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Palladium-Catalyzed Phosphonylation of Pyrazoles Substituted by Electron-Withdrawing Groups

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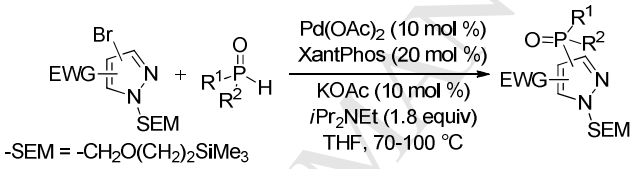


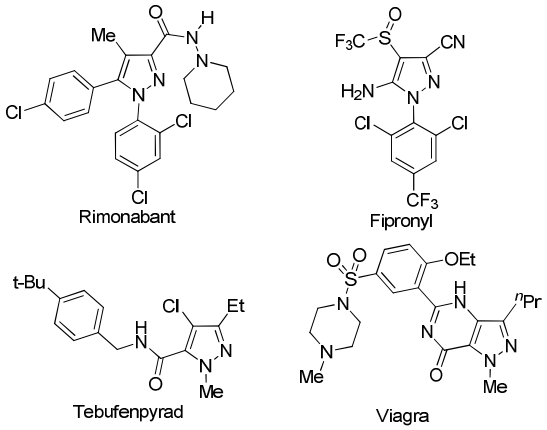
A series of bromopyrazoles substituted by electron-withdrawing groups such as an ester, a trifluoromethyl group or a cyano group were used in Pd-catalyzed phosphonylation. Moderate to good yields were obtained in the corresponding phosphonylated pyrazoles.

Keywords: Pyrazoles, phosphonylation, palladium catalysis

1. Introduction

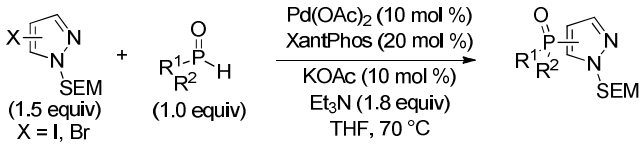
Substituted pyrazoles are important heterocycles as they display a broad range of biological activities and are extensively used in agrochemical and pharmaceutical applications. For example, rimonabant, an anorectic antiobesity product,[1] fipronil, an insecticide,[2] tebufenpyrad, an acaricide,[3] or viagra[4] are commercially available (Figure 1). In addition, pyrazoles can serve as optical brighteners,[5] U.V. stabilizers,[6] ligands in coordinating compounds,[7] and building blocks in supramolecular assemblies.[8]

Figure 1. Selected examples of bioactive pyrazoles.



We were interested in the synthesis of pyrazoles bearing a phosphonyl substituent, as it is known that the introduction of such substituents can modulate the properties of biologically active compounds.[9] Phosphonylated pyrazoles have mainly been synthesized by [3+2]-cycloadditions or ring-closure of acyclic phosphorus-containing compounds, and numerous publications related to these methods have been reported.[10] However, these methods can suffer from a lack of regio-control depending on the substitution pattern of the pyrazoles, and in addition the synthesis of the corresponding phosphonylated starting materials is needed. By contrast, the phosphonylation of a preformed pyrazole ring offers significant advantages in terms of regiocontrol and availability of the starting materials, although the majority of the reported methods is not general due to the use of PCl_3 and related P-Cl intermediates.[10] Indeed, the commercial availability of these intermediates is poor, and their use is usually not compatible with electron-poor pyrazoles. To overcome this issue, and based on seminal reports,[11,12] we recently reported that C3-, C4- or C5-halogenopyrazoles can be phosphonylated by *H*-phosphonates, *H*-phosphinates or secondary phosphine oxides using a $Pd(OAc)_2$/XantPhos catalytic system (Scheme 1).[13] This method proved to be robust and general, providing access to a wide range of compounds which would have required lengthy routes using others methods.

Scheme 1. Previous work on palladium-catalyzed phosphonylation of pyrazoles.

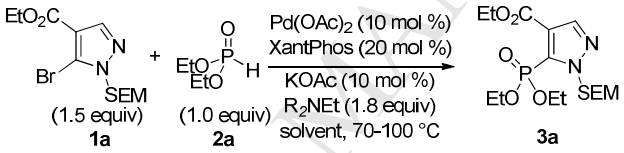


In this paper, we would like to report that this method can also be applied to pyrazoles bearing electron-withdrawing groups, and that the reactivity of such pyrazoles is strongly dependant on stereoelectronic and complexation effects.

2. Results and Discussion

Bromopyrazole ester **1a** was chosen as the model substrate, and the *N*-SEM protecting group was chosen due to its robustness, which allows the use of a wide range of conditions. Pyrazole **1a** was involved in the phosphonylation with diethyl phosphite **2a** using the reaction conditions that have been previously reported for non-functionalized pyrazoles [$Pd(OAc)_2$ (10 mol %), XantPhos (20 mol %), KOAc (10 mol %), Et_3N (1.8 equiv)] (Table 1, entry 1). Under these conditions, the desired product **3a** was obtained in a modest 30% yield, the dehalogenated starting material being the main side-product (25% yield established by ^1H NMR from the crude reaction mixture). In a parallel study, we observed that the presence of diethyl phosphite and Et_3N alone triggered the dehalogenation of **1a**, and that this reaction was efficiently inhibited when Et_3N was replaced by *i*Pr_2NEt. However, when the coupling reaction of **1a** and **2a** was realized in the presence of *i*Pr_2NEt, no significant improvement in the yield of **3a** was observed (Table 1, entry 2). A screening of polar aprotic solvents (Table 1, entries 3–5), hydrocarbon (Table 1, entries 6–8), dioxane (Table 1, entry 9) or halogenated solvants (Table 1, entry 10) was performed, but none of them were better than THF.

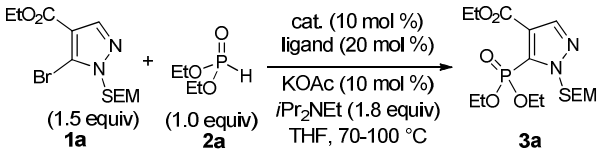
Table 1. Solvent screening.



entry	solvent	base	yield
1	THF	Et_3N	30%
2	THF	*i*Pr_2NEt	32%
3	DMSO	*i*Pr_2NEt	0%
4	MeCN	*i*Pr_2NEt	10%
5	DMA	*i*Pr_2NEt	0%
6	Toluene	*i*Pr_2NEt	22%
7	Toluene/ DME (10:1)	*i*Pr_2NEt	8%
8	$PhCF_3$	*i*Pr_2NEt	17%
9	Dioxane	*i*Pr_2NEt	5%
10	CCl_4	*i*Pr_2NEt	0%

The screening of different palladium catalysts such as $Pd(OAc)_2$, $Pd(OPiv)_2$, $Pd(MeCN)_4(BF_4)$, $Pd(PPh_3)_4$, monodentate phosphines [$(2\text{-furyl})_3P$, *t*-BuXPhos, tetramethyl *t*-BuXPhos] as well as bidentate phosphines (XantPhos, dppf, binap, dppp), revealed that XantPhos was the only suitable ligand for the phosphonylation of **1a**, and that the different screened palladium catalysts performed similarly well (Table 2, entries 7–9)

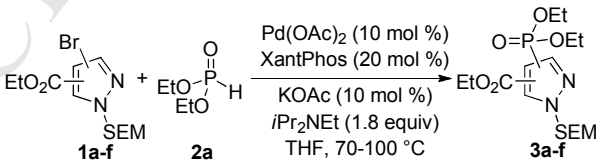
Table 2. Catalyst and ligand screening.

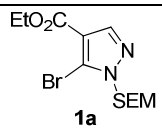
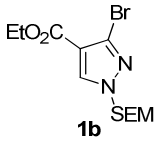


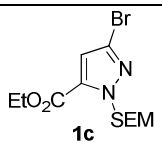
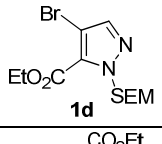
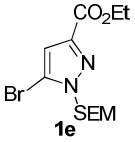
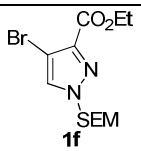
entry	cat.	ligand	yield
1	$Pd(OAc)_2$	Tetramethyl *t*-BuXPhos	0%
2	$Pd(OAc)_2$	*t*-BuXPhos	0%
3	$Pd(OAc)_2$	$(2\text{-Furyl})_3P$	0%
4	$Pd(OAc)_2$	dppp	0%
5	$Pd(OAc)_2$	Binap	0%
6	$Pd(PPh_3)_4$	-	0%
7	$Pd(OAc)_2$	XantPhos	29%
8	$Pd(OPiv)_2$	XantPhos	30%
9	$Pd(MeCN)_4(BF_4)_2$	XantPhos	25%

As changing the catalytic system did not significantly improve the yields in **3a**, we decided to investigate other substrates. Therefore, bromopyrazoles **1b–f** were involved in the phosphonylation using diethyl phosphite as the coupling partner (Table 3), and it seems that when a bromine atom is present at C3, the Pd-catalyzed phosphonylation led to the corresponding pyrazole in good yields, whatever the position of the ester group (Table 3, entries 2 and 3). On the contrary, when a bromine atom is present at C4 or C5, the yields in the phosphonylated pyrazoles were moderate to poor (Table 3, entries 1, 4–6). In all cases, the reactions were run until full consumption of diethyl phosphite **2a**, and the principal side-product of the reaction was the dehalogenated starting materials **1a-f**. However, the observed amounts of dehalogenated starting materials did not seem to be correlated to the yields in phosphonylated pyrazoles, and it is therefore more likely that the moderate yields are due to the competitive degradation of the phosphite **2a**.

Table 3. Influence of the substituent positions.

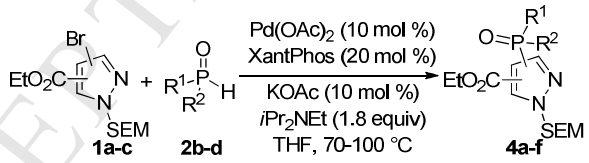


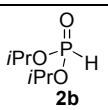
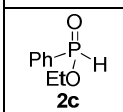
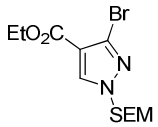
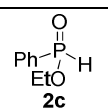
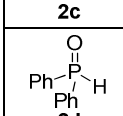
entry	**1a-f**	product
1	 **1a**	**3a** (32%)
2	 **1b**	**3b** (52%)

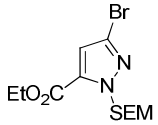
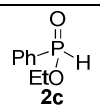
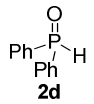
3	 **1c**	**3c** (61%)
4	 **1d**	**3d** (29%)
5	 **1e**	**3e** (37%)
6	 **1f**	**3f** (0%)

Different phosphorous derivatives were also involved in the coupling reaction with pyrazoles **1a–c**, and the results are summarized in Table 4. When the stereoelectronic properties of the phosphonylidene derivatives were changed, two different cases were noticed: when pyrazoles **1a** and **1c** were involved in the cross-coupling, the nature of the phosphorous derivative did not seem to have a strong influence on the yields of the coupling products (Table 4, entries 1–2 and 5–6). On the contrary, when pyrazole **1b** was involved in the cross-coupling with *H*-phosphinates or secondary phosphine oxides, the yield in **4** dropped dramatically (Table 4, entries 3–4).

Table 4. Influence of the phosphorous donor.

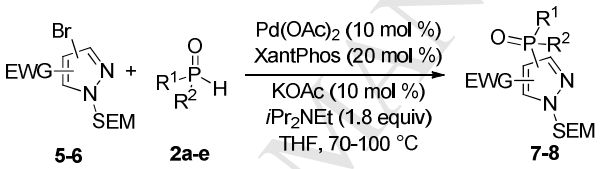


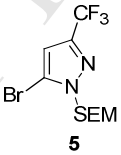
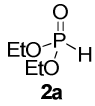
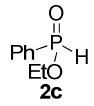
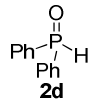
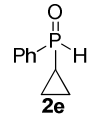
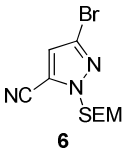
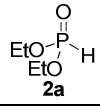
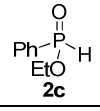
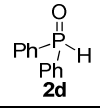
entry	**1a-c**	**2b-d**	product
1	 **1a**	 **2b**	**4a** (29%)
2		 **2c**	**4b** (29%)
3	 **1b**	 **2c**	**4c** (25%)
4		 **2d**	**4d** (11%)

5	 **1c**	 **2c**	**4e** (52%)
6		 **2d**	**4f** (28%)

In metal-catalyzed reactions, and particularly with heteroatom-containing substrates, complexation effects can be detrimental to the success of the reaction. In order to investigate these effects, trifluoromethyl- and cyano-pyrazoles **5** and **6** were involved in the phosphonylation (Table 5). Good to excellent yields in the desired cross-coupling products were obtained, regardless of the phosphorous donors, which is in contrast to the results previously reported (Table 3, entries 3 and 5). Although the trifluoromethyl- and cyano- groups also vary from the ester group by their electron-withdrawing force, the important differences in reactivity between the trifluoromethyl-, cyano- and ester-substituted pyrazoles are suggestive of complexation effects.

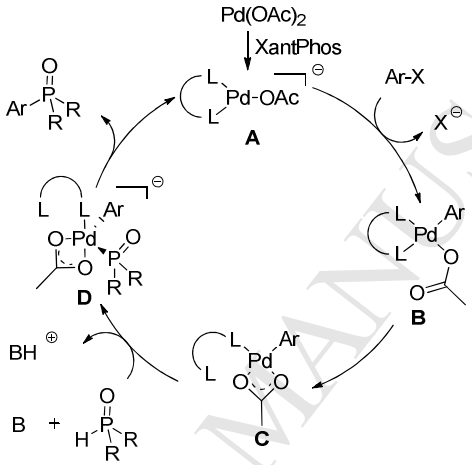
Table 5. Influence of the nature of the substituents.



entry	**5-6**	**2a-e**	product
1	 **5**	 **2a**	**7a** (83%)
2		 **2c**	**7b** (90%)
3		 **2d**	**7c** (57%)
4		 **2e**	**7d** (47%)
5	 **6**	 **2a**	**8a** (81%)
6		 **2c**	**8b** (75%)
7		 **2d**	**8c** (58%)

In terms of mechanistic studies, a solid basis has been provided over the years since the seminal work by Hirao *et al.*,[11,14] and further refinement has recently been proposed by Stawinski *et al.* when KOAc is used as an additive (Scheme 2).[13] After initial formation of the anionic species **A** from $Pd(OAc)_2$ and XantPhos, intermediate **B** is formed by oxidative addition, and a phosphine ligand is then displaced by an oxygen atom of the adjacent acetate. The generated species **C** coordinates a phosphonylidene nucleophile, and a subsequent deprotonation leads to species **D** from which reductive elimination occurs.

Scheme 2. Proposed catalytic cycle.



In considering this catalytic cycle, the results presented in Table 3 and 4 suggest that the rate determining step in the catalytic cycle is related to the substitution pattern of the pyrazoles. With pyrazoles **1a** and **1c**, the oxidative addition is probably determinant as the yield in the cross-coupling products is not influenced by the nature of the phosphorous derivatives. By contrast, the ligand displacement or the reductive elimination are crucial with pyrazole **1b** as the yield ranges from 11% to 52% depending on the nature of the phosphorous partner.

In conclusion, a series of bromopyrazoles substituted by electron-withdrawing groups such as an ester, a trifluoromethyl or a cyano group were involved in a palladium-catalyzed cross-coupling with different phosphorus derivatives. Moderate to good yields were obtained depending on the electron-withdrawing group and its relative position to the bromine atom, which suggests that multiple stereoelectronic and complexation effects can influence the phosphonylation yields. As a general rule, the use of an electron-withdrawing group which would not lead to the formation of a chelating system seems to be beneficial to the cross-coupling, as well as a 1,3-relative relationship between the bromine and the electron-withdrawing group.

3. Experimental Section

3.1. General Experimental. All reactions were carried out under an argon atmosphere unless otherwise specified. Flasks were oven-dried at 120 °C and cooled under argon prior to use. THF was distilled over sodium/benzophenone. Diisopropylethylamine was distilled over CaH_2 and stored under argon. Diethyl phosphite was purchased from Sigma-Aldrich, dried over Na_2SO_4 and distilled prior to use. All other reagents and solvents were used as obtained from Sigma-Aldrich without further purification unless otherwise specified. Flash column chromatographies were carried out by using silica gel (pore size 60 Å, 230 mesh). TLC were performed on silica gel plate (Merck 60F254) and visualized either with a UV lamp (254 nm) or by treatment with an aqueous potassium permanganate solution ($KMnO_4/K_2CO_3$/AcOH) and subsequent heating. Infrared (IR) spectra were recorded on a Bruker TENSOR^{TM} 27 (IRFT), wave numbers are indicated in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker Avance 400 at 400 MHz. The chemical shifts δ are reported in ppm relative to tetramethylsilane. Residual $CHCl_3$ (δ_H = 7.26 ppm) was used as internal reference unless otherwise specified. The multiplicity and shape of signals are designated by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. Coupling constants *J* are reported in Hertz (Hz). ^{13}C-NMR spectra were recorded on a Bruker Avance 400 at 100 MHz. The chemical shifts δ are reported in ppm relative to tetramethylsilane. $CDCl_3$ (δ_C = 77.16 ppm, triplet) was used as internal reference unless otherwise specified. The multiplicity and shape of signals are designated by the following abbreviations: d = doublet, q = quartet. Coupling constants *J* are reported in Hertz (Hz). High resolution mass spectra (HRMS) were realized at the Organic Spectrochemistry Center at the Université Pierre et Marie Curie. No HRMS peaks could be found for intermediate compounds **5** and **6**, presumably due to their degradation. However, the rest of the analysis were consistent with the assigned structures, and the products resulting from the cross-coupling of **5** and **6** were entirely characterized. Most of the products were obtained as oils, most likely due to the aliphatic nature of the SEM- protecting group.

3.3. Synthesis of starting materials 1a-f, 2e, 5 and 6

Ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate[15]

To a suspension of sodium hydride (60% in oil, 1.10 g, 27.5 mmol, 1.6 equiv) in dry THF (40 mL), at 0 °C, was added a solution of ethyl 4-pyrazolecarboxylate (2.47 g, 17.6 mmol, 1.0 equiv) in dry THF (10 mL). The resulting purple suspension was stirred at rt for 3 h. A solution of SEM-Cl (3.75 mL, 21.2 mmol, 1.2 equiv) in

dry THF (10 mL) was then added dropwise at 0 °C. The resulting solution was allowed to warm up to rt and stirred for 3 h. Water was added, and the aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:90) led to the desired product ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate as a colorless oil (4.66 g, 17.23 mmol, 98% yield). **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 8.06 (d, *J* = 0.6 Hz, 1H), 7.94 (d, *J* = 0.6 Hz, 1H), 5.43 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.62 – 3.52 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.95 – 0.86 (m, 2H), -0.02 (s, 9H).

Ethyl 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (1a)

To a solution of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (4.66 g, 17.2 mmol, 1 equiv) in dry THF (47 mL), at −30 °C, was added dropwise a 1.0 M solution of TMPMgCl•LiCl (21.0 mL, 21.0 mmol, 1.22 equiv) in THF/toluene. The resulting mixture was stirred at −30 °C for 2 h and a solution of 1,2-dibromotetrachloroethane (7.41 g, 22.7 mmol, 1.32 equiv) in dry THF (20 mL) was then added dropwise at −30 °C. The reaction mixture was stirred at this temperature for 4 h, and then allowed to warm up to rt and stirred for 12 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture, and the aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown suspension. Purification by flash column chromatography on silica gel (EtOAc/PE = 5:95) led to the desired product **1a** as a pale yellow oil (4.31g, 12.34 mmol, 72% yield).

IR (neat): 2953, 2897, 1720, 1537, 1407, 1395, 1373, 1244, 1209, 1101, 1079, 1040, 976, 858, 833. **^{1}H-NMR ($CDCl_3$, 400 MHz):** *δ* 7.99 (s, 1H), 5.53 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.66–3.56 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.96−0.86 (m, 2H), −0.03 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** *δ* 161.9 (C), 142.6 (CH), 118.5 (C), 115.0 (C), 78.9 (CH_2), 67.4 (CH_2), 60.7 (CH_2), 17.9 (CH_2), 14.4 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+H]^+$ calculated for $C_{12}H_{22}BrN_2O_3Si$: 349.0578 and 351.0557. Found: 349.0580 and 351.0558.

Ethyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (1b)

aThe reaction was performed in an oven-dried vial. To a solution of **1a** (648 mg, 1.86 mmol, 1.0 equiv) in anhydrous MeCN (2.0 mL) was added SEM-Cl (33 μL, 0.186 mmol, 0.1 equiv). The vial was sealed with a teflon-lined cap and stirred at 95 °C for 26 h. The reaction mixture was evaporated to give a yellow solid. Purification by flash column chromatography (EtOAc/PE = 5:95) led to the desired product **1b** as a colorless oil (481 mg, 1.38 mmol, 74% yield). **IR (neat):** 3127, 2953, 2897, 1718, 1536, 1406, 1248, 1211, 1094, 1057, 857, 833. **^{1}H-NMR ($CDCl_3$, 400 MHz):** *δ* 8.02 (s, 1H), 5.38 (s, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.62−3.57 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.94−0.89 (m, 2H), −0.02 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** *δ* 161.6 (C), 135.0

(CH), 128.2 (C), 115.2 (C), 81.2 (CH_2), 67.8 (CH_2), 60.8 (CH_2), 17.9 (CH_2), 14.4 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{21}BrN_2NaO_3Si$: 371.0397 and 373.0377. Found: 371.0399 and 373.0377.

1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole[16]

To a suspension of sodium hydride (3.96 g, 99 mmol, 1.5 equiv) in dry THF (50 mL), at 0 °C, was added a solution of 1*H*-pyrazole (4.50 g, 66.1 mmol, 1 equiv) in dry THF (20 mL). The resulting suspension was stirred at rt for 2 h. The solution was then cooled down to 0 °C and a solution of SEM-Cl (12.9 mL, 72.7 mmol, 1.1 equiv) in dry THF (23 mL) was added dropwise. The solution was then allowed to warm up to rt and stirred overnight. Water was added, and the aqueous phase was extracted 4 times with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (EtOAc/PE = 15:85) led to the desired product 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole as a colorless oil (12.4 g, 62.7 mmol, 95% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.56 (br, d, *J* = 2.4 Hz, 1H), 7.55 (br, d, *J* = 1.6 Hz, 1H), 6.33 (br, t, *J* = 2.1 Hz, 1H), 5.44 (s, 2H), 3.58 – 3.49 (m, 2H), 0.95 – 0.78 (m, 2H), –0.03 (s, 9H).

5-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole[13]

To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (3.00 g, 15.1 mmol, 1 equiv) in dry THF (30 mL), at 0 °C, was added dropwise a 1.0 M solution of TMPMgCl•LiCl (18.0 mL, 18.0 mmol, 1.2 equiv) in THF/toluene. The resulting mixture was allowed to warm up to rt and the completion of the deprotonation was checked by GC/MS analysis of reaction aliquots quenched with I_2. The solution was then cooled down to 0 °C, and a solution of 1,2-dibromotetrachloroethane (5.91 g, 18.2 mmol, 1.2 equiv) in THF (12 mL) was added dropwise. The resulting solution was then allowed to warm up to rt and stirred overnight. Aqueous saturated $NaHCO_3$ was added to the reaction mixture and the aqueous phase was extracted 4 times with EtOAc. The organic phase was collected and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (EtOAc/PE = 5:95 to 15:85) led to the desired product 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole as a pale yellow oil (3.60 g, 13.2 mmol, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 (d, *J* = 1.9 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 5.49 (s, 2H), 3.72 – 3.11 (m, 2H), 1.09 – 0.73 (m, 2H), –0.03 (s, 9H).

3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole

The reaction was performed in an oven-dried vial. To a solution of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (1.34 g, 4.84 mmol, 1.0 equiv) in anhydrous MeCN (2.0 mL) was added SEM-Cl (85 µL, 0.48 mmol, 0.1 equiv). The vial was sealed with a teflon-lined cap and stirred at 95 °C

for 24 h. The reaction mixture was evaporated to give a yellow oil. Purification by flash column chromatography (EtOAc/PE = 5:95 to 10:90) led to the desired product 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole as a colorless oil (1.10 g, 3.80 mmol, 78% yield). **IR (neat):** 2953, 2896, 1501, 1360, 1297, 1248, 1095, 952, 857, 833,745. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.46 (d, J = 2.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 5.37 (s, 2H), 3.59−3.55 (m, 2H), 0.92−0.87 (m, 2H), −0.02 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 131.6 (CH), 126.6 (C), 109.9 (CH), 80.6 (CH_2), 67.2 (CH_2), 17.9 (CH_2), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_9H_{17}BrN_2NaOSi$: 299.0186 and 301.0165. Found: 299.0189 and 301.1411.

Ethyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (1c)

To a solution of 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (417 mg, 1.51 mmol, 1 equiv) in dry THF (3 mL) was added dropwise a 1.0 M solution of TMPMgCl•LiCl (1.80 mL, 1.80 mmol, 1.2 equiv) in THF/toluene. The resulting mixture was allowed to warm up to rt and the completion of the deprotonation was checked by GC/MS analysis of reaction aliquots quenched with I_2. The solution was then cooled down to −30 °C, and a solution of ethyl cyanoformate (158 µL, 1.59 mmol, 1.1 equiv) in THF (2.0 mL) was added dropwise. The reaction was stirred at −30 °C for 3 h, allowed to warm up to rt and stirred at this temperature for 12 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture, and the aqueous phase was extracted 3 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (EtOAc/PE = 5:95) led to the desired product **1c** as a pale yellow oil (454 mg, 1.30 mmol, 86% yield). **IR (neat):** 2953, 2897, 1729, 1368, 1339, 1240, 1078, 961, 858, 834, 764, 743. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 6.89 (s, 1H), 5.79 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.62−3.58 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.91−0.87 (m, 2H), −0.04 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 158.4 (C), 134.8 (C), 125.9 (C), 114.8 (CH), 79.6 (CH_2), 67.2 (CH_2), 61.8 (CH_2), 17.8 (CH_2), 14.3 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{21}BrN_2NaO_3Si$: 371.0397 and 373.0377. Found: 371.0399 and 373.0378.

Ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate

To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (2.48 g, 12.5 mmol, 1 equiv) in dry THF (13 mL), at 0 °C, was added dropwise a 1.0 M solution of TMPMgCl•LiCl (15.0 mL, 15.0 mmol, 1.2 equiv) in THF/toluene. The resulting mixture was allowed to warm up to rt and the completion of the deprotonation was checked by GC/MS analysis of reaction aliquots quenched with I_2. A solution of ethyl cyanoformate (1.61 mL, 16.3 mmol, 1.3 equiv) in dry THF (8 mL) was then added dropwise at −30 °C, the reaction mixture was stirred for 1.5 h, and then allowed to warm up to rt and stirred for 1 h. Aqueous saturated $NaHCO_3$ was added to the

reaction mixture, and the aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a dark brown oil. Purification by flash column chromatography (EtOAc/PE = 5:95 to 10:90) led to the desired product ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate as a pale yellow oil (2.20 g, 8.12 mmol, 65% yield). **IR (neat):** 2953, 2898, 1725, 1521, 1466, 1312, 1246, 1116, 1085, 1020, 858. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.54 (d, J = 1.9 Hz, 1H), 6.90 (d, J = 1.9 Hz, 1H), 5.86 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.60−3.56 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H), 0.91−0.87 (m, 2H), −0.05 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 159.6 (C), 138.9 (CH), 133.0 (C), 112.6 (CH), 79.3 (CH_2), 66.9 (CH_2), 61.3 (CH_2), 17.9 (CH_2), 14.4 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{22}N_2NaO_3Si$: 293.1292. Found: 293.1294.

Ethyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (1d)

Under argon, at −30 °C, to a solution of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (1.66 g, 6.13 mmol, 1.0 equiv) in dry THF (18 mL) was added dropwise a 1.0 M solution of TMPMgCl•LiCl (7.40 mL, 7.40 mmol, 1.2 equiv) in THF/toluene. The resulting mixture was stirred at −30 °C for 5.5 h. A solution of 1,2-dibromotetrachloroethane (2.63 g, 8.09 mmol, 1.3 equiv) in dry THF (6 mL) was added dropwise at −30 °C, the reaction mixture was stirred for 4 h, and then allowed to warm up to rt and stirred for 12 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture, aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a dark brown oil. Purification by flash column chromatography (EtOAc/PE = 1:99, then repurified with CH_2Cl_2/toluene = 15:85 to 30:70) to give **1d** as a colorless oil (211 mg, 0.60 mmol, 10% yield) (the main product of the reaction was **1c**, which was isolated in 28% yield). **IR (neat):** 2953, 2897, 1724, 1509, 1440, 1367, 1306, 1247, 1086, 1024, 975, 834, 751. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.56 (s, 1H), 5.81 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 3.56−3.52 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H), 0.90−0.86 (m, 2H), −0.04 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 158.8 (C), 141.0 (CH), 130.8 (C), 100.9 (C), 80.8 (CH_2), 67.1 (CH_2), 61.9 (CH_2), 17.8 (CH_2), 14.2 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{21}BrN_2NaO_3Si$: 371.0397 and 373.0377. Found: 371.0399 and 373.0377.

Ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate

To a suspension of sodium hydride (60% in oil, 0.45 g, 11.3 mmol, 1.6 equiv) in dry THF (16 mL) was added a solution of ethyl 1*H*-pyrazole-3-carboxylate (1.00 g, 7.14 mmol, 1.0 equiv) in dry THF (16 mL). The resulting dark brown solution was stirred at rt for 3 h. A solution of SEM-Cl (1.52 mL, 8.56 mmol, 1.2 equiv) in dry THF (6 mL) was then added dropwise at 0 °C. The solution was then allowed to warm up to rt and stirred overnight.

Water was added to the reaction mixture, aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a dark red oil. Purification by flash column chromatography (Et_2O/CH_2Cl_2 = 0:100 to 5:95) led to the desired product ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate as a light orange oil (1.22 g, 4.50 mmol, 63% yield). **IR (neat):** 2954, 2897, 1720, 1469, 1370, 1213, 1149, 1095, 1043, 1023, 858, 834, 761. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.61 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 5.51 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 3.59−3.54 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 0.92−0.88 (m, 2H), −0.03 (s, 9H). **^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz):** δ 162.2 (C), 143.9 (C), 130.4 (CH), 109.8 (CH), 80.9 (CH_2), 67.0 (CH_2), 60.9 (CH_2), 17.7 (CH_2), 14.3 (CH_3), −1.5 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{22}N_2NaO_3Si$: 293.1292. Found: 293.1290.

