Supplementary Information

(For review purpose only)

Synthesis of rare earth metals doped upconversion nanoparticles coated with D-glucose or 2-deoxy-D-glucose and their evaluation for diagnosis and therapy in cancer

K. Shitaljit Sharma,[a] Maikho Thoh,[b] Akhil K. Dubey,[c] Prasad P. Phadnis,[a,d]* Deepak Sharma,[b,d], Santosh K. Sandur,[b,d] and Rajesh K. Vatsa[a,d]*

[a] Chemistry Division, Bhabha Atomic Research Centre, Trombay, Mumbai-400 085, India, Email: phadnisp@barc.gov.in, Tel.: +91 22 2559 2229; rkvatsa@barc.gov.in; Tel.: +91 22 2559 2438, Fax: +91 22 2550 5151

[b] Radiation Biology & Health Sciences Division, Bhabha Atomic Research Centre, Mumbai-400 085, India

[c] Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai-400 085, India

[d] Homi Bhabha National Institute, Anushaktinagar, Mumbai-400 094, India

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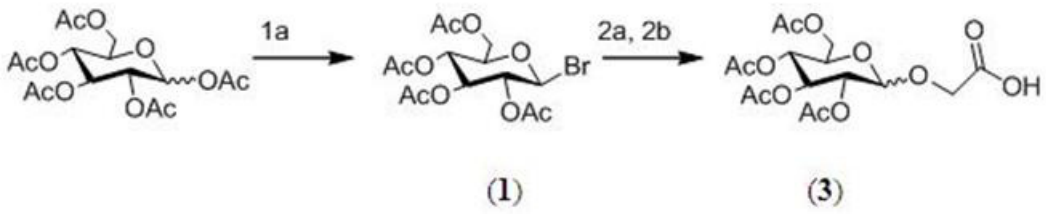
1 Synthesis of carboxyl glucose *i.e.,* 2-[(2,3,4,6-tetra-O-acetyl-D-glucopyranosyl)oxy]acetic acid (3)

Synthesis of carboxyl glucose (3)



(1) (3)

Scheme S 1. (1a) HBr (33%) in acetic acid; (2a) allyl alcohol, Ag_2CO_3 & (2b) $NaIO_4$, $RuCl_3$

General procedure of bromination

5 ml of HBr (33%) in acetic acid was added to a cooled (0 °C) solution of protected sugar (10 g) dichloromethane (5 ml) under argon atmosphere. After completion of reaction, (*cf.* TLC), the reaction mixture was diluted with chloroform (50 ml), washed with ice cooled water, followed by washing with saturated aqueous sodium bicarbonate (50 ml) and concentrated after drying with anhydrous sodium sulphate. The compound used for the next step without any further purification.

Synthesis of 2,3,4,6-tetra-*O*-acetyl-glucopyranosyl bromide (1)

Following the general procedure, bromination of 1,2,3,4,6-penta-*O*-acetyl-glucopyranose (8 g, 25.6 mmol) was done. It was characterized with NMR spectroscopy (Figure 1 and 2). ^{1}H NMR in $CDCl_3$: δ 2.04-2.10 (m, 15 H), 4.12-4.14 (d, J = 12 Hz, 1 H), 4.29-4.35 (m, 2H), 4.83-4.86 (dd, J = 10 Hz, 1 H), 5.14-5.18 (t, J = 10 Hz, 1 H), 5.54-5.58 (m, 1H), 6.61-6.62 (d, J = 3.5 Hz, 1 H) ppm; ^{13}C{^{1}H} NMR in $CDCl_3$: δ 20.47, 20.52, 20.57, 20.61, 60.96, 67.18, 67.22, 67.24, 70.19, 70.61, 72.15, 86.54, 169.37, 169.74, 170.38 ppm.

Synthesis of 2-[2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside]allyl (2)

Activated 4 Å molecular sieves (5 g) and allyl alcohol (2 ml, 29.4 mmol) were added to a solution of 2,3,4,6-tetra-*O*-acetyl–glucopyranosyl bromide (2.5 g, 6 mmol) in dichloromethane (20ml). This suspension was stirred under nitrogen atmosphere for 30 min. Silver carbonate (3.5 g, 12 mmol) was added and the suspension was stirred in the absence of light under nitrogen for 72 h. The reaction was passed through celite, concentrated under reduced pressure and purified by column chromatography to give a solid compound (1.86 g). The compound was characterized by NMR spectroscopy (Figure 3 and 4). ^{1}H NMR in $CDCl_3$: δ 1.97 - 2.09 (m, 12 H), 3.66-3.70 (m, 1 H), 4.05-4.16 (m, 2H), 4.21-4.35 (m, 2H), 4.52-4.56 (m, 1 H), 4.96-5.11 (m, 2 H), 5.16-5.29 (m, 2 H), 5.80-5.88 (m, 1 H) ppm; ^{13}C{^{1}H} NMR in $CDCl_3$: δ 20.53, 20.56, 20.60, 20.65, 61.94, 68.411, 68.44, 69.97, 69.99, 71.27, 71.76, 72.85, 99.53, 117.55, 117.58, 117.63, 133.27, 169.27, 169.34, 170.26, 170.61 ppm.

Synthesis of 2-[(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)oxy]acetic acid (3)

$NaIO_4$ (7.3 g, 34 mmol) and $RuCl_3$. H_2O (28 mg, 0.135 mmol) were added to a stirring solution of 2-[2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside] allyl (1 g, 2.5 mmol) in $CHCl_4$ (23 ml), CH_3CN (23 ml) and water (30 ml) at 0^{o}C. After vigorous stirring for 4 h, the reaction mixture was concentrated under reduced pressure and diluted with 1M HCl (40 ml) and brine (30 ml). The aqueous layer was extracted with chloroform (4 x 100 ml), dried with Na_2SO_4 and characterized with NMR spectroscopy (Figure 5 and 6). ^{1}H NMR in $CDCl_3$: δ 1.99-2.10 (m, 12 H), 3.71-3.73 (m, 1 H), 4.12-4.41 (m, 1 H), 5.01-5.10 (m, 2 H), 5.21-5.25 (m, 1 H), 9.65 (s, 1 H) ppm; ^{13}C{^{1}H} NMR in $CDCl_3$: δ 20.56, 20.64, 20.67, 20.69, 61.72, 65.01, 68.18, 68.21, 70.94, 71.92, 71.94, 72.39, 100.16, 169.50, 169.82, 170.28, 170.85, 172.27 ppm.

2 Characterization of carboxyl glucose *i.e.,* 2-[(2,3,4,6-tetra-O-acetyl-D-glucopyranosyl)oxy]acetic acid: ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectra in $CDCl_3$

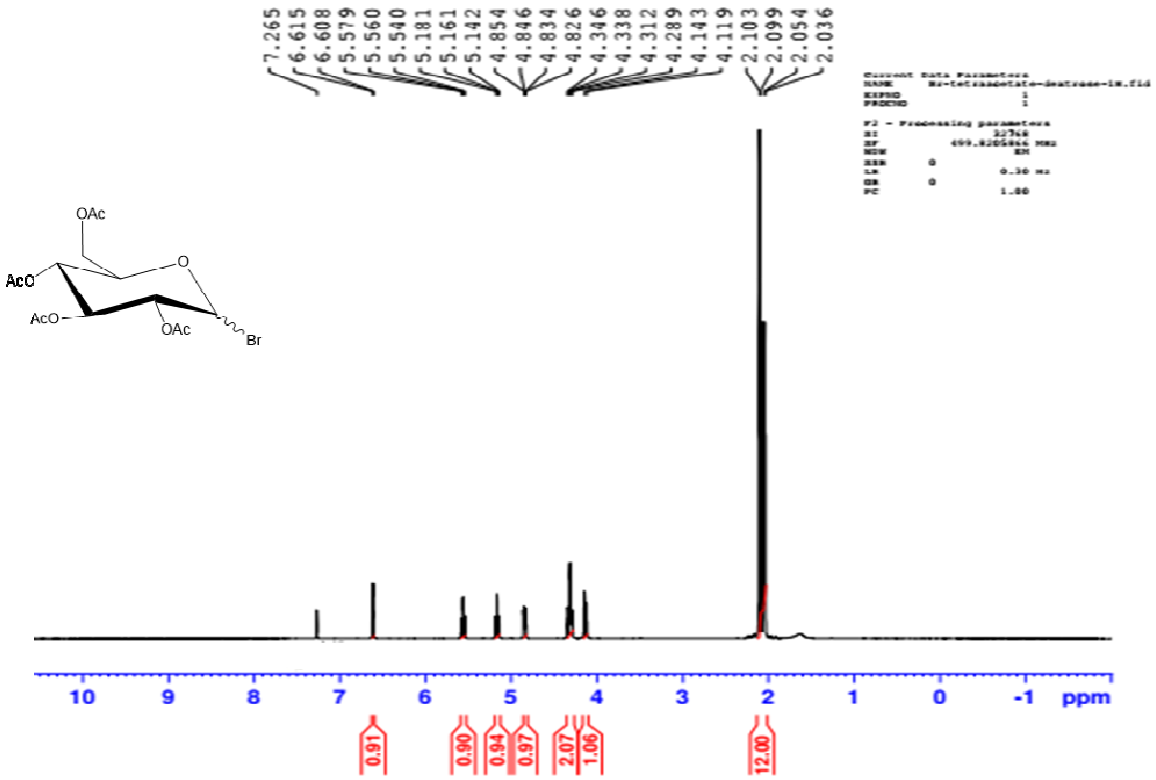


Figure S 1. ^{1}H NMR spectra of 2,3,4,6-tetra-*O*-acetyl-glucopyranosyl bromide (**1**) in $CDCl_3$

