Supporting Information for

Protein Glycoengineering Enabled by the Versatile Synthesis of Aminooxy Glycans and the Genetically Encoded Aldehyde Tag

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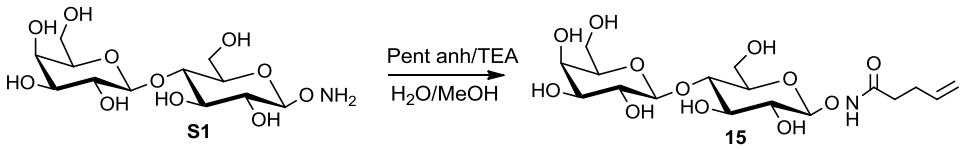
Experimental Procedures.

Materials and Methods.

All chemical reagents were purchased from Sigma-Aldrich, Acros, and TCI and used without purification unless noted otherwise. Anhydrous DMF, MeOH, and pyridine were purchased from Acros in sealed bottles; all other anhydrous solvents were obtained from an alumina column solvent purification system. Molecular sieves were ground to powder, flame-dried under hi-vacuum and used immediately after cooling. All reactions were carried out in flame-dried glassware under N_2 unless otherwise noted. In all cases, solvent was removed by reduced pressure with a Buchi Rotovapor R-114 equipped with a Welch self-cleaning dry vacuum. Products were further dried by reduced pressure with an Edwards RV3 high vacuum. Lyophilization was performed on a LABCONCO FreeZone® instrument equipped with an Edwards RV2 pump. Thin layer chromatography was performed with Silicycle 60 Å silica gel plates and detected by UV lamp or charring with *p*-anisaldehyde in acidic EtOH. Flash chromatography was performed using Silicycle® 60 Å 230-400 mesh silica. Size exclusion chromatography was executed on a 100 cm x 2.5 cm column packed with BioGel P-2 fine resins (Bio-Rad). All 1H and 13C NMR spectra are reported in ppm and referenced to solvent peaks (1H and 13C). Spectra were obtained on Bruker AVQ-400, AVB-400, DRX-500, AV-500, or AV-600 instruments. High resolution electrospray ionization (ESI) mass spectra were obtained from the UC Berkeley Mass Spectrometry Facility.



Scheme S1. Synthesis of *N*-hydroxypentenoyl lactose **15**

***N*-hydroxypent-4-eneamide β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (15):** To a solution of aminooxy lactose **S1**[1] (140 mg, 0.38 mmol) in 2:1 MeOH/H_2O (3 mL) stirring at 0 ºC under N_2 was added TEA (110 µL, 0.77 mmol) and pentenoic anhydride (110 µL, 0.58 mmol) dropwise. The mixture was allowed to warm to rt and after 2 h the solution was concentrated under vacuum. The residue was purified by silica gel column chromatography (10%-20% MeOH/DCM) and after lyophilization gave **15** (127 mg, 76%) as a white powder. ^{1}H NMR (600 MHz, D_2O): δ 5.83 (ddt, *J* = 12.9, 10.4, 6.5 Hz, 1H), 5.07 (dd, *J* = 26.7, 13.7 Hz, 2H), 4.70 (d, *J* = 8.2 Hz, 1H, H-1), 4.44 (d, *J* = 7.8 Hz, 1H, H-1'), 3.91 (d, *J* = 3.1 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.79 – 3.74 (m, 2H), 3.74 – 3.63 (m, 5H), 3.62 – 3.56 (m, 1H), 3.56 – 3.50 (m, 1H), 3.47 (t, *J* = 8.5 Hz, 1H), 2.39 – 2.33 (m, 2H), 2.31-2.29 (m, 2H); ^{13}C NMR (150 MHz, D_2O): δ 172.78, 136.48, 116.00, 105.18, 102.90, 77.79, 75.34, 75.03, 74.12, 72.52, 70.99, 70.93, 68.55, 61.02, 59.88, 31.71, 28.87; HRMS (ESI): calcd for $C_{17}H_{29}NO_{12}$ $[M+Na]^+$ *m/z* = 462.1582, found: 462.1593.

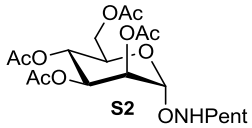
Preparation of the NHPent Glycosides

General Procedure A for preparation from glycosyl bromides and thioimidates:
A solution of glycosyl donor (1 equiv.), *N*-pentenoyl hydroxamic acid **1** (1.5 equiv.), and 4 Å MS in CH_2Cl_2 was stirred at rt for 1 h under N_2. The mixture was cooled to 0 ºC and AgOTf (2 equiv., preactivated by coevaporation with toluene) was added. The reaction was allowed to warm to rt over 1 h and diluted with CH_2Cl_2 before filtering to remove MS. The concentrated residue was purified by silica flash chromatography (Hex/EtOAc gradient) to afford the corresponding N-hydroxypentenoyl glycoside.

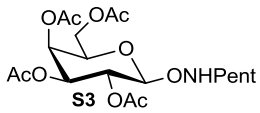
General Procedure B for preparation from thioglycosides:
To a thioglycoside donor (1 equiv.) in CH_2Cl_2 was added 300AW MS and stirred for 45 min at rt under N_2. The solution was cooled to 0 ºC and liquid Br_2 (1 equiv.) was added dropwise. After stirring for 20 min, the reaction was filtered and concentrated under vacuum. The resulting residue was dissolved in CH_2Cl_2 with subsequent addition of *N*-pentenoyl hydroxamic acid **1** (1.5 equiv.) and 4 Å MS. After stirring for 1 h at rt, the mixture was cooled to 0 ºC and AgOTf (1.5 equiv., preactivated by coevaporation with toluene) was added. The reaction was allowed to warm to rt over 1 h, diluted with CH_2Cl_2 and filtered before concentration under vacuum. The resulting residue was purified by silica flash chromatography (Hex/EtOAc gradient) to afford the corresponding N-hydroxypentenoyl glycoside.

General Procedure C for preparation from glycosyl fluorides:
To a solution of a glycosyl fluoride (1 equiv.) and *N*-pentenoyl hydroxamic acid **1** (1.5 equiv.) in CH_2Cl_2 was added 4 Å MS and stirred under N_2 for 1 h at rt. The mixture was chilled to 0 ºC followed by the addition of preactivated AgOTf (2.5 equiv.) and $SnCl_2$ (2.5 equiv.) and stirred for 3 h to rt. The reaction was filtered, concentrated under reduced pressure, and passed through a silica column (Hex/EtOAc gradient) to afford the pure N-hydroxypentenoyl glycoside.

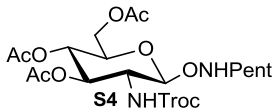
General Procedure D for preparation from glycosyl *N*-phenyl trifluoroacetimidates:
A mixture of glycosyl trifluoroacetimidate donor (1 equiv.), *N*-pentenoyl hydroxamic acid **1** (1.5 equiv.), and 3 Å MS in CH_2Cl_2 was stirred at rt for 1 h under N_2. The reaction mixture was chilled to -20 ºC and TMSOTf (1 equiv.) was added dropwise after which the mixture was allowed to slowly warm to rt while stirring for 2h. The reaction was quenched with dropwise addition of TEA, filtered to remove sieves, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (Tol/Acetone gradient) to afford the corresponding N-hydroxypentenoyl glycoside.



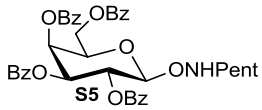
***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranoside (S2)**:
Following procedure A, compound **S2** was given from reaction of 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl bromide **2** as a white solid (95 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 5.78 (ddt, *J* = 12.7, 10.5, 6.4 Hz, 1H), 5.35 (d, *J* = 1.4 Hz, 1H), 5.31 (t, *J* = 10.1 Hz, 1H), 5.23 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.09 – 4.93 (m, 3H), 4.65 (s, 1H), 4.26 (dd, *J* = 12.5, 4.1 Hz, 1H), 4.14 – 4.04 (m, 1H), 2.40 – 2.31 (m, 2H), 2.28 – 2.17 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.02, 170.11 (x2), 169.84 (x2), 136.43, 116.11, 101.68, 70.01, 67.78, 65.44 (x2), 62.24, 20.88 (x2), 20.76 (x4); HRMS (ESI): calcd for $C_{19}H_{27}NO_{11}$ $[M+Na]^+$ *m/z* = 468.1476, found: 468.1474.



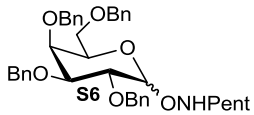
***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (S3):**
Compound **S3** was obtained from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl bromide **3** by procedure A as a white solid (80 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 5.78 (ddt, *J* = 12.7, 10.5, 6.4 Hz, 1H), 5.37 – 5.27 (m, 2H), 5.23 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.08 – 4.95 (m, 3H), 4.73 – 4.56 (m, 1H), 4.26 (dd, *J* = 12.5, 4.1 Hz, 1H), 4.16 – 4.03 (m, 1H), 2.42 – 2.29 (m, 2H), 2.29 – 2.16 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.51, 170.20 (x2), 170.06 (x2), 136.47, 116.08, 104.11, 71.29, 70.55, 66.77 (x2), 61.14, 29.25, 20.89, 20.73, 20.67 (x2), 20.60; HRMS (ESI): calcd for $C_{19}H_{27}NO_{11}$ $[M+Na]^+$ *m/z* = 468.1476, found: 468.1475.



***N*-hydroxypent-4-eneamide *O*-3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxy)carbonylamino-β-D-glucopyranoside (S4):** Protected aminooxy glucosamine **S4** was prepared from thioglycoside **4** by procedure B (74 mg, 76%), from thioimidate **7** following procedure A (74 mg, 70%), or from trifluoroacetimidate **9** by procedure D (58 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 6.12 (app d, 1H), 5.79 (ddt, *J* = 12.9, 10.0, 6.4 Hz, 1H), 5.29 (t, *J* = 9.7 Hz, 1H), 5.10 – 4.91 (m, 4H), 4.86 – 4.74 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.26 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.16 – 4.06 (m, 1H), 3.91 – 3.80 (m, 1H), 3.77 (d, *J* = 7.2 Hz, 1H), 2.42 – 2.32 (m, 2H), 2.29 – 2.15 (m, 2H), 2.07 (s, 3H), 2.00 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.90 (x2), 169.57 (x2), 136.55, 116.05, 95.47, 74.59, 72.33, 71.97, 68.28, 61.88, 54.08, 32.45, 32.16, 29.25, 29.07, 20.82, 20.69, 20.67; HRMS (ESI): calcd for $C_{20}H_{27}N_2O_{11}Cl_3$ $[M+H]^+$ *m/z* = 577.0753, found: 577.0754.

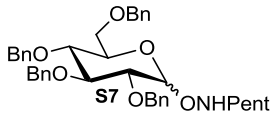


***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (S5):** Glycoside **S5** was obtained from glycosyl fluoride **5** via procedure C (71 mg, 72%) or from glycosyl trifluoroacetimidate **11** following procedure D (85 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.11 (d, *J* = 7.3 Hz, 2H), 8.04 (t, *J* = 6.7 Hz, 4H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.51 (dd, *J* = 14.0, 6.3 Hz, 3H), 7.47 – 7.36 (m, 5H), 7.32 – 7.21 (m, 2H), 6.06 (d, *J* = 3.1 Hz, 1H), 5.92 (dd, *J* = 10.2, 8.2 Hz, 1H), 5.77 – 5.64 (m, 2H), 5.22 (d, *J* = 8.0 Hz, 1H), 5.06 – 4.96 (m, 1H), 4.96 – 4.88 (m, 1H), 4.72 (dd, *J* = 11.0, 6.2 Hz, 1H), 4.53 – 4.40 (m, 2H), 2.43 – 2.30 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.10 (x2), 165.53 (x2), 165.46, 137.94, 136.60, 133.84 (x2), 133.52, 133.48, 130.03 (x3), 129.87 (x6), 129.31, 129.12, 128.81, 128.58 (x3), 128.43 (x2), 128.31, 125.38, 72.04, 71.41, 68.02 (x2), 67.93, 61.97, 21.54 (x2); HRMS (ESI): calcd for $C_{39}H_{35}NO_{11}$ $[M+H]^+$ *m/z* = 694.2283, found: 694.2285.

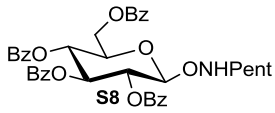


***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (S6):** Galactoside **S6** was given from galactosyl fluoride **6** with procedure C in CH_2Cl_2/Tol (1:1, v:v; 2 mL) as an anomeric mixture (α/β 4:1, 61 mg, 62%) or from galactosyl trifluoroacetimidate **13** via procedure D displaying a

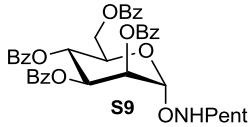
reverse anomeric preference (α/β 1:2, 67 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$, α-isomer) δ 8.12 (s, 1H), 7.51 – 7.18 (m, 20H), 5.79 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 1H), 5.17 (s, 1H), 5.10 – 4.97 (m, 2H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.89 – 4.78 (m, 3H), 4.74 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.29 – 4.09 (m, 2H), 4.01 – 3.90 (m, 2H), 3.61 – 3.51 (m, 2H), 2.44 – 2.32 (m, 2H), 2.35 – 2.06 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.78, 138.56, 138.33, 138.00, 136.68, 128.57, 128.52, 128.50, 128.40, 128.01, 127.95, 127.81, 127.70, 127.63, 116.03, 78.59, 75.73, 74.92, 73.65, 71.15, 69.21, 32.74, 29.83, 29.26; HRMS (ESI): calcd for $C_{39}H_{43}NO_7$ $[M+Na]^+$ *m/z* = 660.2932, found: 660.2937.



***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (S7):** Glucoside **S7** was obtained from thioimidate **8** with procedure A in Et_2O/Tol (4:1, v:v; mL) as an anomeric mixture (α/β 3:1, 74 mg, 65%) or from trifluoroacetimidate **14** via procedure D in CH_2Cl_2/Et_2O (1:1, v:v; mL) as solvent (α/β 1:2.3, 60 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.46 – 7.38 (m, 2H), 7.36 – 7.26 (m, 16H), 7.23 – 7.14 (m, 2H), 5.82 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.18 (s, 1H), 5.09 (d, *J* = 16.3 Hz, 1H), 5.01 (dd, *J* = 22.4, 10.7 Hz, 2H), 4.91 – 4.75 (m, 4H), 4.62 – 4.47 (m, 3H), 4.14 – 4.01 (m, 1H), 3.99 (t, *J* = 9.4 Hz, 1H), 3.76 – 3.65 (m, 3H), 3.62 (t, *J* = 9.5 Hz, 1H), 2.45 – 2.34 (m, 2H), 2.34 – 2.11 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.74, 138.24, 137.98, 137.85, 136.72, 128.59, 128.55, 128.51, 128.48, 128.09, 127.94, 127.83, 127.76, 116.07, 81.62, 78.96, 77.37, 77.16, 76.95, 75.84, 75.17, 73.69, 71.97, 68.75, 32.76, 29.17; HRMS (ESI): calcd for $C_{39}H_{43}NO_7$ $[M+Na]^+$ *m/z* = 660.2932, found: 660.2933.

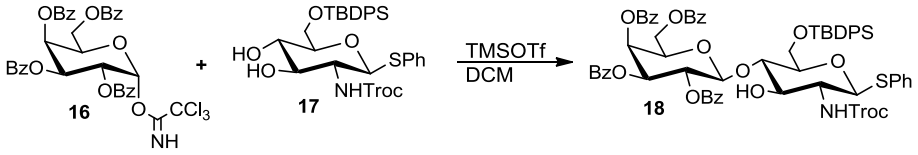


***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (S8):** Following procedure D, glucoside **S8** was given from reaction of trifluoroacetimidate donor **9** as a white solid (110 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.09 – 7.97 (m, 4H), 7.96 – 7.88 (m, 2H), 7.88 – 7.81 (m, 2H), 7.58 – 7.45 (m, 3H), 7.45 – 7.36 (m, 5H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.23 (m, 2H), 6.00 (t, *J* = 9.6 Hz, 1H), 5.74 (t, *J* = 9.7 Hz, 1H), 5.73 – 5.64 (m, 1H), 5.65 (dd, *J* = 9.5, 8.1 Hz, 1H), 5.23 (app d, *J* = 7.5 Hz, 1H), 4.97 (d, *J* = 17.0 Hz, 1H), 4.91 (app d, *J* = 9.1 Hz, 1H), 4.71 (dd, *J* = 12.2, 3.0 Hz, 1H), 4.57 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.32 – 4.22 (m, 1H), 2.36 – 2.23 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.19, 165.75 (x2), 165.20 (x2), 137.92, 136.64, 133.64, 133.45, 133.34, 130.06 (x4), 129.91, 129.85 (x4), 129.83, 129.49, 129.11, 128.67 (x2), 128.52, 128.42, 128.30, 125.38, 77.36, 72.90, 72.58, 70.15, 69.15, 62.76, 21.52 (x2). HRMS (ESI): calcd for $C_{39}H_{35}NO_{11}$ $[M+H]^+$ *m/z* = 694.2283, found: 694.2286.

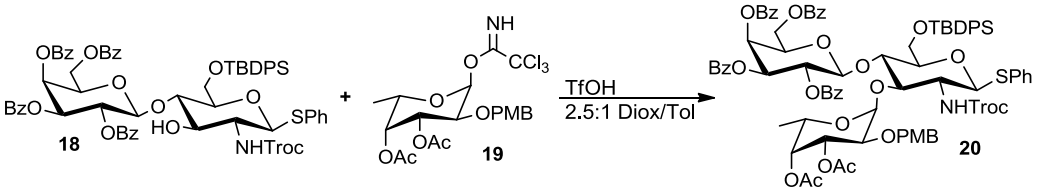


***N*-hydroxypent-4-eneamide *O*-2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (S9):** Compound **S9** was obtained from trifluoroacetimidate donor **12** via procedure D as a white solid (90 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 2H), 7.97 (dd, *J* = 17.1, 7.8 Hz, 4H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.61 – 7.52 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.39 – 7.30 (m, 4H), 7.29 – 7.22 (m, 2H), 6.20 (t, *J* = 9.8 Hz, 1H), 5.93 – 5.87 (m, 2H), 5.87 – 5.79 (m, 1H), 5.41 (s, 1H), 5.30 – 5.15 (m, 1H), 5.08 (dd, *J* = 28.2, 13.7 Hz, 2H), 4.77 (dd, *J* = 12.3, 2.2 Hz, 1H), 4.54 (dd, *J* =

12.4, 3.6 Hz, 1H), 2.47 – 2.38 (m, 2H), 2.35 – 2.26 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.37, 165.92, 165.59, 165.42, 136.57, 133.59, 133.52, 133.40, 133.06, 130.31, 129.98 (x3), 129.98 (x3), 129.96, 129.89, 129.25, 129.21, 129.16, 128.68, 128.65, 128.56 (x2), 128.52 (x2), 128.45, 128.35, 116.16, 102.17, 70.63, 70.60, 68.87, 66.55, 62.91, 32.51, 28.97; HRMS (ESI): calcd for $C_{39}H_{35}NO_{11}$ $[M+Na]^+$ *m/z* = 716.2102, found: 716.2105.

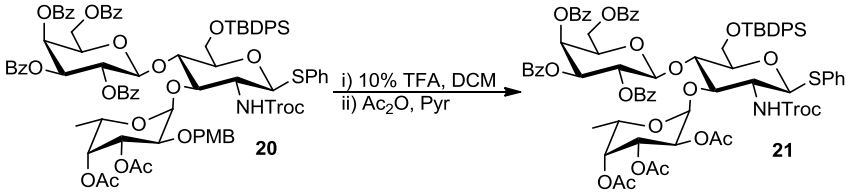


Phenyl (2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-(2,2,2-trichloroethoxy)carbonylamino-1-thio-β-D-glucopyranoside (18): Known galactosyl trichloroacetimidate **16** (738 mg, 0.996 mmol) and glucosamine thioglycoside **17** (750 mg, 1.1 mmol) were dried by coevaporation with anhydrous toluene and left under high vacuum. To the dried mixture was added 4 Å MS and stirred in CH_2Cl_2 (15 mL) for 1h at rt. The solution was cooled to -20 ºC upon which TMSOTf (33 µL, 0.15 mmol) was added dropwise and allowed to warm to rt over 2 h. Upon completion, the reaction was quenched with TEA and filtered to remove sieves. The concentrated residue was purified by silica flash chromatography (Hex/EtOAc gradient) to obtain disaccharide **18** as a white powder (1.01g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.10 (m, 4H), 7.90 – 7.79 (m, 6H), 7.75 (t, *J* = 10.8 Hz, 2H), 7.69 – 7.40 (m, 14H), 7.39 – 7.31 (m, 2H), 7.28 (dd, *J* = 14.3, 6.5 Hz, 2H), 7.26 – 7.17 (m, 5H), 6.06 (d, *J* = 3.3 Hz, 1H), 5.95 (dd, *J* = 10.4, 8.2 Hz, 1H), 5.67 (dd, *J* = 10.5, 3.4 Hz, 1H), 5.55 (d, *J* = 8.6 Hz, 1H), 5.23 (d, *J* = 8.1 Hz, 1H), 4.93 (dd, *J* = 15.5, 11.4 Hz, 2H), 4.81 – 4.70 (m, 2H), 4.61 – 4.50 (m, 1H), 4.40 – 4.32 (m, 1H), 4.22 (t, *J* = 9.1 Hz, 1H), 4.09 – 3.99 (m, 2H), 3.87 (dd, *J* = 35.3, 10.7 Hz, 2H), 3.63 (dd, *J* = 19.1, 9.7 Hz, 1H), 3.40 (d, *J* = 9.5 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.54, 166.06, 165.90, 165.49, 154.72, 136.48, 135.93 (x2), 134.33, 134.23, 133.94 (x2), 132.56, 132.38, 130.71, 130.51, 130.46 (x5), 130.39, 130.28, 130.13, 129.79, 129.41, 129.25, 129.22, 129.11 (x5), 129.06, 129.00, 128.87, 128.63, 128.30, 128.18, 127.99, 101.32, 96.11, 86.66, 78.78, 78.68, 77.95, 77.89, 77.69, 77.44, 75.03, 73.57, 72.84, 72.04, 70.09, 68.71, 62.63, 61.94, 60.97, 57.38, 27.34, 21.58, 19.92, 14.72. HRMS (ESI): calcd for $C_{65}H_{62}NO_{15}Cl_3SSi$ $[M+Na]^+$ *m/z* = 1284.2567, found: 1284.2598.

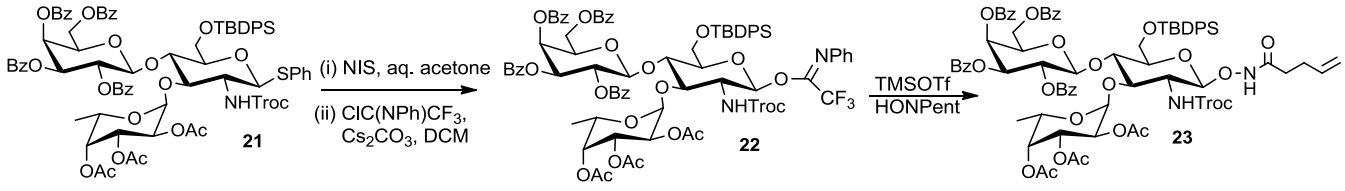


Phenyl (2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)[(1→3)-3,4-di-*O*-acetyl-2-*O*-(*para*-methoxybenzyl)-α-L-fucopyranosyl]-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-(2,2,2-trichloro-ethoxy)carbonylamino-1-thio-β-D-glucopyranoside (20): A mixture of known fucose trichloroacetimidate **19** (153 mg, 0.299 mmol) and disaccharide **18** (210 mg, 0.17 mmol) were dried by coevaporation with anhydrous toluene and left under high vacuum. To the dried mixture was added 4 Å MS and stirred in Tol/Diox (1:2.5, v:v; 3 mL) for 1h at rt. The solution was cooled to -5 ºC upon which TfOH (3 µL, 0.03 mmol) was added dropwise and allowed to warm to rt over 1 h. Upon completion, the reaction was quenched with TEA, filtered, and concentrated under vacuum. The resulting residue was purified by silica flash chromatography (Hex/EtOAc gradient) to obtain trisaccharide **20** as a white solid (190 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.87 – 7.79 (m, 6H), 7.63 – 7.54 (m, 5H), 7.52 – 7.42 (m, 6H), 7.42 – 7.36 (m, 4H), 7.36 – 7.29 (m, 6H), 7.29 – 7.26 (m, 2H), 7.23 – 7.10 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.95 (d, *J* = 2.8 Hz, 1H), 5.69 (dt, *J* = 12.5, 8.2 Hz, 1H), 5.62 – 5.56 (m, 1H), 5.53 (dd, *J* = 10.5, 3.7 Hz, 1H), 5.47 (d, *J* = 2.5 Hz, 1H), 5.41

(dd, *J* = 10.6, 3.1 Hz, 2H), 5.28 (d, *J* = 8.3 Hz, 1H), 5.02 (d, *J* = 4.3 Hz, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.84 (dd, *J* = 11.3, 7.0 Hz, 1H), 4.73 – 4.66 (m, 3H), 4.64 (d, *J* = 10.7 Hz, 1H), 4.27 – 4.14 (m, 3H), 3.99 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.88 (dd, *J* = 22.8, 10.8 Hz, 2H), 3.78 (s, 3H), 3.33 – 3.18 (m, 1H), 3.06 (d, *J* = 8.0 Hz, 1H), 2.21 (s, 3H), 1.98 (s, 3H), 1.29 – 1.23 (m, 3H), 1.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.57, 169.77, 166.15, 165.91, 165.33, 164.91, 159.65, 153.87, 136.16, 135.45, 133.71, 133.44, 133.39, 133.33, 133.20, 132.54, 131.99, 130.51, 130.03, 129.98, 129.91, 129.84, 129.71, 129.51, 129.04, 128.79, 128.57, 128.48, 128.43, 128.37, 127.95, 127.83, 114.10, 100.41, 97.74, 95.78, 79.45, 77.36, 74.56, 74.42, 73.98, 72.39, 71.90, 71.71, 71.20, 69.78, 68.13, 65.08, 61.46, 61.19, 55.39, 27.00, 21.00, 20.96, 19.45, 16.18; HRMS (ESI): calcd for $C_{83}H_{84}NO_{22}Cl_3SSi$ $[M+Na]^+$ *m/z* = 1634.3933, found: 1634.3914.

