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Herein we report the development of radical benzylation reactions of quinones using Selectfluor and catalytic Ag(I) initiators. The reaction is believed to proceed via a C–H abstraction mechanism after Ag(I)-mediated reduction of Selectfluor. This reaction occurs under mild conditions and is effective for a variety of quinones and radical precursors bearing primary ben-zylic carbons. The use of pre-formed Ag(4–OMePy)2NO3 as a catalyst proved effective in improving reaction efficiency by reducing unwanted degradation pathways available to Selectfluor.

Radical Benzylation of Quinones via C–H Abstraction

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ABSTRACT: Herein we report the development of a radical benzylation reaction of quinones using Selectfluor and catalytic Ag(I) initiators. The reaction is believed to proceed via a C–H abstraction mechanism after Ag(I)-mediated reduction of Selectfluor. This reaction occurs under mild conditions and is effective for a variety of quinones and radical precursors bearing primary benzylic carbons. The use of pre-formed Ag(4–OMePy)$_2$NO$_3$ as a catalyst proved effective in improving reaction efficiency by reducing unwanted degradation pathways available to Selectfluor.

Functionalized quinones are well-established as oxidants for organic and organometallic transformations, but are also important structural motifs in biologically active molecules.[1a] Even very simple quinone structures have shown potent biological activity and have been utilized by pharmaceutical and agrochemical industries.[1b-d] Specifically, benzylated quinones have demonstrated enzyme inhibition[1e], antitumor[1f], anticancer[1g], and antifeedant[1h] properties (Figure 1). A benzylated adduct of menadione is responsible for the high potency and antimalarial properties of Plasmidione towards blood-stage parasites.[1j-k]

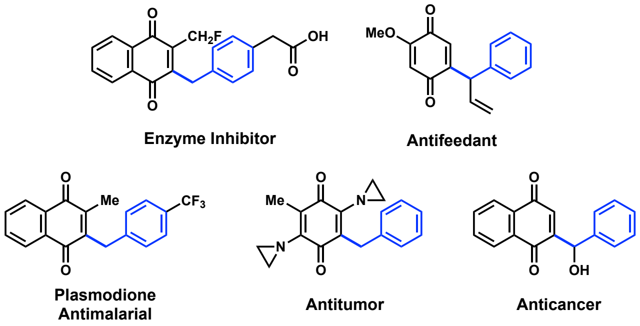
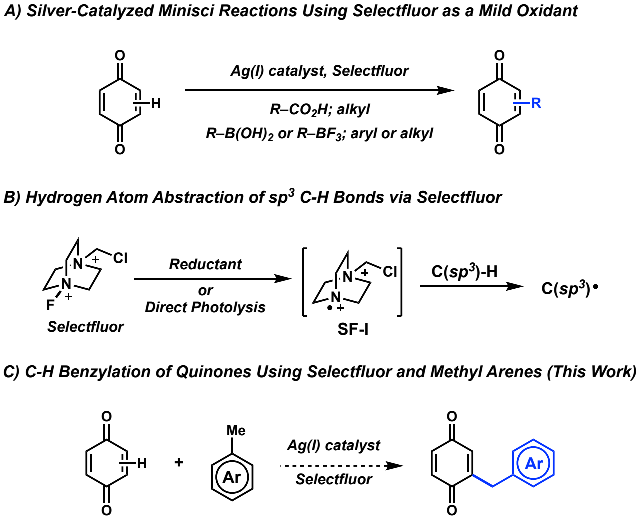


Figure 1. Biologically active quinones bearing benzylic substitution.

Several methods are known for the synthesis of functionalized quinones including palladium-catalyzed coupling reactions[2], alkylation/oxidation of hydroquinones and phenols[3], and direct radical functionalization.[4] In the context of radical functionalizations, several methods have been reported that utilize Minisci-type conditions for radical functionalization of quinones, typically involving pre-functionalized radical precursors and strong oxidants.[5] Oxidative radical processes leading to quinone substitution from unfunctionalized reagents often require air and moisture free conditions, large excess of the radical precursor, and elevated temperatures to circumvent unfavorable radical pathways.

Previously, our group had shown that quinones and aromatic heterocycles could be directly alkylated or arylated via carboxylic or boronic acid radical precursors using Selectfluor and catalytic AgNO$_3$ (Figure 2A).[5] Others have demonstrated that diazabicyclo radical cation **SF-I**, formed after single-electron reduction or direct photolysis of Selectfluor, is a suitable hydrogen atom transfer (HAT) agent to generate carbon centered radicals leading to C–F and C–C bond formation (Figure 2B).[6] We sought to combine mechanistic features of these two protocols to develop a quinone benzylation reaction that operates via C–H abstraction from **SF-I** after single-electron transfer between a Ag(I) source and Selectfluor (Figure 3C).



A) Silver-Catalyzed Minisci Reactions Using Selectfluor as a Mild Oxidant

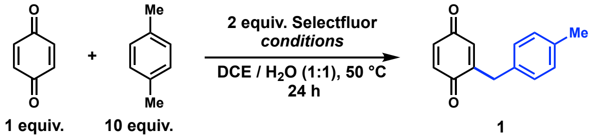
B) Hydrogen Atom Abstraction of sp^3 C-H Bonds via Selectfluor

C) C-H Benzylation of Quinones Using Selectfluor and Methyl Arenes (This Work)

Figure 2. Selectfluor as an oxidant and/or HAT precursor.

Preliminary studies using *p*-xylene as a radical precursor showed that benzoquinone could be directly alkylated in moderate yield using a AgNO$_3$/Selectfluor reagent system (Table 1, entry 1). In our previous studies on radical fluorination via C–H abstraction, we found that pyridine additives lowered the onset oxidation potential of Ag(I) to facilitate single-electron transfer to Selectfluor.[7]

Guided by those results, we examined the effect of pyridine additives on the benzylation reaction. Interestingly, although one equivalent of 4-methoxypyridine had a deleterious effect on the reaction (Table 1, entry 2); catalytic amounts led to a slight increase in conversion (Table 1, entry 3). Because the synthesis of Ag(I)[pyridine]$_2$ salts is straightforward[8], we examined their efficacy as catalysts for the benzylation reaction. A series of conditions were screened, and we discovered that 20 mol % of Ag(4-OMePy)$_2$NO$_3$ was optimum to produce **1** in good yield (73%, Table 1, entry 4). Catalysts with different pyridines led to diminished conversion (Table 1, entries 5 and 6), suggesting the electron-rich nature of 4-methoxypyridine was important for electron transfer. Interestingly, although a control reaction without Ag(I) yielded no product (Table 1, entry 7), one equivalent of 4-methoxypyridine was capable of promoting radical alkylation without a metal initiator (Table 1, entry 8), suggesting that electron transfer between the pyridine and Selectfluor was occurring.[8] Reaction with the standard oxidant for Minisci reactions, $(NH_4)_2S_2O_8$, led to poor conversion and a mixture of benzylated products (Table 1, entry 9).



entry	reaction conditions	Yield of 1^a
1	20 mol % AgNO$_3$	49%
2	20 mol % AgNO$_3$, 1 equiv. 4-methoxypyridine	32%
3	20 mol % AgNO$_3$, 40 mol % 4-methoxypyridine	60%
4	20 mol % Ag(4-OMePy)$_2$NO$_3$	73% (71%)
5	20 mol % Ag(Py)$_2$NO$_3$	62%
6	20 mol % Ag(4-*t*-BuPy)$_2$NO$_3$	47%
7	no Ag(I)	no reaction
8	no Ag(I), 1 equiv. 4-methoxypyridine	17%
9	$(NH_4)_2S_2O_8$ instead of Selectfluor	38% + 14% Bis

Table 1. Optimization of quinone functionalization. Reaction conditions: 1,4-benzoquinone (0.2 mmol), *p*-xylene (2.0 mmol), Selectfluor (0.4 mmol), Ag(4-OMePy)$_2$NO$_3$ (0.04 mmol), 2 mL of DCE/H$_2$O (1:1). [a] ^{1}H-NMR yields to 1,3,5-trimethoxybenzene, values in parentheses indicate isolated yield.

With the optimized conditions established, we examined the scope of the benzylation reaction with a variety of quinones and methyl arene reaction partners (Figure 3). Para substituted toluenes with electron donating groups (**2–3**) benzylated benzoquinone in moderate to good yield. Ortho-substituted arenes with methyl (**4**) or a phenyl group (**5**) furnished product in moderate to poor yield. Meta-methylated (**6**) and tetramethylated (**7**) arenes were also effective partners in generating desired products. Electron-withdrawing methylarenes were ineffective under optimized conditions, resulting in the isolation of unreacted benzoquinone. A variety of quinones were screened to determine the scope of electrophiles suitable for this reaction. Benzylated 1,4-benzoquinone (**8**) was synthesized in moderate yield. It is interesting to note that using solvent quantities of the radical precursor results in largely similar reaction conversions. Both methylated (**9–10**) and halogenated (**11–12**) benzoquinones were effective coupling partners and resulted in moderate yields of benzylated products with no bis-benzylated products observed. Finally, functionalized naphthaquinone (**13**) and associated analogs such as juglone (**14**) and menadione (**15**) can also be accessed. Efforts to extend this method to heterocyclic compounds or other C–H radical precursors[4b] resulted in poor yields.

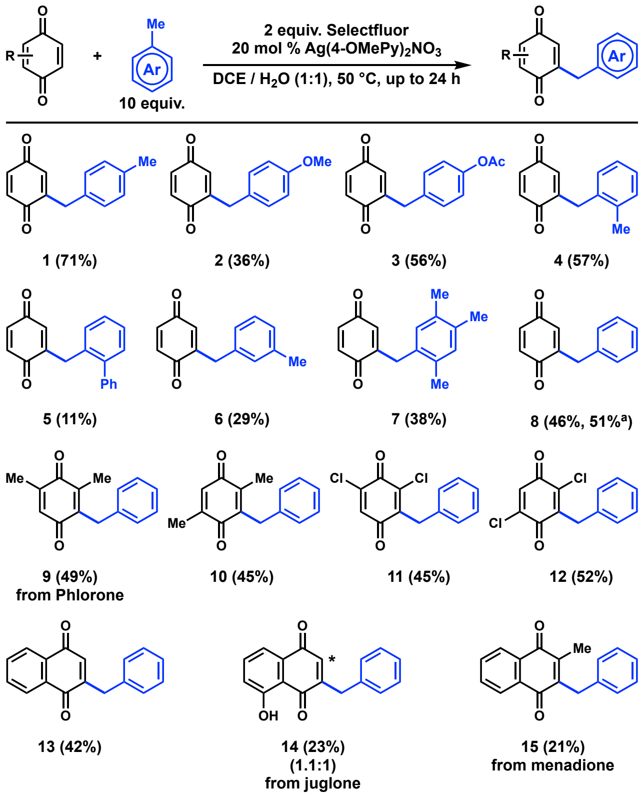


Figure 3. Scope of quinone benzylation. Yields refer to chromatographically pure compounds. [a]Toluene was used instead of DCE as organic solvent.

To better understand the effect of 4-methoxypyridine as a ligand for Ag(I), we tracked the concentration of Selectfluor by ^{19}F-NMR over the course of a typical experiment. Due to the biphasic nature of the reaction, *in situ* reaction monitoring posed a challenge. Instead, small aliquots were removed from the aqueous phase of the reaction to determine Selectfluor concentration against an external standard over the course of 24 hours (see *Supporting Information* for details). Entry 2 from Table 1 suggested that excess 4-methoxypyridine had a negative effect on reaction conversion, and previous work in our group had established that electron-rich pyridines can directly consume Selectfluor in an unproductive manner, an observation that is now extended to this biphasic solvent system.

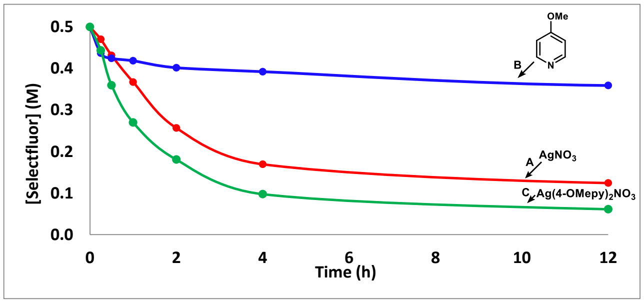


Figure 4. ^{19}F-NMR monitoring of the consumption of Selectfluor (1.0 mmol) with either (**A**) 0.1 mmol of $AgNO_3$, (**B**) 0.2 mmol of 4-methoxypyridine, or (**C**) 0.1 mmol of Ag(4-OMePy)$_2$NO$_3$. Reaction conditions: Selectfluor (1.0 mmol) in DCE/H_2O (4 mL, 1:1) at 50 ºC for up to 24 h. Using a glass microsyringe, 200 µL aliquots were taken from the aqueous phase at specified time points. Conversions were determined by ^{19}F-NMR using trifluorotoluene as an external standard.

We were interested, however, in comparing the use of $AgNO_3$ and catalytic 4-methoxypyridine to Ag(4-OMePy)$_2$NO$_3$ to establish the benefit of the pre-formed catalyst. A catalytic amount of $AgNO_3$ consumed approximately 80% of Selectfluor within 24 hours, confirming that a nitrogen additive is not required for the Ag(I)/(II) redox cycle under these conditions (Figure 4A). A catalytic amount of 4-methoxypyridine consumes Selectfluor in an apparent 1:1 stoichiometry with an initial rate that is on par with the $AgNO_3$-mediated reaction (Figure 4B). Under these conditions only trace amounts of product are formed, confirming that free 4-methoxypyridine has a deleterious effect on the desired transformation even in catalytic quantities. Finally, reaction with pre-formed Ag(4-OMePy)$_2$NO$_3$ produces the highest overall reaction rate for consumption of Selectfluor, while providing the desired product in the highest overall conversion (Figure 4C). These data suggest that the pre-formed catalyst circumvents unfavorable interactions between 4-methoxypyridine and Selectfluor, presumably because strong association to Ag(I) precludes the occurrence of free pyridine in solution.

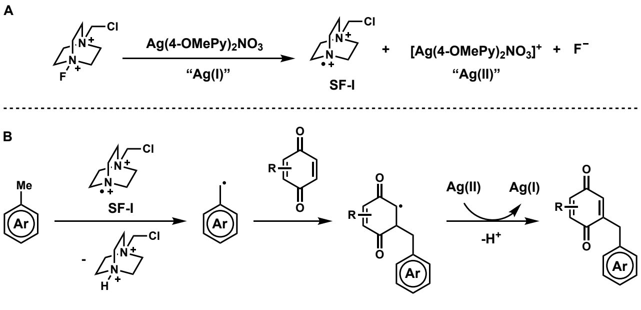


Figure 5. Proposed mechanism for quinone benzylation.

A plausible mechanism for the benzylation of quinone is shown in Figure 5. Single-electron transfer between Ag(4-OMePy)$_2$NO$_3$ and Selectfluor generates **SF-I** and the Ag(II) complex with concomitant generation of fluoride anion (Figure 5A**)**. Hydrogen atom abstraction of a methylarene via **SF-I** leads to a nucleophilic benzyl radical that is trapped by an electrophilic quinone substrate. The resulting radical intermediate is then oxidized, either by Selectfluor or Ag(II), and deprotonated to produce the expected C–H benzylated product (Figure 5B**)**.

In summary, we have developed a robust catalyst system for generating benzylic radicals via C–H abstraction, and combining these radicals with various electrophilic quinones. A pre-formed Ag(I)/pyridine catalyst was found to be optimum for reducing Selectfluor via single-electron transfer to generate diazabicyclo radical cation **SF-I** as hydrogen atom transfer agent. The quinone benzylation reaction is simple to perform and operates under mild reaction conditions without pre-functionalized substrates. Efforts are ongoing to identify new catalyst systems to make the reaction compatible with alternative radical precursors or electrophilic partners such as aromatic heterocycles.

General Considerations

Reagents and solvents were purchased at the highest commercial quality and used without purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR, ^{19}F NMR) homogenous material, unless otherwise noted. Reactions were monitored by GCMS (Agilent Technologies 5975 Series MSD GC MS) and thin-layer chromatography using 0.25 mm E. Merck silica gel plates (60F-254) using UV light. NMR spectra were recorded on a Bruker-INOVA 400 MHz or 500 MHz spectrometer and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ – ^{1}H NMR 7.26 ppm, ^{13}C NMR 77.16 ppm). The following abbreviations were used to explain multiplicities (s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet).

General Reaction Procedures

General Procedure

The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added quinone (0.2 mmol, 1 equiv), benzylic arene (2.0 mmol, 10 equiv) and Selectfluor (141.7 mg, 0.4 mmol, 2 equiv). Dichloroethane (1 mL) and H_2O (1 mL) were then added and stirred for approximately 1 min at room temperature. A solid amount of Ag(4-OMe pyridine)$_2$NO$_3$ (15.5 mg, 0.04 mmol, 20 mol %)was added in one portion. The reaction was capped with a teflon screw cap and rubber septum (24/40). The reaction was heated to 50 °C until reaction was completed as judged by GCMS (up to 24 hours).

Upon completion, the reaction was diluted with ethyl acetate (1 mL) and transferred to a test tube containing H_2O (3 mL). The aqueous phase was extracted with ethyl acetate (3 x 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ethyl acetate:hexanes) to yield the desired product.

Experimental Procedures and Characterization Data

General Conditions for the synthesis of bis(pyridine) silver complexes

To a round bottom containing a stir bar was added $AgNO_3$ (1 – 3.0 mmol) and pyridine (2.1 equiv.) which were mixed in MeCN (0.15M) and stirred at room temperature overnight protected from light. The reaction mixture was filtered through Celite, and the solvent removed from the filtrate under vacuum. The resulting residue was washed with diethyl ether.

bis(pyridine)silver(I) nitrate complex ($Ag(Py)_2NO_3$). The general procedure was employed using $AgNO_3$ (169 mg, 1.0 mmol) and pyridine (170 μL, 2.1 mmol). The reaction afforded **$Ag(Py)_2NO_3$** (259.0 mg, 79% yield) as a white solid. **^{1}H NMR** (400 MHz, CD_3CN): 8.62 – 8.54 (m, 2H), 7.89 (tt, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.4 Hz, 2H). **^{13}C NMR** (100 MHz, CD_3CN): 151.8, 138.9, 125.7. **HRMS (ESI-TOF)**: calcd for $C_{12}H_4AgN_2O_2$ $[M+H]^+$ 264.9889 found 264.9878.

bis(4-(tert-butyl)pyridine)silver(I) nitrate complex (Ag(4-*t*BuPy)$_2$NO$_3$). The general procedure was employed using $AgNO_3$ (169 mg, 1.0 mmol) and 4-tert-Butylpyridine (308 μL, 2.1 mmol). The reaction afforded **Ag(4-*t*BuPy)$_2$NO$_3$** (380.6 mg, 86% yield) as a white solid. **^{1}H NMR** (400 MHz, CD_3CN): 8.49 (dd, *J* = 4.9, 1.6 Hz, 2H), 7.50 (dd, *J* = 4.9, 1.7 Hz, 2H), 1.31 (s, 9H). **^{13}C NMR** (100 MHz, CD_3CN): 163.3, 151.7, 122.8, 35.6, 30.4. **HRMS (ESI-TOF)**: calcd for $C_{12}H_4AgN_2O_2$ $[M+H]^+$ 377.1141 found 377.1126.

bis(4-methoxypyridine)silver(I) nitrate complex ($Ag(OMePy)_2NO_3$). To a round bottom containing a stir bar was added $AgNO_3$ (510 mg, 3.0 mmol) and 4-methoxypyridine (640 μL, 6.3 mmol) which were mixed in MeCN (20 mL) and stirred at room temperature overnight protected from light. The reaction mixture was filtered through Celite, and the solvent removed from the filtrate under vacuum. The resulting residue was washed with diethyl ether to afford **$Ag(OMePy)_2NO_3$** (1,094.5 mg, 94% yield) as a white solid. **^{1}H NMR** (500 MHz, CD_3CN): 8.40 (dd, *J* = 5.1, 1.5 Hz, 2H), 7.02 (dd, *J* = 5.1, 1.5 Hz, 2H), 3.88 (s, 3H). **^{13}C NMR** (125 MHz, CD_3CN): 167.7, 153.3, 111.8, 56.5. **HRMS (ESI-TOF)**: calcd for $C_{12}H_4AgN_2O_2$ $[M+H]^+$ 325.0106 found 325.0101.

Figure 4 Compounds (1–15)

2-(4-methylbenzyl)cyclohexa-2,5-diene-1,4-dione (1). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and *p*-xylene (247 μL, 2.0 mmol). The reaction afforded **1** (30.1 mg, 71% yield) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.13 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 10.1 Hz, 1H), 6.69 (dd, *J* = 10.1, 2.5 Hz, 1H), 6.38–6.35 (m, 1H), 3.70 (s, 2H), 2.33 (s,3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 187.9, 187.4, 149.0, 136.8, 136.4, 133.3, 133.3, 129.7, 129.4, 34.9, 21.2. **HRMS (ESI-TOF)**: calcd for $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0910 found 213.0901.

2-(4-methoxybenzyl)cyclohexa-2,5-diene-1,4-dione (2). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 4-methylanisole (252 μL, 2.0 mmol). The reaction afforded **2** (16.3 mg, 36% yield) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.13–7.08 (m, 2H), 6.88–6.83 (m, 2H), 6.76 (d, *J* = 10.1 Hz, 1H), 6.70 (dd, *J* = 10.1, 2.5 Hz, 1H), 6.36 (dd, *J* = 4.1, 1.6 Hz, 1H), 3.79 (s, 3H), 3.68 (d, *J* = 1.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): 188.0, 187.5, 158.8, 149.2, 136.8, 136.5, 133.3, 130.6, 128.3, 114.4, 55.4, 34.5. **HRMS (ESI-TOF)**: calcd for $C_{14}H_{12}O_3$ $[M+H]^+$ 229.0859 found 229.0853.

4-((3,6-dioxocyclohexa-1,4-dien-1-yl)methyl)phenyl acetate (3). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and *p*-tolyl acetate (287 μL, 2.0 mmol). The reaction afforded **3** (28.6 mg, 56% yield) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.17 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.74 (d, *J* = 10.1 Hz, 1H), 6.68 (dd, *J* = 10.1, 1.1 Hz, 1H), 3.70 (s, 2H), 2.26 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 187.7, 187.2, 169.6, 149.8, 148.4, 136.8, 136.5, 134.0, 133.4, 130.5, 122.1, 34.8, 21.3. **HRMS (ESI-TOF)**: calcd for $C_{15}H_{12}O_4$ $[M+H]^+$ 257.0808 found 257.0798.

