Supplementary Material (ESI) for Organic & Biomolecular Chemistry

# Total synthesis of Le$^{A}$-LacNAc pentasaccharide as a ligand for *Clostridium difficile* toxin A

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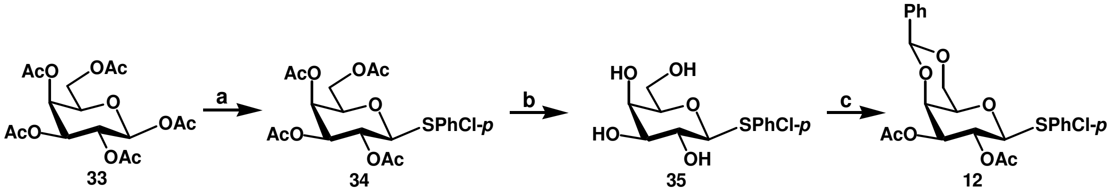


a. *p*-ClPhSH/$BF_3.Et_2O/CH_2Cl_2$; b. NaOMe/MeOH; c. (1) $PhCH(OMe)_2$/CSA/$CH_3CN$, (2) $Ac_2O$/Pyridine.

### *p*-Chlorophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (34)

To a solution containing 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose **33** (20.0 g, 51.2 mmol) and *p*-chlorophenylthiol (11.1 g, 76.9 mmol, 1.5 equiv.) in anhydrous $CH_2Cl_2$ (250 mL), was added boron trifluoride etherate (9.7 mL, 76.9 mmol), and the mixture was stirred at room temperature overnight. The mixture was cooled to 0° C, $Et_3N$ (10 mL) was added to quench the reaction. The unreacted thiol was acetylated by adding acetic anhydride (8.0 mL) to the mixture. After stirring at room temperature for 1 hour, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (300 mL), successively washed with $H_2O$ (2 × 200 mL), 2N NaOH (1 × 100 mL), 2N HCl (1 × 100 mL), dried over anhydrous $Na_2SO_4$, and evaporated. Pure compound **34** was obtained by recrystallization from a mixture of AcOEt – hexane (21.0 g, 86.3% yield) as colorless crystals (Found: C, 50.63; H, 5.05%. $C_{20}H_{23}O_9SCl$ requires C, 50.58; H, 4.88%); $[\alpha]_D$ -1.3° (*c* 0.9, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.47 (d, 2H, *J* 8.6 Hz, SPhCl), 7.29 (d, 2H, *J* 8.6 Hz, SPhCl), 5.41 (dd, 1H, *J* 3.2, 0.7 Hz, H-4), 5.20 (1H, dd, *J* 9.9, 9.9 Hz, H-2), 5.05 (dd, 1H, *J* 9.9, 3.3 Hz, H-3), 4.66 (d, 1H, *J* 9.9 Hz, H-1), 4.18 (dd, 1H, *J* 11.4, 7.0 Hz, H-6a), 4.10 (dd, 1H, *J* 11.4, 6.1 Hz, H-6b), 3.93 (ddd, 1H, *J* 7.0, 6.3, 0.7, H-5), 2.11 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.05 (s, 3H, Ac), 1.98 (s, 3H, Ac); $\delta_C$ (100 MHz, $CDCl_3$) 170.33 (CO), 170.10 (CO), 170.01 (CO), 169.38 (CO), 137.45 C-1_SPhCl), 134.41 (C-3_SPhCl + C-5_SPhCl), 130.33 (C-4_SPhCl), 128.99 (C-2_SPhCl + C-6_SPhCl), 86.06 (C-1), 74.51 (C-5), 71.93 (C-3), 67.15 (C-4 or C-2), 67.12 (C-2 or C-4), 61.58 (C-6), 20.82 (Ac), 20.66 (Ac), 20.59 (Ac), 20.56 (Ac); *m/z* (ESI-HRMS) calcd for $[C_{20}H_{23}O_9SCl + Na]^+$ 497.0644, found 497.0645.

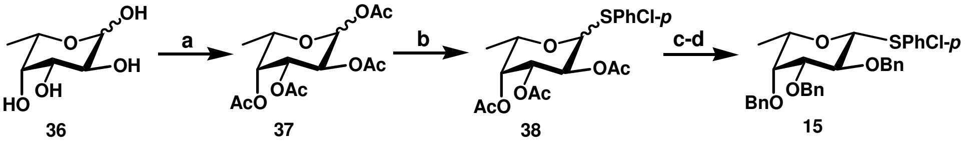
### *p*-Chlorophenyl 1-thio-β-D-galactopyranoside (35)

The per-acetate **34** (20.0 g, 42.1 mmol) was dissolved in anhydrous MeOH (170 mL), a solution of NaOMe in MeOH (1.5 M, 3 mL) was added, and the mixture was stirred at room temperature for 30 minutes. After neutralizing the reaction with Amberlite IR-120 ($H^+$), the mixture was evaporated under reduced pressure to give pure tetraol **35** (12.9 g, 100% yield) as white solid (Found: C, 46.66; H, 5.28%. $C_{12}H_{15}O_5SCl$ requires C, 46.98; H, 4.93%); $[\alpha]_D$ -46.4° (*c* 1.0, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.54 (d, 2H, *J* 8.6 Hz, SPhCl), 7.29 (m, 2H, *J* 8.6 Hz, SPhCl), 4.57 (d, 1H, *J* 9.6 Hz, H-1), 3.90 (dd, 1H, *J* 3.2, 0.6 Hz, H-4), 3.77 (dd, 1H, *J* 11.5, 6.9 Hz, H-6a), 3.71 (dd, 1H, *J* 11.5, 5.1 Hz, H-6b), 3.60 (dd, 1H, *J* 9.3, 9.3 Hz, H-2), 3.57 (ddd, 1H, *J* 0.9, 5.1, 6.9 Hz, H-5), 3.50 (dd, 1H, *J* 9.2, 3.3 Hz, H-3); $\delta_C$ (100 MHz, $CD_3OD$) 133.29 (C-1_SPhCl), 132.66 (C-4_SPhCl), 132.33 (C-3_SPhCl + C-5_SPhCl), 128.43 (C-2_SPhCl + C-6_SPhCl), 88.51 (C-1), 79.27 (C-5), 74.88 (C-3), 69.45 (C-2), 69.01 (C-4), 61.25 (C-6); *m/z* (ESI-HRMS) calcd for $[C_{12}H_{15}O_5SCl + Na]^+$ 329.0221, found 329.0224.

## *p*-Chlorophenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (12)

To a suspension of tetraol **35** (7.24 g, 23.6 mmol) and benzaldehyde dimethyl acetal (7.09 mL, 47.2 mmol) in anhydrous $CH_3CN$ (100 mL) was added (±)-Camphor-10-sulfonic acid (500 mg), and the mixture was stirred for 30 minutes. $Et_3N$ (2.0 mL) was added to quench the reaction. After removing the solvent under reduced pressure, the residue was acetylated with a mixture of acetic anhydride (25 mL) and anhydrous pyridine (30 mL) for 4 hours at room temperature. The reaction mixture was concentrated again and co-evaporated with toluene (3 × 50 mL). After a column chromatography on silica gel using a gradient of AcOEt – toluene (5% → 7%) as the eluent, compound **12** (10.2 g, 90% yield) was obtained in pure form (Found: C, 57.60; H, 5.35%. $C_{23}H_{23}O_7SCl$ requires C, 57.68; H, 4.84%); $[\alpha]_D$ -21.8° (*c* 0.6, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.58 (d, 2H, *J* 8.4 Hz, SPhCl), 7.44 – 7.32 (m, 5H, Ph), 7.21 (d, 2H, *J* 8.5, SPhCl), 5.46 (s, 1H, PhCH), 5.29 (dd, 1H, *J* 9.8, 9.8 Hz, H-2), 5.01 (dd, 1H, *J* 9.9, 3.3 Hz, H-3), 4.65 (d, 1H, *J* 9.7 Hz, H-1), 4.38 – 4.29 (m, 2H, H-4 + H-6a), 3.98 (dd, 1H, *J* 12.1, ~1 Hz, H-6b), 3.56 (m, 1H, H-5), 2.10 (s, 3H, Ac), 2.03 (s, 3H, Ac); $\delta_C$ (100 MHz, $CDCl_3$) 170.53 (CO), 169.03 (CO), 137.44, 135.58, 134.61, 129.25, 128.94, 128.90, 128.23, 126.43, 100.98 (PhCH), 84.22 (C-1), 73.34 (C-4), 73.03 (C-3), 69.66 (C-5), 68.99 (C-6), 66.59 (C-2), 20.89 (Ac), 20.85 (Ac); *m/z* (ESI-HRMS) calcd for $[C_{23}H_{23}O_7SCl + Na]^+$ 501.0745, found 501.0749.

## Synthesis of compound 15



a. $Ac_2O$/pyridine; b. *p*-ClPhSH/$BF_3.Et_2O$/$CH_2Cl_2$; c. NaOMe/MeOH; d. BnBr/NaH/DMF;

## *p*-Chlorophenyl 2,3,4-tri-*O*-acetyl-1-thio-α,β-L-fucopyranoside (38)

A solution of L-fucose (**36**, 20.34 g, 0.124 mol) in a mixture of acetic anhydride (70 mL) and anhydrous pyridine (80 mL) was stirred at 50° C overnight. The mixture was evaporated under vacuum and coevaporated with toluene (3 × 100 mL) to afford the crude 1,2,3,4-tetra-*O*-acetyl-α,β-L-fucopyranose (**37**, 40 g, quantitative). The crude α,β-mixture was dissolved in anhydrous $CH_2Cl_2$ (200 mL), and *p*-chlorophenylthiol (27.9 g, 192.6 mmol, 1.6 equiv.) was added. After the addition of boron trifluoride etherate (22.7 mL, 180.6 mmol, 1.5

equiv.), the mixture was stirred at room temperature overnight. The mixture was cooled to 0° C, $Et_3N$ (20 mL) was added to quench the reaction. The unreacted thiol was acetylated by adding acetic anhydride (16.0 mL) to the mixture. After stirring at room temperature for 1 hour, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (600 mL), successively washed with $H_2O$ (2 × 300 mL), 2N HCl (1 × 300 mL), and 5% $NaHCO_3$ (2 × 300 mL), dried over anhydrous $Na_2SO_4$, and evaporated. Compound **38** (41.15 g, 82% yield) was obtained as an α,β-mixture (1:9) by chromatography on silica gel using a mixture of 5% AcOEt – hexane as eluent (Found: C, 51.95; H, 5.09%. $C_{18}H_{21}O_7SCl$ requires C, 51.86; H, 5.08%); $\delta_H$ (400 MHz, $CDCl_3$) for the β-anomer: 7.49 – 7.45 (m, 2H, SPhCl), 7.32 – 7.27 (m, 2H, SPhCl), 5.26 (dd, 1H, *J* 3.4, 0.8 Hz, H-4), 5.18 (dd, 1H, *J* 9.8, 9.8 Hz, H-2), 5.05 (dd, 1H, *J* 9.9, 3.3 Hz, H-3), 4.65 (d, 1H, *J* 9.8 Hz, H-1), 3.83 (dq, 1H, *J* 6.5, 1.0 Hz, H-5), 2.13 (s, 3H, Ac), 2.09 (s, 3H, Ac), 1.97 (s, 3H, Ac), 1.23 (d, 1H, *J* 6.4 Hz, H-6); $\delta_C$ (100 MHz, $CDCl_3$) 170.43 (CO), 170.01 (CO), 169.35 (CO), 134.40 (Ar), 134.16 (Ar), 130.73 (Ar), 128.91 (Ar), 85.88 (C-1), 73.22 (C-5), 72.35 (C-3), 70.24 (C-4), 67.21 (C-2), 20.79 (Ac), 20.57 (Ac), 20.55 (Ac), 16.40 (C-6); *m/z* (ESI-HRMS) calcd for $[C_{18}H_{21}O_7SCl + Na]^+$ 439.0589, found 439.0590.

## *p*-Chlorophenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (15)

The triacetate **38** (1:9 α:β mixture, 21.5 g, 51.6 mmol) was dissolved in anhydrous MeOH (250 mL), and a solution of NaOMe in MeOH (1.5 M, 3.0 mL) was added. After stirring at room temperature for 2 hours, the mixture was neutralized with Amberlite IR-120 ($H^+$). The resin was removed by filtration and the organic solution was concentrated under reduced pressure to give a syrup (~15 g). The crude triol was dissolved in anhydrous DMF (130 mL), NaH (60% in mineral oil, 10.0g, 250 mmol) was added portion wise, and the reaction mixture was stirred at room temperature for 1 hour. After cooling to 0° C, benzyl bromide (35 mL, 295.2 mmol) was added dropwise, and the mixture was allowed to warm-up to temperature. After stirring overnight, MeOH (15 mL) was added, and the mixture was concentrated under reduced pressure to remove most of the solvent. The mixture was dissolved in EtOAc (400 mL), washed with $H_2O$ (1 × 200 mL), 2N HCl (1 × 200 mL), 10% $NaHCO_3$ (1 × 200 mL), dried over anhydrous $Na_2SO_4$, and evaporated. After a chromatography on silica gel using 3.5% AcOEt – hexane as eluent, the pure β-anomer **15** was obtained (23.6 g, 85.5 yield%) as a white solid (Found: C, 70.70; H, 5.83%. $C_{33}H_{33}O_4SCl$ requires C, 70.63; H, 5.93%); $[\alpha]_D$ +3.8° (*c* 0.7, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.54 (d, 2H, *J* 8.6 Hz, SPhCl), 7.47 – 7.28 (m, 15H, 3 × Bn), 7.15 (d, 2H, *J* 8.6 Hz, SPhCl), 5.03 (d, 1H, *J* 11.4 Hz, Bn), 4.77 (s, 4H, Bn), 4.68 (d, 1H, *J* 11.4 Hz, Bn), 4.58 (d, 1H, *J* 9.6 Hz, H-1), 3.92 (dd, 1H, *J* 9.4, 9.4 Hz, H-2), 3.67 (dd, 1H, *J* 2.3, ~1 Hz, H-4), 3.62 (dd, 1H, *J* 2.7, 9.2 Hz, H-3), 3.56 (dq, 1H, *J* 6.3, ~1 Hz, H-5), 1.30 (d, 3H, *J* 6.4 Hz, H-6); $\delta_C$ (100 MHz, $CDCl_3$) 138.62, 138.29, 133.12, 132.94, 132.57, 128.85, 128.44, 128.33, 128.25, 128.22, 127.98, 127.74, 127.71, 127.59, 127.55 (Ar), 87.12 (C-1), 84.50 (C-3), 76.87 (C-2), 76.55 (C-4), 75.55 (Bn), 74.68 (C-5), 74.67 (Bn), 72.82 (Bn), 17.29 (C-6); *m/z* (ESI-HRMS) calcd for $[C_{33}H_{33}O_4SCl + Na]^+$ 583.1680, found 583.1678.

### *p*-Chlorophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (17)

To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α,β-glucopyranose **16** (40.0 g, 89.4 mmol) and *p*-chlorophenylthiol (20.6 g, 142.4 mmol) in anhydrous $CH_2Cl_2$ (200 mL), was added $BF_3.Et_2O$ (16.8 mL, 134 mmol) dropwise. After stirring for 3 days at rt, the reaction was cooled to 0°, and $Et_3N$ (35 mL) was added to quench the reaction. The unreacted thiol was then acetylated by the addition of excess $Ac_2O$ (15 mL). After 1h at rt, the mixture was concentrated under reduced pressure; the residue was dissolved in EtOAc (600 mL), and the organic solution was washed successively with $H_2O$ (2 × 300 mL), a solution of 2 N HCl (1 × 300 mL) and a 5% solution of aqueous $NaHCO_3$ (1 × 150 mL), dried over anhydrous $Na_2SO_4$, and concentrated to give a syrup which was recrystallized from a mixture of AcOEt –hexane. The desired thioglycoside **17** (38 g, yield 76%) was obtained in pure form as a white solid (Found: C, 55.47; H, 4.69; N, 2.41%. $C_{26}H_{24}NO_9ClS$ requires C, 55.57; H, 4.30; N, 2.49%); $[\alpha]_D$ +39.7° (*c* 1.2, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.88 (m, 2H, Phth), 7.77 (m, 2H, Phth), 7.37 (m, 2H, SPhCl), 7.26 (m, 2H, SPhCl), 5.79 (dd, 1H, *J* 9.7 Hz, H-3), 5.67 (d, 1H, *J* 10.5 Hz, H-1), 5.12 (dd, 1H, *J* 9.7 Hz, H-4), 4.32 (dd, 1H, *J* 10.4, 10.4 Hz, H-2), 4.29 (dd, 1H, *J* 4.9, 12.4 Hz, H-6a), 4.21 (dd, 1H, *J* 2.3, 12.3 Hz, H-6b), 3.90 (ddd, 1H, *J* 2.3, 4.9, 10.2 Hz, H-5), 2.11 (s, 1H, Ac), 2.03 (s, 3H, Ac), 1.84 (s, 3H, Ac); $\delta_C$ (100 MHz, $CDCl_3$) 170.53 (CO), 170.05 (CO), 169.38 (CO), 167.82 (CO), 166.91, (CO), 135.01, 134.99, 129.04, 123.74, 82.70 (C-1), 75.98 (C-5), 71.52 (C-3), 68.59 (C-4), 62.11 (C-6), 53.55 (C-2), 20.75 (Ac), 20.59 (Ac), 20.37 (Ac); *m/z* (ESI-HRMS) calcd for $[C_{26}H_{24}NO_9ClS + Na]^+$ 584.07525, found 584.07542.

### *p*-Chlorophenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (18)

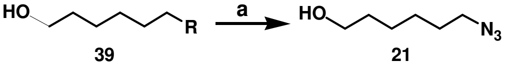
The peracetylated thioglycoside **17** (20.0 g, 35.6 mmol) was added to a solution of ~0.1 M guanidine/guanidinium chloride (400 mL); the starting material was observed to gradually dissolve to give a clear solution followed by the precipitation of desired deacetylated thioglycoside from the reaction mixture. The solid was filtered off under vacuum and washed with MeOH to afford pure **18** (14.53 g); after concentration of the mother liquor, more **18** (0.62 g) was crystallized out from the mixture. The total amount of **18** is 15.15 g (yield: 97.7%) (Found: C, 53.27; H, 4.50; N, 3.04%. $C_{20}H_{20}NO_7ClS.H_2O$ requires C, 52.92; H, 4.44; N, 3.09%); $[\alpha]_D$ +59.5° (*c* 0.34, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.93 – 7.81 (m, 4H, Phth), 7.40 (d, 2H, *J* 8.6 Hz, SPhCl), 7.25 (d, 2H, *J* 8.6 Hz, SPhCl), 5.57 (d, 1H, *J* 10.4 Hz, H-1), 4.24 (dd, 1H, *J* 10.2, 8.5 Hz, H-3), 4.08 (dd, 1H, *J* 10.3, 10.3 Hz, H-2), 3.95 (dd, 1H, *J* 12.1, 2.1 Hz, H-6a), 3.75 (dd, 1H, *J* 12.1, 5.7 Hz, H-6b), 3.49 (ddd, 1H, *J* 9.9, 5.5, 2.0 Hz, H-5), 3.43 (dd, 1H, *J* 9.8, 8.6 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 135.84, 135.79, 135.06, 134.65, 133.12, 130.16, 124.64, 124.34 (Ar), 85.14 (C-1), 82.92 (C-5), 73.96 (C-3), 72.36 (C-4), 62.97 (C-6), 57.84 (C-2); *m/z* (ESI-HRMS) calcd for $[C_{20}H_{18}NO_6ClS + Na]^+$ 458.0436, found 458.0435.

### *p*-Chlorophenyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside

### (14)

To a suspension containing the triol **18** (3.56 g, 8.2 mmol) and benzaldehyde dimethyl acetal (2.38 mL, 15.8 mmol) in anhydrous $CH_3CN$ (20 mL), was added (±)-camphor-10-sulfonic acid (350 mg); the mixture was stirred at rt for 2 hrs. $Et_3N$ (1.0 mL) was added to quench the reaction, and the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and the organic solution was washed with $H_2O$ (2 × 50 mL), dried over anhydrous $Na_2SO_4$ and evaporated under vacuum. The desired compound **14** (4.0 g, yield: 93%) was obtained by column chromatography on silica gel using 5% EtOAc – toluene as eleuent. $[\alpha]_D$ +29.2° (*c* 0.65, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.96 – 7.83 (m, 2H, Phth), 7.81 – 7.72 (m, 2H, Phth), 7.53 – 7.45 (m, 2H, Ph), 7.43 – 7.32 (m, 5H, 3 × Ph + 2 × SPhCl), 7.30 – 7.23 (m, 2H, SPhCl), 5.65 (d, 1H, *J* 10.5 Hz, H-1), 5.57 (s, 1H, PhCH), 4.63 (dd, 1H, *J* 9.5, 9.5 Hz, H-3), 4.40 (dd, 1H, *J* 10.3, 4.8 Hz, H-6a), 4.30 (dd, 1H, *J* 10.3, 10.3 Hz, H-2), 3.81 (dd, 1H, *J* 10.2, 10.2 Hz, H-6b), 3.70 (ddd, 1H, *J* 9.6, 9.6, 4.8 Hz, H-5), 3.58 (dd, 1H, *J* 9.2, 9.2 Hz, H-4), 2.57 (s, 1H, OH-3); $\delta_C$ (100 MHz, $CDCl_3$) 168.20 (CO), 167.45 (CO), 136.81, 134.64, 134.42, 134.31, 131.50, 129.79, 129.40, 129.10, 129.01, 128.38, 128.20, 126.28, 101.97 (PhCH), 83.92 (C-1), 81.79 (C-4), 70.33 (C-3), 69.69 (C-5), 68.49 (C-6), 55.47 (C-2); *m/z* (ESI-HRMS) calcd for $[C_{27}H_{22}NO_6ClS + Na]^+$ 546.0749, found 546.0751.

### Synthesis of compound 21



a. $NaN_3$/DMF, 80° C.

### 6-Azido-1-hexanol (21)

Compound was prepared from 6-chloro-1-hexanol (**39**) according to identical procedure published before (93% yiled). The NMR data is identical to the literature.[1] $\delta_H$ (400 MHz, $CDCl_3$) 3.63 (t, 2H, *J* 6.5 Hz, H-1), 3.26 (t, 2H, *J* 6.9 Hz, H-6), 1.67 – 1.52 (m, 4H, H-2 + H-5), 1.45 – 1.34 (m, 4H, H-3 + H-4). $\delta_C$ (100 MHz, $CDCl_3$) 62.70, 51.37, 32.52, 28.79, 26.51, 25.32.

### Attempt to synthesize *p*-chlorophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl–(1→3)-6-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-2-phthalimido-1-thio-β-D-glucopyranoside (6)

A mixture of imidate **10** (63.8 mg, 0.129 mmol, 3.0 eq), alcohol **13** (27.9 mg, 0.043 mmol) and 4 Å molecular sieves (100 mg) in anhydrous $CH_2Cl_2$ (0.8 mL) was stirred under Ar for 1

h. The mixture was cooled to 0° C, and TMSOTf (3.0 μL) was added. After 1 h, the reaction was neutralized with $Et_3N$ (5 drops). The mixture was filtered off and concentrated. The residue was purified by chromatography on silica gel using a gradient of AcOEt – hexane (7% → 15%) to obtain the recovered acceptor **13** (19 mg) and rearranged imidate **25** (12 mg). No desired disaccharide **6** was formed. Data for **2,3,4,6-Tetra-*O*-acetyl-1-*N*-trichloroacetyl-β-D-galactopyranosylamine (25)**: $[\alpha]_D$ +23.7° (*c* 0.5, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.47 (d, 1H, *J* 8.6 Hz, NH), 5.48 (dd, 1H, *J* 3.1, 0.9 Hz, H-4), 5.24 (dd, 1H, *J* 10.1, 9.0 Hz, H-2), 5.18 (dd, 1H, *J* 9.9, 3.2 Hz, H-3), 5.14 (dd, 1H, *J* 8.9, 8.9 Hz, H-1), 4.18 – 4.11 (m, 2H, H-6a + H-6b), 4.09 (ddd, 1H, *J* 7.0, 5.7, 0.9 Hz, H-5), 2.18 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.02 (s, 3H, Ac); $\delta_C$ (100 MHz, $CDCl_3$) 171.38 (CO), 170.36 (CO), 169.93 (CO), 169.72 (CO), 162.03 (CO), 80.42 (C-1), 72.86 (C-5), 70.43 (C-3), 68.01 (C-2), 66.97 (C-4), 60.95 (C-6), 20.65 (Ac), 20.64 (Ac), 20.59 (Ac), 20.52 (Ac); *m/z* (ESI-MS) calcd for $[C_{16}H_{20}NO_{10}Cl_3 + Na]^+$ 514.0, 516.0, 518.0, found 514.2, 516.1, 518.0.

### Attempt to synthesize *p*-chlorophenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranosyl–(1→3)-6-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-2-phthalimido-1-thio-β-D-glucopyranoside (24)

A mixture of imidate **11** (31 mg, 0.062 mmol, 2.0 eq), alcohol **13** (20 mg, 0.031 mmol) and 4 Å molecular sieves (100 mg) in anhydrous $CH_2Cl_2$ (0.8 mL) was stirred under argon for 1 h. The mixture was cooled to 0° C, and TMSOTf (3.0 μL) was added. After 1 h, the reaction was neutralized with $Et_3N$ (5 drops). The mixture was filtered off and concentrated. The residue was purified by chromatography on silica gel using a gradient of AcOEt – hexane (7% → 15%) to obtain the recovered acceptor **13** (14 mg) and rearranged imidate **26** (21 mg). No desired disaccharide **24** was formed. Data for **2,3-Di-O-acetyl-4,6-O-benzylidene-β-D-galactopyranosylamine trichloroacetate (26)** (Found: C, 46.21; H, 4.43; N, 2.75%. $C_{19}H_{20}NO_8Cl_3$ requires C, 45.94; H, 4.06; N, 2.82%); $[\alpha]_D$ +50.2° (*c* 0.6, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.61 (d, 1H, *J* 8.9 Hz, NH), 7.55 – 7.49 (m, 2H, Ph), 7.43 – 7.34 (m, 3H, Ph), 5.55 (s, 1H, PhCH), 5.44 (dd, 1H, *J* 10.2, 9.4 Hz, H-2), 5.18 (dd, 1H, *J* 9.1, 9.1 Hz, H-1), 5.13 (dd, 1H, *J* 10.3, 3.6 Hz, H-3), 4.50 (dd, 1H, *J* 3.6, 0.8 Hz, H-4), 4.36 (dd, 1H, *J* 12.6, 1.5 Hz, H-6a), 4.09 (dd, 1H, *J* 12.7, 1.8 Hz, H-6b), 3.71 (ddd, 1H, *J* 1.7, 1.7, 1.1 Hz, H-5), 2.13 (s, 3H, Ac), 2.07 (s, 3H, Ac); $\delta_C$ (100 MHz, $CDCl_3$) 171.19 (CO), 170.38 (CO), 162.21 (CO), 137.15, 129.15, 128.26, 126.07 (Ar), 100.75 (PhCH), 80.32 (C-1), 73.21 (C-4), 71.57 (C-3), 68.83 (C-6), 68.29 (C-5), 67.89 (C-2), 20.84 (Ac), 20.66 (Ac); *m/z* (ESI-MS) calcd for $[C_{19}H_{20}NO_8Cl_3 + Na]^+$ 518.0, 520.0, 522.0, found 518.2, 520.1, 522.0.

### 2,3,4-tri-*O*-acetyl-1-thio-α,β-L-fucopyranosyl trichloroacetimidate (28)

Thioglycoside **15** (5.16 g, 9.20 mmol) was dissolved in a mixture of $CH_3CN$ (30 mL) – $H_2O$ (2.8 mL); *N*-iodosuccinimide (4.36 g, 18.39 mmol) was added and the mixture was stirred for 30 minutes at rt. $Et_3N$ (3 mL) was added to quench the reaction. The mixture was diluted with EtOAc (200 mL), and washed with 10% aqueous $Na_2S_2O_3$ solution (2 × 100 mL), dried over anhydrous $Na_2SO_4$ and evaporated. The residue was purified by chromatography on silica gel using 20% AcOEt – toluene as eluent to afford the hemiacetal **27** (3.29 g, 82.3% yield). Part of the hemiacetal (3.0 g, 6.90 mmol) and $CCl_3CN$ (6.3 mL, 62.8 mmol) were dissolved in anhydrous $CH_2Cl_2$ (20 mL), anhydrous $K_2CO_3$ (3.3 g, 23.9 mmol) was added; the mixture was stirred at rt overnight. The reaction was diluted with EtOAc (150 mL), washed with $H_2O$ (2 × 50 mL), and evaporated to dryness. NMR showed that the mixture contained **28**[2] as a mixture (α/β 1:2) which was pure enough for use in next step, no further purification was performed. $\delta_H$ (300 MHz, $CDCl_3$) for α-anomer: 8.49 (s, 1H, C=NH), 7.44 – 7.11 (m, 15H, Ar), 6.51 (d, 1H, *J* 3.4 Hz, H-1), 5.06 – 4.61 (m, 6H, Bn), 1.14 (d, 3H, *J* 6.0 Hz, H-6). For β-anomer 8.59 (s, 1H, C=NH), 7.44 – 7.11 (m, 15H), 5.71 (d, 1H, *J* 8.1 Hz, H-1), 5.06 – 4.61 (m, 6H, Ar), 1.21 (d, 3H, *J* 6.4 Hz, H-6).

## *p*-Chlorophenyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl–(1→3)-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (29) and *p*-Chlorophenyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl–(1→4)-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (30)

A mixture of imidate **28** (1.57 g, 2.7 mmol), diol **19** (1.10 g, 2.09 mmol) and 4 Å molecular sieves (1.5 g) in anhydrous $CH_2Cl_2$ (10 mL) were stirred under Ar for 1 h. The mixture was cooled to -78° C, and TMSOTf (15 μL) was added dropwise. After 30 mins, the reaction was neutralized with $Et_3N$ (0.5 mL). The mixture was diluted with EtOAc (100 mL) and the insoluble molecular sieves were removed by filtration. After concentration, the residue was purified by chromatography on silica gel using a gradient of AcOEt – hexane (15% → 20%) to afford **29** (1.46 g, 52% yield) and **30** (0.760 g, 27% yield).

Data for **29** (Found: C, 68.51; H, 5.56; N, 1.54%. $C_{54}H_{52}NO_{10}SCl$ requires C, 68.81; H, 5.56; N, 1.49%): $[\alpha]_D$ +32.1° (*c* 0.5, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.88 (dd, 1H, *J* 7.4, 1.0 Hz, Phth), 7.73 – 7.66 (m, 2H, 2 × Phth), 7.58 (ddd, 1H, *J* 7.4, 7.4, ~1 Hz, Phth), 7.47 – 7.15 (m, 22H, Ar), 6.99 – 6.93 (m, 2H, Ar), 5.68 (d, 1H, *J* 10.3 Hz, H-1_GlcN), 4.86 (d, 1H, *J* 11.4 Hz, Bn), 4.65 (d, 1H, *J* 12.0, Bn), 4.61 (d, 1H, *J* 12.1 Hz, Bn, overlapped), 4.61 (d, 1H, *J* 3.5 Hz, H-1_Fuc), 4.61 (d, 1H, *J* 12.1 Hz, Bn, overlapped) 4.54 (d, 1H, *J* 11.4 Hz, Bn), 4.53 (d, 1H, *J* 10.9 Hz, Bn), 4.30 (dd, 1H, *J* 10.3, 10.3 Hz, H-2_GlcN), 4.26 (d, 1H, *J* 1.2, OH-4_GlcN), 4.21 (dd, 1H, *J* 10.3, 8.2 Hz, H-3_GlcN), 4.10 (d, 1H, *J* 13.4 Hz, Bn), 4.07 (dq, 1H, *J* 6.6, ~1 Hz, H-5_Fuc), 3.93 (dd, 1H, *J* 10.6, 1.4 Hz, H-6a_GlcN), 3.82 – 3.68 (m, 4H, H-3_Fuc + H-5_GlcN + H-2_Fuc + H-6b_GlcN), 3.57 – 3.49 (m, 2H, H-4_GlcN + H-4_Fuc), 3.39 (d, 1H, *J* 13.0 Hz, Bn), 1.07 (d, 3H, *J* 6.5 Hz, H-6_Fuc); $\delta_C$ (100 MHz, $CDCl_3$) 168.61 (CO), 167.64 (CO), 138.70, 138.43, 138.26, 138.03, 134.33, 134.24, 133.77, 132.38, 131.95, 130.27, 128.95, 128.42, 128.34, 128.25, 128.15, 127.61, 127.59, 127.54, 123.19, 123.00, 100.87 (C-1_Fuc), 84.11 (C-3_GlcN), 82.82 (C-1_GlcN), 79.35 (C-5_GlcN or C-3_Fuc), 78.90 (C-3_Fuc or C-5_GlcN), 77.86 (C-4_Fuc), 74.74 (Bn), 73.85 (C-2_Fuc), 73.42 ($CH_2Ph$), 73.41 ($CH_2Ph$), 72.41 ($CH_2Ph$), 70.99 (C-4_GlcN), 69.37 (C-6_GlcN), 68.52 (C-5_Fuc), 53.52 (C-2_GlcN), 16.43 (C-6_Fuc); *m/z* (ESI-HRMS) calcd for $[C_{54}H_{52}NO_{10}SCl + Na]^+$ 964.2893, found 964.2891.