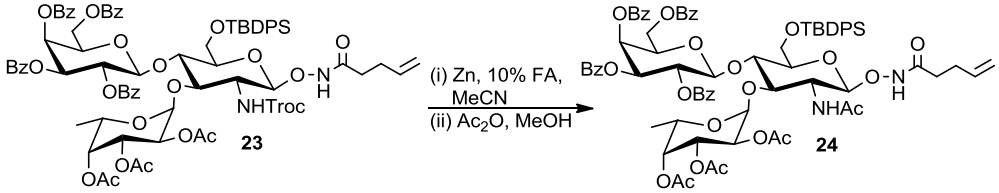


Phenyl (2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)[(1→3)-2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl]-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-(2,2,2-trichloroethoxy)carbonylamino-1-thio-β-D-glucopyranoside (21): Trisaccharide **20** (190 mg, 0.12 mmol) was dissolved in 10% TFA/CH_2Cl_2 (5 mL) and stirred at rt for 30 min. The reaction was concentrated under reduced pressure and excess TFA removed by coevaporation with toluene. To the resulting residue was added pyridine/Ac_2O (2:1, v:v; 3 mL) and stirred for 3 h at rt. The acetylated product was concentrated under vacuum and purified by silica column chromatography (Hex/EtOAc gradient) to afford the differentially protected trisaccharide **21** as a white solid (168 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.12 (m, 2H), 7.95 (dd, *J* = 9.8, 2.7 Hz, 2H), 7.88 – 7.76 (m, 5H), 7.72 (d, *J* = 6.7 Hz, 1H), 7.64 – 7.55 (m, 6H), 7.55 – 7.37 (m, 10H), 7.37 – 7.30 (m, 1H), 7.30 – 7.23 (m, 4H), 7.19 (dt, *J* = 13.3, 7.0 Hz, 4H), 5.96 (d, *J* = 3.7 Hz, 1H), 5.70 (dd, *J* = 10.3, 8.5 Hz, 1H), 5.67 – 5.62 (m, 1H), 5.61 – 5.55 (m, 1H), 5.53 – 5.47 (m, 1H), 5.47 – 5.41 (m, 1H), 5.33 (d, *J* = 8.4 Hz, 1H), 5.20 (dd, *J* = 12.8, 6.3 Hz, 1H), 5.16 – 5.10 (m, 1H), 5.10 – 5.03 (m, 1H), 5.00 – 4.83 (m, 3H), 4.62 – 4.48 (m, 2H), 4.29 (t, *J* = 8.9 Hz, 1H), 4.22 – 4.15 (m, 1H), 4.00 – 3.91 (m, 2H), 3.85 (d, *J* = 11.0 Hz, 1H), 3.12 (d, *J* = 9.5 Hz, 1H), 2.19 (s, 3H), 1.97 (s, 2H), 1.87 (s, 3H), 1.36 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.57, 169.77, 166.15, 165.91, 165.65, 165.33, 164.91, 153.87, 136.16, 135.45, 133.71, 133.44, 133.39, 133.33, 133.20, 132.54, 131.99, 130.51, 130.03, 129.98, 129.91, 129.84, 129.71, 129.51, 129.04, 128.79, 128.57, 128.48, 128.43, 128.37, 127.95, 127.83, 100.41, 97.74, 95.78, 79.45, 77.36, 74.56, 74.42, 73.98, 72.39, 71.90, 71.71, 71.20, 69.78, 68.13, 65.08, 61.46, 61.19, 27.00, 21.00, 20.96, 20.48, 19.45, 16.18; HRMS (ESI): calcd for $C_{77}H_{78}NO_{22}Cl_3SSi$ $[M+Na]^+$ *m/z* = 1556.3463, found: 1556.3441.



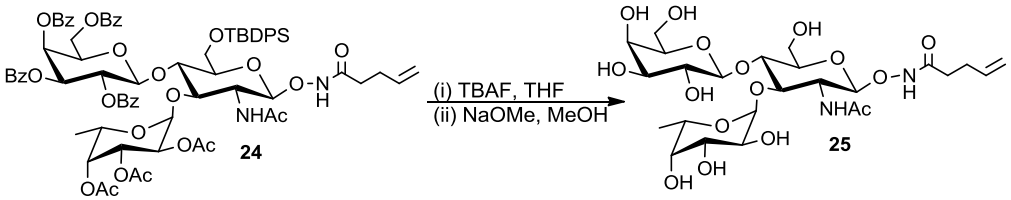
***N*-hydroxypent-4-eneamide (2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)[(1→3)-3,4-di-*O*-acetyl-2-*O*-(*para*-methoxybenzyl)-α-L-fucopyranosyl]-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-(2,2,2-trichloroethoxy)carbonylamino-β-D-glucopyranoside (23):** Thioglycoside **21** (199 mg, 0.128 mmol) was dissolved in acetone/CH_2Cl_2/H_2O (15:1:1, v:v; 6 mL) and NIS (47 mg, 0.21 mmol) was added while stirring at rt. The reaction was monitored by TLC (2:1, Hex/EtOAc) and NBS was added in 2 equivalent portions until complete. Upon full hydrolysis, the resulting hemiacetal was diluted in

CH_2Cl_2 and washed sequentially with $Na_2S_2O_3$ solution, $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (2.5 mL) and Cs_2CO_3 (85 mg, 0.26 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (42 µL, 0.26 mmol) dropwise. The reaction mixture was stirred for 16 h at rt under N_2 after which it was diluted with CH_2Cl_2, filtered, and concentrated under vacuum. The crude residue was passed through a silica chromatography column to give the pure trifluoroacetimidate **22** as a yellow oil (168 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 7.95 (m, 4H), 7.87 – 7.63 (m, 8H), 7.66 – 7.47 (m, 9H), 7.49 – 7.28 (m, 6H), 7.29 – 7.03 (m, 8H), 7.05 – 6.94 (m, 1H), 6.73 – 6.62 (m, 1H), 5.98 (d, *J* = 3.5 Hz, 1H), 5.73 (dt, *J* = 18.7, 9.5 Hz, 1H), 5.67 – 5.53 (m, 2H), 5.53 – 5.45 (m, 2H), 5.31 (dd, *J* = 14.8, 6.4 Hz, 1H), 5.24 – 5.04 (m, 4H), 4.94 (d, *J* = 7.6 Hz, 1H), 4.90 – 4.81 (m, 1H), 4.68 – 4.50 (m, 1H), 4.39 – 4.23 (m, 2H), 4.23 – 3.91 (m, 4H), 3.86 – 3.59 (m, 1H), 3.57 – 3.12 (m, 1H), 2.20 (s, 3H), 1.98 (s, 3H), 1.86 (s, 3H), 1.45 – 1.34 (m, 3H), 1.07 – 0.89 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.33, 169.56, 166.33, 166.03, 165.29, 164.90, 136.14, 135.44, 135.40, 133.51, 133.30, 130.57, 130.15, 130.05, 129.92, 129.84, 129.67, 129.17, 128.89, 128.86, 128.66, 128.60, 128.49, 128.45, 128.37, 127.93, 101.09, 95.51, 75.21, 73.83, 72.09, 71.96, 69.94, 68.67, 65.12, 61.97, 61.60, 27.00, 26.92, 21.04, 20.72, 20.59, 19.35, 16.18, 14.30. A mixture of trifluoroacetimidate **22** (115 mg, 0.0712 mmol) and *N*-pentenoyl hydroxamic acid **1** (12 mg, 0.11 mmol) were dried by coevaporation with anhydrous toluene and left under high vacuum. To the dried mixture was added 3 Å MS and stirred in CH_2Cl_2 (1.5 mL) for 1 h at rt under N_2. The solution was cooled to -20 ºC upon which TMSOTf (13 µL, 0.071 mmol) was added dropwise and allowed to warm to rt over 1.5 h. The reaction was quenched with TEA, filtered, and concentrated under vacuum. The resulting residue was purified by silica flash chromatography (Tol/Acetone gradient) to obtain *N*-hydroxypentenoyl trisaccharide **23** as a white solid (70 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.1 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.86 – 7.75 (m, 4H), 7.75 – 7.63 (m, 4H), 7.63 – 7.36 (m, 14H), 7.31 – 7.12 (m, 4H), 5.96 (d, *J* = 3.4 Hz, 1H), 5.69 (dd, *J* = 10.3, 8.4 Hz, 2H), 5.65 – 5.49 (m, 3H), 5.49 – 5.37 (m, 2H), 5.23 (d, *J* = 8.3 Hz, 1H), 5.20 – 5.06 (m, 2H), 5.05 – 4.89 (m, 4H), 4.85 (dd, *J* = 11.7, 5.7 Hz, 1H), 4.62 (app d, *J* = 11.7 Hz, 2H), 4.27 – 4.10 (m, 2H), 4.05 (app d, *J* = 10.9 Hz, 2H), 3.92 – 3.75 (m, 2H), 3.10 (d, *J* = 9.0 Hz, 1H), 2.41 – 2.22 (m, 4H), 2.19 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 0.99 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.43, 169.69, 166.19, 165.89, 165.20, 164.80, 137.89, 136.11, 135.35, 133.53, 133.30, 133.16, 132.30, 130.49, 130.13, 130.04, 129.81, 129.65, 129.57, 129.30, 129.06, 128.82, 128.78, 128.70, 128.53, 128.32, 128.30, 128.26, 127.89, 125.33, 116.01, 100.81, 95.61, 95.19, 75.47, 74.92, 73.83, 73.63, 72.61, 71.76, 71.48, 69.62, 68.42, 68.16, 67.81, 64.77, 61.54, 60.90, 55.86, 26.86, 21.47, 20.99, 20.77, 20.65, 19.26, 16.01. HRMS (ESI): calcd for $C_{76}H_{81}N_2O_{24}Cl_3Si$ $[M+Na]^+$ *m/z* = 1561.3906, found: 1561.3896.

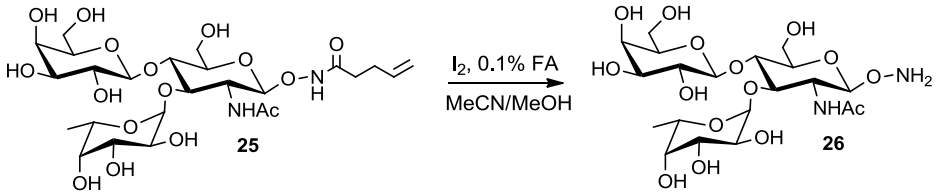


***N*-hydroxypent-4-eneamide (2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)[(1→3)-3,4-di-*O*-acetyl-2-*O*-(*para*-methoxybenzyl)-α-L-fucopyranosyl]-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-acetamido-β-D-glucopyranoside (24):** To a solution of *N*-hydroxypentenoyl trisaccharide **23** (82 mg, .053 mmol) in 10% FA/MeCN (2 mL) was added activated Zn (300 mg) and stirred for 2 h. The suspension was filtered to remove catalyst, concentrated under vacuum, and coevaporated with toluene to remove excess FA. The crude free amine was dissolved in anhydrous MeOH (2 mL) and Ac_2O (25 µL, 0.27 mmol) and DIPEA (11 µL, 0.064 mmol) were added dropwise while stirring at 0 ºC under N_2. After 1.5 h, the reaction was allowed to warm to rt, diluted with MeOH, and concentrated under vacuum. The resulting residue was purified by silica flash chromatography (Tol/Acetone gradient) to

give the acetylated trisaccharide **24** as a white solid (55 mg, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.15 (d, *J* = 6.5 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.79 (dd, *J* = 19.0, 7.2 Hz, 4H), 7.73 – 7.61 (m, 4H), 7.61 – 7.51 (m, 6H), 7.51 – 7.37 (m, 8H), 7.30 – 7.13 (m, 4H), 6.13 (d, *J* = 8.9 Hz, 1H), 5.94 (2s, *J* = 3.6 Hz, 1H), 5.78 – 5.68 (m, 1H), 5.68 – 5.62 (m, 1H), 5.57 – 5.48 (m, 2H), 5.47 – 5.37 (m, 2H), 5.18 (d, *J* = 6.9 Hz, 1H), 5.15 – 5.10 (m, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.92 – 4.85 (m, 1H), 4.54 (d, *J* = 8.1 Hz, 1H), 4.24 – 4.17 (m, 1pH), 4.17 – 4.10 (m, 1H), 4.01 (t, *J* = 9.3 Hz, 2H), 3.81 (d, *J* = 11.3 Hz, 1H), 3.74 (app t, *J* = 6.4 Hz, 2H), 3.09 (d, *J* = 8.8 Hz, 1H), 2.37 – 2.22 (m, 4H), 2.18 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.94 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.63, 171.43, 170.46, 169.76, 166.29, 165.99, 165.27, 165.03, 137.99, 136.51, 136.25, 135.42, 133.60, 133.39, 133.26, 130.58, 130.15, 129.90, 129.74, 129.65, 129.43, 129.16, 128.96, 128.86, 128.81, 128.65, 128.63, 128.45, 128.40, 128.35, 128.08, 125.43, 115.95, 102.43, 100.82, 100.12, 95.71, 75.74, 73.92, 73.66, 72.65, 71.90, 71.59, 69.74, 68.32, 68.28, 68.09, 68.05, 64.87, 61.61, 61.02, 32.67, 29.98, 29.01, 26.91, 25.73, 23.60, 21.57, 21.02, 20.84, 20.76, 19.31, 16.11. HRMS (ESI): calcd for $C_{75}H_{82}N_2O_{23}Si$ $[M+Na]^+$ *m/z* = 1429.4970, found: 1429.4954.

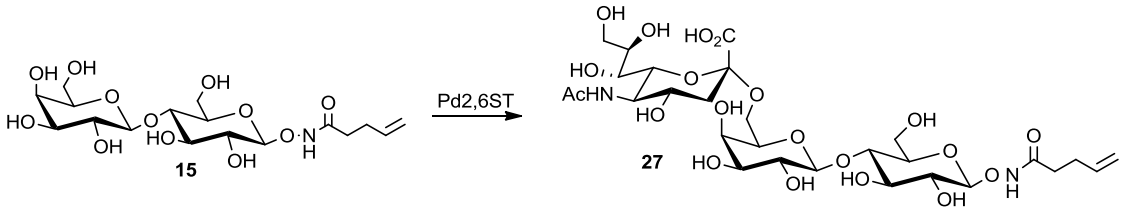


***N*-hydroxypent-4-eneamide (β-D-galactopyranosyl)-(1→4)[(1→3)-α-L-fucopyranosyl]-2-deoxy-2-acetamido-β-D-glucopyranoside (25):** A solution of *N*-hydroxypentenoyl trisaccharide **24** (53 mg, 0.038 mmol) in THF (2 mL) was cooled to 0 ºC and TBAF (1 M in THF, 68 µL) was added dropwise under N_2. The mixture was allowed to warm to rt and stirred 18 h after which it was diluted with EtOAc and concentrated under reduced pressure. The resulting residue was dissolved in MeOH (2 mL) and NaOMe (25% in MeOH, 30 µL) was added dropwise while stirring at rt. After 7 h, the reaction was quenched by addition of Dowex 50W-X8 (H^+) until pH 7 and filtered to remove resin. The crude product was concentrated under vacuum and purified by silica column chromatography (20% - 30% MeOH/CH_2Cl_2). The purified residue was filtered to remove trace silica and lyophilized to yield the deprotected *N*-hydroxypentenoyl Le^x **25** as a white powder (18 mg, 76%). ^{1}H NMR (600 MHz, D_2O) δ 5.81 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.12 – 5.00 (m, 3H), 4.82 (d, *J* = 6.3 Hz, 1H), 4.43 (d, *J* = 7.8 Hz, 1H), 4.02 (t, *J* = 9.3 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.92 – 3.83 (m, 4H), 3.77 (d, *J* = 3.1 Hz, 1H), 3.75 – 3.65 (m, 3H), 3.63 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.61 – 3.55 (m, 2H), 3.47 (dd, *J* = 9.7, 8.0 Hz, 1H), 2.38 – 2.28 (m, 2H), 2.24 (app t, *J* = 7.0 Hz, 2H), 2.02 (s, 3H), 1.15 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, D_2O) δ 174.53, 172.56, 136.58, 115.85, 103.63, 101.81, 98.64, 75.65, 74.92, 74.68, 72.96, 72.46, 71.89, 71.01, 69.21, 68.33, 67.69, 66.73, 61.46, 59.62, 53.60, 46.68, 31.75, 28.82, 22.30, 15.28, 8.21; HRMS (ESI): calcd for $C_{25}H_{42}N_2O_{16}$ $[M+Na]^+$ *m/z* = 649.2427, found: 649.2425.

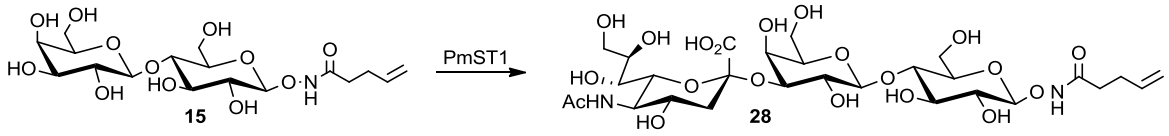


Aminooxy β-D-galactopyranosyl-(1→4)[(1→3)-α-L-fucopyranosyl]-2-deoxy-2-acetamido-β-D-glucopyranoside (26): A solution of *N*-hydroxypentenoyl Le^x **25** (4.8 mg, 0.0077 mmol) in MeCN/MeOH/FA (3:1:0.001, v:v; 1.4 mL) was stirred at rt with dropwise addition of I_2 (0.023 mmol, 0.5 M solution in THF). The mixture was stirred for 1.5 h at rt followed by additional heating at 35 ºC for 30 min after which the reaction was quenched with aqueous NH_4HCO_3 (500 mM) and $Na_2S_2O_3$ (50

mM) until the disappearance of color. The solvent was removed under reduced pressure and the remaining residue was purified by silica flash chromatography (EtOAc/MeOH/H_2O). The desired fractions were pooled and concentrated under vacuum. After redissolving in ddH_2O, the purified product was lyophilized to give the free aminooxy Le^x **26** (2.9 mg, 70%) as a white powder. ^{1}H NMR (500 MHz, D_2O) δ 5.11 (d, *J* = 4.0 Hz, 1H), 4.63 (d, *J* = 8.6 Hz, 1H), 4.44 (d, *J* = 7.8 Hz, 1H), 4.04 – 3.99 (m, 1H), 3.98 – 3.91 (m, 2H), 3.89 (dd, *J* = 9.2, 5.1 Hz, 3H), 3.85 (d, *J* = 4.2 Hz, 1H), 3.78 (d, *J* = 2.9 Hz, 1H), 3.76 – 3.68 (m, 3H), 3.66 (dd, *J* = 6.3, 3.7 Hz, 1H), 3.65 – 3.63 (m, 1H), 3.63 – 3.57 (m, 2H), 3.52 – 3.46 (m, 1H), 2.02 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, D_2O) δ 174.46, 103.36, 101.84, 98.62, 75.32, 74.91, 73.25, 72.47, 71.91, 71.04, 69.21, 68.34, 67.71, 66.72, 61.46, 59.80, 54.01, 22.19, 15.29; HRMS (ESI): calcd for $C_{20}H_{36}N_2O_{15}$ $[M+H]^+$ *m/z* = 545.2188, found: 545.2187.

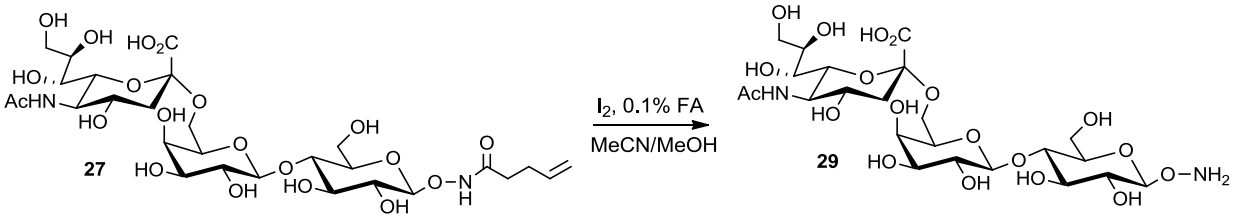


***N*-hydroxypent-4-eneamide (5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosyl-onic acid)-(2→6)-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (27):** To *N*-pentenoyl aminooxy lactose **15** (12 mg, 0.027 mmol) was added *N*-acetylmannosamine (9 mg, 0.04 mmol), sodium pyruvate (15 mg, 0.14 mmol), and CTP•Na (23 mg, 0.041 mmol) and dissolved in H_2O (1.5 mL). A concentrated stock of Tris-HCl buffer pH 8.5 with $MgCl_2$ was added to a final concentration of 100 mM Tris, 20 mM $MgCl_2$. Recombinant *E. coli* K12 sialic acid aldolase (2.5 U), *N. meningitidis* CMP-sialic acid synthetase (1.5 U), and *P. damsela* α-2,6-sialyltransferase (1.5 U) were added followed by H_2O to bring the volume to 2 mL. The reaction mixture was incubated at 37 ºC for 2 h followed by shaking at rt for 16 h. The reaction was monitored by TLC (4:2:1 EtOAc/MeOH/H_2O) and upon completion calf alkaline phosphatase was added to remove remaining nucleotide phosphate. After further incubation at 37 ºC for 1 h, the reaction mixture was quenched with cold MeOH (2 mL) and incubated on ice 20 min. The mixture was centrifuged, precipitates removed, and concentrated under vacuum. The resulting residue was passed through a BioGel P-2 size exclusion column and eluted with water to obtain **27** (16.2 mg, 81%) as a white, fluffy powder after lyophilization. ^{1}H NMR (500 MHz, D_2O) δ 5.96 – 5.79 (m, 1H), 5.19 – 5.05 (m, 2H), 4.76 (d, *J* = 8.3 Hz, 1H, H-1), 4.47 (d, *J* = 7.9 Hz, 1H, H-1'), 4.05 – 3.95 (m, 3H), 3.95 – 3.80 (m, 5H), 3.79 – 3.62 (m, 8H), 3.62 – 3.50 (m, 3H), 2.75 (dd, *J* = 12.4, 4.7 Hz, 1H), 2.41 (dd, *J* = 13.0, 6.2 Hz, 2H), 2.37 – 2.30 (m, 2H), 2.08 (s, 3H), 1.77 (t, *J* = 12.2 Hz, 1H); ^{13}C NMR (125 MHz, D_2O): δ 174.86, 173.44, 172.71, 136.36, 115.98, 104.99, 103.11, 100.24, 78.83, 74.84, 74.82, 74.33, 73.63, 72.47, 72.27, 71.74, 70.84, 70.70, 68.45, 68.30, 63.52, 62.56, 59.92, 51.73, 40.06, 31.68, 28.89, 21.99; HRMS (ESI): calcd for $C_{28}H_{46}N_2O_{20}$ $[M-H]^-$ *m/z* = 729.2571, found: 729.2551.

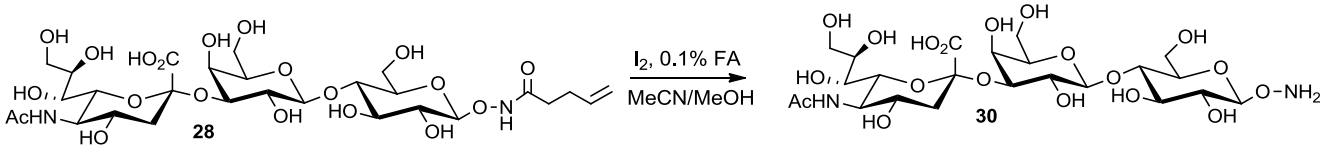


***N*-hydroxypent-4-eneamide (5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→3)-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (28):** To *N*-pentenoyl aminooxy lactose **15** (20 mg, 0.046 mmol) was added *N*-acetyl mannosamine (15 mg, 0.069 mmol), sodium pyruvate (25 mg, 0.23 mmol), and CTP•Na (36 mg, 0.069 mmol) and dissolved in H_2O (2 mL). A concentrated stock of Tris-HCl buffer pH 8.5 with $MgCl_2$ was added to a final concentration of 100 mM Tris, 20 mM $MgCl_2$. Recombinant *E. coli* K12 sialic acid aldolase (2.5 U), *N. meningitidis* CMP-sialic acid synthetase (2.5 U), and *P. multocida* α-2,3-sialyltransferase (1.5 U) were added followed by

H_2O to bring the volume to 4 mL. The reaction mixture was incubated at 37 ºC for 2 h followed by shaking at rt for 16 h. The reaction was monitored by TLC (4:2:1 EtOAc/MeOH/H_2O) and upon completion calf alkaline phosphatase was added to remove remaining nucleotide phosphate. After further incubation at 37 ºC for 2 h, the reaction mixture was quenched with cold MeOH (3 mL) and incubated on ice 20 min. The mixture was centrifuged, precipitates removed, and concentrated under vacuum. The resulting residue was passed through a BioGel P-2 size exclusion column and eluted with water to obtain **28** (32 mg, 95%) as a white, fluffy powder after lyophilization. ^{1}H NMR (500 MHz, D_2O) δ 5.80 (ddt, *J* = 16.9, 10.3, 6.4 Hz, 1H), 5.14 – 4.96 (m, 2H), 4.68 (d, *J* = 8.2 Hz, 1H, H-1), 4.50 (d, *J* = 7.8 Hz, 1H, H-1'), 4.08 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.98 – 3.89 (m, 2H), 3.89 – 3.77 (m, 4H), 3.75 – 3.50 (m, 11H), 3.44 (t, *J* = 8.6 Hz, 1H), 2.72 (dd, *J* = 12.4, 4.6 Hz, 1H), 2.39 – 2.30 (m, 2H), 2.30 - 2.23 (m, 2H), 2.01 (s, 3H), 1.76 (t, *J* = 12.1 Hz, 1H); ^{13}C NMR (126 MHz, D_2O) δ 174.96, 173.84, 136.36, 115.98, 105.14, 102.56, 99.74, 77.49, 75.42, 75.13, 74.98, 74.05, 72.83, 71.73, 70.94, 69.31, 68.31, 68.03, 67.41, 62.52, 60.99, 59.74, 51.63, 39.59, 31.66, 28.89, 21.99; HRMS (ESI): calcd for $C_{28}H_{46}N_2O_{20}$ [M-H]$^-$ *m/z* = 729.2571, found: 729.2559.



Aminooxy (5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (29): A solution of *N*-pentenoyl aminooxy sialoside **27** (5.9 mg, 0.0081 mmol) in MeCN/MeOH/FA (3:1:0.001, v:v; 2 mL) was stirred at rt with dropwise addition of I_2 (.024 mmol, 0.5 M solution in THF). The mixture was heated to 35 ºC and stirred for 3 h after which the reaction was quenched with the addition of aqueous NH_4HCO_3 (500 mM) and $Na_2S_2O_3$ (50 mM) until the disappearance of color. The solvent was removed and the remaining residue was dissolved in ddH_2O followed by purification via size exclusion chromatography (BioGel P-2). The compound was eluted with ddH_2O and desired fractions were pooled and lyophilized to give the free aminooxy sialoside **29** (4.3 mg, 82%) as a white powder. ^{1}H NMR (600 MHz, D_2O) δ 4.65 (d, *J* = 8.3 Hz, 1H, H-1), 4.41 (d, *J* = 8.0 Hz, 1H, H-1'), 4.02 – 3.90 (m, 3H), 3.90 – 3.77 (m, 5H), 3.74 – 3.59 (m, 8H), 3.59 – 3.48 (m, 2H), 3.39 (t, *J* = 8.7 Hz, 1H), 2.70 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.02 (s, 3H), 1.72 (t, *J* = 12.1 Hz, 1H). ^{13}C NMR (151 MHz, D_2O) δ 174.93, 173.42, 104.47, 103.20, 100.29, 79.35, 74.63 (x2), 73.71, 72.54, 72.37, 71.79, 71.25, 70.79 (x2), 68.52, 68.35, 63.57, 62.67, 60.22, 51.79, 40.08, 22.06; HRMS (ESI): calcd for $C_{23}H_{40}N_2O_{19}$ [M-H]$^-$ *m/z* = 647.2152, found: 647.2142.



Aminooxy (5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (30): A solution of *N*-pentenoyl aminooxy sialoside **28** (5.2 mg, 0.0071 mmol) in MeCN/MeOH/FA (3:1:0.001, v:v; 2 mL) was stirred at rt with dropwise addition of I_2 (0.021 mmol, 0.5 M solution in THF). The mixture was heated to 37 ºC and stirred for 2 h after which the reaction was quenched with the addition of 500 mM NH_4HCO_3, 50 mM $Na_2S_2O_3$ in H_2O until clear. The solvent was removed and the remaining residue was passed through a short silica chromatography column (EtOAc/MeOH/H_2O). The desired fractions were pooled and lyophilized to give the free aminooxy sialoside **30** (3.4 mg, 74%) as a white powder. ^{1}H NMR (500 MHz, D_2O) δ 4.57

(d, *J* = 8.3 Hz, 1H, H-1), 4.49 (d, *J* = 7.9 Hz, 1H, H-1'), 4.08 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.98 (dd, *J* = 12.2, 1.9 Hz, 1H), 3.92 (d, *J* = 3.0 Hz, 1H), 3.89 – 3.78 (m, 4H), 3.76 – 3.51 (m, 11H), 3.35 – 3.28 (m, 1H), 2.72 (dd, *J* = 12.4, 4.6 Hz, 1H), 2.00 (s, 3H), 1.77 (t, *J* = 12.1 Hz, 1H); ^{13}C NMR (126 MHz, D_2O) δ 174.95, 173.86, 104.81, 102.58, 99.74, 77.93, 75.40, 75.11, 74.66, 74.33, 72.82, 71.72, 71.30, 69.31, 68.32, 68.03, 67.40, 62.51, 60.98, 59.93, 51.62, 39.57, 21.98; HRMS (ESI): calcd for $C_{23}H_{40}N_2O_{19}$ $[M-H]^-$ *m/z* = 647.2152, found: 647.2144.

