SUPPORTING MATERIAL
Universal Peptidomimetics

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A. Molecular Modeling

Templates For C^{β} - C^{β} Distances And Overlays

Templates for ideal type I β-turns[1,2] and for γ-turns[3] were obtained from standard torsion angles. A standard template for overlays with an α-helix was obtained from Discovery Studio 2.5[4], and a β-sheet template for overlays was obtained by β -sheet builder.

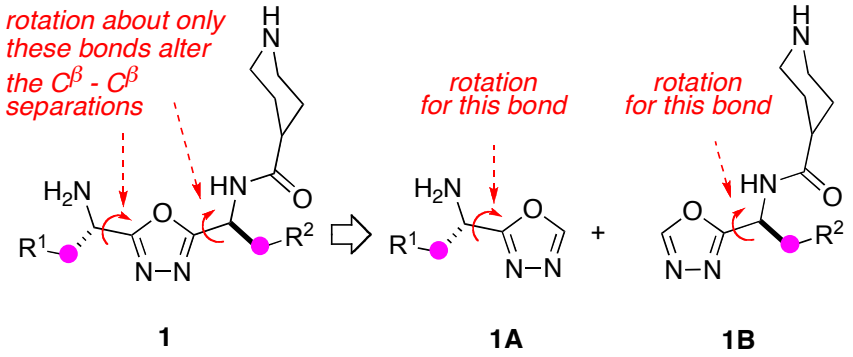
Procedure For Overlays

The contracted and extended C^{β} - C^{β} distances of compound **1** were obtained by rotation of the bonds (red arrows shown below). The possible secondary structures mimicked by compound **1** were obtained by comparing the values between the C^{β} - C^{β} distances for compound **1** against the distances in common secondary structures shown in table 1. After identifying possible secondary structures that compound **1** can mimic, the model of compound **1** was overlayed with the model of the secondary structure. Free rotation about the bonds was allowed to give a good matching of the C^{β} atoms on compound **1** with the secondary structure. The overlays for compounds **2**, **3** and **4** were also obtained in a similar way.

Procedures For Calculating Energy Barriers

Reaction path calculations were performed at the B3LYP level of theory with the 6-31G(d') basis set. Full geometry optimizations were performed for each fragment and stationary points were verified by frequency calculations and water solvation calculations. All B3LYP calculations were performed using Gaussian 03[5].

The energy barriers for rotation of the bonds (red arrows) in compound **1** were calculated on fragments **1A** and **1B**. The energy barrier for the whole structure was calculated by combination of the results for the fragments. The energy barriers for compounds **3** and **4** were also obtained in a similar way. For compound **2**, the whole structure was used for the calculation.



1 **1A** **1B**

Procedure For Quenched Molecular Dynamics Studies

NAMD[6] was used for the molecular simulations performed in this work (compounds **1**, **2**, **3**, **4**). Explicit atom representations were used throughout the study. The protein structure files (PSF) for all the peptidomimetics were built using Discovery Studio 2.5 (Accelrys Inc) using the CHARMm force field.[4]

Quenched molecular dynamics simulations were performed using the CHARMm force field as implemented in Discovery Studio 2.5. All four molecules were modeled as neutral compounds in a dielectric continuum of 80 (simulating H_2O). Thus, the starting conformers were minimized using 3000 steps of conjugate gradient. The minimized structures were then subjected to heating, equilibration, and dynamics simulation. Throughout, the equations of motions were integrated using the Verlet algorithm with a time step 1 fs. Each peptidomimetic was heated to 1000 K over 10 ps and equilibrated for another 10 ps at 1000 K, then molecular dynamics runs were performed for a total time of 600 ps with trajectories saved every 1 ps. The resulting 600 structures were thoroughly minimized using 1000 steps of SD followed by 3000 steps of conjugate gradient. Structures with energies less than 0.3 (compound **1** and **3**) and 1.0 (compound **4**) kcal mol^{-1} relative to the global minimum were selected for further analysis.

The VMD[7] package was again used to display, overlay, and classify the selected structures into conformational groups. The best clustering was obtained using a grouping method based on calculation of RMS deviation of a subset of atoms, in this study these were the C^{α} - and C^{β}- atoms. Thus, threshold cutoff values 0.3 Å were selected to obtain families with reasonable homogeneity. The lowest energy conformation from each family was considered to be a typical representative of the family as a whole.

B. General Methods for Syntheses

All reactions were carried out under an atmosphere of dry nitrogen. Glassware was oven-dried prior to use. Unless otherwise indicted, common reagents or materials were obtained from commercial source and used without further purification. All α-amino acids used were of the L-configuration, except where otherwise indicated. Triethylamine (TEA) was obtained anhydrous by distillation over calcium hydride and tetrahydrofuran (THF) was distilled over sodium metal and benzophenone. Acetonitrile, dichloromethane, methanol and diethyl ether were dried by a Mbraun solvent drying system.

Flash column chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV. Optical rotations were measured on Jasco DIP-360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 (300 MHz ^{1}H; 75 MHz ^{13}C) or Varian 500 (500 MHz ^{1}H; 125 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual $CDCl_3$ (δ 7.27 ppm ^{1}H; δ 77.0 ppm ^{13}C), CD_3OD (δ 3.31 ppm ^{1}H; δ 49.86 ppm ^{13}C), or d^6-DMSO (δ 2.49 ppm ^{1}H; δ 39.5 ppm ^{13}C). NMR chemical shifts were expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz. (br = broad)

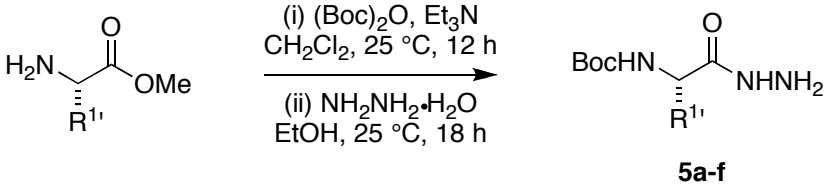
C. Preparation of Oxadiazole-based Mimics

General Procedure for Compounds 5a-g

Boc-protected L-amino acid methyl ester (1.0 equiv) was dissolved in ethanol (0.4 M) and hydrazine monohydrate (3.0 equiv) was added in one portion. The reaction mixture was vigorously stirred at 25 °C for 12 h. The solvents were removed *in vacuo* and the crude amino acid hydrazide product **5a-g** was used in the next step without further purification.

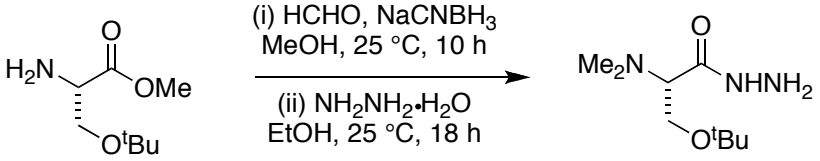
Scheme S1. Synthesis of compounds **5a-g**.

a



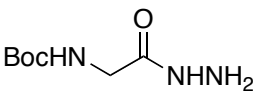
5a-f

b



5g

Preparation of Compound 5a

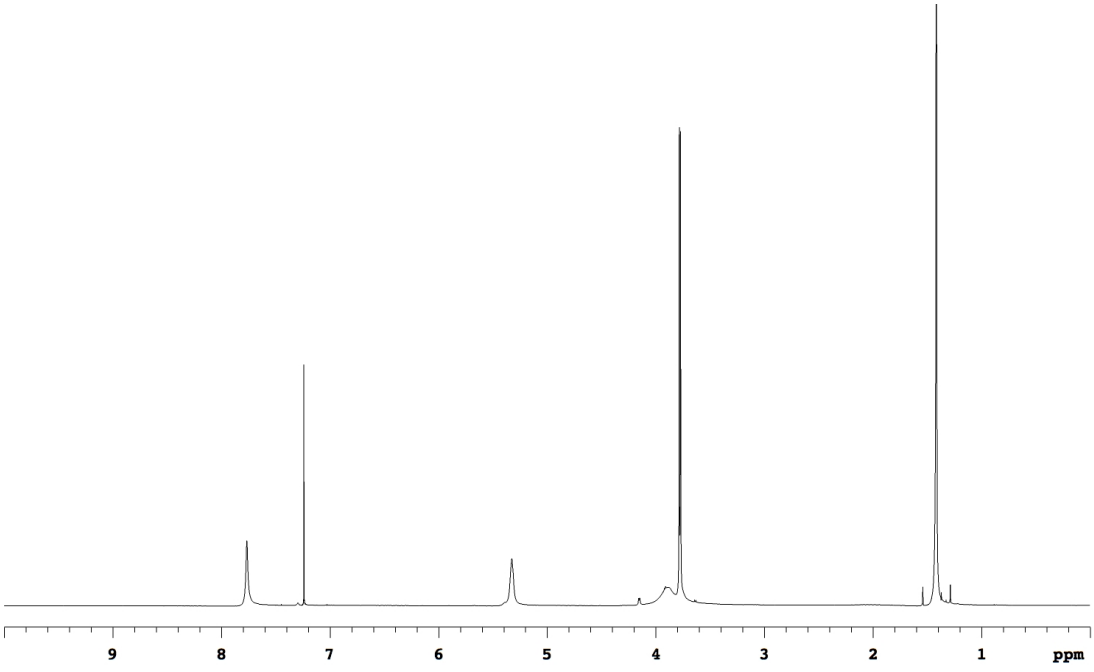


5a

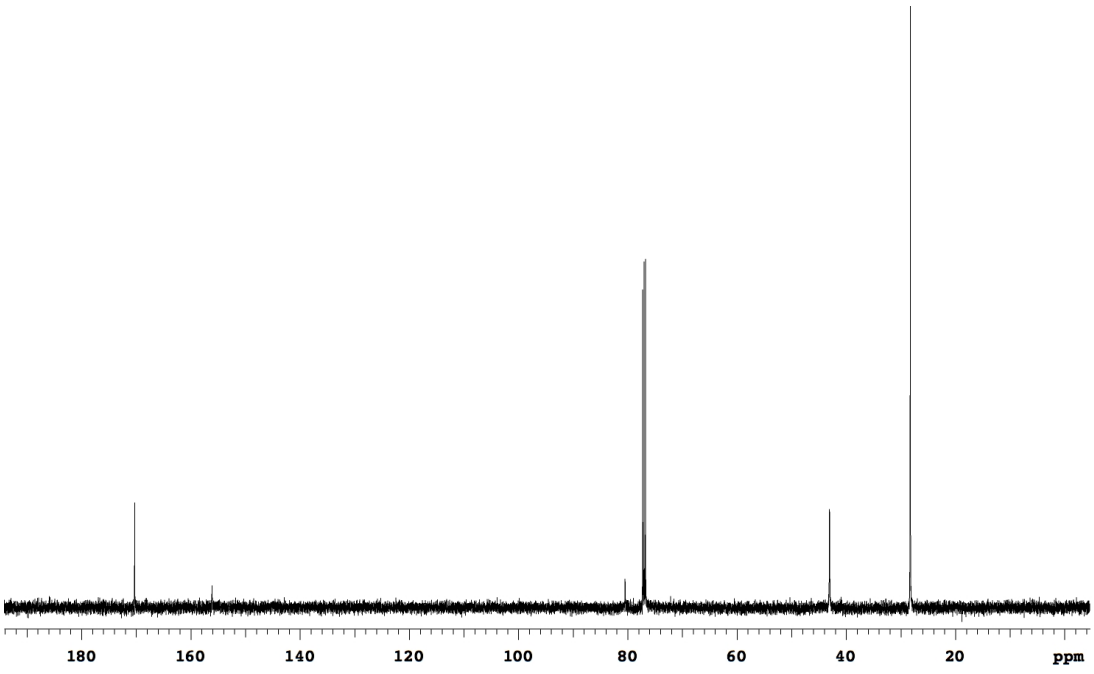
Compound **5a** was prepared from Boc-Gly-OMe (3.78 g, 20.0 mmol) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 5.33 (s, 1H), 3.89 (br, 2H), 3.78 (d, 2H, J = 6.0 Hz), 1.42 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 156.1, 80.5, 43.1, 28.3

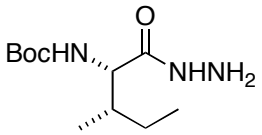


^{1}H NMR of **5a**



^{13}C NMR of **5a**

Preparation of Compound 5b

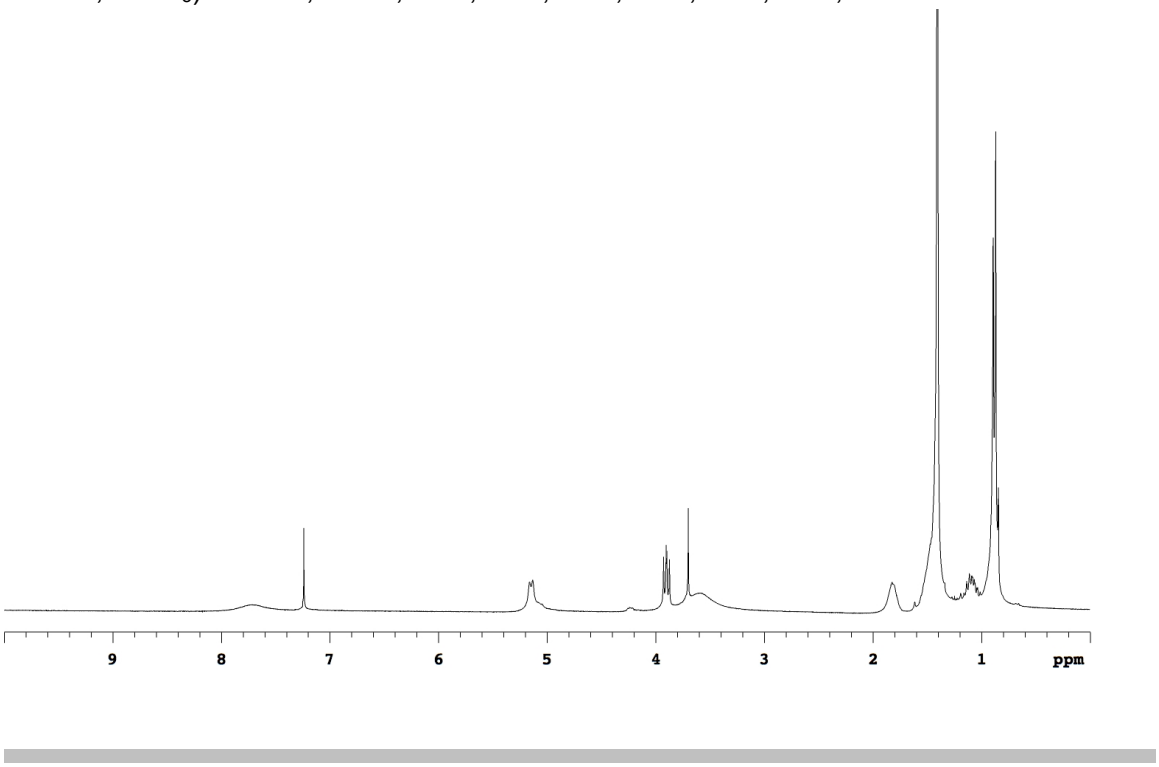


5b

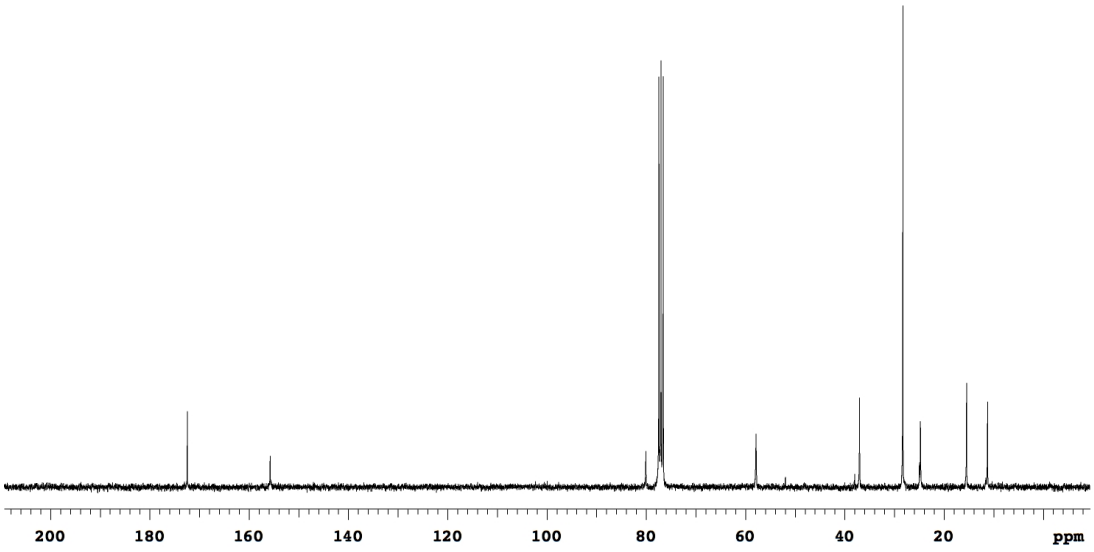
Compound **5b** was prepared from Boc-Ile-OMe (3.68 g, 15.0 mmol) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (br, 1H), 5.15 (d, 1H, J = 8.6 Hz), 4.02-3.30 (m, 3H), 1.82 (br, 1H), 1.60-1.27 (m, 10H), 1.18-1.01 (m, 1H), 1.00-0.75 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.8, 80.1, 57.9, 37.0, 28.3, 24.8, 15.5, 11.2

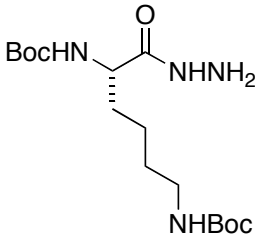


^{1}H NMR of **5b**



^{13}C NMR of **5b**

Preparation of Compound 5c

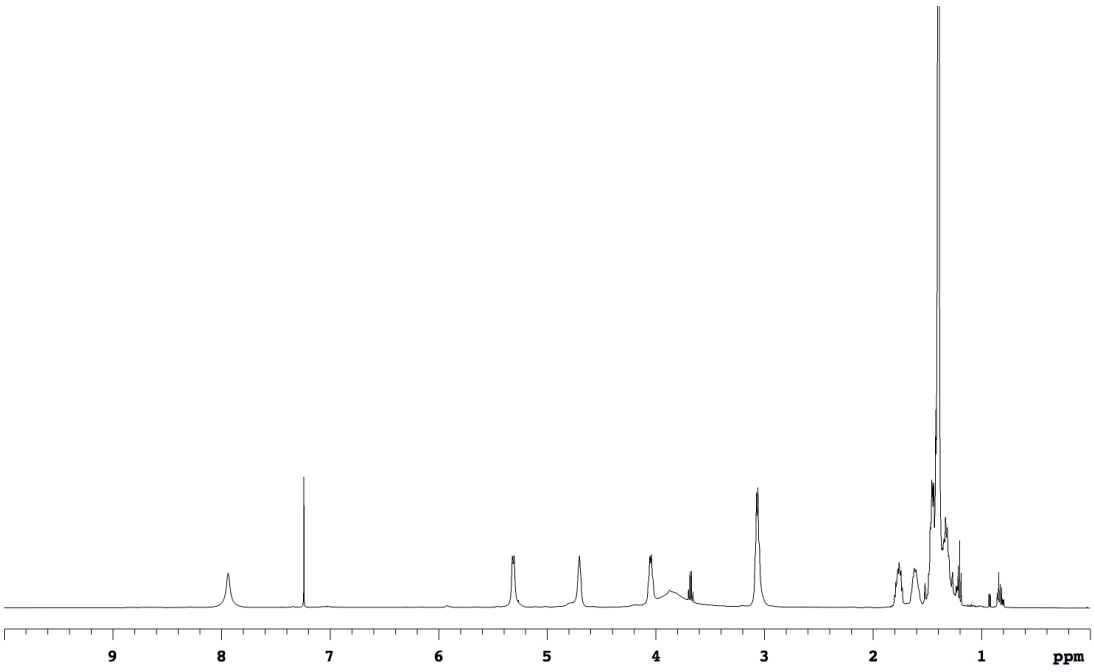


5c

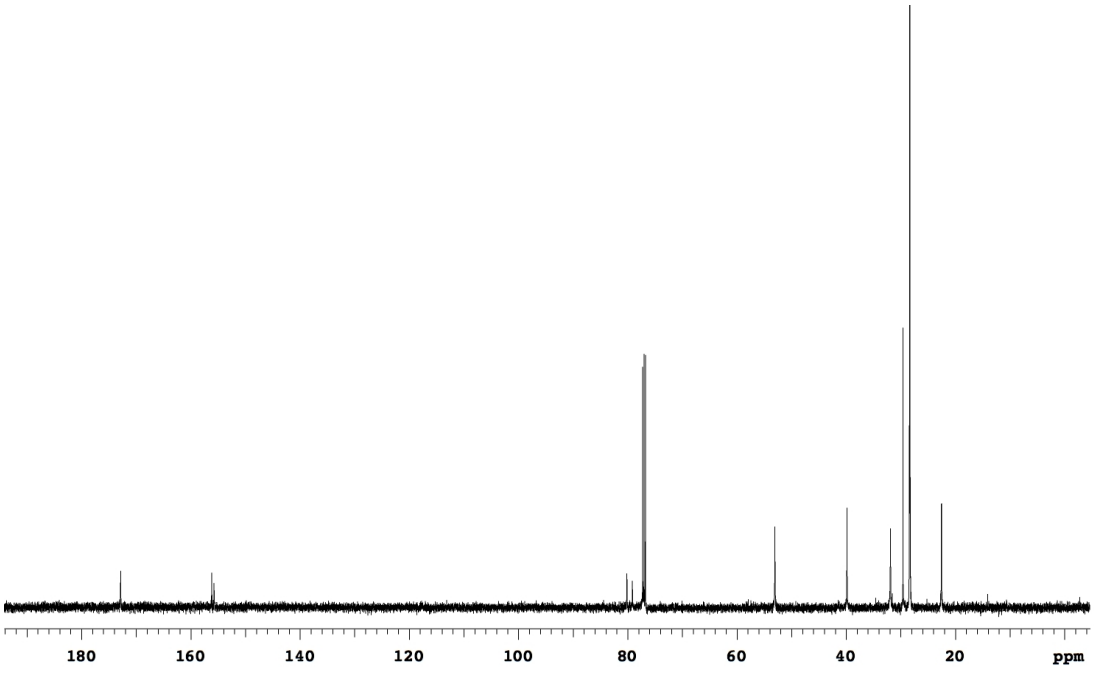
Compound **5c** was prepared from Boc-Lys(Boc)-OMe (5.41 g, 15.0 mmol) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 5.31 (d, 1H, J = 7.5 Hz), 4.70 (br, 1H), 4.13-3.61 (m, 3H), 3.13-2.96 (m, 2H), 1.83-1.71 (m, 1H), 1.67-1.55 (m, 1H), 1.51-1.24 (m, 22H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 156.2, 155.7, 80.1, 79.1, 53.0, 39.8, 31.9, 29.6, 28.4, 28.3, 22.5

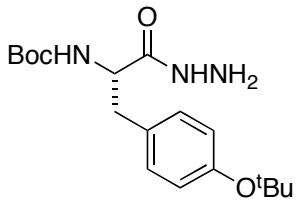


^{1}H NMR of **5c**



^{13}C NMR of 5**c**

Preparation of Compound 5d

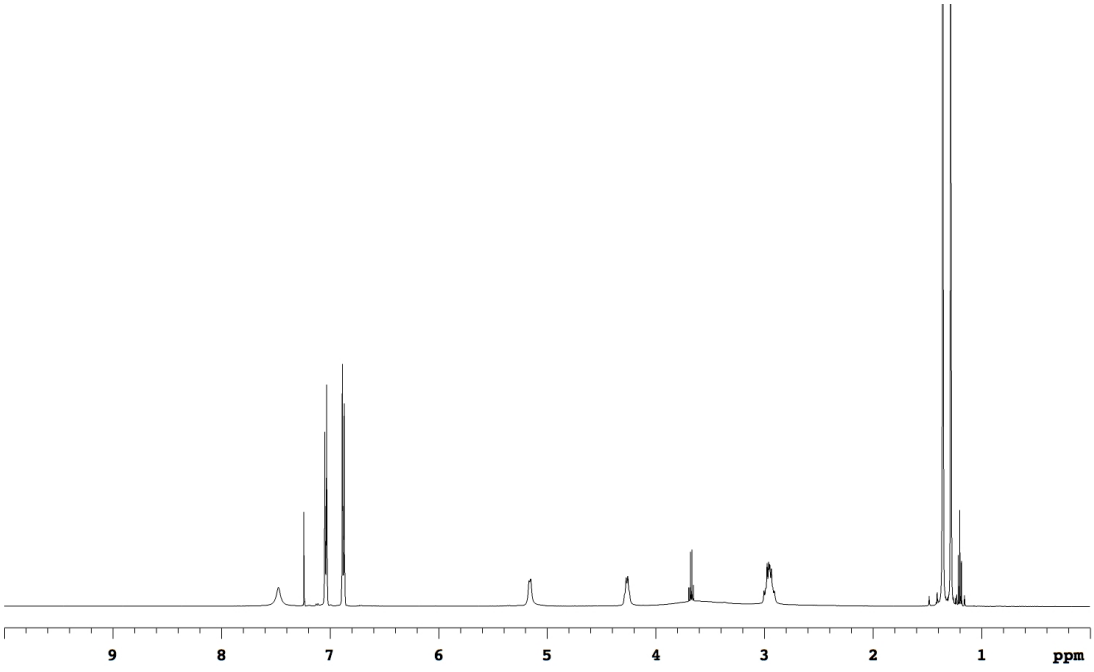


5d

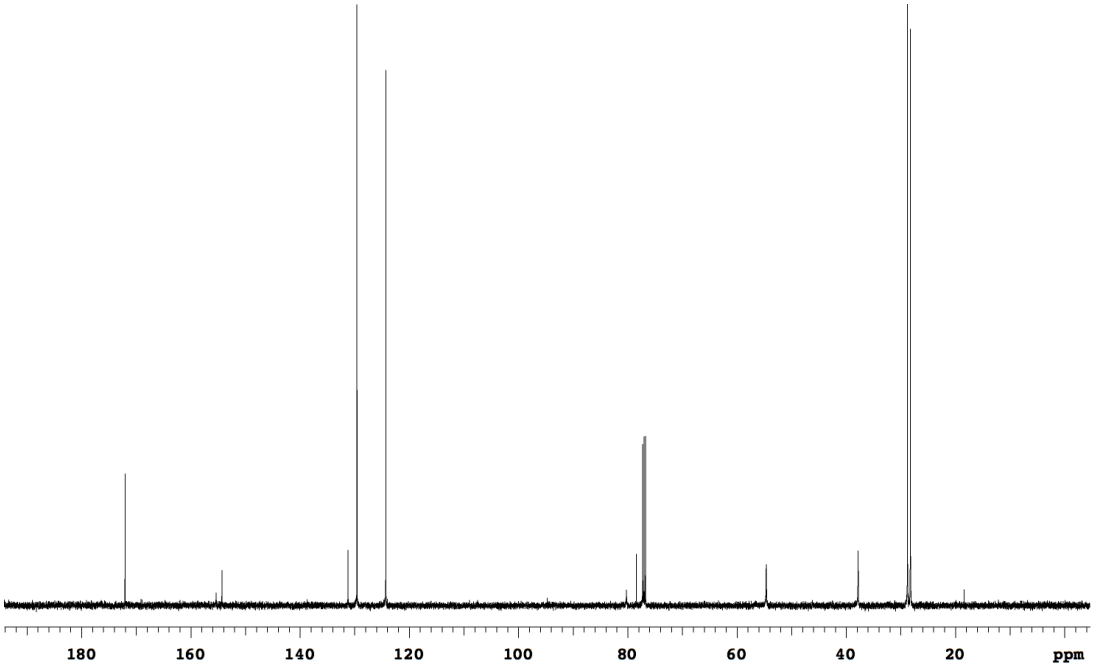
Compound **5d** was prepared from Boc-Tyr(^{t}Bu)-OMe (5.27 g, 15 .0 mmol) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (br, 1H), 7.04 (d, 2H, J = 6.9 Hz), 6.88 (d, 2H, J = 8.5 Hz), 5.16 (d, 1H, J = 7.5 Hz), 4.34-4.18 (m, 1H), 3.75-3.65 (m, 2H), 3.05-2.84 (m, 2H), 1.36 (s, 9H), 1.29 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 155.4, 154.3, 131.2, 129.6, 124.3, 80.2, 78.4, 54.6, 37.8, 28.8, 28.2

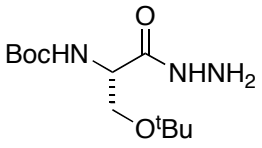


^{1}H NMR of **5d**



^{13}C NMR of **5d**

Preparation of Compound 5e

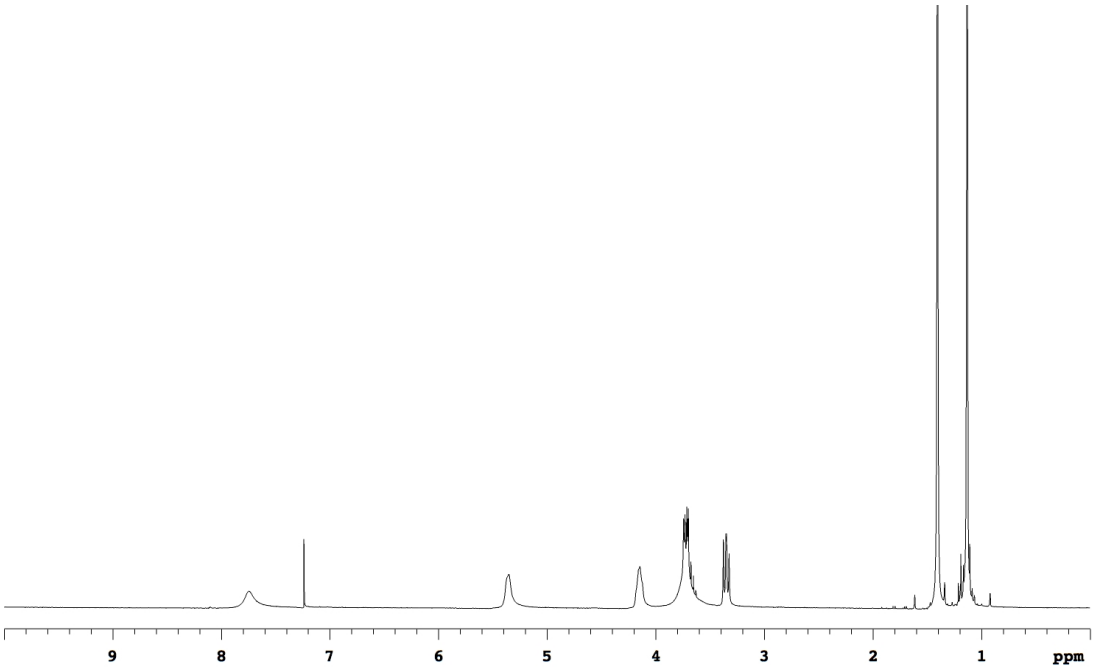


5e

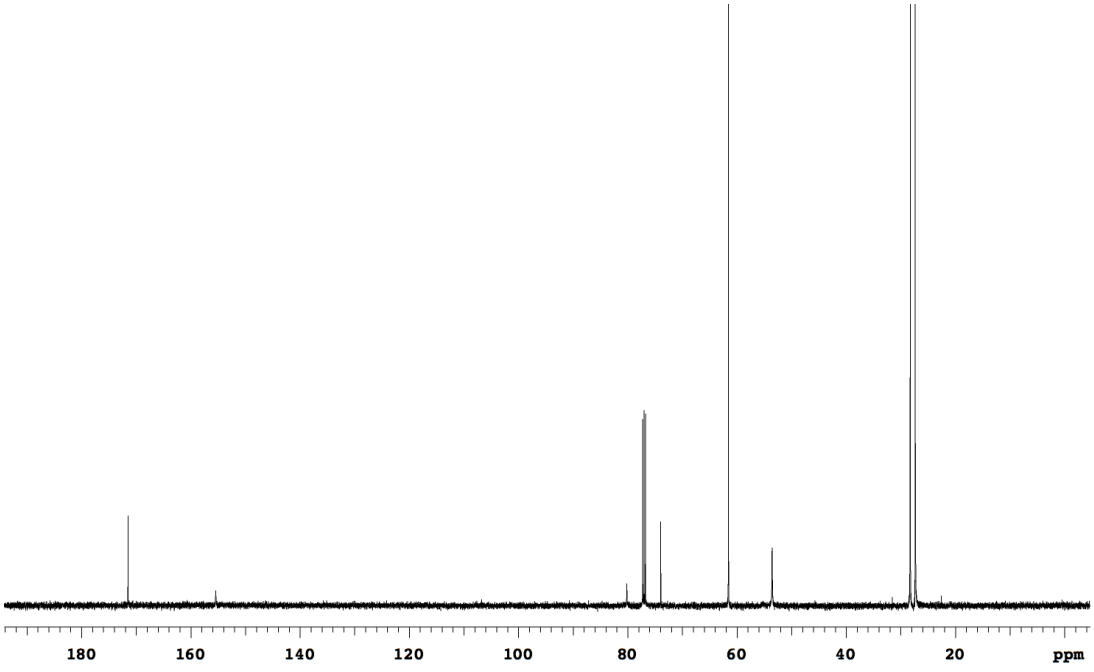
Compound **5e** was prepared from Boc-Ser(^{t}Bu)-OMe (4.13 g, 15.0 mmol) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (br, 1H), 5.35 (br, 1H), 4.15 (br, 1H), 3.88-3.49 (m, 3H), 3.35 (dd, 1H, J = 7.0, 8.7 Hz), 1.41 (s, 9H), 1.13 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 155.4, 80.2, 73.9, 61.5, 53.6, 28.3, 27.3

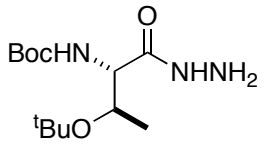


^{1}H NMR of **5e**



^{13}C NMR of **5e**

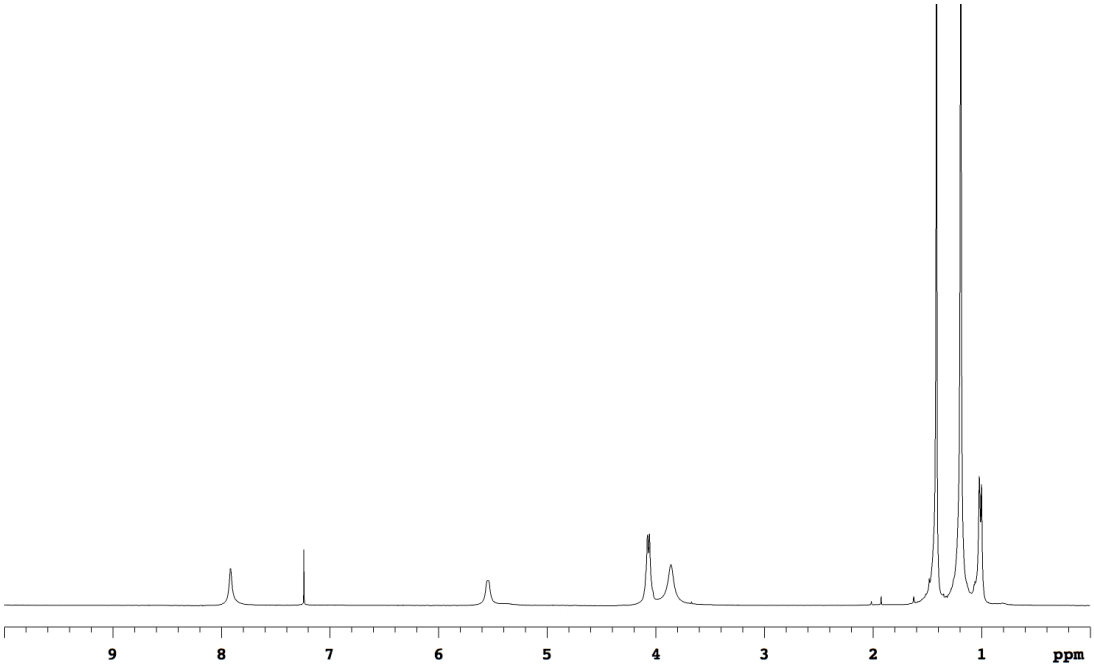
Preparation of Compound 5f



5f

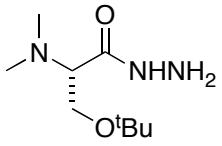
Compound **5f** was prepared from Boc-Thr(^{t}Bu)-OMe (2.89 g, 10.0 mmol) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (br, 1H), 5.54 (br, 1H), 4.20-3.99 (m, 2H), 3.86 (br, 2H), 1.41 (s, 9H), 1.19 (s, 9H), 1.01 (d, 3H, J = 6.0 Hz)



^{1}H NMR of **5f**

Preparation of Compound 5g



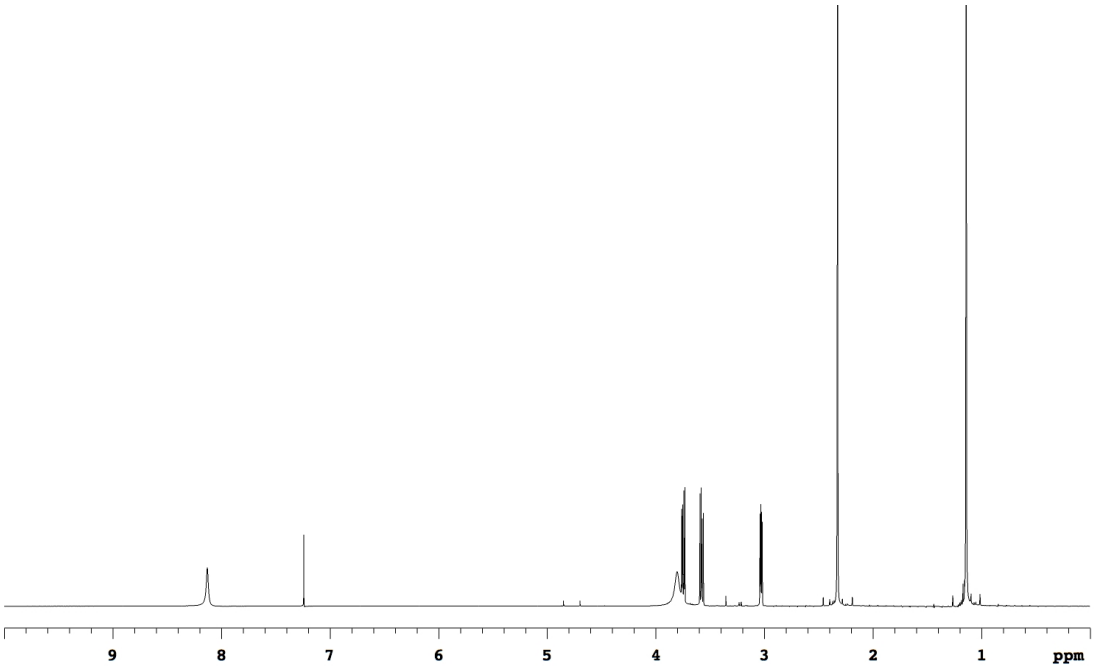
5g

To a solution of H-Ser(^{t}Bu)-OMe (1.06 g, 5.0 mmol) in 16.0 mL CH_3OH was added acetic acid to adjust the pH (~4.0). To this solution was slowly added 37 % formaldehyde solution (4.0 mL, 50.0 mmol), and then $NaCNBH_3$ (471.3 mg, 7.5 mmol) while stirring. The reaction mixture was stirred at 25 °C for 10 h. The solvents were removed under reduced pressure. The residue was washed with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried with Na_2SO_4 and concentrated to dryness. Flash chromatography with EtOAc/hexanes mixtures (20 % to 30 %) afforded pure *N*, *N*-dimethyl-Ser(^{t}Bu)-OMe as colorless oil (761.3 mg, 75 %). Compound **5g** was then prepared from *N*, *N*-dimethyl-Ser(^{t}Bu)-OMe (1.62 g, 8.0 mmol) using a procedure similar to that described for compounds **5a-f**. Compound **5g** was obtained as a white solid and used in the next step without further purification.

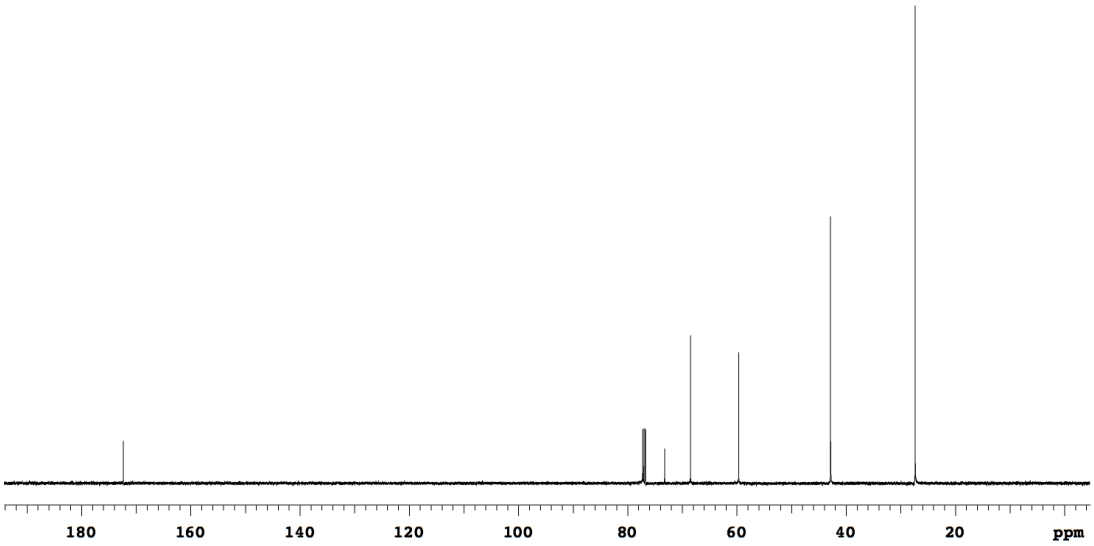
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br, 1H), 3.80 (br, 2H), 3.75 (dd, 1H, J = 4.3, 9.8 Hz), 3.58 (dd, 1H, J = 6.1, 9.8 Hz), 3.03 (dd, 1H, J = 4.3, 6.1 Hz), 2.33 (s, 6H), 1.14 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 73.2, 68.5, 59.6, 42.8, 27.7

MS (APCI, m/z) calcd for $C_9H_{22}N_3O_2$ $(M+H)^+$ 204.2, found 204.0



^{1}H NMR of **5g**

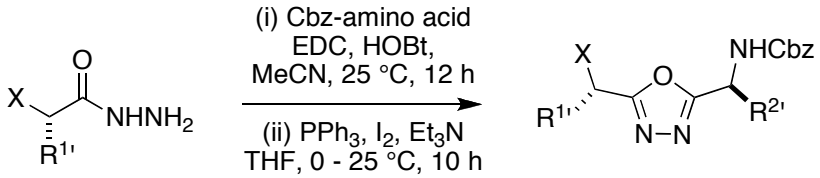


^{13}C NMR of **5g**

General Procedure for Compounds 6a-t

The Cbz protected amino acid (1.0 equiv) was dissolved in dry CH_3CN (0.50 M). 1-Hydroxybenzotriazole (HOBt) (1.1 equiv) was added in one portion followed by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (1.1 equiv). The mixture was stirred at 25 °C for ~ 1h (until all of the acid was converted to the activated form). The resulting mixture was then slowly added to a solution of protected amino acid hydrazide **5a-g** (1.0 equiv) in dry CH_3CN (0.50 M). The reaction mixture was vigorously stirred at 25 °C for 8 h. The solvent was removed under reduced pressure and the residue was washed with H_2O (30.0 mL), 1N HCl (30.0 mL), saturated $NaHCO_3$ (30.0 mL) and brine (30.0 mL). The solid crude product was dried *in vacuo* and used in the next step directly. To a stirred solution of this diacyl hydrazide intermediate in dry THF (0.10 M), PPh_3 (2.0 equiv), I_2 (2.0 equiv) and Et_3N (4.0 equiv) were added at 0 °C. The cooling bath was removed after 30 min and stirring was continued at 25 °C for 4-6 h. Water (30.0 mL) was added and the resulting mixture was stirred for 1 h. The organic phase was separated and dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography with EtOAc/hexanes mixtures to provide pure compounds **6a-t**.

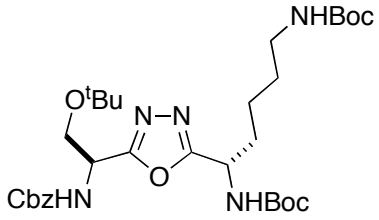
Scheme S2. Synthesis of compounds **6a-t**.



5a-f X = NHBoc
5g X = NMe_2

6a-q X = NHBoc
6r-t X = NMe_2

Preparation of Compound 6a



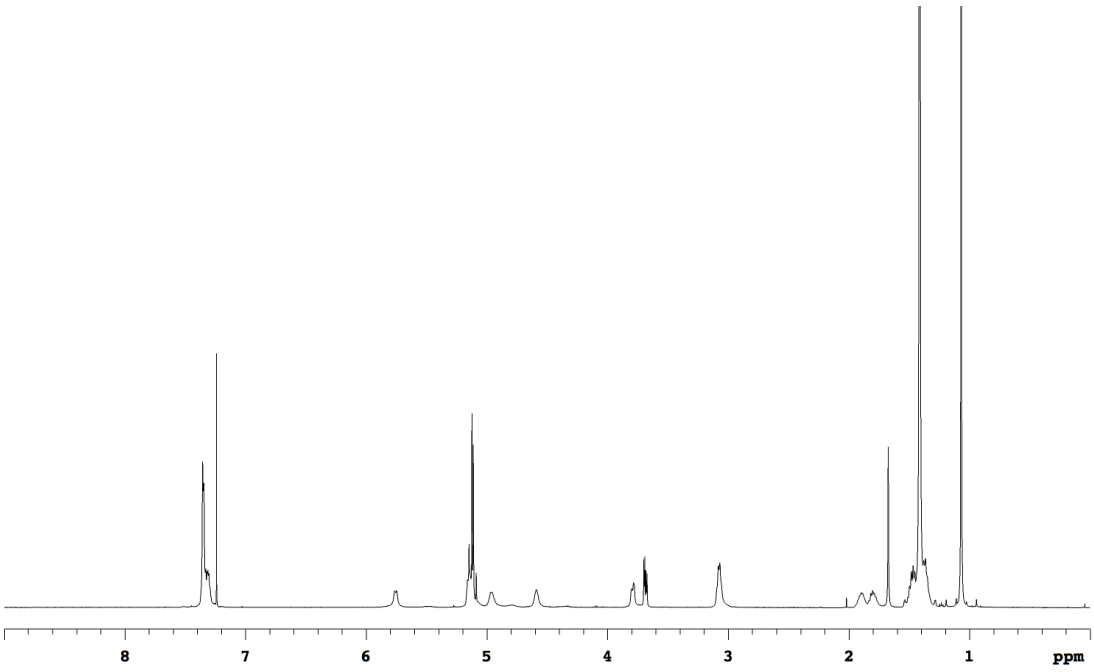
6a

Compound **6a** was prepared from **5c** (4.75 g, 13.2 mmol) and Cbz-Ser(^{t}Bu)-OH (3.89 g, 13.2 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 5.27 g (64 %) **6a** as a white solid.

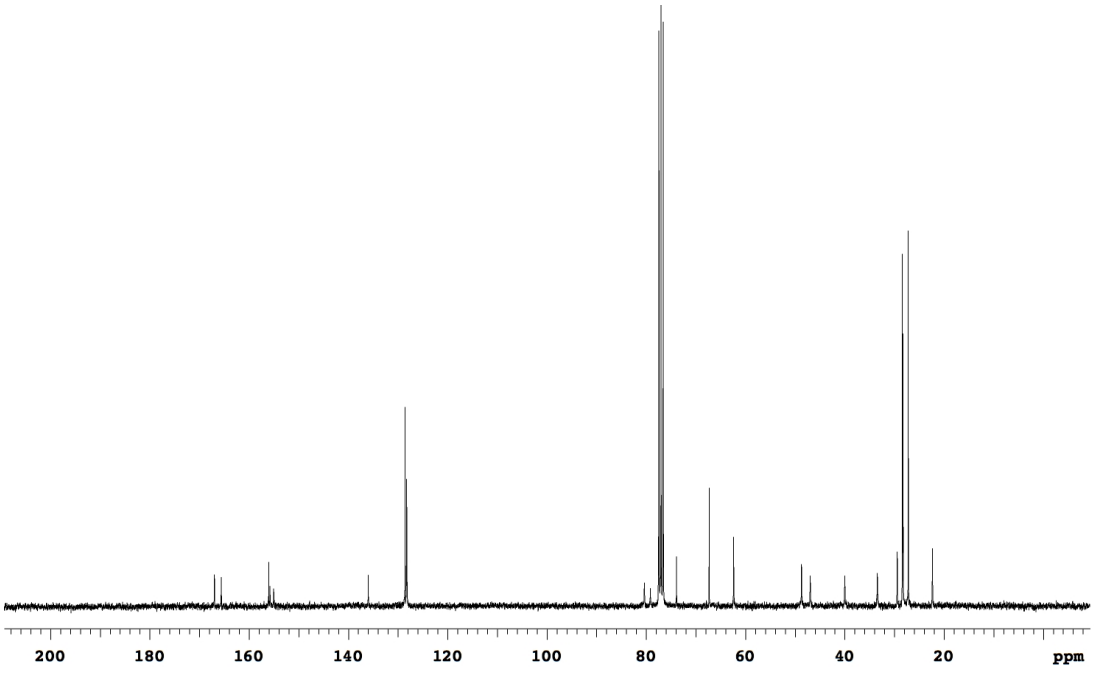
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 5.76 (d, 1H, J = 7.8 Hz), 5.19-5.07 (m, 4H), 4.96 (br, 1H), 4.59 (br, 1H), 3.82-3.76 (m, 1H), 3.69 (dd, 1H, J = 3.9, 9.2 Hz), 3.12-3.02 (m, 2H), 1.96-1.74 (m, 2H), 1.56-1.30 (m, 22H), 1.07 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 165.6, 156.0, 155.8, 155.0, 136.0, 128.6, 128.3, 128.2, 80.4, 79.2, 73.9, 67.3, 62.4, 48.7, 46.9, 40.0, 33.4, 29.4, 28.4, 28.3, 27.2, 22.3

MS (ESI, m/z) calcd for $C_{31}H_{49}N_5NaO_8$ $(M+Na)^+$ 642.3, found 642

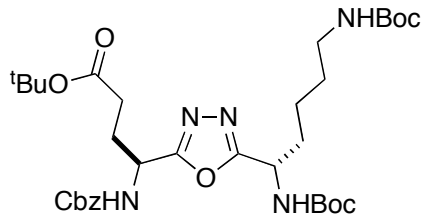


^{1}H NMR of **6a**



^{13}C NMR of **6a**

Preparation of Compound 6b



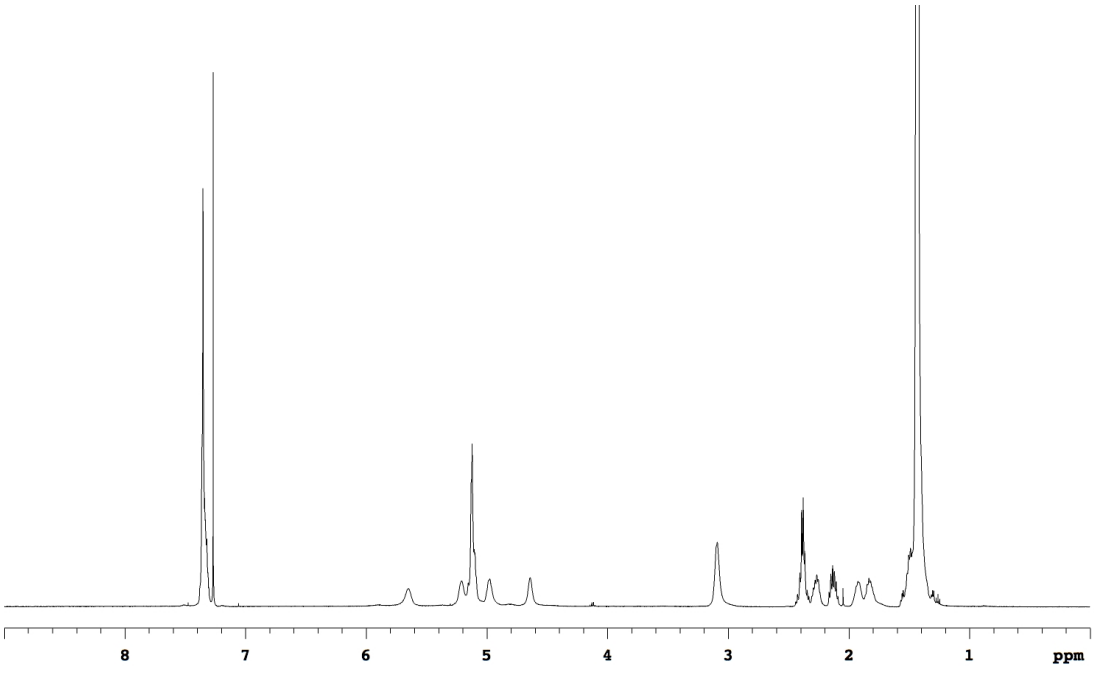
6b

Compound **6b** was prepared from **5c** (3.48 g, 14.2 mmol) and Cbz-Glu(O^{t}Bu)-OH (5.40 g, 14.2 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 4.52 g (48 %) **6b** as a white solid.

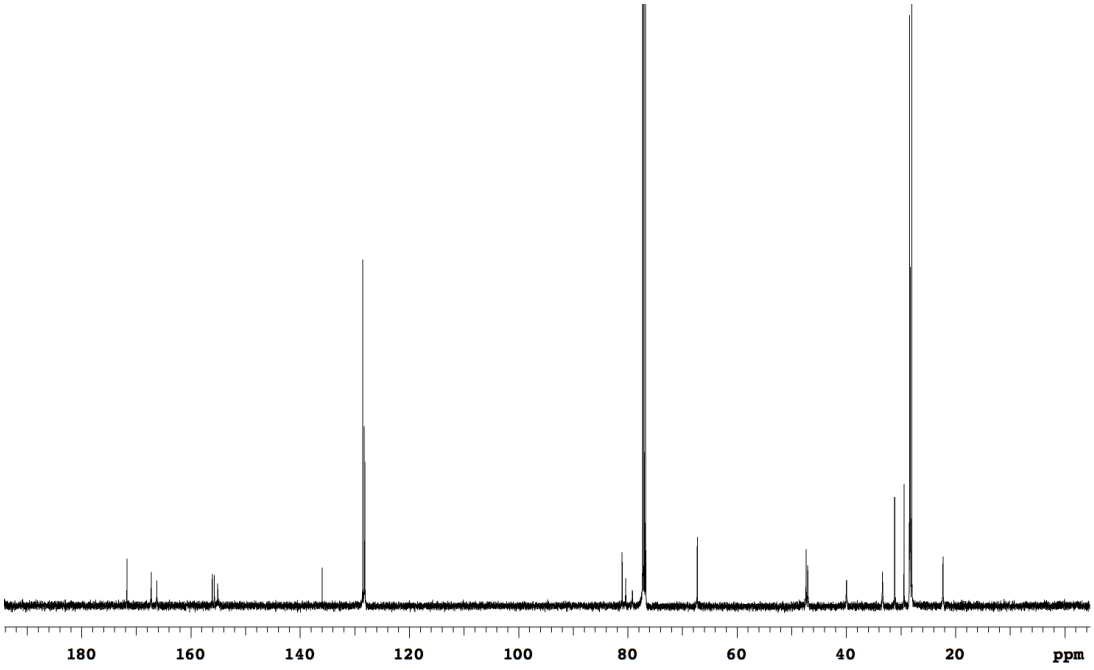
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.65 (br, 1H), 5.27-5.05 (m, 4H), 4.97 (br, 1H), 4.64 (br, 1H), 3.09 (br, 2H), 2.45-2.21 (m, 3H), 1.18-1.08 (m, 1H), 1.58-1.33 (m, 31H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 167.3, 166.2, 156.1, 155.7, 155.1, 135.9, 128.5, 128.3, 128.1, 81.0, 80.4, 79.1, 67.3, 47.4, 47.0, 39.9, 33.4, 31.1, 29.4, 28.4, 28.3, 28.0, 22.3

MS (ESI, m/z) calcd for $C_{33}H_{51}N_5NaO_9$ $(M+Na)^+$ 684.36, found 684

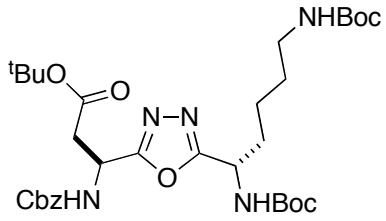


^{1}H NMR of **6b**



^{13}C NMR of **6b**

Preparation of Compound 6c



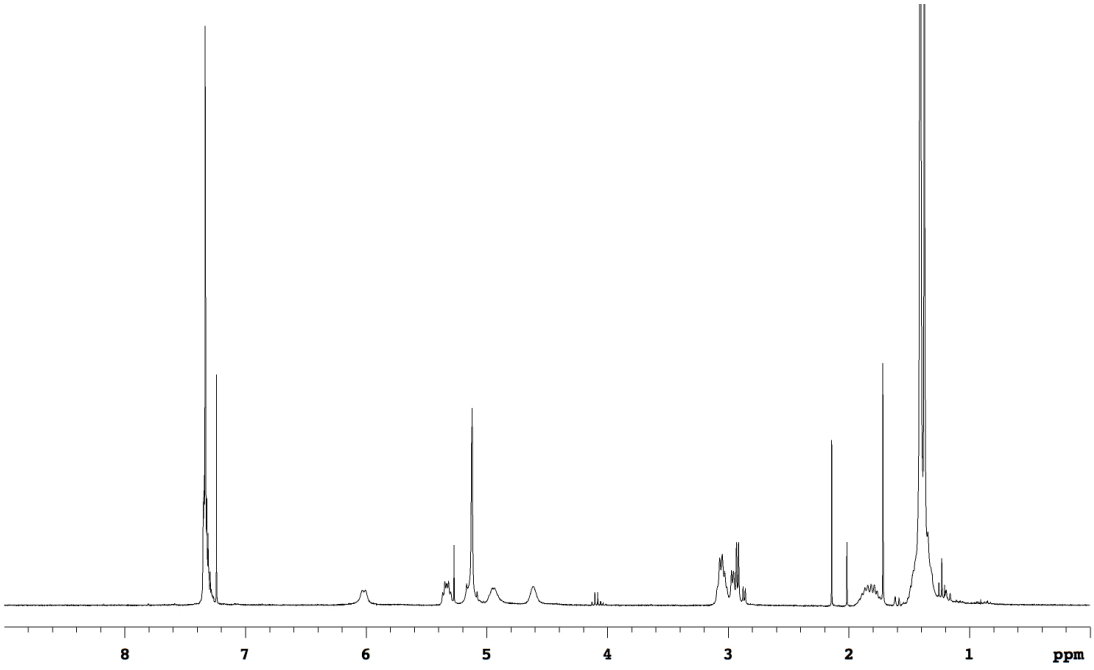
6c

Compound **6c** was prepared from **5c** (4.66 g, 12.9 mmol) and Cbz-Asp(O^{t}Bu)-OH•DCHA (6.53 g, 12.9 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 3.32 g (40 %) **6c** as a white solid.

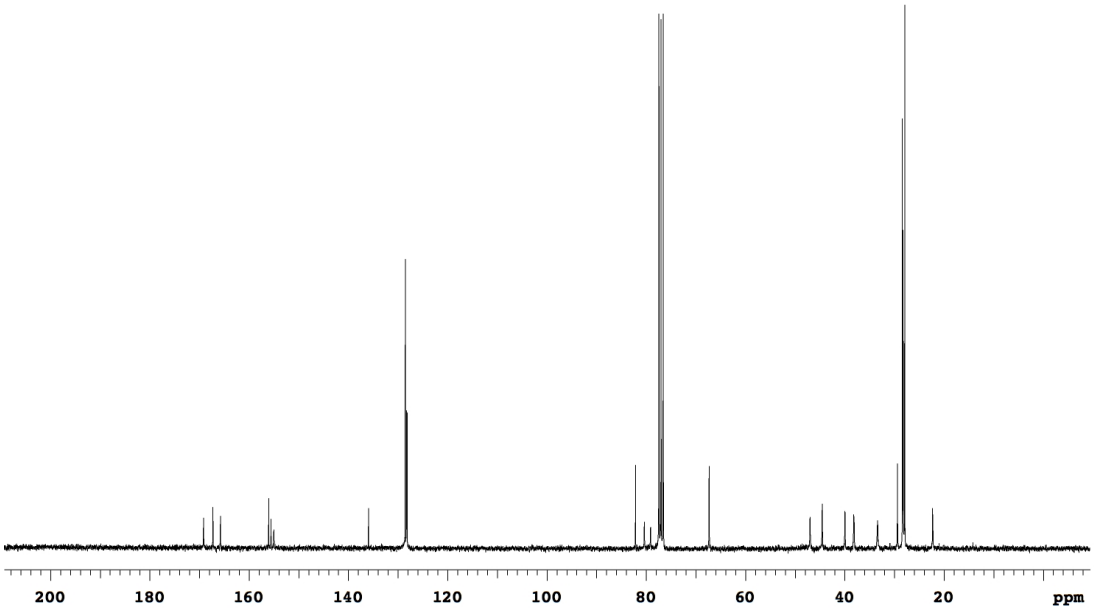
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 6.02 (d, 1H, J = 7.8 Hz), 5.39-5.28 (m, 1H), 5.21-5.06 (m, 3H), 4.95 (br, 1H), 4.61 (br, 1H), 3.12-2.84 (m, 4H), 1.95-1.73 (m, 2H), 1.53-1.27 (m, 31H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 167.3, 165.8, 156.0, 155.6, 155.0, 135.9, 128.5, 128.3, 128.2, 82.1, 80.4, 79.1, 67.3, 47.0, 44.5, 40.0, 38.2, 33.4, 29.4, 28.4, 28.2, 27.9, 22.3

MS (ESI, m/z) calcd for $C_{32}H_{50}N_5O_9$ $(M+H)^+$ 648.36, found 648

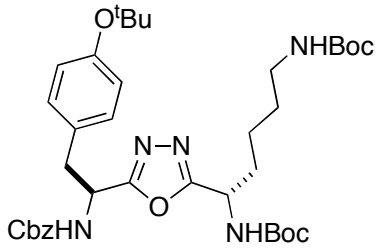


^{1}H NMR of **6c**



^{13}C NMR of **6c**

Preparation of Compound 6d



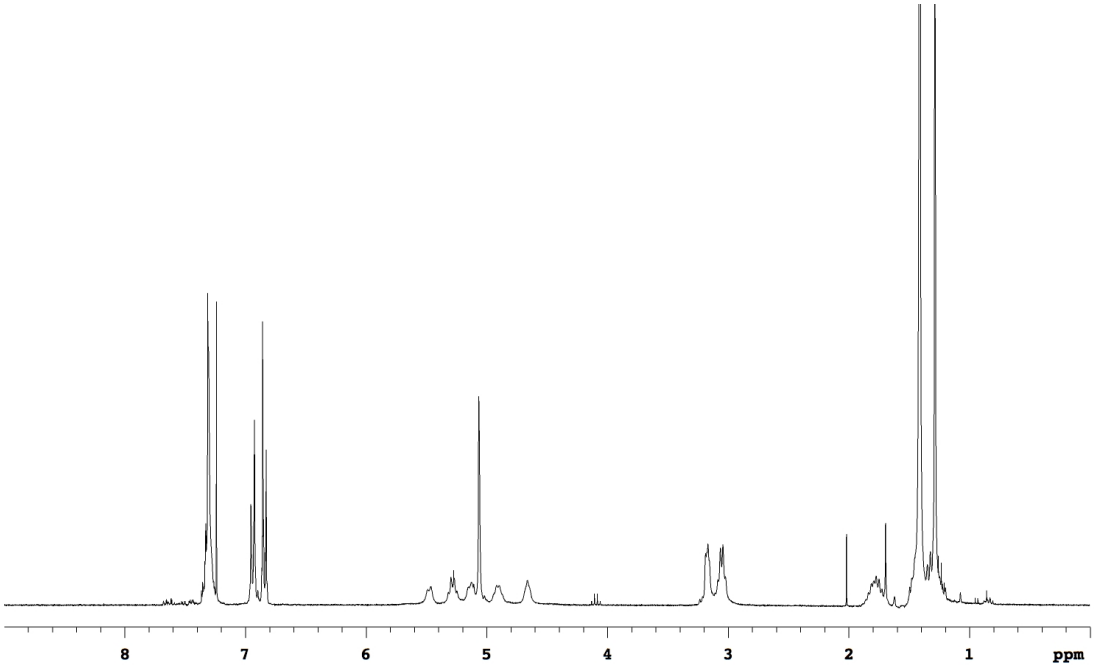
6d

Compound **6d** was prepared from **5c** (4.70 g, 13.0 mmol) and Cbz-Tyr(^{t}Bu)-OH (4.84 g, 13.0 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 3.70 g (41 %) **6d** as a white solid.

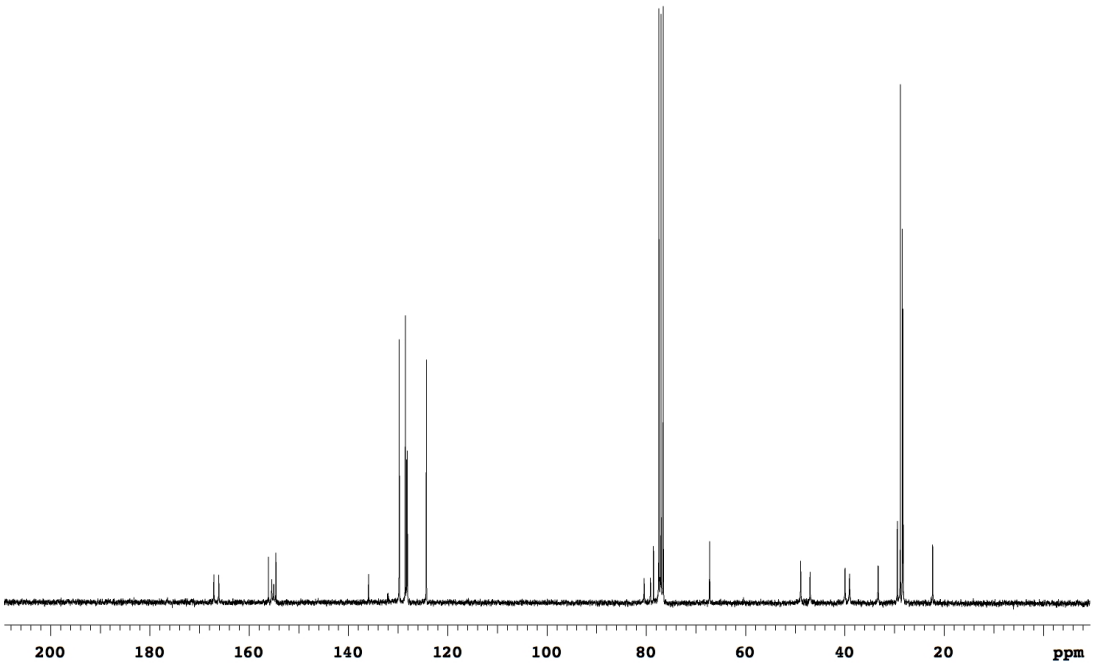
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 6.94 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz), 5.48 (d, 1H, J = 8.0 Hz), 5.36-5.21 (m, 1H), 5.20-5.00 (m, 3H), 4.97-4.84 (m, 1H), 4.66 (br, 1H), 3.25-2.96 (m, 4H), 1.90-1.66 (m, 2H), 1.52-1.19 (m, 31H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 166.1, 156.1, 155.4, 155.0, 154.6, 135.9, 132.1, 129.7, 128.5, 128.3, 128.1, 124.3, 80.4, 79.1, 78.5, 67.2, 48.9, 47.0, 40.0, 39.0, 33.3, 29.4, 28.8, 28.4, 28.3, 22.3

MS (MALDI, m/z) calcd for $C_{37}H_{53}N_5NaO_8$ $(M+Na)^+$ 718.38, found 718

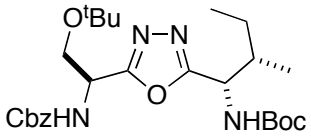


^{1}H NMR of **6d**



^{13}C NMR of **6d**

Preparation of Compound 6e



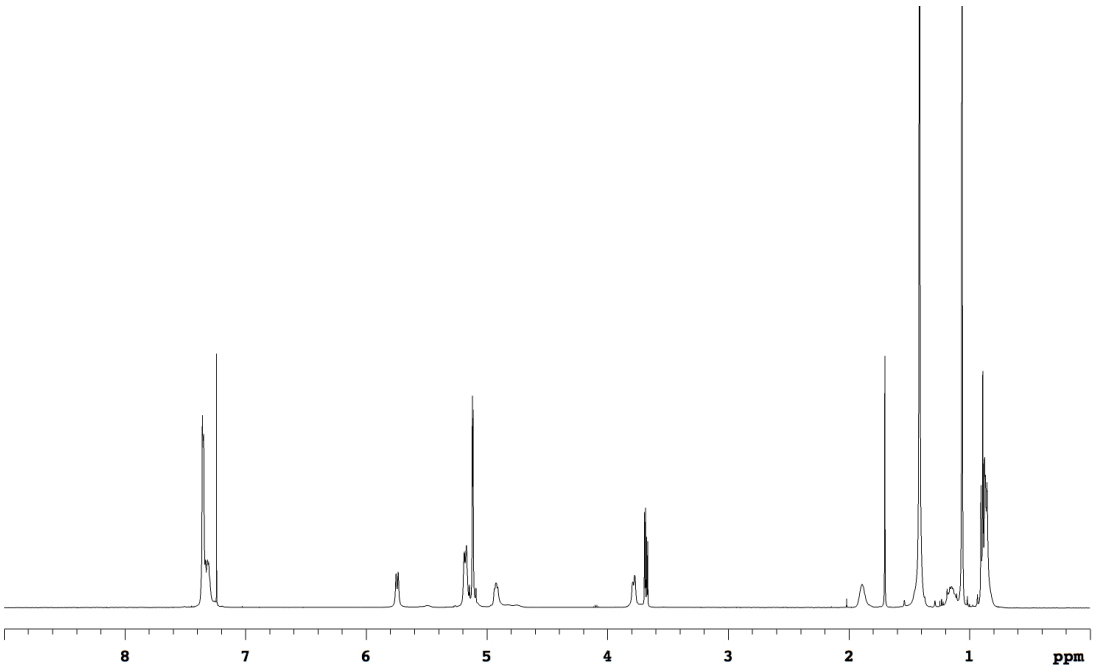
6e

Compound **6e** was prepared from **5b** (3.51 g, 14.3 mmol) and Cbz-Ser(^{t}Bu)-OH (4.22 g, 14.3 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 5.42 g (75 %) **6e** as a white solid.

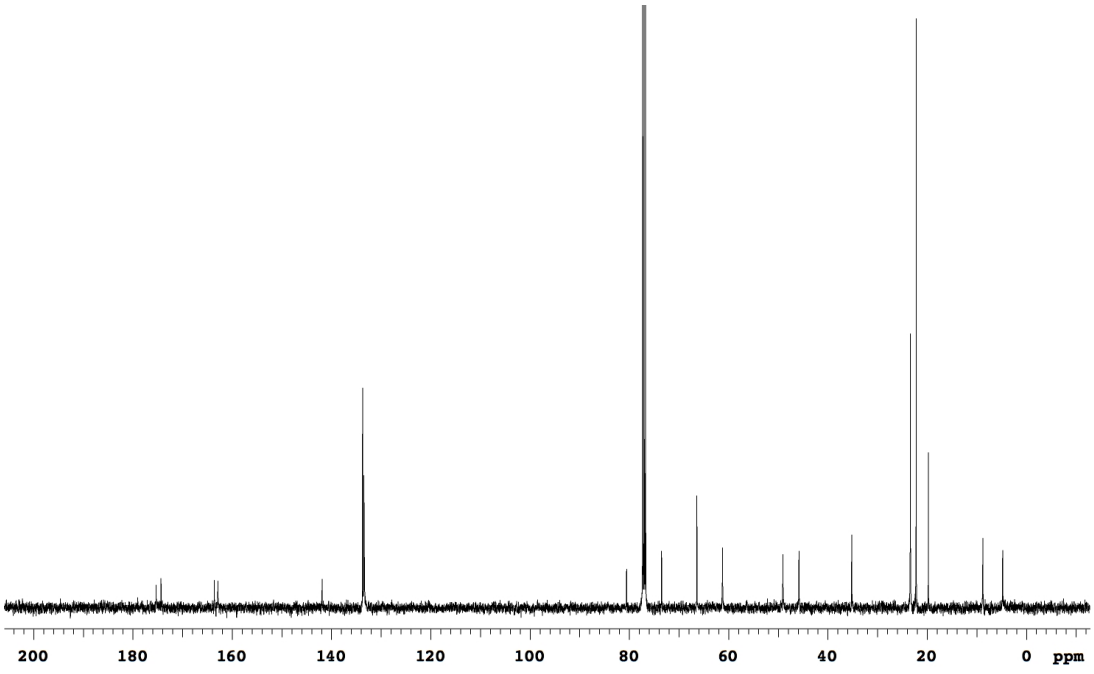
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 5.74 (d, 1H, J = 8.8 Hz), 5.23-5.06 (m, 4H), 4.96-4.88 (m, 1H), 3.83-3.75 (m, 1H), 3.68 (dd, 1H, J = 3.9, 9.1 Hz), 1.89 (br, 1H), 1.48-1.35 (m, 10H), 1.21-1.10 (m, 1H), 1.06 (s, 9H), 0.93-0.80 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 174.3, 163.6, 162.9, 141.9, 133.7, 133.4, 133.4, 80.5, 73.5, 66.4, 61.2, 49.1, 45.8, 35.2, 23.4, 22.2, 19.7, 8.8, 4.8

MS (ESI, m/z) calcd for $C_{26}H_{40}N_4NaO_6$ $(M+Na)^+$ 527.28, found 527

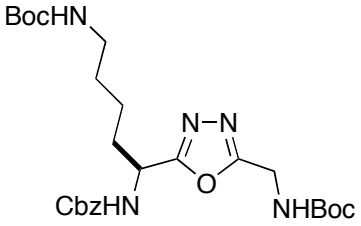


^{1}H NMR of **6e**



^{13}C NMR of **6e**

Preparation of Compound 6f



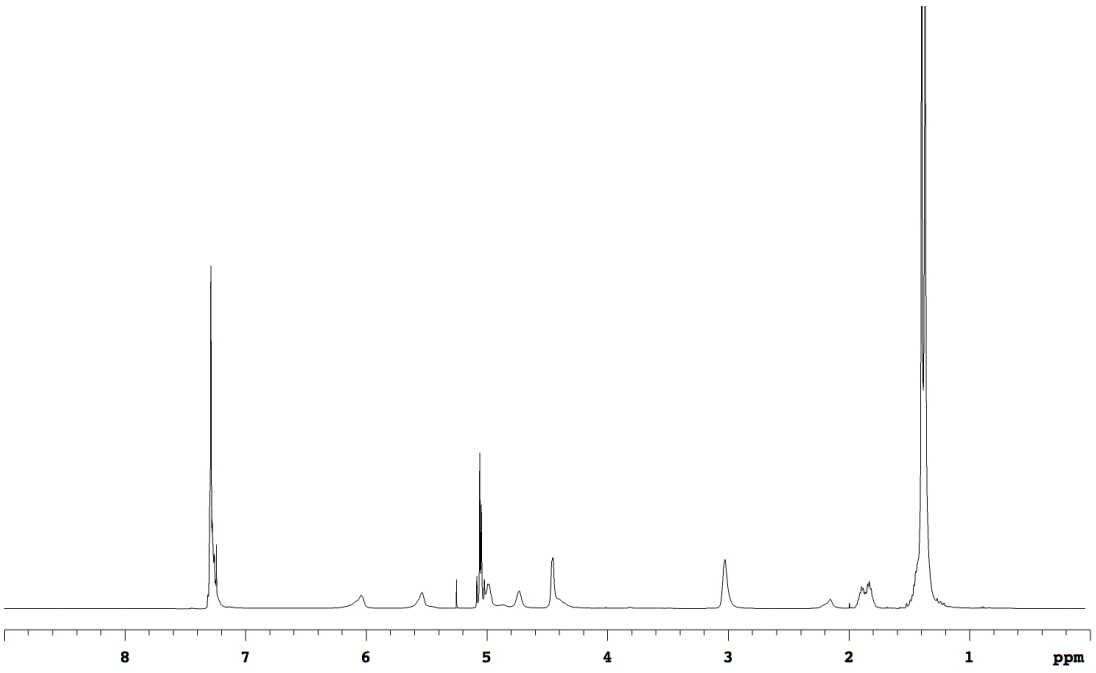
6f

Compound **6f** was prepared from **5a** (3.37 g, 17.8 mmol) and Cbz-Lys(Boc)-OH (6.78 g, 17.8 mmol). Flash chromatography (1:3 to 1:1 EtOAc/Hexanes) afforded 5.57 g (59%) **6f** as a white solid.

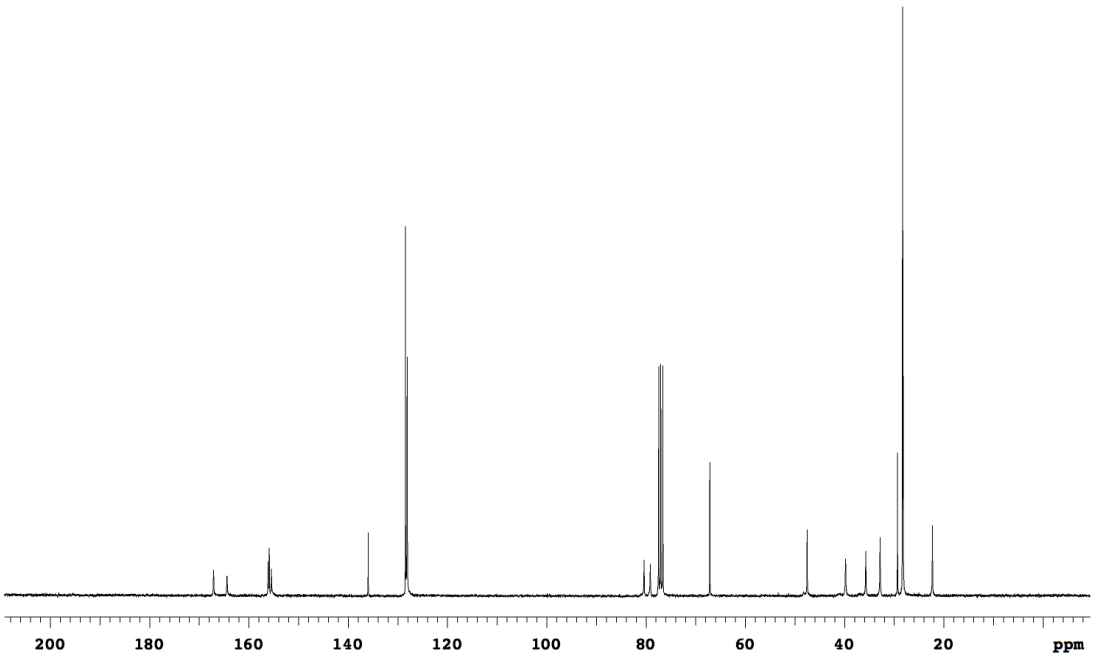
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H), 6.04 (br, 1H), 5.54 (br, 1H), 5.10-4.94 (m, 3H), 4.73 (br, 1H), 4.50-4.30 (br, 2H), 3.03 (br, 2H), 1.96-1.75 (m, 2H), 1.53-1.20 (m, 22H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 164.4, 156.1, 155.9, 155.4, 135.9, 128.4, 128.2, 128.1, 80.4, 79.1, 67.1, 47.5, 39.8, 35.7, 32.8, 29.3, 28.3, 28.2, 22.3

MS (ESI, m/z) calcd for $C_{26}H_{39}N_5NaO_7$ $(M+Na)^+$ 556.27, found 556

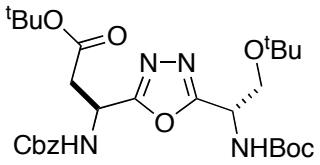


^{1}H NMR of **6f**



^{13}C NMR of **6f**

Preparation of Compound 6g



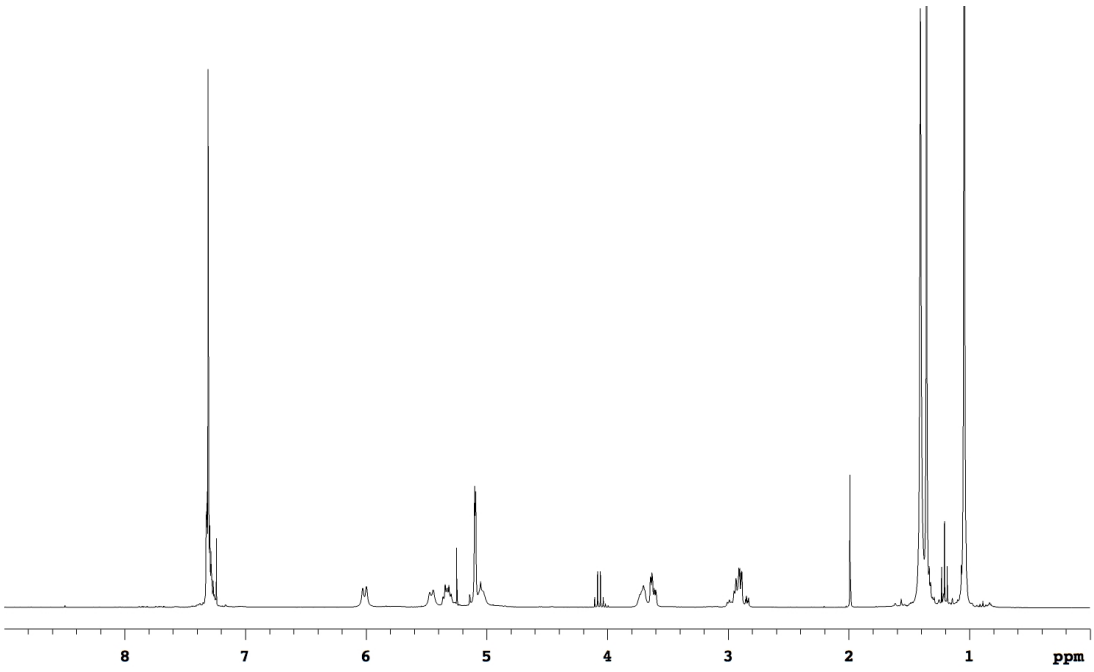
6g

Compound **6g** was prepared from **5e** (4.13 g, 15.0 mmol) and Cbz-Asp(O^{t}Bu)-OH•DCHA (7.57 g, 15.0 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 3.80 g (45 %) **6g** as a white solid.

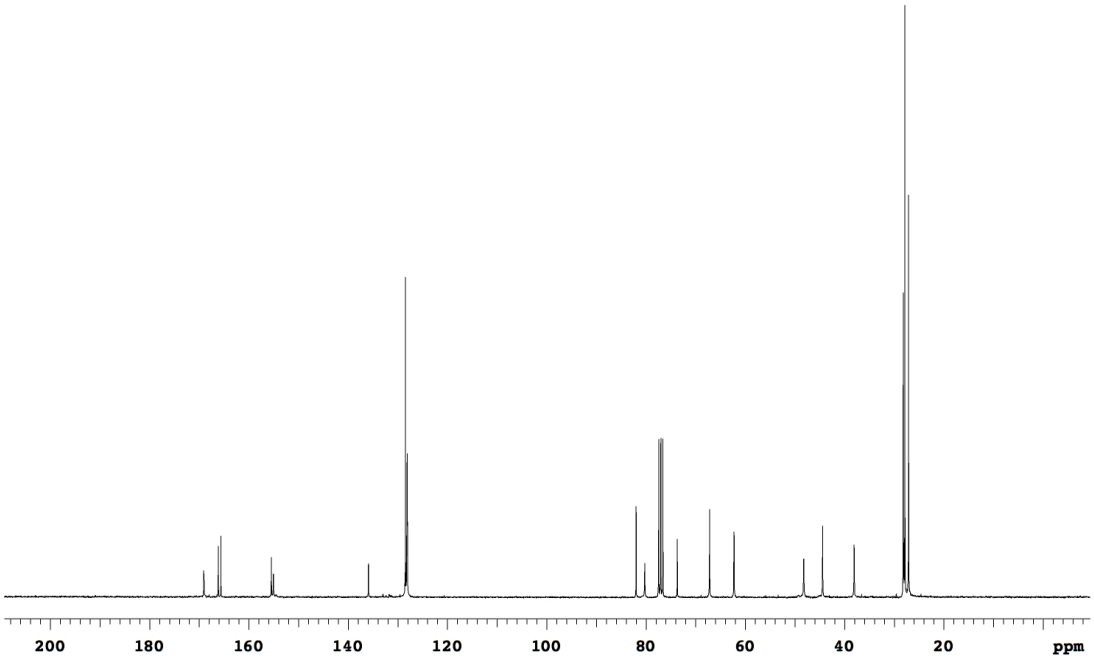
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 6.01 (d, 1H, J = 9.2 Hz), 5.46 (d, 1H J = 8.7 Hz), 5.38-5.28 (m, 1H), 5.16-4.98 (m, 3H), 3.78-3.67 (m, 1H), 3.62 (dd, 1H, J = 4.0, 9.2 Hz), 3.03-2.81 (m, 2H), 1.47-1.29 (m, 18H), 1.04 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 166.2, 165.6, 155.5, 155.0, 135.9, 128.2, 128.1, 128.0, 82.0, 80.2, 73.7, 67.2, 62.2, 48.2, 44.4, 38.0, 28.2, 27.8, 27.1

MS (ESI, m/z) calcd for $C_{28}H_{43}N_4O_8$ $(M+H)^+$ 563.3, found 563

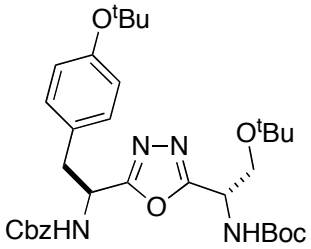


^{1}H NMR of **6g**



^{13}C NMR of **6g**

Preparation of Compound 6h



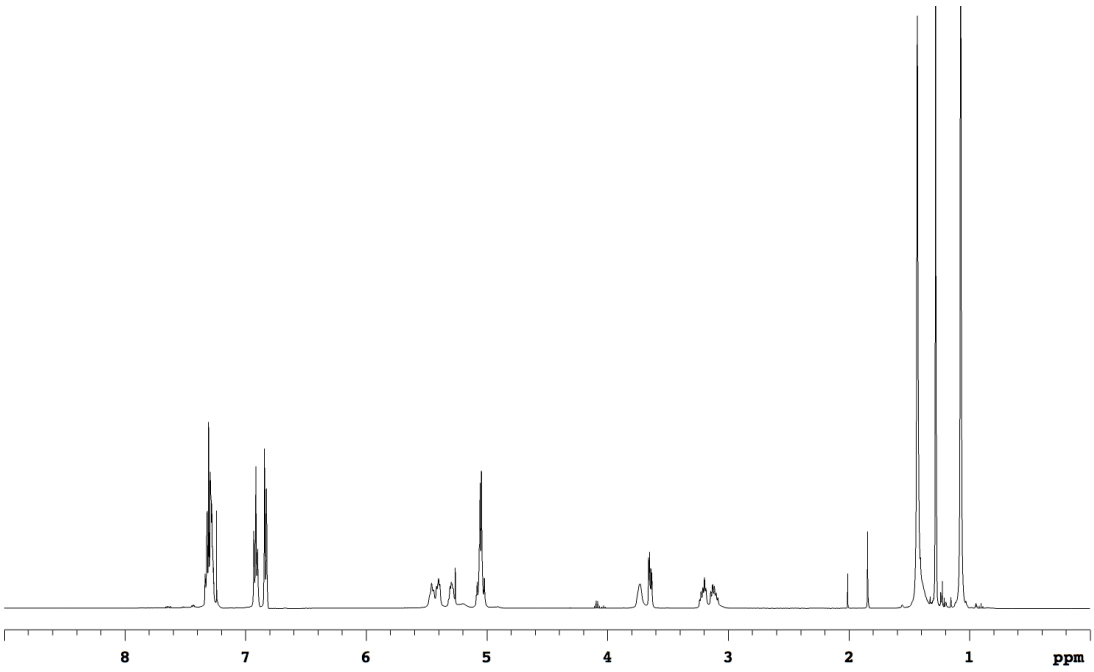
6h

Compound **6h** was prepared from **5e** (2.34 g, 8.5 mmol) and Cbz-Tyr(^{t}Bu)-OH•DCHA (4.70 g, 8.5 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 4.20 g (81%) **6h** as a white solid.

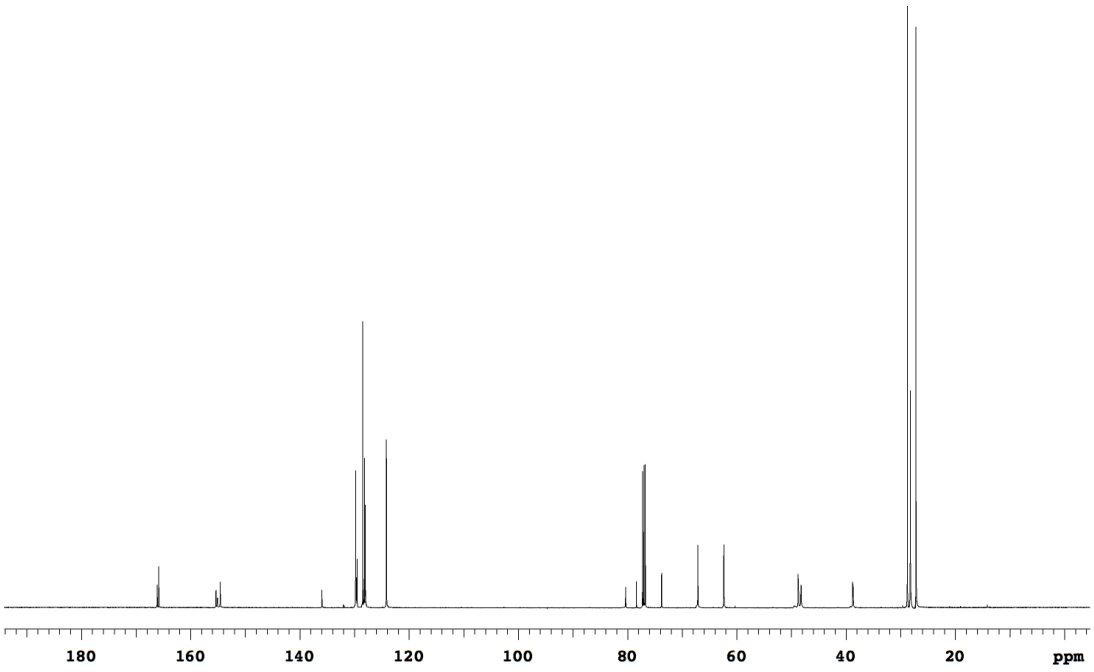
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 6.95-6.88 (m, 2H), 6.86-6.81 (m, 2H), 5.50-5.37 (m, 2H), 5.33-5.25 (m, 1H), 5.10-5.00 (m, 3H), 3.73 (br, 1H), 3.64 (dd, 1H, J = 4.0, 9.2 Hz), 3.26-3.02 (m, 2H), 1.43 (s, 9H), 1.28 (s, 9H), 1.07 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.8, 155.4, 155.1, 154.6, 136.0, 129.8, 129.5, 128.5, 128.2, 128.0, 124.1, 80.4, 78.4, 73.8, 67.1, 62.3, 48.8, 48.2, 38.8, 28.8, 28.2, 27.2

MS (ESI, m/z) calcd for $C_{33}H_{46}N_4NaO_7$ $(M+Na)^+$ 633.33, found 633

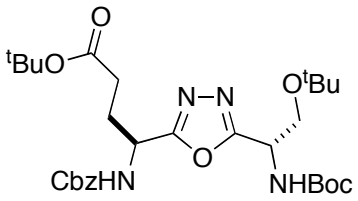


^{1}H NMR of **6h**



^{13}C NMR of **6h**

Preparation of Compound 6i



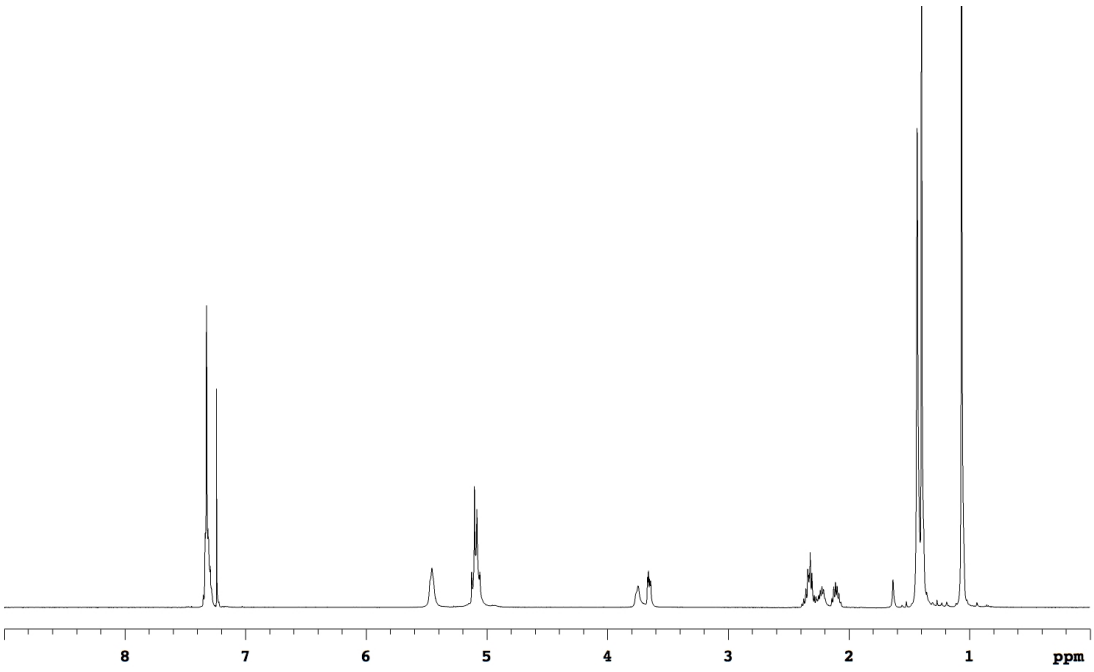
6i

Compound **6i** was prepared from **5e** (3.99 g, 14.5 mmol) and Cbz-Glu(O^{t}Bu)-OH (4.89 g, 14.5 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 7.02 g (48 %) **6i** as a white solid.

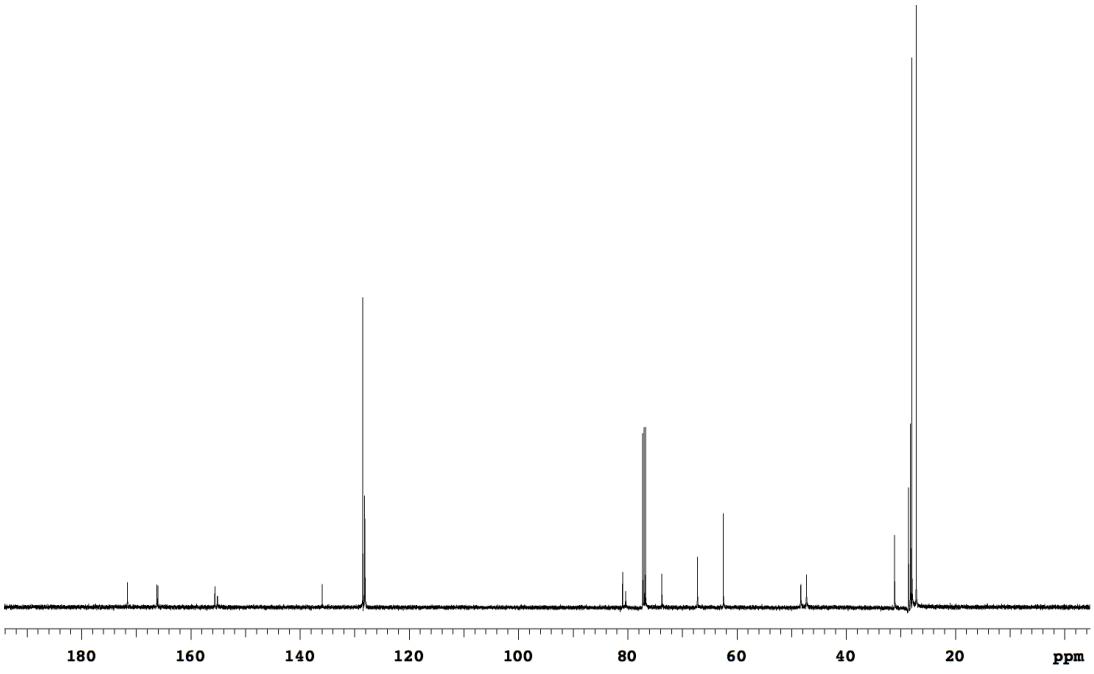
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.45 (br, 2H), 5.15-5.02 (m, 4H), 3.80-3.70 (br, 1H), 3.65 (dd, 1H, J = 3.8, 9.1 Hz), 2.41-2.17 (m, 3H), 2.16-2.05 (m, 1H), 1.49-1.32 (m, 18H), 1.07 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 166.2, 166.0, 155.6, 155.1, 135.9, 128.5, 128.2, 128.1, 80.9, 80.4, 73.7, 67.2, 62.5, 48.3, 47.3, 31.1, 28.6, 28.2, 28.0, 27.2

MS (ESI, m/z) calcd for $C_{29}H_{44}N_4NaO_8$ $(M+Na)^+$ 599.3, found 599

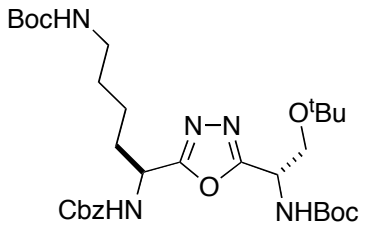


^{1}H NMR of **6i**



^{13}C NMR of **6i**

Preparation of Compound 6j



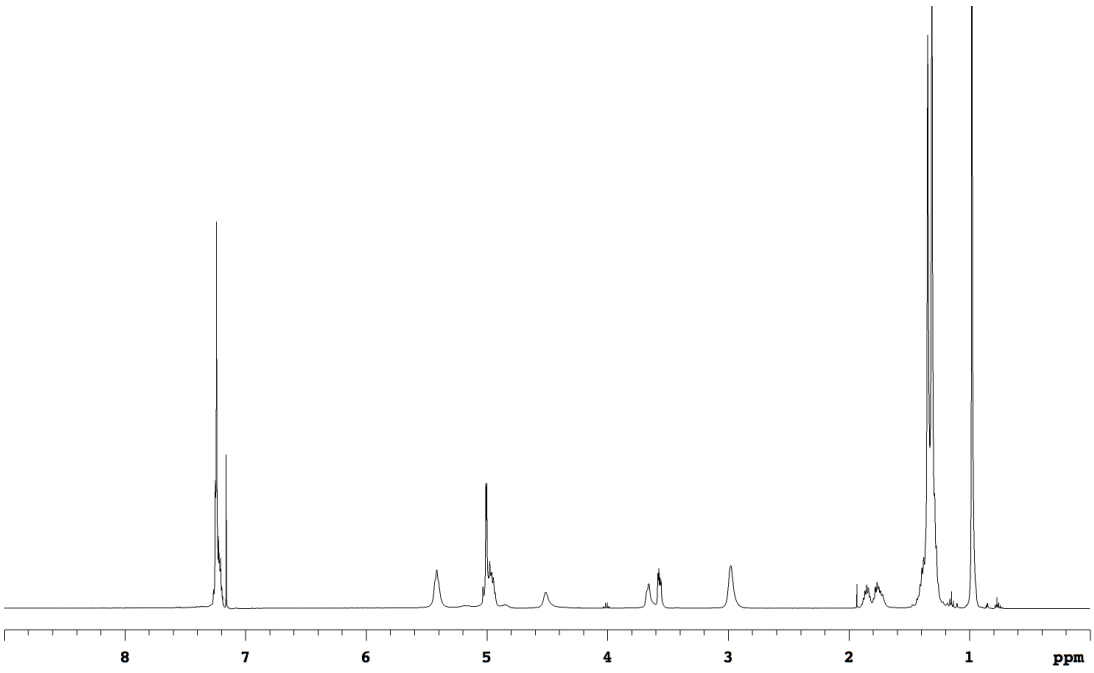
6j

Compound **6j** was prepared from **5e** (3.71 g, 13.5 mmol) and Cbz-Lys(Boc)-OH (4.55 g, 13.5 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 5.0 g (60%) **6j** as a white solid.

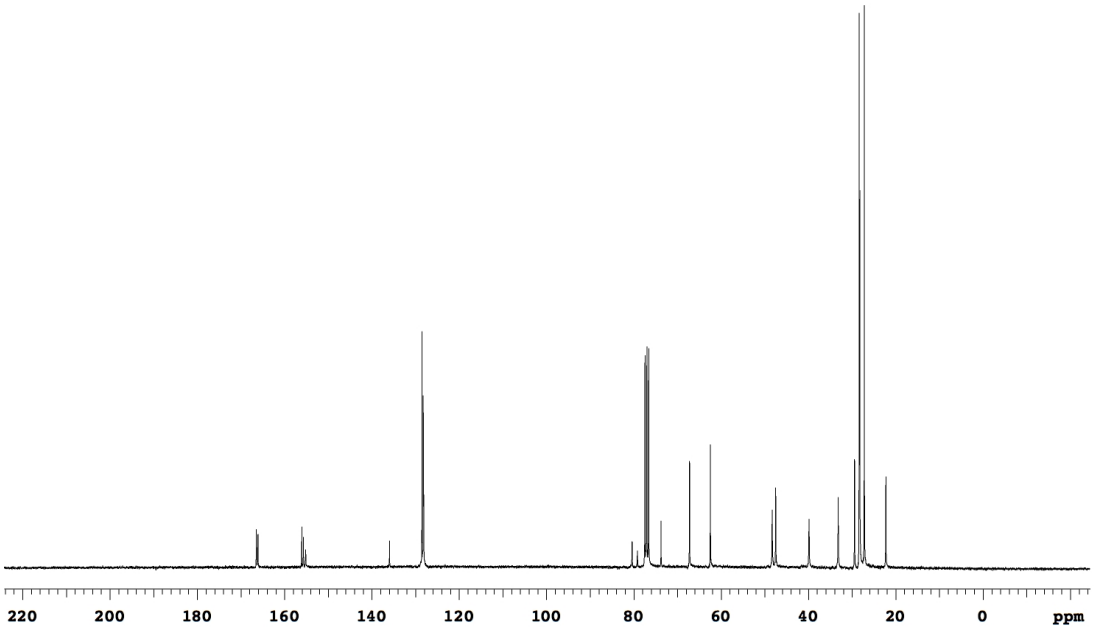
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.50 (br, 2H), 5.15-4.97 (m, 4H), 4.59 (br, 1H), 3.74 (br, 1H), 3.65 (dd, 1H, J = 3.9, 9.1 Hz), 3.06 (br, 2H), 1.99-1.75 (m, 2H), 1.54-1.28 (m, 22H), 1,06 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 166.1, 156.0, 155.7, 155.2, 135.9, 128.5, 128.2, 128.1, 80.4, 79.2, 73.8, 67.2, 62.5, 48.3, 47.5, 39.9, 33.2, 29.4, 28.4, 28.2, 27.2, 22.2

MS (ESI, m/z) calcd for $C_{31}H_{49}N_5NaO_8$ $(M+Na)^+$ 642.3, found 642

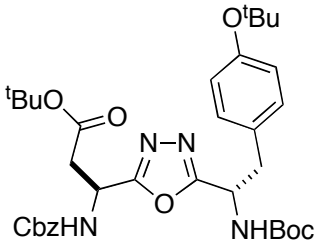


^{1}H NMR of **6j**



^{13}C NMR of **6j**

Preparation of Compound 6k



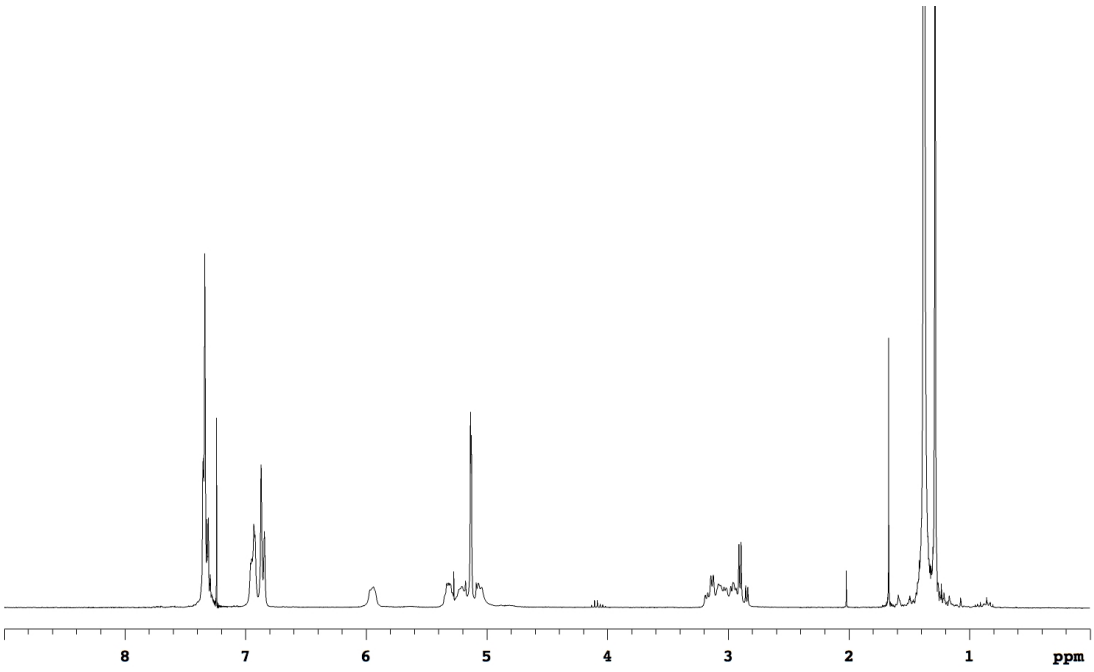
6k

Compound **6k** was prepared from **5d** (4.43 g, 12.6 mmol) and Cbz-Asp(O^{t}Bu)-OH•DCHA (6.36 g, 12.6 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 3.40 g (42%) **6k** as a white solid.

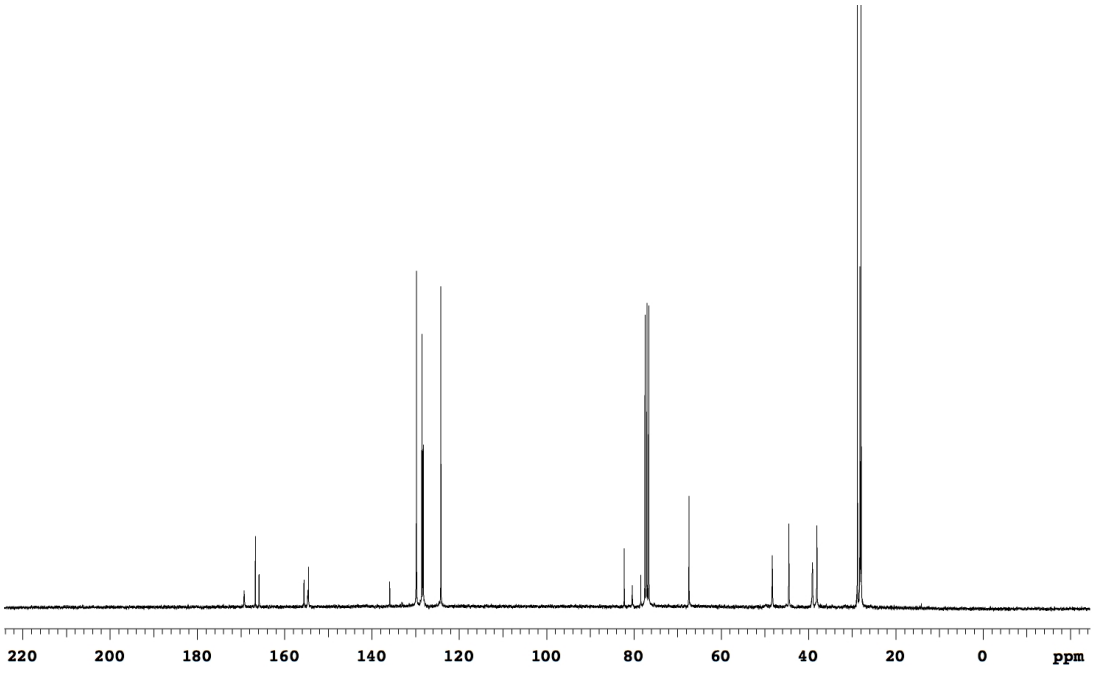
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 6.94 (d, 2H, J = 8.2 Hz), 6.86 (d, 2H, J = 8.2 Hz), 5.94 (br, 1H), 5.38-4.98 (m, 5H), 3.22-2.82 (m, 4H), 1.46-1.20 (m, 18H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.7, 165.8, 155.6, 154.7, 154.5, 135.9, 129.9, 129.8, 128.6, 128.3, 128.2, 124.2, 82.2, 80.4, 78.4, 67.4, 48.3, 44.5, 39.1, 38.1, 28.8, 28.2, 27.9

MS (ESI, m/z) calcd for $C_{34}H_{47}N_4O_8$ $(M+H)^+$ 639.3, found 639

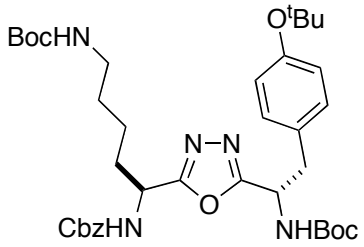


^{1}H NMR of **6k**



^{13}C NMR of **6k**

Preparation of Compound 6l



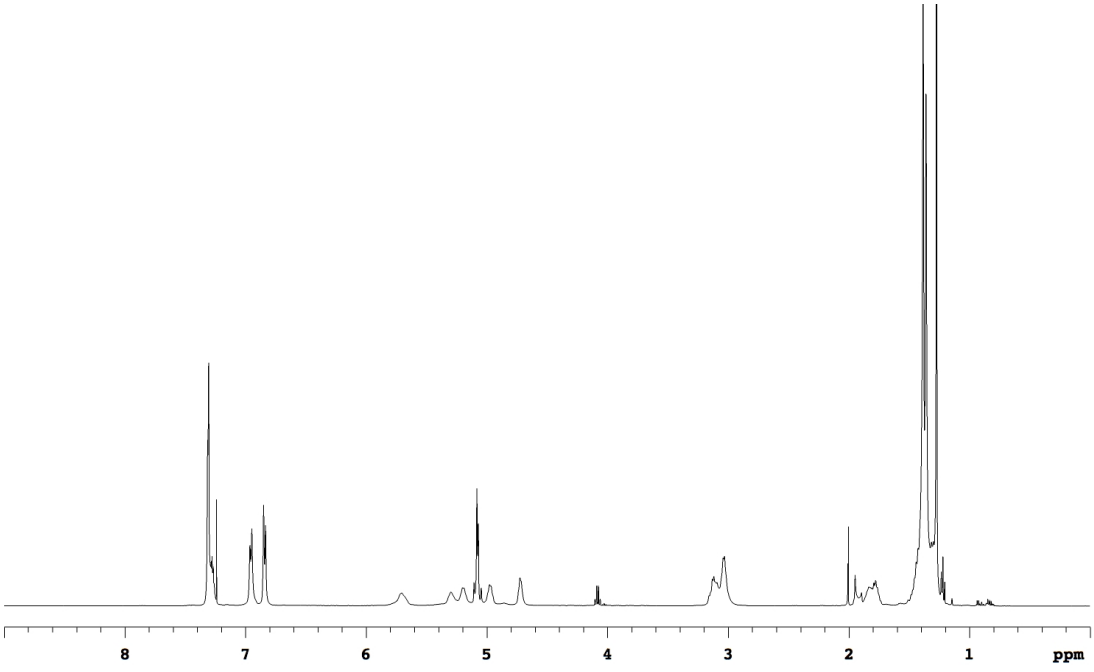
6l

Compound **6l** was prepared from **5d** (4.78 g, 13.6 mmol) and Cbz-Lys(Boc)-OH (5.17 g, 13.6 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 6.20 g (66 %) **6l** as a white solid.