Ethyl 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (1e)

To a solution of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (237 mg, 0.876 mmol, 1 equiv) in dry THF (2.6 mL), at −30 °C, was added dropwise a 1.0 M solution of TMPMgCl•LiCl (1 mL, 1 mmol, 1.14 equiv) in THF/toluene. The resulting mixture was stirred at −30 °C for 6 h. A solution of 1,2-dibromotetrachloroethane (371 mg, 1.14 mmol, 1.3 equiv) in dry THF (1 mL) was then added dropwise at −30 °C, and the reaction mixture was stirred overnight at −30 °C, then allowed to warm up to rt and stirred at rt for 9 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture, and the aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give an orange suspension. Purification by flash column chromatography (EtOAc/PE = 5:95 to 15:85) led to the desired product **1e** as a yellow oil (46 mg, 0.13 mmol, 15% yield). **IR (neat):** 2953, 1721, 1463, 1412, 1384, 1307, 1248, 1092, 1046, 1019, 914, 858, 775, 749. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 6.88 (s, 1H), 5.56 (s, 2H), 4.41 (q, J = 7.1 Hz, 2H), 3.64−3.60 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H), 0.92−0.88 (m, 2H), −0.03 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 161.6 (C), 144.8 (C), 114.6 (C), 112.4 (CH), 79.4 (CH_2), 67.3 (CH_2), 61.5 (CH_2), 17.9 (CH_2), 14.5 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{21}BrN_2NaO_3Si$: 371.0397 and 373.0377. Found: 371.0402 and 373.0377.

Ethyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (1f)

Under air, to a solution of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (685 mg, 2.53 mmol, 1.0 equiv) in $CHCl_3$ (0.7 mL), at 0°C, was added a solution of Br_2 (0.14 mL, 2.73 mmol, 1.08 equiv) in $CHCl_3$ (0.1 mL) and the red-brown mixture was stirred at 0 °C for 3.5 h. The reaction solution was diluted with $CHCl_3$, quenched by $Na_2S_2O_3$ and washed with aqueous saturated $NaHCO_3$ and then brine. The organic phase

was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (EtOAc/PE = 15:85, repurified with Et_2O/toluene = 15:85) led to the desired product **1f** as a pale yellow oil (87 mg, 0.25 mmol, 10% yield). **IR (neat):** 3125, 2953, 2897, 1725, 1463, 1352, 1324, 1211, 1093, 1042, 1011, 915, 858, 834. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.69 (s, 1H), 5.46 (s, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.58−3.54 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H), 0.93−0.88 (m, 2H), −0.02 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 161.2 (C), 140.8 (C), 131.9 (CH), 97.7 (C), 81.8 (CH_2), 67.7 (CH_2), 61.5 (CH_2), 17.9 (CH_2), 14.4 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{12}H_{21}BrN_2NaO_3Si$: 371.0397 and 373.0377. Found: 371.0402 and 373.0378.

Cyclopropyl(phenyl) phosphine oxide (2e)[13]

At –78 °C, to a 1.0 M solution of cyclopropylmagnesium bromide (12.5 mL, 12.5 mmol, 2.1 equiv) in 2-methyl-tetrahydrofuran was added a solution of ethyl phenylphosphinate (1.00 g, 5.88 mmol, 1.0 equiv) in THF (6 mL) dropwise. The resulting yellow solution was stirred at –78 °C for 40 min. An aqueous saturated NH_4Cl solution (6 mL) was then added, and the resulting slurry was allowed to warm up to rt. Water was then added (50 mL), the aqueous phase was washed 2 times with petroleum ether (2 x 30 mL), and then extracted 3 times with $CHCl_3$ (3 x 50 mL). The combined halogenated phases were dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a colorless oil. Distillation *in vacuo* using a Kugelrohr apparatus (90 °C, 0.5 mbar) led to the desired product **2e** as a colorless oil (590 mg, 3.55 mmol, 60% yield). **^{1}H-NMR (400MHz, $CDCl_3$):** δ 7.72 (ddd, J = 13.2, 8.1, 1.3 Hz, 2H), 7.58–7.43 (m, 3H), 7.31 (dd, J = 480.0, 2.2 Hz, 1H), 1.11–0.87 (m, 5H).

3-(Trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole

To a suspension of sodium hydride (60% in oil, 0.97 g, 24.3 mmol, 1.5 equiv) in dry THF (30 mL), at 0 °C, was added a solution of 3-(trifluoromethyl)pyrazole (2.20 g, 16.2 mmol, 1.0 equiv) in dry THF (10 mL). The resulting suspension was stirred at rt for 2 hours. The reaction solution was then cooled down to 0 °C and a solution of SEM-Cl (3.46 mL, 19.5 mmol, 1.2 equiv) in dry THF (10 mL) was added dropwise. The solution gradually turned yellow and was allowed to warm up to rt and stirred for 3 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture and the aqueous phase was extracted 4 times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a colorless oil. Purification by flash column chromatography (EtOAc/PE = 10:90) led to the desired product 3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole as a colorless oil (1.69 g, 6.34 mmol, 39% yield). **IR (neat):** 2957, 2900, 1490, 1341, 1252, 1228, 1172, 1133, 1102, 967, 860, 836, 771, 756. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.62 (m, 1H), 6.60 (br, d, J = 2.4 Hz, 1H), 5.47 (s, 2H), 3.60−3.56 (m, 2H), 0.95−0.83 (m, 2H), −0.03 (s, 9H). **^{13}C-**

NMR ($CDCl_3$, 100 MHz): δ 143.0 (d_{app}, J = 38.0 Hz), 130.8 (CH), 121.3 (C, d_{app}, J = 269 Hz), 105.6 (CH, d_{app}, J = 2 Hz), 80.9 (CH_2), 67.41 (CH_2), 17.8 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** no peak found (see General Experimental).

5-Bromo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (5)

To a solution of 3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (856 mg, 3.22 mmol, 1 equiv) in dry THF (6 mL), at 0 °C, was added dropwise a 1.0 M solution of TMPMgCl•LiCl (3.60 mL, 3.60 mmol, 1.1 equiv) in THF/toluene. The resulting mixture was stirred at 0 °C for 3 h and the completion of the deprotonation was checked by GC/MS analysis of reaction aliquots quenched with I_2. A solution of 1,2-dibromotetrachloroethane (1.27 g, 3.9 mmol, 1.2 equiv) in dry THF (2 mL) was then added dropwise at 0 °C, and the reaction mixture was allowed to warm up to rt and stirred for 4.5 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture, and the aqueous phase was extracted 4 times with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (PE) led to the desired product **5** as a light yellow oil (717 mg, 2.08 mmol, 65% yield). **IR (neat):** 2955, 2898, 1468, 1421, 1396, 1367, 1249, 1211, 1172, 1120, 1091, 1052, 1028, 969, 913, 858. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 6.63 (s, 1H), 5.53 (s, 2H), 3.65−3.61 (m, 2H), 0.92−0.88 (m, 2H), −0.02 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 143.8 (C, q, J = 39 Hz), 120.6 (C, q, J = 269 Hz), 114.9 (C), 108.2 (CH, d_{app}, J = 2 Hz), 79.1 (CH_2), 67.4 (CH_2), 17.7 (CH_2), −1.5 (CH_3). **HRMS (ESI+):** no peak found (see General Experimental).

3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carbonitrile (6)

To a solution of 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (1.08 g, 3.9 mmol, 1.0 equiv) in dry THF (7.6 mL), at 0°C, was added dropwise a 1.0 M solution of TMPMgCl•LiCl (4.70 mL, 4.70 mmol, 1.2 equiv) in THF/toluene. The solution was then stirred at rt for 8 h. The solution was cooled down to −15 °C and a solution of *p*-toluene sulfonyl cyanide (847 mg, 4.67 mmol, 1.2 equiv) in THF (4.0 mL) was added dropwise. The reaction was stirred overnight at −15 °C and then at rt for 0.5 h. Aqueous saturated $NaHCO_3$ was added to the reaction mixture, and the aqueous phase was extracted 4 times with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown suspension. Purification by flash column chromatography (EtOAc/PE = 5:95 to 10:90) led to the desired product **6** as a colorless oil (1.02 g, 3.38 mmol, 87% yield). **IR (neat):** 3143, 2953, 2897, 2239, 1509, 1360, 1297, 1248, 1092, 961, 858, 834, 761. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 6.86 (s, 1H), 5.55 (s, 2H), 3.66−3.62 (m, 2H), 0.96−0.91 (m, 2H), -0.01 (s,

9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 126.8 (C), 117.2 (CH), 116.9 (C), 109.0 (C), 80.1 (CH_2), 68.1 (CH_2), 17.7 (CH_2), −1.3 (CH_3). **HRMS (ESI+):** no peak found (see General Experimental).

3.5. General procedure for the cross-couplings of bromopyrazoles with phosphonylidenes

Pd(OAc)2 (10 mol %), XantPhos (20 mol %), and KOAc (10 mol %), bromopyrazole (1.5 equiv) were weighted in a microwave vial, which was then sealed and flushed with argon. THF (c = 0.25 M) and DIPEA (1.8 equiv) were then added through the septum and the resulting suspension was stirred for 20 min at 70 °C. The phosphonylidene (1.0 equiv) was then added through the septum, and the reaction mixture was stirred at 70 °C and the temperature was increased to 100 °C if necessary until completion of the reaction, as determined by TLC. The reaction mixture was then diluted with EtOAc, an aqueous saturated $NaHCO_3$ solution was added, the layers were separated, and the aqueous phase was extracted 3 more times with EtOAc. The combined organic phases were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel led to the desired cross-coupling products.

Ethyl 5-(diethoxyphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (3a). Pyrazole **1a** (262 mg, 0.75 mmol) and diethyl phosphite **2a** (64 µL, 0.5 mmol) were reacted together according to the general procedure. After 25 h, TLC showed full consumption of **2a**. Purification by flash column chromatography on silica gel (EtOAc/CH_2Cl_2 = 90:10) led to the desired product **3a** as a pale yellow oil (65 mg, 0.16 mmol, 32% yield). **IR (neat):** υ_{max} 2982, 2954, 1735, 1716, 1524, 1379, 1250, 1207, 1114, 1091, 1020, 835, 750. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.97 (d, J = 1.3 Hz, 1H), 5.94 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.29−4.10 (m, 4H), 3.62−3.56 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.32 (td, J = 7.1, 0.7 Hz, 6H), 0.93−0.86 (m, 2H), −0.03 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 162.0 (C), 141.5 (CH, d, J = 14 Hz), 133.1 (C, d, J = 208 Hz), 122.0 (C, d, J = 16 Hz), 80.7 (CH_2), 67.1 (CH_2), 63.5 (CH_2, d, J = 5 Hz), 61.0 (CH_2), 18.0 (CH_2), 16.4 (CH_3, d, J = 7 Hz), 14.4 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+H]^+$ calculated for $C_{17}H_{31}N_2O_6PSi$: 407.1762. Found: 407.1758.

Ethyl 3-(diethoxyphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (3b). Pyrazole **1b** (112 mg, 0.321 mmol) and diethyl phosphite **2a** (27 µL, 0.211 mmol) were reacted together according to the general procedure. After 6 h, TLC showed full consumption of **2a**. Purification by flash column chromatography on silica gel (EtOAc/PE = 20:80 to 100:0) led to the desired product **3b** as a pale yellow oil (45 mg, 0.11 mmol, 52% yield). **IR (neat):** υ_{max} 2981, 2954, 2904, 1725, 1248, 1225, 1085, 1053, 1024, 971, 858, 835, 752. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 8.15 (d, J = 1.9 Hz, 1H), 5.48 (s, 2H), 4.38−4.19 (m, 6H), 3.61−3.55 (m, 2H), 1.39−1.33 (m, 9H), 0.95−0.88 (m, 2H), −0.02 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 161.6 (C),

143.2 (C, d, *J* = 231 Hz), 134.7 (CH, d, *J* = 8 Hz), 119.8 (C, d, *J* = 21 Hz), 81.2 (CH_2), 67.8 (CH_2), 63.2 (CH_2, d, *J* = 6 Hz), 61.0 (CH_2), 17.9 (CH_2), 16.5 (CH_3, d, *J* = 7 Hz), 14.4 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{16}H_{31}N_2NaO_6PSi$: 429.1581. Found: 429.1584.

Ethyl 3-(diethoxyphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (3c). Pyrazole **1c** (130 mg, 0.374 mmol) and diethyl phosphite **2a** (32 µL, 0.250 mmol) were reacted together according to the general procedure. After 2 h, TLC showed full consumption of **2a**. Purification by flash column chromatography on silica gel (EtOAc/PE = 60:40) led to the desired product **3c** as a pale yellow oil (61 mg, 0.15 mmol, 61% yield). **IR (neat):** υ_{max} 2982, 2954, 2904, 1729, 1244, 1081, 1052, 1020, 970, 835, 769, 749. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.32 (d, *J* = 1.4 Hz, 1H), 5.91 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.26−4.10 (m, 4H), 3.63−3.55 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.34 (td, *J* = 7.1, 0.5 Hz, 6H), 0.90−0.86 (m, 2H), −0.06 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 158.9 (C), 141.7 (C, d, *J* = 232 Hz), 134.0 (C, d, *J* = 10 Hz), 118.0 (CH, d, *J* = 23 Hz), 80.2 (CH_2), 67.3 (CH_2), 62.9 (CH_2, d, *J* = 6 Hz), 61.7 (CH_2), 17.9 (CH_2), 16.4 (CH_3, d, *J* = 6 Hz), 14.3 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{16}H_{31}N_2NaO_6PSi$: 429.1581. Found: 429.1580.

Ethyl 4-(diethoxyphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (3d) Pyrazole **1d** (110 mg, 0.315 mmol) and diethyl phosphite **2a** (27 µL, 0.211 mmol) were reacted together according to the general procedure. After 23 h, TLC showed full consumption of **2a**. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:90 to 100:0) led to the desired product **3d** as an orange oil (65 mg, 0.061 mmol, 29% yield). **IR (neat):** υ_{max} 2982, 2954, 2903, 1729, 1519, 1311, 1249, 1092, 1055, 1021, 967, 859, 791. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.82 (d, *J* = 1.4 Hz, 1H), 5.83 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.23−4.04 (m, 4H), 3.60−3.56 (m, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.34 (td, *J* = 7.1, 0.5 Hz, 6H), 0.93−0.84 (m, 2H), −0.05 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 158.8 (C), 144.1 (CH, d, *J* = 11 Hz), 135.9 (C, d, *J* = 22 Hz), 113.0 (C, d, *J* = 217 Hz), 80.1 (CH_2), 67.4 (CH_2), 62.5−62.4 ($3CH_2$), 17.9 (CH_2), 16.5 (CH_3, d, *J* = 7 Hz), 14.1 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{16}H_{31}N_2NaO_6PSi$: 429.1581. Found: 429.1585.

Ethyl 5-(diethoxyphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxylate (3e). Pyrazole **1e** (95 mg, 0.272 mmol) and diethyl phosphite **2a** (23 µL, 0.180 mmol) were reacted together according to the general procedure. After 22 h at 70 °C, TLC showed that **2a** was not fully consumed, so the temperature was increased to 100 °C and the reaction mixture was stirred at this temperature for 6 h. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:90 to 100:0) led to the desired product **3e** as a yellow oil (27 mg, 0.066 mmol, 37% yield). **IR (neat):** υ_{max} 2982, 2954, 1740, 1723, 1509, 1446, 1390, 1369, 1250, 1206, 1090, 1016, 975, 859, 835. **^{1}H-NMR (Acetone-d6, 400 MHz):** δ 7.19 (d, *J* = 2.5 Hz, 1H), 5.77 (s, 2H), 4.34 (q,

J = 7.1 Hz, 2H), 4.26−4.06 (m, 4H), 3.70−3.66 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.33 (td, *J* = 7.2, 0.4 Hz, 6H), 0.93−0.89 (m, 2H), −0.01 (s, 9H). **^{13}C-NMR (Acetone-d6, 100 MHz):** δ 161.9 (C), 144.2 (C, d, *J* = 16 Hz), 134.8 (C, d, *J* = 210 Hz), 118.3 (CH, d, *J* = 17 Hz), 81.0 (CH_2), 67.6 (CH_2), 63.8 (CH_2, d, *J* = 5 Hz), 61.4 (CH_2), 18.2 (CH_2), 16.5 (CH_3, d, *J* = 6 Hz), 14.6 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{16}H_{31}N_2NaO_6PSi$: 429.1581. Found: 429.1583.

Ethyl 5-(diisopropoxyphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (4a). Pyrazole **1a** (266 mg, 0.76 mmol) and diisopropyl phosphite **2b** (84 μL, 0.504 mmol) were reacted together according to the general procedure. After 22 h at 70 °C, TLC showed full consumption of **2b**. Purification by flash column chromatography on silica gel (EtOAc/PE = 15:85) led to the desired product **4a** as a white oil (63 mg, 0.145 mmol, 29% yield). **IR (neat):** υ_{max} 2980, 2954, 1736, 1715, 1524, 1376, 1251, 1206, 1093, 990, 834, 752. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 1.2 Hz, 1H), 5.98 (s, 2H), 4.78 (dhept, *J* = 7.9, 6.2 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.65 – 3.54 (m, 2H), 1.37 (d, *J* = 6.2 Hz, 6H), 1.35 （t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 6H), 0.92 – 0.85 (m, 2H), –0.04 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 162.1 (C), 141.6 (CH, d, *J* = 14 Hz), 134.2 (C, d, *J* = 207 Hz), 121.7 (C, d, *J* = 15 Hz), 80.6 (CH_2), 72.4 (CH, d, *J* = 5 Hz), 67.0 (CH_2), 60.8 (CH_2), 24.1 (CH_3, d, *J* = 5 Hz), 23.7 (CH_3, d, *J* = 5 Hz), 18.0 (CH_2), 14.4 (CH_3), –1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{18}H_{35}N_2NaO_6PSi$: 457.1894. Found: 457.1896.

Ethyl 5-(ethoxy(phenyl)phosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (4b). Pyrazole **1a** (263 mg, 0.734 mmol) and ethyl phenylphosphinate **2c** (81 μL, 0.505 mmol) were reacted together according to the general procedure. After 25 h, TLC showed full consumption of **2c**. Purification by flash column chromatography on silica gel (EtOAc/Toluene = 20:80) led to the desired product **4b** as a pale yellow oil (65 mg, 0.148 mmol, 29% yield). **IR (neat):** υ_{max} 2953, 2899, 1730, 1520, 1439, 1377, 1235, 1206, 1107, 1026, 962, 859, 749. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 8.03–7.95 (m, 2H), 7.93 (d, *J* = 1.1 Hz, 1H), 7.51 (m, 1H), 7.44–7.39 (m, 2H), 6.32 (d, *J* = 9.9 Hz, 1H), 5.78 (d, *J* = 9.9 Hz, 1H), 4.21 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.08 (m, 1H), 3.49 (ddd, *J* = 11.3, 9.6, 5.7 Hz, 1H), 3.39 (ddd, *J* = 11.3, 9.6, 5.7 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.81 (ddd, *J* = 13.8, 11.3, 5.7 Hz, 1H), 0.67 (ddd, *J* = 13.8, 11.3, 5.7 Hz, 1H), –0.09 (9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 162.0 (C), 141.3 (CH, d, *J* = 12 Hz), 135.1 (C, d, *J* = 138 Hz), 132.7 (CH, d, *J* = 3 Hz), 131.8 (CH, d, *J* = 11 Hz), 130.9 (C, d, *J* = 156 Hz), 128.3 (CH, d, *J* = 15 Hz), 121.9 (C, d, *J* = 14 Hz), 81.1 (CH_2), 66.8 (CH_2), 62.2 (CH_2, d, *J* = 6 Hz), 60.9 (CH_2), 17.8 (CH_2), 16.4 (CH_3, d, *J* = 7 Hz), 14.2 (CH_3), –1.4 (CH_3). **HRMS (ESI+):** $[M+H]^+$ calculated for $C_{20}H_{32}N_2O_5PSi$: 439.1813. Found: 439.1814.

Ethyl 3-(ethoxy(phenyl)phosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (4c). Pyrazole **1b** (109 mg, 0.312 mmol) and ethyl phenylphosphinate **2c** (32 μL, 0.212 mmol) were reacted together according to the general procedure. After 6 h at 70 °C, TLC showed that **2c** was not fully consumed, so the temperature was increased to 100 °C and the reaction mixture was stirred at this temperature for 15 h. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:90 to 100:0) led to the desired product **4c** as a pale yellow oil (23 mg, 0.052 mmol, 25% yield). **IR (neat):** υ_{max} 2953, 2900, 1723, 1531, 1439, 1220, 1125, 1080, 1027, 955, 858, 835, 773, 748, 723, 694. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 8.14 (d, *J* = 1.4 Hz, 1H), 7.87 (ddd, *J* = 13.3, 8.3, 1.2 Hz, 2H), 7.50 (m, 1H), 7.46−7.38 (m, 2H), 5.48 (s, 2H), 4.34−4.22 ($pent_{app}$, J = 7.2 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.62−3.52 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.94−0.86 (m, 2H), −0.03 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 161.6 (C), 145.6 (C, d, *J* = 164 Hz), 135.0 (CH, d, *J* = 6 Hz), 132.2 (CH), 131.9 (CH, d, *J* = 11 Hz), 131.5 (C, d, *J* = 153 Hz), 128.2 (CH, d, *J* = 14 Hz), 120.1 (C, d, *J* = 19 Hz), 81.1 (CH_2), 67.7 (CH_2), 62.1 (CH_2, d, *J* = 6 Hz), 60.8 (CH_2), 17.9 (CH_2), 16.6 (CH_3, d, *J* = 6 Hz), 14.2 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{20}H_{31}N_2NaO_5PSi$: 461.1632. Found: 461.1634.

Ethyl 3-(diphenylphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (4d). Pyrazole **1b** (105 mg, 0.301 mmol) and diphenyl phosphine oxide **2d** (40 mg, 0.198 mmol) were reacted together according to the general procedure. After 38 h at 70 °C, TLC showed that **2d** was not fully consumed, so the temperature was increased to 100 °C and the reaction mixture was stirred at this temperature for 48 h. Purification by flash column chromatography on silica gel (EtOAc/CH_2Cl_2 = 60:40 to 100:0) led to the desired product **4d** as a yellow solid (10 mg, 0.021 mmol, 11% yield).

IR (neat): υ_{max} 2953, 1719, 1532, 1438, 1384, 1247, 1197, 1076, 835. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 0.9 Hz, 1H), 7.76–7.69 (m, 4H), 7.55 – 7.48 (m, 2H), 7.47 – 7.39 (m, 4H), 5.39 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.54 – 3.47 (m, 2H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.91 – 0.84 (m, 2H), □0.04 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** 161.7 (C), 146.8 (C, d, *J* = 129 Hz), 135.4 (CH, d, *J* = 5 Hz), 132.8 (C, d, *J* = 112 Hz), 131.8 (CH, d, *J* = 10 Hz), 131.7 (CH), 128.21 (CH, d, *J* = 13Hz), 120.9 (C, d, *J* = 16 Hz), 81.0 (CH_2), 67.7 (CH_2), 60.8 (CH_2), 17.8 (CH_2), 13.8 (CH_3), −1.3 (CH_3). **HRMS (ESI+):** $[M+H]^+$ calculated for $C_{25}H_{31}N_2O_4PSi$: 471.1863. Found: 471.1862.

Ethyl 3-(ethoxy(phenyl)phosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (4e). Pyrazole **1c** (106 mg, 0.303 mmol) and ethyl phenylphosphinate **2c** (32 μL, 0.202 mmol) were reacted together

according to the general procedure. After 2 h at 70 °C, TLC showed full consumption of **2c**. Purification by flash column chromatography on silica gel (EtOAc/PE = 60:40 to 100:0) led to the desired product **4e** as a grey oil (46 mg, 0.10 mmol, 52% yield). **IR (neat):** υ_{max} 2980, 2953, 2900, 1728, 1305, 1236, 1124, 1096, 1080, 1027, 952, 858, 771. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.94−7.88 (m, 2H), 7.53 (m, 1H), 7.49−7.41 (m, 2H), 7.37 (d, *J* = 1.2 Hz, 1H), 5.90 (d, *J* = 10.2 Hz, 1H), 5.87 (d, *J* = 10.2 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.21−4.11 (m, 2H), 3.55−3.51 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.86−0.82 (m, 2H), −0.10 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 158.9 (C), 144.8 (C, d, *J* = 171 Hz), 134.0 (C, d, *J* = 8.1 Hz), 132.6 (CH, d, *J* = 3 Hz), 131.8 (CH, d, *J* = 10 Hz), 130.9 (C, d, *J* = 146 Hz), 128.6 (CH, d, *J* = 14 Hz), 118.2 (CH, d, *J* = 20 Hz), 80.2 (CH_2), 67.2 (CH_2), 61.9 (CH_2, d, *J* = 6 Hz), 61.7 (CH_2), 17.8 (CH_2), 16.6 (CH_3, d, *J* = 7 Hz), 14.3 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{20}H_{31}N_2NaO_5PSi$: 461.1632. Found: 461.1636.

Ethyl 3-(diphenylphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate (4f). Pyrazole **1c** (125 mg, 0.359 mmol) and diphenylphosphine oxide **2d** (48 mg, 0.238 mmol) were reacted together according to the general procedure. After 6 h, TLC showed full consumption of **2d**. Purification by flash column chromatography on silica gel (EtOAc/PE = 50:50) led to the desired product **4f** as a yellow oil (54 mg, 0.11 mmol, 48% yield). **IR (neat):** υ_{max} 2952, 1727, 1438, 1303, 1244, 1201, 1120, 1094, 1079, 857, 748. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.85−7.76 (m, 4H), 7.57-7.50 (m, 2H), 7.49−7.42 (m, 5H), 5.90 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.56−3.52 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.88−0.84 (m, 2H), −0.09 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 159.0 (C), 145.9 (C, d, *J* = 132 Hz), 134.1 (C, d, *J* = 7 Hz), 132.5 (C, d, *J* = 109 Hz), 132.2 (CH, d, *J* = 3 Hz), 131.8 (CH, d, *J* = 10 Hz), 128.6 (CH, d, *J* = 13 Hz), 118.6 (CH, d, *J* = 18 Hz), 80.2 (CH_2), 67.3 (CH_2), 61.7 (CH_2), 17.8 (CH_2), 14.3 (CH_3), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{24}H_{31}N_2NaO_4PSi$: 493.1683. Found: 493.1684.

Diethyl (3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)phosphonate (7a). Pyrazole **5** (330 mg, 0.956 mmol) and diethyl phosphite **2a** (81 µL, 0.633 mmol) were reacted together according to the general procedure. After 3 h, TLC showed full consumption of **2a**. Purification by flash column chromatography on silica gel (EtOAc/toluene = 20:80) led to the desired product **7a** as a yellow oil (212 mg, 0.527 mmol, 83% yield). **IR (neat):** υ_{max} 2984, 2955, 2902, 1530, 1456, 1370, 1252, 1210, 1171, 1133, 1092, 1017, 973, 835, 756. **^{1}H-NMR ($CDCl_3$, 400 MHz):** 7.01 (d, *J* = 2.4 Hz, 1H), 5.73 (s, 2H), 4.29–4.10 (m, 4H), 3.68–3.60 (m, 2H), 1.37 (td, *J* = 7.1, 0.6 Hz, 6H), 0.93–0.84 (m, 2H), –0.02 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 142.3 (C, qd, *J* = 39, 17 Hz), 134.0 (C, d, *J* = 214 Hz), 120.8 (C, q, *J* = 269 Hz), 113.9 (CH, dd_{app}, *J* =

18, 2 Hz), 80.3 (CH_2), 67.4 (CH_2), 63.5 (CH_2, d, J = 6 Hz), 17.8 (CH_2), 16.3 (CH_3, d, J = 7 Hz), −1.5 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{14}H_{26}F_3N_2NaO_4PSi$: 425.1244. Found: 425.1243.

Ethyl phenyl(3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)phosphinate (7b). Pyrazole **5** (112 mg, 0.324 mmol) and ethyl phenylphosphinate **2c** (35 µL, 0.218 mmol) were reacted together according to the general procedure. After 9 h, TLC showed full consumption of **2c**. Purification by flash column chromatography on silica gel (Et_2O/toluene = 35:65) led to the desired product **7b** as a yellow oil (85 mg, 0.20 mmol, 90% yield). **IR (neat):** υ_{max} 2954, 2901, 1527, 1440, 1240, 1209, 1170, 1128, 1091, 1023, 974, 834, 693. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.89−7.78 (m, 2H), 7.58 (m, 1H), 7.53−7.44 (m, 2H), 6.91 (d, J = 2.0 Hz, 1H), 5.91 (d, J = 10.3 Hz, 1H), 5.61 (d, J = 10.3 Hz, 1H), 4.27−4.11 (m, 2H), 3.41 (ddd, J = 11.1, 9.7, 5.8 Hz, 1H), 3.30 (ddd, J = 11.2, 9.7, 5.6 Hz, 1H), 1.40 (t, J =7.1, 3H), 0.68 (ddd, J = 13.8, 11.2, 5.8 Hz, 1H), 0.52 (ddd, J = 13.8, 11.1, 5.6 Hz, 1H), −0.11 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 142.2 (C, qd, J = 39, 14 Hz), 136.8 (C, d, J = 150 Hz), 133.1 (CH, d, J = 3 Hz), 131.9 (CH, d, J = 11 Hz), 130.1 (C, d, J = 150 Hz), 128.9 (CH, d, J = 14 Hz), 120.9 (C, q, J = 269 Hz), 113.5 (CH, d, J = 18 Hz), 80.5 (CH_2), 67.0 (CH_2), 62.4 (CH_2, d, J = 6 Hz), 17.5 (CH_2), 16.6 (CH_3, d, J = 7 Hz), −1.5 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{18}H_{26}F_3N_2NaO_3PSi$: 457.1295. Found: 457.1298.

Diphenyl(3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)phosphine oxide (7c). Pyrazole **5** (132 mg, 0.384 mmol) and diphenylphosphine oxide **2d** (52 mg, 0.255 mmol) were reacted together according to the general procedure. After 9 h, TLC showed full consumption of **2d**. Purification by flash column chromatography on silica gel (Et_2O/toluene = 30:70) led to the desired product **7c** as a yellow oil (68 mg, 0.15 mmol, 57% yield). **IR (neat):** υ_{max} 2953, 2897, 1526, 1438, 1249, 1208, 1170, 1120, 973, 834, 693. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.71−7.63 (m, 4H), 7.66−7.55 (m, 2H), 7.53−7.46 (m, 4H), 6.35 (d, J = 2.1 Hz, 1H), 5.78 (s, 2H), 3.30−3.26 (m, 2H), 0.48−0.43 (m, 2H), −0.14 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 141.9 (C, qd, J = 39, 13 Hz), 137.6 (C, d, J = 108 Hz), 132.9 (CH, broad), 131.7 (CH, d, J = 11 Hz), 131.0 (C, d, J = 112 Hz), 128.9 (CH, d, J = 13 Hz), 120.8 (C, q, J = 269 Hz), 114.4 (CH, d, J = 16 Hz), 80.8 (CH_2), 66.9 (CH_2), 17.3 (CH_2), −1.6 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{22}H_{26}F_3N_2NaO_2PSi$: 489.1346. Found: 489.1347.

