Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Stereoselective Synthesis and Structural Elucidation of Dicarba Peptides

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General Experimental Information

General Considerations

Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled drybox.

Instrumentation

Melting points (m.p.) were determined using a Reichert hot-stage melting point apparatus and are uncorrected.

Infrared spectra (IR) spectra were recorded on a Perkin-Elmer 1600 series Fourier Transform infrared spectrophotometer as thin films of liquid (neat) between sodium chloride plates. IR absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}) with the relative intensities expressed as s (strong), m (medium) or prefixed b (broad).

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Bruker DPX300, DRX400 or DRX600 spectrometers operating at 300, 400 or 600 MHz respectively, as solutions in deuterated solvents as specified. Each resonance was assigned according to the following convention: chemical shift; multiplicity; observed coupling constants (*J* Hz); number of protons. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the solvent used as specified. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), septet (sept), multiplet (m) or prefixed broad (b), or a combination where necessary.

Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on Bruker DPX300, DRX400 or DRX600 spectrometers operating at 75, 100 or 150 MHz respectively, as solutions in deuterated solvents as specified. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the deuterated solvent (as specified).

Low resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer (QMS-quadrupole mass spectrometry) as solutions in specified solvents. Spectra were recorded in positive and negative modes (ESI^{+} and ESI^{-}) as specified. High resolution electrospray mass spectra (HRMS) were recorded on a Bruker BioApex 47e Fourier Transform mass spectrometer (4.7 Tesla magnet) fitted with an analytical electrospray source. The mass spectrometer was calibrated with an internal standard solution of sodium iodide in CH_3OH.

Reverse-phase high performance liquid chromatography (RP-HPLC) was performed on Agilent 1200 series instruments. For analytical experiments, the instrument was equipped with photodiode array (PDA) detection (controlled by ChemStation software) and an automated injector (100 μL loop volume). Experiments were carried

out on a Vydac C18 analytical column (4.6 mm x 250 mm, 5 μm) at a flow rate of 1.5 mL min^{-1}. For preparative runs, the instrument used multivariable wavelength (MVW) detection (controlled by ChemStation software) and an Agilent unit injector (2 mL loop volume). Experiments were carried out on a Vydac C18 preparative column (22 mm x 250 mm, 10 μm) at a flow rate of 10 mL min^{-1}. The solvent systems were buffer A, 0.1% aqueous TFA; buffer B, 0.1% TFA in MeCN.

Chiral high performance liquid chromatography was performed on a Agilent 1220 infinity series instrument. For experiments, the instrument was equipped with photodiode array (PDA) detection (controlled by openLAB software) and an automated injector (100 μL loop volume). Experiments were carried out on a CHIRALPAK QN-AX column (4.6 mm x 150 mm, 5 μm) at a flow rate of 1.0 mL min^{-1}. The solvent system was 92:2:0.5 (v/v/w); MeOH:AcOH:NH_4OAc.

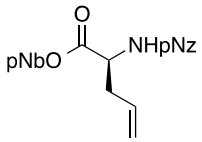
Solvents and Reagents

Dichloromethane (CH_2Cl_2) was supplied by Merck and distilled over CaH_2 prior to use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were supplied by Merck and distilled over potassium prior to use. Acetic acid (AcOH), acetone, dimethylformamide (DMF) ethyl acetate (EtOAc), hexane and methanol (CH_3OH) were used as supplied by Merck. Sodium azide (NaN_3), *p*-nitrobenzyl bromide, ethyl vinyl ether, trifluoroacetic acid, (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (GII), [2-(1-Methylethoxy-*O*)phenylmethyl-*C*](nitrato-*O,O'*){*rel*-(2*R*,5*R*,7*R*)-adamantane-2,1-diyl[3-(2,4,6-trimethylphenyl)-1-imidazolidinyl-2-y lidene]}ruthenium (ZG) and (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (HGII) were supplied by Sigma-Aldrich. D_2O and $CDCl_3$ were purchased from Cambridge Isotopes Laboratory.

Experimental Section

Synthesis of DAS unit

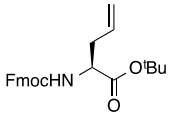
4-Nitrobenzyl (*S*)-2-((((4-nitrobenzyl)oxy)carbonyl)amino)pent-4-enoate 4



A solution of NaN_3 (0.624 g, 9.60 mmol) in H_2O (2.5 mL) was added to a solution of *p*-nitrobenzyl chloroformate (1.73 g, 8.00 mmol) in 1,4-dioxane (3.5 mL). The resulting emulsion was stirred for 2 h at room temperature. Allylglycine (0.920 g, 8.00 mmol) was dissolved in a 1:1 mixture of 1,4-dioxane/2% aqueous Na_2CO_3 (10 mL) and added dropwise to the reaction mixture. The pH was adjusted to between 9 and 10 with 10% aqueous Na_2CO_3. The resultant solution was stirred for 16 h at room temperature. The reaction was diluted with H_2O (50 mL) and washed with Et_2O (50 mL). The aqueous phase was acidified to pH 2 with 6 M aqueous HCl and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in DMF (40 mL) and K_2CO_3 (2.21 g, 16.0 mmol) was added. *p*-Nitrobenzyl bromide (1.89 g, 8.80 mmol) was added and the mixture was stirred for 16 h at room temperature. The reaction was diluted with Et_2O (150 mL) and washed with H_2O (3 x 100 mL), 10% aqueous $CuSO_4$ (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (1:3, EtOAc: hexane) to give the titled compound **4** as a colourless solid (2.71 g, 79%), mp 86.3-88.5 ^oC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 5.71-5.61 (m, 1H), 5.45 (d, J = 8.0 Hz, 1H), 5.26 (s, 2H), 5.19 (s, 2H), 5.14-5.10 (m, 2H), 4.50 (q, J = 8.0 Hz, 1H), 2.65-2.51 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4, 155.4, 147.9, 147.6, 143.7. 142.5, 131.7, 128.6, 128.1, 123.9, 123.8, 119.9, 65.7, 65.5, 53.4, 36.4. IR (neat): 3308m, 3082w, 2948w, 1738m, 1688s 1509s, 1343s, 1270m, 1207m, 1063m cm^{-1}. HRMS (ESI^+, MeOH): *m/z* 430.1248 $[M + H]^+$, $C_{20}H_{20}N_3O_8^+$ requires 430.1245.

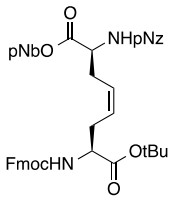
(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoic acid 5

Comment [MU]: Additional synthetic information regarding compound 5



Allyl glycine derivative **5** was prepared according to a modified procedure outlined by Jakopin and coworkers.[1] A solution of *tert*-butyl 2,2,2-trichloroacetimidate (7.65 g, 35.0 mmol) in cyclohexane (5 mL) was added to a solution of *N*-Fmoc allyl glycine (2.36 g, 7.00 mmol) in EtOAc (50 mL). The resulting reaction mixture was stirred for 16 h at room temperature, after which it was concentrated under reduced pressure. The residue was purified by silica column chromatography (1 : 9 – EtOAc : hexane) to give the titled compound **5** as a colourless oil (2.49 g, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.61-7.59 (m, 2H), 7.49-7.38 (m, 2H), 5.75-5.68 (m, 1H), 5.38 (d, *J* = 8.0 Hz, 1H), 5.16-5.13 (m, 2H), 4.40-4.34 (m, 3H), 4.24 (t, *J* = 6.8 Hz, 2.64-2.48 (m, 2H), 1.48 (s, 9H). All data was consistent with that previously reported.[1]

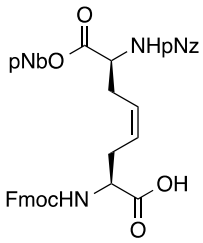
1-(*Tert*-butyl) 8-(4-nitrobenzyl) (2*S*,7*S*,4*Z*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-7-((((4-nitrobenzyl)oxy)carbonyl)amino)oct-4-enedioate, *cis*-6



Amino acid derivatives **5** (118 mg, 0.300 mmol) and **4** (86 mg, 0.20 mmol) were added to a flame dried Schlenk vessel equipped with a stir bar. The vessel was evacuated and backfilled with N_2. A solution of *Z*-selective catalyst **GZ** (25 mg, 0.04 mmol, 20 mol%) in THF (1 mL) was added to the amino acid mixture. The reaction vessel was sealed and stirred at 40 °C for 16 h. The reaction was quenched with ethyl vinyl ether (0.5 mL) and concentrated under reduced pressure. The residue was purified by silica column chromatography (1 : 4 – EtOAc : hexane) to provide the

alkene *cis*-**6** (72 mg, 45%) as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.47 (t, *J* = 8.7 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 5.51-5.43 (m, 3H), 5.38 (br s, 1H), 5.26 (d, *J* = 1.8 Hz, 2H), 5.18 (d, *J* = 3.0 Hz, 2H), 4.52 (q, *J* = 5.7 Hz, 1H), 4.40 (d, *J* = 6.9 Hz, 2H), 4.44-4.33 (m, 1H), 4.20 (t, *J* = 6.9, 1H), 2.72-2.41 (m, 4H), 1.49 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.4, 170.6, 155.7, 155.5, 148.0, 147.7, 143.9, 143.8, 143.5, 142.3, 141.3(9), 141.3(7), 128.6, 128.2, 127.9, 127.2, 125.1, 123.9, 123.8, 120.1, 82.8, 67.3, 65.9, 65.7, 53.8, 53.7, 47.2, 30.5, 30.2, 28.1. IR (neat): 3395w, 3334w, 2977w, 1710s, 1606m, 1518s, 1449m, 1343s, 1246m, 1213m, 1152s, 1049m cm^{-1}. HRMS (ESI^+, MeOH): *m/z* 817.2690 $[M + Na]^+$, $C_{42}H_{42}N_4NaO_{12}^+$ requires 817.2691.

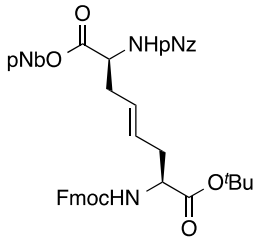
(2*S*,7*S*,4*Z*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-8-((4-nitrobenzyl)oxy)-7-((((4-nitrobenzyl)oxy)carbonyl)amino)-8-oxooct-4-enoic acid, *cis*-2



Trifluoroacetic acid (3 mL) was added to a solution of *cis*-**6** (72 mg, 0.09 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica column chromatography (1 : 2 : 0.05 : 0.1 – EtOAc : hexane : MeOH : AcOH) to give *cis*-acid **2** (55 mg, 82%) as a colourless film which solidified after exposure to CH_2Cl_2, mp 96.7-100.3 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.54 (dd, *J* = 7.6, 2.4 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 5.55 (dt, *J* = 10.4, 6.0 Hz, 1H) 5.52-5.43 (m, 3H), 5.22 (s, 2H), 5.16 (s, 2H), 4.47 (q, *J* = 6.4 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 2H), 4.38-4.34 (m, 1H), 4.17 (t, *J* = 6.8 Hz, 1H), 2.70-2.47 (m, 4H), OH not observed. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 176.4, 171.7, 156.4, 155.7, 147.9, 147.6, 143.7, 143.5, 142.9, 142.3, 141.3, 128.4, 128.0, 127.9, 127.2, 126.8, 125.0, 123.9, 123.7, 120.2, 67.3, 65.9, 65.6, 54.4, 53.9, 47.1,

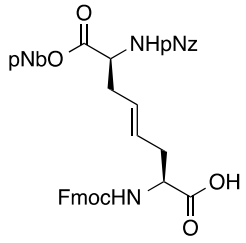
30.2, 30.1. IR (neat): 3380w, 2963w, 2926w, 2855w, 1709s, 1609m, 1518s, 1451m, 1344s, 1261m, 1181m, 1052m cm^{-1}. HRMS (ESI^+, MeOH): *m/z* 761.2063 $[M + Na]^+$, $C_{38}H_{34}N_4NaO_{12}^+$ requires 761.2065. Chiral-HPLC (CHIRALPAK QN-AX analytical column, 92:2:0.5 (v/v/w); MeOH:AcOH:NH_4OAc over 30 min): t_R = 23.7 min (*Z*-isomer): 20.5 min (*E*-isomer), 10:1.

