Electronic Supplementary Material (ESI) for Chemical Science.

Synthesis of Aryl-Thioglycopeptides Through Chemoselective Pd-Mediated Conjugation

David Montoir,[a] Mehdi Amoura,[b] Zine El Abidine Ababsa,[a] T. M. Vishwanatha,[b] Expédite Yen-Pon,[a] Vincent Robert,[c] Massimiliano Beltramo,[c] Véronique Piller,[b] Mouâd Alami,[a] Vincent Aucagne,*[b] and Samir Messaoudi*[a]

[a]: BioCIS, Univ. Paris-Sud, CNRS, University Paris-Saclay, 92296 Châtenay-Malabry, France
[b]: Centre de Biophysique Moléculaire, CNRS UPR4301, 45071 Orléans cedex 2, France
[c]: UMR Physiologie de la Reproduction et des Comportements (INRA, UMR85; CNRS, UMR7247, Université de Tours, IFCE), 37380 Nouzilly, France.

aucagne@cnrs-orleans.fr

samir.messaoudi@u-psud.fr

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General Information

For Pd-catalyzed coupling of thiosugars (1a-h) with iodo-aminoacids (2a-e) and peptides (4a-f)

All reactions were conducted under argon atmosphere. Solvents: cyclohexane, dichloromethane, ethyl acetate and methanol for extraction and chromatography were technical grade.

Instrumentation

These compounds were all identified by usual physical methods, e.g., ^{1}H NMR, ^{13}C NMR (J-MOD), IR, HR-MS (ESI). ^{1}H and ^{13}C NMR spectra were measured in CD_3OD or DMSOd_6, with a Bruker Avance-300. ^{1}H chemical shifts are reported in ppm from an internal standard TMS or of residual methanol (3.31 ppm) or DMSO (2.50 ppm). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets). ^{13}C chemical shift are reported in ppm from central peak of deuteriomethanol (49.00 ppm) or dimethyl sulfoxide-d_6 (39.52 ppm). IR spectra were measured on a Bruker Vector 22 spectrophotometer and are reported in wave numbers (cm^{-1}). The angels of rotation were measured on a PerkinElmer Polarimeter 341 and denoted as specific rotations: $[\alpha]_D$. High-resolution mass spectra (HR-MS) were recorded on a Bruker MicroTOF spectrometer, using ESI with methanol as the carrier solvent. Nominal and exact *m/z* values are reported in Daltons. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (0.015-0.040 mm) was used for column chromatography. Compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with vanillin/Δ. Unless otherwise noted, other materials are obtained from commercial suppliers and were used without further purification

The Xantphos Palladium precatalyst Pd-G3-XantPhos was synthetized according to Buchwald protocol: N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci*., 2013, **4**, 916-920.

For Pd-catalyzed coupling of thiosugars (1c, 1h-i) with iodo-peptides MUC1 (6a-b)

All reagents and solvents were used without further purification. Protected amino acids, Rink's linker and HCTU were purchased from Merck Biosciences (Nottingham, UK). *N*-Fmoc-4iodo-*L*-phenylalanine was purchased from Alfa Aesar (Kandel, Germany). Aminomethyl TentaGel R resin was purchased from Rapp polymers (Tuebingen, Germany). Peptide synthesis grade DMF was purchased from Applied Biosystems (Courtaboeuf, France). Ultrapure water was obtained using a Milli-Q water system from Millipore (Molsheim, France). All other chemicals were from Sigma Aldrich (St-Quentin-Fallavier, France) and solvents from SDS-Carlo Erba (Val de Reuil, France).

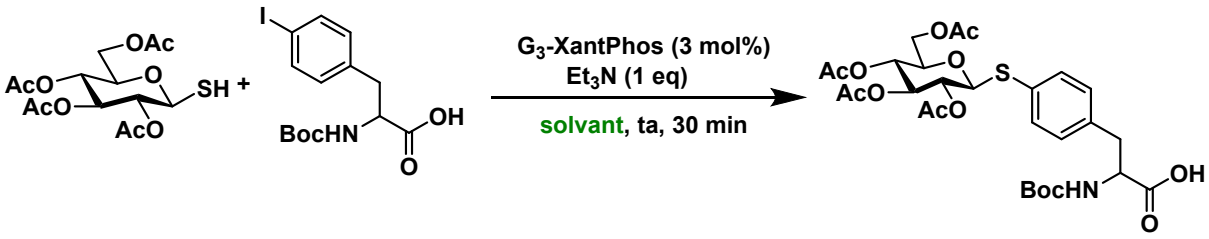
High resolution ESI-MS analyses were performed on a maXis^{TM} ultra-high-resolution Q-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany), using the positive mode.

LC/MS analyses were performed on a 6120B single Quadrupole LC/MS system (Agilent Technologies, Les Ulis, France), using positive mode.

HPLC analyses were carried out on a Chromaster system equipped with a Hitachi 5160 pump, a Hitachi 5260 auto sampler and a Hitachi 5430 diode array detector. Chromolith HighResolution RP-18e (150 Å, 10 × 4.6 mm, 3 mL/min flow rate) column was used for analysis. Semi-preparative HPLC purifications were carried out on a LaChrom Elite system equipped with a Hitachi L-2130 pump, a Hitachi L-2455 diode array detector and a Hitachi L-2200 auto sampler. Nucleosil C18 (300 Å, 5 μm, 250 × 10 mm, 3 mL/min flow rate) or Jupiter C4 (300 Å, 5 μm, 250 × 10 mm, 3 mL/min flow rate) columns were used for purification. Chromatography was conducted at room temperature unless otherwise mentioned. Solvents A and B are 0.1% TFA in H_2O and 0.1% TFA in MeCN, respectively. Each gradient was followed by a washing step (up to 95% B/A over 0.5 min for the HR Chromolith). LC/HRMS and LC/MS analyses were carried out respectively on an Ultimate® 3000 RSLC HPLC system (Dionex, Germering, Germany), coupled with the maXis™ mass spectrometer and on an Agilent 1260 Infinity HPLC system, coupled with the Agilent 6120 mass spectrometer, and both fitted with an Aeris Widepore XB-C18 2 (3.6 μm, 150 × 2.1 mm, 0.5 mL/min flow rate, 40°C) column. Solvents A and B were 0.1% formic acid in H_2O and 0.08% formic acid in MeCN, respectively. Gradient: 3% B/A for 0.6 min, then 3 to 50% B/A over 10.8 min.

For yield calculations purposes, the quantities of purified MUC1-derived peptides (**7a-b** and **8a-f**) were determined by weight, taking into account a molecular weight including trifluoroacetate counter-ions (one per Arg, His, Lys and N-terminal amine of the peptide sequence) but not water content.

Optimization of the reactions conditions of *tetra-O*-acetylated 1-thio-β-D-glucopyranose 1a and N-Boc-DL-4- iodophenylalanine 2a



Entry	Solvent	Yield[b]
1	THF (100)	98 %
2	THF/H_2O (1:2)	92 %
3	DMSO/H_2O (1:2)	58 %[c]
4	CH_3CN/H_2O (1:2)	87 %
5	EtOH/H_2O (1:2)	64 %
6	H_2O (100%)	traces[c]

Reaction conditions: reaction of *tetra-O*-acetylated 1-thio-β-D-glucopyranose **1a** (1 equiv.), *N*-Boc-DL-4- iodophenylalanine **2a** (1 equiv.), XantPhos PdG_3 precatalyst (3 mol %) and Et_3N (1 equiv), solvent (0.1M). [b] Yield of isolated product after purification under flash chromatography. [c] 24 h reaction time.

Screening of other catalytic systems : Et_3N (1 equiv) was used as the base and THF/H_2O (1:2) as the reaction solvant (0.1M):

Entry	Catalyst system (10 mol%)	observation	Yield[b]
7	$Pd(OAc)_2$/SPhos[1]	Product **3a** was not detected	nd
8	$Pd(OAc)_2$/XPhos[2]	Product **3a** was not detected	nd
9	$Pd(OAc)_2$/disodium 2-aminopyrimidine-4,6-diol[3]	Product **3a** was not detected	nd

1 T. P. Pathak, S. J. Miller, *J. Am. Chem. Soc*. 2013, **135**, 8415-8422.
2. T. J. Wadzinski, K. D. Gea, S. J. Miller, *Bioorg. Med. Chem. Lett*. 2016, **26**, 1025-1028
3. S. V. Sharma, X. Tong, C. Pubill-Ulldemolins, C. Cartmell, E. J.A. Bogosyan, E. J. Rackham, E. Marelli, R. B. Hamed, R. J. M. Goss, *Nat. Commun*. 2017, **8**, 229

Typical Procedures

Typical procedure A for Pd-catalyzed coupling of thiosugars (1a-h) with iodo-aminoacids (2a-f) or peptides (4a-f)

A flame-dried sealed tube was charged with thiosugar (0.11-0.51 mmol, 1 equiv.), iodo-aminoacid (0.11-0.51 mmol, 1 equiv.) or peptide (0.11-0.51 mmol, 1 equiv.) and XantPhos PdG_3 precatalyst (0.01-0.02 mmol, 3 mol %). After Argon flushing, a mixture of THF/H_2O (1:2, 0.10 M) was added. Upon stirring the reaction mixture, Et_3N (0.11-0.51 mmol, 1 equiv.) was added to the medium. The reaction mixture was stirred at room temperature under Argon. After completion, the mixture was quenched with 1M HCl and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and

concentrated *in vacuo*. The solid residue was purified by silica gel column chromatography, unless otherwise noted, to give the desired product.

Typical procedures for solid phase peptide synthesis (SPPS)

Fmoc-based solid phase peptide syntheses (SPPS) were carried out on a Prelude synthesizer from Protein Technologies. Standard side-chain protecting groups were used: Arg(Pbf), Asp(O*t*Bu), His(Trt), Ser(*t*Bu), Thr(*t*Bu), Trp(Boc), Tyr(*t*Bu).
Syntheses were performed at a 25 µmol scale. Protected amino acids (0.25 mmol, 10 equiv.) were coupled using HCTU (98 mg, 0.238 mmol, 9.5 equiv.) and *i*Pr_2NEt (87 µL, 0.5 mmol, 20 equiv.) in NMP (3 mL) for 30 min. Capping of potential unreacted amine groups was achieved by treatment with acetic anhydride (143 µL, 1.51 mmol, 60 equiv.), *i*Pr_2NEt (68 µL, 0.39 mmol, 15.5 equiv.) and HOBt (6 mg, 0.044 mmol, 1.8 equiv.) in NMP (3 mL) for 7 min. Fmoc group was removed by three successive treatments with 20% piperidine in NMP (3 mL) for 3 min.

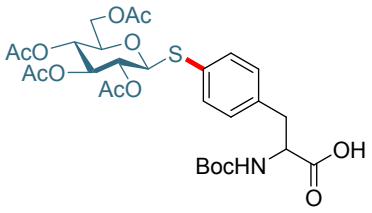
The crude peptides were deprotected and cleaved from the resin through a treatment with TFA/H_2O/*i*Pr_3SiH/1,3-dimethoxybenzene, 88/5/2/5 for 3.5 h, then precipitated by dilution into an ice-cold 1:1 diethyl ether/petroleum ether mixture, recovered by centrifugation and further washed three times with diethyl ether.

Typical procedure B for Pd-catalyzed coupling of thiosugars (1c, 1i-j) with iodo-peptides MUC1 (7a-b)

To a solution of HPLC-purified lyophilized iodopeptide (50 µL, 0.5 µmol, 1 equiv.), in a mixture of THF/H_2O (1:2, 350 µL, 1.0 mM) were added XantPhos PdG_3 precatalyst (25 µL, 2.5-7.5 µmol, 5-15 equiv.) and Et_3N (25 µL, 7.5-12.5 µmol, 15-25 equiv.). The resulting clear solution was then briefly stirred and the thiosugar (50 µL, 1.5 µmol, 3 equiv.) was added. The coupling mixture was stirred at 40°C for 1 h and then quenched by the addition of 3% of aqueous TFA (1 mL) and then MeOH (1 mL). After removal of the volatiles under reduced pressure, the suspension was diluted with 2 mL of H_2O/CH_3CN/TFA 80:20:0.01 and then 12 mL of 0.1% aqueous TFA. The resulting solution was filtrated over a Sep-Pak® Vac 6cc C_{18} cartridge to remove the palladium catalyst. LC-MS analysis showed >99% conversion in all cases. Semi-preparative HPLC purification afforded the pure desired thioglycosylated peptides MUC1 **7a-f**.

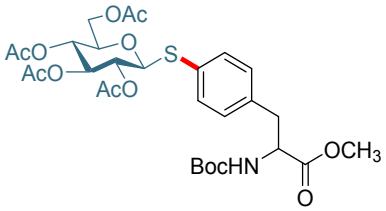
Experimental data for the thioglycosylated aminoacids (3a-r)

2-((*tert*-butoxycarbonyl)amino)-3-(4-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3a)**



Compound **3a** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine **2a** (107.4 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a beige solid (158 mg, 92% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC** R_f = 0.24 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 167 - 168 °C. **$[\alpha]_D^{18}$**: - 13.6 (c 0.51, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2925, 2853, 1756, 1672, 1579, 1402, 1367, 1250, 1213, 1166, 1091, 1061, 1034, 914, 673. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.40 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.30 - 5.28 (m, 1H), 4.99 (dd, *J* = 19.5, 9.8 Hz, 2H), 4.88 (d, *J* = 6.2 Hz, 2H), 4.31 - 4.20 (m, 2H), 4.15 (d, *J* = 12.2 Hz, 1H), 3.91 - 3.87 (m, 1H), 3.18 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.97 - 2.75 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 179.6 (C=O), 172.2 (C=O), 171.5 (C=O), 171.2 (C=O), 171.0 (C=O), 157.6 (C=O), 140.1 (Cq), 138.8 (2 x CH), 131.2 (2 x CH), 131.0 (Cq), 86.5 (CH), 80.3 (Cq), 76.7 (CH), 75.3 (CH), 71.5 (CH), 69.7 (CH), 63.3 (CH_2), 57.8 (CH), 39.0 (CH_2), 28.8 (3 x CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{28}H_{37}NO_{13}SNa$ 650.1883, found 650.1889.

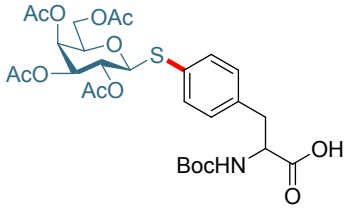
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(3b)**



Compound **3b** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2c** (111.2 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a beige solid (120 mg, 67% **yield** after column chromatography EtOAc/Cyclohexane 60:40). **TLC** R_f = 0.22 (EtOAc/Cyclohexane 60:40, SiO_2). **Mp**: 61 - 62 °C. **$[\alpha]_D^{18}$**: - 9.0 (c 0.55, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2920, 2852, 1756, 1743, 1712, 1494, 1435, 1366, 1249, 1211, 1162, 1091, 1061, 1034, 914, 734, 646. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.44 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.29 (t, *J* = 8.9 Hz, 1H), 5.02 - 4.92 (m, 1H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.43 - 4.32

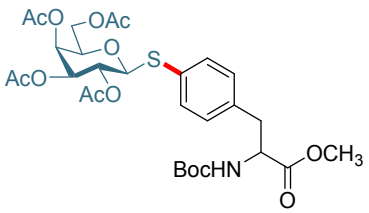
(m, 1H), 4.25 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.18 - 4.09 (m, 1H), 4.00 - 3.83 (m, 1H), 3.70 (s, 3H), 3.11 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.92 (dd, *J* = 13.3, 9.2 Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H), 1.39 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 174.0 (C=O), 172.2 (C=O), 171.5 (C=O), 171.2 (C=O), 170.9 (C=O), 157.8 (C=O), 139.0 (Cq), 134.2 (2 x CH), 131.3 (Cq), 130.9 (2 x CH), 86.2 (CH), 80.7 (Cq), 76.7 (CH), 75.3 (CH), 71.4 (CH), 69.6 (CH), 63.2 (CH_2), 56.3 (CH), 52.7 (CH_3), 38.3 (CH_2), 28.7 (3 x CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{29}H_{39}NO_{13}SNa$ 664.2040, found 664.2044.

2-((tert-butoxycarbonyl)amino)-3-(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3c)**



Compound **3c** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thiogalactose **1a** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine **2a** (107.4 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a white solid (141 mg, 82% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC R_f** = 0.26 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 172 - 174 °C. **$[\alpha]_D^{19}$**: + 3.8 (c 0.48, $CHCl_3$). **IR (thin film, neat) vmax/cm^{-1}**: 2978, 1754, 1670, 1623, 1494, 1407, 1367, 1249, 1212, 1165, 1086, 1052, 1031, 1017, 951, 916, 821, 774. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.40 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.41 (d, *J* = 2.5 Hz, 1H), 5.14 (d, *J* = 8.8 Hz, 2H), 4.91 - 4.87 (m, 1H), 4.24 - 4.20 (m, 2H), 4.13 (s, 2H), 3.18 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.90 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.94 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 179.6 (C=O), 172.0 (C=O), 171.9 (C=O), 171.4 (C=O), 171.2 (C=O), 157.6 (C=O), 139.8 (Cq), 133.3 (2 x CH), 131.7 (Cq), 131.2 (2 x CH), 87.3 (CH), 80.3 (Cq), 75.4 (CH), 73.4 (CH), 69.0 (CH), 68.8 (CH), 62.9 (CH_2), 57.9 (CH), 39.0 (CH_2), 28.8 (3 x CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{28}H_{37}NO_{13}SNa$ 650.1883, found 650.1891.

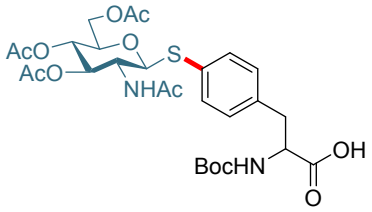
(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(3d)**



Compound **3d** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thiogalactose **1b** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2c** (111.2 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01

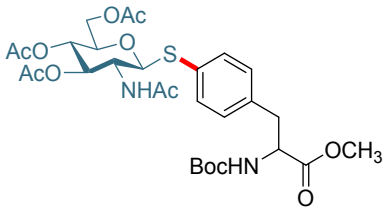
mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a beige solid (166 mg, 94% **yield** after column chromatography EtOAc/Cyclohexane 30:70 → 40:60). **TLC** R_f = 0.33 (EtOAc/Cyclohexane 40:60, SiO_2). **Mp**: 65 - 66 °C. **[α]$_D^{19}$**: + 1.4 (c 0.48, $CHCl_3$. **IR (thin film, neat) vmax/cm^{-1}**: 2921, 1746, 1712, 1494, 1435, 1366, 1211, 1160, 1083, 1056, 1041, 1016, 950, 918. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.46 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.42 (d, *J* = 2.9 Hz, 1H), 5.25 - 5.06 (m, 2H), 4.91 (d, *J* = 9.3 Hz, 2H), 4.45 - 4.28 (m, 1H), 4.15 (s, 3H), 3.70 (s, 3H), 3.11 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.01 - 2.82 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.94 (s, 3H), 1.40 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 174.0 (C=O), 172.0 (C=O), 171.9 (C=O), 171.4 (C=O), 171.2 (C=O), 157.8 (C=O), 138.7 (Cq), 133.6 (2 x CH), 132.0 (Cq), 130.9 (2 x CH), 86.9 (CH), 80.7 (Cq), 75.5 (CH), 73.4 (CH), 69.0 (CH), 68.7 (CH), 62.9 (CH_2), 56.4 (CH), 52.7 (CH_3), 38.2 (CH_2), 28.7 (3 x CH_3), 20.7 (2 x CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{29}H_{39}NO_{13}SNa$ 664.2040, found 664.2029.

3-(4-(((2*S*,3*R*,4*R*,5*R*,6*R*)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid **(3e)**.



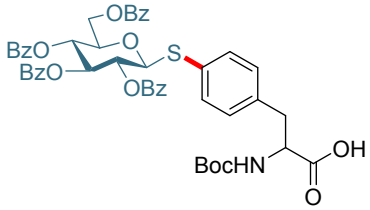
Compound **3e** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucosamine **1c** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine **2a** (107.4 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a white solid (124 mg, 72% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC** R_f = 0.10 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 256 - 257 °C. **[α]$_D^{18}$**: - 8.4 (c 0.33, CH_3OH) **[18]**: **IR (thin film, neat) vmax/cm^{-1}**: 2979, 1748, 1671, 1366, 1249, 1213, 1165, 1048, 1032, 951, 916, 819, 645. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**: 7.29 (d, *J* = 6.6 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 2H), 5.14 (t, *J* = 9.6 Hz, 1H), 5.01 (d, *J* = 8.9 Hz, 1H), 4.82 (t, *J* = 9.8 Hz, 1H), 4.18 - 4.13 (m, 1H), 4.03 (d, *J* = 11.7 Hz, 1H), 3.93 - 3.83 (m, 3H), 3.43 (d, *J* = 7.2 Hz, 1H), 3.08 (d, *J* = 13.9 Hz, 1H), 2.99 - 2.73 (m, 1H), 2.01 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H), 1.79 (s, 3H), 1.32 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 170.0 (C=O), 169.6 (C=O), 169.3 (C=O), 169.2 (C=O), 169.1 (C=O), 154.7 (C=O), 138.5 (2 x Cq), 130.1 (4 x CH), 85.2 (CH), 77.5 (Cq), 74.5 (CH), 73.5 (CH), 68.4 (CH), 62.0 (CH_2), 56.0 (CH), 52.1 (CH), 39.0 (CH_2), 28.2 (3 x CH_3), 22.7 (CH_3), 20.6 (CH_3), 20.4 (CH_3), 20.3 (CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{28}H_{38}N_2O_{12}SNa$ 649.2043, found 649.2046.

(2*R*,3*R*,4*R*,5*R*,6*S*)-5-acetamido-2-(acetoxymethyl)-6-((4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3,4-diyl diacetate **(3f)**



Compound **3f** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucosamine **1c** (100 mg, 0.28 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2c** (111.5 mg, 0.28 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.28 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a white solid (104 mg, 59% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC** R_f = 0.10 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 186 - 188 °C. **[α]$_D^{19}$**: - 7.0 (c 0.60, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2921, 1746, 1712, 1494, 1435, 1366, 1211, 1160, 1083, 1056, 1041, 1016, 950, 918. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**: 7.35 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.13 (t, *J* = 9.6 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 4.82 (t, *J* = 9.7 Hz, 1H), 4.14 (dd, *J* = 11.7, 5.4 Hz, 2H), 4.04 (d, *J* = 11.9 Hz, 1H), 3.93 (d, *J* = 14.7 Hz, 1H), 3.84 (t, *J* = 9.9 Hz, 1H), 3.61 (s, 3H), 2.98 (dd, *J* = 13.6, 4.6 Hz, 1H), 2.87 (s, 1H), 2.02 (s, 3H), 1.98 (s, 3H), 1.92 (s, 3H), 1.79 (s, 3H), 1.32 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 172.5 (C=O), 170.0 (C=O), 169.6 (C=O), 169.3 (C=O), 169.1 (C=O), 155.4 (C=O), 136.8 (Cq), 131.1 (Cq), 130.4 (2 x CH), 129.8 (2 x CH), 84.9 (CH), 78.3 (Cq), 74.5 (CH), 73.4 (CH), 68.4 (CH), 62.0 (CH_2), 55.0 (CH), 52.0 (CH), 51.8 (CH_3), 35.8 (CH_2), 28.1 (3 x CH_3), 22.6 (CH_3), 20.5 (CH_3), 20.4 (CH_3), 20.3 (CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{29}H_{40}N_2O_{12}SNa$ 663.2200, found 663.2195.

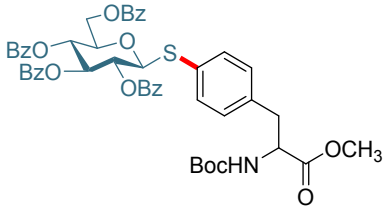
2-((*tert*-butoxycarbonyl)amino)-3-(4-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3g)**.



Compound **3g** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with (2*R*,3*R*,4*S*,5*R*,6*S*)-2-((benzoyloxy)methyl)-6-mercaptotetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate **1d** (100 mg, 0.16 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine **2a** (63.8 mg, 0.16 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (4.6 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (22 µL, 0.16 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.6 mL, 0.10 M) which afforded the product as a pale yellow solid (114 mg, 80% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC** R_f = 0.23 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 180 - 184 °C. **[α]$_D^{19}$**: + 40.3 (c 0.55, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2979, 1735, 1667, 1601, 1395, 1262, 1177, 1067, 1026, 974, 706. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**: 7.97 (d, *J* = 7.3 Hz, 2H), 7.85 (dd, *J* = 13.5, 7.6 Hz, 4H), 7.69 (d, *J* = 7.3 Hz, 3H), 7.65 - 7.43 (m, 9H), 7.37 (t, *J* = 6.0 Hz, 2H), 7.31 - 7.28 (m, 2H), 7.06 (t, *J* = 6.0 Hz, 2H), 6.20 - 6.05 (m, 2H), 5.75 - 5.53 (m, 2H), 5.42 - 5.33 (m, 2H), 4.58 - 4.45 (m, 3H), 3.92 (s, 1H), 3.05 (d, *J* = 11.1 Hz, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 1.30 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 165.3 (C=O), 165.0 (C=O), 164.7 (C=O), 164.5 (C=O), 154.8 (C=O), 154.7 (C=O), 133.8 (CH), 130.7 (CH), 130.1 (CH), 129.2 (9 x CH, 2 Cq), 129.0 (3 x CH),

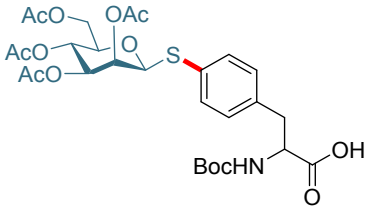
128.8 (9 x CH, 2 Cq), 128.5 (Cq), 128.4 (Cq), 83.7 (CH), 83.6 (CH), 77.4 (Cq), 74.5 (CH), 74.0 (CH), 70.4 (CH), 69.0 (CH), 62.7 (CH_2), 29.0 (CH_2), 28.2 (3 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{48}H_{45}NO_{13}SNa$ 898.2509, found 898.2511.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-((benzoyloxy)methyl)-6-((4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate **(3h)**.



Compound **3h** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with (2*R*,3*R*,4*S*,5*R*,6*S*)-2-((benzoyloxy)methyl)-6-mercaptotetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate **1d** (100 mg, 0.16 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2b** (66.1 mg, 0.16 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (4.6 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (22 µL, 0.16 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.6 mL, 0.10 M) which afforded the product as a pale yellow solid (140 mg, 96% **yield** after column chromatography EtOAc/Cyclohexane 70:30). **TLC** R_f = 0.27 (EtOAc/Cyclohexane 70:30, SiO_2). **Mp**: 91 - 92 °C. **[α]$_D^{19}$**: + 35.5 (c 0.40, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2925, 2363, 1734, 1601, 1452, 1411, 1264, 1068, 707. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 8.06 (d, *J* = 8.0 Hz, 2H), 7.92 (dd, *J* = 12.4, 7.3 Hz, 4H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.60 - 7.47 (m, 4H), 7.47 - 7.31 (m, 7H), 7.28 (t, *J* = 7.6 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 2H), 5.99 (td, *J* = 9.4, 2.4 Hz, 1H), 5.60 (t, *J* = 9.8 Hz, 1H), 5.44 - 5.22 (m, 2H), 4.71 (dd, *J* = 16.1, 6.6 Hz, 1H), 4.60 - 4.44 (m, 1H), 4.41 (d, *J* = 7.1 Hz, 1H), 4.31 (s, 1H), 3.69 (d, *J* = 2.2 Hz, 3H), 3.04 - 2.95 (m, 1H), 2.88 - 2.79 (m, 1H), 1.38 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 167.0 (C=O), 166.7 (C=O), 166.5 (C=O), 166.4 (C=O), 166.3 (C=O), 166.1 (C=O), 139.0 (Cq), 134.7 (4 x CH), 134.5 (2 x CH), 134.4 (2 x CH), 130.8 (4 x CH, 4 x Cq), 130.6 (2 x CH), 130.2 (Cq), 129.8 (2 x CH), 129.6 (2 x CH, 4 x Cq), 129.4 (2 x CH), 86.3 (CH), 80.7 (Cq), 77.0 (CH), 75.8 (CH), 71.9 (CH), 70.7 (CH), 64.0 (CH_2), 56.3 (CH), 52.7 (CH), 38.3 (CH_2), 28.7 (3 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{49}H_{47}NO_{13}SNa$ 912.2666, found 912.2668.

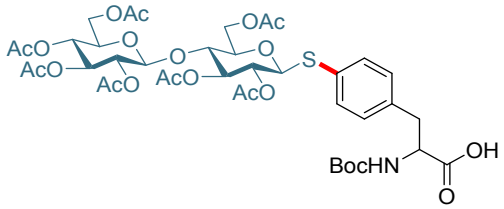
2-((*tert*-butoxycarbonyl)amino)-3-(4-(((2*S*,3*S*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3i)**



Compound **3i** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thiomannose **1a** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine **2a** (107.4 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a white powder (150 mg, 87% **yield** after column

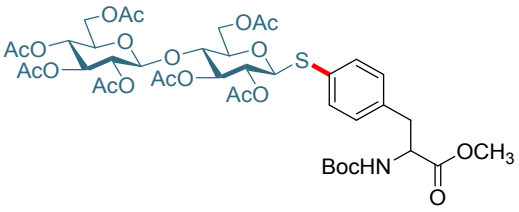
chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC R_f** = 0.23 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 255 - 256 °C. **$[\alpha]_D^{19}$**: - 37.2 (c 0.54, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2979, 1747, 1668, 1592, 1399, 1367, 1305, 1244, 1222, 1207, 1165, 1103, 1049, 1015, 967, 943, 916, 836, 818, 772, 724, 697, 670, 640. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: **)**: 7.40 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.59 (s, 1H), 5.19 (t, *J* = 6.1 Hz, 3H), 4.35 - 4.15 (m, 2H), 4.11 (d, *J* = 11.7 Hz, 1H), 3.84 (s, 1H), 3.17 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.97 - 2.73 (m, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.95 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 178.3 (C=O), 170.9 (C=O), 170.4 (C=O), 170.1 (C=O), 170.0 (C=O), 156.3 (C=O), 138.3 (Cq), 131.1 (2 x CH), 130.0 (2 x CH, Cq), 84.5 (CH), 78.9 (Cq), 75.9 (CH), 71.8 (CH), 71.0 (CH), 65.7 (CH), 62.3 (CH_2), 56.5 (CH), 37.5 (CH_2), 27.4 (3 x CH_3), 19.4 (CH_3), 19.2 (CH_3), 19.1 (CH_3), 19.0 (CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{28}H_{37}NO_{13}SNa$ 650.1883, found 650.1890.

2-((*tert*-butoxycarbonyl)amino)-3-(4-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4-diacetoxy-6-(acetoxymethyl)-5-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3j)**



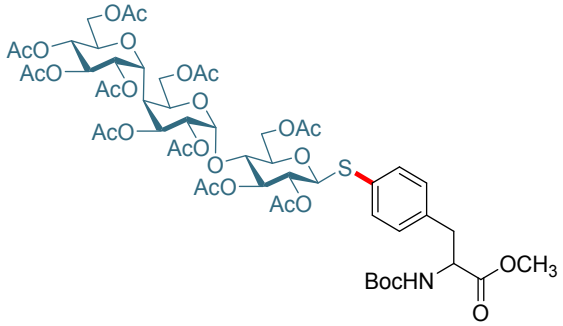
Compound **3j** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thiocellobiose **1f** (75 mg, 0.11 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine **2a** (46.6 mg, 0.11 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (3.3 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (16 µL, 0.11 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.1 mL, 0.10 M) which afforded the product as a white solid (76 mg, 72% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC R_f** = 0.26 (CH_2Cl_2/MeOH, 95:5, SiO_2). **Mp**: 263 - 264 °C. **$[\alpha]_D^{19}$**: - 10.5 (c 0.33, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2850, 1756, 1747, 1740, 1435, 1366, 1230, 1210, 1166, 1034, 905, 819, 772, 724, 696, 644. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**: 7.27 (d, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.24 (t, *J* = 9.5 Hz, 2H), 5.14 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.86 (dd, *J* = 18.9, 9.0 Hz, 2H), 4.68 (dt, *J* = 17.4, 9.5 Hz, 2H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.23 (dd, *J* = 12.4, 3.6 Hz, 1H), 4.13 - 3.84 (m, 5H), 3.74 (t, *J* = 9.4 Hz, 1H), 3.06 (d, *J* = 7.6 Hz, 1H), 2.88 - 2.82 (m, 1H), 2.08 (s, 3H), 2.00 (s, 6H), 1.98 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H), 1.32 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 170.2 (C=O), 170.0 (C=O), 169.6 (C=O), 169.3 (C=O), 169.2 (C=O), 169.1 (C=O), 169.0 (C=O), 154.8.6 (C=O), 154.7 (C=O), 138.8 (Cq), 130.3 (2 x CH), 130.1 (2 x CH), 129.4 (Cq), 99.5 (CH), 83.2 (CH), 77.5 (Cq), 76.4 (CH), 75.4 (CH), 72.9 (CH), 72.2 (CH), 71.1 (CH), 70.4 (CH), 69.9 (CH), 67.7 (CH), 62.3 (CH_2), 61.5 (CH_2), 56.0 (CH), 36.9 (CH_2), 28.2 (3 x CH_3), 20.7 (CH_3), 20.4 (3 x CH_3), 20.3 (CH_3), 20.2 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{40}H_{53}NO_{21}SNa$ 938.2729, found 938.2731.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-diacetoxy-2-(acetoxymethyl)-6-((4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(3k)**



Compound **3k** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thiocellobiose **1f** (75 mg, 0.11 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2b** (46.6 mg, 0.11 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (3.3 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (16 µL, 0.11 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.1 mL, 0.10 M) which afforded the product as a white solid (85 mg, 80% **yield** after column chromatography EtOAc/Cyclohexane 50:50). **TLC** R_f = 0.33 (EtOAc/Cyclohexane, 50:50, SiO_2). **Mp**: 158 - 159 °C. **[α]$_D^{19}$**: - 9.4 (c 0.48, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2925, 2854, 1758, 1740, 1518, 1494, 1435, 1366, 1230, 1209, 1164, 1033, 980, 906, 833, 735, 700, 641. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.42 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.22 (t, *J* = 9.3 Hz, 2H), 5.00 (t, *J* = 9.3 Hz, 2H), 4.87 - 4.78 (m, 2H), 4.71 (d, *J* = 8.0 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.40 (dd, *J* = 12.7, 3.7 Hz, 2H), 4.17 (d, *J* = 4.8 Hz, 1H), 4.15 - 4.07 (m, 1H), 4.04 (dd, *J* = 13.1, 2.4 Hz, 1H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.78 (d, *J* = 6.1 Hz, 1H), 3.70 (s, 3H), 3.10 (d, *J* = 13.2 Hz, 1H), 2.92 (d, *J* = 10.0 Hz, 1H), 2.12 (s, 3H), 2.04 (s, 6H), 2.02 (s, 6H), 1.99 (s, 3H), 1.94 (s, 3H), 1.39 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: **)**: 174.0 (C=O), 172.3 (C=O), 172.1 (C=O), 172.0 (C=O), 171.8 (C=O), 171.6 (C=O), 171.2 (C=O), 171.1 (C=O), 171.0 (C=O), 136.1 (Cq), 134.0 (2 x CH), 131.6 (Cq), 130.9 (2 x CH), 101.8 (CH), 86.1 (CH), 77.9 (CH, Cq), 77.8 (CH), 75.3 (CH), 74.4 (CH), 73.1 (CH), 72.9 (CH), 71.6 (CH), 69.3 (CH), 63.6 (CH_2), 62.8 (CH_2), 56.4 (CH), 52.7 (CH), 38.2 (CH_2), 28.7 (3 x CH_3), 20.9 (2 x CH_3), 20.7 (3 x CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{41}H_{55}NO_{21}SNa$ 952.2885, found 952.2896.

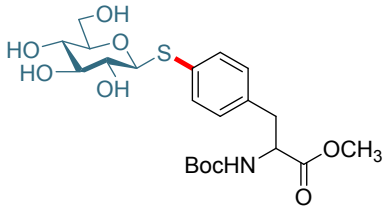
(2*R*,2'*S*,3*S*,3'*R*,4*R*,4'*S*,5*R*,5'*R*,6*R*,6'*R*)-2',6-bis(acetoxymethyl)-6'-(((2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-diacetoxy-2-(acetoxymethyl)-6-((4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3-yl)oxy)octahydro-2*H*,2'*H*-[2,3'-bipyran]-3,4,4',5,5'-pentayl pentaacetate **(3l)**



Compound **3l** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thiomaltotriose **1g** (100 mg, 0.11 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2b** (43.1 mg, 0.11 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (3.0 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (14 µL, 0.11 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.1 mL, 0.10 M) which afforded the product as a white solid (68 mg, 68% **yield** after column chromatography EtOAc/Cyclohexane 50:50). **TLC** R_f = 0.48 (EtOAc/Cyclohexane, 50:50, SiO_2). **Mp**: 98 - 99 °C. **[α]$_D^{21}$**: + 74.2 (c 0.42, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2924, 2853, 1756, 1740, 1490, 1435, 1367, 1235, 1209, 1164, 1028, 898. **^{1}H NMR (300**

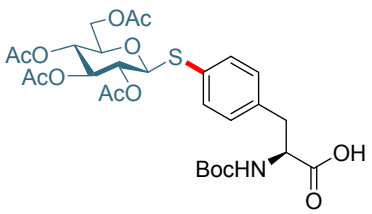
MHz, DMSOd_6) δ (ppm): 7.43 - 7.31 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.41 (t, *J* = 9.0 Hz, 1H), 5.37 - 5.07 (m, 5H), 4.98 (t, *J* = 9.0 Hz, 2H), 4.86 (dd, *J* = 10.0, 3.3 Hz, 1H), 4.76 (dd, *J* = 10.0, 3.3 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 4.43 - 4.33 (m, 2H), 4.25 - 4.14 (m, 4H), 4.07 - 3.79 (m, 5H), 3.61 (s, 3H), 3.09 - 2.91 (m, 1H), 2.91 - 2.75 (m, 1H), 2.07 (s, 6H), 2.01 - 1.93 (m, 24H), 1.32 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 172.5 (C=O), 170.1 (C=O), 170.0 (2 x C=O), 169.9 (2 x C=O), 169.5 (2 x C=O), 169.4 (C=O), 155.6 (C=O), 137.2 (Cq), 131.0 (2 x CH), 130.9 (Cq), 129.8 (2 x CH), 95.5 (2 x CH), 82.7 (CH), 78.3 (Cq), 74.9 (2 x CH), 74.4 (CH), 73.3 (CH), 70.9 (CH), 70.2 (CH), 69.8 (CH), 69.4 (CH), 68.9 (2 x CH), 68.0 (CH), 67.7 (CH), 63.1 (CH_2), 62.5 (CH_2), 61.4 (CH_2), 55.0 (CH), 51.8 (CH_3), 35.9 (CH_2), 28.1 (3 x CH_3), 20.5 (3 x CH_3), 20.4 (3 x CH_3), 20.3 (6 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{53}H_{71}NO_{29}SNa$ 1240.3730, found 1240.3744.

methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoate **(3m)**



Compound **3m** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with desacetylated *β*-thioglucose **1h** (100 mg, 0.51 mmol, 1 equiv.), N-boc-4-iodo-DL-phenylalanine methyl ester **2b** (206.5 mg, 0.51 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (14.5 mg, 0.02 mmol, 0.03 equiv.) and triethylamine (69 µL, 0.51 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 5.1 mL, 0.10 M) which afforded the product as a white solid (151 mg, 63% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC R_f** = 0.40 (CH_2Cl_2/MeOH, 90:10, SiO_2). **Mp**: 65 - 66 °C. **$[\alpha]_D^{19}$**: - 26.2 (c 0.36, $CHCl_3$). **IR (thin film, neat) vmax/cm^{-1}**: 3373, 2978, 1689, 1521, 1494, 1367, 1277, 1251, 1218, 1161, 1106, 1050, 1017, 988, 873, 815, 778, 757. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.50 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.56 (d, *J* = 9.7 Hz, 1H), 4.43 - 4.29 (m, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.69 (s, 3H), 3.38 - 3.35 (m, 2H), 3.28 (s, 1H), 3.20 (t, *J* = 9.0 Hz, 1H), 3.09 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.89 (dd, *J* = 13.6, 9.3 Hz, 1H), 1.39 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 174.1 (C=O), 148.2 (C=O), 137.8 (Cq), 133.5 (Cq), 132.9 (2 x CH), 130.8 (2 x CH), 89.5 (CH), 82.1 (CH), 80.7 (CH_2), 79.7 (CH), 73.8 (CH), 71.3 (CH), 62.9 (CH_2), 56.4 (CH), 52.6 (CH_3), 38.2 (CH_2), 28.7 (3 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{21}H_{31}NO_9SNa$ 496.1617, found 496.1614.

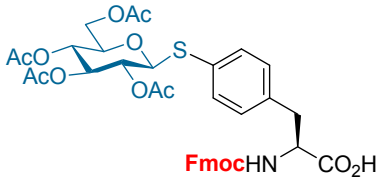
(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3n)**



Compound **3n** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-L-phenylalanine **2d**

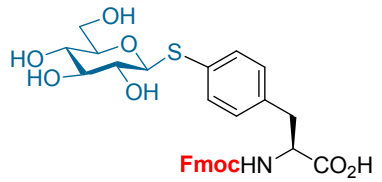
(107.4 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a beige solid (165 mg, 96% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC** R_f = 0.24 (CH_2Cl_2/MeOH, 99:1, SiO_2). **Mp**: 176 - 177 °C. **[α]$_D^{19}$**: - 26.6 (c 0.56, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2951, 1756, 1691, 1659, 1629, 1598, 1398, 1366, 1250, 1211, 1165, 1091, 1061, 1032, 914, 823, 776, 646. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.39 (d, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 5.30 5.25 (m, 1H), 4.98 (t, *J* = 9.8 Hz, 1H), 4.94 - 4.87 (m, 2H), 4.28 - 4.22 (m, 2H), 4.17 - 4.13 (m, 1H), 4.01 - 3.76 (m, 1H), 3.18 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.90 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 179.6 (C=O), 172.2 (C=O), 171.5 (C=O), 171.2 (C=O), 171.0 (C=O), 157.6 (C=O), 140.1 (Cq), 133.8 (2 x CH), 131.3 (2 x CH), 131.0 (Cq), 86.6 (CH), 80.3 (CH_2), 76.7 (CH), 75.3 (CH), 71.5 (CH), 69.6 (CH), 63.3 (CH_2), 57.8 (CH), 39.0 (CH_2), 28.8 (3 x CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{28}H_{37}NO_{13}SNa$ 650.1883, found 650.1876.