Data for **30** (Found: C, 68.61; H, 5.59; N, 1.52%. $C_{54}H_{52}NO_{10}SCl$ requires C, 68.81; H, 5.56; N, 1.49%): $[\alpha]_D$ -14.1° (*c* 0.5, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.92 (m, 1H, Phth), 7.83 (m, 1H, Phth), 7.80 – 7.69 (m, 2H, Phth), 7.45 – 7.20 (m, 22H, 5 × Ph + 2 × SPhCl), 7.13 (d, 2H, *J* 8.3, SPhCl), 5.55 (d, 1H, *J* 10.3, H-1_GlcN), 4.96 (d, 1H, *J* 3.9 Hz, H-1_Fuc), 4.96 (d, 1H, , *J* 11.4 Hz, Bn), 4.84 (d, 1H, *J* 12.1 Hz, Bn), 4.80 (d, 1H, *J* 11.7 Hz, Bn), 4.74 (d, 1H, *J* 11.8 Hz, Bn), 4.66 (d, 1H, *J* 11.6 Hz, Bn), 4.61 (d, 1H, *J* 11.5 Hz, Bn), 4.38 (d, 1H, *J* 11.6 Hz, Hz), 4.35 (d, 1H, *J* 11.9 Hz, Bn), 4.31 (m, 1H, H-3_GlcN), 4.22 (dd, 1H, *J* 9.9, 9.9 Hz, H-2_GlcN), 4.07 (dd, 1H, *J* 10.2, 3.7 Hz, H-2_Fuc), 4.02 (dq, 1H, *J* 6.4, ~1 Hz, H-5_Fuc), 3.95 (high order m, 1H, H-6a_GlcN), 3.87 (dd, 1H, *J* 10.0, 2.9 Hz, H-3_Fuc), 3.81 – 3.72 (m, 2H, H-5_GlcN + H-6b_GlcN), 3.65 (br, 1H, H-4_Fuc), 3.49 (t, 2H, *J* 8.7 Hz, $CH_2N_3$), 1.57 (s, 1H, OH-3_GlcN), 1.07 (d, 3H, *J* 6.5 Hz, H-6_Fuc); *m/z* (ESI-HRMS) calcd for $[C_{54}H_{52}NO_{10}SCl + Na]^+$ 964.2893, found 964.2900.

## II. $^1H$ and $^{13}C$ spectra of all synthesized compounds

The $^1H$ and $^{13}C$ spectra of all synthesized compounds and the $^1H$-$^1H$ GCOSY and $^1H$-$^{13}C$ GHSQC of the final products.

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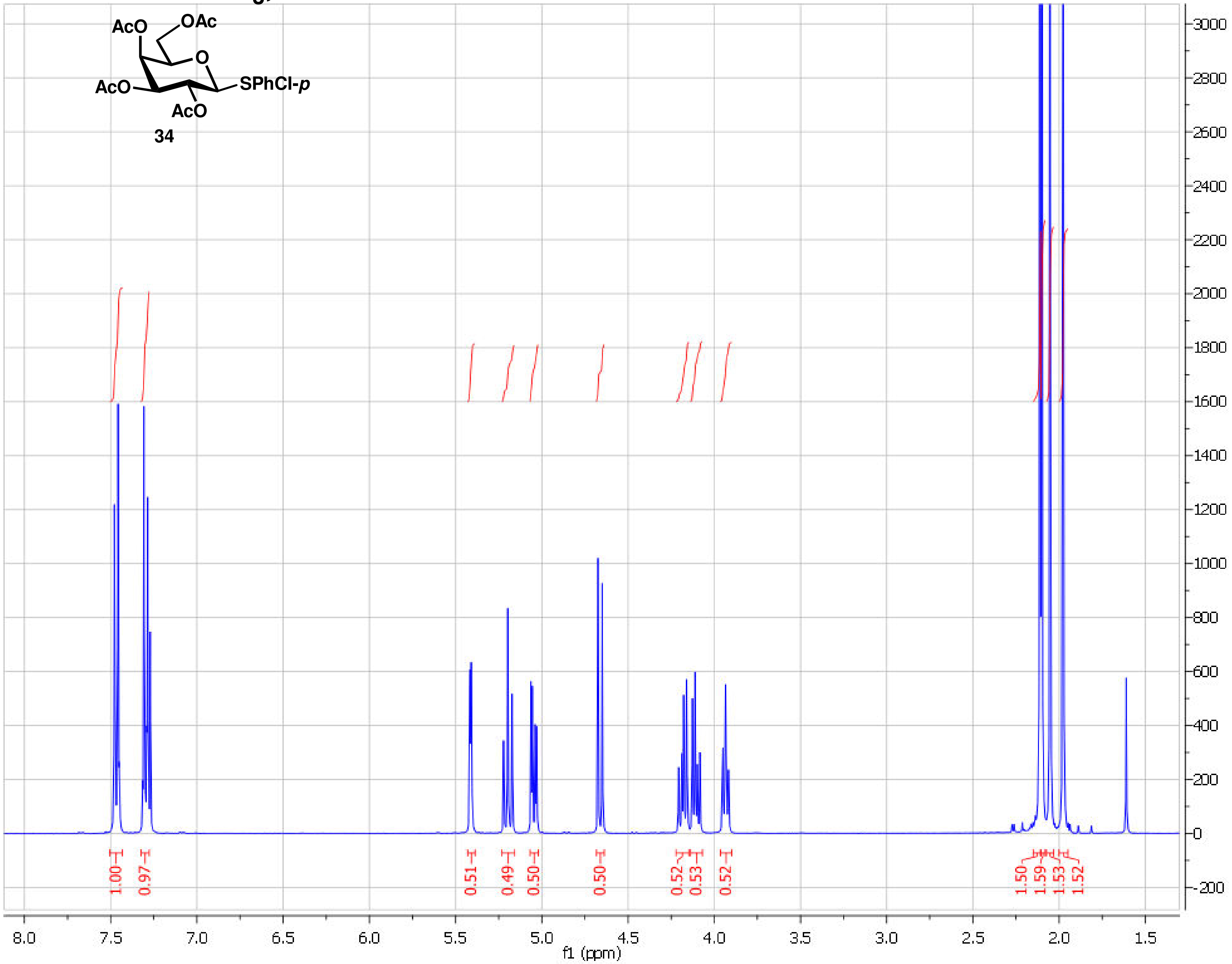
[1] M. Malkoch, K. Schleicher, E. Drockenmuller, C. J. Hawker, T. P. Russel, P. Wu and V. V. Fokin, *Macromolecules*, 2005, **38**, 3663-3678.

[2] (a) H. Rathore, A. H. L. From, K. Ahmed and D. S. Fullerton, *J. Med. Chem.*, 1986, **29**, 1945-1952. (b) D. P. Larson, C. H. Heathcock and H. Clayton, *J. Org. Chem.*, 1997, **62**, 8406-8418.

# $^1H$ NMR in $CDCl_3$, 400 MHz



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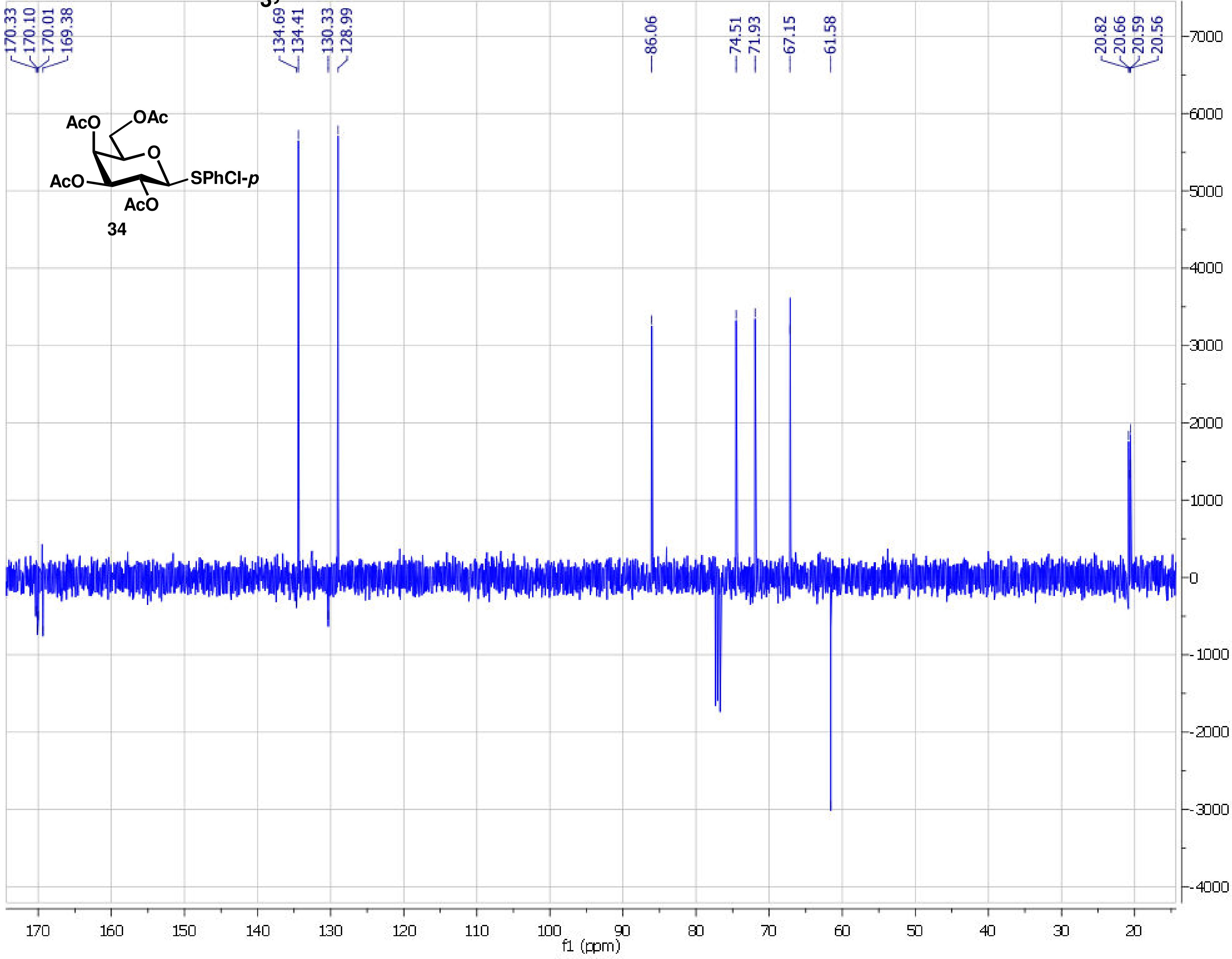

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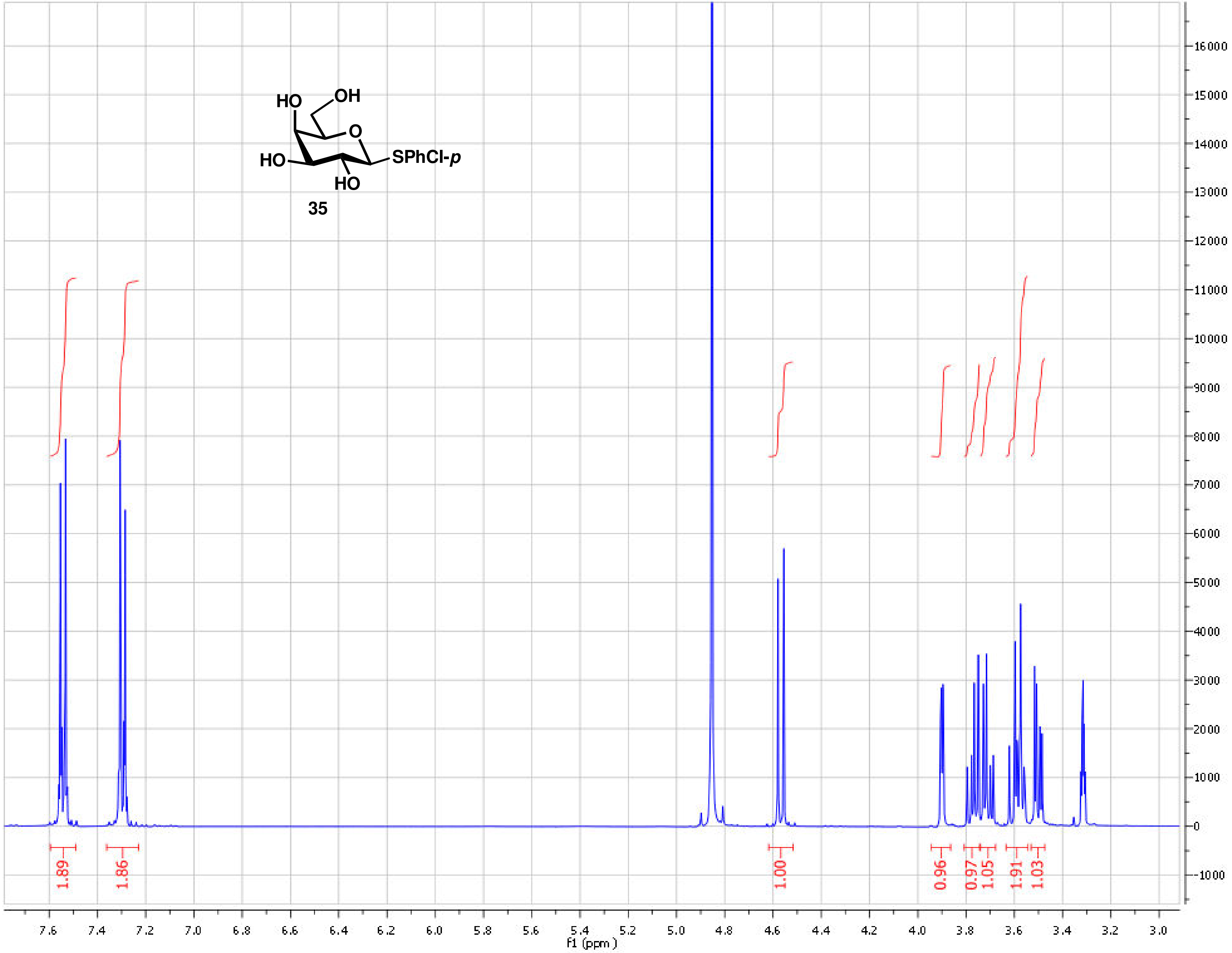

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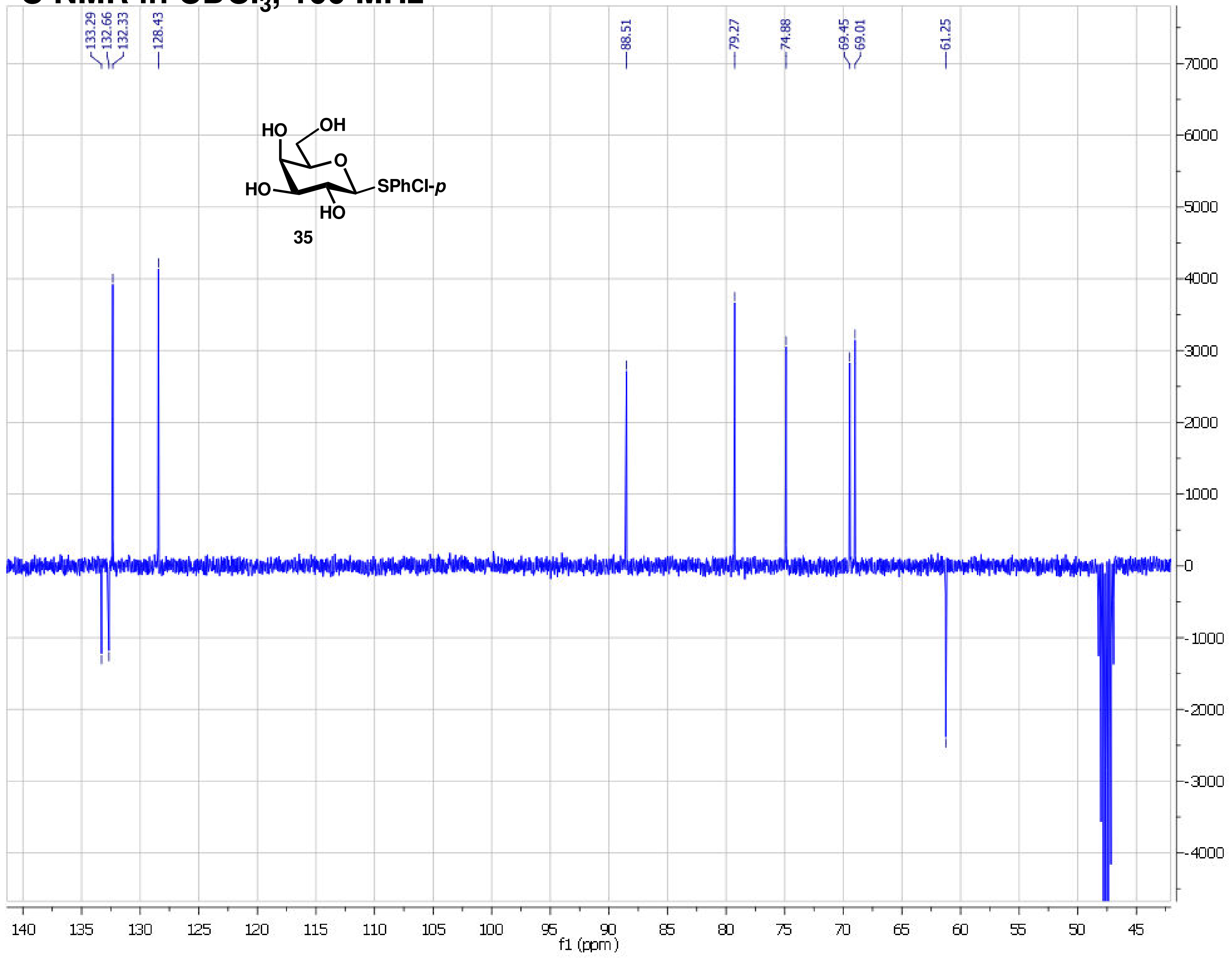

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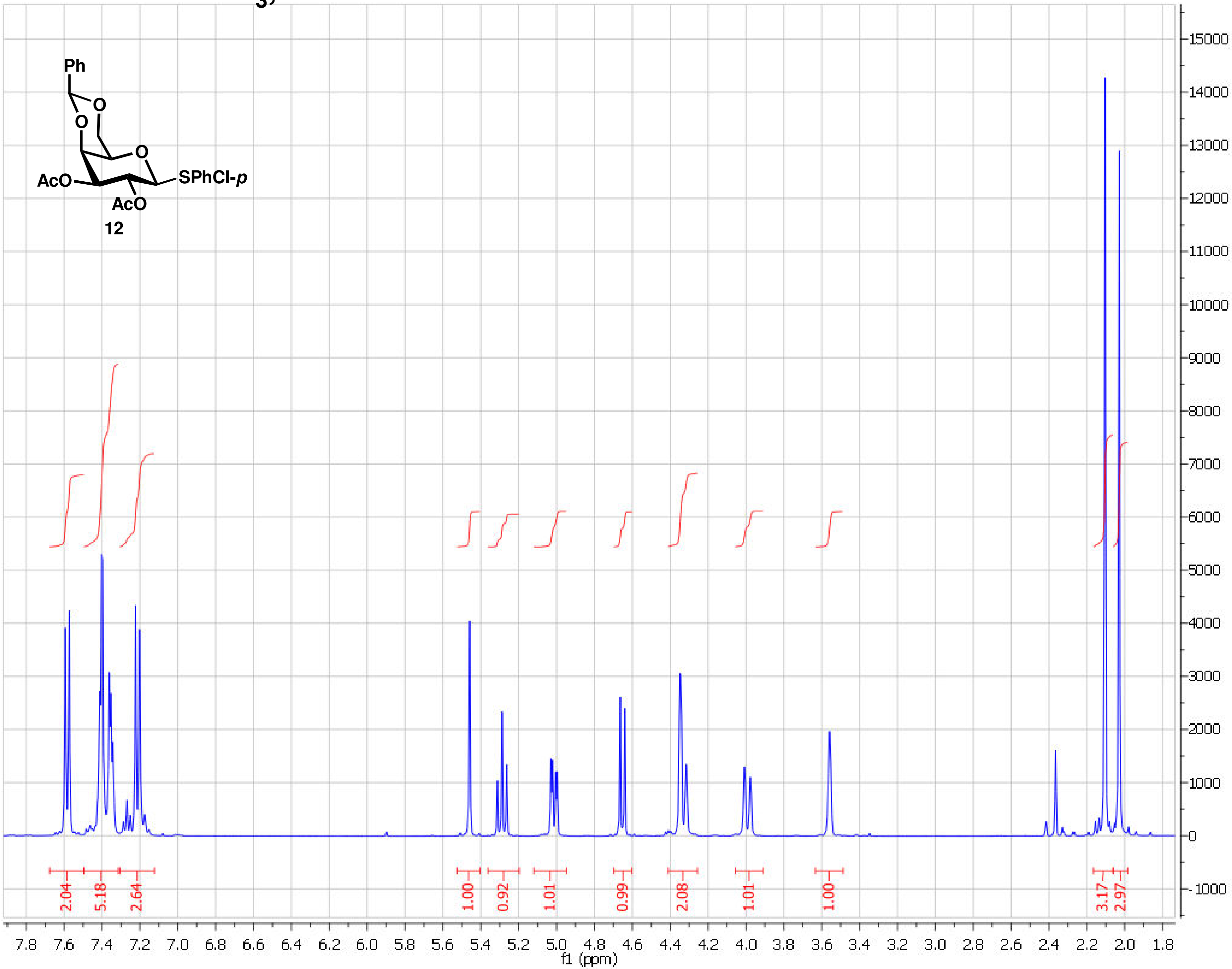

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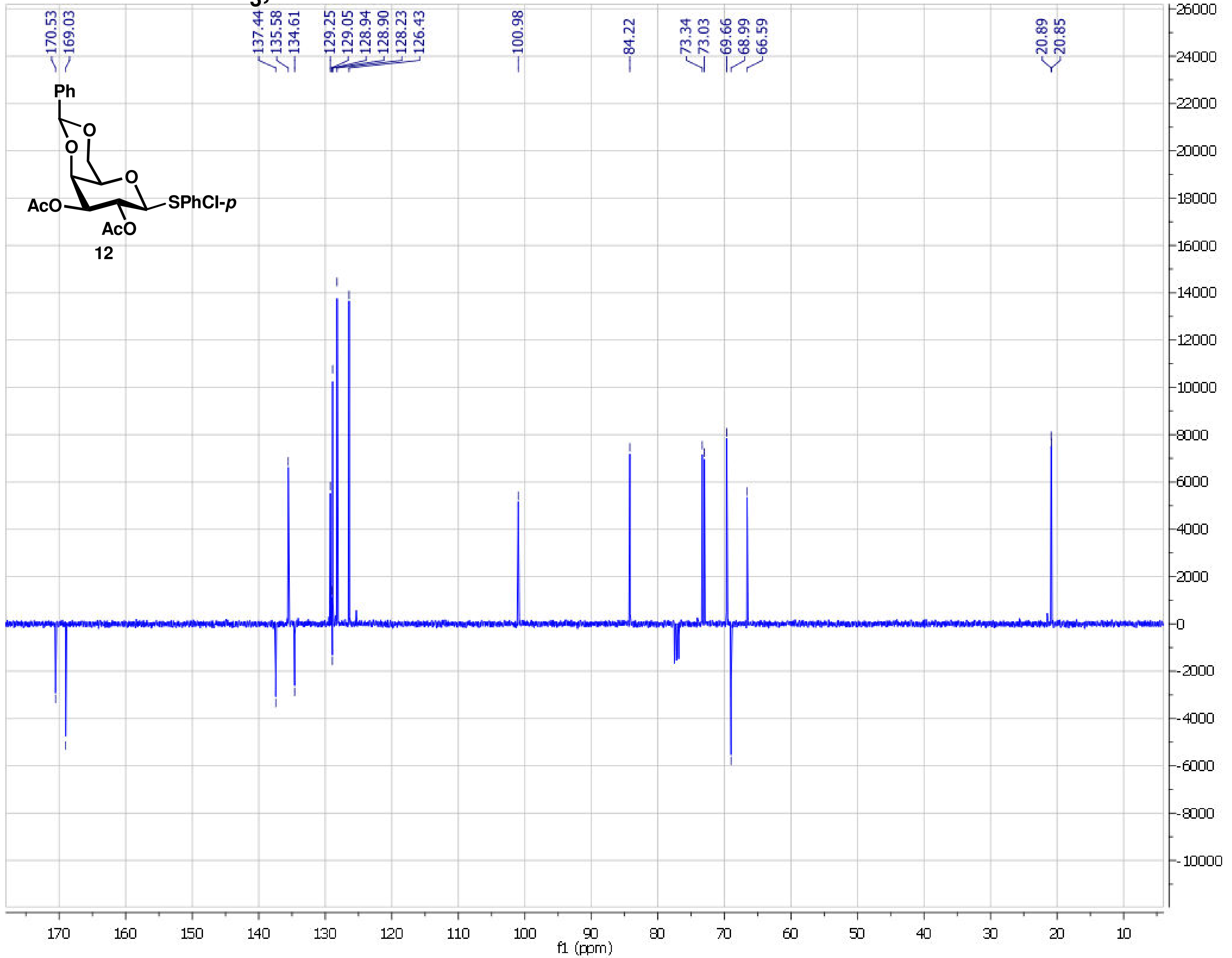

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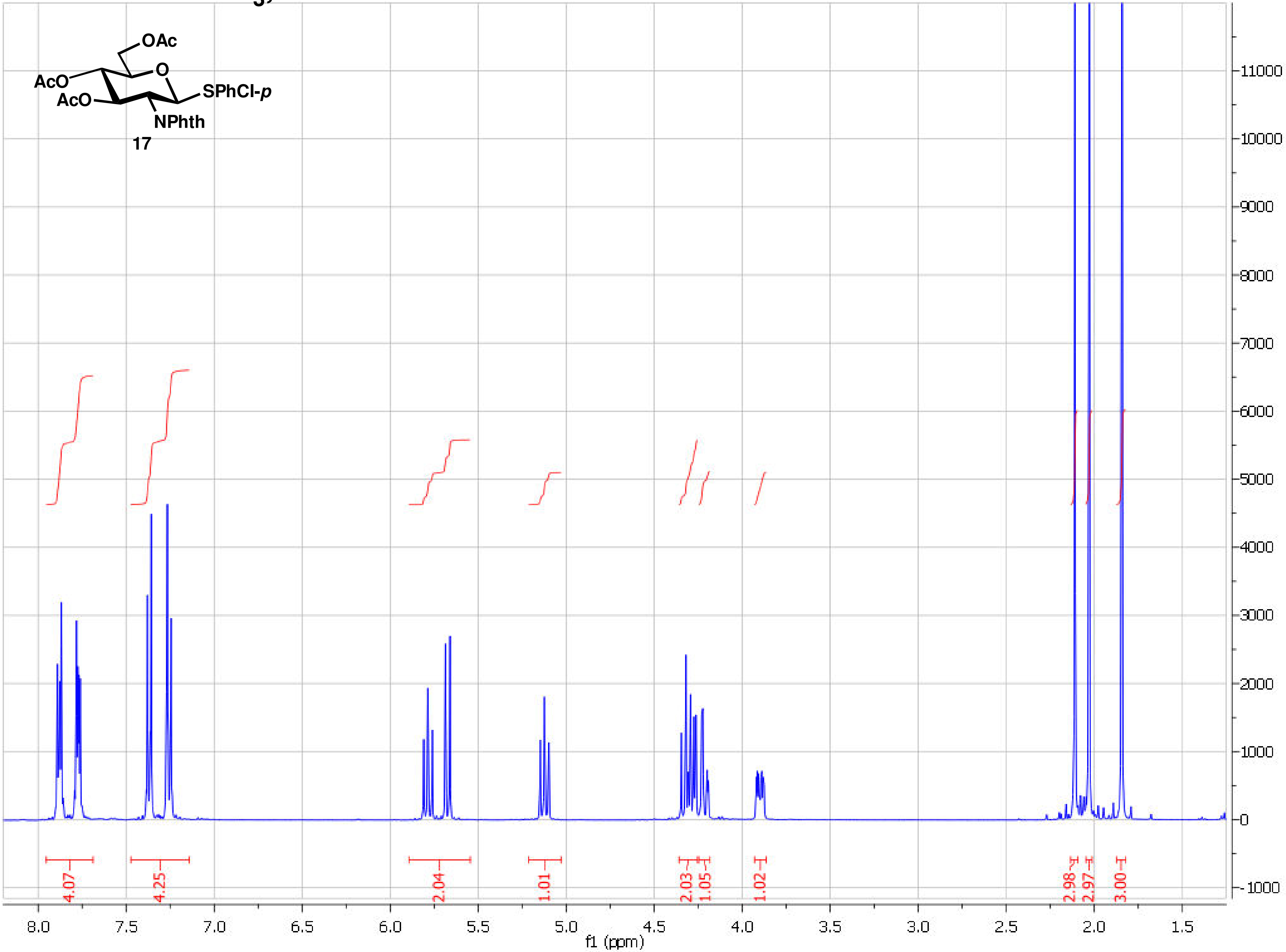

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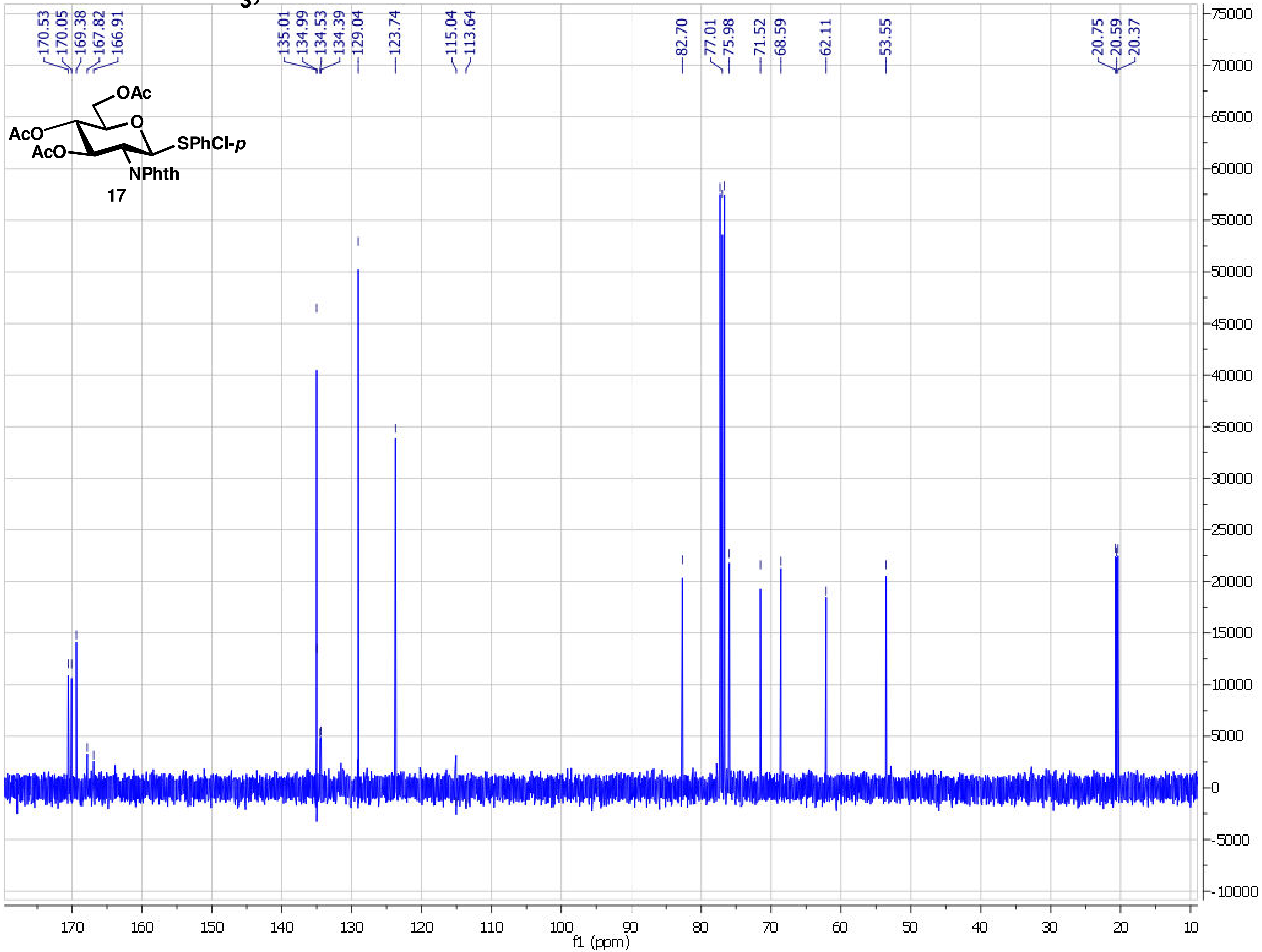