1-(*Tert*-butyl) 8-(4-nitrobenzyl) (2*S*,7*S*,4*E*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-7-((((4-nitrobenzyl)oxy)carbonyl)amino)oct-4-enedioate, *trans*-6



Amino acid derivatives **5** (393 mg, 1.00 mmol) and **4** (215 mg, 0.500 mmol) were added to a flame dried Schlenk vessel equipped with a stir bar. The vessel was evacuated and backfilled with N_2. A solution of **HGII** (63 mg, 0.10 mmol, 20 mol%) in CH_2Cl_2 (3 mL) was added to the amino acid mixture. The reaction vessel was sealed and stirred at 40 ^oC for 16 h. The reaction was quenched with ethyl vinyl ether (0.5 mL) and concentrated under reduced pressure. The residue was purified by silica column chromatography (1 : 4 – EtOAc : hexane) to provide *trans*-alkene **6** (453 mg, 57%) as a clear oil. ^1H-NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.60-7.56 (m, 2H), 7.47-7.36 (m, 6H), 7.30-7.26 (m, 2H), 5.71 (d, *J* = 8.0 Hz, 1H), 5.50 (d, *J* = 8.0 Hz, 1H), 5.47-5.43 (m, 1H), 5.41-5.37 (m, 1H), 5.29-5.25 (m, 2H), 5.22-5.06 (m, 2H), 4.52-4.48 (m, 1H), 4.41-4.31 (m, 3H), 4.19-4.16 (m, 1H), 2.63-2.37 (m, 4H), 1.46 (s, 9H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 171.4, 170.8, 155.8, 155.5, 147.9, 147.6, 144.0, 143.7, 142.4, 141.3, 129.7, 128.5, 128.0, 127.8, 127.1, 125.2, 125.1, 123.9, 123.7, 120.1, 82.6, 67.1, 65.8, 65.5, 54.0, 53.6, 47.2, 35.8, 35.1, 28.1. IR (neat): 3393w, 3068w, 2976w, 1718s, 1607m, 1519s, 1450m, 1345s, 1217m, 1153s, 1052m cm^{-1}. HRMS (ESI^-, MeOH): *m/z* 793.2709 $[M - H]^-$, $C_{42}H_{41}N_4O_{12}^-$ requires 793.2726.

(2*S*,7*S*,4*E*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-8-((4-nitrobenzyl)oxy)-7-((((4-nitrobenzyl)oxy)carbonyl)amino)-8-oxooct-4-enoic acid, *trans*-2



Trifluoroacetic acid (3 mL) was added to a solution of *trans*-**6** (80 mg, 0.10 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica column chromatography (1 : 2 : 0.05 : 0.1 – EtOAc : hexane : MeOH : AcOH) to give *trans*-acid **2** (60 mg, 81%) as a colourless film which solidified on exposure to CH_2Cl_2, mp 96.7-100.3 ^oC. ^1H-NMR (600 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.2 Hz, 2H), 8.01-7.99 (m, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.46-7.44 (m, 2H), 7.36 (d, *J* = 6.6 Hz, 2H), 7.30-7.26 (m, 4H), 7.18-7.15 (m, 2H), 5.68 (m, 1H), 5.51 (m, 1H), 5.38-5.33 (m, 2H), 5.14 (s, 2H), 5.04 (d, *J* = 7.6 Hz, 2H), 5.00-4.98 (m, 1H), 4.40 (s, 1H), 4.25 (m, 2H), 4.05 (m, 1H), 2.43-2.42 (m, 4H), OH not observed. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 175.3, 171.5, 156.2, 155.7, 147.9, 147.6, 143.8, 143.7, 142.3, 141.4, 129.4, 128.6, 128.5, 128.1, 127.9, 127.2, 125.1, 124.0, 123.8, 120.2, 67.3, 65.9, 65.6, 54.1, 53.8, 47.2, 35.5, 35.3. IR (neat): 3393w, 2929w, 1707s, 1606m, 1517s, 1449m, 1343s, 1248m, 1184m, 1052m cm^{-1}. HRMS (ESI^-, MeOH): *m/z* 737.2101 $[M - H]^-$, $C_{38}H_{33}N_4O_{12}^-$ requires 737.2100. Chiral-HPLC (CHIRALPAK QN-AX analytical column, 92:2:0.5 (v/v/w); MeOH:AcOH:NH_4OAc over 30 min): t_R = 20.6 min (*E*-isomer), 23.8 min (*Z*-isomer): 10:1.

General Procedures

General Procedure for Solid-Phase Peptide Synthesis (SPPS)

Manual SPPS was performed in polypropylene Terumo syringes (5 mL) fitted with a porous (20 μm) polyethylene filter. Resin wash and filtering steps were aided by the use of a Visprep SPE DL 24-port model vacuum manifold as supplied by Supelco. Capping reactions and cleavage mixtures were shaken on a KS125 basic KA elliptical shaker supplied by Labortechnik at 400 motions per minute.

Automated micro-wave-accelerated SPPS was carried out using a CEM Liberty-Discover synthesizer, involving the flow of dissolved reagents from external nitrogen pressurized bottles to a resin-containing microwave reactor vessel fitted with a porous filter. Coupling and deprotection reactions were carried out within this vessel and were aided by microwave energy. Each reagent delivery, wash, and evacuation step was carried out according to the automated protocols of the instrument (controlled by PepDriver software). In a 50 mL centrifuge tube, resin was swollen with DMF:CH_2Cl_2 (1:1; 10 mL, 1 x 60 min) and connected to the Liberty resin manifold. The Fmoc-amino acids (0.2 M in DMF), activators (0.5 M HATU: HOBt in DMF), activator base (2 M DIPEA in NMP), and deprotection agent (20% v/v piperidine in DMF) were solubilized in an appropriate volume of specified solvent as calculated by the PepDriver software program. The default microwave conditions used in the synthesis of each linear peptide included: initial deprotection (36 W, 37 °C, 2 min), deprotection (45 W, 75 °C, 10 min), preactivation (0 W, 25 °C, 2 min), and coupling (25 W, 75 °C, 10 min), or initial deprotection (40 W, 75 °C, 0.5 min), deprotection (40 W, 75 °C, 3 min), and coupling (20 W, 75 °C, 5 min). After completion of synthesis, the resin-bound peptides were automatically returned to the Liberty resin manifold as a suspension in DMF:DCM (1:1) and filtered through fritted plastic syringes (5 mL) for acid-mediated cleavage.

TFA Cleavage Procedure

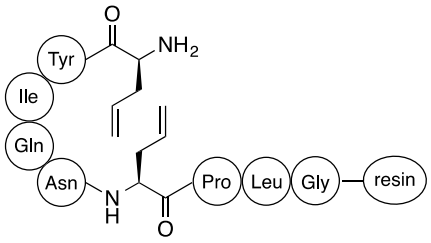
A small aliquot of resin-bound peptide (approximately 3 mg) was suspended in cleavage solution (1 mL; 95:2.5:2.5; TFA:TIPS:water) and shaken gently for 2 h. The mixture was filtered through a fritted syringe and the beads rinsed with TFA (1 × 0.2 mL). The filtrate was concentrated under a constant stream of air, and the resultant oil was induced to precipitate in ice-cold Et_2O (1 mL). Cleaved peptides were collected by centrifugation (3 × 5 min) and dried for analysis by analytical RP-HPLC and mass spectrometry. For full-scale resin cleavages, 10 mL of cleavage solution was used, and after 4 h, the resin was rinsed with TFA (3 × 1 mL). The filtrate was concentrated under a constant stream of air, and the resultant oil was induced to precipitate in ice-cold Et_2O (30−35 mL). Collection by centrifugation was carried out over 5 × 6 min spin times. Cleaved peptides were collected by centrifugation at a speed of 6000 rpm on a Hermle Z200A centrifuge supplied by Medos, or at a speed of 6000 rpm on a TMC-1 mini centrifuge supplied by Thermoline.

General Procedure for RCM of resin-bound peptides

Prior to RCM, the peptidyl-resins were treated with an acetic anhydride capping solution (94:5:1; DMF:acetic anhydride:NMM; 4 mL) for 2 h, filtered, washed with DMF (3 × 1 min) and CH_2Cl_2 (3 × 1 min), and dried in vacuo for 30 min. RCM was carried out on a CEM Discover system fitted with the Benchmate option. Reactions were performed in 10 mL high pressure glass microwave vessels fitted with self-sealing Teflon septa as a pressure relief device. A microwave reactor vessel was loaded with substrate, deoxygenated solvent, deoxygenated chaotropic salt solution, and **GII** in an inert (nitrogen) environment. The system was sealed, and the reaction mixture irradiated with microwave energy while being stirred at a specified temperature for the specified period of time. After cooling to room temperature, the resin-bound peptide was filtered through a fritted syringe and washed with CH_2Cl_2 (4 mL, 3 x 1 min) and DMF (4 mL, 3 x 1 min) and dried *in vacuo* for 30 min. A small aliquot of resin was then subjected to acid-mediated cleavage, and the isolated solid was analyzed by RP-HPLC and mass spectrometry.

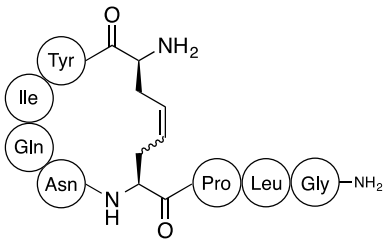
Synthesis of Dicarba Peptides

Linear Peptide 3



Synthesis of linear sequence **3** was performed according to a modified procedure by Vederas and coworkers[2] using a microwave-accelerated SPPS procedure described previously using Fmoc-Rink amide resin (136 mg, 83 μmol). A small aliquot of resin-bound peptide was then subjected to Fmoc-deprotection and acid-mediated cleavage. RP-HPLC and mass spectral analysis of the aliquot supported formation of the required linear sequence **3**. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): m/z 499.1 $[M + 2H]^{2+}$, ½ ($C_{47}H_{74}N_{12}O_{12}$) theoretical 499.3; 997.3 $[M + H]^+$, ($C_{47}H_{74}N_{12}O_{12}$) theoretical 997.5. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 7.4 min.

