Supplementary Information for:

Indium chloride catalysed benzyl bromination using continuous flow technology

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I) General

All reactions were performed in the Standard Vapourtec 10ml PFR coiled reactor (R series) under the nitrogen atmosphere. Nitrogen gas line from the Vapourtec in-built inert gas manifold (outlet pressure 40mbar) was applied only to the feed solution. Reaction completion was initially monitored by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR). Only the steady state section of the reaction product was collected according to the model graph displayed by the R-Series software. The TLC was visualized under ultraviolet light (254 nm and 365 nm). NMR spectra were recorded on Brucker 400MHz on proton and 75MHz on carbon. Peak multiplicities are captured by the following abbreviations: s (singlet), d (doublet), m (multiplet) and coupling constants (J) are reported in hertz (Hz). NMR data were processed using the MestReNova 14 software package. All products were characterized by comparing the corresponding ^{1}H NMR, ^{13}C NMR and GC-MS with those available in the literature. The chemical shifts are reported as δ values in ppm relative to the peak of the deuterated solvent: $CDCl_3$ (δH: 7.2; δC: 77.10), D_20 (δH: 3.3). Conversion of product by $^{1}HNMR$ was determined by comparing integration of reactant (r) peaks ($-CH_3$ at 2.3-2.5 ppm) and product (p) ($-CH_2$ peaks at 4.4-4 .6ppm). The integration was divided by the number of protons they belong to, which was then used in the equation, Conversion (%) = p/(r+p)*100 to determine the conversion of toluene derivatives to yield its corresponding benzylic bromides. GC-MS monitoring was based on electron impact ionization using an HP-5MS column. After 1 min at 50°C, the temperature was increased at 25°C/min in steps to 250°C for 10 min. Helium was used as the carrier gas. All the chemicals and solvents were obtained from merck and used as received without any further purification. All the benzyl bromides synthesized herein are known in the literature. Product purity and identity were confirmed by NMR and GC-MS.

I) General methods

General Procedure for the preparation of benzylic bromination in continuous flow (Table 1).

All the reactions were conducted on a 4 mmol scale. A solution of toluene derivative (1.0 eq) in acetonitrile (0.5M) was placed into a Duran bottle and stirred until the solution was plenarily homogeneous. In another

Duran bottle was loaded NBS (1.2 eq) and 0.05 eq of $InCl_3$ in 0.6M of acetonitrile labelled as Reagent B. Experiments were conducted in a 10ml standard PFR coil reactor (ID : 1.7mm) (Figure S-1) at the desired flow rate of 40°C exposed to white light (broad spectrum). The product was collected from the outlet of the reactor and analyzed by thin layer chromatography (TLC, Mobile phase 7:3 Ethyl acetate and n-hexane) and NMR. Vapourtec R-Series software calculates the "steady state" part of the reaction output and only the steady state section of the reaction product was collected for analysis and workup

Workup: The reaction was added 10Vol of purified water wrt toluene derivative, extracted twice with 2-Methyl THF, further the organic layer was washed utilizing brine solution, dried over sodium sulfate, filtered, and concentrated thoroughly. The crude sample was purified in two different methods.

Purification method-A: The crude sample was added 30ml of 1:1 mixture of dichloromethane and n-hexane and stirred for 30 minutes, filtered the white precipitate, organic layer collected was evaporated under the reduced pressure to yield its corresponding benzyl bromide.

Purification method-B: The crude sample was purified by flash column chromatography using n-Hexane/ethyl acetate as the eluent (1:1 mixture)

Purification method - C: The product collected from the outlet of the reactor was concentrated and purified by flash column chromatography using 10% Methanol in Dichloromethane.

Table S1: Study of optimum reaction conditions.

Entry	Solvent	Catalyst	T (°C)	Flow rate (ml/min)	Res.time (min)	Conversion (2)[c]
1	Acetonitrile	$SnCl_4$ (0.05eqv)	70	0.20	50	15%
2	THF	$SnCl_4$ (0.05eqv)	40	0.20	50	10%
3[a]	THF	$InCl_3$ (0.05eqv)	40	0.20	50	-
4	Ethyl acetate	$InCl_3$ (0.05eqv)	40	0.20	50	~7%
5	Acetonitrile	$InCl_3$ (0.01eqv)	40	0.20	50	80%
6	Acetonitrile	$InCl_3$ (0.025eqv)	40	0.20	50	88%
7[b]	Acetonitrile	$InCl_3$ (0.05eqv)	40	0.20	Over night	82%

[a]Reaction charred; get

[b]Reaction performed in batch [c]Product formation (2) monitored by TLC and NMR; *All the reactions were performed using 4mmol scale, 1.2 eqv of NBS, ambient light (white light, broad spectrum), 10 mL standard PFA coiled reactor is used

Figure S-1 : Standard 10ml PFR coil used for the benzylic bromination experiments

Benzyl Bromide [1,2] (Table 1, entry 1, 4a, Purification A, Figure S-2). Yield: 1039mg, Pale yellow liquid (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.36 (m, 5H), 4.54 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.91, 129.12, 128.6, 128.4, 33.73; MS-EI: m/z 169.90, 91.20, 65.10, 39.0

4-Bromobenzyl Bromide[3] (Table 1, entry 2, 4b, Purification B, Figure S-3). Yield: 760mg, White solid (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.85, 131.91, 130.69,122.30, 32.60; MS-EI: m/z 248, 169, 92.0

3-Bromobenzyl Bromide[4] (Table 1, entry 3, 4c, Purification B, Figure S-4). Yield: 630mg, Half white solid (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.77 131.95, 130.88,122.44, 32.42 MS-EI: m/z 247, 170.50, 92.30

4-Chloro benzyl Bromide[3] (Table 1, entry 4, 4d, Purification B, Figure S-5). Yield: 580mg, White solid (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 -7.26 (s, 4H), 4.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.61, 134.41, 130.96, 129.14, 128.54, 127.57, 31.90; MS-EI: m/z 203, 124.40, 92.40

2-Chloro benzyl Bromide[5] (Table 1, entry 5, 4e, Purification B, Figure S-6). Yield: 545mg, Clear liquid (66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 2H), 7.25(m, 2H), 4.59 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.39, 134.28, 131.26, 130.01, 127.30, 30.69; MS-EI: m/z 204, 124.40, 88.70

4-tert-Butylbenzyl Bromide[1] (Table 1, entry 6, 4f, Purification A, Figure S-7). Yield: 650mg, White solid (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.43 (m, 4H), 4.58 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.57, 134.75, 128.79, 125.83, 34.67, 33.62, 31.19; MS-EI: m/z 226, 146.20, 131.20, 116.40

4-Sulfonyl chloride Benzyl Bromide[6] (Table 1, entry 7, 4g, Purification A, Figure S-8). Yield: 780mg, White crystalline solid, (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 4.50 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.34, 143.87, 130.06, 127.60, 126.91, 126.01, 30.64; MS-EI: m/z 267, 189.0, 124.80, 92, 63, 39

4-Iodo benzyl Bromide[5] (Table 1, entry 8, 4h, Purification A, Figure S-9). Yield: 830mg, White solid (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8 Hz, 2H), 7.12 (d, J = 8 Hz, 2H), 4.40 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.92, 137.38, 130.8, 94.12, 32.51; MS-EI: m/z 297, 216.30

4-Nitro Benzyl Bromide[3] (Table 1, entry 9, 4i, Purification B, Figure S-10). Yield: 613mg, Yellow solid (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (d, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 4.50 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.64, 144.73, 129.88, 127.69, 123.95, 30.01; MS-EI: m/z 216, 135, 106, 88.70

4-Cyano Benzyl Bromide[3] (Table 1, entry 10, 4j, Purification B, Figure S-11). Yield: 530mg, White solid, (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63(d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz , 2H), 4.46 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.81, 132.46, 129.31, 118.31, 112.10, 31.50; MS-EI: m/z 195, 115, 88.70

Methyl 4-(bromomethyl)benzoate[7] (Table 1, entry 11, 4k, Purification B, Figure S-12). Yield: 600mg, White solid, (66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8 Hz, 2H), 7.43(d, J = 8 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.43, 142.57, 130.02, 128.98, 52.15, 32.19; MS-EI: m/z 227.80, 149.80, 89.80

4-(Bromomethyl)pyridine[8], (Table 1, entry 12, 4l, Purification C, Figure S-13). Yield: 400mg, Pale yellow white solid, (59%). ^{1}H NMR (400 MHz, D_20): δ 9.05 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H), 4.63 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.31, 146.37, 127.96, 61.51; MS-EI: m/z 170.90, 92.50, 78.90.

2-Bromomethylphenylboronic acid pinacol ester[9], (Table 1, entry 13, 4m, Purification B, Figure S-14). Yield: 590mg, Pale yellow solid, (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, 1H), 7.42(m, 3H), 4.91 (s, 2H), 1.36 (s, 12H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.22, 136.34, 131.23, 130.03, 127.57, 83.93, 33.93, 24.92; MS-EI: m/z 298.10, 217.20

2-(Bromomethyl)napthalene[10] (Table 1, entry 14, 4n, Purification B, Figure S-15). Yield: 590mg, Pale yellow liquid, (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84−7.79 (m, 4H), δ 7.51−7.47 (m, 3H), 4.65 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.50, 133.14, 133.05, 128.74, 127.93, 127.82, 127.68, 126.73, 126.54, 126.45, 34.03; MS-EI: m/z 219, 140.05, 114.40, 88.0, 62.0

Figure S-2 – ^{1}HNMR of Benzyl bromide (4a)

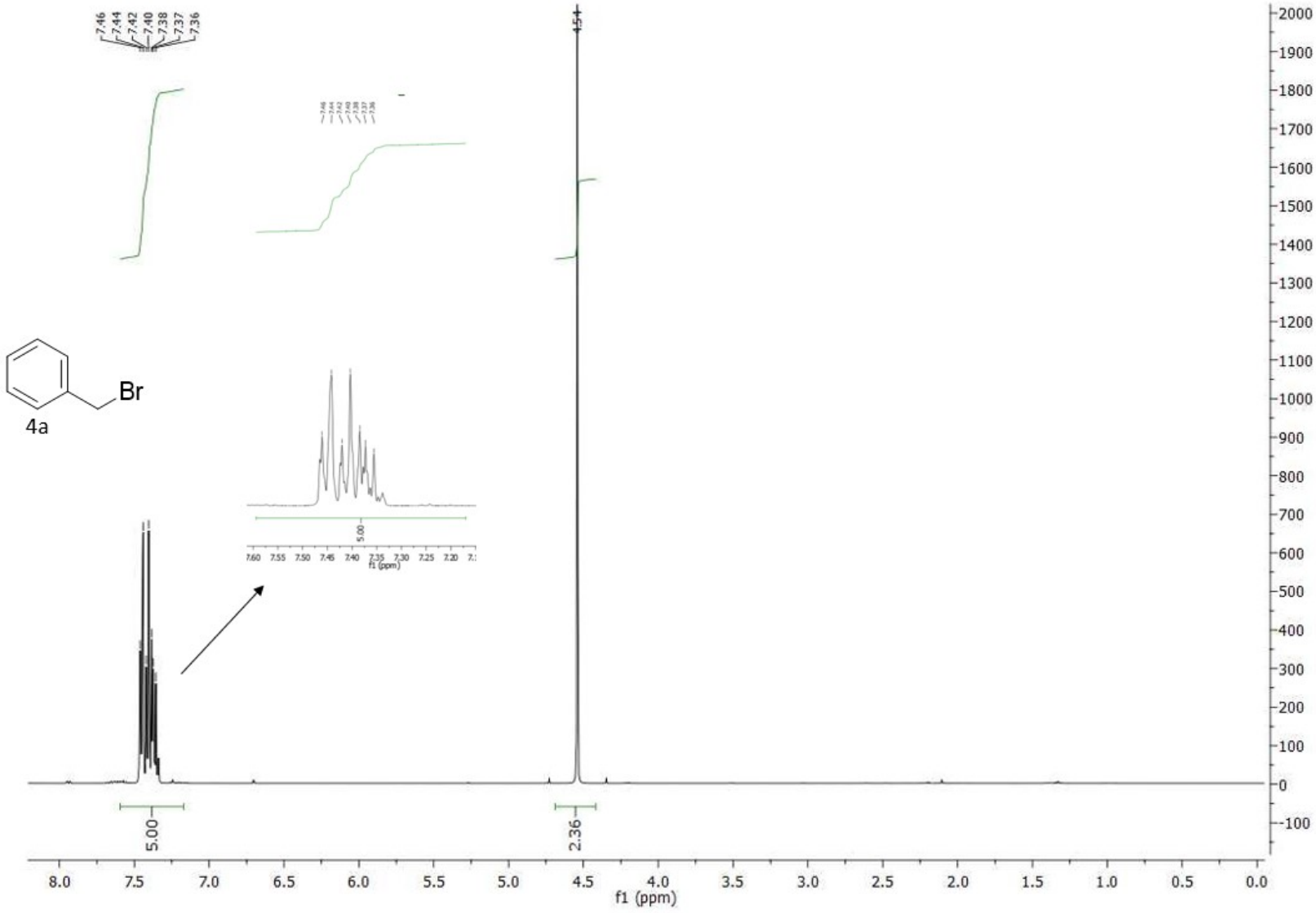


Figure S-2 – ^{13}CNMR of Benzyl bromide (4a)