Table S1. Stability of hGH-Lac glycoconjugate under various storage conditions

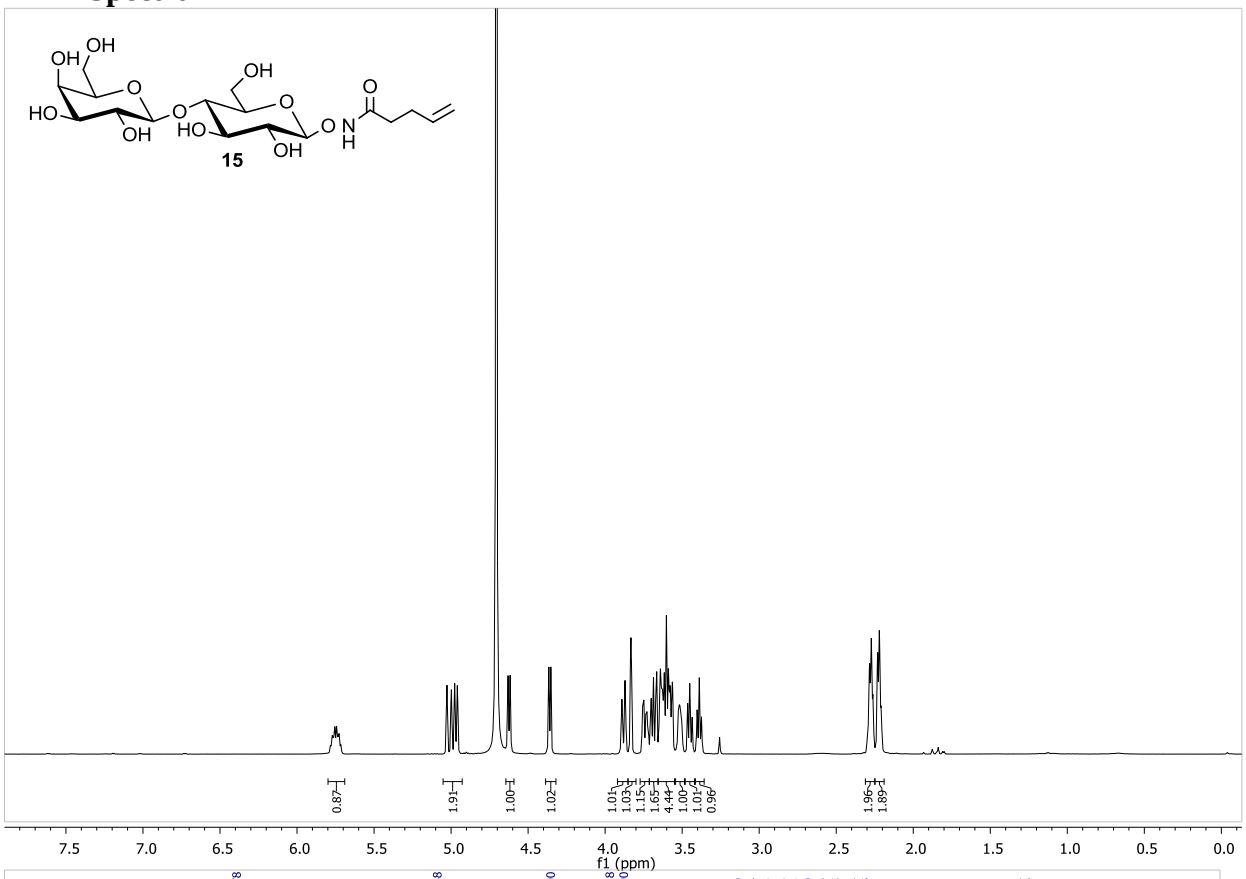
		% remaining conjugate[a]		
Temp	**pH**	**1 day**	**4 days**	**8 days**
-20 ºC	7	100 ± 2	99 ± 2	99 ± 2
4 ºC	7	93 ± 3	96 ± 3	92 ± 3
	4.5	96 ± 2	98 ± 2	92 ± 3
22 ºC (rt)	7	89 ± 4	72 ± 4	N.D.[b]
	4.5	96 ± 4	73 ± 3	N.D.[b]

[a] Percentages of hGH+Lac/hGH were monitored by MALDI-MS and normalized to day 0.
[b] Major protein degradation was observed which hampered MS analysis

References

(1) Rodriguez, E.; Marcaurelle, L.; Bertozzi, C. *J. Org. Chem.* **1998**, *63*, 7134-7135.

NMR Spectra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1.00
1.02
1.01
1.03
1.15
1.65
4.44
1.00
1.01
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1.96
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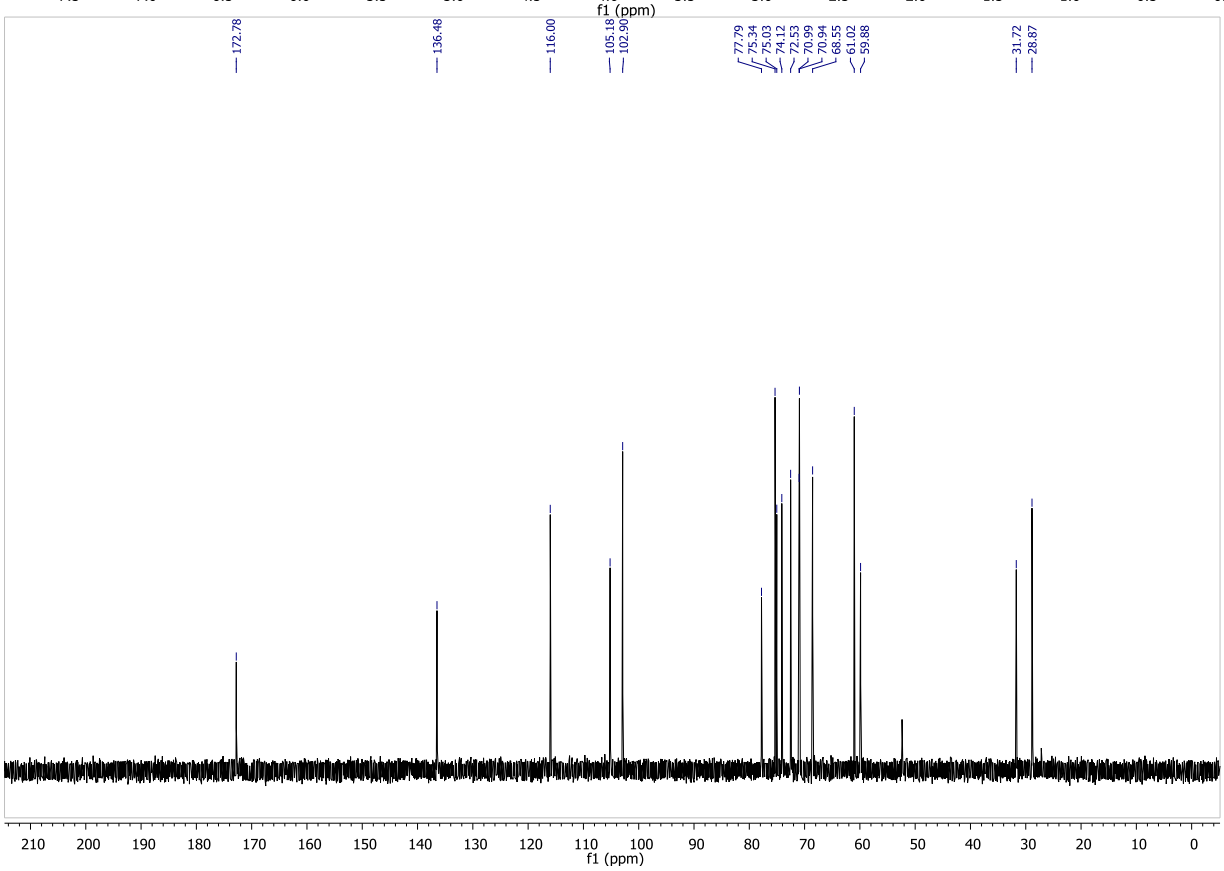
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75.34
75.03
74.12
72.53
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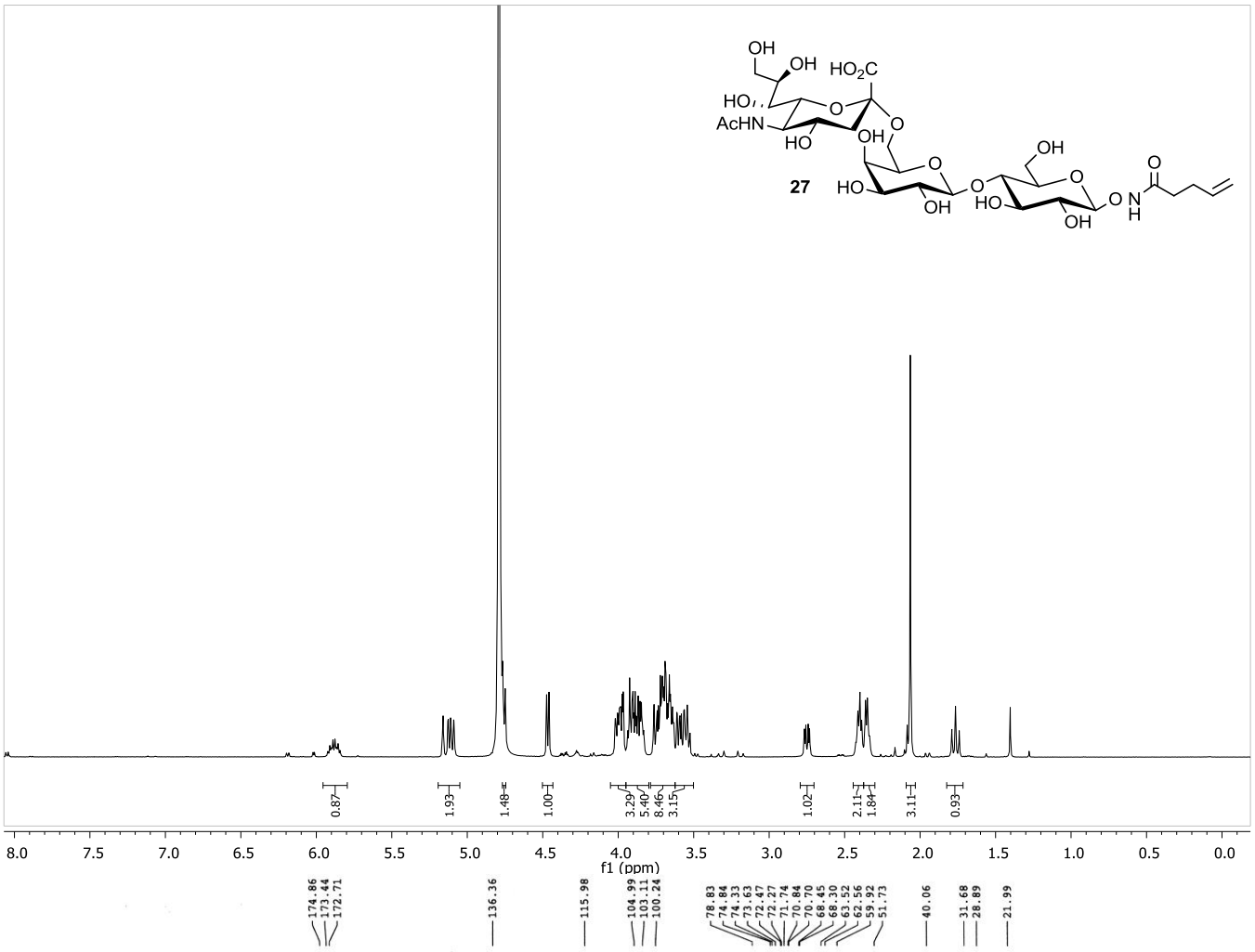
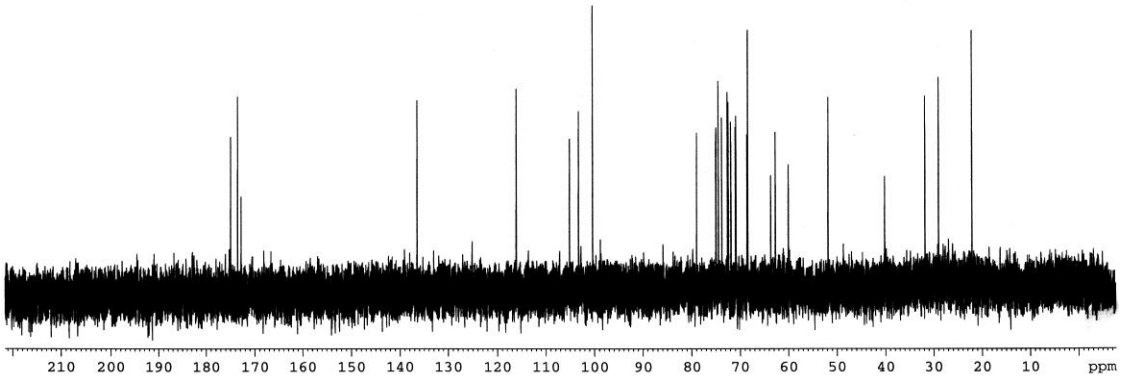
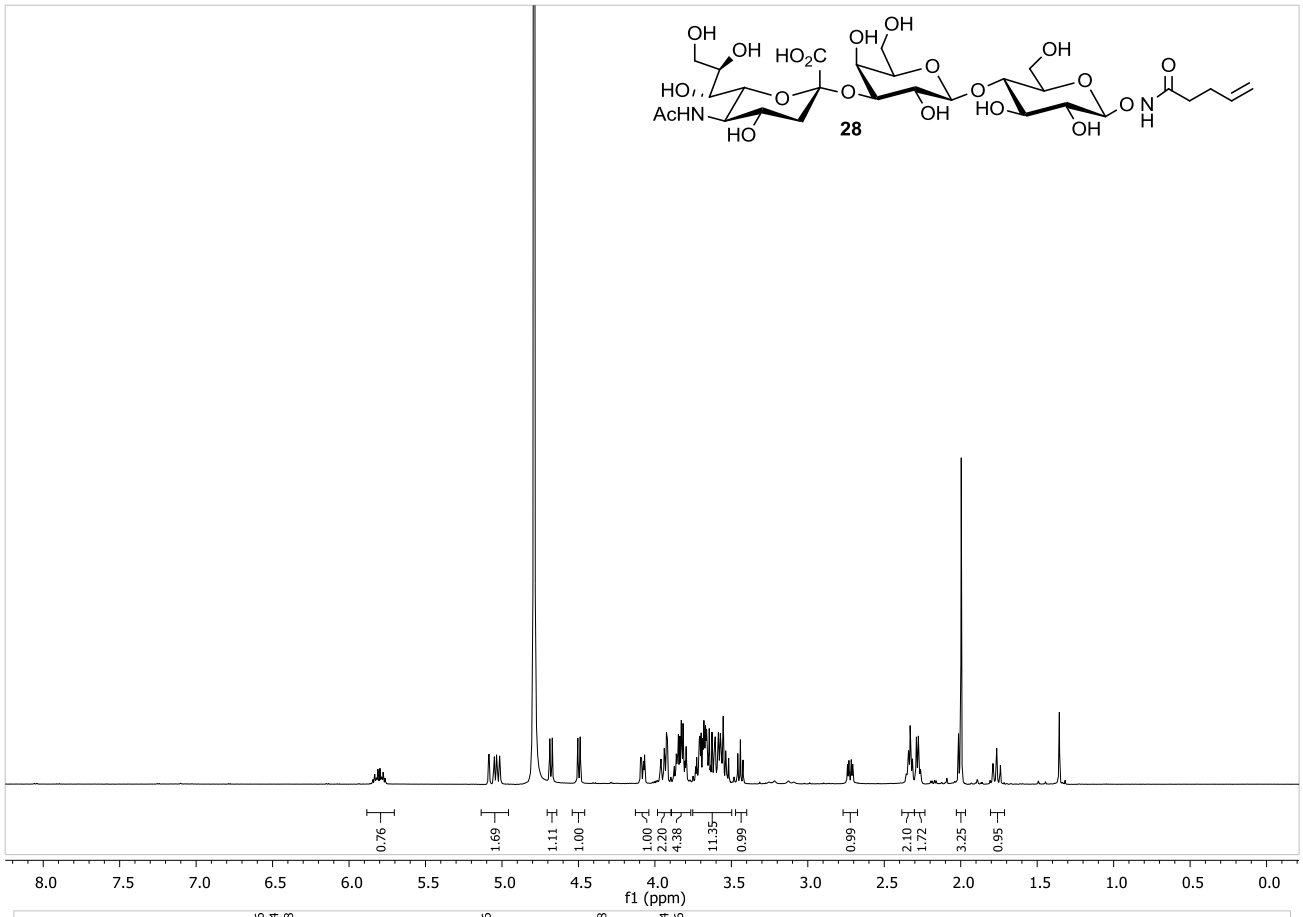
68.55
61.02
59.88
31.72
28.87
f1 (ppm)


27
f1 (ppm)


