Assembly of glycoaminoacid building blocks: A new strategy for the straightforward synthesis of heparan sulfate mimics †

Supplementary Information

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† Dedicated to Guillermo Corrales on the occasion of his retirement.

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1. General Materials and Methods.

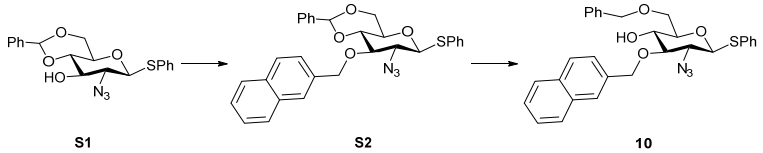
All chemicals were of reagent grade or higher and were purchased from commercial suppliers or purified by standard techniques. Thin-layer chromatography (TLC) was performed on aluminum sheets 60 F254 Merck silica gel, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of Ce_2MoO_4 or 5% H2SO4 in EtOH, followed by heating. Flash column chromatography was performed using silica gel (Merck 60: 0.040-0.063 mm). The eluent used is indicated, and solvent ratios refer to volume. Melting points are not corrected and were measured with a Reicher Jung Thermovar micromelting apparatus. Optical rotations were recorded on a Jasco V-730 Polarimeter (λ = 589 nm, 1 dm cell). FT-IR spectra were recorded with KBr pellets on a Perkin Elmer Spectrum One spectrophotometer. ^{1}H and ^{13}C NMR spectra were registered at 400 or 500 MHz, on a Varian INOVA or Varian UNITY spectrometers, respectively. For compound **7**, ^{1}H and ^{13}C NMR spectra were registered at 800 or 600 MHz, on a AV-800 US2 or AV-600 Brucker spectrometers, respectively. Compound High-resolution mass spectra (HRMS) were recorded on an Agilent 6520 Accurate Mass Q-TOF spectrometer with an ESI source.

1.1. Surface Plasmon Resonance (SPR)

The surface of a CM5 sensor chip (Biacore Inc., GE Healthcare, USA) was activated using freshly mixed N-hydroxysuccimide (NHS; 100 mM) and 1-(3-(dimethylamino)propyl)-ethylcarbodiimide (EDC; 400 mM) (1/1, v/v) in water. Next, FGF2 (50 μg/mL) in aqueous NaOAc (10 mM, pH 5.0) was passed over the surface until a ligand density of 7500-10.000 respectively, was achieved. Quenching of the remaining active esters was accomplished by passing aqueous ethanolamine (1.0 M, pH 8.5) over the surface of the chip. The control flow cell was activated with NHS and EDC, which was then treated with ethanolamine. HBS-EP (0.01 M HEPES, 150 mM NaCl, 3 mM EDTA, 0.005% polysorbate 20; pH 7.4) was employed as the running buffer for immobilization, binding, affinity and kinetic analysis. Serial dilutions of each compound in HBS-EP buffer at a flow rate of 30 μL/min was employed for association and dissociation at a temperature of 25 °C. One 30 s injections of aqueous NaCl (2.0 M) at flow rate of 30 μL/min was employed for regeneration to achieve baseline status. Affinity data were fitted to a ' 1:1 steady state affinity' model and kinetics data to a '1:1 langmuir binding model' except for R8-E29 compound which was adjusted to a 'two state reaction' model. The evaluation was made using a BIAcore X100 evaluation software (Biacore Inc., GE Healthcare).

2. Synthesis of compounds 8-10.

Compounds **8**[1] and **9**[2] were prepared according with procedures described previously. Compound **10** was obtained from **S1**[3] according with the procedure described below.



Phenyl 2-azido-3-O-naphthylmethyl-4,6-O-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (S2). Compound **S1** (3.26 g, 8.46 mmol) and 2-bromomethylnaphthalene (2.337 g, 10.57 mmol) were dissolved in dry DMF (40 mL) at ambient temperature under argon. After cooling at 0 °C, 60 % NaH (0.676 g, 16.91 mmol) was added; the mixture was warmed up at room temperature and stirred for 90 min. The reaction mixture was cooled at 0 °C, diluted with dichloromethane, washed with water. The organics were separated and dried ($MgSO_4$), and solvents removed in vacuo. The residue was crystallized from ethyl acetate-hexane (≈ 1:20), to give the product (4.2 g, 94.5%). $[\alpha]_D$ -109 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.74-7-84 (m, 4H), 7.55-7.59 (m, 2H), 7.43-7.51 (m, 5H), 7-38-7.41 (m, 3H), 7.34-7.37 (m, 3H), 5.59 (s, 1H), 5.07 (d, *J* 11.3 Hz, 1H), 4.96 (d, *J* = 11.3 Hz, 1H), 4.50 (d, *J* = 10.2 Hz, 1H), 4.40 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.75 – 3.63 (m, 2H), 3.52 – 3.34 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ 137.06, 134.99, 133.89, 133.21, 133.10, 130.62, 129.12, 128.72, 128.33, 128.21, 127.96, 127.66, 127.21, 126.14, 126.06, 126.01, 125.99, 101.34, 86.67, 81.29, 80.82, 77.33, 77.01, 76.69, 75.16, 70.47, 68.49, 64.79. HRMS (ESI, positive mode) calcd for $C_{30}H_{27}N_3O_4S$ $[M+H]^+$ *m/z* 526.1795, found 526.1792.

Phenyl 2-azido-6-O-benzyl-2-deoxy-3-O-naphthylmethyl-1-thio-β-d-glucopyranoside (10). Compound **S2** (4.1 g, 7.8 mmol) was dissolved in dichloromethane (63 mL) under Ar with stirring. The mixture was cooled to -10 °C using an acetone-ice bath for 3h. Then first triethylsilane (3.72 mL, 23.4 mmol, 3 equiv) was added followed by $BF_3{\cdot}OEt_2$ (2.89 mL, 23.4 mol, 3 equiv) over 5 min. The mixture was stirred at -10 °C for 3 h and then diluted with dichloromethane (≈ 200 mL), and washed with sat. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (hexane:EtOAc, 5:1 → 1:1) to yield the title (3.28 g, 80 %). Next eluted product was the starting material (0.3 g, 7.3%). $[\alpha]_D$ - 79 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.84 (m, 4H), 7.62 (dd, *J* = 6.9, 2.2 Hz, 2H), 7.53 (m, 3H), 7.43 – 7.27 (m, 8H), 5.10 (d, *J* = 11.3 Hz, 1H), 5.03 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 9.8 Hz, 1H), 3.80 (qd, J = 10.4, 4.6 Hz, 2H), 3.71 (dt, *J* = 9.1, 2.5 Hz, 1H), 3.52 – 3.36 (m, 3H), 2.80 (q, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.70, 135.30, 133.53, 133.33, 133.15, 131.29, 129.03, 128.52, 128.49, 128.40, 128.02, 127.90, 127.75, 127.73, 127.12, 126.23, 126.11, 125.99, 86.28, 84.53, 78.00, 77.39, 77.07, 76.75, 75.52, 73.78, 72.09, 70.34, 64.60. HRMS (ESI, positive mode) calcd for $C_{30}H_{29}N_3O_4S$ $[M+NH_4]^+$ *m/z* 545.2223, found 545.2222.

3. General procedures.

A: Alkylation with *tert*-butyl bromoacetate. To a mixture of 60% NaH (3 eq. per hydroxyl group), TBAI (0.1 eq. per hydroxyl group) and tert-butyl bromoacetate (4 eq. per hydroxyl group) in anhydrous THF (3 mL for 1 mmol of tert-butyl bromoacetate) under argon was added dropwise a solution of the starting material in THF (4 mL/mmol) at room temperature. The mixture was stirred at room temperature overnight. Then, the excess of NaH was quenched by adding AcOH (0.15 mL for 1 mmol of NaH) at 0 °C, and the mixture was concentrated. The residue was purified by flash chromatography to yield the thioglycoside donors.

B: Glycosylation. To a solution of thioglycoside donor (1 eq.) and N-Fmoc- L-serine benzyl ester (**14**, 1.3 eq.) in a mixture of anhydrous Et_2O:CH_2Cl_2 (4:1, 75 mL per mmol donor) powdered molecular sieves (4Å, ≈3.7 g/mmol donor) and NIS (1.5 eq) were added under Ar and the suspension stirred at room temperature. After 30 min, the mixture was cooled to reaction temperature (-30 °C) and trimethylsilyl trifluoromethanesulfonate (0.4 eq.) was added and the reaction mixture was stirred at reaction temperature until TLC indicated completion. Then saturated aq. $NaHCO_3$ (≈ 8 mL per mmol of donor) and 20% aq. $Na_2S_2O_3$ (≈ 8 mL per mmol of donor) were added and the suspension stirred at room temperature for 30 min. The mixture was filtered through celite and the obtained solution was concentrated. The residue was diluted with ethyl acetate (≈ 50 mL per mmol of donor) and washed with saturated aq. $NaHCO_3$ and with 20% aq. $Na_2S_2O_3$. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography to yield the corresponding α anomer.

C: Regioselective deprotection of *terc*-butyl ester. The protected glycoamino acid (1 mmol) was dissolved in a mixture of CH_2Cl_2 and TFA (20:1) (v/v, 50 mL per mmol) and left at room temperature until completion, usually 2 to 3 h. Subsequently the mixture was concentrated and the residue was co-evaporated with anhydrous toluene (4 x 5 mL) under vacuum to remove the traces of TFA that can interfere in the next step. Finally, the residue was dissolved in CH_2Cl_2 and filtered through a pad of silica. The obtained acids were used in the next step without further purification.

D: Regioselective deprotection of Fmoc. The protected glycoamino acid (1 mmol) was dissolved in anhydrous DMF (23 mL per mmol) and piperidine (19 eq.) was added dropwise. The mixture was stirred at room temperature under argon until completion, usually 1 to 2 h. The solvent was evaporated under reduced pressure, and the residue was co-evaporated with anhydrous toluene (4 x 5 mL) under vacuum to remove the traces of piperidine that can interfere in the next step. Finally, the residue was dissolved in CH_2Cl_2 and filtered through a pad of silica. The obtained amines were used in the next step without further purification.

E: Amidic coupling. To a solution of amine (1 mmol) and acid (1.2 eq.) in anhydrous THF (18 mL per mmol of acid) was added EDC (1.2 eq.), DMAP (0.2 eq.) and HOBt (0.5 eq.). The mixture was stirred at room temperature under argon until completion, usually 4-5 h. Subsequently the mixture was concentrated and the residue was purified by flash chromatography to yield the corresponding coupled glycoamino acid.

F: Removal of Nap. To a cooled at 0 °C solution of the coupled glycoamino acid (1 mmol) in CH_2Cl_2 (6.5 mL per mmol) a disodium phosphate buffer (0.1 M, pH 7.5, 0.6 mL per mmol) was added. DDQ (3.1 eq. per Nap) was

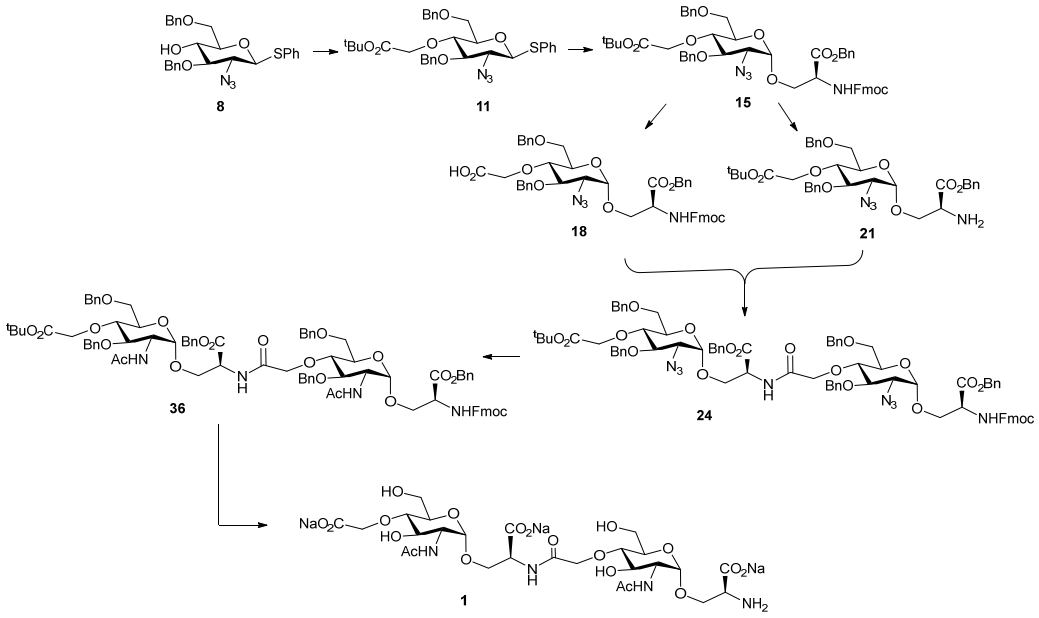
added over 1 h in small portions, after which the mixture was allowed to warm up to room temperature and was stirred for 30 min. The mixture was diluted with $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were dried over $NaSO_4$ and concentrated. Finally the residue was purified by flash chromatography to yield the corresponding selectively deprotected glycoamino acid.

G: Sulfation. A mixture of deprotected glycosamino acid (1 mmol) and sulfur trioxide pyridine complex (5 eq. per hydroxyl group) in pyridine (35 mL per mmol) was heated at 50 °C under argon for 2 h. After this time, the mixture was concentrated and residue was purified by flash chromatography to yield the corresponding sulfated glycosamino acid.

H: One-pot reduction and acetylation of azides with thioacetic acid. Thioacetic acid (30 mL) was added to a solution of the starting material (1 mmol) in anhydrous pyridine (30 mL) at room temperature under argon. The mixture was stirred until completion, usually 24 h. Subsequently the mixture was concentrated and the residue was purified by flash chromatography to yield the corresponding N-acetyl glycol amino acid.

I: Removal of Bn ether. The starting material (0.03 mmol) was solved in MeOH (4 mL) and treated with Pd/C (10%) (40 mg). The mixture was stirred for 6 h under H_2 at room temperature. The mixture was filtered through a pad of Celite and the obtained solution was concentrated. Finally, the residue was solved in the minimum amount of water and passed through a Dowex 500wx8 resin column (Na^+ form, 1 mL) and eluted with water. Finally, the fractions containing the desired product were lyophilized.

4. Synthesis of compound 1



4.1. Synthesis of compound 11

Compound **11** was prepared from compound **8** (1.66 g, 3.5 mmol) following general procedure **A**. The residue was purified by silica gel chromatography (hexane:EtOAc, 6:1) to yield **11** as a foam (1.75 g, 85%). $[\alpha]_D$ -17.3 (c 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.56 (m, 2H), 7.40 – 7.20 (m, 13H), 4.86 (s, 2H), 4.64 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.41 (d, J = 10.1 Hz, 1H), 4.22 (d, J = 15.7 Hz, 1H), 4.12 (d, J = 15.6 Hz, 1H), 3.86 (d, J = 2.0 Hz, 2H), 3.57 – 3.46 (m, 3H), 3.31 (dd, J = 10.1, 8.7 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.81, 138.28, 137.55, 133.64, 131.08, 128.97, 128.50, 128.36, 128.33, 128.31, 128.02, 127.56, 127.51, 85.92, 84.77, 81.67, 78.97, 78.27, 77.35, 77.03, 76.71, 75.80, 73.40, 70.55, 68.78, 64.96, 28.10, 28.06. HRMS (ESI, positive mode) calcd for $C_{32}H_{37}N_3O_6S$ $[M+NH_4]^+$ *m/z* 609.2747, found 609.2949.

4.2. Synthesis of compound 15

Compound **15** was prepared from compound **11** (0.98 g, 1.66 mmol) and N-Fmoc- L-serine benzyl ester (**14**, 0.899 g, 2.15 mmol) according to general procedure **B**. The residue was purified by silica gel chromatography (hexane: EtOAc, 5:1 → 4:1) to yield **15** (0.968 g, 65 %) and the β-anomer (0.261 g, 20%). $[\alpha]_D$ + 73.2 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.41 – 7.28 (m, 19H), 5.95 (d, *J* = 8.3 Hz, 1H, N*H*), 5.25 (s, 2H), 4.92 – 4.83 (m, 2H), 4.81 (d, *J* = 3.7 Hz, 1H), 4.66 – 4.56 (m, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.41 (dd, *J* = 10.4, 7.5 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.28 – 4.19 (m, 2H), 4.10 (dd, *J* = 10.7, 3.2 Hz), 4.04 (d, *J* = 15.6 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.89 – 3.78 (m, 2H), 3.70 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.58 (t, *J* = 9.3 Hz, 1H), 3.27 (dd, *J* = 10.3, 3.6 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.58, 168.70, 155.99, 143.85, 143.83, 141.26, 137.81, 137.77, 135.06, 128.66, 128.57, 128.47, 128.36, 128.32, 128.11, 127.91, 127.82, 127.72, 127.70, 127.69, 127.14, 125.27, 125.25, 119.94, 99.10, 81.64, 79.54, 78.81, 75.29, 73.50, 70.66, 69.39, 68.12, 67.77, 67.47, 63.18, 54.57, 47.08, 28.07. HRMS (ESI, positive mode) calcd for $C_{51}H_{54}N_4O_{11}$ $[M+NH_4]^+$ *m/z* 916.4133, found 916.4136.

4.3. Synthesis of compound 18

Compound **18** was prepared from compound **15** (0.379 g, 0.42 mmol) according to general procedure **C**. The residue was employed directly in the next step without further purification.

4.4. Synthesis of compound 21

Compound **21** was prepared from compound **15** (0.315 g, 0.35 mmol) according to general procedure **D**. The residue was filtered through a pad of silica (hexane – EtOAc, 1:1 → 0:1) and employed directly in the next step without further purification.

4.5 Synthesis of compound 24

Compound **24** was prepared from compound **18** (0.375 g, 0.42 mmol) and **21** (0.207 g, 0.31 mmol, 0.73 eq. per mol of acid) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane: EtOAc, 2:1) to yield **24** as a foam (0.442 g, 96 %). $[\alpha]_D$ +82.3 (c 1.0, $CHCl_3$). IR (KBr): 3422, 3064, 3032, 2928, 2107, 1749, 1687, 1514, 1203, 1151, 1105, 1047, 740 and 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.61 (dd, *J* = 7.5, 3.5 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.44 – 7.12 (m, 34H), 5.94 (d, *J* = 8.5 Hz, 1H, N*H*), 5.23 (d, *J* = 4.5 Hz, 2H), 5.15 (s, 2H), 4.89 – 4.65 (m, 8H), 4.59 (d, *J* = 11.9 Hz, 3H), 4.52 – 4.38 (m, 3H), 4.34 – 4.06 (m, 6H), 4.03 – 3.58 (m, 12H), 3.53 (t, *J* = 9.3 Hz, 1H), 3.23 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.14 (dd, *J* = 10.3, 3.6 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.67, 169.28, 169.16, 168.61, 156.01, 143.88, 143.76, 141.26, 137.81, 137.75, 137.61, 137.47, 135.02, 134.89, 128.67, 128.65, 128.61, 128.59, 128.53, 128.51, 128.48, 128.42, 128.37, 127.99, 127.96, 127.93, 127.84, 127.79, 127.77, 127.73, 127.71, 127.70, 127.09, 127.07, 125.24, 125.18, 119.96, 99.11, 98.76, 81.51, 79.49, 79.41, 78.73, 78.37, 75.33, 75.07, 73.59, 73.46, 71.72, 70.83, 70.78, 70.57, 69.09, 68.08, 67.74, 67.72, 67.42, 63.31, 62.97, 54.56, 52.33, 47.08, 28.06. HRMS (ESI, positive mode) calcd for $C_{83}H_{88}N_8O_{19}$ $[M+H]^+$ *m/z* 1501.6166, found 1501.6270.

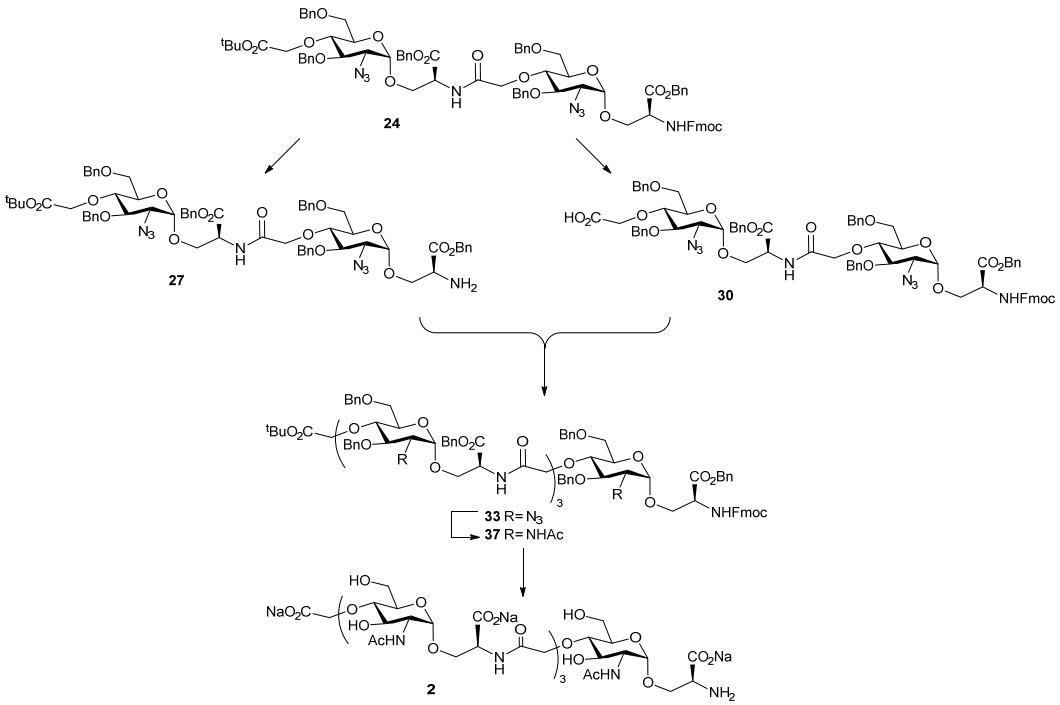
4.6. Synthesis of compound 36

Compound **36** was prepared from compound **24** (0.155 g, 0.1 mmol) according to general procedure **H**. The residue was purified by silica gel chromatography (hexane:EtOAc, 1:1 → 0:1) to yield **36** as an oil (0.15 g, 94%). $[\alpha]_D$ +49.4 (c 1.0, $CHCl_3$). IR (KBr): 3421, 3063, 3032, 2928, 1747, 1680, 1522, 1204, 1142, 1105, 1046, 741 and 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.42-7.12 (m, 33H), 5.98 (d, *J* = 8.4 Hz, N*H*), 5.72 (s, 1H, N*H*), 5.63 (d, *J* = 9.6 Hz, 1H, N*H*), 5.22-5.18 (m, 2H), 5.12 (sq, *J* = 12.1 Hz, 2H), 4.99 (m, 4H), 4.76-4.42 (m, 6H), 4.37 (t, *J* = 8.8 Hz, 1H), 4.30 – 4.15 (m, 2H), 4.10 (d, *J* = 15.5 Hz, 1H), 4.02 (d, *J* = 15.7 Hz, 1H), 3.97-3.56 (m, 5H), 3.52 (t, *J* = 9.2 Hz, 1H), 3.44 (dd, *J* = 10.7, 6.1 Hz, 1H), 1.85 (s, 3H), 1.78 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.59, 141.30, 141.29, 138.16, 138.03, 137.71, 134.76, 134.68, 128.82, 128.81, 128.76, 128.71, 128.57, 128.44, 128.41, 128.35, 128.33, 128.27, 128.10, 127.96, 127.94, 127.90, 127.82, 127.78, 127.75, 127.69, 127.67, 127.62, 127.60, 127.12, 127.11, 125.00, 120.08, 120.05, 99.34, 98.80, 81.51, 80.49, 79.52, 78.68, 78.15, 74.77, 73.89, 73.59, 73.44, 71.20, 70.99, 70.49, 69.28, 68.53, 68.41, 68.27, 67.65, 67.60, 67.18, 54.65, 52.33, 52.31, 52.07, 47.10, 28.06, 23.19, 23.10. HRMS (ESI, positive mode) calcd for $C_{87}H_{96}N_4O_{21}$ $[M+H]^+$ *m/z* 1533.6645, found 1533.6685.

4.7. Synthesis of compound 1

Compound **1** was prepared from compound **36** in three steps. In the first one, the N-Fmoc amine of **36** (0.089 g, 0.058 mmol) was deprotected according to general procedure **D**. The residue was filtered through a pad of silica (EtOAc → EtOAc:MeOH, 5:1) and the amine employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**. The residue was filtered through a pad of silica (EtOAc → EtOAc:MeOH, 10:1) and the amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column to afford compound **1** as a white solid (22.5 mg, 56% from **36**). $[\alpha]_D$ +69.2 (c 1.0, H_2O). IR (KBr): 3428, 2923, 1635, 1415, 1119, 1034 and 584 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 4.74 (d, *J*= 2,6 Hz, 1H), 4.69 (d, *J* = 2.8 Hz, 1H), 4.34 (t, *J* = 3.2, Hz, 1H), 4.25- 4.15 (m, 2H), 4.11 (d, *J* = 16.4Hz, 1H), 4.01- 3.95 (m, 2H), 3.65-3.88 (m, 12 H), 3.53 (dt, *J* = 10.4, 3.4 Hz, 1H), 3.38 (t, *J* = 8.1 Hz, 1H), 3.27 (dd, *J* = 10.0, 7.2, 1H), 1.90 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (125 MHz, D_2O) δ 177.86, 175.06, 174.45, 174.29, 171.82, 171.50, 97.72, 97.24, 79.50, 79.35, 71.14, 71.09, 71.08, 70.58, 70.47, 70.25, 68.36, 66.26, 60.17, 59.95, 54.35, 54.11, 53.49, 53.44, 21.87, 21.85. HRMS (ESI, negative mode) calcd for $C_{26}H_{41}N_4O_{19}$ $[M-H]^-$ *m/z* 713.2444, found 713.2370.

5. Synthesis of compound 2



5.1. Synthesis of 27

Compound **27** was prepared from compound **24** (0.150 g, 0.10 mmol) according to general procedure **D**. The residue was filtered through a pad of silica (hexane – EtOAc, 1:1 → 0:1) and employed directly in the next step without further purification.

5.2. Synthesis of 30

Compound **30** was prepared from compound **24** (0.180 g, 0.12 mmol) according to general procedure **C**. The residue was employed directly in the next step without further purification.

5.3. Synthesis of 33

Compound **33** was prepared from compound **30** (0.153 g, 0.12 mmol) and **27** (0.207 g, 0.10 mmol, 0.73 eq. per mol of acid) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane:

EtOAc, 1:2 → 0:1) to yield **33** as a foam (0.240 g, 87%). $[\alpha]_D$ +96.4 (c 1.0, $CHCl_3$). IR (KBr): 3418, 2926, 2107, 1747, 1683, 1516, 1207, 1151, 1104, 1047, 741 and 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.45-7.10 (m, 64H), 5.97 (d, J = 8.5 Hz, 1H), 5.35 – 5.06 (m, 8H), 4.92 – 4.39 (m, 25H), 4.37 – 4.06 (m, 10H), 4.01 – 3.49 (m, 28H), 3.27 – 2.96 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.66, 169.31, 169.29, 169.21, 168.65, 155.97, 143.89, 143.76, 141.29, 137.85, 137.83, 137.69, 137.61, 137.55, 137.49, 137.41, 137.40, 135.04, 134.96, 134.92, 128.74, 128.70, 128.69, 128.65, 128.62, 128.57, 128.53, 128.50, 128.47, 128.45, 128.39, 128.04, 128.00, 127.98, 127.94, 127.86, 127.83, 127.79, 127.75, 127.13, 127.10, 125.25, 125.17, 120.02, 99.06, 98.72, 98.57, 81.54, 79.54, 79.36, 79.32, 79.25, 78.79, 78.45, 78.26, 77.38, 77.26, 77.06, 76.74, 76.45, 75.31, 75.16, 75.12, 75.08, 73.62, 73.59, 73.49, 71.71, 71.59, 71.50, 70.90, 70.78, 70.70, 70.65, 70.62, 69.20, 68.22, 68.13, 68.10, 67.76, 67.72, 67.67, 67.60, 67.40, 67.29, 63.29, 63.14, 63.09, 63.03, 54.57, 52.41, 52.31, 52.27, 47.12, 28.09.

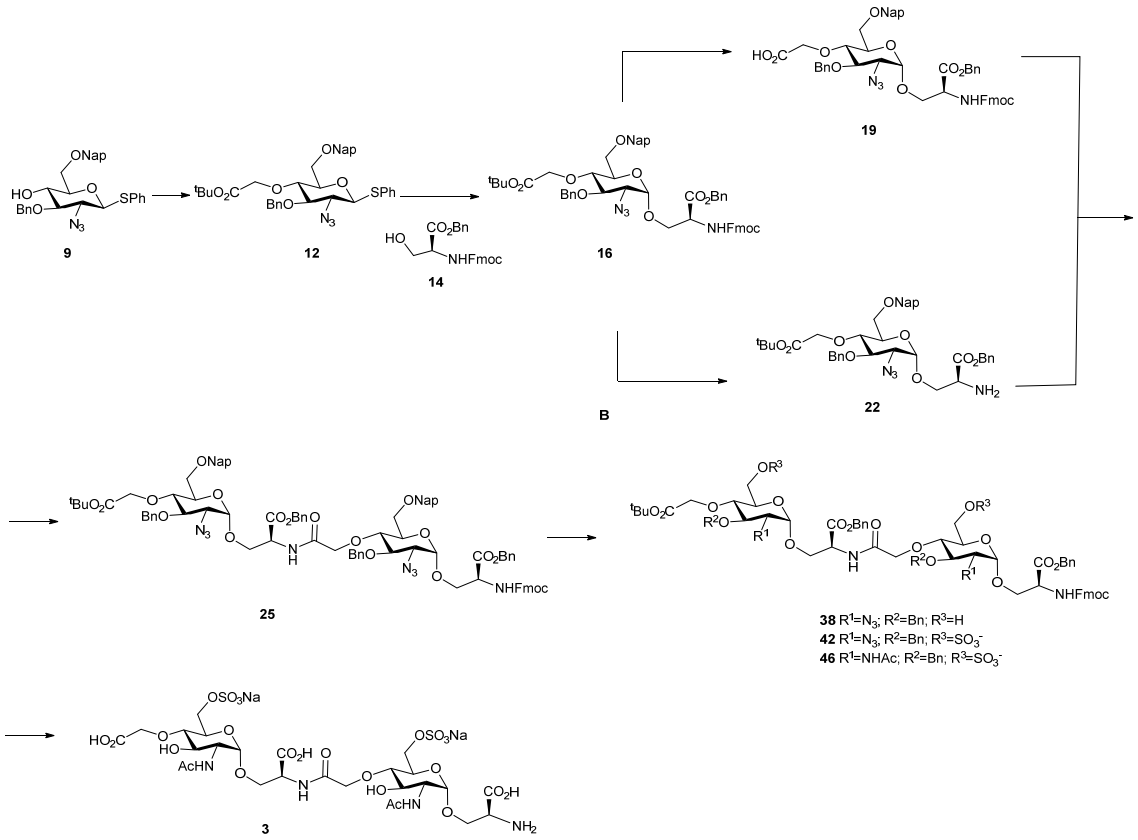
5.4. Synthesis of 37

Compound **37** was prepared from compound **33** (0.240 g, 0.087 mmol) according to general procedure **H**. The residue was purified by silica gel chromatography (EtOAc → EtOAc:MeOH, 10:1) to yield **37** as an oil (0.15 g, 94%). $[\alpha]_D$+64.3 (c 1.0, $CHCl_3$). IR (KBr): 3417, 2926, 1746, 1679, 1523, 1207, 1129, 1102, 1045, 741 and 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.7 Hz, 2H), 7.57 – 7.39 (m, 3H), 7.38 – 6.91 (m, 63H), 5.97 (d, J = 8.4 Hz, 1H), 5.86 (m, 2H), 5.61 (t, J = 9.2 Hz, 2H), 5.06 (m, 8H), 4.69 – 4.29 (m, 27H), 4.28 – 3.90 (m, 14H), 3.88 – 3.40 (m, 27H), 3.34 (mz, 2H), 3.18 – 2.96 (m, 1H), 1.76 (s, 3H), 1.73 (2s, 3H each), 1.69 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.14, 170.08, 169.97, 169.96, 169.86, 169.60, 169.53, 169.19, 169.01, 143.60, 141.33, 138.29, 138.13, 137.82, 137.72, 137.69, 137.64, 137.54, 134.80, 134.76, 134.71, 128.87, 128.84, 128.80, 128.78, 128.76, 128.71, 128.64, 128.55, 128.53, 128.48, 128.47, 128.44, 128.41, 128.36, 128.33, 128.27, 128.12, 128.06, 128.00, 127.97, 127.87, 127.84, 127.80, 127.72, 127.68, 127.65, 127.62, 127.13, 125.00, 120.13, 120.10, 99.08, 98.90, 81.43, 80.67, 80.62, 79.48, 78.69, 78.40, 77.91, 77.40, 77.28, 77.08, 76.76, 74.87, 74.74, 74.71, 73.68, 73.63, 73.57, 73.42, 71.46, 71.15, 70.98, 70.50, 68.54, 68.37, 67.71, 67.65, 67.24, 52.44, 52.37, 52.31, 52.26, 51.95, 47.13, 29.70, 28.09, 23.23, 23.20, 23.15, 22.70.

5.5. Synthesis of 2

Compound **2** was prepared from compound **37** in three steps. In the first one, the N-Fmoc amine of **37** (0.240 g, 0.087 mmol) was deprotected according to general procedure **D**. The residue was filtered through a pad of silica (EtOAc → EtOAc:MeOH, 5:1) and the amine employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**. The residue was filtered through a pad of silica (EtOAc → EtOAc:MeOH, 3:1) and the amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column to afford compound **31** (0.073 g, 54% from **37**). $[\alpha]_D$ +117.3 (c 1.0, H_2O). ^1H NMR (500 MHz, D_2O) δ 4.77- 4.71 (m, 4H), 4.44-4.40 (m, 3H), 4.36- 4.17 (m, 7H), 4.15- 4.08 (d, *J* = 16.6 Hz, 1H), 4.03-3.97 (dd, *J* = 2.8 and 11.3 Hz, 1H), 3.93-3.59 (m, 27H), 3.59-3.54 (m, 1H), 3.40 (t, *J* = 9.1 Hz, 3H), 3.34-3.27 (m, 1H), 1.95-1.86 (12 H). ^{13}C NMR (125 MHz, D_2O) δ 176.58, 174.44, 174.38, 174.35, 174.30, 174.28, 174.25, 172.15, 172.13, 171.38, 97.72, 97.70, 97.64, 97.41, 79.62, 79.56, 79.47, 79.26, 71.19, 71.09, 71.06, 71.00, 70.93, 70.86, 70.82, 70.75, 70.51, 70.50, 70.45, 70.38, 70.03, 68.16, 68.05, 67.99, 66.27, 60.24, 60.15, 60.02, 54.31, 53.95, 53.76, 53.67, 53.64, 53.55, 53.48, 21.92, 21.90. HRMS (ESI, negative mode) calcd for $C_{52}H_{78}N_8Na_2O_{37}$ $[M-2]^{2-}$ *m/z* 726.2131 found 726.2123; calcd for $C_{52}H_{78}N_8NaO_{37}$ $[M-3]^{3-}$ *m/z* 476.4789 found 476.4790; calcd for $C_{52}H_{78}N_8O_{37}$ $[M-4]^{4-}$ *m/z* 351.6117 found 351.6126.