2-(2-methylbenzyl)cyclohexa-2,5-diene-1,4-dione (4). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and *o*-xylene (241 μL, 0.4 mmol). The reaction afforded **5** (24.3 mg, 57% yield) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.22–7.14 (m, 3H), 7.12–7.06 (m, 1H), 6.81 (d, *J* = 10.1 Hz, 1H), 6.71 (dd, *J* = 10.1, 2.6 Hz, 1H), 6.11 (dd, *J* = 4.4, 2.0 Hz, 1H), 3.75 (d, *J* = 1.9 Hz, 2H), 2.21 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 187.8, 187.5, 148.4, 136.8, 136.7, 136.5, 134.4, 133.1, 130.8, 130.5, 127.6, 126.6, 32.7, 19.5. **HRMS (ESI-TOF)**: calcd for $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0910 found 213.0902.

2-([1,1'-biphenyl]-2-ylmethyl)cyclohexa-2,5-diene-1,4-dione (5). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 2-methylbiphenyl (333 μL, 2.0 mmol). The reaction afforded **6** (5.9 mg, 11% yield) as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.39–7.19 (m, 9H), 6.67 (d, *J* = 10.1 Hz, 1H), 6.63 (dd, *J* = 10.1, 2.4 Hz, 1H), 6.05 (dd, *J* = 4.1, 1.9 Hz, 1H), 3.76 (d, *J* = 1.7 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): 187.8, 187.0, 149.0, 142.8, 141.2, 136.7, 136.3, 133.9, 133.7, 130.7, 130.7, 129.0, 128.5, 128.0, 127.4, 127.4, 32.7. **HRMS (ESI-TOF)**: calcd for $C_{19}H_{14}O_2$ $[M+H]^+$ 275.1067 found 275.1062.

2-(3-methylbenzyl)cyclohexa-2,5-diene-1,4-dione (6). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and *m*-xylene (247 μL, 2.0 mmol). The reaction afforded **7** (12.2 mg, 29% yield) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.21 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 7.01–6.96 (m, *J* = 8.2 Hz, 2H), 6.77 (dd, *J* = 10.0, 4.9 Hz, 1H), 6.70 (dd, *J* = 10.1, 2.5 Hz, 1H), 6.37 (dt, *J* = 2.4, 1.6 Hz, 1H), 3.70 (d, *J* = 1.3 Hz, 2H), 2.33 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 187.9, 187.4, 148.9, 138.7, 136.8, 136.5, 136.4, 133.4, 130.2, 128.9, 127.9, 126.5, 35.2, 21.5. **HRMS (ESI-TOF)**: calcd for $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0910 found 213.0907.

2-(2,4,5-trimethylbenzyl)cyclohexa-2,5-diene-1,4-dione (7). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 3'-methylacetophenone (266 μL, 2.0 mmol). The reaction afforded **8** (13.6 mg, 28% yield) as a colorless oils. **^{1}H NMR** (500 MHz, $CDCl_3$): 6.96 (s, 1H), 6.84 (s, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 6.70 (dd, *J* = 10.1, 2.5 Hz, 1H), 6.12 (d, *J* = 1.9 Hz, 1H), 3.68 (s, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 187.9, 187.6, 148.8, 136.8, 136.5, 135.7, 134.6, 133.8, 133.1, 132.2, 131.8, 131.5, 32.3, 19.4, 19.3, 18.9. **HRMS (ESI-TOF)**: calcd for $C_{16}H_{17}O_2$ $[M+H]^+$ 241.1223 found 241.1216.

2-benzylcyclohexa-2,5-diene-1,4-dione (8). The general procedure was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **9** (19.8 mg, 46% yield) as a yellow oil. The data matches those previously reported.[3a] **^{1}H NMR** (400 MHz, $CDCl_3$): 7.33 (t, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.71 (dd, *J* = 10.1, 2.2 Hz, 1H), 6.37 (d, *J* = 1.5 Hz, 1H), 3.75 (s, 2H).

2-benzyl-3,5-dimethylcyclohexa-2,5-diene-1,4-dione (9). The general procedure was employed using 2,6-dimethylbenzoquinone (27 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **10** (22.2 mg, 49% yield) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.29–7.23 (m, 2H), 7.21–7.15 (m, 3H), 6.59 (dd, *J* = 3.0, 1.4 Hz, 1H), 3.86 (s, 2H), 2.10 (s, 3H), 2.05 (d, *J* = 1.6 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 188.5, 187.3, 145.6, 142.9, 141.9, 138.2, 133.2, 128.7, 128.7, 126.5, 31.9, 16.1, 12.9. **HRMS (ESI-TOF)**: calcd for $C_{15}H_{14}O_2$ $[M+H]^+$ 227.1067found 227.1055.

3-benzyl-2,5-dimethylcyclohexa-2,5-diene-1,4-dione (10). The general procedure was employed using 2,5-dimethyl-1,4-benzoquinone (27 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **11** (20.4 mg, 45% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.29–7.23 (m, 2H), 7.21–7.15 (m, 3H), 6.58 (s, 1H), 3.87 (s, 2H), 2.09 (s, 3H), 2.03 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): 188.0, 187.7, 145.5, 143.1, 141.8, 138.2, 133.3, 128.8, 128.7, 126.6, 32.2, 16.1, 12.6. **HRMS (ESI-TOF)**: calcd for $C_{15}H_{14}O_2$ $[M+H]^+$ 227.1067 found 227.1067.

2-benzyl-3,5-dichlorocyclohexa-2,5-diene-1,4-dione (11). The general procedure was employed using 2,6-dichloro-1,4-benzoquinone (35 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **12** (23.9 mg, 45% yield) as a yellow solid. The data matches those previously reported.[4c] **^{1}H NMR** (400 MHz, $CDCl_3$): 7.31–7.19 (m, 5H), 7.03 (s, 1H), 4.01 (s, 2H).

3-benzyl-2,5-dichlorocyclohexa-2,5-diene-1,4-dione (12). The general procedure was employed using 2,5-dichloro-1,4-benzoquinone (35 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **13** (27.7 mg, 52% yield) as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.35–7.21 (m, 5H), 7.10 (s, *J* = 3.3 Hz, 1H), 4.07 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): 177.5, 177.5, 144.4, 144.3, 141.6, 136.0, 133.0, 129.4, 129.0, 127.3, 34.1. **HRMS (ESI-TOF)**: calcd for $C_{13}H_8Cl_2O_2$ $[M+H]^+$ 266.9974 found 266.9972.

2-benzylnaphthalene-1,4-dione (13). The general procedure was employed using 1,4-naphthoquinone (32 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **14**(21.0 mg, 42% yield) as a yellow solid. The data matches those previously reported.[3a] **^{1}H NMR** (500 MHz, $CDCl_3$): 8.17–7.98 (m, 2H), 7.80–7.66 (m, 2H), 7.37–7.30 (m, 2H), 7.29–7.22 (m, 3H), 6.61 (s, 1H), 3.90 (s, 1H).

2-benzyl-5-hydroxynaphthalene-1,4-dione (14-C2) and 2-benzyl-8-hydroxynaphthalene-1,4-dione (14-C3). The general procedure was employed using 5-hydroxy-1,4-naphthoquinone (35 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The regioisomeric ratio of C2:C3 was determined to be 1:1.1 by crude ^{1}H NMR. The reaction afforded **15-C2** (6.0 mg, 11% yield) and **15-C3** (6.1 mg, 11% yield) as yellow solids. **NMR data for 14-C2 ^{1}H NMR** (500 MHz, $CDCl_3$): 11.92 (s, 1H), 7.67–7.58 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30–7.21 (m, 4H), 6.55 (t, J = 1.5 Hz, 1H), 3.89 (d, *J* = 1.2 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): 190.5, 184.4, 161.4, 152.5, 136.6, 136.4, 135.6, 132.2, 129.6, 129.1, 127.2, 124.4, 119.6, 115.1, 35.9. **HRMS (ESI-TOF)**: calcd for $C_{17}H_{12}O_3$ $[M+H]^+$ 265.0859 found 265.0853 **NMR data for 14-C3 ^{1}H NMR** (500 MHz, $CDCl_3$): 12.04 (s, 1H), 7.63–7.56 (m, 2H), 7.37–7.32 (m, 2H), 7.30–7.23 (m, 4H), 6.59 (t, J = 1.5 Hz, 1H), 3.89 (d, J = 1.1 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): 190.4, 184.5, 161.8, 150.9, 136.7, 136.7, 136.5, 132.3, 129.5, 129.1, 127.3, 124.5, 119.0, 115.3, 35.4. **HRMS (ESI-TOF)**: calcd for $C_{17}H_{12}O_3$ $[M+H]^+$ 265.0859 found 265.0849.

2-benzyl-3-methylnaphthalene-1,4-dione (15). The general procedure was employed using 2-methyl-1,4-naphthoquinone (34 mg, 0.2 mmol) and toluene (213 µL, 2.0 mmol). The reaction afforded **16** (11.1 mg, 21% yield) as a yellow solid. The data matches those previously reported.[3h] **^{1}H NMR** (500 MHz, $CDCl_3$): 8.12–8.06 (m, 2H), 7.73–7.68 (m, 2H), 7.30–7.16 (m, 5H), 4.04 (s, 2H), 2.25 (s, 3H).

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, full characterization and copies of all spectra. This material is available free of charge via the internet at http:pubs.acs.org.

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REFERENCES

(1) (a) Popp, B. V.; Stahl, S. S. *Organometallic Oxidation Catalysis, In Topics in Organometallic Chemistry*; Meyer, F.; Limberg, C., Eds.; Springer: Berlin, **2006**. (b) Sunassee, S. N.; Davies-Coleman, M. T. Cytotoxic and antioxidant marine prenylated quinones and hydroquinones. *Nat. Prod. Rep.* **2012**, *29*, 513. (c) Khader, M.; Eckl, P. M. Thymoquinone: an emerging natural drug with a wide range of medical applications. *Iran, J. Basic Med. Sci.* **2014**, *17*, 950–957. (d) Breyer, S.; Effenberger, K.; Schobert, R. Effects of Thymoquinone–Fatty Acid Conjugates on Cancer Cells. *Chem. Med. Chem.* **2009**, *4*, 761. (e) Bauer, H.; Fritz-

Wolf, K.; Winzer, A.; Kühner, S.; Little, S.; Yarley, V.; Vezin, H.; Palfey, B.; Schirmer, R. H.; Davioud-Charvet, E. A Fluoro Analogue of the Menadione Derivative 6-[2'-(3'-Methyl)-1',4'-naphthoquinolyl]hexanoic Acid Is a Suicide Substrate of Glutathione Reductase. Crystal Structure of the Alkylated Human Enzyme. *J. Am. Chem. Soc.* **2006**, *128*, 10784–10794. (f) Nakao, H.; Arakawa, M.; Nakamura, T.; Fukushima, M. *Chem. Pharm. Bull.* **1972**, *20*, 1968. (g) Sunassee, S. N.; Veale, C. G. L.; Shunmoogam-Gounden, N.; Osoniyi, O.; Hendricks, D. T.; Caira, M. R. ; de la Mare, J. O., Edkins, A. L.; Pinto, A. V.; da Silva Júnior, E. N.; Davies-Coleman, M. T. Cytotoxicity of lapachol, β-lapachone and related synthetic 1,4-naphthoquinones against oesophageal cancer cells. *Eur. J. Med. Chem.* **2013**, *62*, 98. (h) Mukai, A.; Takahashi, K.; Kofujita, H.; Ashitani, T. Antitermite and antifungal activities of thujopsene natural autoxidation products. *Eur. J. Wood Prod.* **2019**, *77*, 311–317. (i) Ehrhardt, K.; Deregnaucourt, C.; Goetz, A. A.; Tzanova, T.; Gallo, V.; Arese, P.; Pradines, B.; Adjalley, S. H.; Bagrel, D.; Blandin, S.; Lanzer, M.; Davioud-Charvet, E. The Redox Cycler Plasmodione Is a Fast-Acting Antimalarial Lead Compound with Pronounced Activity against Sexual and Early Asexual Blood-Stage Parasites. *Antimicrob. Agents Chemother.* **2016**, *60*, 5146–5158. (j) Feng, L.; Lanfranchi, D. A.; Cotos, L.; Cesar-Rodo, E.; Ehrhardt, K.; Goetz, A. A.; Zimmermann, H.; Fenaille, F.; Blandin, SA.; Davioud-Charvet, E. Synthesis of plasmodione metabolites and 13C-enriched plasmodione as chemical tools for drug metabolism investigation. *Org. Biomol. Chem.*, **2018**, *16*, 2647–2665.

(2) Select examples of Pd- catalyzed functionalization of quinones. (a) Echavarren, A. M.; de Frutos, Ó.; Tamayo, N.; Noheda, P.; Calle, P. Palladium-Catalyzed Coupling of Naphthoquinone Triflates with Stannanes. Unprecedented Nucleophilic Aromatic Substitution on a Hydroxynaphthoquinone Triflate. *J. Org. Chem.* **1997**, *62*, 4524−4527. (b) Gan, X.; Jiang, W.; Wang, W.; Hu, L. An Approach to 3,6-Disubstituted 2,5-Dioxybenzoquinones via Two Sequential Suzuki Couplings. Three-Step Synthesis of Leucomelone. *Org. Lett.* **2009**, *11*, 589−592. (c) Rao, M. L. N.; Giri, S. Pd-catalyzed threefold arylations of mono, di and tetra-bromoquinones using triarylbismuth reagents. *RSC Adv.* **2012**, *2*, 12739−12750.

(3) Select examples of alkylation/oxidation of phenols and hydroquinones leading to functionalized quinones. (a) Murahashi, S. -I.; Miyaguchi, N.; Noda, S.; Naota, T.; Fujii , A.; Inubushi, Y.; Komiya, N. Ruthenium-Catalyzed Oxidative Dearomatization of Phenols to 4-(*tert*-Butylperoxy)cyclohexadienones: Synthesis of 2-Substituted Quinones from *p*-Substituted Phenols. *Eur. J. Org. Chem.* **2011**, 5355–5365. (b) Miyamura, H.; Shiramizu, M.; Matsubara, R.; Kobayashi, S. Aerobic Oxidation of Hydroquinone Derivatives Catalyzed by Polymer-Incarcerated Platinum Catalyst. *Angew. Chem. Int. Ed.* **2008**, *47*, 8093–8095.

(3) Select examples of radical functionalization of quinones. (a) Hamsath, A.; Galloway, J. D.; Baxter, R. D. Quinone C–H Alkylations via Oxidative Radical Processes. *Synthesis.* **2018**, *50*, 2915–2923. (b) Han, Q.; Jiang, K.; Wei, Y.; Su, W. Transition-Metal-Free, TsOH-Mediated Direct C−H Allylation of 1,4-Benzoquinone with Allylic Alcohols. *Asian J. Org. Chem.* **2018**, *7*, 1385–1389. (c) Yamago, S.; Hashidume, M.; Yoshida, J. -I. A new synthetic route to substituted quinones by radical-mediated coupling of organotellurium compounds with quinones. *Tetrahedron*. **2002**, *58*, 6805. (d) Wang, D.; Ge, B.; Li, L.; Shan, J.; Ding, Y. Transition Metal-Free Direct C–H Functionalization of Quinones and Naphthoquinones with Diaryliodonium Salts: Synthesis of Aryl Naphthoquinones as β-Secretase Inhibitors. J. *Org. Chem.* **2014**, *79*, 8607. (f) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Bel, M. D.; Baran, P. S. Practical C−H Functionalization of Quinones with Boronic Acids. *J. Am. Chem. Soc.* **2011**, *133*, 3292–3295. (g) Baral, E. R.; Kim, S. H.; Lee, Y. R. Copper-Catalyzed $C(sp^2)$–$C(sp^3)$ Cross-Dehydrogenative Coupling of Quinones with Cyclic Alkanes: One-Step Access to Parvaquone and its Analogs. *Asian J. Org. Chem.* **2016**, *5*, 1134−1141. (h) Sutherland, D. R.; Veguillas, M.; Oates, C. L.; Lee, A.-L. Metal-, Photocatalyst-, and Light-Free, Late-Stage C–H Alkylation of Heteroarenes and 1,4-Quinones Using Carboxylic Acids. *Org. Lett.* **2018**, *20*, 6863–6867.

(4) Reviews highlighting radical C-H functionalization of arenes and heteroarenes using the Minisci reaction. (a) Minsici, F. Novel Applications of Free-Radical Reactions in Preparative Organic Chemistry. *Synthesis*. **1973**, *1,* 1–24. (b) Duncton, A. J. Minisci reactions: Versatile CH-functionalizations for medicinal chemists. *Med. Chem. Commun.* **2011**, *2*, 1135–1161. (c) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C–H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016−9085. Seminal work by Minisci. (d) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic character of alkyl radicals–VI : A new convenient selective alkylation of heteroaromatic bases. *Tetrahedron*. **1971**, *27*, 3575–3579. (e) Minisci, F.; Vismara, E.; Morini, G.; Fontana, F.; Levi, S.; Serravalle, M.; Giordano, C. Polar effects in free-radical reactions. Selectivity and reversibility in the homolytic benzylation of protonated heteroaromatic bases *J. Org. Chem.* **1986**, *51*, 476–479. Select examples of radical C-H functionalization of arenes and heteroarenes from a variety of radical precursers. (f) Gutiérrez-Bonet, Á.; Remeur, C.; Matsui, J. K.; Molander, G. A. Late-Stage C–H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines. *J. Am. Chem. Soc.* **2017**, *139*, 12251−12258. (g) Mai, D. N.; Baxter, R. D. Unprotected Amino Acids as Stable Radical Precursors for Heterocycle C–H Functionalization. *Org. Lett.* **2016**, *18*, 3738 – 3741. (h) Yuan, J.-W.; Yang, L.-R.; Mao, P.; Qu, L.-B. $AgNO_3$-catalyzed direct C–H arylation of quinolines by oxidative decarboxylation of aromatic carboxylic acids. *Org. Chem. Front.* **2017**, *4*, 545 – 554. (i) Wan, M.; Lou, H.; Liu, L. C_1-Benzyl and benzoyl isoquinoline synthesis through direct oxidative cross-dehydrogenative coupling with methyl arenes. *Chem. Commun.* **2015***, 51,* 13953*–13956.* (j) Shi, X.; Zhang, F.; Luo, W. –K.; Yang, L. Oxidant-Triggered C1-Benzylation of Isoquinoline by Iodine--Catalyzed Cross-Dehydrogenative-Coupling with Methylarenes. *Synlett.* **2017**, *28*. 494-498. (k) Antonchick, A. P.; Burgmann, L. Direct Selective Oxidative Cross-Coupling of Simple Alkanes with Heteroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267.

(5) Galloway, J. D.; Mai, D. N.; Baxter, R. D. Silver-Catalyzed Minisci Reactions Using Selectfluor as a Mild Oxidant. *Org. Lett.* **2017**, *19*, 5772−5775.

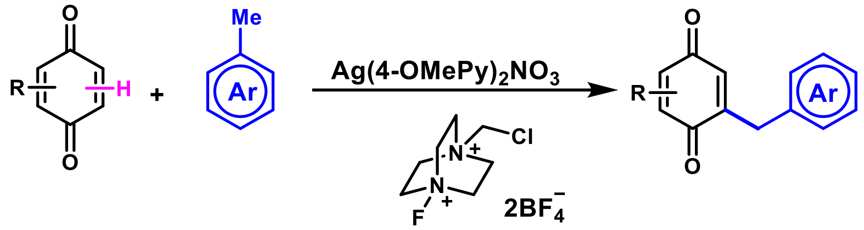
(6) (a) Bume, D. D.; Harry, A. H.; Lectka, T.; Pitts, C. R. Catalyzed and Promoted Aliphatic Fluorination. *J. Org. Chem.* **2018**, *83*, 8803–8814. (b) Pitts, C. R.; Bloom, S.; Woltornist,

R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. Direct, Catalytic Monofluorination of sp^3 C–H Bonds: A Radical-Based Mechanism with Ionic Selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 9780–9791. (c) Pitts, C. R.; Ling, B.; Snyder, J. A.; Bragg, A. E.; Lectka, T. Aminofluorination of Cyclopropanes: A Multifold Approach through a Common, Catalytically Generated Intermediate. *J. Am. Chem. Soc.* **2016**, *138*, 6598–6609. (d) Liang, X. -A.; Niu, L.; Wang, S.; Liu, J.; Lei, A. Visible-Light-Induced C(sp3)–H Oxidative Arylation with Heteroarenes. *Org. Lett.* **Article ASAP**. DOI: 10.1021/acs.orglett.9b00744. (e) Niu, L.; Liu, J.; Liang, X. -A.; Wang, S.; Lei, A. Visible Light-Induced Direct α C–H Functionalization of Alcohols. *Nat. Commun.* **2019**, *10*, 467.

(7) Hua, A. M.; Mai, D. N.; Martinez, R.; Baxter, R. D. Radical C–H Fluorination Using Unprotected Amino Acids as Radical Precursors. *Org. Lett.* **2017**, *19*, 2949−2952.

(8) Di Nicola, C.; Effendy.; Marchetti, F.; Nervi, C.; Pettinari, C.; Robinson, W. T.; Sobolev, A. N.; White, A. H. Syntheses, structures and spectroscopy of uni- and bi-dentate nitrogen base complexes of silver(I) trifluoromethanesulfonate. *Dalton Trans.* **2010**, *39*, 908–922.

(9) (a) Hua, A. M.; Bidwell, S. L.; Baker, S. I.; Hratchian, H. P.; Baxter, R. D. Experimental and Theoretical Evidence for Nitrogen–Fluorine Halogen Bonding in Silver-Initiated Radical Fluorinations. *ACS Catal.* **2019**, *9,* 3322–3326. (b) Danahy, K. E.; Cooper, J. C.; Van Humbeck, J. F. Benzylic Fluorination of Aza-Heterocycles Induced by Single-Electron Transfer to Selectfluor. *Angew. Chem. Int. Ed.* **2018**, *57*, 5134–5138.