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(((2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)propanoic acid (**3o**)



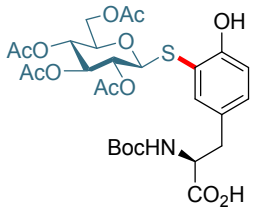
Compound **3o** was prepared by using the general procedure A of coupling (reaction time: 30 min, with β-thioglucose **1a** (75 mg, 0.2 mmol, 1 equiv.), N-Fmoc-4-iodo-L-phenylalanine **2d** (100 mg, 0.2 mmol, 1 equiv.), XantPhos PdG3 precatalyst (5 mg, 0.006 mmol, 0.03 equiv.) and triethylamine (27 µL, 0.2 mmol, 1 equiv.) in a mixture of THF/H2O (1:2, 2.1 mL, 0.10 M) which afforded the product as a beige solid (127 mg, 85% yield after column chromatography CH_2Cl_2/MeOH 100:0 → 90:10). **TLC** Rf = 0.4 (CH_2Cl_2/MeOH, 95:5, SiO2). **mp** : 117.9 – 118.9°C; **[α]$_D^{14}$**: – 4 (c 0.2, CHCl3); **IR** (thin film, neat) νmax/cm^{-1}: 621, 647, 682, 741, 761, 828, 915, 978, 1033, 1060, 1087, 1106, 1211, 1248, 1357, 1450, 1519, 1755; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.20 (m, 6H), 5.31 (t, *J* = 9.5 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 4.84 (dt, *J* = 18.9, 9.7 Hz, 2H), 4.27 – 4.06 (m, 6H), 4.03 – 3.92 (m, 2H), 3.32 (s, 2H), 3.16 – 3.06 (m, 1H), 2.95 – 2.82 (m, 1H), 2.06 – 1.96 (m, 9H), 1.94 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8(C), 170.3(C), 169.5(2C), 143.8(C), 143.6(C), 141.3(2CH), 133.4(2CH), 130.1(C), 128.0(2CH), 127.4(C), 125.3(CH), 125.1(CH), 120.3(2CH), 85.8(CH), 75.6(CH), 74.0(CH), 70.0(CH), 68.3(CH), 67.3(CH2), 62.2(CH2), 47.1(CH), 20.9(CH3), 20.7(3CH3); **HRMS** (ESI) (M + Na)+ m/z calculated for $C_{38}H_{39}NO_{13}SNa$ 772.2045, found 772.2051.

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)propanoic acid (**3p**)



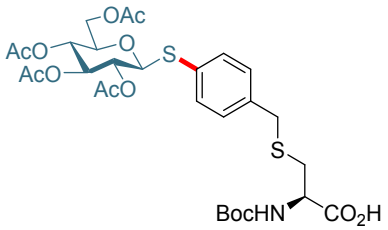
Compound **x** was prepared by using the general procedure A of coupling (reaction time: 1h30 min, with β-thioglucose **1h** (134 mg, 0.68 mmol, 1 equiv.), N-Fmoc-4-iodo-L-phenylalanine **2e** (350 mg, 0.68 mmol, 1 equiv.), XantPhos PdG3 precatalyst (19 mg, 0.02 mmol, 0.03 equiv.) and triethylamine (100 µL, 0.68 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 7.5 mL, 0.10 M) which afforded the product as a white solid (220 mg, 55% yield after column chromatography CH_2Cl_2/MeOH 100:0 → 60:40). **TLC** Rf = 0.1 (CH_2Cl_2/MeOH, 75:25, SiO2). **mp** : 129.9 – 130.6°C; **[α]**$_D^{14}$: – 3.9 (c 0.5, MeOH); **IR** (thin film, neat) νmax/cm^{-1}: 621, 647, 682, 741, 761, 828, 915, 978, 1033, 1060, 1087, 1106, 1211, 1248, 1357, 1450, 1519, 1697, 1957, 2133, 2928, 3156, 3452; **^{1}H NMR** (300 MHz, MeOD) δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 3H), 7.33 (t, *J* = 5.0 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 4.56 (d, *J* = 9.7 Hz, 1H), 4.50 – 4.16 (m, 6H), 3.84 (d, *J* = 12.3 Hz, 1H), 3.65 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.31 – 3.16 (m, 4H), 3.02 – 2.90 (m, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.1 (C), 189.5(C), 173.3(C), 170.7(C), 166.5(C), 161.5(C), 161.1(2CH), 159.0(2CH), 156.9(2CH), 156.3(2CH), 154.4(CH), 154.4(CH), 149.1(2CH), 117.7(CH), 110.1(CH), 107.8(CH), 101.9(CH), 99.4(CH), 96.1(CH_2), 90.9(CH_2), 84.8(CH), 76.5(CH), 66.3(CH_2); **HRMS** (ESI) (M + Na)+ m/z calculated for $C_{30}H_{31}NO_9SNa$ 604.1617, found 604.1614.

(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxy-3-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)phenyl)propanoic acid **(3q)**



Compound **3q** was prepared by using the general procedure **A** of coupling (reaction time: 3.0 h), with *β*-thioglucose **1a** (75 mg, 0.21 mmol, 1 equiv.), N-boc-3-iodo-L-tyrosine **2e** (83.8 mg, 0.21 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (5.9 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (28 µL, 0.21 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.1 mL, 0.10 M) which afforded the product as a white solid (108 mg, 82% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 80:20). **TLC** R_f = 0.17 (CH_2Cl_2/MeOH, 95:5, SiO_2). **Mp**: 199 - 200 °C. **[α]$_D^{21}$**: - 16.1 (c 0.59, $CHCl_3$). **IR (thin film, neat) vmax/cm^{-1}**: 2926, 2845, 1756, 1676, 1587, 1487, 1367, 1251, 1210, 1164, 1032, 914, 816. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.29 (s, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 5.28 (t, *J* = 9.0 Hz, 1H), 5.08 - 4.97 (m, 2H), 4.94 (d, *J* = 6.4 Hz, 1H), 4.27 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.20 (d, *J* = 4.5 Hz, 1H), 4.12 (d, *J* = 11.7 Hz, 1H), 3.97 - 3.94 (m, 1H), 3.10 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.82 (dd, *J* = 13.9, 8.1 Hz, 1H), 2.06 (s, 6H), 2.00 (s, 3H), 1.96 (s, 3H), 1.39 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 179.8 (C=O), 179.5 (C=O), 172.4 (C=O), 171.5 (C=O), 171.2 (C=O), 157.7 (C=O), 157.1 (Cq), 136.4 (CH), 132.6 (CH), 131.3 (Cq), 118.0 (Cq), 116.4 (CH), 86.5 (CH), 80.3 (Cq), 76.7 (CH), 75.4 (CH), 71.6 (CH), 69.6 (CH), 63.2 (CH_2), 57.9 (CH), 38.5 (CH_2), 28.9 (3 x CH_3), 20.8 (2 x CH_3), 20.5 (2 x CH_3).
HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{28}H_{37}NO_{14}SNa$ 666.1832, found 666.1832.

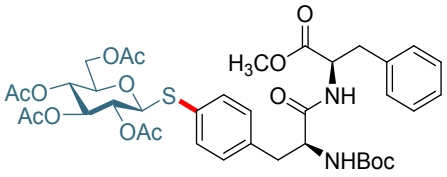
N-(*tert*-butoxycarbonyl)-*S*-(4-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)benzyl)-*L*-cysteine **(3r)**



Compound **3r** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (100 mg, 0.27 mmol, 1 equiv.), N-boc-4-iodo-L-cysteine **2f** (120.0 mg, 0.27 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (7.8 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (37 µL, 0.27 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.7 mL, 0.10 M) which afforded the product as a yellow solid (138 mg, 75% **yield** after column chromatography CH_2Cl_2/MeOH 100:0 → 90:10). **TLC** R_f = 0.16 (CH_2Cl_2/MeOH, 95:5, SiO_2). **Mp**: 122 - 123 °C. **$[\alpha]_D^{19}$**: - 24.7 (c 0.35, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 2364, 1752, 1593, 1366, 1248, 1211, 1163, 1127, 1091, 1061, 1031, 913, 833, 679. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.45 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 5.31 (t, *J* = 8.9 Hz, 1H), 4.98 (dd, *J* = 18.5, 9.3 Hz, 3H), 4.34 - 4.12 (m, 3H), 3.93 - 3.89 (m, 1H), 3.78 (s, 2H), 2.94 (d, *J* = 9.6 Hz, 1H), 2.78 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.07 (s, 6H), 2.02 (s, 3H), 1.97 (s, 3H), 1.47 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 178.5 (C=O), 172.5 (C=O), 171.8 (C=O), 171.5 (C=O), 171.3 (C=O), 158.0 (C=O), 140.8 (Cq), 134.2 (2 x CH), 132.0 (Cq), 131.0 (2 x CH), 86.7 (CH), 80.7 (Cq), 77.0 (CH), 75.6 (CH), 71.8 (CH), 69.9 (CH), 63.6 (CH_2), 56.4 (CH), 37.2 (CH_2), 35.7 (CH_2), 29.1 (3 x CH_3), 21.1 (CH_3), 21.0 (CH_3), 20.8 (2 x CH_3).
HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{29}H_{39}NO_{13}S_2Na$ 696.1761, found 696.1766.

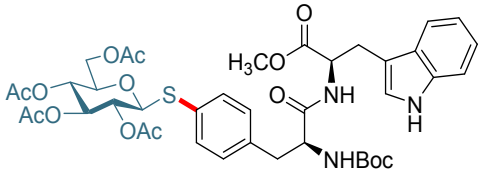
Solution phase synthesis of the thioglycosylated peptides (5a-f)

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(5a)**



Compound **5a** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (75 mg, 0.21 mmol, 1 equiv.), methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoyl)-D-phenylalaninate **4a** (113.7 mg, 0.21 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (5.9 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (28 µL, 0.21 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.1 mL, 0.10 M) which afforded the product as a white solid (120 mg, 74% **yield** after column chromatography EtOAc/Cyclohexane 30:70 → 50:50). **TLC** R_f = 0.42 (EtOAc/Cyclohexane, 50:50, SiO_2). **Mp**: 155 - 156 °C. **[α]$_D^{21}$** + 10.5 (c 0.43, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 3355, 2952, 1745, 1690, 1664, 1519, 1374, 1249, 1218, 1164, 1099, 1035, 915, 815, 753, 706, 680, 617. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**: 8.35 (d, *J* = 7.4 Hz, 1H), 7.34 - 7.21 (m, 9H), 6.89 (d, *J* = 8.8 Hz, 1H), 5.36 (t, *J* = 9.4 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.89 (t, *J* = 9.5 Hz, 1H), 4.81 (t, *J* = 9.7 Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 4.10 (dd, *J* = 25.7, 11.7 Hz, 4H), 3.58 (s, 3H), 3.16 - 2.94 (m, 2H), 2.94 - 2.75 (m, 1H), 2.75 - 2.62 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.93 (s, 3H), 1.29 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 171.8 (C=O), 171.7 (C=O), 169.9 (C=O), 169.5 (C=O), 169.3 (C=O), 169.0 (C=O), 155.1 (C=O), 137.8 (Cq), 137.0 (Cq), 130.7 (2 x CH), 129.9 (2 x CH), 129.7 (Cq), 129.1 (2 x CH), 128.3 (2 x CH), 126.6 (CH), 83.5 (CH), 78.1 (Cq), 74.2 (CH), 72.9 (CH), 69.6 (CH), 68.0 (CH), 61.2 (CH_2), 55.3 (CH), 53.5 (CH), 51.8 (CH_3), 36.8 (CH_2), 36.7 (CH_2), 28.1 (3 x CH_3), 20.6 (CH_3), 20.4 (2 x CH_3), 20.3 (CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{38}H_{48}N_2O_{14}SNa$ 811.2724, found 811.2742.

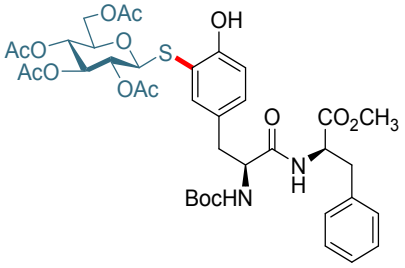
(2*S*,3*R*,4*S*,5*R*,6*R*)-2-((4-((*S*)-3-(((*R*)-3-(1h-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-2-((*tert*-butoxycarbonyl)amino)-3-oxopropyl)phenyl)thio)-6-(acetoxymethyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(5b)**



Compound **5b** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (75 mg, 0.21 mmol, 1 equiv.), methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoyl)-D-tryptophanate **4c** (121.7 mg, 0.21 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (5.9 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (28 µL, 0.21 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.6 mL, 0.10 M) which afforded the product as a beige solid (108 mg, 63% **yield** after column chromatography EtOAc/Cyclohexane 30:70 → 50:50). **TLC** R_f = 0.23 (EtOAc/Cyclohexane, 50:50, SiO_2). **Mp**: 101 - 102 °C. **[α]$_D^{21}$** + 8.5 (c 0.65, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 3362, 2928,

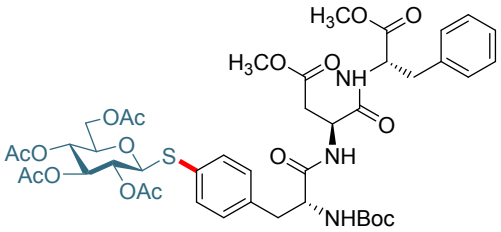
1756, 1740, 1658, 1493, 1436, 1366, 1249, 1212, 1163, 1093, 1034, 914, 743. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**: 10.90 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.42 - 7.28 (m, 3H), 7.28 - 7.14 (m, 3H), 7.08 (t, *J* = 6.3 Hz, 1H), 7.02 (t, *J* = 6.3 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 5.36 (t, *J* = 9.3 Hz, 1H), 5.24 (d, *J* = 10.1 Hz, 1H), 4.86 (dt, *J* = 23.1, 9.6 Hz, 2H), 4.56 (t, *J* = 6.3 Hz, 1H), 4.17 - 4.04 (m, 4H), 3.56 (s, 3H), 3.17 - 3.08 (m, 2H), 2.92 (d, *J* = 12.0 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.03 (s, 6H), 1.99 (s, 3H), 1.94 (s, 3H), 1.30 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 172.1 (C=O), 172.2 (C=O), 170.0 (C=O), 169.5 (C=O), 169.3 (C=O), 169.0 (C=O), 155.2 (C=O), 137.9 (Cq), 136.1 (Cq), 130.7 (2 x CH), 130.0 (2 x CH), 129.7 (Cq), 127.1 (Cq), 123.6 (CH), 121.0 (CH), 118.4 (CH), 118.0 (CH), 111.4 (CH), 109.1 (Cq), 83.5 (CH), 78.1 (Cq), 74.2 (CH), 72.9 (CH), 69.7 (CH), 68.0 (CH), 61.9 (CH_2), 55.3 (CH), 53.0 (CH), 51.8 (CH_3), 36.9 (CH_2), 28.1 (3 x CH_3), 27.1 (CH_2), 20.6 (CH_3), 20.4 (2 x CH_3), 20.7 (CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{40}H_{49}N_3O_{14}SNa$ 850.2833, found 850.2839.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((5-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)-2-hydroxyphenyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(5c)**



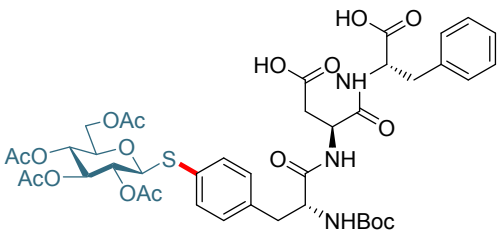
Compound **5c** was prepared by using the general procedure **A** of coupling (reaction time: 4.0 h), with *β*-thioglucose **1a** (60 mg, 0.16 mmol, 1 equiv.), methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxy-3-iodophenyl)propanoyl)-D-phenylalaninate **4b** (93.6 mg, 0.16 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (4.7 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (22 µL, 0.16 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1.6 mL, 0.10 M) which afforded the product as a white solid (70 mg, 53% **yield** after column chromatography EtOAc/Cyclohexane 30:70 → 50:50 and trituration in *n*-pentane). **TLC R_f** = 0.41 (EtOAc/Cyclohexane, 50:50, SiO_2). **Mp**: 90 - 91 °C. **$[\alpha]_D^{21}$** + 10.6 (c 0.49, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 3357, 2926, 1744, 1661, 1518, 1488, 1436, 1366, 1248, 1214, 1163, 1033, 914, 814, 751, 702. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.55 - 6.80 (m, 7H), 6.77 (d, *J* = 5.9 Hz, 1H), 5.40 - 5.18 (m, 1H), 4.75 - 4.49 (m, 3H), 4.27 (d, *J* = 6.8 Hz, 2H), 4.15 (d, *J* = 13.4 Hz, 2H), 3.97 - 3.93 (m, 1H), 3.66 (s, 3H), 3.11 - 3.10 (m, 1H), 3.03 - 2.90 (m, 2H), 2.69 (t, *J* = 16.4 Hz, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 173.9 (C=O), 173.0 (C=O), 172.5 (C=O), 171.6 (C=O), 171.2 (2 x C=O), 157.5 (C=O), 157.1 (Cq), 137.9 (Cq), 135.9 (CH), 132.3 (CH), 130.3 (2 x CH), 130.2 (Cq), 129.5 (2 x CH), 127.9 (CH), 118.5 (Cq), 116.4 (CH), 86.4 (CH), 80.7 (Cq), 76.7 (CH), 75.4 (CH), 71.5 (CH), 69.6 (CH), 63.3 (CH_2), 57.1 (CH), 55.1 (CH), 52.8 (CH_3), 38.6 (CH_2), 38.4 (CH_2), 28.7 (3 x CH_3), 20.8 (2 x CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{38}H_{48}N_2O_{15}SNa$ 827.2673, found 827.2681.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-4-methoxy-1-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-oxopropyl)phenyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(5d)**



Compound **5d** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (75 mg, 0.21 mmol, 1 equiv.), methyl (6*R*,9*S*,12*S*)-12-benzyl-6-(4-iodobenzyl)-9-(2-methoxy-2-oxoethyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **4d** (140.3 mg, 0.21 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (5.9 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (28 µL, 0.21 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 2.1 mL, 0.10 M) which afforded the product as a beige solid (158 mg, 84% **yield** after column chromatography EtOAc/Cyclohexane 50:50 → 70:30). **TLC** R_f = 0.42 (EtOAc/Cyclohexane, 70:30, SiO_2). **Mp**: 129 - 130 °C. **[α]$_D^{21}$** : - 3.9 (c 0.62, $CHCl_3$). **IR (thin film, neat) vmax/cm^{-1}**: 3357, 2975, 2924, 2840, 1769, 1727, 1688, 1642, 1470, 1354, 1261, 1191, 1141, 1074, 995, 926, 902, 764, 726, 696, 627. **^{1}H NMR (300 MHz, DMSOd_6) δ (ppm)**:
8.32 (d, *J* = 7.4 Hz, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.45 - 7.15 (m, 9H), 6.94 (d, *J* = 8.5 Hz, 1H), 5.36 (t, *J* = 9.4 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 4.90 (t, *J* = 9.6 Hz, 1H), 4.82 (t, *J* = 9.7 Hz, 1H), 4.66 (dd, *J* = 13.6, 7.4 Hz, 1H), 4.46 (dd, *J* = 13.8, 7.6 Hz, 1H), 4.23 - 4.01 (m, 4H), 3.59 (2 x s, 6H), 3.11 - 2.81 (m, 3H), 2.75 - 2.67 m, 2H), 2.62 - 2.53 (m, 1H), 2.02 (s, 6H), 1.99 (s, 3H), 1.93 (s, 3H), 1.29 (s, 9H). **^{13}C NMR (75 MHz, DMSOd_6) δ (ppm)**: 171.5 (2 x C=O), 170.3 (C=O), 170.2 (C=O), 169.9 (C=O), 169.5 (C=O), 169.3 (C=O), 169.0 (C=O), 155.2 (C=O), 138.0 (Cq), 136.9 (Cq), 130.7 (2 x CH), 129.9 (2 x CH), 129.7 (Cq), 129.0 (2 x CH), 128.3 (2 x CH), 126.5 (CH), 83.5 (CH), 78.1 (Cq), 74.2 (CH), 72.9 (CH), 69.7 (CH), 68.0 (CH), 61.9 (CH_2), 55.4 (CH), 53.8 (CH), 51.9 (CH), 51.5 (CH_3), 49.1 (CH_3), 36.8 (CH_2), 36.5 (CH_2), 36.2 (CH_2), 20.5 (CH_3), 20.4 (2 x CH_3), 20.3 (CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{43}H_{55}N_3O_{17}SNa$ 940.3150, found 940.3149.

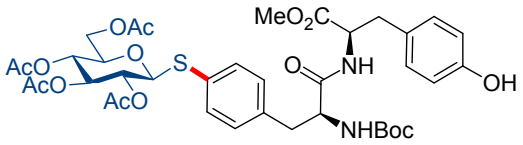
(6*R*,9*S*,12*S*)-12-benzyl-9-(carboxymethyl)-2,2-dimethyl-4,7,10-trioxo-6-(4-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)thio)benzyl)-3-oxa-5,8,11-triazatridecan-13-oic acid **(5e)**



Compound **5e** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (75 mg, 0.21 mmol, 1 equiv.), (6*R*,9*S*,12*S*)-12-benzyl-9-(carboxymethyl)-6-(4-iodobenzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oic acid **4e** (134.5 mg, 0.21 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (5.9 mg, 0.01 mmol, 0.03 equiv.) and triethylamine (28 µL, 0.21 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2,

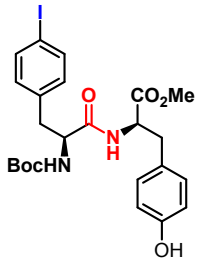
2.1 mL, 0.10 M) which afforded the product as a white solid (160 mg, 87% **yield** after column chromatography CH_2Cl_2/MeOH/CH_3CO_2H 99:1:1 → 90:9:1). **TLC** R_f = 0.43 (CH_2Cl_2/MeOH, 90:10, SiO_2). **Mp**: 187 - 188 °C. **[α]$_D^{21}$** : - 11.5 (c 0.51, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 3329, 2924, 1757, 1495, 1367, 1250, 1212, 1164, 1034, 915, 701. **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)**: 7.42 (d, *J* = 7.5 Hz, 2H), 7.24 - 7.16 (m, 6H), 5.30 - 5.26 (m, 1H), 5.01 - 4.94 (m, 2H), 4.69 - 4.51 (m, 2H), 4.28 - 4.23 (m, 1H), 4.25 (dd, *J* = 12.3, 5.1 Hz, 1H), 4.15 (d, *J* = 11.9 Hz, 1H), 3.90 - 3.87 (m, 1H), 3.18 (d, *J* = 10.3 Hz, 2H), 3.11 - 2.88 (m, 1H), 2.80 2 .74 (m, 3H), 2.07 (s, 2H), 2.04 (s, 2H), 2.00 (s, 3H), 1.95 (s, 2H), 1.45 (s, 9H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)**: 173.7 (C=O), 172.2 (C=O), 171.5 (2 x C=O), 171.2 (2 x C=O), 171.0 (2 x C=O), 157.6 (C=O), 139.3 (Cq), 138.7 (Cq), 133.9 (2 x CH), 131.3 (Cq), 131.2 (2 x CH), 130.3 (2 x CH), 129.4 (2 x CH), 127.7 (CH), 86.6 (CH), 80.7 (Cq), 76.7 (CH), 75.3 (CH), 71.5 (CH), 69.6 (CH), 63.3 (CH_2), 57.1 (CH), 55.8 (CH), 51.3 (CH), 38.7 (CH_2), 38.6 (CH_2), 38.4 (CH_2), 28.7 (3 x CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.5 (2 x CH_3). **HRMS (ESI) (M + Na)$^+$** *m/z* calculated for $C_{41}H_{51}N_3O_{17}SNa$ 912.2837, found 912.2825.

(*2R,3R,4S,5R,6S*)-2-(acetoxymethyl)-6-((4-((S)-2-((tert-butoxycarbonyl)amino)-3-(((R)-3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)phenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**5f**)



Compound **5f** was prepared by using the general procedure **A** of coupling (reaction time: 0.5 h), with *β*-thioglucose **1a** (37 mg, 0.1 mmol, 1 equiv.), methyl ((S)-2-((tert-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoyl)-D-phenylalaninate **4f** (58 mg, 0.1 mmol, 1 equiv.), XantPhos PdG_3 precatalyst (3 mg, 0.003 mmol, 0.03 equiv.) and triethylamine (14 µL, 0.1 mmol, 1 equiv.) in a mixture of THF/H_2O (1:2, 1 mL, 0.10 M) which afforded the product as a yellow amorphous solid (78 mg, 96% **yield** after column chromatography (heptane: EtOAc, 100/0 to 2/8). **TLC** R_f = 0.48 (heptane: EtOAc 2/8, SiO_2). **[α]$_D^{28}$** : + 4.7 (c 0.017, $CHCl_3$). **IR (thin film, neat) νmax/cm^{-1}**: 3330, 2900, 1757, 1494, 1367, 1213, 1061, 958, 732. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)**: 7.39 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.30 – 4.91 (m, 5H), 4.79 – 4.60 (m, 2H), 4.36 (bs, 1H), 4.26 – 4.03 (m, 3H), 3.69 (s, 3H), 3.12 – 2.88 (m, 4H), 2.07 (s, 6H), 2.01 (s, 3H), 1.98 (s, 3H), 1.40 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)**: 171.6 (C=O), 170.8 (2 x C=O), 170.3(C=O), 169.5 (C=O), 169.5 (C=O), 169.4 (C=O), 155.5 (C=O), 137.1 (Cq), 133.1 (2 x CH), 130.4 (2 x CH), 130.1 (2 x CH), 126.9 (Cq), 115.6 (2 x CH), 85.9 (CH), 80.5 (Cq), 75.8 (CH), 74.3 (CH), 70.0 (CH), 69.6 (CH), 65.9 (Cq), 62.2 (CH_2), 55.4 (CH), 53.6 (CH), 52.4 (CH_3), 37.9 (CH_2), 37.1 (CH_2), 28.3 (3 x CH_3), 20.8 (2 xCH_3), 20.6 (2 x CH_3). **HRMS (ESI) (M + NH_4)$^+$** *m/z* calculated for $C_{38}H_{52}N_3O_{15}S$ 822.3113, found 822.3119.

Synthesis of (R)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-iodophenyl)propanamido)-3-(4-hydroxyphenyl)propanoate (**4f**)



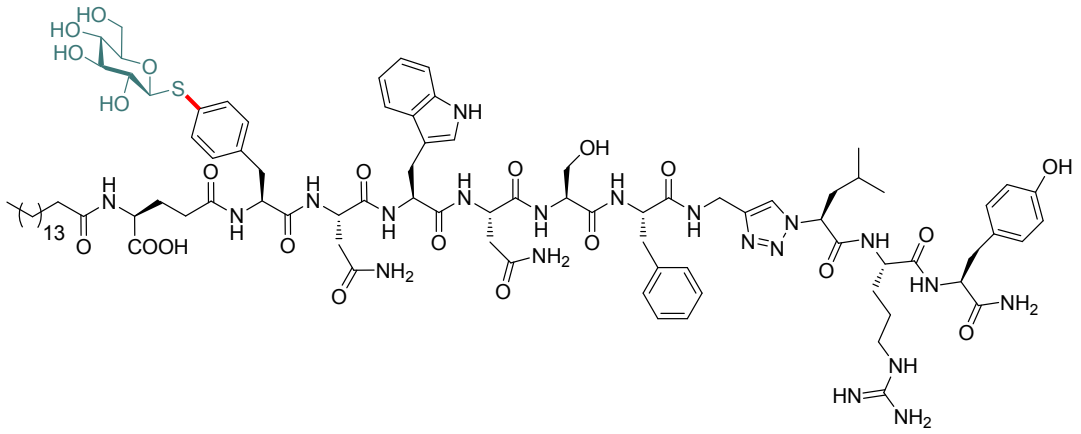
Compound **4f** was prepared as follow: L-tyrosine methyl ester (195.2 mg, 0.51 mmol, 1 equiv.) and N-boc-4-iodo-L-phenylalanine (240.5 mg, 0.61 mmol, 1.2 equiv.) were dissolved in DCM (1 mL), followed by addition of HBTU (233 mg, 0.61 mmol, 1.2 equiv.) and DiPEA (312 µL, 1.79 mmol, 3.5 equiv.). After stirring overnight, the reaction mixture was concentrated *in vacuo* and re-dissolved in EtOAc, washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (3x) and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (eluant: heptane/EtOAc 100/0 -> 6/4) afforded the desired compound as a white solid (159 mg, 0.28 mmol, 46% yield). **TLC** R_f = 0.32 (heptane/EtOAc 6/4, SiO_2). **Mp**: 147 - 149 °C. **IR (thin film, neat) νmax/cm^{-1}**: 3400, 2929, 2360, 1755, 1683, 1515, 1291, 1163, 1007, 732. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)**: 7.58 (d, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.81 (s, 1H), 5.00 (bs, 1H), 4.73 (s, 1H), 4.28 (bs, 1H), 3.70 (s, 3H), 3.02-2.93 (m, 4H), 1.41 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)**: 171.4 (C=O), 170.5 (C=O), 155.0 (C=O), 137.6 (2 x CH), 136.1 (Cq), 131.3 (2 x CH), 130.3 (2 x CH), 127.2 (Cq), 115.5 (2 x CH), 92.4 (Cq), 81.0 (Cq), 53.4 (CH), 53.3(CH), 52.4(CH_3), 37.8(CH_2), 37.1(CH_2), 28.7 (3 x CH_3). **HRMS (ESI) (M + H)$^+$** *m/z* calculated for $C_{24}H_{30}N_2O_6I$ 569.1149, found 569.1154.

Solid phase synthesis of lipo-triazolopeptide 6a and thioglyco-lipo-triazolopeptide 6b

Lipo-triazolopeptide **6a** was synthesized as described elsewhere.[1]

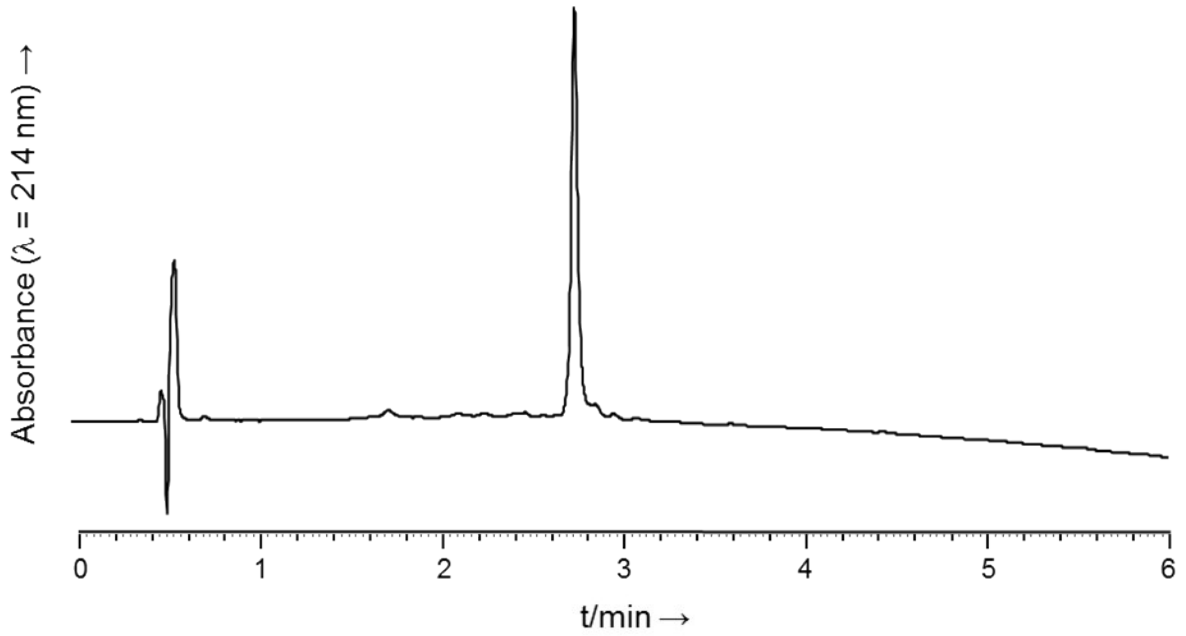
The elongation of the peptide was performed by standard automated solid phase synthesis up to Arg[9] (KP-10 numeration). The coupling of (2*S*)-2-azido-4-methylpentanoic acid (N_3Leu-OH) was also performed by the automated procedure. Triazole formation was performed by reaction with *N*-Fmoc-α-aminoalkyne (0.4 mmol, 4 equiv.) and CuBr·Me_2S (82 mg, 0.4 mmol, 4 equiv.) were dissolved in NMP (10 mL) under argon. After addition of *i*Pr_2NEt (70 µL, 0.4 mmol, 4 equiv.), the mixture was transferred into a syringe fitted with a frit containing azidopeptide resin (0.1 mmol) swollen in NMP. The suspension was stirred by syringe rotation for 2 h at room temperature, and the resin was flow-washed successively with NMP (3 × 2 min), CH_2Cl_2 (2 × 2 min), 1 M pyridine hydrochloride in CH_2Cl_2/MeOH 95:5 (2 × 2 min), CH_2Cl_2 (2 × 2 min), and DMF (2 × 2 min). Elongation of the peptide was continued by standard solid phase synthesis up to Asn[2]. Thioglyco-aminoacid **3p** (3 equiv.) was coupled using HATU (2.9 equiv.) in the presence of *i*Pr_2NEt (6 equiv.) in NMP. After standard deprotection of the Fmoc group, Fmoc-Glu-O*t*Bu (10 equiv.) was coupled by standard SPPS protocol followed by standard Fmoc deprotection. Then, hexadecanoic acid (10 equiv.) was coupled using HCTU (9.5 equiv.) and *i*Pr_2NEt (20 equiv.) in NMP/CH_2Cl_2 (1:4) for 2 h. Peptide-resin was deprotected and cleaved to afford crude peptides **6b** that was purified by semi-preparative RP-HPLC.

Characterization of 6b

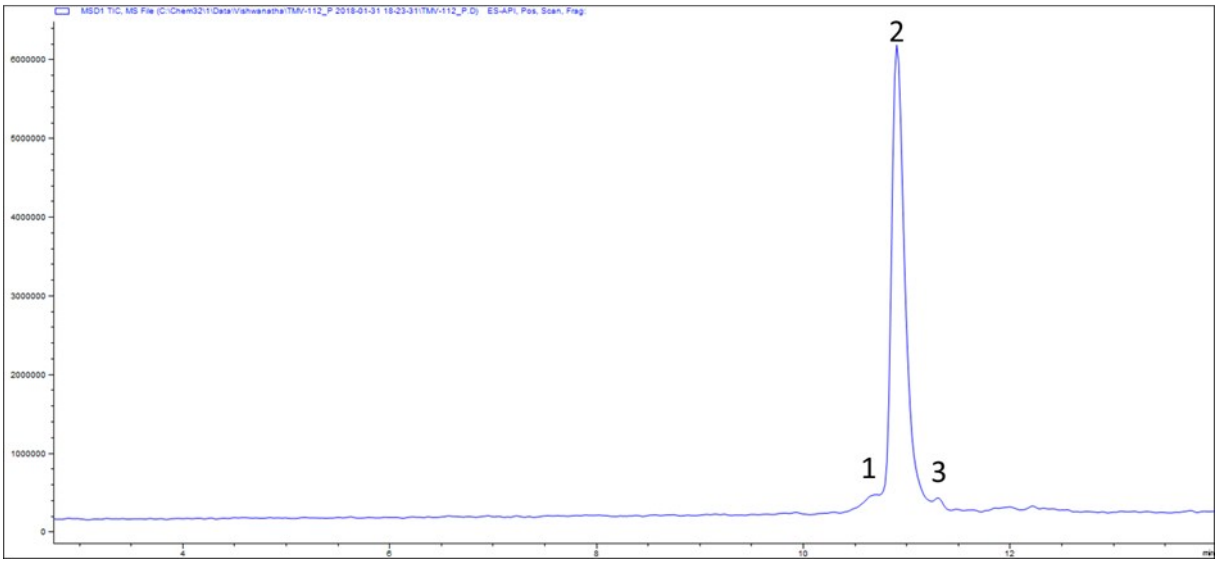


HPLC analysis: t_R = 2.74 min (Chromolith, gradient: 50-90% B/A over 5 min)
HPLC purification: Jupiter C18, gradient: 50-90% B/A over 20 min, 25 °C
Yield: 81%

[1] Decourt, C. *et al. Sci. Rep.* **2016**, *6*, 26908.

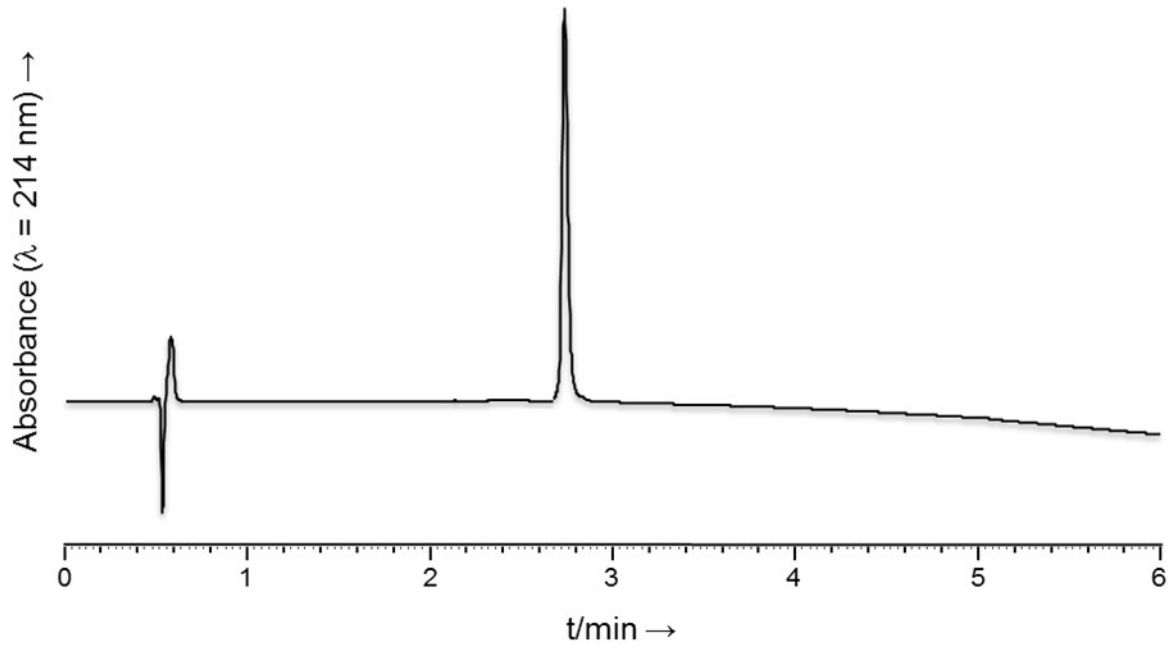


HPLC trace of crude **6b**



LC/MS analysis: total ion chromatogram of crude **6b:**

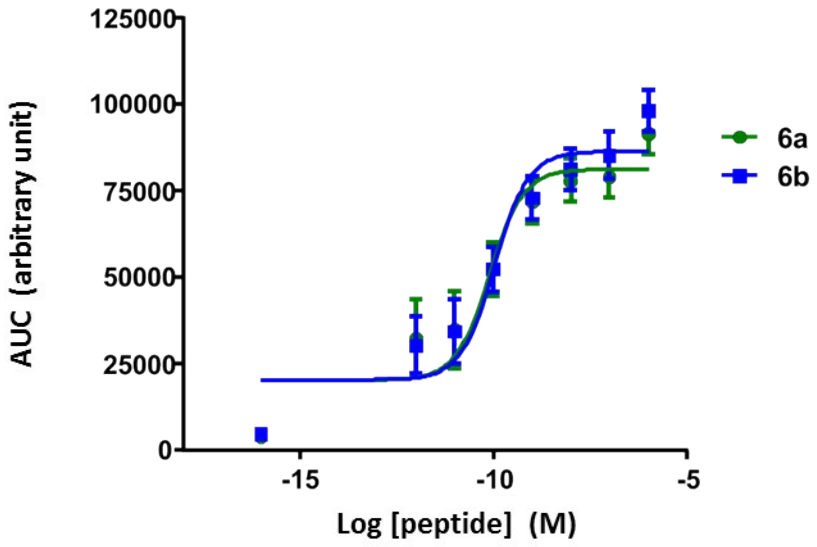
Peak number (t_R (min))	$[M+2H]^{2+}$ (*m/z*) calcd.	*m/z* found	Attributed to
1 (10.71)		900.2	Not attributed
2 (10.90)	944.5	944.8	**6b**
3 (11.30)	935.4	935.8	Water loss from **6b**



HPLC trace of purified **6b**

Concentration-activity response of compounds 6a-b: potency and efficacy at hKISS1R

Human KISS1R receptor was cloned into the pcDNA3.1 expression vector (Invitrogen, Cergy Pontoise, France) in fusion at its 5' end with a HA tag. The resulting construct was transfected in HEK293 cell line and selected for stable expression using geneticin. HEK293. Transfected cells were grown in DMEM (with glutamax, high glucose and without pyruvate) 10% fetal calf serum, 1% penicillin, 1% streptomycin, 200 µg/mL geneticin and HEPES (25 mM). KISS1R is a Gq-coupled receptor and to assess ligands potency and efficacy the dynamics of intracellular Ca^{2+} mobilization induced by test compound application was monitored using Fluo4 NW Ca^{2+} assay kit. Cells were plated 48 h before the experiment into 96-well blackplate (Dutscher, Brumath, France) at a concentration of 40,000 cells/well. The day of the experiment test compounds were diluted from stock solution in LoBind Tube (Eppendorf, Hamburg, Germany) or in non-binding plate (VWR, Strasbourg, France) to 20x the final desired concentration (ranging from 1 pM to 1 µM). The media was discharged, cell rinsed once with PBS, and incubated with the kit's dye (95 µL/well) for 30 min at 37 °C and 30 min at RT. Basal fluorescence was measured 5 times at 7 s interval with a plate reader (PolarStar Optima, BMG Labtech). Immediately after basal reading 5 µL of test compound were added to each well to obtain the final test concentration. Intracellular Ca^{2+} dynamic was monitored for 7 min. To generate concentration activity curves mean basal was subtracted to value obtained after stimulation. The area under the curve (AUC) was calculated and plotted against concentrations. Concentration-activity data points were fitted to sigmoid curve generated by GraphPad Prism 5 and EC_{50} automatically calculated. To check for non-specific signal control experiments were performed in non-transfected HEK293 cells using the same method.