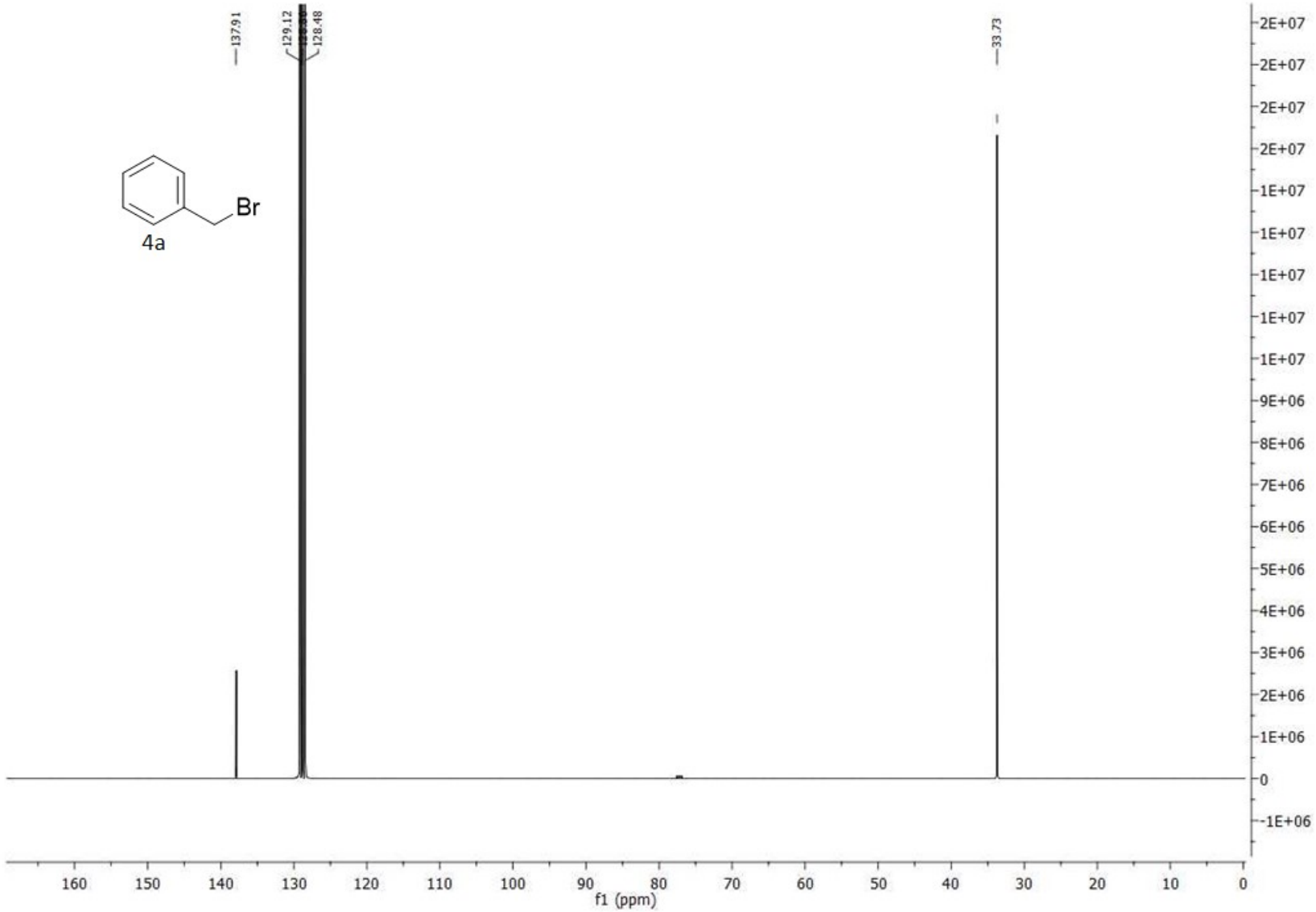


Figure S-3 – [1]HNMR of 4- Bromo Benzyl bromide (4b)

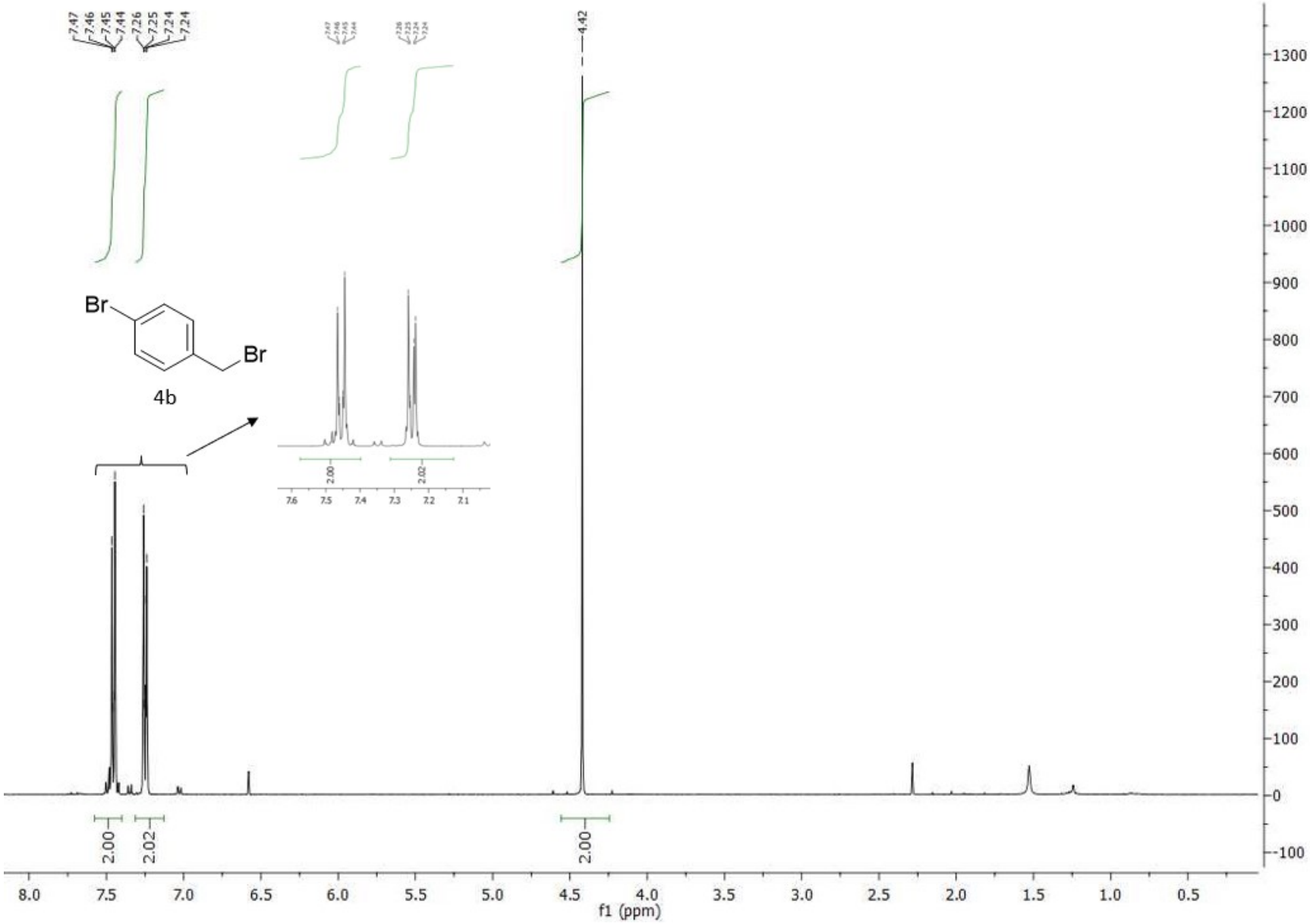


Figure S-3 – ^{13}CNMR of 4-Bromo Benzyl bromide (4b)

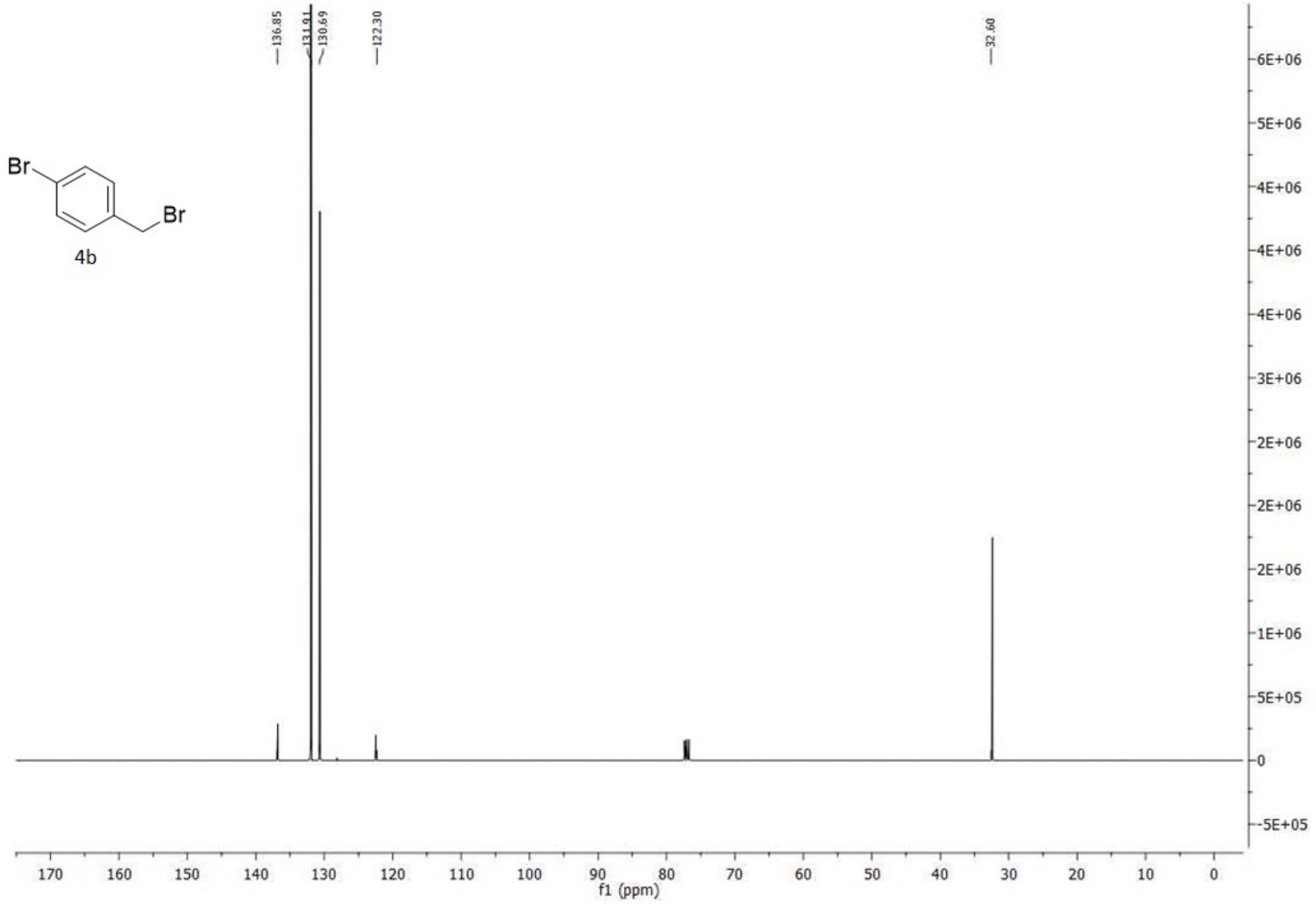


Figure S-4 – [1]HNMR of 3- Bromo Benzyl bromide (4c)

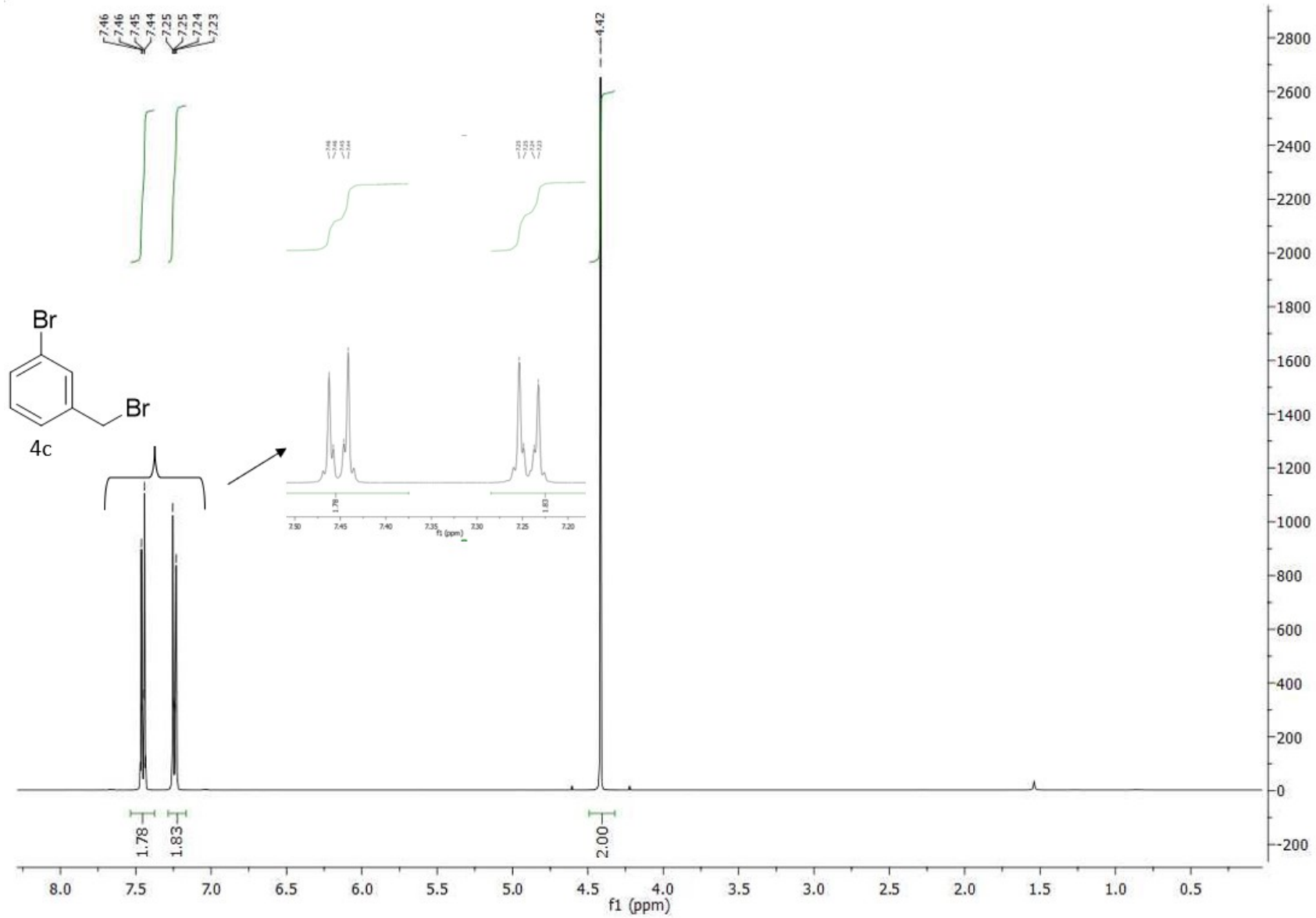


Figure S-4 – ^{13}CNMR of 3- Bromo benzyl bromide (4c)