[1,6]-Dicarba Oxytocin 1

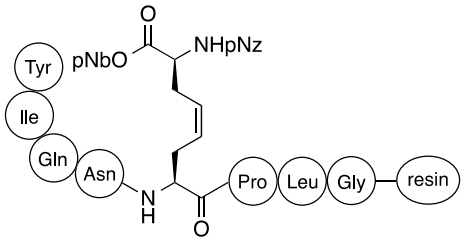


Cyclisation of the linear sequence **3** was performed according to a modified procedure by Vederas and coworkers.[2] Resin-bound peptide was subjected to microwave-accelerated RCM procedure described previously under the following conditions: resin-bound linear peptide (83 μmol), CH_2Cl_2 (4 mL), 0.4M LiCl in DMF (0.2 mL), second generation Grubbs' catalyst (14 mg, 17 μmol), 100 W microwave, 100 °C, 2 h, 100% conversion to the target peptide. The resin-bound peptide was then subjected to Fmoc-deprotection and acid mediated cleavage to give an off-white solid. The white solid was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-30% buffer B over 40 min, t_R = 17.8 and 18.9 min). Selected fractions were combined and lyophilized to give the two geometric isomers as colourless solids.

Cis-[1,6]-Dicarba Oxytocin, *cis*-**1**. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): m/z 485.3 $[M + 2H]^{2+}$, ½ ($C_{45}H_{69}N_{12}O_{12}$) theoretical 485.3; 969.4 $[M + H]^+$, ($C_{45}H_{68}N_{12}O_{12}$) theoretical 969.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 10.5 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.69 (dt, *J* = 10.5, 7.5 Hz, 1H), 5.61 (dt, *J* = 10.5, 7.5 Hz, 1H), 4.72 (m, 1H), 4.66 (dd, *J* = 7.8, 5.4 Hz, 2H), 4.34-4.29 (m, 2H), 4.10-4.07 (m, 2H), 3.92 (AB quartet, *J* = 17.2 Hz, 2H), 3.75 (dt, *J* = 10.2, 6.6 Hz, 1H) 3.63 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.19 (dd, *J* = 14.4, 6.6 Hz, 1H), 3.03 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.90-2.73 (m, 5H), 2.56-2.51 (m, 2H), 2.41 (oct, *J* = 7.9 Hz, 2H), 2.35-2.31 (m, 1H), 2.08-1.92 (m, 6H), 1.73-1.69 (m, 2H), 1.65-1.62 (m, 1H), 1.28-1.25 (m, 1H), 1.06-1.02 (m, 1H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.93-0.88 (m, 9H). ^{13}C-NMR (150 MHz, D_2O): δ 178.8, 175.9, 175.6. 175.2, 174.5, 174.1, 172.7, 172.1, 170.8, 164.3, 164.0, 155.7, 131.6, 130.4, 129.0, 125.9, 116.8, 61.6, 59.5, 56.6, 56.1, 53.8, 53.4, 52.8, 51.5, 49.2, 43.2, 40.5, 37.9, 36.9, 36.2, 32.2, 30.8, 30.5, 29.7, 27.1, 25.8, 24.8, 23.3, 21.8, 16.2, 12.0.

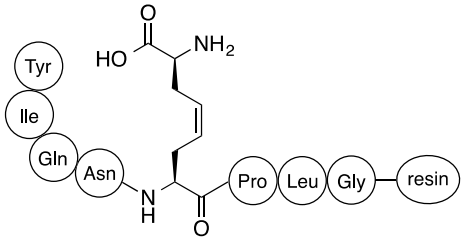
Trans-[1,6]-Dicarba Oxytocin *trans*-**1**- Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): m/z 485.3 [M + 2H]$^{2+}$, ½ ($C_{45}H_{69}N_{12}O_{12}$) theoretical 485.3; 969.4 [M + H]$^+$, ($C_{45}H_{68}N_{12}O_{12}$) theoretical 969.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 11.2 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 (d, 8.4 Hz, 2H), 5.67 (dt, *J* = 15.0, 6.0 Hz, 1H), 5.55 (dt, *J* = 15.0, 6.0 Hz, 1H), 4.75-4.71 (m, 2H), 4.66 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.45 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.32 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.15-4.12 (m, 2H), 4.03 (d, *J* = 6.0 Hz, 1H), 3.92 (AB quartet, *J* = 16.8 Hz, 2H), 3.73 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.65 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.16 (dd, *J* = 14.4, 6.6 Hz, 1H), 3.04 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.99 (dd, 15.6, 4.8 Hz, 1H), 2.81-2.75 (m, 2H), 2.66-2.61 (m, 1H), 2.56-2.53 (m, 1H), 2.47-2.29 (m, 4H), 2.150-2.08 (m, 1H), 2.08-2.00 (m, 3H), 1.95-1.87 (m, 2H), 1.73-1.69 (m, 2H), 1.65-1.60 (m, 1H), 1.44-1.37 (m, 1H), 1.16-1.10 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92-0.89 (m, 9H). ^{13}C-NMR (150 MHz, D_2O): δ 178.5, 176.2, 175.4, 174.9, 174.3, 172.5, 171.6, 170.3, 164.0, 163.7, 163.5, 155.5, 131.5, 131.2, 128.6, 126.2, 116.6, 61.2, 60.9, 56.5, 55.6, 53.6, 53.0, 52.1, 51.4, 48.6, 42.9, 40.2, 37.0, 36.9, 36.5, 34.6, 34.2, 31.9, 30.1, 26.4, 25.1, 22.9, 21.6, 15.3, 11.4.

Linear octapeptide, *cis*-7



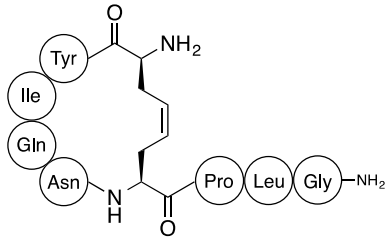
Synthesis of the linear sequence *cis*-**7** was performed according to the microwave-accelerated SPPS procedure described previously using Fmoc-Rink amide resin (74 mg, 20 μmol). RP-HPLC and mass spectral analysis of an aliquot of resin-cleaved peptide supported formation of the required linear sequence *cis*-**7**. Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 651.2 [M + 2H]$^{2+}$, ½ ($C_{60}H_{82}N_{14}O_{19}$) theoretical 651.3; 1301.5 [M + H]$^+$, ($C_{60}H_{81}N_{14}O_{19}$) theoretical 1301.6. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 22.9 min.

Linear peptide *cis*-8



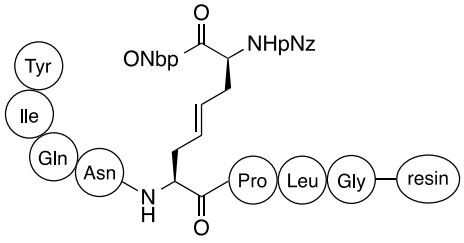
Deprotection of *cis*-**7** was performed according a modified procedure by Liu and coworkers.[3] The pNb and pNz protecting groups were removed from the resin-bound peptide (20 μmol) *via* repeated treatments with a solution of $SnCl_2$ (6 M) and HCl/DMF (5 mM) in DMF (3 x 2 mL) for 0.5 h. The resin was then washed with DMF (6 x 4 mL), CH_2Cl_2 (5 x 4 mL), 1:1 DMF/H_2O (4 x 3 mL), 1:1 THF/H_2O (4 x 3 mL) and DMF (6 x 4 mL). RP-HPLC and mass spectral analysis of an aliquot of resin-cleaved peptide supported formation of the required linear sequence *cis*-**8**. Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 494.2 $[M + 2H]^{2+}$, ½ ($C_{45}H_{72}N_{12}O_{13}$) theoretical 494.3; 987.4 $[M + H]^+$, ($C_{45}H_{71}N_{12}O_{13}$) theoretical 987.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 6.7 min.

Cis-[1,6]-Dicarba Oxytocin, _cis_-1



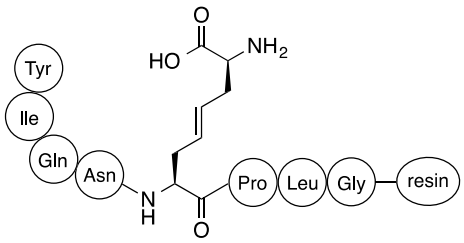
Cyclisation of intermediate *cis*-**8** was performed according to a modified procedure by Liu and coworkers.[3] A solution of PyBOP (11 mg, 21 μmol), HOBt (3 mg, 20 μmol) and NMM (3 μL, 27 μmol) in DMF (0.5 mL) was added to the resin-bound peptide (2.0 μmol) and shaken for 6 h at RT. The resin was washed with DMF (5 x 0.5 mL) and CH_2Cl_2 (5 x 0.5 mL). The resin bound peptide was then subjected to acid mediated cleavage to give a colourless solid. RP-HPLC and mass spectral analysis of a peptide supported formation of the required cyclised *cis*-[1,6]-Dicarba Oxytocin, *cis*-**1**. Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): m/z 485.3 $[M + 2H]^{2+}$, ½ ($C_{45}H_{69}N_{12}O_{12}$) theoretical 485.3; 969.4 $[M + H]^+$, ($C_{45}H_{68}N_{12}O_{12}$) theoretical 969.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 10.6 min.

Linear octapeptide, *trans*-7



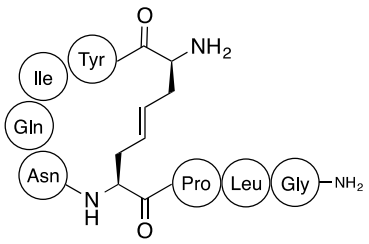
Synthesis of linear sequence *trans*-**7** was performed according to the microwave-accelerated SPPS procedure described previously using Fmoc-Rink amide resin (74 mg, 25 μmol). RP-HPLC and mass spectral analysis of an aliquot of resin-cleaved peptide supported formation of the required linear sequence *trans*-**7**. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 651.3 $[M + 2H]^{2+}$, ½ ($C_{60}H_{82}N_{14}O_{19}$) theoretical 651.3; 1301.5 $[M + H]^+$, ($C_{60}H_{81}N_{14}O_{19}$) theoretical 1301.6. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 25.2 min.

Linear peptide, *trans*-8



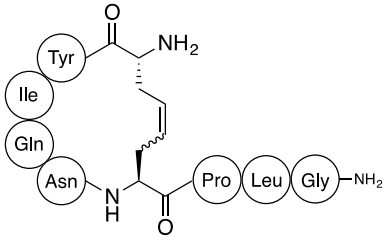
Deprotection of *trans*-**7** was performed according to a modified procedure by Liu and coworkers.[3] The pNb and pNz protecting groups were removed from the resin-bound peptide (25 μmol) *via* repeated treatments with a solution of $SnCl_2$ (6 M) and HCl/DMF (5 mM) in DMF (3 x 2 mL) for 0.5 h. The resin was then washed with DMF (6 x 4 mL), CH_2Cl_2 (5 x 4 mL), 1:1 DMF/H_2O (4 x 3 mL), 1:1 THF/H_2O (4 x 3 mL) and DMF (6 x 4 mL). RP-HPLC and mass spectral analysis of an aliquot of resin-cleaved peptide supported formation of the required linear sequence *trans*-**8**. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 494.2 $[M + 2H]^{2+}$, ½ ($C_{45}H_{72}N_{12}O_{13}$) theoretical 494.3; 987.4 $[M + H]^+$, ($C_{45}H_{71}N_{12}O_{13}$) theoretical 987.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 6.6 min.