Evaluation of compounds **6a** and **6b** potency and efficacy at hKISS1R. Data are means±SEM of a representative experiment that has been repeated three times for a total of 8 replicates.

Solid phase synthesis of the MUC1-derived mono-iodo peptide (7a) and tri-iodo peptide (7b)

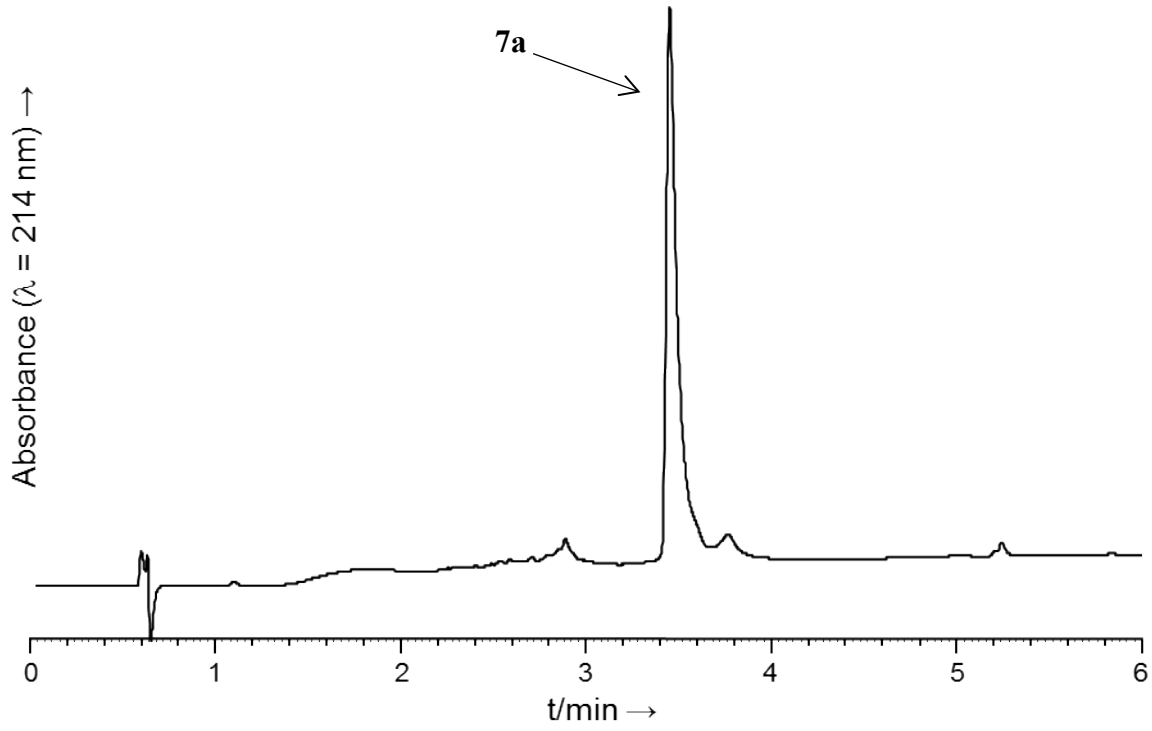
The two iodophenylalanine-containing peptides were synthesized through standard Fmoc-based SPPS on a Tentagel R resin (125 mg, 0.20 mmol/g, 25 µmol). After completion of SPPS elongation, peptide-resins were deprotected and cleaved to afford crude peptides **7a** and **7b** that were purified by semi-preparative RP-HPLC.

Amino acids sequence of mono-iodo MUC1-derived peptide (7a)

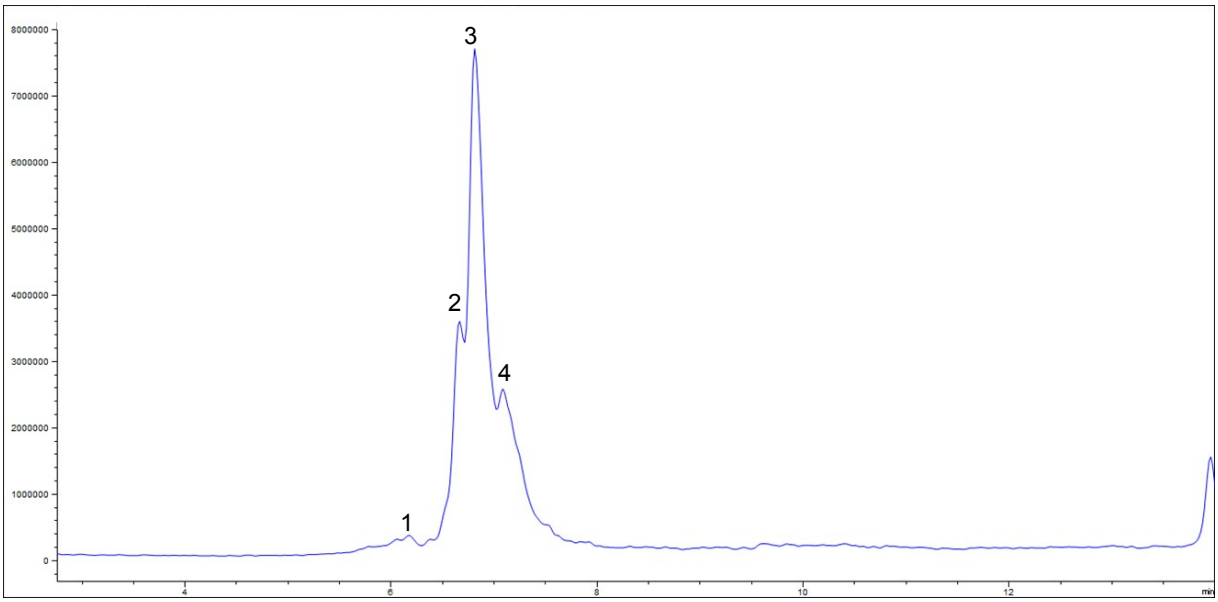
H-^{1}APDTRPAPGSTAPPAHGVTSAPDXRPAPGSTAPPAHGVTSAPDTRPAPGSTAP PAHGVT^{60}S-NH_2

X = 4-Iodophenylalanine (IPhe)

ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{245}H_{379}N_{76}O_{80}I$: 5792.6970, found: 5792.7115
HPLC analysis: t_R = 3.44 min (Chromolith, gradient: 5-50% B/A over 5 min)
HPLC purification: Jupiter C4, gradient: 20-21% B/A over 12 min, 70 °C
Yield: 38%



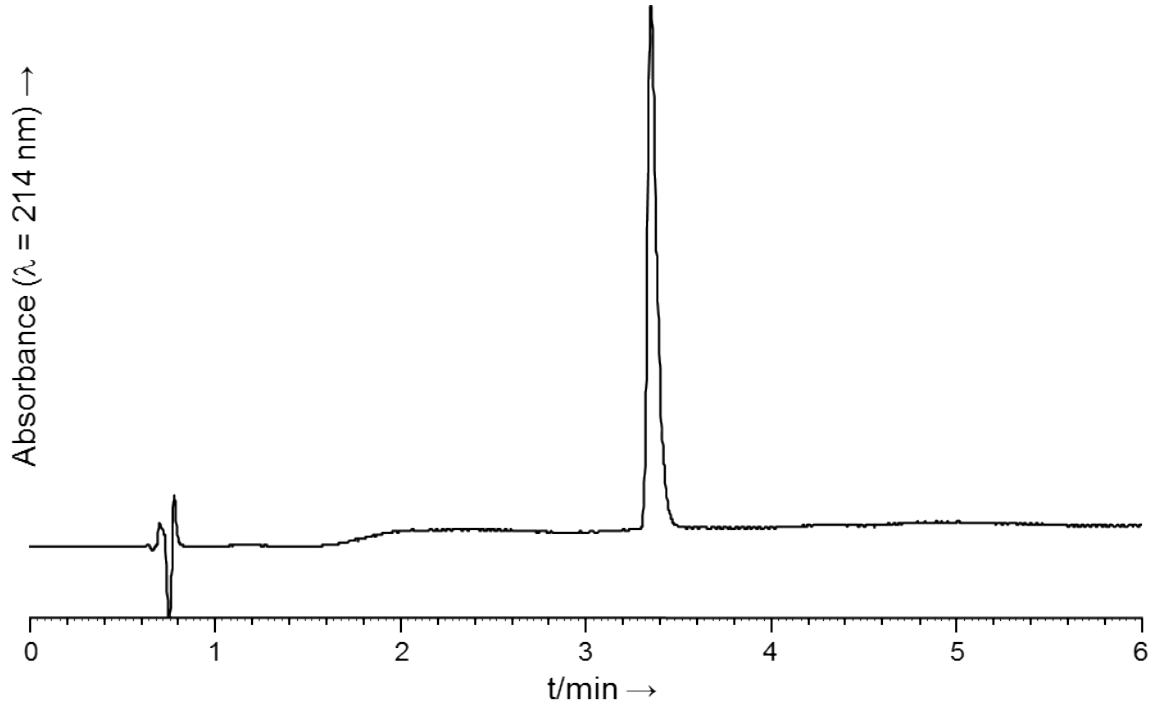
HPLC trace of crude **7a**



LC/MS analysis: total ion chromatogram of crude **7a**

Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (6.17)	3256.5	3256.7	Ac-[26-60]
2 (6.66)	5778.1	5778.2	Water loss from **7a**
3 (6.81)	5796.1	5796.1	**7a**
4 (7.08)	5778.1	5777.8	Water loss from **7a**

Attribution of the main peaks observed during LC/MS analysis of crude **7a**



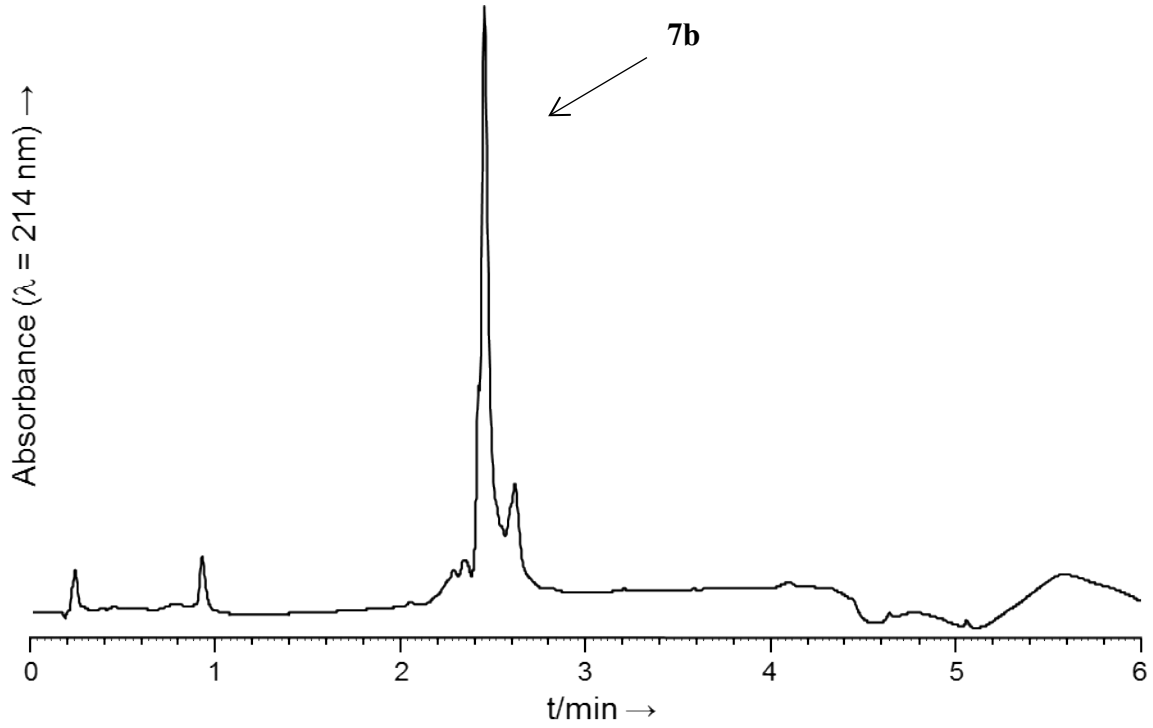
HPLC trace of purified **7a**

Amino acids sequence of tri-iodo MUC1-derived peptide (7b)

H-^{1}APDXRPAPGSTAPPAHGVTSAPDXRPAPGSTAPPAHGVTSAPDXRPAPGSTAP
PAHGVT^{60}S-NH_2

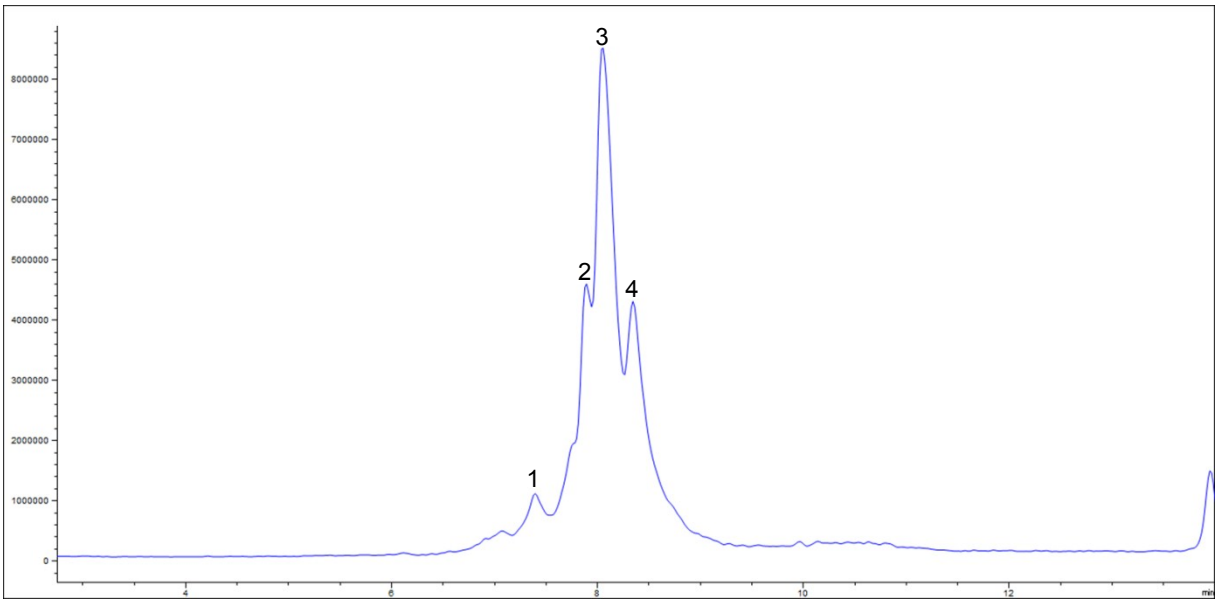
X = 4-Iodophenylalanine (IPhe)

ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{255}H_{381}N_{76}O_{78}I_3$: 6136.5318, found: 6136.5479
HPLC analysis: t_R = 3.99 min (Chromolith, gradient: 05-50% B/A over 5 min)
HPLC purification: Jupiter C4, gradient: 25-26% B/A over 12 min, 70 °C
Yield: 30%



H

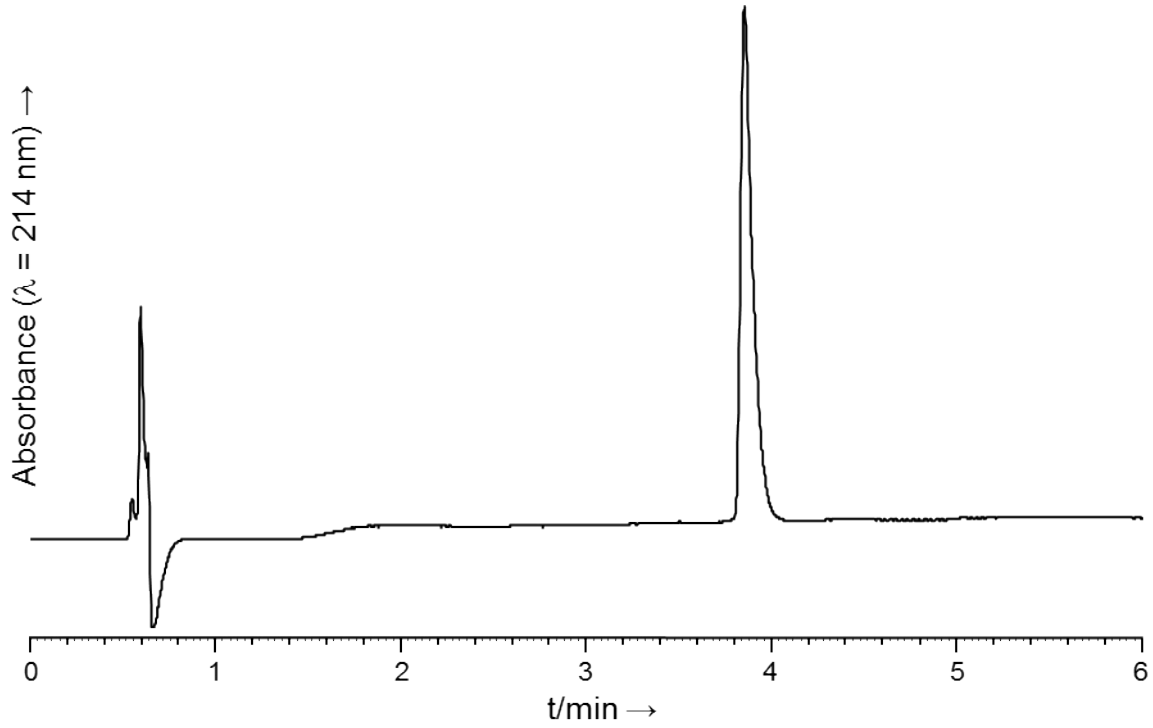
PLC trace of crude **7b**



LC/MS analysis: total ion chromatogram of crude **7b**

Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (7.39)	3815.74	3815.65	[24-60]
2 (7.88)	6121.99	6122.32	Water loss from **7b**
3 (8.04)	6140.00	6140.05	**7b**
4 (8.34)	6121.99	6122.08	Water loss from **7b**

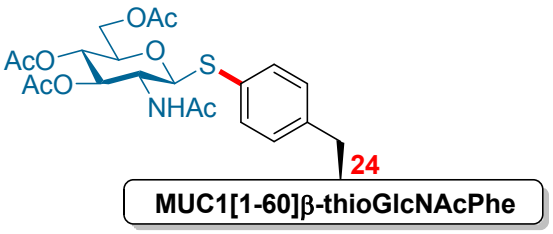
Attribution of the main peaks observed during LC/MS analysis of crude **7b**



HPLC trace of purified **7b**.

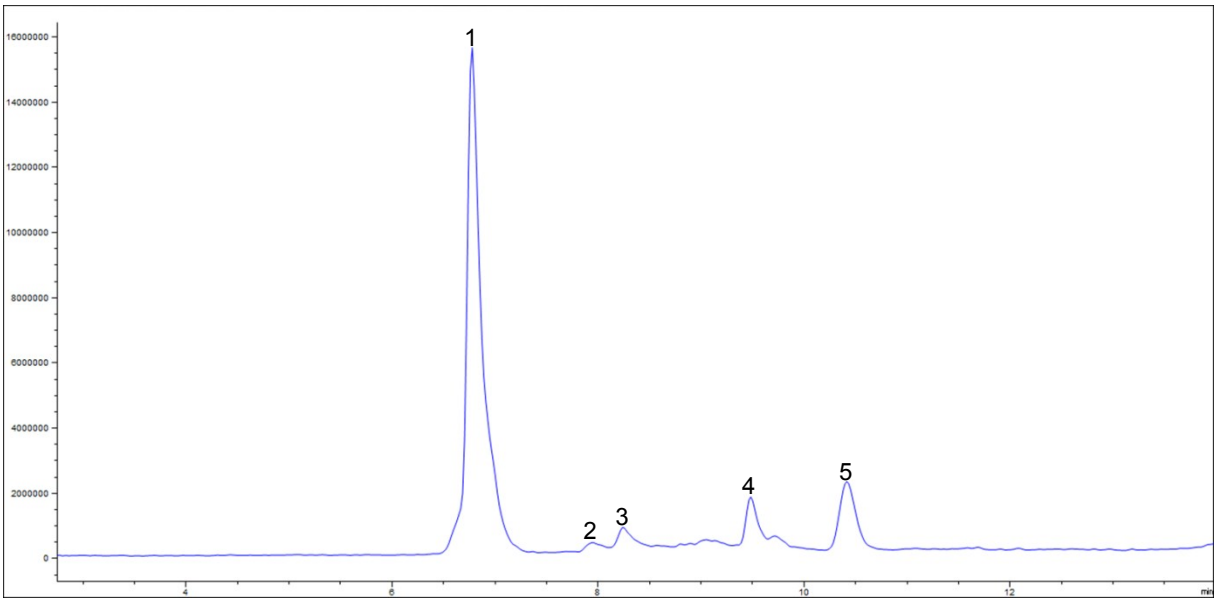
Experimental data for the thioglycosylated MUC1-derived peptides (8a-f)

Mono-thioglycosylated MUC1-derived peptide (**8a**)



Compound **8a** was prepared by using the general procedure **B** of coupling (reaction time: 1.0 h), with HPLC-purified lyophilized mono-iodopeptide **7a** (50 µL, 0.5 µmol, 1 equiv.), protected *β*-thioglucosamine **1c** (50 µL, 1.5 µmol, 3 equiv.), XantPhos PdG_3 precatalyst (25 µL, 2.5 µmol, 5 equiv.) and Et_3N (25 µL, 7.5 µmol, 15 equiv.) in a mixture of THF/H_2O (1:2, 500 µL, 1.0 mM) which afforded the mono-thioglycosylated MUC1-derived peptide **8a**.

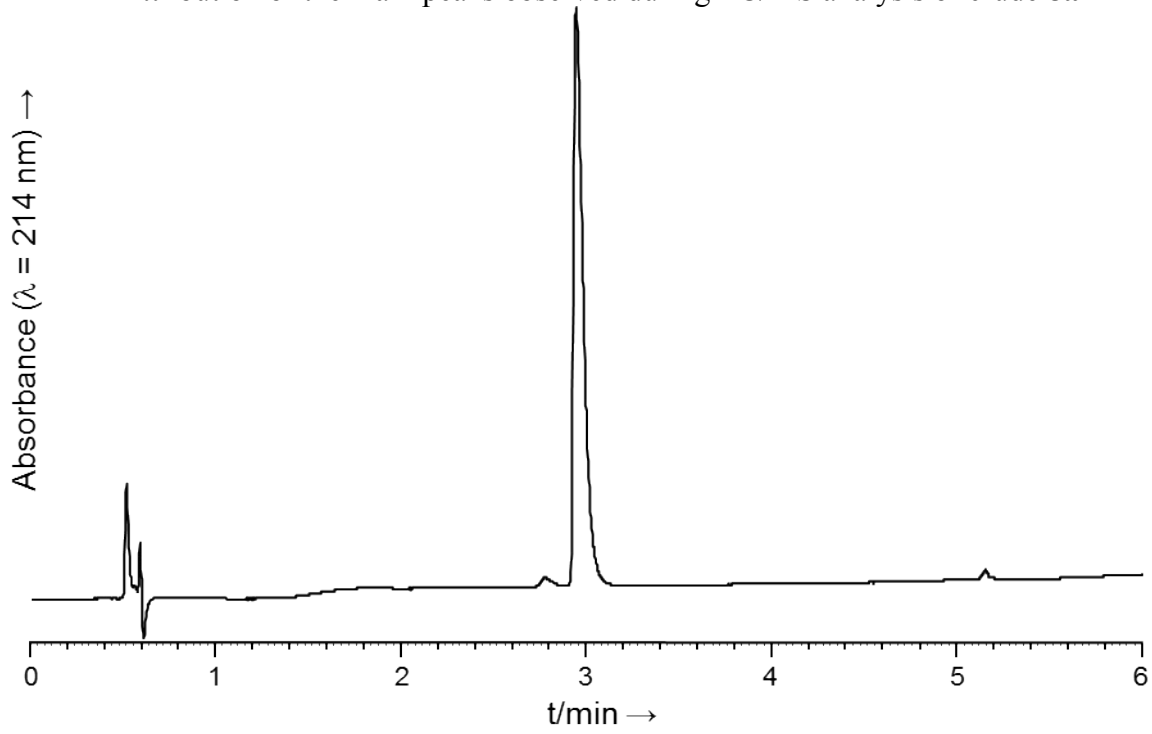
ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{259}H_{399}N_{77}O_{88}S$: 6027.8835, found: 6027.9033
HPLC analysis: t_R = 3.00 min (Chromolith, gradient: 10-50% B/A over 5 min)
HPLC purification: Nucleosil C18, gradient: 19-22% B/A over 15 min
Yield: 80%



LC/MS analysis: total ion chromatogram of crude **8a**

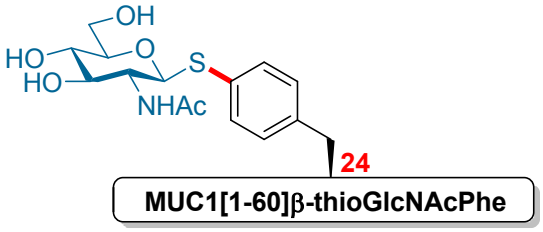
Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (6.78)	6031.53	6030.81	**8a**
2 (8.04)	-	170.00	Not attributed
3 (8.26)	-	6713.21	Not attributed
4 (9.48)	-	6353.16	Not attributed
5 (10.43)	-	530.13	Not attributed

Attribution of the main peaks observed during LC/MS analysis of crude **8a**



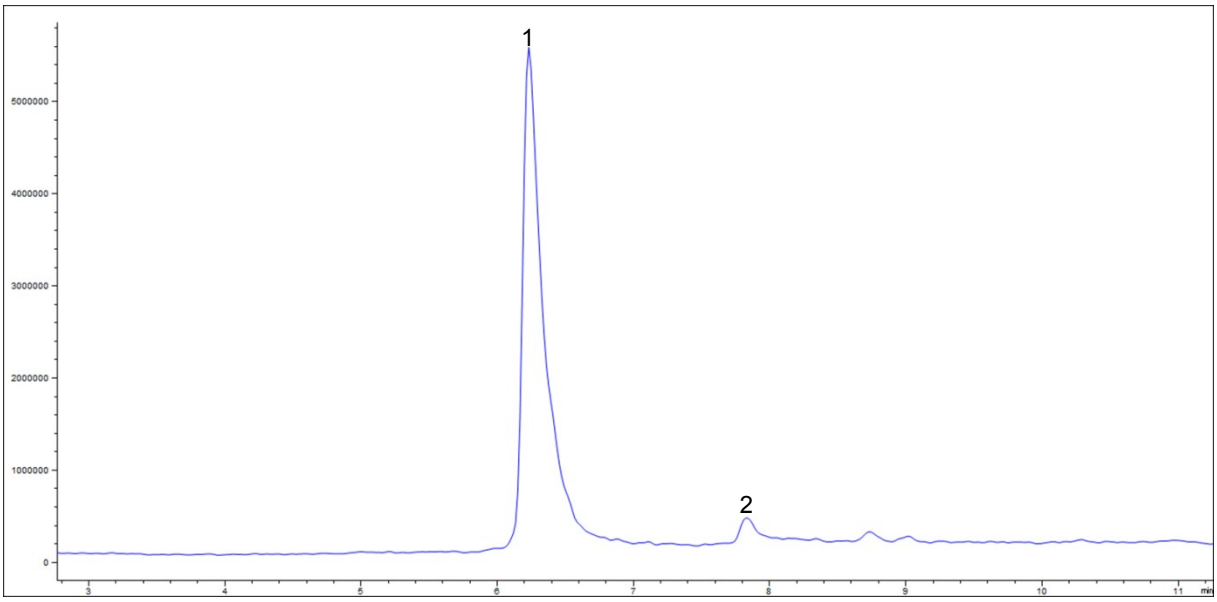
HPLC trace of purified **8a**

Mono-thioglycosylated MUC1-derived peptide (**8b**)



Compound **8b** was prepared by using the general procedure **B** of coupling (reaction time: 1.0 h), with HPLC-purified lyophilized mono-iodopeptide **7a** (50 µL, 0.5 µmol, 1 equiv.), unprotected *β*-thioglucosamine **1i** (50 µL, 1.5 µmol, 3 equiv.), XantPhos PdG_3 precatalyst (25 µL, 2.5 µmol, 5 equiv.) and Et_3N (25 µL, 7.5 µmol, 15 equiv.) in a mixture of THF/H_2O (1:2, 500 µL, 1.0 mM) which afforded the mono-thioglycosylated MUC1-derived peptide **8b**.

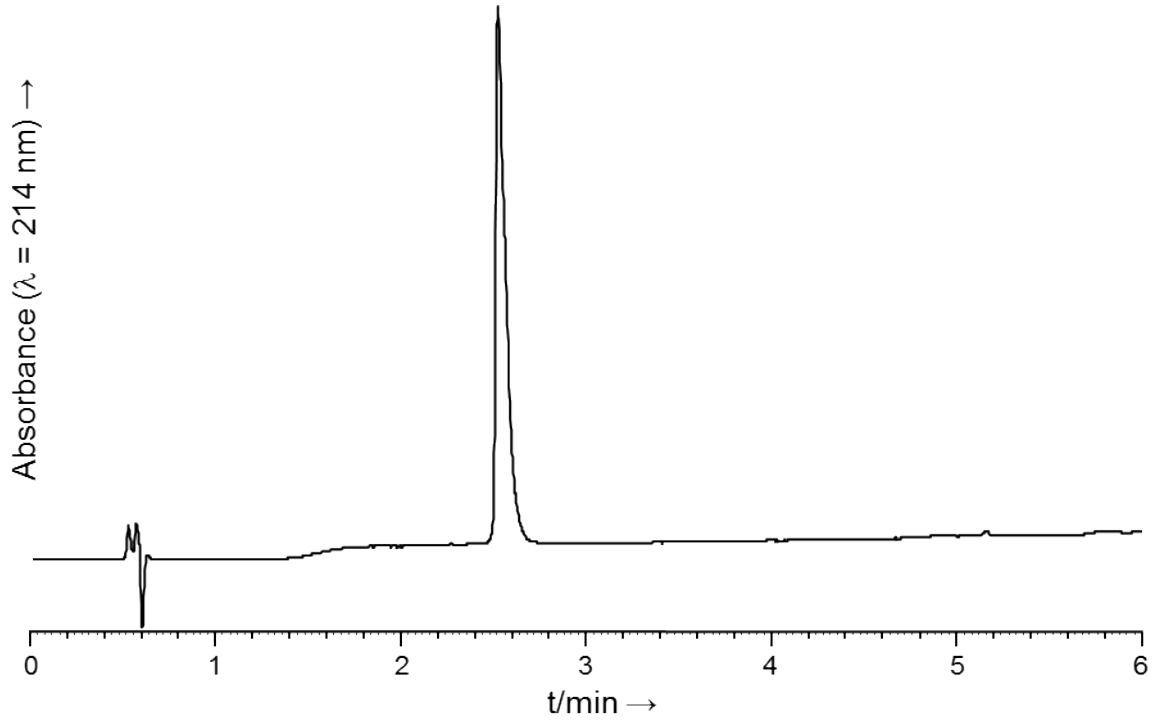
ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{253}H_{393}N_{77}O_{85}S$: 5901.8518, found: 5901.8669
HPLC analysis: t_R = 2.57 min (Chromolith, gradient: 10-50% B/A over 5 min)
HPLC purification: Nucleosil C18, gradient: 15-20% B/A over 16 min
Yield: 76%



LC/MS analysis: total ion chromatogram of crude **8b**

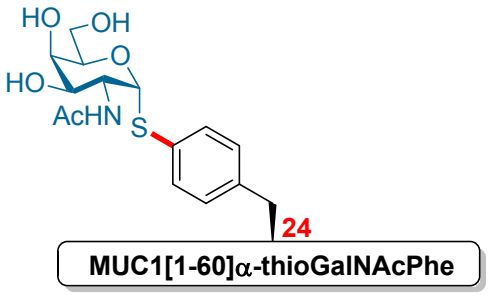
Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (6.23)	5904.42	5904.56	**8b**
2 (7.83)	-	170.0	Not attributed

Attribution of the main peaks observed during LC/MS analysis of crude **8b**



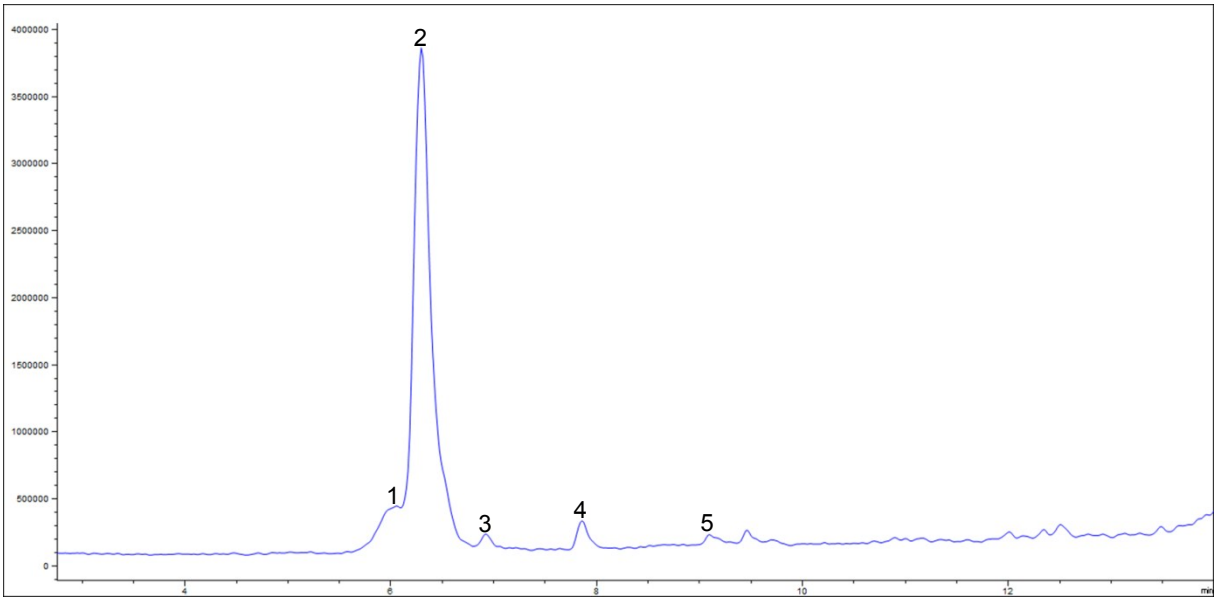
HPLC trace of purified **8b**

Mono-thioglycosylated MUC1-derived peptide (**8c**)



Compound **8c** was prepared by using the general procedure **B** of coupling (reaction time: 1.0 h), with HPLC-purified lyophilized mono-iodopeptide **7a** (50 µL, 0.5 µmol, 1 equiv.), *α*-thiogalactosamine **1j**[2] (50 µL, 1.5 µmol, 3 equiv.), XantPhos PdG_3 precatalyst (25 µL, 2.5 µmol, 5 equiv.) and Et_3N (25 µL, 7.5 µmol, 15 equiv.) in a mixture of THF/H_2O (1:2, 500 µL, 1.0 mM) which afforded the mono-thioglycosylated MUC1-derived peptide **8c**.

ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{253}H_{393}N_{77}O_{85}S$: 5901.8518, found: 5901.8675
HPLC analysis: t_R = 2.58 min (Chromolith, gradient: 10-50% B/A over 5 min)
HPLC purification: Nucleosil C18, gradient: 15-20% B/A over 16 min
Yield: 71%

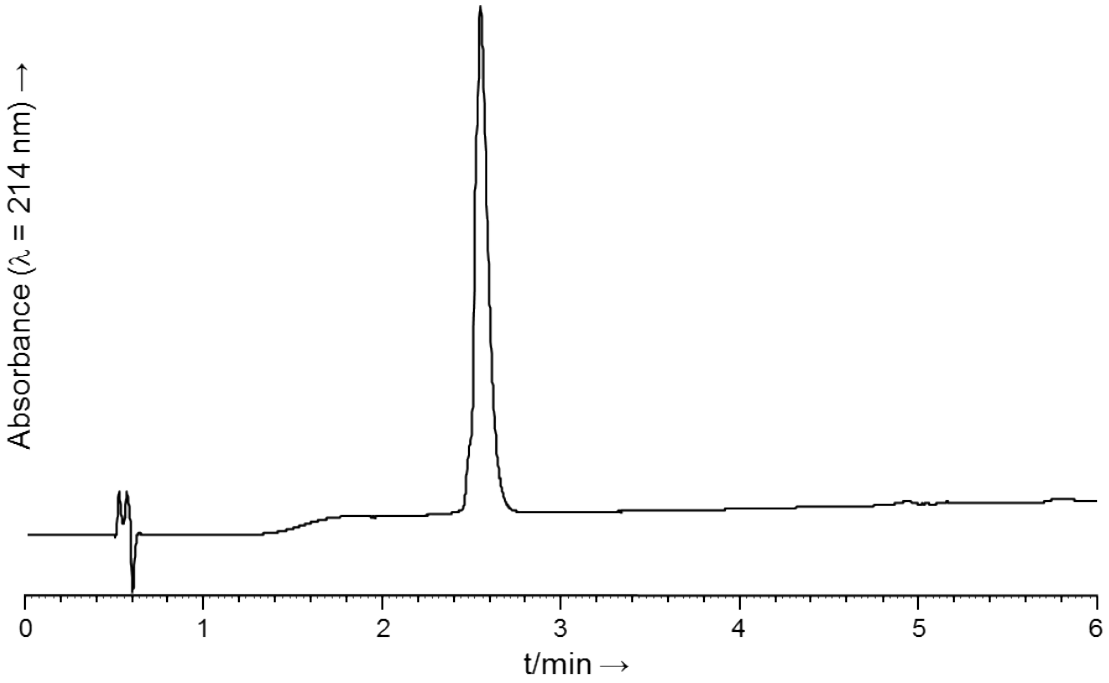


LC/MS analysis: total ion chromatogram of crude **8c**

[2] Dowlut, M. *et al*. *J. Org. Chem.*, **2005**, *70*, 9809-9813; Knapp, S.; Myers, D. S. *J. Org. Chem.* **2002,** *67,* 2995-2999.

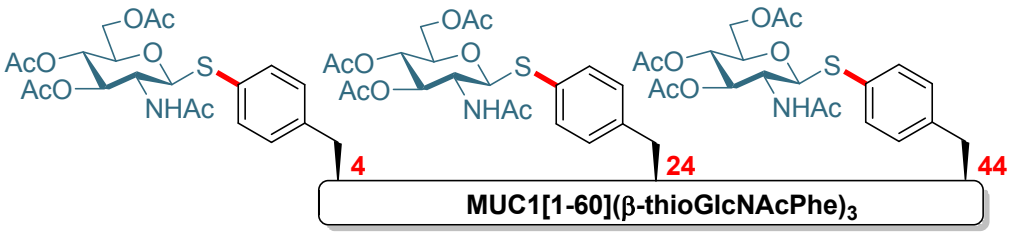
Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (6.05)	-	830.14	Not attributed
2 (6.29)	5904.42	5904.54	**8c**
3 (6.92)	-	2898.53	Not attributed
4 (7.85)	-	170.2	Not attributed
5 (9.09)	-	6351.64	Not attributed

Attribution of the main peaks observed during LC/MS analysis of crude **8c**



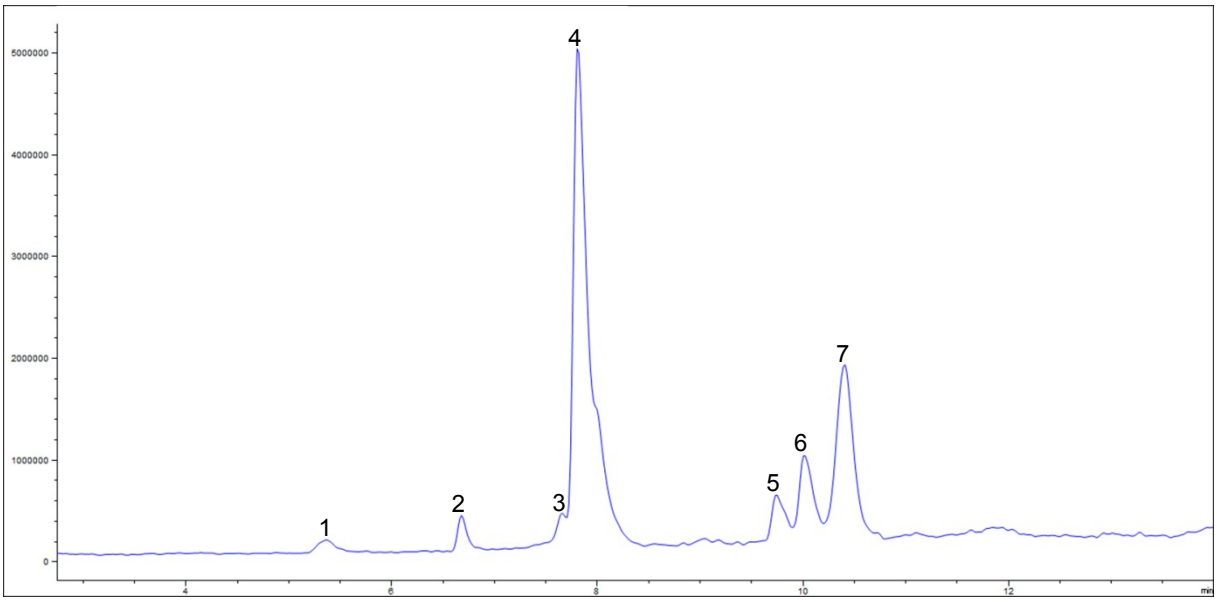
HPLC trace of purified **8c**

Tri-thioglycosylated MUC1-derived peptide (**8d**)



Compound **8d** was prepared by using the general procedure **B** of coupling (reaction time: 1.0 h), with HPLC-purified lyophilized tri-iodopeptide **7b** (50 µL, 0.5 µmol, 1 equiv.), *β*-thioglucosamine **1c** (50 µL, 4.5 µmol, 9 equiv.), XantPhos PdG_3 precatalyst (25 µL, 7.5 µmol, 15 equiv.) and Et_3N (25 µL, 12.5 µmol, 25 equiv.) in a mixture of THF/H_2O (1:2, 500 µL, 1.0 mM) which afforded the tri-thioglycosylated MUC1-derived peptide **8d**.