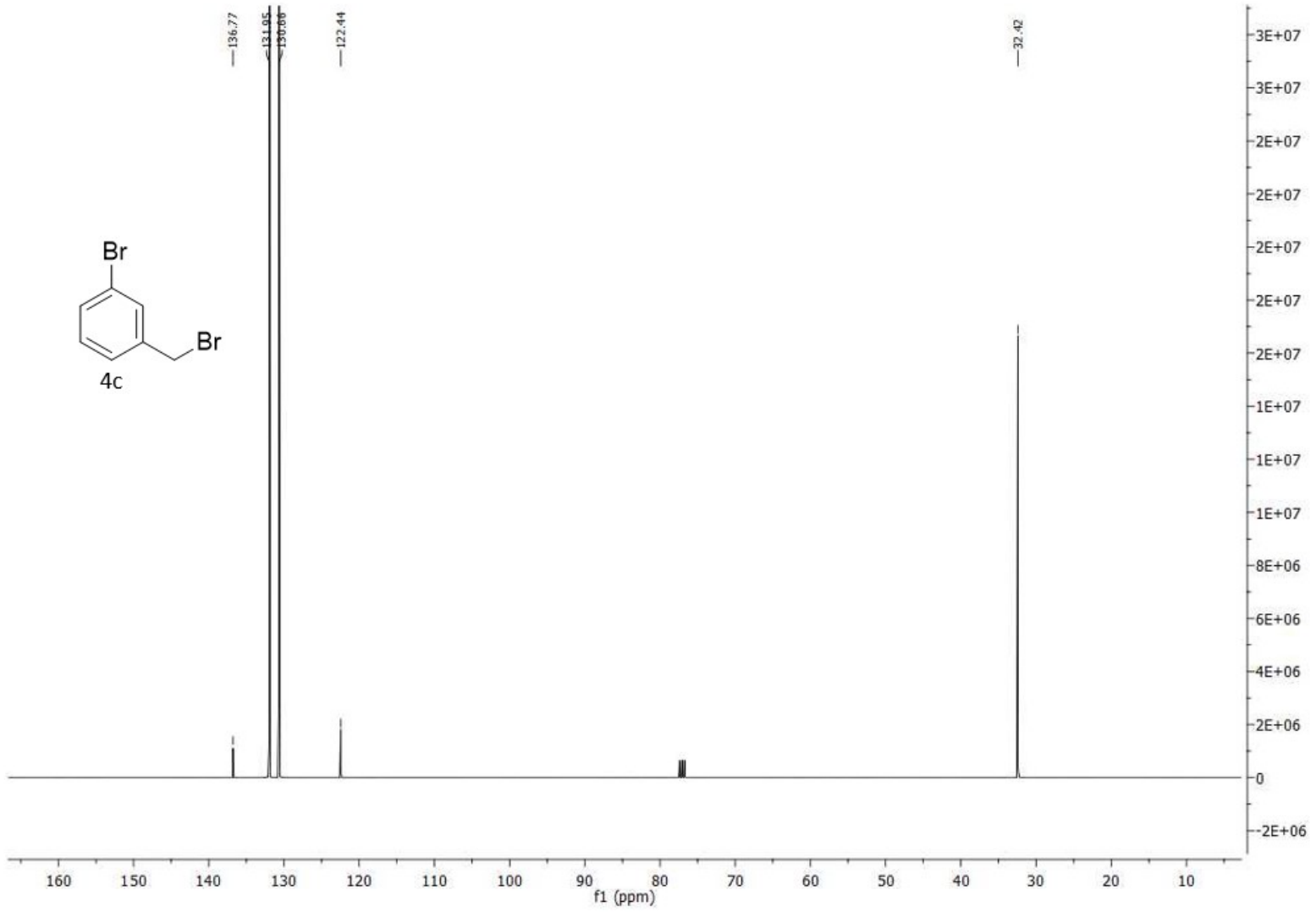


Figure S-5 – [1]HNMR of 4-Chloro Benzyl bromide (4d)

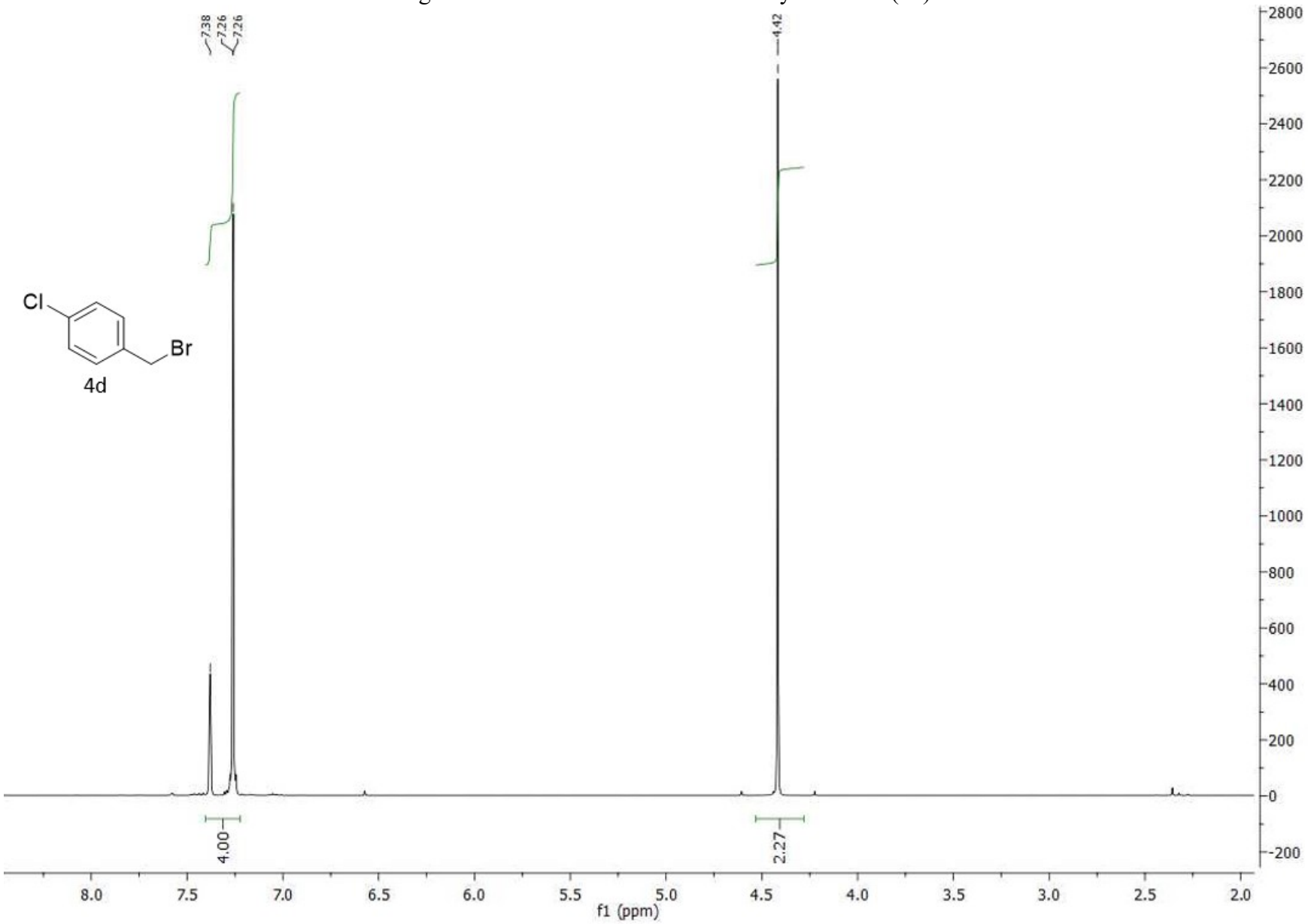


Figure S-5 – ^{13}CNMR of 4-Chloro Benzyl bromide (4d)

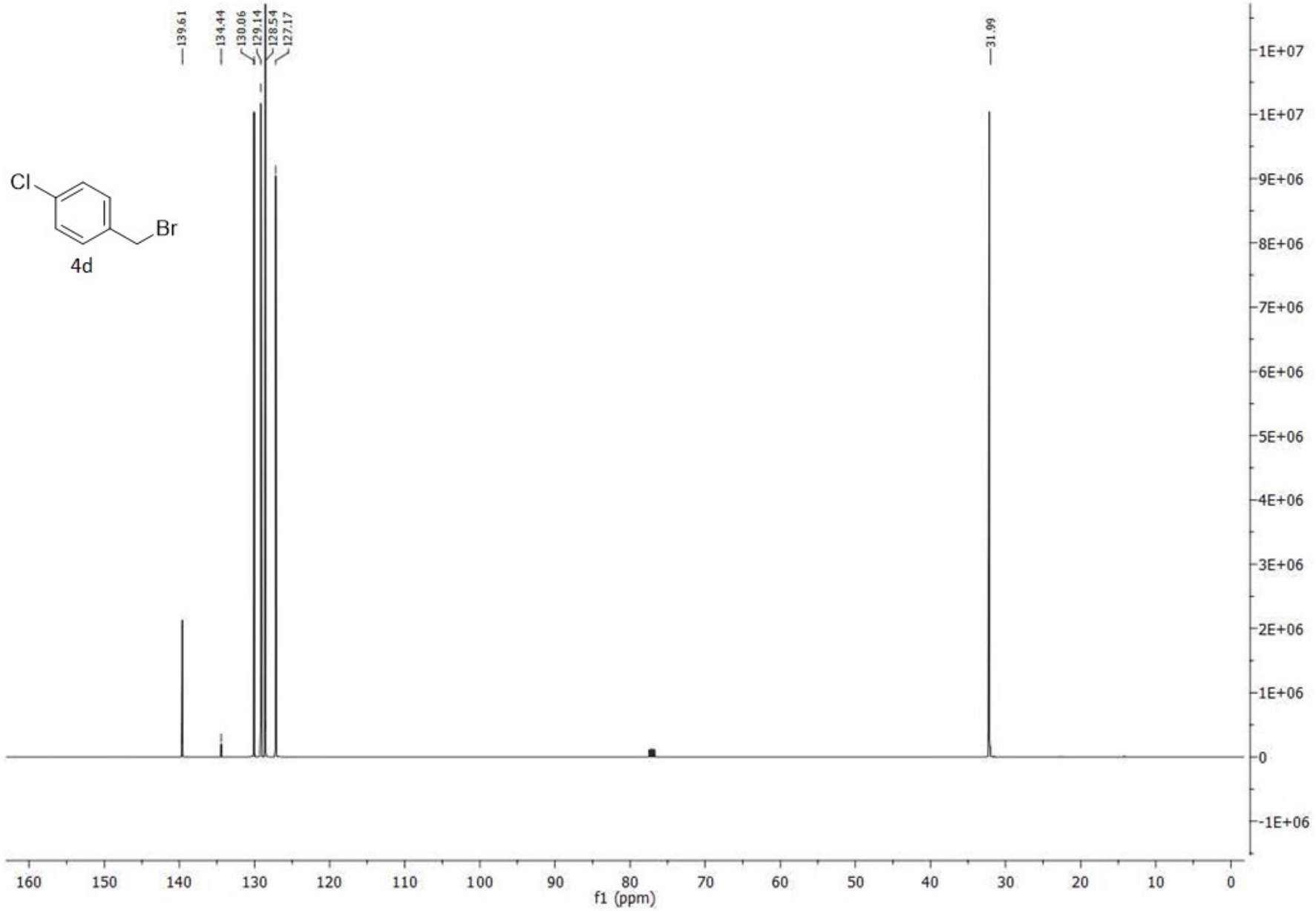


Figure S-6 – [1]HNMR of 2- Chloro Benzyl bromide (4e)

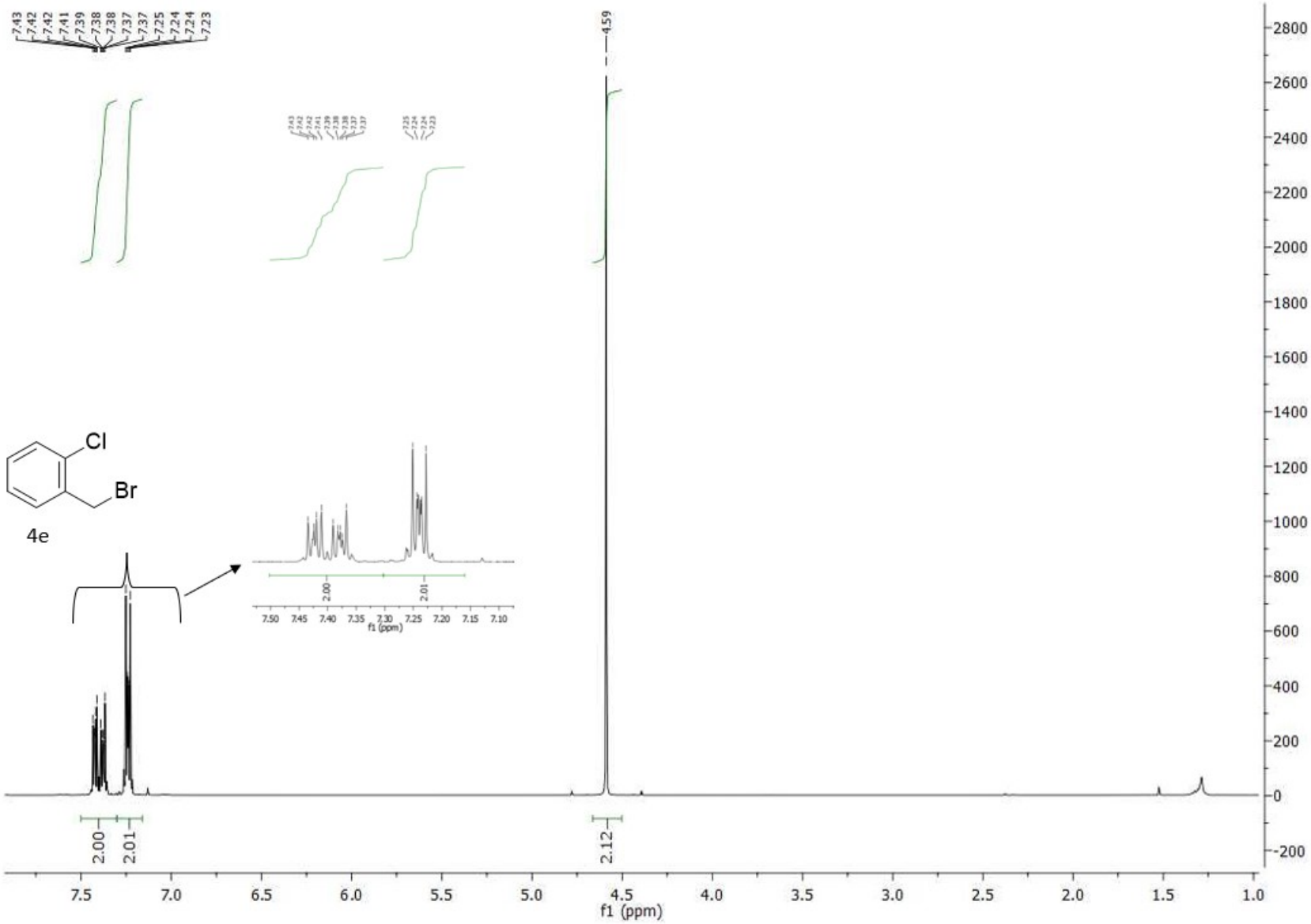


Figure S-6 – ^{13}CNMR of 2-Chloro Benzyl bromide (4e)