Radical Benzylation of Quinones via C–H Abstraction

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Supporting Information

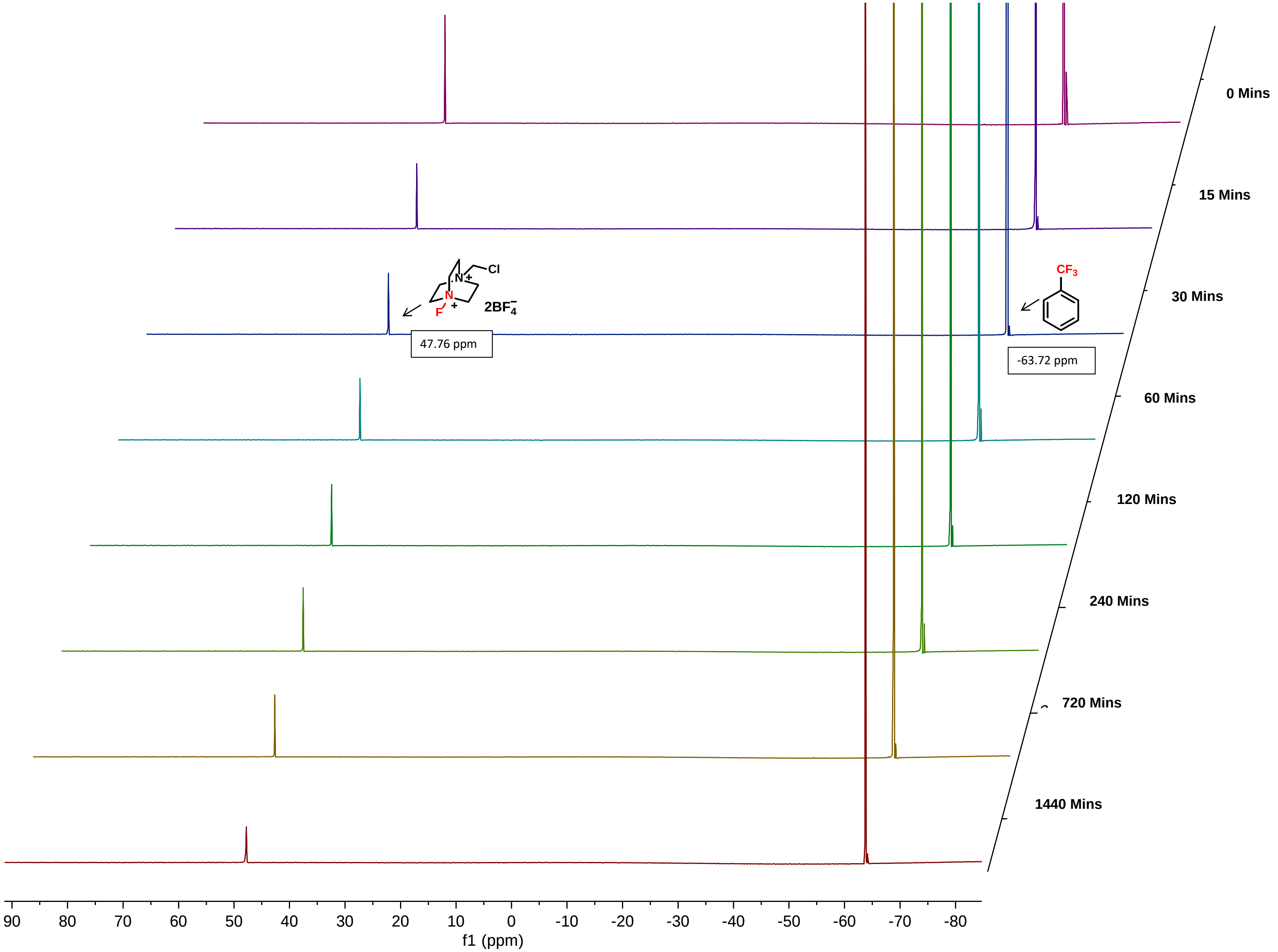
Experimental procedures for ^{19}F NMR studies and copies of NMR spectra for isolated compounds.

Table of Contents

^{19}F-NMR studies

Representative Experimental Procedure for ^{19}F-NMR Data

The threads of a 4 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added Selectfluor® (354 mg, 1.0 mmol) and $AgNO_3$ (17.0 mg, .10 mmol). Dichloroethane (2 mL) and H_2O (2 mL) were then added to the vial. The solution was allowed to stir at 50 °C for 24 h. Using a glass microsyringe, 200 µL aliquots were taken from the aqueous phase at specified time points and diluted with 400 µL of D_2O. Decrease in Selectfluor concentration were determined by ^{19}F-NMR. All ^{19}F-NMR experiments were compared to α,α,α-Trifluorotoluene as standard which was added to the NMR tube in a sealed capillary tube. All data represented in Figure 4A-C were acquired in an analogous fashion.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CF3
-63.72 ppm
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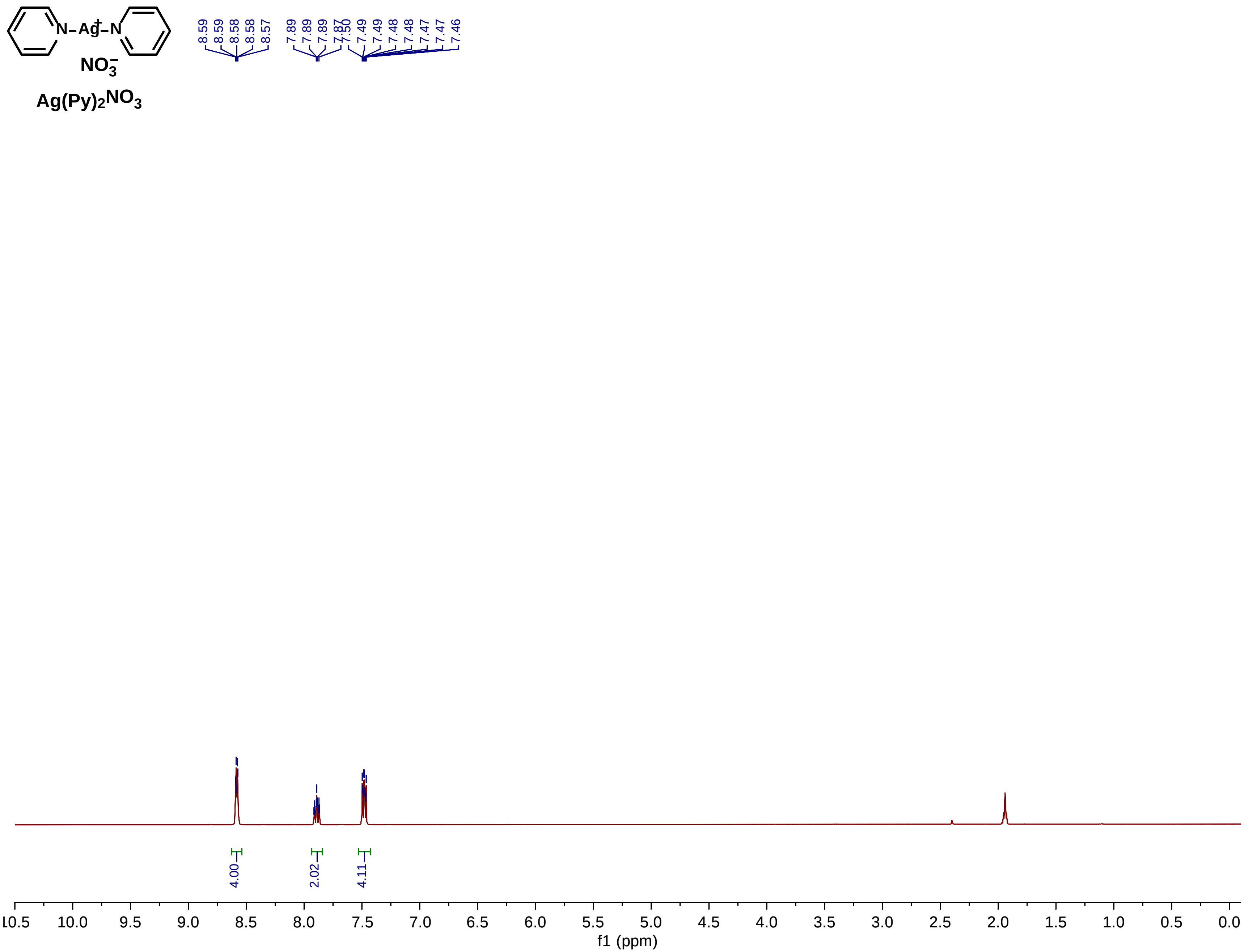
f1 (ppm)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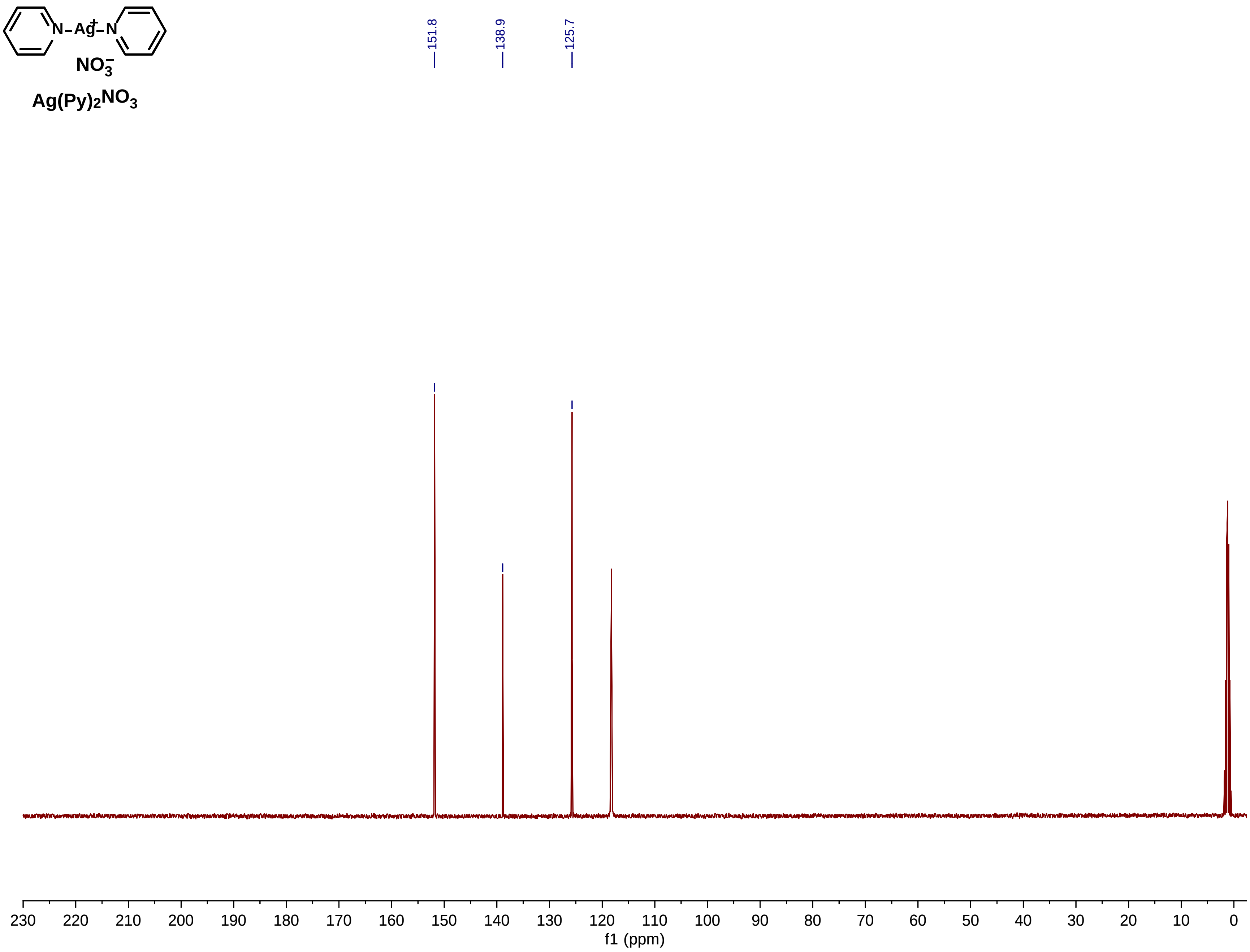

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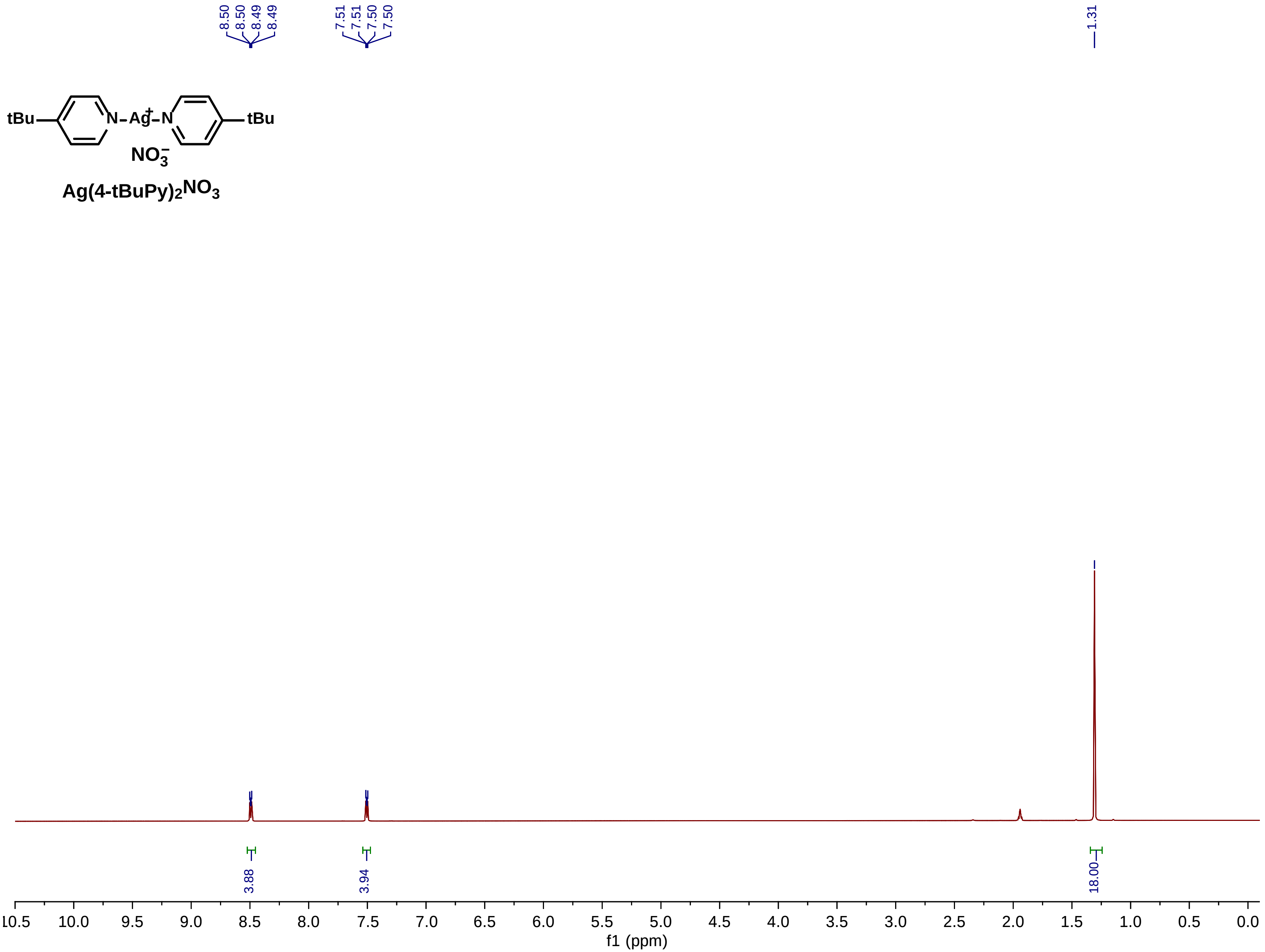

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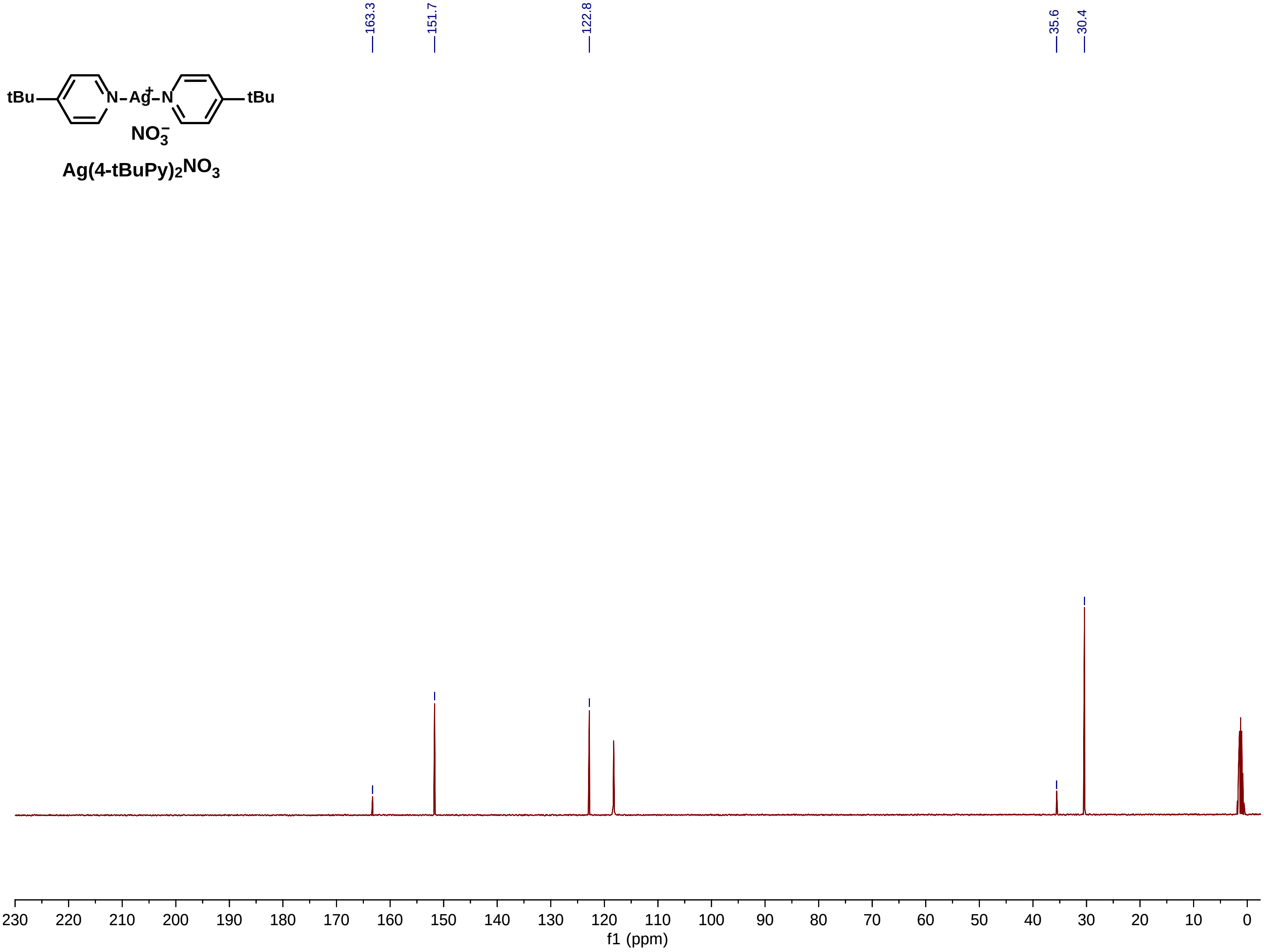

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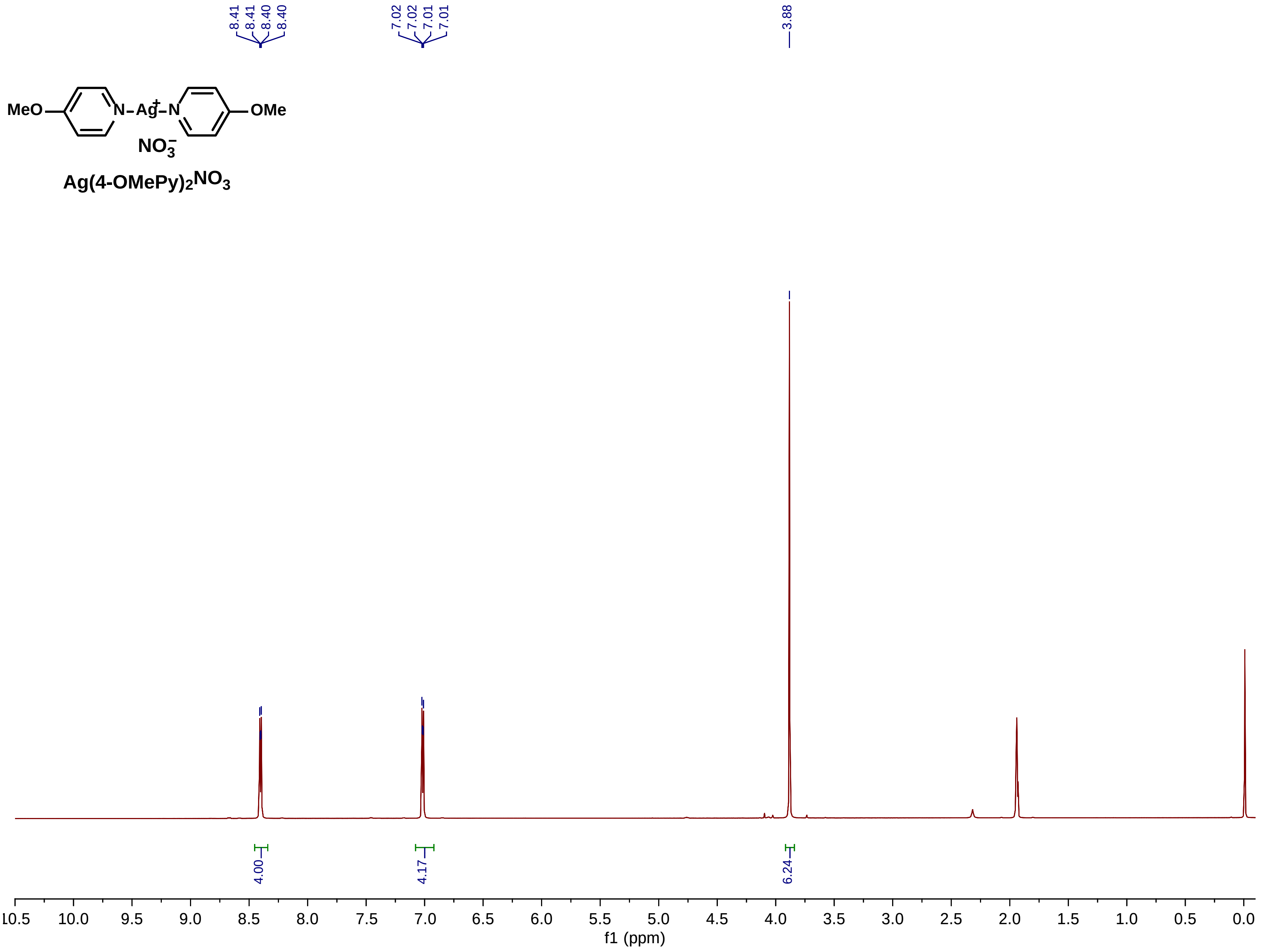