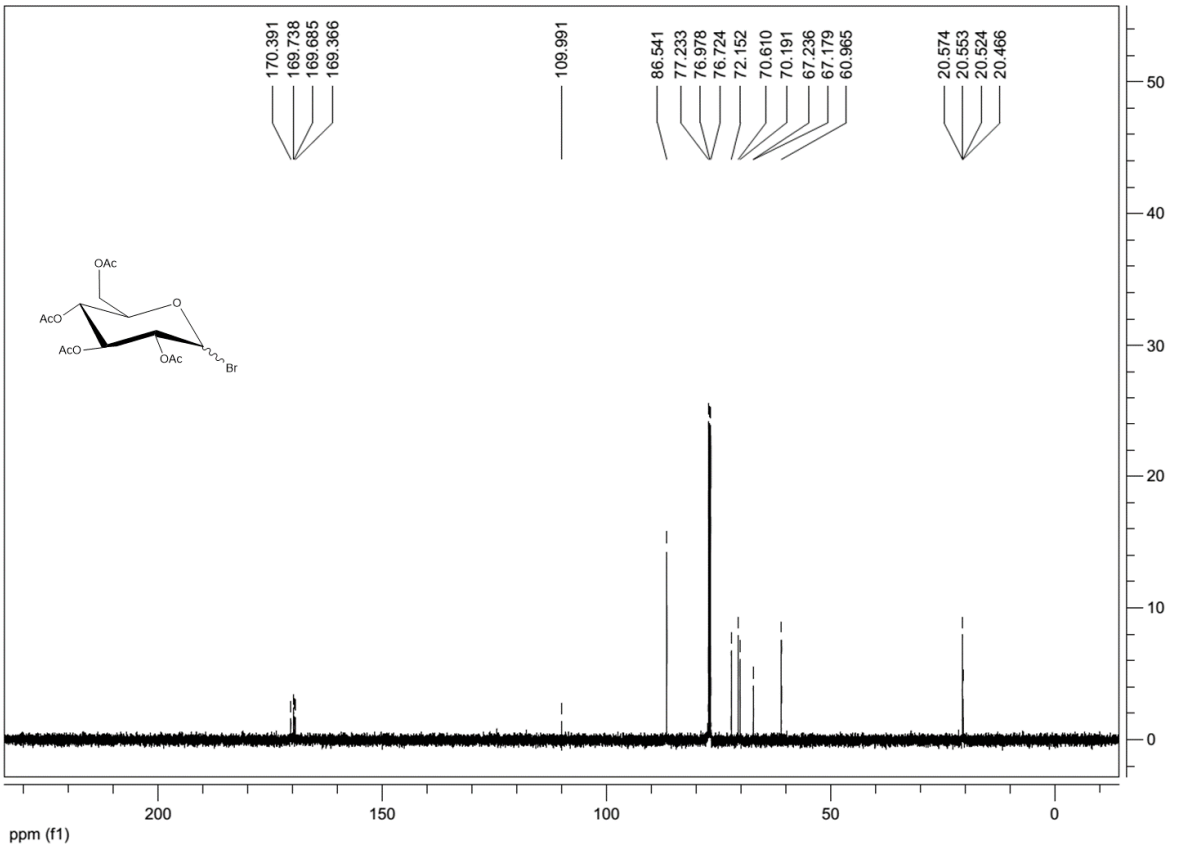


Figure S 2. $^{13}C\{^{1}H\}$ NMR spectra of 2,3,4,6-tetra-*O*-acetyl-glucopyranosyl bromide (**1**) in $CDCl_3$

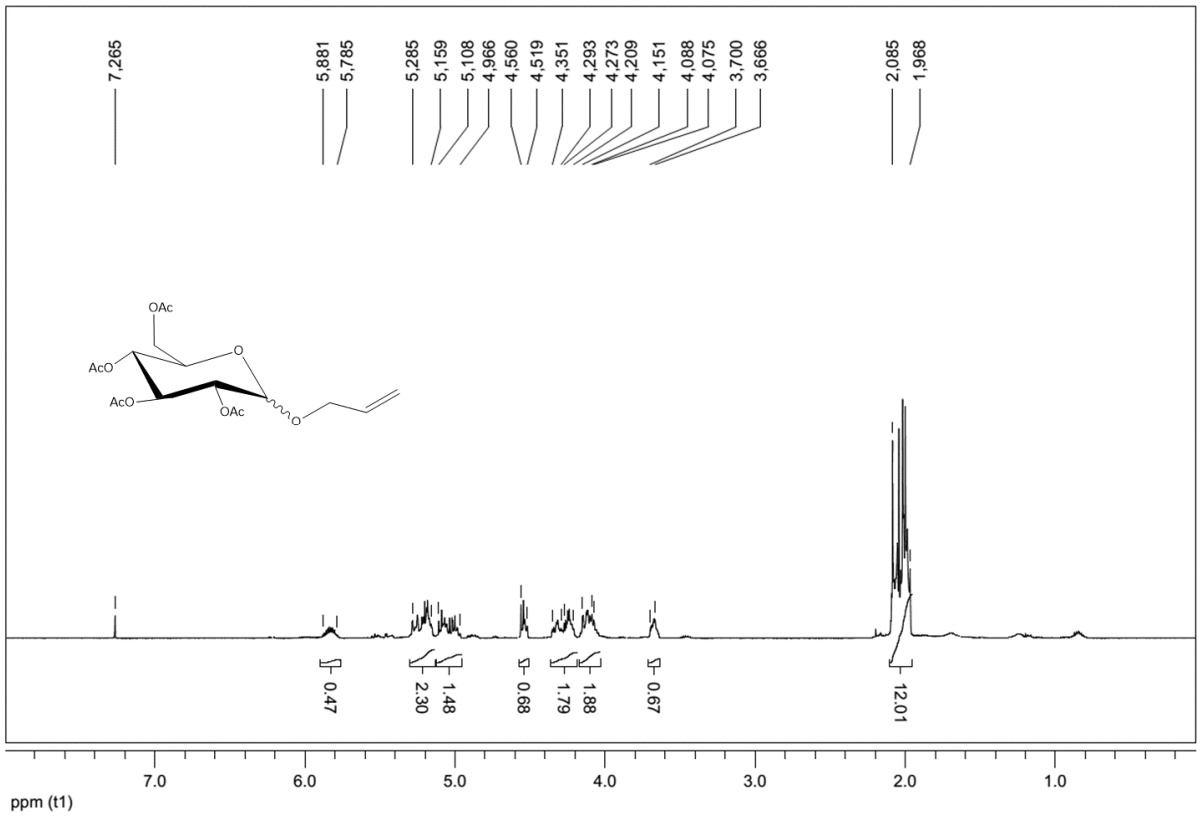


Figure S 3. ^{1}H NMR spectra of 2-[2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside] allyl (**2**) in $CDCl_3$