ppm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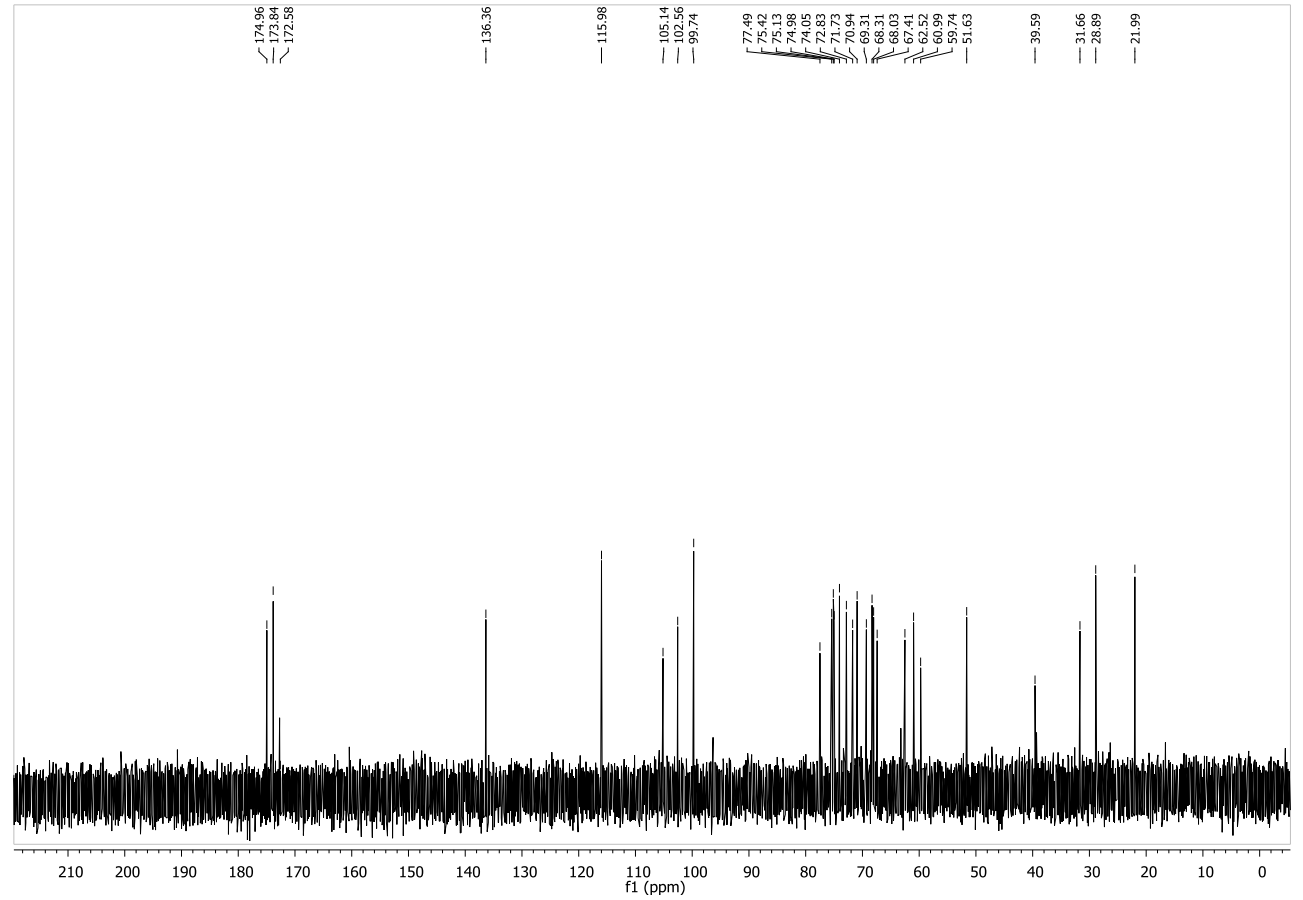
f1 (ppm)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75.13
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72.83
71.73
70.94
69.31
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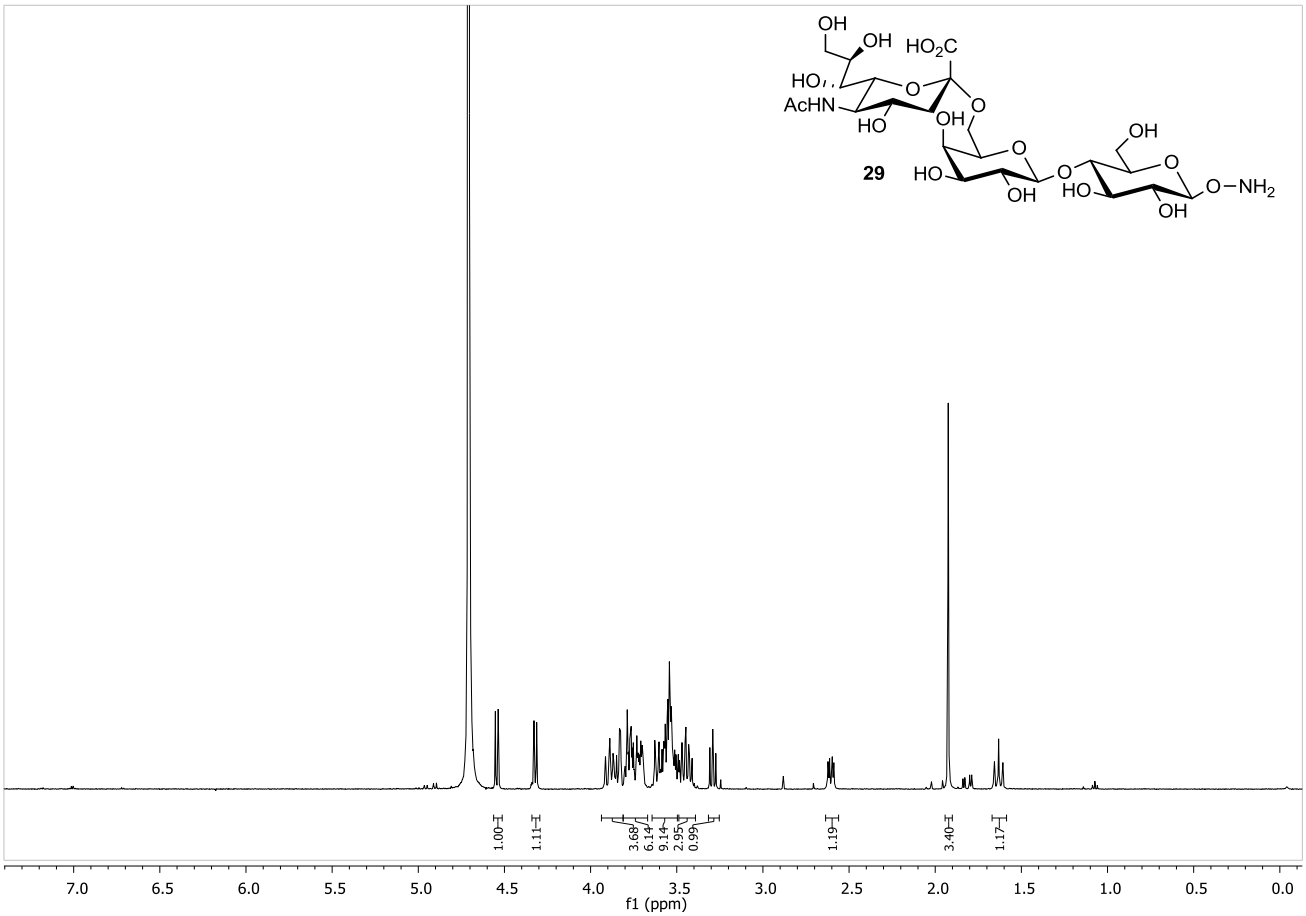
21.99
f1 (ppm)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OH
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HO
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HO
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1.11
3.69
6.14
9.14
2.95
0.99
1.19
3.40
1.17
7.0
6.5
6.0
5.5
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3.5
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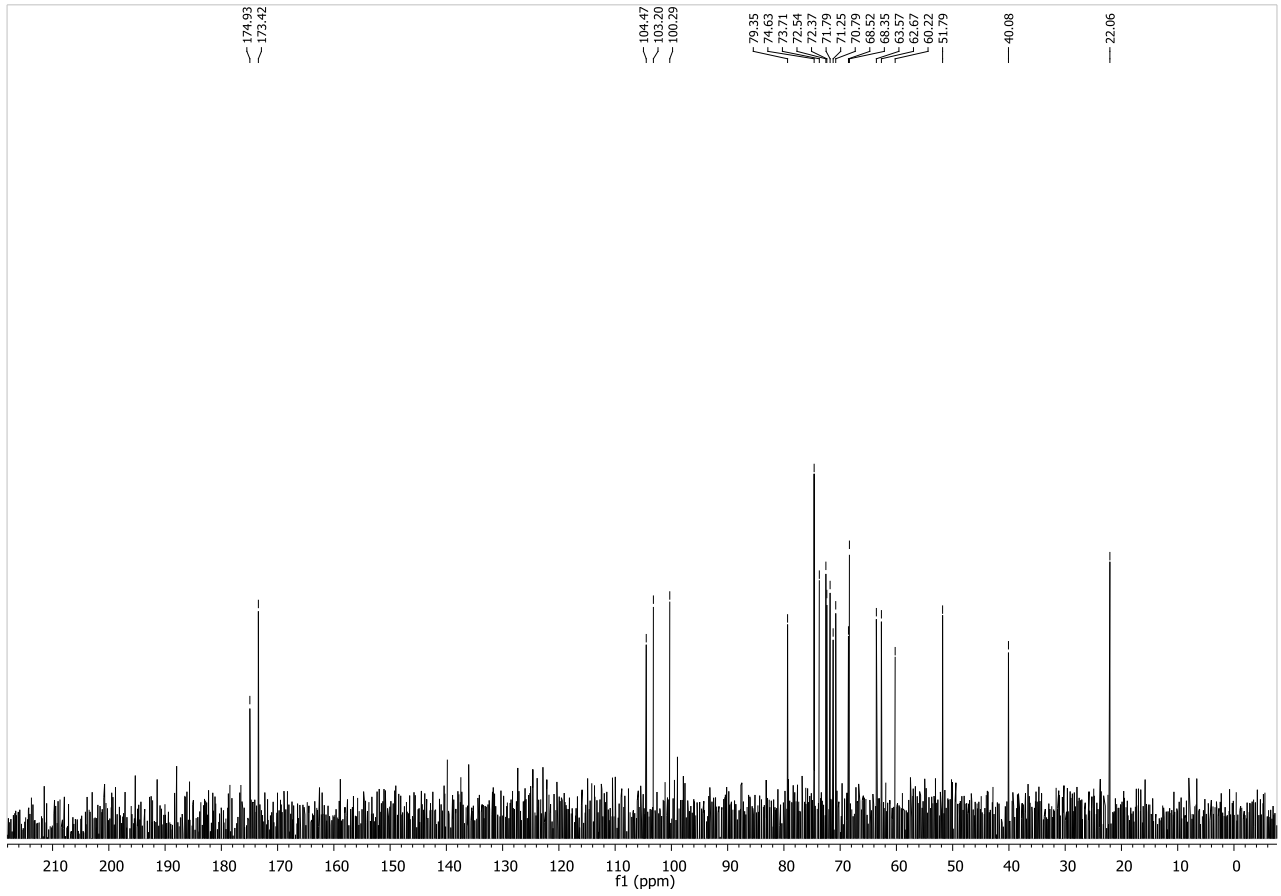
f1 (ppm)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68.52
68.35
63.57
62.67
60.22
51.79
40.08
22.06
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200
190
180
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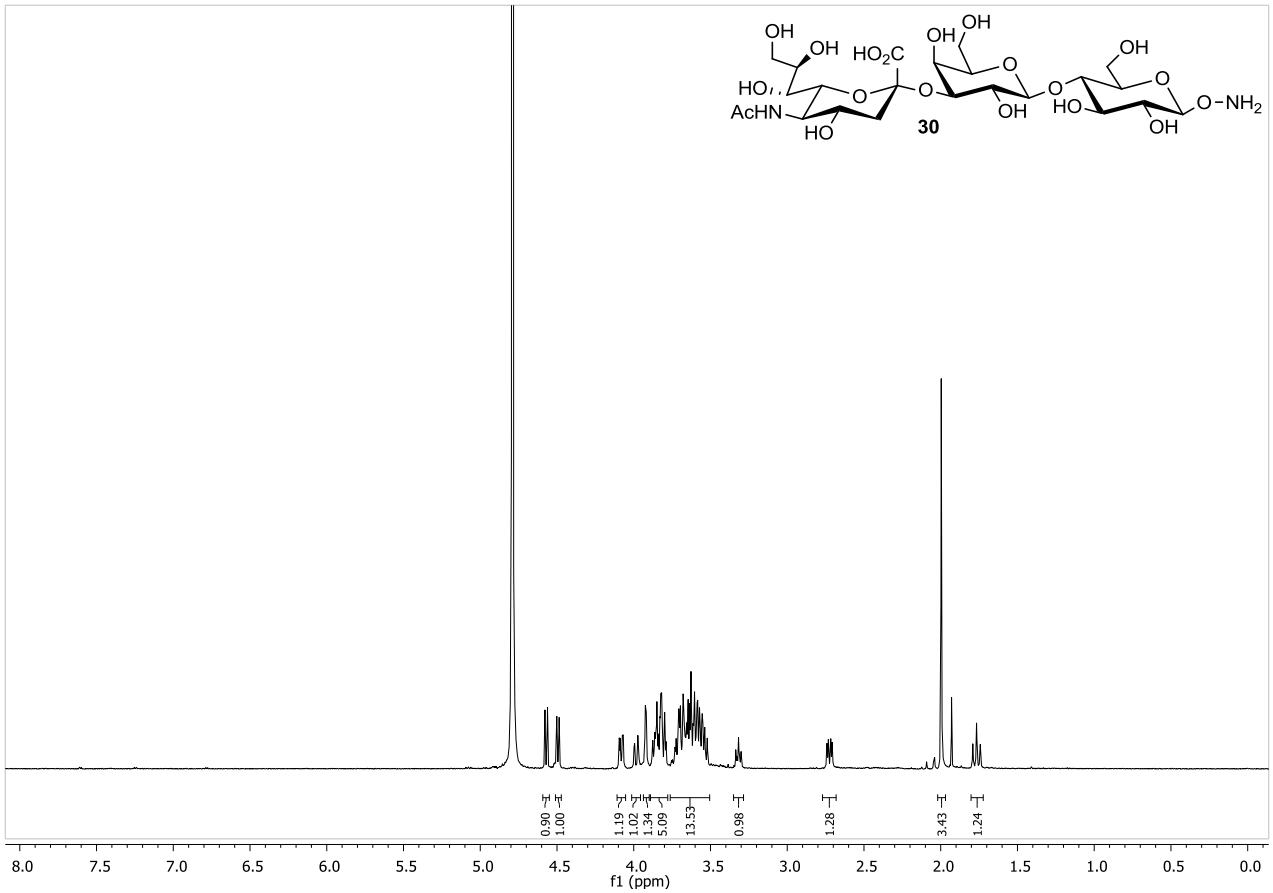
10
0
f1 (ppm)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1.00
1.19
1.02
1.34
5.09
13.53
0.98
1.28
3.43
1.24
8.0
7.5
7.0
6.5
6.0
5.5
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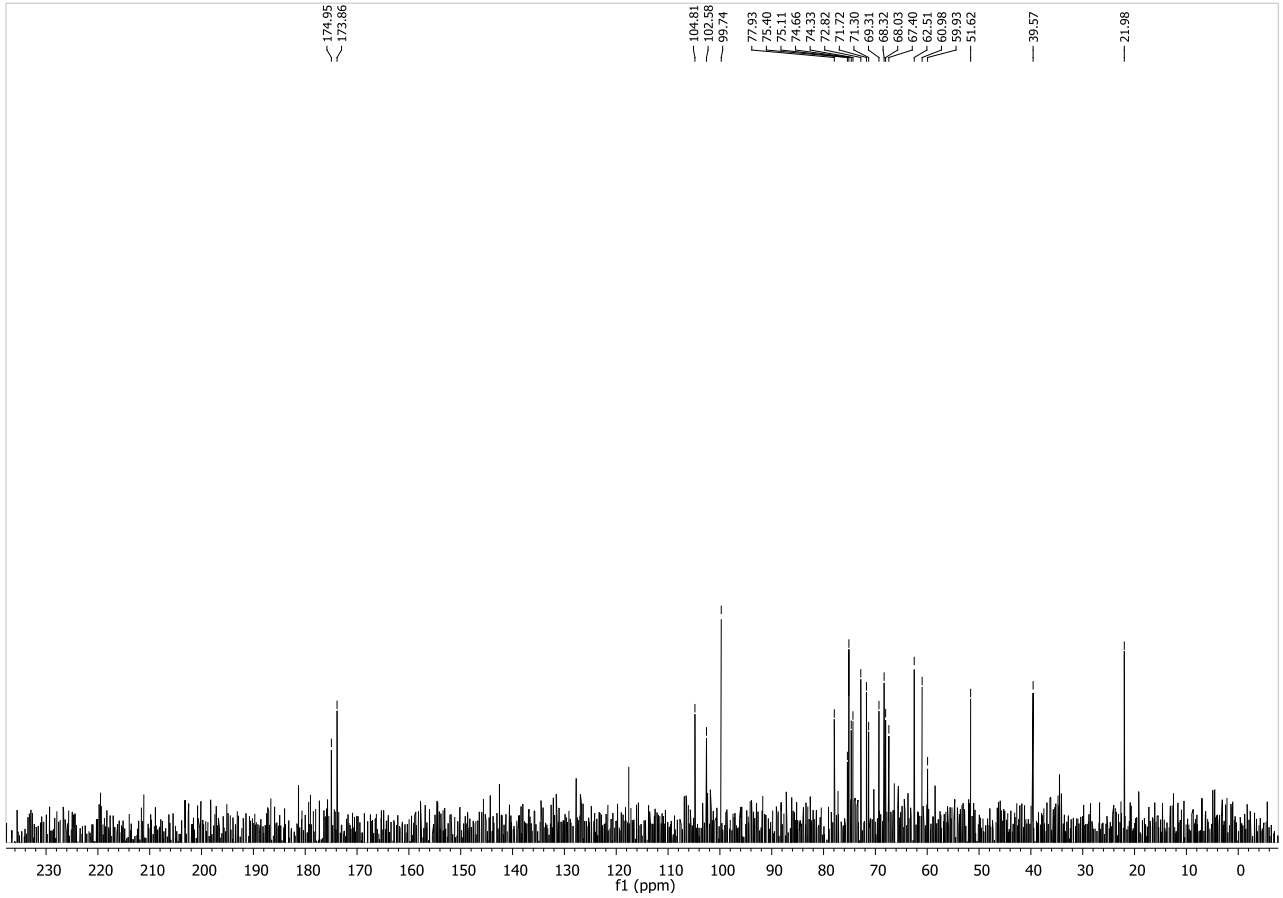
f1 (ppm)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200
190
180
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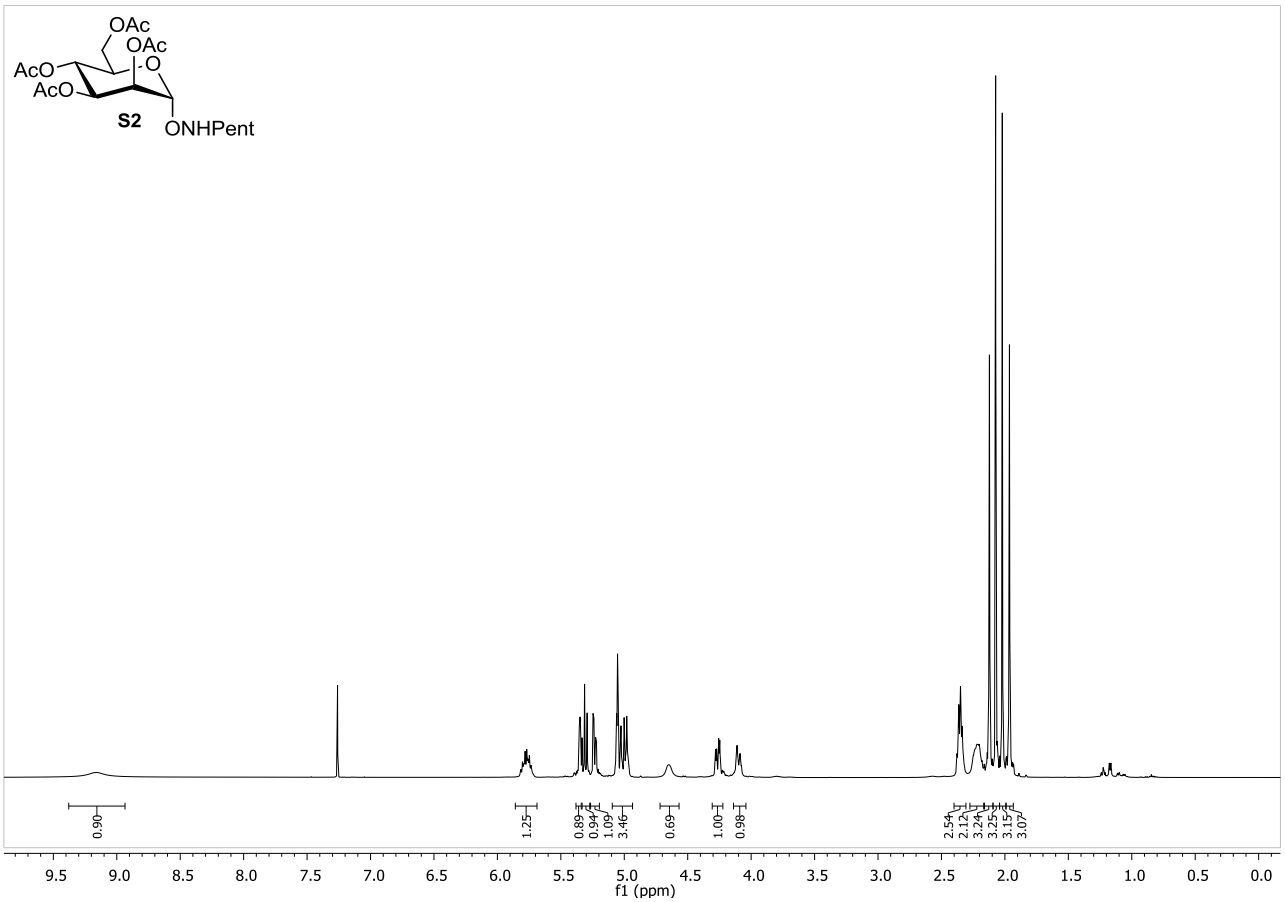
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AcO
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S2
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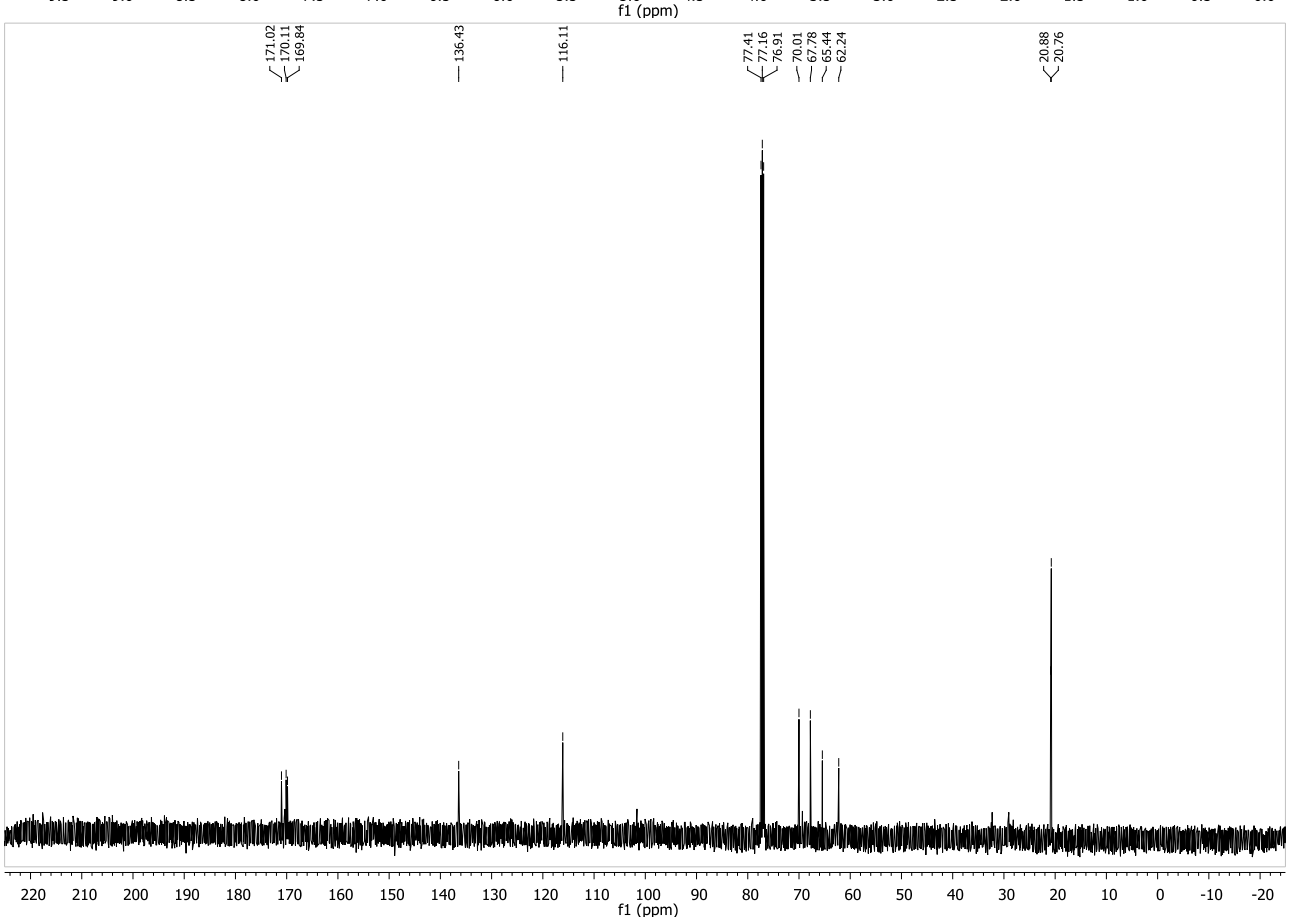
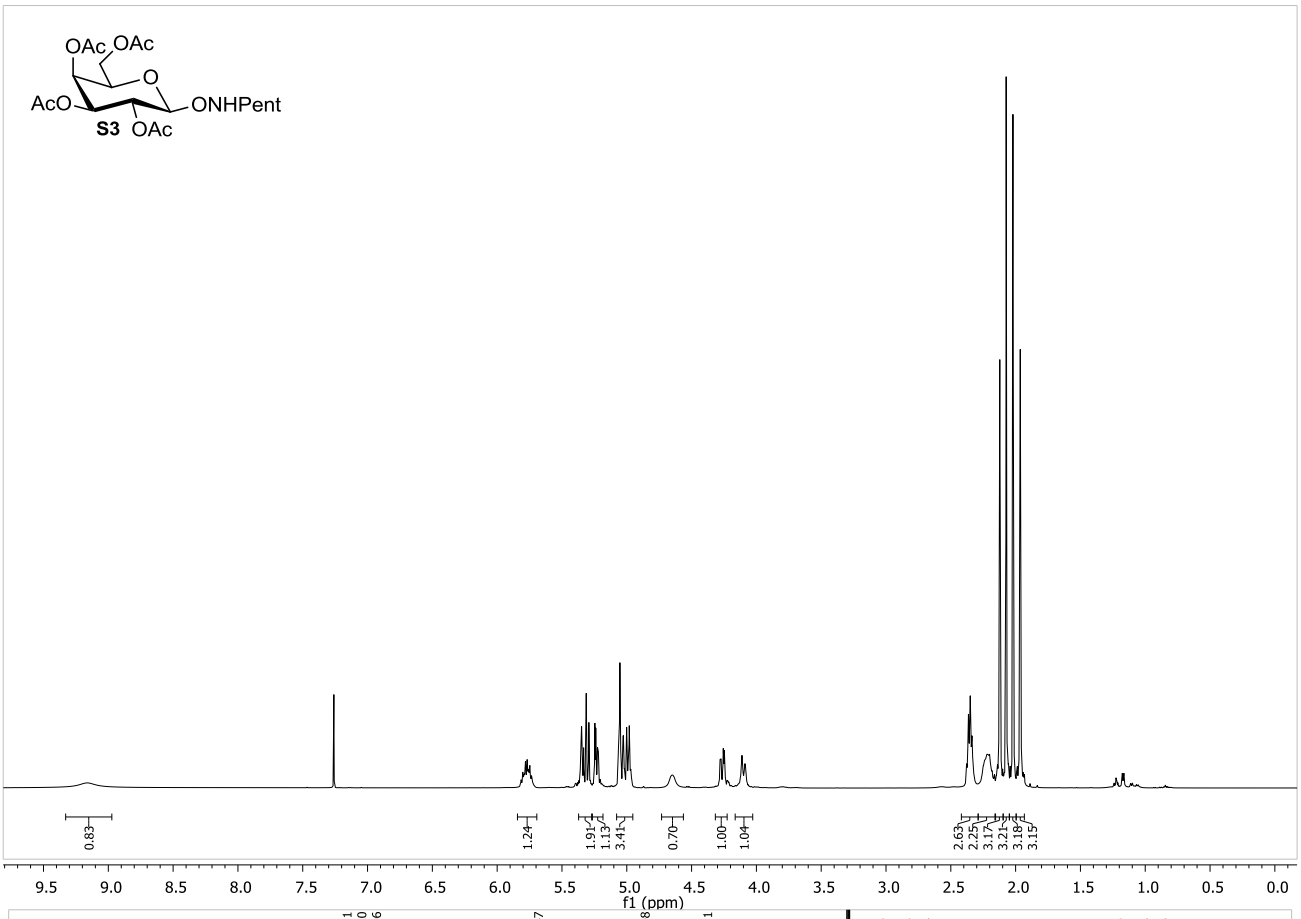
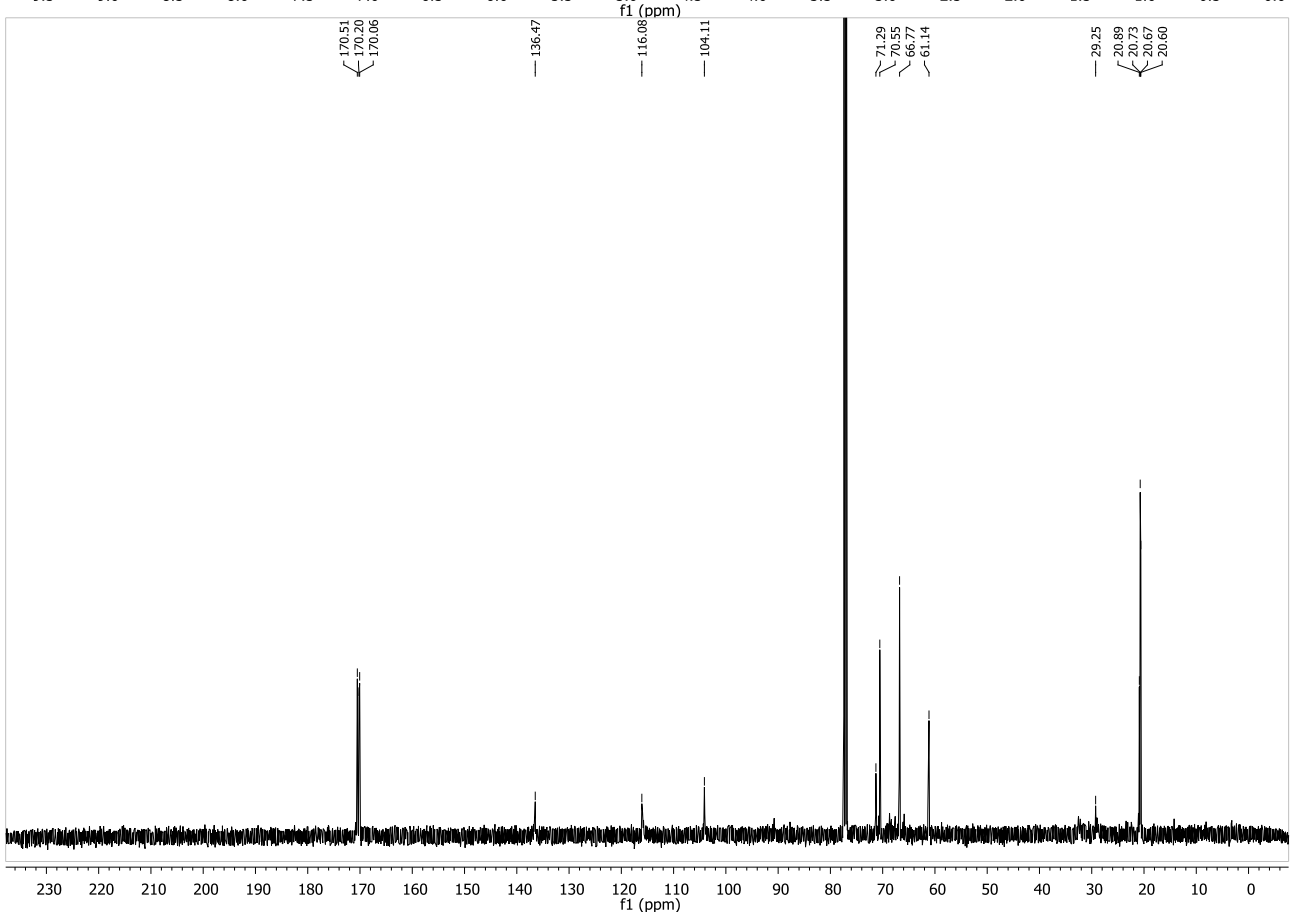
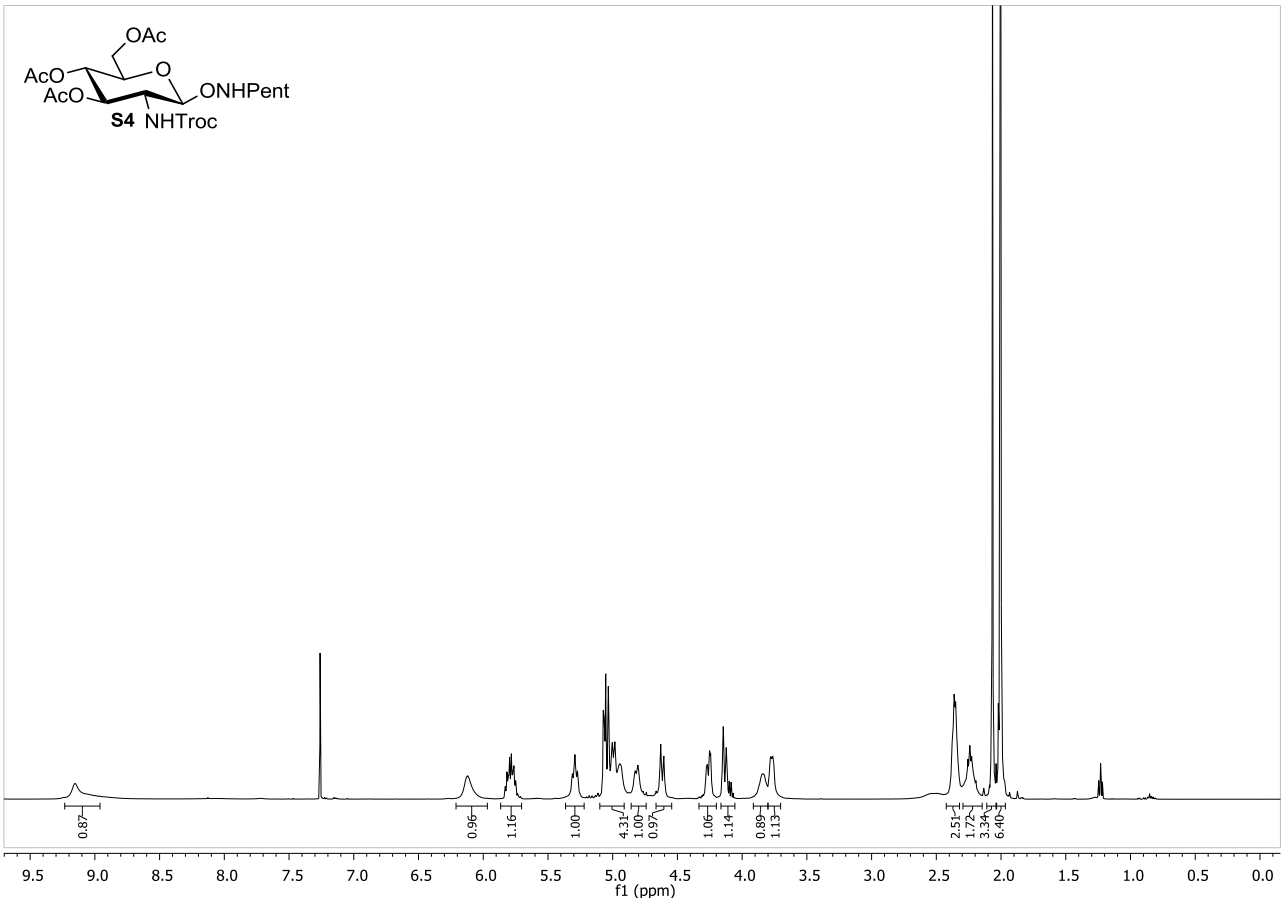
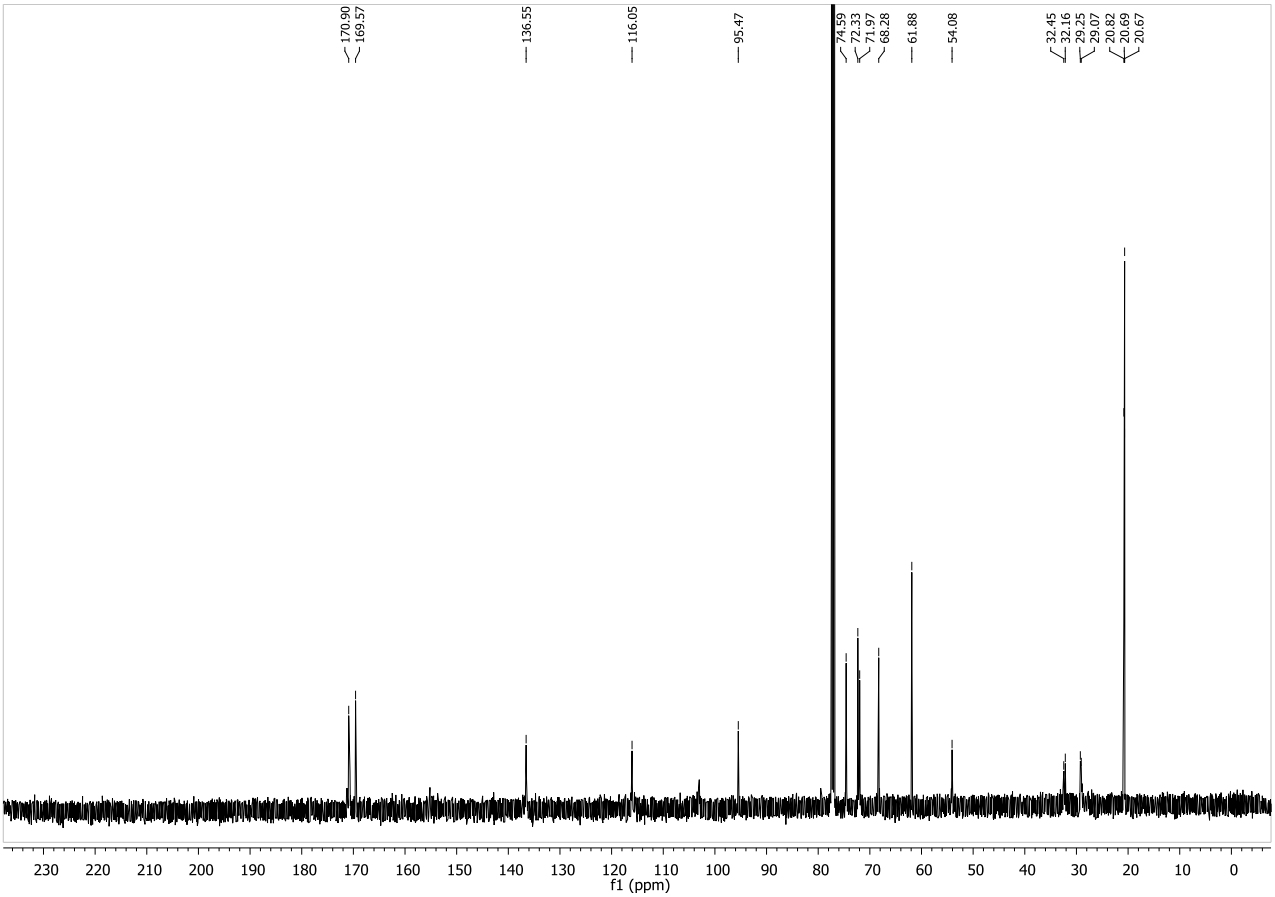
0.69
1.00
0.98
2.54
2.12
3.24
3.25
3.15
3.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

