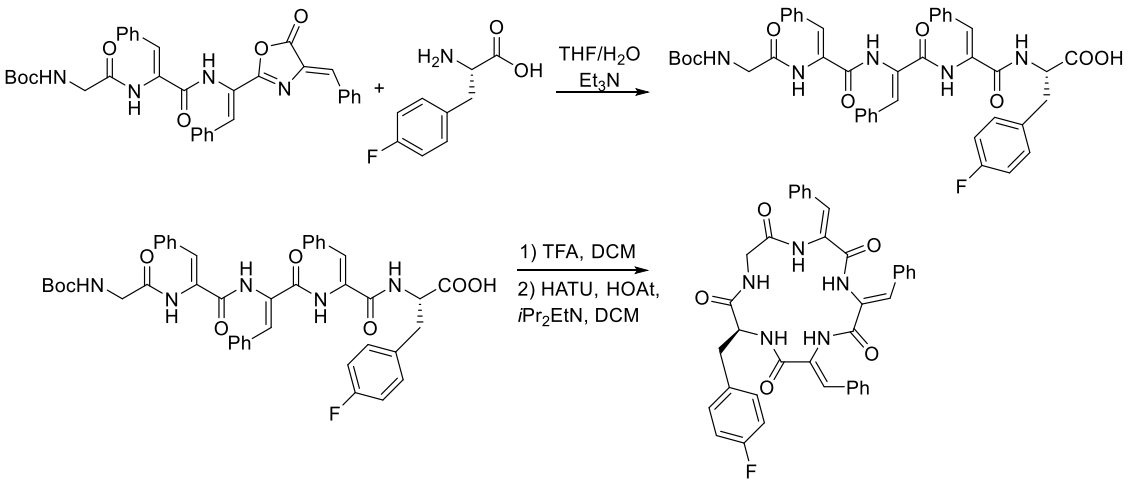
[a] The difference in the yield to obtain cyclic peptide **5a'** and **5a** is due to the number of isolations in the overall reaction sequence. The macrocyclization yield of **5a'** is 12% over 4 steps from oxazolone **S2.** This had to be completed over 4 steps due to difficulty in the isolation of pentapeptide intermediate (Boc-Gly-ΔPhe-ΔPhe-ΔPhe-ΔPhe(4-F)$_{ox}$). In comparison, macrocyclization yield of **5a** is 81% yield over 2 steps from oxazolone **4.**

added to precipitate the oxazolone. The solvent was decanted and the solid was washed 2x with hexanes to afford the desired oxazolone which was used in the next step without further purification.

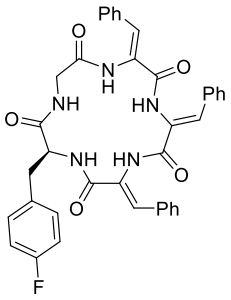
To a round bottom flask equipped with a stir bar under N_2 was added the resulting oxazolone (3.37 mmol) and anhydrous DCM (34 mL). The reaction mixture was cooled to 0 °C and TFA (5.20 mL, 67.4 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 2 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure. The crude reaction mixture was further dried on the high vacuum and subsequently triturated with Et_2O to afford TFA·amine salt and was immediately used in the next reaction without further purification.

TFA·amine salt (3.37 mmol) was dissolved in anhydrous DCM (67 mL, 0.05 M) and to this solution was added anhydrous Et_3N (0.94 mL, 6.74 mmol) and DMAP (41 mg, 0.34 mmol). The reaction mixture was stirred at rt for 3 h and subsequently concentrated under reduced pressure. The crude reaction mixture was then purified via column chromatography (eluting with 25% DCM/Acetone) to afford cyclic pentapeptide **5a'** as a light yellow solid (235 mg, 12% yield over 4 steps). ^{1}H NMR (499 MHz, DMSO, 373 K, d1=25 s) δ 9.65 (s, 1H), 9.40 (s, 1H), 9.35 (s, 1H), 9.22 (s, 1H), 8.09 (s, 1H), 7.71 – 7.53 (m, 7H), 7.49 – 7.31 (m, 10H), 7.27 (s, 1H), 7.25 – 7.15 (m, 4H), 7.09 (s, 1H), 4.00 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO, 373 K, d1=25 s) δ 169.1, 165.3, 165.3, 164.8, 163.9, 161.6 (d, *J* = 247.5 Hz), 133.8, 133.5, 133.3, 131.2 (d, *J* = 8.3 Hz), 130.5 (d, *J* = 3.1 Hz), 129.5, 129.4, 129.4, 129.3, 129.2, 129.1, 128.7, 128.5, 128.4, 128.4, 128.4, 128.3, 127.99, 127.97, 127.8, 127.4, 127.4, 114.7 (d, *J* = 21.6 Hz), 43.4. ^{19}F NMR (376 MHz, DMSO, 298 K) δ -112.20. ^{19}F NMR (376 MHz, DMSO, 373 K) δ -112.34. IR (ATR): 3050, 1633, 1601, 1509, 1233, 1203 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{30}FN_5O_5Na$ $[M+Na]^+$: 678.2129, found: 678.2134.

iii) Synthesis of pentapeptide **5b'**



(*S*)-6,9,12-tri((*Z*)-benzylidene)-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone **(5b')**



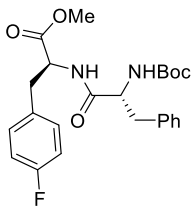
To a solution of L-Phe(4-F)-OH (0.602 g, 3.29 mmol) in THF/H_2O (1:1, 0.1 M) was added Et_3N (459 µL, 3.29 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **S2** (1.50 g, 2.53 mmol) in THF (25 mL). The reaction was stirred at rt for 11 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used in the next step without further purification.

To a round bottom flask equipped with a stir bar under N_2 was added the carboxylic acid (2.53 mmol) and anhydrous DCM (32 mL). The reaction mixture was cooled to 0 °C and TFA (2.9 mL, 38.0 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 22 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure. The crude reaction mixture was further dried on the high vacuum and subsequently triturated with Et_2O to afford TFA·amine salt and was immediately used in the next reaction without further purification. To a round bottom flask equipped with a stir bar was added the TFA·amine salt (2.53 mmol), HOAt (0.688 g, 5.06 mmol), and anhydrous DCM (51 mL, 0.05 M). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (2.2 mL, 12.7 mmol) was added. HATU (2.40 g, 6.33 mmol) was

added in portions and the reaction warmed to rt and stirred for 4 h. The solvent was removed under reduced pressure and the product was purified by column chromatography (eluting with hexanes/EtOAc) to afford the product as a yellow solid (365 mg, 22% over 3 steps). ^{1}H NMR (499 MHz, DMSO, 368 K) δ 9.56 (s, 1H), 9.35 (s, 1H), 9.25 (s, 1H), 8.05 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.52 (m, 5H), 7.47 – 7.29 (m, 12H), 7.20 (s, 1H), 7.18 (s, 1H), 7.15 (s, 1H), 7.07 (t, *J* = 8.8 Hz, 2H), 4.71 – 4.63 (m, 1H), 4.20 (dd, *J* = 14.9, 7.1 Hz, 1H), 3.59 (dd, *J* = 14.9, 4.5 Hz, 1H), 3.21 (dd, *J* = 13.9, 7.2 Hz, 1H), 3.00 – 2.96 (m, 1H). ^{13}C NMR (126 MHz, DMSO, 368 K, d1=10 s) δ 171.0, 169.2, 165.0, 164.9, 163.6, 160.6 (d, *J* = 242.0 Hz), 133.8, 133.6 (d, *J* = 3.6 Hz), 133.6, 133.4, 130.3 (d, *J* = 7.9 Hz), 129.2, 129.1, 129.06, 129.01, 128.9, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.4, 114.2 (d, *J* = 21.1 Hz), 54.8, 43.1, 35.5. ^{19}F NMR (376 MHz, DMSO) δ -117.00. IR (ATR): 3055, 3027, 2910, 1652, 1640, 1501, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{32}FN_5O_5Na$ [M+Na]$^{+}$: 680.2285, found: 680.2289. [α]$^{25}_{D}$ +175 (*c* = 0.25, $CHCl_3$).

iv) Synthesis of pentapeptide **5c'**

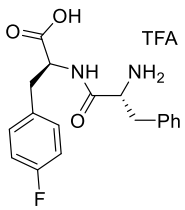
methyl (*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(4-fluorophenyl)propanoate (S4)



To a round bottom flask equipped with a stir bar was added Boc-D-Phe-OH (2.00 g, 7.50 mmol), 4-fluoro-L-Phe-OMe (1.90 g, 8.25 mmol), HOBt·H_2O (1.50 g, 9.00 mmol), and DCM (94 mL). The mixture was cooled to 0 °C and *i*-Pr_2EtN (4.00 mL, 22.5 mmol) was subsequently added. EDCI·HCl (1.73 g, 9.00 mmol) was added in portions and the reaction gradually warmed to rt and stirred for 22 h. The reaction mixture was transferred to a separatory funnel and was washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The unpurified reaction mixture was then purified by column chromatography (eluting with 7:3 hexanes/EtOAc) to afford dipeptide **S4** as a white solid (3.1 g, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.23 (m, 1H), 7.20 – 7.17 (m, 2H), 6.97 – 6.83 (m, 4H), 6.39 (br s, 1H), 4.89 (br s, 1H), 4.86 – 4.76 (m, 1H), 4.36 (br s, 1H), 3.67 (s, 3H), 3.08 (dd, *J* = 13.8, 7.1 Hz, 1H), 3.00 (dd, *J* = 14.0, 5.5 Hz, 2H), 2.92 (dd, *J* = 14.0, 5.8 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 171.0, 162.1 (d, *J* = 245.3 Hz), 155.5, 136.7, 131.4 (d, *J* = 2.9 Hz), 130.8 (d, *J* = 7.6 Hz), 129.5, 128.9, 127.2, 115.6 (d, *J* = 21.2 Hz), 80.5, 55.9, 53.2, 52.5,

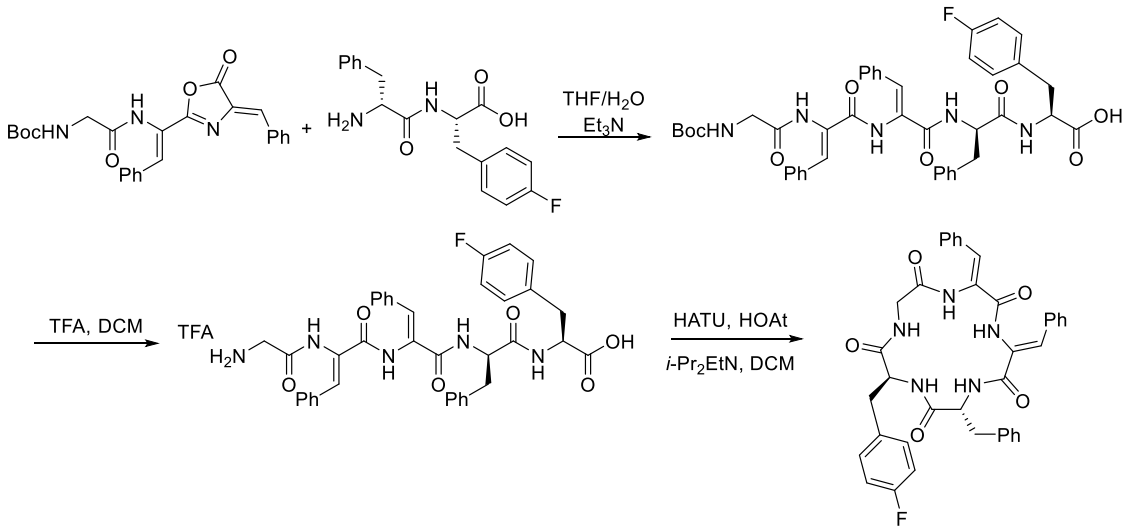
38.3, 37.2, 28.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.04. IR (ATR): 3044, 2972, 1741, 1674, 1657, 1517, 1232, 1160 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{24}H_{29}FN_2O_5Na$ $[M+Na]^+$: 467.1958, found: 467.1953. $[\alpha]^{26}_D$ –13 (*c* = 0.24, $CHCl_3$).

(*S*)-2-((*R*)-2-amino-3-phenylpropanamido)-3-(4-fluorophenyl)propanoic acid (S5)

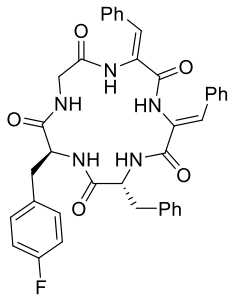


To a round bottom flask equipped with a stir bar was added methyl ester **S4** (1.5 g, 3.4 mmol), THF (16 mL), and H_2O (13 mL). The mixture was cooled to 0 °C and 1 M LiOH (aq) (6.1 mL, 6.1 mmol) was subsequently added. The reaction gradually warmed to rt and stirred for 23 h. The reaction mixture was acidified with 10% $KHSO_4$ (aq), and the THF was concentrated under reduced pressure. The reaction mixture was transferred to a separatory funnel where it was extracted with EtOAc (3 x 100 mL). The organic layer was washed with 100 mL brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired carboxylic acid which was used in the next step without further purification.

To a round bottom flask equipped with a stir bar was added the resulting carboxylic acid (3.4 mmol), triisopropylsilane (0.70 mL, 3.4 mmol), and DCM (42 mL). The reaction mixture was cooled to 0 °C and TFA (3.8 mL, 5.1 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 24 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure. The reaction mixture was further dried on the high vacuum and subsequently triturated with Et_2O to afford amine **S5** as a white solid (1.5 g, 99%). ^{1}H NMR (400 MHz, DMSO) δ 8.92 (d, *J* = 7.7 Hz, 1H), 8.14 (br s, 2H), 7.33 – 7.17 (m, 5H), 7.10 (t, *J* = 8.9 Hz, 2H), 7.04 – 6.98 (m, 2H), 4.54 (td, *J* = 9.1, 4.8 Hz, 1H), 4.12 – 3.98 (m, 1H), 3.06 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.90 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.82 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.69 (dd, *J* = 13.9, 7.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 172.3, 167.9, 161.2 (d, *J* = 242.3 Hz), 134.6, 133.3 (d, *J* = 2.8 Hz), 131.2 (d, *J* = 8.0 Hz), 129.5, 128.5, 127.2, 115.0 (d, *J* = 21.1 Hz), 53.6, 53.2, 37.0, 36.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.84. IR (ATR): 3055, 2949, 1730, 1685, 1506, 1199, 1182, 1148 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{18}H_{19}FN_2O_3Na$ $[M+Na]^+$: 353.1277, found: 353.1268. $[\alpha]^{25}_D$ +3 (*c* = 0.29, MeOH).



(3*S*,6*R*)-6-benzyl-9,12-di((*Z*)-benzylidene)-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone **(5c')**

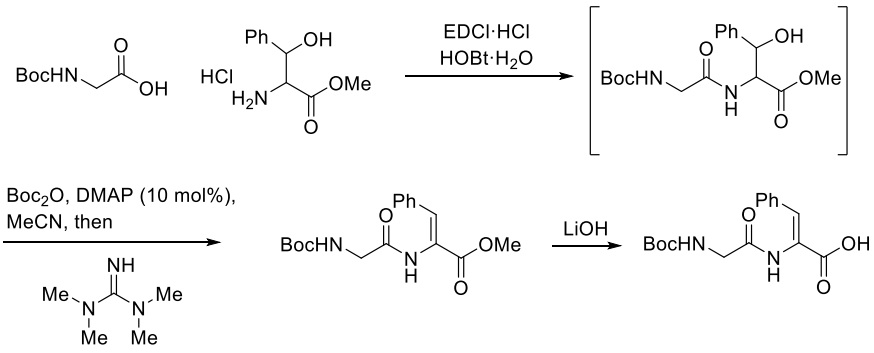


To a solution of dipeptide **S5** (764 mg, 1.72 mmol) in THF/H_2O (1:1, 0.1 M) was added Et_3N (240 µL, 4.05 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **3** (700 mg, 1.56 mmol) in THF (16 mL). The reaction was stirred at rt for 15 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used in the next step without further purification.

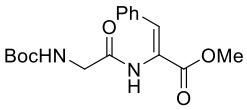
To a round bottom flask equipped with a stir bar under N_2 was added the resulting carboxylic acid (1.56 mmol) and anhydrous DCM (20 mL). The reaction mixture was cooled to 0 °C and TFA (1.8 mL, 23.4 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 2 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure. The crude reaction mixture was further dried on the high vacuum and subsequently triturated with Et_2O to afford TFA·amine salt and was immediately used in the next reaction without further purification. To a round bottom flask equipped with a stir bar was added the corresponding TFA·amine salt (1.56 mmol), HOAt (0.212 g, 1.56 mmol), and DMF (31 mL, 0.05 M). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (0.679 mL, 3.90 mmol) was added. HATU (711 mg, 1.87 mmol) was added in portions and the reaction warmed to rt and stirred for 24 h. The solvent was removed

under reduced pressure and the product was purified by column chromatography (eluting with 1:4 hexanes/EtOAc) to afford the product as a white solid (167 mg, 16% over 3 steps). ^{1}H NMR (400 MHz, DMSO, 330 K) δ 9.85 (s, 1H), 9.44 (s, 1H), 8.33 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 5.5 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.65 – 7.50 (m, 4H), 7.47 – 7.27 (m, 7H), 7.25 – 7.06 (m, *J* = 22.5, 6.2 Hz, 8H), 7.01 (t, *J* = 8.8 Hz, 2H), 6.86 (s, 1H), 4.62 – 4.47 (m, 2H), 4.19 (dd, *J* = 16.7, 6.4 Hz, 1H), 3.75 (dd, *J* = 16.2, 4.5 Hz, 1H), 3.12 – 3.06 (m, 1H), 3.01 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.86 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.79 (dd, *J* = 14.3, 9.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO, 368 K, d1=10 s) δ 171.4, 170.2, 169.6, 164.4, 163.9, 160.5, (d, *J* = 242.1 Hz), 137.6, 133.9, 133.5 (d, *J* = 2.9 Hz), 133.3, 130.1 (d, *J* = 7.9 Hz), 130.0, 129.04, 128.94, 128.84, 128.4, 128.20, 128.18, 128.0, 127.8, 127.7, 127.5, 126.4, 125.5, 114.2 (d, *J* = 21.1 Hz), 54.7, 54.2, 42.1, 36.4, 34.2. ^{19}F NMR (376 MHz, DMSO) δ -117.19. IR (ATR): 3050, 2910, 1657, 1646, 1545, 1506, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{34}N_5O_5Na$ $[M+Na]^+$: 682.2441, found: 682.2449. $[\alpha]^{26}_D$ +202 (*c* = 0.25, DMF).

v) Synthesis of pentapeptide **5d'**



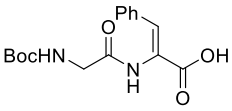
methyl (*Z*)-2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-phenylacrylate (S6)



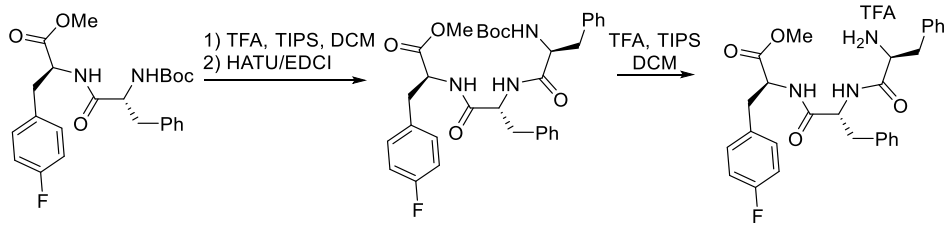
To a round bottom flask equipped with a stir bar was added Boc-Gly-OH (3.00 g, 17.1 mmol), DL-(β-OH)–Phe–OMe (4.20 g, 18.0 mmol), HOBt·H_2O (3.50 g, 20.5 mmol), and DCM (214 mL). The mixture was cooled to 0 °C and *i*-Pr_2EtN (8.90 mL, 51.3 mmol) was subsequently added. EDCI·HCl (3.93 g, 20.5 mmol) was added in portions and the reaction gradually warmed to rt and stirred for 22 h. The reaction mixture was transferred to a separatory funnel and was washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the corresponding dipeptide which was used in the next step without further purification.

The procedure was adapted from Suárez.[7] To a round bottom flask equipped with a stir bar was added the corresponding dipeptide (17.1 mmol), DMAP (209 mg, 1.71 mmol) and MeCN (52 mL). The mixture was cooled to 0 °C and Boc_2O (3.91 g, 18.0 mmol) was quickly added. After disappearance of starting material analyzed via LC-MS, tetramethylguanidine (2.1 mL, 17.1 mmol) was added. After 12 h, the reaction mixture was concentrated under reduced pressure and then purified by column chromatography (eluting with 3:2 hexanes/EtOAc) to afford the unsaturated dipeptide **S6** as a white solid (1.83 g, 32%, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.57 – 7.28 (m, 6H), 5.25 (s, 1H), 3.92 (s, 2H), 3.83 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.54, 165.59, 156.30, 133.54, 133.26, 129.91, 129.76, 128.81, 123.66, 80.65, 52.87, 44.90, 28.42. IR (ATR): 3066, 2988, 1718, 1652, 1545, 1529, 1255, 1165 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{17}H_{22}N_2O_5Na$ $[M+Na]^+$: 357.1426, found: 357.1422

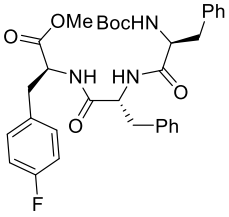
(*Z*)-2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-phenylacrylic acid (S7)



To a round bottom flask equipped with a stir bar was added methyl ester **S6** (1.82 g, 5.44 mmol), THF (26 mL), and H_2O (21 mL). The mixture was cooled to 0 °C and 1 M LiOH (aq) (8.2 mL, 8.2 mmol) was subsequently added. The reaction gradually warmed to rt and stirred for 13 h. The reaction mixture was acidified with 10% $KHSO_4$ (aq), and the THF was concentrated under reduced pressure. The reaction mixture was transferred to a separatory funnel where it was extracted with EtOAc (3 x 100 mL). The organic layer was washed with 100 mL brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford carboxylic acid **S7** as a pale yellow oil (1.6 g, 92%). ^{1}H NMR (400 MHz, DMSO) δ 12.70 (s, 1H), 9.42 (s, 1H), 7.71 – 7.53 (m, 2H), 7.42 – 7.34 (m, 3H), 7.27 (s, 1H), 7.06 (br t, *J* = 5.8 Hz, 1H), 3.69 (d, *J* = 6.0 Hz, 2H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 169.3, 166.3, 155.9, 133.6, 131.7, 130.1, 129.2, 128.5, 126.5, 78.1, 43.3, 28.2. IR (ATR): 3256, 3021, 2982, 1705, 1666, 1634, 1510, 1403, 1271, 1263, 1153 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{16}H_{20}N_2O_5Na$ $[M+Na]^+$: 343.1270, found: 343.1277

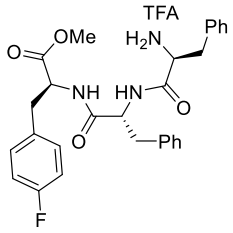


Methyl (6*S*,9*R*,12*S*)-6,9-dibenzyl-12-(4-fluorobenzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (S8)

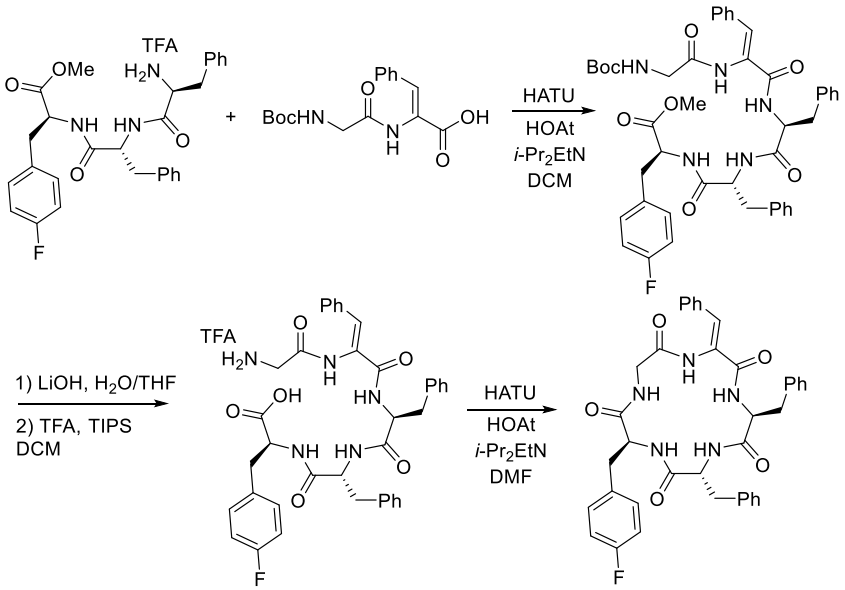


To a round bottom flask equipped with a stir bar was added the Boc-protected dipeptide **S4** (3.5 g, 7.9 mmol), triisopropylsilane (1.62 mL, 7.9 mmol), and DCM (98 mL). The reaction mixture was cooled to 0 °C and TFA (7.7 mL, 101 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 24 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure to afford the TFA·amine salt which was used in the next step without further purification. To a round bottom flask equipped with a stir bar was added the TFA·amine salt (7.9 mmol), Boc-L-Phe-OH (2.1 g, 7.9 mmol), HOBt·H_2O (1.6 g, 9.5 mmol), and DCM (100 mL). The mixture was cooled to 0 °C and *i*-Pr_2EtN (10.3 mL, 59.3 mmol) was subsequently added. EDCI·HCl (1.8 g, 9.5 mmol) was added in portions and the reaction gradually warmed to rt and stirred for 17 h. The reaction mixture was transferred to a separatory funnel and was washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified via column chromatography (eluting with 55:45 hexanes/EtOAc) to afford tripeptide **S8** as a white solid (4.8 g, >99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 7H), 7.16 – 7.11 (m, 2H), 7.02 – 6.82 (m, 6H), 6.64 (s, 1H), 6.24 (s, 1H), 5.03 – 4.95 (m, 1H), 4.79 – 4.66 (m, 1H), 4.67 – 4.55 (m, 1H), 4.21 – 4.12 (m, 1H), 3.63 (s, 3H), 3.05 – 2.86 (m, 5H), 2.83 – 2.71 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 171.3, 170.2, δ 162.1 (d, *J* = 245.5 Hz), 155.59, 155.57, 136.6, 136.2, 131.6 (d, *J* = 1.7 Hz), 130.9 (d, *J* = 7.9 Hz), 129.6, 129.4, 128.89, 128.83, 127.3, 115.5 (d, *J* = 21.3 Hz), 80.6, 56.7, 54.0, 53.6, 52.4, 38.3, 37.4, 37.2, 28.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.04. IR (ATR): 3033, 2915, 1758, 1724, 1629, 1489, 1221, 1160 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{33}H_{38}FN_3O_6Na$ $[M+Na]^+$: 614.2642, found: 614.2623. $[\alpha]^{23}_D$ +38 (*c* = 0.29, $CHCl_3$).

Methyl (*S*)-2-((*R*)-2-((*S*)-2-amino-3-phenylpropanamido)-3-phenylpropanamido)-3-(4-fluorophenyl)propanoate (S9)



To a round bottom flask equipped with a stir bar was added tripeptide **S8** (3.0 g, 5.1 mmol), triisopropylsilane (1.0 mL, 5.1 mmol), and DCM (98 mL). The reaction mixture was cooled to 0 °C and TFA (5.7 mL, 76.5 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 42 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure and triturated with Et_2O to afford tripeptide **S9** as a pale yellow solid (3.3g, >99%). ^{1}H NMR (600 MHz, DMSO) δ 8.89 – 8.86 (d, *J* = 8.3 Hz, 1H), 8.84 (d, *J* = 8.8 Hz, 1H), 8.00 (br s, 2H), 7.34 – 7.28 (m, 2H), 7.25 – 7.19 (m, 5H), 7.19 – 7.14 (m, 1H), 7.14 – 7.07 (m, 4H), 6.95 – 6.87 (m, 2H), 4.71 (m, 1H), 4.54 (m, 1H), 4.00 (br s, 1H), 3.64 (s, 3H), 3.09 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.85 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.78 (dd, *J* = 14.1, 4.5 Hz, 1H), 2.69 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.53 (d, *J* = 14.4, 8.2 Hz, 1H), 2.46 (dd, *J* = 13.6, 10.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 171.8, 170.7, 167.7, 161.2 (d, *J* = 242.3 Hz), 137.3, 134.6, 133.2 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 8.1 Hz), 129.5, 129.4, 128.4, 128.1, 127.1, 126.6, 115.0 (d, *J* = 21.1 Hz), 53.8, 53.4, 53.2, 52.1, 38.4, 36.9, 36.2. ^{19}F NMR (376 MHz, DMSO) δ -116.62. IR (ATR): 3061, 2932, 1741, 1652, 1512, 1143 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{28}H_{30}FN_3O_4H$ $[M+H]^+$: 492.2299, found: 492.2282. $[\alpha]^{26}_D$ +3 (*c* = 0.35, MeOH).



Methyl (12*S*,15*R*,18*S*)-12,15-dibenzyl-9-((*Z*)-benzylidene)-18-(4-fluorobenzyl)-2,2-dimethyl-4,7,10,13,16-pentaoxo-3-oxa-5,8,11,14,17-pentaazanonadecan-19-oate (S10)

To a round bottom flask equipped with a stir bar was added the dipeptide **S7** (1.6 g, 5.0 mmol), tripeptide **S9** (3.0 g, 5.0 mmol), HOAt (681 mg, 5.0 mmol), and DCM (63 mL). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (4.4 mL, 25 mmol) was added. HATU (2.3 g, 6.0 mmol) was added in portions and the reaction warmed to rt and stirred for 14 h. The reaction mixture was transferred to a separatory funnel and was washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified via column chromatography (eluting with 1:1 hexanes/EtOAc) to afford pentapeptide **S10** as a pale yellow solid (3.3 g, 83%). ^{1}H NMR (400 MHz, DMSO) δ 9.59 (s, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.03 (m, 17H), 7.01 (br t, *J* = 5.8 Hz, 1H), 6.87 (s, 1H), 4.60 – 4.49 (m, 2H), 4.49 – 4.38 (m, 1H), 3.81 – 3.67 (m, *J* = 5.2 Hz, 2H), 3.33 (s, 3H), 3.07 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.90 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.86 – 2.57 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 171.8, 171.2, 170.5, 169.8, 164.9, 161.1 (d, *J* = 242.2 Hz), 156.0, 138.0, 137.8, 133.8, 133.2 (d, *J* = 2.8 Hz), 131.2 (d, *J* = 8.0 Hz), 129.6, 129.3, 129.2, 128.9, 128.7, 128.5, 128.0, 127.8, 126.3, 126.1, 114.9 (d, *J* = 21.1 Hz), 78.2, 54.6, 54.0, 53.5, 52.0, 43.6, 37.9, 36.9, 36.1, 28.2. ^{19}F NMR (376 MHz, DMSO) δ -116.89. IR (ATR): 3055, 2966, 1663, 1506, 1216, 1165 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{44}H_{48}FN_5O_8Na$ $[M+Na]^+$: 816.3384, found: 816.3364. $[\alpha]^{24}_D$ +98 (*c* = 0.19, $CHCl_3$).

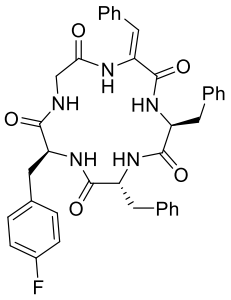
(2*S*,5*R*,8*S*)-14-amino-5,8-dibenzyl-11-((*Z*)-benzylidene)-2-(4-fluorobenzyl)-4,7,10,13-tetraoxo-3,6,9,12-tetraazatetradecanoic acid (S11)

To a round bottom flask equipped with a stir bar was added pentapeptide **S10** (710 mg, 0.93 mmol), THF (4.4 mL), and H_2O (3.6 mL). The mixture was cooled to 0 °C and 1 M LiOH (aq) (1.9 mL, 1.9 mmol) was subsequently added. The reaction gradually warmed to rt and stirred for 39 h. The reaction mixture was acidified with 10% $KHSO_4$ (aq), and the THF was concentrated under reduced pressure. The reaction mixture was transferred to a separatory funnel where it was extracted with DCM (3 x 30 mL). The organic layer was washed with 50 mL

brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired carboxylic acid which was then used in the next step without further purification.

To a round bottom flask equipped with a stir bar was added the pentapeptide carboxylic acid (670 mg, 0.86 mmol), triisopropylsilane (0.18 mL, 0.86 mmol), and DCM (11 mL). The reaction mixture was cooled to 0 °C and TFA (1.0 mL, 12.9 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 49 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure and triturated with Et_2O to afford pentapeptide **S11** as white solid (839 mg, >99%). ^{1}H NMR (600 MHz, DMSO) δ 9.47 (br s, 2H), 8.50 (d, *J* = 7.6 Hz, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.30 – 7.02 (m, 15H), 6.90 (s, 1H), 4.63 – 4.57 (m, 1H), 4.57 – 4.49 (m, 1H), 4.49 – 4.41 (m, 1H), 3.84 – 3.72 (m, 2H), 3.11 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.85 (dd, *J* = 13.5, 9.8 Hz, 1H), 2.81 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.62 (dd, *J* = 13.4, 10.5 Hz, 1H), 2.57 (dd, *J* = 12.8, 11.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 173.0, 171.0, 170.5, 166.5, 164.4, 161.1 (d, *J* = 241.8 Hz), 138.1, 137.8, 133.9 (d, *J* = 2.4 Hz), 133.6, 131.2 (d, *J* = 8.0 Hz), 129.6, 129.3, 129.2, 128.9, 128.7, 128.2, 128.2, 128.00, 127.98, 126.3, 126.2, 114.8 (d, *J* = 21.0 Hz), 54.4, 53.8, 53.7, 40.7, 38.0, 37.1, 36.5. ^{19}F NMR (376 MHz, DMSO) δ -116.99. IR (ATR): 3027, 2932, 1668, 1624, 1534, 1523, 1199, 1132 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{38}FN_5O_6Na$ $[M+Na]^+$: 702.2704, found: 702.2684. $[\alpha]^{26}_D$ +114 (*c* = 0.47, MeOH).

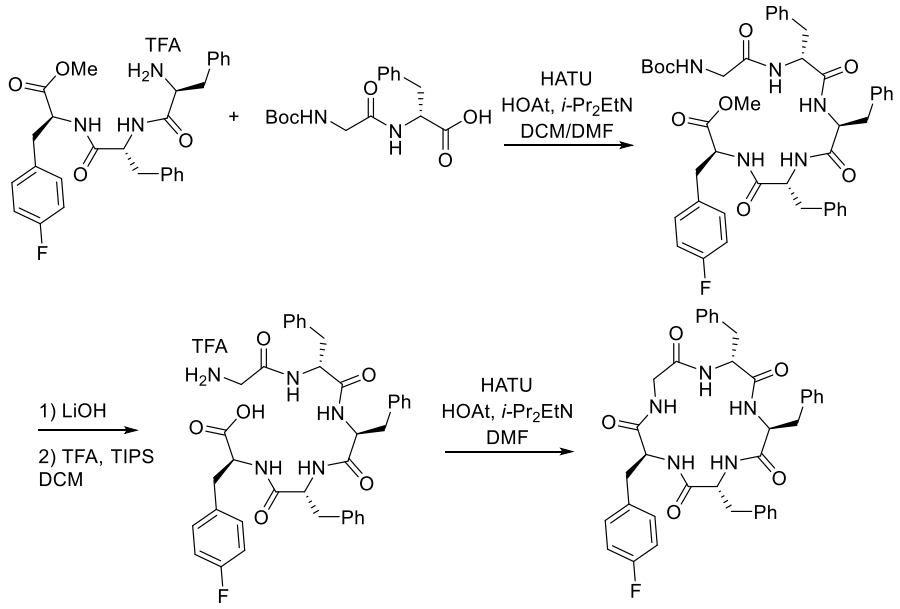
(3*S*,6*R*,9*S*)-6,9-dibenzyl-12-((*Z*)-benzylidene)-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (5d')



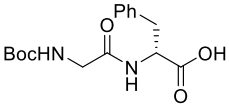
To a round bottom flask equipped with a stir bar was added pentapeptide **S11** (1 g, 1.26 mmol), HOAt (343 mg, 2.52 mmol), and DMF (252 mL). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (1.1 mL, 6.3 mmol) was added. HATU (1.2 g, 3.15 mmol) was added in portions and the reaction warmed to rt and stirred for 25 h. The solvent was removed under reduced pressure and the product was filtered and triturated with methanol and DCM to afford the product as a white solid (398 mg, 48%). ^{1}H NMR (499 MHz, DMSO) δ 9.97 (s, 1H), 8.70 (d, *J* = 7.4 Hz, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 8.20 (t, *J* = 5.0 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.46 – 7.30 (m, 4H), 7.25 – 7.13 (m, *J* = 21.7, 12.0, 4.6 Hz, 8H), 7.11 – 7.02 (m, 4H), 7.01 –

6.95 (m, 3H), 4.57 (dd, *J* = 13.5, 7.0 Hz, 1H), 4.51 (td, *J* = 9.7, 4.4 Hz, 1H), 4.39 (dd, *J* = 14.6, 7.5 Hz, 1H), 3.90 (dd, *J* = 15.2, 6.6 Hz, 1H), 3.83 (dd, *J* = 15.2, 3.8 Hz, 1H), 3.00 (m, 2H), 2.88 – 2.72 (m, 3H), 2.67 (dd, *J* = 14.1, 8.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO, d1=5 s) δ 171.9, 171.2, 170.9, 169.2, 165.0, 160.9 (d, *J* = 241.6 Hz), 137.5, 137.3, 134.0 (d, *J* = 3.0 Hz), 133.6, 130.7 (d, *J* = 8.0 Hz), 129.6, 129.2, 128.9, 128.8, 128.7, 128.6, 128.1, 128.1, 128.0, 126.2, 126.1, 114.8 (d, *J* = 21.0 Hz), 54.4, 54.3, 54.2, 42.4, 37.8, 35.9, 35.0. ^{19}F NMR (376 MHz, DMSO) δ -117.17. IR (ATR): 3089, 2954, 1634, 1551, 1506, 1210 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{36}FN_5O_5Na$ $[M+Na]^+$: 684.2598, found: 684.2586. $[\alpha]^{26}_D$ +154 (*c* = 0.27, DMF).

vi) Synthesis of pentapeptide **6a'**



(*tert*-butoxycarbonyl)glycyl-D-phenylalanine **(S12)**

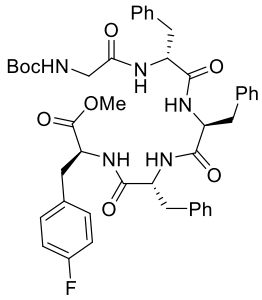


To a round bottom flask equipped with a stir bar was added the Boc-Gly-OH (2 g, 11.4 mmol), Boc-D-Phe-OH (2.7 g, 7.9 mmol), HOBt·H_2O (2.3 g, 13.7 mmol), and DCM (143 mL). The mixture was cooled to 0 °C and *i*-Pr_2EtN (6 mL, 34.2 mmol) was subsequently added. EDCI·HCl (2.6 g, 13.7 mmol) was added in portions and the reaction gradually warmed to rt and stirred for 6 h. The reaction mixture was transferred to a separatory funnel and was washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified via column chromatography (eluting with 2:3 hexanes/EtOAc) to

afford the dipeptide as a colorless oil (3.5 g, 92%). Characterization data was consistent with those previously reported.[8]

To a round bottom flask equipped with a stir bar was added Boc-Gly-Phe-OMe (3.5 g, 10.4 mmol), THF (49 mL), and H_2O (40 mL). The mixture was cooled to 0 °C and 1 M LiOH (aq) (18.7 mL, 18.7 mmol) was subsequently added. The reaction gradually warmed to rt and stirred for 31 h. The reaction mixture was acidified with 10% $KHSO_4$ (aq), and the THF was concentrated under reduced pressure. The reaction mixture was transferred to a separatory funnel where it was extracted with DCM (3 x 100 mL). The organic layer was washed with 100 mL brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a white solid (3.5 g, >99%). Characterization data was consistent with those previously reported.[9]

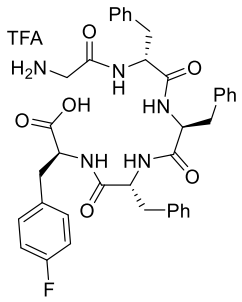
Methyl (9*R*,12*S*,15*R*,18*S*)-9,12,15-tribenzyl-18-(4-fluorobenzyl)-2,2-dimethyl-4,7,10,13,16-pentaoxo-3-oxa-5,8,11,14,17-pentaazanonadecan-19-oate (S13)



To a round bottom flask equipped with a stir bar was added the dipeptide **S12** (536 mg, 1.65 mmol), tripeptide **S9** (1 g, 1.65 mmol), DCM (10 mL), and DMF (2.5 mL). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (2.0 mL, 11.6 mmol) was added. HATU (743 mg, 1.98 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The reaction mixture was washed with sat. $NaHCO_3$ (aq), 10% $KHSO_4$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was dried further on the high vacuum and was purified via column chromatography (eluting with 20:1 DCM/MeOH) to afford a white solid. The solid was further triturated with Et_2O to give pentapeptide **S13** as a white solid (669 mg, 51%). ^{1}H NMR (600 MHz, DMSO) δ 8.69 (d, *J* = 8.2 Hz, 1H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.05 (m, 17H), 6.91 – 6.78 (m, 2H), 4.66 – 4.58 (m, 1H), 4.57 – 4.51 (m, 1H), 4.51 – 4.45 (m, 1H), 3.64 (s, 3H), 3.47 (dd, *J* = 16.8, 5.7 Hz, 1H), 3.39 (dd, *J* = 16.9, 6.1 Hz, 1H), 3.07 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.85 (dd, *J* = 13.6, 10.1 Hz, 1H), 2.70 (dd, *J* = 13.1, 3.1 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.40 – 2.27 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (151 MHz, DMSO) δ 171.8, 171.1, 170.8, 170.4, 168.8, 161.1 (d, *J* = 242.2 Hz), 155.6, 137.9, 137.6, 137.4, 133.2 (d, *J* = 2.8 Hz), 131.2 (d, *J* = 8.0 Hz), 129.37, 129.35, 129.2, 127.91, 127.89, 127.8, 126.3, 126.2, 126.0, 114.9 (d, *J* = 21.1 Hz), 78.0, 53.8, 53.5, 53.34, 53.27, 52.0, 43.0, 38.3, 38.04, 37.99, 36.2, 28.1. ^{19}F NMR

(376 MHz, DMSO) δ -116.67. IR (ATR): 3083, 3027, 2927, 1629, 1534, 1495, 1227, 1154 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{44}H_{50}FN_5O_8Na$ $[M+Na]^+$: 818.3541, found: 818.3521. $[\alpha]^{24}_D$ +18 (*c* = 0.28, $CHCl_3$).

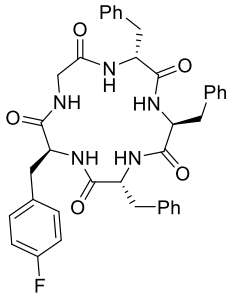
(2*S*,5*R*,8*S*,11*R*)-14-amino-5,8,11-tribenzyl-2-(4-fluorobenzyl)-4,7,10,13-tetraoxo-3,6,9,12-tetraazatetradecanoic acid (S14)



To a round bottom flask equipped with a stir bar was added pentapeptide **S13** (550 mg, 0.69 mmol), THF (7 mL), and H_2O (5 mL). The mixture was cooled to 0 °C and 1 M LiOH (aq) (2.3 mL, 2.3 mmol) was subsequently added. The reaction gradually warmed to rt and stirred for 35 h. The reaction mixture was acidified with 10% $KHSO_4$ (aq), and the THF was concentrated under reduced pressure. The reaction mixture was transferred to a separatory funnel where it was extracted with DCM (3 x 100 mL). The organic layer was washed with 100 mL brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired carboxylic acid which was then used in the next step without further purification.

To a round bottom flask equipped with a stir bar was added the pentapeptide carboxylic acid (0.69 mmol), triisopropylsilane (0.2 mL, 0.79 mmol), and DCM (9.6 mL). The reaction mixture was cooled to 0 °C and TFA (0.900 mL, 11.9 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 12 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure and triturated with Et_2O to afford pentapeptide **S14** as a white solid (621 mg, >99%). ^{1}H NMR (600 MHz, DMSO, 330 K) δ 8.37 – 8.19 (m, 4H), 7.27 – 6.96 (m, 19H), 4.66 – 4.53 (m, 3H), 4.50 – 4.41 (m, 1H), 3.44 (d, *J* = 16.1 Hz, 1H), 3.31 (d, *J* = 16.1 Hz, 1H), 3.09 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.85 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.78 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.68 – 2.59 (m, 1H), 2.53 (dd, *J* = 13.5, 10.6 Hz, 1H), 2.44 – 2.37 (m, 2H). ^{13}C NMR (151 MHz, DMSO, 330 K) δ 173.1, 171.3, 171.1, 170.6, 166.3, 161.6 (d, *J* = 241.9 Hz), 138.23, 138.17, 137.9, 134.2 (d, *J* = 3.1 Hz), 131.6 (d, *J* = 7.9 Hz), 129.78, 129.76, 129.6, 128.4, 128.34, 128.29, 126.69, 126.65, 126.63, 115.2 (d, *J* = 21.2 Hz), 54.2, 54.2, 54.1, 54.0, 40.8, 38.7, 38.6, 38.5, 37.0. ^{19}F NMR (376 MHz, DMSO) δ -117.01. IR (ATR): 3061, 3016, 2910, 1640, 1545, 1501, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{40}FN_5O_6Na$ $[M+Na]^+$: 704.2860, found: 704.2859. $[\alpha]^{26}_D$ +7 (*c* = 0.52, MeOH).

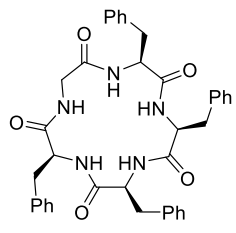
(3*S*,6*R*,9*S*,12*R*)-6,9,12-tribenzyl-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (6a')



To a round bottom flask equipped with a stir bar was added pentapeptide **S14** (200 mg, 0.250 mmol), HOAt (85.1 mg, 0.625 mmol), and DMF (250 mL). The reaction mixture was cooled to 0 ºC and *i*-Pr_2EtN (0.22 mL, 1.25 mmol) was added. HATU (238 mg, 0.625 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The solvent was removed under reduced pressure and then purified by column chromatography (eluting with 4:1 DCM/EtOH) to afford a solid. This solid was further triturated with MeOH and Et_2O to give the title compound as a white solid (20 mg, 12%, >20:1 *dr*). ^{1}H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 6.8 Hz, 1H), 8.54 (d, *J* = 8.3 Hz, 1H), 8.38 (t, *J* = 6 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.28 – 6.96 (m, 19H), 4.65 – 4.55 (m, 1H), 4.54 – 4.43 (m, 2H), 4.40 – 4.32 (m, 1H), 4.26 – 4.16 (m, 1H), 3.71 (dd, *J* = 16.2, 6.4 Hz, 1H), 3.47 (dd, *J* = 16.0, 5.2 Hz, 1H), 3.00 – 2.57 (m, 8H). ^{13}C NMR (151 MHz, DMSO) δ 171.3, 170.9, 170.7, 170.1, 168.4, 160.8 (d, *J* = 242.0 Hz), 137.51, 137.50, 136.9, 133.4 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 8.0 Hz), 128.7, 128.43, 128.42, 127.8, 127.8, 127.7, 126.0, 125.80, 125.76, 114.6 (d, *J* = 21.1 Hz), 55.1, 54.0, 53.3, 53.0, 42.9, 37.4, 36.1, 35.0, 34.8. ^{19}F NMR (376 MHz, DMSO) δ -116.93. IR (ATR): 3055, 2927, 1646, 1540, 1204 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{38}FN_5O_5Na$ $[M+Na]^+$: 686.2755, found: 686.2742. $[\alpha]^{27}_D$ +6 (*c* = 0.18, DMF).

vii) SPPS Syntheses

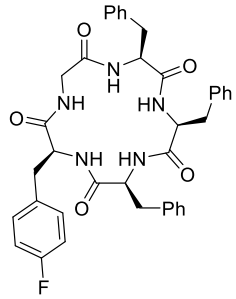
(3*S*,6*S*,9*S*,12*S*)-6,9,12-tribenzyl-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (S15)



The corresponding linear pentapeptide was manually synthesized via Fmoc solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride (CTC) resin (substitution 1.1 mmol/g). The resin (0.360 g, 0.400 mmol) was swelled in anhydrous DCM (20 mL) for 45 min. The beads were washed once with DMF (peptide grade). DMF (10 mL), Fmoc-Phe-OH (620 mg, 1.60 mmol) and *i*-Pr_2EtN (2.5 mL) were added and allowed to mix under N_2 for 15 minutes. The coupling with Fmoc-Phe-OH was repeated again. After the double coupling, the beads were washed with DMF and the Fmoc group was deprotected with 20% 4-methylpiperidine in DMF (20 mL) for 15 minutes.

This deprotection was repeated again. The resin was washed three times with DMF (15 mL) and a Kaiser test was performed to determine presence of deprotected amine. The beads were washed once with *N*-methyl-2-pyrrolidone (15 mL). To begin the next coupling, NMP (10 mL), Fmoc-Phe-OH (620 mg, 1.6 mmol), HBTU (610 mg, 1.6 mmol), and *i*-Pr_2EtN (2.5 mL) were added and the resin bubbled under N_2 for 30 min. The completion of the coupling was monitored by the Kaiser test. If incomplete, the coupling step was repeated again. The resin was washed three times with DMF (15 mL). The deprotection of the Fmoc group was repeated as above two times. To elongate the peptide, the coupling and deprotection steps were performed with Fmoc-Phe-OH, Fmoc-Phe-OH, and Fmoc-Gly-OH. After the last amino acid was deprotected, the beads were washed three times with DMF. To the resin was added 40 mL cleavage solution (95% TFA, 2.5% H_2O, 2.5% triisopropylsilane), and the resin bubbled under N_2 for 3 h. A new receiving flask was replaced on the peptide synthesizer and the TFA was drained into the new flask. The TFA solution was separated into 4 conical vials and cold ether (–20 °C) was added to precipitate the peptide. The vials were centrifuged (3000 rpm, 0–4 °C) for 20 minutes. The remaining TFA and ether solution was decanted from the conical vials and the peptide precipitate was concentrated. Then to a round bottom flask equipped with a stir bar was added the linear pentapeptide (0.400 mmol), HOAt (136 mg, 1.00 mmol), and DMF (400 mL). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (0.348 mL, 2.00 mmol) was added. HATU (380 mg, 1.00 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The solvent was concentrated under reduced pressure and a white solid formed. This solid was then filtered and triturated with DCM, MeOH, and Et_2O to afford the title compound as a white solid (92 mg, 36% overall). The ^{1}H-NMR spectrum was consistent with the cyclic pentapeptide **6b** obtained after asymmetric hydrogenation (Supplementary Figure 6 and 7).