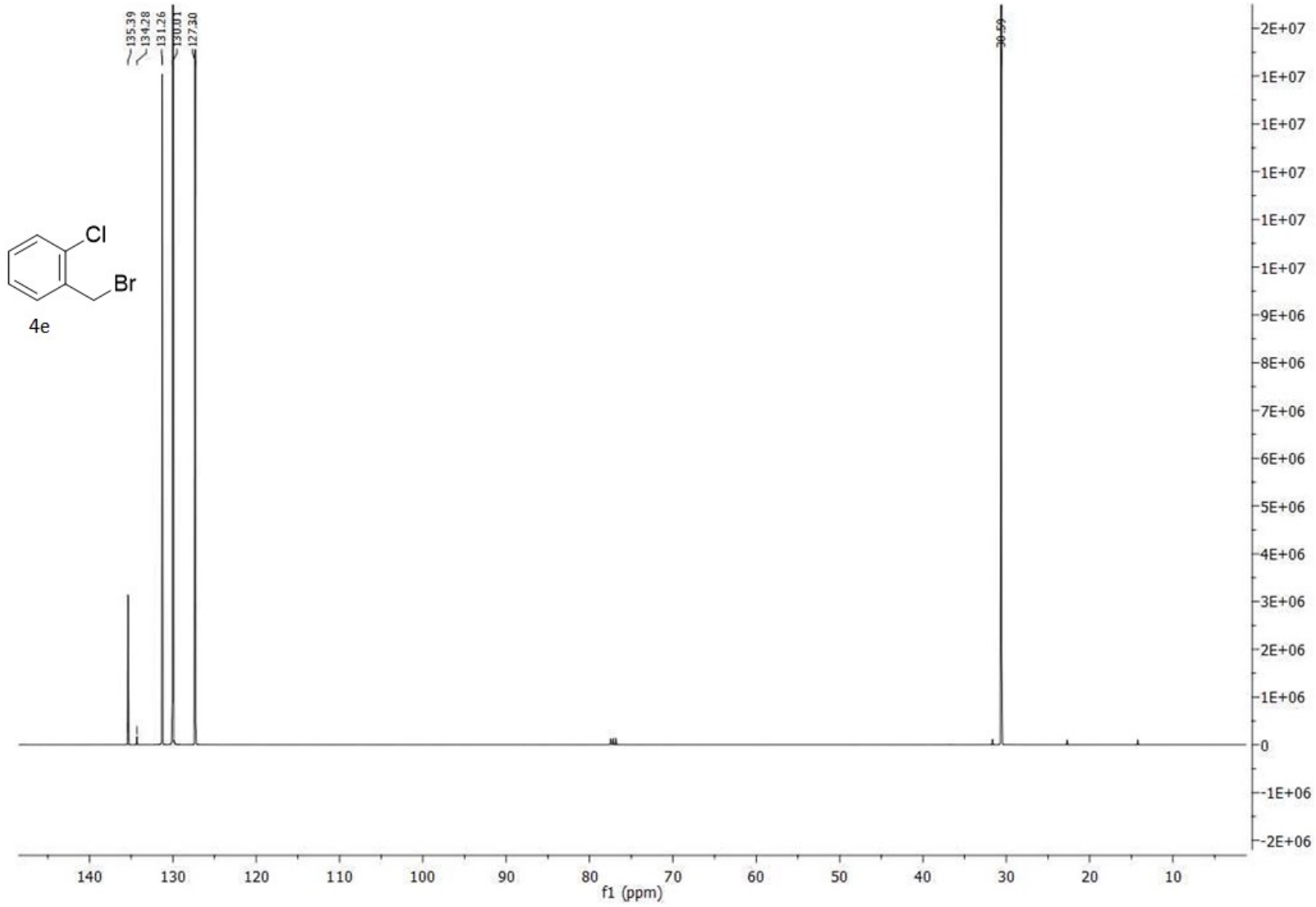


Figure S-7 – ^{1}HNMR of 4-tert-Butylbenzyl Bromide (4f)

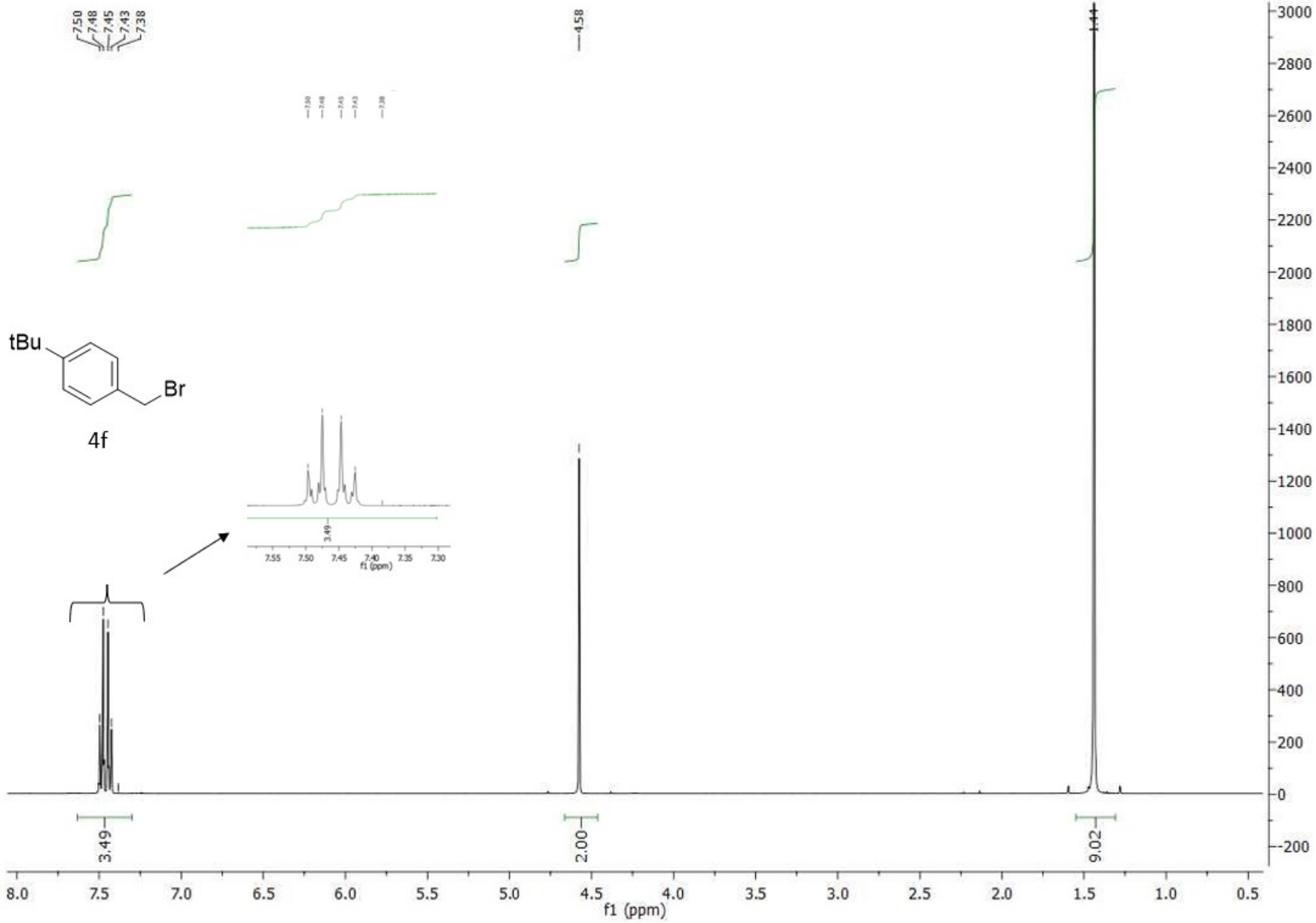


Figure S-7 – ^{13}CNMR of 4-tert-Butylbenzyl Bromide (4f)

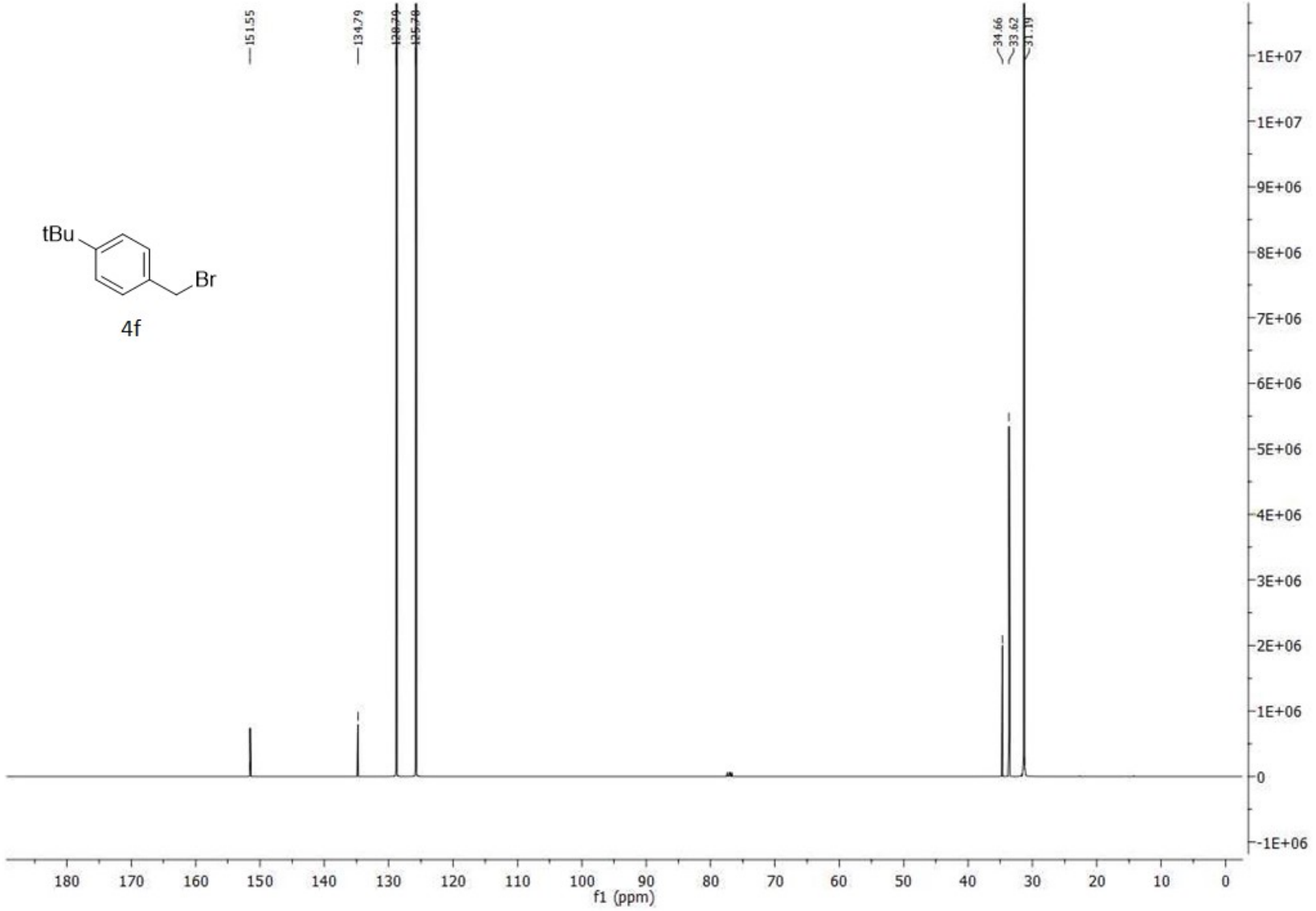


Figure S-8 – ^{1}HNMR of 4-Sulfonyl Chloride Benzyl Bromide (4g)

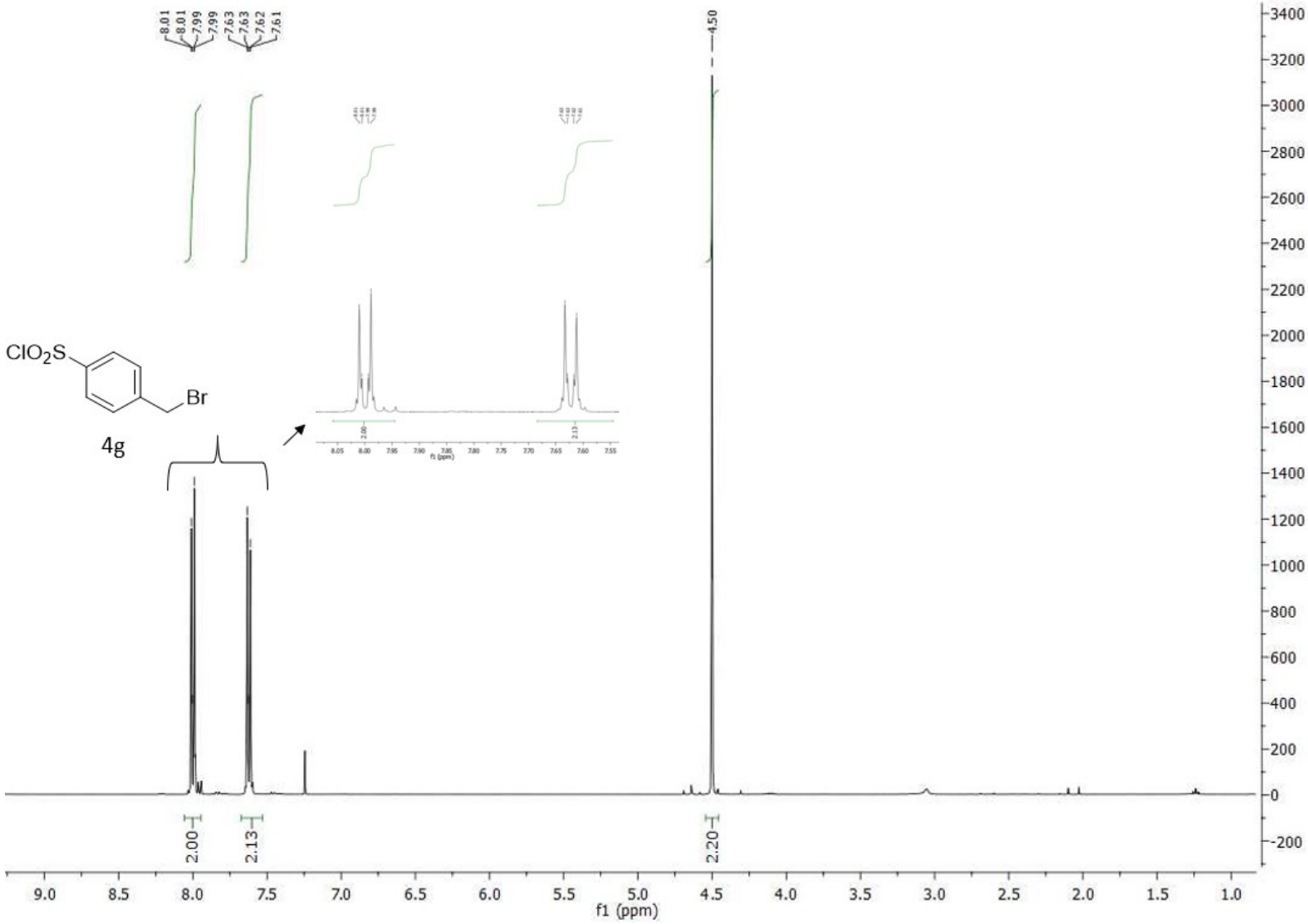


Figure S-8 – ^{13}CNMR of 4-Sulfonyl Chloride Benzyl Bromide (4g)

