Selenoglycosides in Carbohydrate Synthesis

By

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CHAPTER 1

SIGNIFICANCE AND PREPARATION OF SELENOGLYCOSIDES

1.1 Introduction and Background

Carbohydrates are among the most abundant biomolecules found in nature. They are substituted with a variety of functionalities and exist in both conjugated and unconjugated forms. Their high level of structural diversity enables carbohydrates to mediate complex biological processes such as protein folding, immunological responses, cell signaling, embryogenesis, and cell proliferation.[1-4] Studies probing the diverse functions of carbohydrates have generally been impeded by the limited availability of homogeneous, chemically-defined oligosaccharides and glycoconjugates.[2,5-7] Synthetic routes to access structurally complex oligosaccharides are, therefore, essential to further investigate biological functions.[1,5,8-9] As such, efforts to advance our understanding of glycosylation as well as methods to form glycosidic bonds in stereocontrolled and regiocontrolled ways are consistently being made.[1-2,5]

While the synthesis of polypeptides and polynucleotides, two other main classes of biopolymers, can be achieved using well-established protocols and automated processes, the production of oligosaccharides in such general procedures is hindered by their intrinsic complexity.[2-4,6,9] In response to the challenge of carbohydrate synthesis, methodology development for oligosaccharide synthesis has focused on forming glycosidic bonds, the fundamental bonds that link monosaccharides.[1] One tool used to address the challenges of regiocontrol and stereocontrol in glycosylation is enzymatic synthesis. This method uses enzymes, such as glycosidases and glycosyltransferases, to assemble and elaborate glycan intermediates.[1,4] Despite the success and high efficiency of the enzymatic approach, this method is restricted due to the limited availability of glycosyltransferases and the high substrate specificity

of the enzymes.[1-2,4,10]

In contrast to the enzymatic approach, chemical synthesis offers more flexibility. In general, the chemical synthesis of glycosides involves a fully-protected glycosyl donor with a latent leaving group at the anomeric position, and a glycosyl acceptor with a free hydroxyl group (**Figure 1**).[11] Activators are used to promote the formation of the oxocarbenium ion intermediate which is attacked by the nucleophile to form the glycoside product. There are many well-studied glycosyl donors available to synthetic chemists, including glycosyl trichloroacetamidates, glycosyl halides, glycosyl sulfoxides, glycosyl phosphates and phosphites, *n*-pentenyl glycosides, glycals, and thioglycosides.[11] Additionally, there is the class of selenoglycoside donors, which are relatively underdeveloped in comparison to other chalcogen-derived donors.[12]

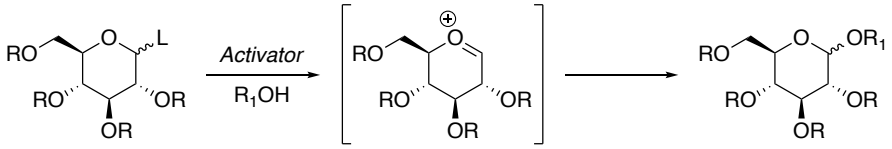


Figure 1. General Glycosylation Reaction

Although in the same family on the periodic table, the chalcogens (O, S, Se, and Te) have distinct characteristics and activities.[13-14] As seen with the reactivity differences of *O*- and *S*-glycosides, there are reactivity differences between *S*- and *Se*-glycosides, even though they share the same oxidation states.[14] Selenium is less basic, larger, more polarizable, and more nucleophilic than sulfur.[13,15] The soft, nucleophilic nature of the selenium enables selenoglycosides to be activated by a variety of soft electrophiles through either cation- or radical-cation-based processes.[14,16] In addition to undergoing direct activation for glycosylation, selenoglycosides are synthetically useful because they cap the reducing end and are easily converted into other glycosyl donors.[14,17] Several comprehensive reviews have been published on the topic of selenoglycosides.[13-14,18]

The use of selenoglycosides as donors began with the seminal work by Seema Mehta and B. Mario Pinto in 1991 which exhibited this class of glycans as versatile building blocks.[19] Their work demonstrated that both armed and disarmed phenyl selenoglycoside donors could be selectively activated over armed ethyl thioglycosides in glycosylation reactions using silver trifluoromethanesulfonate (AgOTf) and anhydrous potassium carbonate (K_2CO_3) (**Figure 2**).[10,19] They also reported the activation of glycosyl bromides in the presence of AgOTf and collidine as a base with phenyl selenoglycoside acceptors. Furthermore, a glycosyl trichloroacetimidate donor was activated with triethyl silyl trifluoromethanesulfonate (TESOTf) over phenyl selenoglycoside acceptors.[10] The work by Mehta and Pinto highlighted the ability to selectively activate one class of donors over another, allowing selenoglycoside building blocks to function as both glycosyl donors and glycosyl acceptors while eliminating the need for functional group conversion at the anomeric center.

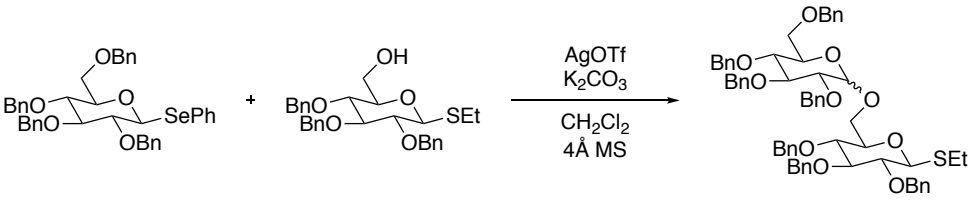


Figure 2. Mehta and Pinto Selective Activation Conditions

1.2 Established Methods for Preparing Selenoglycosides

Since being established as a versatile class of glycosyl building blocks, a number of methods have been developed to produce and activate phenyl selenoglycosides. Selenoglycosides can be readily prepared from the corresponding glycosyl acetate with phenylselenol obtained by hypophosphorus acid (H_3PO_2) reduction of diphenyldiselenide (PhSeSePh).[10,14] Similarly, they can be prepared by treating the corresponding glycosyl halide with phenylselenol from the reduction of PhSeSePh with sodium borohydride ($NaBH_4$) (**Figure 3**).[14]

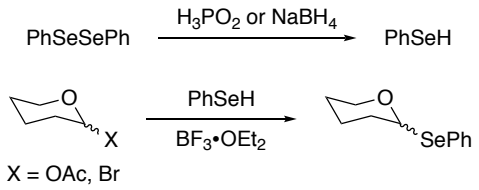


Figure 3. Selenoglycosides Prepared from Reduced PhSeSePh

One drawback to working with thiols and selenols is the malodorous odor, and thus, methods to minimize or eliminate the odor have been developed. A convenient, odorless way to produce selenoglycosides is to react selenides derived from a zinc-mediated cleavage of PhSeSePh in situ with glycosyl bromides (**Figure 4**).[20]

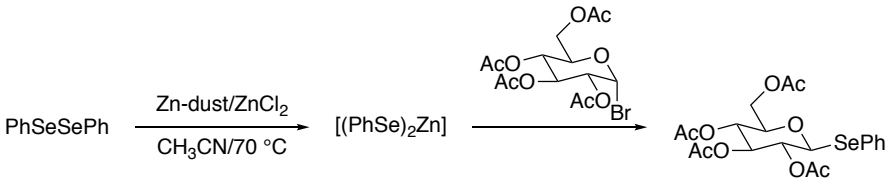


Figure 4. Odorless Method for Selenoglycoside Synthesis

The classic azidonitration method developed by Lemieux and Ratcliffe is a popular tool for the synthesis of 2-amino-2-deoxy sugars.[21] Similarly, the azido-phenylselenation of glycals is a useful method to install two functionalities in one step (**Figure 5**).[13,22] This method has been applied to access a variety of 2-azido-2-deoxy selenoglycosides.[13]

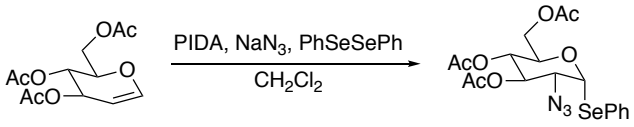


Figure 5. Azido-phenylselenation of Glycals

Another method to access selenoglycosides from glycals is through a 1,2-anhydro derivative followed by a displacement step to install the anomeric seleno-moiety (**Figure 6**). Applying the direct epoxidation method developed by Danishefsky, the α-phenyl selenoglycoside is produced.[23,24] In contrast, when Gin's direct oxidative glycosylation method is applied, the β-

phenyl selenoglycoside product is formed.[24] Crotti and coworkers rationalized that the different stereochemical outcomes of the protocols was the result of the nature of the nucleophile (PhSeH vs. $PhSe^-$) and its effect on the ring-opening of the intermediate α-epoxy glycal.

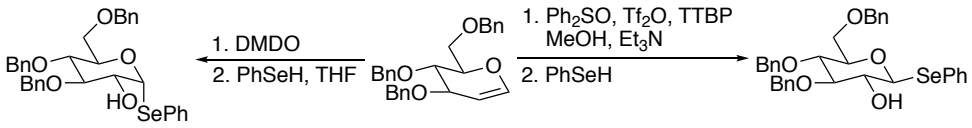


Figure 6. Oxidative Preparation of Selenoglycosides from Glycals

A common trait with the methods provided above is that they all produce phenyl selenoglycosides. While proven to be stable tools in carbohydrate synthesis,[10,13-14,16-18,24-27] the use of selenoglycosides as glycosyl donors has been limited to phenyl selenoglycosides due to the lack of diverse available donors.[16] In chapter 2, a method developed in the Townsend group to access a variety of novel aryl selenoglycosides is described.

CHAPTER 2

PREPARATION OF NOVEL SELENOGLYCOSIDES

2.1 Background

Organoselenium compounds have attracted considerable attention as synthetic targets due to their applications in organic synthesis and potential biological activity.[28-29] Consequently, new and efficient methods for the preparation of organoselenium compounds are being explored.[30] To this end, work in the Townsend group has focused on the arylation of a masked selenium dianion using diaryliodonium salts to produce organoselenides.[31]

Diaryliodonium salts are air- and moisture-stable compounds that have proven to be valuable synthetic tools.[32-34] As iodine(III) reagents, diaryliodonium salts serve as efficient alternatives to transition metal-catalyzed arylation and cross-coupling reactions.[33]

In an effort to produce organoselenium compounds under mild conditions, the Townsend group developed a one-pot method to produce organoselenides and selenoglycosides (**Figure 7**).[31] In this methodology, a diaryliodonium salt **1** is reacted with potassium selenocyanate (KSeCN), a masked selenium dianion, to produce aryl selenocyanate **2**. The selenocyanate **2** is then reduced with $NaBH_4$ in the same pot and reacted with a second electrophile to produce the desired organoselenide **3a** or selenoglycoside **3b**. An advantage of this one-pot methodology is that it requires aqueous work up and product isolation only after the last step.