(3*S*,6*S*,9*S*,12*S*)-6,9,12-tribenzyl-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (S16)



The corresponding linear pentapeptide was manually synthesized via Fmoc solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride (CTC) resin (substitution 1.1 mmol/g). The resin (0.360 g, 0.400 mmol) was swelled in anhydrous DCM (20 mL) for 45 min. The beads were washed once with DMF (peptide grade). DMF (10 mL), Fmoc-4-fluoro-Phe-OH (649 mg, 1.60 mmol) and *i*-Pr_2EtN (2.5 mL) were added and allowed to mix under N_2 for

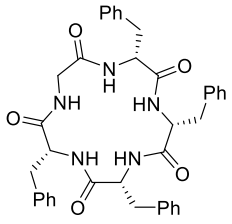
15 minutes. The coupling with Fmoc-4-fluoro-Phe-OH was repeated again. After the double coupling, the beads were washed with DMF and the Fmoc group was deprotected with 20% 4-methylpiperidine in DMF (20 mL) for 15 minutes. This deprotection was repeated again. The resin was washed three times with DMF (15 mL) and a Kaiser test was performed to determine presence of deprotected amine. The beads were washed once with *N*-methyl-2-pyrrolidone (15 mL). To begin the next coupling, NMP (10 mL), Fmoc-Phe-OH (620 mg, 1.6 mmol), HBTU (610 mg, 1.6 mmol), and *i*-Pr_2EtN (2.5 mL) were added and the resin bubbled under N_2 for 30 min. The completion of the coupling was monitored by the Kaiser test. If incomplete, the coupling step was repeated again. The resin was washed three times with DMF (15 mL). The deprotection of the Fmoc group was repeated as above two times. To elongate the peptide, the coupling and deprotection steps were performed with Fmoc-Phe-OH, Fmoc-Phe-OH, and Fmoc-Gly-OH. After the last amino acid was deprotected, the beads were washed three times with DMF. To the resin was added 40 mL cleavage solution (95% TFA, 2.5% H_2O, 2.5% triisopropylsilane), and the resin bubbled under N_2 for 3 h. A new receiving flask was replaced on the peptide synthesizer and the TFA was drained into the new flask. The TFA solution was separated into 4 conical vials and cold ether (–20 °C) was added to precipitate the peptide. The vials were centrifuged (3000 rpm, 0–4 °C) for 20 minutes. The remaining TFA and ether solution was decanted from the conical vials and the peptide precipitate was concentrated. Then to a round bottom flask equipped with a stir bar was added the linear pentapeptide (0.400 mmol), HOAt (136 mg, 1.00 mmol), and DMF (400 mL). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (0.348 mL, 2.00 mmol) was added. HATU (380 mg, 1.00 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The solvent was concentrated under reduced pressure and a white solid formed. This solid was then filtered and triturated with DCM, MeOH, and Et_2O to afford the title compound as a white solid (61 mg, 23% overall). ^{1}H NMR (600 MHz, DMSO) δ 8.52 (br t, *J* = 5.2 Hz, 1H), 8.35 (d, *J* = 7.5 Hz, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.32 – 6.98 (m, 19H), 4.37 – 4.29 (m, 1H), 4.29 – 4.19 (m, 2H), 4.08 – 3.97 (m, 1H), 3.92 (dd, *J* = 14.4, 5.8 Hz, 1H), 3.29 (dd, *J* = 14.3, 4.8 Hz, 1H), 3.12 – 2.84 (m, 7H), 2.80 – 2.69 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 171.4, 171.1, 170.7, 170.6, 169.2, 161.0 (d, *J* = 241.6 Hz), 137.7, 137.5, 137.4, 134.2 (d, *J* = 2.8 Hz), 130.9 (d, *J* = 8.0 Hz), 129.2, 129.1, 129.0, 128.9, 128.3, 128.2, 126.39, 126.37, 126.35, 114.9 (d, *J* = 21.0 Hz), 57.4, 55.9, 55.8, 54.6, 43.3, 36.9, 36.5, 35.7, 30.7. ^{19}F NMR (376 MHz, DMSO) δ -117.17. IR (ATR): 3083, 3022, 2932, 1640, 1495, 1216 cm^{-1}. HRMS (ESI-

TOF) *m/z* calc'd for $C_{38}H_{38}FN_5O_5$ $[M+Na]^+$: 686.2755, found: 686.2736. $[\alpha]^{27}_D$ –97 (*c* = 0.22, DMF).

3) General procedures for hydrogenation

Representative examples:

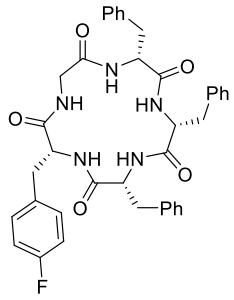
Method A – Hydrogenation using Schlenk tube



(3*R*,6*R*,9*R*,12*R*)-3,6,9,12-tetrabenzyl-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (6b)

In a nitrogen-filled glove box, to a Schlenk vial equipped with a stir bar was added (*R*,*R*',*S*,*S*')-DuanPhos (3 mg, 0.0079 mmol) and $[Rh(cod)_2]BF_4$ (3 mg, 0.0075 mmol) in dry and degassed MeOH (2 mL). This mixture was stirred at rt for 5 min, then cyclic peptide **5a** (128 mg, 0.2 mmol) in MeOH (4 mL) was added to this mixture. The Schlenk tube was sealed, removed from the nitrogen box, and then connected to a Schlenk line (vacuum gas manifold). The pre-catalyst solution was degassed via three cycles of 'freeze-pump-thaw'. On the last 'thaw' cycle, the Schlenk tube was backfilled with H_2 gas and subsequently sealed while the reaction mixture was still frozen. The Schlenk tube was allowed to thaw to pressurize the vial and the reaction mixture was stirred at rt for 48 h, over which an off-white solid precipitated from the solution. The heterogeneous mixture was then collected into a scintillation vial and concentrated under reduced pressure. The resulting crude solid was triturated in DCM and MeOH and then filtered to afford an off-white solid (108 mg, 86%, >99% *ee*). ^{1}H NMR (300 MHz, DMSO) δ 8.53 (t, *J* = 5.4 Hz, 1H), 8.34 (d, *J* = 7.4 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.10 (m, 18H), 7.09 - 7.02 (m, 2H), 4.35 (m, 1H), 4.24 (m, 2H), 4.04 (q, *J* = 7.8 Hz, 1H), 3.92 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.28 (dd, *J* = 14.5, 5.1 Hz, 1H), 3.17 (d, *J* = 5.3 Hz, 1H), 3.11 (dd, *J* = 13.8, 5.5 Hz, 1H), 3.02 - 2.85 (m, 6H), 2.74 (dd, *J* = 14.1, 9.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 171.5, 171.1, 170.7, 170.6, 169.1, 138.0, 137.7, 137.5, 137.4, 129.1, 129.1, 129.0, 128.8, 128.19, 128.17, 126.3, 57.4, 56.0, 55.8, 54.6, 43.3, 36.9, 36.8, 36.6, 36.5. IR (ATR): 3295, 3028, 2926, 1615, 1528, 1496, 1454, 837 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{39}N_5O_5$ $[M+H]^+$: 646.3020, found 646.3023.

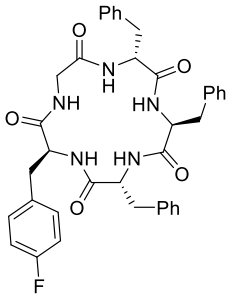
(3*R*,6*R*,9*R*,12*R*)-3,6,9,12-tetrabenzyl-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (6b')



In a nitrogen-filled glove box, to a Schlenk vial equipped with a stir bar was added (*R,R',S,S'*)-DuanPhos (0.29 mg, 0.00076 mmol) and $[Rh(cod)_2]BF_4$ (0.31 mg, 0.00076 mmol) in dry and degassed MeOH (0.350 mL). This mixture was stirred at rt for 5 min, then cyclic peptide **1** (10 mg, 0.015 mmol) in MeOH (0.300 mL) was added to this mixture. The Schlenk tube was sealed, removed from the nitrogen box, and then connected to a Schlenk line (vacuum gas manifold). The pre-catalyst solution was degassed via three cycles of 'freeze-pump-thaw'. On the last 'thaw' cycle, the Schlenk tube was backfilled with H_2 gas and subsequently sealed while the reaction mixture was still frozen. The Schlenk tube was allowed to thaw to pressurize the vial and the reaction mixture was stirred at 50 °C for 48 h, over which an off-white solid precipitated from the solution. The heterogeneous mixture was then collected into a scintillation vial and concentrated under reduced pressure. The resulting crude solid was triturated in DCM and MeOH and then filtered to afford an off-white solid (7.2 mg, 72%, 20:<1 *dr*). The diastereoselectivity was determined by ^{19}F-NMR analysis of the unpurified reaction mixture The ^{1}H-NMR spectrum of **6b'** was consistent with an authentic sample synthesized via SPPS (page 26). ^{1}H NMR (400 MHz, DMSO) δ 8.52 (br t, *J* = 5.4 Hz, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 5.3 Hz, 1H), 7.32 – 6.96 (m, 19H), 4.38 – 4.29 (m, 1H), 4.29 – 4.19 (m, 2H), 4.07 – 3.99 (m, 1H), 3.92 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.30 – 3.24 (m, 1H), 3.14 – 2.81 (m, 7H), 2.81 – 2.63 (m, 1H).

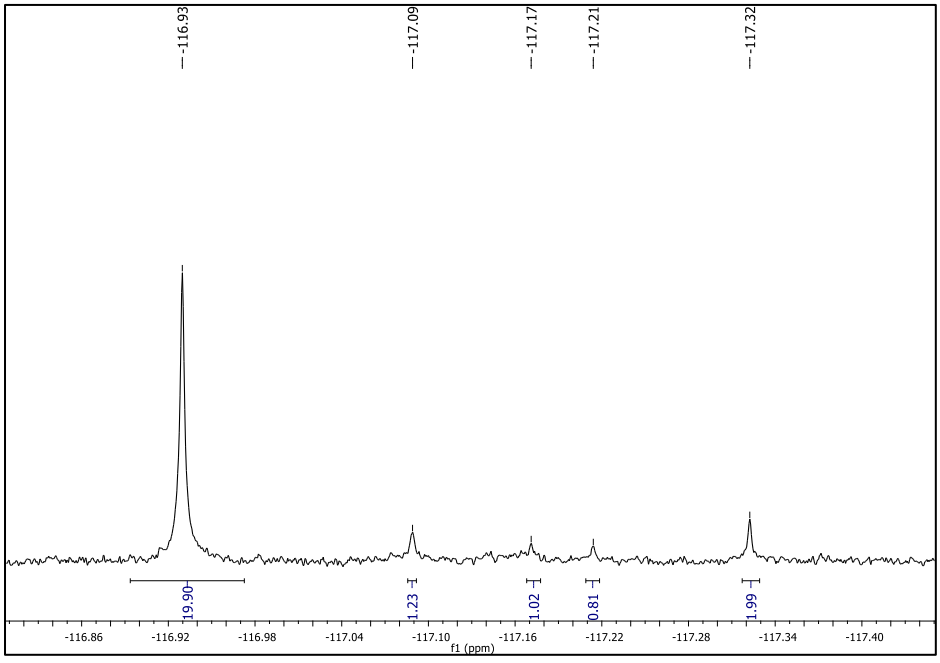
Method B – Hydrogenation using Hel Reactor

(3*S*,6*R*,9*S*,12*R*)-6,9,12-tribenzyl-3-(4-fluorobenzyl)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (±)**-6a'**



In a N_2-filled glovebox, $[Rh(cod)_2]BF_4$ (0.31 mg, 0.00076 mmol, 5 mol%) and dppp (0.32 mg, 0.00076 mmol, 5 mol%) in MeOH/DMF (4:1, 306 µL, 0.05 M) were added to a ½ dr vial equipped with a stir bar containing pentapeptide **5a'** (10 mg, 0.0153 mmol). The vial was capped with a screwcap with a slitted rubber septum and taken outside of the glovebox. The vial was sonicated to ensure all contents were dissolved and then placed in the HEL CATalyst block and the head was screwed into place. The block was filled then purged three times with hydrogen,

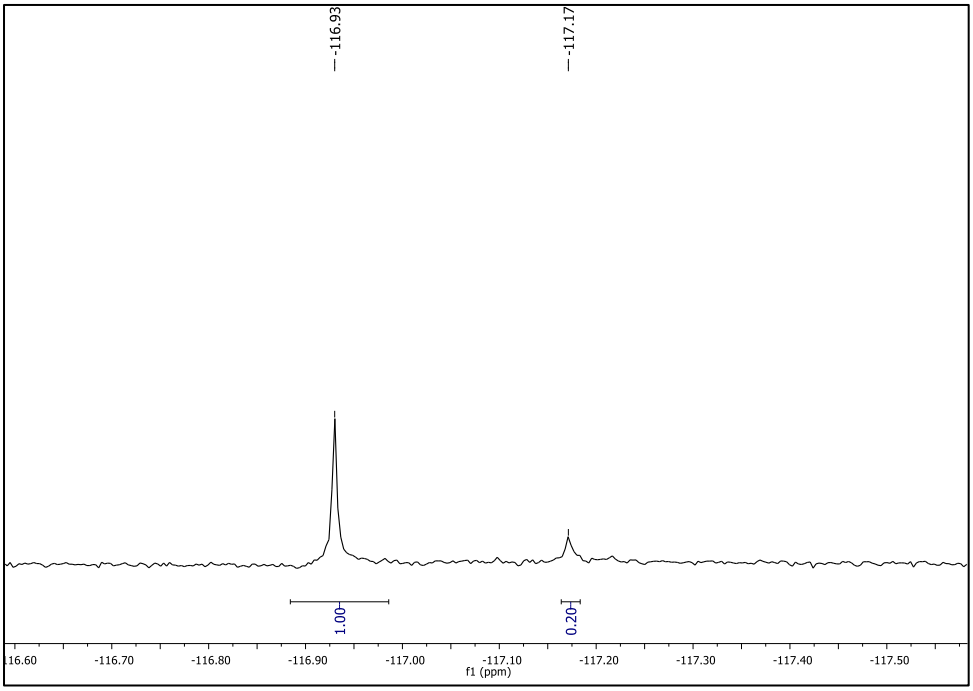
and then pressurized with hydrogen to 7 atm (100 psi). The reaction stirred at 40 ºC and was stopped after 48 h. The solvent was concentrated under reduced pressure and the reaction mixture was triturated with DCM to afford the title compound as an off-white solid (8.9 mg, 88%, 20:2:1:1:1 *dr*).[b] The diastereoselectivity was determined by ^{19}F-NMR analysis of the unpurified reaction mixture (For representative example, see Supplementary Figure 1). ^{1}H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 6.8 Hz, 1H), 8.54 (d, *J* = 8.3 Hz, 1H), 8.38 (t, *J* = 6 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.28 – 6.96 (m, 19H), 4.65 – 4.55 (m, 1H), 4.54 – 4.43 (m, 2H), 4.40 – 4.32 (m, 1H), 4.26 – 4.16 (m, 1H), 3.71 (dd, *J* = 16.2, 6.4 Hz, 1H), 3.47 (dd, *J* = 16.0, 5.2 Hz, 1H), 3.00 – 2.57 (m, 8H). ^{13}C NMR (151 MHz, DMSO) δ 171.3, 170.9, 170.7, 170.1, 168.4, 160.8 (d, *J* = 242.0 Hz), 137.5, 137.5, 136.9, 133.4 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 8.0 Hz), 128.7, 128.43, 128.42, 127.81, 127.75, 127.7, 126.0, 125.8, 125.7, 114.6 (d, *J* = 21.1 Hz), 55.1, 54.0, 53.3, 53.0, 42.9, 37.4, 36.1, 35.0, 34.8. ^{19}F NMR (376 MHz, DMSO) δ -116.93. IR (ATR): 3055, 2927, 1646, 1540, 1204 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{38}H_{38}FN_5O_5Na$ $[M+Na]^+$: 686.2755, found: 686.2742.



Supplementary Figure 1. Representative example for determination of diastereoselectivity by ^{19}F-NMR

[b] (±) Diastereomer **6a'** was observed as the major product (20:2:1:1:1). Four additional minor diastereomers were observed by ^{19}F-NMR spectroscopy. The other three possible diastereomers were not observed.

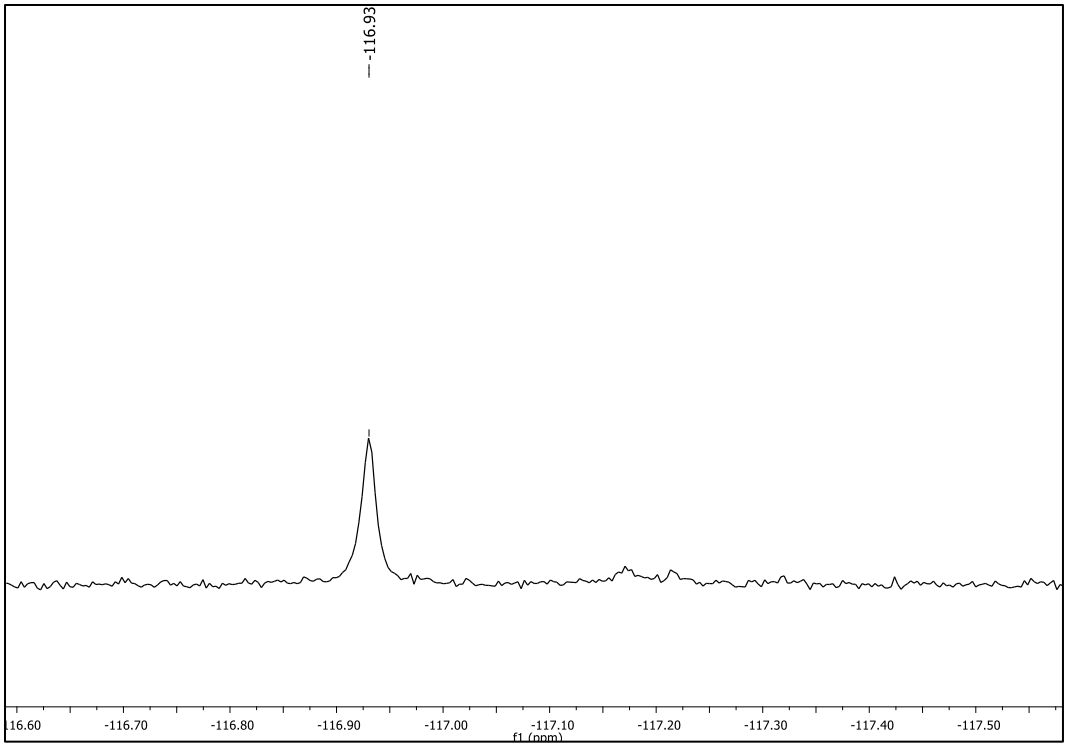
Figure 4b, entry 1: 6a' was prepared according to method B using $[Rh(cod)_2]BF_4$ (0.31 mg, 0.00076 mmol, 5 mol%) and dppp (0.32 mg, 0.00076 mmol, 5 mol%) in MeOH/DMF (4:1, 306 µL, 0.05 M), and pentapeptide **5b'** (10 mg, 0.0153 mmol). The diastereoselectivity was determined by ^{19}F-NMR analysis of the unpurified reaction mixture. The product was isolated as an off white solid (7.7 mg, 76%, 20:<1:<1:<1:<1 *dr*).



Supplementary Figure 2. ^{19}F-NMR of unpurified reaction mixture for entry 1. Peak at 117.17 ppm represents cyclic peptide intermediate **5d'**.

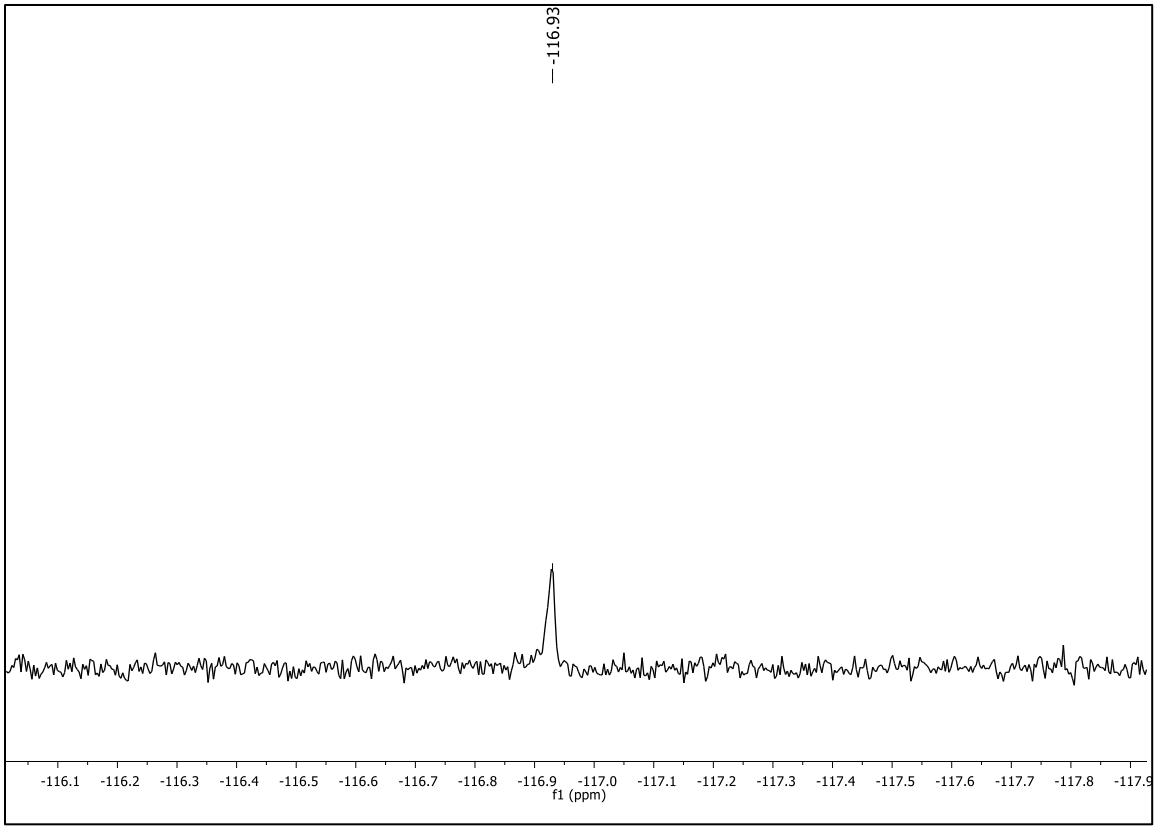
Figure 4b, entry 2[c]: 6a' was prepared according to method B using $[Rh(cod)_2]BF_4$ (0.15 mg, 0.00038 mmol, 5 mol%) and dppp (0.16 mg, 0.00038 mmol, 5 mol%) in MeOH/DMF (4:1, 304 µL, 0.025 M), and pentapeptide **5c'** (5 mg, 0.0076 mmol) stirring at 60 °C and H_2 (20 atm). The diastereoselectivity was determined by ^{19}F-NMR analysis of the unpurified reaction mixture. The product was isolated as an off white solid (5.0 mg, 99%, 20:<1:<1:<1:<1 *dr*).

[c] Figure 4b entries 2 and 3 required higher temperature, pressure, and/or solvent due to difficulties with solubility as the number of dehydrophenylalanines decreases in the starting compound.

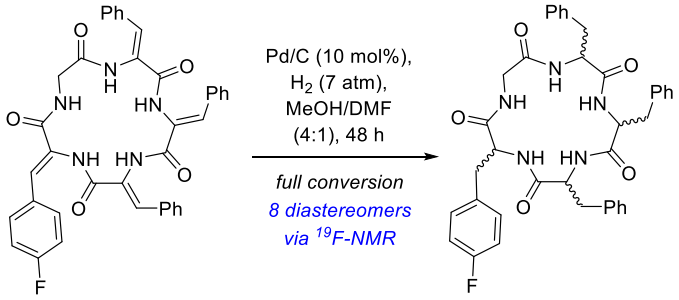


Supplementary Figure 3. ^{19}F-NMR of unpurified reaction mixture for entry 2.

Figure 4b, entry 3: 6a' was prepared according to method B using $[Rh(cod)_2]BF_4$ (0.31 mg, 0.00076 mmol, 10 mol%) and dppp (0.31 mg, 0.00076 mmol, 10 mol%) in THF (500 µL, 0.015 M), and pentapeptide **5d'** (5 mg, 0.0076 mmol) stirring at 80 °C and H_2 (40 atm). The diastereoselectivity was determined by ^{19}F-NMR analysis of the unpurified reaction mixture. The product was isolated as an off white solid (5.0 mg, 99%, 20:<1:<1:<1:<1 *dr*).

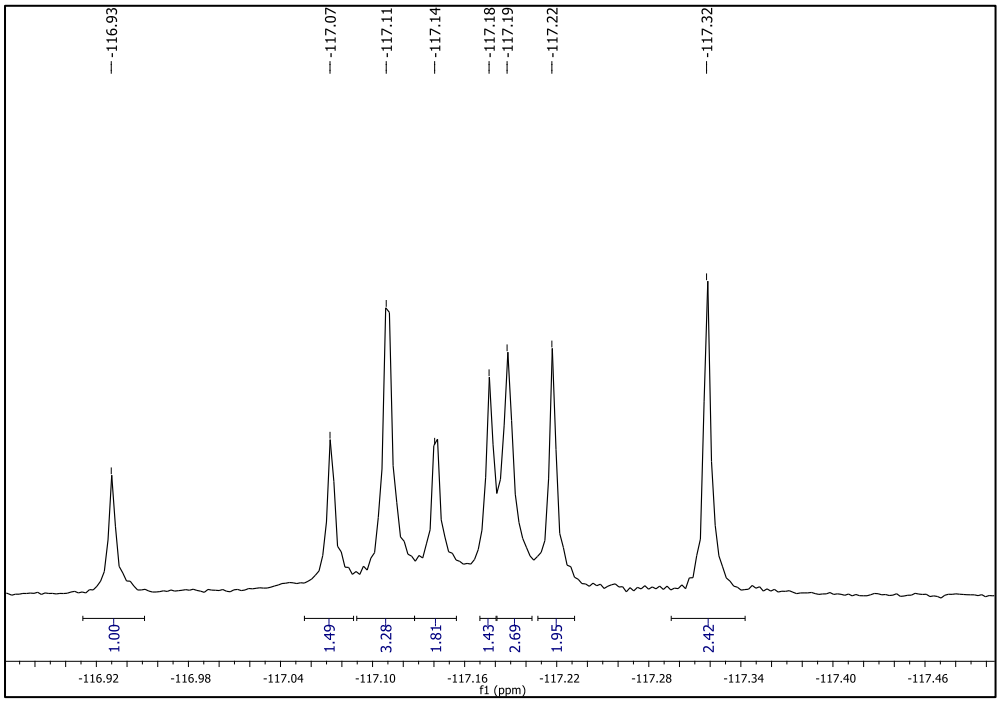


Supplementary Figure 4. ^{19}F-NMR of unpurified reaction mixture for entry 3.



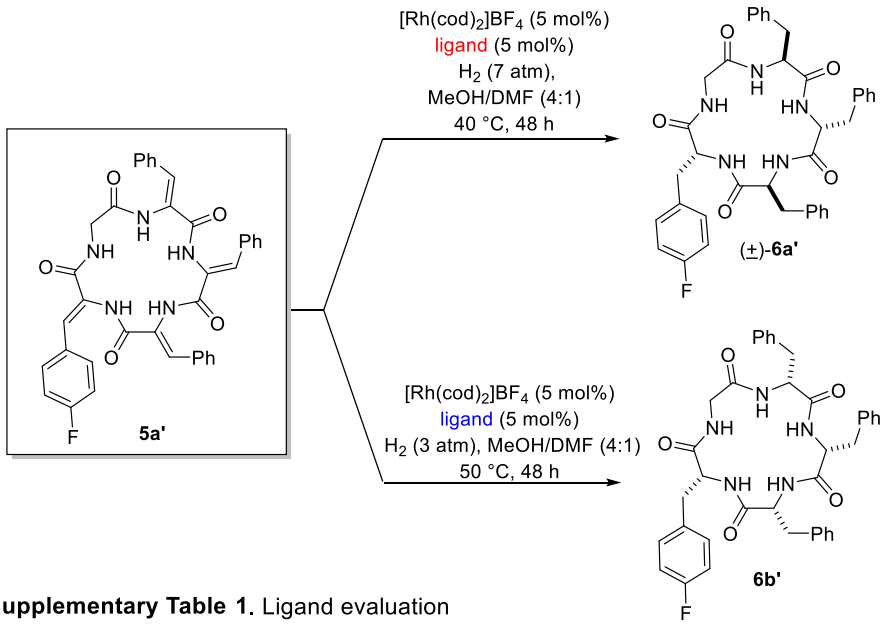
To a ½ dr vial equipped with a stir bar was added cyclic pentapeptide **5a'** (10 mg, 0.0153 mmol) and 10% Pd/C (1.6 mg, 0.00153 mmol, 10 mol%). The contents were dissolved in MeOH/DMF (4:1, 306 µL, 0.05 M) and the vial was capped with a screwcap with a slitted rubber septum. The vial was sonicated to ensure all contents were dissolved and then placed in the HEL CATalyst block and the head was screwed into place. The block was filled then purged three times with hydrogen, and then pressurized with hydrogen to 7 atm. After 48 h and the reaction mixture was filtered through a plug of celite, eluted with MeOH, concentrated under reduced pressure and then

analyzed by ^{19}F-NMR and LC-MS analysis, which showed the presence of 8 diastereomers (Supplementary Figure 5).

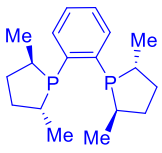
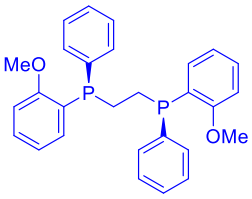
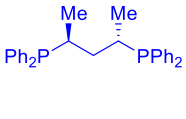
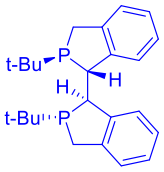
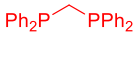
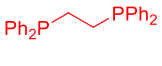
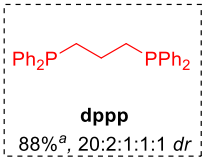
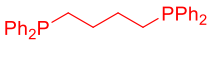
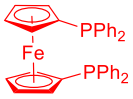


Supplementary Figure 5. ^{19}F-NMR of unpurified reaction mixture after Pd/C hydrogenation (1.0:1.5:3.3:1.8:1.4:2.7:2.0:2.4 *dr*)

4) Ligand evaluation



Supplementary Table 1. Ligand evaluation

chiral ligands (yield of **6b'**)			
			
(*R*,*R*)-Me-DuPhos 0%	**(*R*,*R*)-DIPAMP** 0%	**(*S*,*S*)-BDPP** 13%, *dr* n.d	**(*R*,*R'*,*S*,*S'*)-DuanPhos** 72%[a], 20:<1 *dr*
achiral ligands (yield of (±)-6a')			
				
dppm 0%	**dppe** 0%	**dppp** 88%[a], 20:2:1:1:1 *dr*	**dppb** 50%, 20:<1:<1:<1:<1 *dr*	**dppf** 0%

[a] Isolated yield

For the ligand evaluation of cyclic pentapeptide **5a'** to form **6b'**, method A was used for the hydrogenation (Supplementary Table 1). For the reaction of cyclic peptide **5a'** to form (±)-**6a'**, method B was used for the hydrogenation. Yields and diastereoselectivity were determined by ^{19}F-NMR spectroscopy analysis of the unpurified reaction mixture.

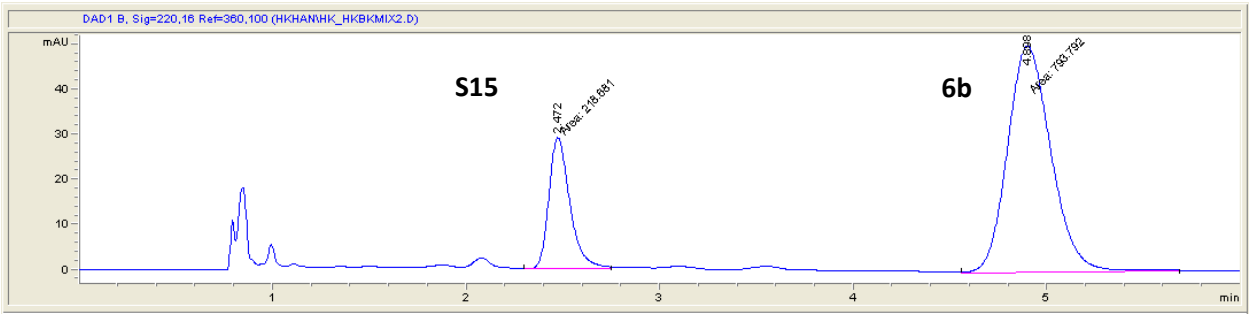
5) NMR time trace

Five independent hydrogenations were set up using general hydrogenation procedure method B. The reaction was quenched at incomplete conversion at t=0 min, 7 min, 1 h, 16 h, and 48 h by opening the reaction to air. ^{19}F-NMR time points in Figure 4a were performed on a 400 MHz Bruker DRX400 spectrometer at 298 K, 8 scans, and 30 s relaxation delay. The NMR spectra was taken in DMSO-d_6 solvent.

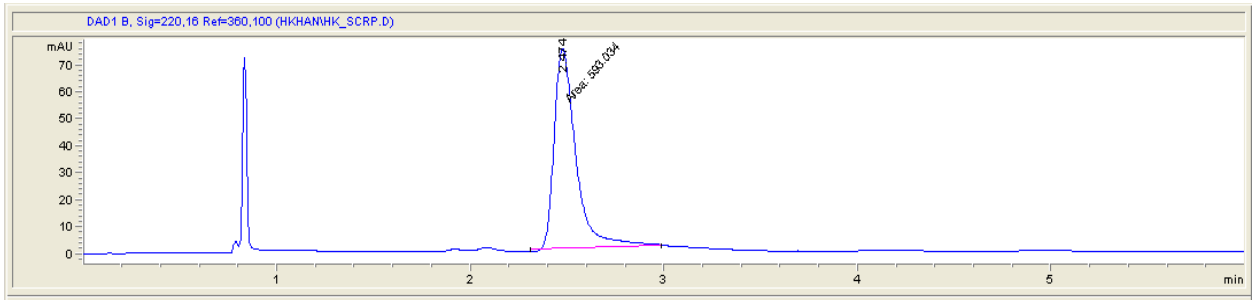
6) Determination of absolute stereochemistry via SFC analysis

Column: IC, 40% MeOH isocratic, thermostat set to 44 ˚C, sample prepared in 1:1 DCM/MeOH

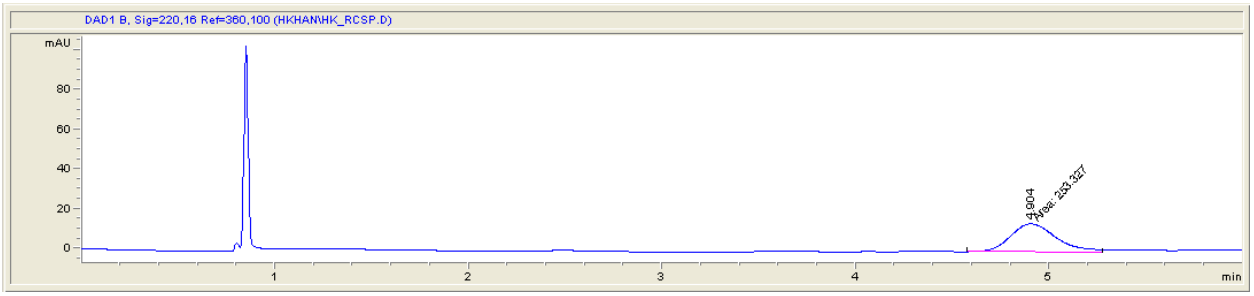
1. Cyclo(Gly-L-Phe-L-Phe-L-Phe-L-Phe) (**S15**) made from authentic (L-Phe)$_4$-OH and **6b**

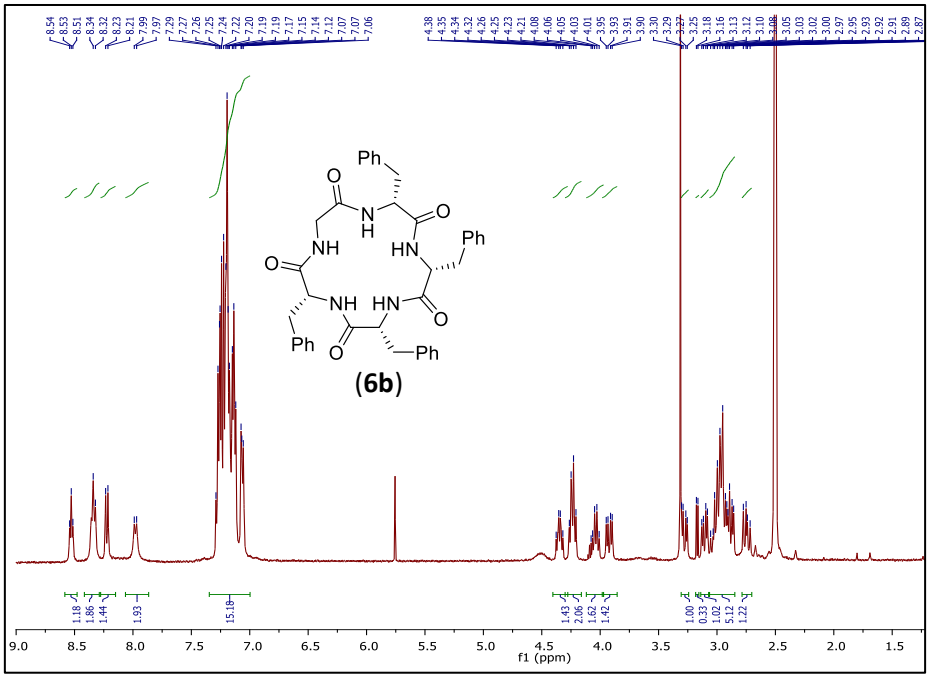


2. **S15** made from hydrogenation of pentapeptide **5a** with (*S,S',R,R'*)-DuanPhos as the ligand

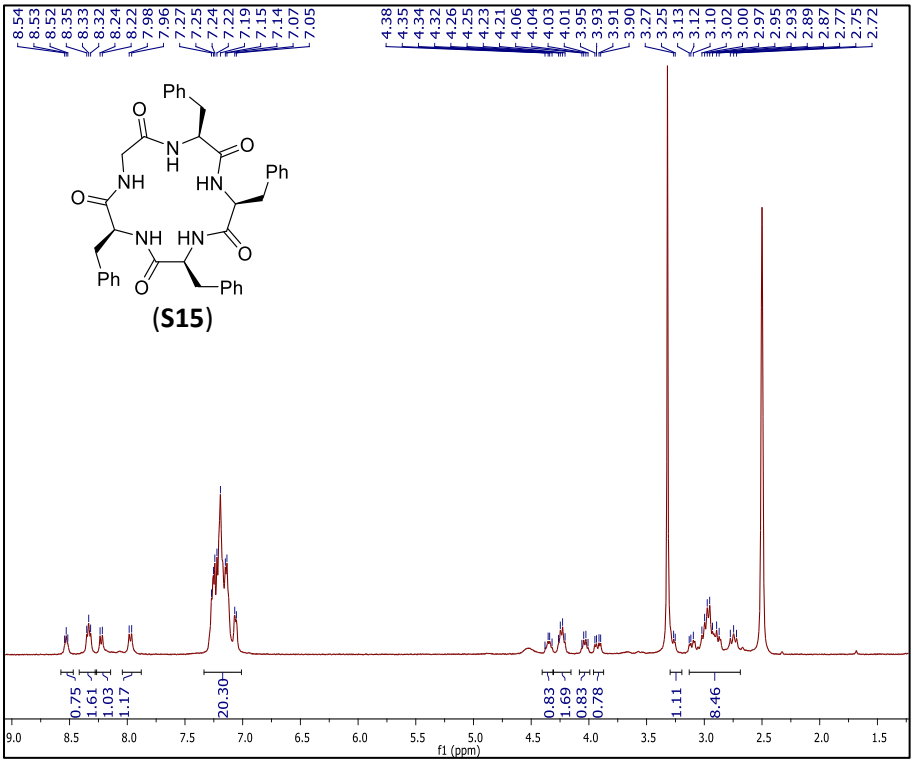


3. **6b** made from hydrogenation of **5a** using (*R,R',S,S'*)-Duanphos



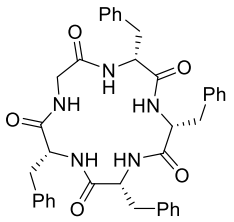


Supplementary Figure 6. ^{1}H-NMR of cyclic pentapeptide **6b** after hydrogenation using (*R*,*R*',*S*,*S*')-Duanphos



Supplementary Figure 7. ^{1}H-NMR of cyclic pentapeptide **S15** made via SPPS

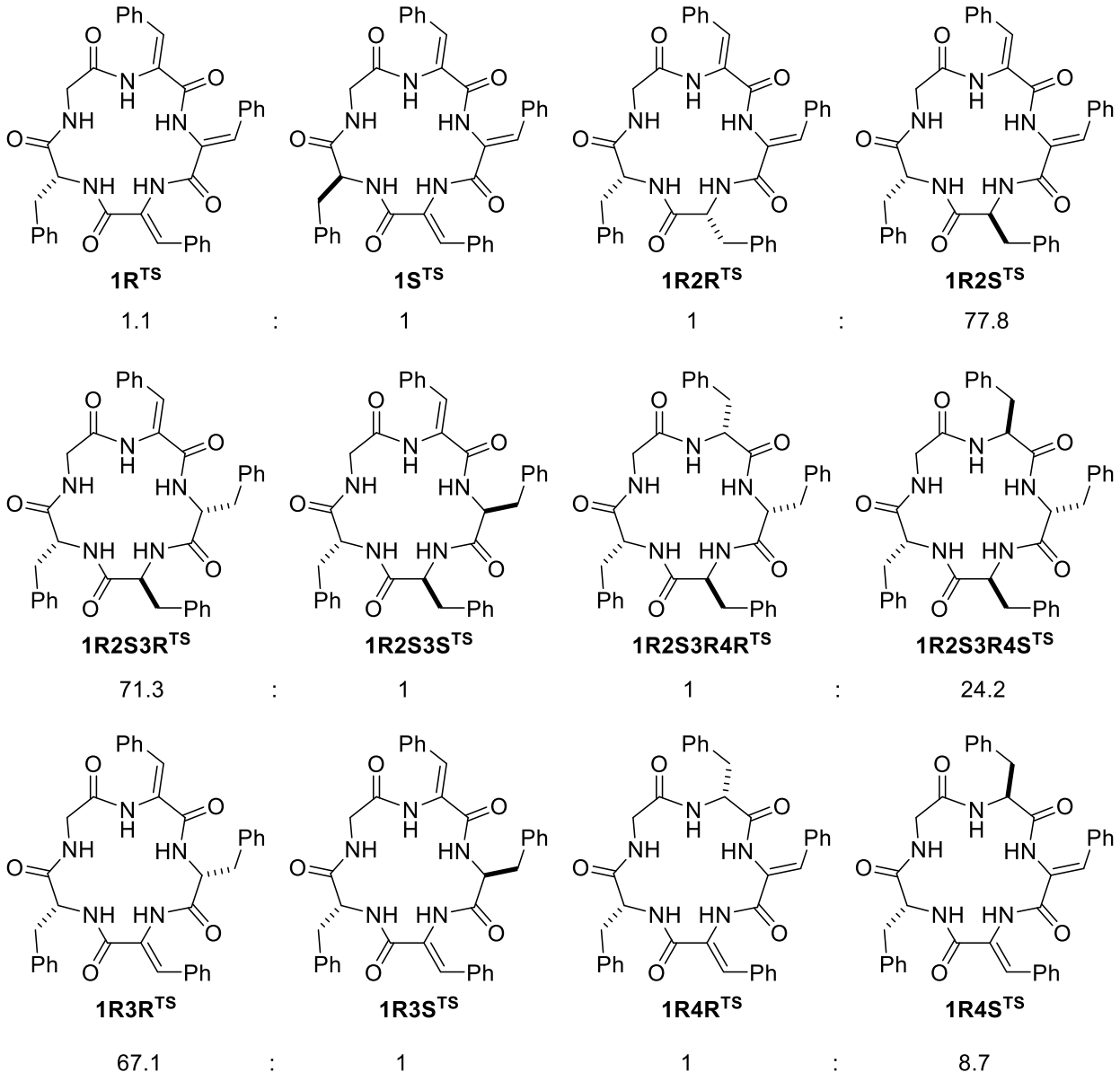
The absolute stereochemistry of **6b** when using $Rh(cod)_2BF_4$ and (*R,R',S,S'*)–Duanphos gives the D-amino acid configuration.



7) Computational Data

i) Transition state force field sampling

The Q2MM transition state force field for the rhodium catalyzed hydrogenation of enamides, previously developed in our group,[10,11] was used to study the various hydrogenation transition states leading to the oligopeptides shown in Supplementary Figure 8. Various conformational search algorithms in MacroModel (2016 release 3) were used for the sampling, including MacroModel's Monte Carlo multiple minimum searching (MCMM),[12,13] low-mode conformational searching (LMCS), [14,15] and low-mode conformational searching for large molecules (LMC2).[16,17] The results of all the searches using the various methods are aggregated into the final ensembles used for Boltzmann averaging. The extent of the sampling is shown in Supplementary Table 2.



Supplementary Figure 8. The rhodium catalyzed diastereomeric hydrogenation transition states leading to these oligopeptides were extensively sampled using the Q2MM TSFF. The predicted *anti* : *syn* ratio, predicted from the TSFF Boltzmann populations, is shown below each pair of diastereomeric transition states.