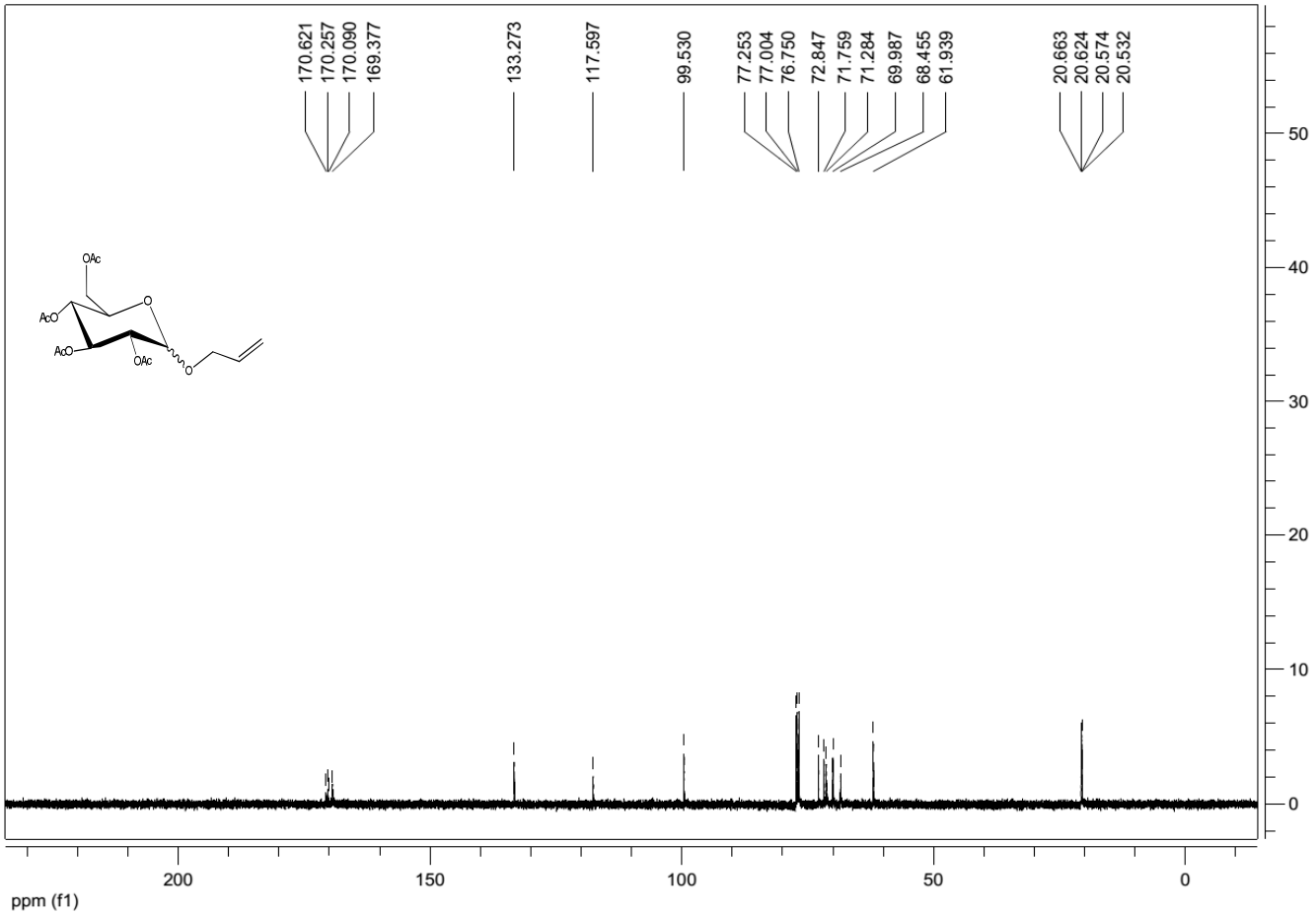


Figure S 4. $^{13}C\{^{1}H\}$ NMR spectra of 2-[2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside] allyl (**2**) in $CDCl_3$

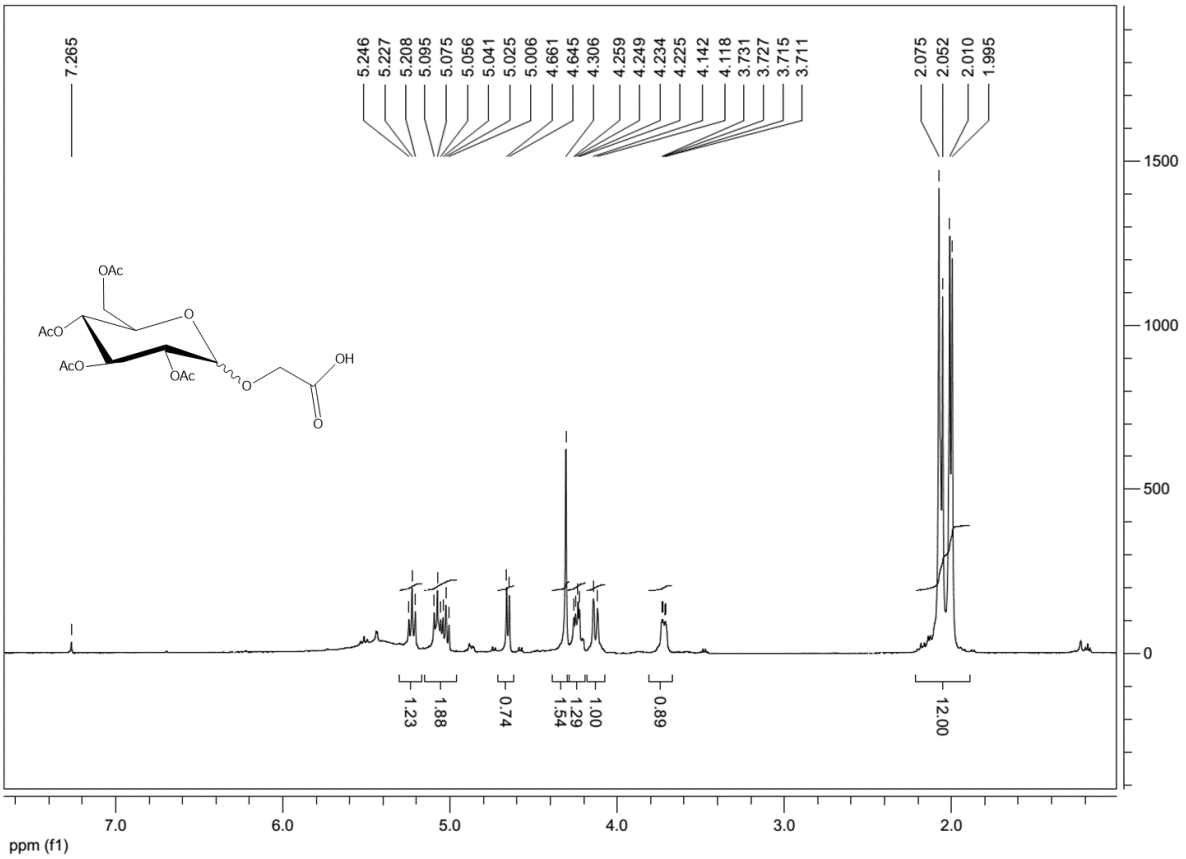


Figure S 5. ^{1}H NMR spectra of 2-[(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl) oxy] acetic acid (**3**) in $CDCl_3$

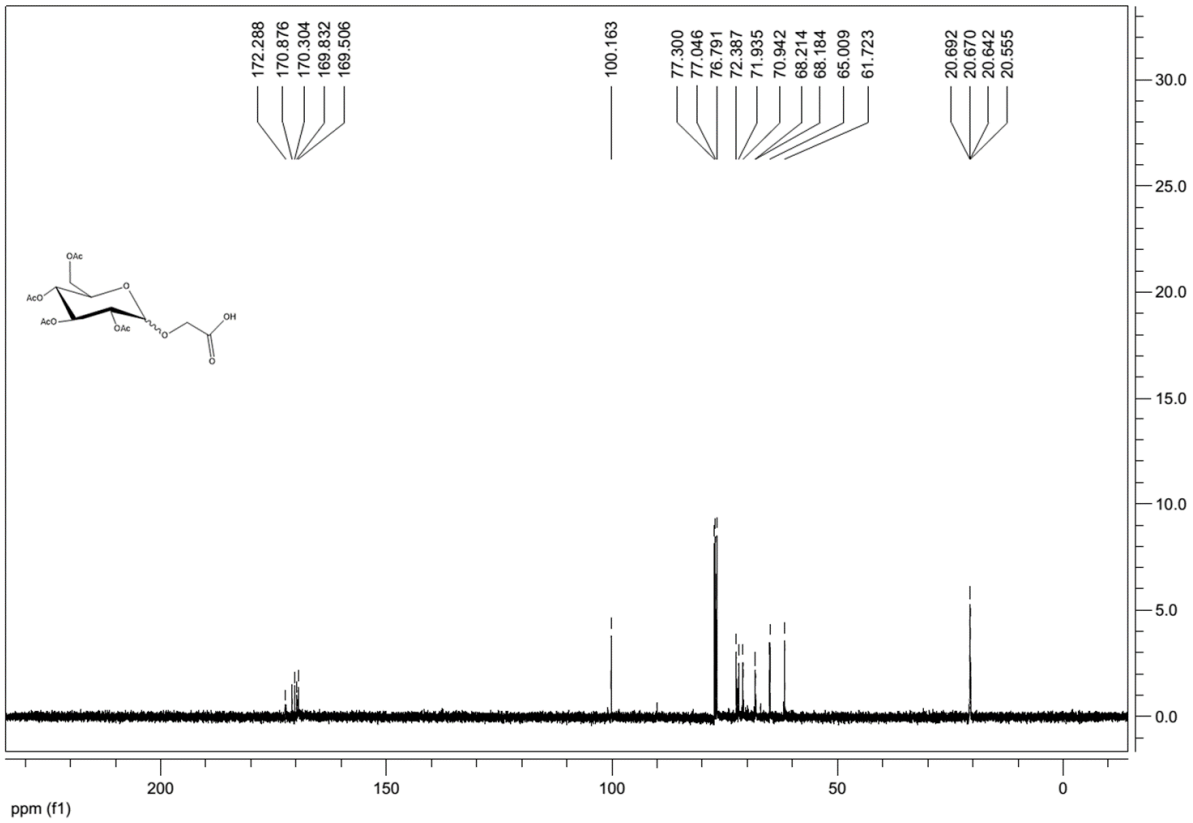
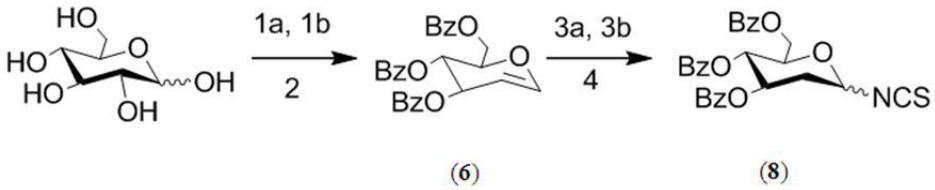


Figure S 6. $^{13}C\{^{1}H\}$ NMR spectra of 2-[(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl) oxy] acetic acid (**3**) in $CDCl_3$

3 Synthesis of isothiocyanate glucose *i.e.,* 3,4,5-tri-O-benzoyl-2-deoxy-D-glycopyranosyl isothiocyanate (8)

Synthesis of isothiocyante glucose (8)



(6) (8)

Scheme S 2. (1a) benzoyl chloride, pyridine; (1b) HBr (33%) in acetic acid, DCM; (2) Zn, NH_4Cl in acetonitrile, reflux; (3a) Dowex resin, LiBr, H_2O, CH_3CN; (3b) HBr (33%) in acetic acid, DCM; (4) AgSCN, toluene, reflux.