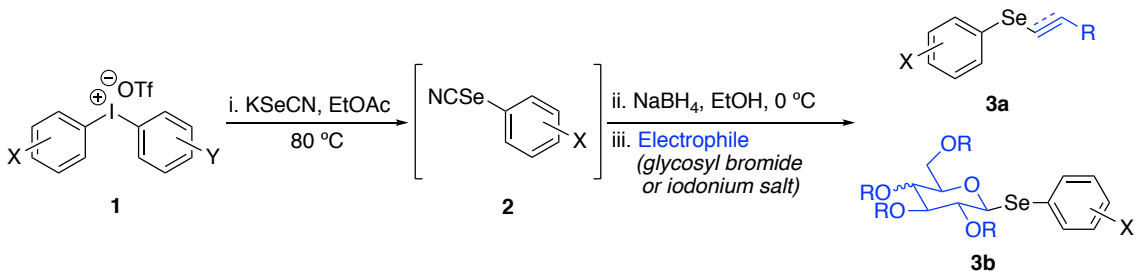


Figure 7. General Scheme of Townsend One-Pot Reaction

The scope of the reaction methodology allowed for the production of substituted aryl selenoglycosides with electron-donating as well as electron-withdrawing substituents on the aryl ring. To our knowledge, many of the selenoglycosides produced were not previously reported in literature, and we recognized the potential for these novel compounds to be used as glycosyl donors in carbohydrate synthesis.

Expanding on previous studies with selenoglycosides, we propose to use the novel aryl selenoglycoside donors we have synthesized as chemoselective donors. The ability to tune the reactivity of coupling components in a highly chemoselective manner will enable chemists to rapidly synthesize oligosaccharides.[35] Owing to the soft nature of selenium, soft heavy metals can be employed for activation.[13] Thus, we propose that soft metals can be used to chemoselectively activate electron-rich donors (**4** and **5**) over more electron-poor donors (**6** and **7**) (**Figure 8**).

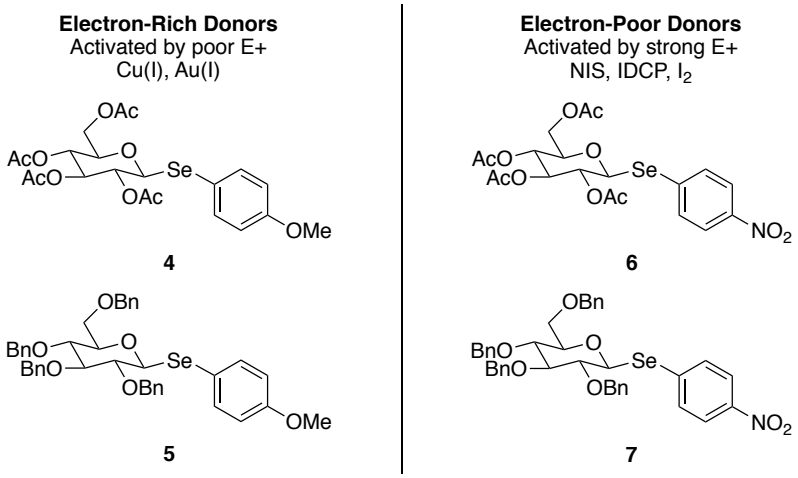


Figure 8. Proposed Glycosylation Conditions for Selective Activation

2.2 Preparation of Selenoglycosides for Future Studies

To begin screening for metal-promoted glycosylation conditions, large quantities of aryl selenoglycoside donors **4** and **6** were prepared. In addition to synthesizing peracetylated aryl selenoglycosides from diaryliodonium salts (**Figure 7**), they can also be prepared from the appropriate diazonium salts (**Figure 9**). Working on a larger scale, we preferred to use the

diazonium salt method. Accessing the diazonium salts was more reliable and avoided the use of stoichiometric amounts of triflic acid (TfOH) required to make the diaryliodonium salts.

Starting from the corresponding aniline derivative (**8a** and **8b**), a diazotization with nitrous acid generated in situ from sodium nitrite and hydrochloric acid produced the diazonium salt. In the same pot, KSeCN is added to produce the corresponding aryl selenocyanate (**9a** and **9b**). Following the procedure developed by Yong Guan in the Townsend group, the selenocyanate (**9a** and **9b**) was reacted with $NaBH_4$ to produce a nucleophilic selenol in a Grieco-type reduction.[31,36] The liberated selenol then reacts with electrophilic glycosyl bromide **10** to produce the corresponding selenoglycoside (**4** and **6**).

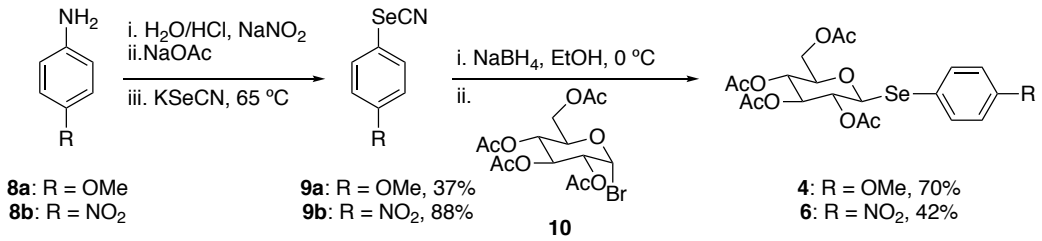


Figure 9. Synthesis of Peracetylated "Disarmed" Donor

In addition to the peracetylated selenoglycoside, we propose to use the benzylated "armed" derivative for screening glycosylation conditions. From peracetylated donor **4**, we readily accessed the corresponding perbenzylated donor **5** in two steps (**Figure 10**).

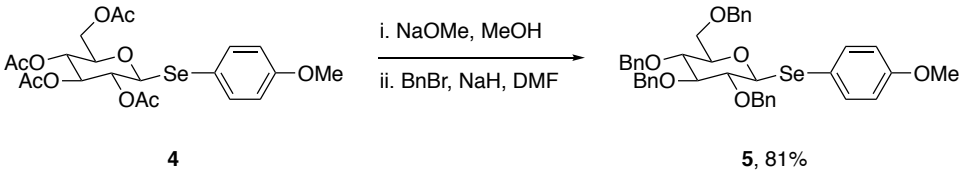


Figure 10. Synthesis of Perbenzylated "Armed" Donor

With the differentially substituted selenoglycosides in hand, the future directions of this work will focus on screening glycosylation conditions to chemoselectively activate

selenoglycosides. Initial results indicate that AuCl or a AuCl/AgOTf system are potential activators for electron-rich selenoglycoside donors **4** and **5**. Successful development of a metal-promoted glycosylation method would not only add to the field of synthetic carbohydrate chemistry, but it would also add new glycosyl donors and glycosyl acceptors to be used as building blocks in oligosaccharide synthesis.

Synthetic carbohydrate chemistry is fundamentally important to the advancement of glycobiology and glycomedicine. Expanding our accessibility to and understanding of synthetic tools will help facilitate the development of improved oligosaccharide syntheses and, thus, will further expand our ability to investigate the role of carbohydrates in nature.

2.3 Experimental Methods

General Procedure

All moisture-sensitive reactions were performed in flame-dried or oven-dried glassware under an atmosphere of argon or nitrogen. Oven-dried stainless steel syringes or cannulas were used to transfer moisture- and air-sensitive liquids. Reaction temperatures were controlled and monitored using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (approx. 23 °C), unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on Sorbtech Silica XHL UV254, glass-backed, 250 µm plates. Plates were visualized first using a UV lamp (254 nm), and then stained with cerium ammonium molybdate or potassium permanganate, followed by heating. Flash column chromatography was performed as described by Still et. al. using silica gel 230-400 mesh. Yields were reported as purified, isolated compounds.

Materials

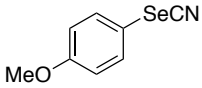
Solvents were obtained from either Sigma Aldrich or Fisher Chemical. Solvents were obtained from a MBraun MB-SPS solvent system or dried over 3 Å or 4 Å molecular sieves. Ethanol (EtOH) was degassed using the freeze, pump, thaw protocol. Commercial reagents were used as received.

Instrumentation

^{1}H NMR spectra were obtained on a Bruker 400 MHz or 600 MHz spectrometers, and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are presented as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz) and integration. Deuterated chloroform was standardized to 7.26 ppm. ^{13}C NMR spectra were obtained on a Bruker 100 MHz or 150 MHz spectrometers, and are reported relative to deuterated solvent signals. Deuterated chloroform was standardized to 77.0 ppm.