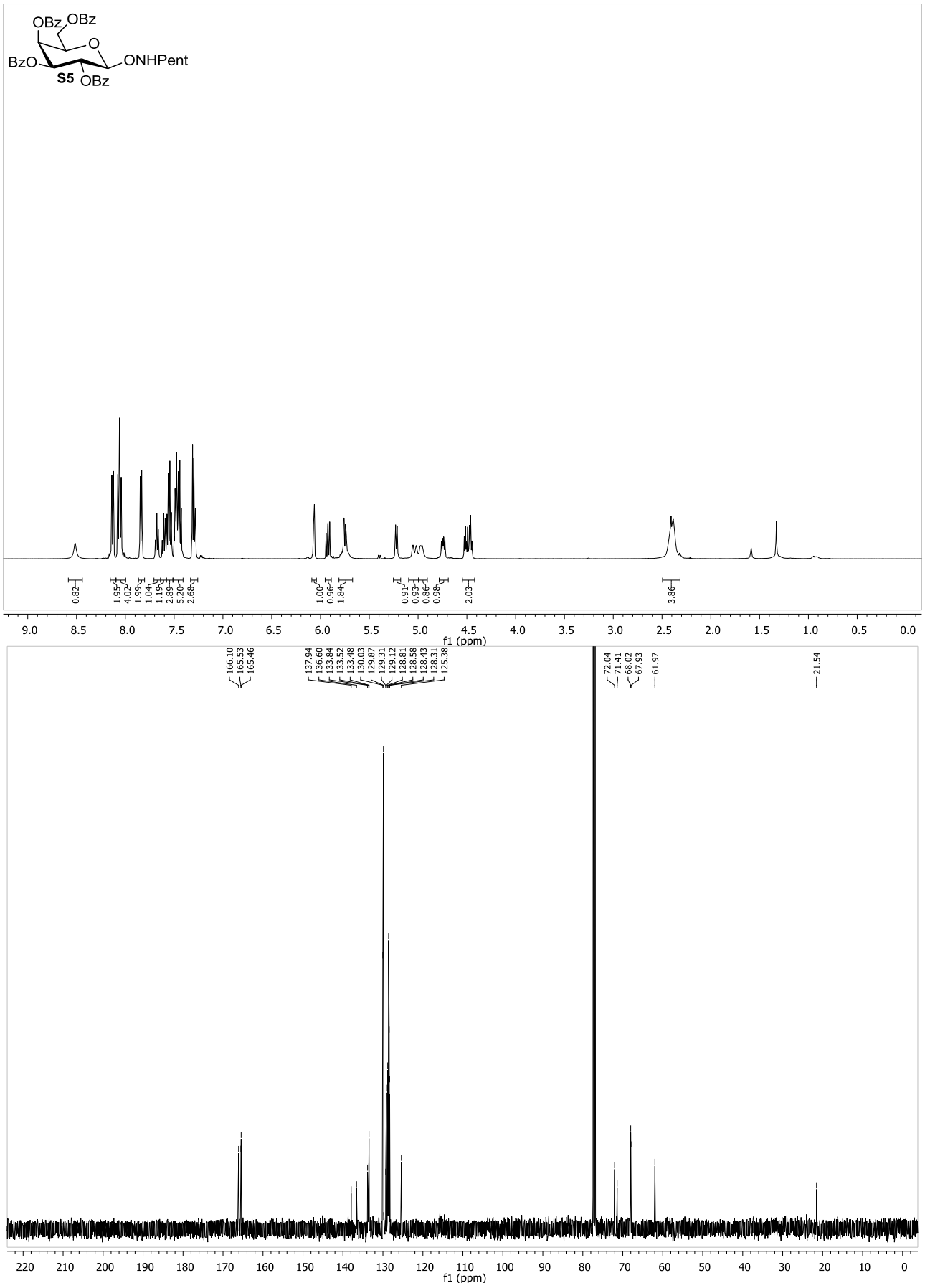

171.02
170.11
169.84
136.43
116.11
77.41
77.16
76.91
70.01
67.78
65.44
62.24
20.88
20.76
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

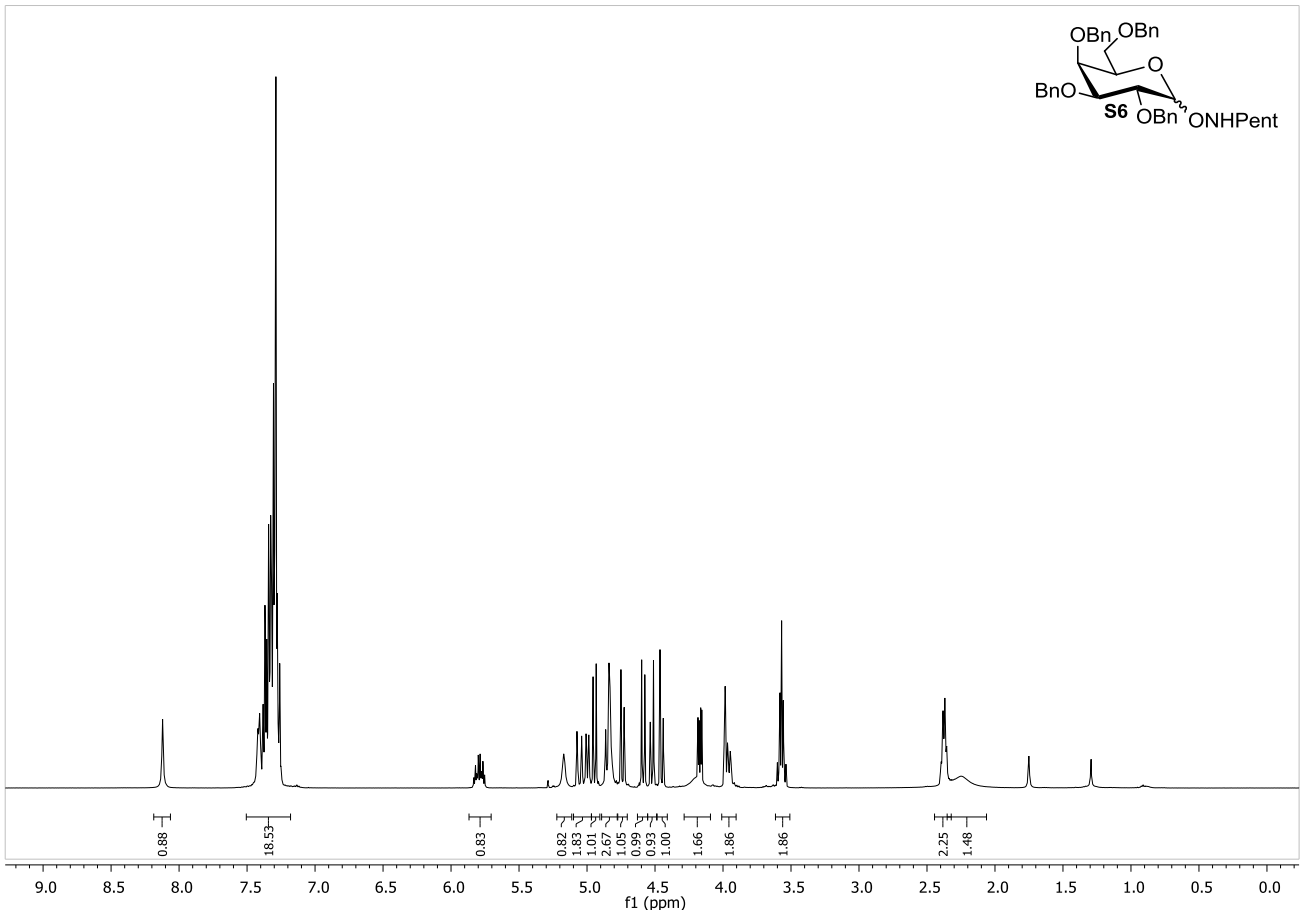

OAc OAc
O
AcO
ONHPent
S3 OAc
0.83
1.24
1.91
1.13
3.41
0.70
1.00
1.04
2.63
2.25
3.17
3.21
3.18
3.15
f1 (ppm)

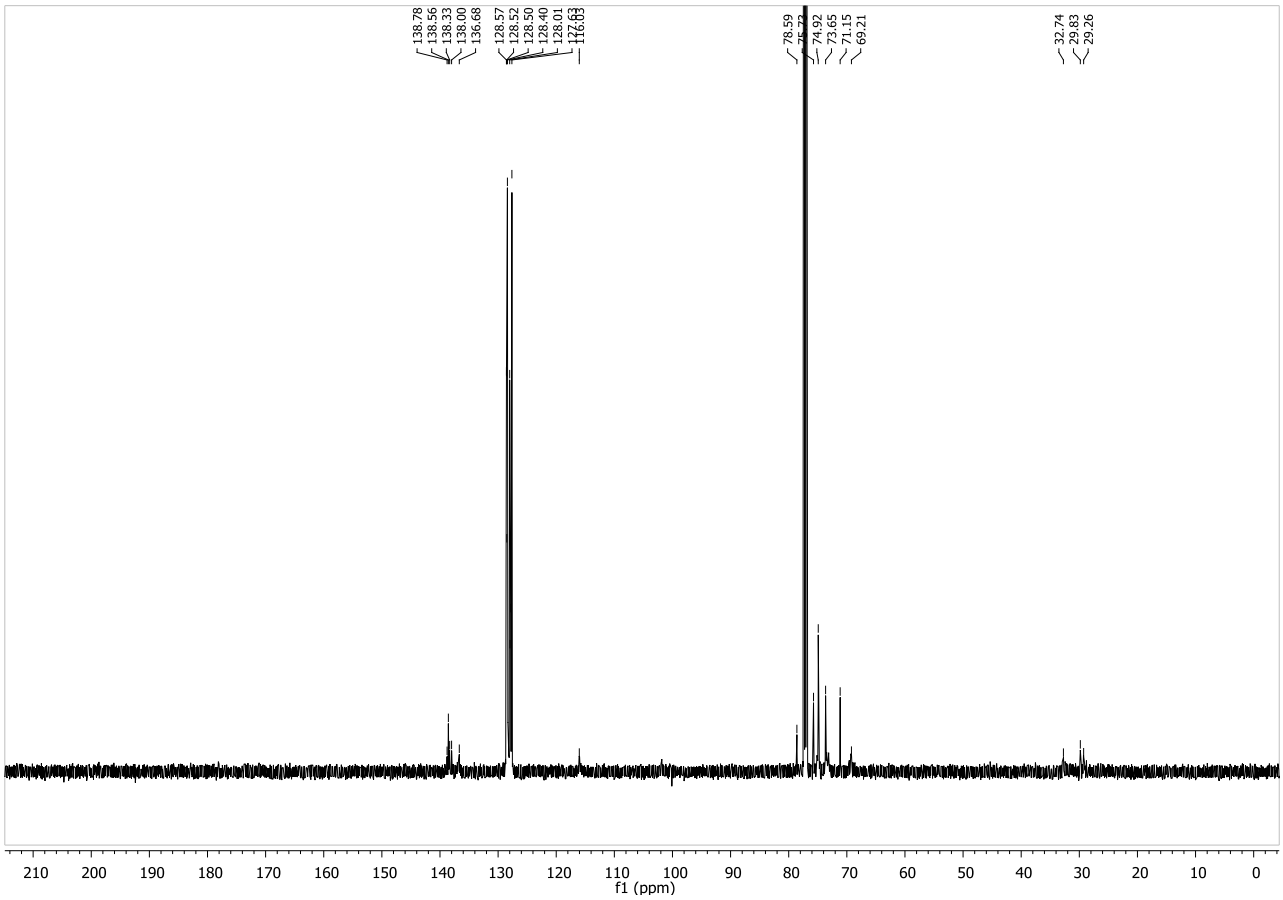

170.51
170.20
170.06
136.47
116.08
104.11
71.29
70.55
66.77
61.14
29.25
20.89
20.73
20.67
20.60
f1 (ppm)

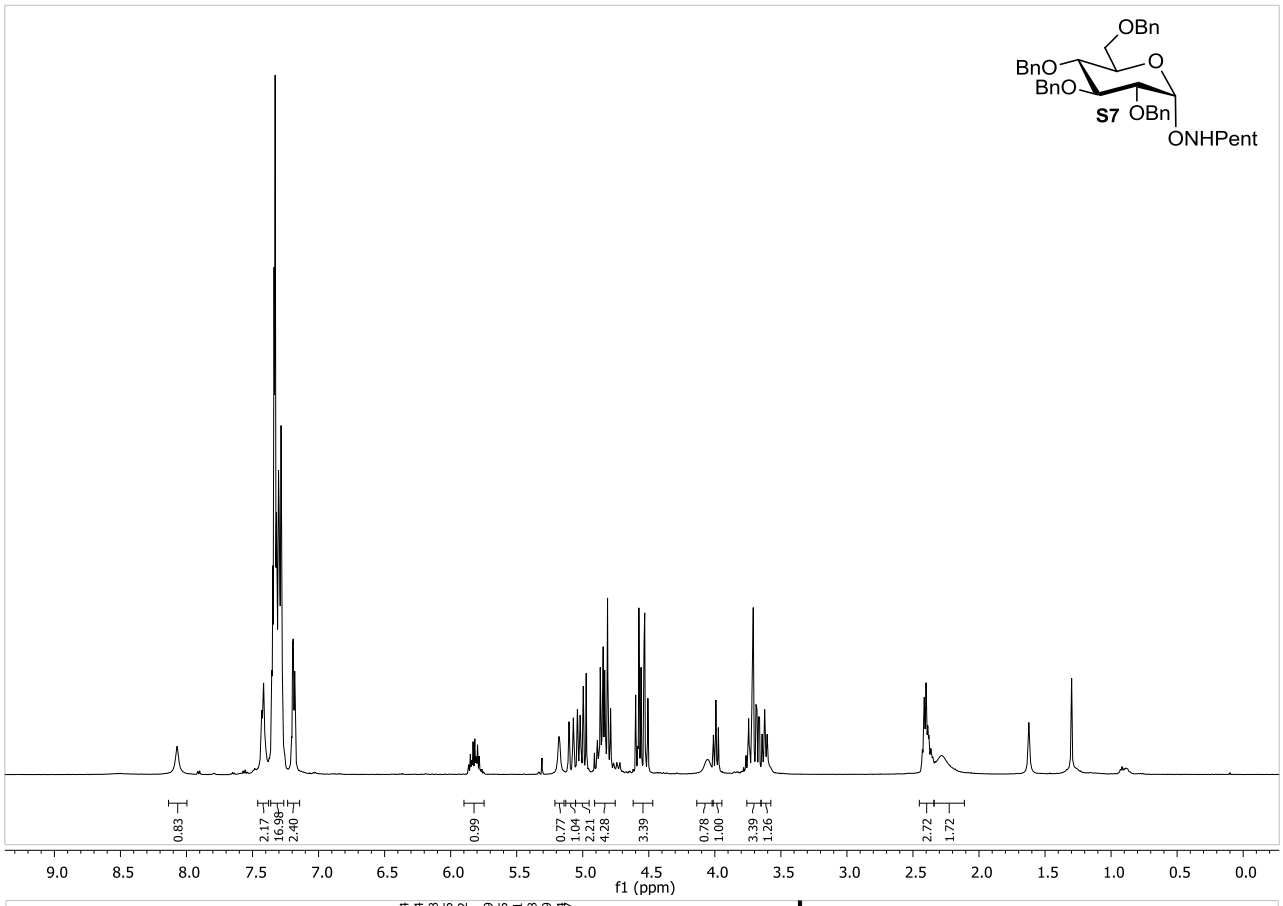

OAc
AcO
AcO
O
ONHPent
S4 NHTroc
0.87
0.96
1.16
1.00
4.31
1.00
0.97
1.06
1.14
0.89
1.13
2.51
1.72
3.34
6.40
f1 (ppm)

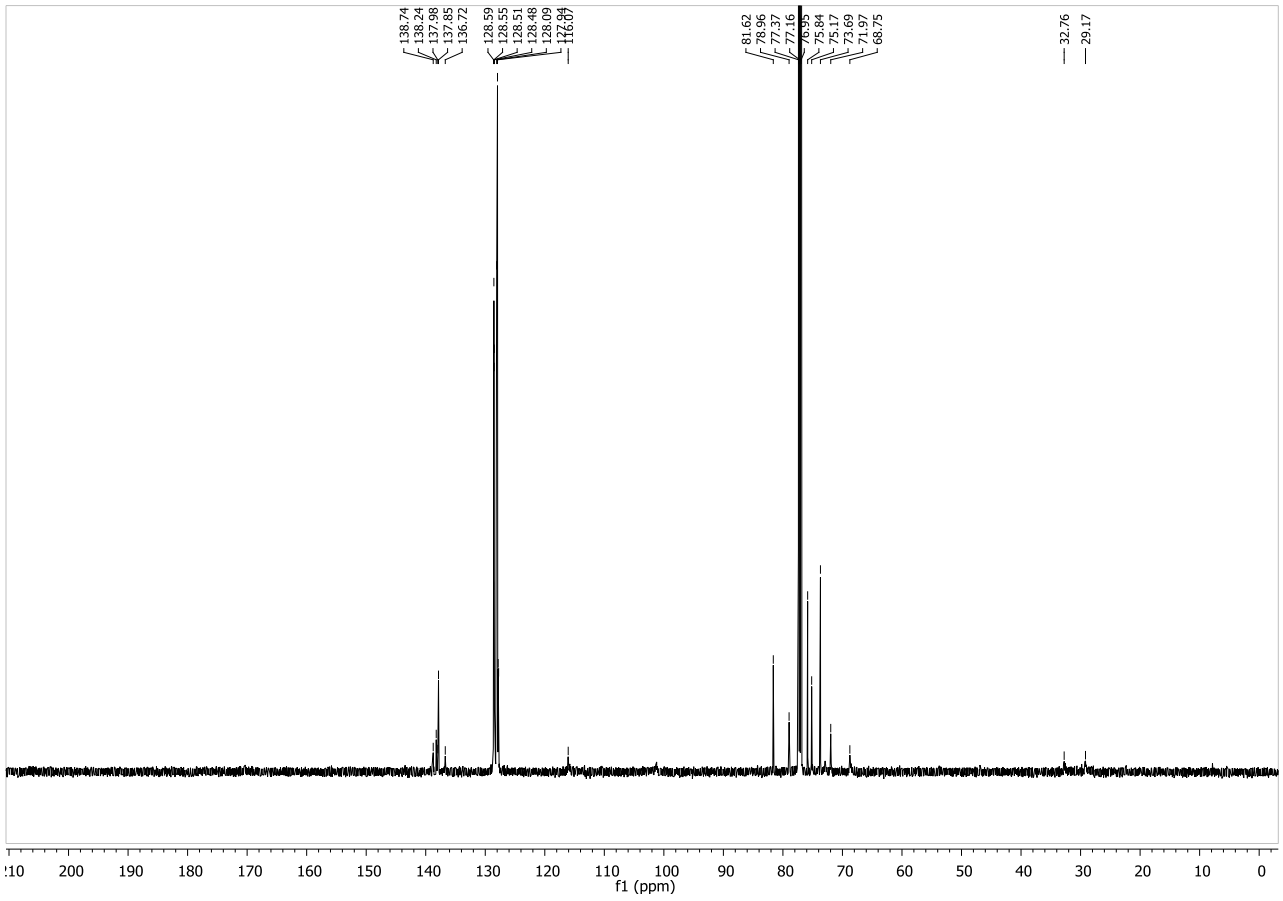

170.90
169.57
136.55
116.05
95.47
74.59
72.33
71.97
68.28
61.88
54.08
32.45
32.16
29.25
29.07
20.82
20.69
20.67
f1 (ppm)

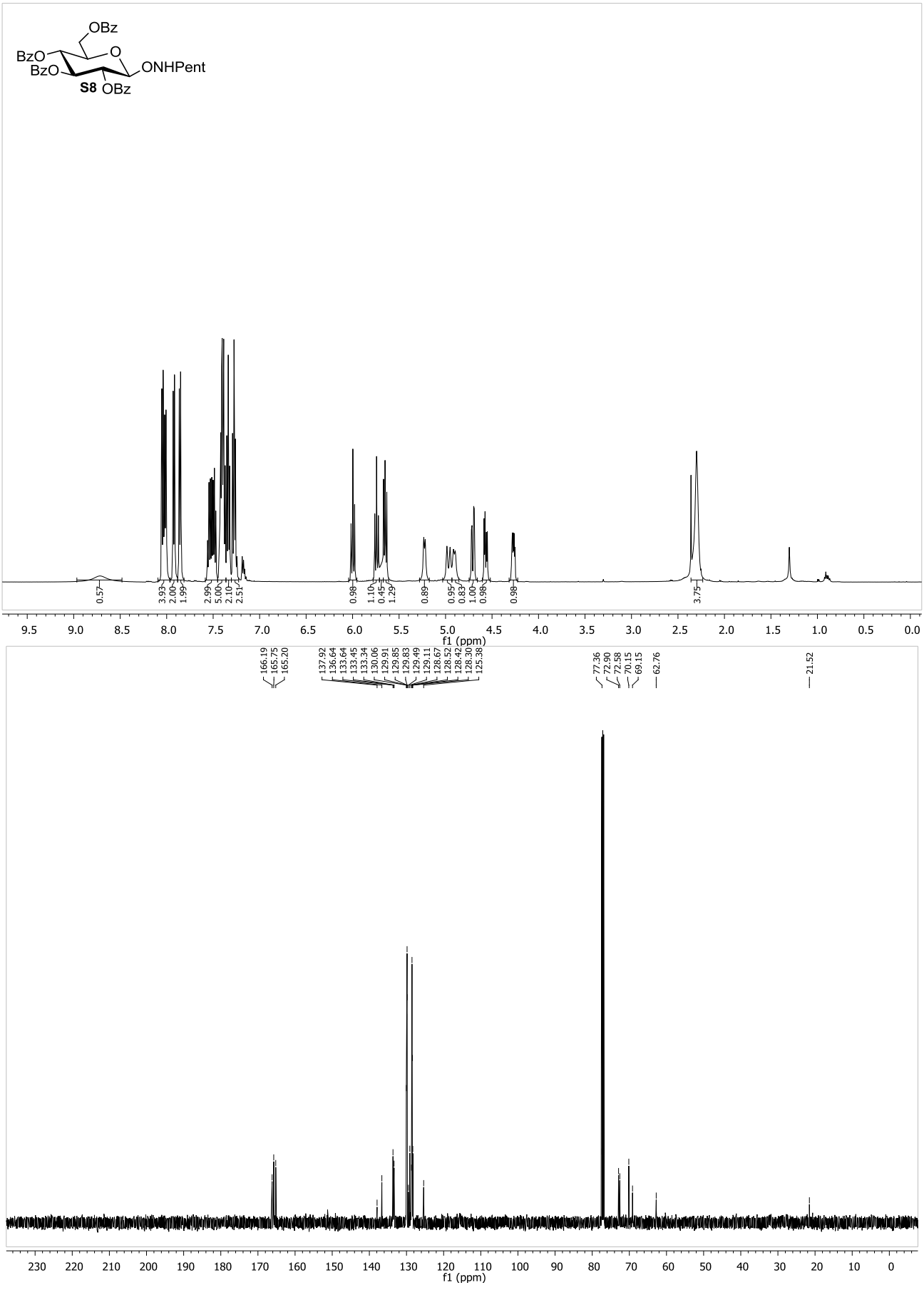

OBz
OBz
O
BzO
ONHPent
S5
OBz
0.82
1.95
4.02
1.99
1.04
1.19
2.89
5.20
2.68
1.00
0.96
1.84
0.91
0.93
0.86
0.98
2.03
3.86
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
166.10
165.53
165.46
137.94
136.60
133.84
133.52
133.48
130.03
129.87
129.31
129.12
128.81
128.58
128.43
128.31
125.38
72.04
71.41
68.02
67.93
61.97
21.54
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

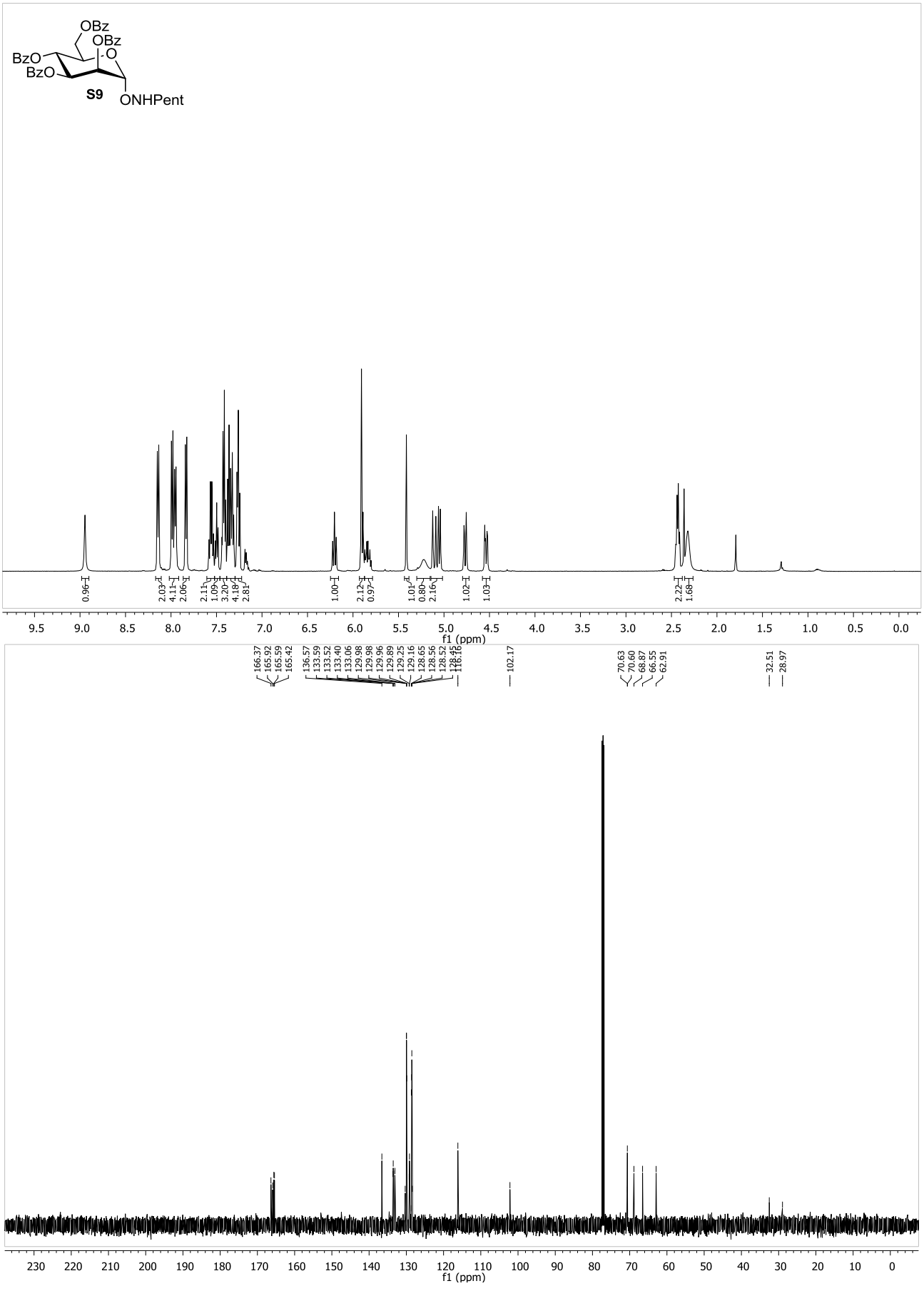

OBn
OBn
O
BnO
S6
OBn
ONHPent
0.88
18.53
0.83
0.82
1.83
1.01
2.67
1.05
0.99
0.93
1.00
1.66
1.86
1.86
2.25
1.48
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

