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Supporting Information

Decarboxylative Peptide Macrocyclization through Photoredox Catalysis

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Contents:

1. General Experimental

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was prepared according to the literature procedure.[2] 2,4,6-Triisopropylbenzenethiol was prepared according to literature procedure and purified by distillation prior to use.[3] All solvents were purified according to the method of Grubbs.[4] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath or using a Genevac® EZ-2 Plus Personal Evaporator. Solid phase peptide synthesis was performed on 2-chlorotrityl chloride resin (100-200 mesh, 1.2 meq/g, crosslinked polystyrene) manually or on a Prelude automated peptide synthesizer. 2-Chlorotrityl chloride resin, 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU), 4-methylmorpholine (NMM), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), *N*,*N*-diisopropylethylamine (DIPEA), and Fmoc-amino acids were purchased from Chem Impex Int'l Inc. and used as received. 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was purchased from Oakwood Chemical and used as received. ^{1}H NMR spectra were recorded on a Bruker UltraShield Plus 500 MHz unless otherwise noted and are internally referenced to residual protio CD_3OD signals (3.31 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad), coupling constant (Hz), and integration. $(CD_3)_2SO$ was added for solubility when necessary. 2D NMR spectroscopy was utilized for the assignment of γ-amino acid residue ^{1}H signals. High Resolution Mass Spectra were obtained from the Princeton University Mass Spectral Facility.

2. Amino Acid Abbreviations

Aba	γ-aminobutyric acid
Aba(2-Ph)	2-phenyl-γ-aminobutyric acid
Aba(4-*i*Bu)	4-isobutyl-γ-aminobutyric acid
Aba(4-Me)	4-methyl-γ-aminobutyric acid
(Me)Aaa	*N*-methyl amino acid
Pra	*L*-propargylglycine
Acc	1-aminocyclopropane-1-carboxylic acid
Acpc	1-aminocyclopentane-1-carboxylic acid
Phe(4-Br)	4-bromo-phenylalanine

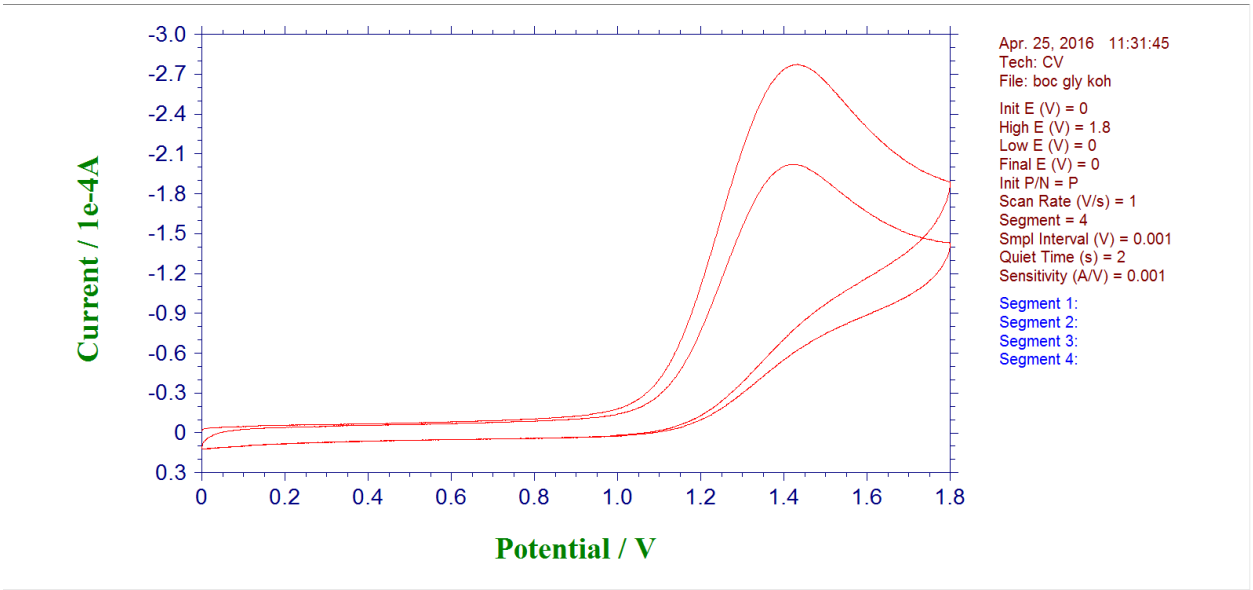
[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd ed*. Pergamon Press: Oxford, 1988.
[2] Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, Jr., R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712.
[3] Renard, M.; Ghosez, L. A. *Tetrahedron* **2001**, *57*, 2597.
[4] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518.

$Arg(Boc)_2$	*N*-α-Fmoc-*N*-ω,*N*-ω-bis-*tert*-butoxycarbonyl-arginine
Ahda	4-aminoheptanedioic acid
(3-Ac)pa	3-(1-aminocyclopropyl)propanoic acid
(3-Acp)pa	3-(1-aminocyclopentyl)propanoic acid

3. Boc-Glycine Cyclic Voltammetry

Cyclic voltammetry was performed using a CH Instruments Electrochemical Workstation model CHI600E with a scan rate of 1.0 V/s, 4 sweep segments, a sample interval of 0.001 V, and a sensitivity of 0.001 A/V.

N-(*tert*-Butoxycarbonyl)glycine (18 mg, 0.2 mmol) and NBu_4PF_6 (390 mg, 1 mmol) were dissolved in MeCN (10 mL) and KOH (6 mg, 0.2 mmol in 100 μL H_2O) was added. The solution was degassed by sparging with N_2 for 15 minutes before the electrochemical measurement. An irreversible oxidation peak was observed at $E_{p/2}$ +1.22 V vs. SCE.



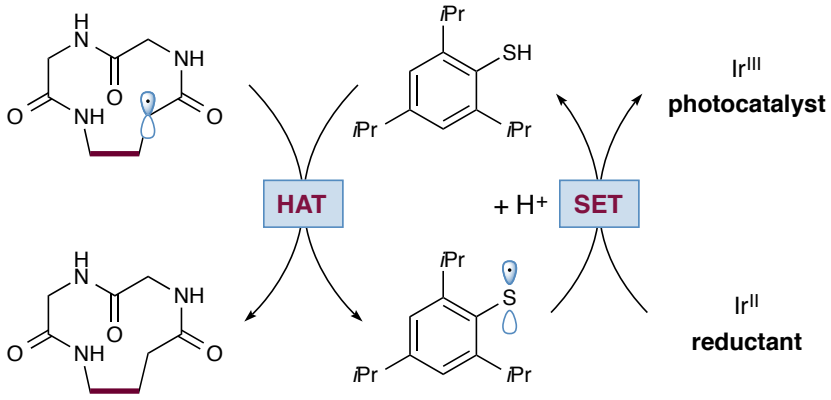
4. Effect of 2,4,6-triisopropylbenzenethiol

For substrates where cyclization was inefficient due to reversible radical conjugate addition, we recognized that the inclusion of an aryl thiol co-catalyst might provide significant improvements in the ratio of monomeric cyclization adducts to higher order couplings arising from a radical oligomerization sequence. More specifically, thiols are well known to undergo nearly diffusion- limited hydrogen atom transfer (HAT) to carbon-centered radicals.[5] As such, we felt an alternative pathway to product formation might involve conjugate addition of carbon-centered radicals to Michael acceptors followed by rapid

[5] J. A. Franz, B. A. Bushaw, M. S. Alnajjar, *J. Am. Chem. Soc.* **1989**, *111*, 268.

HAT from the thiol catalyst to the macrocyclic α-acyl radical to generate the desired macrocycle. The resulting thiyl radical would then be reduced by Ir(II) to close the photocatalytic cycle. The results of thiol addition for 3 substrates is shown in the table below. For all other examples, addition of this co-catalyst led to either no change in or lower levels of reaction efficiency.

#	Sequence	% Yield (no thiol)	% Yield (10% thiol)
8	acryloyl-Phe-Met-Leu-Glu(O*t*Bu)-Gly	64%	73%
10	acryloyl-Phe-Arg(Boc)$_2$-Ser(*t*Bu)-Ala-Gly	32%	45%
21	acryloyl-Phe-Ala-Pro-Glu(O*t*Bu)-Leu-Phe-Ala-Gly	26%	52%



5. Synthesis of Linear Peptide Sequences

General solid phase loading procedure

Into a 12 mL filtration tube with luer adapter was added 2-chlorotrityl chloride resin (500 mg, 600 µmol) followed by a solution of the Fmoc amino acid (1.8 mmol, 3 equiv.) and DIPEA (0.627 mL, 3.6 mmol, 6 equiv.) in CH_2Cl_2 (8 mL). The tube was capped and shaken for 15 minutes and then an additional 2 equiv. of DIPEA added. After a further hour of shaking, 2 equiv. DIPEA and 1 mL MeOH was added and the mixture agitated for 20 minutes. The tube was then drained, rinsed with CH_2Cl_2 (3x 8 mL) and dried. The amino acid loading of the resin was then measured by Fmoc determination.[6]

General solid phase synthesis procedure

The resin was treated with 20% piperidine/DMF (6 mL) for 5 minutes followed by thorough washing with DMF (6x 6 mL). Deprotection was performed twice.

A solution of Fmoc-protected amino acid (1.8 mmol, 3 equiv.) and HBTU (0.68 g, 1.8 mmol, 3 equiv.) in DMF (6 mL) followed by DIPEA (0.627 mL, 3.6 mmol, 6 equiv.) was added to the resin and the mixture

[6] Boll, E.; Drobecq, H.; Ollivier, N.; Blanpain, A.; Raibaut, L.; Desmet, R.; Vicogne, J.; Melnyk, O. *Nature Protocols* **2015**, *10*, 269.

shaken for 2 hours. The resin was then drained and rinsed with DMF (6x 6 mL). If necessary, the coupling procedure was repeated until completion.

General solid phase synthesis procedure on Prelude Peptide Synthesizer

The peptide elongation was performed on a 0.250 mmol scale using Prelude Peptide Synthesizer. Prior to amino acid coupling, all peptide synthesis sequences began with a resin-swelling procedure. Coupling of amino acids to a primary amine N-terminus used the "Single-coupling procedure" described below. Coupling of amino acids to a secondary amine N-terminus or to the N-terminus of Arg(Boc) used the "Double-coupling procedure" described below. For the last amino acid on the sequence performed on Prelude, manual removal of the Fmoc group used the "Manual removal of Fmoc group procedure" described below.

Resin-swelling procedure

To a 45-mL polypropylene solid-phase reaction vessel was added the preloaded resin (0.250 mmol). The resin was washed (swelled) two times as follows: to the reaction vessel was added DMF (8.0 mL) through the top of the vessel "DMF top wash" upon which the mixture was periodically agitated for 10 minutes before the solvent was drained through the frit.

Single-coupling procedure

To the reaction vessel containing the resin from the previous step was added piperidine:DMF (1:4 v/v, 7.0 mL). The mixture was periodically agitated for 5 minutes and then the solution was drained through the frit. To the reaction vessel was added piperidine:DMF (1:4 v/v, 7.0 mL). The mixture was periodically agitated for 5 minutes and then the solution was drained through the frit. The resin was washed successively five times as follows: for each wash, DMF (8.0 mL) was added through the top of the vessel and the resulting mixture was periodically agitated for 1.5 minutes before the solution was drained through the frit. To the reaction vessel was added the amino acid (0.2 M in DMF, 5.0 mL, 4 equiv.), then HATU (0.4 M in DMF, 2.5 mL, 4 equiv.), and finally NMM (0.8 M in DMF, 2.5 mL, 8 equiv.). The mixture was periodically agitated for 1 hour, then the reaction solution was drained through the frit. The resin was washed successively four times as follows: for each wash, DMF (8.0 mL) was added through the top of the vessel and the resulting mixture was periodically agitated for 1.5 minutes before the solution was drained through the frit.

Double-coupling procedure

To the reaction vessel containing the resin from the previous step was added piperidine:DMF (1:4 v/v, 8.0 mL). The mixture was periodically agitated for 5 minutes and then the solution was drained through the frit. To the reaction vessel was added piperidine:DMF (1:4 v/v, 8.0 mL). The mixture was periodically agitated for 5 minutes and then the solution was drained through the frit. The resin was washed successively four times as follows: for each wash, DMF (10.0 mL) was added through the top of the

vessel and the resulting mixture was periodically agitated for 1.5 minutes before the solution was drained through the frit. To the reaction vessel was added the amino acid (0.2 M in DMF, 5.0 mL, 4 equiv.) and agitated for 15 seconds, then HATU (0.4 M in DMF, 2.5 mL, 4 equiv.) and agitated for 15 seconds, and finally NMM (0.8 M in DMF, 2.5 mL, 8 equiv.). The mixture was periodically agitated for 1 hour, then the reaction solution was drained through the frit. DMF (10.0 mL) was added through the top of the vessel and the resulting mixture was periodically agitated for 1.5 minutes before the solution was drained through the frit. To the reaction vessel was added the amino acid (0.2 M in DMF, 5.0 mL, 4 equiv.) and agitated for 15 seconds, then HATU (0.4 M in DMF, 2.5 mL, 4 equiv.) and agitated for 15 seconds, and finally NMM (0.8 M in DMF, 2.5 mL, 8 equiv.). The mixture was periodically agitated for 1 hour, then the reaction solution was drained through the frit. The resin was successively washed four times as follows: for each wash, DMF (10.0 mL) was added through the top of the vessel and the resulting mixture was periodically agitated for 1.5 minutes before the solution was drained through the frit. The resulting resin was used directly in the next step.

Manual removal of Fmoc group procedure

To the reaction vessel containing the resin from the previous step was added piperidine:DMF (1:4 v/v, 8.0 mL) using the manual operation commend. The mixture was periodically agitated for 10 minutes and then the solution was drained through the frit. To the reaction vessel was added piperidine:DMF (1:4 v/v, 8.0 mL) using the manual operation commend. The mixture was periodically agitated for 10 minutes and then the solution was drained through the frit. The resin was washed successively with DMF twice and then DCM twice using the manual operation commend as follows: for each wash, DMF (10.0 mL) or DCM (10 mL) was added through the top of the vessel and the resulting mixture was periodically agitated for 5 minutes before the solution was drained through the frit.

General acryloyl capping procedure

A solution of pentafluorophenyl acrylate (0.43 g, 1.8 mmol, 3 equiv., prepared according to literature procedure)[7] and DIPEA (0.627 mL, 3.6 mmol, 6 equiv.) in DMF (6 mL) was added to the resin and the mixture shaken for 4 hours. The resin was drained and rinsed with DMF (6x 6 mL). The procedure was repeated twice.

General resin cleavage procedure

After completion of synthesis, resin was thoroughly rinsed with DMF (6x 6 mL) then CH_2Cl_2 (6x 6 mL). The resin was then treated with 4:1 CH_2Cl_2:HFIP twice for 1 hour each. The combined CH_2Cl_2:HFIP solutions were concentrated under reduced pressure. Cold Et_2O was added to the remaining solid, which was then centrifuged and decanted; this procedure was repeated twice. The remaining solid was dried

[7] Choi, J.; Schattling, P.; Jochum, F. D.; Pyun, J.; Char, K.; Theato, P. *J. Polym. Sci. A Polym. Chem.* **2012**, *50*, 4010.

under a stream of N_2 and then under reduced pressure to yield the desired crude peptide. If necessary, preparative HPLC purification was carried out.

6. General Decarboxylative Macrocyclization Procedure

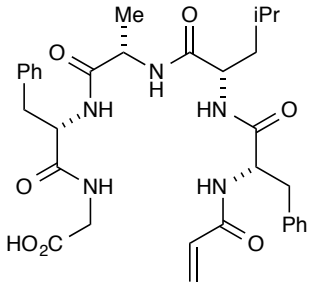
General procedure for the decarboxylative macrocyclization of* N-*acryloyl peptides:

To a dry 8 mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.3 mg, 1.2 μmol, 0.12 equiv.), peptide (10.0 μmol, 1.0 equiv.), K_2HPO_4 (3.5 mg, 20.0 μmol, 2.0 equiv.) as a solution in H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4 mL). The vial was capped and the reaction mixture was degassed by sparging with N_2 while stirring at 800 RPM for 20 min before sealing the vial with Parafilm. The reaction was stirred at 800 RPM and irradiated with a 34 W blue LED lamp until complete consumption of the starting material, typically within 10 hours. The reaction was centrifuged and subjected to RP-HPLC analysis for yield determination. Yields were determined using an HPLC calibration curve based on absorbance at 210 nm using the LINEST function in Excel. Concentration of standard solutions was determined by ^1H NMR against maleic acid as standard by integrating either the aromatic or methyl resonances of the peptide.

The crude materials were purified via preparative LC/MS with the following conditions: Column: XBridge C18, 30 x 150 mm, 5-μm particles; Mobile Phase A: 5:95 MeCN: water with 0.1% TFA; Mobile Phase B: 95:5 MeCN:H_2O with 0.1% TFA; Gradient: 10-70% B over 20 minutes, then a 2-minute hold at 100% B; Flow: 40 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation.

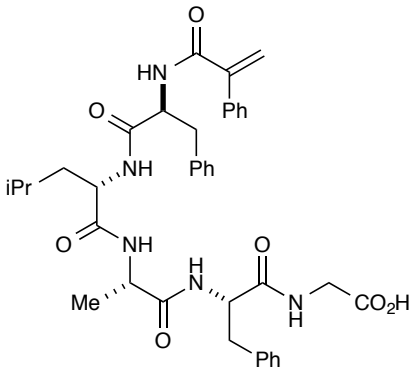
Two analytical LC/MS injections were used to determine the final purity. Injection 1 conditions: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 MeCN:H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 MeCN:H_2O with 10 mM NH_4OAc; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm. Injection 2 conditions: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7- μm particles; Mobile Phase A: 5:95 MeCN:H_2O with 0.1% TFA; Mobile Phase B: 95:5 MeCN:H_2O with 0.1% TFA; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

7. Experimental Data for Linear Peptides



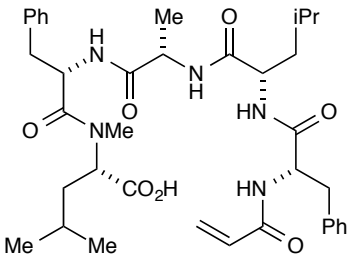
acryloyl-Phe-Leu-Ala-Phe-Gly

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.32–7.13 (m, 11H), 6.28 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.17 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.65 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.65 (m, 2H), 4.31 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 3.93–3.81 (m, 2H), 3.23 (m, 1H), 3.18–3.12 (m, 1H), 3.02–2.92 (m, 2H), 1.63–1.47 (m, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.91 (m, 7H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{32}H_{42}N_5O_7$ ([M+H]$^+$) 608.30842, found 608.30862.



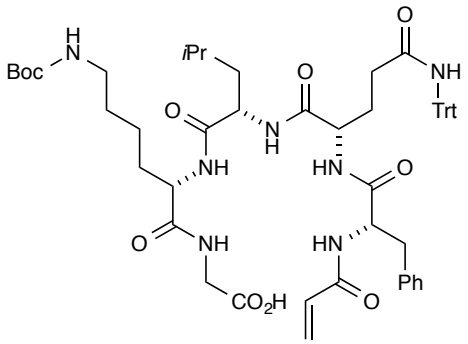
α-phenylacryloyl-Phe-Leu-Ala-Phe-Gly

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.34–7.14 (m, 16H), 5.70 (s, 1H), 5.63 (s, 1H), 4.81 (m, 1H), 4.63 (m, 1H), 4.40 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 1H), 3.94–3.81 (m, 2H), 3.22 (m, 2H), 2.95 (m, 2H), 1.75–1.50 (m, 4H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.94 (m, 6H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{38}H_{46}N_5O_7$ ([M+H]$^+$) 684.33972, found 684.33990.



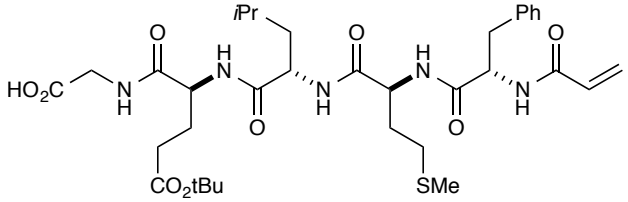
acryloyl-Phe-Leu-Ala-Phe-(Me)Leu

Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) δ 7.33–7.14 (m, 10H), 6.26 (dd, *J* = 17.1, 10.1 Hz, 1H), 6.16 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.63 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.24–5.06 (m, 1H), 5.02 (m, 1H), 4.69 (m, 1H), 4.47–4.24 (m, 2H), 3.16 (m, 2H), 2.99–2.89 (m, 2H), 2.86 (s, 3H), 1.82–1.50 (m, 5H), 1.49–1.37 (m, 1H), 1.32–1.23 (m, 3H), 1.01–0.75 (m, 12H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{37}H_{52}N_5O_7$ ($[M+H]^+$) 678.38667, found 678.38581.



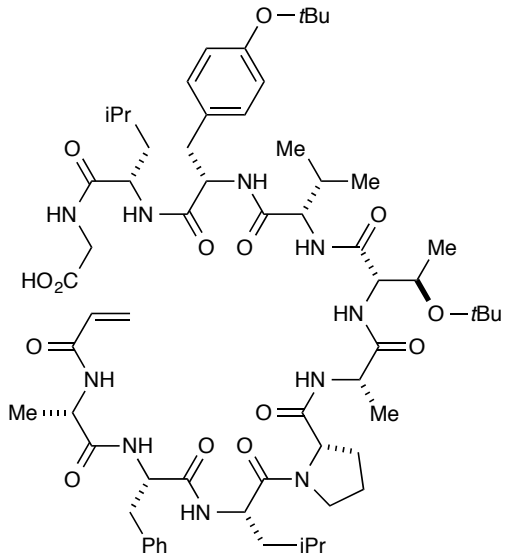
acryloyl-Phe-Gln(Trt)-Leu-Lys(Boc)-Gly

Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) δ 7.35–7.17 (m, 20H), 6.23 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.13 (d, *J* = 16.8 Hz, 1H), 5.67–5.58 (m, 1H), 4.69 (p, *J* = 6.5 Hz, 1H), 4.61 (m, 1H), 4.39–4.31 (m, 2H), 4.29–4.24 (m, 1H), 3.84 (qm, 2H), 3.21–3.12 (m, 1H), 3.06–2.92 (m, 4H), 2.46 (m, 2H), 2.12–1.99 (m, 1H), 1.96–1.88 (m, 1H), 1.83 (d, *J* = 7.1 Hz, 1H), 1.67 (m, 4H), 1.49–1.39 (m, 11H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{55}H_{70}N_7O_{10}$ ($[M+H]^+$) 988.51842, found 988.51858.



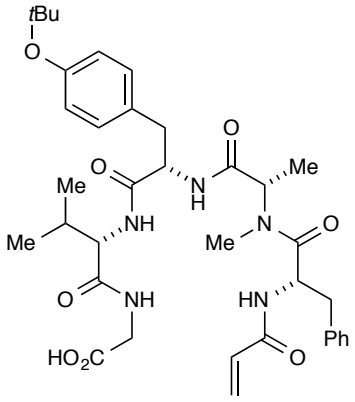
acryloyl-Phe-Met-Leu-Glu(O*t*Bu)-Gly

Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) δ 7.33–7.16 (m, 5H), 6.30 (dd, *J* = 17.1, 10.1 Hz, 1H), 6.19 (d, *J* = 17.0 Hz, 1H), 5.66 (d, *J* = 10.1 Hz, 1H), 4.65 (dd, *J* = 8.7, 5.9 Hz, 1H), 4.46–4.32 (m, 3H), 3.88 (m, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.49 (m, 1H), 2.43–2.30 (m, 3H), 2.18–2.08 (m, 2H), 2.07 (s, 3H), 2.00–1.88 (m, 2H), 1.72–1.60 (m, 3H), 1.44 (s, 9H), 0.94 (m, 6H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{34}H_{52}N_5O_9S$ ($[M+H]^+$) 706.34858, found 706.34792.



acryloyl-Ala-Phe-Leu-Pro-Ala-Thr(*t*Bu)-Val-Tyr(*t*Bu)-Leu-Gly

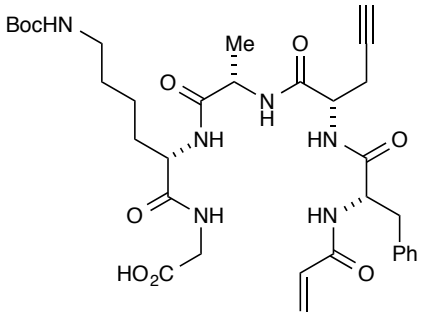
Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) δ 7.28–7.15 (m, 7H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.32–6.20 (m, 2H), 5.68 (dd, *J* = 9.0, 3.1 Hz, 1H), 4.71–4.57 (m, 4H), 4.53–4.29 (m, 4H), 4.26 (s, 1H), 4.21–4.14 (m, 1H), 4.10 (s, 1H), 3.79 (m, 1H), 3.55 (q, *J* = 7.4, 7.0 Hz, 1H), 3.19–3.10 (m, 2H), 2.98–2.87 (m, 2H), 2.24 (m, 1H), 2.13–1.90 (m, 4H), 1.74–1.52 (m, 7H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.30 (s, 9H), 1.28 (d, *J* = 7.3 Hz, 3H), 1.18 (s, 9H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.97–0.84 (m, 18H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{63}H_{97}N_{10}O_{14}$ ($[M+H]^+$) 1217.71857, found 1217.71846.



acryloyl-Phe-(Me)Ala-Tyr(*t*Bu)-Val-Gly

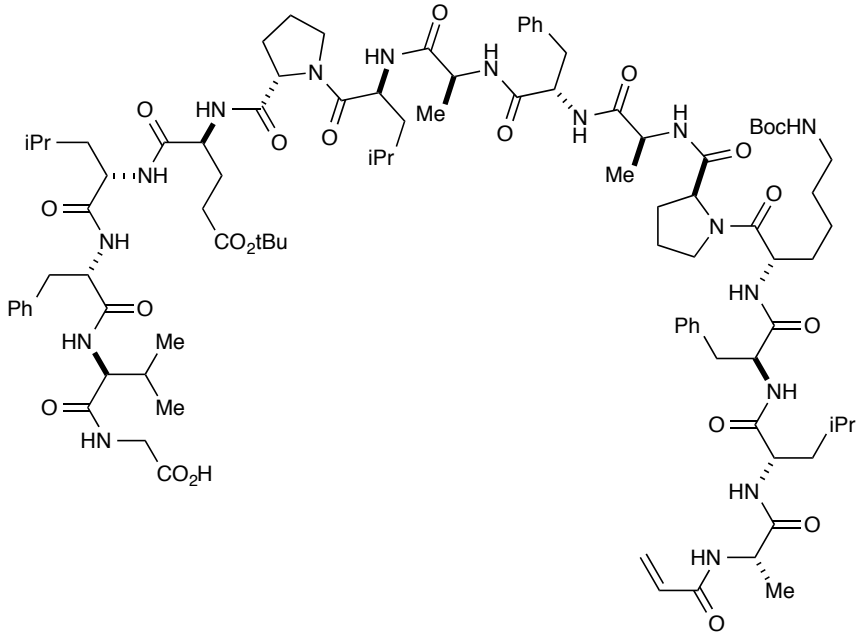
Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) rotameric NMR δ 7.34–7.21 (m, 5H), 7.14 (d, *J* = 8.3 Hz, 0.4H), 7.12–7.07 (m, 1.6H), 6.87 (d, *J* = 8.6, 2.9 Hz, 2H), 6.47–6.35 (m, 1.6H), 6.35–6.13 (m, 0.2H), 5.76 (dd, *J* = 8.9, 3.1 Hz, 0.8H), 5.64 (m, 0.2H), 5.22 (m, 1H), 4.67 (q, *J* = 6.8 Hz, 1H), 4.58 (m, 0.2H), 4.46 (m, 0.8H), 4.36 (d, *J* = 6.0 Hz, 0.8H), 4.29 (d, *J* = 6.6 Hz,

0.2H), 3.81–3.74 (m, 2H), 3.25–3.10 (m, 2H), 3.10–2.96 (m, 1.6H), 2.97–2.88 (m, 0.4H), 2.21 (m, 0.2H), 2.14 (h, *J* = 6.6 Hz, 0.8H), 2.03 (s, 3H), 1.29 (s, 7.2H), 1.28 (s, 1.8H), 1.02–0.86 (m, 6H), 0.24 (d, *J* = 6.7 Hz, 3H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{36}H_{50}N_5O_8$ ($[M+H]^+$) 680.36594, found 680.36560.



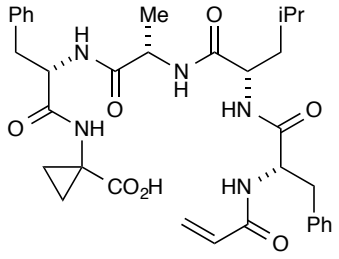
acryloyl-Phe-Pra-Ala-Lys(Boc)-Gly

Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) δ 7.29–7.24 (m, 4H), 7.23–7.17 (m, 1H), 6.27 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.17 (dd, *J* = 17.1, 2.1 Hz, 1H), 5.64 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.71 (m, 1H), 4.45 (t, *J* = 6.8 Hz, 1H), 4.39–4.28 (m, 2H), 3.83–3.72 (m, 2H), 3.20 (m, 1H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.95 (m, 1H), 2.79–2.70 (m, 1H), 2.69–2.60 (m, 1H), 1.97 (s, 1H), 1.93–1.85 (m, 1H), 1.74–1.63 (m, 1H), 1.53–1.35 (m, 16H). HRMS (ESI-TOF) *m*/*z* calcd. for $C_{33}H_{47}N_6O_9$ ($[M+H]^+$) 671.34045, found 671.34032.



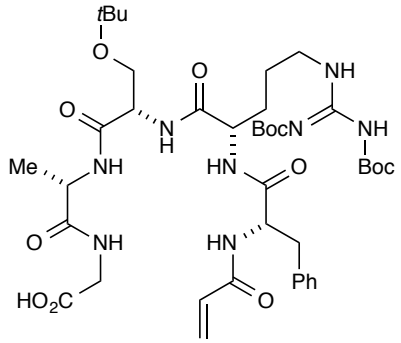
acryloyl-Ala-Leu-Phe-Lys(Boc)-Pro-Ala-Phe-Ala-Leu-Pro-Glu(O*t*Bu)-Leu-Phe-Val-Gly

Prepared following the general solid phase synthesis procedure. 1H NMR (500 MHz, CD_3OD) δ 7.28–7.15 (15H), 6.38–6.27 (2H), 5.72 (1H), 4.69–4.59 (4H), 4.55–4.51 (2H), 4.43–4.40 (1H), 4.38–4.29 (3H), 4.25–4.19 (3H), 4.14–4.09 (1H), 3.92–3.86 (2H), 3.82–3.75 (1H), 3.73–3.62 (2H), 3.58–3.53 (1H), 3.23–3.12 (3H), 3.05–2.95 (5H), 2.44–2.35 (2H), 2.30–2.13 (3H), 2.08–1.73 (12H), 1.67–1.55 (5H), 1.50–1.28 (30H), 1.26 (3H), 1.00–0.94 (12H), 0.91–0.88 (6H), 0.85–0.82 (6H). HRMS (ESI-TOF) *m/z* calcd. for $C_{94}H_{142}N_{16}O_{21}$ ($[M+2H]^{+2}$) 915.52678, found 915.52660.



acryloyl-Phe-Leu-Ala-Phe-Acc

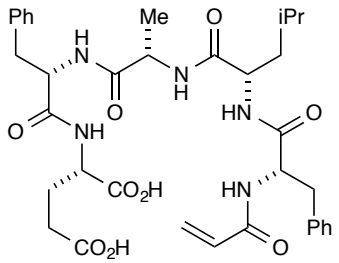
Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.34 – 7.05 (m, 10H), 6.28 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.17 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.65 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.67 (m, 1H), 4.54 (dt, *J* = 7.3, 4.9 Hz, 1H), 4.43–4.24 (m, 1H), 4.17 (q, *J* = 8.1, 7.3 Hz, 1H), 3.24–3.07 (m, 2H), 3.08–2.66 (m, 2H), 1.71–1.50 (m, 3H), 1.49–1.33 (m, 2H), 1.23 (d, *J* = 7.3 Hz, 3H), 1.22–1.14 (m, 1H), 1.07–0.82 (m, 8H). HRMS (ESI-TOF) *m/z* calcd. for $C_{34}H_{44}N_5O_7$ ($[M+H]^+$) 634.32407, found 634.32421.



acryloyl-Phe-Arg(Boc)$_2$-Ser(*t*Bu)-Ala-Gly

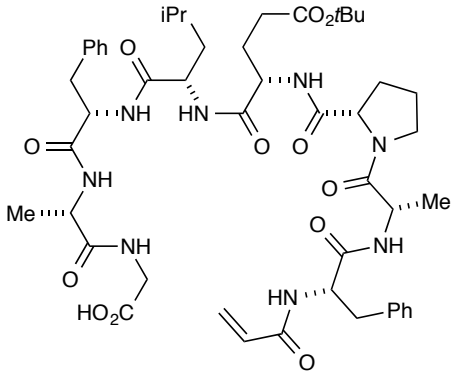
Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.33–7.15 (m, 5H), 6.27 (dd, *J* = 17.1, 10.1 Hz, 1H), 6.18 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.64 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.69 (dd, *J* = 8.7, 5.7 Hz, 1H), 4.46 (t, *J* = 5.2 Hz, 1H), 4.40–4.29 (m, 2H), 3.96–3.82 (m, 2H), 3.76–3.68 (m, 1H), 3.63–3.56 (m, 1H), 3.35 (t, *J* = 7.4 Hz, 2H), 3.21–3.13 (m, 1H), 3.04–2.88 (m, 1H), 1.86

(m, 1H), 1.71 (m, 1H), 1.63–1.54 (m, 2H), 1.55–1.50 (m, 9H), 1.49–1.45 (m, 9H), 1.43–1.38 (m, 3H), 1.21–1.16 (m, 9H). HRMS (ESI-TOF) *m/z* calcd. for $C_{40}H_{63}N_8O_{12}$ ($[M+H]^+$) 847.45655, found 847.45706.



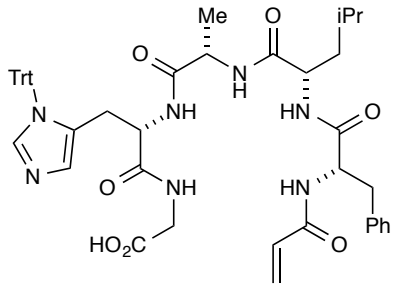
acryloyl-Phe-Leu-Ala-Phe-Glu

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.30–7.15 (m, 10H), 6.27 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.17 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.65 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.68 (m, 1H), 4.59 (m, 1H), 4.43 (m, 1H), 4.30 (m, 1H), 4.20 (q, *J* = 6.8 Hz, 1H), 3.26–3.11 (m, 2H), 2.97 (m, 2H), 2.37 (q, *J* = 7.2, 6.8 Hz, 2H), 2.18 (m, 1H), 1.99–1.91 (m, 1H), 1.65–1.46 (m, 3H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.91 (m, 5H). HRMS (ESI-TOF) *m/z* calcd. for $C_{35}H_{46}N_5O_9$ ($[M+H]^+$) 680.32955, found 680.32932.



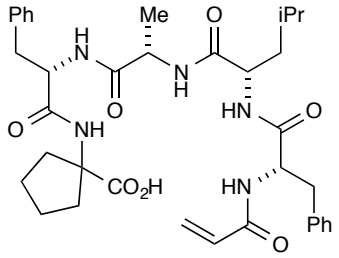
acryloyl-Phe-Ala-Pro-Glu(O*t*Bu)-Leu-Phe-Ala-Gly

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.31–7.23 (m, 8H), 7.23–7.15 (m, 2H), 6.27 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.18 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.65 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.76 (m, 1H), 4.57 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 1H), 4.33 (m, 1H), 4.21 (m, 2H), 3.92–3.87 (m, 2H), 3.59 (m, 1H), 3.54–3.46 (m, 1H), 3.25–3.13 (m, 2H), 2.95 (m, 2H), 2.42 (hept, *J* = 9.0, 8.1 Hz, 2H), 2.22 (m, 1H), 2.06 (m, 1H), 2.02–1.85 (m, 4H), 1.64–1.51 (m, 2H), 1.45 (s, 9H), 1.39 (m, 7H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H). HRMS (ESI-TOF) *m/z* calcd. for $C_{49}H_{69}N_8O_{12}$ ($[M+H]^+$) 961.50350, found 961.50406.



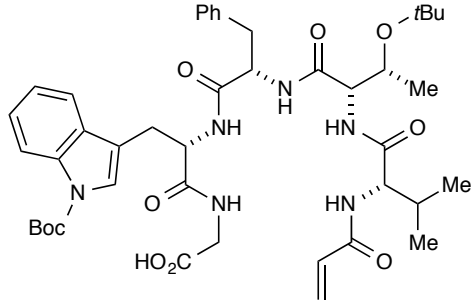
acryloyl-Phe-Leu-Ala-His(Trt)-Gly

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.45–7.31 (m, 10H), 7.30–7.17 (m, 5H), 7.18–7.08 (m, 7H), 6.25 (dd, *J* = 17.2, 10.1 Hz, 1H), 6.13 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.62 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.70–4.55 (m, 2H), 4.34 (t, *J* = 6.5 Hz, 1H), 4.22 (hept, *J* = 7.5, 7.1 Hz, 1H), 3.89–3.73 (m, 2H), 3.12 (m, 2H), 3.01 (m, 1H), 2.90 (m, 1H), 1.79 (q, *J* = 5.7 Hz, 1H), 1.59 (m, 2H), 1.34–1.28 (m, 3H), 0.97–0.81 (m, 6H). HRMS (ESI-TOF) *m/z* calcd. for $C_{48}H_{54}N_7O_7$ ($[M+H]^+$) 840.40847, found 840.40902.



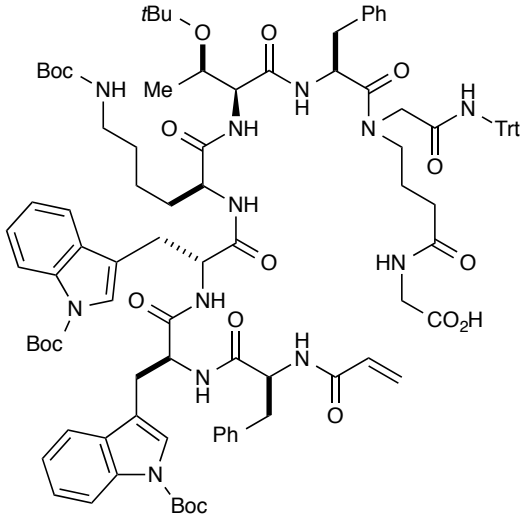
acryloyl-Phe-Leu-Ala-Phe-Acpc

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.29–7.14 (m, 10H), 6.28 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.17 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.65 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.70–4.63 (m, 1H), 4.57 (m, 1H), 4.36–4.28 (m, 1H), 4.23–4.14 (m, 1H), 3.22–3.09 (m, 2H), 3.02–2.90 (m, 2H), 2.23–2.17 (m, 1H), 2.09 (m, 1H), 1.95 (m, 2H), 1.73–1.47 (m, 7H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.98–0.85 (m, 6H). HRMS (ESI-TOF) *m/z* calcd. for $C_{36}H_{48}N_5O_7$ ($[M+H]^+$) 662.35537, found 662.35560.



acryloyl-Val-Thr(*t*Bu)-Phe-Trp(Boc)-Gly

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (m, 1H), 7.71 (m, 1H), 7.59–7.45 (m, 1H), 7.29 (m, 1H), 7.24 (m, 1H), 7.22–7.11 (m, 5H), 6.44 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.31 (d, *J* = 17.0 Hz, 1H), 5.75 (d, *J* = 10.3 Hz, 1H), 4.78 (m, 1H), 4.60–4.51 (m, 1H), 4.19 (m, 1H), 4.08–3.96 (m, 2H), 3.96–3.79 (m, 2H), 3.34–3.31 (m, 1H), 3.21–3.14 (m, 1H), 3.09–3.02 (m, 1H), 2.95 –2.85 (m, 1H), 2.09 (q, *J* = 6.8 Hz, 1H), 1.62 (s, 9H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H). HRMS (ESI-TOF) *m/z* calcd. for $C_{43}H_{59}N_6O_{10}$ ($[M+H]^+$) 819.42927, found 819.42813.

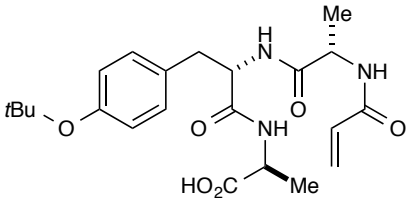


acryloyl-Phe-Trp(Boc)-(*D*)Trp(Boc)-Lys(Boc)-Thr(*t*Bu)-Phe-(4-acetamide)Aba-Gly

Prepared following the general solid phase synthesis procedure.

Side chain installation. Following Fmoc deprotection, the resin was washed 3x with CH_2Cl_2 then NMP. A solution of 2,4,6-trimethylpyridine (0.79 mL, 6.0 mmol, 10 equiv.) and 4-nitrobenzenesulfonyl chloride (0.53 g, 2.4 mmol, 4 equiv.) in NMP was added to the resin and agitated for 15 minutes. The resin was then drained and washed 3x with NMP. DBU (0.27 mL, 1.8 mmol, 3 equiv.) in NMP was added and agitated for 5 minutes, followed by the addition of 2-bromo-*N*-tritylacetamide (0.46 g, 1.2 mmol, 2 equiv.) in NMP. The reaction was allowed to continue for 2 hours before draining and washing the resin. The alkylation procedure was repeated two more times. Sulfonamide deprotection was effected by treatment with DBU (0.45 mL, 3.0 mmol, 5 equiv.) and mercaptoethanol (0.42 mL, 6.0 mmol, 10 equiv.) in NMP twice for 5 minutes each. The resin was then thoroughly washed with NMP (3x), CH_2Cl_2 (3x), and DMF (3x).