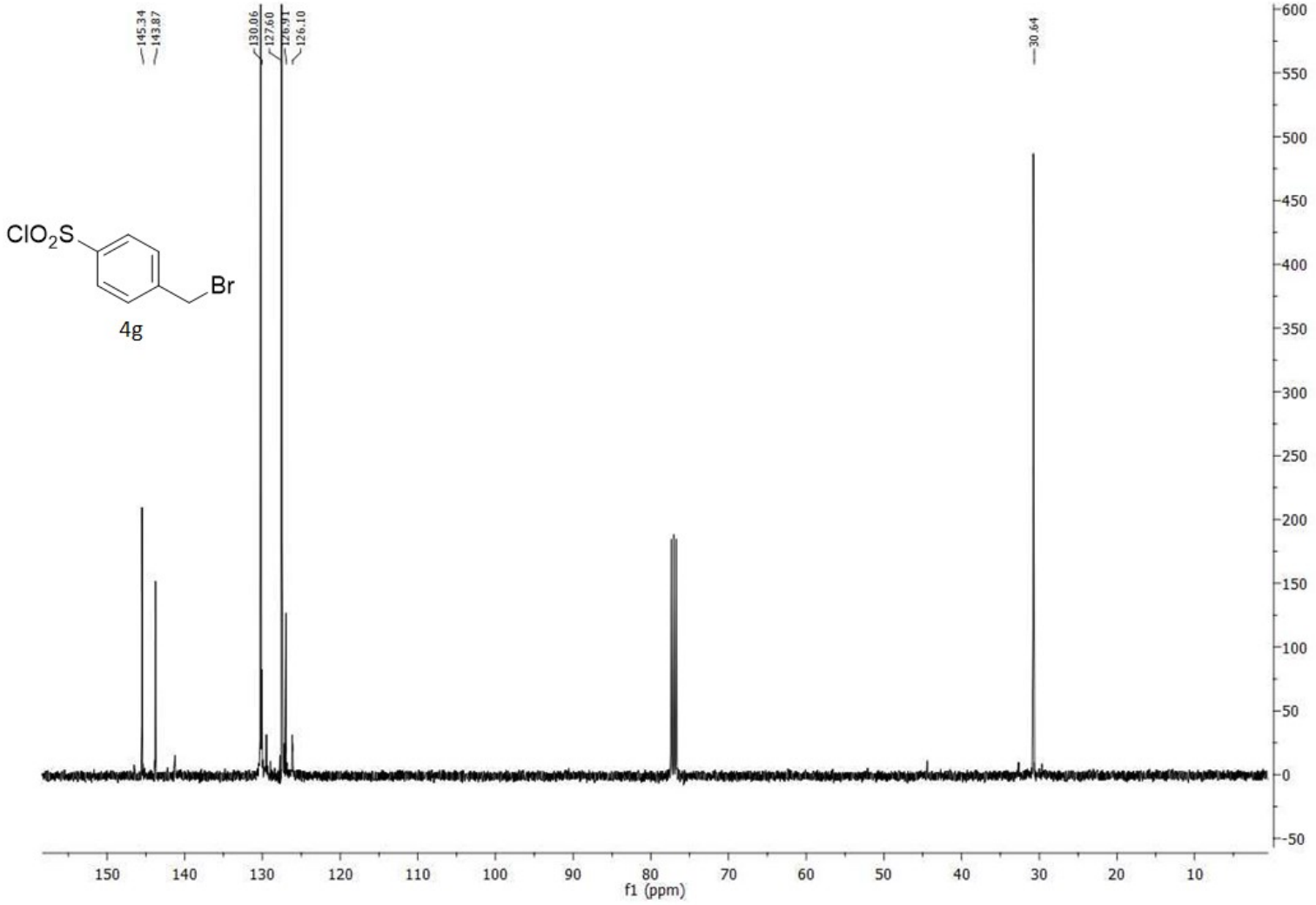


Figure S-9 – [1]HNMR of 4-Iodo Benzyl Bromide (4h)

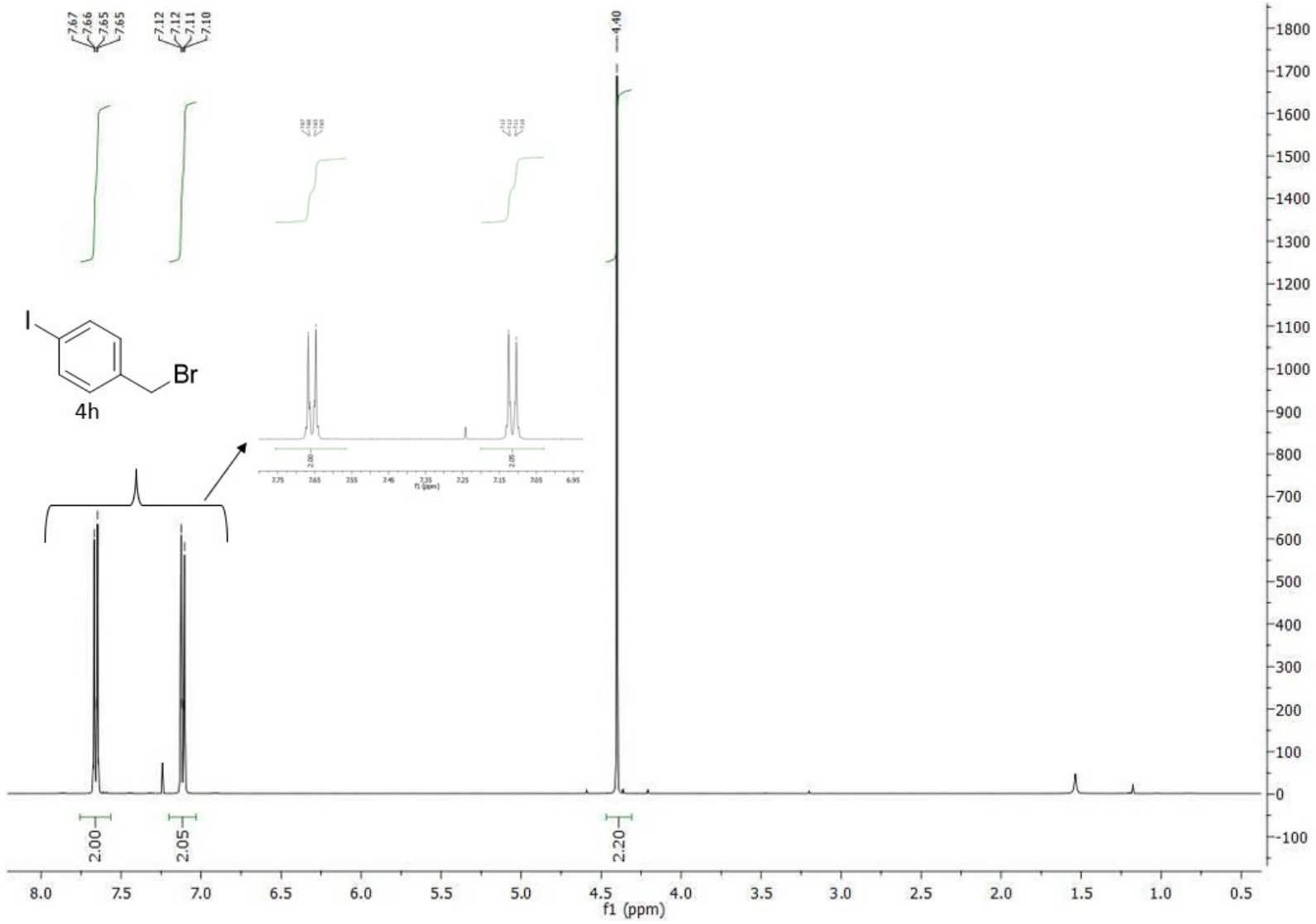


Figure S-9 – ^{13}CNMR of 4-Iodo Benzyl Bromide (4h)

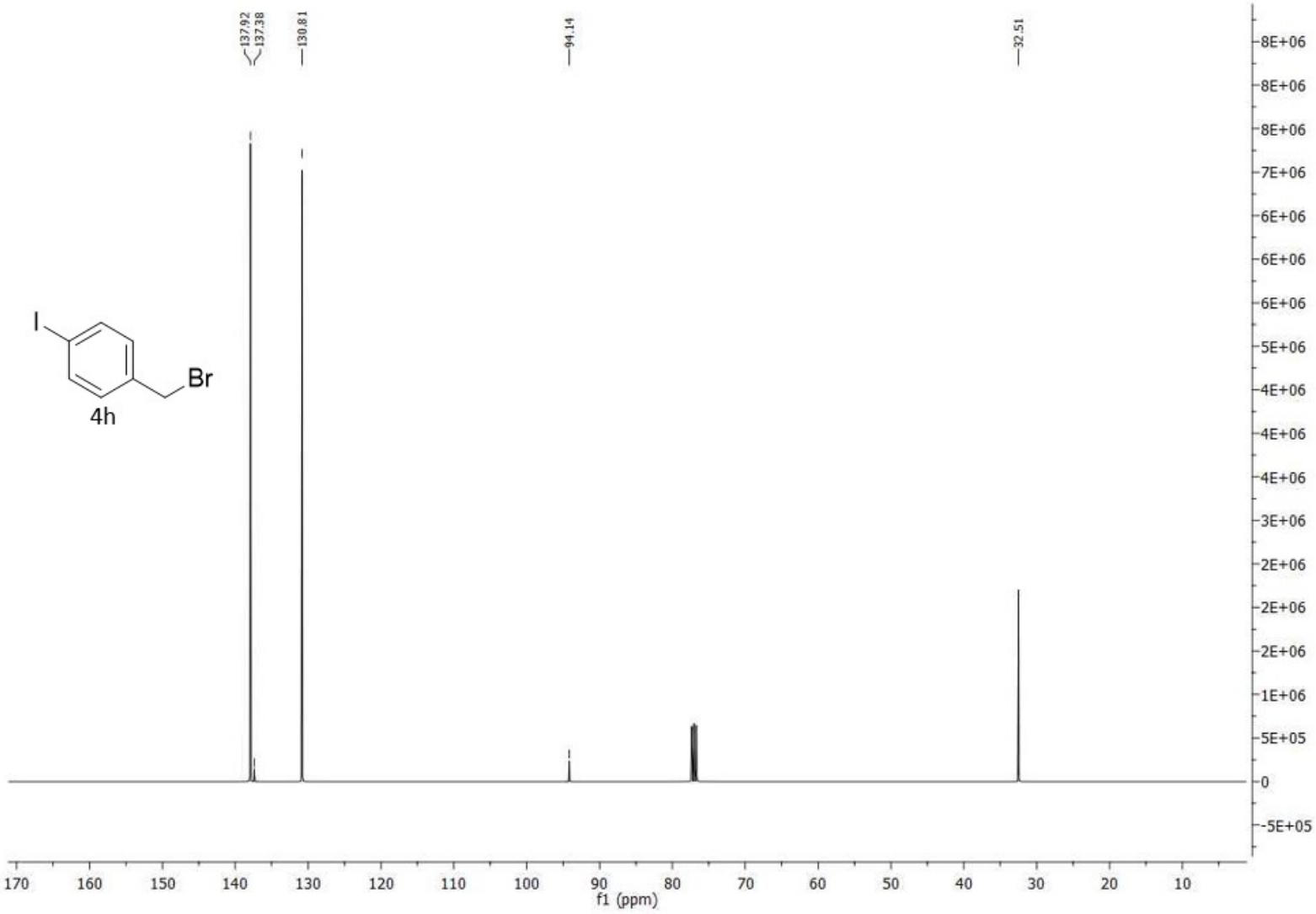


Figure S-10 – ^{1}HNMR of 4-Nitro Benzyl Bromide (4i)

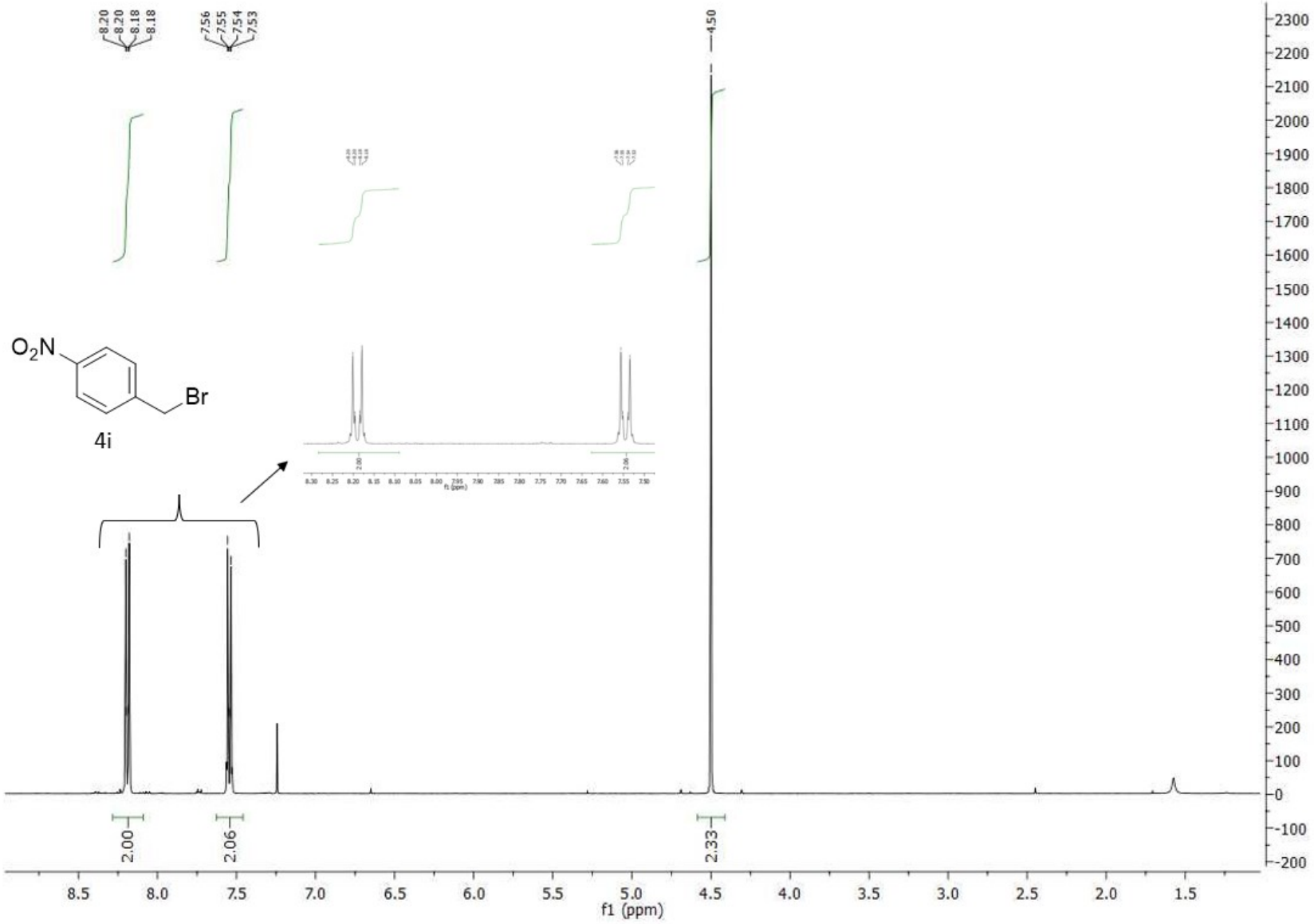


Figure S-10 – ^{13}CNMR of 4-Nitro Benzyl Bromide (4i)