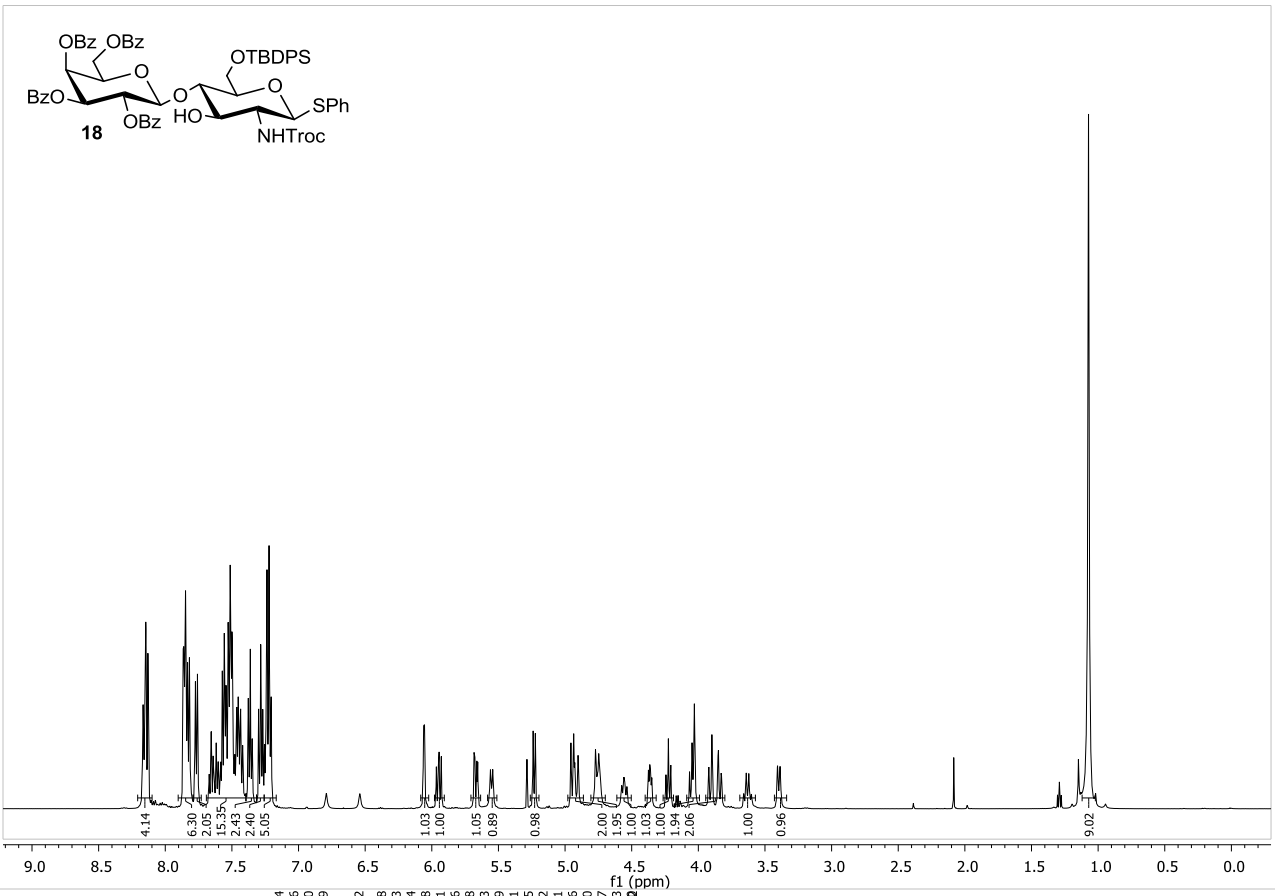

138.78
138.56
138.33
138.00
136.68
128.57
128.52
128.50
128.40
128.01
78.59
74.92
73.65
71.15
69.21
32.74
29.83
29.26
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

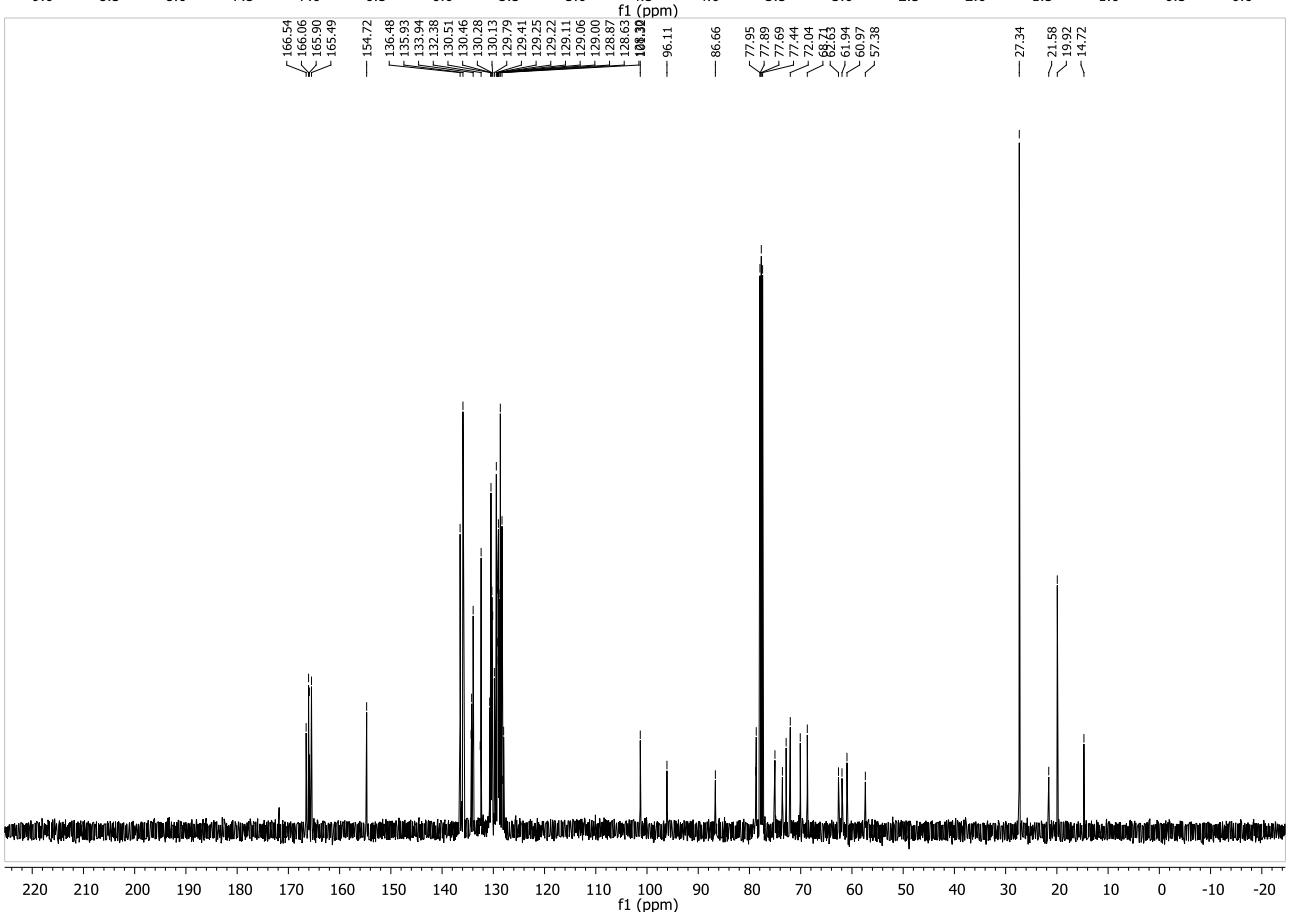

OBn
BnO
BnO
O
S7
OBn
ONHPent
0.83
2.17
16.98
2.40
0.99
0.77
1.04
2.21
4.28
3.39
0.78
1.00
3.39
1.26
2.72
1.72
f1 (ppm)

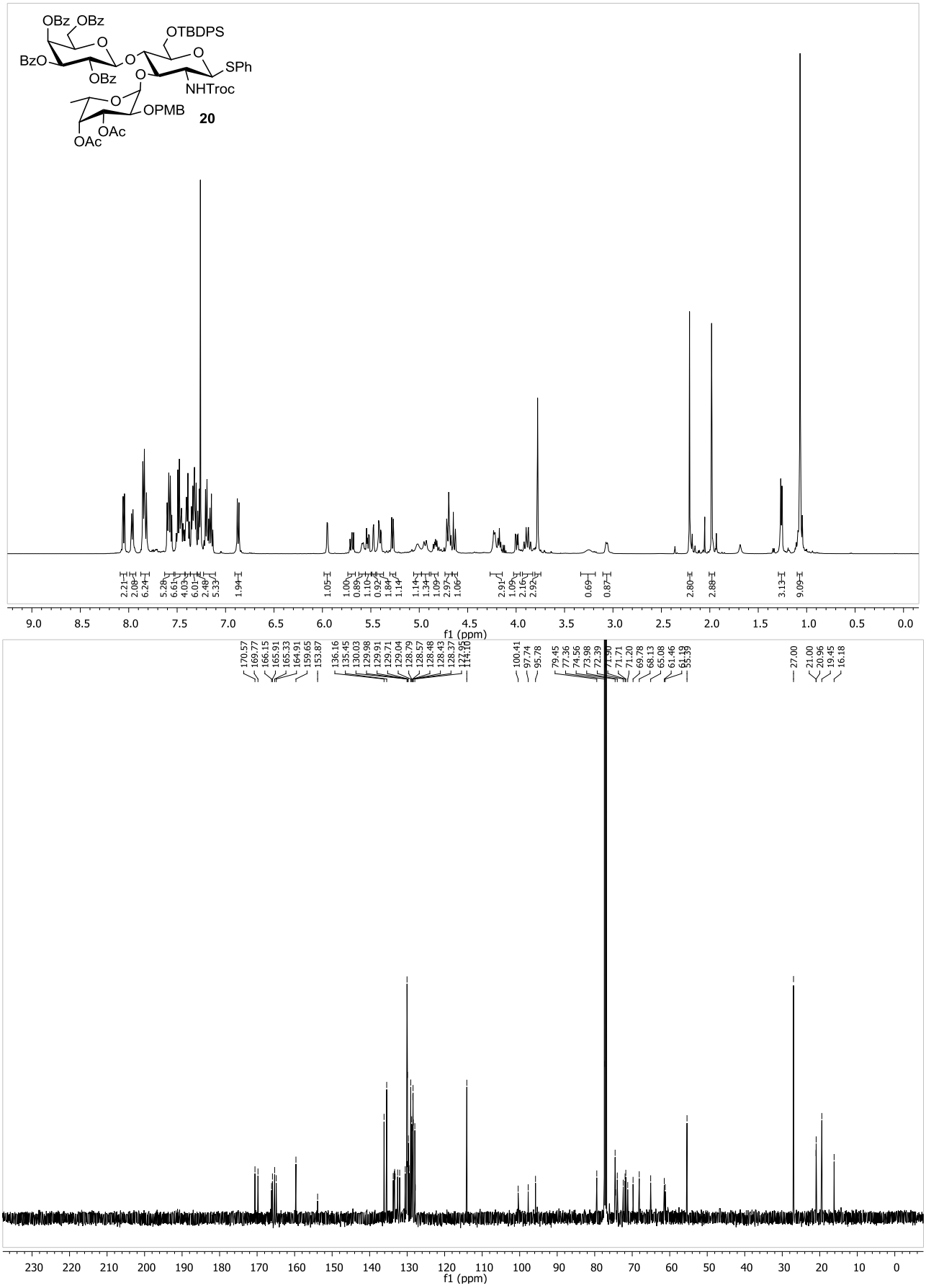

138.74
138.24
137.98
137.85
136.72
128.59
128.55
128.51
128.48
128.09
127.84
116.07
81.62
78.96
77.37
77.16
76.95
75.84
75.17
73.69
71.97
68.75
32.76
29.17
f1 (ppm)

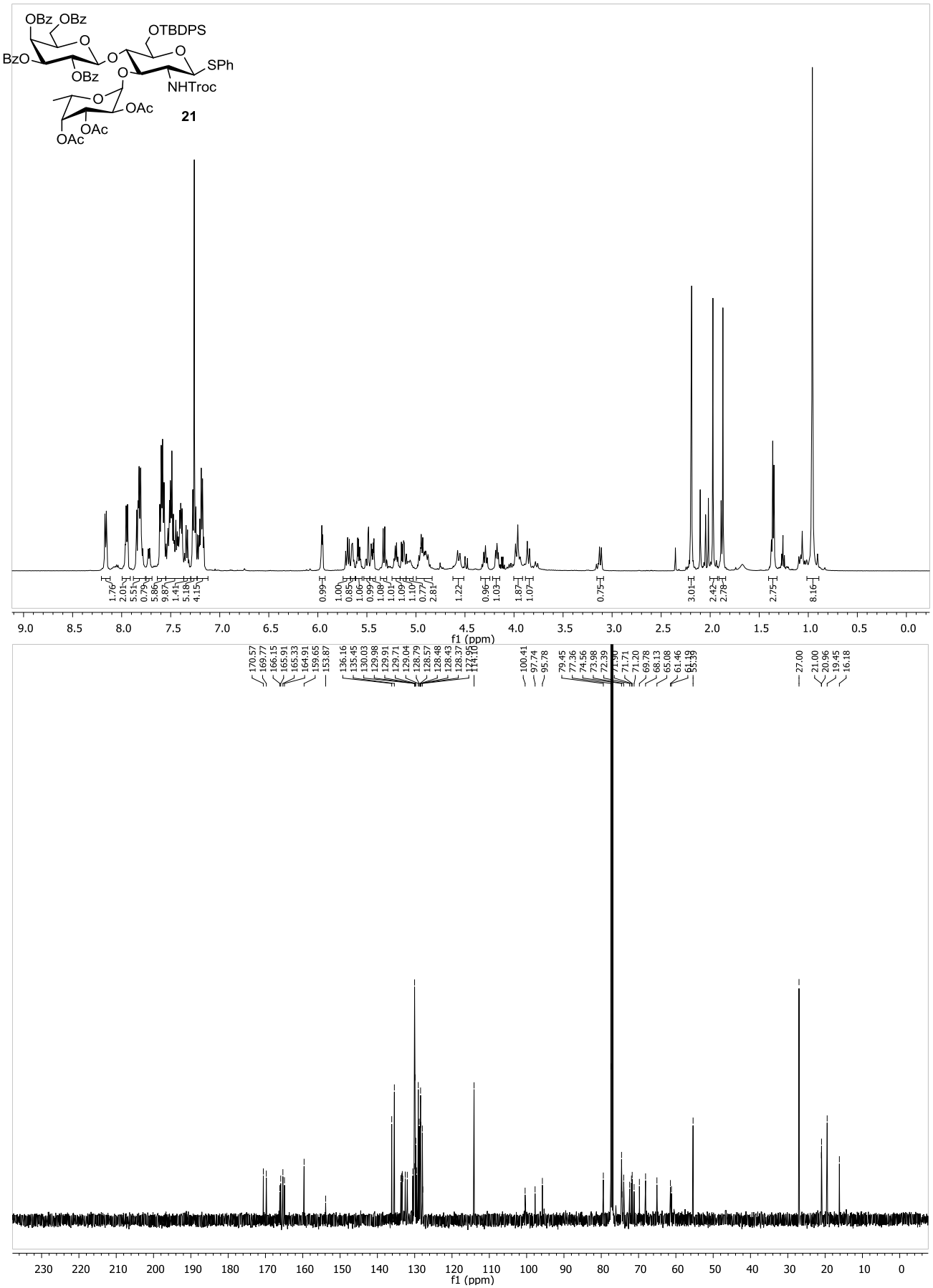

OBz
BzO
O
BzO
ONHPent
S8 OBz
0.57
3.93
2.00
1.99
2.99
5.00
2.10
2.51
0.98
1.10
0.45
1.29
0.89
0.95
0.83
1.00
0.98
0.98
3.75
f1 (ppm)
166.19
165.75
165.20
137.92
136.64
133.64
133.45
133.34
130.06
129.91
129.85
129.83
129.49
129.11
128.67
128.52
128.42
128.30
125.38
77.36
72.90
72.58
70.15
69.15
62.76
21.52
f1 (ppm)

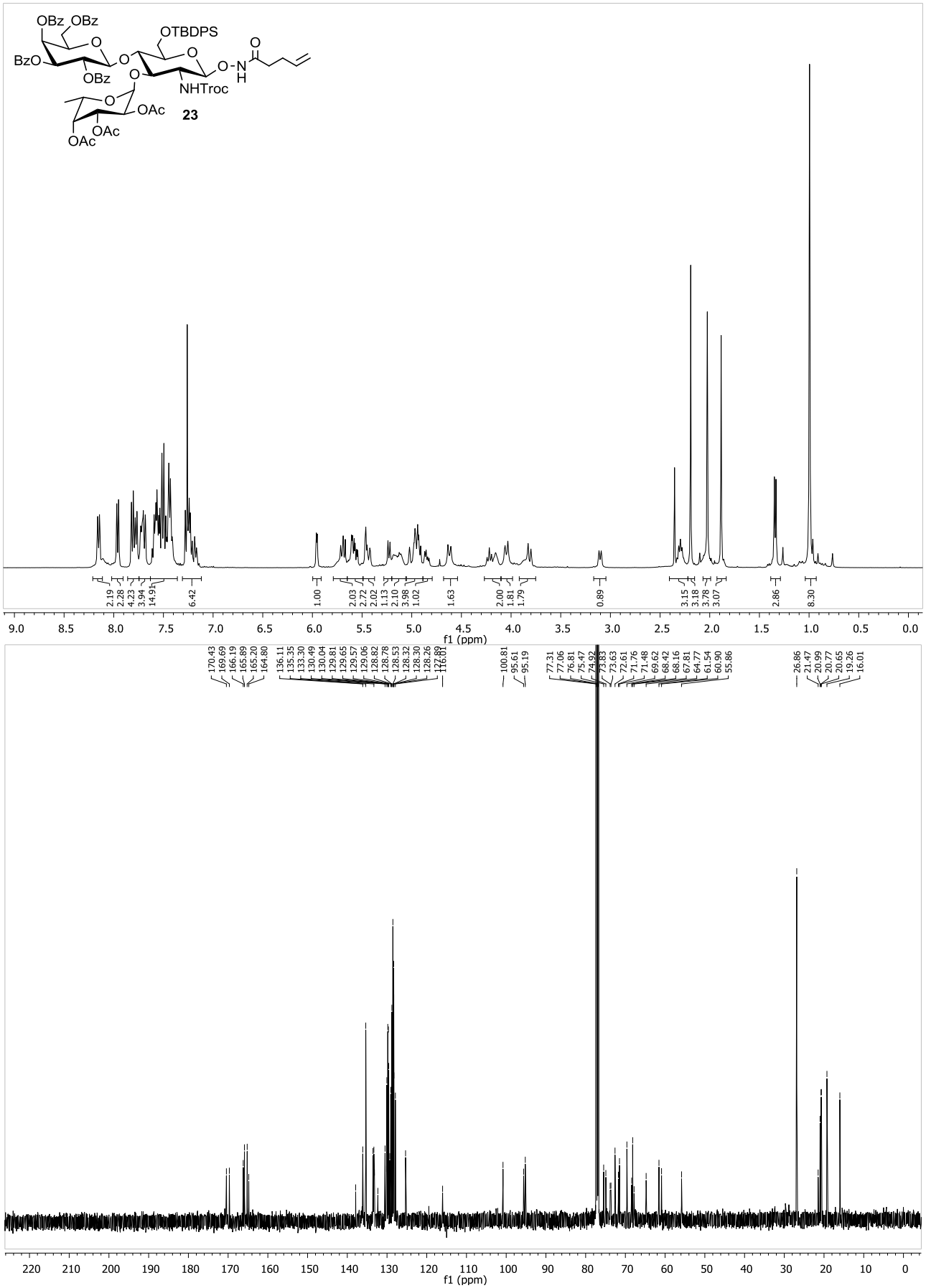

OBz
OBz
BzO
BzO
O
S9
ONHPent
0.96
2.03
4.11
2.06
2.11
1.09
3.20
4.18
2.81
1.00
2.12
0.97
1.01
0.80
2.16
1.02
1.03
2.22
1.68
f1 (ppm)
166.37
165.92
165.59
165.42
136.57
133.59
133.52
133.40
133.06
129.98
129.96
129.89
129.25
129.16
128.65
128.56
128.52
128.45
116.16
102.17
70.63
70.60
68.87
66.55
62.91
32.51
28.97
f1 (ppm)

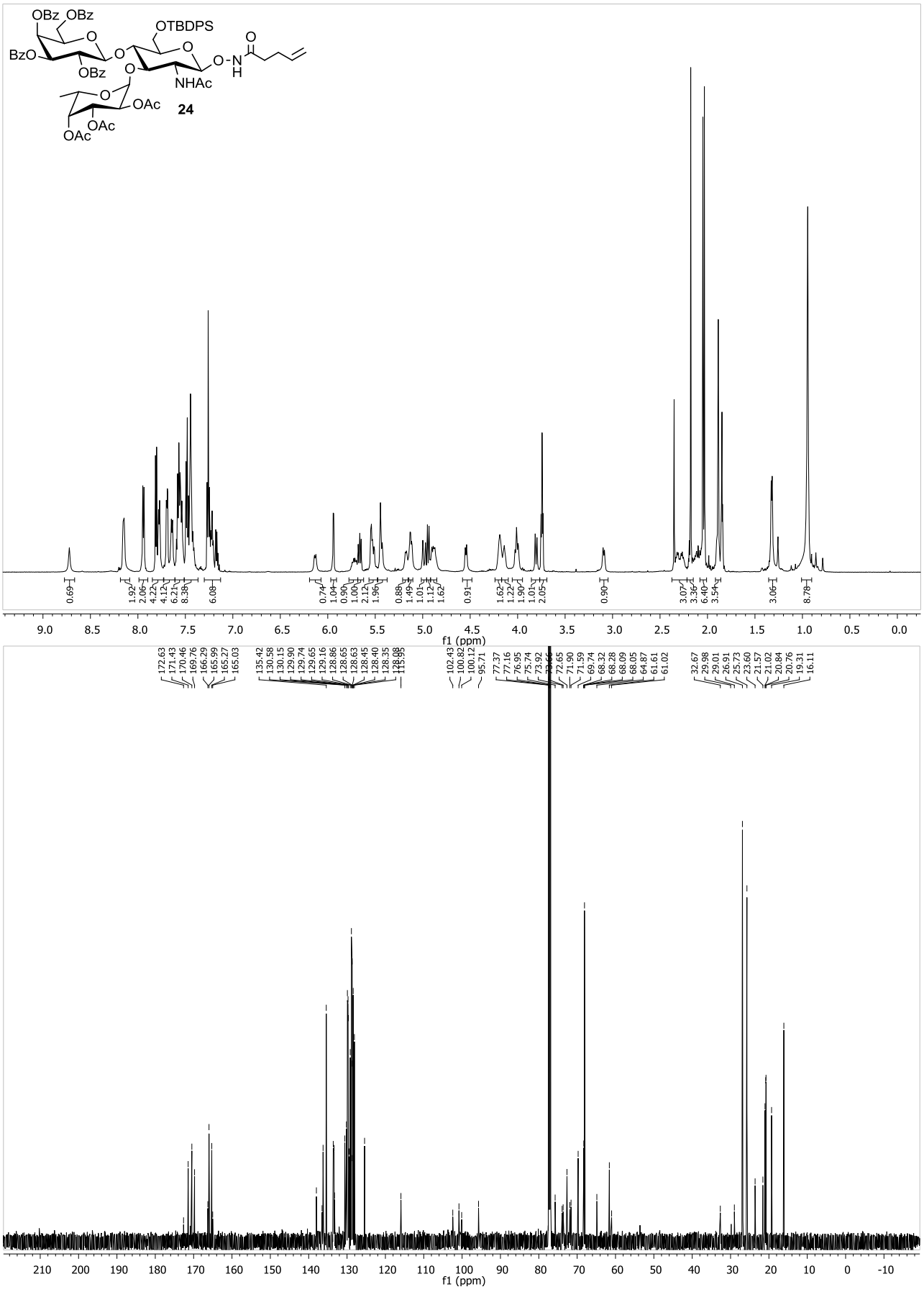

OBz
OBz
OTBDPS
O
O
BzO
O
O
SPh
HO
OBz
NHTroc
18
4.14
6.30
2.05
15.35
2.43
2.40
5.05
1.03
1.00
1.05
0.89
0.98
2.00
1.95
1.00
1.03
1.00
1.94
2.06
1.00
0.96
9.02
f1 (ppm)