6. Synthesis of compound 3



6.1. Synthesis of 12

Compound **12** was prepared from compound **9** (2.7 g, 5.2 mmol) following general procedure **A**. The residue was purified by silica gel chromatography (hexane:EtOAc, 5:1) to yield **12** as a foam (2.9 g, 90%). $[\alpha]_D$ -27.0 (c 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.75 (m, 4H), 7.60 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.39 – 7.19 (m, 8H), 4.85 (s, 2H), 4.79 (d, *J* = 12.1 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.41 (d, *J* = 10.1 Hz, 1H), 4.22 (d, *J* = 15.6 Hz, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 3.94 – 3.83 (m, 2H), 3.58 – 3.45 (m, 3H), 3.32 (t, *J* = 9.5 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.97, 137.72, 135.91, 133.79, 133.43, 133.12, 131.29, 129.15, 128.66, 128.52, 128.46, 128.26, 128.18, 128.05, 127.85, 126.36, 126.25, 125.99, 125.80, 86.14, 84.98, 81.83, 79.20, 78.49, 75.96, 73.69, 70.74, 69.01, 65.18, 28.19. HRMS (ESI, positive mode) calcd for $C_{36}H_{42}N_3O_7S$ $[M+H_3O]^+$ 659.2625, found 659.2772

6.2. Synthesis of 16

Compound **16** was prepared from compound **12** (1.57 g, 2.44 mmol) and **14** (1.32 g, 3.18 mmol) following general procedure **B**. The residue was purified by silica gel chromatography (hexane:EtOAc, 2:1) to yield **16** as a foam (1.24 g, 53%). $[\alpha]_D$ +64.4 (c 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.67 (m, 6H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.52 – 7.20 (m, 17H), 5.97 (d, *J* = 8.3 Hz, 1H), 5.29 – 5.20 (m, 2H), 4.87 (m, 2H), 4.82 (d, *J* = 3.0 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.67 – 4.60 (m, 1H), 4.34 (m, 1H), 4.24 – 4.19 (m, 1H), 4.16 (dd, *J* = 61.9, 15.7 Hz, 2H), 4.15 – 3.98 (m, 2H), 3.99 – 3.93 (m, 1H), 3.87 (m, 2H), 3.76 (d, J = 9.6 Hz, 1H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.28 (dd, *J* = 10.2, 3.3 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.73, 168.84, 156.14, 143.99, 143.95, 141.40, 137.94, 135.39, 135.21, 133.34, 133.11, 128.80, 128.69, 128.60, 128.30, 128.24, 128.05, 128.03, 127.80, 127.26, 126.74, 126.24, 126.03, 125.91, 125.40, 120.07, 99.29, 81.77, 79.73, 79.01, 77.16, 75.42, 73.79, 71.09, 70.82, 68.48, 67.89, 67.57, 63.35, 54.72, 47.20, 28.14. HRMS (ESI, positive mode) calcd for $C_{55}H_{56}N_4O_{11}Na$ $[M+Na]^+$ 971.3843, found 971.3880.

6.3. Synthesis of 19

Compound **19** was prepared from compound **16** (0.57 g, 0.60 mmol) according to general procedure **C**. The residue was employed directly in the next step without further purification.

6.4. Synthesis of 22

Compound **22** was prepared from compound **16** (0.60 g, 0.63 mmol) according to general procedure **D**. The residue was filtered through a pad of silica (hexane – EtOAc, 2:1 → 0:1) and employed directly in the next step without further purification.

6.5. Synthesis of 25

Compound **25** was prepared from compound **19** (0.51 g, 0.58 mmol) and **22** (0.35 g, 0.48 mmol, 0.73 eq. per mol of acid) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane: EtOAc, 2:1) to yield **25** as a foam (0.72 g, 93%). $[\alpha]_D$ + 73.6 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.15 (m, 42H), 5.95 (d, *J* = 8.4 Hz, 1H), 5.26 – 5.16 (m, 2H), 5.13 (s, 2H), 4.83 (d, *J*= 10.7 Hz, 1H), 4.77 (dt, *J* = 5.1, 2.1 Hz, 1H), 4.75 – 4.71 (m, 1H), 4.71 – 4.63 (m, 3H), 4.63-4.52 (m, 3H), 4.38 (dd, *J* = 9.7, 6.6 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 4.28 – 4.13 (m, 4H), 4.10 (dd, *J* = 11.0, 3.3 Hz, 1H), 4.01 (d, J = 15.6 Hz, 1H), 3.95 (dd, *J* = 13.8, 2.7 Hz, 1H), 3.91 – 3.85 (m, 2H), 3.85 – 3.73 (m, 5H), 3.74 – 3.63 (m, 3H), 3.53 (t, *J* = 9.2 Hz, 1H), 3.23 (dd, *J* = 10.2, 3.6 Hz), 3.14 (dd, *J* = 10.3, 3.4 Hz), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.84, 169.43, 169.31, 168.77, 156.16, 144.02, 143.89, 141.40, 137.87, 137.60, 135.42, 135.24, 135.17, 135.05, 133.35, 133.32, 133.11, 128.80, 128.73, 128.68, 128.62, 128.55, 128.40, 128.31, 128.14, 128.05, 127.98, 127.82, 127.23, 126.69, 126.28, 126.24, 126.06, 126.04, 125.90, 125.82, 125.38, 125.31, 120.10, 99.29, 98.87, 81.65, 79.67, 79.56, 78.93, 78.61, 75.46, 75.20, 73.89, 73.74, 71.93, 70.98, 70.93, 70.73, 69.34, 68.49, 68.41, 67.92, 67.86, 67.54, 63.48, 63.13, 54.71, 52.45, 47.20, 28.14. HRMS (ESI, positive mode) calcd for $C_{91}H_{92}N_8NaO_{19}$ $[M+Na]^+$ 1624.7638, found 1624.6435.

6.6. Synthesis of 38

Compound **38** was prepared from compound **25** (0.16 g, 0.09 mmol) according to general procedure **F**. The residue was purified by silica gel chromatography (hexane: EtOAc, 1:1 → 0:1) to yield **38** as a foam (0.093 g, 71%). $[\alpha]_D$ + 86.85 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.1 Hz, 3H), 7.41 – 7.14 (m, 24H), 6.11 (d, J = 8.5 Hz, 1H), 5.24 (sq, *J* = 12.2 Hz, 2H), 5.16 (s, 2H), 4.89 – 4.68 (m, 6H), 4.64 (d, *J* = 8.1 Hz, 1H), 4.89 – 4.68 (m, 7H), 4.64 (d, *J* = 8.1 Hz, 1H), 4.45 – 4.34 (m, 3H), 4.34 – 4.17 (m, 2H), 4.16 – 4.04 (m, 2H), 4.04 – 3.95 (m, 2H), 3.92 (t, *J* = 9.5 Hz, 1H), 3.52 (m, 3H), 3.24 (dd, J = 10.1, 3.2 Hz, 1H), 3.15 (dd, J = 10.1, 3.2 Hz, 1H), 3.07 (s, 1H), 2.36 (s, 1H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.82, 169.00, 168.43, 155.21, 142.96, 140.44, 136.58, 136.51, 134.17, 134.08, 128.18, 127.83, 127.78, 127.76, 127.74, 127.66, 127.64, 127.58, 127.37, 127.21, 127.16, 127.13, 126.88, 126.25, 126.21, 124.38, 124.34, 119.15, 98.30', 98.13, 81.86, 79.56, 78.75, 77.79, 76.84, 74.35, 74.20, 70.94, 70.82, 68.59, 68.54, 68.38, 66.93, 66.49, 62.60, 62.49, 60.43, 60.32, 53.72, 51.81, 46.26, 27.15. HRMS (ESI, positive mode) calcd for $C_{69}H_{76}N_8NaO_{19}$ $[M+Na]^+$ 1343.5124, found 1343.5127.

6.7 Synthesis of 42

Compound **42** was prepared from compound **38** (0.074 g, 0.056 mmol) according to general procedure **G**. The residue was purified by silica gel chromatography (CH_2Cl_2:MeOH, 9:1) to yield **42** as a foam (0.068 g, 75%). $[\alpha]_D$ + 71.70 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.78 (d, J = 7.5 Hz, 2H), 7.66 (t, J = 6.9 Hz, 2H), 7.43 – 7.18 (m, 27H), 5.24 – 5.09 (m, 5H), 4.90 – 4.76 (m, 43H), 4.69 (dd, J = 21.8, 10.9 Hz, 3H), 4.58 (s, 1H), 4.51 – 4.31 (m, 8H), 4.28 – 4.16 (m, 9H), 4.16 – 4.08 (m, 2H), 4.08 – 3.97 (m, 6H), 3.92 (ddd, J = 13.1, 9.1, 3.6 Hz, 4H), 3.83 (dd, J = 16.9, 7.7 Hz, 3H), 3.65 – 3.57 (m, 2H), 3.50 – 3.39 (m, 2H), 3.27 (s, J = 2.1 Hz, 5H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 172.20, 171.39, 170.81, 170.53, 158.57, 145.26, 142.58, 139.40, 139.34, 137.05, 136.84, 129.72, 129.62, 129.58, 129.52, 129.46, 129.33, 129.12, 128.92, 128.82, 128.71, 128.26, 126.42, 126.37, 120.95, 99.99, 99.65, 82.77, 81.02, 80.81, 79.53, 79.47, 76.18, 75.89, 72.54, 71.41, 71.28, 71.00, 69.08, 68.68, 68.41, 68.33, 67.77, 67.54, 64.77, 64.36, 55.98, 53.86, 48.45, 28.39. HRMS (ESI, negative mode) calcd for $C_{69}H_{76}N_8O_{25}S_2$ $[M-2]^{2-}$ *m/z* 739.2109, found 739.2097.

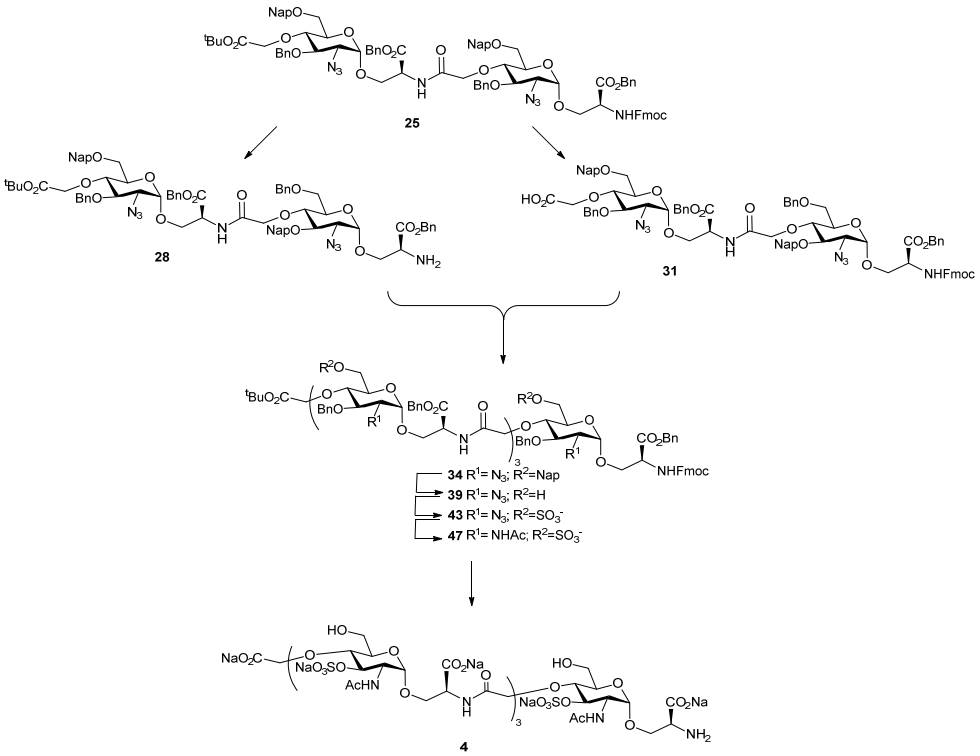
6.8 Synthesis of 46

Compound **46** was prepared from compound **42** (0.12 g, 0.082 mmol) according to general procedure **H**. The residue was purified by silica gel chromatography (CH_2Cl_2:MeOH, 9:1 → 7:1) to yield **46** as a foam (0.098 g, 75%). $[\alpha]_D$ + 48.66 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) 7.78 (d, J = 7.5 Hz, 2H), 7.70 (m, 2H), 7.43 – 7.19 (m, 24H), 5.19 (m, 4H), 4.96 (d, J = 3.1 Hz, 1H), 4.84 (m, 1H), 4.72 (m, 4H), 4.60 (d, J = 3.1 Hz, 1H), 4.57 – 4.15 (m, 14H), 4.07 (m, 3H), 4.01 – 3.89 (m, 3H), 3.82 (m, 1H), 3.74 – 3.67 (m, 1H), 3.55 (t, J = 9.4 Hz, 1H), 3.48 (t, J = 9.4 Hz, 1H), 1.97 (s, 3H), 1.90 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 173.85, 173.23, 172.17, 171.87, 171.06, 170.83, 158.81, 145.24, 142.57, 139.98, 139.75, 136.88, 129.83, 129.65, 129.38, 128.86, 128.79, 128.60, 128.29, 126.40, 120.88, 101.06, 99.76, 82.67, 81.67, 81.22, 80.55, 79.41, 76.50, 76.08, 73.06, 72.14, 71.89, 71.63, 70.85, 68.59, 68.27, 67.25, 56.35, 54.66, 54.29, 48.36, 28.37, 23.11, 22.90. HRMS (ESI, negative mode) calcd for $C_{73}H_{84}N_4O_{27}S_2$ $[M-2]^{2-}$ *m/z* 755.2309, found 755.2289.

6.9. Synthesis of 3

Compound **3** was prepared from compound **46** in three steps. In the first one, the N-Fmoc amine of **46** (72 mg, 0.046 mmol) was deprotected according to general procedure **D**. The amine was employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**. The amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column (Na^+ form) and eluted with water to afford compound **3** as a foam (20 mg, 73%). $[\alpha]_D$ + 26.04 (c 1.0, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 4.90 (t, J = 3.6 Hz, 1H), 4.87 (d, J = 3.4 Hz, 1H), 4.53 – 4.44 (m, 1H), 4.42 (dd, J = 8.6, 3.2 Hz, 1H), 4.39 – 4.23 (m, 5H), 4.19 – 4.14 (m, 1H), 4.15 – 4.10 (m, 1H), 4.08 – 3.87 (m, 6H), 3.86 – 3.76 (m, 1H), 3.59 (ddt, J = 11.7, 8.9, 4.4 Hz, 1H), 3.50 – 3.43 (m, 1H), 2.16 – 1.98 (s, 6H). ^{13}C NMR (126 MHz, D_2O) δ 178.24, 175.16, 174.18, 173.98, 173.93, 171.60, 171.51, 171.25, 162.80, 162.52, 119.47, 117.15, 114.82, 112.50, 97.58, 97.51, 97.42, 97.33, 79.28, 79.19, 79.09, 79.04, 78.89, 71.31, 71.24, 71.12, 71.05, 70.83, 70.23, 70.11, 69.93, 69.87, 69.85, 69.26, 68.96, 68.93, 68.91, 68.88, 68.83, 68.14, 66.27, 66.25, 66.20, 66.17, 66.00, 65.98, 65.70, 62.14, 54.25, 54.09, 54.05, 53.97, 53.87, 53.61, 53.30, 53.22, 53.19, 53.09, 53.05, 52.93, 52.81, 21.73, 21.66, 21.64, 21.62, 21.59, 19.71. HRMS (ESI, negative mode) calcd for $C_{26}H_{42}N_4O_{25}S_2$ $[M-2]^{2-}$ *m/z* 436.0717, found 436.0714

7. Synthesis of compound 4



7.1. Synthesis of 28

Compound **28** was prepared from compound **25** (0.256 g, 0.16 mmol) according to general procedure **D**. The residue was filtered through a pad of silica (hexane: EtOAc, 1:2 → 0:1) and employed directly in the next step without further purification.

7.2. Synthesis of 31

Compound **31** was prepared from compound **25** (0.313 g, 0.19 mmol) according to general procedure **C**. The residue was employed directly in the next step without further purification.

7.3. Synthesis of 34

Compound **34** was prepared from compound **28** (0.189 g, 0.137 mmol) and **31** (0.23 g, 0.15 mmol) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane: EtOAc, 1:1) to yield **34** as a foam (0.30 g, 76%). $[\alpha]_D$ +86.6 (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 6.96 (m, 76H), 5.87 (d, J = 8.5 Hz, 1H), 5.19 – 5.07 (m, 2H), 5.05 – 4.90 (m, 7H), 4.73 (d, J = 10.7 Hz, 1H), 4.69 – 4.43 (m, 25H), 4.32 – 4.24 (m, 1H), 4.23 – 4.03 (m, 7H), 4.01 (s, 0H), 3.93 (d, J = 15.7 Hz, 1H), 3.79 – 3.40 (m, 30H), 3.08 (td, J = 10.7, 3.6 Hz, 2H), 2.95 (ddd, J = 19.7, 10.3, 3.5 Hz, 2H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.88, 143.73, 141.28, 137.78, 137.45, 137.39, 137.37, 135.32, 135.17, 135.08, 135.03, 134.94, 134.92, 133.22, 133.18, 133.01, 132.99, 128.85, 128.67, 128.61, 128.57, 128.52, 128.47, 128.44, 128.42, 128.31, 128.28, 128.17, 128.05, 128.03, 128.00, 127.95, 127.92, 127.91, 127.83, 127.74, 127.70, 127.11, 127.08, 126.61, 126.56, 126.54, 126.20, 126.17, 126.14, 125.99, 125.97, 125.93, 125.82, 125.78, 125.71, 125.68, 125.23, 125.15, 120.00, 99.10, 98.69, 98.52, 81.51, 79.57, 79.37, 79.33, 79.25, 78.85, 78.50, 78.35, 78.30, 75.30, 75.09, 75.04, 73.75, 73.72, 73.70, 73.60, 71.73, 71.64, 71.52, 70.90, 70.77, 70.67, 70.62, 69.31, 68.42, 68.30, 67.74, 67.68, 67.63, 67.56, 67.36, 65.58, 63.31, 63.13, 63.08, 63.03, 54.57, 52.40, 52.27, 52.22, 47.09, 28.03. HRMS (ESI, positive mode) calcd for $C_{163}H_{164}N_{16}NaO_{35}$ $[M+Na]^+$ *m/z* 2929.1476, found 2929.1523.

7.4. Synthesis of 39

Compound **39** was prepared from compound **34** (0.16 g, 0.055 mmol) according to general procedure **F**. The residue was purified by silica gel chromatography (CH_2Cl_2: MeOH, 10:1) to yield **39** as a foam (84 mg, 65%). $[\alpha]_D$ + 92.0 (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.60 (m, 3H,), 7.53 (m, 4H), 7.24 (m, 44H), 5.93 (d, J = 8.6 Hz, 1H), 5.22 – 4.99 (m, 8H), 4.83 – 4.46 (m, 16H), 4.44 – 3.26 (m, 27H), 3.21 – 2.97 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.61, 169.89, 169.69, 169.64, 169.57, 169.54, 169.52, 169.35, 156.02, 143.82, 141.29, 137.47, 137.41, 137.38, 135.02, 134.93, 134.90, 128.73, 128.70, 128.68, 128.61, 128.58, 128.54, 128.47, 128.41, 128.13, 128.10, 128.06, 128.04, 128.00, 127.96, 127.75, 127.12, 125.22, 120.01, 99.26, 99.06, 98.98, 98.92, 82.63, 80.37, 79.60, 78.93, 78.81, 78.57, 77.84, 77.37, 77.26, 77.05, 76.74, 75.27, 75.06, 75.01, 71.70, 69.47, 69.22, 67.85, 67.79, 67.38, 63.40, 63.33, 61.26, 61.20, 54.53, 52.70, 52.63, 52.51, 47.12, 28.04. HRMS (ESI, positive mode) calcd for $C_{119}H_{135}N_{16}O_{36}$ $[M+H_3O]^+$ *m/z* 2363,9225, found 2363.9504.

7.5. Synthesis of 43

Compound **43** was prepared from compound **39** (83 mg, 0.035 mmol) according to general procedure **G**. The residue was purified by silica gel chromatography (CH_2Cl_2: MeOH, 10:1) to yield **43** as a foam (60 mg, 60%). $[\alpha]_D$ + 69.4 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.76 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 8.8 Hz, 2H), 7.54 – 7.07 (m, 44H), 5.15 m, 8H), 4.83 – 4.61 (m,11H), 4.60 – 4.49 (m, 1H), 4.49 – 3.73 (m, 34H), 3.71 – 3.50 (m, 3H), 3.45 (t, J = 9.3 Hz,1H), 3.28 – 3.06 (m, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 171.12, 170.87, 169.99, 169.45, 169.30, 169.26, 157.07, 143.92, 143.80, 141.16, 138.07, 137.98, 137.92, 135.58, 135.48, 135.37, 128.47, 128.40, 128.36, 128.25, 128.21, 128.19, 128.16, 128.12, 128.09, 128.00, 127.98, 127.93, 127.79, 127.75, 127.60, 127.53, 127.46, 127.36, 126.91, 125.02, 119.63, 98.67, 98.60, 98.46, 98.30, 81.41, 79.64, 79.31, 79.29, 79.26, 78.18, 78.05, 74.70, 74.47, 71.24, 71.07, 71.06, 71.03, 70.04, 69.81, 69.63, 67.61, 67.22, 67.16, 67.05, 66.97, 66.21, 66.10, 66.04, 65.95, 63.15, 62.96, 54.48, 52.54, 52.40, 48.28, 48.13, 48.06, 47.92, 47.85, 47.64, 47.43, 47.21, 47.00, 46.92, 29.35, 27.04. HRMS (ESI, negative mode) calcd for $C_{119}H_{132}N_{16}O_{47}S_4$ $[M-4]^{4-}$ *m/z* 665.1755, found 665.4258.

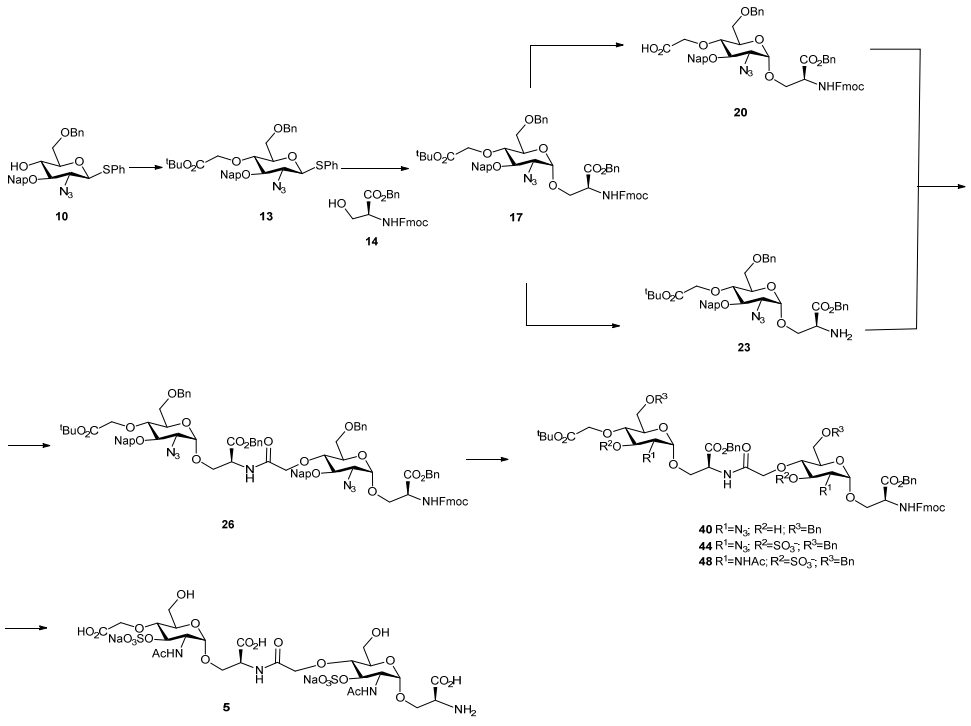
7.6. Synthesis of 47

Compound **47** was prepared from compound **43** (94 mg, 0.035 mmol) according to general procedure **H**. The residue was purified by silica gel chromatography (EtOAc: MeOH, 4:1) to yield **47** as a foam (80 mg, 82%). $[\alpha]_D$ + 58.3 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.77 (dd, J = 7.6, 4.8 Hz, 2H), 7.66 (dd, J = 18.5, 7.6 Hz, 2H), 7.26 (m, 45H), 5.25 – 4.99 (m, 8H), 4.9 - 4.7 (m), 4.57 (bs, 3H), 4.51 – 3.74 (m, 39H), 3.67 – 3.37 (m, 5H), 2.05 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H), 1.85 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 172.58, 172.49, 172.06, 171.86, 171.17, 170.78, 170.56, 170.31, 169.87, 169.55, 169.49, 157.21, 143.89, 143.74, 141.22, 141.15, 138.59, 138.55, 138.53, 135.61, 135.58, 135.40, 128.39, 128.35, 128.30, 128.19, 128.13, 128.07, 128.03, 128.00, 127.97, 127.94, 127.90, 127.75, 127.47, 127.28, 126.91, 125.03, 124.91, 119.63, 99.39, 99.09, 98.33, 81.55, 98.29, 80.13, 79.89, 79.80, 79.07, 78.74, 78.54, 78.24, 75.20, 74.99, 74.84, 74.54, 71.65, 71.57, 70.06, 69.80, 69.56, 67.05, 69.45, 66.96, 66.89, 66.10, 54.72, 53.47, 53.37, 53.13, 53.06, 52.75, 52.38, 27.01, 21.98, 21.91, 21.80, 21.72. HRMS (ESI, negative mode) calcd for $C_{127}H_{144}N_8O_{51}S_4$ [M-4]$^{4-}$ *m/z* 681.1958, found 681.6987.

7.7. Synthesis of 4

Compound **4** was prepared from compound **47** in three steps. In the first one, the N-Fmoc amine of **47** (0.12 g, 0.044 mmol) was deprotected according to general procedure **D**. The amine was employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**. The amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column (Na^+ form) and eluted with water to afford compound **4** as a foam (36.5 mg, 57%). $[\alpha]_D$ + 83.4 (c 1.0, H_2O) ^{1}H NMR (500 MHz, D_2O) δ 4.80 – 4.70 (m, 4H), 4.41 – 4.08 (m, 18H), 4.06 – 3.63 (m, 22H), 3.44 (m, 3H), 3.36 – 3.27 (m, 1H), 1.92 (m, 12H). ^{13}C NMR (101 MHz, D_2O) δ 175.44, 174.46, 174.31, 172.10, 172.01, 98.12, 97.75, 97.57, 79.42, 79.36, 79.29, 71.43, 71.15, 71.04, 70.46, 70.40, 70.06, 69.37, 69.14, 68.96, 68.49, 66.83, 66.55, 66.40, 66.21, 54.88, 54.79, 54.69, 54.47, 53.49, 53.38, 53.32, 22.01, 21.97, 21.94. HRMS (ESI, negative mode) calcd for $C_{52}H_{69}N_8NaO_{49}S_4$ [M+Na-5]$^{5-}$ *m/z* 291.0401, found 291.0397.

8. Synthesis of compound 5



8.1. Synthesis of compound 13

Compound **13** was prepared from compound **10** (1.0 g, 1.9 mmol) following general procedure **A**. The residue was purified by silica gel chromatography (hexane:EtOAc, 5:1) to yield **11** as a foam (1.14 g, 93%). $[\alpha]_D$ -27.0 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.5 Hz, 4H), 7.64 (dd, J = 6.9, 1.7 Hz, 2H), 7.54 – 7.47 (m, 3H), 7.42 – 7.25 (m, 9H), 5.06 (s, 2H), 4.68 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 10.1 Hz, 1H), 4.28 (d, J = 15.6 Hz, 1H), 4.17 (d, J = 15.7 Hz, 1H), 3.90 (d, J = 2.1 Hz, 2H), 3.65 – 3.52 (m, 3H), 3.38 (t, J = 9.5 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.84, 138.31, 135.13, 133.67, 133.33, 133.11, 131.15, 129.00, 128.39, 128.37, 128.26, 127.99, 127.69, 127.60, 127.55, 127.08, 126.12, 126.11, 126.03, 86.03, 84.78, 81.70, 79.03, 78.44, 75.82, 73.45, 70.64, 68.82, 65.07, 28.09.

8.2. Synthesis of compound 17

Compound **17** was prepared from compound **13** (1.22 g, 1.9 mmol) and N-Fmoc- L-serine benzyl ester (**14**, 1.03 g, 2.47 mmol) according to general procedure **B**. The residue was purified by silica gel chromatography (hexane: EtOAc, 5:1 → 3:1) to yield **17** (1.17 g, 65 %) and the β-anomer (0.39 g, 22%). $[\alpha]_D$ + 67.0 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 4H), 7.78 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.55 – 7.46 (m, 3H), 7.41 – 7.25 (m, 14H), 5.97 (d, J = 8.3 Hz, 1H), 5.24 (s, 2H), 5.05 (m, 2H), 4.83 (d, J = 3.6 Hz, 1H), 4.67 – 4.58 (m, 2H)), 4.49 (d, J = 12.0 Hz, 1H), 4.41 (dd, J = 10.5, 7.6 Hz, 1H), 4.34 (dd, J = 10.4, 7.3 Hz, 1H), 4.29 – 4.23 (m, 2H), 4.15 – 3.98 (m, 4H), 3.92 – 3.79 (m, 2H), 3.71 (dd, J = 10.9, 1.8 Hz, 1H), 3.62 (t, J = 9.4 Hz, 1H), 3.31 (dd, J = 10.3, 3.6 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.57, 168.72, 155.99, 143.86, 143.83, 141.27, 137.76, 135.35, 135.06, 133.32, 133.06, 128.66, 128.56, 128.47, 128.45, 128.37, 128.20, 127.97, 127.84, 127.73, 127.71, 127.70, 127.67, 127.15, 126.78, 126.07, 125.98, 125.95, 125.26, 119.95, 99.12, 81.65, 79.60, 78.94, 77.36, 77.05, 76.73, 75.33, 73.52, 70.95, 70.72, 69.40, 68.14, 67.77, 67.47, 63.22, 54.58, 47.09, 28.06. HRMS (ESI, positive mode) calcd for $C_{55}H_{56}N_4O_{11}$ $[M+NH_4]^+$ *m/z* 966.42838, found 966.42881.

8.3. Synthesis of compound 20

Compound **20** was prepared from compound **17** (0.706 g, 0.74 mmol) according to general procedure **C**. After concentration the residue was purified by flash column chromatography (hexane – EtOAc, 2:1 → 0:1) to give a syrup that was employed directly in the next step without further purification.

8.4. Synthesis of compound 23

Compound **23** was prepared from compound **17** (0.5 g, 0.53 mmol) according to general procedure **D**. The residue was filtered through a pad of silica (hexane – EtOAc, 1:1 → 0:1) and employed directly in the next step without further purification.

8.5 Synthesis of compound 26

Compound **26** was prepared from compound **20** (0.24 g, 0.155 mmol) and **21** (0.388 g, 0.53 mmol) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane: EtOAc, 2:1) to yield **26** (0.731 g, 86 %). $[\alpha]_D$ +75.0 (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 10H), 7.52 – 7.46 (m, 2H), 7.44 – 7.10 (m, 32H), 5.86 (d, J = 8.5 Hz, 1H), 5.16 – 4.97 (m, 4H), 4.85 (m, 4H), 4.70 (d, J = 3.5 Hz, 1H), 4.64 – 4.56 (m, 2H), 4.49 (m, 3H), 4.43 – 4.22 (m, 4H), 4.20 – 3.97 (m, 5H), 3.96 – 3.78 (m, 4H), 3.77 – 3.52 (m, 6H), 3.46 (t, J = 9.3 Hz, 1H), 3.17 (dd, J = 10.2, 3.6 Hz, 1H), 3.07 (dd, J = 10.3, 3.5 Hz, 1H), 1.31 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.44, 169.03, 168.97, 168.42, 155.79, 143.55, 141.05, 137.61, 137.41, 119.75, 98.93, 98.58, 81.31, 79.39, 79.23, 78.65, 78.23, 77.16, 76.84, 76.52, 75.21, 74.88, 73.41, 73.27, 71.57, 70.66, 70.59, 70.41, 68.93, 67.93, 67.59, 67.52, 67.49, 67.22, 63.16, 62.82, 60.17, 54.38, 52.16, 46.86, 27.79. HRMS (ESI, positive mode) calcd for $C_{91}H_{92}N_8O_{19}$ $[M+Na]^+$ *m/z* 1623.63709, found 1623.63735.

8.6 Synthesis of compound 40

Compound **40** was prepared from compound **26** (0.5 g, 0.312 mmol) according to general procedure **F**. The residue was purified by silica gel chromatography (hexane: EtOAc, 3:1 → 1:1) to yield **40** (0.31 g, 75%). $[\alpha]_D$ +97.1 (c 1.0,

$CHCl_3$). IR (KBr): 3420, 2925, 2109, 1728, 1682, 1250, 1037, 741 and 698 cm-^{1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 6.5 Hz, 2H), 7.39 – 7.12 (m, 24H), 5.96 (d, J = 8.2 Hz, 1H), 5.33 (d, J = 1.6 Hz, 1H), 5.17 (d, J = 14.2 Hz, 4H), 4.85 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 3.3, Hz, 1H), 4.67 (d, J = 3.3, 1H) 4.63 – 4.22 (m, 9H), 4.17 (t, J = 7.4 Hz, 1H), 4.12 – 3.74 (m, 11H), 3.73 – 3.48 (m, 6H), 3.44 (t, J = 9.4 Hz, 1H), 3.33 (q, J = 9.2, 8.4 Hz, 1H), 3.08 (dd, J = 10.3, 3.6 Hz, 1H), 2.97 (dd, J = 10.3, 3.6 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 172.02, 170.74, 170.08, 169.57, 155.99, 143.91, 143.86, 141.28, 137.41, 135.07, 134.83, 128.73, 128.68, 128.66, 128.55, 128.48, 128.46, 128.07, 128.00, 127.93, 127.69, 127.10, 125.25, 125.20, 119.94, 98.97, 98.80, 83.13, 81.12, 80.68, 77.36, 77.24, 77.04, 76.72, 73.65, 73.63, 71.54, 70.78, 70.56, 70.44, 70.22, 69.03, 68.13, 68.05, 67.80, 67.71, 67.42, 63.19, 63.10, 54.59, 52.23, 47.08, 29.70, 28.02. HRMS (ESI, positive mode) calcd for $C_{69}H_{76}N_8O_{19}$ $[M+NH4]^+$ *m/z* 1338.5565, found 1338.55276.

8.7 Synthesis of compound 44

Compound **44** was prepared from compound **40** (0.08 g, 0.06 mmol) according to general procedure **F**. The residue was purified by flash chromatography (EtOAc:MeOH, 1:0 → 10:1) to yield **44** (0.088 g, 90%).$[\alpha]_D$ +43.6 (c 1.0, $CHCl_3$). IR (KBr): 3424, 2928, 2116, 1737, 1682, 1251, 1046, 740 and 698 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.40 – 7.21 (m, 24H), 5.24 – 5.08 (m, 4H), 4.90 (d, J = 3.5 Hz, 2H), 4.82 (m, 3H), 4.61 – 4.40 (m, 6H), 4.32 (dd, J = 10.4, 7.3 Hz, 1H), 4.28 – 4.12 (m, 2H), 4.02 (m, 4H), 3.93 – 3.75 (m, 2H), 3.73 – 3.65 (m, 3H, H-6), 3.58 (t, J = 9.4 Hz, 1H), 3.49 (dd, J = 11.0, 7.9 Hz, 1H), 3.15 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.32, 170.48, 169.88, 169.17, 157.11, 143.85, 141.15, 138.07, 138.01, 135.59, 135.55, 128.23, 128.21, 128.10, 128.04, 128.02, 127.97, 127.91, 127.72, 127.63, 127.43, 127.38, 127.30, 126.89, 125.07, 125.00, 119.55, 99.01, 98.75, 81.91, 78.13, 77.68, 77.45, 76.99, 73.06, 70.54, 70.49, 70.08, 68.64, 68.33, 67.11, 67.06, 66.96, 61.91, 61.80, 54.57, 52.54, 27.02. HRMS (ESI, negative mode) calcd for $C_{69}H_{76}N_8O_{25}S_2$ $[M-2H]^{2-}$ *m/z* 739.21087, found 739.20596.