Conformer	MCMM steps	LMCS steps	LMC2 steps	Total steps	Energy (kJ/mol)	Total conformers
1R^{TS}	200000	5000	401000	606000	544.5	2142
1R2R^{TS}	10000	55000	50000	115000	600.1	2650
1R2S^{TS}	10000	55000	50000	115000	586.3	989
1R2S3R^{TS}	20000	105000	50000	175000	621.2	699

Conformer	MCMM steps	LMCS steps	LMC2 steps	Total steps	Energy (kJ/mol)	Total conformers
1R2S3R4R^{TS}	10000	55000	50000	115000	681.5	2215
1R2S3R4S^{TS}	10000	55000	50000	115000	673.1	1160
1R2S3S^{TS}	30000	105000	50000	185000	633.4	1674
1R3R^{TS}	0	100000	0	100000	566.5	437
1R3S^{TS}	0	100000	0	100000	572.7	714
1R4R^{TS}	0	55000	0	55000	577.9	787
1R4S^{TS}	0	55000	0	55000	573.1	721
1S^{TS}	10000	5000	261000	276000	544.5	648
1S2R^{TS}	20000	5000	100000	125000	586.3	2086
1S2S^{TS}	20000	5000	100000	125000	600.1	4713

Supplementary Table 2. Extent of conformational sampling done on all diastereomeric transition states. Energies shown are the TSFF potential energies for the minimum energy conformers identified in each ensemble.

ii) Example MacroModel conformational search command

The following is an example MacroModel conformational search input file for diastereomeric transition state **1R2S^{TS}**. Various combinations of MCMM, LMCS and LMC2 were used (this example shows MCMM).

```
c1r2s_004.mae
c1r2s_005.mae
 MMOD       0      1      0      0     0.0000     0.0000     0.0000     0.0000
 DEBG      55    179      0      0     0.0000     0.0000     0.0000     0.0000
 SEED   40000      0      0      0     0.0000     0.0000     0.0000     0.0000
 FFLD       2      1      0      0     1.0000     0.0000     0.0000     0.0000
 EXNB       0      0      0      0     0.0000     0.0000     0.0000     0.0000
 BDCO       0      0      0      0    89.4427 99999.0000     0.0000     0.0000
 READ       0      0      0      0     0.0000     0.0000     0.0000     0.0000
 CRMS       0      0      0      0     0.0000     0.5000     0.0000     0.0000
 MCMM   10000      0      0      0     0.0000     0.0000     0.0000     0.0000
 NANT       0      0      0      0     0.0000     0.0000     0.0000     0.0000
 MCNV       1      5      0      0     0.0000     0.0000     0.0000     0.0000
 MCSS       2      0      0      0    50.0000     0.0000     0.0000     0.0000
 MCOP       1      0      0      0     0.5000     0.0000     0.0000     0.0000
 DEMX       0   1000      0      0    50.0000   100.0000     0.0000     0.0000
 COMP       1      2      3      4     0.0000     0.0000     0.0000     0.0000
 COMP       5      6      7      8     0.0000     0.0000     0.0000     0.0000
 COMP       9     12     13     14     0.0000     0.0000     0.0000     0.0000
 COMP      15     16     17     20     0.0000     0.0000     0.0000     0.0000
 COMP      21     22     23     24     0.0000     0.0000     0.0000     0.0000
 COMP      25     28     29     30     0.0000     0.0000     0.0000     0.0000
 COMP      31     32     33     48     0.0000     0.0000     0.0000     0.0000
 COMP      49     50     51     52     0.0000     0.0000     0.0000     0.0000
 COMP      53     55     56     58     0.0000     0.0000     0.0000     0.0000
 COMP      59     60     61     62     0.0000     0.0000     0.0000     0.0000
 COMP      63     69     70     71     0.0000     0.0000     0.0000     0.0000
```

```
COMP      72     73     74     75     0.0000     0.0000     0.0000     0.0000
COMP      76     77     78     79     0.0000     0.0000     0.0000     0.0000
COMP      80     81     82     83     0.0000     0.0000     0.0000     0.0000
COMP      84     85     86     87     0.0000     0.0000     0.0000     0.0000
COMP      88     89     90     91     0.0000     0.0000     0.0000     0.0000
COMP      92     93     94     95     0.0000     0.0000     0.0000     0.0000
COMP      96     97     98     99     0.0000     0.0000     0.0000     0.0000
COMP     100    101    102    103     0.0000     0.0000     0.0000     0.0000
COMP     104    105    132    133     0.0000     0.0000     0.0000     0.0000
MSYM       0      0      0      0     0.0000     0.0000     0.0000     0.0000
CHIG      82      0      0      0     0.0000     0.0000     0.0000     0.0000
AUOP       0      0      0      0   100.0000     0.0000     0.0000     0.0000
TORS       1    133      0      0     0.0000   180.0000     0.0000     0.0000
TORS       2      7      0      0     0.0000   180.0000     0.0000     0.0000
TORS       2     15      0      0     0.0000   180.0000     0.0000     0.0000
TORS       2     48      0      0     0.0000   180.0000     0.0000     0.0000
TORS       3     23      0      0     0.0000   180.0000     0.0000     0.0000
TORS       3     31      0      0     0.0000   180.0000     0.0000     0.0000
TORS       3     48      0      0     0.0000   180.0000     0.0000     0.0000
TORS       3    132      0      0     0.0000   180.0000     0.0000     0.0000
TORS      48     52      0      0     0.0000   180.0000     0.0000     0.0000
TORS      48     56      0      0     0.0000   180.0000     0.0000     0.0000
TORS      50     51      0      0     0.0000   180.0000     0.0000     0.0000
TORS      50     77      0      0     0.0000   180.0000     0.0000     0.0000
TORS      51     52      0      0     0.0000   180.0000     0.0000     0.0000
TORS      52     53      0      0     0.0000   180.0000     0.0000     0.0000
TORS      52     84      0      0     0.0000   180.0000     0.0000     0.0000
TORS      53     61      0      0     0.0000   180.0000     0.0000     0.0000
TORS      69     71      0      0     0.0000   180.0000     0.0000     0.0000
TORS      70     80      0      0     0.0000   180.0000     0.0000     0.0000
TORS      71     72      0      0     0.0000   180.0000     0.0000     0.0000
TORS      72     74      0      0     0.0000   180.0000     0.0000     0.0000
TORS      73     89      0      0     0.0000   180.0000     0.0000     0.0000
TORS      74     76      0      0     0.0000   180.0000     0.0000     0.0000
TORS      76     77      0      0     0.0000   180.0000     0.0000     0.0000
TORS      78     79      0      0     0.0000   180.0000     0.0000     0.0000
TORS      80     81      0      0     0.0000   180.0000     0.0000     0.0000
TORS      81     82      0      0     0.0000   180.0000     0.0000     0.0000
TORS      82     83      0      0     0.0000   180.0000     0.0000     0.0000
TORS      82     86      0      0     0.0000   180.0000     0.0000     0.0000
TORS      83     84      0      0     0.0000   180.0000     0.0000     0.0000
TORS      86     90      0      0     0.0000   180.0000     0.0000     0.0000
TORS     132    133      0      0     0.0000   180.0000     0.0000     0.0000
RCA4      52     48     49     50     0.5000     2.5000     0.0000     0.0000
RCA4      52     53     56     48     0.5000     2.5000     0.0000     0.0000
RCA4      71     69     70     80     0.5000     2.5000     0.0000     0.0000
RCA4     133      1      2     48     0.5000     2.5000     0.0000     0.0000
CONV       2      0      0      0     0.0500     0.0000     0.0000     0.0000
MINI       1      0   2500      0     0.0000     0.0000     0.0000     0.0000
```

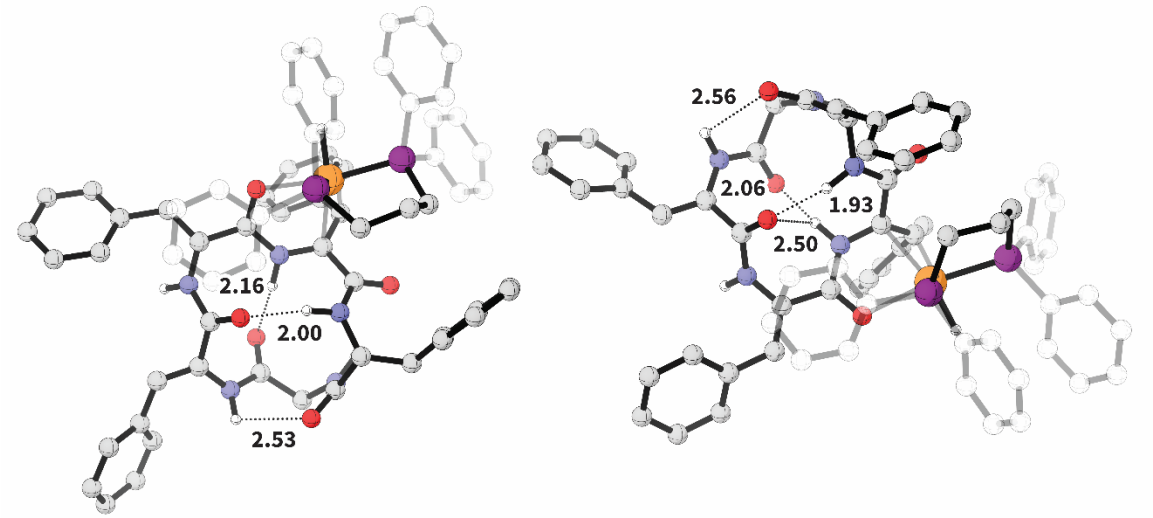
After the conformational searches were completed, redundant conformers were eliminated using the following MacroModel command file. The energies reported during conformational searches using MacroModel 2016 version 3 vary from the single point energies. This step ensures that the energies reported in the output file match the single point energy calculations.

```
c1r2s_005.mae
c1r2s_005_opt.mae
```

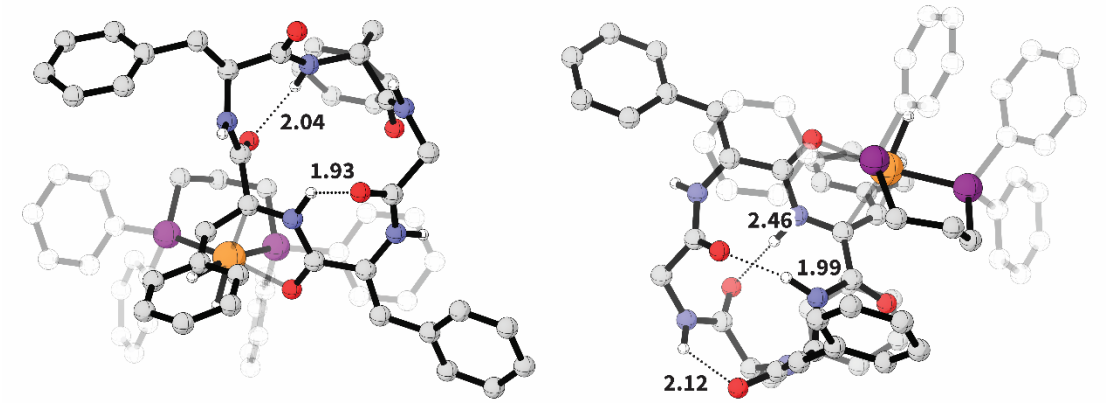
```
MMOD        0       1       0       0       0.0000      0.0000      0.0000      0.0000
FFLD        2       1       0       0       1.0000      0.0000      0.0000      0.0000
BGIN        0       0       0       0       0.0000      0.0000      0.0000      0.0000
READ        0       0       0       0       0.0000      0.0000      0.0000      0.0000
COMP        0       0       0       0       0.0000      0.0000      0.0000      0.0000
MINI        9       0    2500       0       0.0000      0.0000      0.0000      0.0000
END         0       0       0       0       0.0000      0.0000      0.0000      0.0000
```

iii) Hydrogen bonding in diastereomeric TSs

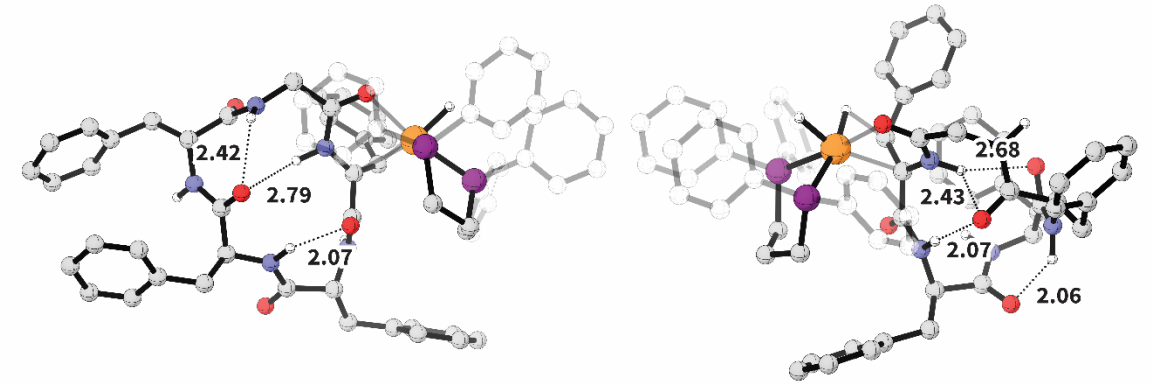
For each minimum energy conformer obtained from the full sampling, the hydrogen bonding within the oligopeptide was analyzed using Chimera. The hydrogen bonds present during the 2nd, 3rd and 4th hydrogenation are shown below.



Supplementary Figure 9. Hydrogen bonding in *pro-syn* **1R2R^{TS}** (left) and *pro-anti* **1R2S^{TS}** (right). There is an additional 2.50 Å interior hydrogen bond in the *pro-anti* transition state. The other two interior hydrogen bonds are also shorter in the *pro-anti* transition state.



Supplementary Figure 10. Hydrogen bonding in *pro-syn* **1R2S3S^{TS}** (left) and *pro-anti* **1R2S3R^{TS}** (right). There is an additional exterior hydrogen bond in the *pro-anti* transition state, and the interior hydrogens bonds are also shorter in this diastereomer.



Supplementary Figure 11. Hydrogen bonding in *pro-syn* **1R2S3R4R^{TS}** (left) and *pro-anti* **1R2S3R4S^{TS}** (right). There is an additional exterior hydrogen bond in the *pro-anti* diastereomer.

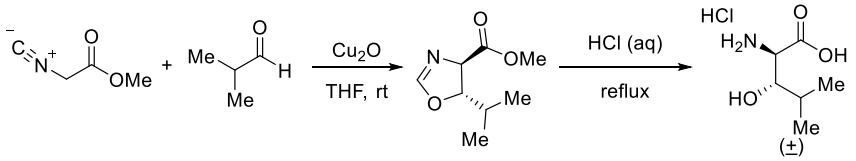
iv) Details of QM calculations

Clustering was done on **1R^{TS}**, **2R^{TS}**, **3R^{TS}**, **4R^{TS}**, **1R2R^{TS}** and **1R2S^{TS}** (Supplementary Figure 8) to narrow down the conformational space to 5 representative conformers for each ensemble. Each of these representative conformers was fully optimized to a transition state using G09 and B3LYP/LANL2DZ/6-31G* with Grimme's empirical dispersion.[18] Transition states were confirmed using harmonic frequency analysis. All 5 representatives were optimized to QM transition states for every conformer besides **1R^{TS}**, for which only 4 transition states could be located. The coordinates, energies and frequencies are found in Supplementary Tables 3-31 in the

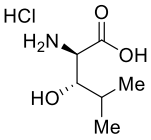
additional information file (.doc) under the supplementary information. Energies are reported in hartrees.

8) Additional Experiments

*i) Synthesis of pentapeptide **8***

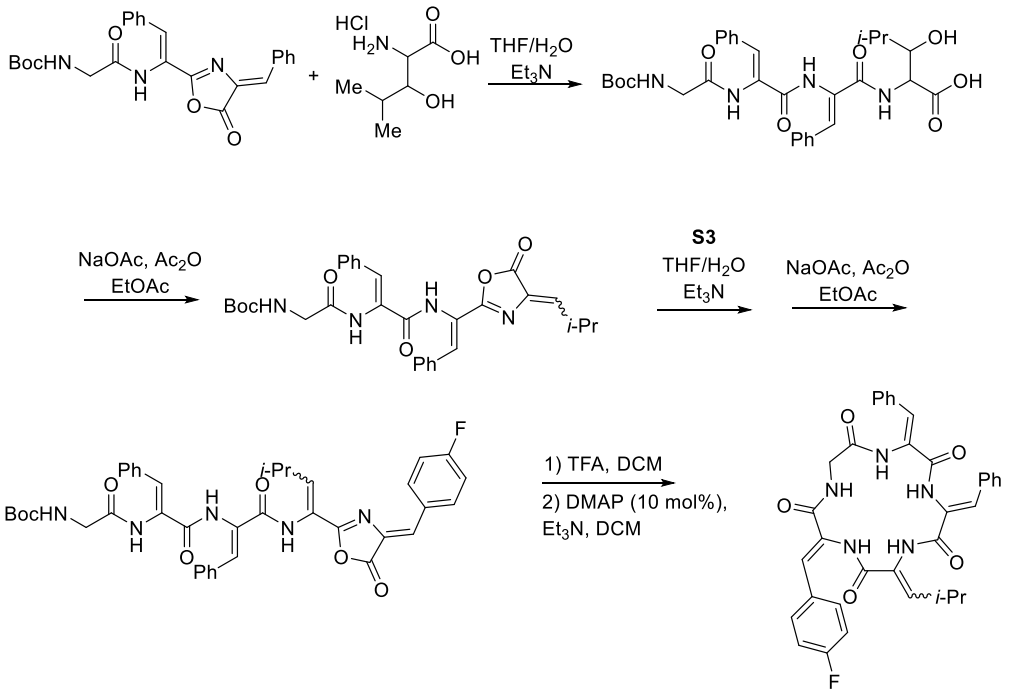


(±)-(2*R*,3*R*)-2-amino-3-hydroxy-4-methylpentanoic acid (S17)

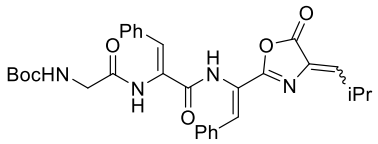


In a nitrogen-filled glovebox, to a round bottom flask equipped with a stir bar was added isobutyl aldehyde (0.48 mL, 5.25 mmol), Cu_2O (10 mol%), and THF (20 mL) at rt. Methyl isocyanoacetate (0.45 mL, 5.0 mmol) was then added. The solution was a brown suspension, and it was stirred for 12 h. The solution was concentrated under reduced pressure to give a beige solid. The solid filtered through a short plug of silica gel to remove Cu. The solid was concentrated under reduced pressure to give the oxazoline, which was used in the next step without further purification.

To the oxazoline (5 mmol) at rt was added 6 N aqueous HCl (25 mL). The solution was heated to reflux and stirred for 22 h. The solution was cooled to room temperature and was concentrated under reduced pressure to give **S17** as a beige solid (845 mg, 92%). Characterization data was consistent with those previously reported.[19]



***tert*-butyl (2-(((1*Z*)-3-(((1*Z*)-1-(4-(2-methylpropylidene)-5-oxo-4,5-dihydrooxazol-2-yl)-2-phenylvinyl)amino)-3-oxo-1-phenylprop-1-en-2-yl)amino)-2-oxoethyl)carbamate (S18)**

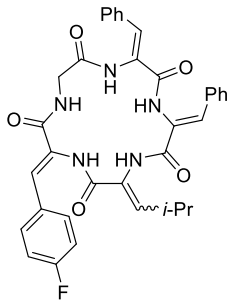


To a solution of **S17** (492 mg, 2.68 mmol) in THF/H_2O (1:1, 0.1 M) was added triethylamine (621 µL, 4.46 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **3** (1.00 g, 2.23 mmol) in THF (22 mL). The reaction was stirred at rt for 36 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used without further purification.

To a round bottom flask equipped with a stir bar was added the carboxylic acid (2.23 mmol) and EtOAc (5.0 mL). To this solution was added acetic anhydride (2.10 mL, 22.3 mmol) and sodium acetate (366 mg, 4.46 mmol) and the mixture was stirred at rt for 18 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure. The oil was dissolved in a minimal amount of DCM and hexanes was added to precipitate the oxazolone. The solvent was decanted and the solid was washed 2x with

hexanes to afford the desired oxazolone **S18** as a light yellow solid (1.2 g, 92%, 4:1 *dr*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (br, 0.13H), 8.24 (br, 0.64H), 7.87 (br, 0.17H), 7.85 (br, 0.67H), 7.69-7.64 (m, 2H), 7.47-7.31 (m, 10H), 6.58 (d, *J* = 11.0 Hz, 0.17H), 6.48 (d, *J* = 9.9 Hz, 1H), 5.29 (br, 1H), 3.87 (d, *J* = 4.6 Hz, 1.65H), 3.83 (br, 0.42H), 3.56-3.64 (m, 0.16H), 3.16-3.28 (m, 0.78H), 1.37 (s, 9H), 1.15 (d, *J* = 6.6 Hz, 5.63H), 1.09 (d, *J* = 6.7 Hz, 1.23H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.6, 166.0, 164.6, 164.3, 164.2, 161.6, 160.4, 156.7, 151.4, 146.1, 134.3, 134.2, 133.5, 133.4, 133.3, 133.2, 131.8, 130.8, 130.3, 129.8, 129.7, 129.1, 129.0, 128.9, 127.5, 127.0, 119.8, 81.1, 45.1, 28.6, 28.4, 26.9, 22.5, 22.1. IR (ATR): 3270, 2974, 1812, 1668, 1630, 1563, 1496, 1367, 1250, 1216, 1165, 1029, 751, 733, 690 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{31}H_{34}N_4O_6Na$ $[M+Na]^+$: 581.2376, found: 581.2388.

9,12-di((*Z*)-benzylidene)-3-((*Z*)-4-fluorobenzylidene)-6-(2-methylpropylidene)-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (8)



To a solution of **S3** (591 mg, 2.51 mmol) in THF/H_2O (1:1, 0.1 M) was added triethylamine (350 µL, 2.51 mmol) and the mixture was sonicated until homogeneous. The mixture was added to a solution of oxazolone **S18** (1.00 g, 1.79 mmol) in THF (18 mL). The reaction was stirred at rt for 24 h. The mixture was acidified with 10% $KHSO_4$ (aq), extracted with 3x with EtOAc, and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired carboxylic acid which was used without further purification.

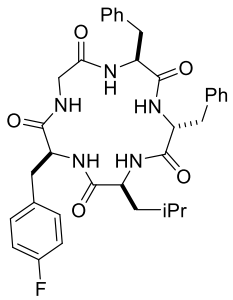
To a round bottom flask equipped with a stir bar was added the carboxylic acid (1.79 mmol) and EtOAc (3.6 mL). To this solution was added acetic anhydride (1.70 mL, 17.9 mmol) and sodium acetate (294 mg, 3.58 mmol) and the mixture was stirred at rt for 40 h. Sat. $NaHCO_3$ (aq) was added to quench excess acetic anhydride and acetic acid until the reaction mixture stopped bubbling. The mixture was extracted 3x with EtOAc and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and solvent was evaporated under reduced pressure. The oil was dissolved in a minimal amount of DCM and hexanes was added to precipitate the oxazolone. The solvent was decanted and the solid was washed 2x with hexanes to afford the desired oxazolone as a light yellow solid which was used in the next step without further purification.

To a round bottom flask equipped with a stir bar under N_2 was added the corresponding oxazolone (1.79 mmol) and anhydrous DCM (18 mL). The reaction mixture was cooled to 0 °C and TFA (2.74 mL, 35.8 mmol) was slowly added. The reaction slowly warmed to rt and stirred for 3 h. The DCM was concentrated under reduced pressure and to the mixture was added toluene to form a TFA azeotrope, which was subsequently concentrated under reduced pressure. The crude reaction mixture was further dried on the high vacuum and subsequently triturated with Et_2O to afford TFA·amine salt and was immediately used in the next reaction without further purification.

TFA·amine salt (1.79 mmol) was dissolved in anhydrous DCM (36 mL, 0.05 M) and to this solution was added anhydrous Et_3N (1.00 mL, 7.16 mmol) and DMAP (22 mg, 0.18 mmol). The reaction mixture was stirred at rt for 7 h and subsequently concentrated under reduced pressure. The crude reaction mixture was then purified via column chromatography (eluting with 80% EtOAc/hexanes) to afford cyclic pentapeptide **8** as a light yellow solid (170 mg, 15% yield over 4 steps, 8:1 *Z/E* at ΔLeu). ^{1}H NMR (600 MHz, DMSO, 373 K) δ 9.41 (s, 1H), 9.36 (s, 1H), 9.13 (s, 1H), 9.02 (s, 1H), 8.05 (s, 1H), 7.61 – 7.53 (m, 6H), 7.44 – 7.38 (m, 5H), 7.38 – 7.34 (m, 3H), 7.29 (s, 1H), 7.21 – 7.16 (m, 4H), 7.06 (s, 1H), 6.17 (d, *J* = 9.8 Hz, 1H), 3.97 (d, *J* = 5.2 Hz, 2H), 2.77 – 2.70 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, DMSO, 373 K) δ 169.2, 165.4, 164.7, 163.7, 161.6 (d, *J* = 247.5 Hz), 140.2, 133.9, 133.3, 131.1 (d, *J* = 8.3 Hz), 130.5 (d, *J* = 3.2 Hz), 129.4, 129.12, 129.07, 128.4, 128.3, 128.2, 128.02, 127.98, 127.8, 127.7, 127.5, 127.4, 127.0, 114.6 (d, *J* = 21.6 Hz), 43.4, 26.4, 21.2. ^{19}F NMR (376 MHz, DMSO, 373 K) δ -112.44. IR (ATR): 3072, 2960, 2915, 1640, 1506, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{35}H_{24}FN_5O_5Na$ $[M+Na]^+$: 644.2285, found: 644.2273.

ii) SPPS syntheses

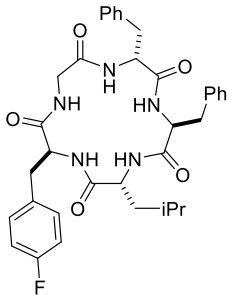
(3*S*,6*S*,9*R*,12*S*)-9,12-dibenzyl-3-(4-fluorobenzyl)-6-isobutyl-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (9b)



The corresponding linear pentapeptide was manually synthesized via Fmoc solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride (CTC) resin (substitution 1.1 mmol/g). The resin (0.360 g, 0.400 mmol) was swelled in DMF (peptide grade) (20 mL) for 20 min. The beads were washed once with DMF. DMF (10 mL), Fmoc-Phe(4-F)-OH (649 mg, 1.60 mmol) and *i*-Pr_2EtN (2.5 mL) were added and allowed to mix under N_2 for 15 minutes. The coupling with Fmoc-Phe(4-F)-OH was repeated again. After the double coupling, the beads were washed with DMF and the Fmoc group was deprotected with 20% 4-methylpiperidine in DMF (20 mL) for 15 minutes. This deprotection was repeated again. The resin was washed three times with DMF (15 mL) and a Kaiser test was performed to determine presence of deprotected amine. The beads were washed once with *N*-methyl-2-pyrrolidone (15 mL). To begin the next coupling, NMP (10 mL), Fmoc-L-Leu-OH (620 mg, 1.6 mmol), HBTU (610 mg, 1.6 mmol), and *i*-Pr_2EtN (2.5 mL) were added and the resin bubbled under N_2 for 30 min. The completion of the coupling was monitored by the Kaiser test. If incomplete, the coupling step was repeated again. The resin was washed three times with DMF (15 mL). The deprotection of the Fmoc group was repeated as above two times. To elongate the peptide, the coupling and deprotection steps were performed with Fmoc-D-Phe-OH, Fmoc-Phe-OH, and Fmoc-Gly-OH. After the last amino acid was deprotected, the beads were washed three times with DMF. To the resin was added 40 mL cleavage solution (95% TFA, 2.5% H_2O, 2.5% triisopropylsilane), and the resin bubbled under N_2 for 3 h. A new receiving flask was replaced on the peptide synthesizer and the TFA was drained into the new flask. The TFA solution containing the linear pentapeptide (0.400 mmol) was concentrated under reduced pressure. Then to the same round bottom flask equipped with a stir bar was added HOAt (136 mg, 1.00 mmol), and DMF (400 mL). The reaction mixture was cooled to 0 ^oC and *i*-Pr_2EtN (1.40 mL, 8.00 mmol) was added. HATU (760 mg, 2.00 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The solvent was concentrated under reduced pressure and a white solid formed. This solid was then filtered and triturated with DCM, MeOH, and Et_2O to afford the title compound as a white solid (69 mg, 27% overall). ^1H NMR (400 MHz, DMSO)

δ 8.65 – 8.58 (m, 1H), 8.52 (d, *J* = 7.2 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.01 (m, 14H), 4.62 – 4.52 (m, 1H), 4.43 – 4.31 (m, 2H), 4.03 (dd, *J* = 14.1, 7.4 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.07 – 2.86 (m, 3H), 2.79 – 2.67 (m, 3H), 1.36 – 1.23 (m, 2H), 1.23 – 1.14 (m, 1H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.60 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 171.87, 171.19, 170.72, 170.52, 169.52, 160.91 (d, *J* = 241.7 Hz), 137.57, 137.03, 133.75 (d, *J* = 2.8 Hz), 130.94 (d, *J* = 7.9 Hz), 129.03, 129.00, 128.09, 128.06, 126.28, 126.23, 114.79 (d, *J* = 21.0 Hz), 54.79, 54.02, 53.25, 52.17, 43.73, 37.40, 36.33, 35.95, 23.66, 22.96, 20.94. ^{19}F NMR (376 MHz, DMSO) δ -117.22. IR (ATR): 3072, 3033, 2966, 1635, 1534, 1501, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{35}H_{40}FN_5O_5Na$ $[M+Na]^+$: 652.2911, found: 652.2906. $[\alpha]^{23}_D$ –37 (*c* = 0.33, DMF).

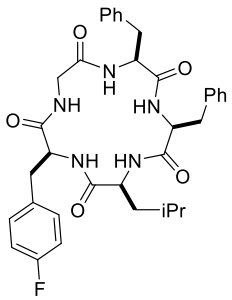
(3*S*,6*R*,9*S*,12*R*)-9,12-dibenzyl-3-(4-fluorobenzyl)-6-isobutyl-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (9c)



The corresponding linear pentapeptide was manually synthesized via Fmoc solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride (CTC) resin (substitution 1.1 mmol/g). The resin (0.360 g, 0.400 mmol) was swelled in DMF (peptide grade) (20 mL) for 20 min. The beads were washed once with DMF. DMF (10 mL), Fmoc-Phe(4-F)-OH (649 mg, 1.60 mmol) and *i*-Pr$_2$EtN (2.5 mL) were added and allowed to mix under N_2 for 15 minutes. The coupling with Fmoc-Phe(4-F)-OH was repeated again. After the double coupling, the beads were washed with DMF and the Fmoc group was deprotected with 20% 4-methylpiperidine in DMF (20 mL) for 15 minutes. This deprotection was repeated again. The resin was washed three times with DMF (15 mL) and a Kaiser test was performed to determine presence of deprotected amine. The beads were washed once with *N*-methyl-2-pyrrolidone (15 mL). To begin the next coupling, NMP (10 mL), Fmoc-D-Leu-OH (620 mg, 1.6 mmol), HBTU (610 mg, 1.6 mmol), and *i*-Pr$_2$EtN (2.5 mL) were added and the resin bubbled under N_2 for 30 min. The completion of the coupling was monitored by the Kaiser test. If incomplete, the coupling step was repeated again. The resin was washed three times with DMF (15 mL). The deprotection of the Fmoc group was repeated as above two times. To elongate the peptide, the coupling and deprotection steps were performed with Fmoc-Phe-OH, Fmoc-D-Phe-OH, and Fmoc-Gly-OH. After the last amino acid was deprotected, the beads were washed three times with DMF. To the resin was added 40 mL cleavage solution (95% TFA, 2.5% H_2O, 2.5% triisopropylsilane), and the resin bubbled under N_2 for 3 h. A new

receiving flask was replaced on the peptide synthesizer and the TFA was drained into the new flask. The TFA solution containing the linear pentapeptide (0.400 mmol) was concentrated under reduced pressure. Then to the same round bottom flask equipped with a stir bar was added HOAt (136 mg, 1.00 mmol), and DMF (400 mL). The reaction mixture was cooled to 0 °C and *i*-Pr_2EtN (1.40 mL, 8.00 mmol) was added. HATU (760 mg, 2.00 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The solvent was concentrated under reduced pressure and a white solid formed. This solid was then filtered and triturated with DCM, MeOH, and Et_2O to afford the title compound as a white solid (112 mg, 45% overall). ^{1}H NMR (400 MHz, DMSO) δ 8.79 (d, *J* = 7.3 Hz, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.21 (t, *J* = 5.6 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.29 – 6.97 (m, 14H), 4.55 – 4.44 (m, 1H), 4.42 – 4.35 (m, 1H), 4.32 – 4.22 (m, 2H), 3.67 (dd, *J* = 15.1, 5.7 Hz, 1H), 3.55 (dd, *J* = 15.3, 5.2 Hz, 1H), 3.04 – 2.85 (m, 3H), 2.83 – 2.65 (m, 3H), 1.33 – 1.14 (m, 2H), 1.12 – 1.03 (m, 1H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 172.4, 171.2, 171.0, 170.5, 168.6, δ 161.0 (d, *J* = 241.9 Hz), 137.7, 133.9 (d, *J* = 2.8 Hz), 130.9 (d, *J* = 8.0 Hz), 129.4, 129.2, 128.9, 128.7, 128.1, 128.0, 126.1, 114.8 (d, *J* = 21.1 Hz), 55.3, 54.1, 53.3, 51.1, 43.3, 40.6, 35.8, 35.4, 35.0, 23.9, 22.4, 22.3. ^{19}F NMR (376 MHz, DMSO) δ -117.20. IR (ATR): 3083, 3027, 2960, 1640, 1545, 1501, 1221 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{35}H_{40}FN_5O_5Na$ $[M+Na]^+$: 652.2911, found: 652.2939. $[\alpha]^{24}_D$ +29 (*c* = 0.23, DMF).

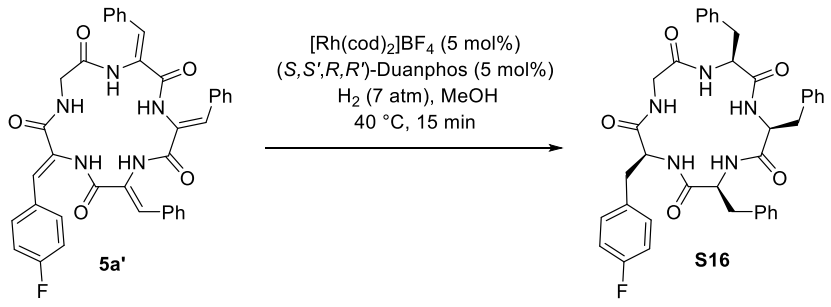
(3*S*,6*S*,9*S*,12*S*)-9,12-dibenzyl-3-(4-fluorobenzyl)-6-isobutyl-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (S19)



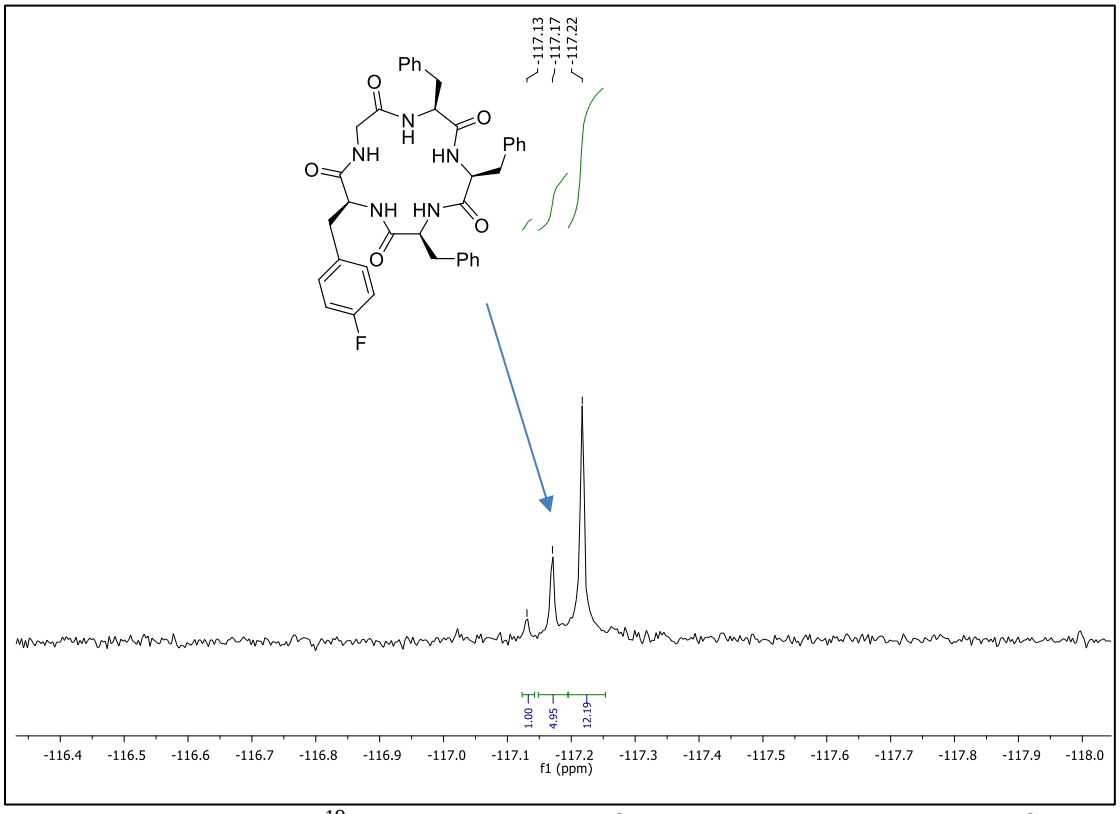
The corresponding linear pentapeptide was manually synthesized via Fmoc solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride (CTC) resin (substitution 1.1 mmol/g). The resin (0.360 g, 0.400 mmol) was swelled in DMF (peptide grade) (20 mL) for 20 min. The beads were washed once with DMF. DMF (10 mL), Fmoc-Phe(4-F)-OH (649 mg, 1.60 mmol) and *i*-Pr_2EtN (2.5 mL) were added and allowed to mix under N_2 for 15 minutes. The coupling with Fmoc-Phe(4-F)-OH was repeated again. After the double coupling, the beads were washed with DMF and the Fmoc group was deprotected with 20% 4-methylpiperidine in DMF (20 mL) for 15 minutes. This deprotection was repeated again. The resin was washed three times with DMF (15 mL) and a Kaiser test was performed to determine presence of deprotected amine. The

beads were washed once with *N*-methyl-2-pyrrolidone (15 mL). To begin the next coupling, NMP (10 mL), Fmoc-Leu-OH (620 mg, 1.6 mmol), HBTU (610 mg, 1.6 mmol), and *i*-Pr_2EtN (2.5 mL) were added and the resin bubbled under N_2 for 30 min. The completion of the coupling was monitored by the Kaiser test. If incomplete, the coupling step was repeated again. The resin was washed three times with DMF (15 mL). The deprotection of the Fmoc group was repeated as above two times. To elongate the peptide, the coupling and deprotection steps were performed with Fmoc-Phe-OH, Fmoc-Phe-OH, and Fmoc-Gly-OH. After the last amino acid was deprotected, the beads were washed three times with DMF. To the resin was added 40 mL cleavage solution (95% TFA, 2.5% H_2O, 2.5% triisopropylsilane), and the resin bubbled under N_2 for 3 h. A new receiving flask was replaced on the peptide synthesizer and the TFA was drained into the new flask. The TFA solution containing the linear pentapeptide (0.400 mmol) was concentrated under reduced pressure. Then to the same round bottom flask equipped with a stir bar was added HOAt (136 mg, 1.00 mmol), and DMF (400 mL). The reaction mixture was cooled to 0 ^oC and *i*-Pr_2EtN (1.40 mL, 8.00 mmol) was added. HATU (760 mg, 2.00 mmol) was added in portions and the reaction warmed to rt and stirred for 12 h. The solvent was concentrated under reduced pressure and a white solid formed. This solid was then filtered and triturated with DCM, MeOH, and Et_2O to afford the title compound as a white solid (23 mg, 9% overall). The ^{1}H-NMR spectrum was consistent with the cyclic pentapeptide **9a** obtained after hydrogenation (Supplementary Figure 16 and 17).

*iii) Analysis of timepoint (t=15 min) for asymmetric hydrogenation of **5a'** using Duanphos to probe sequential cascade hydrogenation*

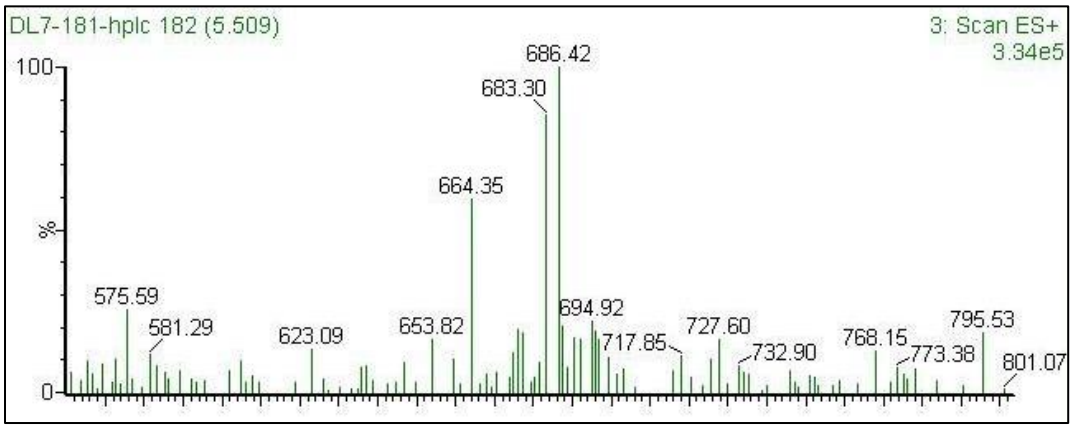


Cyclic dehydropeptide **5a'** (5.0 mg, 0.0076 mmol) was subjected to the Rh-catalyzed hydrogenation using method B. After 15 min, LC-MS and ^{19}F-NMR analysis (Supplementary Figure 12) for the asymmetric hydrogenation of **5a'** showed formation of product at 117.17 ppm and two additional unsaturated intermediates.



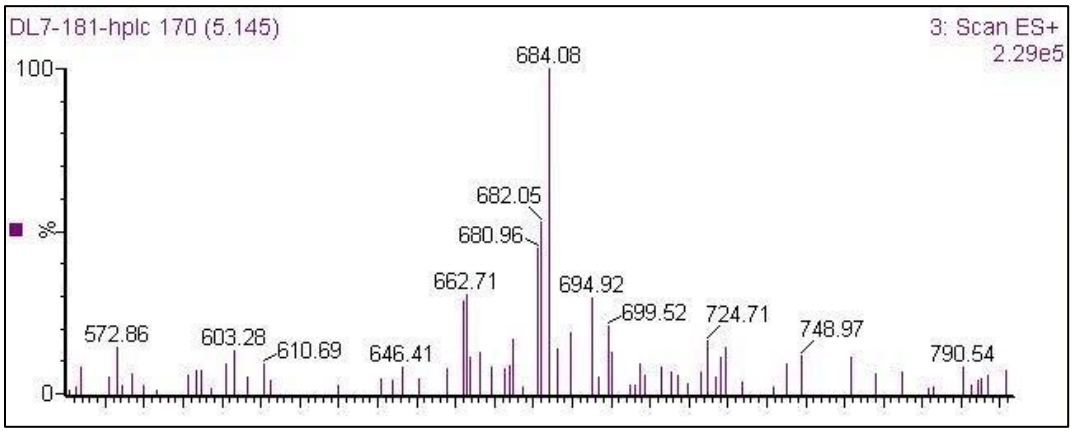
Supplementary Figure 12. ^{19}F-NMR at t=15 min for asymmetric hydrogenation of **5a'** using Duanphos

LC-MS analysis for the asymmetric hydrogenation of **5a'** (t=15 min) showed formation of product. The product is represented by major peaks, m/z = 664.35 (M+H) and 686.42 (M+Na) (Supplementary Figure 13).



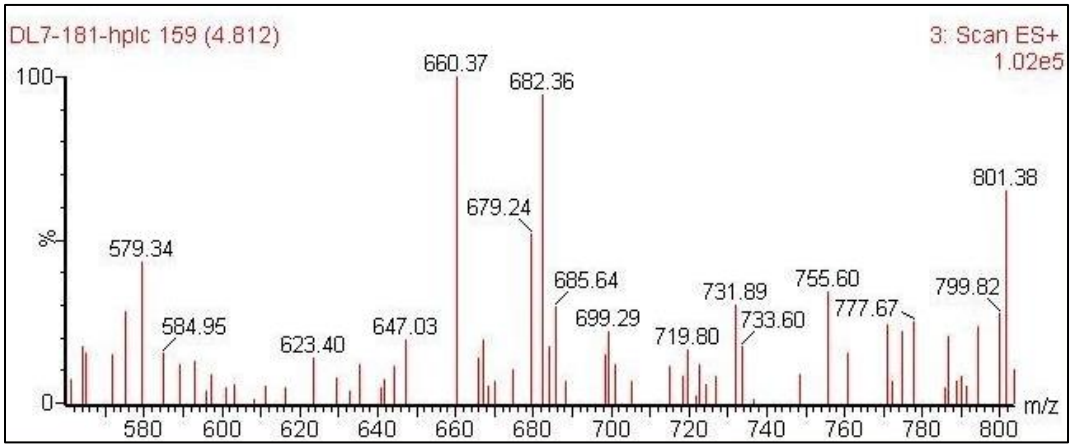
Supplementary Figure 13. LC-MS analysis for asymmetric hydrogenation of **5a'** using Duanphos for product formation.

LC-MS analysis for the asymmetric hydrogenation of **5a'** (t=15 min) showed the mass for the tri-hydrogenated intermediate. This intermediate is represented by major peaks, m/z = 662.71 (M+H) and 684.08 (M+Na) (Supplementary Figure 14).



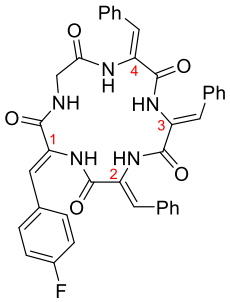
Supplementary Figure 14. LC-MS analysis for asymmetric hydrogenation of **5a'** using Duanphos for tri-hydrogenated intermediate.

LC-MS analysis for the asymmetric hydrogenation of **5a'** (t=15 min) showed the mass for the di-hydrogenated intermediate. This intermediate is represented by major peaks, m/z = 660.37 (M+H) and 682.36 (M+Na) (Supplementary Figure 15).



Supplementary Figure 15. LC-MS analysis for asymmetric hydrogenation of **5a'** using Duanphos for di-hydrogenated intermediate.

Calculation of number of possible diastereomers for intermediates in asymmetric hydrogenation of cyclic dehydropeptide ***5a'***



Because it is possible to see the different diastereomers via ^{19}F-NMR, we will list off the possibilities comprised of one set of enantiomers below:

n = number of enamides reduced

n = 1

1^S
2^S
3^S
4^S

After n=1 reduction, we would see a possibility of 4 diastereomers via ^{19}F-NMR.

n = 2

1^S-2^S
1^S-2^R
1^S-3^S
1^S-3^R
1^S-4^S
1^S-4^R
2^S-3^S
2^S-3^R
2^S-4^S
2^S-4^R
3^S-4^S
3^S-4^R

After n=2 reductions, we would see a possibility of 12 diastereomers via ^{19}F-NMR.

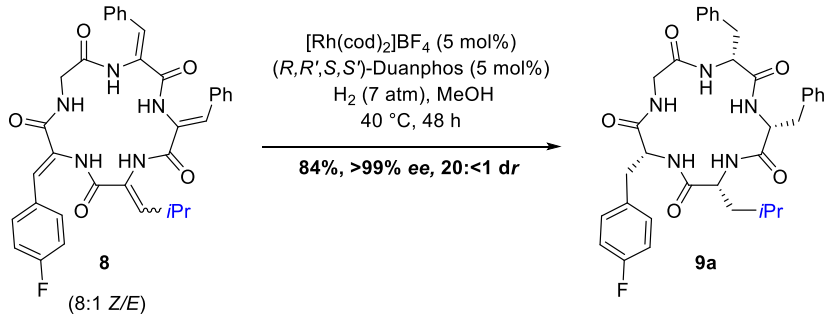
n = 3

1^S-2^S-3^S
1^S-2^R-3^S
1^S-2^S-3^R
1^S-2^R-3^R
1^S-2^S-4^S
1^S-2^R-4^S
1^S-2^S-4^R
1^S-2^R-4^R
1^S-3^S-4^S
1^S-3^R-4^S
1^S-3^S-4^R
1^S-3^R-4^R
2^S-3^S-4^S
2^S-3^R-4^S
2^S-3^S-4^R
2^S-3^R-4^R

After n=3 reductions, we would see a possibility of 16 diastereomers via ^{19}F-NMR.

Thus, in total we would see a maximum of 32 intermediates via ^{19}F-NMR for the for asymmetric hydrogenation of cyclic dehydropeptide **5a'** if the process were random and non-sequential. If the process were sequential, we would see a maximum of 3 intermediates. Because we observe the di- and tri-hydrogenated masses via LC-MS analysis, and only see two intermediates via ^{19}F-NMR, we conclude that the Duanphos reaction likely proceeds through a sequential reduction.

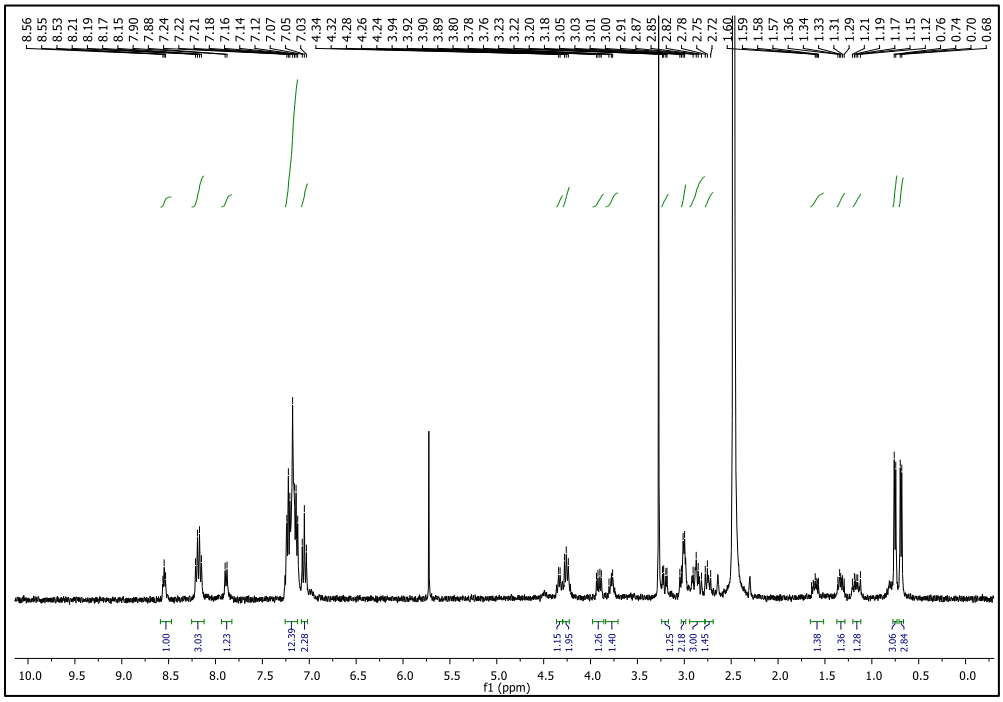
*iv) Asymmetric hydrogenation of cyclic dehydropeptide **8***



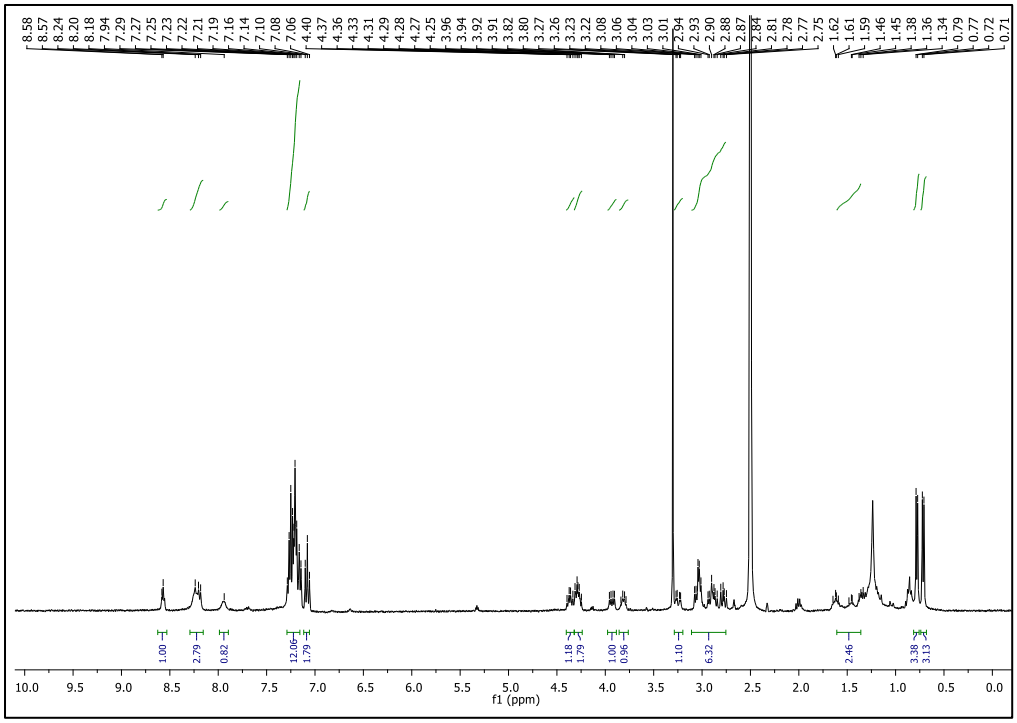
(3*R*,6*R*,9*R*,12*R*)-9,12-dibenzyl-3-(4-fluorobenzyl)-6-isobutyl-1,4,7,10,13-pentaazacyclopentadecane-2,5,8,11,14-pentaone (9a)

Cyclic dehydropeptide **8** (6.3 mg, 0.010 mmol) was subjected to the Rh-catalyzed hydrogenation using method B. After 48 h, the reaction went to full conversion to product via LC-MS analysis

and *dr* was determined to be 20:<1 *dr* via ^{19}F-NMR. After preparative thin layer chromatography (eluting with 95:5 DCM/MeOH), the product was obtained as a white solid (5.3 mg, 84%, >99% *ee*). ^{1}H NMR (400 MHz, DMSO) δ 8.58 (t, *J* = 5.5 Hz, 1H), 8.29 – 8.14 (m, 3H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.13 (m, 12H), 7.08 (m, 2H), 4.36 (dd, *J* = 14.8, 8.6 Hz, 1H), 4.32 – 4.23 (m, 2H), 3.94 (dd, *J* = 14.5, 6.4 Hz, 1H), 3.80 (dd, *J* = 14.9, 7.6 Hz, 1H), 3.23 (dd, *J* = 14.2, 4.8 Hz, 1H), 3.11 – 2.97 (m, 3H), 2.97 – 2.84 (m, 2H), 2.77 (dd, *J* = 13.7, 9.6 Hz, 1H), 1.70 – 1.58 (m, 1H), 1.42 – 1.32 (m, 1H), 1.26 – 1.13 (m, 1H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 172.05, 171.44, 170.58, 170.53, 169.12, 160.93 (d, *J* = 241.8 Hz), 137.71, 137.39, 133.97 (d, *J* = 2.6 Hz), 130.92 (d, *J* = 8.0 Hz), 129.04, 128.85, 128.21, 128.16, 126.34, 114.73 (d, *J* = 21.0 Hz), 56.10, 55.70, 54.44, 54.03, 43.28, 36.86, 36.48, 35.98, 24.14, 22.63, 21.57. ^{19}F NMR (376 MHz, DMSO) δ -117.27. IR (ATR): 3072, 2977, 1635, 1506, 1210 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{35}H_{40}FN_5O_5Na$ $[M+Na]^+$: 652.2911, found: 652.2912. $[\alpha]^{27}_D$ +39 (*c* = 0.27, DMF).