Cyclopropyl(phenyl)(3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)phosphine oxide (7d) Pyrazole **5** (101 mg, 0.293 mmol) and cyclopropylphenylphosphine oxide **2e** (35 mg, 0.211 mmol) were reacted together according to the general procedure. After 23 h, TLC showed full consumption of **2e.** Purification by flash column chromatography on silica gel (Et_2O/toluene = 35:65) led to the desired product **7d** as a yellow oil (43 mg, 0.10 mmol, 47% yield). **IR (neat):** υ_{max} 2953, 2916, 1528, 1249, 1216, 1172, 1123, 1106,

1087, 973, 932, 895, 763. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.76−7.70 (m, 2H), 7.57 (m, 1H), 7.52−7.47 (m, 2H), 6.91 (d, *J* = 1.8 Hz, 1H), 5.75 (d, *J* = 10.4 Hz, 1H), 5.58 (d, *J* = 10.4 Hz, 1H), 3.40 (ddd, *J* = 11.1, 9.6, 5.9 Hz, 1H), 3.30 (ddd, *J* = 11.1, 9.6, 5.6 Hz, 1H), 1.38 (m, 1H), 1.18−0.95 (m, 4H), 0.64 (ddd, *J* = 13.8, 11.1, 5.9 Hz, 1H), 0.51 (ddd, *J* = 13.8, 11.1, 5.6 Hz, 1H), −0.11 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 142.2 (C, qd, *J* = 39, 13 Hz), 138.6 (C, d, *J* = 106 Hz), 132.6 (CH, d, *J* = 3 Hz), 131.8 (C, d, *J* = 112 Hz), 130.9 (CH, d, *J* = 10 Hz), 128.9 (CH, d, *J* = 13 Hz), 121.0 (C, q, *J* = 269 Hz), 112.8 (CH, d, *J* = 14 Hz), 80.5 (CH_2), 67.0 (CH_2), 17.5 (CH_2), 8.3 (CH, d, *J* = 112 Hz), 3.7 (CH_2, d, *J* = 5 Hz), 3.4 (CH_2, d, *J* = 4 Hz), −1.5 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{19}H_{26}F_3N_2NaO_2PSi$: 453.1346. Found: 453.1347.

Diethyl (5-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)phosphonate (8a). Pyrazole **6** (101 mg, 0.293 mmol) and diethyl phosphite **2a** (36 μL, 0.282 mmol) were reacted together according to the general procedure. After 5 h, TLC showed full consumption of **2a**. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:100 to 100:0) led to the desired product **8a** as an orange oil (82 mg, 0.23 mmol, 81% yield). **IR (neat):** υ_{max} 2983, 2954, 2901, 2240, 1393, 1299, 1249, 1095, 1051, 1019, 972, 858, 835, 762. **^{1}H-NMR (Acetone-d6, 400 MHz):** δ 7.49 (d, *J* = 1.5 Hz, 1H), 5.76 (s, 2H), 4.23−4.07 (m, 4H), 3.72−3.65 (m, 2H), 1.30 (td, *J* = 7.1, 0.5 Hz, 6H), 0.97−0.90 (m, 2H), −0.02 (s, 9H). **^{13}C-NMR (Acetone-d6, 100 MHz):** δ 144.7 (C, d, *J* = 230 Hz), 121.1 (CH, d, *J* = 23 Hz), 116.9 (C, d, *J* = 11 Hz), 110.3 (C), 81.2 (CH_2), 68.2 (CH_2), 63.4 (CH_2, d, *J* = 6 Hz), 18.1 (CH_2), 16.6 (CH_3, d, *J* = 6 Hz), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{14}H_{26}N_3NaO_4PSi$: 382.1322. Found: 382.1326.

Ethyl (5-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)(phenyl)phosphinate (8b) Pyrazole **6** (123 mg, 0.409 mmol) and ethyl phenylphosphinate **2c** (44 μL, 0.273 mmol) were reacted together according to the general procedure. After 5 h, TLC showed full consumption of **2c**. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:100 to 100:0) led to the desired product **8b** as a yellow oil (80 mg, 0.20 mmol, 75% yield). **IR (neat):** υ_{max} 2953, 2899, 2239, 1439, 1297, 1234, 1124, 1093, 1025, 953, 858, 751. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.93−7.86 (m, 2H), 7.56 (m, 1H), 7.51−7.43 (m, 2H), 7.31 (d, *J* = 1.2 Hz, 1H), 5.63 (s, 2H), 4.23−4.09 (m, 2H), 3.61−3.53 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.94−0.84 (m, 2H), −0.07 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 146.9 (C, d, *J* = 169 Hz), 133.0 (CH, d, *J* = 3 Hz), 131.9 (CH, d, *J* = 10 Hz), 130.1 (C, d, *J* = 145 Hz), 128.8 (CH, d, *J* = 14 Hz), 120.3 (CH, d, *J* = 20 Hz), 116.2 (C, d, *J* = 9 Hz), 109.5 (C), 80.4 (CH_2), 68.1 (CH_2), 62.1 (CH_2, d, *J* = 6 Hz), 17.7 (CH_2), 16.6 (CH_3, d, *J* = 6 Hz), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{18}H_{26}N_3NaO_3PSi$: 414.1373. Found: 414.1376.

3-(Diphenylphosphoryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carbonitrile (8c). Pyrazole **6** (117 mg, 0.388 mmol) and diphenylphosphine oxide **2d** (52 mg, 0.258 mmol) were reacted together according to the general procedure. After 23 h, TLC showed full consumption of **2d**. Purification by flash column chromatography on silica gel (EtOAc/PE = 10:100 to 100:0) led to the desired product **8c** as a yellow oil (63 mg, 0.15 mmol, 58% yield). **IR (neat):** υ_{max} 2952, 2896, 2238, 1438, 1296, 1248, 1200, 1118, 1093, 980, 834, 752. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 7.82−7.73 (m, 4H), 7.60−7.52 (m, 2H), 7.50−7.43 (m, 4H), 7.37 (d, J = 1.5 Hz, 1H), 5.64 (s, 2H), 3.65−3.50 (m, 2H), 0.98−0.76 (m, 2H), −0.06 (s, 9H). **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 148.2 (C, d, J = 129 Hz), 132.5 (CH, d, J = 3 Hz), 131.758 (CH, d, J = 10 Hz), 131.755 (C, d, J = 109 Hz), 128.7 (CH, d, J = 13 Hz), 120.9 (CH, d, J = 18 Hz), 116.4 (C, d, J = 8 Hz), 109.5 (C), 80.4 (CH_2), 68.1 (CH_2), 17.7 (CH_2), −1.4 (CH_3). **HRMS (ESI+):** $[M+Na]^+$ calculated for $C_{22}H_{26}N_3NaO_2PSi$: 446.1424. Found: 446.1426.

Associated Content

The ^{1}H and ^{13}C NMR for compounds **1a–f**, **2e**, **3a–e**, **4a–f**, **5**, **6** , **7a–d** and **8a–c** are provided in the supporting information. This material is available free of charge via the internet at http://www.sciencedirect.com.

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Palladium-Catalyzed Phosphonylation of Substituted Pyrazoles

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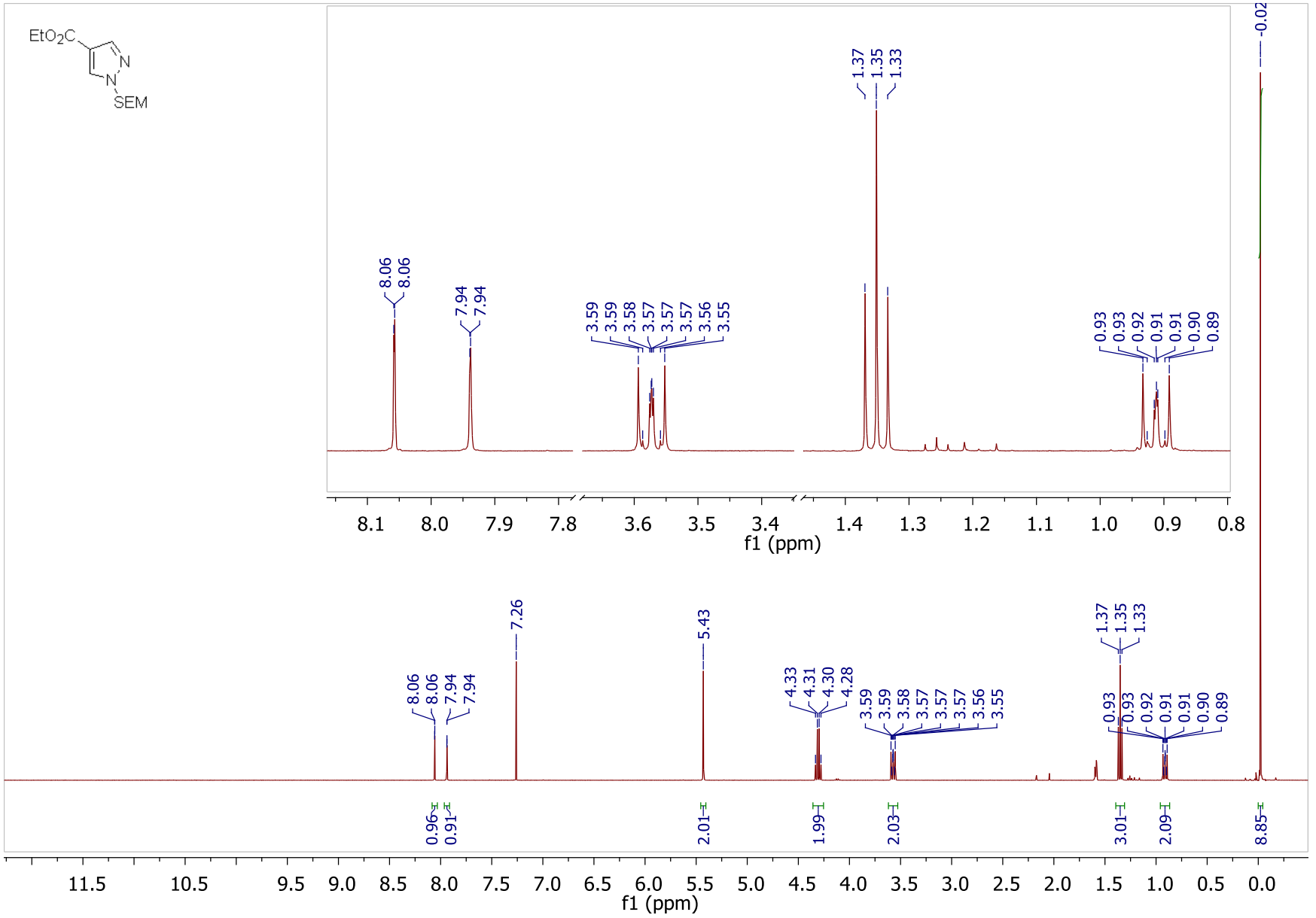
Supporting Information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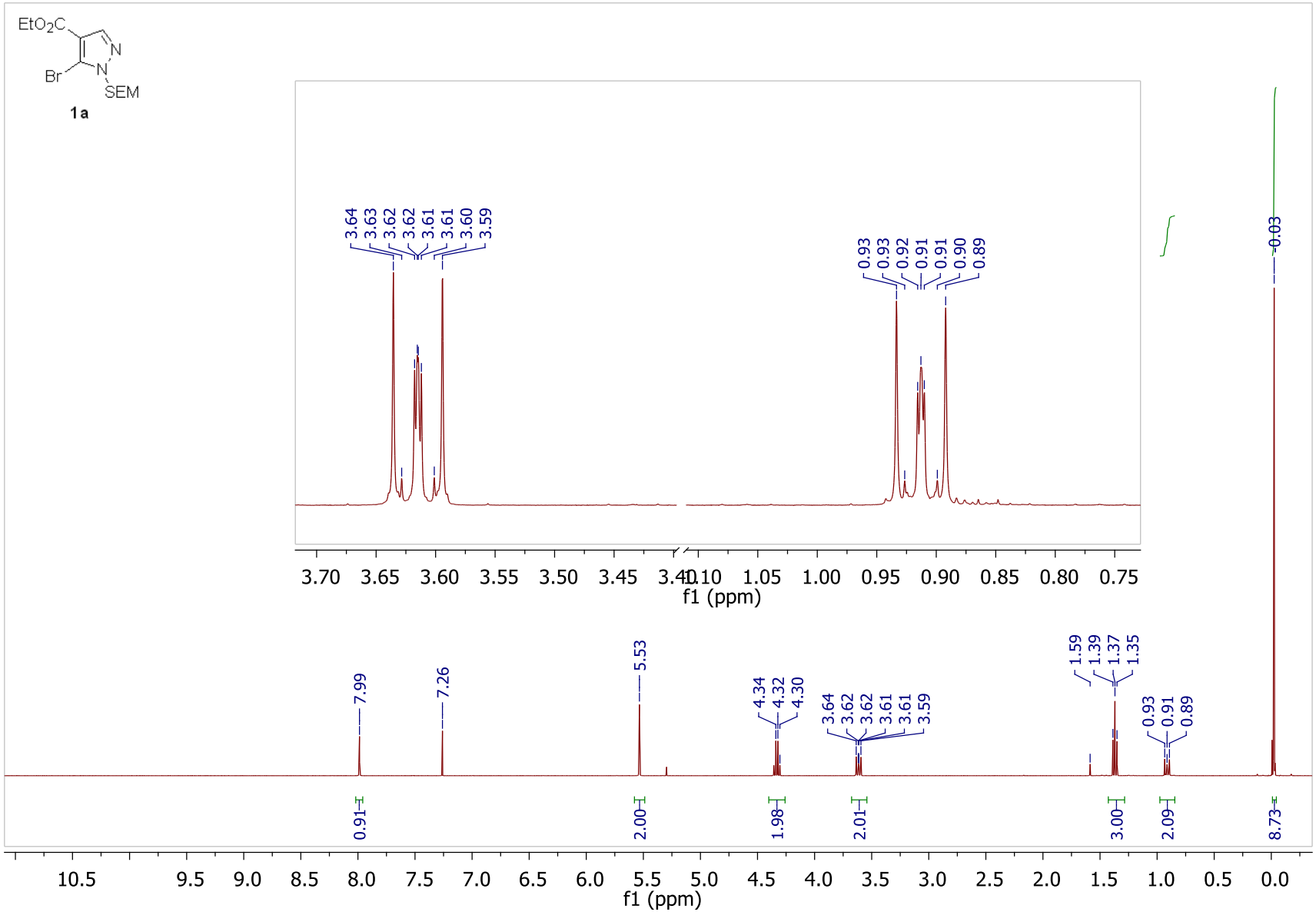
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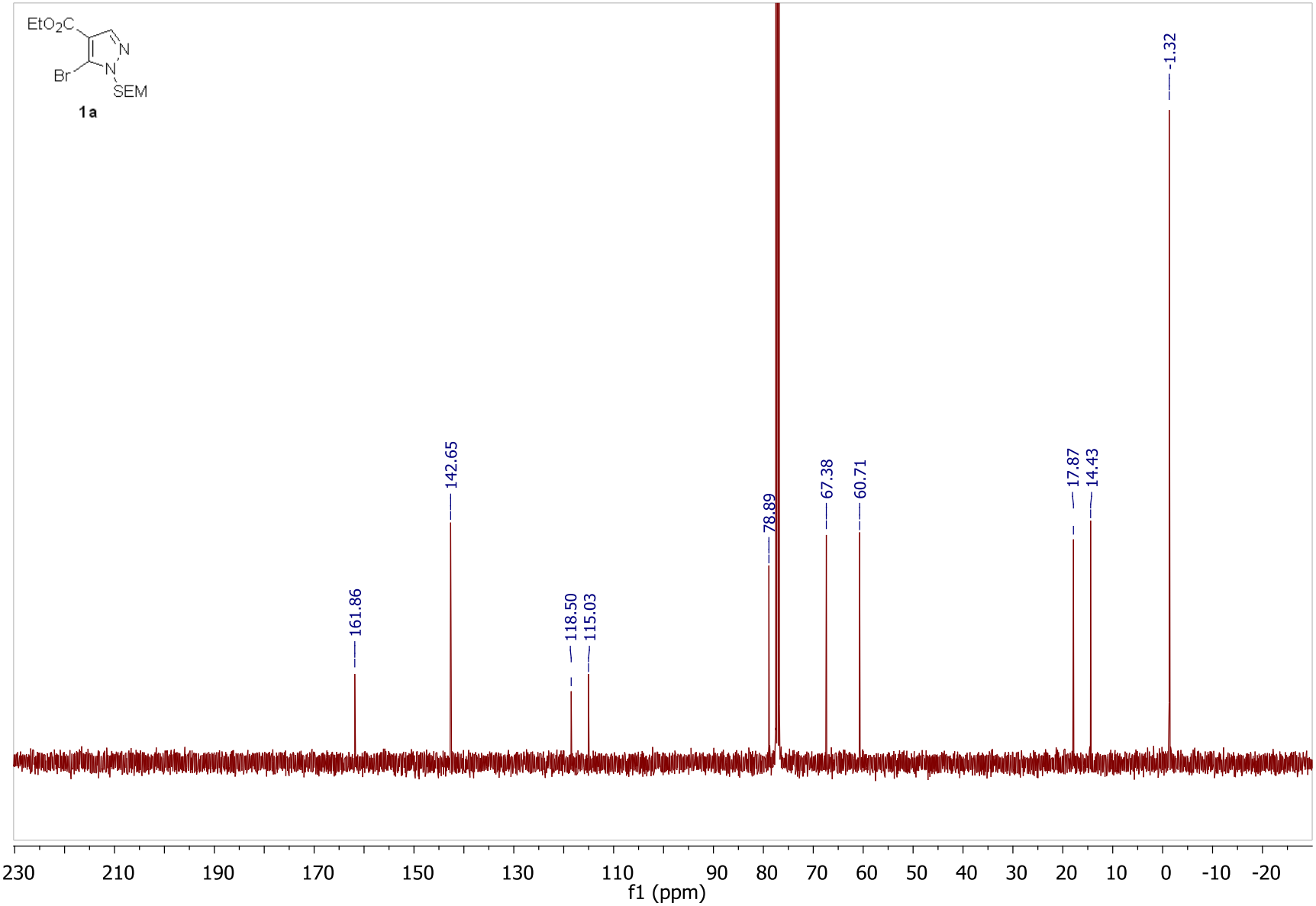
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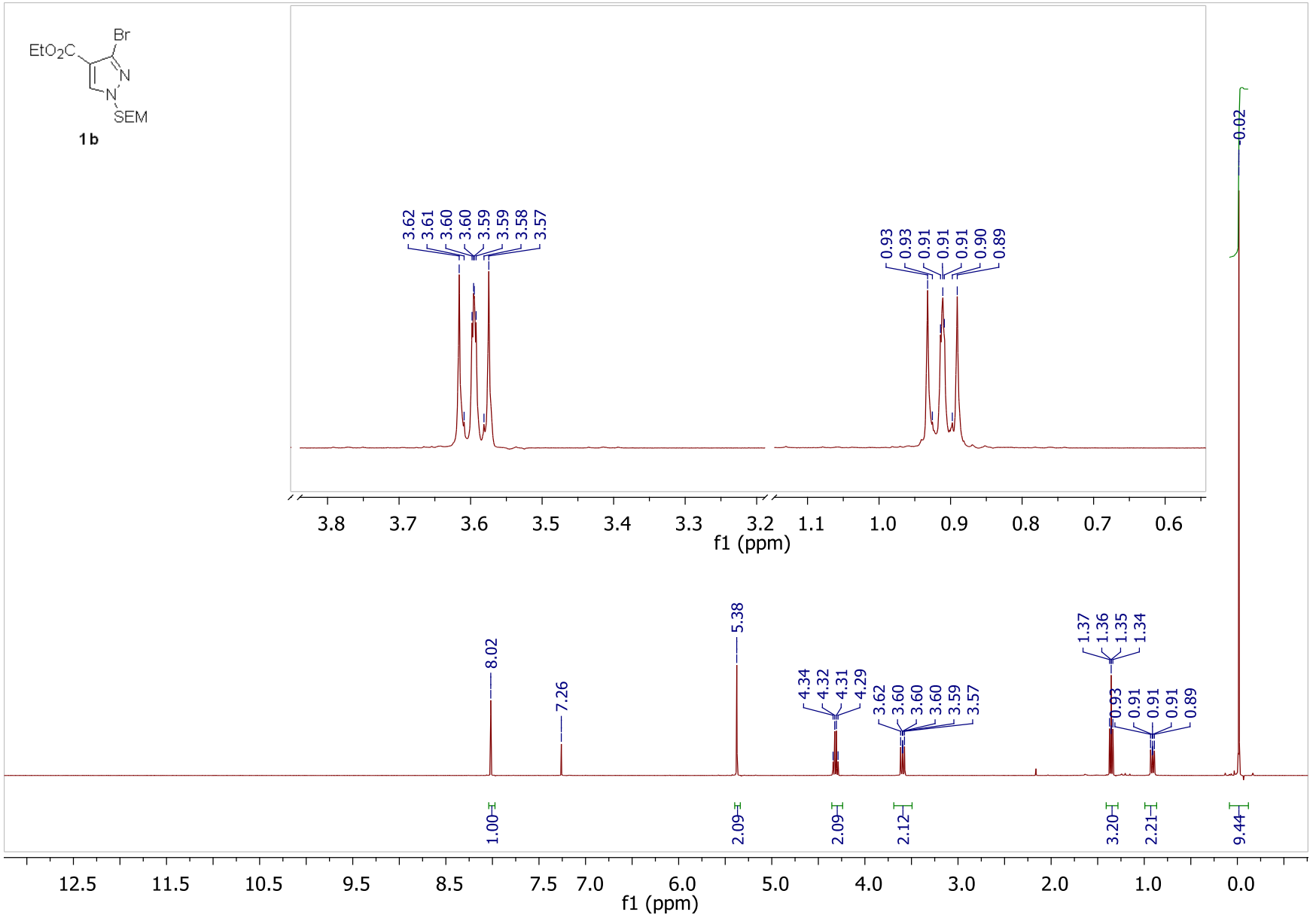
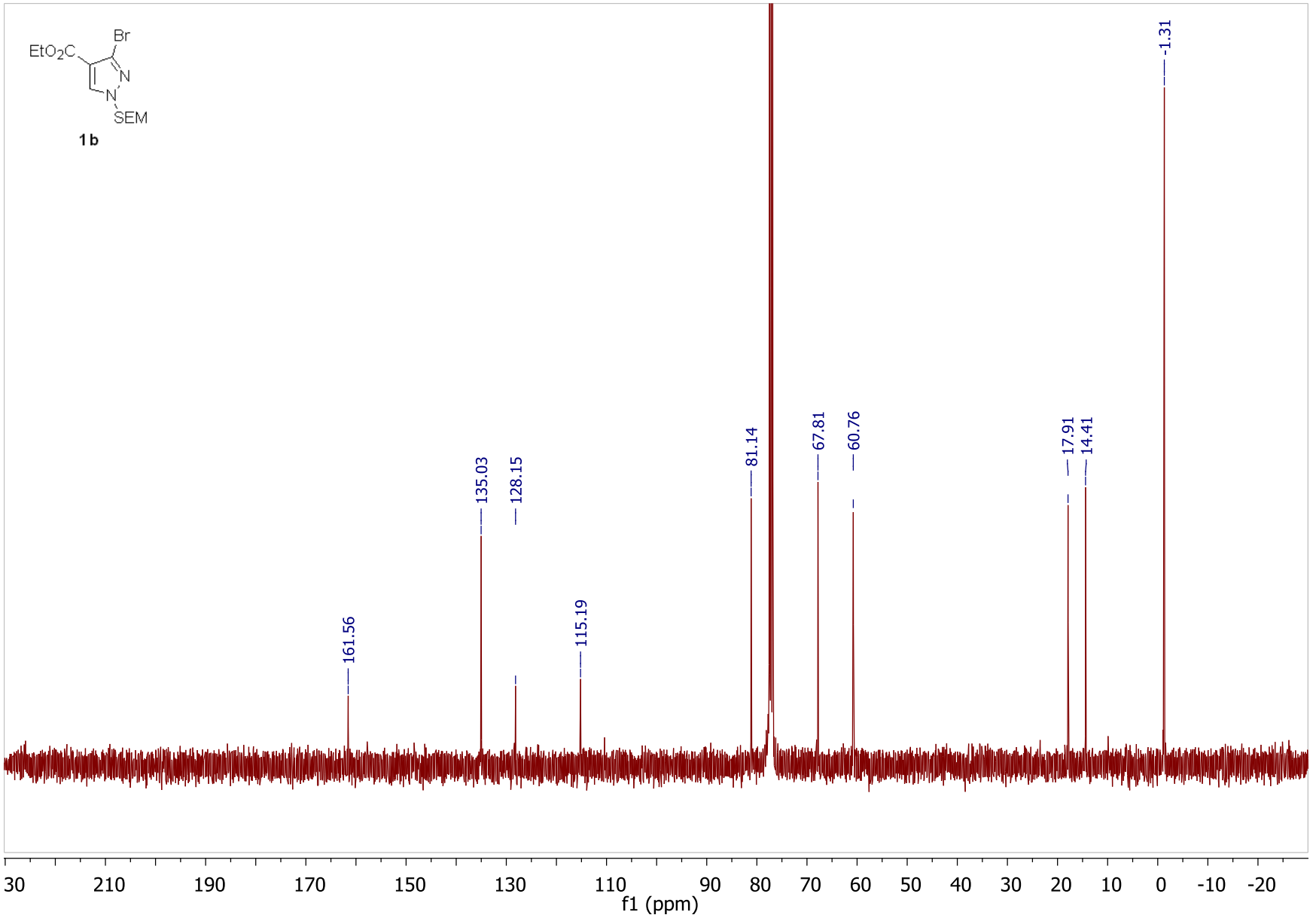
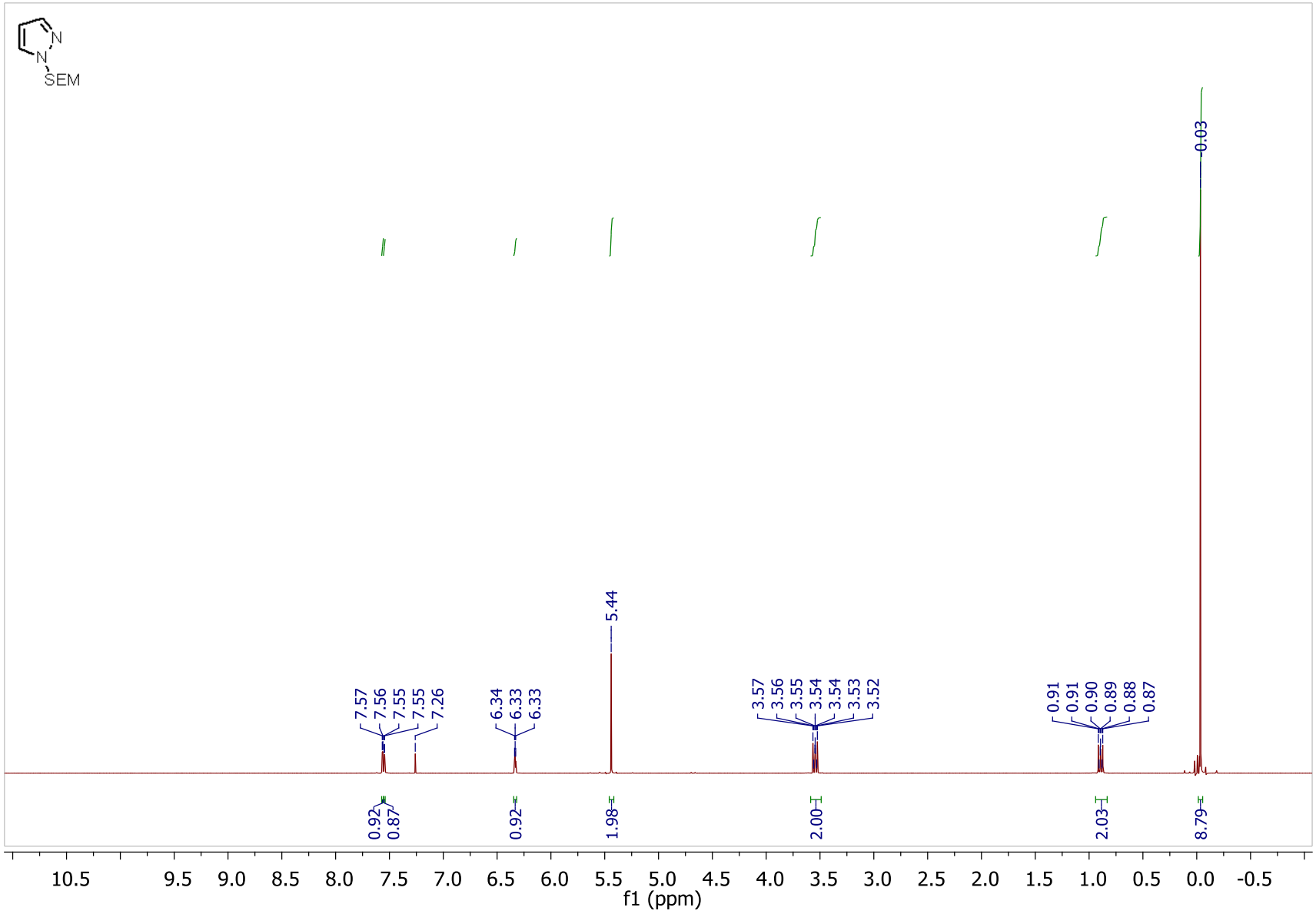
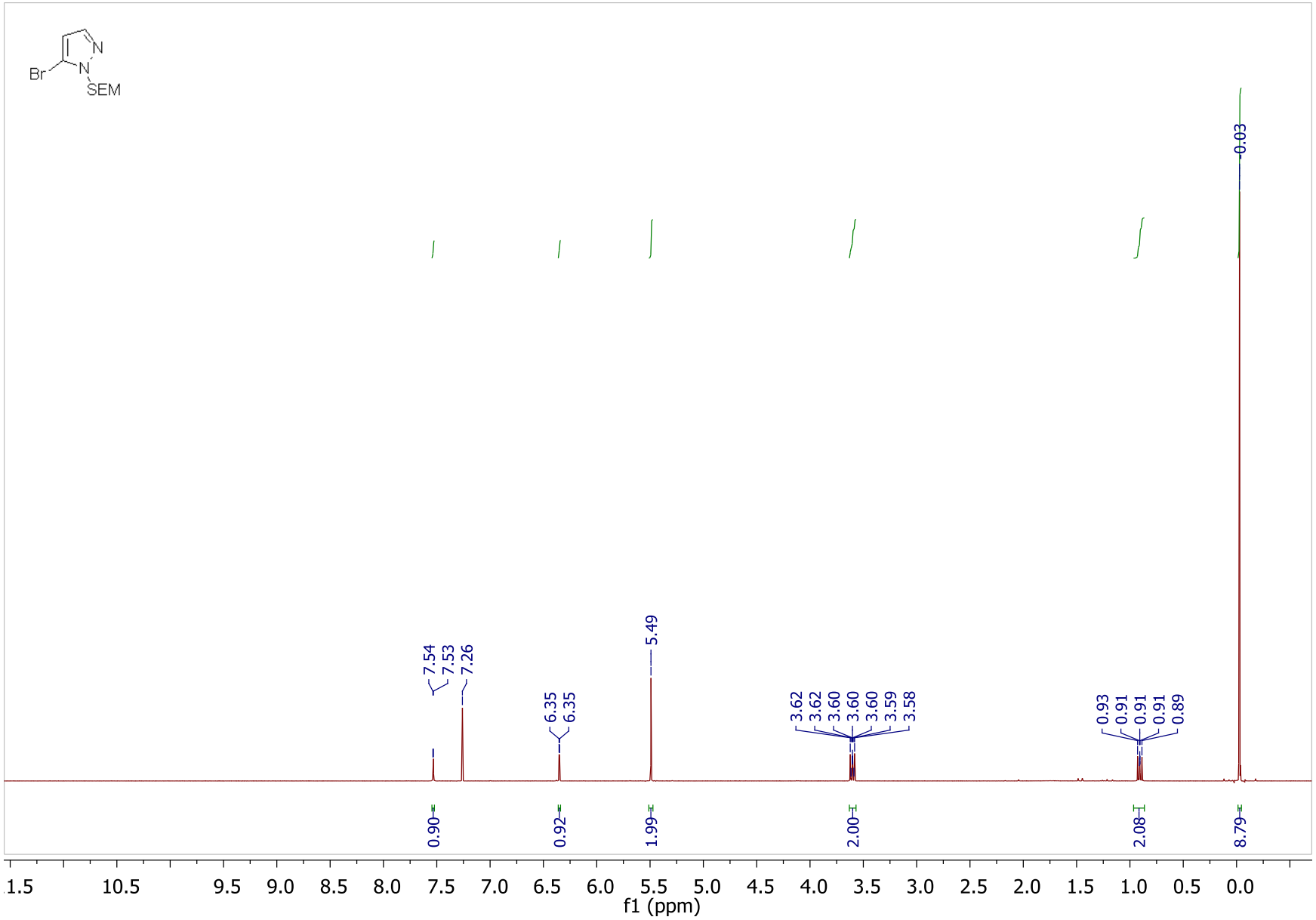
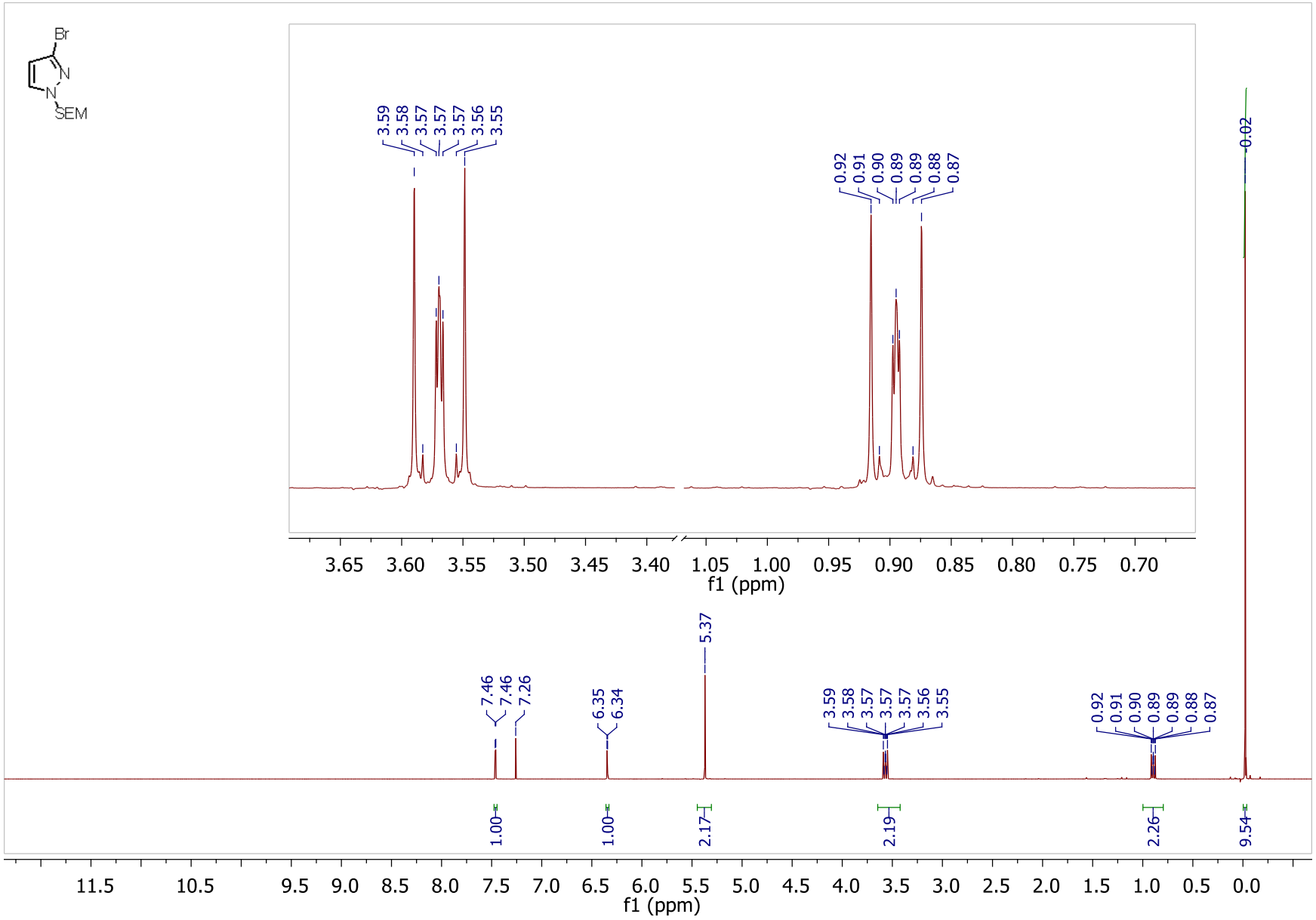
-20
f1 (ppm)