***Trans*-[1,6]-Dicarba Oxytocin, *trans*-1**



Cyclisation of intermediate *trans*-**8** was performed according to a modified procedure by Liu and coworkers.[3] A solution of PyBOP (11 mg, 21 μmol), HOBt (3 mg, 20 μmol) and NMM (3 μL, 27 μmol) in DMF (0.5 mL) was added to the resin-bound peptide (2.0 μmol) and shaken for 6 h at rt. The resin was washed with DMF (5 x 0.5 mL) and CH_2Cl_2 (5 x 0.5 mL). The resin bound peptide was then subjected to acid mediated cleavage to give *trans*-**1** as a colourless solid. RP-HPLC and mass spectral analysis of the major component supported formation of the required cyclised *trans*-[1,6]-Dicarba Oxytocin. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 485.3 $[M + 2H]^{2+}$, ½ ($C_{45}H_{69}N_{12}O_{12}$) theoretical 485.3; 969.4 $[M + H]^+$, ($C_{45}H_{68}N_{12}O_{12}$) theoretical 969.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 11.3 min.

[D1,6]-Dicarba Oxytocin, [D]-1



Cyclisation of the linear sequence was performed according to a modified procedure by Vederas and coworkers.[2] Resin-bound peptide was subjected to microwave-accelerated RCM procedure described previously under the following conditions: resin-bound linear peptide (100 μmol), CH_2Cl_2 (4 mL), 0.4M LiCl in DMF (0.2 mL), second generation Grubbs' catalyst (18 mg, 17 μmol), 100 W microwave, 100 °C, 2 h, 100% conversion to the target peptide. The resin-bound peptide was then subjected to

Fmoc-deprotection and acid mediated cleavage to give an off-white solid. The white solid was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-30% buffer B over 40 min, t_R = 19.5 and 20.7 min). Selected fractions were combined and lyophilized to give the two geometric isomers as colourless solids.

Cis-[D1,6]-Dicarba Oxytocin, *cis*[D]-**1**. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 485.3 $[M + 2H]^{2+}$, ½ ($C_{45}H_{69}N_{12}O_{12}$) theoretical 485.3; 969.4 $[M + H]^+$, ($C_{45}H_{68}N_{12}O_{12}$) theoretical 969.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 11.9 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.60 (dt, *J* = 10.8, 6.0 Hz, 1H) , 5.50 (dt, *J* = 10.8, 6.0 Hz, 1H), 4.67 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.52-4.46 (m, 2H), 4.31-4.27 (m, 2H), 4.10 (t, *J* = 6.6 Hz, 1H), 4.06 (d, *J* = 7.2 Hz, 1H), 3.90 (AB quartet, *J* = 16.8 Hz, 2H), 3.83 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.66 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.24 (dd, *J* = 14.4 Hz, 6.6 Hz, 1H), 3.20 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.93 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.85 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.63-2.59 (m, 1H), 2.54-2.43 (m, 2H), 2.38-2.29 (m, 2H), 2.16-2.02 (m, 5H), 1.95-1.88 (m, 2H), 1.70-1.58 (m, 3H), 1.34-1.30 (m, 1H), 1.10-1.03 (m, 1H), 0.97-0.85 (m, 12H). ^{13}C-NMR (150 MHz, D_2O): δ 179.0, 176.6, 176.2, 175.7, 175.3, 174.2, 173.4, 172.3, 171.3, 164.4, 164.2, 155.8, 131.7, 130.8, 129.4, 125.0, 116.9, 61.6, 61.0, 58.5, 55.2, 54.0, 53.8, 52.7, 52.4, 49.1, 43.3, 40.7, 37.1, 36.3, 35.6, 32.3, 30.6, 29.4, 26.9, 26.2, 26.0, 25.6, 23.3, 22.1, 16.2, 11.4.

Trans-[D1,6]-Dicarba Oxytocin, *trans*[D]-**1**. Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 485.3 $[M + 2H]^{2+}$, ½ ($C_{45}H_{69}N_{12}O_{12}$) theoretical 485.3; 969.4 $[M + H]^+$, ($C_{45}H_{68}N_{12}O_{12}$) theoretical 969.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 12.7 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.19 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.64 (dt, *J* = 15.0, 6.0 Hz, 1H), 5.60 (dt, *J* = 15.0, 6.0 Hz, 1H), 4.75-4.72 (m, 1H), 4.56 (t, *J* = 7.2 Hz, 1H), 4.49-4.46 (m, 2H), 4.29-4.26 (m, 2H), 4.17 (t, *J* = 5.4 Hz, 1H), 4.02 (d, *J* = 7.2 Hz, 1H), 3.91 (AB quartet, *J* = 17.4 Hz, 2H), 3.79 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.66 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.25-3.18 (m, 2H), 2.95-2.88 (m, 2H), 2.62 (t, *J* = 5.4 Hz, 2H), 2.53-2.51 (m, 2H), 2.44-2.29 (m, 3H), 2.15-1.91 (m, 6H), 1.70-1.58 (m, 3H), 1.37-1.30 (m, 1H), 1.11-1.04 (m, 1H), 0.92-0.86 (m, 12H). ^{13}C-NMR (150 MHz, D_2O): δ 179.0, 176.6, 176.0, 175.3, 174.9, 174.5, 173.2, 172.2, 170.9, 164.4, 164.2, 155.8, 132.1, 131.7,

129.3, 127.2, 116.9, 61.6, 61.1, 58.5, 55.4, 54.4, 54.1, 52.7, 49.1, 43.3, 40.7, 37.2, 36.7, 35.9, 34.7, 34.3, 32.3, 30.6, 27.6, 26.2, 26.0, 25.6, 23.3, 22.1, 16.2, 11.4.

[2,7]-Dicarba Vapreotide

The *cis*-unsaturated dicarba vapreotide and *trans*-unsaturated dicarba vapreotide were synthesized according to a previously reported procedure.[4]

^{1}H NMR Chemical shifts (ppm) of *cis*-unsaturated dicarba vapreotide (500 MHz, DMSO-d_6)

Residue	NH	α -H	β -H	Others
D-Phe	8.07	4.13	2.88, 3.09	7.22, 7.30
Agl	8.83	4.69	2.08, 2.19	5.21
Tyr	8.19	4.58	2.61, 2.72	6.85, 6.55
D-Trp	8.57	4.23	2.76, 3.00	7.09, 7.47, 6.98, 7.05, 7.31, 10.79
Lys	8.34	3.93	1.65	0.79, 1.29, 2.56, 7.61
Val	7.55	4.51	2.02	0.81
Agl	8.06	4.52	2.20	5.30
Trp	7.88	4.54	3.01, 3.13	7.09, 7.59, 6.94, 7.02, 7.29, 10.76

^{13}C NMR Chemical shifts (ppm) of *cis*-unsaturated dicarba vapreotide (125 MHz, DMSO-d_6)

Residue	α -C	β -C	Others
D-Phe	53.6	37.5	129.7, 111.5, 128.7
Agl	53.3	30.7	127.8
Tyr	53.9	37.9	130.2, 115.1
D-Trp	55.1	27.1	123.8, 118.4, 118.4, 121.0, 121.1
Lys	53.2	30.9	30.0, 30.9, 38.8
Val	57.9	30.0	30.0
Agl	53.6	30.7	128.0
Trp	53.5	28.5	123.8, 118.7, 118.4, 118.3, 127.4

^{1}H NMR Chemical shifts (ppm) of *trans*-unsaturated dicarba vapreotide (500 MHz, DMSO-d_6)

Residue	NH	α -H	β -H	Others
D-Phe	8.09	4.16	2.92	7.19, 7.21, 7.27
Agl	8.40	4.33	2.03	5.14
Tyr	7.96	4.62	2.44, 2.57	6.75, 6.49
D-Trp	8.33	4.36	2.91, 3.10	7.18, 7.57, 6.95, 7.04, 7.29, 10.83
Lys	8.20	3.96	1.59	1.00, 1.39, 2.62, 7.59
Val	7.43	3.88	2.02	0.84
Agl	7.26	4.14	1.96, 2.25	4.94
Trp	7.67	4.39	2.94, 3.15	7.11, 7.52, 6.92, 7.01, 7.28, 10.76

^{13}C NMR Chemical shifts (ppm) of *trans*-unsaturated dicarba vapreotide (125 MHz, DMSO-d_6)

Residue	α -C	β -C	Others
D-Phe	53.1	37.6	124.2, 127.5
Agl	52.4	36.0	129.5
Tyr	53.5	39.9	130.4, 115.0
D-Trp	54.6	28.0	124.3, 118.6, 121.2, 128.8
Lys	54.2	30.8	22.2, 26.8, 38.8
Val	59.6	36.0	19.1
Agl	53.1	34.9	126.9
Trp	53.7	28.1	123.6