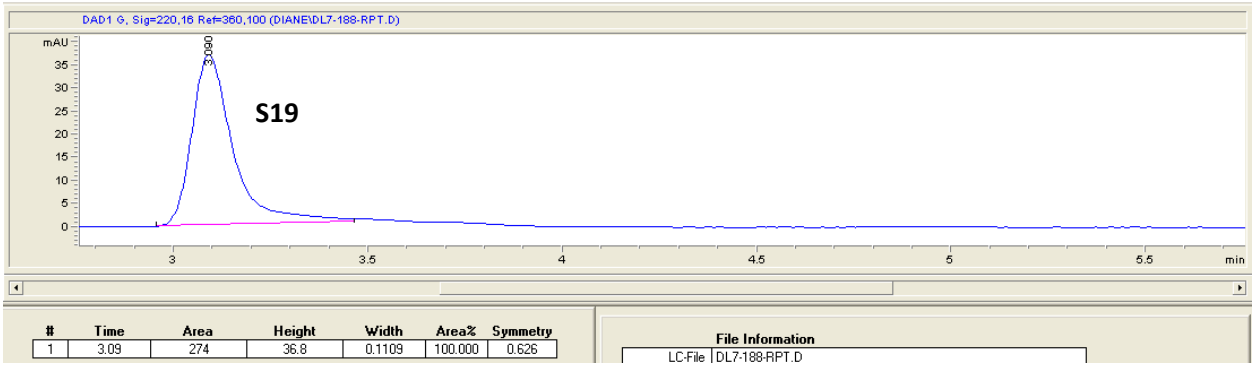
Supplementary Figure 16. ^{1}H-NMR of cyclic pentapeptide **S19** made via SPPS



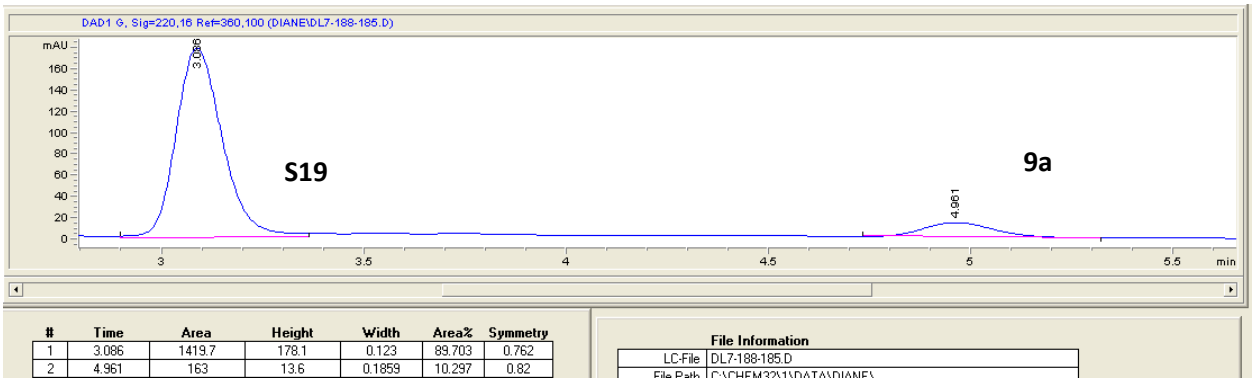
Supplementary Figure 17. ^{1}H-NMR of cyclic pentapeptide **9a** after hydrogenation using (*R*,*R*',*S*,*S*')-Duanphos

Column: IC, 40% MeOH isocratic, thermostat set to 44 ˚C, sample prepared in 1:1 DCM/MeOH

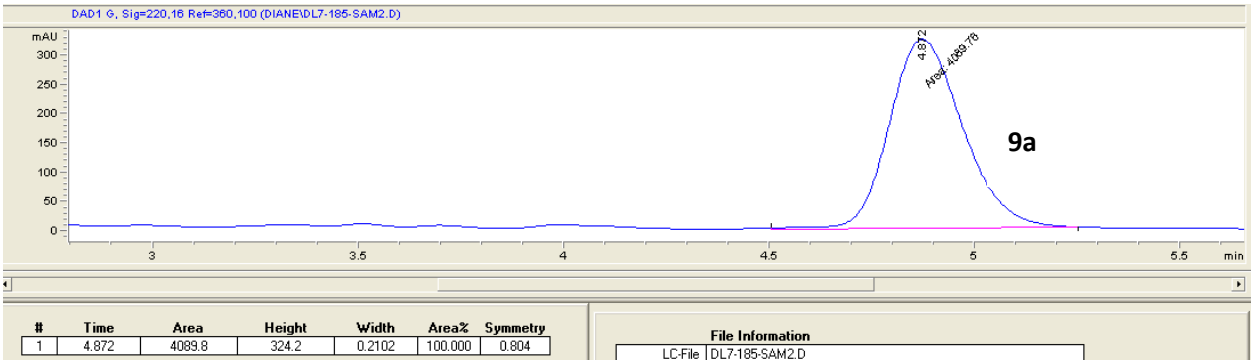
1. Authentic Cyclo(Gly-L-Phe-L-Phe-L-Leu-L-Phe(4-F)) (**S19**) made from SPPS synthesis



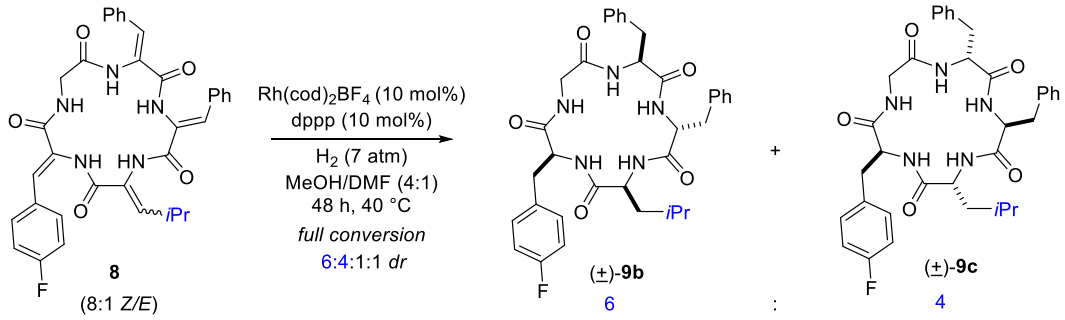
2. Cyclic peptide **S19** and cyclic peptide **9a**



3. **9a** made from hydrogenation of **8** using (*R,R',S,S'*)-Duanphos



v) Additional substrate

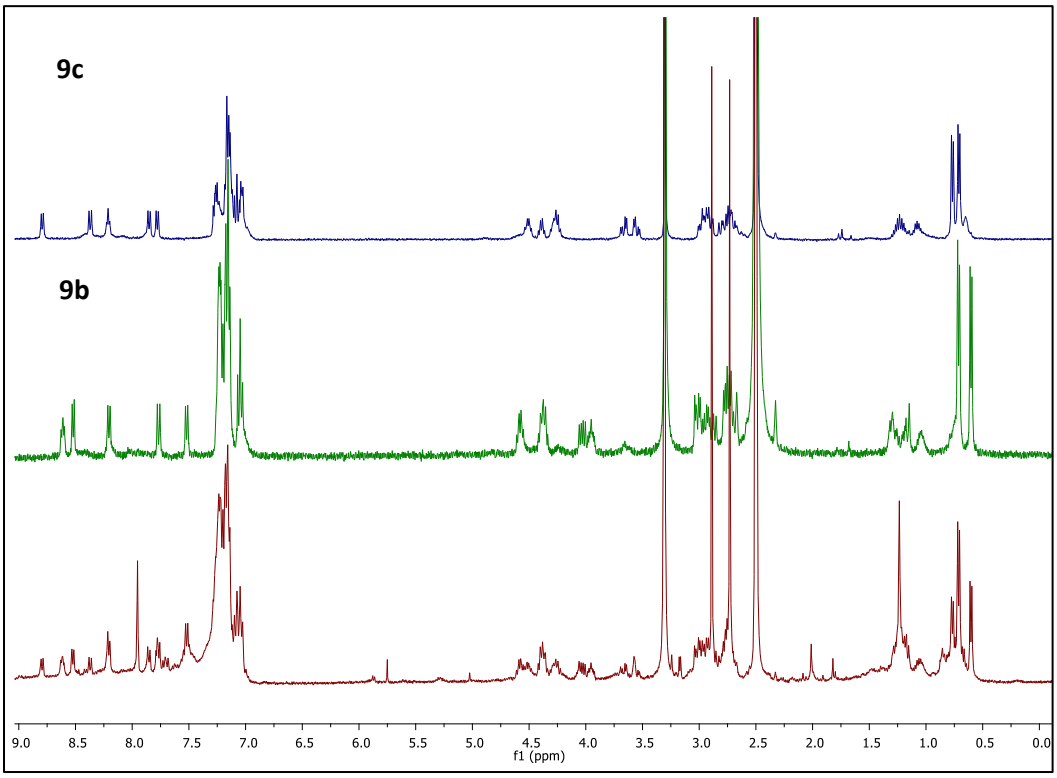


Supplementary Figure 18. Demonstrating hydrogenation of cyclic dehydropeptide **8** bearing non-aromatic side chain using Rh-dppp catalyst

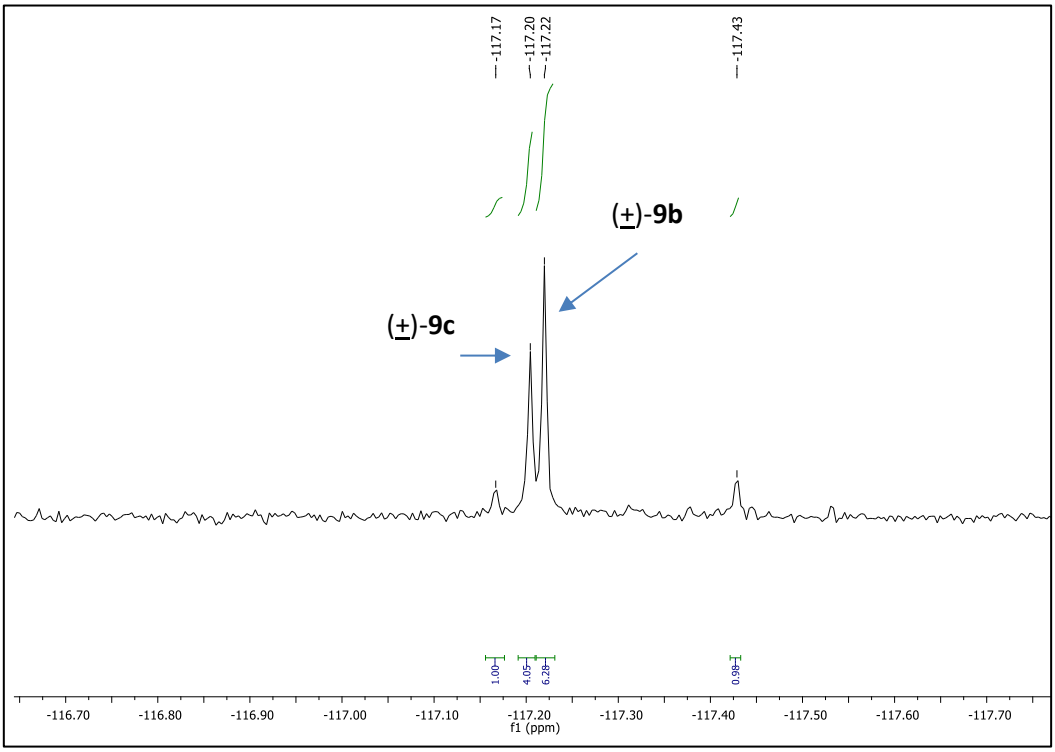
Cyclic dehydropeptide **8** (6.3 mg, 0.010 mmol) was subjected to the Rh-catalyzed hydrogenation using method B. After 48 h, the reaction went to full conversion to product via LC-MS analysis and *dr* was determined to be 6:4:1:1 via ^{19}F-NMR (Supplementary Figure 18). The major diastereomers were determined to be (±)-**9b** and (±)-**9c** through synthesis of authentic material *via*

SPPS. The ^{1}H-NMR and ^{19}F-NMR of the unpurified reaction mixture is shown in Supplementary Figure 19 and 20 with comparison to the authentic sample.

Analysis: Given that the side chains of leucine and phenylalanine are similar in size,[20] substituting the Ph for an *i*Pr group in cyclic dehydropeptide **8** emphasizes the importance of π-stacking for the stereoselectivity of the reaction. Further studies are underway to understand the impact of dehydroleucine on the stereocontrol of the cascade hydrogenation.

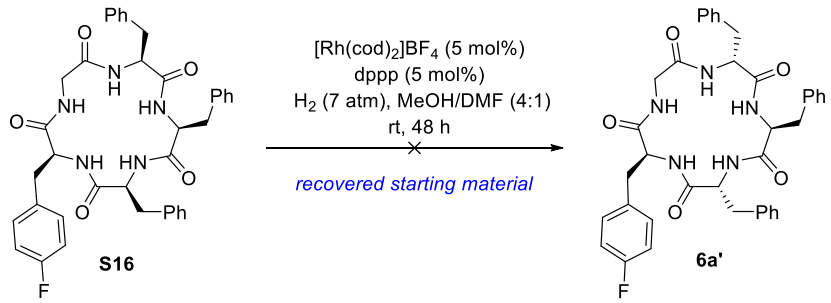


Supplementary Figure 19. ^{1}H-NMR analysis for hydrogenation of **8** using dppp ligand. Blue spectrum represents authentic sample of **9c**, green spectrum represents authentic sample of **9b**, red spectrum represents spectrum of unpurified reaction mixture.



Supplementary Figure 20. ^{19}F-NMR analysis of unpurified reaction mixture for hydrogenation of **8**.

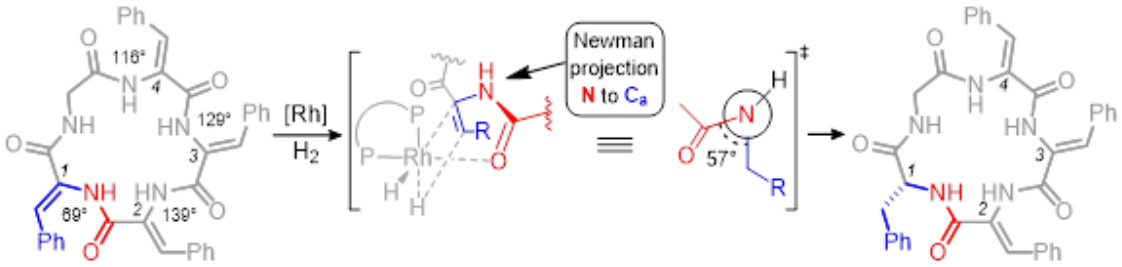
vi) Experiment to probe reversibility of Rh-catalyzed hydrogenation



Cyclic peptide **S16** (6.6 mg, 0.010 mmol) was subjected to the Rh-catalyzed hydrogenation using method B. After 48 h, no desired product formation was observed and **S16** was recovered quantitatively.

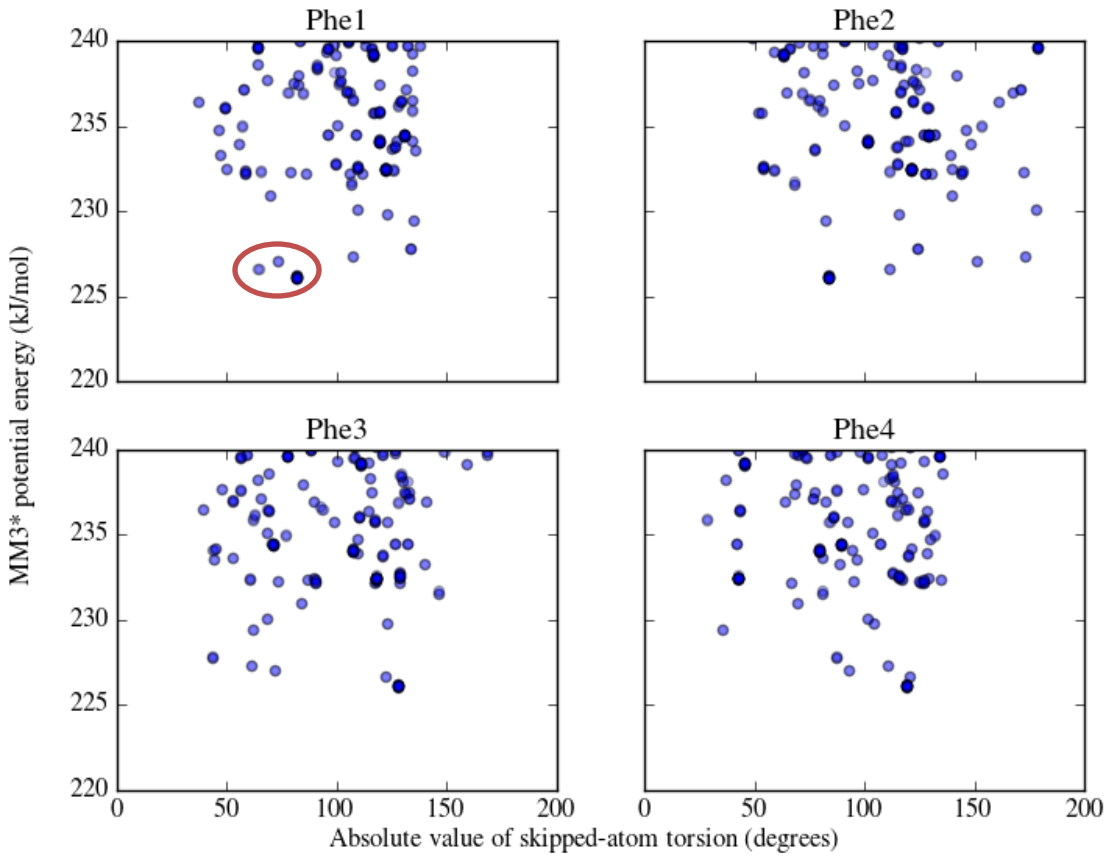
vii) Supplemental explanation of initial regioselectivity

Here we present a supplemental approach to addressing the question of why the initial hydrogenation at ΔPhe$_1$ is favored over ΔPhe$_4$, i.e. why the *N*-terminal rather than the *C*-terminal is preferred. In the key hydride transfer transition state, the Rh catalyst coordinates to both the carbonyl and the olefin of the reacting enamide. The ideal geometry in this transition state, as determined by DFT calculations and the TSFF fitted to them,[10] can expressed as a skipped dihedral as shown below and has an optimal value of 57^o (Supplementary Figure 21).



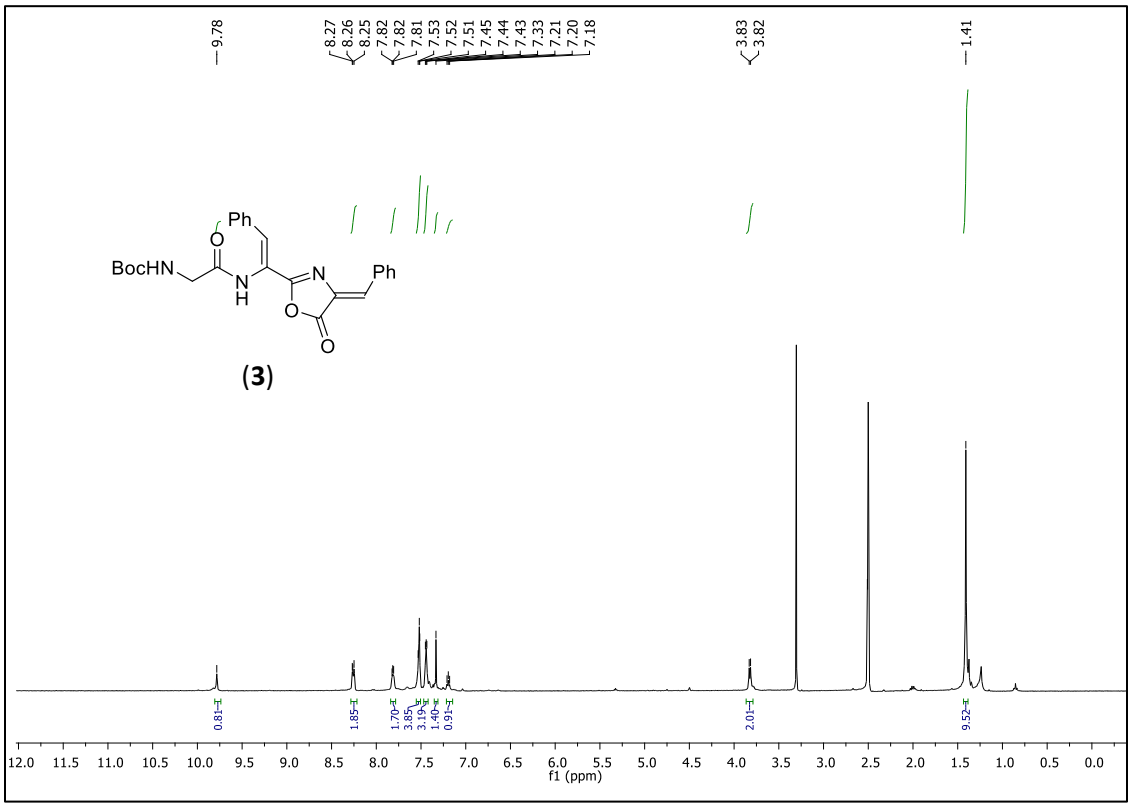
Supplementary Figure 21. Depiction of the ideal value of the skipped dihedral at the transition state.

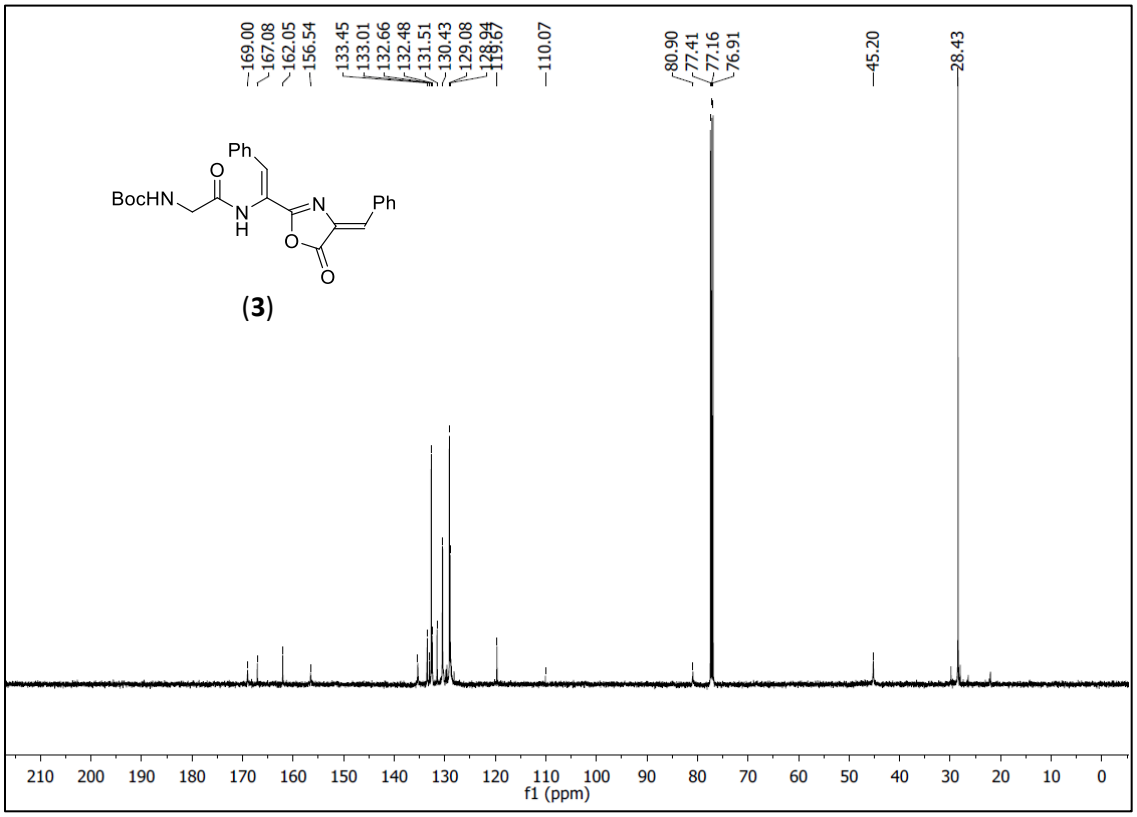
Shown below in Supplementary Figure 22 are the results from a Monte Carlo conformational search of the substrate using the MM3* force field in analogy to the studies described above. The value of the skipped dihedral is plotted against the potential energy. It can be seen that for ΔPhe$_1$, there are several low-energy conformations values for the skipped dihedral close to the optimal geometry for catalyst binding (57°, marked by red circle) while there are none for ΔPhe$_4$. As a consequence of this additional conformational strain in the transition state-like geometry for the hydrogenation at ΔPhe$_4$, the initial reaction at this position is disfavored.

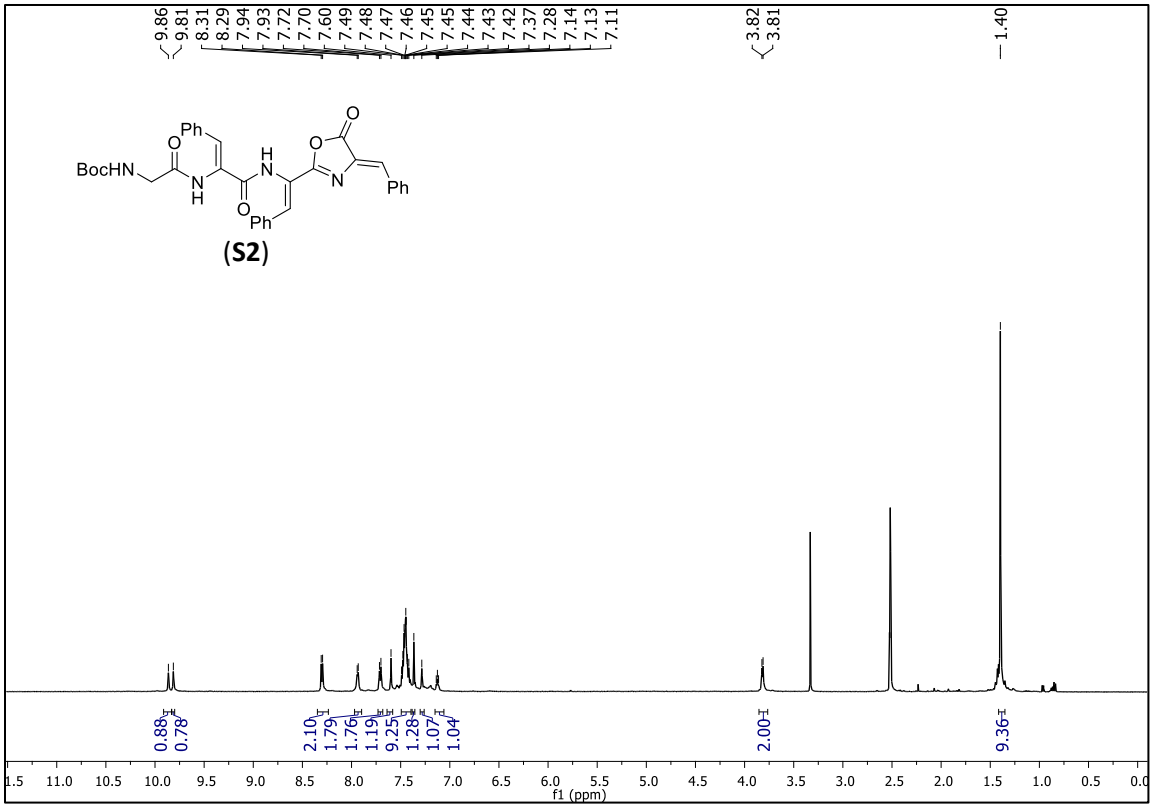


Supplementary Figure 22. Results from the Monte Carlo conformational search of the substrate. For skipped dihedral ΔPhe$_1$, there is a cluster of low energy conformers with values of about 57°, the optimal geometry for catalyst binding.

9) NMR Spectra



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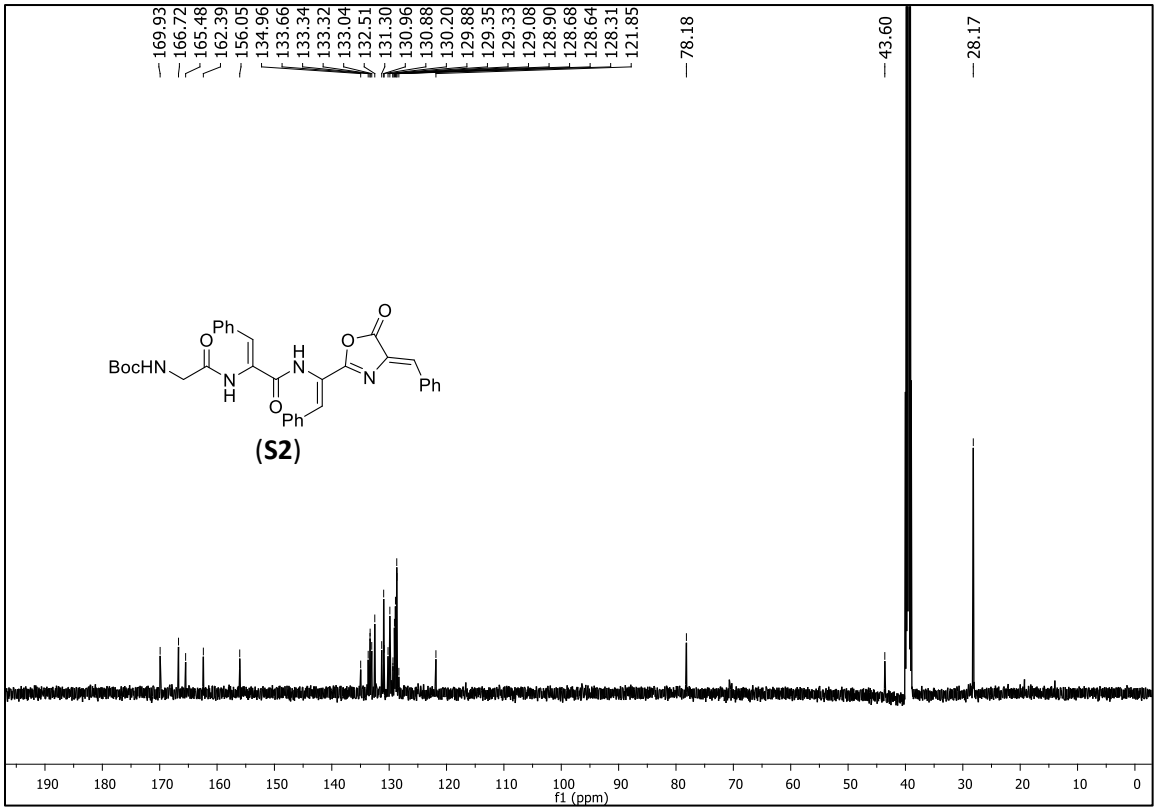
9.81
8.31
8.29
7.94
7.93
7.72
7.70
7.60
7.49
7.48
7.47
7.46
7.45
7.45
7.44
7.43
7.42
7.37
7.28
7.14
7.13
7.11
3.82
3.81
1.40
BocHN
Ph
O
N
H
Ph
Ph
(S2)
0.88
0.78
2.10
1.79
1.76
1.19
9.25
1.28
1.07
1.04
2.00
9.36
f1 (ppm)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166.72
165.48
162.39
156.05
134.96
133.66
133.34
133.32
133.04
132.51
131.30
130.96
130.88
130.20
129.88
129.35
129.33
129.08
128.90
128.68
128.64
128.31
121.85
78.18
43.60
28.17
BocHN
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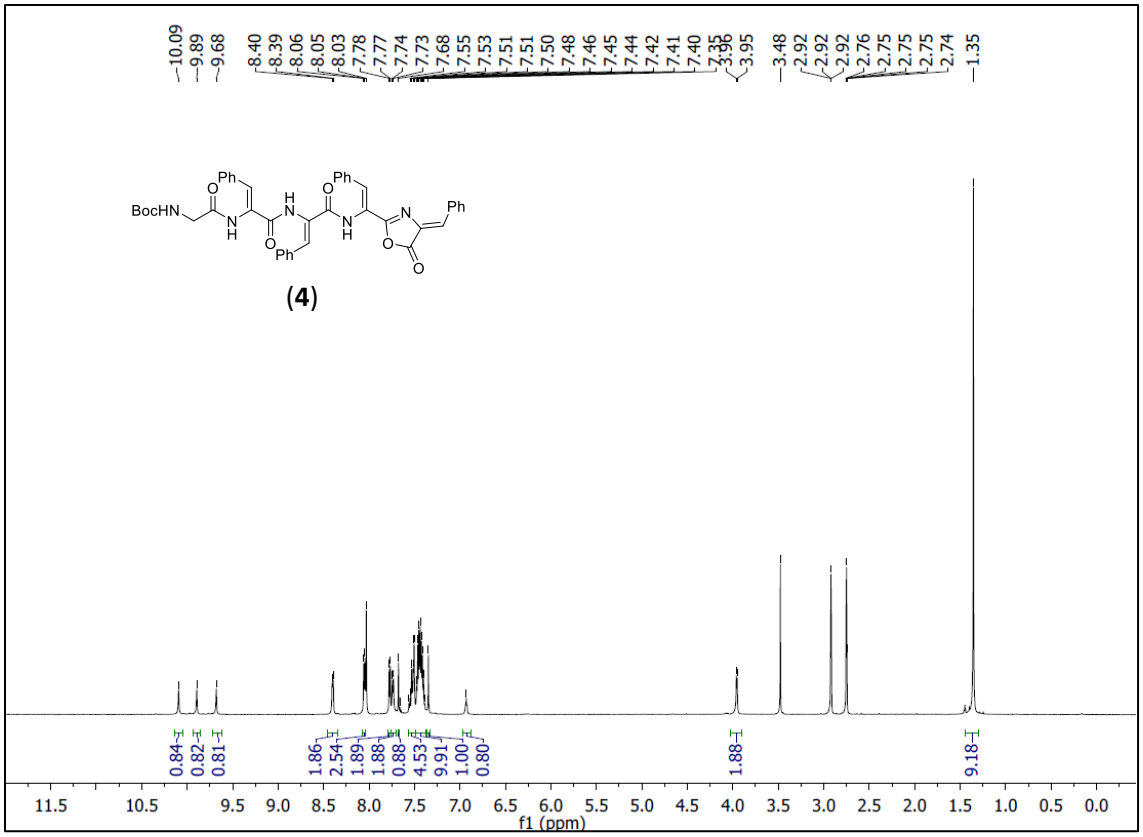
O
N
H
Ph
Ph
(S2)
f1 (ppm)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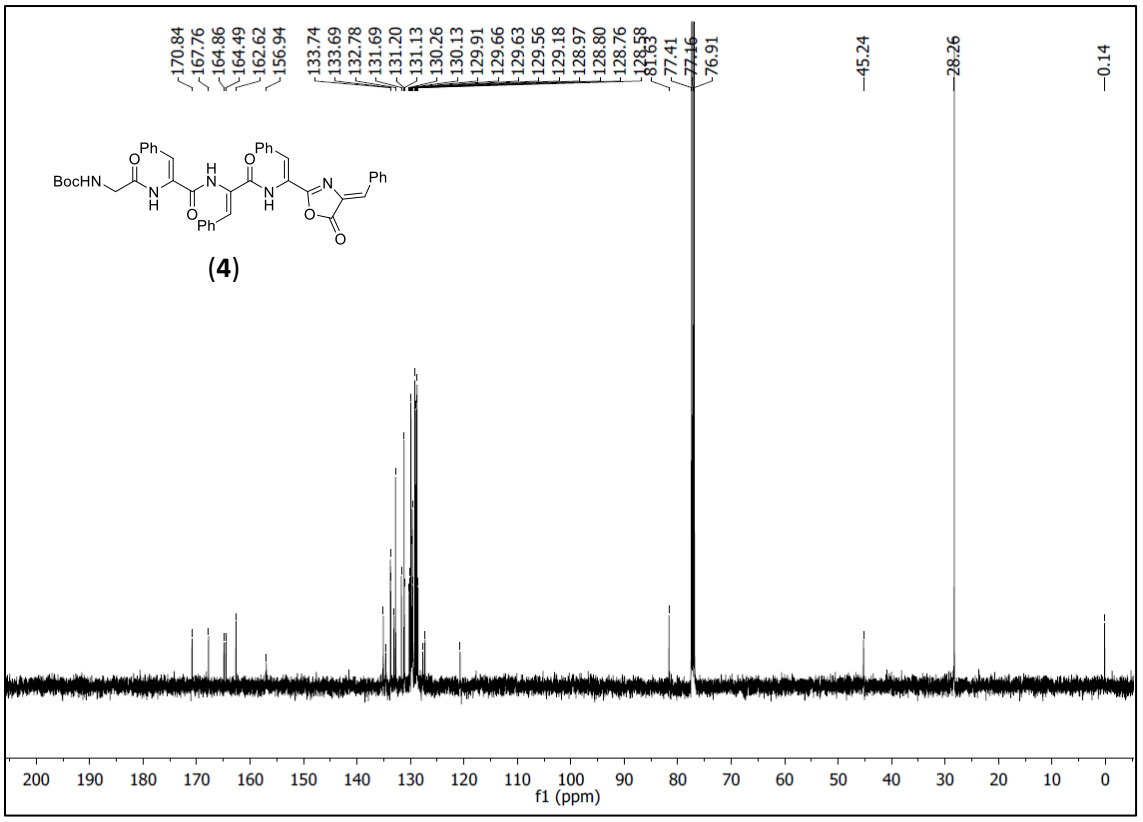
8.39
8.06
8.05
8.03
7.78
7.77
7.74
7.73
7.68
7.55
7.53
7.51
7.51
7.50
7.48
7.46
7.45
7.44
7.42
7.41
7.40
7.35
3.96
3.95
3.48
2.92
2.92
2.92
2.76
2.75
2.75
2.75
2.74
1.35
BocHN
Ph
O
N
H
Ph
O
(4)
0.84
0.82
0.81
1.86
2.54
1.89
1.88
0.88
4.53
9.91
1.00
0.80
1.88
9.18
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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164.49
162.62
156.94
133.74
133.69
132.78
131.69
131.20
131.13
130.26
130.13
129.91
129.66
129.63
129.56
129.18
128.97
128.80
128.76
128.58
81.63
77.41
77.16
76.91
45.24
28.26
0.14
BocHN
Ph
O
N
H
Ph
O
(4)
200
190
180
170
160
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140
130
120
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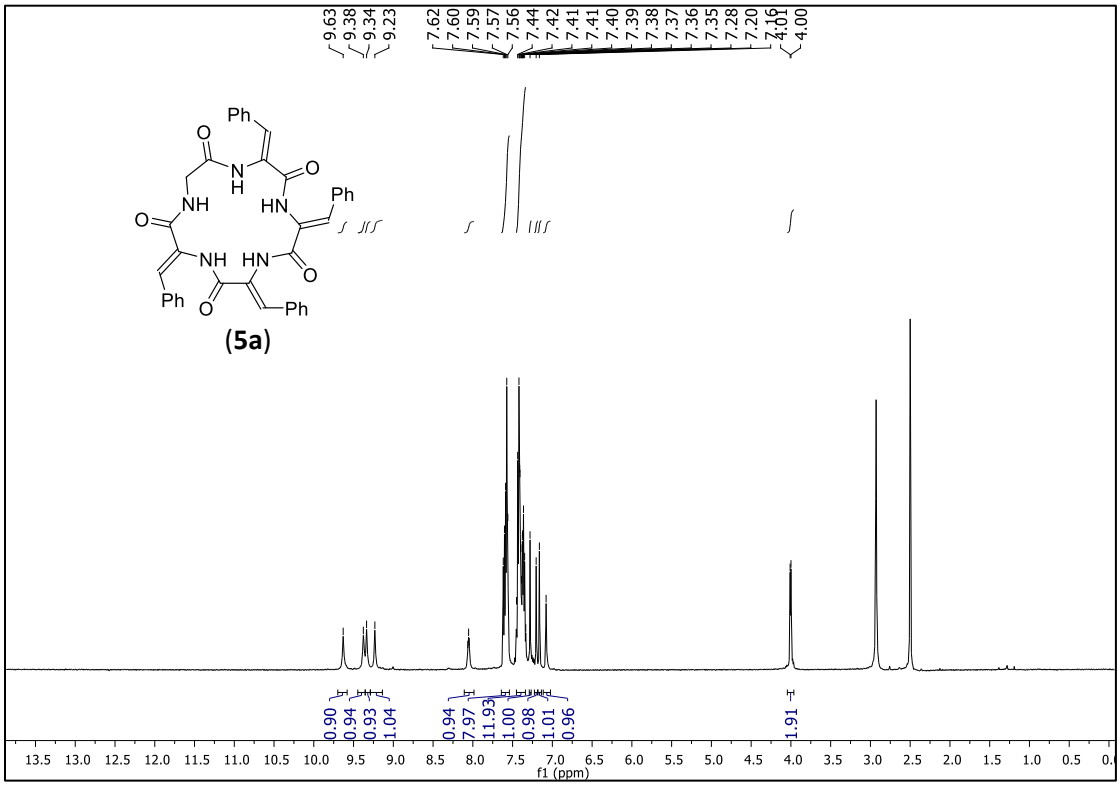
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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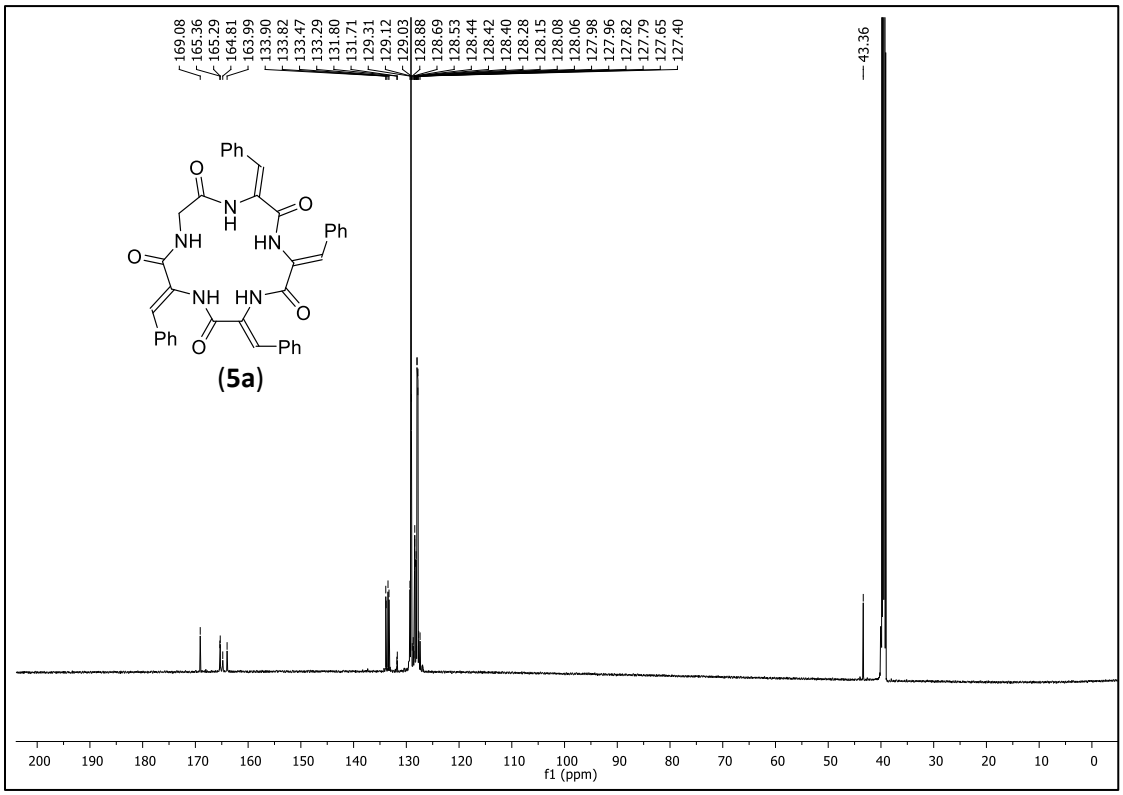
9.34
9.23
7.62
7.60
7.59
7.57
7.56
7.44
7.42
7.41
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.28
7.20
4.01
4.00
Ph
O
N
H
O
HN
Ph
NH
O
NH
HN
O
Ph
O
Ph
(5a)
0.90
0.94
0.93
1.04
0.94
7.97
11.93
1.00
0.98
1.01
0.96
1.91
f1 (ppm)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131.71
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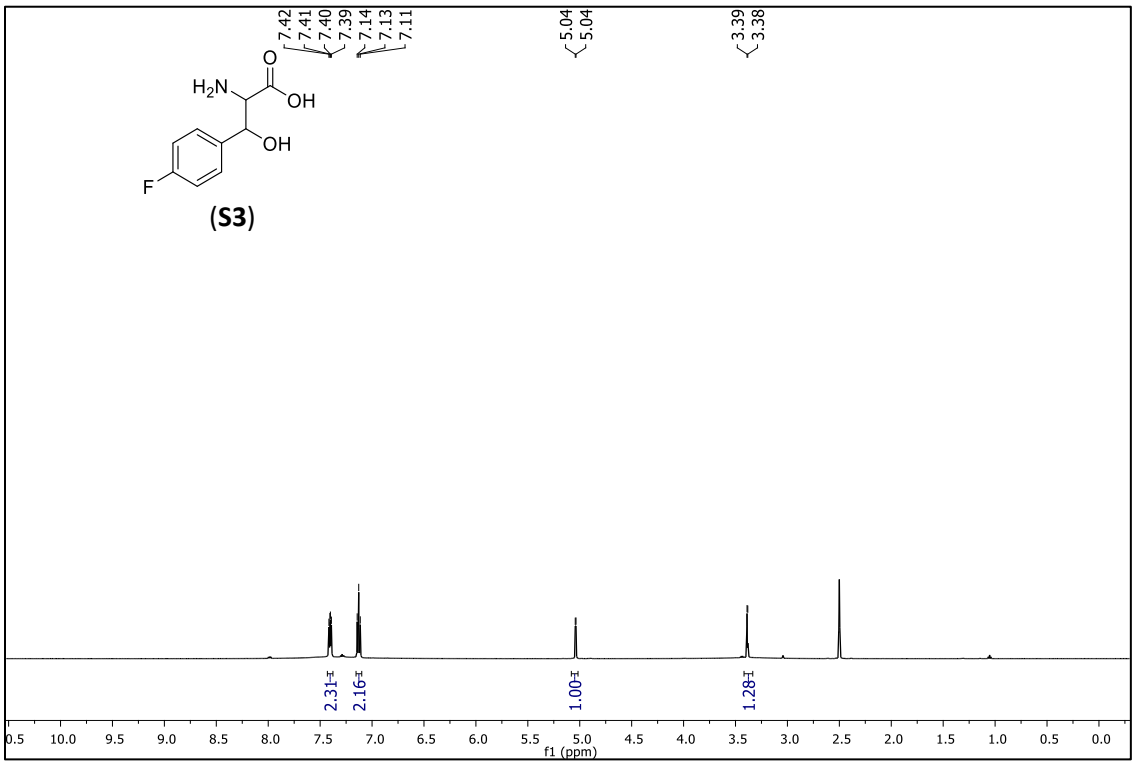
129.12
129.03
128.88
128.69
128.53
128.44
128.42
128.40
128.28
128.15
128.08
128.06
127.98
127.96
127.82
127.79
127.65
127.40
43.36
Ph
O
N
H
O
HN
Ph
NH
O
NH
HN
O
Ph
O
Ph
(5a)
f1 (ppm)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7.39
7.14
7.13
7.11
5.04
5.04
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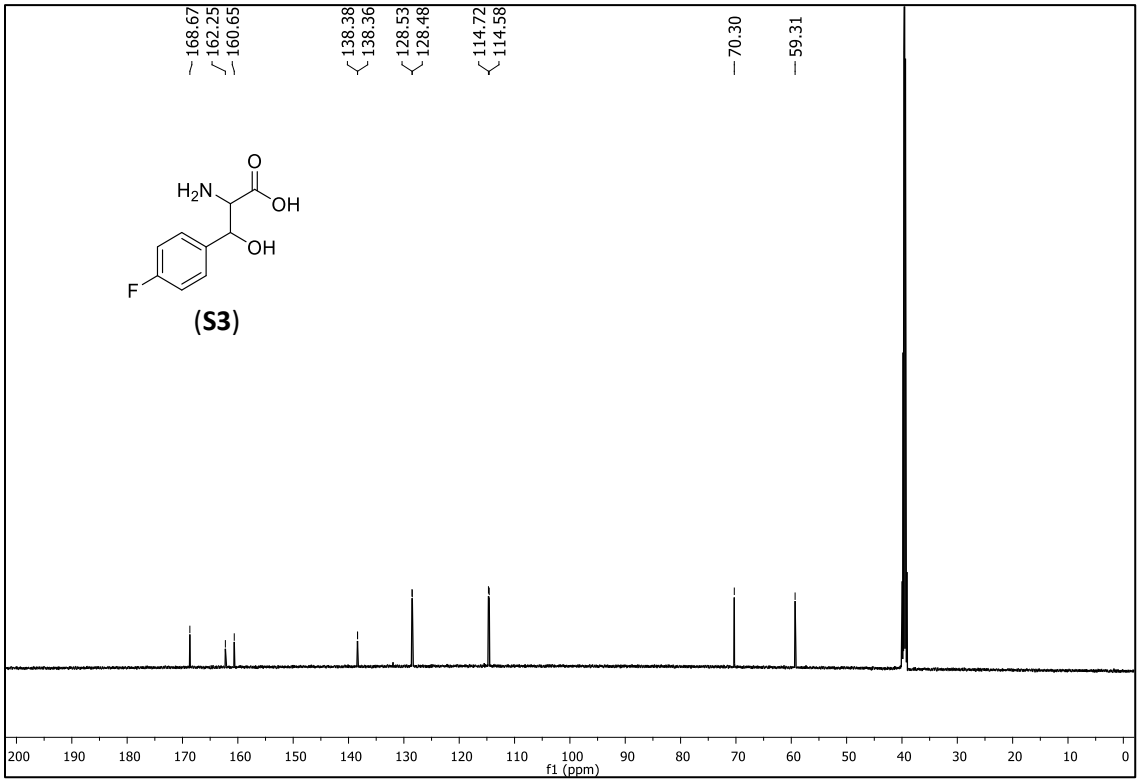
OH
OH
F
(S3)
2.31
2.16
1.00
1.28
f1 (ppm)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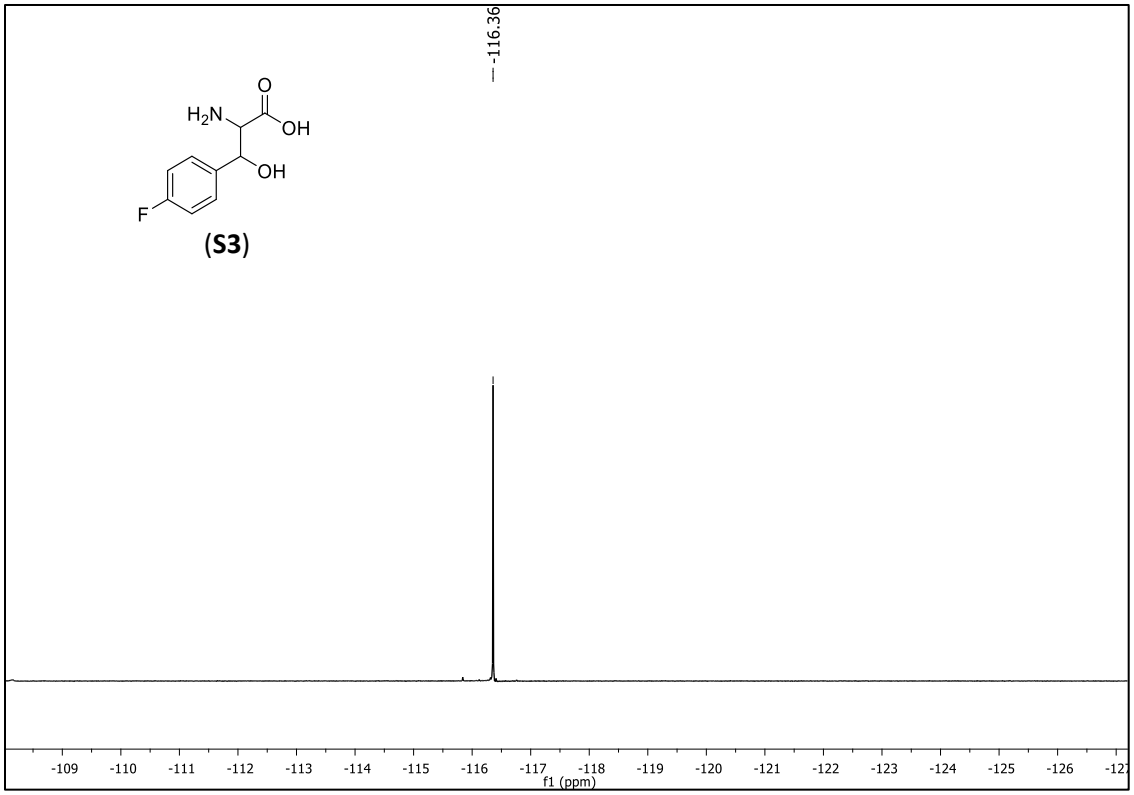
OH
OH
F
(S3)
f1 (ppm)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H2N
OH
OH
F
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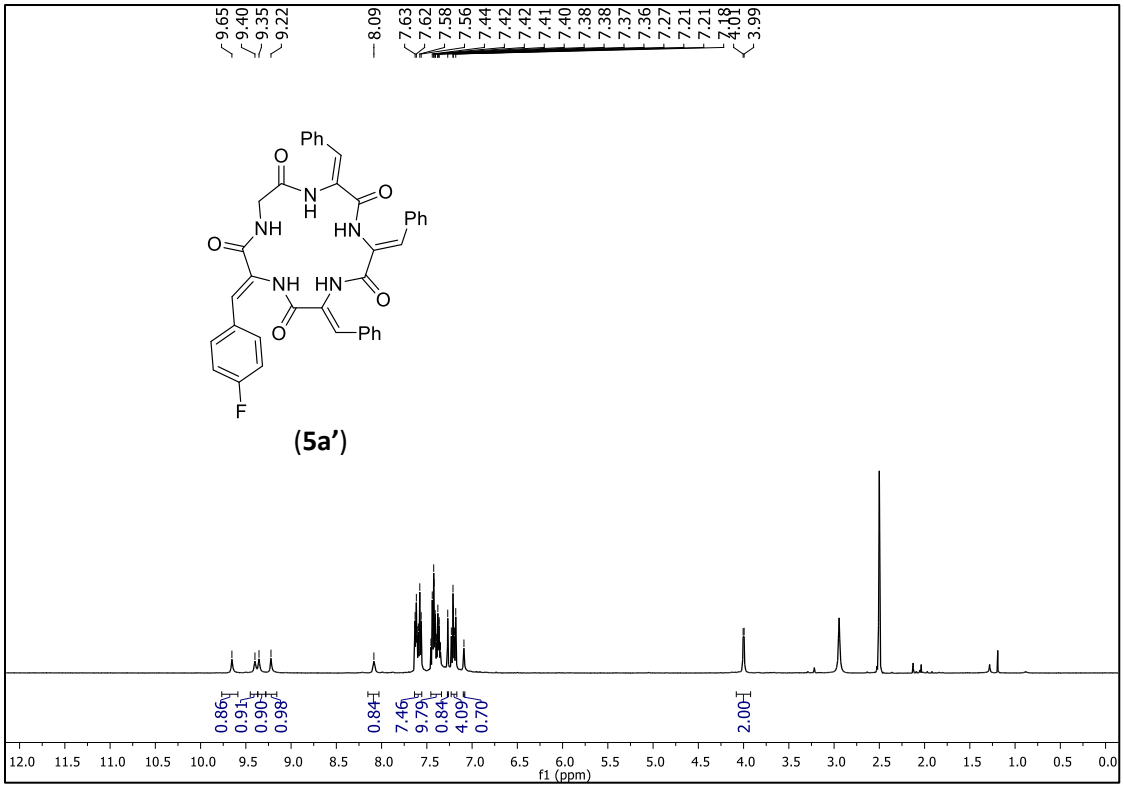
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
f1 (ppm)