Synthesis of 1,2,3,4,5-penta-*O*-benzoyl-glucopyranose (4)

To D-Glucose (10 g, 60 mmol) in pyridine (40 ml) at 0 ^{o}C, benzoyl chloride (39 ml, 300 mmol) was added under argon atmosphere. The reaction was allowed to stir at room temperature for overnight. After completion of reaction, it was diluted with chloroform (50 ml) and washed with ice cooled HCl solution, followed by washing with saturated aqueous solution of sodium carbonate. The organic layer was concentrated to give a gel which was dissolved in a mixture of ether and hexane in the ratio of 10:90 and kept at 0 ^{o}C. The obtained fine powder (22.8 g)r was precipitated and characterized with NMR spectroscopy (Figure 7 and 8). ^{1}H NMR in $CDCl_3$: δ 4.50 (dd, 1 H), 4.64 (d, 2 H), 5.70 (dd, 1 H), 5.88 (t, 1 H), 6.34 (t, 1 H), 6.87 (d, 1 H), 7.30-7.57 (m, 16 H) 7.67 (t, 1 H), 7.90 (d, 4 H), 7.96 (d, 2 H), 8.04 (d, 2 H), 8.18 (d, 2 H) ppm; $^{13}C\{^{1}H\}$ NMR in $CDCl_3$: δ 62.47, 68.93, 70.49, 90.05, 128.34, 128.37, 128.41, 128.77, 129.72, 129.77, 129.82, 129.86, 130.00, 133.07, 133.30, 133.44, 133.48, 133.68, 164.37, 165.12, 165.32, 165.89, 166.08 ppm.

Synthesis of 2,3,4,5-tetra-*O*-benzoyl-glucopyranosyl bromide (5)

Following the general procedure, bromination of 1,2,3,4,5-penta-*O*-benzoyl-glucopyranose (5 g, 7 mmol) was done. A white precipitated obtained (7 g) which was then characterized with NMR spectroscopy (Figure 9 and 10). ^{1}H NMR in $CDCl_3$: δ 4.52 (d, 1 H), 4.68 (d, 1 H), 4.74 (d, 1 H), 5.34 (d, 1 H), 5.83 (t, 1 H), 6.27 (t, 1 H), 6.89 (s, 1 H), 7.30-7.58 (m, 12 H), 7.88 (d, 2 H), 7.95 (d, 2 H), 8.01 (d, 2 H), 8.07 (d, 2 H) ppm; $^{13}C\{^{1}H\}$ NMR in $CDCl_3$: δ 61.97, 68.02, 70.64, 71.47, 72.73, 86.87, 128.33, 128.42, 128.45, 128.52, 129.72, 129.80, 129.91, 130.06, 133.12, 133.23, 133.26, 133.29, 133.31, 133.34, 133.58, 133.62, 133.63, 133.74, 133.77, 133.78, 133.80, 165.07, 165.28, 165.54, 165.98 ppm.

Synthesis of 1-*O*-acetyl-3,4,5-tri-*O*-benzoyl-2-deoxy-D-glycopyranose (6)

2,3,4,5-tetra-*O*-benzoyl-glucopyranosyl bromide (3 g, 5 mmol) was dissolved in acetonitrile (15ml) under argon atmosphere, Zn metal (2.3 g, 40 mmol) and NH_4Cl (2 g, 40 mmol) were added. The reaction mixture was refluxed till the completion of the reaction. After cooling to room temperature, the reaction mixture was filtered through Whatman filter paper (no. 41) and the precipitate was removed. The reaction was worked up with chloroform and concentrated to give 3,4,5-tri-*O*-benzoyl-glycal.

Further o a solution of 3,4,5-tri-*O*-benzoyl-glycal (2 g, 4.3 mmol) in acetonitrile (50 ml), acidic resin (DOWEX resin, 4 g) and LiBr (4 g, 46 mmol) were added. Water (4 ml) was added and stirred it for 24 h at RT. After completion of the reaction, the resin was removed by filtration and concentrated under reduced pressure. The reaction mixture was worked up with chloroform. The obtained compound was further dissolved in DCM (10 ml) and pyridine (2 ml). Acetic anhydride (2 ml) was added to the reaction mixture at 0 ^{o}C and allowed to stir overnight at RT. The reaction mixture was worked up with chloroform. The compound was purified by the crystallization technique (1.7 g) and characterized with NMR

spectroscopy (Figure 11 and 12). ^{1}H NMR in $CDCl_3$: δ 3.21 (s, 3 H), 2.55 (dd, 1 H), 4.42-4.46 (m, 2 H), 4.60 (dd, 1 H), 5.66-5.75 (m, 2 H), 6.38 (d, 1 H), 7.35-7.56 (m, 10 H), 7.95 (dt, 4 H), 8.02 (dd, 2 H) ppm.; $^{13}C\{^{1}H\}$ NMR in $CDCl_3$: δ 21.02, 34.56, 63.03, 69.46, 69.70, 70.61, 91.03, 128.30, 128.37, 129.68, 129.71, 129.74, 132.98, 133.23, 133.32, 165.35, 165.81, 166.11, 168.89 ppm.

Synthesis of 3,4,5-tri-*O*-benzoyl-2-deoxy-D-glycopyranosyl bromide (7)

Following the general procedure, bromination of 1-*O*-acetyl-3,4,5-tri-O-benzoyl-2-deoxy-D-glycopyranose (1 g, 1.9 mmol) was done, characterized with NMR spectroscopy (Figure 13 and 14) and without any further purification, the obtained compound was used for next reaction. ^{1}H NMR in $CDCl_3$: δ 2.49 (td, 1 H), 2.94 (dd, 1 H), 4.49 (dd, 2 H), 4.65 (dd, 3 H), 5.73 (t, 1 H), 5.90-5.96 (m, 1 H), 6.68 (d, 1 H) ppm; $^{13}C\{^{1}H\}$ NMR in CDCl3: δ 40.49, 62.26, 69.04, 69.85, 72.96, 85.47, 128.30, 128.38, 128.44, 129.70, 129.77, 129.83, 133.12, 133.26, 133.48, 165.34, 165.59, 166.01 ppm.

Synthesis of 3,4,5-tri-*O*-benzoyl-2-deoxy-D-glycopyranosyl isothiocyanate (8)

Freshly prepared silver thiocyante was added to acetonitrile (15 ml) containing molecular sieves 4 Å (1.5 g). The silver thiocyante was prepared by mixing stoichiometric amounts of silver nitrate and potassium thiocynate. After stirring for 3 h, 3,4,5-tri-*O*-benzoyl-2-deoxy-D-glycopyranosyl bromide was added and refluxed for 3 h at dark condition. The reaction mixture was filtered using Whatman filter paper (No. 41), the organic layer was removed, worked up with chloroform, concentrated under reduced pressure and characterized with NMR spectroscopy (Figure 15 and 16). ^{1}H NMR in $CDCl_3$: δ 2.14-2.21 (m, 2 H), 2.67 (dd, 1 H), 2.80 (dq, 1 H), 4.06-4.08 (m, 1 H), 4.46-4.49 (m, 3 H), 4.62-4.71 (m, 3 H), 5.20 (dd, 1 H), 5.38-5.43 (m, 1 H), 5.58-5.72 (m, 3 H), 5.82 (dd, 1 H), 7.34-7.58 (m, 23 H), 7.93-8.06 (m, 14 H) ppm; $^{13}C\{^{1}H\}$ NMR in $CDCl_3$: δ 36.13, 37.95, 62.71, 63.11, 69.25, 69.32,

69.36, 70.89, 71.74, 74.44, 79.08, 81.61, 82.25, 128.34, 128.37, 128.41, 128.44, 129.74, 129.74, 129.79. 133.10, 133.31, 133.44, 133.47, 142.01, 142.50, 165.33, 165.38, 165.58, 165.67, 144.04, 166.08 ppm.