Compound Preparation and Characterization

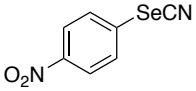
Aryl Selenocyanates:



9a

1-methoxy-4-selenocyanatobenzene (9a). To a solution of 4-methoxyaniline (2.5 g, 20 mmol) in water (12 mL) cooled to 0 °C was added concentrated hydrochloric acid (12.0 N in H_2O, 7.4 mL, 90 mmol). A solution of sodium nitrite (1.4 g, 20 mmol) in water (12 mL) was added to the stirring solution at 0 °C. After stirring at 0 °C for 20 min, the reaction was neutralized by the addition of sodium acetate (6.2 g, 76 mmol). The resulting mixture was cooled to 0 °C, and a solution of potassium selenocyanate (KSeCN, 3.5 g, 24 mmol) in water (8 mL) was added dropwise via a syringe pump. The reaction was stirred at room temperature for

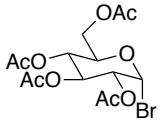
15 min, and then heated to 65 °C. After stirring at 65 °C for 2 h, the mixture was extracted with $CHCl_3$ (3 X 12 mL). The layers were separated and the organic layer was washed with water (3 X 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:3 hexanes/CH_2Cl_2) to yield aryl selenocyanate **9a** (1.6 g, 7.4 mmol, 37%) as a yellow solid: R_f 0.4 (2:3 hexanes/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (app. dt, J = 9.0, 2.6 Hz, 2H), 6.91 (app. dt, J = 9.0, 2.6 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3, 136.0, 115.9, 111.0, 102.0, 55.4. Spectral data for **9a** was consistent with literature values.[31,37]



9b

1-nitro-4-selenocyanatobenzene (9b). To a solution of 4-nitrobenzenediazonium tetrafluoroborate (0.24 g, 1.0 mmol) in water (2 mL) was slowly added a solution of KSeCN (0.23 g, 1.6 mmol) in water (500 µL). The reaction was heated to 65 °C. After stirring at 65 °C for 4 h, the mixture was extracted with $CHCl_3$ (3 X 2 mL). The layers were separated and the organic layer was washed with water (3 X 6 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:3 hexanes/CH_2Cl_2) to yield aryl selenocyanate **9b** (0.2 g, 0.9 mmol, 88%) as a yellow solid: R_f 0.5 (4:1 hexanes/ CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (app. dt, J = 8.9, 2.3 Hz, 2H), 7.78 (app. dt, J = 9.0, 2.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.4, 131.5, 130.9, 125.1, 99.4. Spectral data for **9b** was consistent with literature values.[31,38]

Glycosyl Bromide:

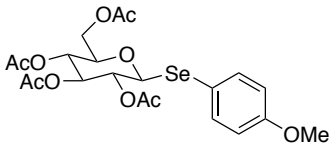


10

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-bromotetrahydro-2*H*-pyran-3,4,5-triyl triacetate (10). A solution of glucose pentaacetate (10 g, 26 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To the stirring solution was added HBr (33% in AcOH,

10 mL) dropwise via a syringe pump. The reaction was warmed to room temperature. After stirring for 4.5 h, the reaction solution was poured over ice (25 g) and diluted with CH_2Cl_2. The acid was quenched by addition of solid potassium carbonate (K_2CO_3). The layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate ($NaHCO_3$) (2 X 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude solid was recrystallized from warm Et_2O/hexanes to produce glycosyl bromide **10** (9.8 g, 24 mmol, 93%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, *J* = 4.2 Hz, 1H), 5.55 (t, *J* = 9.8 Hz, 1H), 5.16 (t, *J* = 9.9 Hz, 1H), 4.83 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.31 (m, 2H), 4.13 (d, *J* = 10.8 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). Spectral data for **10** was consistent with literature values.[39]

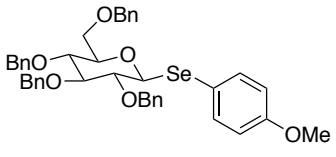
Aryl Selenoglycosides:



4

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-methoxyphenyl) selanyl)tetra hydro-2*H*-pyran-3,4,5-triyl triacetate (4). *Method C – Using Impure Aryl Selenocyanate*: A suspension of synthesized, impure aryl selenocyanate **9a** (1.8 g, 8.5 mmol) in degassed EtOH (30 mL) was cooled to 0 °C and purged with argon. To the stirring suspension was added $NaBH_4$ (1.3 g, 36 mmol) portion-wise. Under argon, the reaction stirred at 0 °C for 50 min. Once gas production subsided, glycosyl bromide **10** (2.8 g, 6.8 mmol) was added to the solution cooled to 0 °C. The reaction was warmed to room temperature and continued to stir for 23 h. The mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous NH_4Cl (4 X 40 mL), water (40 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc) to produce aryl selenoglycoside **4** (2.6 g, 5.0 mmol, 74% β only) as a white solid: R_f 0.3 (3:2 hexanes/EtOAc). *Method A – Using Pure Aryl*

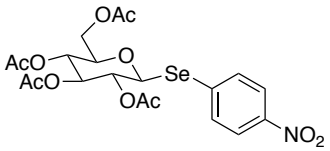
Selenocyanate: Followed the same procedure as Method A above starting from synthesized, pure aryl selenocyanate **9a** (0.2 g, 0.8 mmol). Upon complete addition of glycosyl bromide **10**, the reaction stirred at room temperature for 3 h. After aqueous work up and purification, aryl selenoglycoside **4** (0.3 g, 0.5 mmol, 70% β only) was isolated as a white solid: R_f 0.3 (3:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (app. dt, *J* = 8.8, 2.5 Hz, 2H), 6.82 (app. dt, *J* = 8.8, 2.5 Hz, 2H), 5.16 (t, *J* = 9.4 Hz, 1H), 4.98 (t, *J* = 9.8 Hz, 1H), 4.92 (t, *J* = 9.9 Hz, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 4.17 (d, *J* = 3.7 Hz, 2H), 3.81 (s, 3H), 3.65 (dt, *J* = 10.1, 3.6 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.0 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.4, 169.3, 160.4, 137.9, 116.2, 114.6, 80.5, 76.7, 73.9, 70.7, 68.1, 62.0, 55.3, 20.8, 20.7, 20.6, 20.6. Spectral data for **4** was consistent with literature values.[31]



5

(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-2-((benzyloxy) methyl)-6-((4-methoxyphenyl)selanyl)tetrahydro-2*H*-pyran (5). To a suspension of peracetylated selenoglycoside **4** (0.52 g, 1.0 mmol) in MeOH (10 mL) at ambient temperature was added 2.0 M NaOMe solution (0.5 mL). After stirring for 1 h, the reaction was neutralized with Dowex-50Wx8, filtered and concentrated *in vacuo*. The resulting deacetylated product was carried forward without purification. In a separate flame-dried flask, sodium hydride (NaH) (0.24 g, 6.0 mmol) was suspended in DMF (2 mL) under nitrogen. The crude deacetylated product was dissolved in DMF (5 mL), and slowly transferred via cannula to the stirring NaH solution. The reaction solution was cooled to -5 °C with a NaCl/ice bath, and benzyl bromide (BnBr) (0.7 mL, 5.0 mmol) was added dropwise. Upon complete addition of BnBr, the reaction mixture warmed to room temperature, and stirred for 23 h. The reaction was quenched with MeOH, and diluted with EtOAc (15 mL). The organics were washed with water (3 X 15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

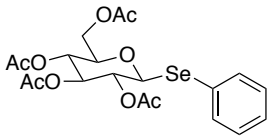
The crude solid was purified by flash column chromatography (4:1 hexanes/EtOAc) to produce benzylated selenoglycoside **5** (0.58 g, 0.8 mmol, 81%) as a white solid: R_f 0.2 (9:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (app. dt, *J* = 8.8, 2.5 Hz, 2H), 7.42-7.41 (m, 2H), 7.36-7.34 (m, 6H), 7.33-7.27 (m, 10H), 7.21-7.20 (m, 2H), 6.70 (app. dt, *J* = 8.8, 2.5 Hz, 2H), 4.89-4.84 (m, 3H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.76 (d, *J* = 9.9 Hz, 1H), 4.74 (d, *J* = 10.3 Hz, 1H), 4.61-4.59 (m, 2H), 4.53 (d, *J* = 11.8 Hz, 1H), 3.80-3.74 (m, 5H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.63 (t, *J* = 9.5 Hz, 1H), 3.47-3.44 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 138.4, 138.3, 138.1, 136.9, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.5, 118.0, 114.6, 86.8, 82.8, 81.1, 80.0, 77.8, 75.8, 75.1, 75.0, 73.4, 69.0, 55.2.



6

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-nitrophenyl) selanyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6). *Method A – Using Pure Aryl Selenocyanate*: A suspension of synthesized aryl selenocyanate **9b** (0.10 g, 0.5 mmol) in degassed EtOH (2 mL) was cooled to 0 °C and purged with argon. To the stirring suspension was added $NaBH_4$ (54 mg, 1.3 mmol). Under argon, the reaction stirred at 0 °C for 30 min, and then glycosyl bromide **10** (0.15 g, 0.4 mmol) was added. The reaction was warmed to room temperature. Upon complete consumption of starting material, the reaction was diluted with Et_2O, washed with saturated aqueous NH_4Cl, water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (1:1 hexanes/EtOAc) to produce aryl selenoglycoside **6** (81 mg, 0.15 mmol, 42% β only) as a white solid. *Method B – Using One-Pot Diaryliodonium Salt Procedure*: To a suspension of (4-nitrophenyl)(phenyl)iodonium trifluoromethanesulfonate (0.50 g, 1.0 mmol) in dry EtOAc (12 mL) was added KSeCN (0.32 g, 2.2 mmol). The reaction stirred at 80 °C for 45 h, and then concentrated *in vacuo*. The resulting product was suspended in degassed EtOH (5 mL)

and purged with argon. To the mixture was added $NaBH_4$ (0.11 g, 3.0 mmol) in one portion. After stirring at room temperature for 15 m, the reaction was cooled to 0 °C. Glycosyl bromide **10** (0.33 g, 0.8 mmol) was added, and the reaction was warmed to room temperature. Upon complete consumption of starting material, the reaction was transferred to a separatory funnel and diluted with Et_2O. The mixture was washed with saturated aqueous NH_4Cl, water and brine sequentially. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc) to produce aryl selenoglycoside **6** (0.31 g, 0.6 mmol, 72% α/β 1:24) as a white solid: R_f 0.3 (3:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (app. dt, *J* = 8.9, 2.2 Hz, 2H), 7.74 (app. dt, *J* = 8.9, 2.2 Hz, 2H), 5.25-5.20 (m, 1H), 5.06-4.98 (m, 3H), 4.25-4.16 (m, 2H), 3.78-3.74 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 169.3, 169.2, 147.7, 136.7, 134.4, 123.7, 80.5, 77.1, 73.5, 70.4, 67.9, 62.0, 20.7, 20.7, 20.5. Spectral data for **6** was consistent with literature values.[31]