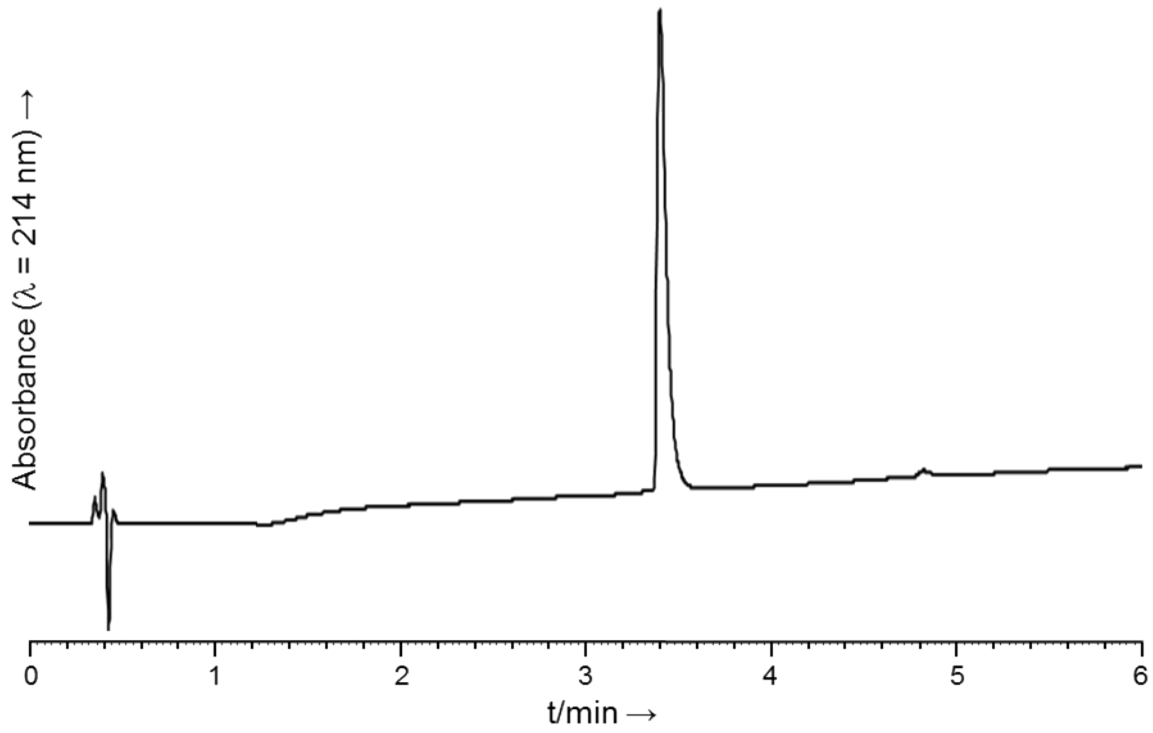
ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{297}H_{441}N_{79}O_{102}S_3$: 6842.0912, found: 6842.1112
HPLC analysis: t_R = 3.44 min (Chromolith, gradient: 05-50% B/A over 5 min)
HPLC purification: Nucleosil C18, gradient: 23-26% B/A over 15 min
Yield: 58%



LC/MS analysis: total ion chromatogram of crude **8d**

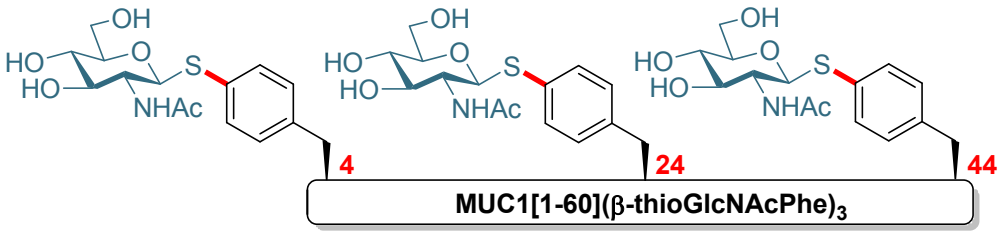
Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (5.36)	101.19	102.2	Et_3N
2 (6.68)	-	800.19	Not attributed
3 (7.66)	-	6803.42	Not attributed
4 (7.81)	6846.43	6845.47	**8d**
5 (9.74)	-	7167.04	Not attributed
6 (10.02)	-	7166.81	Not attributed
7 (10.41)	-	530.13	Not attributed

Attribution of the main peaks observed during LC/MS analysis of crude **8d**



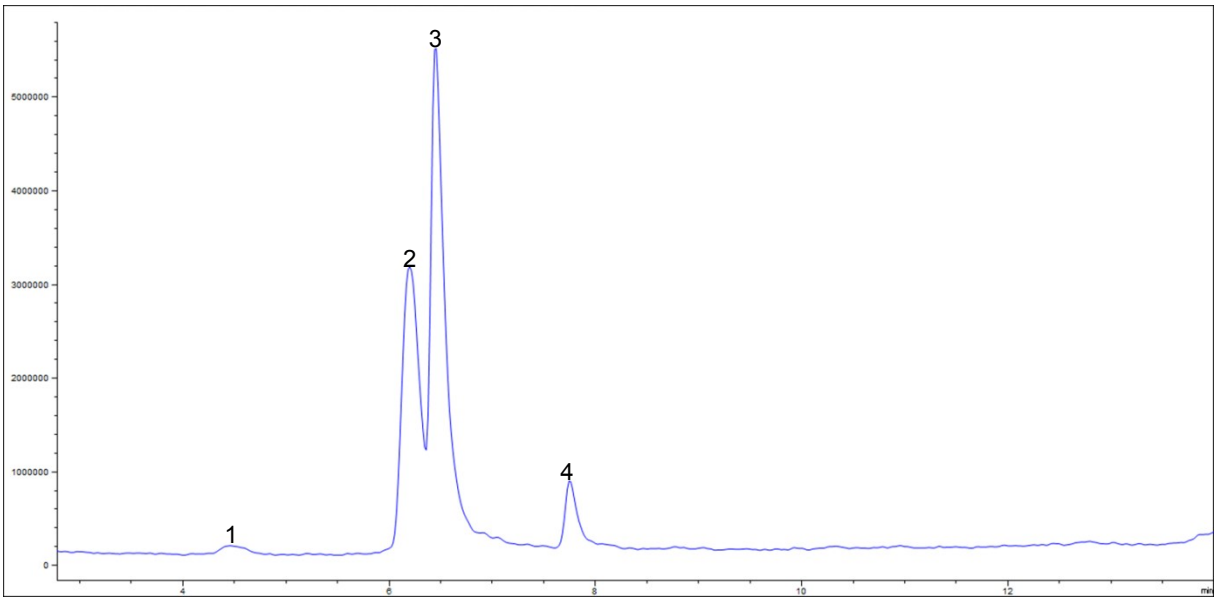
HPLC trace of purified **8d**

Tri-thioglycosylated MUC1-derived peptide (**8e**)



Compound **8e** was prepared by using the general procedure **B** of coupling (reaction time: 1.0 h), with HPLC-purified lyophilized tri-iodopeptide **7b** (50 µL, 0.5 µmol, 1 equiv.), unprotected *β*-thioglucosamine **1i** (50 µL, 4.5 µmol, 9 equiv.), XantPhos PdG_3 precatalyst (25 µL, 7.5 µmol, 15 equiv.) and Et_3N (25 µL, 12.5 µmol, 25 equiv.) in a mixture of THF/H_2O (1:2, 500 µL, 1.0 mM) which afforded the tri-thioglycosylated MUC1-derived peptide **8e**.

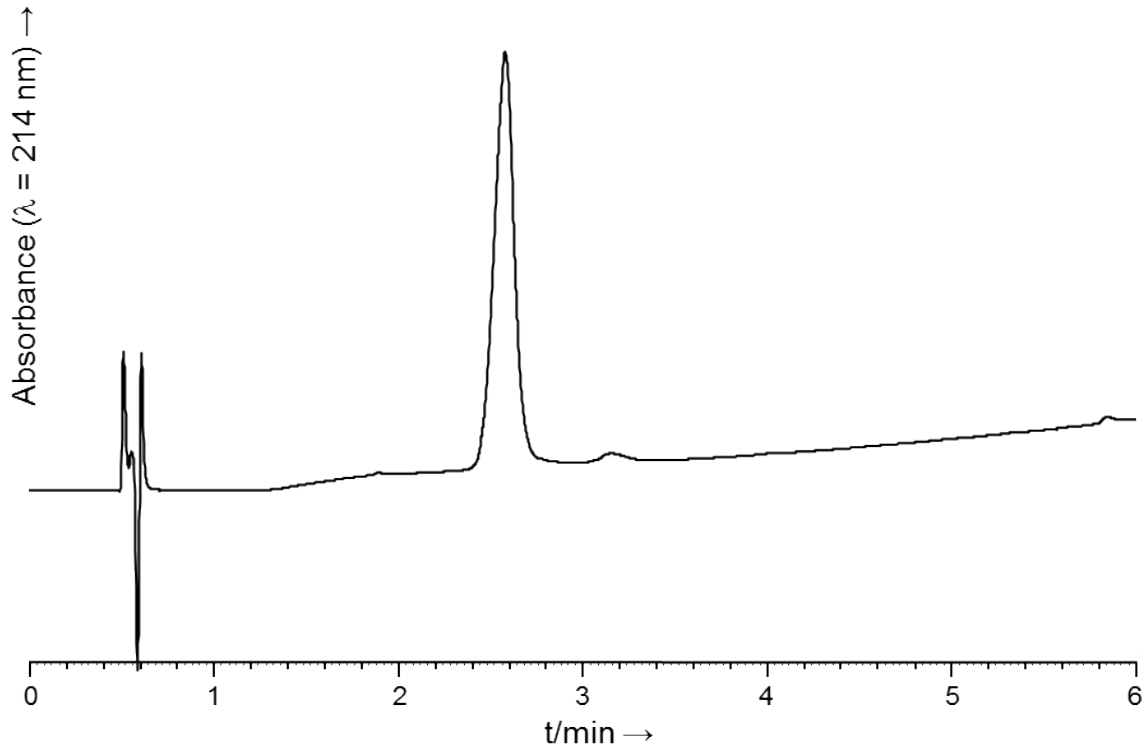
ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{279}H_{423}N_{79}O_{93}S_3$: 6463.9961, found: 6464.0105
HPLC analysis: t_R = 2.59 min (Chromolith, gradient: 10-50% B/A over 5 min)
HPLC purification: Nucleosil C18, gradient: 15-16% B/A over 16 min
Yield: 50%



LC/MS analysis: total ion chromatogram of crude **8e**

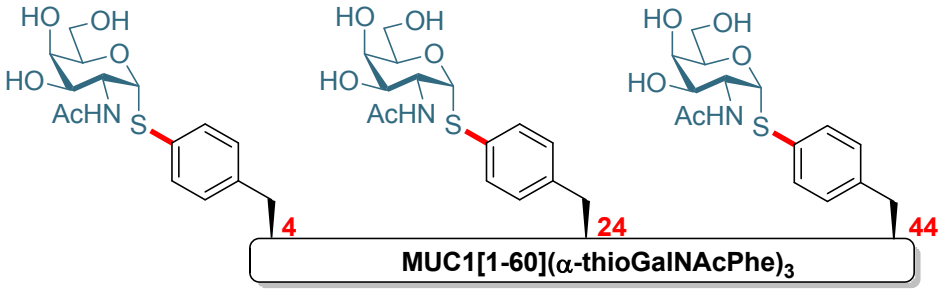
Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (4.46)	-	648.08	Not attributed
2 (6.19)	-	405.0	Not attributed
3 (6.44)	6468.10	6467.20	**8e**
4 (7.75)	-	170.0	Not attributed

Attribution of the main peaks observed during LC/MS analysis of crude **8e**



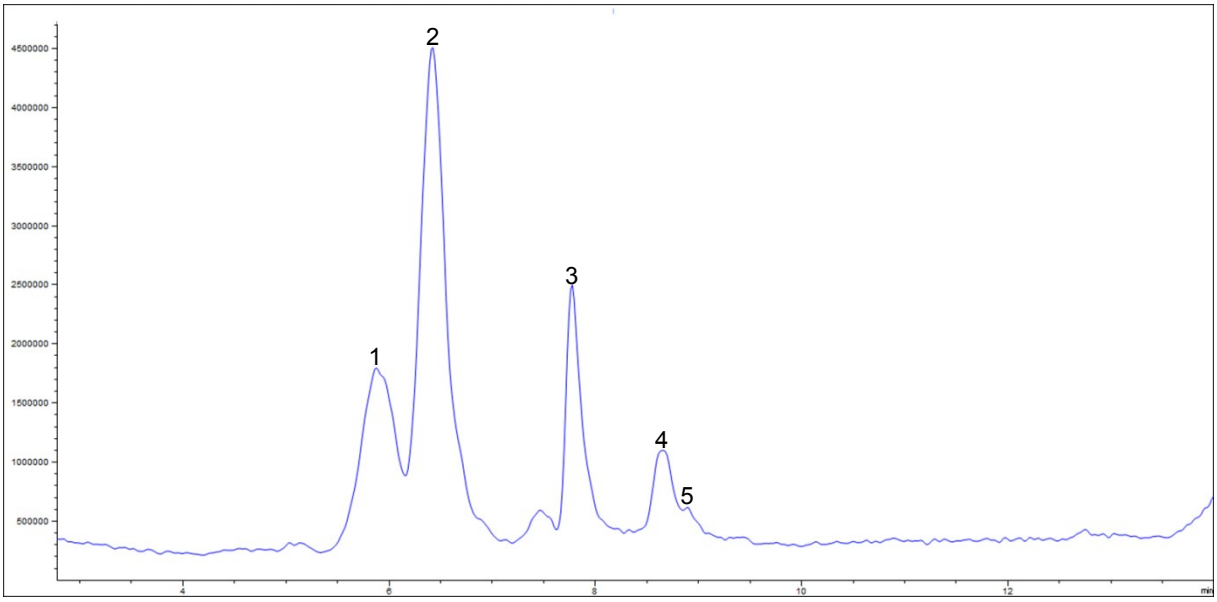
HPLC trace of purified **8e**

Tri-thioglycosylated MUC1-derived peptide (**8f**)



Compound **8f** was prepared by using the general procedure **B** of coupling (reaction time: 1.0 h), with HPLC-purified lyophilized tri-iodopeptide **7b** (50 µL, 0.5 µmol, 1 equiv.), unprotected α-thiogalactosamine **1j** (50 µL, 4.5 µmol, 9 equiv.), XantPhos PdG_3 precatalyst (25 µL, 7.5 µmol, 15 equiv.) and Et_3N (25 µL, 12.5 µmol, 25 equiv.) in a mixture of THF/H_2O (1:2, 500 µL, 1.0 mM) which afforded the tri-thioglycosylated MUC1-derived peptide **8f**.

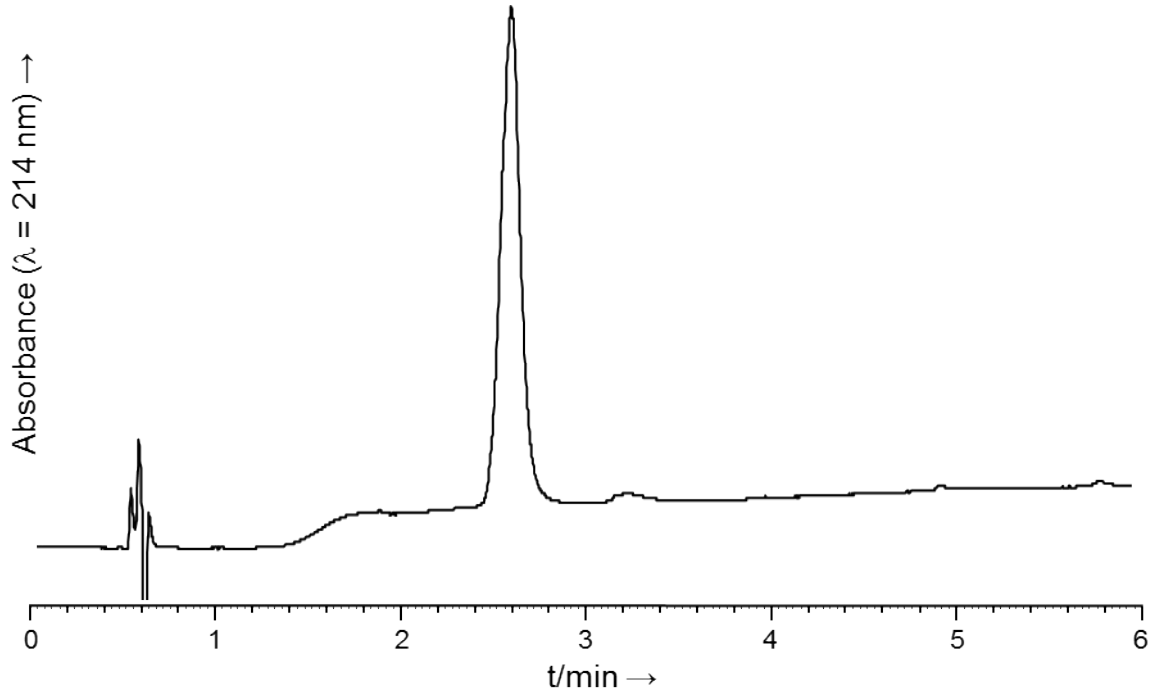
ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{279}H_{423}N_{79}O_{93}S_3$: 6463.9961, found: 6464.0102
HPLC analysis: t_R = 2.60 min (Chromolith, gradient: 10-50% B/A over 5 min)
HPLC purification: Nucleosil C18, gradient: 15-30% B/A over 20 min
Yield: 60%



LC/MS analysis: total ion chromatogram of crude **8f**

Peak number (t_R (min))	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
1 (5.84)	-	830.20	Not attributed
2 (6.41)	6468.10	6467.34	**8f**
3 (7.77)	-	170.0	Not attributed
4 (8.65)	-	6764.12	Not attributed
5 (8.89)	-	7001.46	Not attributed

Attribution of the main peaks observed during LC/MS analysis of crude **8f**



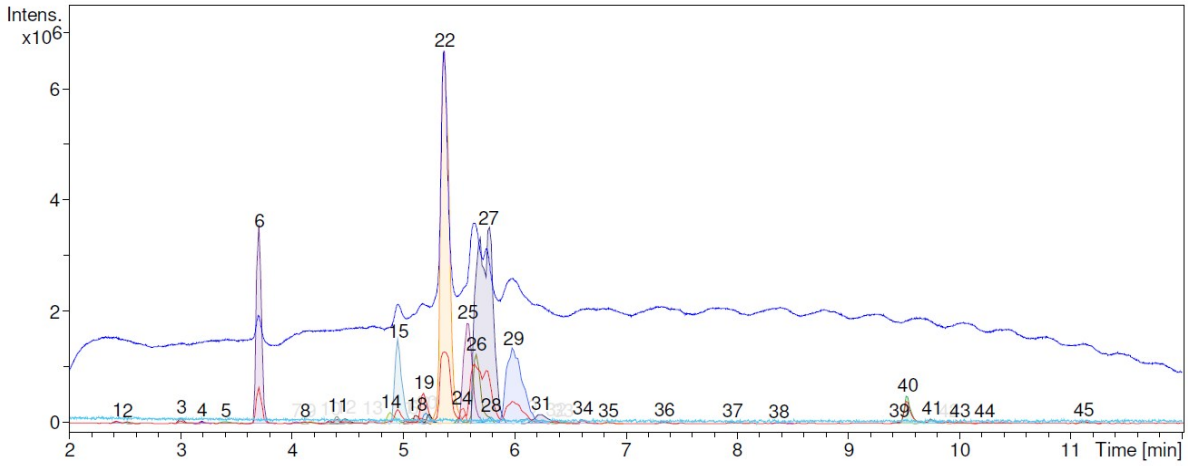
HPLC trace of purified **8f**

N-terminal biotinylation of peptide 7a, 7b, 8c and 8f

Optimization of the N-terminal biotinylation conditions

Initial attempts of N-terminal biotinylation were carried out on compound **7a** following a standard procedure: the peptide was first dissolved in 50 mM carbonate/bicarbonate buffer pH 9.6, then 20 equivalents of sulfo-NHS-biotin-solution in DMSO were added. The final peptide concentration was 0.45 mM in a DMSO/buffer ratio of 20/80.

Surprisingly, after 30 minutes of reaction, in addition to the biotinylated peptide, several by-products appeared. LC/HRMS analysis indicated that the observed mass of the corresponding peaks matched the one of peptide **7a** with multiple-biotinylation.



LC/HRMS analysis of the initial attempt of N-terminal biotinylation of **7a**
blue trace: UV (λ = 214 nm); red trace: base peak chromatogram

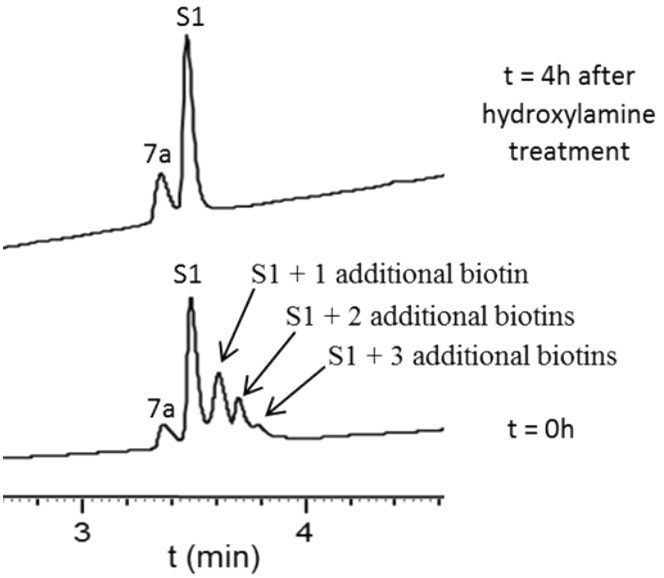
Peak number	$[MH]^+$ (*m/z*) calcd.	$[MH]^+$ (*m/z*) found	Attributed to
15	5792.6970	5792.7079	Unreacted **7a**
22	6019.7824	6019.7828	**S1**
25,26,27	6245.8614	6245.8618	**S1** + 1 additional biotin
29	6471.9404	6471.9363	**S1** + 2 additional biotins
31	6698.0194	6698.0151	**S1** + 3 additional biotins

Attribution of the main peaks observed during the LC/HRMS analysis.

We hypothesized that this over-biotinylation is due to an acylation of some amino acid side chains. Indeed, previous studies have shown that side chain hydroxyl groups on certain Ser, Tyr and Thr residues can readily react with NHS-esters if the hydroxyl amino acid is nearby a His residu.[3]

[3] See for example : (a) B. T. Miller, T. J. Collinst, G. T. Nagle, A. Kurosky, *J. Biol. Chem.*, **1992**, *267*, 5060-5069; (b) B. T. Miller, A. Kurosky, *Biochem. Bioph. Res. Commun.*, **1993**, *196*, 461-467; (c) B. T. Miller, M. E. Rogers, J. S. Smith, A. Kurosky, *Anal. Biochem.*, **1994**, *219*, 240-248; (d) S. Mädler, S. Gschwind, R. Zenobi, *Anal. Biochem.*, **2010**, *398*, 123-125.

It has been shown that hydroxylamine can selectively cleave such esters while leaving intact the *N*-acylation products.[3] Treatment of our biotinylation mixture with 1 M aqueous hydroxylamine in borate buffer pH 8.2 for 4 h at room temperature resulted in the complete disappearance of over-biotinylated compounds, supporting this *O*-acylation hypothesis.



HPLC trace of over-biotinylated peptide and treatment with hydroxylamine

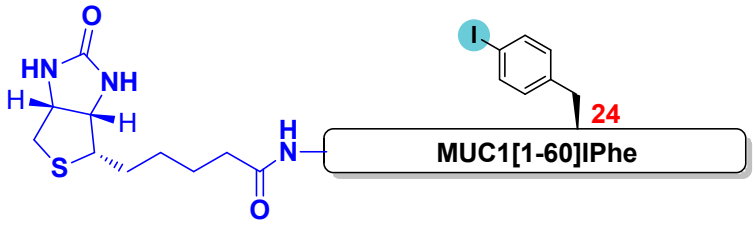
It has been shown that the addition of an organic co-solvent (DMF) can inhibit this sequence-specific *O*-acylation.[4] Gratifyingly, simple increase of the DMSO/water ratio from 20/80 to 80/20 completely suppresses over-biotinylation, and we kept these conditions for the biotinylation of **7b**, **8c** and **8f**.

[4] B. T. Miller, T. J. Collins, M. E. Rogers, A. Kurosky, *Peptides*, **1997**, *18*, 1585-1595.

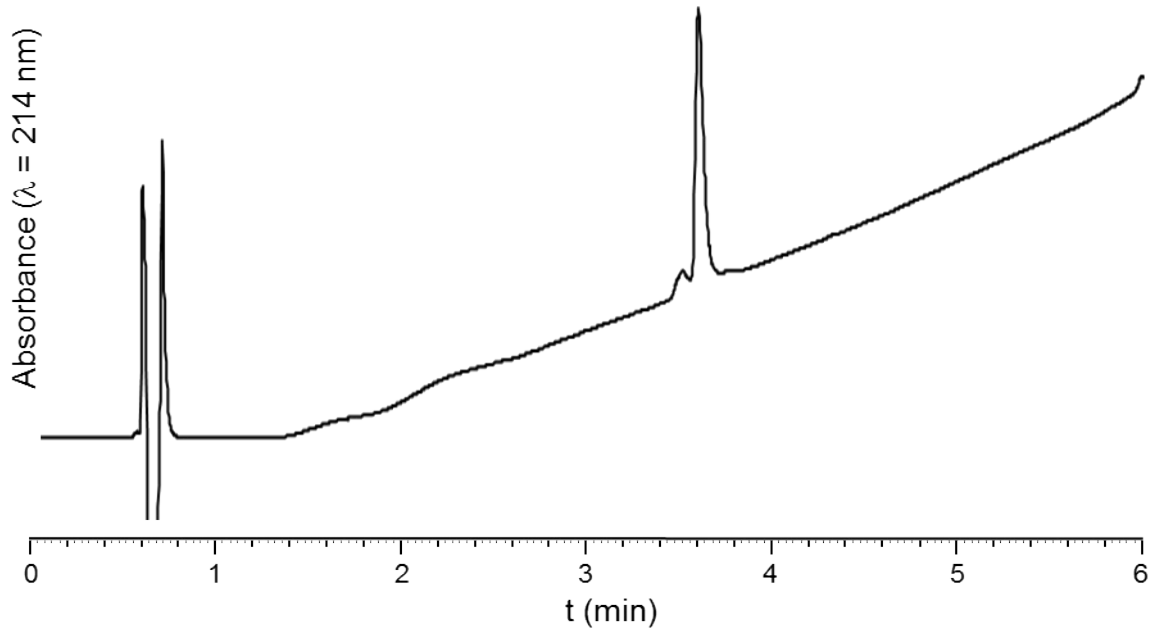
General procedure for the N-terminal biotinylation

To a solution of HPLC-purified lyophilized thioglycosylated MUC1-derived peptide (60 µL, 0.15 µmol, 1 equiv., final concentration 0.45 mM) in a mixture of 50 mM carbonate-bicarbonate buffer pH 9.6/DMSO 2:8), was added sulfo-NHS biotin (280µL, 3 µmol, 20 equiv.). The coupling mixture was stirred at room temperature for 30 minutes then quenched by the addition of 0.1% of aqueous TFA (500 µL) and lyophilized. Biotinylated peptides were purified by gel filtration on a column (5 cm x 0.75 cm) of superfine Bio-Gel P2 (Bio-Rad) run at 2 mL/h in 9:1 water/EtOH. Yield of biotinylated peptides were evaluated by integration at λ = 214 nm of the HPLC peak corresponding to the biotinylated peptide, compared with the area of the starting material at t = 0, without taking into account differences in molar absorption coefficients.

Biotinylated mono-iodo MUC1-derived peptide (**S1**)

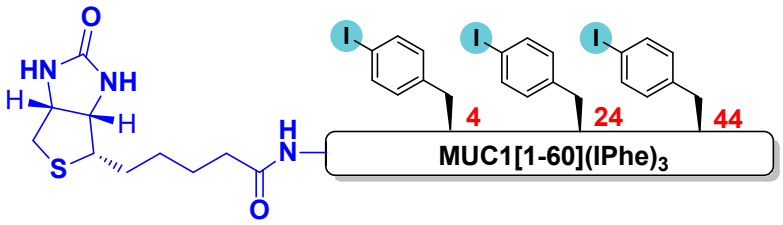


ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{255}H_{394}N_{78}O_{82}IS$: 6019.7824, found: 6019.7782
HPLC analysis: t_R = 3.58 min (Chromolith, gradient: 20-70% B/A over 5 min)
Yield: 90%

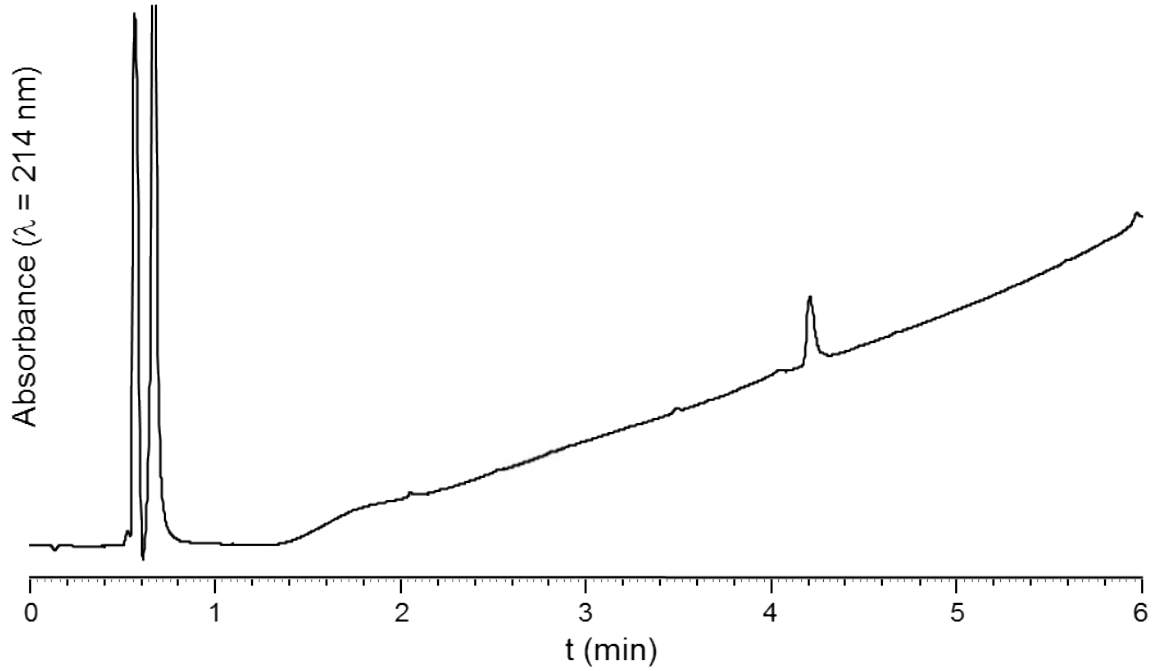


HPLC trace of purified **S1**

Biotinylated tri-iodo MUC1-derived peptide (**S2**)

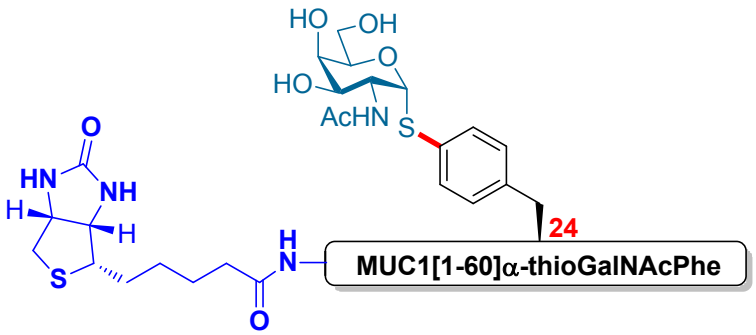


ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{265}H_{396}N_{78}O_{80}I_3S$: 6363.6272, found: 6363.6098
HPLC analysis: t_R = 4.18 min (Chromolith, gradient: 20-70% B/A over 5 min)
Yield: 60%

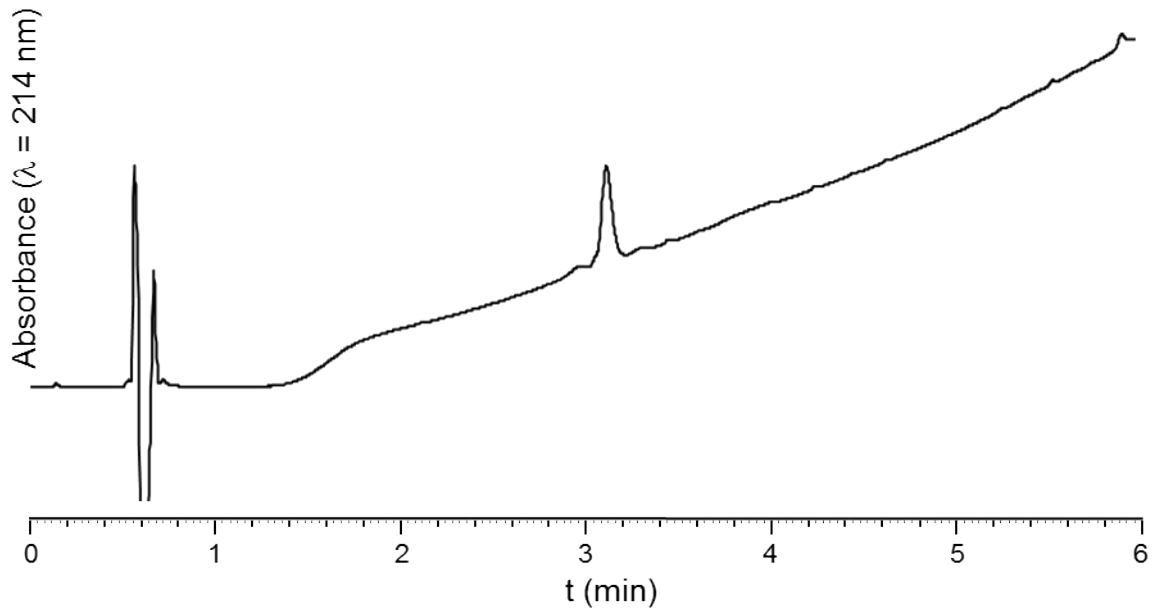


HPLC trace of purified **S2**

Biotinylated Mono-thioglycosylated MUC1-derived peptide (**S3**)

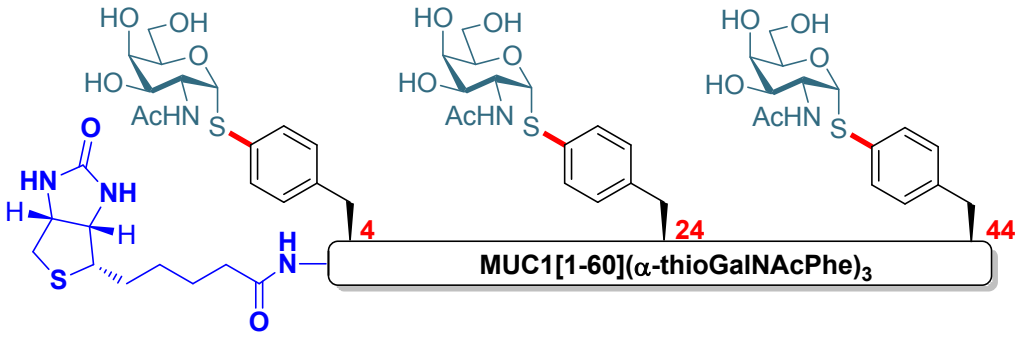


ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{253}H_{393}N_{77}O_{85}S$: 6128.9372, found: 6128.9359
HPLC analysis: t_R = 2.58 min (Chromolith, gradient: 10-50% B/A over 5 min)
Yield: 85%

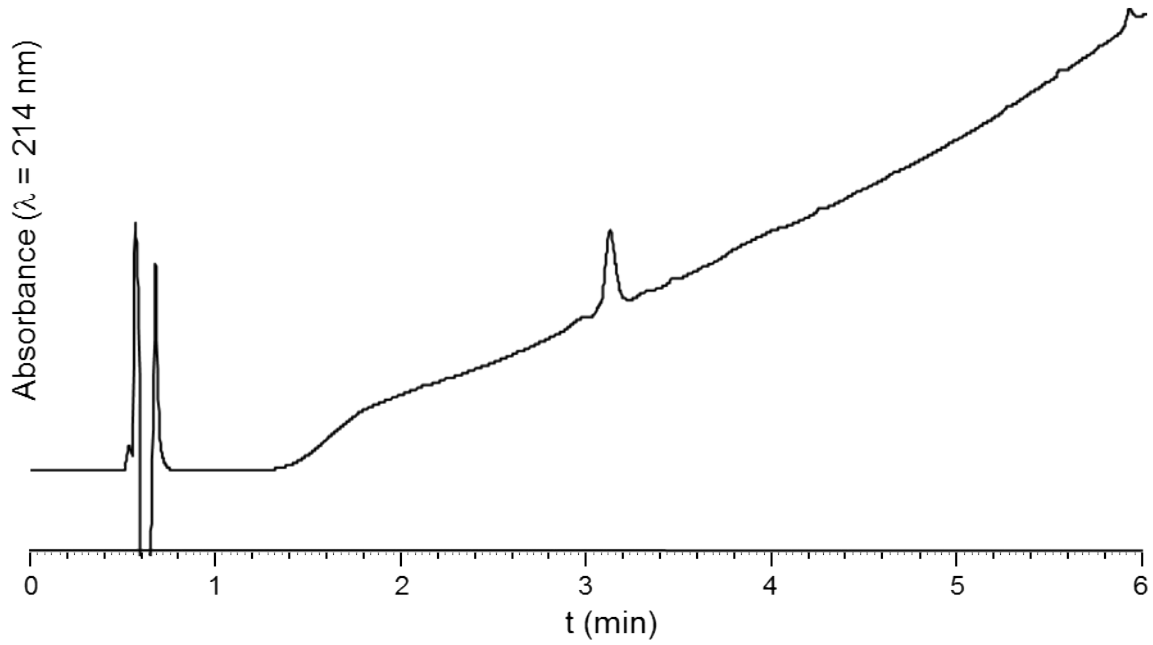


HPLC trace of purified **S3**

Biotinylated tri-thioglycosylated MUC1-derived peptide (**S4**)



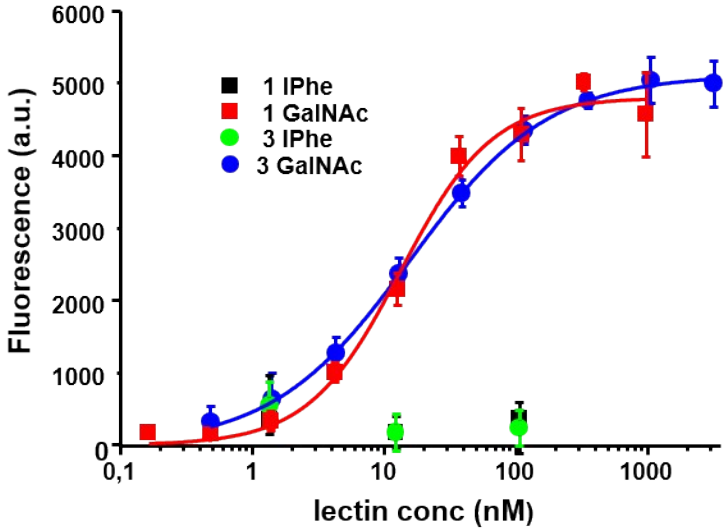
ESI-HRMS (*m/z*): $[MH]^+$ calcd. for $C_{289}H_{438}N_{81}O_{95}S_4$: 6691.0894, found: 6691.0803
HPLC analysis: t_R = 3.11 min (Chromolith, gradient: 20-70% B/A over 5 min)
Gel filtration: Bio-Gel P2, 2 mL/h in 9:1 water/EtOH
Yield: 50%



HPLC trace of purified **S4**

Binding of lectins and antibodies with compound S1-S4

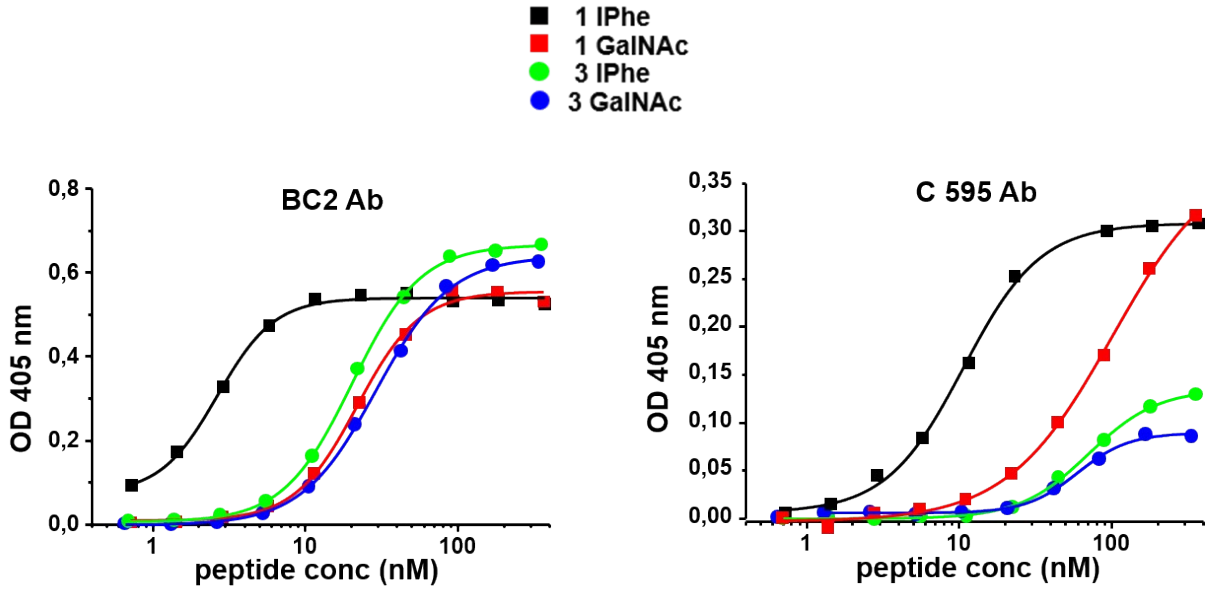
Peptides **S1-S4** were dissolved in water at 1 mg/mL. Aliquots of this solution (from 0.15 to 500 ng in 100 µL) were captured for 2 h at room temperature on 96-well Neutravidin-coated plates (Pierce) according to manufactor's instruction.
For the lectin recognition experiments, 75 or 100 or 200 ng/100 µL of peptides **S1-S4** (10 to 29 pmoles/well) were first incubated on Neutravidin-coated plates as described above. After 3 washings, FITC–labelled Vicia villosa lectin (VVL) from Vector Labs was added at concentrations ranging from 2.3 ng to 450 µg/100 µL (160 pM to 3.17 µM) and let for 30 min at room temperature. After 3 washings the bound FITC was read in a Victor Plate-Reader (exc. 485 nm, em. 535 nm). For the apparent Kd measurements, 3 concentrations of each glycopeptide were incubated in triplicate with a series of VVL concentrations. Fluorescence data for a given glycopeptide triplicate were averaged. The apparent Kd values were determined by plotting the bound fluorescence values against the lectin concentration and estimating the lectin concentration at half maximal bound fluorescence using the scientific graphing and analysis software ORIGIN 9. The SD values of the apparent Kds were obtained from the mean of 3 different concentrations for both immobilized glycopeptides.