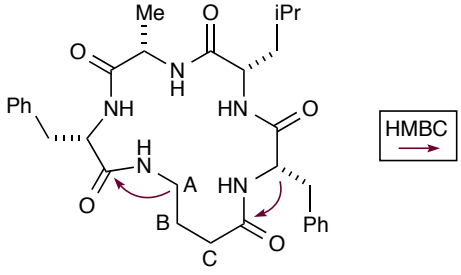
^{1}H NMR (500 MHz, CD_3OD) δ 8.13–8.03 (m, 2H), 7.72–7.40 (m, 4H), 7.34–7.08 (m, 28H), 7.04 (m, 1H), 6.19 (ddd, *J* = 17.1, 10.0, 5.0 Hz, 1H), 6.10 (ddd, *J* = 18.8, 17.1, 2.0 Hz, 1H), 5.56 (m, 1H), 4.78–4.53 (m, 3H), 4.34–4.14 (m, 3H), 4.01–3.91 (m, 1H), 3.91–3.74 (m, 2H), 3.21–2.74 (m, 11H), 2.15 (m, 2H), 1.86–1.63 (m, 4H), 1.59 (s, 18H), 1.55–1.40 (m, 3H), 1.38 (s, 9H), 1.33 (m, 2H), 1.13 (m, 9H), 1.07 (m, 1H), 1.02 (m, 3H), 1.01–0.94 (m, 1H). HRMS (ESI-TOF) *m/z* calcd. for $C_{99}H_{122}N_{12}O_{18}$ ($[M+2H]^{2+}$) 883.45001, found 883.44960.



acryloyl-Ala-Tyr(*t*Bu)-Ala

Prepared following the general solid phase synthesis procedure. ^{1}H NMR (500 MHz, CD_3OD) δ 7.18–7.13 (m, 2H), 6.90–6.85 (m, 2H), 6.33–6.20 (m, 2H), 5.68 (dd, *J* = 9.4, 2.6 Hz, 1H), 4.59 (dd, *J* = 9.1, 5.1 Hz, 1H), 4.35 (m, 2H), 3.20–3.13 (m, 1H), 2.94–2.85 (m, 1H), 1.39 (d, *J* = 7.3 Hz, 3H), 1.30 (s, 9H), 1.27 (d, *J* = 7.2 Hz, 3H). HRMS (ESI-TOF) *m/z* calcd. for $C_{22}H_{32}N_3O_6$ ($[M+H]^+$) 434.22911, found 434.22910.

8. Experimental Data for Products



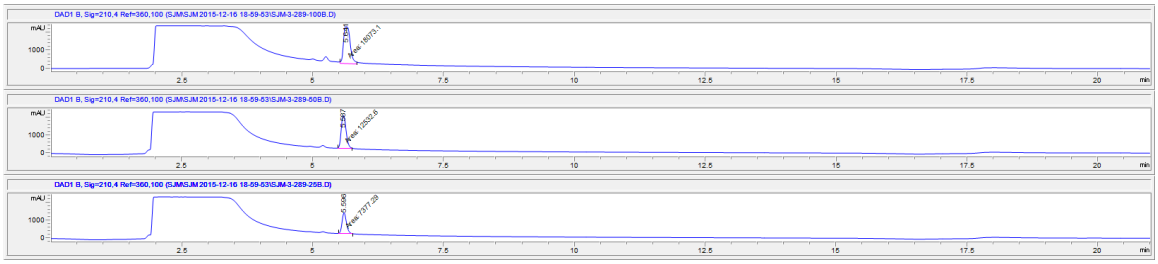
***cyclo*-[Aba-Phe-Leu-Ala-Phe] (7)**

Prepared following the general procedure outlined above using acryloyl-Phe-Leu-Ala-Phe-Gly (6.1 mg, 10 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 6 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 86% by HPLC. The product was purified using solid phase extraction (C18, 2.5 g, 12 mL) rinsing with H_2O (1 column volume) and then eluted with 50% MeCN/H_2O (2 CV). The product was obtained as an off-white solid (4 mg, 7.1 mmol, 71% yield). ^{1}H

NMR (500 MHz, CD_3OD) δ 7.34–7.17 (m, 10H), 4.50 (t, J = 7.8 Hz, 1H), 4.24 (m, 1H), 3.96 (q, J = 7.2 Hz, 1H), 3.81 (m, 1H), 3.37 (m, 1H, H_A), 3.27 (m, 2H), 3.17 (m, 1H, H_A) 3.09 (m, 1H), 3.00 (dd, J = 7.5 Hz, 1H), 2.29 (m, 2H, H_C), 1.92 (q, J = 6.5 Hz, 2H, H_B), 1.80 (m, 1H), 1.52 (m, 1H), 1.28 (d, J = 7.2 Hz, 3H), 1.21–1.09 (m, 1H), 1.00–0.89 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H); HRMS (ESI-TOF) m/z calcd. for $C_{31}H_{42}N_5O_5$ ($[M+H]^+$) 564.31805, found 564.31752.

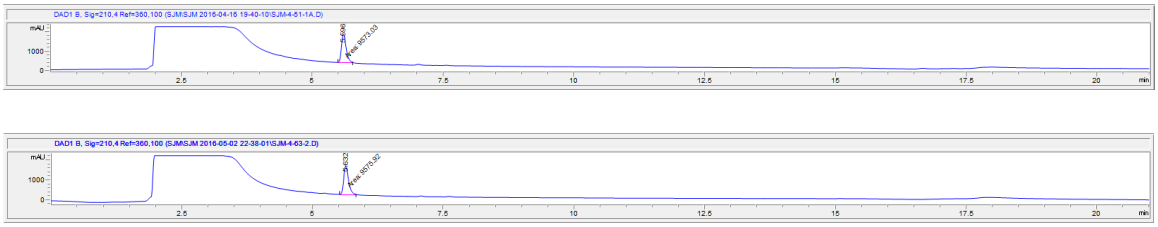
δ H_A 3.37, 3.17; H_B 1.92; H_C 2.29

HPLC Assay Calibration

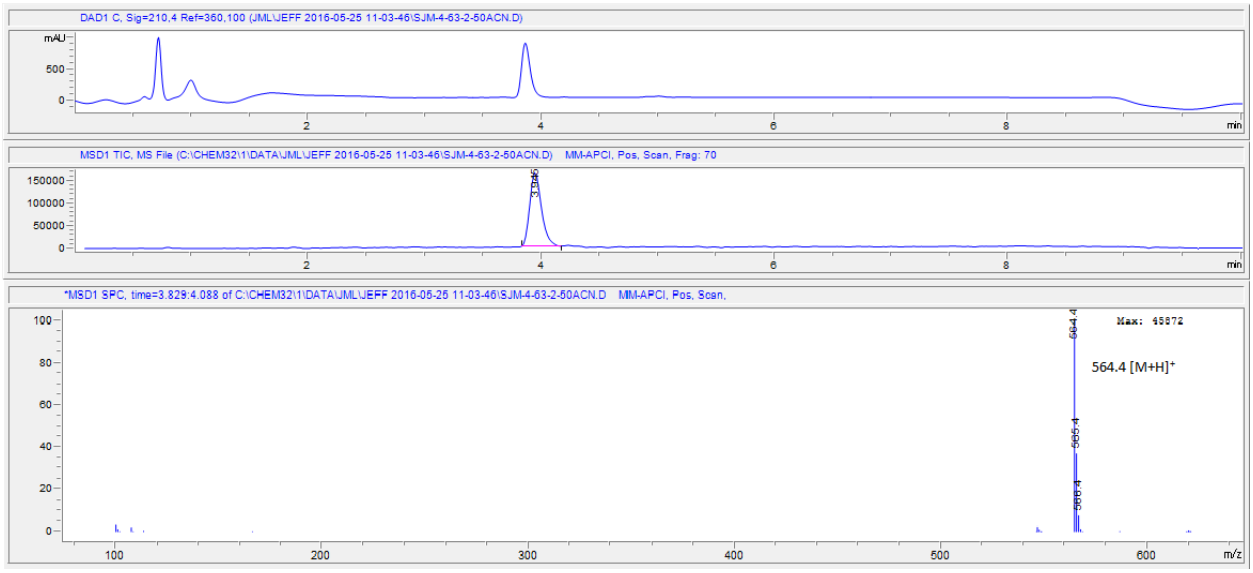


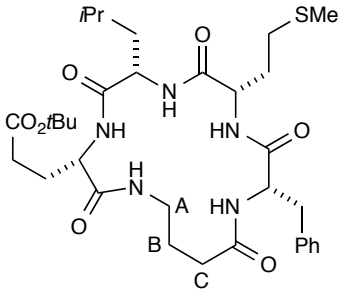
Concentration in DMF: 4.5 mM, 2.25 mM, 1.13 mM.

Reaction HPLC Traces



LCMS data for purified peptide



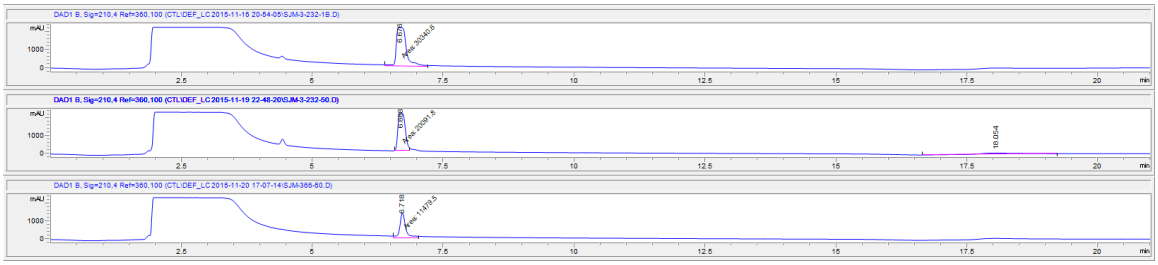


***cyclo*-[Aba-Phe-Met-Leu-Glu(O*t*Bu)] (8)**

Prepared following the general procedure outlined above using acryloyl-Phe-Met-Leu-Glu(*t*Bu)-Gly (7.1 mg, 10 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), 2, 4, 6-triisopropylbenzenethiol (0.24 mg, 1 μmol, 0.1 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 12 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 73%. Preparative HPLC provided the product (2.2 mg, 33%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.35–7.22 (m, 5H), 4.41 (t, J = 7.8 Hz, 1H), 4.26–4.22 (m, 1H), 3.96 (m, 1H), 3.87 (m, 1H), 3.36 (m, 1H, H_A) 3.13 (m, 1H, H_A), 3.07 (m, 1H), 3.03–2.94 (m, 1H), 2.48 (m, 1H), 2.33 (m, 1H), 2.30 (m, 2H, H_C), 2.26 (m, 2H), 2.14 (m, 2H), 2.05 (m, 2H), 2.04–1.96 (m, 2H, H_B), 2.02 (s, 3H), 1.86–1.79 (m, 1H), 1.74 (m, 1H), 1.68–1.60 (m, 1H), 1.46 (s, 9H), 0.95 (m, 6H); HRMS (ESI-TOF) *m*/*z* calcd. for $C_{33}H_{52}N_5O_7S$ ($[M+H]^+$) 662.35820, found 662.35806.

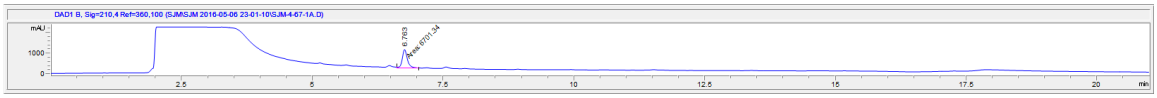
δ H_A 3.36, 3.13; H_B 2.00, 1.83; H_C 2.30

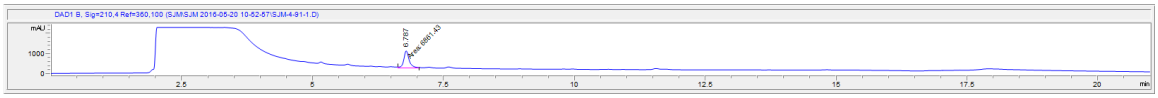
HPLC Assay Calibration



Concentration in DMF: 9.0 mM, 4.5 mM, 2.5 mM.

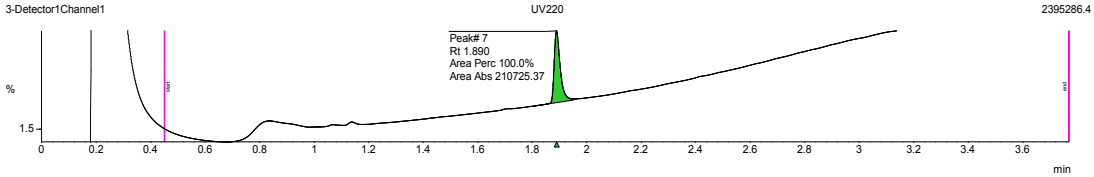
Reaction HPLC Traces

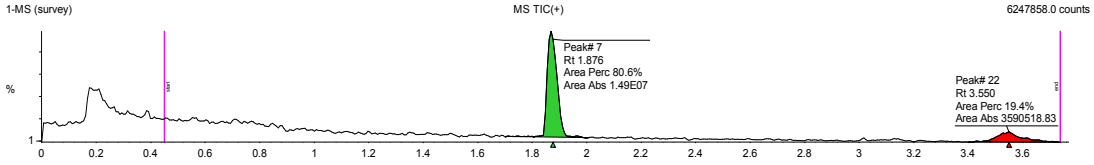


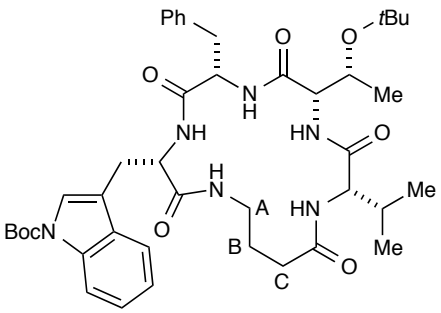


LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Area % Found	Area % UV220	Width50% UV220
2				No	0.0	0.000
3				No	0.0	0.000
6				No	0.0	0.000
7	C33H51N5O7S	661.3509	1.890	Yes	100.0	0.023
10				No	0.0	0.000
11				No	0.0	0.000
13				No	0.0	0.000
16				No	0.0	0.000
20				No	0.0	0.000
22				No	0.0	0.000





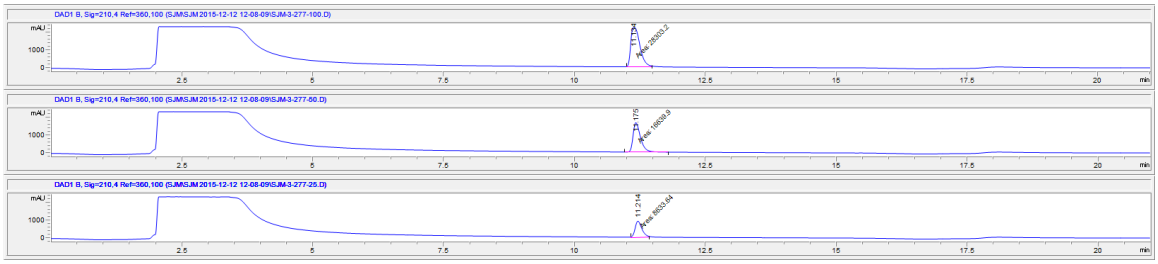


***cyclo*-[Aba-Val-Thr(*t*Bu)-Phe-Trp(Boc)] (9)**

Prepared following the general procedure outlined above using acryloyl-Val-Thr(*t*Bu)-Phe-Trp(Boc)-Gly (8.2 mg, 10 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 12 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 46%. Preparative HPLC provided the product (1.9 mg, 25%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.12 (m, 1H), 7.63 (m, 1H), 7.38 (s, 1H), 7.32 (m, 1H), 7.25 (m, 1H), 7.16–7.03 (m, 5H), 4.28 (m, 1H), 4.19 (m, 2H), 4.13 (m, 1H), 4.09–4.01 (m, 1H), 3.49–3.38 (m, 2H), 3.36–3.26 (m, 2H, H_A), 3.05–2.94 (m, 2H), 2.45 (m, 1H, H_C), 2.27 (m, 1H), 2.23 (m, 1H, H_C), 1.94 (m, 2H, H_B), 1.59 (s, 9H), 1.18 (s, 9H), 1.07 (d, J = 6.5 Hz, 3H), 0.97 (m, 6H); HRMS (ESI-TOF) m/z calcd. for $C_{42}H_{59}N_6O_8$ ([M+H]$^+$) 775.43889, found 775.43881.

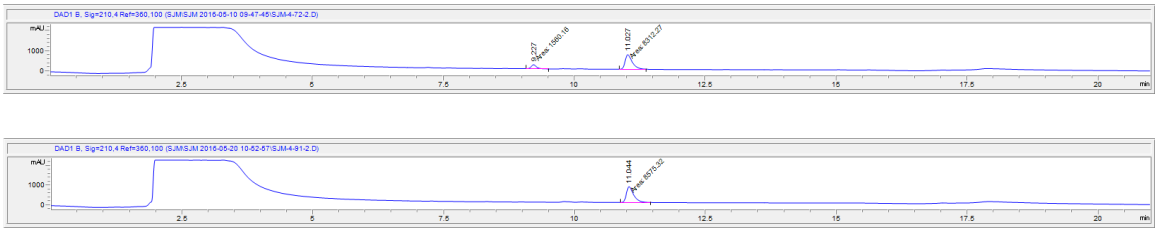
δ H_A 3.30; H_B 1.94; H_C 2.45, 2.23

HPLC Assay Calibration



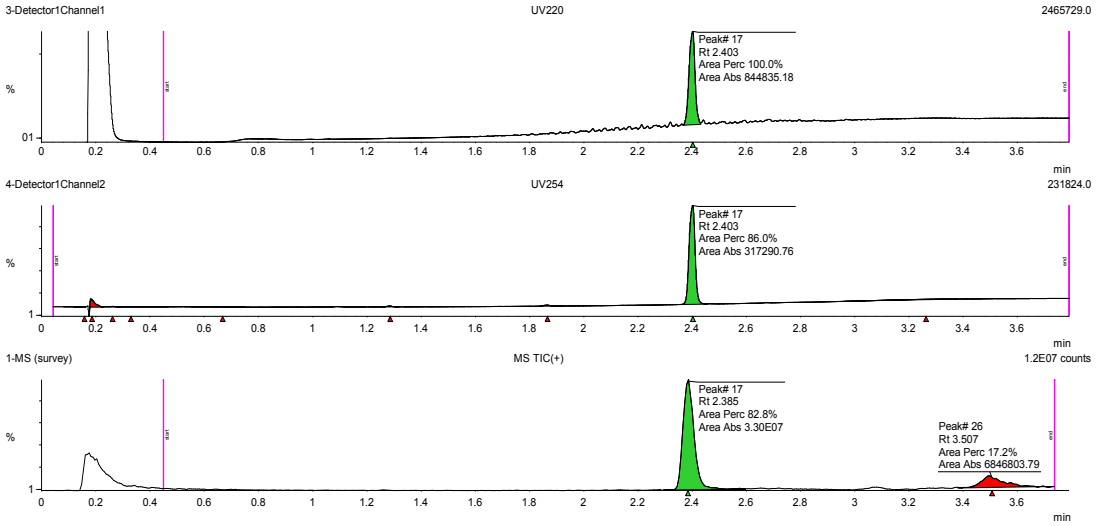
Concentration in DMF: 4.0 mM, 2.0 mM, 1.0 mM.

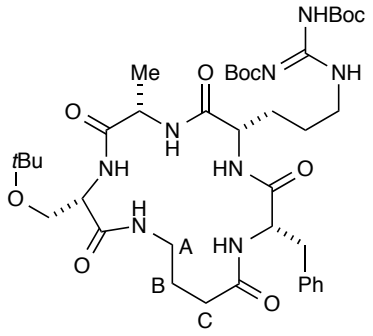
Reaction HPLC Traces



LCMS data for purified peptide

			Time			Area %		Width50%	
Peak #	Formula	Target Mass	UV220	UV254	Found	UV220	UV254	UV220	UV254
2				0.186	No	0.0	5.6	0.000	0.017
3				0.261	No	0.0	1.0	0.000	0.052
4				0.329	No	0.0	1.2	0.000	0.176
5				0.668	No	0.0	1.1	0.000	0.140
17	C42H58N6O8	774.4316	2.403	2.403	Yes	100.0	86.0	0.024	0.024
19					No	0.0	0.0	0.000	0.000
20					No	0.0	0.0	0.000	0.000
21					No	0.0	0.0	0.000	0.000
25				3.263	No	0.0	2.9	0.000	0.068
26					No	0.0	0.0	0.000	0.000





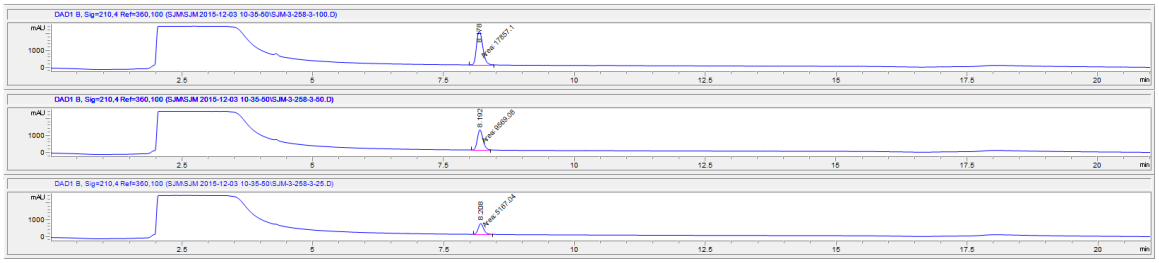
***cyclo*-[Aba-Phe-Arg(Boc)$_2$-Ser(*t*Bu)-Ala] (10)**

Prepared following the general procedure outlined above using acryloyl-Phe-Arg(Boc)$_2$-Ala-Ser(*t*Bu)-Gly (6.5 mg, 7.6 μmol, 1.0 equiv.), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 mg, 2.0 μmol, 0.26 equiv.), K$_2$HPO$_4$ (3.5 mg, 20 μmol, 2.6 equiv.), 2, 4, 6-triisopropylbenzenethiol (0.24 mg, 1 μmol, 0.13 equiv.), H$_2$O (20 μL, 1.1 mmol, 146 equiv), and DMF (4.0 mL). After 16 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H$_2$O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 45%. Preparative HPLC provided the product (2.7 mg, 44%). ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.33–7.19 (m, 5H), 4.50 (t, J = 7.7 Hz, 1H), 4.23 (m, 1H), 4.06 (q, J = 7.2 Hz, 1H), 3.98–3.86 (m, 2H), 3.76 (m, 1H), 3.34 (m, 1H, H$_A$), 3.28 (m, 2H), 3.13 (m, 1H, H$_A$), 3.09 (m, 1H), 2.97 (m, 1H), 2.29 (m, 1H, H$_C$), 2.21 (m, 1H, H$_C$), 1.91 (m, 2H, H$_B$), 1.86 (m, 1H), 1.78 (m, 1H), 1.54 (s, 9H), 1.46 (s,

9H), 1.44–1.38 (m, 1H), 1.35–1.27 (m, 1H), 1.23 (s, 9H), 1.20–1.16 (m, 2H); HRMS (ESI-TOF) *m/z* calcd. for $C_{39}H_{63}N_8O_{10}$ ($[M+H]^+$) 803.46617, found 803.46697.

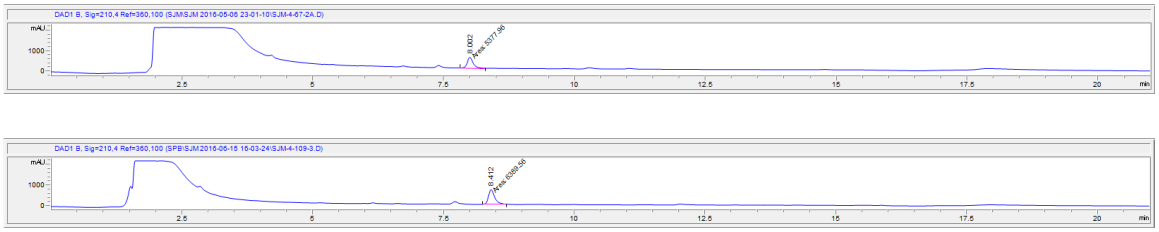
δ H_A 3.34, 3.13; H_B 1.91; H_C 2.29, 2.21

HPLC Assay Calibration



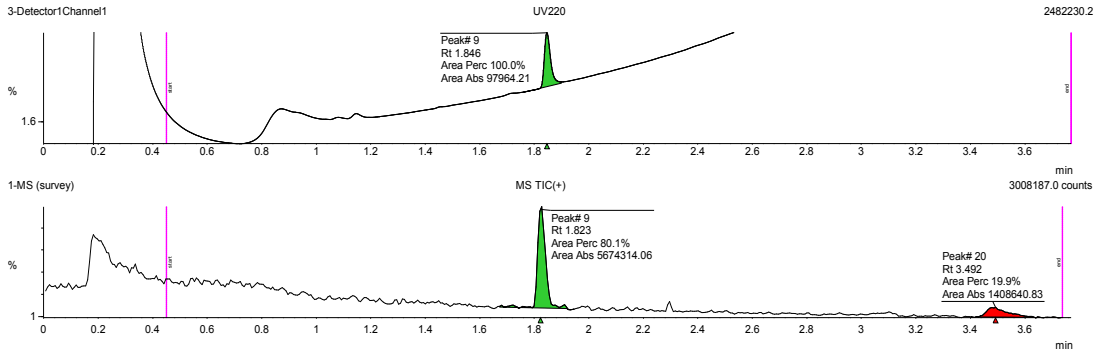
Concentration in DMF: 2.6 mM, 1.3 mM, 0.65 mM.

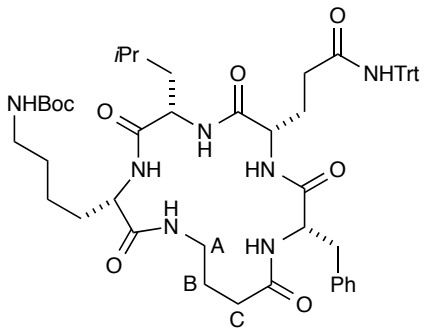
Reaction HPLC Traces



LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Found	Area % UV220	UV220	Width50%
1				No	0.0	0.000	
3				No	0.0	0.000	
6				No	0.0	0.000	
9	C39H62N8O10	802.4589	1.846	Yes	100.0	0.024	
10				No	0.0	0.000	
12				No	0.0	0.000	
16				No	0.0	0.000	
17				No	0.0	0.000	
18				No	0.0	0.000	
20				No	0.0	0.000	



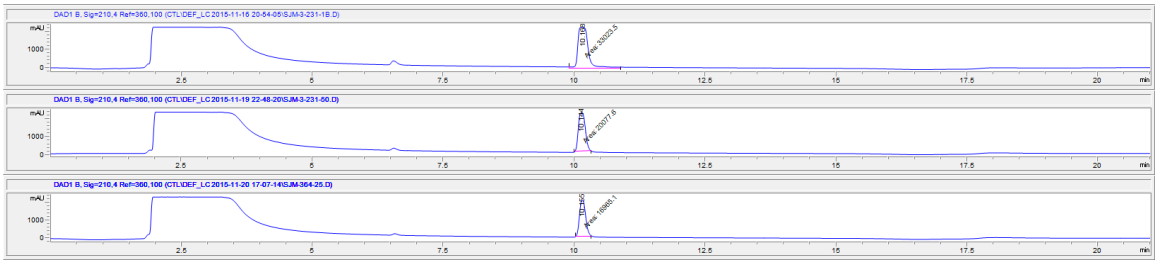


***cyclo*-[Aba-Phe-Gln(Trt)-Leu-Lys(Boc)](11)**

Prepared following the general procedure outlined above using acryloyl-Phe-Gln(Trt)-Leu-Lys(Boc)-Gly (9.9 mg, 10 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 10 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 77%. Preparative HPLC provided the product (4.6 mg, 70%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.33–7.16 (m, 20H), 4.38 (m, 1H), 4.10 (m, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.30 (m, 1H, H_A), 3.15 (m, 1H, H_A), 3.13–2.92 (m, 4H), 2.25 (m, 2H, H_C), 2.22 (m, 2H), 2.15–2.02 (m, 2H), 1.95 (m, 1H, H_B), 1.93 (m, 2H), 1.82 (m, 1H, H_B), 1.78–1.63 (m, 2H), 1.50–1.42 (m, 12H), 1.34–1.29 (m, 1H), 0.95 (m, 6H); HRMS (ESI-TOF) *m/z* calcd. for $C_{54}H_{70}N_7O_8$ ($[M+H]^+$) 944.52084, found 944.52716.

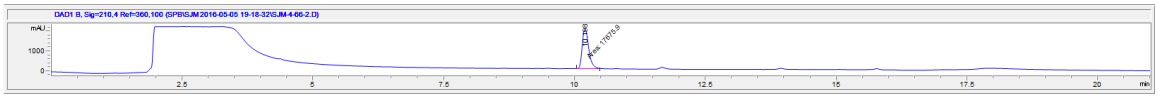
δ H_A 3.30, 3.14; H_B 1.95, 1.82; H_C 2.25

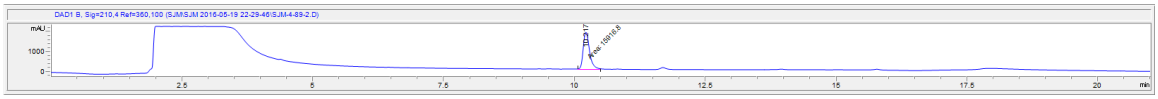
HPLC Assay Calibration



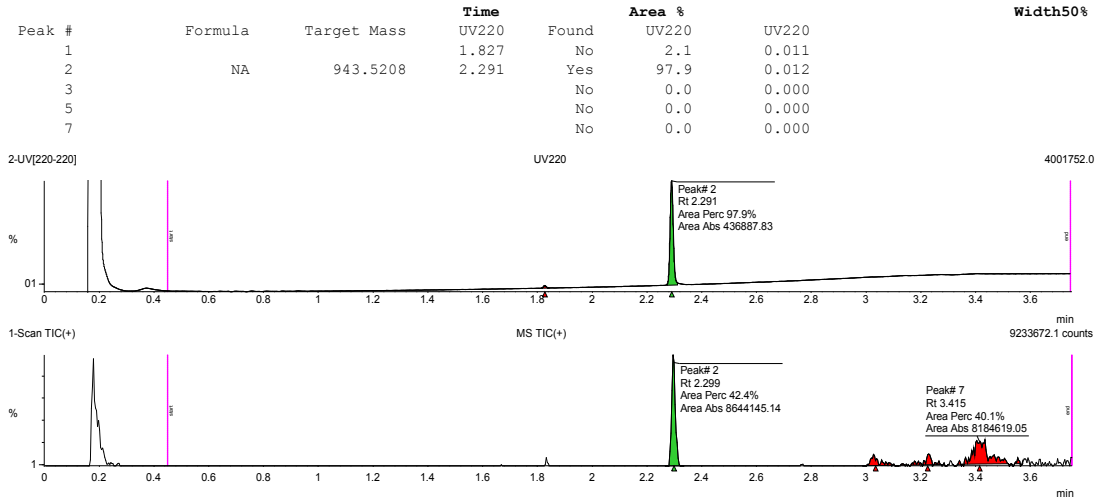
Concentration in DMF: 4.30 mM, 2.15 mM, 1.10 mM.

Reaction HPLC Traces

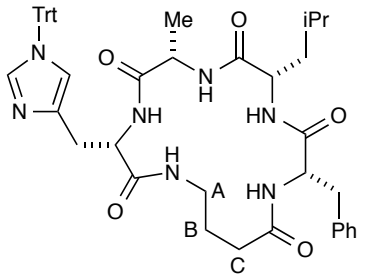




LCMS data for purified peptide



Peak #	Formula	Target Mass	Time UV220	Found	Area % UV220	UV220	Width50%
1			1.827	No	2.1	0.011	
2	NA	943.5208	2.291	Yes	97.9	0.012	
3				No	0.0	0.000	
5				No	0.0	0.000	
7				No	0.0	0.000	

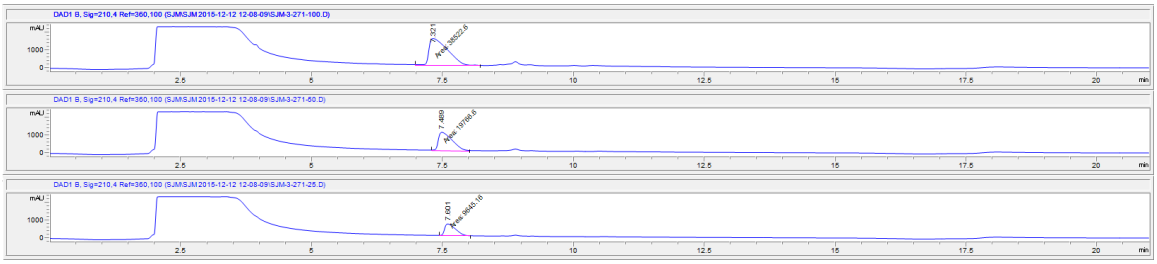


***cyclo*-[Aba-Phe-Leu-Ala-His(Trt)] (12)**

Prepared following the general procedure outlined above using acryloyl-Phe-Leu-Ala-His(Trt)-Gly (6.1 mg, 7.3 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.3 mg, 1.2 μmol, 0.16 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.7 equiv.), H_2O (20 μL, 1.1 mmol, 152 equiv), and DMF (10.0 mL). After 16 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 67%. Preparative HPLC provided the product (1.6 mg, 27%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.40–6.60 (m, 25H), 4.44 (m, 1H), 4.31 (m, 1H), 4.00 (q, J = 7.1, 1H), 3.87 (m, 1H), 3.36 (m, 1H, H_A), 3.18 (m, 2H), 3.14 (m, 1H, H_A), 3.04 (m, 1H), 2.95 (m, 1H), 2.26 (m, 2H, H_C), 1.85 (m, 2H, H_B), 1.75 (m, 1H), 1.54 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H), 1.17 (m, 1H), 0.83 (m, 6H); HRMS (ESI-TOF) m/z calcd. for $C_{47}H_{54}N_7O_5$ ($[M+H]^+$) 796.41809, found 796.41739.

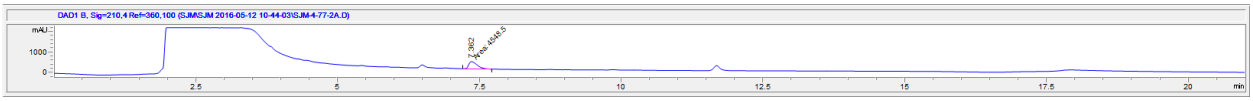
δ H_A 3.36, 3.14; H_B 1.85; H_C 2.26

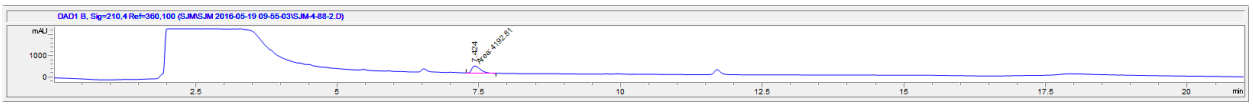
HPLC Assay Calibration



Concentration in DMF: 4.2 mM, 2.1 mM, 1.1 mM.

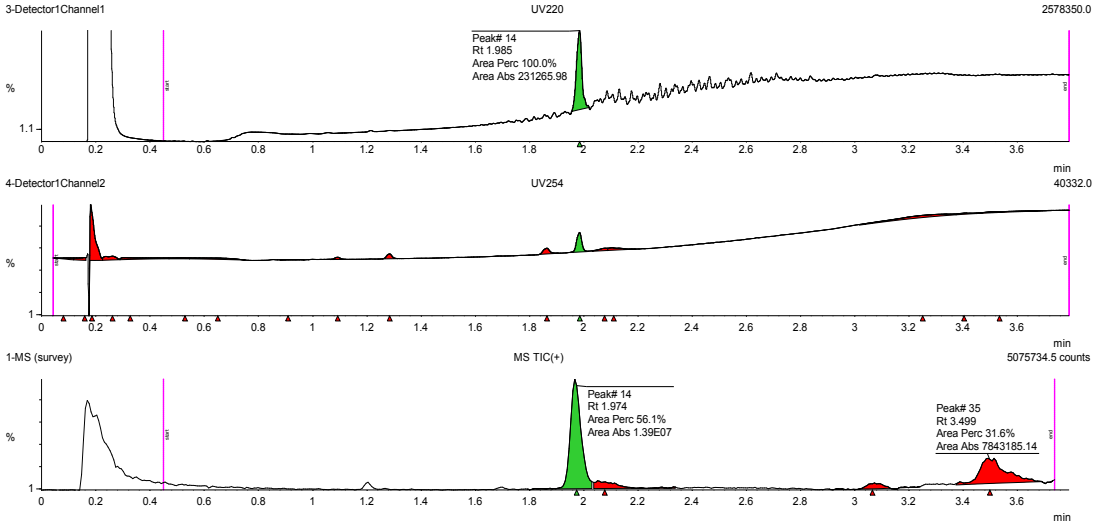
Reaction HPLC Traces

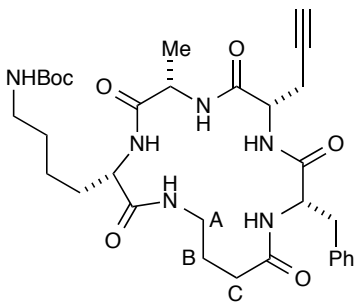




LCMS data for purified peptide

			Time			Area %		Width50%	
Peak #	Formula	Target Mass	UV220	UV254	Found	UV220	UV254	UV220	UV254
3				0.185	No	0.0	30.0	0.000	0.016
4				0.261	No	0.0	5.1	0.000	0.054
5				0.327	No	0.0	6.0	0.000	0.179
7				0.650	No	0.0	5.4	0.000	0.140
13				1.864	No	0.0	4.3	0.000	0.026
14	C47H53N7O5	795.4108	1.985	1.986	Yes	100.0	11.8	0.021	0.021
15				2.077	No	0.0	2.4	0.000	0.030
31					No	0.0	0.0	0.000	0.000
32				3.251	No	0.0	13.7	0.000	0.071
35				3.534	No	0.0	4.3	0.000	0.020





***cyclo*-[Aba-Phe-Pra-Ala-Lys(Boc)] (13)**

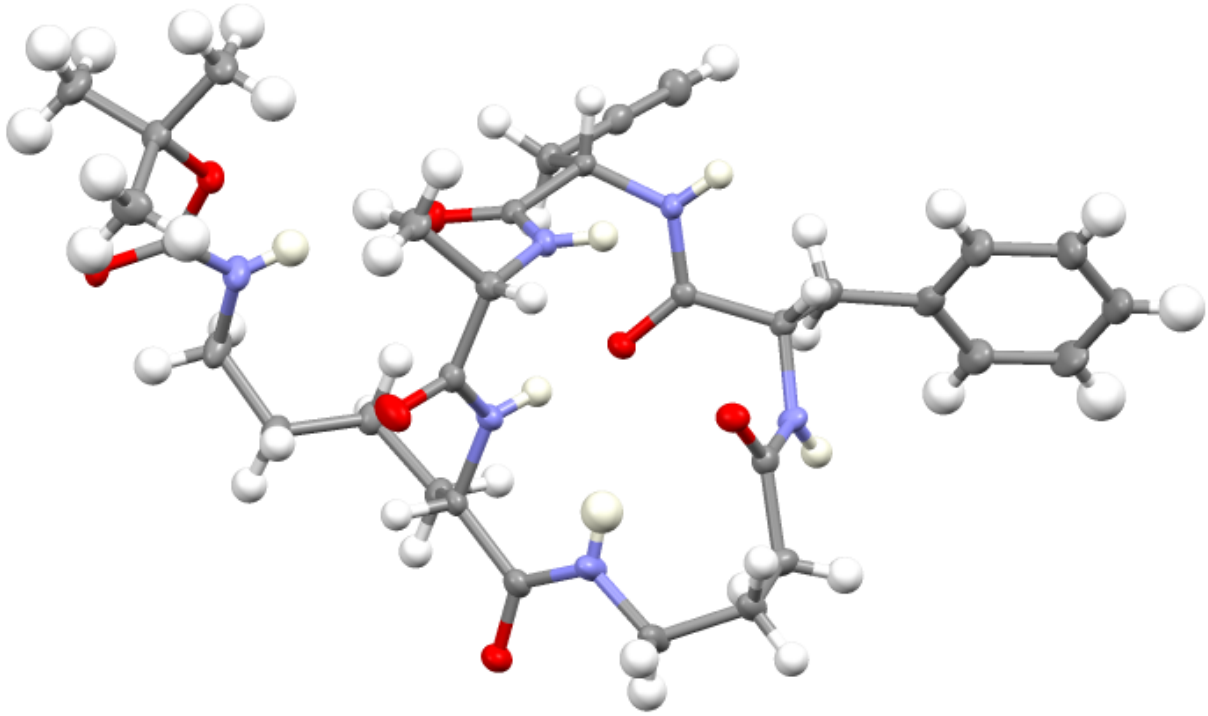
Prepared following the general procedure outlined above using acryloyl-Phe-Pra-Ala-Lys(Boc)-Gly (5.4 mg, 8 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.9 mg, 0.8 μmol, 0.10 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.5 equiv.), H_2O (20 μL, 1.1 mmol, 139 equiv), and DMF (2.0 mL). After 10 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 83%. Preparative HPLC provided the product (3.1 mg, 60%). Rotameric ^1H NMR spectrum. ^1H NMR (500 MHz, CD_3OD) δ 7.38–7.29 (m, 4H), 7.26–7.21 (m, 1H), 4.43 (m, 1H), 4.35 and 4.25 (m, 1H), 3.98 (m, 2H), 3.33 and 3.09 (m, 2H, H_A), 3.28 and 2.90 (m, 2H), 3.07 and 2.95 (m, 2H), 2.93 and 2.81 (m, 2H), 2.40 (apparent dt, J = 2.6 Hz, 1H), 2.26 (m, 2H, H_C), 2.03 and 1.74 (m, 2H, H_B), 1.93 and 1.82 (m, 2H), 1.66 and 1.45 (m, 2H), 1.50 and 1.35 (m, 2H), 1.44 (s, 9H); HRMS (ESI-TOF) m/z calcd. for $C_{32}H_{47}N_6O_7$ ($[M+H]^+$) 627.35007, found 627.34889.