11

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(phenylselanyl)tetra hydro-2*H*-pyran-3,4,5-triyl triacetate (11). <u>*Method A – Using Pure Aryl Selenocyanate*</u>: A mixture of commercially available phenyl selenocyanate (1.3 mL, 10 mmol) in degassed EtOH (75 mL) was cooled to -5 °C with NaCl/ice bath and purged with argon. To the cooled solution was added solid sodium borohydride ($NaBH_4$) (1.5 g, 38 mmol) portion-wise over 30 min. Under argon, the reaction stirred at 0 °C for 1 h. Glycosyl bromide **10** (3.3 g, 8.0 mmol) was added in one portion. The reaction was warmed to room temperature. Upon complete consumption of starting material, the mixture was transferred to a separatory funnel with Et_2O and washed with saturated aqueous ammonium chloride (NH_4Cl), water and brine sequentially. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude

residue was purified by flash column chromatography (1:1 hexanes/EtOAc) to produce phenyl selenoglycoside **11** (2.6 g, 5.3 mmol, 67% β only) as a white solid: R_f 0.5 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.37-7.27 (m, 3H), 5.19 (t, *J* = 9.4 Hz, 1H), 5.01 (q, *J* = 9.5 Hz, 2H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.22-4.14 (m, 2H), 3.71-3.66 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 169.4, 169.3, 135.2, 129.0, 128.5, 126.9, 80.9, 76.8, 73.8, 70.7, 68.1, 62.1, 20.8, 20.7, 20.6, 20.5. Spectral data for **11** was consistent with literature values.[31,40]

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APPENDIX

^{1}H AND ^{13}C SPECTRA OF PREPARED COMPOUNDS

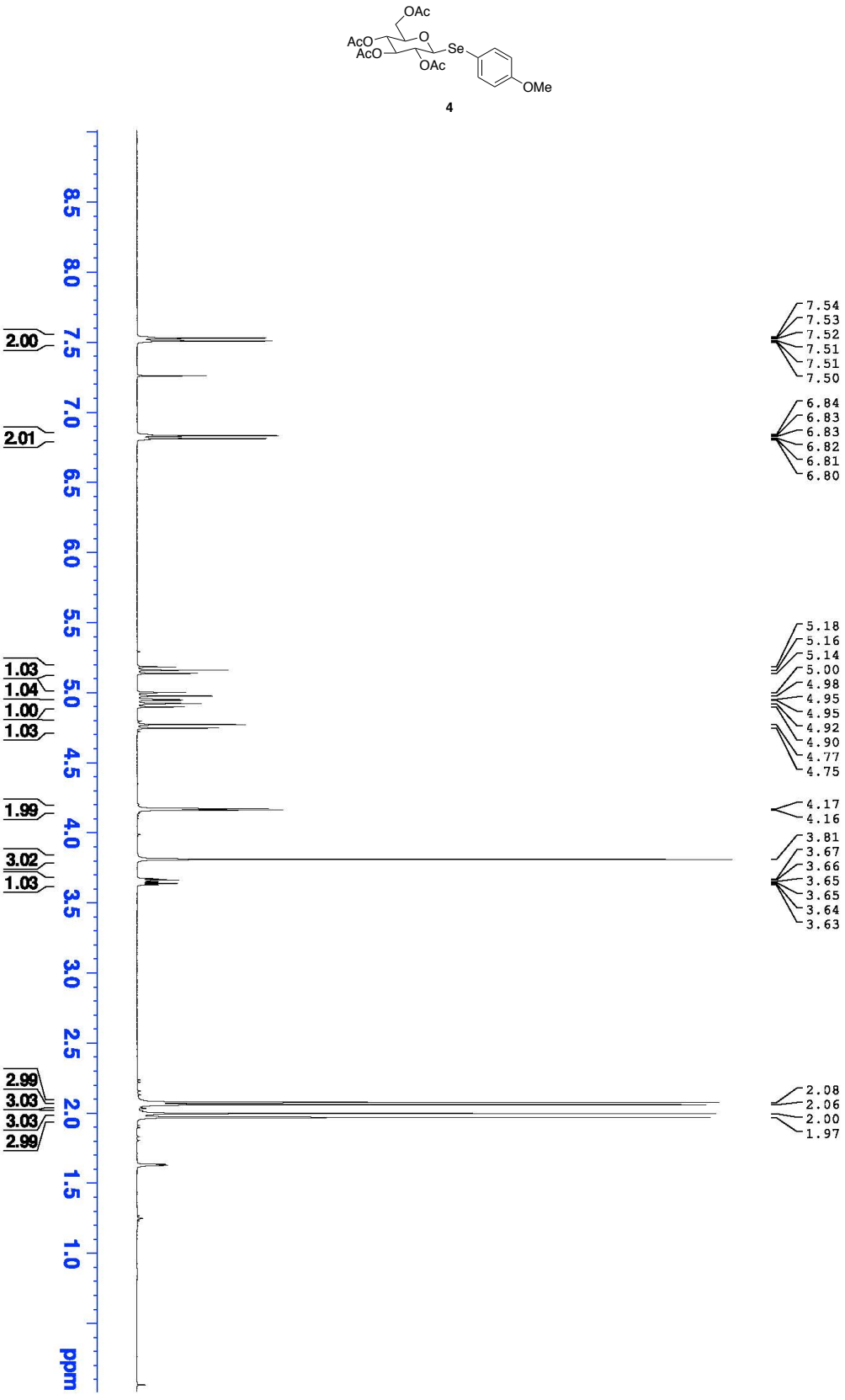

Figure A1. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **4**.

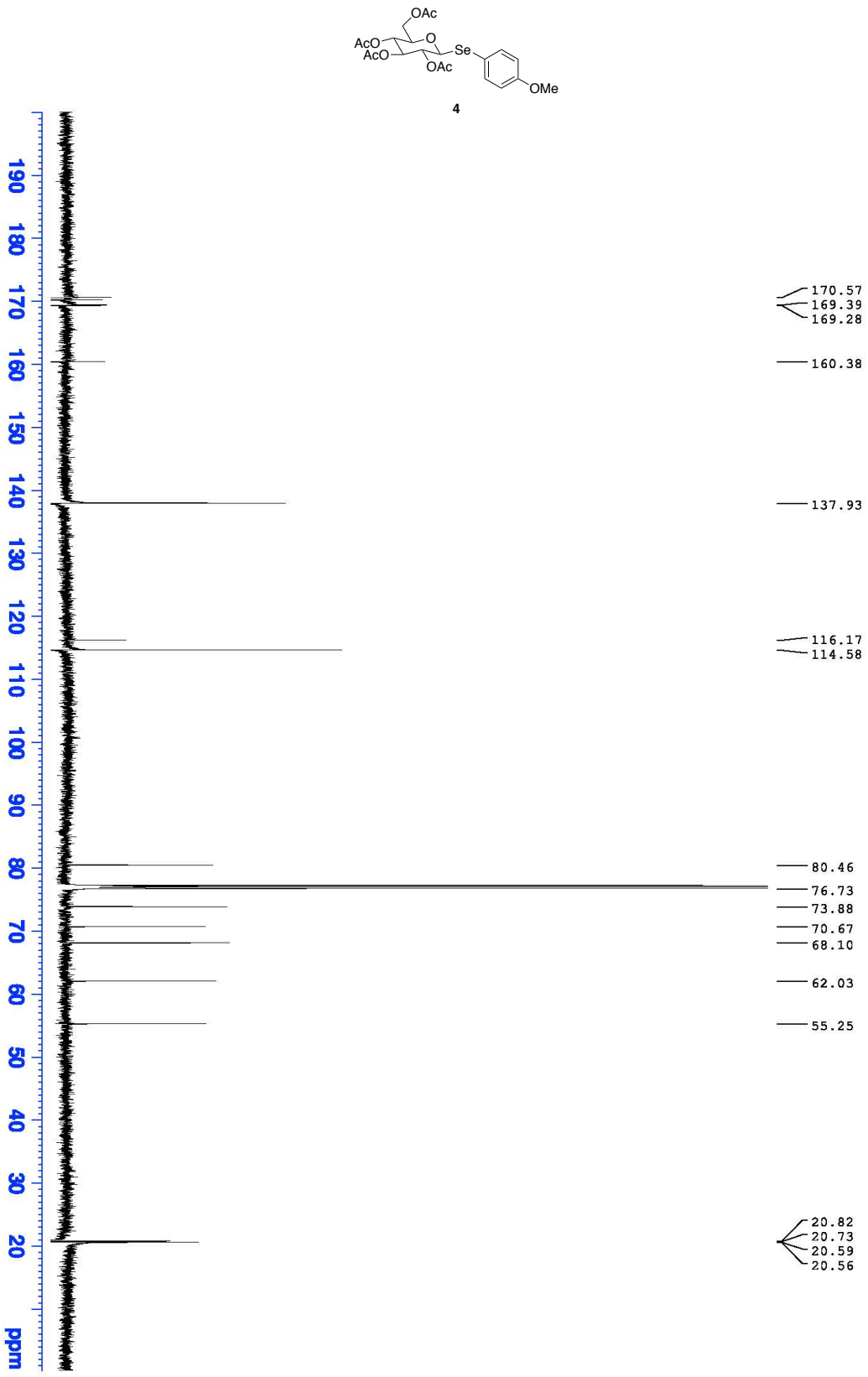

Figure A2. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of **4**.