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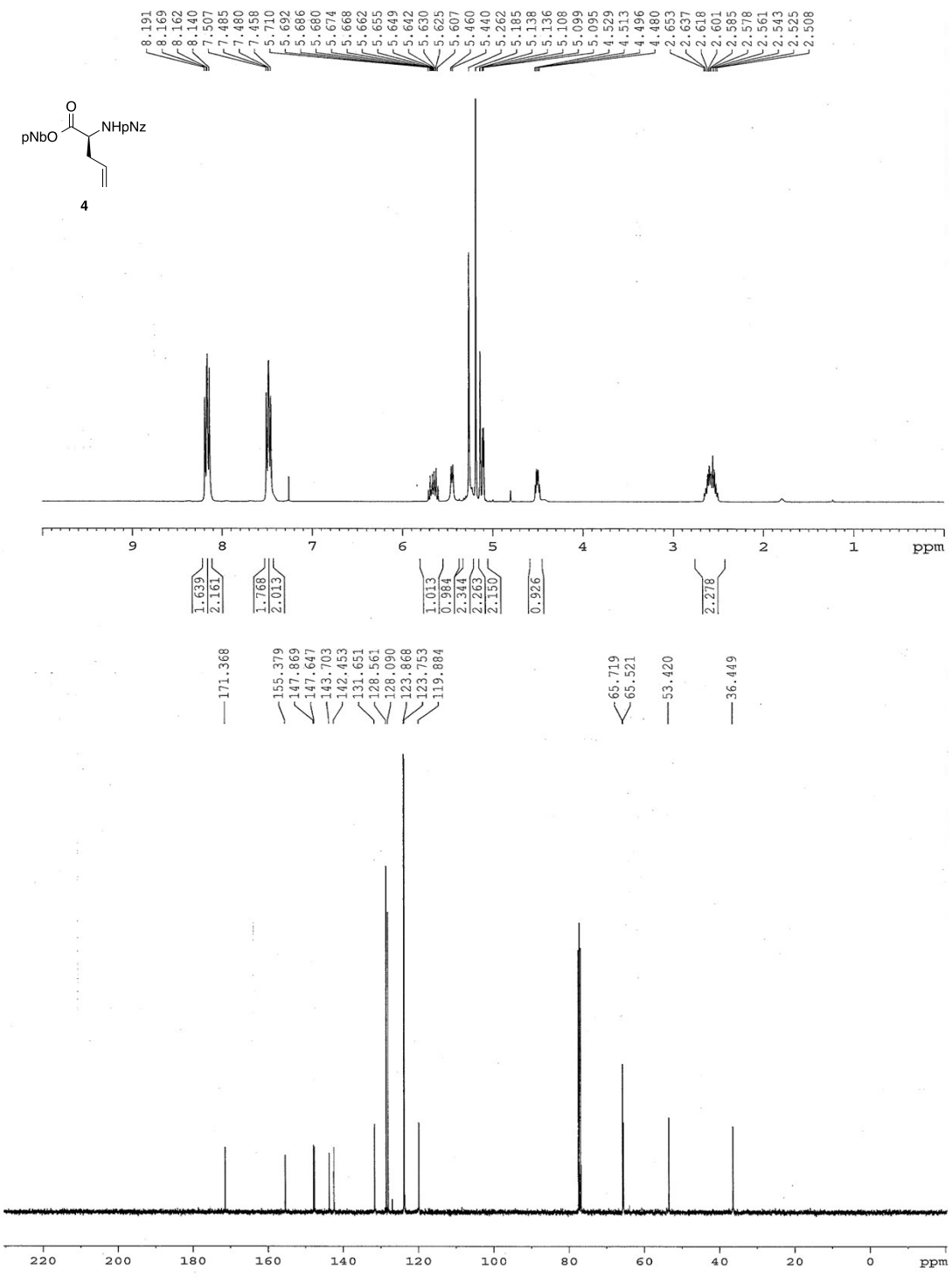
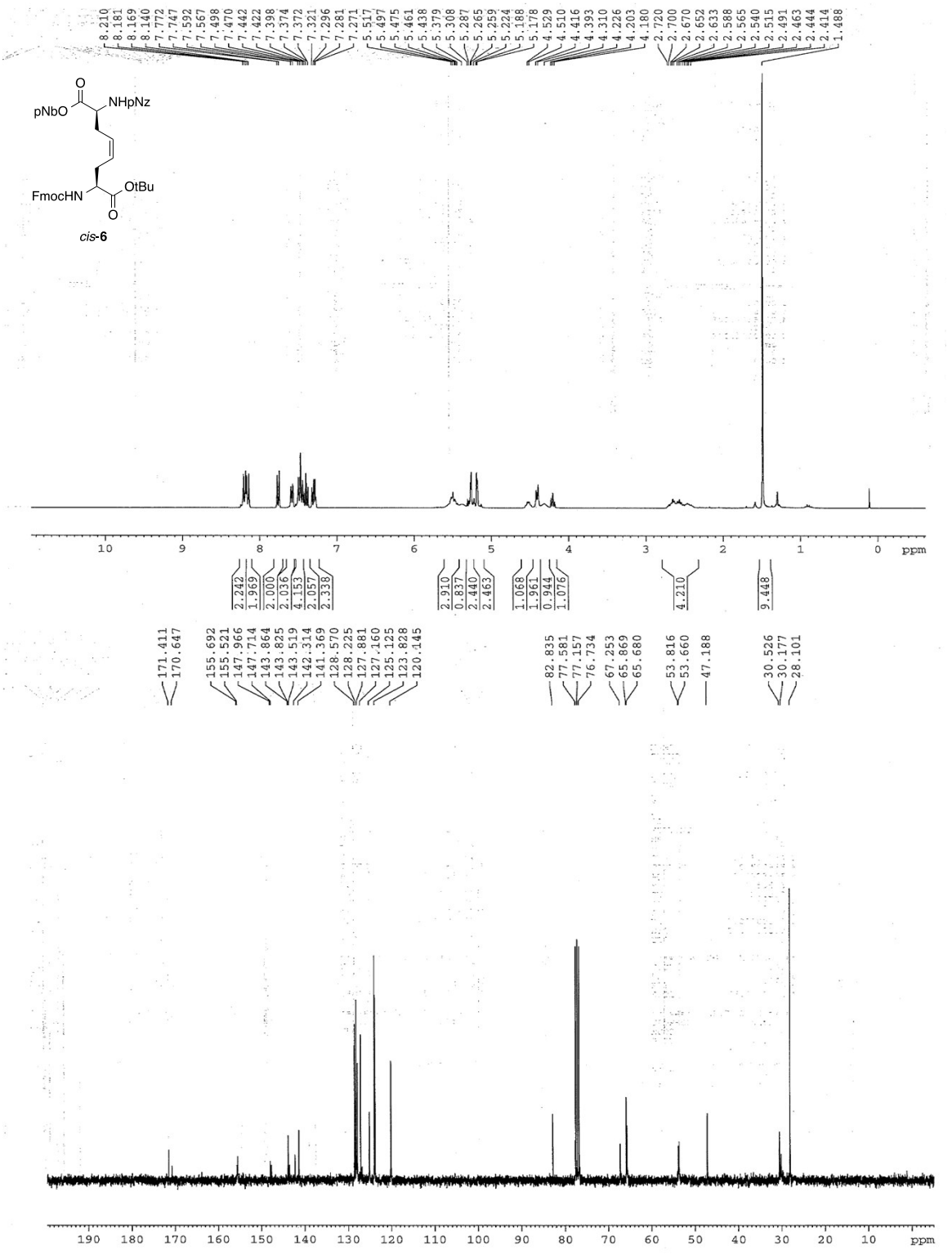
3. H-K. Cui, Y. Guo, Yao He, F-L. Wang, H-N. Chang, Y-J. Wang, F-M. Wu, C-L Tian and L. Liu, *Angew. Chem. Int. Ed.*, 2013, **52**, 9558-9562.
4. A. M. Whelan, PhD thesis, Monash University, 2009.