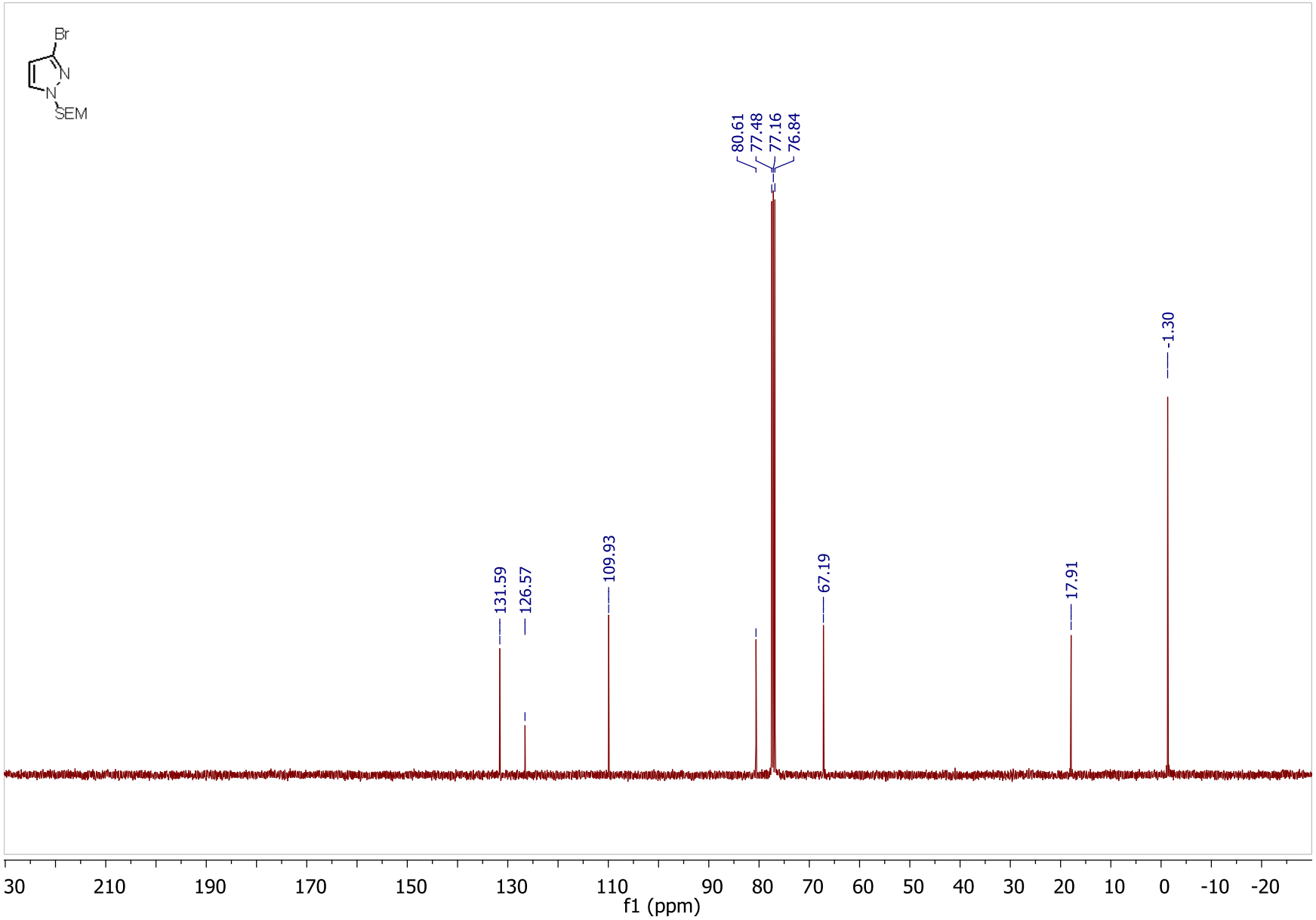

EtO2C
Br
N
N
SEM
1b
3.62
3.61
3.60
3.60
3.59
3.59
3.58
3.57
0.93
0.93
0.91
0.91
0.91
0.90
0.89
f1 (ppm)
8.02
7.26
5.38
4.34
4.32
4.31
4.29
3.62
3.60
3.60
3.60
3.59
3.57
1.37
1.36
1.35
1.34
0.93
0.91
0.91
0.91
0.89
0.02
1.00
2.09
2.09
2.12
3.20
2.21
9.44
f1 (ppm)

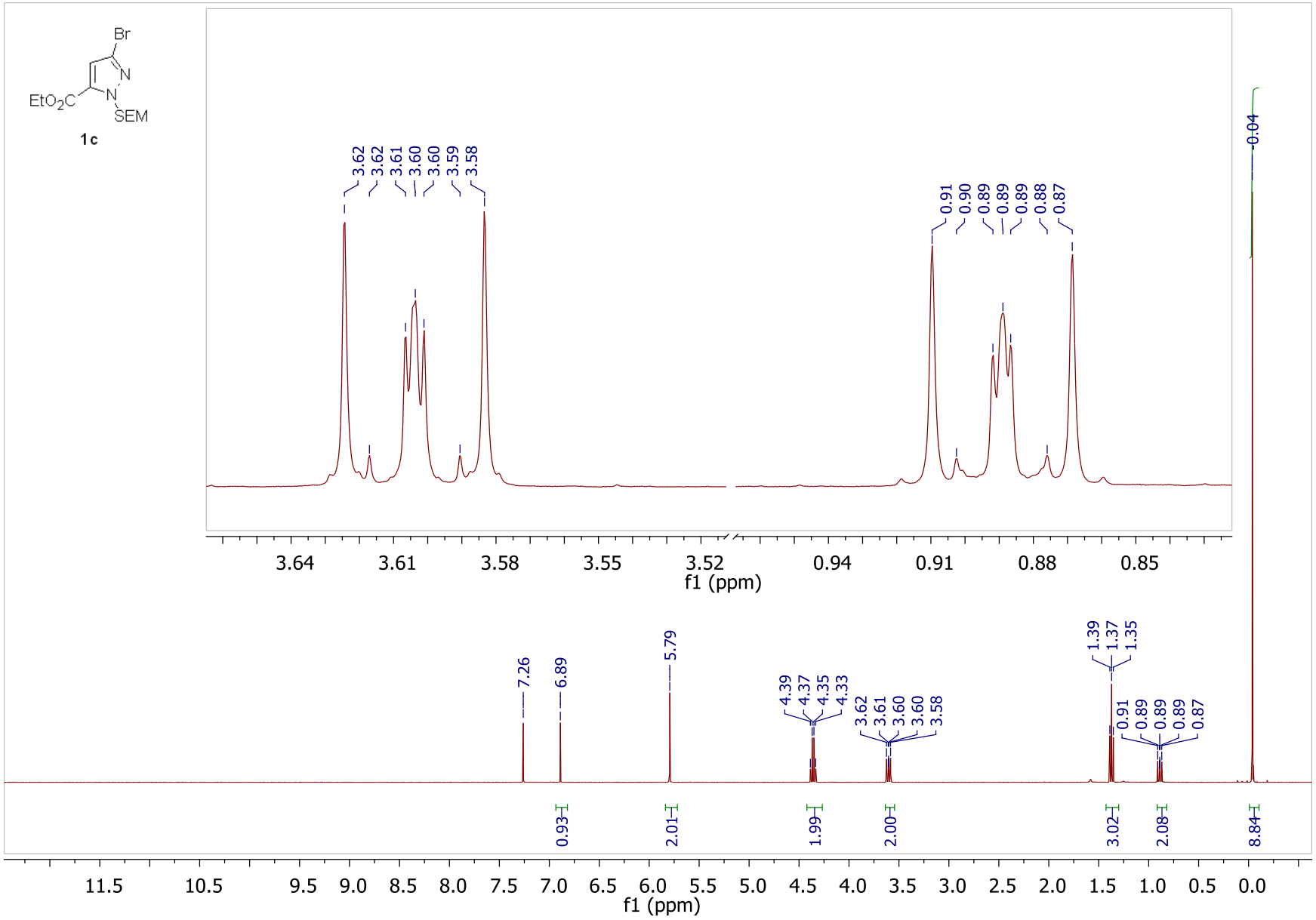

EtO2C
Br
N
N
SEM
1b
161.56
135.03
128.15
115.19
81.14
67.81
60.76
17.91
14.41
-1.31
30
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

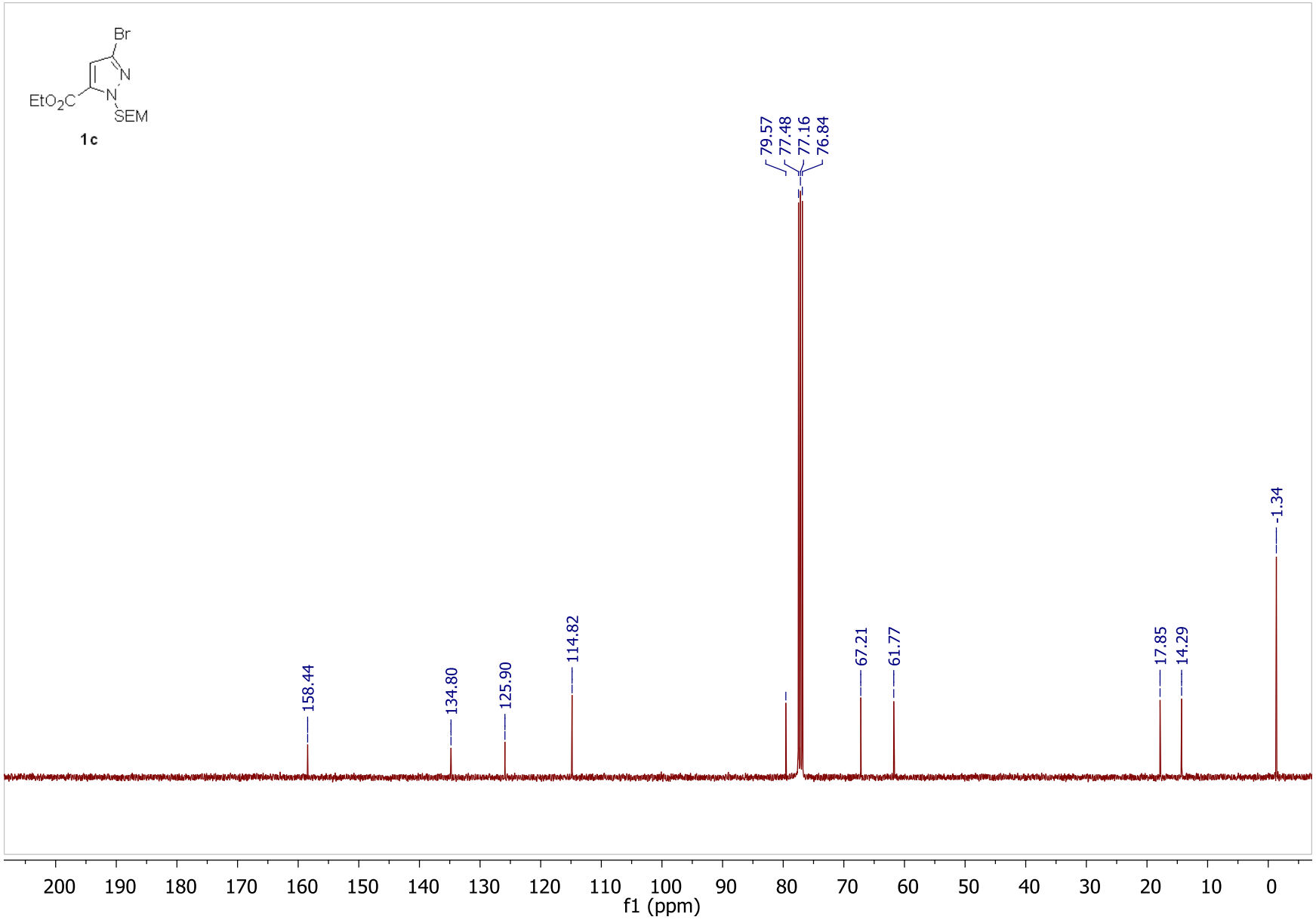

N
N
SEM
7.57
7.56
7.55
7.55
7.26
6.34
6.33
6.33
5.44
3.57
3.56
3.55
3.54
3.54
3.53
3.52
0.91
0.91
0.90
0.89
0.88
0.87
0.03
0.92
0.87
0.92
1.98
2.00
2.03
8.79
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

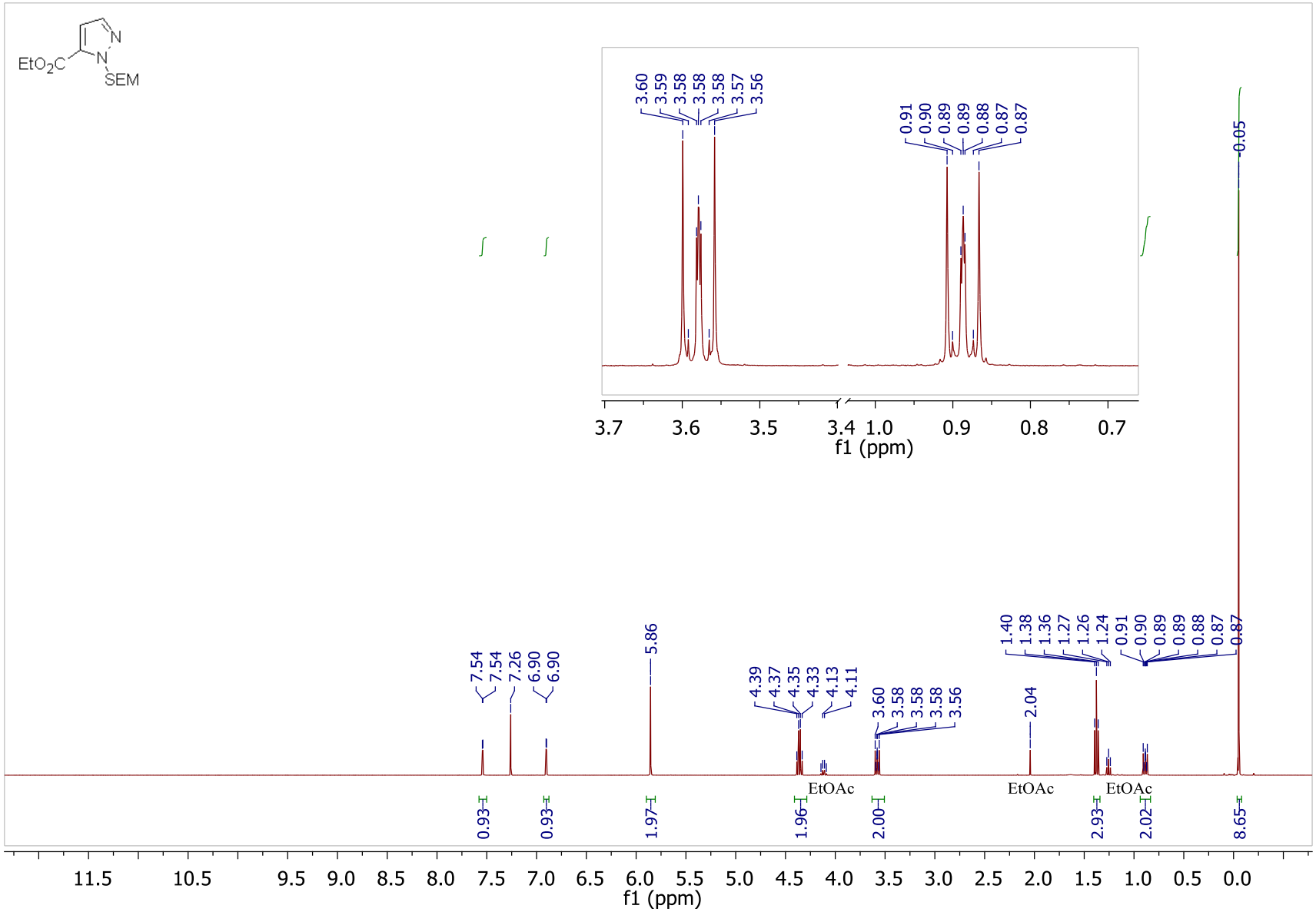

Br
N
N
SEM
7.54
7.53
7.26
6.35
6.35
5.49
3.62
3.62
3.60
3.60
3.60
3.59
3.58
0.93
0.91
0.91
0.91
0.89
0.03
0.90
0.92
1.99
2.00
2.08
8.79
f1 (ppm)

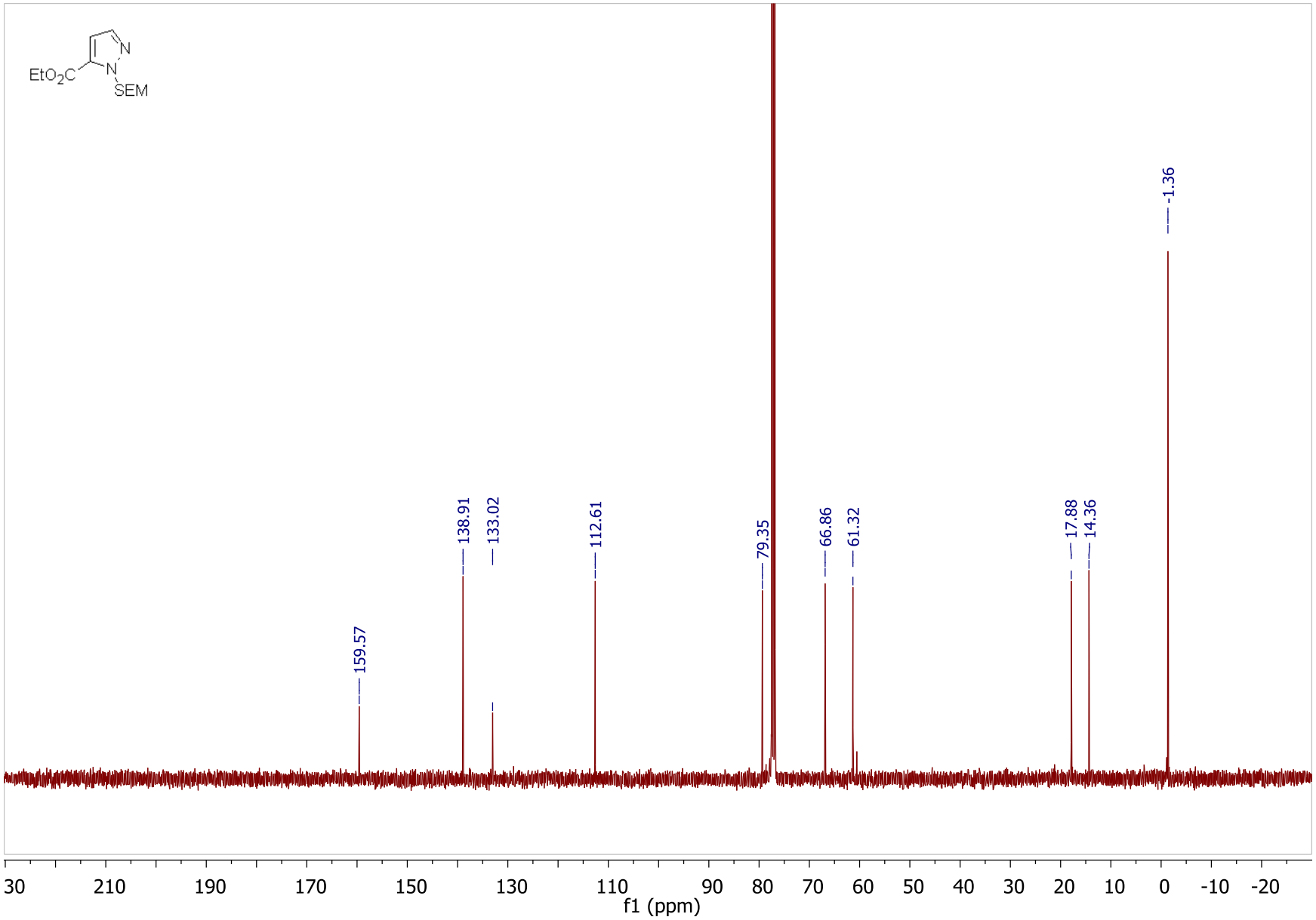

Br
N
N
SEM
3.59
3.58
3.57
3.57
3.57
3.56
3.55
0.92
0.91
0.90
0.89
0.89
0.88
0.87
0.02
3.65 3.60 3.55 3.50 3.45 3.40 1.05 1.00 0.95 0.90 0.85 0.80 0.75 0.70
f1 (ppm)
7.46
7.46
7.26
6.35
6.34
5.37
1.00
1.00
2.17
2.19
2.26
9.54
11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

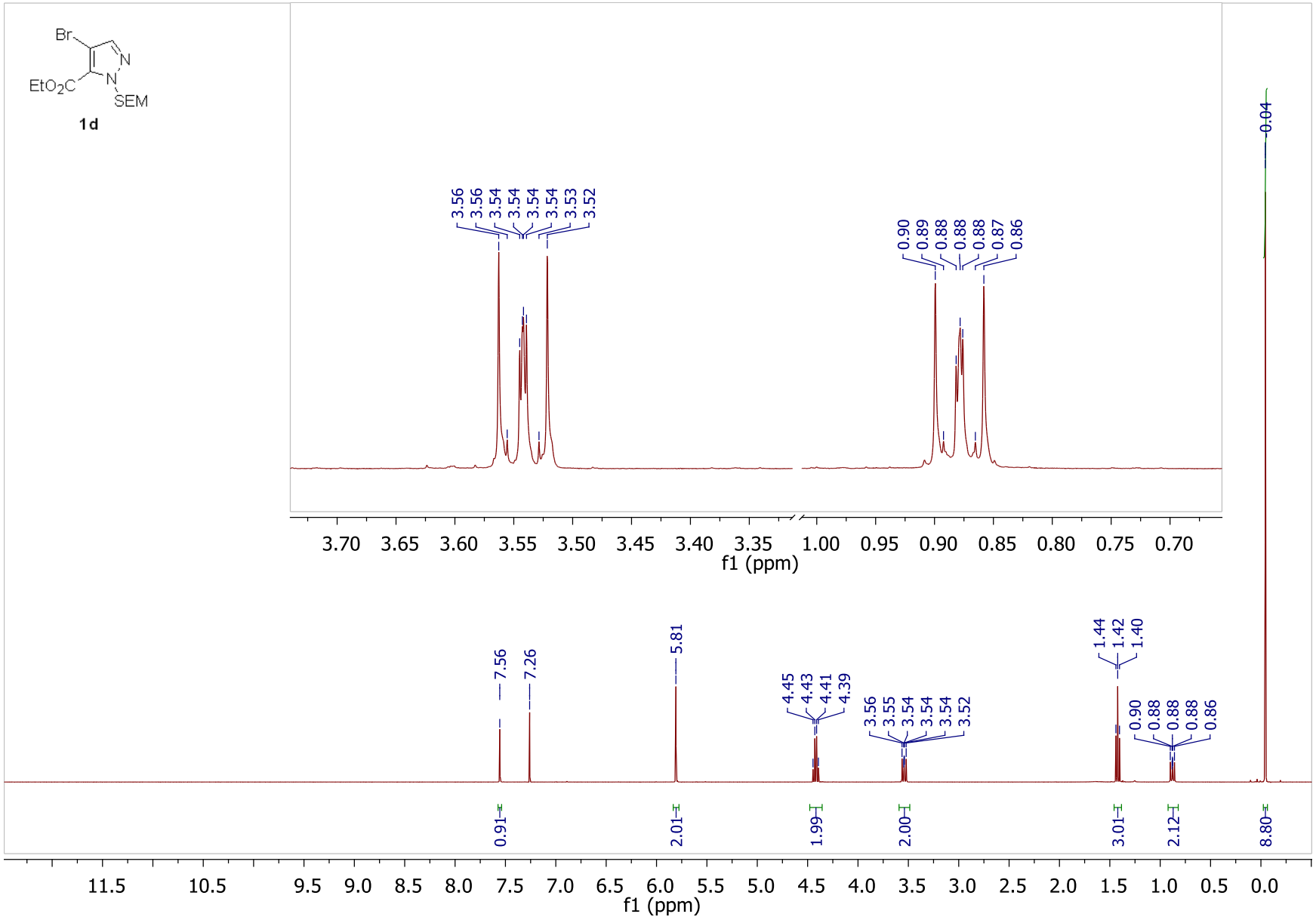

Br
N
N
SEM
80.61
77.48
77.16
76.84
131.59
126.57
109.93
67.19
17.91
-1.30
30
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