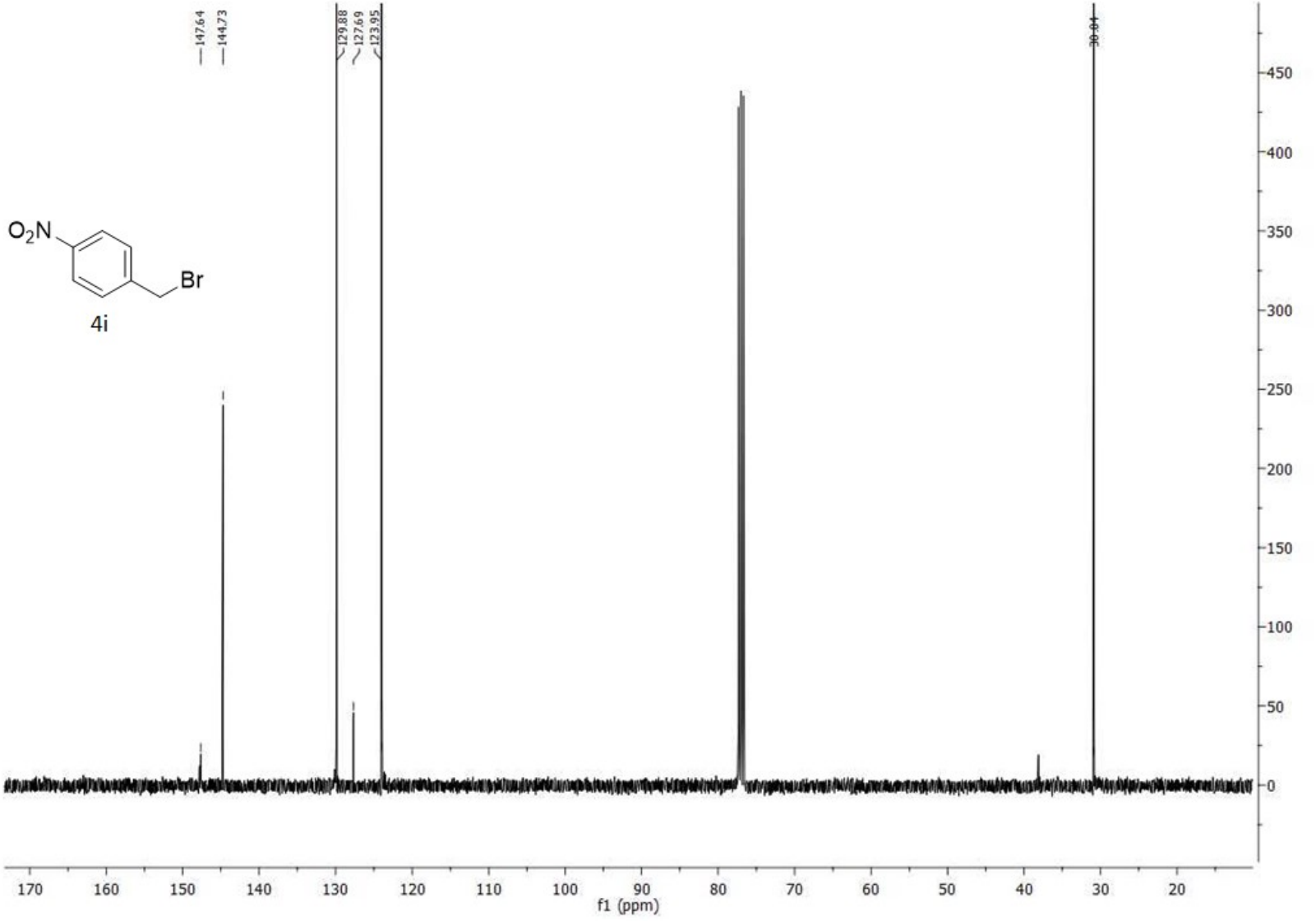


Figure S-11 – ^{1}HNMR of 4-Cyano benzyl Bromide (4j)

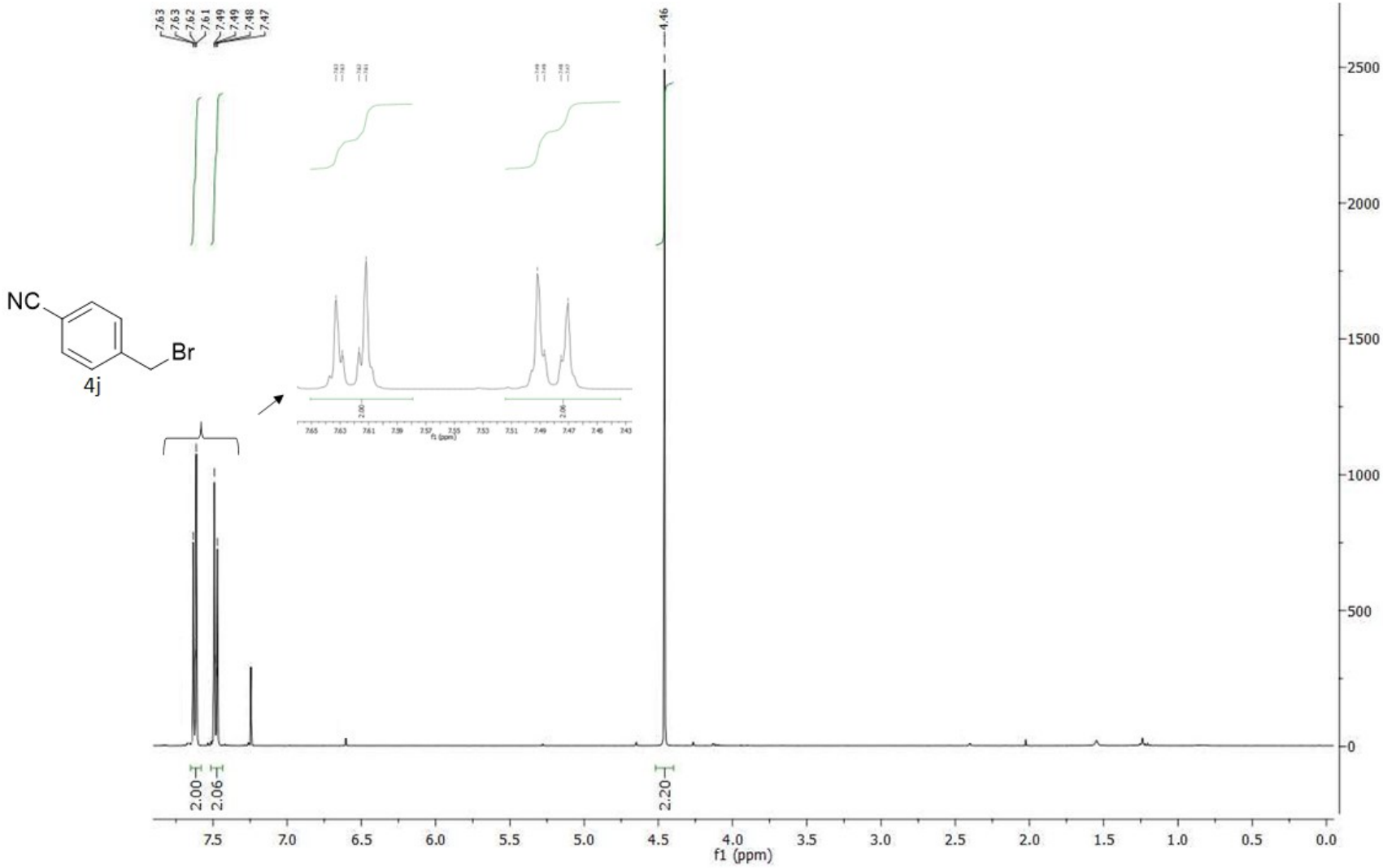


Figure S-11 – ^{13}CNMR of 4-Cyano Benzyl Bromide (4j)

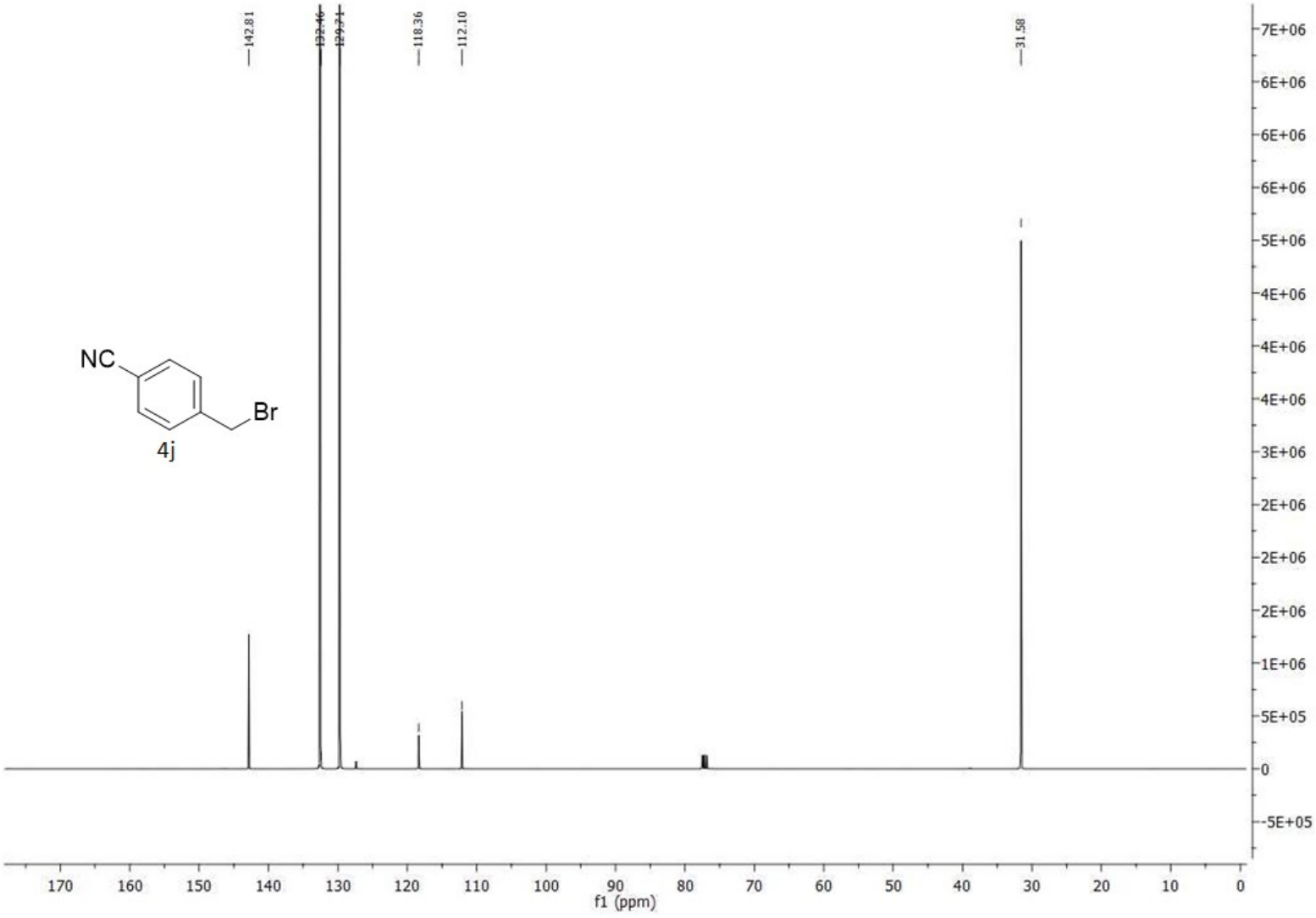


Figure S-12 ^{1}HNMR of Methyl 4-(bromomethyl)benzoate (4k)