Supporting Spectra

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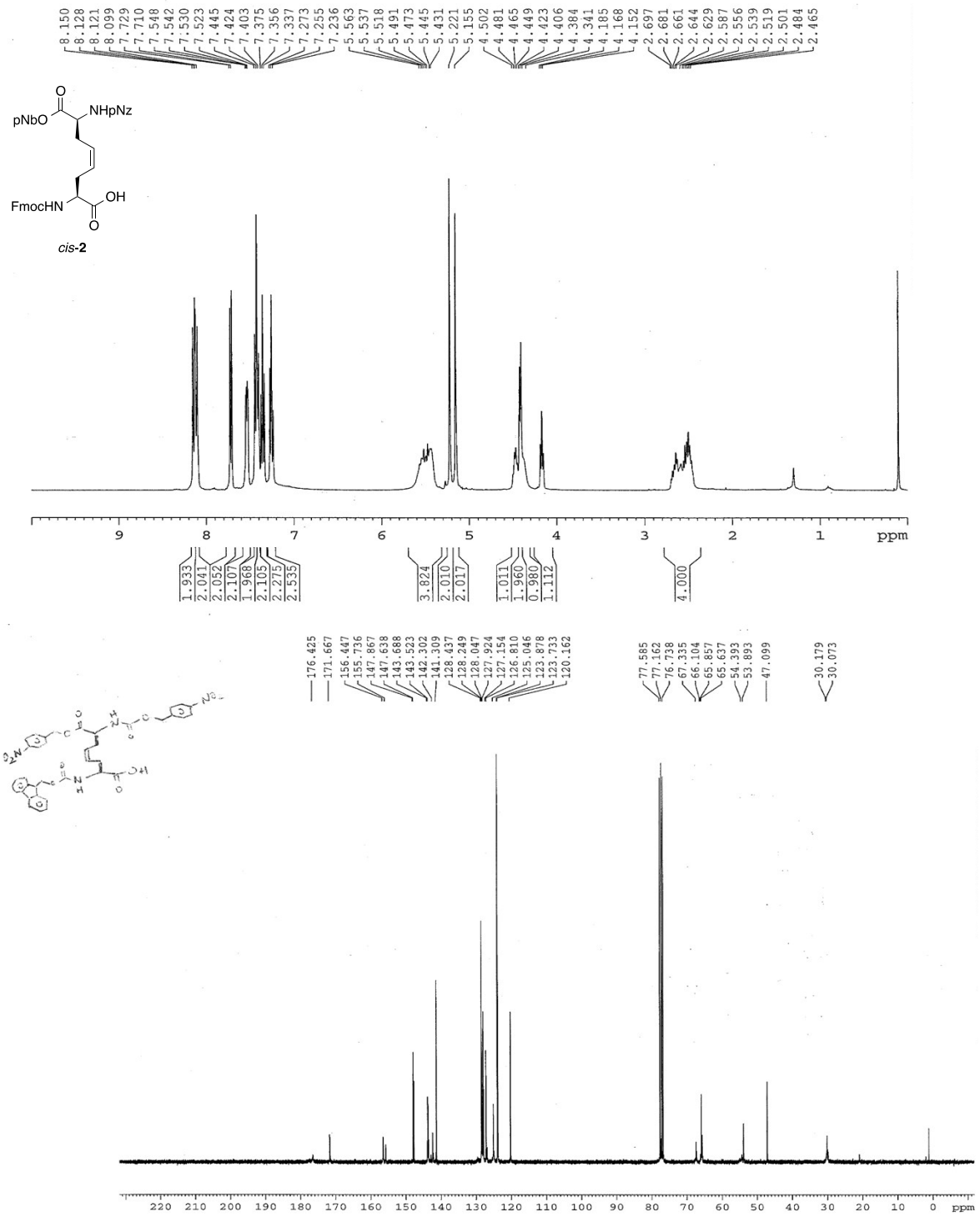
28.101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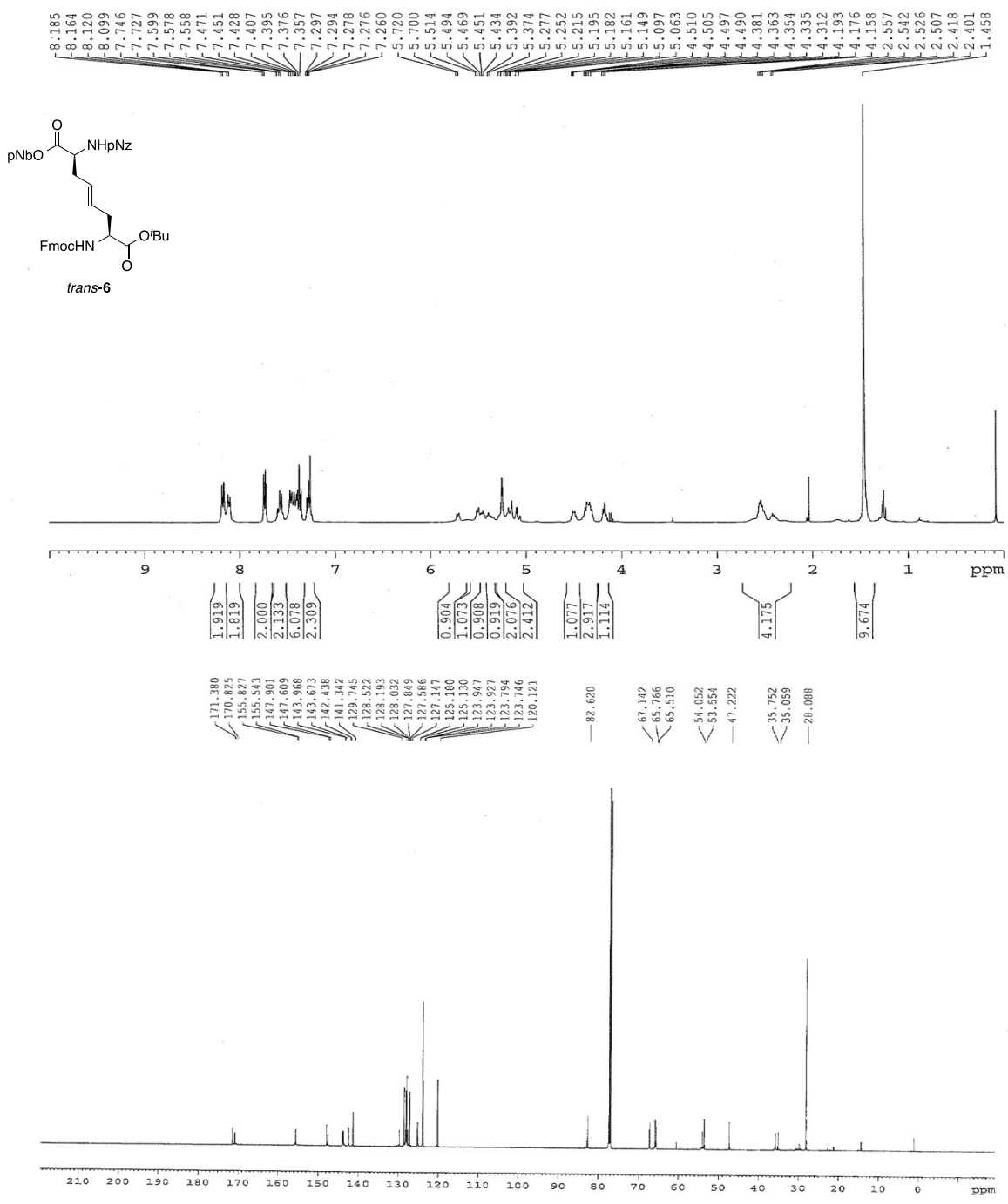
7.403
7.375
7.356
7.337
7.273
7.255
7.236
5.563
5.537
5.518
5.491
5.473
5.445
5.431
5.221
5.155
4.502
4.481
4.465
4.449
4.423
4.406
4.384
4.341
4.185
4.168
4.152
2.697
2.681
2.661
2.644
2.629
2.587
2.556
2.539
2.519
2.501
2.484
2.465
pNbO
NHpNz
FmocHN
OH
cis-2
ppm
1.933
2.041
2.052
2.107
1.968
2.105
2.275
2.535
3.824
2.010
2.017
1.011
1.960
0.980
1.112
4.000
176.425
171.667
156.447
155.736
147.867
147.638
143.688
143.523
142.302
141.309
128.437
128.249
128.047
127.924
127.154
126.810
125.046
123.878
123.733
120.162
77.585
77.162
76.738
67.335
66.104
65.857
65.637
54.393
53.893
47.099
30.179
30.073
ppm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8.120
8.099
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7.599
7.578
7.558
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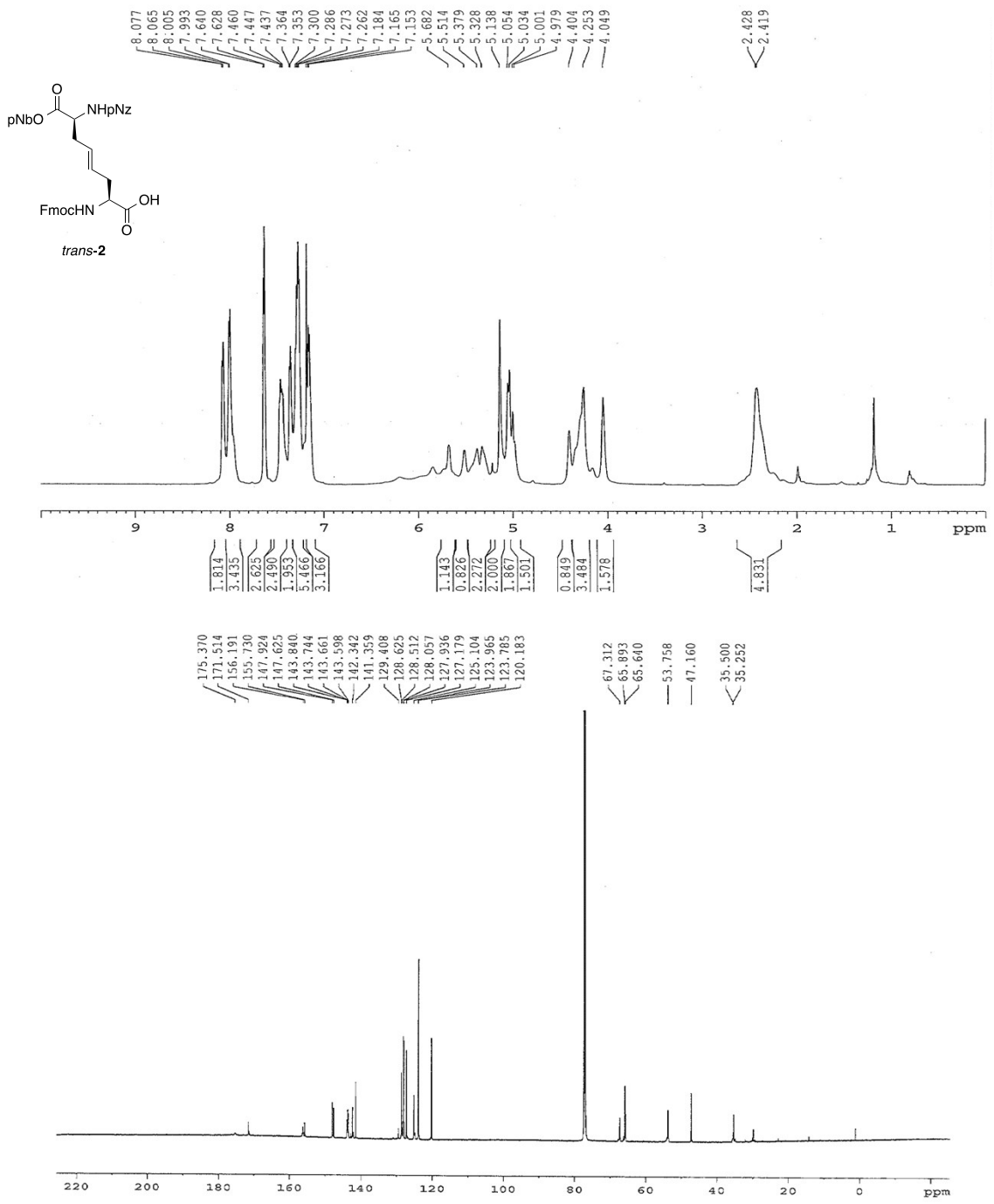
7.451
7.428
7.407
7.395
7.376
7.357
7.297
7.294
7.278
7.276
7.260
5.720
5.700
5.514
5.494
5.469
5.451
5.434
5.392
5.374
5.277
5.252
5.215
5.195
5.182
5.161
5.149
5.097
5.063
4.510
4.505
4.497
4.490
4.381
4.363
4.354
4.335
4.312
4.193
4.176
4.158
2.557
2.542
2.526
2.507
2.418
2.401
1.458
pNbO
NHpNz
FmocHN
O'Bu
trans-6
9
8
7
6
5
4
3
2
1
ppm
1.919
1.819
2.000
2.133
6.078
2.309
0.904
1.073
0.908
0.919
2.076
2.412
1.077
2.917
1.114
4.175
9.674
171.380
170.825
155.827
155.543
147.901
147.609
143.968
143.673
142.438
141.342
129.745
128.522
128.193
128.032
127.849
127.586
127.147
125.180
125.130
123.947
123.927
123.794
123.746
120.121
82.620
67.142
65.766
65.510
54.052
53.554
47.222
35.752
35.059
28.088
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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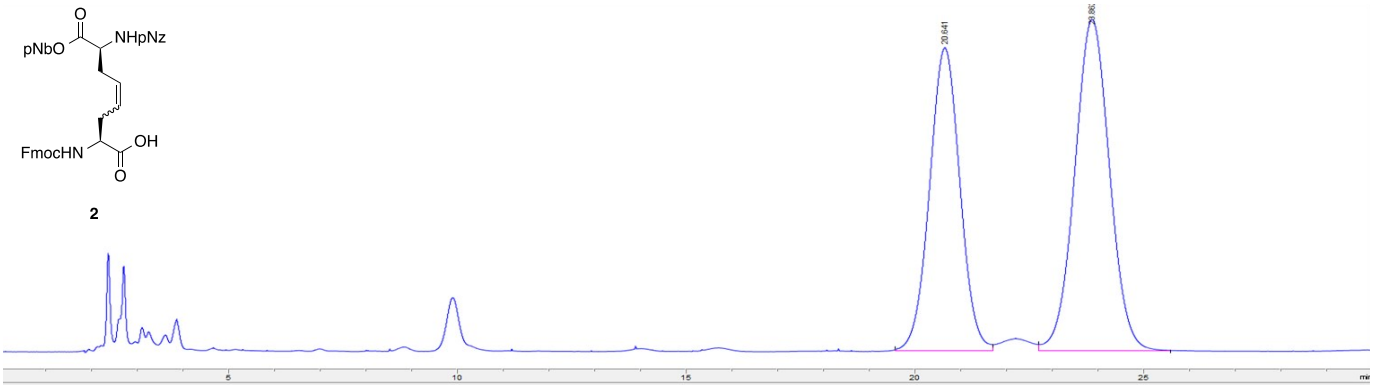
8.065
8.005
7.993
7.640
7.628
7.460
7.447
7.437
7.364
7.353
7.300
7.286
7.273
7.262
7.184
7.165
7.153
5.682
5.514
5.379
5.328
5.138
5.054
5.034
5.001
4.979
4.404
4.253
4.049
2.428
2.419
pNbO
NHpNz
FmocHN
OH
trans-2
9
8
7
6
5
4
3
2
1
ppm
1.814
3.435
2.625
2.490
1.953
5.466
3.166
1.143
0.826
2.272
2.000
1.867
1.501
0.849
3.484
1.578
4.831
175.370
171.514
156.191
155.730
147.924
147.625
143.840
143.744
143.661
143.598
142.342
141.359
129.408
128.625
128.512
128.057
127.936
127.179
125.104
123.965
123.785
120.183
67.312
65.893
65.640
53.758
47.160
35.500
35.252
220
200
180
160
140
120
100
80
60
40
20
0
ppm