4 Characterization of isothiocyanate glucode *i.e.*, 3,4,5-tri-O-benzoyl-2-deoxy-D-glycopyranosyl isothiocyanate: ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectra in $CDCl_3$

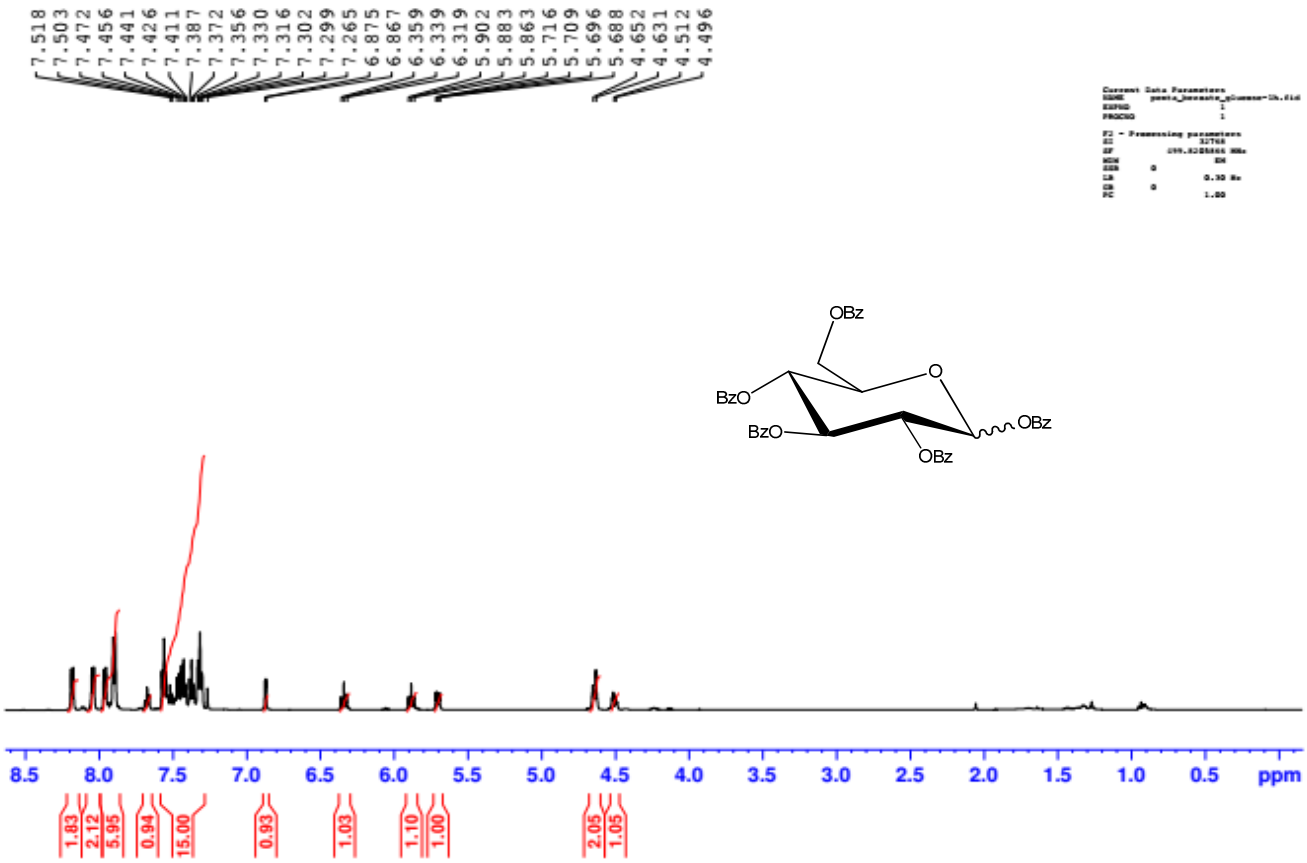


Figure S 7. ^{1}H NMR spectrum of 1,2,3,4,5-penta-*O*-benzoyl-glucopyranose (**4**) in $CDCl_3$

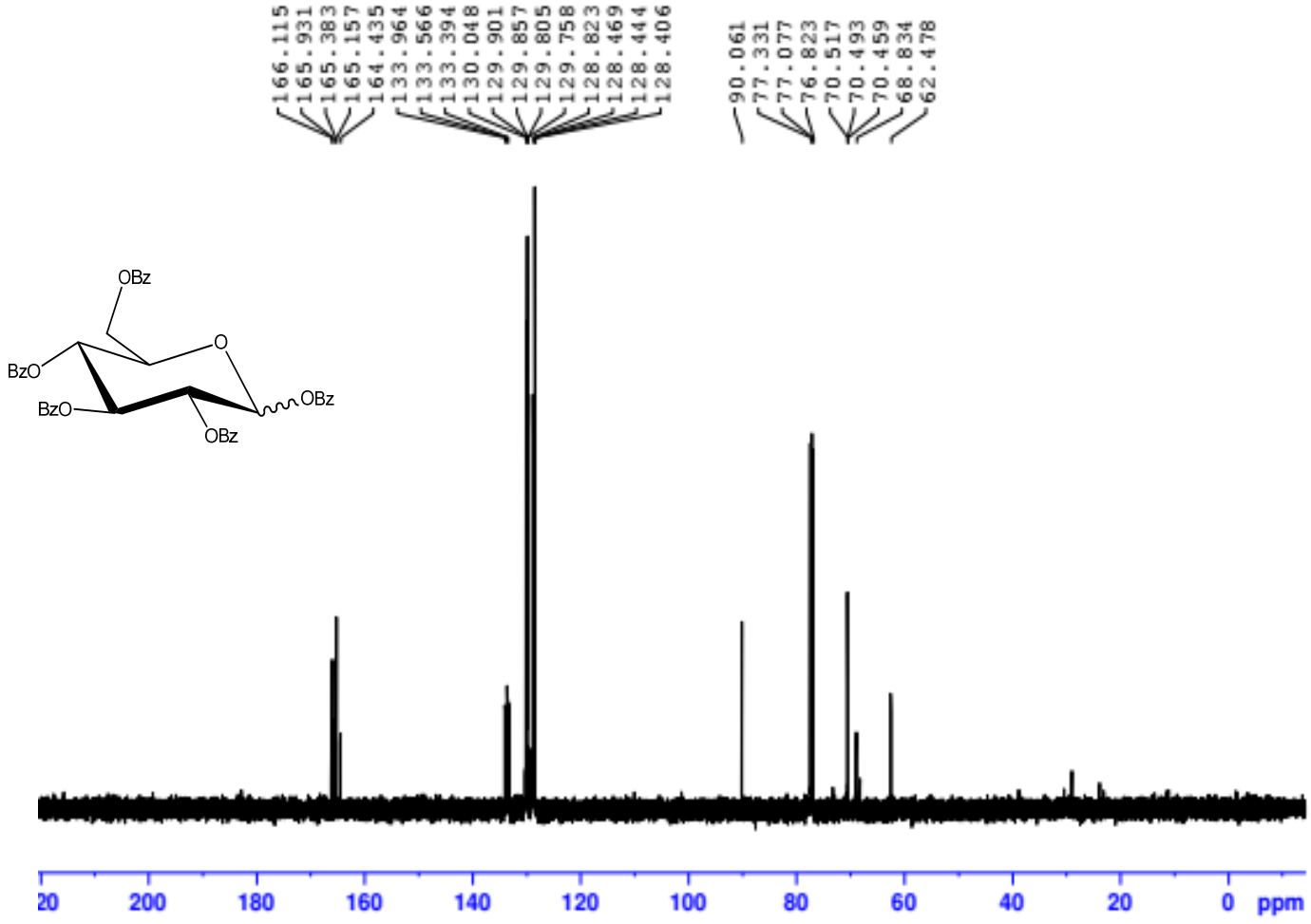


Figure S 8. $^{13}C\{^{1}H\}$ NMR spectrum of 1,2,3,4,5-penta-*O*-benzoyl-glucopyranose (**4**) in $CDCl_3$