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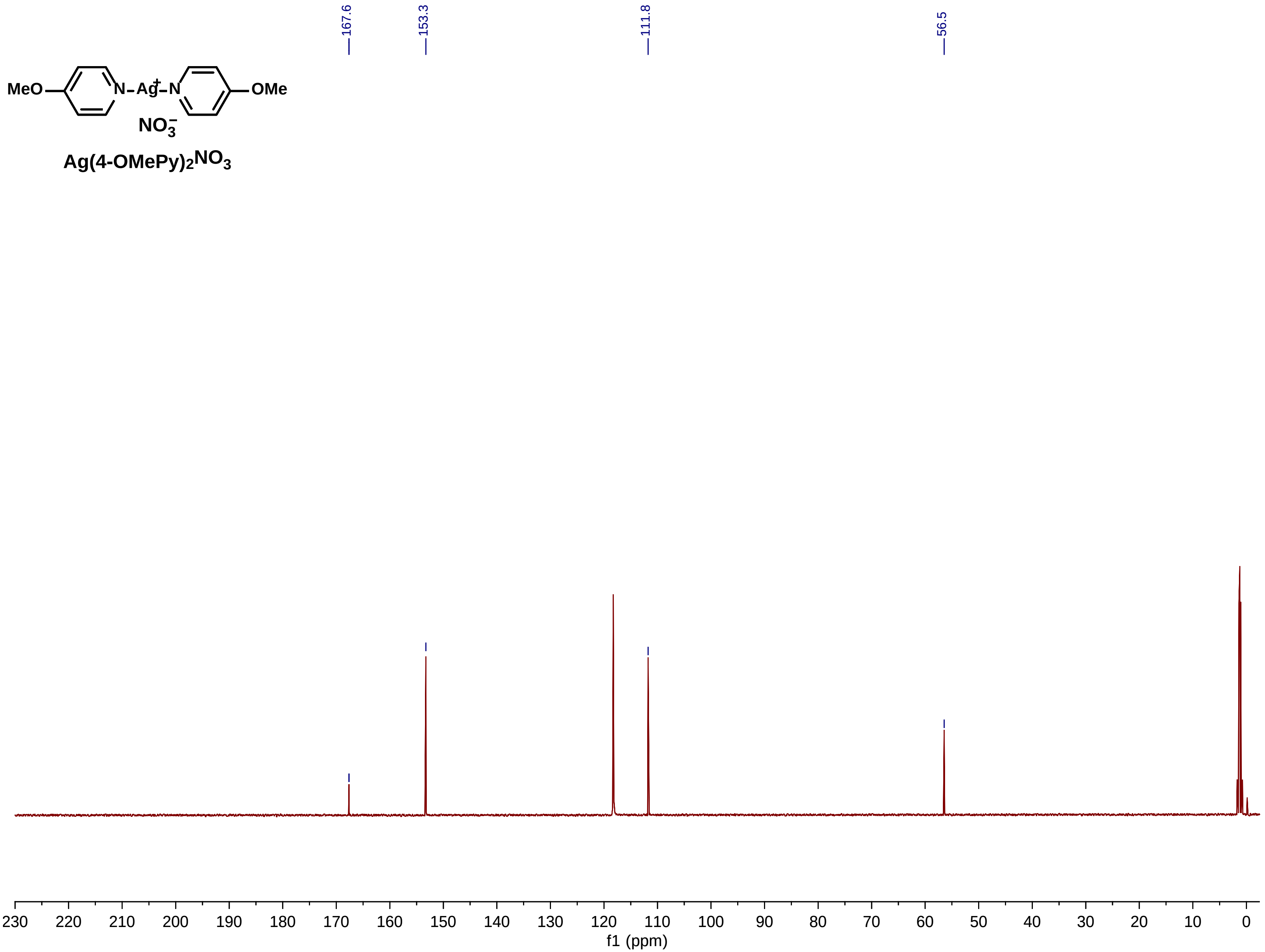

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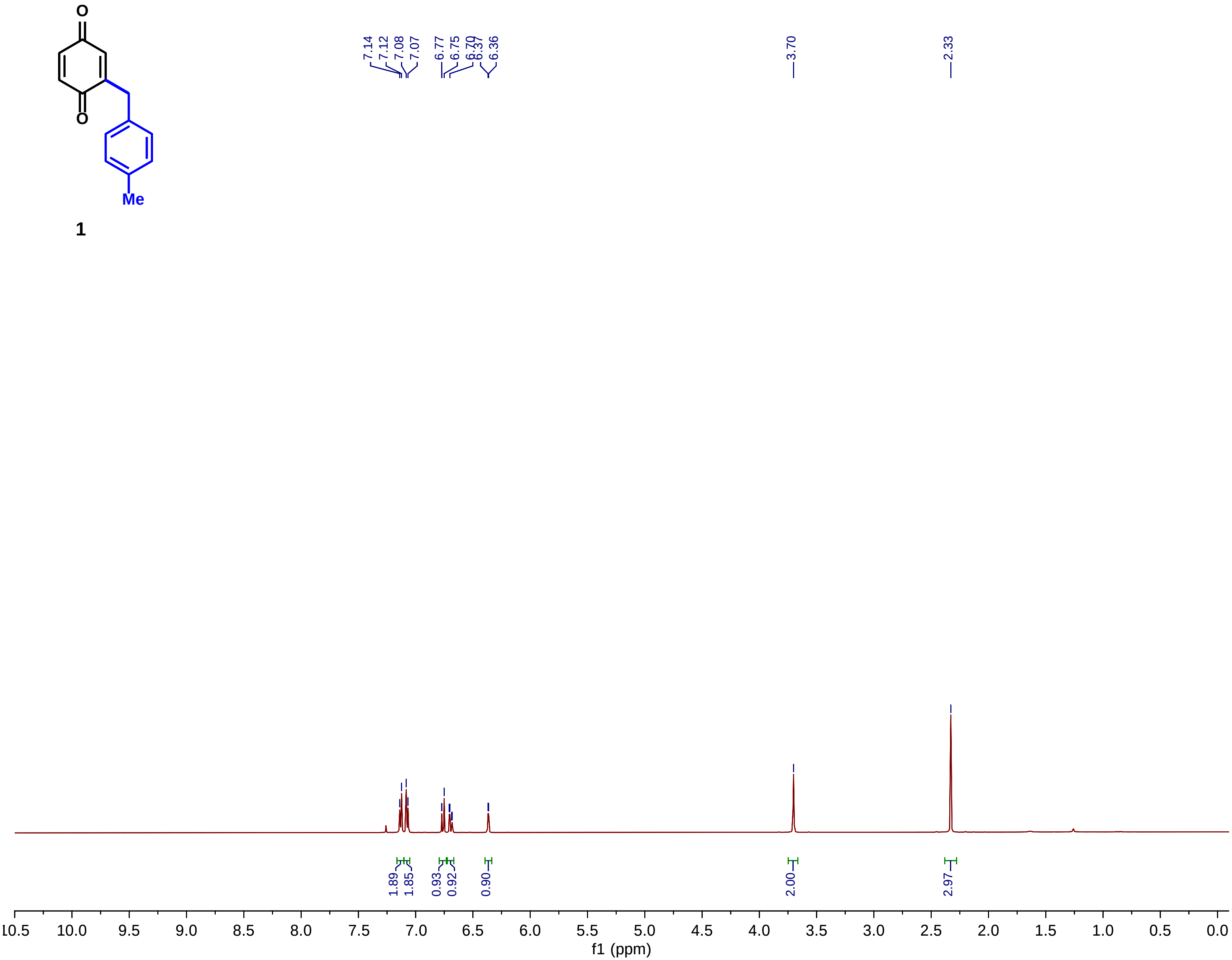
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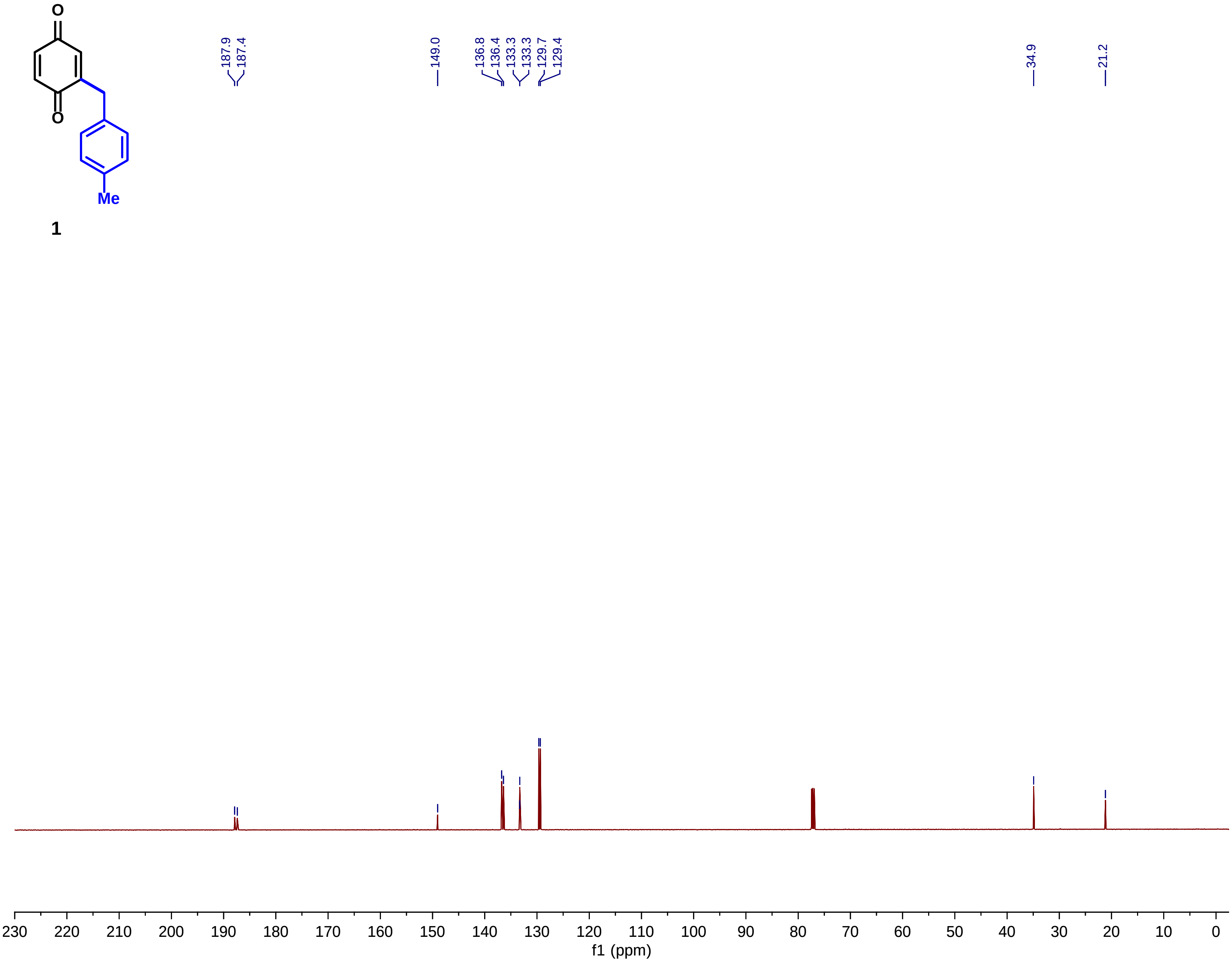
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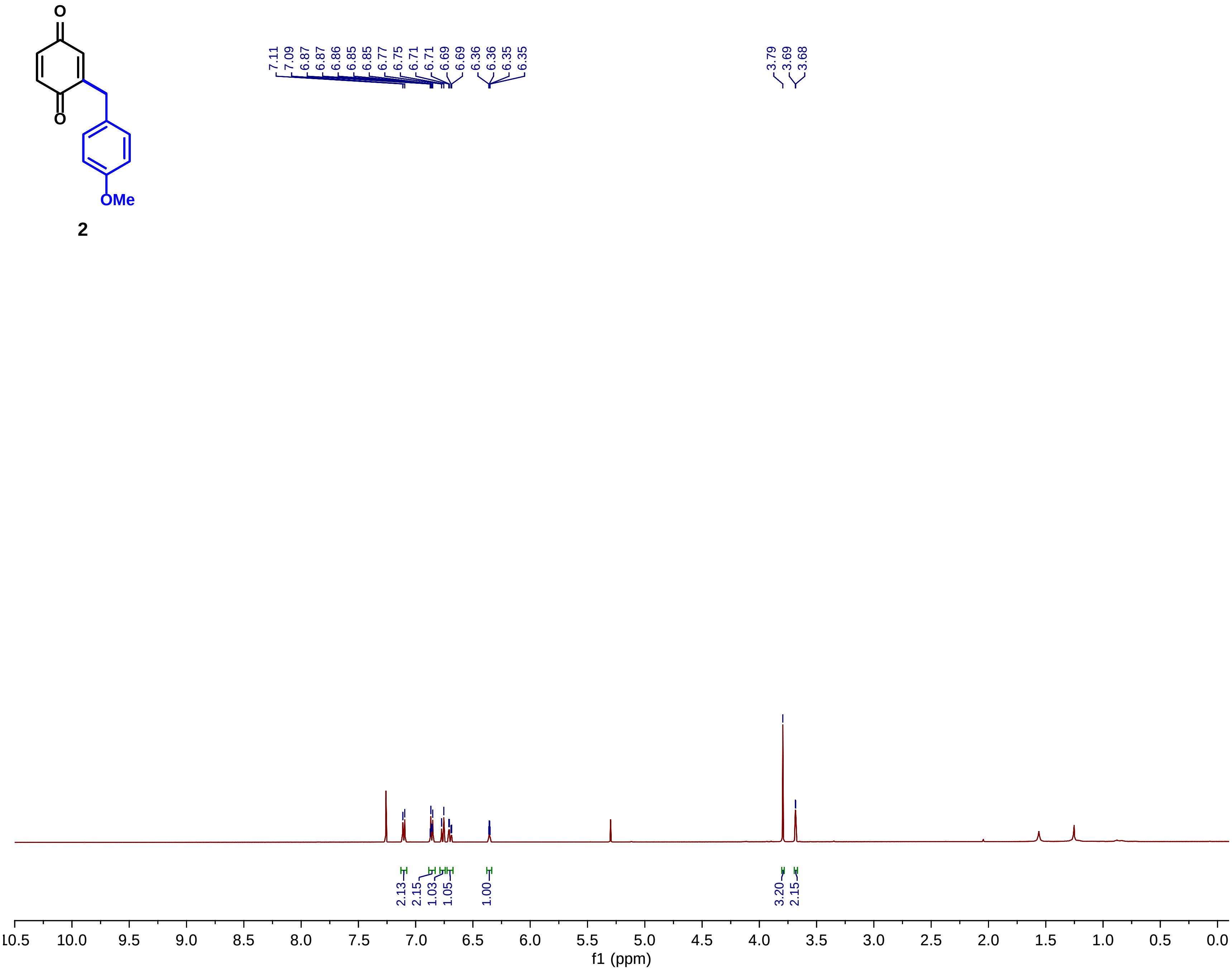
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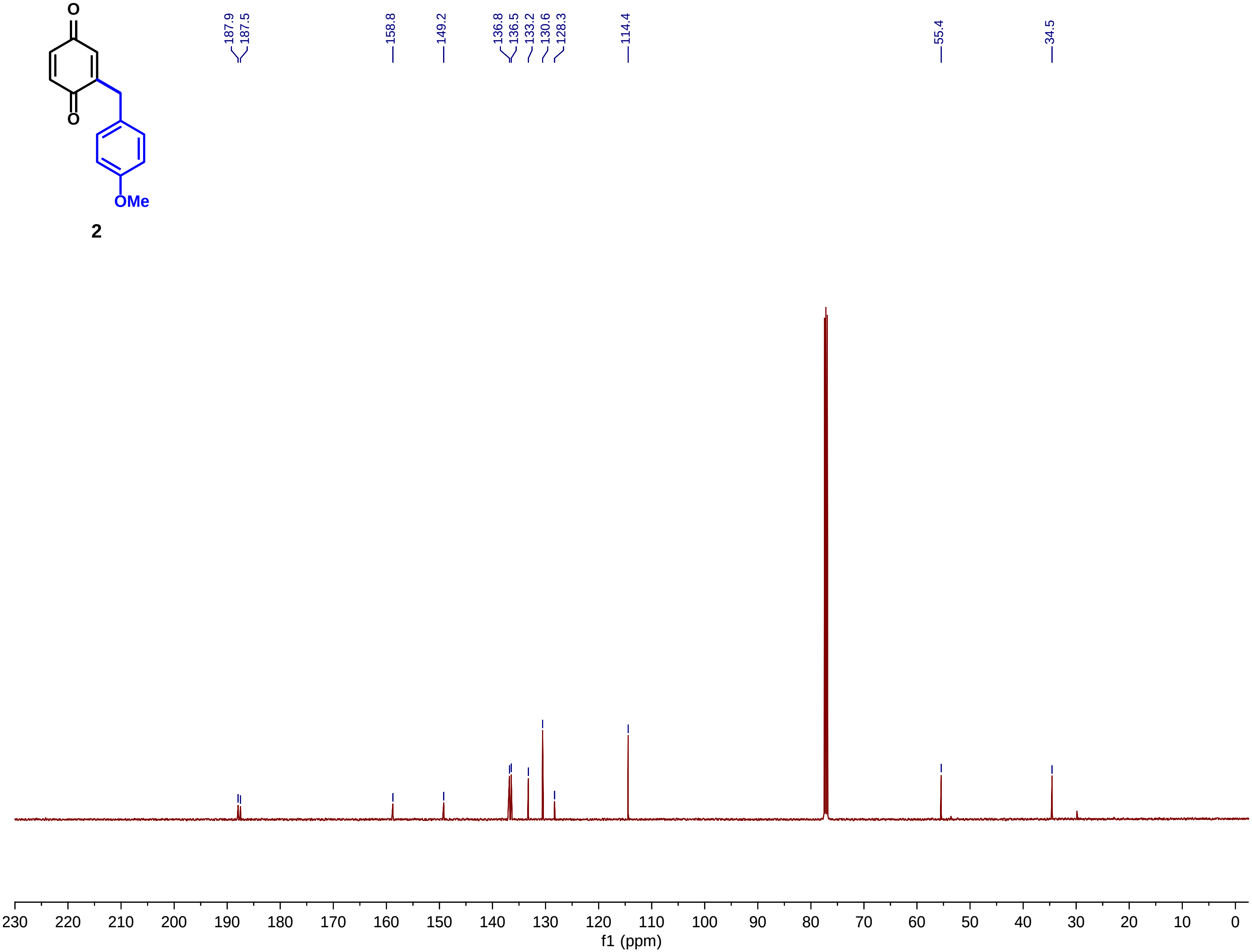
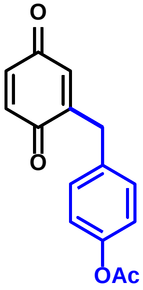
1.03
1.05
1.00
3.20
2.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

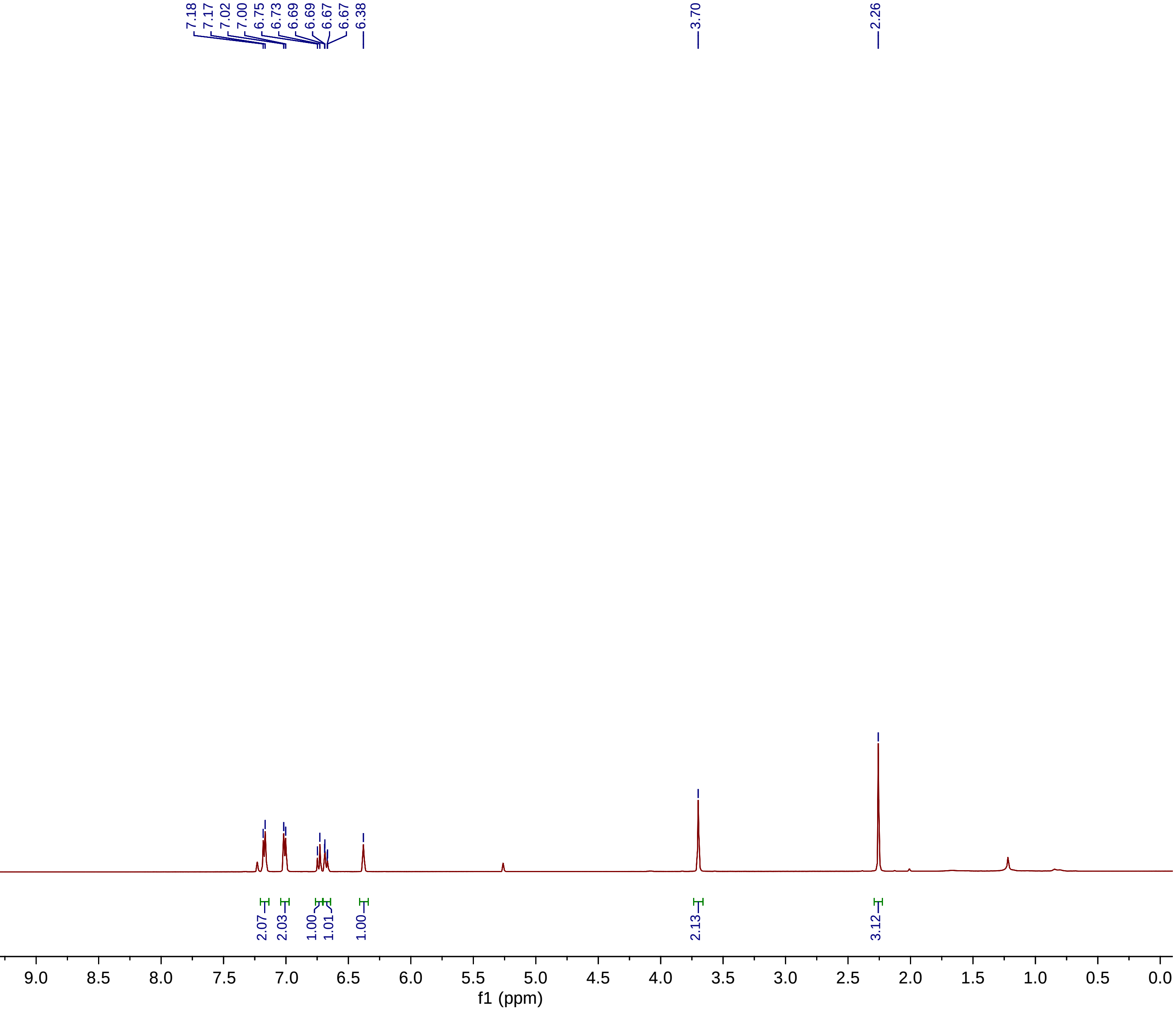

O
O
OMe

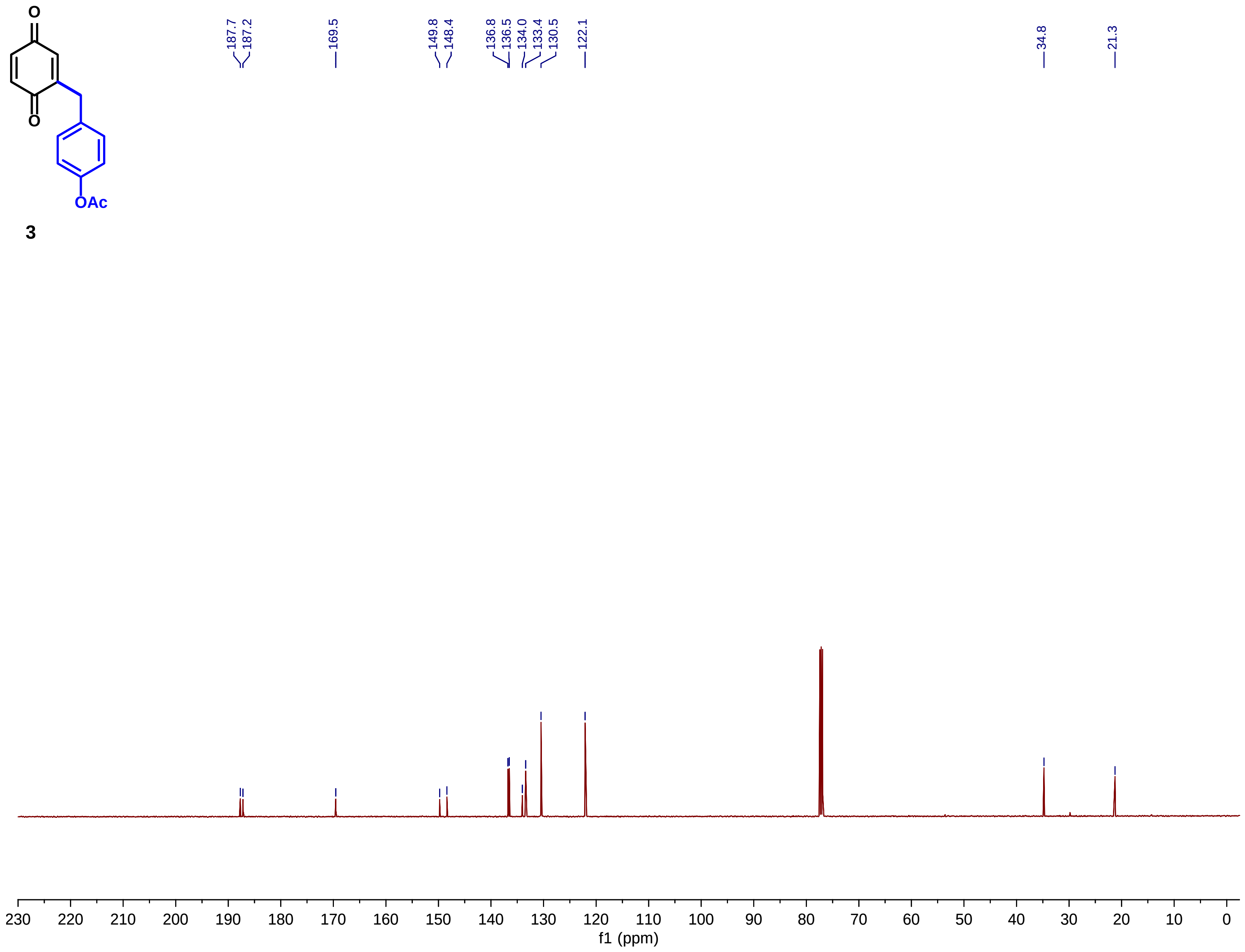
2

187.9
187.5
158.8
149.2
136.8
136.5
133.2
130.6
128.3
114.4
55.4
34.5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