ELISA-based assay showing FITC-labeled VVL binding of peptides **S1-S4**. The fluorescence values are the means of three independent experiments realized at the same peptide concentration and error bars indicate the standard deviation.

For antibodies recognition, after 3 washings, the bound peptides were incubated with mouse antibodies MUC1-specific (BC2 from Abcam 1/100 or C595 from Bio-Rad 1/200) for 30 min at room temperature and the unbound antibodies were removed by 3 washings. A goat anti-mouse linked to Horse Radish Peroxidase (HRP) from Pierce was used as secondary antibody, diluted 1/10,000 and let in the wells for 30 min at room temperature. After 3 washings, a HRP substrate (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt from Sigma-Aldrich) was added in each well (100 µL of at 365 µM solution in 100 mM acetate buffer pH 5.0 , 17.6 mM H_2O_2). After 20 min at room temperature the reaction was stopped

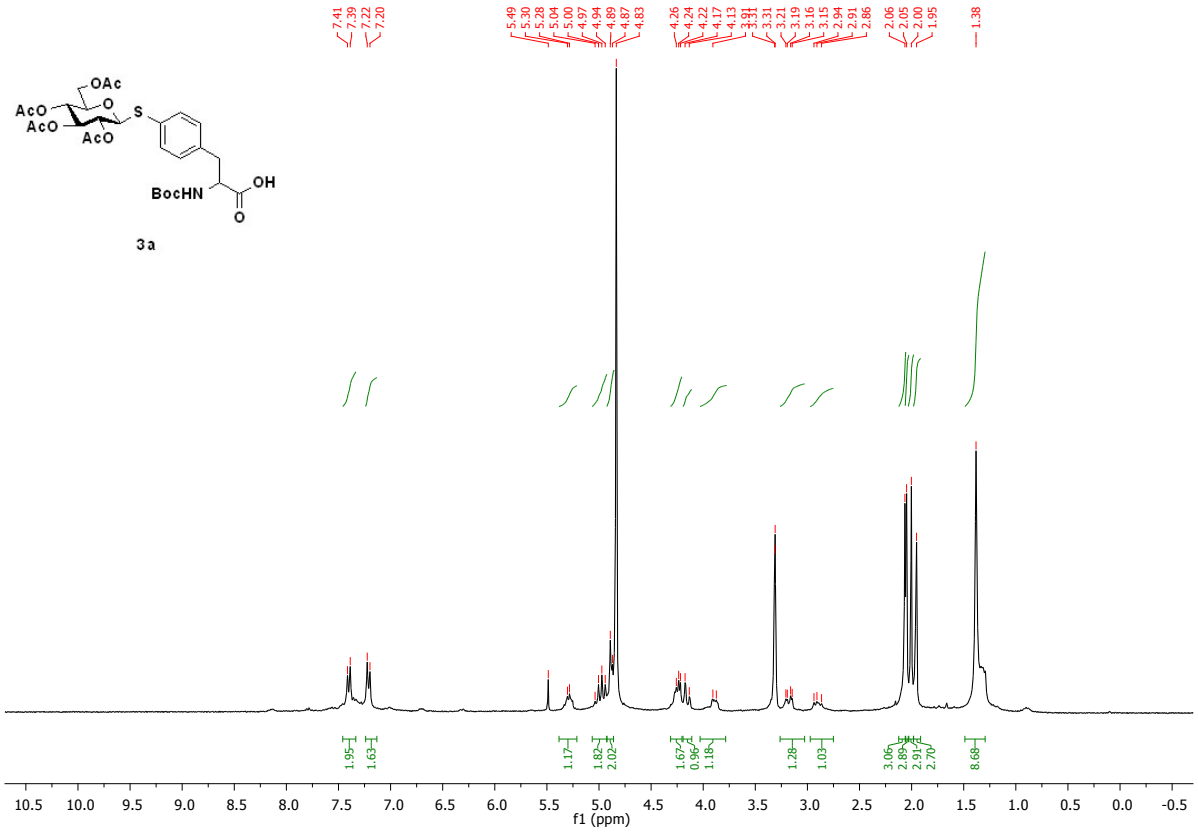
by addition of 50 µl of 2 % (w/vol) oxalic acid in water and the plate was scanned at 405 nm in a Victor microplate-reader (Perkin Elmer).



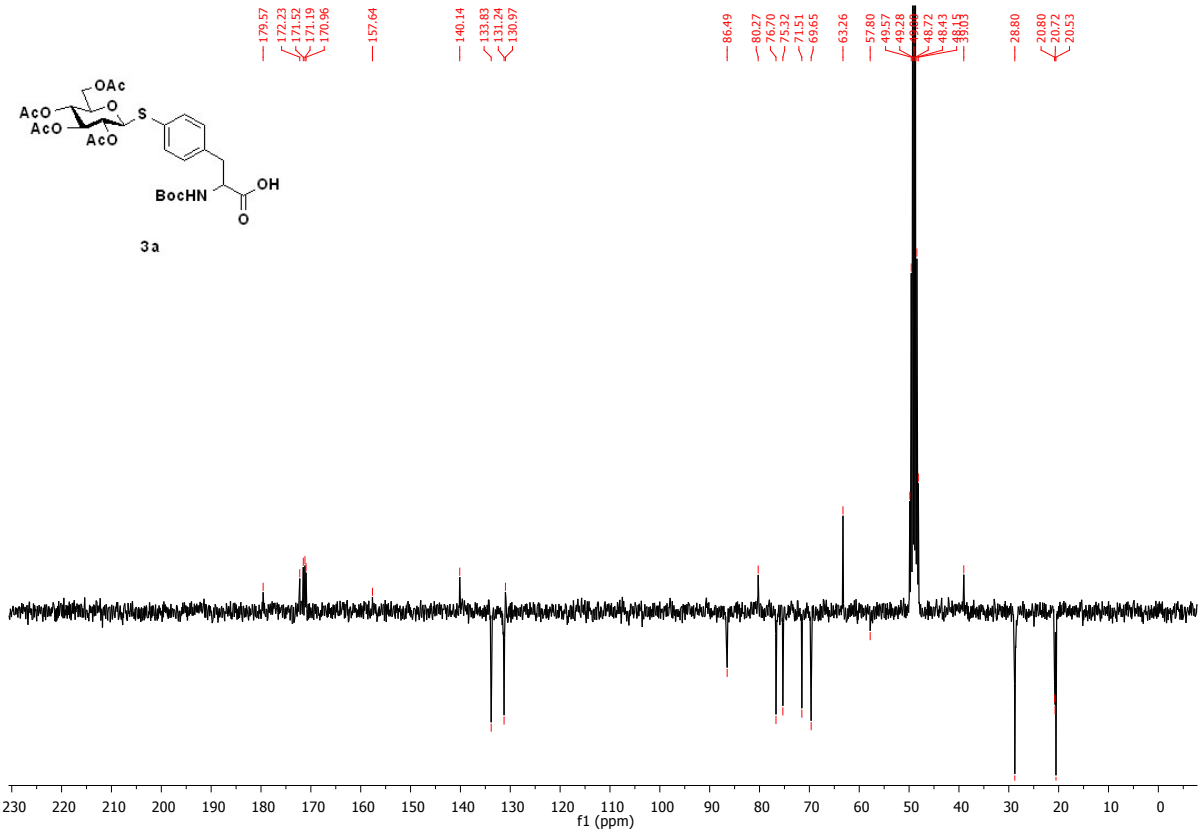
ELISA-Based assay showing recognition by the specific anti-MUC1 antibodies (a) BC2 and (b) C595 of peptides **S1**-**S4**. Peptide concentrations were varied from 0.5 to 250 ng/well while BC2 Ab and C595 Ab were diluted 1/100 and 1/200, respectively.

The results show (see figure above) that all peptides, glycosylated or not, were recognized by both antibodies (Abs) although to different extent. First of all and surprisingly, if the immobilized mono iodo MUC1-derived peptide was still efficiently bound by both Abs, this binding was significantly reduced (about 10 times) for the immobilized mono thioGalNAc peptide. This observation could suggest that the presence of a GalNAc residue on the Phe 24 of the 60-mer MUC1 sequence may provoke such a change in the total conformation of the immobilized peptide that access by the Abs to the unmasked and still available epitopes is clearly precluded. To further test this hypothesis is clearly beyond the scope of the present paper. However the ELISA tests presented here show that in the case of the BC2 Ab an increasing number of IPhe residues in the MUC1 sequence from 1 to 3 decreased the Ab binding while the addition of GalNAc on 1 or 3 Phe did not further diminished the Ab binding. Thus the BC2 Ab which was raised against the APDTR epitope can also recognize the APD-IPhe-R sequence, but even also whith a GalNAc *S*-linked to the Phe included in the epitope sequence. In the case of the C595 Ab an increasing density of IPhe on the MUC1 sequence also diminished the Ab recognition and the presence of 3 GalNAc residues further reduced the Ab binding, as compared to 1 GalNAc, showing a partial masking of the RPAP epitope by the GalNAc *S*-linked to the adjacent Phe residues. Altogether, our results show that the synthetic peptides **7a** and **7b** and glycopeptides **8c** and **8d** are effectively bound on the neutravidin-coated plates in a quantitative and saturable manner and are still able to interact with specific anti-MUC1 Abs.

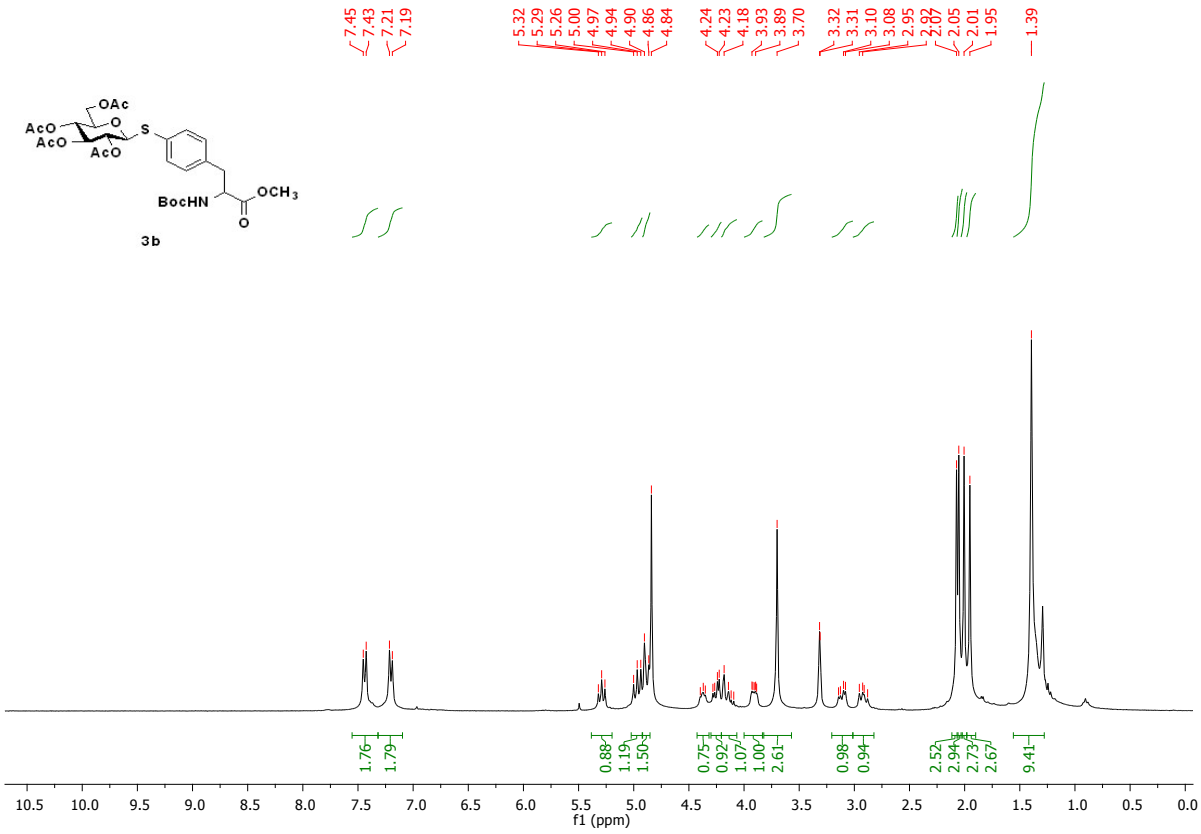
^{1}H and ^{13}C NMR spectra for the coupling products



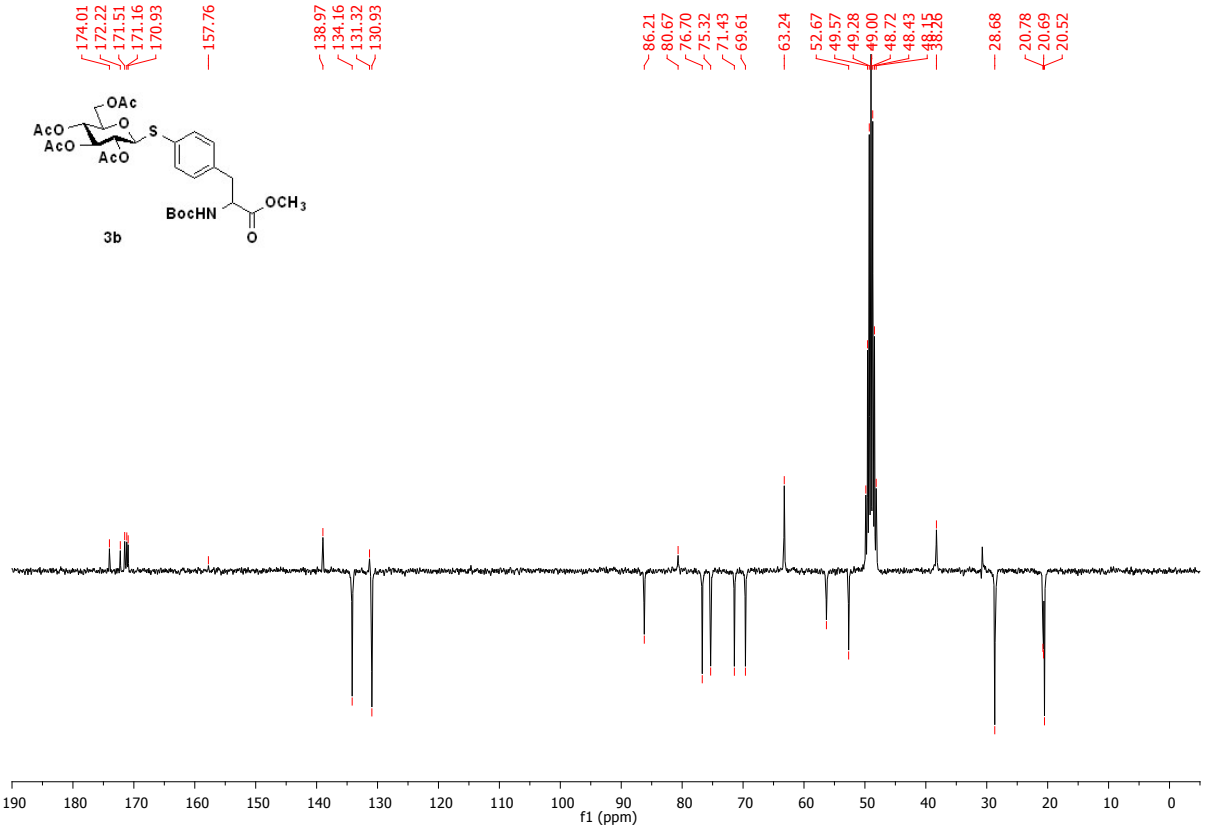
^{1}H NMR spectrum of **3a** (300 MHz, CD_3OD)



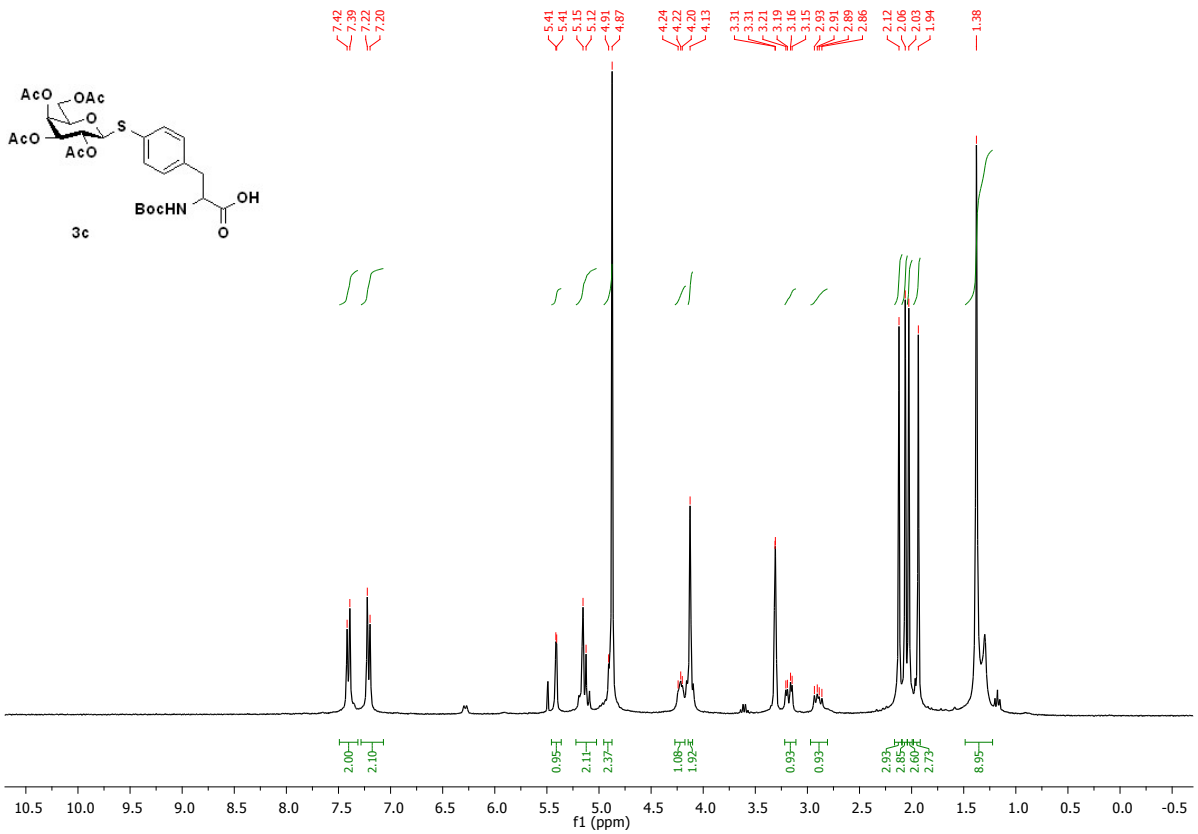
^{13}C NMR spectrum of **3a** (75 MHz, CD_3OD)



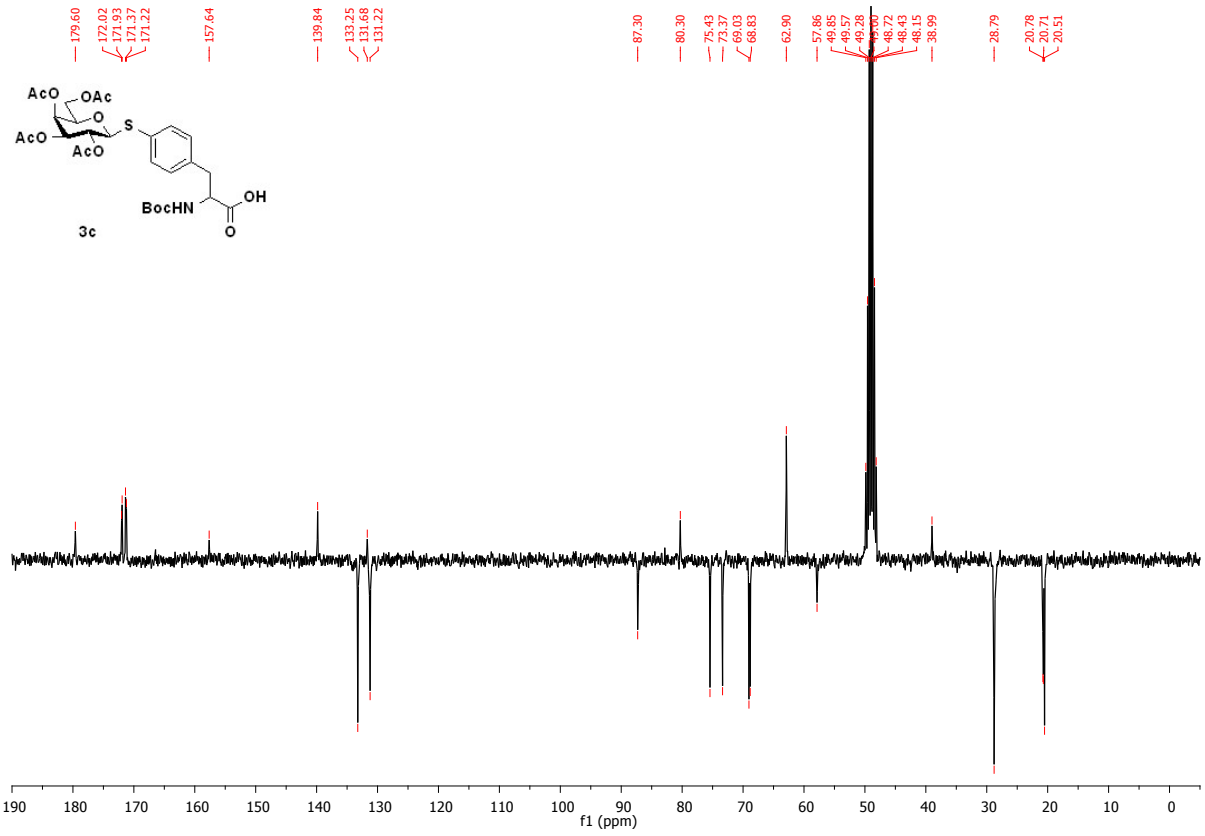
^{1}H NMR spectrum of **3b** (300 MHz, CD_3OD)



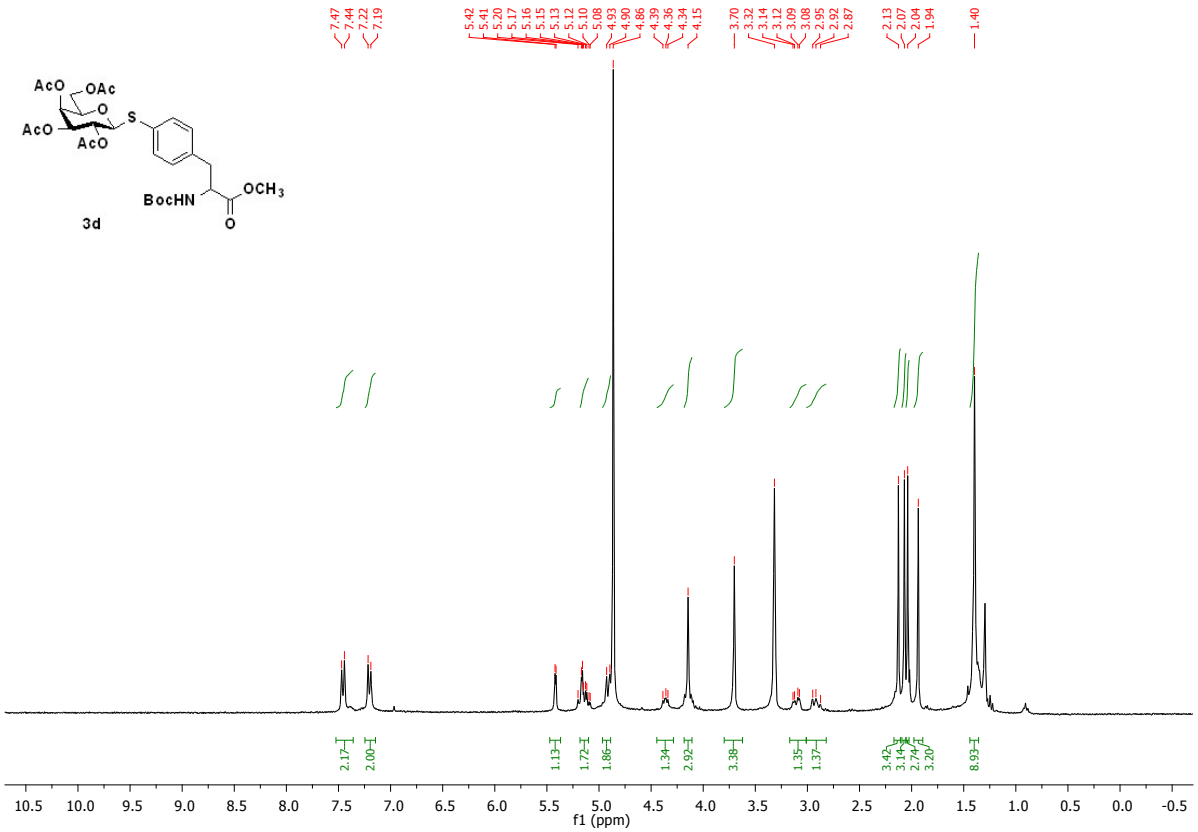
^{13}C NMR spectrum of **3b** (75 MHz, CD_3OD)



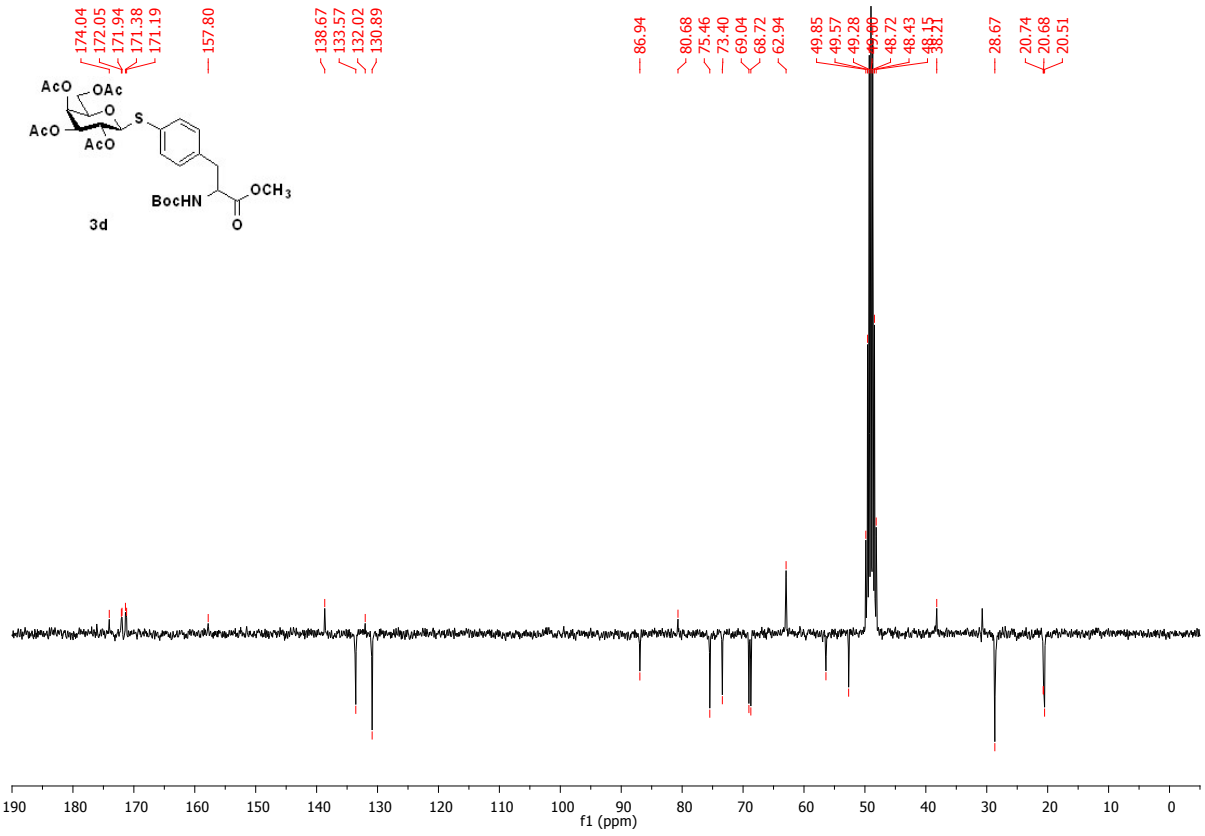
^{1}H NMR spectrum of **3c** (300 MHz, CD_3OD)



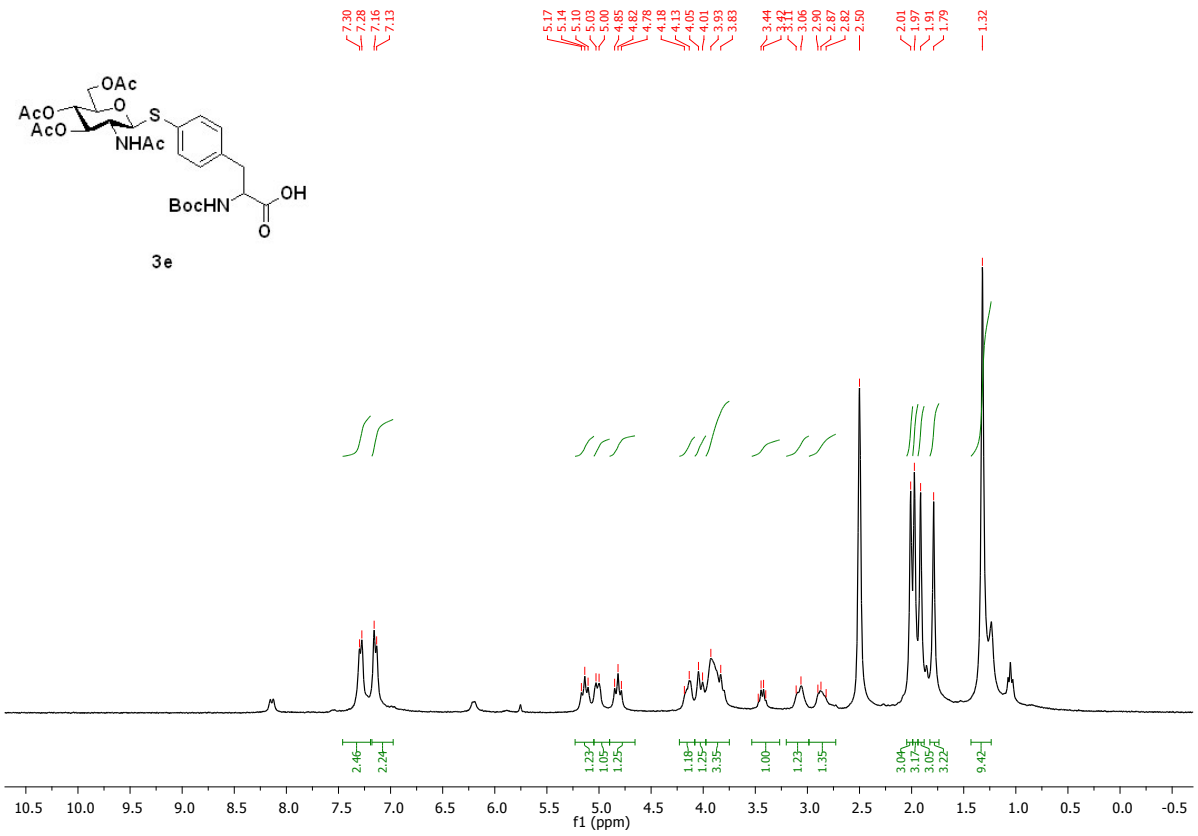
^{13}C NMR spectrum of **3c** (75 MHz, CD_3OD)



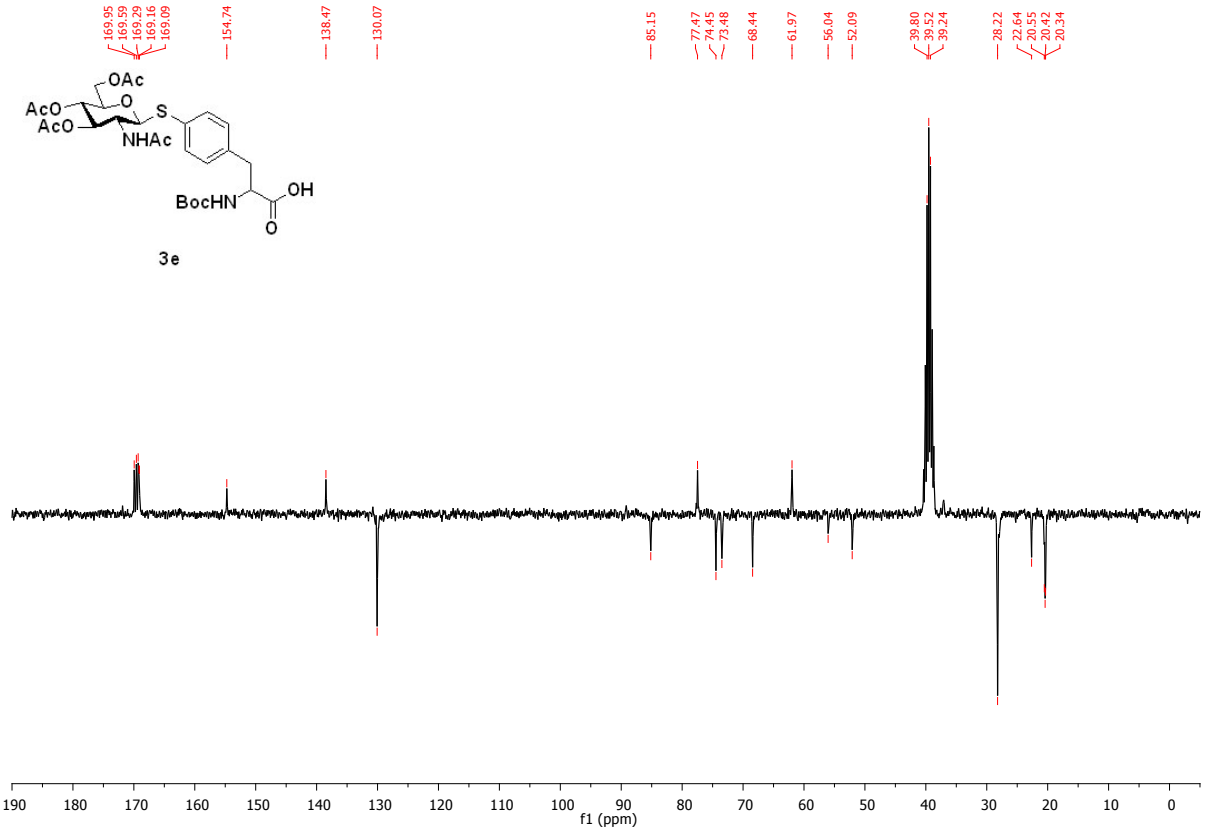
^{1}H NMR spectrum of **3d** (300 MHz, CD_3OD)



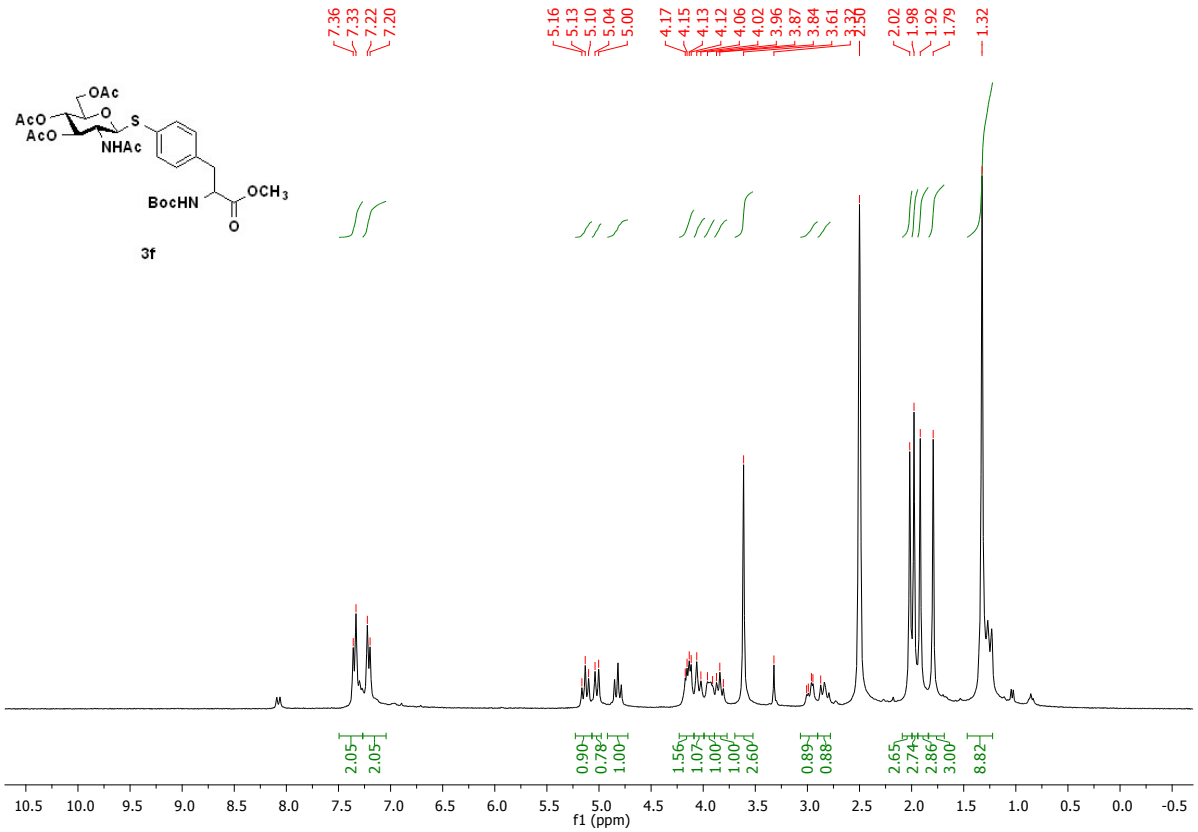
^{13}C NMR spectrum of **3d** (75 MHz, CD_3OD)