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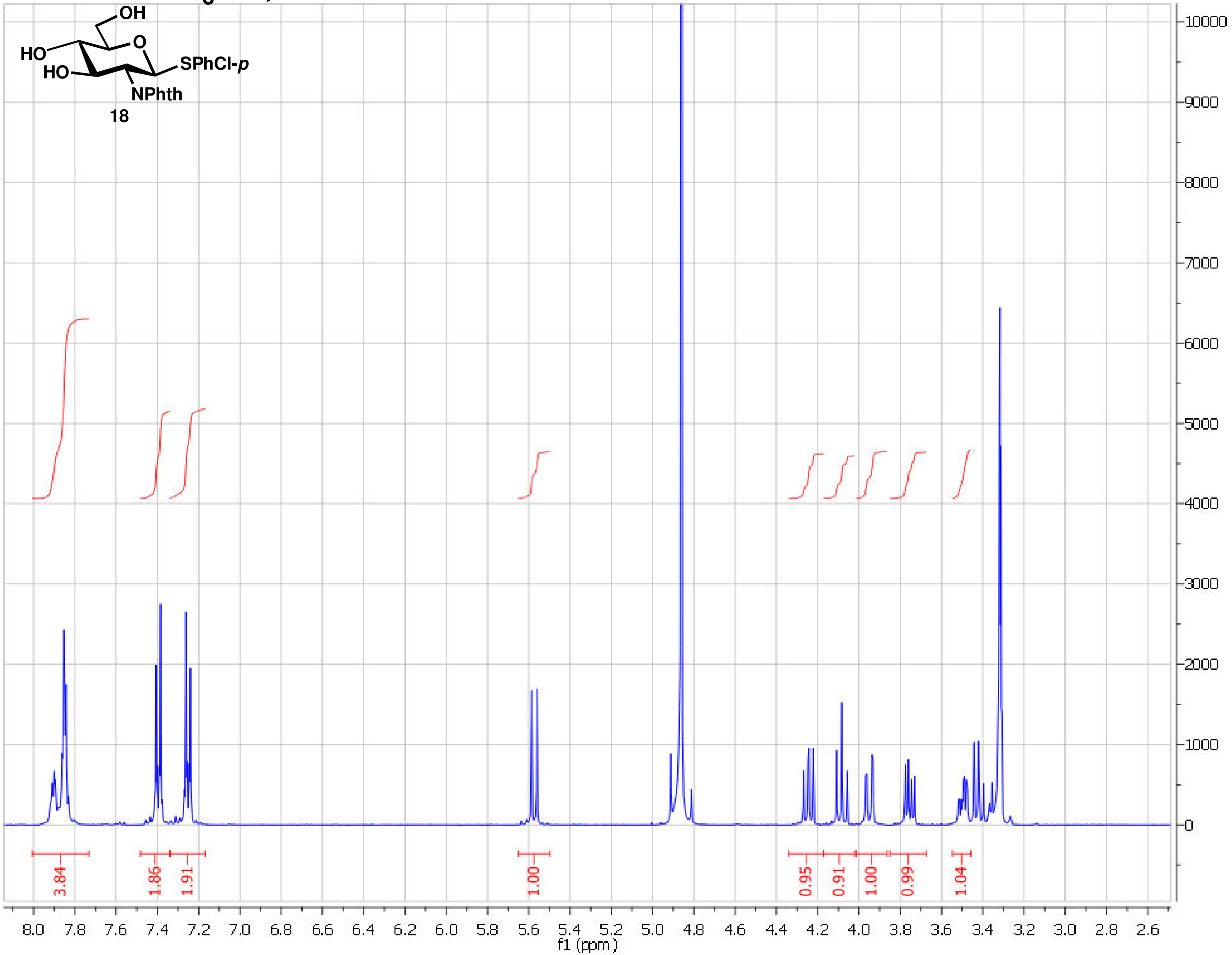

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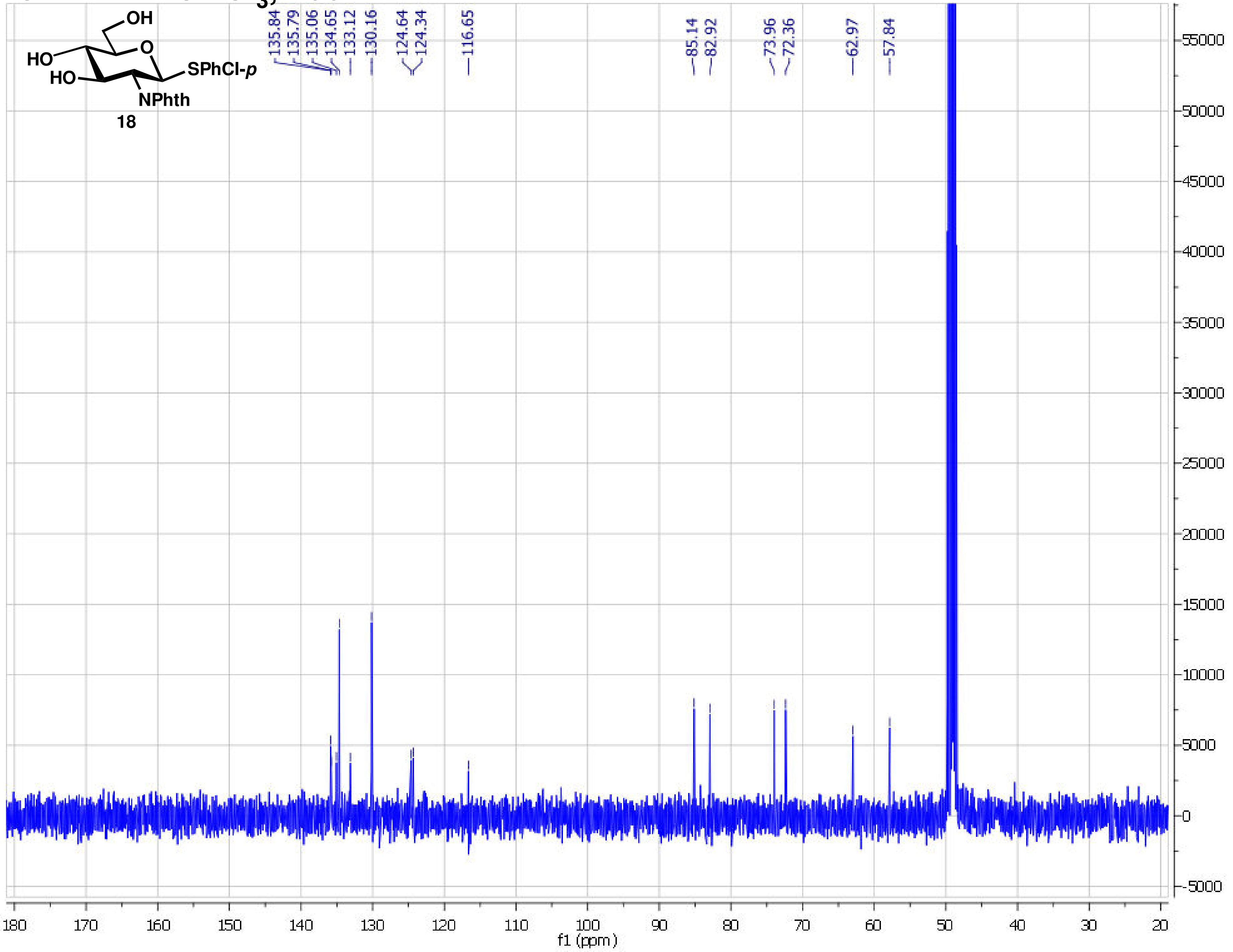

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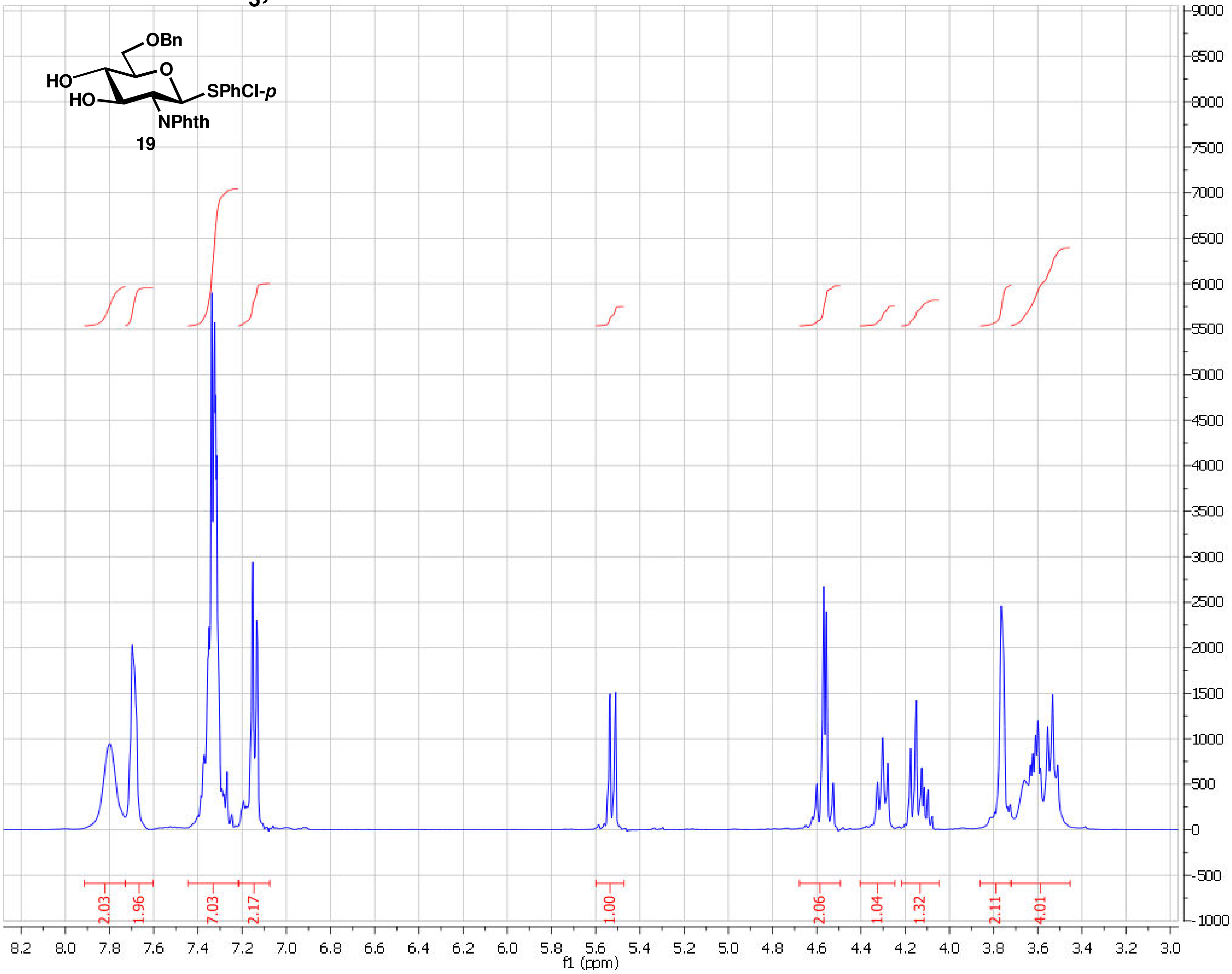

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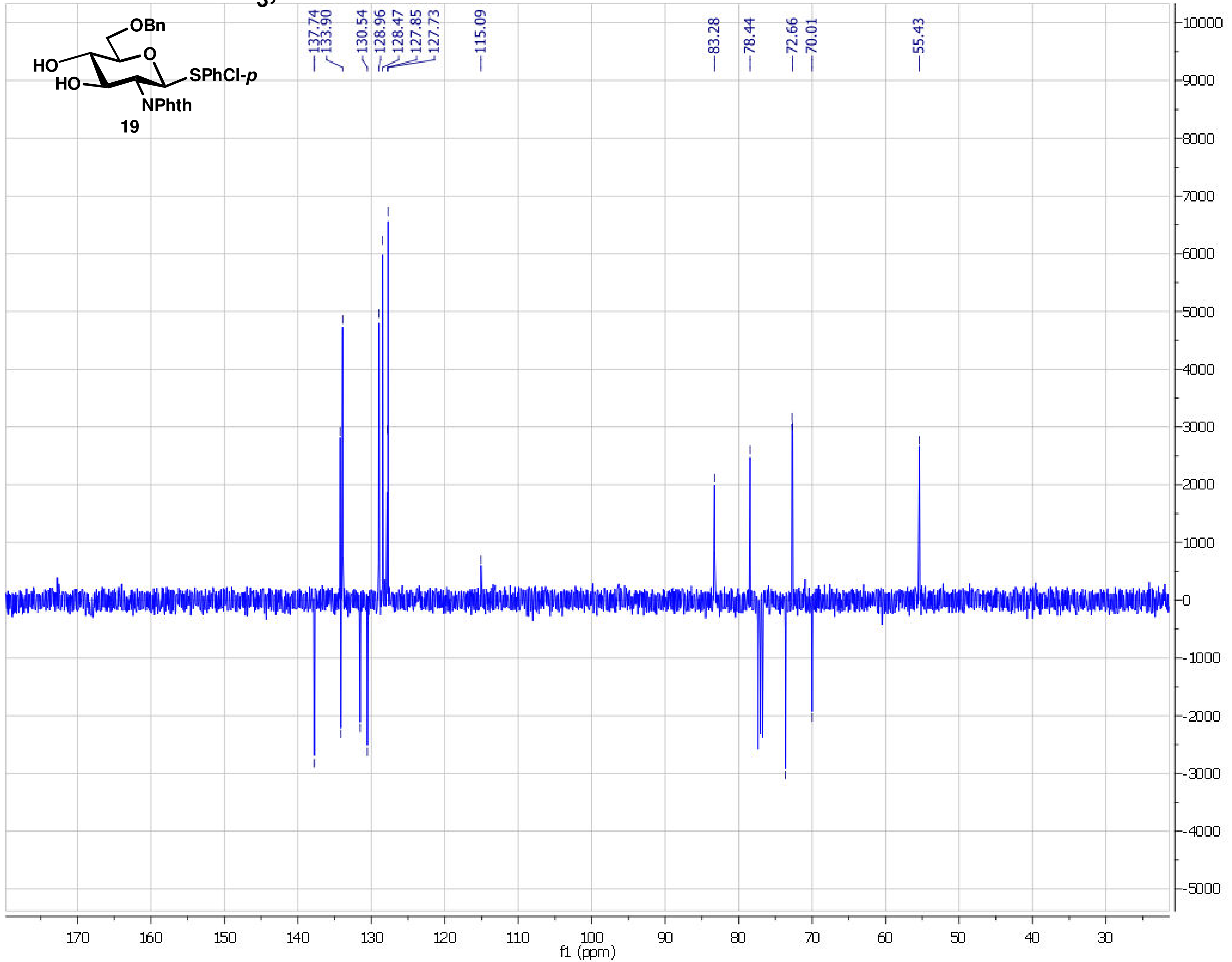

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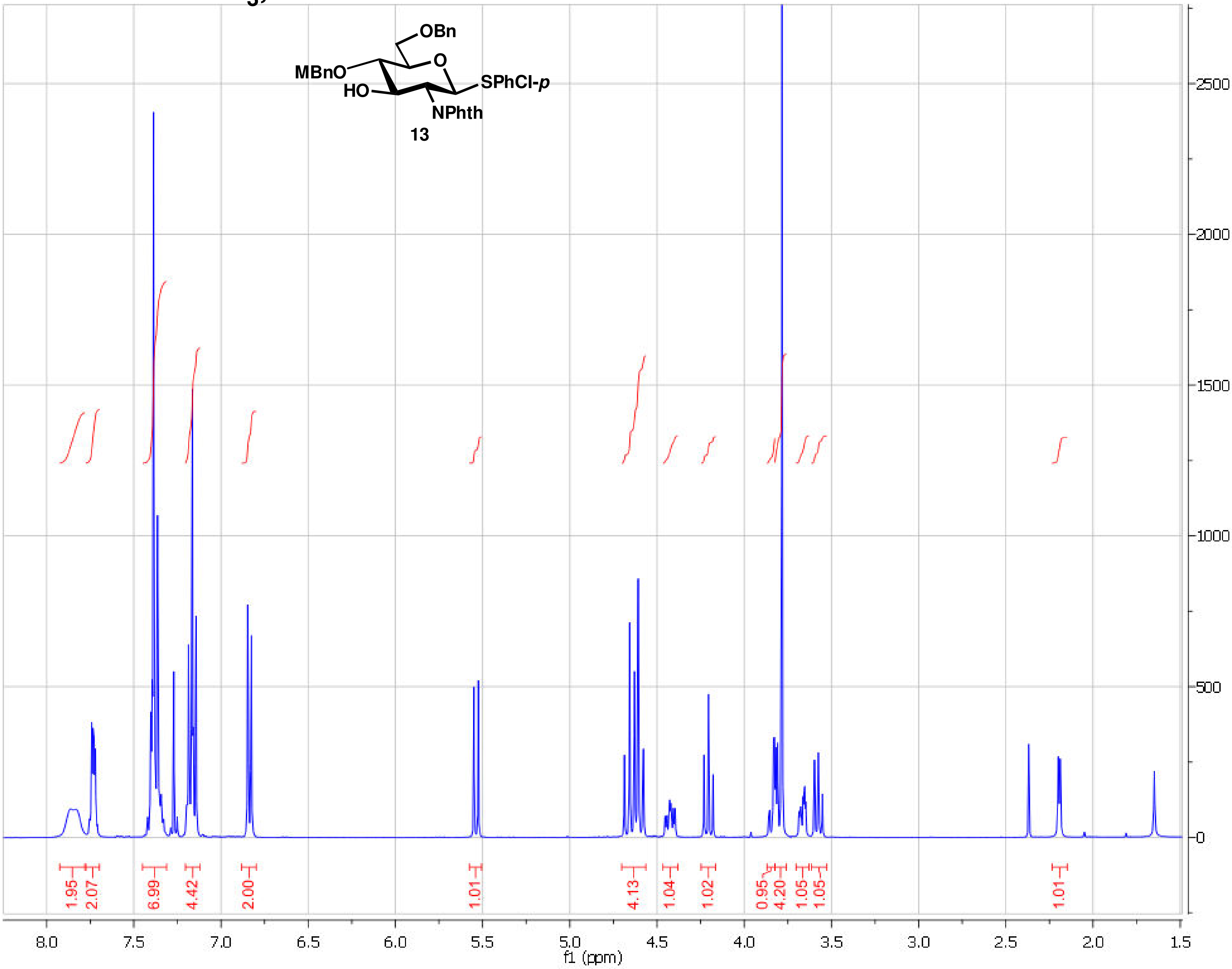

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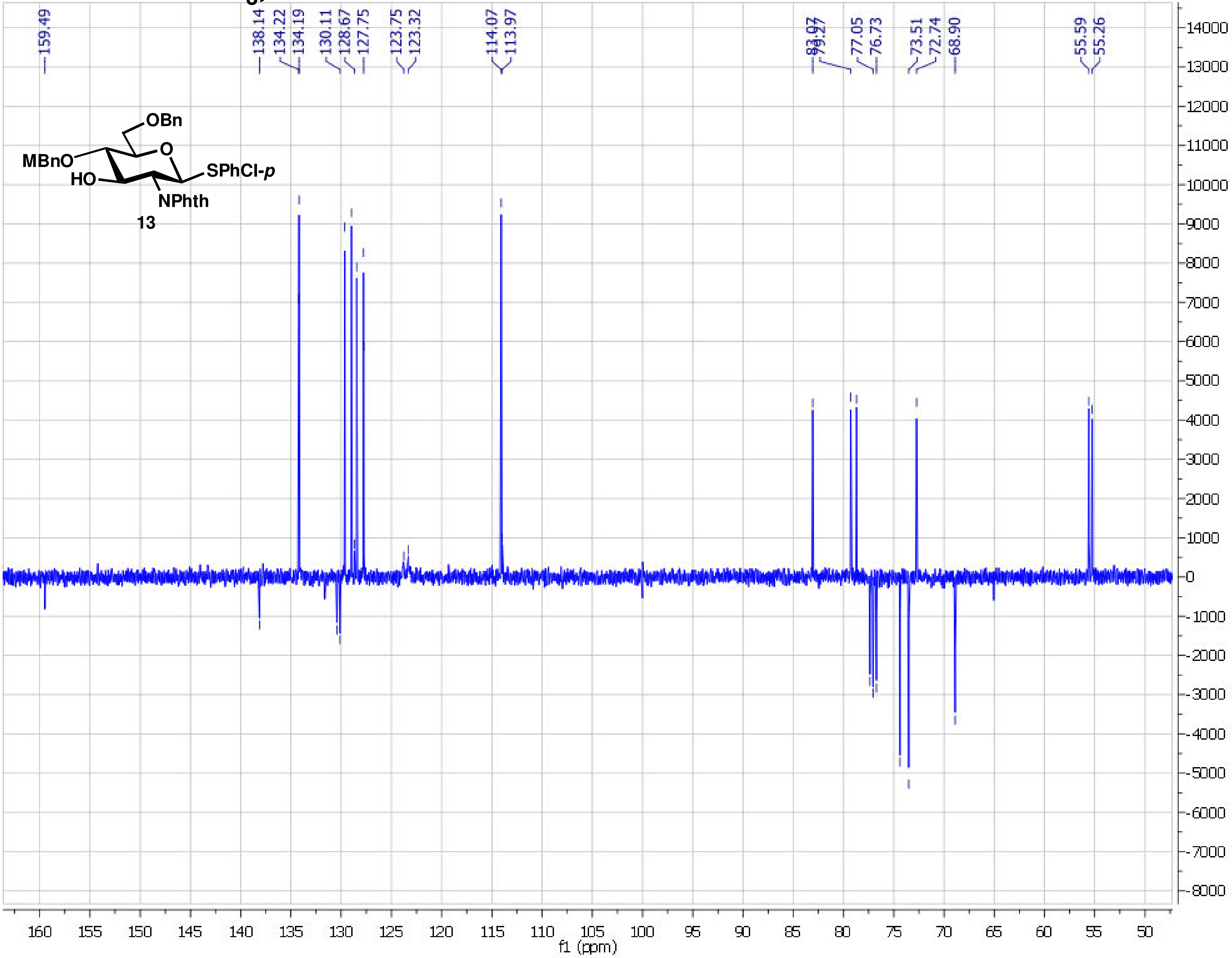

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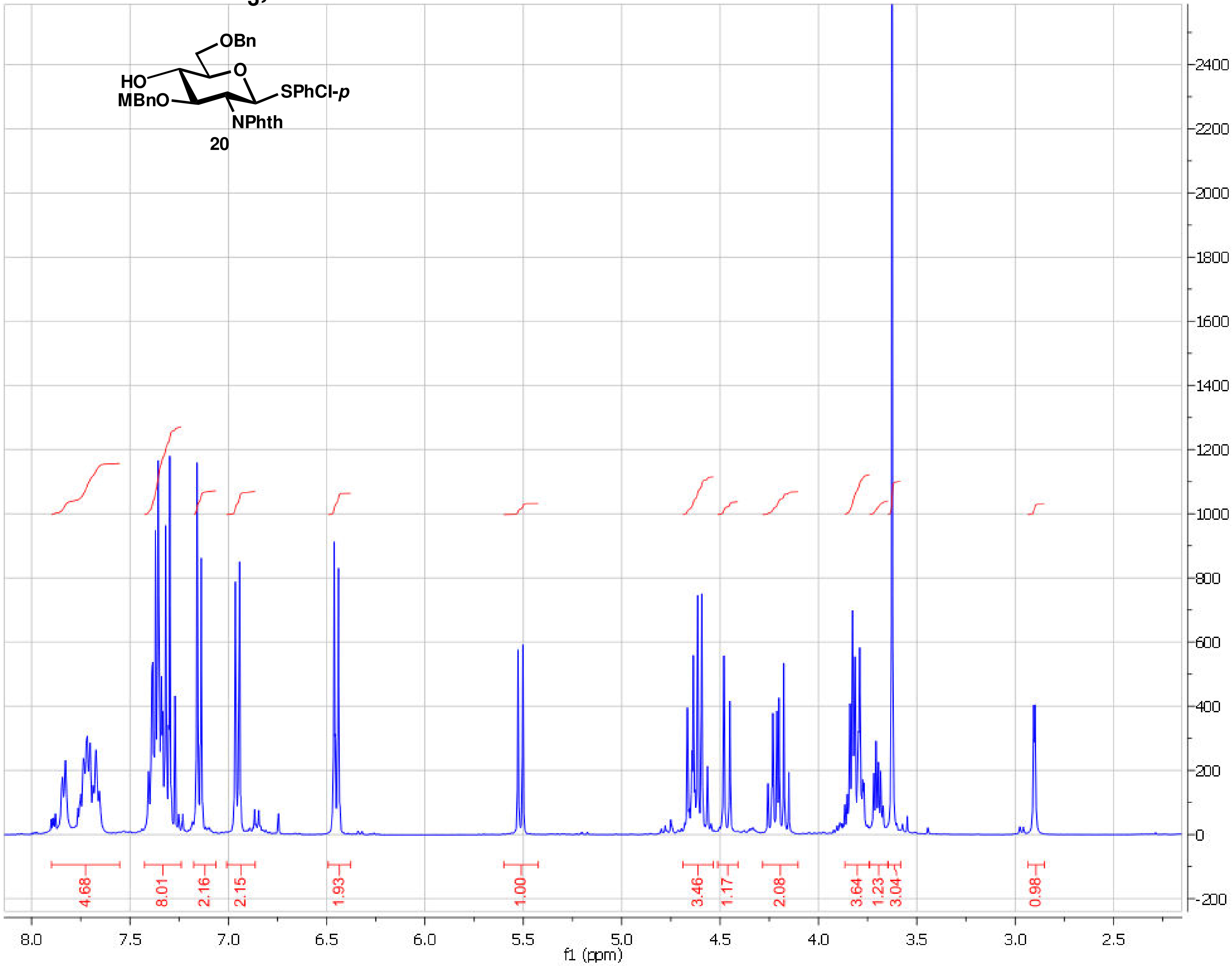

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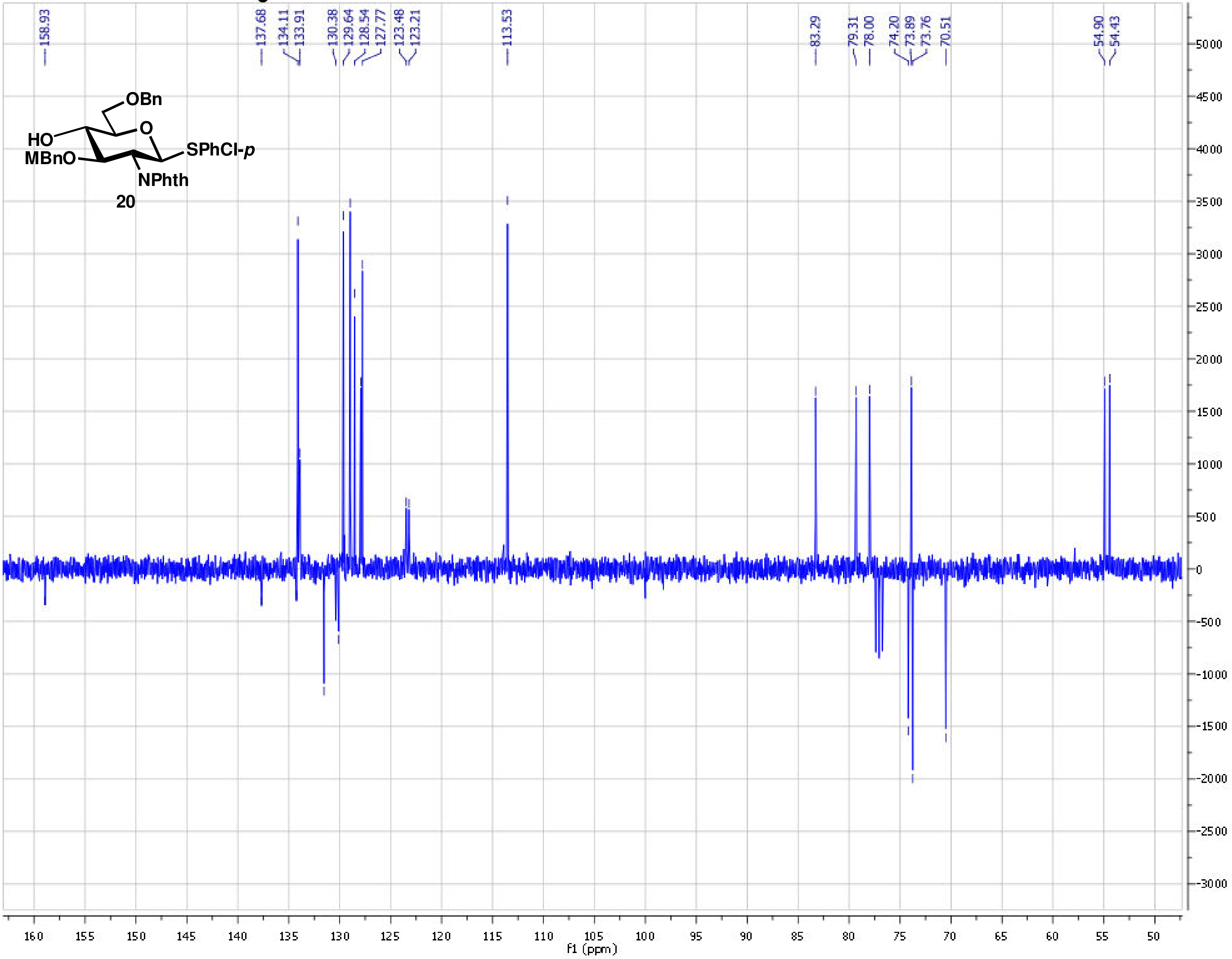

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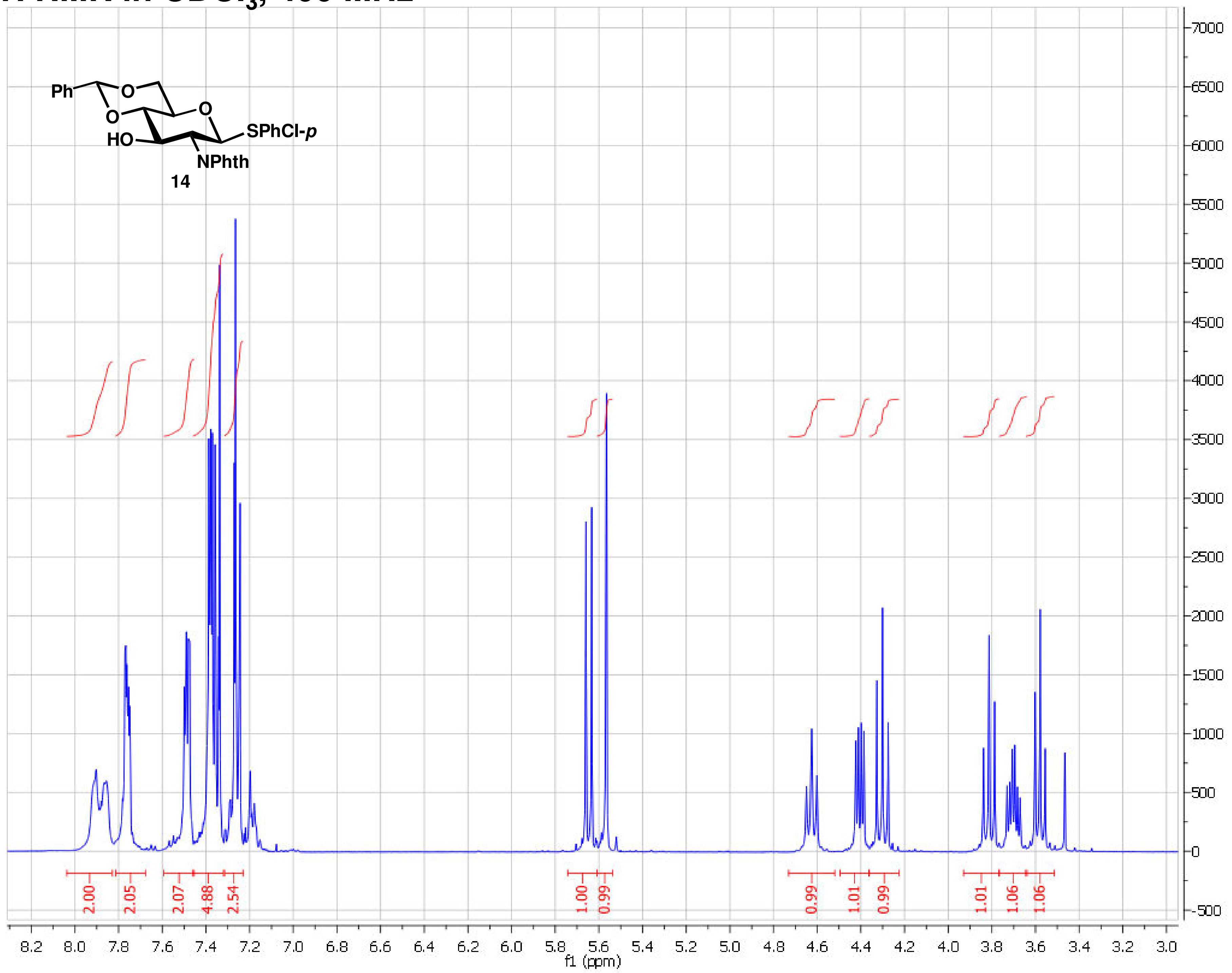