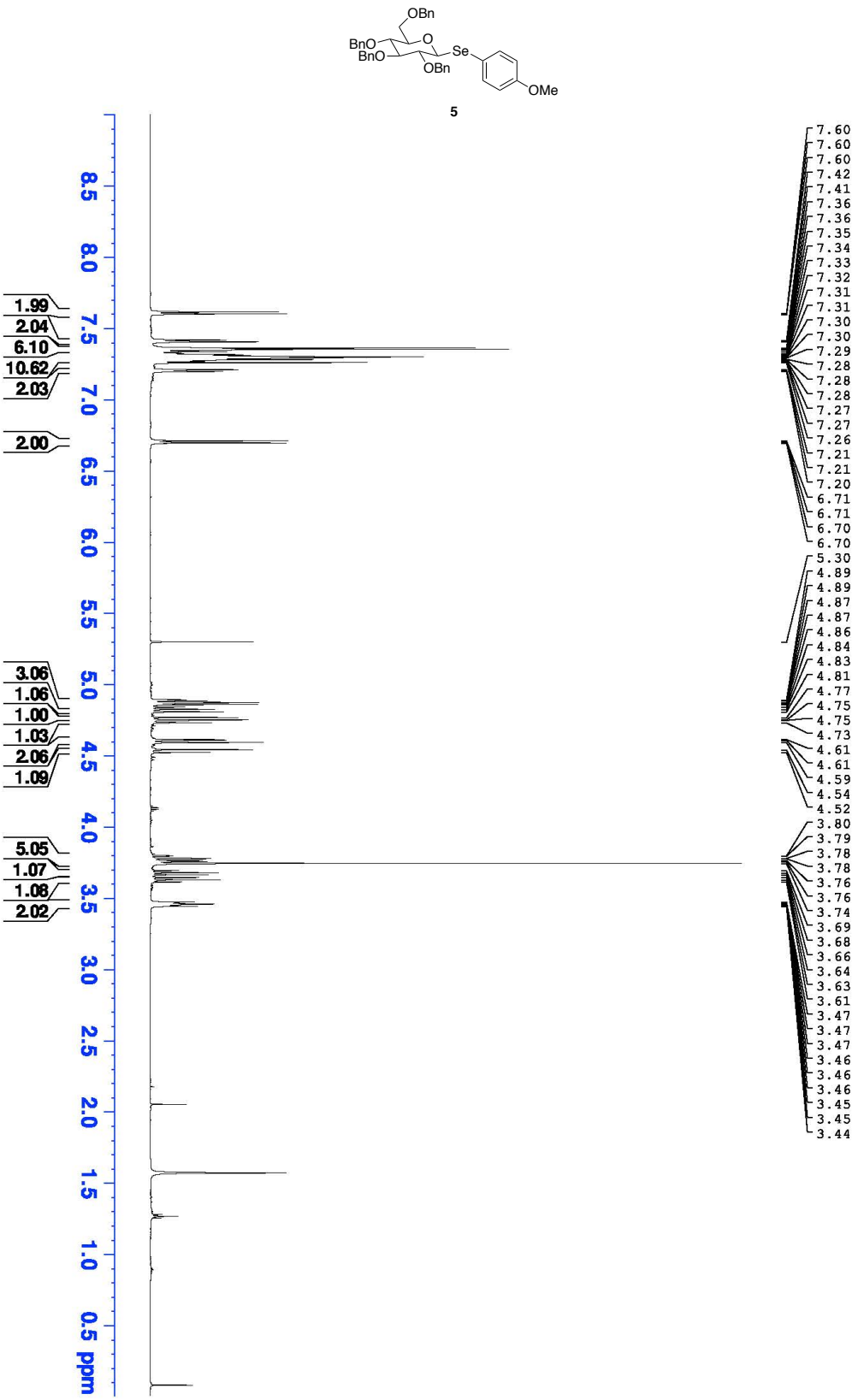

Figure A3. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of **5**.

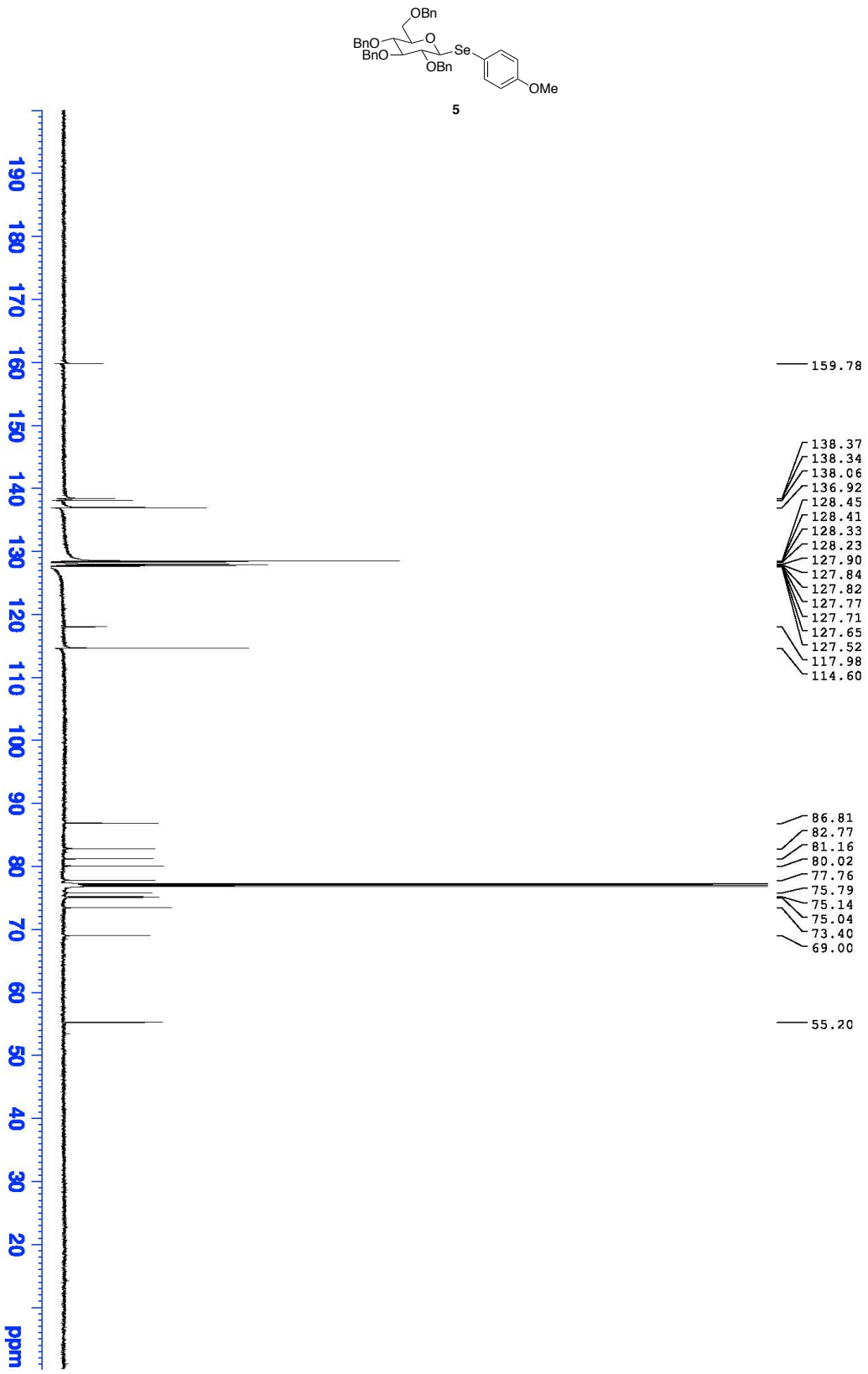

Figure A4. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of **5**.

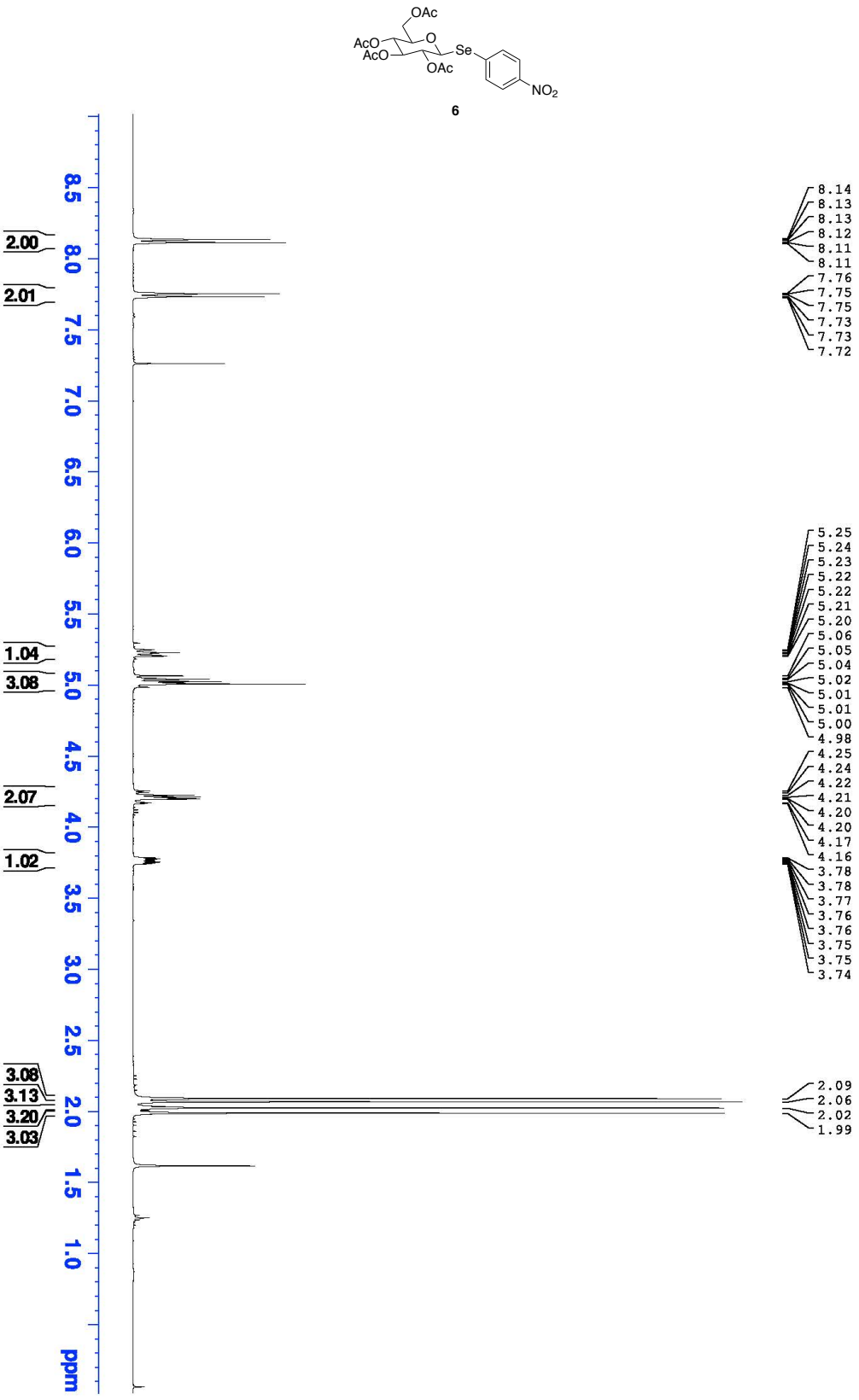

Figure A5. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **6**.