δ H_A 3.33 and 3.09; H_B 2.03 and 1.74; H_C 2.26

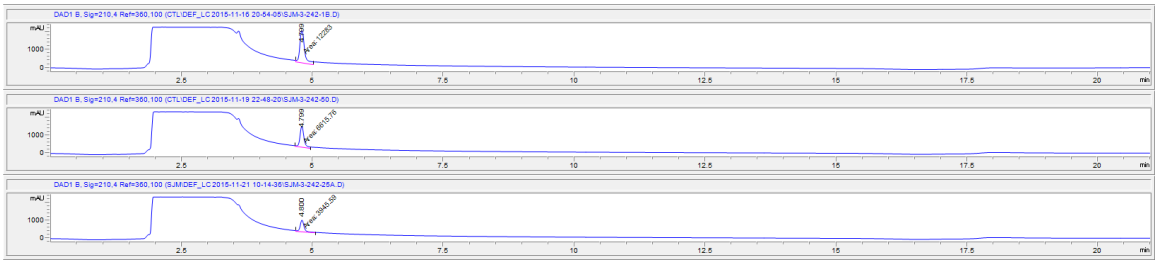
Single crystals of **13** suitable for x-ray diffraction analysis were grown by slow evaporation from CD_3OD in a thin capillary.

A irregular plate-like specimen of $C_{32}H_{40}D_6N_6O_7$, approximate dimensions 0.115 mm x 0.202 mm x 0.314 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 4830 frames were collected. The total exposure time was 18.90 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 26489 reflections to a maximum θ angle of 70.27° (0.82 Å resolution), of which 6934 were independent (average redundancy 3.820, completeness = 98.8%, R_{int} = 2.17%, R_{sig} = 1.88%) and 6837 (98.60%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 9.3343(3) Å, $\underline{b}$ = 23.9338(9)Å, $\underline{c}$ = 9.3939(3) Å, β = 118.3090(11)°, volume = 1847.65(11) $Å^3$, are based upon the refinement of the XYZ-centroids of 132 reflections above 20 σ(I) with 7.373° < 2θ < 79.15°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.853. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8200 and 0.9280.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21 1, with Z = 2 for the formula unit, $C_{32}H_{40}D_6N_6O_7$. The final anisotropic full-matrix least-squares refinement on F^2 with 413 variables converged at R1 = 2.73%, for the observed data and wR2 = 6.96% for all data. The goodness-of-fit was 1.039. The largest peak in the final difference electron density synthesis was 0.200 $e^-/Å^3$ and the largest hole was -0.132 $e^-/Å^3$ with an RMS deviation of 0.031 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.137 g/cm^3 and F(000), 672 e^-.

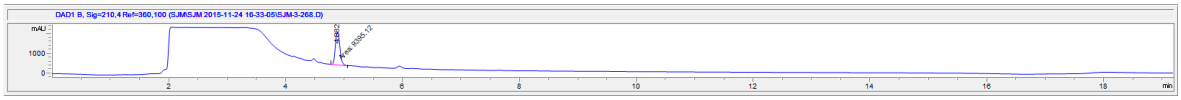


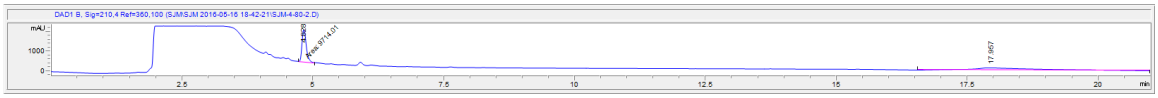
HPLC Assay Calibration



Concentration in DMF: 4.4 mM, 2.2 mM, 1.1 mM.

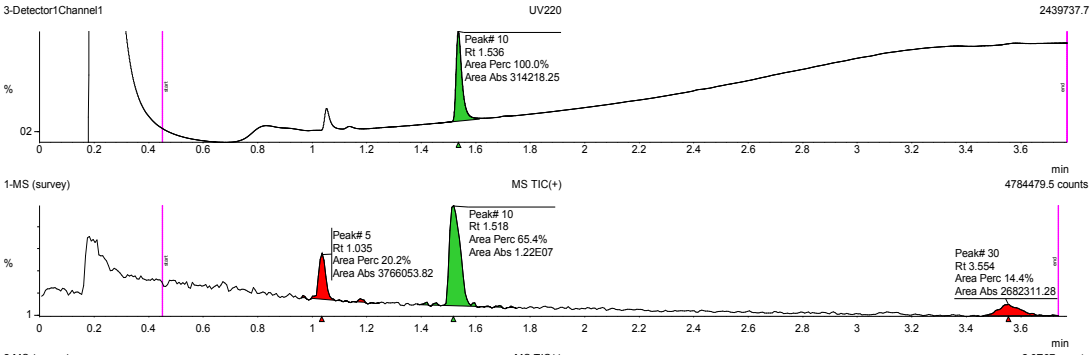
Reaction HPLC Traces

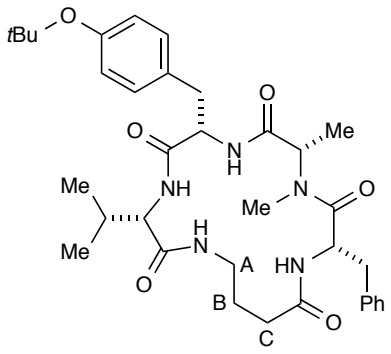




LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Area % Found	Area % UV220	Width50% UV220
1				No	0.0	0.000
5				No	0.0	0.000
6				No	0.0	0.000
10	C32H46N6O7	626.3428	1.536	Yes	100.0	0.022
14				No	0.0	0.000
16				No	0.0	0.000
18				No	0.0	0.000
27				No	0.0	0.000
29				No	0.0	0.000
30				No	0.0	0.000





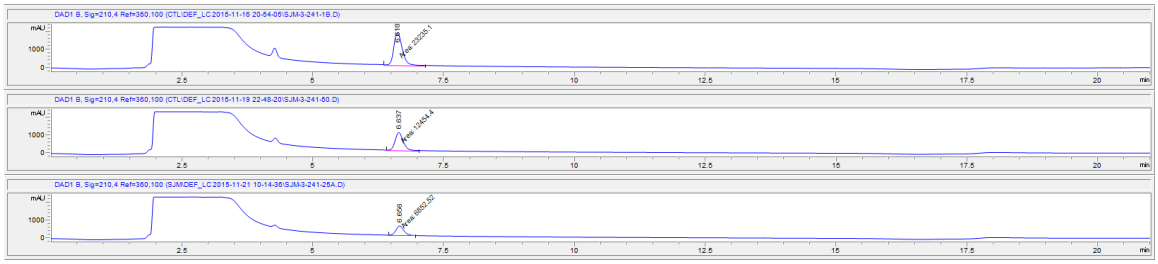
cyclo-[Aba-Phe-(Me)Ala-Tyr(*t*Bu)-Val] (14)

Prepared following the general procedure outlined above using acryloyl-Phe-(Me)Ala-Tyr(*t*Bu)-Val-Gly (3.7 mg, 5.5 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.9 mg, 0.8 μmol, 0.15 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 3.6 equiv.), H_2O (20 μL, 1.1 mmol, 202 equiv), and DMF (2.0 mL). After 10 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 82%. Preparative HPLC provided the product (2.4 mg,

67%). ^{1}H NMR (500 MHz, CD_3OD) NMR spectrum complicated due to the presence of rotamers. δ 7.34–7.19 (m, 5H), 7.17 and 7.13 (d, J = 8.1 Hz, 2H), 6.96 and 6.92 (d, J = 8.1 Hz, 2H), 5.01 and 4.86 (m, 1H), 4.37 and 4.17 (m, 1H), 4.30 (q, J = 6.9 Hz, 1H), 4.15 (m, 1H), 3.37 and 3.09 (m, 1H, H_A), 3.25 (m, 1H, H_A), 3.24 (m, 2H), 2.98 (m, 2H), 2.64 (s, 3H), 2.53 and 2.40 (m, 1H, H_C), 2.40 and 2.37 (m, 1H), 2.31 and 2.21 (m, 1H, H_C), 1.91, (m, 1H, H_B), 1.81 (m, 1H, H_B), 1.34 and 1.32 (s, 9H), 1.06 and 0.88 (apparent dd, J = 6.8 Hz, 6H), 0.40 and 0.36 (d, J = 6.7 Hz, 3H); HRMS (ESI-TOF) m/z calcd. for $C_{35}H_{50}N_5O_6$ ($[M+H]^+$) 636.37556, found 636.37528.

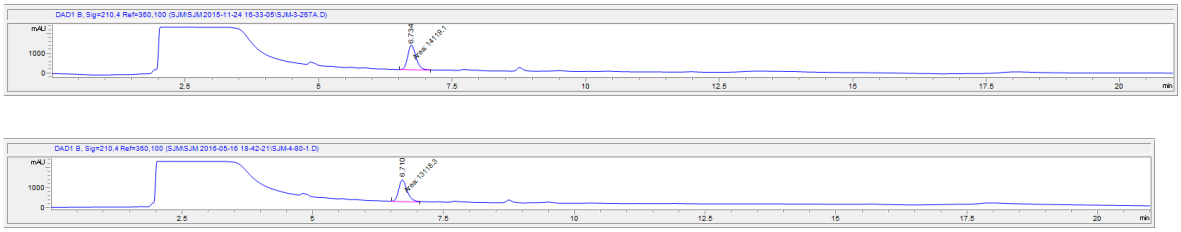
δ H_A 3.37 and 3.09, 3.25; H_B 1.91, 1.81; H_C 2.53 and 2.40, 2.31 and 2.21

HPLC Assay Calibration



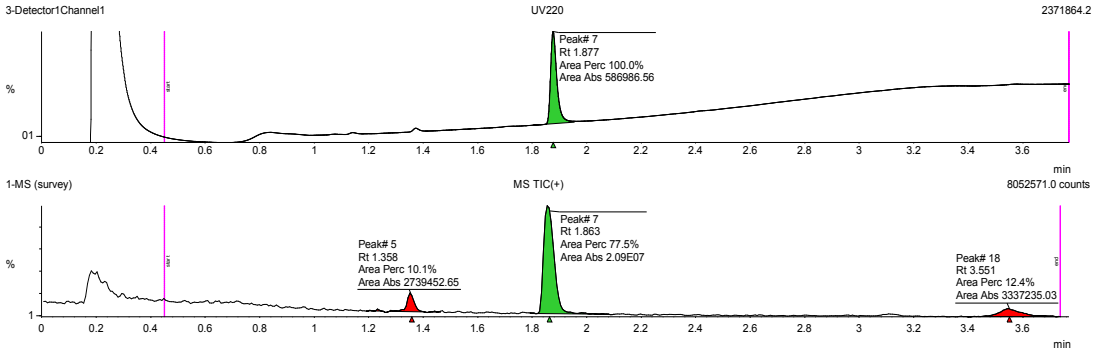
Concentration in DMF: 4.0 mM, 2.0 mM, 1.0 mM.

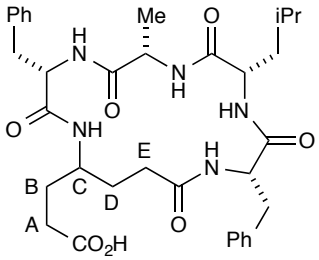
Reaction HPLC Traces



LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Area % Found	Area % UV220	Width50% UV220
2				No	0.0	0.000
4				No	0.0	0.000
5				No	0.0	0.000
6				No	0.0	0.000
7	C35H49N5O6	635.3683	1.877	Yes	100.0	0.023
8				No	0.0	0.000
13				No	0.0	0.000
14				No	0.0	0.000
17				No	0.0	0.000
18				No	0.0	0.000





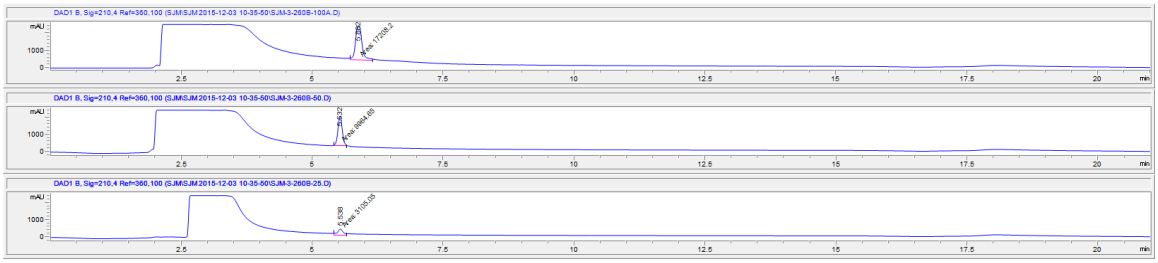
***cyclo*-[Ahda-Phe-Leu-Ala-Phe] (15)**

Prepared following the general procedure outlined above using acryloyl-Phe-Leu-Ala-Phe-Glu•TFA (7.4 mg, 10 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (10.5 mg, 60 μmol, 6.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 12 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 50%. Preparative HPLC provided the product as a mixture of diastereomers (1.6 mg, 25%, 2:1 dr). ^{1}H NMR (500 MHz, CD_3OD) δ Major diastereomer: 7.31–7.18 (m, 10H), 4.56 (m, 1H), 4.06 (m, 1H), 3.83 (m, 2H), 3.68 (m, 1H, H_C), 3.35 (m, 2H), 3.07 (m, 1H), 2.95 (m, 1H), 2.48 (m, 1H, H_A), 2.35 (m, 1H, H_E), 2.31 (m, 1H, H_A), 2.20 (m, 1H, H_E), 2.03 (m, 2H, H_B), 1.99 (m, 1H, H_D), 1.76 (m, 1H, H_D), 1.75 (m, 1H), 1.42 (m, 1H), 1.30 (d, J = 7.1 Hz, 3H), 1.25 (br s, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H) Minor diastereomer: 7.37–7.18 (m, 10H), 4.51 (m, 1H), 4.34 (m, 1H), 4.12 (m, 1H), 3.87 (m, 1H, H_C), 3.73 (m, 1H), 3.25 (m, 2H), 3.07 (m, 1H), 3.00 (m, 1H), 2.34 (m, 1H, H_A), 2.22 (m, 1H, H_A), 2.14 (m, 2H, H_E), 1.87 (m, 1H), 1.84 (m, 2H, H_B), 1.75 (m, 1H, H_D), 1.59 (m, 1H, H_D), 1.49 (m, 1H), 1.29 (d, J = 7.2 Hz, 3H), 1.07 (m, 1H), 0.83 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H); HRMS (ESI-TOF) m/z calcd. for $C_{34}H_{46}N_5O_7$ ($[M+H]^+$) 636.33918, found 636.33862.

Major diastereomer δ H_A 2.48, 2.31; H_B 2.03; H_C 3.69; H_D 1.99, 1.76; H_E 2.35, 2.20

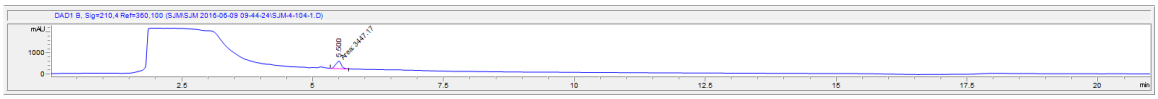
Minor diastereomer δ H_A 2.34, 2.22; H_B 1.84; H_C 3.87; H_D 1.75, 1.59; H_E 2.14

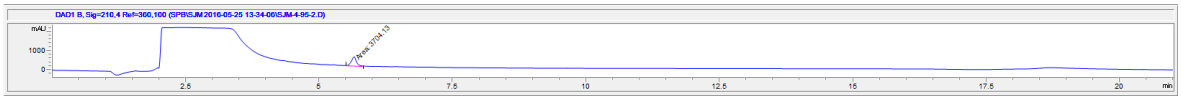
HPLC Assay Calibration



Concentration in DMF: 6.2 mM, 3.1 mM, 1.55 mM.

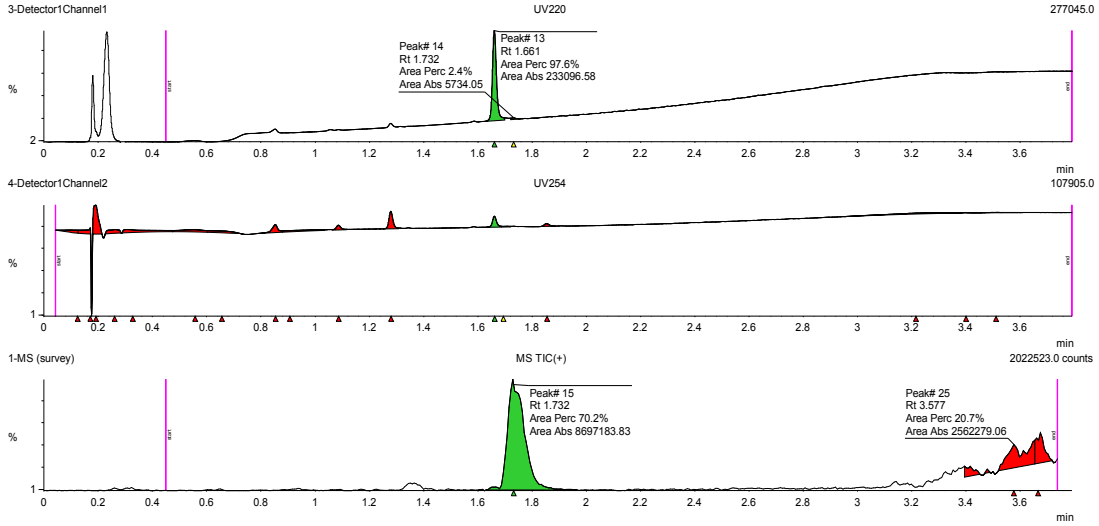
Reaction HPLC Traces

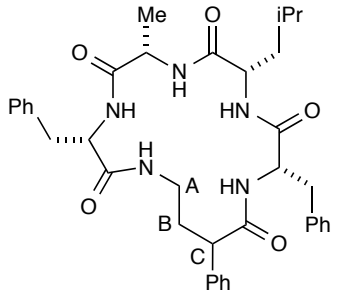




LCMS data for purified peptide

			Time			Area %		Width50%	
Peak #	Formula	Target Mass	UV220	UV254	Found	UV220	UV254	UV220	UV254
3				0.192	No	0.0	19.7	0.000	0.021
5				0.327	No	0.0	10.7	0.000	0.183
6				0.557	No	0.0	7.3	0.000	0.129
12				1.280	No	0.0	9.7	0.000	0.016
13	C34H45N5O7	635.3319	1.661	1.662	Yes	97.6	6.3	0.015	0.016
14			1.732	1.694	No	2.4	0.6	0.028	0.033
15	C34H45N5O7	635.3319			Yes	0.0	0.0	0.000	0.000
21				3.216	No	0.0	6.5	0.000	0.150
25					No	0.0	0.0	0.000	0.000
26					No	0.0	0.0	0.000	0.000





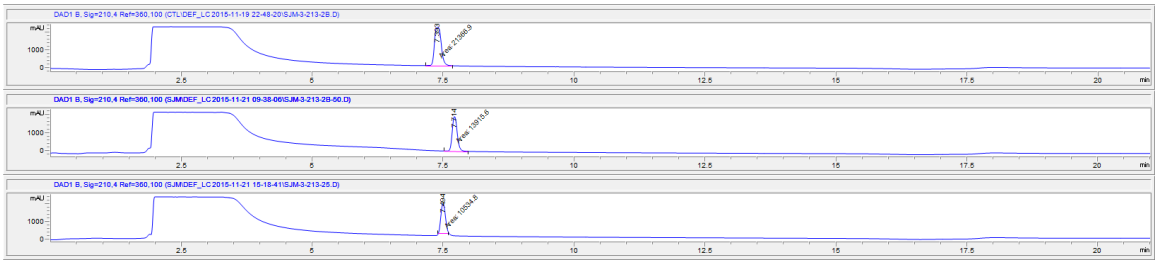
***cyclo*-[Aba(2-Ph)-Phe-Leu-Ala-Phe] (16)**

Prepared following the general procedure outlined above using α-phenylacryloyl-Phe-Leu-Ala-Phe-Gly (6.8 mg, 10 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 6 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 85%, 10:1 dr. Preparative HPLC provided the product (2.6 mg, 41%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.38–7.13 (m, 15H), 4.59 (t, J = 7.9 Hz, 1H), 4.28 (m, 1H), 3.97 (q, J = 7.2 Hz, 1H), 3.80 (m, 1H), 3.53 (m, 1H, H_C), 3.36 (m, 2H), 3.35 (m, 1H, H_A), 3.27 (m, 1H, H_A), 3.03 (m, 1H), 2.89 (m, 1H), 2.24 (m, 1H, H_B), 2.08 (m, 1H, H_B), 1.83 (m, 1H), 1.50 (m, 1H), 1.28 (d,

J = 7.3 Hz, 3H), 1.17 (m, 1H), 0.86 (apparent dd, J = 6.5 Hz, 6H); HRMS (ESI-TOF) *m/z* calcd. for $C_{37}H_{46}N_5O_5$ ([M+H]$^+$) 640.34935, found 640.35003.

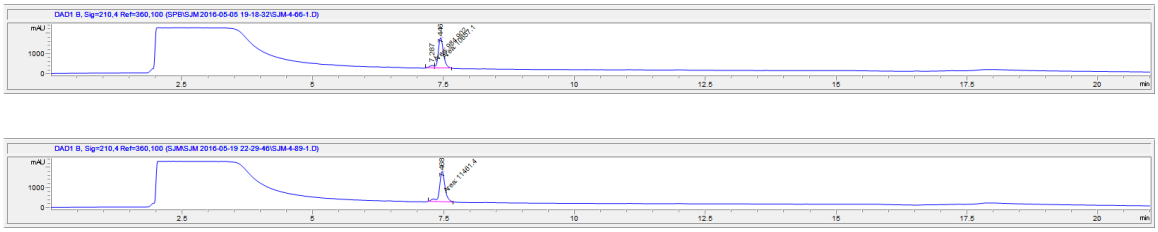
δ H_A 3.35, 3.27; H_B 2.24, 2.08; H_C 3.53

HPLC Assay Calibration



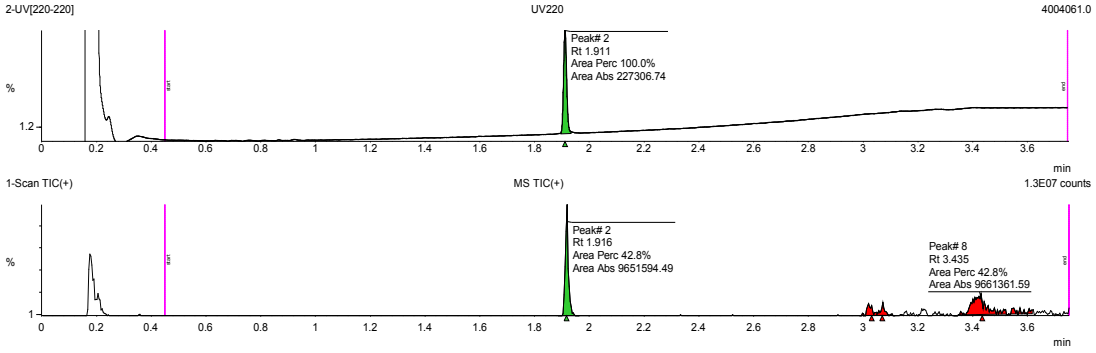
Concentration in DMF: 4.71 mM, 2.35 mM, 1.18 mM.

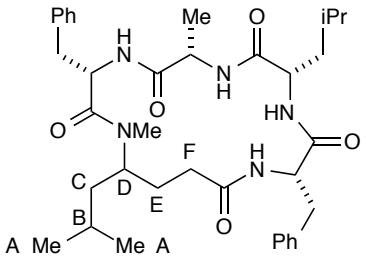
Reaction HPLC Traces



LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Found	Area % UV220	Width50% UV220
2	C37H45N5O5	639.3421	1.911	Yes	100.0	0.012
4				No	0.0	0.000
5				No	0.0	0.000
8				No	0.0	0.000





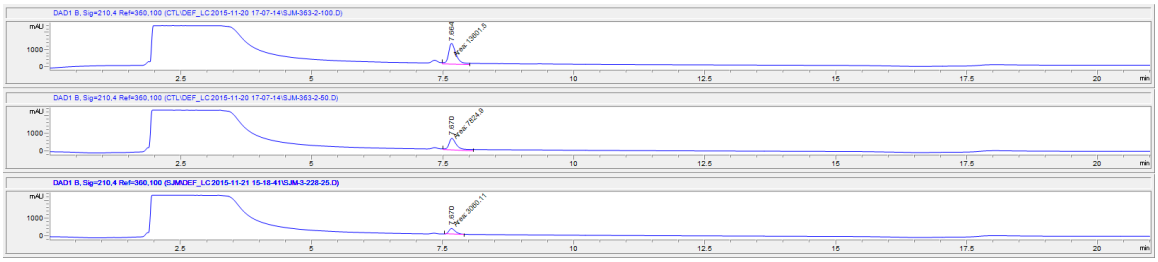
***cyclo*-[(Me)Aba(4-*i*Bu)-Phe-Leu-Ala-Phe] (17)**

Prepared following the general procedure outlined above using acryloyl-Phe-Leu-Ala-Phe-(Me)Leu (5.0 mg, 7.4 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.16 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.7 equiv.), H_2O (20 μL, 1.1 mmol, 150 equiv), and DMF (4.0 mL). After 10 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 51%, 1.6:1 dr. Preparative HPLC provided the product (1.3 mg, 28%). ^{1}H NMR (500 MHz, CD_3OD) Major diastereomer: δ 7.32–7.16 (m, 10H), 4.82 (m, 1H), 4.67 (m, 1H), 4.56 (m, 1H), 4.19 (m, 1H), 3.97 (m, 1H, H_D), 3.08–3.03 (m, 3H), 2.94 (m, 1H), 2.62 (s, 3H), 2.16 (m, 2H, H_F), 1.80 (m, 1H, H_E), 1.77 (m, 1H, H_C), 1.59 (m, 1H, H_C), 1.44–1.32 (m, 4H), 1.30 (m, 1H), 1.19 (m, 1H, H_B), 1.00 (m, 1H), 0.93–0.82 (m, 2H), 0.87 (d, J = 6.6 Hz, 3H, H_A), 0.79 (m, 9H); Minor diastereomer: δ 7.34–7.15 (m, 10H), 4.50 (m, 1H), 4.34 (m, 2H), 4.02 (m, 1H), 3.89 (m, 1H, H_D), 3.21 (m, 1H), 3.10 (m, 2H), 2.96 (m, 1H), 2.67 (s, 3H), 2.35 (m, 1H, H_F), 2.16 (m, 1H, H_F), 1.90 (m, 1H), 1.78 (m, 1H, H_E), 1.63 (m, 1H, H_E), 1.58 (m, 1H, H_C), 1.41 (d, *J* = 7.0 Hz, 3H), 1.40–1.19 (m, 3H), 1.18 (m, 1H, H_B), 0.93–0.77 (m, 6H), 0.90 (m, 3H, H_A), 0.80 (m, 3H, H_A), 0.64 (m, 1H); HRMS (ESI-TOF) *m*/*z* calcd. for $C_{36}H_{52}N_5O_5$ ([M+H]$^+$) 634.39630, found 634.39733.

Major diastereomer δ H_A 0.85, 0.79; H_B 1.19; H_C 1.77, 1.59; H_D 3.97; H_E 2.16

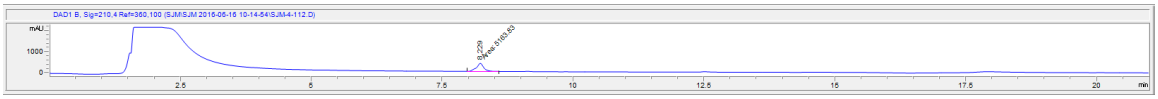
Minor diastereomer δ H_A 0.90, 0.80; H_B 1.18; H_C 1.76, 1.58; H_D 1.78, 1.63; H_E 2.35, 2.16

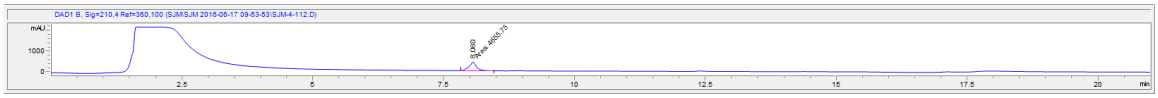
HPLC Assay Calibration



Concentration in DMF: 2.70 mM, 1.35 mM, 0.67 mM.

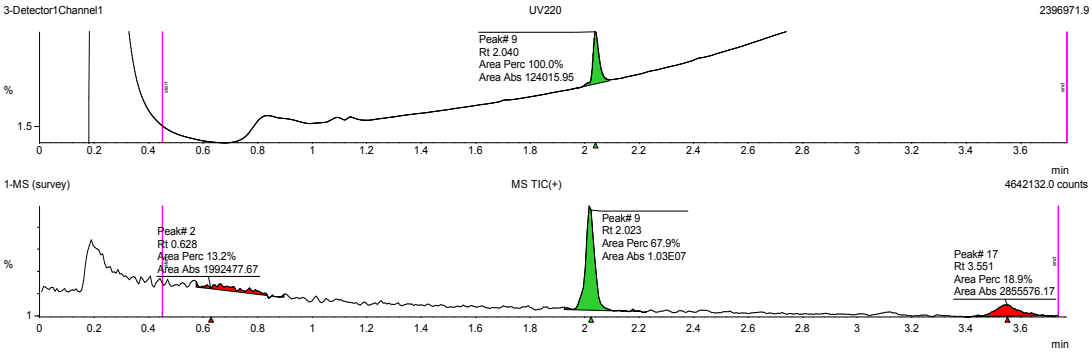
Reaction HPLC Traces

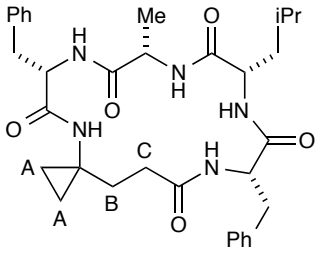




LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Area % Found	Area % UV220	Width50% UV220
1				No	0.0	0.000
2				No	0.0	0.000
3				No	0.0	0.000
4				No	0.0	0.000
8				No	0.0	0.000
9	C36H51N5O5	633.3890	2.040	Yes	100.0	0.023
10				No	0.0	0.000
11				No	0.0	0.000
12				No	0.0	0.000
17				No	0.0	0.000





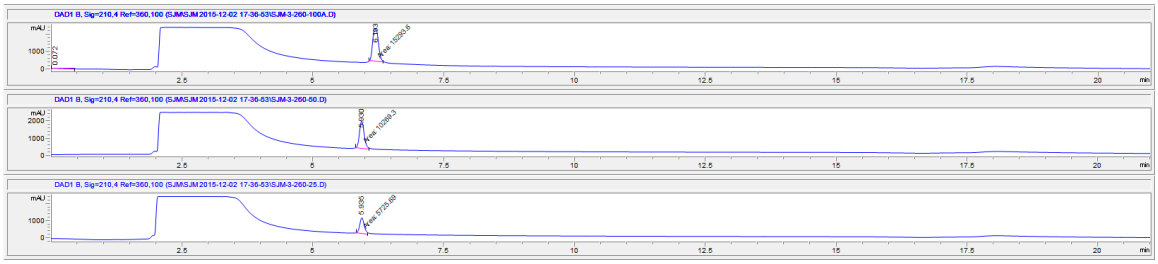
***cyclo*[(3-Ac)pa-Phe-Leu-Ala-Phe] (18)**

Prepared following the general procedure outlined above using acryloyl-Phe-Leu-Ala-Phe-Acc (4.5 mg, 7.2 μmol, 1.0 equiv.), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (1.3 mg, 1.2 μmol, 0.17 equiv.), K$_2$HPO$_4$ (3.5 mg, 20 μmol, 2.8 equiv.), H$_2$O (20 μL, 1.1 mmol, 154 equiv), and DMSO (4.0 mL). After 12 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H$_2$O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 51%. Preparative HPLC provided the product (0.9 mg, 21%). ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.32–7.19 (m, 10H), 4.70 (t, *J* = 7.9 Hz, 1H), 4.09 (m, 1H), 3.86 (q, *J* = 7.3 Hz, 1H), 3.78 (m, 1H), 3.30 (m, 2H), 3.08 (m, 1H), 2.97 (m, 1H), 2.31 (m, 2H, H$_C$), 2.06 (m,

1H, H_B), 1.89 (m, 1H, H_B), 1.85 (m, 1H), 1.44 (m, 1H), 1.24 (d, J = 7.3 Hz, 3H), 1.22 (m, 1H), 0.94 (m, 1H, H_A), 0.91 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H), 0.72 (m, 1H, H_A), 0.60 (m, 2H, H_A); HRMS (ESI-TOF) m/z calcd. for $C_{33}H_{44}N_5O_5$ ($[M+H]^+$) 590.33370, found 590.33304.

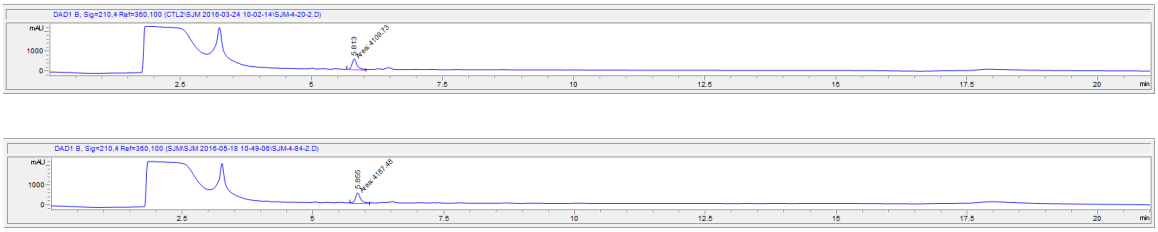
δ H_A 0.94, 0.72, 0.60; H_B 2.06, 1.89; H_C 2.31

HPLC Assay Calibration



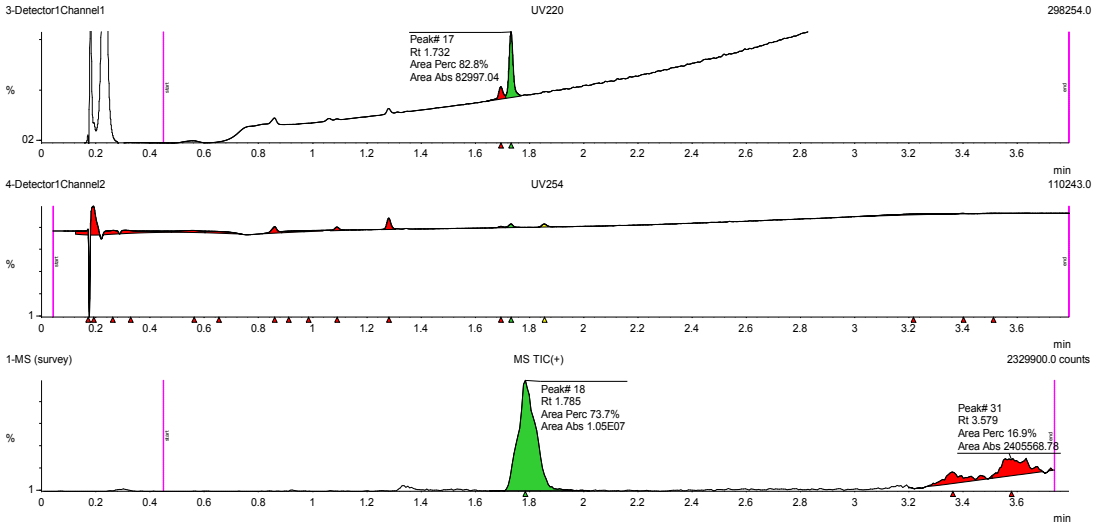
Concentration in DMF: 3.8 mM, 1.9 mM, 0.95 mM.

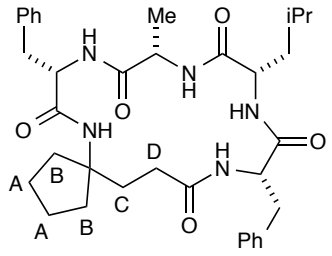
Reaction HPLC Traces



LCMS data for purified peptide

			Time			Area %		Width50%	
Peak #	Formula	Target Mass	UV220	UV254	Found	UV220	UV254	UV220	UV254
2				0.192	No	0.0	22.5	0.000	0.021
4				0.328	No	0.0	12.8	0.000	0.185
15					No	0.0	0.0	0.000	0.000
16			1.695	1.695	No	17.2	1.1	0.017	0.018
17	C33H43N5O5	589.3264	1.732	1.732	Yes	82.8	2.6	0.016	0.017
18	C33H43N5O5	589.3264			Yes	0.0	0.0	0.000	0.000
19				1.856	No	0.0	2.4	0.000	0.020
27					No	0.0	0.0	0.000	0.000
31					No	0.0	0.0	0.000	0.000
32					No	0.0	0.0	0.000	0.000



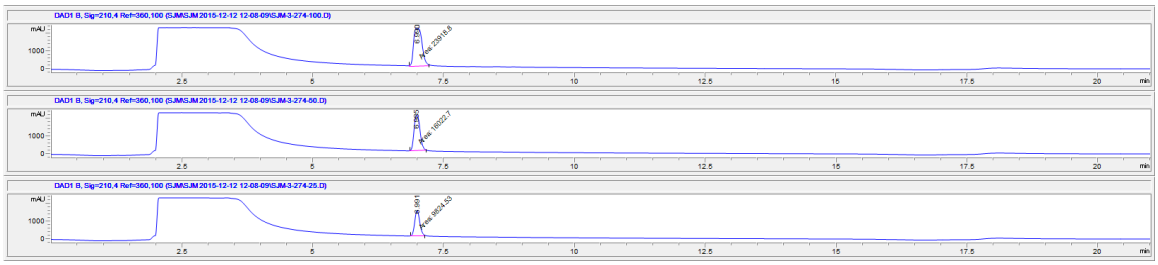


***cyclo*[(3-Acp)pa-Phe-Leu-Ala-Phe] (19)**

Prepared following the general procedure outlined above using acryloyl-Phe-Leu-Ala-Phe-Acpc (6.6 mg, 10 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMSO (4.0 mL). After 12 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 56%. Preparative HPLC provided the product (3.2 mg, 51%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.33–7.18 (m, 10H), 4.65 (t, J = 7.8 Hz, 1H), 4.16 (m, 1H), 3.94 (q, J = 7.2 Hz, 1H), 3.68 (m, 1H), 3.31–3.27 (m, 1H), 3.22 (m, 1H), 3.07–2.96 (m, 2H), 2.32 (m, 1H, HD), 2.30 (m, 1H, HA), 2.25 (m, 1H, HD), 2.18 (m, 1H, HC), 2.11 (m, 1H, HC), 2.07 (m, 1H, HB), 1.27 (d, J = 7.3 Hz, 3H), 1.19–1.09 (m, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H); HRMS (ESI-TOF) m/z calcd. for $C_{35}H_{47}N_5O_5$ ([M+H]$^+$) 618.36500, found 618.36465.

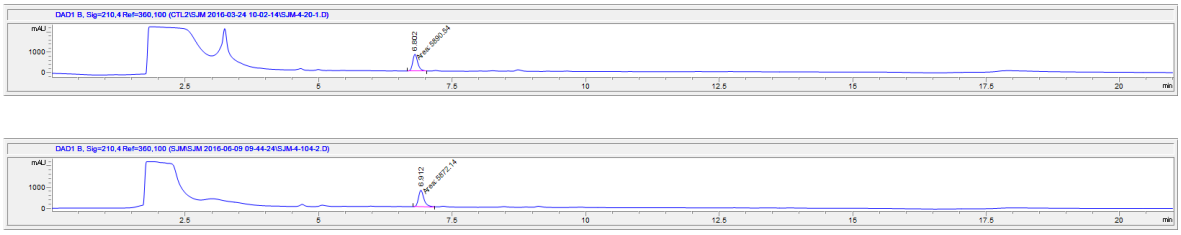
δ H_A 2.30, 1.55, 1.45; H_B 2.07, 1.78, 1.58; H_C 2.18, 2.11; H_D 2.32, 2.25

HPLC Assay Calibration



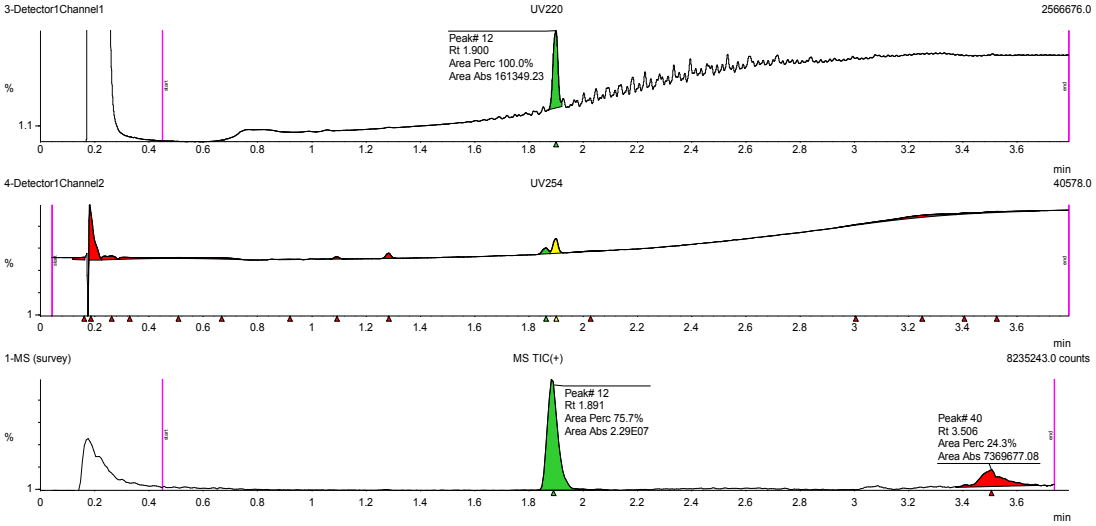
Concentration in DMF: 6.4 mM, 3.2 mM, 1.6 mM.