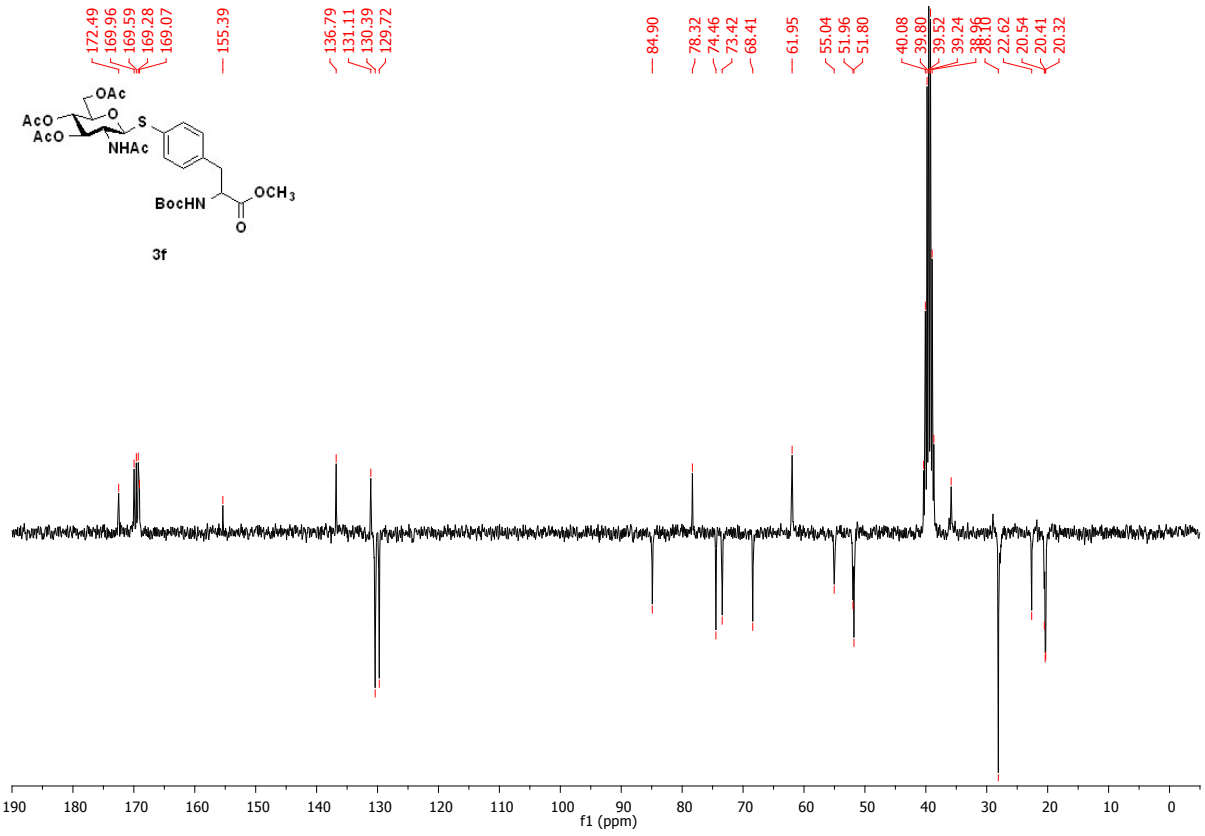
^{1}H NMR spectrum of **3e** (300 MHz, DMSOd_6)



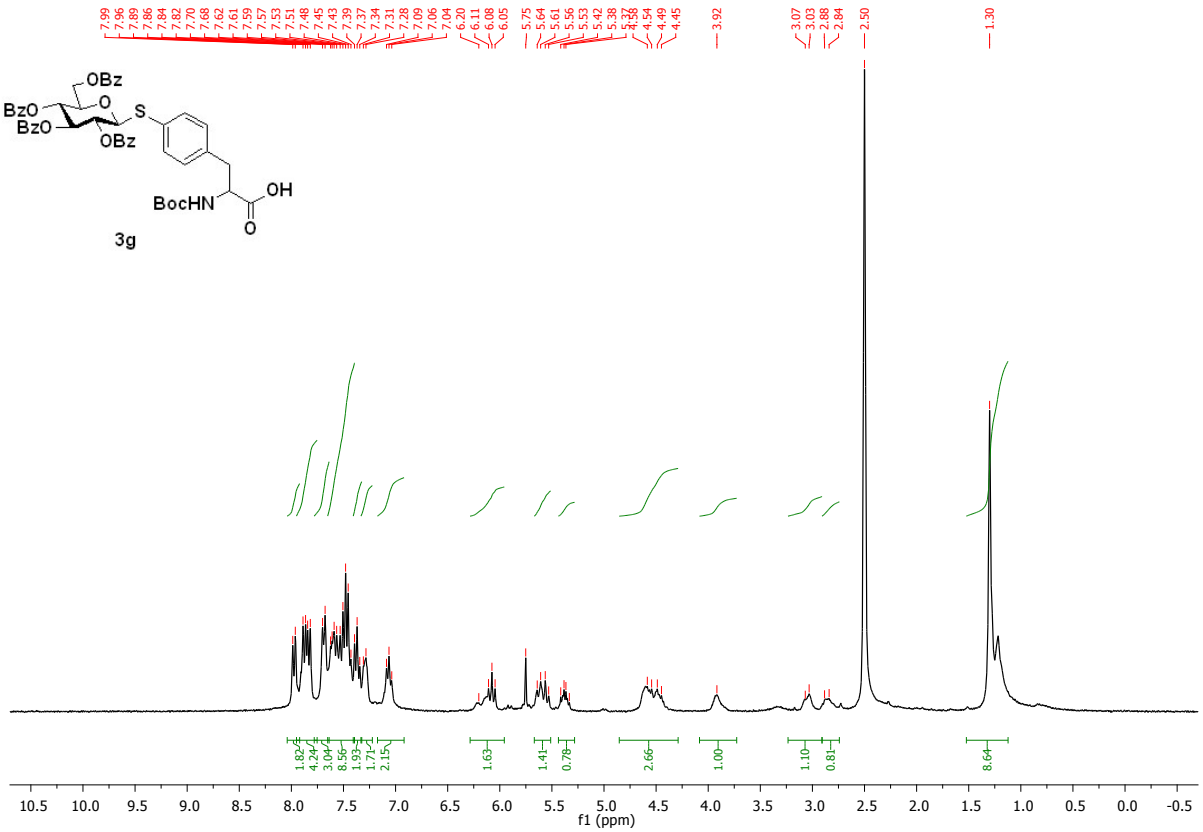
^{13}C NMR spectrum of **3e** (300 MHz, DMSOd_6)



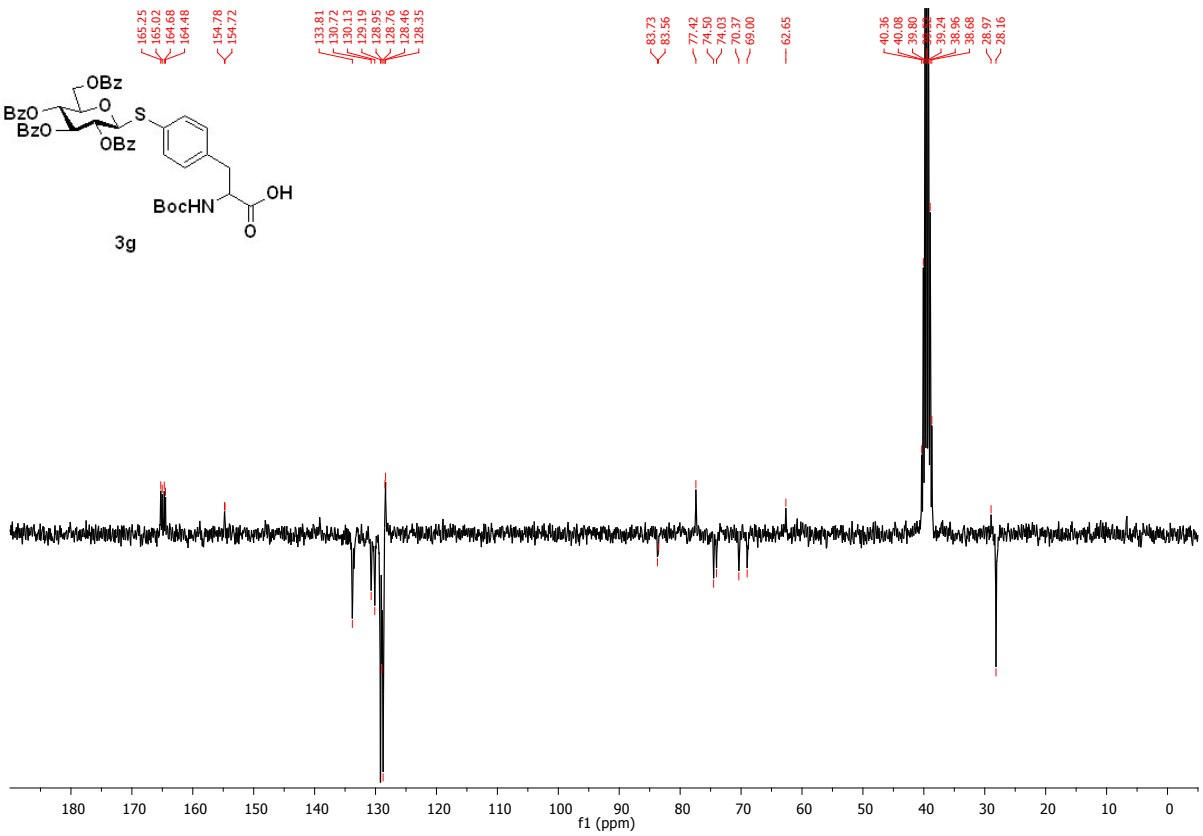
^{1}H NMR spectrum of **3f** (300 MHz, DMSOd_6)



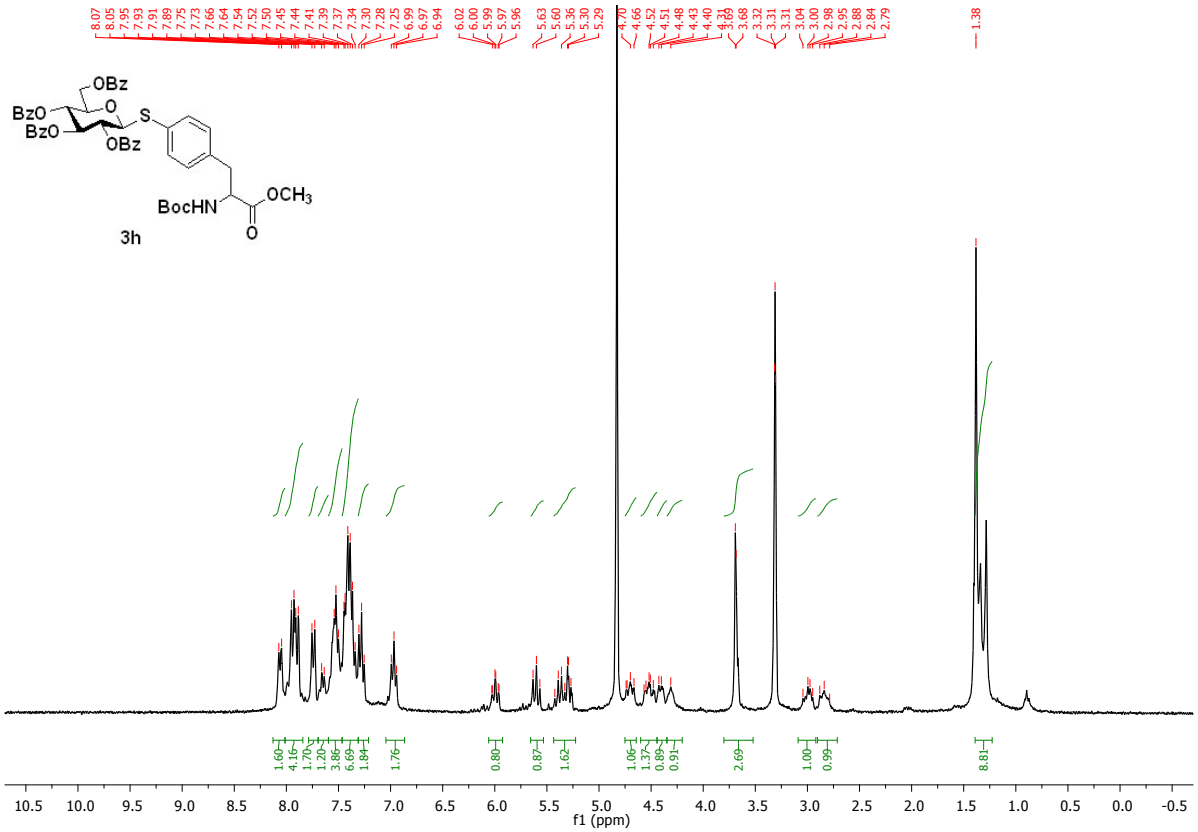
^{13}C NMR spectrum of **3f** (75 MHz, DMSOd_6)



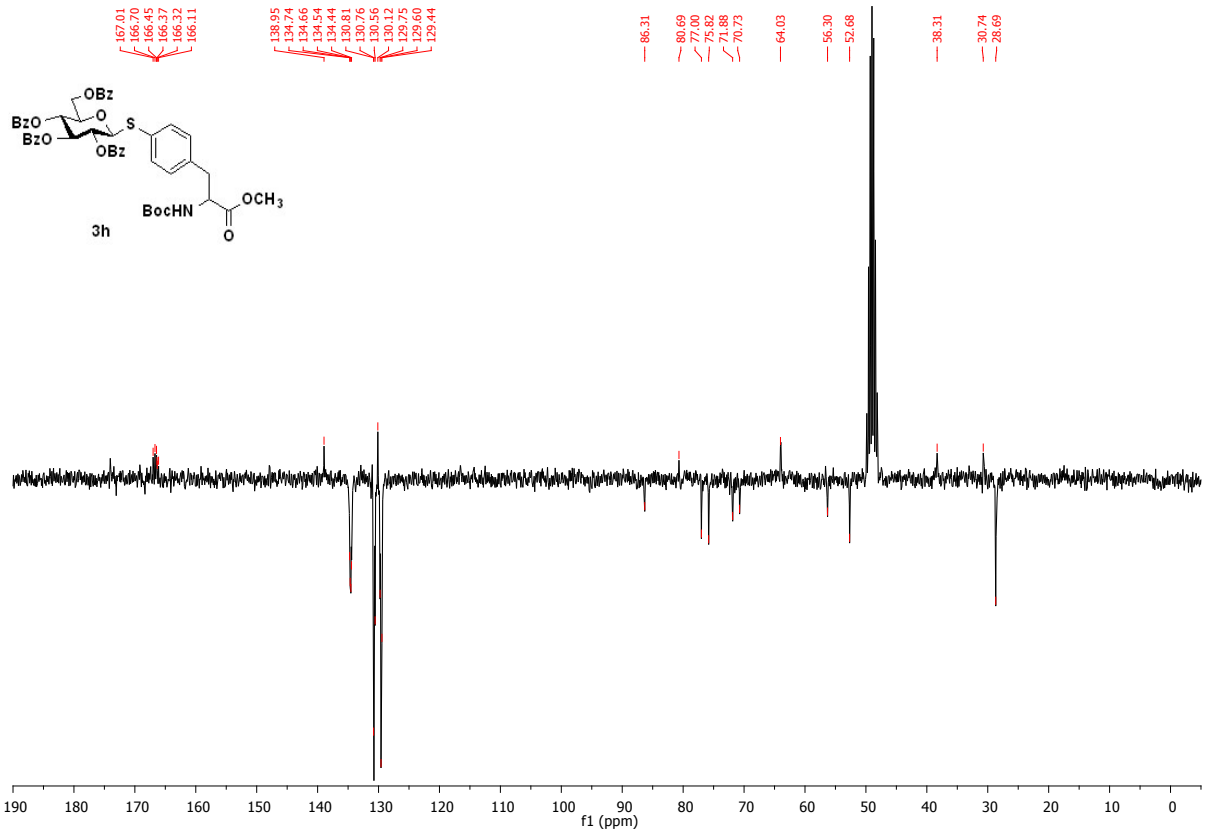
^{1}H NMR spectrum of **3g** (300 MHz, DMSOd_6)



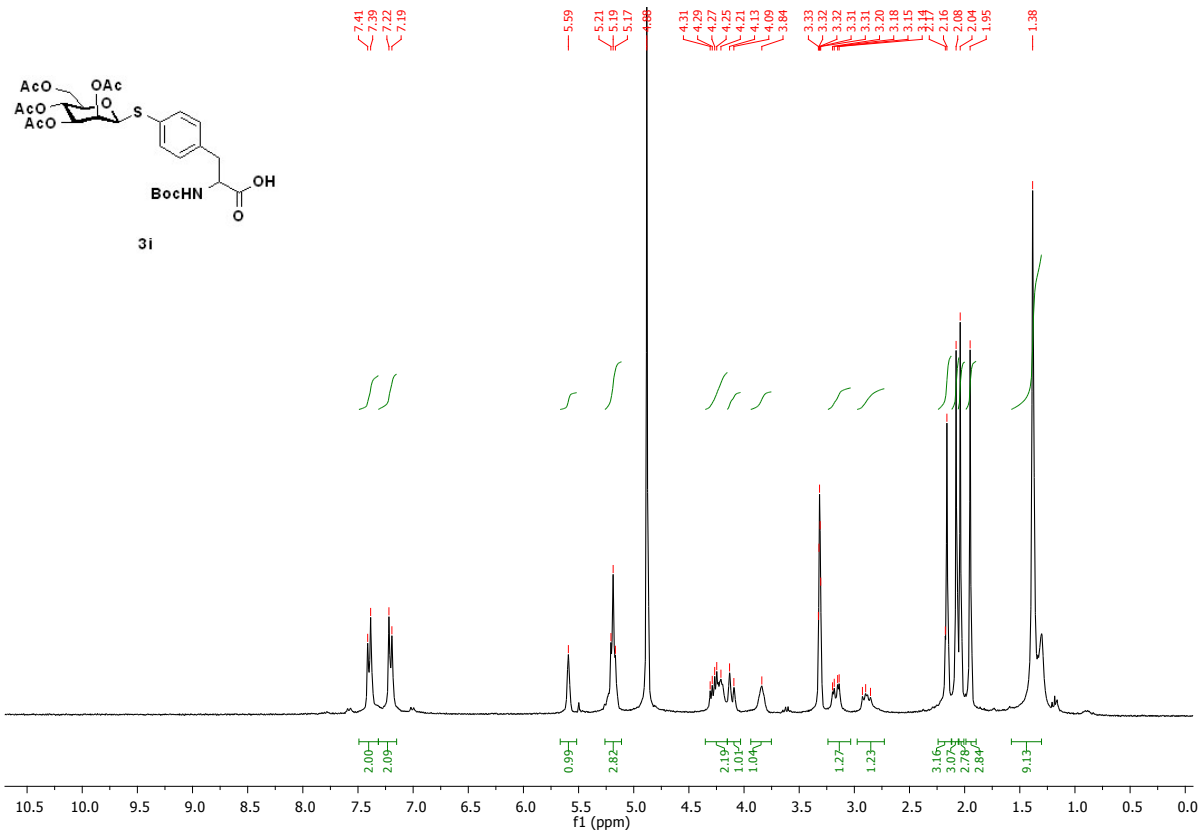
^{13}C NMR spectrum of **3g** (75 MHz, DMSOd_6)



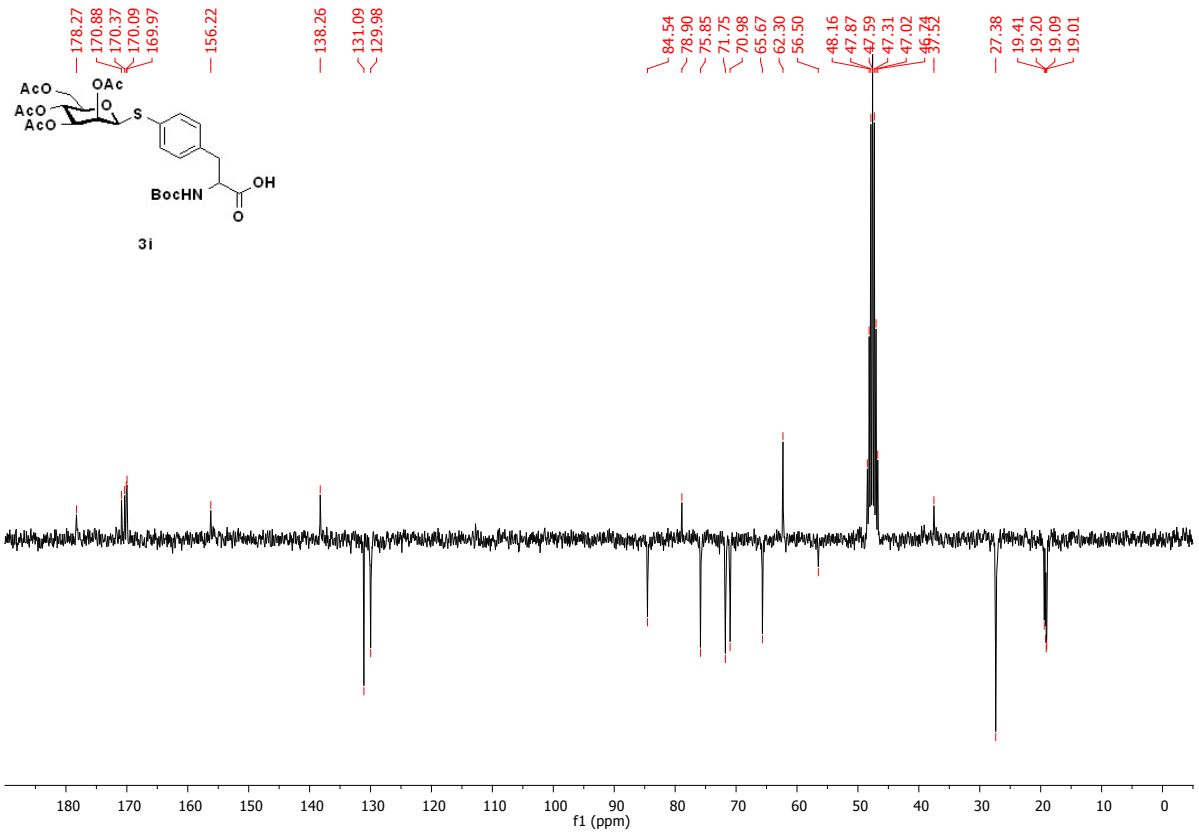
^{1}H NMR spectrum of **3h** (300 MHz, CD_3OD)



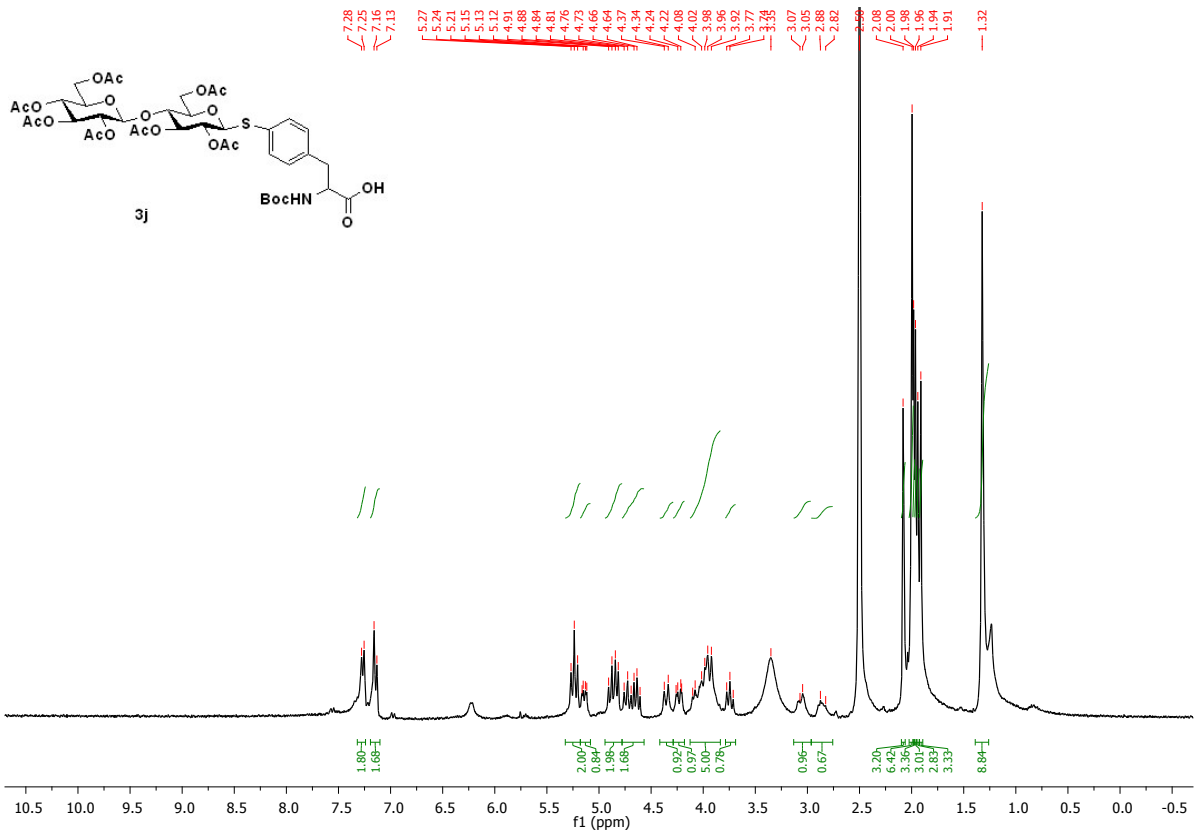
^{13}C NMR spectrum of **3h** (75 MHz, CD_3OD)



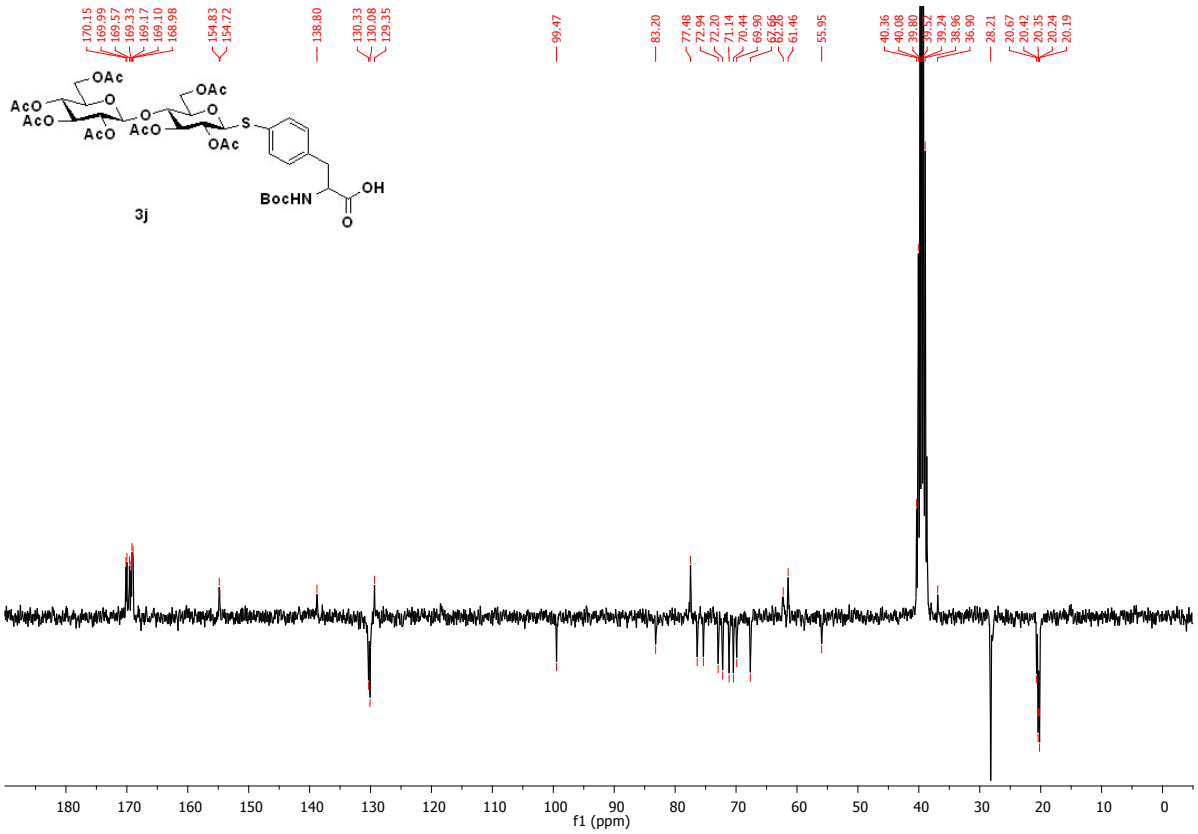
^{1}H NMR spectrum of **3i** (300 MHz, CD_3OD)



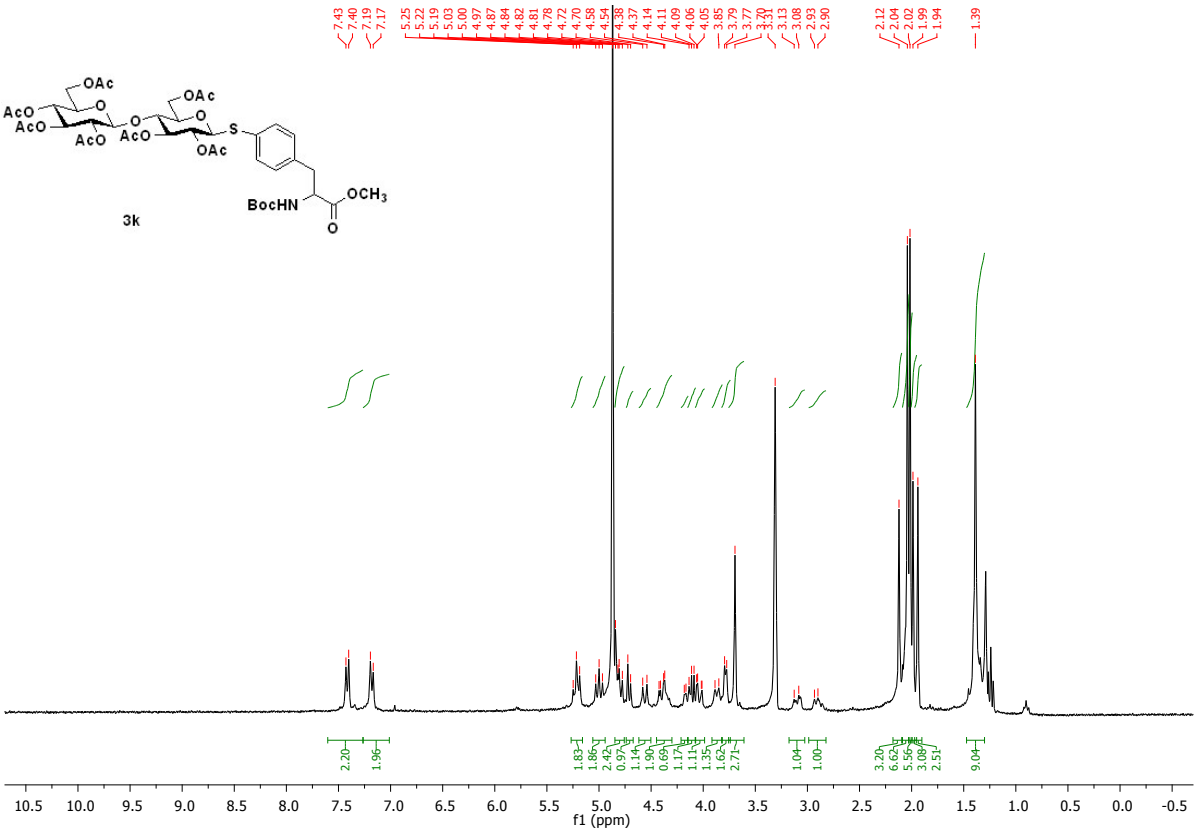
^{13}C NMR spectrum of **3i** (75 MHz, CD_3OD)



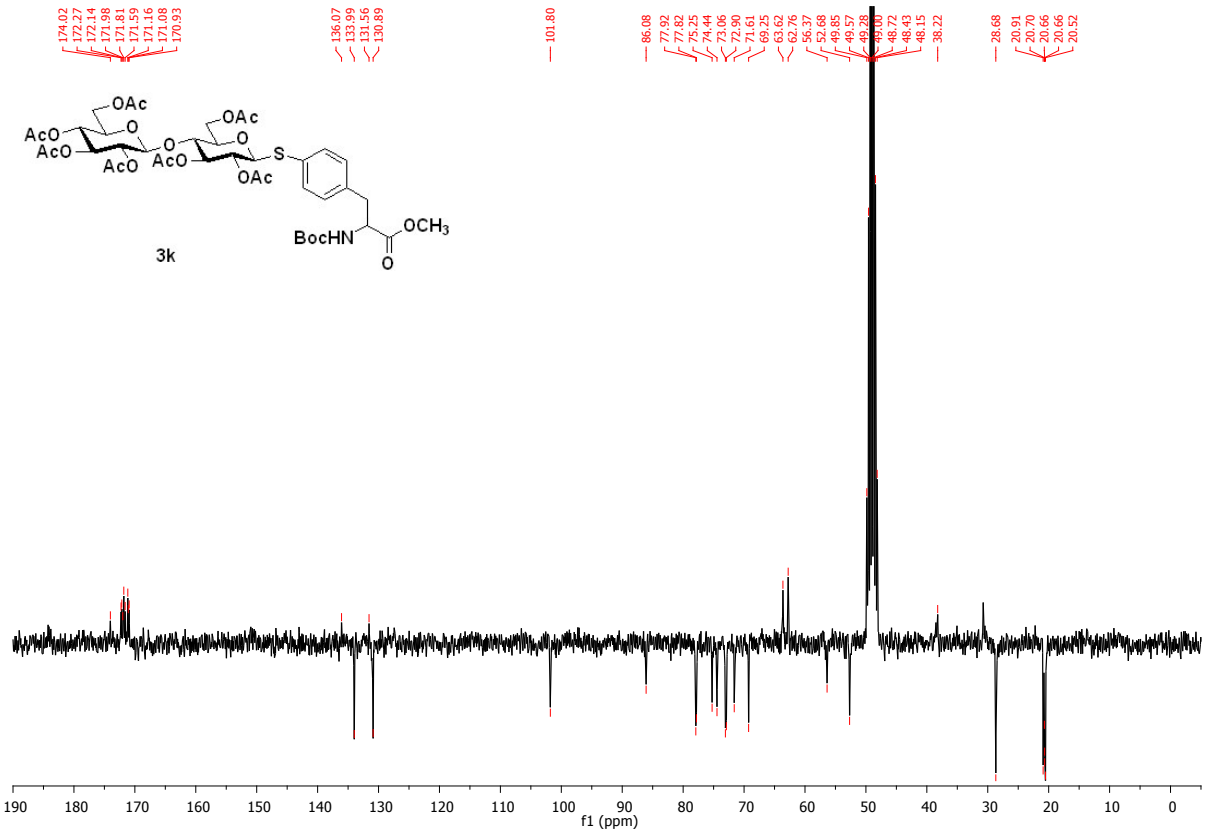
^{1}H NMR spectrum of **3j** (300 MHz, DMSOd_6)



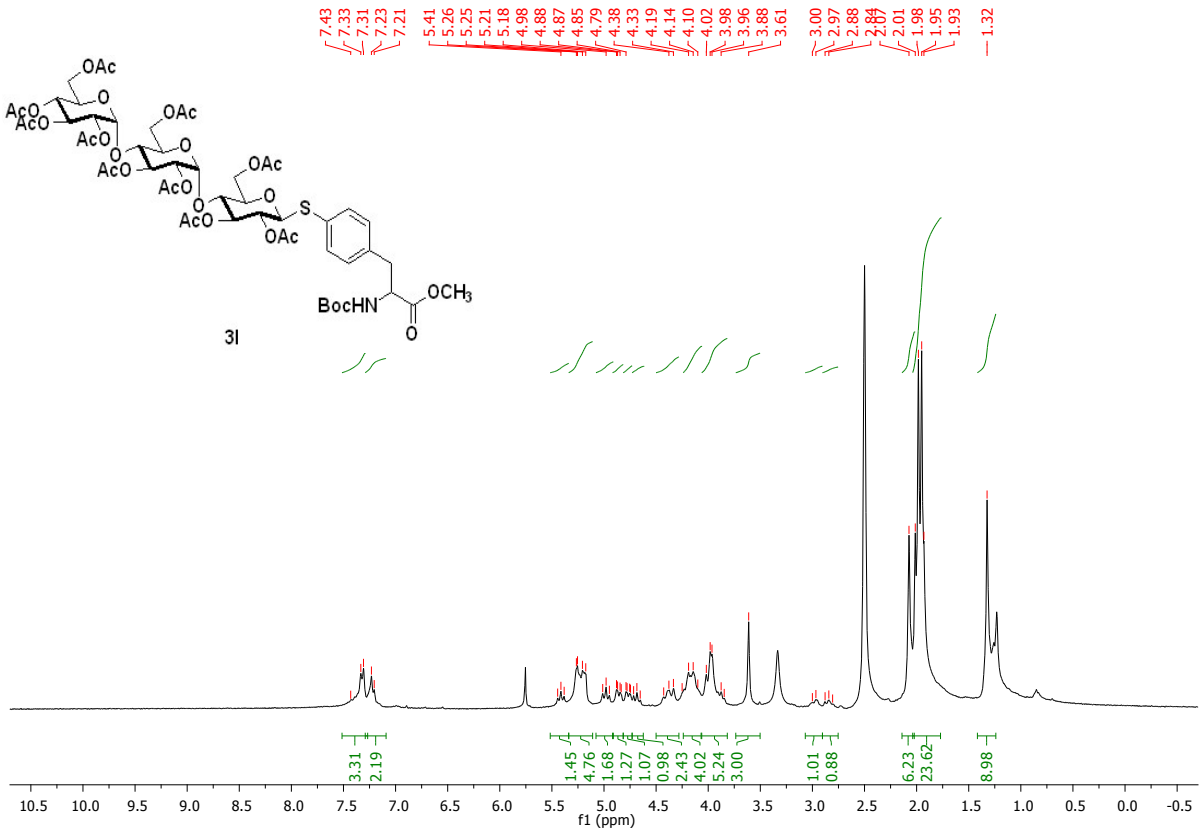
^{13}C NMR spectrum of **3j** (75 MHz, DMSOd_6)



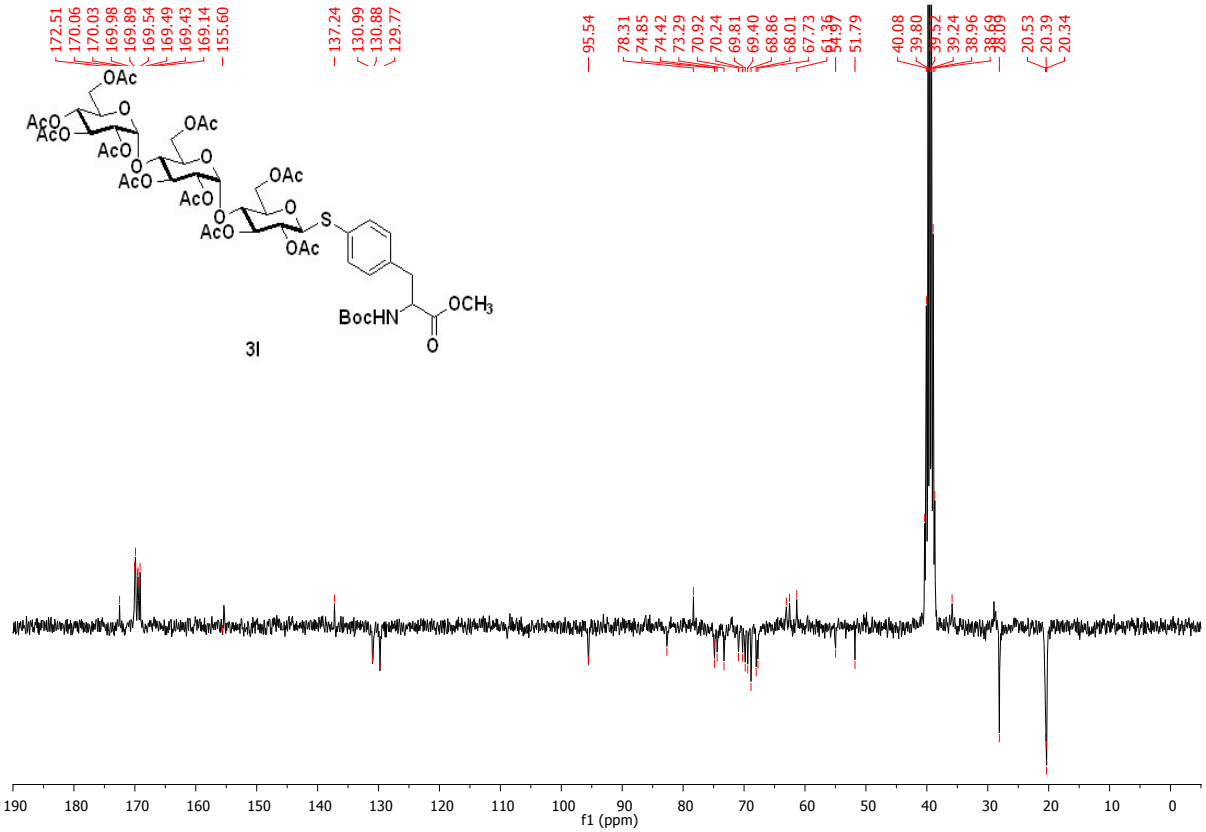
^{1}H NMR spectrum of **3k** (300 MHz, CD_3OD)