(**S3**)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7.63
7.62
7.58
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7.40
7.38
7.38
7.37
7.36
7.27
7.21
7.21
4.18
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3.99
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
(5a')
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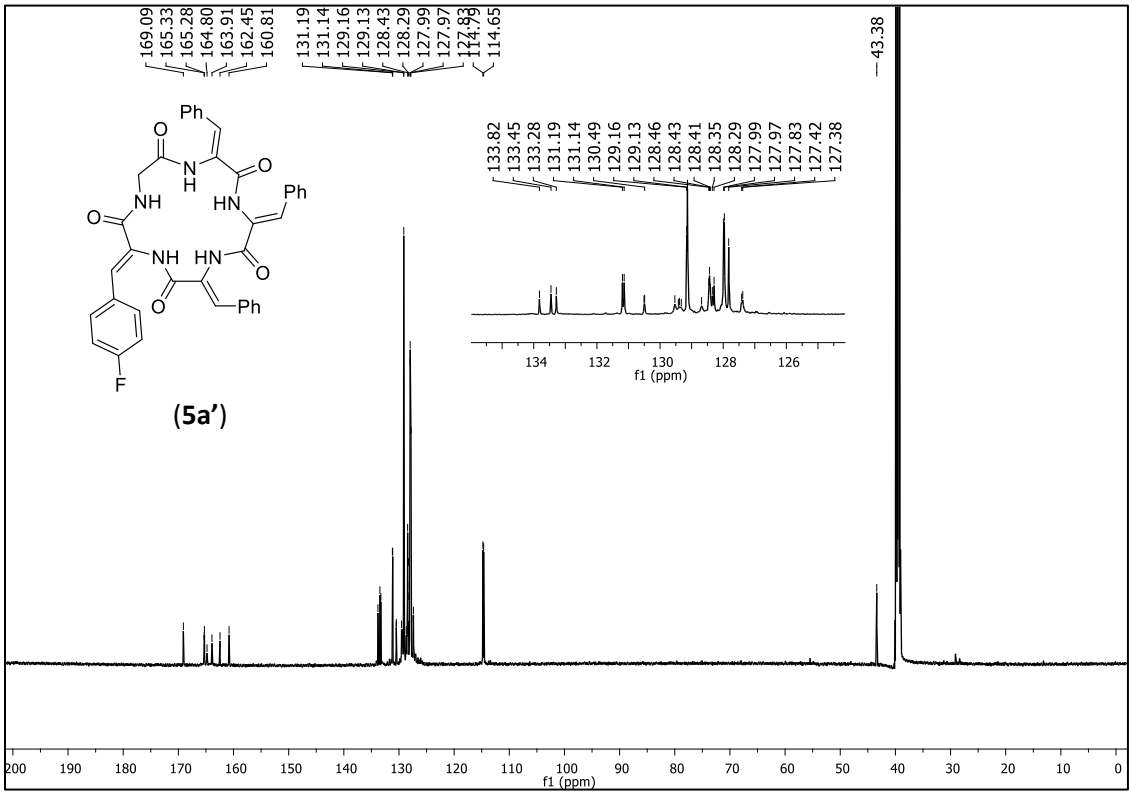
0.91
0.90
0.98
0.84
7.46
9.79
0.84
4.09
0.70
2.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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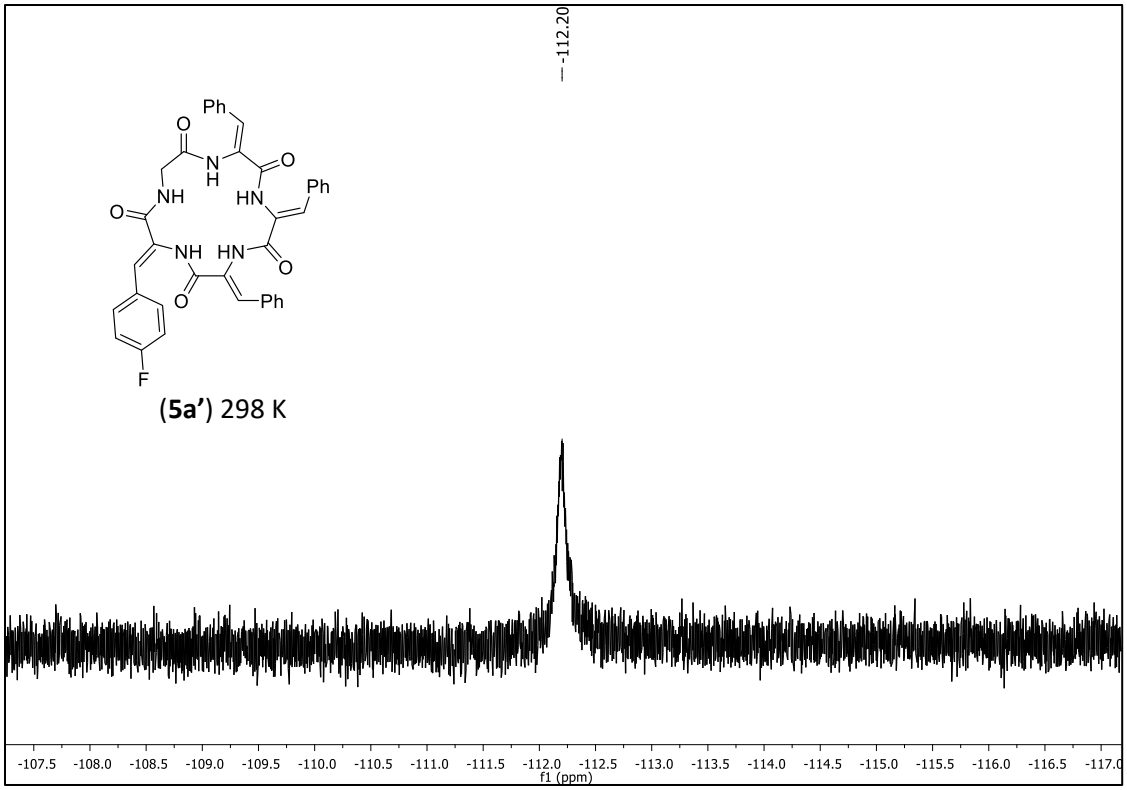
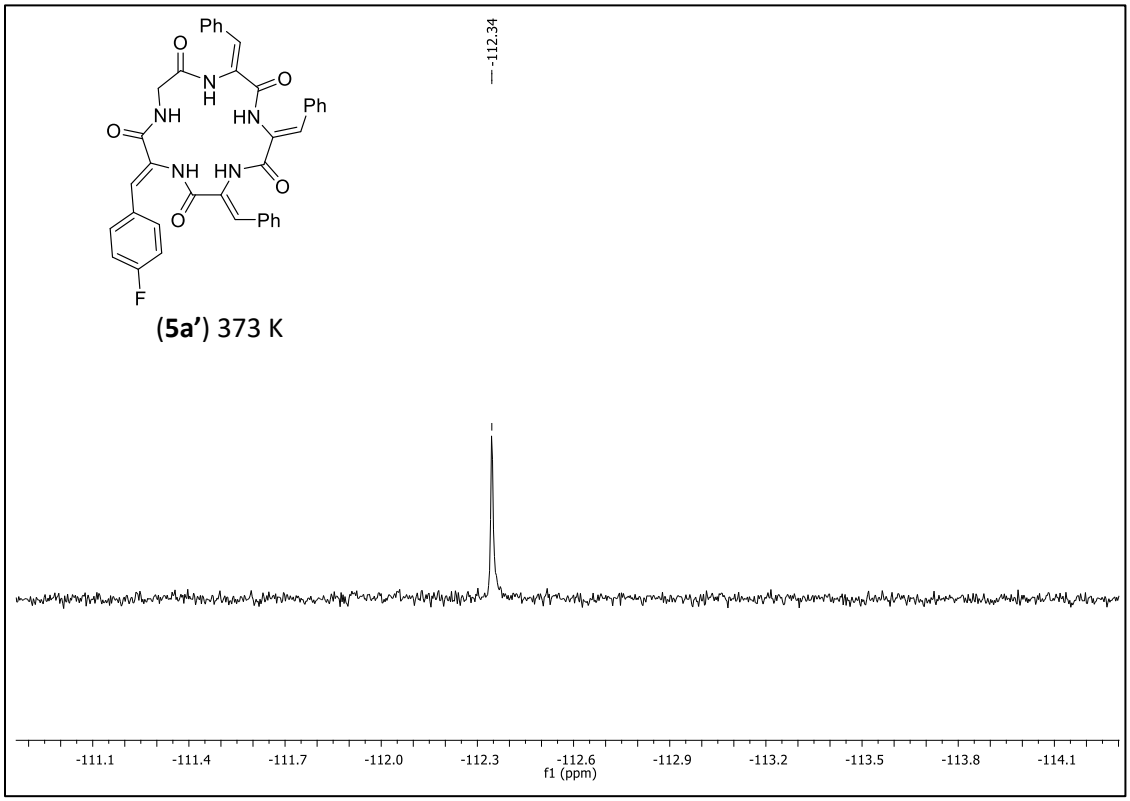
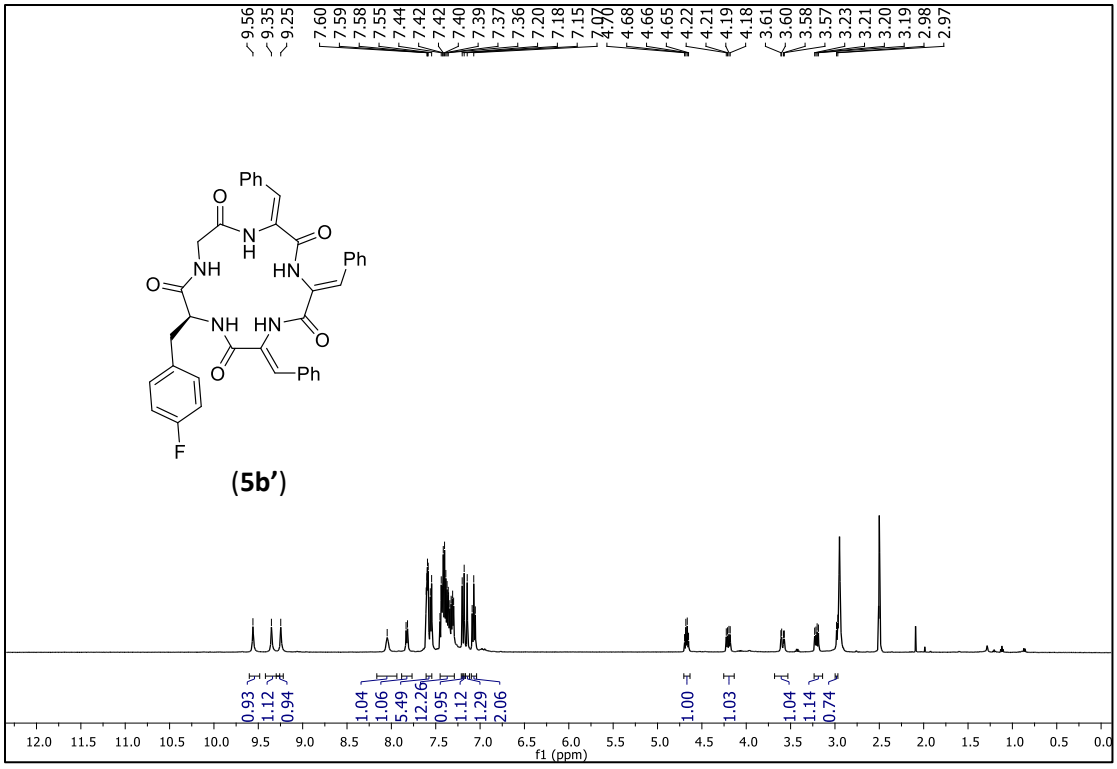
128.29
127.99
127.97
127.83
127.42
114.79
114.65
43.38
133.82
133.45
133.28
131.19
131.14
130.49
129.16
129.13
128.46
128.43
128.41
128.35
128.29
127.99
127.97
127.83
127.42
127.38
134 132 130 128 126
f1 (ppm)
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
(5a')
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



(**5a'**) 298 K



(**5a'**) 373 K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7.60
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7.58
7.55
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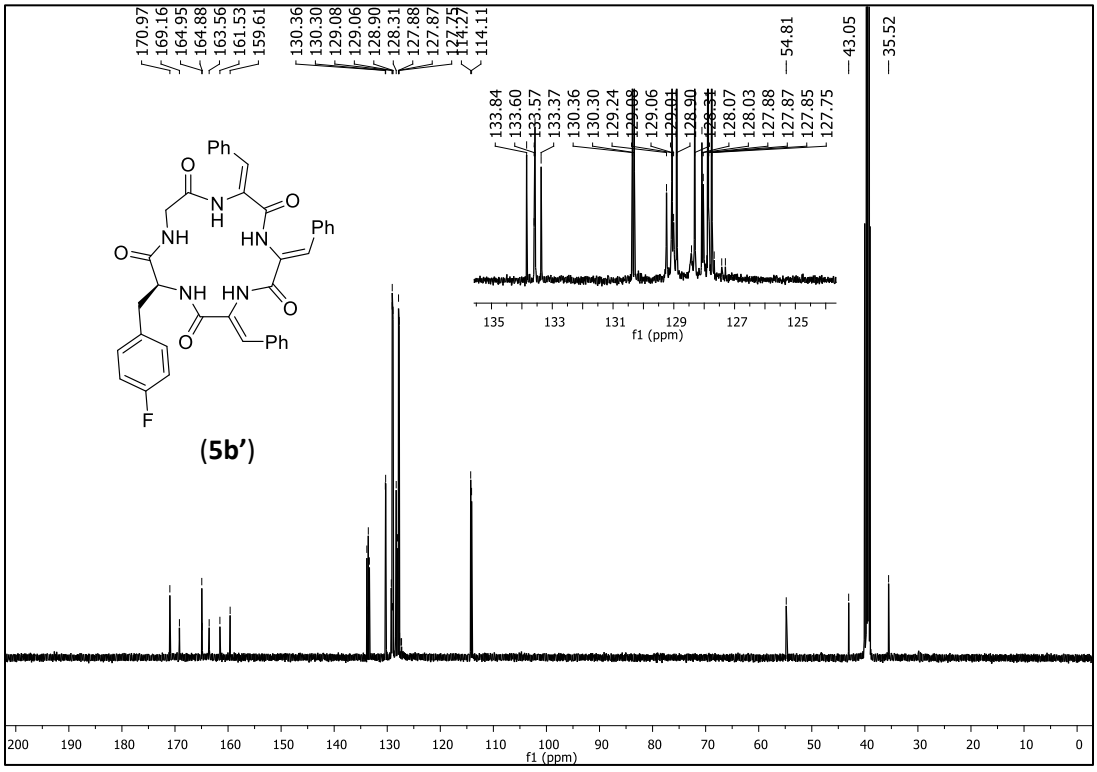
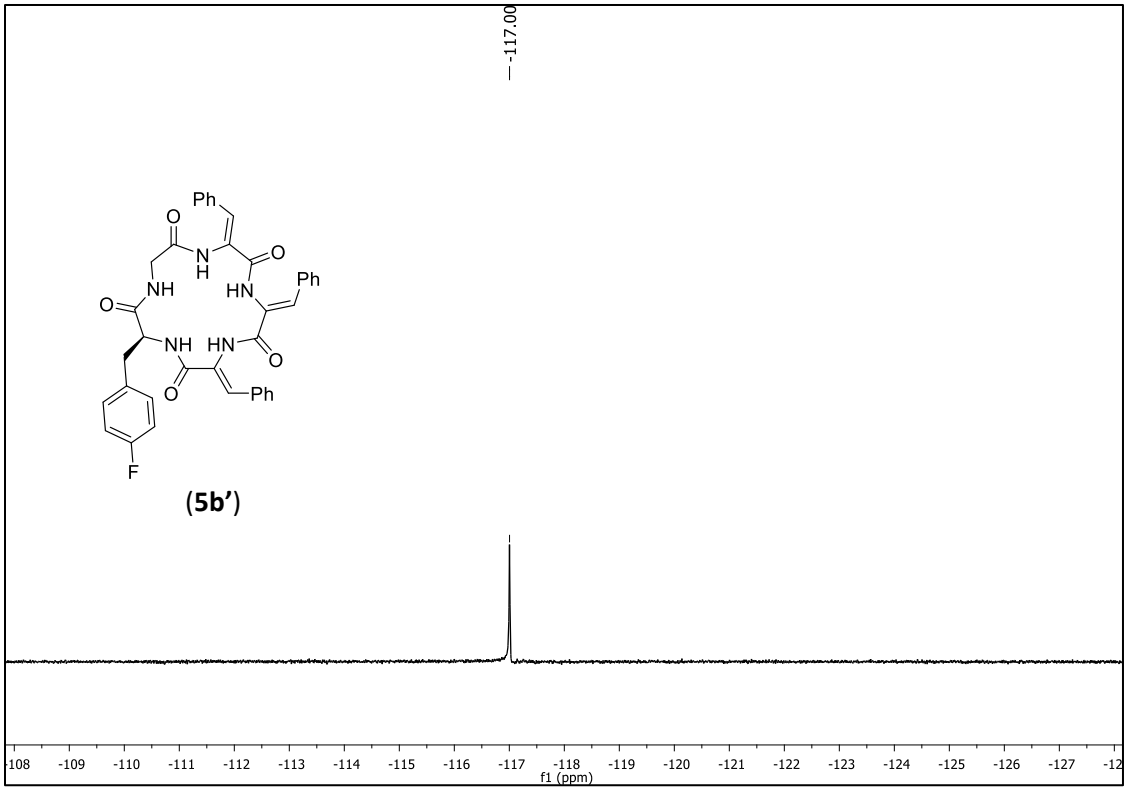
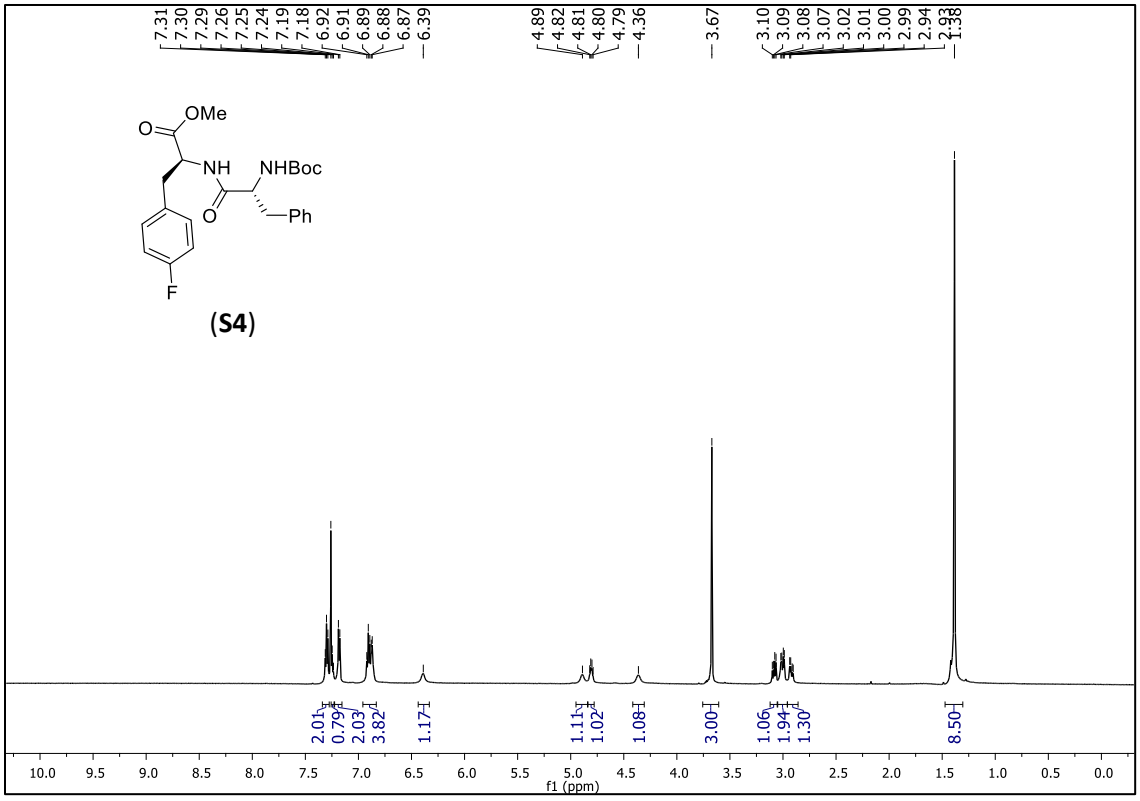
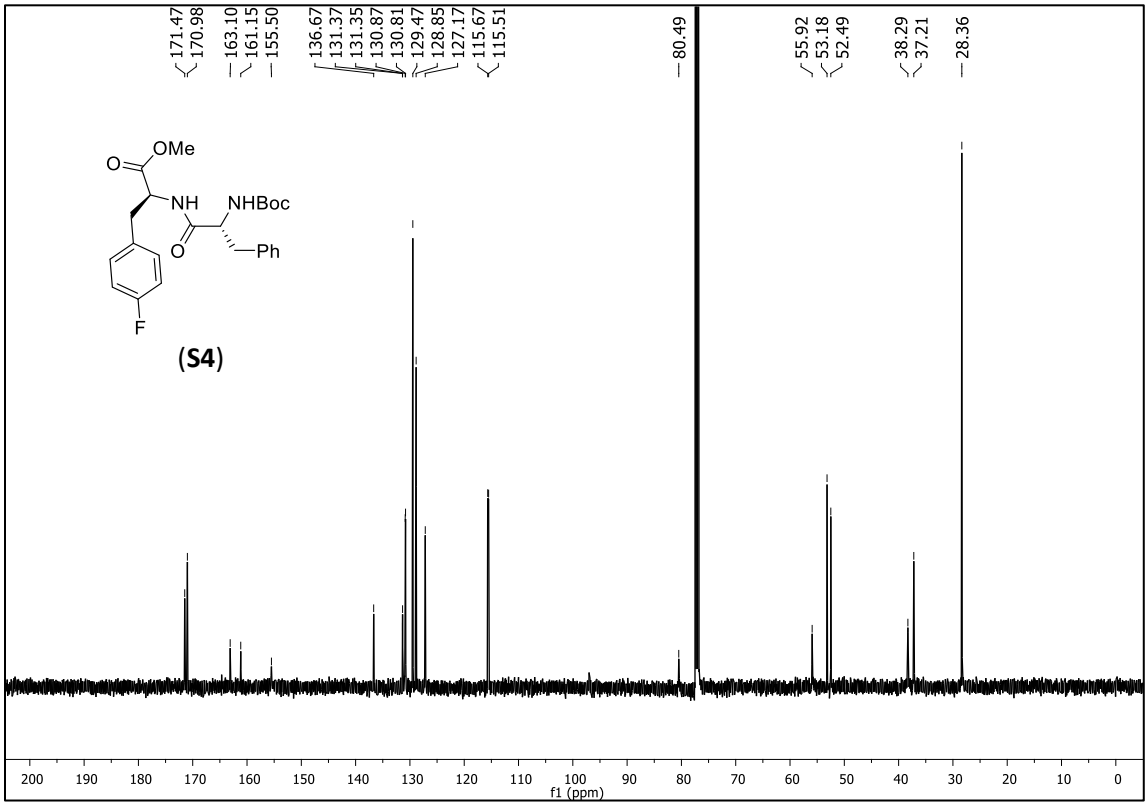
7.42
7.42
7.40
7.39
7.37
7.36
7.20
7.18
7.15
4.70
4.68
4.66
4.65
4.22
4.21
4.19
4.18
3.61
3.60
3.58
3.57
3.23
3.21
3.20
3.19
2.98
2.97
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
(5b')
0.93
1.12
0.94
1.04
1.06
5.49
12.26
0.95
1.12
1.29
2.06
1.00
1.03
1.04
1.14
0.74
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

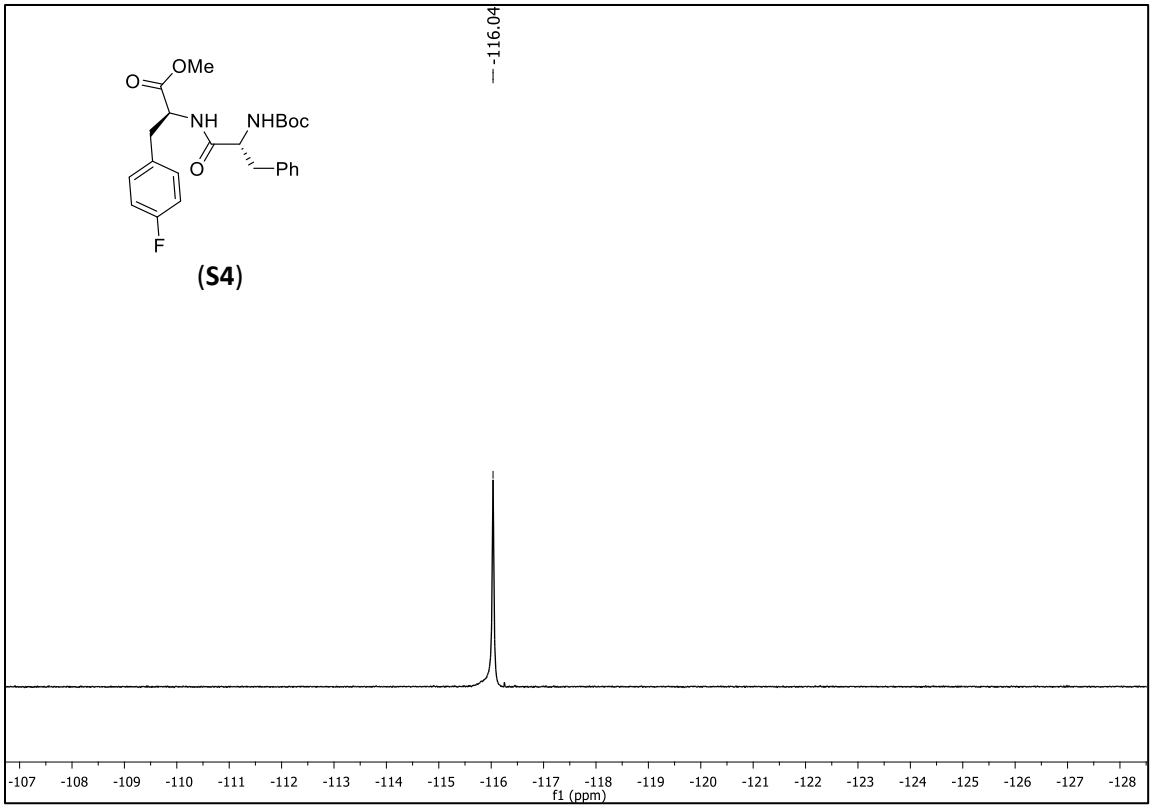

170.97
169.16
164.95
164.88
163.56
161.53
159.61
130.36
130.30
129.08
129.06
128.90
128.31
127.88
127.87
127.75
127.27
114.11
54.81
43.05
35.52
133.84
133.60
133.57
133.37
130.36
130.30
129.24
129.08
129.06
129.01
128.90
128.31
128.07
128.03
127.88
127.87
127.85
127.75
135
133
131
129
127
125
f1 (ppm)
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
(5b')
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

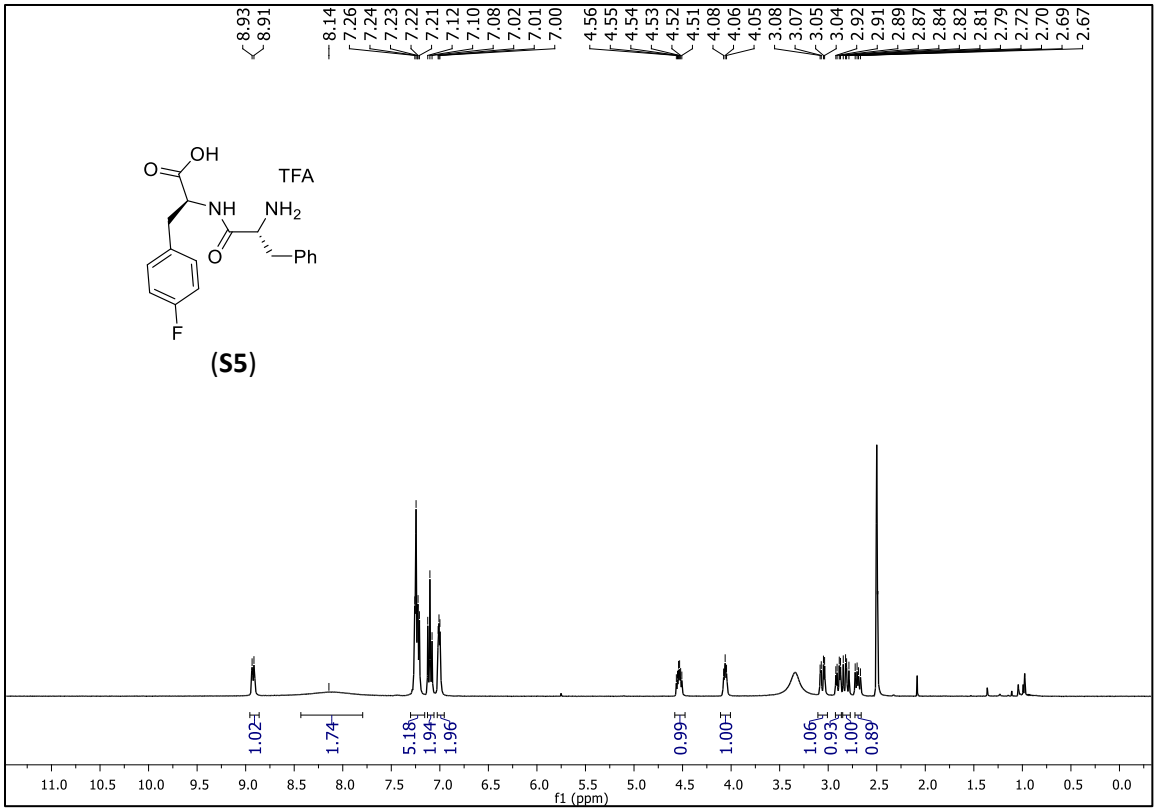

-117.00
Ph
O
N
H
O
HN
Ph
NH
O
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

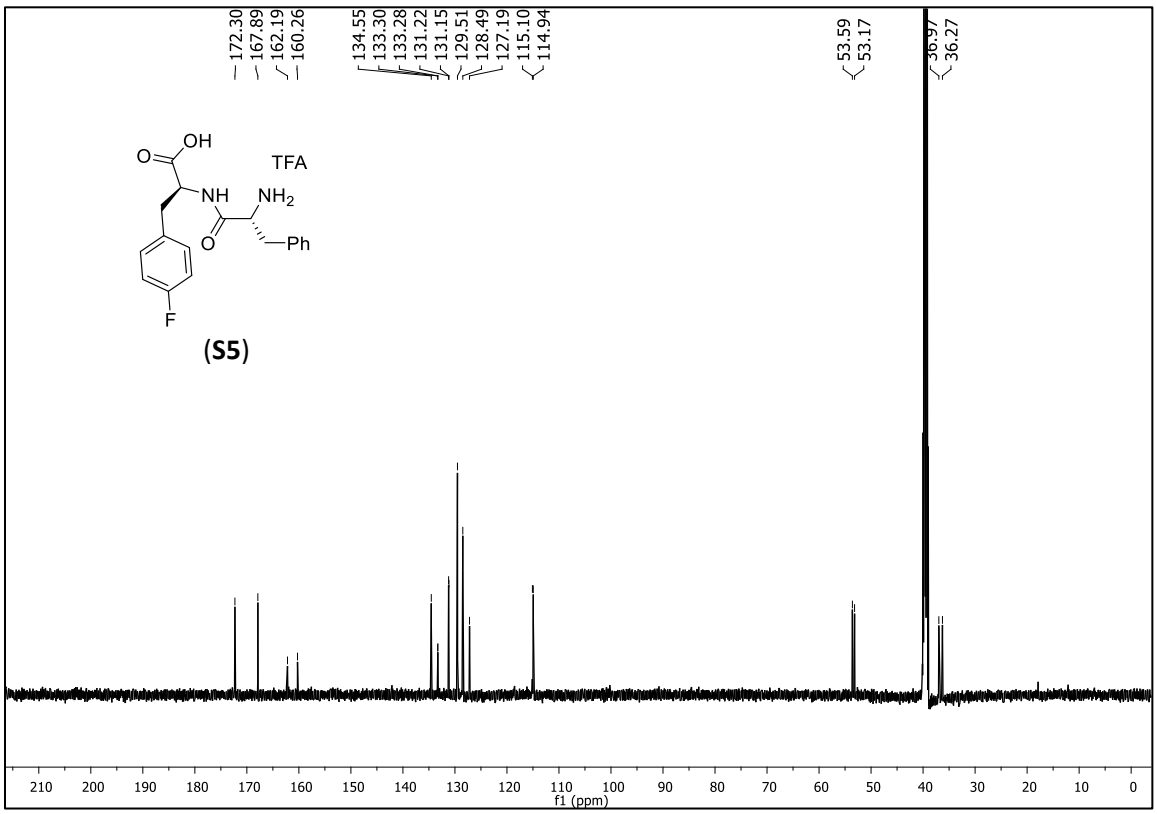
(**5b'**)

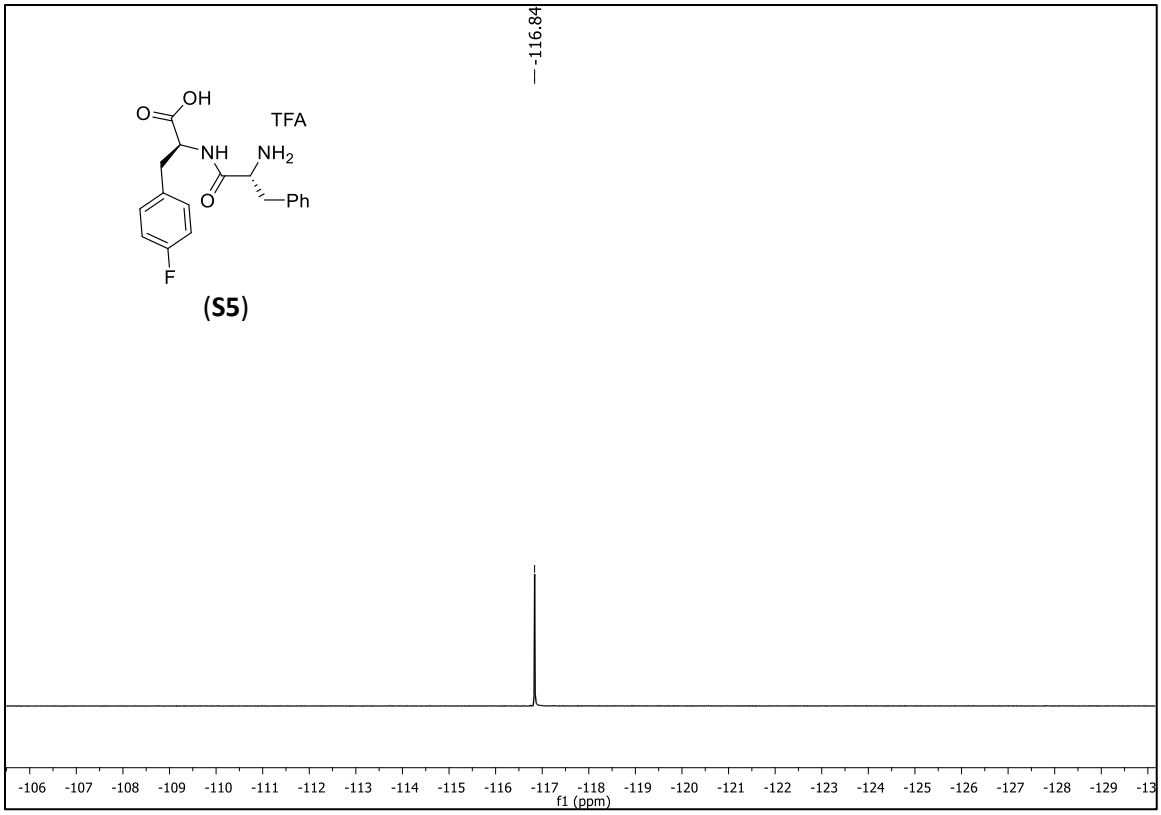

7.31
7.30
7.29
7.26
7.25
7.24
7.19
7.18
6.92
6.91
6.89
6.88
6.87
6.39
4.89
4.82
4.81
4.80
4.79
4.36
3.67
3.10
3.09
3.08
3.07
3.02
3.01
3.00
2.99
2.94
2.93
1.38
OMe
O
NH
NHBoc
O
Ph
F
(S4)
2.01
0.79
2.03
3.82
1.17
1.11
1.02
1.08
3.00
1.06
1.94
1.30
8.50
f1 (ppm)

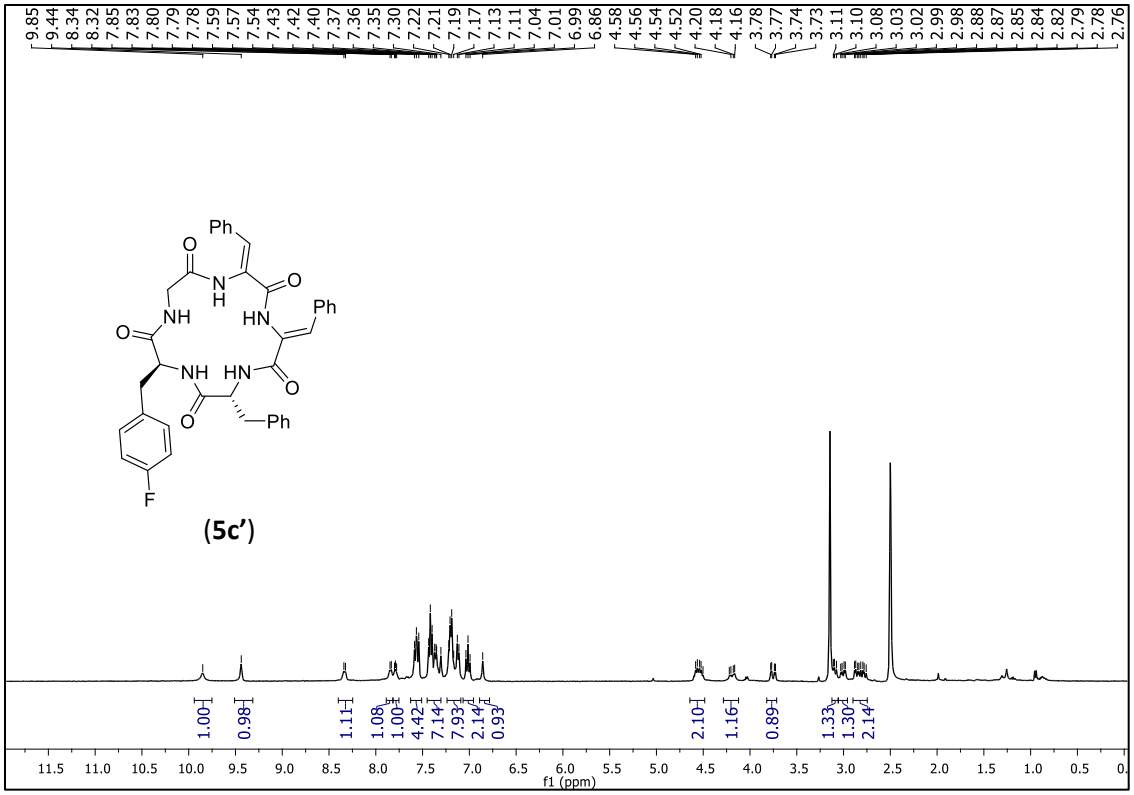

171.47
170.98
163.10
161.15
155.50
136.67
131.37
131.35
130.87
130.81
129.47
128.85
127.17
115.67
115.51
80.49
55.92
53.18
52.49
38.29
37.21
28.36
OMe
O
NH
NHBoc
O
Ph
F
(S4)
f1 (ppm)

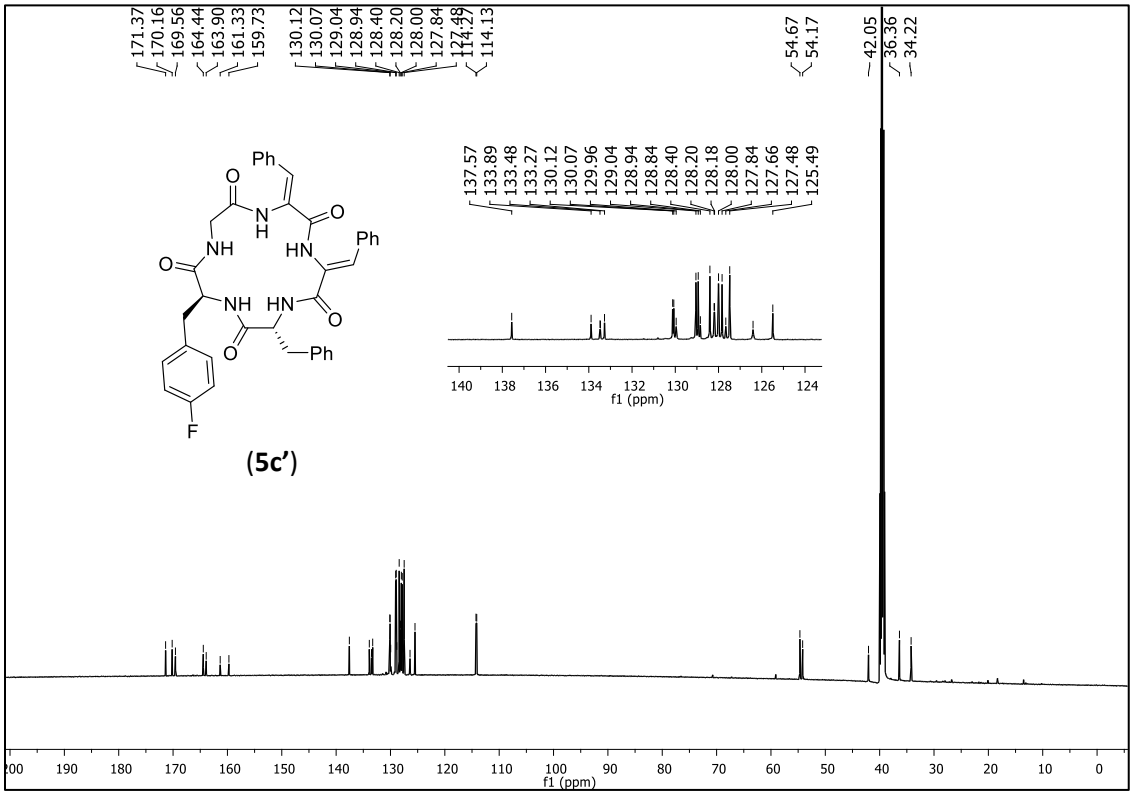

-116.04
OMe
O
NH
NHBoc
O
Ph
F
(S4)
-107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128
f1 (ppm)