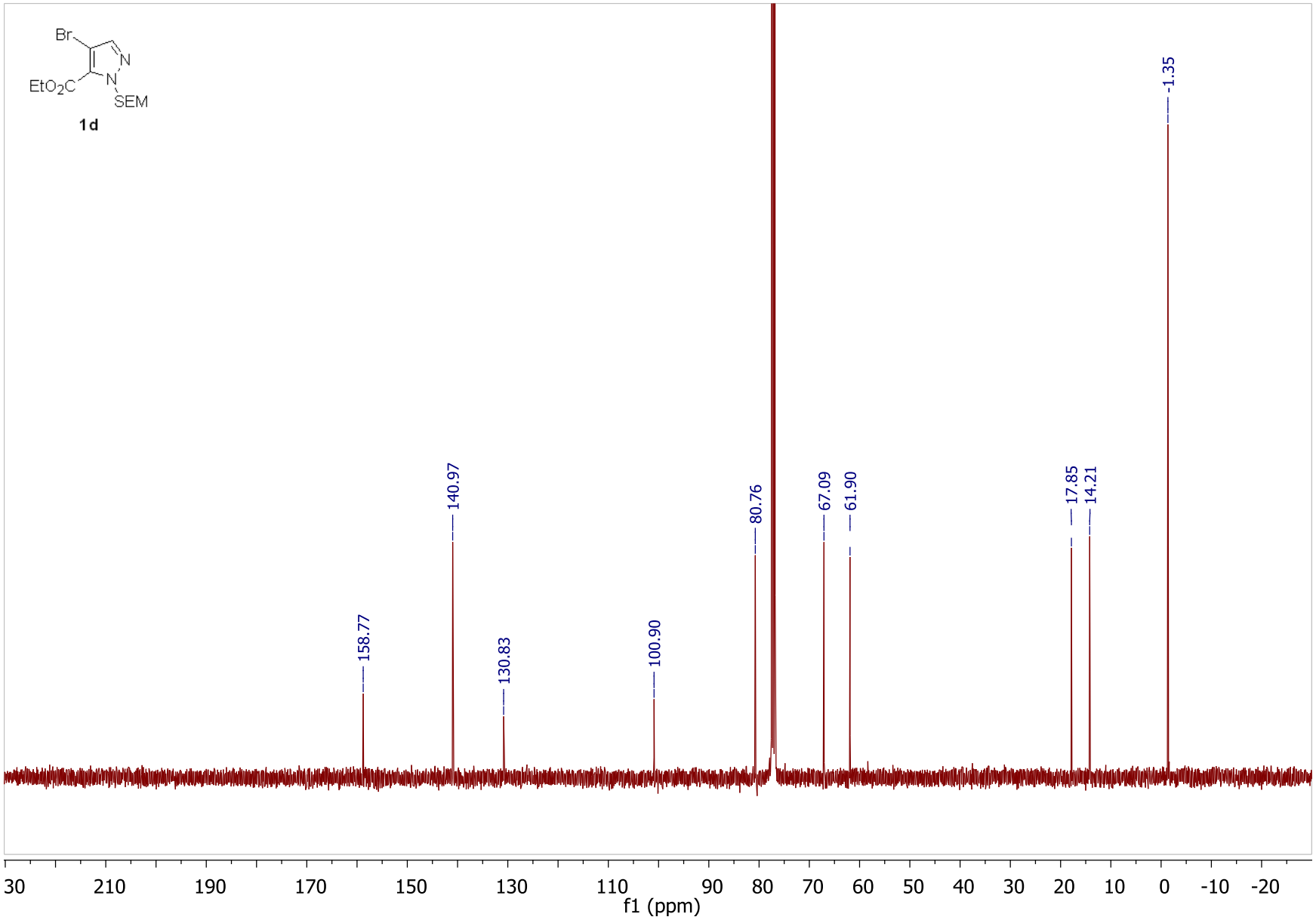

Br
N
N
SEM
EtO2C
1c
3.62
3.62
3.61
3.60
3.60
3.59
3.58
0.91
0.90
0.89
0.89
0.89
0.88
0.87
0.04
3.64
3.61
3.58
3.55
3.52
0.94
0.91
0.88
0.85
f1 (ppm)
7.26
6.89
5.79
4.39
4.37
4.35
4.33
3.62
3.61
3.60
3.60
3.58
1.39
1.37
1.35
0.91
0.89
0.89
0.89
0.87
0.93
2.01
1.99
2.00
3.02
2.08
8.84
11.5
10.5
9.5
9.0
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)

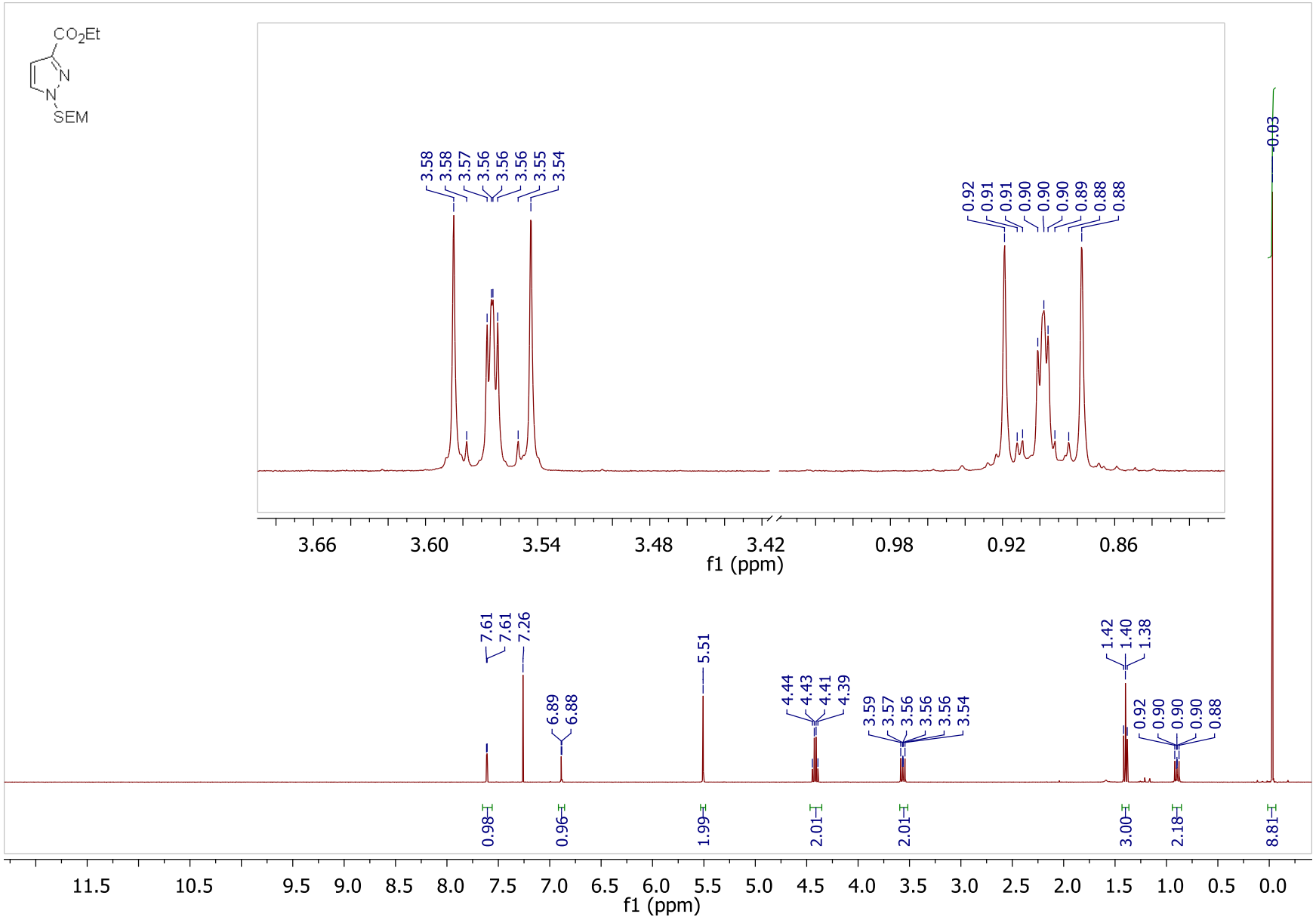

Br
N
N
SEM
EtO2C
1c
79.57
77.48
77.16
76.84
158.44
134.80
125.90
114.82
67.21
61.77
17.85
14.29
-1.34
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

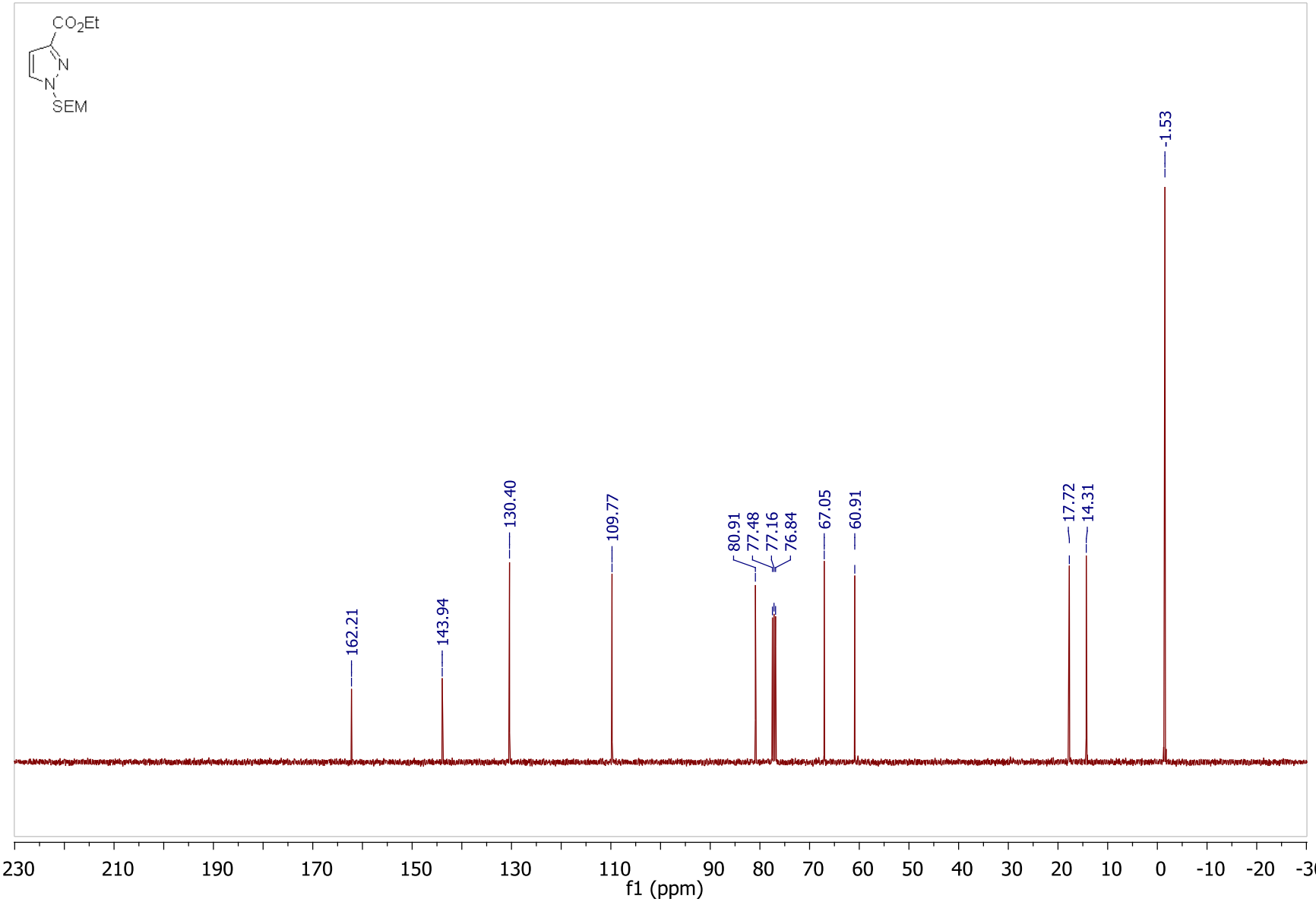

EtO2C
N
N
SEM
3.60
3.59
3.58
3.58
3.58
3.57
3.56
0.91
0.90
0.89
0.89
0.88
0.87
0.87
0.05
3.7
3.6
3.5
3.4
1.0
0.9
0.8
0.7
f1 (ppm)
7.54
7.54
7.26
6.90
6.90
5.86
4.39
4.37
4.35
4.33
4.13
4.11
3.60
3.58
3.58
3.58
3.56
1.40
1.38
1.36
1.27
1.26
1.24
0.91
0.90
0.89
0.89
0.88
0.87
0.87
2.04
EtOAc
EtOAc
EtOAc
0.93
0.93
1.97
1.96
2.00
2.93
2.02
8.65
11.5
10.5
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)

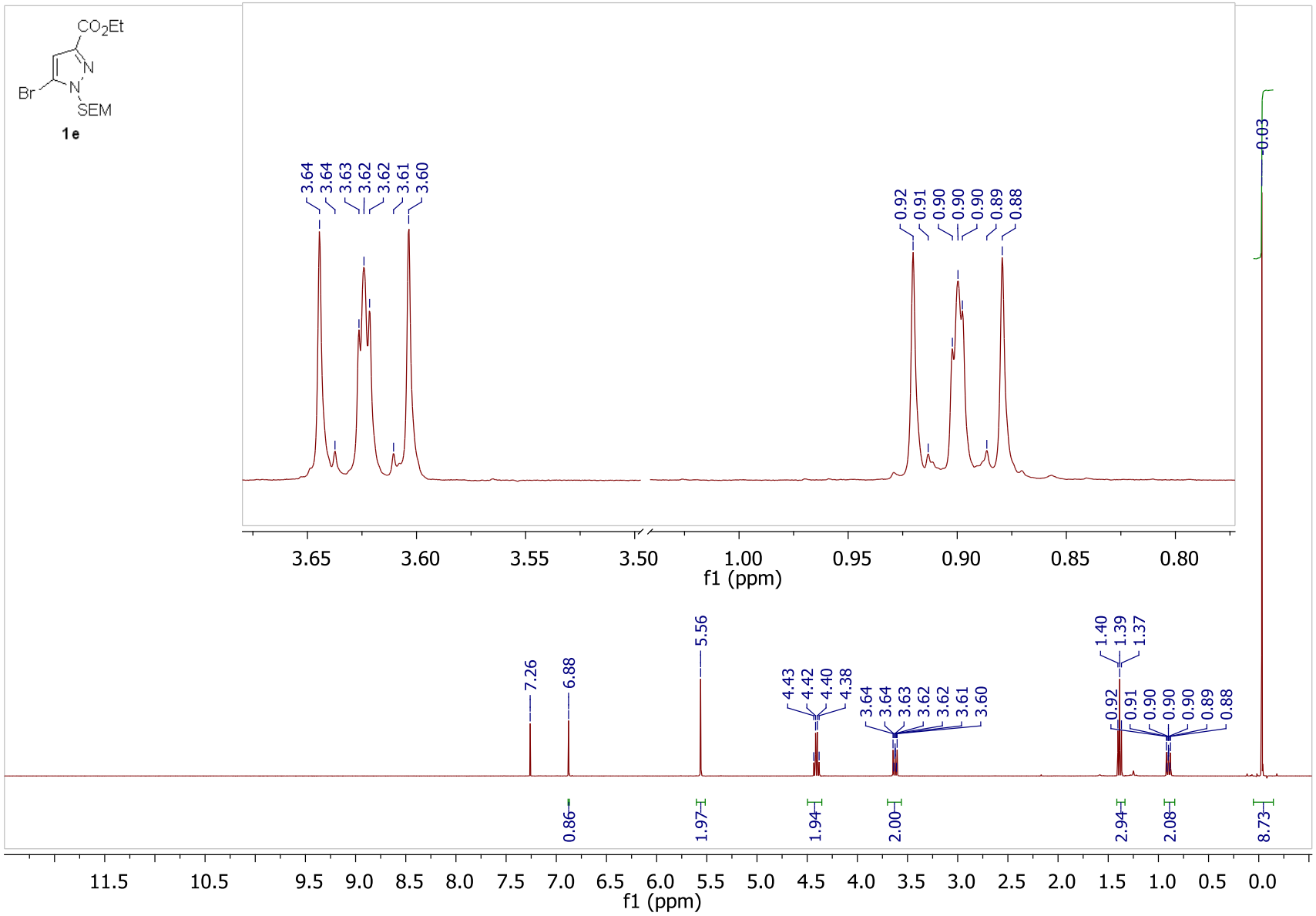

EtO2C
N
N
SEM
159.57
138.91
133.02
112.61
79.35
66.86
61.32
17.88
14.36
-1.36
30
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

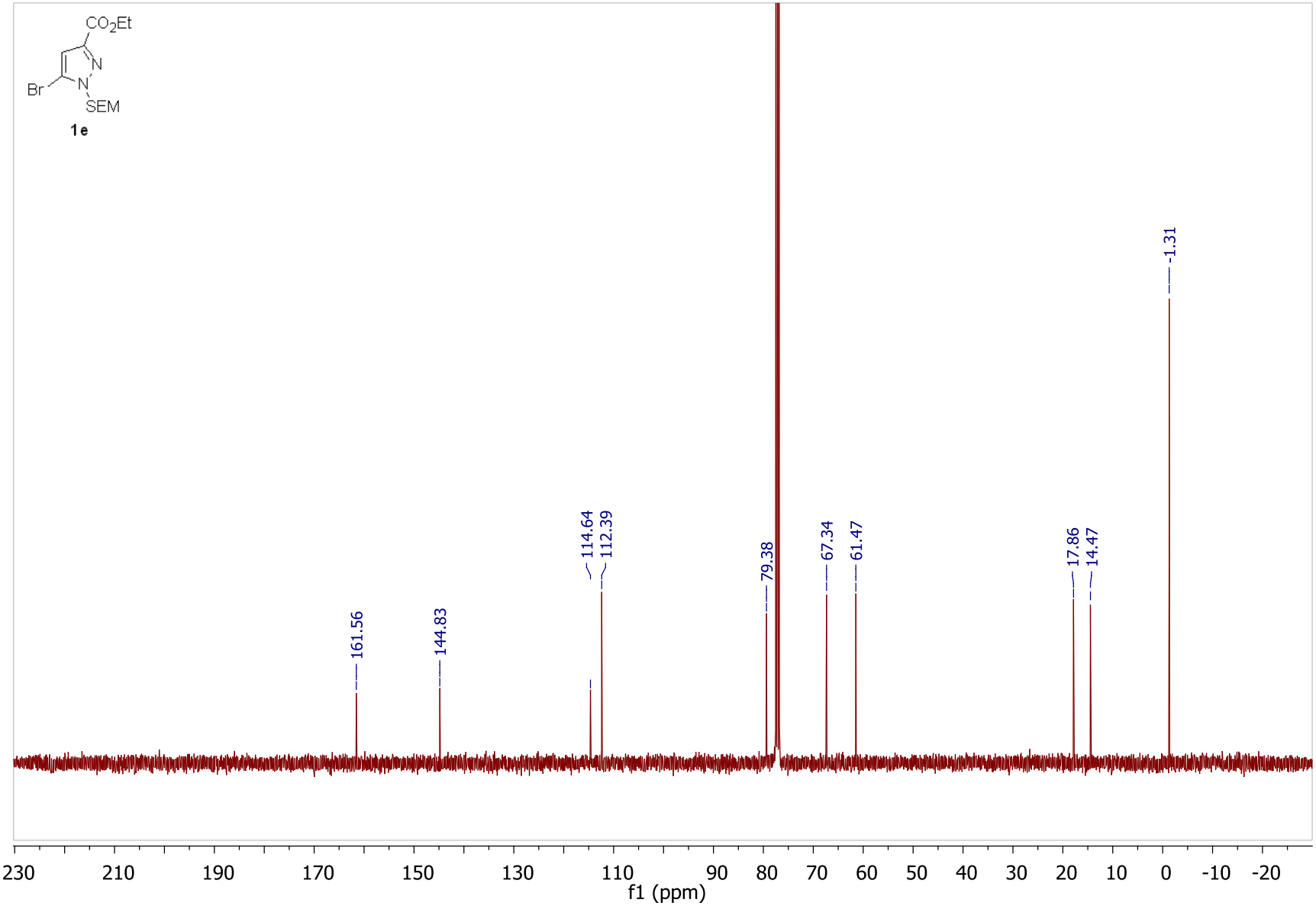

Br
N
N
EtO2C
SEM
1d
3.56
3.56
3.54
3.54
3.54
3.54
3.53
3.52
0.90
0.89
0.88
0.88
0.88
0.87
0.86
0.04
3.70 3.65 3.60 3.55 3.50 3.45 3.40 3.35 1.00 0.95 0.90 0.85 0.80 0.75 0.70
f1 (ppm)
7.56
7.26
5.81
4.45
4.43
4.41
4.39
3.56
3.55
3.54
3.54
3.54
3.52
1.44
1.42
1.40
0.90
0.88
0.88
0.88
0.86
0.91
2.01
1.99
2.00
3.01
2.12
8.80
11.5 10.5 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)

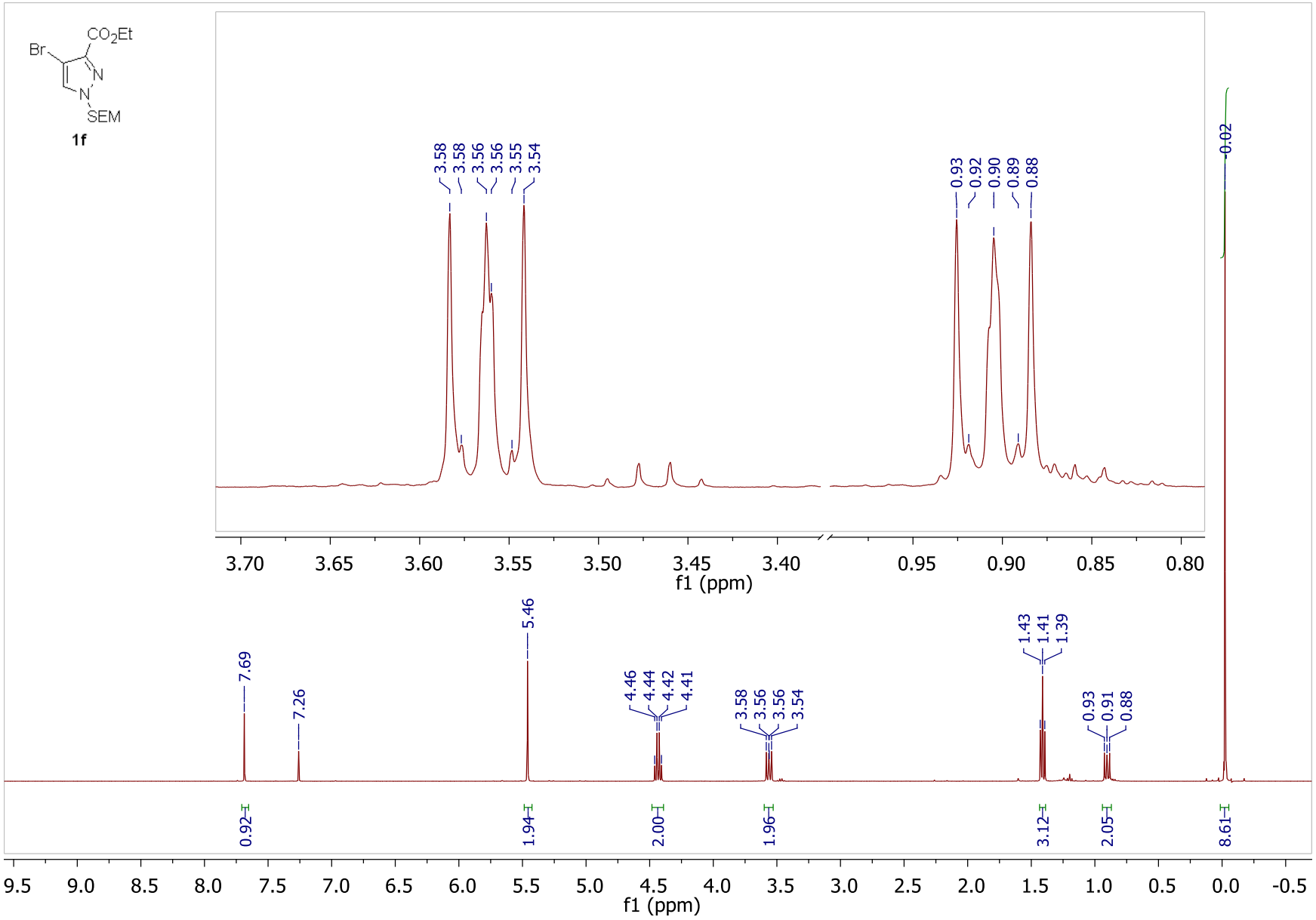

Br
N
N
EtO2C
SEM
1d
158.77
140.97
130.83
100.90
80.76
67.09
61.90
17.85
14.21
-1.35
30
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

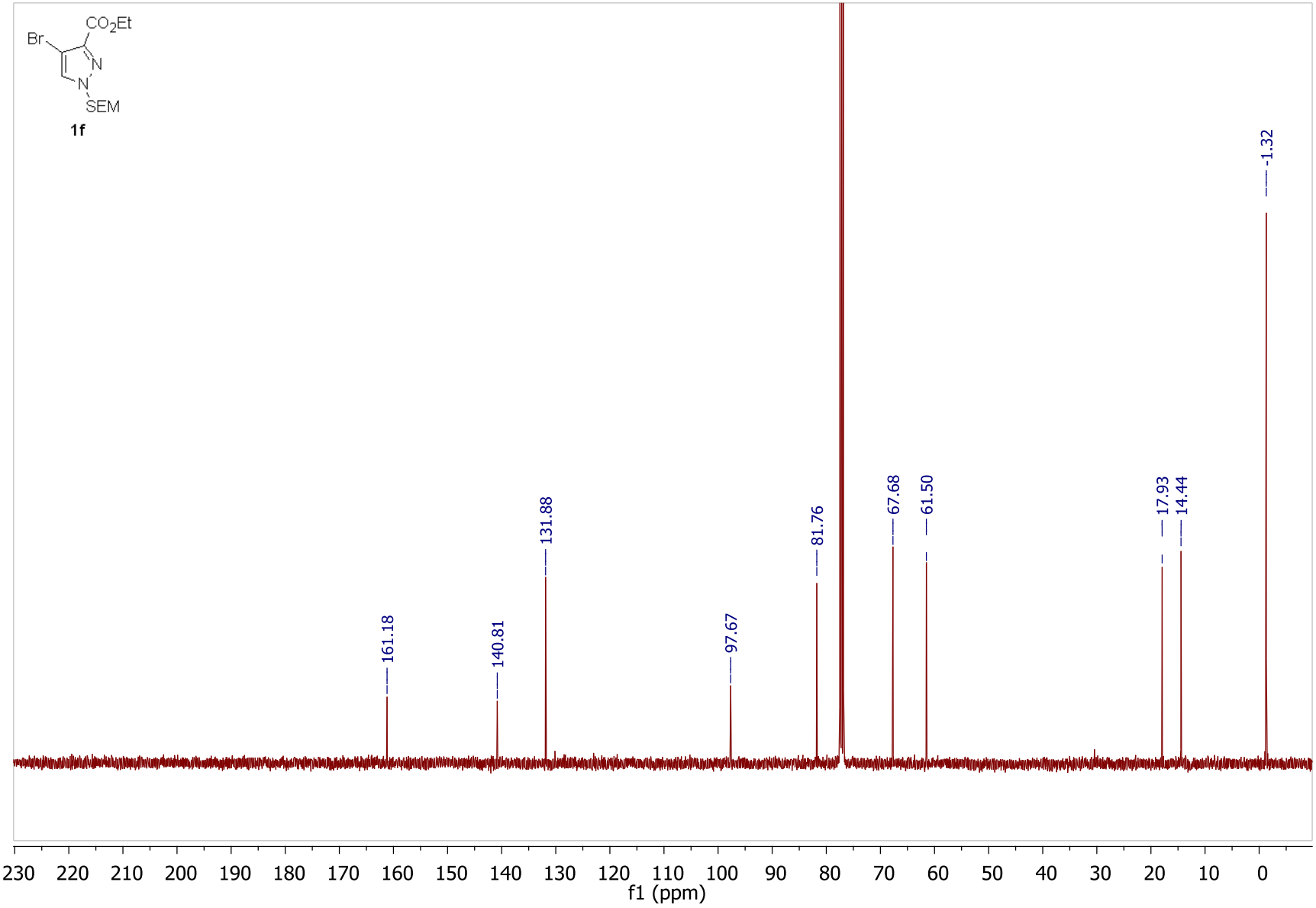

CO2Et
N
N
SEM
3.58
3.58
3.57
3.56
3.56
3.56
3.55
3.54
0.92
0.91
0.91
0.90
0.90
0.90
0.89
0.88
0.88
0.03
3.66
3.60
3.54
3.48
3.42
0.98
0.92
0.86
f1 (ppm)
7.61
7.61
7.26
6.89
6.88
5.51
4.44
4.43
4.41
4.39
3.59
3.57
3.56
3.56
3.56
3.54
1.42
1.40
1.38
0.92
0.90
0.90
0.90
0.88
0.98
0.96
1.99
2.01
2.01
3.00
2.18
8.81
11.5
10.5
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)