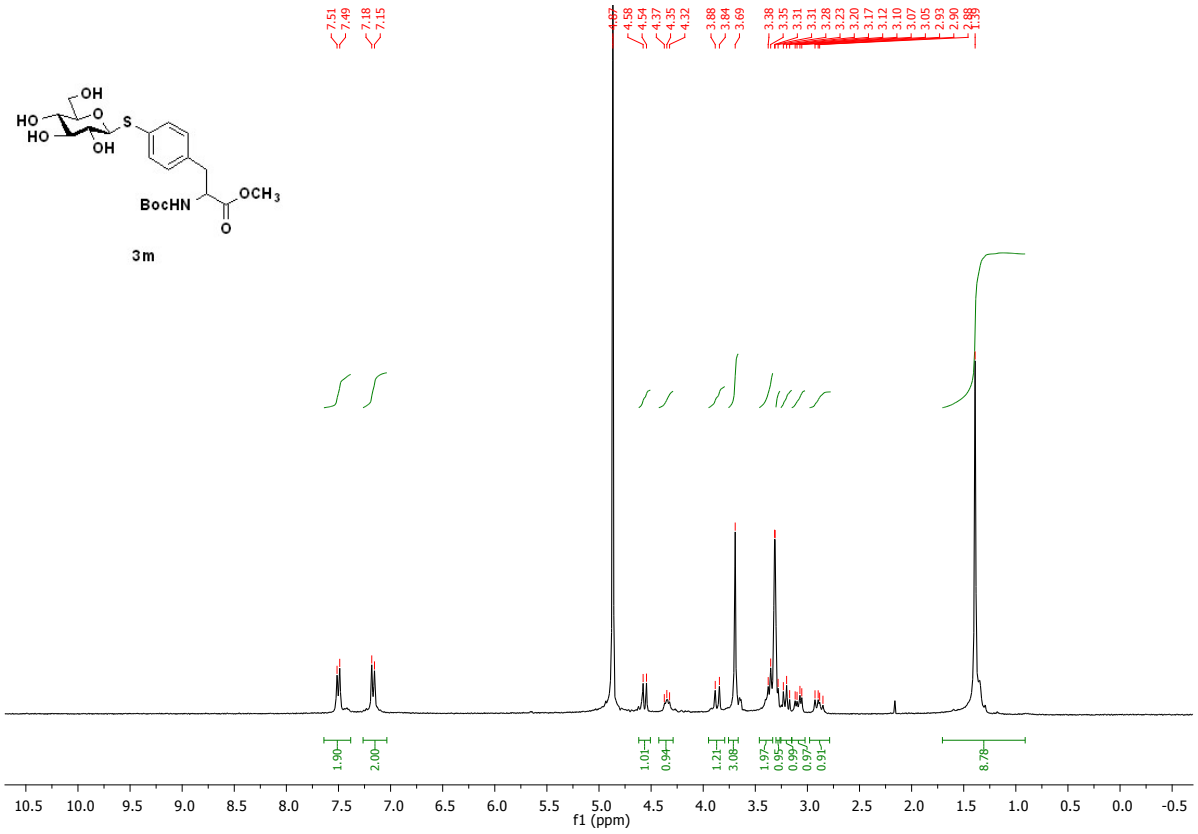
^{13}C NMR spectrum of **3k** (75 MHz, CD_3OD)



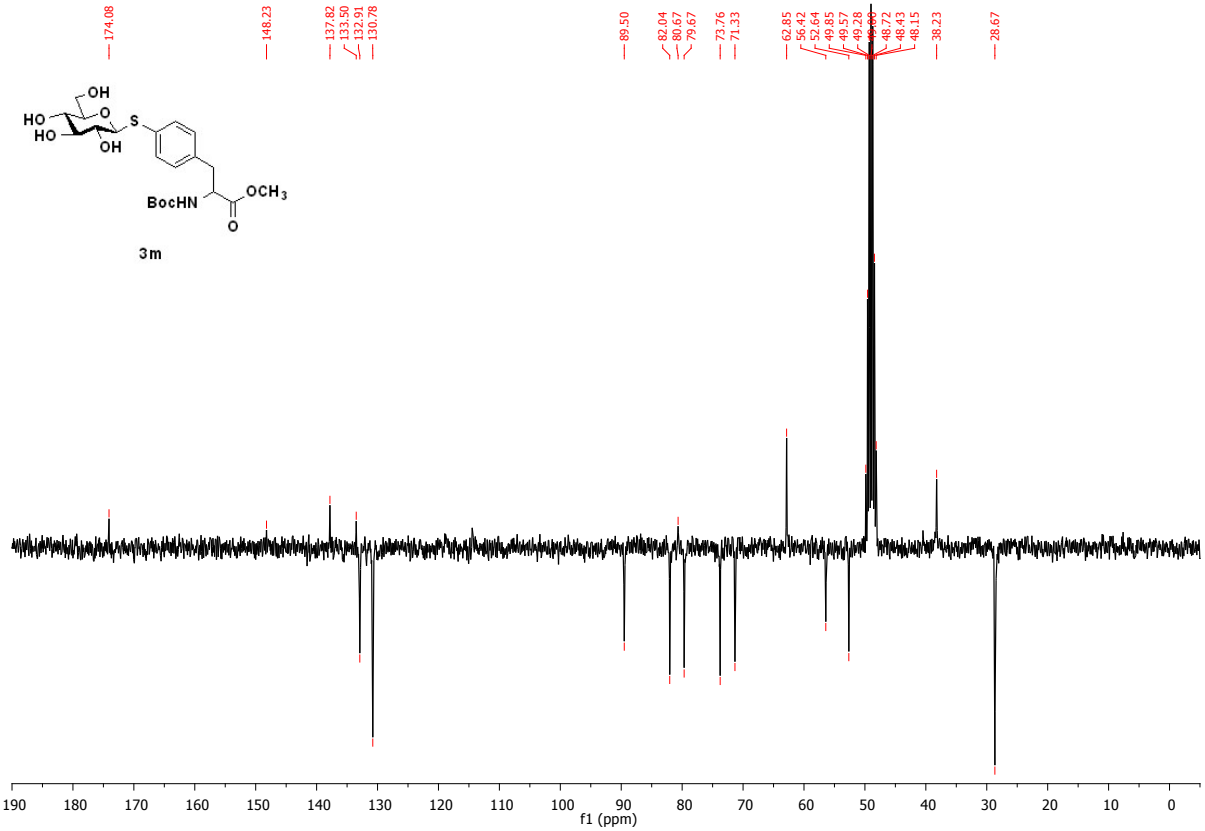
^{1}H NMR spectrum of **3l** (300 MHz, DMSO)



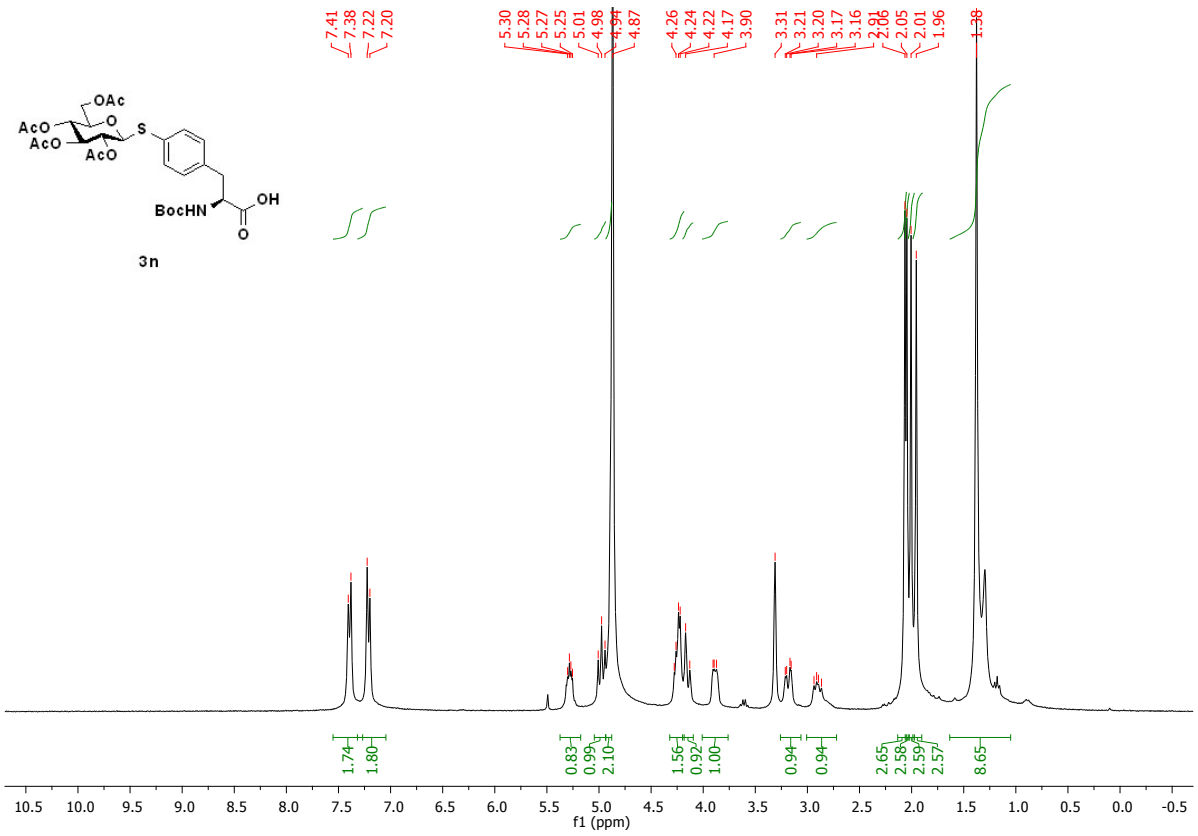
^{13}C NMR spectrum of **3l** (75 MHz, DMSOd_6)



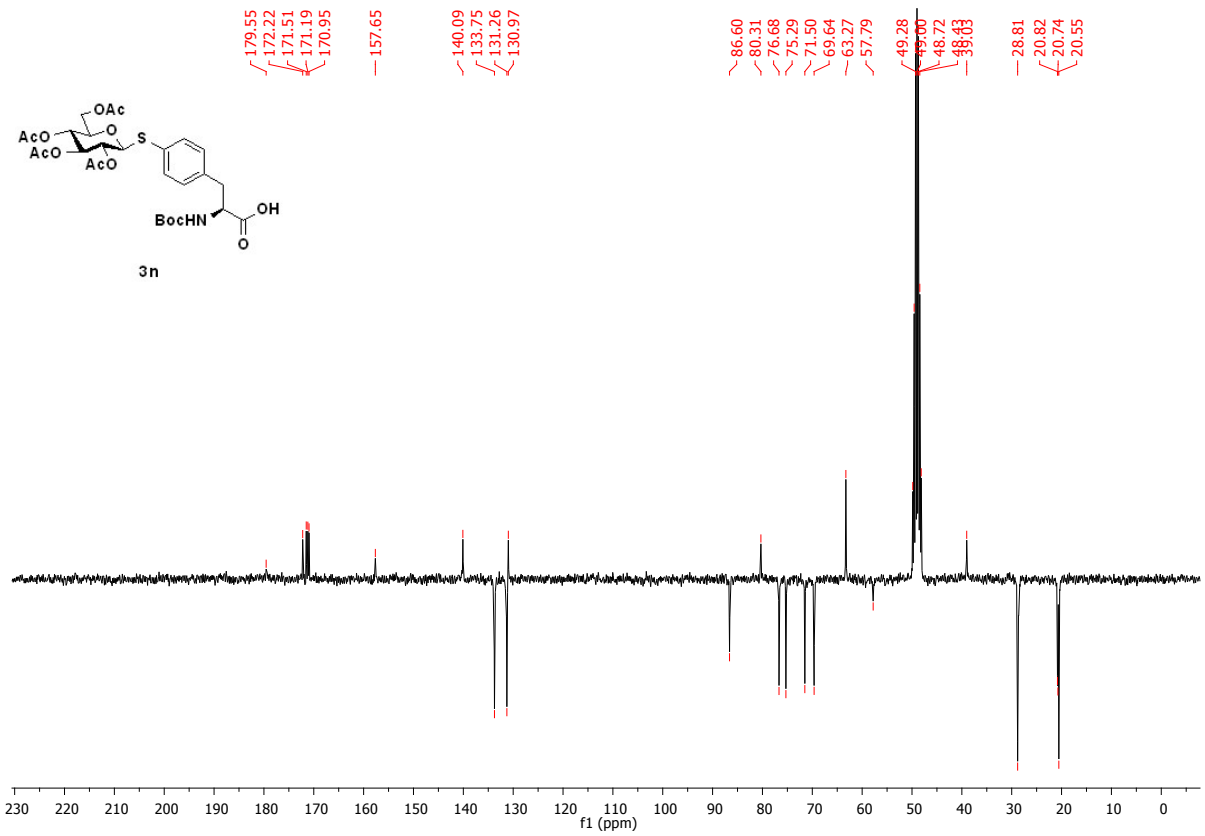
^{1}H NMR spectrum of **3m** (300 MHz, CD_3OD)



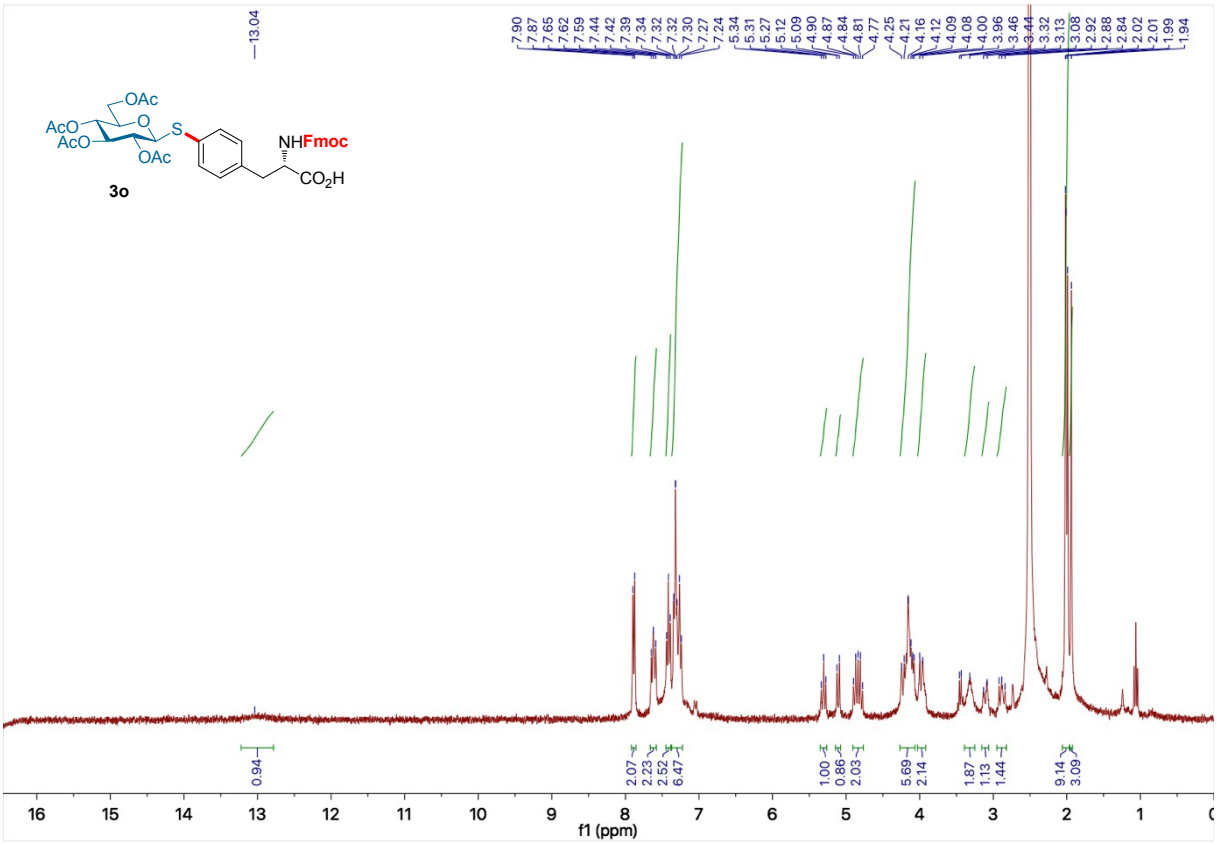
^{1}H NMR spectrum of **3m** (300 MHz, CD_3OD)



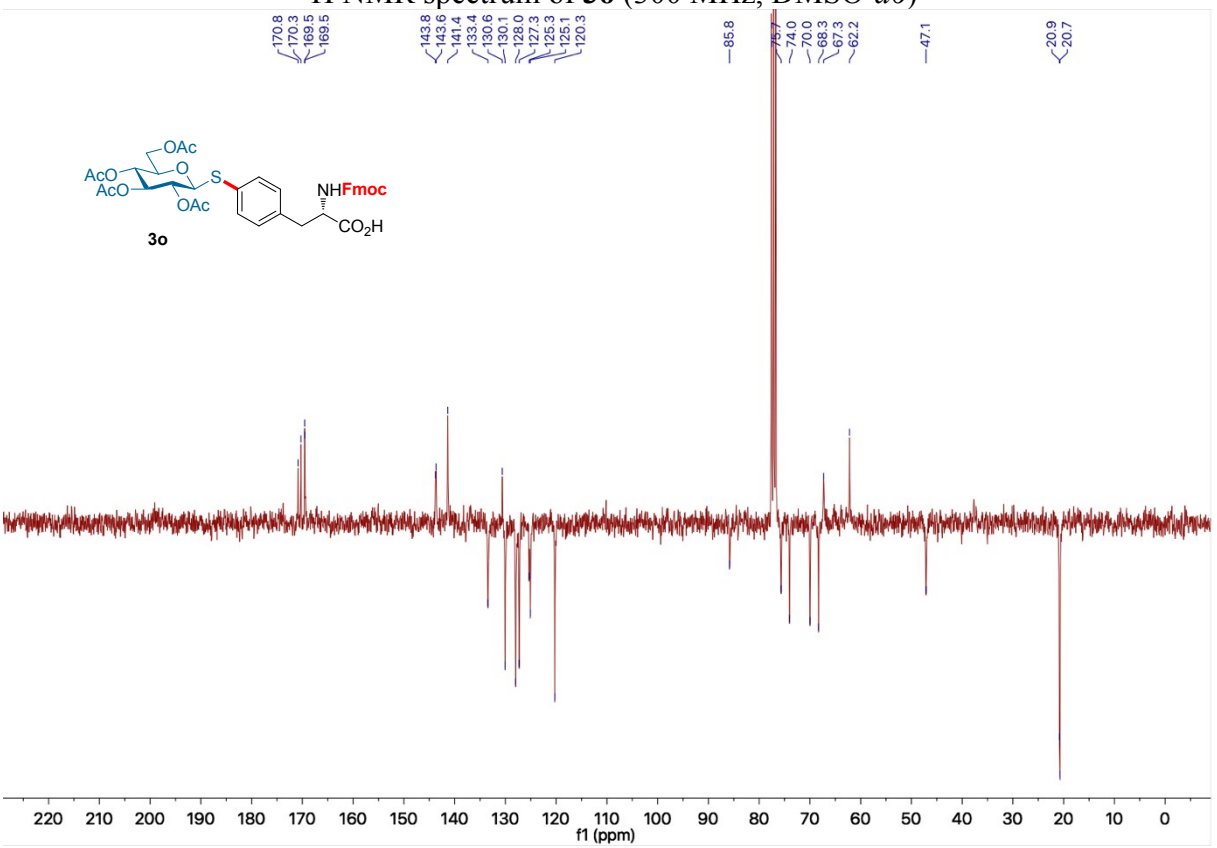
^{13}C NMR spectrum of **3n** (75 MHz, CD_3OD)



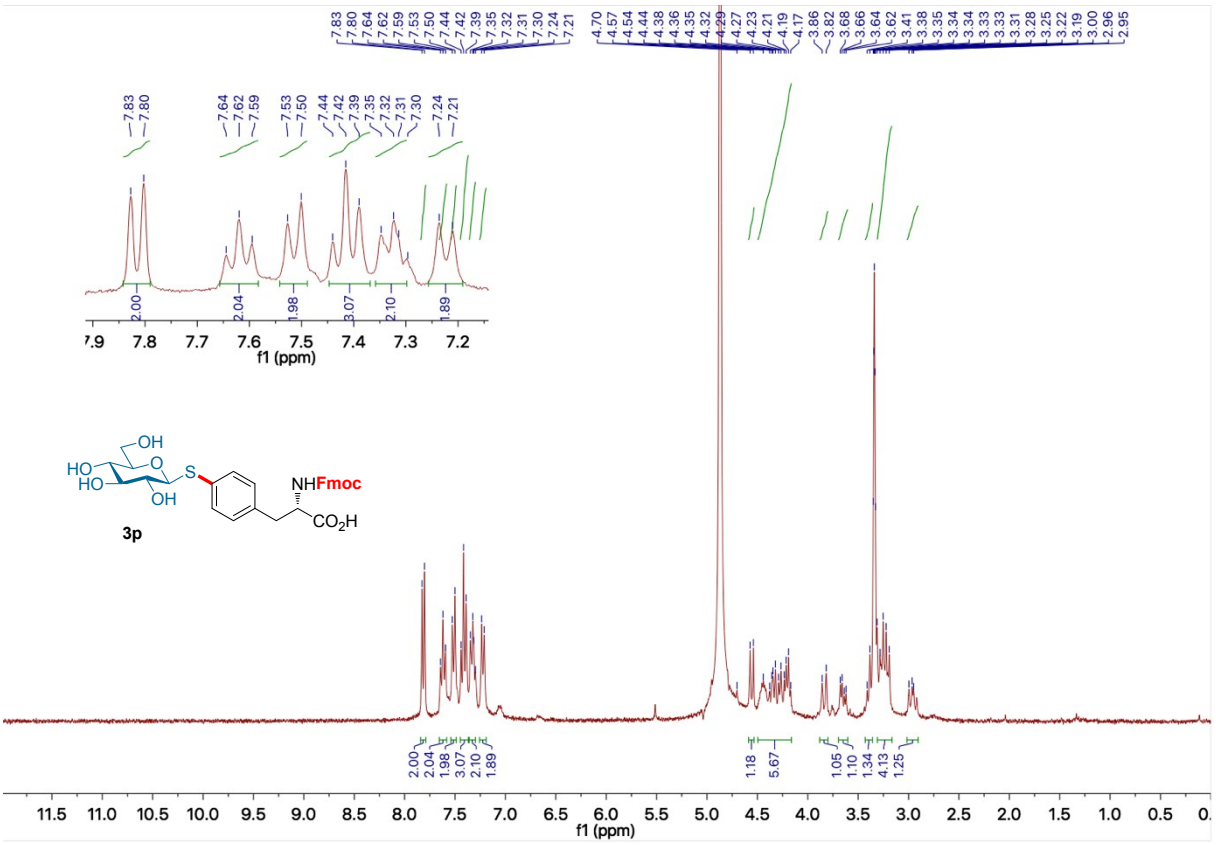
^{13}C NMR spectrum of **3n** (75 MHz, CD_3OD)



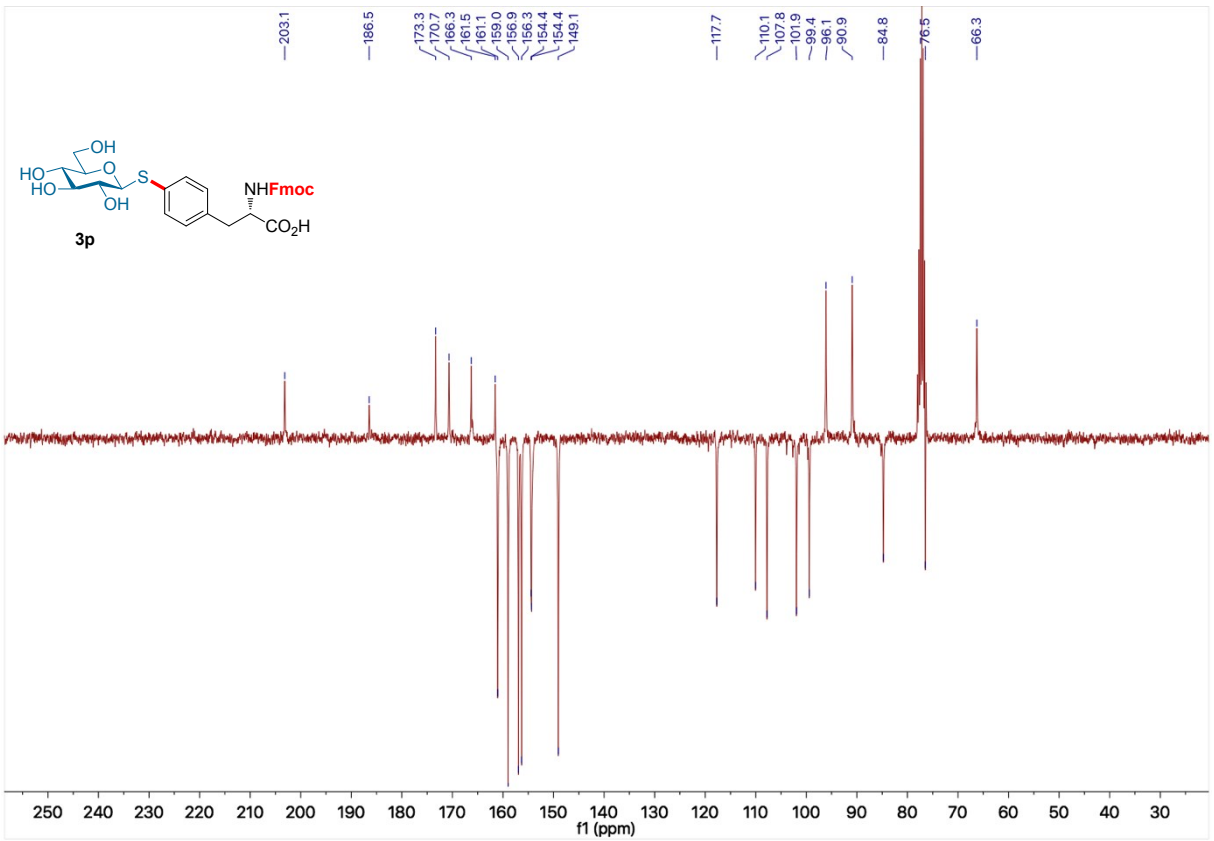
^{1}H NMR spectrum of **3o** (300 MHz, DMSO-*d6*)



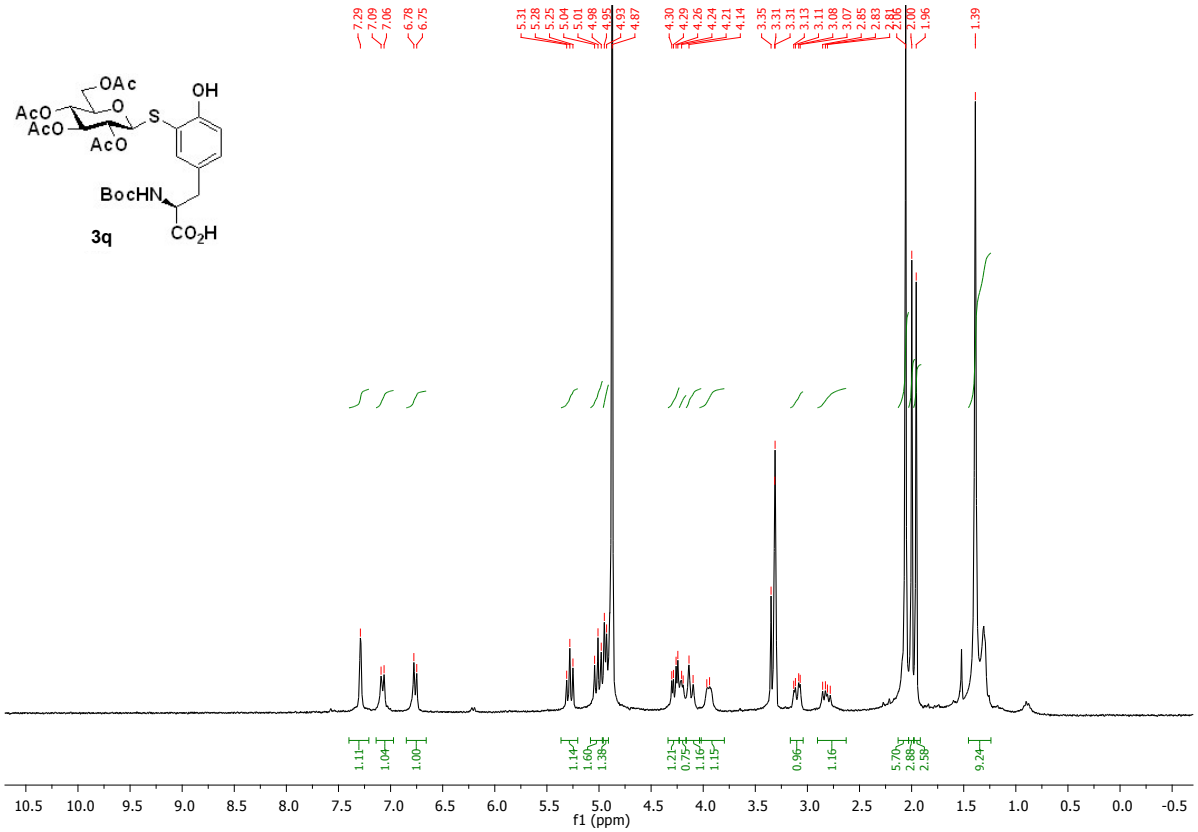
^{13}C NMR spectrum of **3o** (75 MHz, DMSO-*d6*)



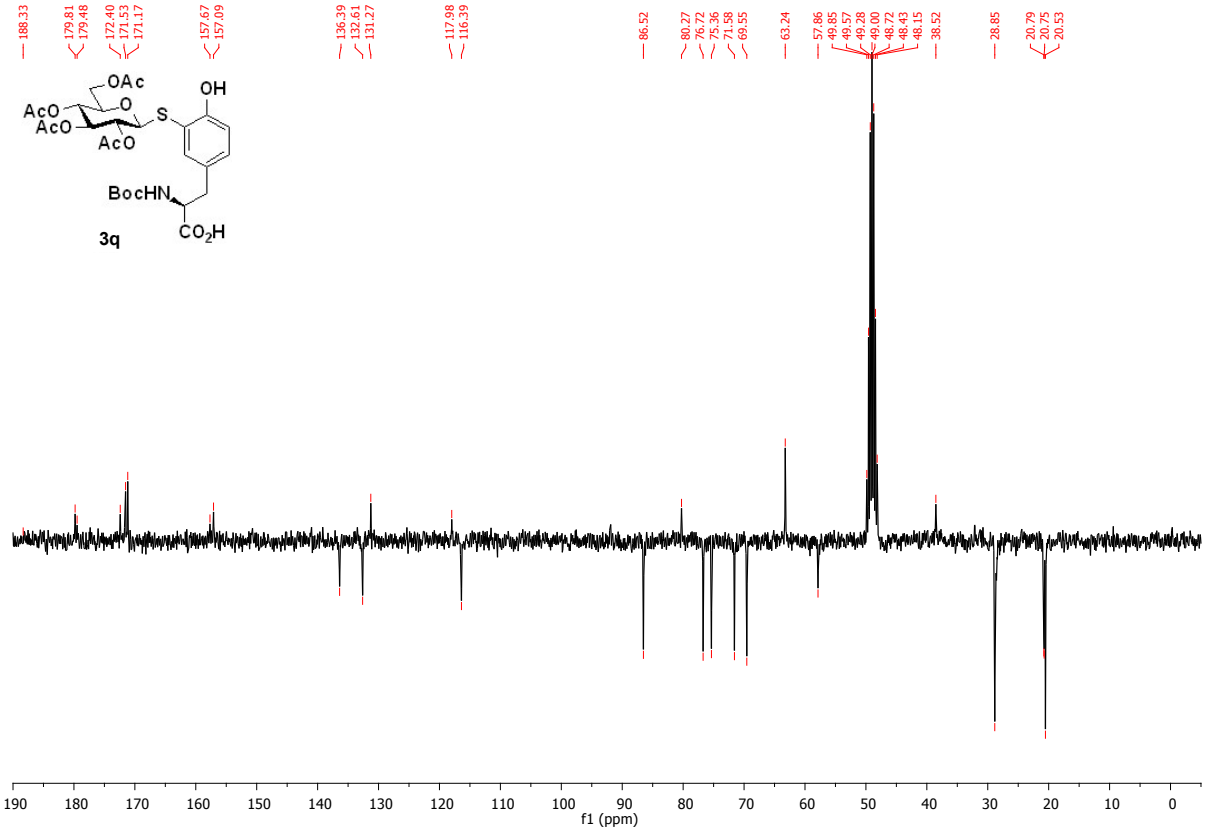
^{1}H NMR spectrum of **3p** (300 MHz, CD_3OD)



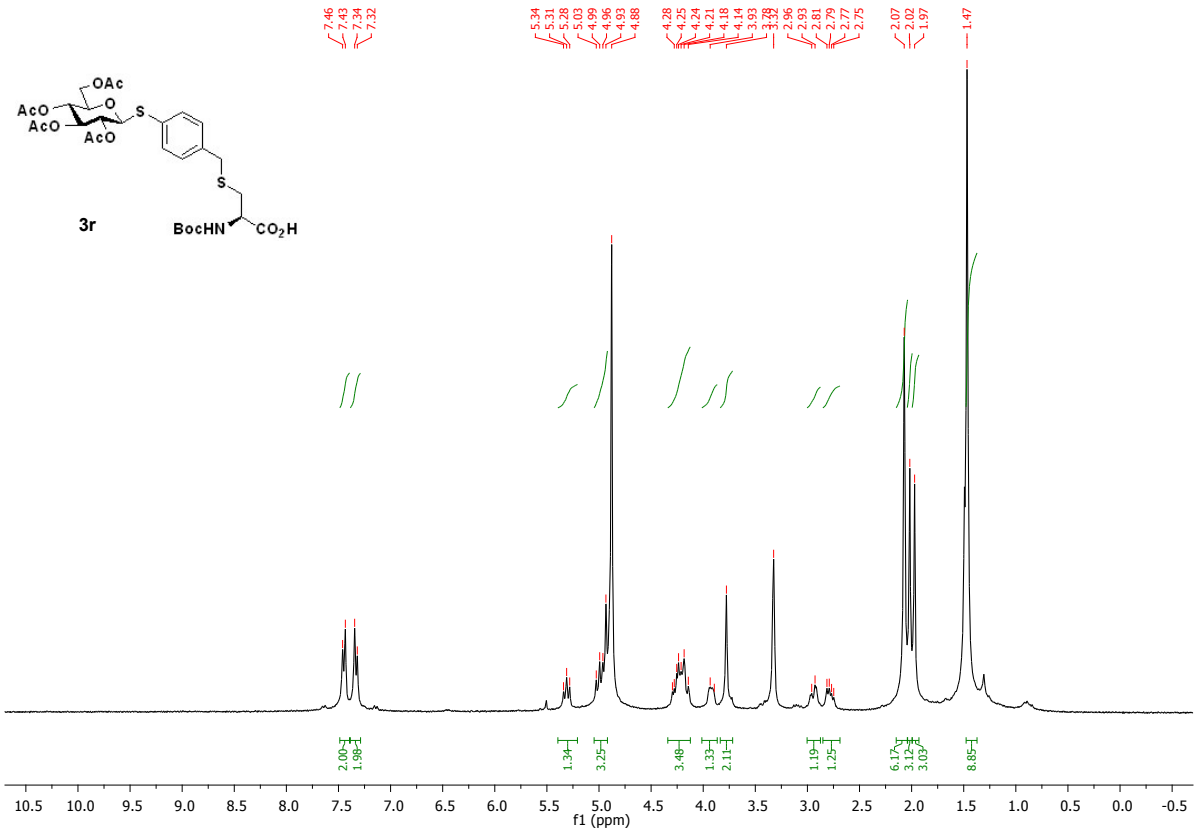
^{13}C NMR spectrum of **3p** (75 MHz, CD_3Cl_3)



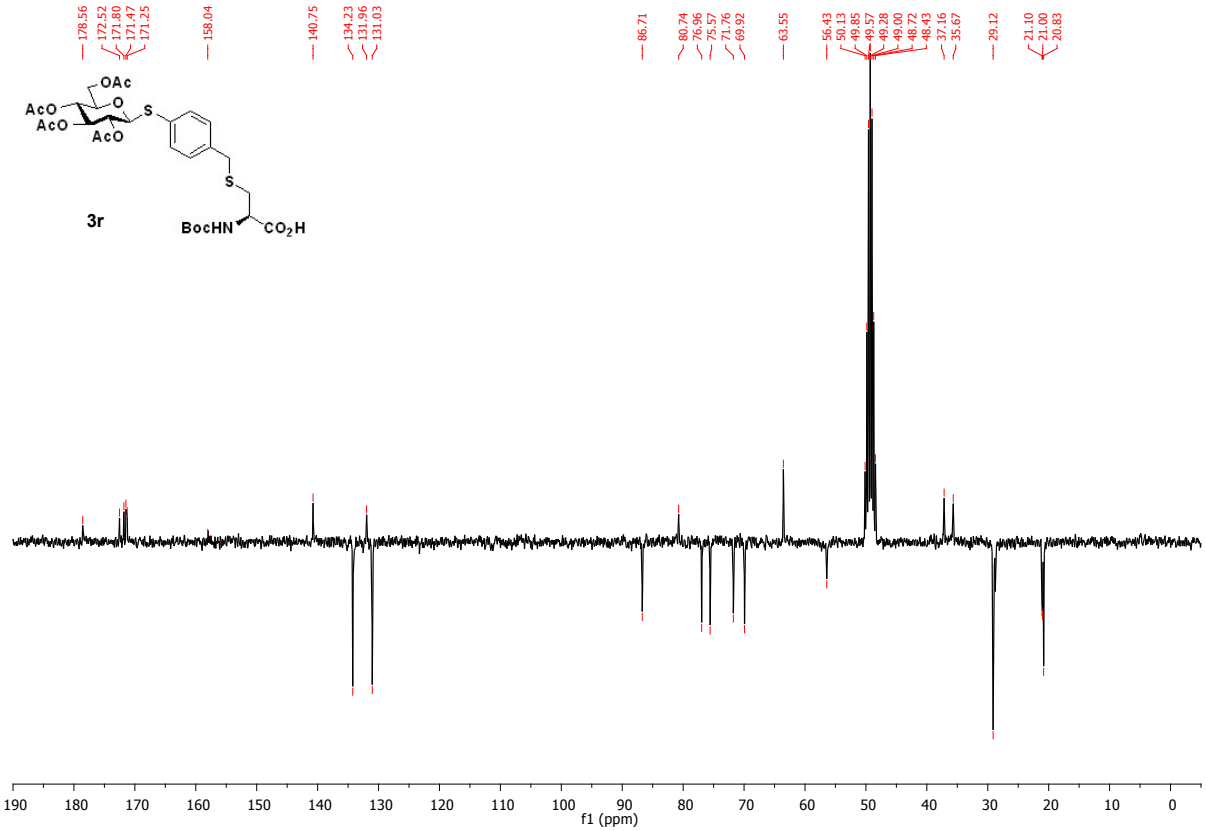
^{1}H NMR spectrum of **3q** (300 MHz, CD_3OD)



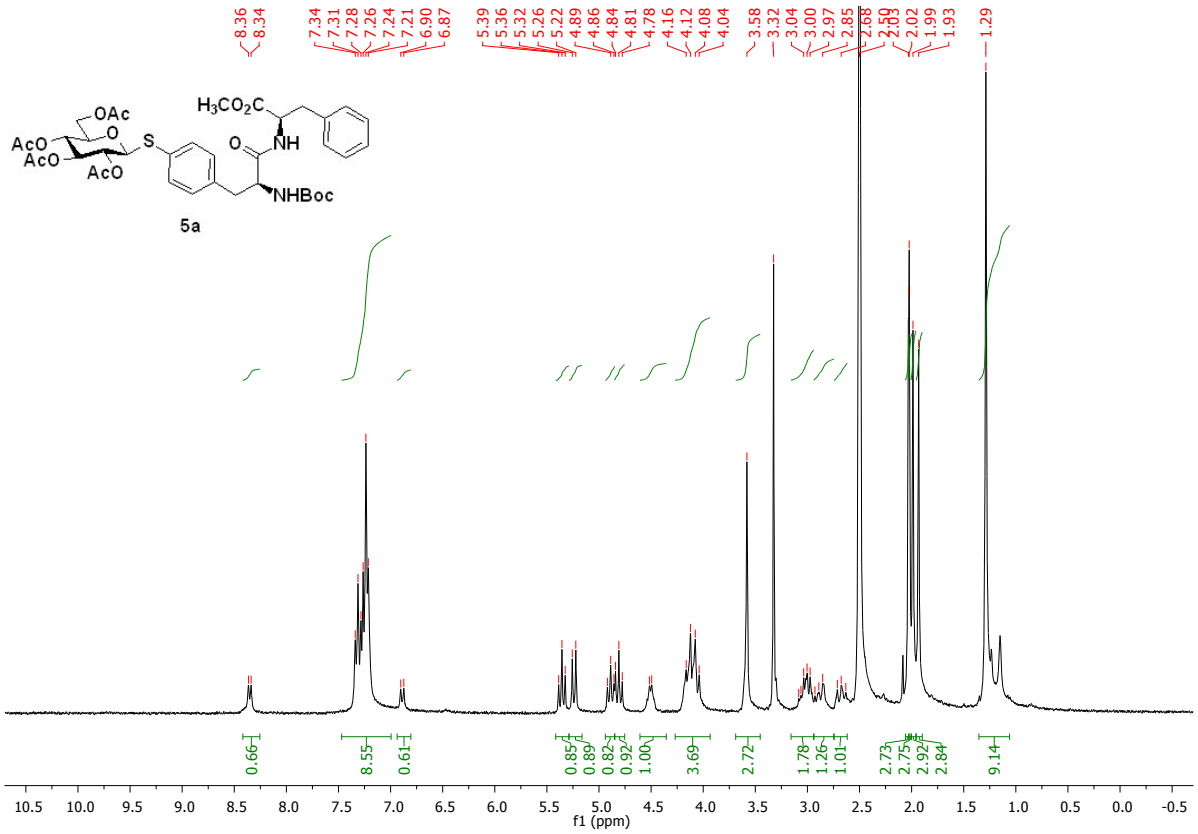
^{13}C NMR spectrum of **3q** (75 MHz, CD_3OD)