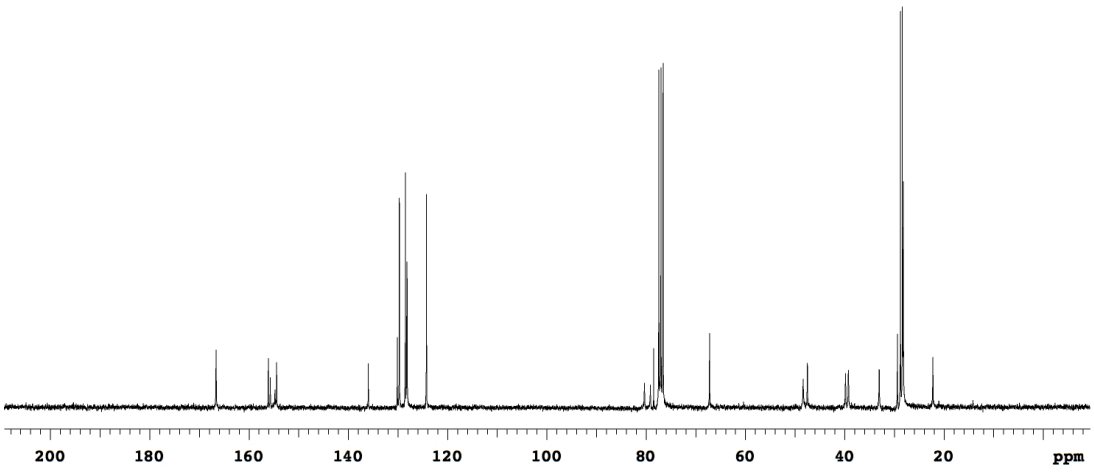
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 6.96 (d, 2H, J = 7.9 Hz), 6.84 (d, 2H, J = 7.9 Hz), 5.71 (br, 1H), 5.36-4.93 (m, 5H), 4.73 (br, 1H), 3.20-2.94 (m, 4H), 1.98-1.72 (m, 2H), 1.53-1.20 (m, 31H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 156.1, 155.7, 154.8, 154.4, 135.9, 130.1, 129.7, 128.5, 128.2, 128.1, 124.2, 80.3, 79.1, 78.5, 67.2, 48.4, 47.5, 39.8, 39.2, 33.0, 29.4, 28.7, 28.4, 28.2, 22.2

MS (ESI, m/z) calcd for $C_{37}H_{53}N_5NaO_8$ $(M+Na)^+$ 718.4, found 718

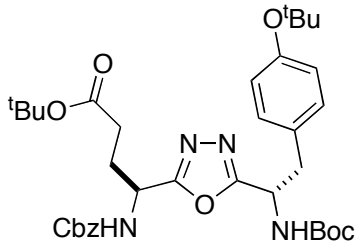


^{1}H NMR of **6l**



^{13}C NMR of **6l**

Preparation of Compound 6m



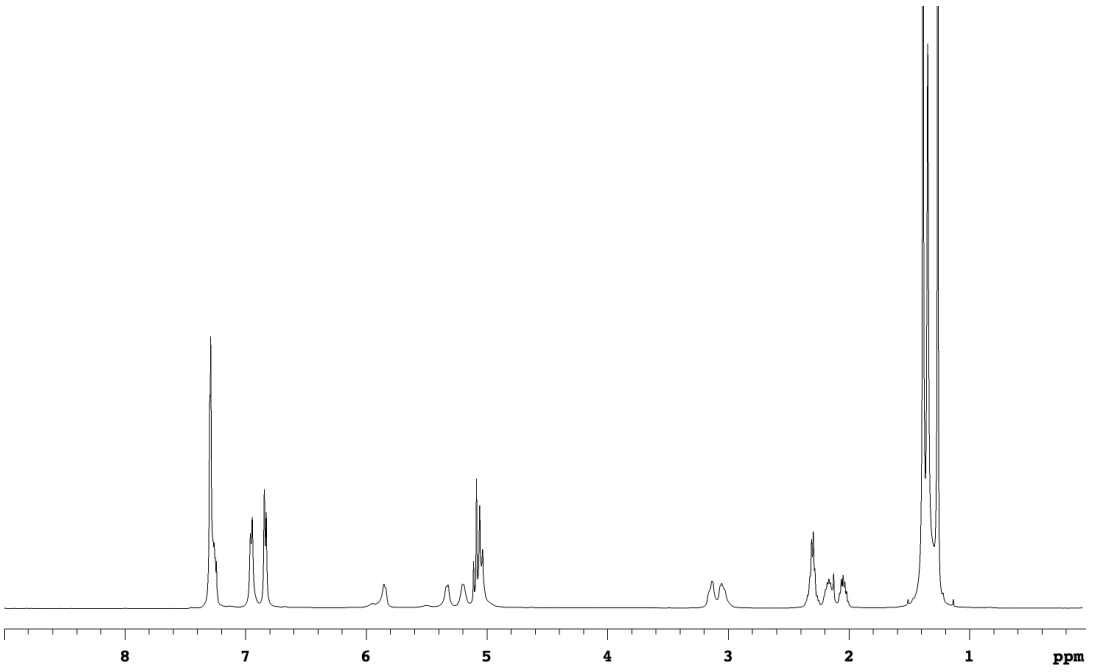
10m

Compound **6m** was prepared from **5d** (5.00 g, 14.2 mmol) and Cbz-Glu(O^{t}Bu)-OH (4.80 g, 14.2 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 4.79 g (52 %) **6m** as a white solid.

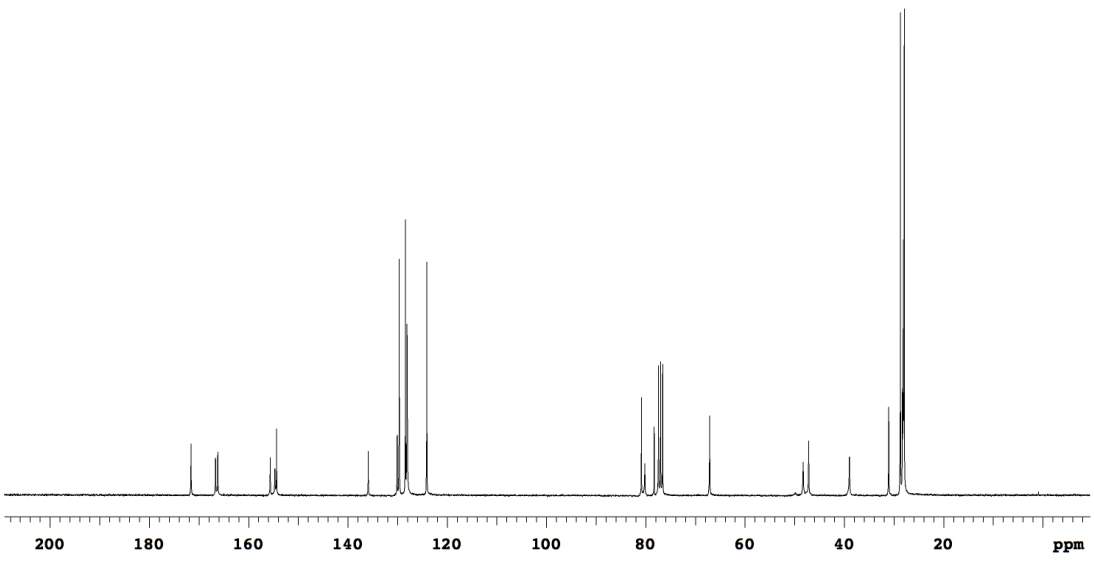
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 6.95 (d, 2H, J = 7.8 Hz), 6.84 (d, 2H, J = 7.8 Hz), 5.85 (br, 1H), 5.32 (br, 1H), 5.20 (br, 1H), 5.14-4.93 (m, 3H), 3.22-2.93 (m, 2H), 2.38-2.24 (m, 2H), 2.23-1.98 (m, 2H), 1.48-1.20 (m, 27H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 166.6, 166.2, 155.6, 154.7, 154.3, 135.9, 130.1, 129.6, 128.4, 128.1, 128.0, 124.1, 80.9, 80.2, 78.3, 67.1, 48.3, 47.2, 39.0, 31.0, 28.7, 28.3, 28.1, 27.9

MS (ESI, m/z) calcd for $C_{35}H_{48}N_4NaO_8$ $(M+Na)^+$ 675.3, found 675

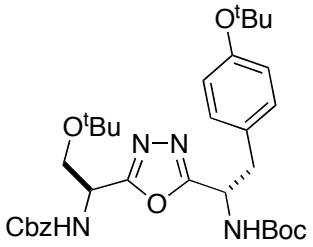


^{1}H NMR of **6m**



^{13}C NMR of **6m**

Preparation of Compound 6n



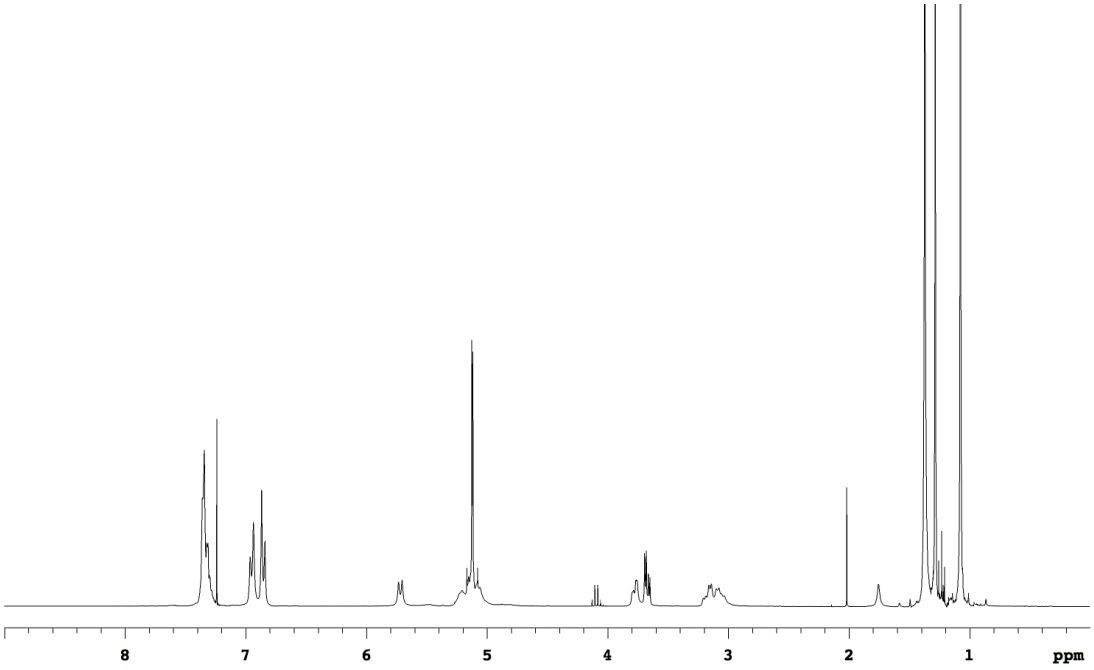
6n

Compound **6n** was prepared from **5d** (5.00 g, 14.2 mmol) and Cbz-Ser(^{t}Bu)-OH (4.20 g, 14.2 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 3.75 g (43 %) **6n** as a white solid.

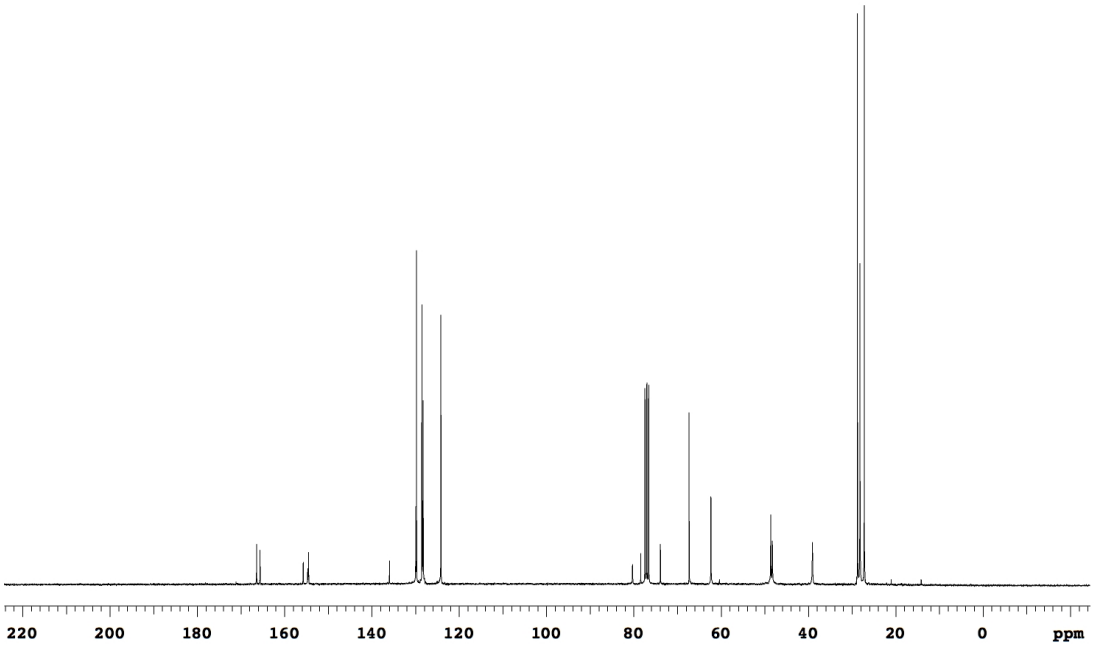
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 6.95 (d, 2H, J = 8.3 Hz), 6.85 (d, 2H, J = 8.3 Hz), 5.72 (d, 1H, J = 8.7 Hz), 5.28-4.98 (m, 5H), 3.78 (dd, 1H, J = 3.0, 9.2 Hz), 3.67 (dd, 1H, J = 3.9, 9.2 Hz), 3.23-2.98 (m, 2H), 1.48-1.19 (m, 18H), 1.08 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 165.6, 155.7, 154.7, 154.5, 136.0, 130.0, 129.8, 128.5, 128.3, 128.2, 124.2, 80.4, 78.4, 73.9, 67.3, 62.3, 48.6, 48.3, 39.1, 28.8, 28.2, 27.2

MS (ESI, m/z) calcd for $C_{33}H_{46}N_4NaO_7$ $(M+Na)^+$ 633.3, found 633

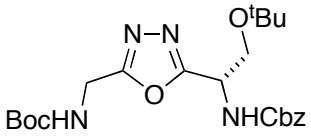


^{1}H NMR of **6n**



^{13}C NMR of **6n**

Preparation of Compound 6o



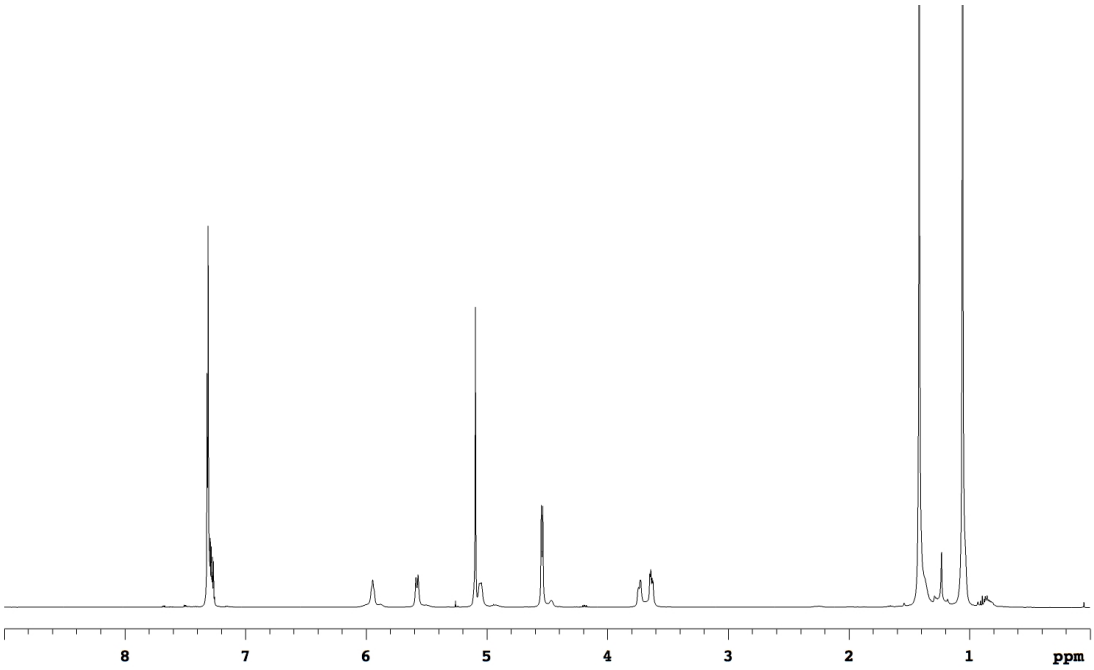
6o

Compound **6o** was prepared from **5a** (0.38 g, 2.0 mmol) and Cbz-Ser(^{t}Bu)-OH (0.59 g, 2.0 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 0.36 g (40 %) **6o** as a white solid.

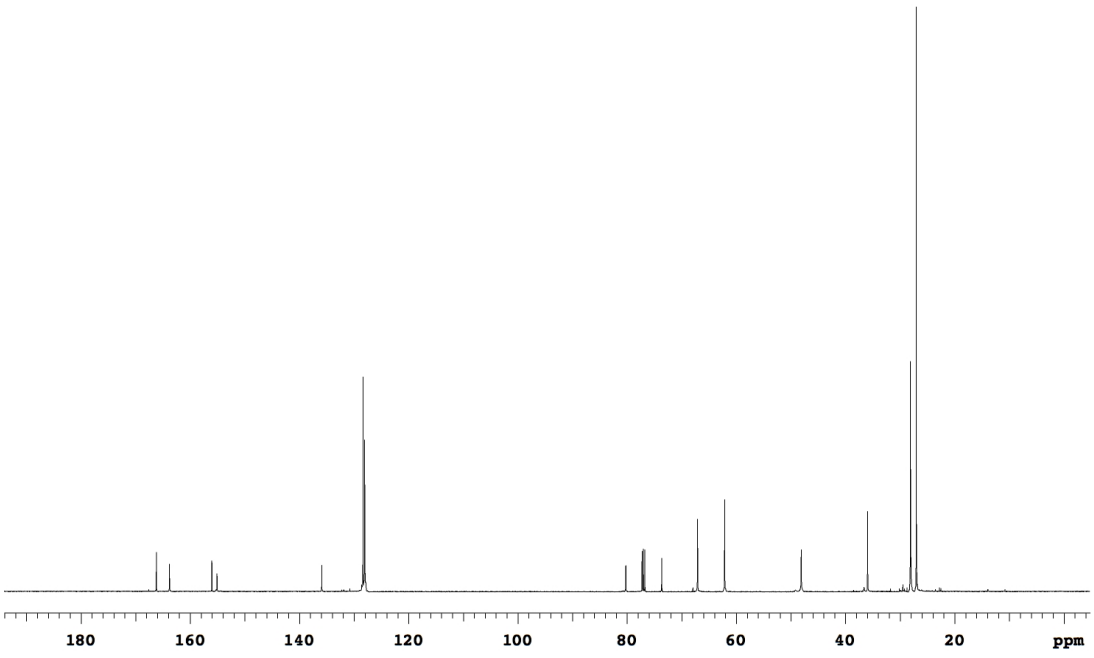
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 5.95 (br, 1H), 5.58 (d, 1H, J = 8.8 Hz), 5.14-5.01 (m, 3H), 4.54 (d, 2H, J = 6.0 Hz), 3.77-3.70 (m, 1H), 3.64 (dd, 1H, J = 4.0, 9.1 Hz), 1.42 (s, 9H), 1.06 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 163.8, 156.0, 155.1, 135.9, 128.4, 128.1, 128.0, 80.2, 73.7, 67.1, 62.1, 48.1, 36.0, 28.1, 27.0

MS (ESI, m/z) calcd for $C_{22}H_{32}N_4NaO_6$ $(M+Na)^+$ 471.2, found 471

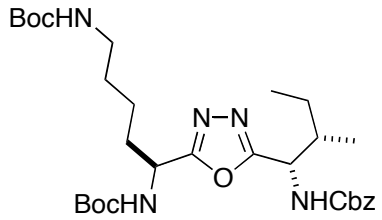


^{1}H NMR of **6o**



^{13}C NMR of **6o**

Preparation of Compound 6p



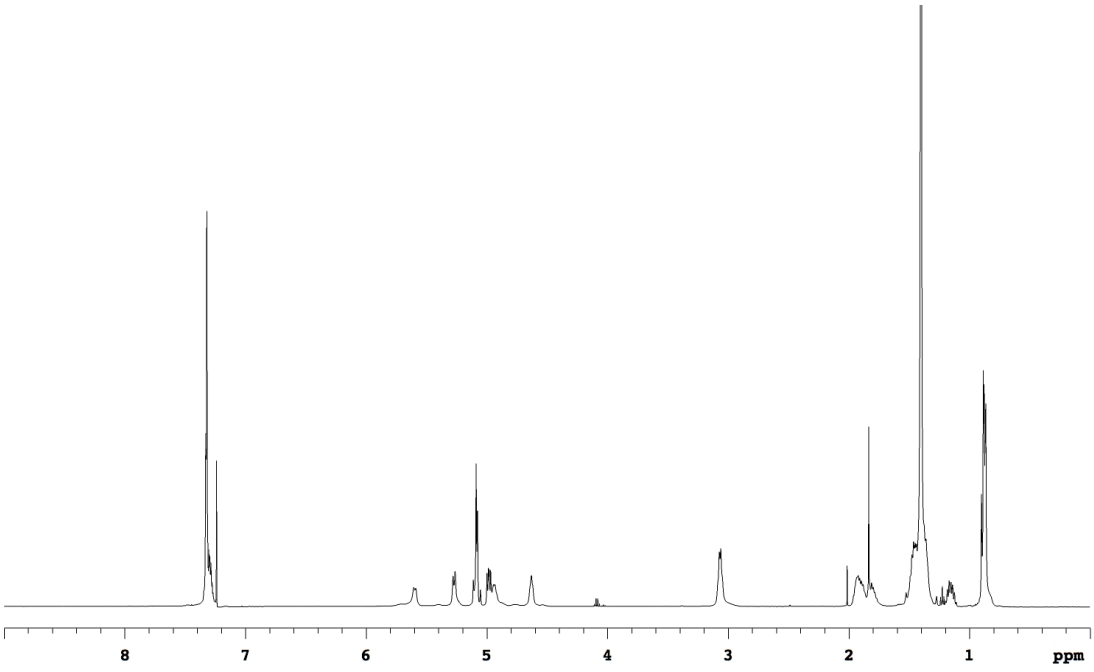
6p

Compound **6p** was prepared from **5c** (2.26 g, 6.3 mmol) and Cbz-Ile-OH•DCHA (2.80 g, 6.3 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 2.26 g (61 %) **6p** as a white solid.

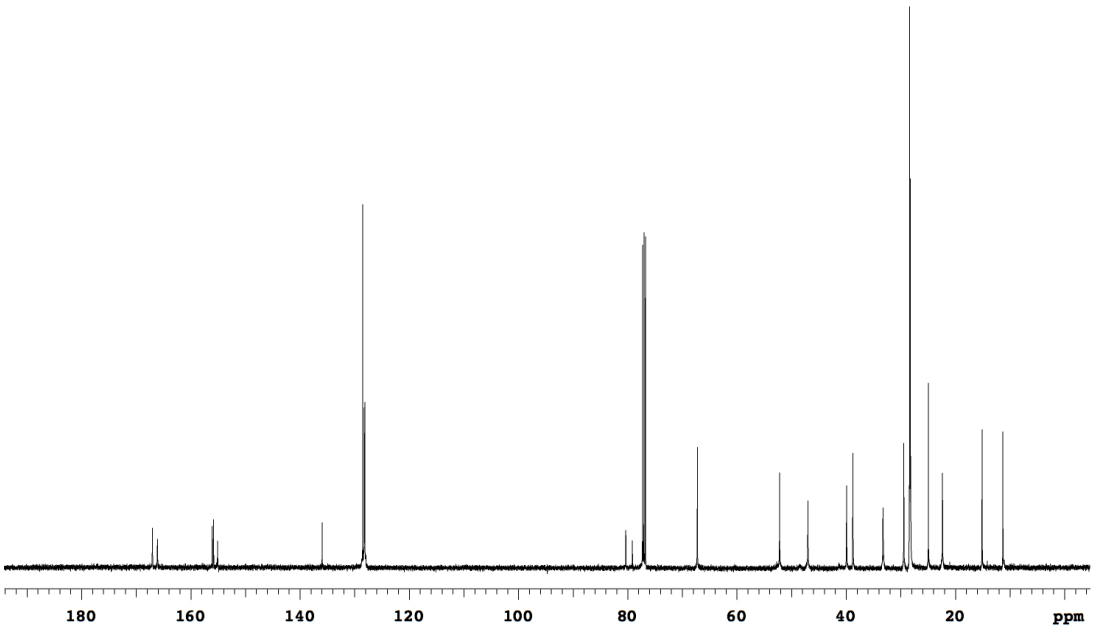
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.60 (d, 1H, J = 8.5 Hz), 5.27 (d, 1H, J = 8.6 Hz), 5.14-5.03 (m, 2H), 5.02-4.84 (m, 2H), 4.63 (br, 1H), 3.13-3.00 (m, 2H), 2.00-1.73 (m, 3H), 1.55-1.30 (m, 23H), 1.21-1.10 (m, 1H), 0.94-0.80 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.1, 156.1, 155.8, 155.1, 135.9, 128.5, 128.2, 128.1, 80.3, 79.1, 67.2, 52.2, 47.0, 39.9, 38.8, 33.2, 29.4, 28.4, 28.2, 24.9, 22.3, 15.1, 11.3

MS (ESI, m/z) calcd for $C_{30}H_{48}N_5O_7$ $(M+H)^+$ 590.35, found 590

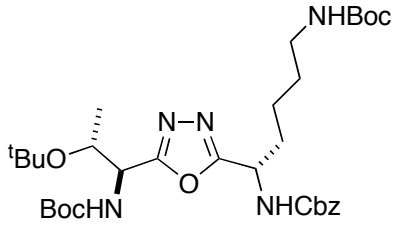


^{1}H NMR of **6p**



^{13}C NMR of **6p**

Preparation of Compound 6q



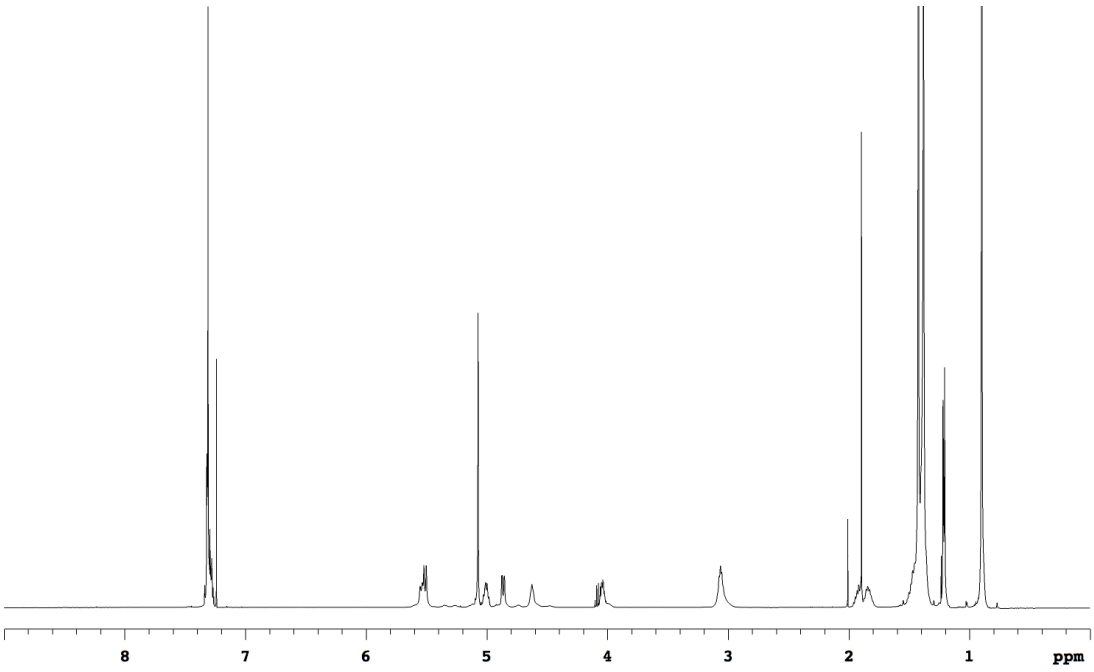
6q

Compound **6q** was prepared from **5f** (2.59 g, 8.9 mmol) and Cbz-Lys(Boc)-OH (3.48 g, 8.9 mmol). Flash chromatography (1:4 to 3:7 EtOAc/Hexanes) afforded 3.42 g (60%) **6q** as a white solid.

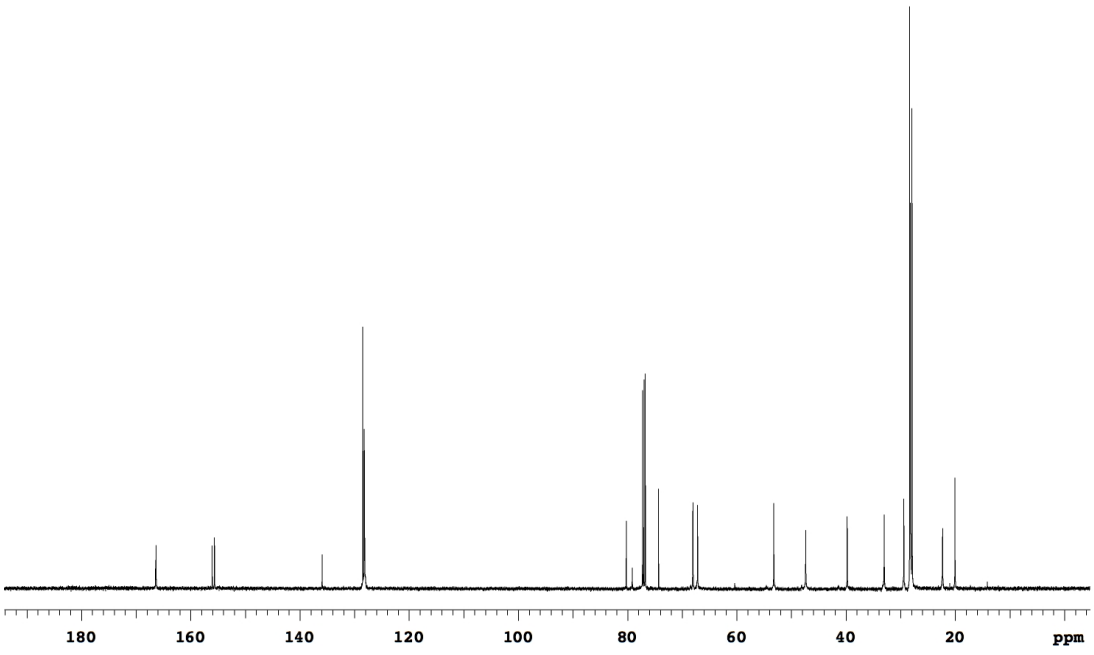
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 5.60-5.46 (m, 2H), 5.07 (s, 2H), 5.05-4.97 (m, 1H), 4.87 (dd, 1H, J = 1.5, 9.6 Hz), 4.63 (br, 1H), 4.10-3.95 (m, 1H), 3.14-2.95 (m, 2H), 1.98-1.77 (m, 2H), 1.53-1.30 (m, 22H), 1.21 (d, 3H, J = 6.1 Hz), 0.90 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 166.3, 156.1, 155.7, 155.1, 135.9, 128.5, 128.2, 128.1, 80.2, 79.1, 74.3, 68.0, 67.2, 53.2, 47.4, 39.8, 33.0, 29.4, 28.3, 28.2, 27.9, 22.3, 20.0

MS (ESI, m/z) calcd for $C_{32}H_{52}N_5O_8$ $(M+H)^+$ 634.38, found 634

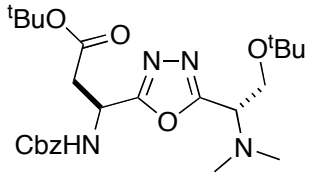


^{1}H NMR of **6q**



^{13}C NMR of **6q**

Preparation of Compound 6r



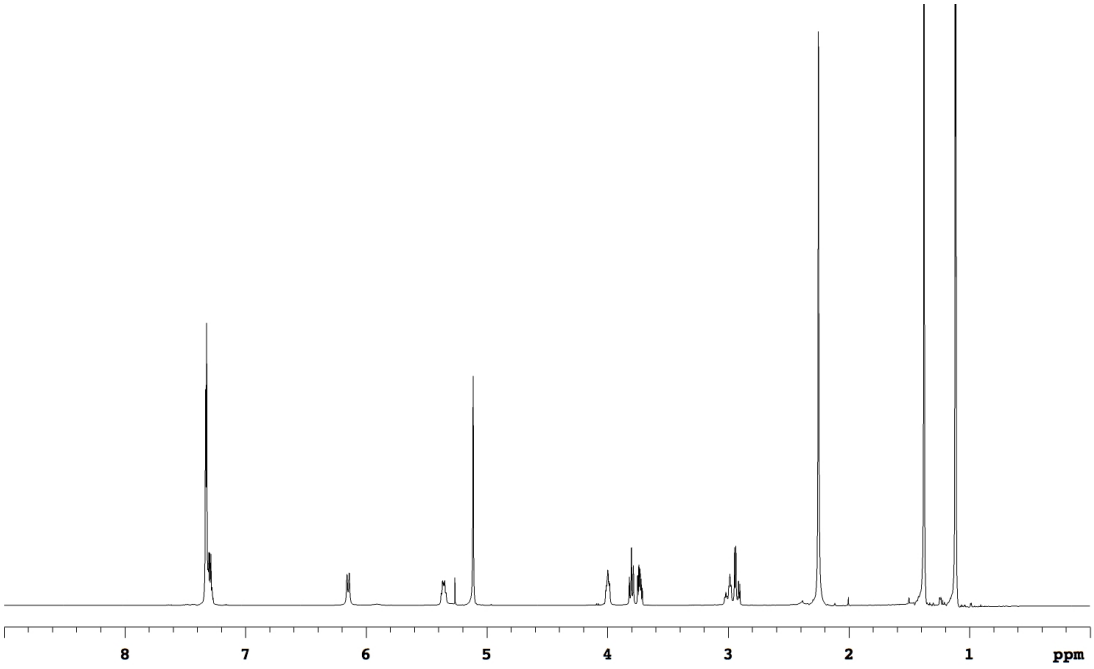
6r

Compound **6r** was prepared from **5g** (1.42 g, 7.0 mmol) and Cbz-Asp(O^{t}Bu)-OH•DCHA (3.53 g, 7.0 mmol). Flash chromatography (1:4 to 1:1 EtOAc/Hexanes) afforded 1.51 g (44 %) **6r** as a white solid.

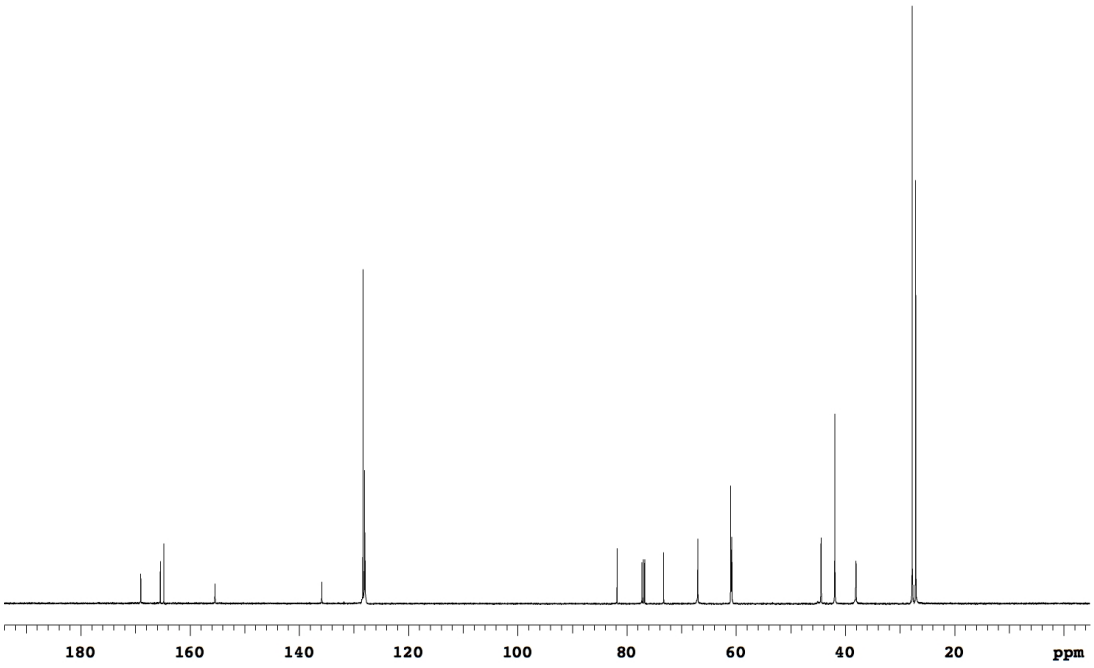
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 6.15 (d, 1H, J = 9.2 Hz), 5.36 (dt, 1H, J = 5.2, 9.2 Hz), 5.11 (s, 2H), 4.03-3.96 (m, 1H), 3.84-3.70 (m, 2H), 3.00 (dt, 1H, J = 4.7, 16.6 Hz), 2.92 (dd, 1H, J = 5.4, 16.6 Hz), 2.25 (s, 6H), 1.38 (s, 9H), 1.11 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 165.4, 164.8, 155.4, 135.9, 128.3, 128.1, 127.9, 81.8, 73.3, 67.0, 61.0, 60.8, 44.4, 41.9, 38.1, 27.8, 27.1

MS (ESI, m/z) calcd for $C_{25}H_{39}N_4O_6$ $(M+H)^+$ 491.29, found 491

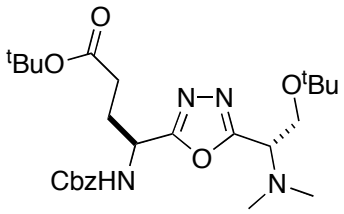


^{1}H NMR of **6r**



^{13}C NMR of **6r**

Preparation of Compound 6s



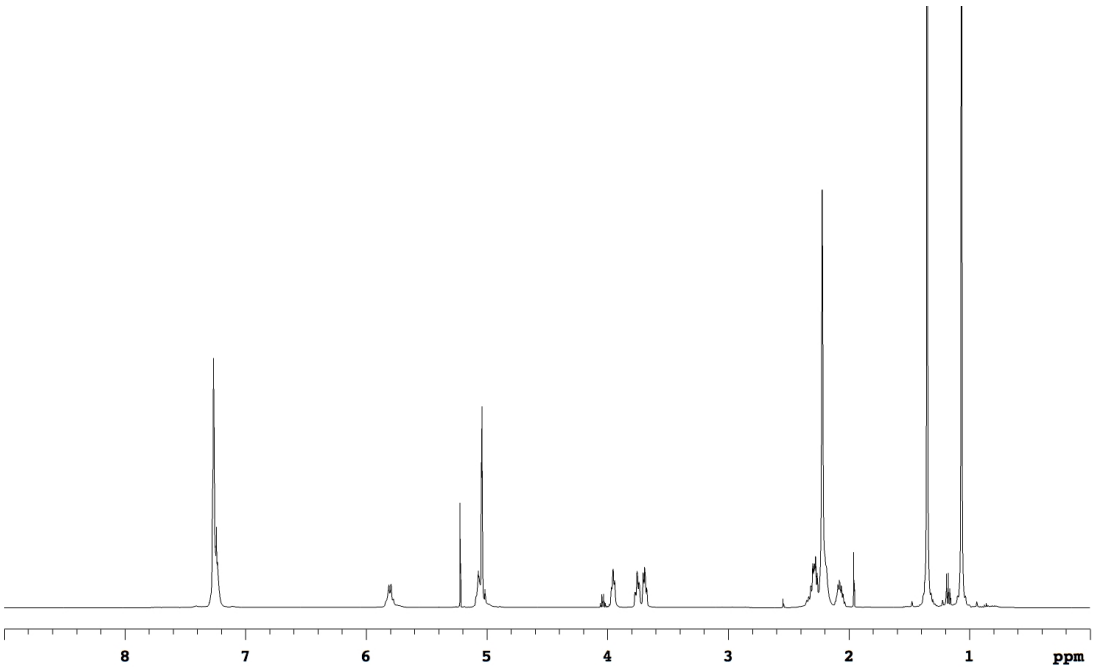
6s

Compound **6s** was prepared from **5g** (1.02 g, 5.0 mmol) and Cbz-Glu(O^{t}Bu)-OH (1.69 g, 7.0 mmol). Flash chromatography (1:4 to 1:1 EtOAc/Hexanes) afforded 1.02 g (40 %) **6s** as a white solid.

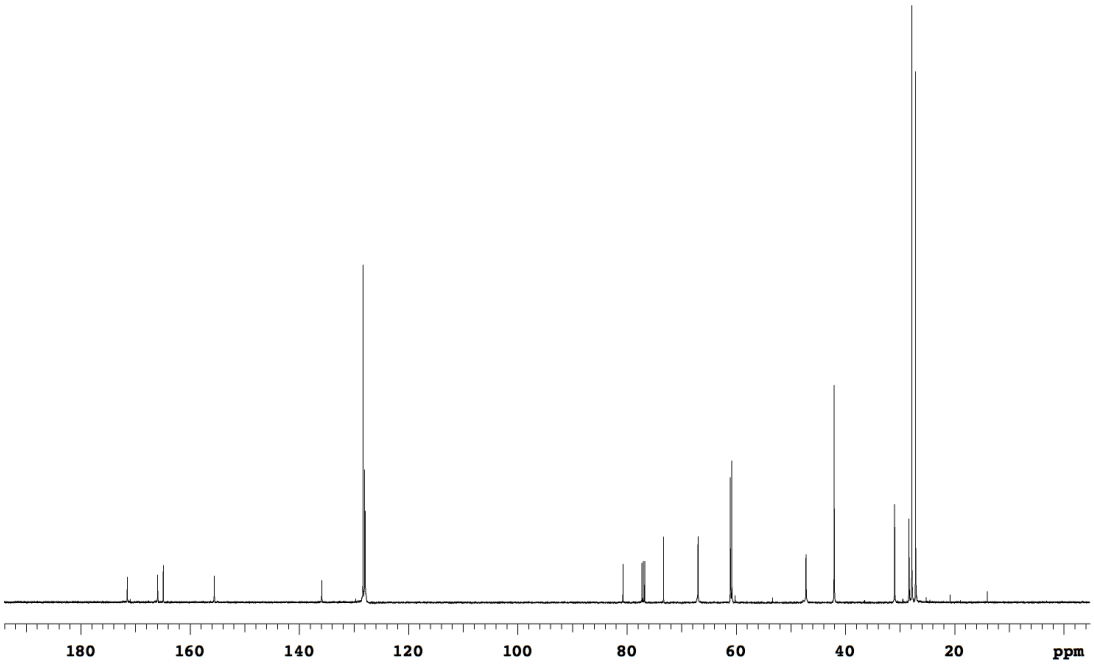
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.17 (m, 5H), 5.86-5.75 (m, 1H), 5.12-4.97 (m, 3H), 3.99-3.91 (m, 1H), 3.79-3.65 (m, 2H), 2.36-2.14 (m, 9H), 2.12-2.02 (m, 1H), 1.35 (s, 9H), 1.07 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 165.9, 164.9, 155.6, 135.9, 128.3, 128.0, 127.9, 80.7, 73.3, 67.0, 61.1, 60.8, 47.2, 42.1, 31.0, 28.4, 27.8, 27.2

MS (ESI, m/z) calcd for $C_{26}H_{41}N_4O_6$ $(M+H)^+$ 505.30, found 505

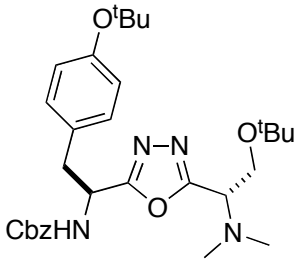


^{1}H NMR of **6s**



^{13}C NMR of **6s**

Preparation of Compound 6t



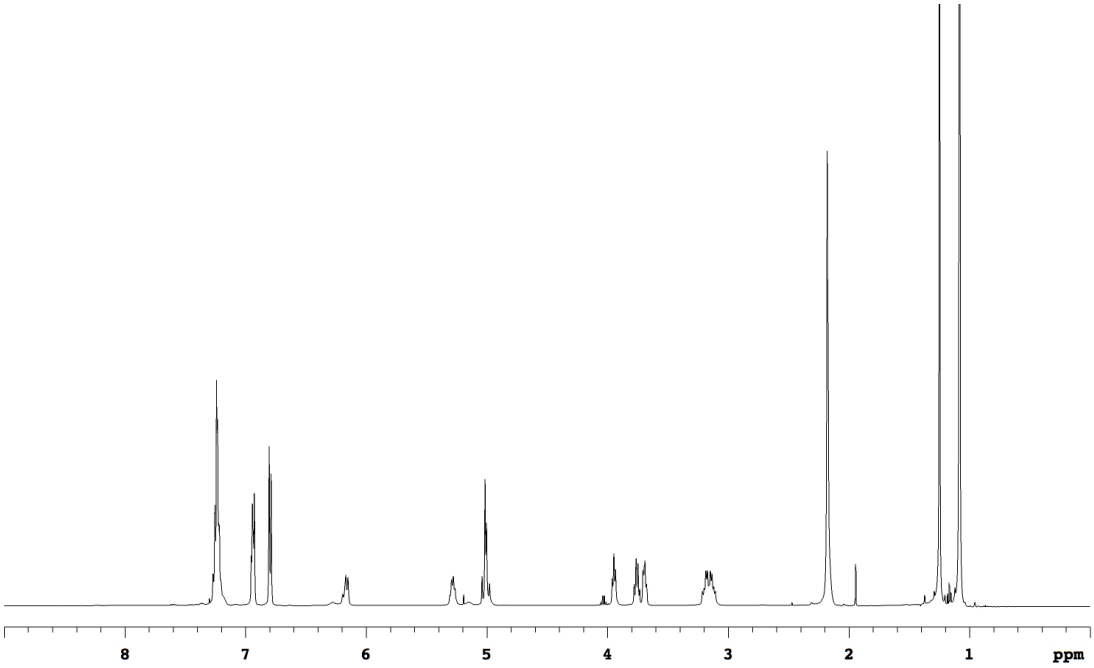
6t

Compound **6t** was prepared from **5g** (2.66 g, 7.0 mmol) and Cbz-Tyr(^{t}Bu)-OH (2.60 g, 7.0 mmol). Flash chromatography (1:4 to 1:1 EtOAc/Hexanes) afforded 2.72 g (72 %) **6t** as a white solid.

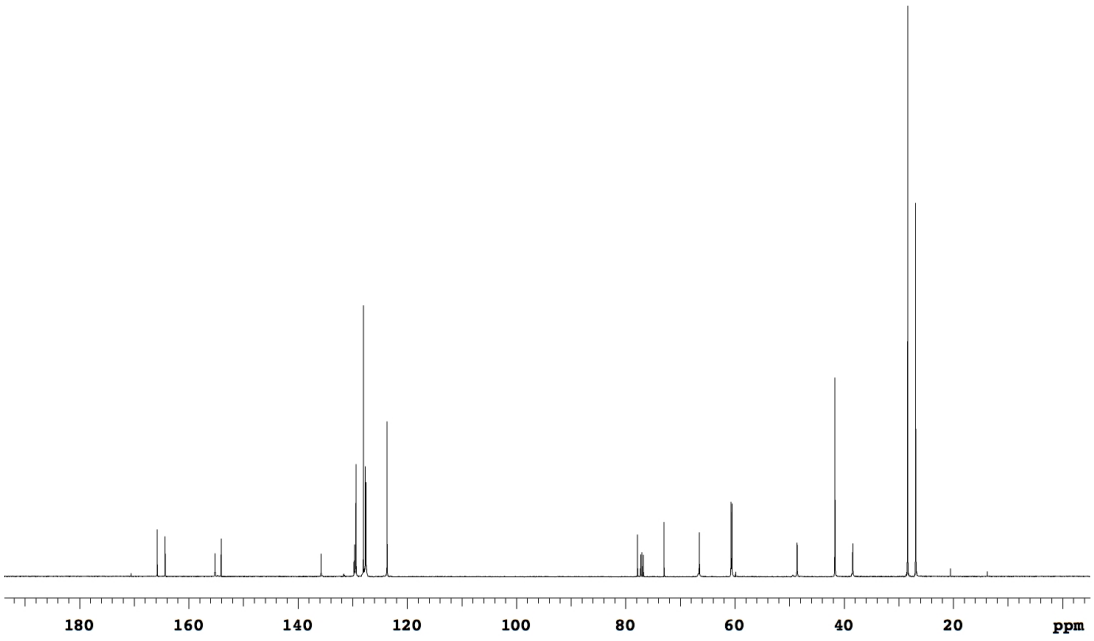
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5H), 6.98-6.90 (m, 2H), 6.80 (d, 2H, J = 8.0 Hz), 6.22-6.13 (m, 1H), 5.33-5.23 (m, 1H), 5.06-4.94 (m, 2H), 3.99-3.90 (m, 1H), 3.80-3.66 (m, 2H), 3.26-3.07 (m, 2H), 2.18 (s, 6H), 1.25 (s, 9H), 1.09 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 164.3, 155.2, 154.1, 135.8, 129.6, 129.4, 128.0, 127.7, 127.6, 123.7, 77.8, 73.0, 66.5, 60.7, 60.5, 48.6, 41.7, 38.4, 28.4, 26.9

MS (ESI, m/z) calcd for $C_{30}H_{43}N_4O_5$ $(M+H)^+$ 539.32, found 539



^{1}H NMR of **6t**

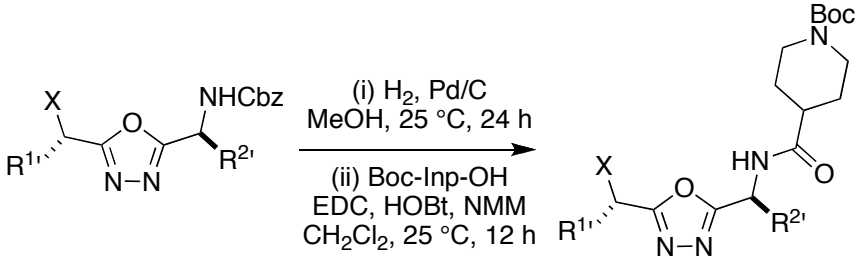


^{13}C NMR of **6t**

General Procedure for Compounds 7a-t

A solution of Cbz protected oxadiazole **6a-t** (1.0 equiv) in dry methanol (0.10 M) was stirred vigorously with 10 % Pd/C (0.1 equiv) under a H_2 atmosphere for 12 h at 25 °C until the reaction was complete. Filtration and evaporation of the solvent *in vacuo* yielded the crude product and it was used directly in the next step. The amine residue (1.0 equiv) and Boc-Inp-OH (1.0 equiv) were dissolved in dry CH_2Cl_2 (0.15 M). *N*-methylmorpholine (2.1 equiv) was added to the above solution followed by HOBt (1.1 equiv) and EDC (1.1 equiv). The resulting solution was stirred at 25 °C for 12h. The reaction mixture was washed with H_2O (30.0 mL), 1N HCl (30.0 mL), saturated $NaHCO_3$ (30.0 mL) and brine (30.0 mL). The organic layer was separated and dried with Na_2SO_4 and concentrated to dryness to afford the crude product. Flash chromatography with EtOAc/hexanes mixtures provided pure compounds **7a-t**.

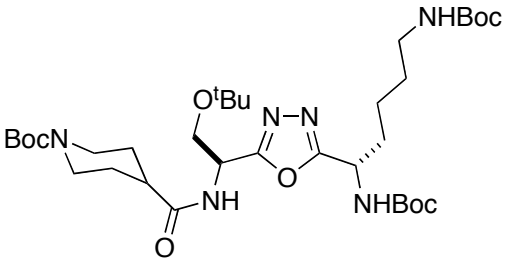
Scheme S3. Synthesis of monovalent compounds **7a-t**.



6a-q X = NHBoc
6r-t X = NMe_2

7a-q X = NHBoc
7r-t X = NMe_2

Preparation of Compound 7a



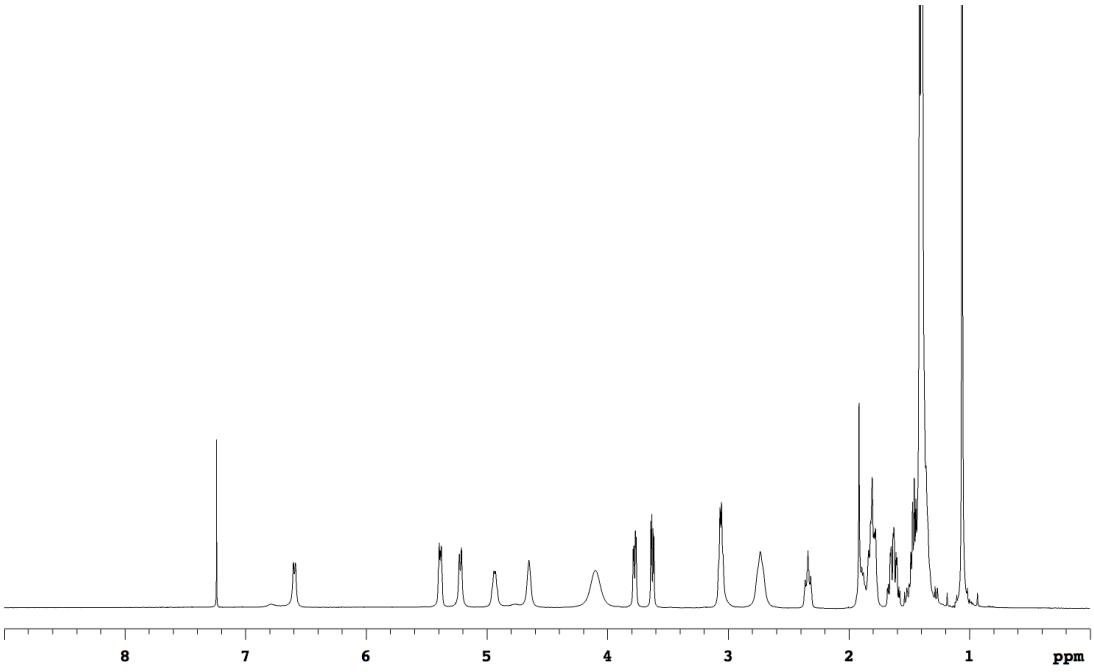
7a

Compound **7a** was prepared from (4.83 g, 7.8 mmol) of **6a**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 3.78 g (70 %) **7a** as a white solid.

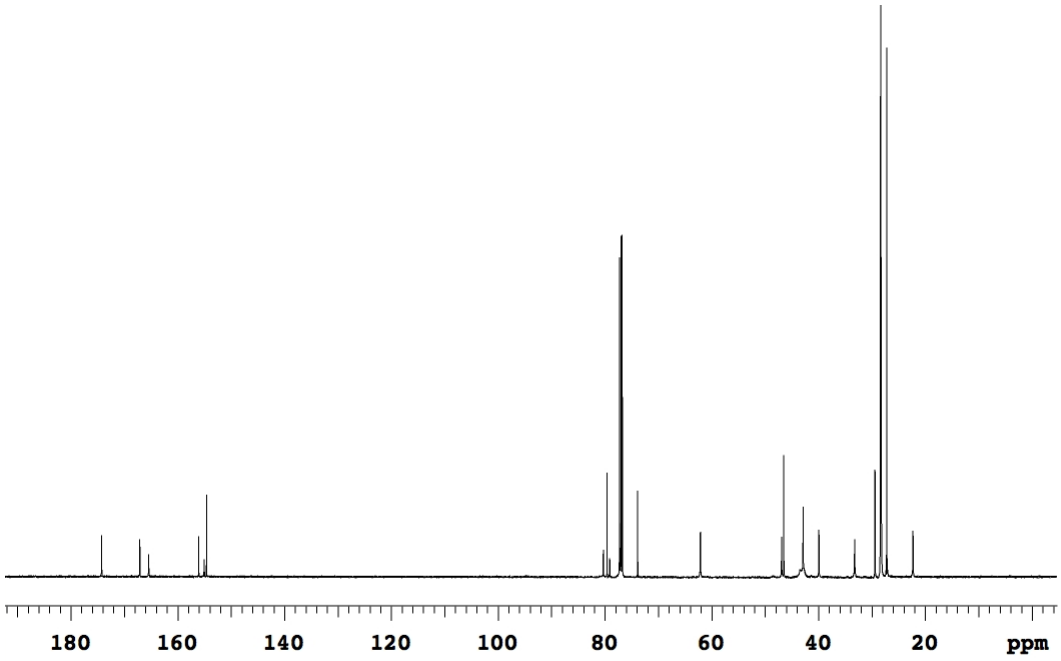
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, 1H, J = 8.2 Hz), 5.42-5.36 (m, 1H), 5.22 (d, 1H, J = 8.5 Hz), 4.98-4.89 (m, 1H), 4.65 (br, 1H), 4.10 (br, 2H), 3.78 (dd, 1H, J = 3.2, 9.4 Hz), 3.15-2.94 (dd, 1H, J = 3.9, 9.4 Hz), 3.12-2.99 (m, 2H), 2.81-2.65 (br, 2H), 2.39-2.30 (m, 1H), 1.94-1.75 (m, 4H), 1.70-1.57 (m, 2H), 1.51-1.31 (m, 31H), 1.06 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 167.1, 165.4, 156.1, 155.0, 154.6, 80.3, 80.0, 79.6, 79.1, 73.8, 62.1, 46.9, 46.5, 42.9, 39.9, 33.2, 29.4, 28.4, 28.4, 28.3, 28.2, 27.2, 22.3

MS (ESI, m/z) calcd for $C_{34}H_{60}N_6NaO_9$ $(M+Na)^+$ 719.43, found 719

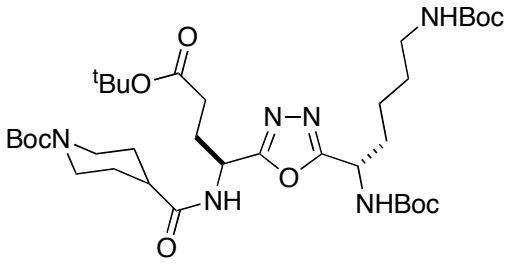


^{1}H NMR of **7a**



^{13}C NMR of **7a**

Preparation of Compound 7b



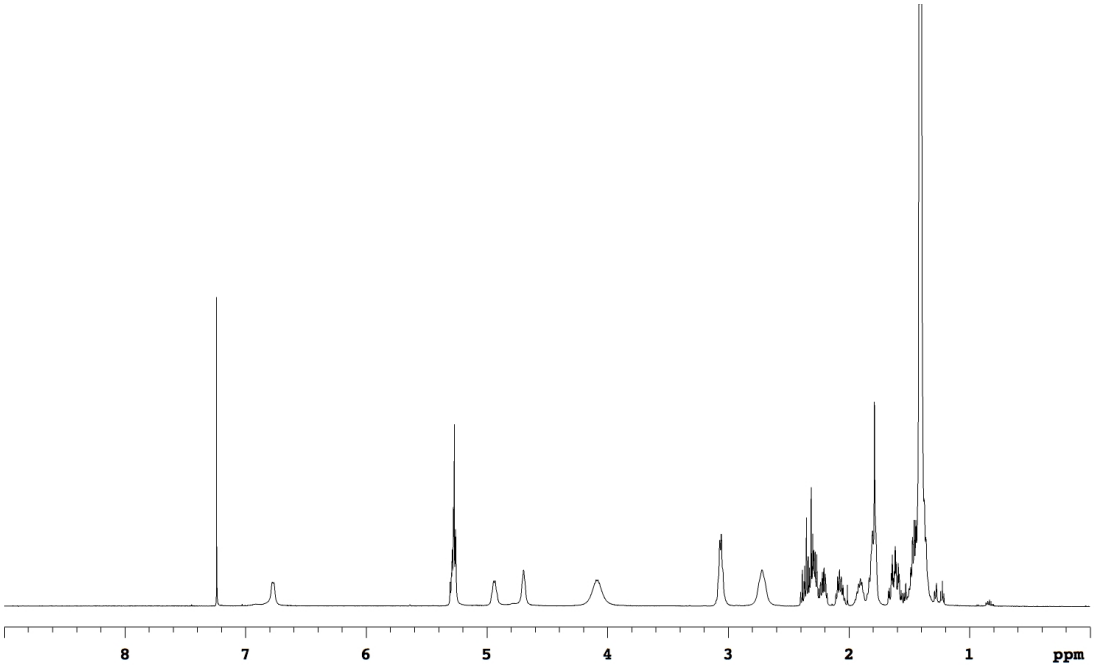
7b

Compound **7b** was prepared from (4.43 g, 6.7 mmol) of **6b**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 3.83 g (77 %) **7b** as a white solid.

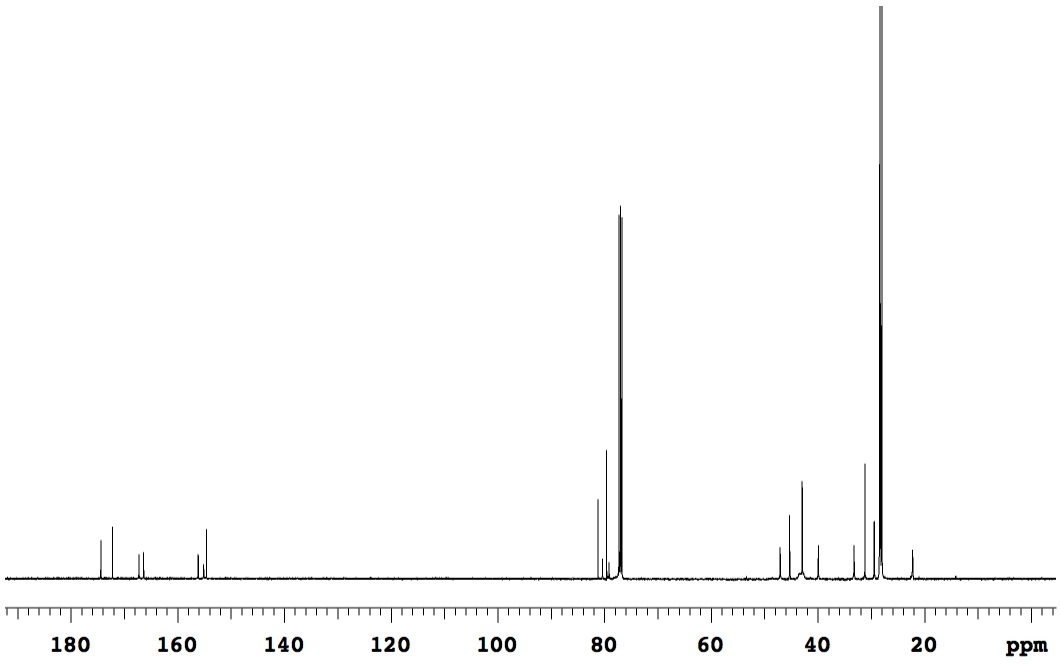
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (br, 1H), 5.32-5.23 (m, 2H), 4.98-4.89 (m, 1H), 4.70 (br, 1H), 4.09 (br, 2H), 3.12-3.01 (m, 2H), 2.72 (br, 2H), 2.41-2.17 (m, 4H), 2.12-2.02 (m, 1H), 1.96-1.74 (m, 4H), 1.69-1.55 (m, 2H), 1.52-1.32 (m, 40H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 172.2, 167.3, 166.4, 156.1, 155.1, 154.6, 81.2, 80.4, 79.6, 79.1, 47.1, 45.3, 42.9, 39.9, 33.2, 31.2, 29.4, 28.5, 28.4, 28.4, 28.3, 28.3, 28.0, 22.3

MS (ESI, m/z) calcd for $C_{36}H_{62}N_6NaO_{19}$ $(M+Na)^+$ 761.44, found 761

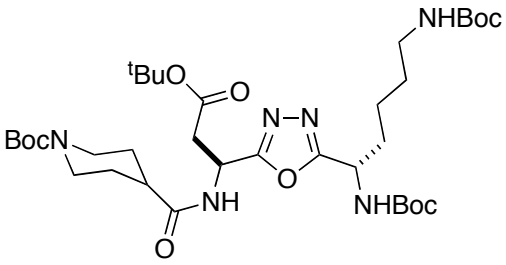


^{1}H NMR of **7b**



^{13}C NMR of **7b**

Preparation of Compound 7c



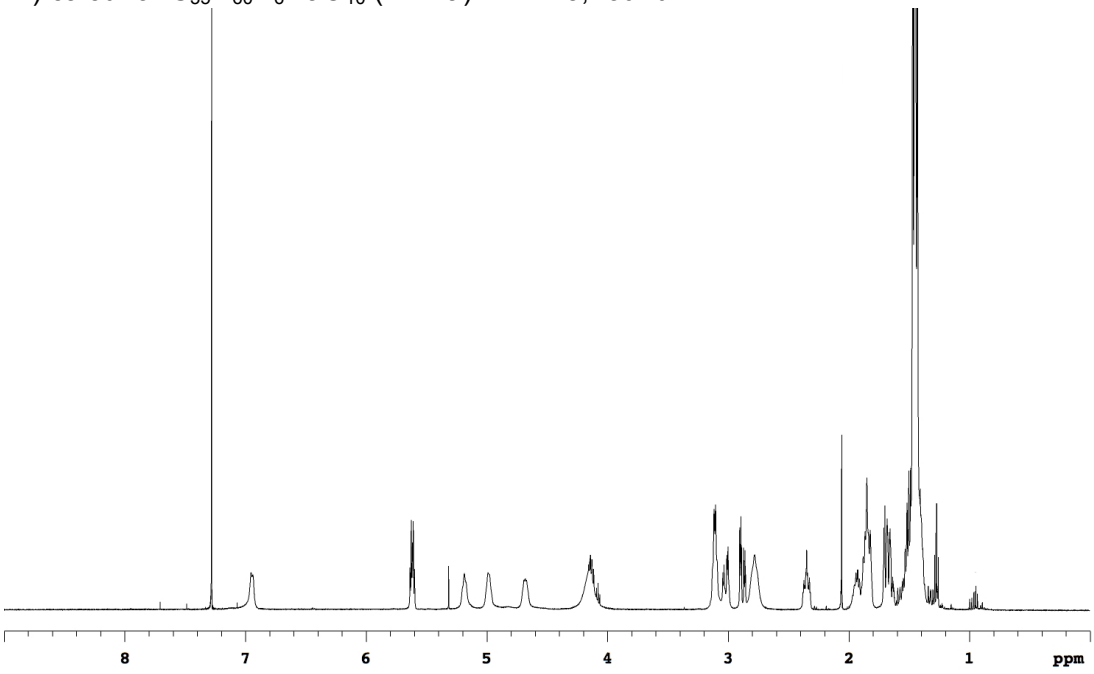
7c

Compound **7c** was prepared from (3.27 g, 5.0 mmol) of **6c**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 2.60 g (71 %) **7c** as a white solid.

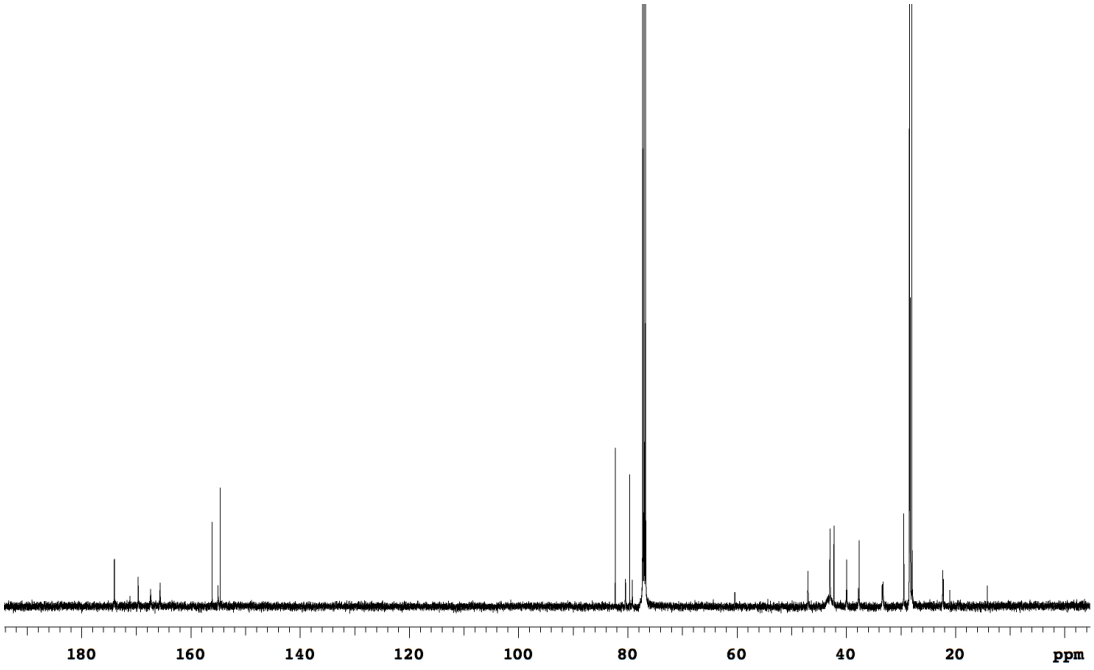
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (br, 1H), 5.66-5.58 (m, 1H), 5.24-5.13 (m, 1H), 5.03-4.93 (m, 1H), 4.73-4.63 (m, 1H), 4.25-4.05 (br, 2H), 3.16-3.06 (m, 2H), 3.06-2.97 (m, 1H), 2.88 (ddd, 1H, J = 2.3, 5.2, 16.5 Hz), 2.78 (br, 2H), 2.35 (tt, 1H, J = 3.7, 11.5 Hz), 2.00-1.79 (m, 4H), 1.73-1.62 (m, 2H), 1.57-1.36 (m, 40H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 169.6, 167.4, 165.6, 156.1, 155.0, 154.6, 82.3, 80.4, 79.6, 79.2, 47.0, 43.0, 42.2, 40.0, 37.6, 33.4, 33.2, 29.4, 28.4, 28.3, 28.3, 28.0, 22.3, 22.2

MS (ESI, m/z) calcd for $C_{35}H_{60}N_6NaO_{10}$ $(M+Na)^+$ 747.43, found 747

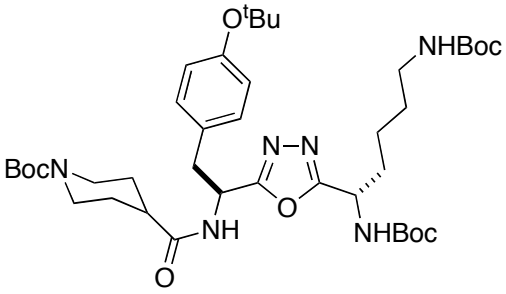


^{1}H NMR of **7c**



^{13}C NMR of **7c**

Preparation of Compound 7d



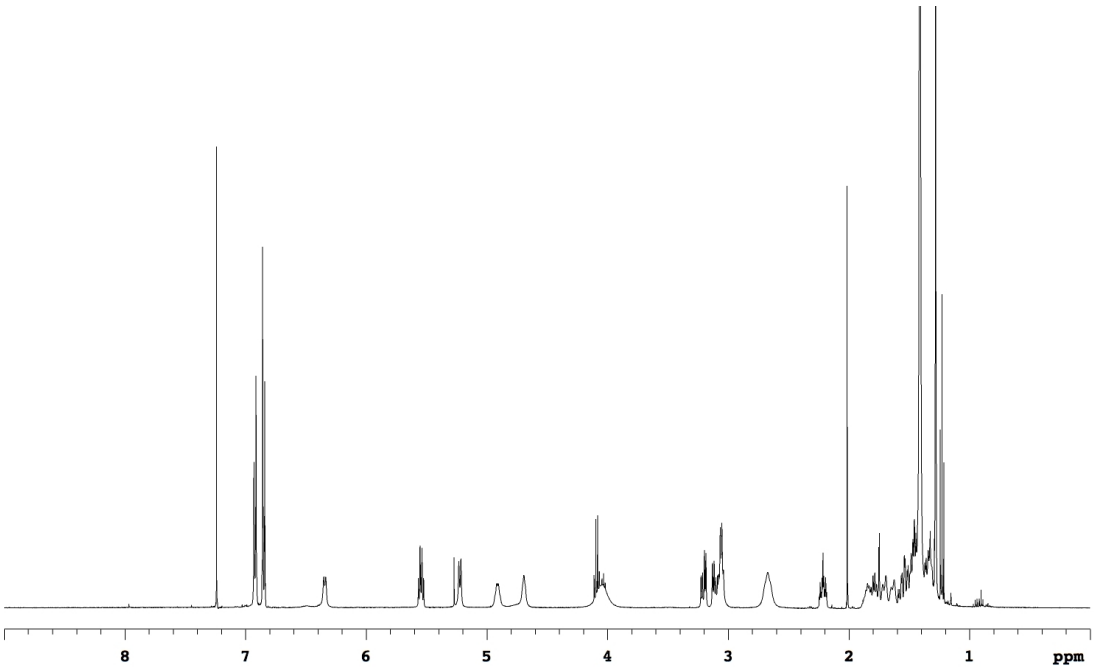
7d

Compound **7d** was prepared from (3.66 g, 5.3 mmol) of **6d**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 3.80 g (93 %) **7d** as a white solid.

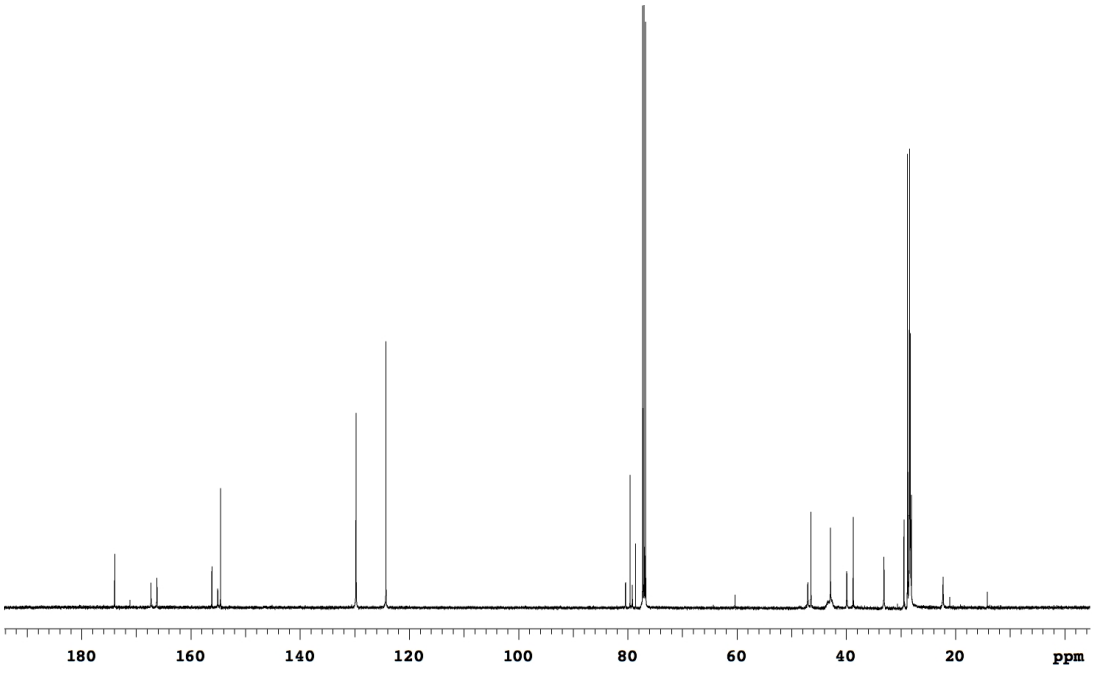
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 8.5 Hz), 6.34 (d, 1H, J = 8.2 Hz), 5.58-5.51 (m, 1H), 5.22 (d, 1H, J = 8.5 Hz), 4.96- 4.86 (m, 1H), 4.69 (br, 1H), 4.05 (br, 2H), 3.21 (dd, 1H, J = 6.2, 14.0 Hz), 3.15-3.01 (m, 3H), 2.74-2.60 (br, 2H), 2.21 (tt, 1H, J = 3.7, 11.5 Hz), 1.91-1.60 (m, 4H), 1.60-1.30 (m, 33H), 1.28 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 171.2, 167.3, 166.2, 156.1, 155.1, 154.6, 129.8, 129.7, 124.3, 80.4, 79.2, 78.6, 47.0, 45.5, 42.9, 39.9, 38.7, 33.1, 29.4, 28.8, 28.6, 28.4, 28.4, 28.3, 28.1, 22.3

MS (ESI, m/z) calcd for $C_{40}H_{64}N_6NaO_9$ $(M+Na)^+$ 795.96, found 795

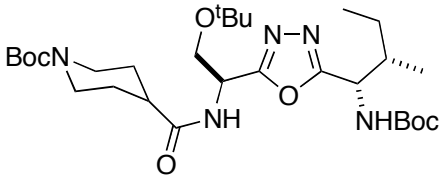


^{1}H NMR of **7d**



^{13}C NMR of **7d**

Preparation of Compound 7e



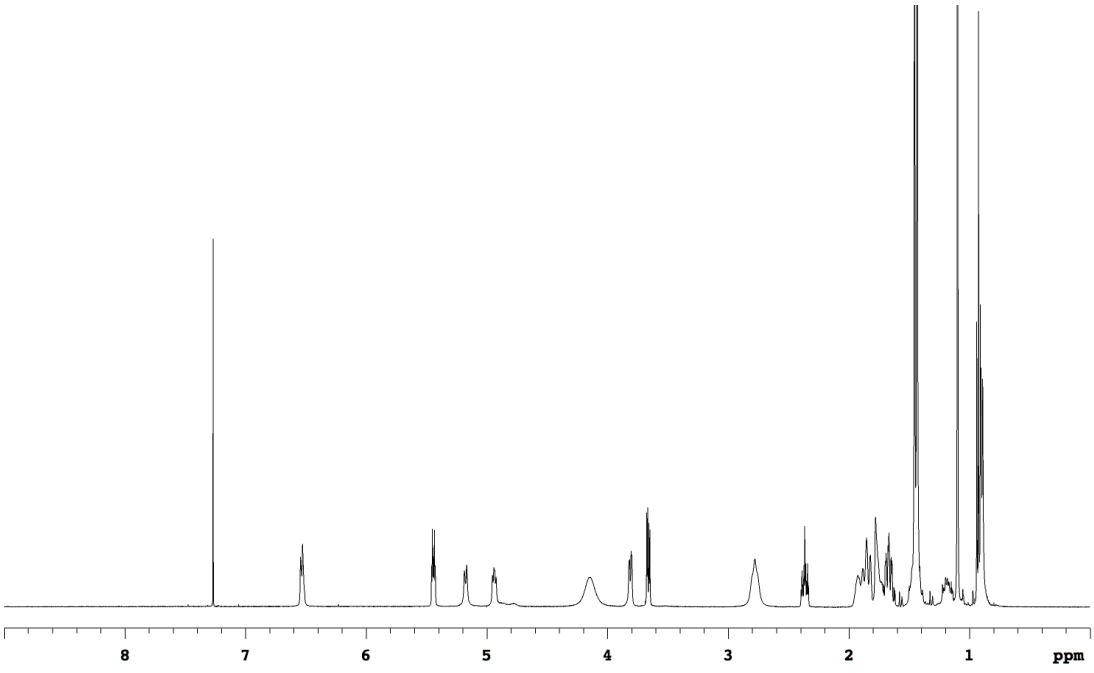
7e

Compound **7e** was prepared from (5.26 g, 10.4 mmol) of **6e**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 4.80 g (78 %) **7e** as a white solid.

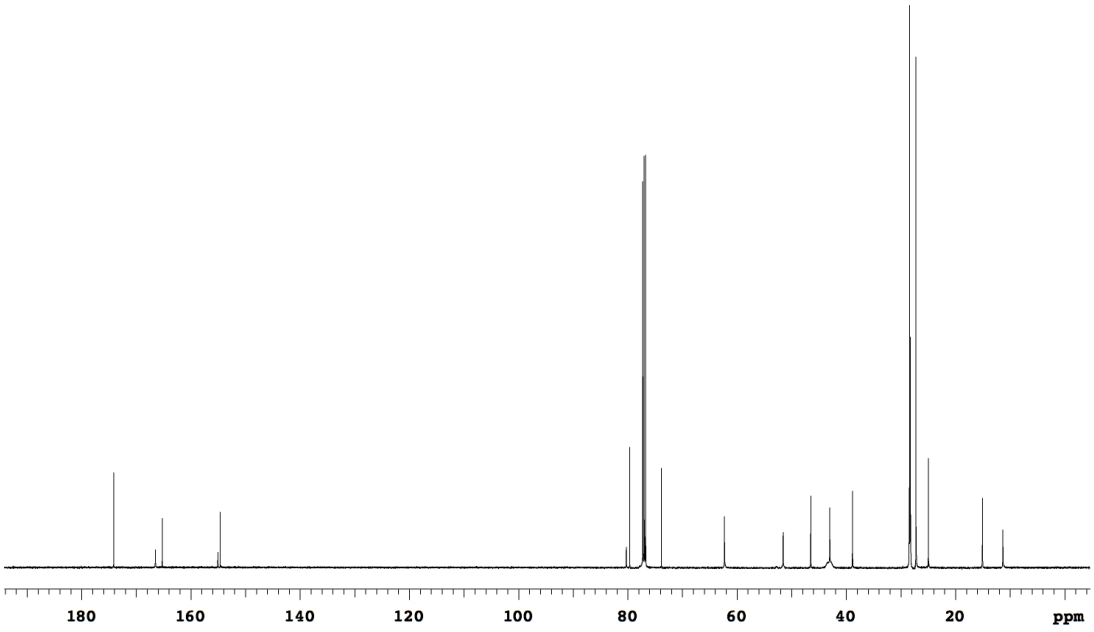
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (d, 1H, J = 8.6 Hz), 5.44 (dt, 1H, J = 3.5, 8.6 Hz), 5.18 (d, 1H, J = 9.2 Hz), 4.98-4.90 (m, 1H), 4.14 (br, 2H), 3.81 (dd, 1H, J = 2.6, 9.2 Hz), 3.66 (dd, 1H, J = 3.7, 9.2 Hz), 2.78 (br, 2H), 2.37 (tt, 1H, J = 3.7, 11.5 Hz), 1.97-1.61 (m, 5H), 1.51-1.38 (m, 19H), 1.24-1.13 (m, 1H), 1.10 (s, 9H), 0.95-0.87 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 166.5, 165.2, 155.1, 154.6, 80.3, 79.6, 73.8, 62.3, 51.6, 46.5, 43.0, 38.9, 28.5, 28.4, 28.3, 28.2, 27.2, 25.0, 15.1, 11.3

MS (ESI, m/z) calcd for $C_{29}H_{51}N_5NaO_7$ $(M+Na)^+$ 604.37, found 604

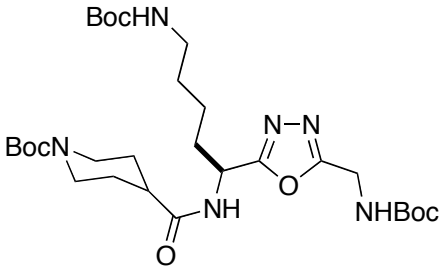


^{1}H NMR of **7e**



^{13}C NMR of **7e**

Preparation of Compound 7f



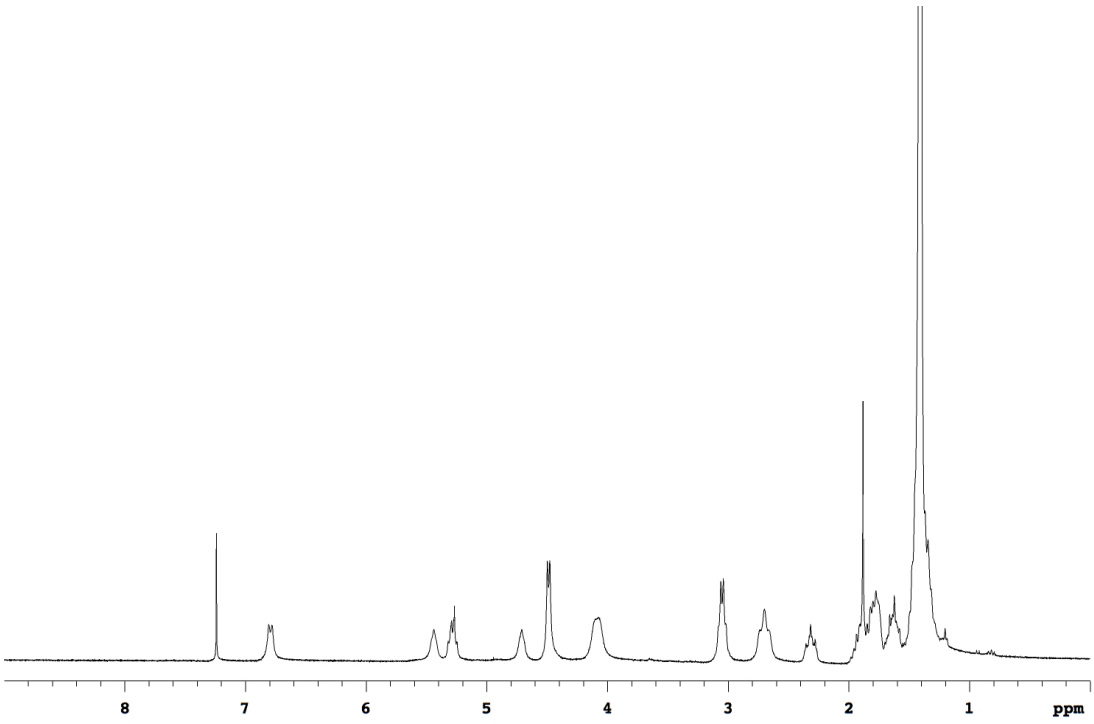
7f

Compound **7f** was prepared from (5.41 g, 10.1 mmol) of **6f**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 5.10 g (83 %) **7f** as a white solid.

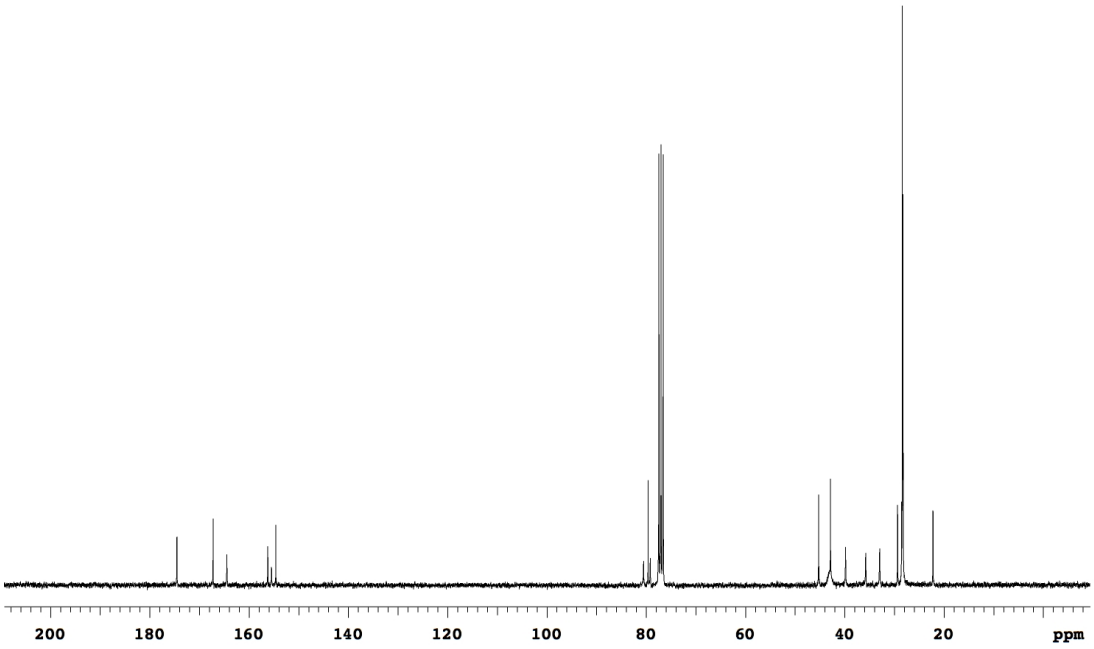
^{1}H NMR (300MHz, $CDCl_3$) δ 6.80 (d, 1H, J = 7.8 Hz), 5.44 (br, 1H), 5.35-5.21 (m, 1H), 4.71 (br, 1H), 4.49 (d, 2H, J = 5.9 Hz), 4.07 (br, 2H), 3.14-2.96 (m, 2H), 2.80-2.60 (m, 2H), 2.40-2.24 (m, 1H), 2.01-1.56 (m, 6H), 1.54-1.25 (m, 31H)

^{13}C NMR (75MHz, $CDCl_3$) δ 174.5, 167.2, 164.5, 156.2, 155.5, 154.6, 80.5, 79.6, 79.2, 77.2, 45.2, 42.9, 39.8, 35.8, 33.0, 29.3, 28.5, 28.4, 28.4, 28.2, 22.2

MS (ESI, m/z) calcd for $C_{29}H_{50}N_6NaO_8$ $(M+Na)^+$ 633.36, found 633

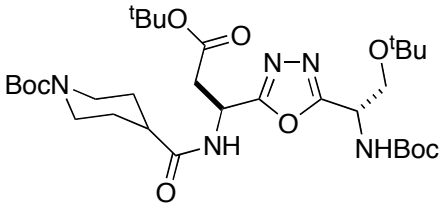


^{1}H NMR of **7f**



^{13}C NMR of **7f**

Preparation of Compound 7g



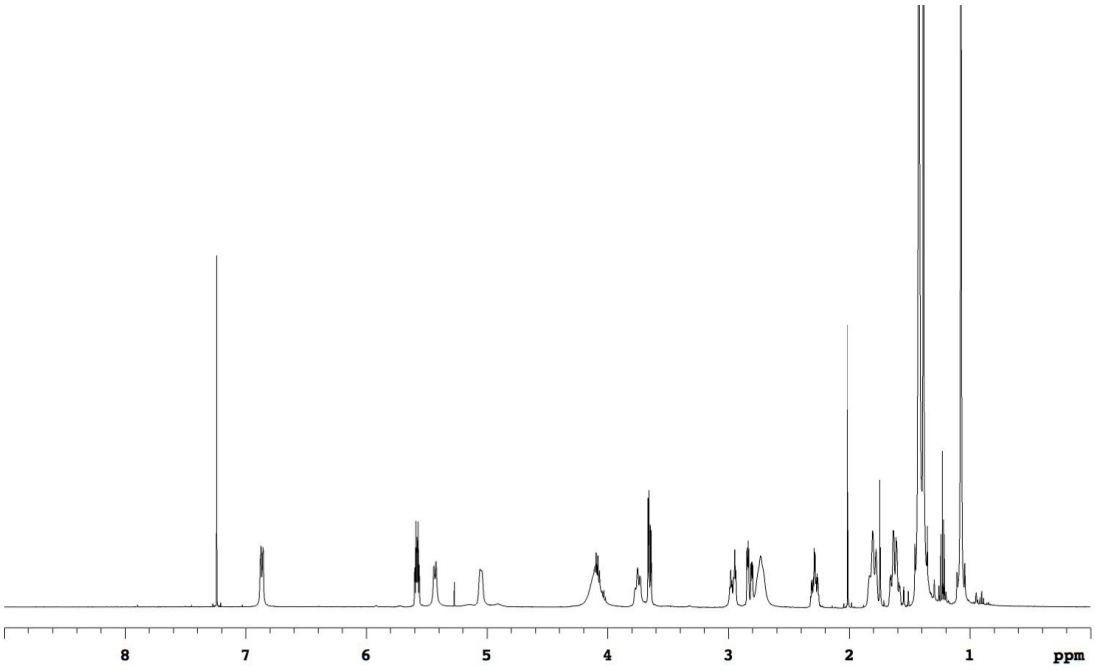
7g

Compound **7g** was prepared from (3.62 g, 6.4 mmol) of **6g**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 3.50 g (84 %) **7g** as a white solid.

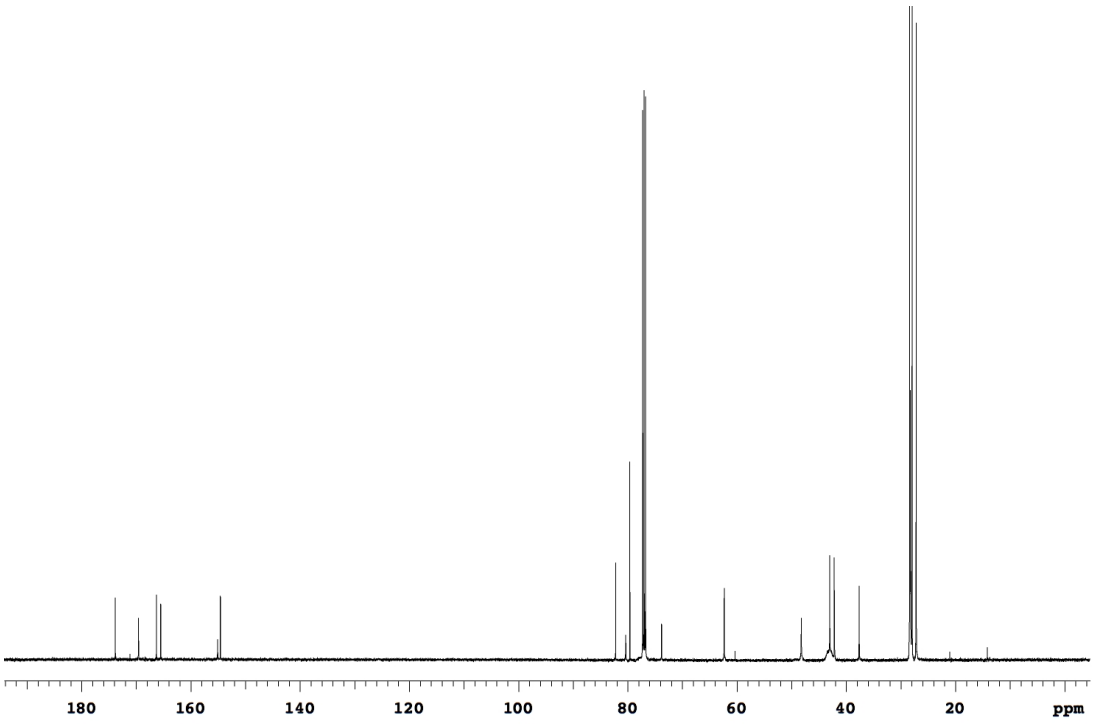
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91-6.82 (m, 1H), 5.58 (dt, 1H, J = 4.9, 8.8 Hz), 5.43 (d, 1H, J = 8.8 Hz), 5.06 (br, 1H), 4.10 (br, 2H), 3.80-3.71 (m, 1H), 3.65 (dd, 1H, J = 4.1, 9.2 Hz), 2.97 (dt, 1H, J = 4.5, 16.5 Hz), 2.82 (ddd, 1H, J = 2.6, 5.2, 16.5 Hz), 2.73 (br, 2H), 2.33-2.25 (m, 1H), 1.87-1.76 (m, 2H), 1.68-1.57 (m, 2H), 1.42 (br, 18H), 1.39 (s, 9H), 1.08 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 169.6, 166.3, 165.5, 155.1, 154.6, 82.2, 80.4, 79.6, 73.8, 62.3, 48.2, 43.0, 42.2, 37.6, 28.4, 28.4, 28.3, 28.2, 27.9, 27.2

MS (ESI, m/z) calcd for $C_{31}H_{53}N_5NaO_9$ $(M+Na)^+$ 662.37, found 662

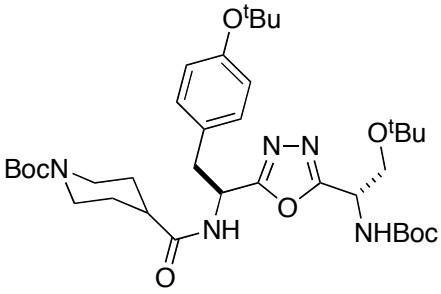


^{1}H NMR of **7g**



^{13}C NMR of **7g**

Preparation of Compound 7h



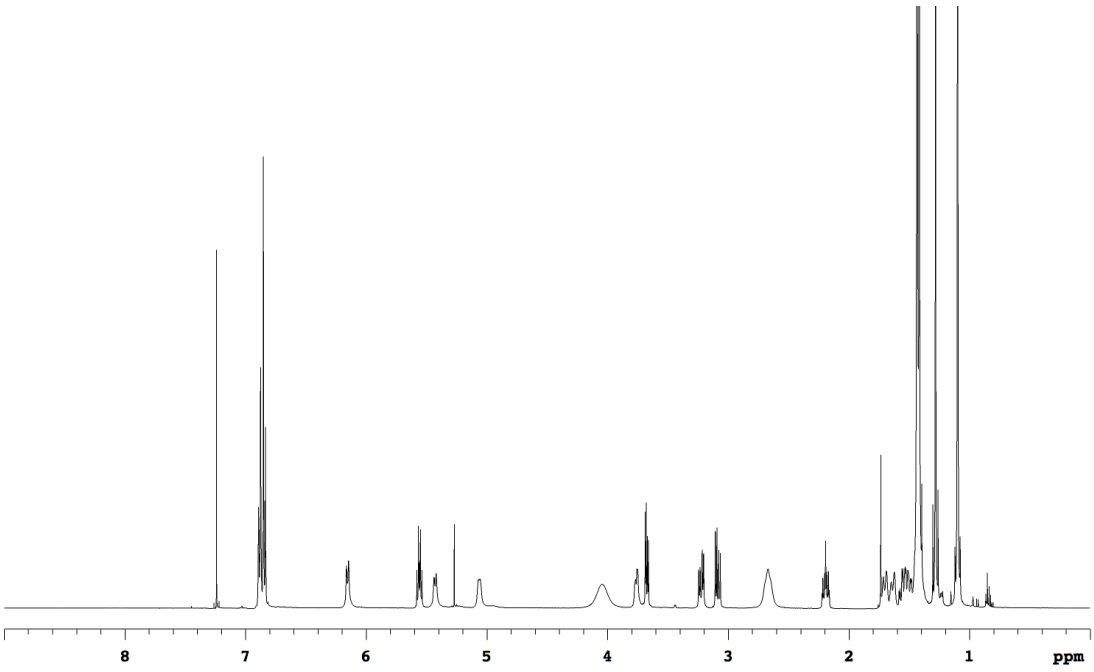
7h

Compound **7h** was prepared from (4.12 g, 6.7 mmol) of **6h**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 3.70 g (80 %) **7h** as a white solid.

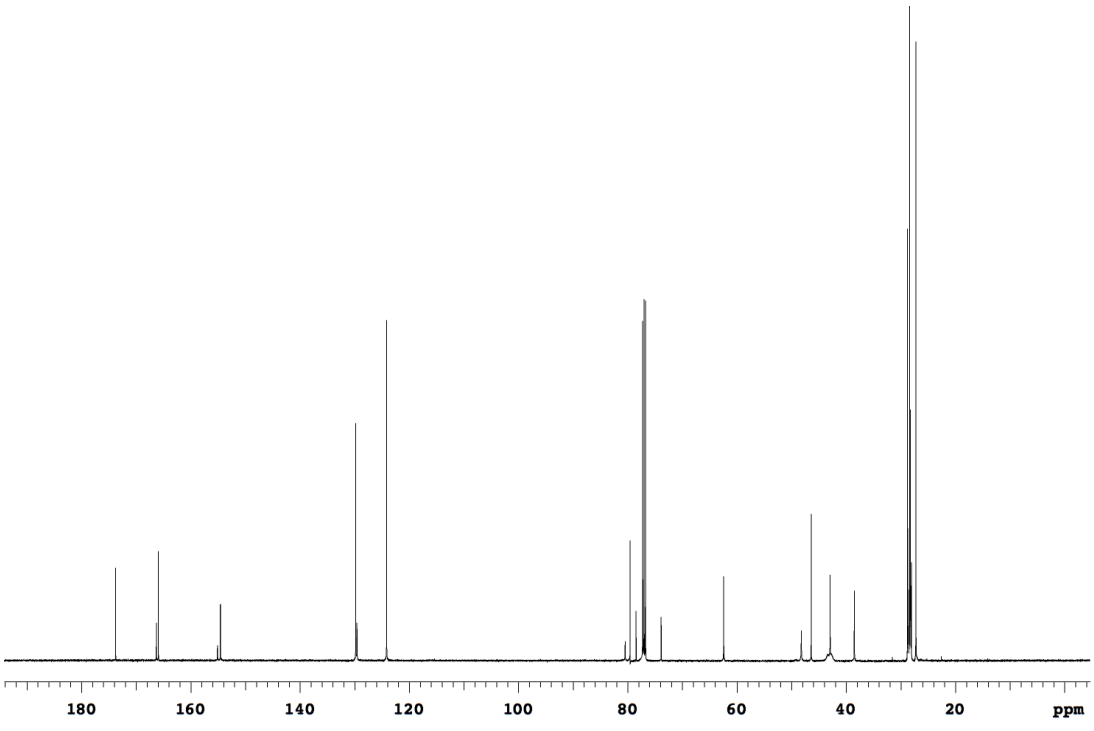
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92-6.81 (m, 4H), 6.15 (d, 1H, J = 8.4 Hz), 5.59-5.53(m, 1H), 5.43 (d, 1H, J = 8.4 Hz), 5.11-5.02 (m, 1H), 4.04 (br, 2H), 3.80-3.72 (m, 1H), 3.23 (dd, 1H, J = 6.0, 14.1 Hz), 3.09 (dd, 1H, J = 6.5, 14.1 Hz), 2.67 (dd, 1H, J = 4.1, 9.3 Hz), 2.19 (tt, 1H, J = 3.7, 11.5 Hz), 1.75-1.47 (m, 4H), 1.43 (s, 9H), 1.42 (s, 9H), 1.28 (s, 9H), 1.10 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 166.3, 165.9, 155.1, 154.6, 154.5, 129.8, 129.6, 124.2, 80.5, 79.6, 78.5, 73.9, 62.4, 48.2, 46.4, 42.9, 38.5, 28.8, 28.6, 28.4, 28.3, 28.1, 27.2

MS (ESI, m/z) calcd for $C_{36}H_{57}N_5NaO_8$ $(M+Na)^+$ 710.41, found 710

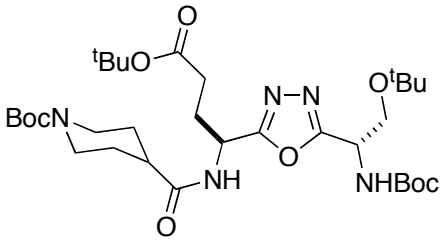


^{1}H NMR of **7h**



^{13}C NMR of **7h**

Preparation of Compound 7i



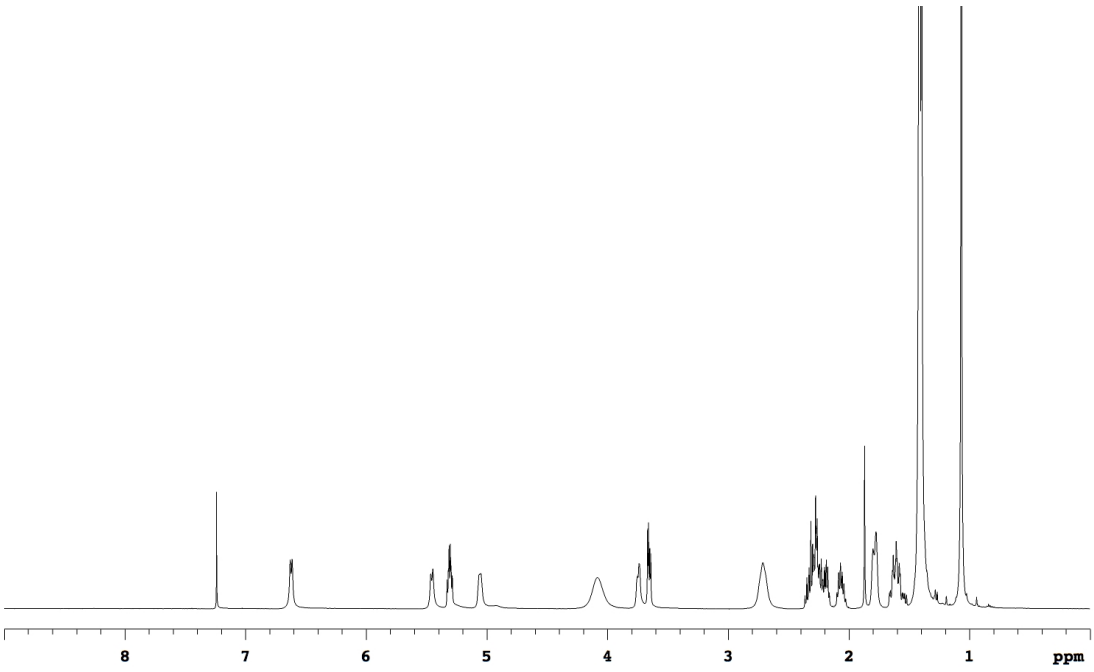
7i

Compound **7i** was prepared from (7.02 g, 12.2 mmol) of **6i**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 8.30 g (82 %) **7i** as a white solid.