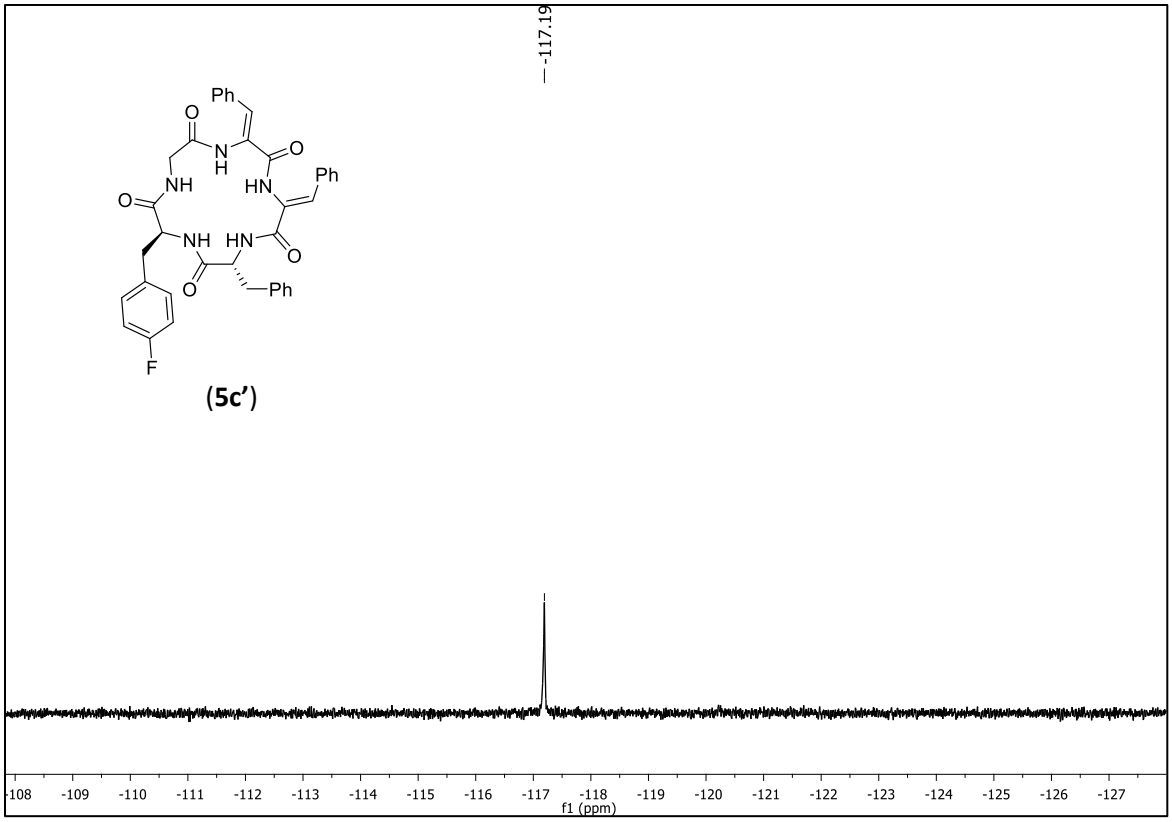

8.93
8.91
8.14
7.26
7.24
7.23
7.22
7.21
7.12
7.10
7.08
7.02
7.01
7.00
4.56
4.55
4.54
4.53
4.52
4.51
4.08
4.06
4.05
3.08
3.07
3.05
3.04
2.92
2.91
2.89
2.87
2.84
2.82
2.81
2.79
2.72
2.70
2.69
2.67
OH
O
NH
NH2
O
Ph
TFA
F
(S5)
1.02
1.74
5.18
1.94
1.96
0.99
1.00
1.06
0.93
1.00
0.89
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.30
167.89
162.19
160.26
134.55
133.30
133.28
131.22
131.15
129.51
128.49
127.19
115.10
114.94
53.59
53.17
36.97
36.27
OH
O
NH
NH2
O
Ph
TFA
F
(S5)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

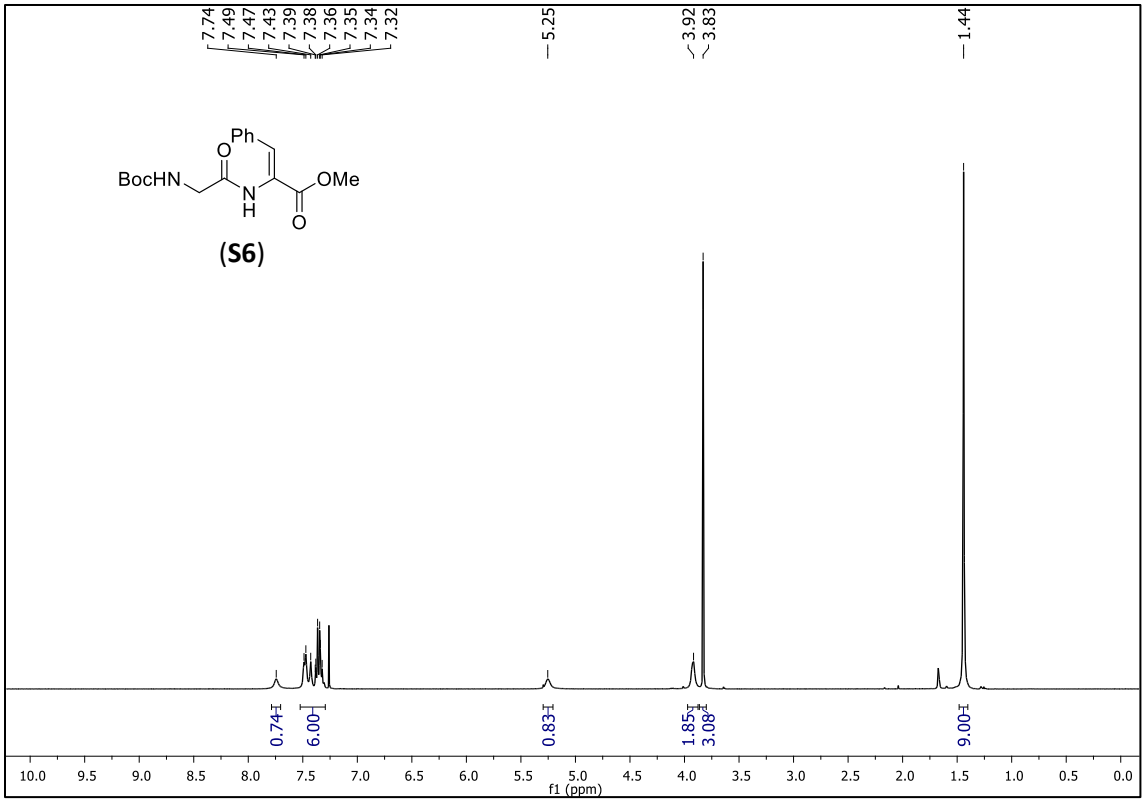

-116.84
OH
O
TFA
NH
NH2
O
Ph
F
(S5)
-106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128 -129 -13
f1 (ppm)

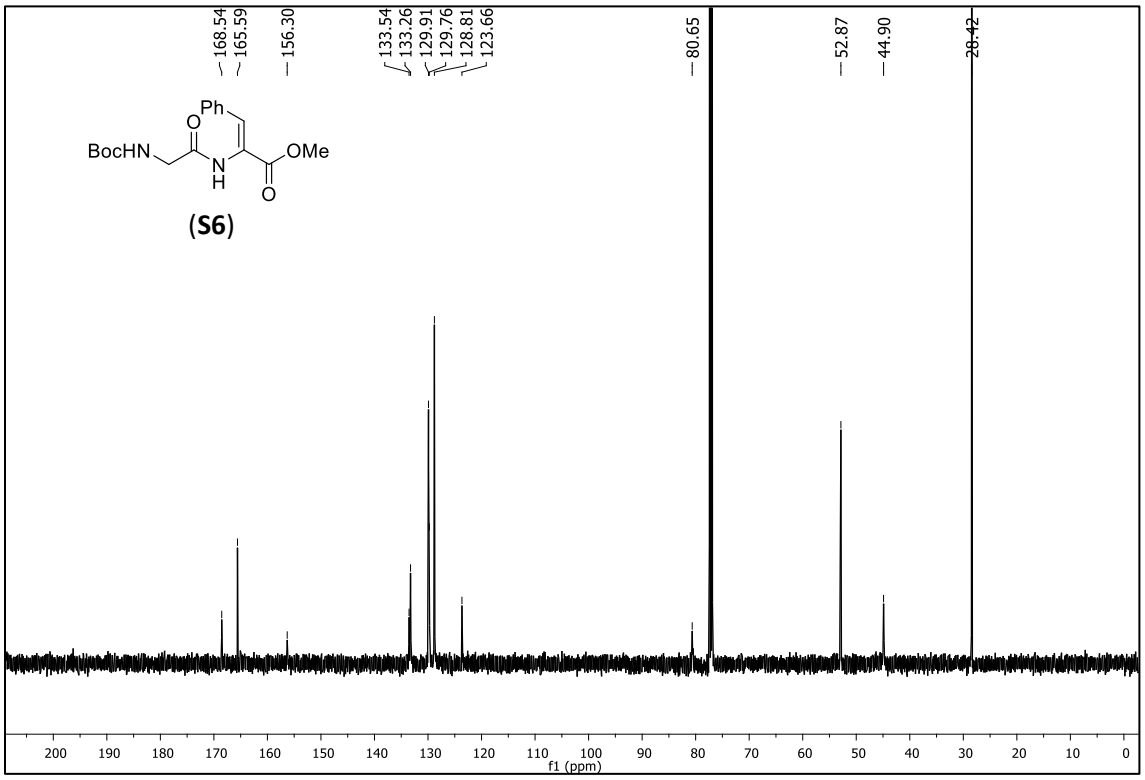

(5c')
f1 (ppm)

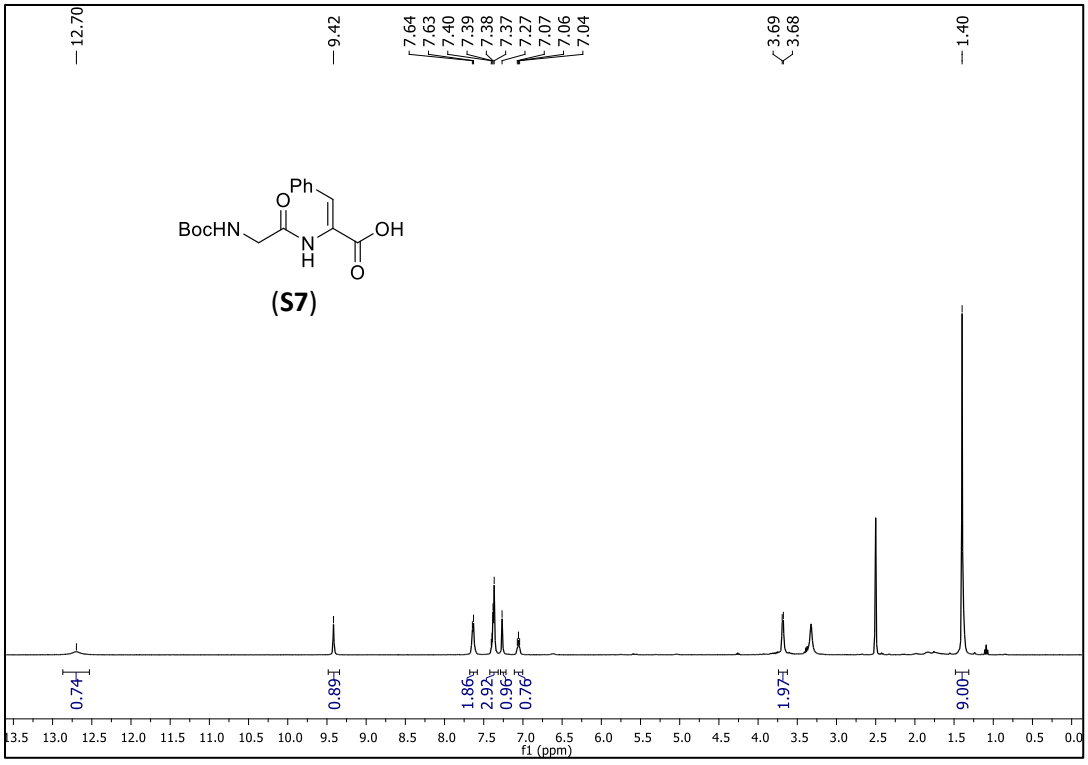

(5c')
f1 (ppm)
f1 (ppm)

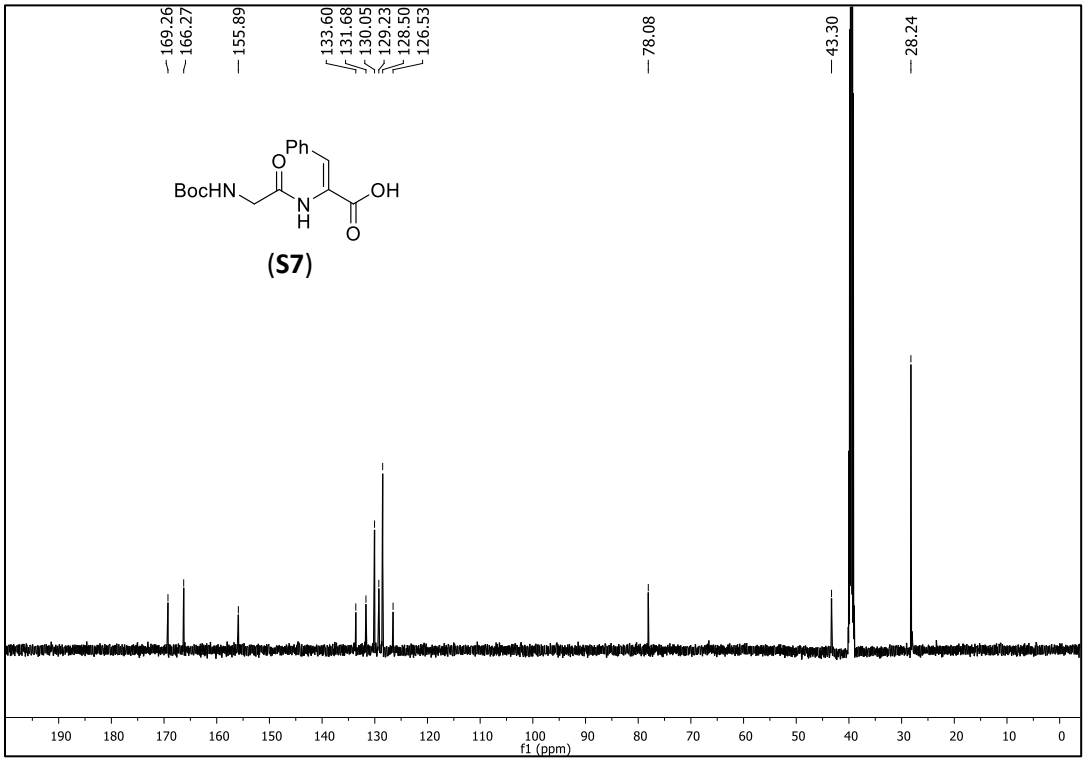

-117.19
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

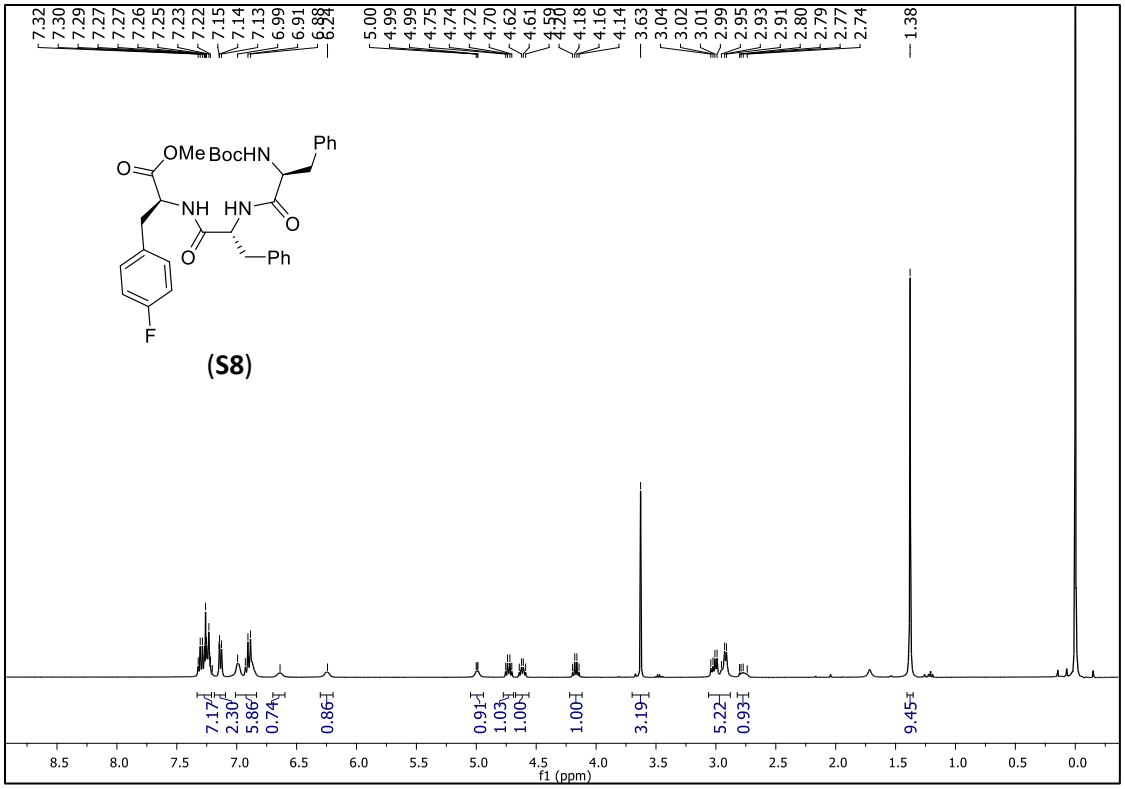
(**5c'**)

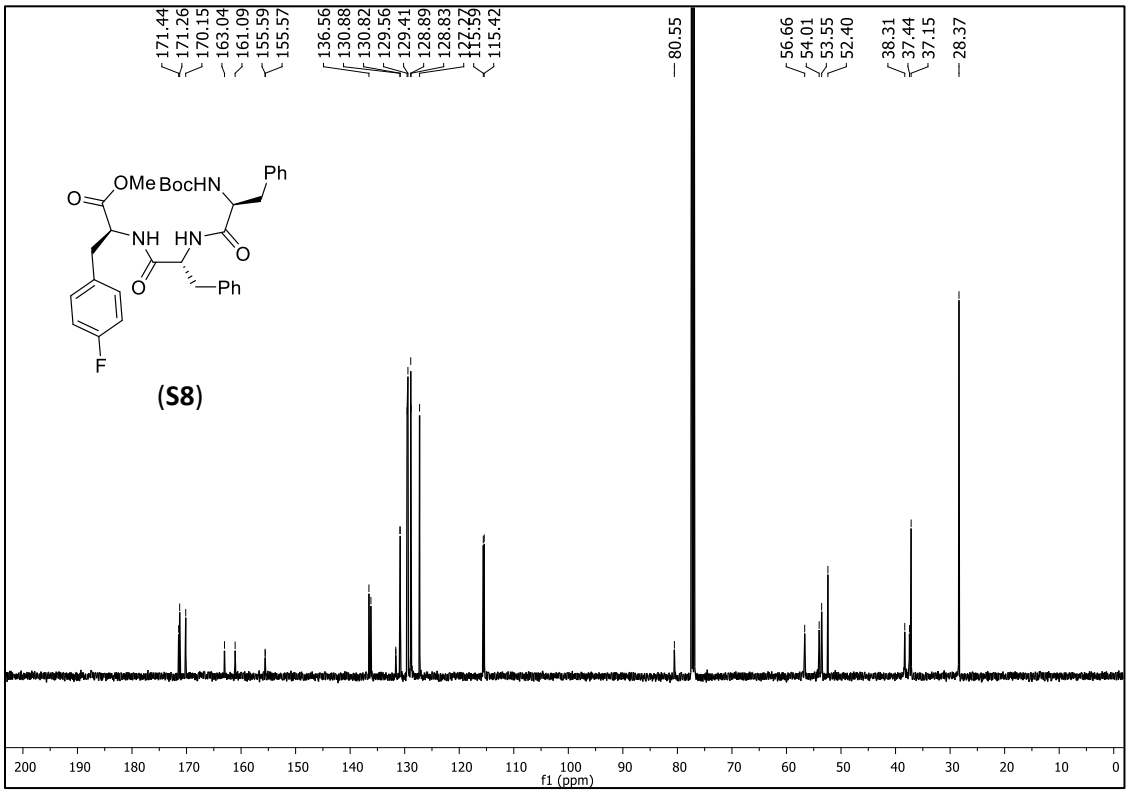

7.74
7.49
7.47
7.43
7.39
7.38
7.36
7.35
7.34
7.32
5.25
3.92
3.83
1.44
Ph
O
BocHN
N
H
OMe
O
(S6)
0.74
6.00
0.83
1.85
3.08
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

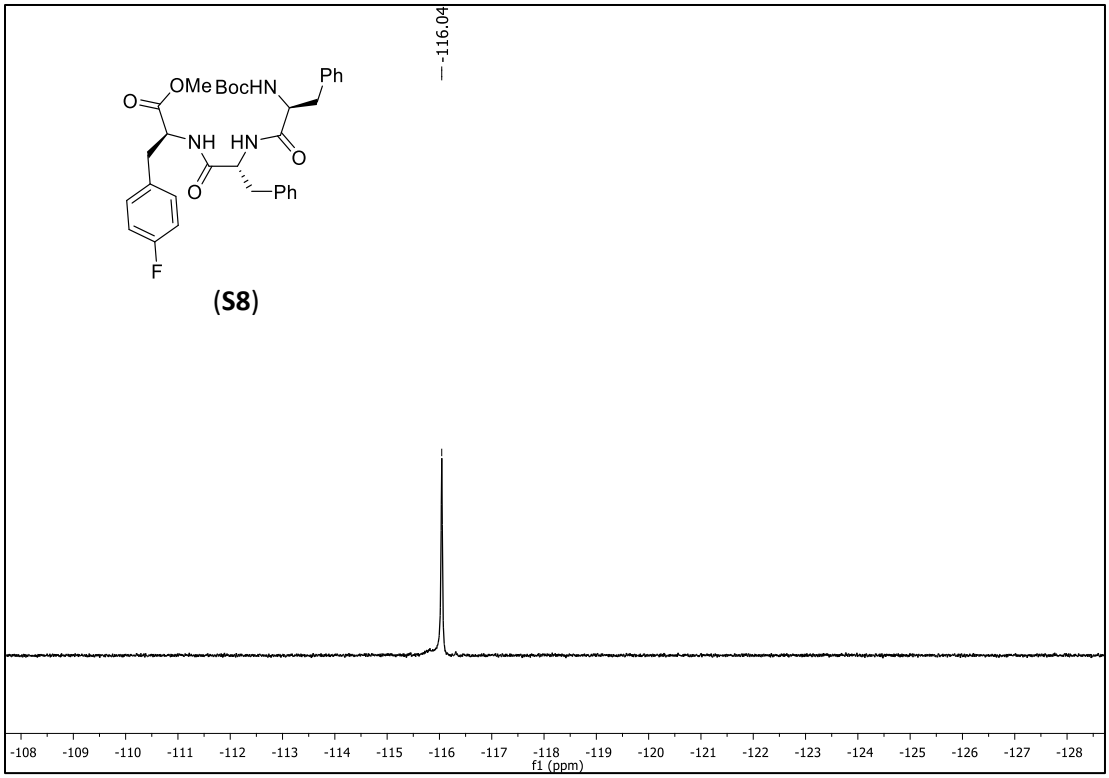

168.54
165.59
156.30
133.54
133.26
129.91
129.76
128.81
123.66
80.65
52.87
44.90
28.42
Ph
O
BocHN
N
H
OMe
O
(S6)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


12.70
9.42
7.64
7.63
7.40
7.39
7.38
7.37
7.27
7.07
7.06
7.04
3.69
3.68
1.40
Ph
O
BocHN
N
H
OH
O
(S7)
0.74
0.89
1.86
2.92
0.96
0.76
1.97
9.00
f1 (ppm)

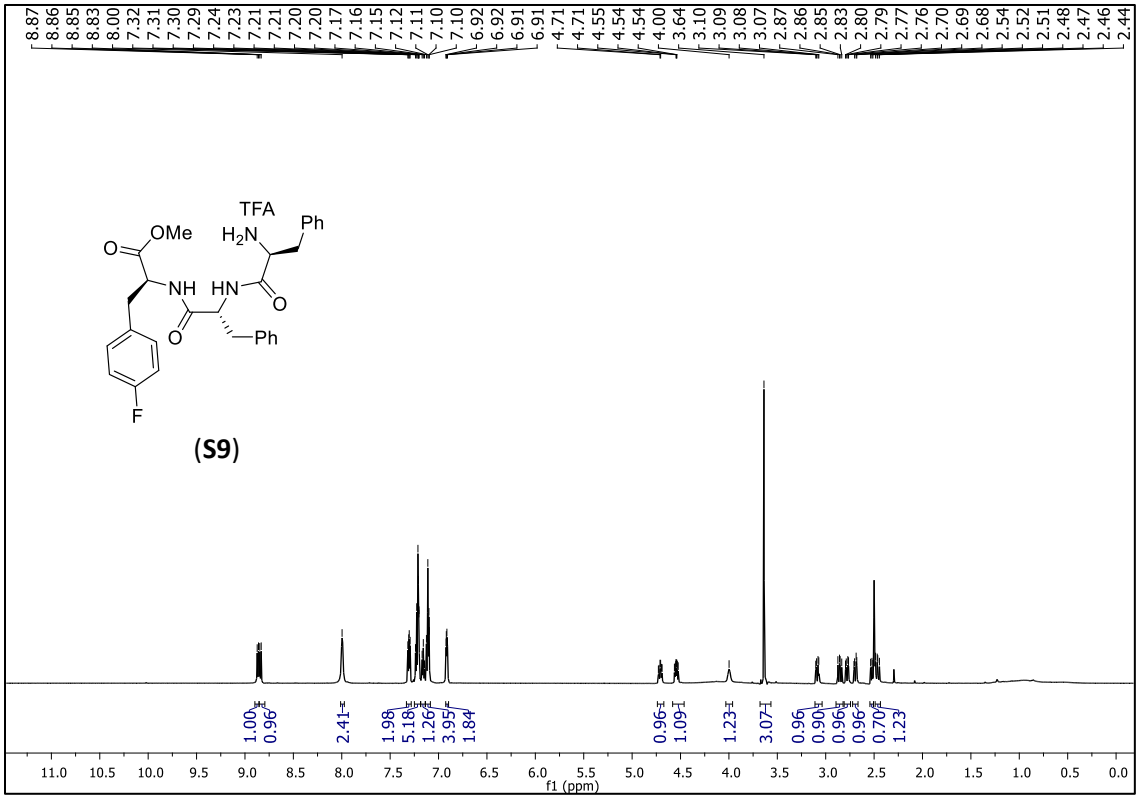

169.26
166.27
155.89
133.60
131.68
130.05
129.23
128.50
126.53
78.08
43.30
28.24
Ph
O
BocHN
N
H
OH
O
(S7)
f1 (ppm)

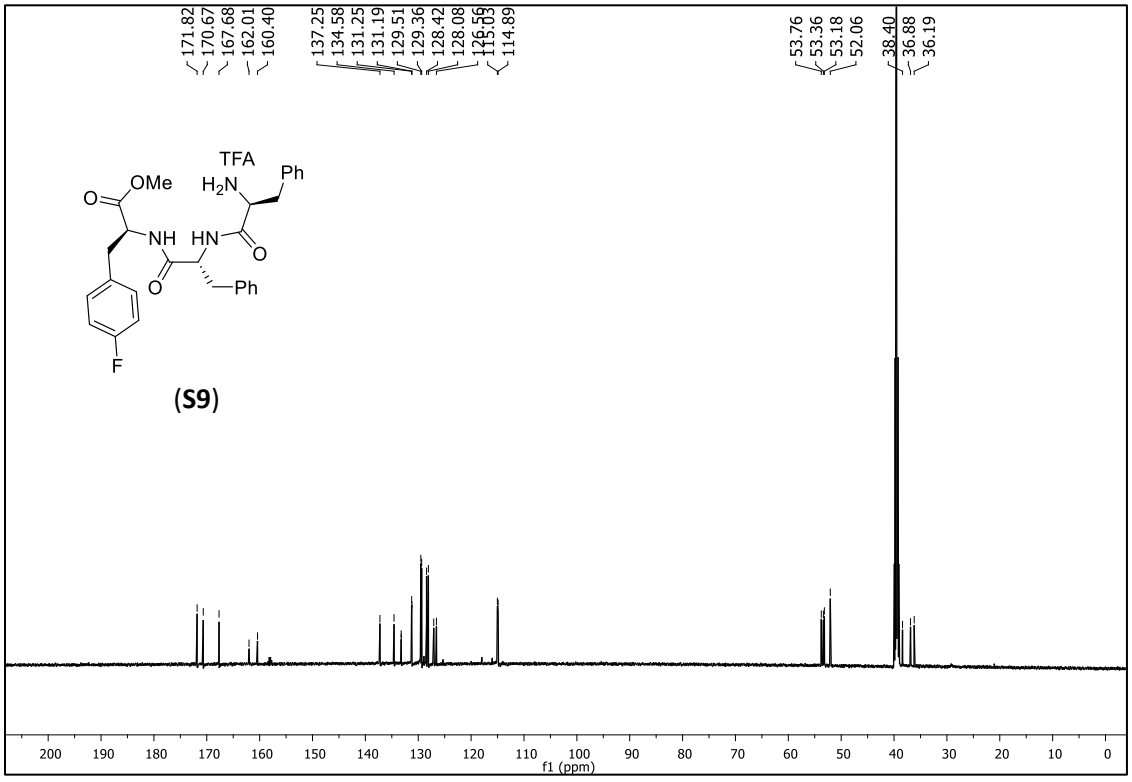

7.32
7.30
7.29
7.27
7.27
7.26
7.25
7.23
7.22
7.15
7.14
7.13
6.99
6.91
6.24
5.00
4.99
4.99
4.75
4.74
4.72
4.70
4.62
4.61
4.59
4.20
4.18
4.16
4.14
3.63
3.04
3.02
3.01
2.99
2.95
2.93
2.91
2.80
2.79
2.77
2.74
1.38
OMe
BocHN
Ph
NH
HN
O
Ph
F
(S8)
7.17
2.30
5.86
0.74
0.86
0.91
1.03
1.00
1.00
3.19
5.22
0.93
9.45
f1 (ppm)

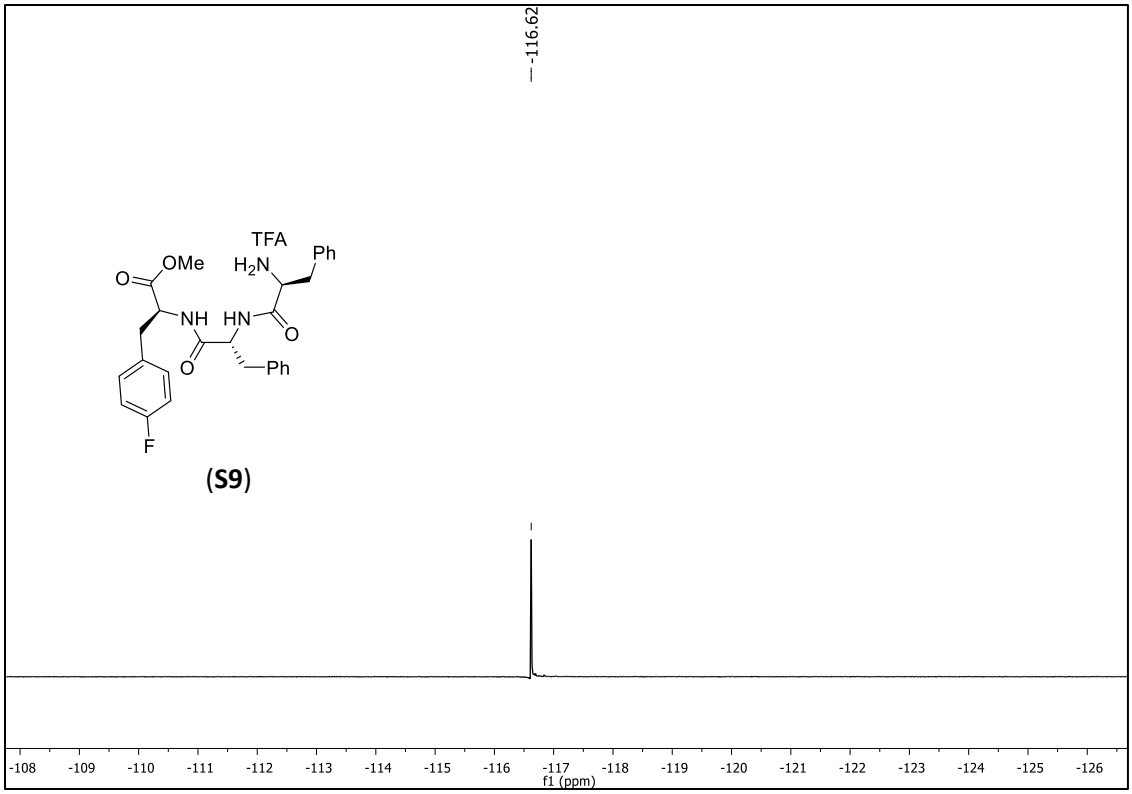

171.44
171.26
170.15
163.04
161.09
155.59
155.57
136.56
130.88
130.82
129.56
129.41
128.89
128.83
127.27
115.59
115.42
80.55
56.66
54.01
53.55
52.40
38.31
37.44
37.15
28.37
OMe
BocHN
Ph
NH
HN
O
Ph
F
(S8)
f1 (ppm)


-116.04
OMe
BocHN
Ph
O
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
-128
f1 (ppm)

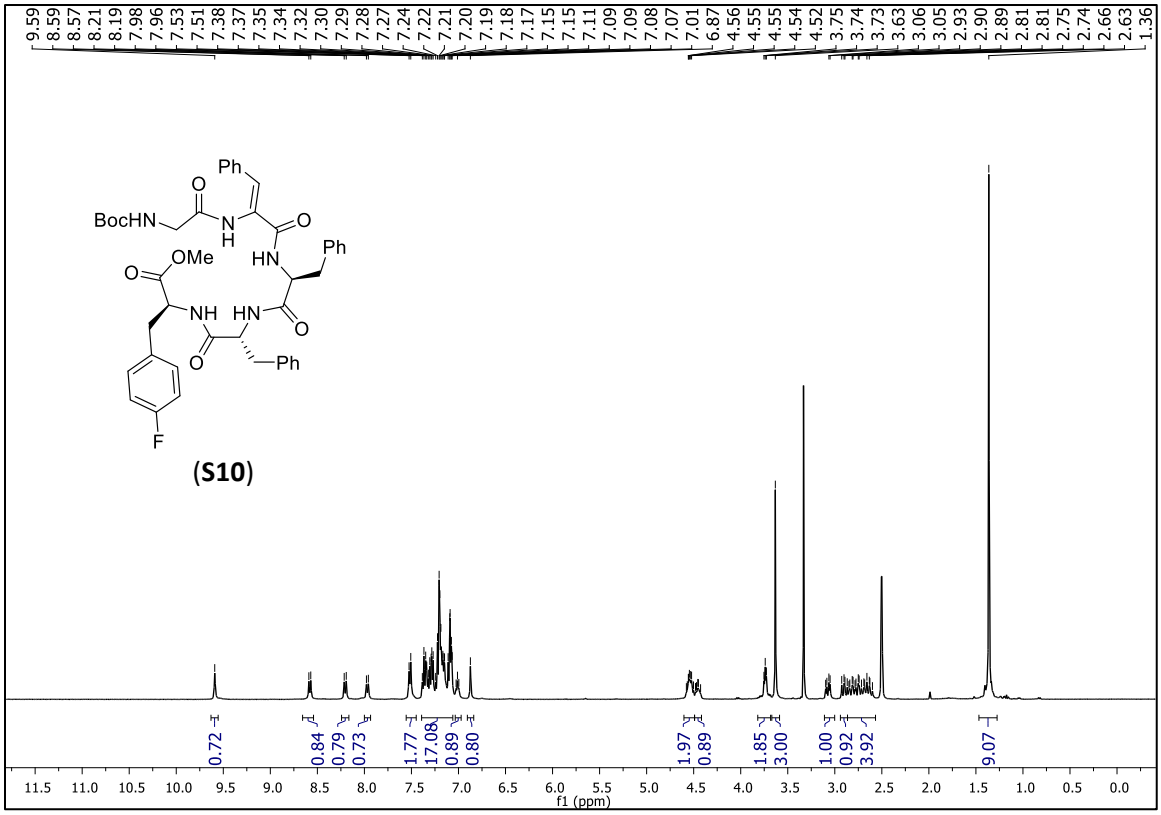
(**S8**)

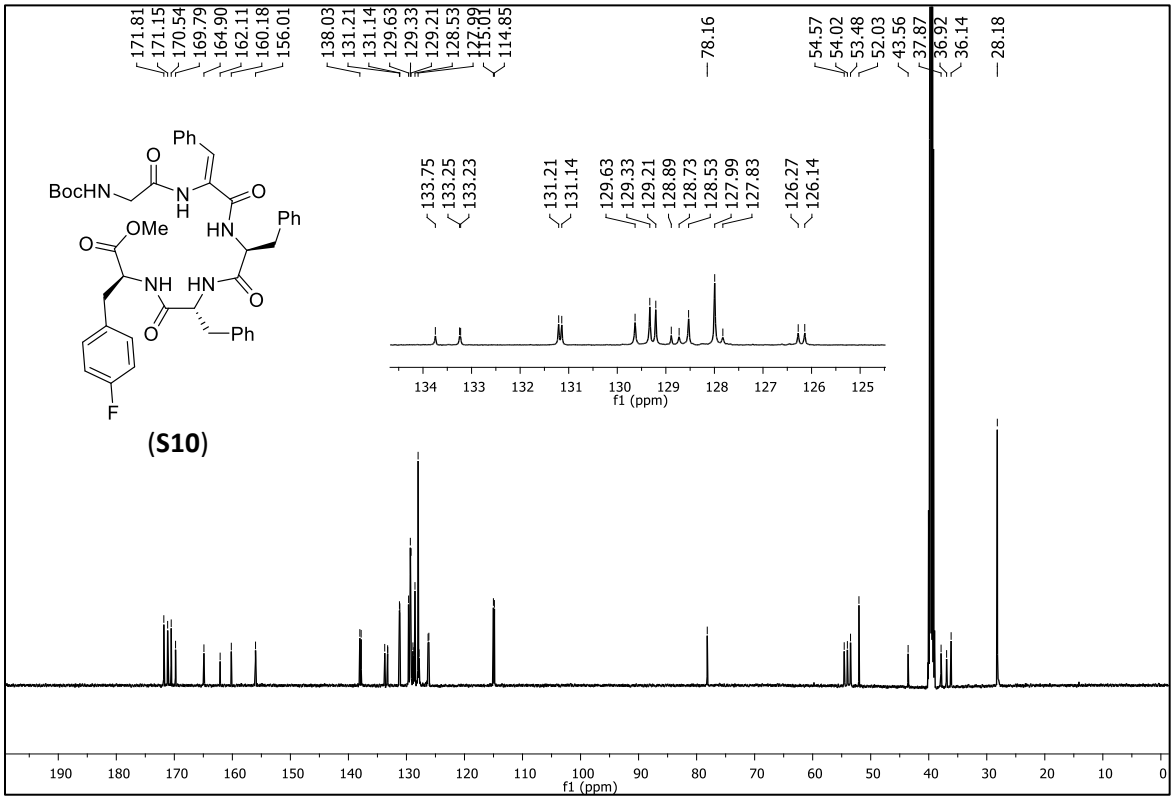

TFA
OMe
H_2N
Ph
NH
HN
O
Ph
F
(S9)
f1 (ppm)

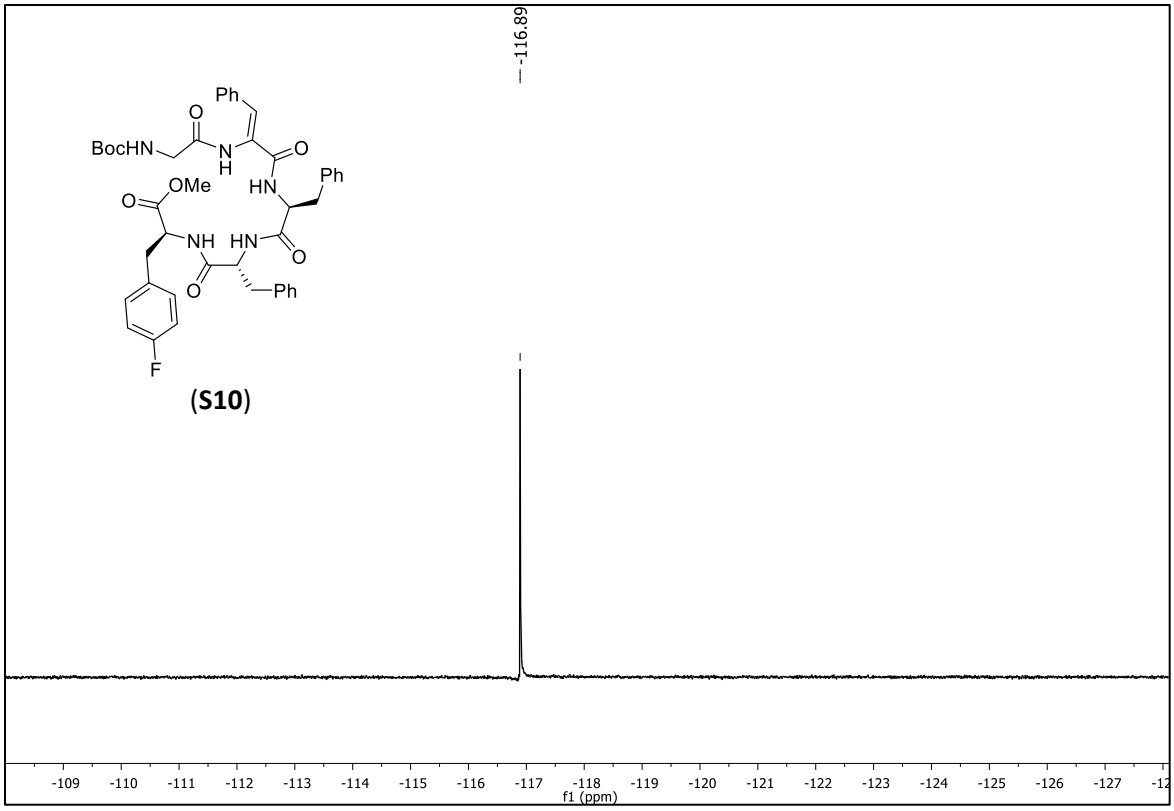

TFA
OMe
H_2N
Ph
NH
HN
O
Ph
F
(S9)
f1 (ppm)


-116.62
TFA
OMe
Ph
O
H_2N
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
f1 (ppm)

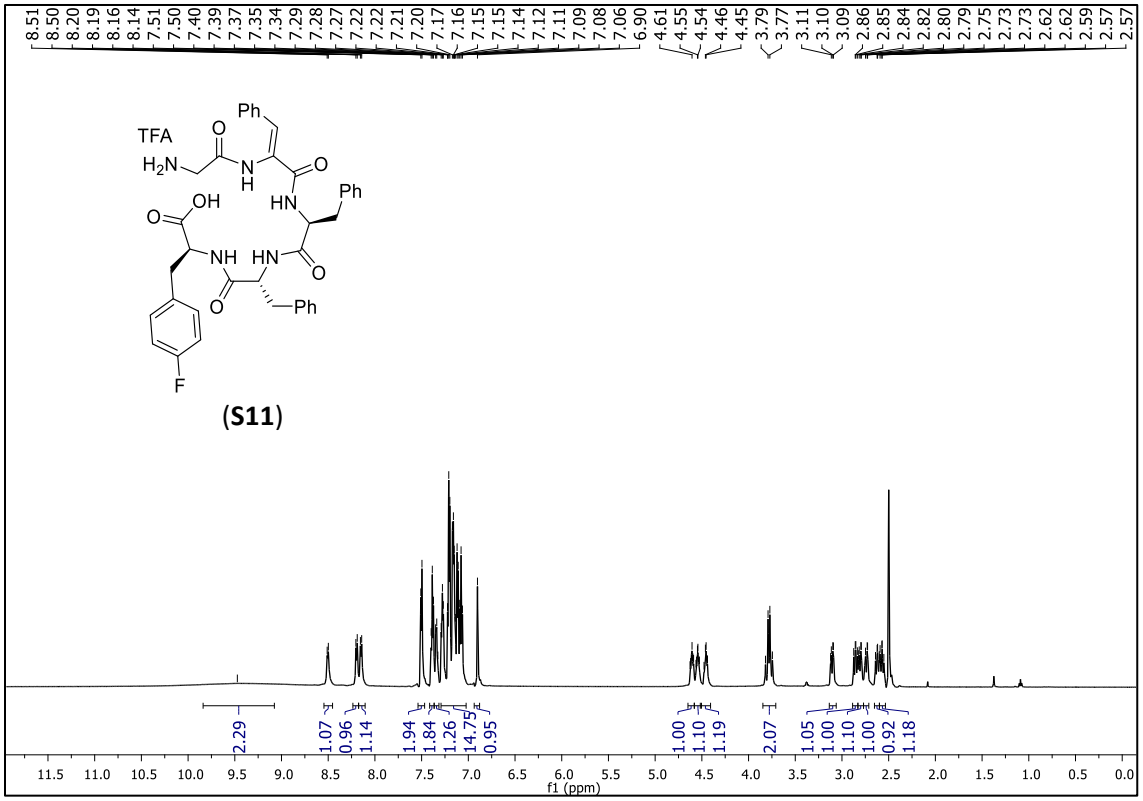
(**S9**)


(S10)
f1 (ppm)

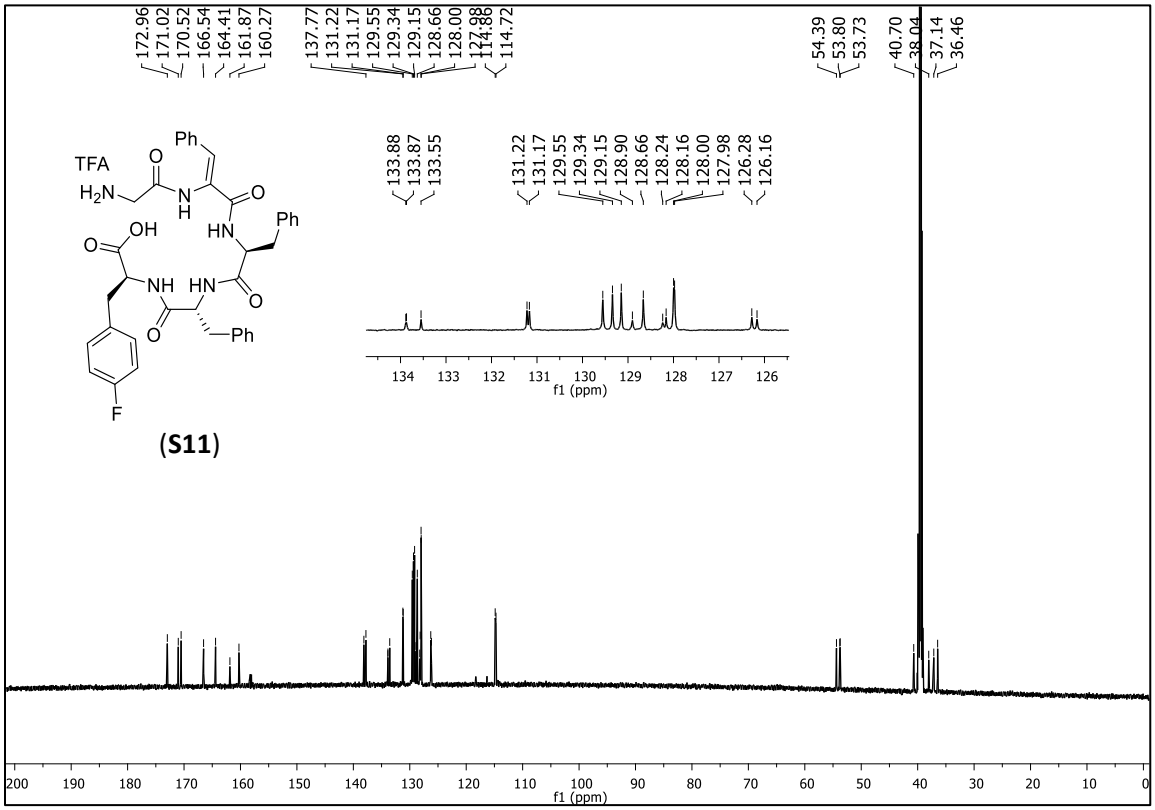

(S10)
f1 (ppm)
f1 (ppm)


-116.89
Ph
O
BocHN
N
H
O
HN
Ph
OMe
O
NH
HN
O
O
Ph
F
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