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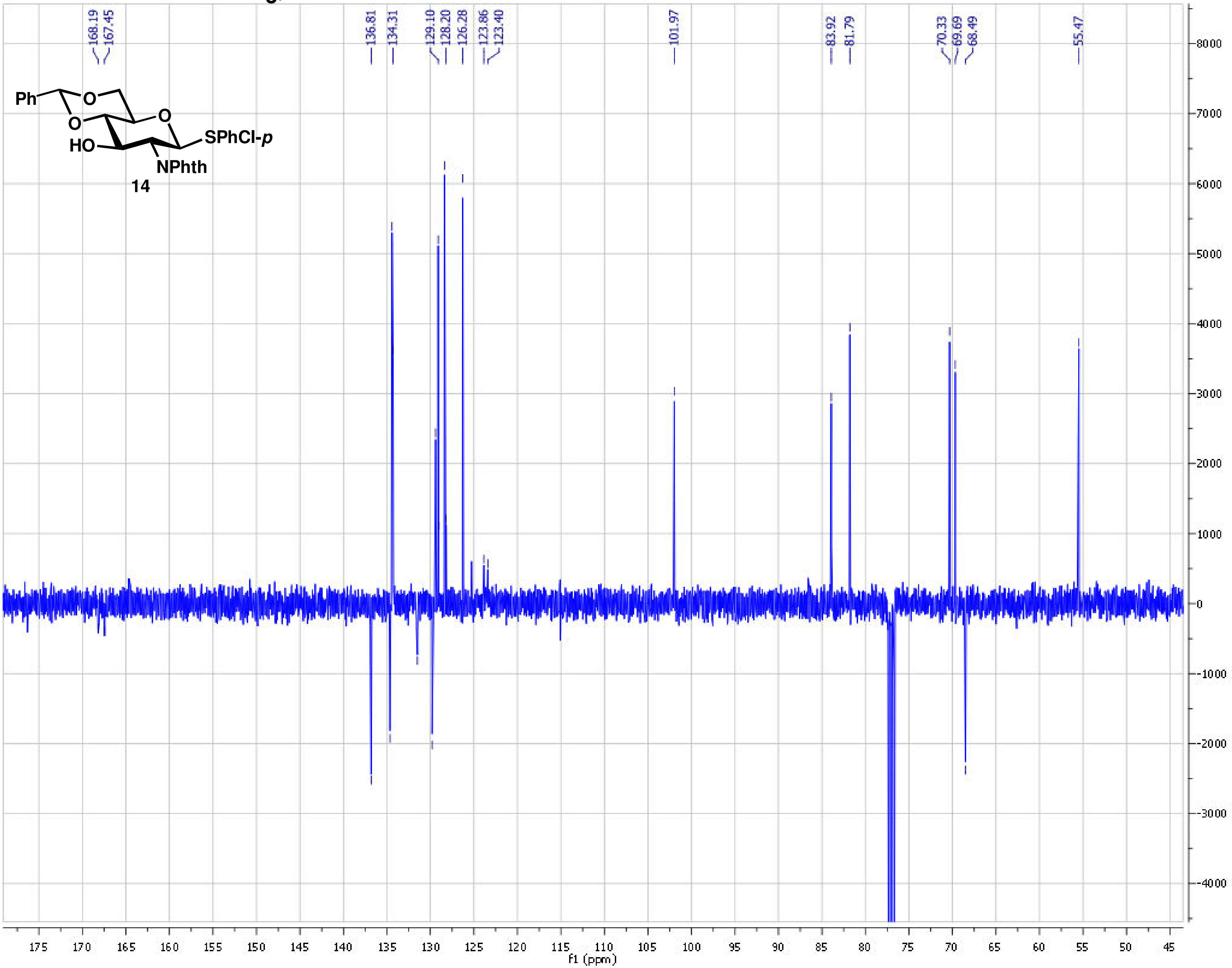

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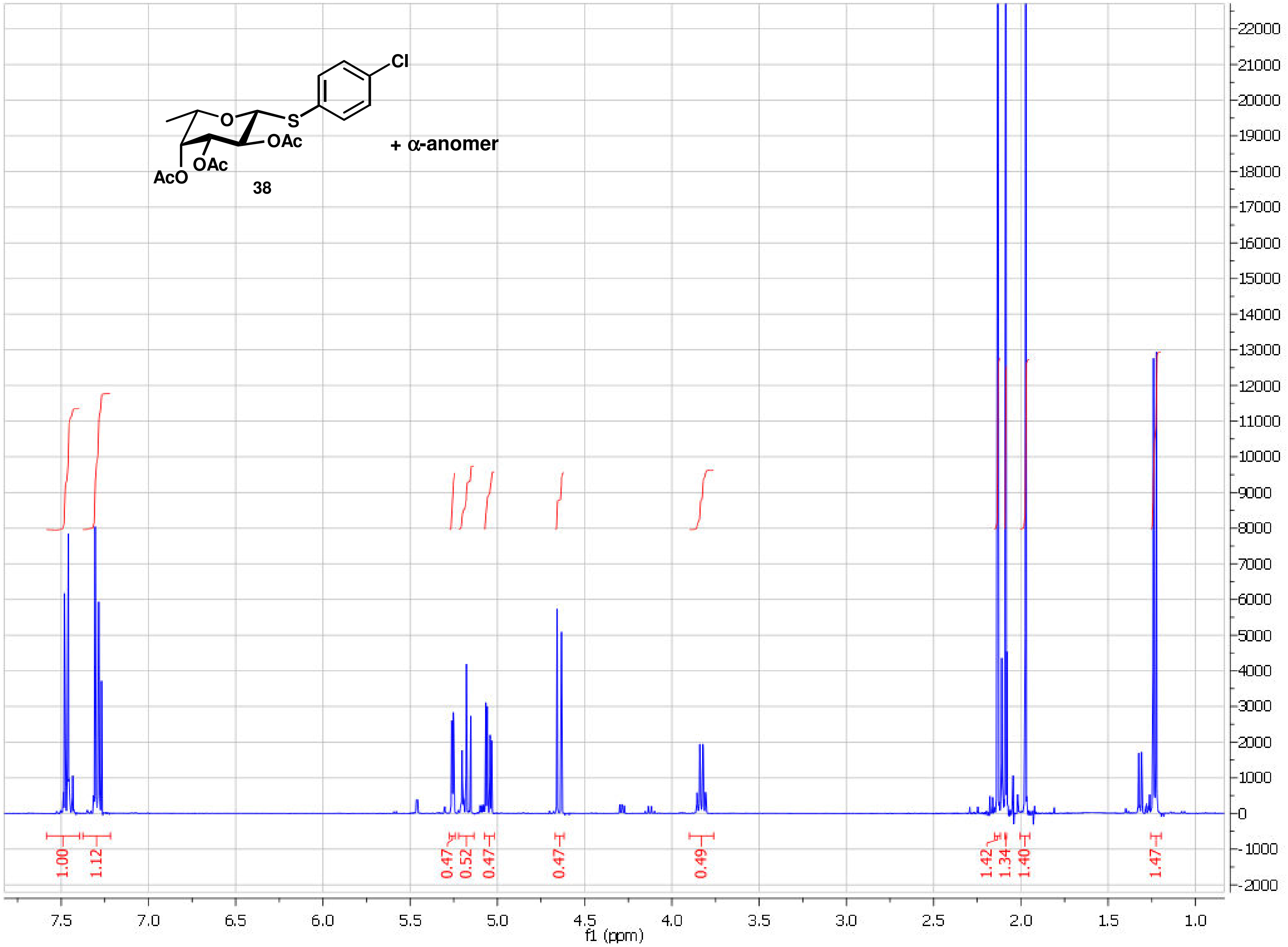

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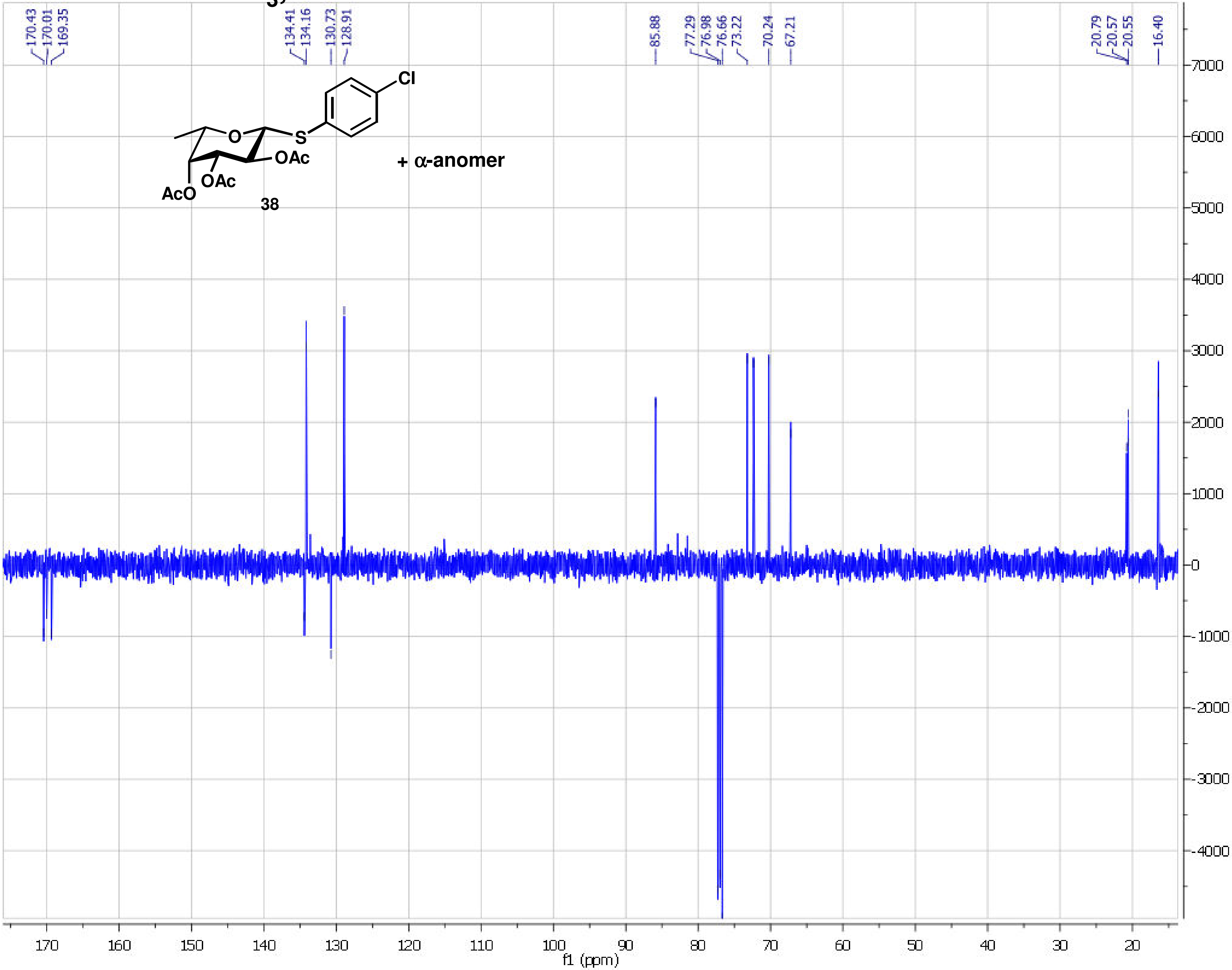
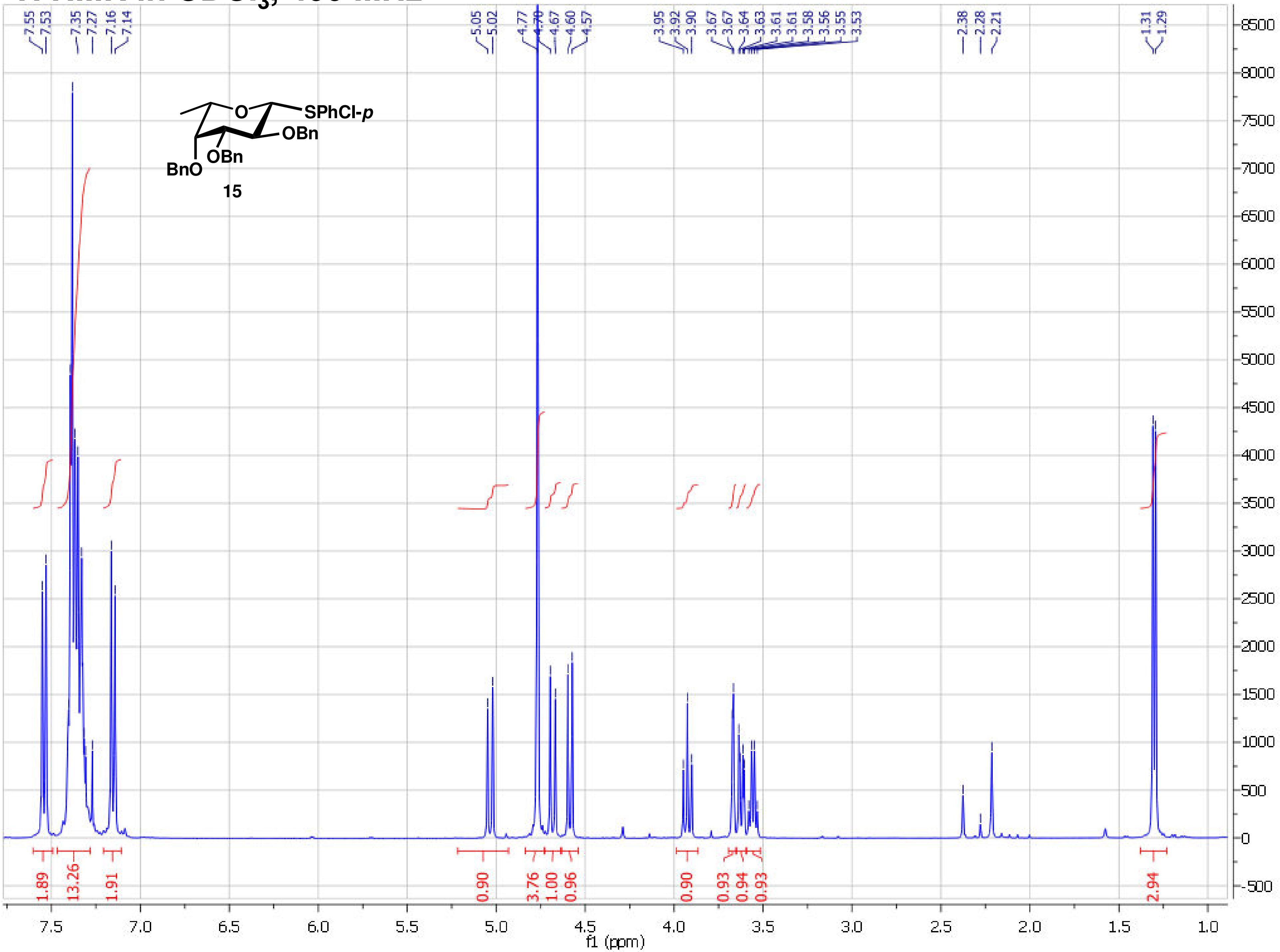

38

+ α-anomer

# $^1$H NMR in $CDCl_3$, 400 MHz



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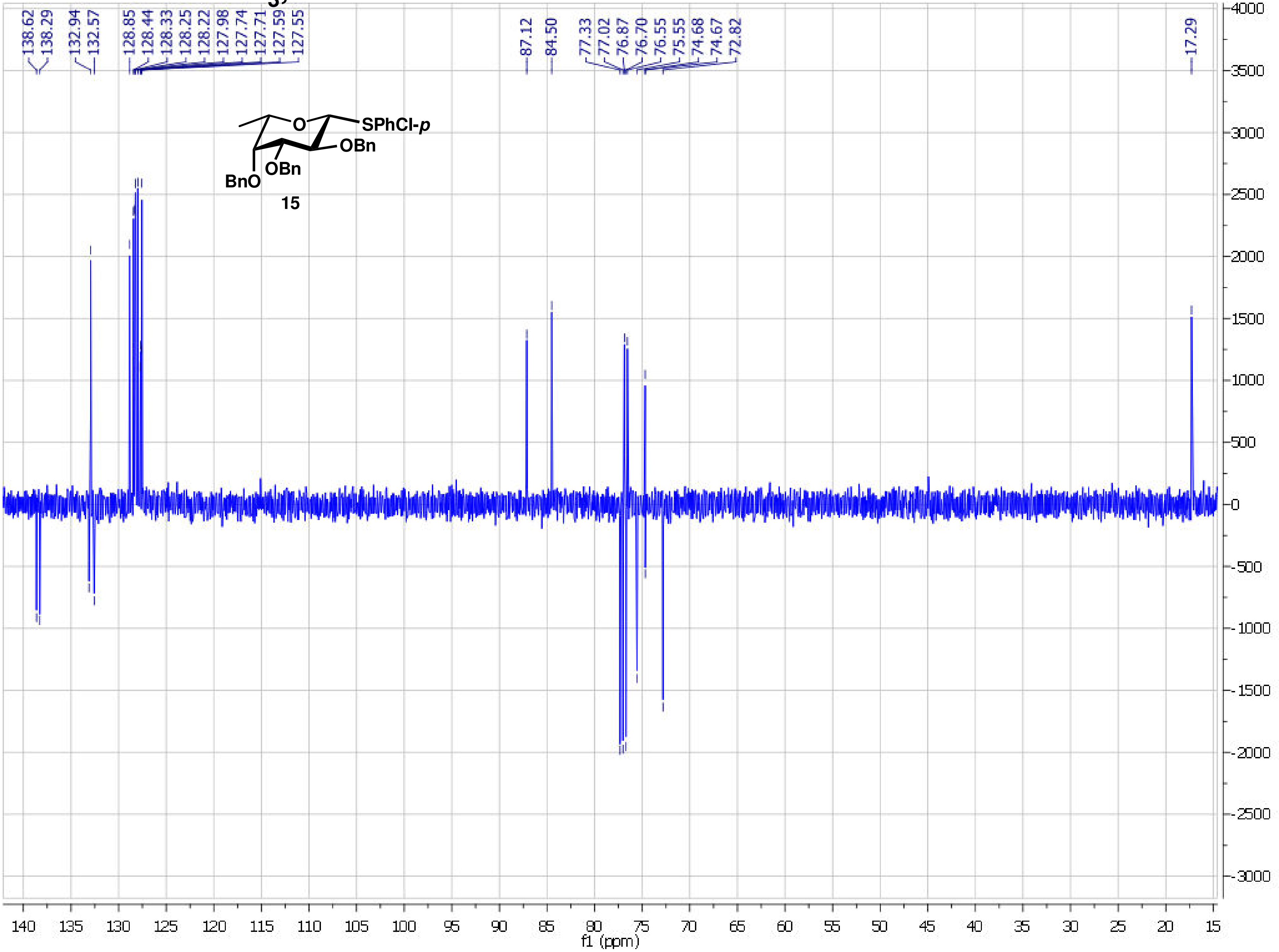

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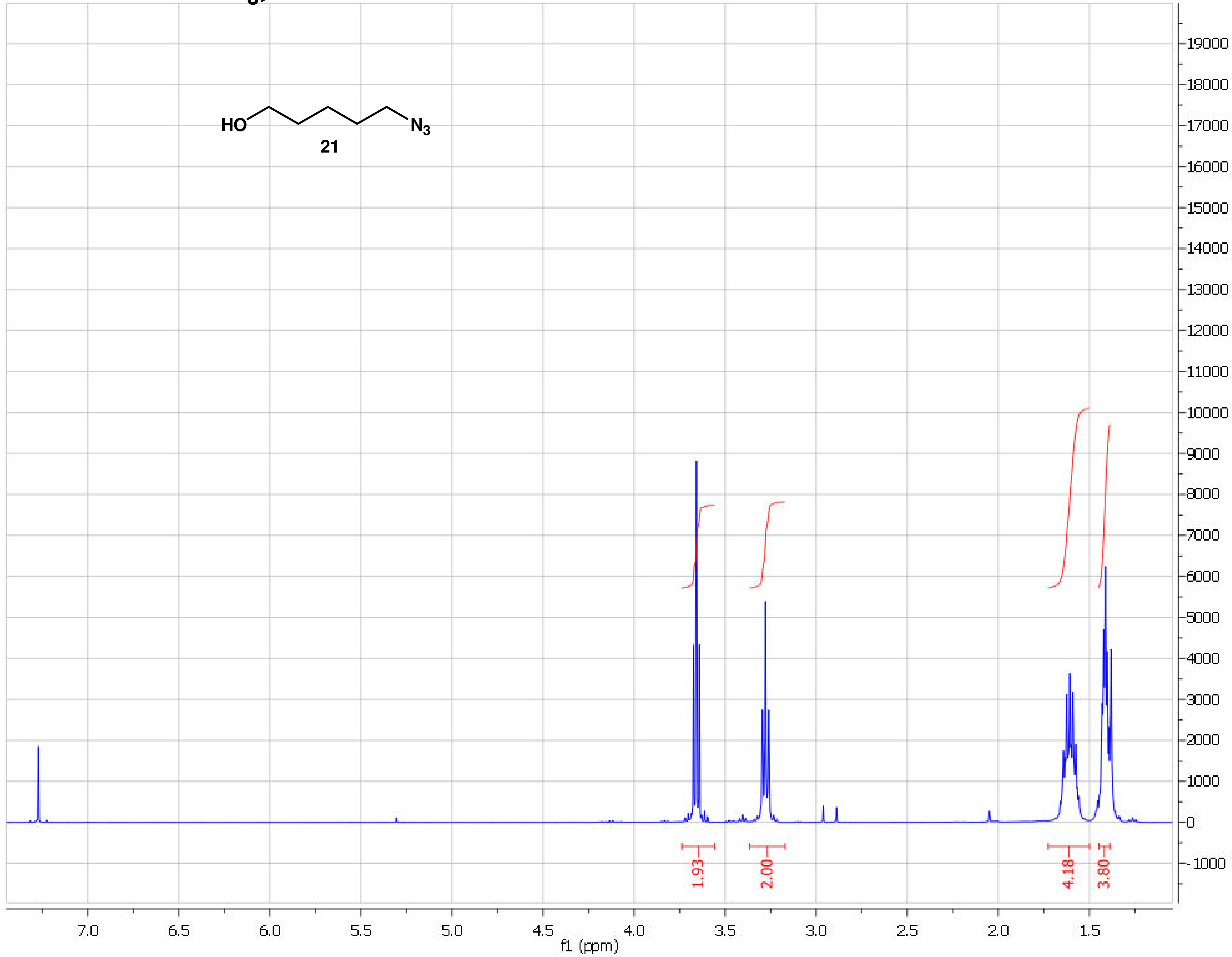

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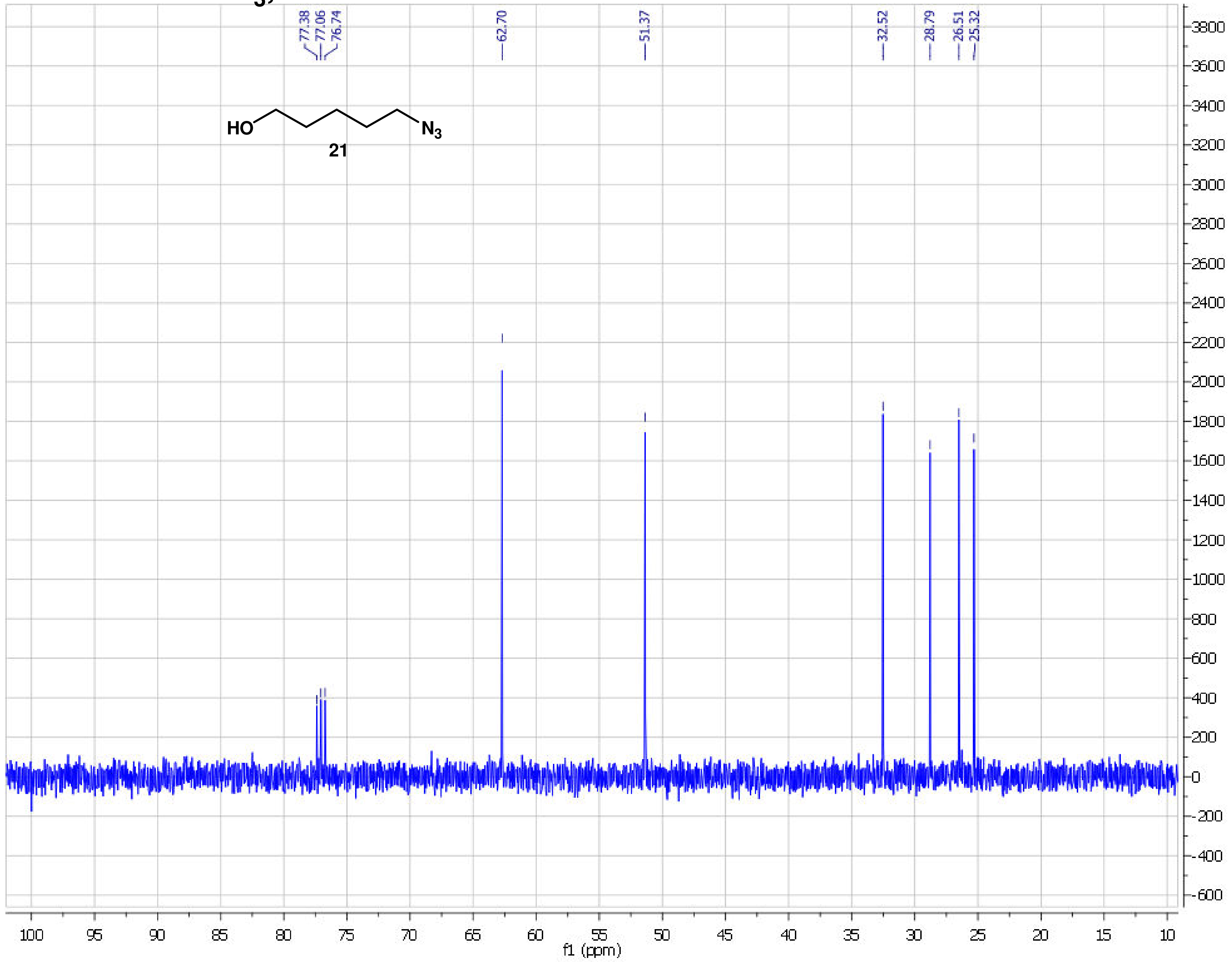

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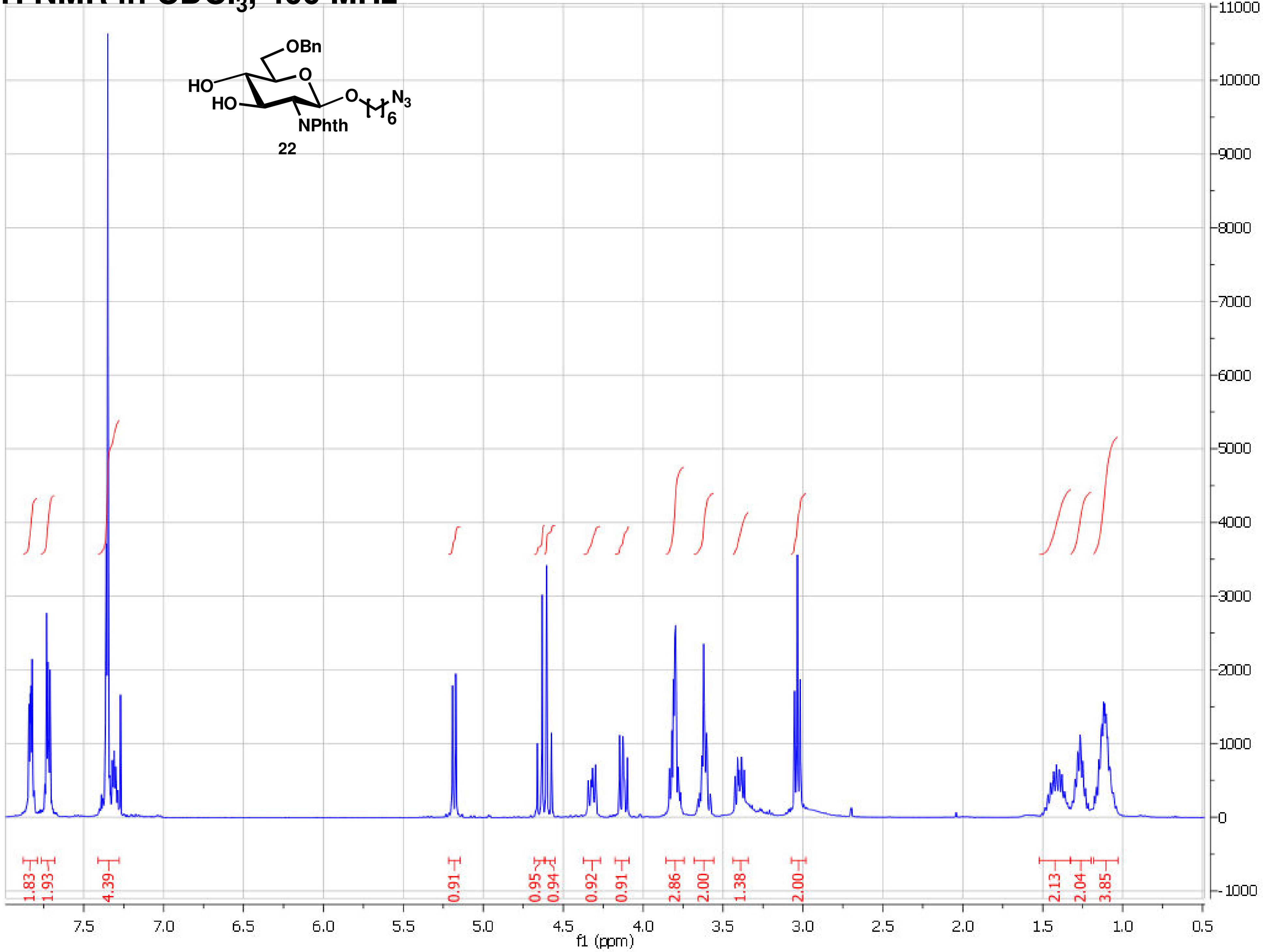

22

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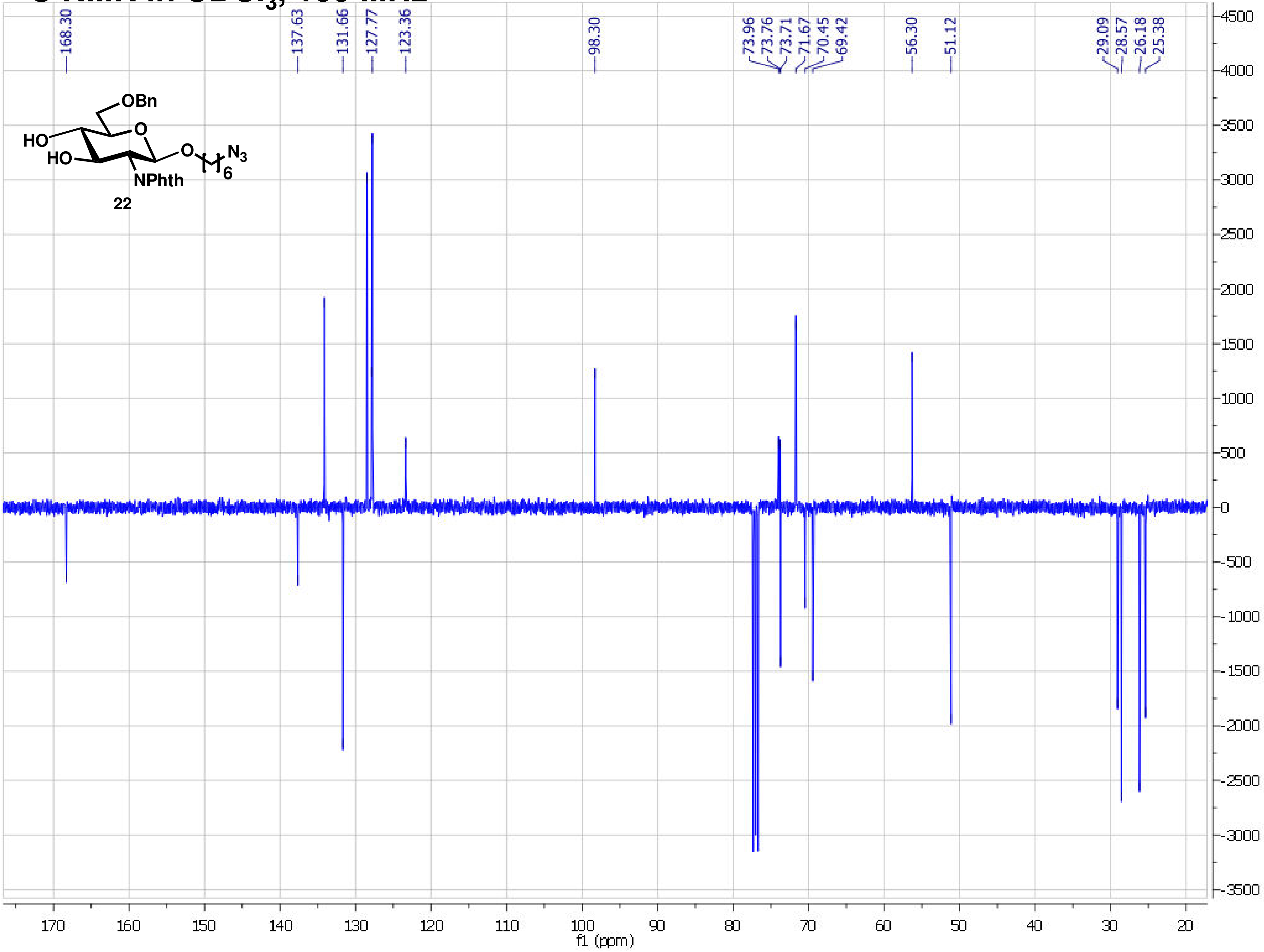