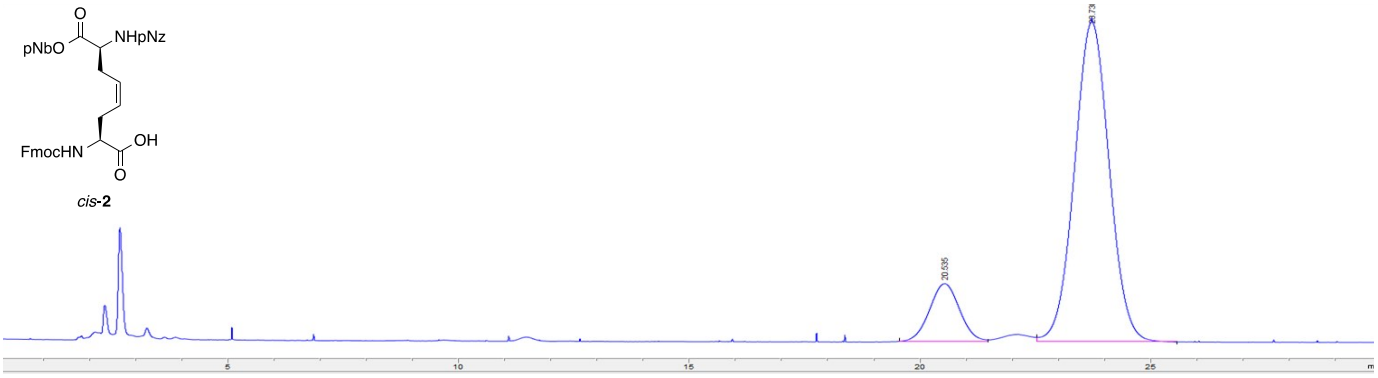
HPLC traces for *cis*- and *trans*-2:

Mixture of *cis* and *trans* **2**, i) ~1:1), ii) 1:10, and iii) 10:1
Chiral-HPLC (CHIRALPAK QN-AX analytical column, 92:2:0.5 (v/v/w);
MeOH:AcOH:NH_4OAc over 30 min):

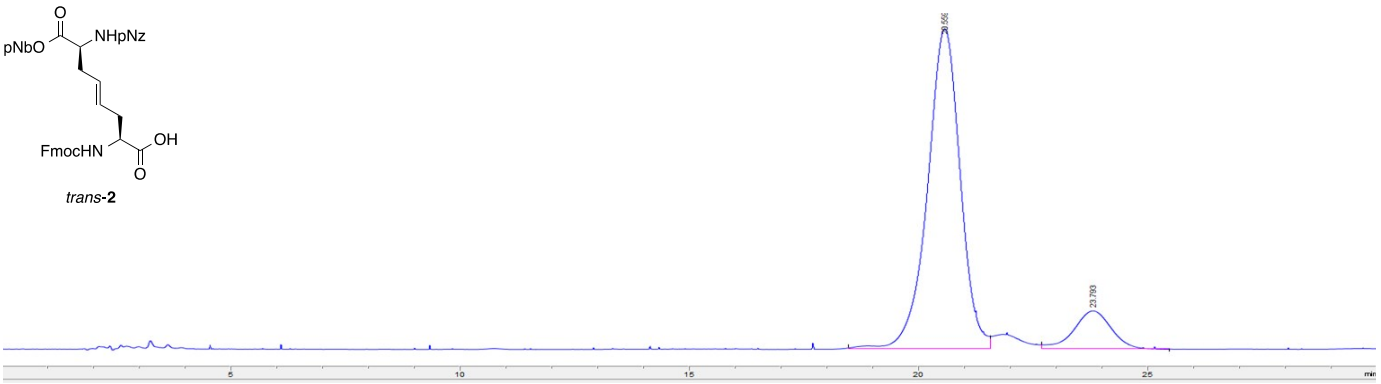
i)

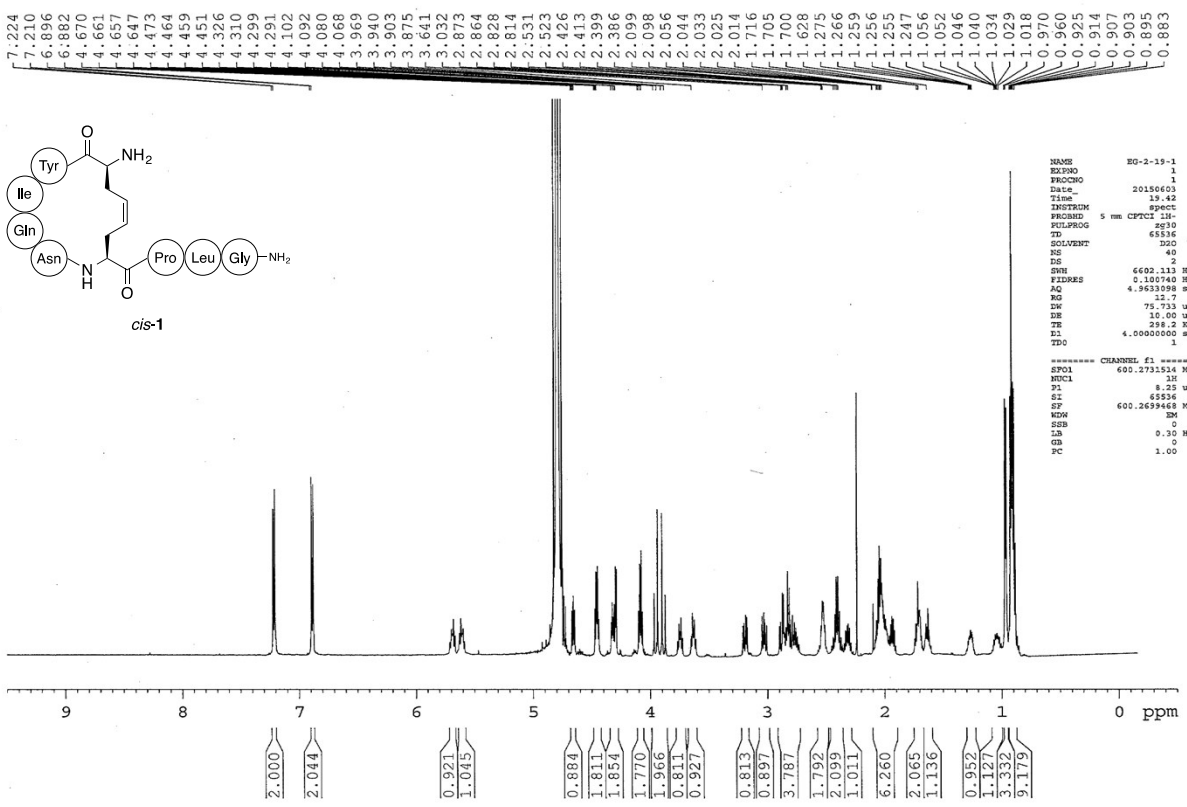


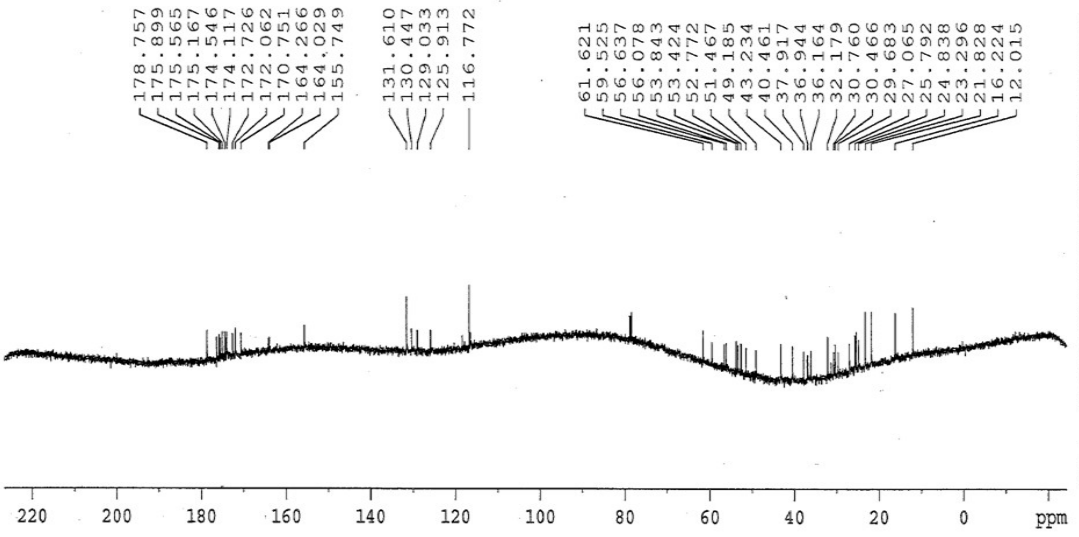
ii)