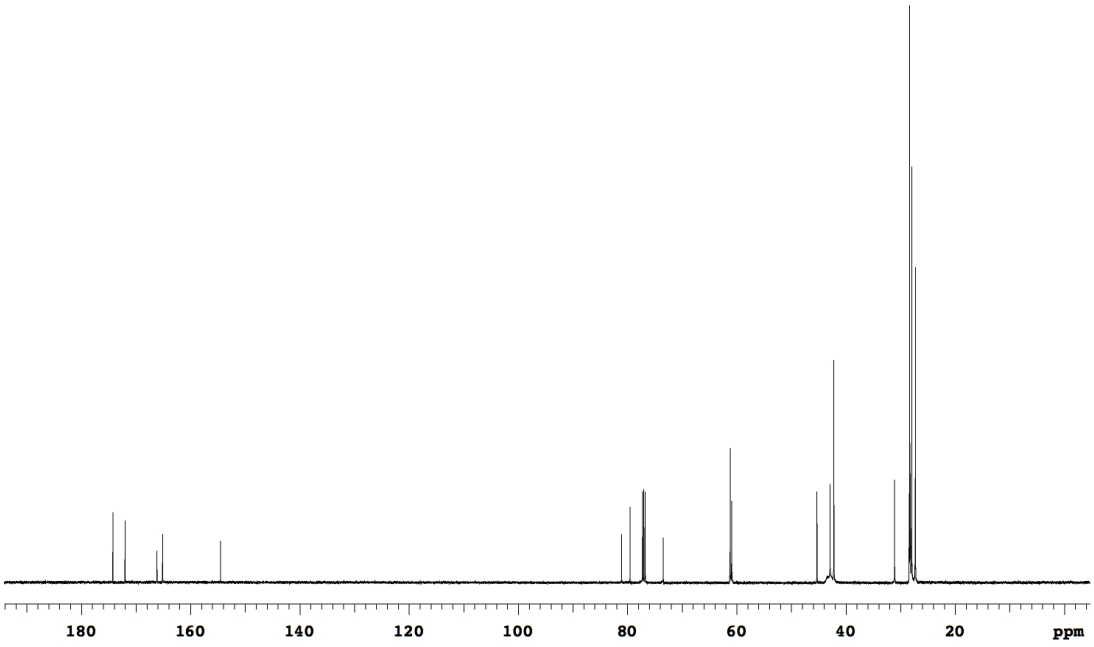
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (d, 1H, J = 8.0 Hz), 5.46 (d, 1H, J = 8.5 Hz), 5.35-5.26(m, 1H), 5.06 (br, 1H), 4.09 (br, 2H), 3.78-3.70 (br, 1H), 3.65 (dd, 1H, J = 4.0, 9.2 Hz), 2.71 (br, 2H), 2.38-2.15 (m, 4H), 2.11-2.01 (m, 1H), 1.83-1.74 (m, 2H), 1.68-1.54 (m, 2H), 1.49-1.31 (m, 27H), 1.07 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 172.3, 166.5, 155.4, 154.9, 81.4, 80.7, 79.8, 74.1, 62.8, 48.5, 45.4, 43.2, 31.4, 28.7, 28.7, 28.6, 28.5, 28.3, 27.5

MS (ESI, m/z) calcd for $C_{32}H_{55}N_5NaO_9$ $(M+Na)^+$ 676.39, found 676

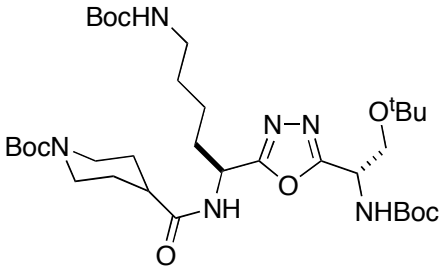


^{1}H NMR of **7i**



^{13}C NMR of **7i**

Preparation of Compound 7j



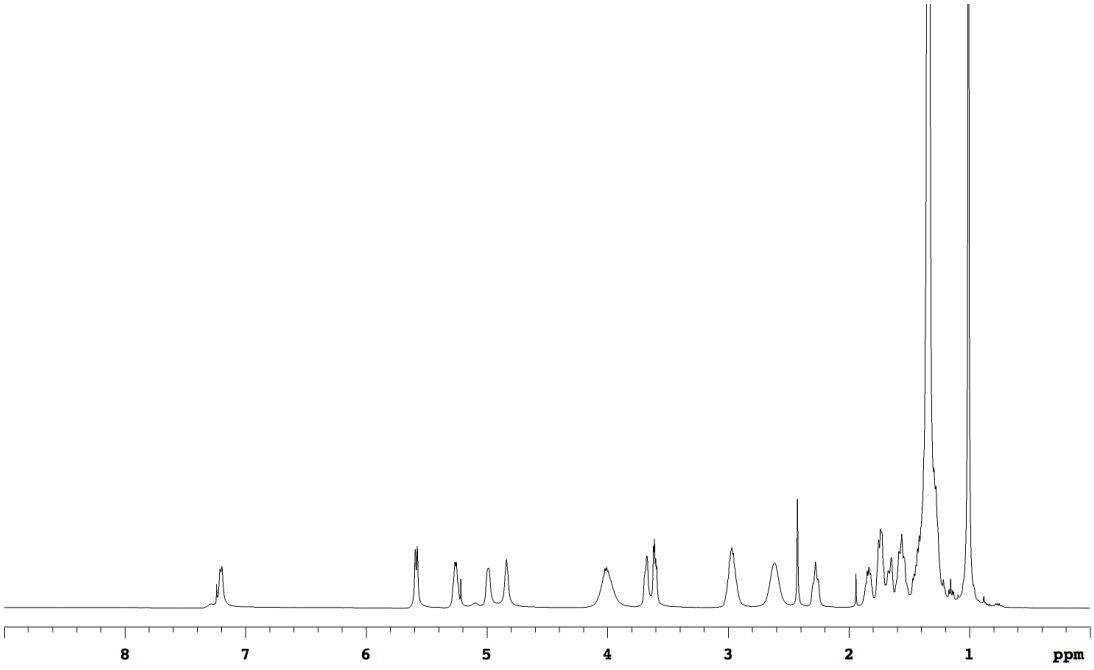
7j

Compound **7j** was prepared from (6.54 g, 10.6 mmol) of **6j**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 5.60 g (77 %) **7j** as a white solid.

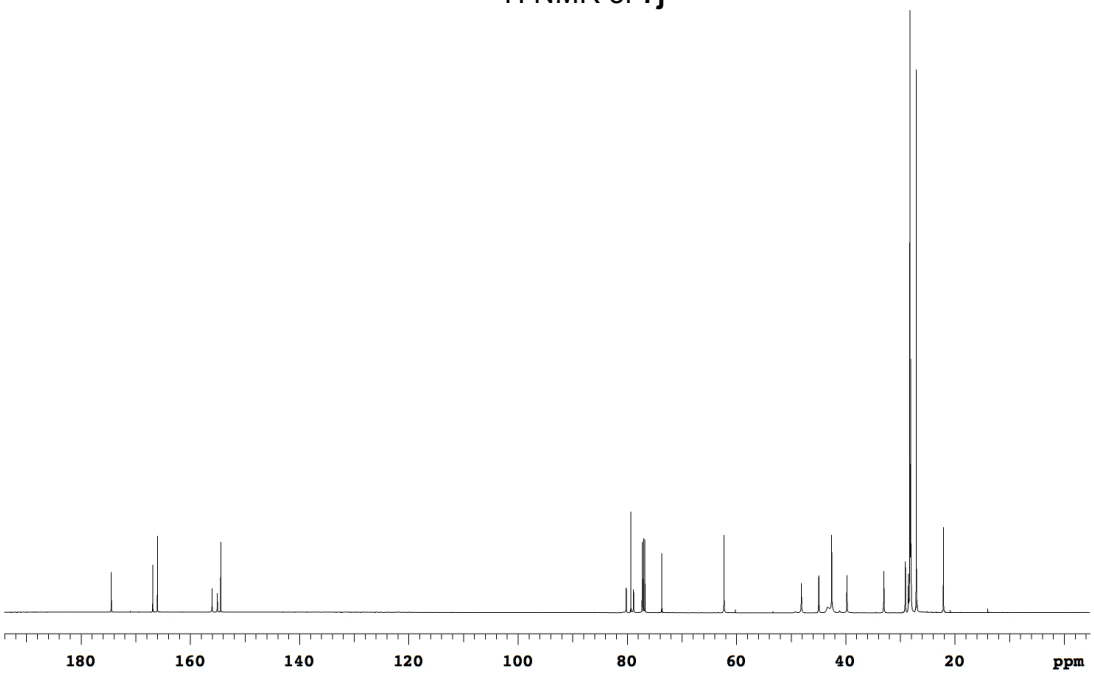
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, 1H, J = 7.6 Hz), 5.59 (d, 1H, J = 8.5 Hz), 5.32-5.19(m, 1H), 4.99 (br, 1H), 4.84 (br, 1H), 4.01 (br, 2H), 3.73-3.55 (m, 2H), 3.05-2.87 (m, 2H), 2.62 (br, 2H), 2.33-2.21 (m, 1H), 1.90-1.50 (m, 6H), 1.49-1.23 (m, 31H), 1.01 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 166.9, 166.0, 156.0, 155.1, 154.4, 80.2, 79.3, 78.8, 73.7, 62.3, 48.1, 44.9, 42.6, 39.8, 33.0, 29.1, 28.5, 28.3, 28.2, 28.1, 28.0, 27.1, 22.1

MS (ESI, m/z) calcd for $C_{34}H_{60}N_6NaO_9$ $(M+Na)^+$ 719.43, found 719

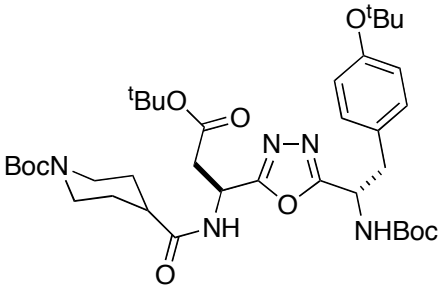


^{1}H NMR of **7j**



^{13}C NMR of **7j**

Preparation of Compound 7k



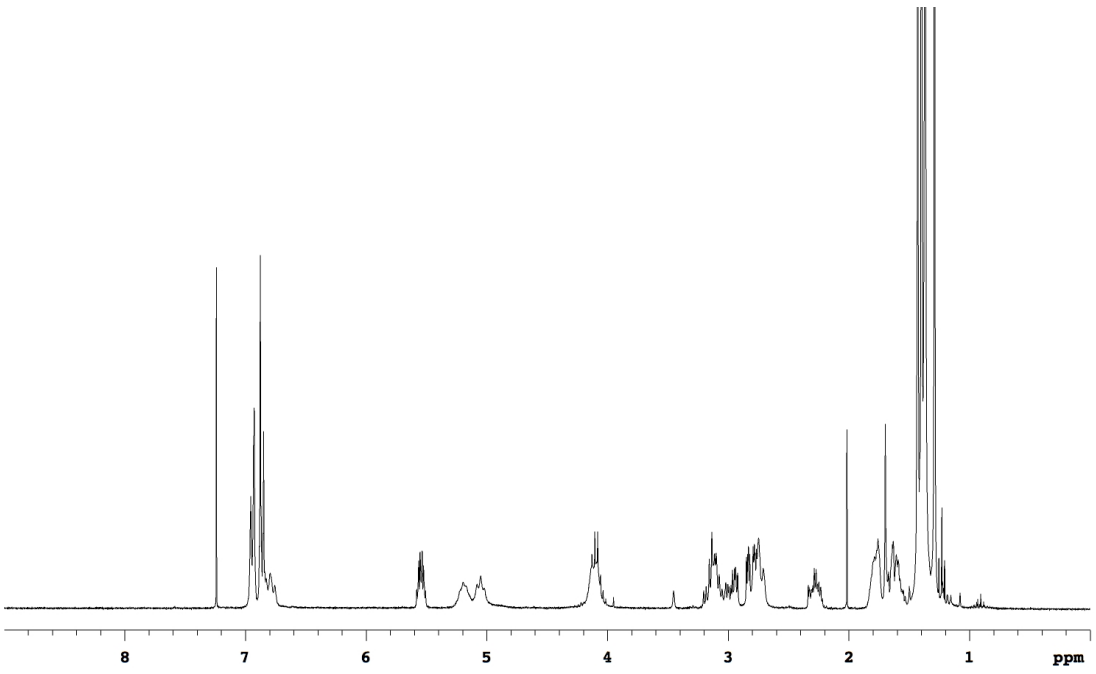
7k

Compound **7k** was prepared from (3.35 g, 5.2 mmol) of **6k**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 2.80 g (74 %) **7k** as a white solid.

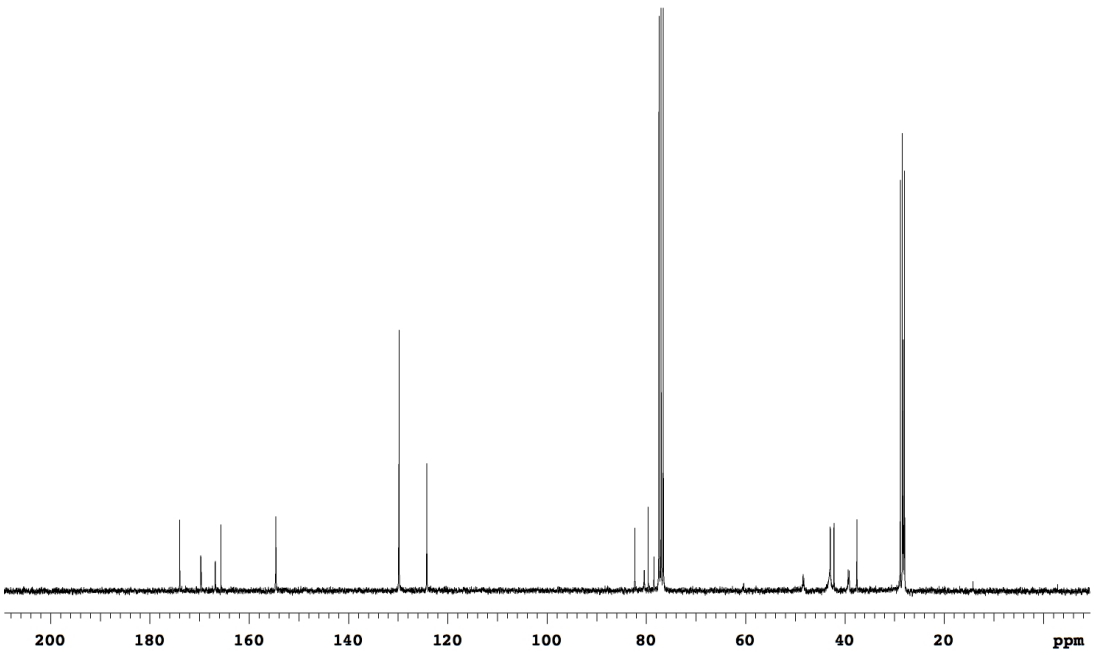
^{1}H NMR (300MHz, $CDCl_3$) δ 6.99-6.72 (m, 4H), 5.59-5.50 (m, 2H), 5.28-4.96(m, 2H), 4.11 (br, 2H), 3.23-2.90 (m, 3H), 2.87-2.88 (m, 3H), 2.35-2.21 (m, 1H), 1.86-1.52 (m, 4H), 1.48-1.32 (m, 27H), 1.29 (s, 9H)

^{13}C NMR (75MHz, $CDCl_3$) δ 174.0, 169.8, 169.7, 166.9, 166.8, 165.7, 154.6, 129.9, 129.8, 124.2, 82.3, 80.4, 79.6, 78.5, 48.4, 43.0, 42.2, 39.3, 37.6, 28.8, 28.4, 28.4, 28.3, 28.2, 28.0

MS (ESI, m/z) calcd for $C_{37}H_{57}N_5NaO_9$ $(M+Na)^+$ 738.41, found 738

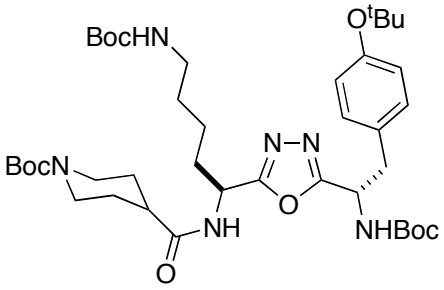


^{1}H NMR of **7k**



^{13}C NMR of **7k**

Preparation of Compound 7l



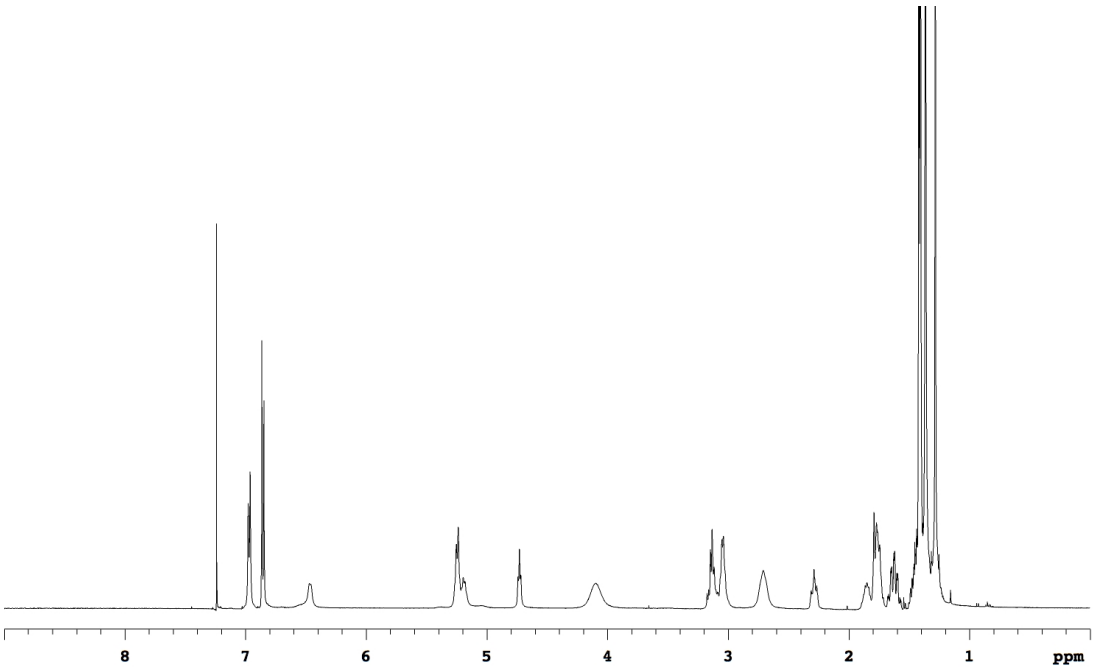
7l

Compound **7l** was prepared from (5.96 g, 8.6 mmol) of **6l**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 5.20 g (78 %) **7l** as a white solid.

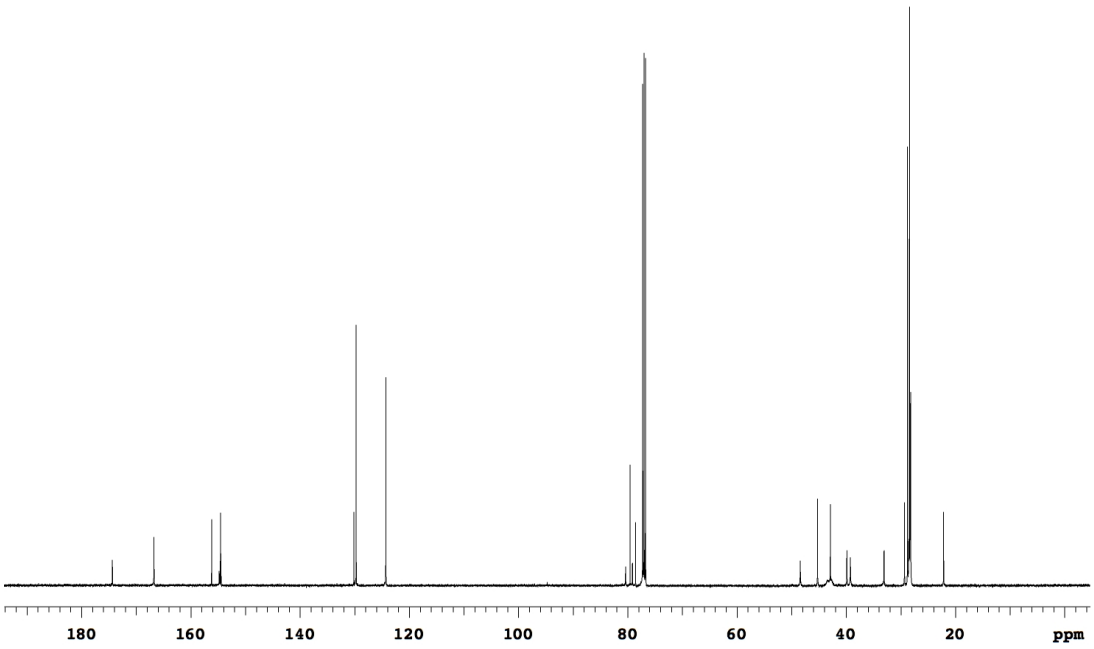
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, 2H, J = 8.3 Hz), 6.86 (d, 2H, J = 8.3 Hz), 6.54-6.41(br, 1H), 5.30-5.13 (m, 3H), 4.73 (t, 1H, J = 5.7 Hz), 4.10 (br, 2H), 3.20-2.98 (m, 4H), 2.71 (b, 2H), 2.34-2.24 (m, 1H), 1.92-1.69 (m, 4H), 1.51-1.20 (m, 40H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 166.8, 156.2, 154.8, 154.6, 154.5, 130.1, 129.7, 124.3, 80.4, 79.6, 79.1, 78.5, 48.4, 45.2, 42.9, 39.9, 39.2, 33.1, 29.3, 28.8, 28.6, 28.4, 28.4, 28.3, 28.2, 22.2

MS (ESI, m/z) calcd for $C_{40}H_{64}N_6NaO_9$ $(M+Na)^+$ 795.46, found 795

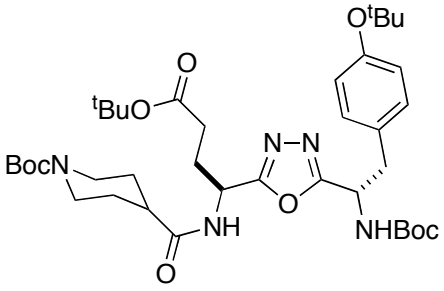


^{1}H NMR of **7l**



^{13}C NMR of **7l**

Preparation of Compound 7m



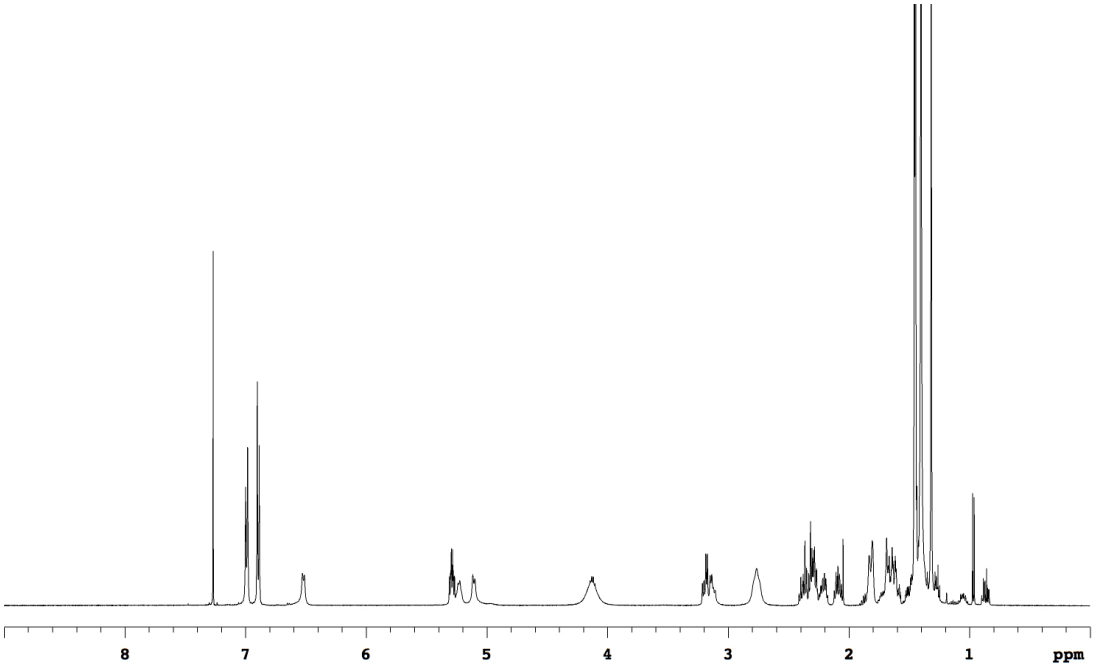
7m

Compound **7m** was prepared from (4.58 g, 7.0 mmol) of **6m**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 4.60 g (89 %) **7m** as a white solid.

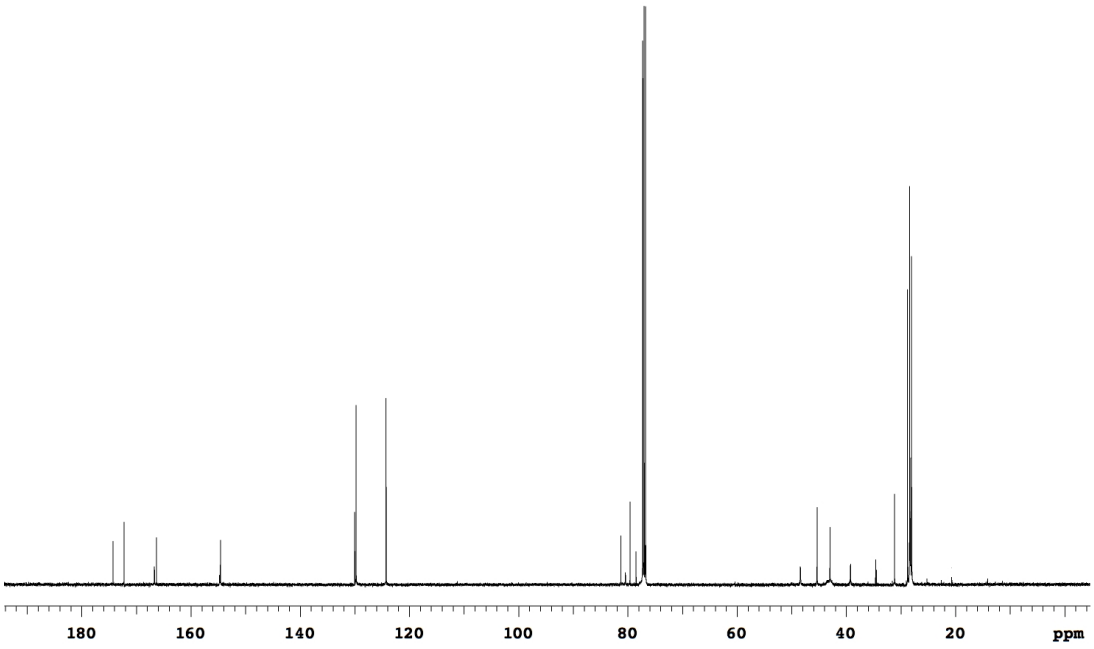
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, 2H, J = 8.3 Hz), 6.89 (d, 2H, J = 8.3 Hz), 6.52 (d, 1H, J = 7.6 Hz), 5.32-5.18 (m, 2H), 5.11 (d, 1H, J = 8.4 Hz), 4.13 (br, 2H), 3.19 (dd, 1H, J = 6.5, 14.0 Hz), 3.13 (dd, 1H, J = 6.6, 14.0 Hz), 2.77 (br, 2H), 2.43-2.16 (m, 4H), 2.14-2.04 (m, 1H), 1.90-1.56 (m, 4H), 1.50-1.34 (m, 27H), 1.32 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 172.2, 166.7, 166.3, 154.7, 154.6, 154.6, 130.0, 129.8, 124.3, 81.3, 80.4, 79.6, 78.5, 48.4, 45.3, 43.0, 39.2, 34.6, 31.2, 28.8, 28.5, 28.4, 28.3, 28.2, 28.0

MS (ESI, m/z) calcd for $C_{38}H_{59}N_5NaO_9$ $(M+Na)^+$ 752.42, found 752

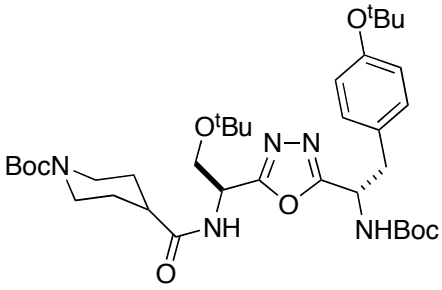


^{1}H NMR of **7m**



^{13}C NMR of **7m**

Preparation of Compound 7n



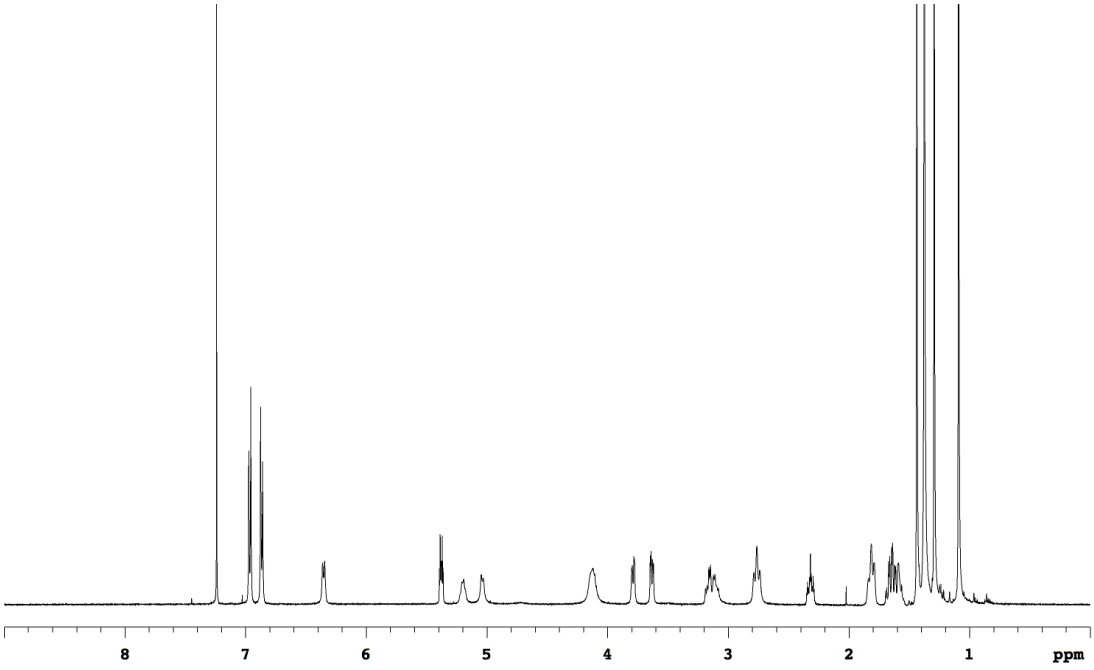
7n

Compound **7n** was prepared from (3.63 g, 5.9 mmol) of **6n**. Flash chromatography (3:7 to 1:1 EtOAc/Hexanes) afforded 3.50 g (85 %) **7n** as a white solid.

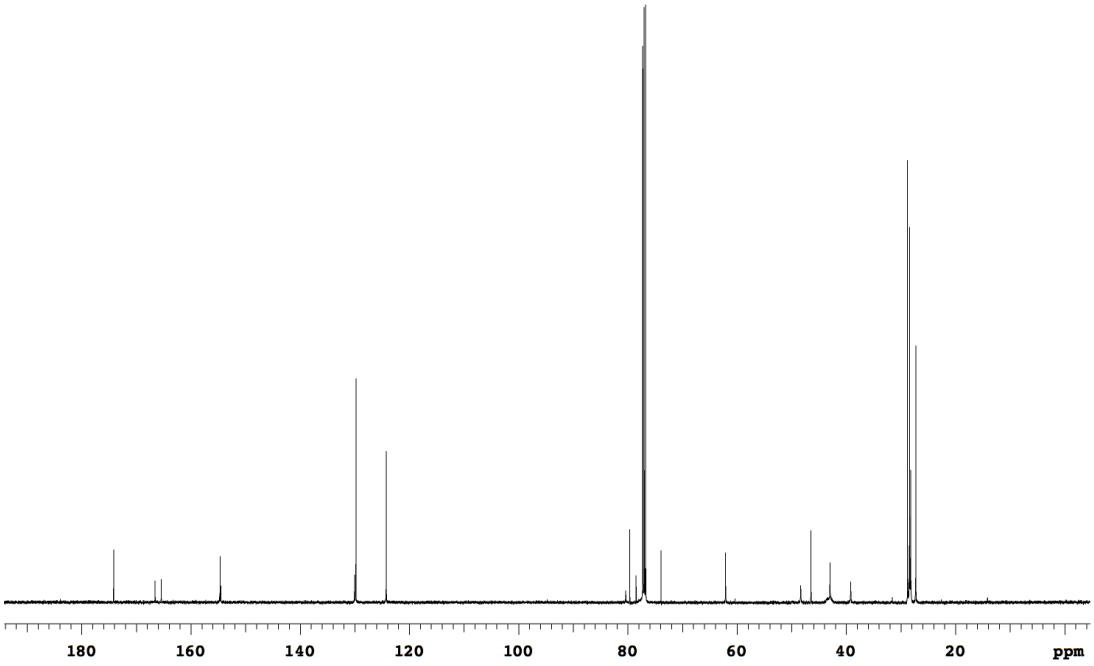
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, 2H, J = 8.4 Hz), 6.87 (d, 2H, J = 8.4 Hz), 6.35 (d, 1H, J = 8.3 Hz), 5.38 (dt, 1H, J = 3.5, 8.4 Hz), 5.25-5.15 (m, 1H), 5.04 (d, 1H, J = 8.3 Hz), 4.12 (br, 2H), 3.79 (dd, 1H, J = 2.7, 9.2 Hz), 3.63 (dd, 1H, J = 3.6, 9.2 Hz), 3.21-3.04 (m, 2H), 2.76 (t, 2H, J = 12.2 Hz), 2.32 (tt, 1H, J = 3.7, 11.5 Hz), 1.86-1.76 (m, 2H), 1.71-1.54 (m, 2H), 1.44 (s, 9H), 1.38 (s, 9H), 1.29 (s, 9H), 1.09 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.6, 165.4, 154.7, 154.6, 154.5, 130.0, 129.8, 124.2, 80.4, 79.6, 78.5, 73.9, 62.1, 48.3, 46.5, 43.0, 39.2, 28.8, 28.5, 28.4, 28.3, 28.2, 27.3

MS (ESI, m/z) calcd for $C_{36}H_{57}N_5NaO_8$ $(M+Na)^+$ 710.41, found 710

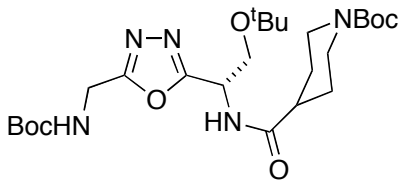


^{1}H NMR of **7n**



^{13}C NMR of **7n**

Preparation of Compound 7o



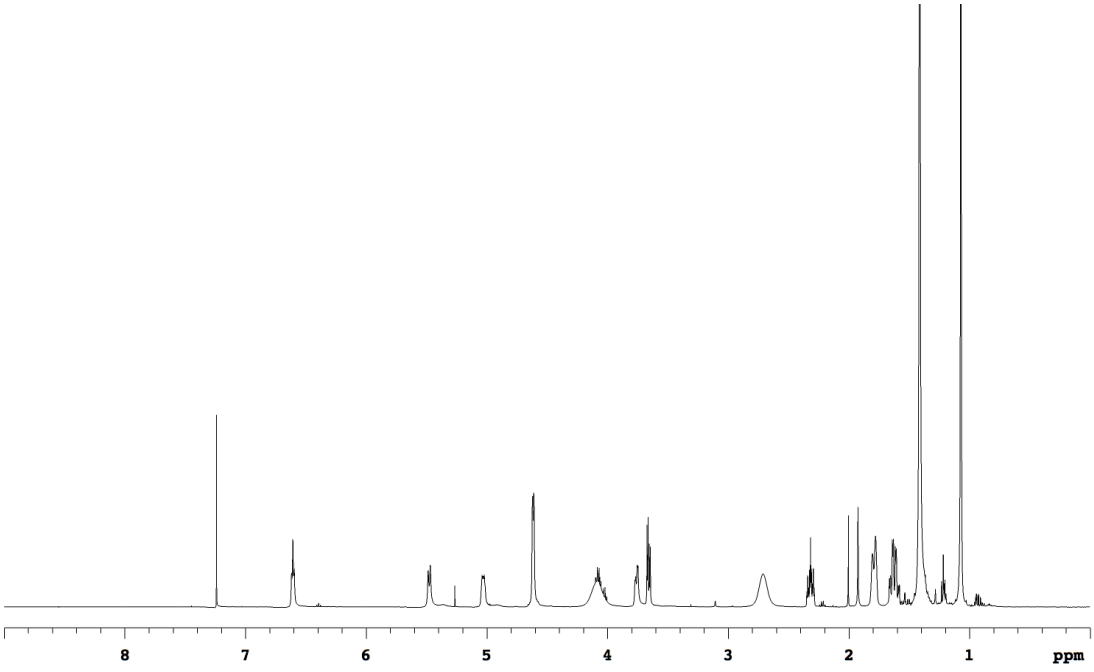
7o

Compound **7o** was prepared from (0.36 g, 0.8 mmol) of **6o**. Flash chromatography (3:7 to 7:3 EtOAc/Hexanes) afforded 0.31 g (74 %) **7o** as a white solid.

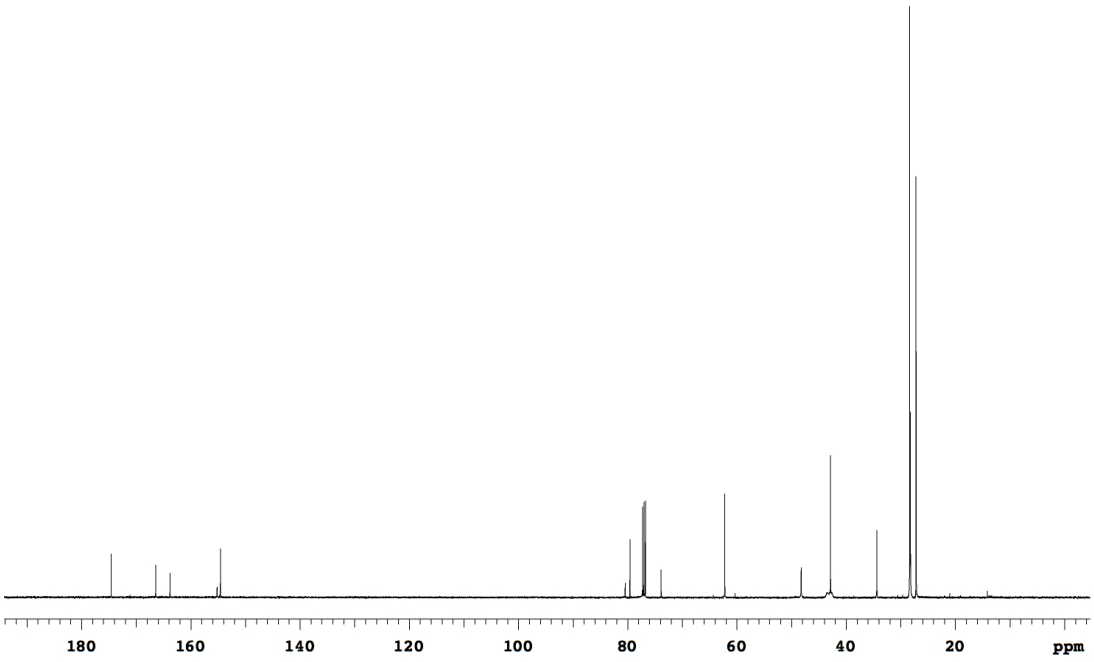
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (t, 1H, J = 5.4 Hz), 5.48 (d, 1H, J = 8.6 Hz), 5.07-4.99 (m, 1H), 4.62 (d, 2H, J = 5.4 Hz), 3.76 (dd, 1H, J = 3.2, 9.3 Hz), 3.66 (dd, 1H, J = 4.0, 9.3 Hz), 2.71 (br, 2H), 2.32 (tt, 1H, J = 3.7, 11.5 Hz), 1.84-1.74 (m, 2H), 1.69-1.57 (m, 2H), 1.41 (s, 18 H), 1.07 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 166.4, 163.8, 155.2, 154.6, 80.4, 79.6, 73.9, 62.2, 48.2, 42.8, 34.4, 28.4, 28.2, 27.2

MS (ESI, m/z) calcd for $C_{25}H_{43}N_5NaO_7$ $(M+Na)^+$ 548.31, found 548

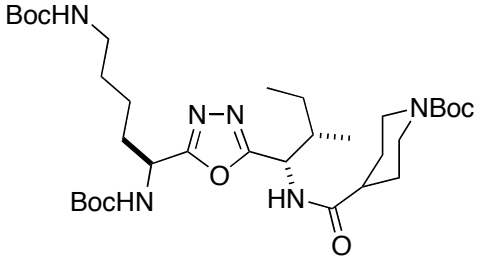


^{1}H NMR of **7o**



^{13}C NMR of **7o**

Preparation of Compound 7p



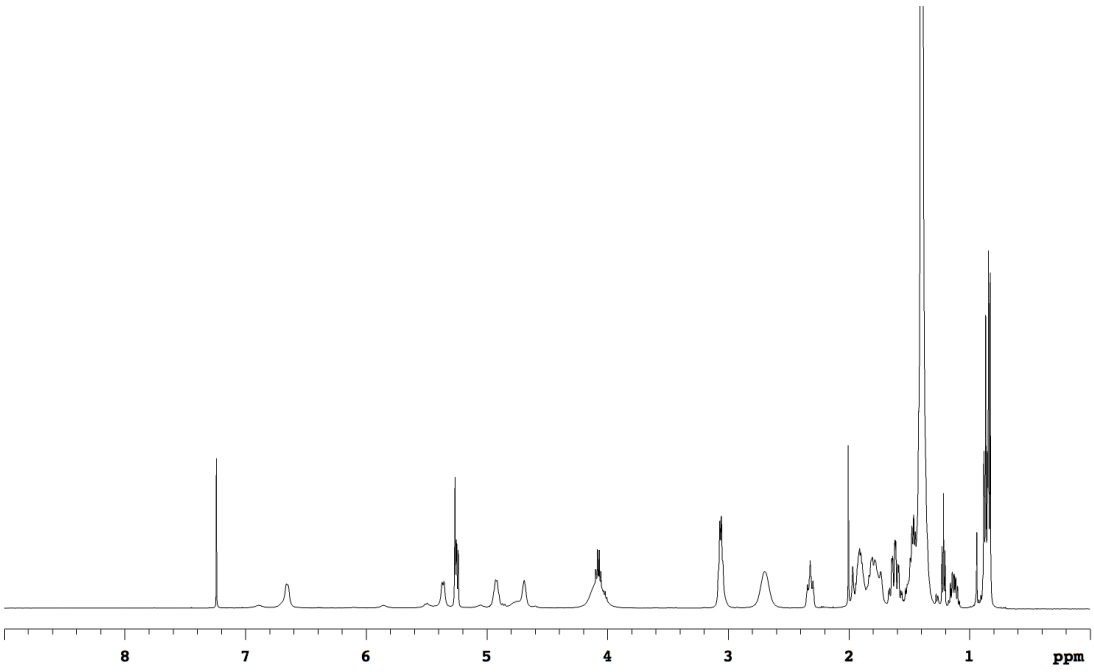
7p

Compound **7p** was prepared from (1.18 g, 1.9 mmol) of **6p**. Flash chromatography (3:7 to 7:3 EtOAc/Hexanes) afforded 1.16 g (92 %) **7p** as a white solid.

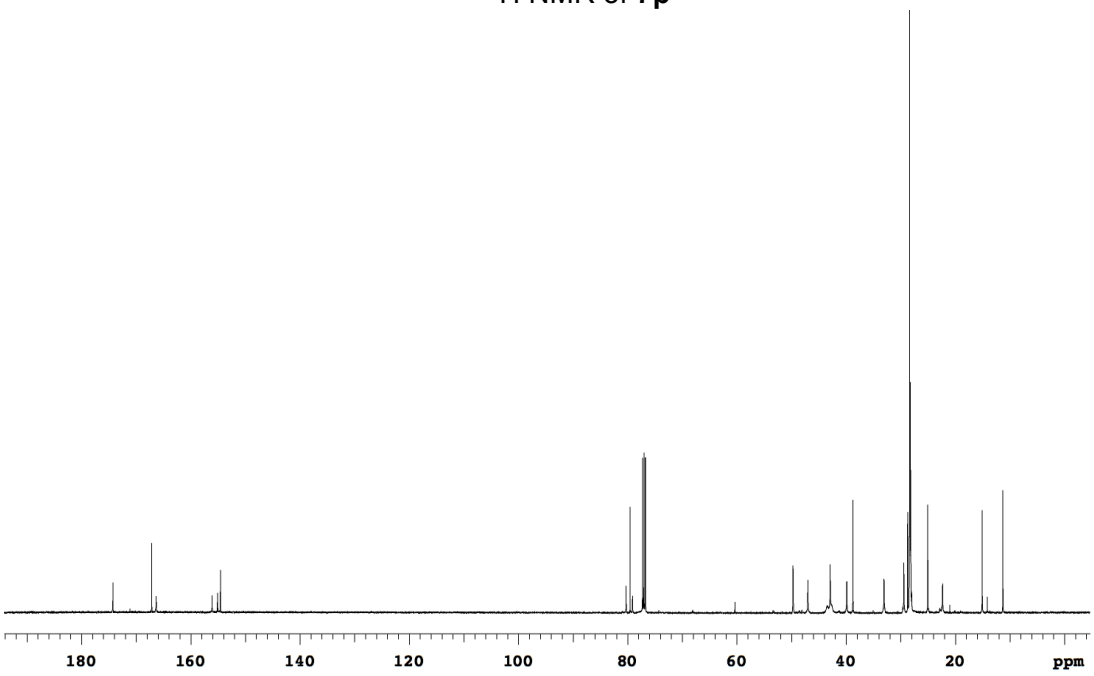
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, 1H, J = 7.2 Hz), 5.36 (d, 1H, J = 7.8 Hz), 5.30-5.21 (m, 1H), 4.93 (br, 1H), 4.69 (br, 1H), 4.08 (br, 2H), 3.13-2.99 (m, 2H), 2.70 (br, 2H), 2.32 (tt, 1H, J = 3.7, 11.5 Hz), 1.99-1.70 (m, 5H), 1.69-1.55 (m, 2H), 1.54-1.29 (m, 32 H), 1.19-1.07 (m, 1H), 0.91-0.80 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 167.2, 166.3, 156.1, 155.1, 154.6, 80.3, 79.6, 79.1, 49.7, 47.0, 42.9, 39.9, 38.7, 33.1, 29.4, 28.7, 28.4, 28.3, 28.2, 28.1, 25.0, 22.3, 15.1, 11.3

MS (ESI, m/z) calcd for $C_{33}H_{58}N_6NaO_8$ $(M+Na)^+$ 689.42, found 689

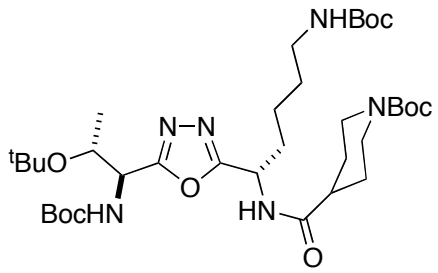


^{1}H NMR of **7p**



^{13}C NMR of **7p**

Preparation of Compound 7q



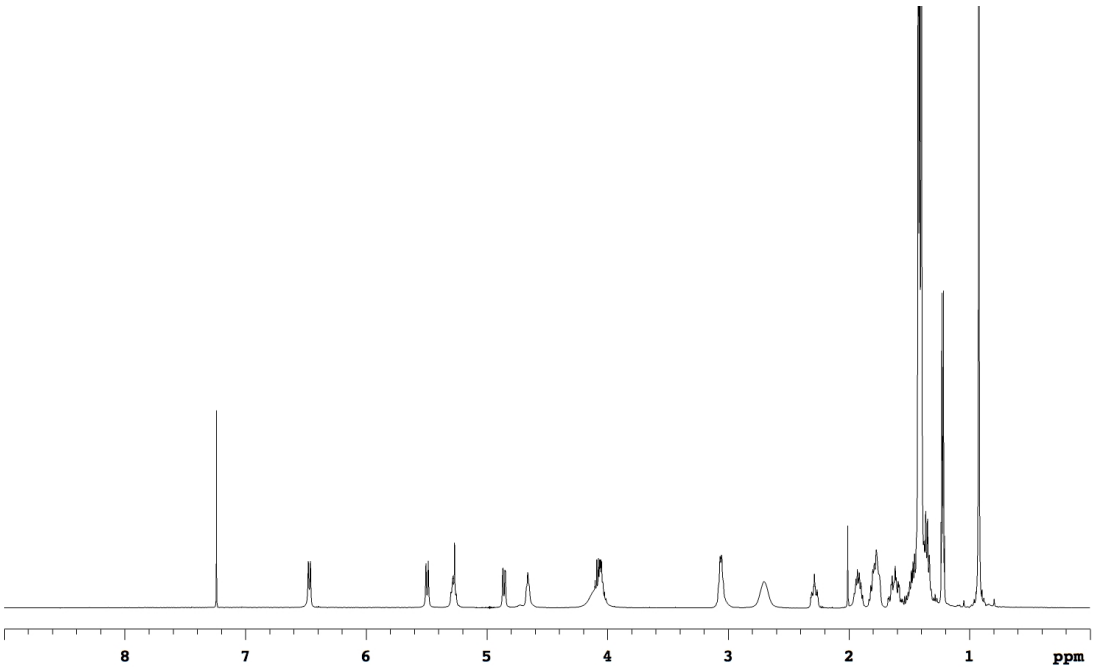
7q

Compound **7q** was prepared from (1.70 g, 2.7 mmol) of **6q**. Flash chromatography (3:7 to 7:3 EtOAc/Hexanes) afforded 1.35 g (70 %) **7q** as a white solid.

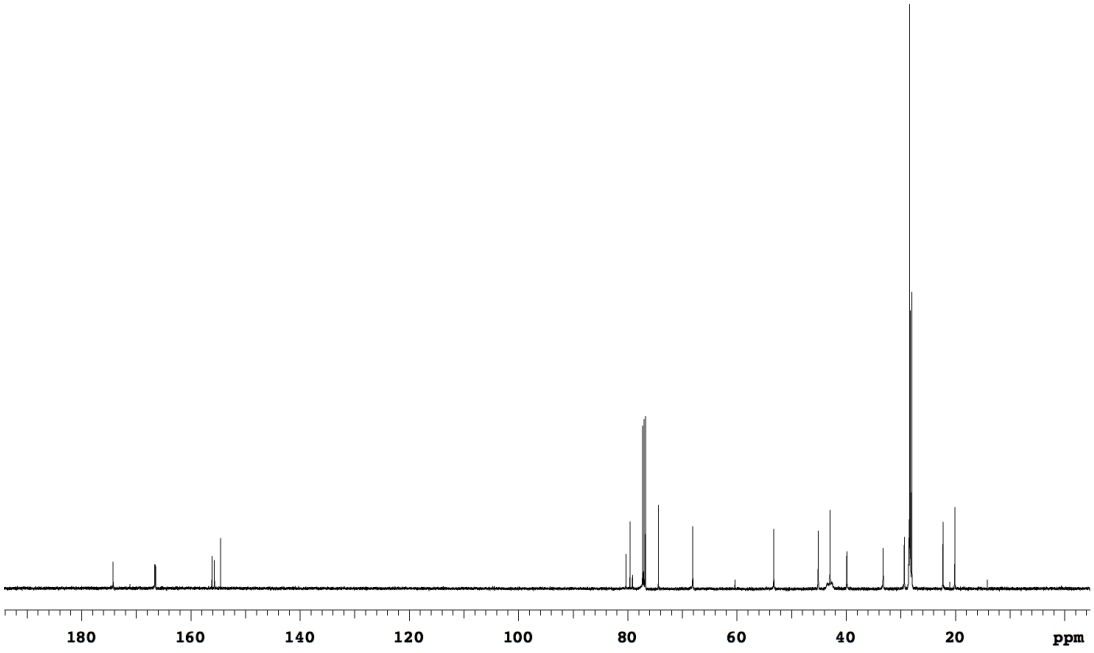
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, 1H, J = 8.5 Hz), 5.49 (d, 1H, J = 9.5 Hz), 5.33-5.22 (m, 1H), 4.86 (dd, 1H, J = 1.7, 9.5 Hz), 4.70-4.60 (m, 1H), 4.22-3.96 (m, 3H), 3.13-2.98 (m, 2H), 2.70 (br, 2H), 2.29 (tt, 1H, J = 3.7, 11.5 Hz), 1.98-1.86 (m, 2H), 1.85-1.71 (m, 2H), 1.69-1.55 (m, 2 H), 1.54-1.21 (m, 31H), 1.22 (d, 3H, J = 6.2 Hz), 0.92 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.6, 166.5, 156.1, 155.7, 154.6, 80.3, 79.6, 79.1, 74.4, 68.1, 53.3, 45.1, 42.9, 39.9, 33.2, 29.3, 28.7, 28.5, 28.4, 28.4, 28.3, 28.0, 22.3, 20.1

MS (ESI, m/z) calcd for $C_{35}H_{62}N_6NaO_9$ $(M+Na)^+$ 733.45, found 733

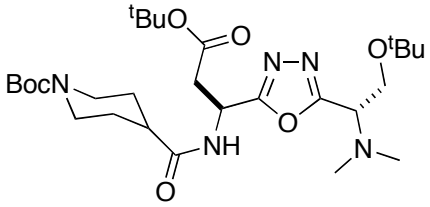


^{1}H NMR of **7q**



^{13}C NMR of **7q**

Preparation of Compound 7r



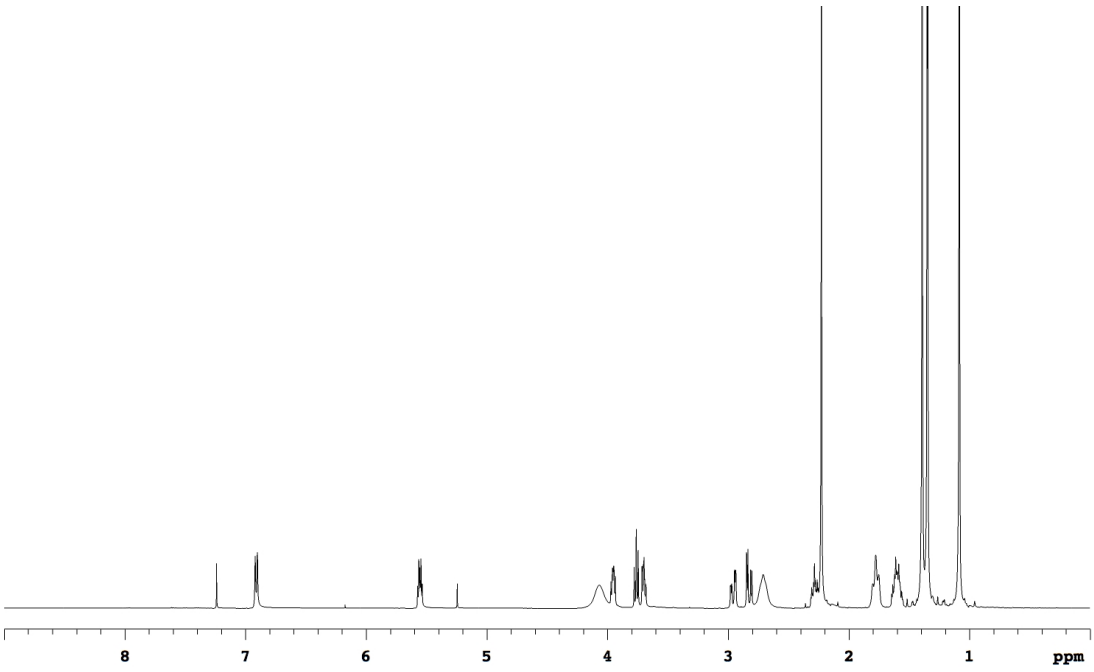
7r

Compound **7r** was prepared from (0.93 g, 2.6 mmol) of **6r**. Flash chromatography (1:19 MeOH/CH_2Cl_2) afforded 1.21 g (82 %) **7r** as a white solid.

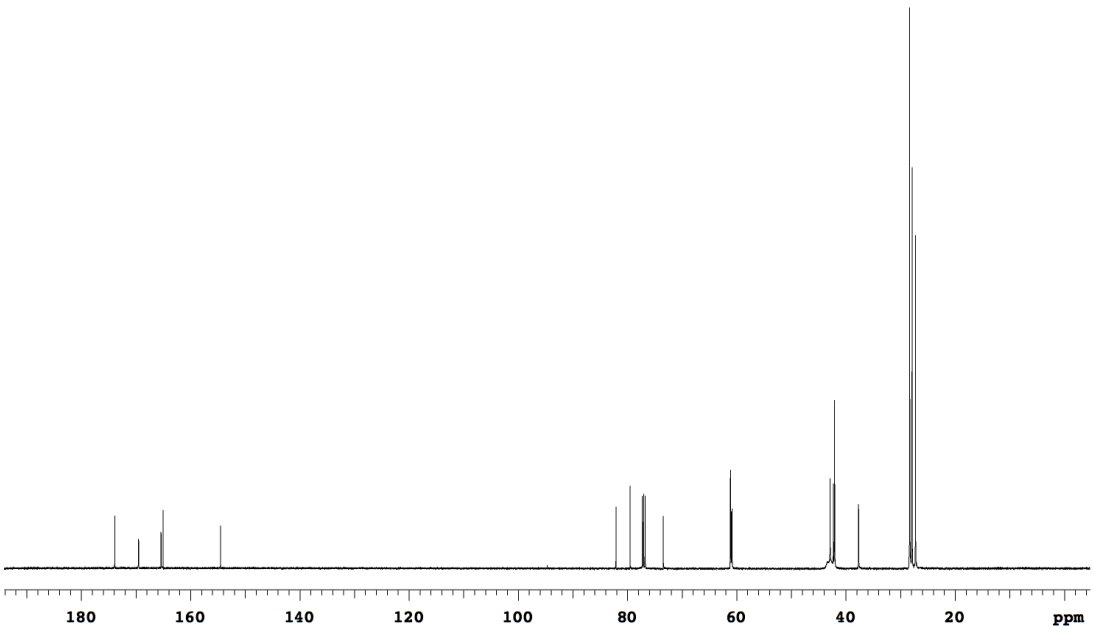
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, 1H, J = 8.8 Hz), 5.55 (dt, 1H, J = 5.0, 8.8 Hz), 4.16-3.92 (m, 3H), 3.80-3.66 (m, 2H), 2.96 (ddd, 1H, J = 1.5, 4.7, 16.6 Hz), 2.83 (dd, 1H, J = 5.1, 16.6 Hz), 2.71 (br, 2H), 2.28 (tt, 1H, J = 3.7, 11.5 Hz), 2.23 (s, 6H), 1.84-1.72 (m, 2H), 1.66-1.54 (m, 2H), 1.45-1.28 (m, 18H), 1.09 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 169.6, 165.4, 165.0, 154.5, 82.1, 79.5, 73.4, 61.2, 61.0, 60.8, 42.9, 42.3, 42.3, 42.1, 37.7, 28.3, 27.9, 27.2

MS (ESI, m/z) calcd for $C_{28}H_{50}N_5O_7$ $(M+H)^+$ 568.73, found 568

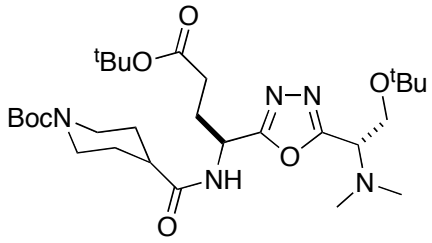


^{1}H NMR of **7r**



^{13}C NMR of **7r**

Preparation of Compound 7s



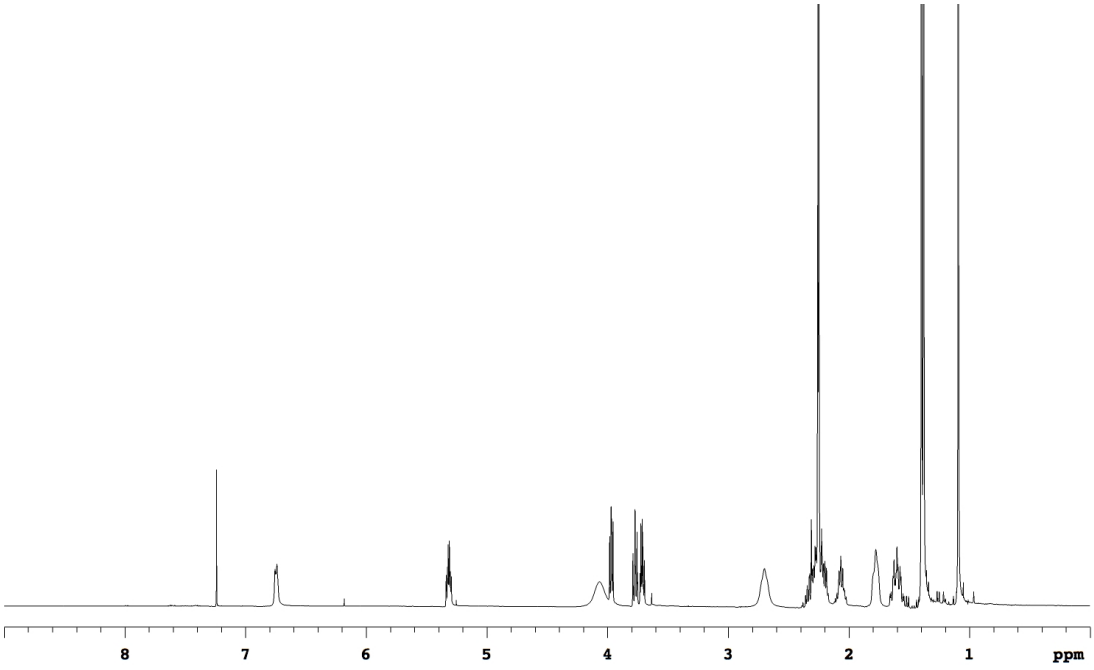
7s

Compound **7s** was prepared from (0.44 g, 1.2 mmol) of **6s**. Flash chromatography (1:19 to 1:9 MeOH/CH_2Cl_2) afforded 0.62 g (89 %) **7s** as a white solid.

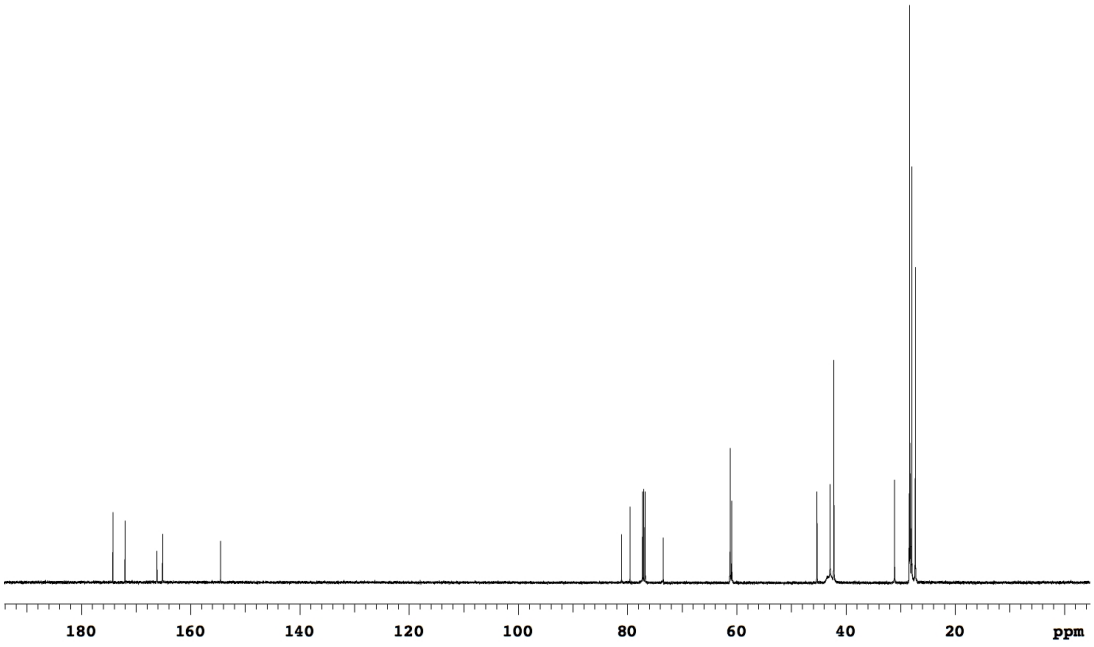
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (br, 1H), 5.32 (dt, 1H, J = 4.9, 8.2 Hz), 4.20-3.90 (m, 3H), 3.82-3.67 (m, 2H), 2.70 (br, 2H), 2.37-2.15 (m, 10H), 2.13-2.01 (m, 1H), 1.78 (br, 2H), 1.67-1.54 (m, 2H), 1.42-1.35 (m, 18H), 1.09 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 172.0, 166.2, 165.1, 154.5, 81.1, 79.5, 73.4, 61.2, 60.9, 45.3, 42.9, 42.2, 42.2, 31.1, 28.4, 28.3, 28.2, 28.0, 27.3

MS (ESI, m/z) calcd for $C_{29}H_{52}N_5O_7$ $(M+H)^+$ 582.39, found 582

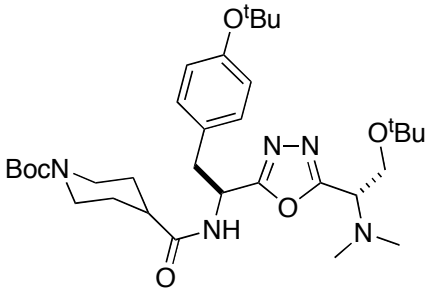


^{1}H NMR of **7s**



^{13}C NMR of **7s**

Preparation of Compound 7t



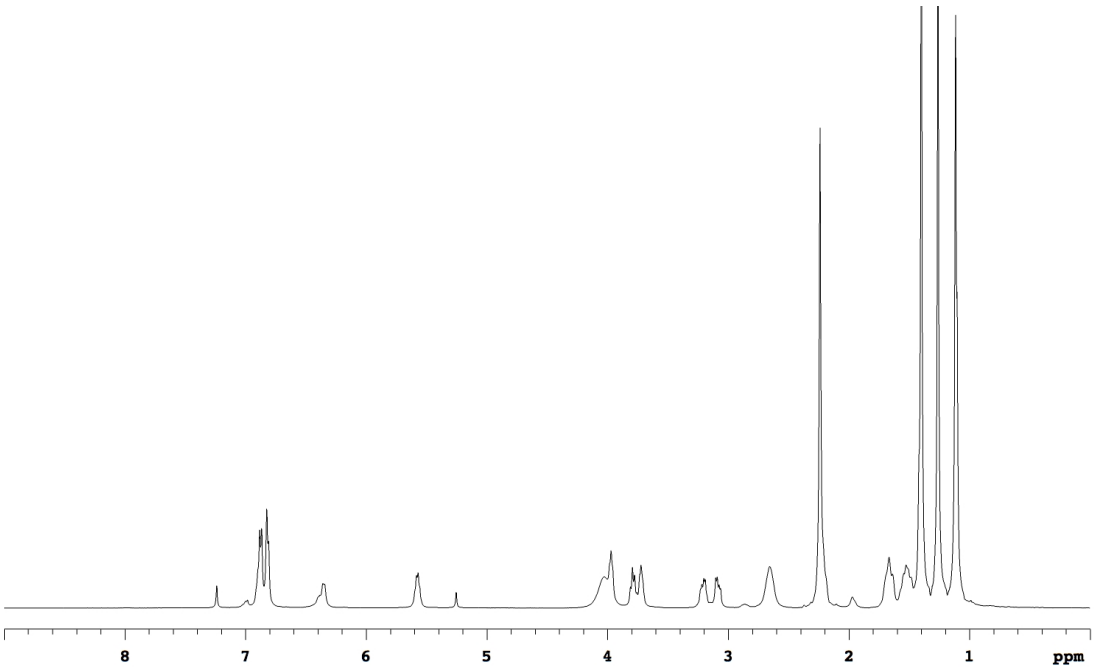
7t

Compound **7t** was prepared from (1.54 g, 3.8 mmol) of **6t**. Flash chromatography (2:98 to 3:97 MeOH/CH_2Cl_2) afforded 1.65 g (71 %) **7t** as a white solid.

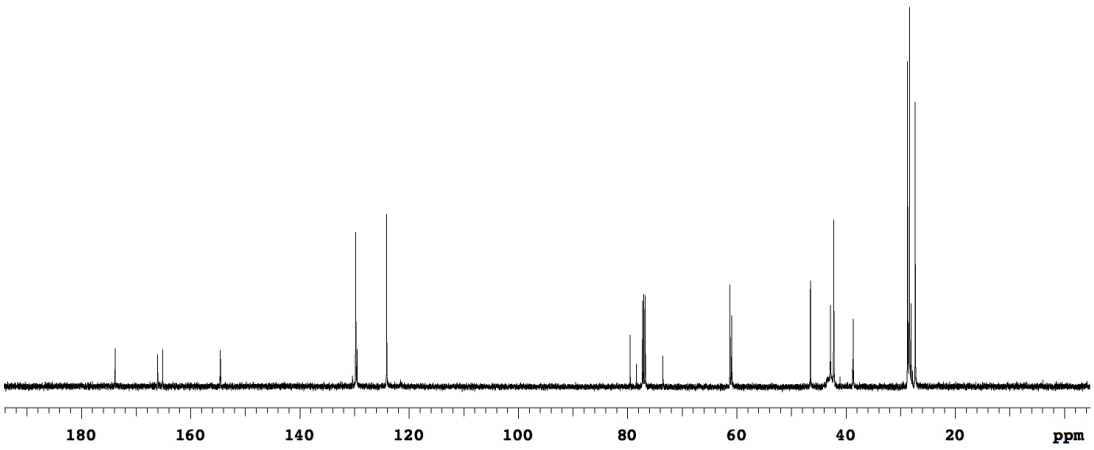
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96-6.75 (m, 4H), 6.36 (rb, 1H), 5.65-5.51 (m, 1H), 4.20-3.88 (m, 3H), 3.86-3.66 (m, 2H), 3.21 (dd, 1H, J = 5.8, 13.6 Hz), 3.08 (dd, 1H, J = 5.7, 13.6 Hz), 2.66 (br, 2H), 2.30-2.16 (m, 7H), 1.75-1.61 (m, 2H), 1.60-1.46 (m, 2H), 1.40 (s, 9H), 1.26 (s, 9H), 1.12 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 166.0, 165.1, 154.6, 154.5, 129.8, 129.5, 124.1, 79.5, 78.4, 73.5, 61.2, 61.0, 60.9, 46.5, 42.8, 42.2, 38.7, 38.6, 28.7, 28.3, 27.3

MS (ESI, m/z) calcd for $C_{33}H_{54}N_5O_6$ $(M+H)^+$ 616.41, found 616



^{1}H NMR of **7t**

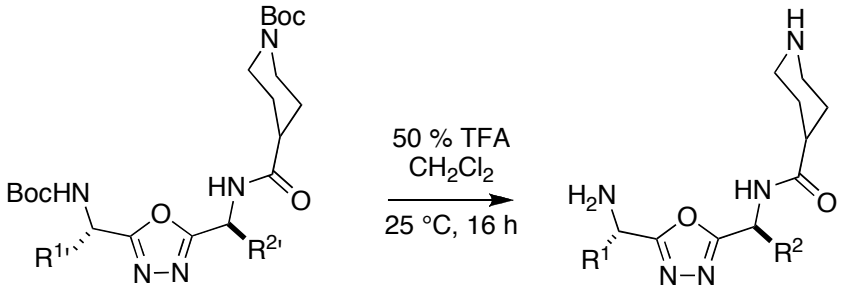


^{13}C NMR of **7t**

General Procedure for Compounds 1a-f

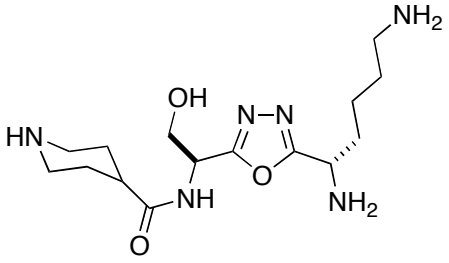
The compound **1a-f** was treated with 50% TFA/CH_2Cl_2 at 25 ^{o}C for 16 h. Evaporating solvent under nitrogen afforded the desired product **1a-f**.

Scheme S4. Synthesis of monovalent compounds **1a-f**.



7a-f **1a-f**

Preparation of Compound 1a



1a

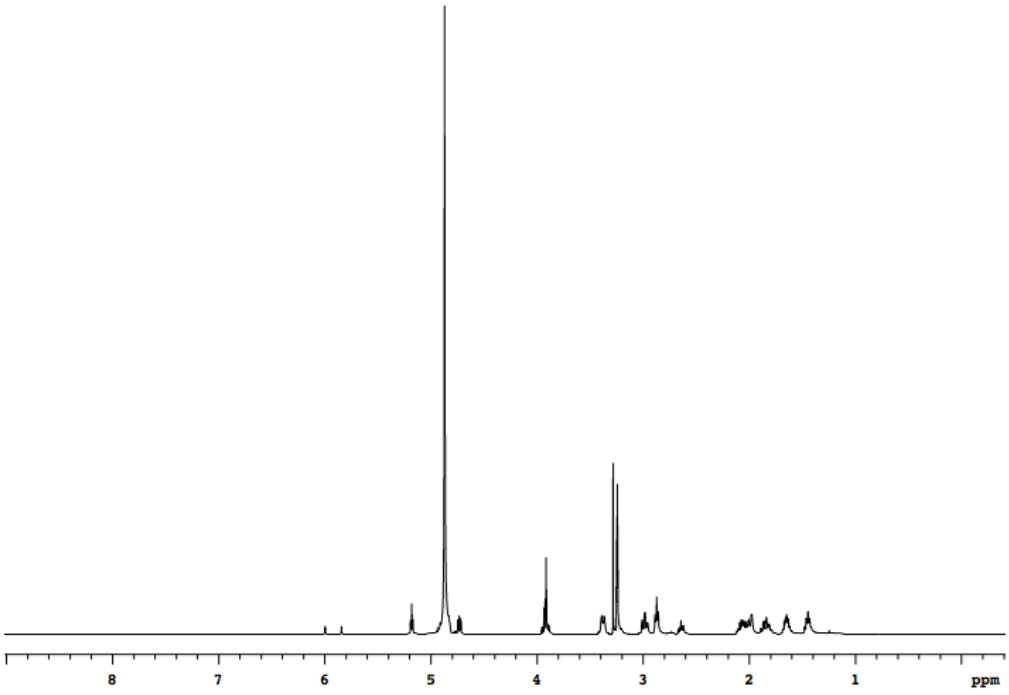
Compound **1a** was prepared from **7a** (32.30 mg, 0.046 mmol). **1a** was obtained as a colorless amorphous solid (quant., 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 5.18 (dd, 1H, J = 5.5, 5.5 Hz), 4.73 (dd, 1H, J = 6.0, 8.0 Hz), 3.94 (dd, 1H, J = 5.0, 11.0 Hz), 3.90 (dd, 1H, J = 2.5, 8.0 Hz), 3.39-3.36 (m, 2H), 2.98 (t, 2H, J = 12.0 Hz), 2.87 (t, 2H, J = 8.0 Hz), 2.64 (tt, 1H, J = 4.0, 11.0 Hz), 2.12-2.03 (m, 2H), 2.02-1.97 (m, 2H), 1.89-1.78 (m, 2H), 1.69-1.61 (m, 2H), 1.49-1.42 (m, 2H)

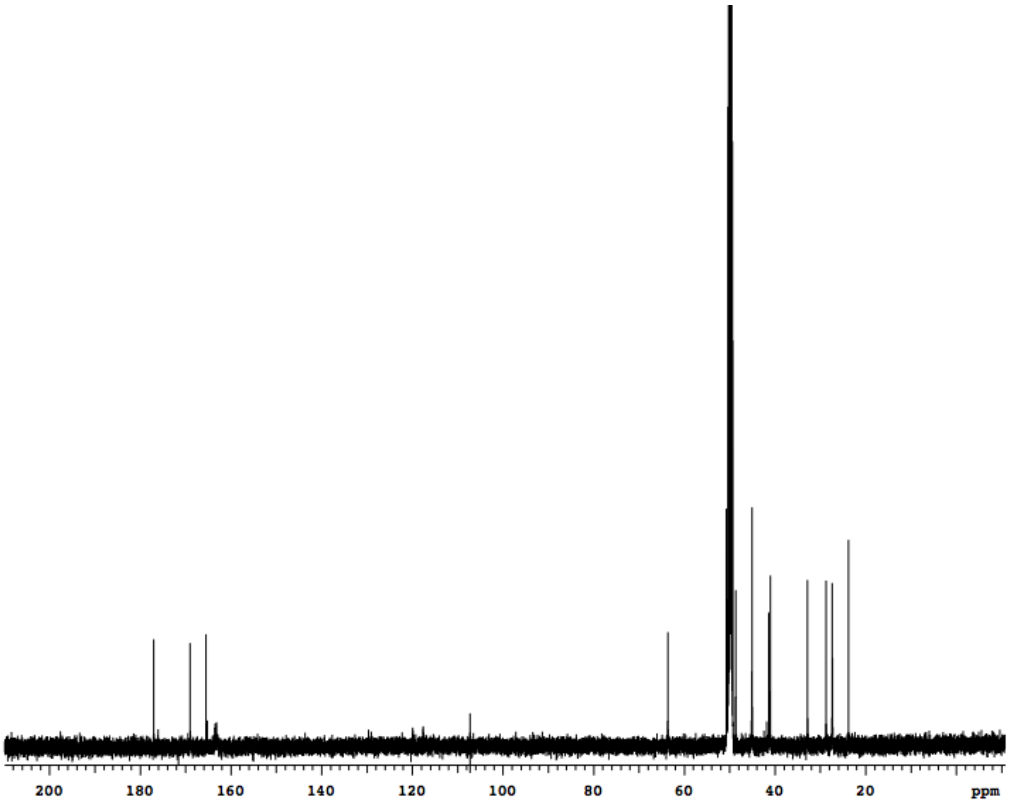
^{13}C NMR (125 MHz, CD_3OD) δ 177.02, 168.99, 165.50, 63.63, 50.71, 50.57, 48.64, 45.06, 41.34, 41.03, 32.83, 28.72, 27.39, 27.36, 23.79 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{15}H_{29}N_6O_3$ $(M+H)^+$ 341.43, found 341.22

optical rotation $[\alpha]_D^{19.8}$ = -12.6 (*c* = 3.79 in MeOH)

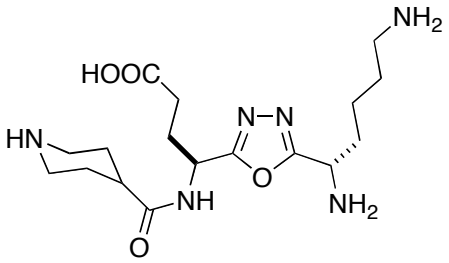


^{1}H NMR of **1a**



^{13}C NMR of **1a**

Preparation of Compound 1b



1b

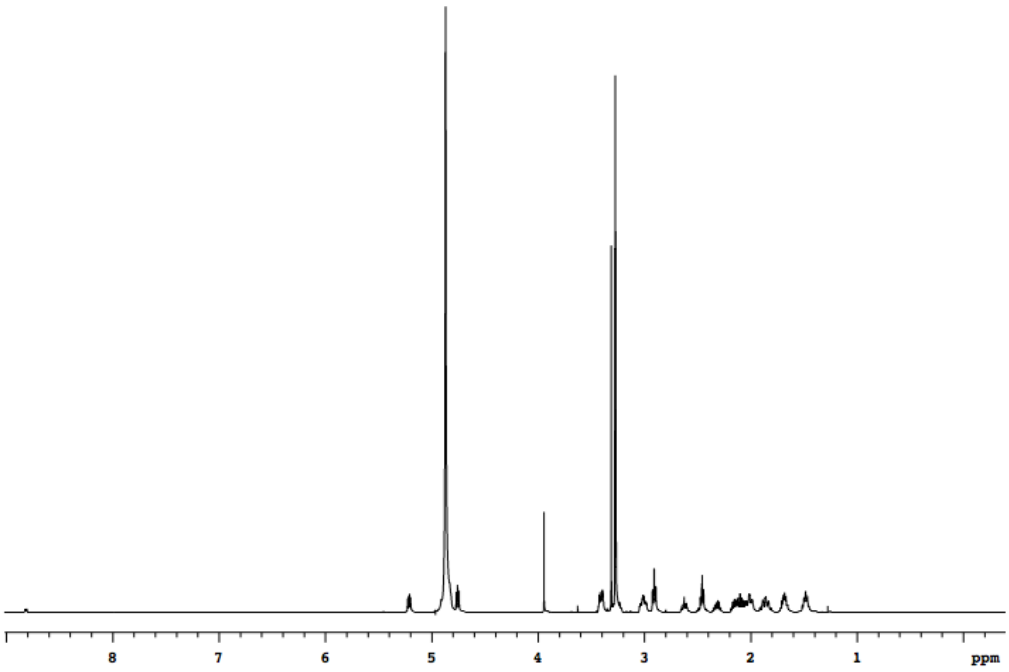
Compound **1b** was prepared from **7b** (30.40 mg, 0.041 mmol). **1b** was obtained as a colorless amorphous solid (quant., 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 5.22 (dd, 1H, J = 5.5, 9.0 Hz), 4.76 (dd, 1H, J = 6.0, 8.0 Hz), 3.43-3.39 (m, 2H), 3.05-2.98 (m, 2H), 2.91 (t, 2H, J = 7.5 Hz), 2.63 (tt, 1H, J = 4.0, 11.0 Hz), 2.46 (t, 2H, J = 7.0 Hz), 2.35-2.28 (m, 1H), 2.19-2.12 (m, 1H), 2.11-2.06 (m, 2H), 2.04-1.99 (m, 2H), 1.95-1.81 (m, 2H), 1.72-1.64 (m, 2H), 1.52-1.45 (m, 2H)

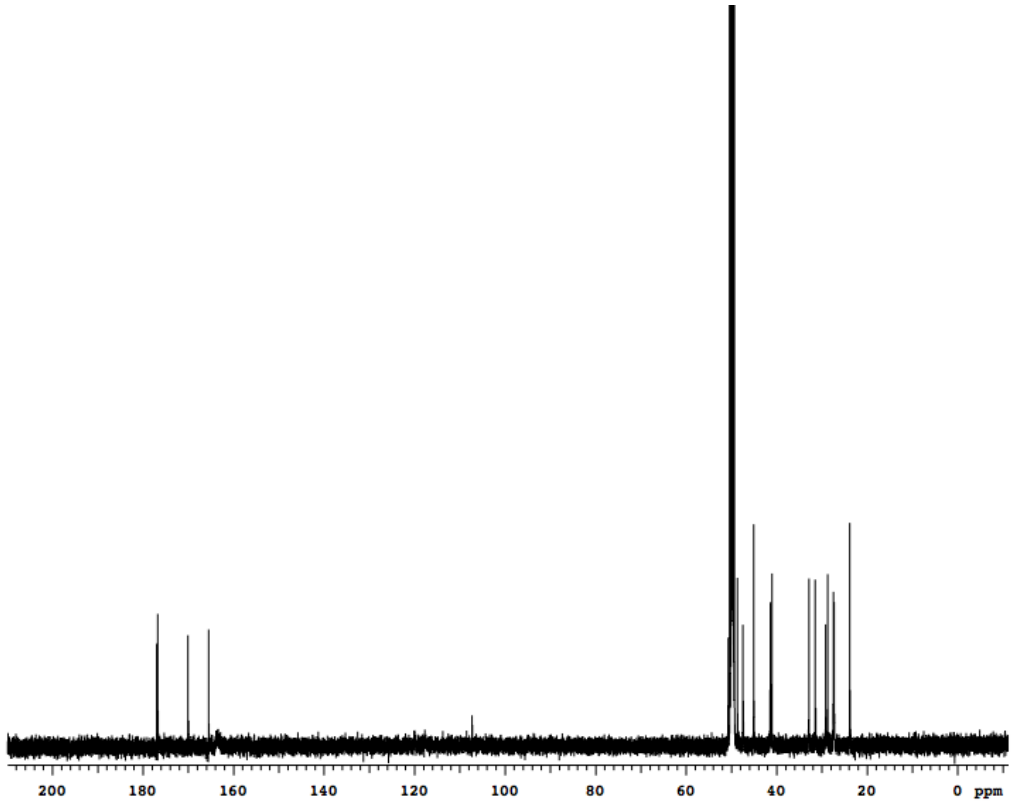
^{13}C NMR (125 MHz, CD_3OD) δ 176.96, 176.70, 170.06, 165.46, 50.71, 48.64, 47.42, 45.04, 41.41, 41.03, 32.84, 31.47, 29.16, 28.72, 27.45, 27.27, 23.81 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{17}H_{31}N_6O_4$ $(M+H)^+$ 383.24, found 383.23

optical rotation $[\alpha]_D^{19.8}$ = -16.6 (*c* = 3.46 in MeOH)

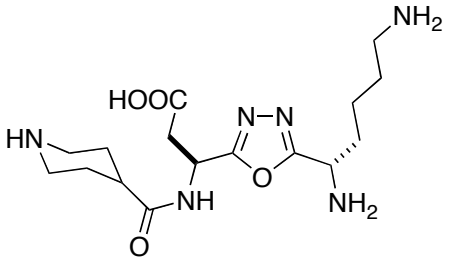


^{1}H NMR of **1b**



^{13}C NMR of **1b**

Preparation of Compound 1c



1c

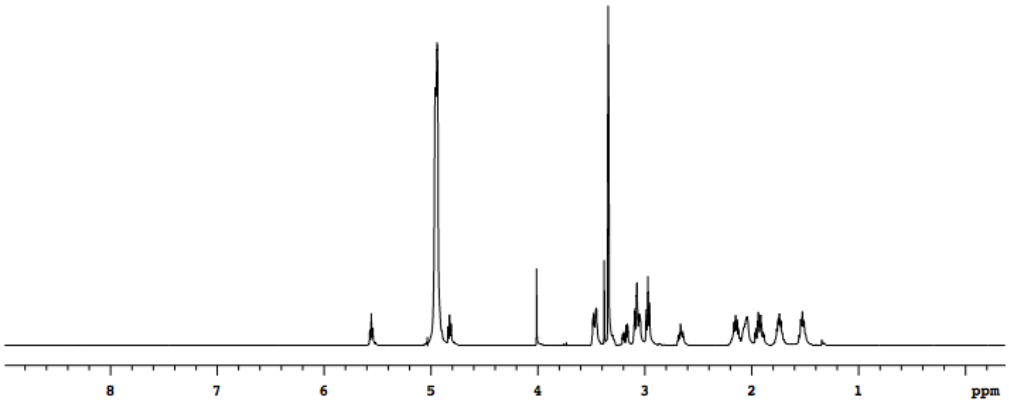
Compound **1c** was prepared from **7c** (30.70 mg, 0.042 mmol). **1c** was obtained as a colorless amorphous solid (quant., 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 5.56 (dd, 1H, J = 6.0, 6.0 Hz), 4.83 (dd, 1H, J = 7.5, 7.5 Hz), 3.48-3.45 (m, 2H), 3.18 (ddd, 1H, J = 3.0, 6.5, 17.5 Hz), 3.10-3.07 (m, 2H), 3.05-3.04 (m, 1H), 2.97 (t, 7.5 Hz), 2.66 (tt, 1H, J = 4.0, 11.5 Hz), 2.19-2.11 (m, 2H), 2.08-2.04 (m, 2H), 1.97-1.88 (m, 2H), 1.78-1.70 (m, 2H), 1.56-1.51 (m, 2H)

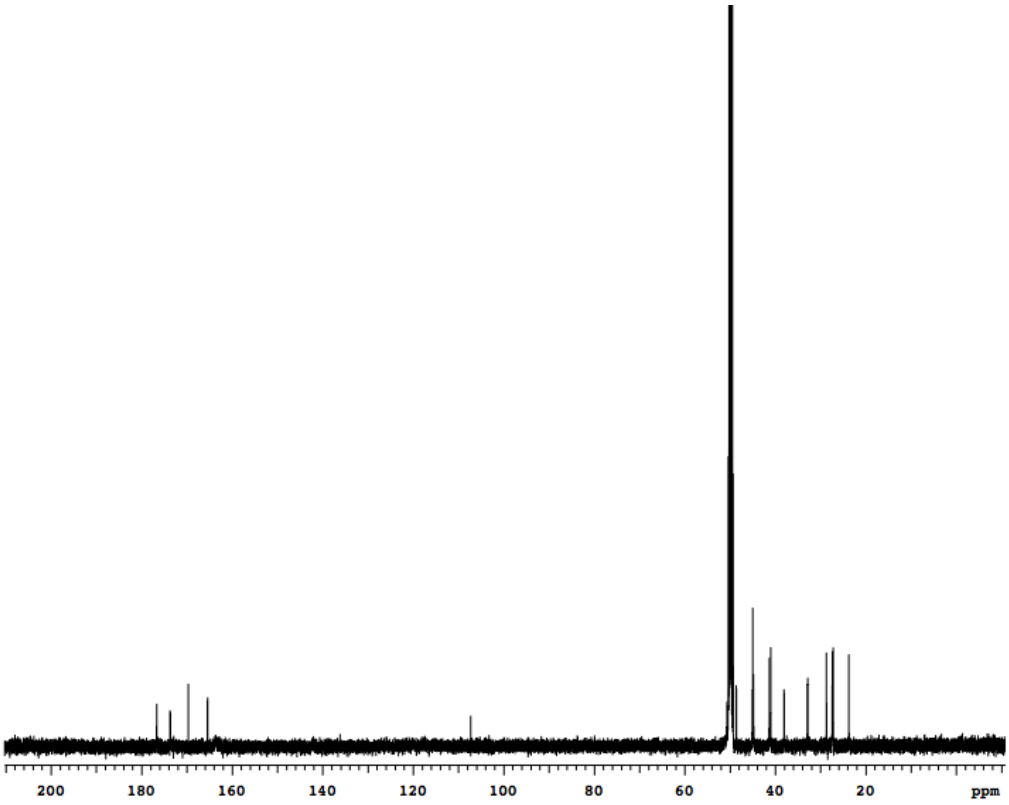
^{13}C NMR (125 MHz, CD_3OD) δ 176.69, 173.71, 169.69, 165.45, 50.71, 48.63, 48.60, 45.00, 41.29, 41.03, 38.02, 32.87, 28.68, 27.39, 27.21, 23.74 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{16}H_{29}N_6O_4$ $(M+H)^+$ 369.22, found 369.22

optical rotation $[\alpha]_D^{20.0}$ = 0.4 (*c* = 3.60 in MeOH)

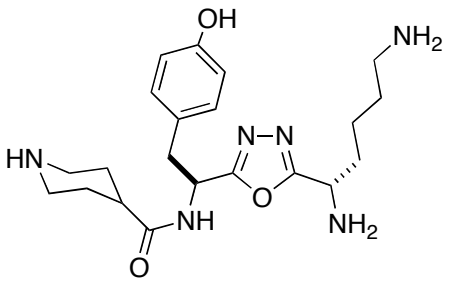


^{1}H NMR of **1c**



^{13}C NMR of **7c**

Preparation of Compound 1d



1d

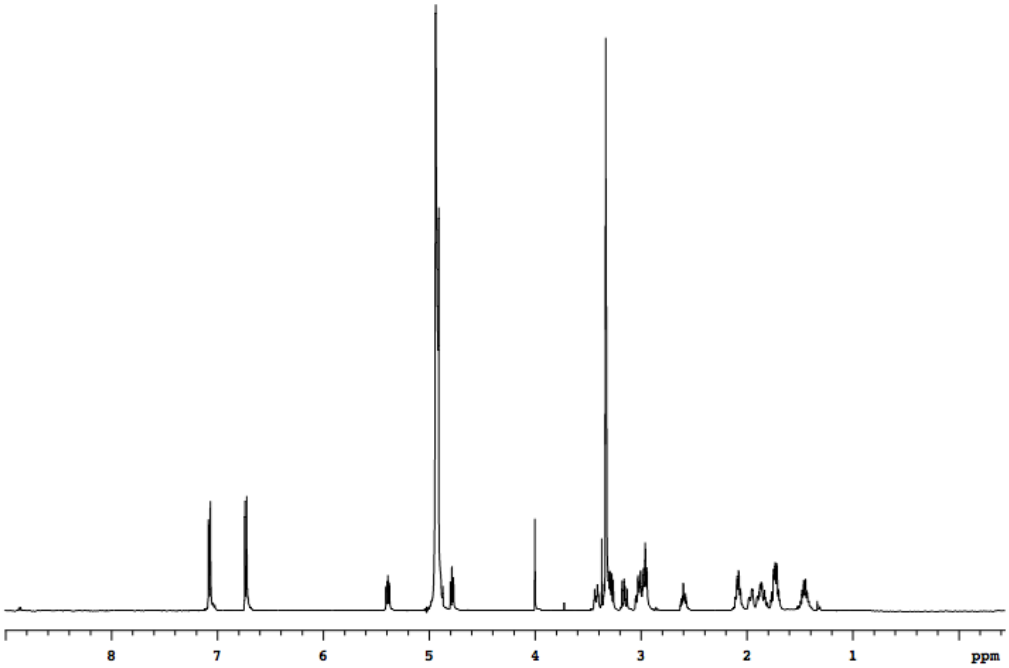
Compound **1d** was prepared from **7d** (36.50 mg, 0.047 mmol). **1d** was obtained as a yellowish amorphous solid (quant., 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 7.08 (d, 2H, J = 8.5 Hz), 6.74 (d, 2H, J = 8.5 Hz), 5.40 (dd, 1H, J = 7.0, 9.5 Hz), 4.79 (dd, 1H, J = 7.5 Hz), 3.43 (ddd, 1H, J = 3.5, 13.0 Hz), 3.36-3.34 (m, 1H), 3.29 (dt, 1H, J = 6.5, 6.5 Hz), 3.16 (dt, 1H, J = 9.5, 9.5 Hz), 3.06-2.99 (m, 2H), 2.97 (t, 2H, J = 7.5 Hz), 2.61 (tt, 1H, J = 3.5, 10.5 Hz), 2.12-2.05 (m, 2H), 1.99-1.96 (m, 1H), 1.91-1.81 (m, 2H), 1.78-1.70 (m, 3H), 1.50-1.42 (m, 2H)

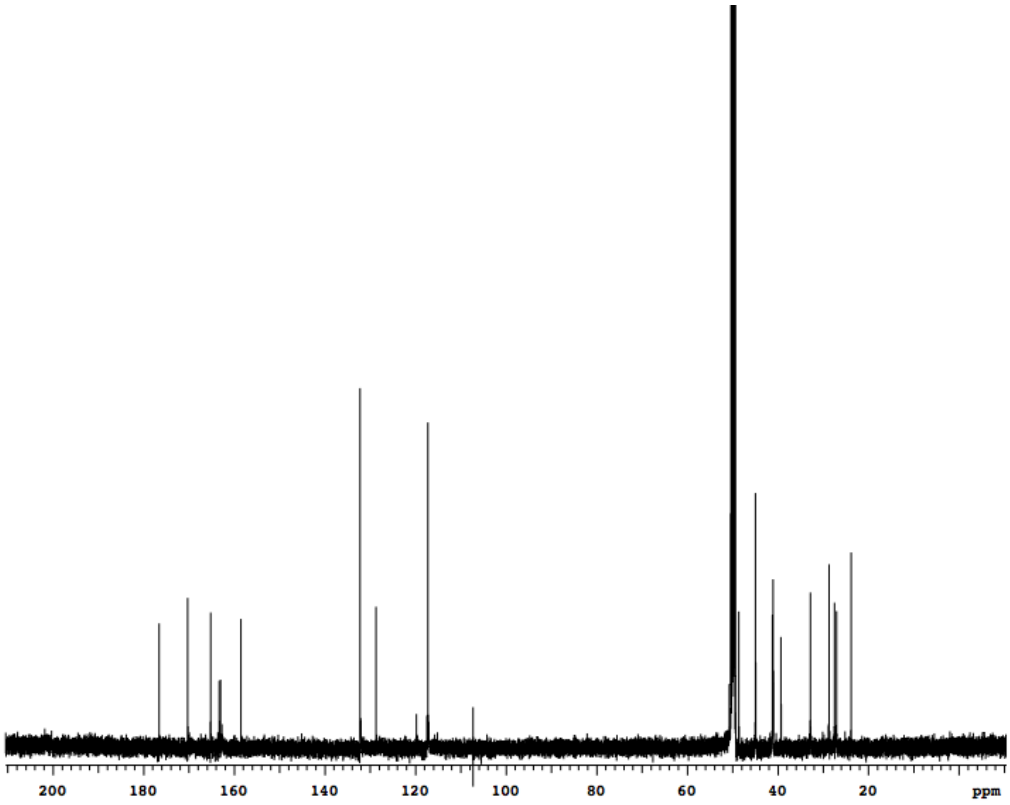
^{13}C NMR (125 MHz, CD_3OD) δ 174.33, 168.01, 162.96, 156.28, 129.97, 126.45, 114.98, 50.71, 50.05, 46.33, 42.66, 38.90, 38.75, 37.04, 30.55, 26.43, 25.23, 24.76, 21.54 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{21}H_{33}N_6O_3$ $(M+H)^+$ 417.52, found 417.25

optical rotation $[\alpha]_D^{19.4}$ = -7.9 (*c* = 4.16 in MeOH)

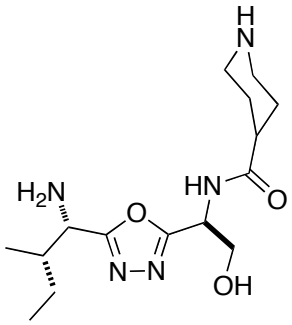


^{1}H NMR of **1d**



^{13}C NMR of **1d**

Preparation of Compound 1e



1e

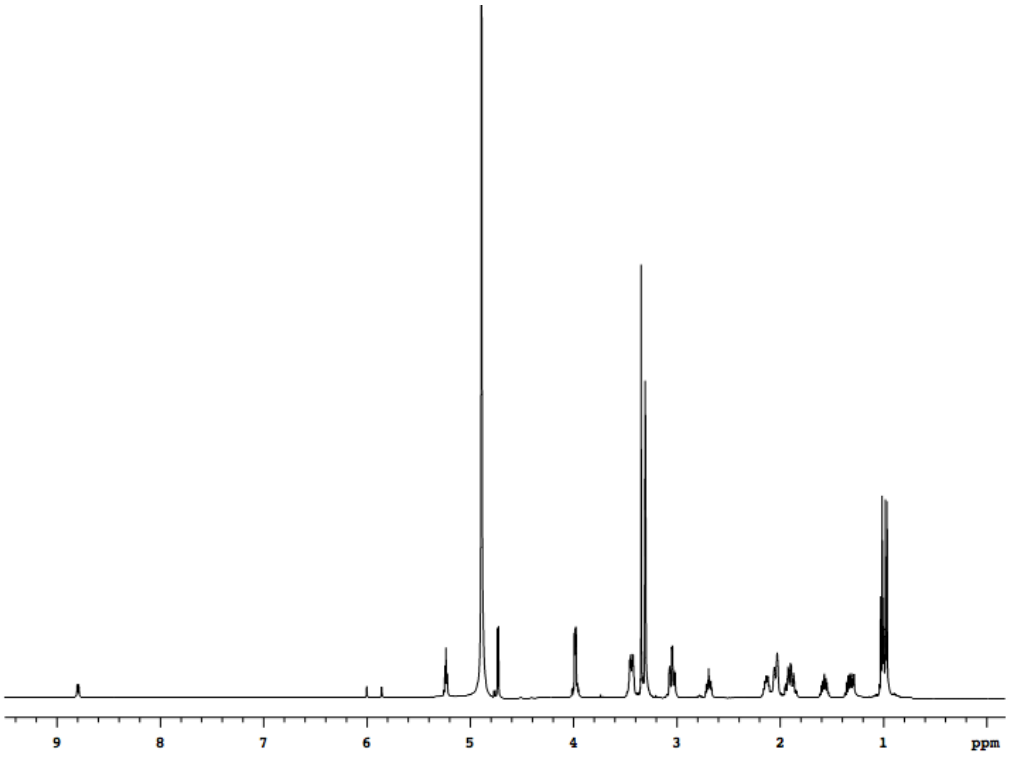
Compound **1e** was prepared from **7e** (30.00 mg, 0.052 mmol). **1e** was obtained as a colorless amorphous solid (quant., 2TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 5.27 (dd, 1H, J = 5.5, 5.5 Hz), 4.76 (d, 1H, J = 55.0 Hz), 4.02-3.97 (m, 2H), 3.49-3.46 (m, 2H), 3.38 (s, 3H), 3.08 (td, 2H, J = 3.0, 7.5 Hz), 2.73 (tt, 1H, J = 4.0, 10.5 Hz), 2.19-2.13 (m, 1H), 2.09-2.06 (m, 2H), 1.99-1.87 (m, 2H), 1.63-1.57 (m, 1H), 1.41-1.32 (m, 1H), 1.05 (t, 3H, J = 7.5 Hz), 1.01 (d, 3H, J = 7.0 Hz)

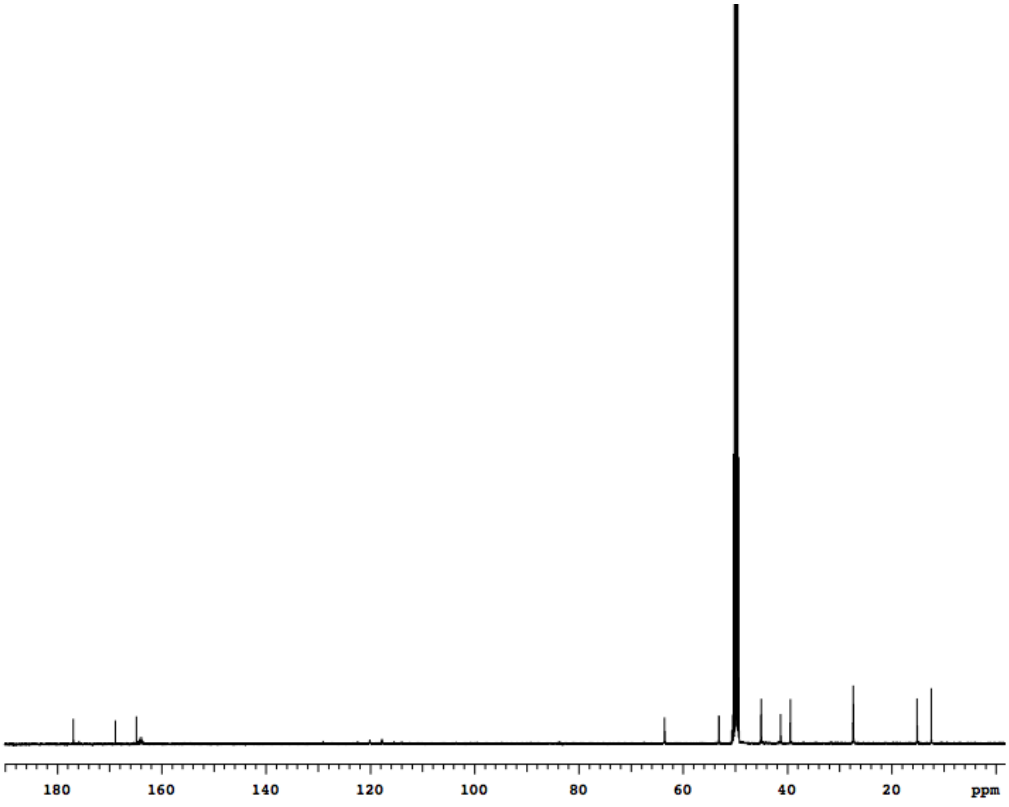
^{13}C NMR (125 MHz, CD_3OD) δ 176.95, 168.92, 164.85, 63.56, 53.14, 50.50, 45.06, 45.05, 41.30, 39.46, 27.42, 27.40, 27.36, 15.13, 12.42

MS (ESI, m/z) calcd for $C_{15}H_{28}N_5O_3$ $(M+H)^+$ 326.22, found 326.30

optical rotation $[\alpha]_D^{20.7}$ = -23.7 (*c* = 1.205 in MeOH)

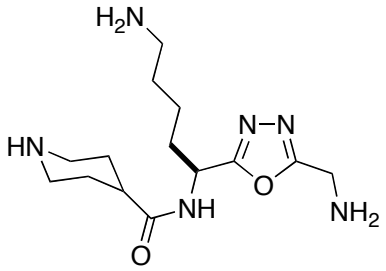


^{1}H NMR of **1e**



^{13}C NMR of **1e**

Preparation of Compound 1f



1f

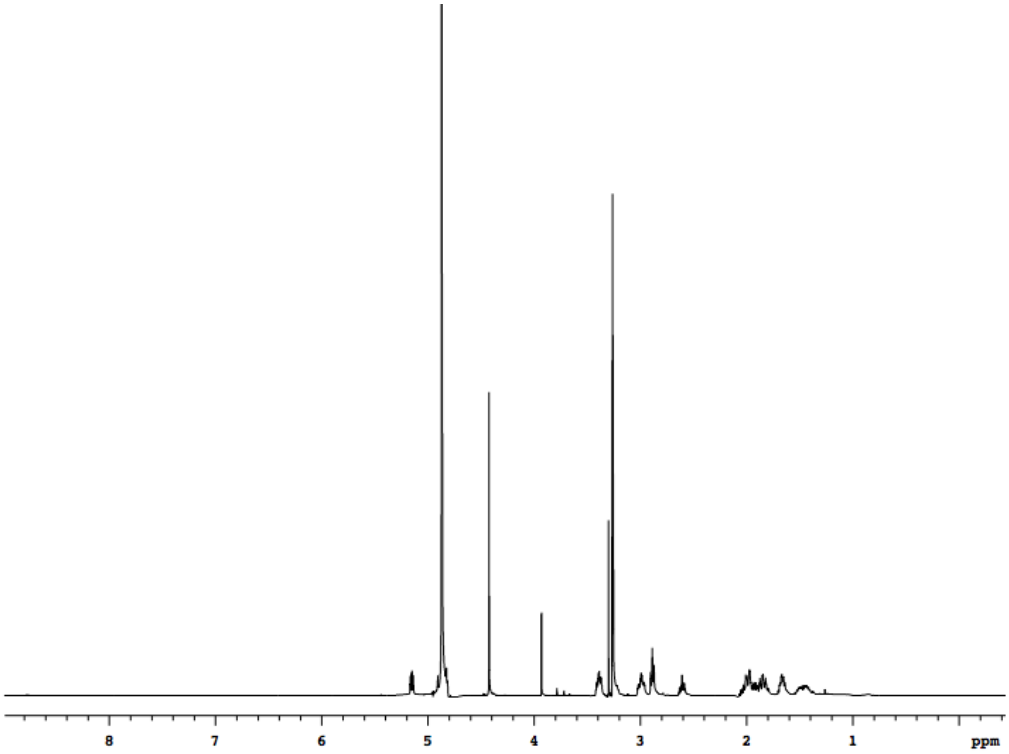
Compound **1f** was prepared from **7f** (29.90 mg, 0.049 mmol). **1f** was obtained as a yellowish amorphous solid (quant., 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 5.23 (dd, 1H, J = 5.5, 9.0 Hz), 4.50 (s, 2H), 3.50-3.38 (m, 2H), 3.11-3.04 (m, 2H), 2.97 (t, 2H, J = 7.5 Hz), 2.69 (tt, 1H, J = 4.0, 11.0 Hz), 2.15-2.10 (m, 1H), 2.09-2.04 (m, 2H), 2.03-1.98 (m, 1H), 1.96-1.90 (m, 2H), 1.79-1.72 (m, 2H), 1.62-1.48 (m, 2H)

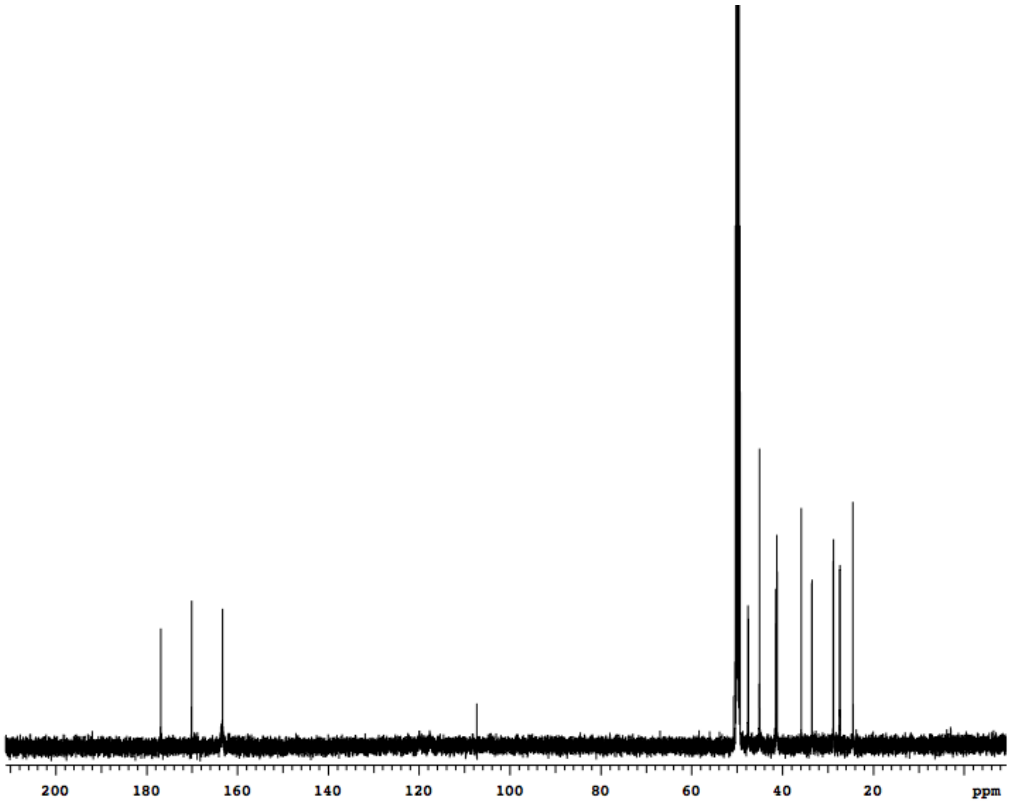
^{13}C NMR (125 MHz, CD_3OD) δ 176.86, 170.09, 163.28, 50.71, 47.55, 45.06, 41.43, 41.20, 35.85, 33.50, 28.79, 27.42, 27.33, 24.48 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{14}H_{27}N_6O_2$ $(M+H)^+$ 311.22, found 311.22

optical rotation $[\alpha]_D^{20.0}$ = -19.8 (*c* = 3.72 in MeOH)



^{1}H NMR of **1f**



^{13}C NMR of **1f**

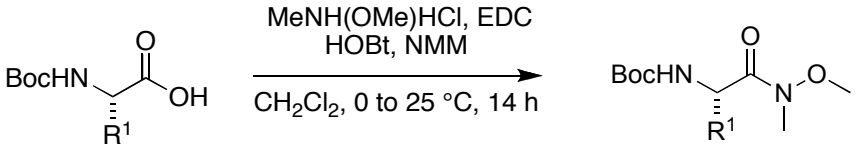
D. Preparation of Diyne-based Mimics

General Procedure for Compound 8a-h

To a solution of Boc-L-amino acid (1.0 equiv) in dichloromethane (0.24 M) were added HOBt (1.1 equiv) and EDC (1.2 equiv) at 0 °C. The solution was stirred at 0 °C for 15 min and then *N,O*-dimethylhydroxylamine hydrochloride salt (1.15 equiv) and *N*-methyl morpholine (1.2 equiv) were added. The reaction mixture was stirred at 25 °C for 14 h. After the solvent was removed under vacuum, the resulting residue was partitioned between 1*N* HCl (aq.) and EtOAc. The phases were separated and the organic layer was washed with 1*N* HCl (aq.), followed by saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$. After completely removing the solvent, the Weinreb's amides **8a-d, f-h** were purified by flash chromatography.