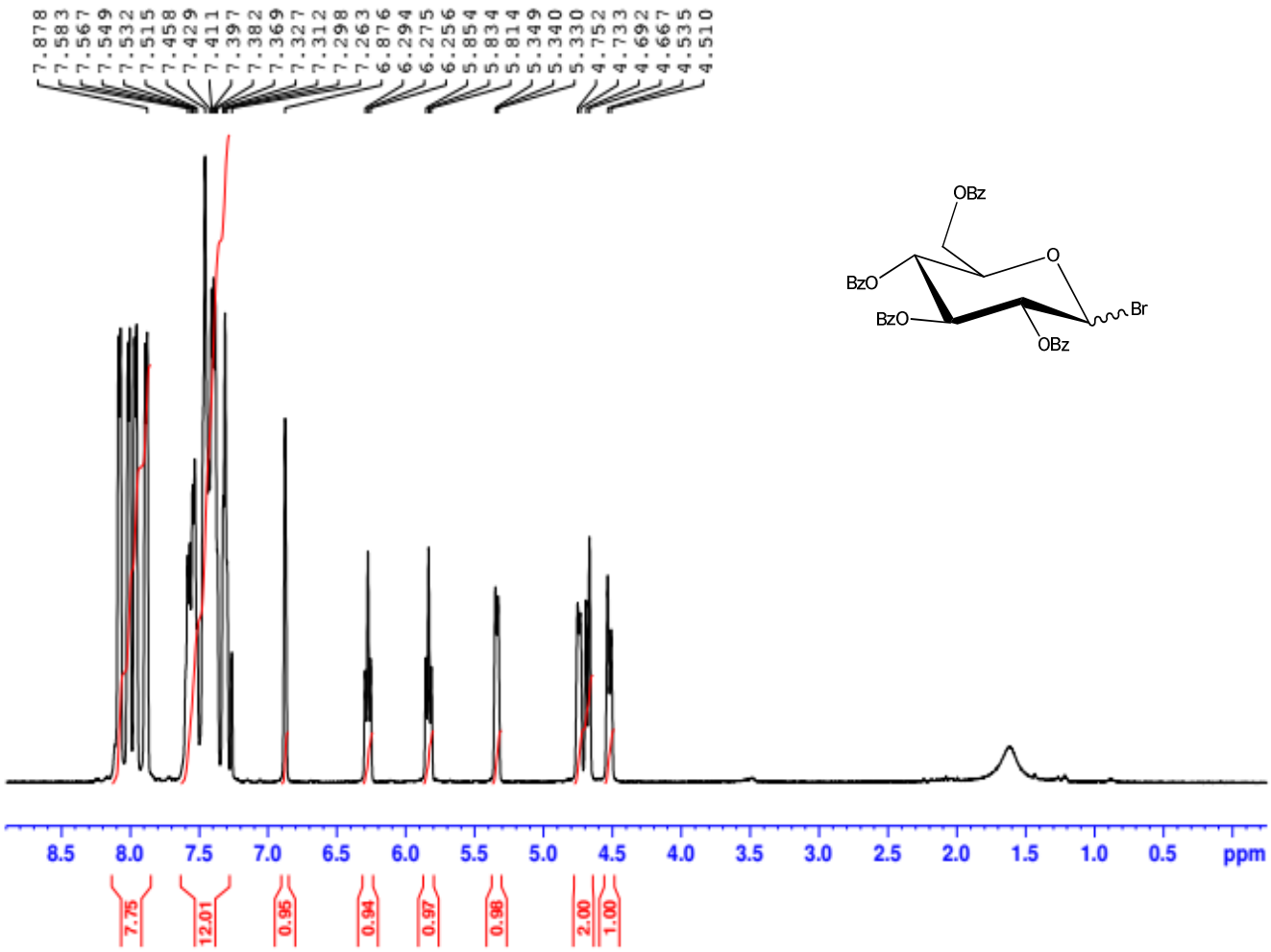


Figure S 9. ^{1}H MNR spectrum of 2,3,4,5-tetra-*O*-benzoyl-glucopyranosyl bromide(**5**) in $CDCl_3$

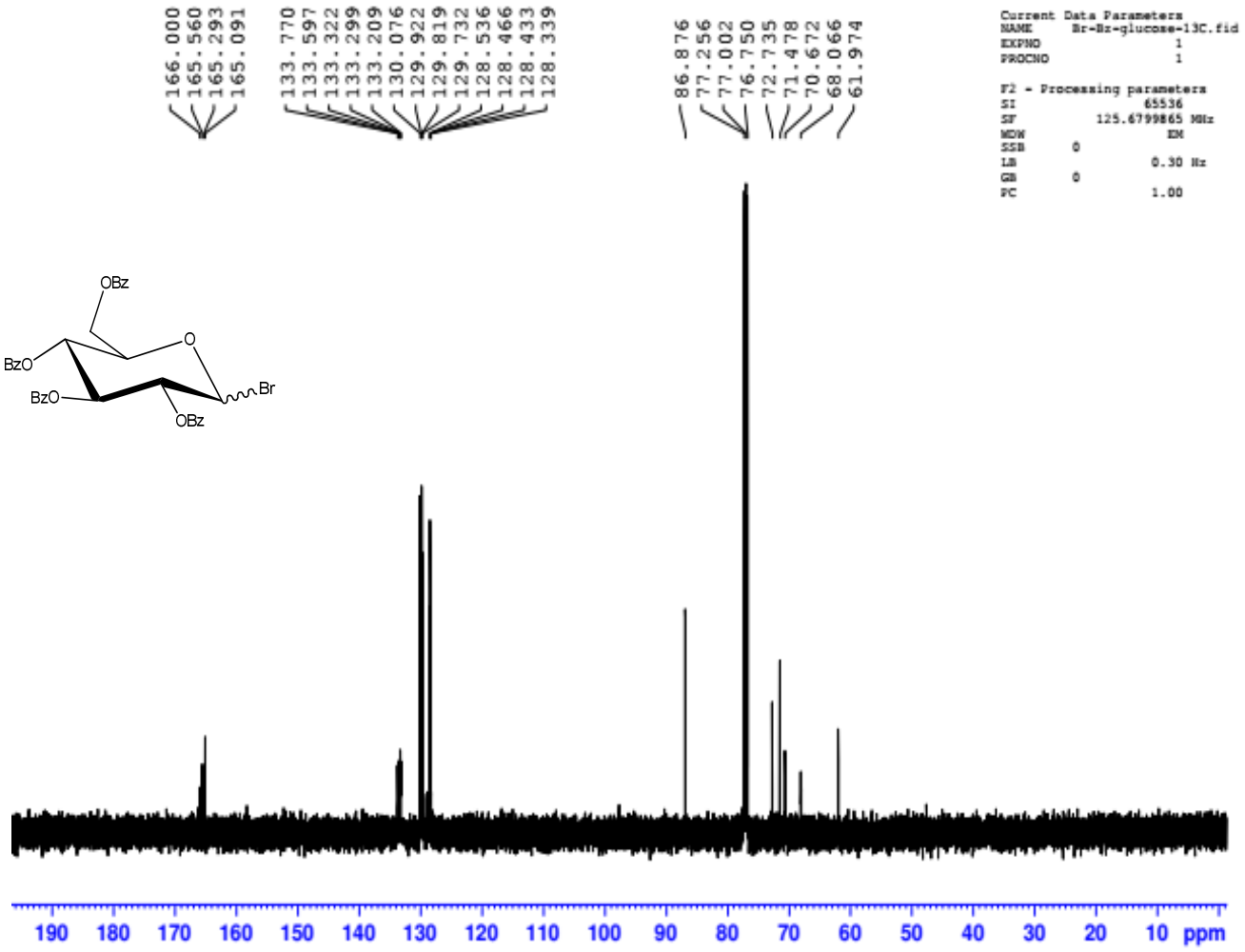


Figure S 10. $^{13}C\{^{1}H\}$ NMR spectrum of 2,3,4,5-tetra-*O*-benzoyl-glucopyranosyl bromide (**5**) in $CDCl_3$

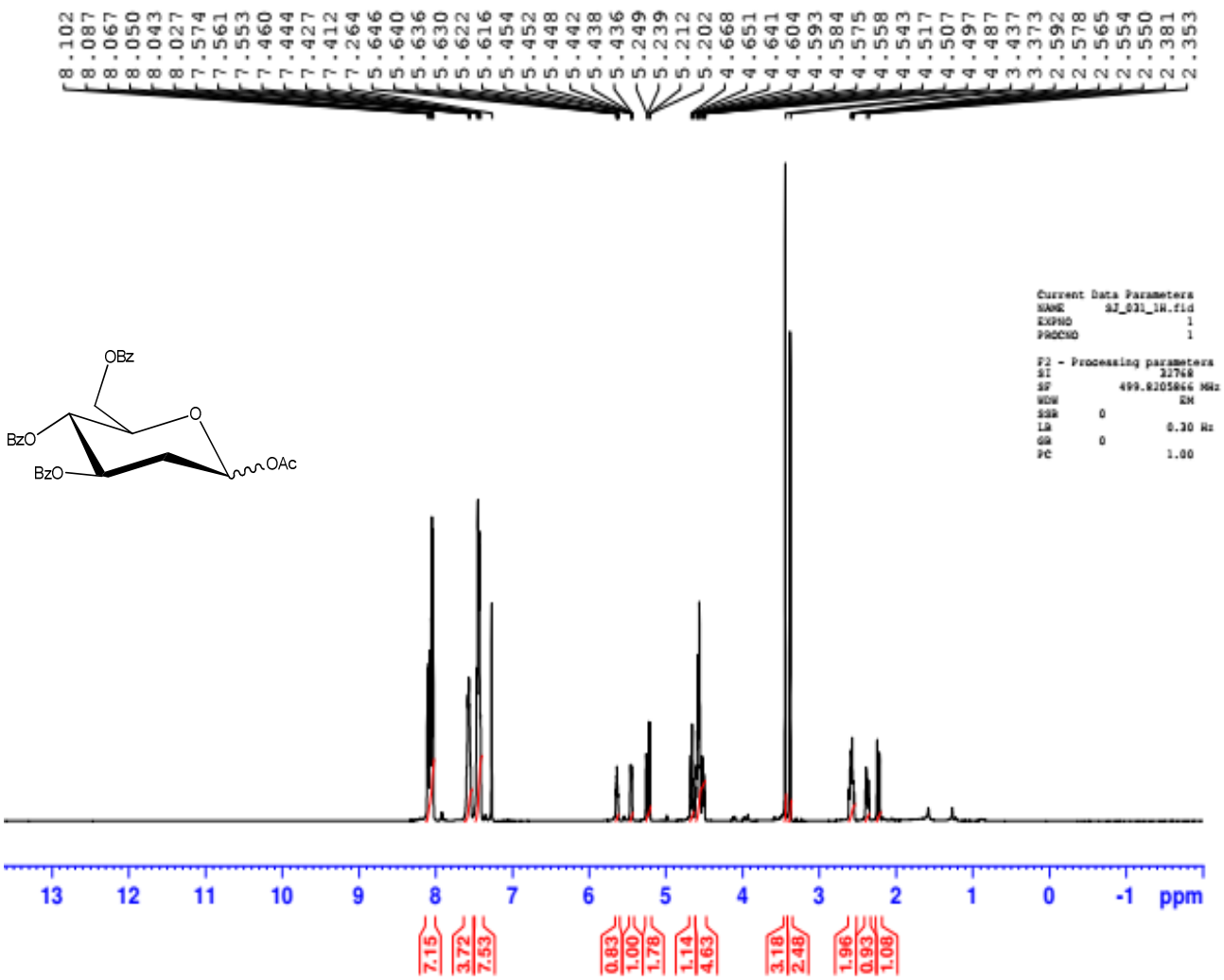


Figure S 11. ^{1}H NMR spectrum of 1-O-acetyl-3,4,5-tri-*O*-benzoyl-2-deoxyglycopyranose (**6**) in $CDCl_3$