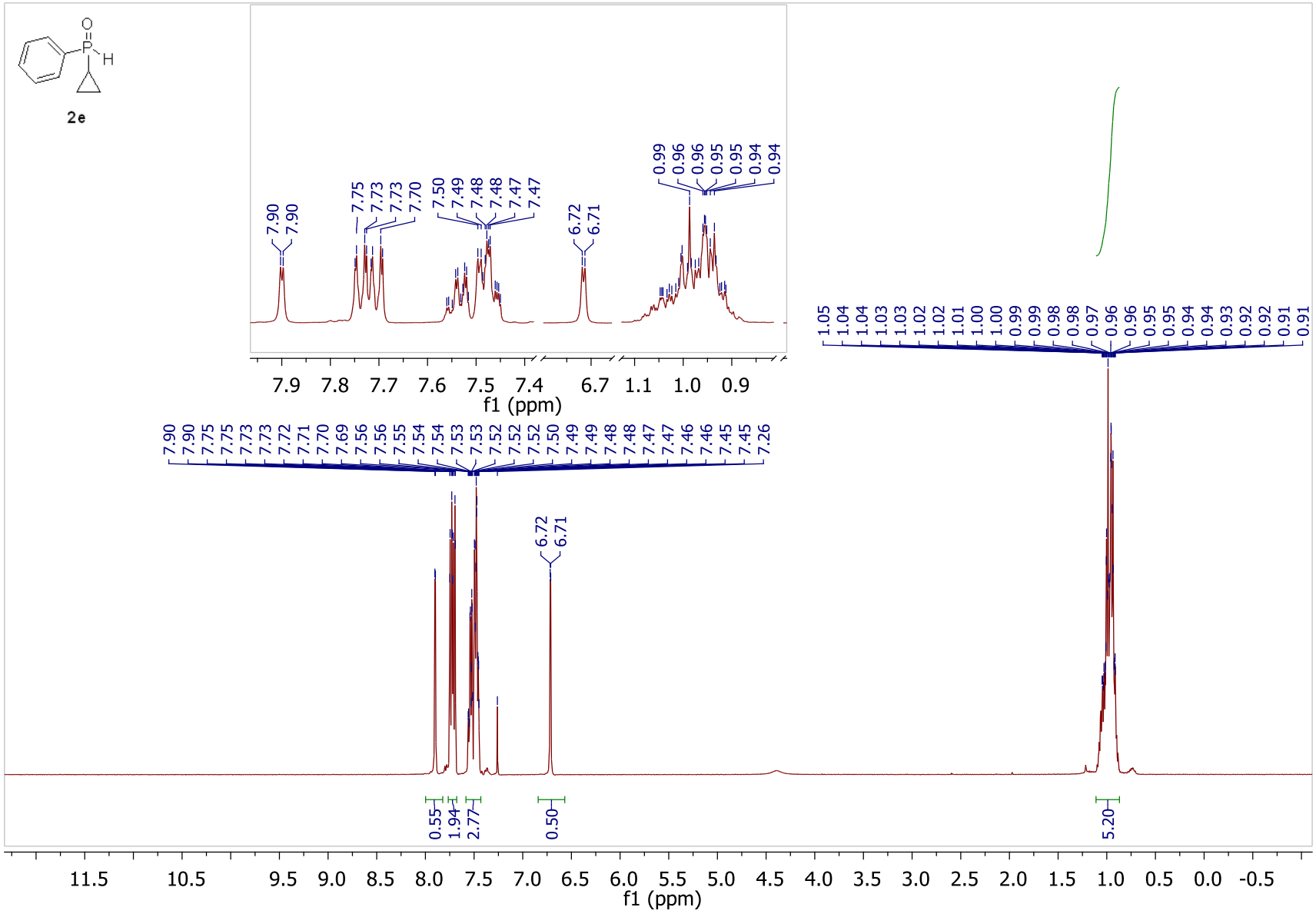

CO2Et
N
N
SEM
-1.53
162.21
143.94
130.40
109.77
80.91
77.48
77.16
76.84
67.05
60.91
17.72
14.31
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

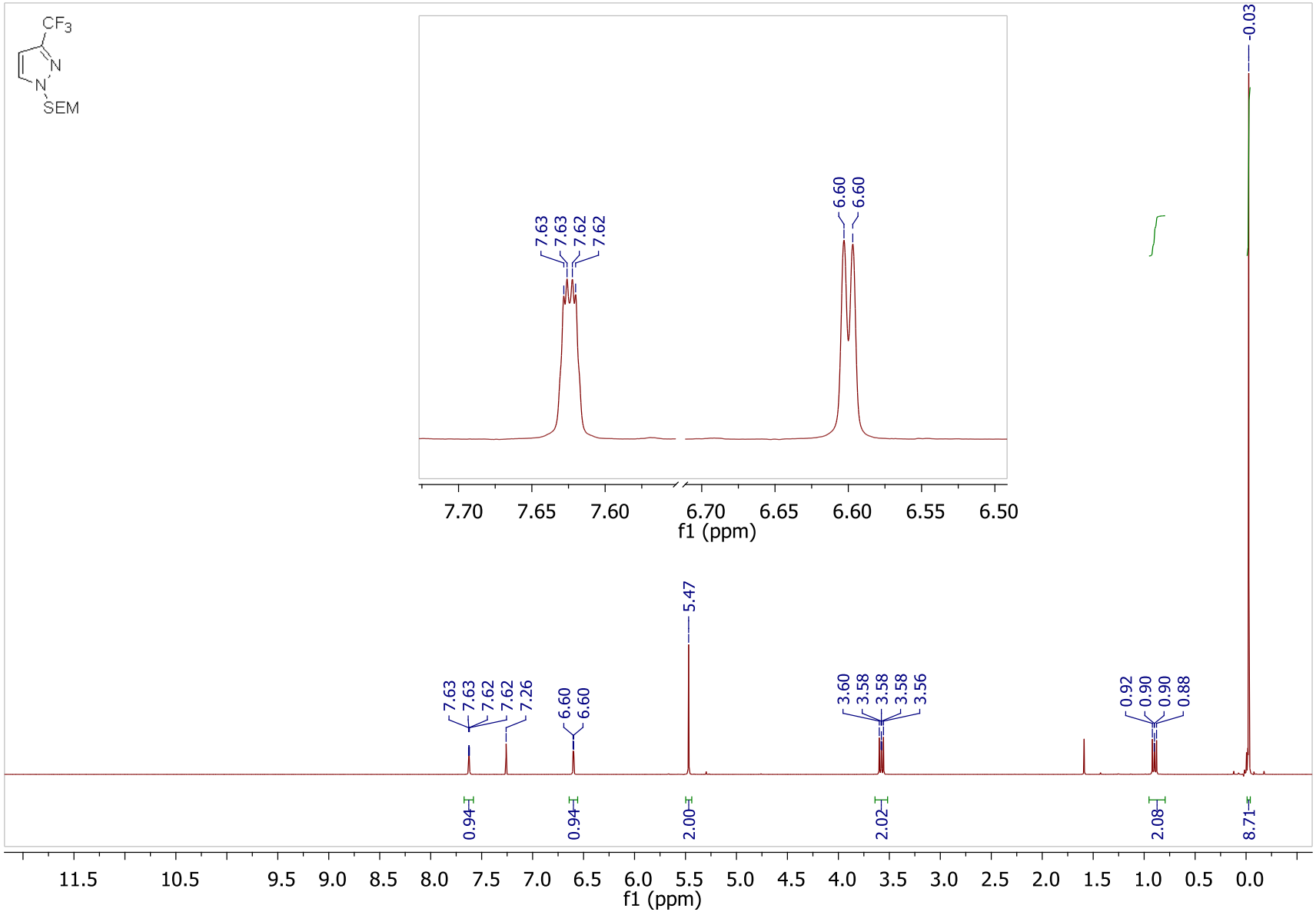

CO2Et
N
Br
N
SEM
1e
3.64
3.64
3.63
3.62
3.62
3.61
3.60
0.92
0.91
0.90
0.90
0.90
0.89
0.88
0.03
3.65
3.60
3.55
3.50
1.00
0.95
0.90
0.85
0.80
f1 (ppm)
7.26
6.88
5.56
4.43
4.42
4.40
4.38
3.64
3.64
3.63
3.62
3.62
3.61
3.60
1.40
1.39
1.37
0.92
0.91
0.90
0.90
0.90
0.89
0.88
0.86
1.97
1.94
2.00
2.94
2.08
8.73
11.5
10.5
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)

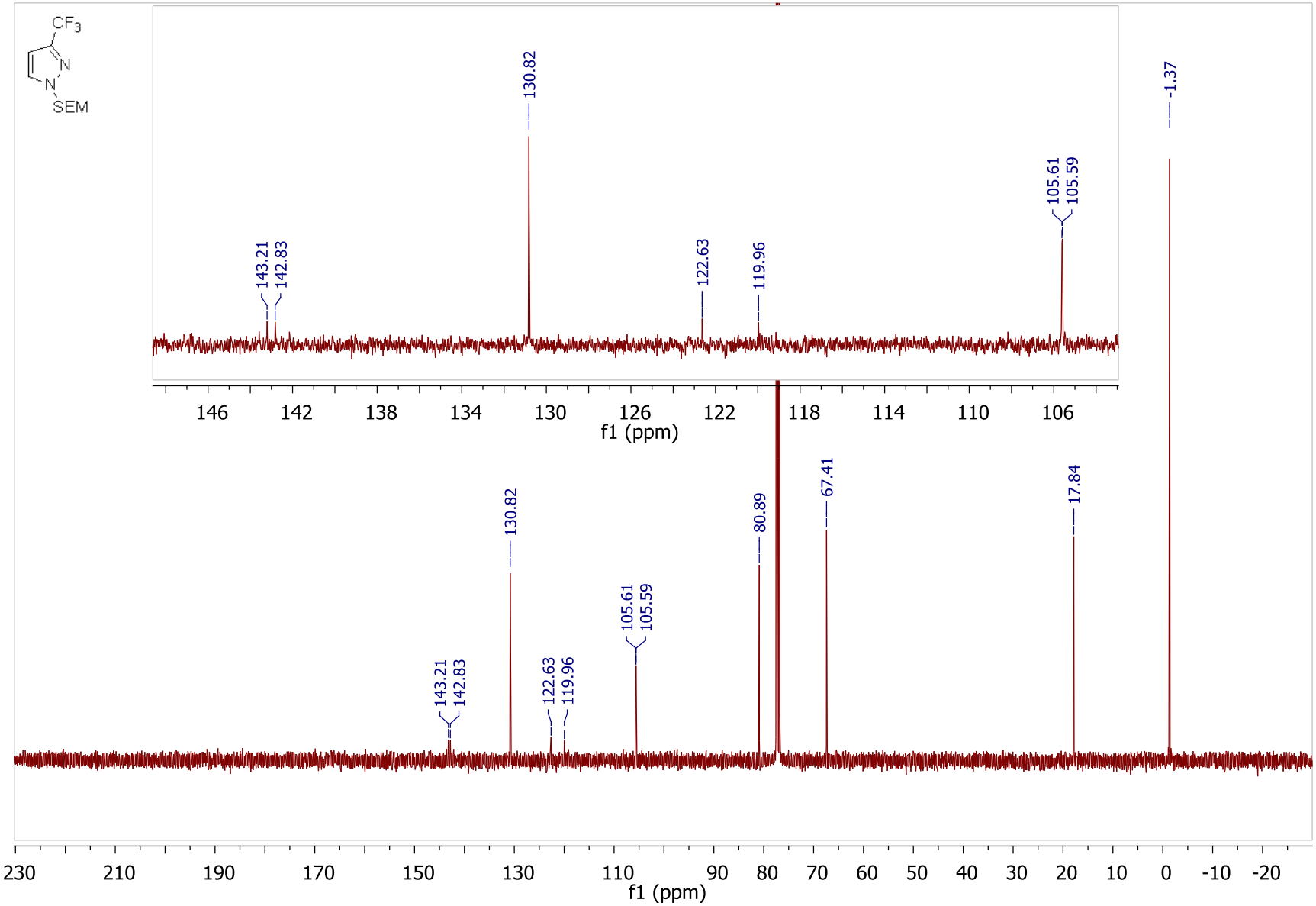

CO2Et
N
Br
N
SEM
1e
161.56
144.83
114.64
112.39
79.38
67.34
61.47
17.86
14.47
-1.31
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

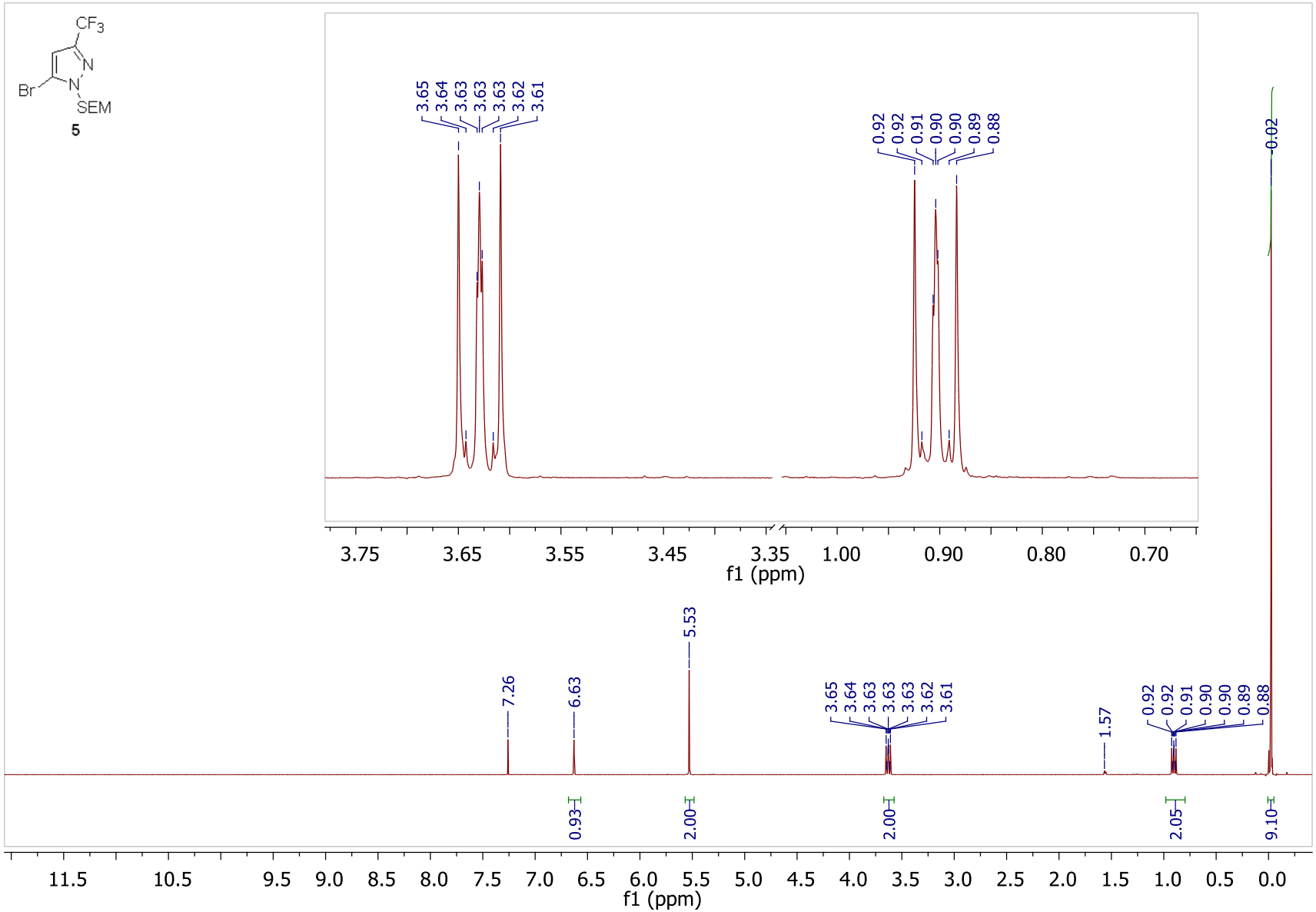

CO2Et
Br
N
N
SEM
1f
3.58
3.58
3.56
3.56
3.55
3.54
0.93
0.92
0.90
0.89
0.88
-0.02
3.70
3.65
3.60
3.55
3.50
3.45
3.40
0.95
0.90
0.85
0.80
f1 (ppm)
7.69
7.26
5.46
4.46
4.44
4.42
4.41
3.58
3.56
3.56
3.54
1.43
1.41
1.39
0.93
0.91
0.88
0.92
1.94
2.00
1.96
3.12
2.05
8.61
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

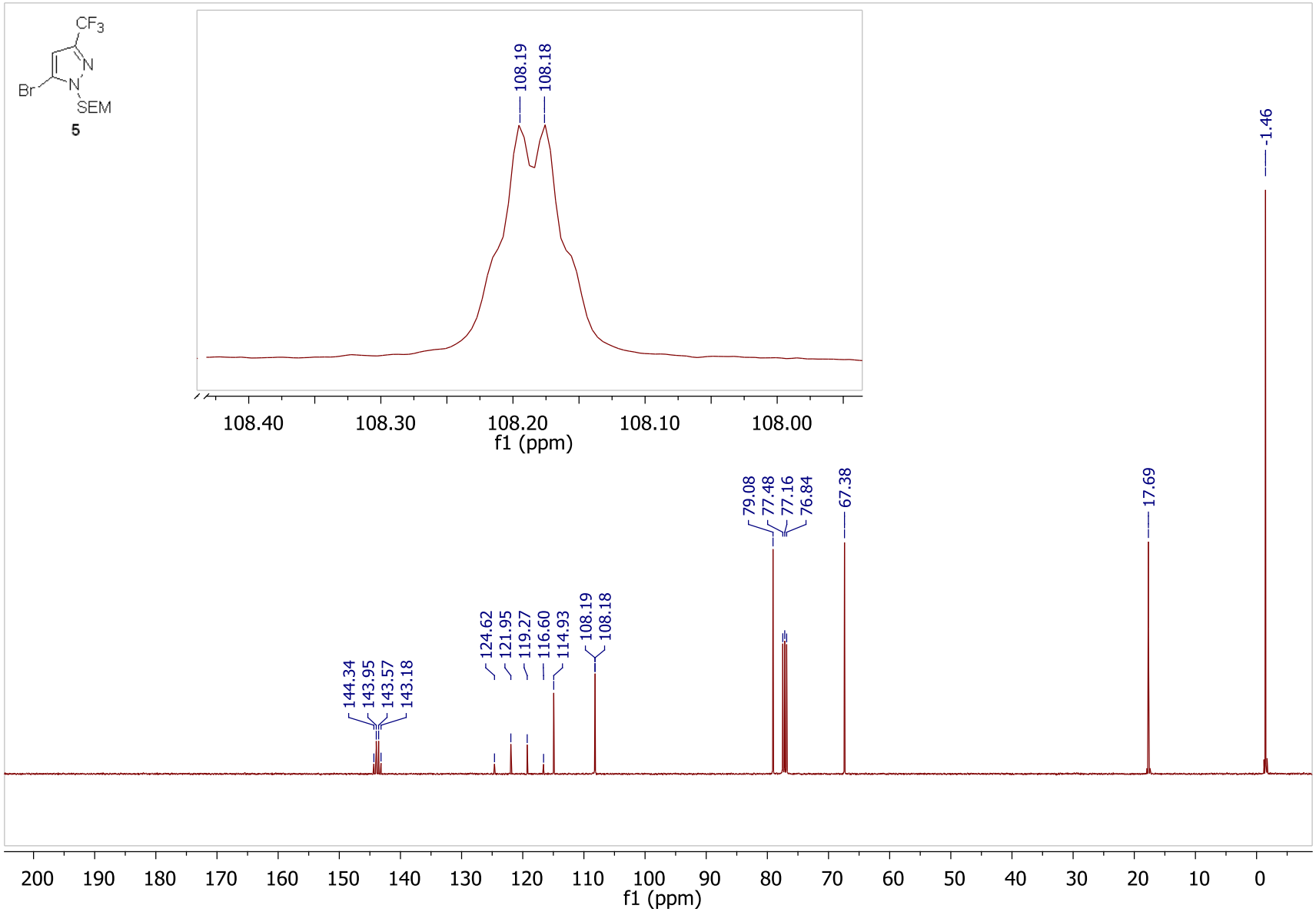

CO2Et
Br
N
N
SEM
1f
161.18
140.81
131.88
97.67
81.76
67.68
61.50
17.93
14.44
-1.32
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

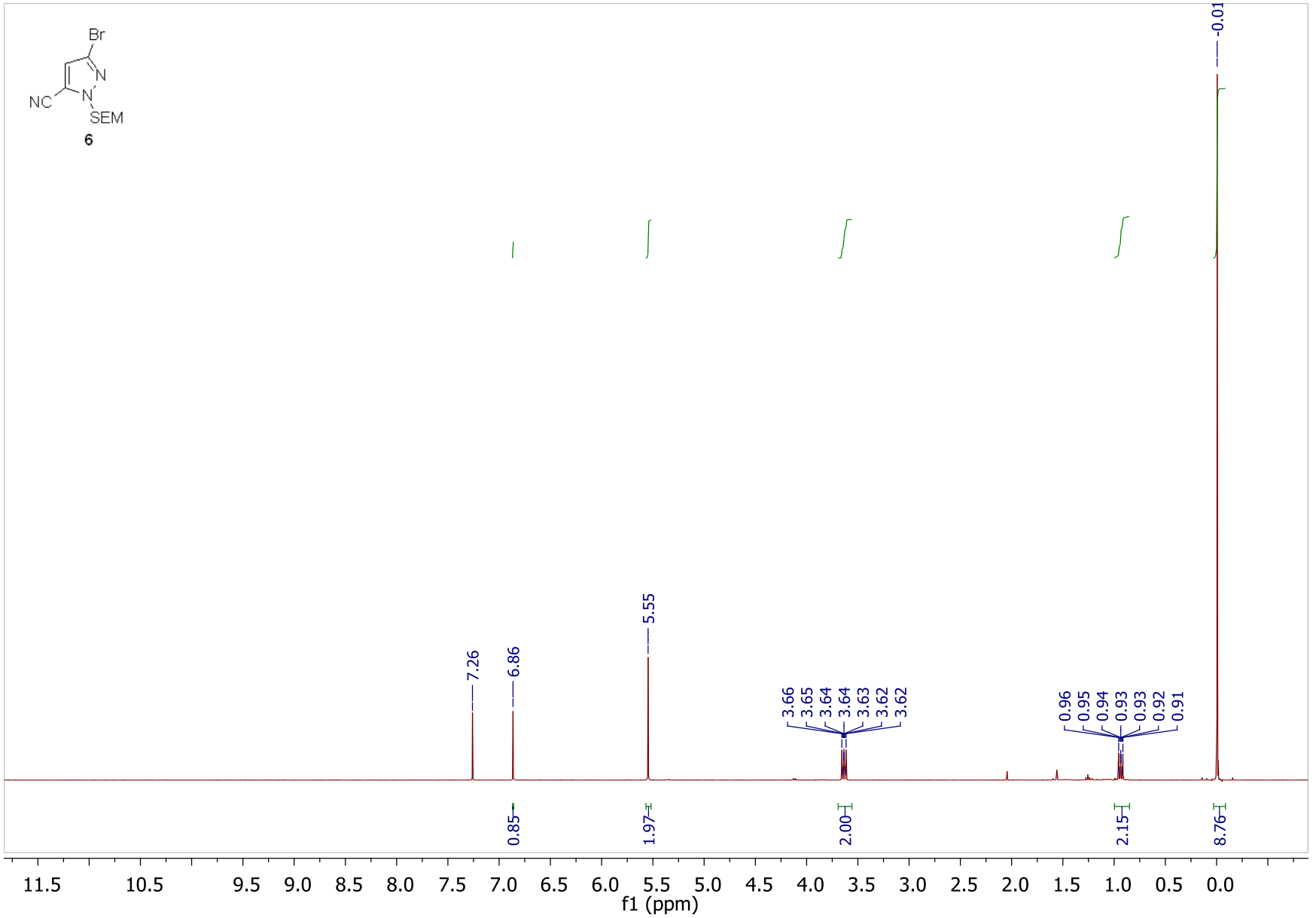

2e
7.90
7.90
7.75
7.73
7.73
7.70
7.50
7.49
7.48
7.48
7.47
7.47
6.72
6.71
0.99
0.96
0.96
0.95
0.95
0.94
0.94
7.9 7.8 7.7 7.6 7.5 7.4 6.7 1.1 1.0 0.9
f1 (ppm)
1.05
1.04
1.04
1.03
1.03
1.02
1.02
1.01
1.00
1.00
0.99
0.99
0.98
0.98
0.97
0.96
0.96
0.95
0.95
0.94
0.94
0.93
0.92
0.92
0.91
0.91
7.90
7.90
7.75
7.75
7.73
7.73
7.72
7.71
7.70
7.69
7.56
7.56
7.55
7.54
7.54
7.53
7.53
7.52
7.52
7.52
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.26
6.72
6.71
0.55
1.94
2.77
0.50
5.20
11.5 10.5 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
f1 (ppm)

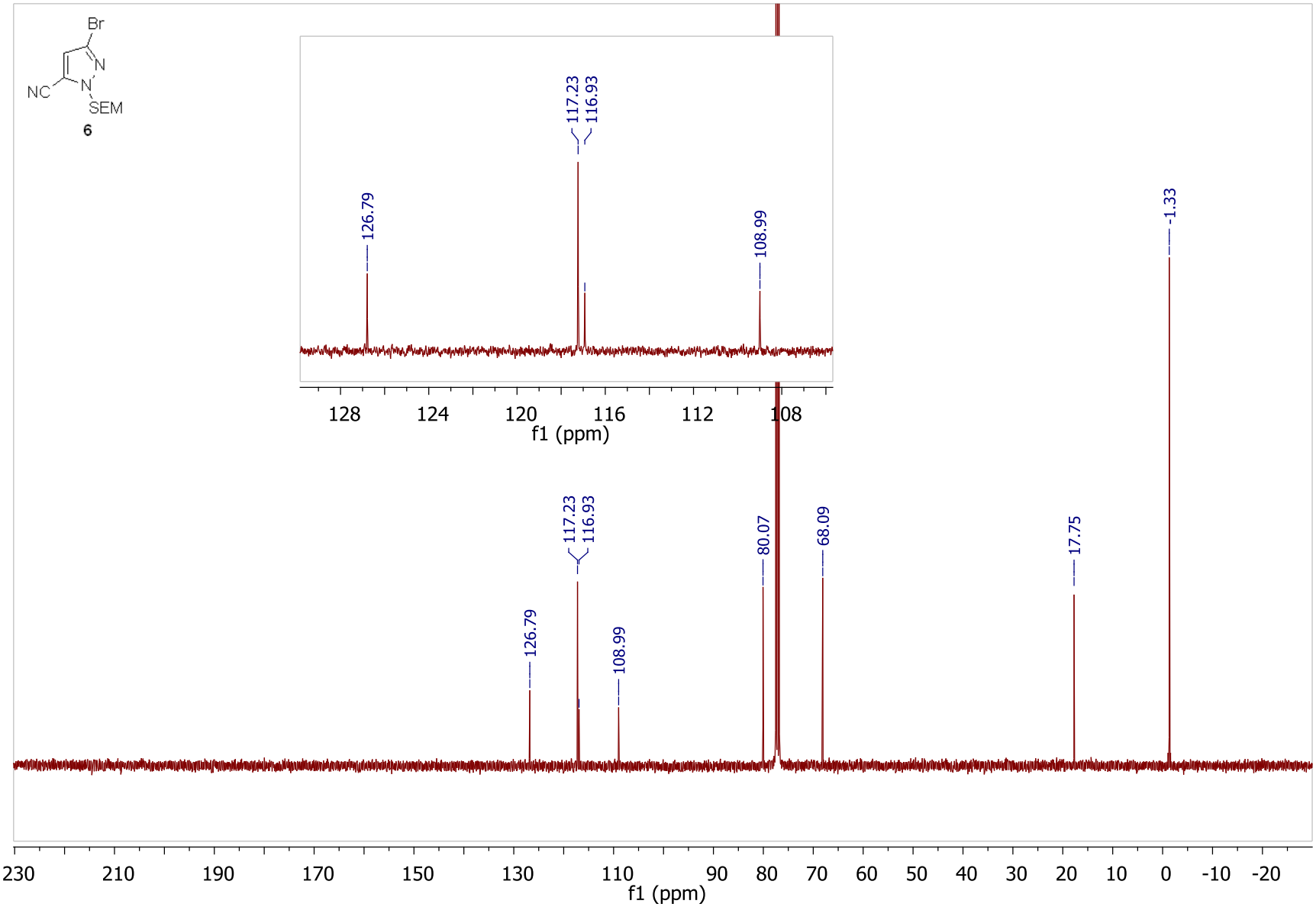

CF3
N
N
SEM
7.63
7.63
7.62
7.62
6.60
6.60
7.70
7.65
7.60
6.70
6.65
6.60
6.55
6.50
f1 (ppm)
-0.03
5.47
7.26
3.60
3.58
3.58
3.56
0.92
0.90
0.90
0.88
0.94
0.94
2.00
2.02
2.08
8.71
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

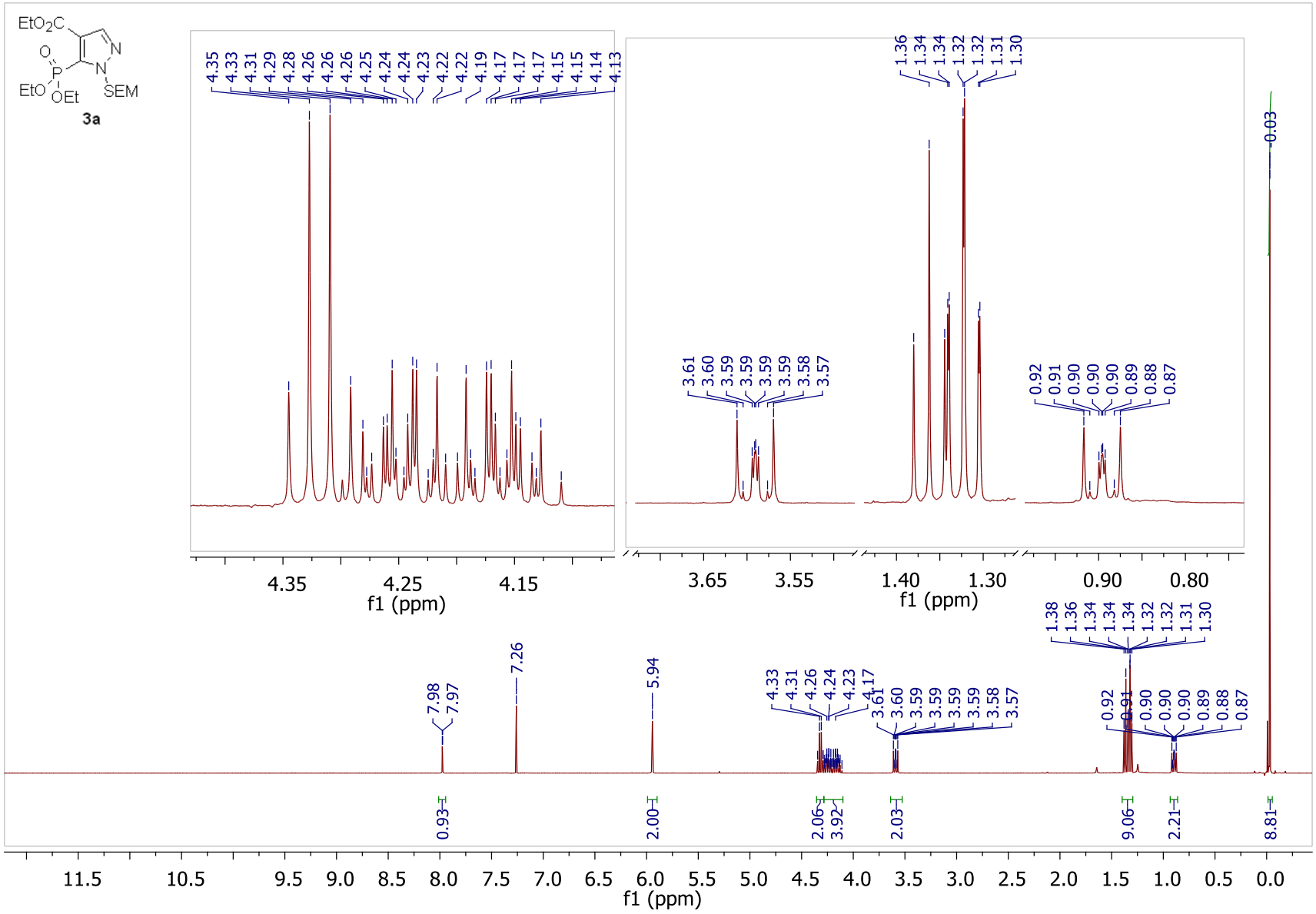

CF3
N
N
SEM
130.82
143.21
142.83
122.63
119.96
105.61
105.59
-1.37
146
142
138
134
130
126
122
118
114
110
106
f1 (ppm)
130.82
80.89
67.41
17.84
105.61
105.59
143.21
142.83
122.63
119.96
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