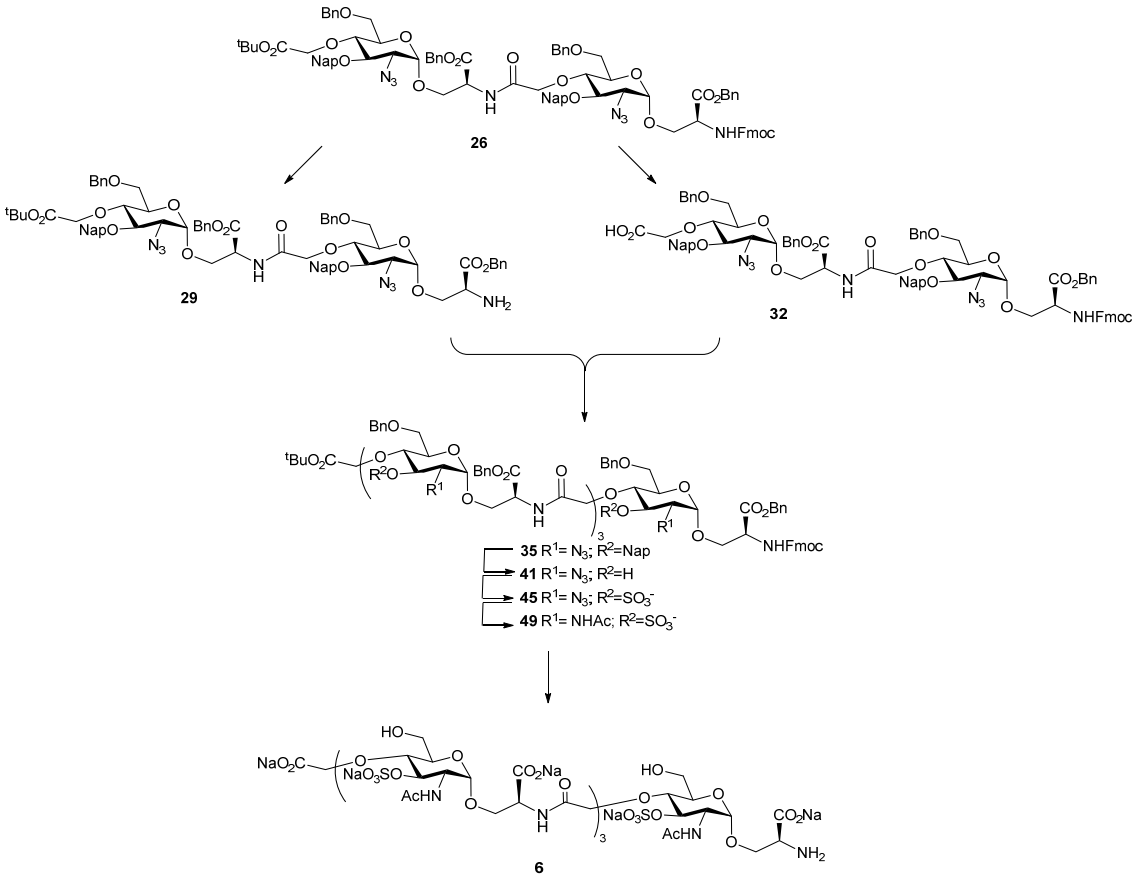
8.8 Synthesis of compound 48

Compound **48** was prepared from compound **44** (0.05 g, 0.03 mmol) according to general procedure **H**. The residue was purified by silica gel chromatography (EtOAc:MeOH, 8:0 → 8:1) to yield **48** (0.047 g, 91%). $[\alpha]_D$ +64.3 (c 1.0, $CHCl_3$). IR (KBr): 3438, 2930, 2468, 1741, 1664, 1256, 1041, 741 and 698 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 7.6 Hz, 2H), 7.66 (dd, J = 7.6, 3.6 Hz, 2H), 7.30 (m, 24H), 5.17 (s, 2H), 5.14 (s, 2H), 4.93 (d, J = 3.4 Hz, 1H), 4.88 (d, J = 3.4 Hz, 1H), 4.73 (t, J = 5.2 Hz, 1H), 4.70 – 4.58 (m, 2H), 4.58- 4.26 (m, 8H), 4.19 (d, J = 11.5 Hz, 2H), 4.09 (d, J = 16.2 Hz, 1H), 4.02 – 3.67 (m, 10H), 3.60 (t, J = 9.5 Hz, 1H), 3.51 (t, J = 9.4 Hz, 1H), 1.94 (s, 3H), 1.93 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 173.96, 173.90, 172.79, 171.90, 171.65, 170.90, 158.76, 145.43, 145.38, 142.77, 142.74, 139.74, 139.64, 137.14, 137.11, 129.86, 129.80, 129.68, 129.62, 129.58, 129.56, 129.51, 129.20, 129.14, 129.01, 128.88, 128.47, 128.44, 126.57, 126.48, 121.14, 99.63, 99.36, 83.22, 79.86, 79.04, 78.94, 78.24, 74.64, 74.59, 73.16, 72.53, 72.34, 71.47, 70.20, 70.11, 69.57, 68.55, 68.46, 56.26, 55.04, 54.92, 54.10, 28.58, 23.38, 23.35. HRMS (ESI, negative mode) calcd for $C_{73}H_{84}N_4O_{27}S_2$ $[M-2H]^{2-}$ *m/z* 755.23094, found 755.23141.

8.9 Synthesis of compound 5

Compound **5** was prepared from compound **48** in three steps. In the first one, the N-Fmoc amine of **48** (45 mg, 0.028 mmol) was deprotected according to general procedure **D**. The amine was employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**. The amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column (Na^+ form) and eluted with water to afford compound **5** (18 mg, 63% from **48**). $[\alpha]_D$ +76.4 (c 0.9, H_2O). IR (KBr): 3443, 2950, 1681, 1549, 1426, 1237, 1208, 1139, 1052, 826, 802, 723 and 587 cm^{-1}. ^{1}H NMR (500 MHz, D_2O) δ 4.79 (d, J = 3.6 Hz, 1H), 4.77 (d, J = 3.6 Hz, 1H), 4.56 (dd, J = 10.7, 8.9 Hz, 1H), 4.49 – 4.39 (m, 2H), 4.37 (dd, J = 5.0, 3.5 Hz, 1H), 4.31 (d, J = 16.2 Hz, 1H), 4.13 (d, J = 15.6 Hz, 1h), 4.10 (d, J = 8.5 Hz, 1H), 4.04 (ddd, J = 10.1, 8.8, 3.3 Hz, 2H), 3.98 (dd, J = 10.7, 3.7 Hz, 1H), 3.93 – 3.86 (m, 2H), 3.84-3.66 (m, 7H), 3.64 – 3.59 (m, 1H), 3.56 (t, J = 9.4 Hz, 1H), 3.48 (t, J = 9.5 Hz, 1H), 1.91 – 1.88 (2s, 3H each).^{13}C NMR (126 MHz, D_2O) δ 176.46, 174.48, 174.42, 171.62, 98.02, 97.87, 79.58, 78.65, 77.00, 76.60, 71.16, 71.11, 71.09, 70.35, 68.60, 66.12, 60.24, 60.18, 54.31, 52.22, 52.04, 22.10. HRMS (ESI, negative mode) calcd for $C_{26}H_{39}N_4O_{25}S_2$ $[M-3H]^{3-}$ m/z 290.3782, found 290.37828.

9. Synthesis of compound 6



9.1. Synthesis of 29

Compound **29** was prepared from compound **26** (0.29 g, 0.18 mmol) according to general procedure **D**. The residue was filtered through a pad of silica (hexane – EtOAc, 1:1 → 0:1) and employed directly in the next step without further purification.

9.2. Synthesis of 32

Compound **32** was prepared from compound **26** (0.282 g, 0.176 mmol) according to general procedure **C**. The residue was filtered through a pad of silica (hexane – EtOAc, 1:1 → 0:1) and employed directly in the next step without further purification.

9.3. Synthesis of 35

Compound **35** was prepared from compound **32** (0.20 g, 0.13 mmol) and **29** (0.17 g, 0.12 mmol) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane: EtOAc, 3:1 → 1:1) to yield **35** as a foam (0.272 g, 75%). $[\alpha]_D$ +86.8 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.65 (m, 20H), 7.57 (d, J = 7.5 Hz, 2H), 7.51 – 7.15 (m, 42H), 5.94 (d, J = 8.4 Hz, 1H), 5.23 – 4.77 (m, 18H), 4.75 (d, J = 3.6 Hz, 1H), 4.70 – 4.35 (m, 16H), 4.31 (d, J = 15.3 Hz, 1H), 4.29 – 4.01 (m, 10H), 4.00 – 3.79 (m, 8H), 3.21 – 3.17 (m, 1H), 3.15 (dd, J = 10.3, 3.6 Hz, 1H), 3.08 (dd, J = 10.2, 3.6 Hz, 1H), 3.02 (dd, J = 10.2, 3.6 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.62, 169.30, 169.27, 169.22, 169.20, 168.64, 155.93, 143.86, 143.72, 141.26, 137.79, 137.65, 137.63, 137.57, 137.50, 135.34, 134.99, 134.97, 134.94, 134.87, 134.83, 133.28, 133.26, 133.24, 133.21, 133.05, 132.99, 128.71, 128.65, 128.59, 128.57, 128.48, 128.45, 128.43, 128.38, 128.36, 128.32, 128.28, 128.14, 128.06, 128.04, 127.96, 127.91, 127.86, 127.82, 127.79, 127.75, 127.73, 127.65, 127.57, 127.11, 127.08, 126.92, 126.66, 126.59,

126.14, 126.12, 126.10, 126.05, 126.03, 126.00, 125.92, 125.88, 125.85, 125.78, 125.72, 125.68, 125.23, 125.15, 119.99, 99.04, 98.71, 98.57, 81.53, 79.59, 79.35, 79.30, 79.27, 78.84, 78.42, 78.27, 78.23, 77.31, 77.06, 76.80, 75.38, 75.20, 75.18, 75.09, 73.57, 73.54, 73.52, 73.45, 71.71, 71.61, 71.51, 70.86, 70.71, 70.65, 70.63, 70.60, 69.19, 68.17, 68.07, 68.05, 67.73, 67.71, 67.68, 67.63, 67.55, 67.38, 67.29, 63.28, 63.11, 63.06, 63.00, 54.54, 52.39, 52.28, 52.25, 47.07, 28.06. HRMS (ESI, positive mode) calcd for $C_{163}H_{164}N_{16}O_{35}$ $[M+Na]^+$ *m/z* 2930.15002, found 2930.15644.

9.4. Synthesis of 41

Compound **41** was prepared from compound **35** (0.2 g, 0.07 mmol) according to general procedure **F**. The residue was purified by silica gel chromatography (hexane: EtOAc, 1:1 → 1:2) to yield **41** (0.11 g, 69%). $[\alpha]_D$ +91.8 (c 1.0, $CHCl_3$). IR (KBr): 3417, 2925, 2109, 1731, 1676, 1252, 1147, 1040, 741 and 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 6.4 Hz, 2H), 7.21 (m, 44H), 6.33 (d, J = 8.4 Hz, 1H), 5.31 (s, 1H), 5.18 – 4.96 (m, 9H), 4.91 – 4.17 (m, 20H), 4.16 – 3.70 (m, 14H), 3.69 – 3.36 (m, 17H), 3.30 (t, J = 9.2 Hz, 1H), 3.05 (dd, J = 10.3, 3.6 Hz, 1H), 2.91 (m, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.98, 171.25, 170.83, 170.60, 170.17, 170.03, 169.92, 169.73, 156.25, 143.95, 141.36, 137.75, 137.65, 137.60, 137.51, 135.24, 135.05, 135.00, 128.84, 128.80, 128.77, 128.71, 128.67, 128.63, 128.59, 128.49, 128.15, 128.11, 128.09, 128.05, 128.01, 127.99, 127.84, 127.21, 125.39, 125.32, 120.07, 99.02, 98.84, 98.63, 83.17, 80.86, 80.56, 80.31, 80.22, 77.48, 77.36, 77.16, 76.84, 73.75, 73.72, 73.69, 71.27, 70.96, 70.67, 70.59, 70.55, 70.44, 70.34, 70.04, 69.23, 69.16, 68.49, 68.22, 68.03, 67.84, 67.47, 65.97, 63.49, 63.28, 54.66, 52.37, 52.20, 47.19, 29.19, 28.15, 27.80. HRMS (ESI, positive mode) calcd for $C_{119}H_{132}N_{16}O_{35}$ $[M+NH4]^+$ *m/z* 2363.94104, found 2363.94203.

9.5 Synthesis of compound 45

Compound **45** was prepared from compound **41** (0.101 g, 0.043 mmol) according to general procedure **F**. The residue was purified by flash chromatography (CH_2Cl_2:MeOH, 20:1) to yield **45** (0.076 g, 67%).$[\alpha]_D$ +48.2 (c 1.0, $CHCl_3$). IR (KBr): 3436, 2927, 2457, 2116, 1741, 1673, 1259, 1151, 1044, 741 and 699 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.40 – 7.18 (m, 44H), 5.23 – 5.06 (m, 8H), 4.89 (m, 4H), 4.63 – 4.36 (m, 13H), 4.36 – 3.56 (m, 33H), 3.52 (t, J = 9.4 Hz, 1H), 3.17 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.59, 171.41, 170.55, 169.85, 169.25, 169.12, 169.06, 157.10, 143.84, 141.15, 138.12, 138.10, 138.05, 135.60, 135.56, 135.52, 128.26, 128.23, 128.22, 128.10, 128.06, 128.05, 127.98, 127.93, 127.71, 127.68, 127.63, 127.44, 127.38, 127.31, 126.90, 125.08, 125.01, 119.56, 98.97, 98.76, 81.92, 77.94, 77.81, 77.67, 76.85, 73.10, 73.08, 73.04, 70.96, 70.81, 70.50, 70.30, 70.11, 68.42, 67.92, 67.22, 67.13, 67.05, 61.92, 61.84, 61.78, 54.56, 53.75, 52.68, 52.59, 27.03. HRMS (ESI, negative mode) calcd for $C_{119}H_{132}N_{16}O_{47}S_4$ $[M-4H]^{4-}$ *m/z* 665.42632, found 665.42323.

9.6 Synthesis of compound 49

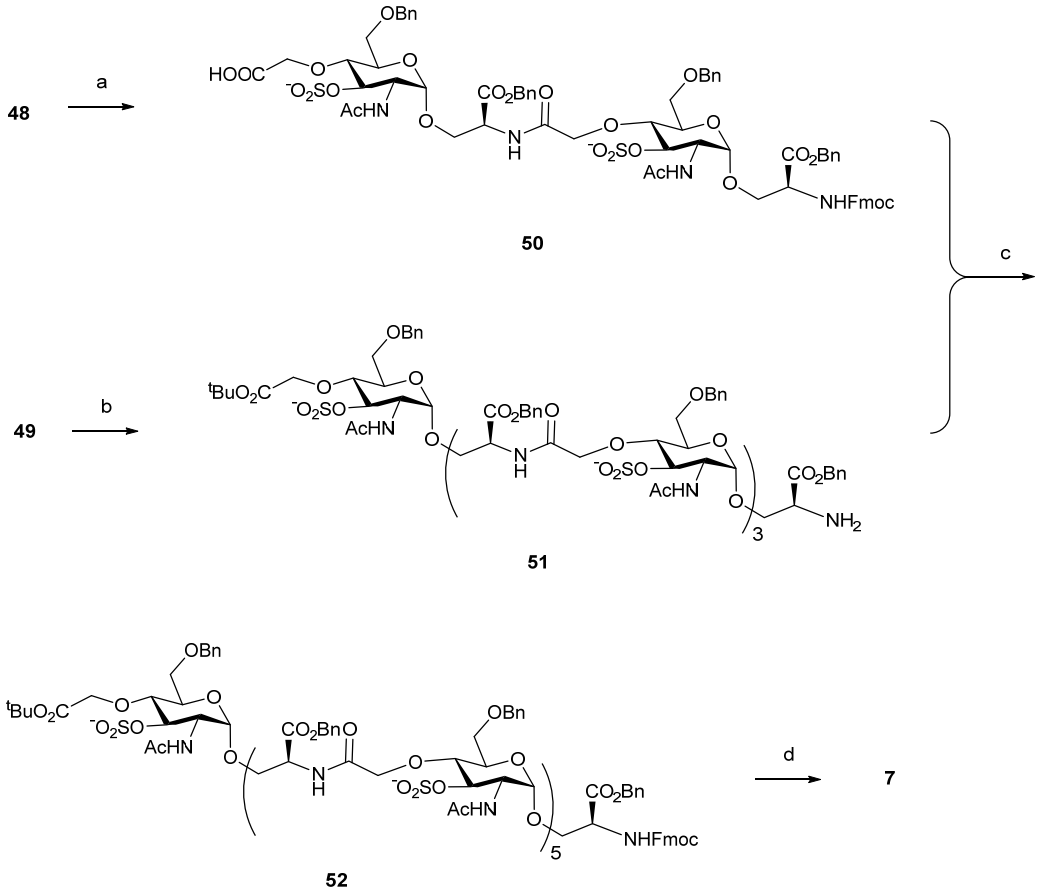
Compound **49** was prepared from compound **45** (0.075 g, 0.028 mmol) according to general procedure **H**. The residue was purified by silica gel chromatography (EtOAc:MeOH, 8:0 → 8:1) to yield **49** (0.05 g, 66%). $[\alpha]_D$ +45.6 (c 1.0, $CHCl_3$). IR (KBr): 3427, 2928, 2454, 1741, 1664, 1258, 1048, 742 and 699 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.77 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 2H), 7.41 – 7.14 (m, 44H), 5.15 (broad s, 8H), 4.92 (m, 4H), 4.72 (m, 3H), 4.69 – 4.59 (m, 4H), 4.55-4.45 (m, 10H), 4.41 – 4.13 (m, 9H), 4.09 (d, J = 16.4 Hz, 1H), 4.04 – 3.56 (m, 30H), 3.52 (t, J = 9.4 Hz, 1H), 2.00-1.93 (12H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 172.66, 172.63, 172.58, 172.39, 171.38, 171.30, 170.32, 170.07, 169.33, 169.30, 157.15, 143.87, 143.77, 141.19, 141.17, 138.14, 138.03, 135.56, 135.53, 128.30, 128.26, 128.24, 128.08, 128.04, 128.02, 127.97, 127.95, 127.66, 127.63, 127.60, 127.54, 127.46, 127.36, 127.34, 126.92, 126.89, 125.04, 124.92, 119.59, 98.08, 97.90, 97.79, 81.68, 78.33, 77.63, 77.47, 76.73, 73.11, 73.04, 71.62, 71.41, 70.97, 70.79, 70.66, 69.91, 68.55, 68.03, 67.81, 67.13, 67.01, 66.91, 62.85, 54.69, 53.77, 53.38, 53.28, 52.74, 52.64, 27.03, 21.97, 21.83. HRMS (ESI, negative mode) calcd for $C_{127}H_{148}N_8O_{51}S_4$ $[M-4H]^{4-}$ *m/z* 681.44643, found 681.44615.

9.7 Synthesis of compound 6

Compound **6** was prepared from compound **49** in three steps. In the first one, the N-Fmoc amine of **49** (50 mg, 0.018 mmol) was deprotected according to general procedure **D**. The amine was employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**.

The amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column (Na^+ form) and eluted with water to afford compound **6** (27 mg, 75% from **49**). $[\alpha]_D$ +85.5 (c 1.0, H_2O). IR (KBr): 3433, 2933, 2482, 1647, 1548, 1422, 1237, 1135, 1055, 824, 802, 723 and 586 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 4.82 – 4.73 (m, 4H), 4.55 (dd, J=9.0 and 10.4 Hz, 1H), 4.52 – 4.32 (m, 8H), 4.29 (d, J =15.8, 1H), 4.20 – 4.07 (m, 4H), 4.07 – 3.95 (m, 5H), 3.94 – 3.86 (m, 4H), 3.84 – 3.61 (m, 16H), 3.59 – 3.45 (m, 5H), 1.92 – 1.87 (12H). ^{13}C NMR (126 MHz, D_2O) δ 174.67, 174.45, 174.40, 174.36, 171.68, 171.67, 171.65, 171.44, 98.03, 97.93, 97.82, 97.77, 79.52, 79.00, 78.87, 78.72, 77.43, 77.41, 77.06, 76.54, 71.12, 71.09, 71.06, 71.00, 70.92, 70.90, 70.43, 68.55, 68.16, 68.01, 66.17, 63.52, 60.29, 60.25, 60.21, 54.38, 54.30, 54.27, 54.23, 52.25, 52.22, 52.19, 52.05, 43.08, 22.18, 22.15, 22.13, 22.08. HRMS (ESI, negative mode) calcd for $C_{52}H_{81}N_8NaO_{49}S_4$ $[M\text{-}6H]^{6-}$ *m/z* 291.20776, found 291.20714.

10. Synthesis of compound 7



10.1. Synthesis of 50

Compound **50** was prepared from compound **48** (43 mg, 0.025 mmol) according to general procedure **C**. The residue was employed directly in the next step without further purification.

10.2. Synthesis of 51

Compound **51** was prepared from compound **49** (50 mg, 0.018 mmol) according to general procedure **C**. The residue was employed directly in the next step without further purification.

10.3. Synthesis of 52

Compound **52** was prepared from compound **50** (34 mg, 0.021 mmol) and **51** (47 mg, 0.018 mmol) according to general procedure **E**. The residue was purified by silica gel chromatography (hexane: EtOAc, 5:1) to yield **52** (44 mg, 60%). $[\alpha]_D$ +52.0 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CD3OD) δ 7.66 (d, J = 7.3 Hz, 2H), 7.4-7.6 (m, 6H), 7.1-73(m, 67H), 5.12 – 4.95 (bs, 12H), 4.88 – 3.34 (m, 112H), 1.90 (3H), 1.89 (3H), 1.88 (3H), 1.86 (3H), 1.85 (3H), 1.84 (3H), 132 (s, 9H).

10.4. Synthesis of 7

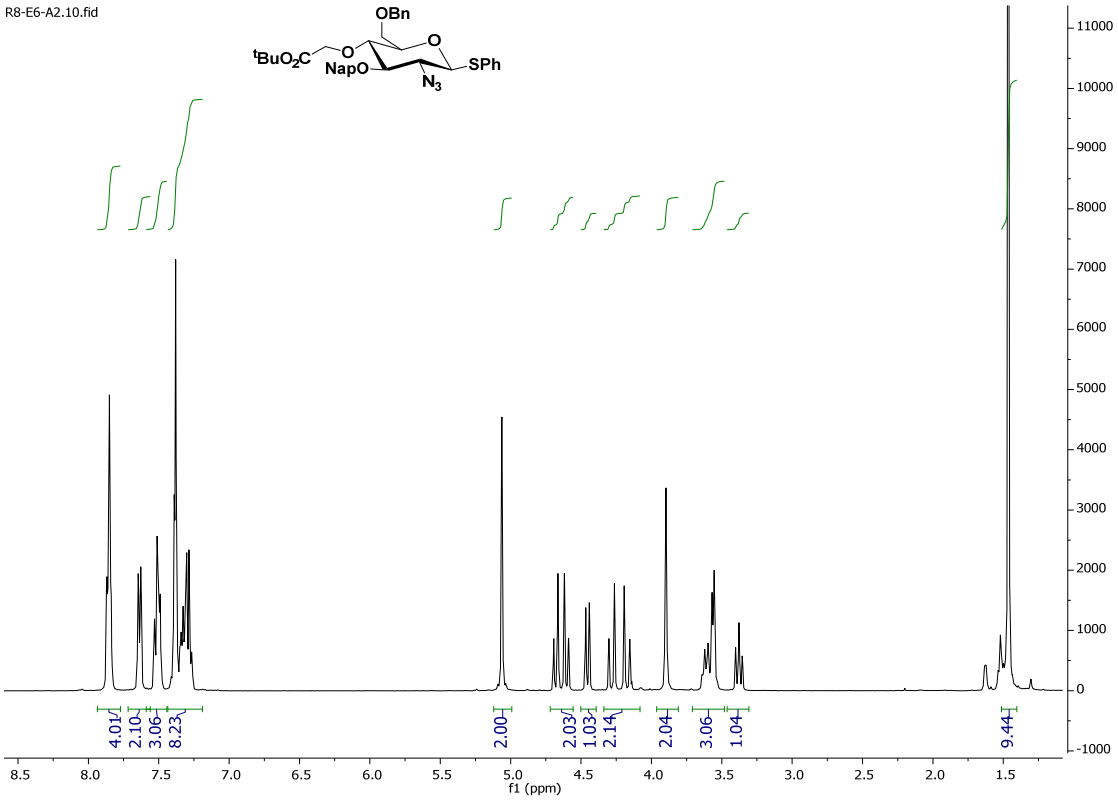
Compound **7** was prepared from compound **52** in three steps. In the first one, the N-Fmoc amine of **52** (36 mg, 9 μmol) was deprotected according to general procedure **D**. The amine was employed directly in the next step without further purification. In this the t*ert*-butyl esther was deprotected according to general procedure **E**. The amino acid employed directly in the next step without further purification. Finally, the benzyl groups were removed by hydrogenation according to general procedure **I**. The residue was passed through a Dowex 500WX8 resin column (Na^+ form) and eluted with water to afford compound **7** (16 mg, 64% from **52**). $[\alpha]_D$ +55.2 (c 0.9, H_2O). IR (KBr): 3422, 2943, 1681, 1549, 1414, 1384, 1236, 1209, 1139, 1053, 838, 803, 724 and 589 cm^{-1}. ^{1}H NMR (500 MHz, D_2O) δ 4.75-4.85 (bs, 6H), 4.55 (m, 2H), 4.3-4.5 (m, 16H), 3.65-4.25 (m, 51H), 3.45-3.60 (m, 9H), 3.42 (dd, J= 6.6 and 11.6 Hz, 1H), 185-1.95 (18 H). ^{13}C NMR (201 MHz, D_2O) 175.22, 174.55, 174.47, 172.57, 171.69, 171.40, 163.28, 163.10, 162.93, 162.75, 98.12, 98.00, 97.94, 97.82, 96.78, 79.77, 79.55, 79.42, 79.21, 79.06, 78.87, 78.80, 78.67, 77.83, 77.68, 77.52, 77.35, 77.08, 76.95, 76.86, 76.56, 72.06, 71.18, 71.08, 70.98, 69.29, 68.84, 68.77, 68.57, 68.38, 68.32, 68.22, 66.28, 66.22, 62.48, 60.38, 60.29, 60.10, 55.47, 54.83, 54.68, 54.63, 54.41, 53.59, 53.20, 52.30, 52.19, 52.12, 22.26, 22.16, 20.01.

11. References

1. S.U. Hansen, G.J. Miller, M. Baráth, K.R. Broberg, E. Avizienyle, M. Helliwell, J. Raftery, G.C. Jayson and J.M. Gardiner, *J. Org. Chem*., 2012, **77**, 7823−7843.
2. H. Tanaka, Y. Tateno and T. Takahashi, *Org. Biomol. Chem*., 2012, **10**, 9570–9582.
3. T. Buskas, P.J. Garegg, P. Konradsson and J.-L. Maloisel, *Tetrahedron: Asymm.,* 1992, **5**, 2187-2194.

Figure S1. ^{1}H (**A**), ^{13}C (**B**) and HSQC (**C**) NMR spectra of compound **13**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

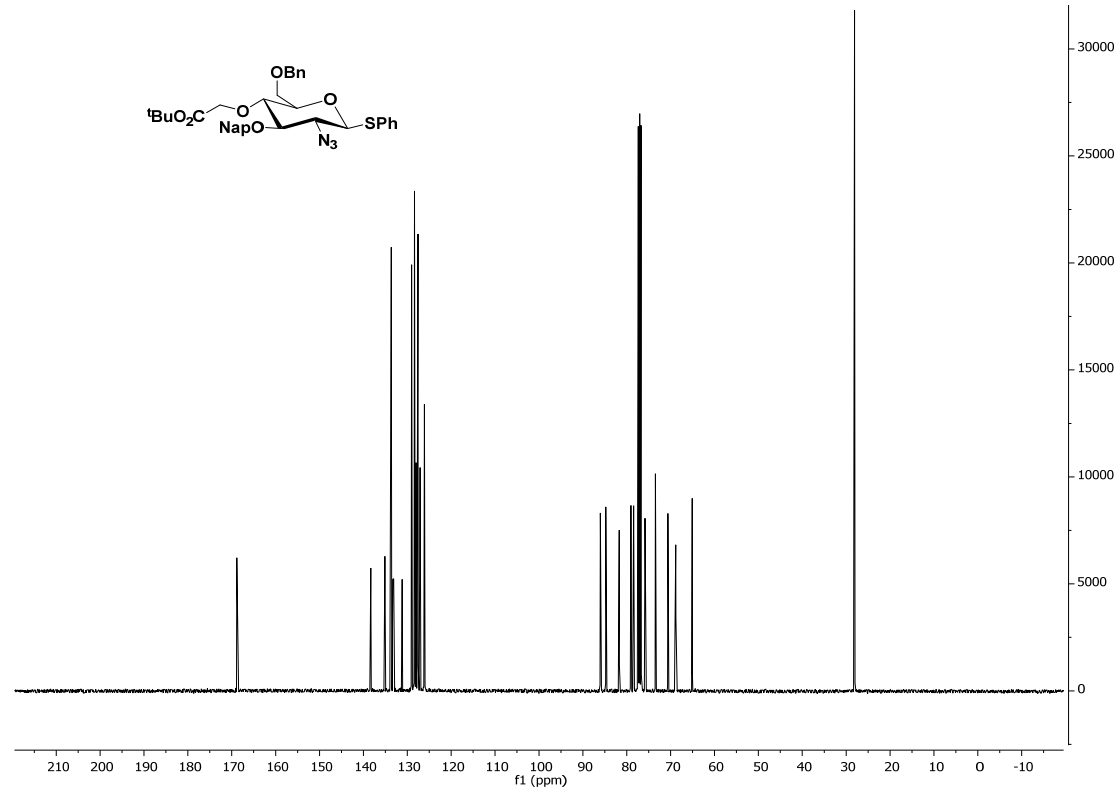


Figure S1 (continuation).
(**C**) HSQC

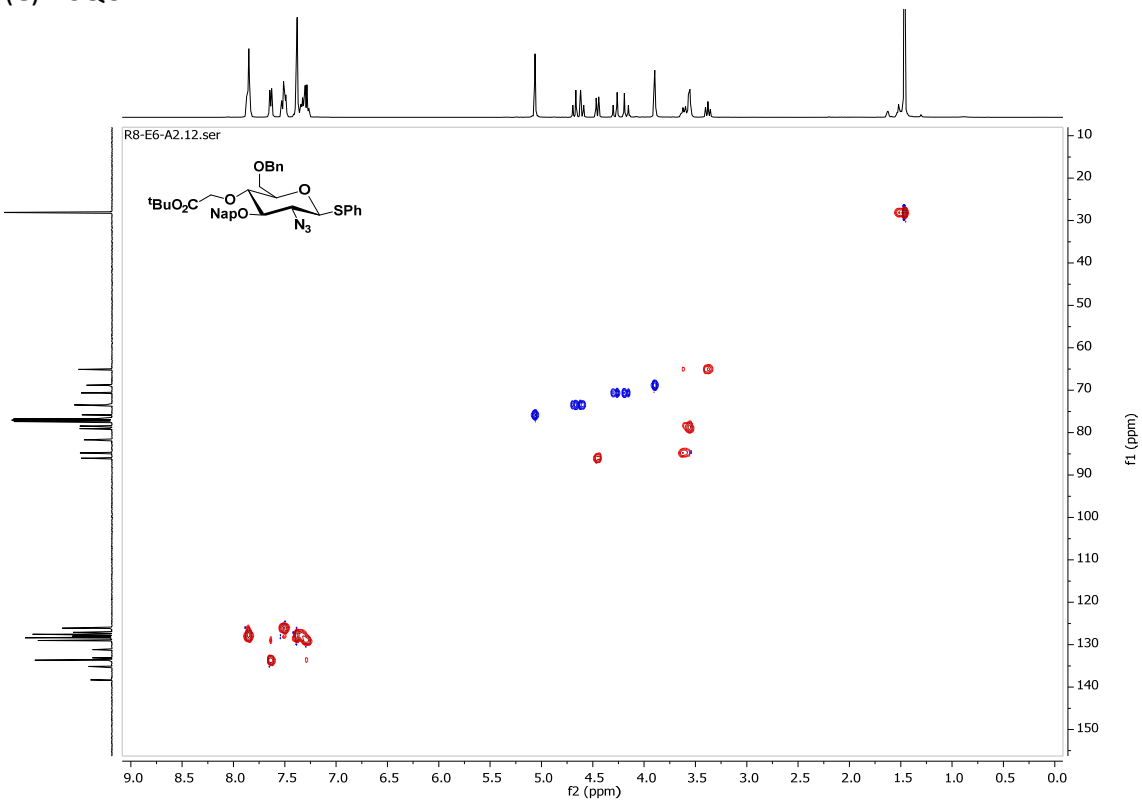


Figure S2. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **17**.
(**A**) ^{1}H-NMR

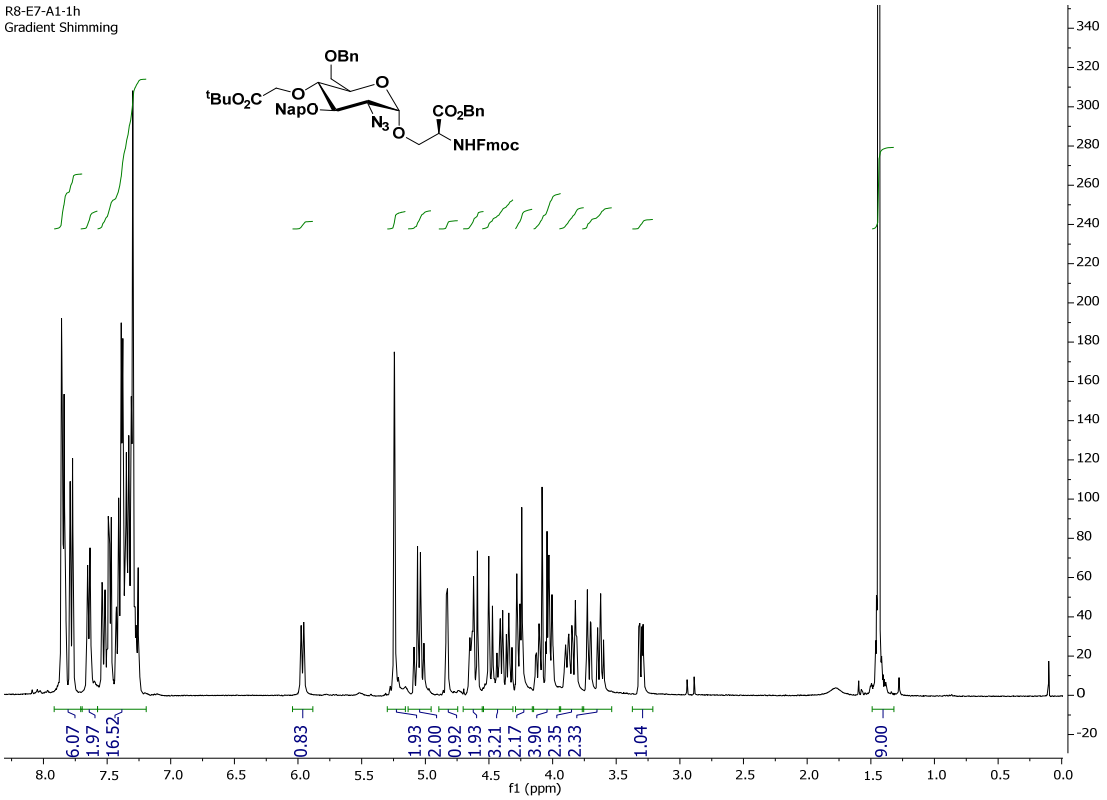
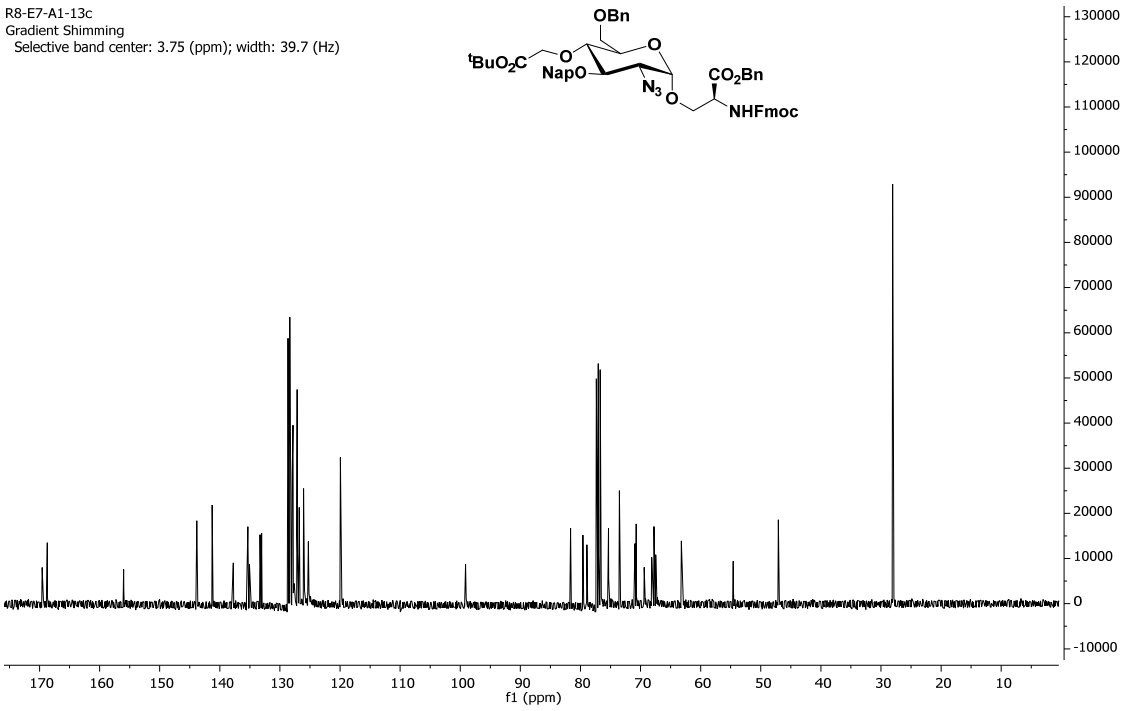


Figure S2 (continuation).