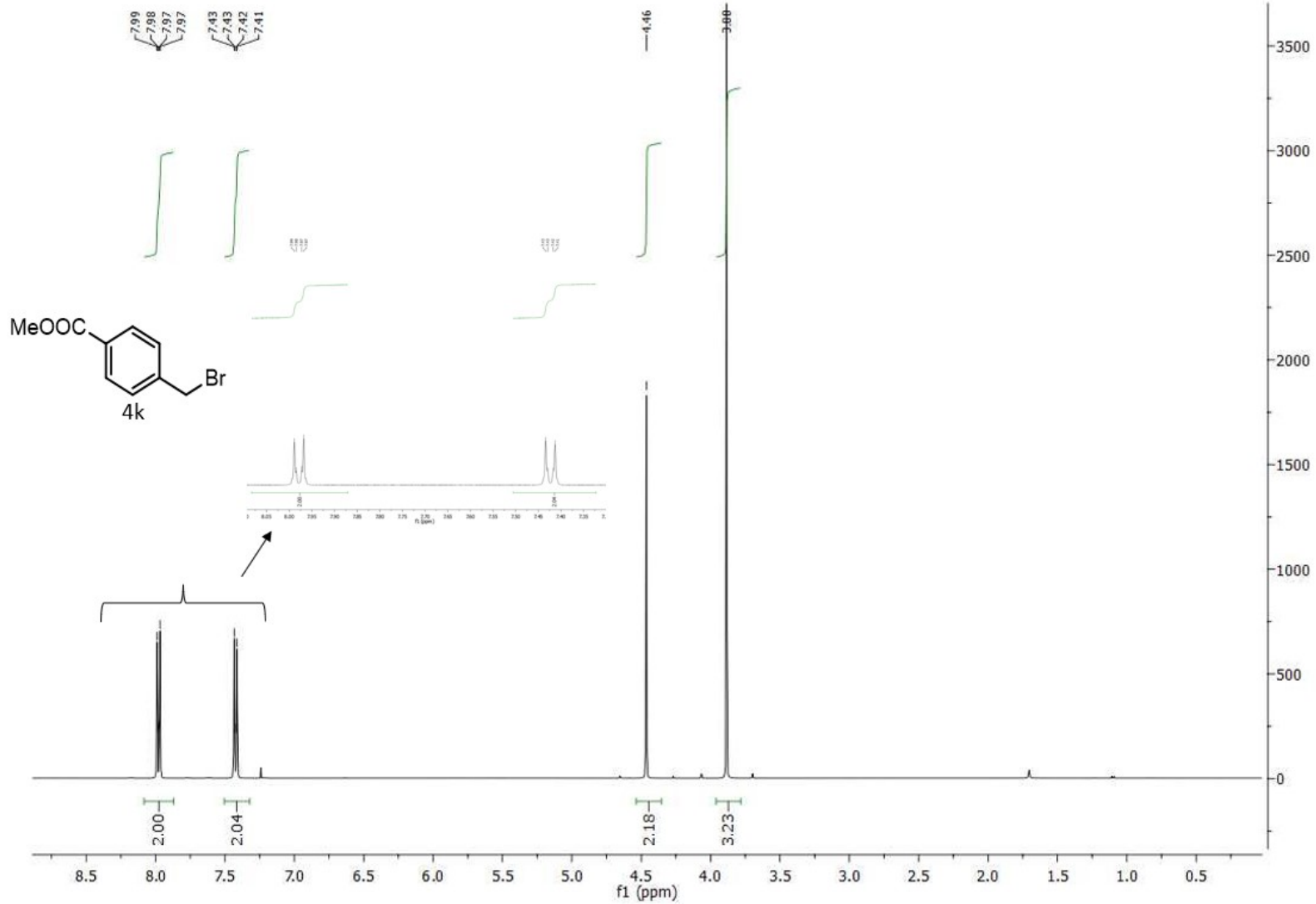


Figure S-12 ^{13}CNMR of Methyl 4-(bromomethyl)benzoate (4k)

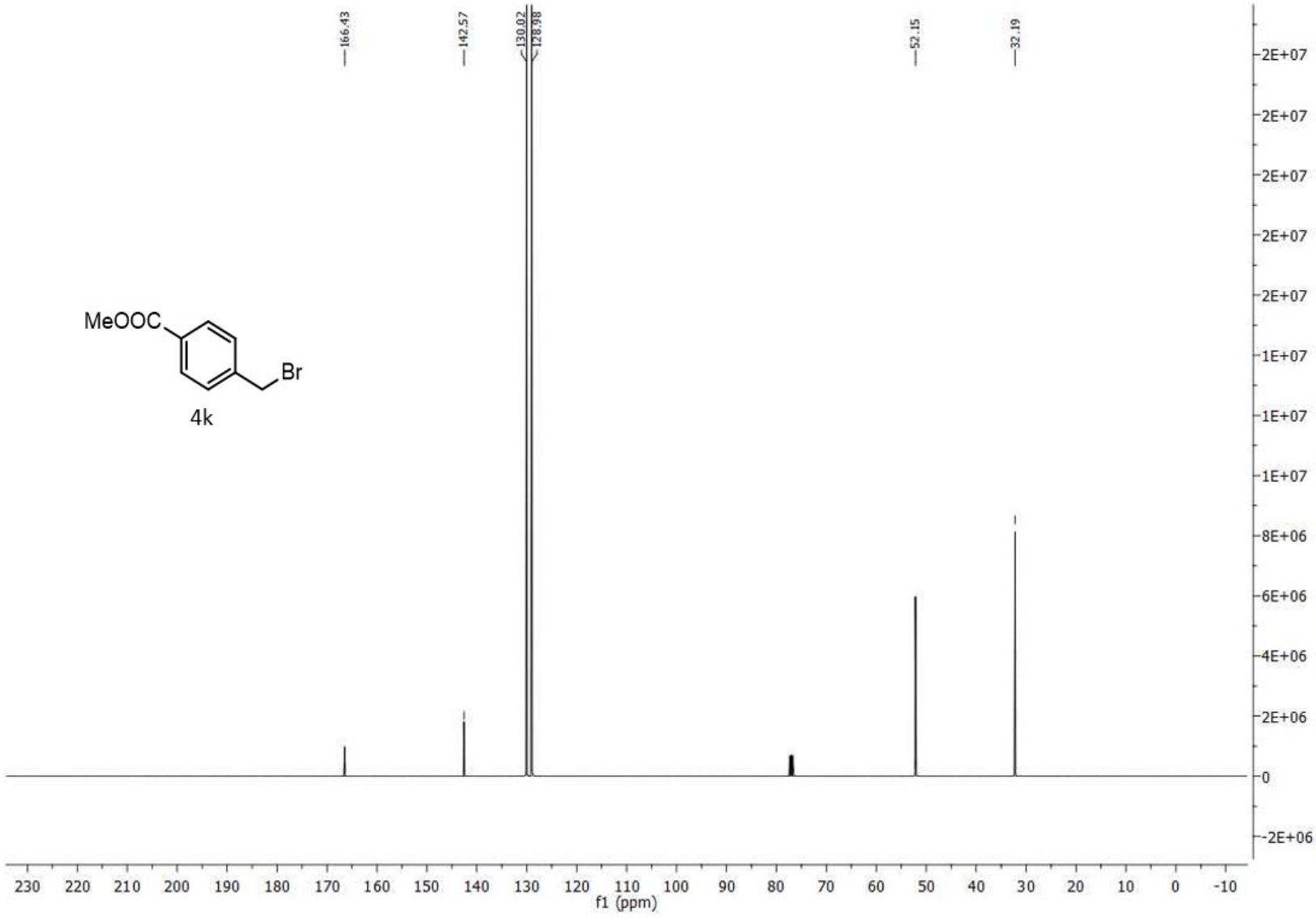


Figure S-13 [1]HNMR of 4-(Bromomethyl)pyridine (4l)

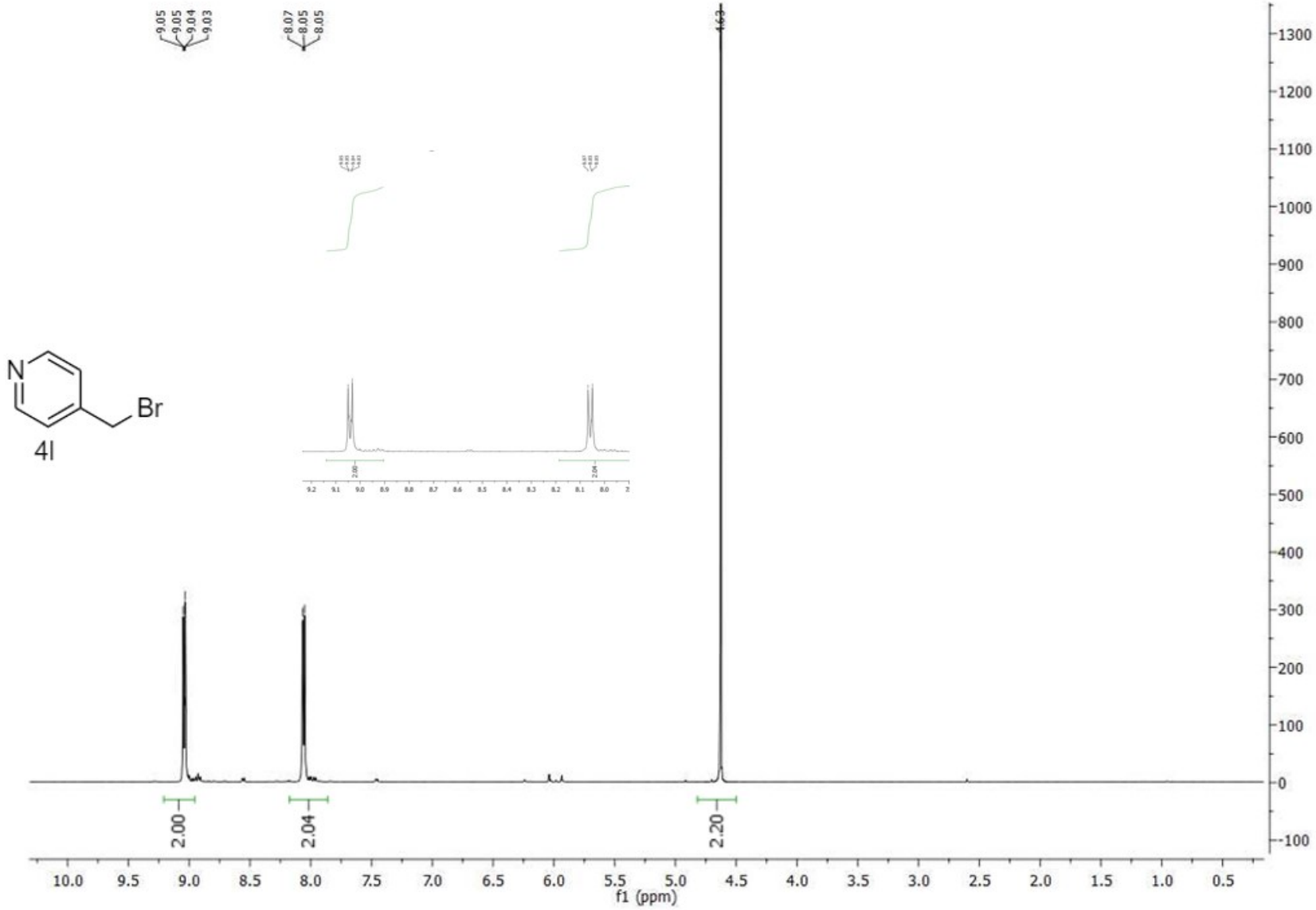


Figure S-13 ^{13}CNMR of 4-(Bromomethyl)pyridine (4l)

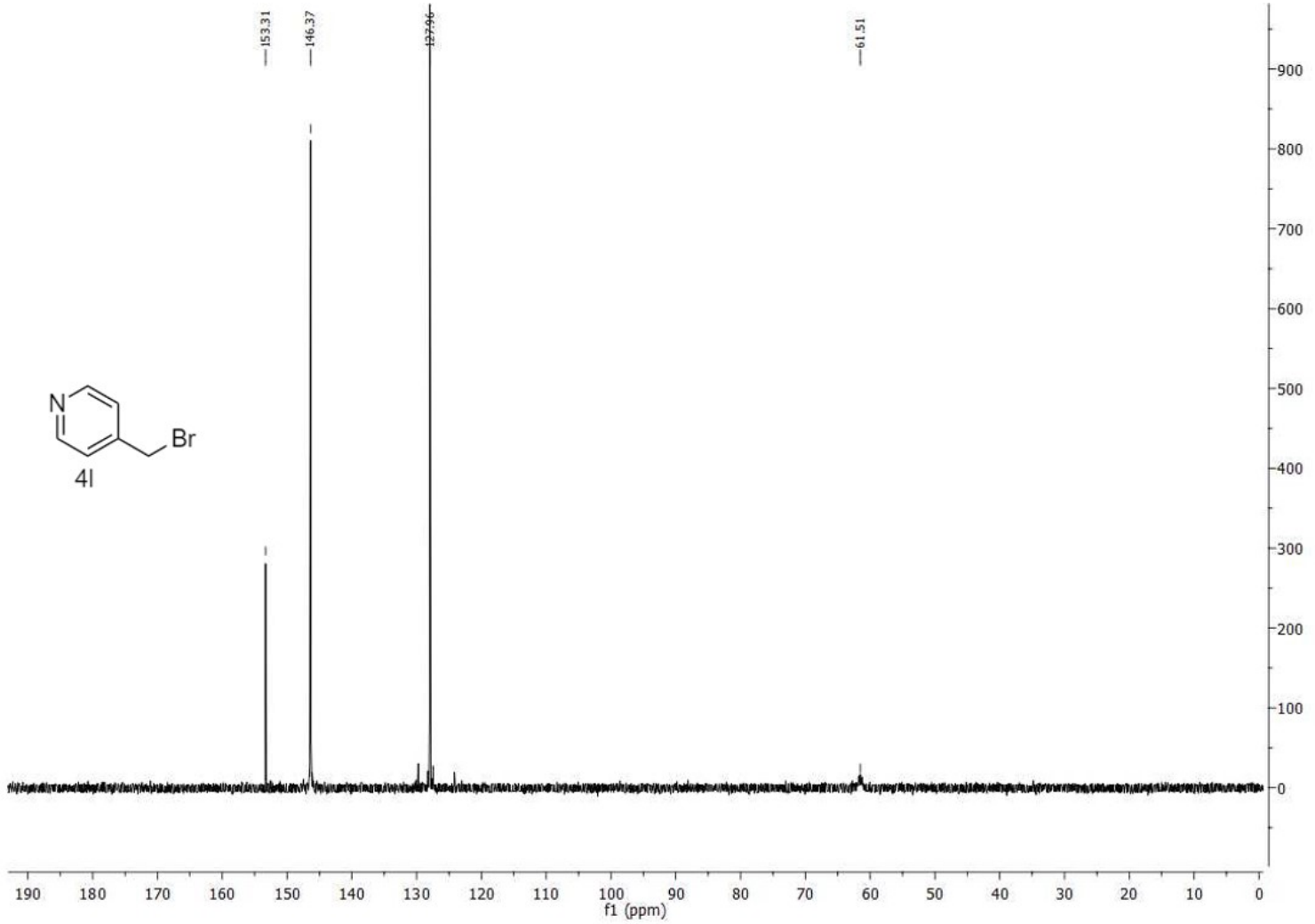


Figure S-14 [1]HNMR of 2-Bromomethylphenylboronic acid pinacol ester (4m)