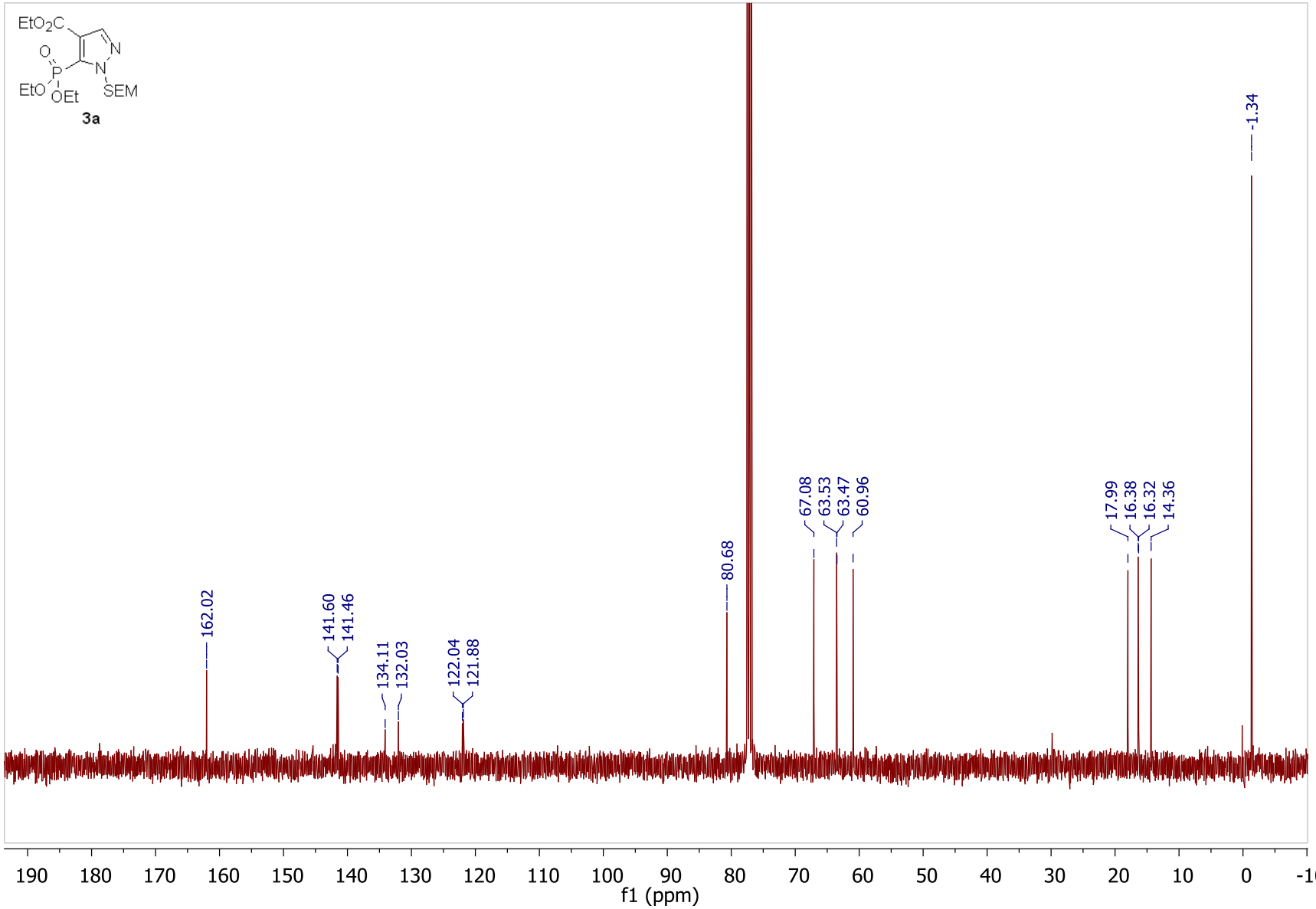

CF3
N
Br
N
SEM
5
3.65
3.64
3.63
3.63
3.63
3.62
3.61
0.92
0.92
0.91
0.90
0.90
0.89
0.88
0.02
3.75
3.65
3.55
3.45
3.35
1.00
0.90
0.80
0.70
f1 (ppm)
7.26
6.63
5.53
1.57
0.93
2.00
2.00
2.05
9.10
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

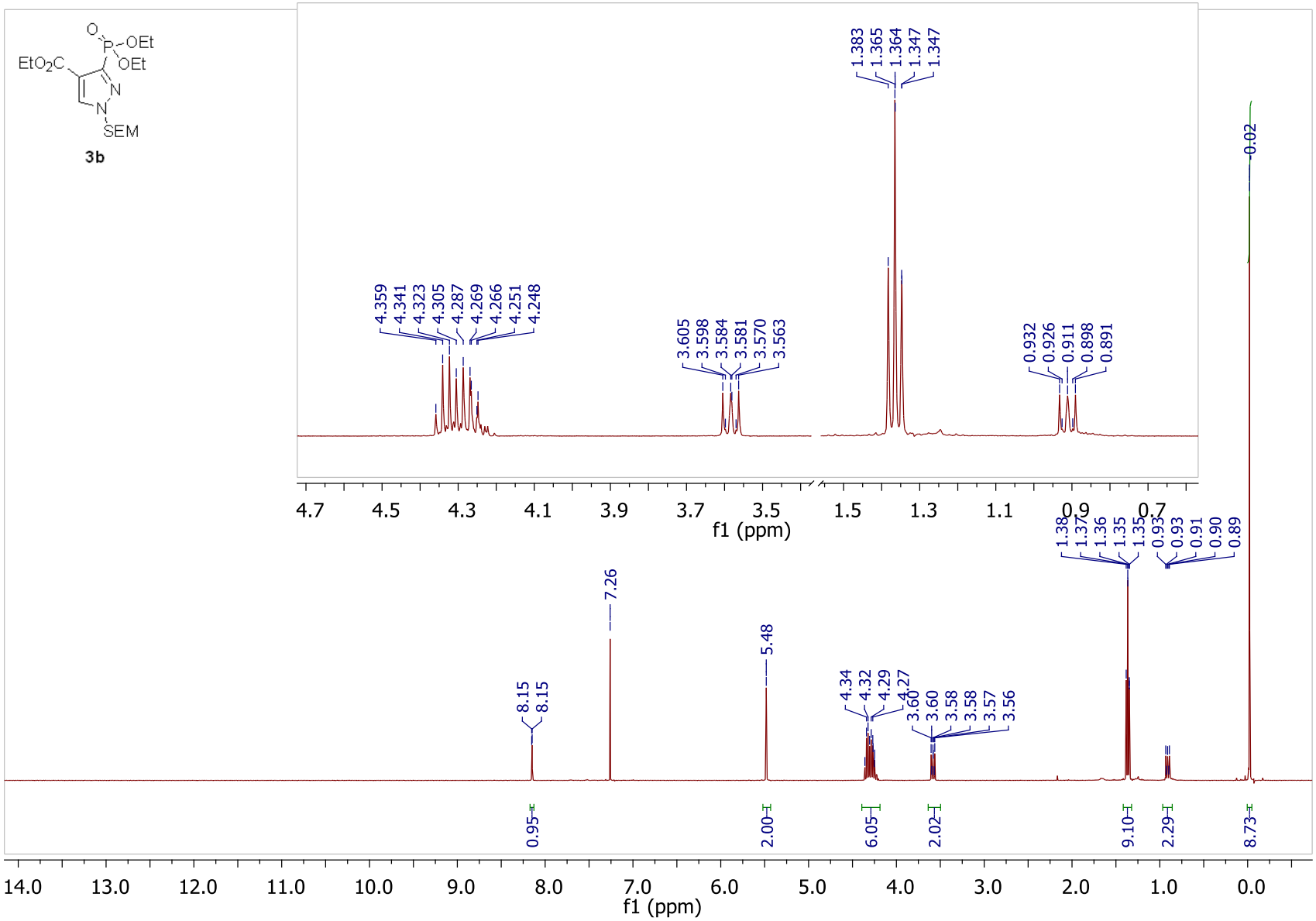

CF3
N
Br
N
SEM
5
108.19
108.18
108.40
108.30
108.20
108.10
108.00
f1 (ppm)
-1.46
79.08
77.48
77.16
76.84
67.38
17.69
144.34
143.95
143.57
143.18
124.62
121.95
119.27
116.60
114.93
108.19
108.18
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

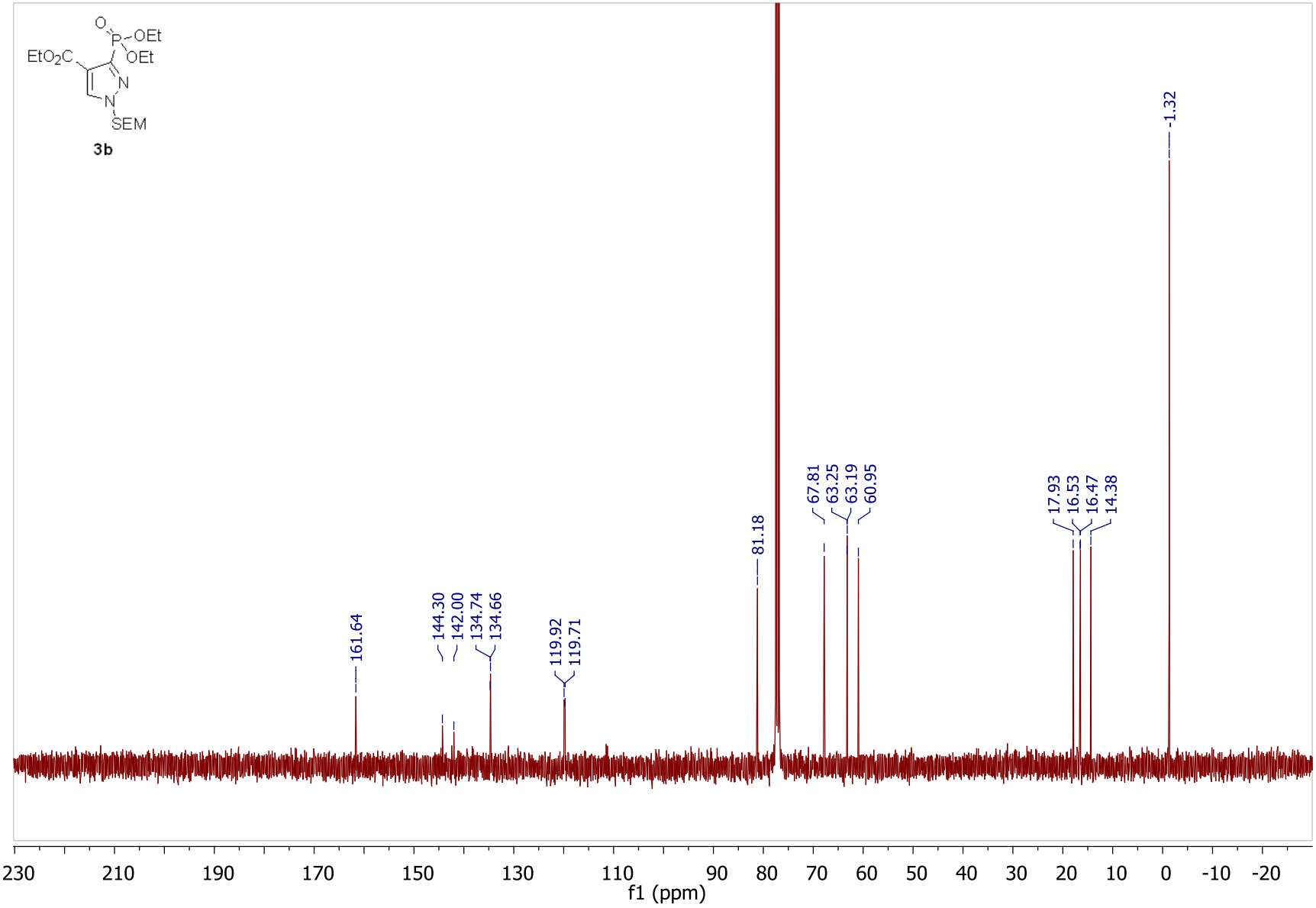

Br
N
NC
N
SEM
6
-0.01
7.26
6.86
5.55
3.66
3.65
3.64
3.64
3.63
3.62
3.62
0.96
0.95
0.94
0.93
0.93
0.92
0.91
0.85
1.97
2.00
2.15
8.76
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

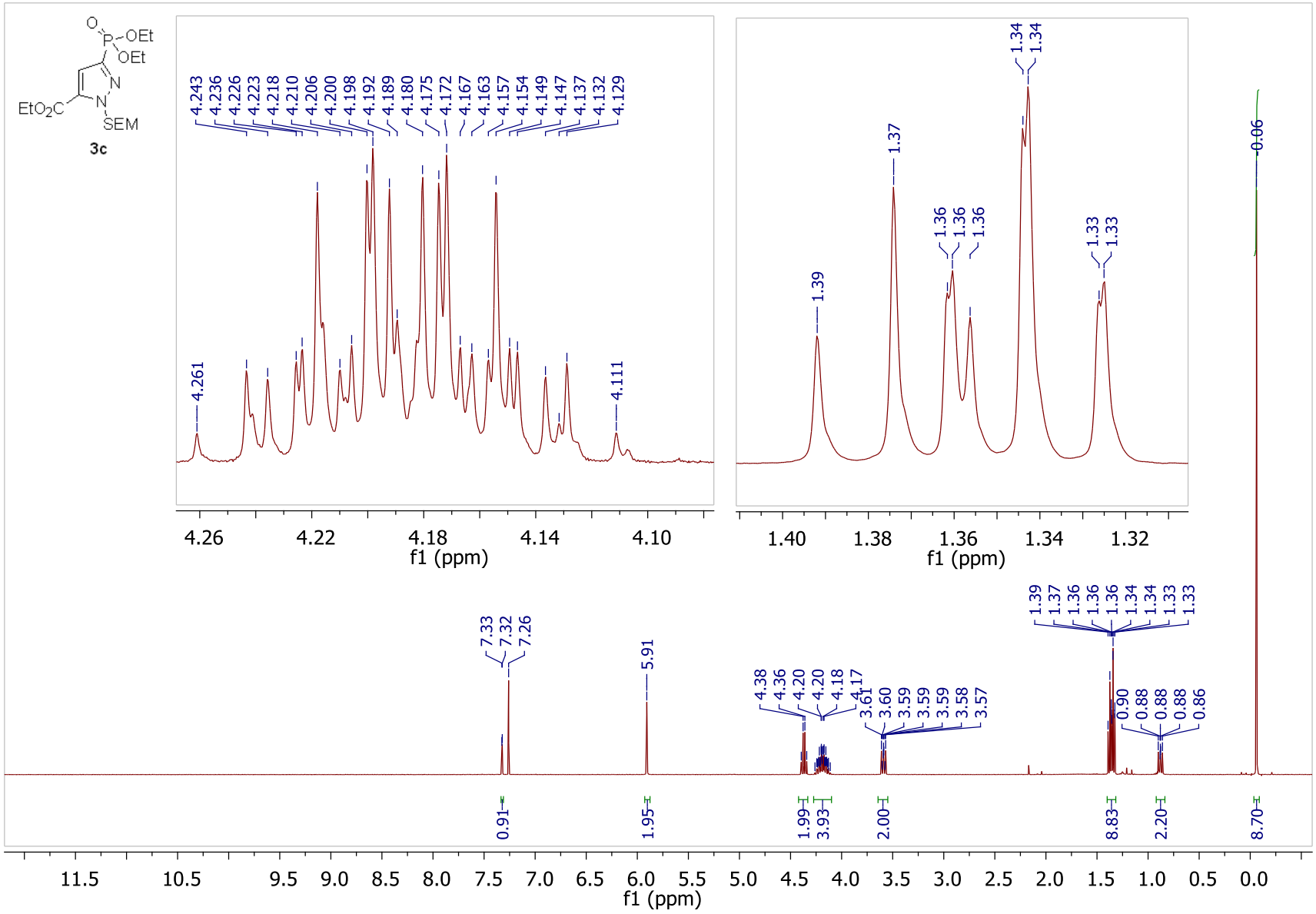

Br
N
NC
N
SEM
6
126.79
117.23
116.93
108.99
128
124
120
116
112
108
f1 (ppm)
-1.33
126.79
117.23
116.93
108.99
80.07
68.09
17.75
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

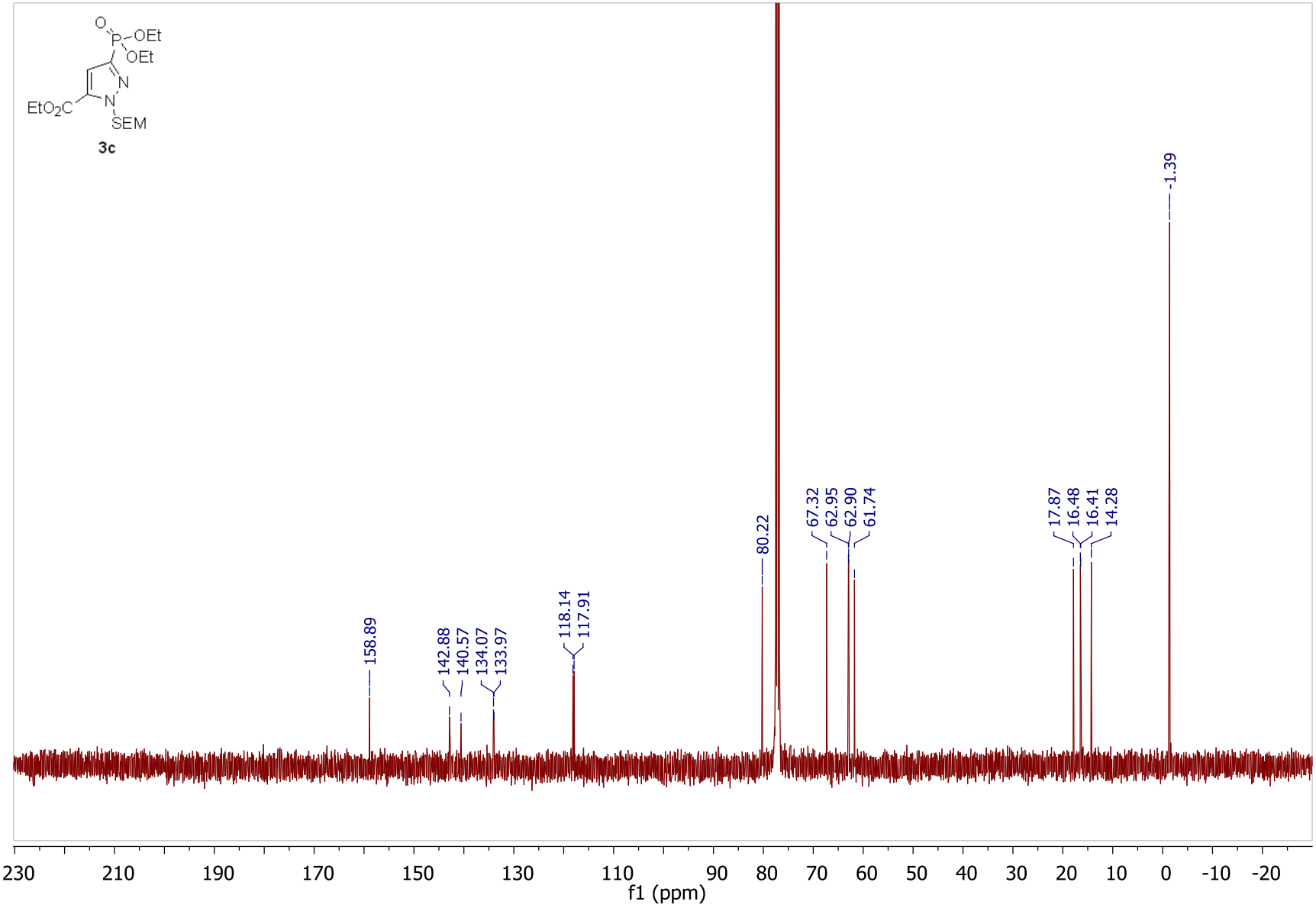

EtO2C
O
P
N
N
EtO
OEt
SEM
3a
4.35 4.33 4.31 4.29 4.28 4.26 4.26 4.26 4.25 4.24 4.24 4.23 4.22 4.22 4.19 4.17 4.17 4.17 4.15 4.15 4.14 4.13
1.36 1.34 1.34 1.32 1.32 1.31 1.30
3.61 3.60 3.59 3.59 3.59 3.59 3.58 3.57
0.92 0.91 0.90 0.90 0.90 0.89 0.88 0.87
0.03
4.35 4.25 4.15
f1 (ppm)
3.65 3.55 1.40 1.30 0.90 0.80
f1 (ppm)
7.98 7.97 7.26 5.94
4.33 4.31 4.26 4.24 4.23 4.17 3.61 3.60 3.59 3.59 3.59 3.58 3.57
1.38 1.36 1.34 1.34 1.34 1.32 1.32 1.31 1.30
0.92 0.91 0.90 0.90 0.90 0.89 0.88 0.87
0.93 2.00 2.06 3.92 2.03 9.06 2.21 8.81
11.5 10.5 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)

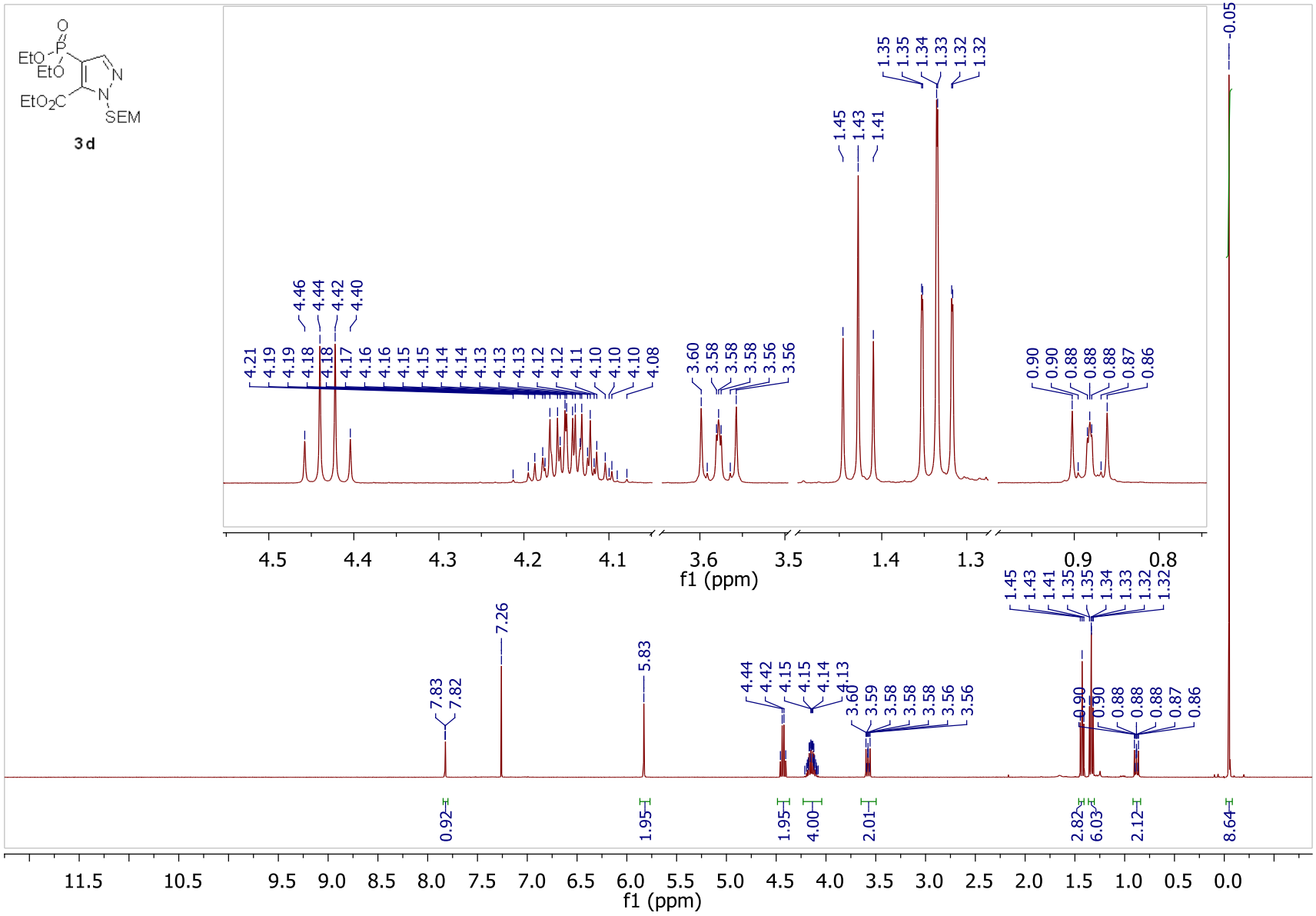

EtO2C
O
P
EtO
OEt
N
N
SEM
3a
162.02
141.60
141.46
134.11
132.03
122.04
121.88
80.68
67.08
63.53
63.47
60.96
17.99
16.38
16.32
14.36
-1.34
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

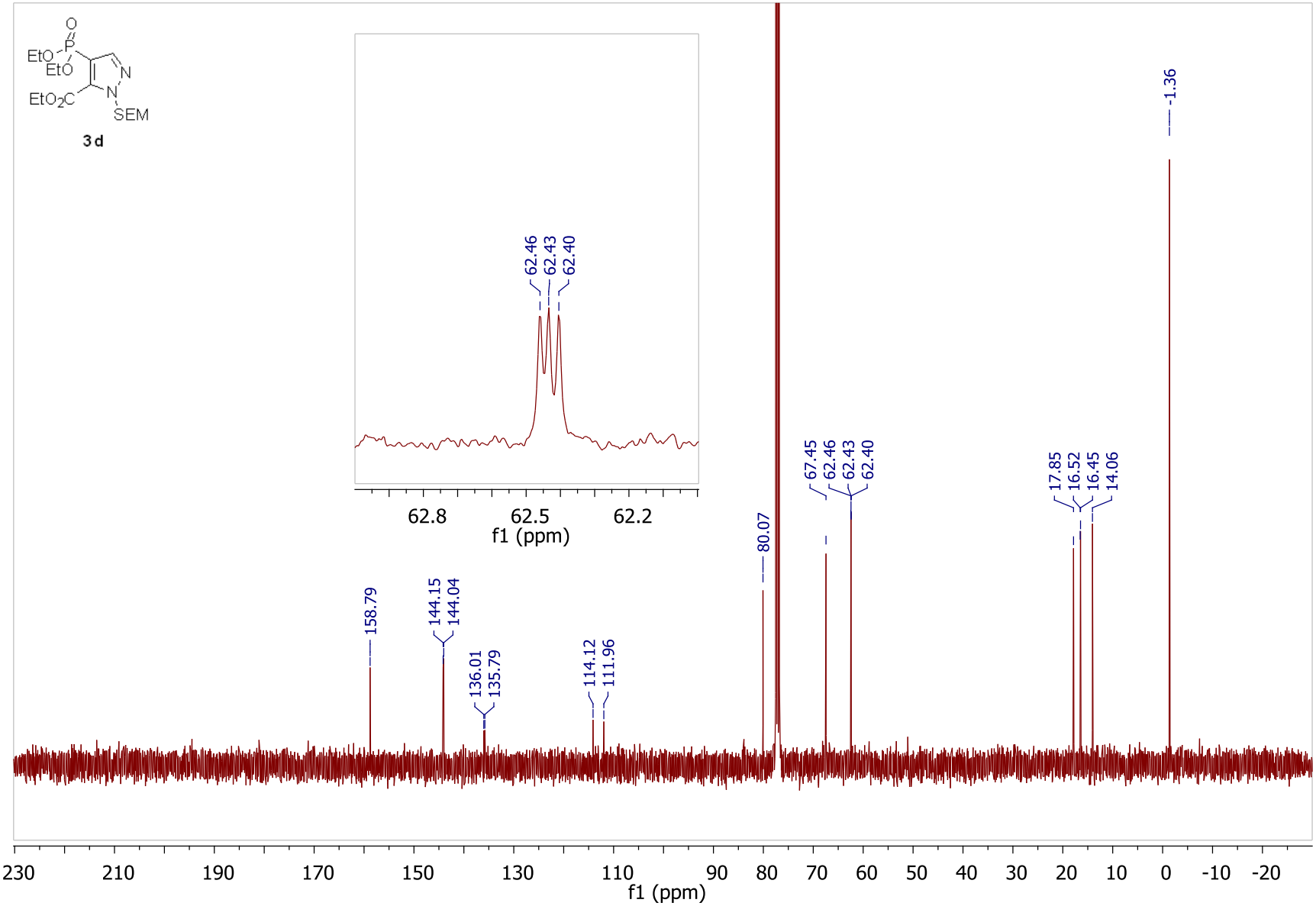

3b
4.359
4.341
4.323
4.305
4.287
4.269
4.266
4.251
4.248
3.605
3.598
3.584
3.581
3.570
3.563
1.383
1.365
1.364
1.347
1.347
0.932
0.926
0.911
0.898
0.891
f1 (ppm)
8.15
8.15
7.26
5.48
4.34
4.32
4.29
4.27
3.60
3.58
3.58
3.57
3.56
1.38
1.37
1.36
1.35
1.35
0.93
0.93
0.91
0.90
0.89
0.02
0.95
2.00
6.05
2.02
9.10
2.29
8.73
f1 (ppm)