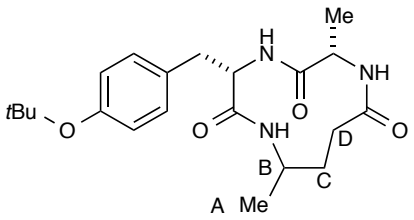
Reaction HPLC Traces



LCMS data for purified peptide

			Time			Area %		Width50%	
Peak #	Formula	Target Mass	UV220	UV254	Found	UV220	UV254	UV220	UV254
2				0.185	No	0.0	33.1	0.000	0.016
3				0.262	No	0.0	5.7	0.000	0.053
4				0.328	No	0.0	6.9	0.000	0.180
6				0.668	No	0.0	6.0	0.000	0.141
11				1.284	No	0.0	3.6	0.000	0.021
12	C35H47N5O5	617.3577	1.900	1.863	Yes	100.0	4.5	0.020	0.026
13				1.901	No	0.0	10.2	0.000	0.021
26					No	0.0	0.0	0.000	0.000
37				3.250	No	0.0	14.5	0.000	0.075
40				3.526	No	0.0	4.0	0.000	0.020



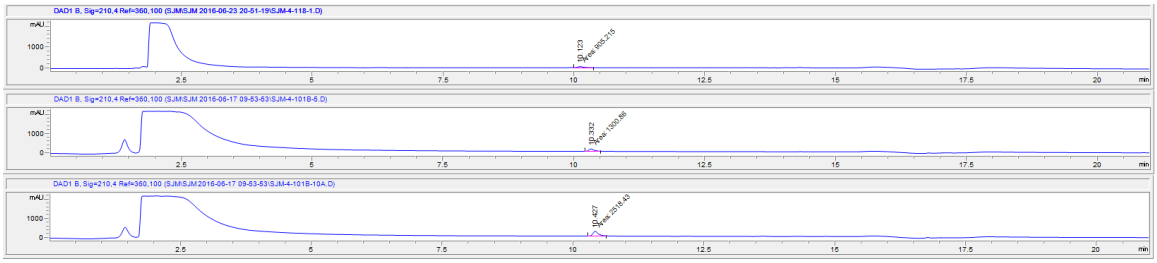


***cyclo*-[Aba(4-Me)-Ala-Tyr(*t*Bu)] (20)**

Prepared following the general procedure outlined above using acryloyl-Ala-Tyr(*t*Bu)-Ala (2.5 mg, 5.8 μmol, 1.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.8 mg, 1.6 μmol, 0.28 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 3.4 equiv.), and DMF (20.0 mL). After 20 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 10-50% $MeCN/H_2O$ + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 36%, 4.3:1 dr. Preparative HPLC provided the product (0.5 mg, 22%). ^1H NMR (500 MHz, CD_3OD) δ 7.20 (2H), 6.93 (2H), 4.69 (1H), 4.05 (1H, H_B), 3.97 (1H), 2.90 (2H), 2.18 (1H, H_D), 2.14 (1H, H_D), 1.92 (1H, H_C), 1.77 (1H, H_C), 1.32 (9H), 1.14 (3H), 1.01 (3H, H_A); HRMS (ESI-TOF) *m*/*z* calcd. for $C_{21}H_{32}N_3O_4$ ($[M+H]^+$) 390.23928, found 390.23918.

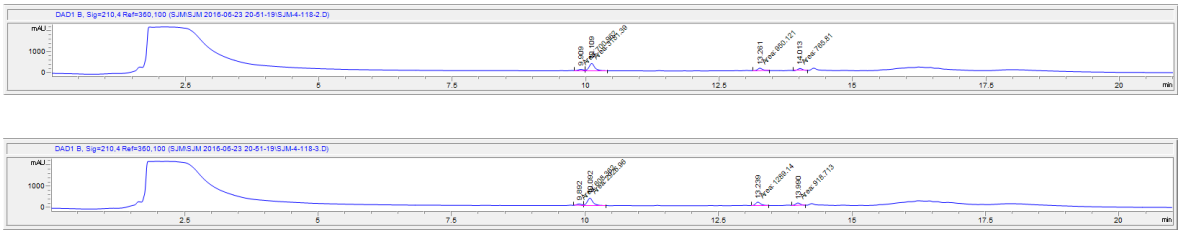
δ H_A 1.01; H_B 4.05; H_C 1.92, 1.77; H_D 2.18, 2.14

HPLC Assay Calibration

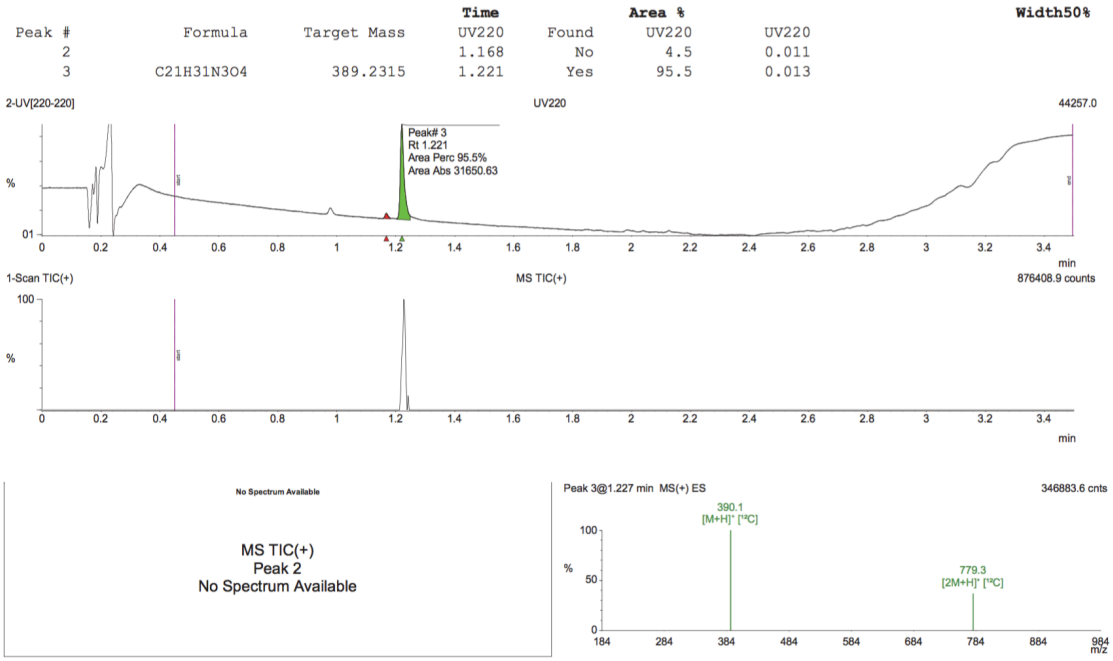


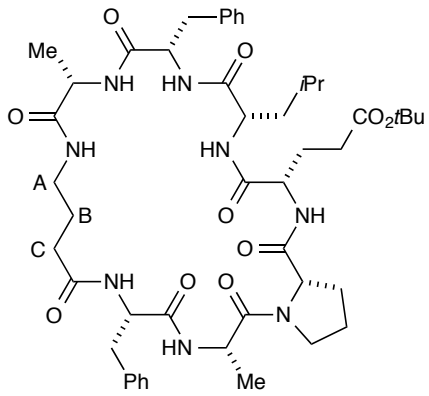
Concentration in DMF: 1.33 mM, 0.65 mM, 0.55 mM.

Reaction HPLC Trace: Product concentration



LCMS data for purified peptide





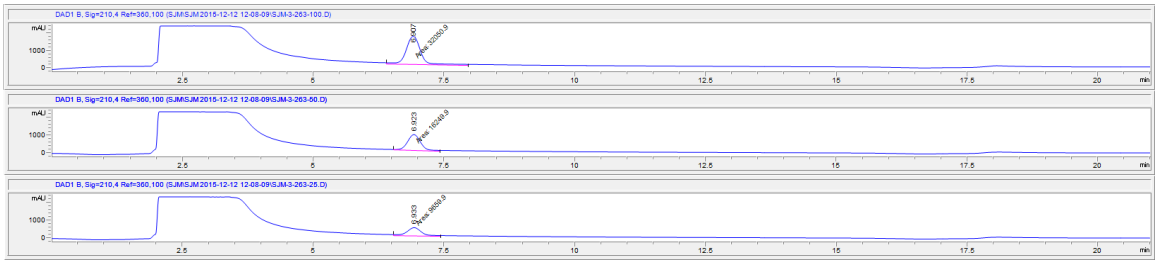
***cyclo*-[Aba-Phe-Leu-Ala-Phe] (21)**

Prepared following the general procedure outlined above using acryloyl-Phe-Ala-Pro-Glu(O*t*Bu)-Leu-Phe-Ala-Gly (9.6 mg, 10 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), 2, 4, 6-triisopropylbenzenethiol (0.24 mg, 1 μmol, 0.1 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 16 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 52%. Preparative HPLC provided the product (3.8 mg, 41%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.31–7.15 (m, 10H), 4.93 (m, 1H), 4.70 (m, 1H), 4.61 (m, 1H), 4.52 (m, 1H), 4.40–4.30 (m, 1.4H), 4.15–4.06 (m, 1.6H), 4.04–3.98 (m, 1H), 3.81 (m, 0.4H), 3.63 (m, 1H), 3.56 (m, 1H, H_A), 3.54 (m, 0.6 H), 3.34 (m, 2.4H), 3.14 (m, 1H), 2.91 (m, 1H, H_A), 2.79 (m, 1H), 2.40 (m, 1H, H_B), 2.35 (m, 1H, H_B),

, 2.27 (m, 1H), 2.19 (m, 1H), 2.07 (m, 1H), 1.93 (m, 2H, H_C), 2.03 and 1.82 (m, 2H, H_B), 1.96 (m, 2H), 1.83 and 1.63 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.53 and 1.38 (m, 1H), 1.48 and 1.46 (s, 9H), 1.36 and 1.32 (d, J = 7.1 Hz, 3H), 1.30 and 1.28 (d, J = 6.9 Hz, 3H), 0.92 and 0.91 and 0.88 and 0.80 (d, J = 6.5 Hz, 6H); HRMS (ESI-TOF) m/z calcd. for $C_{48}H_{69}N_8O_{10}$ ($[M+H]^+$) 917.51312, found 917.51229.

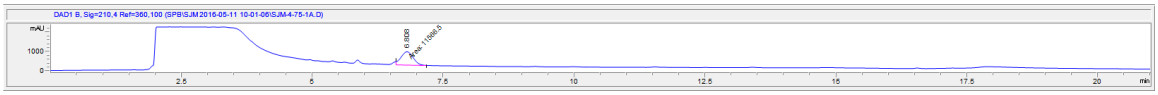
δ H_A 3.56, 2.91; H_B 2.40, 2.35; H_C 1.93

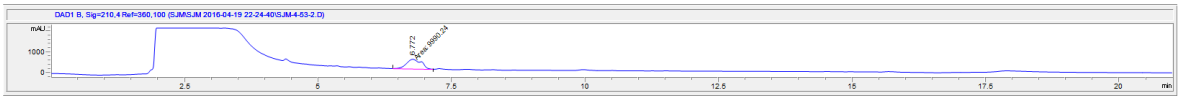
HPLC Assay Calibration



Concentration in DMF: 3.9 mM, 1.96 mM, 0.98 mM.

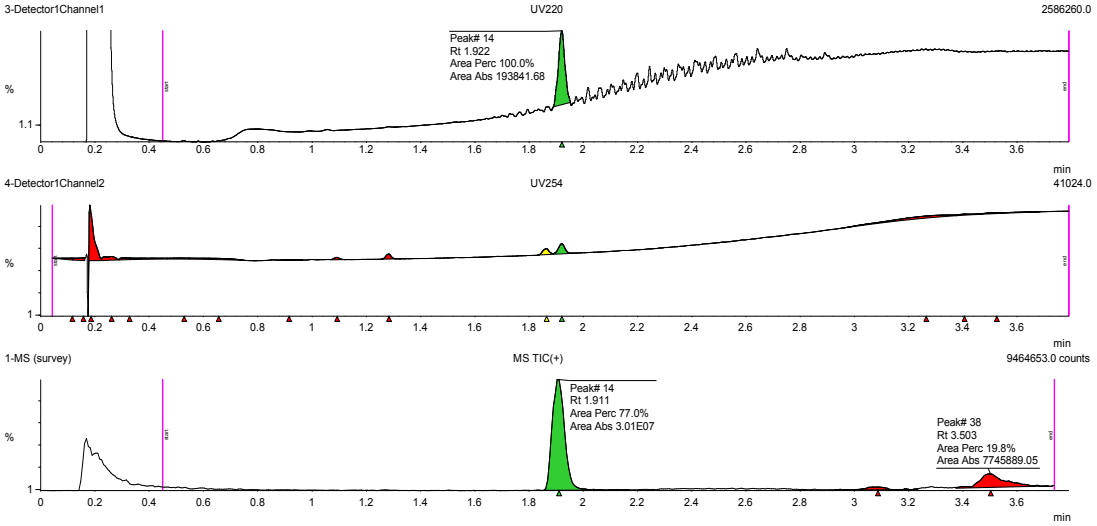
Reaction HPLC Traces

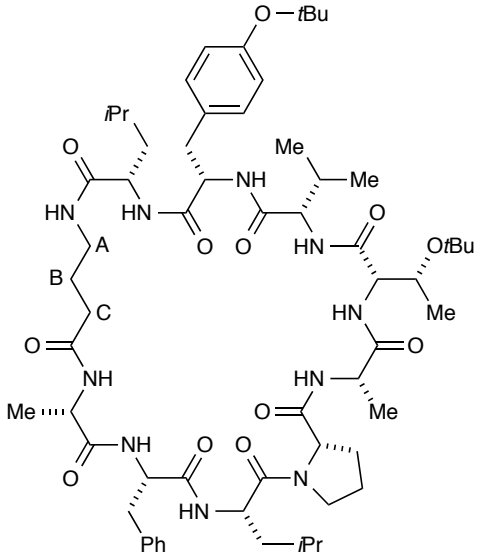




LCMS data for purified peptide

			Time			Area %		Width50%	
Peak #	Formula	Target Mass	UV220	UV254	Found	UV220	UV254	UV220	UV254
3				0.185	No	0.0	33.3	0.000	0.016
4				0.261	No	0.0	5.6	0.000	0.054
5				0.327	No	0.0	6.5	0.000	0.175
7				0.656	No	0.0	6.0	0.000	0.137
12				1.284	No	0.0	3.6	0.000	0.022
13				1.865	No	0.0	5.0	0.000	0.026
14	C48H68N8O10	916.5058	1.922	1.921	Yes	100.0	8.8	0.026	0.026
33					No	0.0	0.0	0.000	0.000
35				3.265	No	0.0	15.7	0.000	0.070
38				3.525	No	0.0	4.3	0.000	0.029





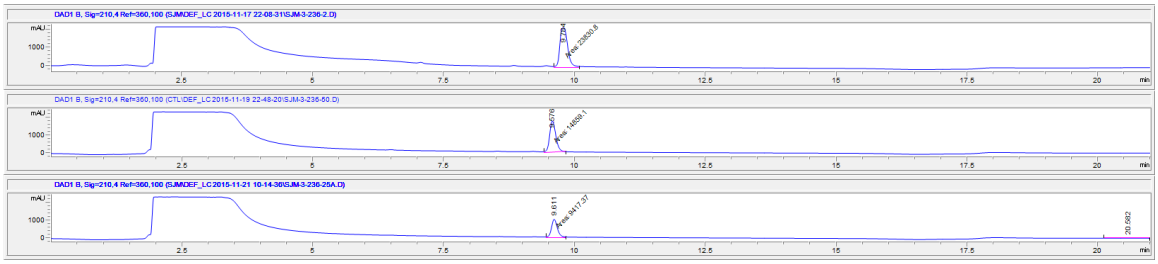
***cyclo*-[Aba-Ala-Phe-Leu-Pro-Ala-Thr(*t*Bu)-Val-Tyr(*t*Bu)-Leu] (22)**

Prepared following the general procedure outlined above using acryloyl-Ala-Phe-Leu-Pro-Ala-Thr(*t*Bu)-Val-Tyr(*t*Bu)-Leu-Gly (12.2 mg, 10 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.3 mg, 1.2 μmol, 0.12 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.0 equiv.), H_2O (20 μL, 1.1 mmol, 111 equiv), and DMF (4.0 mL). After 16 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 55%. Preparative HPLC

provided the product (3.2 mg, 27%). ^{1}H NMR (500 MHz, CD_3OD) NMR spectrum is complicated by the presence of rotamers. δ 77.29–7.19 (m, 5H), 7.18–7.14 (m, 2H), 6.87 (m, 2H), 4.82 (q, J = 7.2 Hz, 1H), 4.71 (q, J = 7.7 Hz, 1H), 4.68–4.62 (m, 1H), 4.58–4.47 (m, 1H), 4.39 (t, J = 7.1 Hz, 1H), 4.34 (m, 1H), 4.32–4.24 (m, 2H), 4.12 (q, J = 7.0 Hz, 1H), 3.81–3.74 (m, 1H), 3.66 (m, 1H), 3.46 (m, 1H, H_A), 3.17 (m, 2H), 3.03–2.88 (m, 2H), 2.95 (m, 1H, H_A), 2.38 (m, 1H, H_C), 2.28 (m, 2H), 2.12 (m, 1H, H_C), 1.99 (m, 3H), 1.94 (m, 1H), 1.82 (m, 1H, H_B), 1.70 (m, 1H, H_B), 1.76–1.61 (m, 4H), 1.59 (t, J = 7.1 Hz, 2H), 1.46 (d, J = 7.2 Hz, 2H), 1.31 (s, 9H), 1.29 (s, 9H), 1.04–0.86 (m, 18H); HRMS (ESI-TOF) m/z calcd. for $C_{62}H_{97}N_{10}O_{12}$ ($[M+H]^+$) 1173.72820, found 1173.72778.

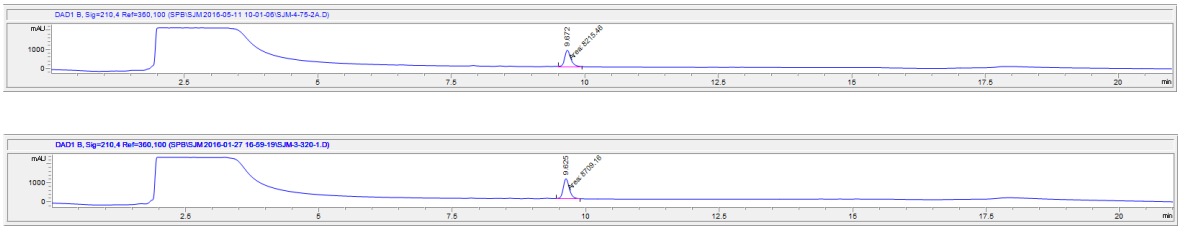
δ H_A 3.46, 2.95; H_B 1.82, 1.70; H_C 2.38, 2.12

HPLC Assay Calibration



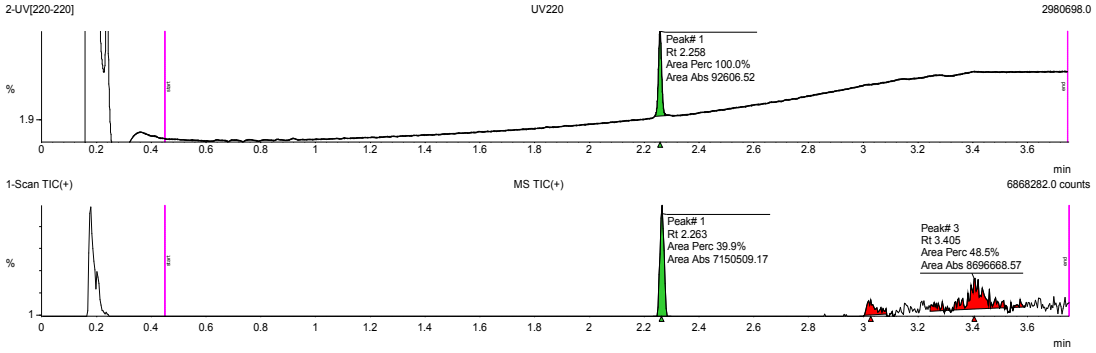
Concentration in DMF: 4.4 mM, 2.2 mM, 1.1 mM.

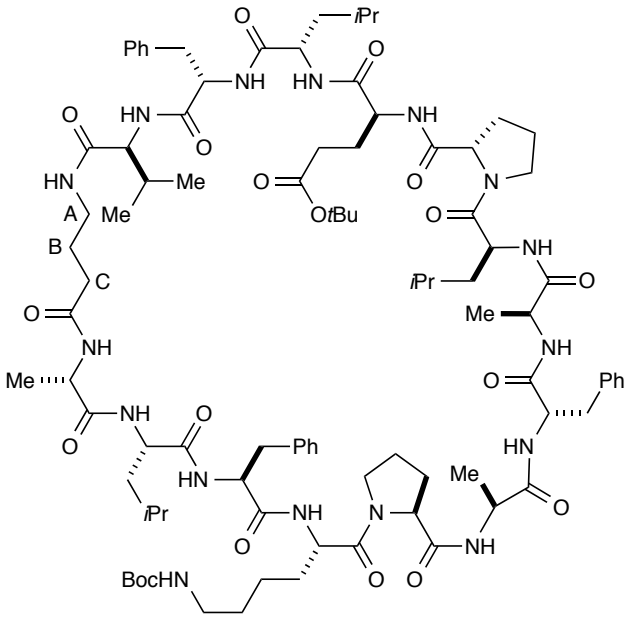
Reaction HPLC Traces



LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Area % Found	Area % UV220	Width50% UV220
1	C62H96N10O12	1172.7209	2.258	Yes	100.0	0.013
2				No	0.0	0.000
3				No	0.0	0.000





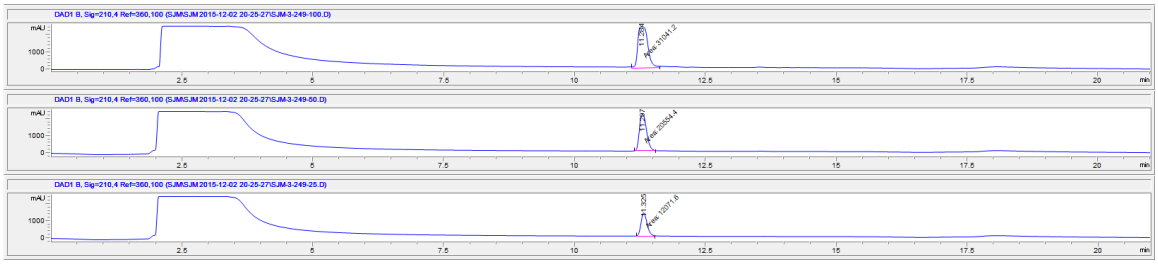
***cyclo*-[Aba-Ala-Leu-Phe-Lys(Boc)-Pro-Ala-Phe-Ala-Leu-Pro-Glu(O*t*Bu)-Leu-Phe-Val] (23)**

Prepared following the general procedure outlined above using acryloyl-Ala-Leu-Phe-Lys(Boc)-Pro-Ala-Phe-Ala-Leu-Pro-Glu(O*t*Bu)-Leu-Phe-Val-Gly (13.7 mg, 7.5 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.2 mg, 2.0 μmol, 0.27 equiv.), K_2HPO_4 (3.5 mg, 20 μmol, 2.7 equiv.), H_2O (20 μL, 1.1 mmol, 148 equiv), and DMF (40.0 mL). After 48 h, the reaction mixture was removed from LED irradiation, centrifuged, and subjected to HPLC analysis. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 53%. Preparative HPLC provided the product (5.2 mg, 39%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.37–7.02 (15 H), 4.76 (1H), 4.74 (1H), 4.71 (1H), 4.68 (1H), 4.64 (1H), 4.49 (1H), 4.44 (1H), 4.36 (1H), 4.34 (1H), 4.23 (1H), 4.04 (1H), 3.93 (1H), 3.86 (1H), 3.75 (1H, H), 3.65 (1H, H), 3.63 (1H, H_A), 3.50 (1H), 3.48 (m, 1H, H_A), 3.16 (2H), 3.07 (2H), 2.93 (2H), 2.68–2.60 (2H), 2.42 (1H), 2.31 (1H),

2.13 (2H, H_C), 2.09 (1H), 2.02 (1H), 1.97 (2H), 1.90 (2H), 1.88 (2H), 1.81 (2H, H_B), 1.83–1.75 (2H), 1.77 (3H), 1.65 (2H), 1.63 (2H), 1.56 (2H), 1.51 (2H), 1.46 (2H), 1.45 (9H), 1.44 (4H), 1.39 (9H), 1.35 (3H), 1.28 (3H), 1.23 (3H), 0.99 (6H), 0.97 (6H), 0.91 (6H), 0.85 (6H); HRMS (ESI-TOF) *m/z* calcd. for $C_{93}H_{142}N_{16}O_{19}$ ($[M+2H]^{2+}$) 893.53187, found 893.53163.

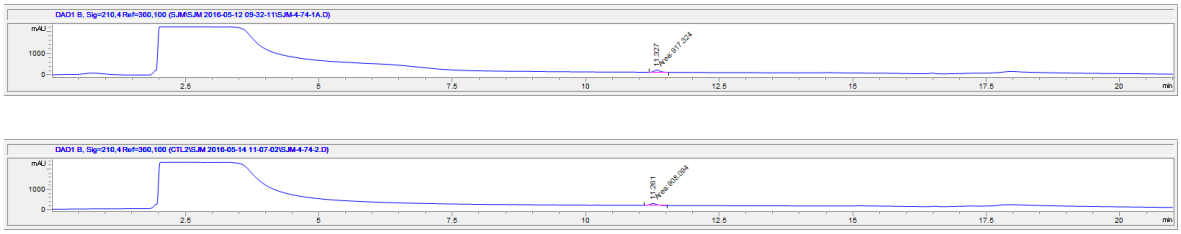
δ H_A 3.63, 3.48; H_B 1.81; H_C 2.13

HPLC Assay Calibration



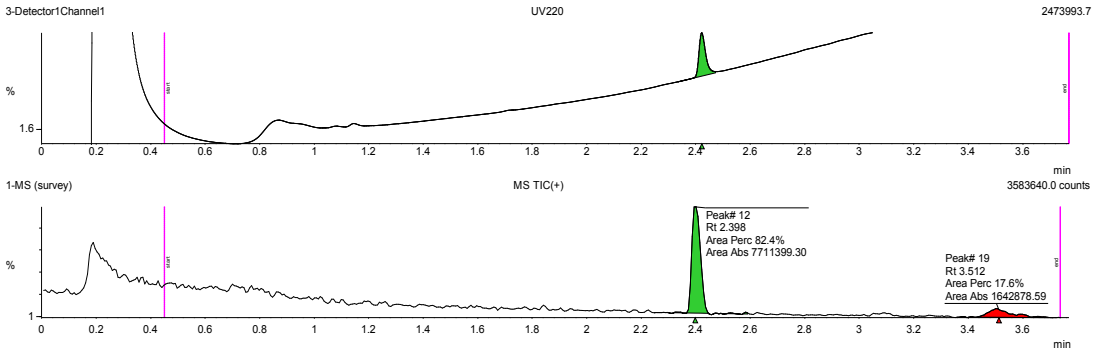
Concentration in DMF: 3.78 mM, 1.89 mM, 0.95 mM.

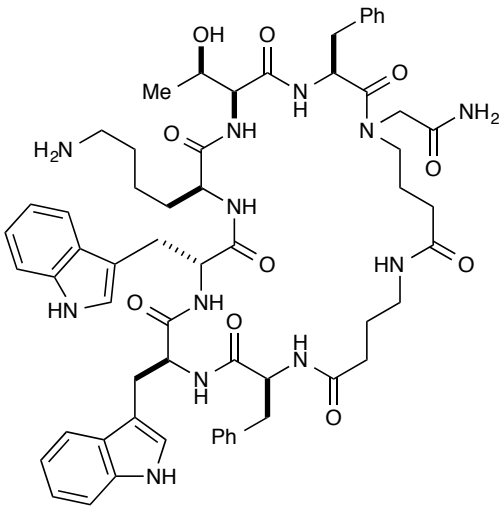
Reaction HPLC Traces



LCMS data for purified peptide

Peak #	Formula	Target Mass	Time UV220	Found	Area % UV220	Width50% UV220
1				No	0.0	0.000
3				No	0.0	0.000
6				No	0.0	0.000
7				No	0.0	0.000
10				No	0.0	0.000
12	C93H140N16O19	1786.0511	2.422	Yes	100.0	0.026
13				No	0.0	0.000
16				No	0.0	0.000
18				No	0.0	0.000
19				No	0.0	0.000

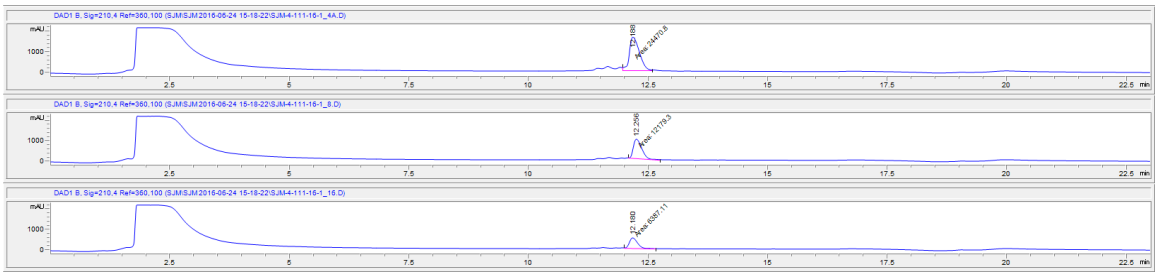




***cyclo*-[Aba-(4-acetamide)Aba-Phe-Thr-Lys-(*D*)Trp-Trp-Phe] (25)**

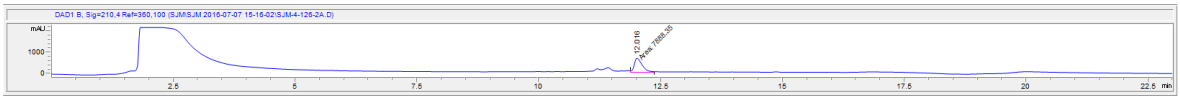
Prepared following the general procedure outlined above using acryloyl-Phe-Trp(Boc)-(*D*)Trp(Boc)-Lys(Boc)-Thr(*t*Bu)-Phe-(4-acetamide)Aba-Gly (8.8 mg, 5 μmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.1 mg, 1.0 μmol, 0.20 equiv.), K_2HPO_4 (1.7 mg, 10 μmol, 2.0 equiv.), H_2O (10 μL, 0.56 mmol, 111 equiv), and DMF (4.0 mL). After 12 h, the reaction mixture was removed from LED irradiation, centrifuged, and decanted. Solvent was removed under vacuum and the residue treated with TFA:phenol:H_2O:triisopropylsilane (88:5:5:2) at 0 C for 2 hours. Cold Et_2O was added and the mixture was centrifuged and decanted. Trituration with Et_2O was repeated twice. The residue was dissolved in 5 mL DMF and analyzed by HPLC. Conditions: Vydac 218TP C18 5μ, length 150 mm, ID 4.6 mm, 40-80% MeCN/H_2O + 0.1% formic acid over 12 minutes. Reaction yield was determined to be 56% (over 2 steps) by HPLC. Preparative HPLC provided the product (2.6 mg, 47%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.51–6.68 (20H), 5.00–4.84 (2H), 4.61 (1H), 4.51–4.47 (1H), 4.37–4.28 (1H), 4.21–4.00 (2H), 3.87–3.72 (1H), 3.25–3.17 (4H), 3.17–2.92 (8H), 2.88–2.72 (4H), 2.15–2.06 (2H), 1.88–1.59 (2H), 1.56–1.39 (4H), 1.16–0.97 (5H); HRMS (ESI-TOF) *m*/*z* calcd. for $C_{60}H_{75}N_{12}O_{10}$ ($[M+H]^+$) 1123.57921, found 1123.57206.

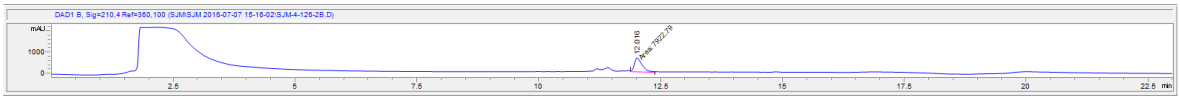
HPLC Assay Calibration



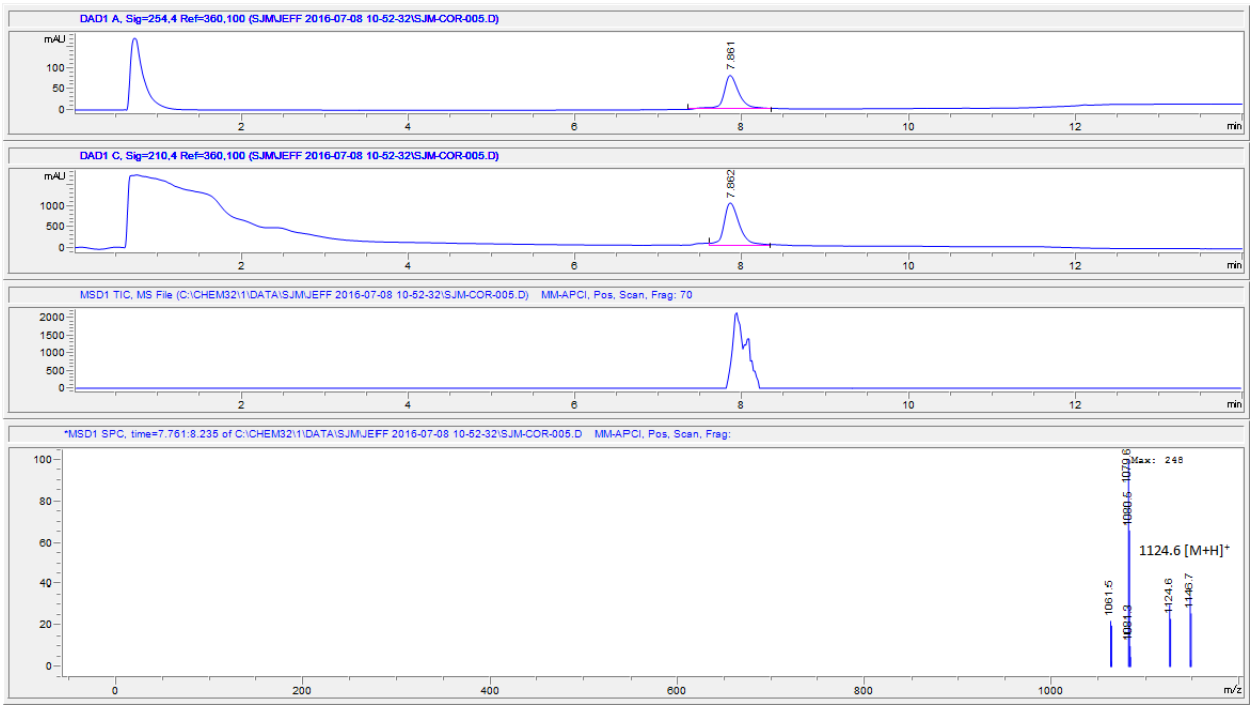
Concentration in DMF: 1.73 mM, 0.86 mM, 0.43 mM.