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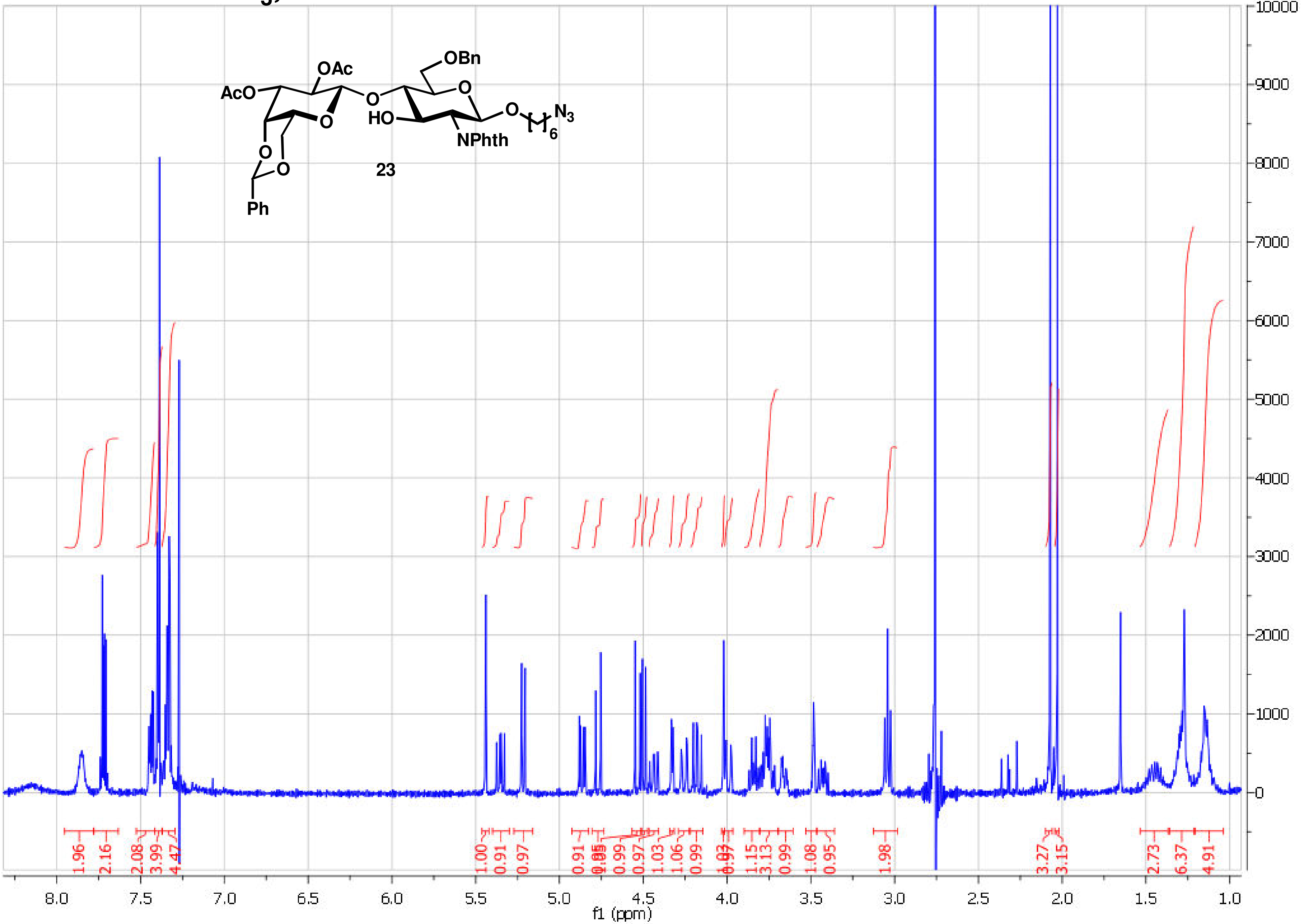

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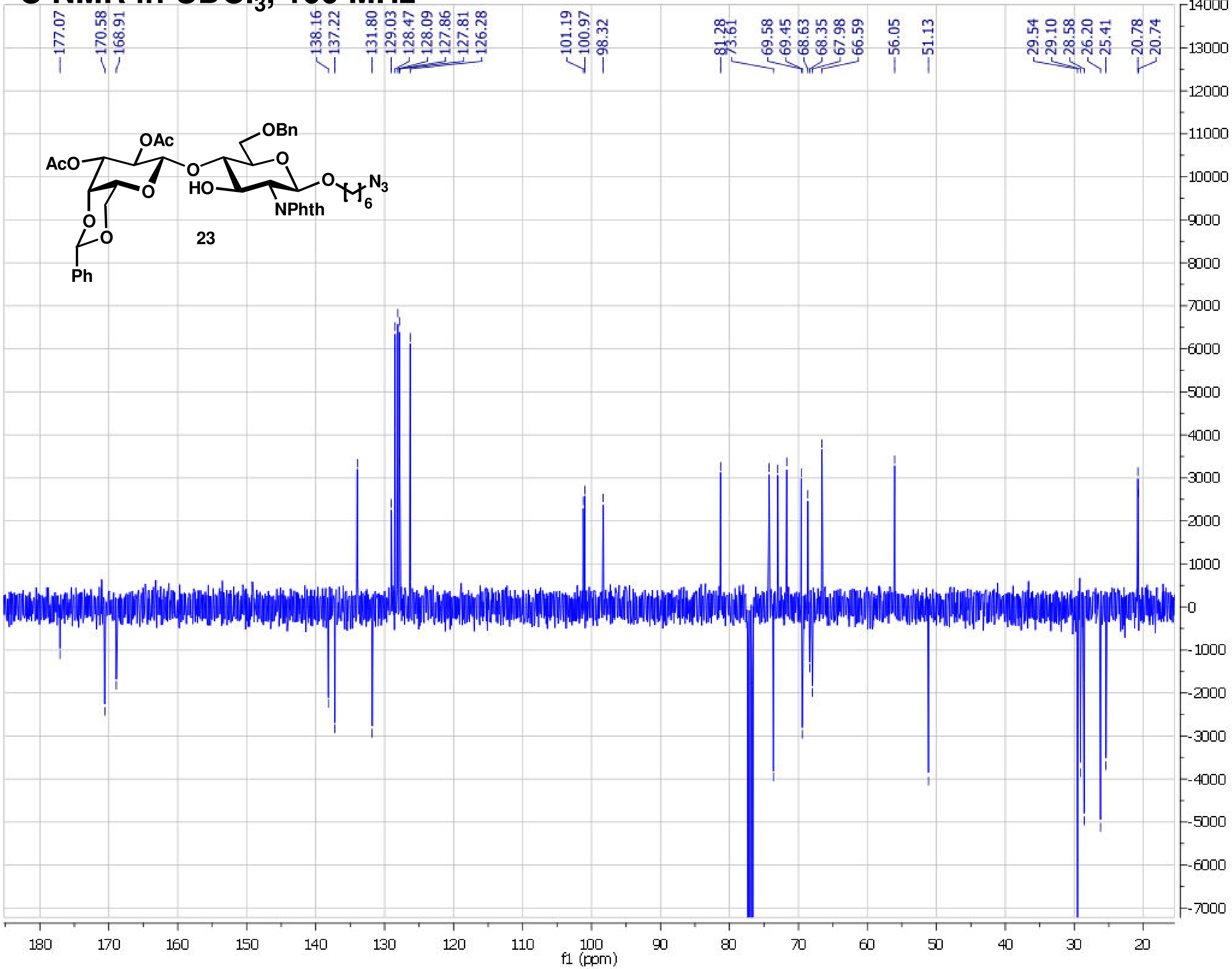

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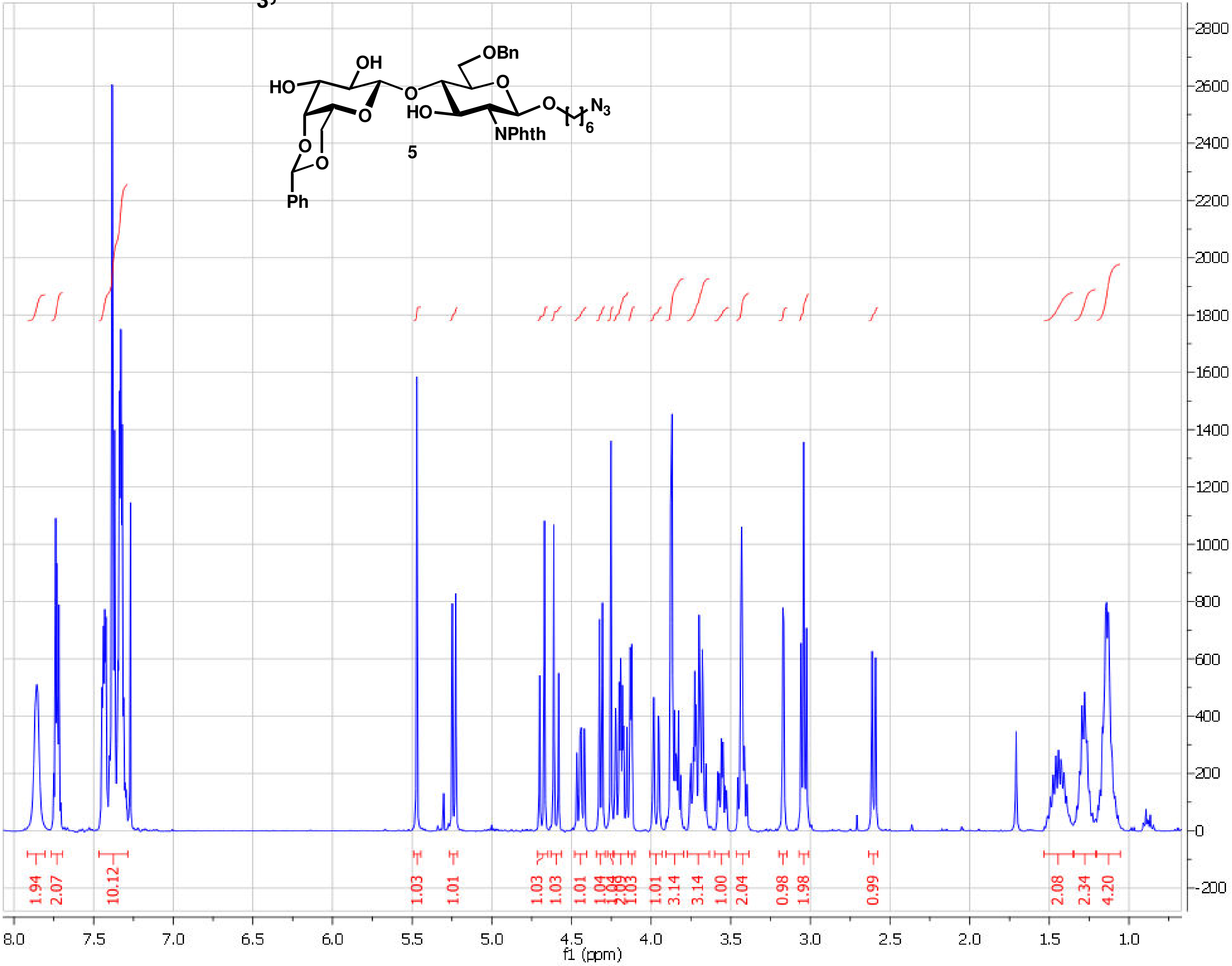

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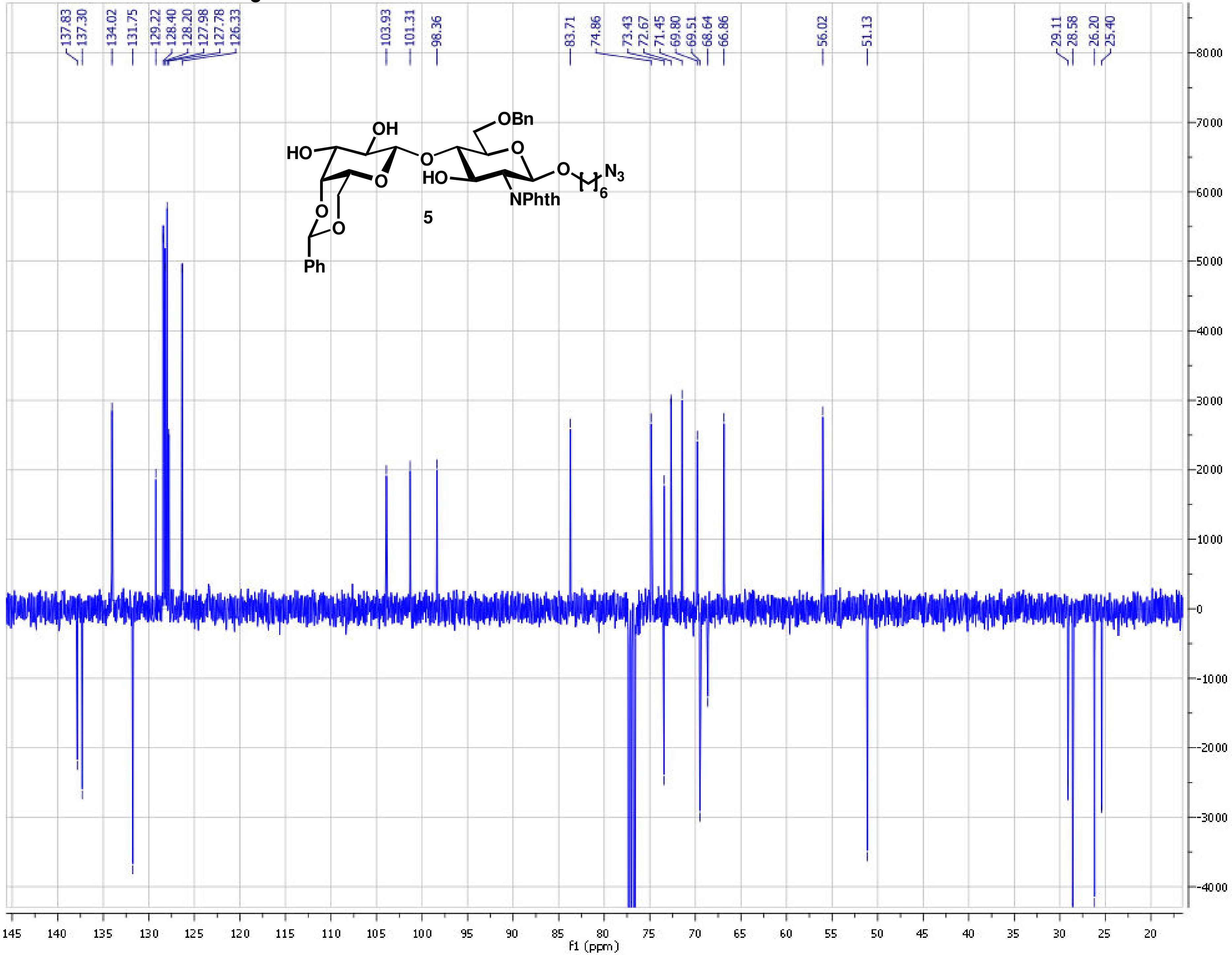

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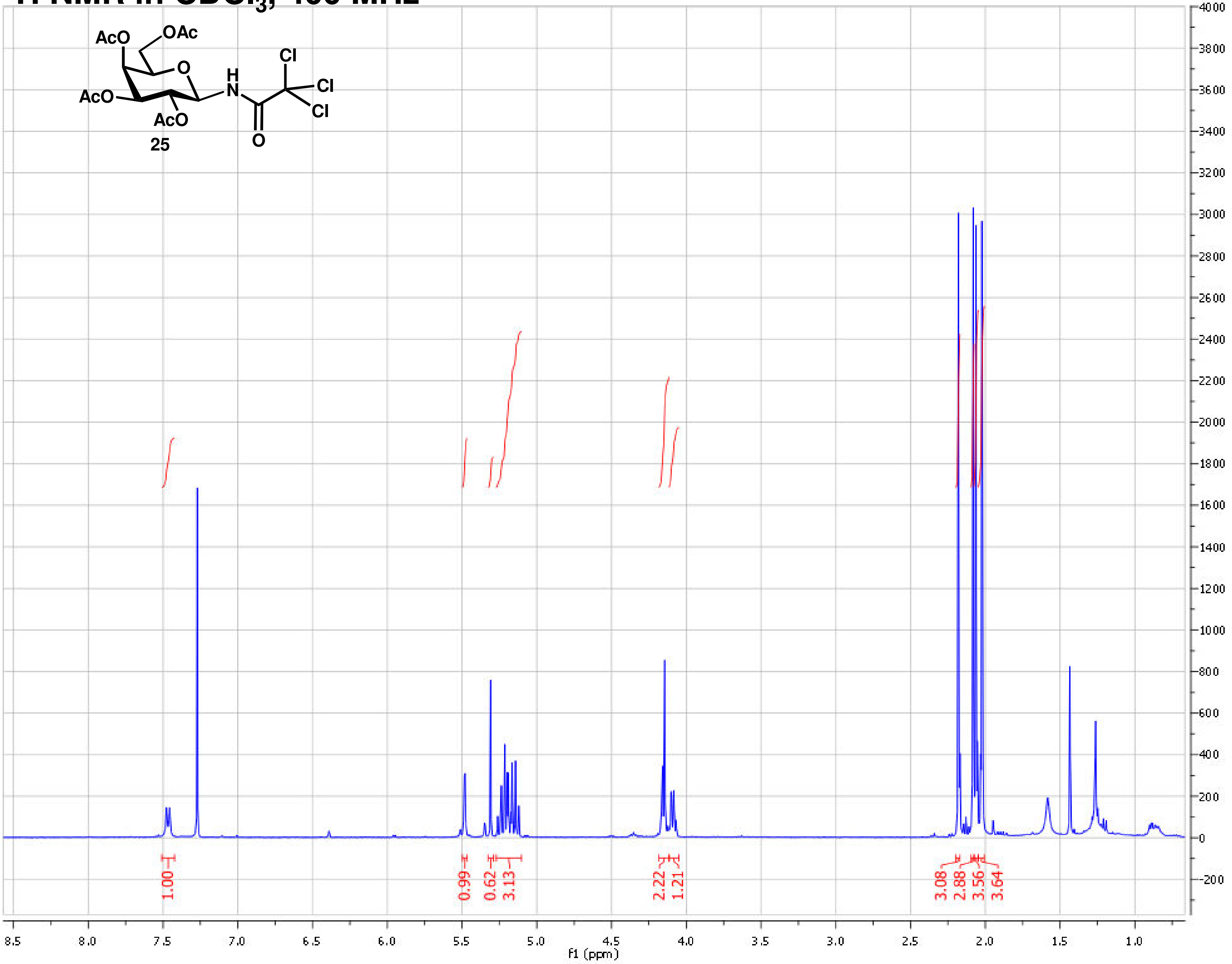
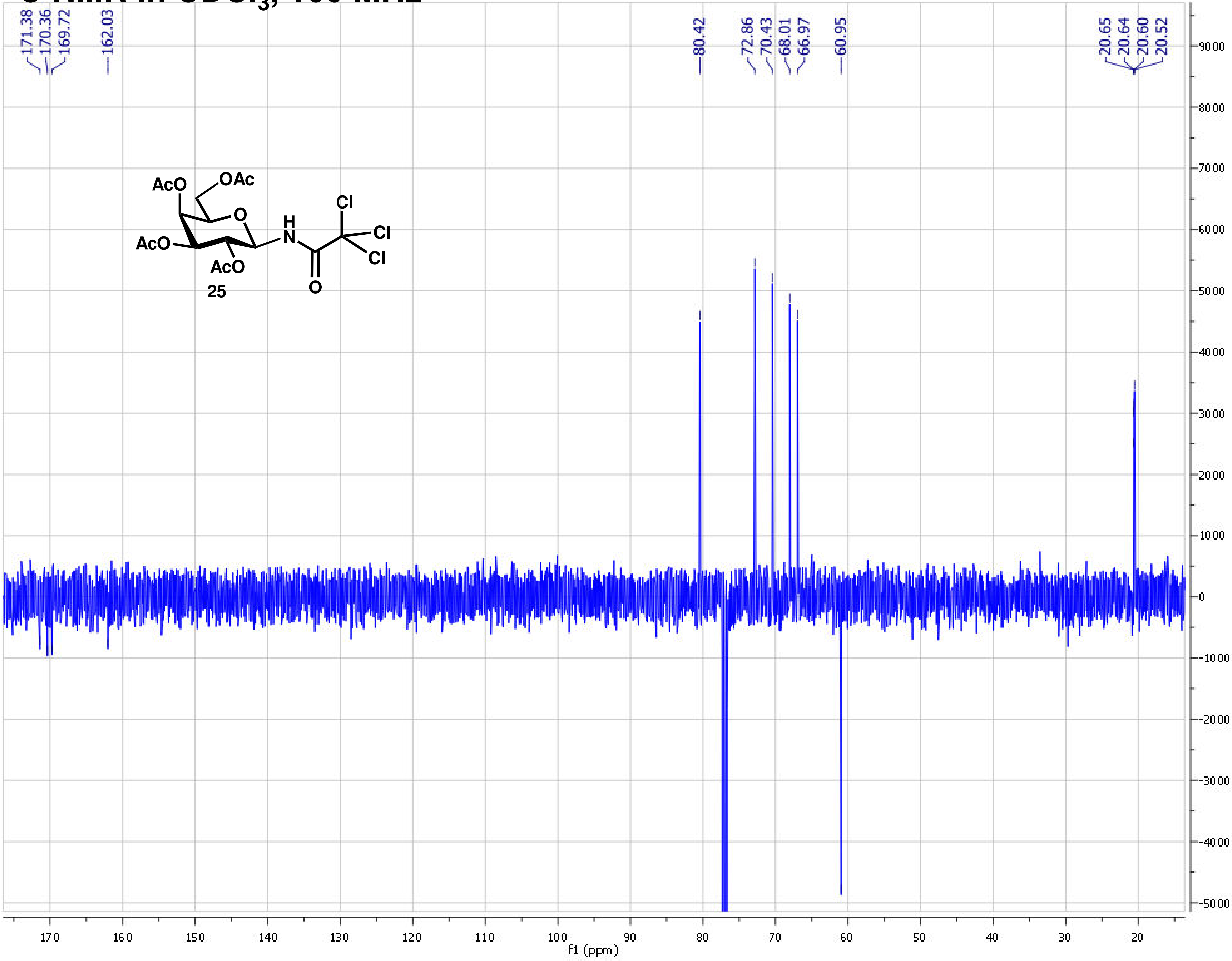
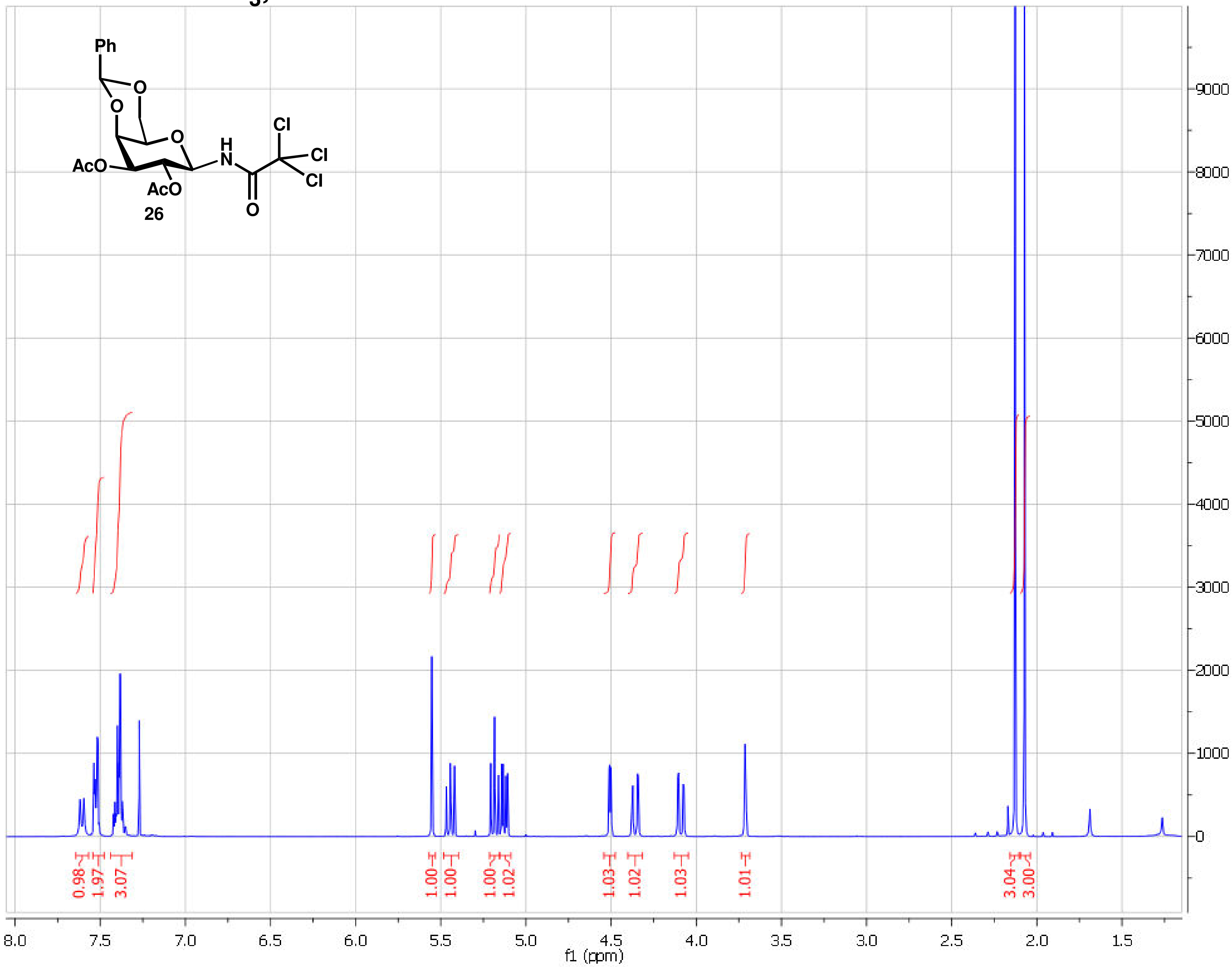


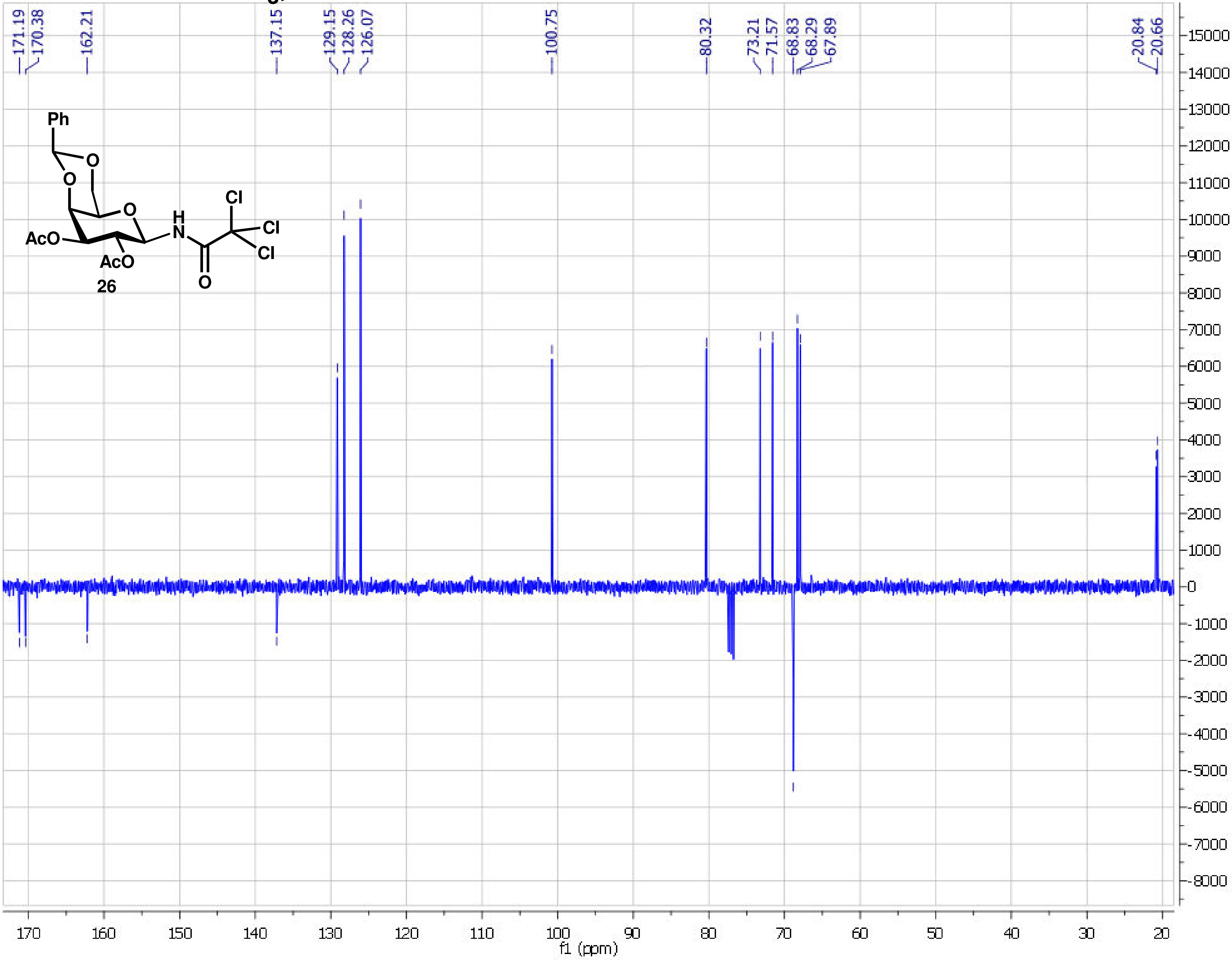
# $^{13}$C NMR in CDCl$_3$, 100 MHz



# $^1$H NMR in $CDCl_3$, 400 MHz



# $^{13}$C NMR in $CDCl_3$, 100 MHz



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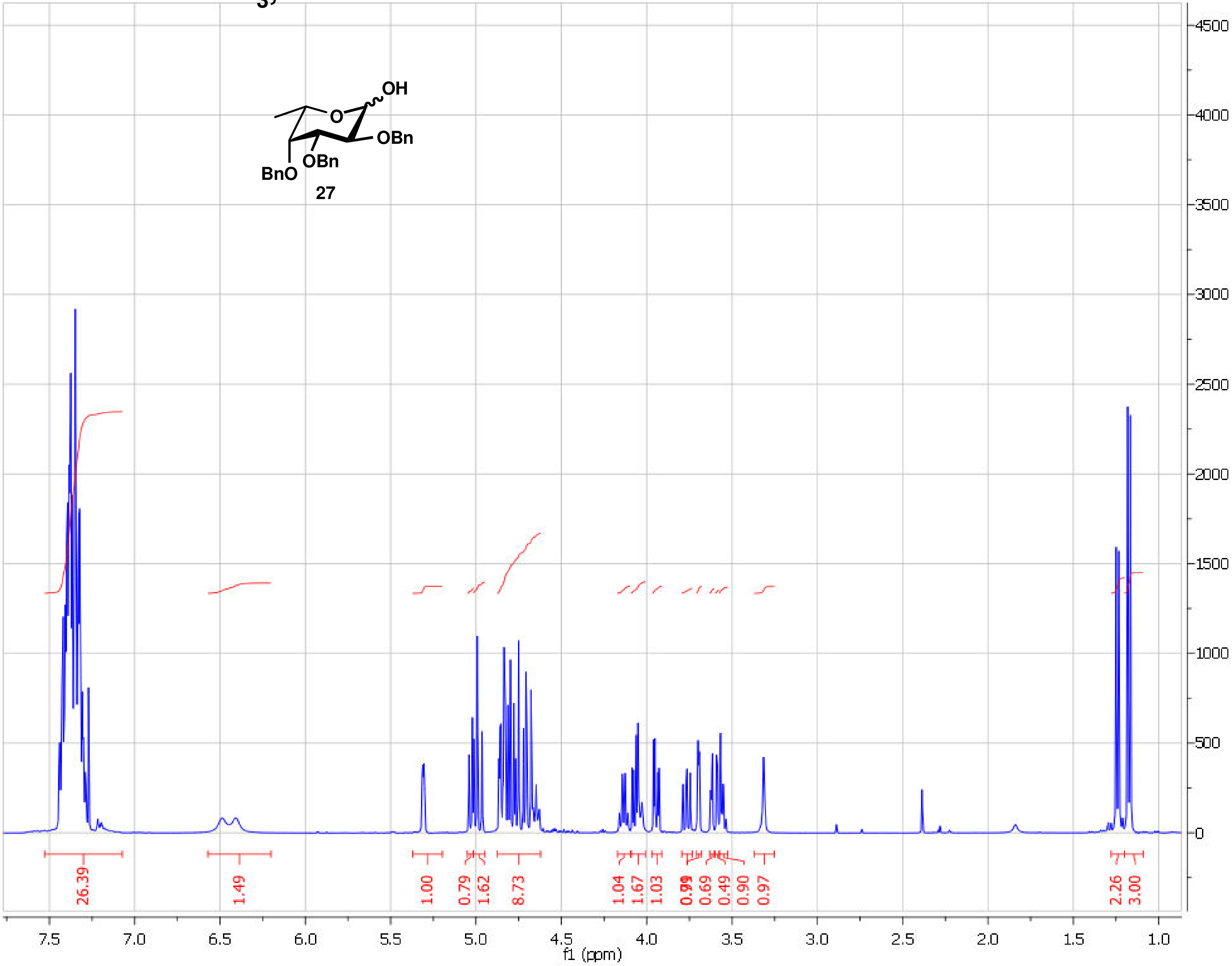
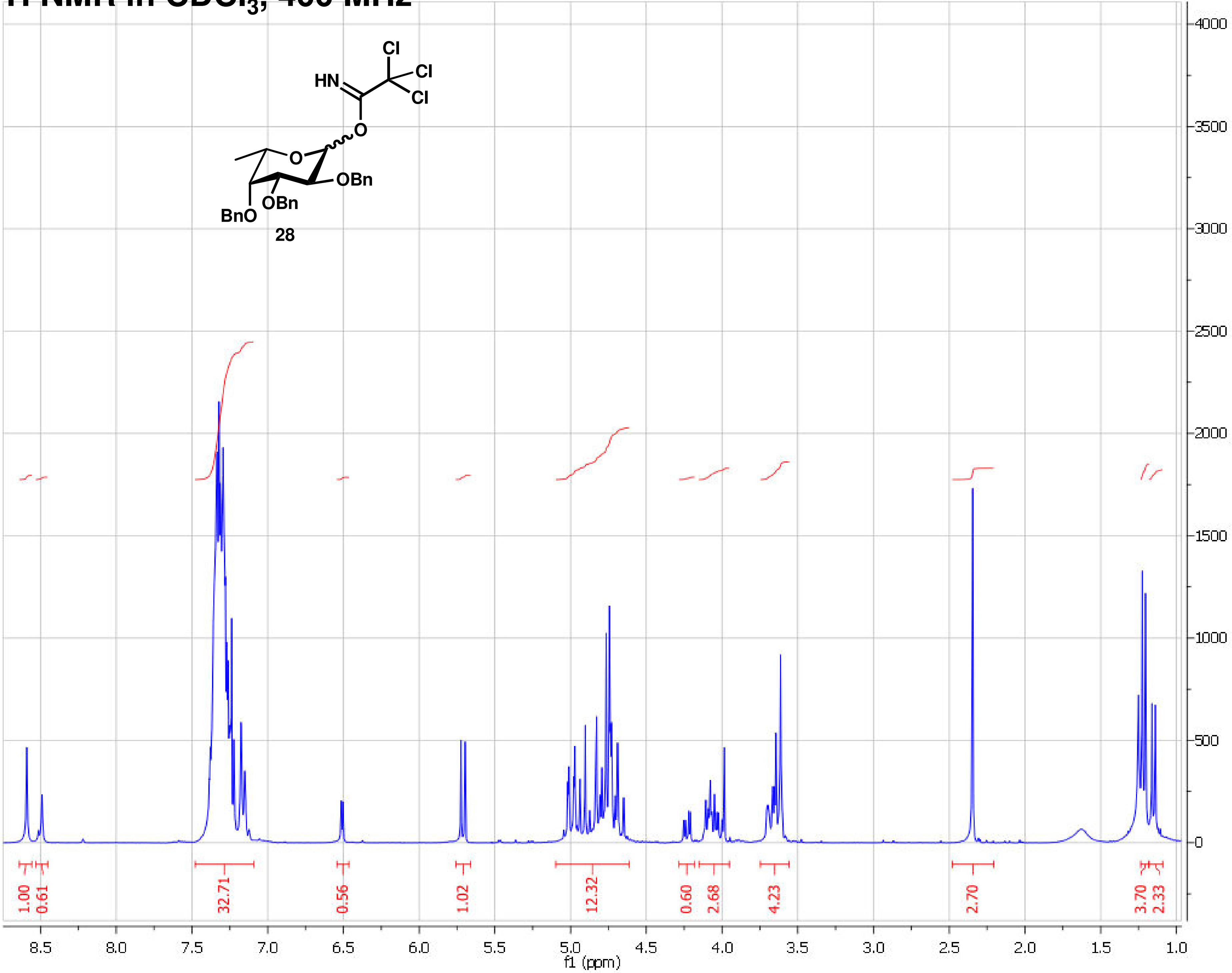
# $^1$H NMR in CDCl$_3$, 400 MHz