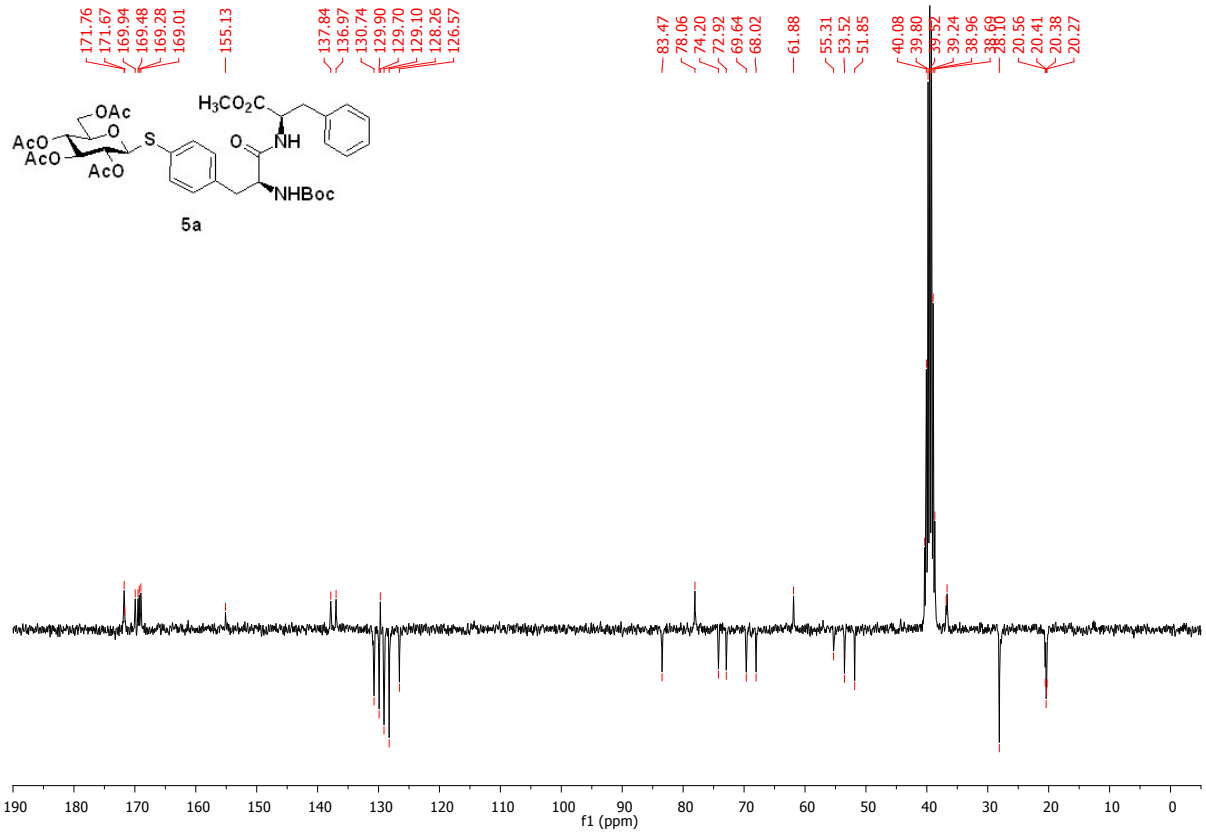
^{1}H NMR spectrum of **3r** (300 MHz, CD_3OD)



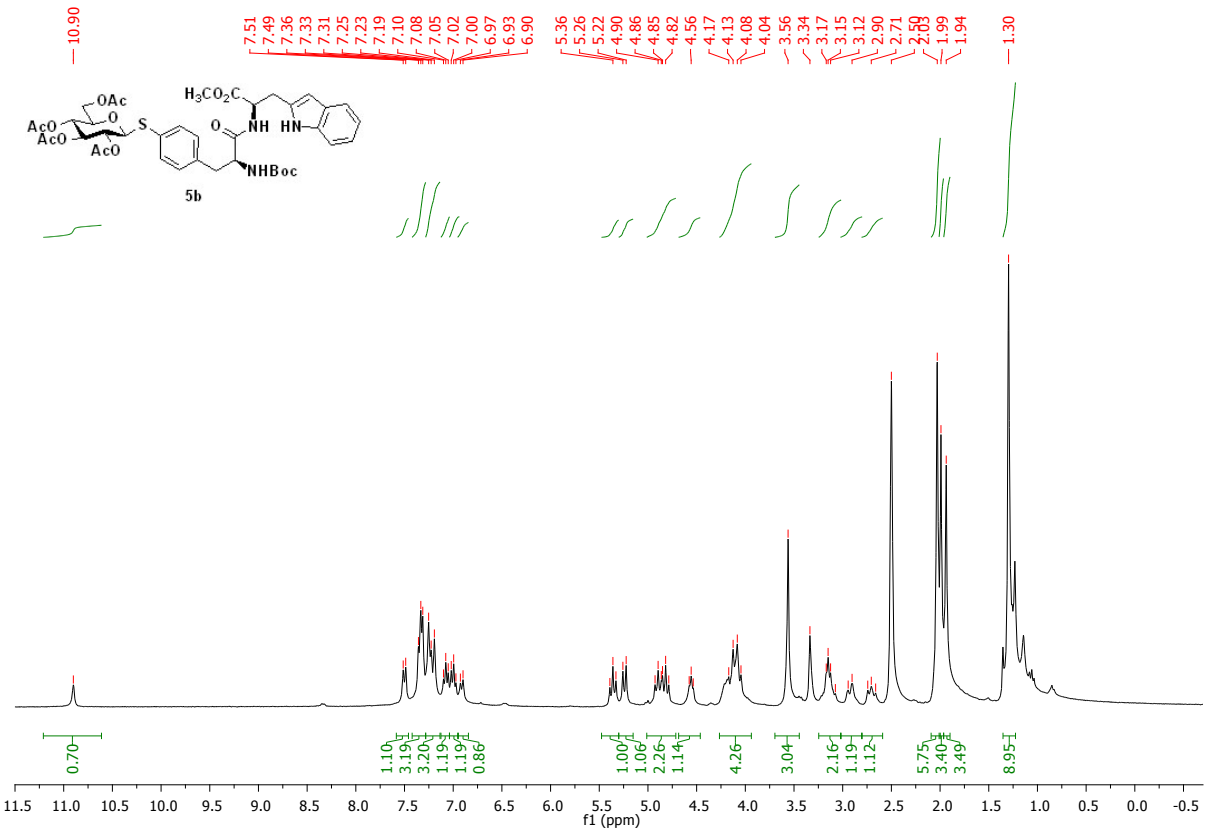
^{13}C NMR spectrum of **3r** (75 MHz, CD_3OD)



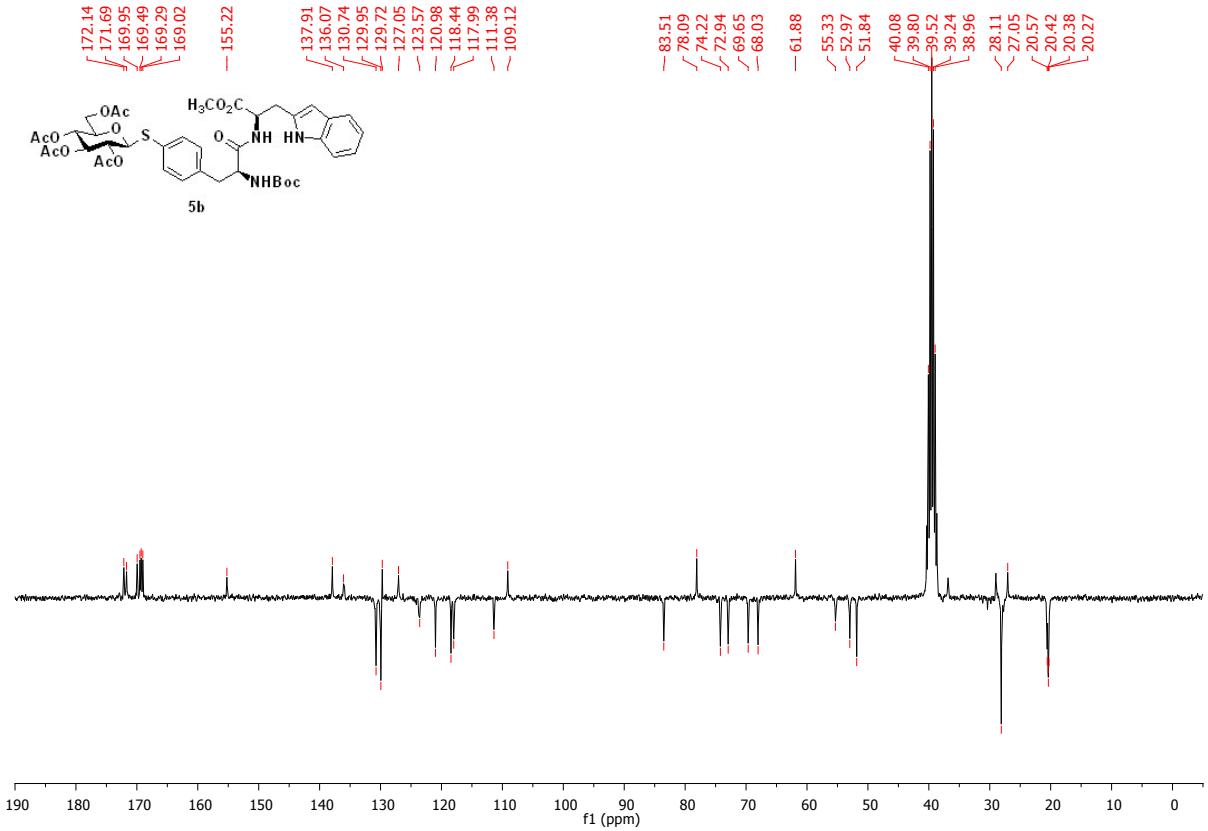
^{1}H NMR spectrum of **5a** (300 MHz, DMSOd_6)



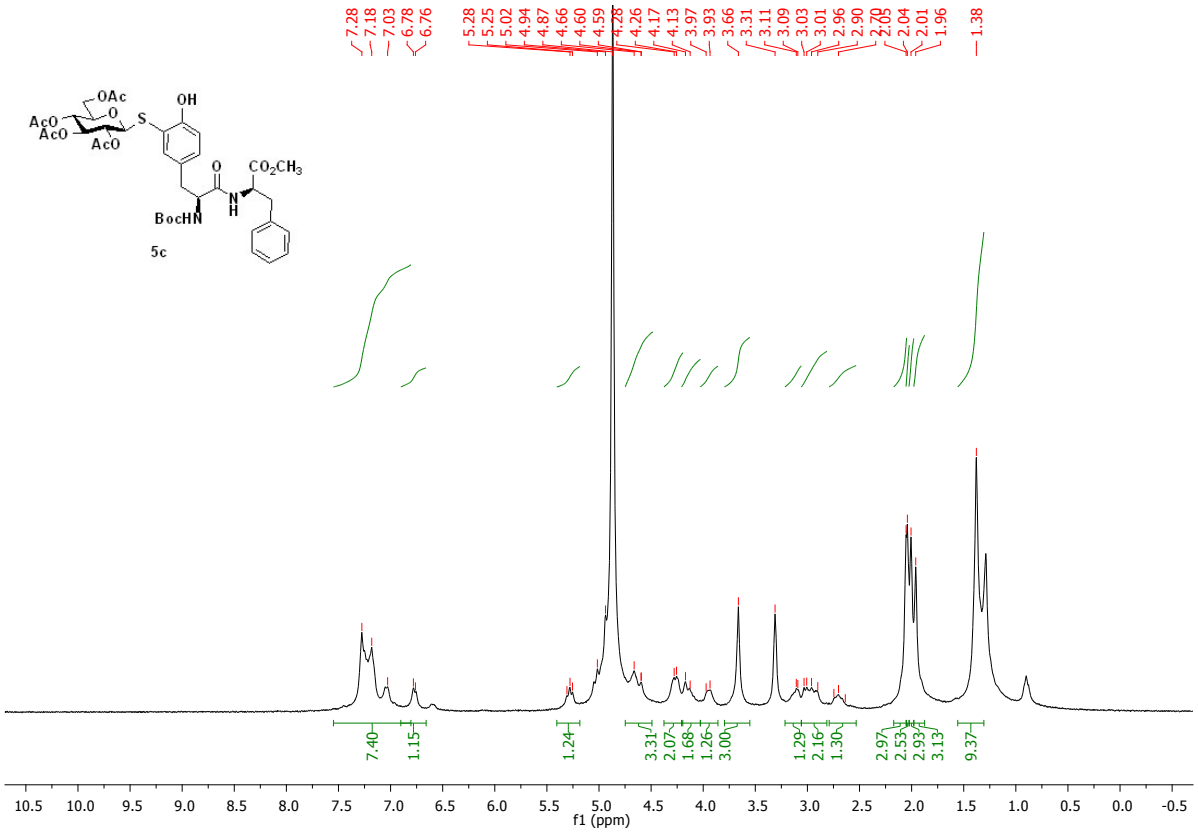
^{13}C NMR spectrum of **5a** (75 MHz, DMSOd_6)



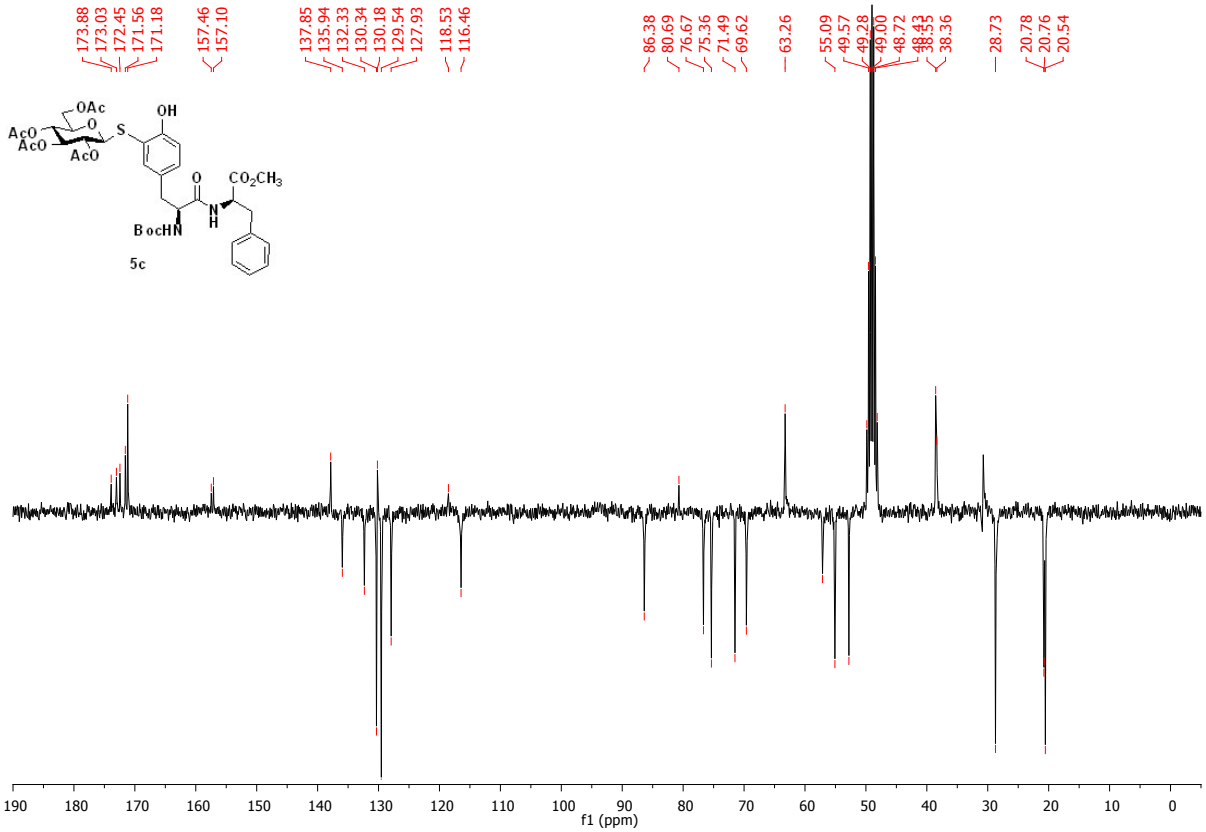
^{1}H NMR spectrum of **5b** (300 MHz, DMSOd_6)



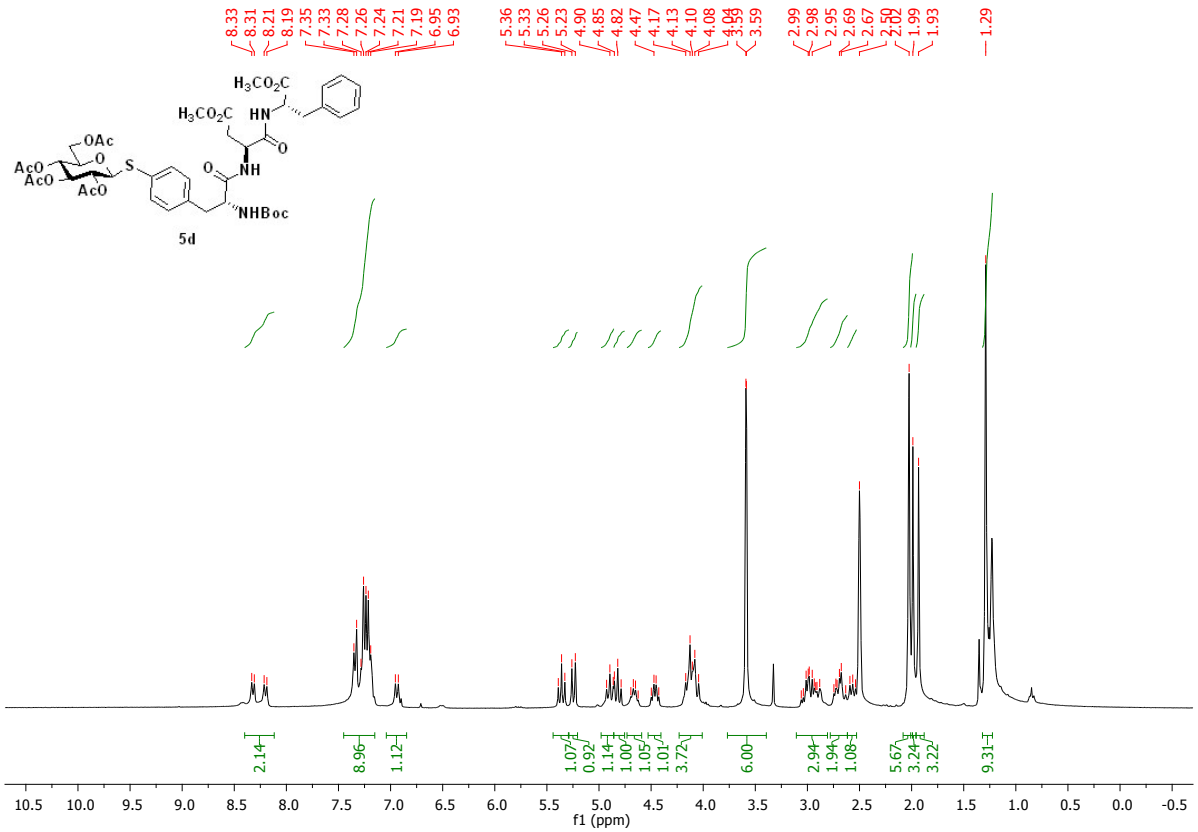
^{13}C NMR spectrum of **5b** (75 MHz, DMSOd_6)



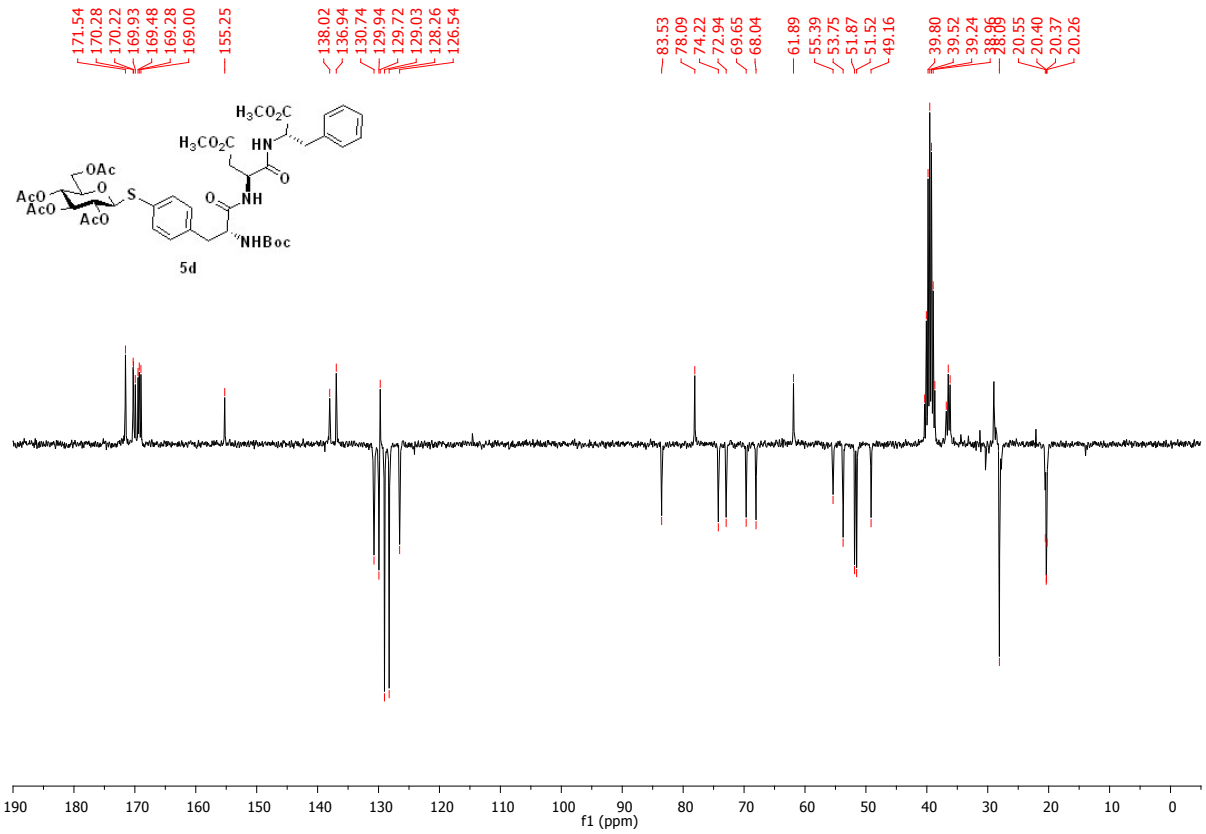
^{1}H NMR spectrum of **5c** (300 MHz, CD_3OD)



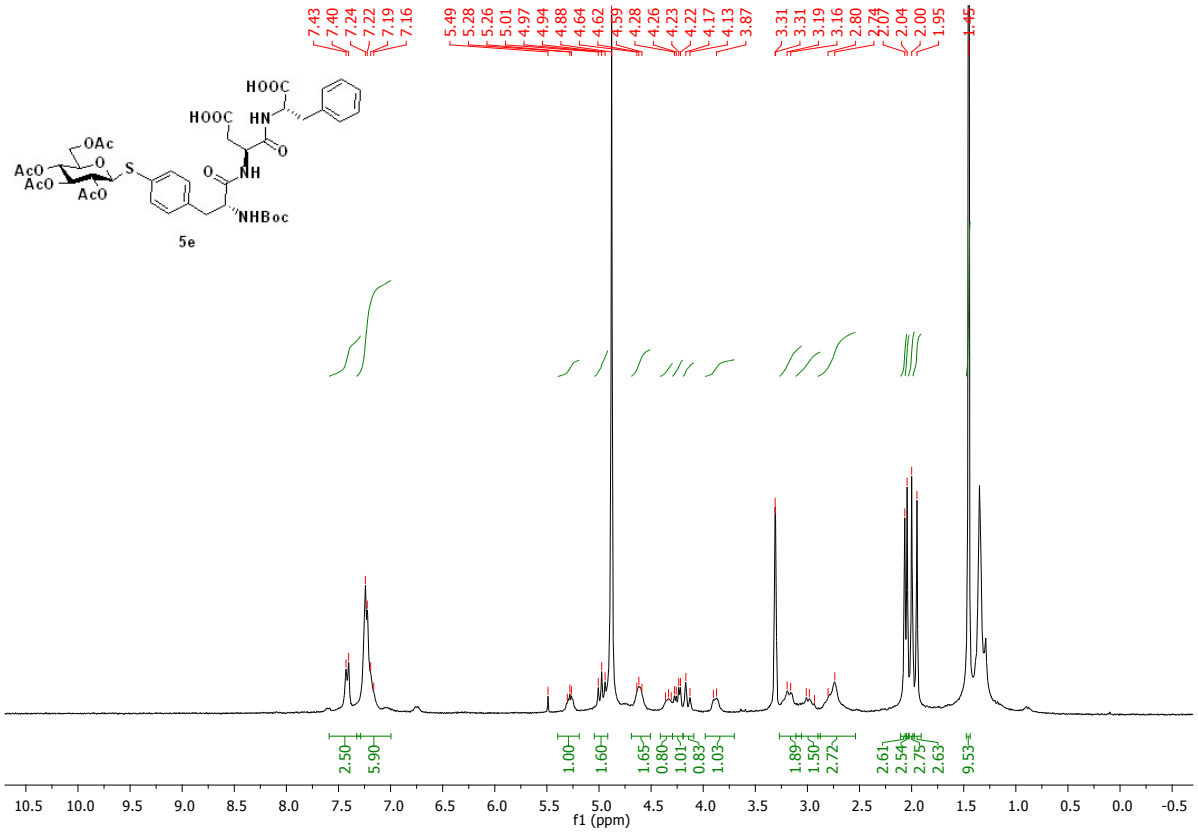
^{13}C NMR spectrum of **5c** (75 MHz, CD_3OD)



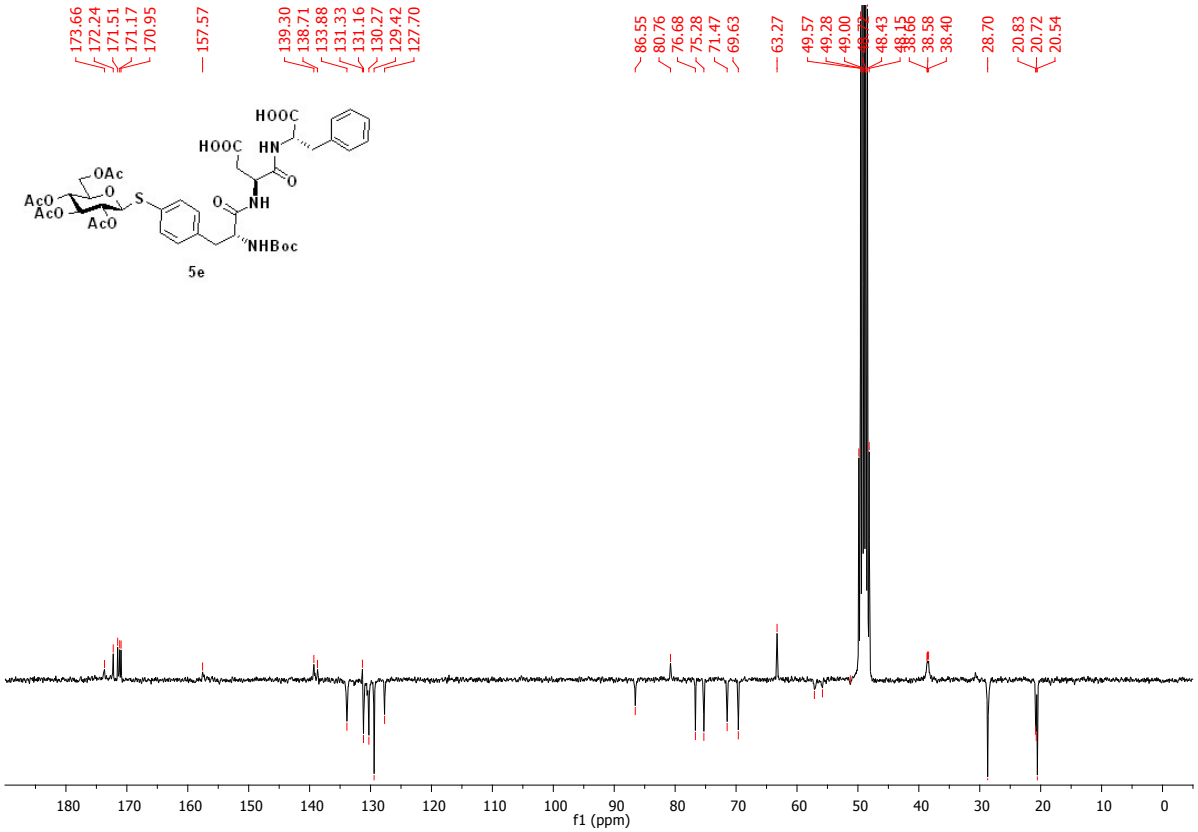
^{1}H NMR spectrum of **5d** (300 MHz, DMSOd_6)



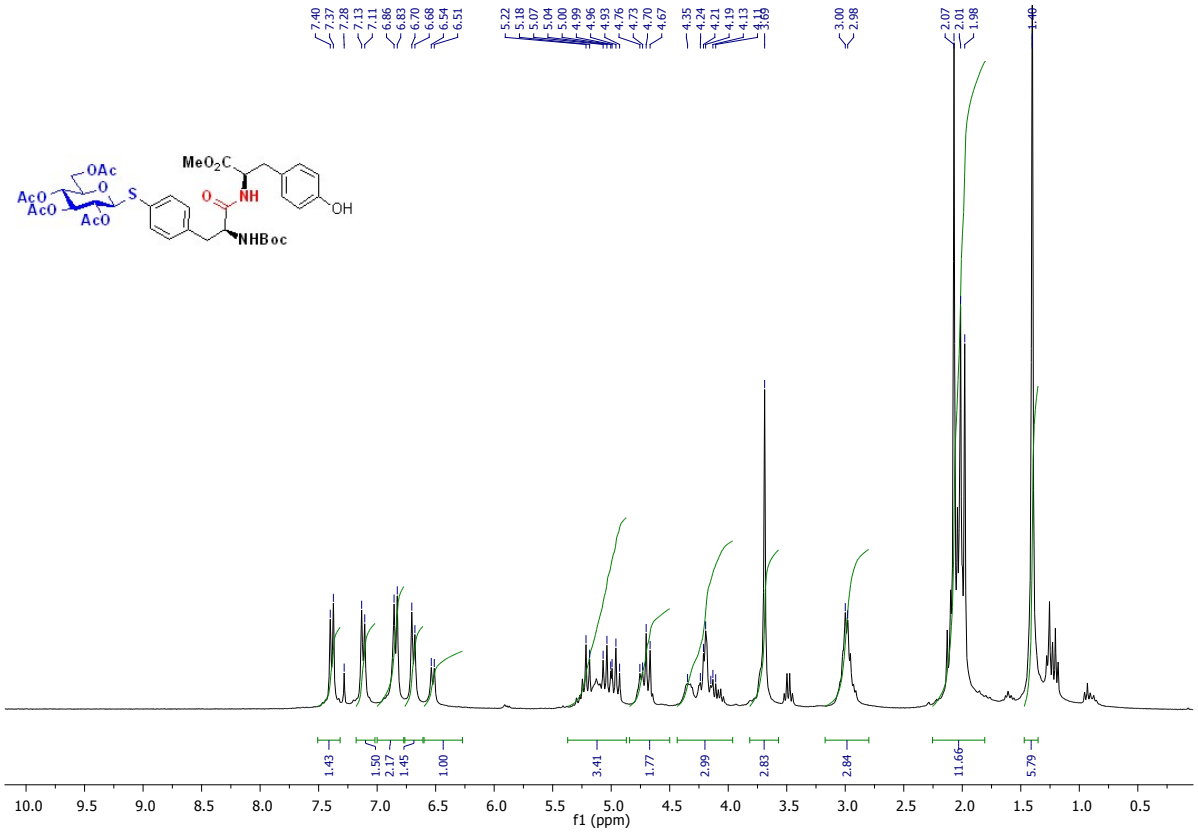
^{13}C NMR spectrum of **5d** (75 MHz, DMSOd_6)



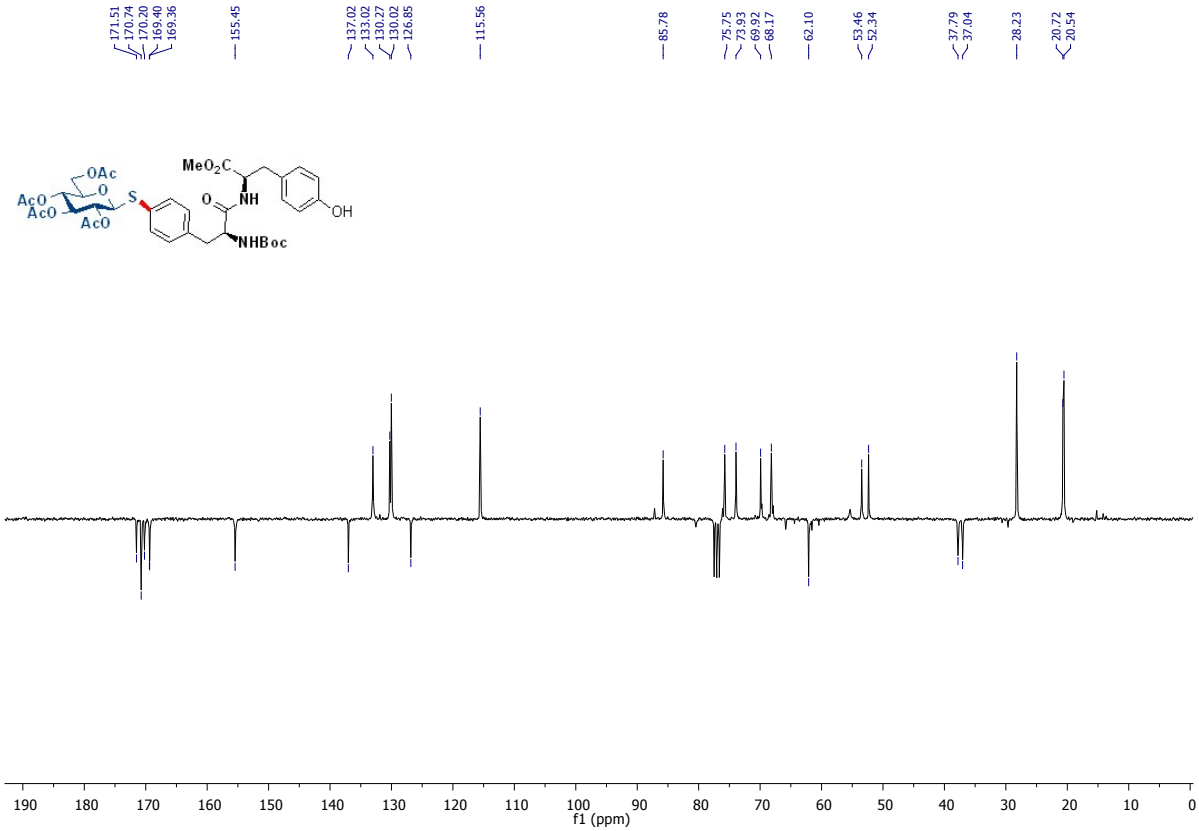
^{1}H NMR spectrum of **5e** (300 MHz, CD_3OD)



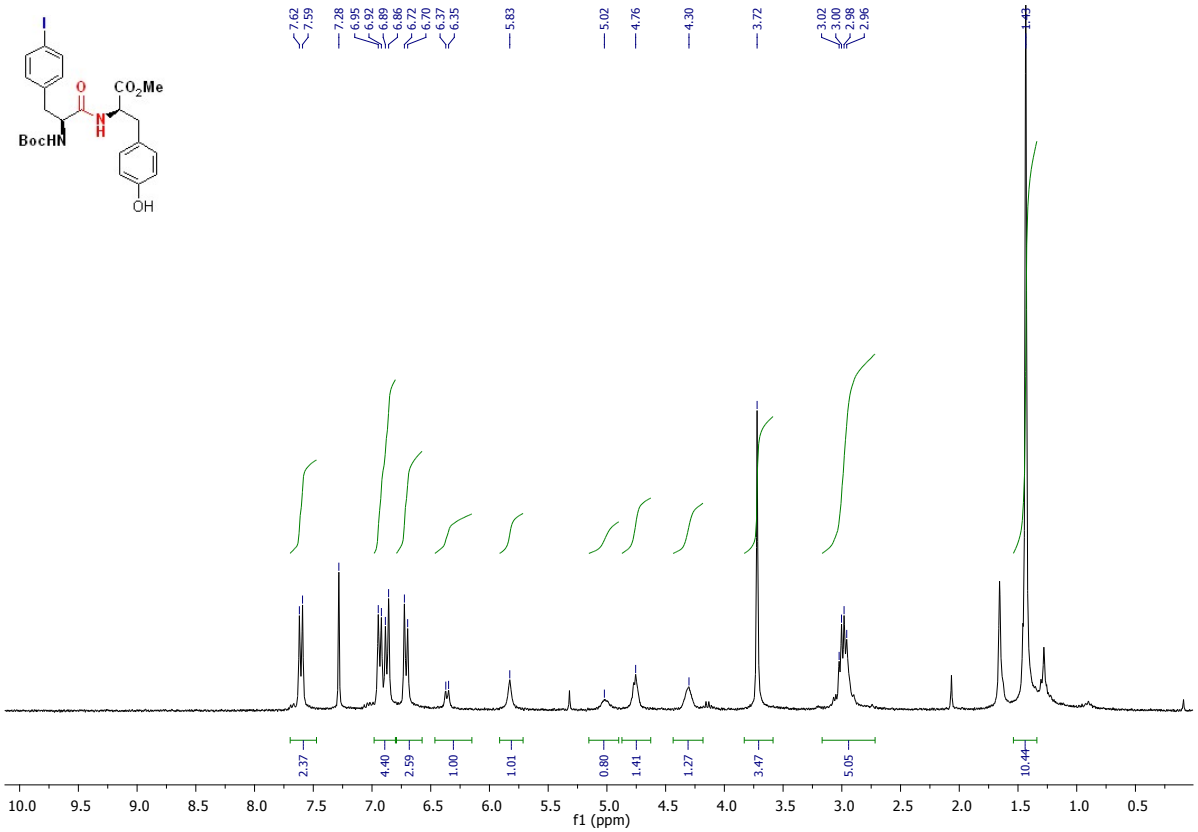
^{13}C NMR spectrum of **5e** (75 MHz, CD_3OD)



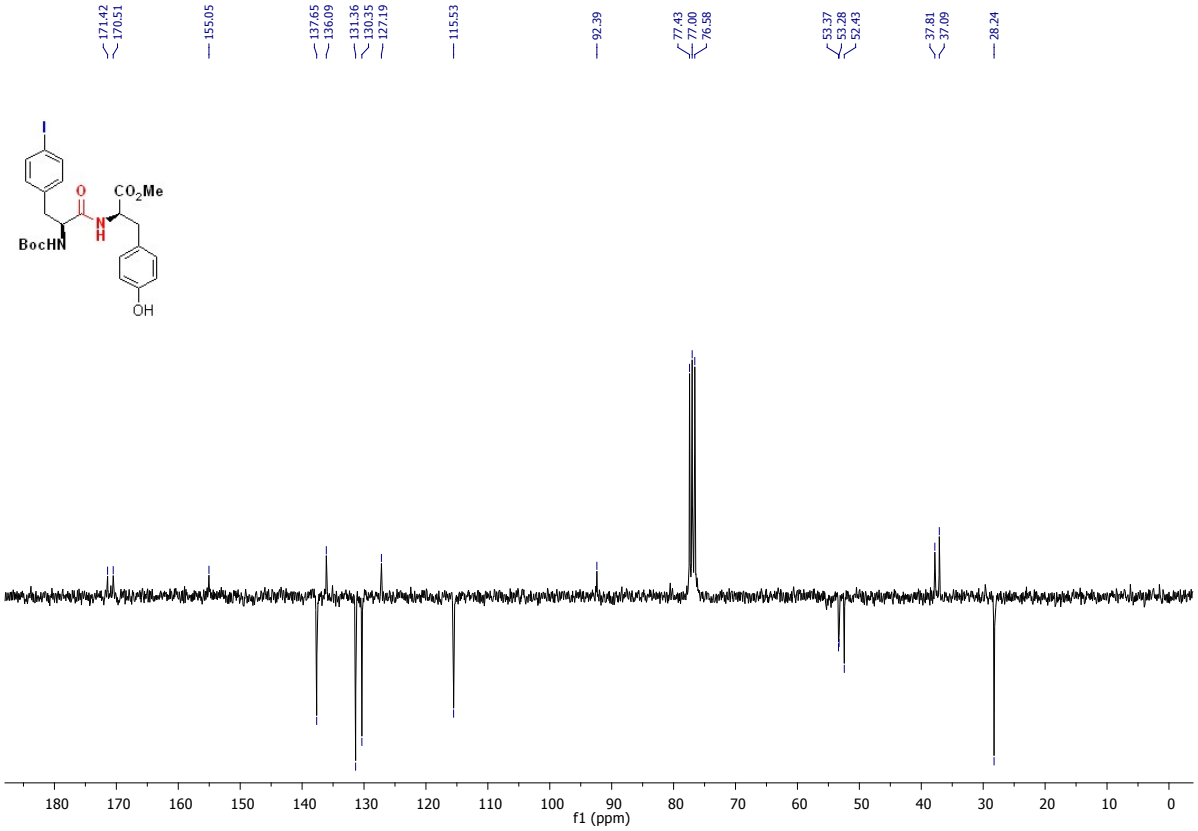
^{1}H NMR spectrum of **5f** (300 MHz, $CDCl_3$)



^{13}C NMR spectrum of **5f** (75 MHz, $CDCl_3$)



^{1}H NMR spectrum of **4e** (300 MHz, CD_3OD)



^{13}C NMR spectrum of **4e** (75 MHz, CD_3OD)