Reaction HPLC Traces

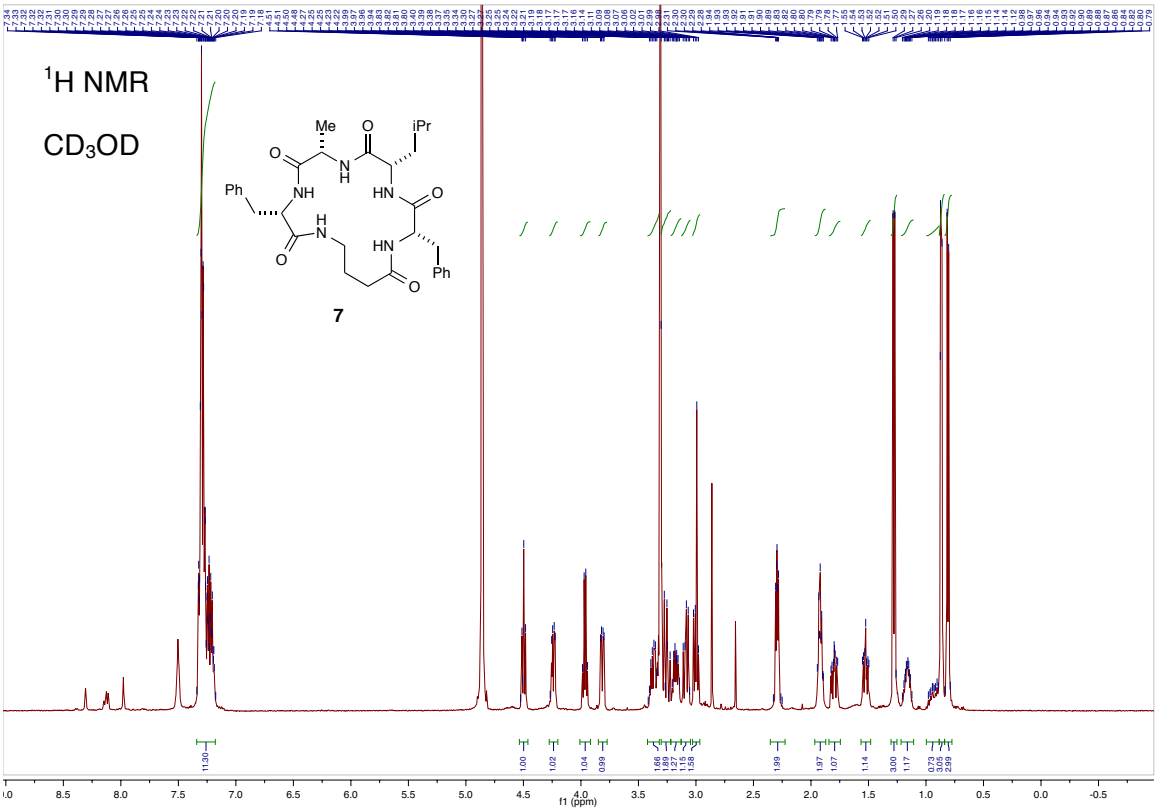


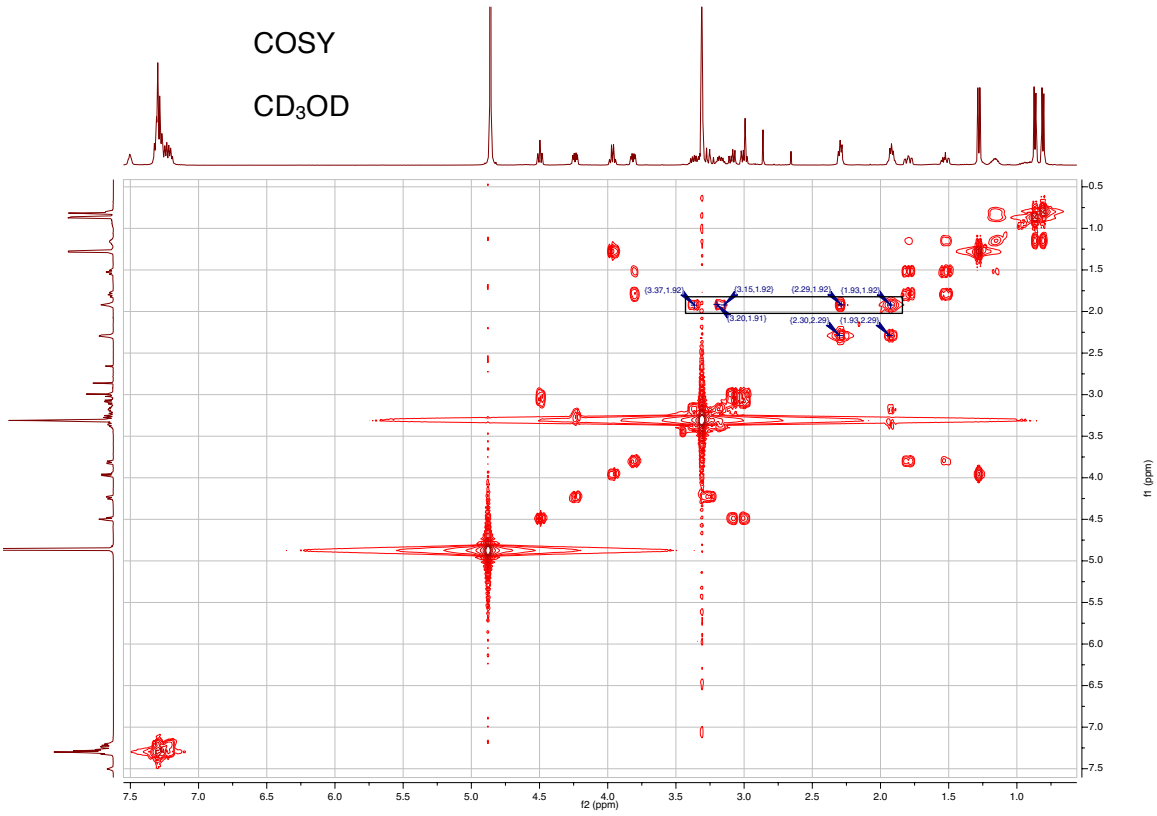


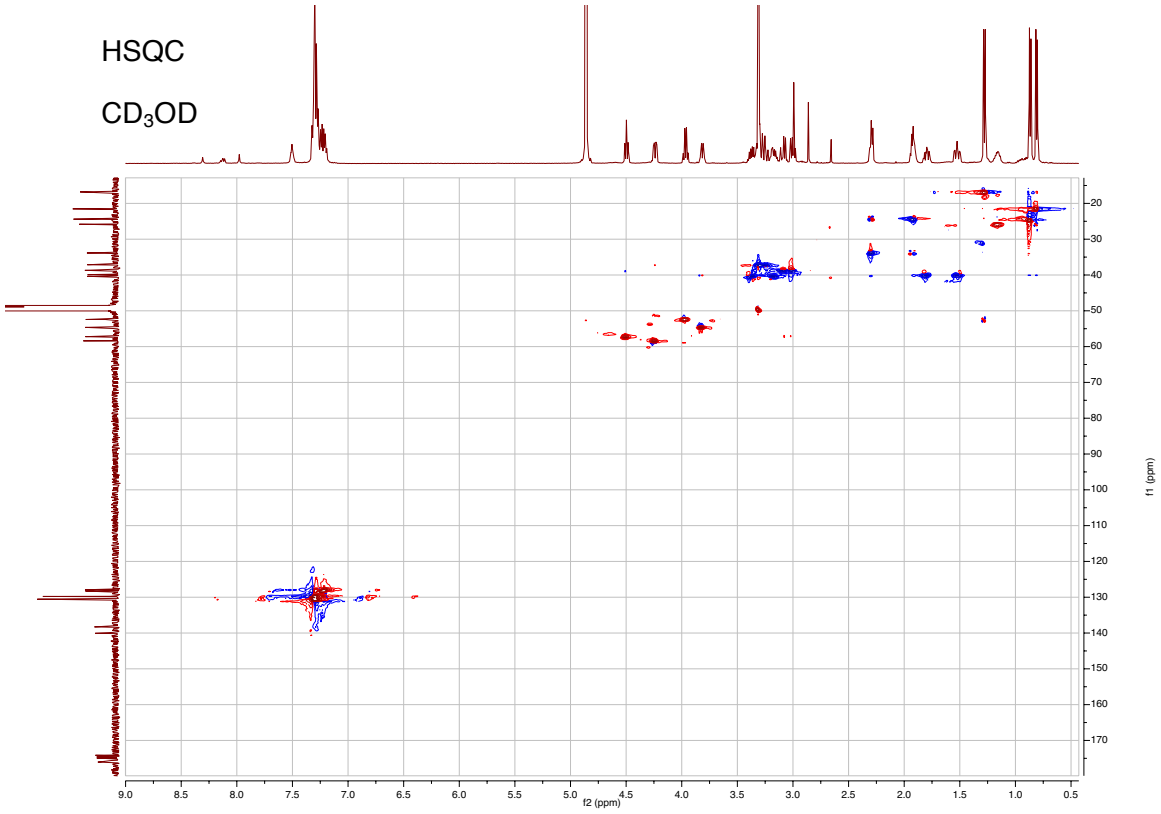
LCMS data for purified peptide

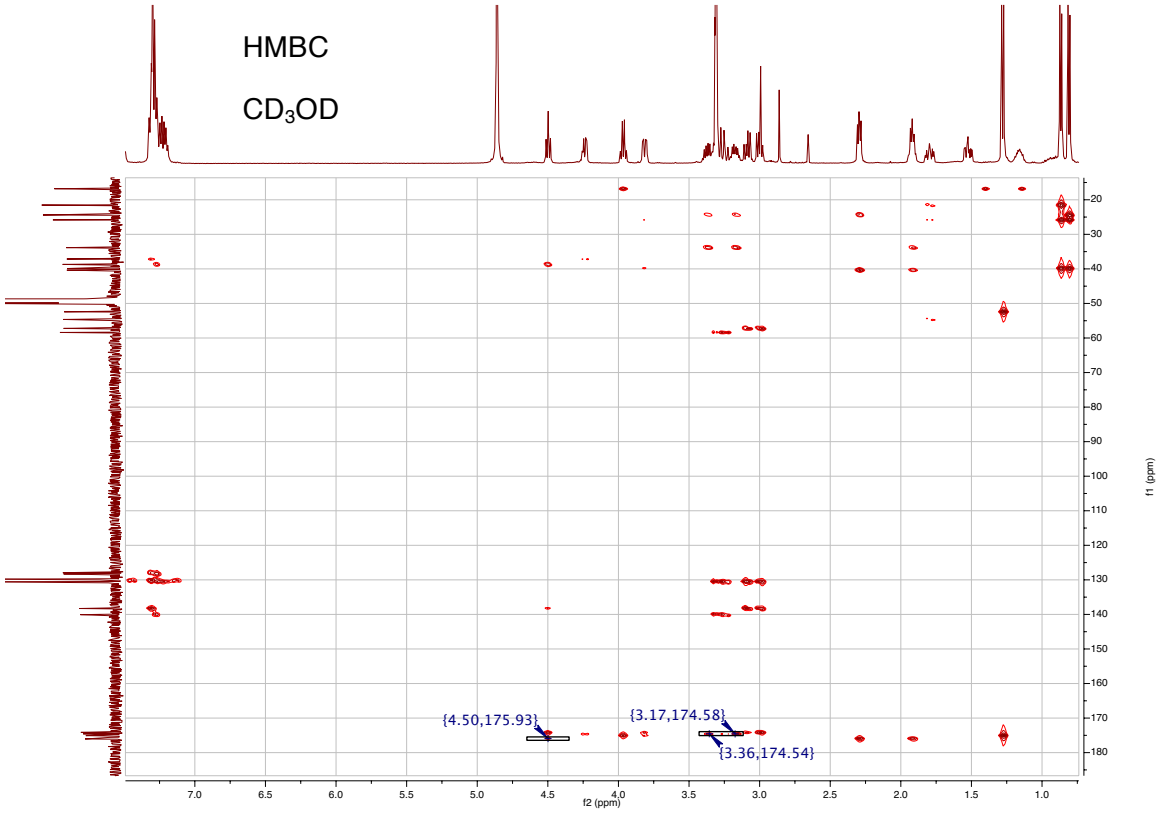


9. Spectral Data

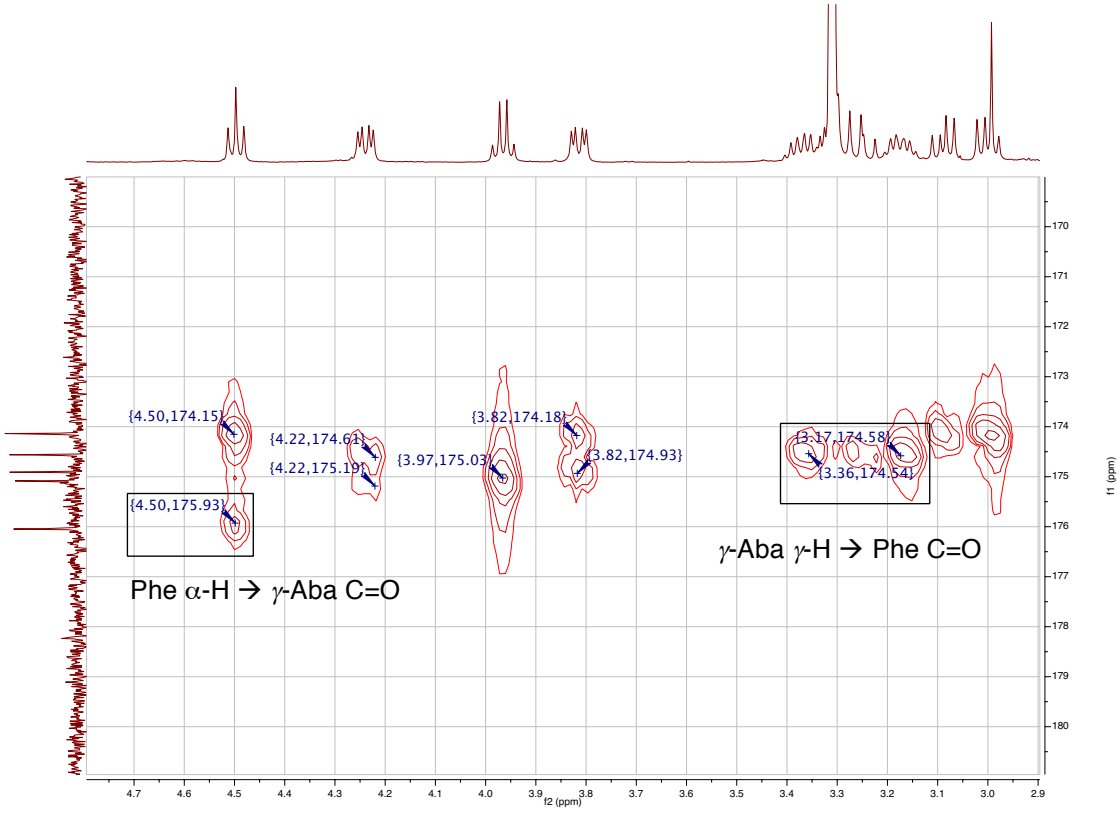


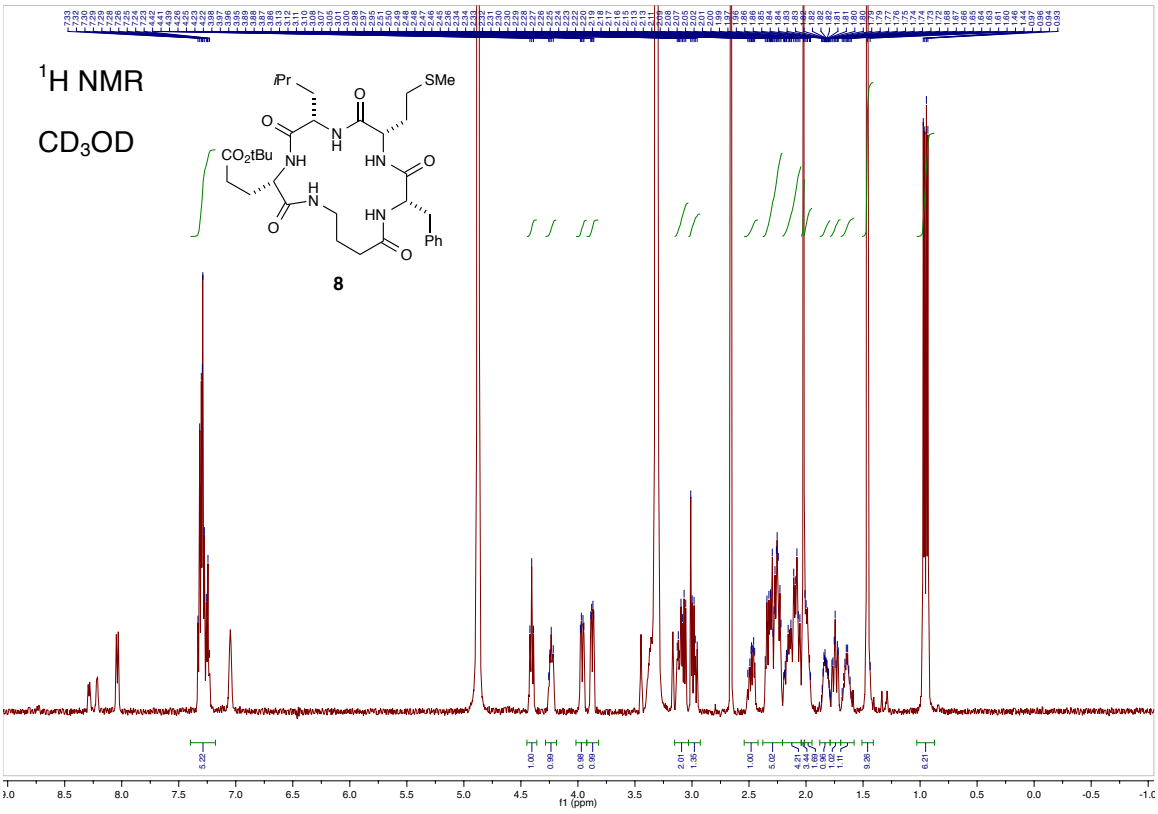


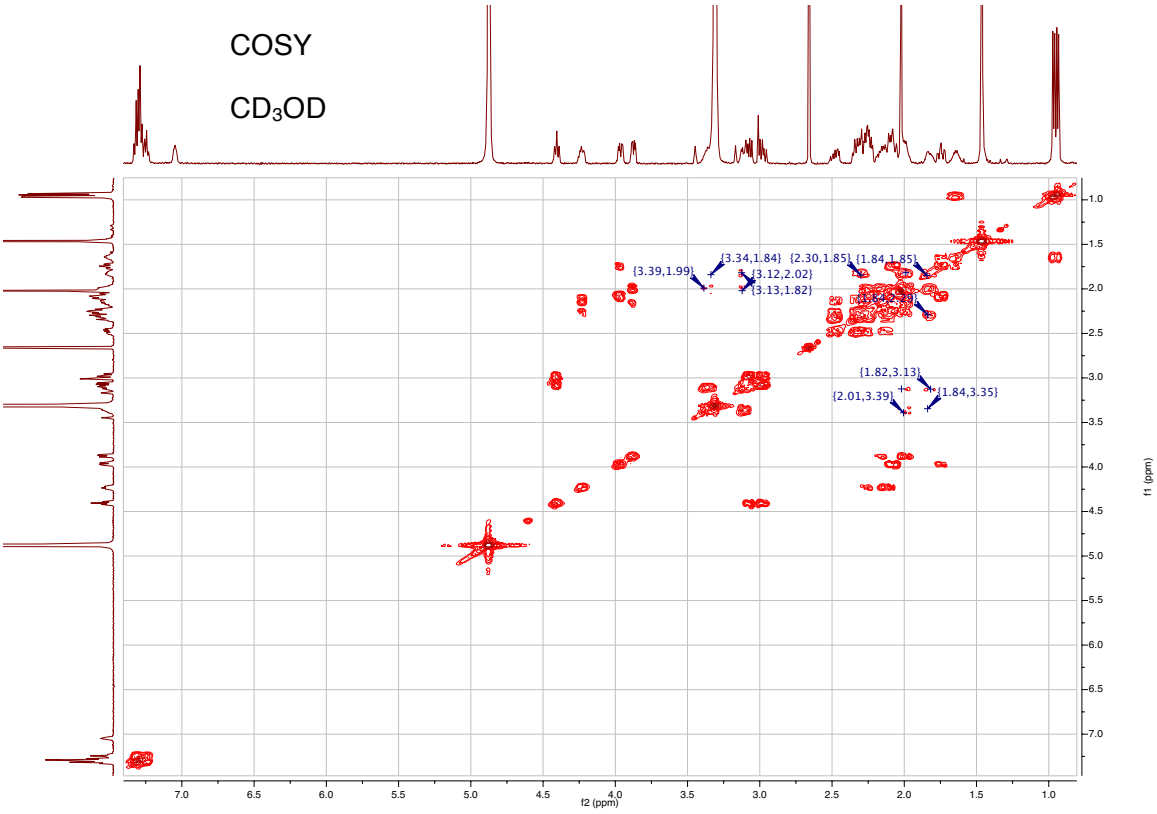

HSQC
CD3OD
f2 (ppm)
f1 (ppm)

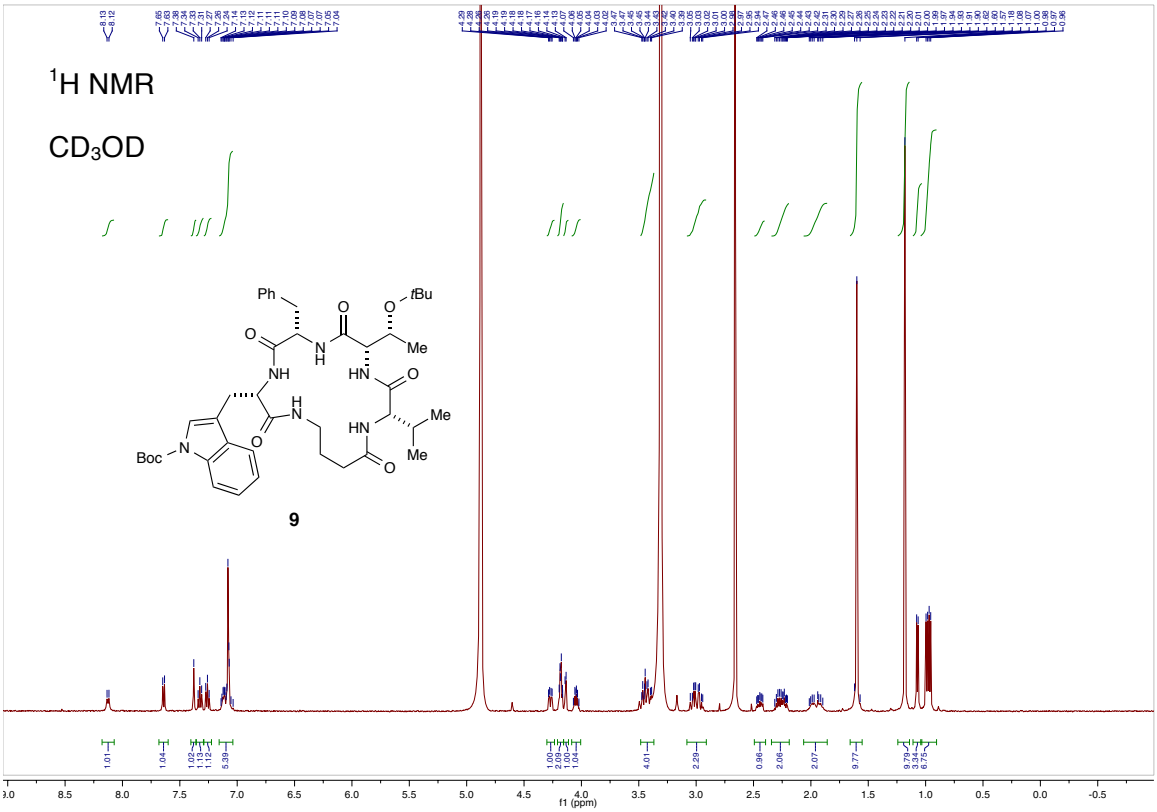

HMBC
CD3OD
{4.50,175.93}
{3.17,174.58}
{3.36,174.54}
f2 (ppm)
f1 (ppm)

Key HMBC correlations for product **7**.



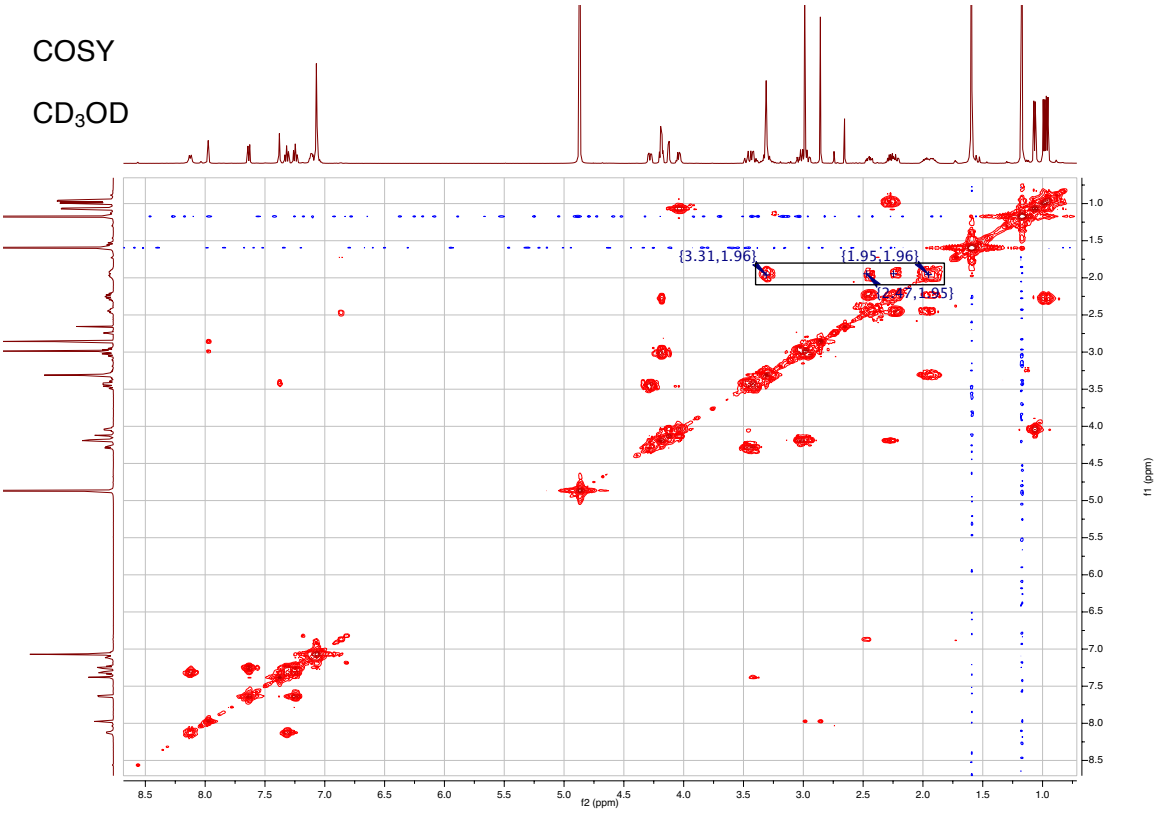



COSY
CD3OD
{3.39,1.99}
{3.34,1.84}
{3.12,2.02}
{3.13,1.82}
{2.30,1.85}
{1.84,1.85}
{1.82,3.13}
{2.01,3.39}
{1.84,3.35}
f2 (ppm)
f1 (ppm)


1H NMR
CD3OD
Ph
O
O
tBu
Me
NH
HN
O
H
N
Me
HN
Me
Boc
N
O
O
9
f1 (ppm)

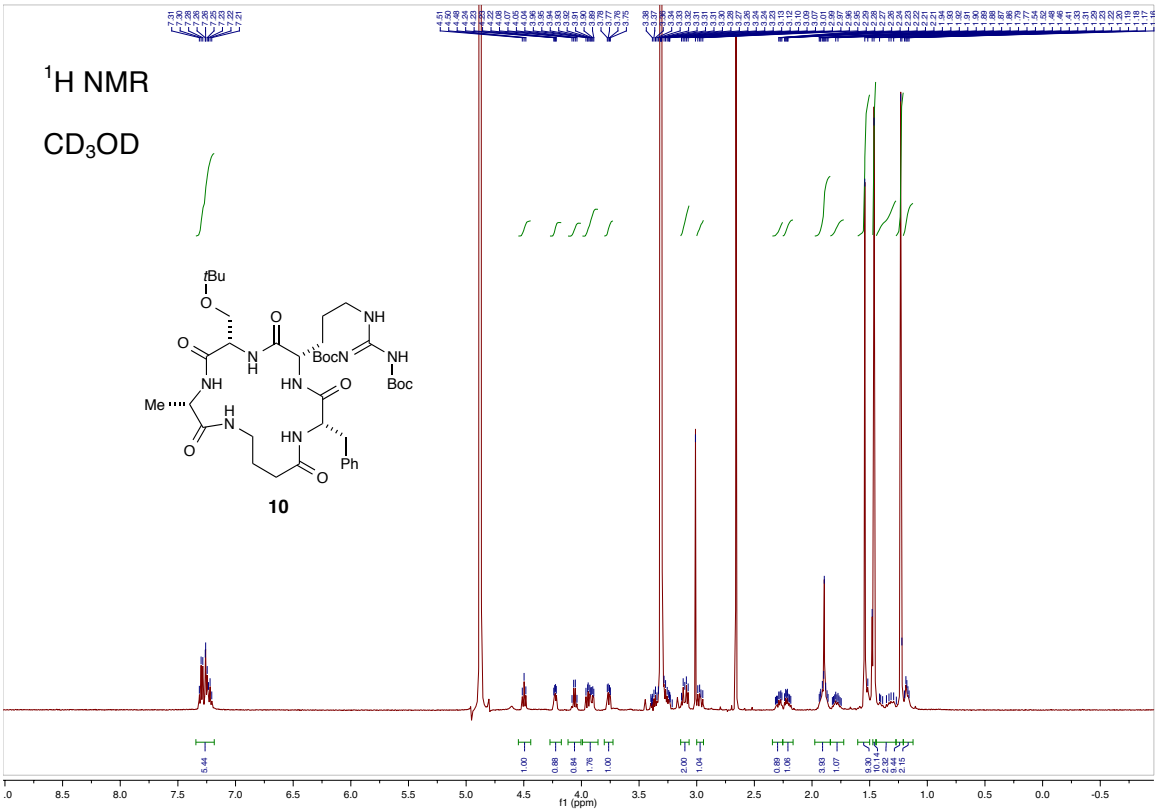
COSY

CD_3OD

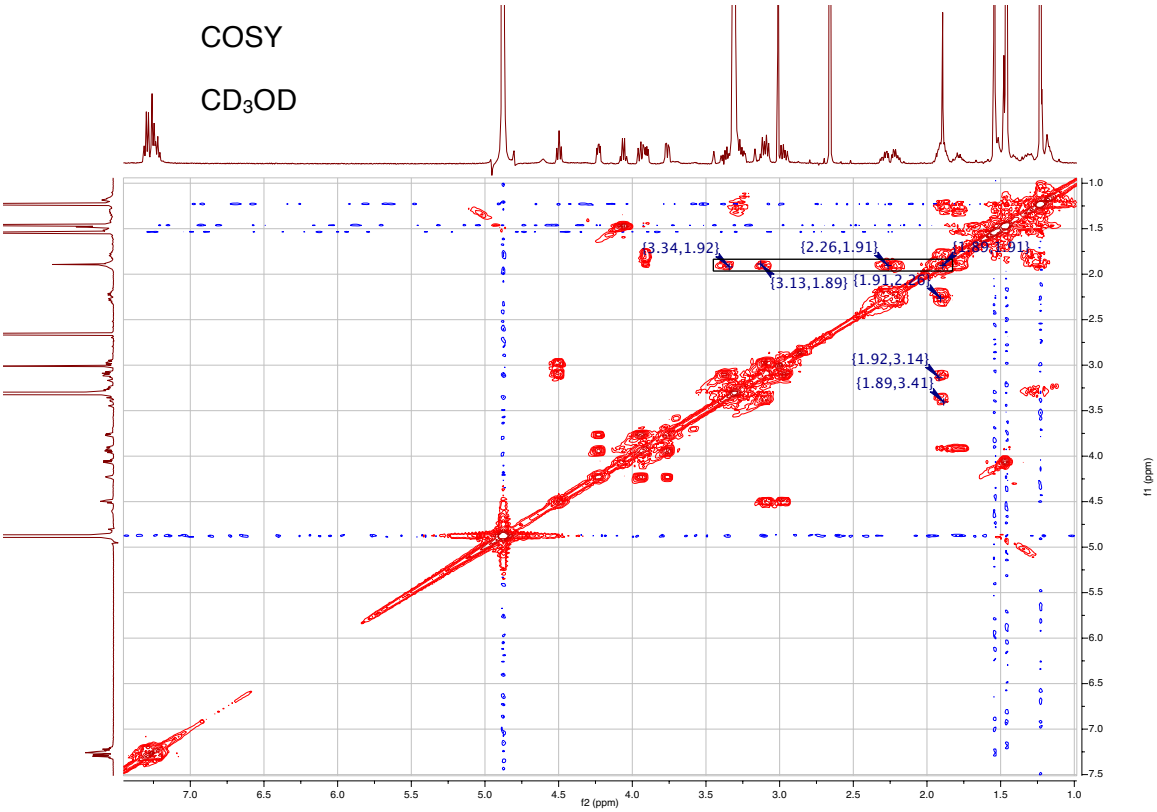


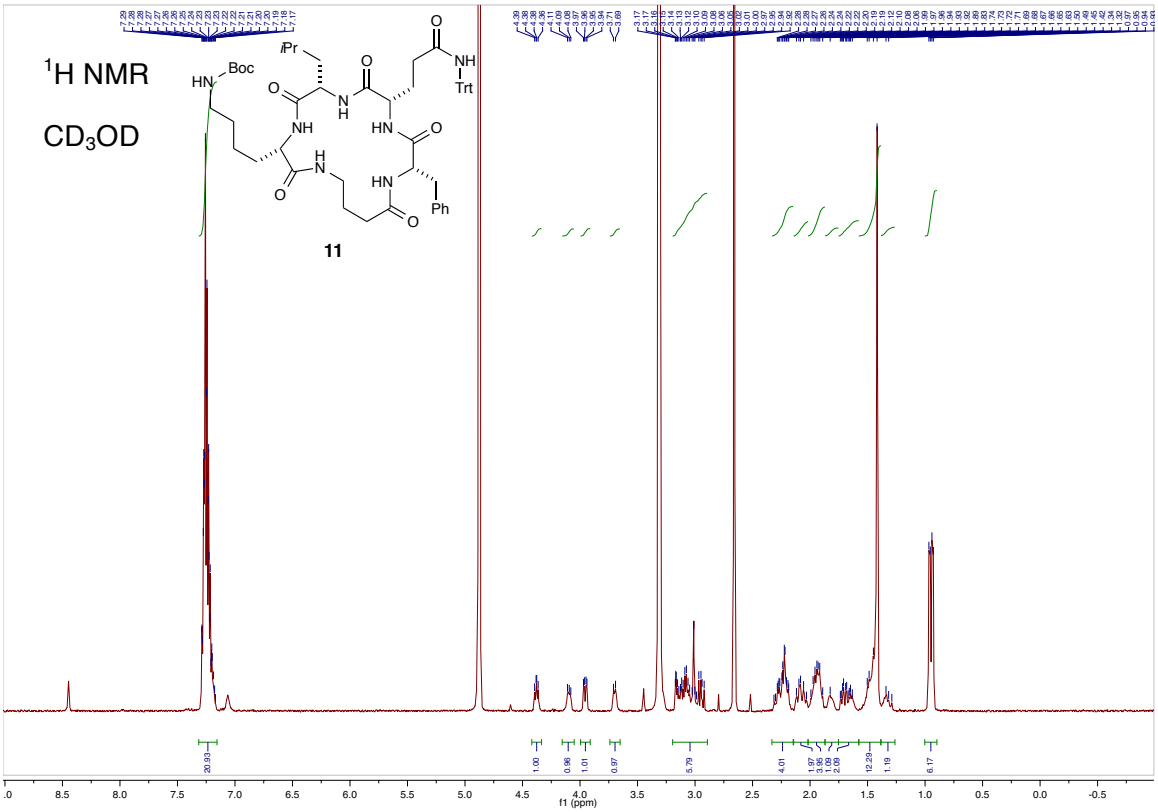
^1H NMR

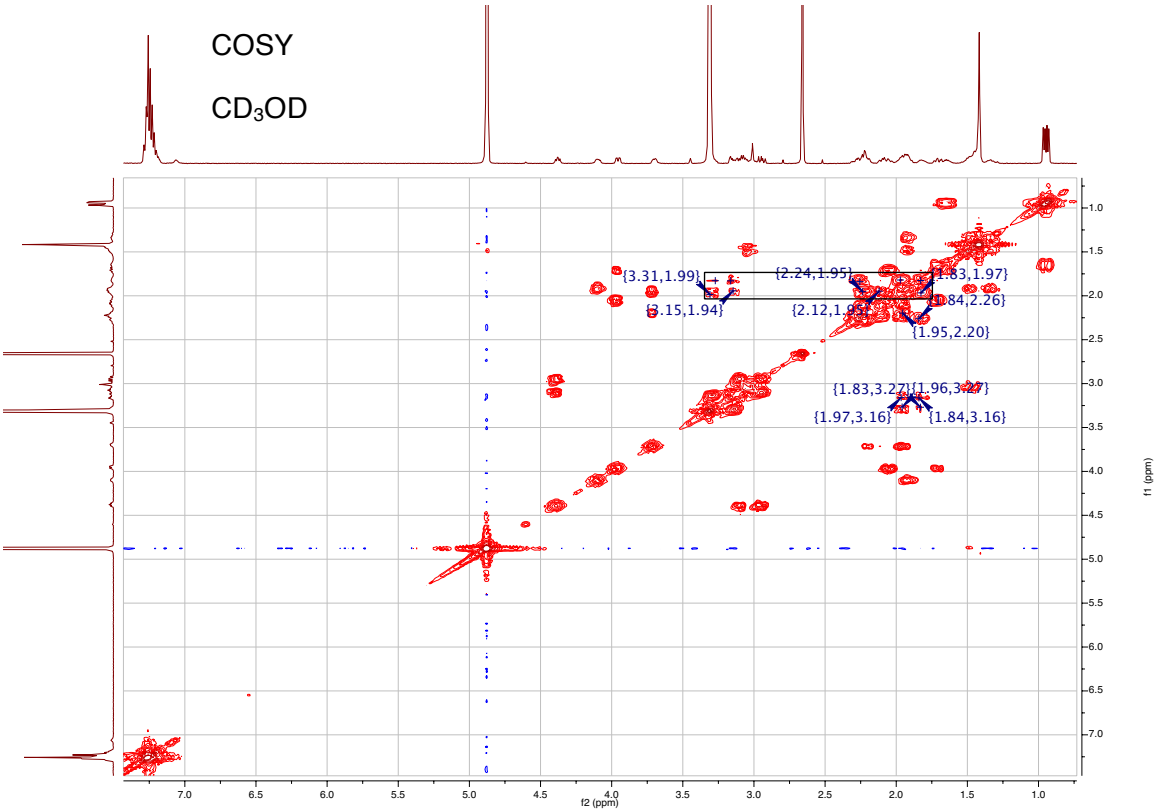
CD_3OD

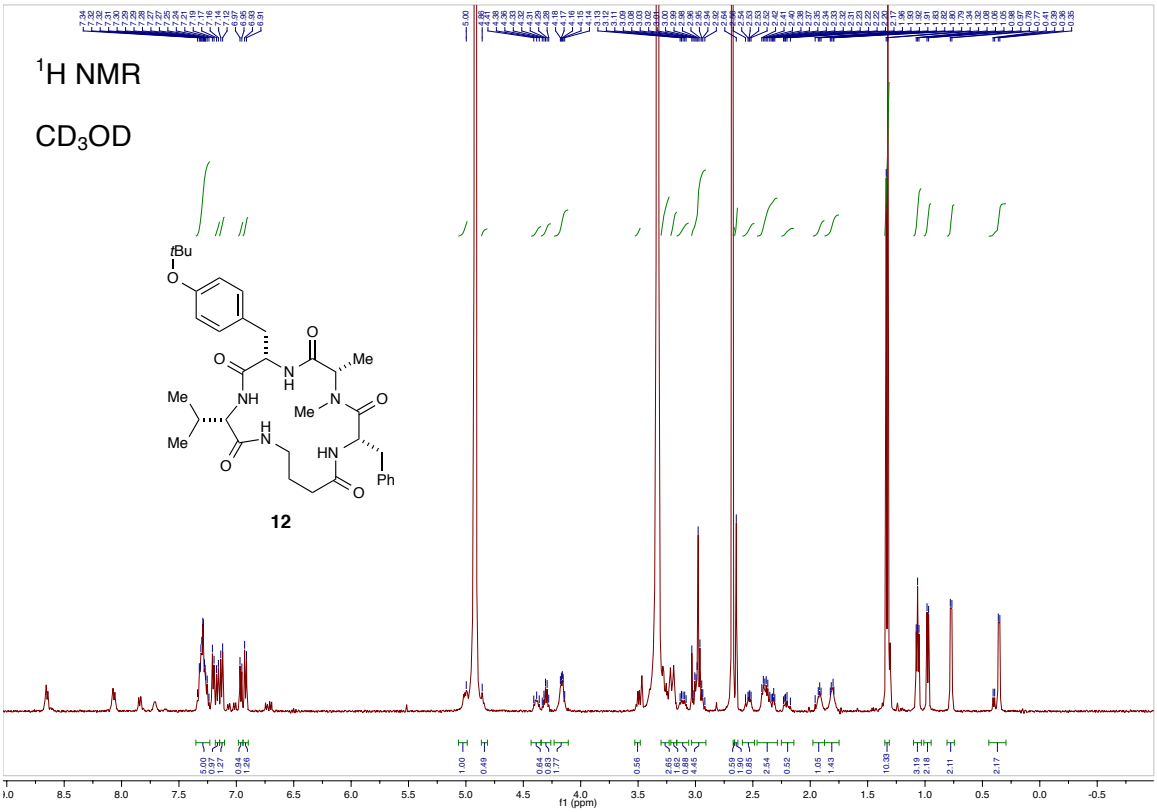


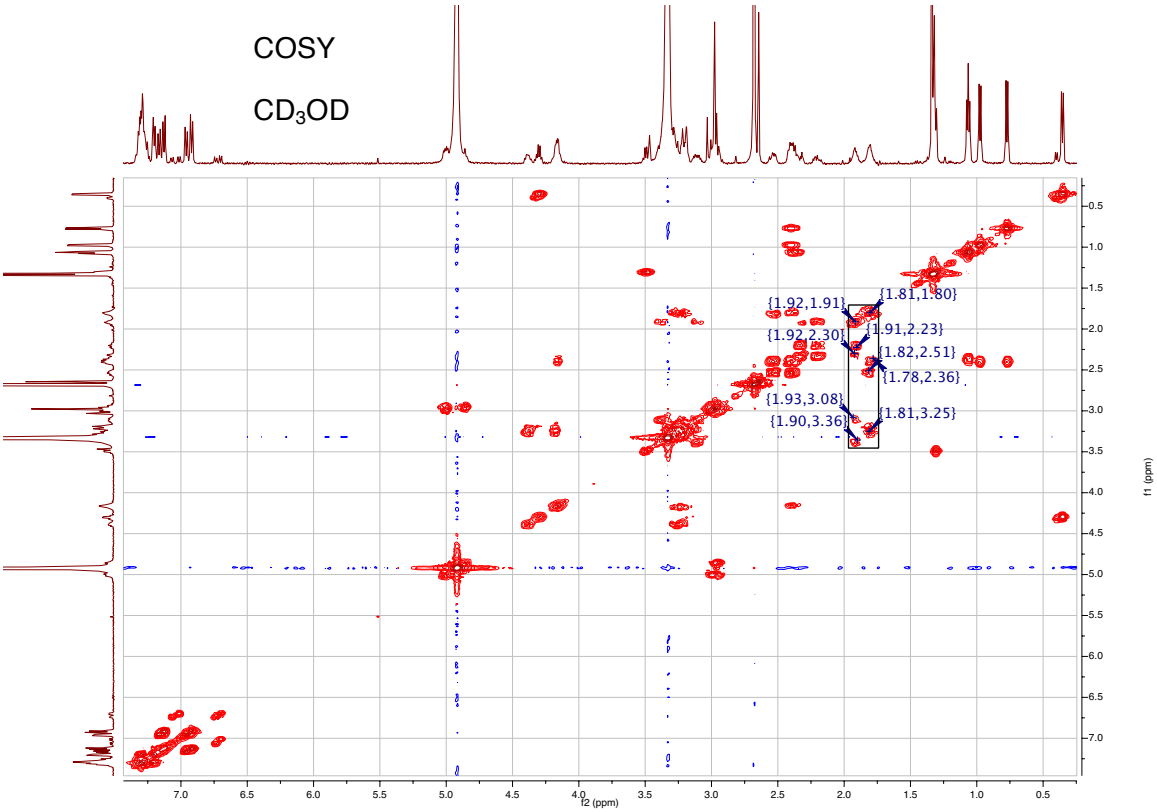
10

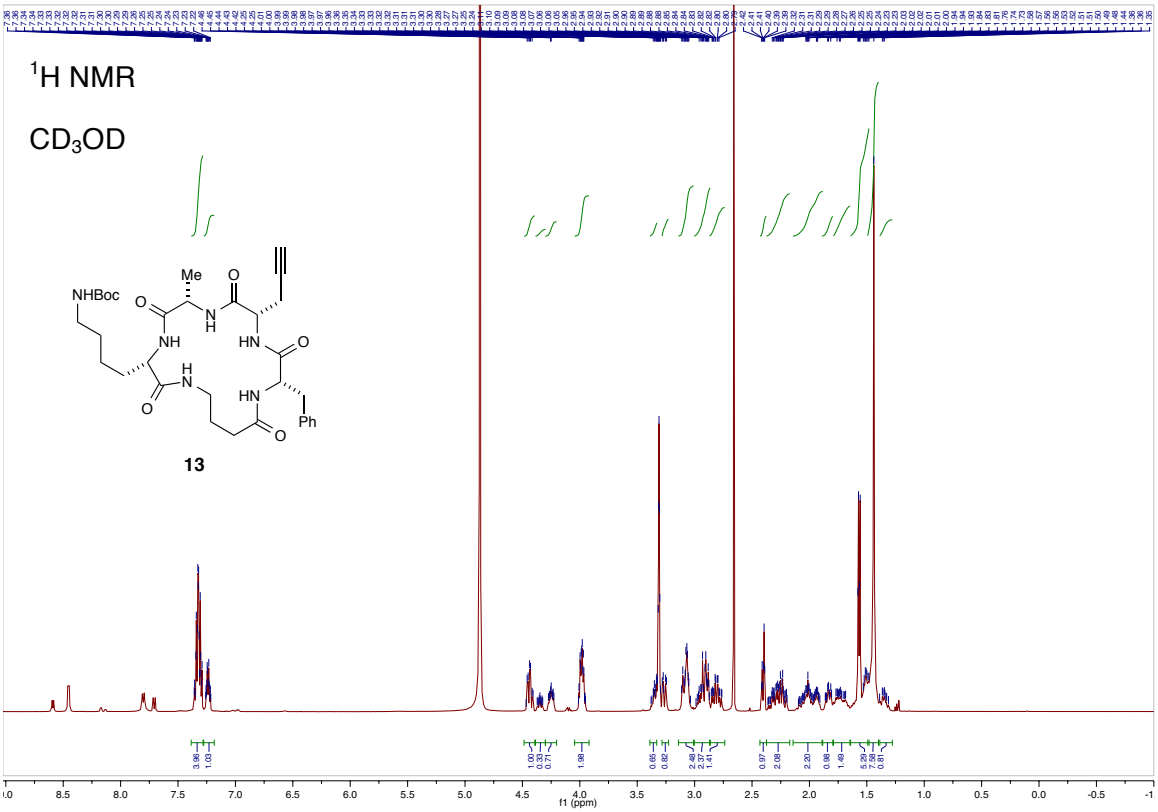

COSY
CD3OD
{3.34,1.92}
{2.26,1.91}
{3.13,1.89}
{1.92,3.14}
{1.89,3.41}
f2 (ppm)
f1 (ppm)