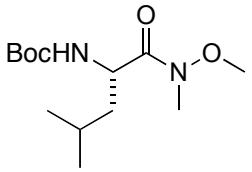
For compound **8e**, the obtained Boc-Tyr-Weinreb amide was used for next step without further purification. To a solution of Boc-Tyr-Weinreb amide (1.0 equiv) in DMF (0.25 M) was added imidazole (3.0 equiv) and TBDPS-Cl (1.7 equiv) at 0 °C. The reaction mixture was stirred at 25 °C for 18 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$. After completely removing the solvent, the **8e** was purified by flash chromatography.

Scheme S5. Synthesis of compounds **8a-h**.



8a-h

Preparation of Compound 8a



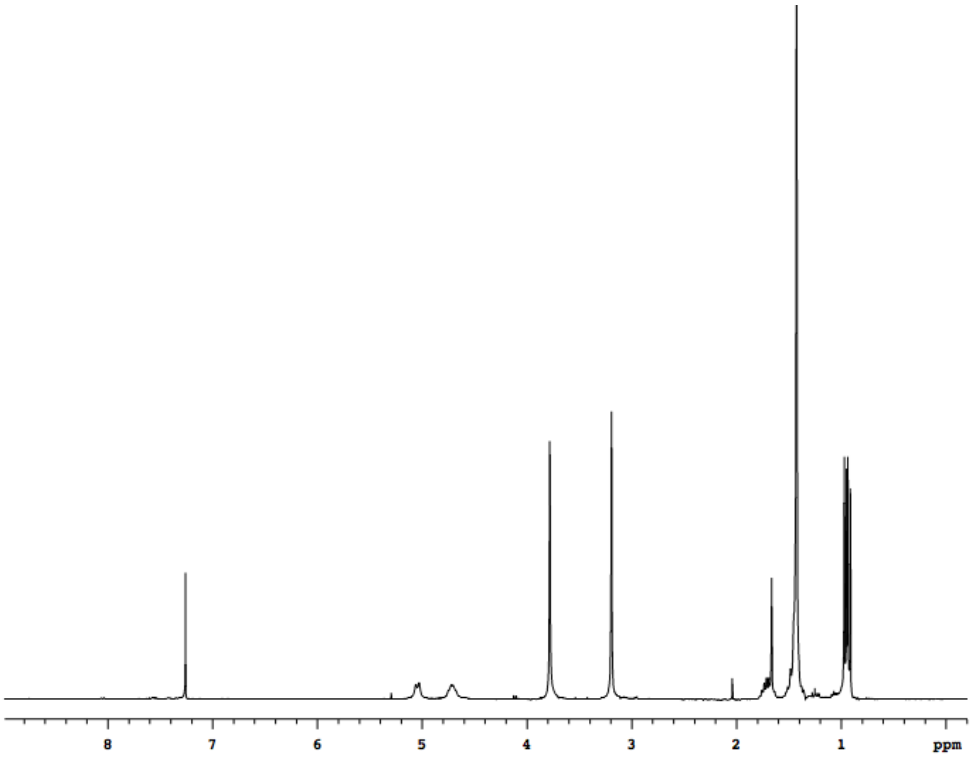
8a

Compound **8a** was prepared from Boc-Leu-OH (9.00 g, 38.9 mmol). Flash chromatography (1:4 EtOAc/Hexanes) afforded 10.7 g (quant.) **8a** as a white solid.

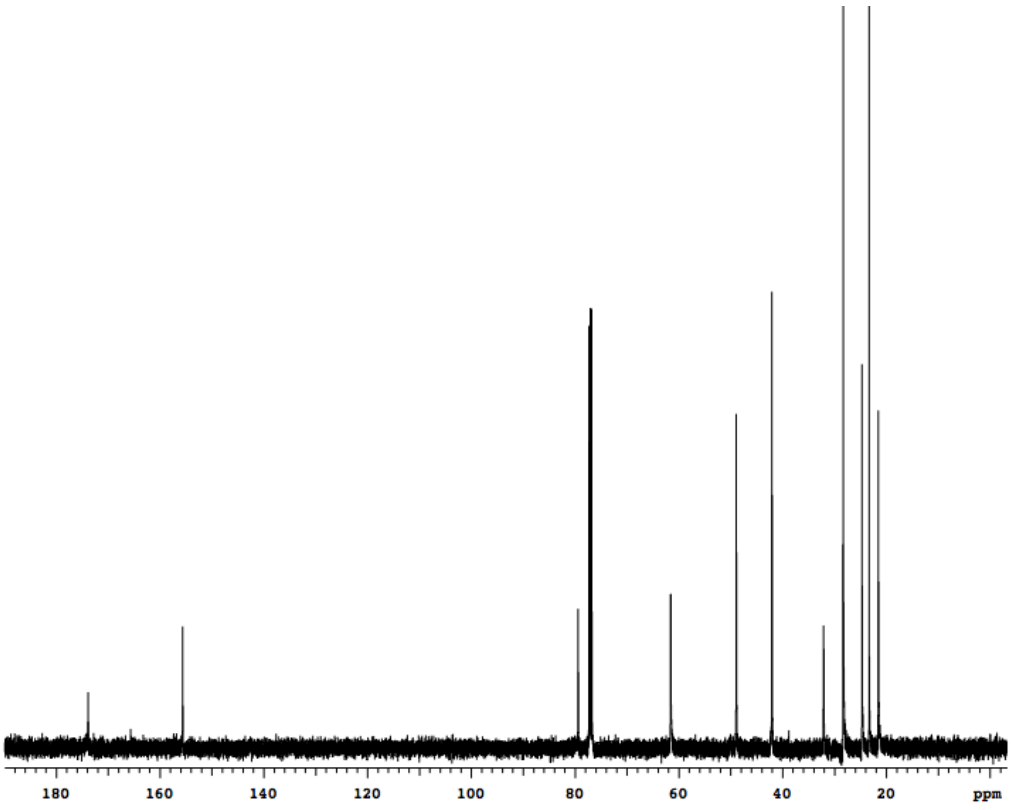
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (d, 1H, J = 14.0 Hz), 4.72 (br, 1H), 3.78 (s, 3H), 3.19 (s, 3H), 1.76-1.66 (m, 2H), 1.42 (br, 10H), 0.96 (d, J = 11.0 Hz), 0.92 (d, J = 11.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.85, 155.61, 79.40, 61.54, 48.92, 42.04, 32.08, 28.32, 24.69, 23.32, 21.54

MS (ESI, m/z) calcd for $C_{13}H_{27}N_2O_4$ $(M+H)^+$ 275.20, found 275.20

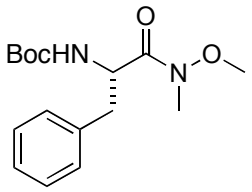


^{1}H NMR of **8a**



^{13}C NMR of **8a**

Preparation of Compound 8b



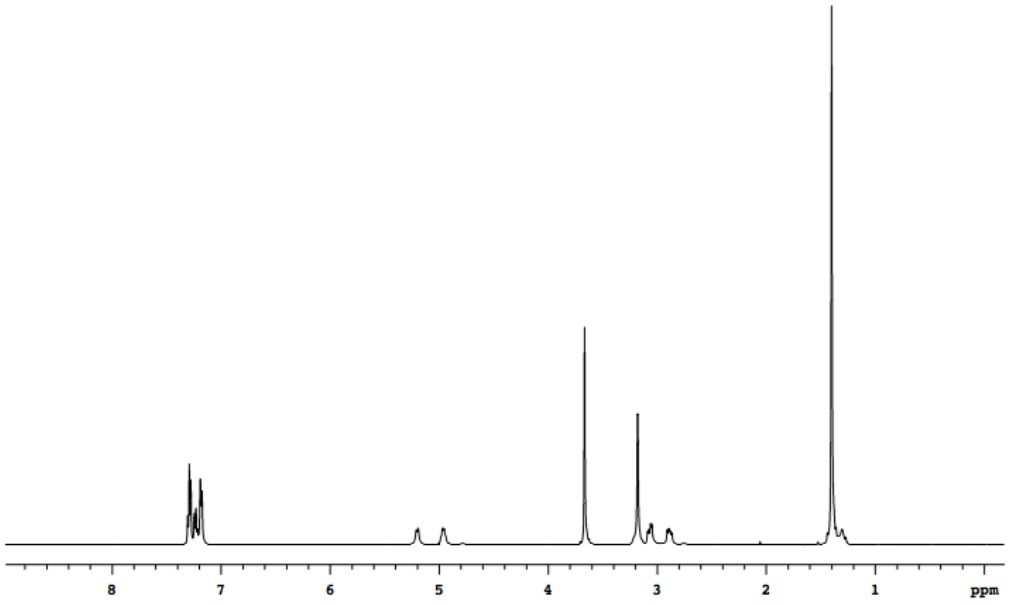
8b

Compound **8b** was prepared from Boc-Phe-OH (4.00 g, 15.0 mmol). Flash chromatography (1:5 EtOAc/Hexanes) afforded 4.65 g (quant.) **8b** as a yellowish oil.

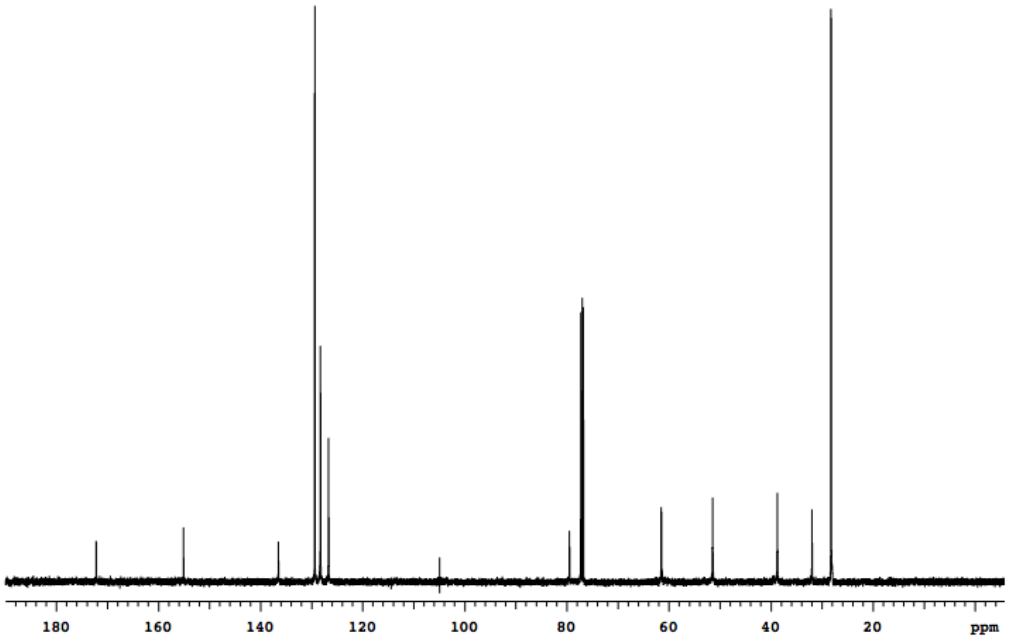
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, 2H, J = 7.5 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.26 (d, 2H, J = 7.0), 5.17 (d, 1H, J = 7.0 Hz), 4.94 (br, 1H), 3.64 (s, 3H), 3.15 (s, 3H), 3.04 (dd, 1H, J = 4.5, 13.5 Hz), 2.86 (dd, 1H, J = 7.0, 13.0 Hz), 1.37 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.18, 155.07, 136.50, 129.37, 128.25, 126.66, 79.47, 61.48, 51.42, 38.74, 31.96, 28.23 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{16}H_{25}N_2O_4$ $(M+H)^+$ 309.18, found 309.17

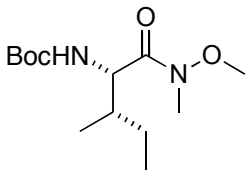


^{1}H NMR of **8b**



^{13}C NMR of **8b**

Preparation of Compound 8c



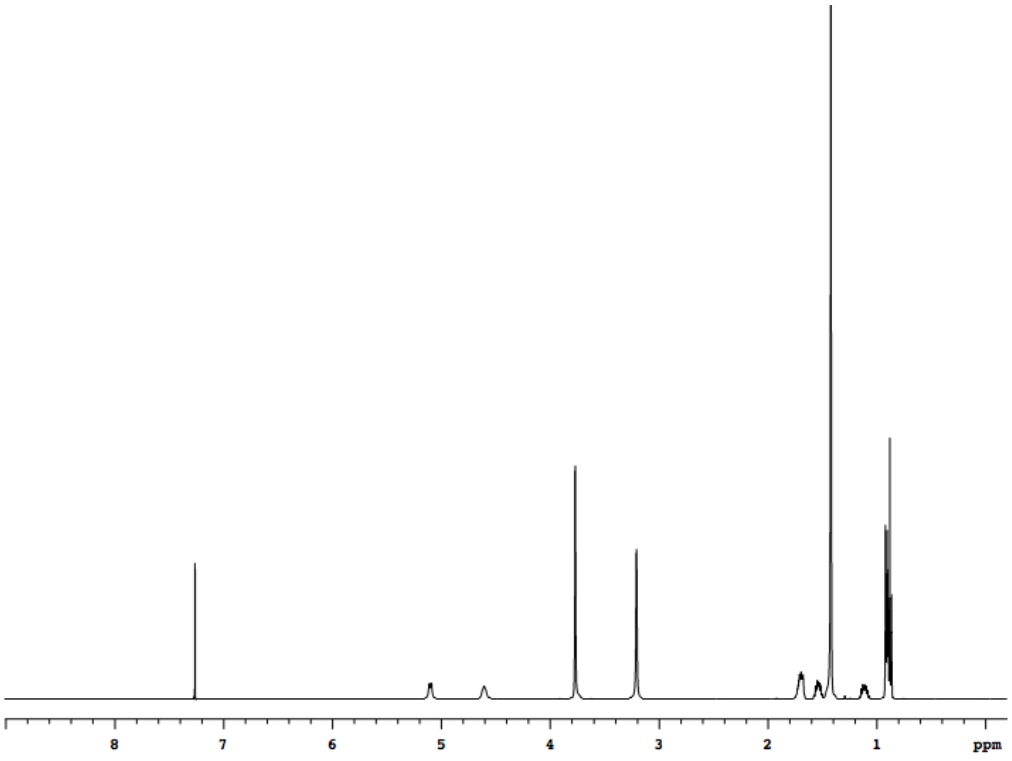
8c

Compound **5c** was prepared from Boc-Ile-OH (5.00 g, 21.6 mmol). Flash chromatography (1:3 EtOAc/Hexanes) afforded 5.93 g (quant.) **5c** as a colorless oil.

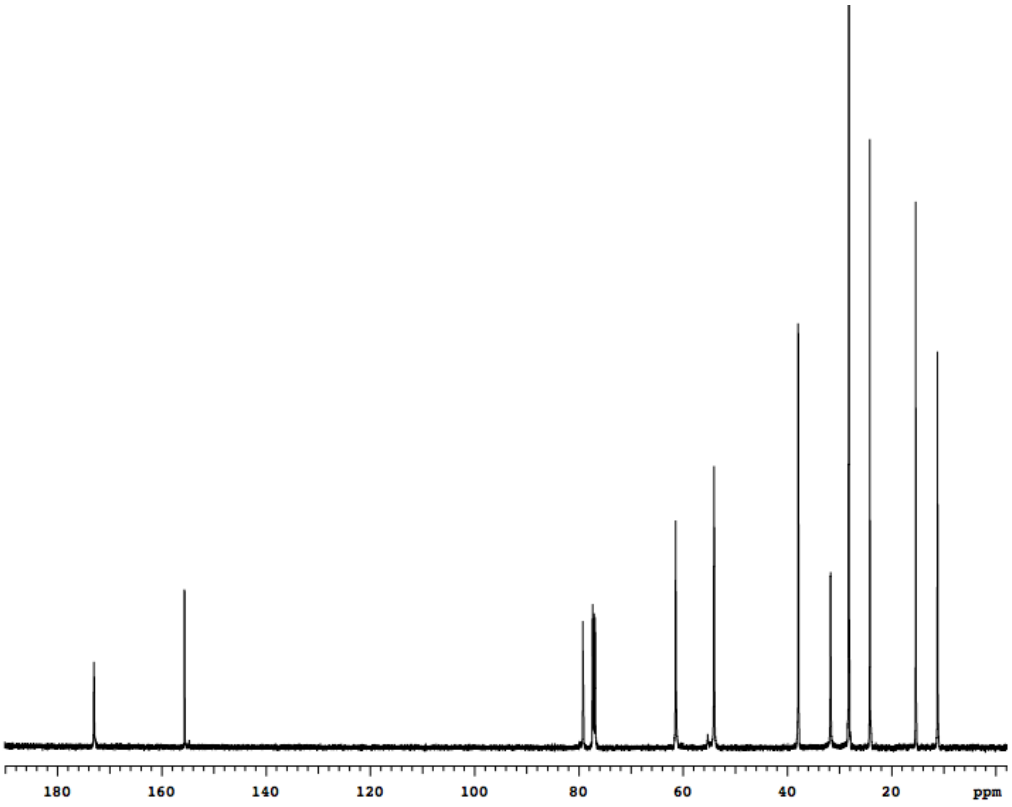
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (d, 1H, J = 10.0 Hz), 4.61 (br, 1H), 3.78 (s, 3H), 3.22 (s, 3H), 1.75-1.69 (m, 2H), 1.59-1.51 (m, 1H), 1.43 (s, 9H), 0.92 (d, 3H, J = 6.5 Hz), 0.89 (t, 3H, J = 8.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.89, 155.52, 79.12, 61.32, 53.94, 37.80, 31.60, 28.13, 24.07, 15.27, 11.12

MS (ESI, m/z) calcd for $C_{13}H_{27}N_2O_4$ $(M+H)^+$ 275.20, found 275.19

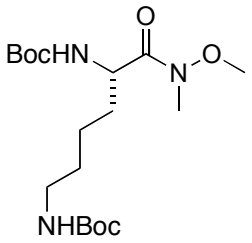


^{1}H NMR of **8c**



^{13}C NMR of **8c**

Preparation of Compound 8d



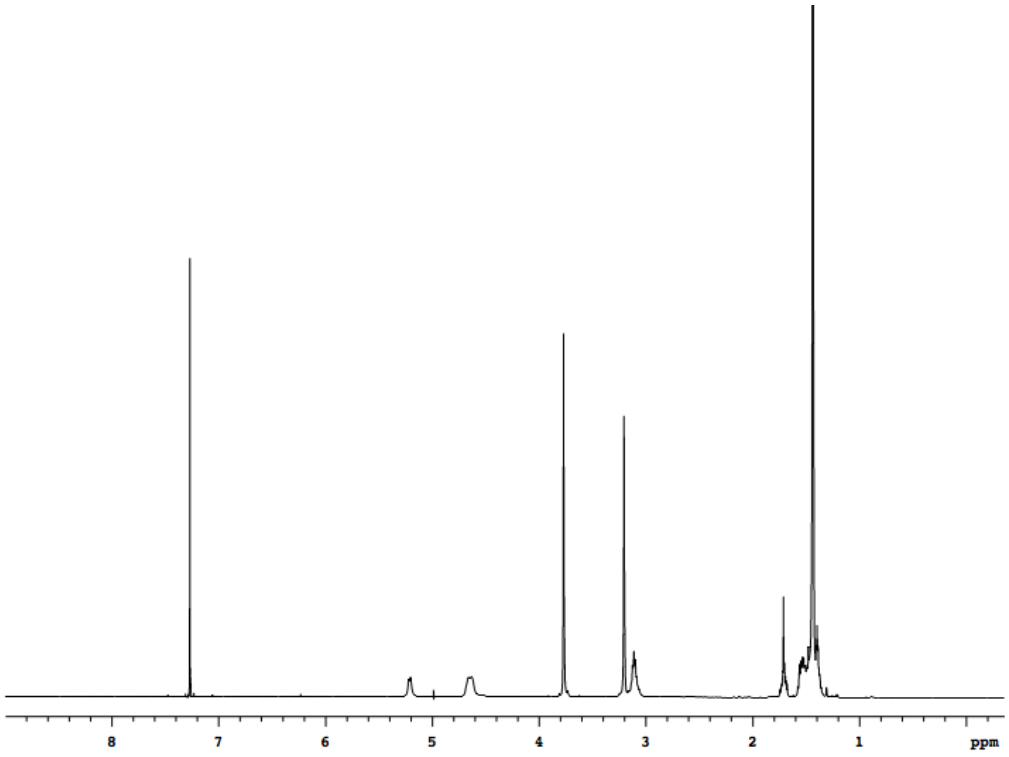
8d

Compound **8d** was prepared from Boc-Lys(Boc)-OH (5.00 g, 14.4 mmol). Flash chromatography (1:3 EtOAc/Hexanes) afforded 5.40 g (96 %) **8d** as a colorless oil.

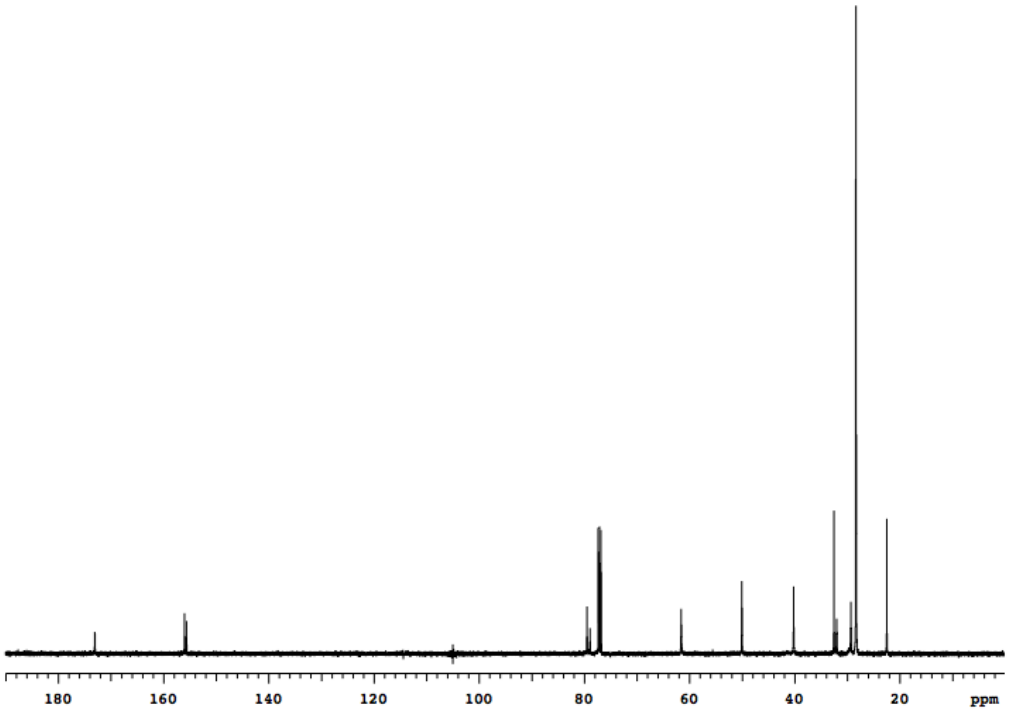
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, 1H, J = 8.5 Hz), 4.66 (br, 1H), 4.63 (br, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 3.15-3.09 (m, 2H), 1.75-1.68 (m, 2H), 1.58-1.49 (m, 2H), 1.44 (s, 18H), 1.42-1.37 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.97, 155.91, 155.56, 79.42, 78.83, 61.49, 49.96, 40.12, 32.46, 31.94, 29.24, 28.31, 28.25, 22.42 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{18}H_{36}N_3O_6$ $(M+H)^+$ 390.26, found 390.27

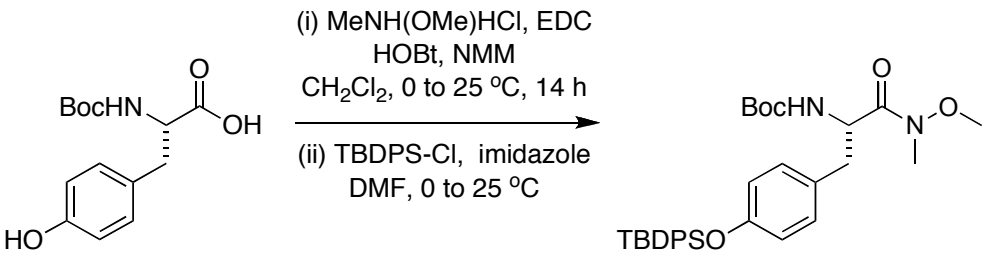


^{1}H NMR of **8d**



^{13}C NMR of **8d**

Preparation of Compound 8e



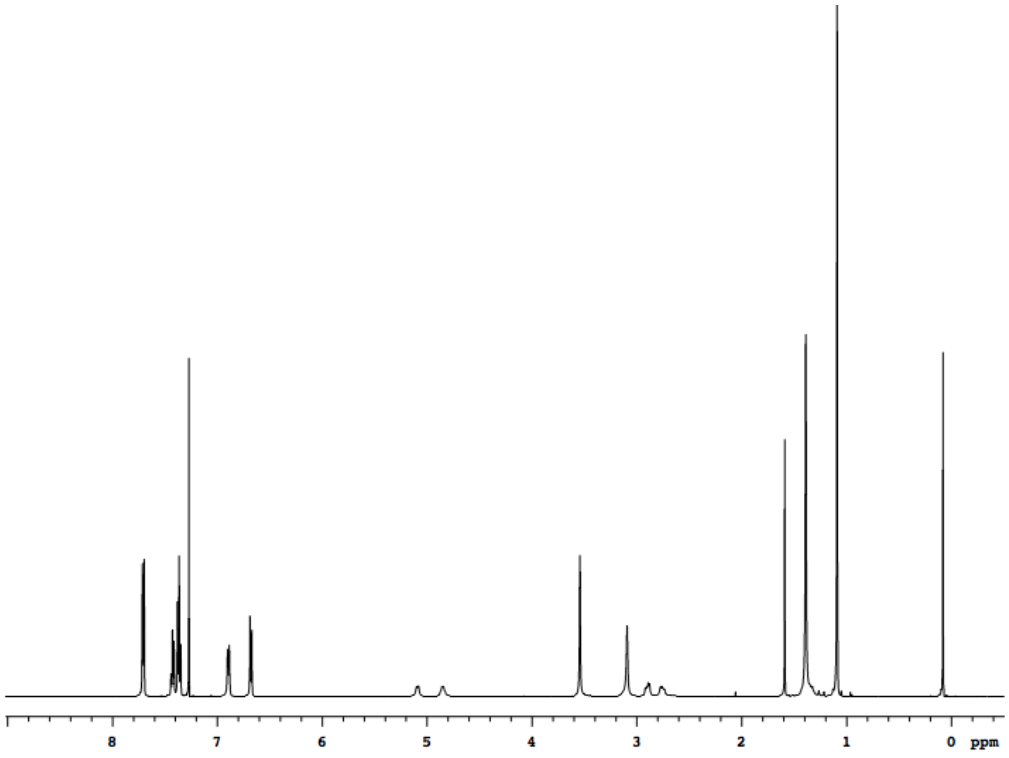
8e

Compound **8e** was prepared from Boc-Tyr-OH (3.1 g, 11.0 mmol). Flash chromatography (1:6 EtOAc/Hexanes) afforded 2.5 g (71 % over 2 steps) **8e** as a white solid.

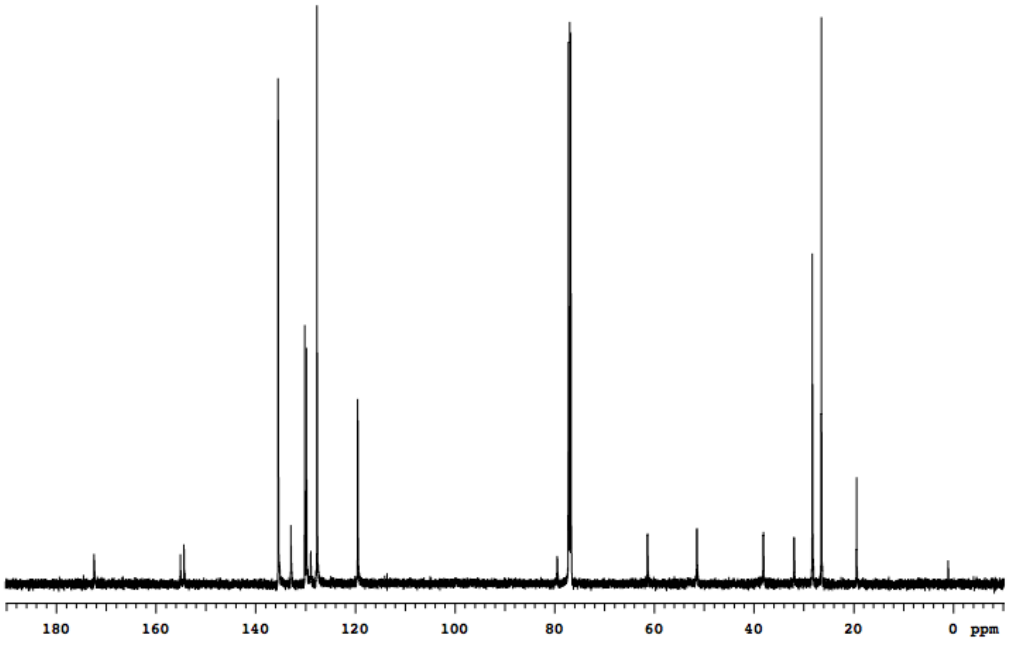
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 4H, J = 7.0 Hz), 7.43 (dd, 2H, J = 7.5, 7.5 Hz), 7.36 (dd, 4H, J = 7.5, 7.5 Hz), 6.89 (d, 2H, J = 8.0 Hz), 6.68 (d, 2H, 8.5 Hz), 5.09 (d, 1H, J = 8.5 Hz), 4.86-4.84 (m, 1H), 3.54 (s, 3H), 3.09 (s, 3H), 2.90 (dd, 1H, J = 6.5, 13.5 Hz), 1.39 (s, 9H), 1.09 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.46, 155.15, 154.44, 135.53, 132.98, 130.20, 129.86, 128.98, 127.74, 119.56, 79.52, 61.42, 51.49, 38.16, 31.98, 28.34, 26.53, 19.47

MS (ESI, m/z) calcd for $C_{32}H_{42}N_2NaO_5Si$ $(M+Na)^+$ 585.28, found 585.26

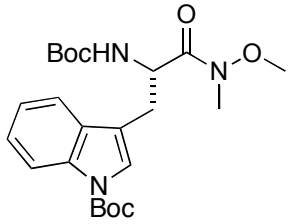


^{1}H NMR of **8e**



^{13}C NMR of **8e**

Preparation of Compound 8f



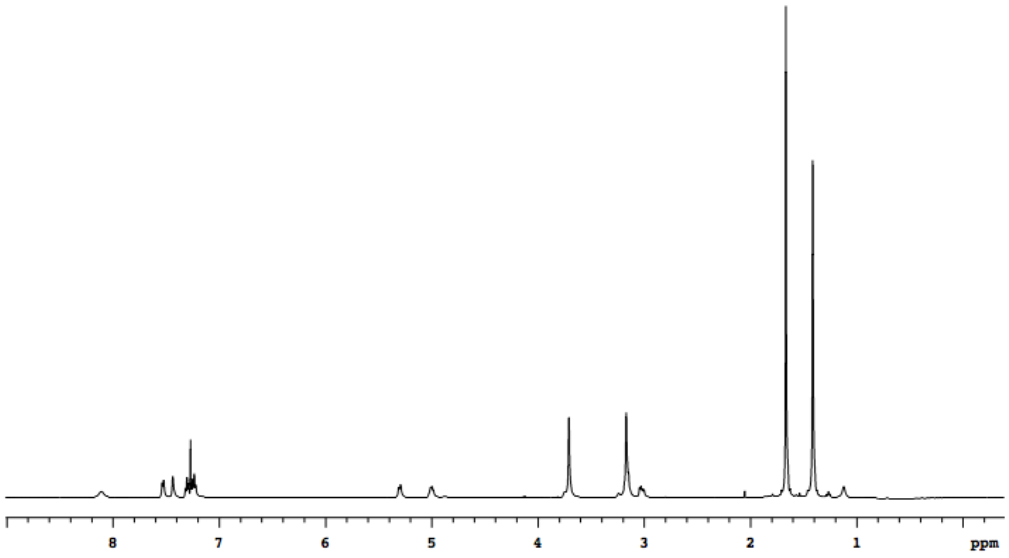
8f

Compound **8f** was prepared from Boc-Trp(Boc)-OH (3.00 g, 9.9 mmol). Flash chromatography (1:7 EtOAc/Hexanes) afforded 3.30 g (quant.) **8f** as a white solid.

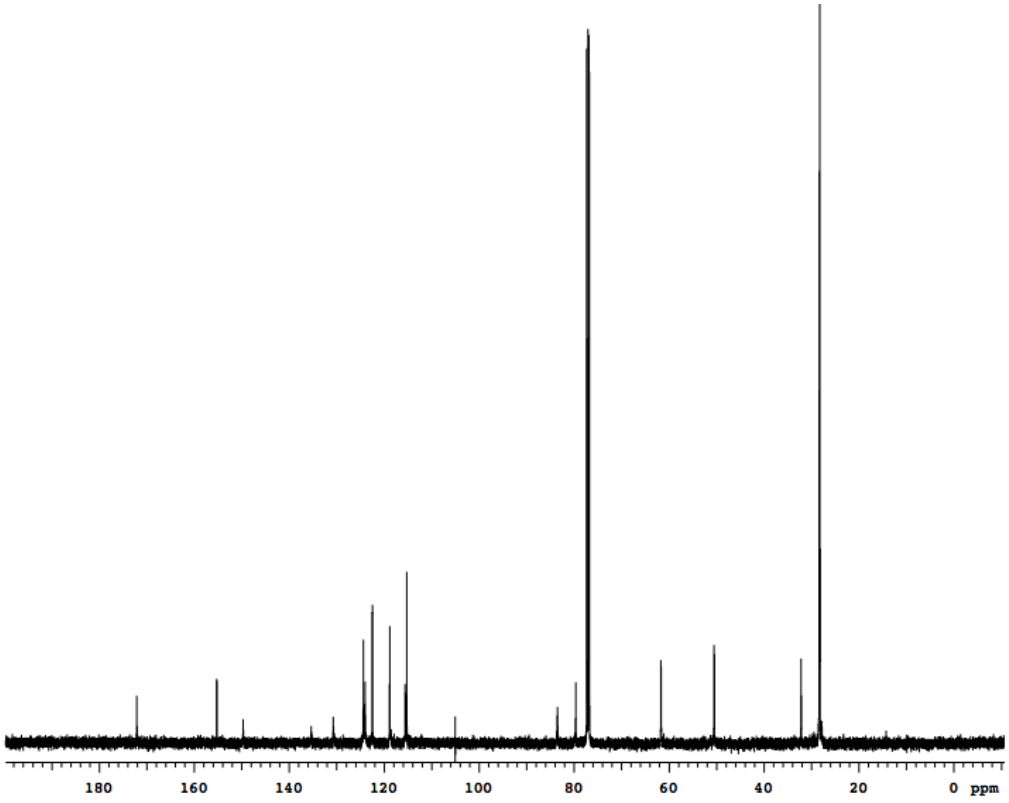
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.53 (d, 1H, J = 7.5 Hz), 7.44 (s, 1H), 7.30 (t, 1H, J = 7.5 Hz), 7.23 (t, 1H, 8.0 Hz), 5.30 (d, 1H, J = 7.5 Hz), 5.01-4.96 (m, 1H), 3.71 (s, 3H), 3.17 (s 3H), 3.17-3.15 (m, 1H), 3.02 (dd, 1H, J = 6.5, 14.0 Hz), 1.67 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.03, 155.16, 149.62, 135.29, 130.65, 124.30, 123.95, 122.41, 118.76, 115.49, 115.19, 83.42, 79.58, 61.62, 50.42, 32.10, 28.29, 28.18, 27.71 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{23}H_{34}N_3O_6$ $(M+H)^+$ 448.24, found 448.25

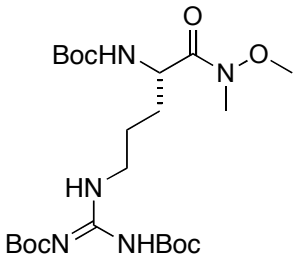


^{1}H NMR of **8f**



^{13}C NMR of **8f**

Preparation of Compound 8g



8g

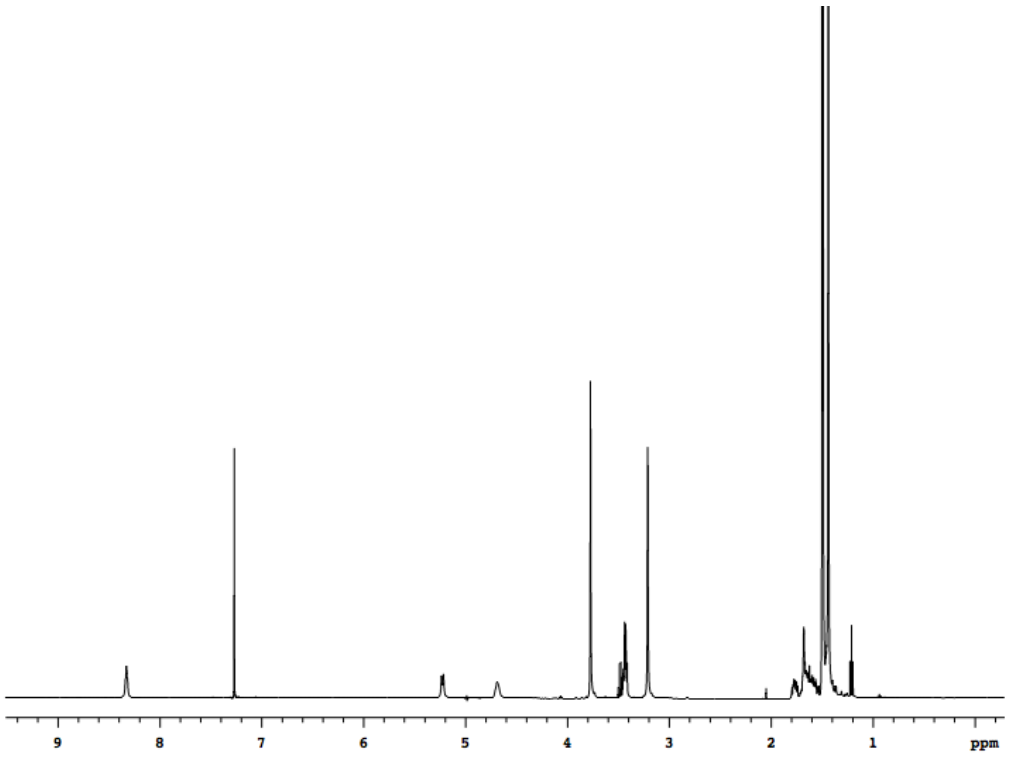
Boc-Arg(Boc)$_2$-OH was prepared from H-Orn-OH· HCl according to the literature procedure.[8,9]

Compound **8g** was prepared from Boc-Arg(Boc)$_2$-OH (3.10 g, 6.5 mmol). Flash chromatography (1:3 to 1:2 EtOAc/Hexanes) afforded 3.38 g (68 %) **8g** as a white solid.

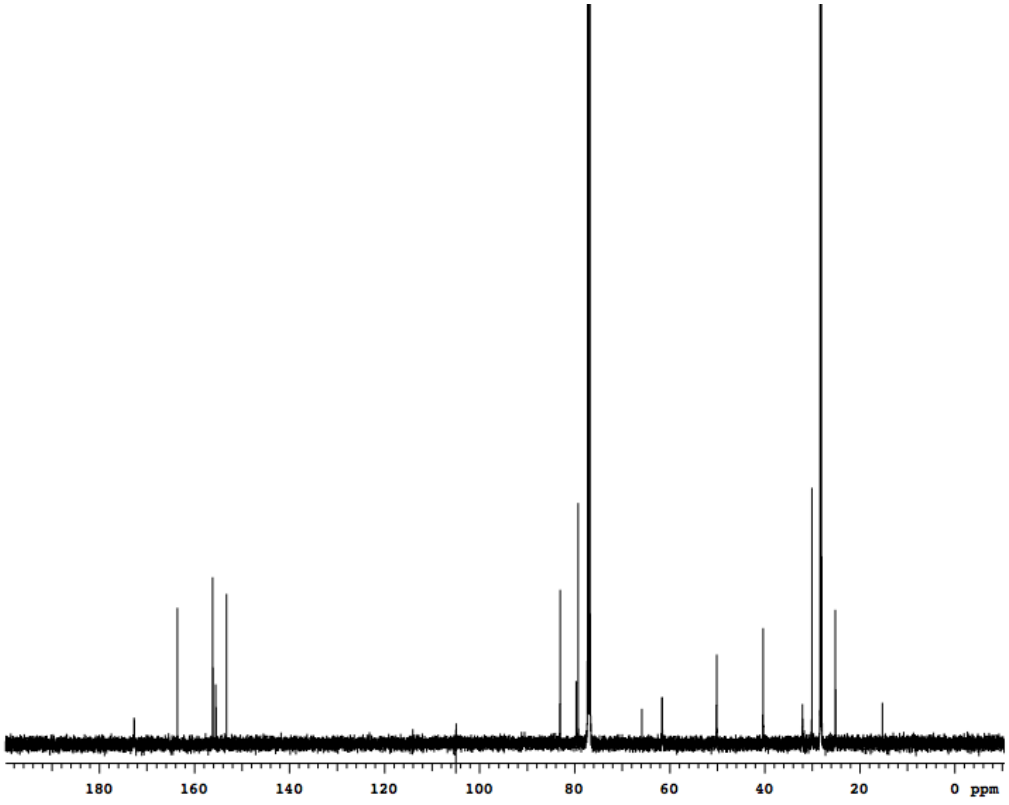
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 5.23 (d, 1H, J = 9.0 Hz), 4.69 (br, 1H), 3.77 (s, 3H), 3.43 (td, 2H, J = 3.5, 10.0 Hz), 3.21 (s, 3H), 1.80-1.74 (m, 1H), 1.69-1.52 (m, 3H), 1.52 (s, 9H), 1.51 (s, 9H), 1.45 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.69, 163.58, 156.14, 155.50, 153.23, 83.05, 79.64, 79.22, 61.60, 50.11, 40.33, 32.04, 30.07, 28.33, 28.27, 28.04, 25.12 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{23}H_{44}N_5O_8$ $(M+H)^+$ 518.32, found 518.34

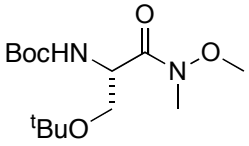


^{1}H NMR of **8g**



^{13}C NMR of **8g**

Preparation of Compound 8h



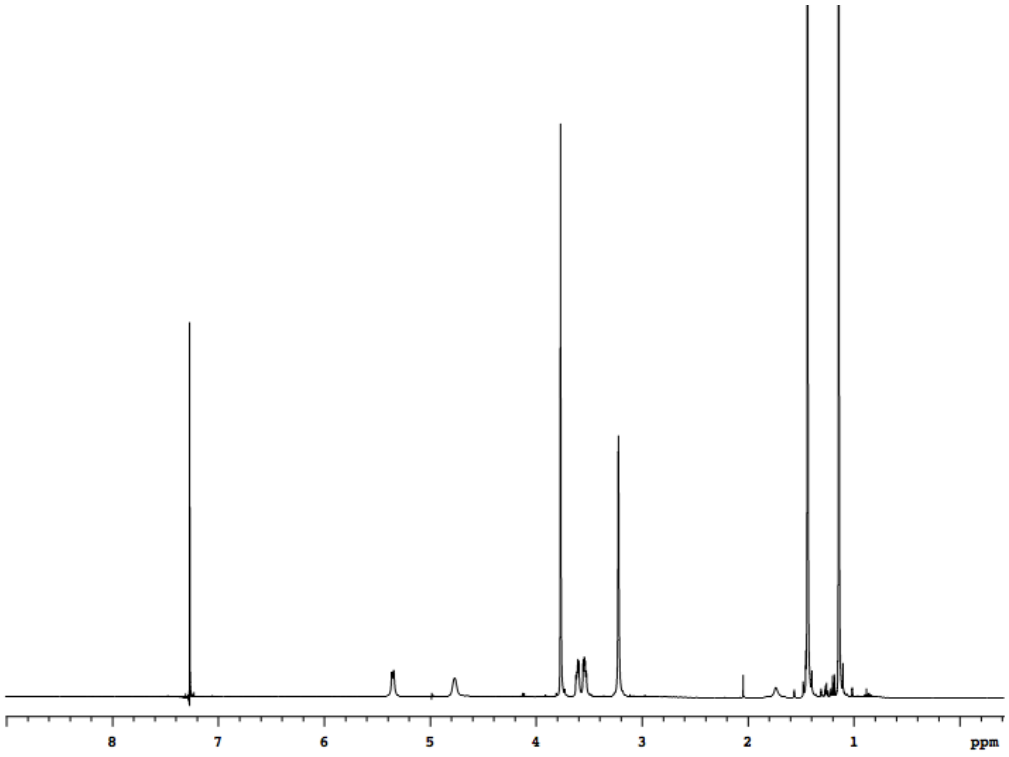
8h

Compound **8h** was prepared from Boc-Ser(^{t}Bu)-OH (3.50 g, 13.4 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 4.06 g (quant.) **8h** as a colorless oil.

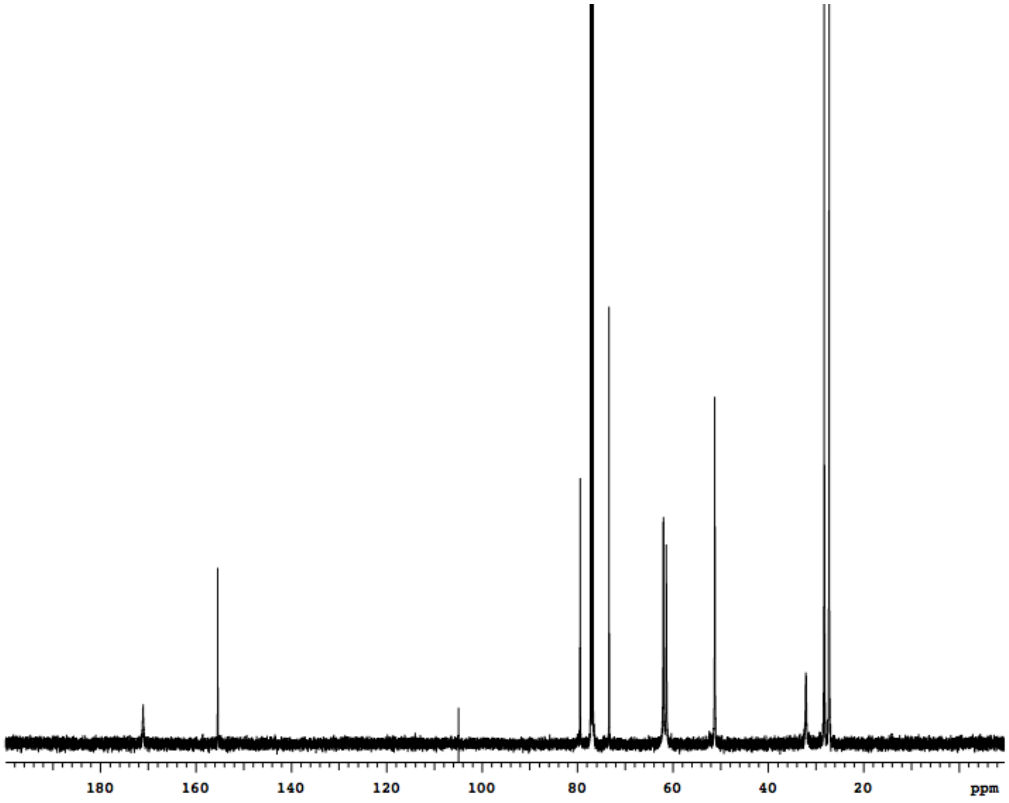
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (d, 1H, J = 9.0 Hz), 4.77 (br, 1H), 3.77 (s, 3H), 3.61 (dd, 1H, J = 5.0, 9.0 Hz), 3.55 (dd, 1H, J = 5.0, 8.5 Hz), 3.22 (s, 3H), 1.44 (s, 9H), 1.14 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.06, 155.41, 79.43, 73.36, 61.97, 61.35, 51.19, 32.08, 28.26, 27.23 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{14}H_{29}N_2O_5$ $(M+H)^+$ 305.21, found 305.20



^{1}H NMR of **8h**



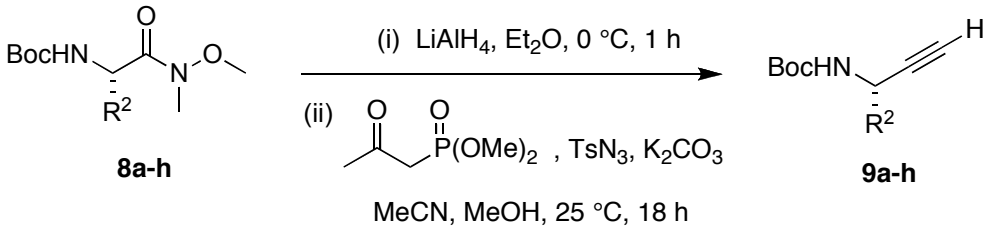
^{13}C NMR of **8h**

General Procedure for Compounds 9a-h

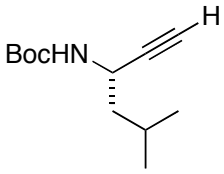
The alkynes **9a-h** were prepared by a procedure previously described in detail [10-12]. The Weinreb's amide (1.0 equiv) was dissolved in dry ether (0.15 M) and cooled to 0 °C under N_2 (g). A solution of LiAlH (1.1 equiv, 1.0 M in Et_2O) was added via syringe over a period of 20 min. The resulting reaction mixture was stirred at 0 °C for 1 h and then quenched by dropwise addition of 5% $KHSO_4$ (aq.). The phases were separated and the aqueous phase was extracted with ether. The combined organic phases were dried over $MgSO_4$, and then the solvent was removed to get the amino aldehyde, which was used immediately for next step without further purification.

To a solution of TsN_3 (1.3 equiv) in dry MeCN (0.1 M) were added K_2CO_3 (3.0 equiv) and dimethyl 2-oxopropylphosphonate (1.3 equiv), and was stirred at 25 °C for 2 hours. The amino acid aldehyde obtained above was dissolved in MeOH (0.37 M) and this solution was added into the reaction mixture all in once. The resulting solution was stirred at 25 °C for 18 hours before the solvent was removed. The residue was partitioned between ether and water. The layers were separated and the aqueous phase was extracted with ether. The combined organic phases were dried over $MgSO_4$. After completely removing the solvent, the amino alkynes **9a-h** were purified by flash chromatography.

Scheme S6. Synthesis of compounds **9a-h**.



Preparation of Compound 9a



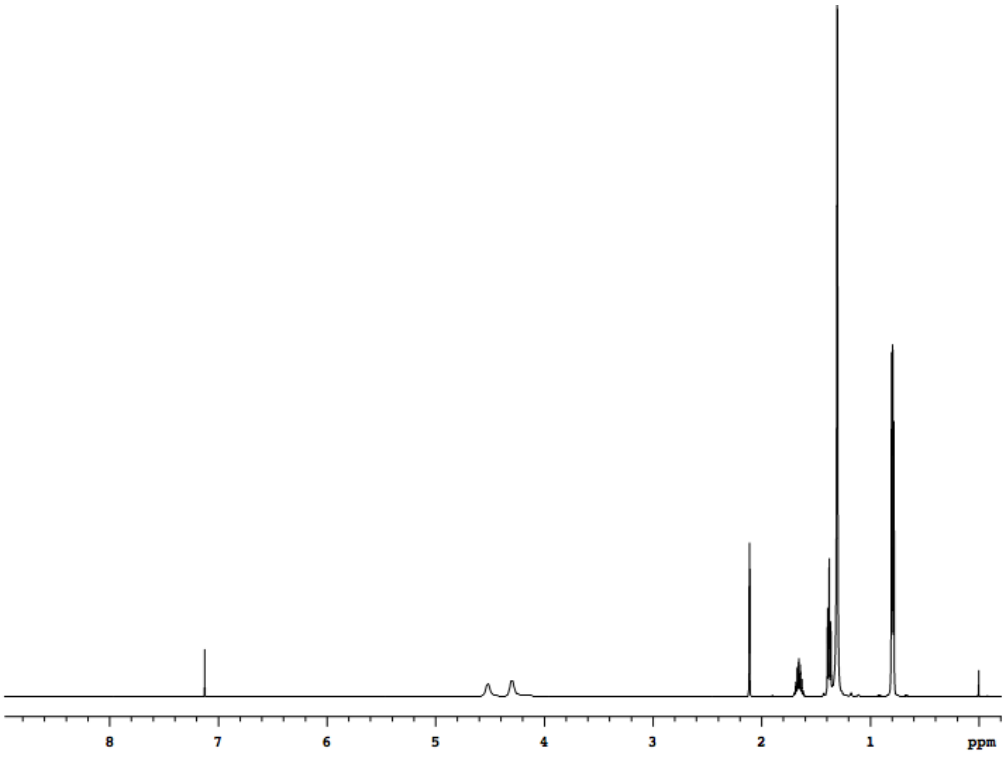
9a

Compound **9a** was prepared from **8a** amide (3.90 g, 18.1 mmol). Flash chromatography (1:6 EtOAc/Hexanes) afforded 2.57 g (67 %) **9a** as a white solid.

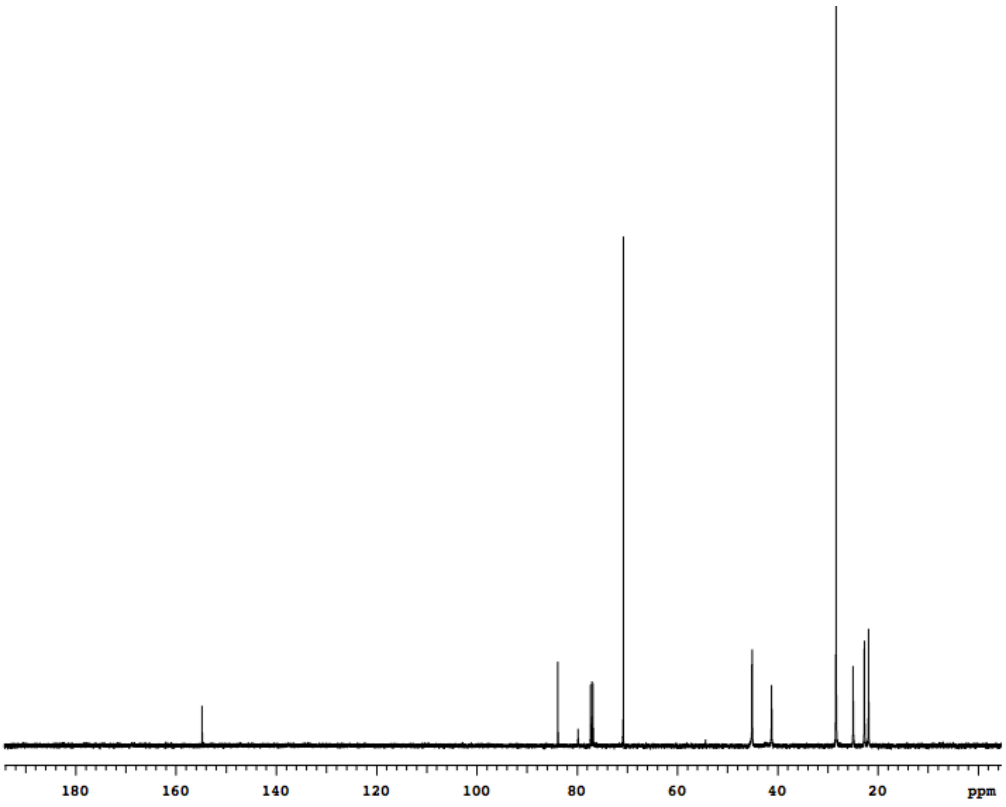
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52(br, 1H), 4.30 (br, 1H), 2.11 (d, 1H, J = 3.0 Hz), 1.70-1.62 (m, 1H), 1.38 (t, 2H, J = 7.5 Hz), 1.30 (s, 9H), 0.80 (d, 3H, J = 5.0 Hz), 0.79 (d, 3H, J = 5.0 Hz)

^{13}C NMR (500 MHz, $CDCl_3$) δ 154.78, 83.82, 79.79, 70.77, 45.09, 41.20, 28.35, 24.95, 22.70, 21.85

MS (ESI, m/z) calcd for $C_{13}H_{27}N_2O_4$ $(M+H)^+$ 212.17, found 212.16

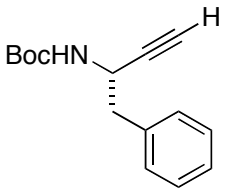


^{1}H NMR of **9a**



^{13}C NMR of **9a**

Preparation of Compound 9b



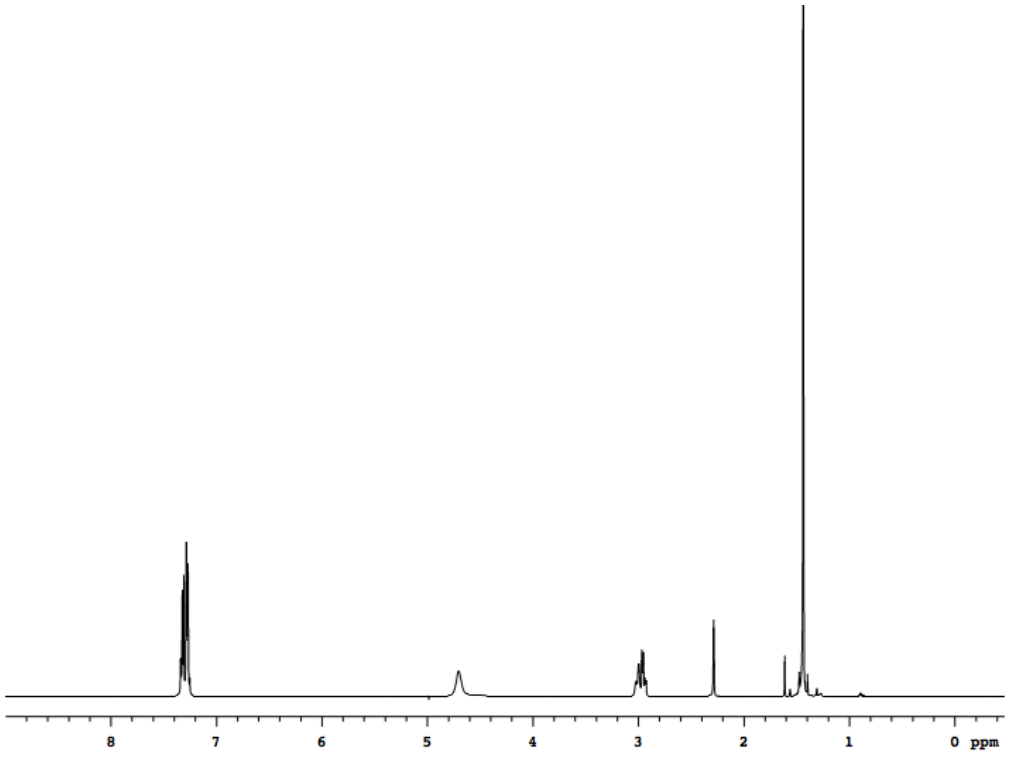
9b

Compound **9b** was prepared from **8b** amide (4.00 g, 13.0 mmol). Flash chromatography (1:5 EtOAc/Hexanes) afforded 2.07 g (65 %) **9b** as a white solid.

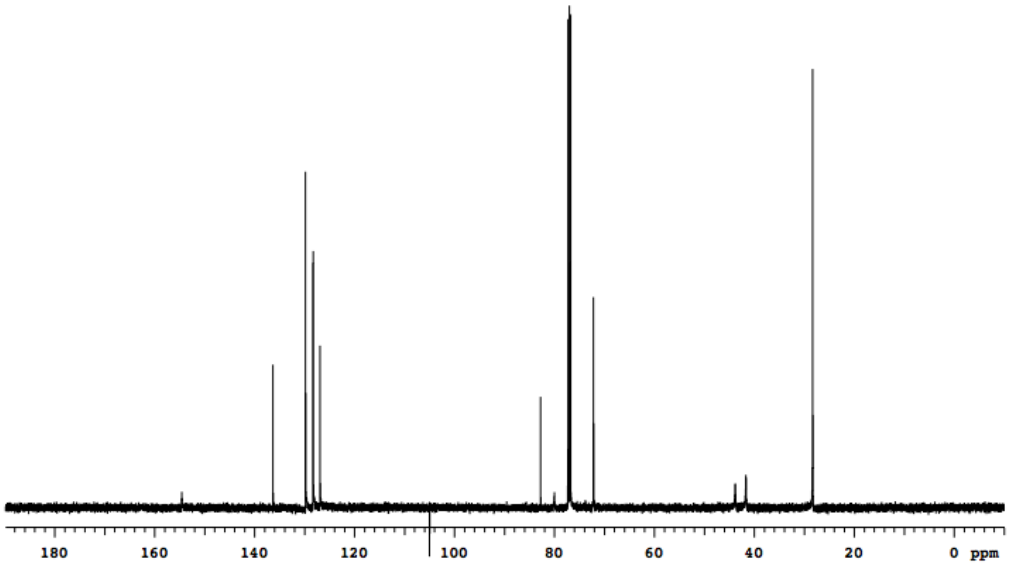
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 4.70 (br, 2H), 3.02-3.00 (m, 1H), 2.95 (dd, 1H, J = 7.0, 13.5 Hz), 2.29 (s, 1H), 1.45 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.56, 136.29, 129.78, 128.28, 126.88, 82.74, 80.00, 72.15, 43.80, 41.66, 28.30 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{15}H_{20}NO_2$ $(M+H)^+$ 246.15, found 246.14

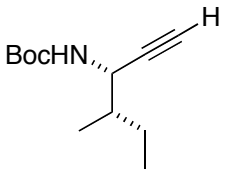


^{1}H NMR of **9b**



^{13}C NMR of **9b**

Preparation of Compound 9c



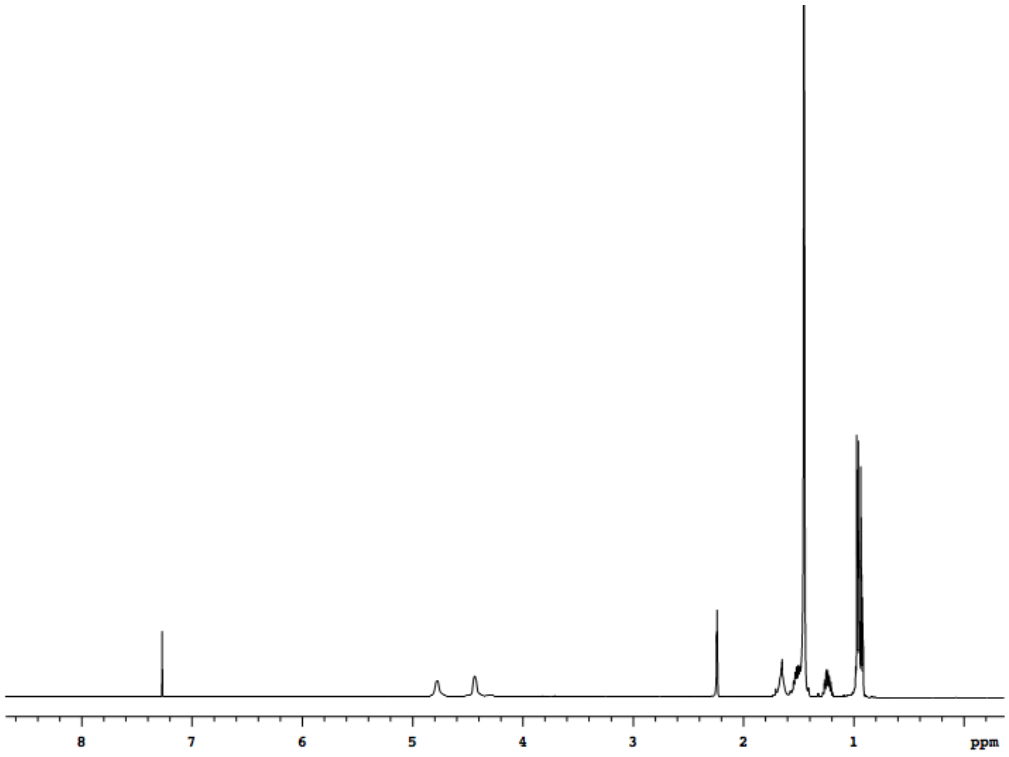
9c

Compound **9c** was prepared from **8c** (5.00 g, 18.2 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 2.41 g (63 %) **9c** as a colorless oil.

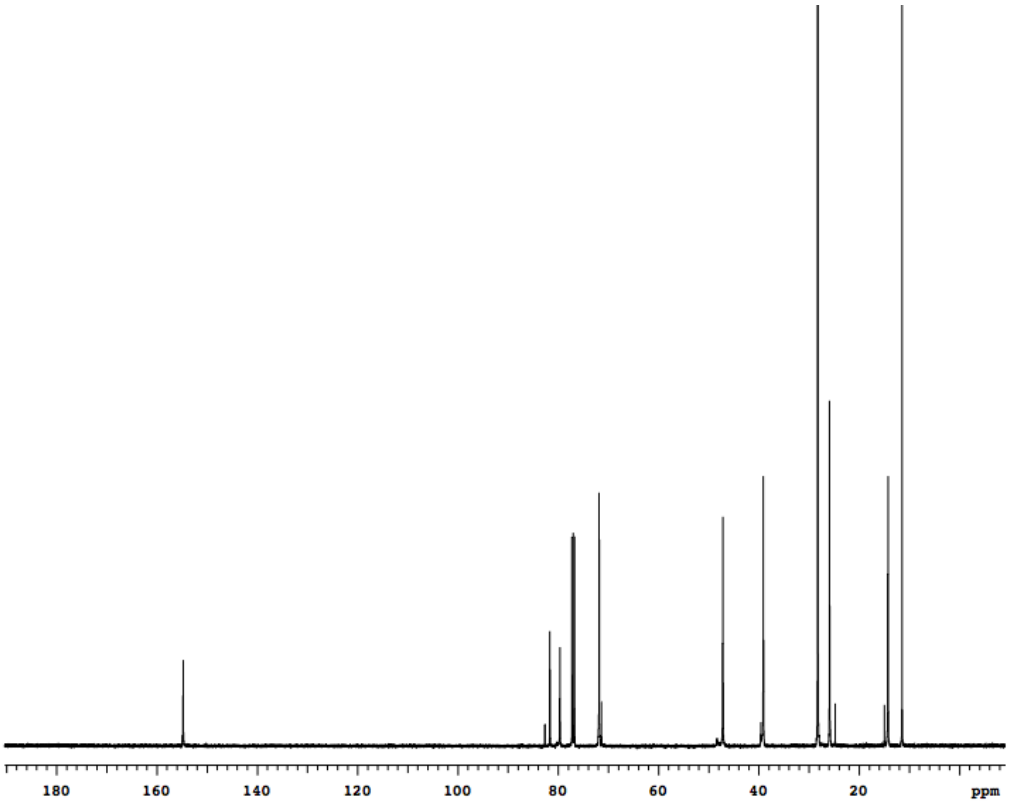
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (br, 1H), 4.44 (br, 1H), 2.24 (s, 1H), 1.65 (br, 1H), 1.55-1.49 (m, 1H), 1.45 (s, 9H) 1.28-1.19 (m, 1H), 0.97 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 8.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.84, 81.72, 79.73, 71.91, 47.24, 39.17, 28.33, 25.98, 14.31, 11.51

MS (ESI, m/z) calcd for $C_{12}H_{22}NO_2$ $(M+H)^+$ 212.16, found 212.16

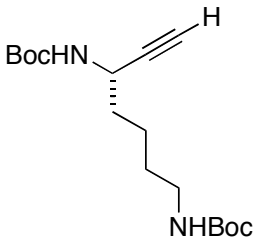


^{1}H NMR of **9c**



^{13}C NMR of **9c**

Preparation of Compound 9d



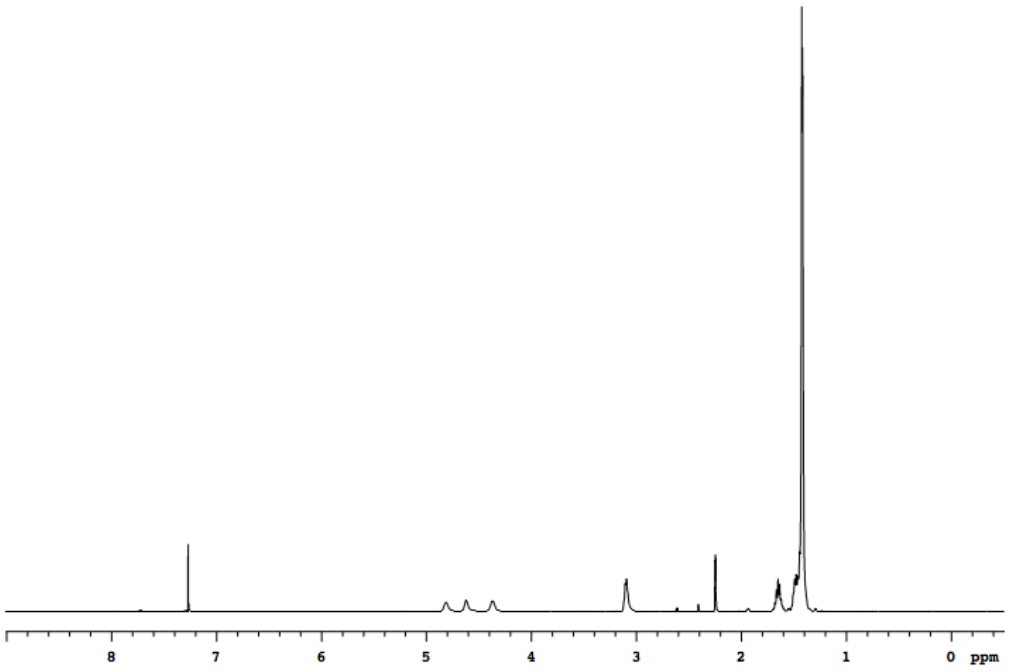
9d

Compound **9d** was prepared from **8d** (5.20 g, 13.4 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 2.18 g (51 %) **9d** as a white solid.

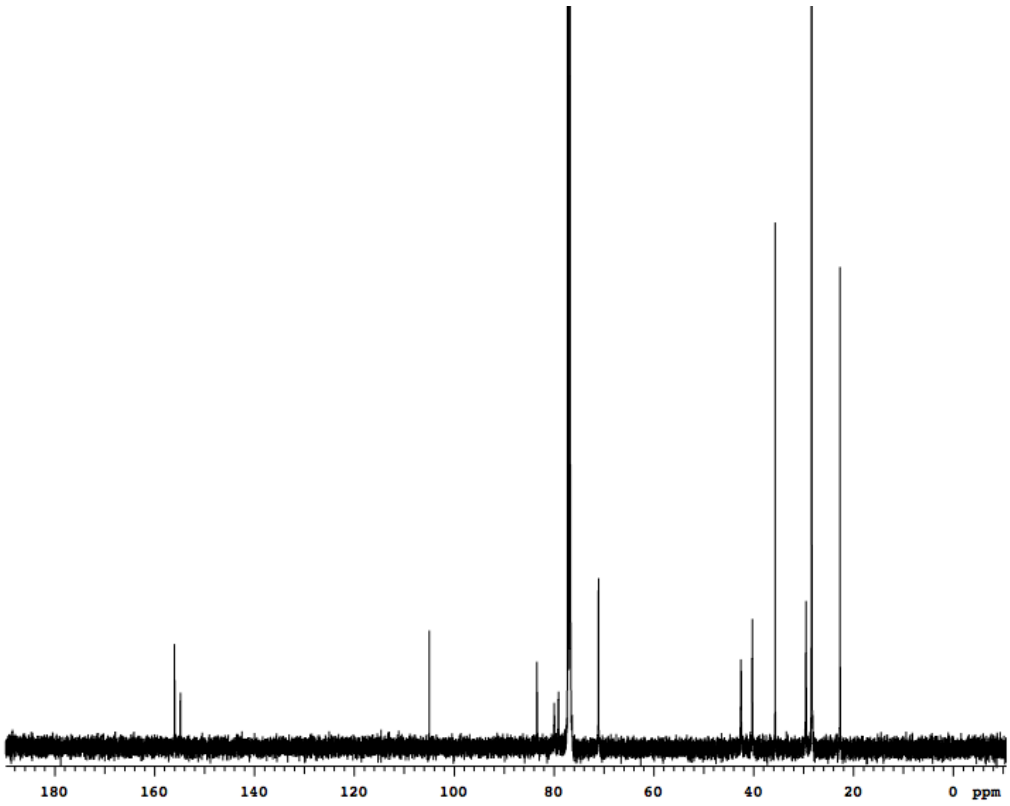
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (br, 1H), 4.56 (br, 1H), 4.39 (br, 1H), 3.14-3.12 (m, 2H), 2.26 (s, 1H), 1.72-1.63 (m, 2H), 1.55-1.45 (m, 4H), 1.45 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.99, 154.82, 83.39, 79.92, 79.09, 71.07, 42.53, 40.26, 35.70, 29.51, 28.41, 28.34, 22.69 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{17}H_{31}N_2O_4$ $(M+H)^+$ 327.23, found 327.20

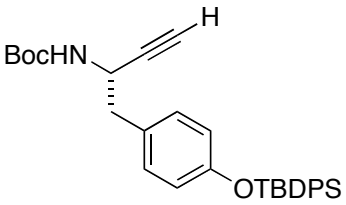


^{1}H NMR of **9d**



^{13}C NMR of **9d**

Preparation of Compound 9e



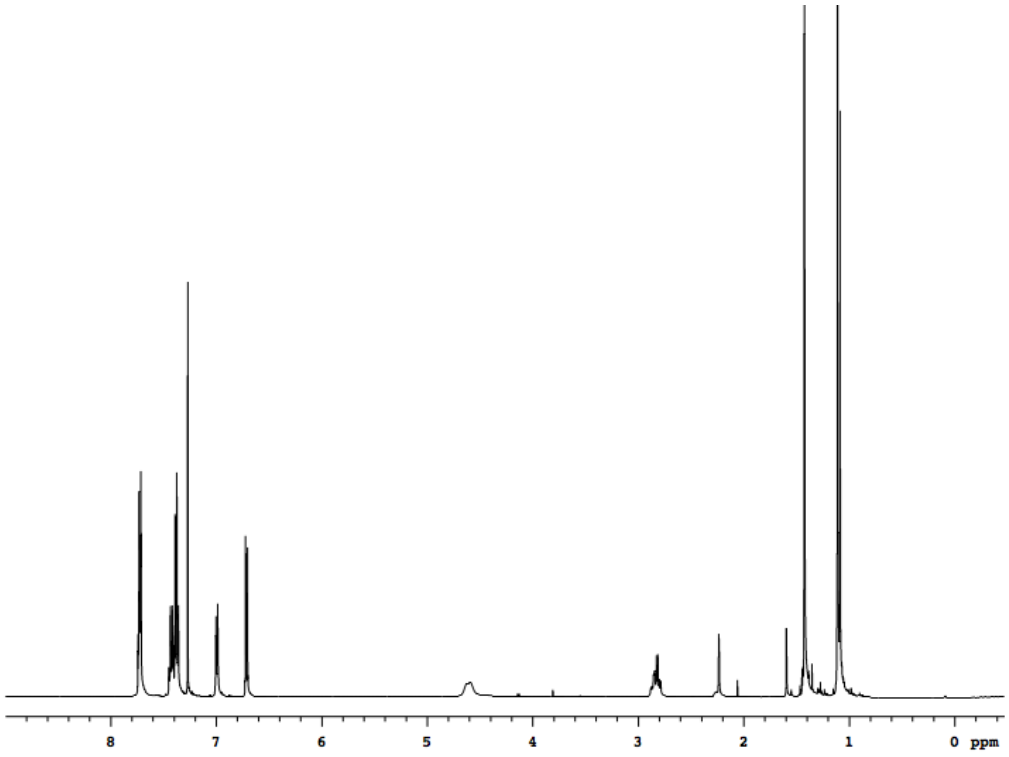
9e

Compound **9e** was prepared from **8e** (2.5 g, 4.4 mmol). Flash chromatography (3:97 EtOAc/Hexanes) afforded 1.50 g (67 %) **9e** as a yellowish oil.

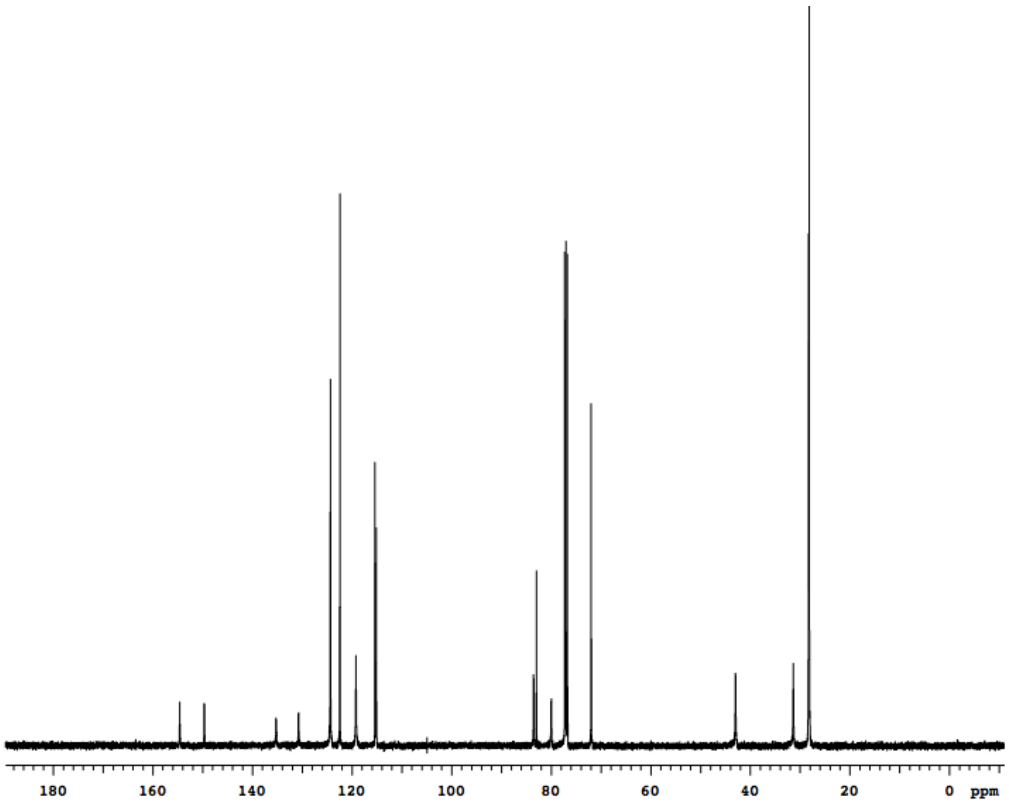
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 4H, J = 8.0 Hz), 7.43 (dd, 2H, J = 7.0, 15.0 Hz), 7.39 (dd, 4H, J = 8.5, 8.5 Hz), 6.99 (d, 2H, J = 8.5 Hz), 6.71 (d, 2H, 8.5 Hz), 4.63 (br, 1H), 4.59 (br, 1H), 2.86 (dd, 1H, J = 5.0, 14.0 Hz), 2.81 (dd, 1H J = 7.0, 13.5 Hz), 2.23 (s, 1H), 1.42 (s, 9H), 1.11 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.50, 154.45, 135.42, 135.41, 134.75, 132.86, 130.43, 129.77, 129.38, 128.70, 127.65, 127.53, 119.41, 82.86, 79.74, 71.93, 43.73, 40.69, 28.23, 26.45, 19.35 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{31}H_{37}NNaO_3Si$ $(M+Na)^+$ 522.71, found 522.20

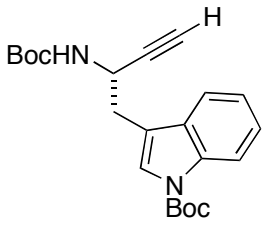


^{1}H NMR of **9e**



^{13}C NMR of **9e**

Preparation of Compound 9f



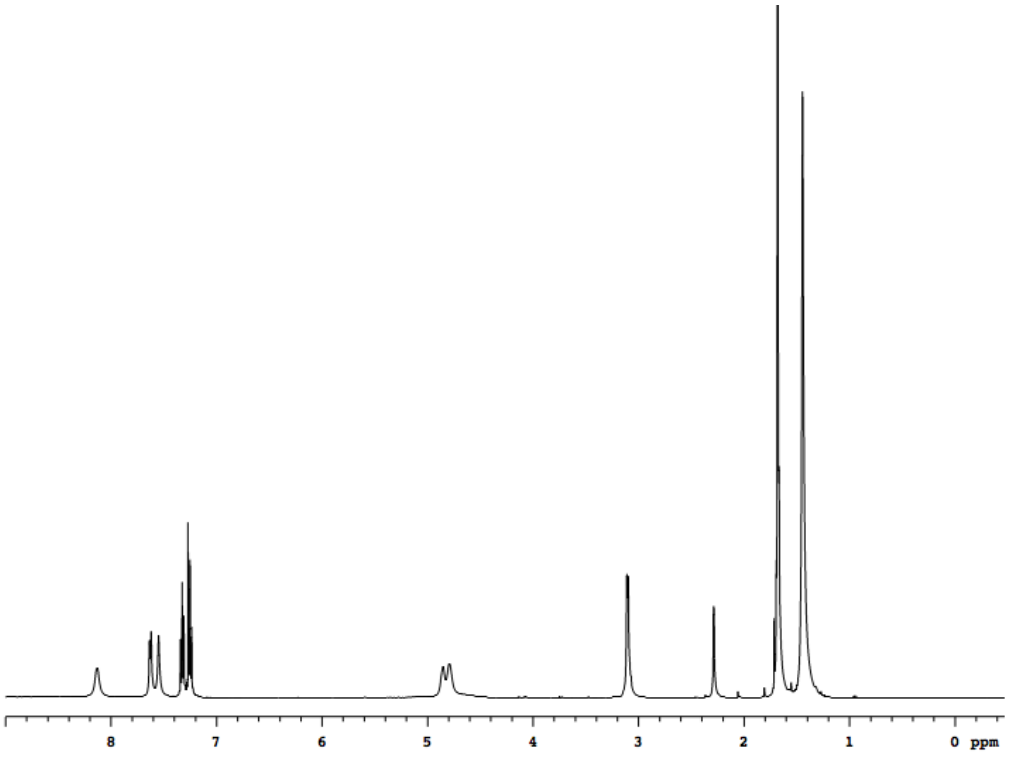
9f

Compound **9f** was prepared from **8f** (3.20 g, 7.2 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 1.90 g (77 %) **9f** as a white solid.

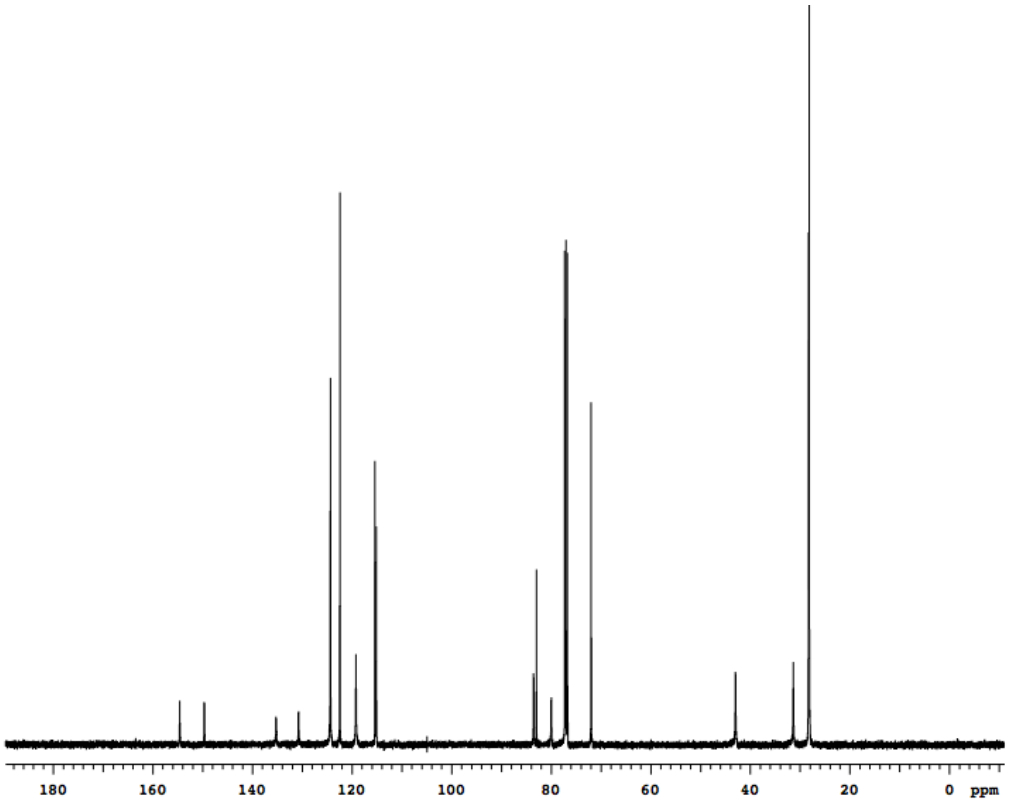
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br, 1H), 7.63 (d, 1H, J = 6.5 Hz), 7.55 (s, 1H), 7.33 (t, 1H, J = 8.5 Hz), 7.25 (t, 1H, 8.5 Hz), 4.85 (br, 1H), 4.79 (br, 1H), 3.10 (d, 2H, J = 6.5 Hz), 2.29 (s, 1H), 1.68 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.60, 149.66, 135.23, 130.73, 124.32, 124.32, 122.43, 119.21, 115.36, 115.13, 83.52, 82.96, 79.96, 71.96, 42.97, 31.35, 28.27, 28.17 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{22}H_{29}N_2O_4$ $(M+H)^+$ 385.21, found 385.21

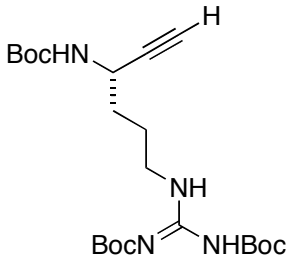


^{1}H NMR of **9f**



^{13}C NMR of **9f**

Preparation of Compound 9g



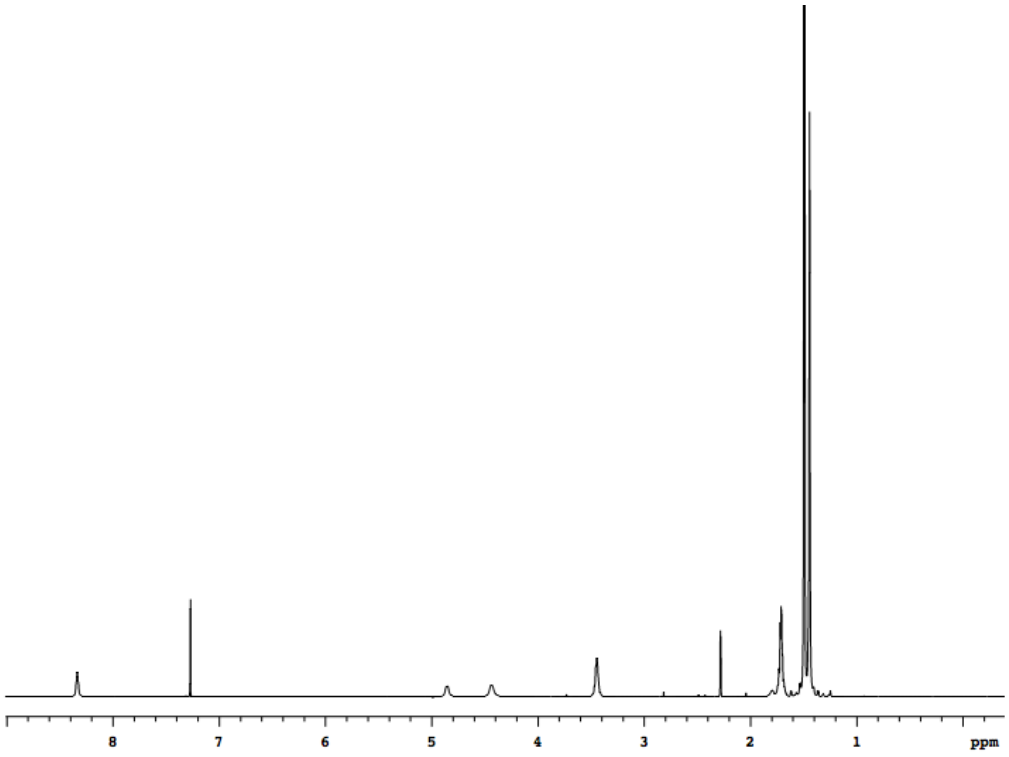
9g

Compound **9g** was prepared from **8g** (1.86 g, 3.6 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 0.50 g (31 %) **9g** as a colorless oil.

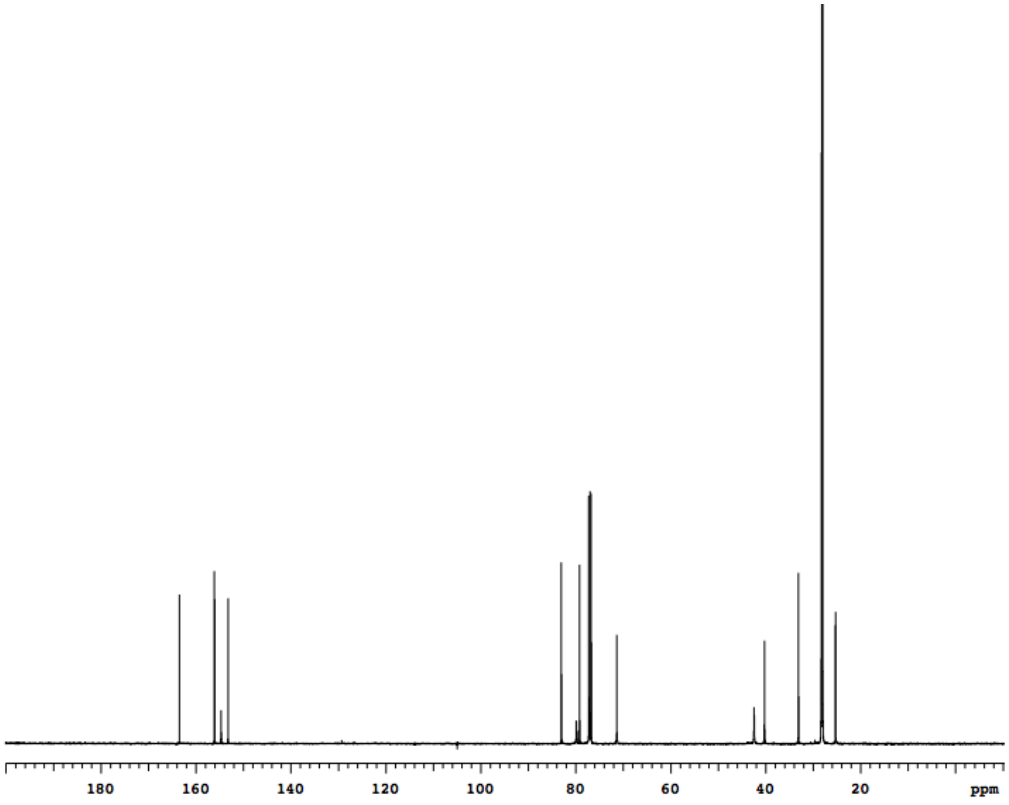
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 4.86 (d, 1H, J = 6.5 Hz), 4.44 (br, 1H), 3.46-3.44 (m, 2H), 2.28 (s, 1H), 1.73-1.70 (m, 4H), 1.50 (s, 9H), 1.49 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.47, 156.08, 154.68, 153.20, 83.03, 79.88, 79.50, 79.18, 71.35, 42.43, 40.24, 33.08, 28.26, 28.21, 27.98, 25.29 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{22}H_{39}N_4O_6$ $(M+H)^+$ 455.29, found 455.23

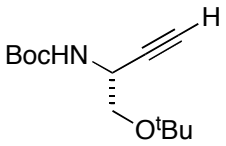


^{1}H NMR of **9g**



^{13}C NMR of **9g**

Preparation of Compound 9h



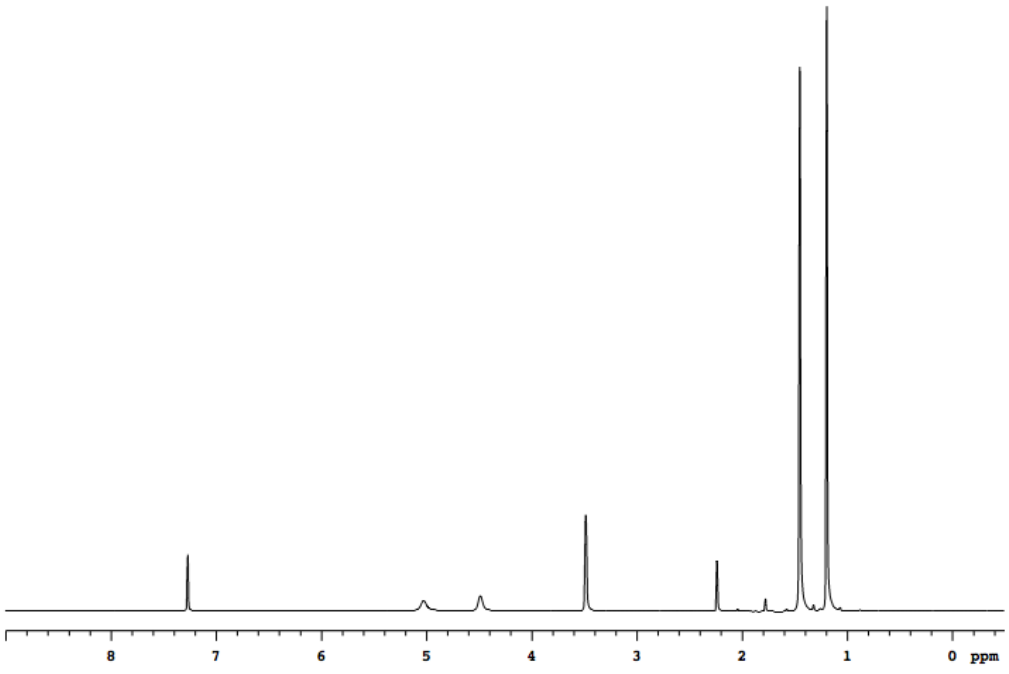
9h

Compound **9h** was prepared from **8h** (2.30 g, 9.2 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 1.50 g (68 %) **9h** as a colorless solid.

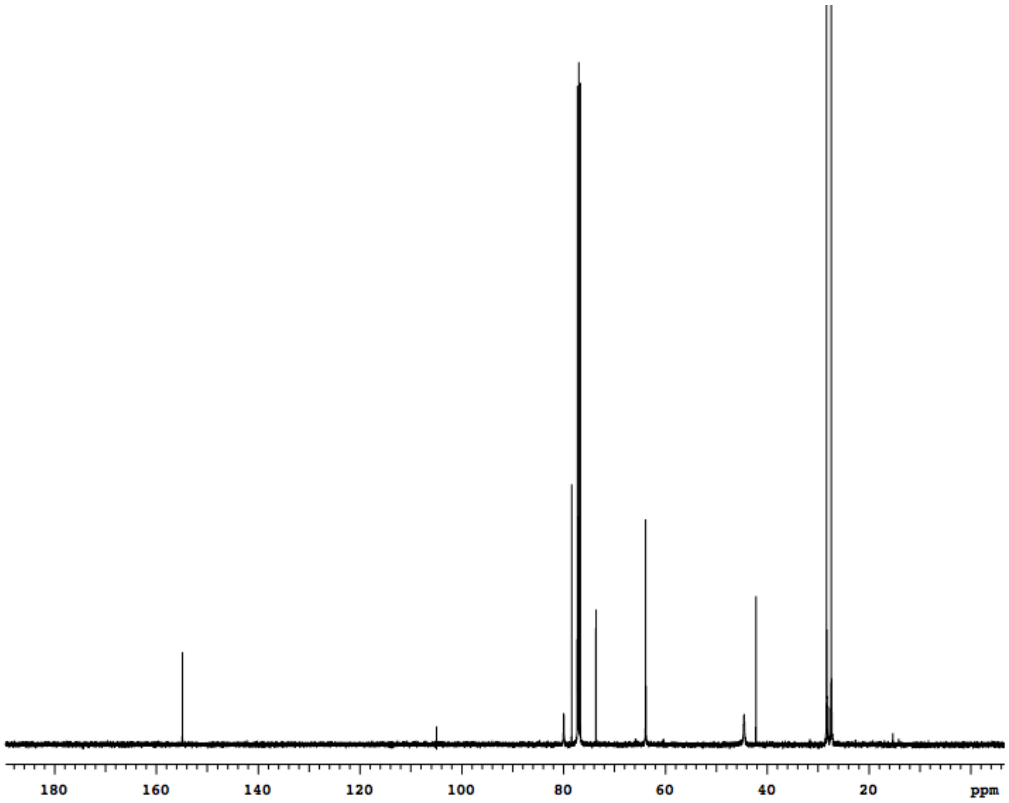
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (br, 1H), 4.49 (br, 1H), 3.49 (br, 2H), 2.24 (s, 1H), 1.45 (s, 9H), 1.20 (s, 9H

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.93, 82.11, 79.87, 73.50, 70.60, 63.84, 43.38, 28.31, 27.39 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{13}H_{24}NO_3$ $(M+H)^+$ 242.18, found 242.18



^{1}H NMR of **9h**

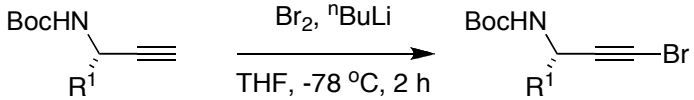


^{13}C NMR of **9h**

General Procedure for Compounds 10a-c

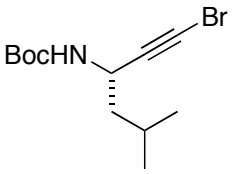
To a solution of the amino acid alkyne (1.0 equiv) in anhydrous THF (0.37 M) was added ^{n}BuLi (2.0 equiv, 2.5 M in hexane) at -78 ^{o}C under N_2 (g). After stirring for 1h, bromine (1.0 equiv) was added dropwise to the solution of the lithium acetylide. The reaction mixture was stirred at -78 ^{o}C under N_2 (g) for 2 h. The mixture was then quenched by adding saturated $Na_2S_2O_3$ (aq.) and allowed to heat up to 25 ^{o}C. The reaction mixture was extracted with diethyl ether. The combined ether fractions were washed with brine, dried over $MgSO_4$ and then concentrated under vacuum. The compounds **10a-c** were purified by Flash chromatography.

Scheme S7. Synthesis of compounds **10a-c**.



9a, c, h **10a-c**

Preparation of Compound 10a

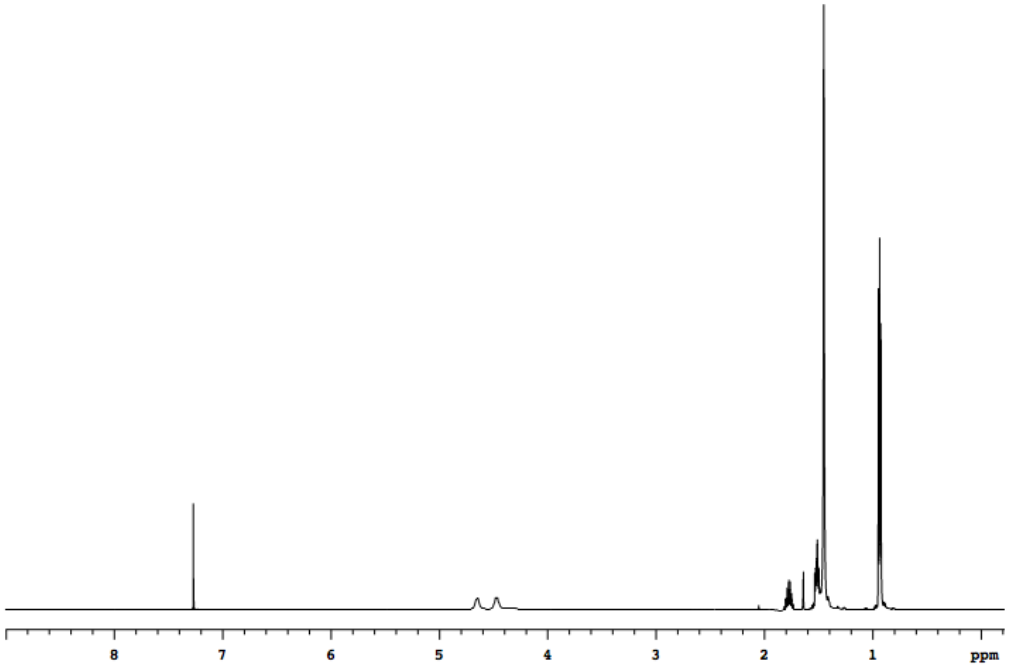


10a

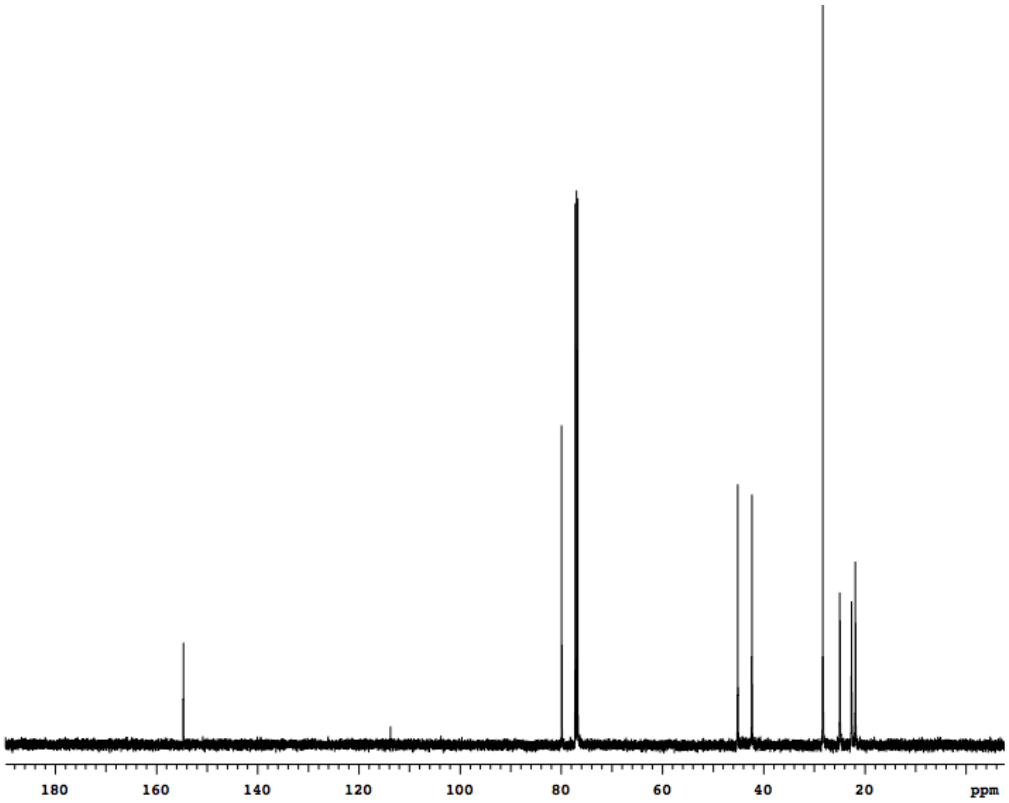
Compound **10a** was prepared from **9a** (1.50 g, 7.1 mmol). Flash chromatography (3:97 EtOAc/Hexanes) afforded 2.01 g (98 %) **10a** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (br, 1H), 4.49-4.46 (m, 1H), 1.82-1.73 (m, 1H), 1.53-1.50 (m, 2H), 1.45 (s, 9H), 0.94 (d, 3H, J = 5.5 Hz), 0.93 (d, 3H, J = 5.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.72, 113.78, 79.95, 45.16, 42.33, 28.36, 24.99, 22.67, 21.91

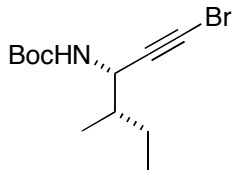


^{1}H NMR of **10a**



^{13}C NMR of **10a**

Preparation of Compound 10b

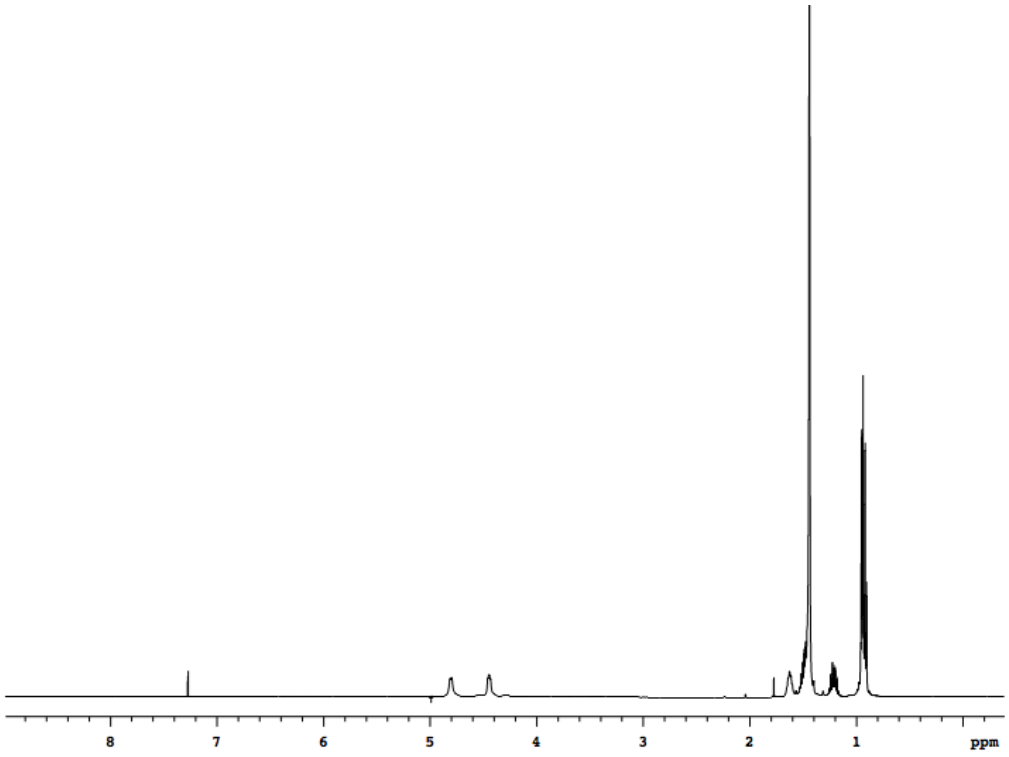


10b

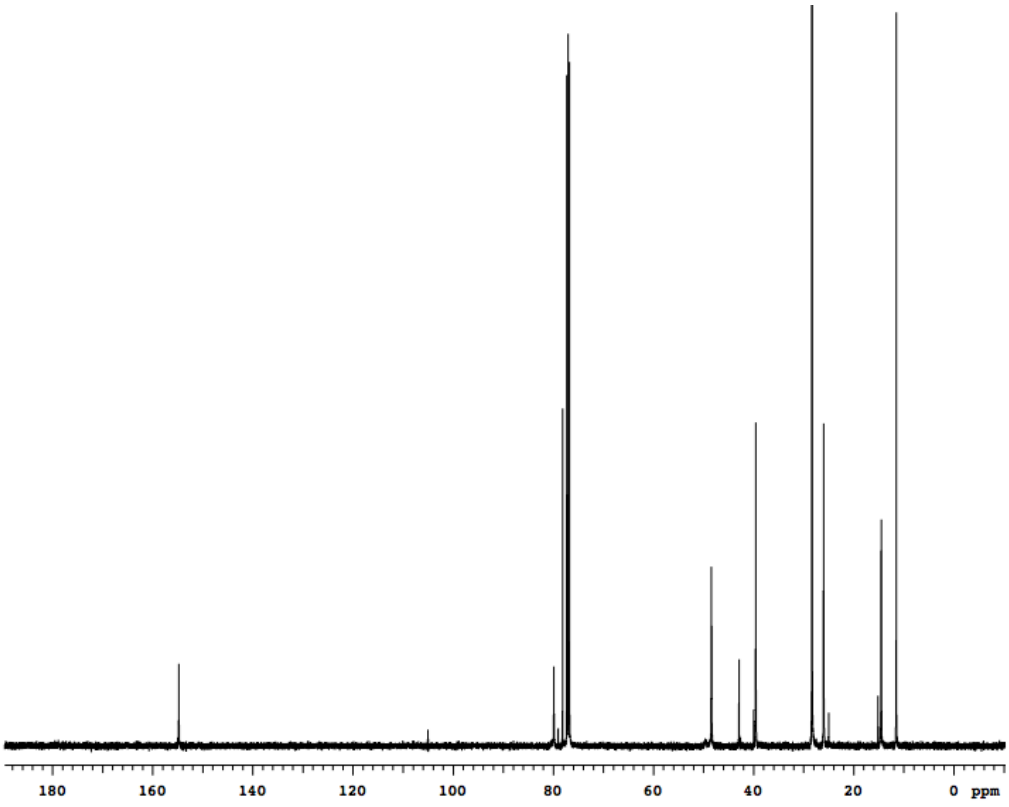
Compound **10b** was prepared from **9b** (0.68 g, 3.2 mmol). Flash chromatography (1:19 EtOAc/Hexanes) afforded 0.88 g (94 %) **10b** as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (d, 1H, J = 3.0 Hz), 4.45 (dd, 1H, J = 5.0, 8.5 Hz), 1.64-1.60 (m, 1H), 1.53-1.46 (m, 1H), 1.44 (s, 9H), 1.26-1.17 (m, 1H), 0.94 (d, 3H, J = 6.5 Hz), 0.92 (t, 3H, J = 8.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.75, 79.85, 78.11, 48.39, 42.86, 39.54, 28.31, 25.99, 14.48, 11.49 (107.25 is noise from NMR.)