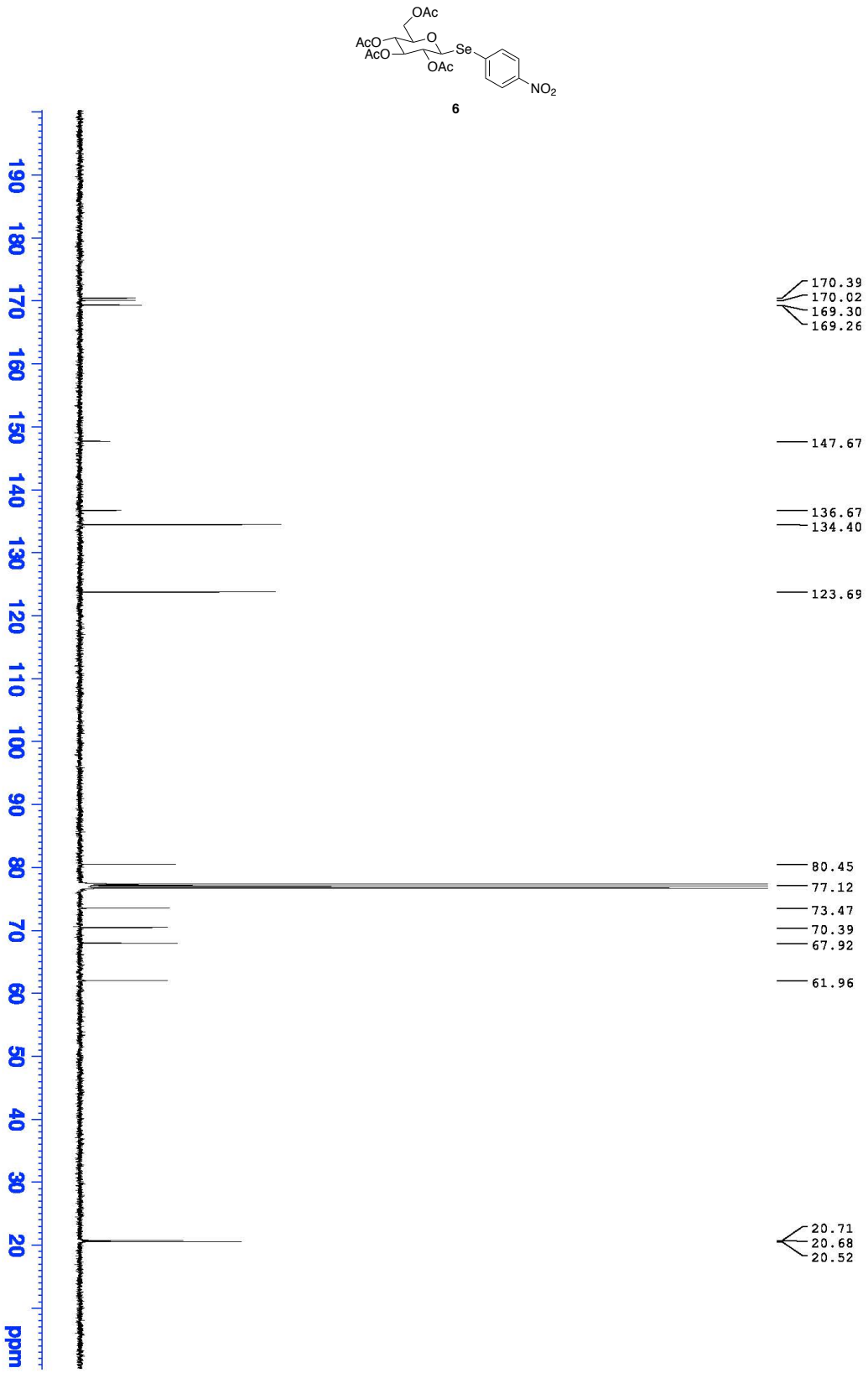

Figure A6. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of **6**.

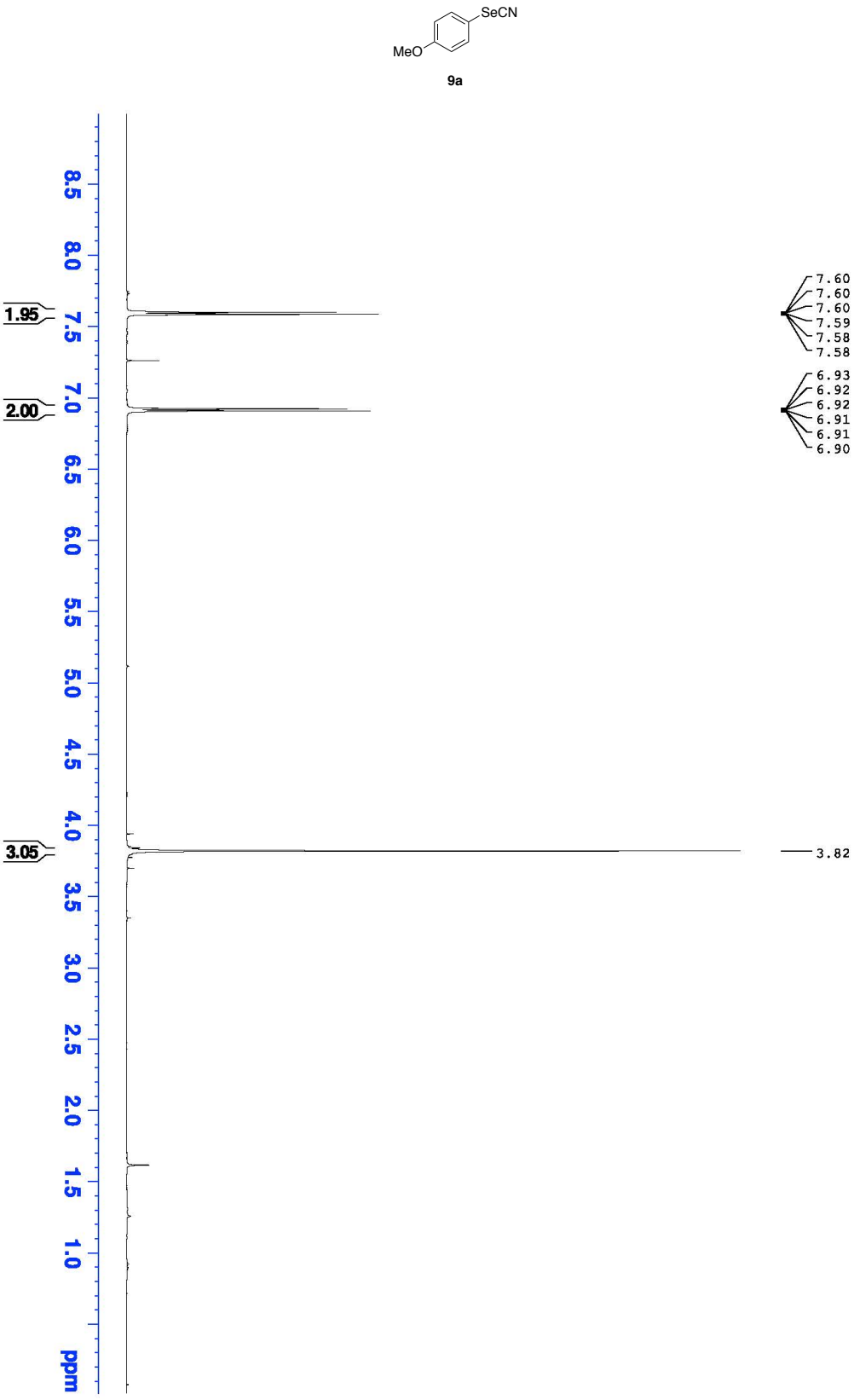

Figure A7. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of **9a**.

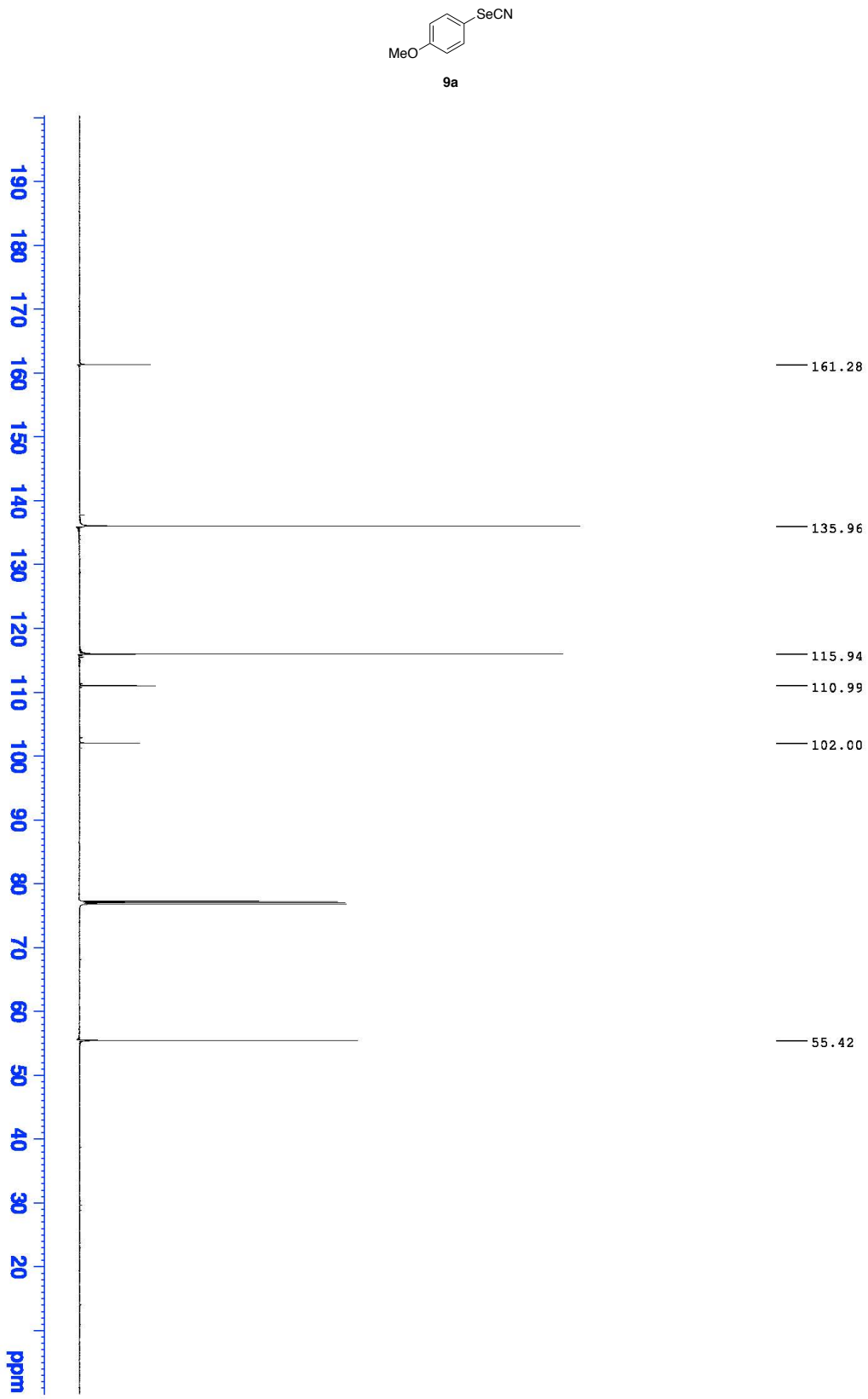

Figure A8. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of **9a**.