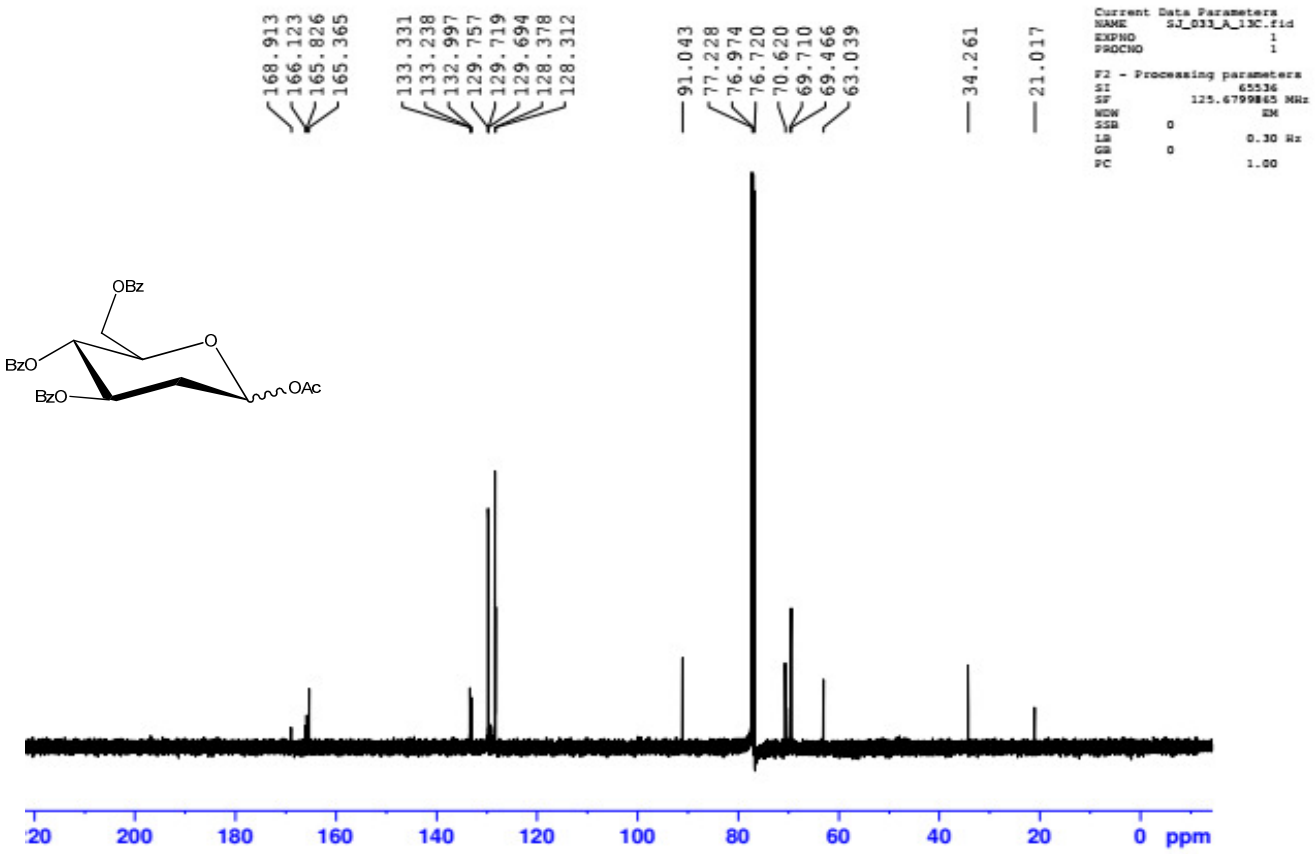


Figure S 12. $^{13}C\{^{1}H\}$ NMR spectrum of 1-O-acetyl-3,4,5-tri-*O*-benzoyl-2-deoxyglycopyranose (**6**) in $CDCl_3$

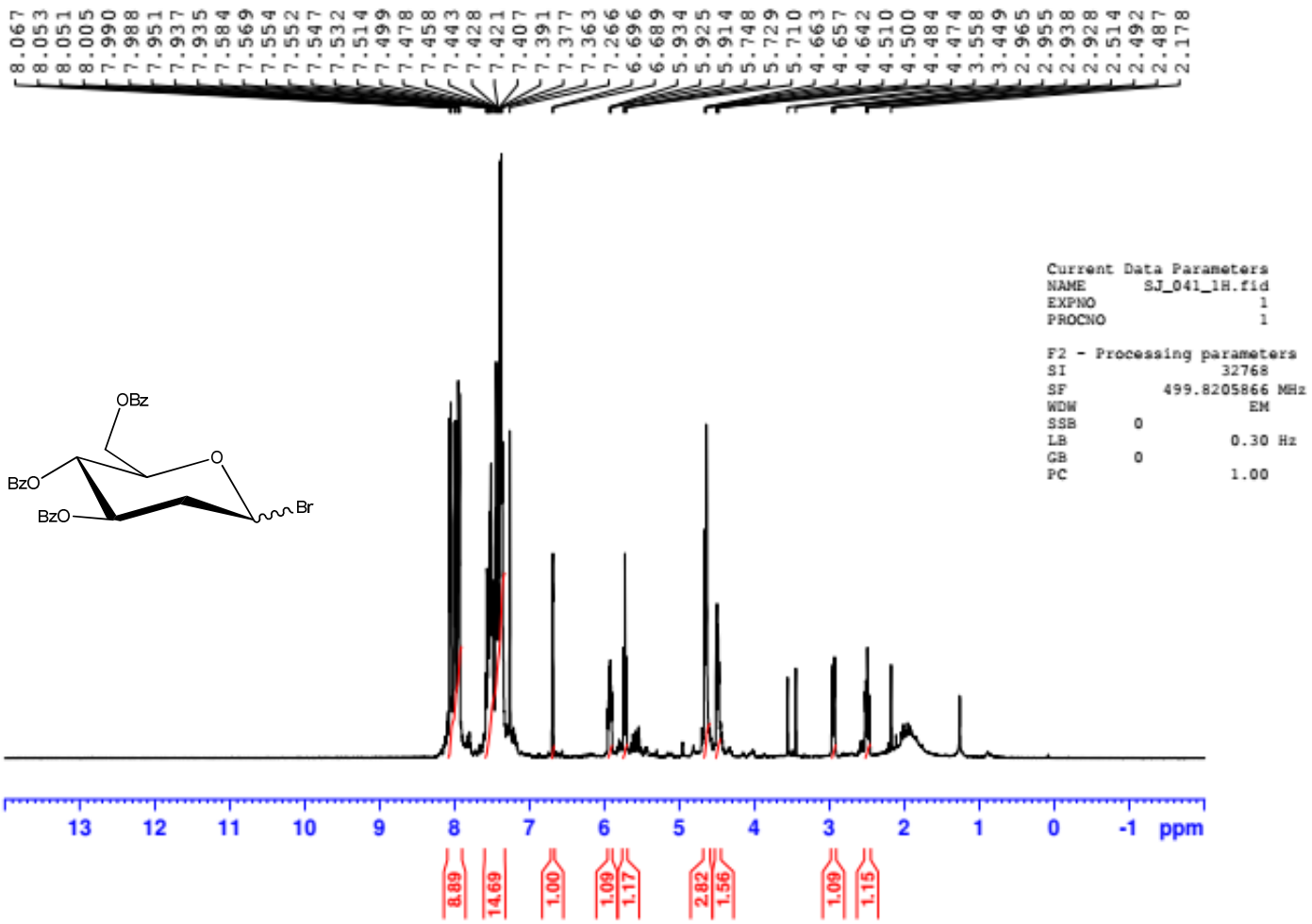


Figure S 13. ^{1}H NMR spectrum of 3,4,5-tri-*O*-benzoyl-2-deoxyglycopyranosyl bromide (**7**) in $CDCl_3$