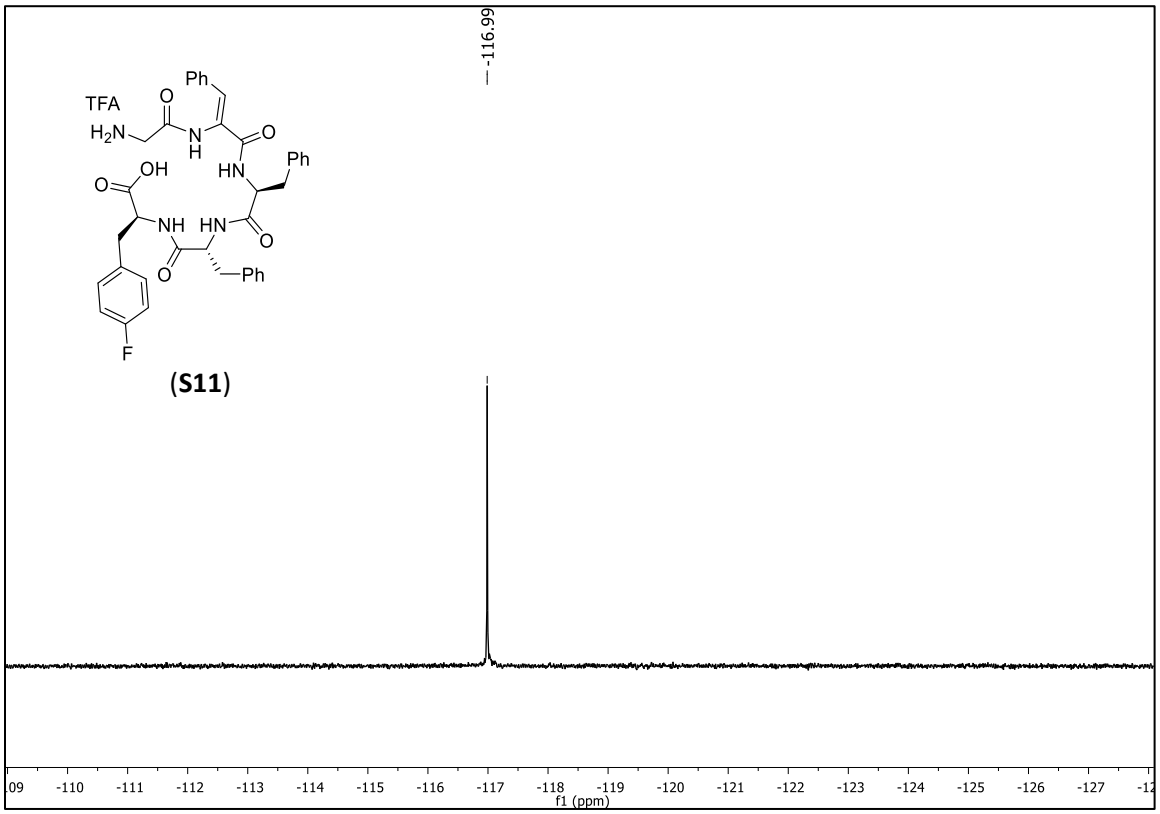
(**S10**)

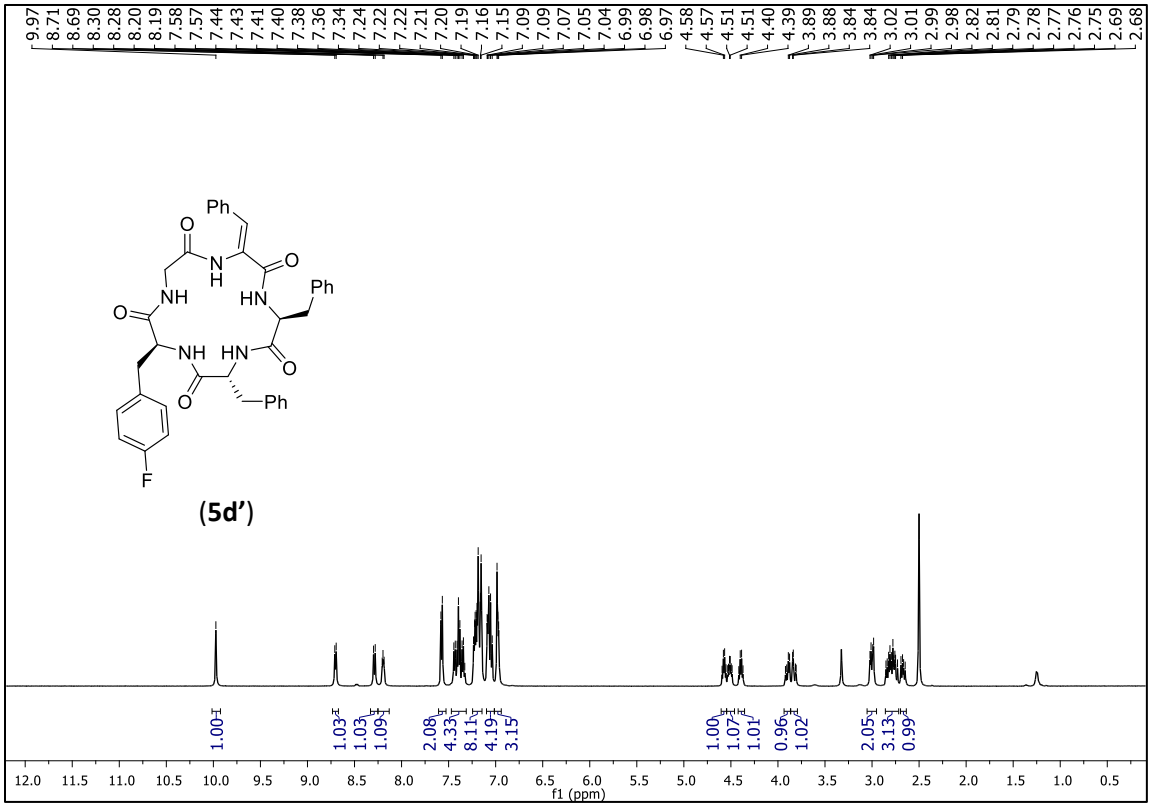


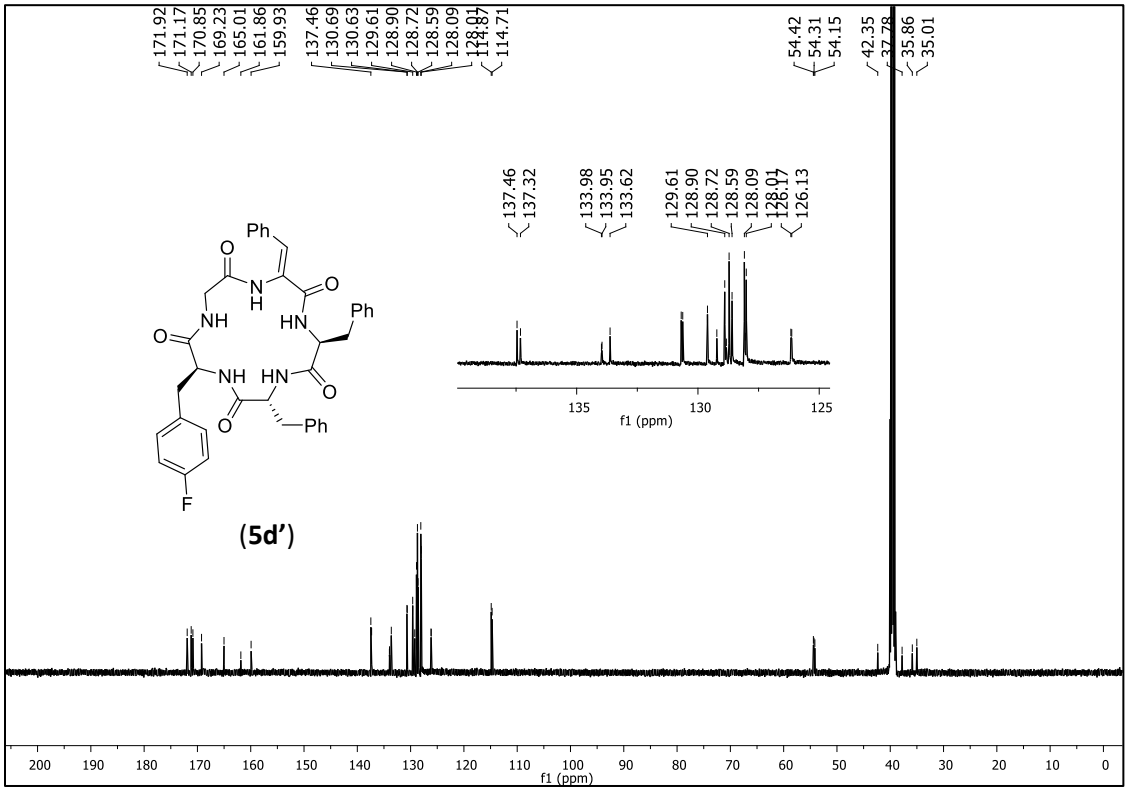
(**S11**)

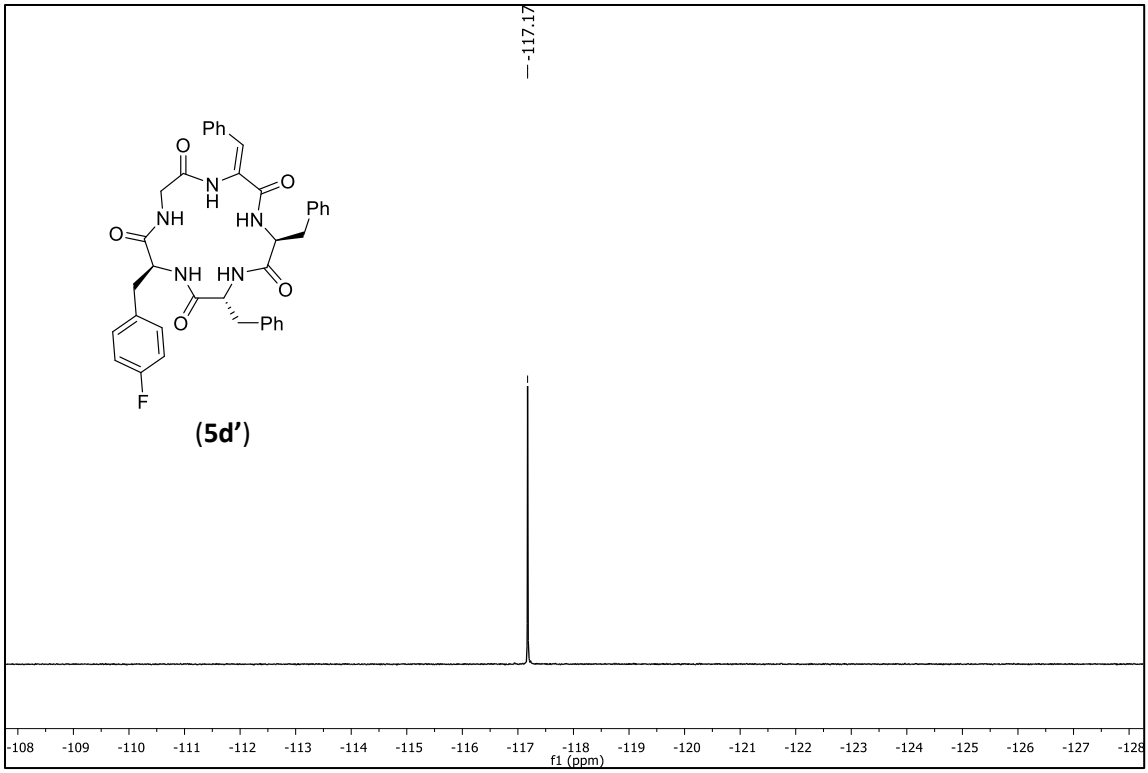


(**S11**)

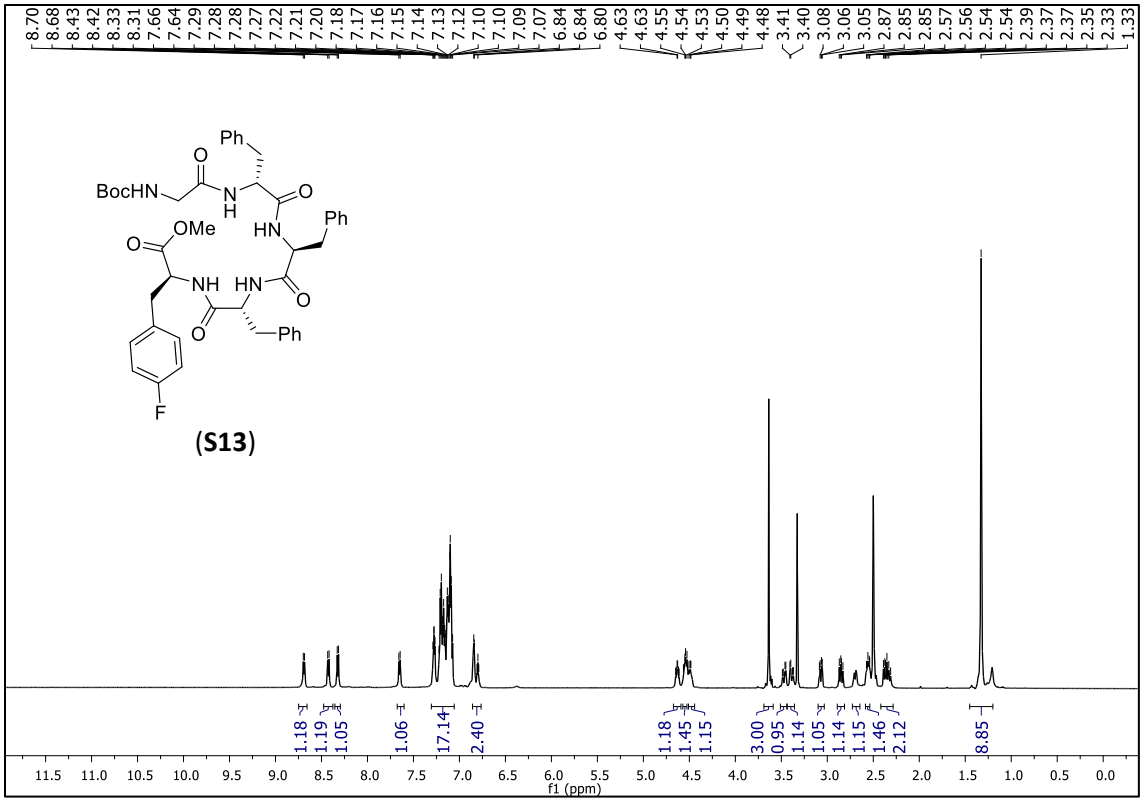

-116.99
TFA
H_2N
O
N
H
O
Ph
HN
Ph
OH
O
NH
HN
O
O
Ph
F
(S11)
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

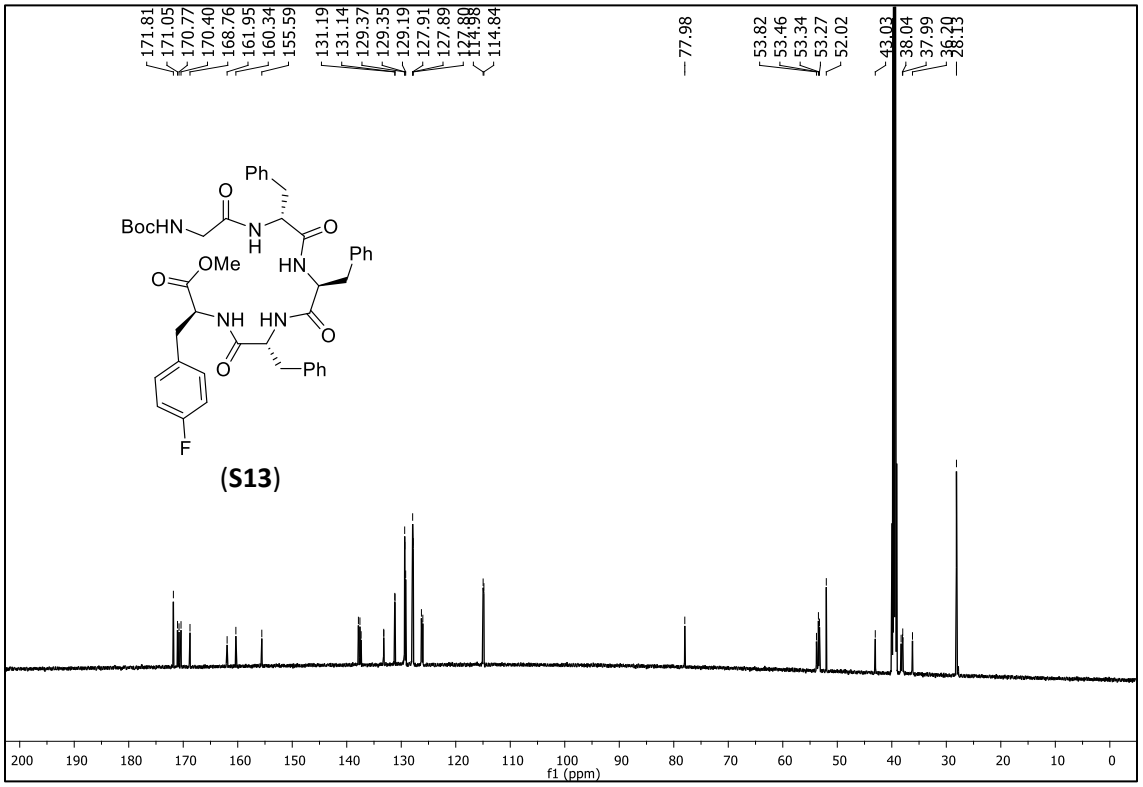

(5d')
f1 (ppm)

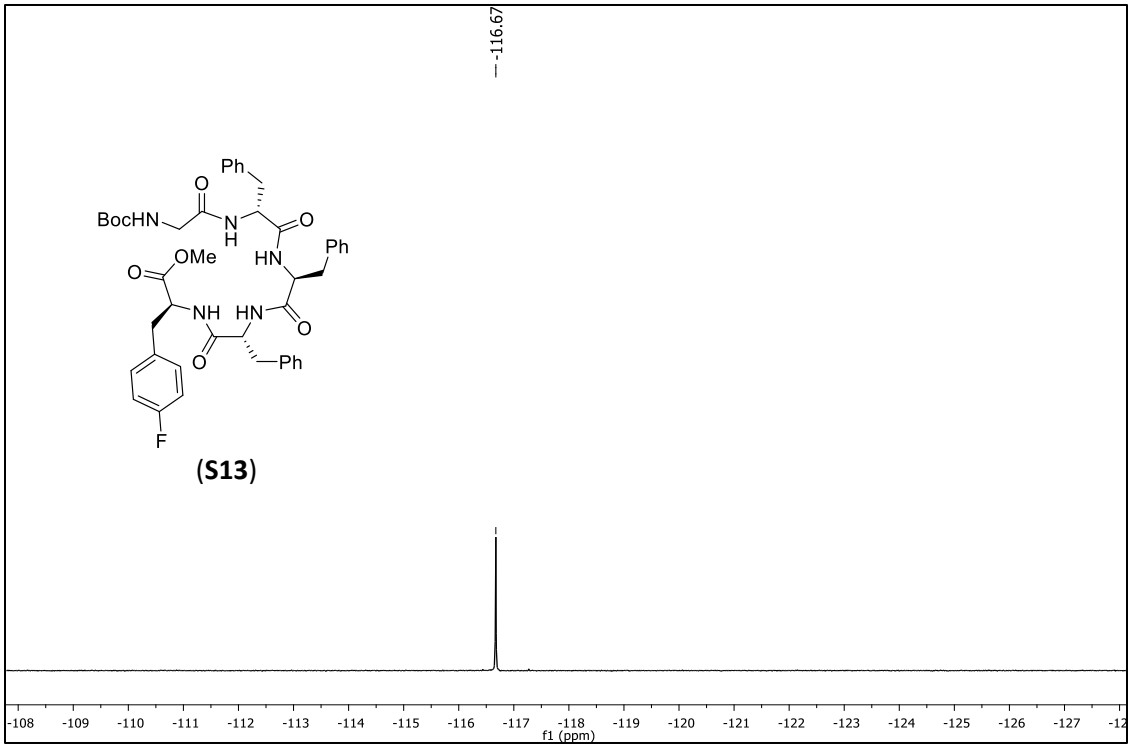

(5d')
f1 (ppm)


-117.17
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
-128
f1 (ppm)

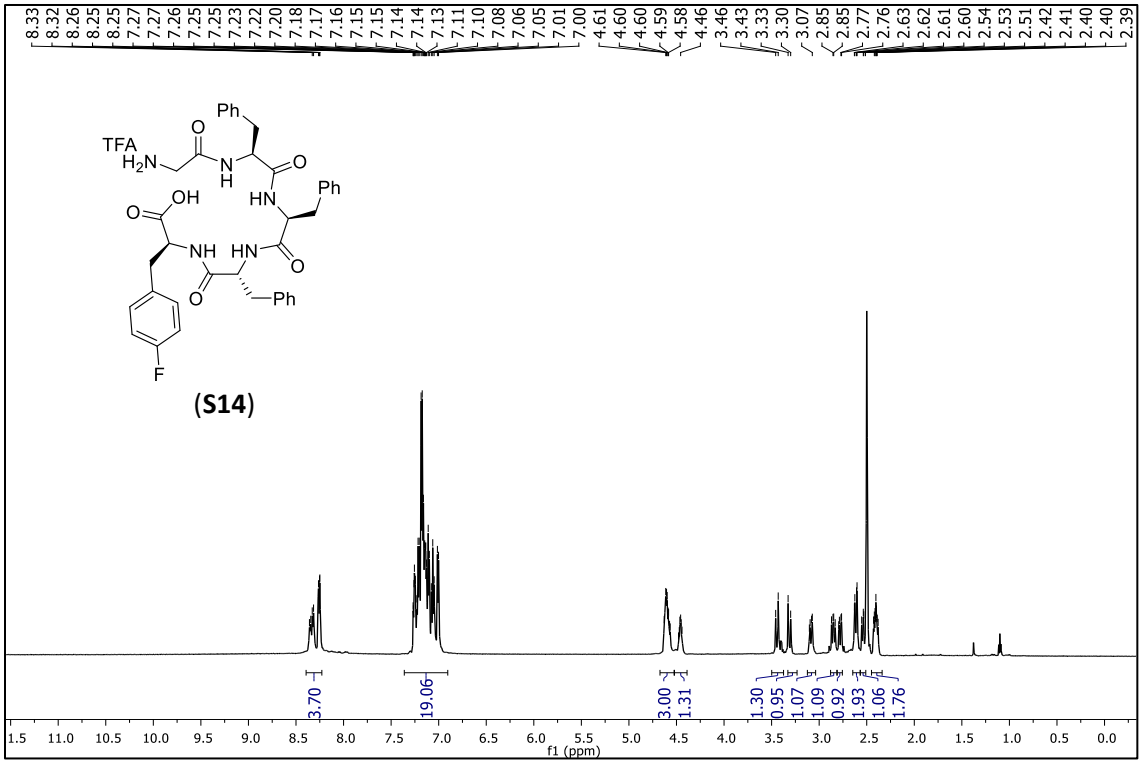
(**5d'**)

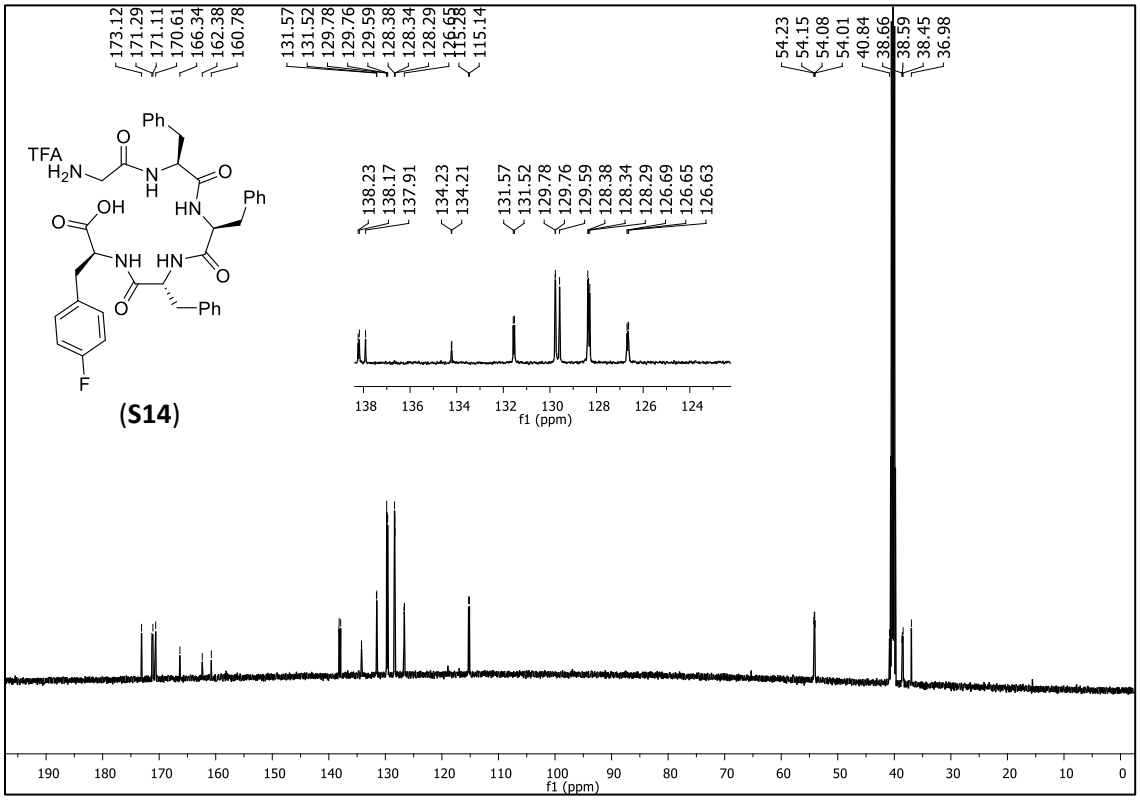

8.70 8.68 8.43 8.42 8.33 8.31 7.66 7.64 7.29 7.28 7.28 7.27 7.22 7.21 7.20 7.18 7.17 7.16 7.15 7.14 7.13 7.12 7.10 7.10 7.09 7.07 6.84 6.84 6.80 4.63 4.63 4.55 4.54 4.53 4.50 4.49 4.48 3.41 3.40 3.08 3.06 3.05 2.87 2.85 2.85 2.57 2.56 2.54 2.54 2.39 2.37 2.37 2.35 2.33 1.33
Ph
O
BocHN
N
H
O
HN
Ph
OMe
O
NH
HN
O
O
Ph
F
(S13)
1.18 1.19 1.05 1.06 17.14 2.40 1.18 1.45 1.15 3.00 0.95 1.14 1.05 1.14 1.15 1.46 2.12 8.85
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

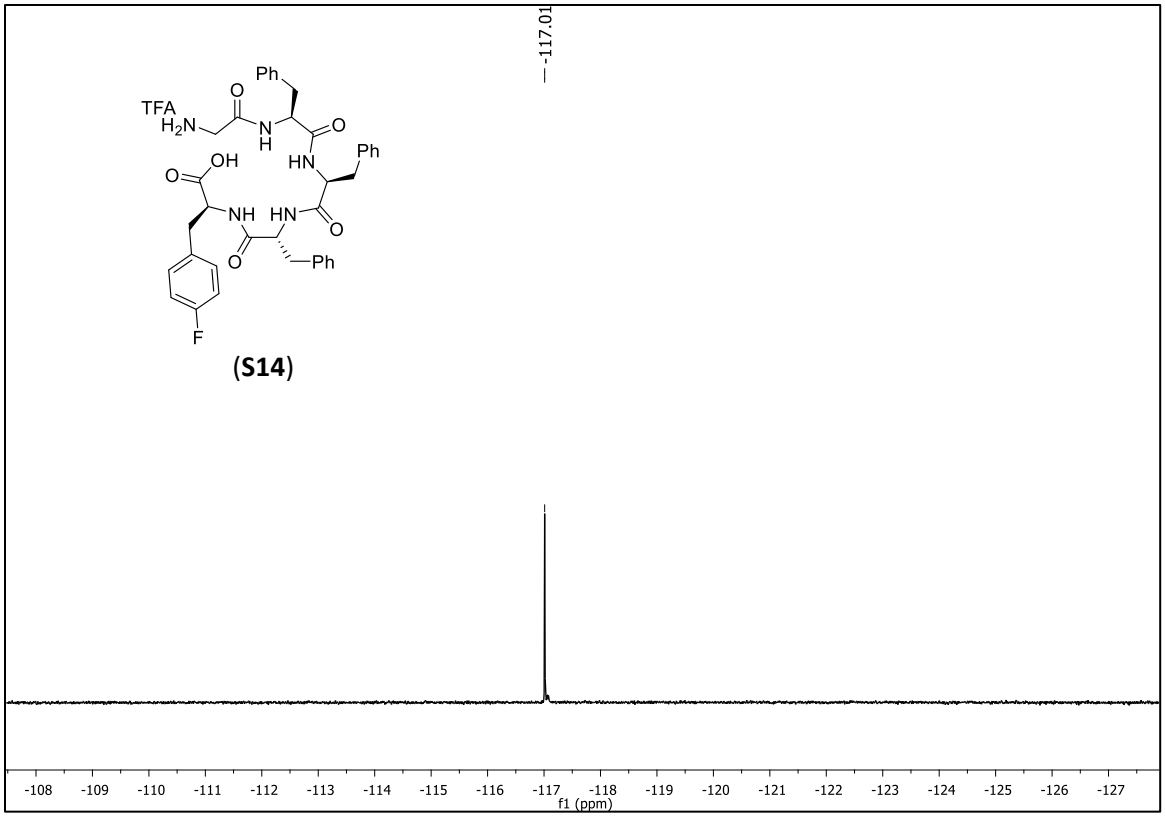

171.81 171.05 170.77 170.40 168.76 161.95 160.34 155.59 131.19 131.14 129.37 129.35 129.19 127.91 127.89 114.84 77.98 53.82 53.46 53.34 53.27 52.02 43.03 38.04 37.99 28.13
Ph
O
BocHN
N
H
O
HN
Ph
OMe
O
NH
HN
O
O
Ph
F
(S13)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-116.67
Ph
O
BocHN
N
H
O
HN
Ph
OMe
O
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

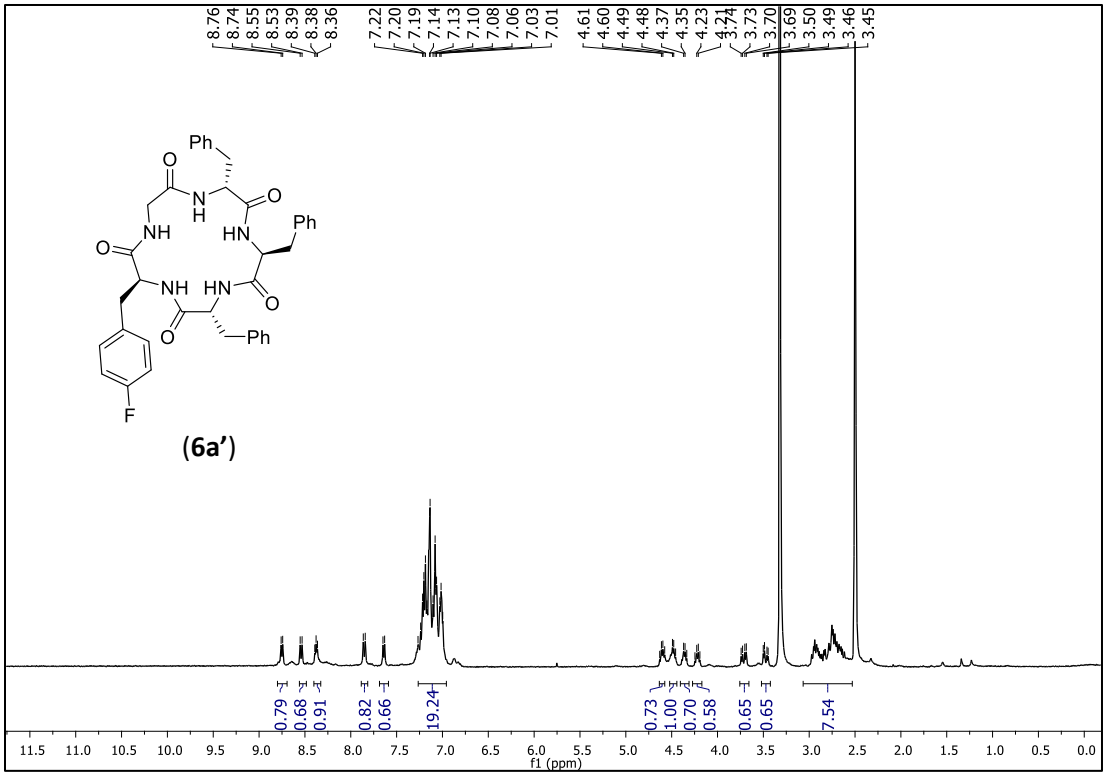
(**S13**)

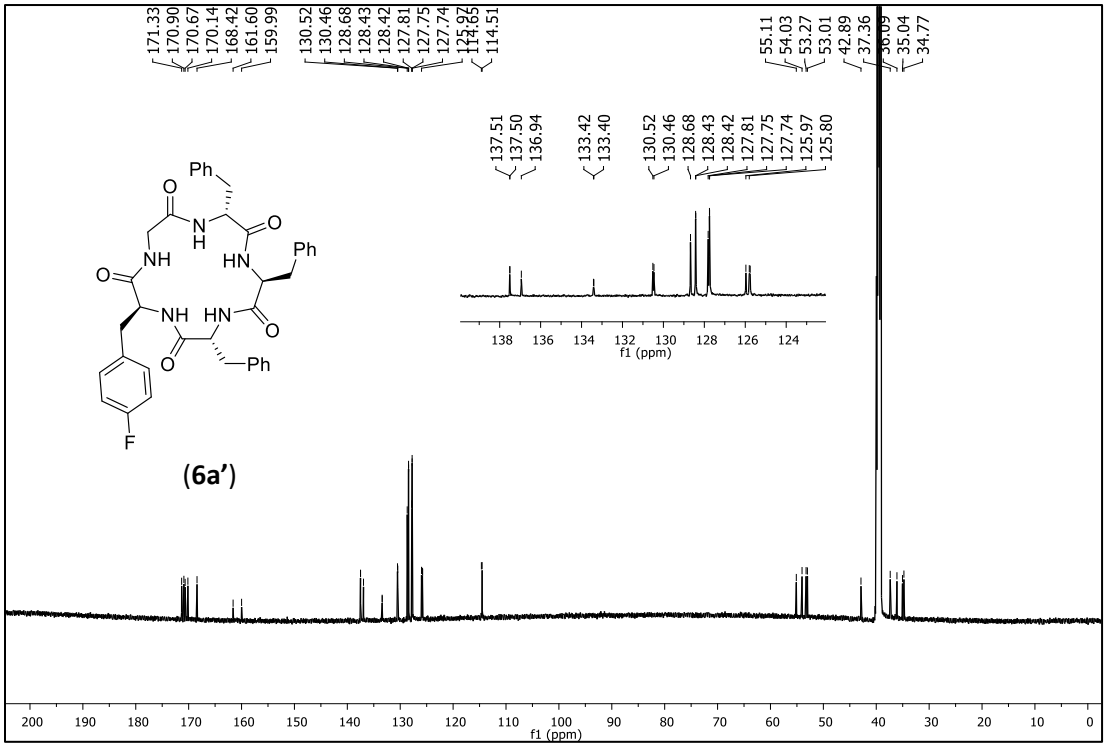

(S14)
f1 (ppm)

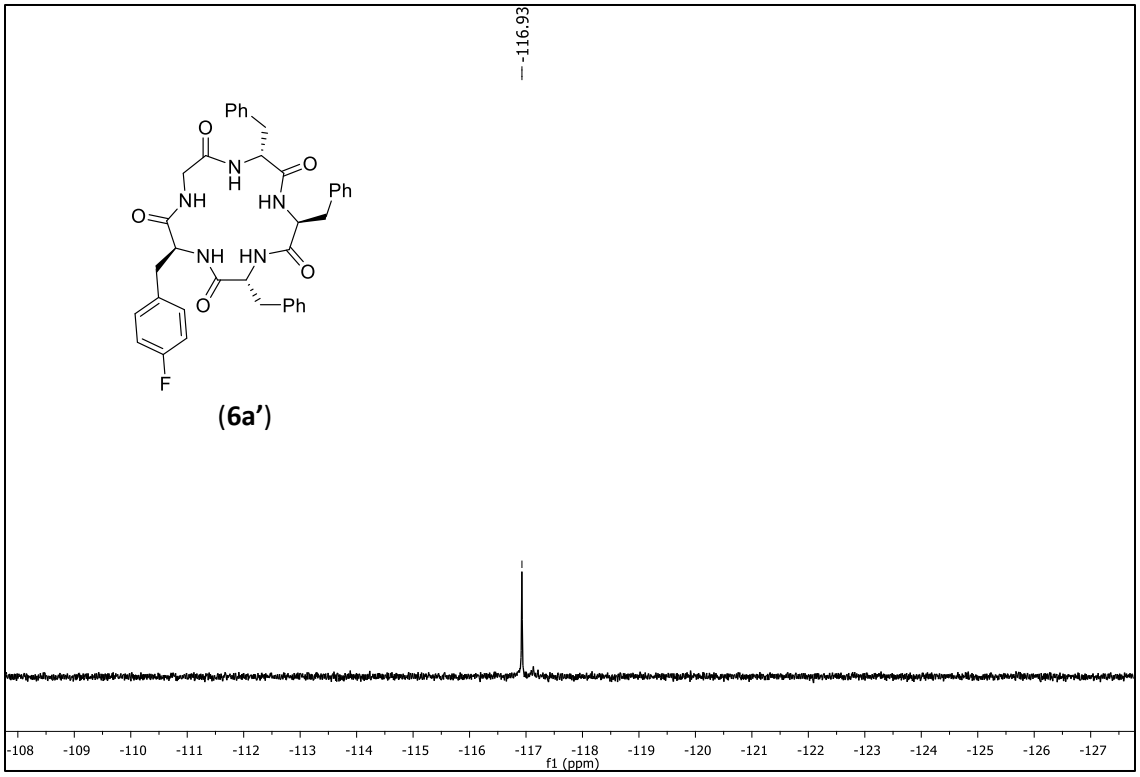

(S14)
f1 (ppm)


-117.01
TFA
H2N
O
N
H
Ph
O
HN
Ph
O
OH
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

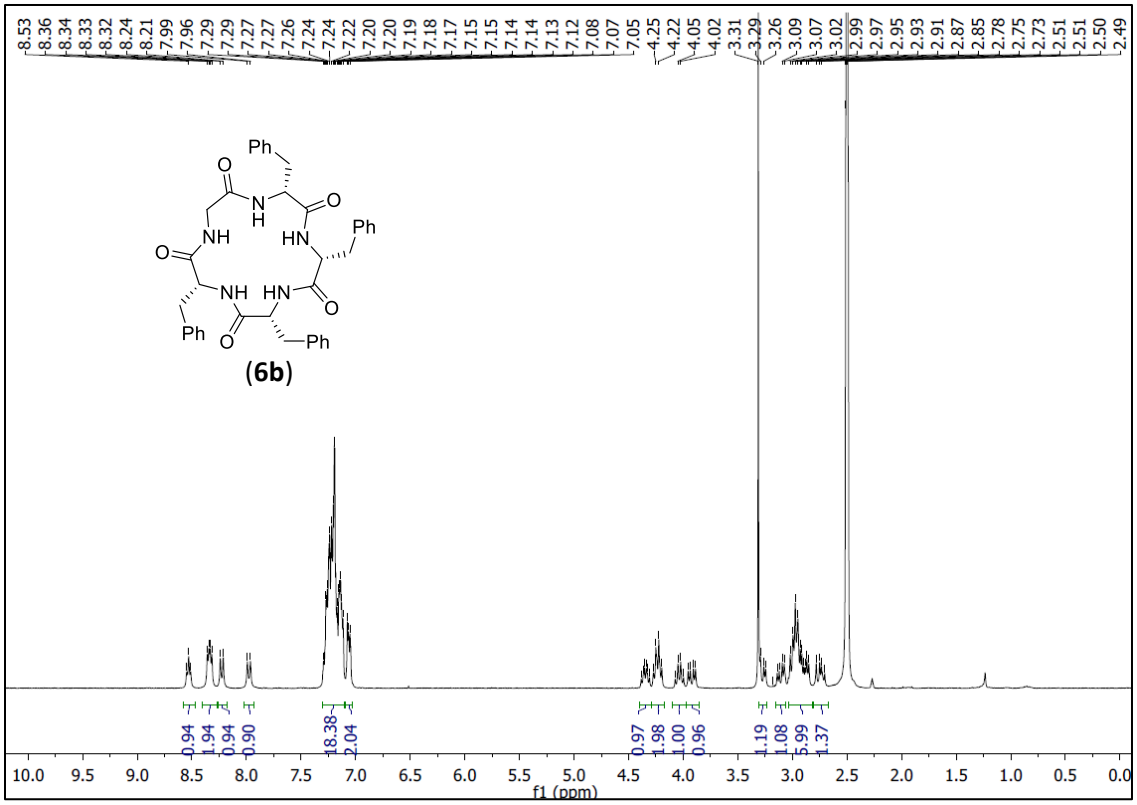
(**S14**)

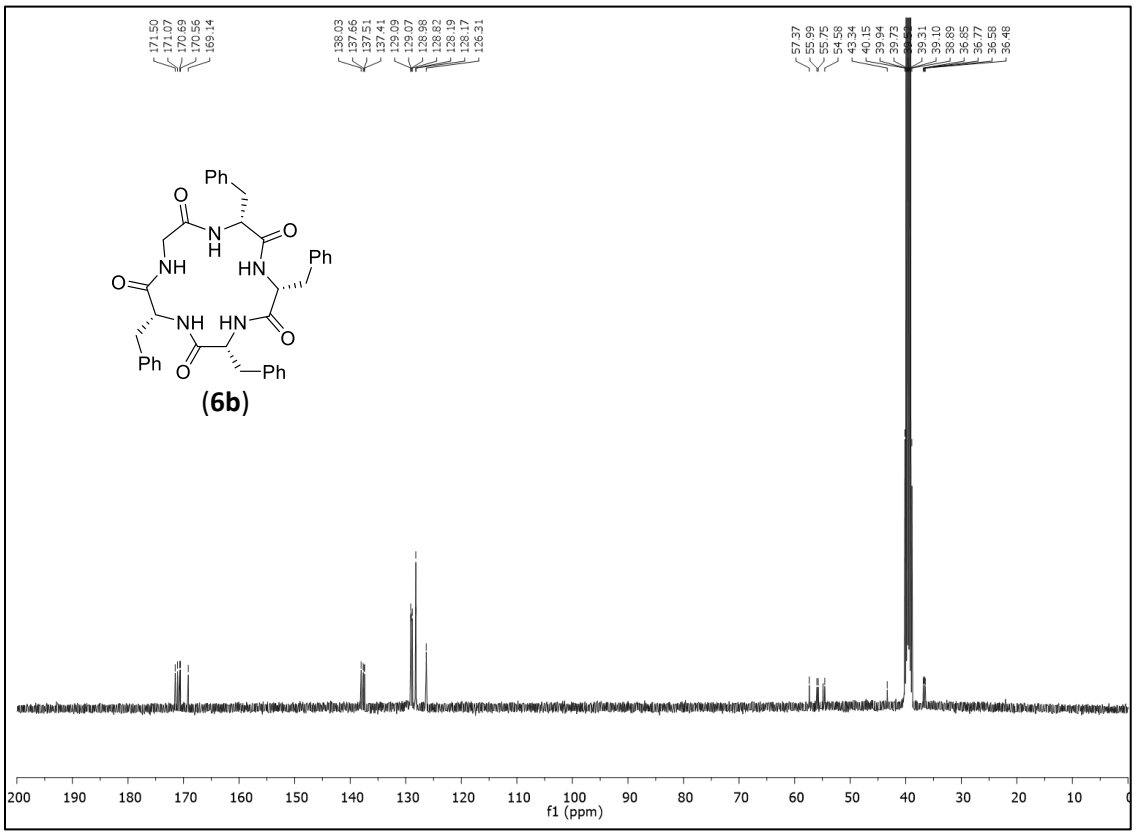

8.76
8.74
8.55
8.53
8.39
8.38
8.36
7.22
7.20
7.19
7.14
7.13
7.10
7.08
7.06
7.03
7.01
4.61
4.60
4.49
4.48
4.37
4.35
4.23
4.21
3.73
3.70
3.69
3.50
3.49
3.46
3.45
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
(6a')
0.79
0.68
0.91
0.82
0.66
19.24
0.73
1.00
0.70
0.58
0.65
0.65
7.54
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

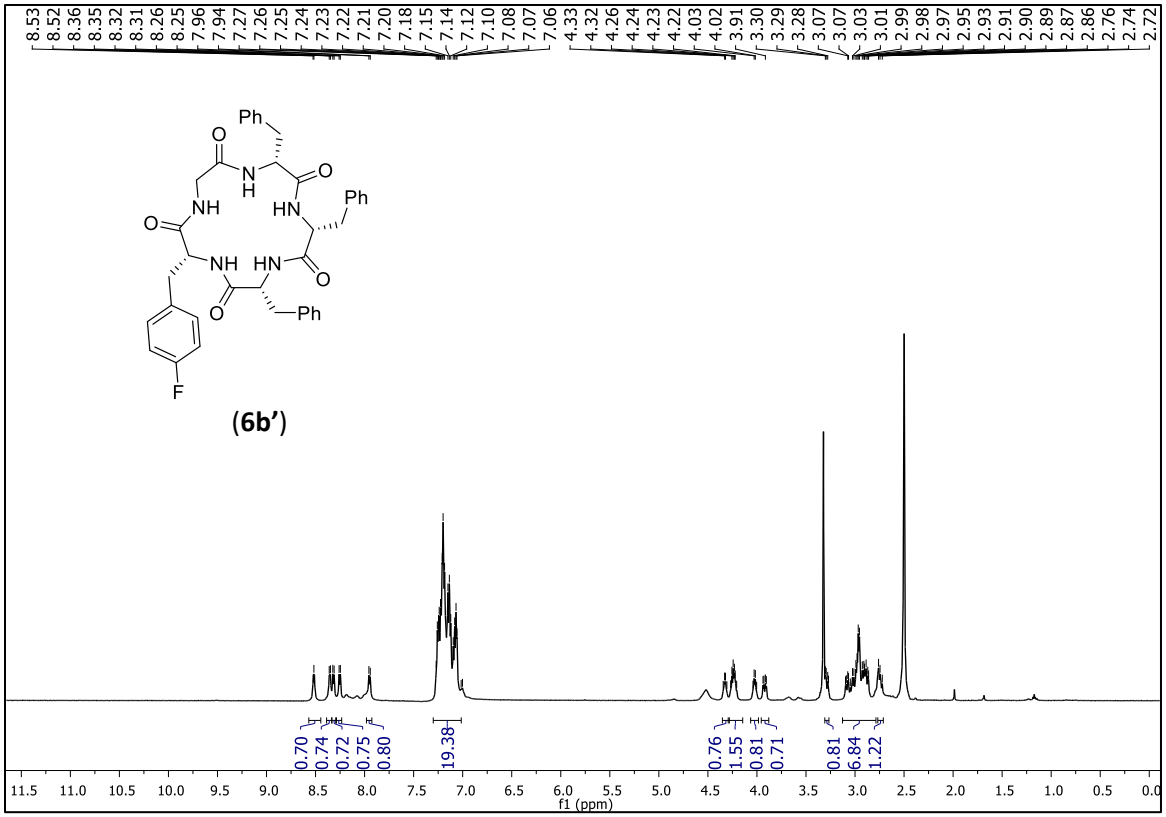

171.33
170.90
170.67
170.14
168.42
161.60
159.99
130.52
130.46
128.68
128.43
128.42
127.81
127.75
127.74
125.97
114.65
114.51
55.11
54.03
53.27
53.01
42.89
37.36
30.09
35.04
34.77
137.51
137.50
136.94
133.42
133.40
130.52
130.46
128.68
128.43
128.42
127.81
127.75
127.74
125.97
125.80
138 136 134 132 130 128 126 124
f1 (ppm)
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
(6a')
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

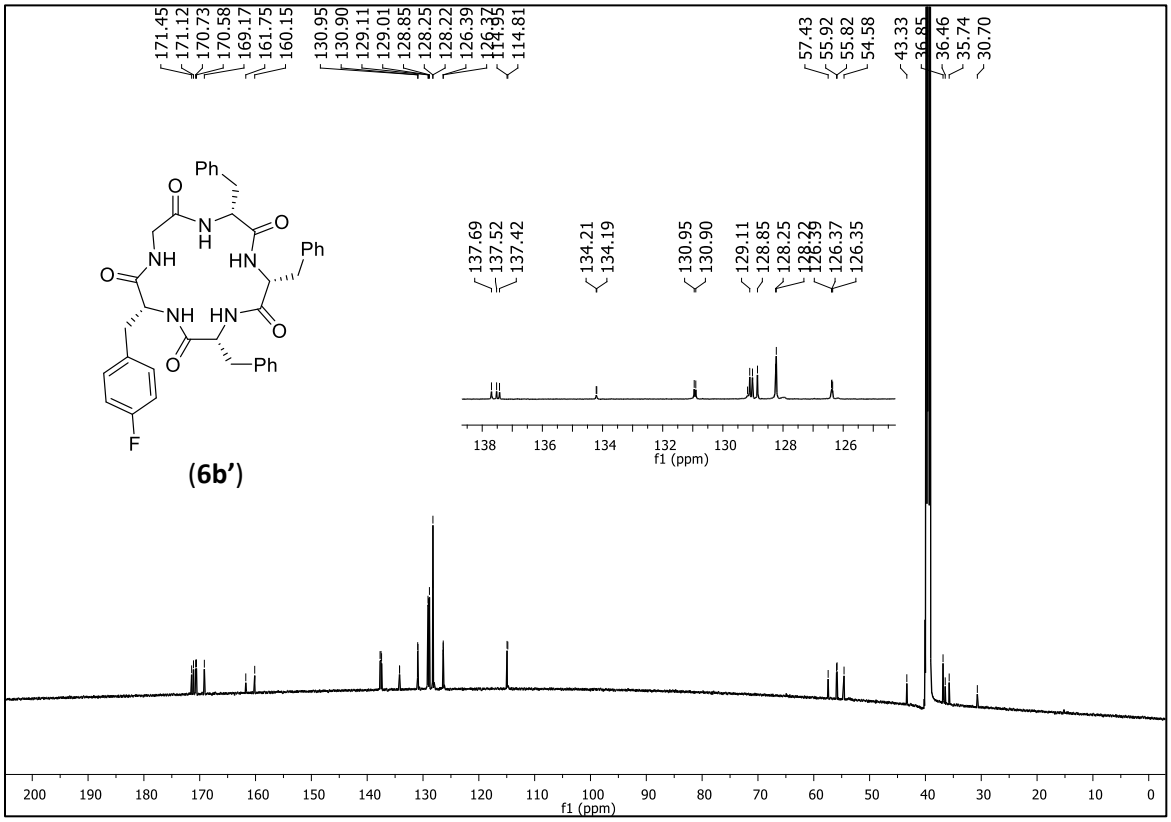

-116.93
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
-125
-126
-127
f1 (ppm)