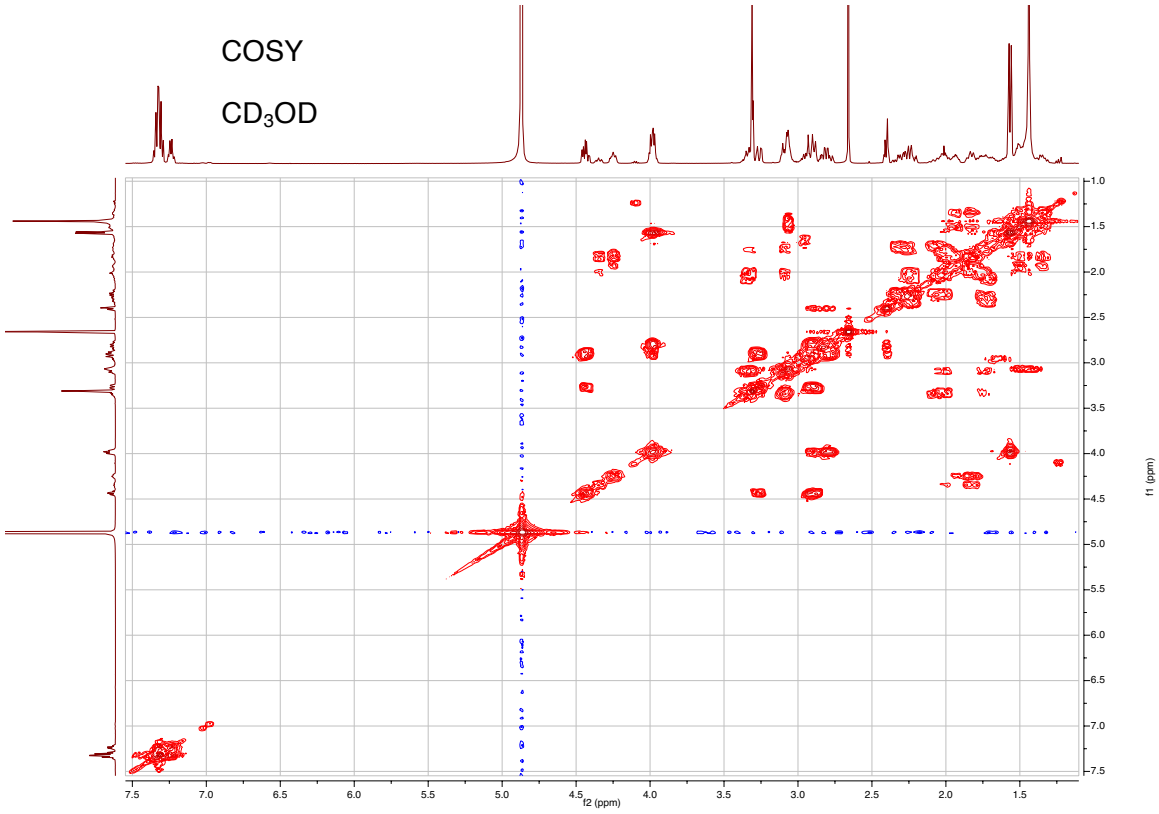

1H NMR
CD3OD
Boc
iPr
NH
Trt
Ph
11
f1 (ppm)

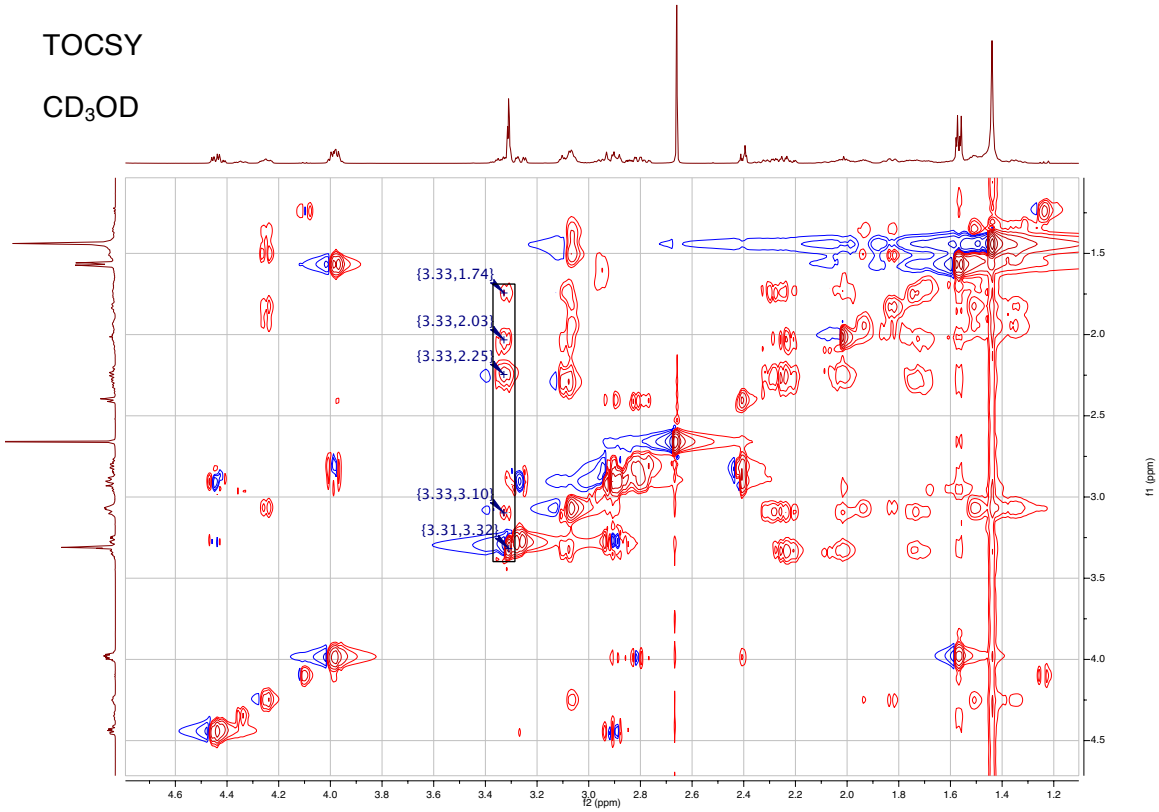

COSY
CD3OD
{3.31,1.99}
{2.24,1.95}
{3.15,1.94}
{1.95,2.20}
{1.83,3.27}
{1.97,3.16}
{1.84,3.16}
f2 (ppm)
f1 (ppm)

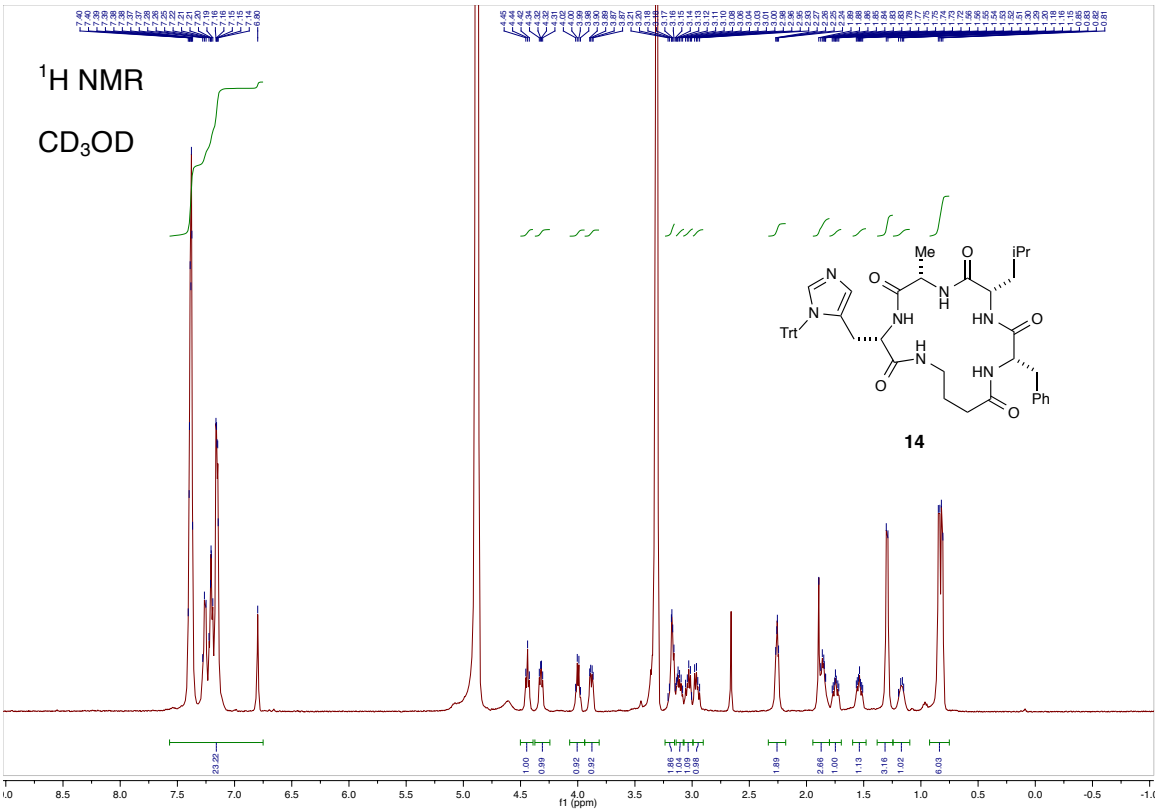

1H NMR
CD3OD
tBu
Me
Me
Me
Me
Ph
12
f1 (ppm)

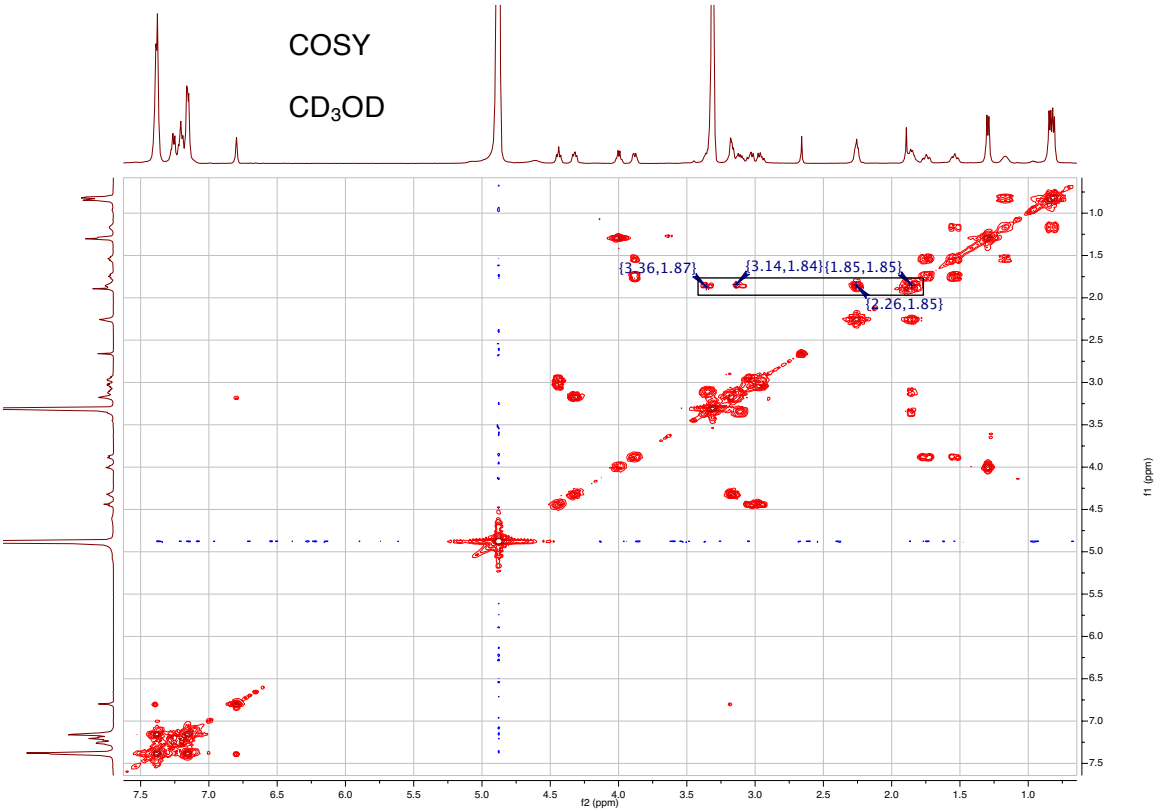

COSY
CD3OD
{1.92,1.91}
{1.81,1.80}
{1.92,2.30}
{1.91,2.23}
{1.82,2.51}
{1.78,2.36}
{1.93,3.08}
{1.90,3.36}
{1.81,3.25}
f2 (ppm)
f1 (ppm)

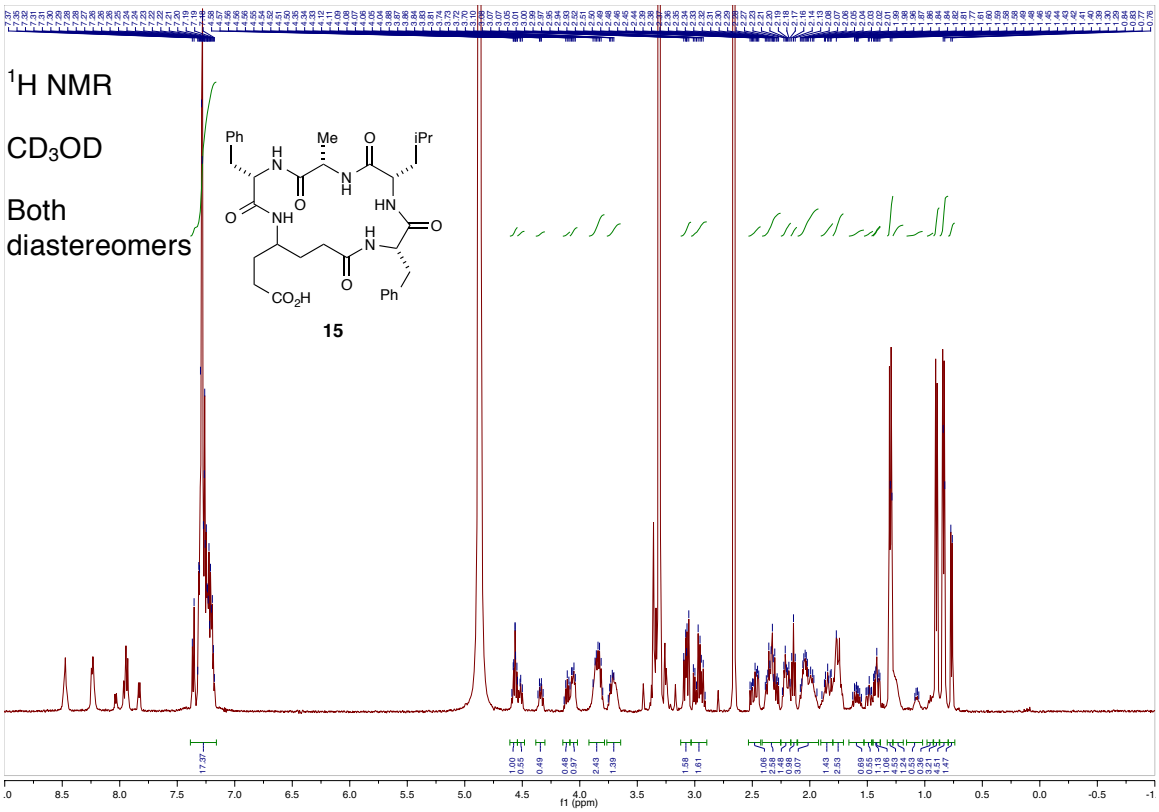

1H NMR
CD3OD
NHBoc
Me
O
N
H
NH
HN
Ph
13
f1 (ppm)

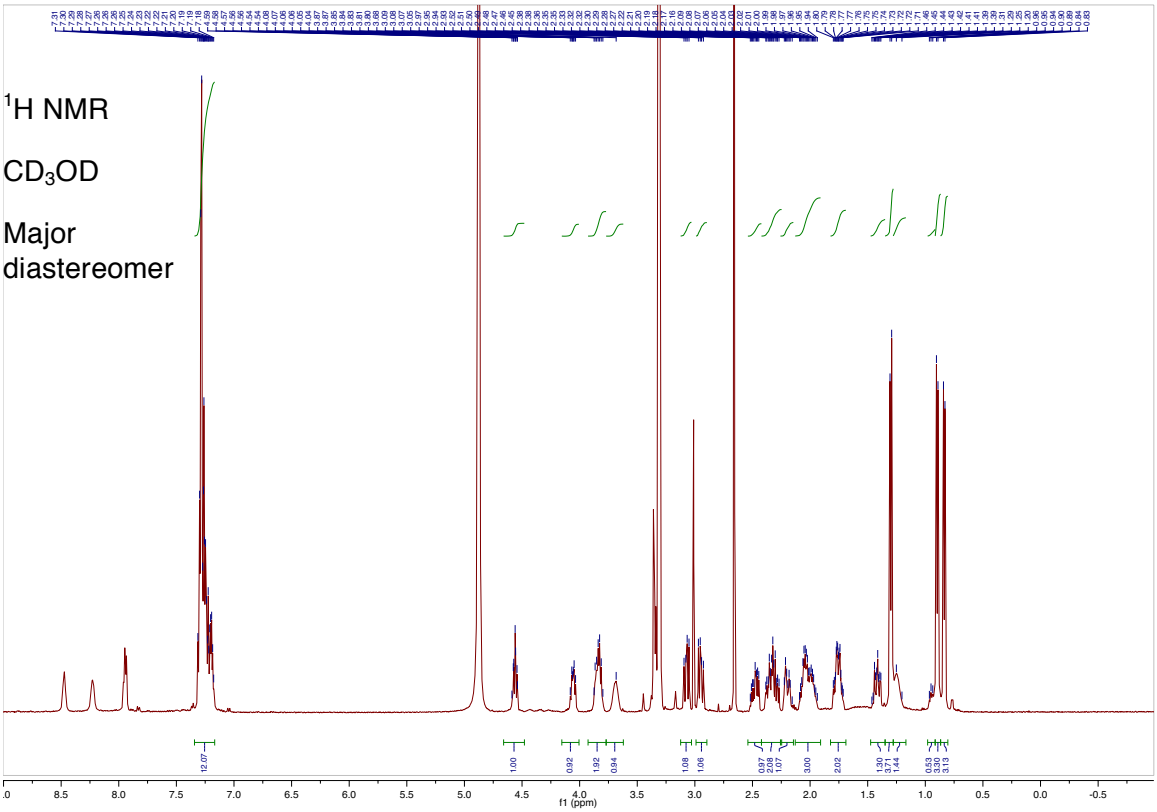

COSY
CD3OD
f2 (ppm)
f1 (ppm)

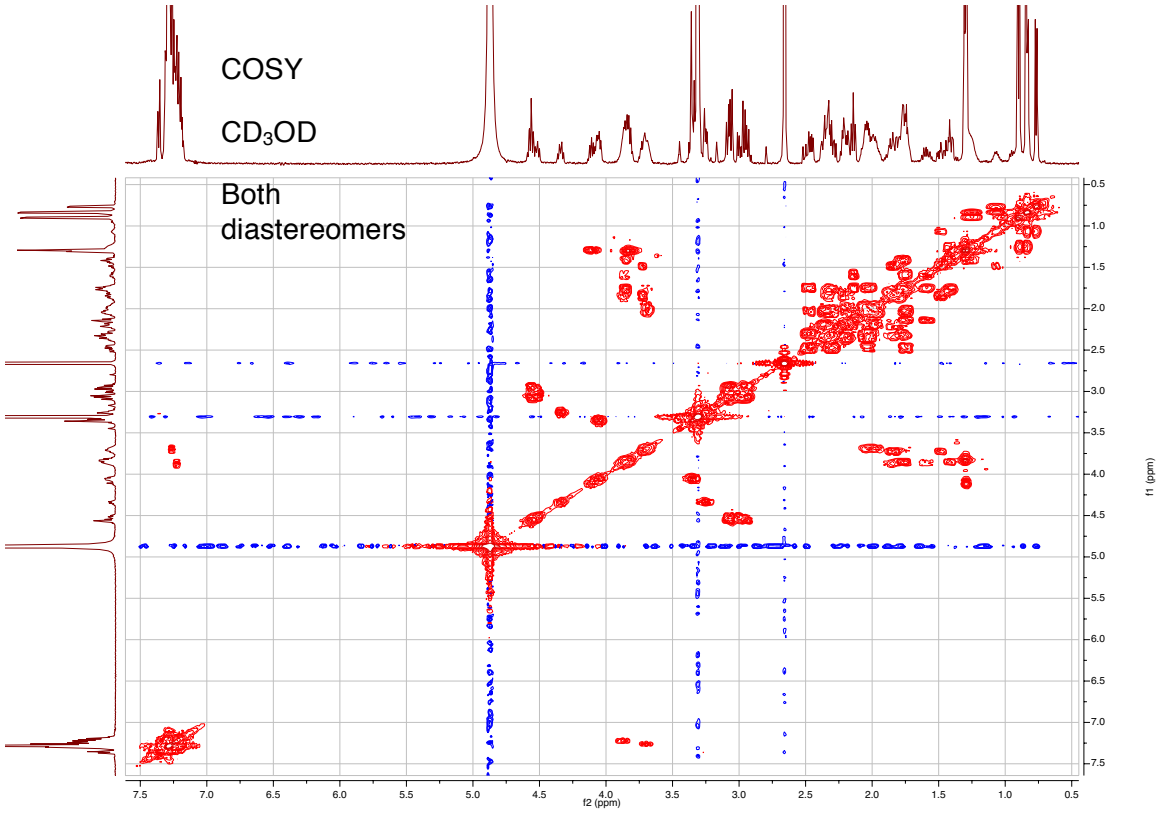

TOCSY
CD3OD
{3.33,1.74}
{3.33,2.03}
{3.33,2.25}
{3.33,3.10}
{3.31,3.32}
f2 (ppm)
f1 (ppm)

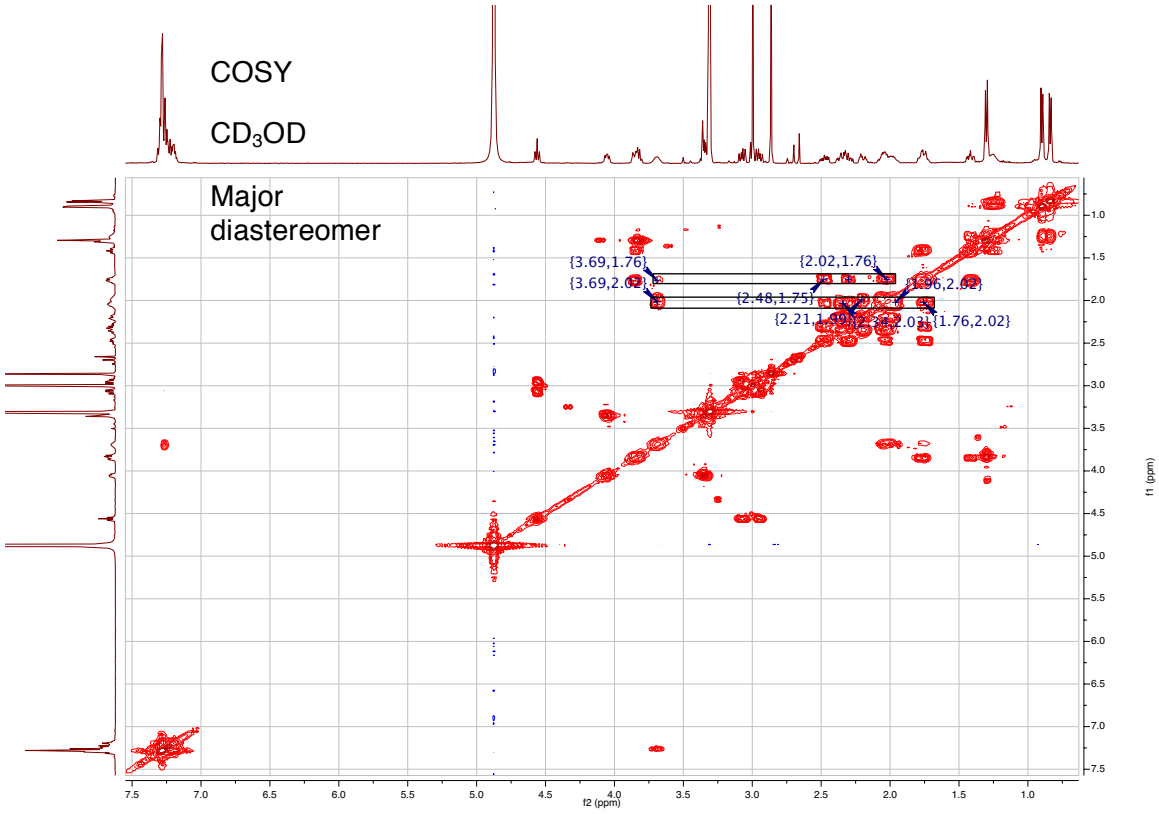

^{1}H NMR
CD_3OD
Me
O
iPr
N
N
Trt
O
NH
N
H
HN
O
H
N
O
HN
Ph
O
14
f1 (ppm)

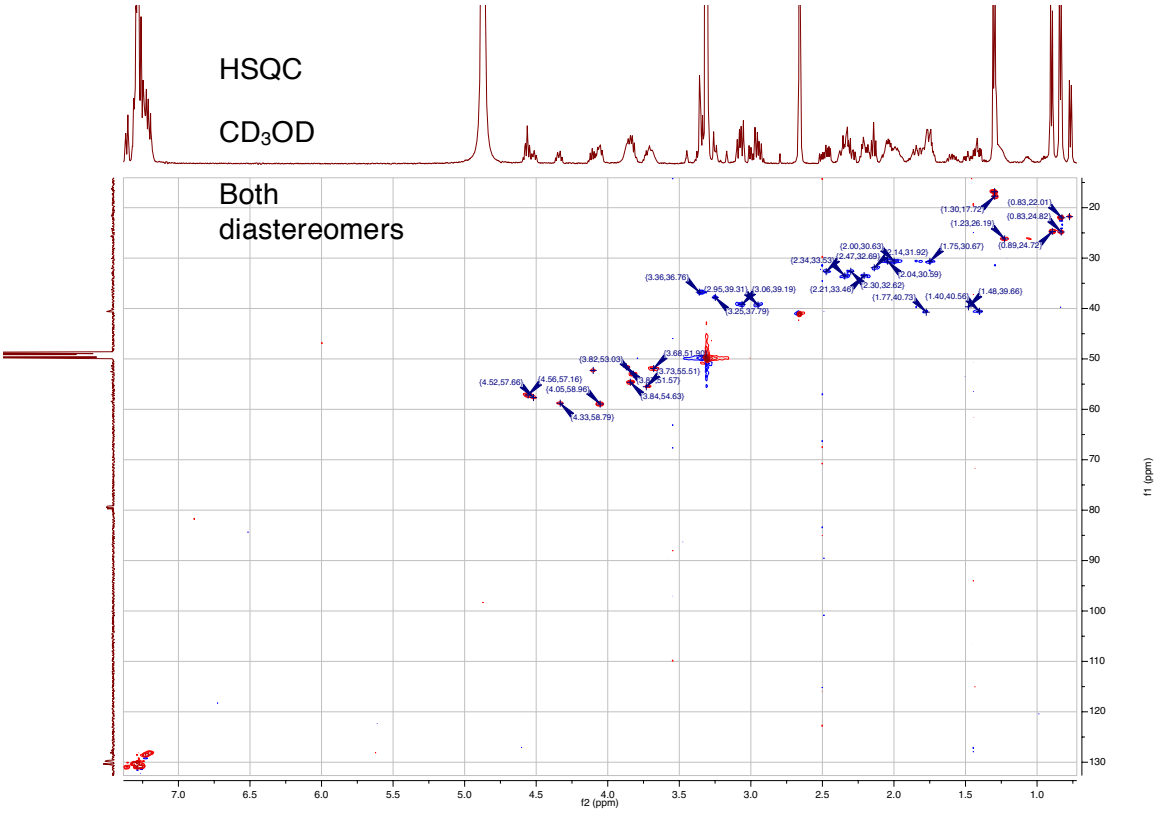

COSY
CD_3OD
{3.36,1.87}
{3.14,1.84}{1.85,1.85}
{2.26,1.85}
f2 (ppm)
f1 (ppm)

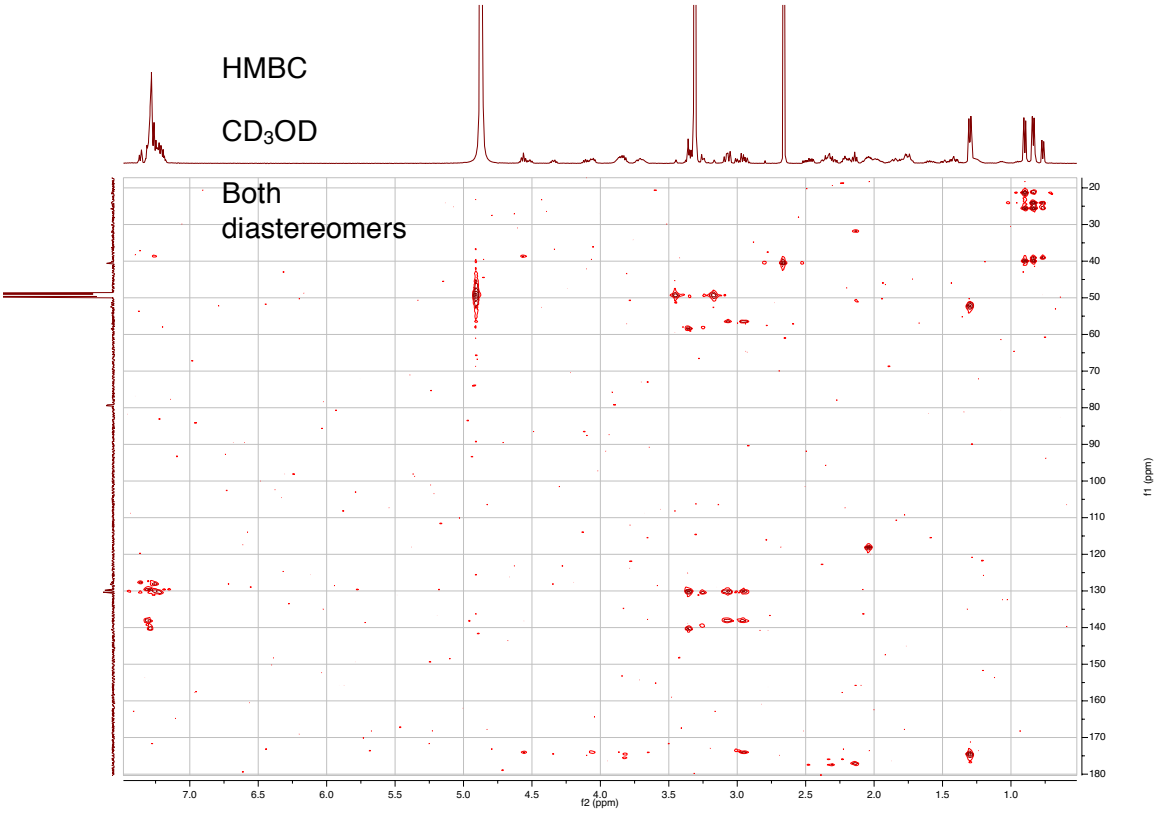

^{1}H NMR
CD_3OD
Both diastereomers
Ph
Me
iPr
CO_2H
15
f1 (ppm)

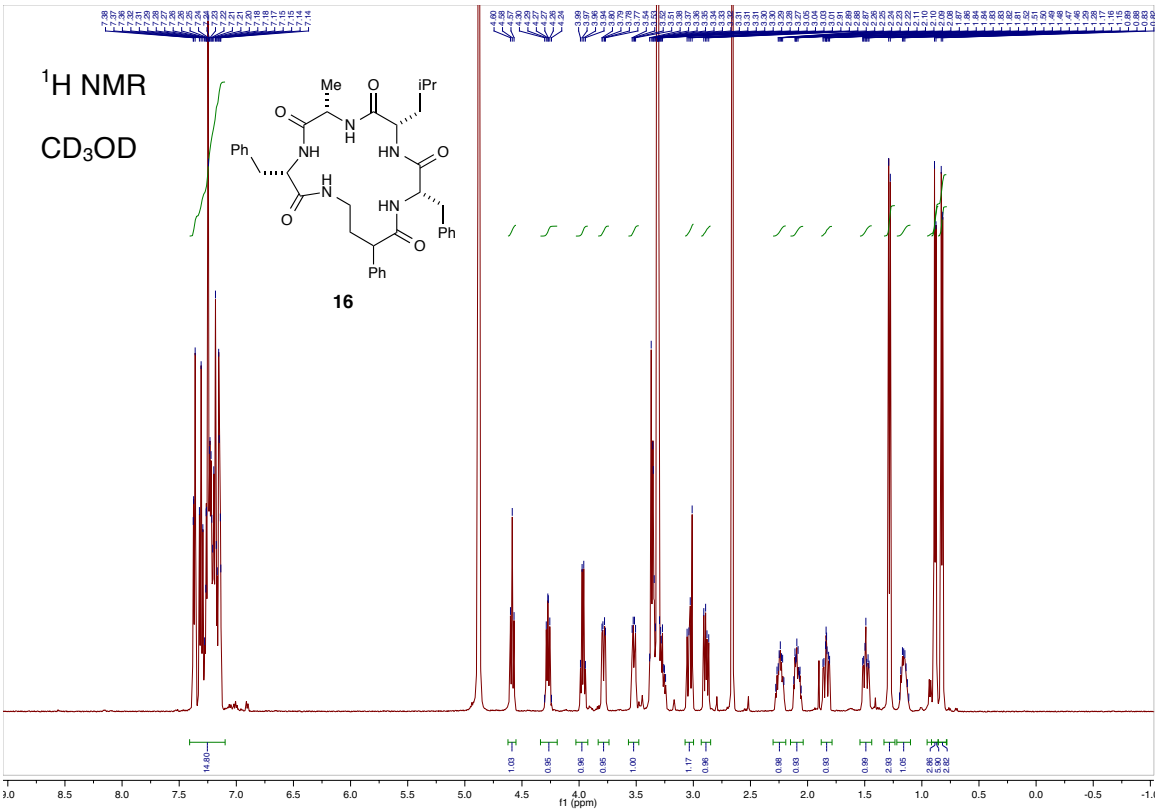

^{1}H NMR
CD_3OD
Major diastereomer
f1 (ppm)

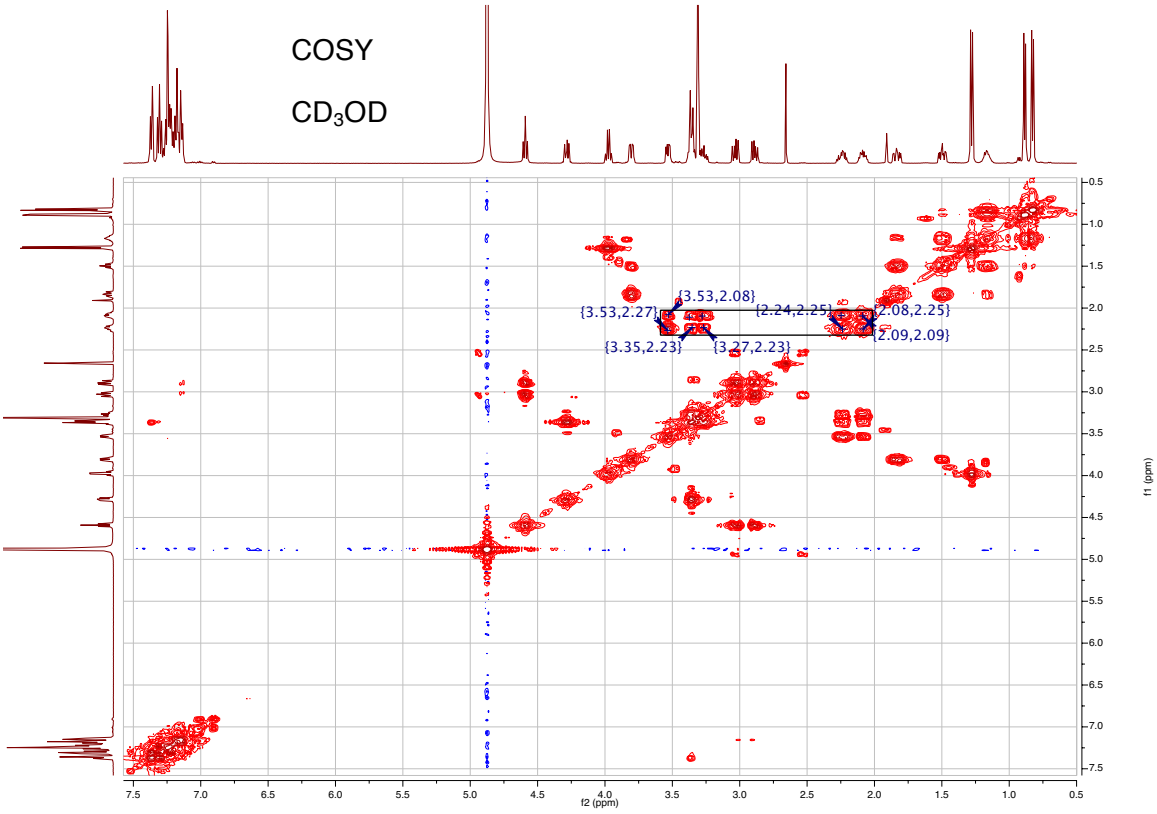

COSY
CD3OD
Both
diastereomers
f2 (ppm)
f1 (ppm)

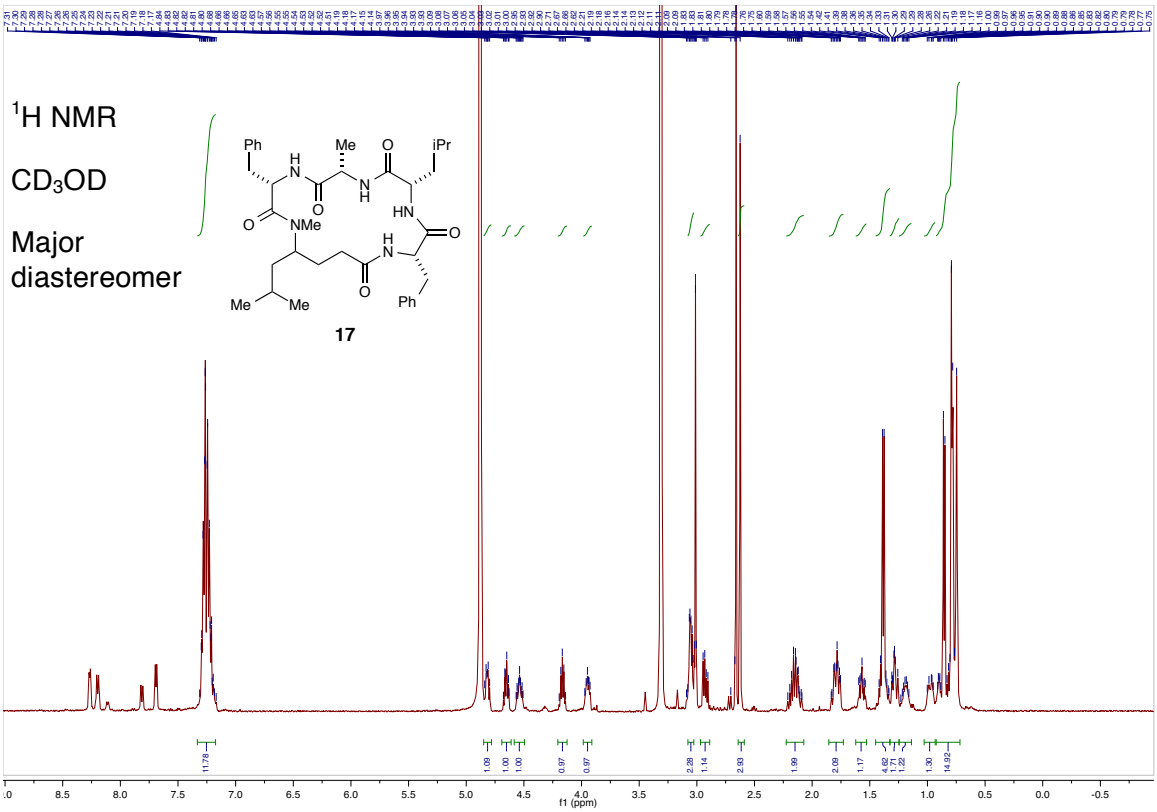

COSY
CD3OD
Major
diastereomer
{3.69,1.76}
{3.69,2.02}
{2.02,1.76}
{2.48,1.75}
{1.76,2.02}
f2 (ppm)
f1 (ppm)

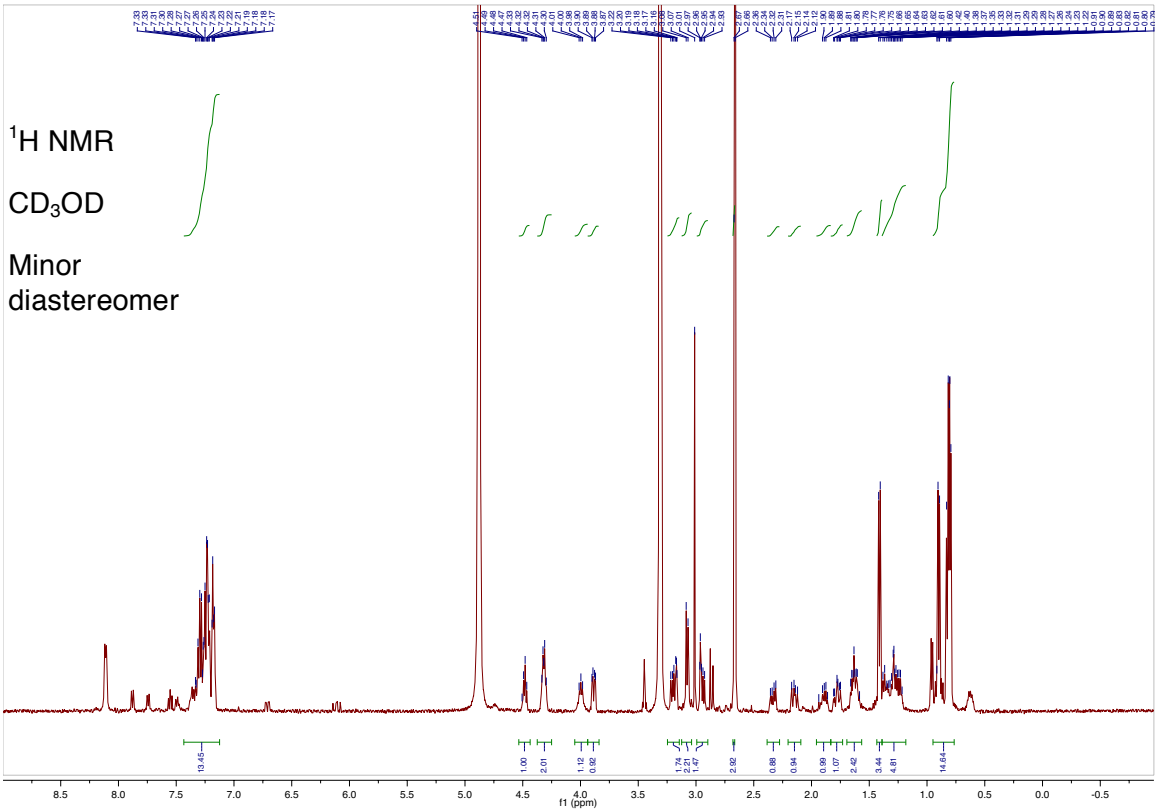

HSQC
CD3OD
Both
diastereomers
f2 (ppm)
f1 (ppm)