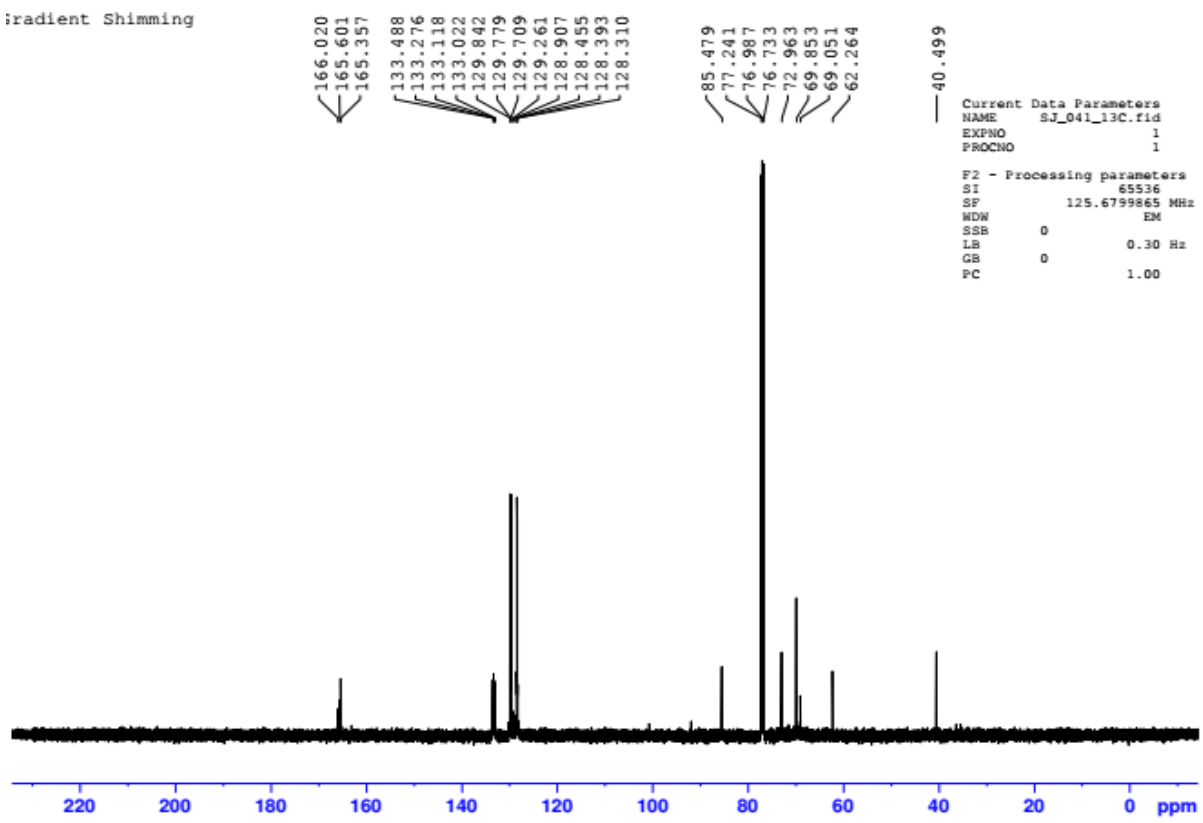


Figure S 14. $^{13}C\{^{1}H\}$ NMR spectrum of 3,4,5-tri-*O*-benzoyl-2-deoxyglycopyranosyl bromide (**7**) in $CDCl_3$

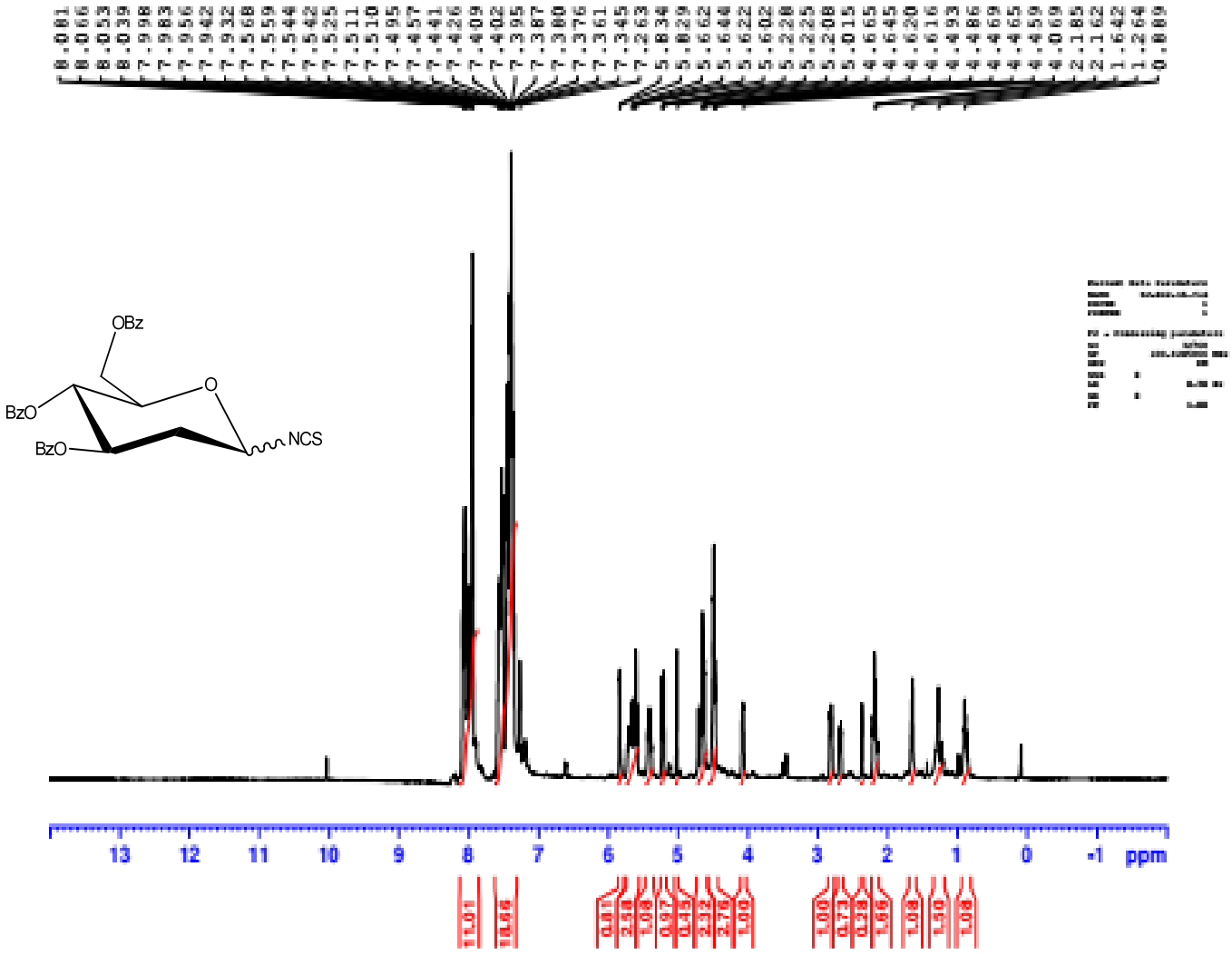


Figure S 15. ^{1}H NMR spectrum of 3,4,5-tri-*O*-benzoyl-2-deoxyglycopyranosyl isothiocyanate (**8**) in $CDCl_3$

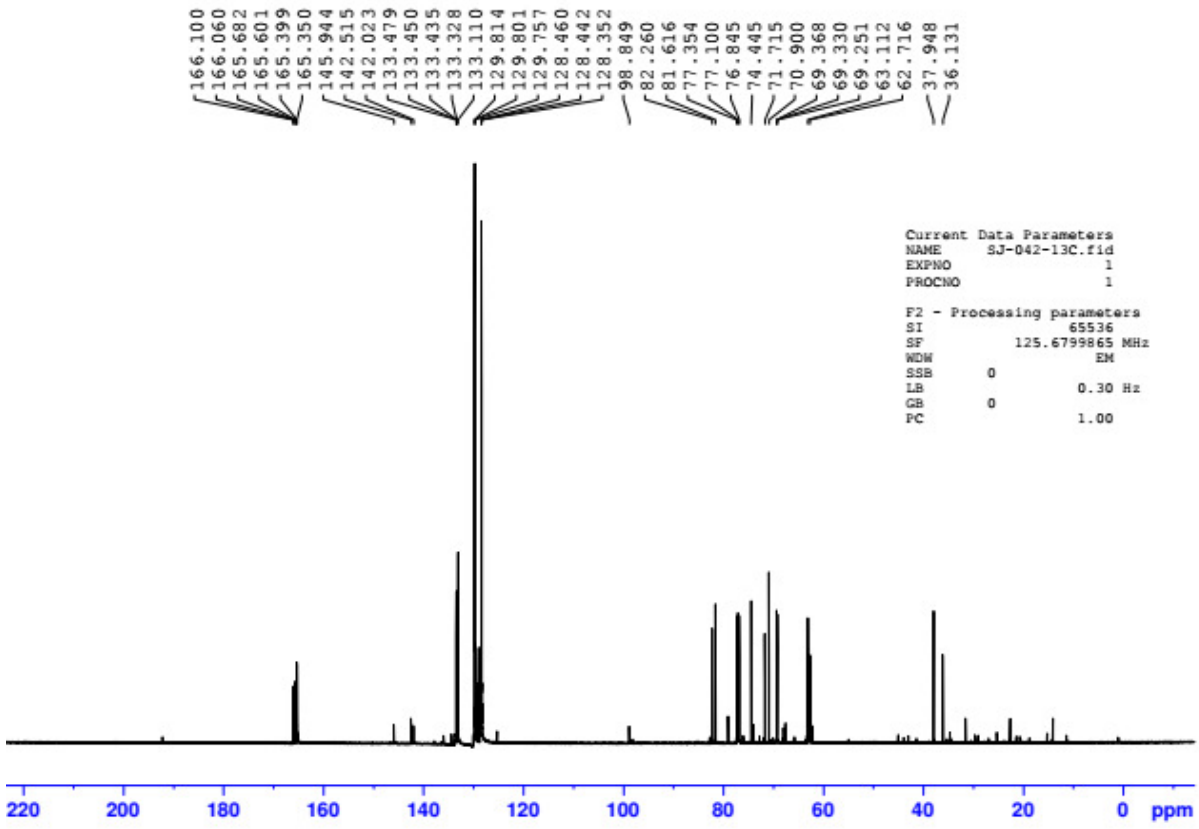


Figure S 16. $^{13}C\{^{1}H\}$ NMR spectrum of 3,4,5-tri-*O*-benzoyl-2-deoxyglycopyranosyl isothiocyanate (**8**) in $CDCl_3$