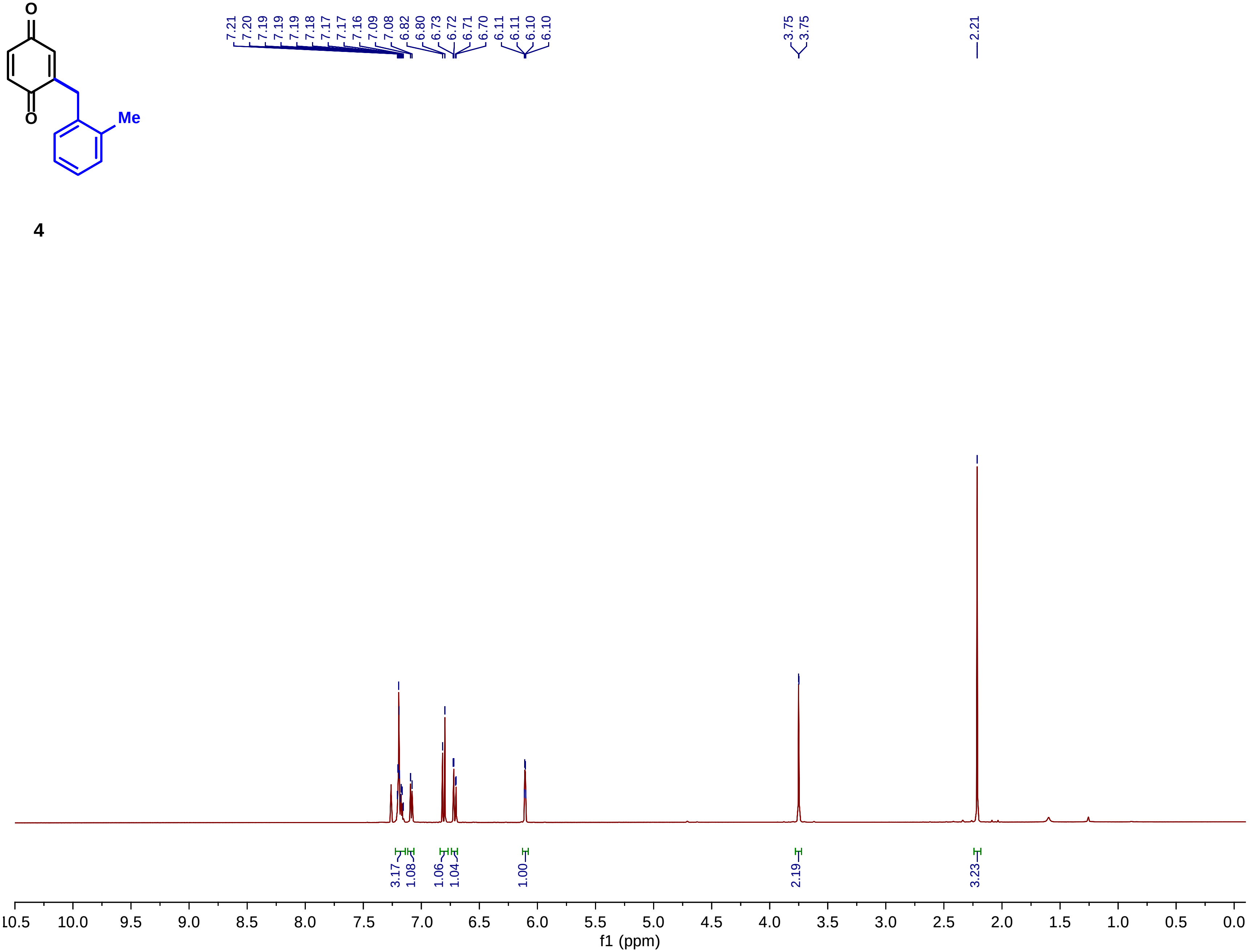

O
O
OAc

3

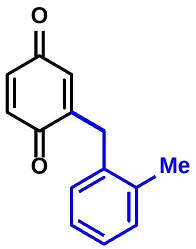

7.18
7.17
7.02
7.00
6.75
6.73
6.69
6.69
6.67
6.67
6.38
3.70
2.26
2.07
2.03
1.00
1.01
1.00
2.13
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
OAc
187.7
187.2
169.5
149.8
148.4
136.8
136.5
134.0
133.4
130.5
122.1
34.8
21.3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

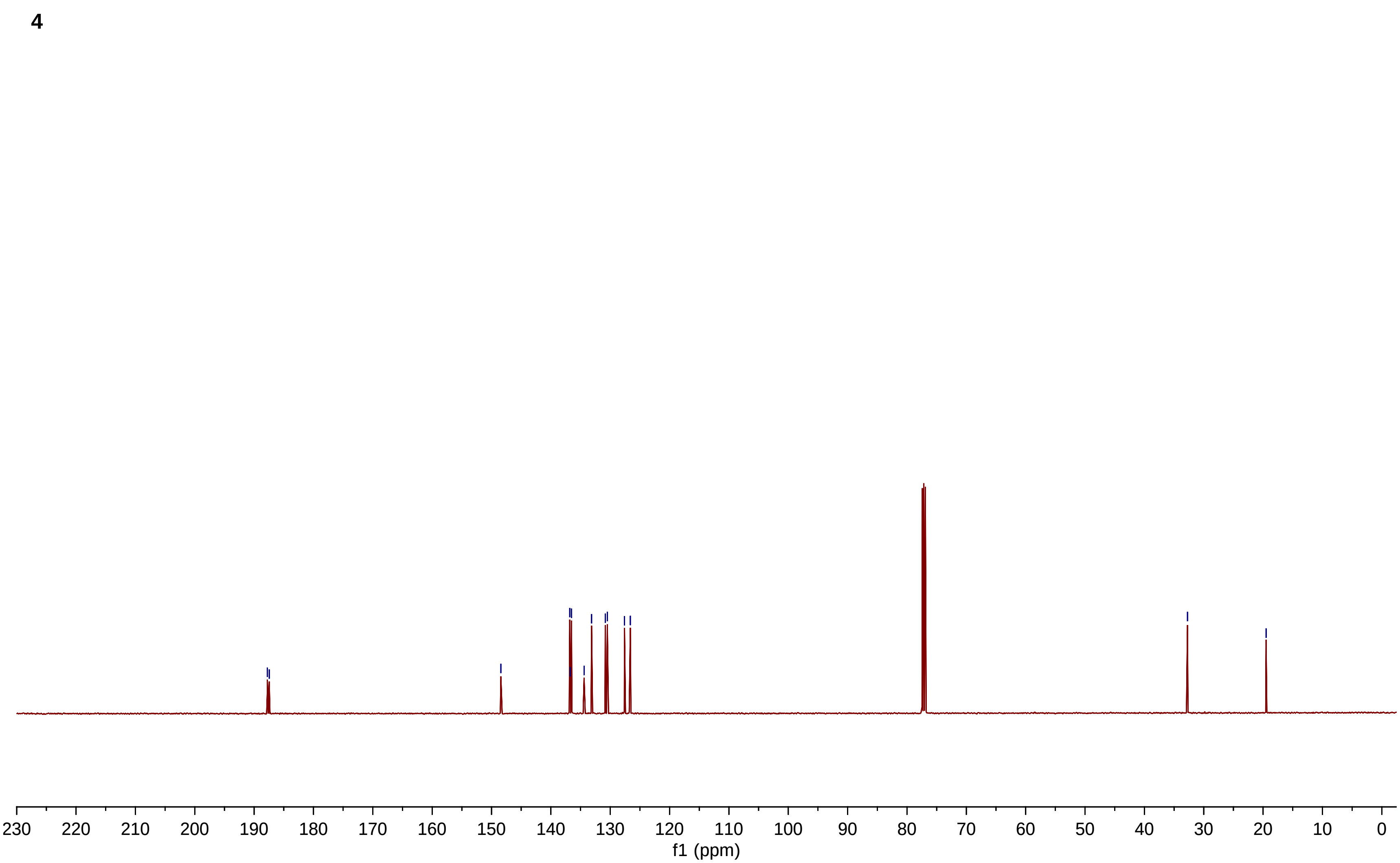
3

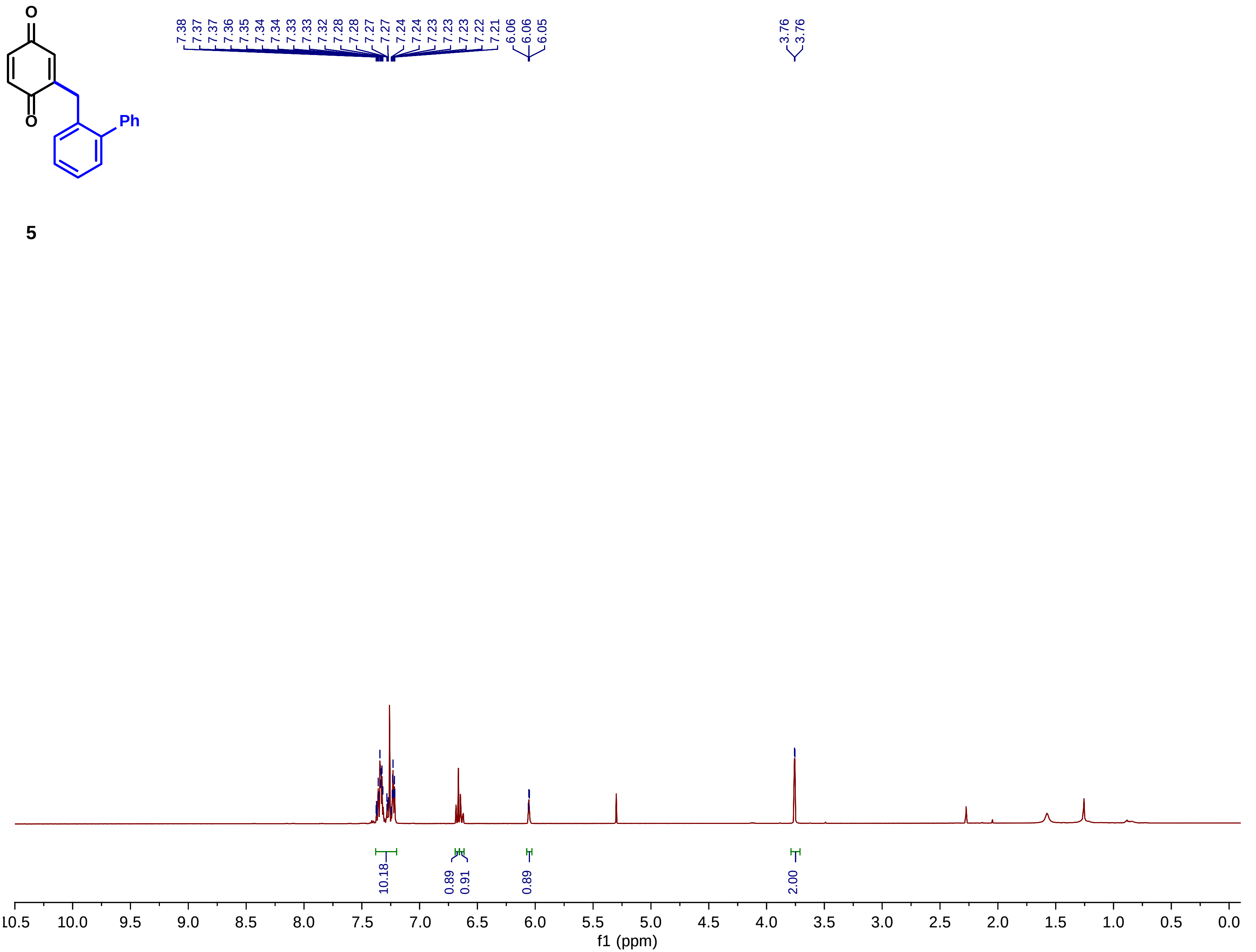

O
O
Me
7.21
7.20
7.19
7.19
7.19
7.18
7.17
7.17
7.16
7.09
7.08
6.82
6.80
6.73
6.72
6.71
6.70
6.11
6.11
6.10
6.10
3.75
3.75
2.21
3.17
1.08
1.06
1.04
1.00
2.19
3.23
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