(**B**) ^{13}C-NMR



(**C**) COSY

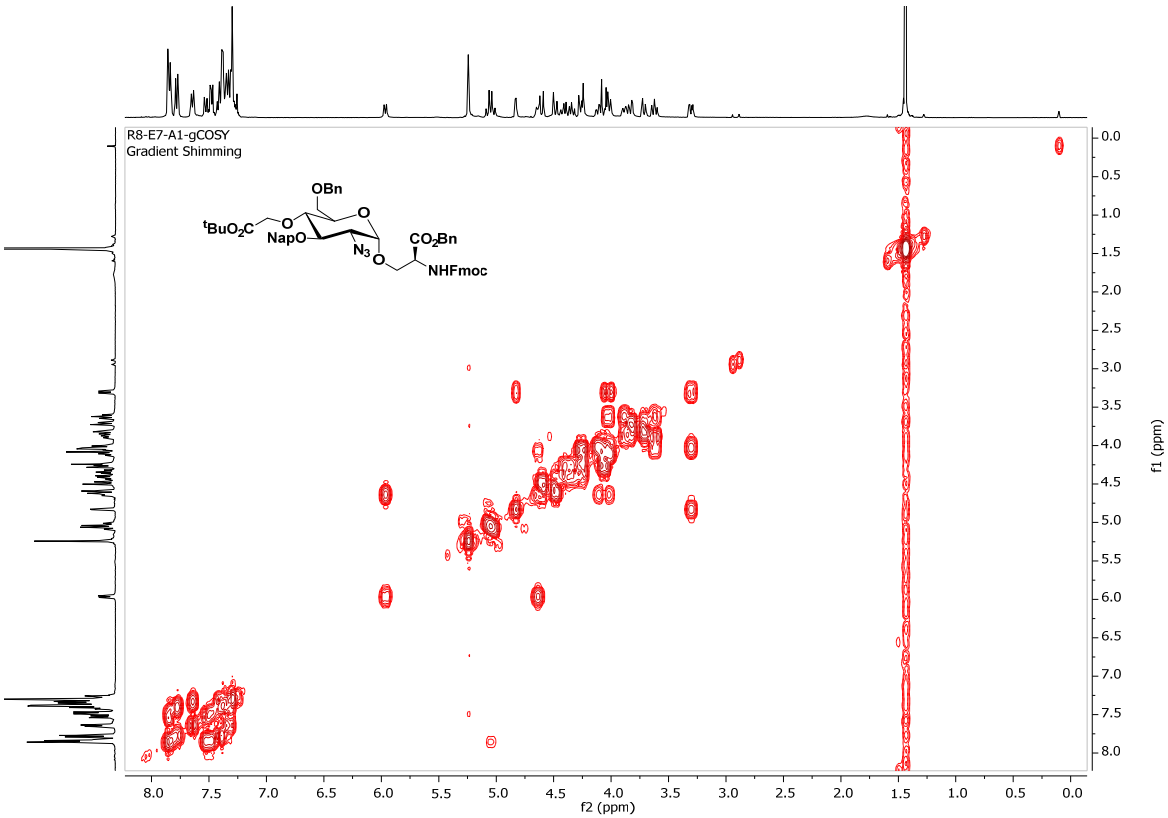


Figure S2 (continuation)

(**D**) HSQC

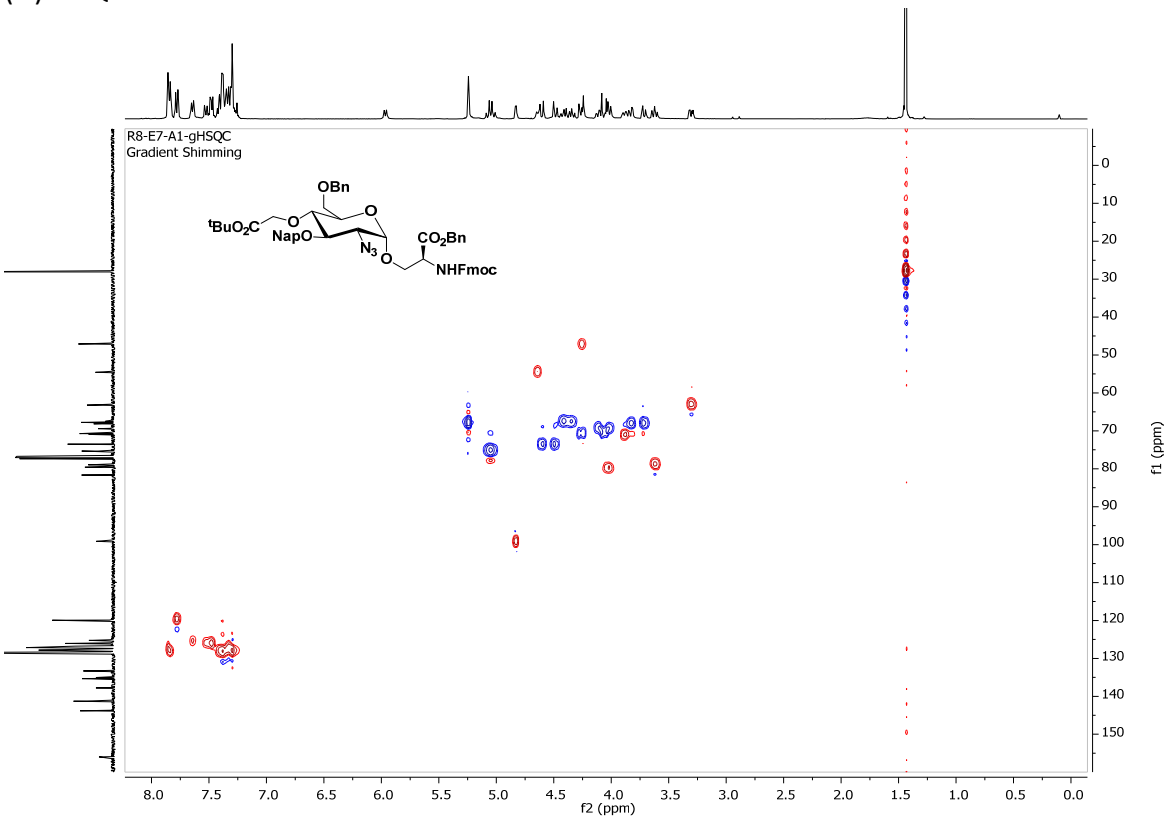


Figure S3. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **26**.

(**A**) ^{1}H-NMR

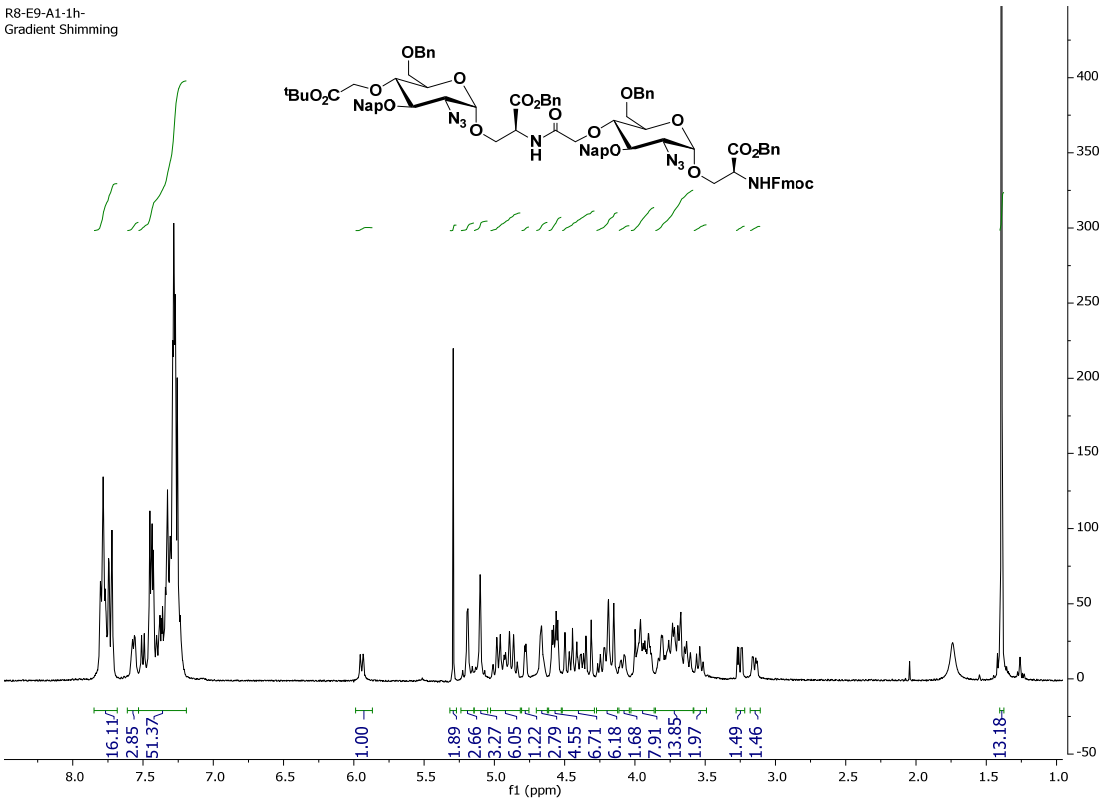
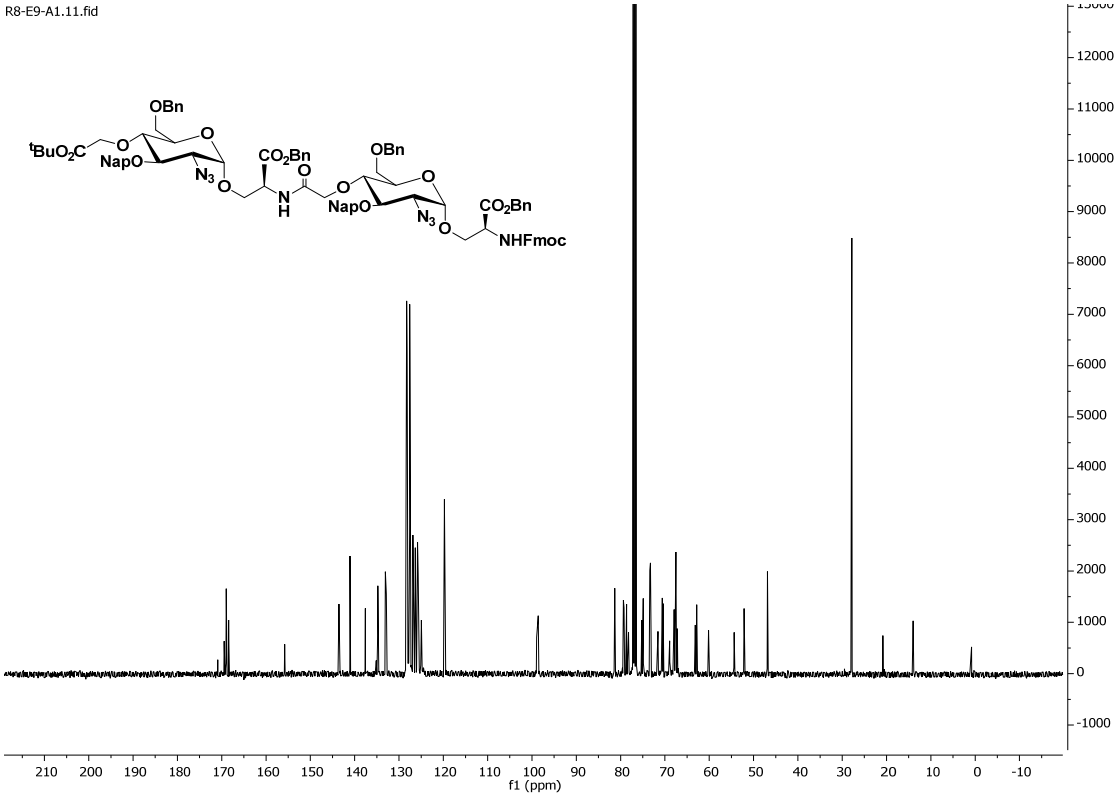


Figure S3 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

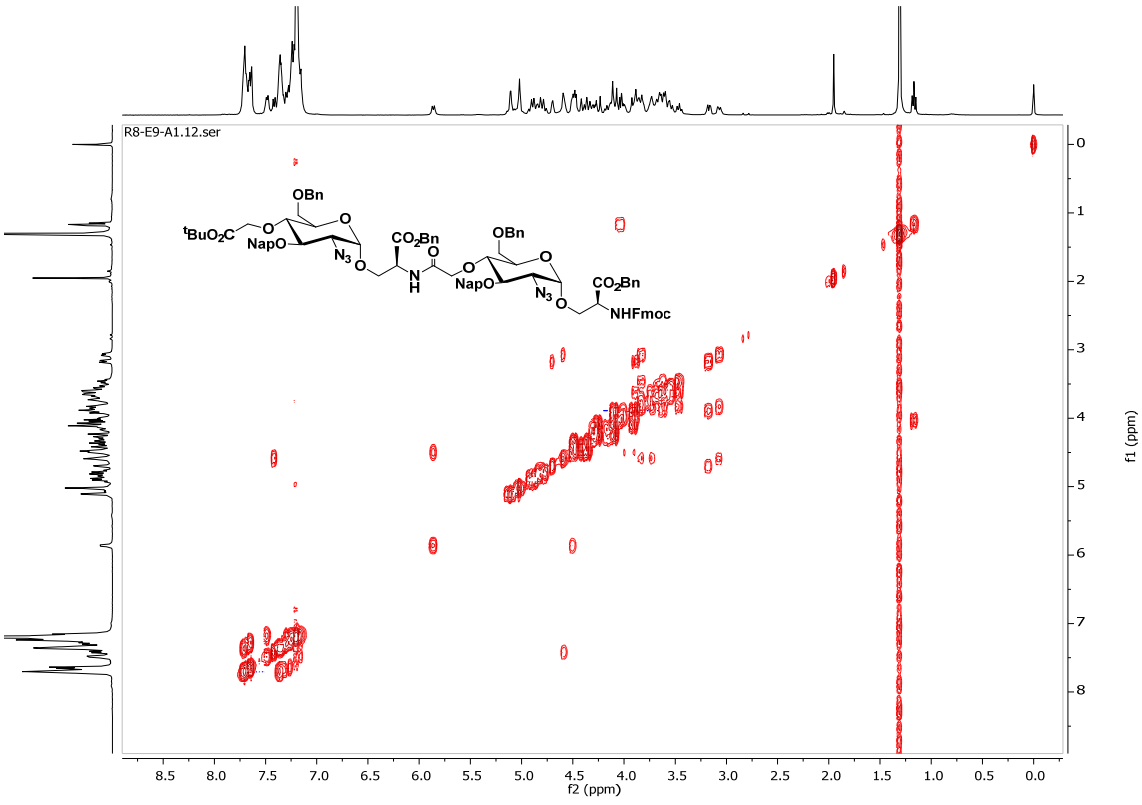


Figure S3 (continuation)

(**D**) HSQC

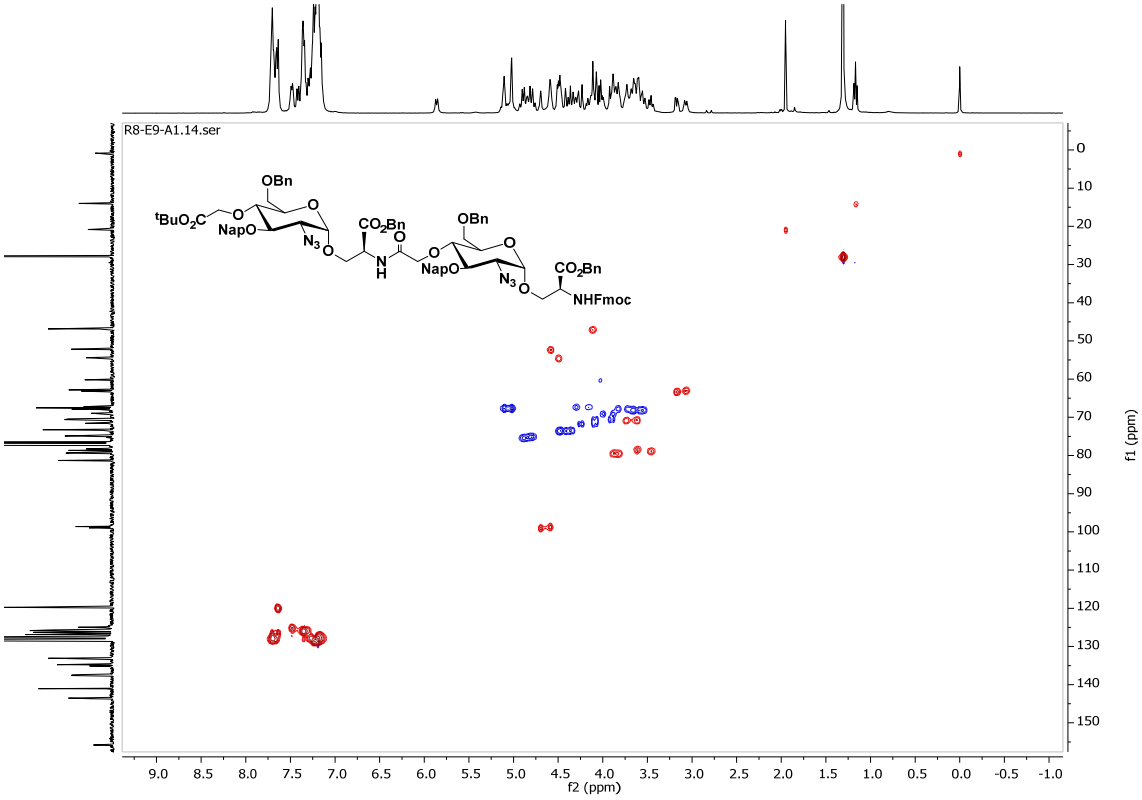


Figure S4. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **35**.

(A) ^{1}H-NMR

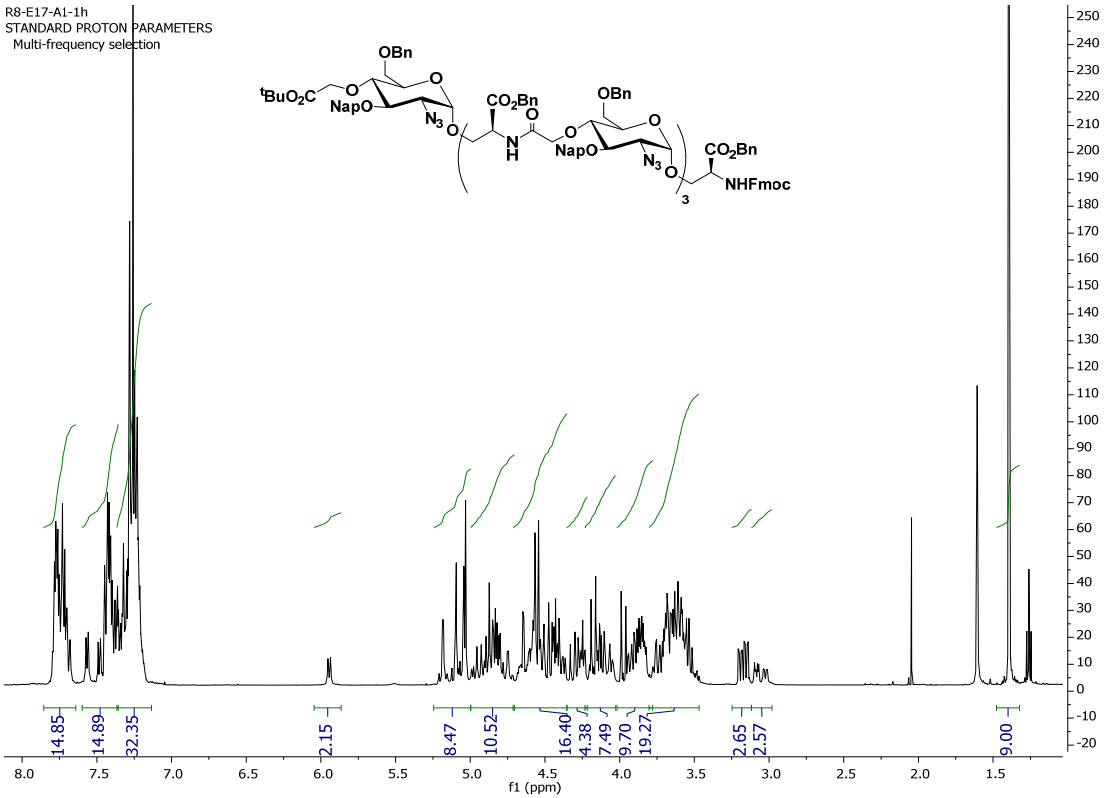
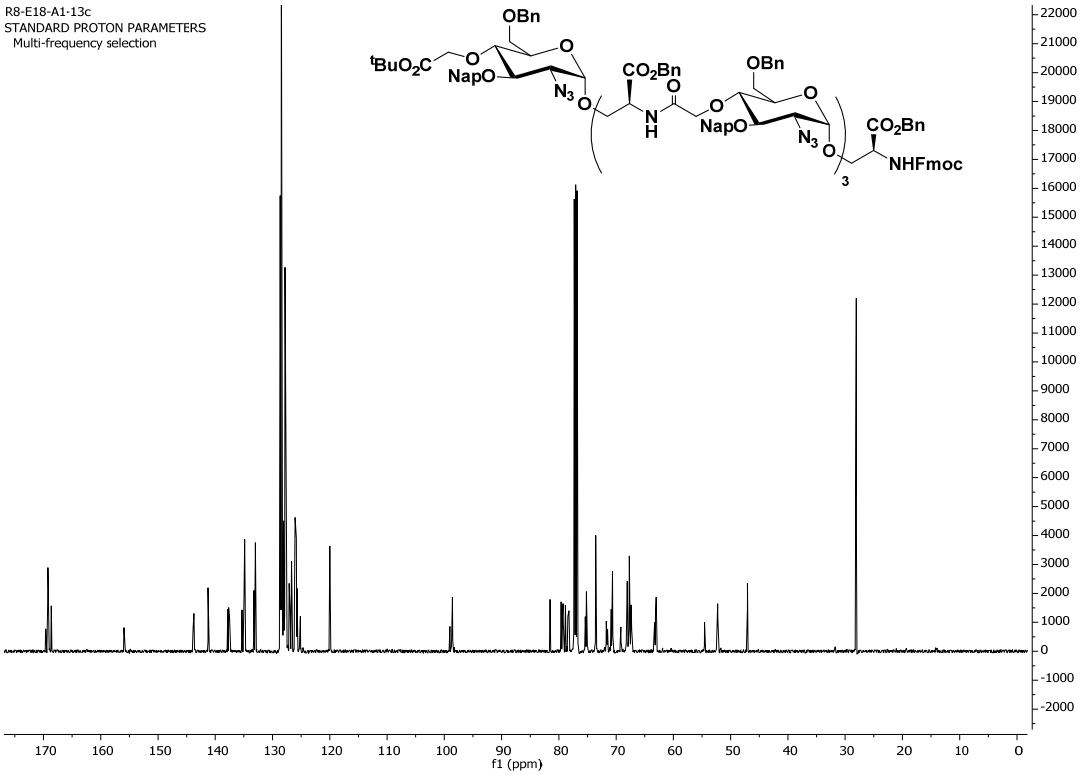


Figure S4 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

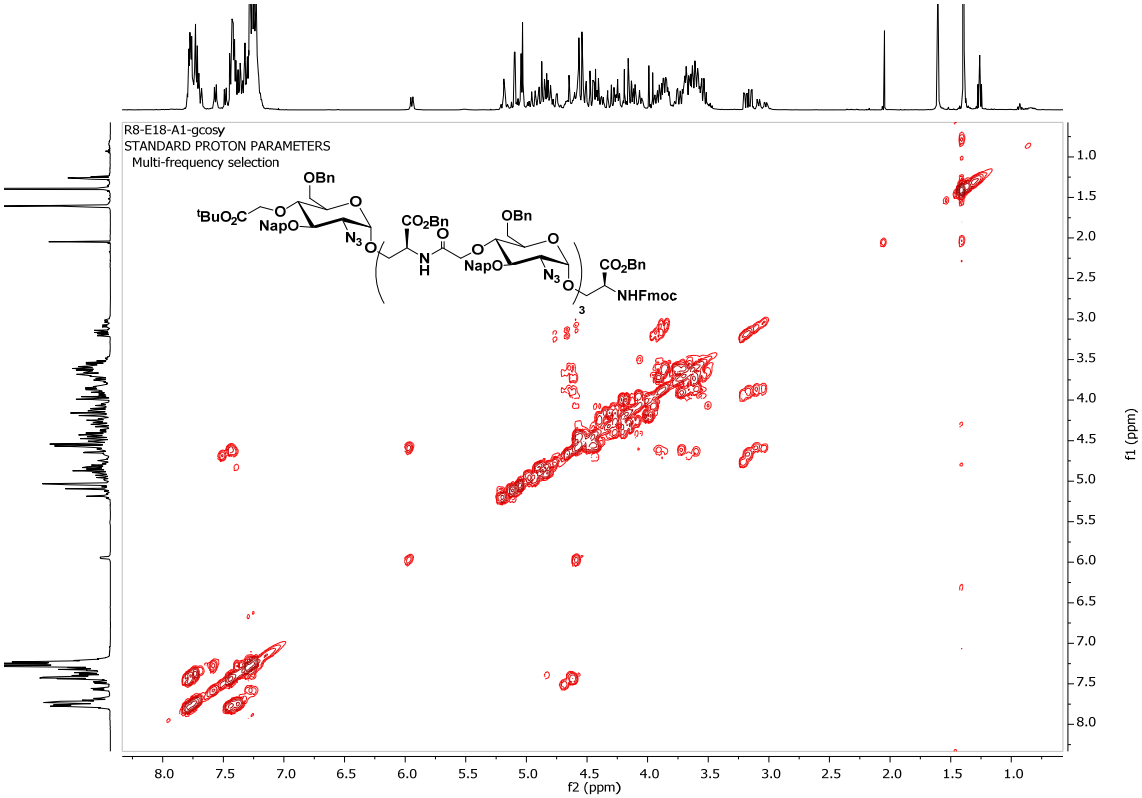


Figure S4 (continuation)

(**D**) HSQC

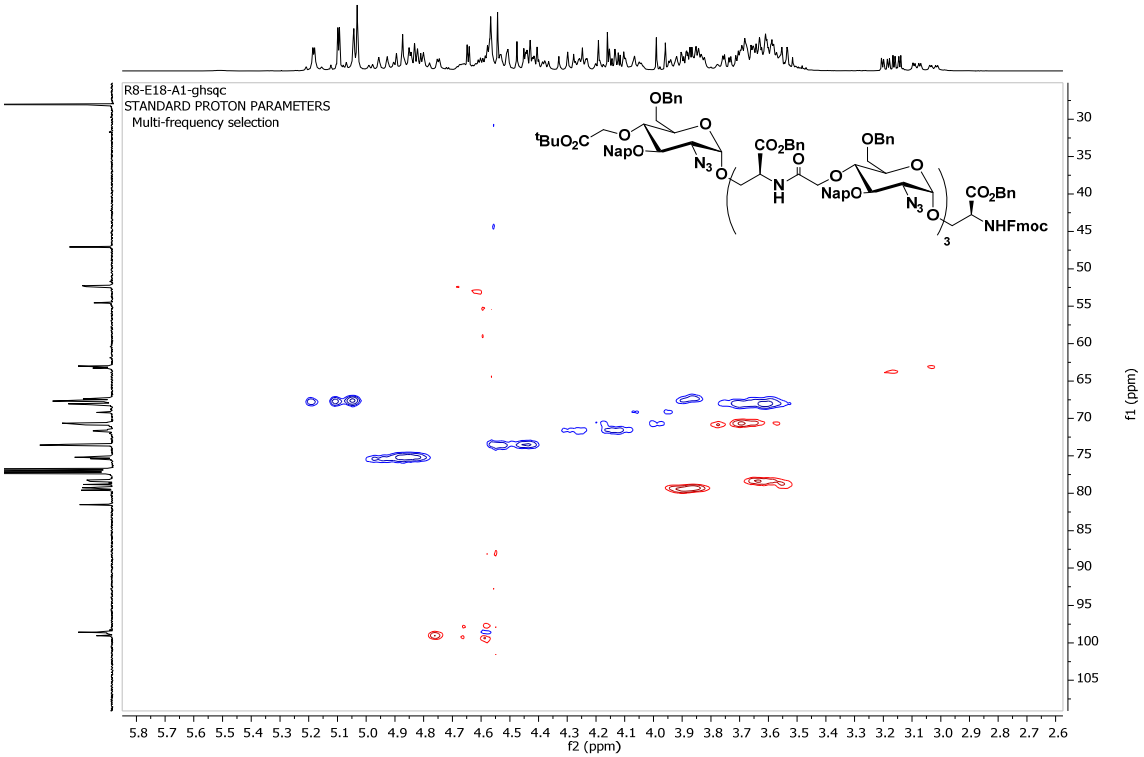


Figure S5. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **40**.