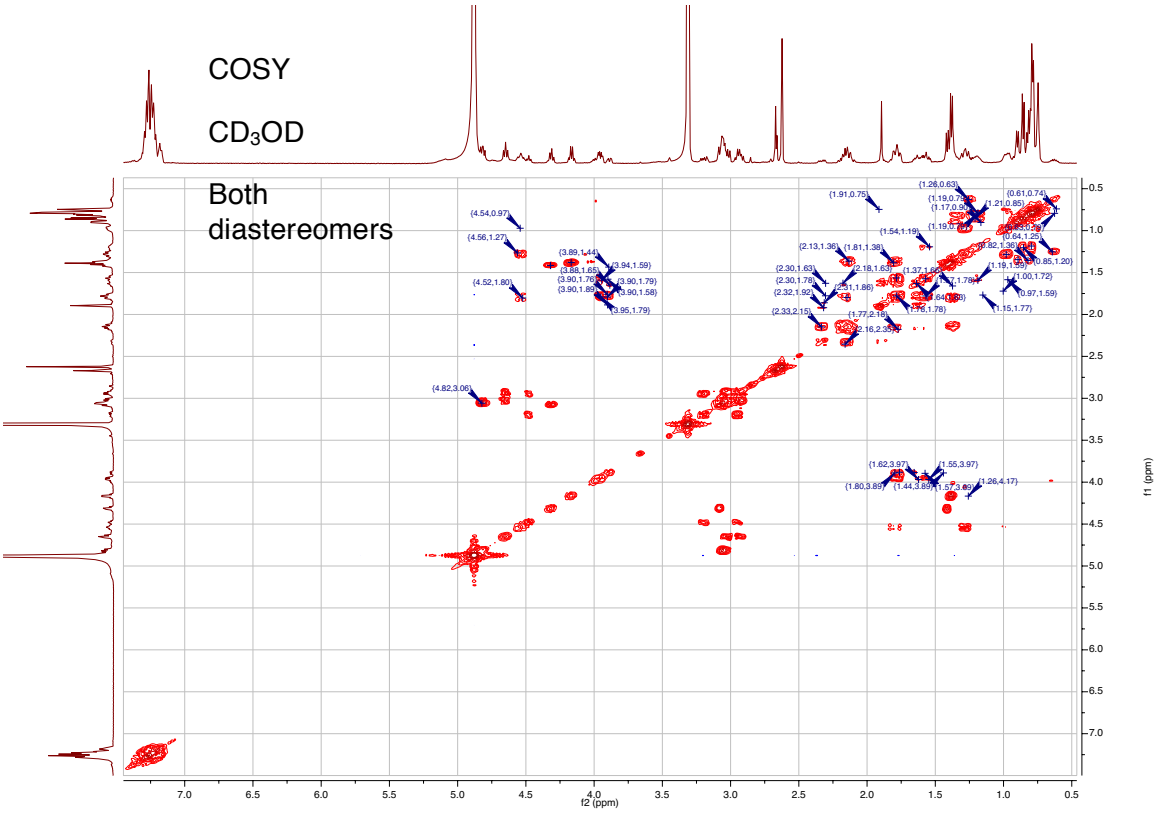

HMBC
CD3OD
Both
diastereomers
f2 (ppm)
f1 (ppm)

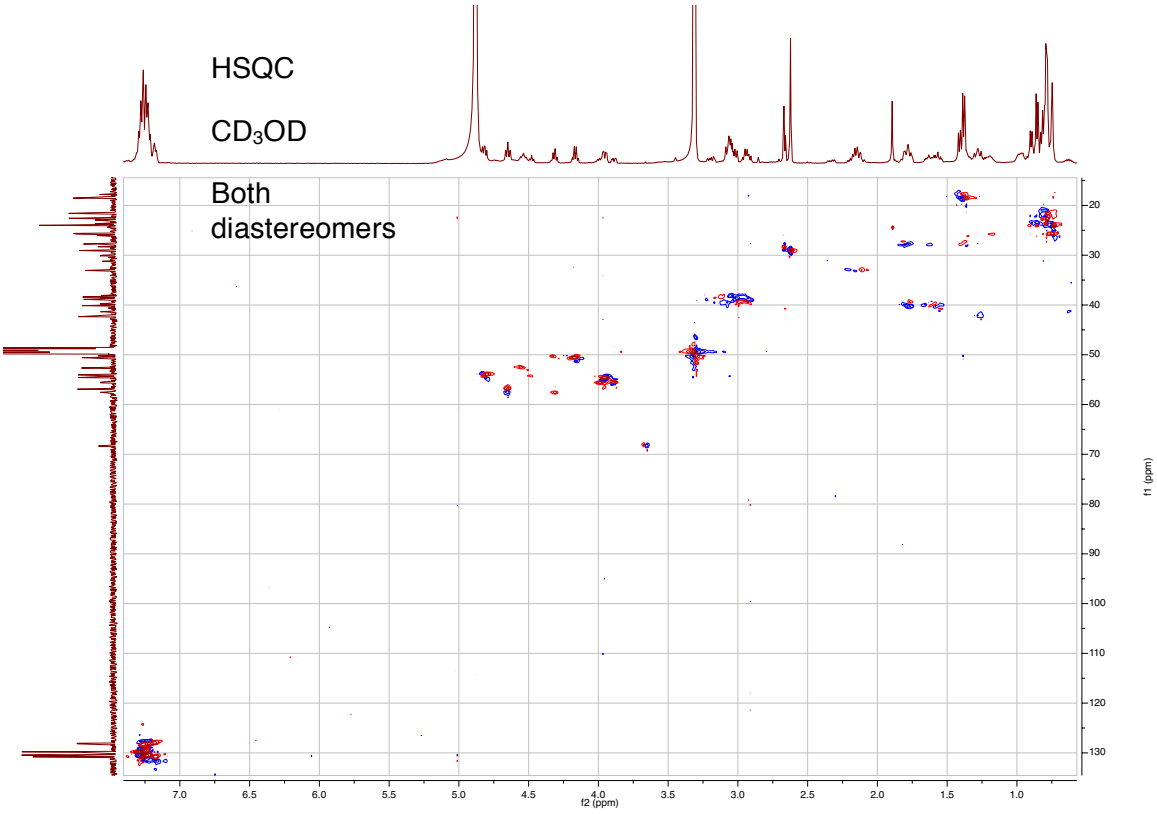

^{1}H NMR
CD_3OD
Me
O
iPr
O
N
H
NH
HN
O
Ph
H
N
HN
O
Ph
O
Ph
16
f1 (ppm)

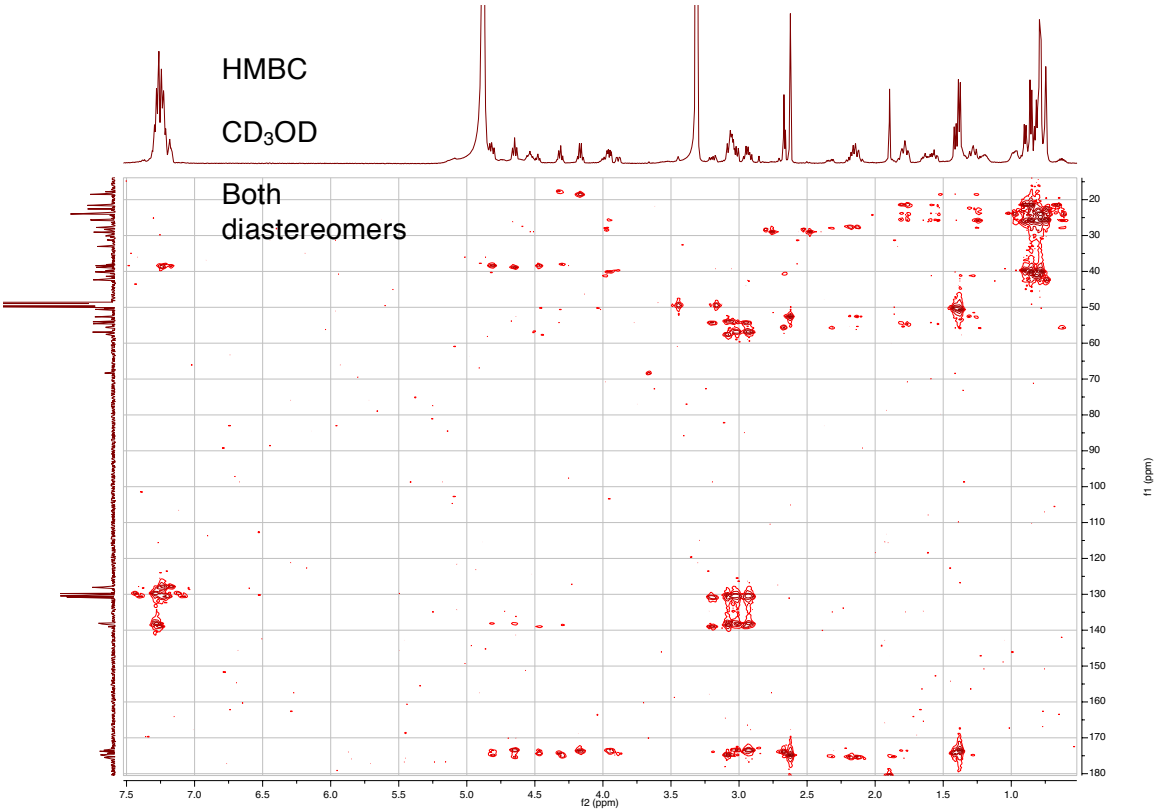

COSY
CD_3OD
{3.53,2.08}
{3.53,2.27}
{2.24,2.25}
{2.08,2.25}
{3.35,2.23}
{3.27,2.23}
{2.09,2.09}
f2 (ppm)
f1 (ppm)

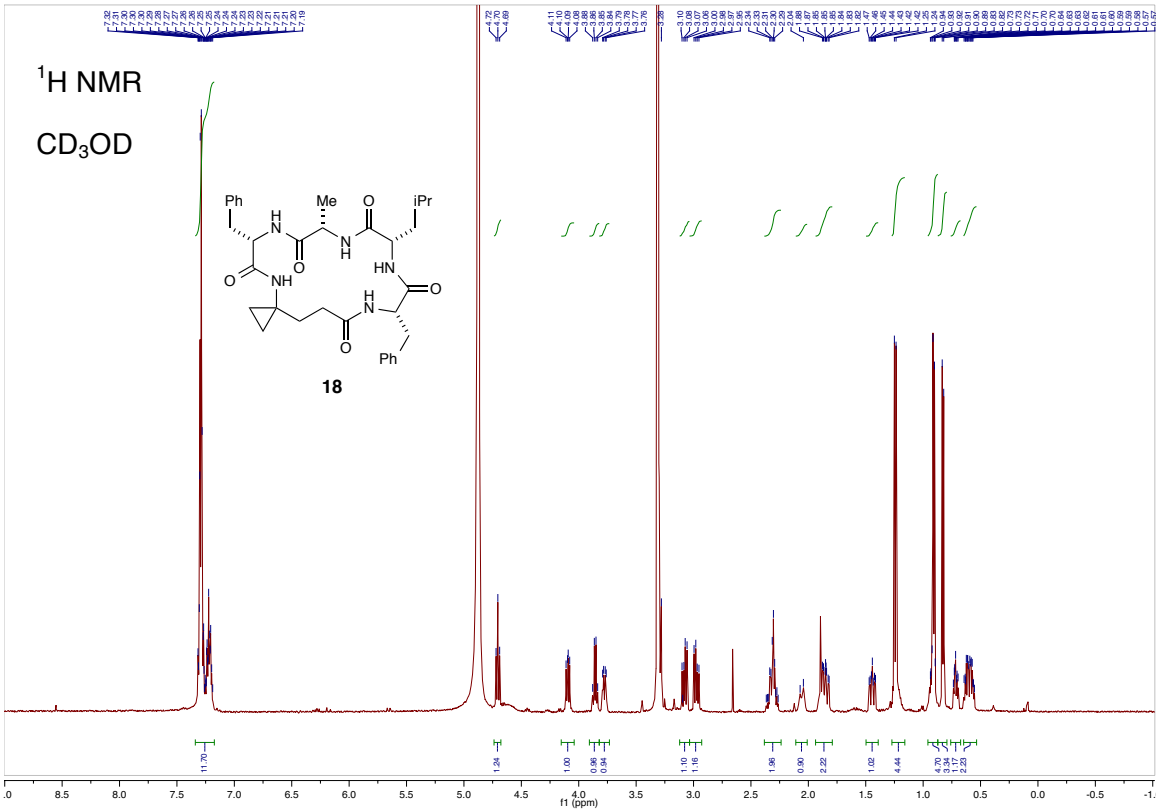

^{1}H NMR
CD_3OD
Major
diastereomer
Ph
Me
O
iPr
H
N
N
H
HN
O
O
O
NMe
H
N
O
Me
Me
Ph
17
11.78
1.09
1.00
1.00
0.97
0.97
2.28
1.14
2.93
1.99
2.09
1.17
4.62
1.71
1.22
1.30
14.92
f1 (ppm)

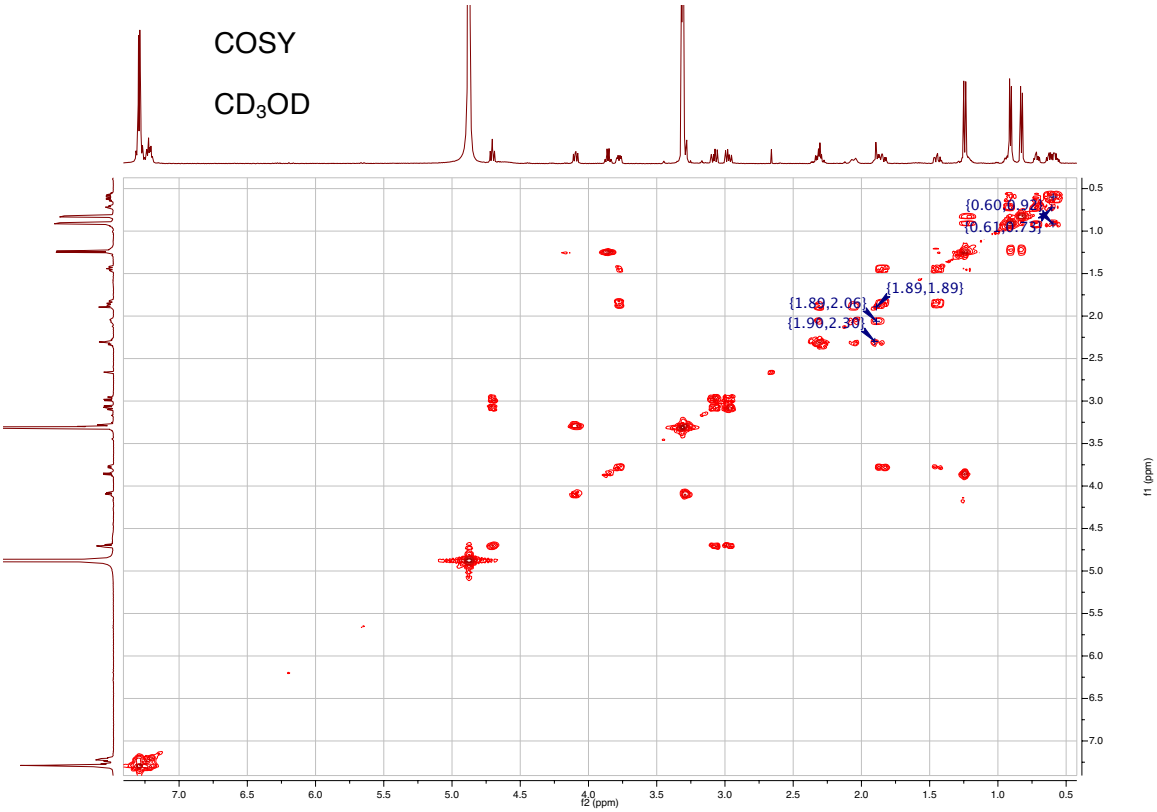

^{1}H NMR
CD_3OD
Minor
diastereomer
13.45
1.00
2.01
1.12
0.92
1.74
2.21
1.47
2.92
0.88
0.94
0.99
1.07
2.42
3.44
4.81
14.64
f1 (ppm)

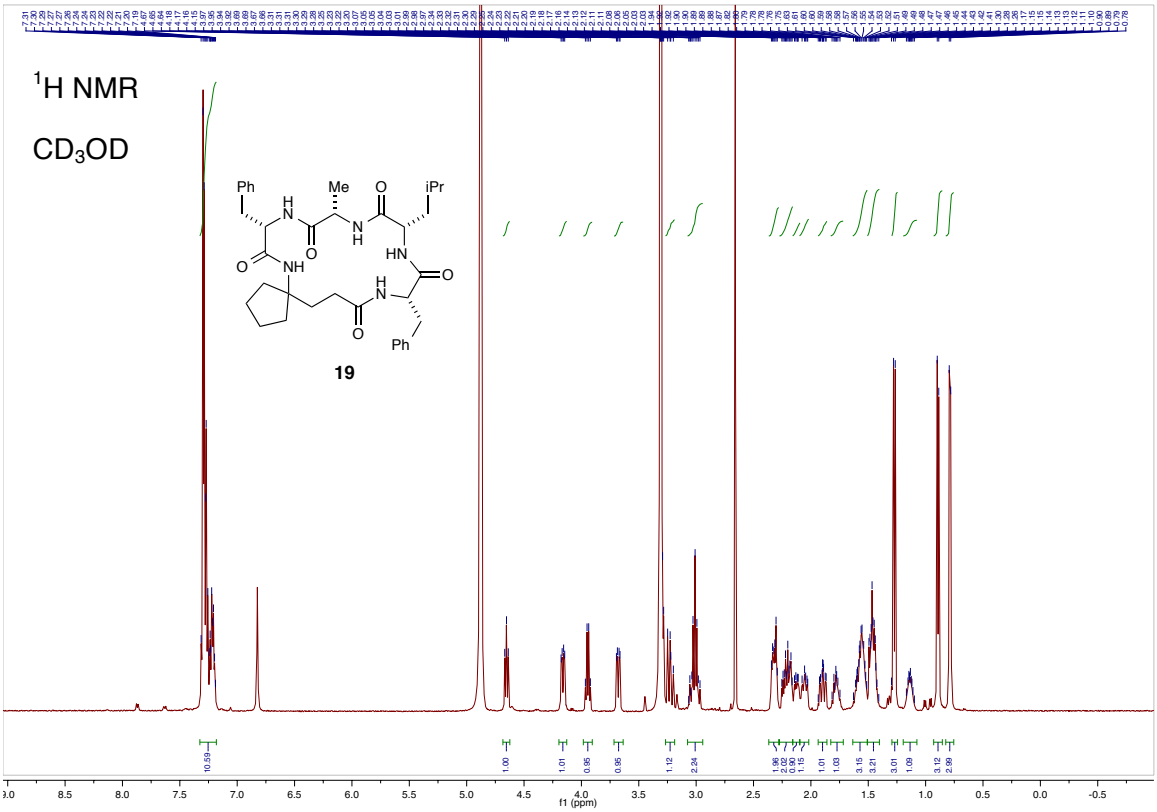

COSY
CD3OD
Both
diastereomers
f2 (ppm)
f1 (ppm)

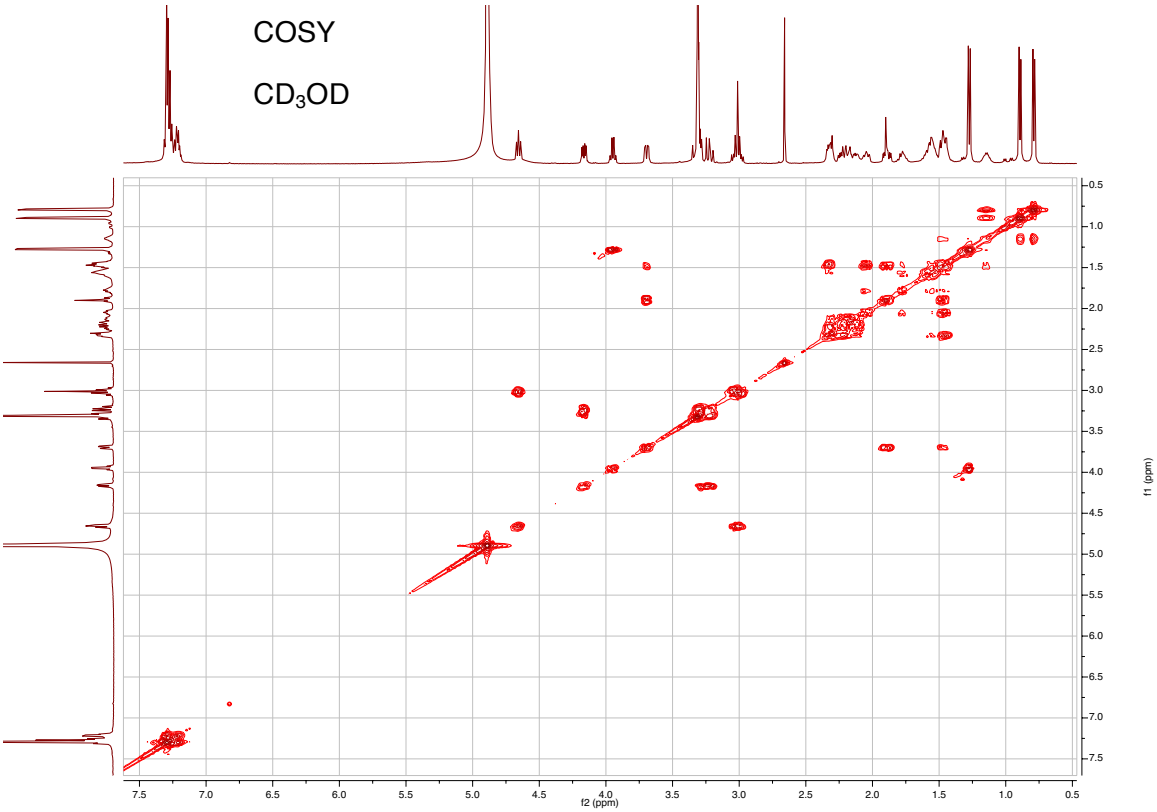

HSQC
CD3OD
Both
diastereomers
f2 (ppm)
f1 (ppm)

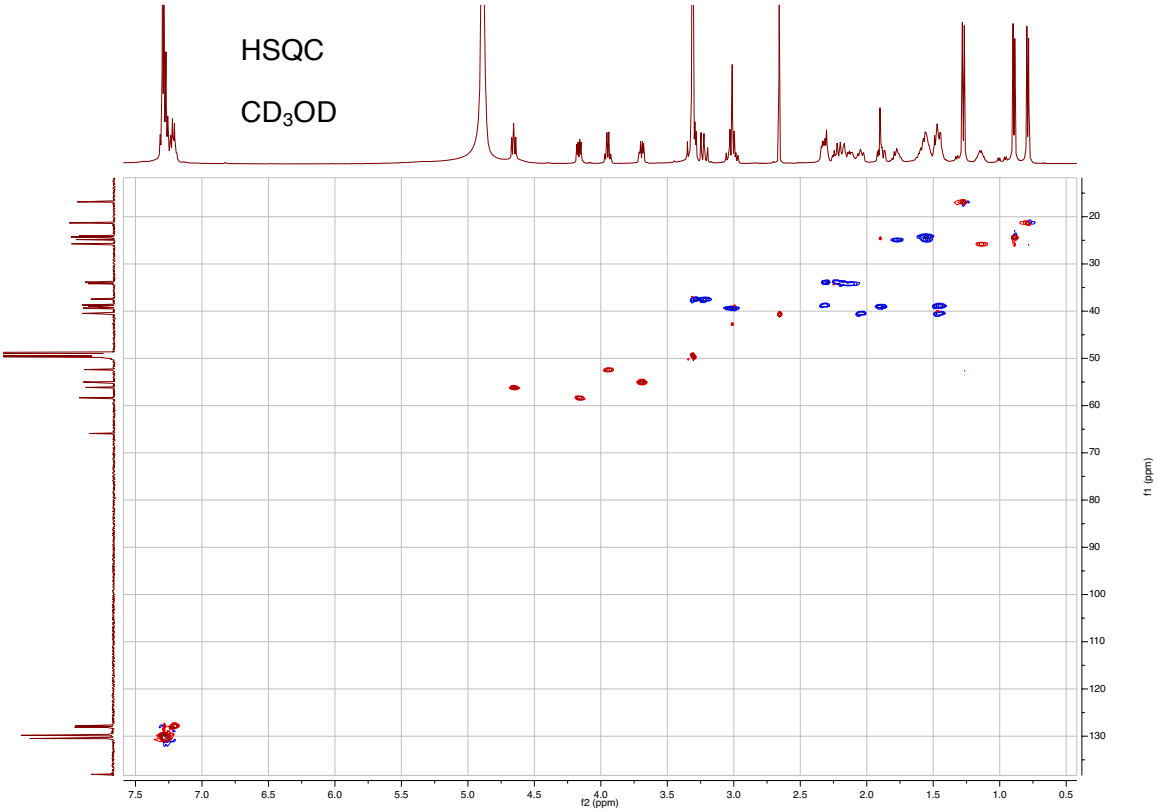

HMBC
CD3OD
Both
diastereomers
f2 (ppm)
f1 (ppm)

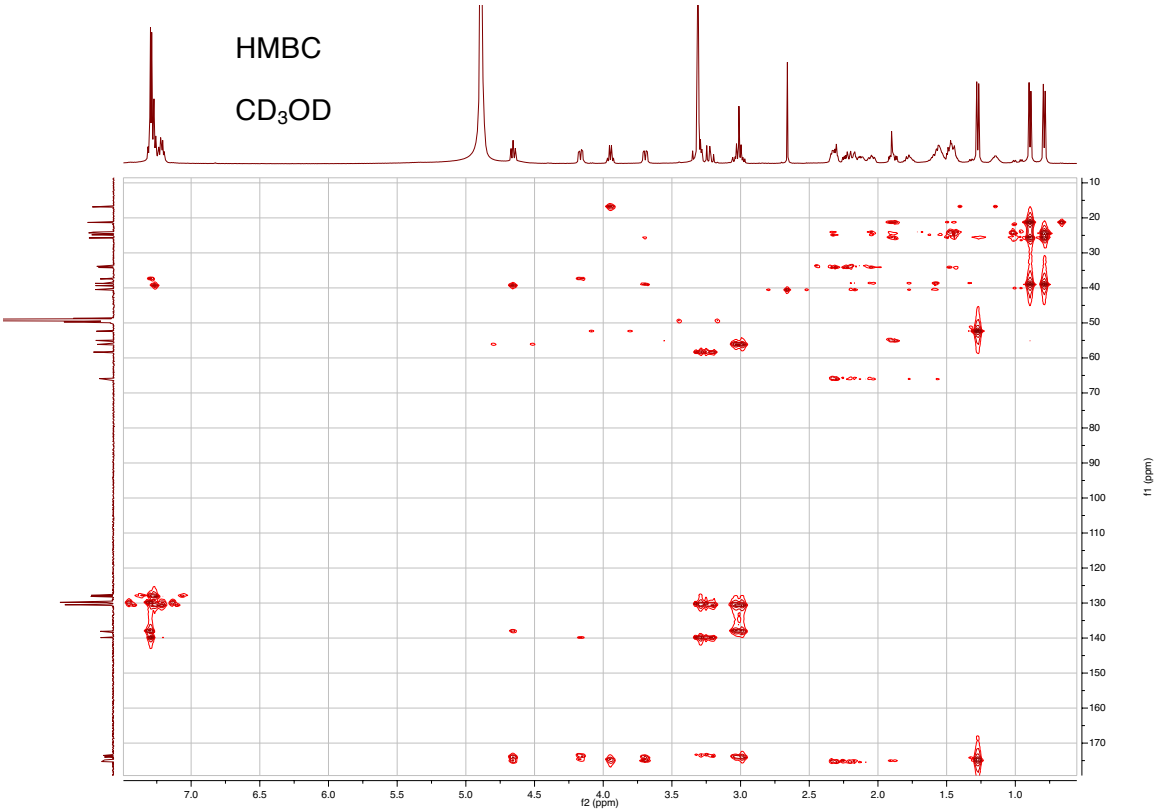

1H NMR
CD3OD
Ph
Me
iPr
18
f1 (ppm)

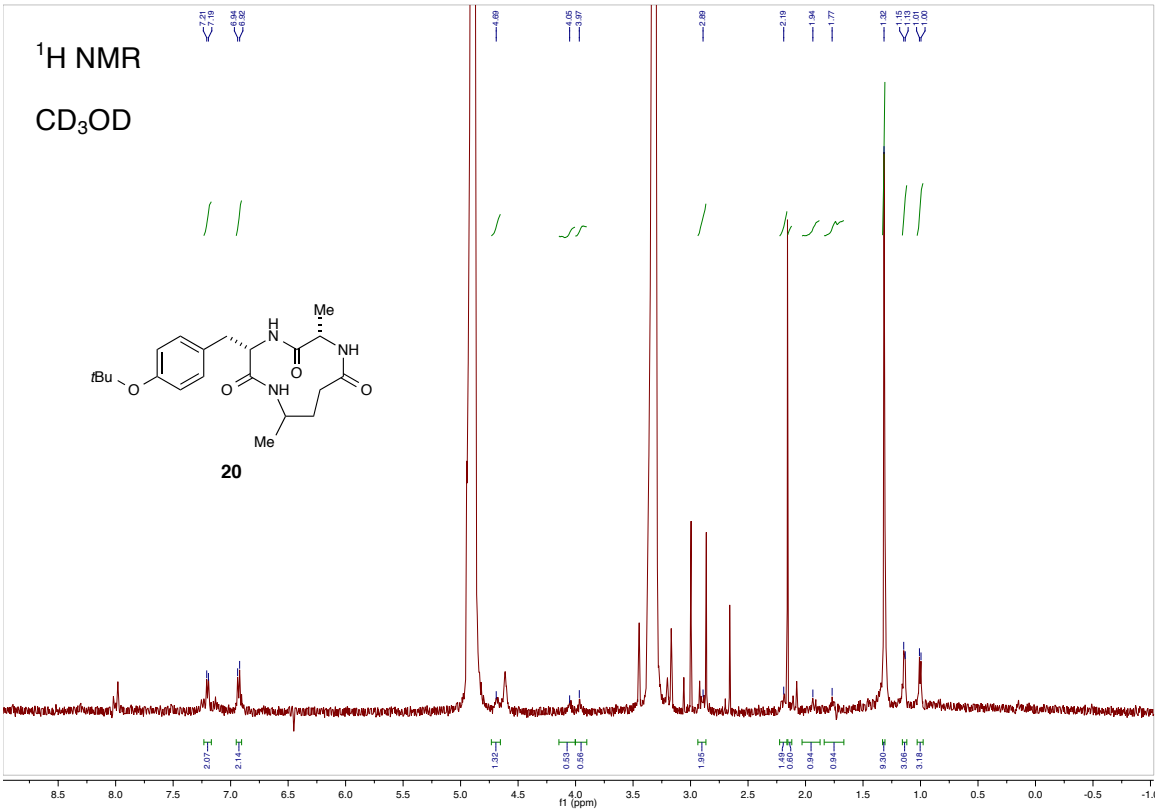

COSY
CD3OD
{1.89,1.89}
{1.89,2.06}
{1.90,2.30}
f2 (ppm)
f1 (ppm)


1H NMR
CD3OD
Ph
Me
iPr
19
f1 (ppm)


COSY
CD3OD
f2 (ppm)
f1 (ppm)

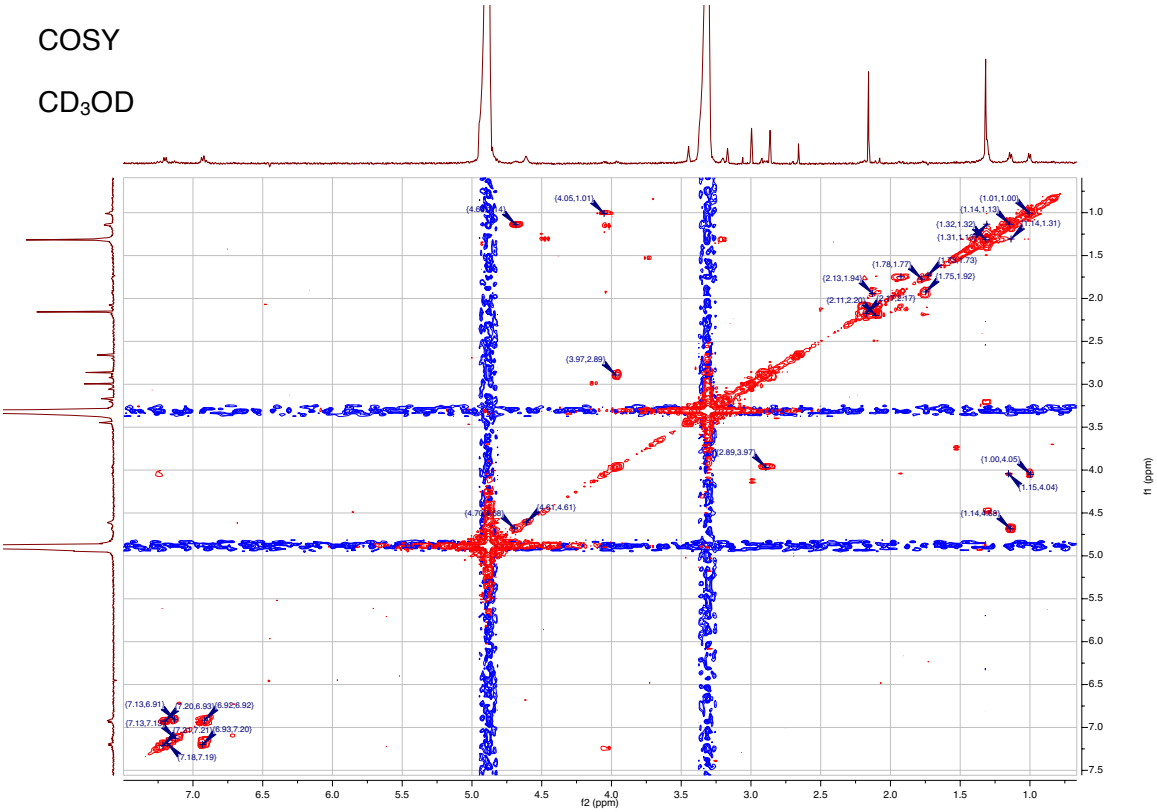

HSQC
CD3OD
f2 (ppm)
f1 (ppm)


HMBC
CD3OD
f2 (ppm)
f1 (ppm)


1H NMR
CD3OD
tBu
Me
Me
20
f1 (ppm)