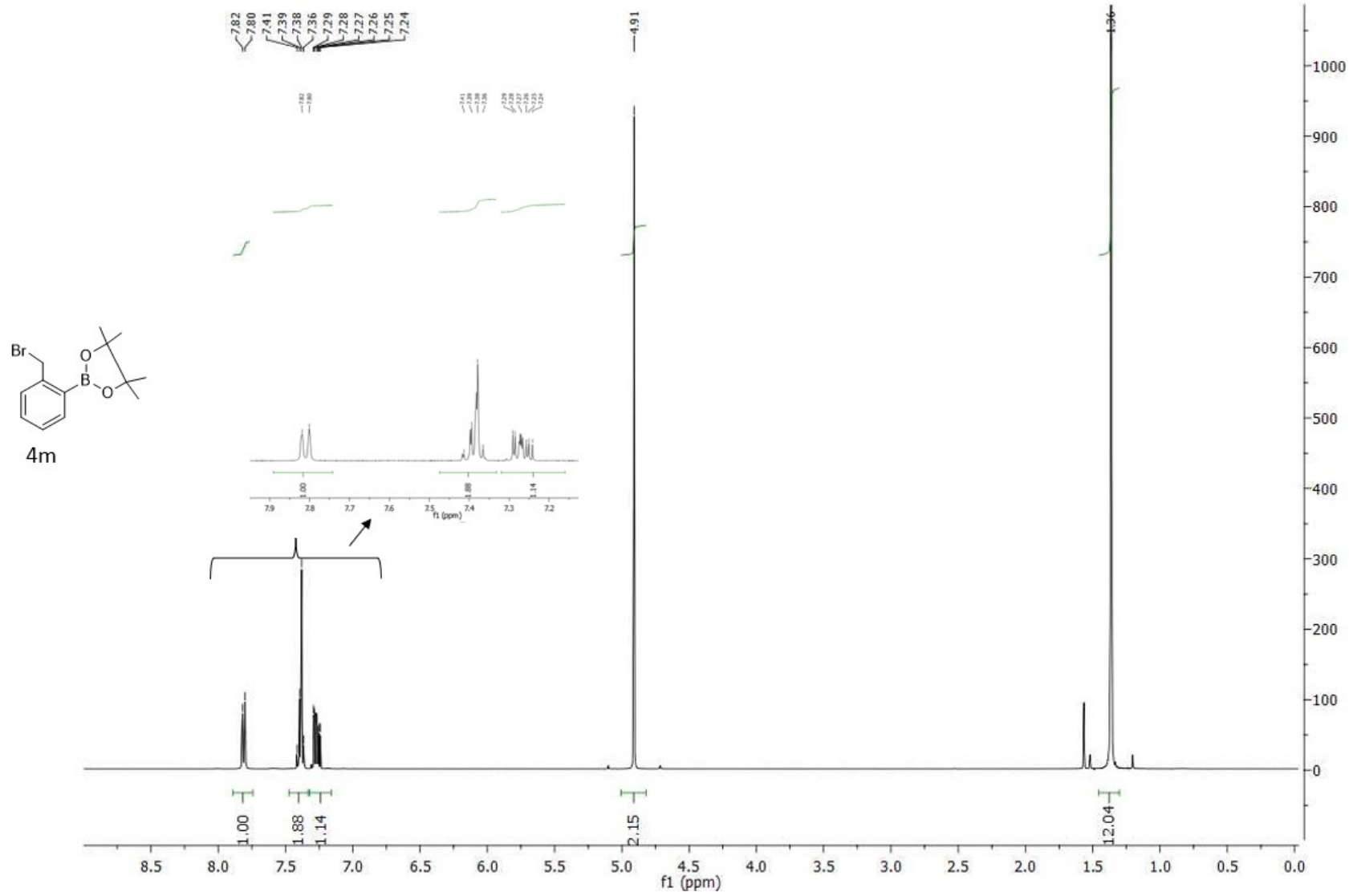


Figure S-14 ^{13}CNMR of 2-Bromomethylphenylboronic acid pinacol ester (4m)

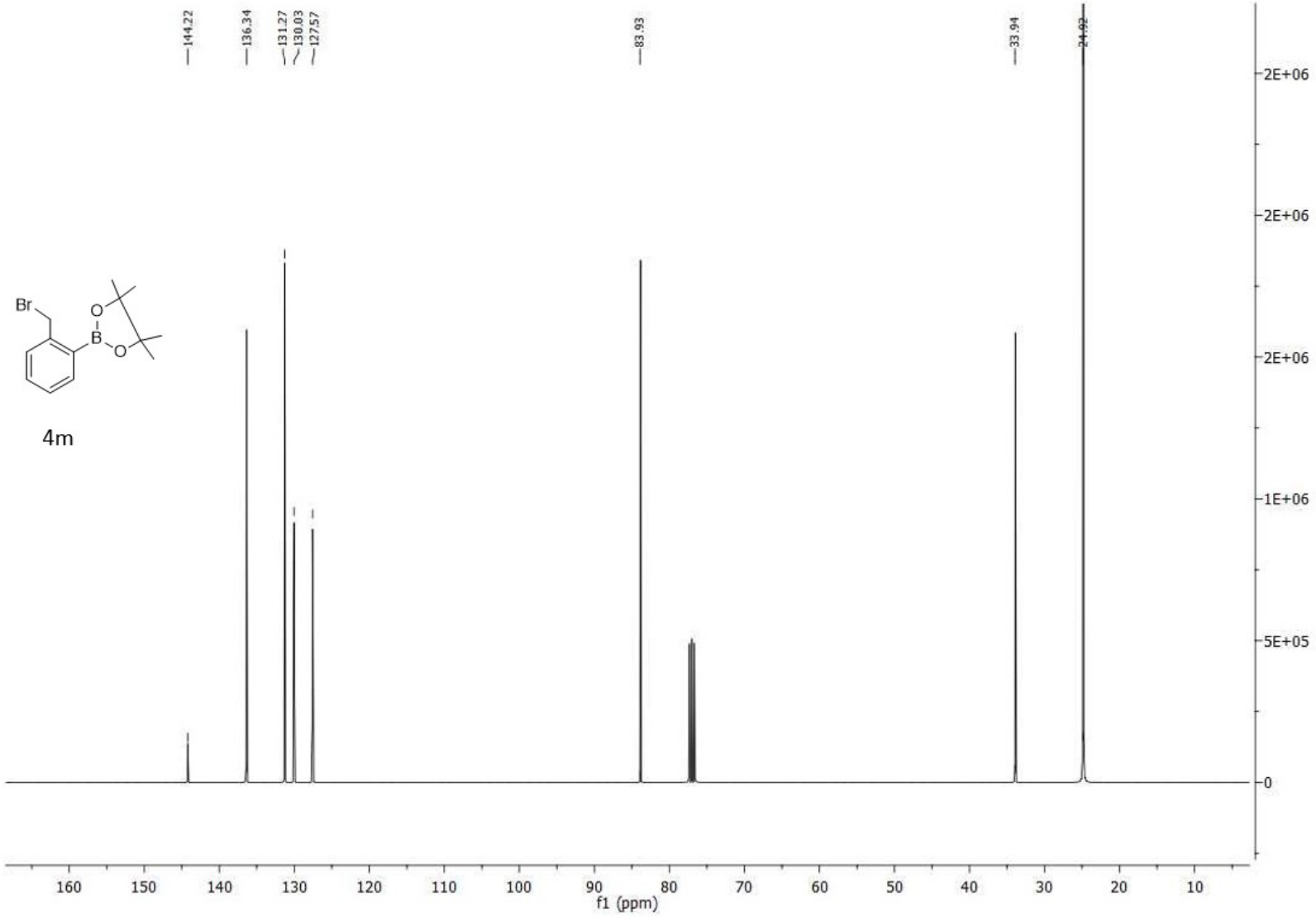


Figure S-15 [1]HNMR of (Bromomethyl)naphthalene (4n)

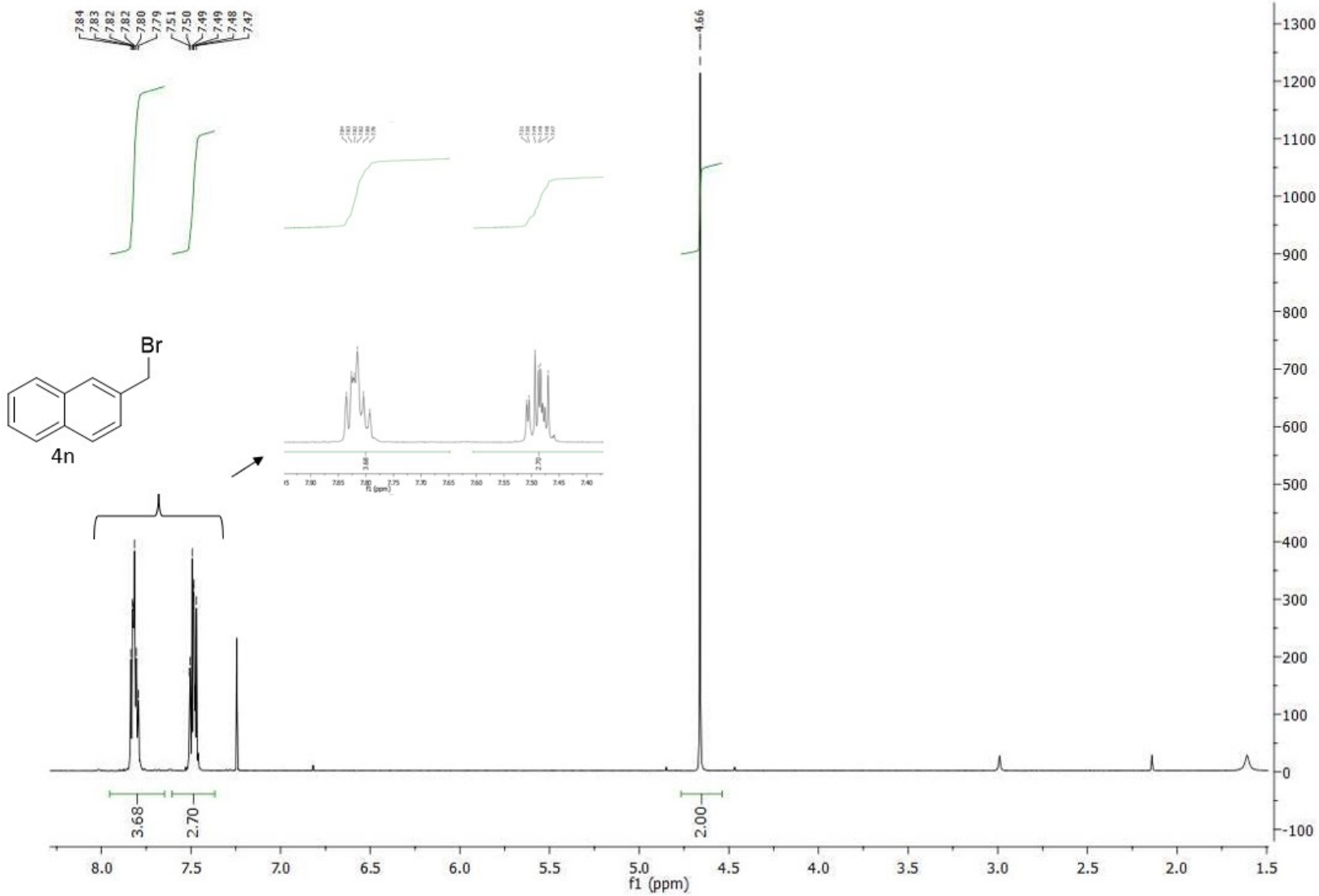
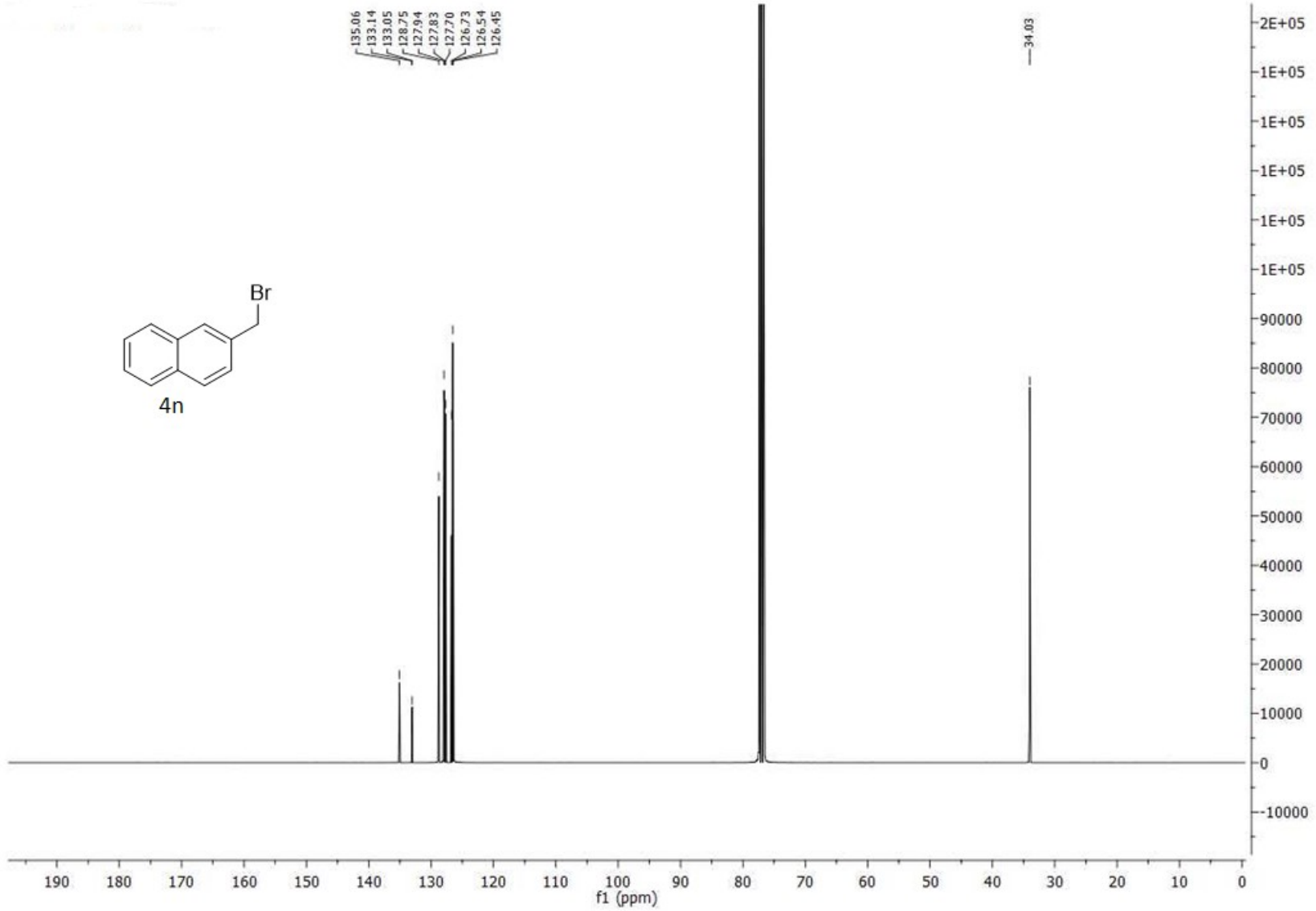


Figure S-15 ^{13}CNMR of (Bromomethyl)naphthalene (4n)



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