(**A**) ^{1}H-NMR

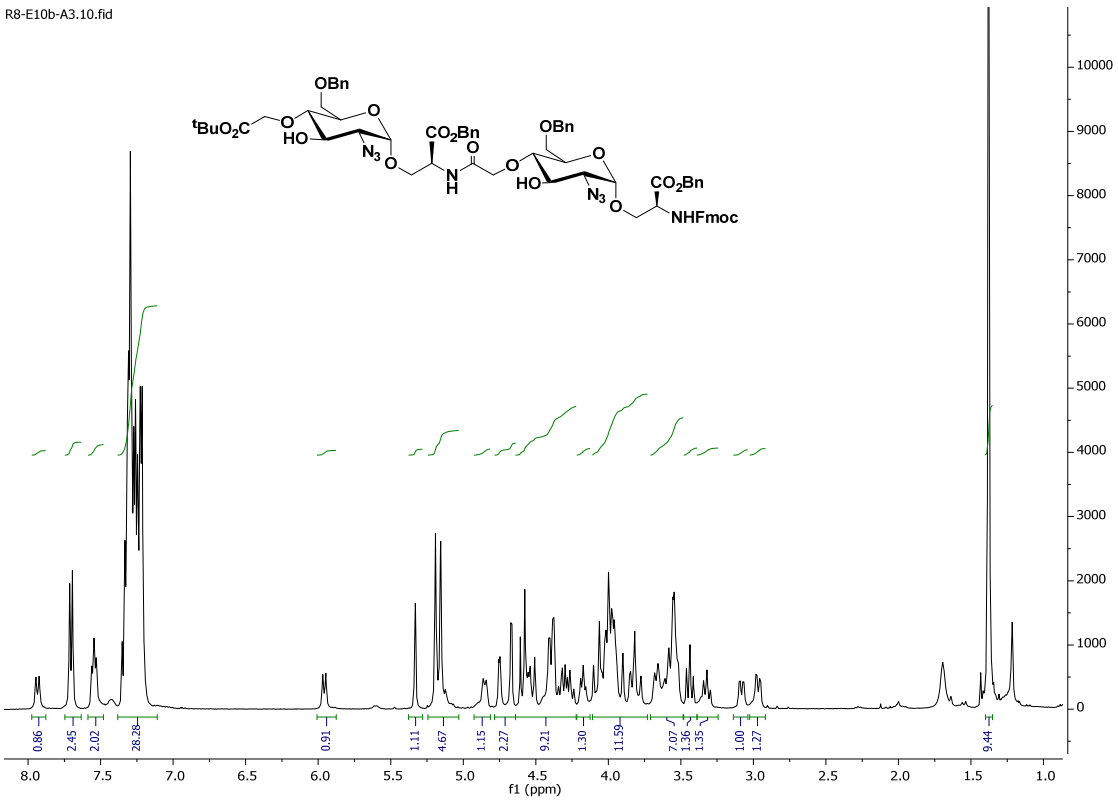
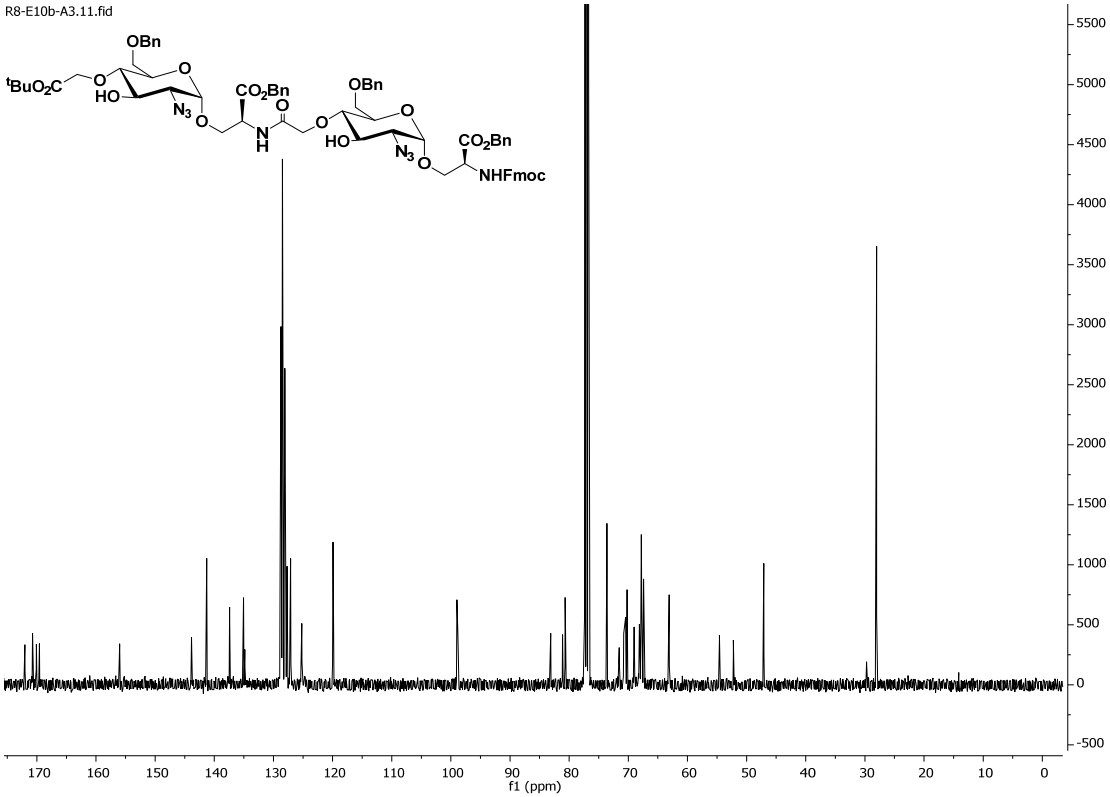


Figure S5 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

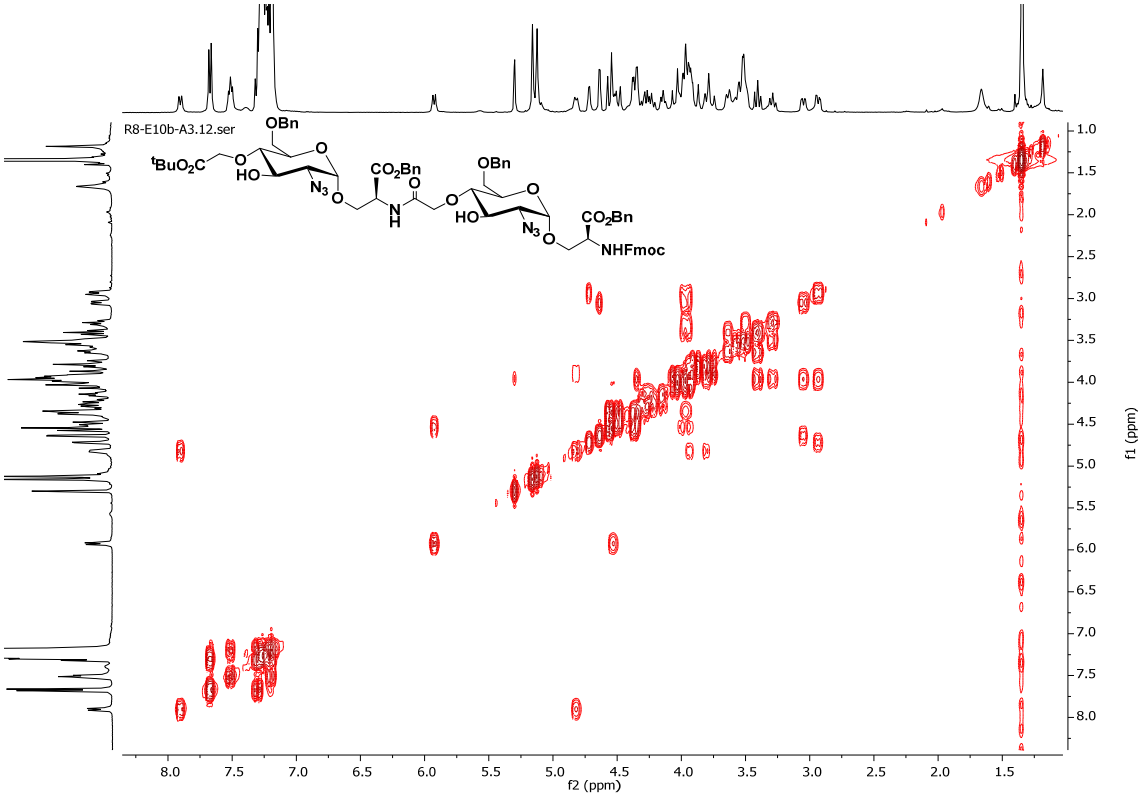


Figure S5 (continuation)

(**D**) HSQC

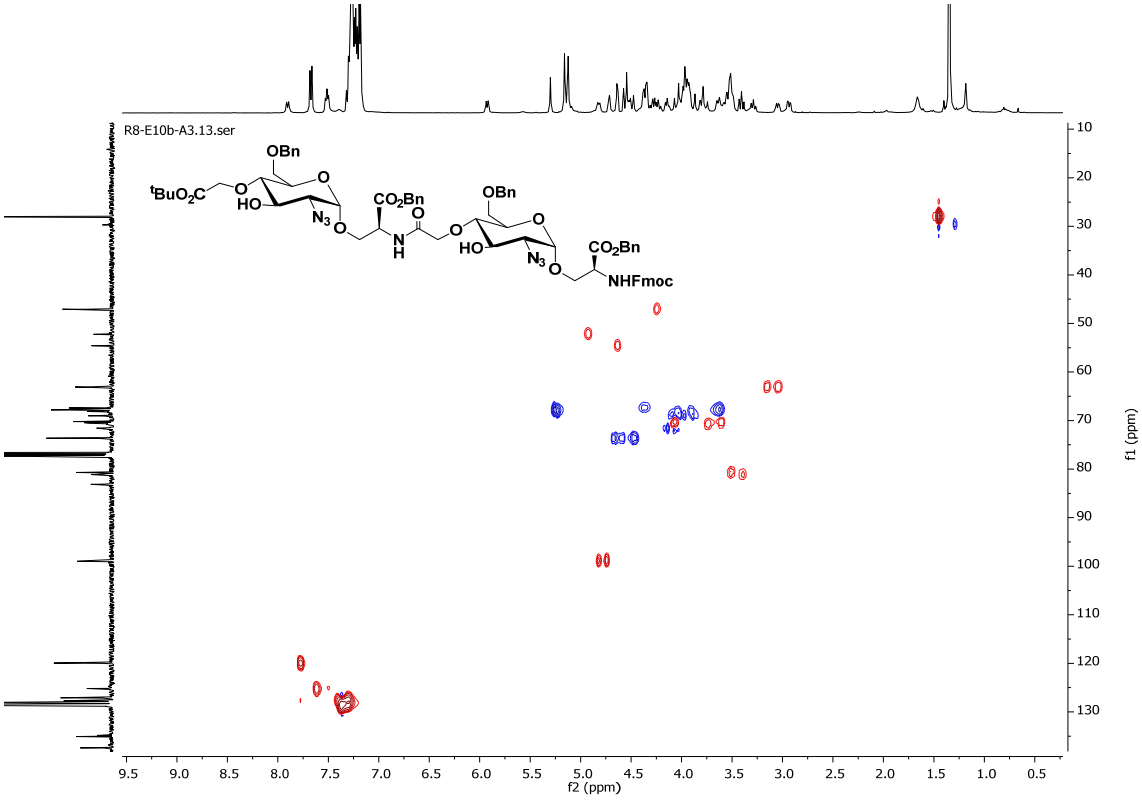


Figure S6. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **44**.

(**A**) ^{1}H-NMR

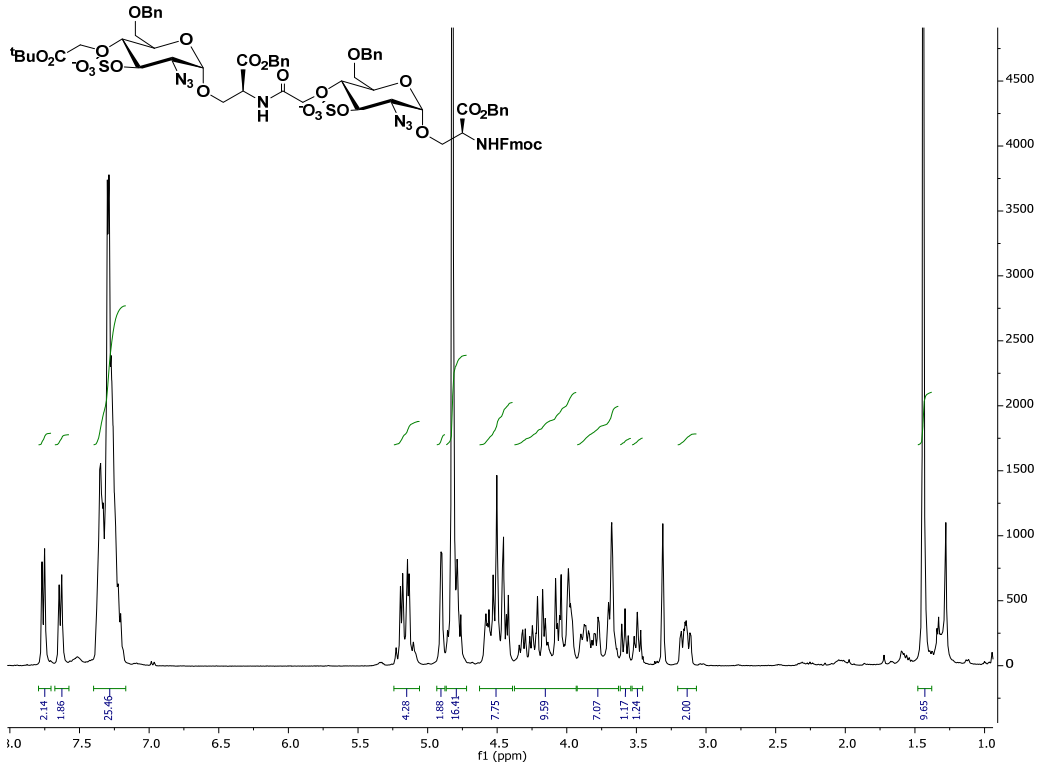
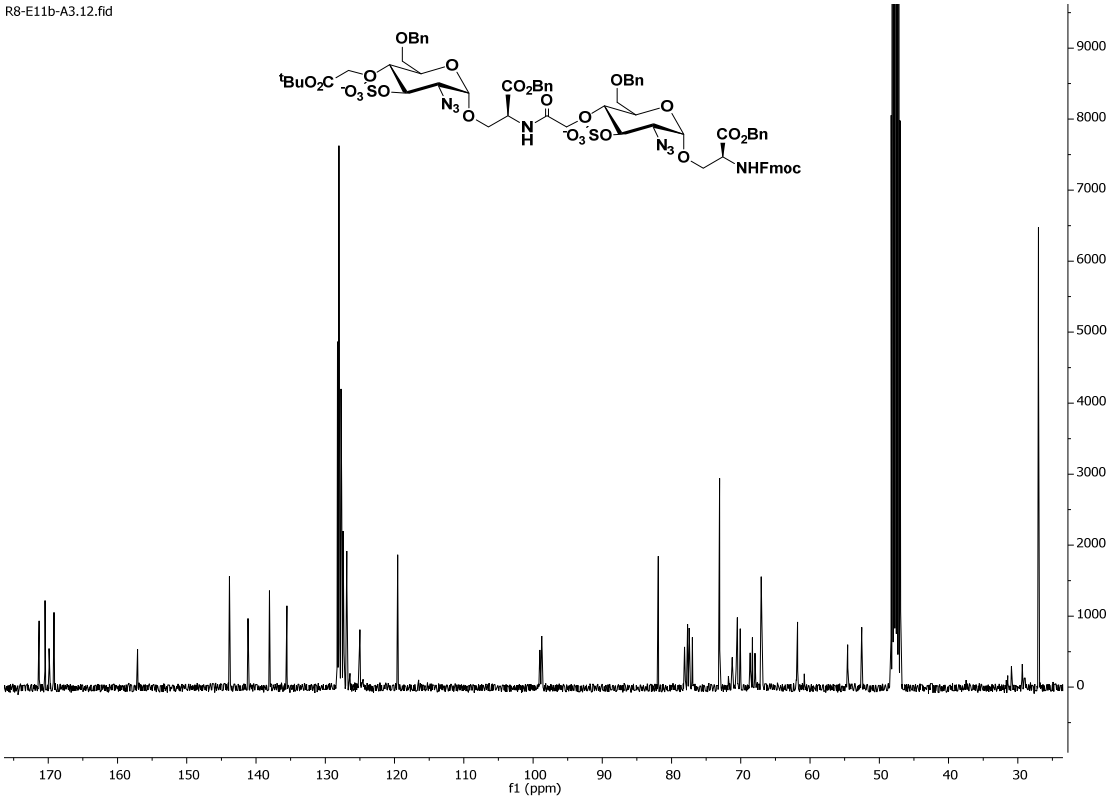


Figure S6 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

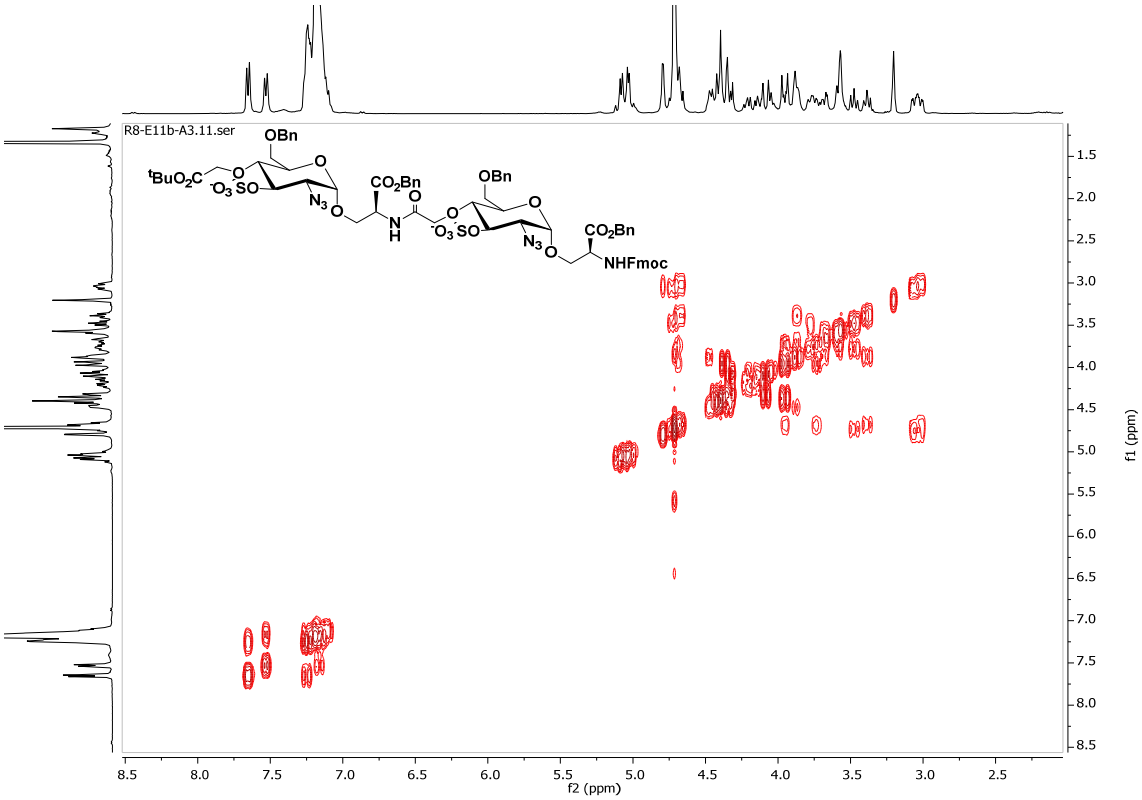


Figure S6 (continuation)

(**D**) HSQC

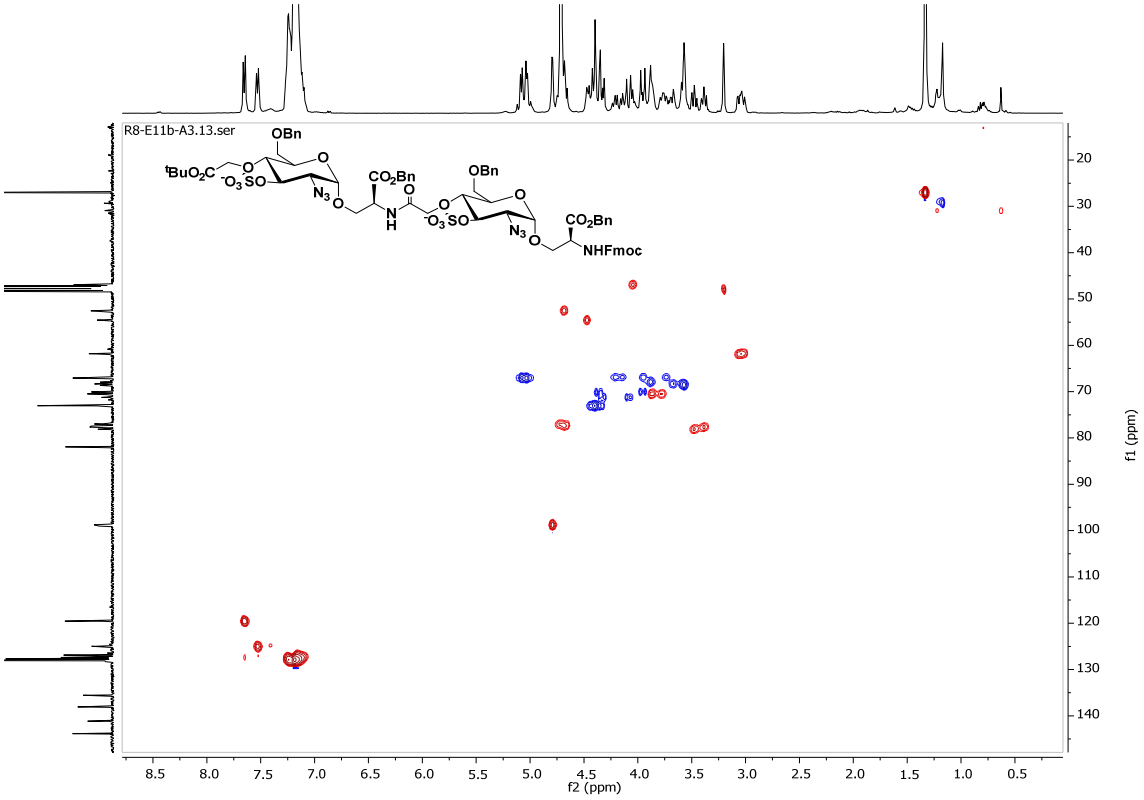


Figure S7. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **48**.

(**A**) ^{1}H-NMR

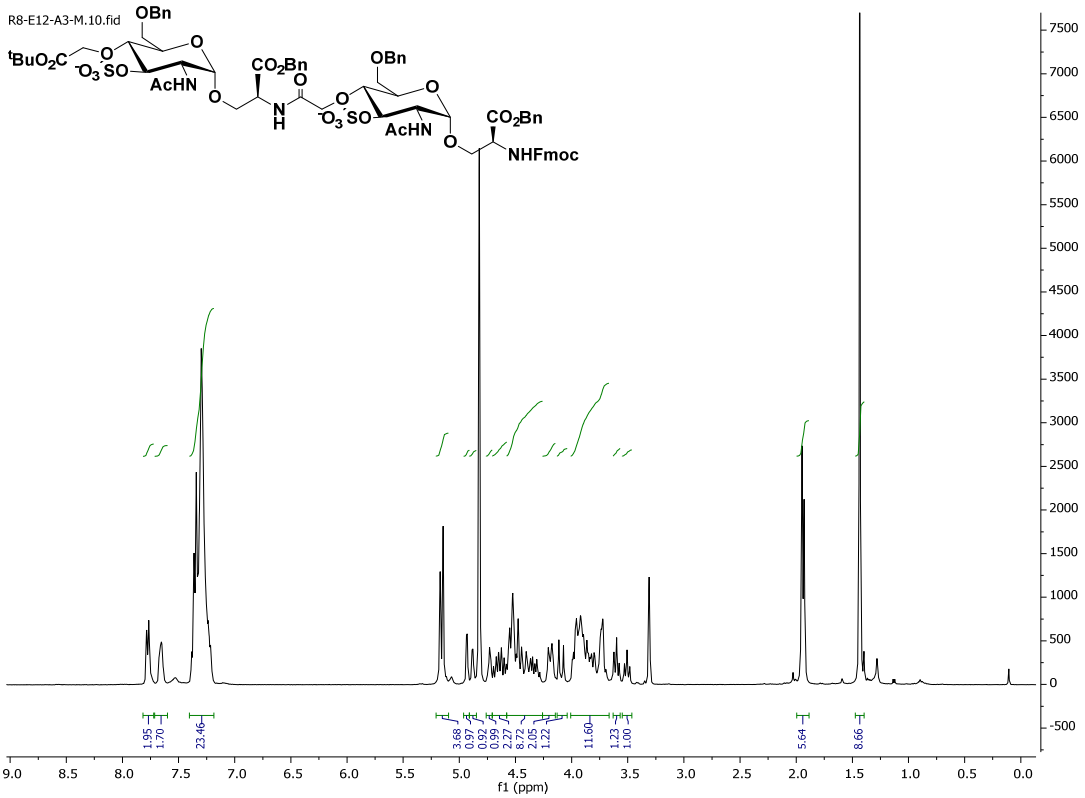
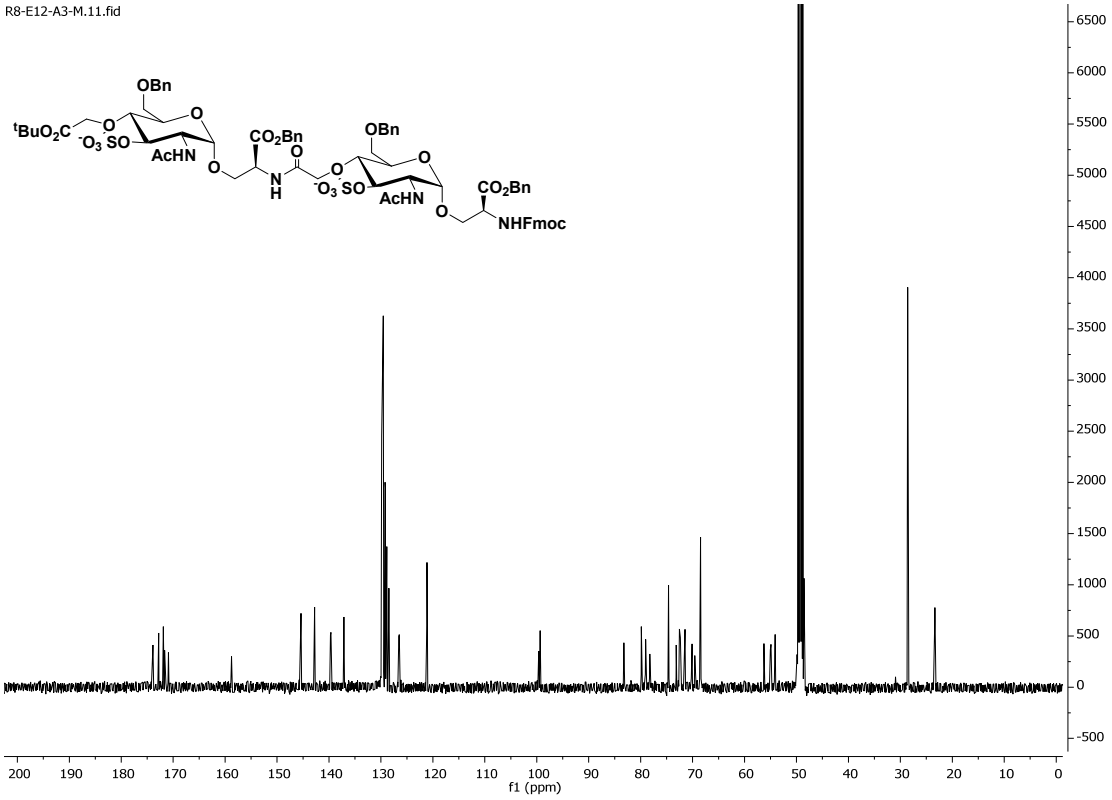


Figure S7 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

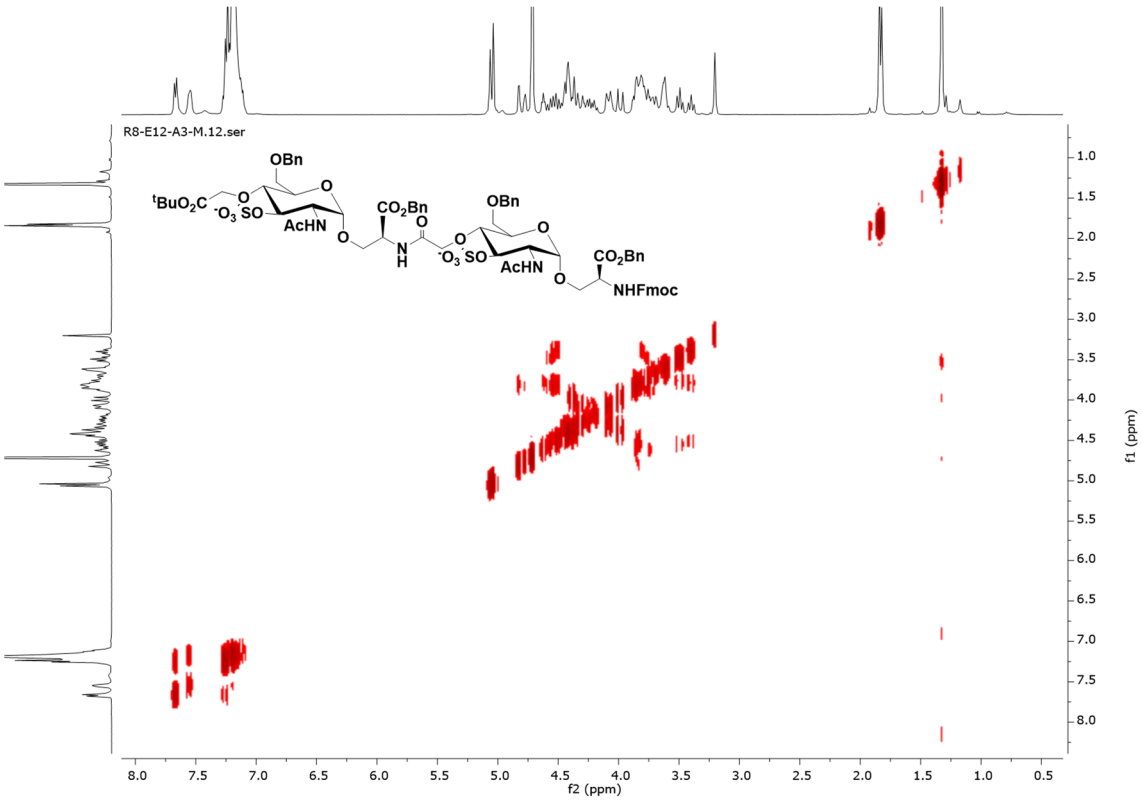


Figure S7 (continuation)

(**D**) HSQC

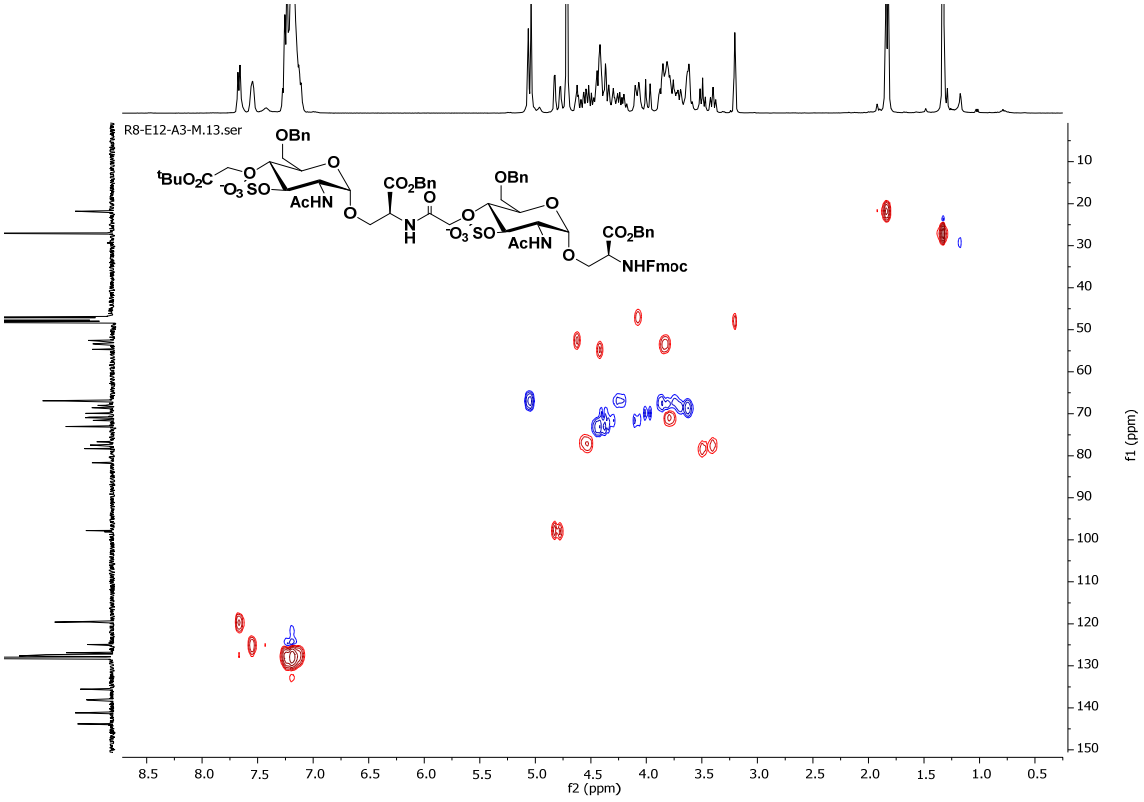


Figure S8. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **41**.

(**A**) ^{1}H-NMR

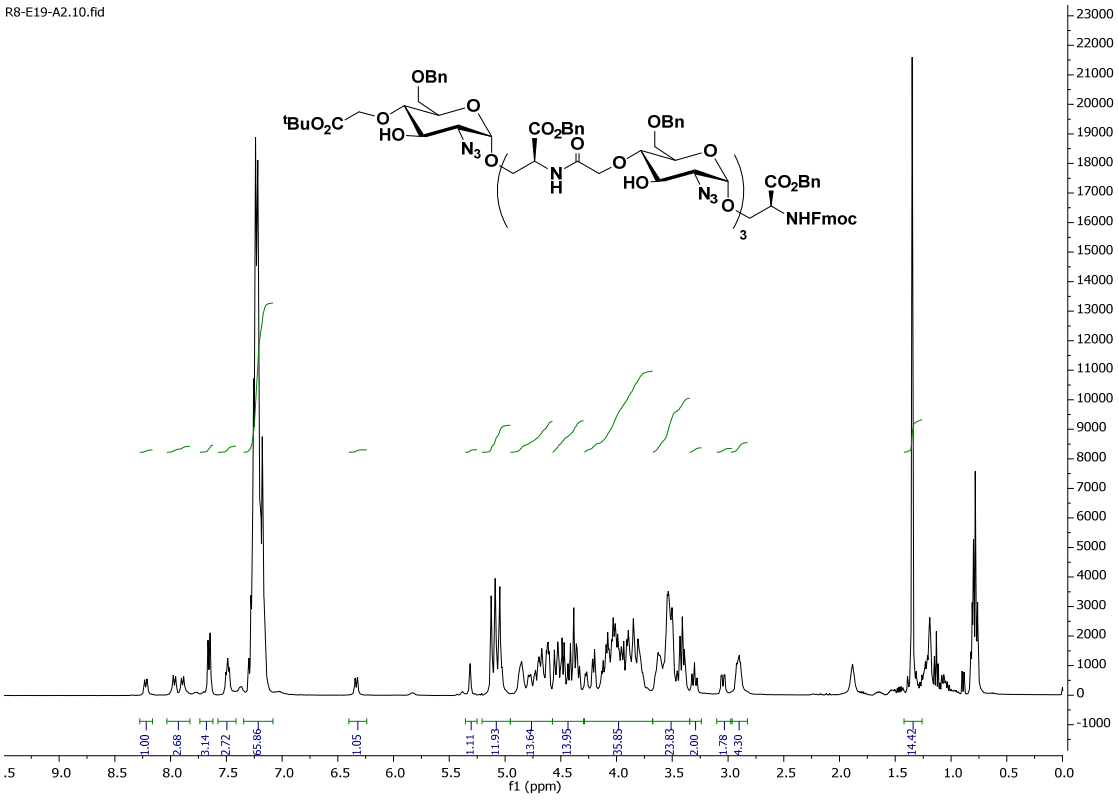
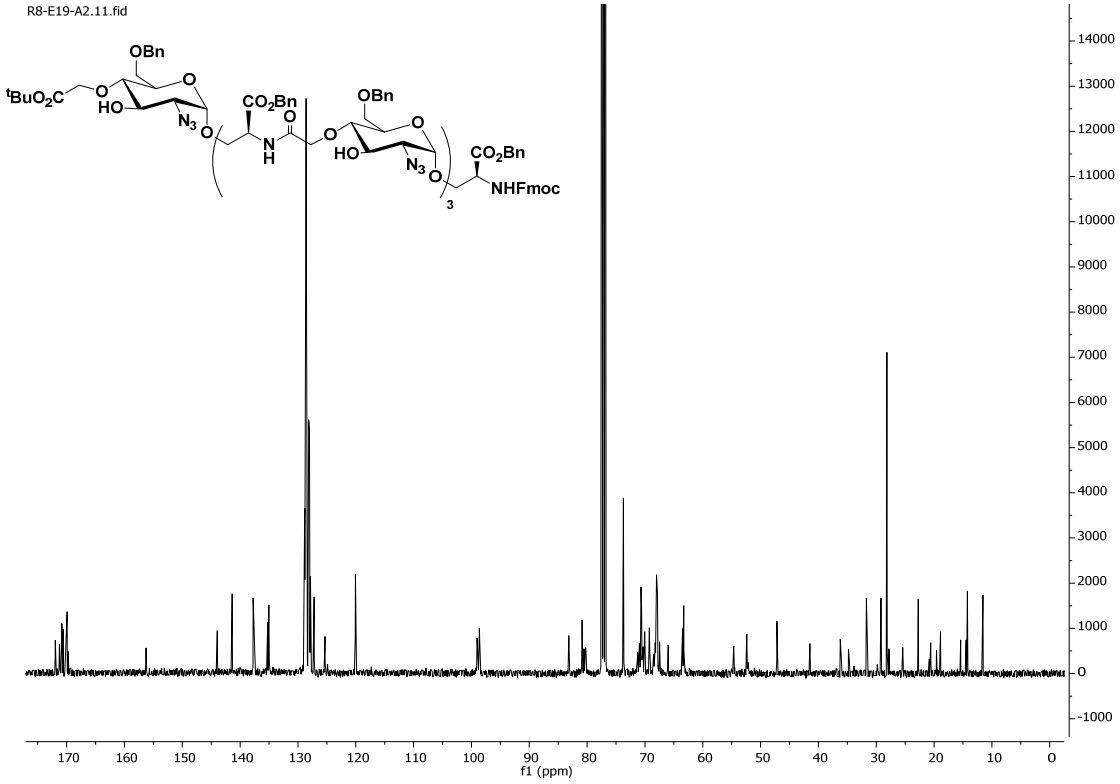