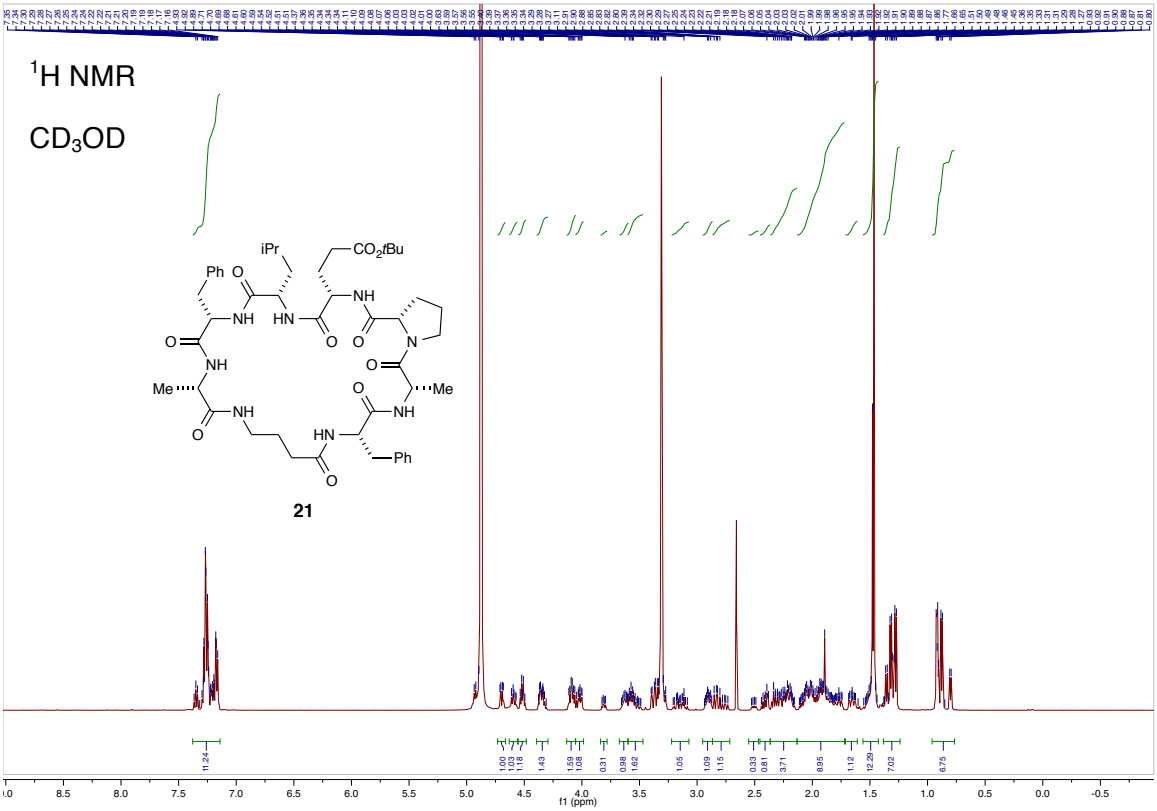
COSY

CD_3OD

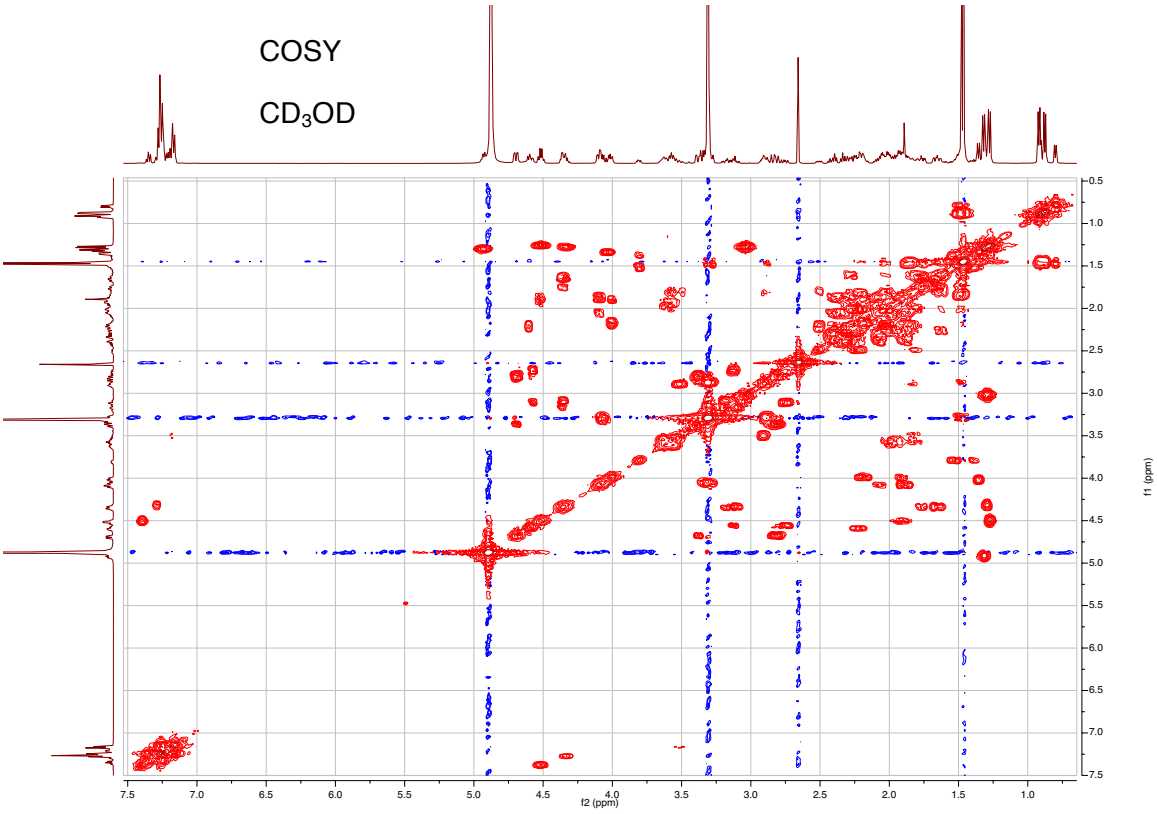


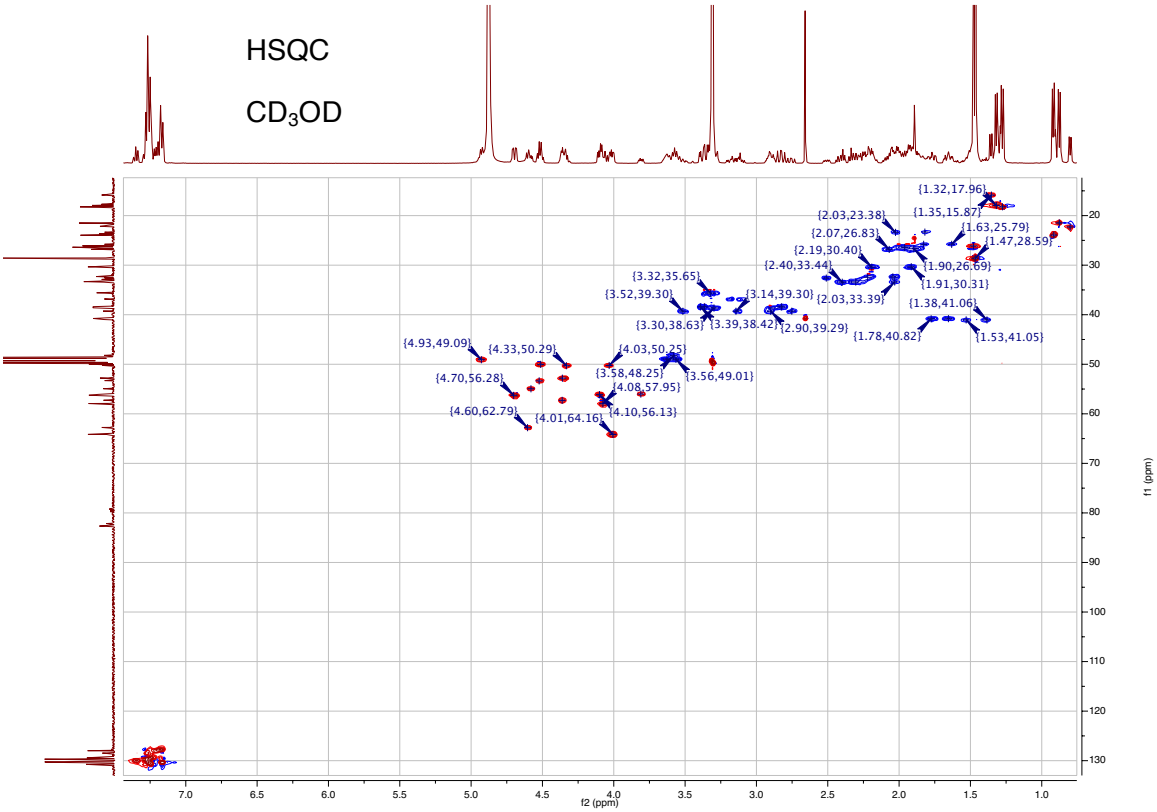
^1H NMR

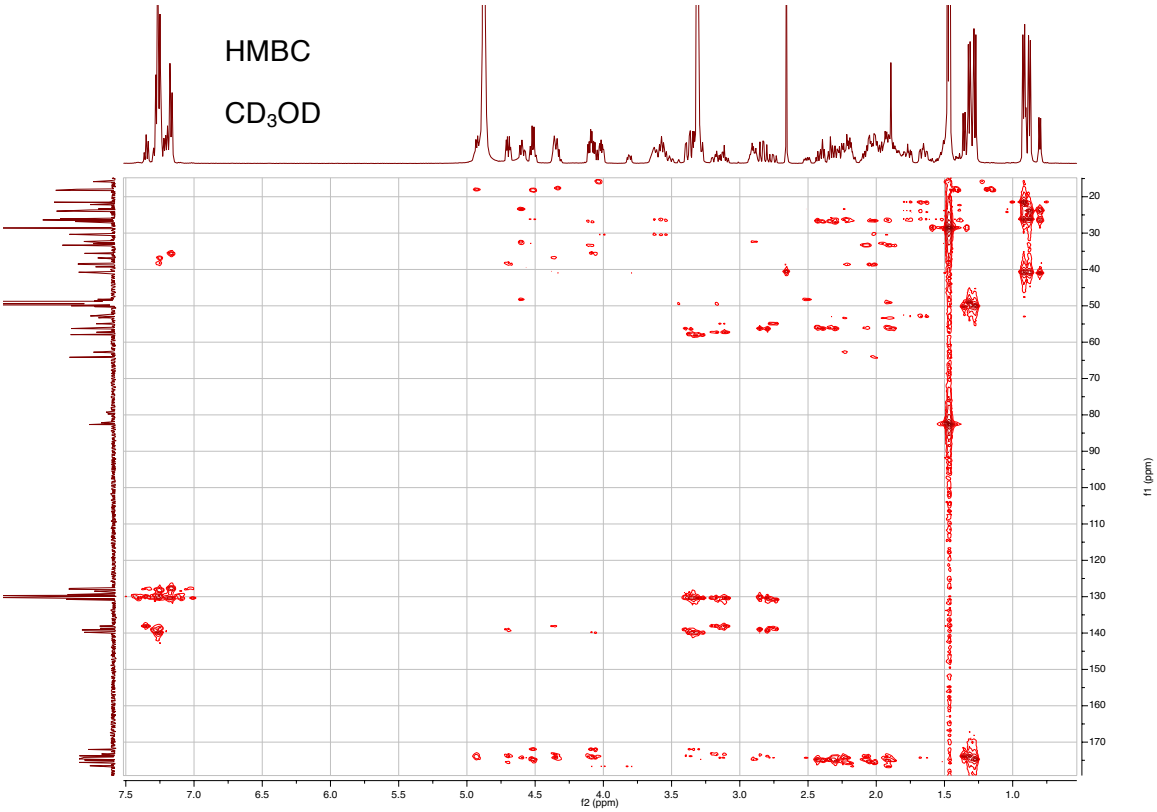
CD_3OD

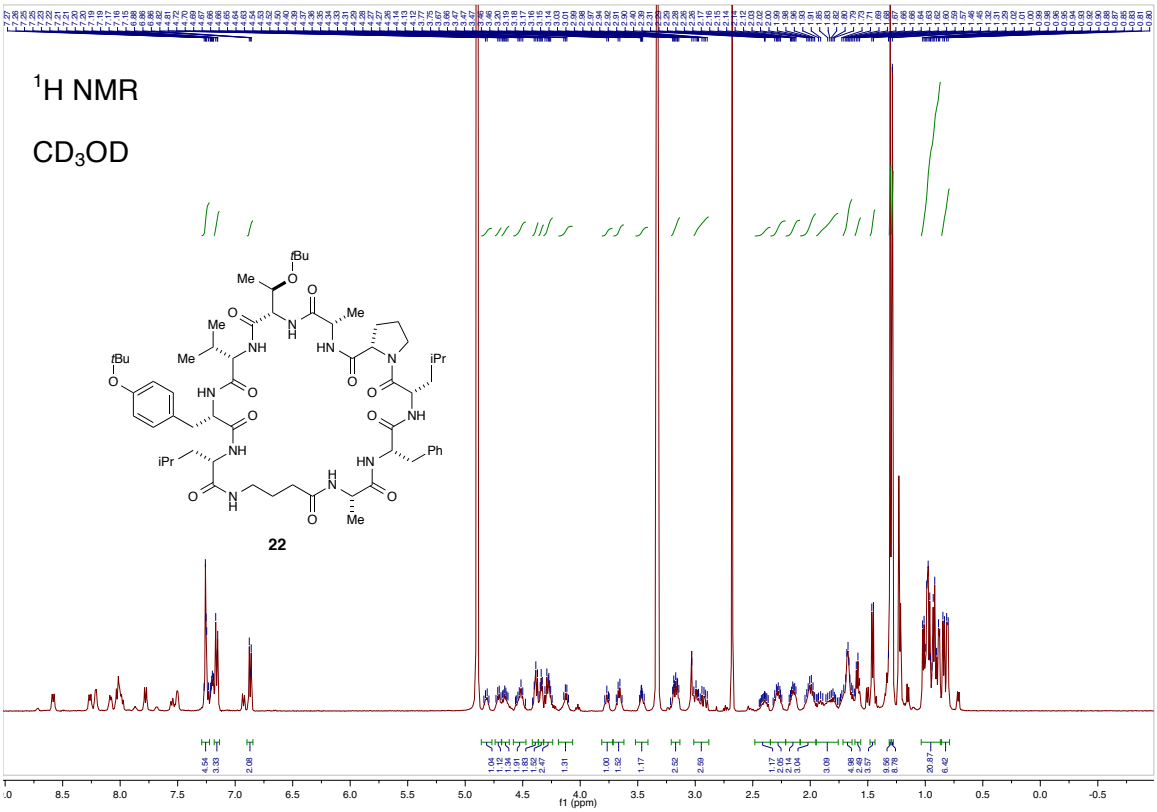


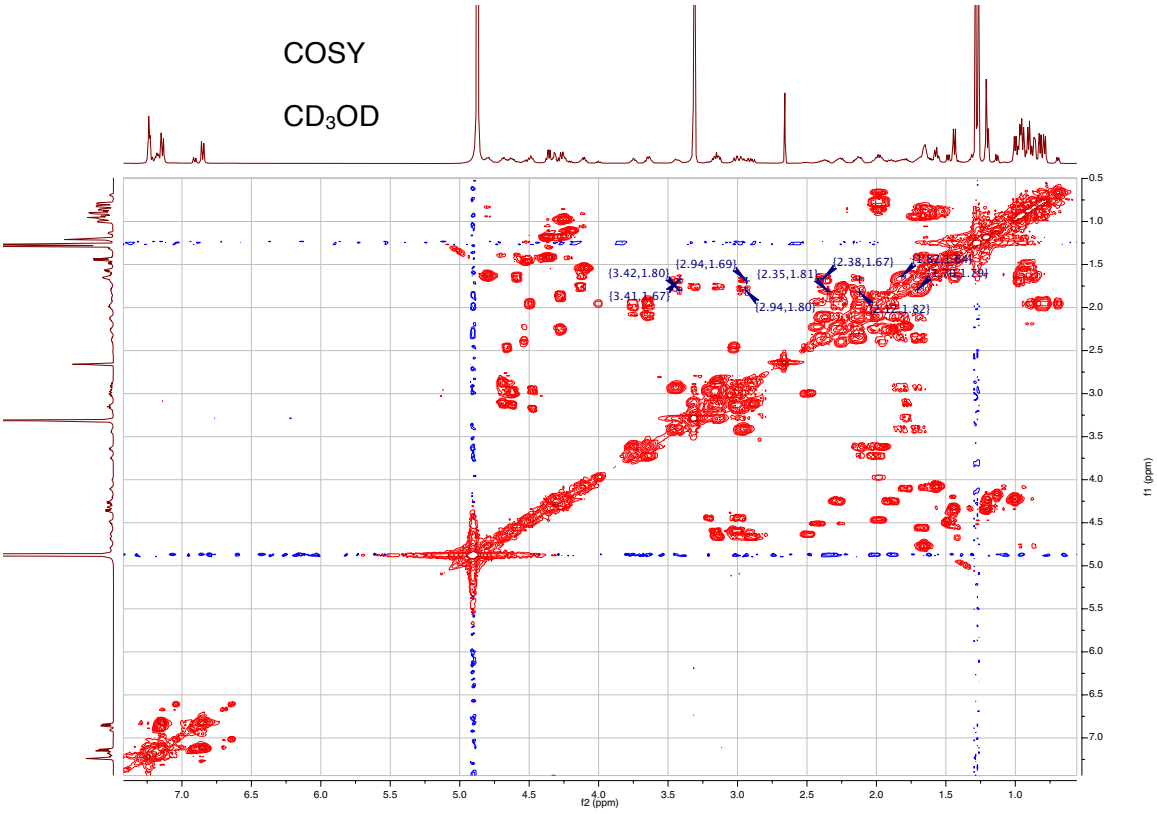
21

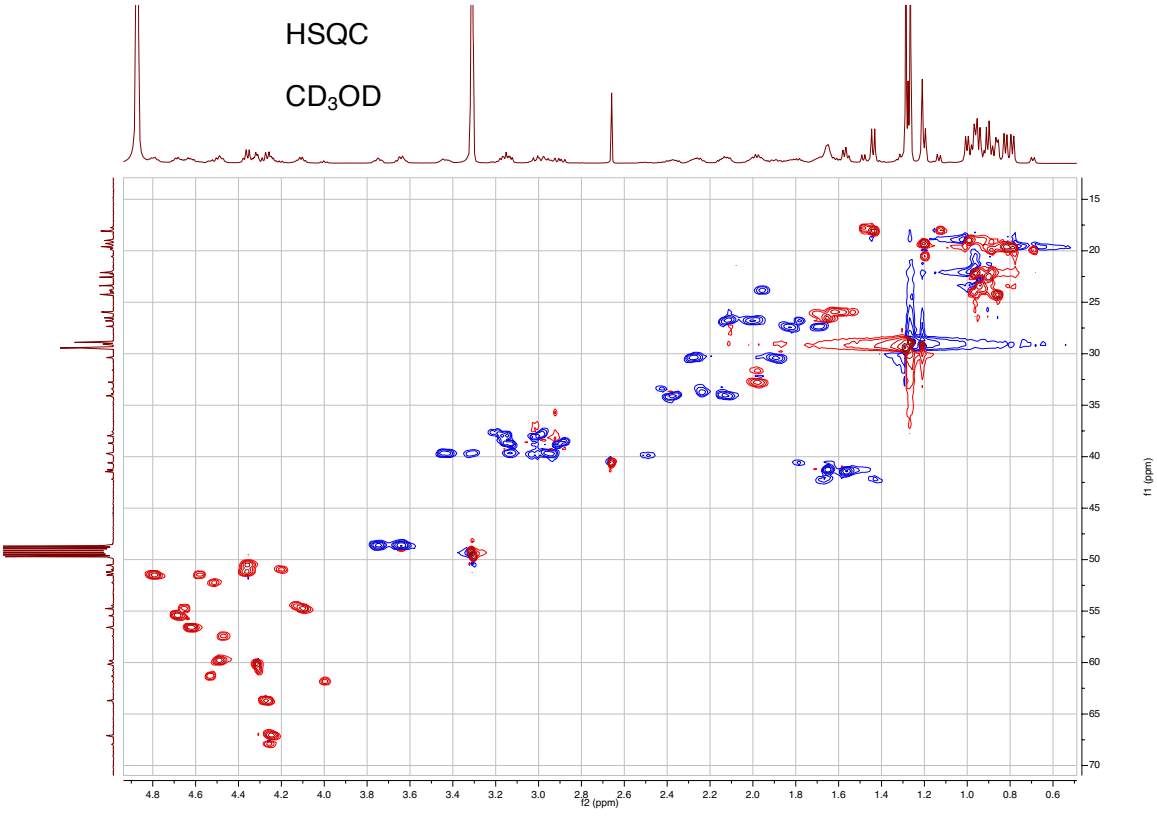

COSY
CD3OD
f2 (ppm)
f1 (ppm)

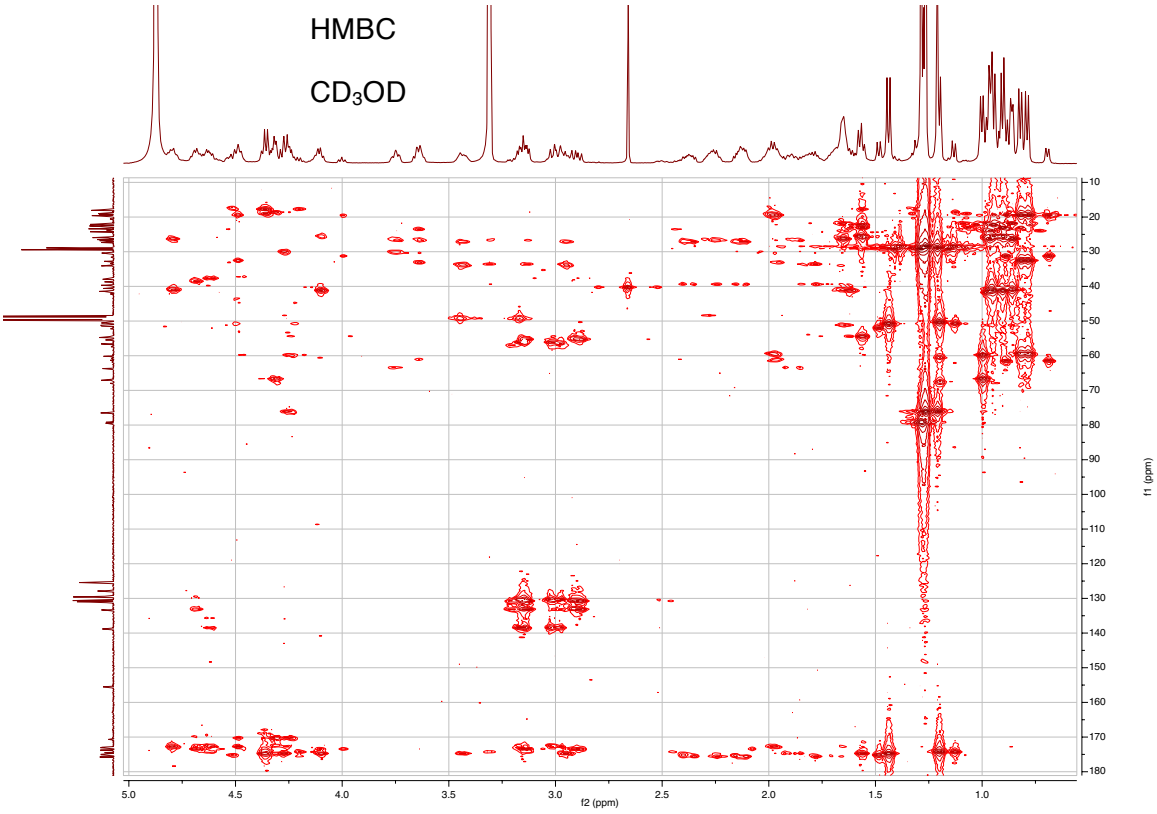

HSQC
CD3OD
{1.32,17.96}
{1.35,15.87}
{2.03,23.38}
{1.63,25.79}
{2.07,26.83}
{1.47,28.59}
{2.19,30.40}
{2.40,33.44}
{1.90,26.69}
{1.91,30.31}
{3.32,35.65}
{3.52,39.30}
{3.14,39.30}
{2.03,33.39}
{1.38,41.06}
{3.30,38.63}
{3.39,38.42}
{2.90,39.29}
{1.78,40.82}
{1.53,41.05}
{4.93,49.09}
{4.33,50.29}
{4.03,50.25}
{4.70,56.28}
{3.58,48.25}
{3.56,49.01}
{4.08,57.95}
{4.60,62.79}
{4.01,64.16}
{4.10,56.13}
f2 (ppm)
f1 (ppm)

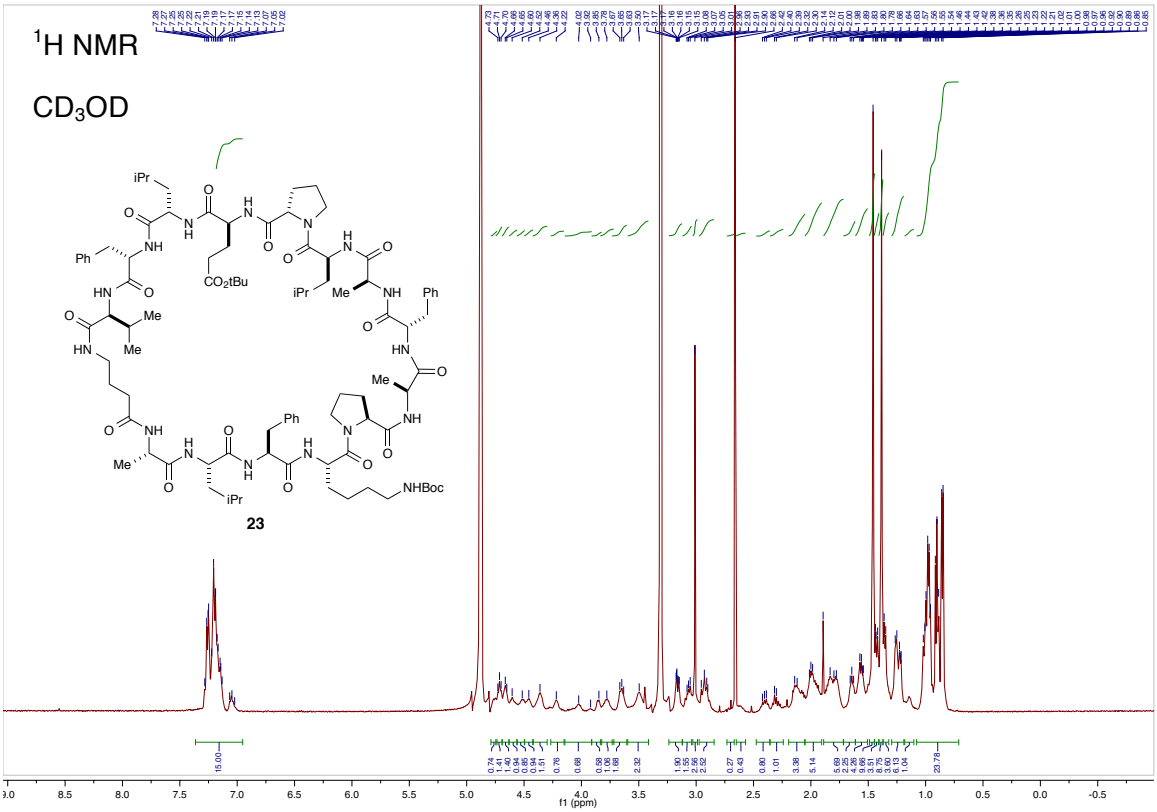

HMBC
CD3OD
f2 (ppm)
f1 (ppm)

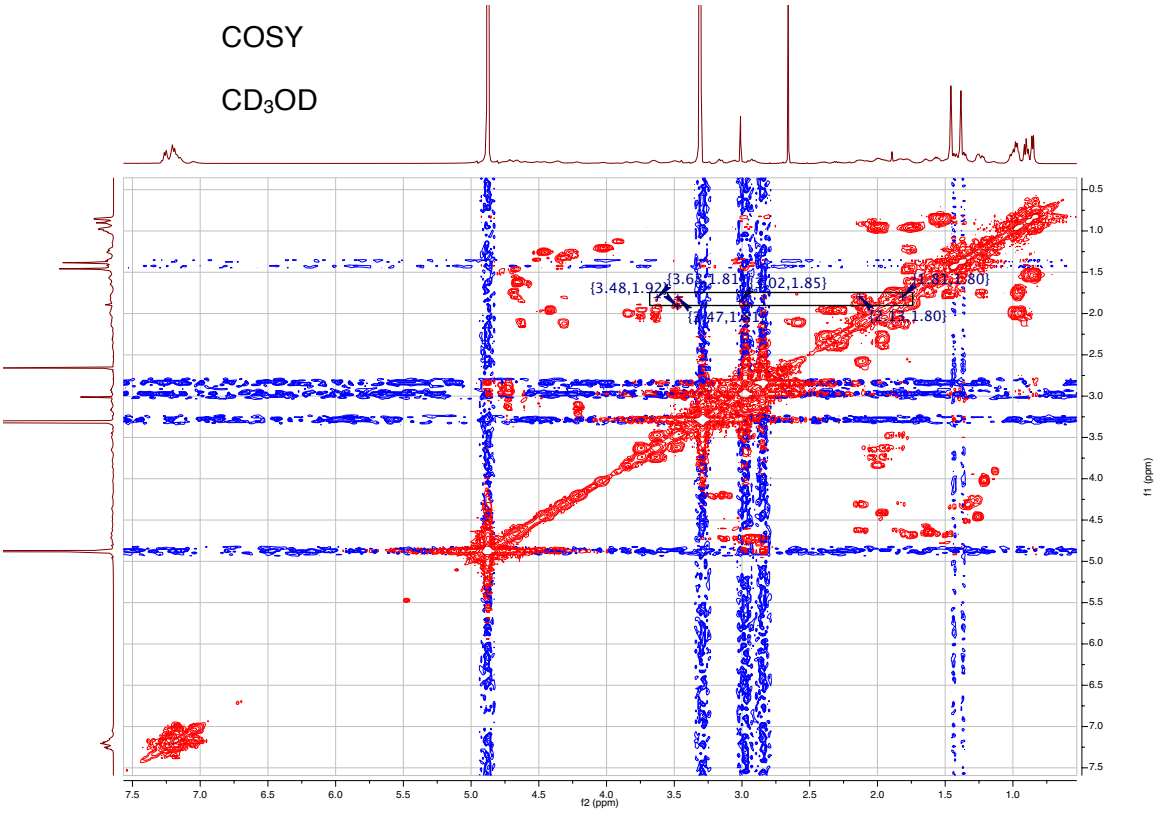

1H NMR
CD3OD
22
f1 (ppm)

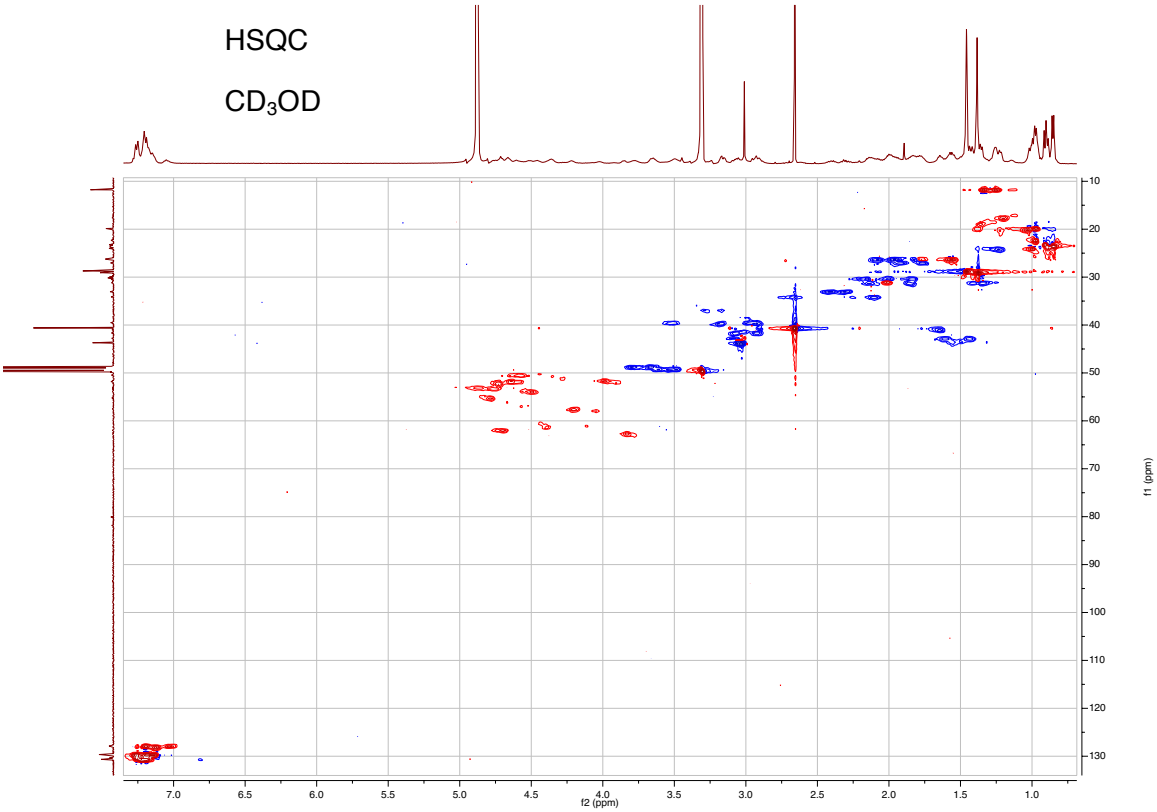

COSY
CD3OD
{3.42,1.80}
{2.94,1.69}
{2.35,1.81}
{2.38,1.67}
{3.41,1.67}
{2.94,1.80}
f2 (ppm)
f1 (ppm)

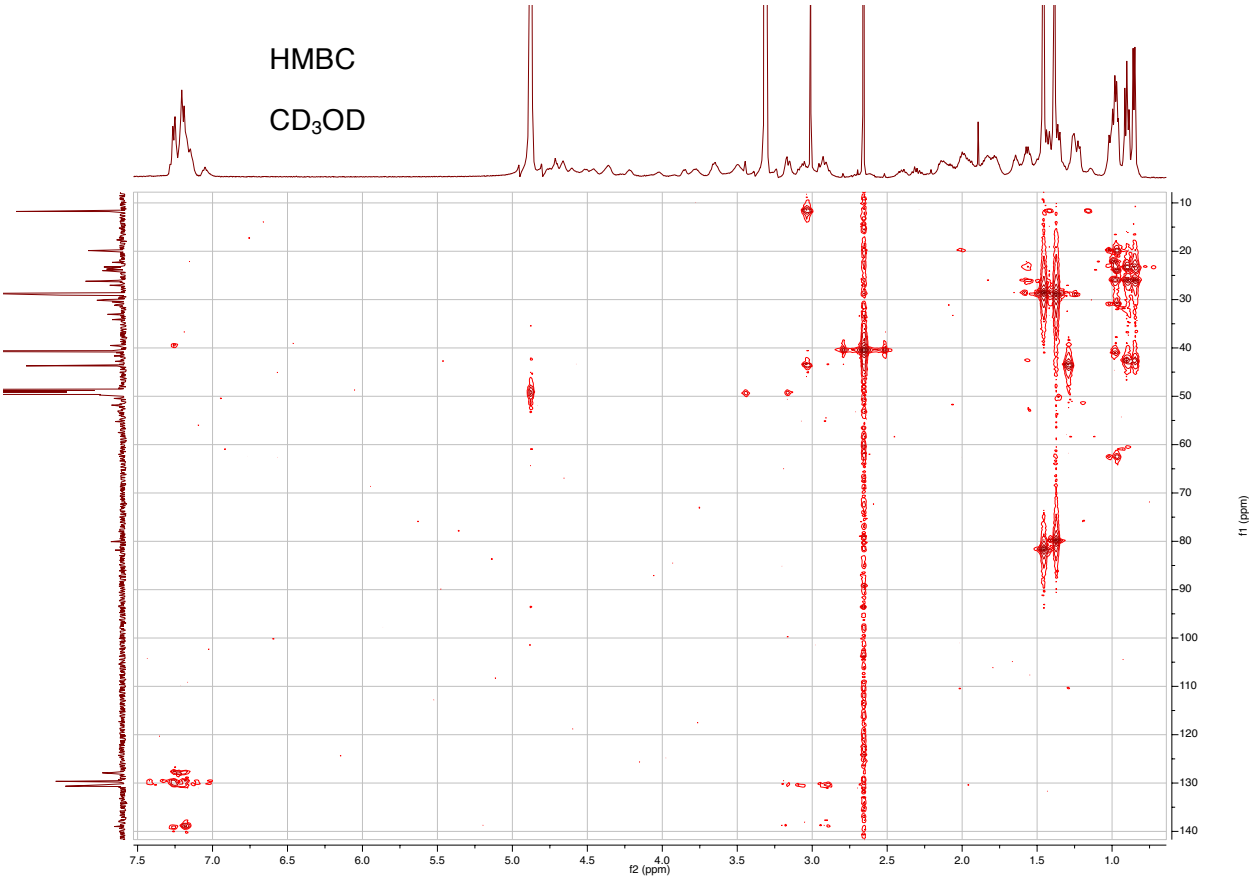

HSQC
CD3OD
f2 (ppm)
f1 (ppm)

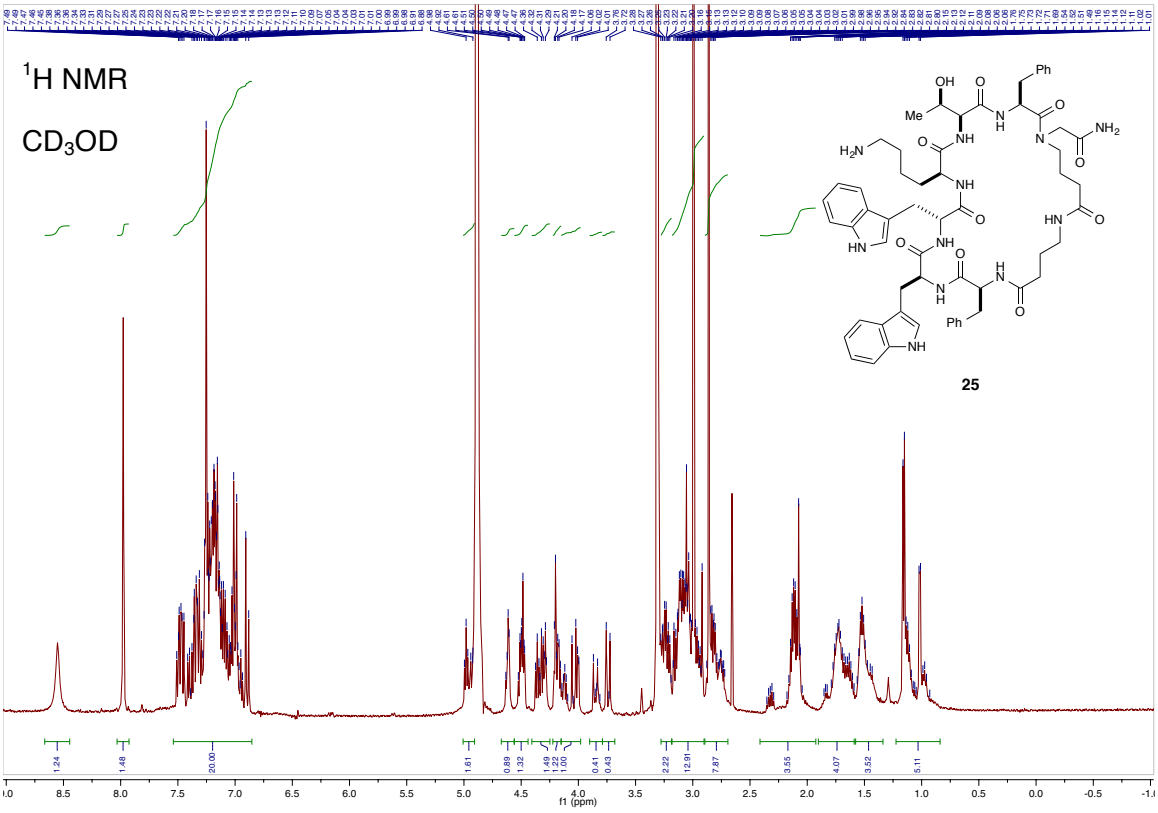

HMBC
CD3OD
f2 (ppm)
f1 (ppm)


1H NMR
CD3OD
iPr
Ph
CO2tBu
Me
NHBoc
23
f1 (ppm)

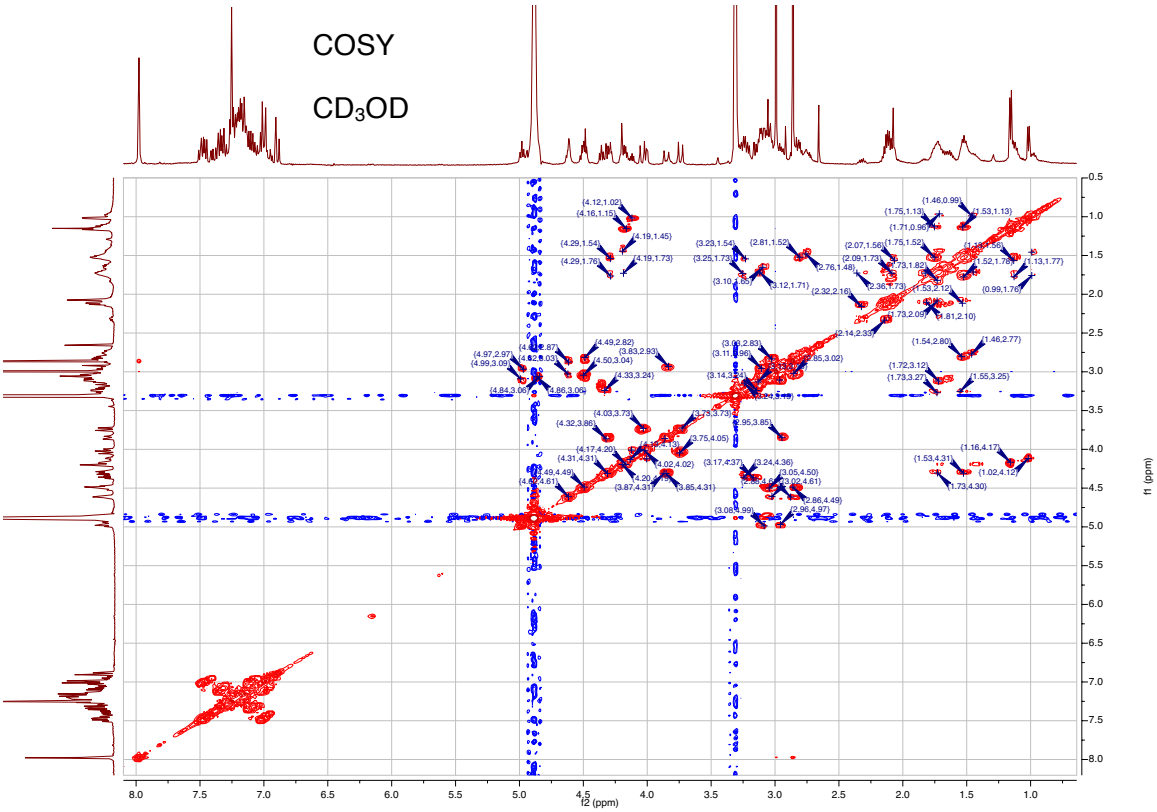

COSY
CD3OD
{3.48,1.92}
f2 (ppm)
f1 (ppm)

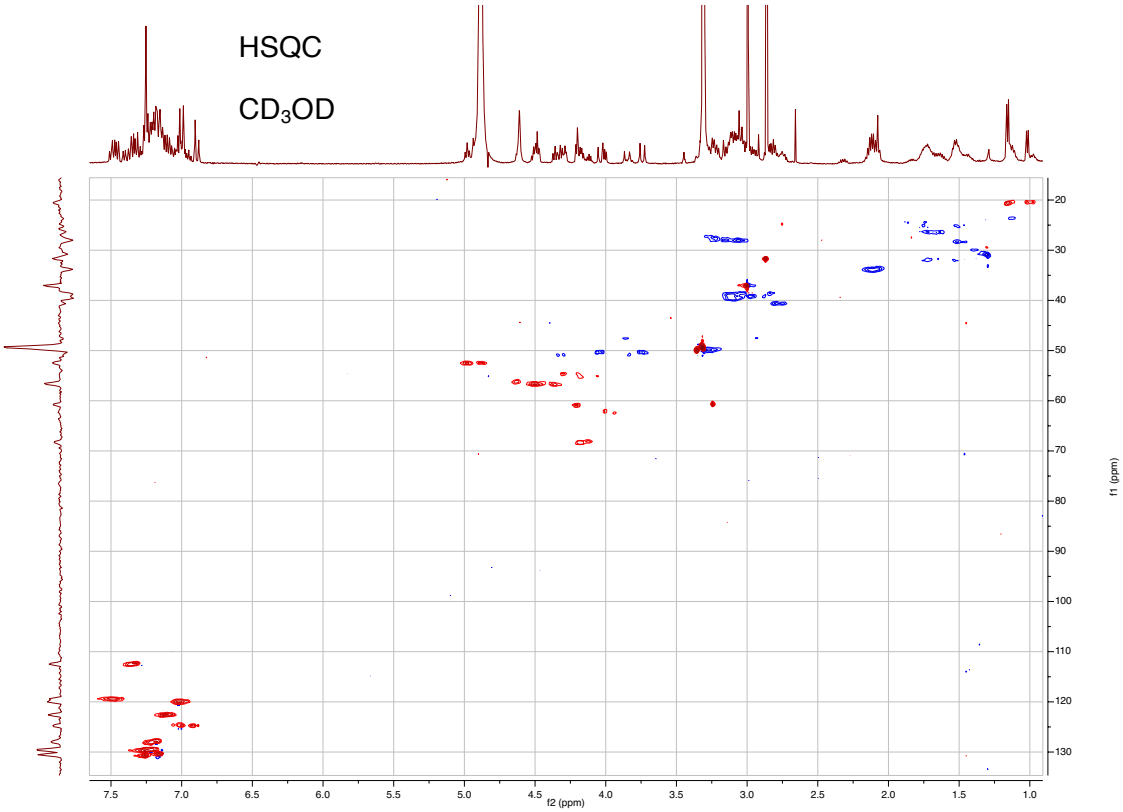

HSQC
CD3OD
f2 (ppm)
f1 (ppm)

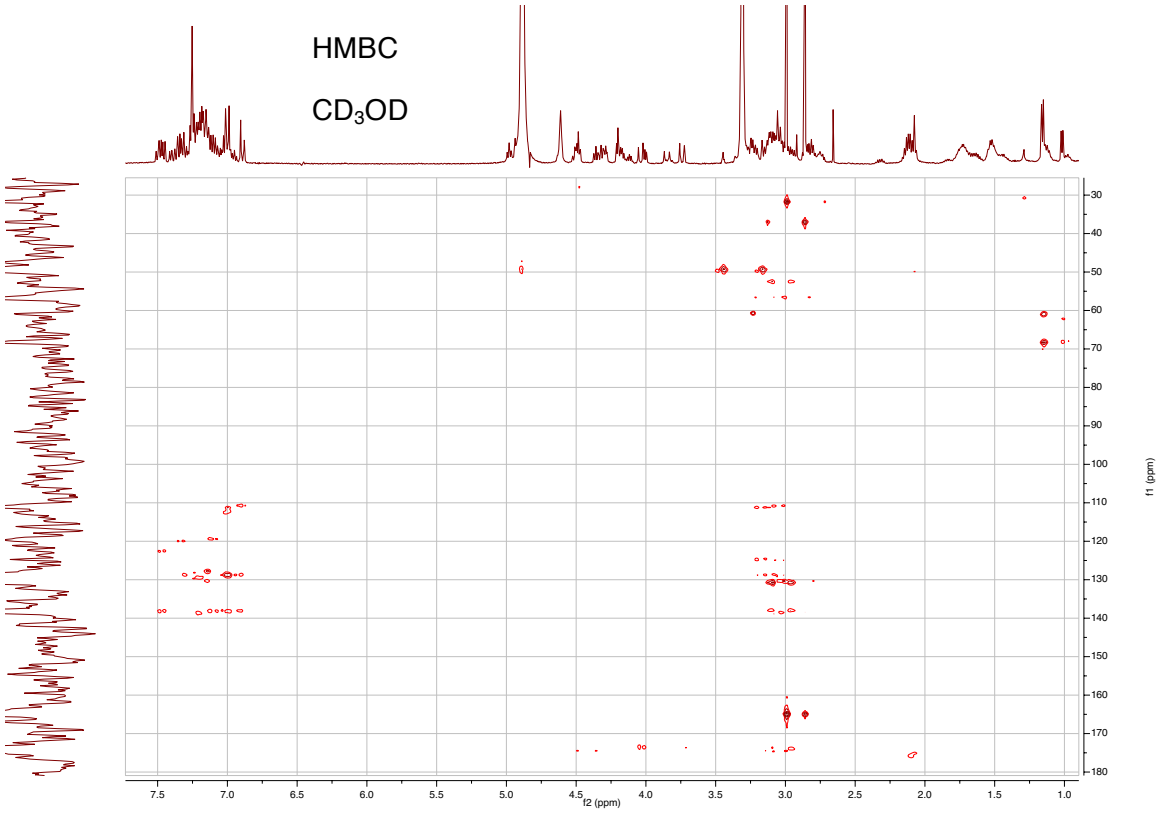




25


COSY
CD3OD
f2 (ppm)
f1 (ppm)


HSQC
CD3OD
f2 (ppm)
f1 (ppm)


HMBC
CD3OD
f2 (ppm)
f1 (ppm)