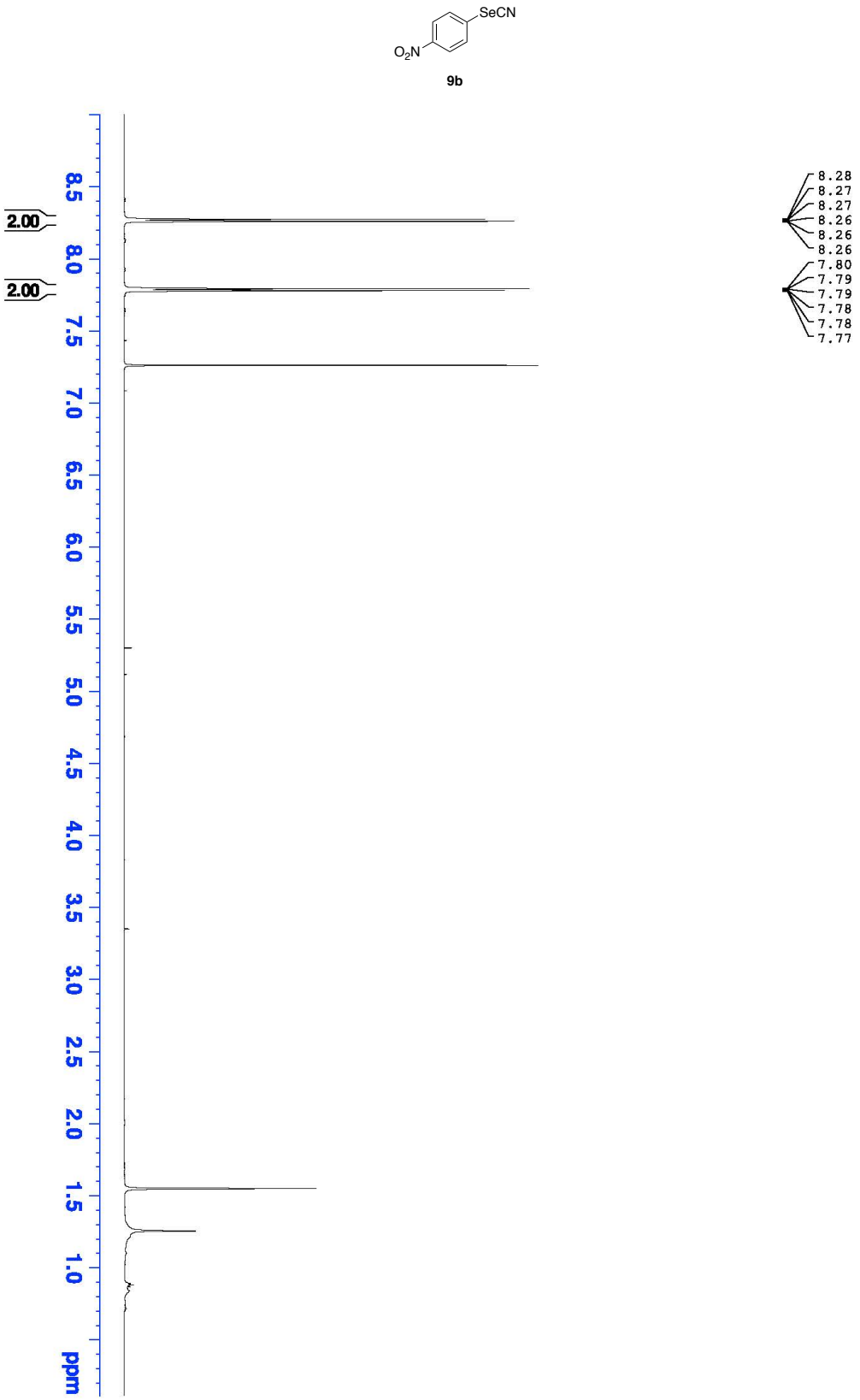

Figure A9. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of **9b**.

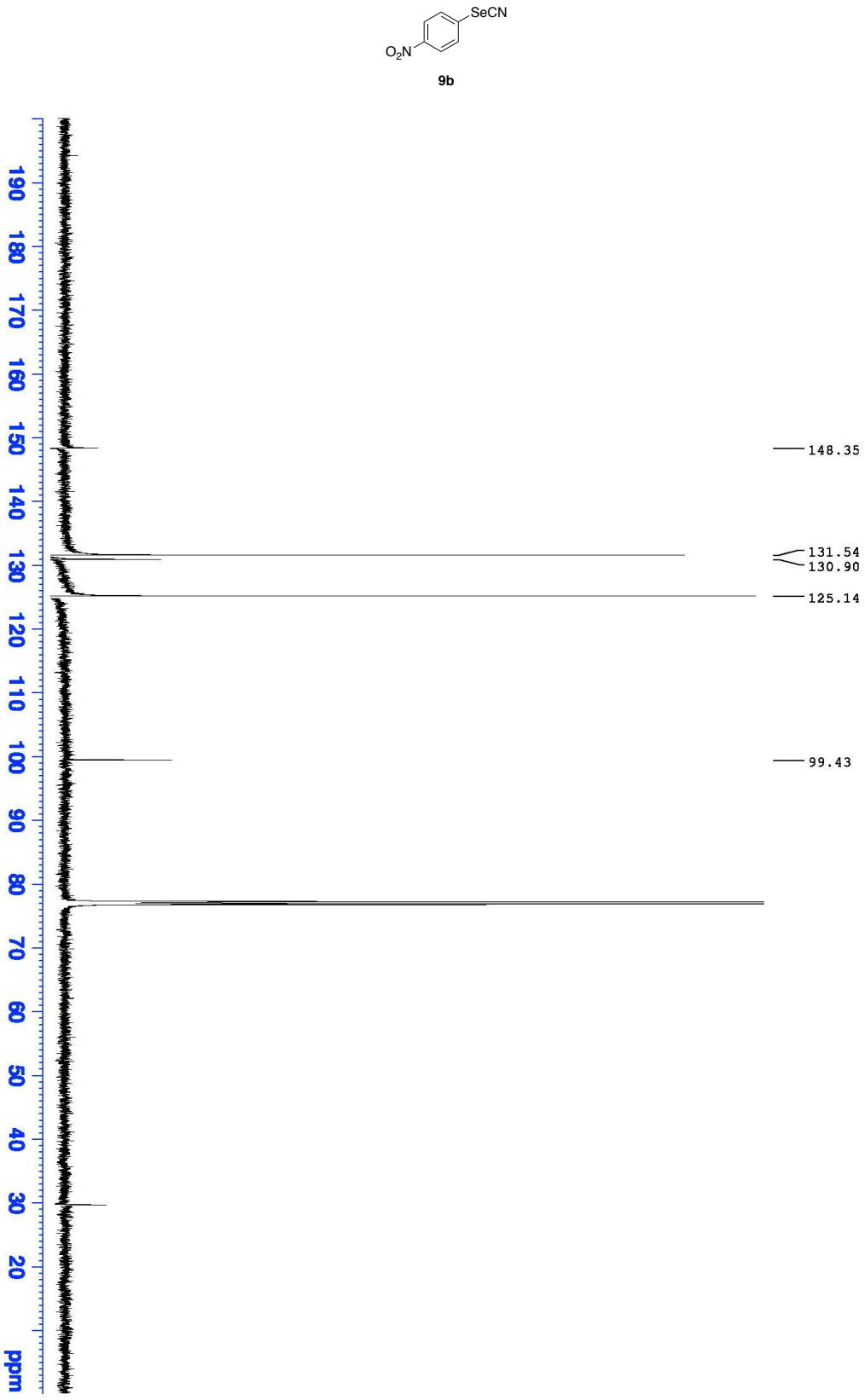

Figure A10. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of **9b**.