Figure S8 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

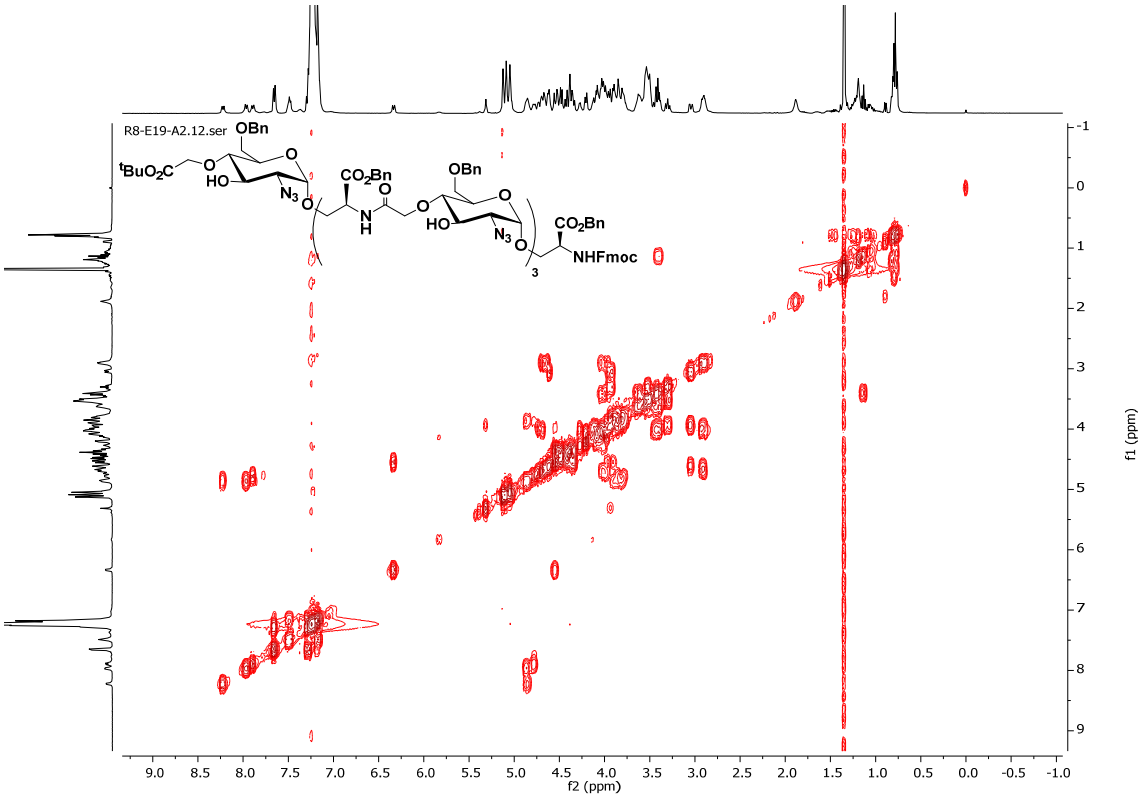


Figure S8 (continuation)

(**D**) HSQC

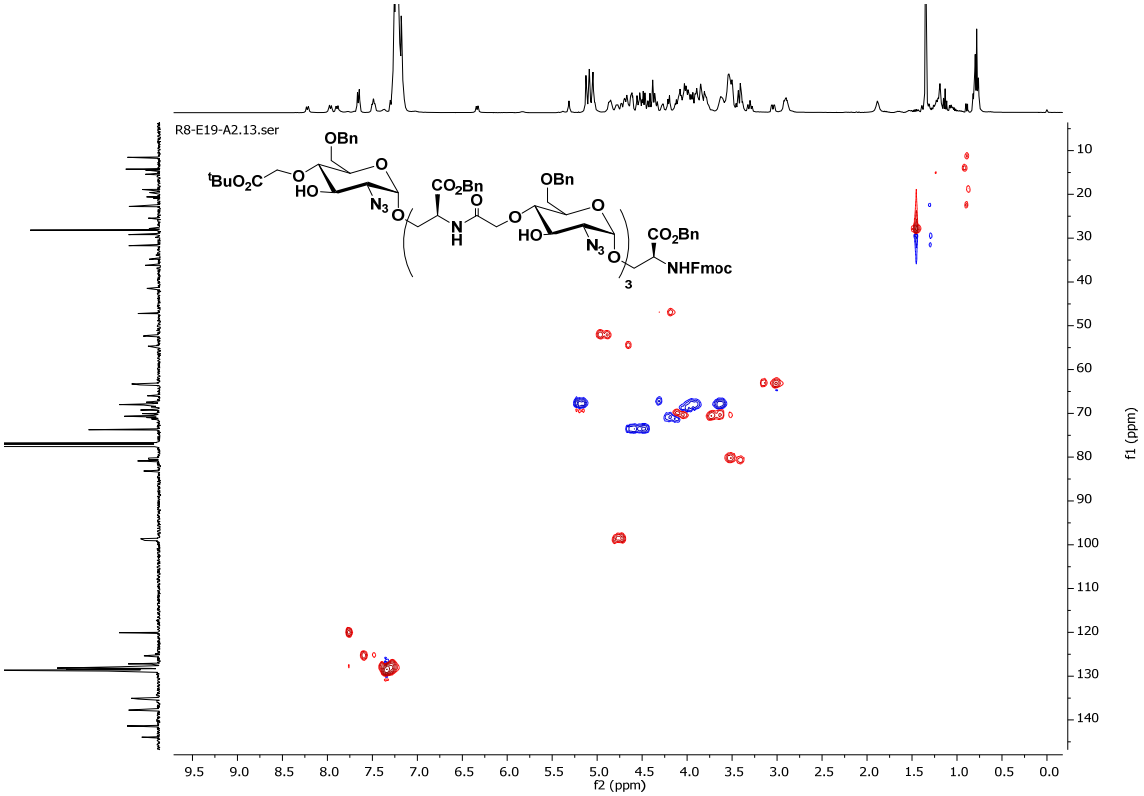


Figure S9. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **45**.

(**A**) ^{1}H-NMR

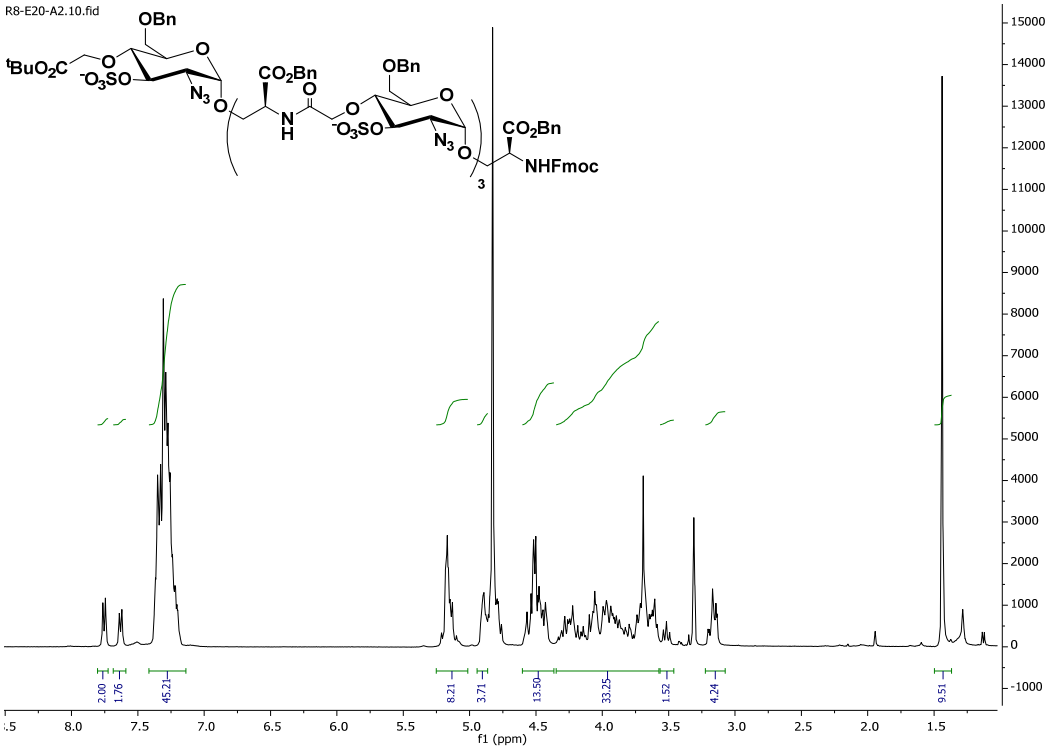
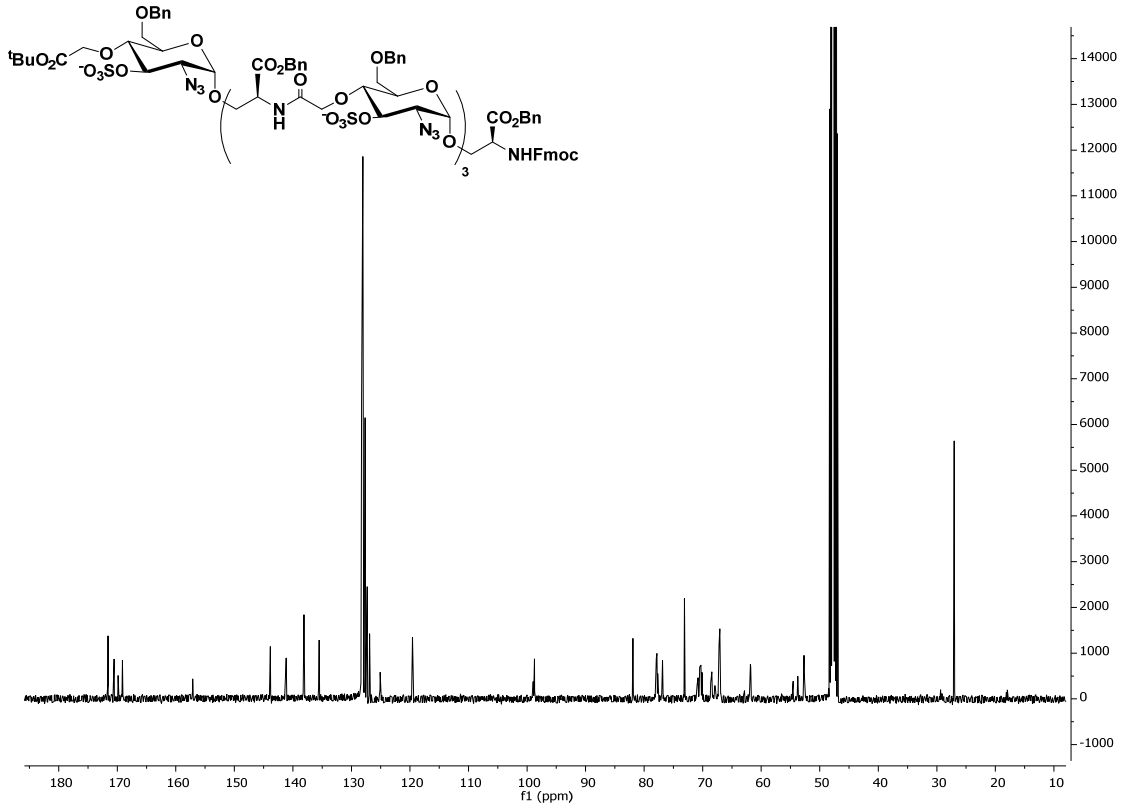


Figure S9 (continuation)

(**B**) ^{13}C-NMR



(**C**) COSY

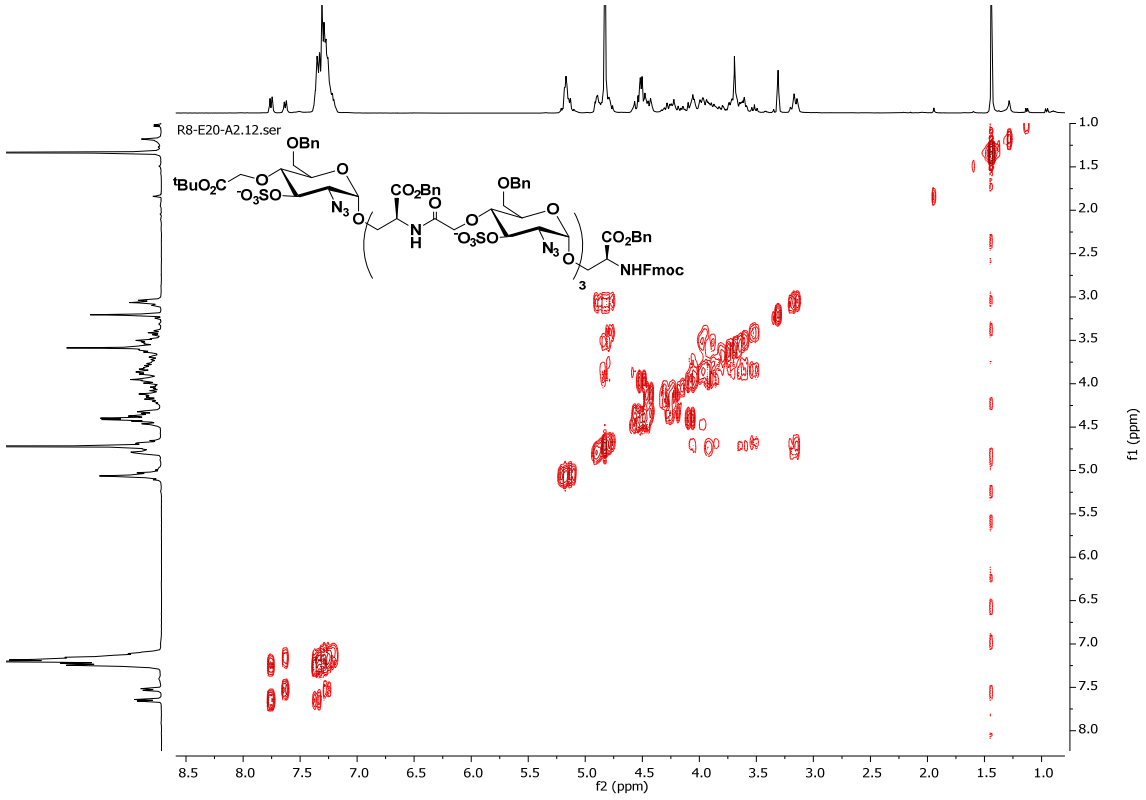


Figure S9 (continuation)

(**D**) HSQC

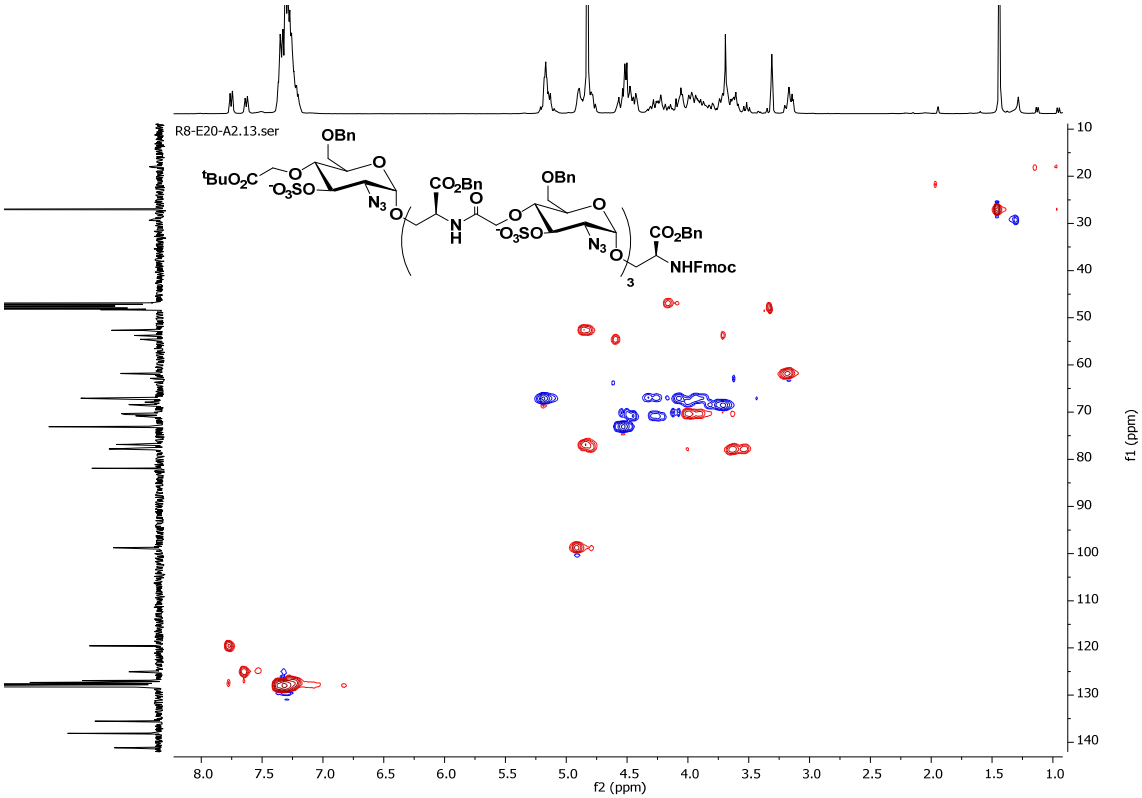


Figure S10. ^{1}H (**A**), ^{13}C (**B**) and HSQC (**C**) NMR spectra of compound **49**.

(**A**) ^{1}H-NMR

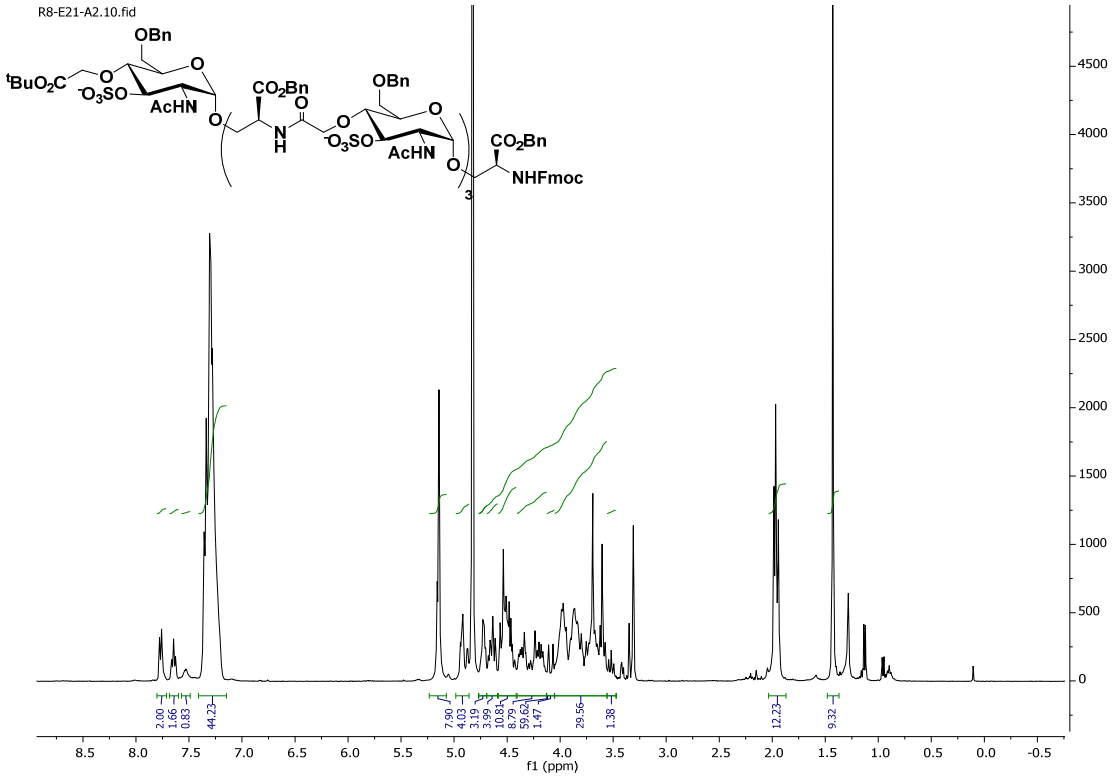
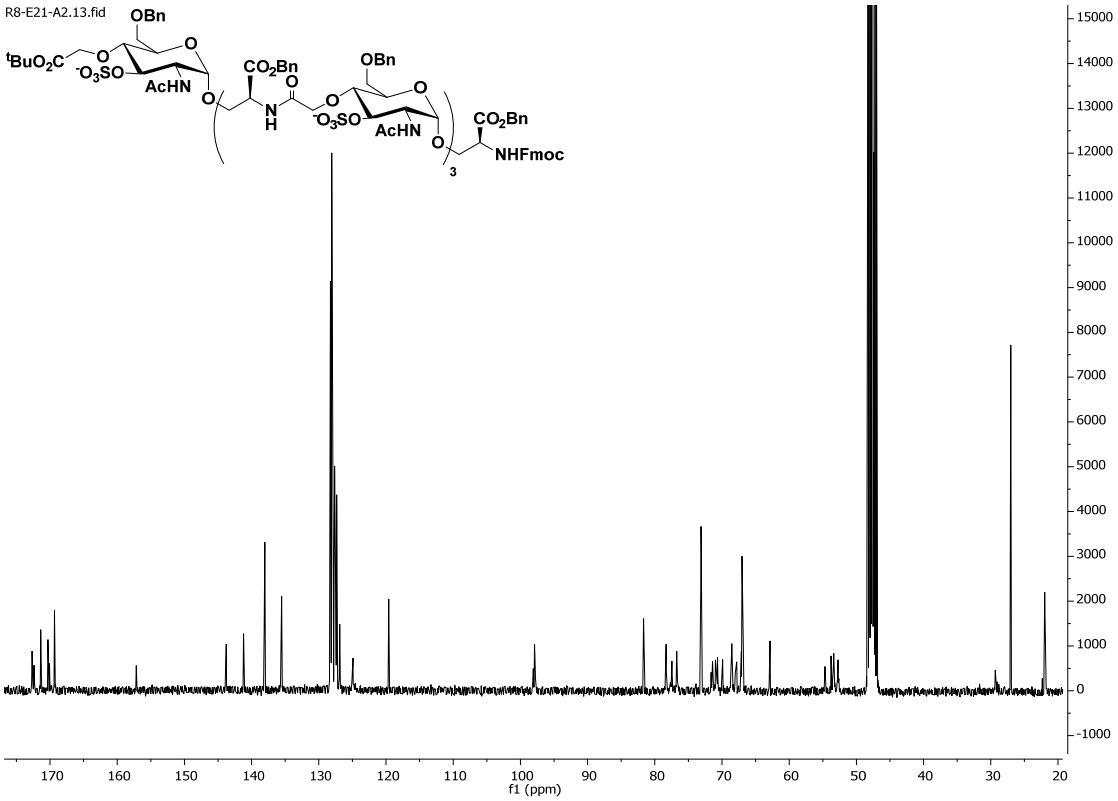


Figure S10 (continuation)

(**B**) ^{13}C-NMR



(**C**) HSQC

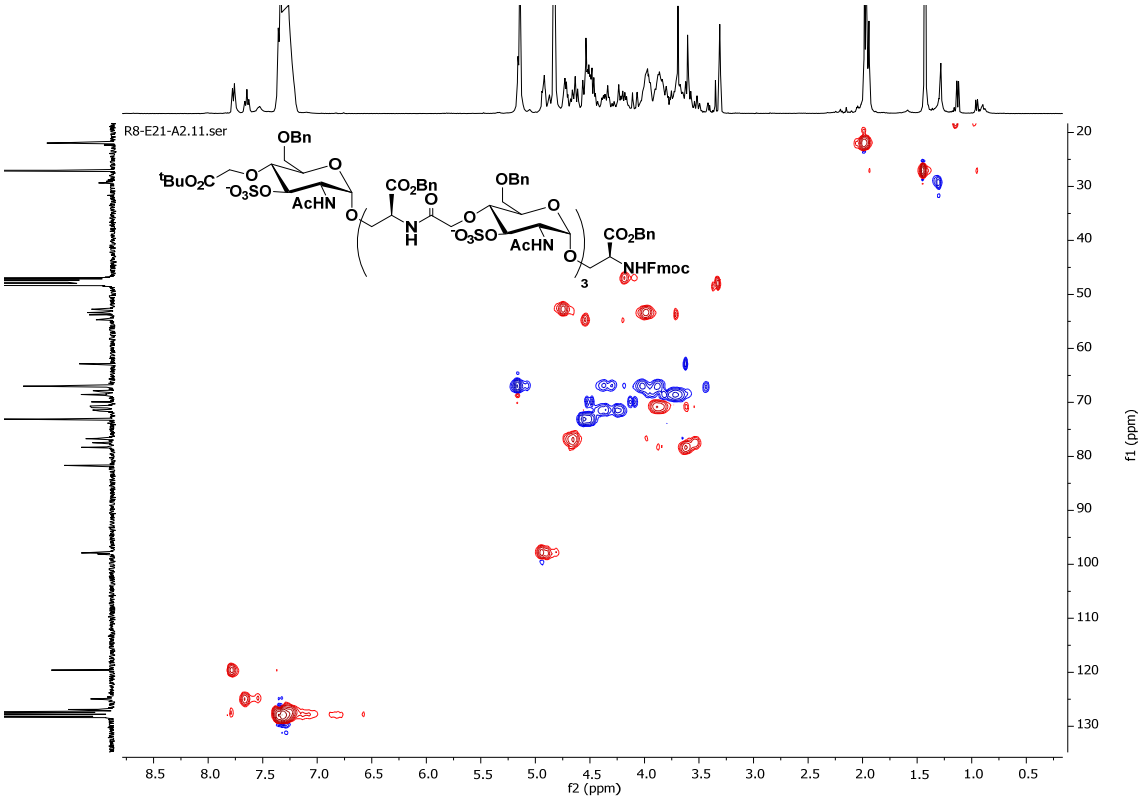
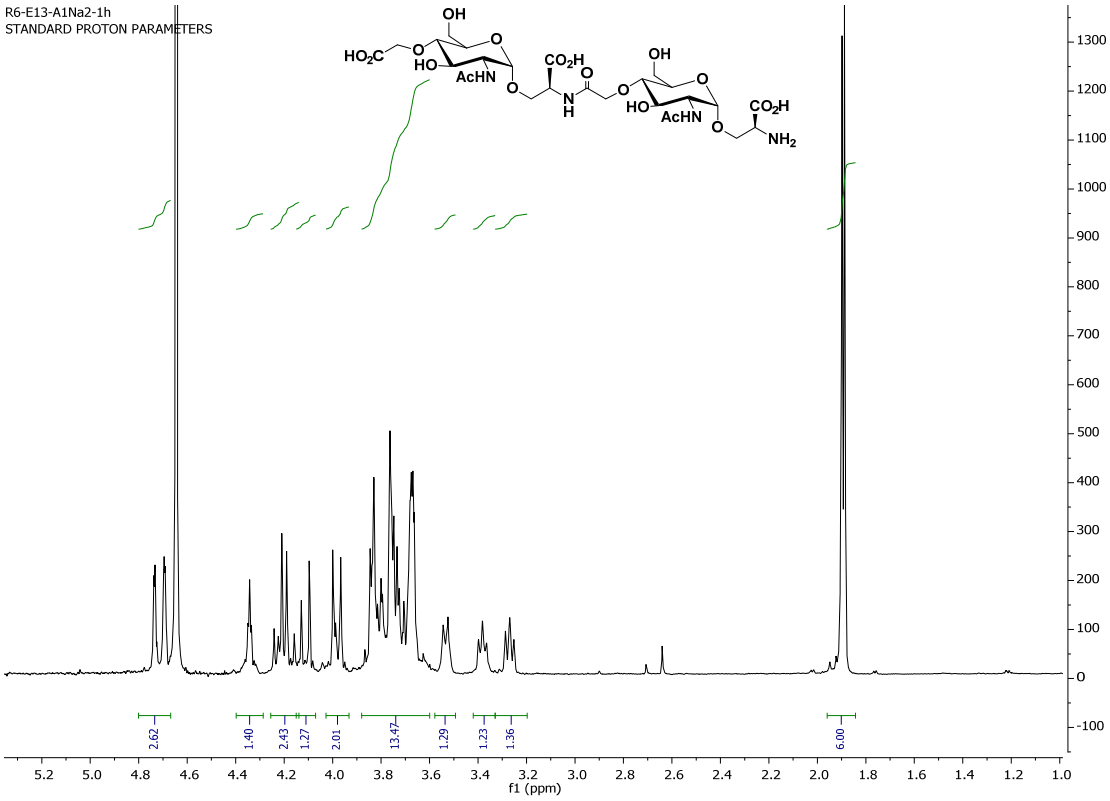


Figure S11. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **1**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

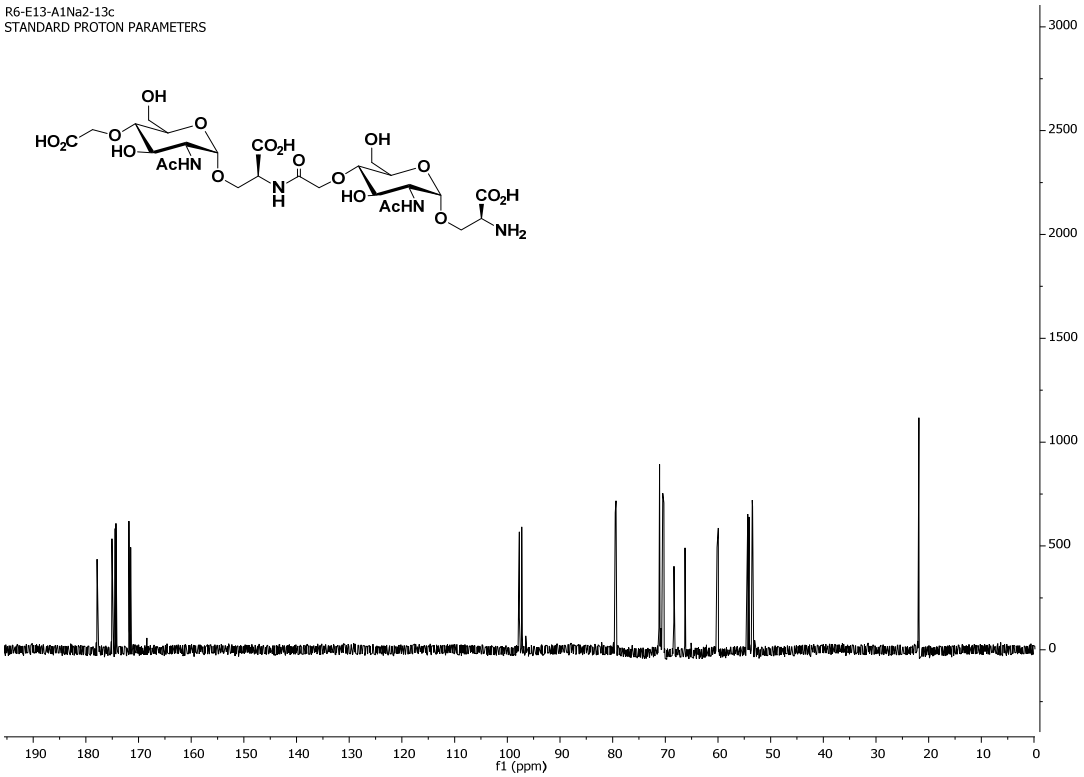
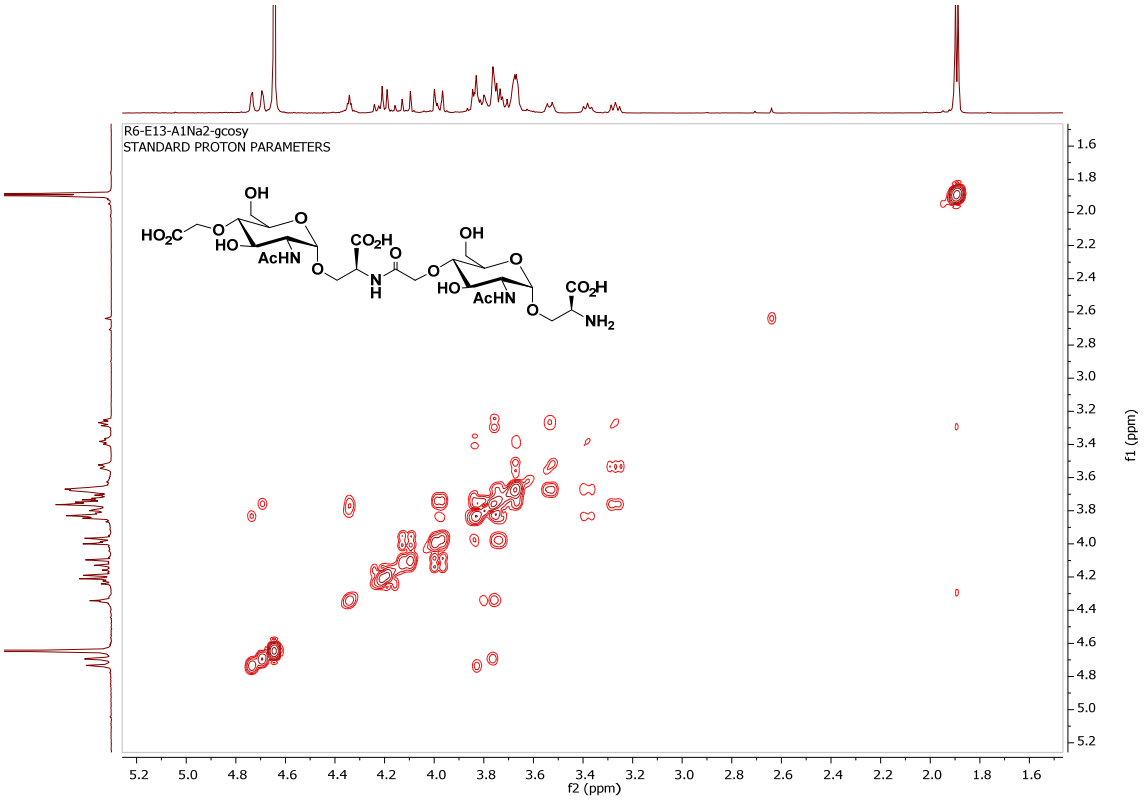


Figure S11 (continuation)