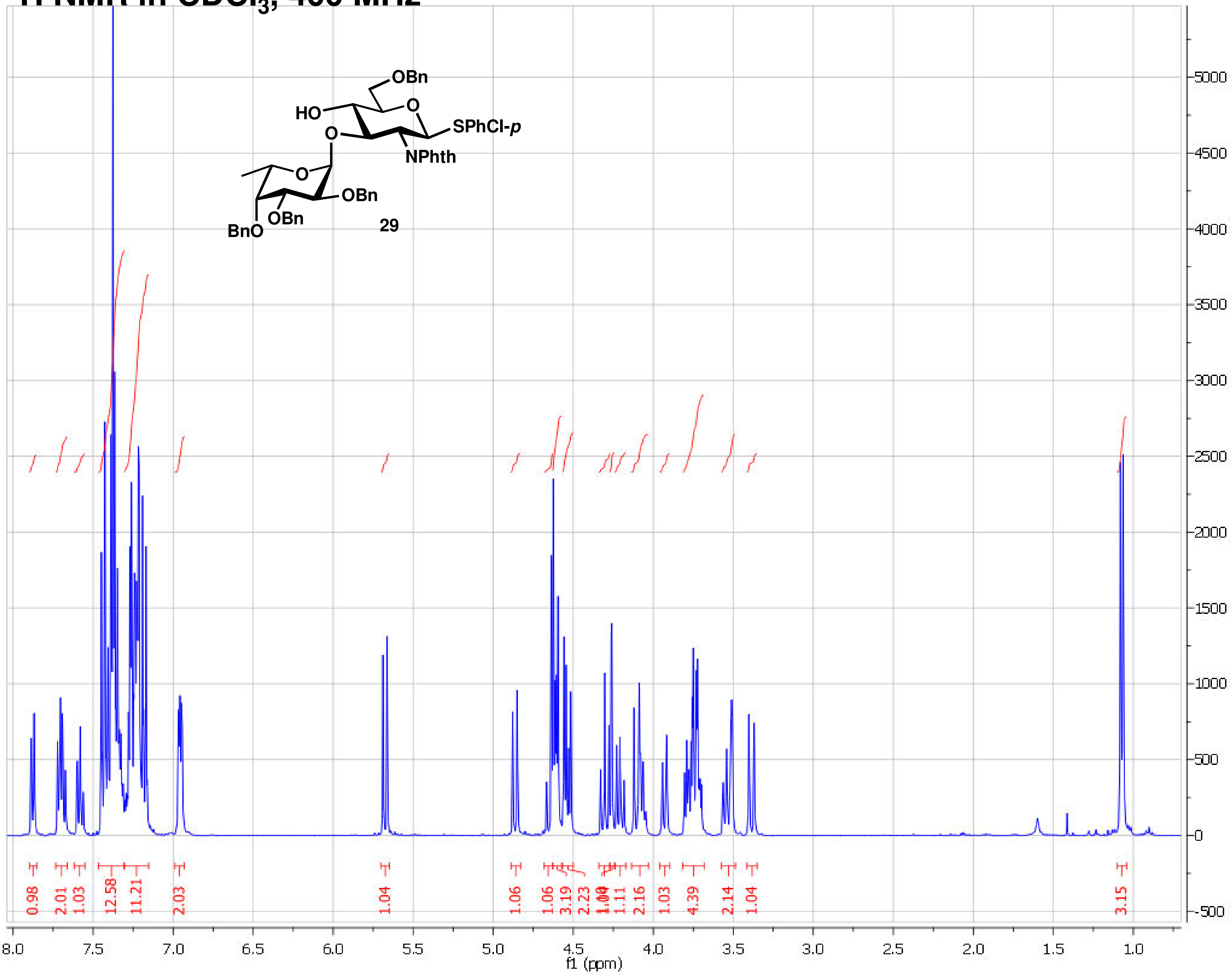


## $^{1}H$ NMR in $CDCl_3$, 400 MHz



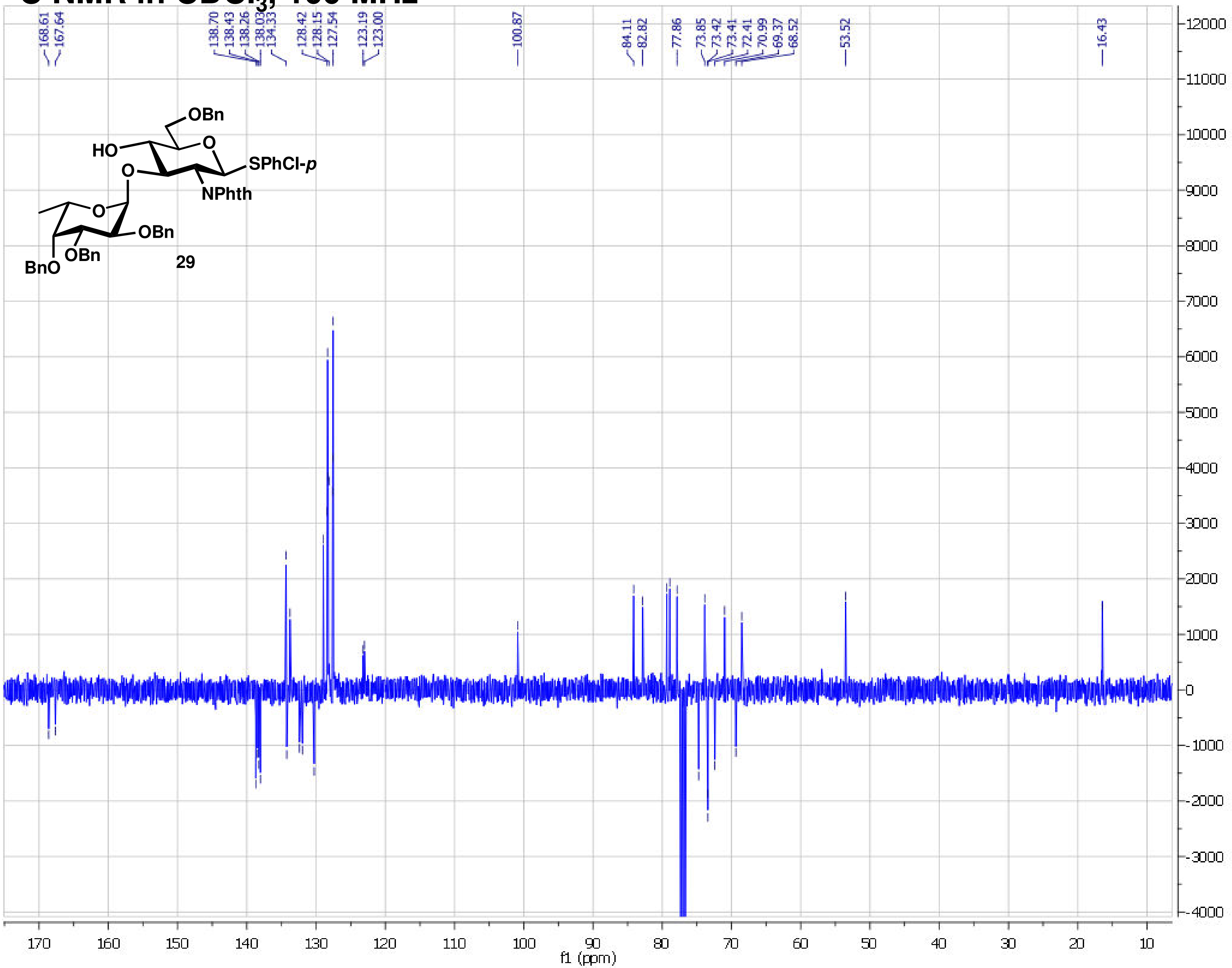
**28**

# $^1$H NMR in CDCl$_3$, 400 MHz

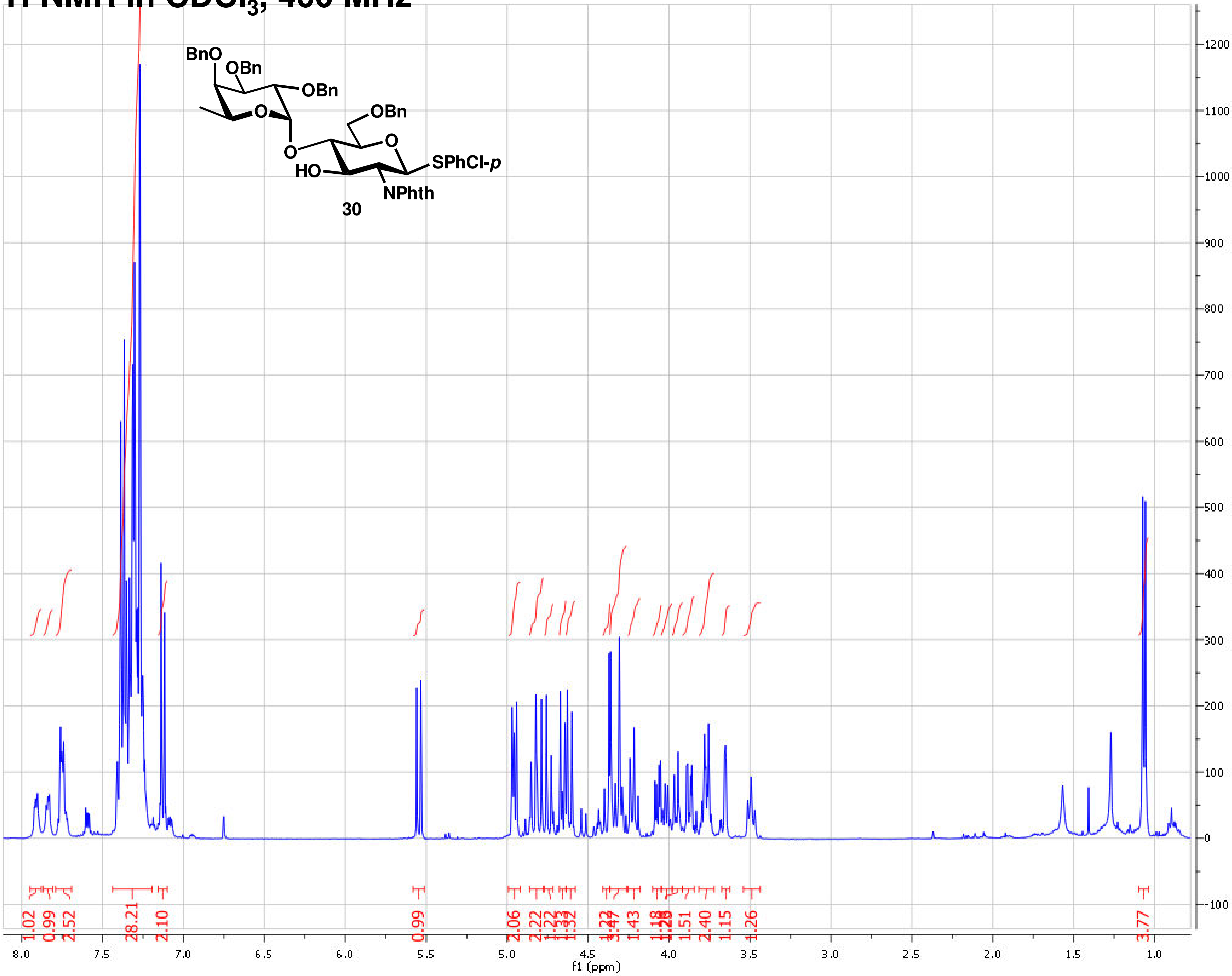


29

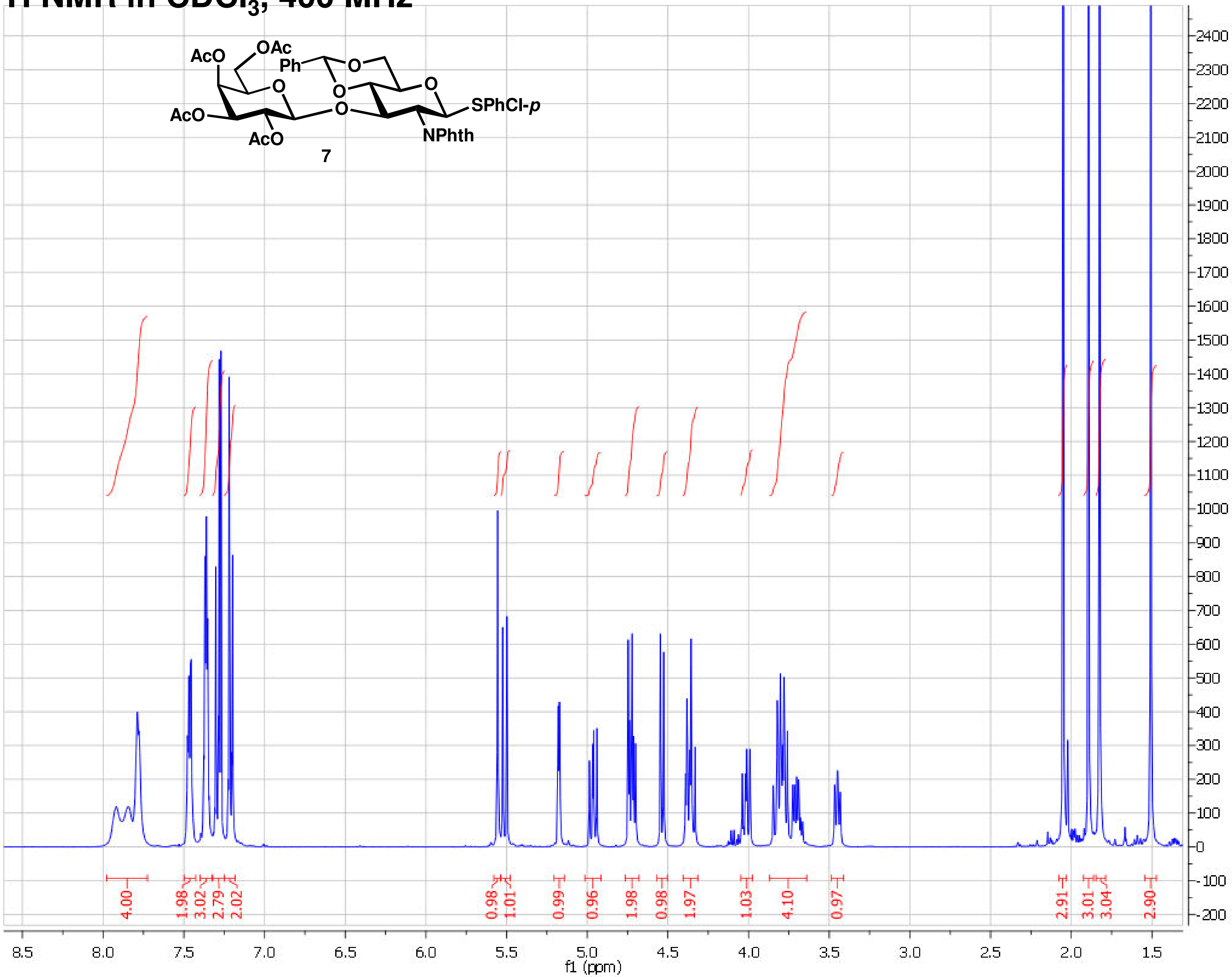
# $^{13}C$ NMR in $CDCl_3$, 100 MHz



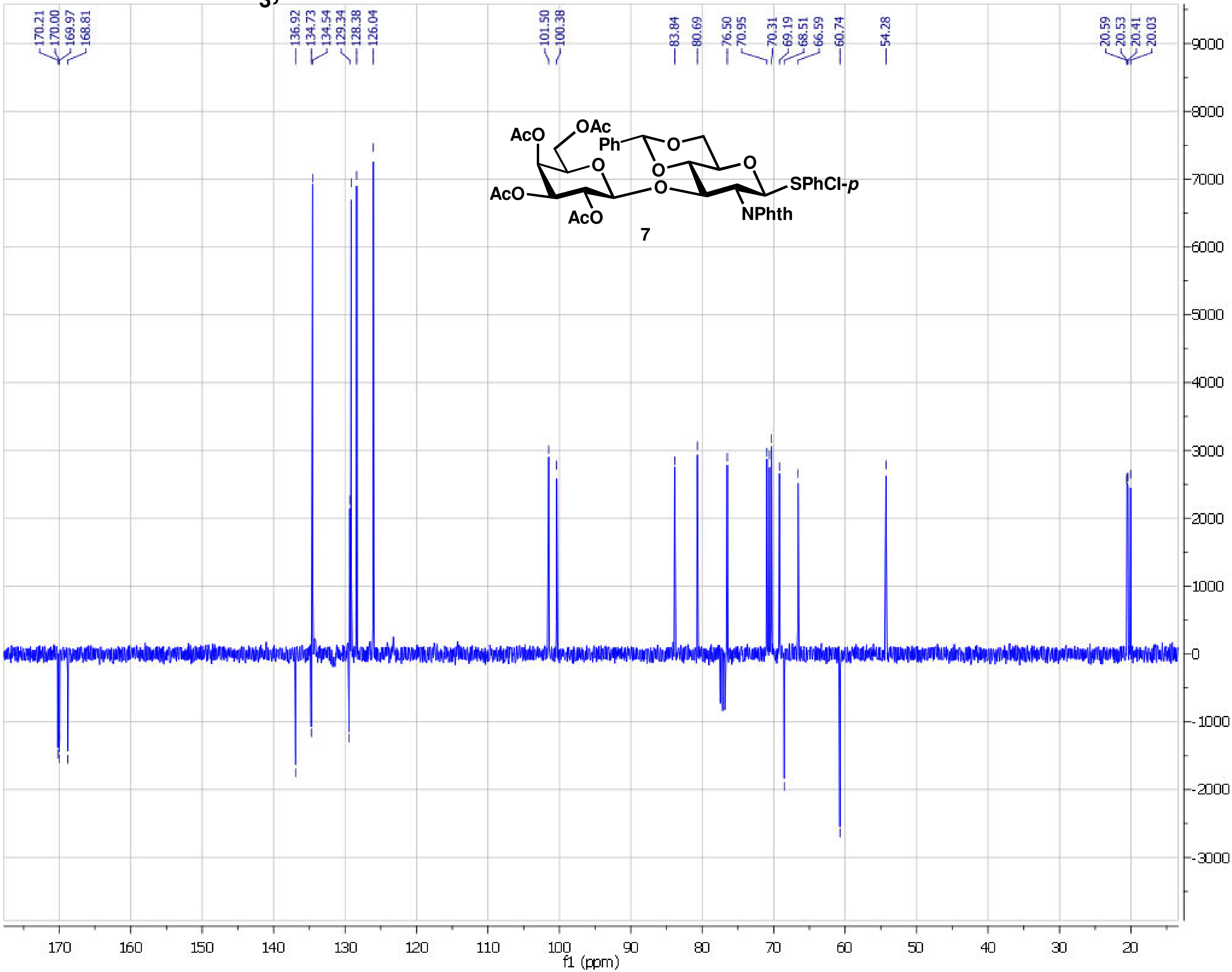
$^1$H NMR in $CDCl_3$, 400 MHz



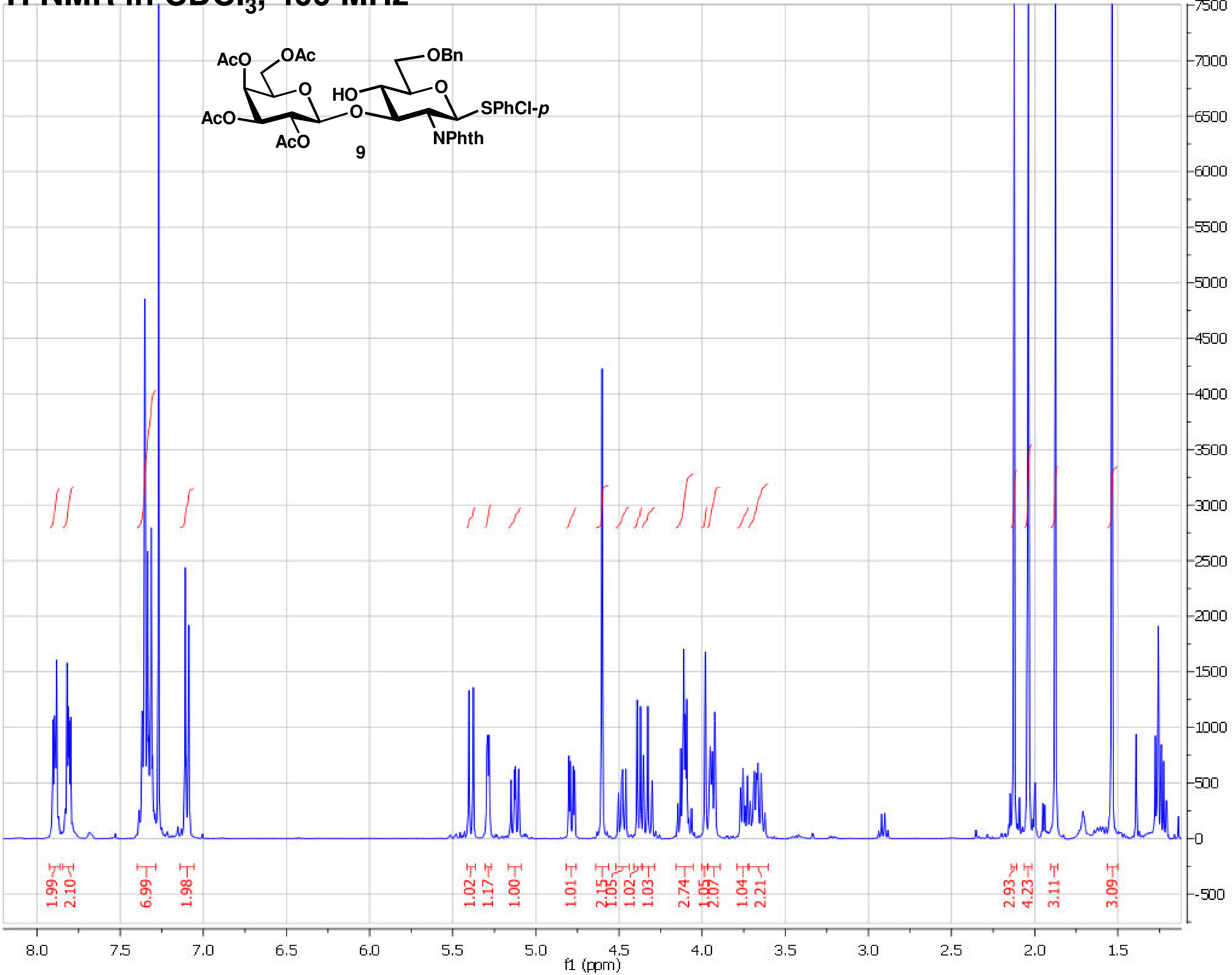
## $^1$H NMR in $CDCl_3$, 400 MHz



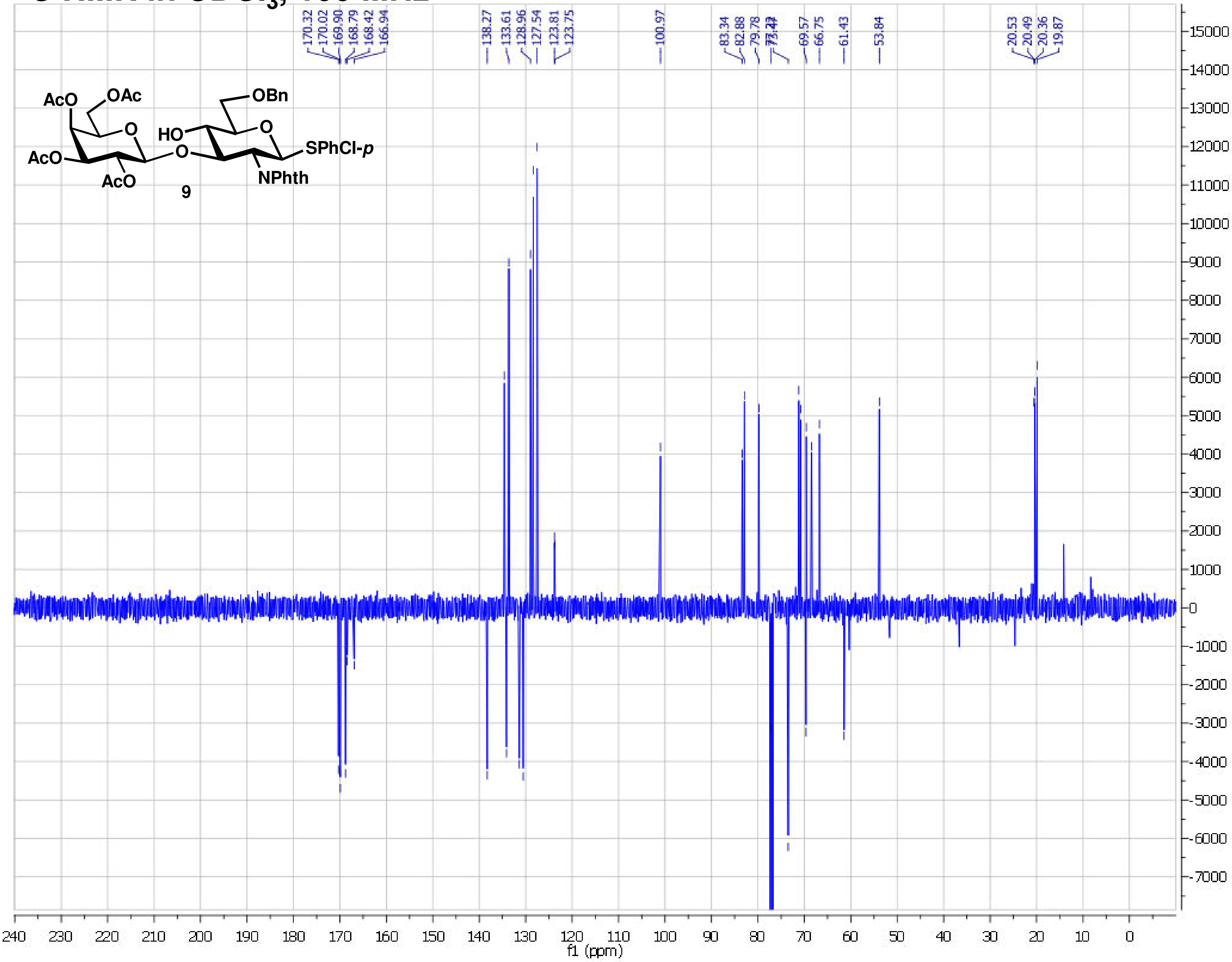
# $^{13}$C NMR in $CDCl_3$, 100 MHz



$^1$H NMR in $CDCl_3$, 400 MHz



# $^{13}$C NMR in $CDCl_3$, 100 MHz



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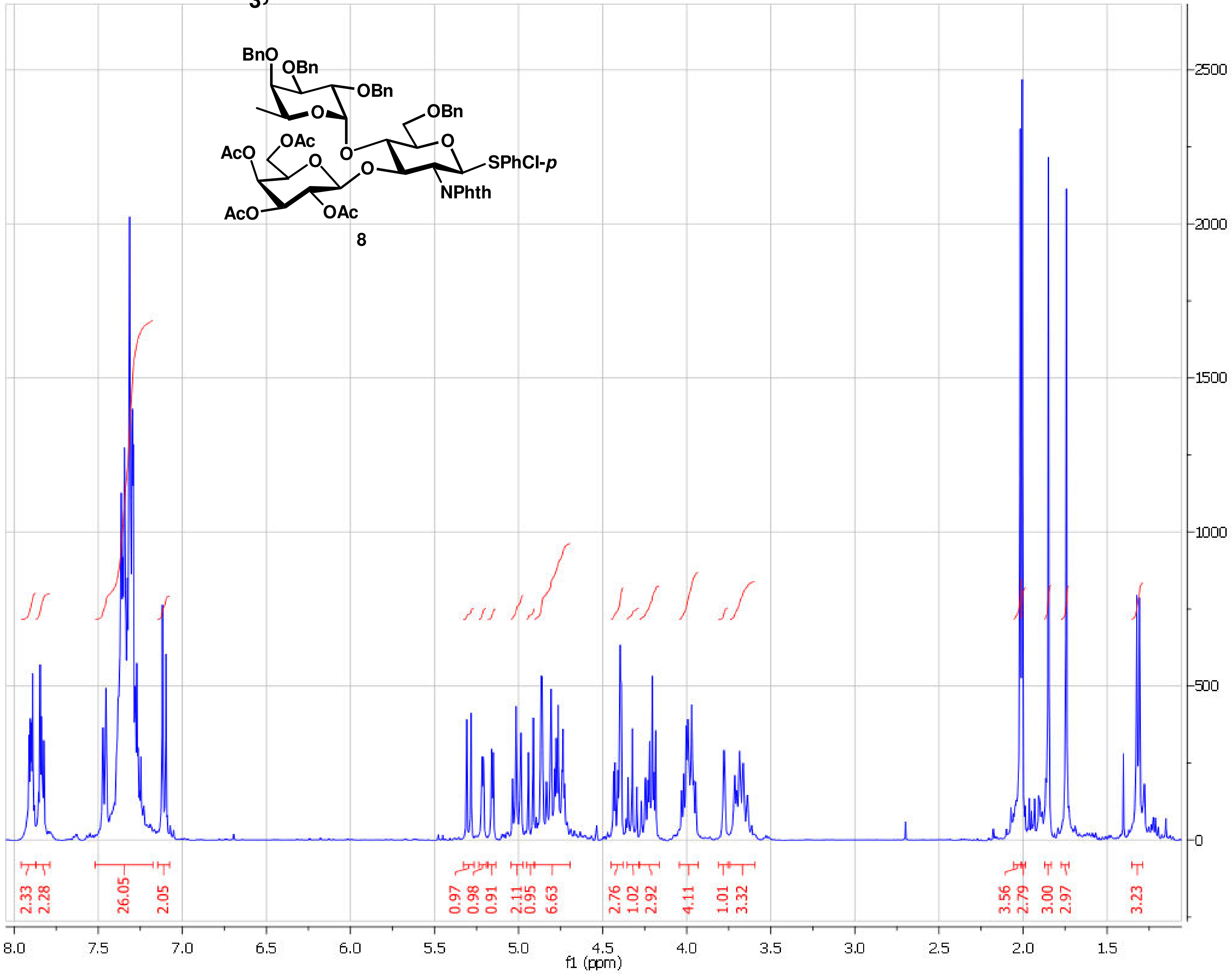
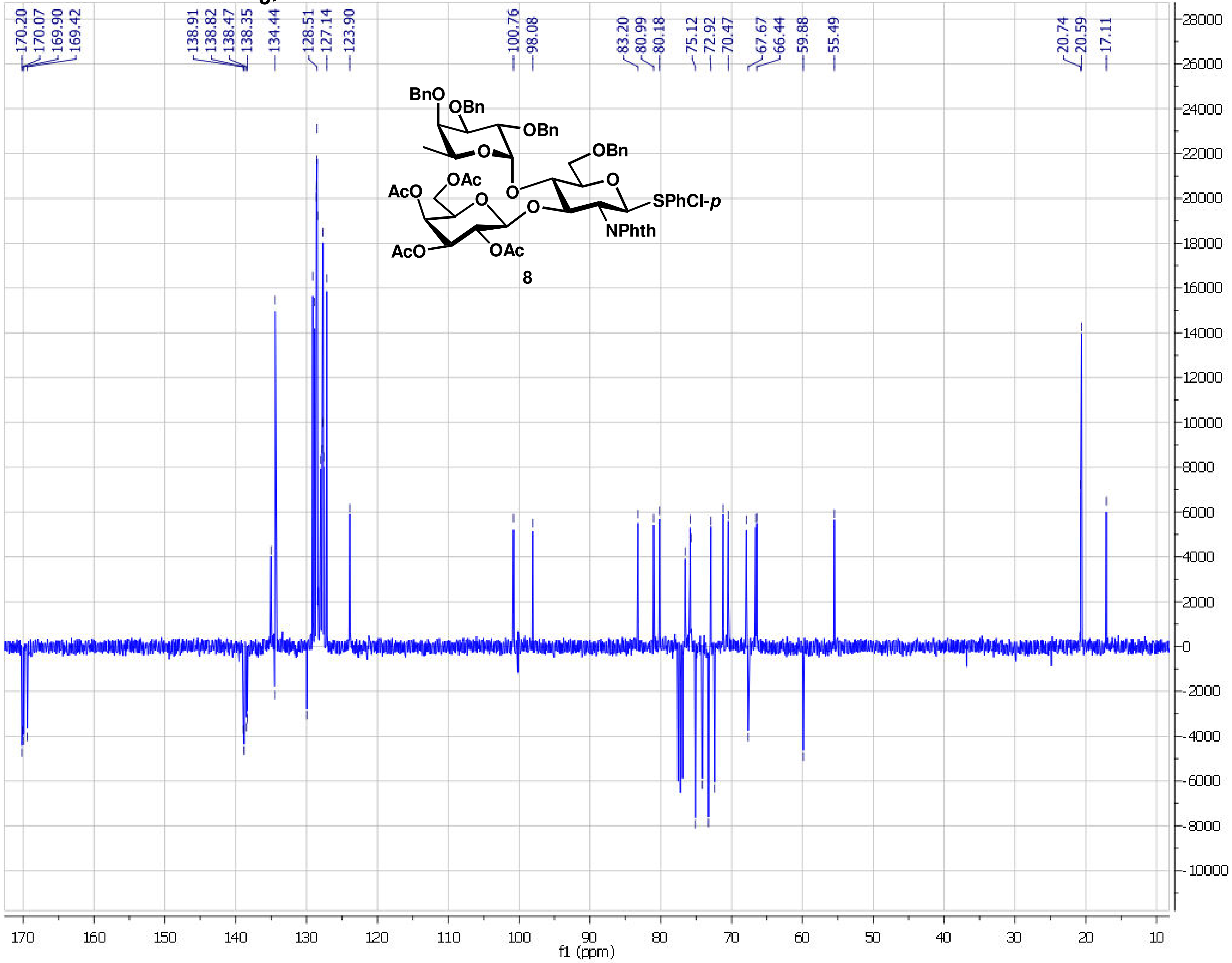