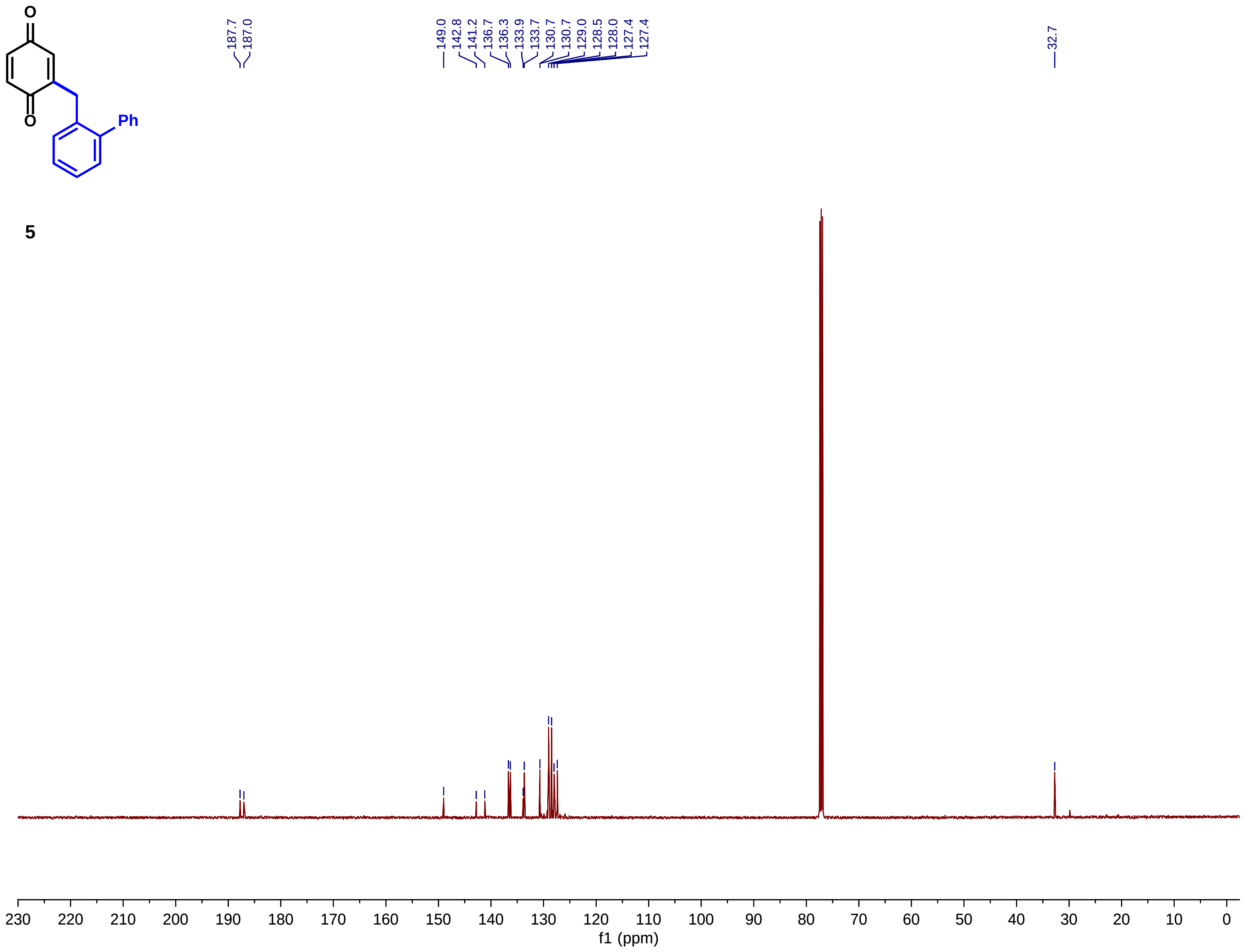
4

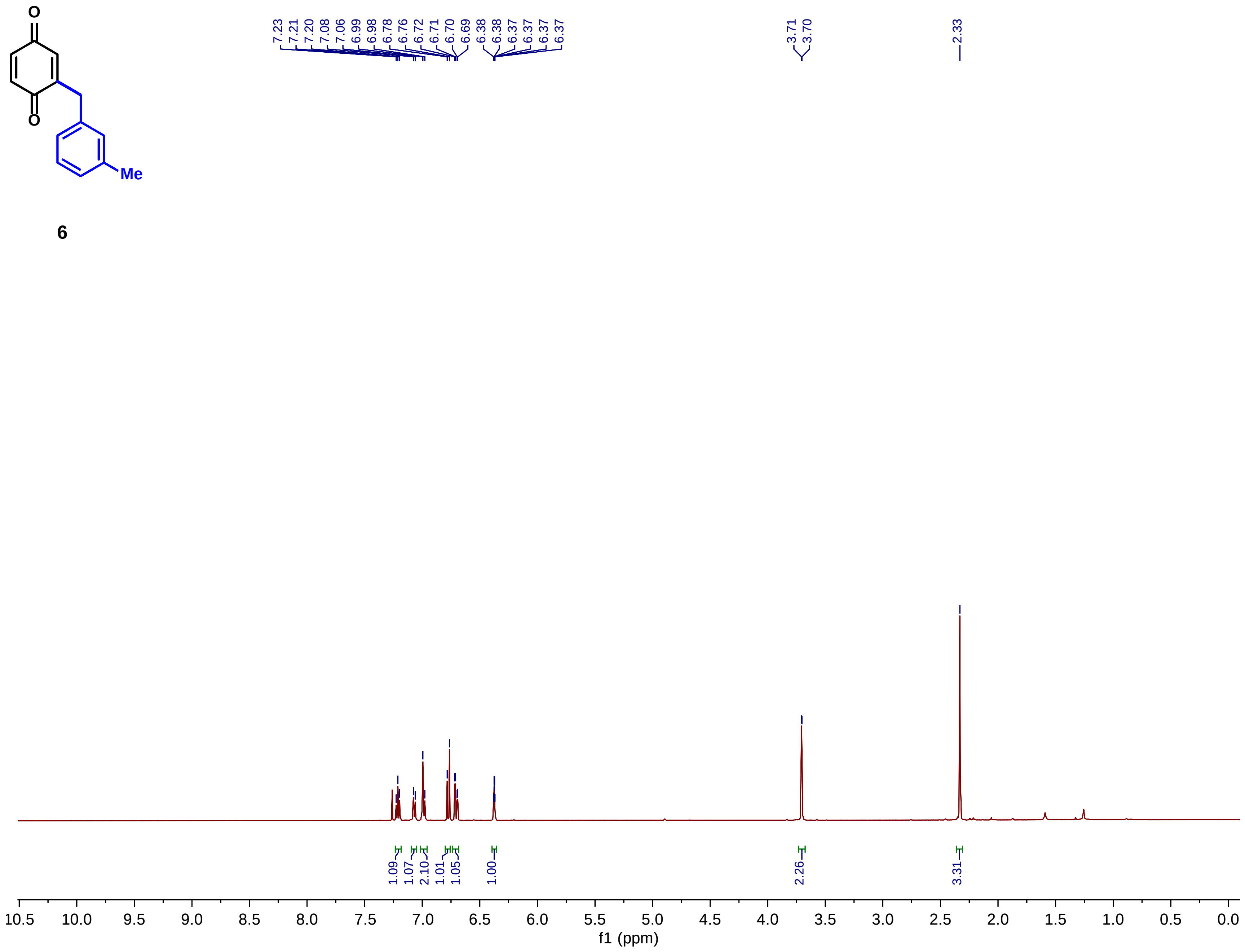

O
O
Me

4

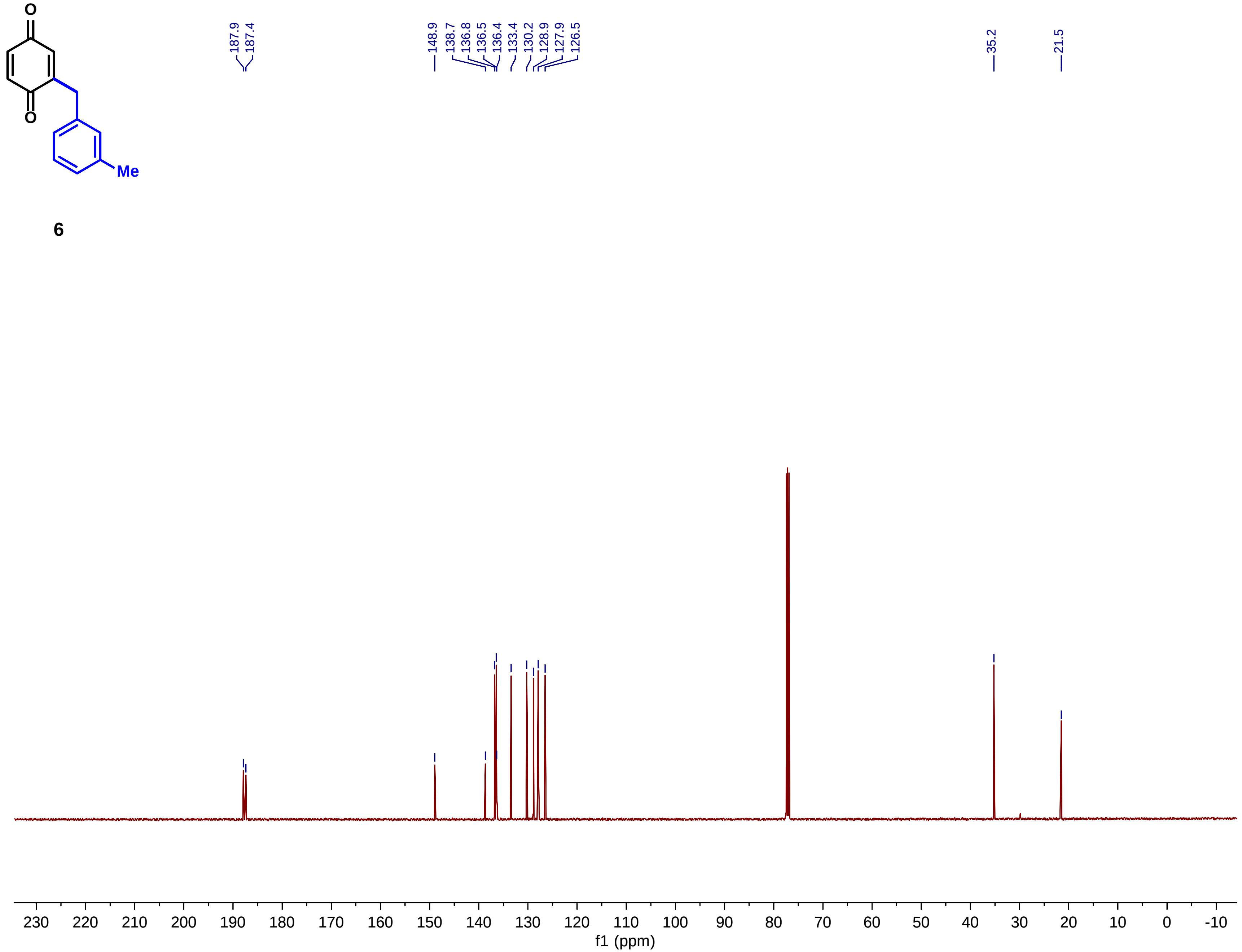

187.8
187.5
148.4
136.8
136.7
136.5
134.4
133.1
130.8
130.5
127.6
126.6
32.7
19.5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
Ph
5
7.38
7.37
7.37
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.28
7.28
7.27
7.27
7.24
7.24
7.23
7.23
7.23
7.22
7.21
6.06
6.06
6.05
3.76
3.76
10.18
0.89
0.91
0.89
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

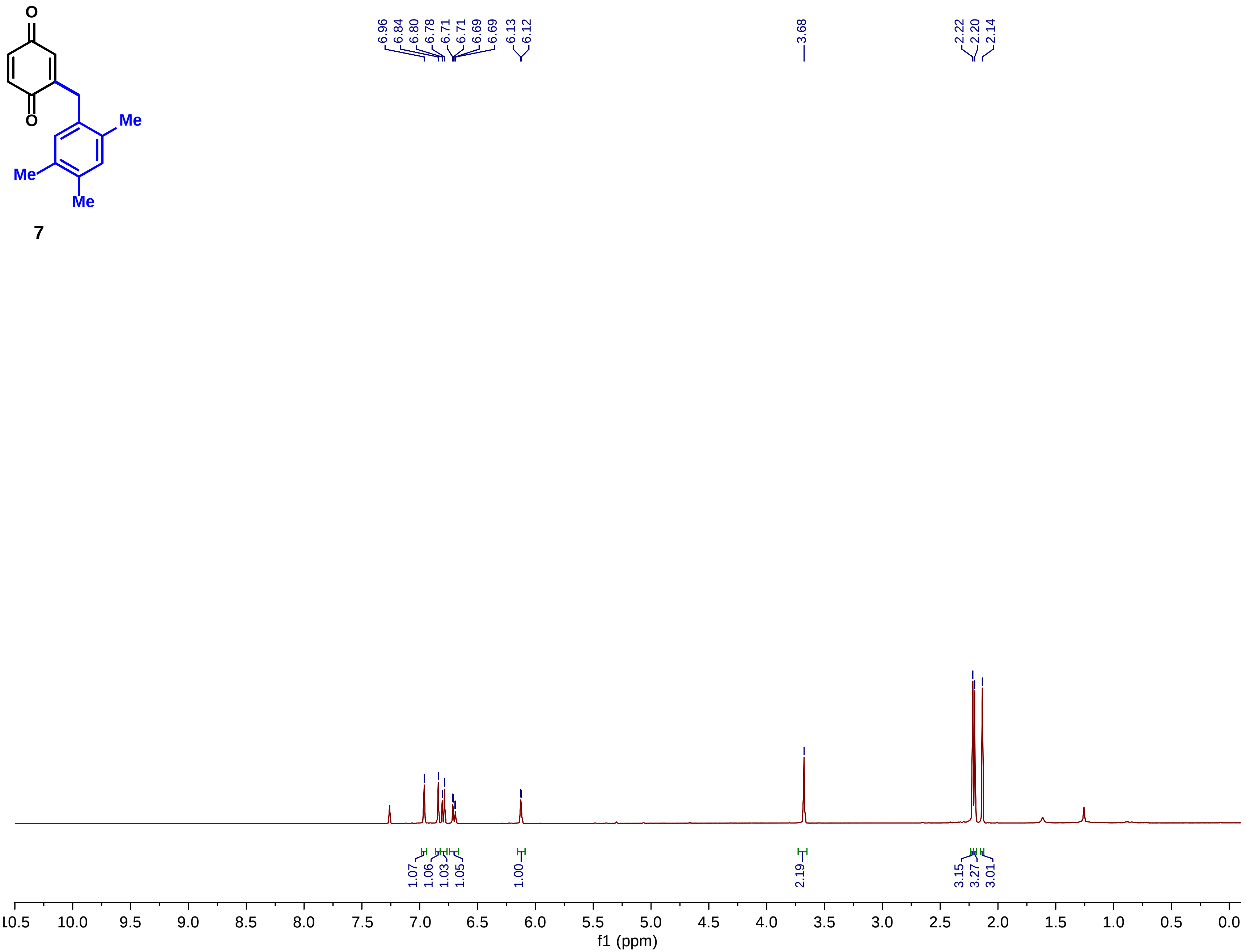

O
O
Ph
5
187.7
187.0
149.0
142.8
141.2
136.7
136.3
133.9
133.7
130.7
130.7
129.0
128.5
128.0
127.4
127.4
32.7
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

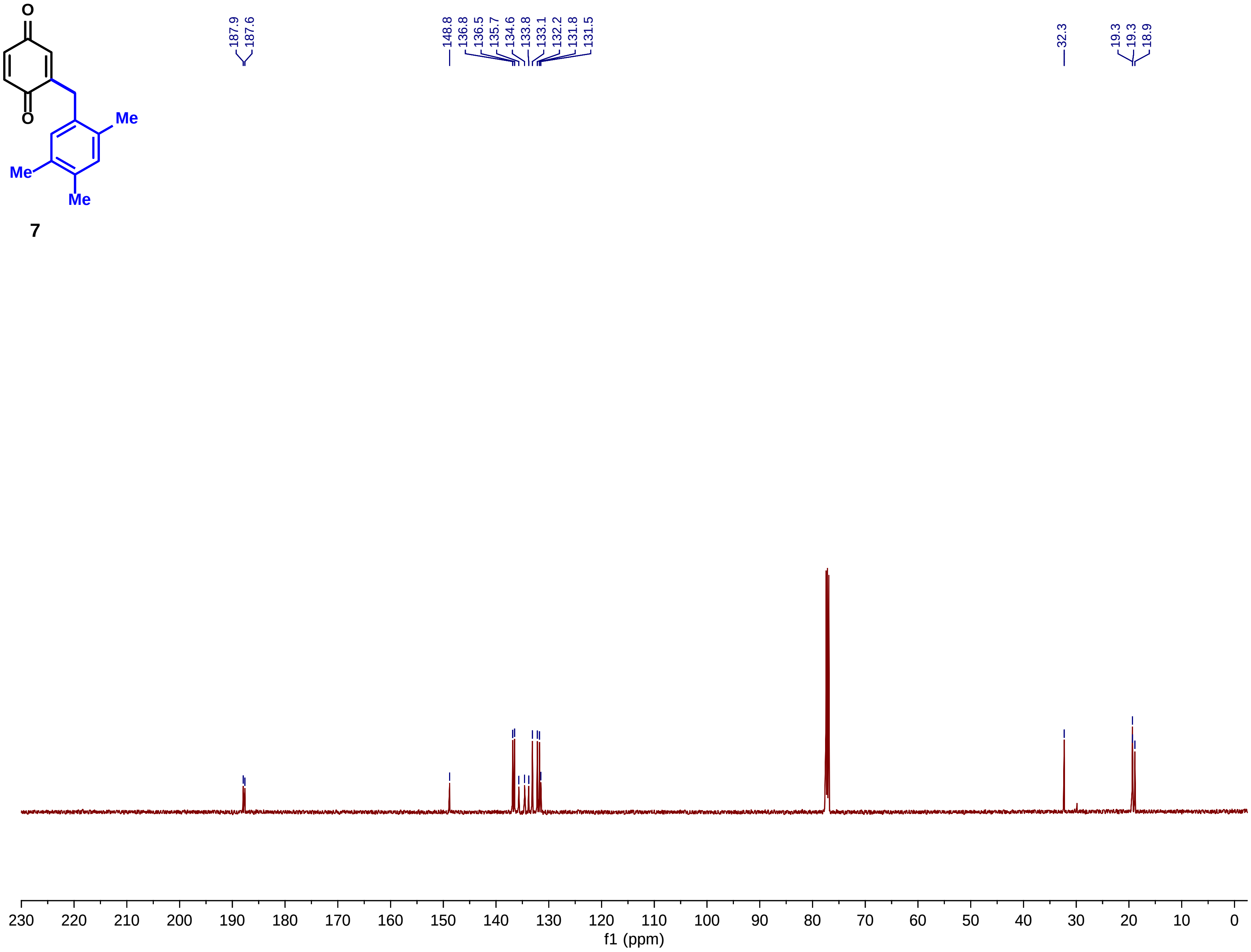

O
O
Me
7.23
7.21
7.20
7.08
7.06
6.99
6.98
6.78
6.76
6.72
6.71
6.70
6.69
6.38
6.38
6.37
6.37
6.37
6.37
3.71
3.70
2.33
1.09
1.07
2.10
1.01
1.05
1.00
2.26
3.31
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

6

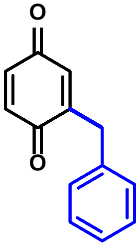

O
O
Me
187.9
187.4
148.9
138.7
136.8
136.5
136.4
133.4
130.2
128.9
127.9
126.5
35.2
21.5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

6

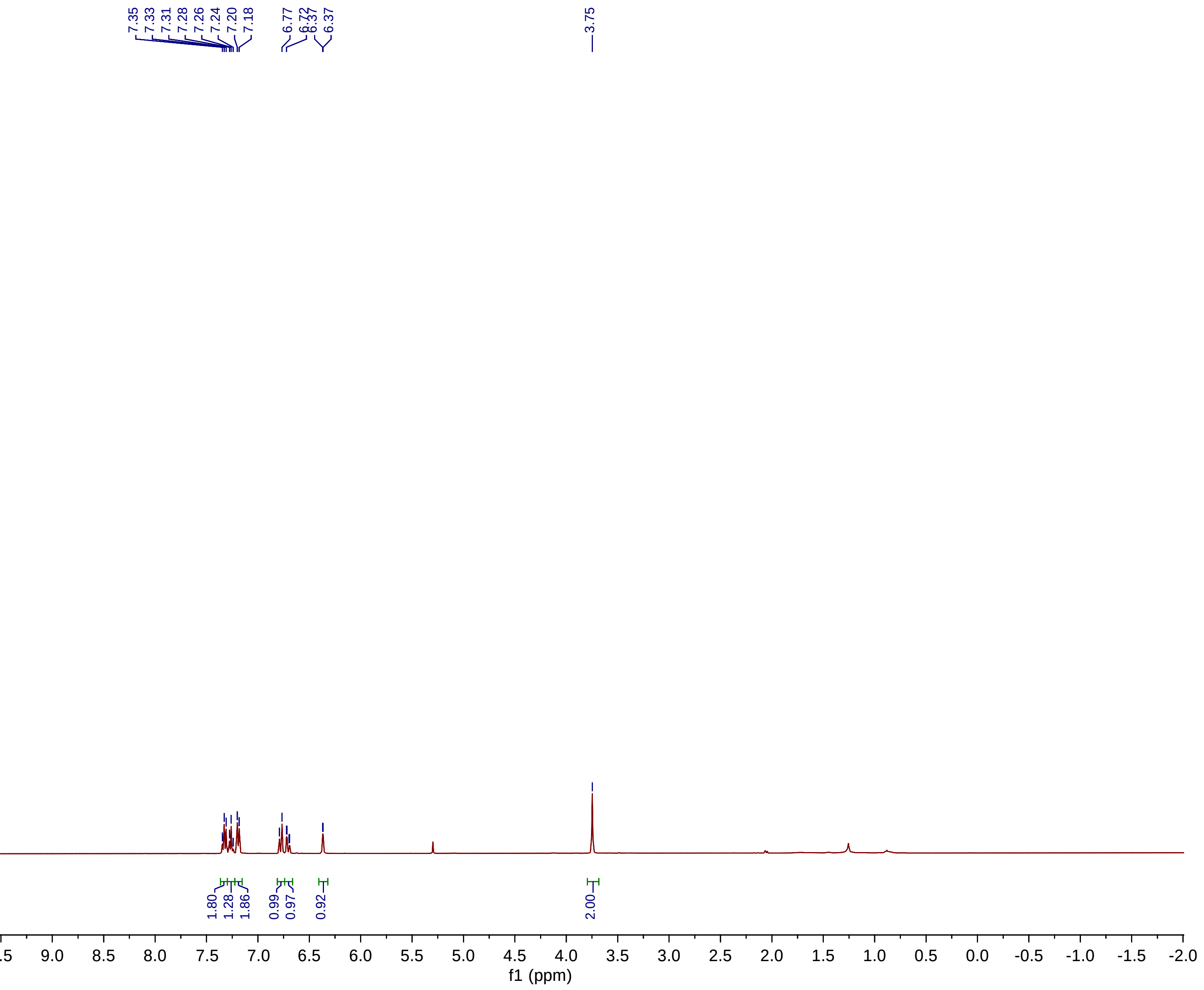

O
O
Me
Me
Me
7
6.96
6.84
6.80
6.78
6.71
6.71
6.69
6.69
6.13
6.12
3.68
2.22
2.20
2.14
1.07
1.06
1.03
1.05
1.00
2.19
3.15
3.27
3.01
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

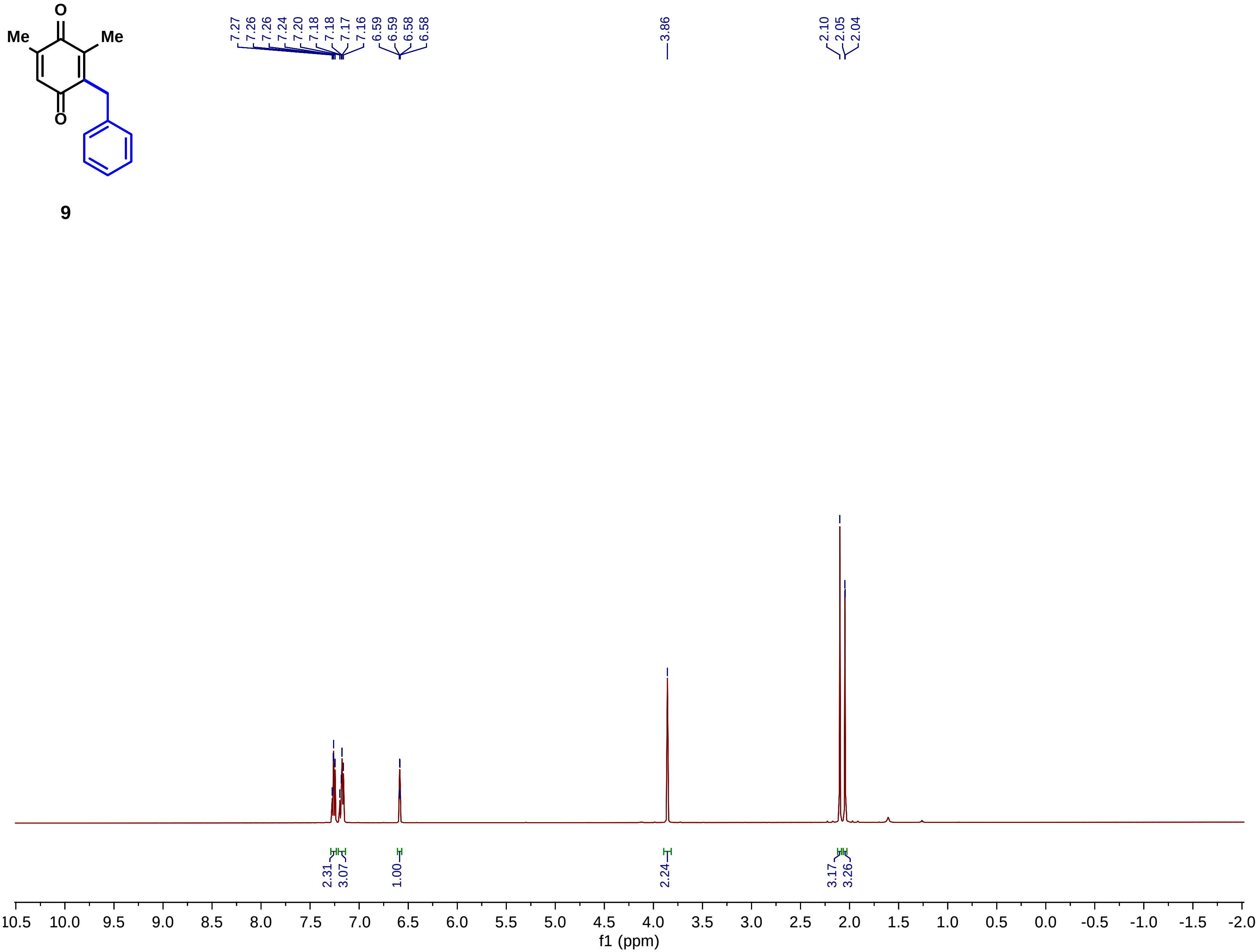

O
O
Me
Me
Me

7
187.9
187.6
148.8
136.8
136.5
135.7
134.6
133.8
133.1
132.2
131.8
131.5
32.3
19.3
19.3
18.9
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

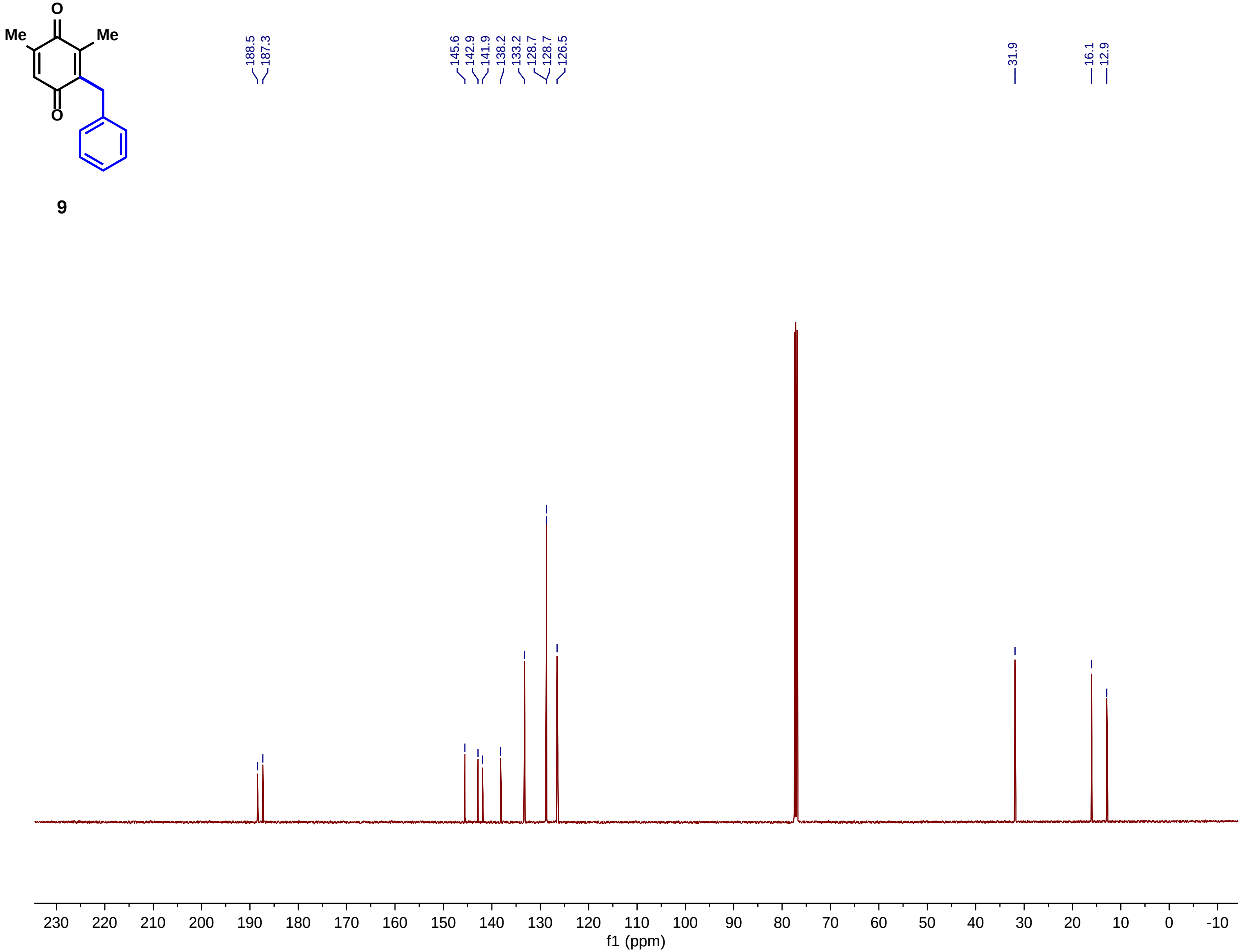

O
O

8


7.35
7.33
7.31
7.28
7.26
7.24
7.20
7.18
6.77
6.72
6.37
6.37
3.75
1.80
1.28
1.86
0.99
0.97
0.92
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)