(**C**) COSY



(**D**) HSQC

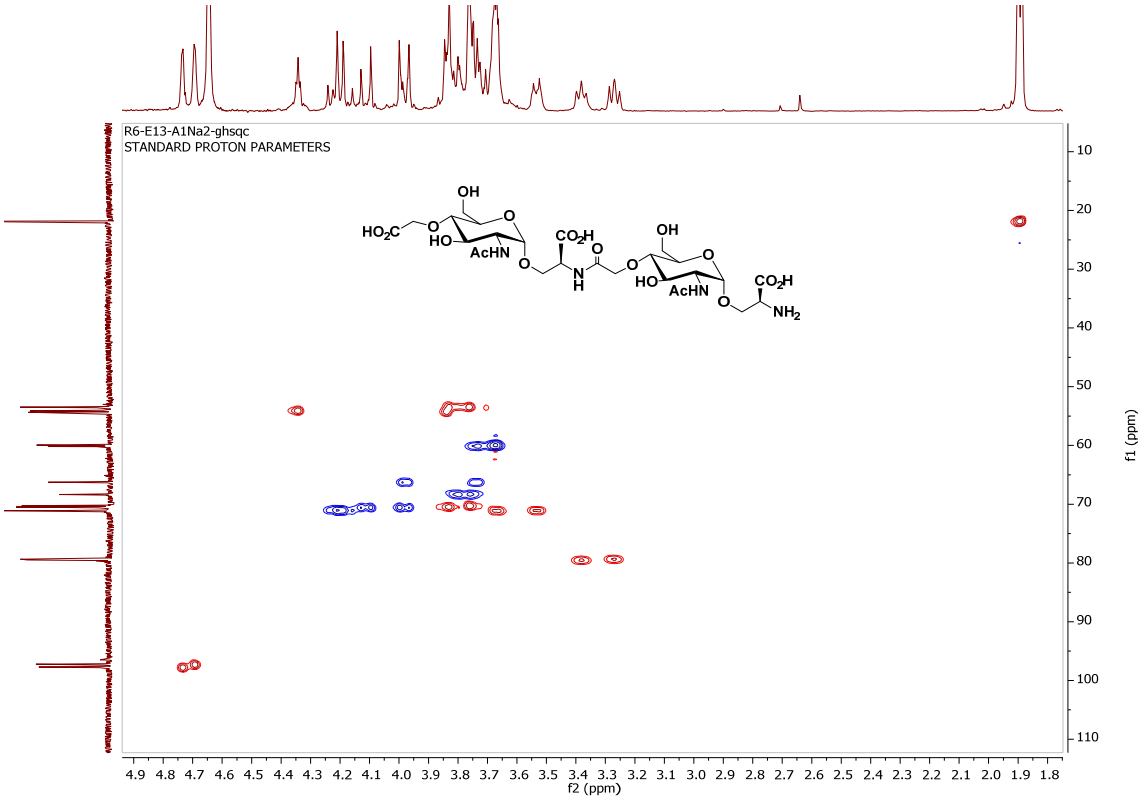
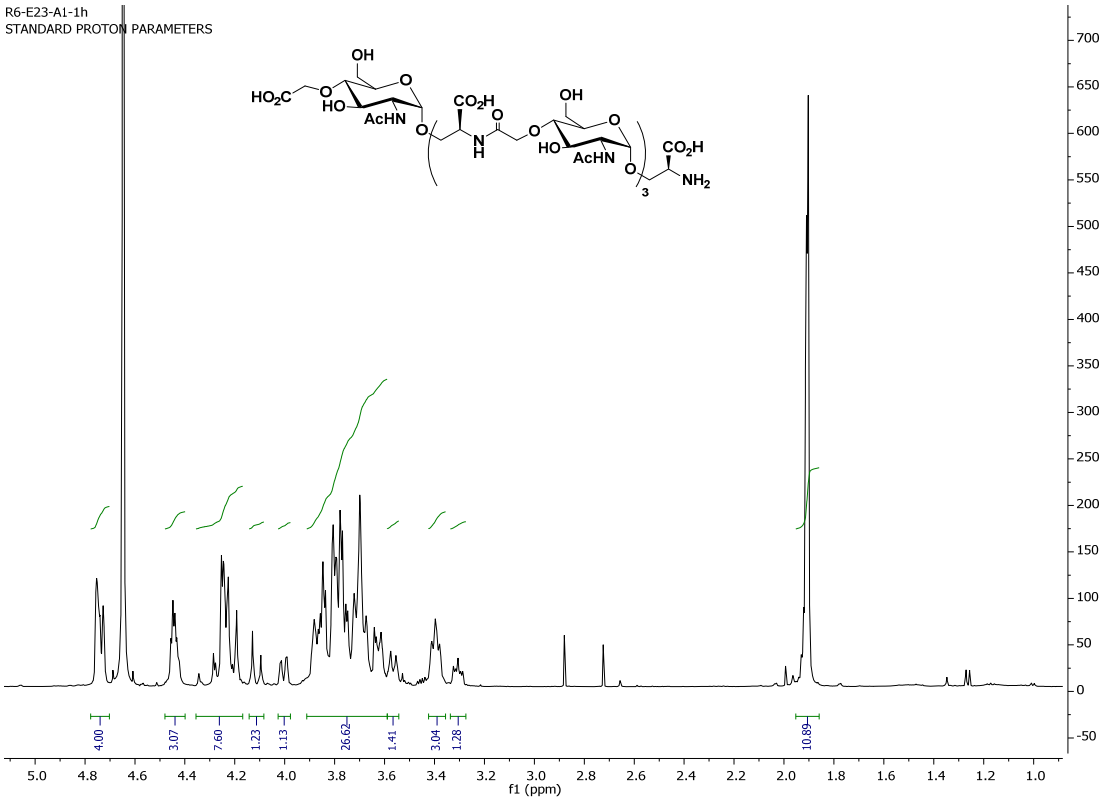


Figure S12. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **2**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

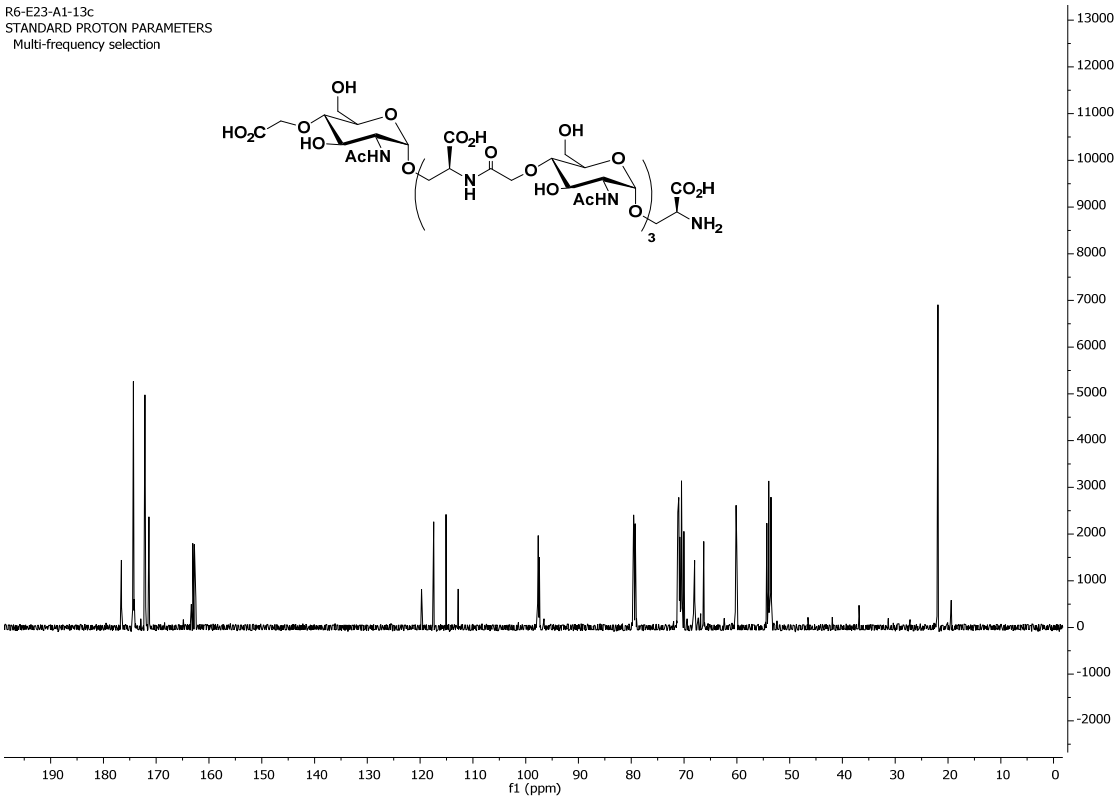
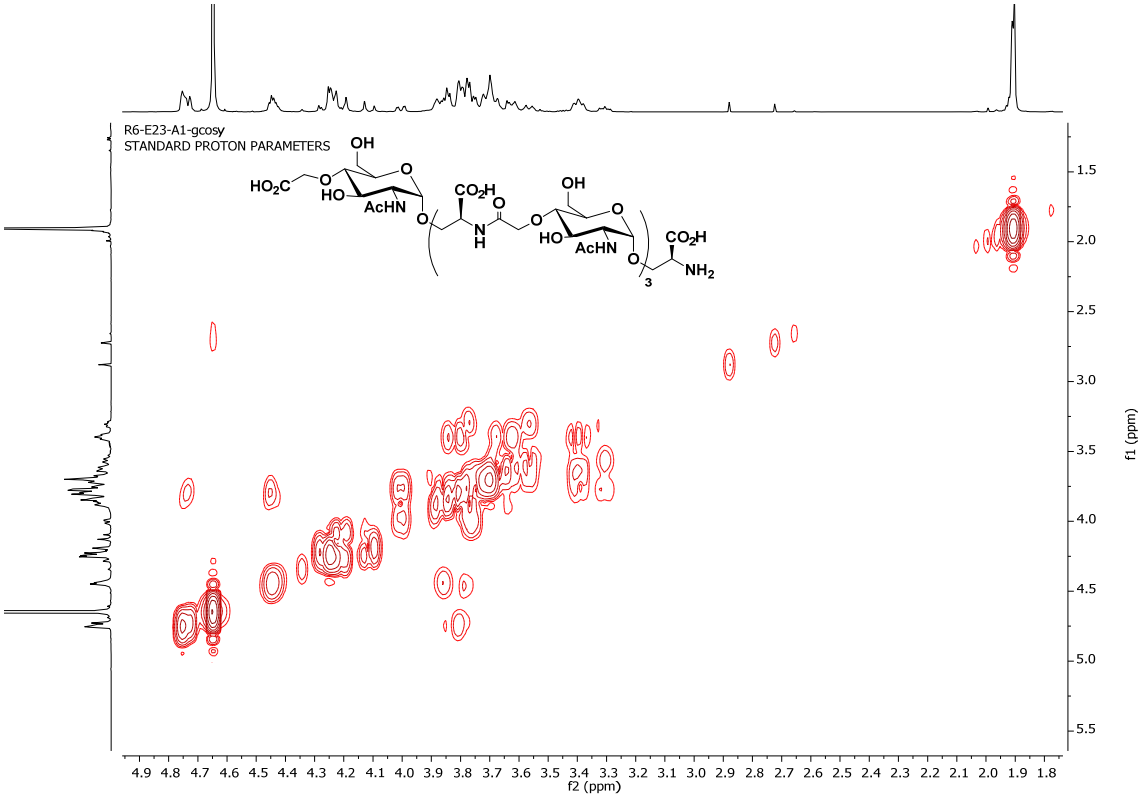


Figure S12 (continuation)

(**C**) COSY



(**D**) HSQC

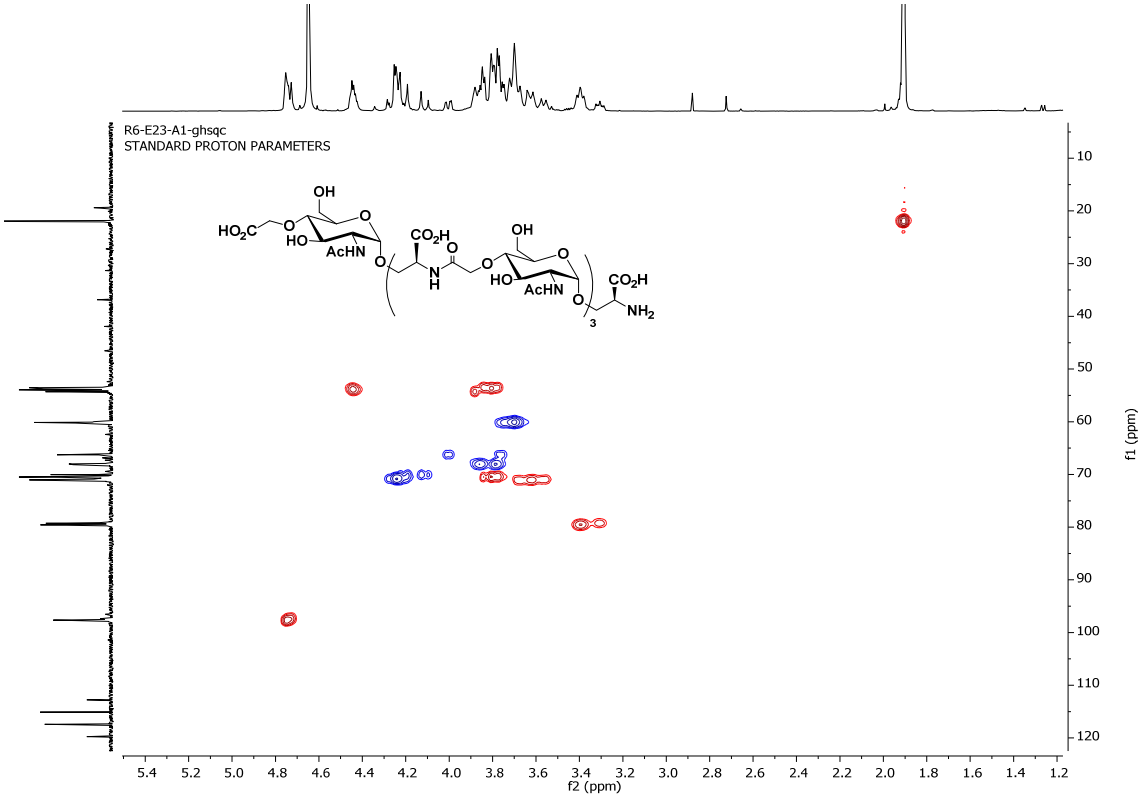
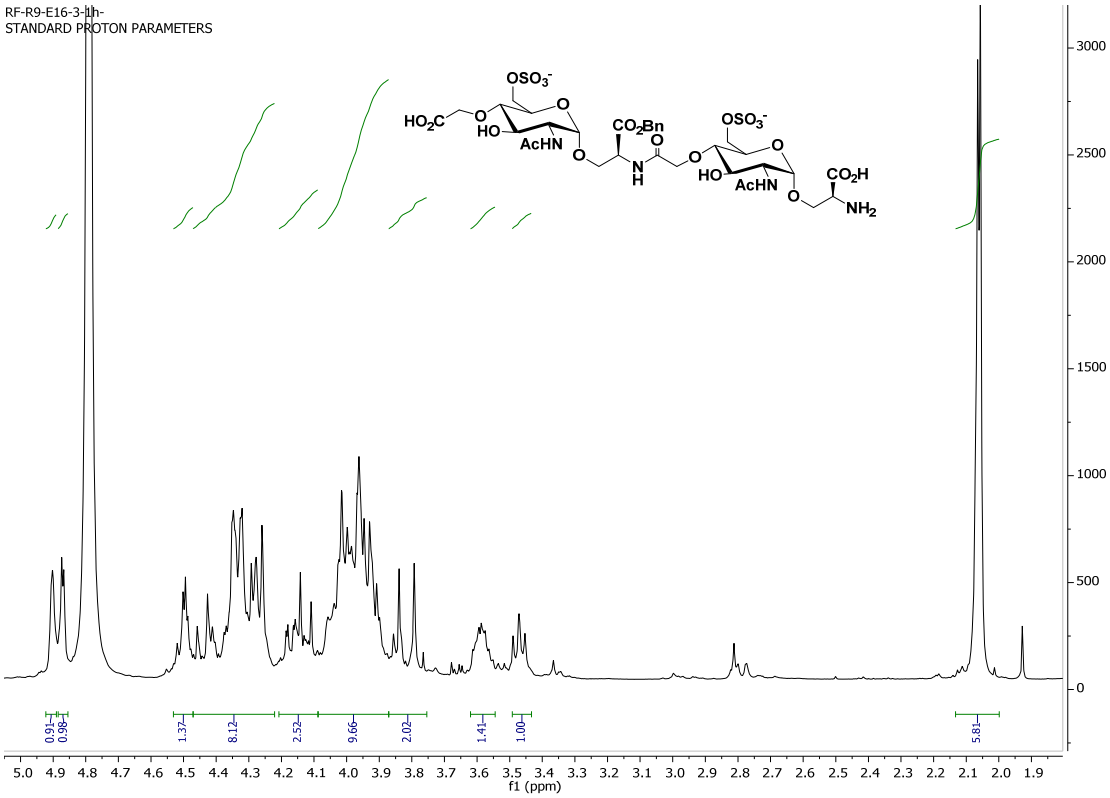


Figure S13. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **3**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

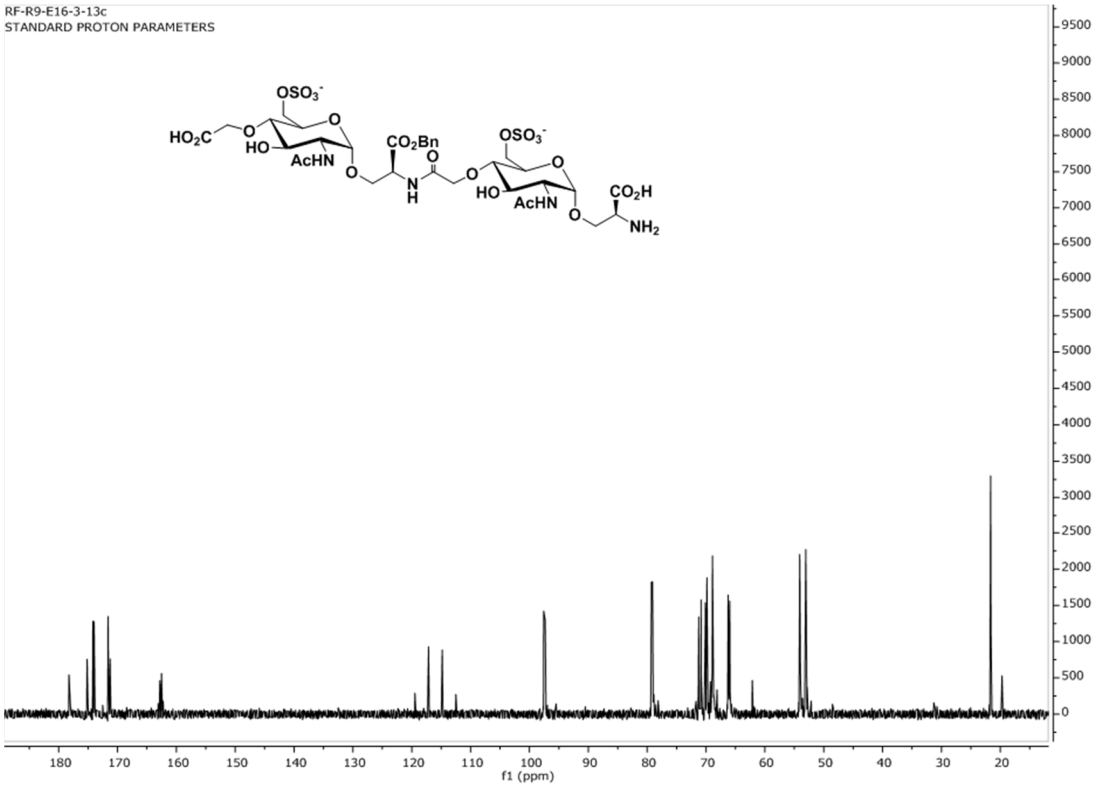
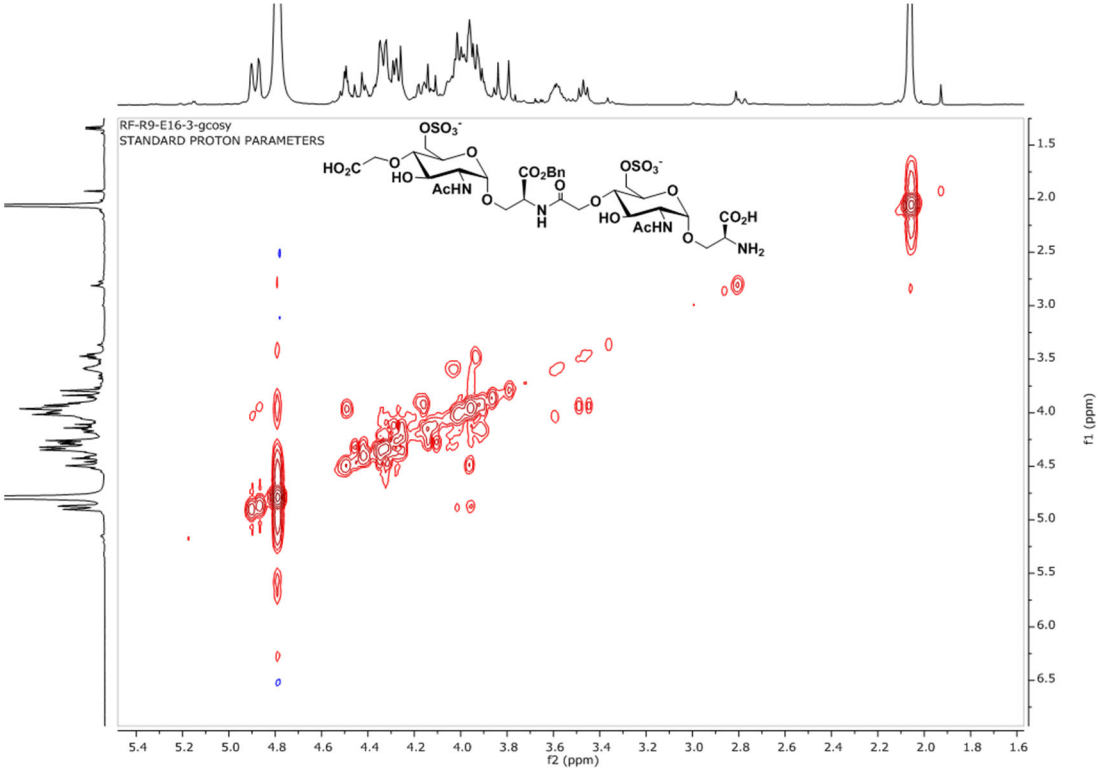


Figure S13 (continuation)

(**C**) COSY



(**D**) HSQC

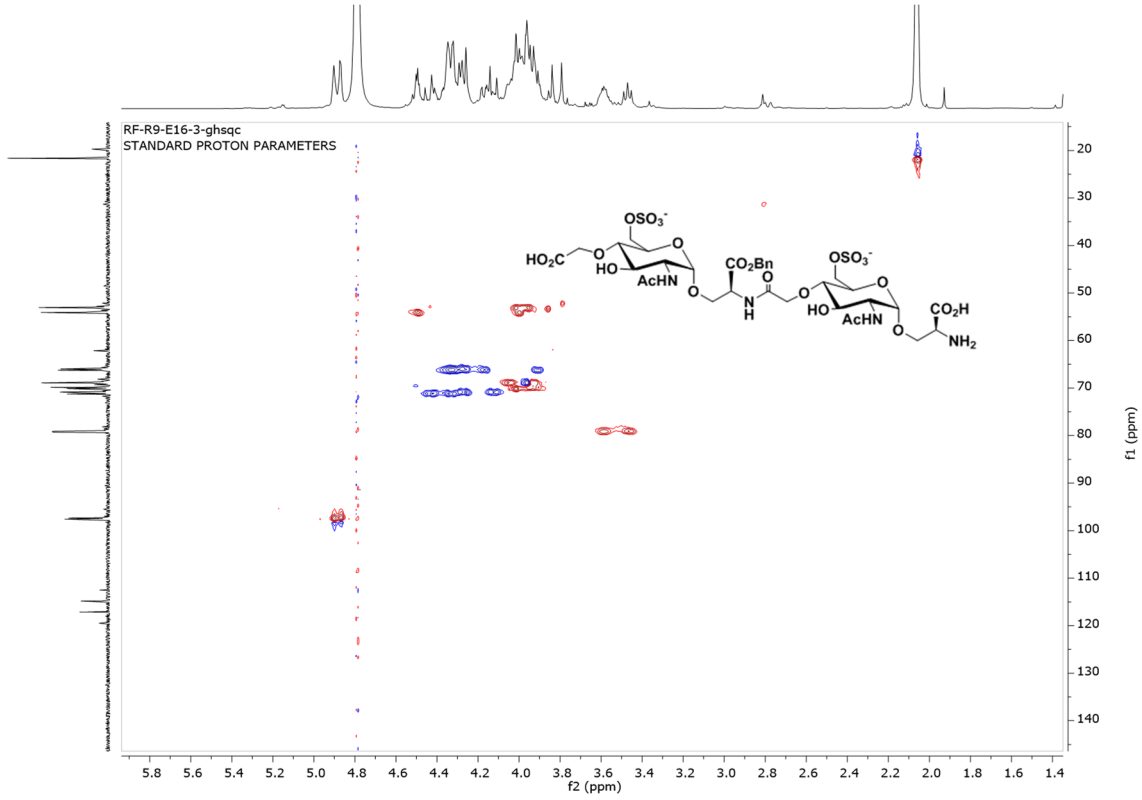
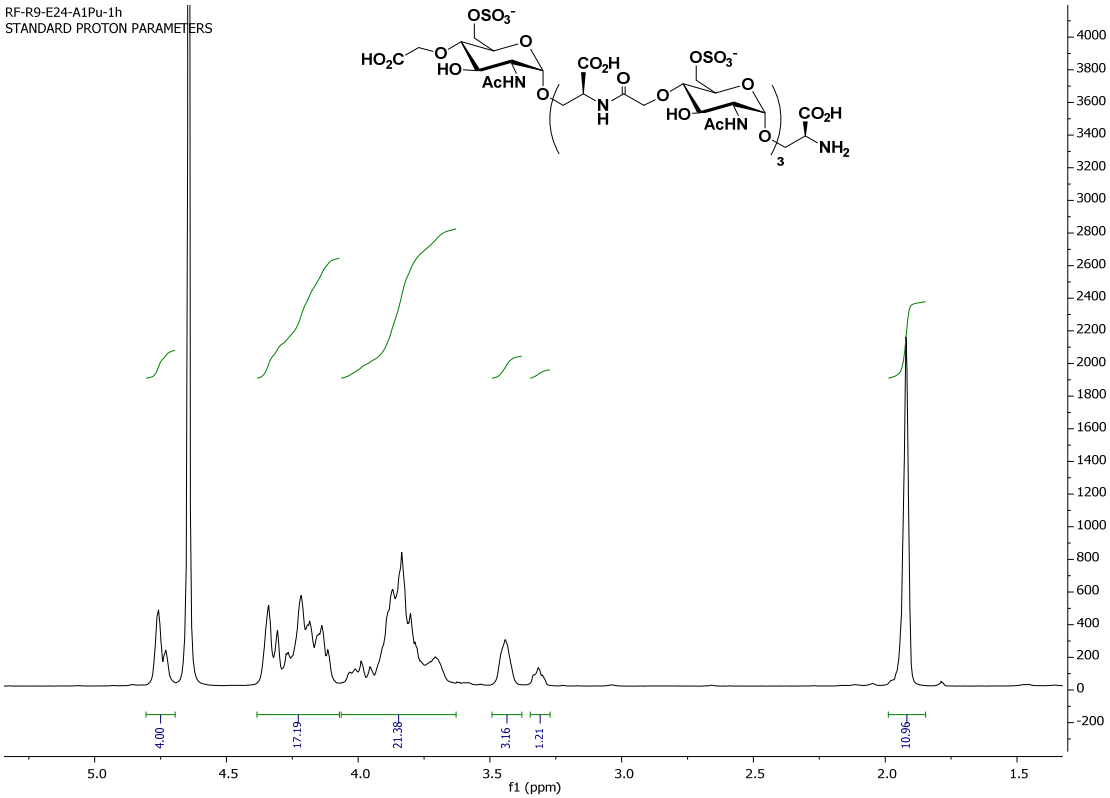


Figure S14. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **4**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

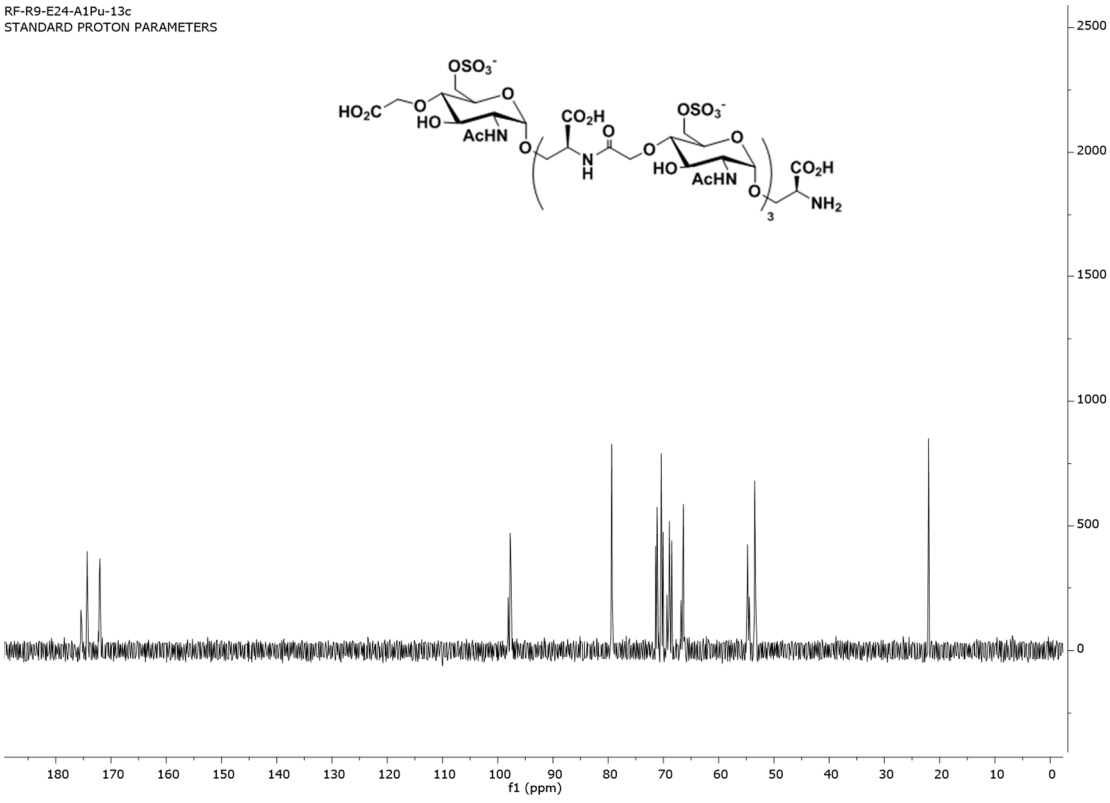
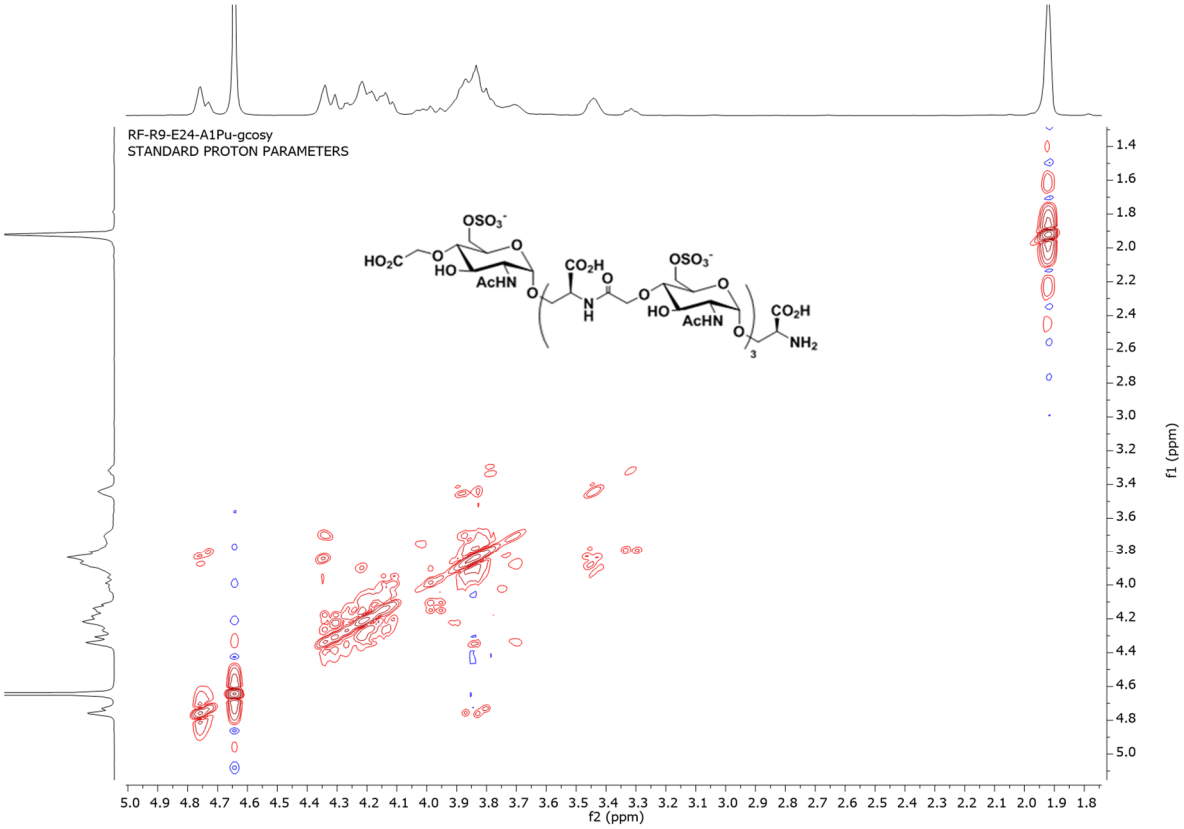


Figure S14 (continuation)

(**C**) COSY



(**D**) HSQC

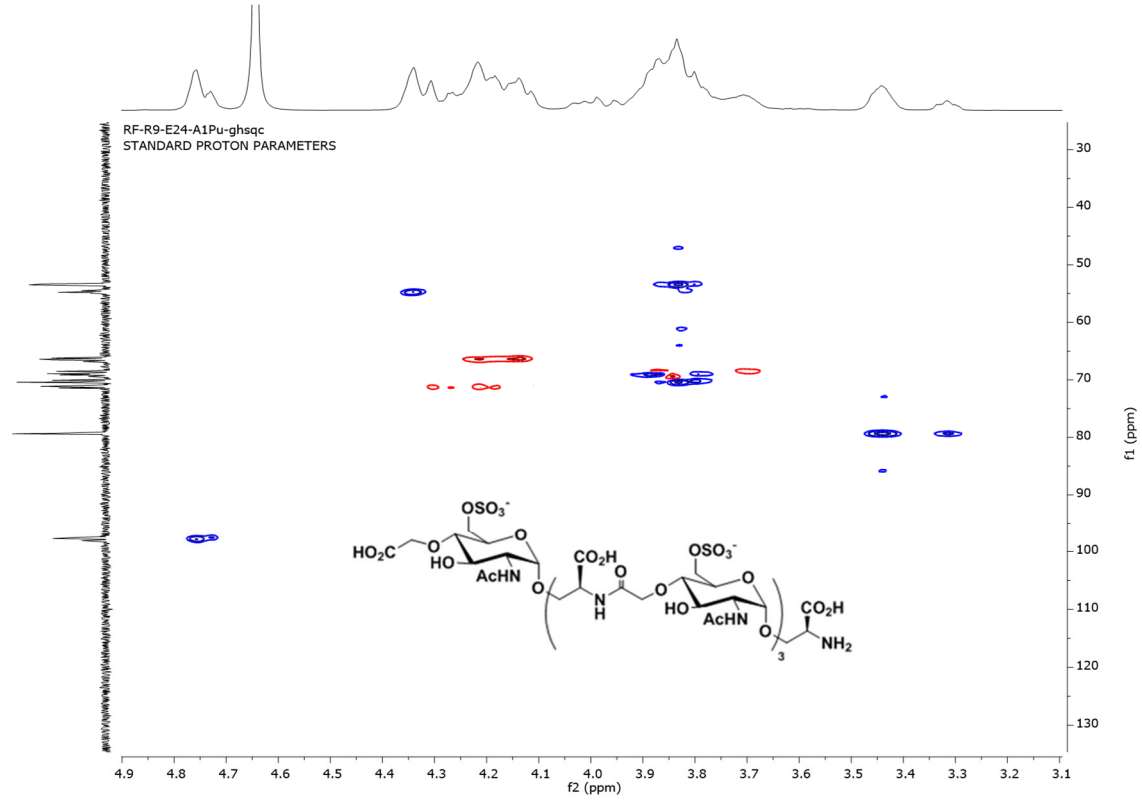
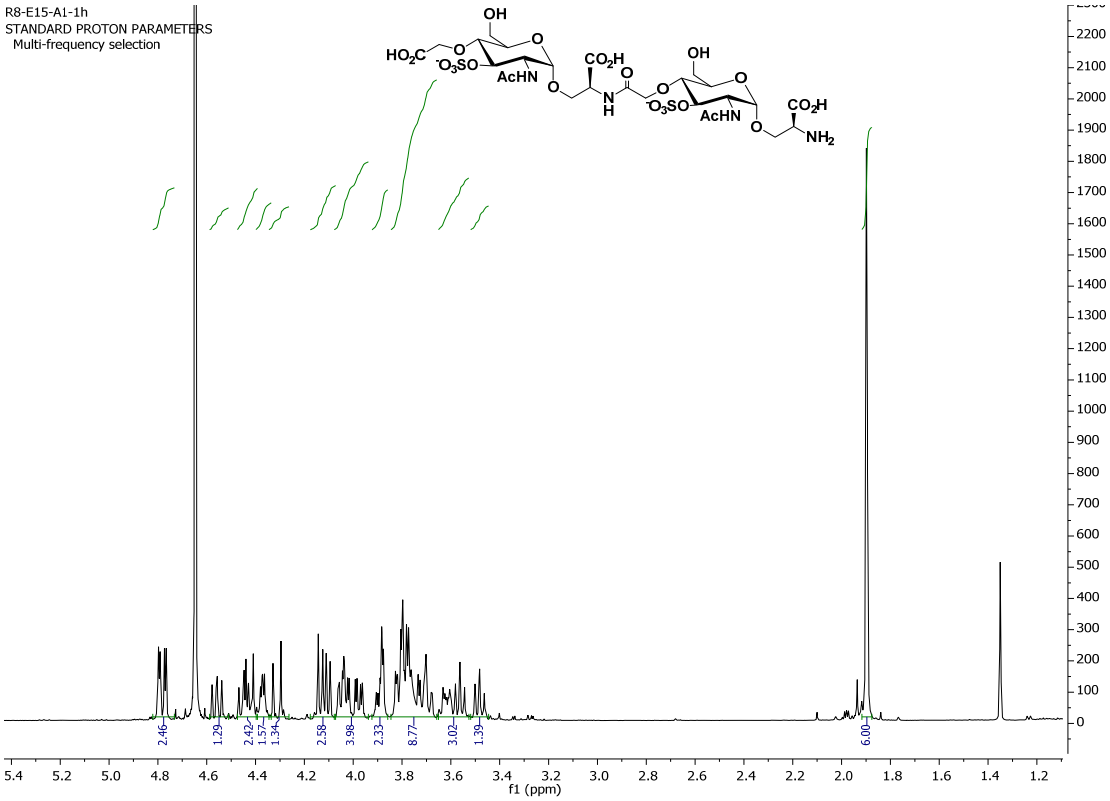