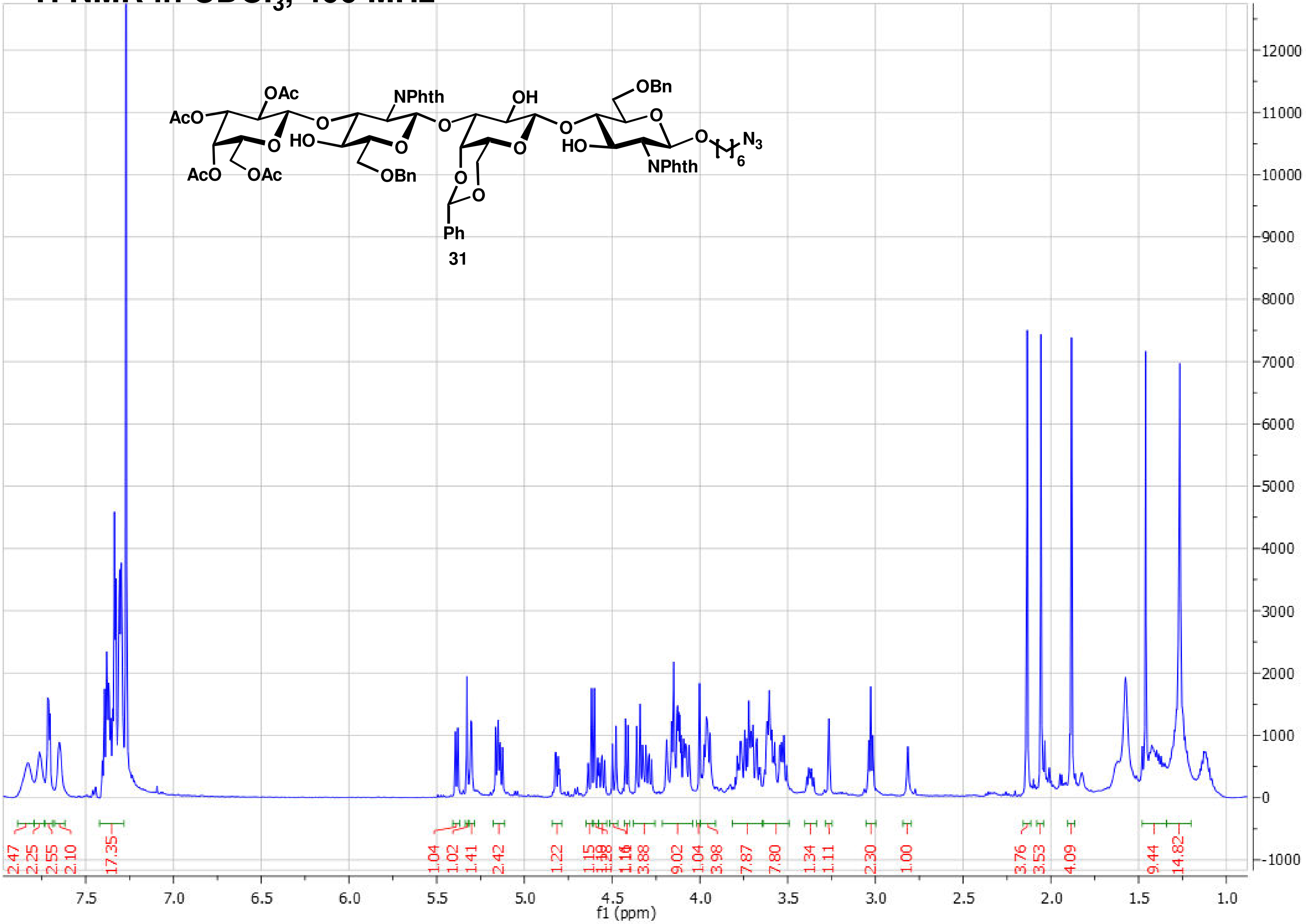
## $^1$H NMR in $CDCl_3$, 400 MHz



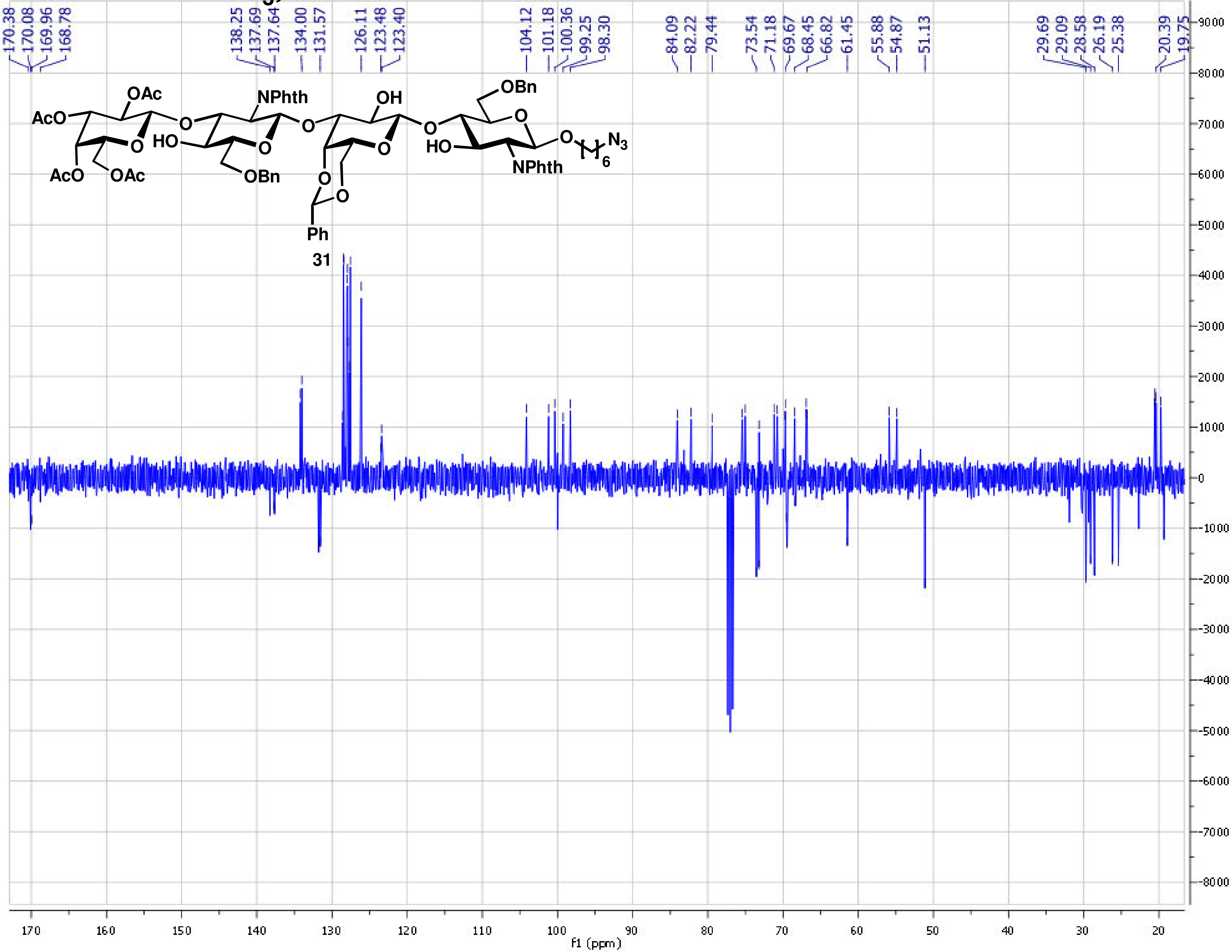
# $^{13}C$ NMR in $CDCl_3$, 100 MHz



# $^1$H NMR in $CDCl_3$, 400 MHz



# $^{13}$C NMR in CDCl$_3$, 100 MHz



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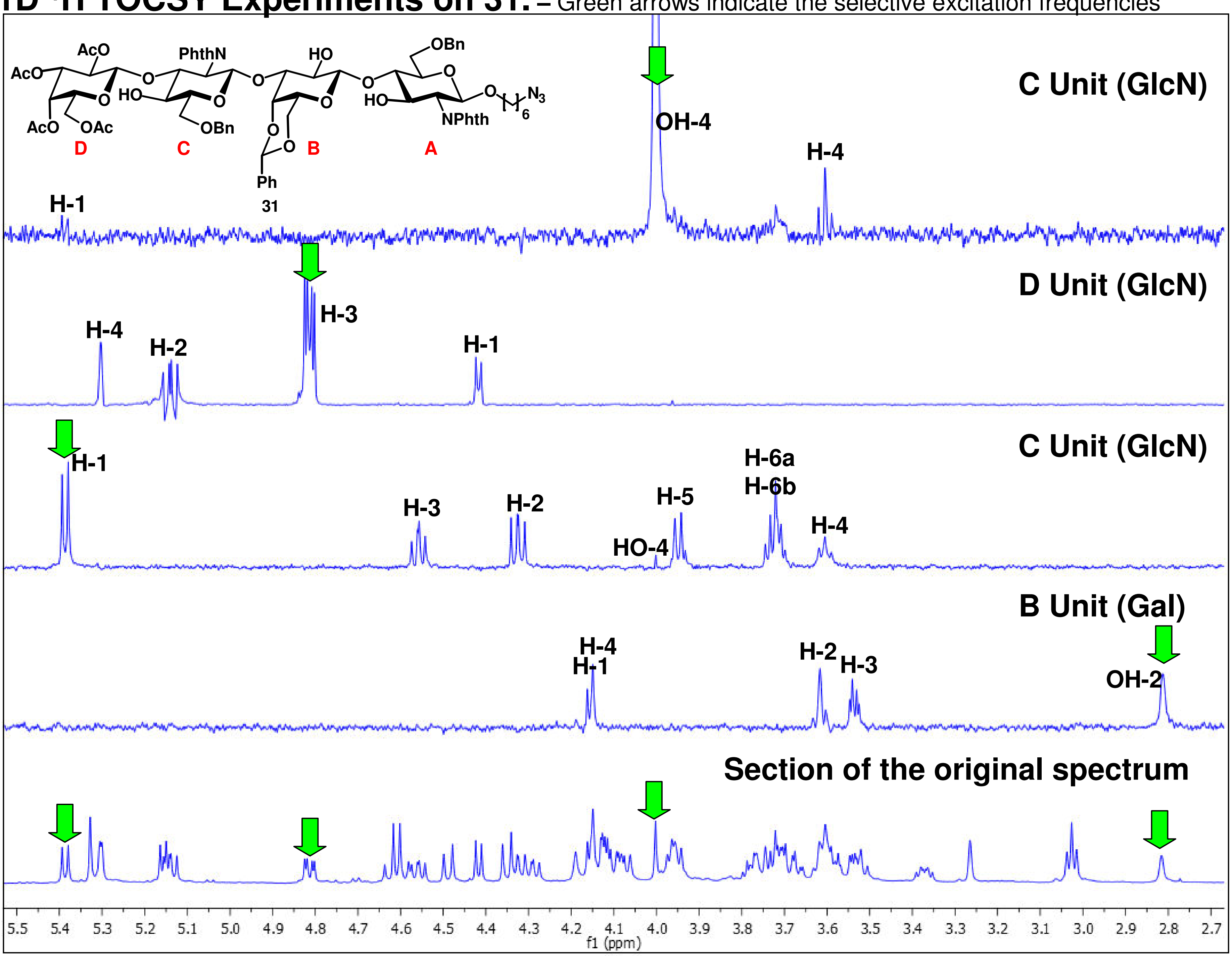
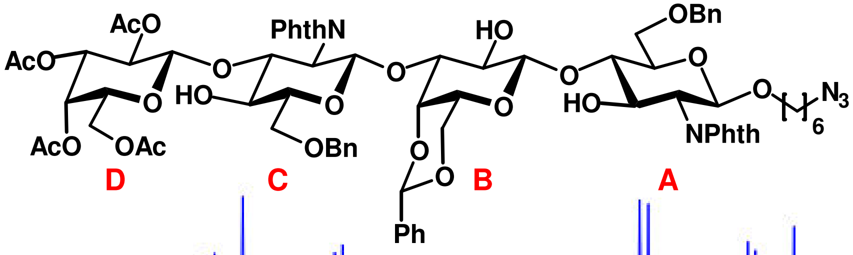
# 1D $^{1}$H TOCSY Experiments on 31. – Green arrows indicate the selective excitation frequencies





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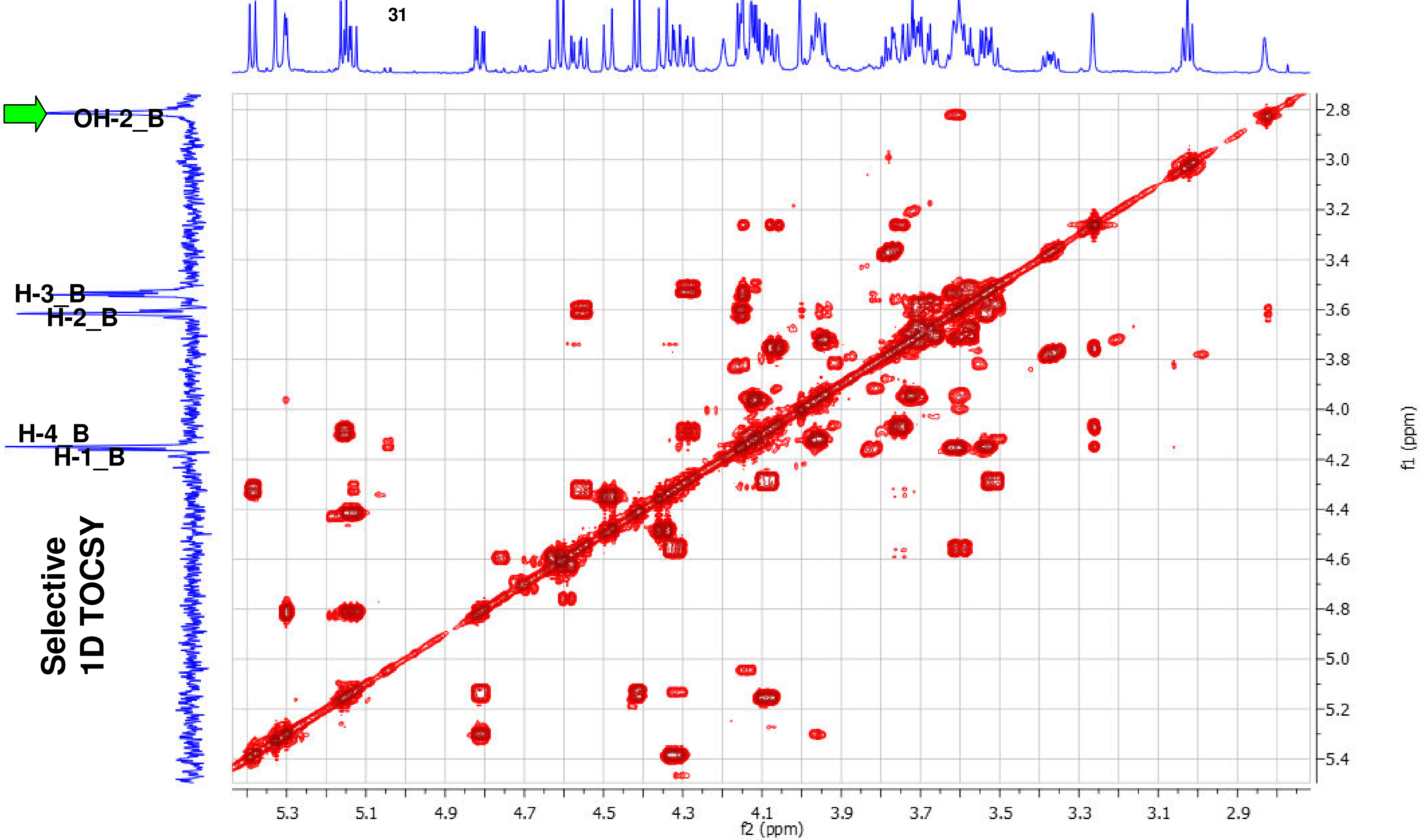
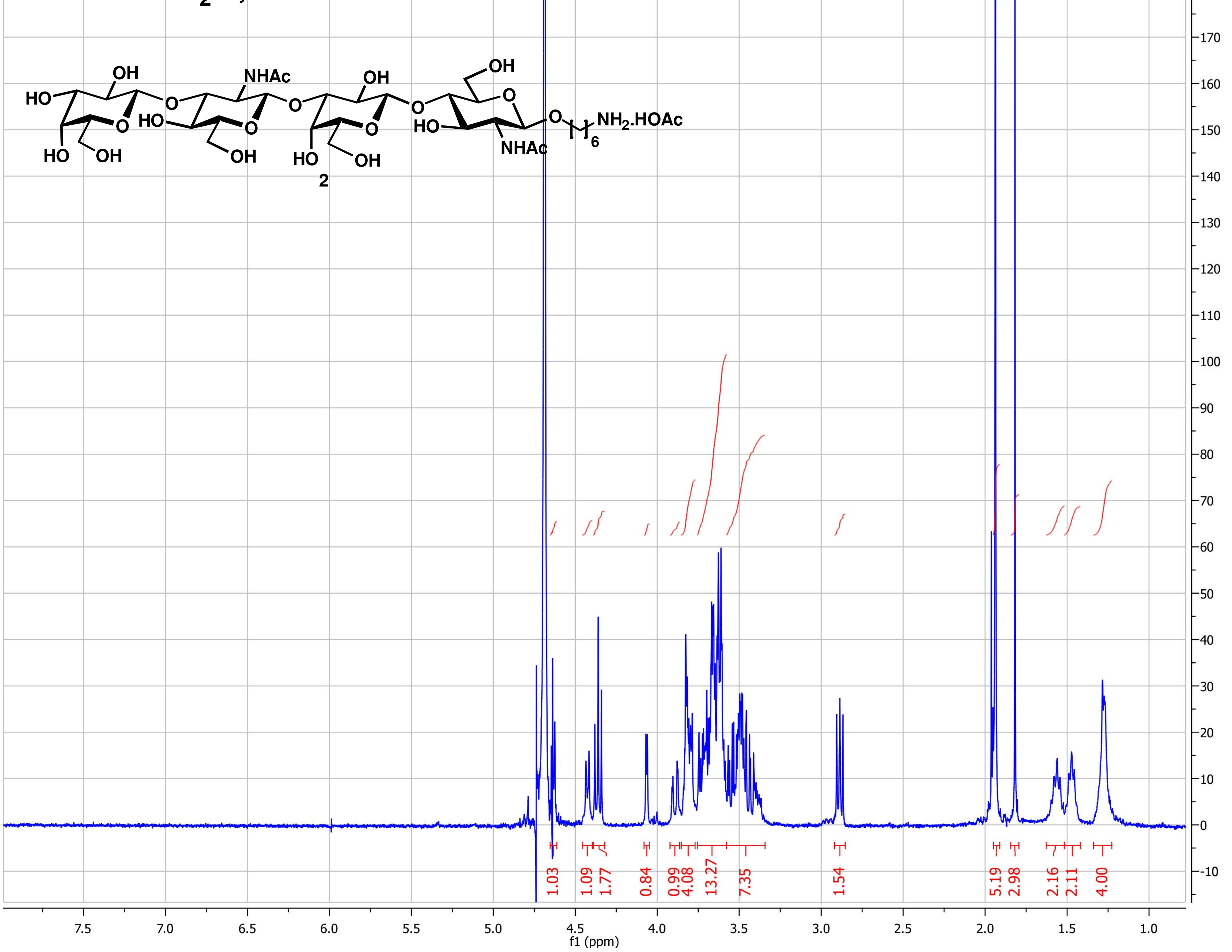
## $^1$H-$^1$H COSY NMR ($CDCl_3$, 600 MHz)

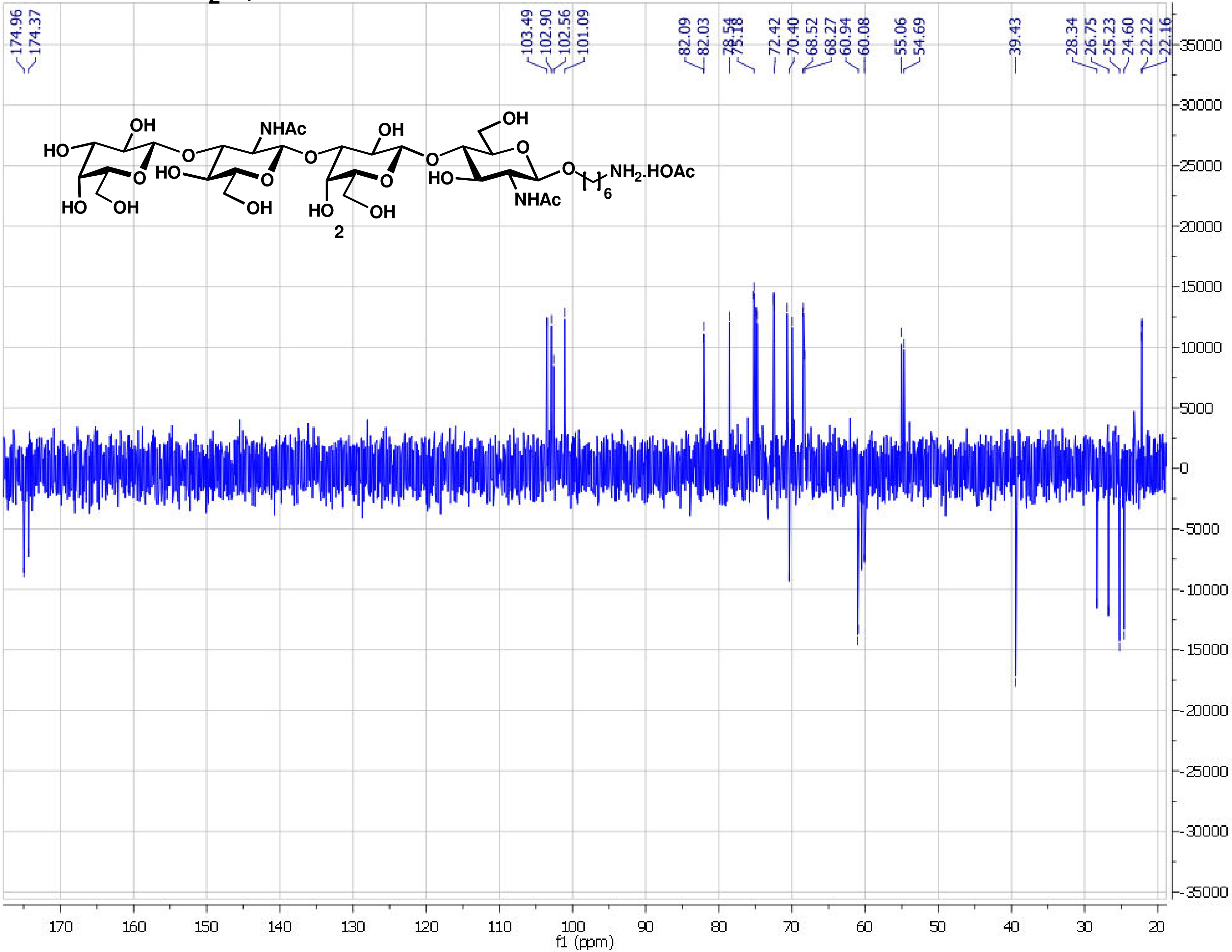
**combined with a 1D TOCSY trace (OH-2' was excited)**