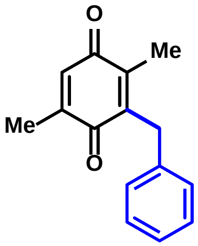

O
Me
Me
O
7.27
7.26
7.26
7.24
7.20
7.18
7.18
7.17
7.16
6.59
6.59
6.58
6.58
3.86
2.10
2.05
2.04
2.31
3.07
1.00
2.24
3.17
3.26
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)

9

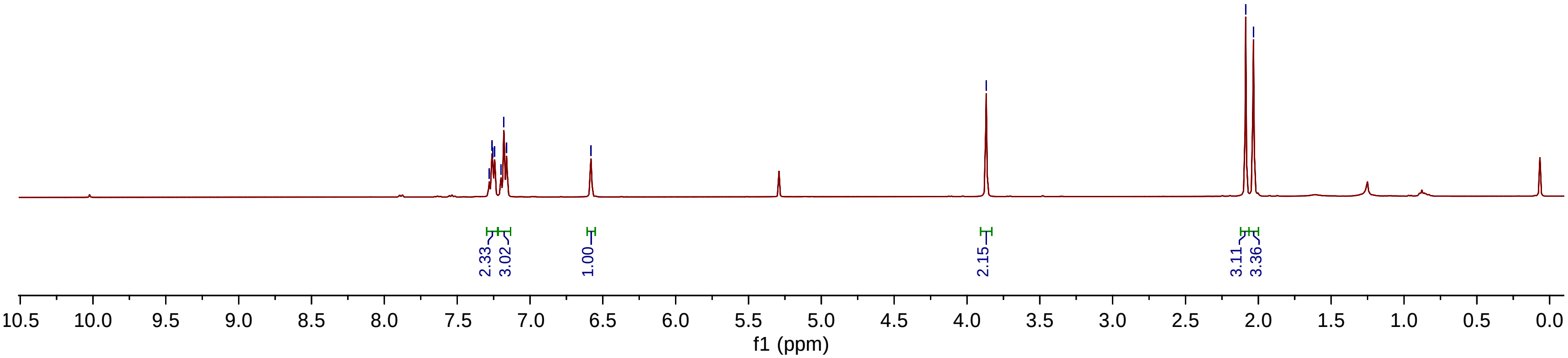


9

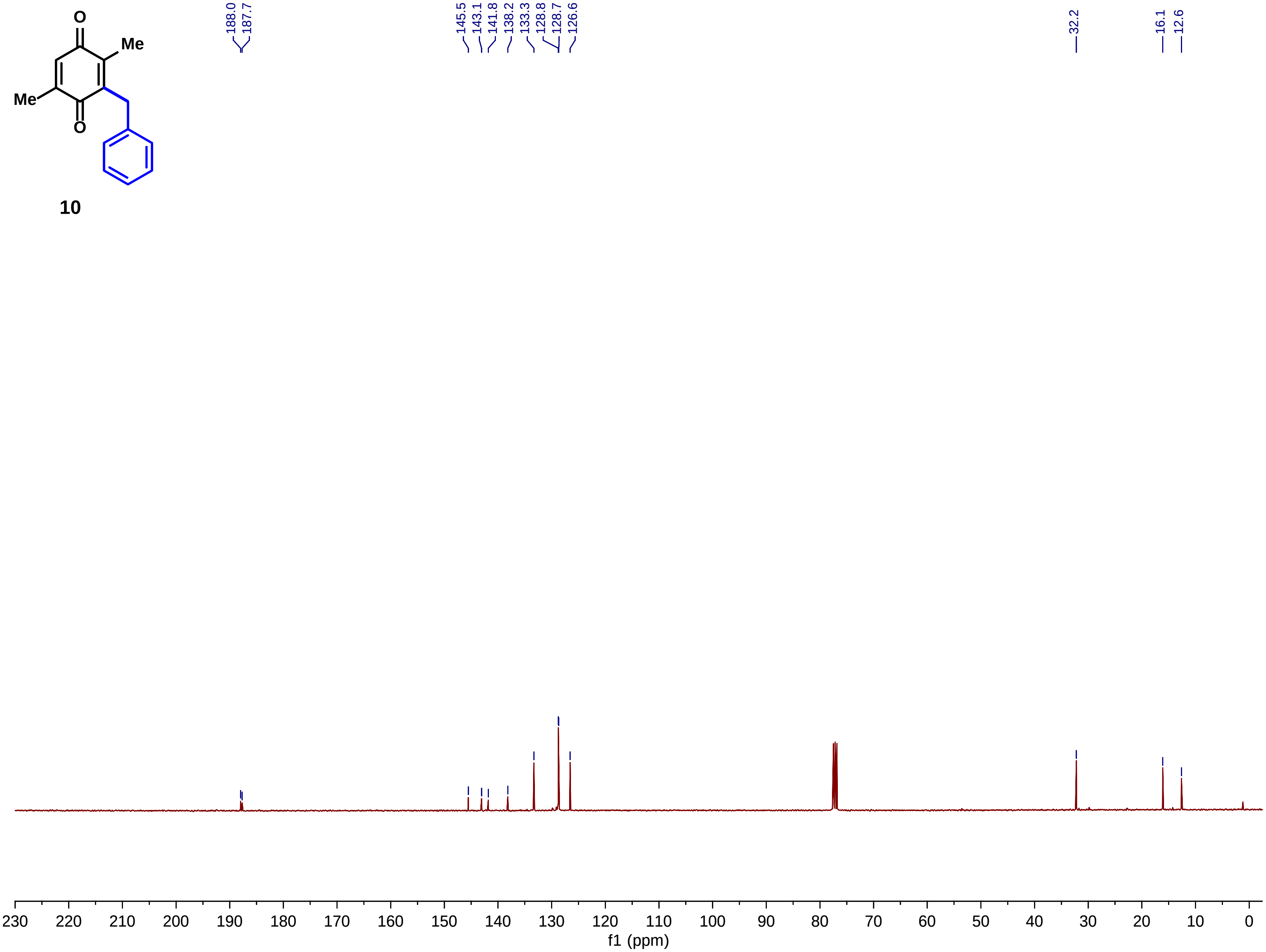
O
Me
Me
O
188.5
187.3
145.6
142.9
141.9
138.2
133.2
128.7
128.7
126.5
31.9
16.1
12.9
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

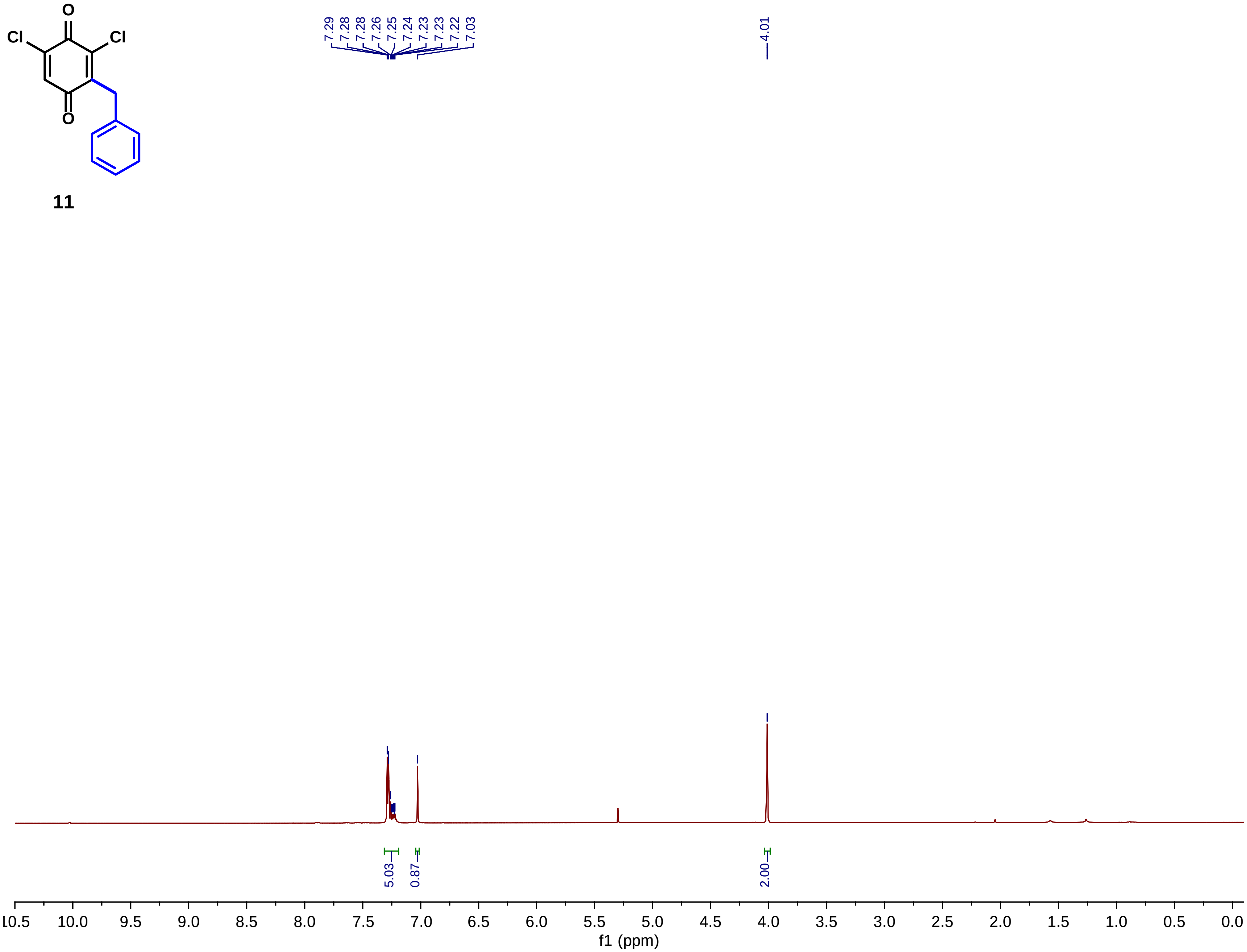

O
Me
Me
O

10


7.28
7.26
7.26
7.24
7.20
7.18
7.16
6.58
3.87
2.09
2.03
2.33
3.02
1.00
2.15
3.11
3.36
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

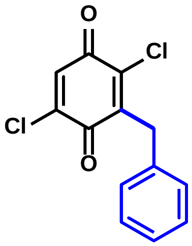
10


188.0
187.7
145.5
143.1
141.8
138.2
133.3
128.8
128.7
126.6
32.2
16.1
12.6
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

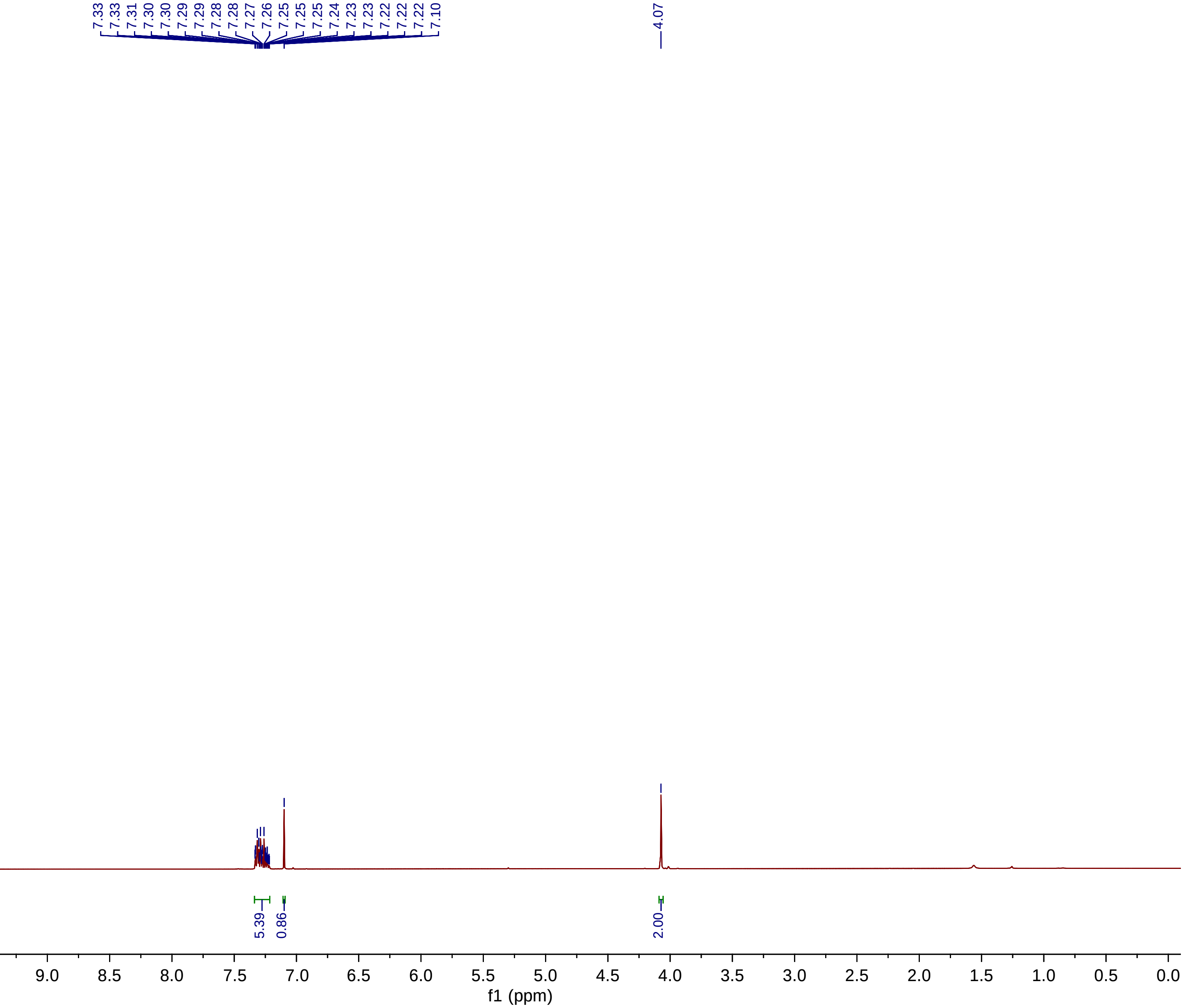


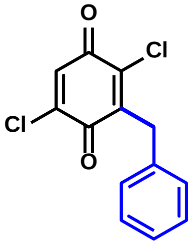
11

7.29
7.28
7.28
7.26
7.25
7.24
7.23
7.23
7.22
7.03
4.01
5.03
0.87
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

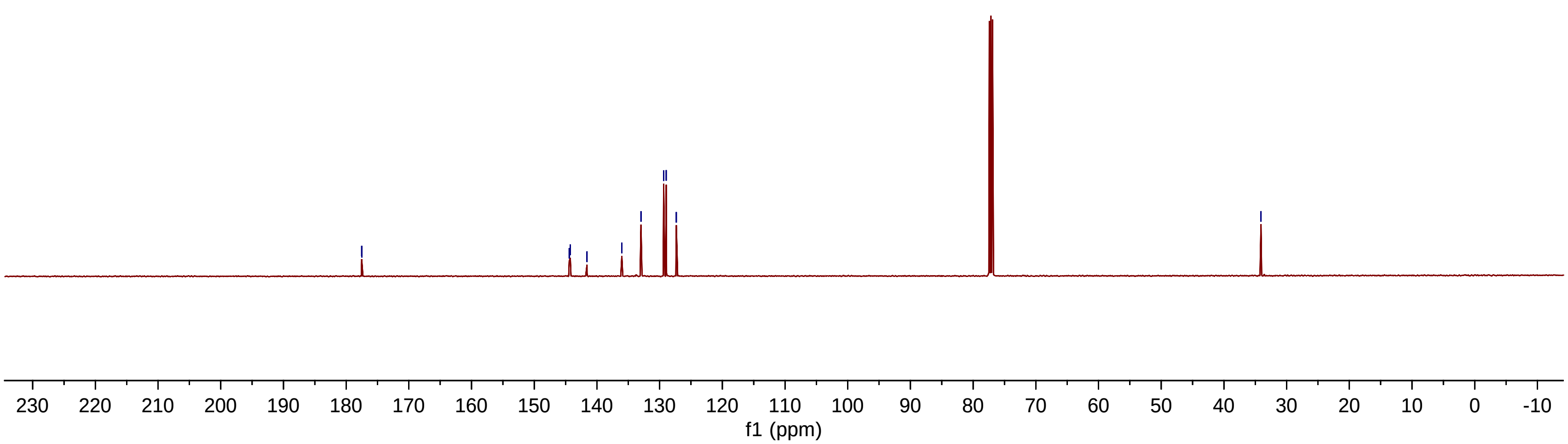

O
Cl
Cl
O

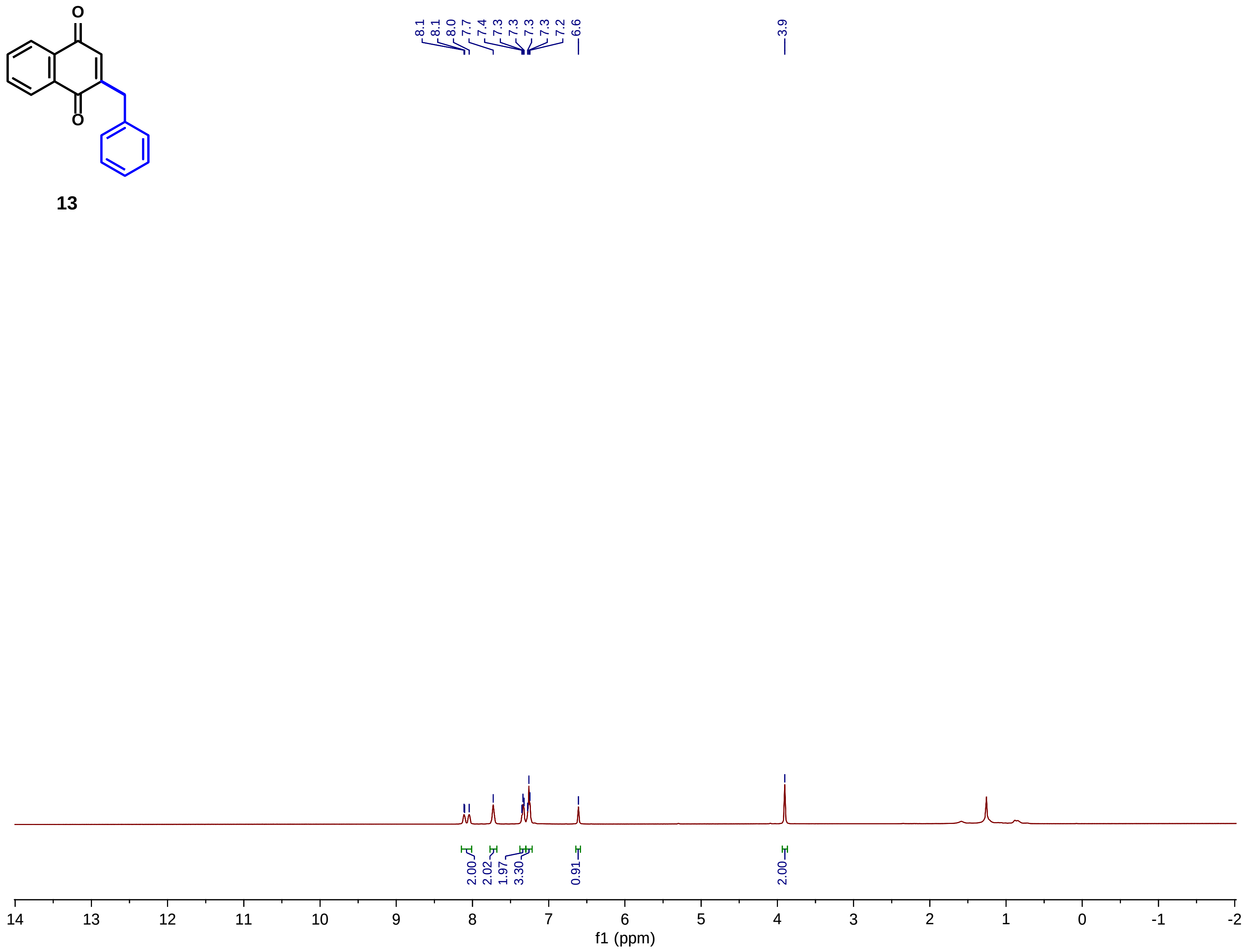
12


7.33
7.33
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.25
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.22
7.10
4.07
5.39
0.86
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
Cl
Cl
O