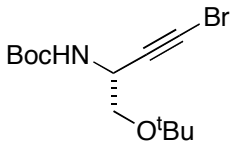


^{1}H NMR of **10b**



^{13}C NMR of **10b**

Preparation of Compound 10c

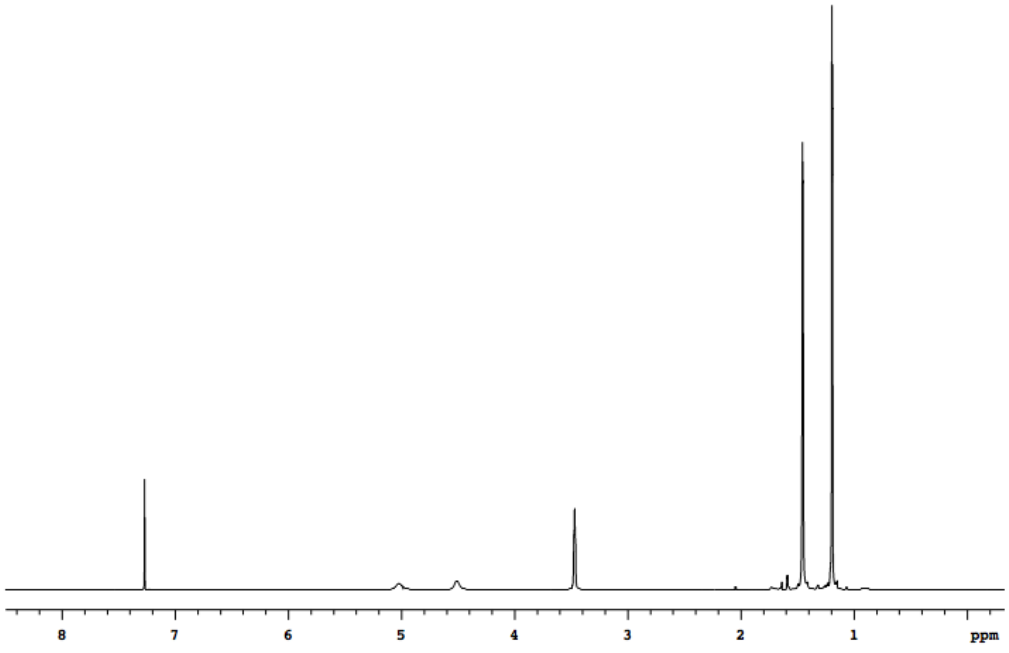


10c

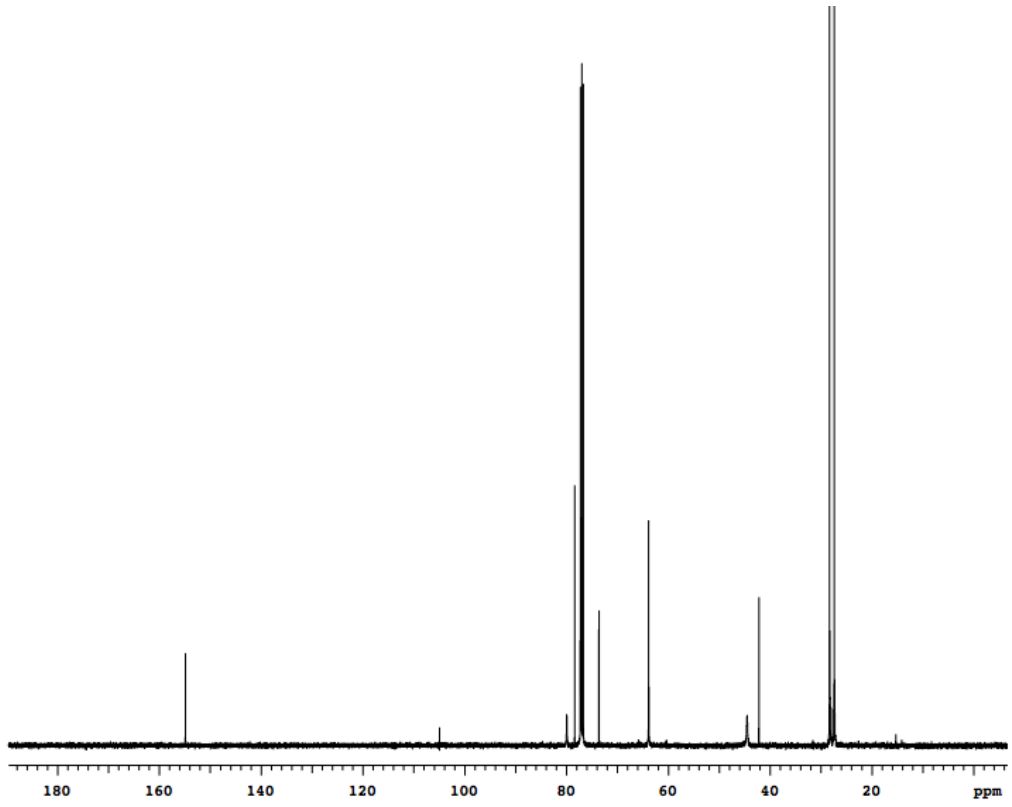
Compound **10c** was prepared from **9h** (0.40 g, 1.7 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 0.45 g (84 %) **10c** as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (br, 1H), 4.51 (br, 1H), 3.47 (br, 2H), 1.45 (s, 9H), 1.20 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.86, 79.95, 78.38, 73.61, 63.85, 44.50, 42.18, 28.31, 27.40 (107.25 is noise from NMR.)



^{1}H NMR of **10c**



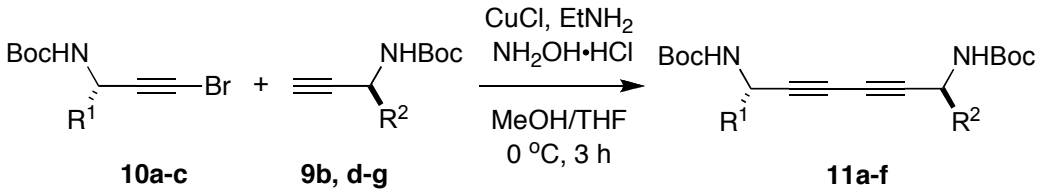
^{13}C NMR of **10c**

General Procedure for Compounds 11a-f

To a solution of **9b, d-g** (1.0 equiv) in MeOH (0.72 M) were added CuCl (0.1 equiv), $NH_2OH{\cdot}H_2O$ (0.95 equiv) and ethyl amine (25.0 equiv) at 0 ^{o}C under N_2 (g). A THF solution of **10a-c** (1.2 equiv) was added dropwise to the reaction mixture at 0 ^{o}C over 1 h. After adding the THF solution, the mixture was stirred at 0 ^{o}C for 2 h. The mixture was then quenched by added H_2O and extracted with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and then concentrated under vacuum. The compounds **11a-f** were purified by Flash chromatography. [13]

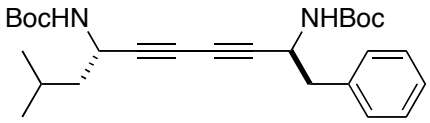
For compound **11d'**, to a solution of **11d** (1.0 equiv) in THF (0.082 M) was added TBAF (1.2 equiv) at 0 ^{o}C. After stirring at 0 ^{o}C for 15 min, the reaction mixture was warmed to 25 ^{o}C and then stirred for 45 min. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$. After completely removing the solvent, the **11d'** was purified by flash chromatography.

Scheme S8. Synthesis of compounds **11a-f**.



10a-c **9b, d-g** **11a-f**

Preparation of Compound 11a



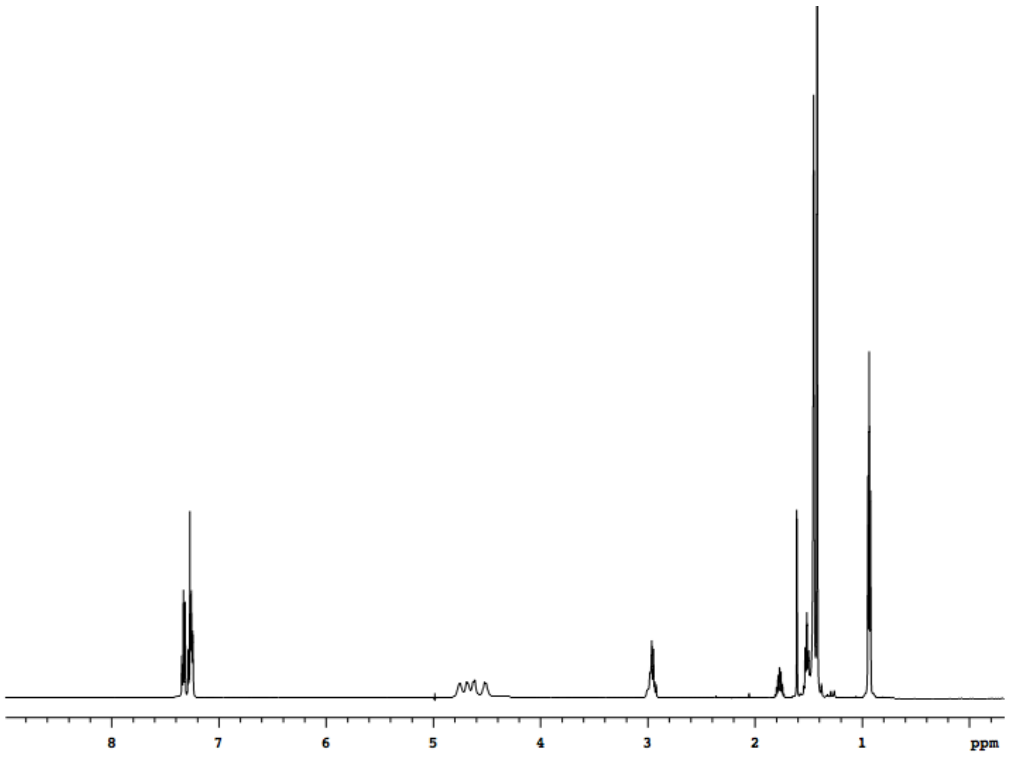
11a

Compound **11a** was prepared from **10a** (0.26 g, 0.88 mmol) and **9b** (0.18 g, 0.73 mmol). Flash chromatography (1:19 to 1:9 EtOAc/Hexanes) afforded 0.31g (94 %) **11a** as a white solid.

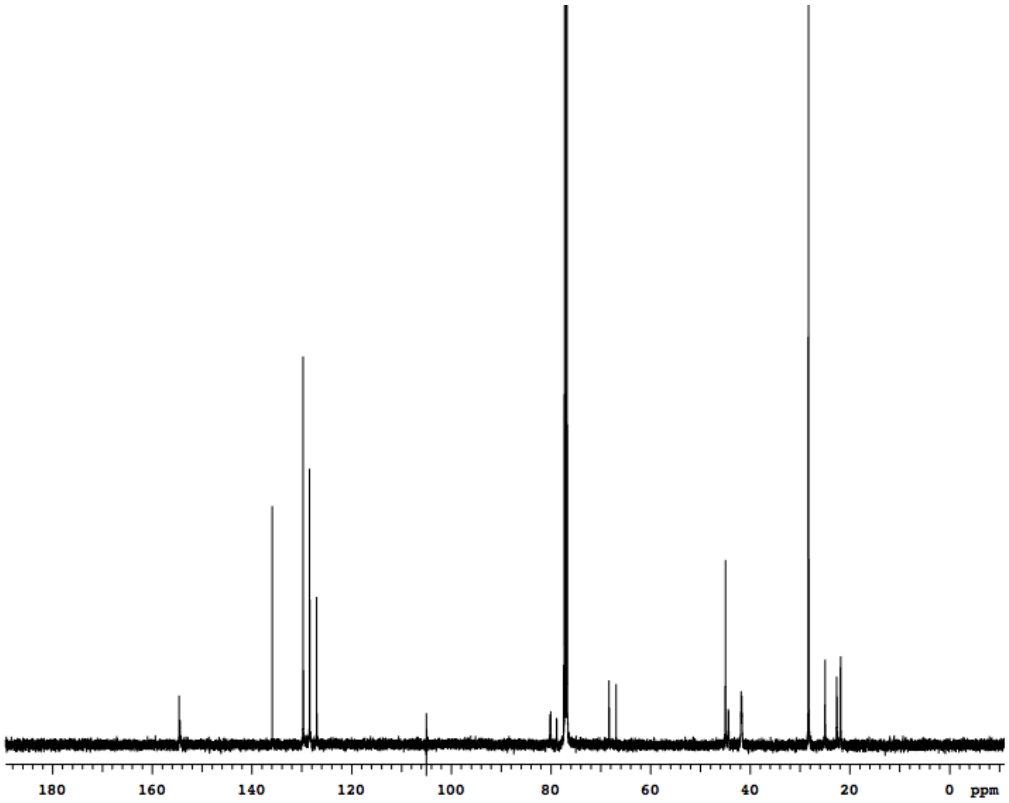
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, 2H, J = 7.5 Hz), 7.29-7.24 (m, 3H), 4.76 (br, 1H), 4.69 (br, 1H), 4.62 (br, 1H), 4.52 (br, 1H), 3.00-2.98 (m, 1H), 2.94 (dd, 1H, J = 7.0, 13.5 Hz), 1.81-1.73 (m, 1H), 1.52 (dd, 2H, J = 7.5, 7.5 Hz), 1.45 (s, 9H), 1.42 (s, 9H), 0.94 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 5.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.61, 154.44, 135.93, 129.70, 128.41, 126.99, 80.15, 80.04, 78.84, 77.44, 68.31, 66.91, 44.96, 44.37, 41.84, 28.32, 28.27, 24.97, 22.63, 21.85 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{27}H_{38}N_2NaO_4$ $(M+Na)^+$ 477.27, found 477.34

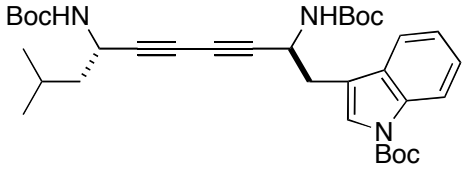


^{1}H NMR of **11a**



^{13}C NMR of **11a**

Preparation of Compound 11b



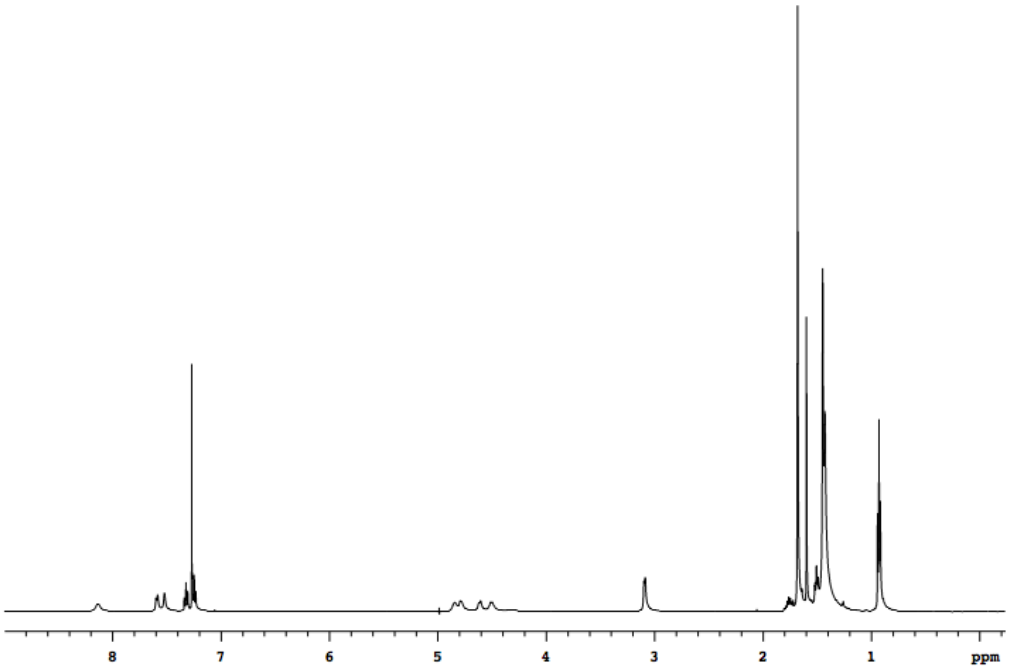
11b

Compound **11a** was prepared from **10a** (0.27 g, 0.94 mmol) and **9f** (0.30 g, 0.78 mmol). Flash chromatography (1:9 EtOAc/Hexanes) afforded 0.39 g (84 %) **11a** as a white solid.

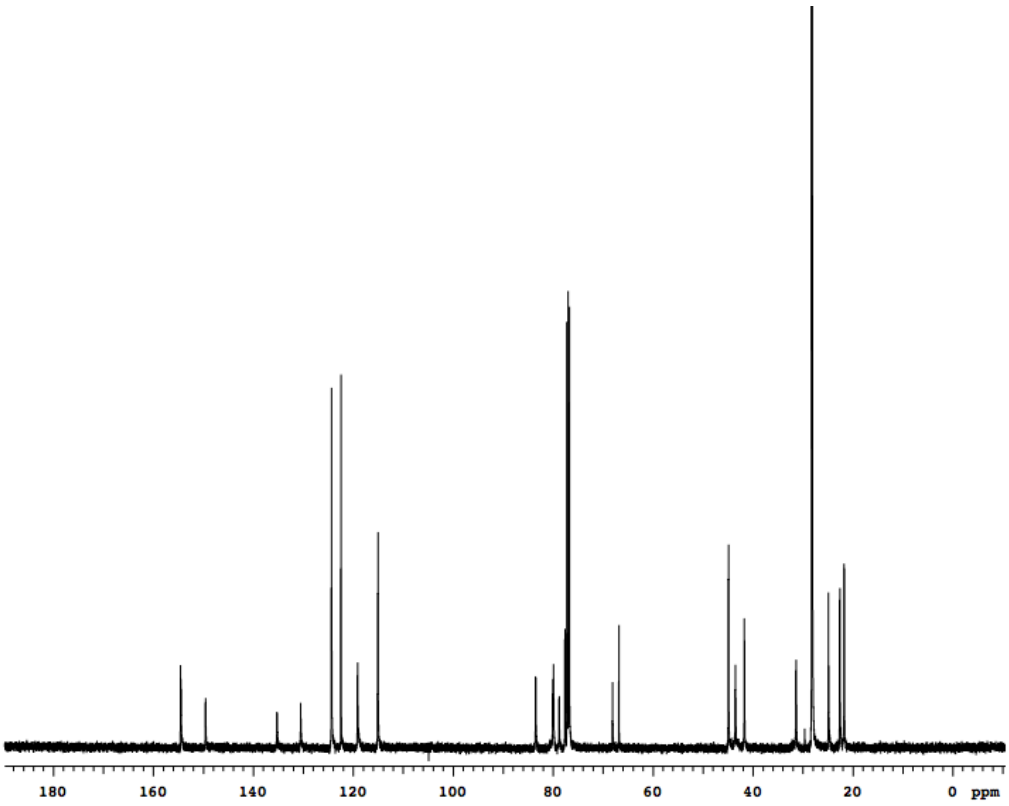
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br, 1H), 7.59 (d, 1H. J = 8.0 Hz), 7.52 (br, 1H), 7.32 (t, 1H, J = 7.0 Hz), 7.25 (t, 1H, J = 8.0 Hz), 4.85 (br, 1H), 4.79 (br, 1H), 4,61 (br, 1H), 4.50 (br, 1H), 3.09 (d, 2H, 6.0 Hz), 1.79-1.72 (m, 1H), 1.68 (s, 9H), 1.51 (dd, 2H, J = 7.5, 7.5 Hz), 1.45 (s, 9H), 1.43 (s, 9H), 0.94 (d, 3H, 7.0 Hz), 0.92 (d, 3H, 6.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.56, 154.47, 149.55, 135.25, 130.51, 124.34, 124.34, 122.46, 119.12, 115.09, 115.03, 83.48, 80.06, 79.90, 78.78, 77.63, 68.10, 66.82, 44.89, 43.51, 41.71, 31.36, 28.26, 28.22, 28.13, 24.89, 22.61, 21.74

MS (MALDI, m/z) calcd for $C_{34}H_{47}N_3NaO_6$ $(M+Na)^+$ 616.34, found 616.40

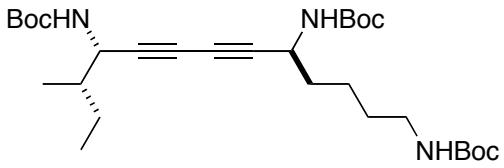


^{1}H NMR of **11b**



^{13}C NMR of **11b**

Preparation of Compound 11c



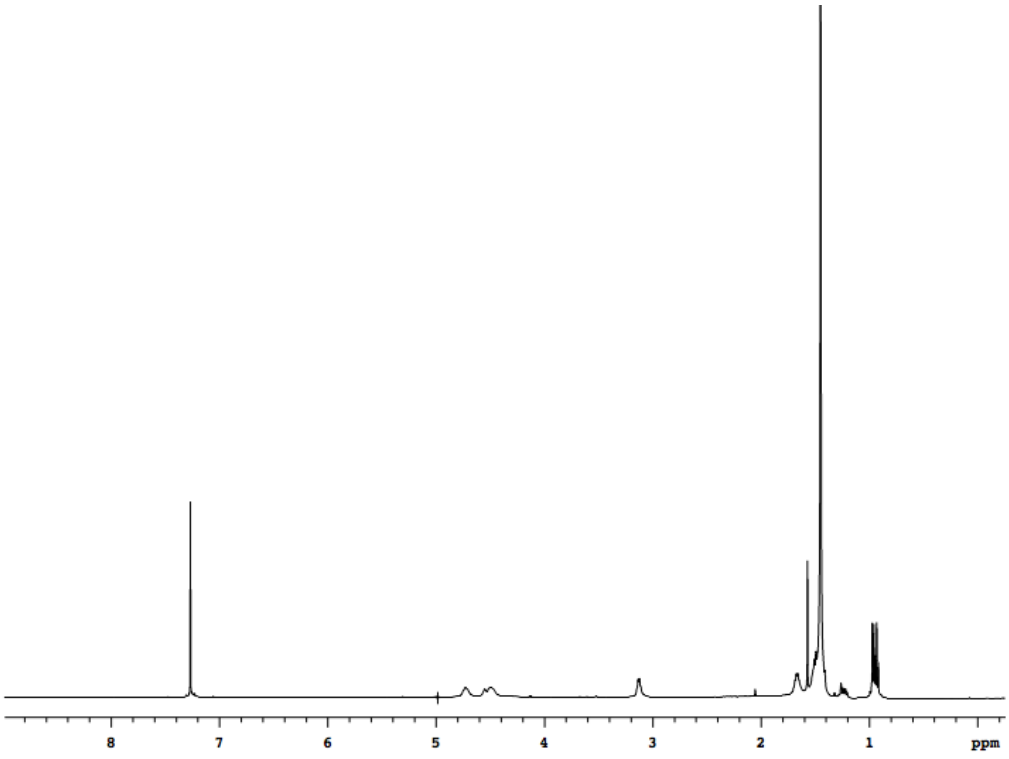
11c

Compound **11c** was prepared from **10b** (0.25 g, 0.85 mmol) and **9d** (0.23 g, 0.70 mmol). Flash chromatography (1:19 EtOAc/Hexanes) afforded 0.27 g (71 %) **11c** as a colorless oil.

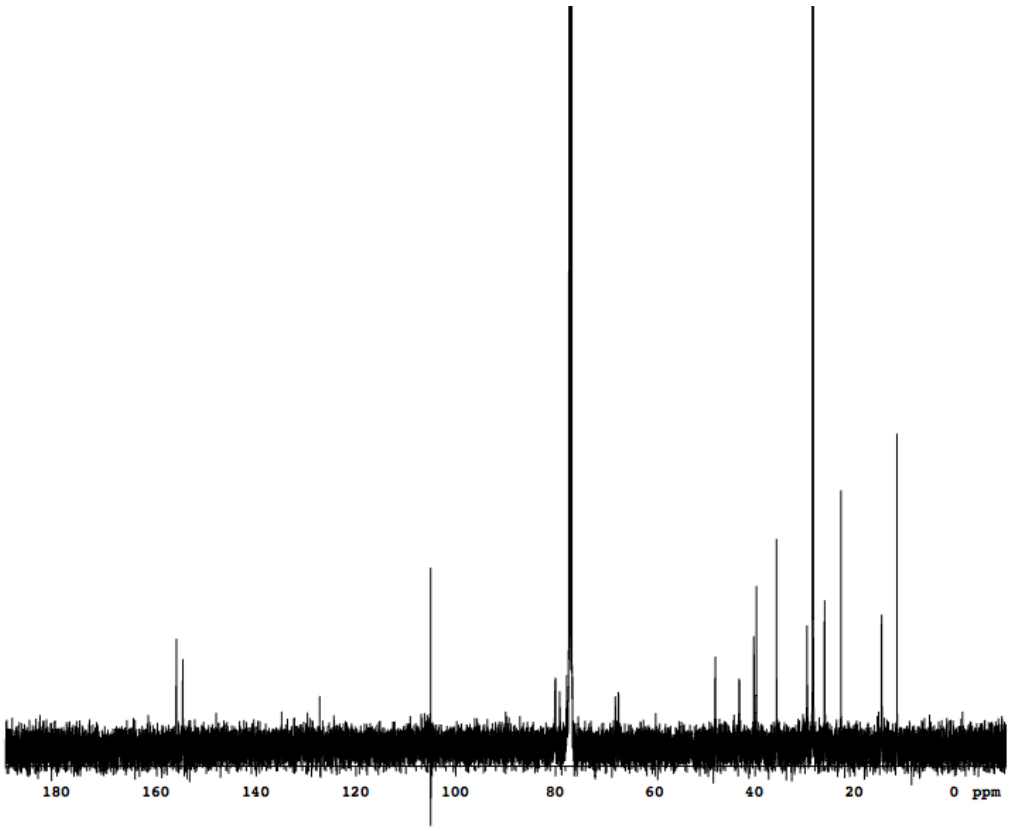
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (br, 2H), 4.55 (br, 1H), 4.49 (br, 2H), 3.14-3.12 (m, 2H), 1.69-1.61 (m, 3H), 1.54-1.45 (m, 5H), 1.28-1.20 (m, 1H), 0.97 (d, 3H, J = 6.5 Hz), 0.92 (t, 3H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.02, 154.71, 154.71, 80.12, 80.01, 80.01, 79.14, 77.71, 67.97, 67.36, 47.95, 43.14, 40.21, 39.70, 35.66, 29.53, 28.42, 28.33, 28.33, 26.04, 22.74, 14.60, 11.50 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{29}H_{49}N_3NaO_6$ $(M+Na)^+$ 558.35, found 558.17

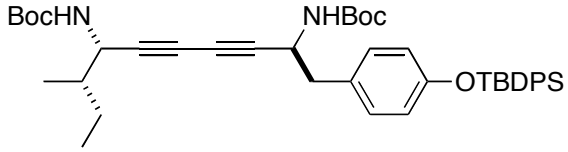


^{1}H NMR of **11c**



^{13}C NMR of **11c**

Preparation of Compound 11d



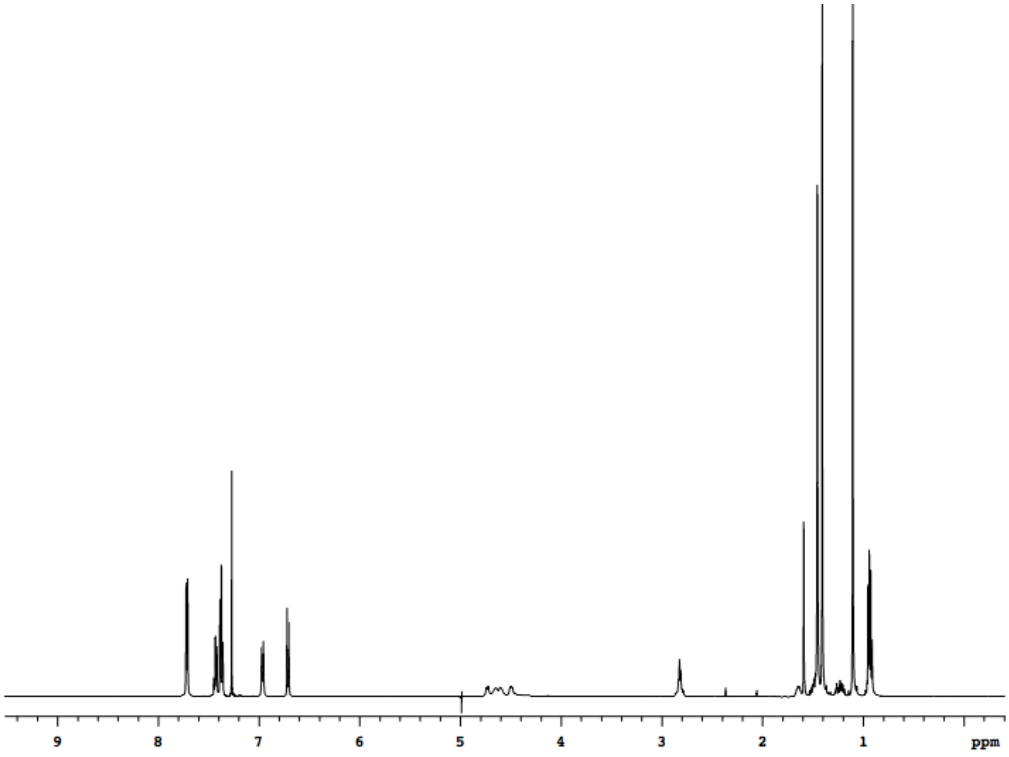
11d

Compound **11d** was prepared from **10b** (0.12 g, 0.41 mmol) and **9e** (0.17 g, 0.34 mmol). Flash chromatography (1:19 EtOAc/Hexanes) afforded 0.18 g (74 %) **11d** as a yellowish solid.

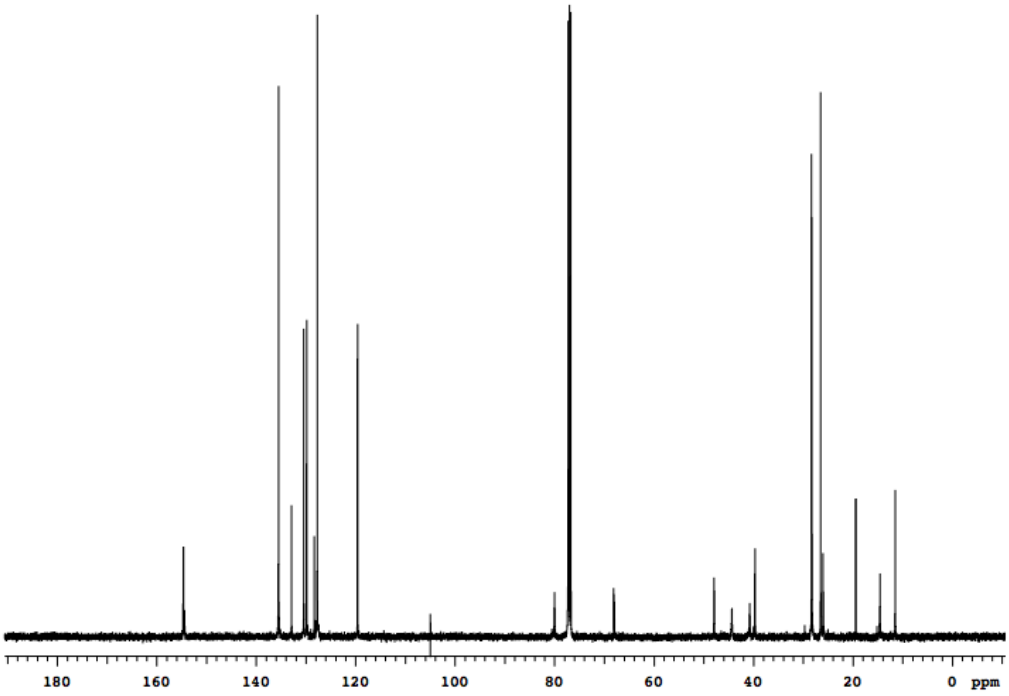
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 4H, J = 7.0 Hz), 7.43 (dd, 2H, J = 7.5, 7.5 Hz), 7.37 (dd, 4H, J = 7.5, 7.5 Hz), 6.97 (d, 2H, J = 8.5 Hz), 6.71 (d, 2H, J = 9.0 Hz), 4.73 (d, 1H, J = 8.5 Hz), 4.65 (br, 1H), 4.61 (br, 1H), 4.50 (br, 1H), 2.88-2.83 (m, 1H), 2.81 (dd, 1H, J = 6.5, 13.5 Hz), 1.68-1.62 (m, 1H), 1.53-1.46 (m, 1H), 1.46 (s, 9H), 1.41 (s, 9H), 1.27-1.19 (m, 1H), 1.10 (s, 9H), 0.95 (d, 3H, J = 6.0 Hz), 0.93 (t, 3H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.71, 154.62, 154.41, 135.49, 132.89, 130.42, 129.84, 128.31, 127.71, 119.61, 79.99, 79.99, 77.34, 77.34, 68.09, 67.97, 47.90, 44.34, 40.76, 39.68, 28.31, 28.26, 26.49, 26.00, 19.3, 14.56, 11.49 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{43}H_{56}N_2NaO_5Si$ $(M+Na)^+$ 731.39, found 731.40

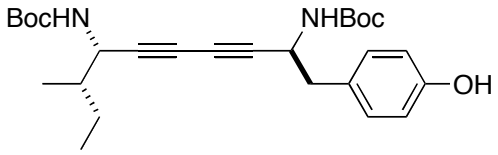


^{1}H NMR of **11d**



^{13}C NMR of **11d**

Preparation of Compound 11d'



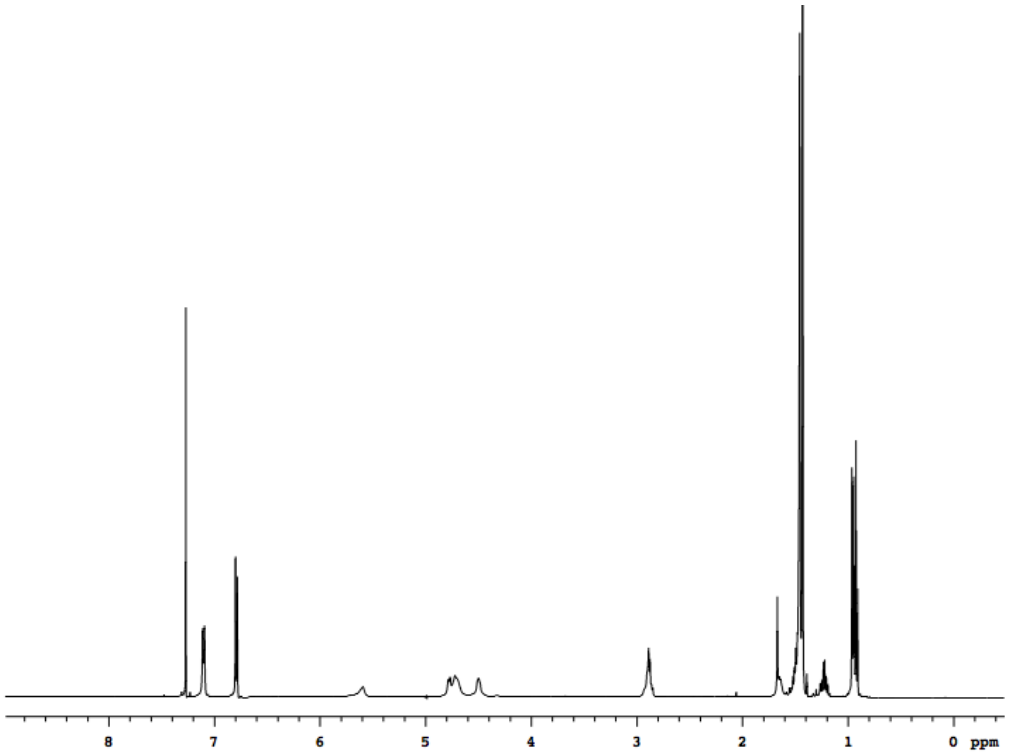
11d'

Compound **11d'** was prepared from **11d** (94.50 mg, 0.13 mmol). Flash chromatography (1:5 EtOAc/Hexanes) afforded (57.10 mg, 91 %) **11d'** as a yellowish solid.

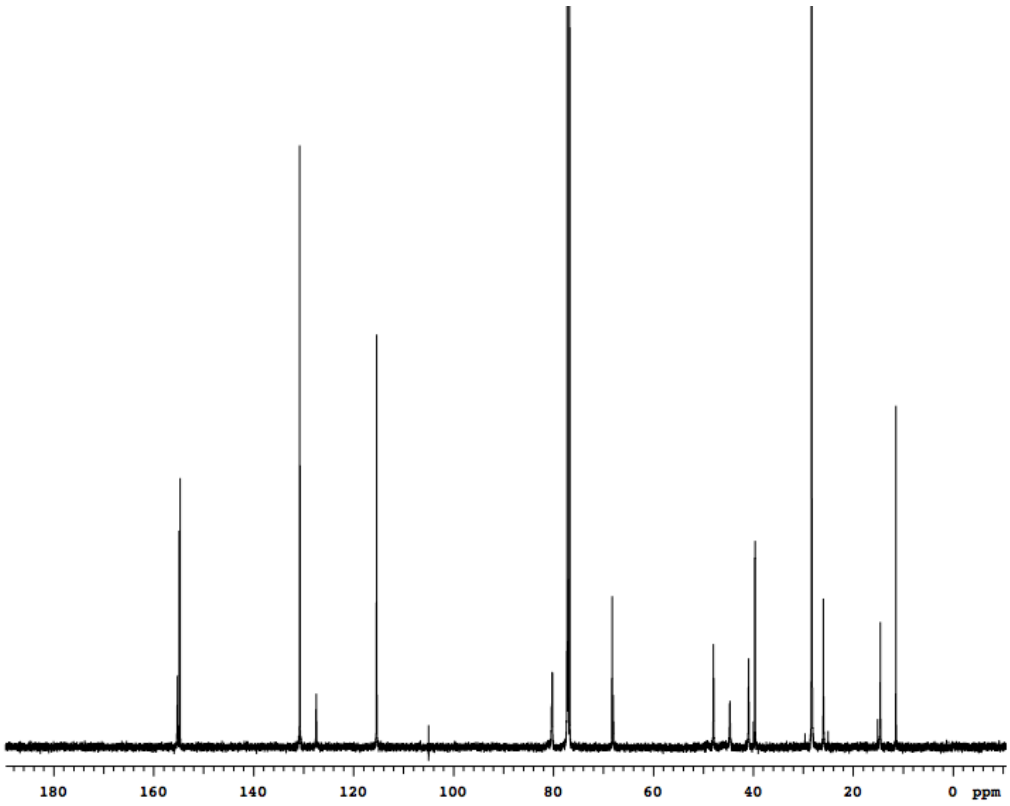
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, 2H, J = 8.0 Hz), 6.79 (d, 2H, J = 8.5 Hz), 5.59 (br, 1H), 4.78 (d, 1H, J = 8.0 Hz), 4.72 (br, 2H), 4.50 (br, 1H), 2.94-2.89 (m, 1H), 2.87 (dd, 1H, J = 6.5, 13.0 Hz), 1.67-1.64 (m, 1H), 1.54-1.46 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H), 1.27-1.18 (m, 1H), 0.96 (d, 3H, J = 7.0 Hz), 0.92 (d, 3H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.23, 154.89, 154.69, 130.75, 127.45, 115.37, 80.34, 80.21, 77.13, 77.13, 68.24, 68.00, 47.96, 44.68, 40.91, 39.65, 28.31, 28.27, 25.97, 14.57, 11.45 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{27}H_{38}N_2NaO_5$ $(M+Na)^+$ 493.27, found 493.33

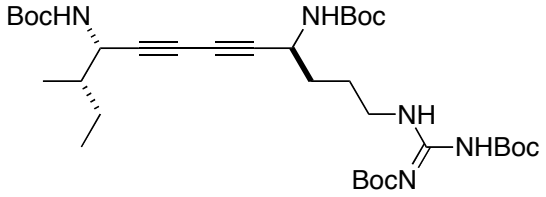


^{1}H NMR of **11d'**



^{13}C NMR of **11d'**

Preparation of Compound 11e



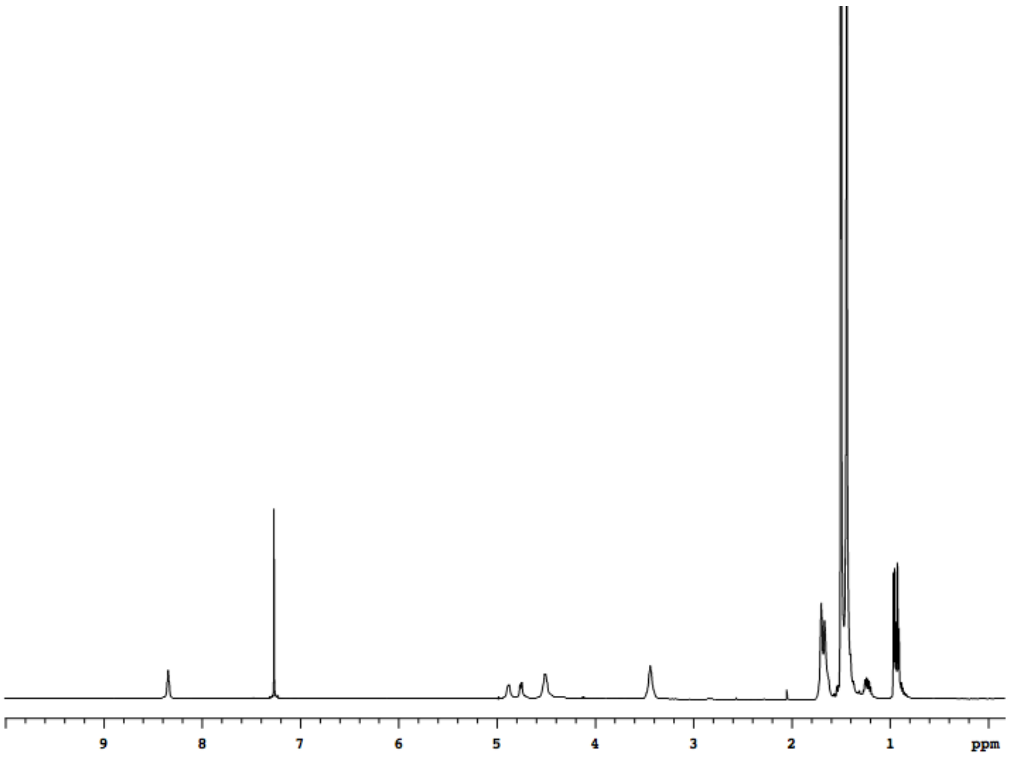
11e

Compound **11e** was prepared from **10b** (0.11 g, 0.4 mmol) and **9g** (0.15 g, 0.33 mmol). Flash chromatography (1:19 to 1:5 % EtOAc/Hexanes) afforded 0.21 g (95 %) **11e** as a yellowish solid.

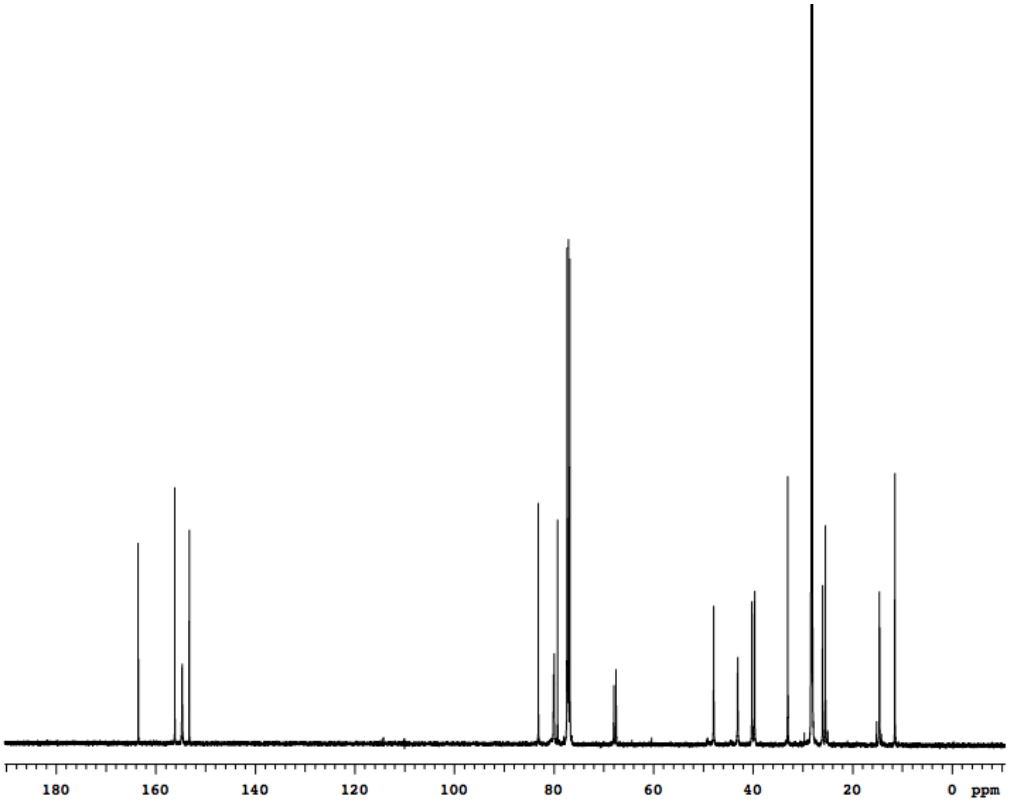
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (t, 1H, J = 4.5 Hz), 4.88 (d, 1H, J = 7.5 Hz), 4.76 (d, 1H, J = 13.5 Hz), 4.51 (br, 2H), 3.44 (br, 2H), 1.71-1.67 (m, 7H), 1.54-1.51 (m, 1H), 1.51 (s, 9H), 1.50 (s, 9H), 1.44 (s, 18H), 1.30-1.15 (m, 1H), 0.96 (d, 3H, J = 6.5 Hz), 0.93 (d, 1H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.42, 156.08, 154.66, 154.58, 153.18, 83.05, 83.05, 79.99, 79.88, 79.18, 79.18, 67.86, 67.43, 47.82, 42.99, 40.14, 39.59, 32.94, 28.24, 28.18, 27.97, 27.97, 25.94, 25.38, 14.51, 11.43

MS (MALDI, m/z) calcd for $C_{34}H_{57}N_5NaO_8$ $(M+Na)^+$ 686.41, found 686.43

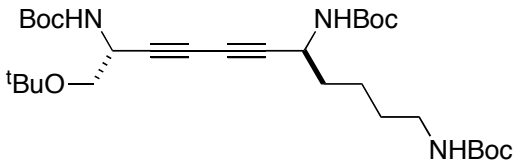


^{1}H NMR of **11e**



^{13}C NMR of **11e**

Preparation of Compound 11f



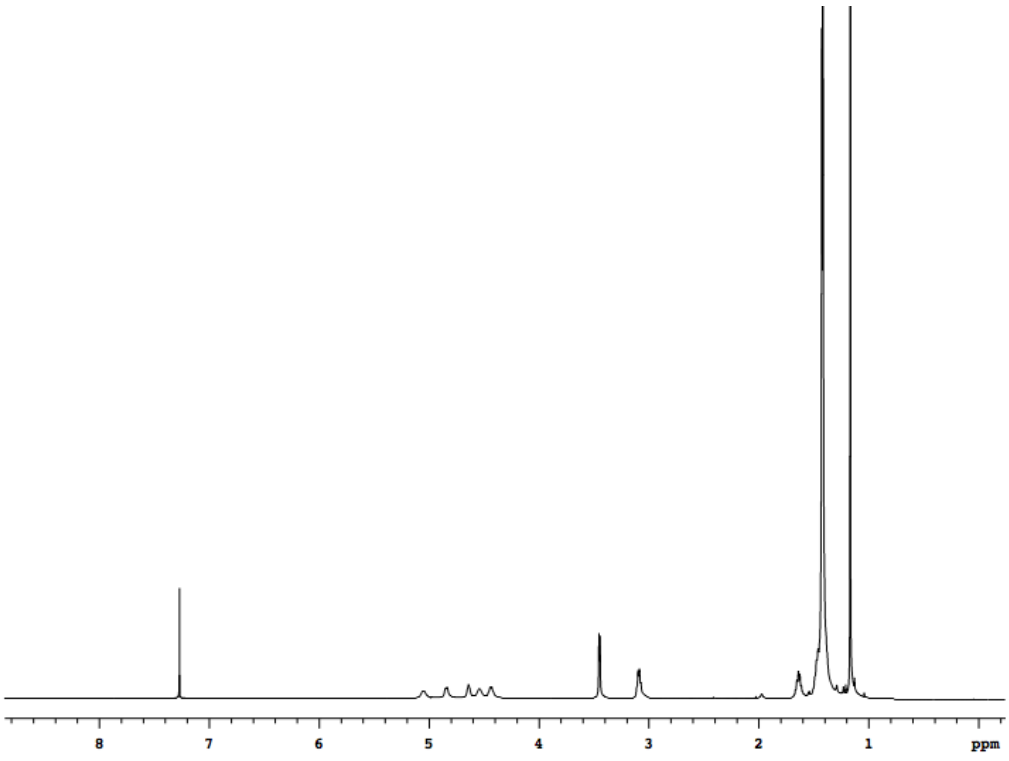
11f

Compound **11f** was prepared from **10c** (0.16 g, 0.51 mmol) and **9d** (0.14 g, 0.43 mmol). Flash chromatography (1:19 EtOAc/Hexanes) afforded 0.18 g (73 %) **11f** as a yellowish oil.

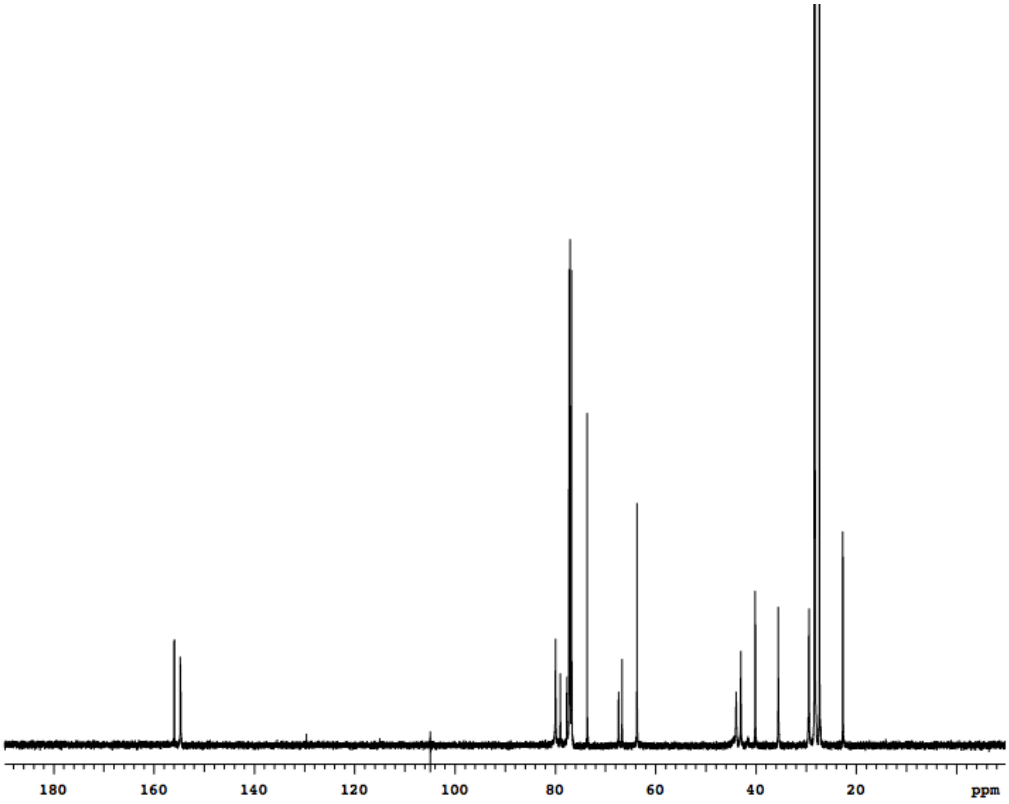
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (br, 1H), 4.84 (d, 1H, J = 8.0 Hz), 4.64 (br, 1H), 4.54 (br, 1H), 4.46-4.40 (m, 1H), 3.45 (d, 2H, J = 4.5 Hz), 3.11-3.07 (m, 1H), 1.67-1.59 (m, 2H), 1.49-1.42 (br, 31H), 1.17 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.96, 154.74, 154.69, 79.95, 78.99, 78.99, 77.66, 77.11, 73.63, 67.38, 66.68, 63.71, 43.93, 43.00, 40.13, 35.54, 29.42, 28.35, 28.25, 28.25, 27.33, 22.66 (107.25 is noise from NMR.)

MS (MALDI, m/z) calcd for $C_{30}H_{51}N_3NaO_7$ $(M+Na)^+$ 588.36, found 588.41



^{1}H NMR of **11f**

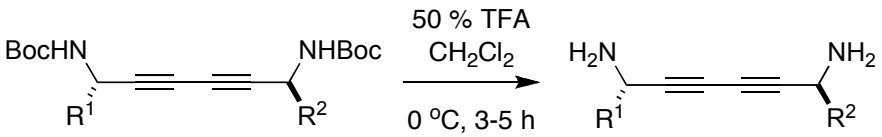


^{13}C NMR of **11f**

General Procedure for Compounds 2a-f

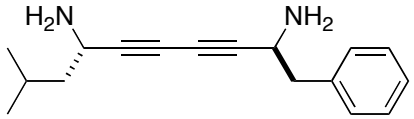
The compounds **11a-f** were treated with 50% TFA/CH_2Cl_2 at 0 ^{o}C for 3-5 h. Evaporating solvent under nitrogen afforded the desired product **2a-f**.

Scheme S9. Synthesis of compounds **2a-f**.



11a-f **2a-f**

Preparation of Compound 2a



2a

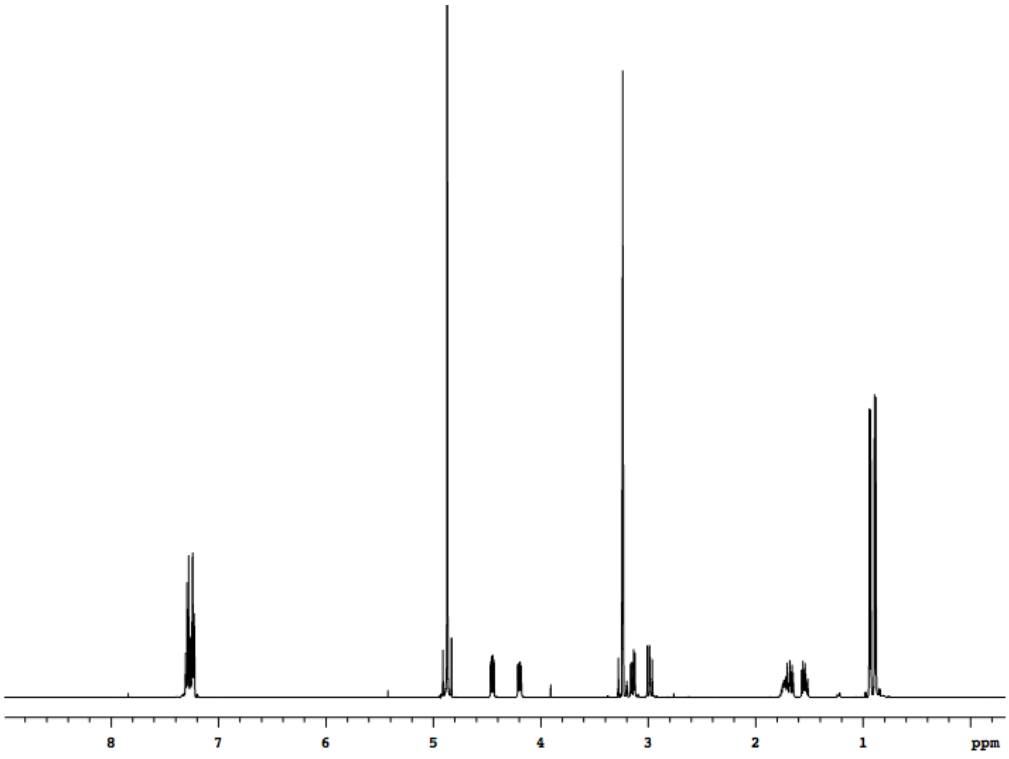
Compound **2a** was prepared from **11a** (10.0 mg, 0.022 mmol). **2a** was obtained as a yellowish amorphous solid (90 %, 2TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 7.31-7.23 (m, 5H), 4.45 (dd, 1H, J = 5.5, 9.5 Hz), 4.20 (dd, 1H, J = 5.5, 10.5 Hz), 3.15 (dd, 1H, J = 5.5, 13.5 Hz), 2.99 (dd, 1H, J = 9.5, 13.5 Hz), 1.76-1.71 (m, 1H), 1.71-1.65 (m, 1H), 1.57-1.52 (m, 1H), 0.94 (d, 3H, J = 6.5 Hz), 0.89 (d, 3H, J = 6.5 Hz)

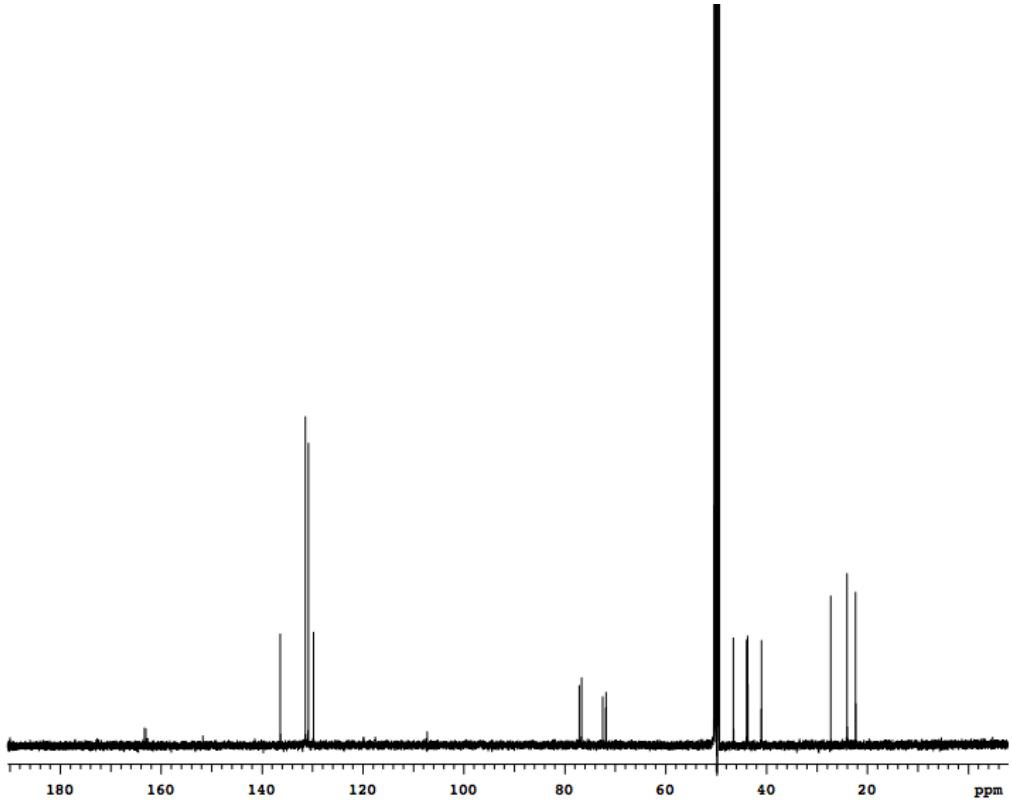
^{13}C NMR (125 MHz, CD_3OD) δ 136.36, 131.40, 130.81, 129.80, 77.11, 76.67, 72.48, 71.82, 46.55, 43.95, 43.71, 41.01, 27.26, 24.01, 22.32 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{17}H_{23}N_2$ $(M+H)^+$ 255.19, found 255.21

optical rotation $[\alpha]_D^{19.6}$ = +63.7 (*c* = 0.96 in MeOH)

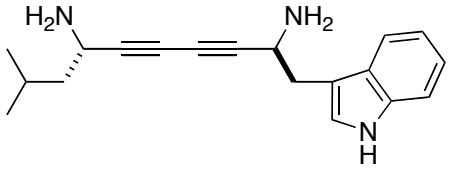


^{1}H NMR of **2a**



^{13}C NMR of **2a**

Preparation of Compound 2b



2b

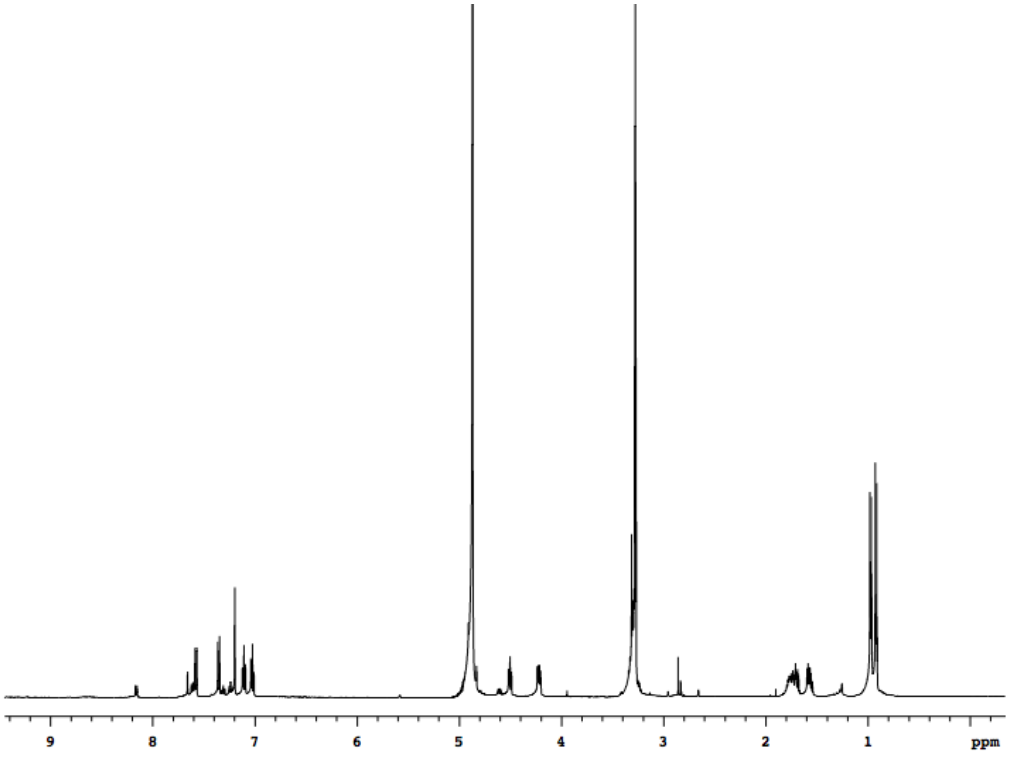
Compound **2b** was prepared from **11b** (9.50 mg, 0.016 mmol). **2b** was obtained as a yellowish amorphous solid (87 %, 2TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 7.57 (d, 1H, J = 8.0 Hz), 7.35 (d, 1H. J = 8.5 Hz), 7.20 (s, 1H), 7.10 (dd, 1H, J = 9.5, 9.5 Hz), 7.02 (dd, 1H, J = 8.0 Hz), 4.51 (dd, 1H, 7.5, 8.5 Hz), 4.22 (dd, 1H, J = 5.0, 10.5 Hz), 3.31-3.29 (m, 2H), 1.79-1.74 (m, 1H), 1.74-1,67 (m, 1H), 1.60-1.54 (m, 1H), 0.97 (d, 3H, J = 9.0 Hz), 0.92 (d, 3H, J = 6.5 Hz)

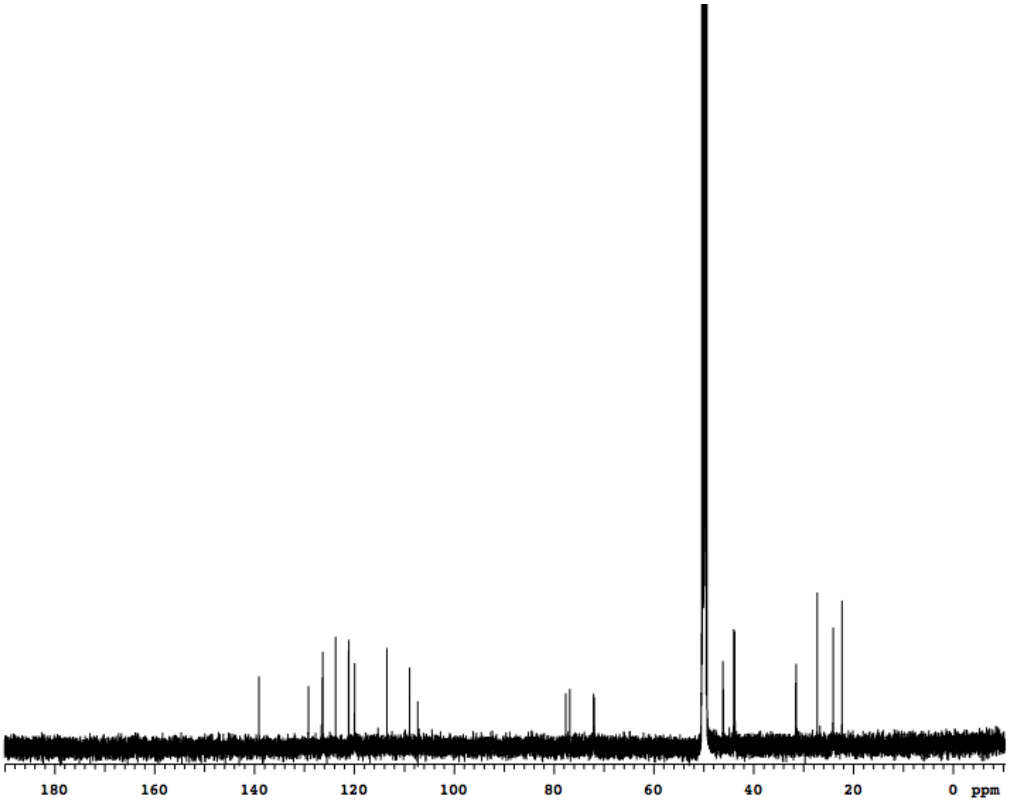
^{13}C NMR (125 MHz, CD_3OD) δ 136.79, 126.89, 124.07, 121.46, 118.83, 117.66, 111.18, 106.63, 75.34, 74.52, 69.79, 69.66, 43.85, 41.69, 41.48, 29.22, 24.95, 21.78, 20.00 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{19}H_{24}N_3$ $(M+H)^+$ 294.20, found 294.21

optical rotation $[\alpha]_D^{18.3}$ = +34.8 (*c* = 0.72 in MeOH)

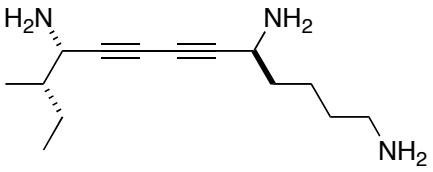


^{1}H NMR of **2b**



^{13}C NMR of **2b**

Preparation of Compound 2c



2c

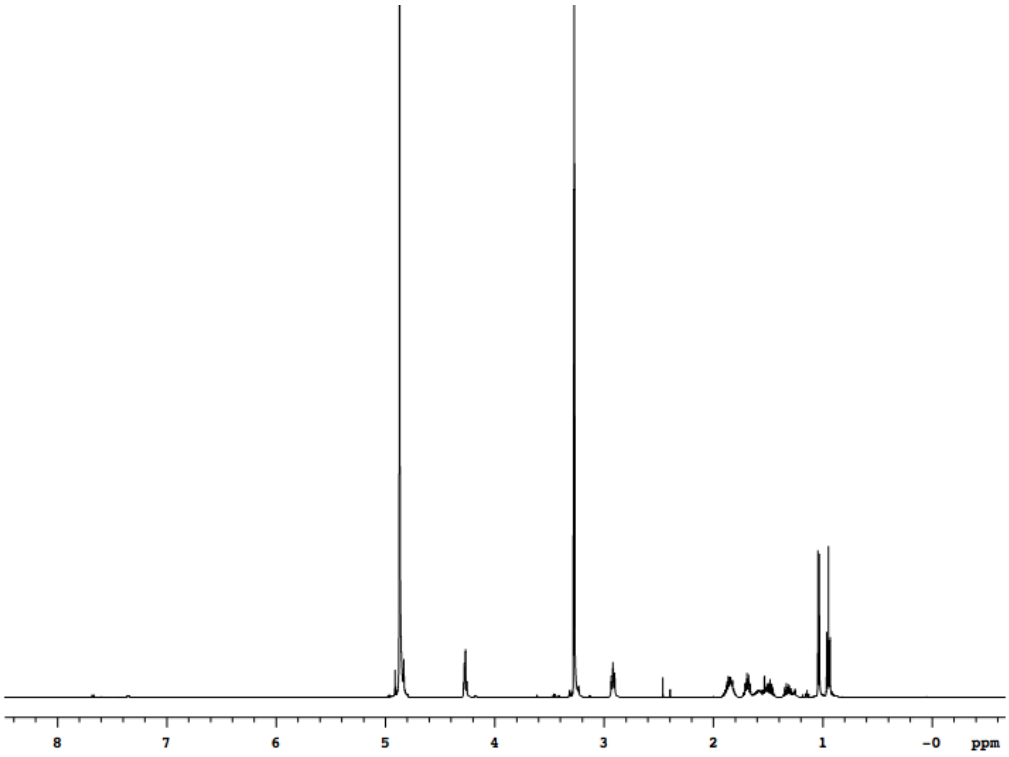
Compound **2c** was prepared from **11c** (4.80 mg, 0.009 mmol). **2c** was obtained as a yellowish amorphous solid (quant., 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 4.28 (d, 2H, J = 3.5 Hz), 4.27 (d, 2H, J = 10.5 Hz), 2.92 (t, 2H, J = 8.0 Hz), 1.90-1.80 (m, 3H), 1.73-1.66 (m, 2H), 1.53-1.44 (m, 2H), 1.35-1.27 (m, 2H), 1.04 (d, 3H, J = 6.5 Hz), 0.95 (t, 3H, J = 10.5 Hz)

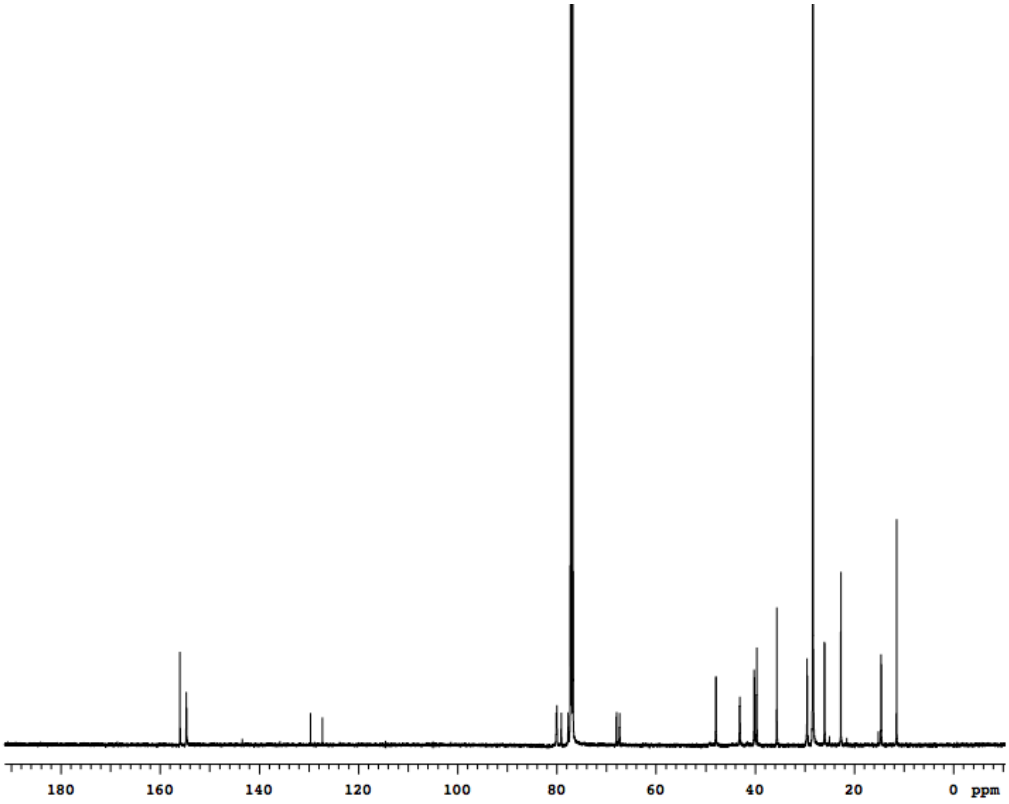
^{13}C NMR (125 MHz, CD_3OD) δ 76.31, 75.45, 72.55, 71.85, 44.89, 40.95, 39.75, 34.42, 28.56, 28.15, 24.26, 24.26, 14.81, 12.22

MS (ESI, m/z) calcd for $C_{14}H_{26}N_3$ $(M+H)^+$ 236.21, found 236.22

optical rotation $[\alpha]_D^{19.8}$ = +32.6 (*c* = 0.21 in MeOH)

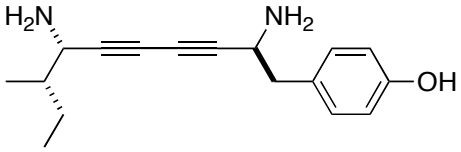


^{1}H NMR of **2c**



^{13}C NMR of **2c**

Preparation of Compound 2d



2d

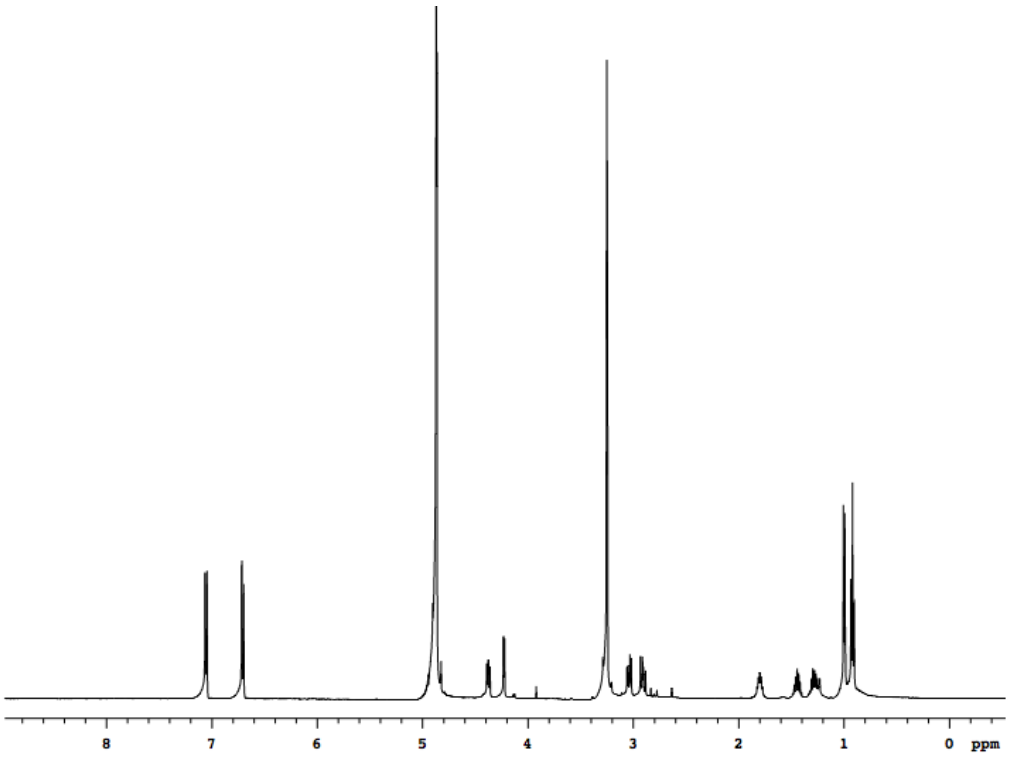
Compound **2d** was prepared from **11d** (10.0 mg, 0.013 mmol). **2d** was obtained as a yellowish amorphous solid (93 %, 2TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 7.05 (d, 2H, J = 8.5 Hz), 6.71 (d, 2H, J = 8.5 Hz), 4.38 (dd, 1H, J = 5.5, 9.0 Hz), 4.23 (d, 1H, J = 5.0 Hz), 3.04 (dd, 1H, J = 5.5, 13.5 Hz), 2.91 (dd, 1H, J = 9.5, 13.5 Hz), 1.83-1.78 (m, 1H), 1.83-1.78 (m, 1H), 1.47 (m, 1H), 1.30 (m, 1H), 1.00 (d, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.5 Hz)

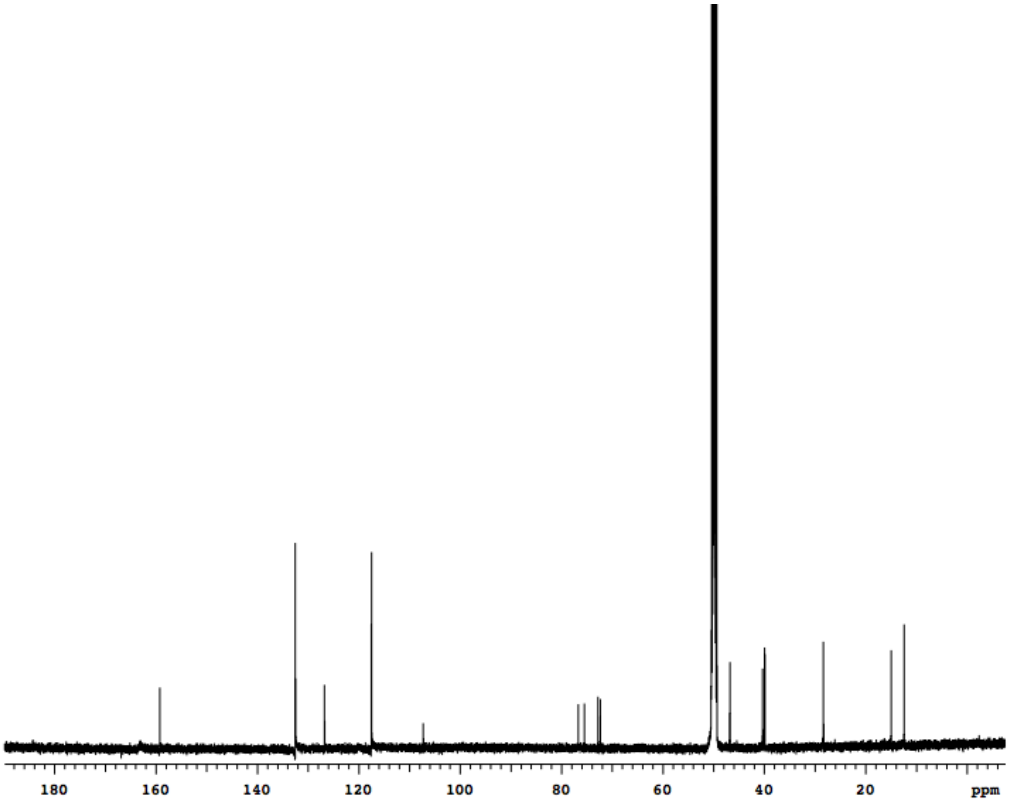
^{13}C NMR (125 MHz, CD_3OD) δ 156.98, 130.21, 124.46, 115.20, 74.40, 73.19, 70.50, 70.08, 44.49, 44.49, 38.03, 37.61, 26.03, 12.66, 10.11 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{17}H_{23}N_2O$ $(M+H)^+$ 271.18, found 271.19

optical rotation $[\alpha]_D^{18.6}$ = +40.2 (*c* = 0.60 in MeOH)

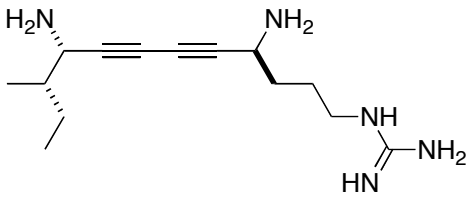


^{1}H NMR of **2d**



^{13}C NMR of **2d**

Preparation of Compound 2e



2e

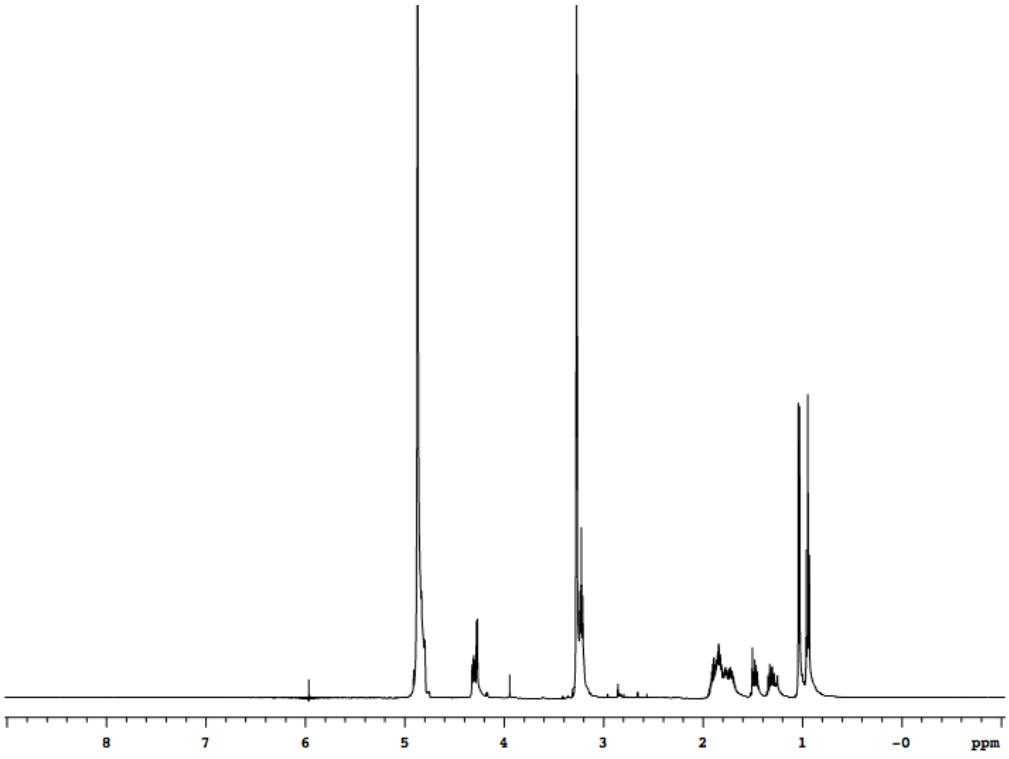
Compound **2e** was prepared from **11e** (9.80 mg, 0.015 mmol). **2e** was obtained as a yellowish amorphous solid (93 %, 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 4.31 (dd, 1H, J = 5.5, 9.0 Hz), 4.27 (d, 1H, J = 4.5 Hz), 3.22 (t, 2H, J = 7.0 Hz), 1.94-1.87 (m, 1H), 1.86-1.80 (m, 2H), 1.79-1.66 (m, 2H), 1.50-1.44 (m, 1H), 1.36-1.25 (m, 1H), 1.03 (d, 3H, J = 6.5 Hz), 0.95 (t, 3H, J = 10.5)

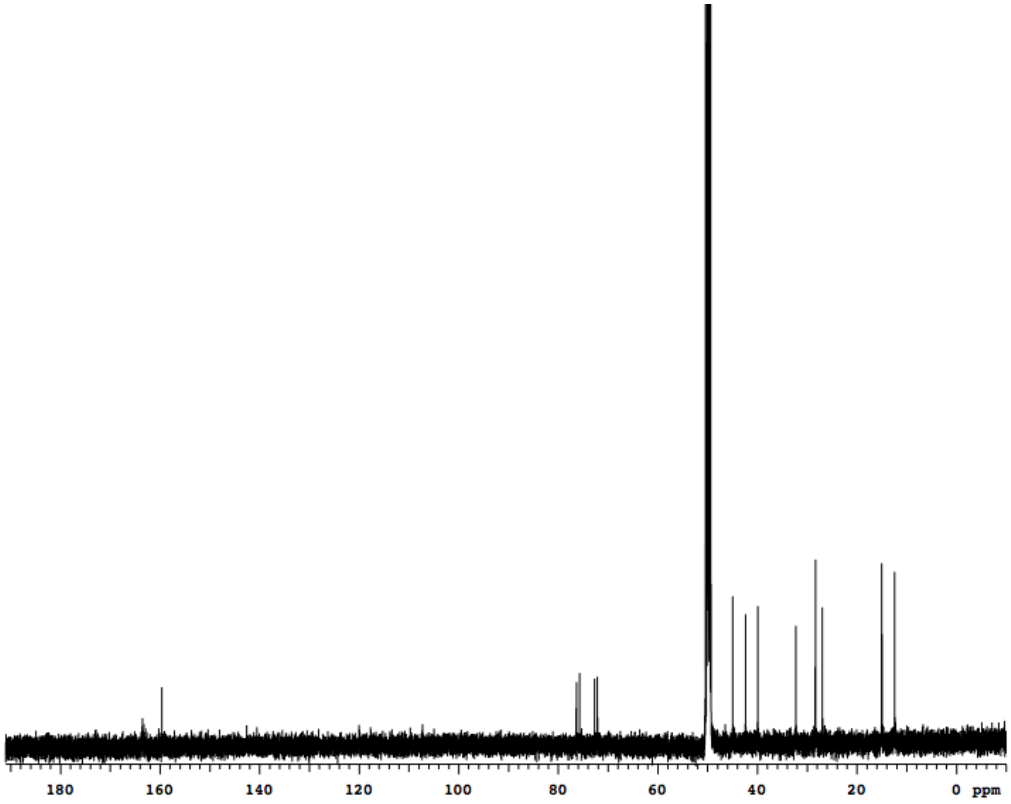
^{13}C NMR (125 MHz, CD_3OD) δ 157.32, 74.04, 73.40, 70.39, 69.82, 42.65, 40.07, 37.62, 37.62, 29.96, 26.04, 24.63, 12.68, 10.11

MS (ESI, m/z) calcd for $C_{14}H_{26}N_5$ $(M+H)^+$ 264.39, found 264.23

optical rotation $[\alpha]_D^{19.4}$ = +8.7 (*c* = 0.84 in MeOH)

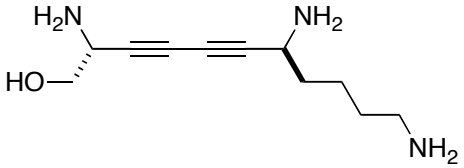


^{1}H NMR of **2e**



^{13}C NMR of **2e**

Preparation of Compound 2f



2f

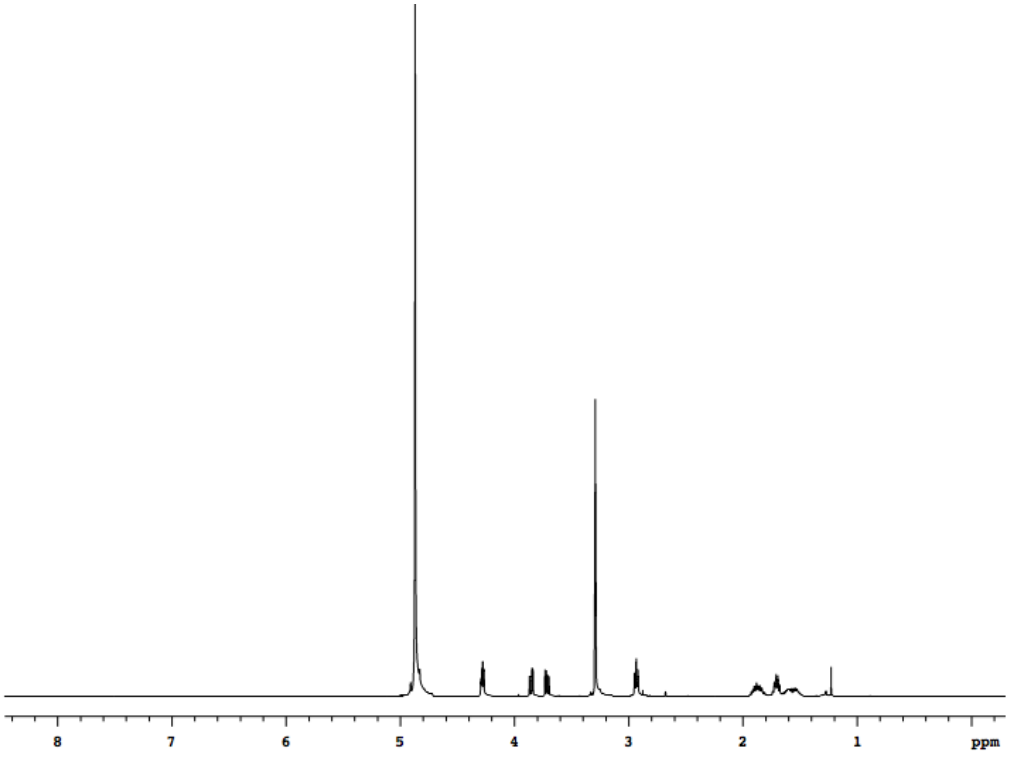
Compound **2f** was prepared from **11f** (10.30 mg, 0.018 mmol). **2f** was obtained as a yellowish amorphous solid (90%, 3TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 4.24 (dd, 1H, J = 1.5, 2.0 Hz), 4.22 (d, 1H, J = 5.0 Hz), 3.80 (dd, 1H, J = 4.5, 11.5 Hz), 3.66 (dd, 1H, J = 6.5, 11.5 Hz), 2.88 (t, 2H, J = 7.5 Hz), 1.87-1.75 (m, 2H), 1.68-1.62 (m, 2H), 1.58-1.52 (m, 1H), 1.50-1.45 (m, 1H)

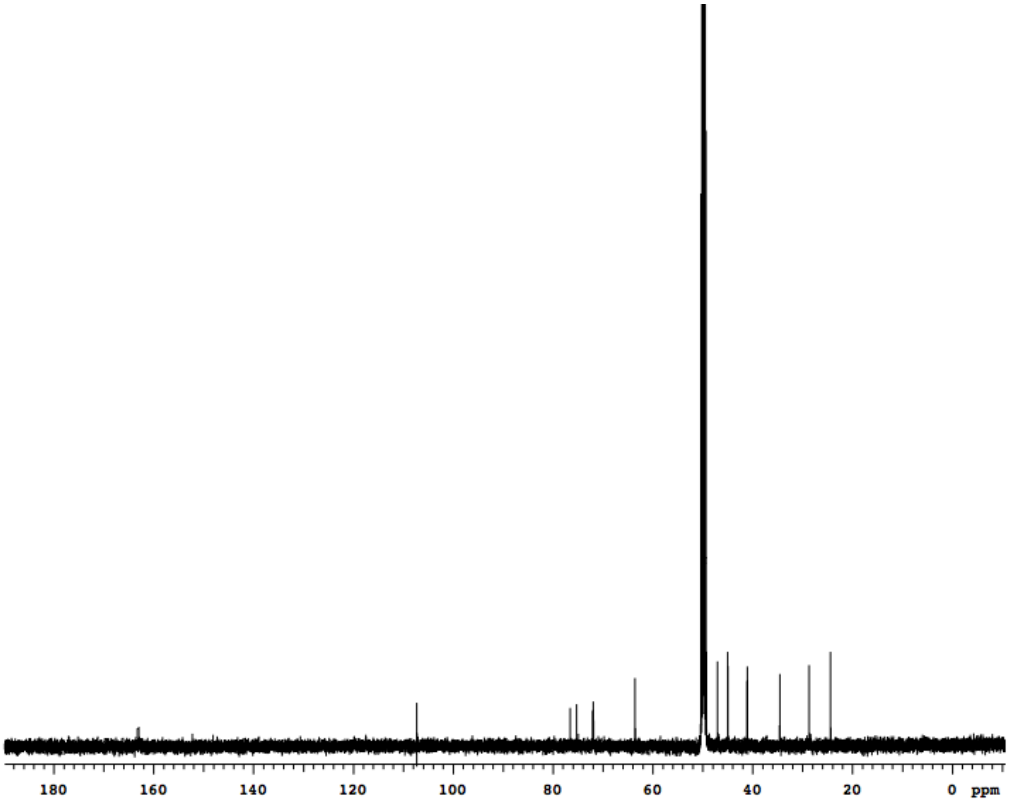
^{13}C NMR (125 MHz, CD_3OD) δ 76.56, 75.25, 72.10, 71.91, 63.56, 47.05, 44.98, 41.10, 34.57, 28.70, 24.40 (107.25 is noise from NMR.)

MS (ESI, m/z) calcd for $C_{11}H_{20}N_3O$ $(M+H)^+$ 210.16, found 210.17

optical rotation $[\alpha]_D^{19.1}$ = +1.4 (*c* = 0.85 in MeOH)



^{1}H NMR of **2f**



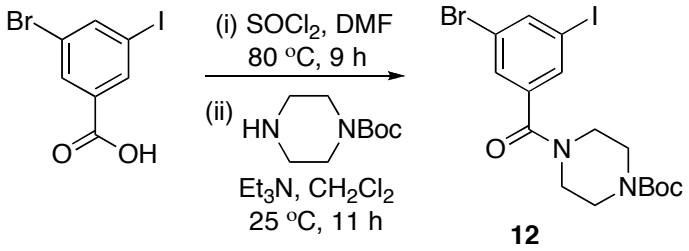
^{13}C NMR of **2f**

E. Preparation of Kinked Bistriazole Mimics

Procedure for Compound 12

To a suspension of 3-bromo-5-iodobenzoic acid (40.00 g, 122.35 mmol) in thionyl chloride (150 mL) was added DMF (0.40 mL) slowly at 25 ºC under nitrogen. The mixture was stirred at 80 °C for 9 h under nitrogen. The thionyl chloride was distilled away to give a brown solid. The resulting brown solid was dissolved in dichloromethane (200 mL), and Et_3N (50 mL) and *N*-Boc-piperazine (23.48 g, 126.00 mmol) were added slowly. The mixture was stirred for 11 h at 25 ºC. The reaction mixture was poured into water, extracted with EtOAc and dried over $MgSO_4$. The crude product was recrystallized from 95% EtOH to give **12** (51.83 g, 86%) as a pale yellowish solid.

Scheme S10. Synthesis of compound **12.**

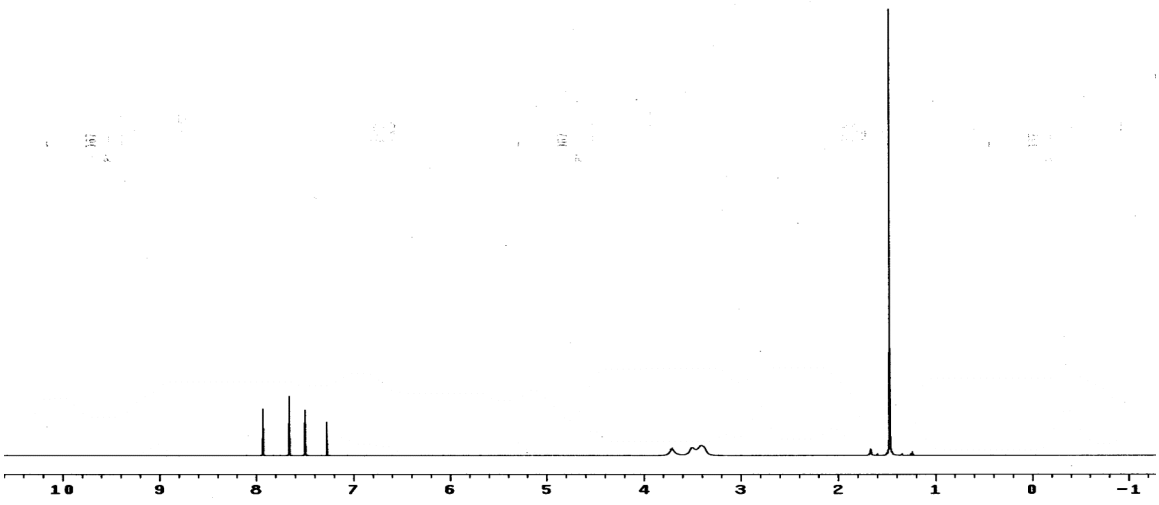


12

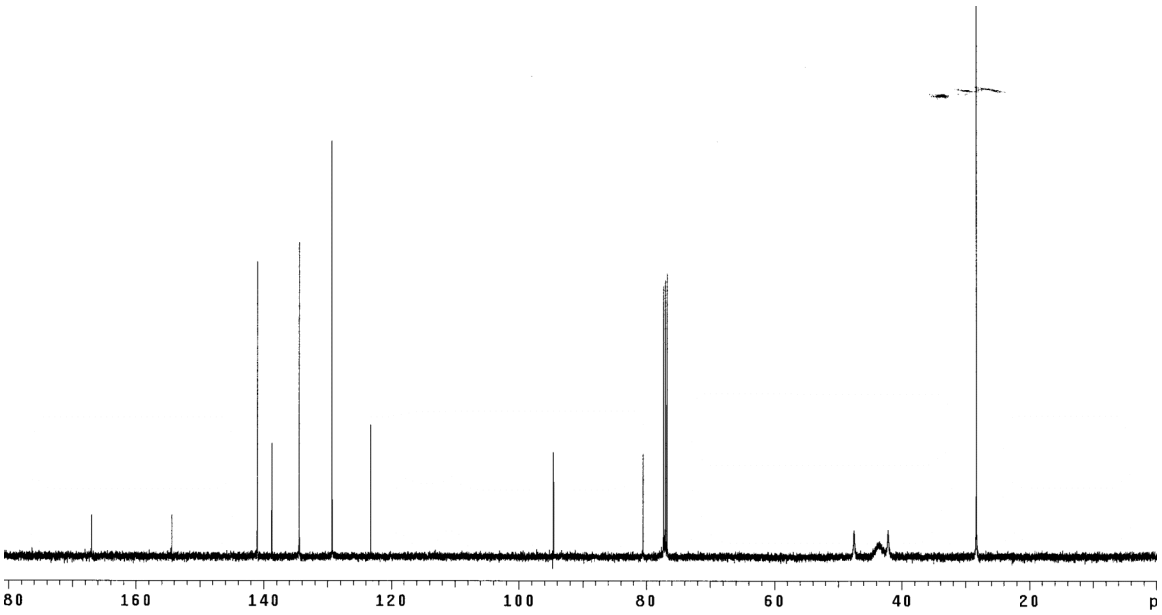
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (t, 1H, J = 1.8 Hz), 7.66 (t, 1H, J = 1.5 Hz), 7.50 (t, 1H, J = 1.8 Hz), 3.75-3.35 (m, 8H), 1.47 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 154.4, 141.0, 138.7, 134.4, 129.3, 123.2, 94.6, 80.5, 47.5, 43.4 (br), 42.1, 28.3

MS (ESI) calcd for $C_{16}H_{20}BrIN_2O_3$ $(M+H)^+$ 494.98, found 494.97



^{1}H NMR of **12**

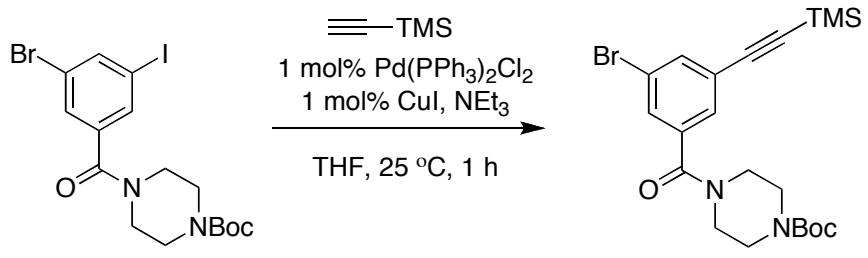


^{13}C NMR of **12**

Procedure for Compound 13

To a solution of $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol) and CuI (0.038 g, 0.20 mmol) in THF (200 mL) was added Et_3N (11.0 mL), **12** (19.81 g, 40.00 mmol) and trimethylsilyl-acetylene (6.8 mL, 48 mmol) under nitrogen. The mixture was stirred at 25 ºC for 1 h. After evaporation of solvent under reduced pressure, the crude product was purified by flash chromatography eluting with EtOAc/hexane (1:3) to give **13** (17.42 g, 94%) as a pale yellowish solid.

Scheme S11. Synthesis of compound **13.**

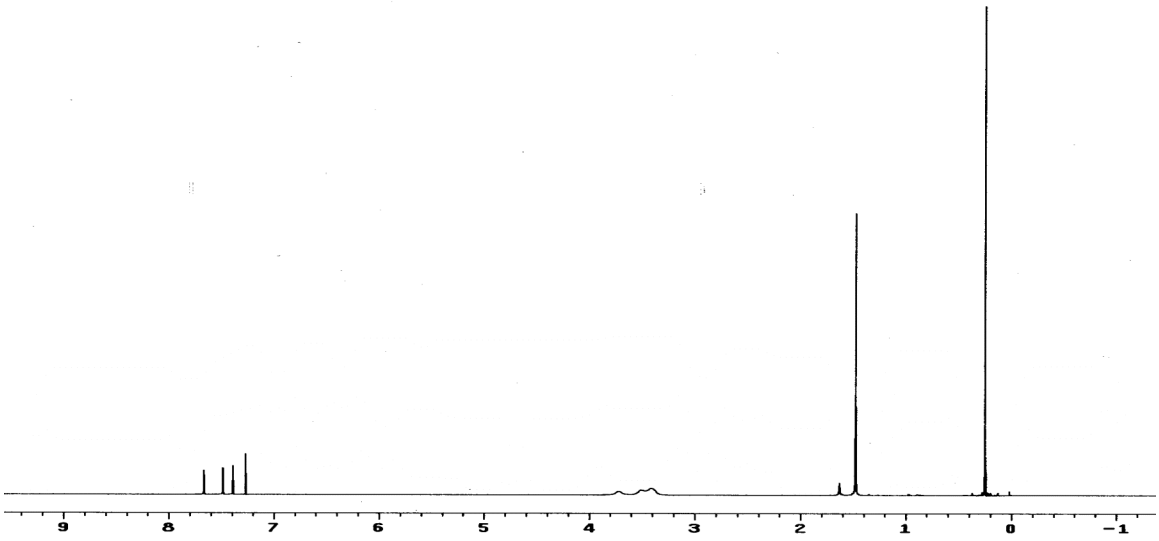


12 **13**

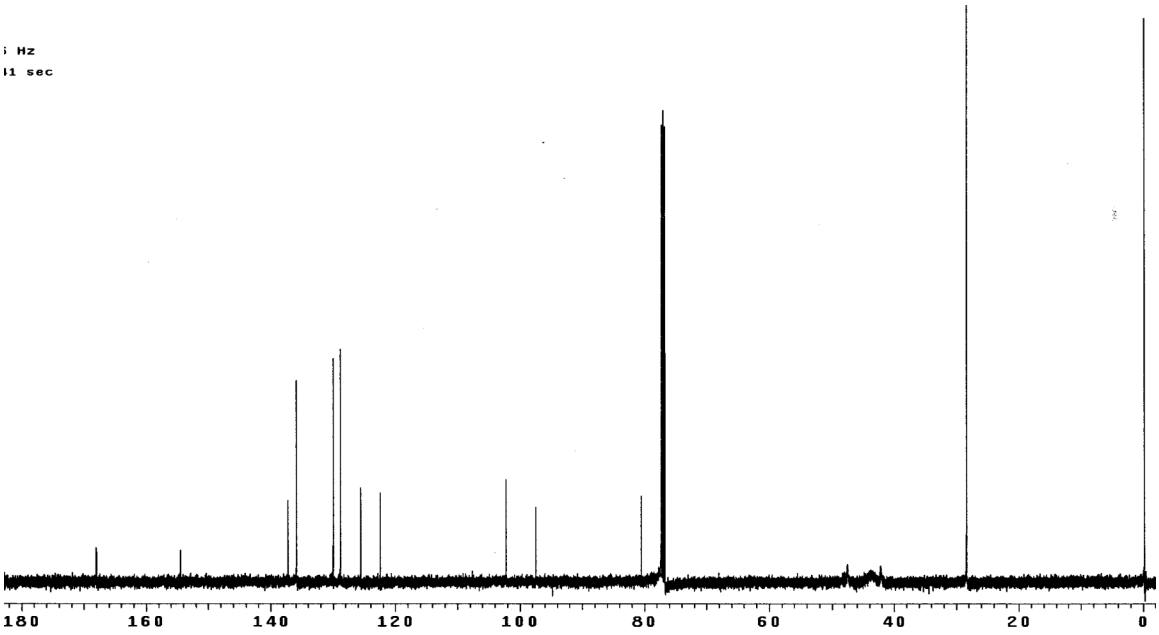
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (t, 1H, J = 1.5 Hz), 7.49 (t, 1H, J = 1.8 Hz), 7.39 (t, 1H, J = 1.3 Hz), 3.75-3.35 (m, 8H), 1.48 (s, 9H), 0.25 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 154.5, 137.2, 135.8, 130.0, 128.8, 125.5, 122.4, 102.2, 97.4, 80.5, 47.5, 43.7 (br), 42.1, 28.3, -0.27

MS (ESI) calcd for $C_{21}H_{29}BrN_2O_3Si$ $(M+H)^+$ 465.12, found 465.12



^{1}H NMR of **13**

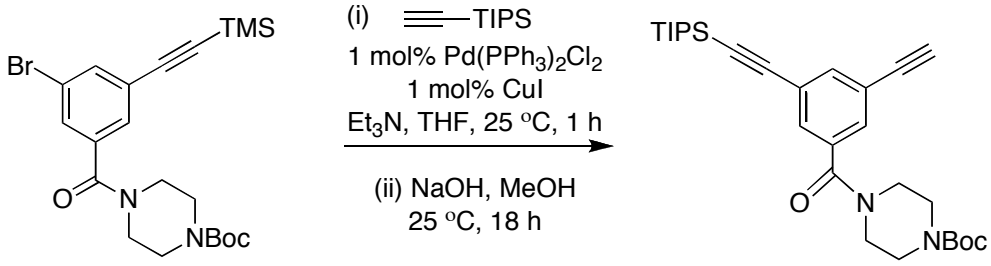


^{13}C NMR of **13**

Procedure for Compound 14

To a solution of **13** in THF (250 mL) under nitrogen was added $Pd(PPh_3)_2Cl_2$ (1.14 g, 1.62 mmol), CuI (0.31 g, 1.62 mmol), Et_3N (25.2 mL, 180 mmol) and triisopropylsilyl-acetylene (21.8 mL, 97.4 mmol). The mixture was stirred at 70 ºC for 12 h under nitrogen. After this time, the solvent was evaporated, and the mixture was filtered through a plug of silica eluting with EtOAc/hexane (1:20) followed by EtOAc/hexane (1:3). The eluant was washed with 0.5 M EDTA solution and the solvent was evaporated to give the crude coupled product with triisopropylsilylacetylene (46.1 g) as a yellow foam. To a solution of the intermediate coupling product in MeOH (300 mL) was added 1 *N* NaOH (0.30 mL). The reaction mixture was stirred at 25 ºC for 18 h. After this time, the solvent was evaporated, and the resulting residue was purified by flash chromatography eluting with hexane/EtOAc (10:1) followed by hexane/EtOAc (1:3) to give **14** (39.61 g, 99%) as a yellow solid.