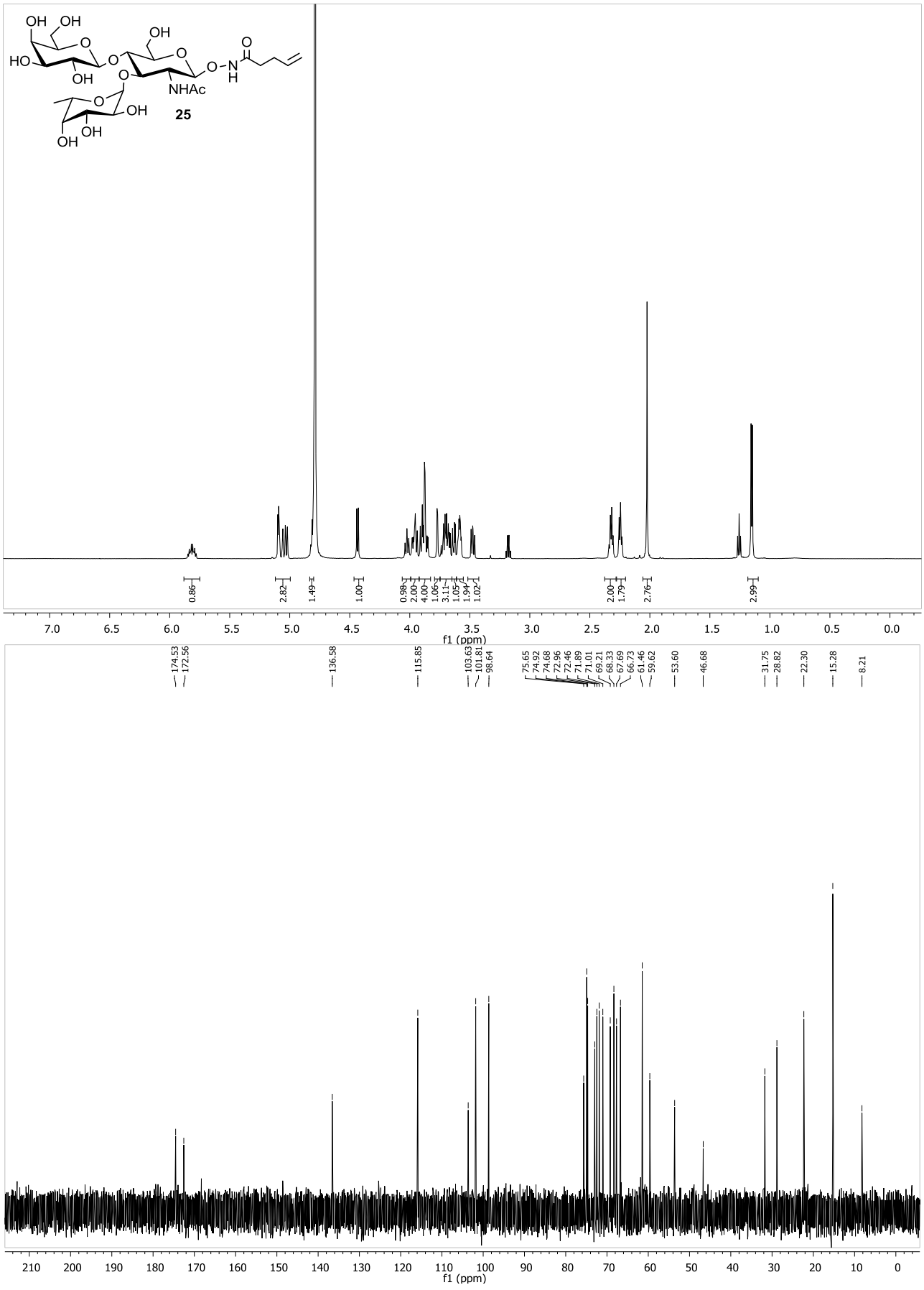

166.54
166.06
165.90
165.49
154.72
136.48
135.93
133.94
132.38
130.51
130.46
130.28
130.13
129.79
129.41
129.25
129.22
129.11
129.06
129.00
128.87
128.63
96.11
86.66
77.95
77.89
77.69
77.44
72.04
61.94
60.97
57.38
27.34
21.58
19.92
14.72
f1 (ppm)

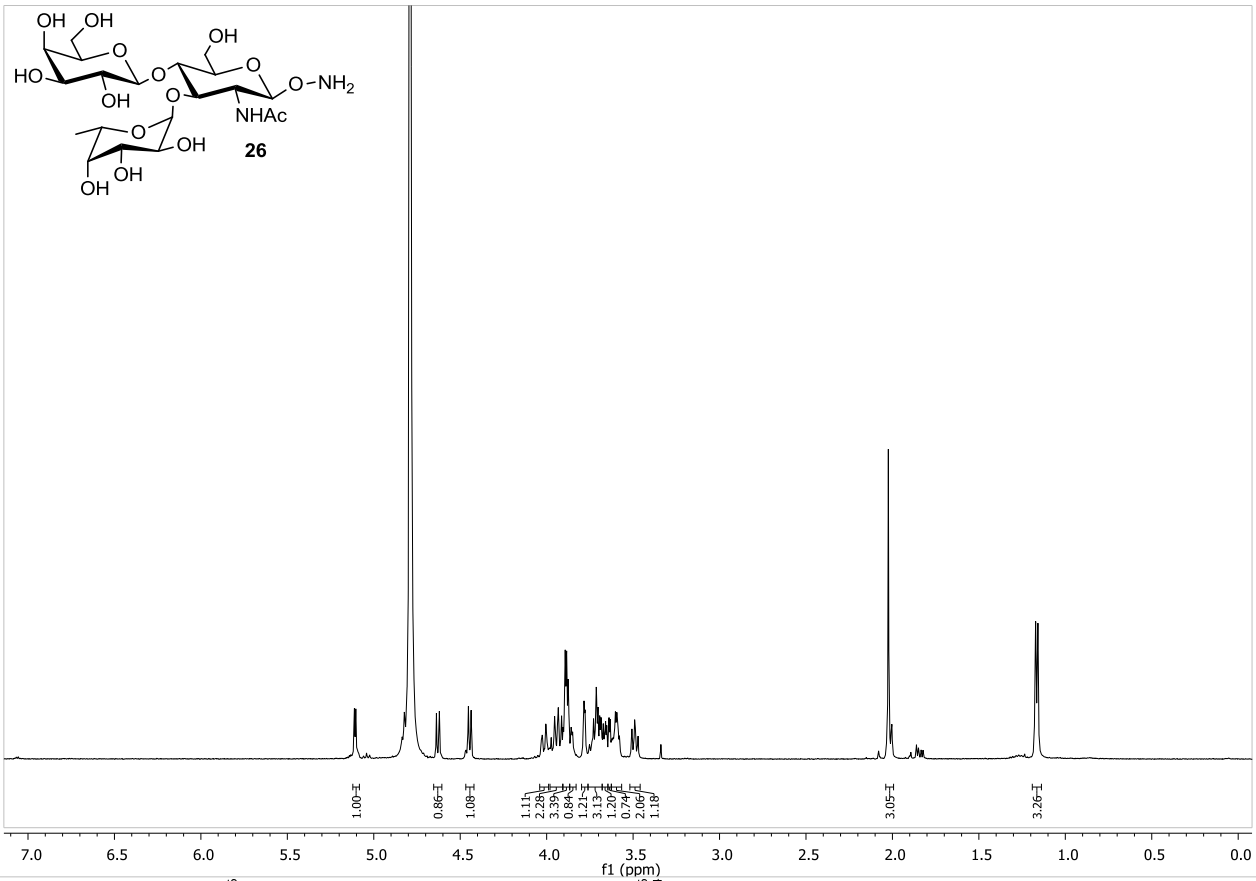

OBz OBz
BzO
OBz
OTBDPS
SPh
NHTroc
OPMB
OAc
OAc
20
f1 (ppm)
f1 (ppm)

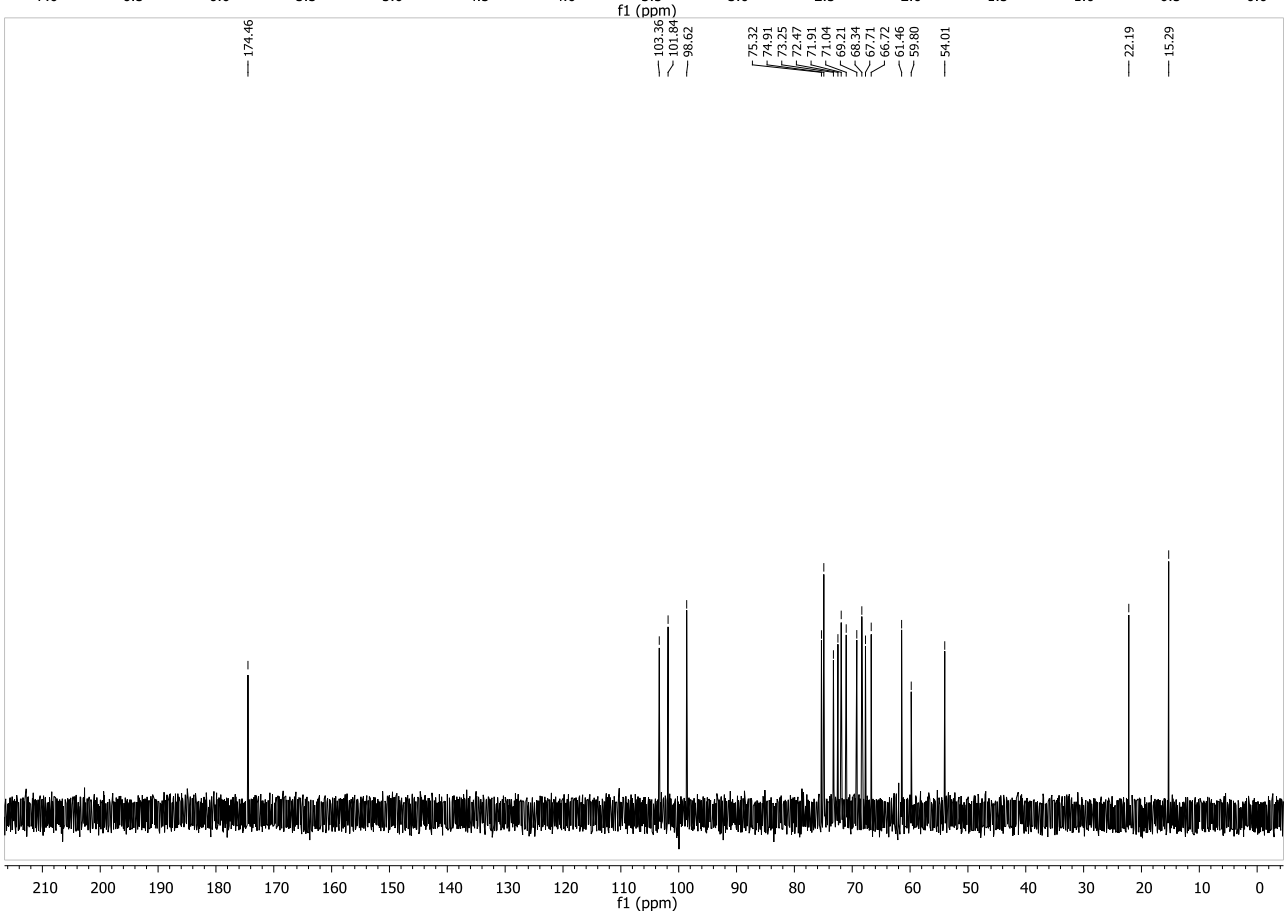

OBz
OBz
OTBDPS
BzO
O
O
SPh
OBz
O
NHTroc
O
OAc
OAc
OAc
21
1.76
2.01
5.51
0.79
5.86
9.87
1.41
5.18
4.15
0.99
1.00
0.85
1.06
0.99
1.08
1.01
1.09
1.10
0.77
2.81
1.22
0.96
1.03
1.87
1.07
0.75
3.01
2.42
2.78
2.75
8.16
f1 (ppm)
170.57
169.77
166.15
165.91
165.33
164.91
159.65
153.87
136.16
135.45
130.03
129.98
129.91
129.71
129.04
128.79
128.57
128.48
128.43
128.37
128.15
114.10
100.41
97.74
95.78
79.45
77.36
74.56
73.98
72.39
71.90
71.71
71.20
69.78
68.13
65.08
61.46
55.39
27.00
21.00
20.96
19.45
16.18
f1 (ppm)

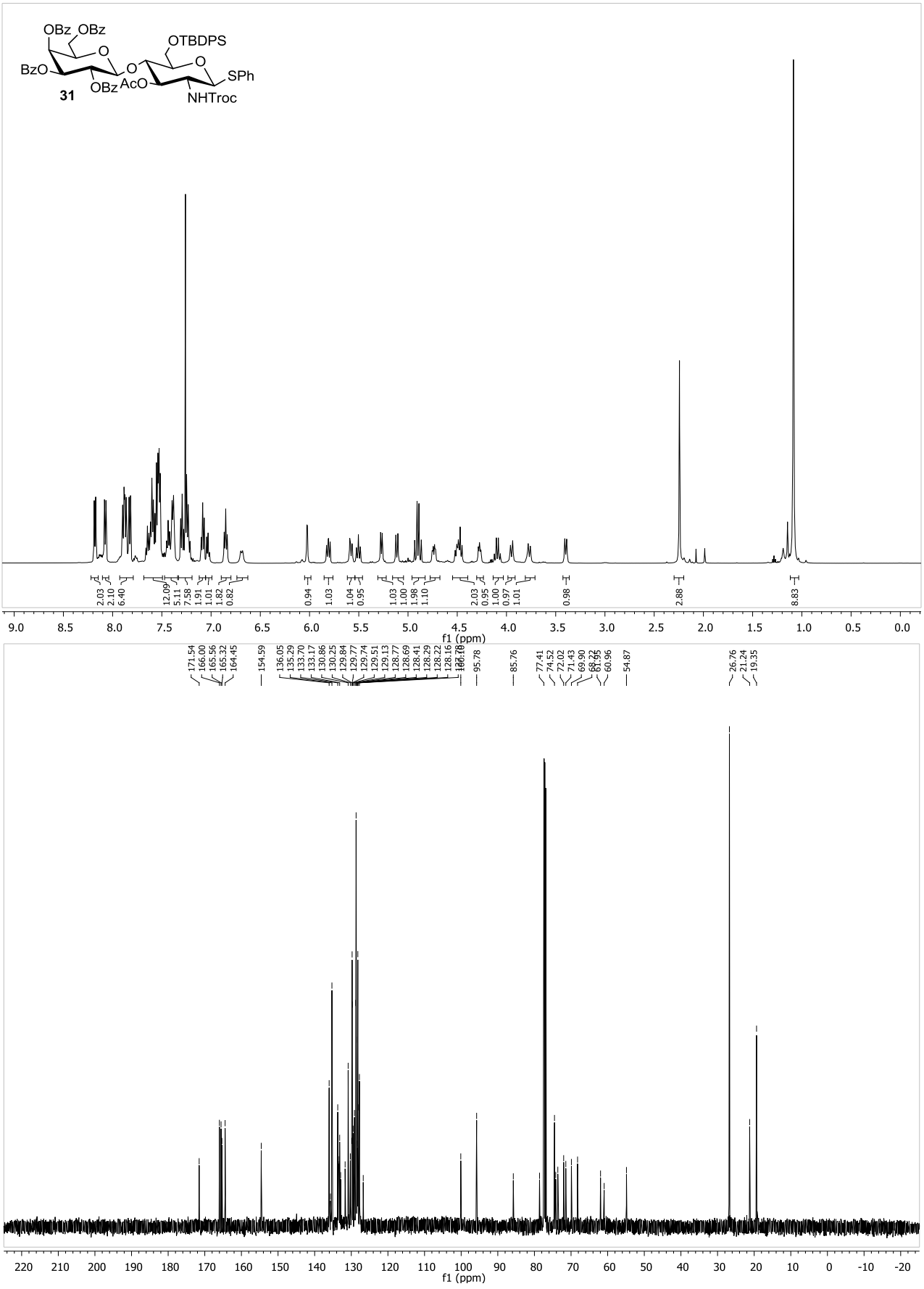

OBz
OBz
OTBDPS
BzO
OBz
NHTroc
OAc
OAc
OAc
23
f1 (ppm)
f1 (ppm)

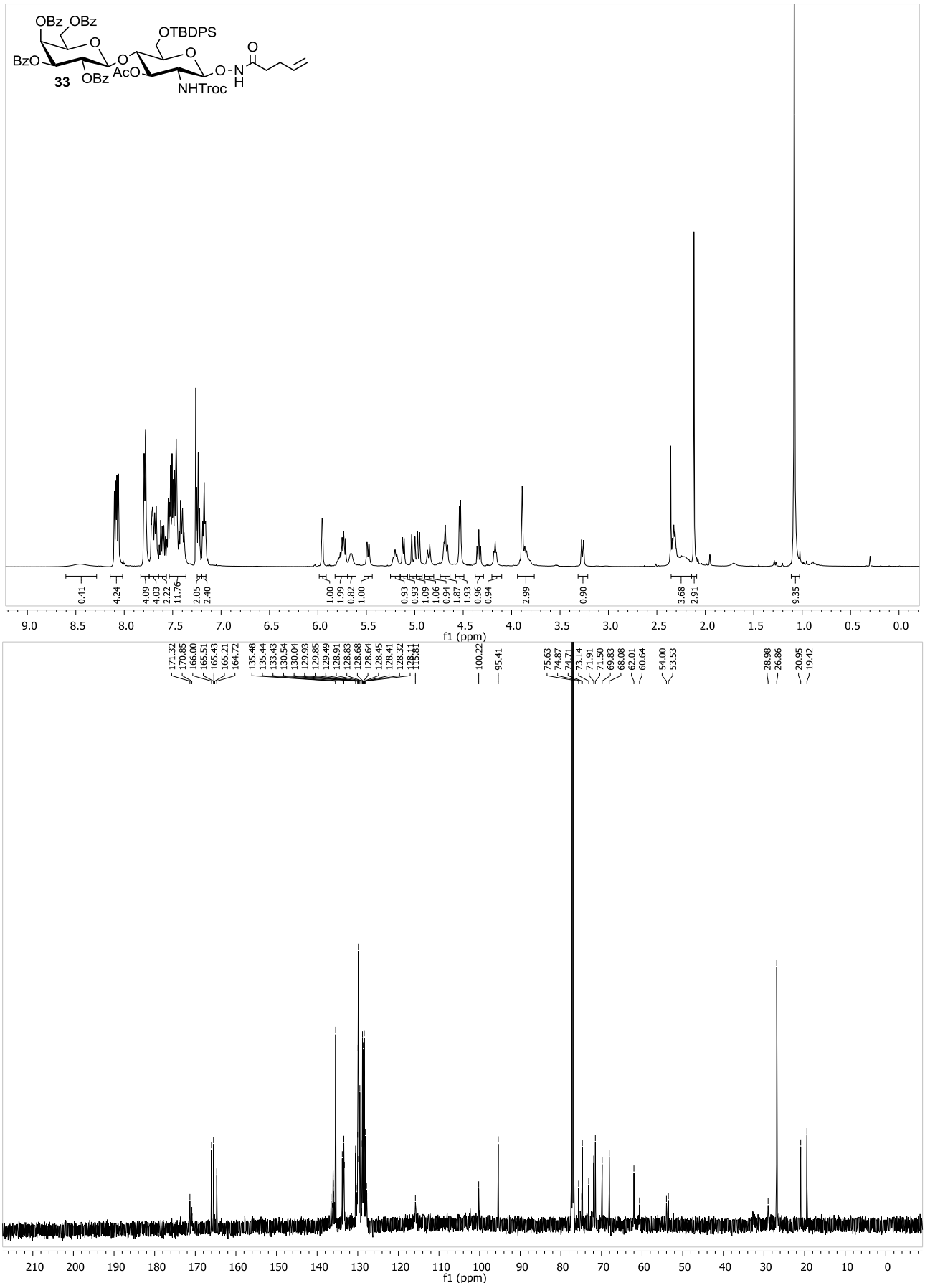

OBz OBz
OTBDPS
BzO
OBz
NHAc
OAc
OAc
OAc
24
f1 (ppm)
f1 (ppm)

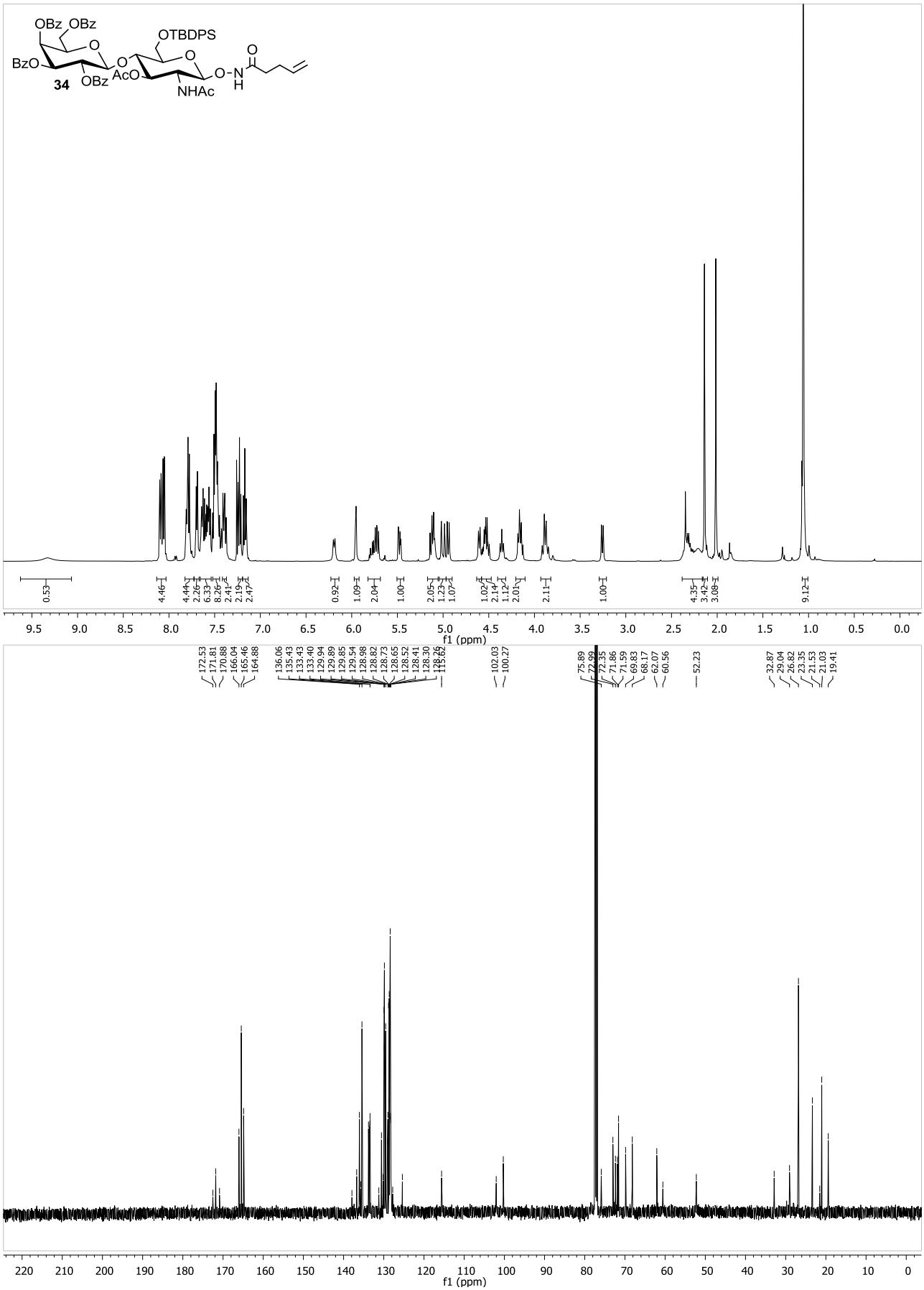

OH
OH
HO
O
O
OH
O
O
O
N
H
NHAc
OH
OH
OH
25
0.86
2.82
1.49
1.00
0.98
2.00
4.00
1.06
3.11
1.05
1.94
1.02
2.00
1.79
2.76
2.99
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
174.53
172.56
136.58
115.85
103.63
101.81
98.64
75.65
74.92
74.68
72.96
72.46
71.89
71.01
69.21
68.33
67.69
66.73
61.46
59.62
53.60
46.68
31.75
28.82
22.30
15.28
8.21
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

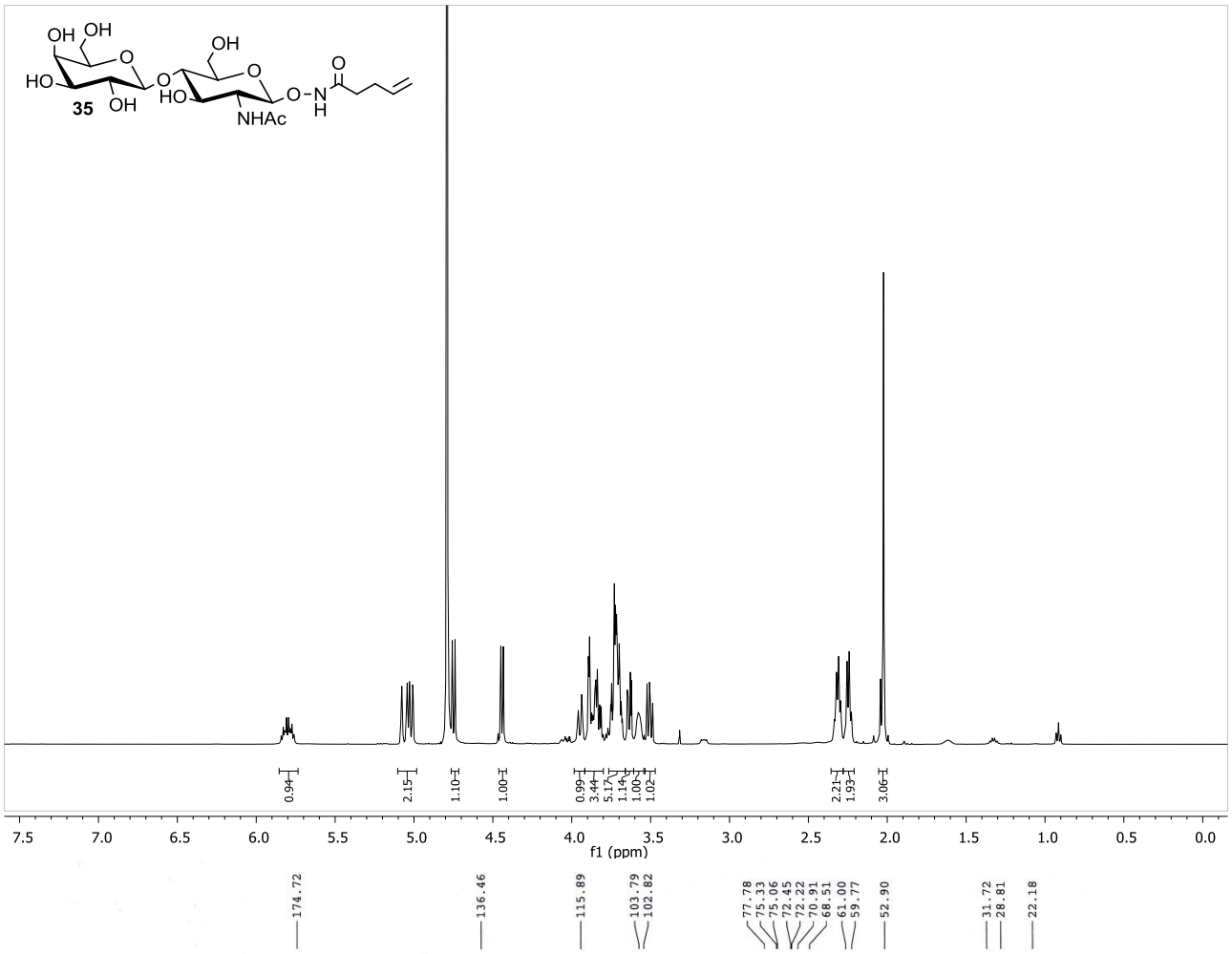

OH
OH
HO
O
O
OH
O
O
O-NH2
NHAc
O
OH
OH
OH
26
1.00
0.86
1.08
1.11
2.28
3.39
0.84
1.21
3.13
1.20
0.74
2.06
1.18
3.05
3.26
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