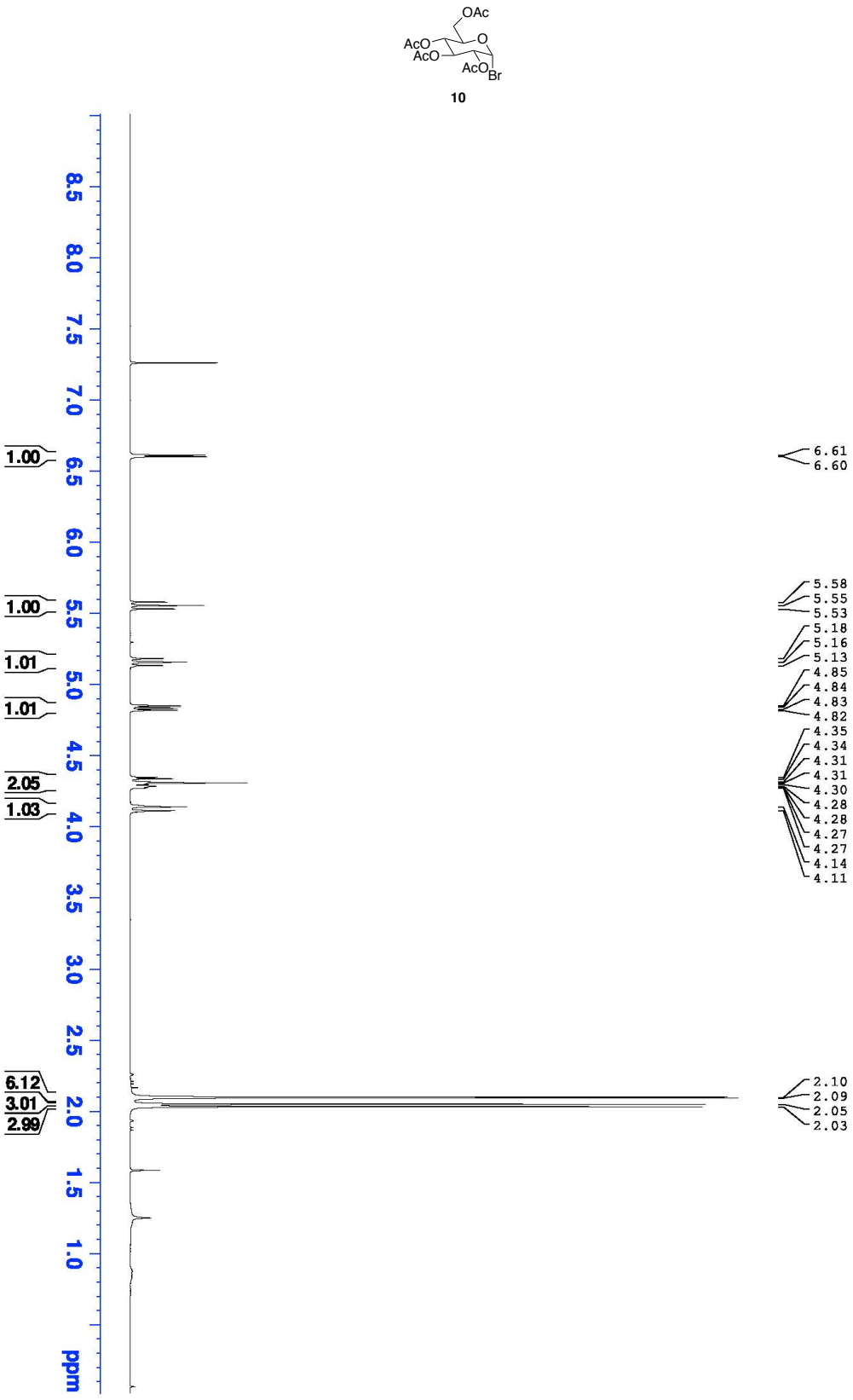

Figure A11. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **10**.

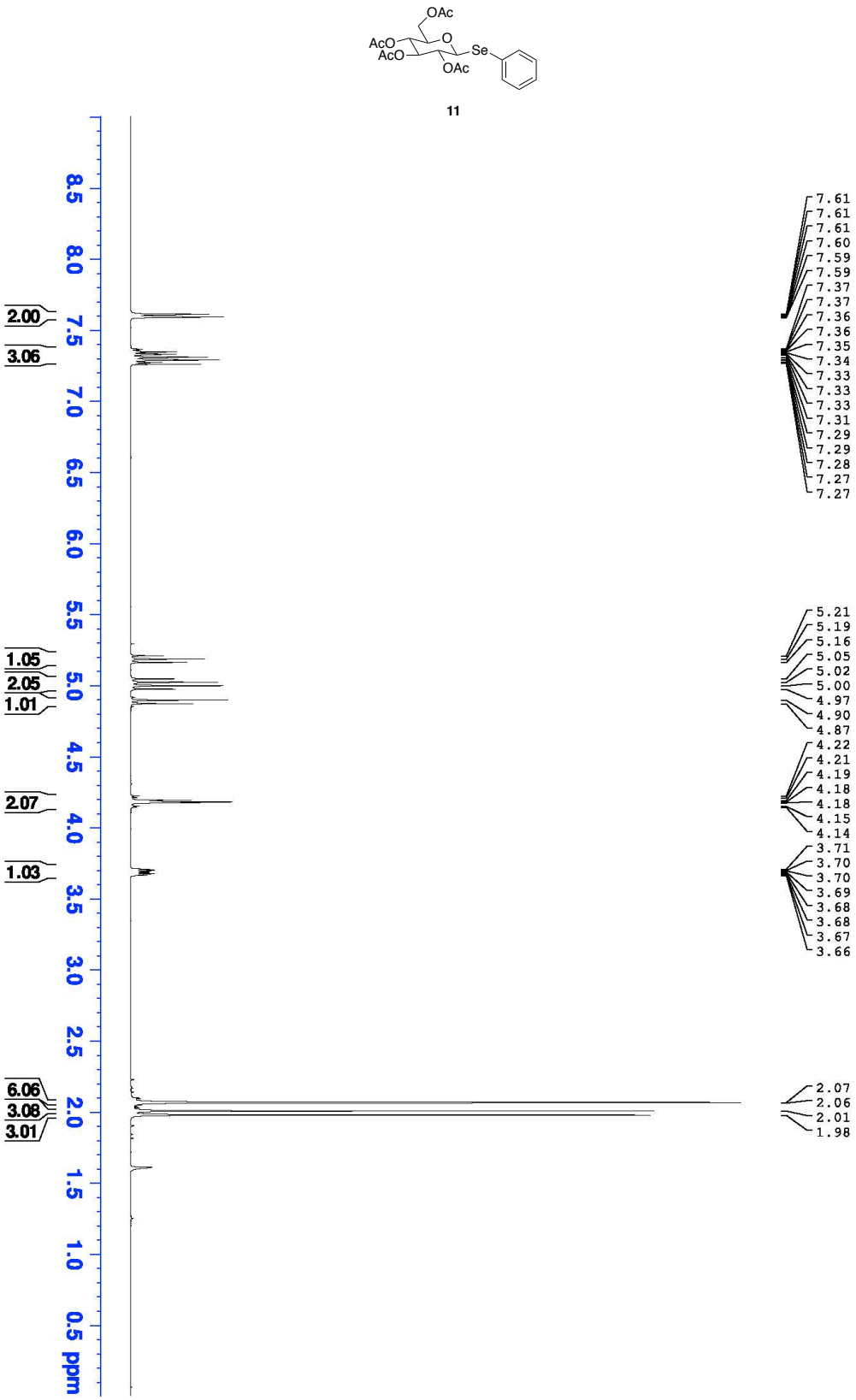

Figure A12. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **11**.

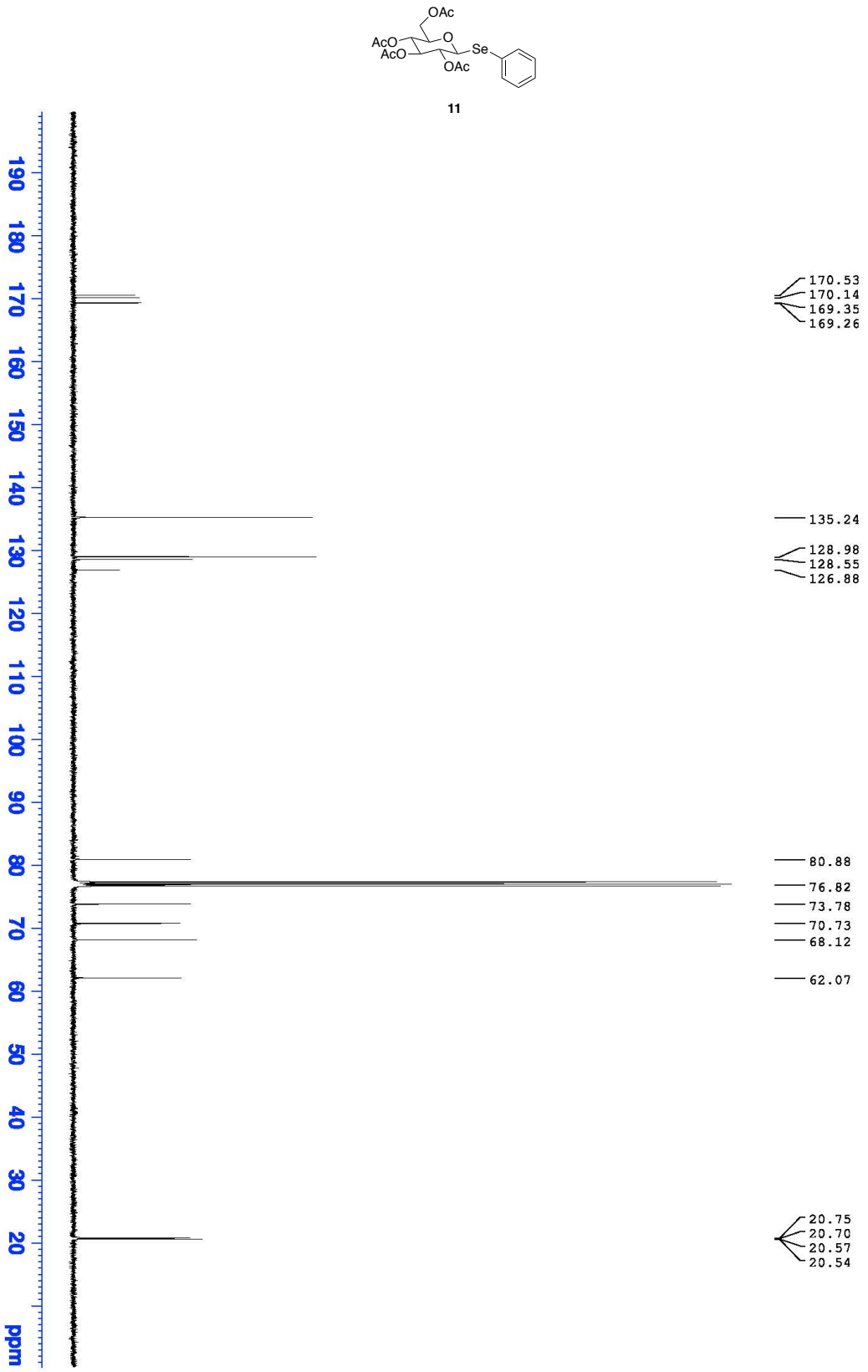

Figure A13. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of **11**.