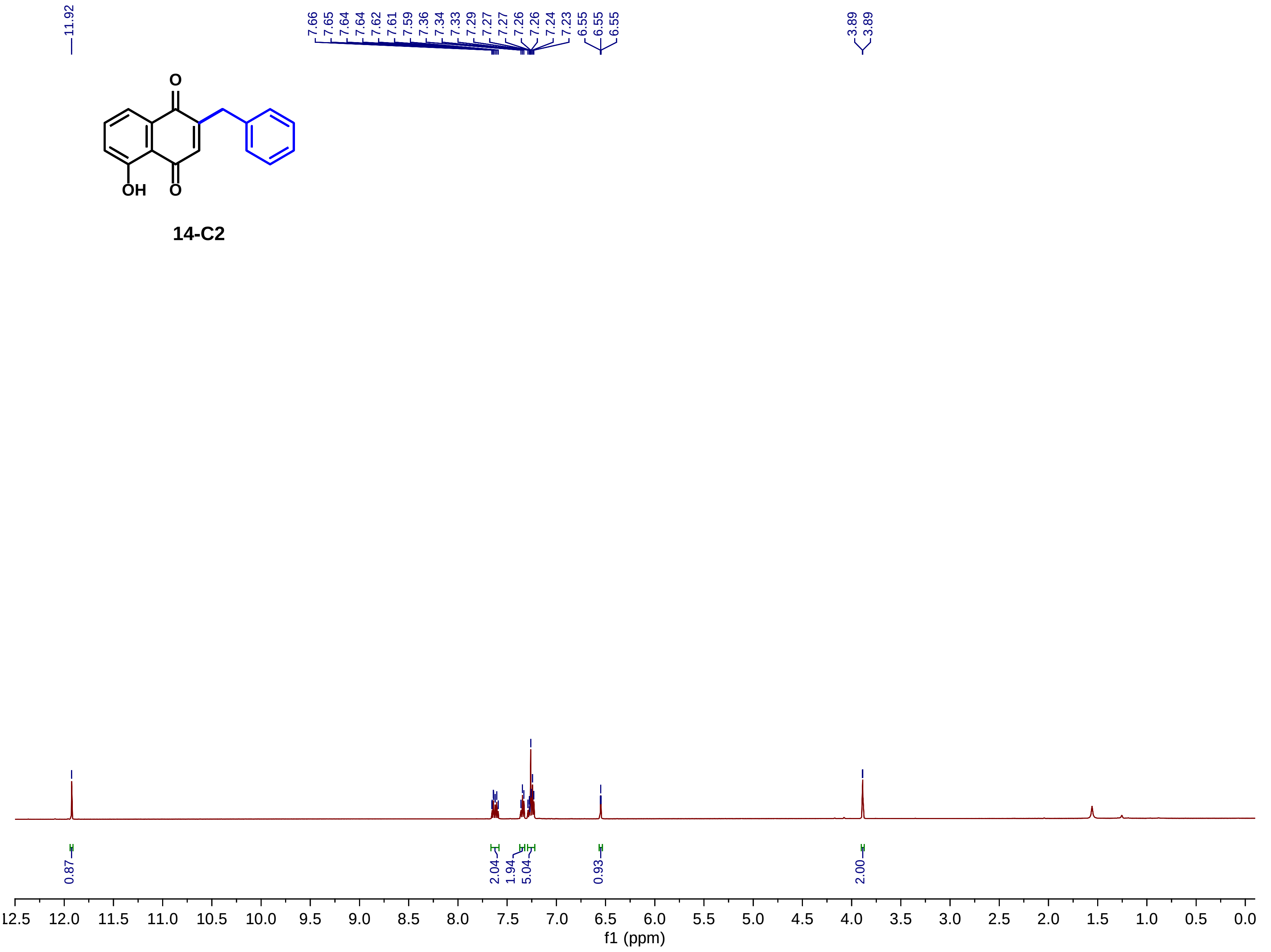
12


177.5
177.5
144.4
144.3
141.6
136.0
133.0
129.4
129.0
127.3
34.1
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

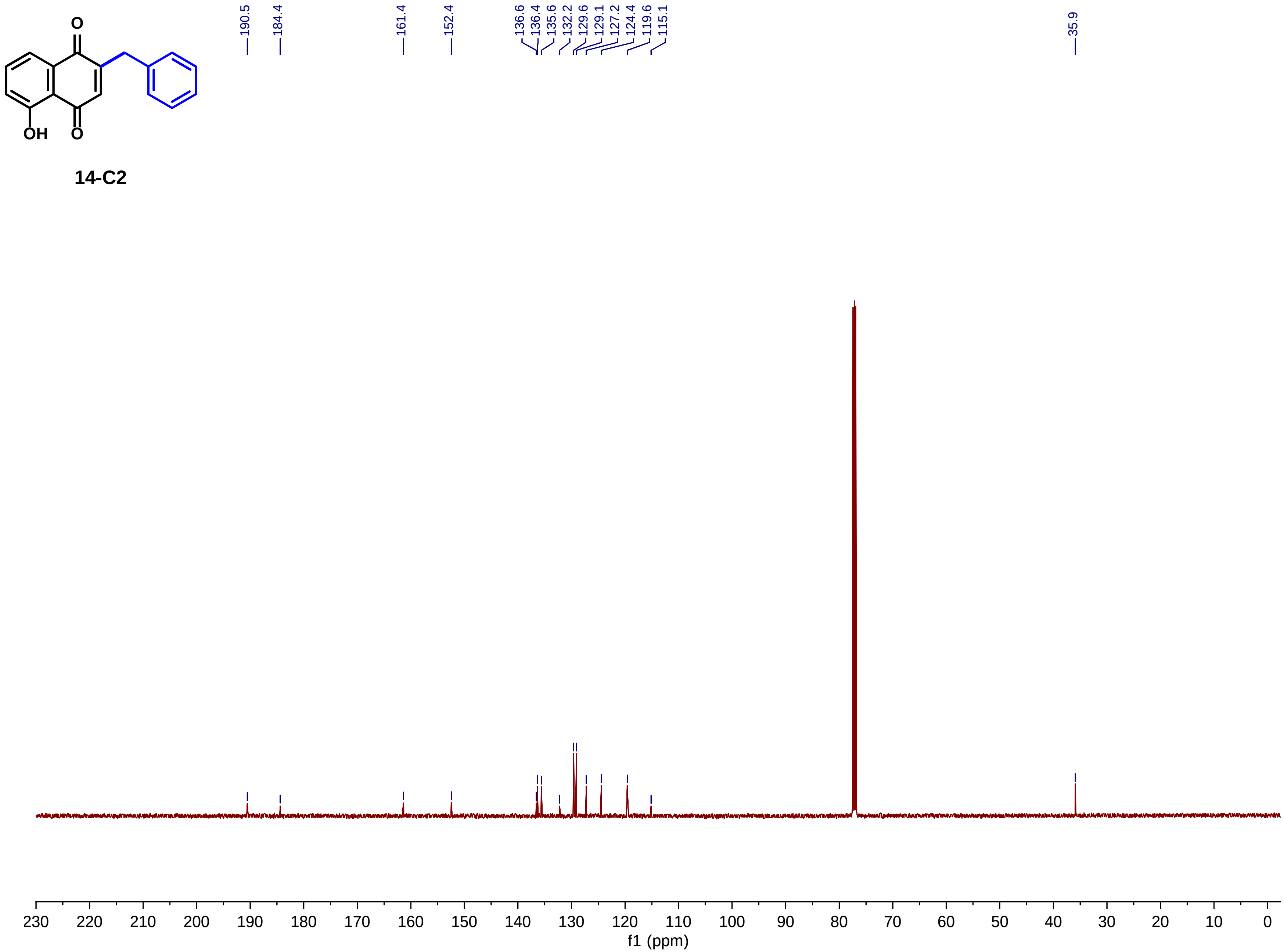


13

O
O
8.1
8.1
8.0
7.7
7.4
7.3
7.3
7.3
7.3
7.2
6.6
3.9
2.00
2.02
1.97
3.30
0.91
2.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

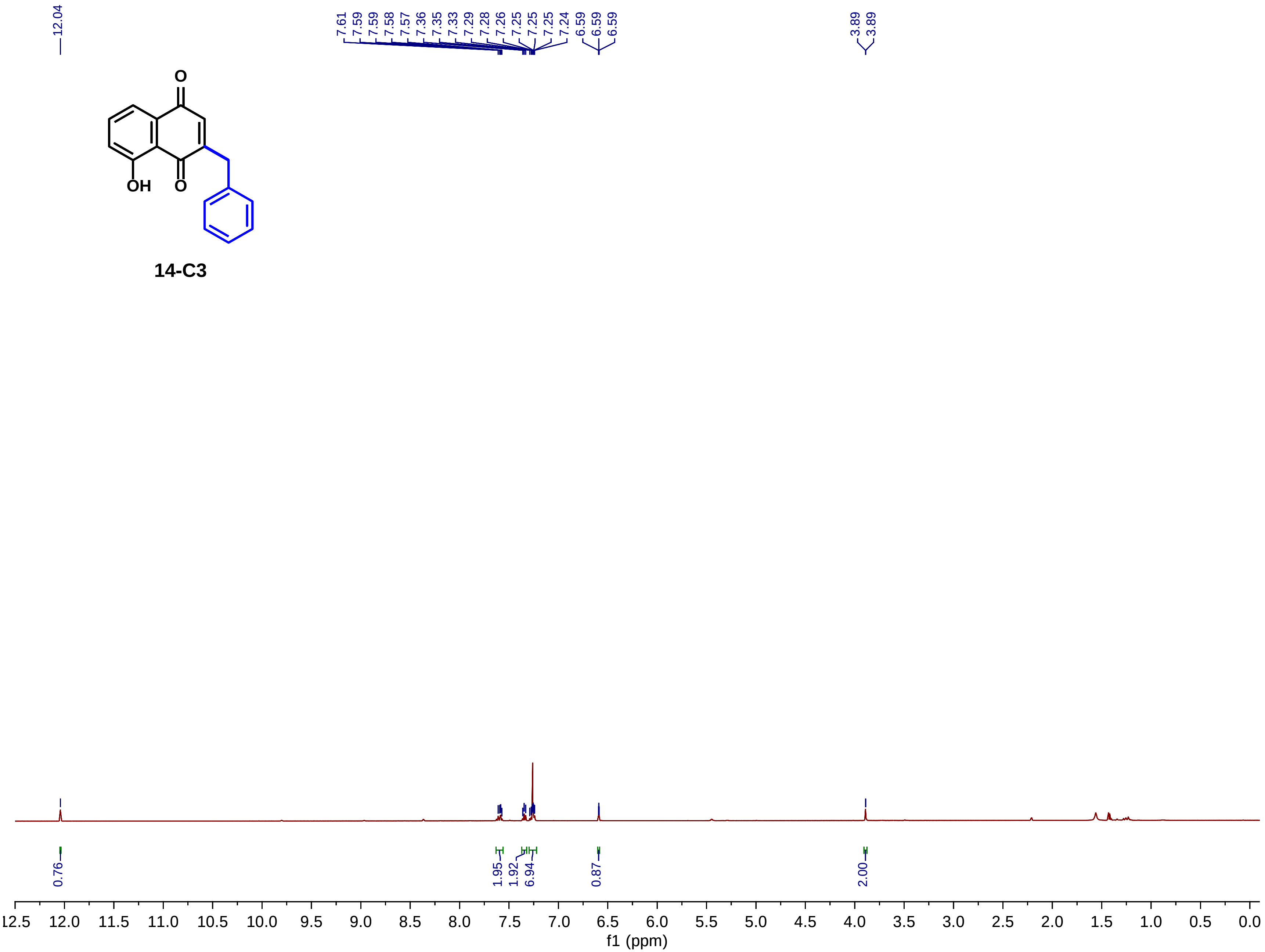

11.92
7.66
7.65
7.64
7.64
7.62
7.61
7.59
7.36
7.34
7.33
7.29
7.27
7.27
7.26
7.26
7.24
7.23
6.55
6.55
6.55
3.89
3.89
O
OH
O
0.87
2.04
1.94
5.04
0.93
2.00
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

14-C2



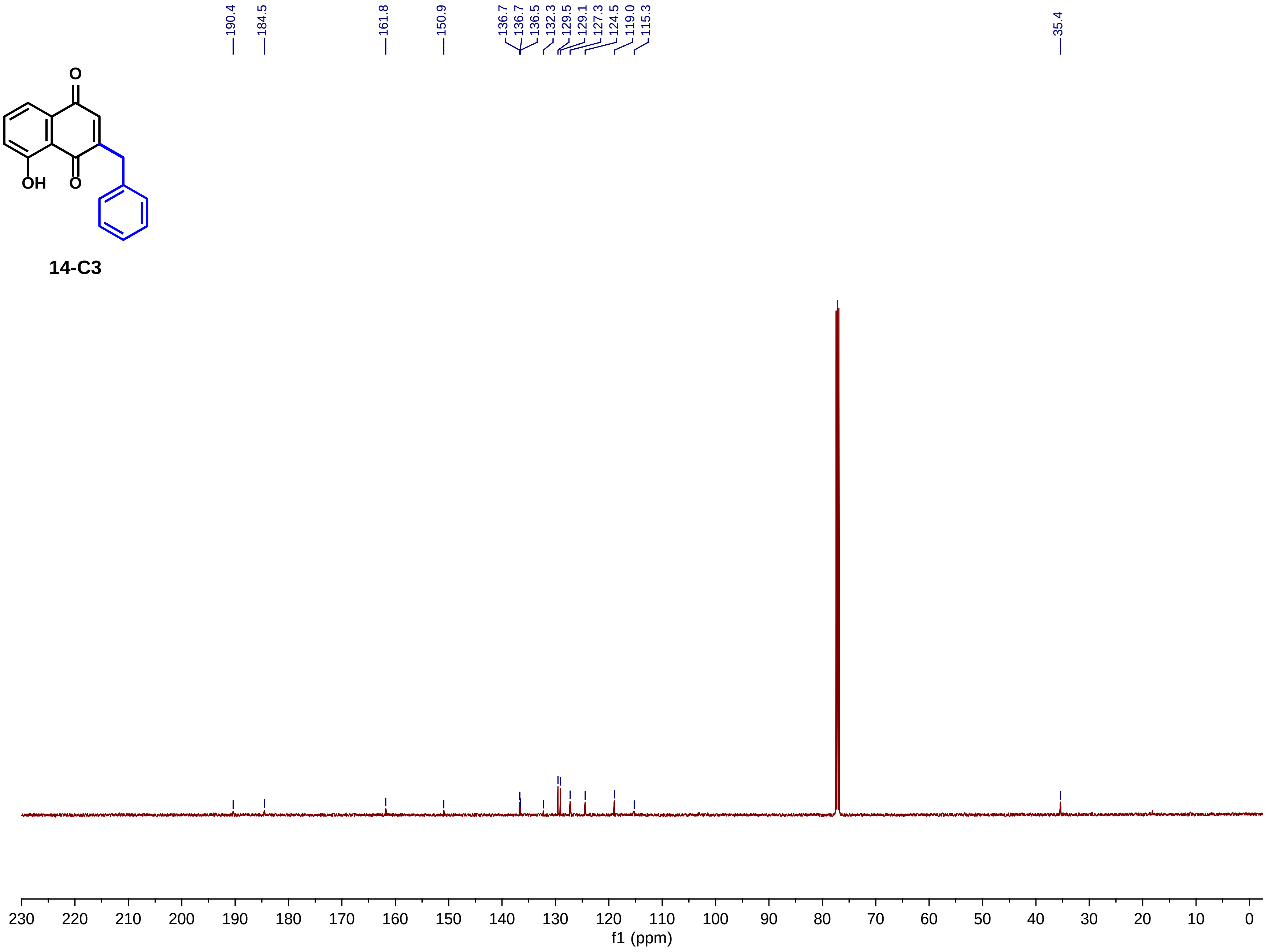
14-C2

O
OH
O
190.5
184.4
161.4
152.4
136.6
136.4
135.6
132.2
129.6
129.1
127.2
124.4
119.6
115.1
35.9
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

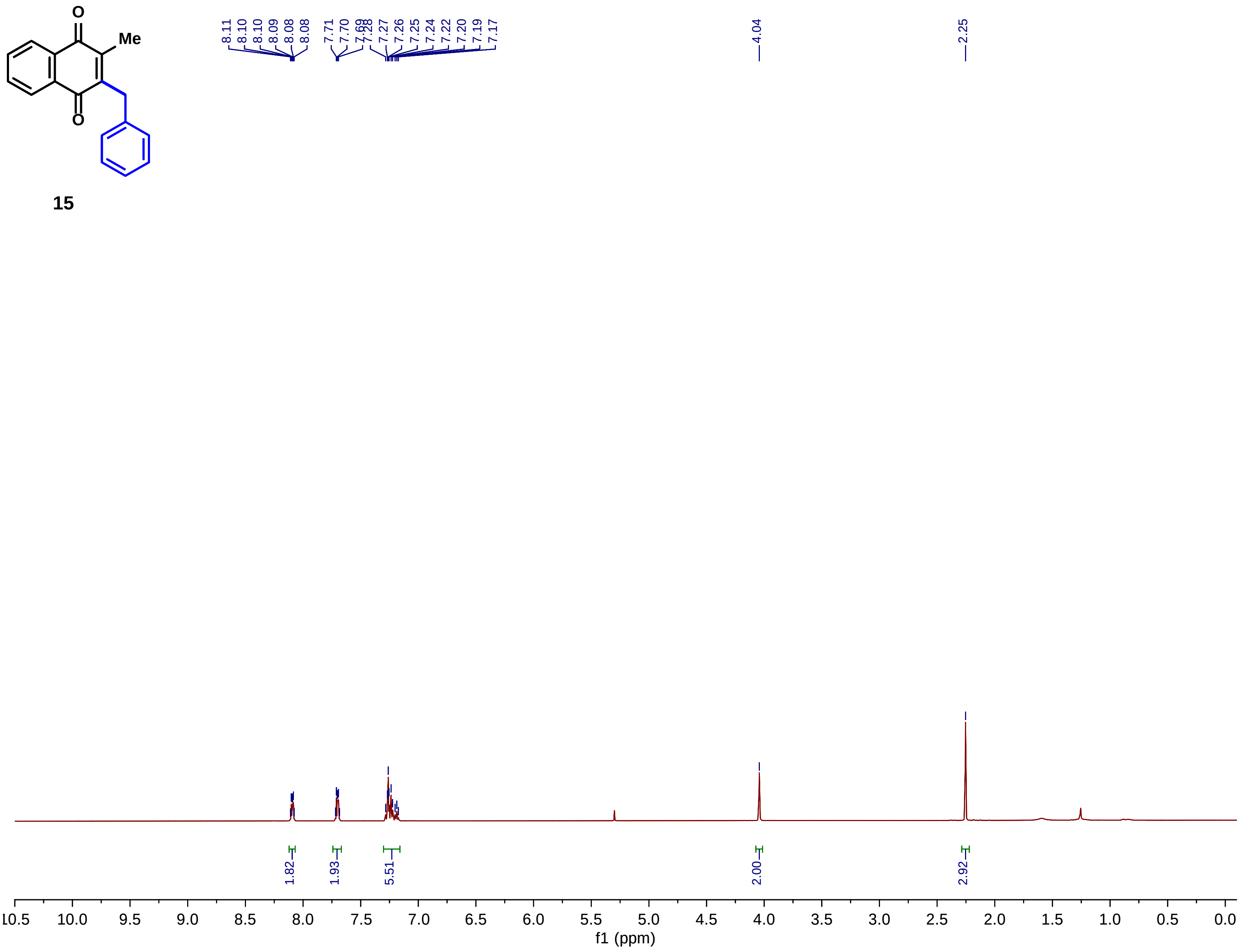


14-C3

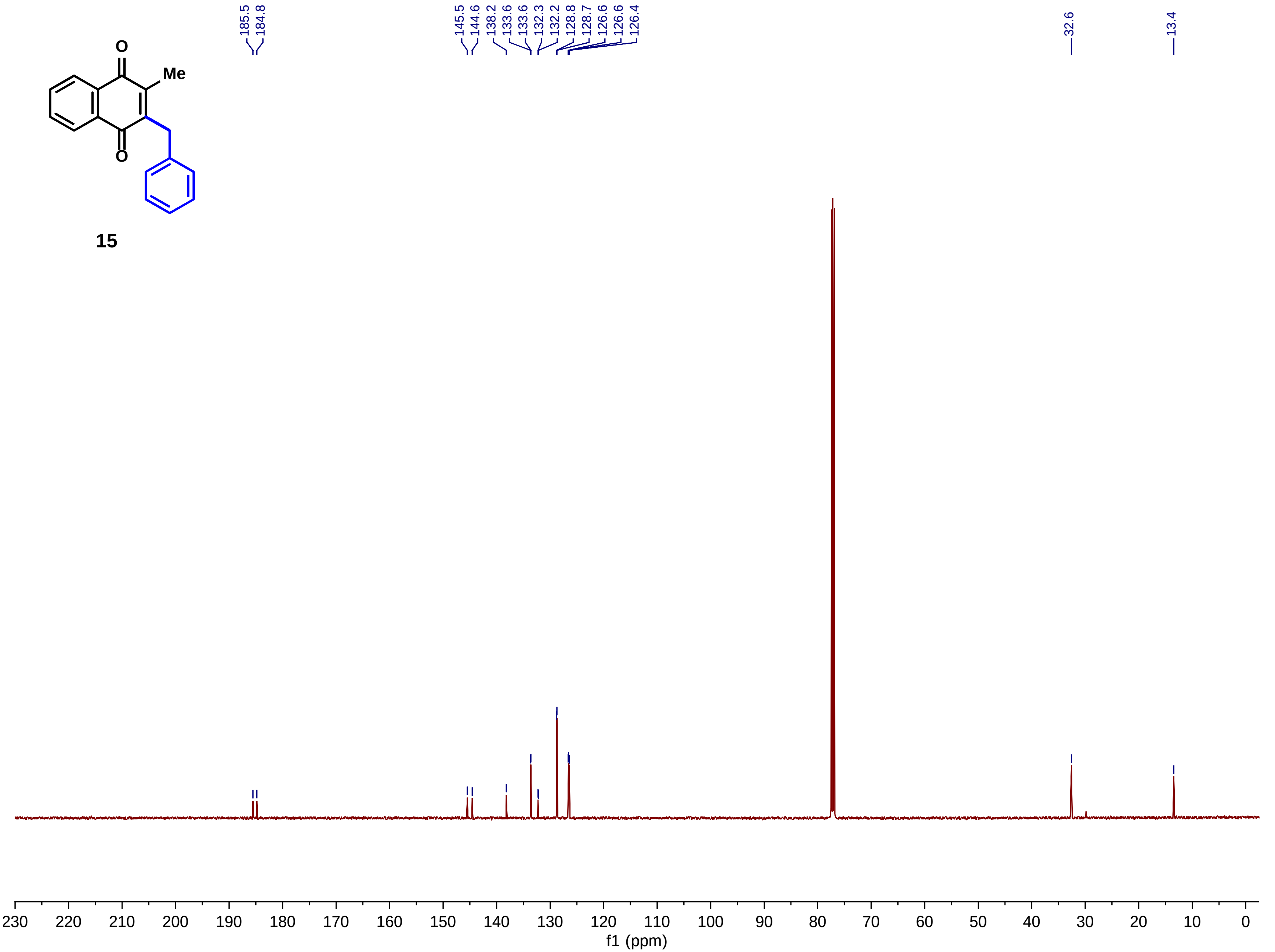
12.04
7.61
7.59
7.59
7.58
7.57
7.36
7.35
7.33
7.29
7.28
7.26
7.25
7.25
7.25
7.24
6.59
6.59
6.59
3.89
3.89
O
O
OH
0.76
1.95
1.92
6.94
0.87
2.00
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190.4
184.5
161.8
150.9
136.7
136.7
136.5
132.3
129.5
129.1
127.3
124.5
119.0
115.3
35.4
O
OH
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

14-C3


O
Me
O
8.11
8.10
8.10
8.09
8.08
8.08
7.71
7.70
7.69
7.28
7.27
7.26
7.25
7.24
7.22
7.20
7.19
7.17
4.04
2.25
1.82
1.93
5.51
2.00
2.92
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

15



15

185.5
184.8
145.5
144.6
138.2
133.6
133.6
132.3
132.2
128.8
128.7
126.6
126.6
126.4
32.6
13.4
O
Me
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)