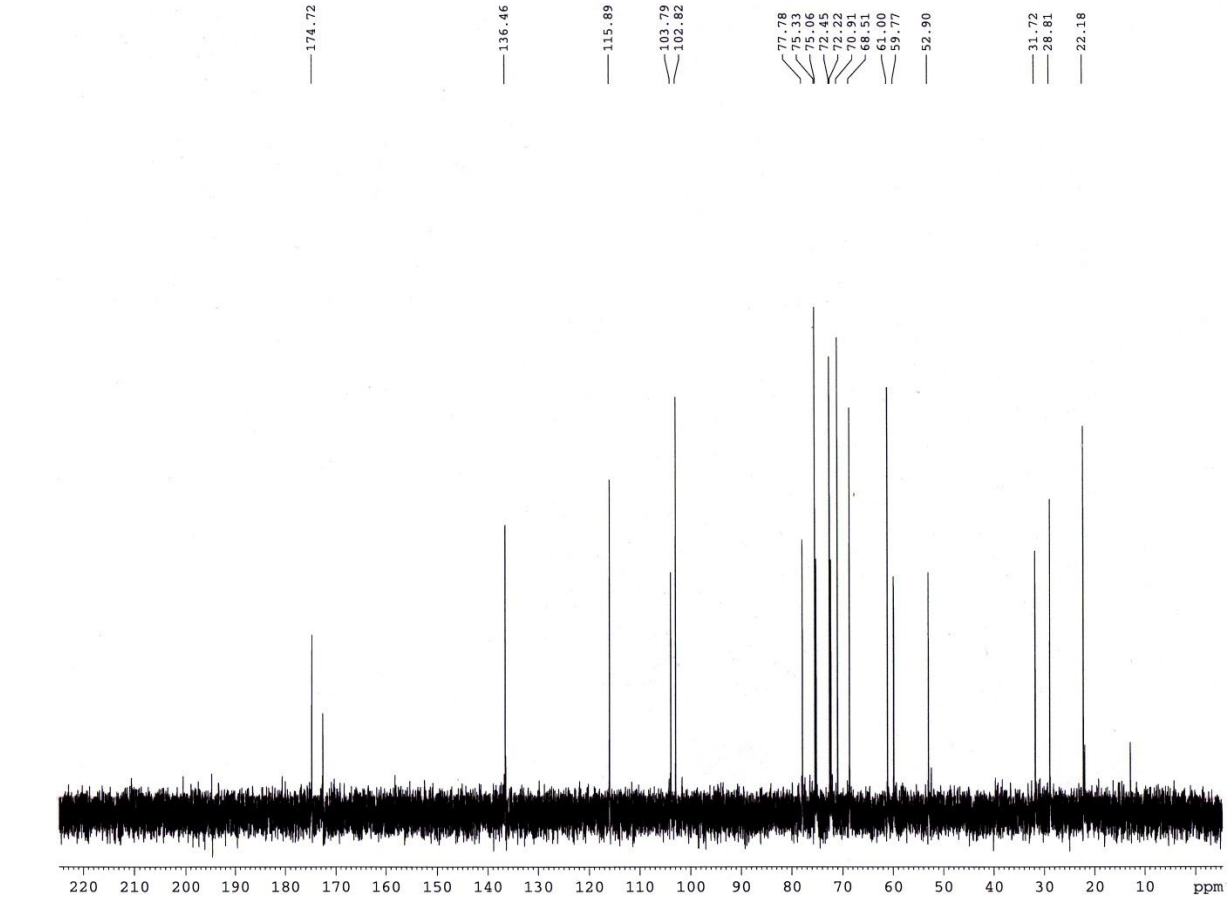

174.46
103.36
101.84
98.62
75.32
74.91
73.25
72.47
71.91
71.04
69.21
68.34
67.71
66.72
61.46
59.80
54.01
22.19
15.29
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

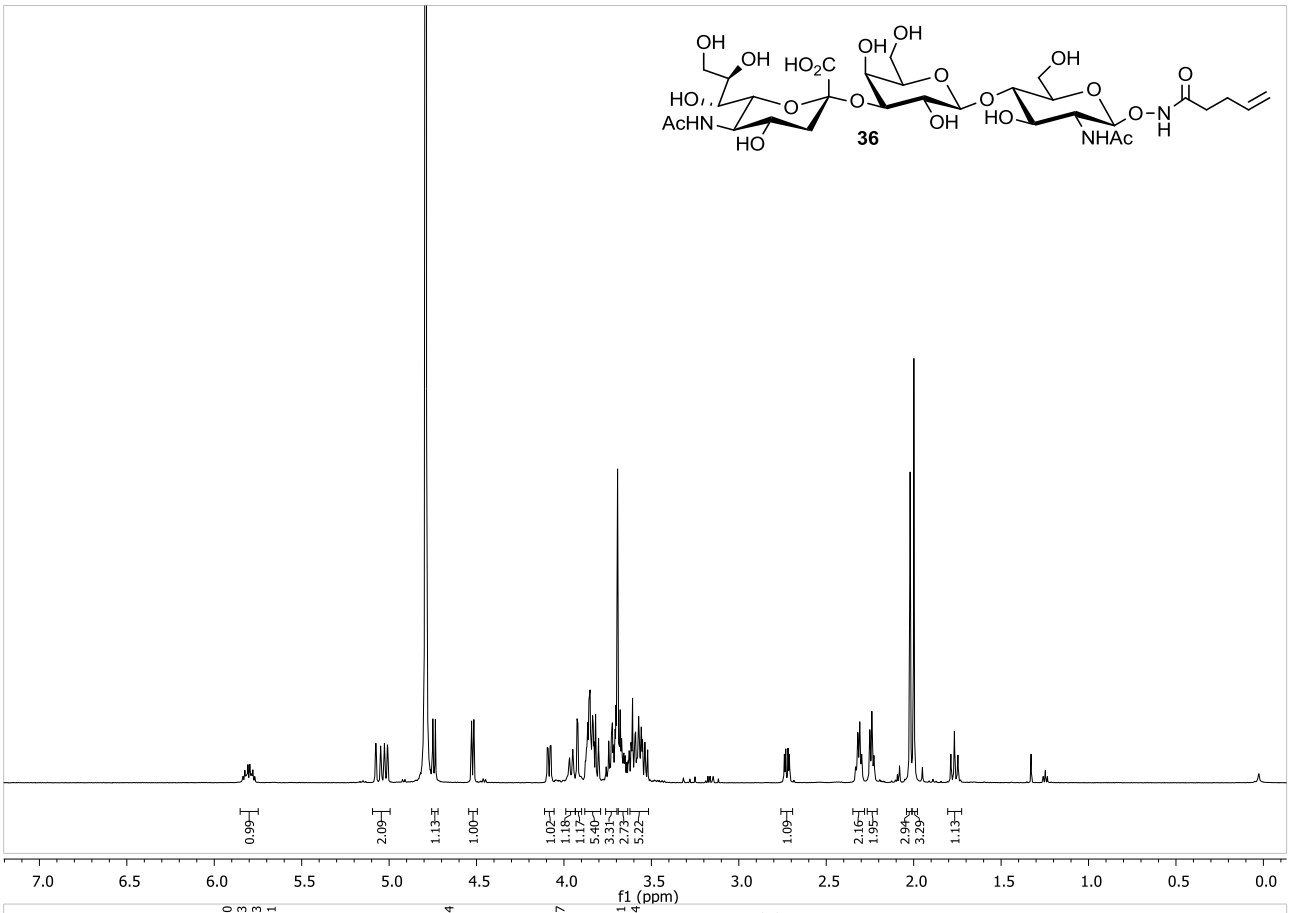

OBz OBz
OTBDPS
BzO
OBz AcO
SPh
NHTroc
31
f1 (ppm)

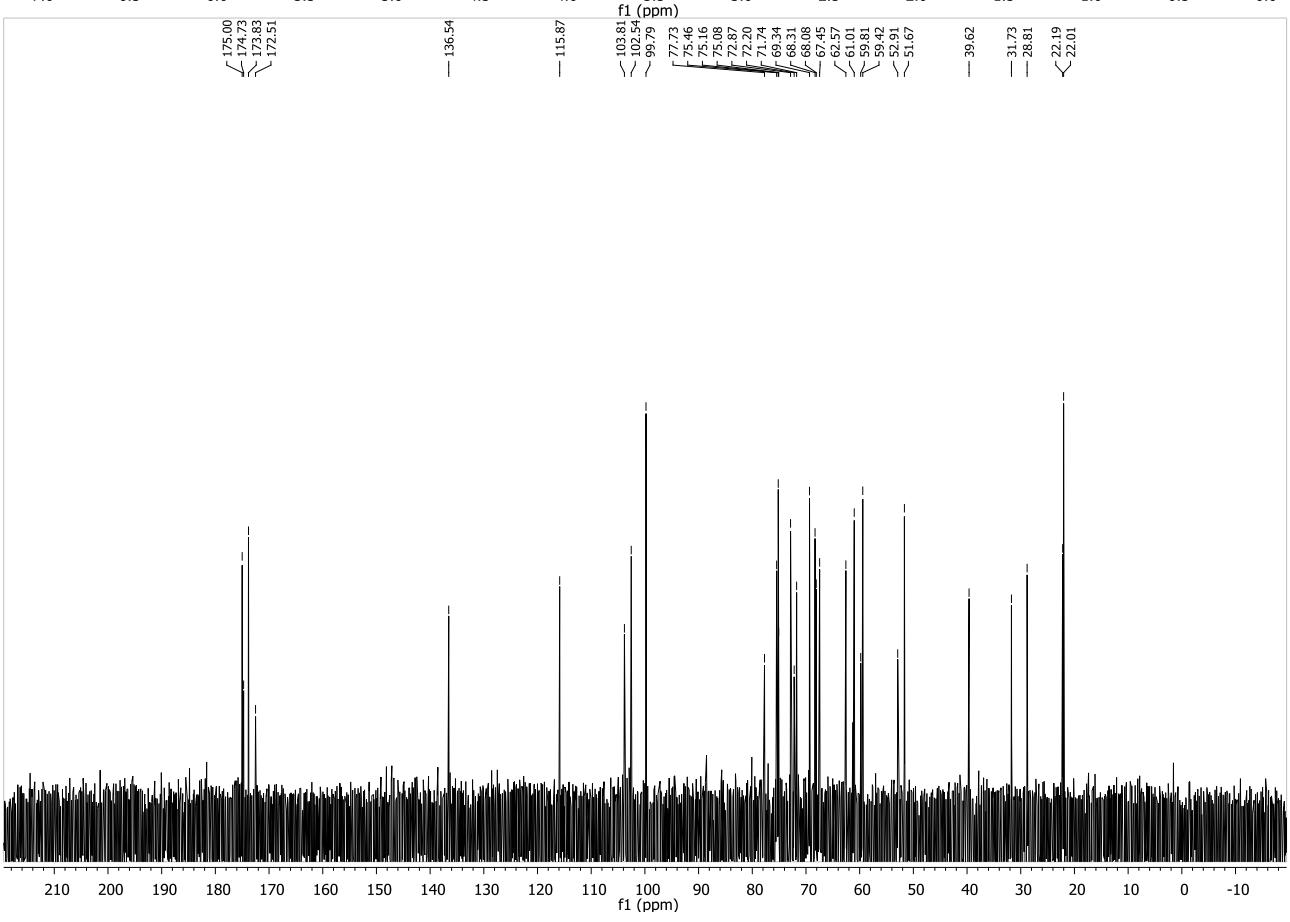

OBz OBz
O
BzO
OBz
33
O
AcO
OTBDPS
O
O
O-N
H
NHTroc
f1 (ppm)
f1 (ppm)

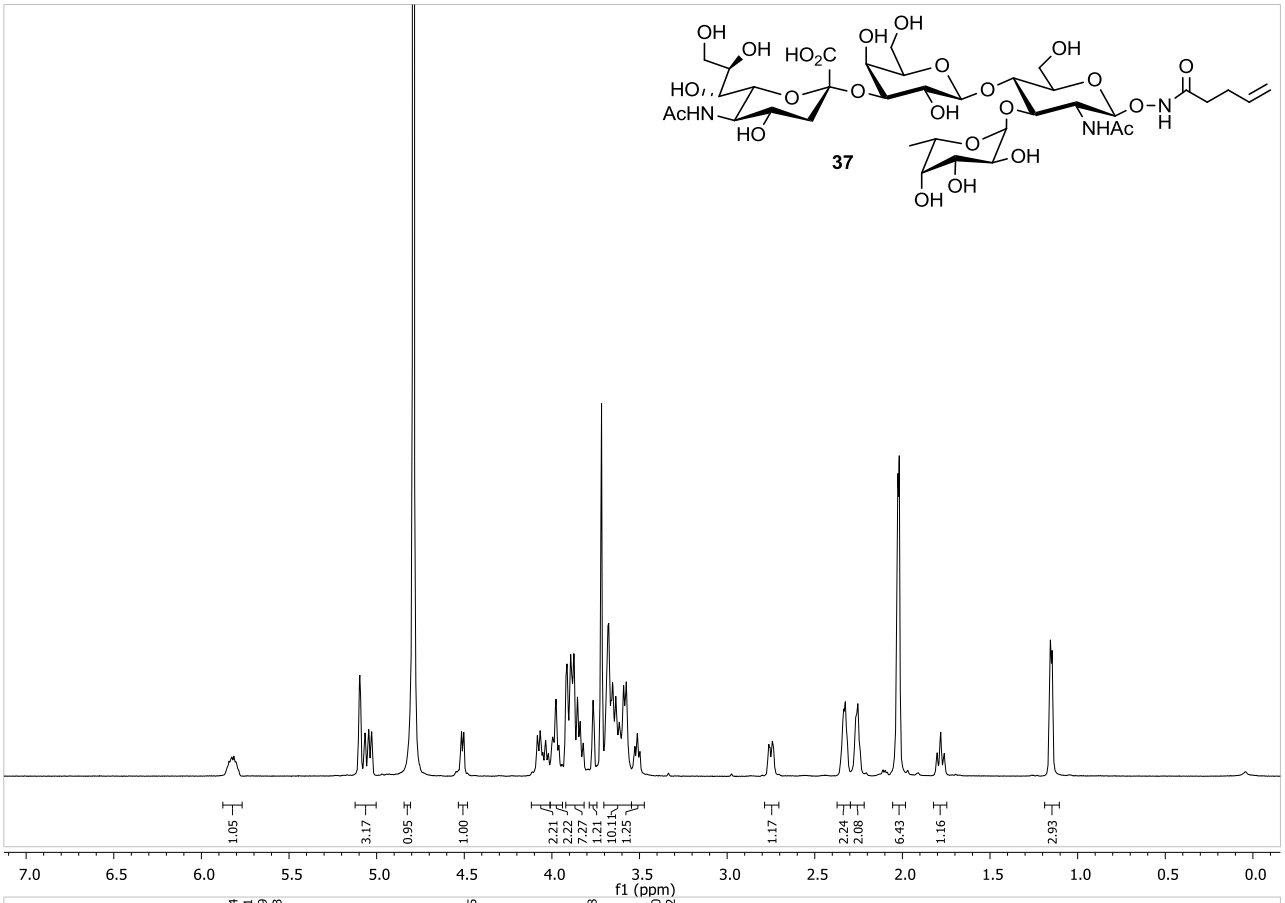

OBz OBz
OTBDPS
BzO
AcO
O-N
H
34
OBz
NHAc
0.53
4.46
4.44
2.26
6.33
8.26
2.41
2.19
2.47
0.92
1.09
2.04
1.00
2.05
1.23
1.07
1.02
2.14
1.12
2.01
2.11
1.00
4.35
3.42
3.08
9.12
f1 (ppm)
172.53
171.81
170.88
166.04
165.46
164.88
136.06
135.43
133.43
133.40
129.94
129.89
129.85
129.54
128.98
128.82
128.73
128.65
128.52
128.41
128.30
128.26
115.62
102.03
100.27
75.89
72.49
72.35
71.86
71.59
69.83
68.17
62.07
60.56
52.23
32.87
29.04
26.82
23.35
21.53
21.03
19.41
f1 (ppm)

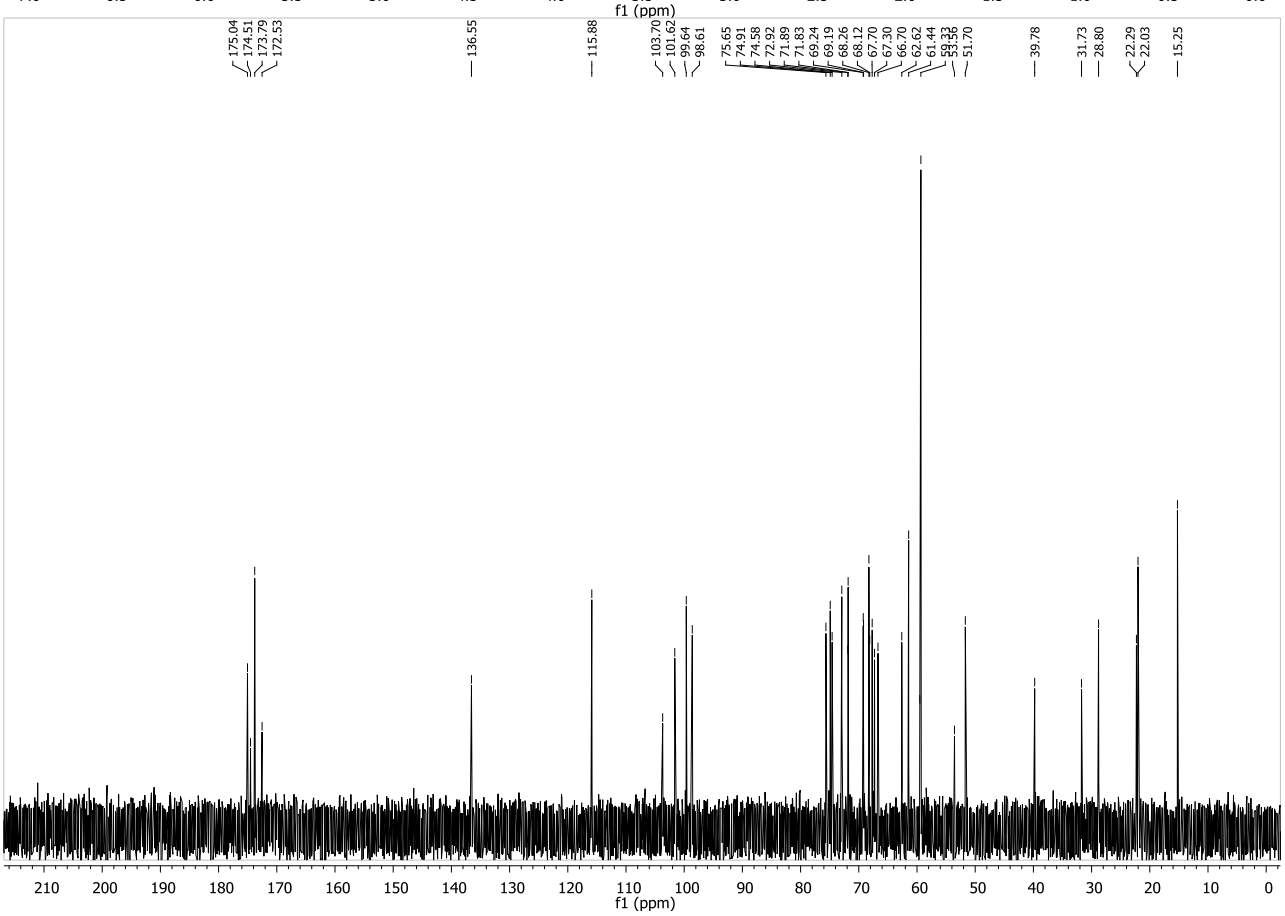

OH
OH
HO
35
OH
O
OH
HO
NHAc
O
O-N
H
O
0.94
2.15
1.10
1.00
0.99
3.44
5.17
1.14
1.00
1.02
2.21
1.93
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

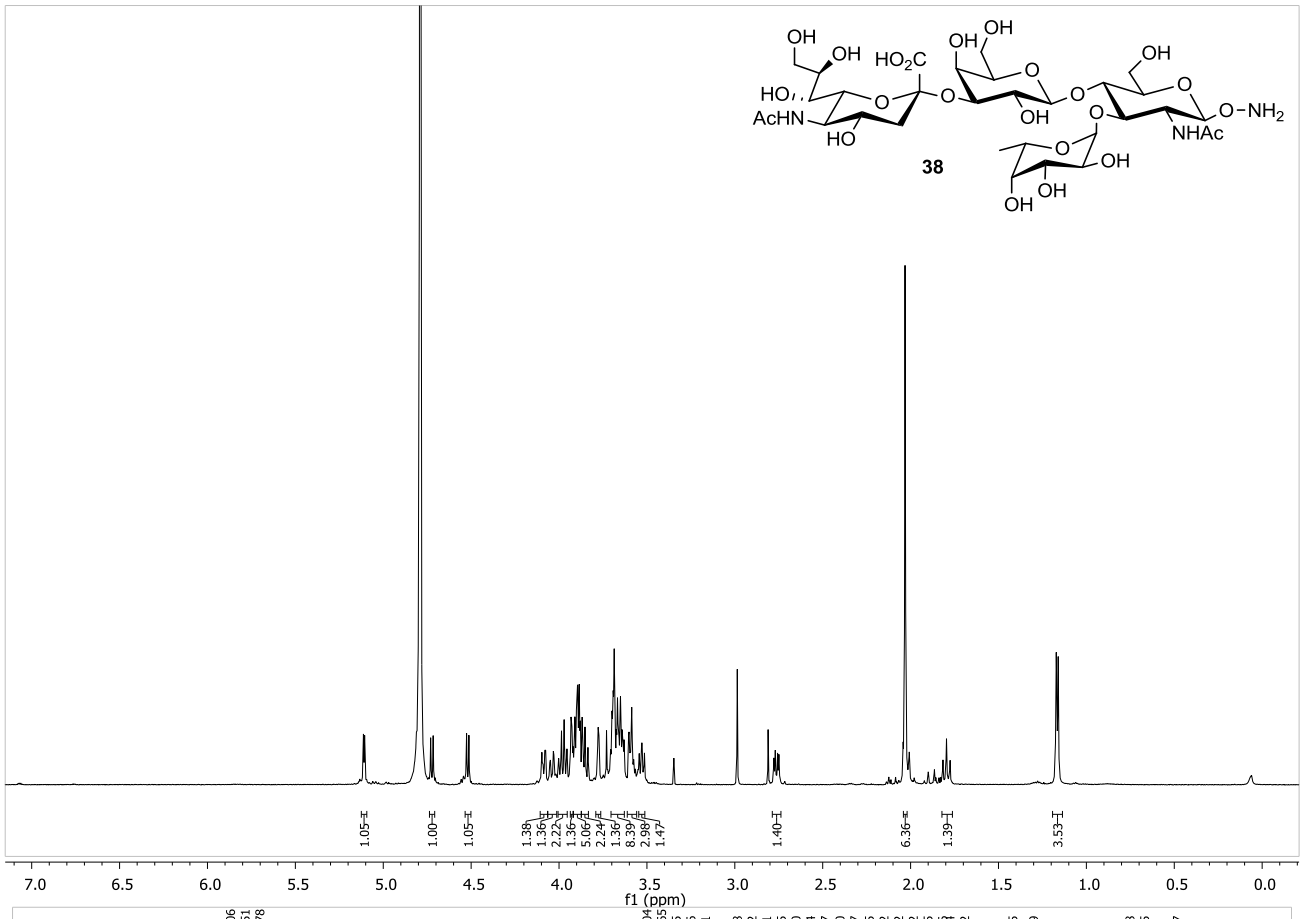

174.72
136.46
115.89
103.79
102.82
77.78
75.33
75.06
72.45
72.22
70.91
68.51
61.00
59.77
52.90
31.72
28.81
22.18
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

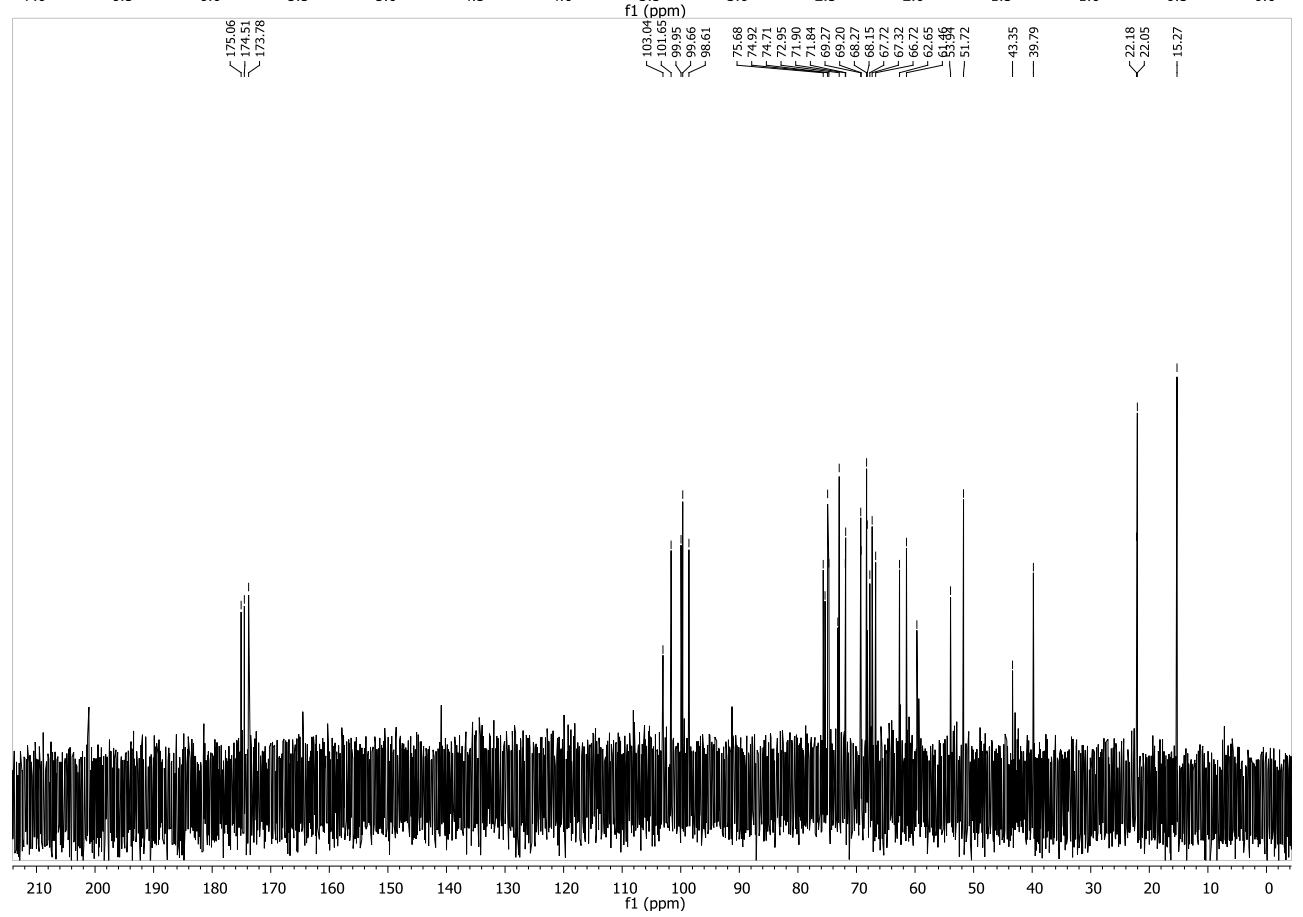

OH
OH
HO2C
OH
OH
O
O
HO
O
O
O
AcHN
OH
HO
HO
O
O
O-N
H
NHAc
36
0.99
2.09
1.13
1.00
1.02
1.18
1.17
5.40
3.31
2.73
5.22
1.09
2.16
1.95
2.94
3.29
1.13
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


175.00
174.73
173.83
172.51
136.54
115.87
103.81
102.54
99.79
77.73
75.46
75.16
75.08
72.87
72.20
71.74
69.34
68.31
68.08
67.45
62.57
61.01
59.81
59.42
52.91
51.67
39.62
31.73
28.81
22.19
22.01
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


37
1.05
3.17
0.95
1.00
2.21
2.22
2.27
1.21
10.11
1.25
1.17
2.24
2.08
6.43
1.16
2.93
f1 (ppm)


175.04
174.51
173.79
172.53
136.55
115.88
103.70
101.62
99.64
98.61
75.65
74.91
74.58
72.92
71.89
71.83
69.24
69.19
68.26
68.12
67.70
67.30
66.70
62.62
61.44
53.58
51.70
39.78
31.73
28.80
22.29
22.03
15.25
f1 (ppm)


38
1.05
1.00
1.05
1.38
1.36
2.22
1.36
5.06
2.24
1.36
8.39
2.98
1.47
1.40
6.36
1.39
3.53
f1 (ppm)


175.06
174.51
173.78
103.04
101.65
99.95
99.66
98.61
75.68
74.92
74.71
72.95
71.90
71.84
69.27
69.20
68.27
68.15
67.72
67.32
66.72
62.65
51.72
43.35
39.79
22.18
22.05
15.27
f1 (ppm)

Complete ref 68:

(68) Cho, H.; Daniel, T.; Buechler, Y. J.; Litzinger, D. C.; Maio, Z. Putnam, A. M. H.; Kraynov, V. S.; Sim, B.-C.; Bussell, S.; Javahishvili, T.; Kaphle, S.; Viramontes, G.; Ong, M.; Chu, S.; GC, B.; Lieu, R. Knudsen, N.; Castiglioni, P.; Norman, T. C.; Axelrod, D. W.; Hoffman, A. R.; Schultz, P. G. DiMarchi, R. D.; Kimmel, B. E. *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 9060 -9065.