Scheme S12. Synthesis of compound **14.**

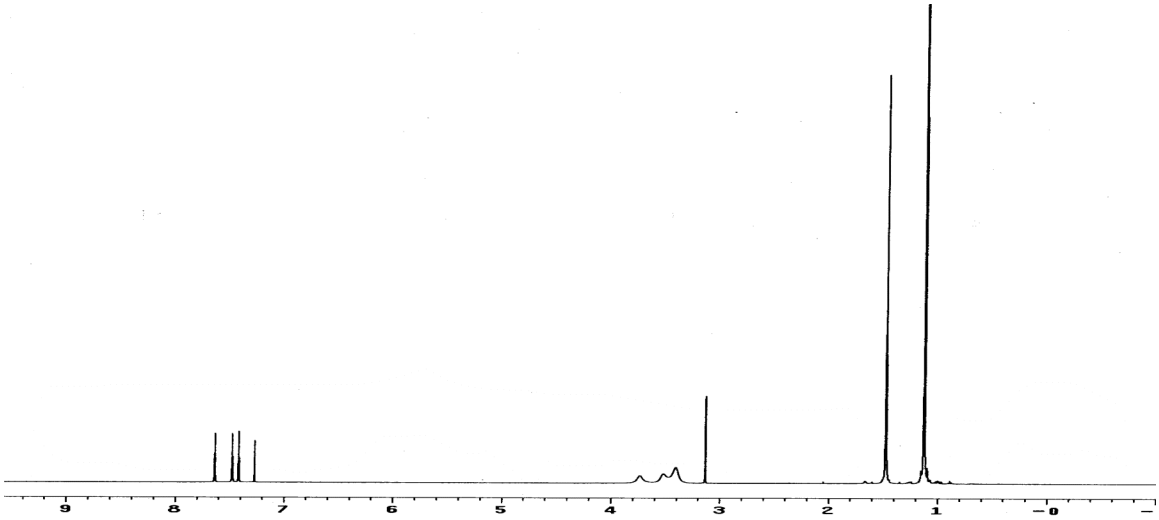


13 **14**

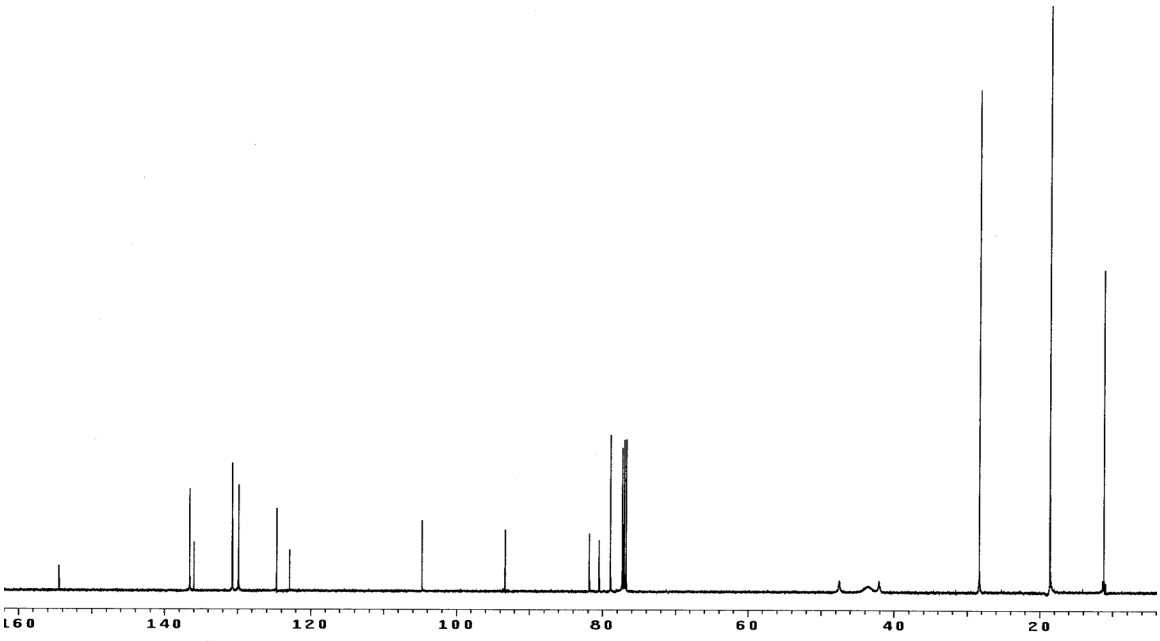
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (t, 1H, J = 1.5 Hz), 7.47 (t, 1H, J = 1.5 Hz), 7.41 (t, 1H, J = 1.5 Hz), 3.75-3.35 (m, 8H), 3.13 (s, 1H), 1.47 (s, 9H), 1.12 (s, 18H), 1.11 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 154.5, 136.5, 136.0, 130.7, 129.8, 124.6, 122.9, 104.7, 93.3, 81.8, 80.4, 78.9, 47.4, 43.5 (br), 42.1, 28.3, 18.6, 11.2

MS (ESI) calcd for $C_{29}H_{42}N_2O_3Si$ $(M+H)^+$ 495.30, found 495.30



^{1}H NMR of **14**



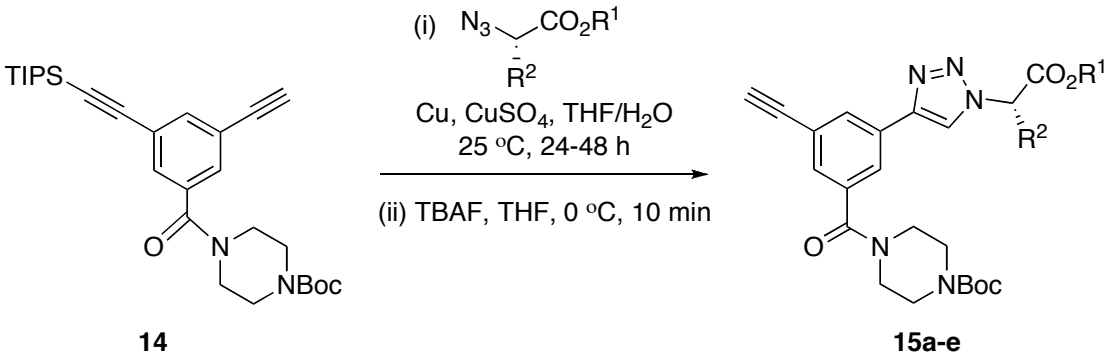
^{13}C NMR of **14**

General Procedure for Synthesis of 15a-e.

Amino ester azides were prepared from the corresponding amino esters following the procedure reported previously by Lundquist and Pelletier.[14] In general, a solution of sodium azide (10.0 equiv to amino ester) was dissolved in a 1:1 mixture of H_2O and CH_2Cl_2 (to give a 3M solution of sodium azide) and cooled in an ice bath. Triflic anhydride (2.0 equiv) was added over 5 min and the solution was then stirred at 0 °C for 2 h. The CH_2Cl_2 phase was separated, and the aqueous portion was extracted twice with CH_2Cl_2. The organic phases were combined, washed once with saturated Na_2CO_3, and the solution was used without further purification. The amino ester (1.0 equiv) was suspended in a solution of H_2O and CH_3OH (1:2, 0.1 M in amino ester) and K_2CO_3 (1.5 equiv), and $CuSO_4 \cdot 5H_2O$ (0.1 equiv), were added. The CH_2Cl_2 solution of triflyl azide prepared above was added in one portion, and the mixture was stirred at 25 °C for 16 h. The organic solvents were removed under reduced pressure, and the resulting aqueous solution was saturated with NaCl. This solution was extracted four times with ethyl acetate, the solvent was removed under reduced pressure, and the azido ester was purified by a short silica column.

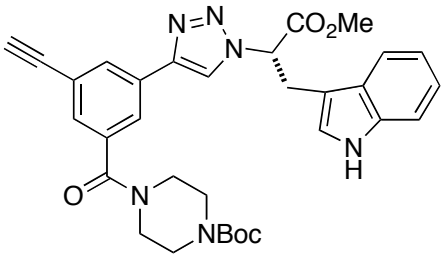
To a solution of **14** (1.0 equiv) and azido acid (1.3 equiv) in THF (3.5 mL/1.0 mmol **14**) and H_2O (3.5 mL/1.0 mmol **14**) was added Cu powder (1.0 equiv) and $CuSO_4$ (0.1 equiv., 1 *N* aqueous solution). The mixture was stirred at 25 ºC for 24-48 h. The reaction mixture was filtered through a plug of Celite and washed with EtOAc. The organic layer was washed with 3% EDTA solution, and dried ($MgSO_4$) to afford a crude product as a white solid. To a solution of the triazole product in THF (4.0 mL/1.0 mmol **3**) at 0 ºC was added TBAF (1.5 equiv, 1.0 M in THF) slowly. The mixture was stirred at 0 ºC for 10 min, poured into brine, extracted with EtOAc, and dried (Na_2SO_4) to give a crude product. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane to yield **15**.

Scheme S13. Synthesis of compound **15a-e.**



14 **15a-e**

Preparation of Compound15a



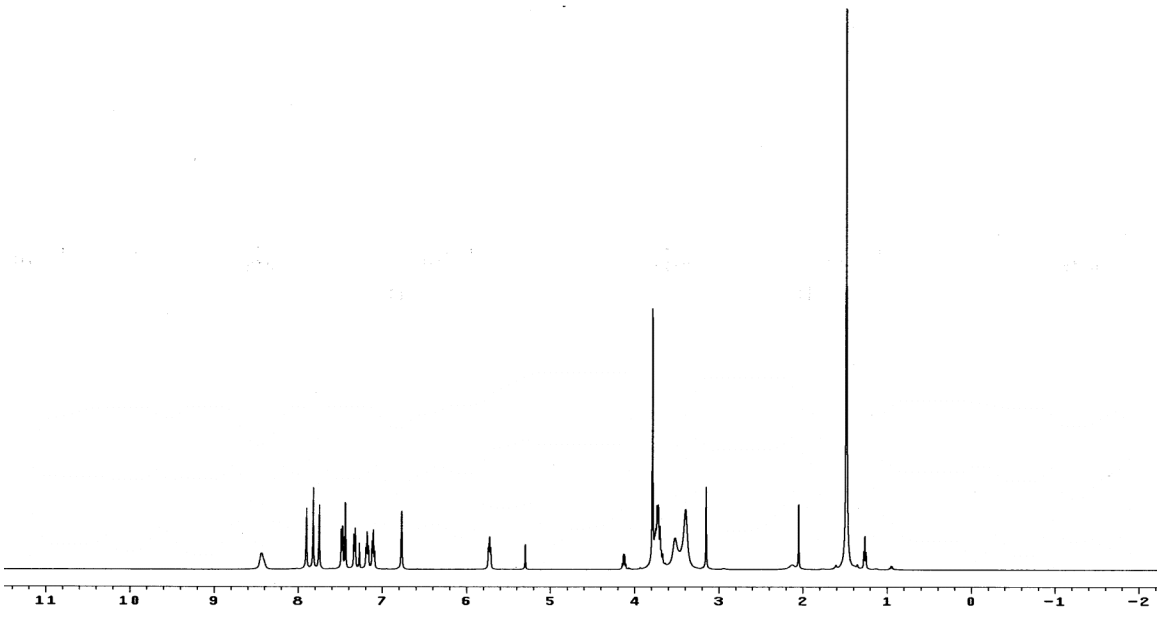
15a

Compound **15a** was prepared from (9.89 g, 20.0 mmol) of **14**. Flash chromatography (1:1 to 3:1 EtOAc/Hexane) afforded 10.95 g (94 % over two steps) **15a** as a pale green solid.

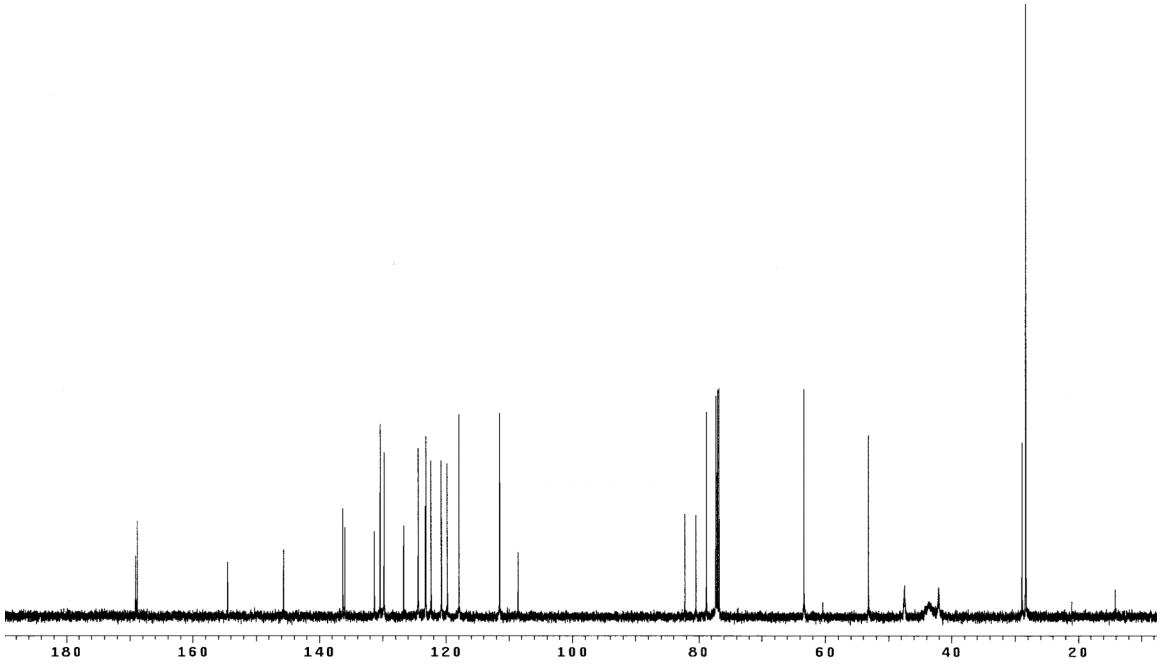
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.75 (s, 1H), 7.47 (d, 1H, J = 8.0 Hz), 7.44 (s, 1H), 7.33 (d, 1H, J = 8.0 Hz), 7.19 (t, 1H, J = 7.5 Hz), 7.10 (t, 2H, J = 7.3 Hz), 6.77 (s, 1H), 5.72 (t, 1H, J = 7.0 Hz), 3.79 (s, 3H), 3.76-3.35 (m, 10H), 3.15 (s, 1H), 1.48 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ169.1, 168.8, 154.5, 145.6, 136.3, 136.0, 131.3, 130.4, 129.8, 126.7, 124.4, 123.3, 123.2, 122.4, 120.7, 119.8, 117.9, 111.5, 108.5, 82.2, 80.4, 78.7, 63.3, 53.2, 47.5, 43.6 (br), 42.1, 28.9, 28.3

MS (ESI) calcd for $C_{32}H_{34}N_6O_5Na$ $(M+Na)^+$ 605.25, found 605.37

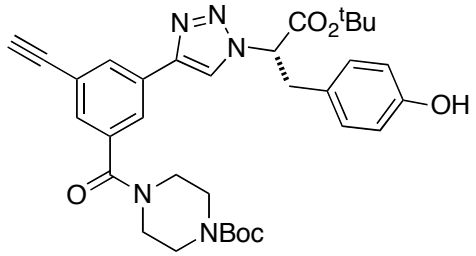


^{1}H NMR of **15a**



^{13}C NMR of **15a**

Preparation of Compound 15b



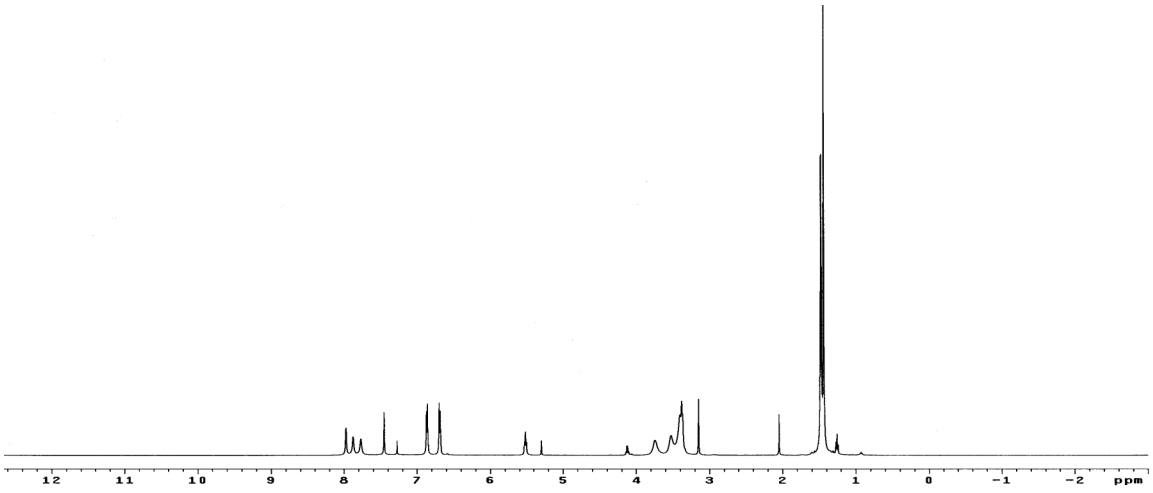
15b

Compound **15b** was prepared from (9.89 g, 20.0 mmol) of **14**. Flash chromatography (1:1 to 3:1 EtOAc/Hexane) afforded 11.92 g (99 % over two steps) **15b** as a yellow solid.

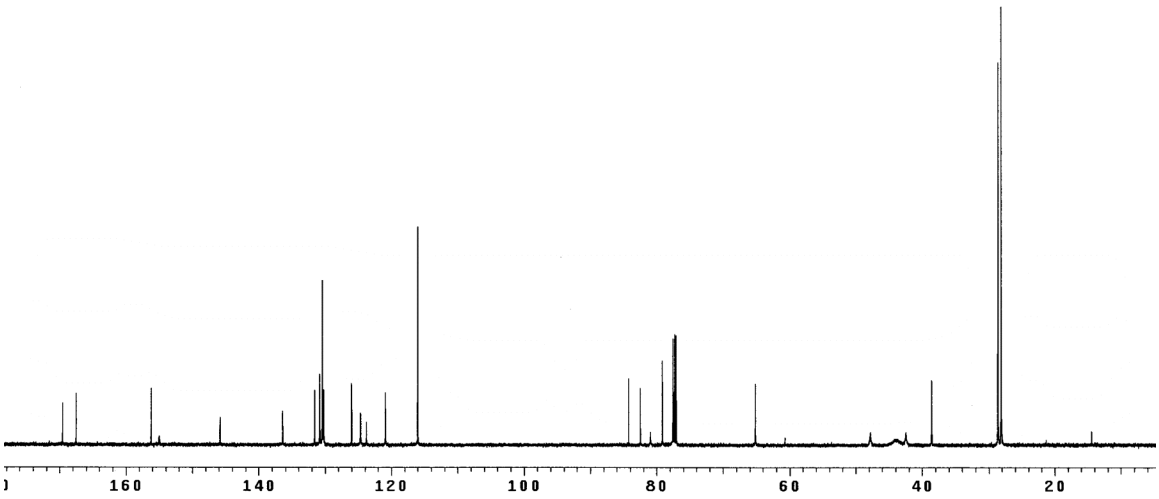
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.45 (s, 1H), 6.86 (d, 2H, J = 8.0 Hz), 6.69 (d, 2H, J = 8.0 Hz), 5.51 (t, 1H, J = 7.0 Hz), 3.80-3.35 (m, 11H), 3.15 (s, 1H), 1.47 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 167.5, 156.2, 155.0, 145.8, 136.4, 131.6, 130.8, 130.4, 130.2, 126.0, 124.7, 123.7, 120.9, 116.0, 84.2, 82.4, 80.9, 79.1, 65.2, 47.8, 43.9 (br), 42.4, 28.6, 28.1

MS (ESI) calcd for $C_{33}H_{40}N_5O_6$ $(M+H)^+$ 602.30, found 602.33

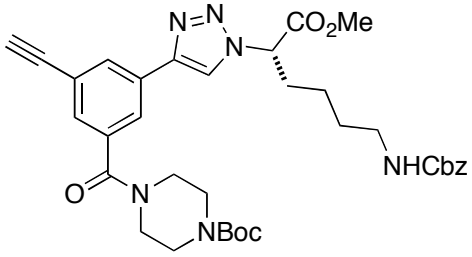


^{1}H NMR of **15b**



^{13}C NMR of **15b**

Preparation of Compound 15c



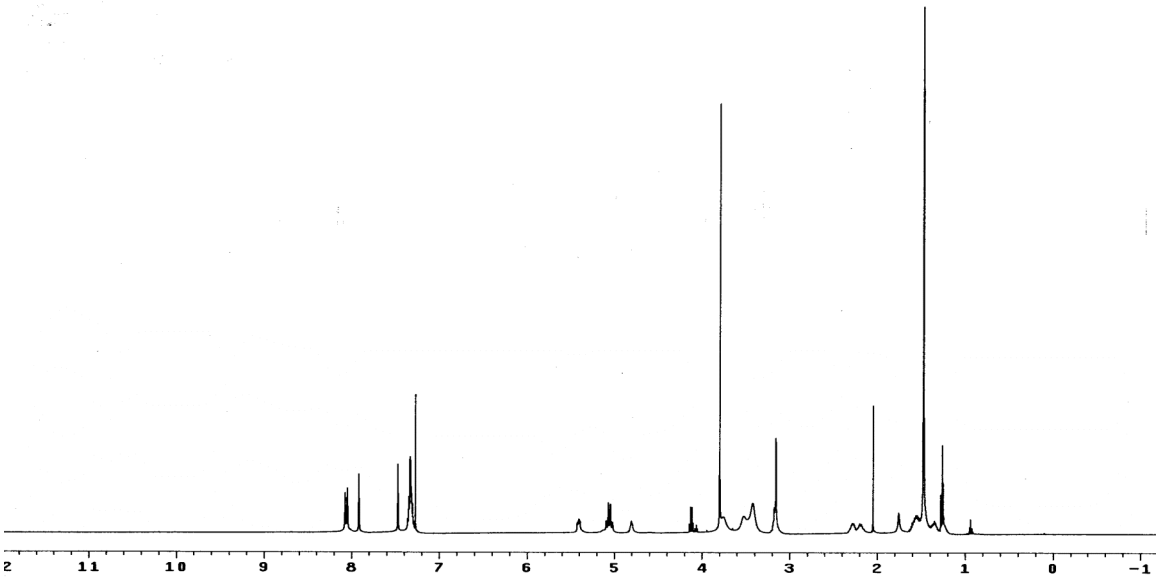
15c

Compound **15c** was prepared from (6.43 g, 13.0 mmol) of **14**. Flash chromatography (1:1 EtOAc/Hexane) afforded 6.17 g (71 % over two steps) **15c** as a white solid.

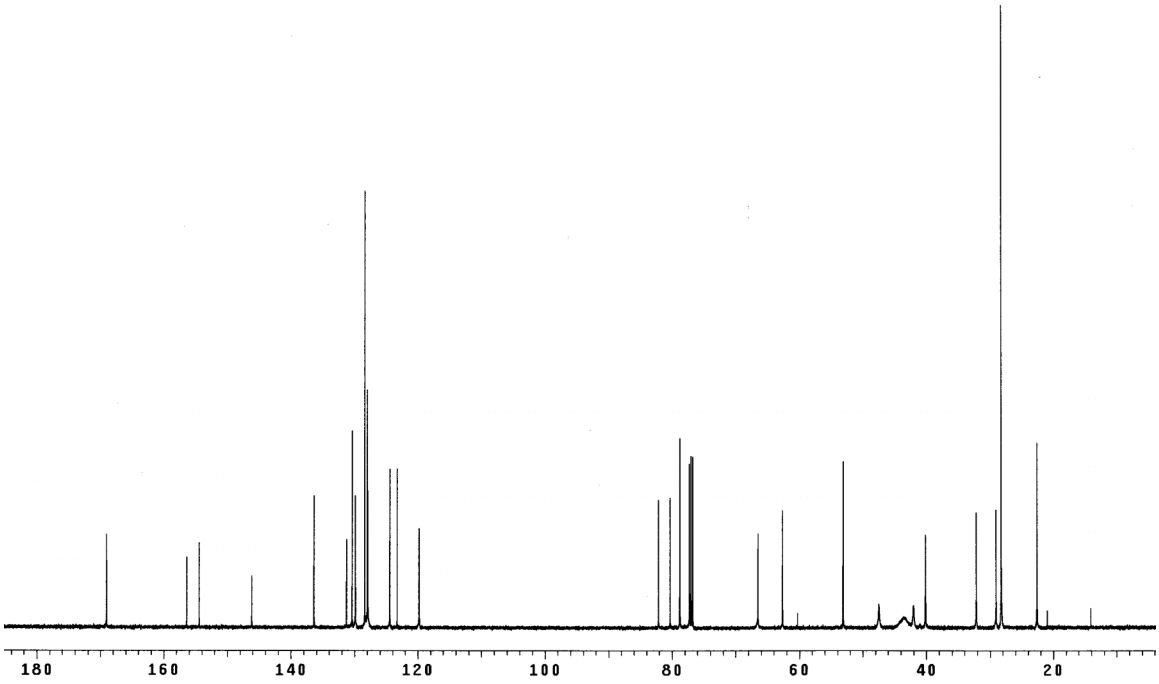
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.05 (s, 1H), 7.91 (t, 1H, J = 1.5 Hz), 7.47 (t, 1H, J = 1.5 Hz), 7.36-7.26 (m, 5H), 5.40 (dd, 1H, J = 10.0, 5.0 Hz), 5.08 (d, 1H, J = 12.5 Hz), 5.03 (d, 1H, J = 12.5 Hz), 4.80 (br, 1H), 3.80 (s, 3H), 3.75-3.35 (m, 8H), 3.20-3.14 (m, 3H), 2.26-2.12 (m, 2H), 1.57-1.45 (m, 2H), 1.45 (s, 9H), 1.30-1.20 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 156.4, 154.4, 146.1, 136.4, 136.3, 131.2, 130.4, 129.9, 128.4, 128.0, 127.9, 124.4, 123.3, 119.8, 82.1, 80.3, 78.8, 66.5, 62.7, 53.1, 47.5, 43.6 (br), 42.0, 40.1, 32.2, 29.1, 28.2, 22.6

MS (ESI) calcd for $C_{35}H_{43}N_6O_7$ $(M+H)^+$ 659.32, found 659.36

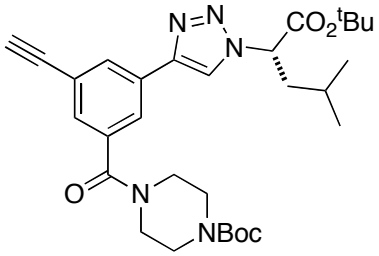


^{1}H NMR of **15c**



^{13}C NMR of **15c**

Preparation of Compound 15d



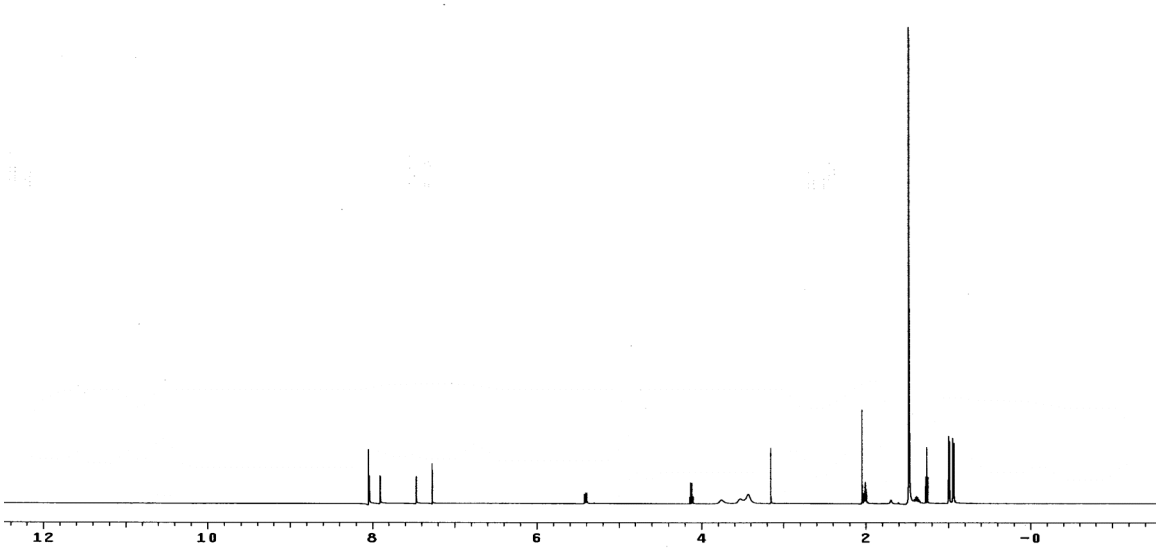
15d

Compound **15d** was prepared from (4.94 g, 10.0 mmol) **14**. Flash chromatography (1:3 EtOAc/Hexane) afforded 5.12 g (93 % over two steps) **15d** as a white solid.

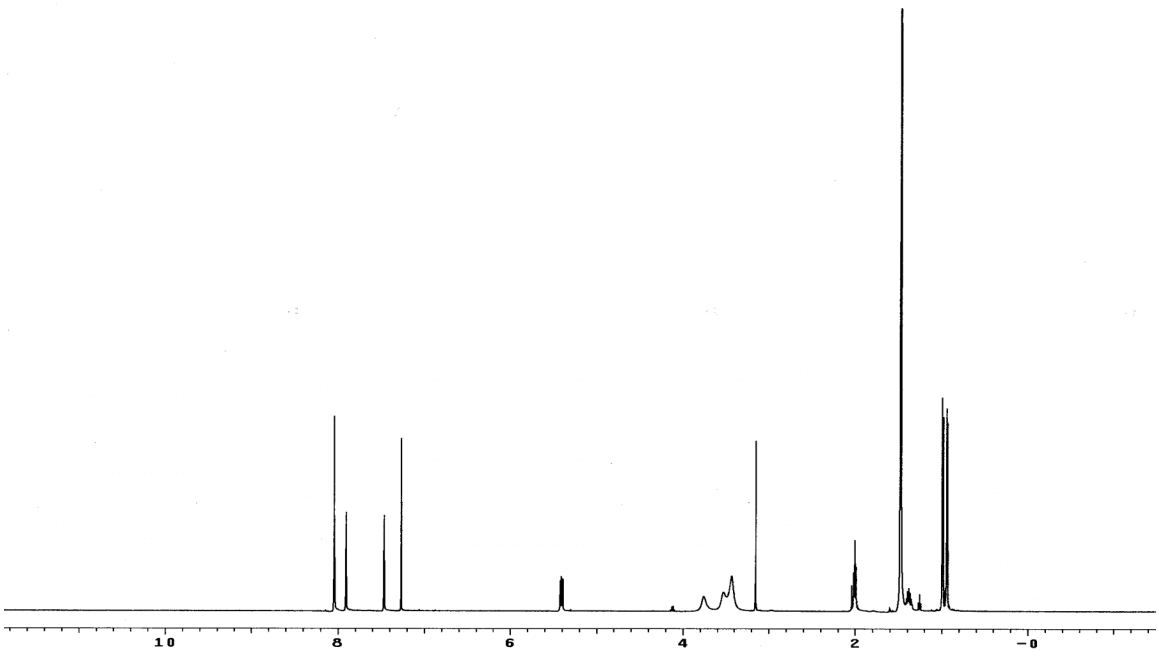
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 8.04 (t, 1H, J = 1.5 Hz), 7.90 (t, 1H, J = 1.5 Hz), 7.47 (t, 1H, J = 1.5 Hz), 5.40 (dd, 1H, J = 9.0, 7.0 Hz), 3.75-3.35 (m, 8H), 3.16 (s, 1H), 2.02-1.99 (m, 2H), 1.48 (s, 9H), 1.47 (s, 9H), 1.41-1.34 (m, 1H), 0.99 (d, 3H, J = 6.5 Hz), 0.94 (d, 3H, J = 7.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 168.3, 154.5, 146.0, 136.4, 131.5, 130.4, 129.8, 124.5, 123.3, 119.4, 83.6, 82.2, 80.4, 78.6, 62.0, 47.5, 43.6 (br), 42.1, 41.8, 28.3, 27.8, 24.7, 22.7, 22.5, 21.3

MS (ESI) calcd for $C_{30}H_{42}N_5O_5$ $(M+H)^+$ 552.32, found 552.34

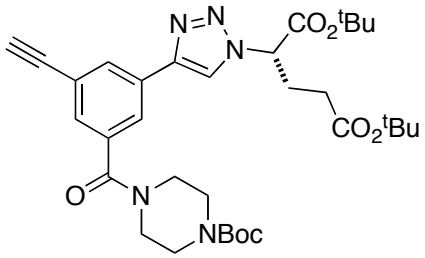


^{1}H NMR of **15d**



^{13}C NMR of **15d**

Preparation of Compound **15e**



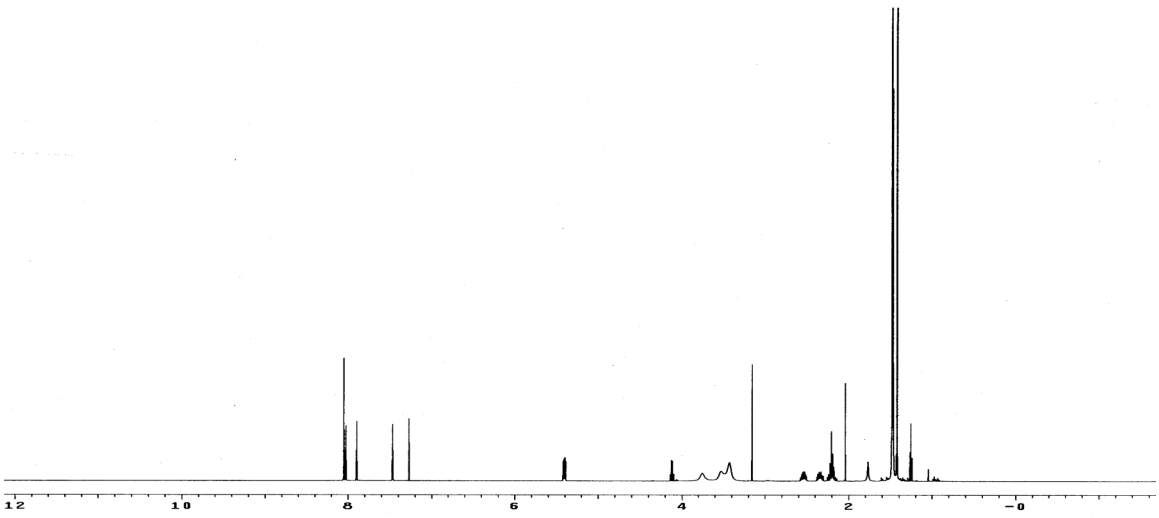
15e

Compound **15e** was prepared from (7.42 g, 15.0 mmol) of **14**. Flash chromatography (1:1 EtOAc/Hexane) afforded 8.77 g (94 % over two steps) **15e** as a white solid.

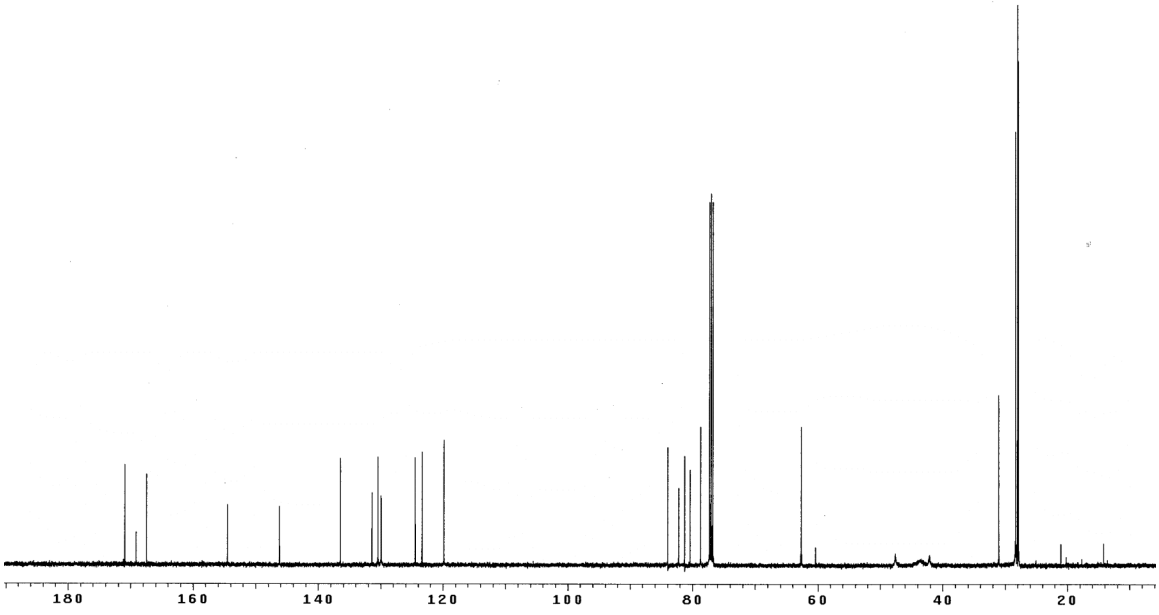
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 8.03 (t, 1H, J = 1.8 Hz), 7.90 (t, 1H, J = 1.5 Hz), 7.47 (t, 1H, J = 1.5 Hz), 5.40 (dd, 1H, J = 10.0, 5.0 Hz), 3.77-3.35 (m, 8H), 3.16 (s, 1H), 2.57-2.50 (m, 1H), 2.25-2.14 (m, 2H), 1.48 (s, 9H), 1.47 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 169.1, 167.4, 154.5, 146.2, 136.4, 131.4, 130.4, 129.9, 124.5, 123.4, 119.8, 83.8, 82.2, 81.3, 80.4, 78.7, 62.6, 47.5, 43.5 (br), 42.1, 31.0, 28.3, 28.04, 28.00, 27.9

MS (ESI) calcd for $C_{33}H_{46}N_5O_7$ $(M+H)^+$ 624.34, found 624.35



^{1}H NMR of **15e**



^{13}C NMR of **15e**

General Procedure for Synthesis of 16a, 16c-f, 16h-l and 16m-o.

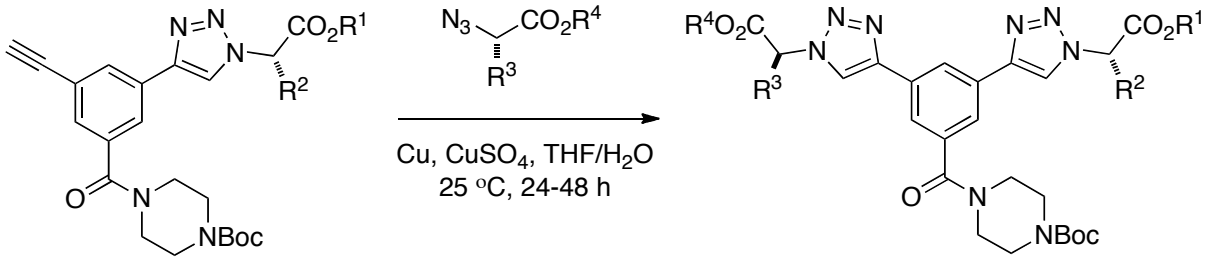
To a solution of **15** (1.0 equiv) and azide (1.3 equiv) in THF (5.0 mL/1.0 mmol **15**) and H_2O (5.0 mL/1.0 mmol **15**) was added Cu powder (1 equiv) and $CuSO_4$ (0.1 equiv, 1 *N* aqueous solution). The mixture was stirred at 25 ºC for 24-48 h. The reaction mixture was filtered through a plug of Celite and washed with EtOAc. The organic layer was washed with 3% EDTA solution, and dried ($MgSO_4$) to afford a crude product as a white solid. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane to yield **16a, c-f, h-l and m-o** as a white solid or pale yellow solid.

General Procedure for Synthesis of 16b, 16g and 16j-l.

To a solution of **15** (1.0 equiv) and azide (1.3 equiv) in THF (5.0 mL/1.0 mmol **15**) and H_2O (5.0 mL/1.0 mmol **15**) was added Cu powder (1 equiv) and $CuSO_4$ (0.1 equiv, 1 N aqueous solution). The mixture was stirred at 25

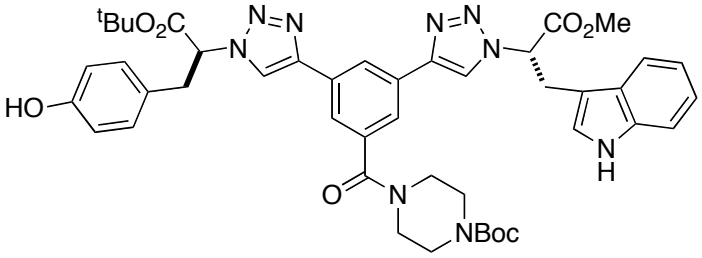
ºC for 24-48 h. The reaction mixture was filtered through a plug of Celite and washed with EtOAc. The organic layer was washed with 3% EDTA solution, and dried ($MgSO_4$) to afford a crude product as a white solid. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane to yield bistriazole as a white solid or pale yellow solid. To a solution of the above bistriazole product (1.0 equiv) and Boc_2O (1.2 equiv) in MeOH (0.05 M) at 0 °C was added 10% Pd/C (0.1 equiv) slowly. The mixture was stirred at 25 °C under 1 atm H_2 for 24 h and filtered through Celite. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane to yield **16b, g and j-l** as a white solid or pale yellow solid.

Scheme S14. Synthesis of compound **16a-o.**



15a-e **16a-o**

Preparation of Compound 16a



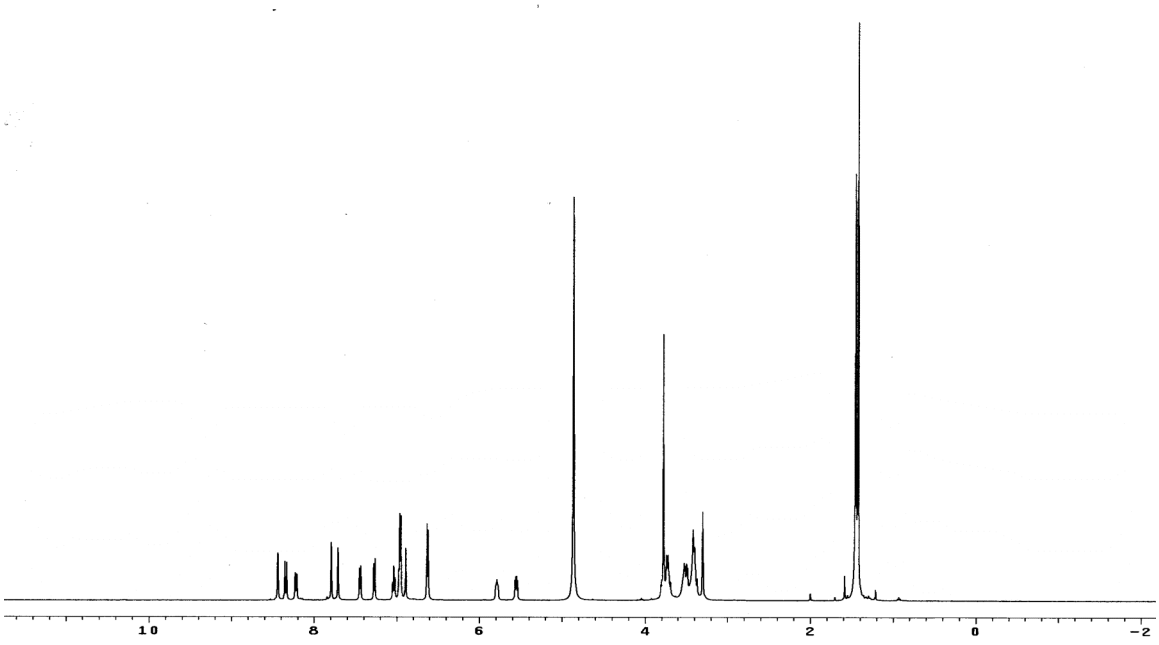
16a

Compound **16a** was prepared from (2.11 g, 3.6 mmol) of **15a**. Flash chromatography (3:1 EtOAc/Hexane) afforded 3.02 g (99 %) **16a** as a yellowish solid.

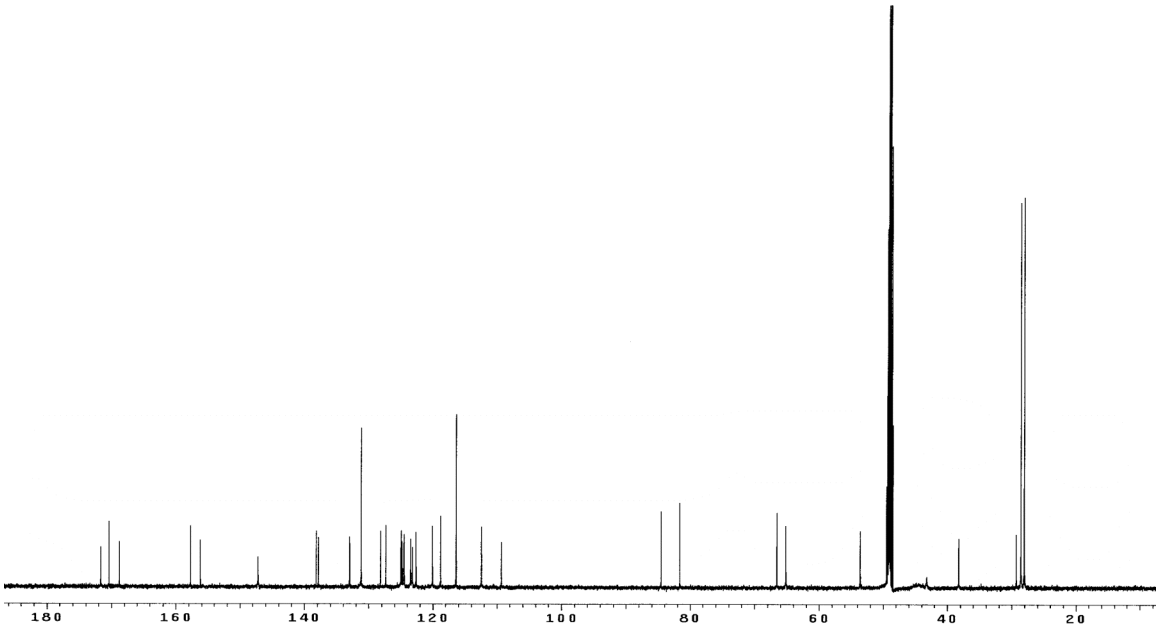
^{1}H NMR (500 MHz, CD_3OD) δ 8.44 (d, 1H, J = 3.0 Hz), 8.34 (d, 1H, J = 11.0 Hz), 8.21 (d, 1H, J = 9.5 Hz), 7.79 (s, 1H), 7.71 (s, 1H), 7.44 (d, 1H, J = 7.5 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.04 (t, 1H, J = 7.5 Hz), 6.98-6.95 (m, 3H), 6.89 (s, 1H), 6.62 (d, 2H, J = 8.5 Hz), 5.80-5.77 (m, 1H), 5.55 (dd, 1H, J = 9.5, 6.0 Hz), 3.81-3.67 (m, 15H), 1.45 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (125 MHz, CD_3OD) δ 171.7, 170.3, 168.8, 157.7, 156.2, 147.2, 138.1, 137.8, 133.0, 131.2, 128.2, 127.4, 125.0, 124.79, 124.76, 124.5, 123.5, 123.2, 122.6, 120.1, 118.8, 116.3, 112.4, 109.3, 84.5, 81.6, 66.5, 65.2, 53.6, 44.8, 43.2, 38.2, 29.3, 28.6, 28.0

MS (MALDI) calcd for $C_{45}H_{52}N_9O_8$ $(M+H)^+$ 846.39, found 846.39

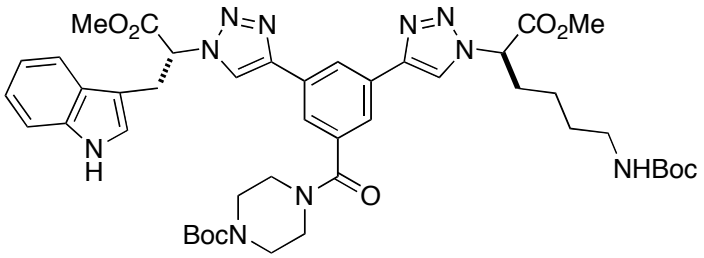


^{1}H NMR of **16a**



^{13}C NMR of **16a**

Preparation of Compound 16b



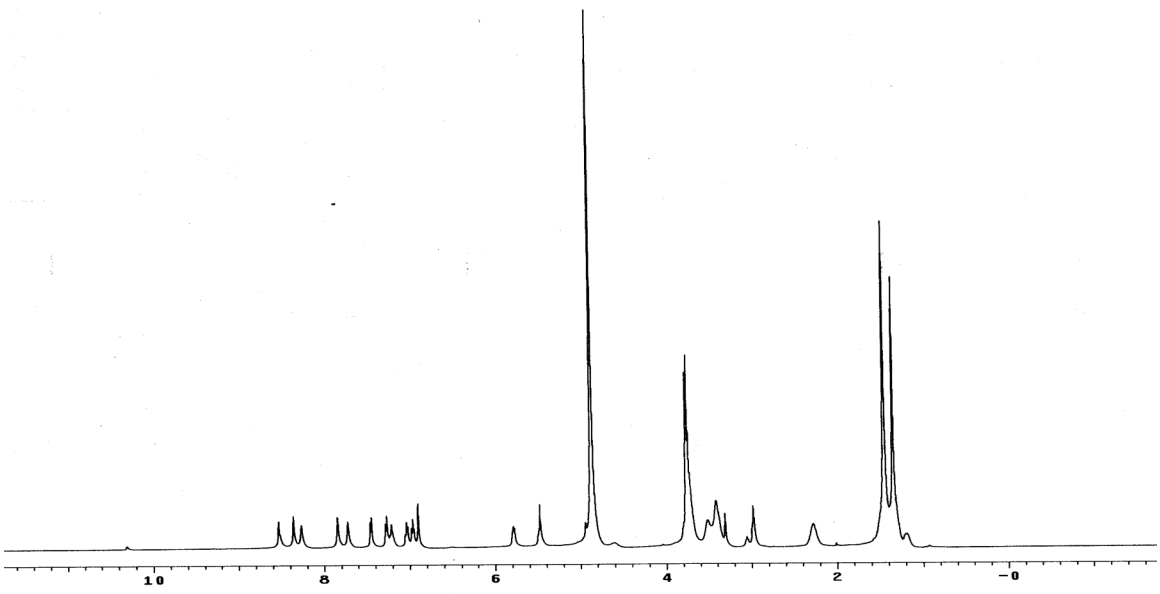
16b

Compound **16b** was prepared from (1.11 g, 1.9 mmol) of **15a**. Flash chromatography (9:1 EtOAc/Hexane) afforded 1.23 g (74 % over two steps) **16b** as a white solid.

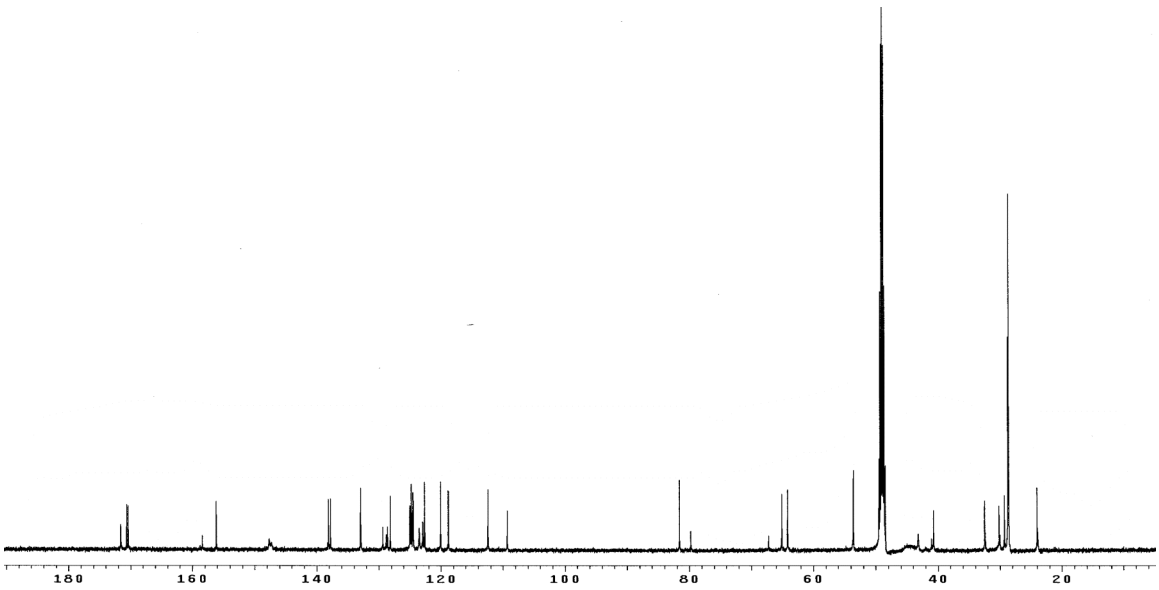
^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.45 (d, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 8.5 Hz), 7.21 (s, 1H), 7.04 (t, 1H, J = 7.5 Hz), 6.96 (t, 1H, J = 7.3 Hz), 6.90 (s, 1H), 5.80-5.77 (m, 1H), 5.49-5.46 (m, 1H), 3.77-3.38 (m, 16H), 2.98 (t, 2H, J = 6.5), 2.31-2.23 (m, 2H), 1.45 (s, 9H), 1.34 (s, 9H), 1.33-1.14 (m, 4H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 170.6, 170.4, 158.4, 156.2, 147.6, 138.1, 137.8, 132.9, 129.4, 128.8, 128.6, 128.1, 125.0, 124.8, 124.5, 123.5, 122.9, 122.6, 120.1, 118.8, 112.4, 109.3, 81.6, 79.8, 67.2, 65.1, 64.2, 53.6, 45.0 (br), 43.2, 40.7, 32.5, 30.1, 29.3, 28.7, 28.6, 24.0

MS (MALDI) calcd for $C_{44}H_{57}N_{10}O_9$ $(M+H)^+$ 869.43, found 869.13

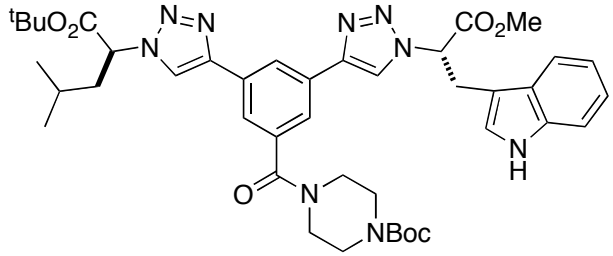


^{1} H NMR of **16b**



^{13}C NMR of **16b**

Preparation of Compound 16c



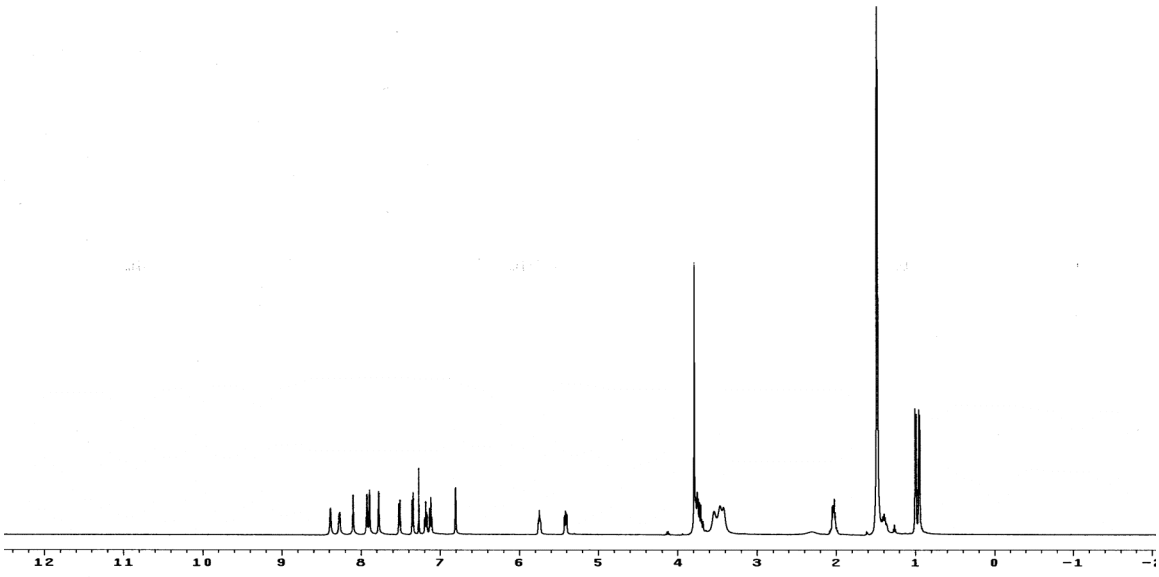
16c

Compound **16c** was prepared from (2.04 g, 3.5 mmol) of **15a**. Flash chromatography (2:1 to 3:1 EtOAc/Hexane) afforded 2.58 g (93 %) **16c** as a yellowish solid.

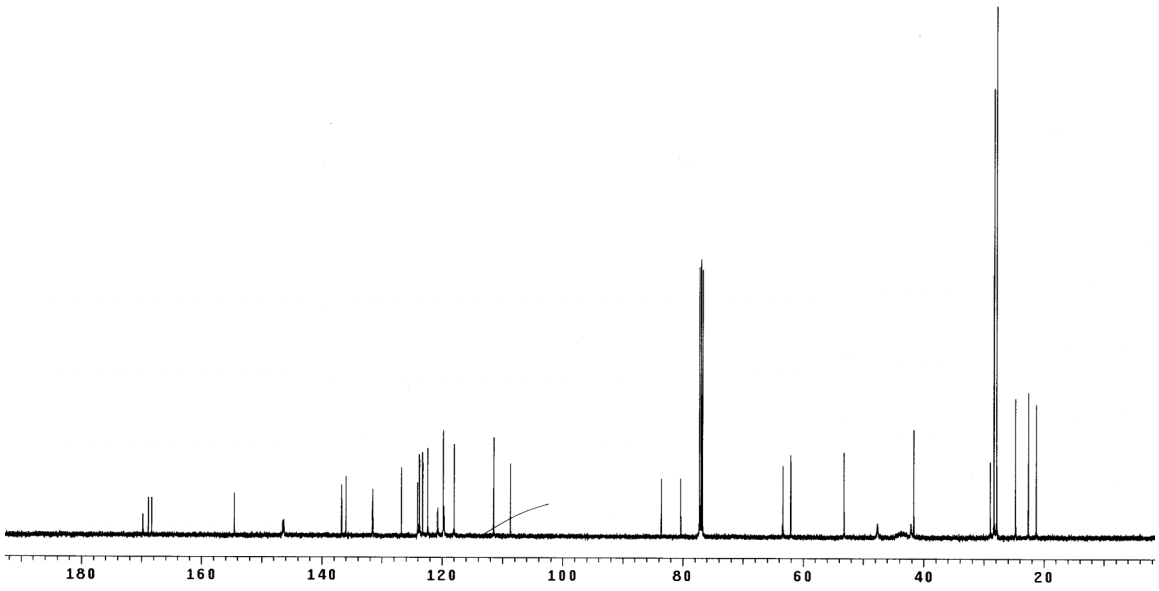
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.27 (d, 1H, J = 5.0 Hz), 8.10 (s, 1H), 7.93 (s, 1H), 7.89 (s, 1H), 7.77 (s, 1H), 7.51 (d, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.18 (t, 1H, J = 7.5 Hz), 7.12 (t, 1H, J = 7.5 Hz), 6.81 (s, 1H), 5.76-5.73 (m, 1H), 5.41 (dd, 1H, J = 9.5, 6.0 Hz), 3.79 (s, 3H), 3.75-3.35 (m, 10H), 2.05-2.01 (m, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.47-1.37 (m, 2H), 0.99 (d, 3H, J = 3.3 Hz), 0.95 (d, 3H, J = 3.3 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 168.9, 168.8, 168.3, 154.5, 146.5, 146.3, 136.7, 136.0, 131.6, 131.5, 126.7, 124.0, 123.8, 123.2, 122.4, 120.7, 119.8, 119.7, 118.0, 111.5, 108.7, 83.6, 80.3, 63.4, 62.1, 53.2, 47.6, 43.7 (br), 42.1, 41.6, 29.0, 28.3, 27.9, 24.7, 22.6, 21.3

MS (MALDI) calcd for $C_{42}H_{54}N_9O_7$ $(M+H)^+$ 796.41, found 796.20

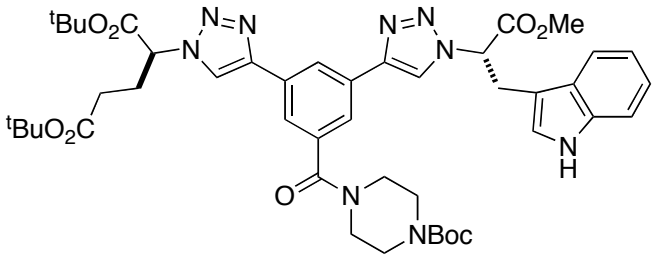


^{1}H NMR of **16c**



^{13}C NMR of **16c**

Preparation of Compound 16d



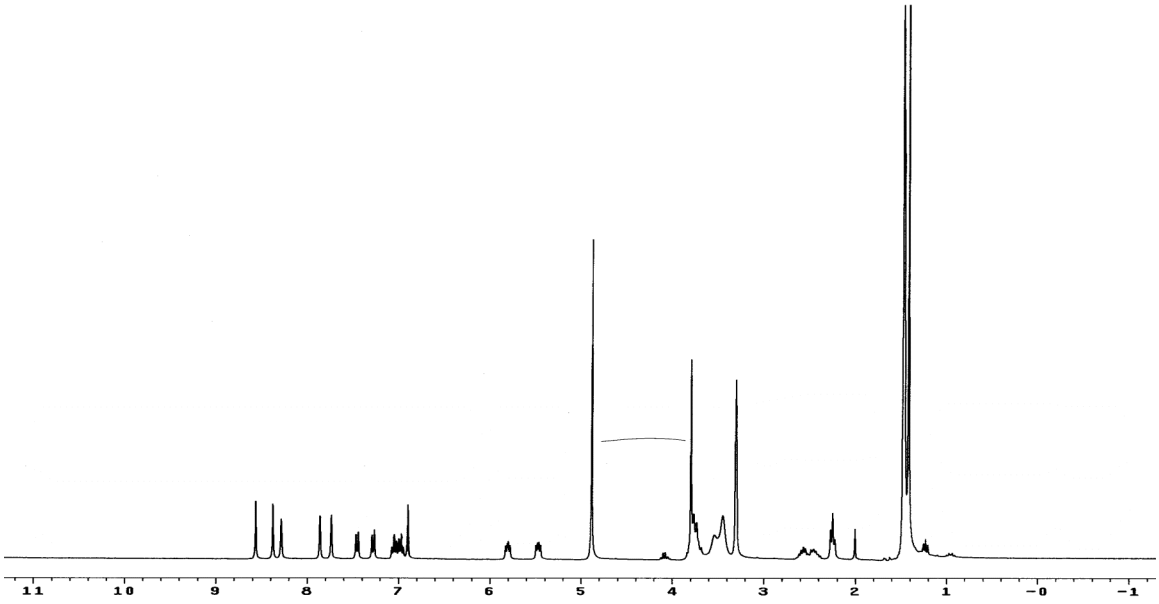
16d

Compound **16d** was prepared from (2.62 g, 4.5 mmol) of **15a**. Flash chromatography (1:1 EtOAc/Hexane) afforded 3.52 g (90 %) **16d** as a white solid.

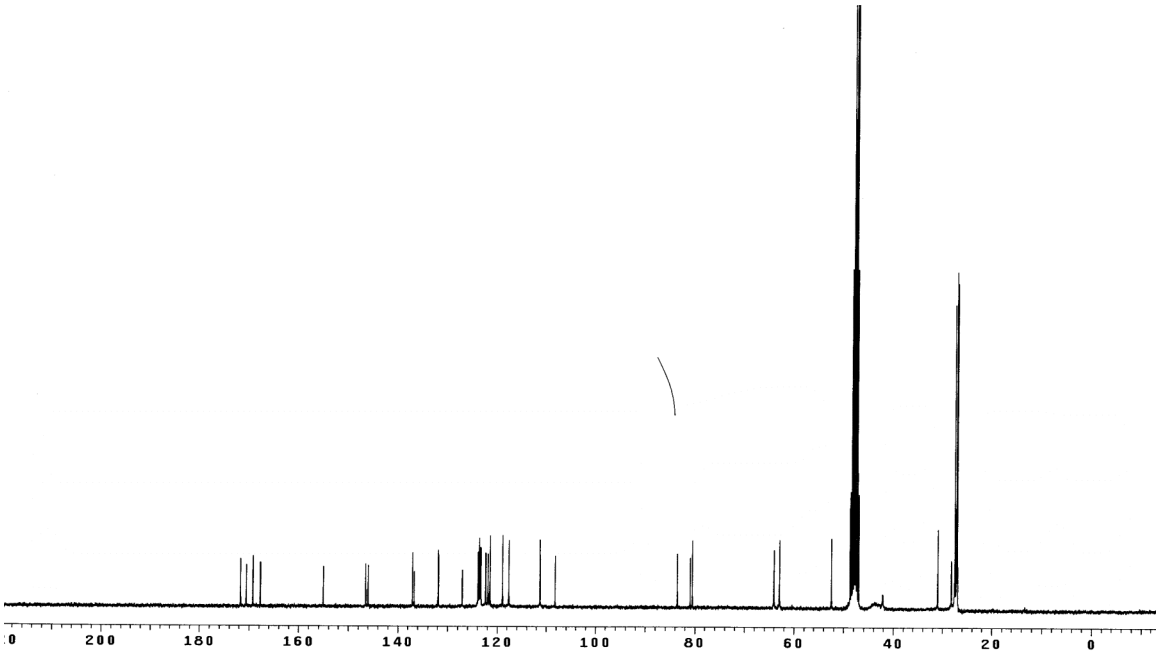
^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 7.45 (d, 1H, J = 7.8 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.05 (t, 1H, J = 7.4 Hz), 6.97 (t, 1H, J = 7.4 Hz), 6.90 (s, 1H), 5.80 (dd, 1H, J = 9.3, 5.4 Hz), 5.47 (dd, 1H, J = 9.9, 5.4 Hz), 3.79 (s, 3H), 3.78-3.40 (m, 10H), 2.61-2.38 (m, 2H), 2.45 (t, 2H, J = 6.9 Hz), 1.47 (s, 9H), 1.46 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 170.6, 169.2, 167.7, 155.0, 146.5, 146.0, 137.1, 136.7, 131.9, 131.9, 127.0, 123.9, 123.6, 123.4, 123.3, 122.3, 121.9, 121.5, 118.9, 117.6, 111.3, 108.2, 83.5, 80.9, 80.5, 64.0, 62.9, 52.4, 43.7 (br), 42.1, 30.9, 28.2, 27.4, 27.1, 27.0, 26.9

MS (MALDI) calcd for $C_{45}H_{59}N_9O_9$ $(M+2H)^+$ 869.44, found 869.42

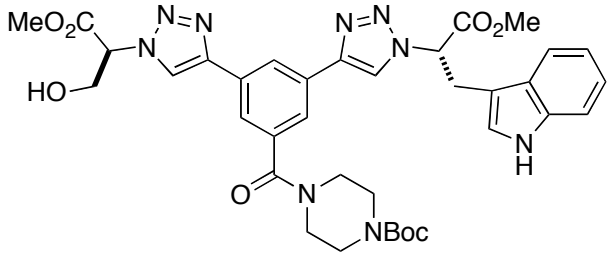


^{1}H NMR of **16d**



^{13}C NMR of **16d**

Preparation of compound 16e



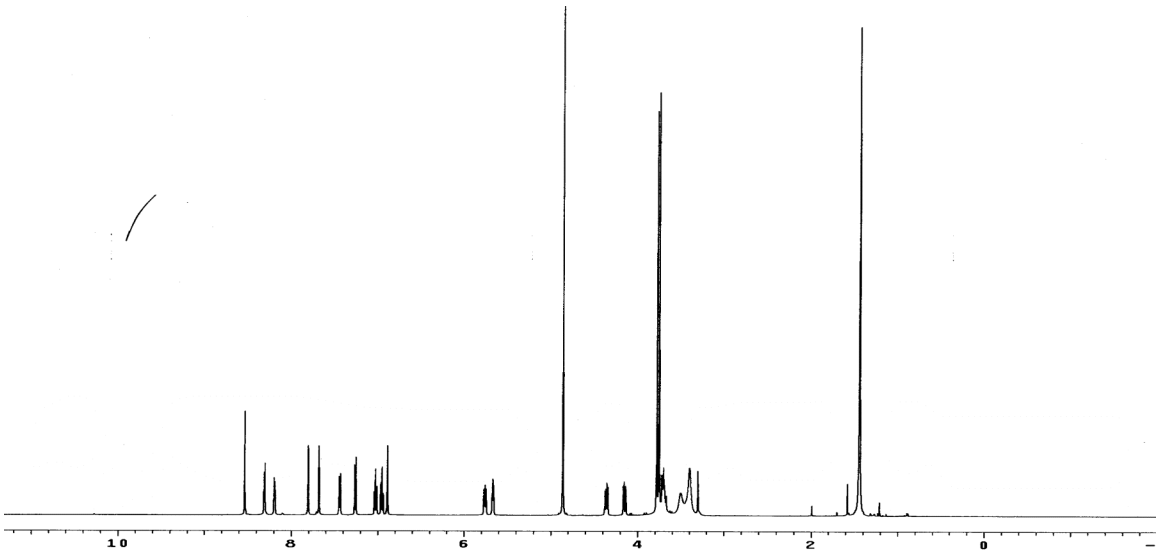
16e

Compound **16e** was prepared from (2.04 g, 3.5 mmol) of **15a**. Flash chromatography (100 % EtOAc) afforded 2.14 g (93 %) **16e** as a white solid.

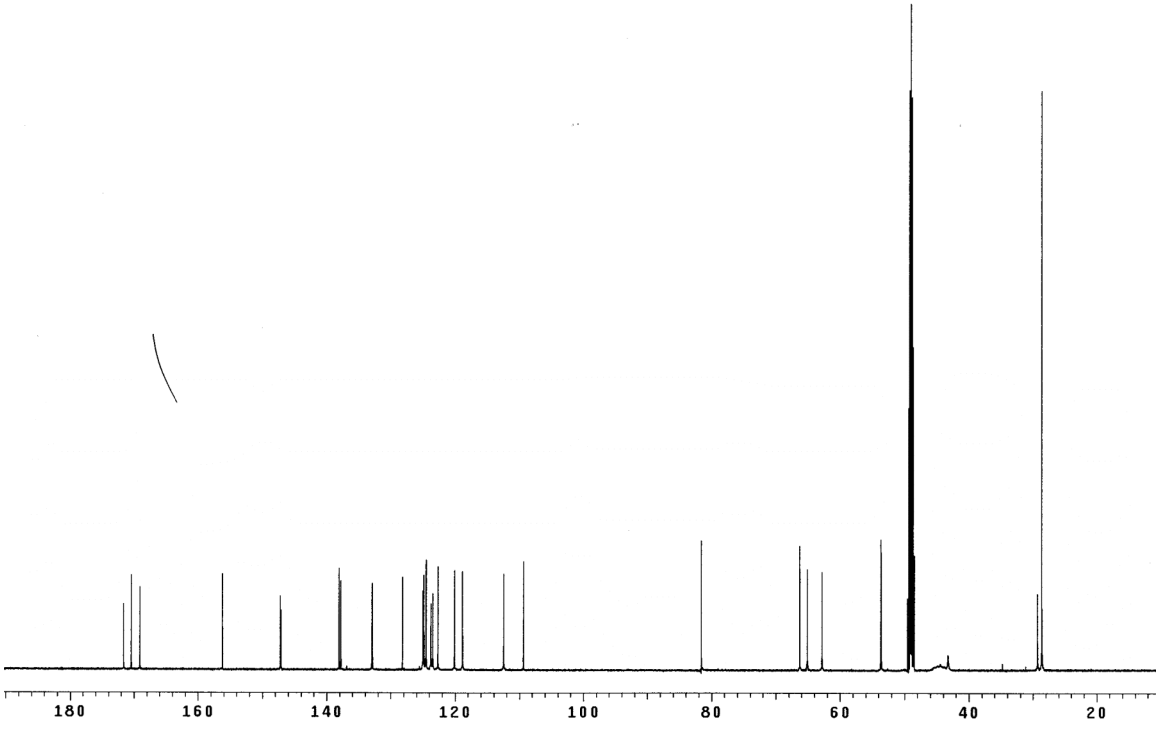
^{1}H NMR (500 MHz, CD_3OD) δ 9.53 (s, 1H), 8.30 (d, 1H, J = 4.0 Hz), 8.19 (d, 1H, J = 5.0 Hz), 7.80 (s, 1H), 7.68 (s, 1H), 7.44 (d, 1H, J = 8.0 Hz), 7.26 (d, 1H, J = 8.5 Hz), 7.02 (t, 1H, J = 7.5 Hz), 6.95 (t, 1H, J = 7.5 Hz), 6.87 (s, 1H), 5.75 (dd, 1H, J = 9.5, 5.0 Hz), 5.66 (dd, 1H, J = 6.0, 3.5 Hz), 4.36 (dd, 1H, J = 12.0, 5.5 Hz), 4.14 (dd, 1H, J = 12.5, 3.5 Hz), 3.77 (s, 3H), 3.75 (s, 3H), 3.74-3.38 (m, 10H), 1.44 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 170.4, 169.1, 156.2, 147.2, 147.1, 138.1, 137.8, 133.0, 132.9, 128.2, 125.0, 124.9, 124.5, 123.7, 123.4, 122.6, 120.1, 118.8, 112.5, 109.4, 81.6, 66.3, 65.1, 62.8, 53.62, 53.61, 42.4 (br), 43.2, 29.3, 28.6

MS (MALDI) calcd for $C_{36}H_{42}N_9O_8$ $(M+H)^+$ 728.32, found 728.32

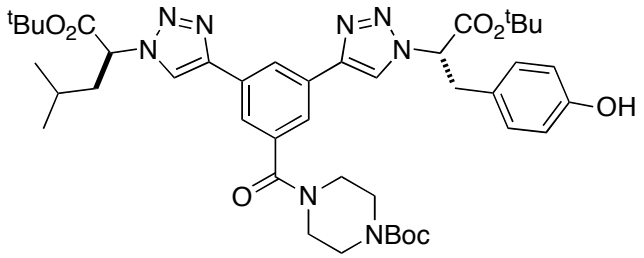


^{1}H NMR of **16e**



^{13}C NMR of **16e**

Preparation of Compound 16f



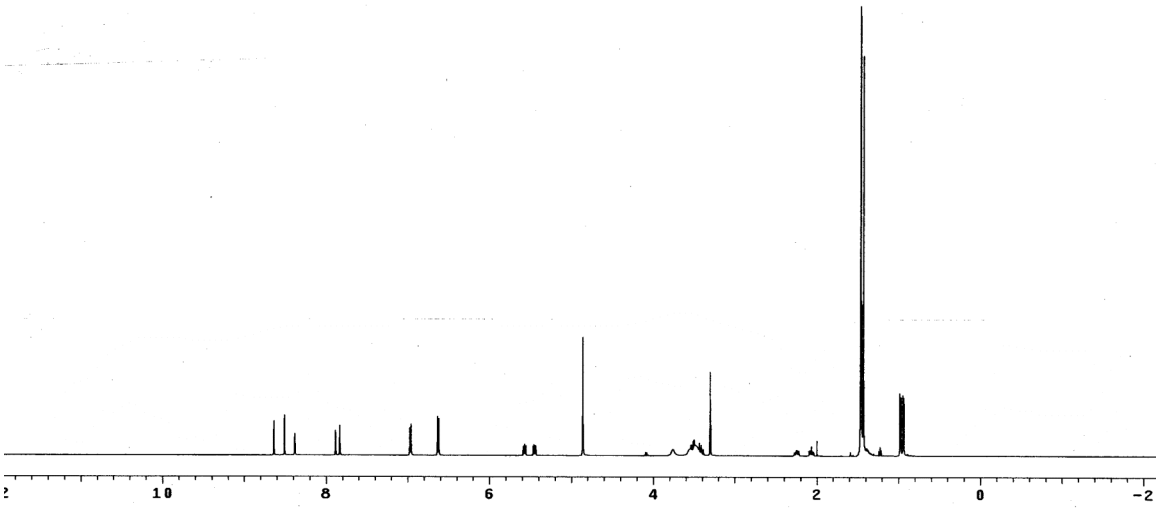
16f

Compound **16f** was prepared from (2.11 g, 3.5 mmol) of **15b**. Flash chromatography (2:1 to 3:1 EtOAc/Hexane) afforded 2.50 g (88 %) **16f** as a white solid.

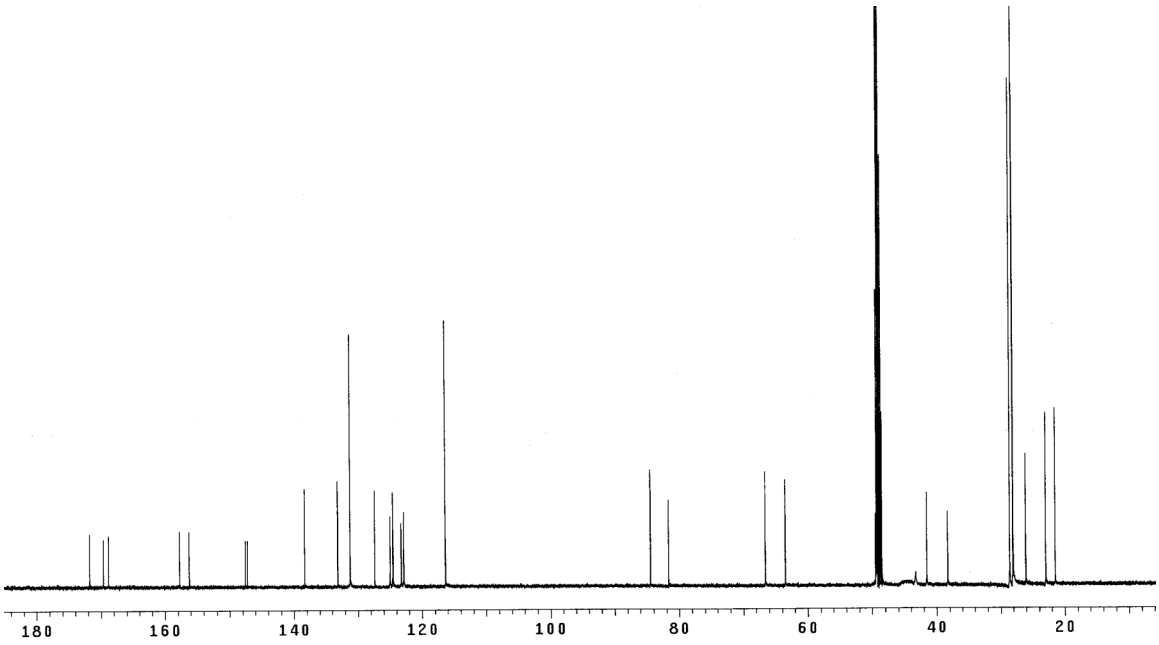
^{1}H NMR (500 MHz, CD_3OD) δ 8.64 (t, 1H, J = 1.5 Hz), 8.51 (s, 1H), 8.38 (t, 1H, J = 1.5 Hz), 7.88 (s, 1H), 7.83 (t, 1H, J = 1.5 Hz), 6.96 (d, 2H, J = 8.5 Hz), 6.63 (d, 2H, J = 8.5 Hz), 5.57 (dd, 1H, J = 10.0, 6.0 Hz), 5.44 (dd, 1H, J = 11.0, 5.5 Hz), 3.77-3.38 (m, 10H), 2.28-2.22 (m, 1H), 2.10-2.04 (m, 1H), 1.47 (s, 9H), 1.46 (s, 9H), 1.43 (s, 9H), 1.42-1.39 (m, 1H), 0.98 (d, 3H, J = 6.5 Hz), 0.94 (d, 3H, J = 5.0 Hz)

^{13}C NMR (125 MHz, CD_3OD δ 171.7, 169.6, 168.8, 157.7, 156.2, 147.5, 147.2, 138.3, 133.2, 131.2, 127.4, 125.0, 124.5, 123.2, 122.8, 116.4, 84.5, 84.4, 81.7, 66.6, 63.5, 44.0 (br), 43.3, 41.6, 38.3, 28.6, 28.11, 28.09, 26.1, 23.0, 21.5

MS (MALDI) calcd for $C_{43}H_{58}N_8O_8Na$ $(M+Na)^+$ 837.43, found 837.57

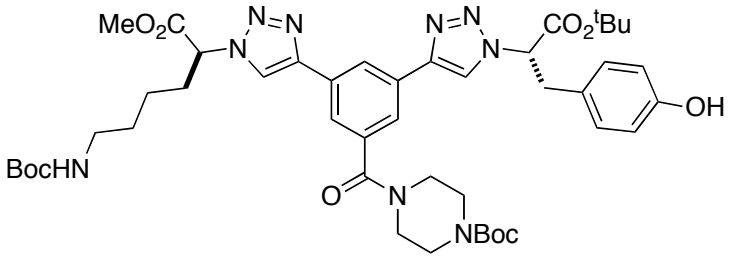


^{1}H NMR of **16f**



^{13}C NMR of **16f**

Preparation of Compound 16g



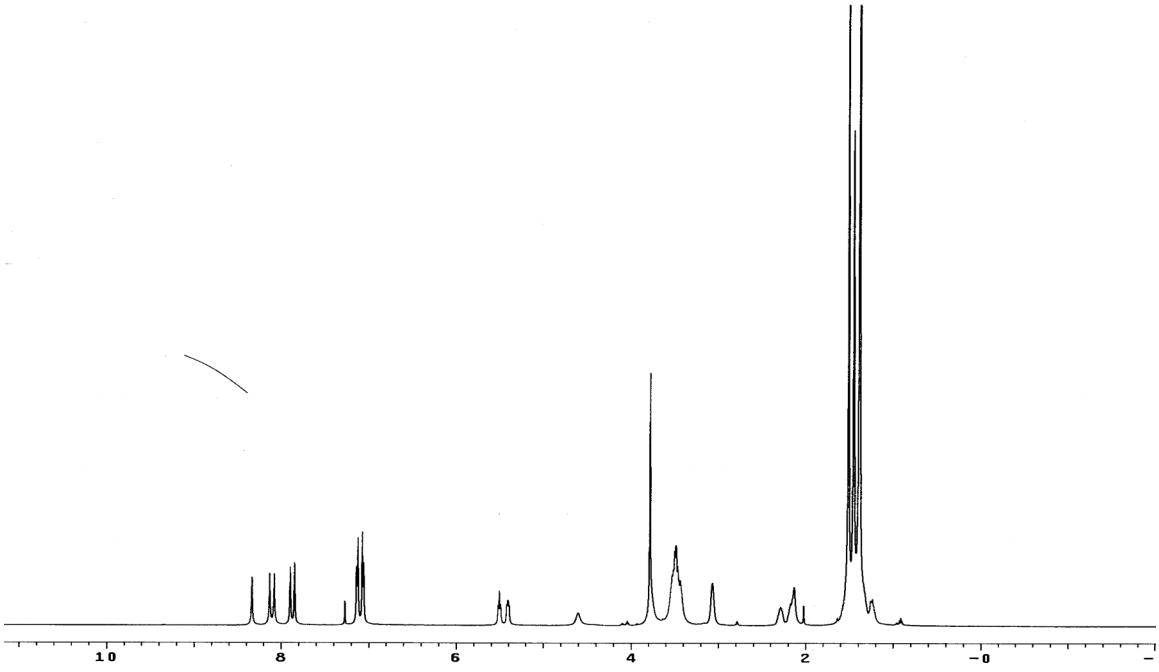
16g

Compound **16g** was prepared from (2.41 g, 4.0 mmol) of **15b**. Flash chromatography (1:1 EtOAc/Hexane) afforded 2.76 g (85 % over two steps) **16g** as a white solid.

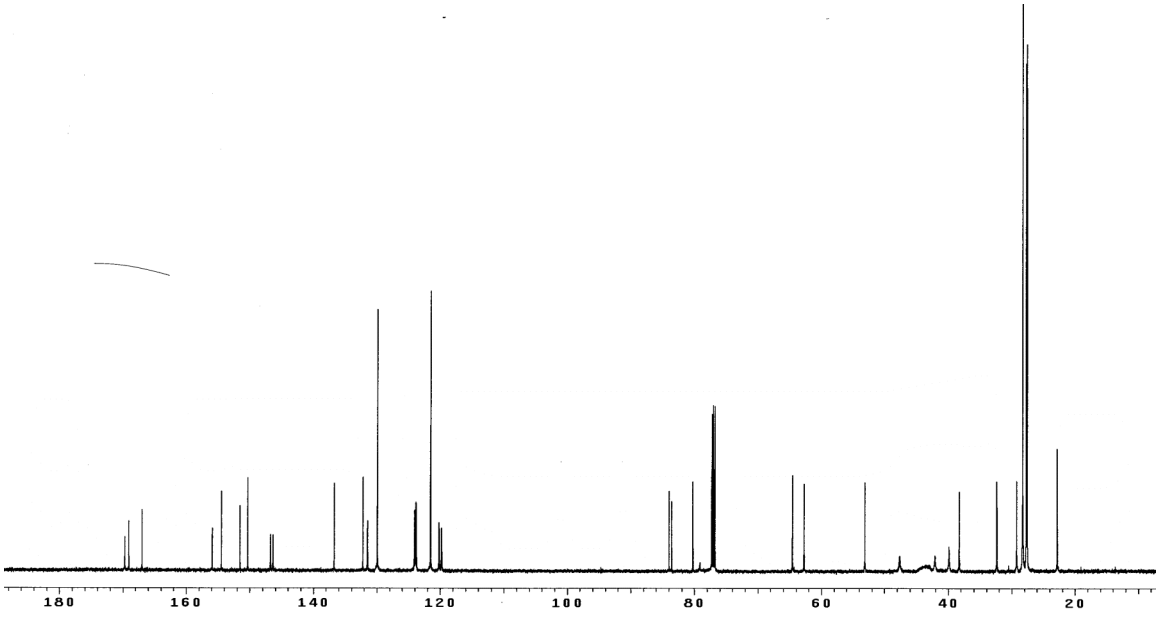
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.13 (s, 1H), 8.08 (s, 1H), 7.90 (s, 1H), 7.84 (s, 1H), 7.12 (d, 2H, J = 8.0 Hz), 7.06 (d, 2H, J = 8.0 Hz), 5.50 (t, 1H, J = 7.3 Hz), 5.40 (dd, 1H, J = 9.0, 5.0 Hz), 4.60 (s, 1H), 3.78 (s, 6H), 3.75-3.38 (m, 10H), 3.07 (br, 2H), 2.25-2.13 (m, 2H), 1.53-1.23 (m, 40H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.1, 167.0, 155.9, 154.4, 151.5, 150.3, 146.8, 146.3, 136.7, 132.2, 131.5, 131.4, 129.9, 124.0, 123.8, 123.7, 121.5, 120.2, 119.8, 84.0, 83.5, 80.2, 64.6, 62.7, 53.1, 47.6, 43.5 (br), 42.1, 39.8, 38.3, 32.4, 29.2, 28.28, 28.26, 27.7, 27.6, 22.8

MS (MALDI) calcd for $C_{50}H_{68}N_9O_{12}$ $(M+H)^+$ 888.46, found 888.44

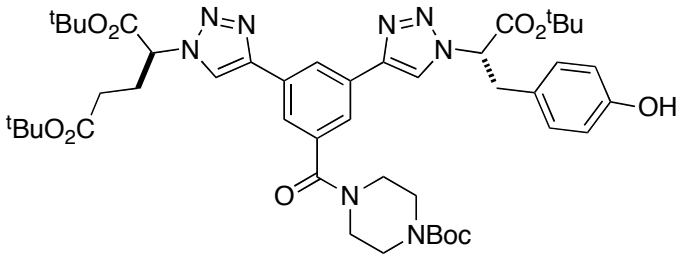


^{1}H NMR of **16g**



^{13}C NMR of **16g**

Preparation of Compound 16h



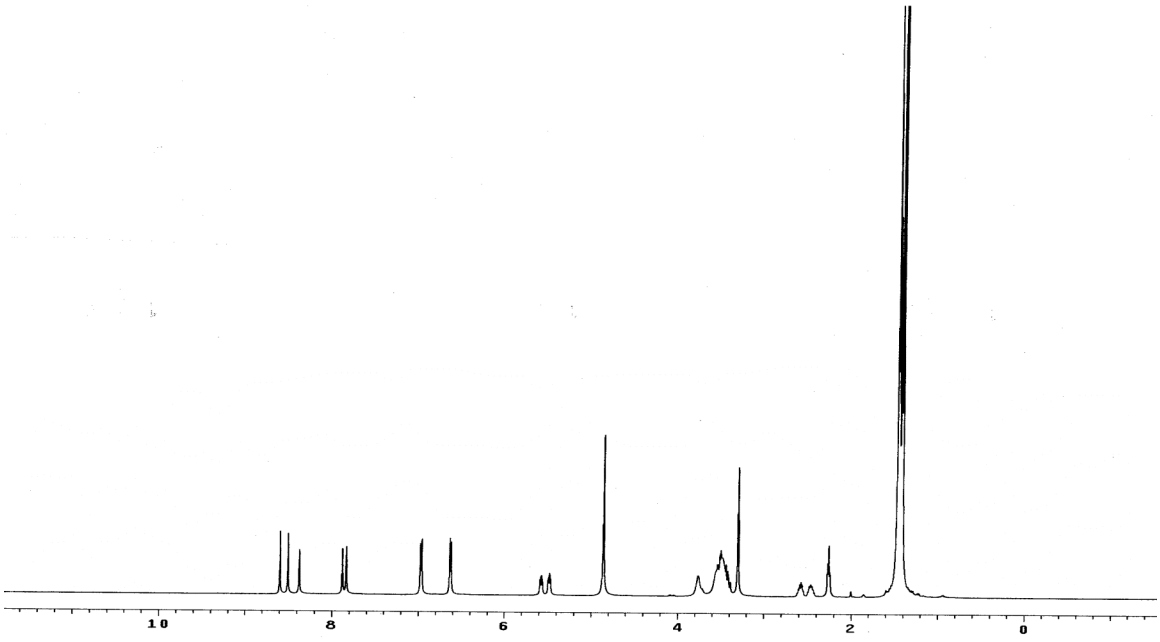
16h

Compound **16h** was prepared from (2.49 g, 4.0 mmol) of **15e**. Flash chromatography (1:1 EtOAc/Hexane) afforded 3.24 g (91 %) **16h** as a white solid.

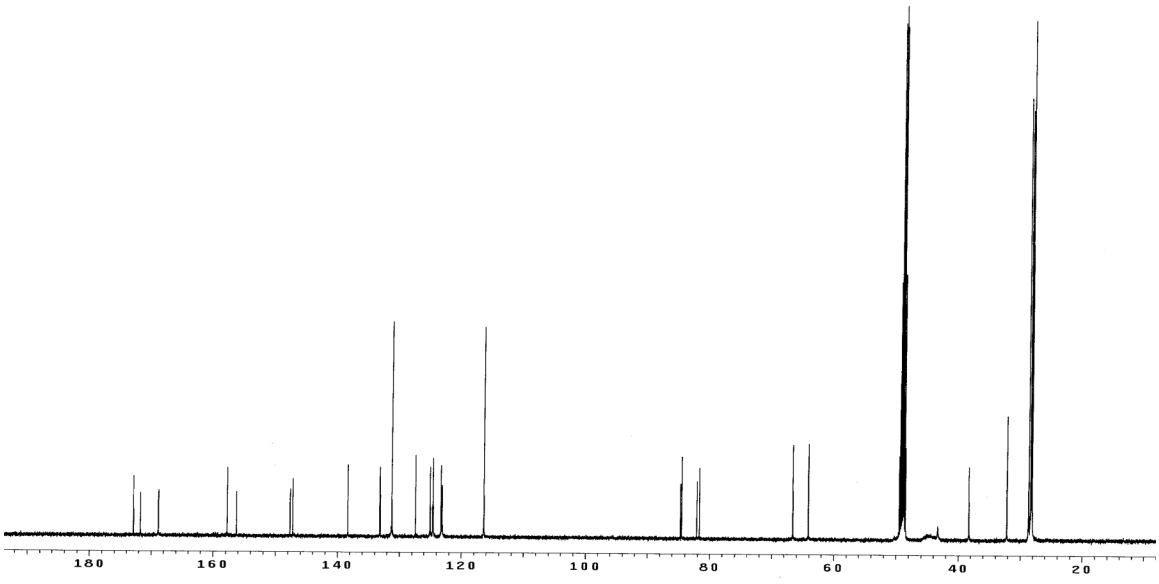
^{1}H NMR (500 MHz, CD_3OD) δ 8.60 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 7.88 (s, 1H), 7.83 (s, 1H), 6.97 (d, 2H, J = 8.0 Hz), 6.63 (d, 2H, J = 8.0 Hz), 5.57 (dd, 1H, J = 10.0, 6.5 Hz), 5.48 (dd, 1H, J = 9.5, 5.5 Hz), 3.77-3.39 (m, 10H), 2.60-2.56 (m, 1H), 2.49-2.42 (m, 1H), 2.26 (m, 2H), 1.47 (s, 9H), 1.46 (s, 9H), 1.43 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (125 MHz, CD_3OD) δ 172.9, 171.8, 168.9, 168.8, 157.7, 156.2, 147.6, 147.2, 138.3, 133.2, 133.1, 131.2, 127.4, 125.0, 124.6, 124.5, 123.3, 123.1, 116.4, 84.7, 84.5, 82.1, 81.7, 66.6, 64.1, 44.4 (br), 43.3, 38.3, 32.1, 28.6, 28.32, 28.25, 28.12, 28.10

MS (MALDI) calcd for $C_{46}H_{63}N_8O_{10}$ $(M+H)^+$ 887.47, found 887.38

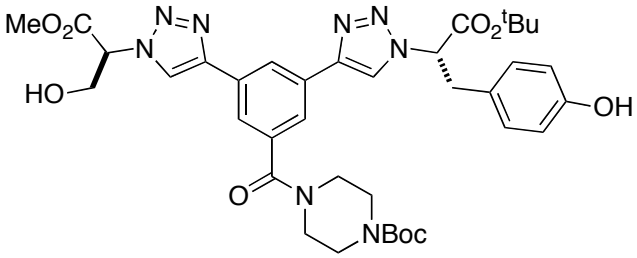


^{1}H NMR of **16h**



^{13}C NMR of **16h**

Preparation of Compoun 16i



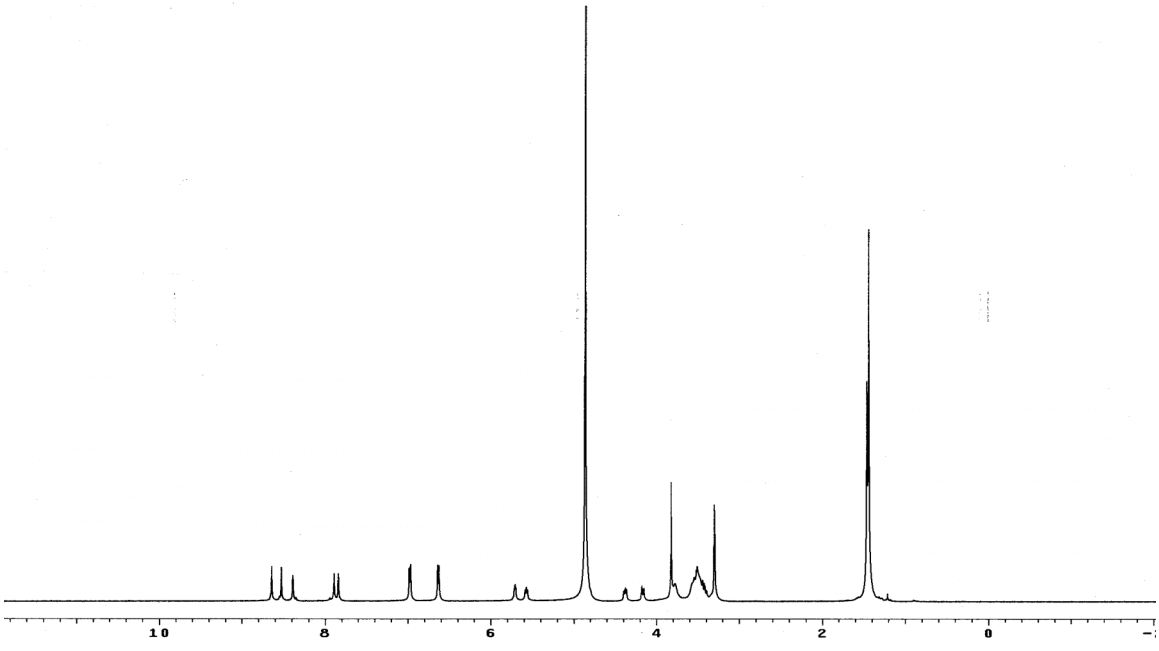
16i

Compound **16i** was prepared from (1.81 g, 3.0 mmol) of **15b**. Flash chromatography (EtOAc) afforded 1.48 g (67 %) **16i** as a white solid.

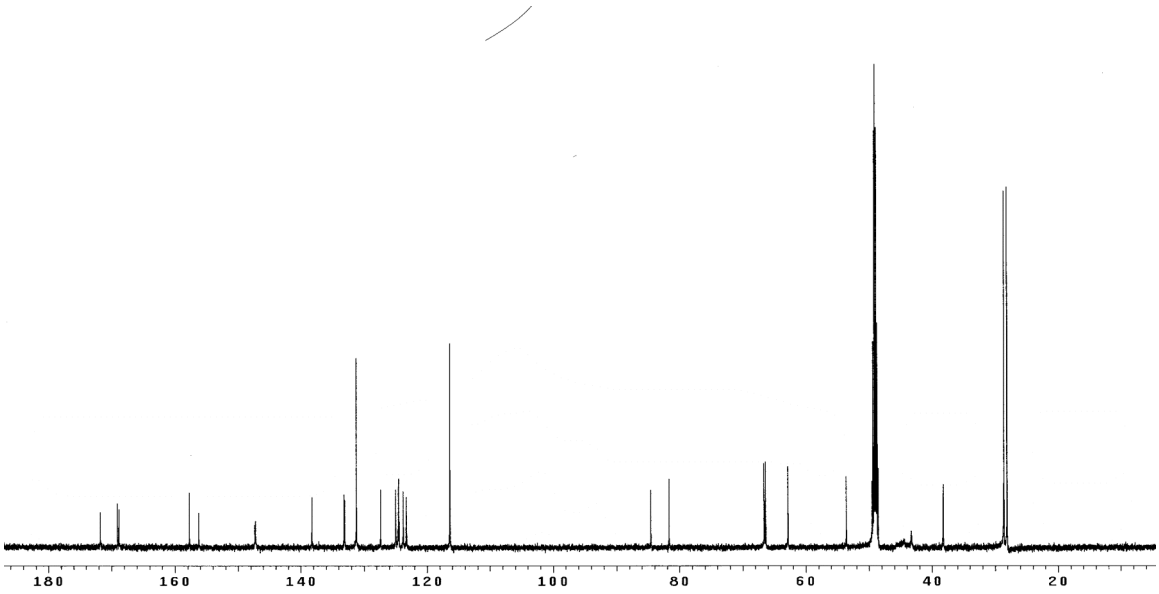
^{1}H NMR (500 MHz, CD_3OD) δ 8.64 (s, 1H), 8.52 (s, 1H), 8.39 (s, 1H), 7.89 (s, 1H), 7.84 (s, 1H), 6.97 (d, 2H, J = 8.0 Hz), 6.63 (d, 2H, J = 8.5 Hz), 5.71 (dd, 1H, J = 6.5, 4.0 Hz), 5.57 (dd, 1H, J = 9.5, 6.0 Hz), 4.38 (dd, 1H, J = 12.0, 6.5 Hz), 4.16 (dd, 1H, J = 12.0, 3.0 Hz), 3.82 (s, 3H), 3.79-3.39 (m, 10H), 1.46 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (125 MHz, CD_3OD) δ 171.8, 169.1, 168.8, 157.7, 156.2, 147.3, 147.2, 138.3, 133.2, 133.1, 131.2, 127.4, 125.0, 124.55, 124.49, 123.8, 123.3, 116.3, 84.6, 81.6, 66.6, 66.4, 62.8, 53.6, 44.5 (br), 43.3, 38.3, 28.6, 28.1

MS (MALDI) calcd for $C_{37}H_{47}N_8O_9$ $(M+H)^+$ 747.35, found 747.26

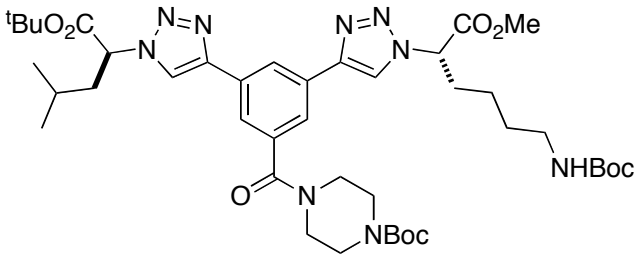


^{1}H NMR of **16i**



^{13}C NMR of **16i**

Preparation of Compound 16j



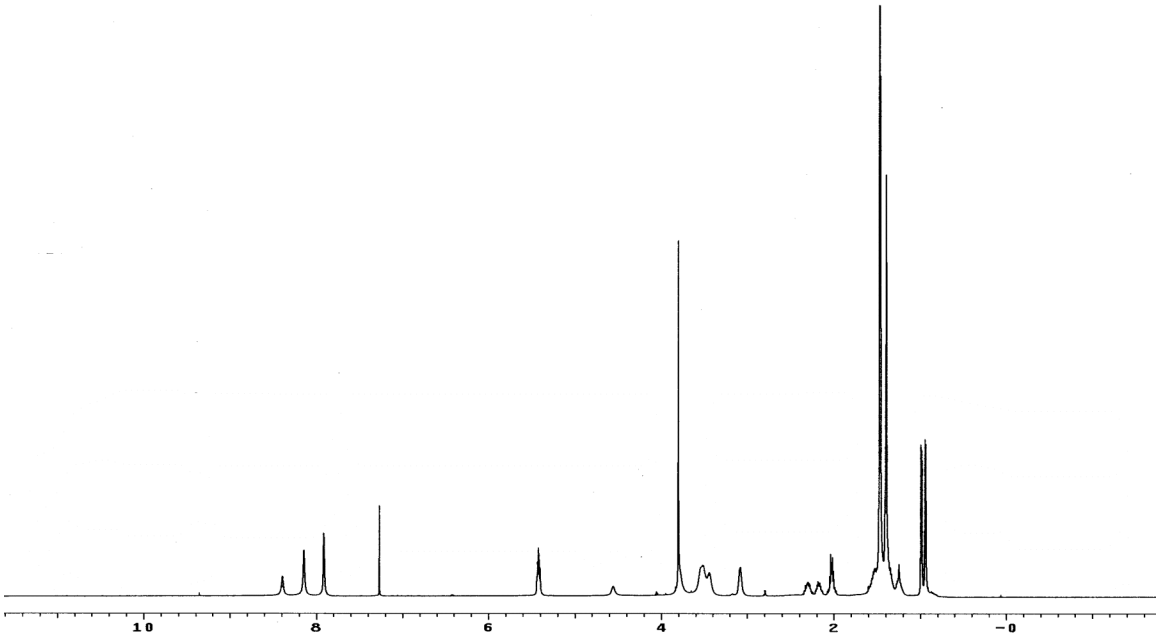
16j

Compound **16j** was prepared from (2.66 g, 4.3 mmol) of **15c**. Flash chromatography (3:1 EtOAc/Hexane) afforded 3.25 g (91 % over two steps) **16j** as a white solid.

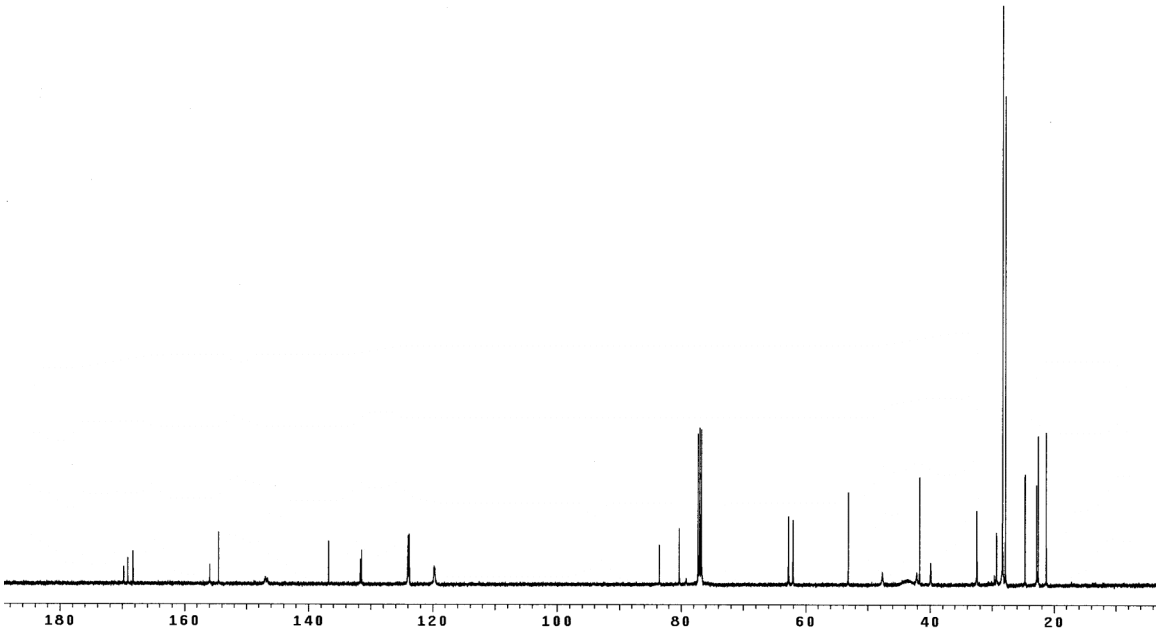
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.14 (s, 2H), 7.91 (s, 2H), 5.44-5.40 (m, 2H), 4.56 (br, 1 H), 3.80 (s, 3H), 3.78-3.40 (m, 8H), 3.08 (br, 2H), 2.34-2.26 (m, 1H), 2.21-2.17 (m, 1H), 2.08-1.98 (m, 2H), 1.54-1.24 (m, 32H), 0.98 (d, 3H, J = 6.5 Hz), 0.94 (d, 3H, J = 6.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.1, 168.3, 155.9, 154.5, 146.9, 146.7, 136.8, 131.7, 131.5, 124.0, 123.9, 123.8, 119.8, 119.6, 83.5, 80.3, 79.2, 62.8, 62.0, 53.1, 47.7, 43.6 (br), 42.1, 41.7, 39.9, 32.5, 29.3, 28.3, 27.9, 24.7, 22.8, 22.6, 21.3

MS (MALDI) calcd for $C_{42}H_{64}N_9O_9$ $(M+H)^+$ 838.48, found 838.45

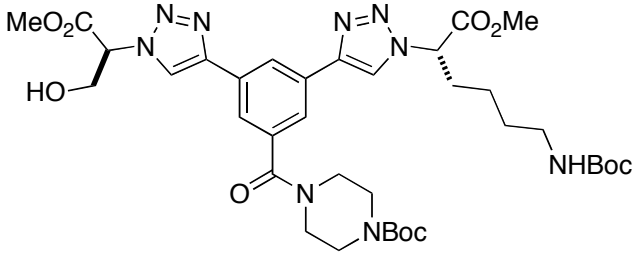


^{1}H NMR of **16j**



^{13}C NMR of **16j**

Preparation of compound 16k



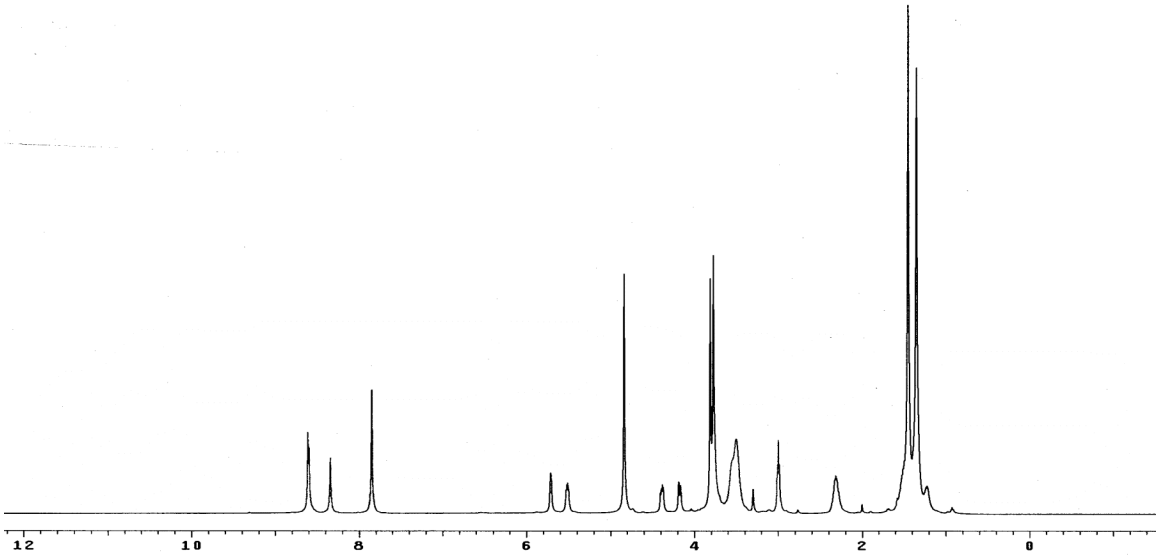
16k

Compound **16k** was prepared from (2.31 g, 3.5 mmol) of **15c**. Flash chromatography (9:1 EtOAc/Hexane) afforded 1.15 g (69 % over two steps) **16k** as a white solid.