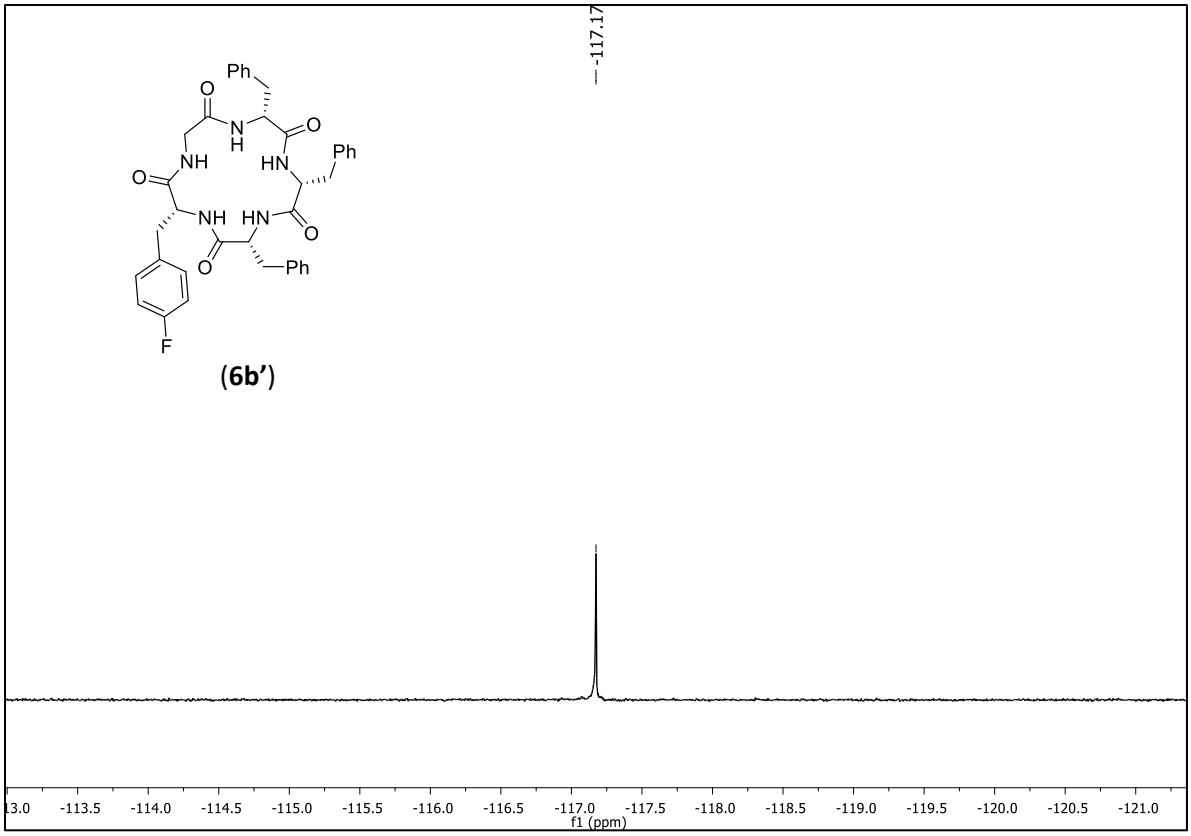
(**6a'**)


(6b)
f1 (ppm)

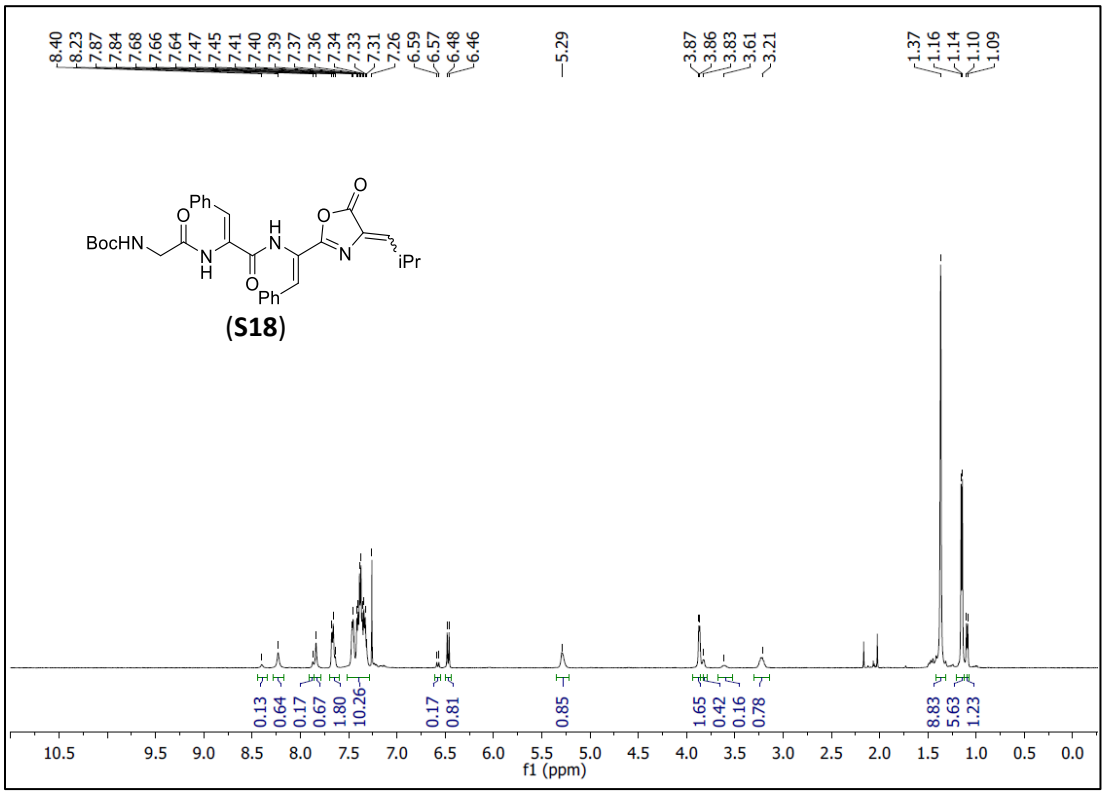

(6b)
f1 (ppm)

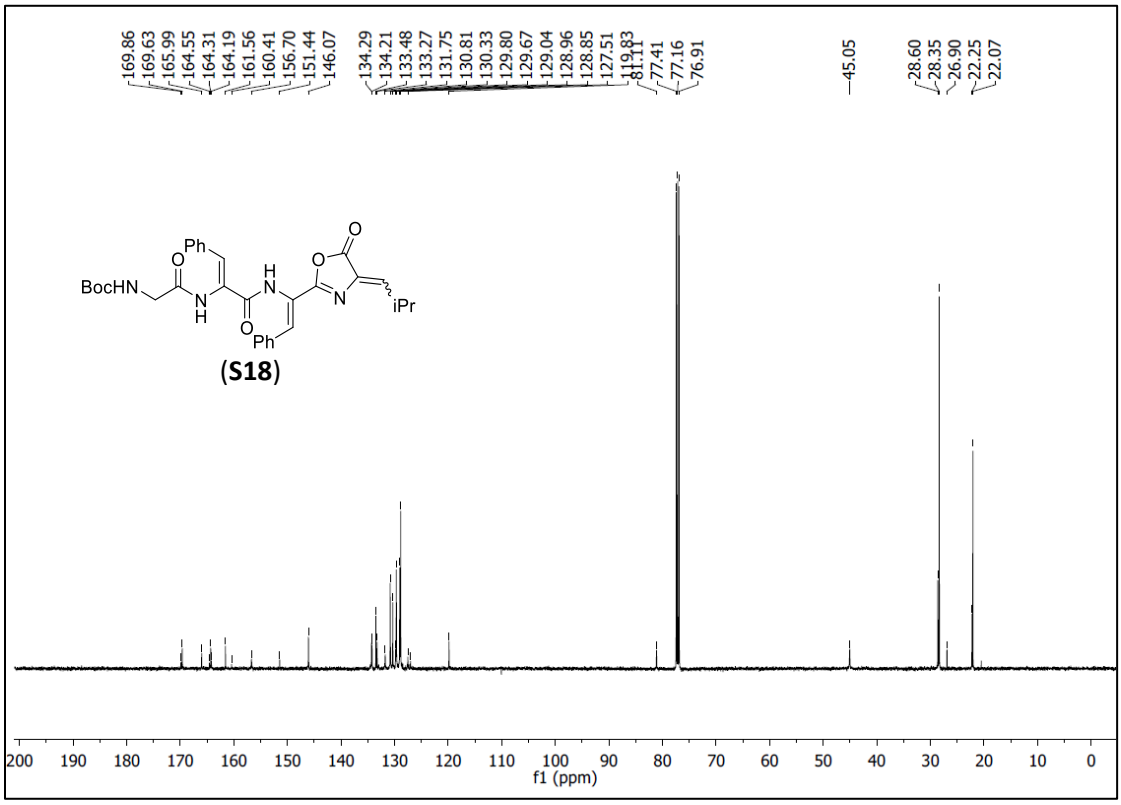

(6b')
f1 (ppm)

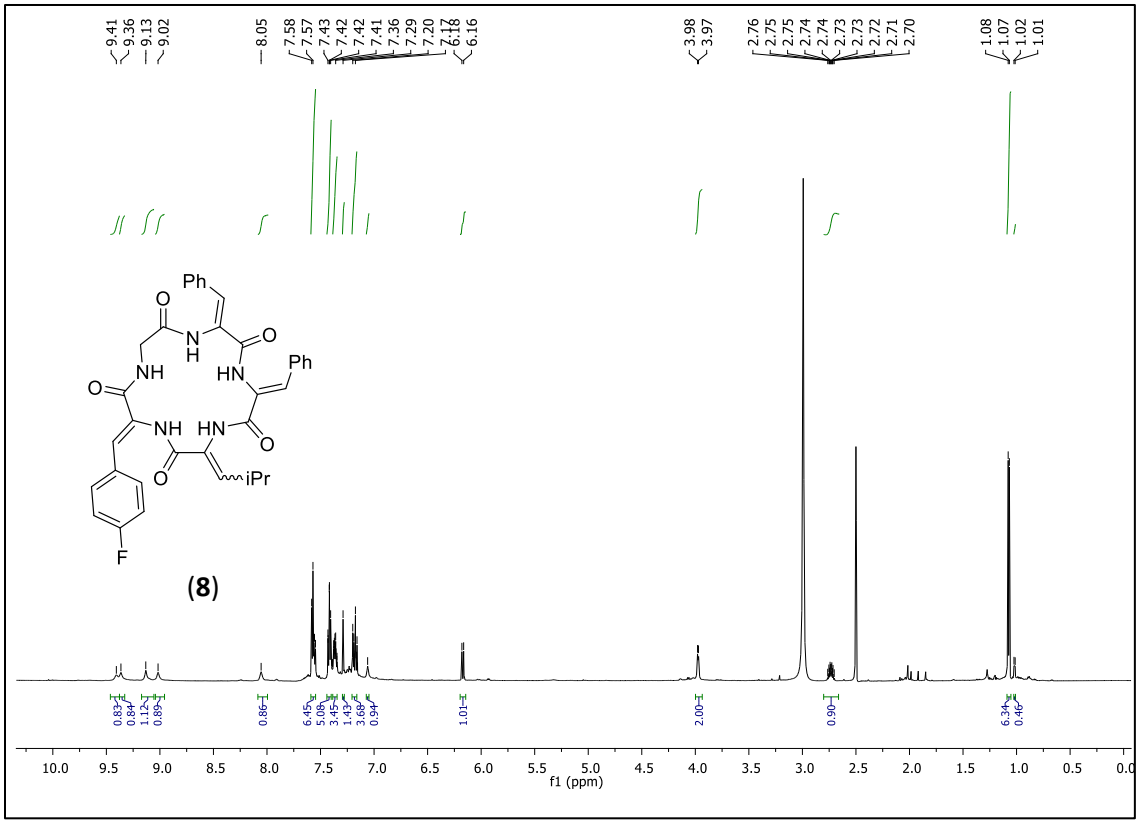

(6b')
f1 (ppm)
f1 (ppm)

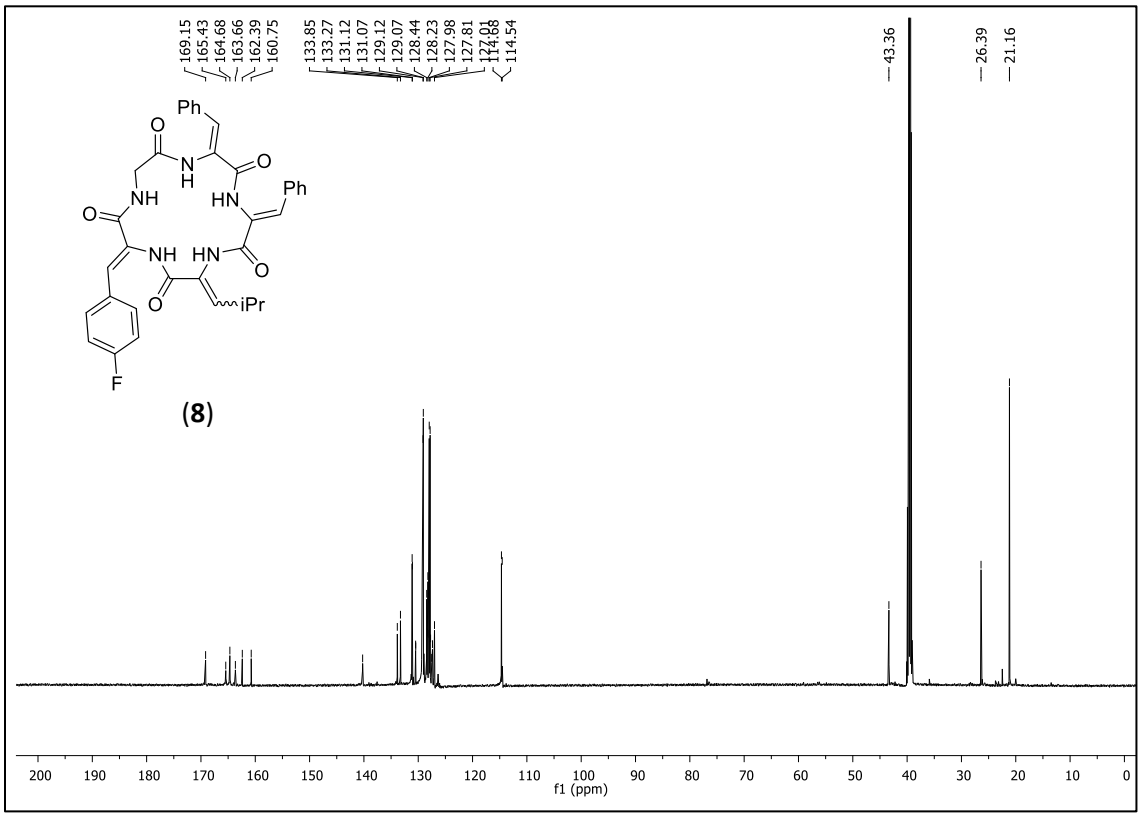

-117.17
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
Ph
F
13.0
-113.5
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
-117.0
-117.5
-118.0
-118.5
-119.0
-119.5
-120.0
-120.5
-121.0
f1 (ppm)

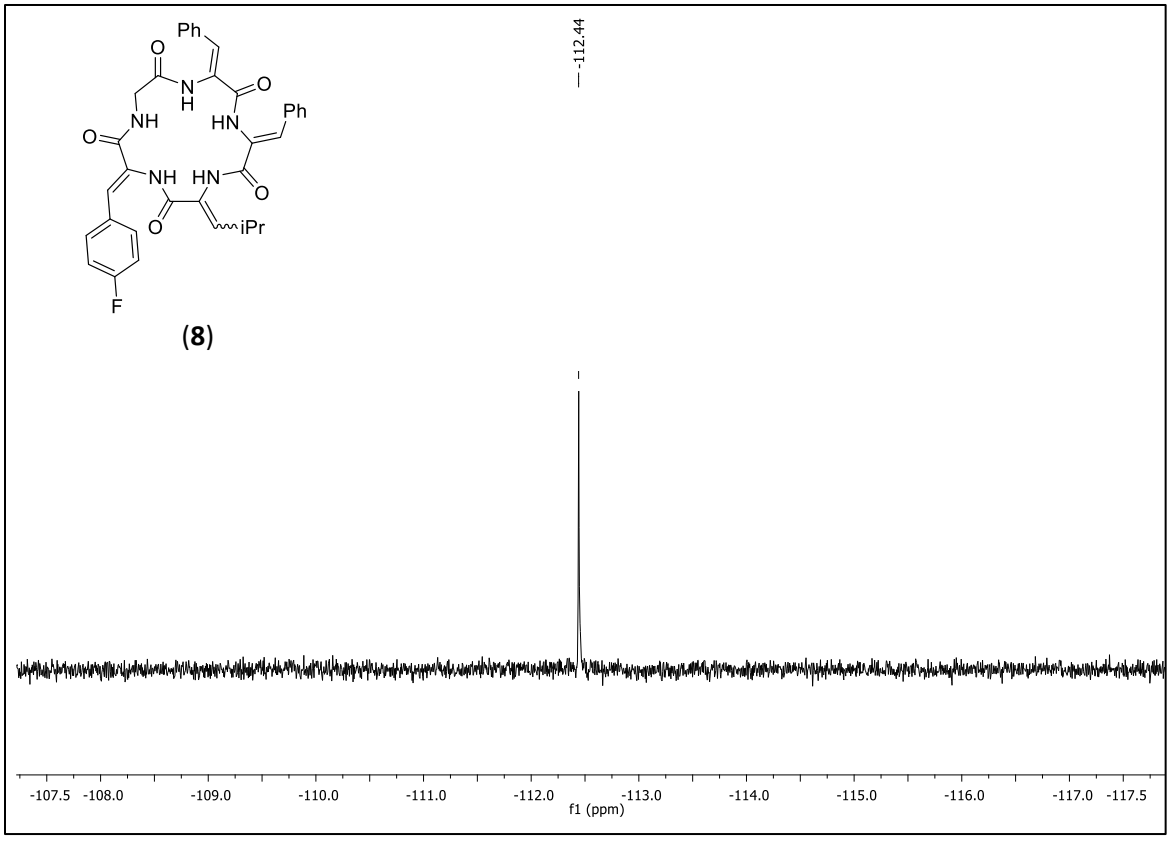
(**6b'**)


8.40
8.23
7.87
7.84
7.68
7.66
7.64
7.47
7.45
7.41
7.40
7.39
7.37
7.36
7.34
7.33
7.31
7.26
6.59
6.57
6.48
6.46
5.29
3.87
3.86
3.83
3.61
3.21
1.37
1.16
1.14
1.10
1.09
BocHN
Ph
O
N
H
H
N
O
O
O
N
iPr
Ph
(S18)
0.13
0.64
0.17
0.67
1.80
10.26
0.17
0.81
0.85
1.65
0.42
0.16
0.78
8.83
5.63
1.23
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

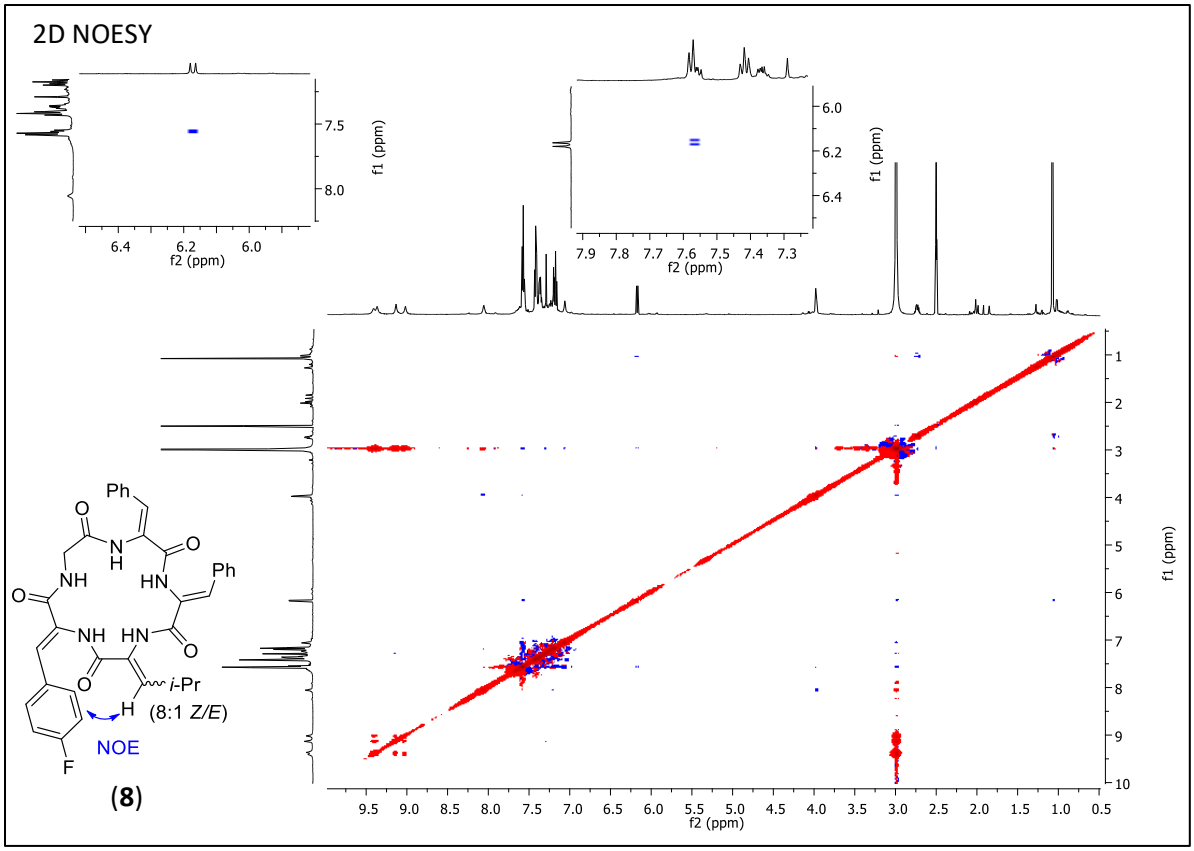

169.86
169.63
165.99
164.55
164.31
164.19
161.56
160.41
156.70
151.44
146.07
134.29
134.21
133.48
133.27
131.75
130.81
130.33
129.80
129.67
129.04
128.96
128.85
127.51
119.83
81.11
77.41
77.16
76.91
45.05
28.60
28.35
26.90
22.25
22.07
BocHN
Ph
O
N
H
H
N
O
O
O
N
iPr
Ph
(S18)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

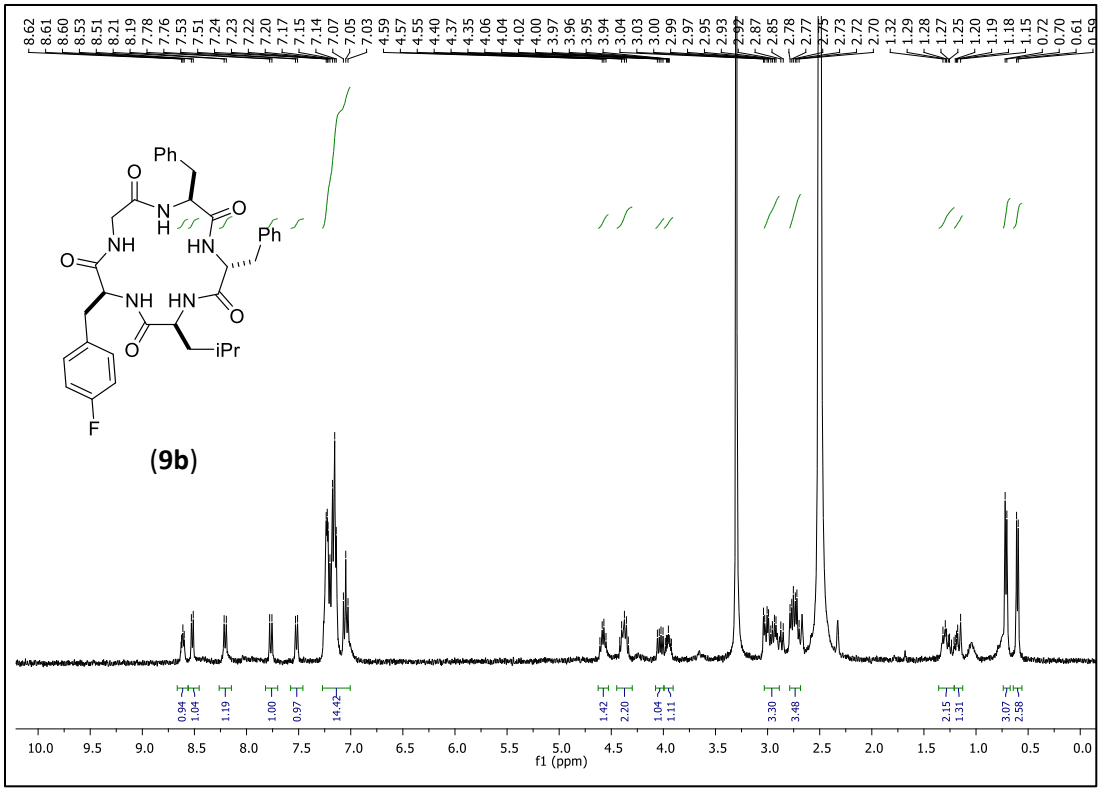

9.41
9.36
9.13
9.02
8.05
7.58
7.57
7.43
7.42
7.42
7.41
7.36
7.29
7.20
6.18
6.16
3.98
3.97
2.76
2.75
2.75
2.74
2.74
2.73
2.73
2.72
2.71
2.70
1.08
1.07
1.02
1.01
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
(8)
0.83
0.84
1.12
0.89
0.86
6.45
5.08
3.45
1.43
3.68
0.94
1.01
2.00
0.90
6.34
0.46
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

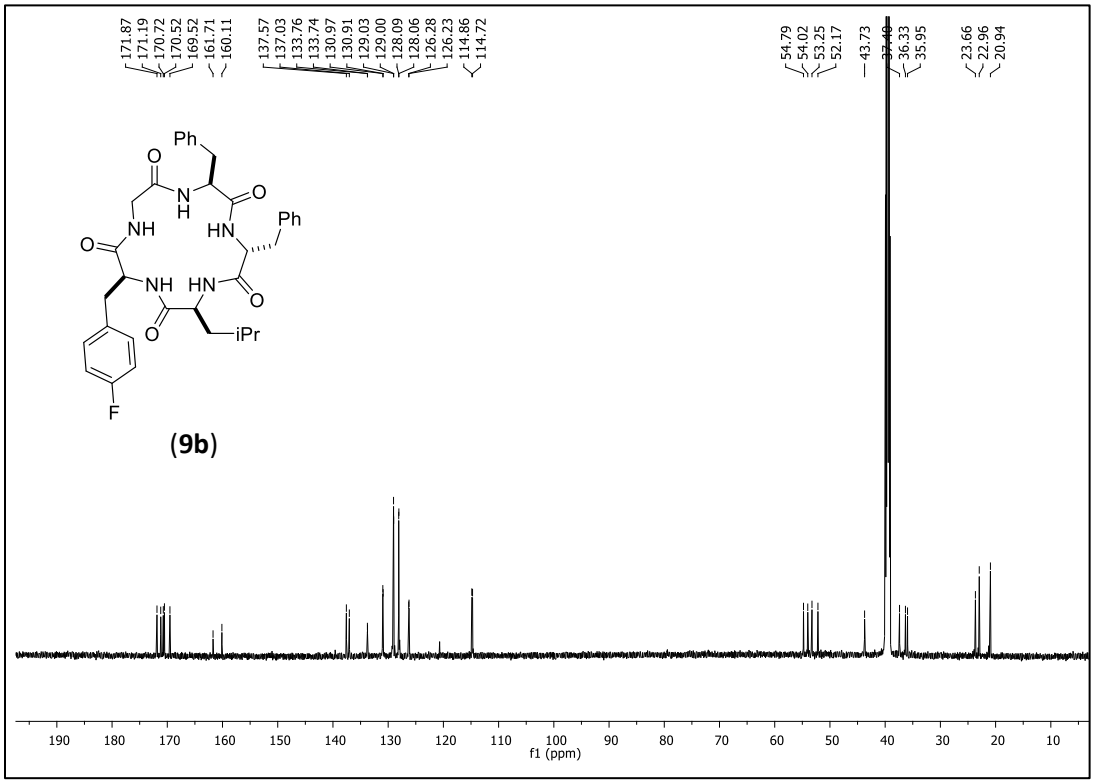

169.15
165.43
164.68
163.66
162.39
160.75
133.85
133.27
131.12
131.07
129.12
129.07
128.44
128.23
127.98
127.81
114.54
43.36
26.39
21.16
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
(8)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

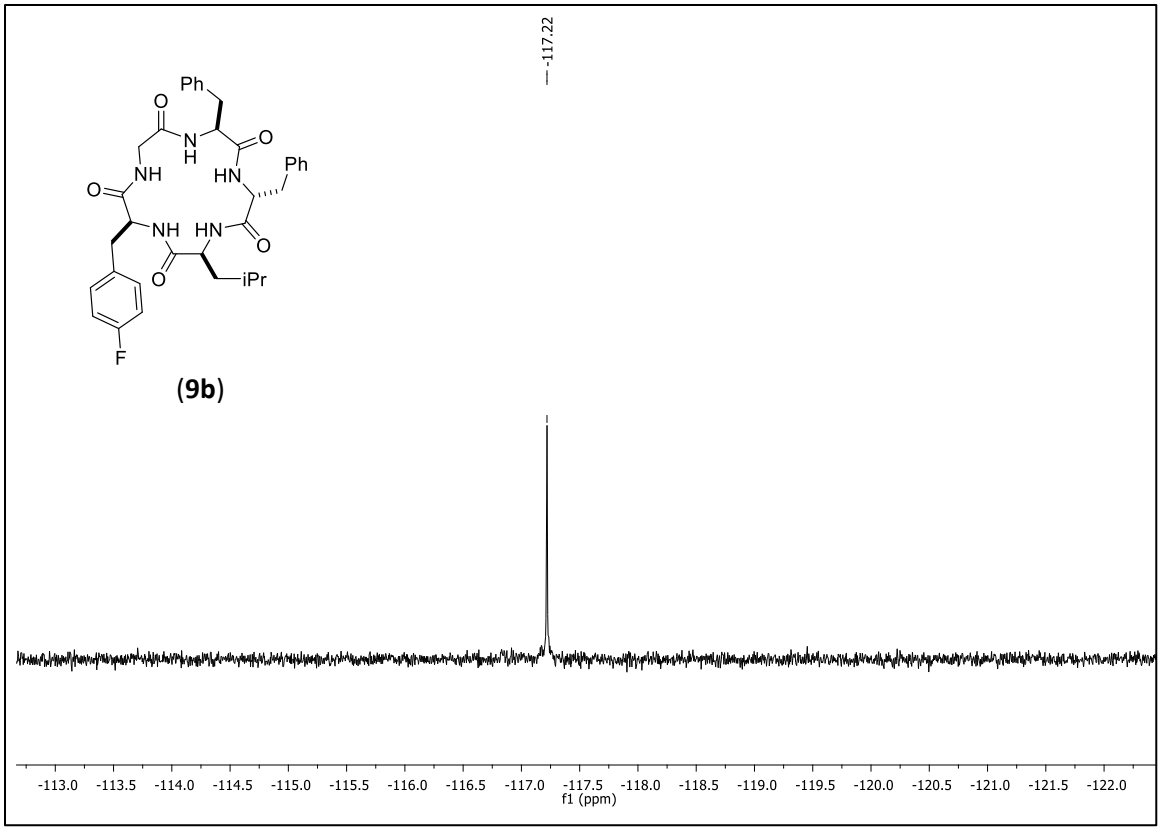

Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
-112.44
-107.5
-108.0
-109.0
-110.0
-111.0
-112.0
-113.0
-114.0
-115.0
-116.0
-117.0
-117.5
f1 (ppm)

(**8**)

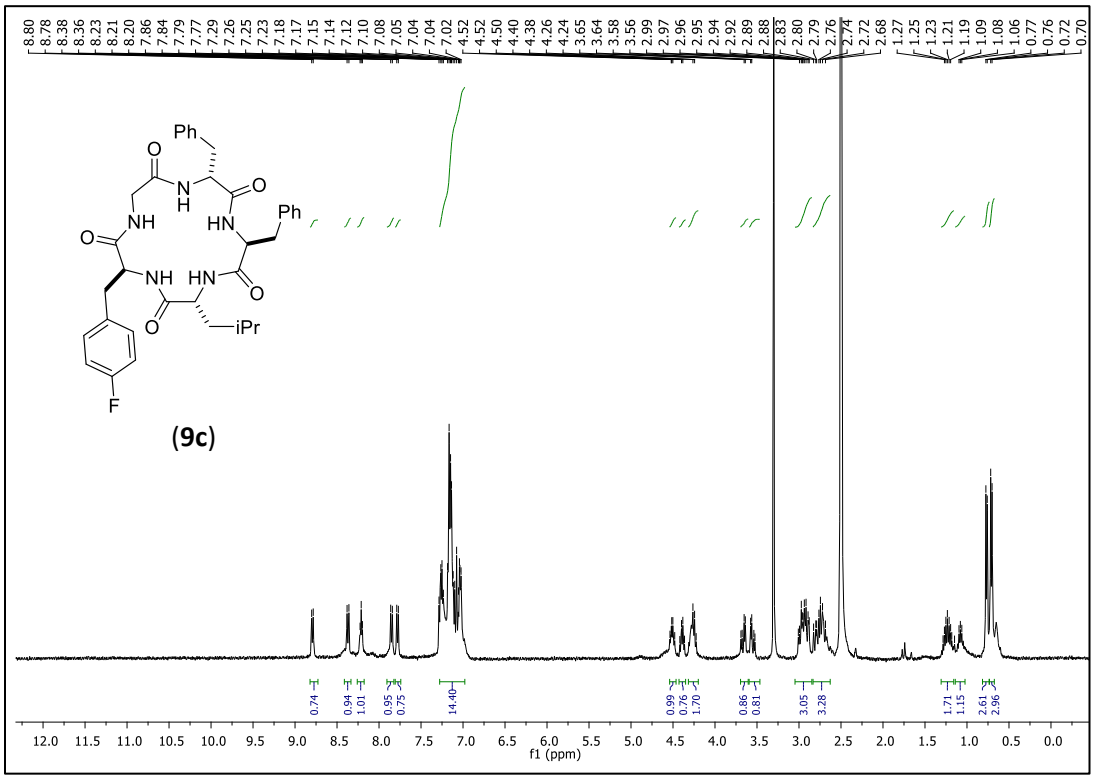

2D NOESY
f1 (ppm)
f2 (ppm)
Ph
NH
HN
i-Pr
H
(8:1 Z/E)
NOE
F
(8)

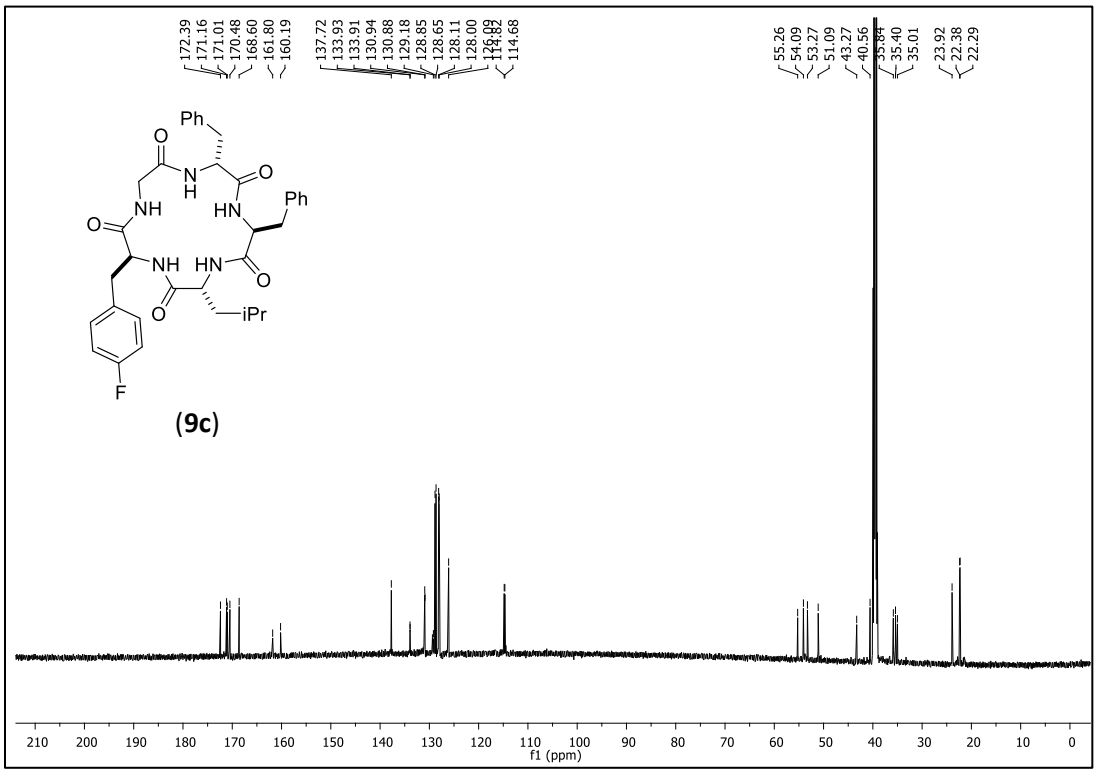

(9b)
f1 (ppm)

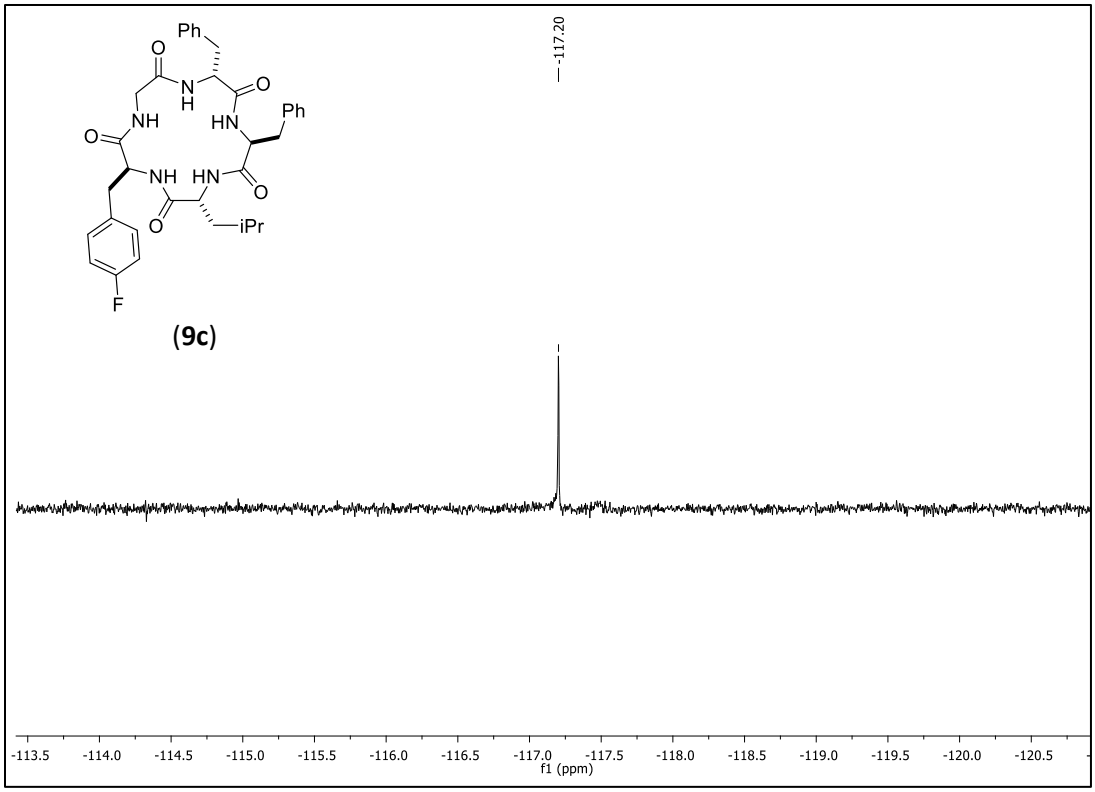

(9b)
f1 (ppm)


-117.22
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
-113.0
-113.5
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
-117.0
-117.5
-118.0
-118.5
-119.0
-119.5
-120.0
-120.5
-121.0
-121.5
-122.0
f1 (ppm)

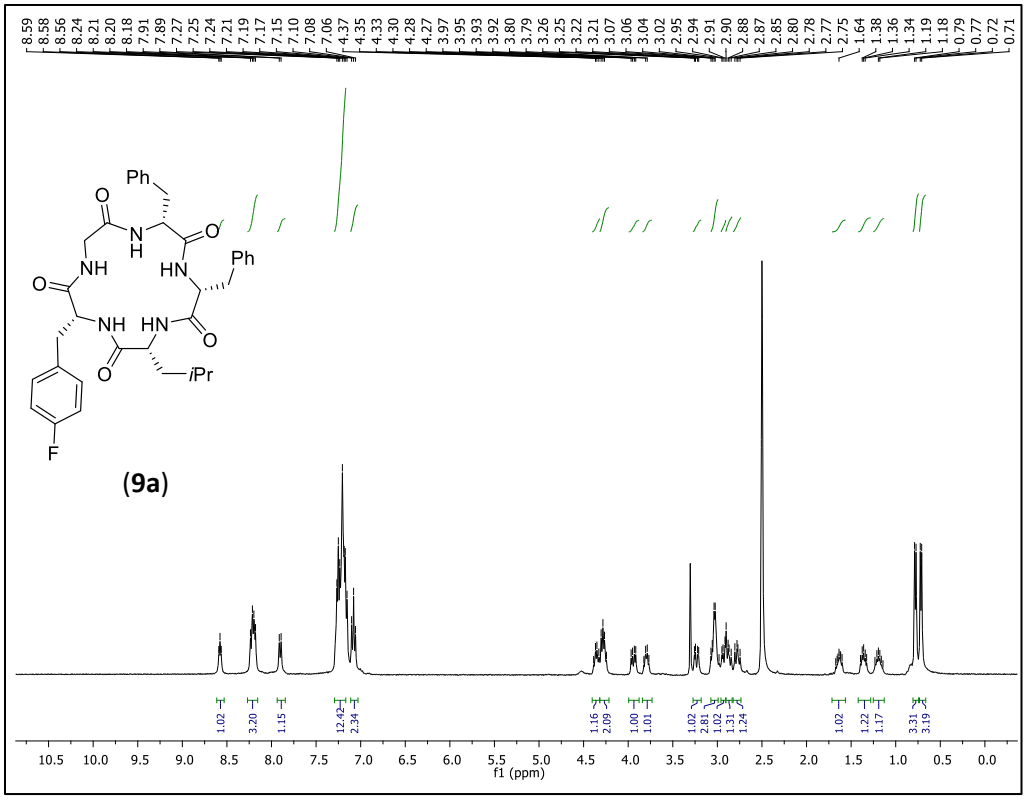
(**9b**)

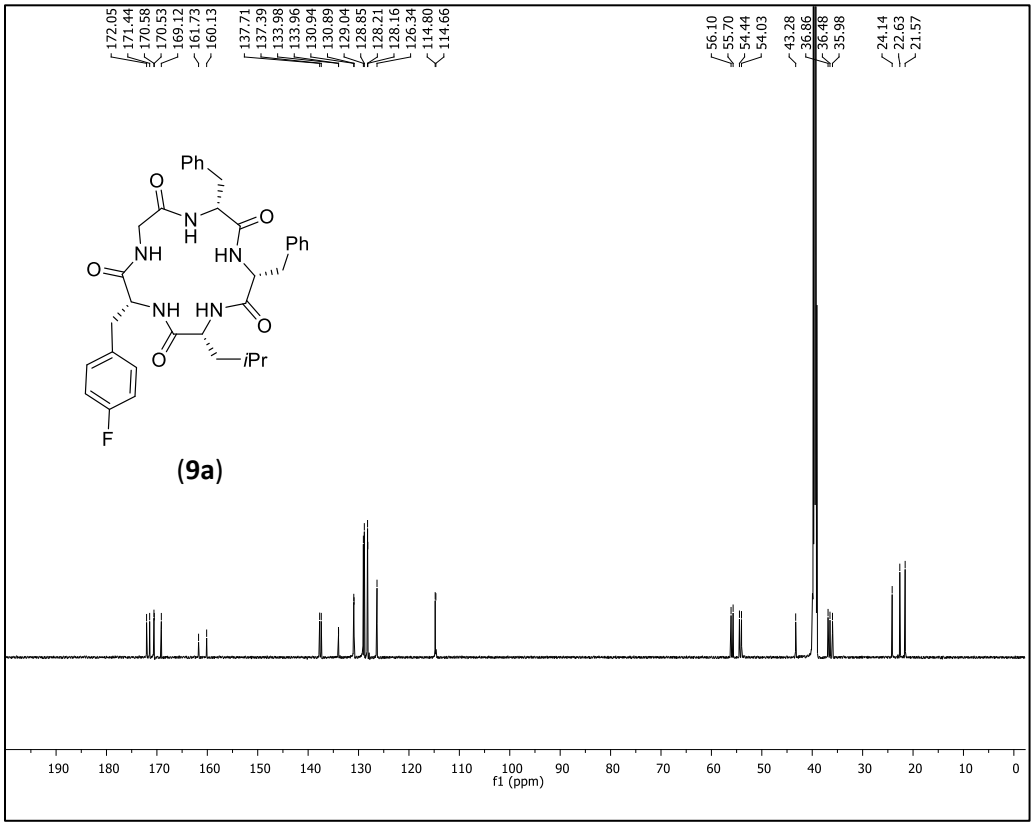

(9c)
f1 (ppm)

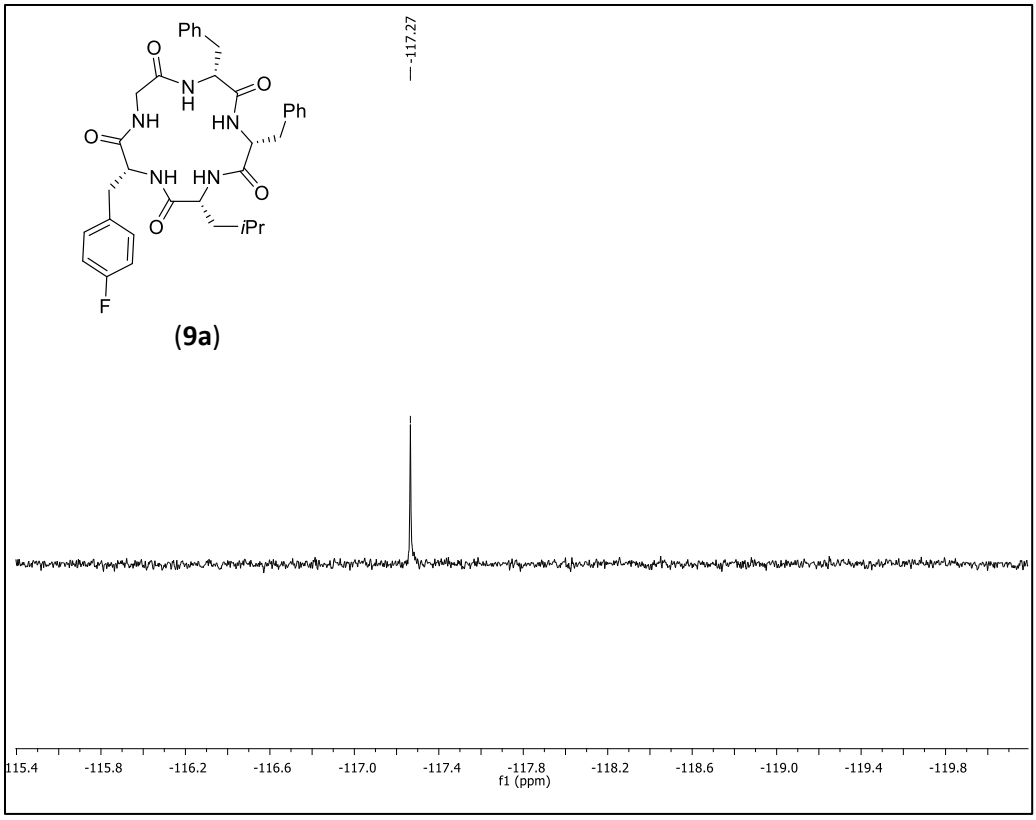

(9c)
f1 (ppm)


Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
-117.20
-113.5
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
-117.0
-117.5
-118.0
-118.5
-119.0
-119.5
-120.0
-120.5
f1 (ppm)

(**9c**)


8.59 8.58 8.56 8.24 8.21 8.20 8.18 7.91 7.89 7.27 7.25 7.24 7.21 7.19 7.17 7.15 7.10 7.08 7.06 4.37 4.35 4.33 4.30 4.28 4.27 3.97 3.95 3.93 3.92 3.80 3.79 3.26 3.25 3.22 3.21 3.07 3.06 3.04 3.02 2.95 2.94 2.91 2.90 2.88 2.87 2.85 2.80 2.78 2.77 2.75 1.64 1.38 1.36 1.34 1.19 1.18 0.79 0.77 0.72 0.71
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
(9a)
1.02 3.20 1.15 12.42 2.34 1.16 2.09 1.00 1.01 1.02 2.81 1.02 1.31 1.24 1.02 1.22 1.17 3.31 3.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


172.05 171.44 170.58 170.53 169.12 161.73 160.13 137.71 137.39 133.98 133.96 130.94 130.89 129.04 128.85 128.21 128.16 126.34 114.80 114.66 56.10 55.70 54.44 54.03 43.28 36.86 36.48 35.98 24.14 22.63 21.57
Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
iPr
F
(9a)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
O
N
H
O
NH
HN
Ph
O
NH
HN
O
O
O
iPr
F
-117.27
115.4
-115.8
-116.2
-116.6
-117.0
-117.4
-117.8
-118.2
-118.6
-119.0
-119.4
-119.8
f1 (ppm)

(**9a**)

10. References

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