Figure S15. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **5**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

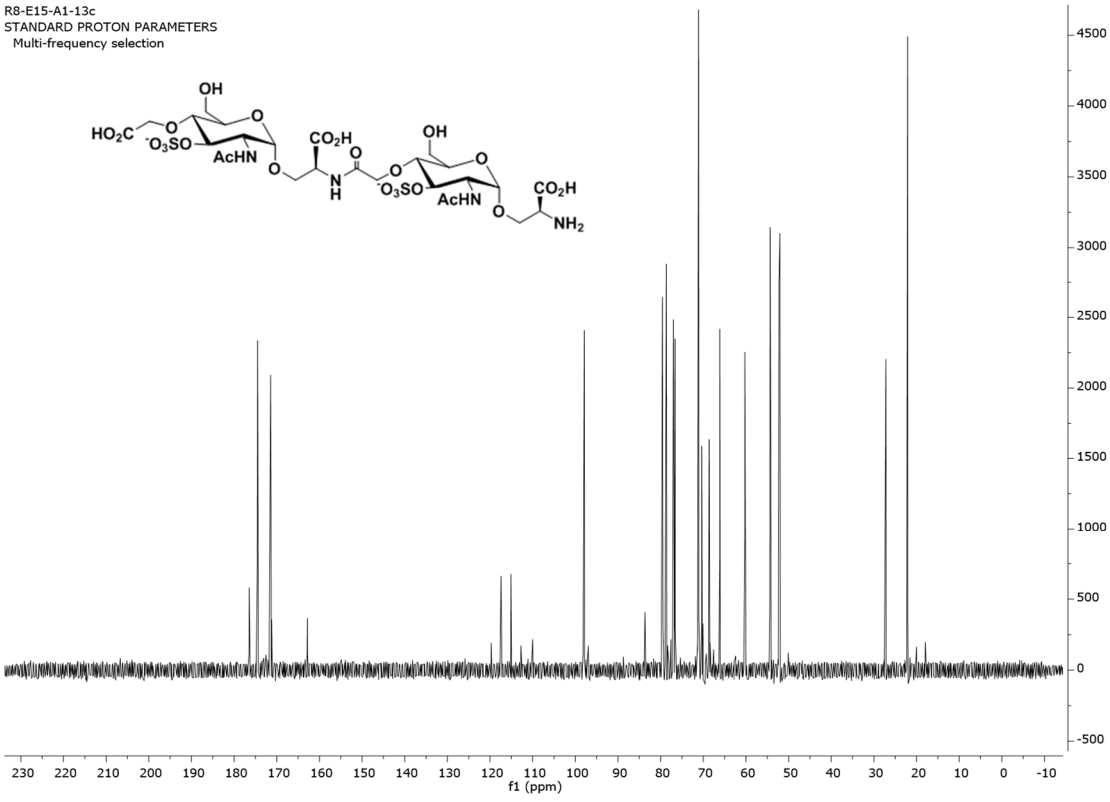
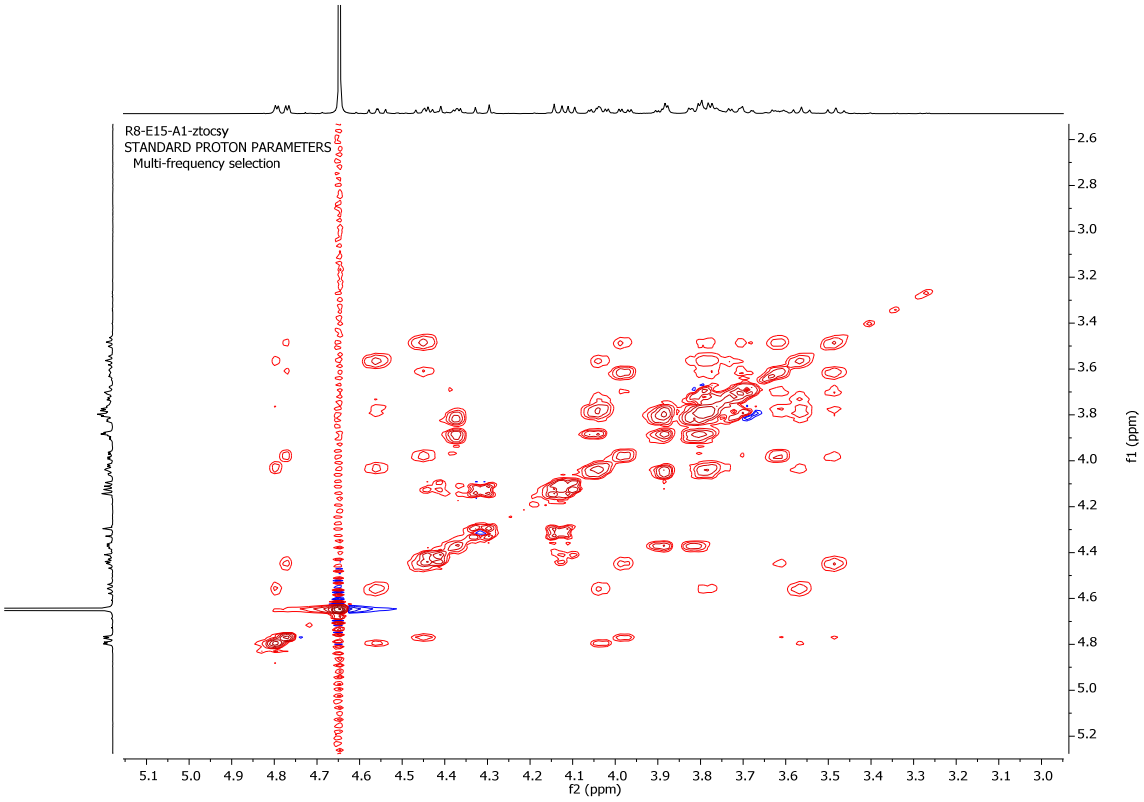


Figure S15 (continuation)

(**C**) COSY



(**D**) HSQC

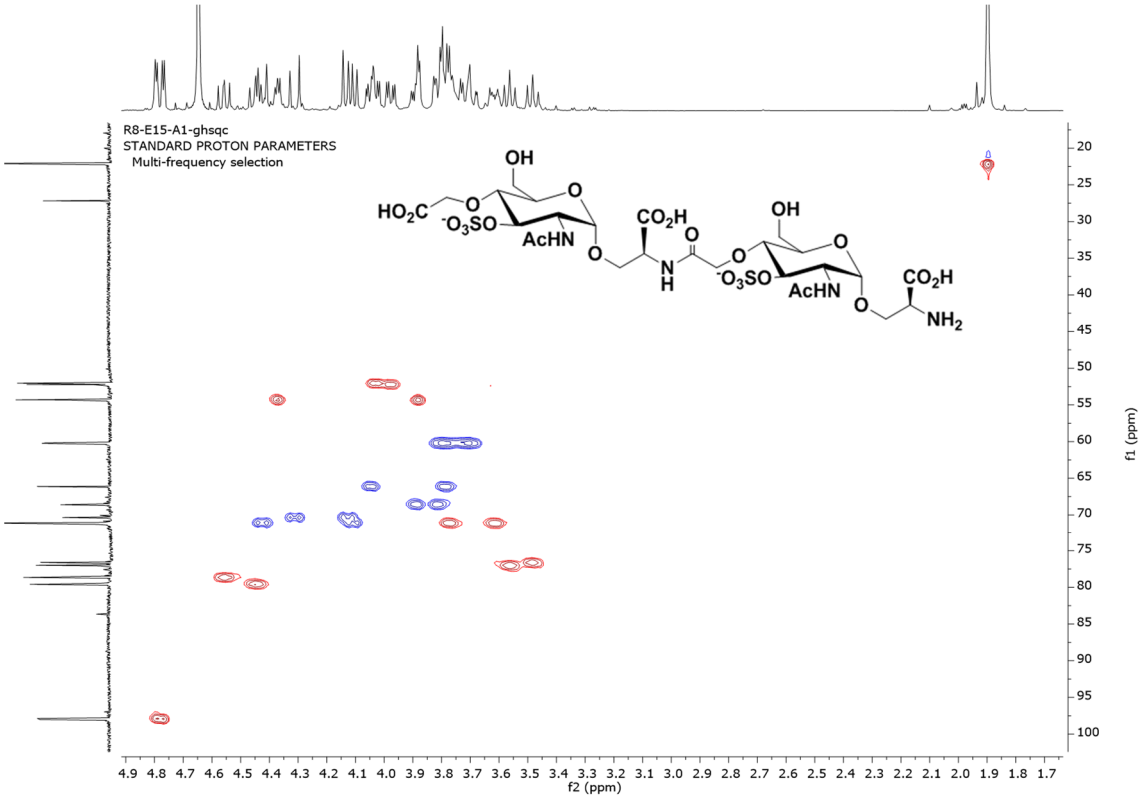
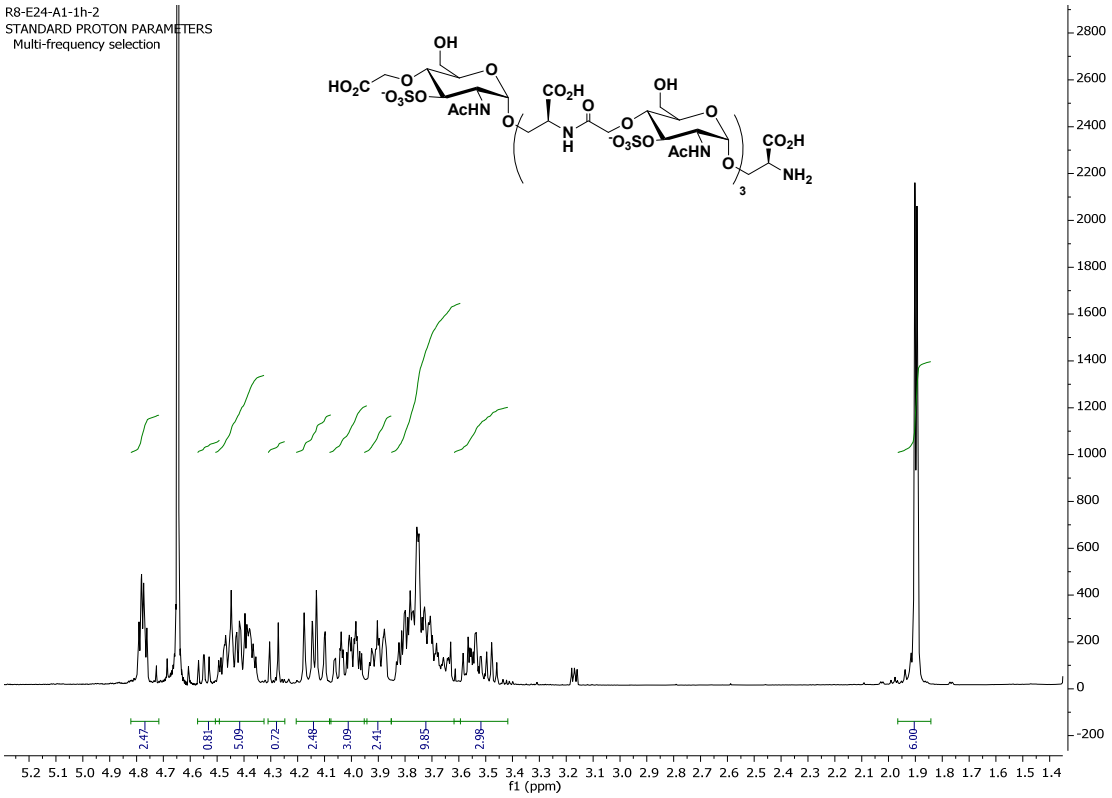


Figure S16. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **6**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

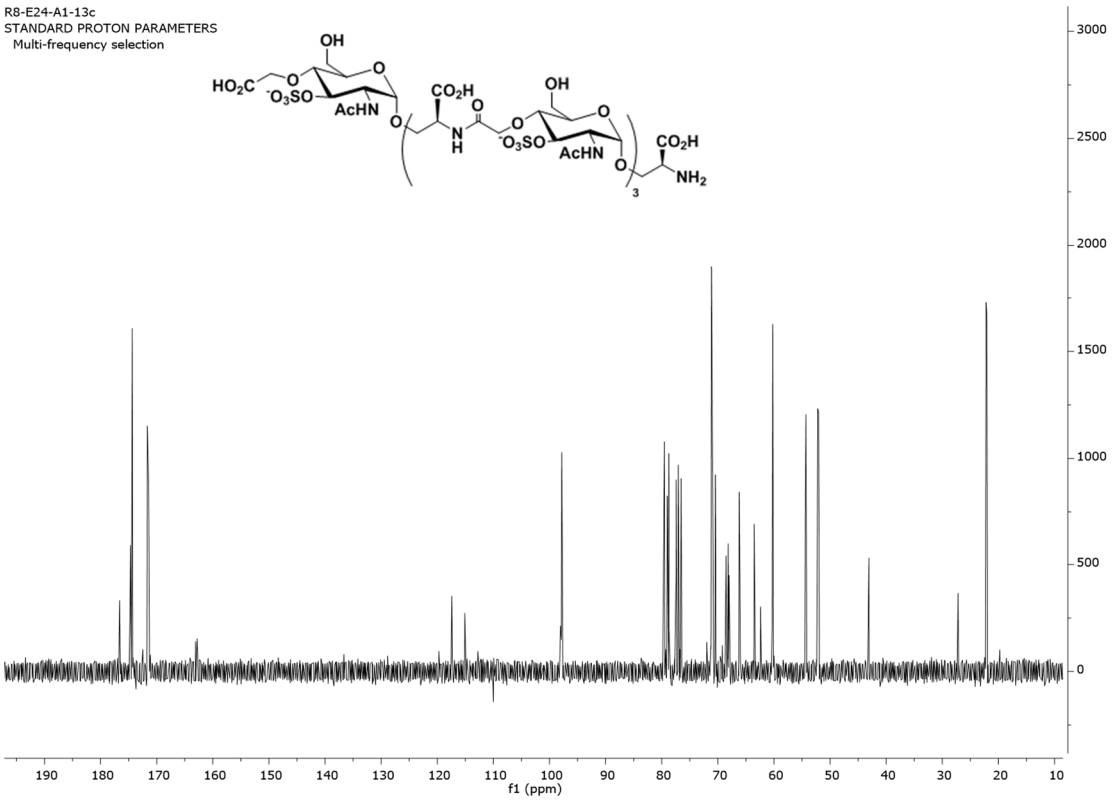
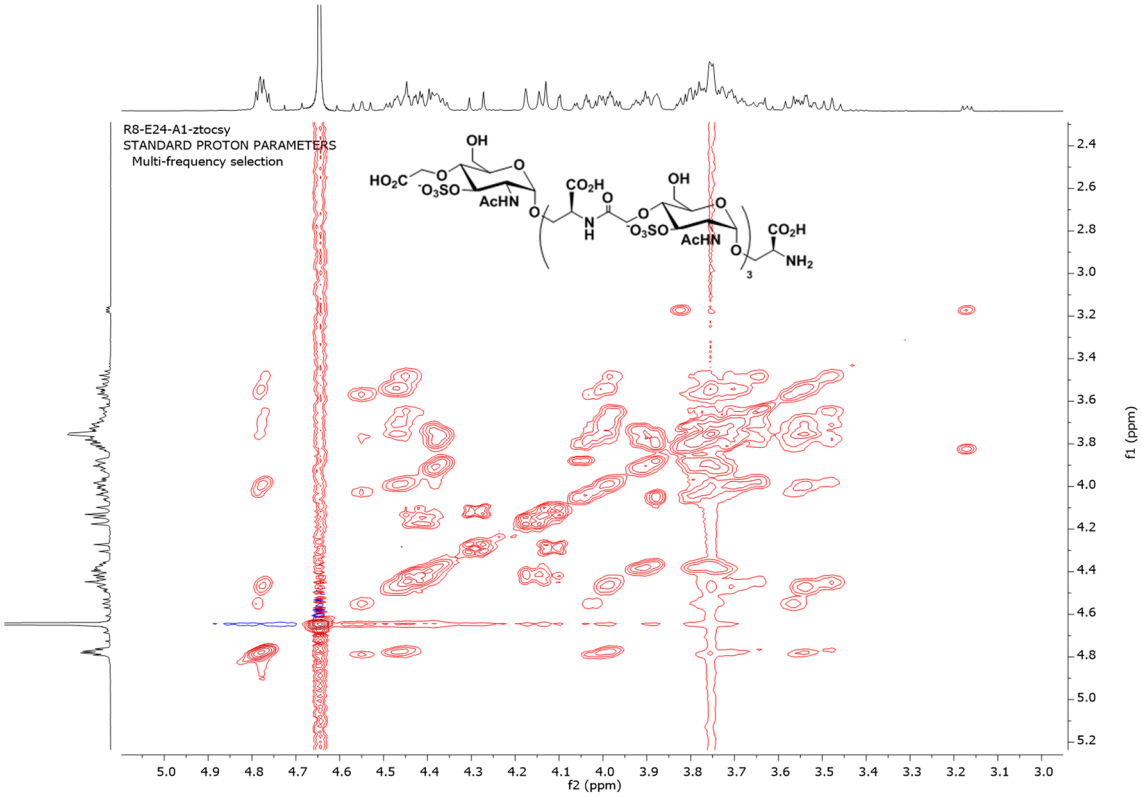


Figure S16 (continuation)

(**C**) COSY



(**D**) HSQC

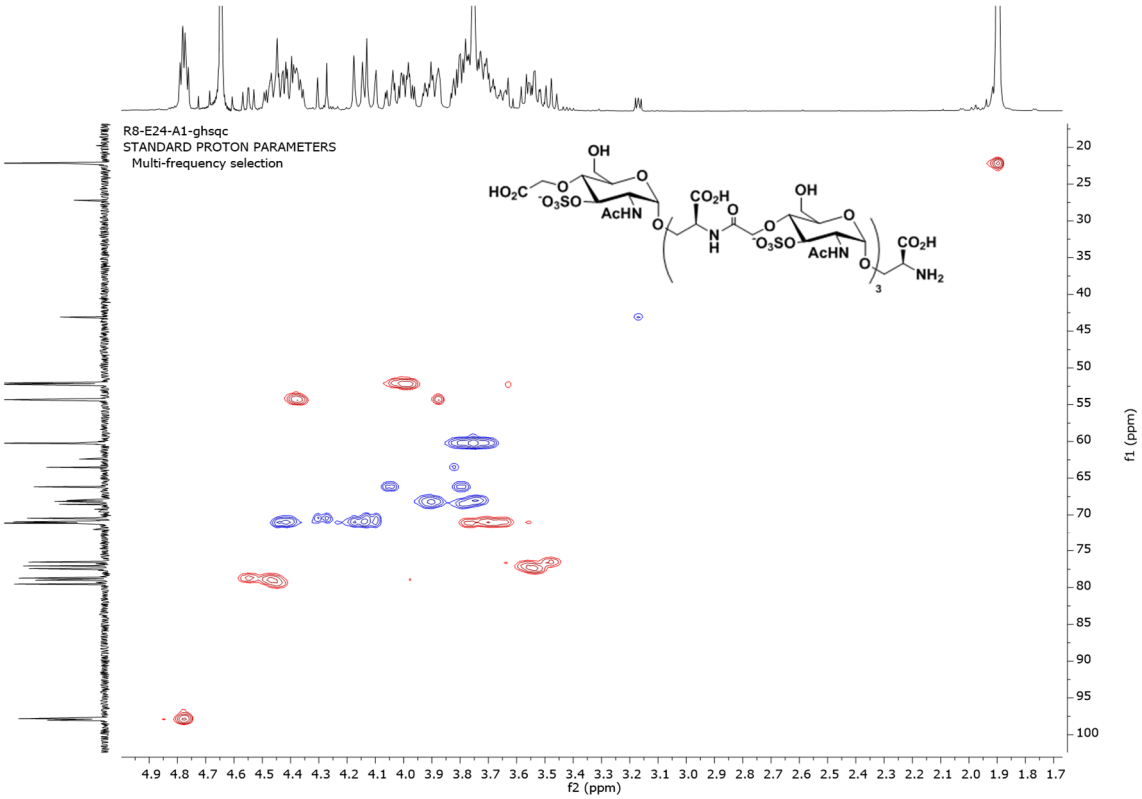
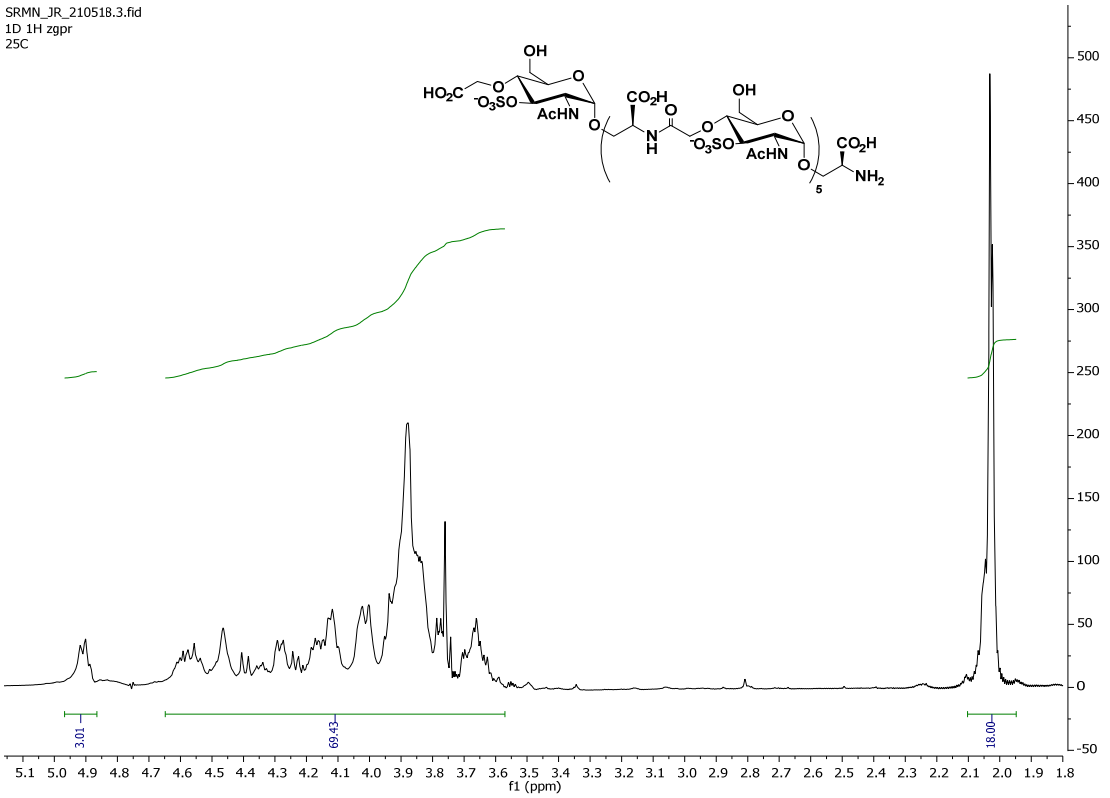


Figure S17. ^{1}H (**A**), ^{13}C (**B**), COSY (**C**) and HSQC (**D**) NMR spectra of compound **7**.

(**A**) ^{1}H-NMR



(**B**) ^{13}C-NMR

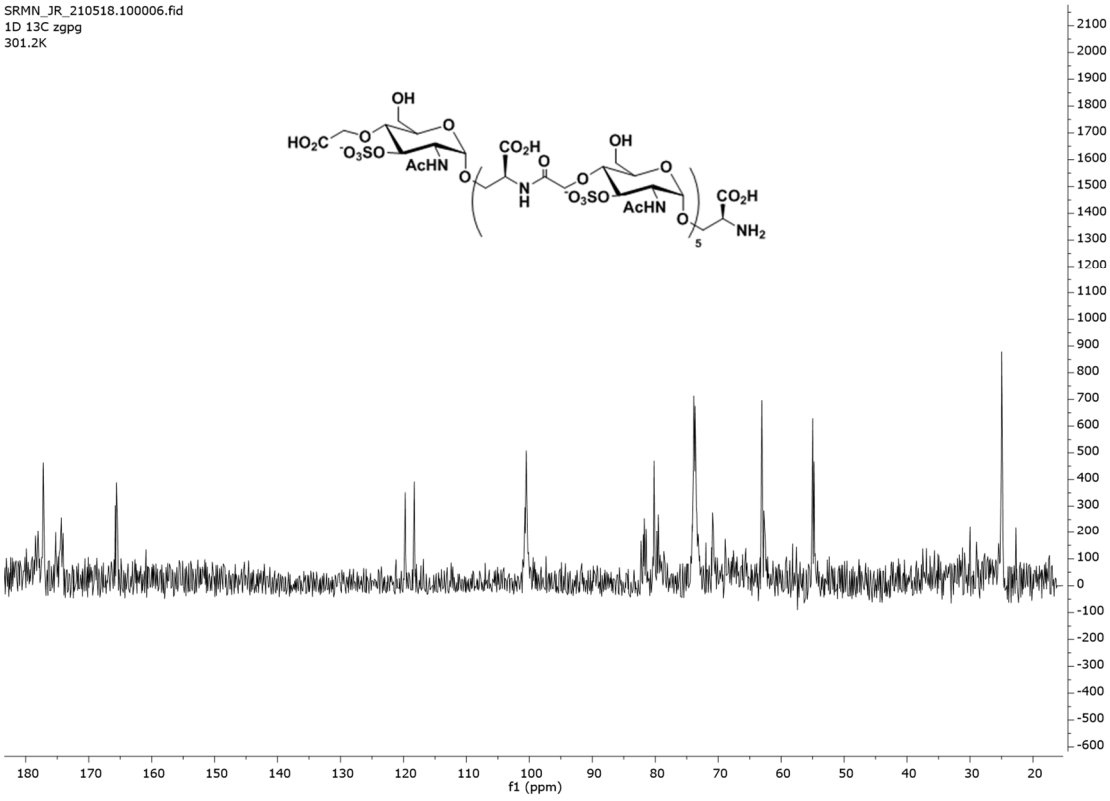
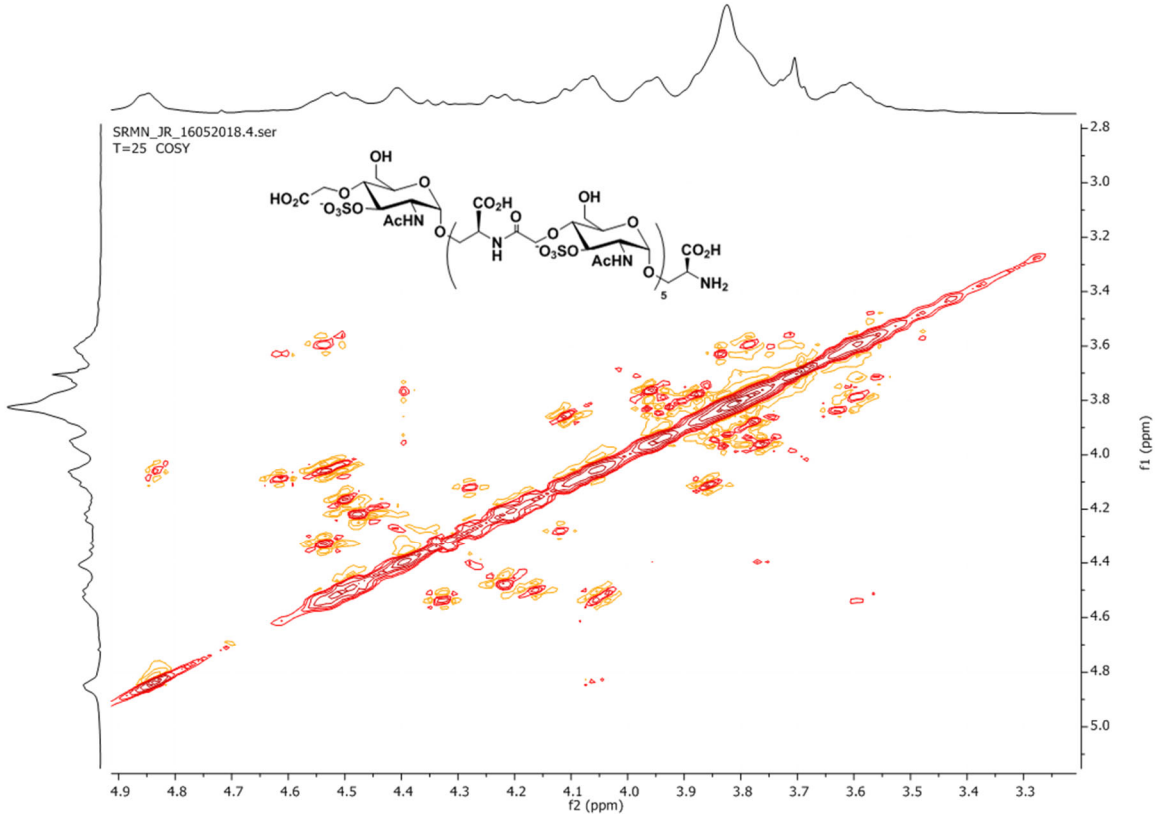


Figure S17 (continuation)

(**C**) COSY



(**D**) HSQC

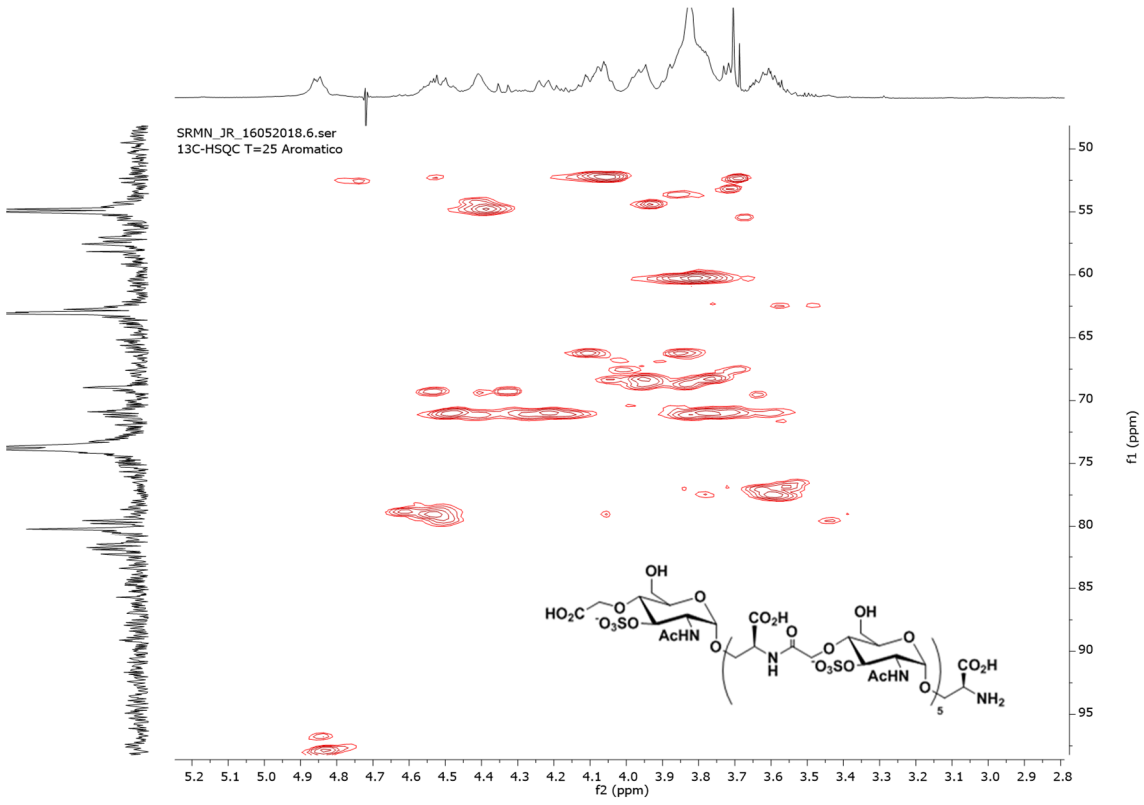


Figure S18. Sensorgrams for binding of compound 7 using increasing concentrations of the ligand in the range 50-1000 µM.

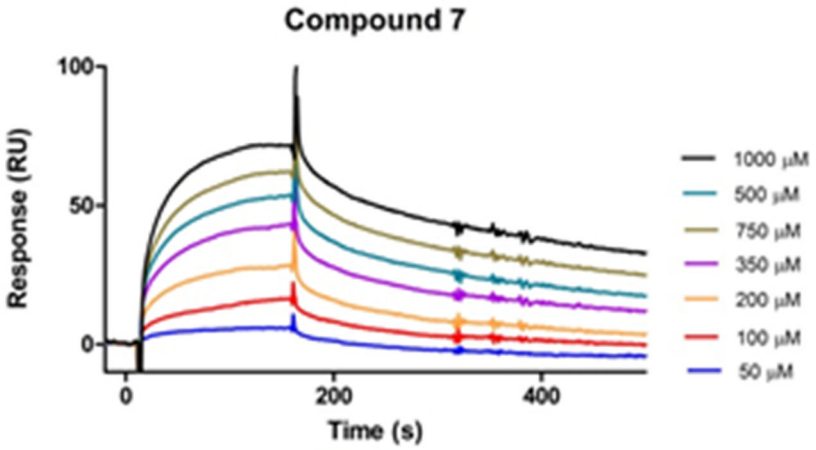


Figure S19. SPR binding plot adjusted with one site specific binding model. RU, resonance units.