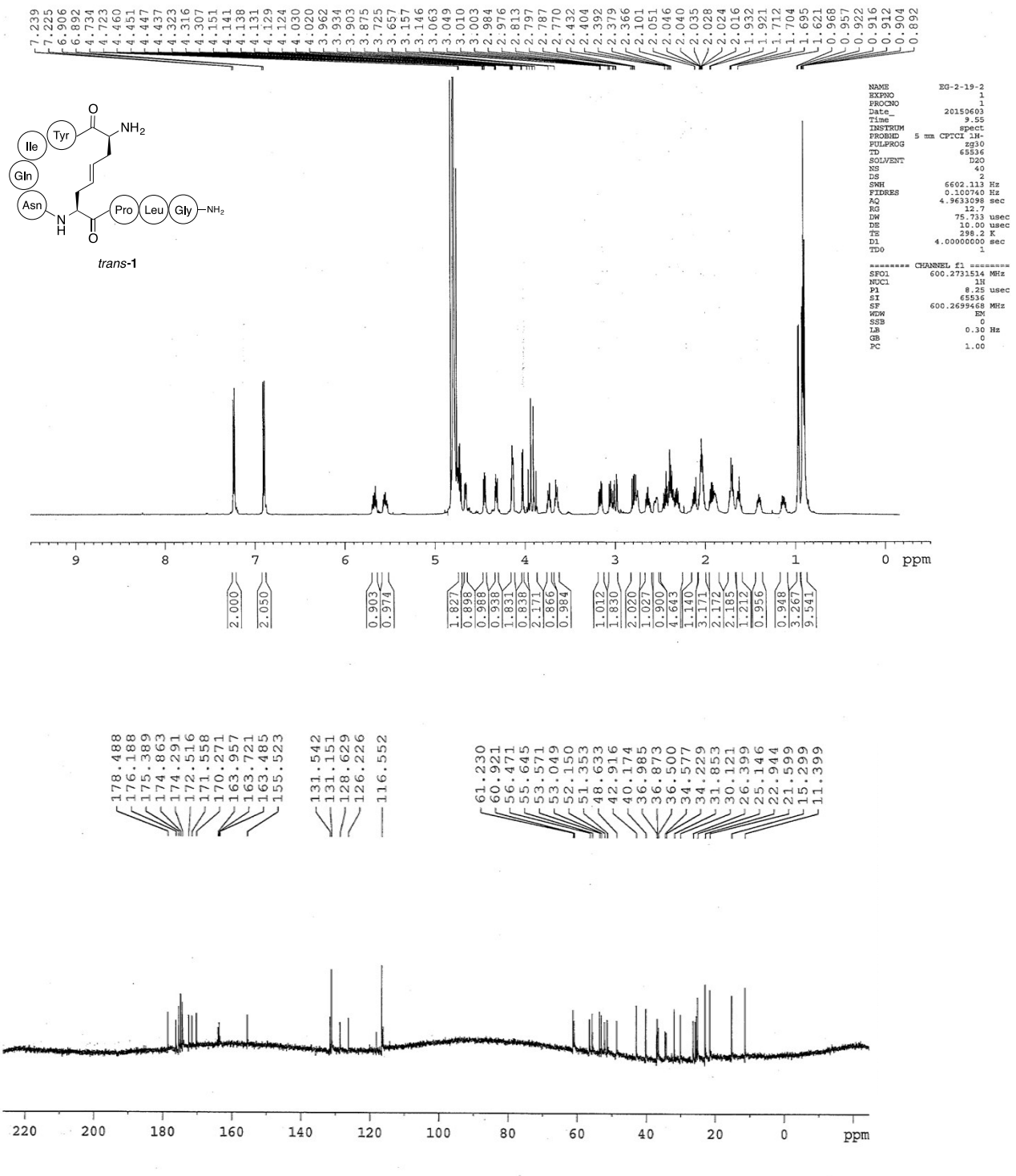


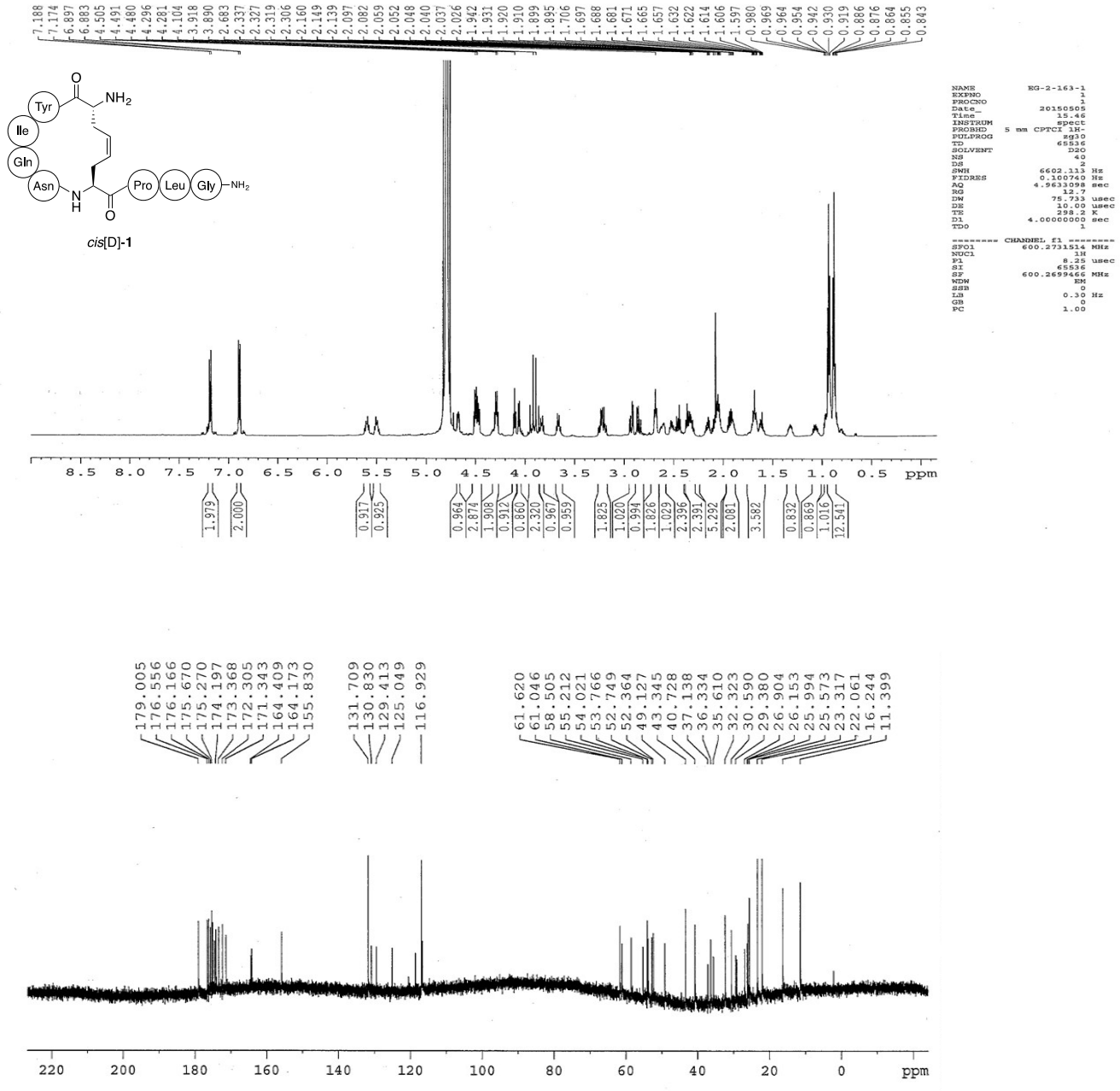
iii)



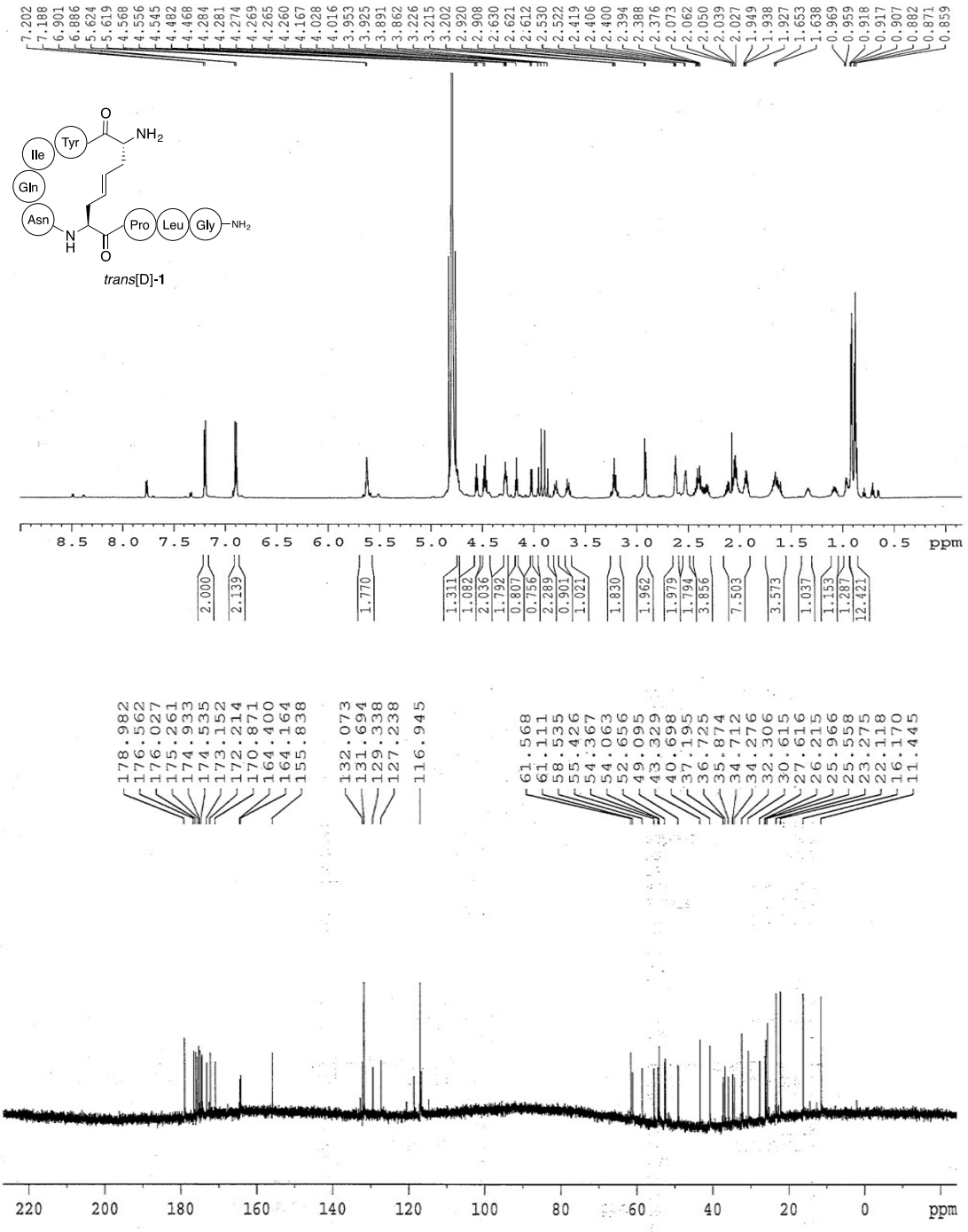

Tyr
Ile
Gln
Asn
Pro
Leu
Gly
NH2
cis-1




Ile
Tyr
Gln
Asn
Pro
Leu
Gly
NH2
trans-1
ppm


Tyr
Ile
Gln
Asn
Pro
Leu
Gly
NH2
cis[D]-1
NAME EG-2-163-1
EXPNO 1
PROCNO 1
Date_ 20150505
Time 15.46
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT D2O
NS 40
DS 2
SWH 6602.113 Hz
FIDRES 0.100740 Hz
AQ 4.9633098 sec
RG 12.7
DW 75.733 usec
DE 10.00 usec
TE 298.2 K
D1 4.00000000 sec
TD0 1
CHANNEL f1
SFO1 600.2731514 MHz
NUC1 1H
P1 8.25 usec
SI 65536
SF 600.2699466 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm

ppm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7.188
6.901
6.886
5.624
5.619
4.568
4.556
4.545
4.482
4.468
4.284
4.281
4.274
4.269
4.265
4.260
4.167
4.028
4.016
3.953
3.925
3.891
3.862
3.226
3.215
3.202
2.920
2.908
2.630
2.621
2.612
2.530
2.522
2.419
2.406
2.400
2.394
2.388
2.376
2.073
2.062
2.050
2.039
2.027
1.949
1.938
1.927
1.653
1.638
0.969
0.959
0.918
0.917
0.907
0.882
0.871
0.859
Ile
Tyr
NH2
Gln
Asn
N
H
Pro
Leu
Gly
NH2
trans[D]-1
NAME EG-2-163-2
EXPNO 1
PROCNO 1
Date_ 20150505
Time 14.26
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT D2O
NS 40
DS 2
SWH 6602.113 Hz
FIDRES 0.100740 Hz
AQ 4.9633098 sec
RG 12.7
DW 75.733 usec
DE 10.00 usec
TE 298.2 K
D1 4.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.2731514 MHz
NUC1 1H
P1 8.25 usec
SI 65536
SF 600.2699468 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.000
2.139
1.770
1.311
1.082
2.036
1.792
0.807
0.756
2.289
0.901
1.021
1.830
1.962
1.979
1.794
3.856
7.503
3.573
1.037
1.153
1.287
12.421
178.982
176.562
176.027
175.261
174.933
174.535
173.152
172.214
170.871
164.400
164.164
155.838
132.073
131.694
129.338
127.238
116.945
61.568
61.111
58.535
55.426
54.367
54.063
52.656
49.095
43.329
40.698
37.195
36.725
35.874
34.712
34.276
32.306
30.615
27.616
26.215
25.966
25.558
23.275
22.118
16.170
11.445
220 200 180 160 140 120 100 80 60 40 20 0 ppm