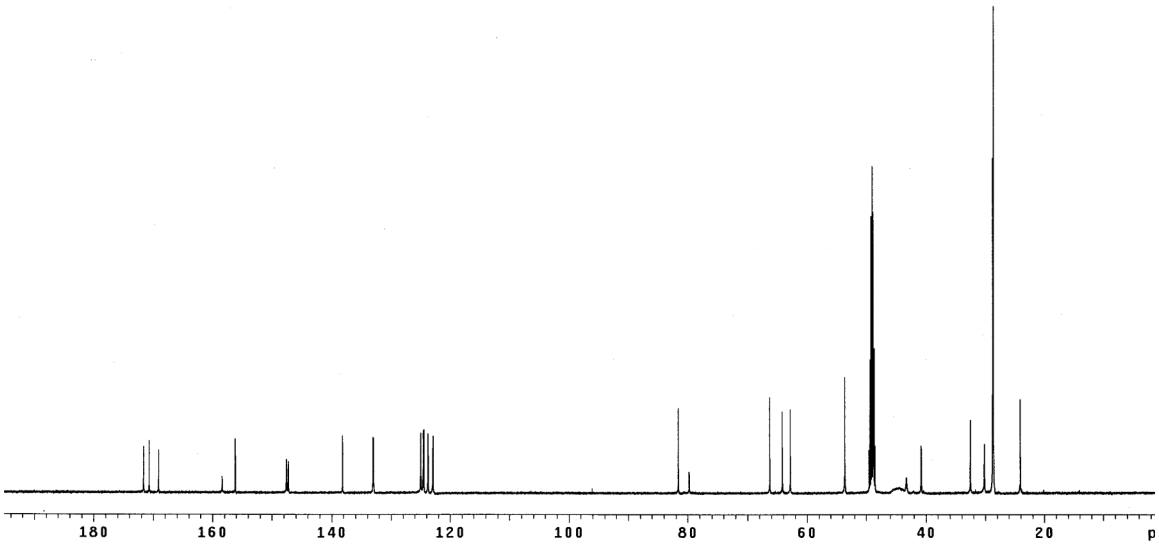
^{1}H NMR (500 MHz, CD_3OD) δ 8.61 (s, 1H), 8.60 (s, 1H), 8.34 (s, 1H), 7.85 (s, 2H), 5.72-5.70 (m, 1H), 5.44 (dd, 1H, J = 9.0, 5.5 Hz), 4.38 (dd, 1H, J = 12.0, 6.0 Hz), 4.17 (d, 1H, J = 9.5 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.77-3.42 (m, 8H), 3.00 (t, 2H, J = 6.5 Hz), 2.37-2.25 (m, 2H), 1.58-1.19 (m, 22H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 170.7, 169.1, 158.4, 156.2, 147.6, 147.3, 138.2, 133.1, 132.9, 125.0, 124.5, 124.4, 123.7, 122.9, 81.6, 79.8, 66.3, 64.2, 62.8, 53.6, 44.4 (br), 43.3, 40.8, 32.5, 30.2, 28.8, 28.7, 28.6, 24.1

MS (MALDI) calcd for $C_{36}H_{52}N_9O_{10}$ $(M+H)^+$ 770.38, found 770.29

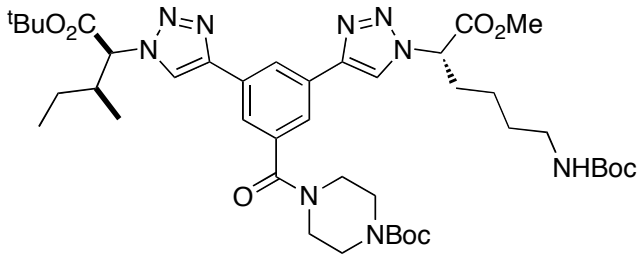


^{1}H NMR of **16k**



^{13}C NMR of **16k**

Preparation of Compound 16l



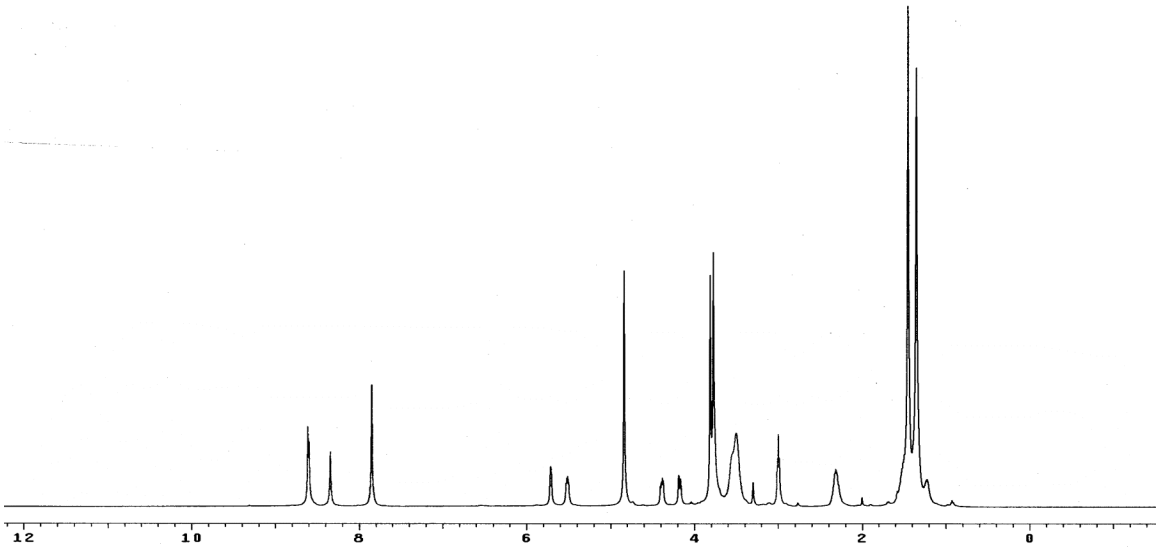
16l

Compound **16l** was prepared from (2.67 g, 4.1 mmol) of **15c**. Flash chromatography (3:1 EtOAc/Hexane) afforded 3.10 g (96 % over two steps) **16l** as a white solid.

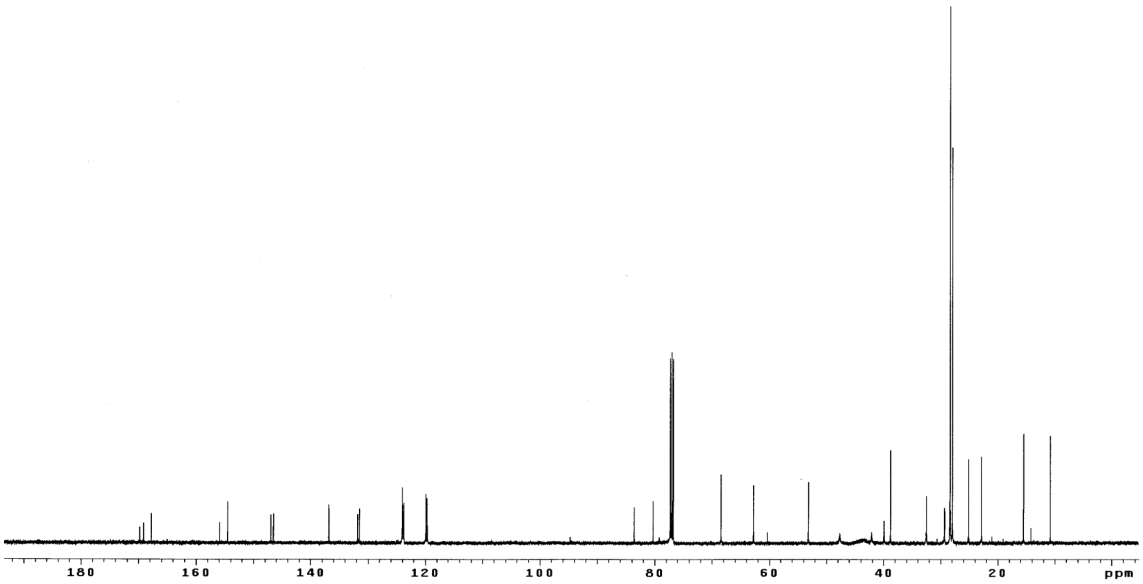
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 7.92 (s, 2H), 5.42 (dd, 1H, J = 10.0, 5.0 Hz), 5.18 (d, 1H, J = 8.5 Hz), 4.54 (br, 1 H), 3.81 (s, 3H), 3.80-3.42 (m, 8H), 3.10-3.07 (m, 2H), 2.31-2.04 (m, 3H), 1.63-1.26 (m, 33H), 1.05 (d, 3H, J = 6.5 Hz), 0.91 (t, 3H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.1, 167.8, 155.9, 154.5, 146.9, 146.5, 136.8, 131.8, 131.5, 124.0, 123.9, 123.8, 119.9, 119.7, 83.6, 80.3, 68.4, 62.8, 53.1, 47.6, 43.4 (br), 42.1, 39.9, 38.8, 32.5, 29.3, 28.3, 27.9, 25.1, 22.8, 15.5, 10.8

MS (MALDI) calcd for $C_{42}H_{64}N_9O_9$ $(M+H)^+$ 838.48, found 838.43

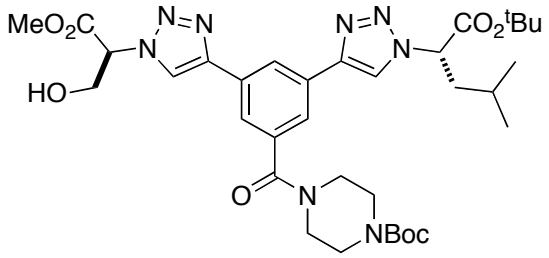


^{1}H NMR of **16l**



^{13}C NMR of **16l**

Preparation of Compound 16m



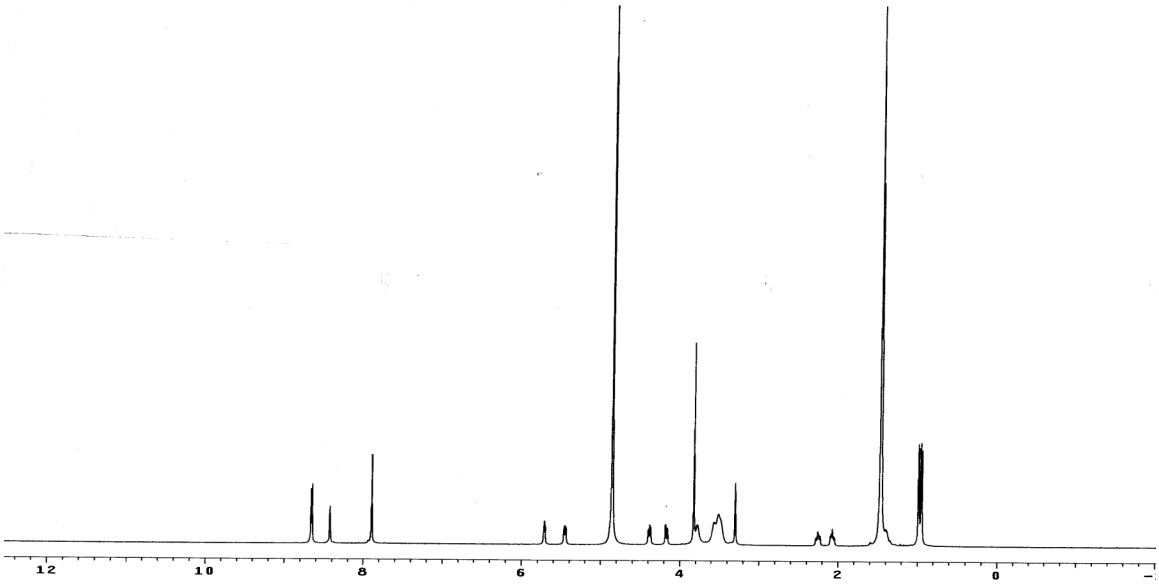
16m

Compound **16m** was prepared from (1.65 g, 3.0 mmol) of **15d**. Flash chromatography (3:1 EtOAc/Hexane) afforded 1.94 g (93 %) **16m** as a white solid.

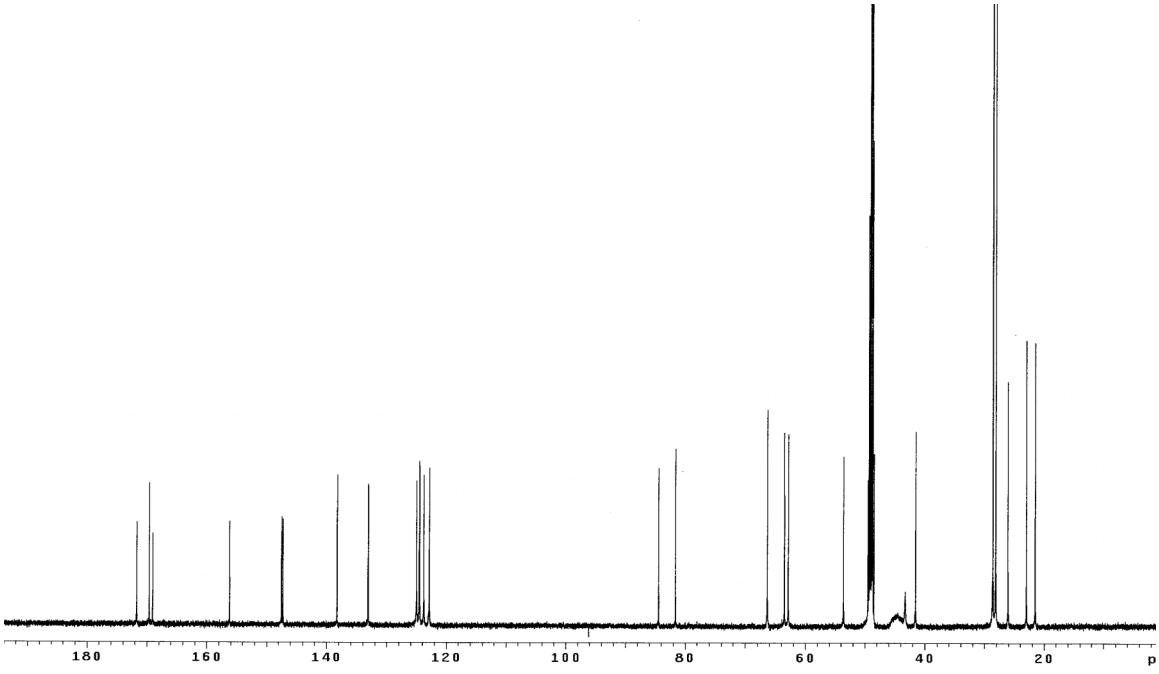
^{1}H NMR (500 MHz, CD_3OD) δ 8.86 (s, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 7.89 (s, 2H), 5.71 (dd, 1H, J = 6.0, 3.5 Hz), 5.45 (dd, 1H, J = 10.5, 5.0 Hz), 4.38 (dd, 1H, J = 12.0, 6.0 Hz), 4.16 (dd, 1H, J = 12.0, 3.0 Hz), 3.82 (s, 3H), 3.81-3.45 (m, 8H), 2.29-2.22 (m, 1H), 2.10-2.04 (m, 1H), 1.47 (s, 9H), 1.46 (s, 9H), 1.46-1.34 (m, 1H), 0.98 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 6.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 169.6, 169.0, 156.2, 147.5, 147.2, 138.2, 133.1, 133.0, 125.0, 124.5, 124.4, 123.8, 122.9, 84.4, 81.6, 66.3, 63.5, 62.8, 53.6, 44.5 (br), 43.2, 41.5, 28.6, 28.1, 26.0, 23.0, 21.5

MS (ESI) calcd for $C_{34}H_{49}N_8O_8$ $(M+H)^+$ 697.37, found 697.39

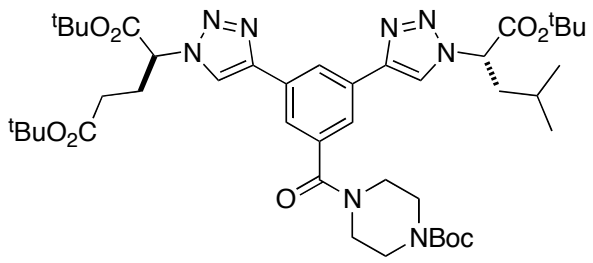


^{1}H NMR of **16m**



^{13}C NMR of **16m**

Preparation of Compound 16n



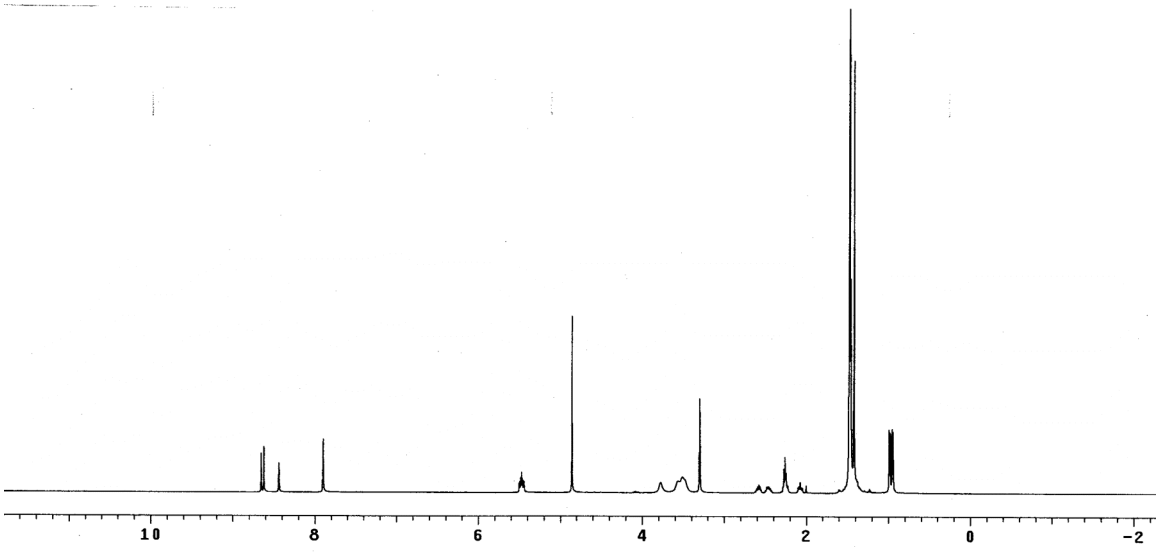
16n

Compound **16n** was prepared from (2.49 g, 4.0 mmol) of **15e**. Flash chromatography (1:1 EtOAc/Hexane) afforded 3.07 g (92 %) **16n** as a white solid.

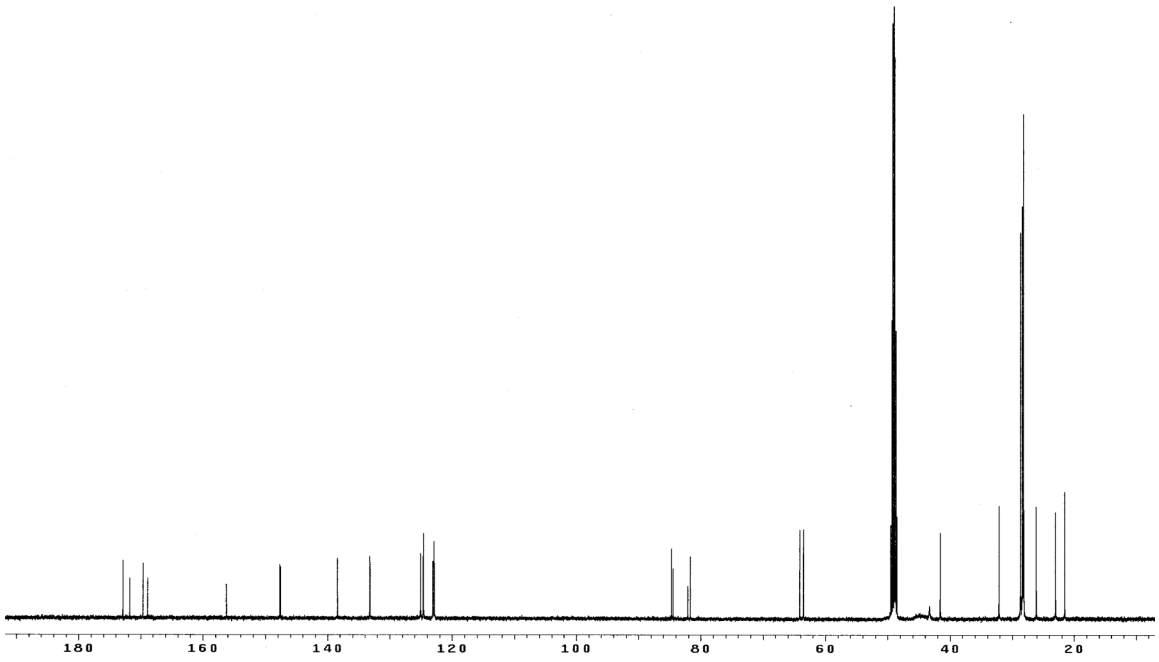
^{1}H NMR (500 MHz, CD_3OD) δ 8.66 (s, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 7.90 (s, 2H), 5.50-5.44 (m, 2H), 3.82-3.45 (m, 8H), 2.60-2.55 (m, 1H), 2.48-2.44 (m, 1H), 2.27-2.22 (m, 3H), 2.10-2.04 (m, 1H), 1.48 (s, 9H), 1.47 (s, 9H), 1.46 (s, 9H), 1.42 (s, 9H), 1.41-1.34 (m, 1H), 0.98 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 7.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.8, 169.6, 168.9, 156.2, 147.7, 147.6, 138.4, 133.2, 133.1, 125.0, 124.6, 123.1, 122.9, 84.7, 84.5, 82.1, 81.7, 64.1, 63.5, 44.8 (br), 43.3, 41.6, 32.1, 28.6, 28.32, 28.27, 28.12, 28.11, 26.1, 23.0, 21.5

MS (MALDI) calcd for $C_{37}H_{53}N_8O_{10}$ $(M+H)^+$ 837.49, found 837.42

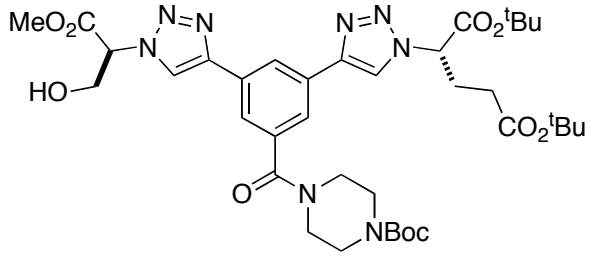


^{1}H NMR of **16n**



^{13}C NMR of **16n**

Preparation of Compound 16o



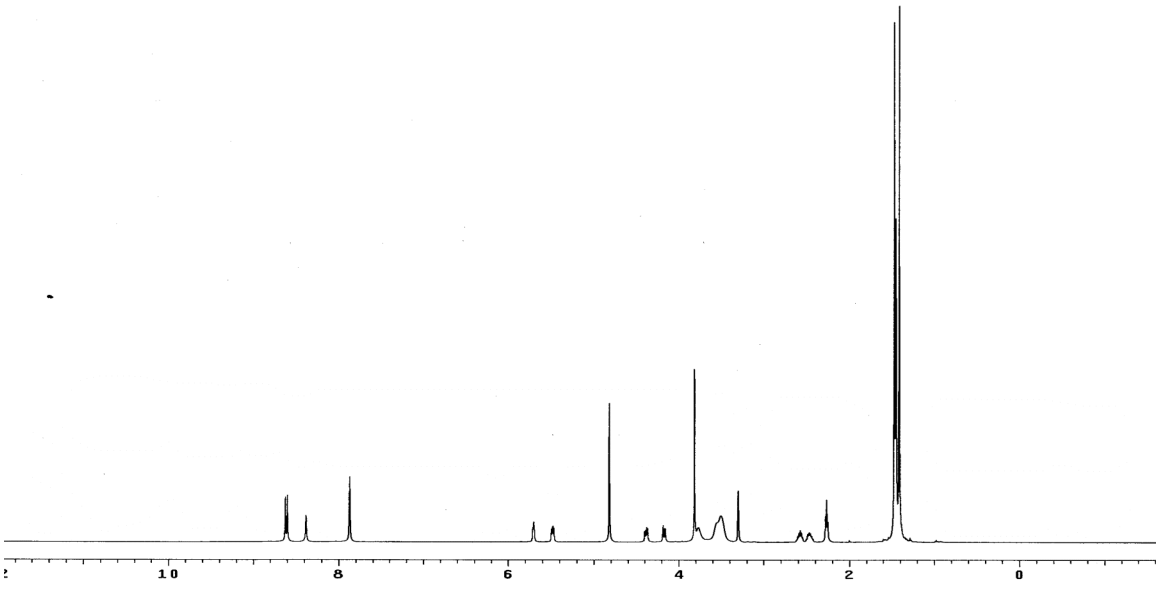
16o

Compound **16o** was prepared from (2.49 g, 4.0 mmol) of **15e**. Flash chromatography (3:1 EtOAc/Hexane to EtOAc) afforded 2.87 g (93 %) **16o** as a white solid.

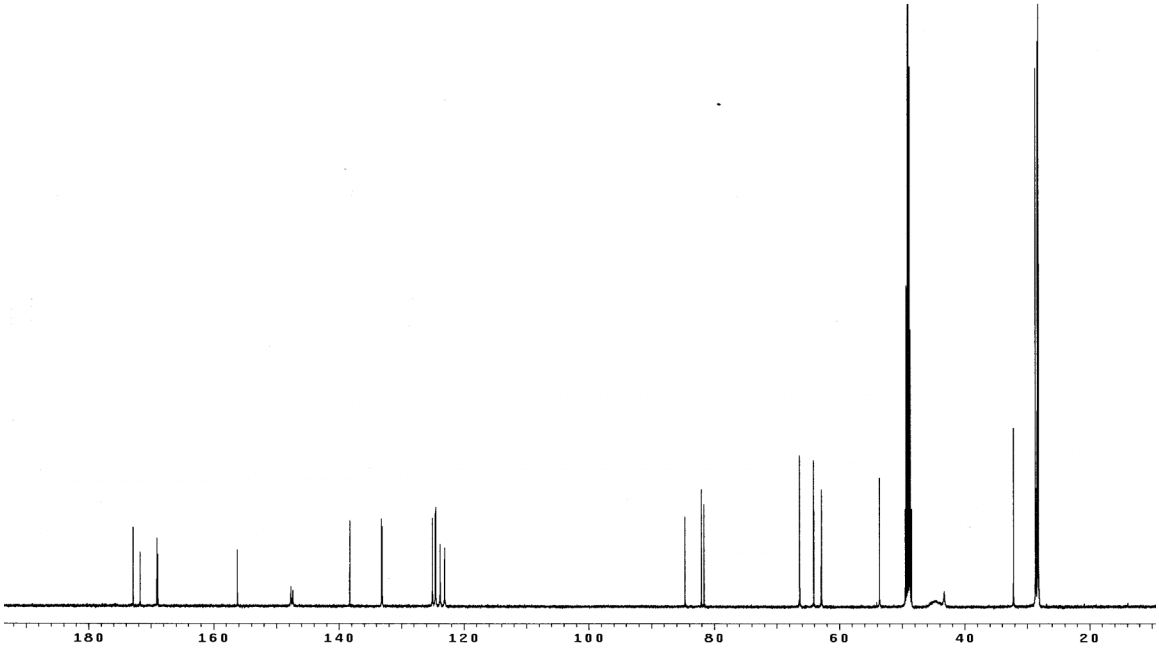
^{1}H NMR (500 MHz, CD_3OD) δ 8.62 (s, 1H), 8.60 (s, 1H), 8.38 (s, 1H), 7.87 (s, 2H), 5.70 (dd, 1H, J = 6.0, 3.5 Hz), 5.48 (dd, 1H, J = 10.0, 5.5 Hz), 4.49 (dd, 1H, J = 12.0, 6.0 Hz), 4.17 (dd, 1H, J = 11.5, 3.0 Hz), 3.82 (s, 3H), 3.81-3.45 (m, 8H), 2.60-2.55 (m, 1H), 2.50-2.43 (m, 1H), 2.27 (t, 2H, J = 7.3 Hz), 1.47 (s, 9H), 1.45 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.7, 169.1, 168.9, 156.2, 147.7, 147.4, 138.3, 133.2, 133.0, 125.0, 124.6, 124.5, 123.8, 123.1, 84.7, 82.1, 81.6, 66.3, 64.1, 62.9, 53.6, 44.5 (br), 43.3, 32.2, 28.6, 28.3, 28.2, 28.1

MS (ESI) calcd for $C_{43}H_{65}N_8O_9$ $(M+H)^+$ 769.39, found 769.36



^{1}H NMR of **16o**

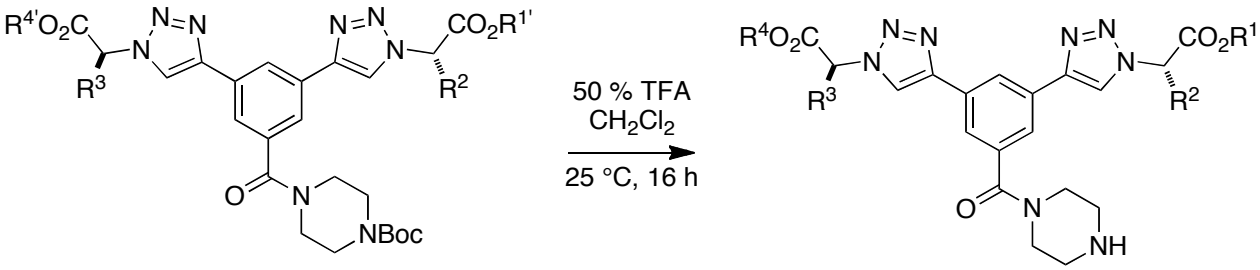


^{13}C NMR of **16o**

General Procedure for Deprotection of Monomers 3a-e and m.

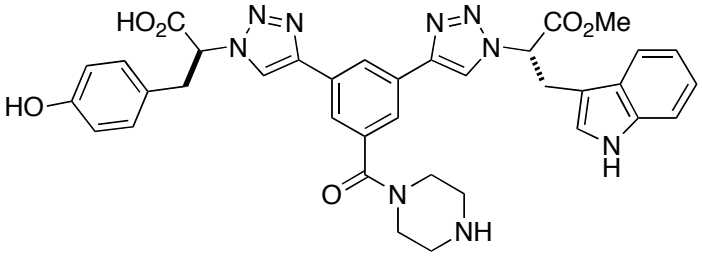
The compounds **3a-e and m** were treated with 50% TFA/CH_2Cl_2 at 25 ^{o}C for 16 h. Evaporating solvent under nitrogen afforded the desired product **3a-e and m**.

Scheme S15. Synthesis of compound **3a-e and m.**



16a-e, m **3a-e, m**

Preparation of Compound 3a



3a

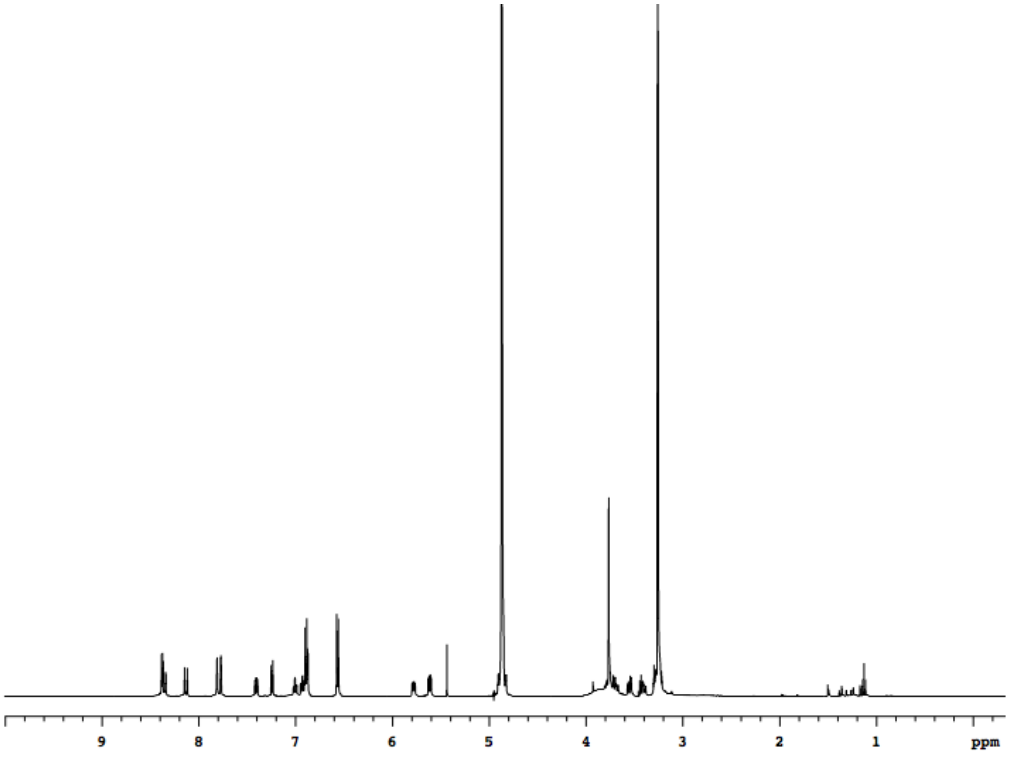
Compound **3a** was prepared from **16a** (33.90 mg, 0.035 mmol). **3a** was obtained as a gray amorphous solid (quant., TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 8.38 (d, 1H, J = 4.0 Hz), 8.35 (d, 1H, J = 13.5 Hz), 8.13 (ddd, 1H, J = 1.5, 13.5 Hz), 7.81 (s, 1H), 7.77 (s, 1H), 7.41 (dd, 1H, J = 5.5, 8.0 Hz), 7.24 (d, 1H, J = 8.0 Hz), 7.02-6.99 (m, 1H), 6.95-6.93 (m, 1H), 6.90 (d, 2H, J = 13.0 Hz), 6.87 (d, 1H, J = 2.0 Hz), 6.56 (d, 2H, J = 8.5 Hz), 5.78 (dd, 1H, J = 5.5, 9.5 Hz), 5.62 (dd, 1H, J = 4.5, 10.5 Hz), 3.93-3.67 (m, 4H), 3.55 (dd, 1H, J = 4.5, 14.5 Hz), 3.42 (dd, 1H, J = 1.5, 10.5 Hz), 3.31-3.21 (m, 6H)

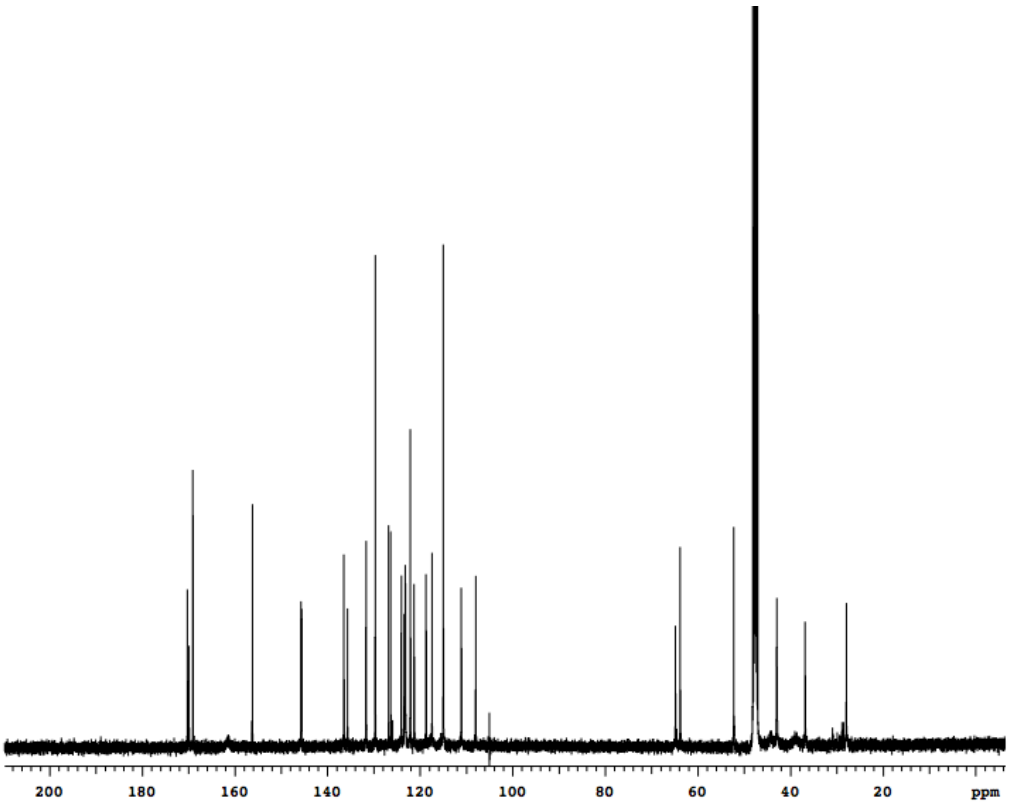
^{13}C NMR (125 MHz, CD_3OD) δ 172.50, 172.15, 171.31, 158.45, 147.96, 147.85, 138.70, 137.91, 133.93, 133.90, 133.89, 131.93, 129.05, 128.56, 126.30, 125.71, 125.67, 125.44, 124.36, 123.53, 120.96, 119.68, 117.23, 113.34, 110.24, 67.10, 66.07, 54.50, 54.50, 45.20, 39.10, 30.18 (107.25 is noise from NMR.)

MS (MALDI) calcd for $C_{36}H_{36}N_9O_6$ $(M+H)^+$ 690.28, found 690.34

optical rotation $[\alpha]_D^{20.3}$ = -68.7 (*c* = 0.362 in MeOH)

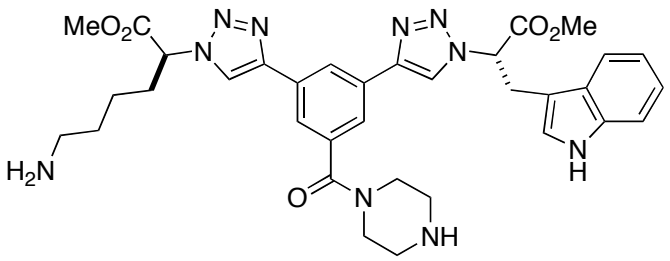


^{1}H NMR of **3a**



^{13}C NMR of **3a**

Preparation of Compound 3b



3b

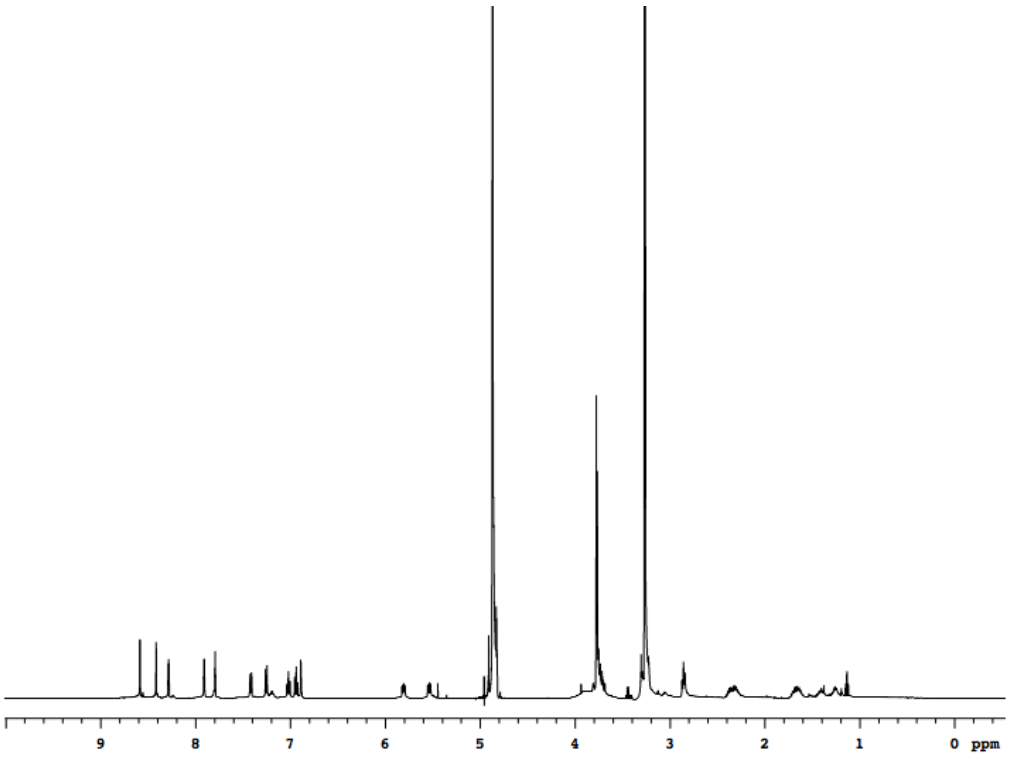
Compound **3b** was prepared from **16b** (33.90 mg, 0.039 mmol). **3b** was obtained as a purple amorphous solid (quant., 2TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 8.58 (d, 1H, J = 1.0 Hz), 8.41 (d, 1H, J = 1.0 Hz), 8.29-8.28 (m, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 7.42 (d, 1H, J = 7.5 Hz), 7.25 (d, 1H, J = 8.0 Hz), 7.02 (dd, 1H, J= 7.0, 7.0 Hz), 6.94 (dd, 1H, J = 8.0 Hz), 6.89 (s, 1H), 5.81 (dd, 1H, J = 5.5, 10.0 Hz), 5.54 (dd, 1H, J = 5.0, 10.0 Hz), 3.94-3.79 (m, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 3.30-3.22 (m, 4H), 2.86 (t, 2H, J = 8.0 Hz), 2.41-2.27 (m, 2H), 1.71-1.61 (m, 2H), 1.46-1,38 (m, 2H), 1.33-1.25 (m, 2H)

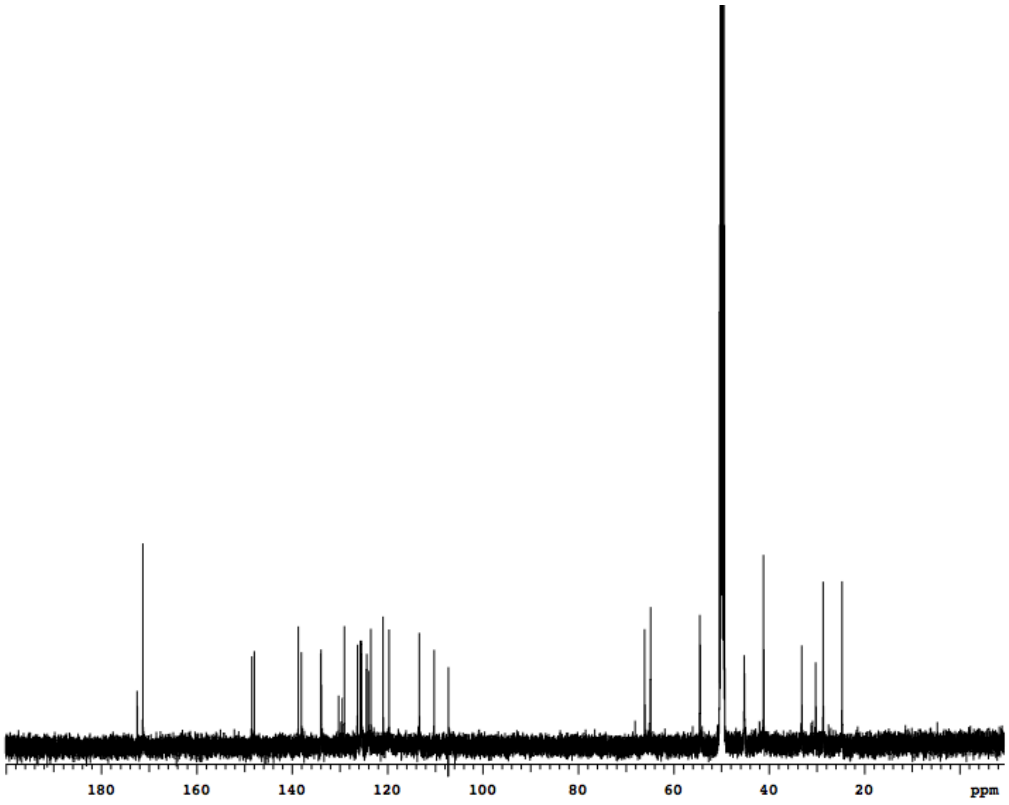
^{13}C NMR (125 MHz, CD_3OD) δ 172.50, 172.50, 171.32, 148.46, 147.95, 138.73, 138.07, 133.99, 133.92, 130.26, 129.06, 126.30, 125.68, 125.49, 124.39, 124.00, 123.50, 120.94, 110.67, 113.33, 110.23, 66.09, 64.86, 54.54, 54.54, 54.50, 45.20, 41.15, 33.13, 30.22, 28.66, 24.69 (107.25 is noise from NMR.)

MS (MALDI) calcd for $C_{34}H_{41}N_{10}O_5$ $(M+H)^+$ 669.75, found 669.37

optical rotation $[\alpha]_D^{20.4}$ = -8.3 (*c* = 0.603 in MeOH)

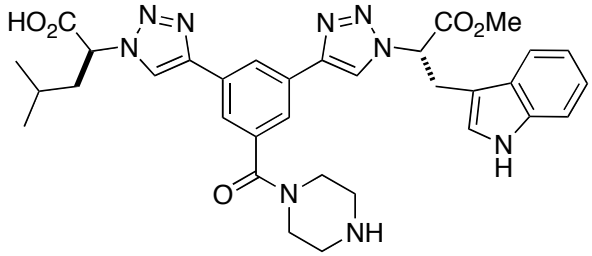


^{1}H NMR of **3b**



^{13}C NMR of **3b**

Preparation of Compound 3c



3c

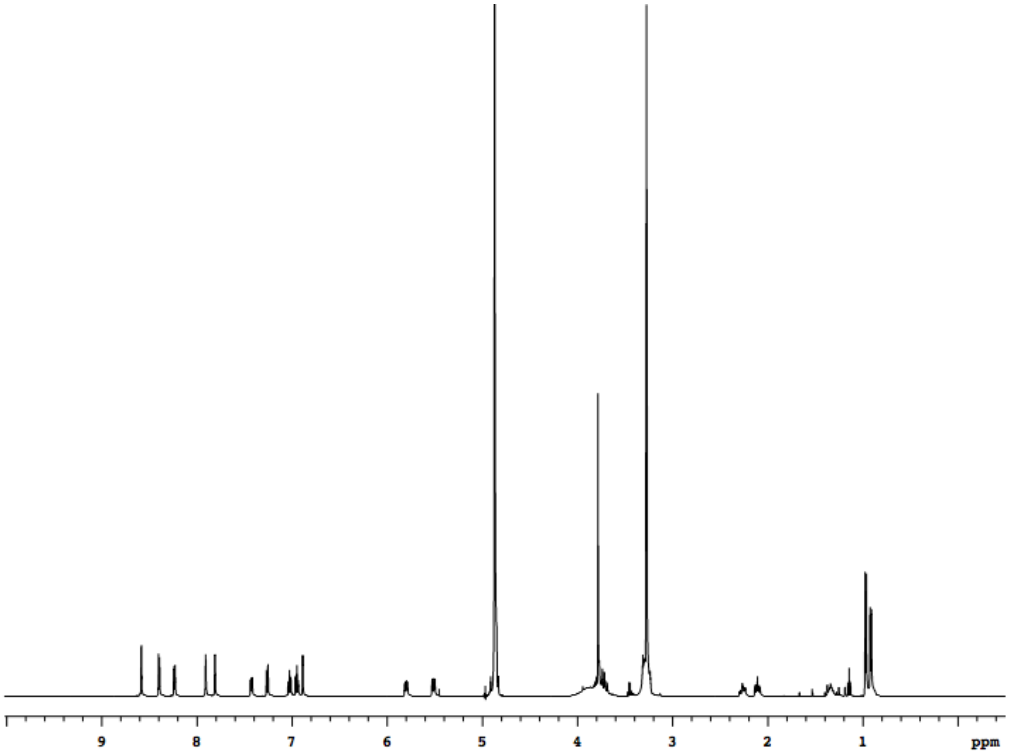
Compound **3c** was prepared from **16c** (34.50 mg, 0.043 mmol). **3c** was obtained with as a gray amorphous solid (quant., TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 8.58 (d, 1H, J = 2.5 Hz), 8.39 (d, 1H, J = 6.0 Hz), 8.23 (ddd, 1H, J = 1.5, 6.0 Hz), 7.91 (s, 1H) 7.81 (s, 1H), 7.45 (d, 1H, J = 8.0 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.02 (dd, 1H, J= 7.0, 8.0 Hz), 6.95 (dd, 1H, J = 7.0, 7.0 Hz), 6.88 (s, 1H), 5.80 (dd, 1H, J = 5.5, 13.5 Hz), 5.51 (dd, 1H, J = 5.5, 11.0 Hz), 3.94-3.68 (m, 4H), 3.27 (s, 3H), 3.32-3.23 (m, 6H), 2.30-2.23 (m, 1H), 2.13-2.08 (m, 1H), 1.37-1.32 (m, 1H), 0.97 (d, 3H, J = 6.5 Hz), 0.92 (d, 3H, J = 7.0 Hz)

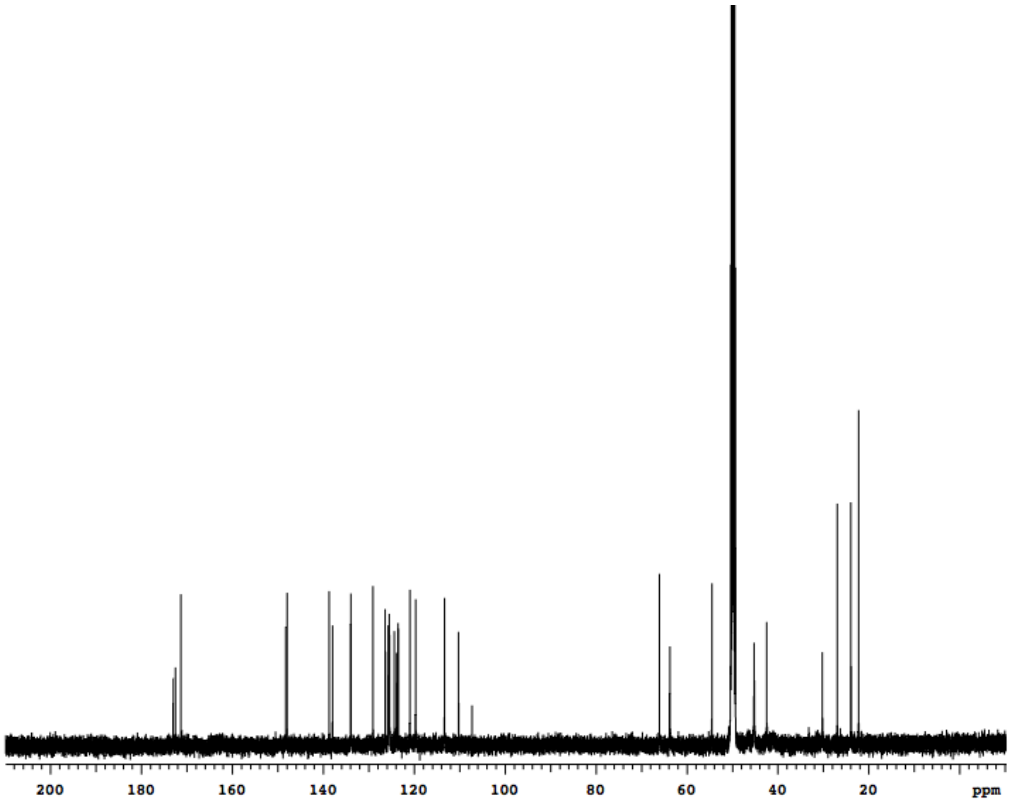
^{13}C NMR (125 MHz, CD_3OD) δ 172.99, 172.51, 171.32, 148.26, 147.96, 138.71, 137.97, 133.95, 133.93, 129.04, 126.35, 125.69, 125.47, 125.44, 124.35, 123.81, 123.50, 120.94, 119.68, 113.33, 110.23, 66.06, 63.76, 54.50, 45.21, 42.45, 30.21, 26.93, 23.91, 22.23 (107.25 is noise from NMR.)

MS (MALDI) calcd for $C_{33}H_{38}N_9O_5$ $(M+H)^+$ 640.30, found 640.35

optical rotation $[\alpha]_D^{20.4}$ = 0.3 (*c* = 1.050 in MeOH)

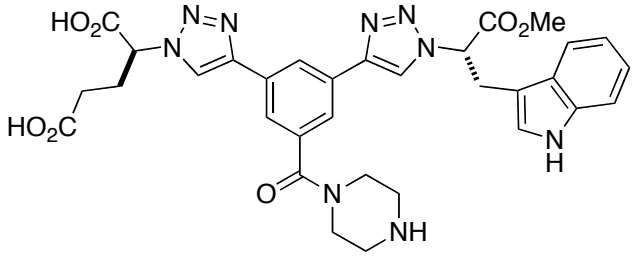


^{1}H NMR of **3c**



^{13}C NMR of **3c**

Preparation of Compound 3d



3d

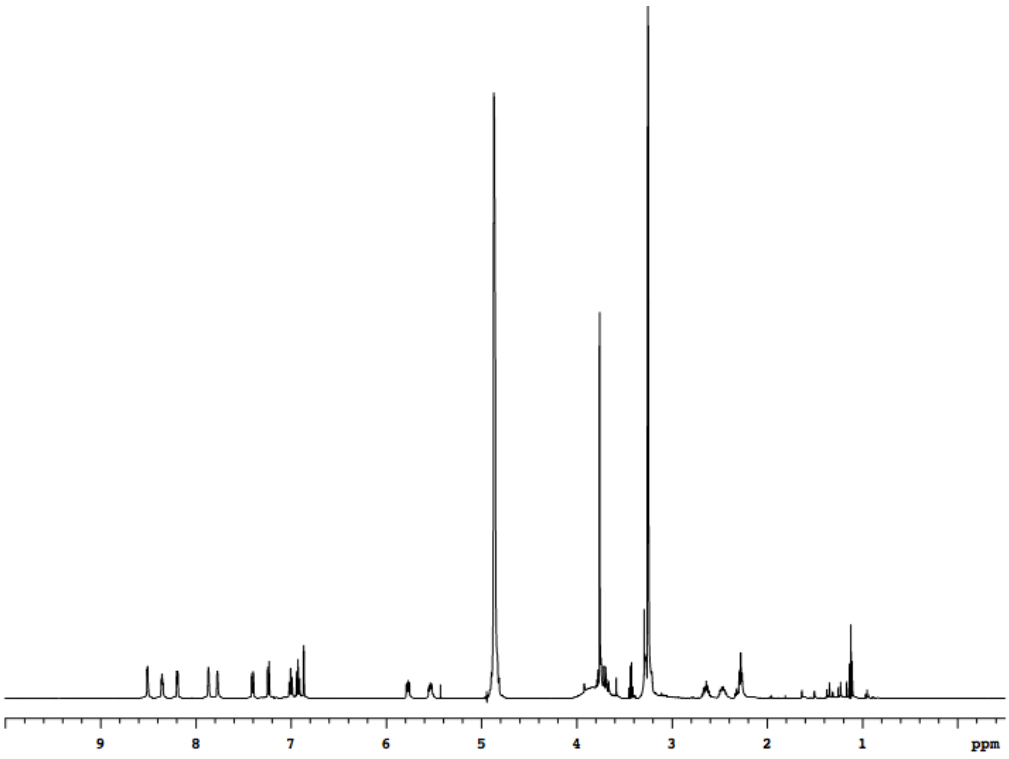
Compound **3d** was prepared from **16d** (32.70 mg, 0.038 mmol). **3d** was obtained with as a gray amorphous solid (quant., TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (d, 1H, J = 3.0 Hz), 8.35 (t, 1H, J = 4.5 Hz), 8.20-8.19 (m, 1H), 7.87 (s, 1H) 7.77 (s, 1H), 7.40 (d, 1H, J = 8.5 Hz), 7.24 (d, 1H, J = 8.0 Hz), 7.00 (dd, 1H, J= 8.0, 8.0 Hz), 6.92 (dd, 1H, J = 8.0, 8.0 Hz), 6.87 (s, 1H), 5.78 (dd, 1H, J = 5.5, 10.0 Hz), 5.54 (dd, 1H, J = 5.5, 11.5 Hz), 3.92-3.66 (m, 4H), 3.76 (s, 3H), 3.29-2.37 (m, 4H), 3.22-3.21 (m, 2H) 2.69-2.61 (m, 1H), 2.50-2.43 (m, 1H), 2.28 (t, 2H, J = 6.5 Hz)

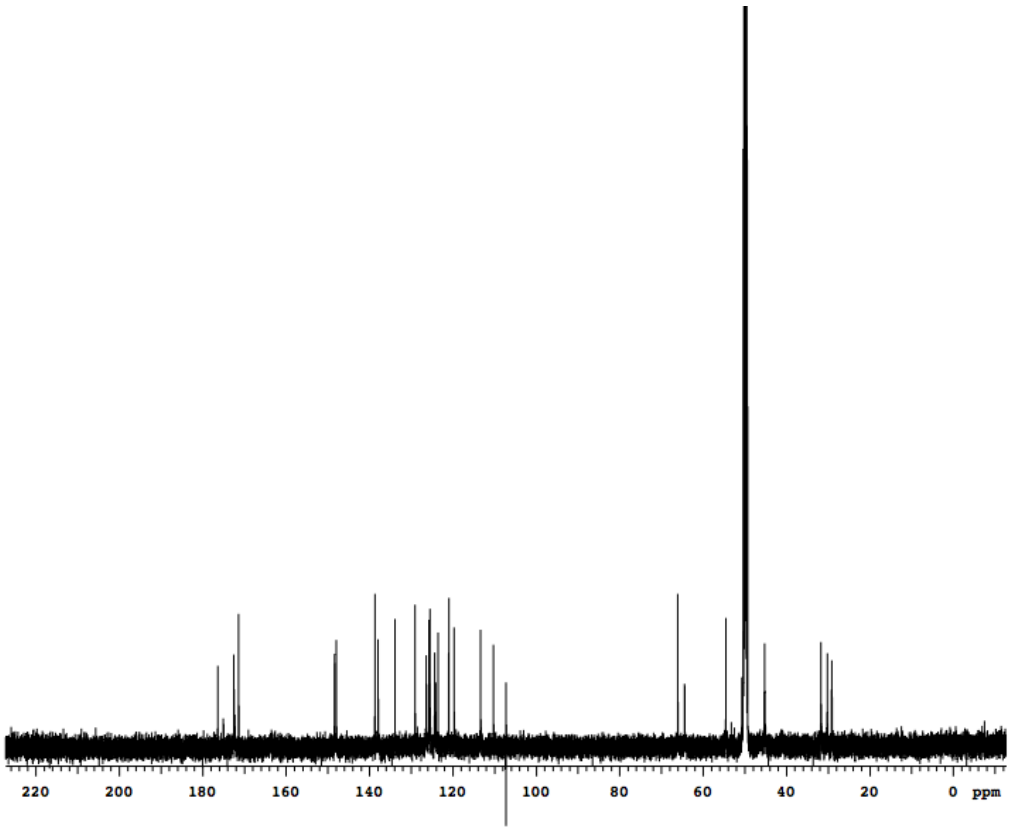
^{13}C NMR (125 MHz, CD_3OD) δ 176.38, 175.02, 172.50, 171.36, 148.32, 147.94, 138.70, 137.91, 133.88, 133.88, 129.04, 129.04, 126.36, 125.70, 125.49, 124.35, 124.08, 123.53, 120.96, 119.70, 113.35, 110.25, 66.05, 64.40, 54.52, 54.52, 45.23, 31.70, 30.20, 29.14 (107.25 is noise from NMR.)

MS (MALDI) calcd for $C_{32}H_{34}N_9O_7$ $(M+H)^+$ 656.26, found 656.30

optical rotation $[\alpha]_D^{20.3}$ = -8.3 (*c* = 0.403 in MeOH)

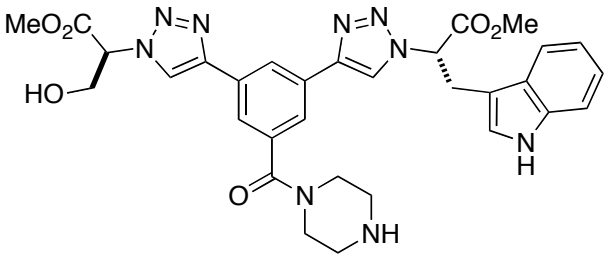


^{1}H NMR of **3d**



^{13}C NMR of **3d**

Preparation of Compound 3e



3e

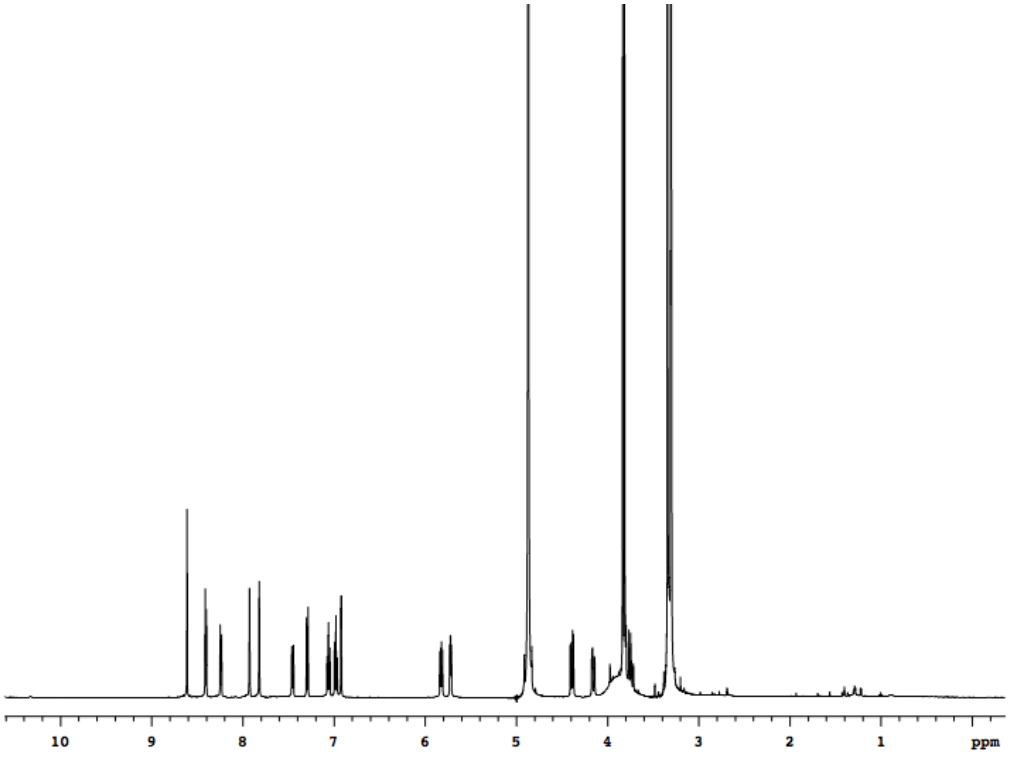
Compound **3e** was prepared from **16e** (29.70 mg, 0.041 mmol). **3e** was obtained as a gray amorphous solid (quant., TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 8.61 (s, 1H), 8.41 (d, 1H, J = 6.5 Hz), 8.24 (ddd, 1H, J = 1.5, 6.5 Hz), 7.93 (s, 1H) 7.82 (s, 1H), 7.45 (d, 1H, J = 8.0 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.06 (dd, 1H, J= 8.0, 8.0 Hz), 6.98 (dd, 1H, J = 7.5, 7.5 Hz), 6.92 (d, 1H, J = 2.0 Hz), 5.82 (dd, 1H, J = 5.5, 14.5 Hz), 5.72 (dd, 1H, J = 3.5, 6.0 Hz), 4.39 (dd, 1H, J = 5.5, 12.0 Hz), 4.15 (dd, 1H, J = 3.5, 12.0 Hz), 3.97-3.36 (m, 4H), 3.83 (s, 3H) 3.81 (s, 3H), 3.30 (m, 5H)

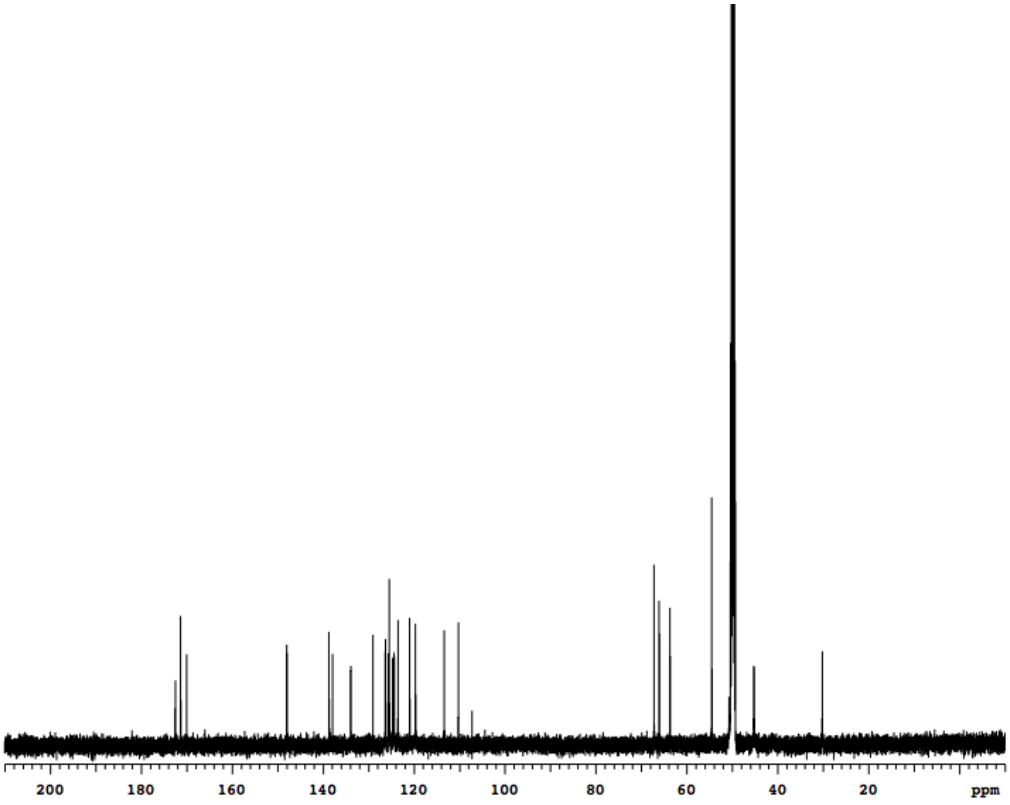
^{13}C NMR (125 MHz, CD_3OD) δ 172.53, 171.36, 170.03, 148.03, 147.94, 138.72, 137.94, 133.95, 133.88, 129.06, 129.06, 126.31, 125.69, 125.45, 124.67, 124.39, 123.54, 120.96, 119.69, 113.36, 110.25, 67.21, 66. 07, 63.69, 54.51, 54.51, 50.71, 45.26, 30.20 (107.25 is noise from NMR.)

MS (MALDI) calcd for $C_{31}H_{34}N_9O_6$ $(M+H)^+$ 628.26, found 628.31

optical rotation $[\alpha]_D^{20.4}$ = 8.5 (*c* = 1.875 in MeOH)

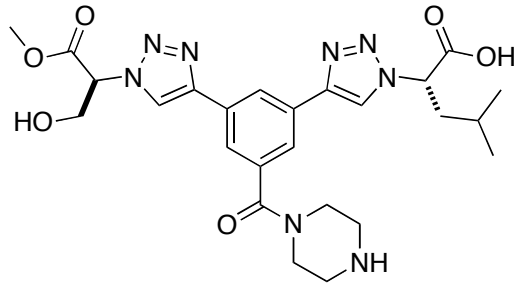


^{1}H NMR of **3e**



^{13}C NMR of **3e**

Preparation of Compound 3m



3m

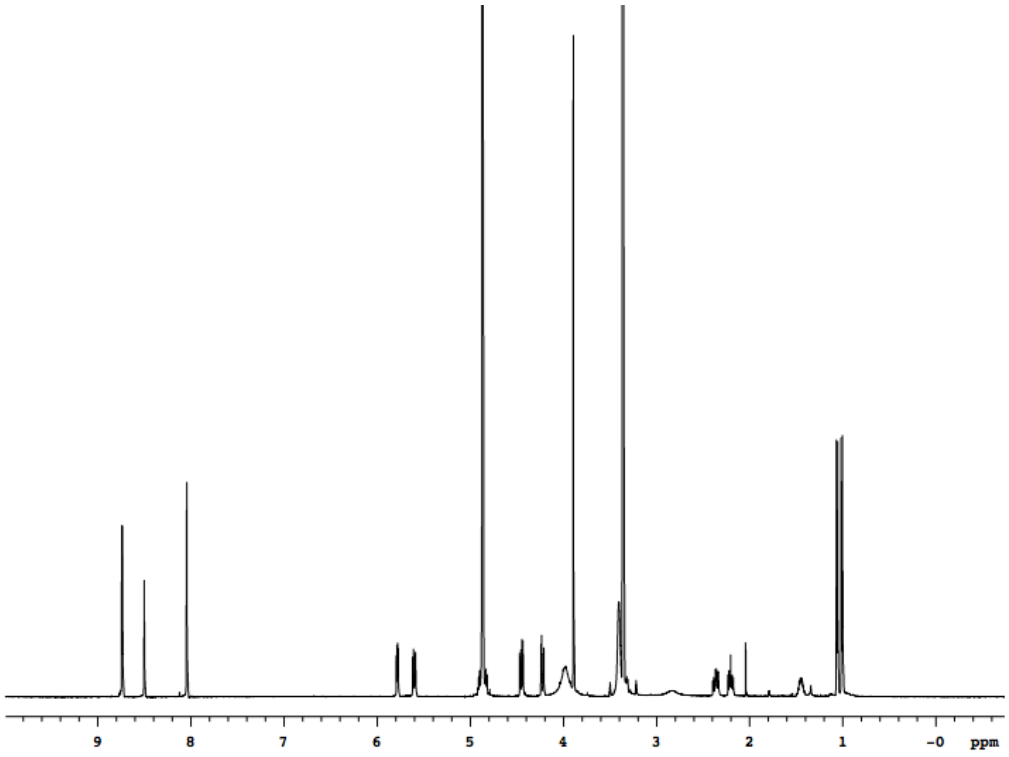
Compound **3m** was prepared from **16m** (31.20 mg, 0.045 mmol). **3m** was obtained as a white amorphous solid (quant., TFA salt).

^{1}H NMR (500 MHz, CD_3OD) δ 8.72 (d, 2H, J = 3.5 Hz), 8.48 (t, 1H, J = 1.5 Hz), 8.02 (d, 2H, J = 1.5 Hz), 5.76 (dd, 1H, J = 6.0, 3.5 Hz), 5.58 (dd, 1H, J = 11.0, 4.5 Hz), 4.43 (dd, 1H, J = 12.0, 6.0 Hz), 4.20 (dd, 1H, J = 12.0, 3.5 Hz), 3.88-4.04 (br, 3H), 3.87 (s, 3H), 3.36-3.42 (br, 1H), 2.31-2.39 (m, 1H), 2.15-2.22 (m, 1H), 1.38-1.46 (m, 1H), 1.03 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.5 Hz)

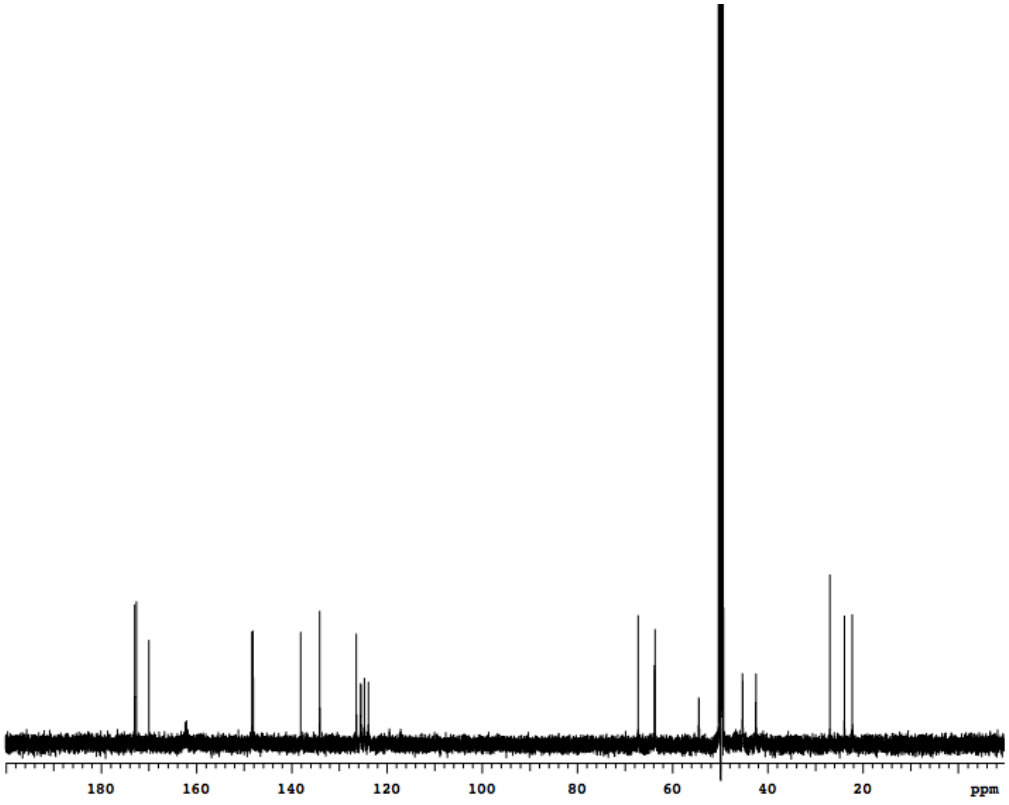
^{13}C NMR (125 MHz, CD_3OD) δ 172.9, 172.6, 169.9, 148.3, 148.1, 138.1, 134.1, 134.0, 126.4, 125.5, 125.4, 124.7, 123.9, 67.2, 62.8, 63.7, 54.5, 54.4, 45.3, 42.5, 26.9, 23.9, 22.2

MS (MALDI) calcd for $C_{25}H_{32}N_8O_6$ $(M+H)^+$ 541.20, found 541.27

optical rotation $[\alpha]_D^{20.2}$ = 2.9 (*c* = 3.51 in MeOH)



^{1}H NMR of **3m**



^{13}C NMR of **3m**

F. Preparation of Linear Bistriazole Mimics

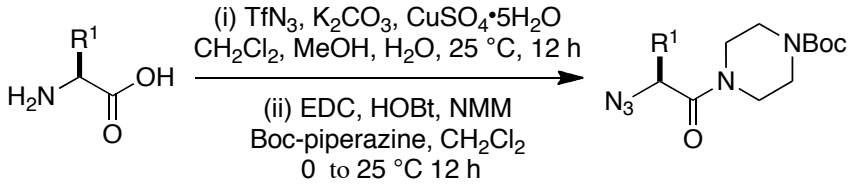
General Procedure for Compounds 17a-c

Amino acid azides were prepared from the corresponding amino acids following the procedure reported previously by Lundquist and Pelletier.[14] In general, to an ice-cooled solution of NaN_3 in CH_2Cl_2/water (0.70 M, 10.0 equiv) was added triflic anhydride (2.0 equiv), drop-wise, over 10 minutes. The reaction mixture was allowed to warm to room temperature and vigorously stirred at 25 °C for 6 h. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 twice, and the organic phases were combined. The combined phases were washed with saturated Na_2CO_3 twice, and then dried over Na_2SO_4 to yield TfN_3 in solution.

To a solution of L-amino acid (1.0 equiv) in methanol (0.20 M) was added freshly prepared triflic azide (2.0 equiv) solution, K_2CO_3 (2.0 equiv), and $CuSO_4 \bullet 5H_2O$ (1.0 mol %). The reaction mixture was stirred at 25 °C for 12 h after which time the solvents were removed under vacuum. The product residue was suspended in water (100 mL) and extracted with EtOAc (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, and then concentrated under reduced pressure.

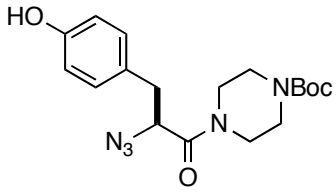
The crude azido-acid was then dissolved in CH_2Cl_2 (0.2 M) and cooled to 0 °C. To this solution was added HOBt (1.1 equiv), and EDC (1.1 equiv), and the resulting mixture was stirred at 0 °C for 20 minutes. Boc-piperazine (1.1 equiv), and *N*-methylmorpholine (2.0 equiv) were subsequently added. The reaction mixture was allowed to warm to 25 °C while stirring for 12 h. The solvents were removed under reduced pressure, and the resulting product residue was dissolved in EtOAc (0.20 M), and extracted with equal volumes of 5 % HCl, water, 5 % Na_2CO_3, water, and then brine. The organic phase was dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography.

Scheme S16. Synthesis of compound **17a-c.**



17a-c

Preparation of Compound 17a

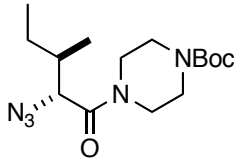


17a

Compound **17a** was prepared from L-Tyr (9.05 g, 50.0 mmol). The crude product was purified on silica gel (1:3 EtOAc/Hexanes) to afford 3.91 g (21%) as a white foam.

Spectral data matched that previously reported.[10,15]

Preparation of Compound 17b

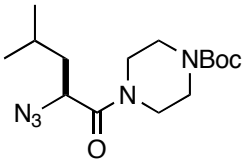


17b

Compound **17b** was prepared from L-Ile (6.6 g, 50.0 mmol). The crude product was purified by column chromatography on silica gel (1:2 EtOAc/Hexanes) to afford 7.0 g (43 %) as a white solid.

Spectral data matched that previously reported.[10,15]

Procedure and preparation of Compound 17c



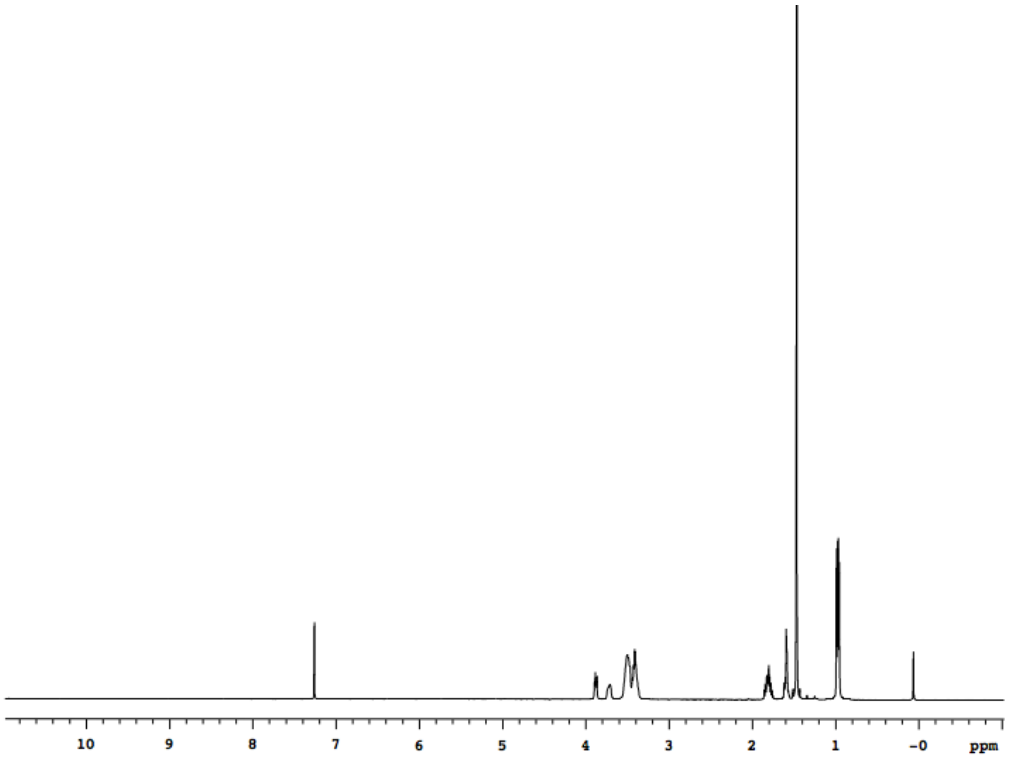
17c

Compound **17c** was prepared from L-Leu (6.6 g, 50.0 mmol). The crude product was purified by column chromatography on silica (1:3 EtOAc/Hexanes) to afford 12.9 g (80 %) as a white solid.

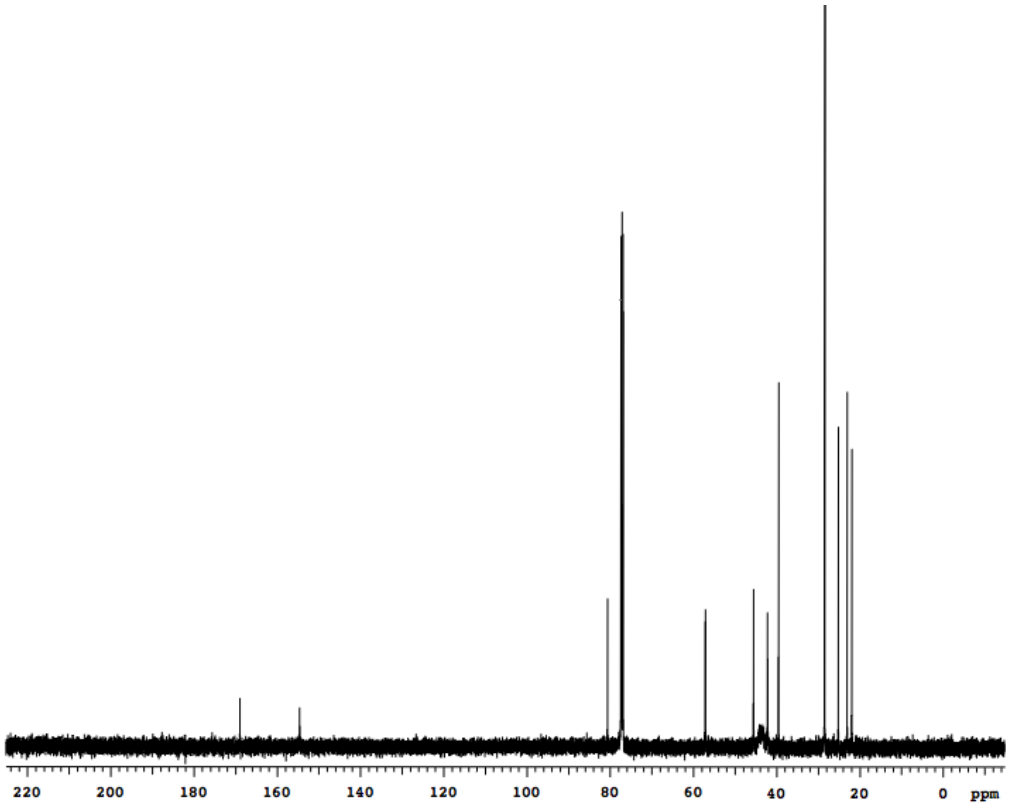
^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90-3.95 (m, 1H), 3.75-3.69 (m, br, 1H), 3.56-3.36 (m, br, 8H), 1.85-1.75 (m, 1H), 1.62-1.52 (m, 1H under water peak), 1.47 (s, 9H), 0.97 (app dd, 6H, J = 10.0, J = 6.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 154.6, 80.7, 57.1, 45.6, 42.2, 39.6, 28.5, 25.2, 23.1, 22.0

MS (ESI, m/z) calcd for $C_{18}H_{25}N_5O_4$ $(M+H)^+$ 326.2, found 326.2



^{1}H NMR of **17c**



^{13}C NMR of **17c**

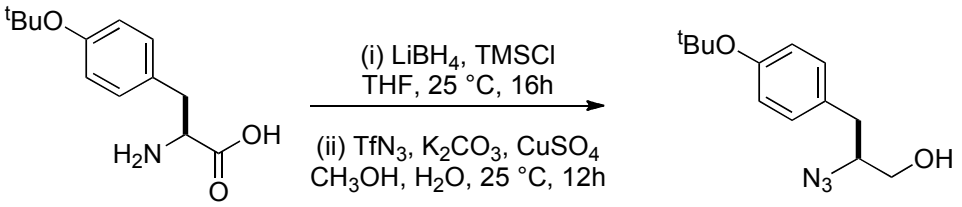
Preparation of Compound 18a

To an ice bath-cooled suspension of *tert*-butyl protected L-Tyrosine (15.6 g, 86.0 mmol 1.0 equiv) and $LiBH_4$ (2.0 equiv) in THF (0.70 M) was added TMSCl (4.0 equiv), drop-wise, over 10 minutes. The reaction mixture was then allowed to warm to 25 °C and stirred at 25 °C for 16 h. After this time, methanol was added to quench the reaction. The reaction mixture was concentrated under reduced pressure and the resulting product residue was dissolved in 14 % NaOH and extracted with CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, and then concentrated under vacuum. The crude amino alcohol was used directly.

To an ice-cooled solution of NaN_3 in CH_2Cl_2/water (0.70 M, 1.0 equiv) was added triflic anhydride (5.0 equiv), drop-wise, over 10 minutes. The reaction mixture was allowed to warm to room temperature and vigorously stirred at 25 °C for 6 h. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 twice, and the organic phases were combined. The combined phases were washed with saturated Na_2CO_3, and then dried over Na_2SO_4 to yield TfN_3 in solution.

The TfN_3 solution was added to a solution of amino alcohol (1.0 equiv) in water and methanol and vigorously stirred at 25 °C for 12 h. The solvent was removed *in vacuo*, the resulting aqueous slurry was diluted with water (0.25 M), the pH was adjusted to 6 with 12 *N* HCl, and extracted three times with an equal volume of ethyl acetate. The organic phases were combined, dried over Na_2SO_4, concentrated under reduced pressure. The azido alcohol product was purified on silica gel (5:1 EtOAc/hexanes) to afford 3.4 g (21 %) as a yellow oil.

Scheme S17. Synthesis of compound **18a.**



18a

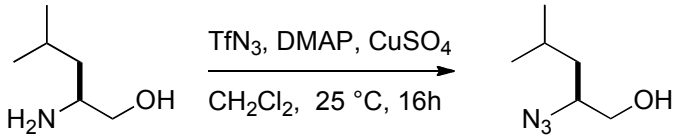
Spectral data for the compounds obtained matched that previously reported. [16]

Preparation of Compound 18b

To an ice-cooled solution of NaN_3 (5.85 g, 90.0 mmol) in CH_2Cl_2 (4.0 M) and water (7.0 M) was added triflic anhydride (3.0 mL, 18 mmol), drop-wise, over 10 minutes. The reaction mixture was vigorously stirred at 0 °C for 2.5 hours after which time, the layers were separated. The aqueous layer was extracted twice with 10 mL CH_2Cl_2, and the combined organic phases were washed with 10 mL saturated sodium carbonate, brine and then dried over Na_2SO_4 to yield TfN_3 in solution.

Commercially obtained *S*-Leucineol (0.47 g, 4.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and 4-Dimethylaminopyridine (0.28g, 0.6 equiv) was added. To this solution was added the solution of triflic azide followed by a catalytic amount of copper sulfate (0.4 mL, 1M solution). The reaction was allowed to stir at 25 °C for 16 hours overnight. A 5% aqueous solution of citric acid (30 mL) was added to the reaction and the phases were separated. The aqueous phase was back-extracted with 15 mL CH_2Cl_2. The organic phases were combined and washed with 20 mL each of saturated sodium bicarbonate solution and brine. The organic phase was dried with sodium sulfate, decanted and concentrated under reduced pressure. The crude product was purified by column chromatography using CH_2Cl_2 as eluant to yield the azido alcohol (0.35 g, 59 %) as a pale yellow oil.

Scheme S18. Synthesis of compound **18b.**

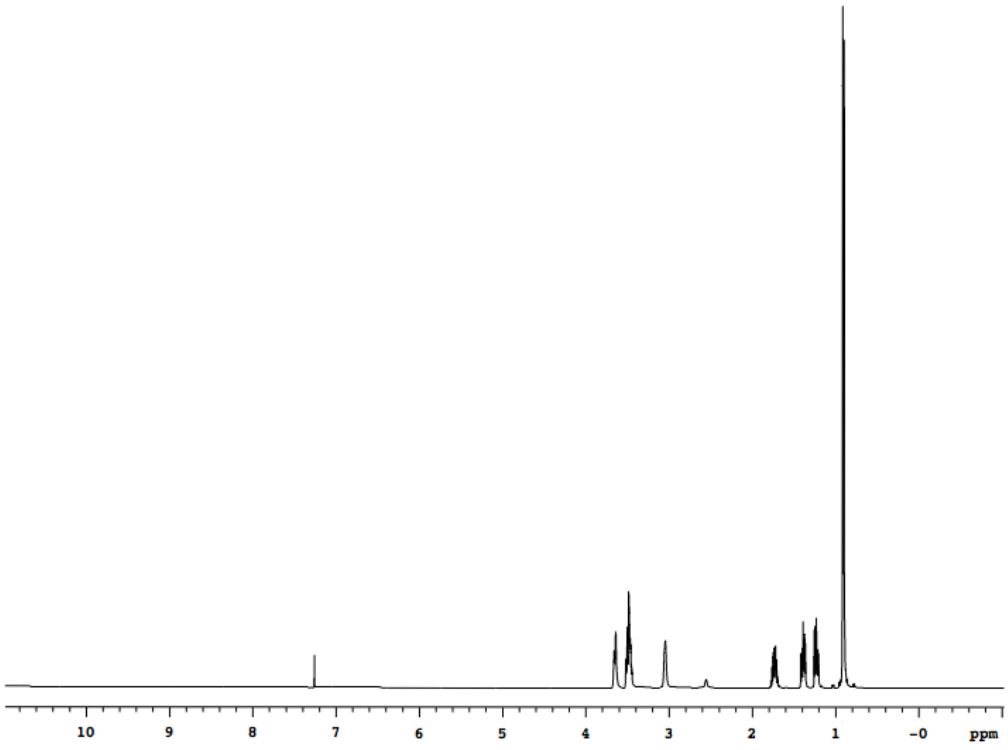


18b

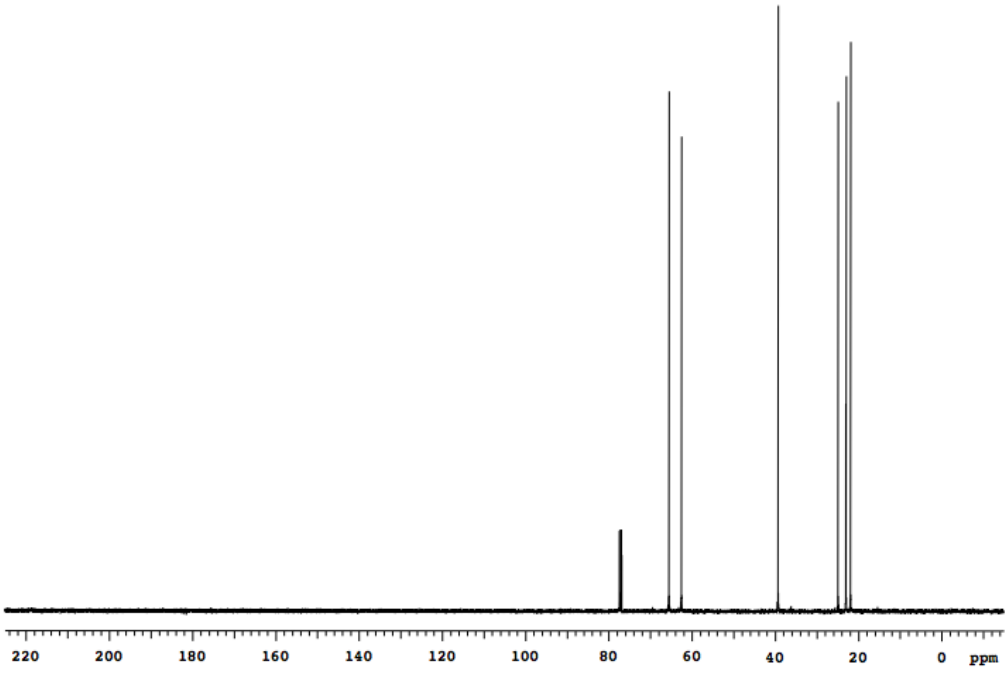
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.65 (d, 1H, J = 8.5 Hz), 3.52-3.44 (m, 2H), 3.04 (s, b, 1H), 1.73 (sept, 1H, J = 7.0 Hz), 1.42-1.35 (m, 1H), 1.26-1.20 (m, 1H), 0.91 (app dd, 6H, J = 7.0 Hz, J = 1.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 65.6, 62.6, 39.4, 25.0, 23.0, 22.0

MS (ESI, m/z) calcd for $C_6H_{13}N_3O$ $(M+Li)^+$ 150.2, found 150.1



^{1}H NMR of **18b**

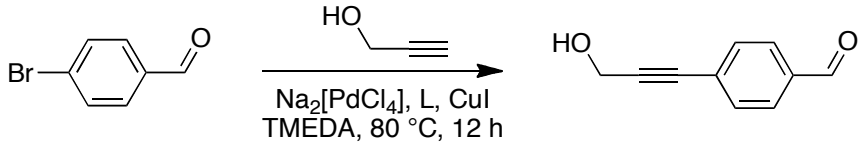


^{13}C NMR of **18b**

Procedure and preparation for Compound 19

To a solution of 4-bromobenzaldehyde (9.25 g, 50.0 mmol, 1.0 equiv) in tetramethylethylenediamine (50 mL, 1.0 M) was added sodium tetrachloropalladate(II) (70.4 mg, 0.25 mmol, 0.50 mol%), 2-(di-tert-butylphosphine)-1-phenylindole (169 mg, 0.5 mmol, 1 mol%), copper(I) iodide (95.3 mg, 0.50 mmol, 1.0 mol%), and propargyl alcohol (5.80 mL, 100.0 mmol, 2.0 equiv). The reaction flask was equipped with a reflux condenser and the reaction mixture was stirred under an inert atmosphere at 80 °C for 12 h. After this time, the reaction was quenched by addition of water, extracted with diethyl ether (3 x 150 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified via column chromatography on silica gel (2:3 EtOAC/ hexanes) to afford 6.7 g (84 %) of **19** as a white solid. [17]

Scheme S19. Synthesis of compound **19.**

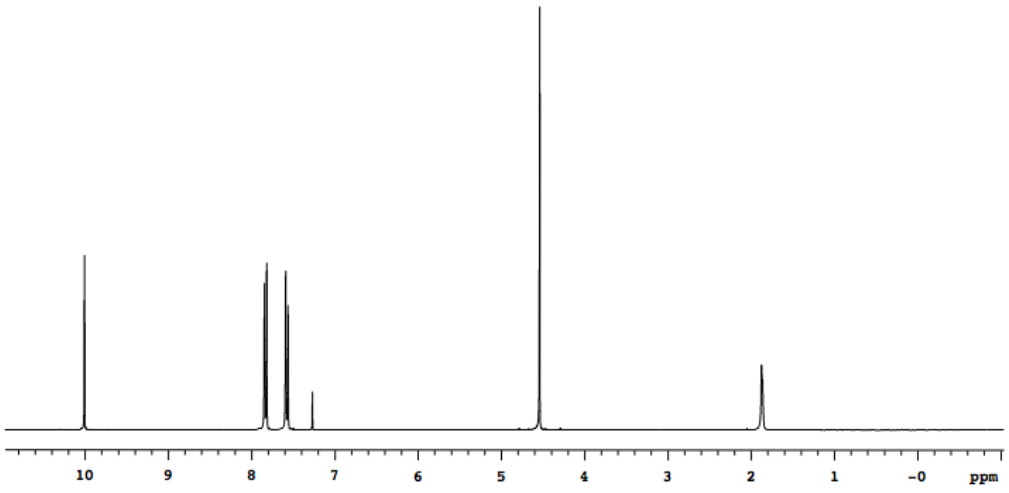


(L = 2-(di-tert-butylphosphine)-1-phenylindole) **19**

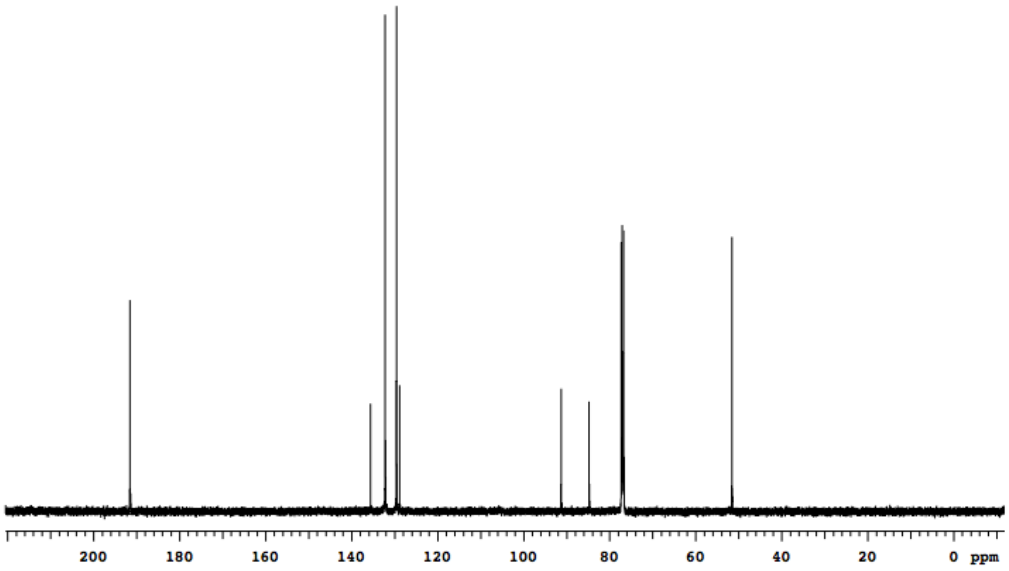
^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.00 (s, 1H), 7.83 (d, 2H, J = 14.0 Hz), 7.58 (d, 2H, J = 14.0 Hz), 4.54 (s, 2H), 1.87 (s, br, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.5, 135.6, 132.1, 129.5, 128.8, 91.2, 84.7, 51.5

MS (ESI, m/z) calcd for $C_{10}H_8O_2$ $(M+H)^+$ 161.0, found 161.0



^{1}H NMR of **19**

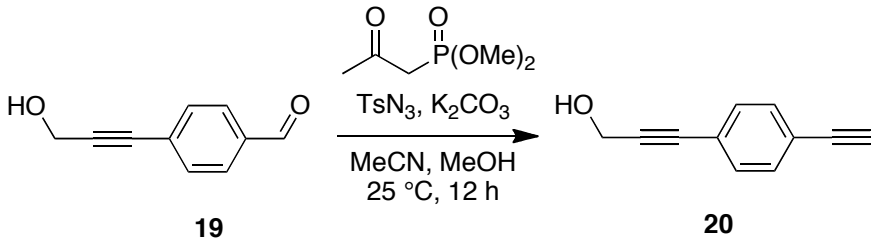


^{13}C NMR of **19**

Procedure and preparation for Compound 20

To a solution of dimethyl 2-oxopropylphosphonate in acetonitrile (1.2 equiv, 0.25 M) was added 4-toluenesulfonyl azide (1.2 equiv), and K_2CO_3 (3.0 equiv). The reaction mixture was stirred at 25 °C for 2 h (forming dimethyl 1-diazo-2-oxopropylphosphonate *in situ*). At the end of the reaction time, a solution of **19** in methanol (0.35 M, 1.0 equiv) was added in one portion and the resulting solution was stirred at 25 °C for 12 h. The reaction mixture was diluted with Et_2O, washed with 5 % $NaHCO_3$, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography on silica (1:4 EtOAC/hexanes). The reaction was repeated in different scales to yield 8.3 g (75 %) of **19** as a white solid.

Scheme S20. Synthesis of compound **20.**

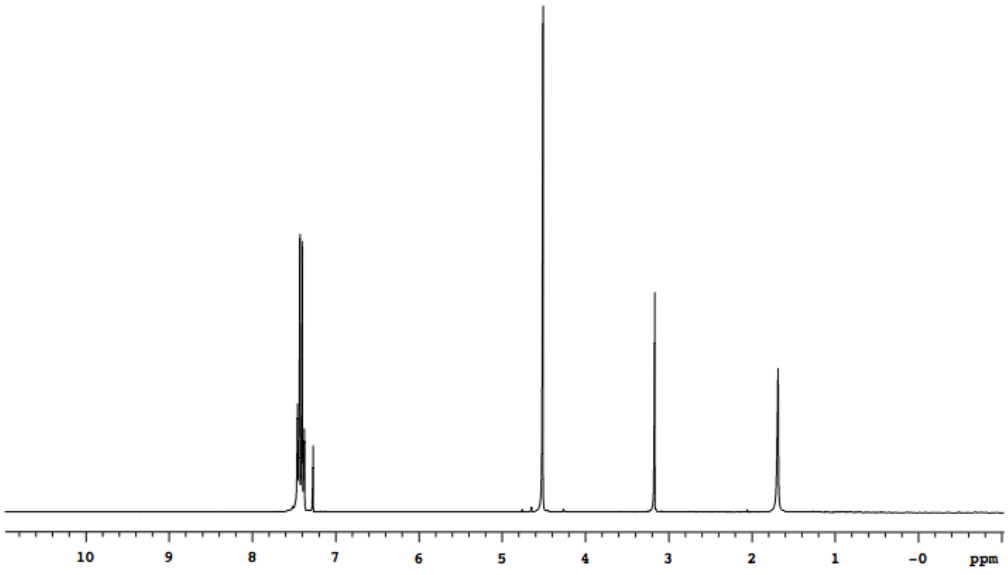


19 **20**

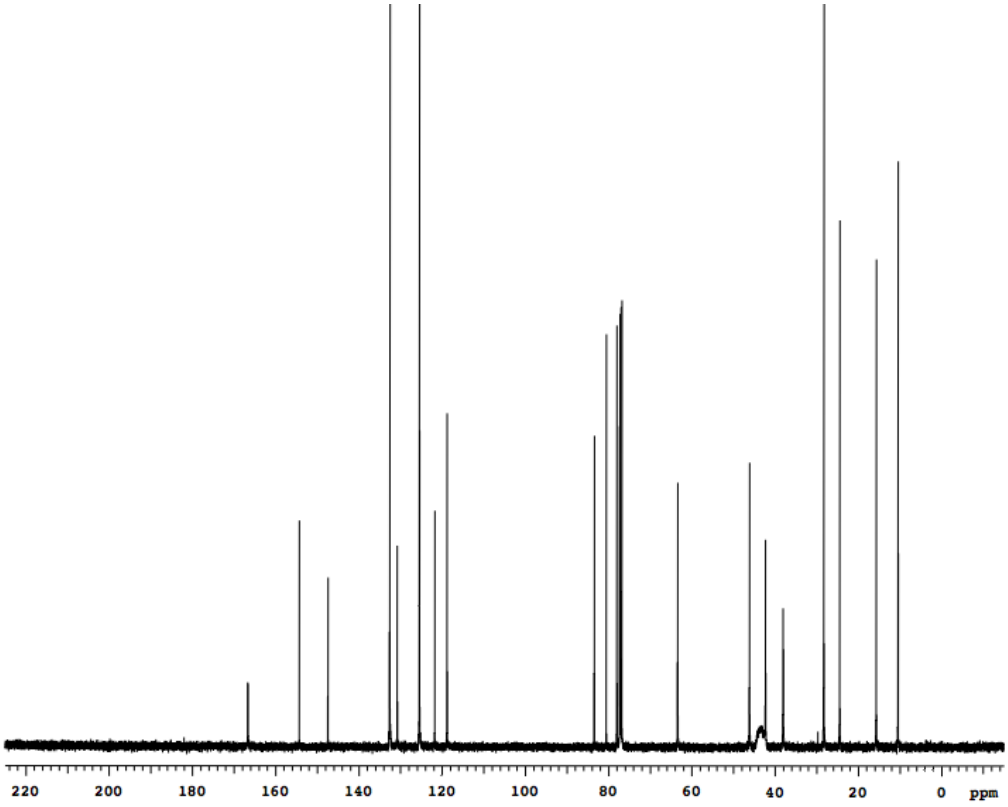
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46-7.35 (m, 4H), 4.51 (s, 2H), 3.17 (s, 1H), 1.69 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.2, 131.7, 123.1, 122.3, 89.3, 85.3, 83.3, 79.1, 51.7

MS (ESI, m/z) calcd for $C_{11}H_8O$ $(M+Li)^+$ 163.0, found 163.0



^{1}H NMR of **20**

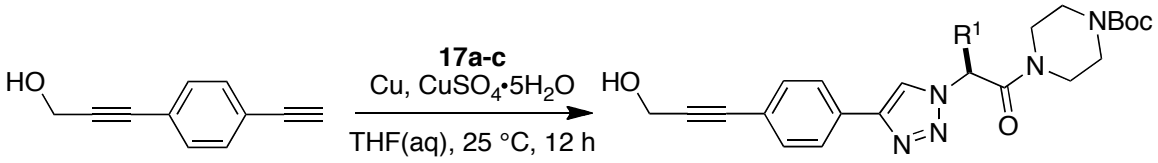


^{13}C NMR of **20**

General Procedure for Compounds 21a-c

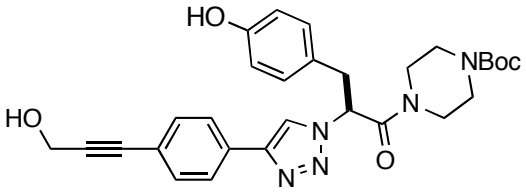
To a solution of **20** (1.0 equiv) and **17a-c** (1.0 equiv) in 90 % THF/H_2O (0.30 M) was added powdered copper (1.0 equiv), and $CuSO_4$•$5H_2O$ (0.10 equiv in 1 N solution) in one portion. The reaction mixture was stirred at 25 °C for 12 h. The reaction was then diluted with ethyl acetate, and filtered through Celite to remove the copper. The Celite was washed with copious amounts of ethyl acetate. The product was extracted with 25 % NH_4OH, 2 % EDTA solution and then brine. The organic phase was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude triazole product was then purified by column chromatography on silica using a mixture of ethyl acetate and hexanes as eluant.

Scheme S21. Synthesis of compound **21a-c.**



20 **21a-c**

Preparation of Compound 21a



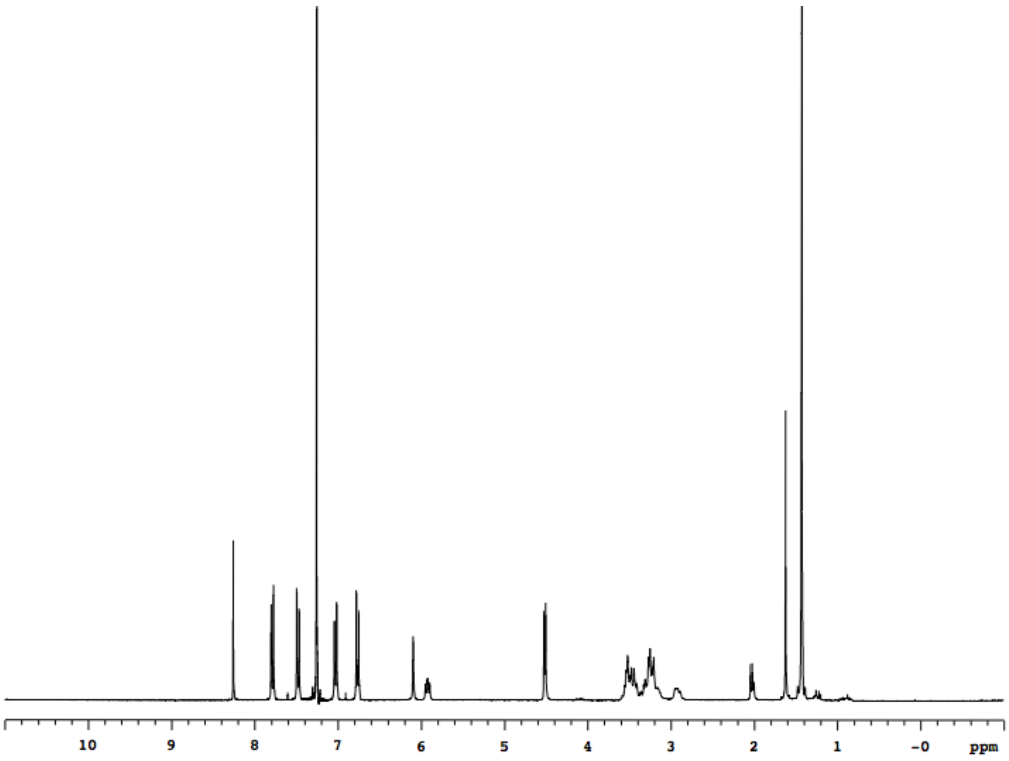
21a

Compound **21a** was prepared from **19** (1.0 g, 6.41 mmol) and **17a** (2.08 g, 6.41 mmol). The coupled product was purified by column chromatography on silica gel (2:1 EtOAc:Hexanes) to afford 1.91 g (62 %) as a white foam.

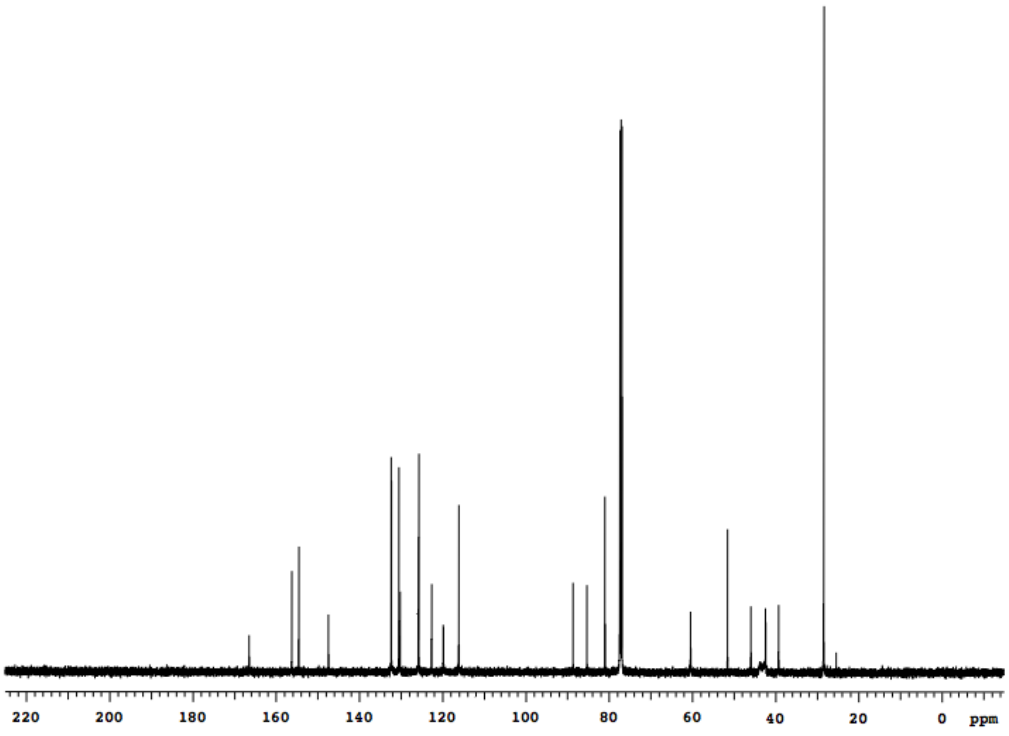
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.79 (d, 2H, J = 14.0 Hz), 7.48 (d, 2H, J = 14.0 Hz), 7.03 (d, 2H, J = 14.0 Hz), 6.77 (d, 2H, J = 14.0 Hz), 6.10 (s, 1H), 5.92 (dd, J = 15.0, 11.0 Hz), 4.52 (d, 2H, J = 10.5 Hz), 3.59-3.37 (m, 4H), 3.32-3.10 (m, 6H), 2.96-2.85 (m, 1H), 2.02 (t, 1H, J = 10.0 Hz), 1.43 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.5, 156.3, 154.6, 147.4, 132.4, 130.5, 130.2, 125.8, 125.7, 122.7, 119.8, 116.1, 88.7, 85.3, 81.0, 60.4, 51.6, 46.0, 42.4, 39.3, 28.5

MS (MALDI, m/z) calcd for $C_{29}H_{33}N_5O_5$ $(M+H)^+$ 532.2, found 532.1

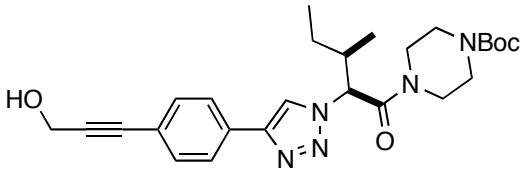


^{1}H NMR of **21a**



^{13}C NMR of **21a**

Preparation of Compound 21b



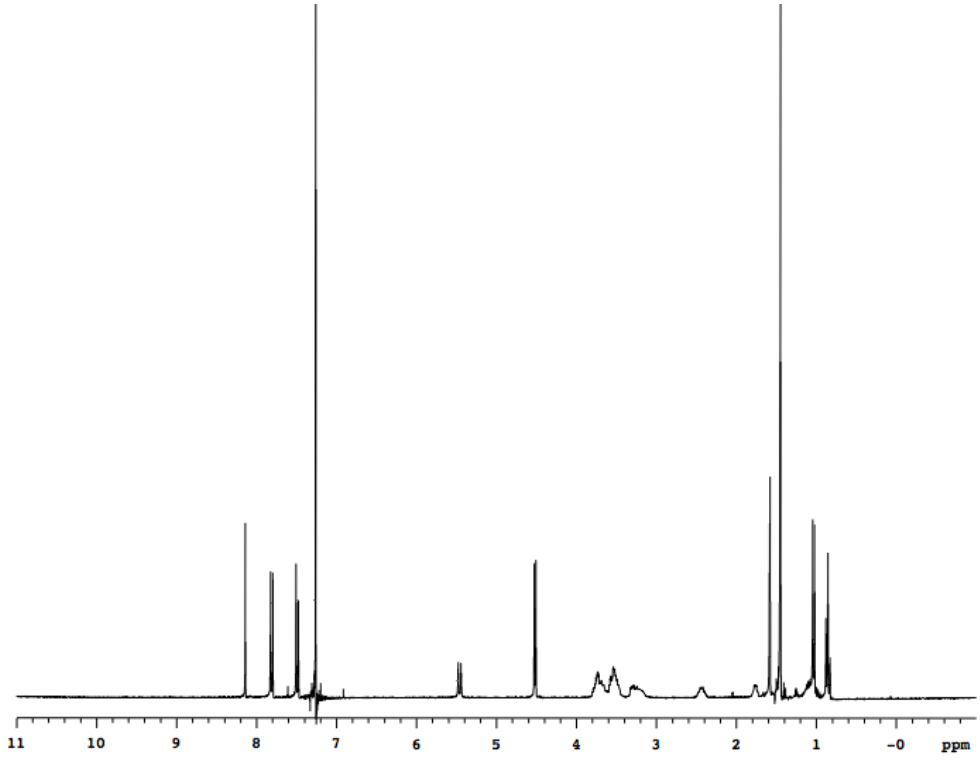
21b

Compound **21b** was prepared from **19** (1.0 g, 6.41 mmol) and **17b** (1.57 g, 6.41 mmol). The crude product was purified on a silica gel column (2:3 EtOAc:Hexanes) to afford 1.92 g (75 %) as a white solid.