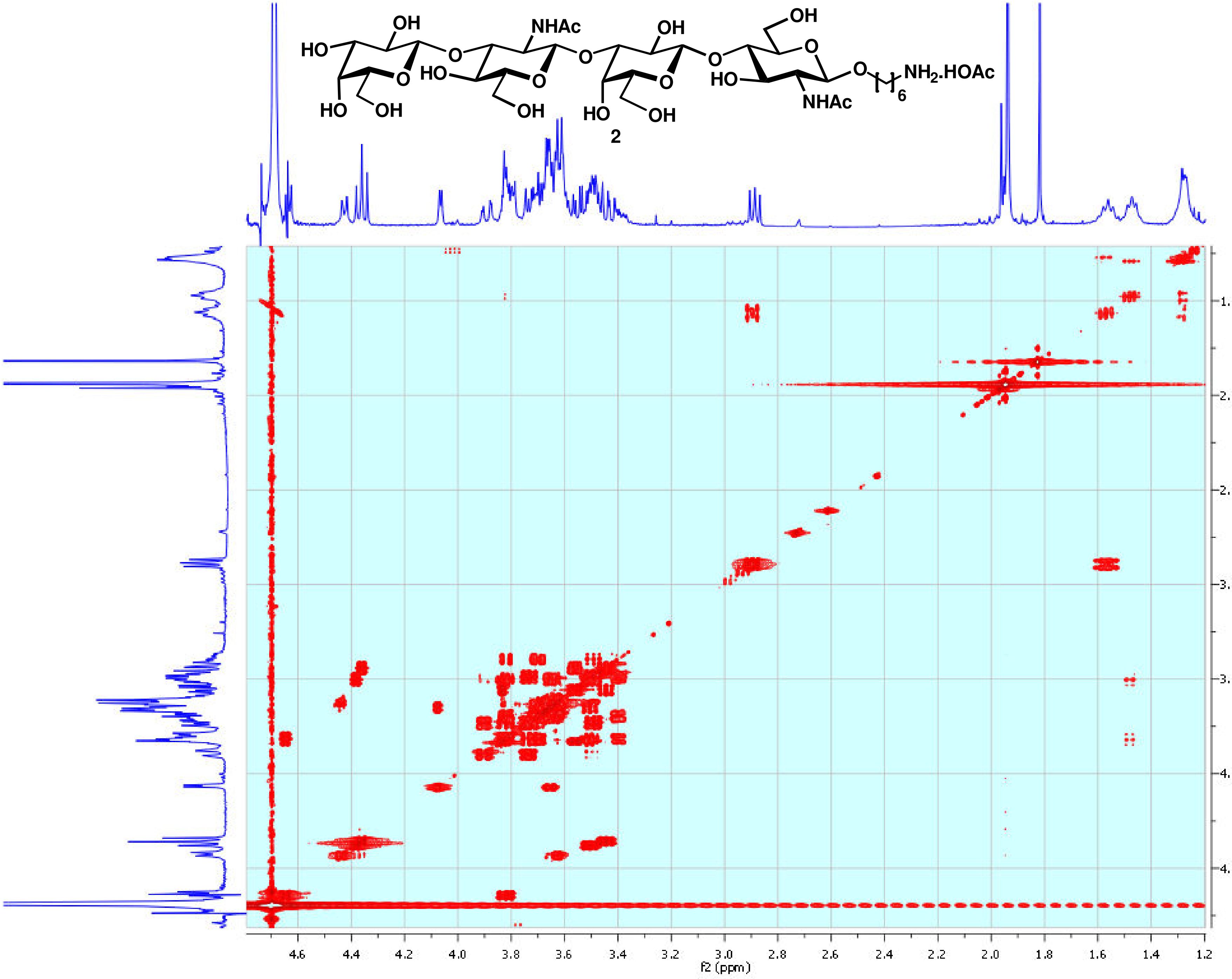
# $^1$H NMR in $D_2O$, 400 MHz



## $^{13}C$ NMR in $D_2O$, 100 MHz

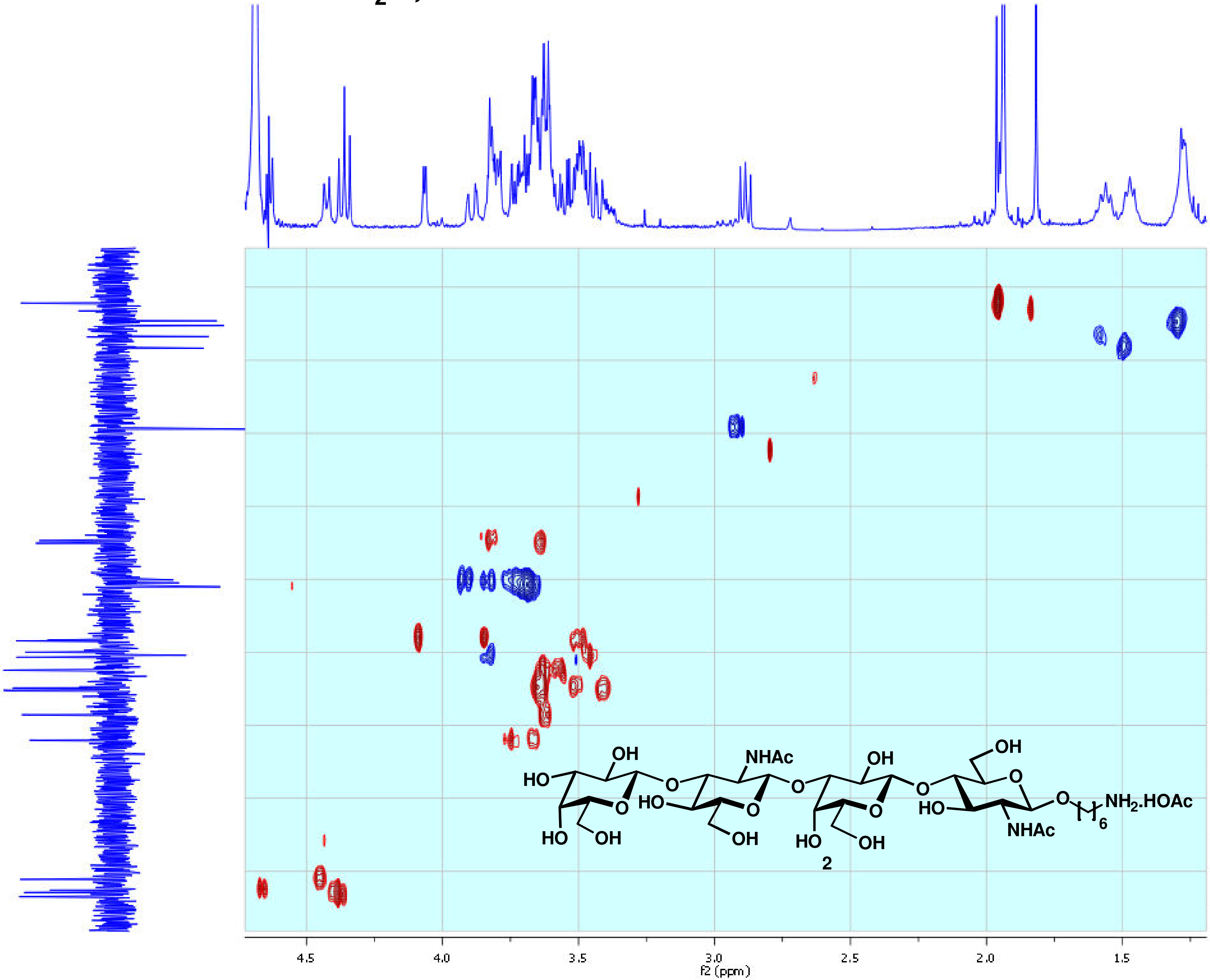


# $^1H$-$^1H$ 2D GCOSY NMR in $D_2O$, 400 MHz

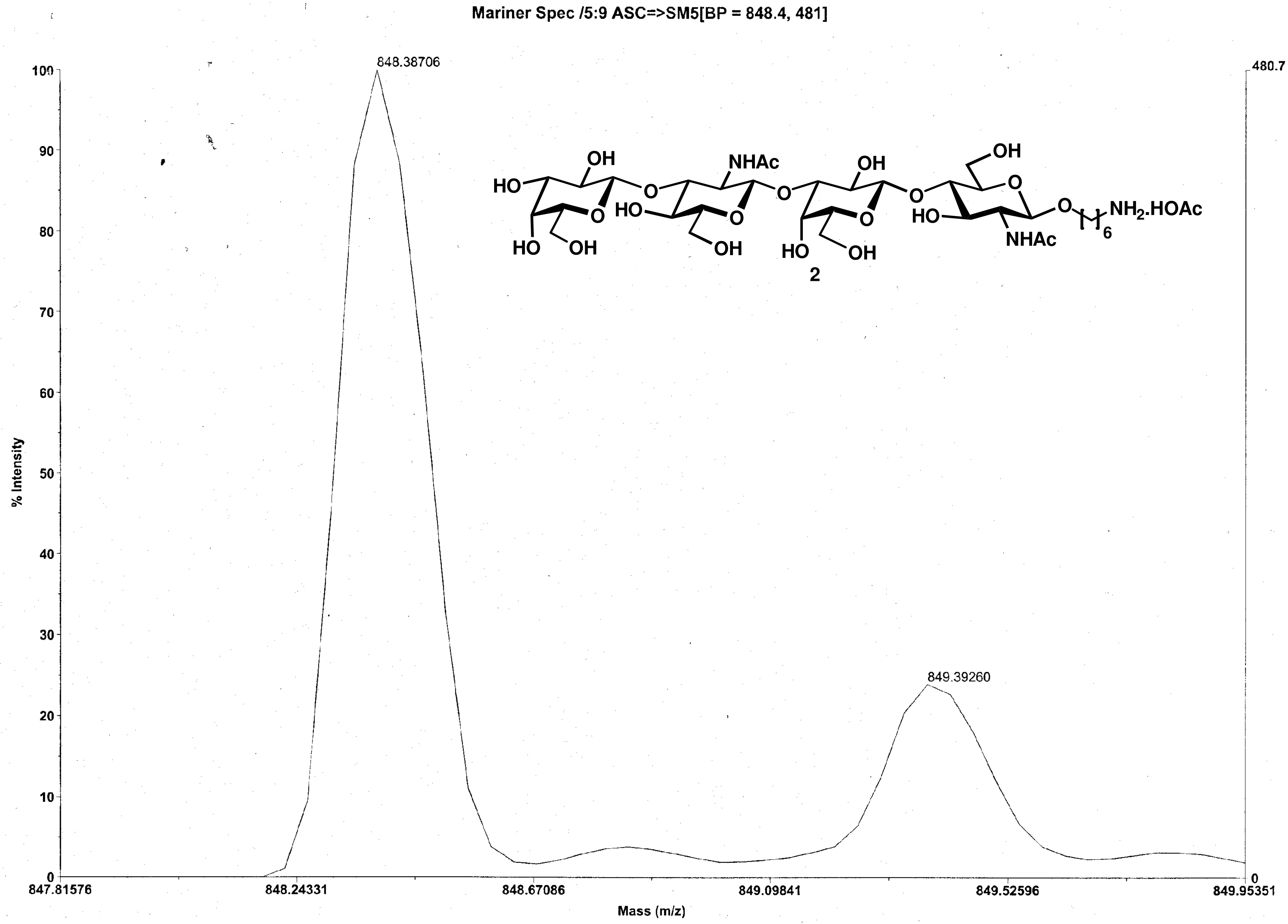


2

## $^{1}H$-$^{13}C$ GHSQC NMR in $D_2O$, 400 MHz

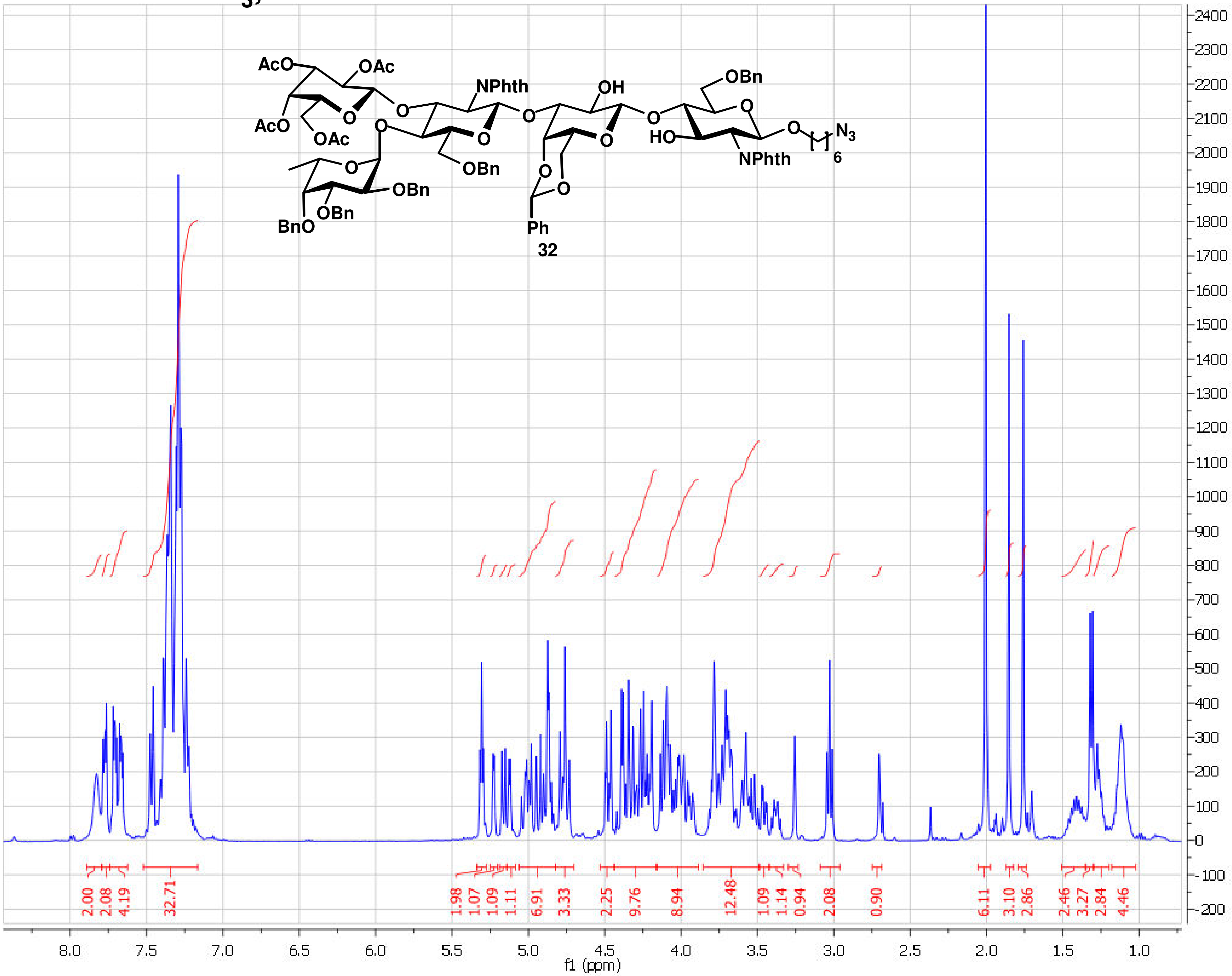


# High Resolution ESI Mass Spectra

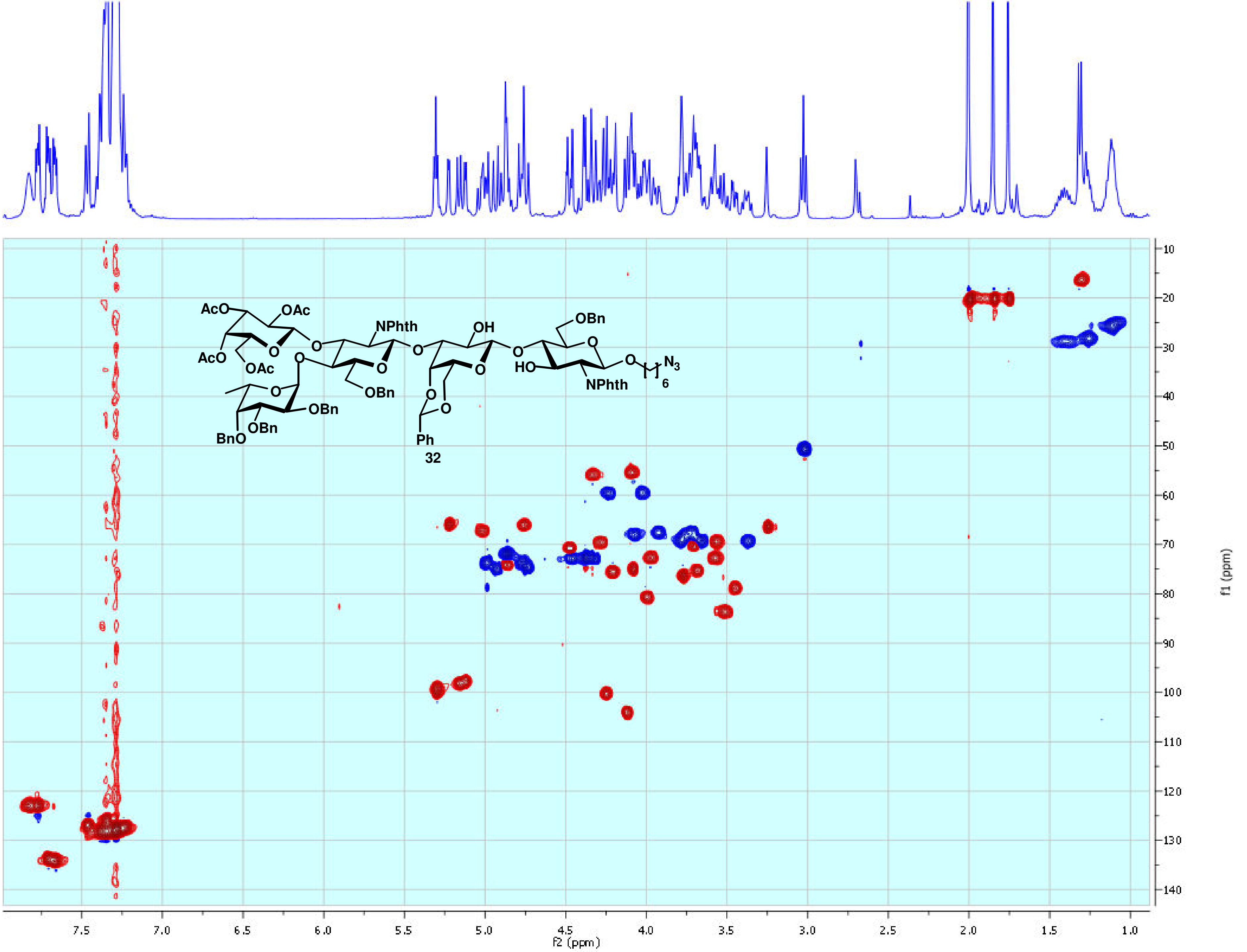


P. Zhang pz.i.142 pos es
C:\...\09010608.dat
Acquired: 15:47, January 06, 2009

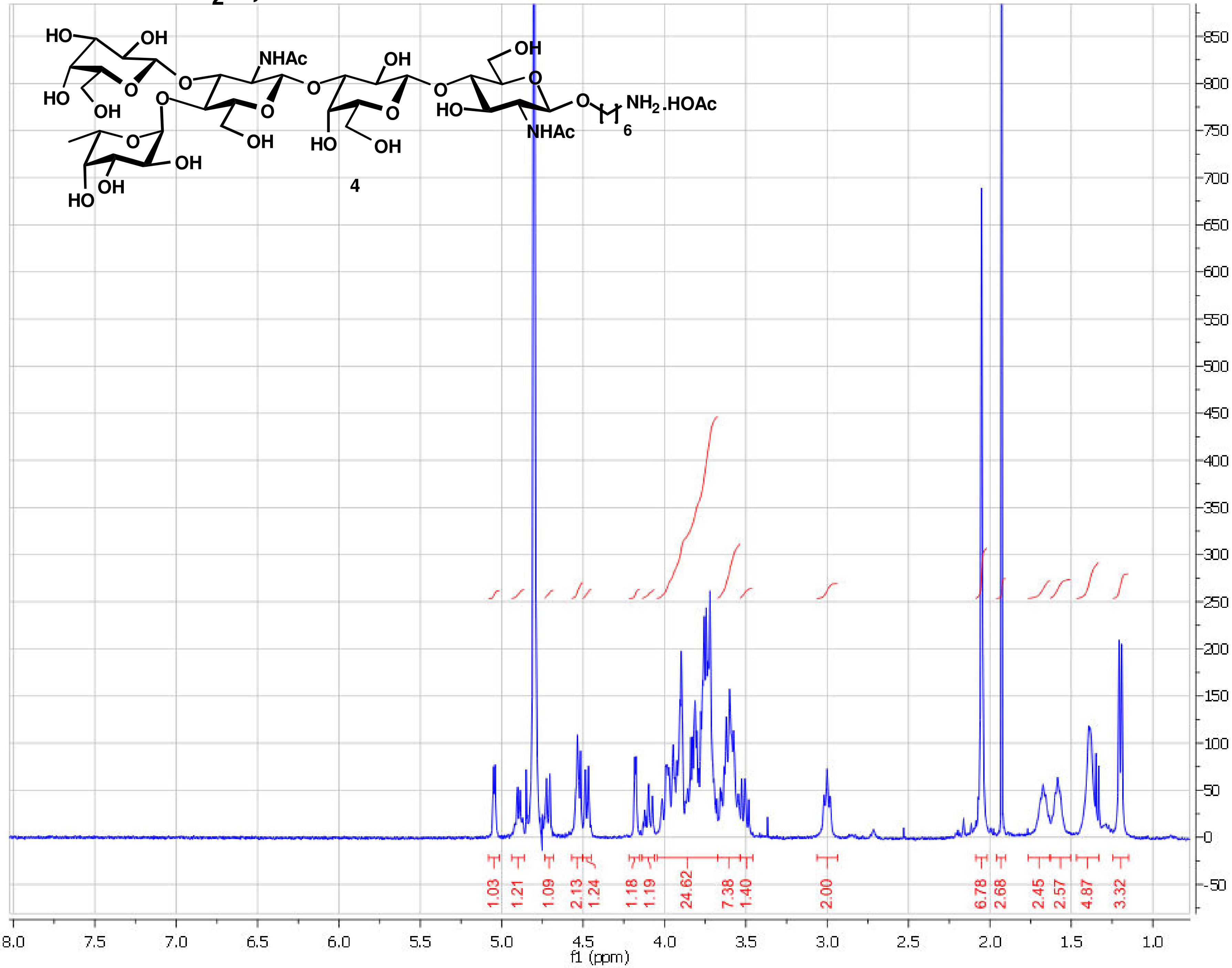
# $^1$H NMR in $CDCl_3$, 400 MHz



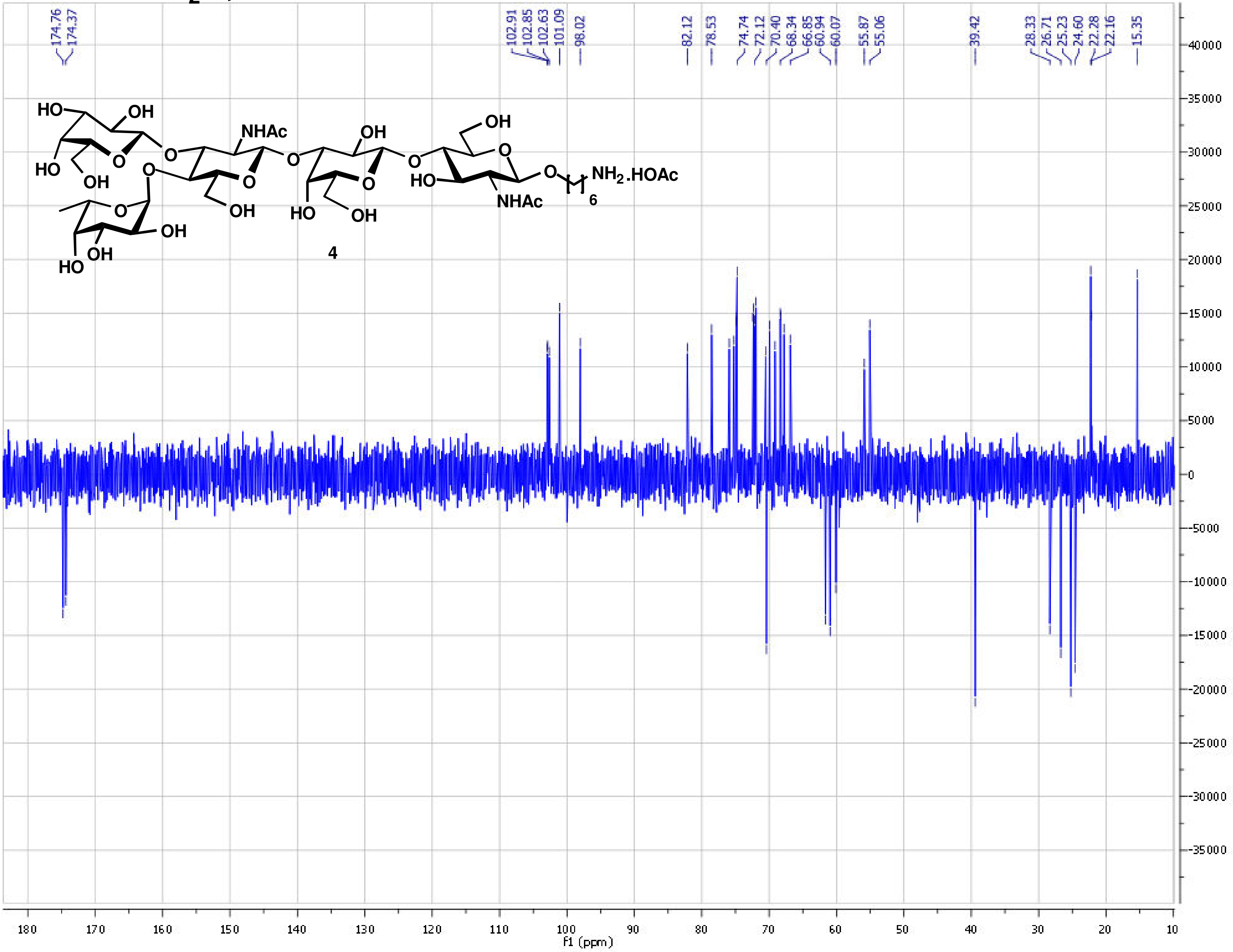
# $^1H$-$^{13}C$ GHSQC NMR in $CDCl_3$, 400 MHz



# $^1$H NMR in $D_2O$, 400 MHz



# $^{13}$C NMR in $D_2O$, 100 MHz



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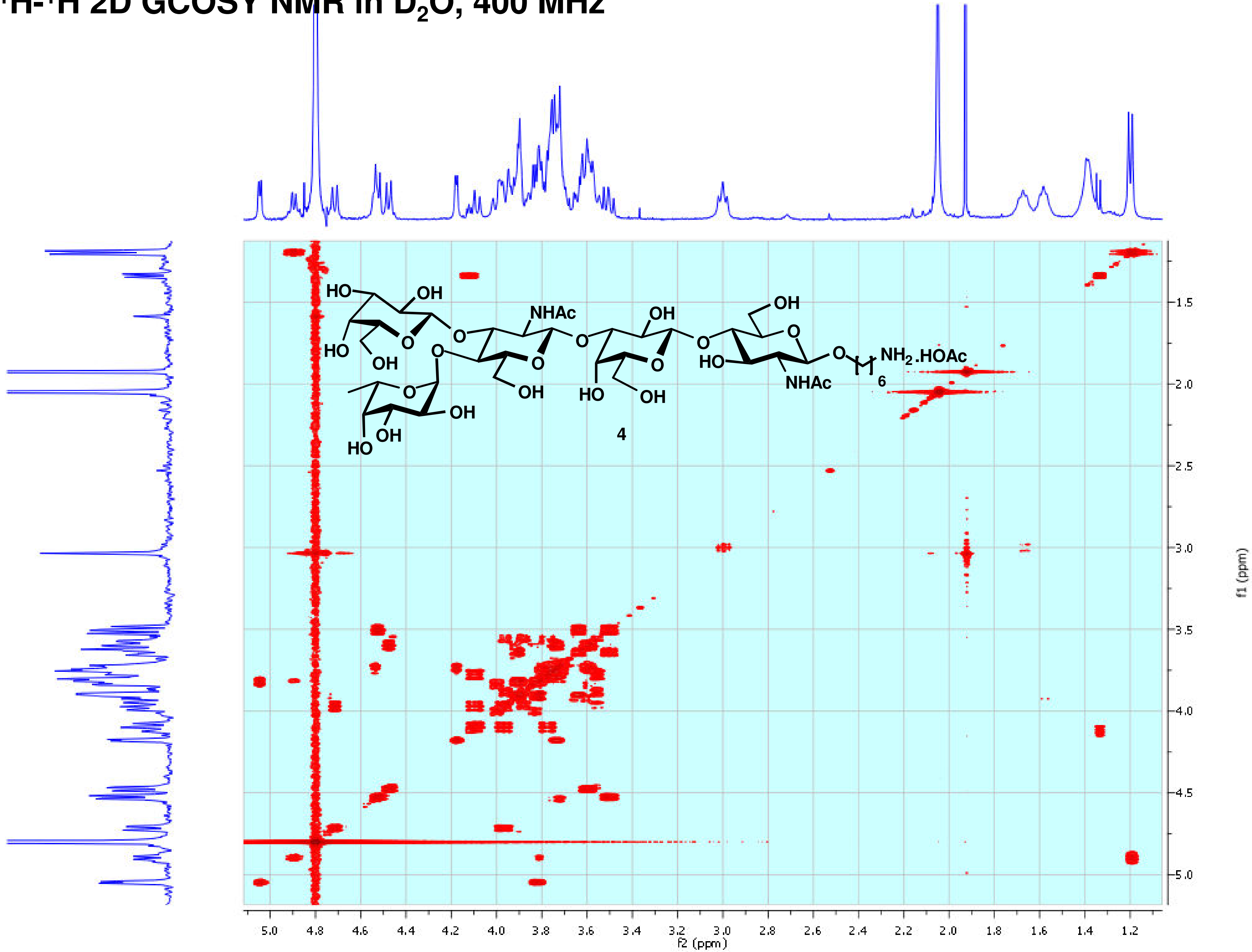
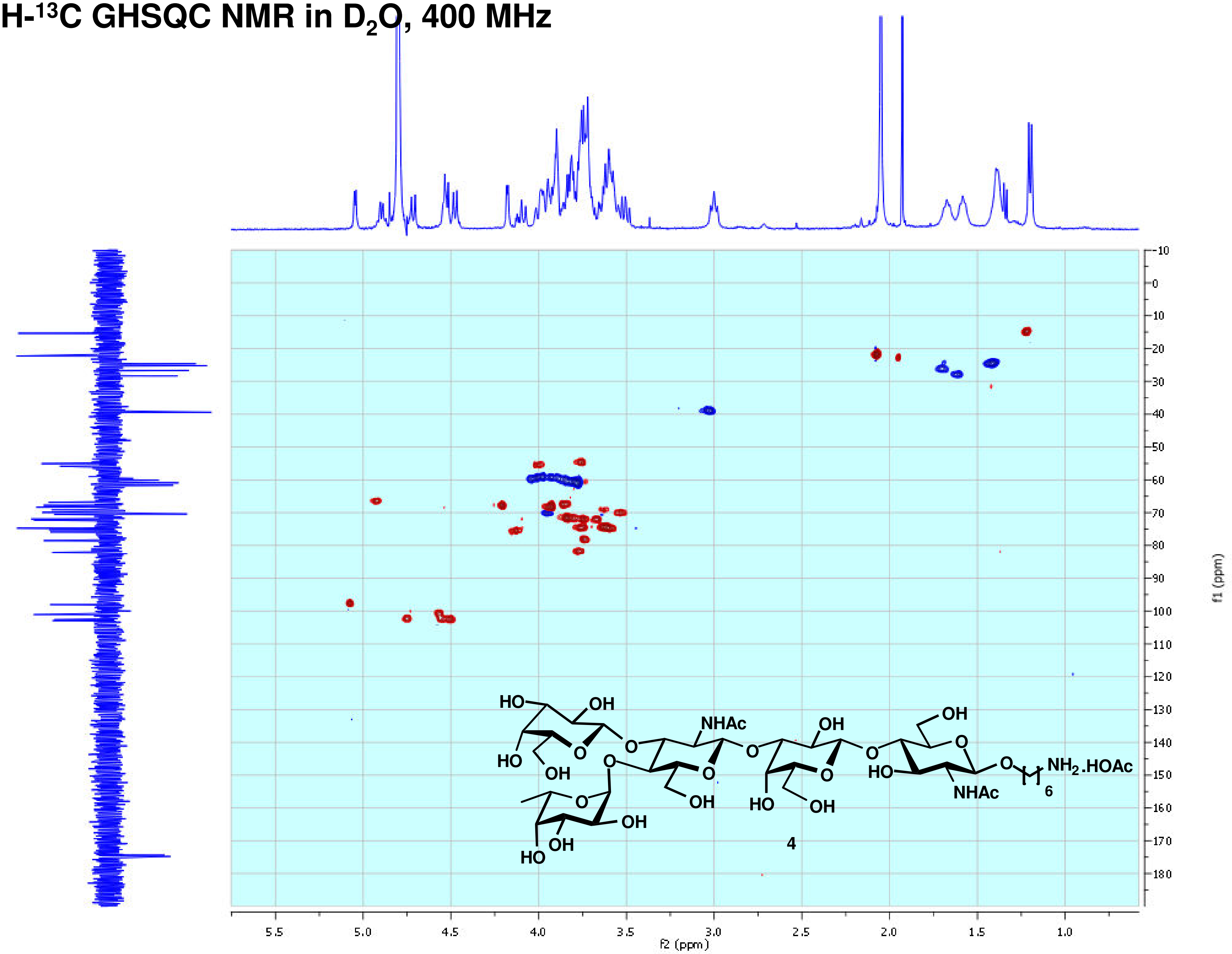
## $^1H$-$^1H$ 2D GCOSY NMR in $D_2O$, 400 MHz

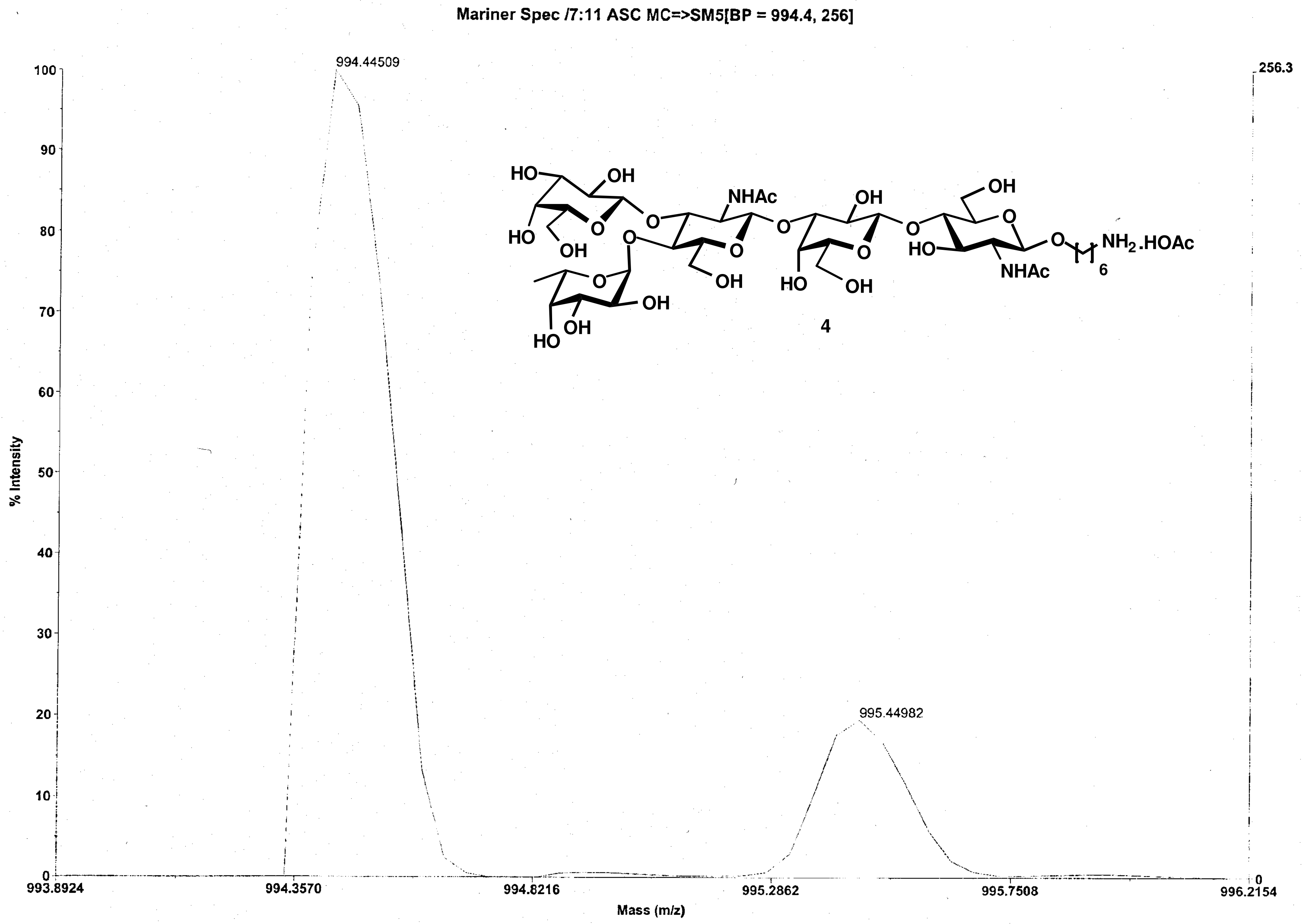


# $^1H$-$^{13}C$ GHSQC NMR in $D_2O$, 400 MHz



4

# High Resolution ESI Mass Spectra



P. Zhang pz.i.92 pos es
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