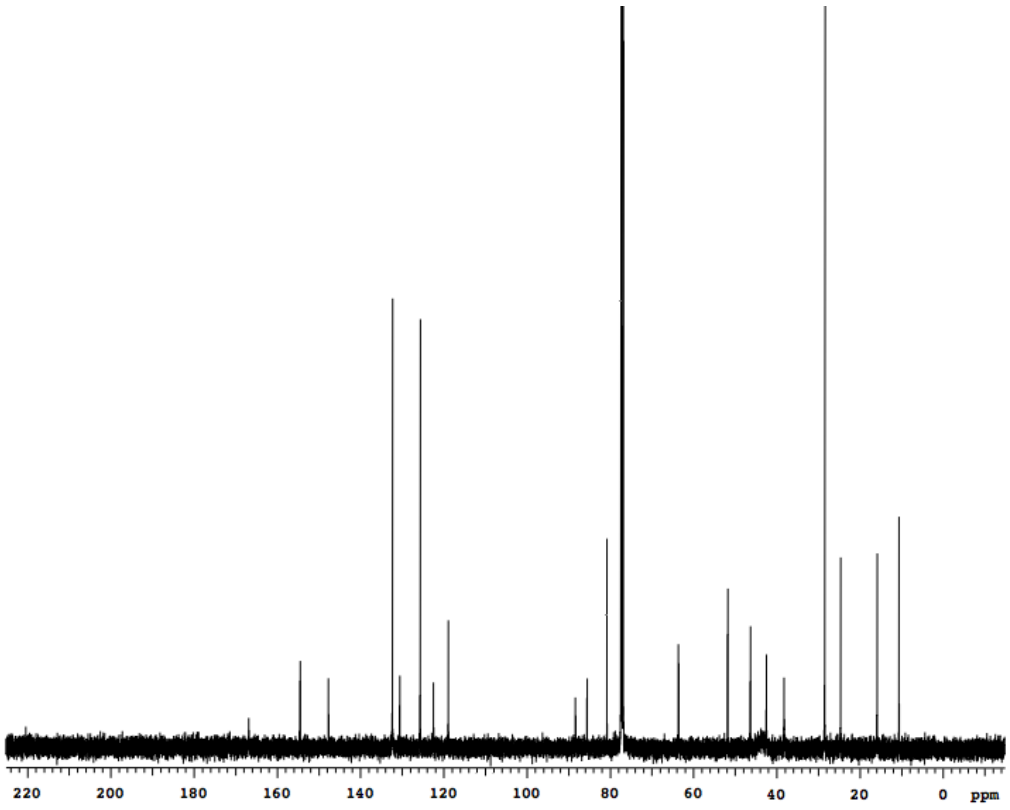
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.81 (d, 2H, J = 13.5 Hz), 7.49 (d, 2H, J = 14.0 Hz), 5.46 (d, 1H, J = 18.0 Hz), 4.51 (d, 2H, J = 10.0 Hz), 3.81-3.45 (m, 6H), 3.34-3.15 (m, 2H), 2.49-2.37 (m, 1H), 1.85-1.72 (m, 1H), 1.45 (s, 9H), 1.15-1.06 (m, 1H), 1.03 (d, 3H, J = 11.0 Hz), 0.85 (t, 3H, J = 12.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 154.5, 147.7, 132.3, 130.6, 125.7, 122.5, 118.9, 88.4, 85.6, 80.8, 63.6, 51.8, 46.3, 42.5, 38.2, 28.5, 24.7, 15.9, 10.6

MS (MALDI, m/z) calcd for $C_{26}H_{35}N_5O_4$ $(M+H)^+$ 482.3, found 482.2.

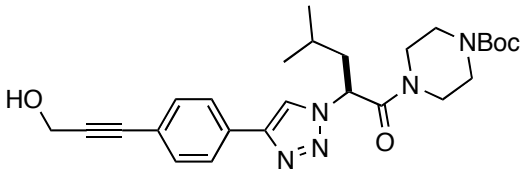


^{1}H NMR of **21b**



^{13}C NMR of **21b**

Preparation of Compound 21c



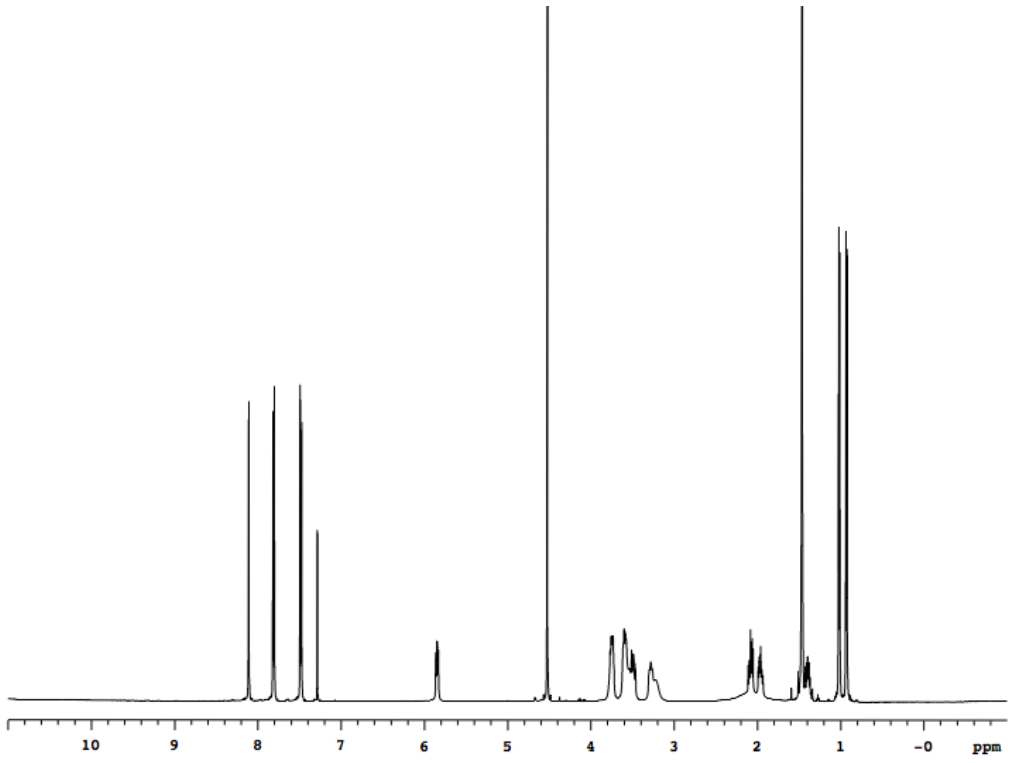
21c

Compound **21c** was prepared from **19** (1.0 g, 6.41 mmol) and **17c** (1.57 g, 6.41 mmol). The crude product was purified by column chromatography on silica gel (2:3 EtOAc: Hexanes) to afford 1.64 g (64 %) as a white solid.

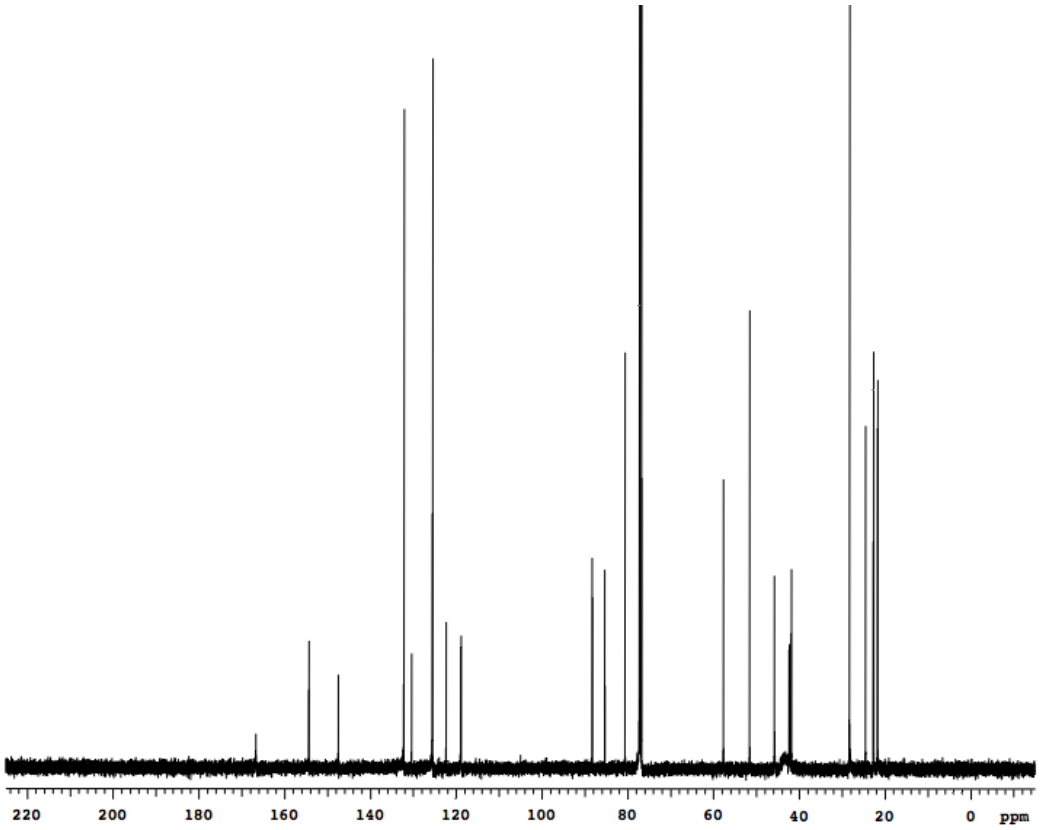
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.81 (d, 2H, J = 8.5 Hz), 7.48 (d, 2H, J = 8.5 Hz), 5.84 (dd, 1H, J = 9.5, 6.0 Hz), 4.53 (s, 2H), 3.80-3.71 (m, 2H), 3.64-3.45 (m, 4H), 3.32-3.14 (m, 2H), 2.12-2.04 (m, 1H), 2.00-1.91 (m, 1H), 1.47 (s, 9H), 1.42-1.36 (m, 1H), 1.02 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 154.5, 147.6, 132.2, 130.5, 125.7, 122.5, 119.0, 88.4, 85.5, 80.8, 57.8, 51.7, 45.9, 42.5, 42.0, 28.5, 24.7, 22.9, 21.9

MS (MALDI, m/z) calcd for $C_{26}H_{35}N_5O_4$ $(M+H)^+$ 482.3, found 482.2



^{1}H NMR of **21c**

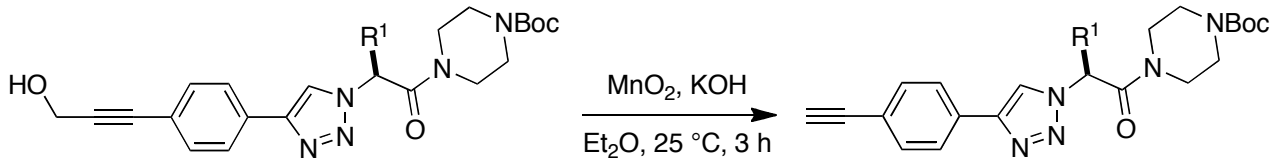


^{13}C NMR of **21c**

General Procedure for Compounds 22a-c

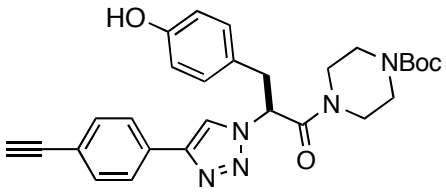
Preparation of terminal alkynes followed the procedures reported by Yang *et. al.* and Godt *et. al.* [18,19] To a solution of **22a-c** (1.0 equiv) in diethyl ether (0.05 M) was added powdered KOH (10.0 equiv), and MnO_2 (20.0 equiv). The reaction mixture was vigorously stirred at 25 °C and monitored by TLC until complete. The reaction mixture was diluted, filtered through Celite, and the Celite was washed with copious amounts of ethyl acetate. The solvents were removed under reduced pressure and the resulting crude product was purified by column chromatography using a mixture of ethyl acetate in hexanes as eluant.

Scheme S22. Synthesis of compound **22a-c.**



21a-c **22a-c**

Preparation of Compound 22a



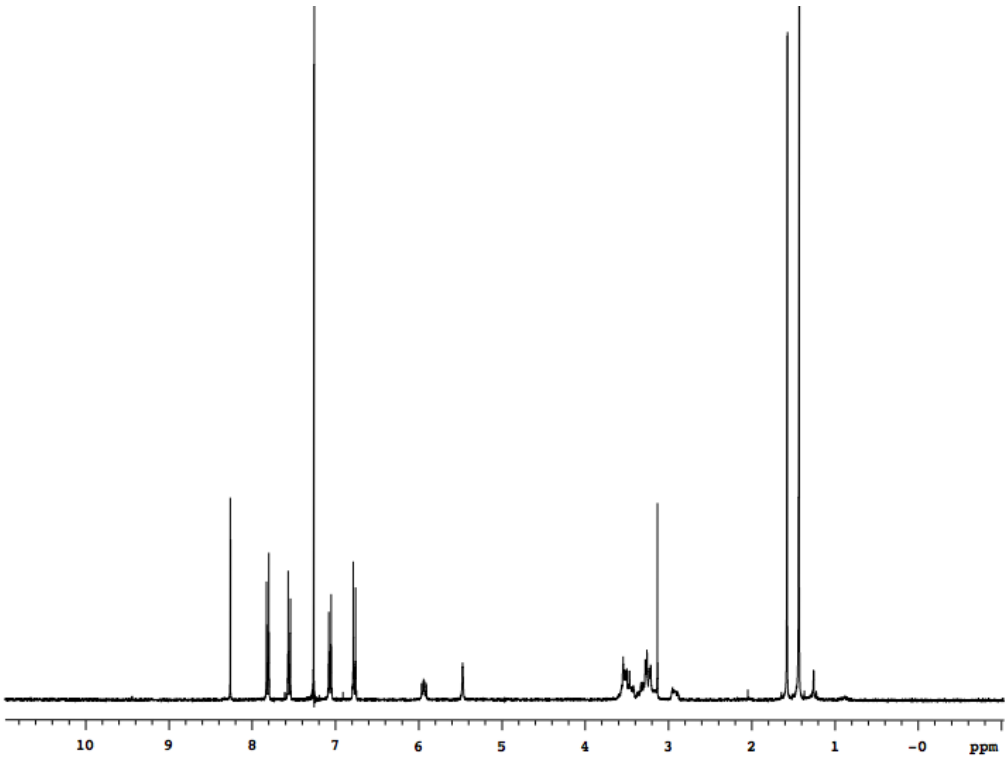
22a

Compound **22a** was prepared from **21a** (1.91 g, 3.17 mmol) as described above, however, due to poor solubility of **21a** in diethyl ether, THF was used as the reaction solvent. The crude product was purified by flash chromatography on silica using (1:1 EtOAc:Hexanes) to afford 0.352 g (19 %) as a white solid.

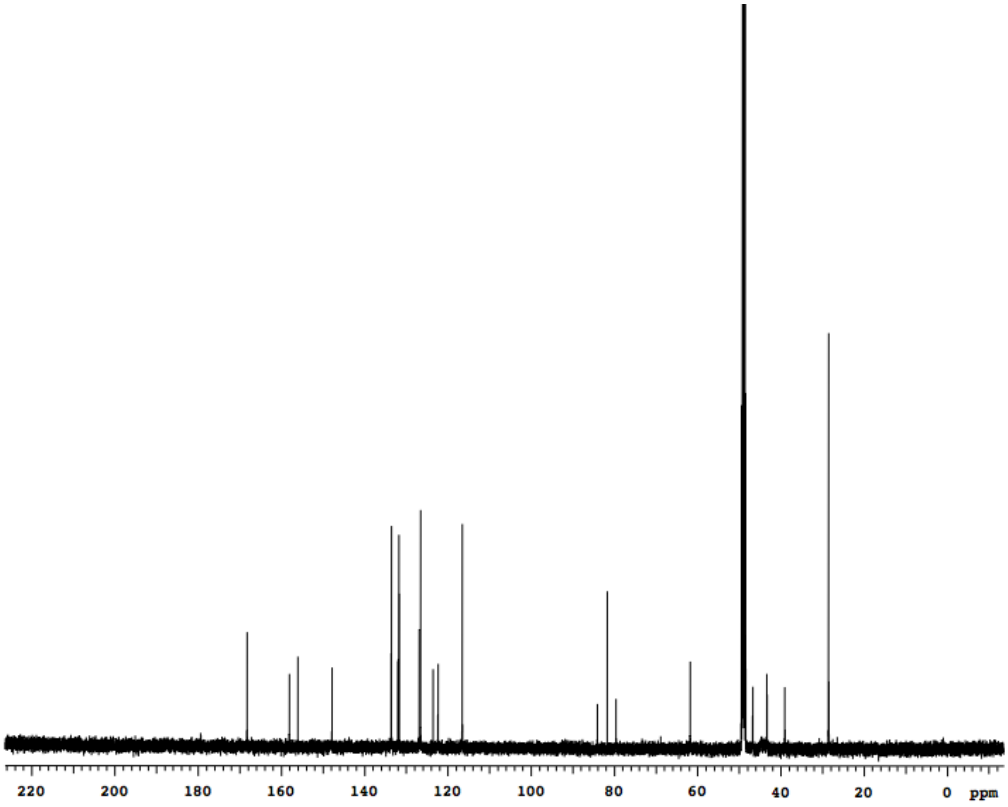
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.81 (d, 2H, J = 14.0 Hz), 7.55 (d, 2H, J = 14.0 Hz), 7.06, (d, 2H, J = 14.0 Hz), 6.77 (d, 2H, J = 14.0 Hz), 5.94 (dd, 1H, J = 16.0, 10.0 Hz), 5.47 (s, 1H), 3.58-3.40 (m, 4H), 3.40-3.20 (m, 5H), 3.13 (s, 1H), 2.98-2.88 (m, 1H), 1.43 (s, 9H)

^{13}C NMR (125 MHz, CD_3OD) δ: 168.3, 158.1, 156.1, 147.8, 133.6, 132.0, 131.8, 126.9, 126.6, 123.6, 122.4, 116.6, 84.1, 81.7, 78.6, 61.8, 46.8, 43.4, 39.1, 28.6

MS (ESI, m/z) calcd for $C_{28}H_{31}N_5O_4$ $(M+H)^+$ 502.2, found 502.2

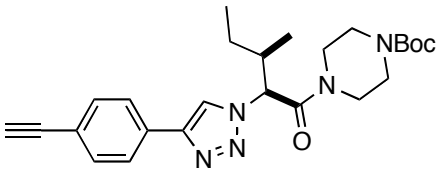


^{1}H NMR of **22a**



^{13}C NMR of **22a**

Preparation of Compound 22b



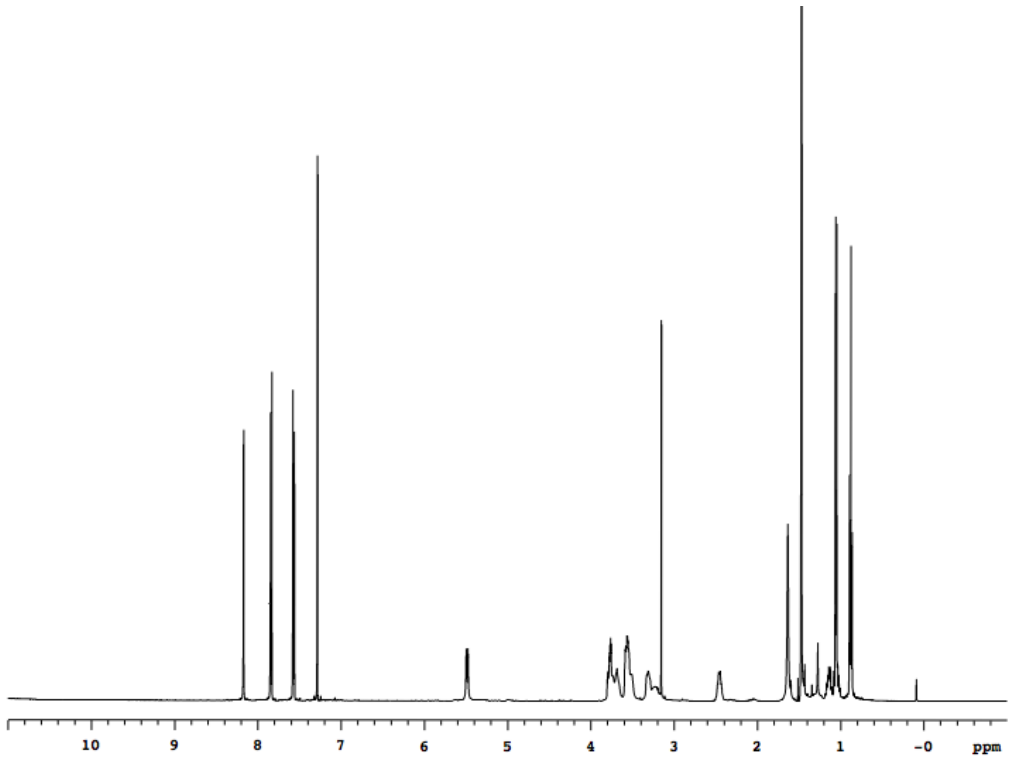
22b

Compound **22b** was prepared from **21b** (1.92 g, 3.98 mmol) and the crude product was purified by flash chromatography on silica gel (2:3 EtOAc/Hexanes) to afford 1.1 g (60 %) as a white solid.

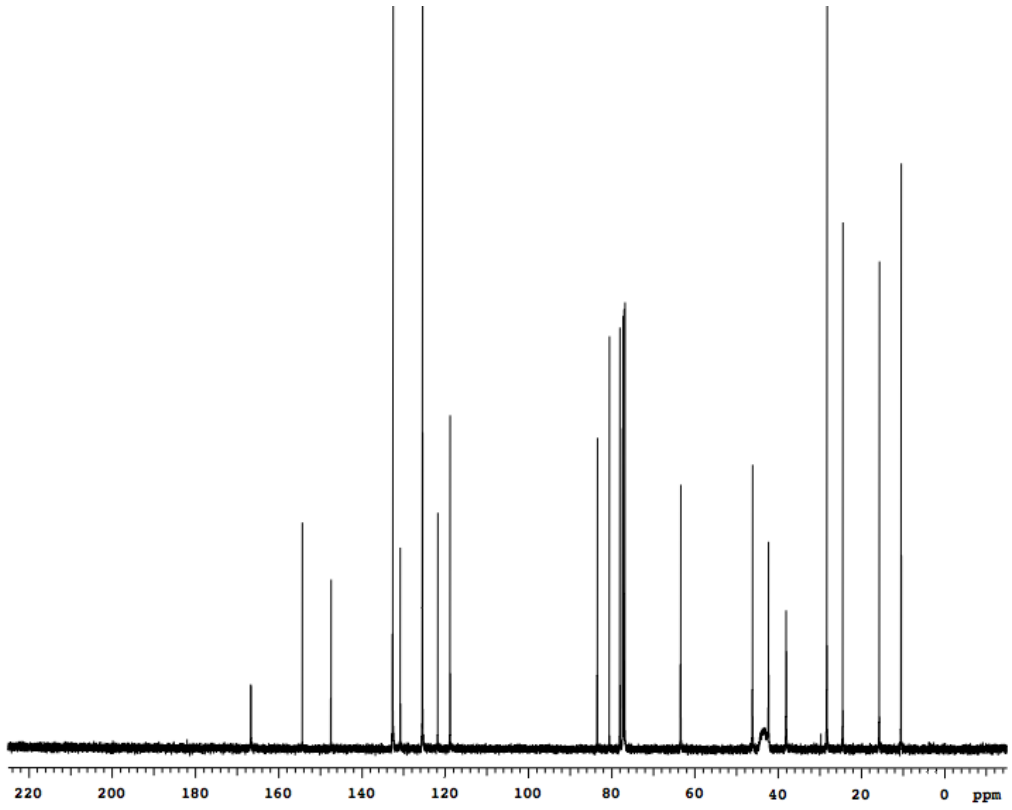
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.81 (d, 2H, J = 14.5 Hz), 7.53 (d, 2H, J = 14.0 Hz), 5.46 (d, 1H, J = 18.0 Hz), 3.80-3.62 (m, 3H), 3.59-3.42 (m, 3H), 3.31-3.14 (m, 2H), 3.12 (s, 1H), 2.49-2.35 (m, 1H), 1.44 (s, 9H), 1.18-1.05 (m, 1H), 1.02 (d, 3H, J = 11.0 Hz), 0.84 (t, 3H, J = 12.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 154.4, 147.5, 132.7, 130.9, 125.6, 121.9, 118.9, 83.6, 80.7, 78.1, 77.4, 63.5, 46.2, 42.4, 38.2, 28.4, 24.6, 15.8, 10.6

MS (MALDI, m/z) calcd for $C_{25}H_{33}N_5O_3$ Formula $(M+H)^+$ 452.3, found 452.2

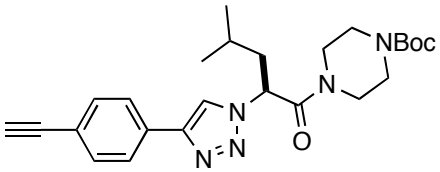


^{1}H NMR of **22b**



^{13}C NMR of **22b**

Preparation of Compound 22c



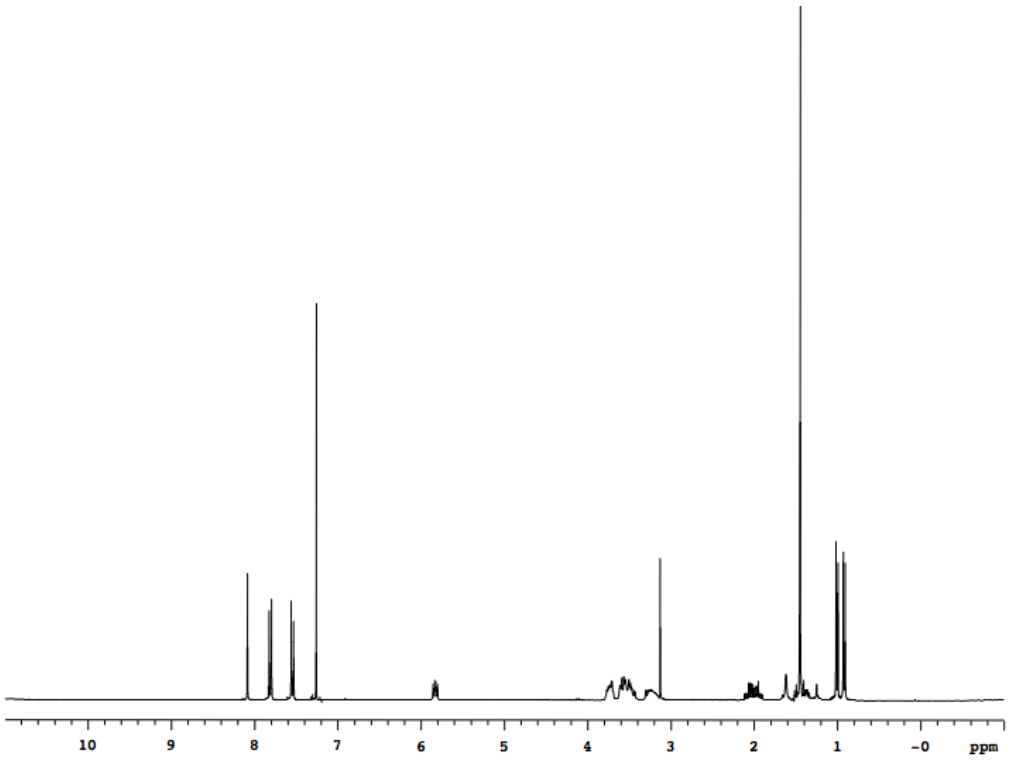
22c

Compound **22c** was prepared from **21c** (1.64 g, 3.17 mmol) and purified by column chromatography (2:3 EtOAc/Hexanes) to afford 1.13 g (73 %) as a white solid.

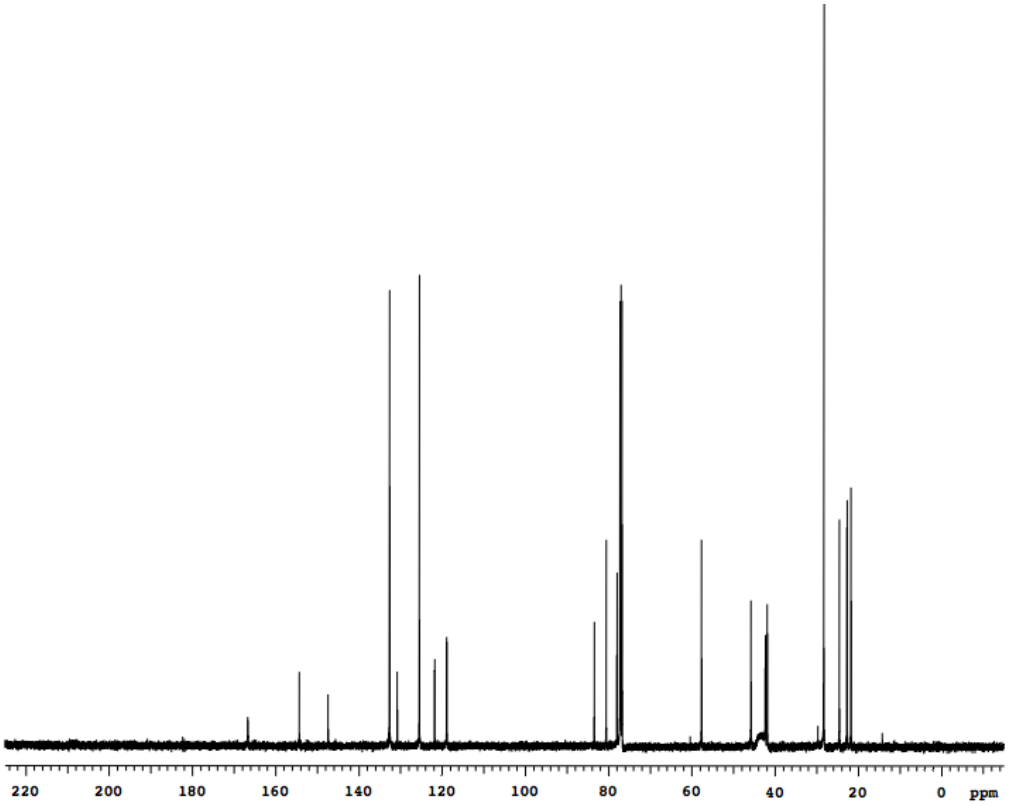
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.85 (d, 2H, J = 8.6 Hz), 7.58 (d, 2H, J = 8.5 Hz), 7.26 (m, 6H), 5.87 (m, 1H), 3.60 (m, 8H), 2.39 (s, 4H), 2.04 (m, 2H), 1.49 (s, 9H), 1.00 (m, 6H)

^{13}C NMR (300 MHz, $CDCl_3$) δ 154.37, 147.43, 137.90, 132.67, 130.80, 129.09, 129.08, 128.26, 125.52, 125.33, 121.82, 118.91, 83.48, 80.62, 78.05, 57.70, 45.83, 42.37, 41.90, 28.36, 24.60, 22.79, 21.80, 21.52

MS (MALDI, m/z) calcd for $C_{25}H_{33}N_5O_3$ $(M+H)^+$ 452.3, found 452.2



^{1}H NMR of **22c**

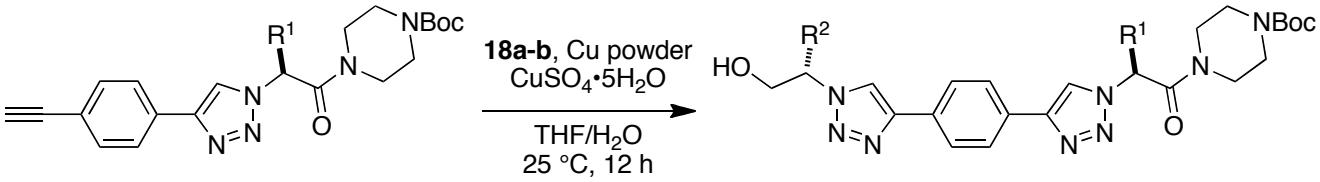


^{13}C NMR of **22c**

General Procedure for Compounds 23a-e

To a solution of **22a-c** (1.0 equiv) and **18a-b** (1.0 equiv) in 90 % THF/H_2O (0.30 M) was added powdered copper (1.0 equiv), and $CuSO_4$•$5H_2O$ (0.10 equiv in 1 N solution) in one portion. The reaction mixture was vigorously stirred at 25 °C for 12 h. The reaction mixture was then diluted with ethyl acetate, and filtered through Celite to remove the copper. The Celite was washed with copious amounts of ethyl acetate. The product was extracted with 25 % NH_4OH, 2 % EDTA solution and then brine. The organic phase was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude click product was then purified by column chromatography on silica using a mixture of ethyl acetate and hexanes as eluant.

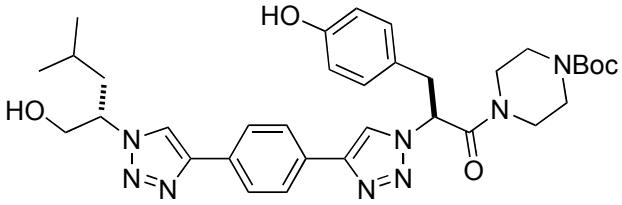
Scheme S23. Synthesis of compound **23a-e.**



22a-c
19 - 73%

23a-e
26 - 60%

Preparation of Compound 23a



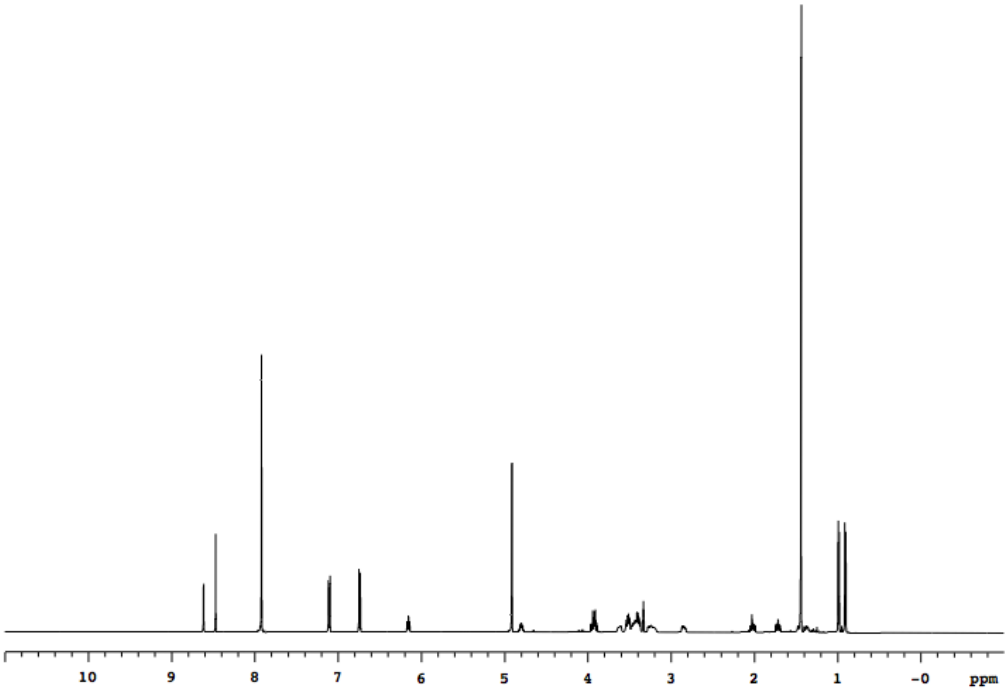
23a

Compound **23a** was prepared from **22a** (62.0 mg, 0.12 mmol) and **18b** (36 mg, 0.25 mmol). The crude product was purified on silica gel (1:1 to 4:1 EtOAc/Hexanes) to afford 50.5 mg (63 %) of the desired product as a white solid.

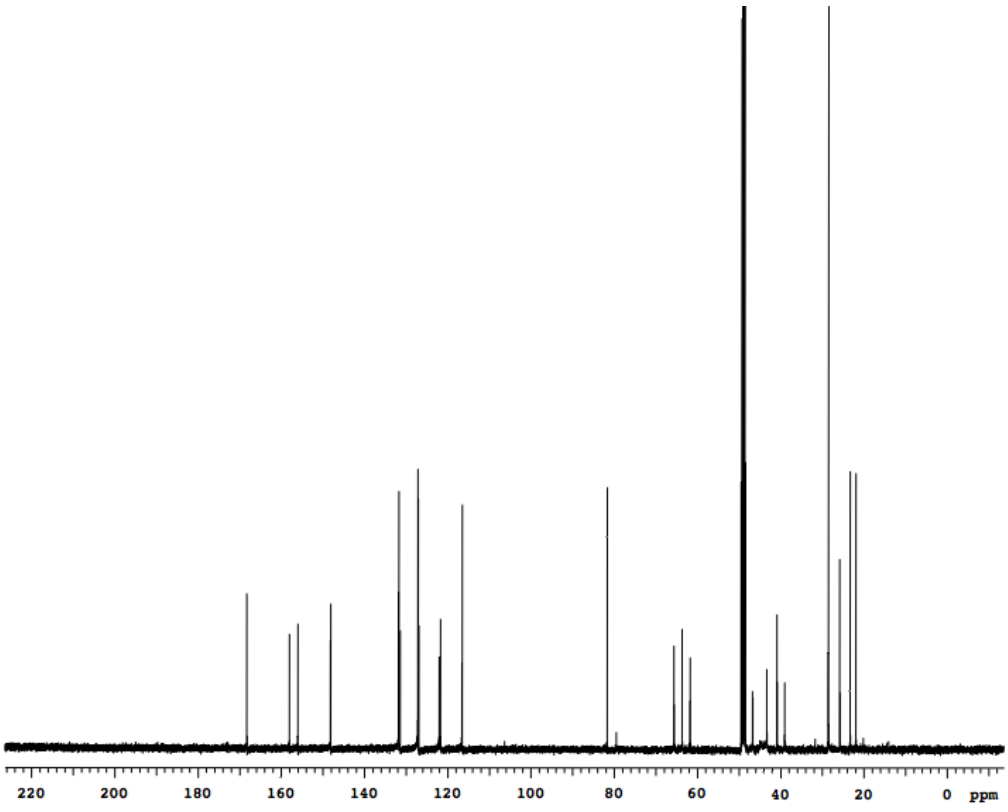
^{1}H NMR (500 MHz, CD_3OD) δ: 8.62 (s, 1H), 8.47 (s, 1H), 7.92 (s, 4H), 7.10 (d, 2H, J = 8.5 Hz), 6.74 (d, 2H, J = 8.5 Hz), 6.14 (t, 1H, J = 8.0 Hz), 4.82-4.75 (m, 1H), 3.95-3.86 (m, 2H), 3.64-3.55 (m, 1H), 3.53-3.47 (m, 2H), 3.46-3.34 (m, 4H), 3.27-3.14 (m, 2H), 2.86-2.77 (m, 1H), 1.74-1.66 (m, 1H), 1.42 (s, 9H), 1.39-1.31 (m, 1H), 0.97 (d, 3H, J = 6.5 Hz), 0.89 (d, 3H, J = 6.5 Hz)

^{13}C NMR (125 MHz, CD_3OD) δ: 168.2, 158.0, 156.0, 148.2, 148.0, 131.8, 131.7, 131.4, 127.2, 127.1, 126.9, 122.0, 121.7, 116.5, 81.7, 65.6, 63.7, 61.8, 43.3, 40.9, 28.5, 25.8, 23.3, 21.9

MS (ESI, m/z) calcd for $C_{34}H_{44}N_8O_5$ $(M+H)^+$ 645.3, found 645.3

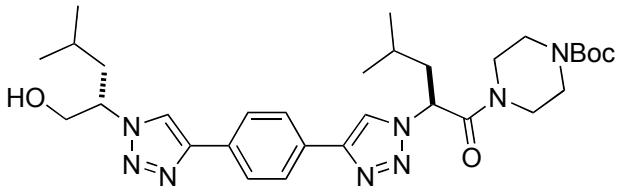


^{1}H NMR of **23a**



^{13}C NMR of **23a**

Preparation of Compound 23b



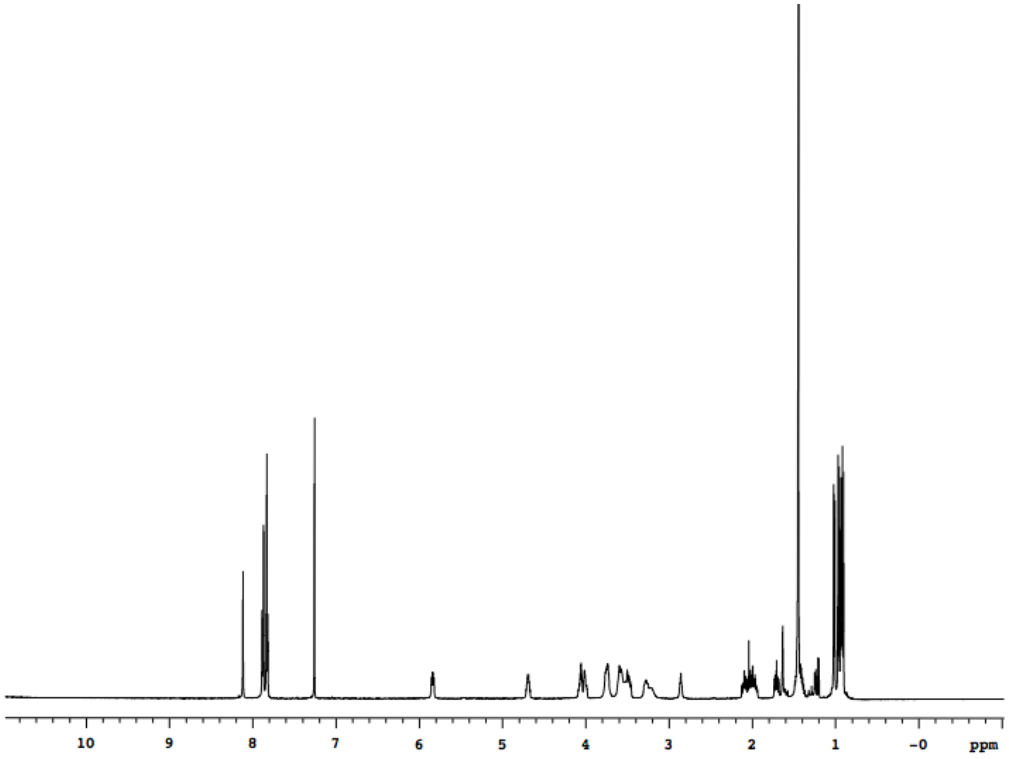
23b

Compound **23b** was prepared from **22c** (90.0 mg, 0.20 mmol) and **18b** (29.0 mg, 0.20 mmol). The crude click product was purified by flash chromatography on silica gel using a gradient from 1:3 to 2:1 ethyl acetate in hexanes to afford 60.5 mg (65 %) as a white solid.

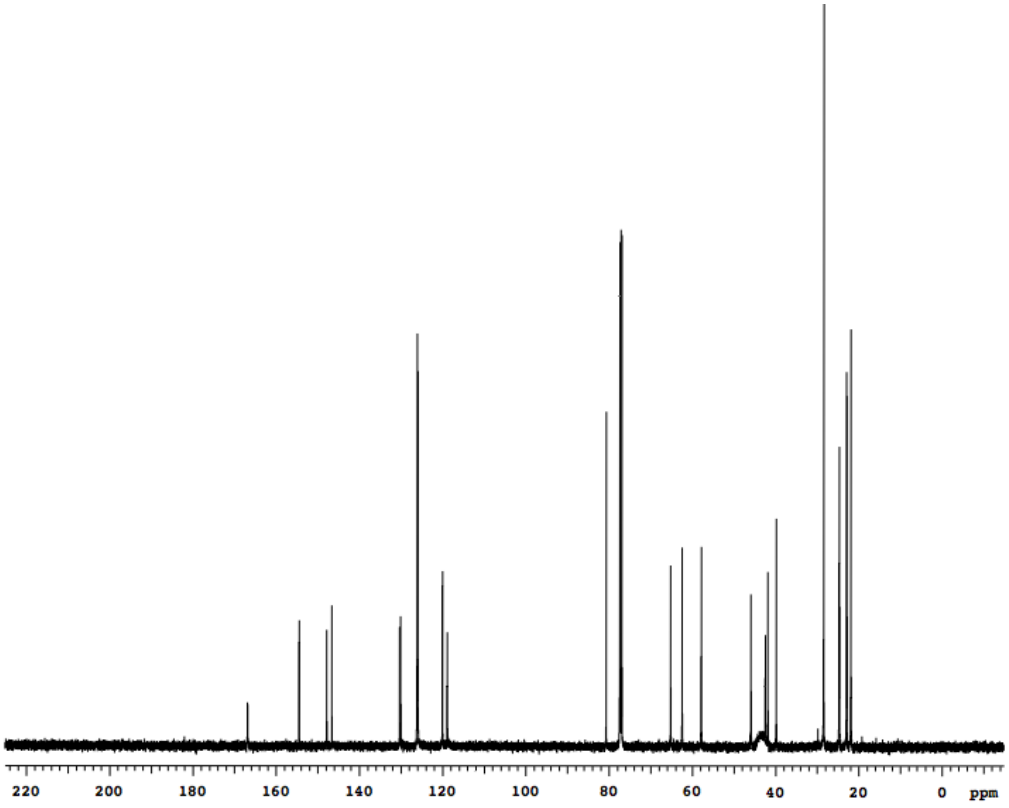
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.88 (d, 2H, J = 8.5 Hz), 7.83 (app d, 3H, J = 8.0 Hz), 5.84 (dd, 1H, J = 10.5, 8.0 Hz), 4.71-4.67 (m, 1H), 4.09-3.98 (m, 2H), 3.78-3.70 (m, 2H), 3.62-3.43 (m, 4H), 3.32-3.13 (m, 2H), 2.86 (s, br, 1H), 2.12-1.94 (m, 3H), 1.74-1.68 (m, 1H), 1.49-1.38 (m, 1H), 1.45 (s, 9H), 1.01 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.5 Hz), 0.92 (app dd, 6H, J = 10.5, 7.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.9, 154.5, 147.8, 146.6, 130.3, 130.1, 126.1, 126.0, 120.0, 118.9, 80.7, 65.2, 62.5, 57.9, 45.9, 42.5, 41.9, 39.8, 28.4, 24.7, 24.6, 23.0, 22.9, 21.9, 21.9

MS (ESI, m/z) calcd for $C_{31}H_{46}N_8O_4$ $(M+H)^+$ 595.4, found 595.4

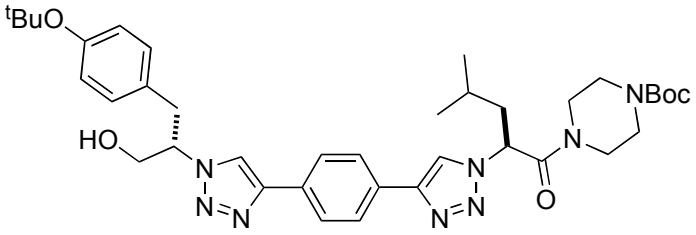


^{1}H NMR of **23b**



^{13}C NMR of **23b**

Preparation of Compound 23c



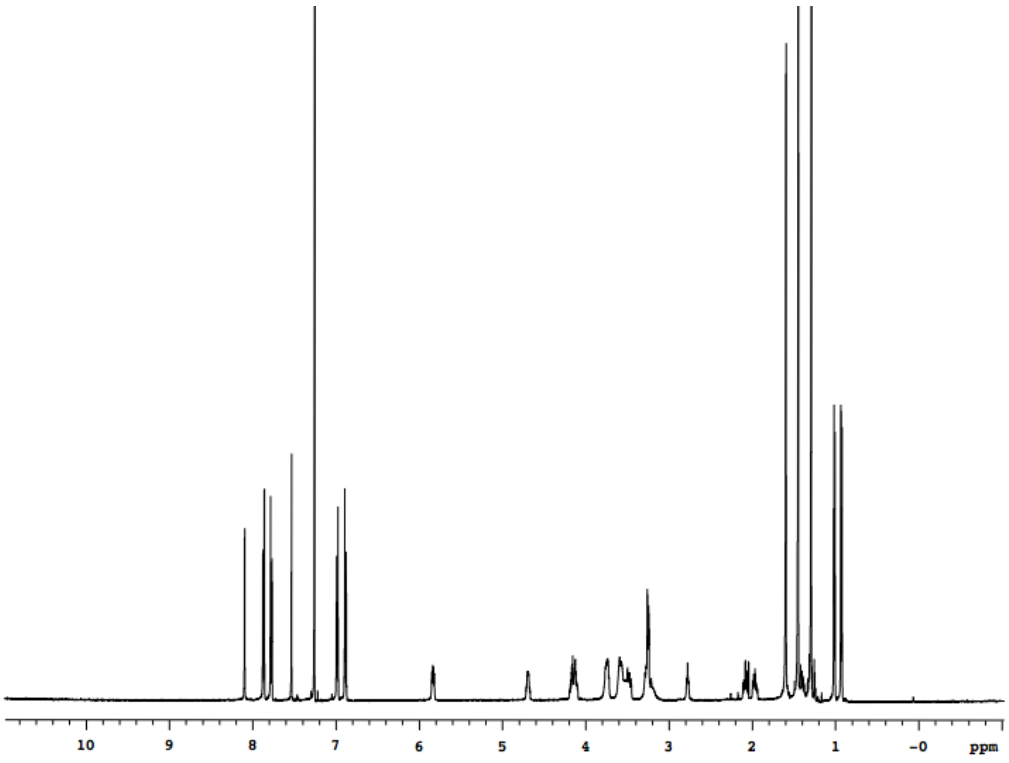
23c

Compound **23c** was prepared from **22c** (565.0 mg, 1.4 mmol) and **18a** (354.0 mg, 1.4 mmol). Purification by silica gel chromatography (4:1 EtOAc/Hexanes) afforded **23c** (247 mg, 27 %) as a white solid.

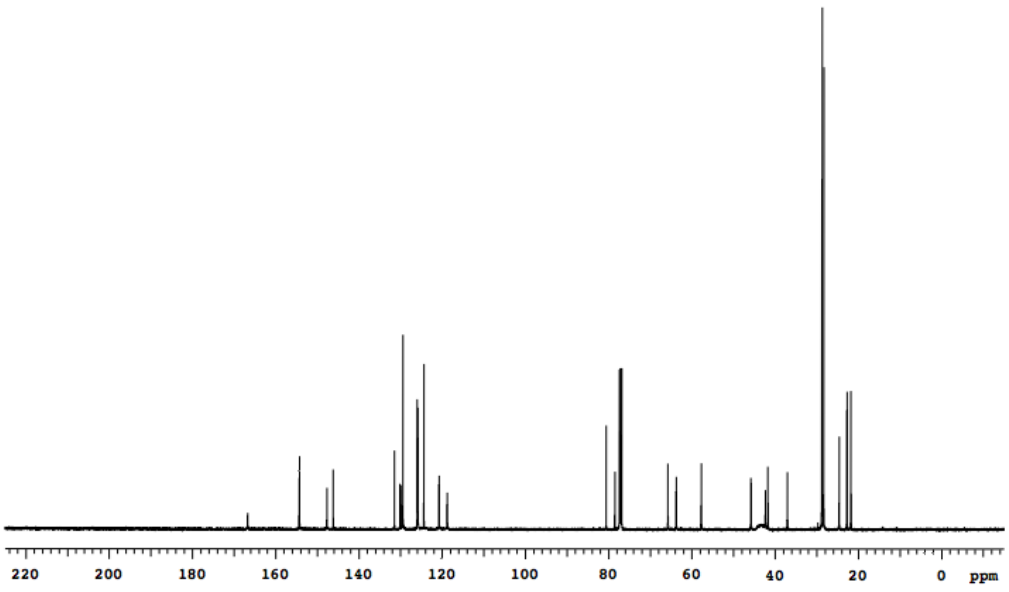
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.87 (d, 2H, J = 8.0 Hz), 7.78 (d, 2H, J = 8.5 Hz), 7.54 (s, 1H), 6.99 (d, 2H, J = 8.5 Hz), 6.89 (d, 2H, J = 8.5 Hz), 5.83 (dd, 1H, J = 9.5, 6.0 Hz), 4.72-4.66 (m, 1H), 4.20-4.08 (m, 2H), 3.80-3.71 (m, 2H), 3.62-3.44 (m, 4H), 3.30-3.16 (m, 4H), 2.78 (app t, 1H, J = 6 Hz), 2.12-2.04 (m, 1H), 2.02-1.94 (m, 1H), 1.45 (s, 9H), 1.29 (s, 9H), 1.01 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 154.4, 154.3, 147.7, 146.2, 131.5, 130.2, 130.0, 129.5, 126.0, 125.9, 124.5, 120.8, 118.8, 80.6, 78.6, 65.8, 63.8, 57.8, 45.9, 42.4, 41.8, 37.1, 28.8, 28.4, 24.7, 22.8, 21.8

MS (MALDI, m/z) calcd for $C_{38}H_{52}N_8O_5$ $(M+H)^+$ 701.4, found 701.3

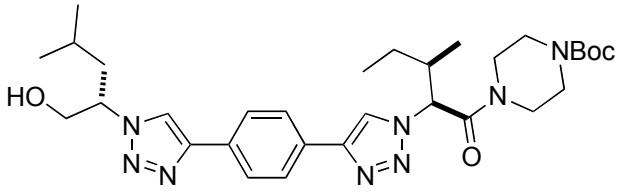


^{1}H NMR of **23c**



^{13}C NMR of **23c**

Preparation of Compound 23d



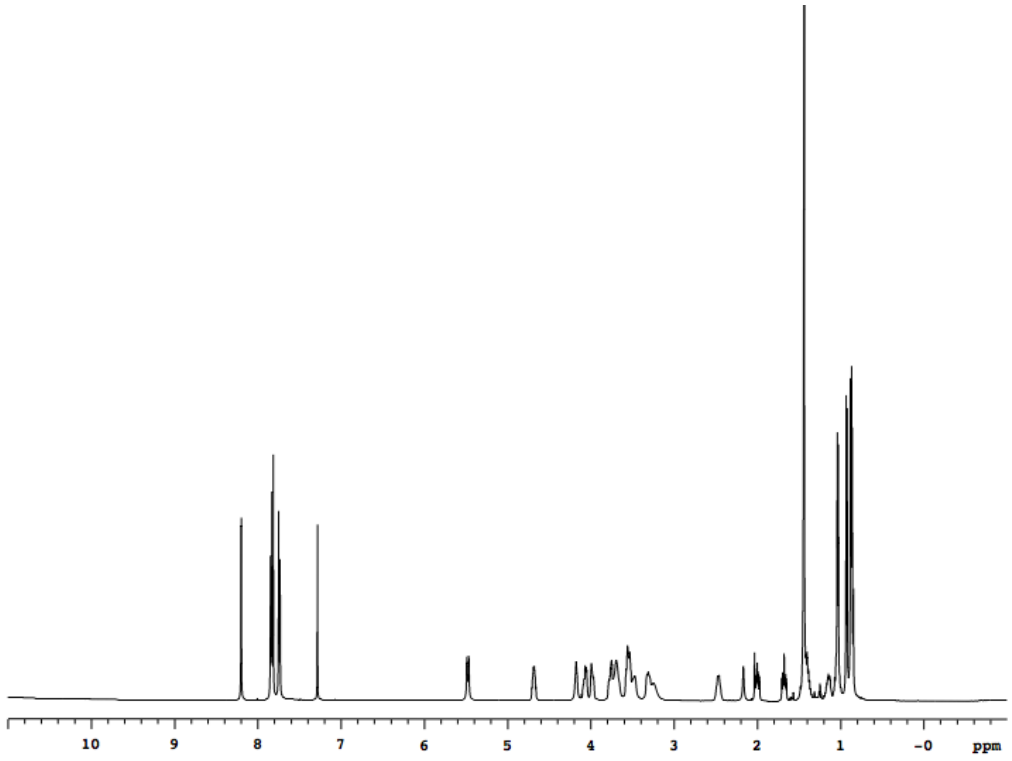
23d

Compound **23d** was prepared from **22b** (152.0 mg, 0.34 mmol) and **18b** (48.0 mg, 0.34 mmol). Purification of the crude product by column chromatography on silica using a gradient from 1:3 to 2:1 ethyl acetate in hexanes afforded **23d** (159.0 mg, 79 %) as a white solid.

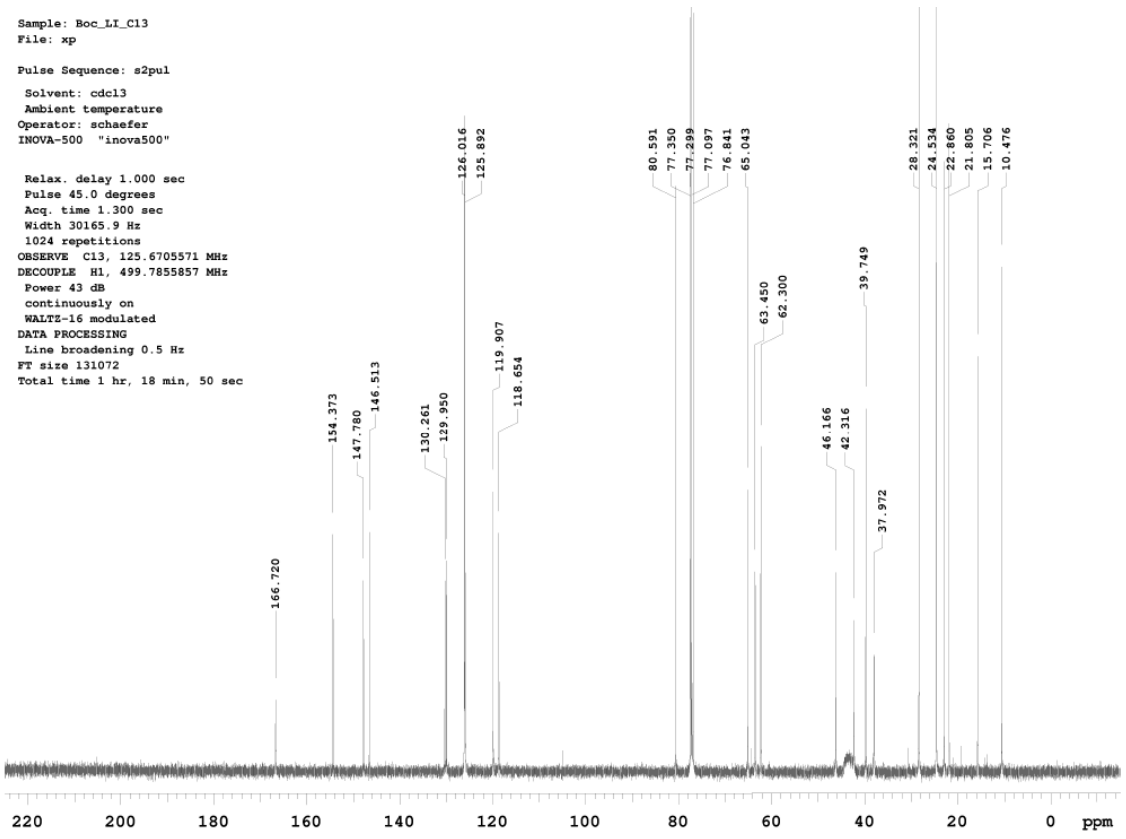
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 7.88 (d, 2H, J = 7.0 Hz), 7.83 (app d, 3H, J = 6.0 Hz), 5.74 (d, 1H, J = 11.0 Hz), 4.72-4.67 (m, 1H), 4.10-4.04 (m, 1H), 4.02-3.98 (m, 1H), 3.80-3.62 (m, 3H), 3.58-3.45 (m, 3H), 3.35-3.15 (m, 2H), 2.93-2.82 (m, br, 1H), 2.52-2.42 (m, br, 1H), 2.06-1.98 (m, 1H), 1.74-1.67 (m, 1H), 1.67-1.64 (m, 2H), 1.45 (s, 9H), 1.19-1.10 (m, 1H), 1.04 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.5 Hz), 0.91 (d, 3H, J = 6.5 Hz), 0.86 (t, 3H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 154.5, 147.9, 146.6, 130.4, 130.1, 126.1, 126.0, 120.0, 118.8, 80.7, 65.1, 63.6, 62.4, 46.3, 42.4, 39.9, 38.1, 28.4, 24.6, 23.0, 21.9, 15.8, 10.6

MS (ESI, m/z) calcd for $C_{31}H_{46}N_8O_4$ $(M+H)^+$ 595.4, found 595.3

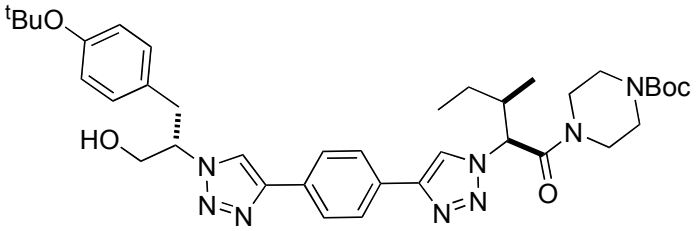


^{1}H NMR of **23d**



^{13}C NMR of **23d**

Preparation of Compound 23e



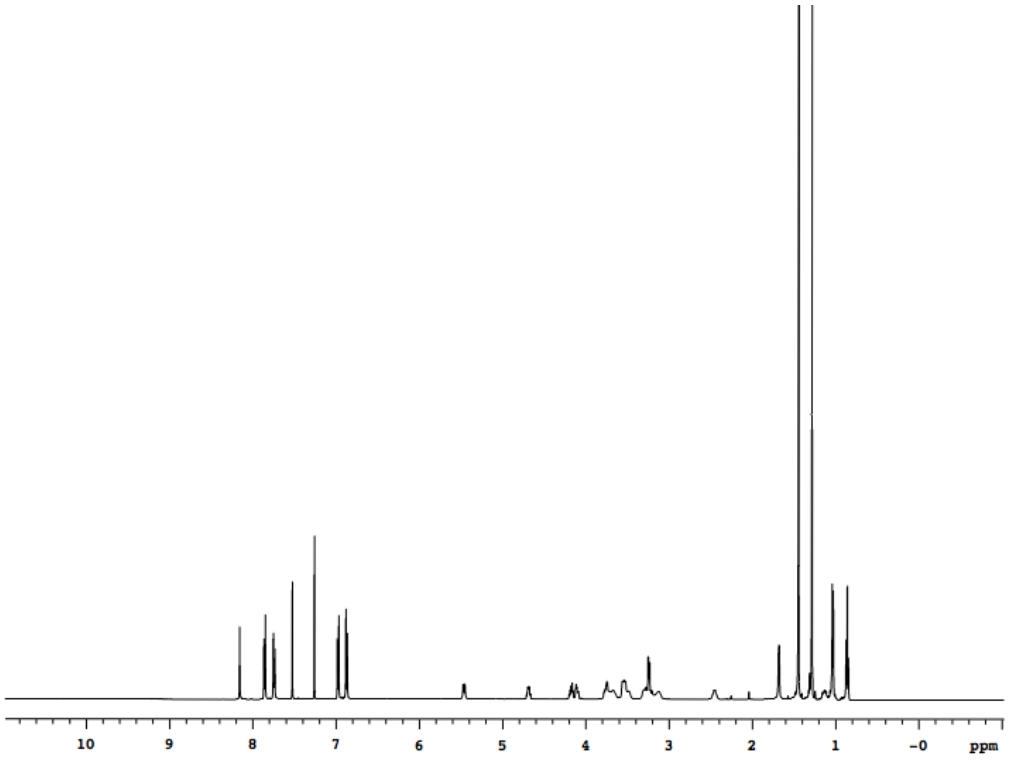
23e

Compound **23e** was prepared from **22b** (540.0 mg, 0.78 mmol) and **18a** (336.0 mg, 0.78 mmol). Purification of the crude product on silica (4:1 EtOAc/Hexanes) afforded **23e** (529 mg, 60 %) as a white solid.

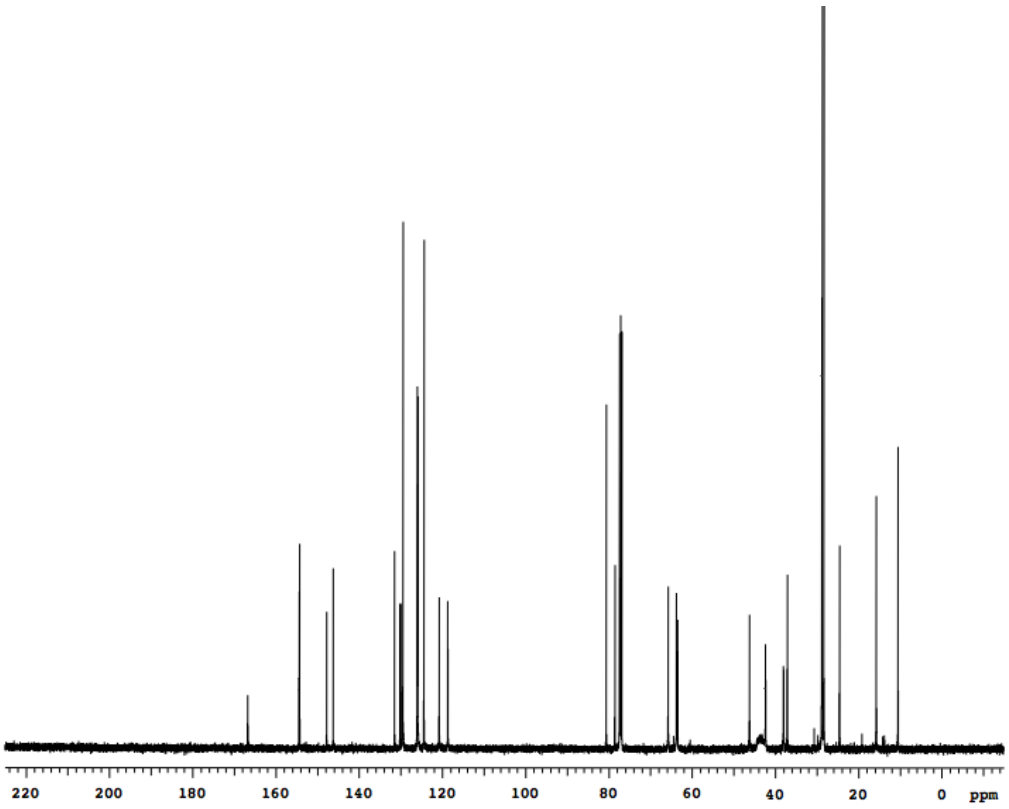
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 7.86 (d, 2H, J = 8.5 Hz), 7.74 (d, 2H, J = 8.0 Hz), 7.52 (s, 1H), 6.98 (d, 2H, J = 8.5 Hz), 5.46 (d, 1H, J = 10.5 Hz), 4.71-4.66 (m, 1H), 3.80-3.60 (m, 3H), 3.58-3.40 (m, 3H), 3.32-3.07 (m, 5H), 2.50-2.40 (m, 1H), 1.44 (s, 9H), 1.28 (s, 9H), 1.16-1.10 (m, 1H), 1.08-1.02 (m, 1H), 1.03 (d, 3H, J = 7.0 Hz), 0.86 (t, 3H, J = 7.5 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 154.4, 154.3, 147.8, 146.3, 131.5, 130.2, 130.0, 129.5, 126.0, 125.9, 124.4, 120.8, 118.7, 80.6, 78.6, 77.4, 65.8, 63.8, 63.5, 46.2, 42.4, 38.0, 37.1, 28.8, 28.4, 24.6, 15.8, 10.5

MS (MALDI, m/z) calcd for $C_{38}H_{52}N_8O_5$ $(M+H)^+$ 701.4, found 701.3



^{1}H NMR of **23e**

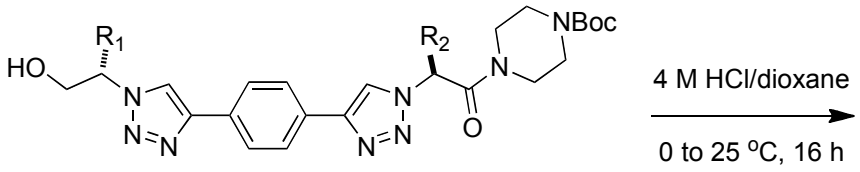


^{13}C NMR of **23e**

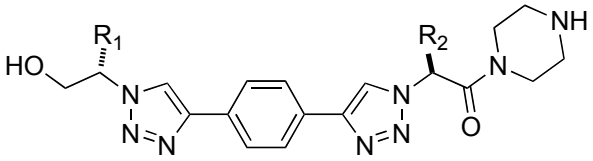
General Procedure for Compounds 4a-e

To the compounds **23a-e** was added 4 M HCl/dioxane (40.0 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and vigorously stirred at 25 °C for 16 h. The solvents were removed under reduced pressure. The residue was dissolved in a minimum amount of MeOH, and then precipitated with ether. Removing solvent under reduced pressure afforded the desired product **4a-e**.

Scheme S24. Synthesis of compound **4a-e.**

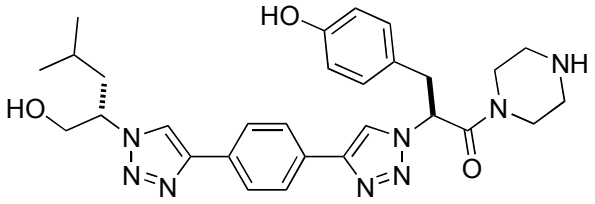


23a-e



4a-e

Preparation of Compound 4a



4a

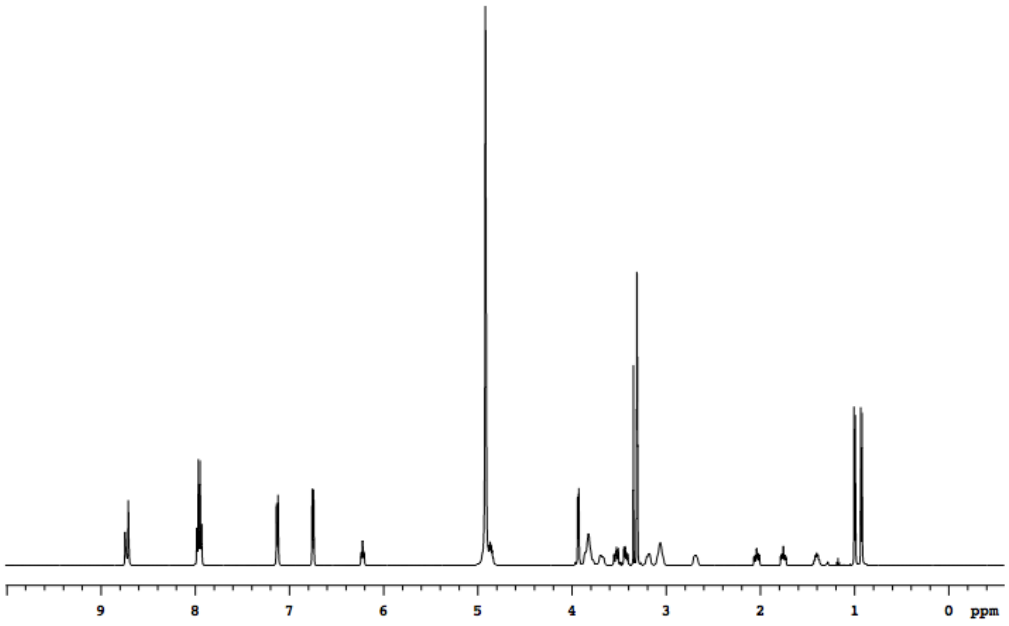
Compound **4a** was prepared from **23a** (30.0 mg, 0.047 mmol). **4a** was obtained as a white amorphous solid (quant., HCl salt).

^{1}H NMR (500 MHz, CD_3OD) δ: 8.74 (s, 1H), 8.71 (s, 1H), 7.97 (d, 2H, J = 8.0 Hz), 7.96 (d, 2H, J = 8.5 Hz), 7.13 (d, 1H, J = 8.0 Hz), 6.75 (d, 1H, J= 8.5 Hz), 6.22 (dd, 1H, J = 7.5 Hz), 4.88-4.84 (m, 1H), 3.93 (d, 2H, J = 6.0 Hz), 3.83 (br, 3H), 3.67 (br, 1H), 3.53 (dd, 1H, J = 7.5, 12.5 Hz), 3.43 (dd, 1H, J = 7.0, 12.5 Hz), 3.18 (br, 1H), 3.06 (br, 2H), 2.69 (br, 1H), 2.04 (ddd, 1H, J = 5.0, 10.5, 15.0 Hz), 1.76 (ddd, 1H, J = 4.5, 8.5, 14.0 Hz), 1.44-1.36 (m, 1H), 1.00 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.5 Hz)

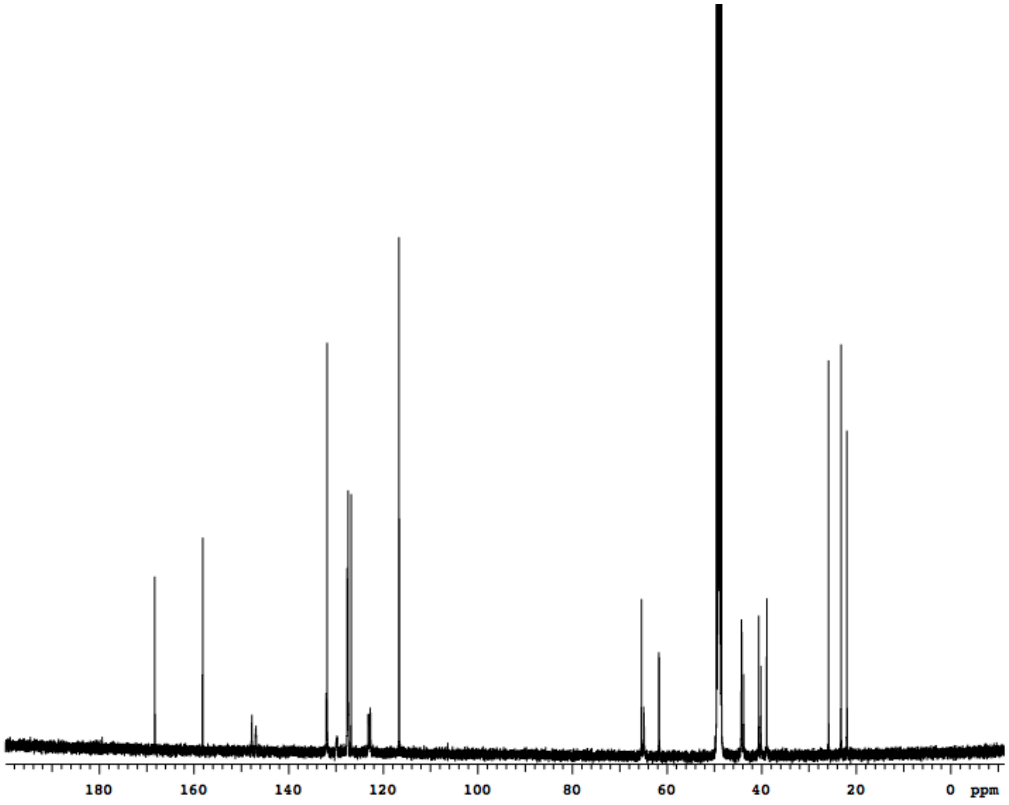
^{13}C NMR (125 MHz, CD_3OD) δ: 168.3, 158.1, 147.7, 146.8, 132.0, 131.8, 129.8, 217.6, 127.4, 126.8, 123.1, 122.7, 116.6, 65.4, 64.9, 61.7, 44.3, 43.8, 40.6, 40.2, 38.9, 38.9, 25.8, 23.2, 22.0

MS (MALDI, m/z) calcd for $C_{29}H_{37}N_8O_3$ $(M+H)^+$ 545.30, found 545.42

optical rotation $[\alpha]_D^{19.5}$ = -5.1 (*c* = 2.55 in MeOH)

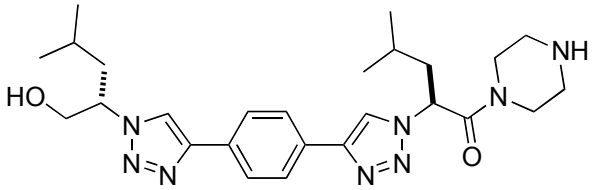


^{1}H NMR of **4a**



^{13}C NMR of **4a**

Preparation of Compound 4b



4b

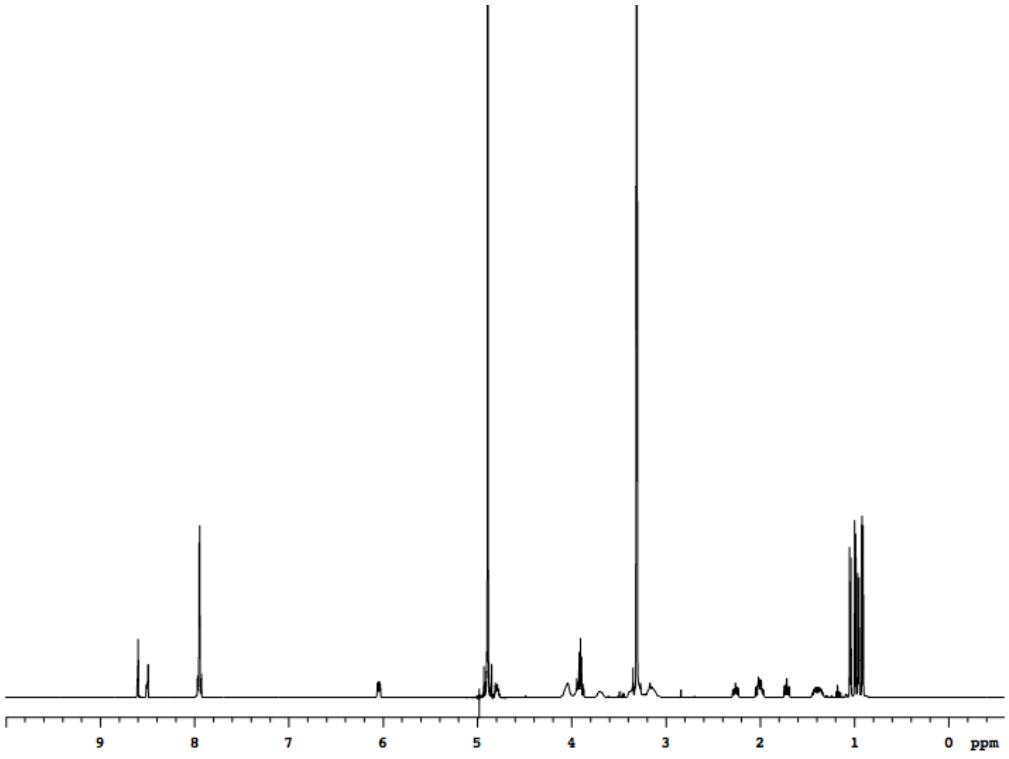
Compound **4b** was prepared from **23b** (12.0 mg, 0.020 mmol). **4b** was obtained as a white amorphous solid (58 %, HCl salt).

^{1}H NMR (500 MHz, CD_3OD) δ: 8.60 (s, 1H), 8.49 (s, 1H), 7.95 (d, 4H, J = 3.0 Hz), 6.04 (dd, 1H, J = 5.0, 10.0 Hz), 4.81-4.77 (m, 1H), 4.04 (br, 2H), 3.94-3.87 (m, 4H), 3.50 (br, 2H), 3.36 (br, 1H), 3.17 (br, 3H), 2,26 (ddd, 1H, J = 5.5, 10.5, 14.5 Hz), 2.05-1.97 (m, 2H), 1.72 (ddd, 1H, 4.5, 9.0, 14.0 Hz), 1.45-1.34 (m, 2H), 1.04 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.5 Hz), 0.91 (d, 3H, J = 6.5 Hz)

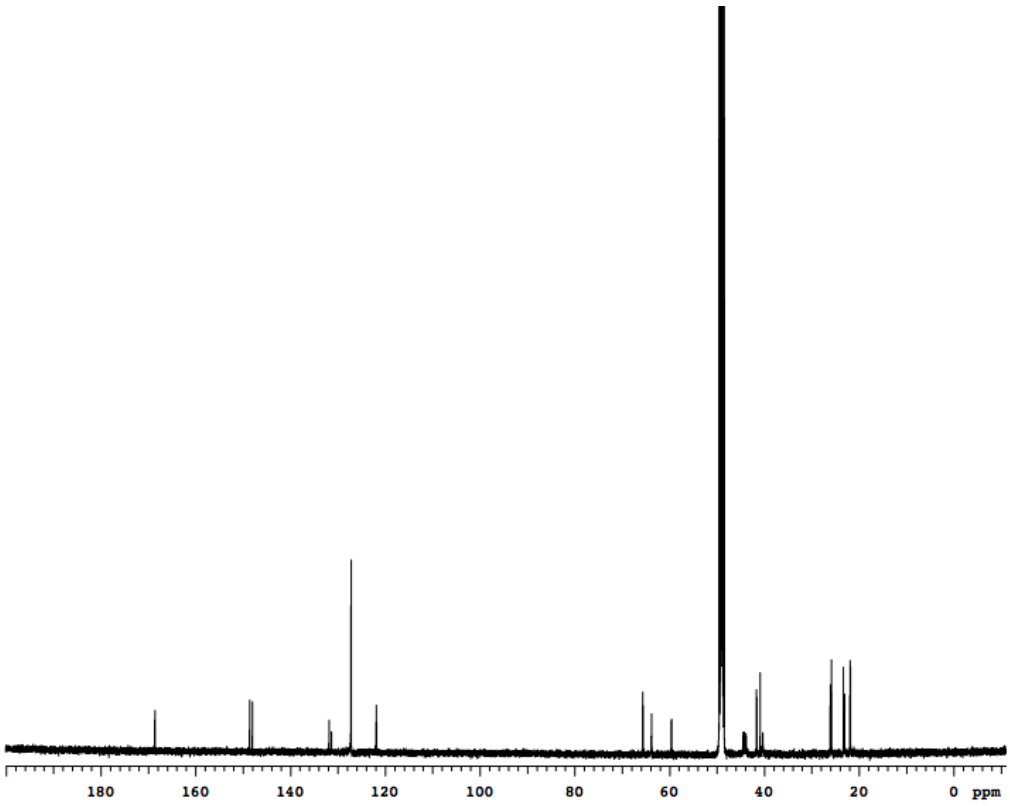
^{13}C NMR (125 MHz, CD_3OD) δ: 168.6, 148.6, 148.0, 131.8, 131.4, 127.2, 127.2, 121.9, 121.9, 65.6, 63.8, 59.6, 44.5, 44.3, 43.9, 41.6, 40.9, 40.3, 26.1, 25.9, 23.3, 23.1, 21.9, 21.8

MS (MALDI, m/z) calcd for $C_{26}H_{39}N_8O_2$ $(M+H)^+$ 495.32, found 495.31

optical rotation $[\alpha]_D^{19.8}$ = +47.3 (*c* = 0.62 in MeOH)

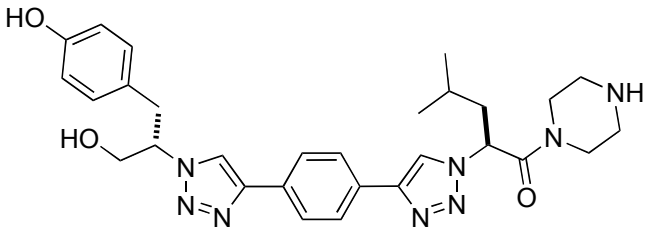


^{1}H NMR of **4b**



^{13}C NMR of **4b**

Preparation of Compound 4c



4c

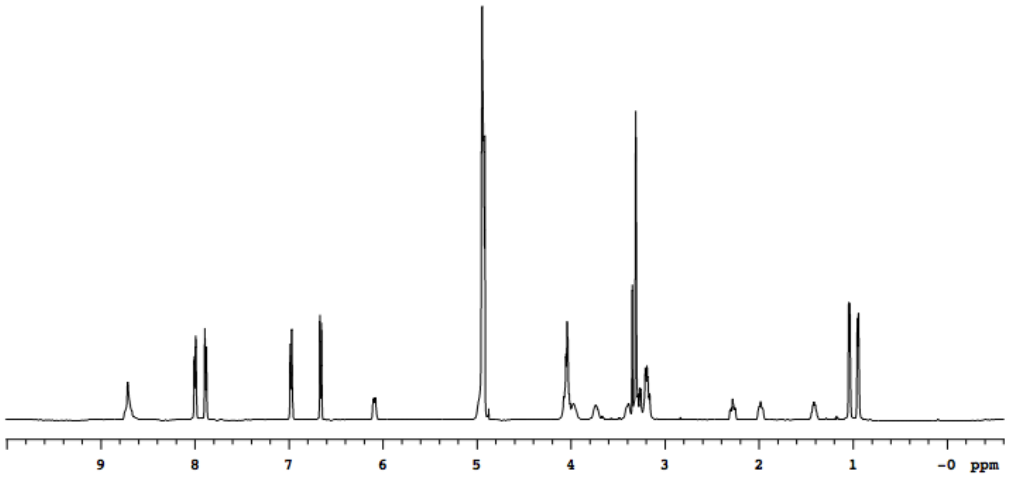
Compound **4c** was prepared from **23c** (30.0 mg, 0.043 mmol). **4c** was obtained as a white amorphous solid (92 %, HCl salt).

^{1}H NMR (500 MHz, CD_3OD) δ: 8.71 (br, 2H), 8.00 (d, 2H, J = 8.0 Hz), 7.89 (d, 2H, J = 7.5 Hz), 6.98 (d, 2H, J = 8.5 Hz), 6.66 (d, 2H, J = 8.0 Hz), 6.09 (dd, 1H, J = 4.0, 10.0 Hz), 4.08-4.01 (m, 4H), 3.74 (br, 2H), 3.39 (br, 1H), 3.27 (br, 1H), 3.26 (d, 1H, J = 6.0 Hz), 3.20 (d, 2H, J = 4.0 Hz), 3.17 (d, 1H, J = 9.5 Hz), 2.28 (ddd, 1H, J = 4.5, 10.5, 14.5 Hz), 1.98 (br, 1H), 1.42 (br, 1H), 1.04 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 6.5 Hz)

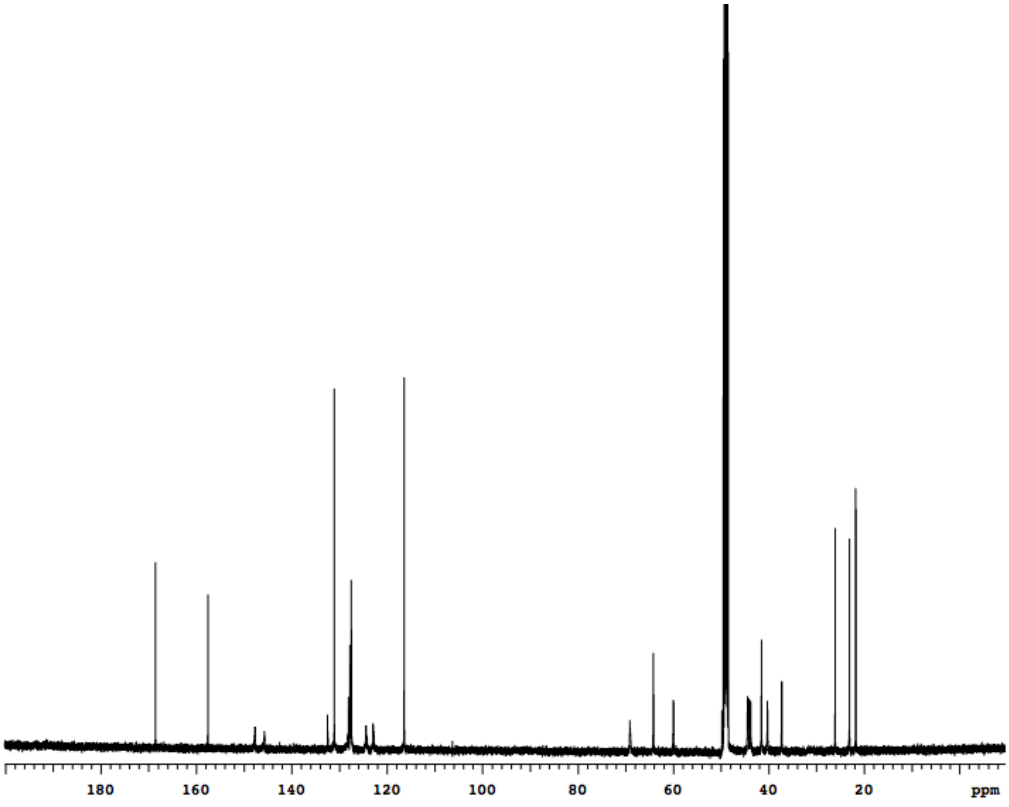
^{13}C NMR (125 MHz, CD_3OD) δ: 168.6, 157.6, 147.7, 145.7, 132.5, 131.1, 128.2, 128.1, 127.8, 127.5, 124.4, 123.0, 116.4, 69.1, 64.2, 60.0, 44.5, 44.3, 43.8, 41.5, 40.3, 37.3, 26.1, 23.1, 21.8

MS (MALDI, m/z) calcd for $C_{29}H_{37}N_8O_3$ $(M+H)^+$ 545.30, found 545.32

optical rotation $[\alpha]_D^{21.2}$ = -40.2 (*c* = 2.30 in MeOH)

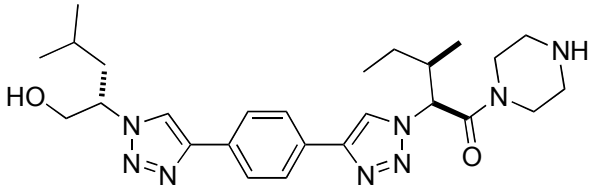


^{1}H NMR of **4c**



^{13}C NMR of **4c**

Preparation of Compound 4d



4d

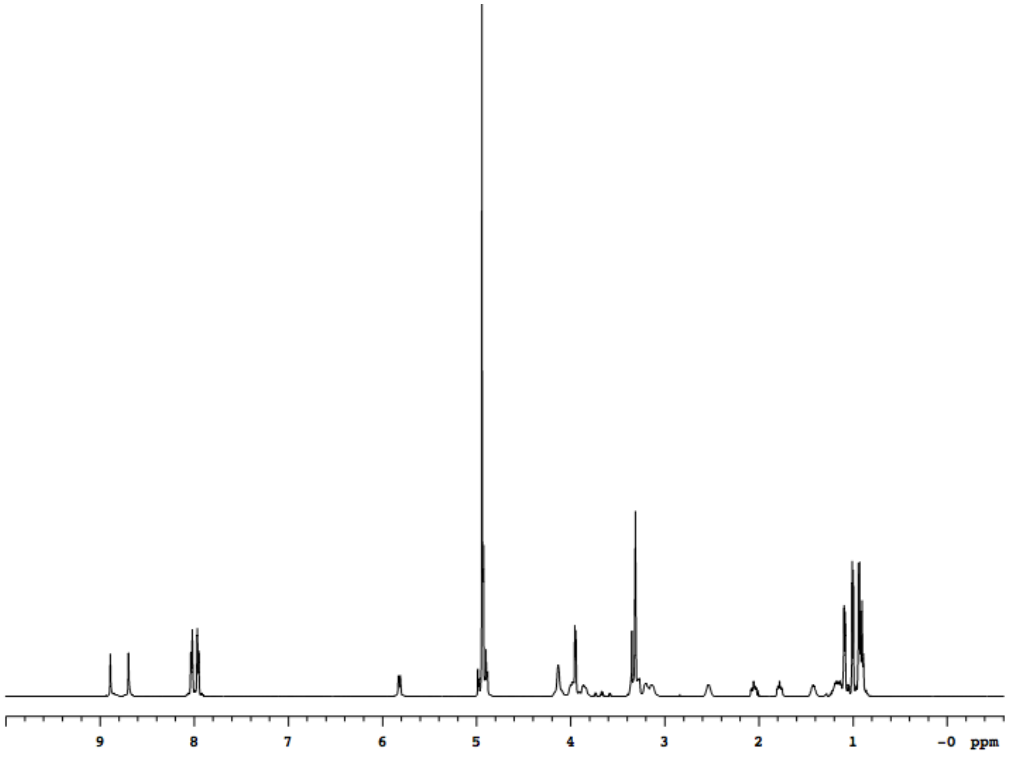
Compound **4d** was prepared from **23d** (30.0 mg, 0.050 mmol). **4d** was obtained as a colorless amorphous solid (quant., HCl salt).

^{1}H NMR (500 MHz, CD_3OD) δ: 8.89 (s, 1H), 8.70 (s, 1H), 8.03 (d, 2H, J = 8.5 Hz), 7.96 (d, 2H, J = 8.0 Hz), 5.82 (d, 1H, J = 10.0 Hz), 4.13 (br, 2H), 3.98 (br, 1H), 3.95 (d, 2H, J = 5.5 Hz), 3.86 (br, 1H), 3.36 (br, 1H), 3.27 (br, 1H), 3.20 (br, 1H), 3.14 (br, 1H), 2.53 (br, 1H), 2.06 (ddd, 1H, J = 5.5, 10.5, 15.0 Hz), 1.78 (ddd, 1H, J = 4.5, 8.5, 13.5 Hz), 1.43-1.40 (m, 1H), 1.23-1.18 (m, 1H), 1.15-1.13 (m, 1H), 1.09 (d, 3H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.5 Hz), 0.90 (t, 3H, J = 7.5 Hz)

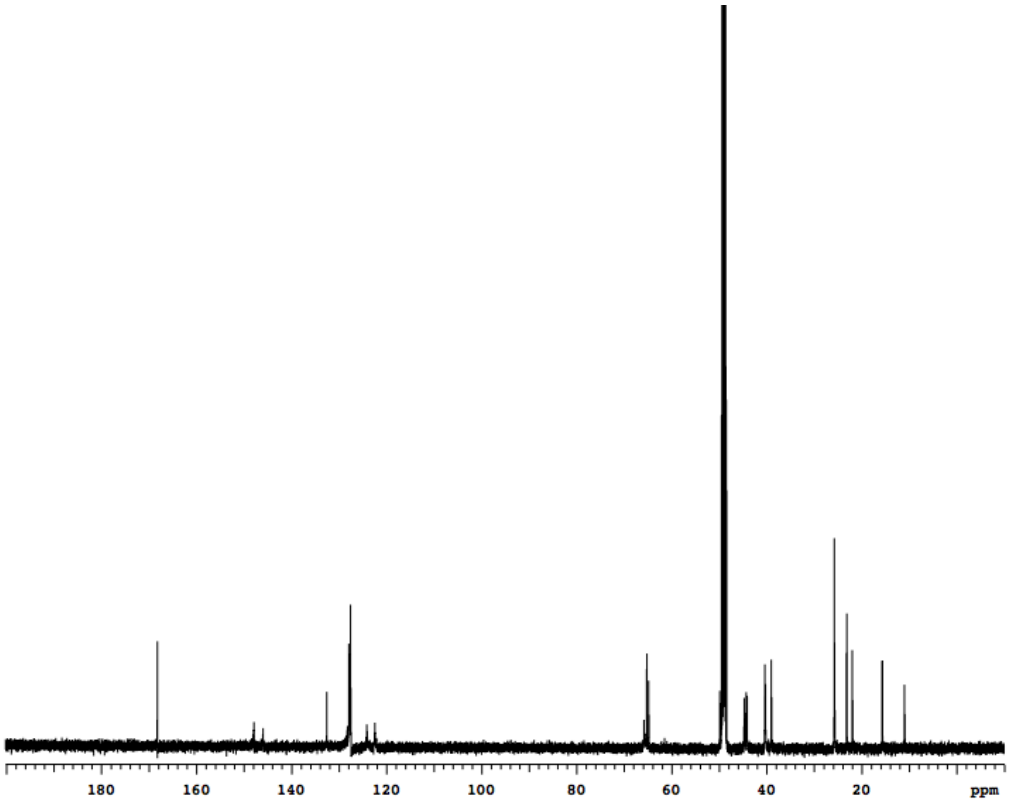
^{13}C NMR (125 MHz, CD_3OD) δ: 168.2, 147.9, 146.0, 132.6, 128.2, 127.9, 127.6, 124.2, 122.5, 65.8, 65.2, 64.9, 44.8, 44.3, 44.2, 40.4, 40.3, 39.0, 25.8, 25.7, 23.2, 22.0, 15.7, 11.0

MS (MALDI, m/z) calcd for $C_{26}H_{39}N_8O_2$ $(M+H)^+$ 495.32, found 495.37

optical rotation $[\alpha]_D^{24.8}$ = +68.9 (*c* = 2.676 in MeOH)

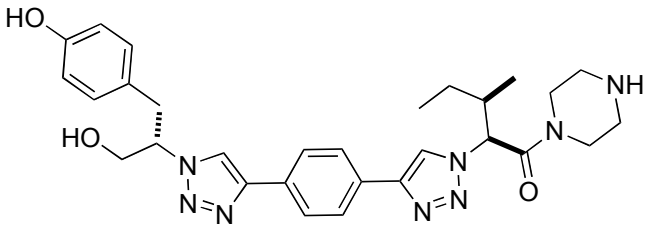


^{1}H NMR of **4d**



^{13}C NMR of **4d**

Preparation of Compound 4e



4e

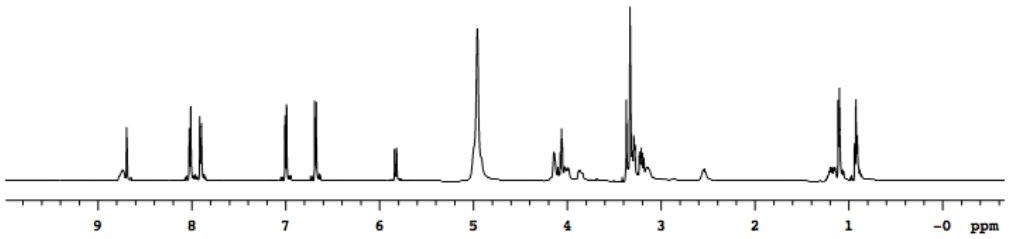
Compound **4e** was prepared from **23e** (35.0 mg, 0.050 mmol). **4e** was obtained as a white amorphous solid (quant., HCl salt).

^{1}H NMR (500 MHz, CD_3OD) δ: 8.72 (br, 1H), 8.67 (s, 1H), 8.00 (d, 2H, J = 8.5 Hz), 7.88 (d, 2H. J = 8.5 Hz), 6.98 (d, 2H, J = 8.5 Hz), 6.66 (d, 2H, J = 8.5 Hz), 5.81 (d, 1H, J = 10.0 Hz), 4.92 (br, 1H), 4.12 (br, 2H), 4.05-4.03 (m, 2H), 4.02-3.97 (m, 1H), 3.86-3.82 (m, 1H), 3.26-3.21 (m, 3H), 3.19 (dd, 2H, J = 9.0, 13.5 Hz), 3.12 (br, 1H), 2.53 (br, 1H), 1.21-1.11 (m, 2H), 1.09 (d, 3H, J = 6.5 Hz), 0.90 (t, 3H, J = 7.5 Hz)

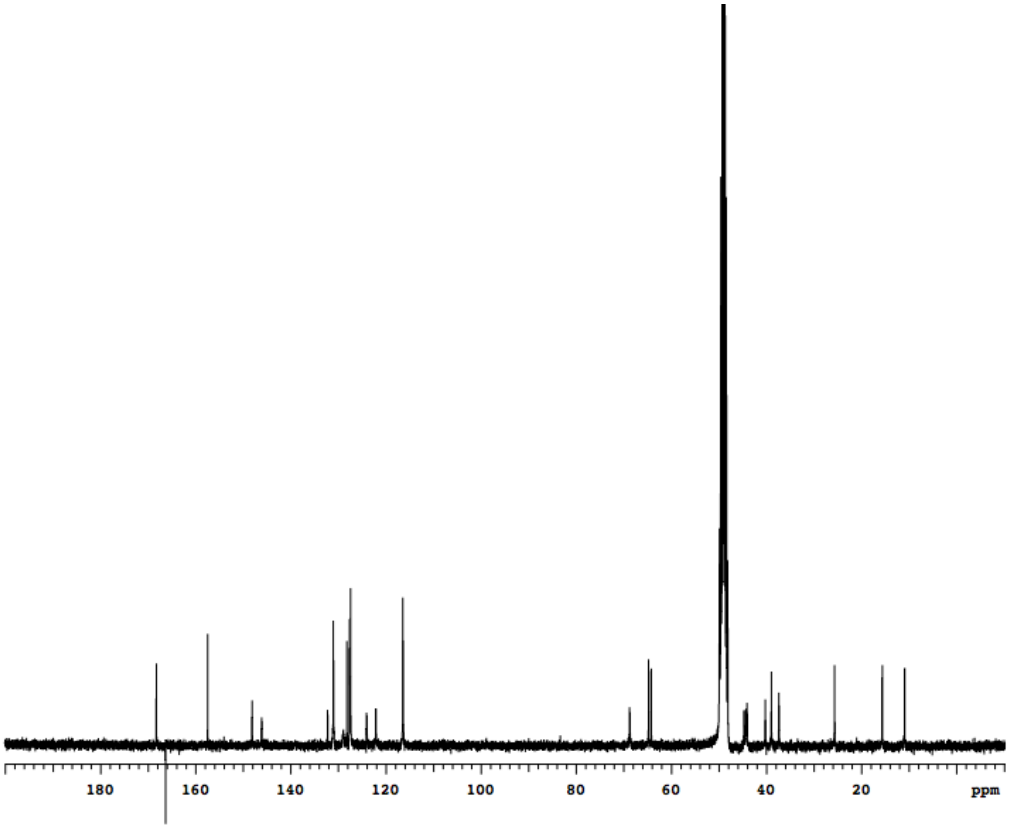
^{13}C NMR (75 MHz, CD_3OD) δ: 168.3, 157.5, 148.1, 146.1, 132.3, 131.0, 129.0, 128.2, 127.7, 127.4, 124.1, 122.1, 116.4, 68.7, 64.8, 64.2, 44.7, 44.3, 44.1, 40.2, 39.0, 37.4, 25.7, 15.7, 10.9

MS (MALDI, m/z) calcd for $C_{29}H_{37}N_8O_3$ $(M+H)^+$ 545.30, found 545.35

optical rotation $[\alpha]_D^{20.6}$ = -18.9 (*c* = 2.94 in MeOH)



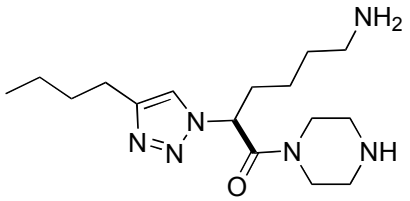
^{1}H NMR of **4e**



^{13}C NMR of **4e**

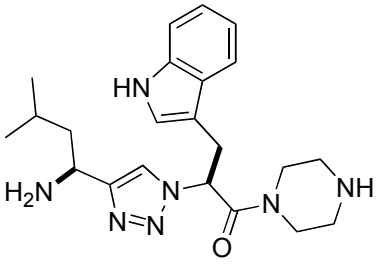
G. Outline Of Data Reported From The MLSMR

Data from first pass assays alone that appears on PubChem gives indications regarding possible applicability of the compound designs; some of this information is available for the compounds presented here. An assay for the protein-protein interactions involving the Bcl-2 family proteins Mcl-1 and Bid (PubChem Assay ID, AID, 1021) showed some activities for compounds **1f** (PubChem Structure ID, SID, 24708217) and **3e** (SID 24707927). Another active compound, the peptidomimetic with scaffold **A** where R^1 = n-butyl, R^2 = Lys (SID, 24708065) shown below, was detected in a related study, also dealing with interactions between Bcl-2 proteins, but this time Bcl-XL with Bim (AID 2129). Compound **16a** (SID 24707900) was identified as active in a high-throughput screening assay (AID 1899) to identify inhibitors of the hepatitis C virus core protein dimerization. However, all this data is from first-pass assays so no concrete conclusions can be drawn.

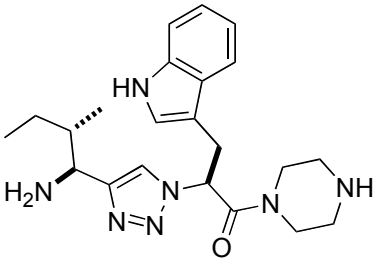


A; R^1 = n-butyl, R^2 = Lys

In some other cases, hits from first pass assays have been selected for confirmatory screens and that data has been released to PubChem. Two assays identified small molecules that inhibited the PB1-domain interaction of MEK5 with either native or a Lys-Ala mutant of MEKK2. Peptidomimetics **3a** (SID 24708115), **3b** (SID 24708166) and two mimics derived from scaffold **B** (R^1 = Leu, R^2 = Trp, SID 24707989 and also R^1 = Ile, R^2 = Trp, SID 24708162) were active in the assay with the native MEKK2 protein (AID 1531). Compound **3b** was also active in the assay using a Lys-Ala mutant of MEKK2 (AID 1530). In confirmation assays, compound **3b** showed inhibition of MEK5 with MEK Kinase 2 (WT, AID 1897) with an EC_{50} value of 5.51 μM. For the inhibition of MEK5 with MEK Kinase 2 (Lys-Ala mutant, AID 1895) the compound was active with an EC_{50} value of 4.44 μM.

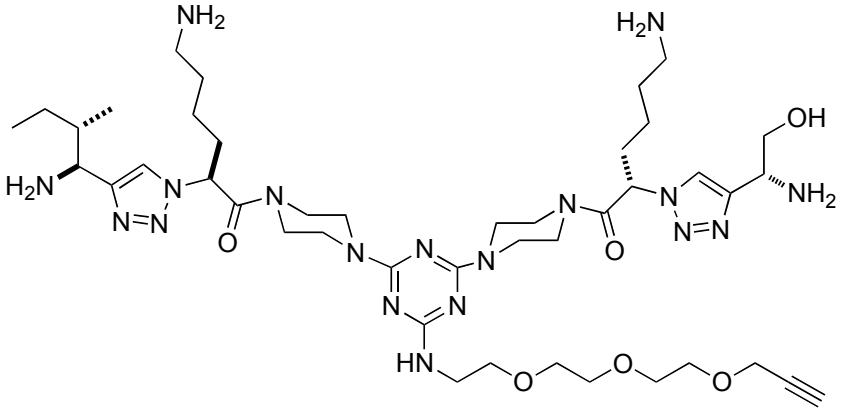


B; R^1 = Leu, R^2 = Trp



B; R^1 = Ile, R^2 = Trp

Peptidomimetics **A** and **B** were also assembled into bivalent forms via attachment to a 1,3,5-triazine ring, [10,15] and these "bivalent mimics" were also submitted to the NIH Molecular Libraries Small Molecule Repository for screening. These bivalent mimics could span two hot-spots in protein-protein interactions, and they might be expected to generate more hits than the monovalent compounds. The data emerging on PubChem indicates this may be so. For example, the assay to identify inhibitors of the interaction between Mcl-1 and Bid identified only two monomeric peptidomimetics as active in the initial high-throughput screen (see above) but the same assay assay identified 23 active "bivalent" compounds. Eight of these bivalents were confirmed as active in the dose-response confirmation assay (AID 1418), and the most promising of these compounds, SID 24833217 shown below, was reported to have an IC_{50} value of 0.63 mM.



Heterobivalent compound of scaffold **B**

H. Literature Citied

The full citation[20] in the text is given here (a partial one was used in the text).

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