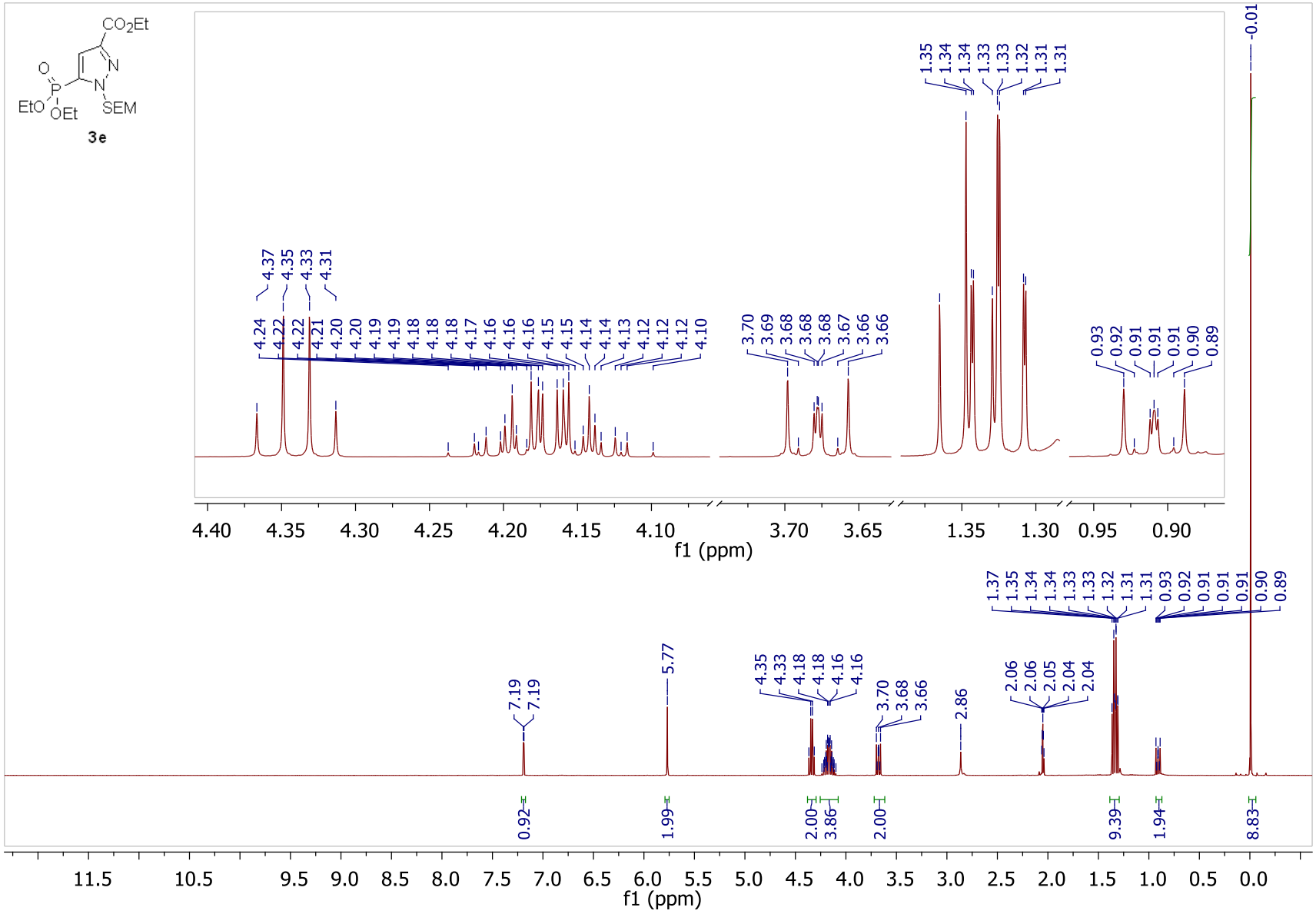

O
P
OEt
OEt
EtO2C
N
N
SEM
3b
161.64
144.30
142.00
134.74
134.66
119.92
119.71
81.18
67.81
63.25
63.19
60.95
17.93
16.53
16.47
14.38
-1.32
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

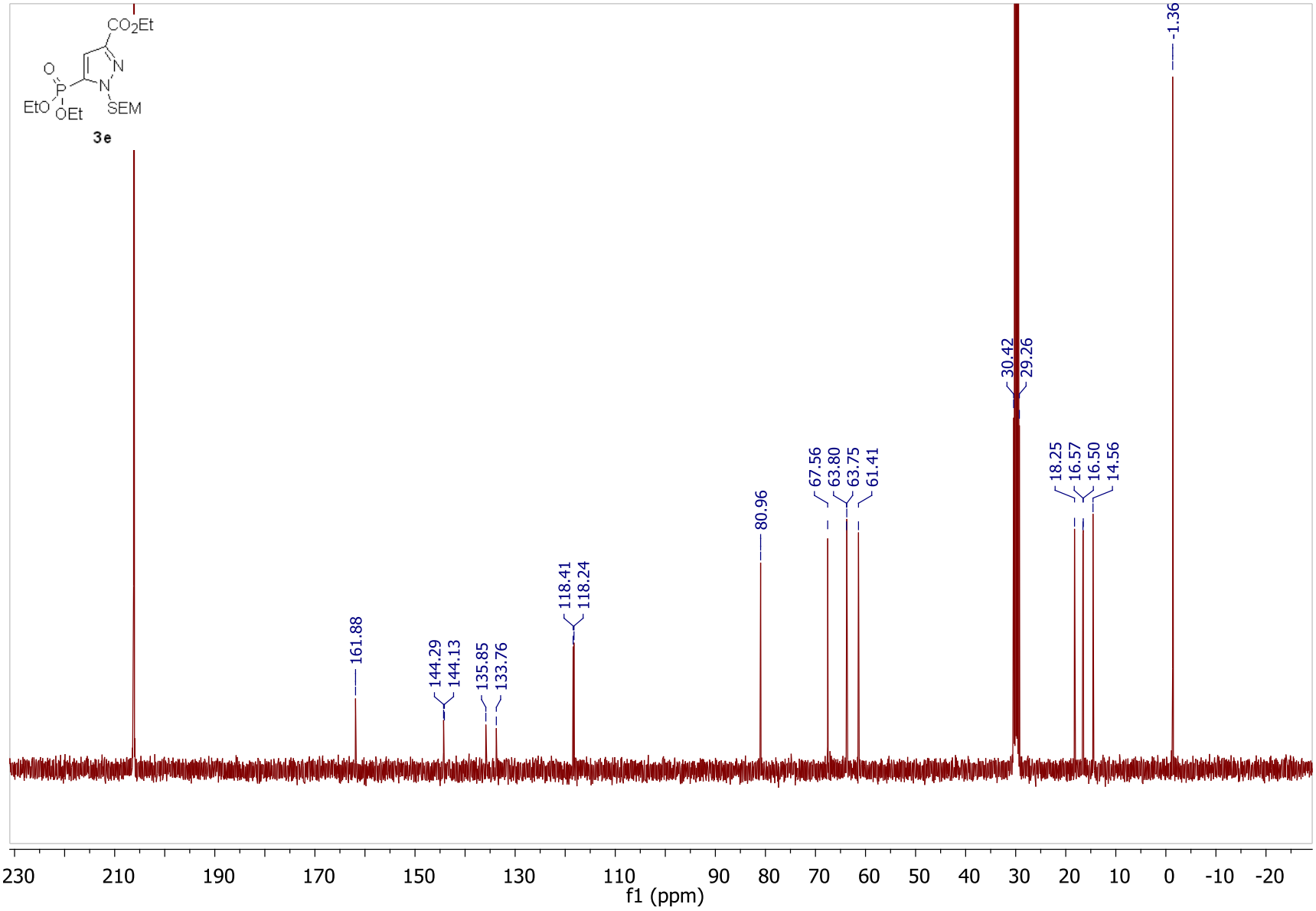

3c
4.243
4.236
4.226
4.223
4.218
4.210
4.206
4.200
4.198
4.192
4.189
4.180
4.175
4.172
4.167
4.163
4.157
4.154
4.149
4.147
4.137
4.132
4.129
4.261
4.111
1.39
1.37
1.36
1.36
1.36
1.34
1.34
1.33
1.33
0.06
f1 (ppm)
7.33
7.32
7.26
5.91
4.38
4.36
4.20
4.20
4.18
4.17
3.61
3.60
3.59
3.59
3.59
3.58
3.57
0.90
0.88
0.88
0.88
0.86
0.91
1.95
1.99
3.93
2.00
8.83
2.20
8.70
f1 (ppm)

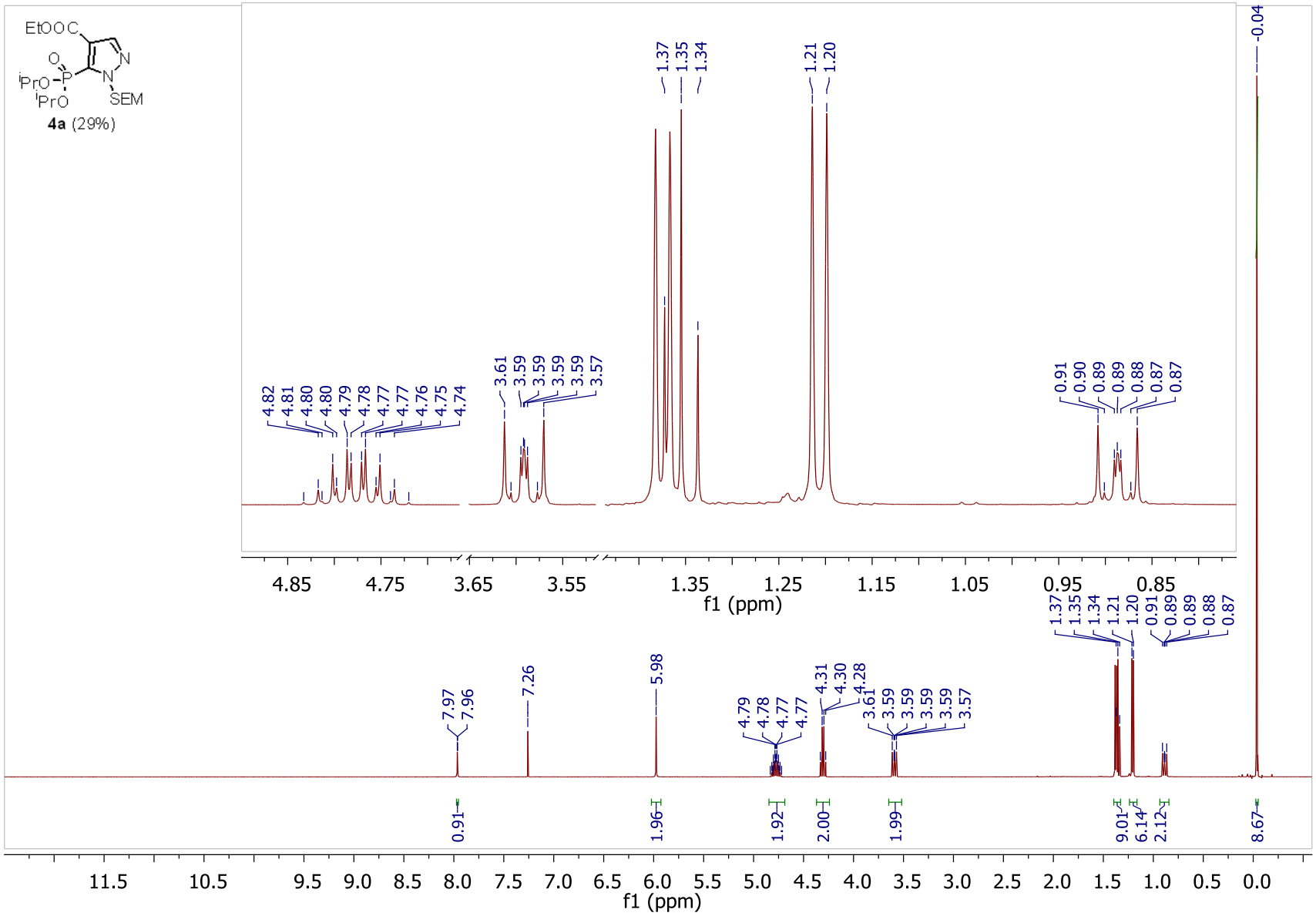

O
P
OEt
OEt
N
N
SEM
EtO2C
3c
158.89
142.88
140.57
134.07
133.97
118.14
117.91
80.22
67.32
62.95
62.90
61.74
17.87
16.48
16.41
14.28
-1.39
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

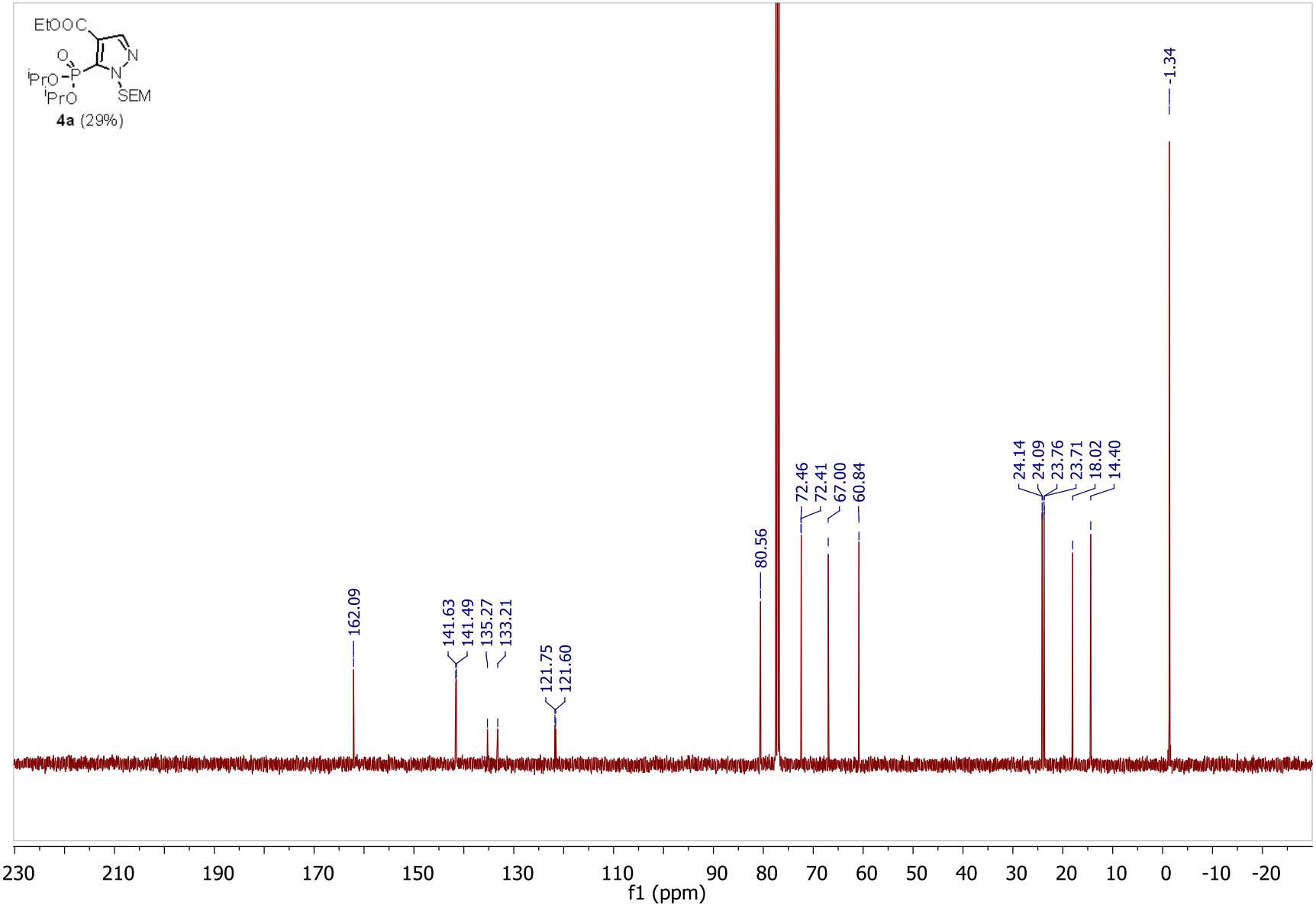

3d
f1 (ppm)
f1 (ppm)

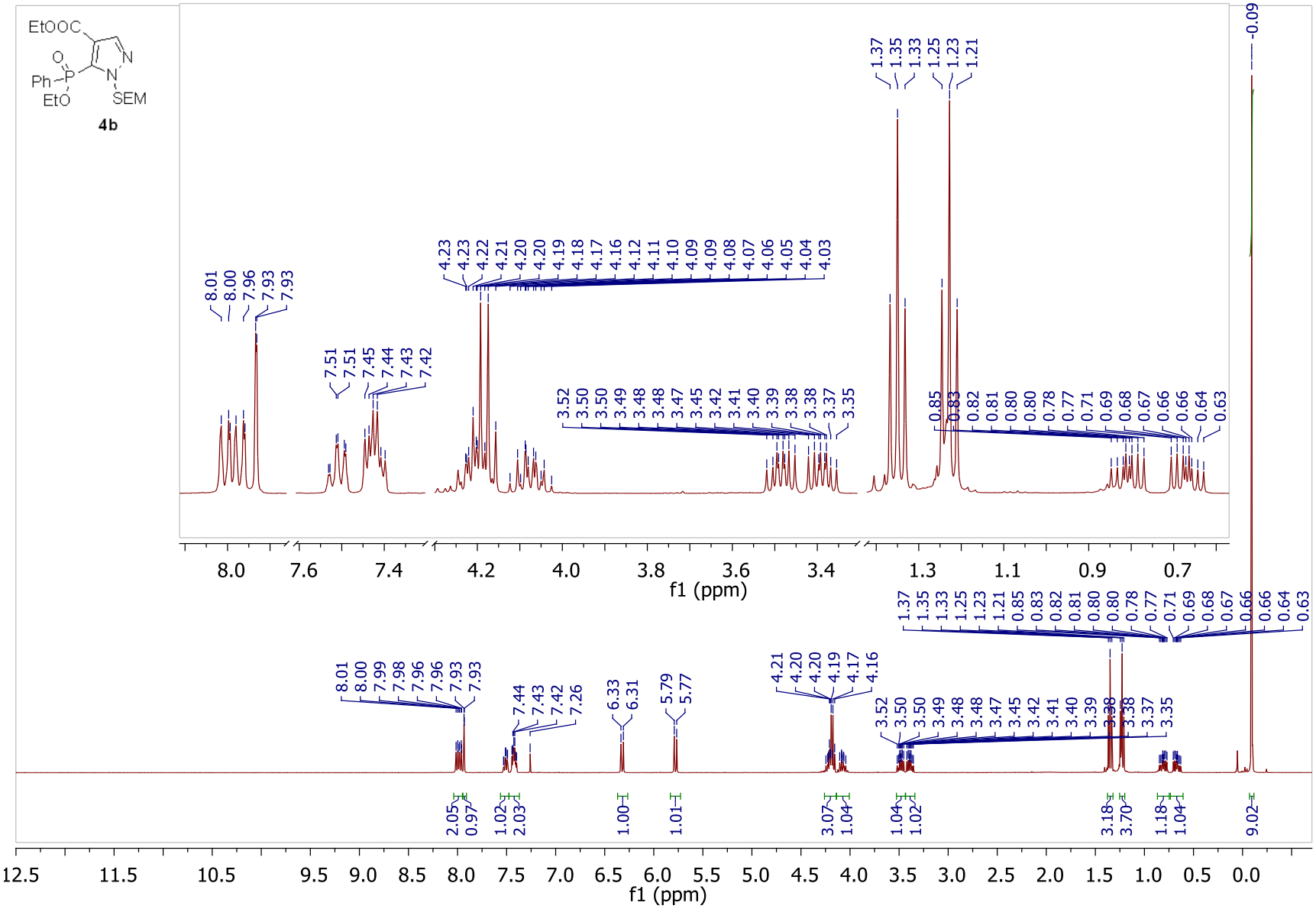

3d
62.46
62.43
62.40
62.8
62.5
62.2
f1 (ppm)
158.79
144.15
144.04
136.01
135.79
114.12
111.96
80.07
67.45
62.46
62.43
62.40
17.85
16.52
16.45
14.06
-1.36
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

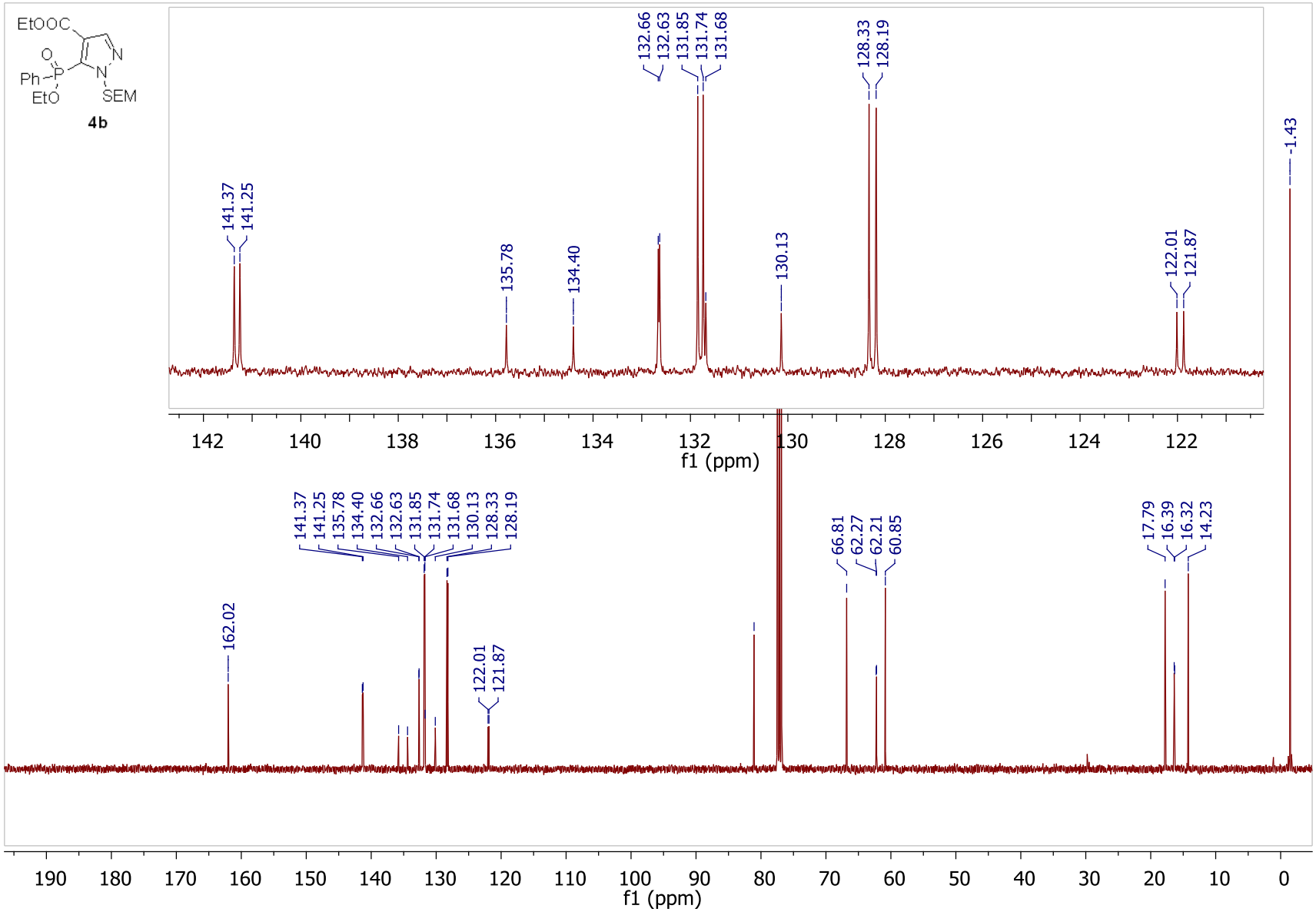

CO2Et
O
P
EtO
OEt
N
N
SEM
3e
f1 (ppm)
f1 (ppm)

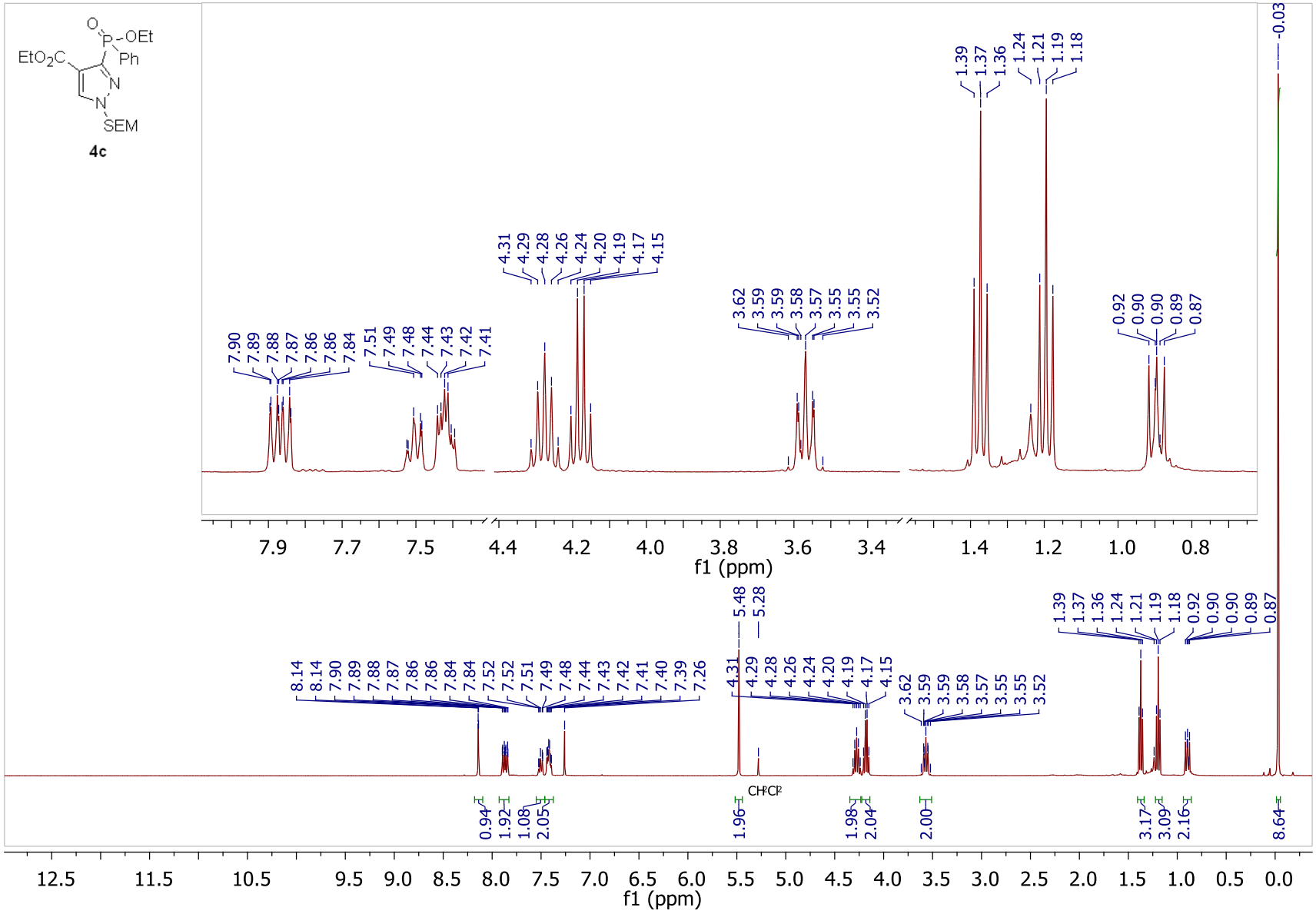

CO2Et
O
P
EtO
OEt
N
N
SEM
3e
-1.36
30.42
29.26
18.25
16.57
16.50
14.56
67.56
63.80
63.75
61.41
80.96
118.41
118.24
161.88
144.29
144.13
135.85
133.76
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

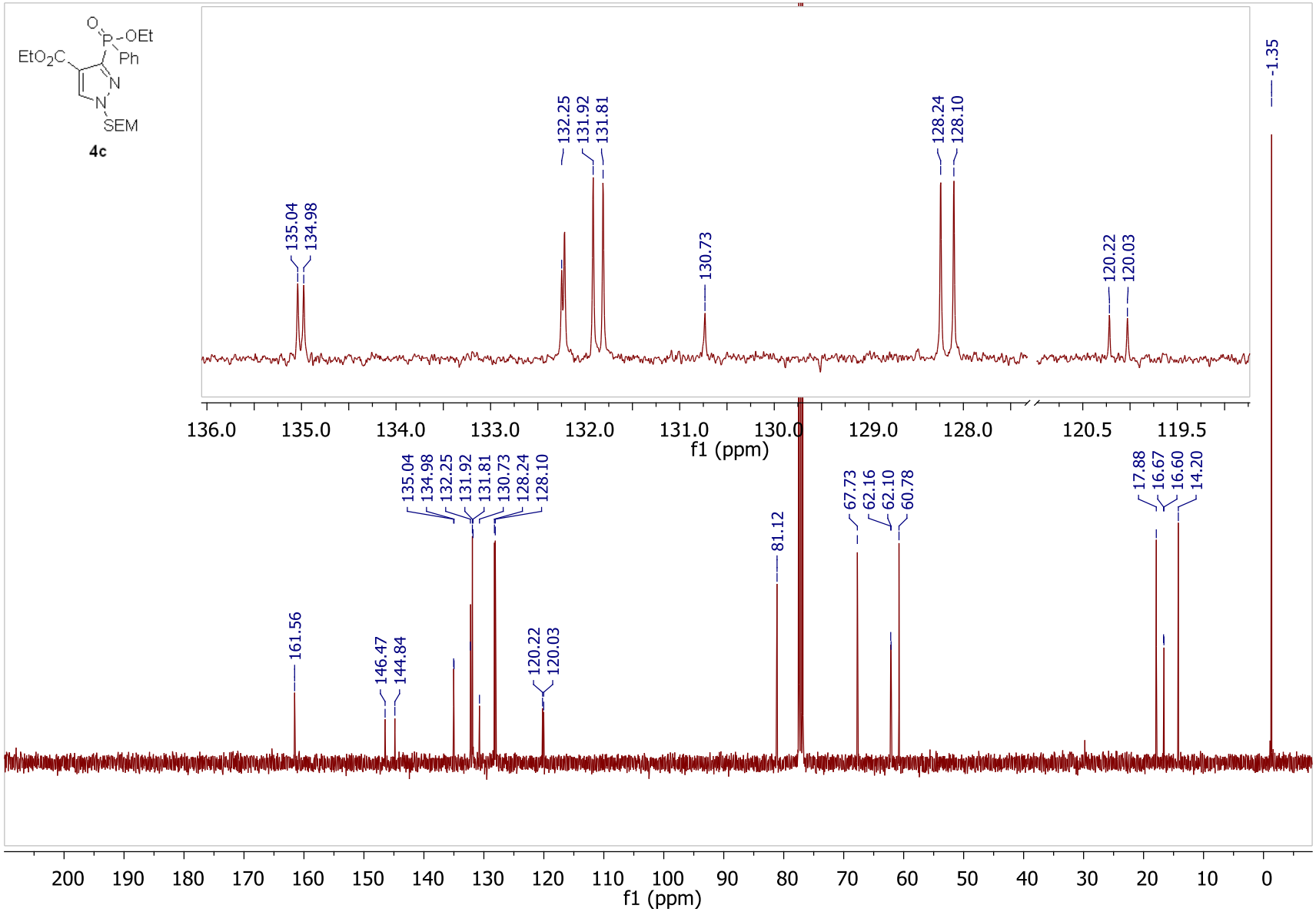

EtOOC
O
iPrO
P
iPrO
N
N
SEM
4a (29%)
f1 (ppm)
f1 (ppm)

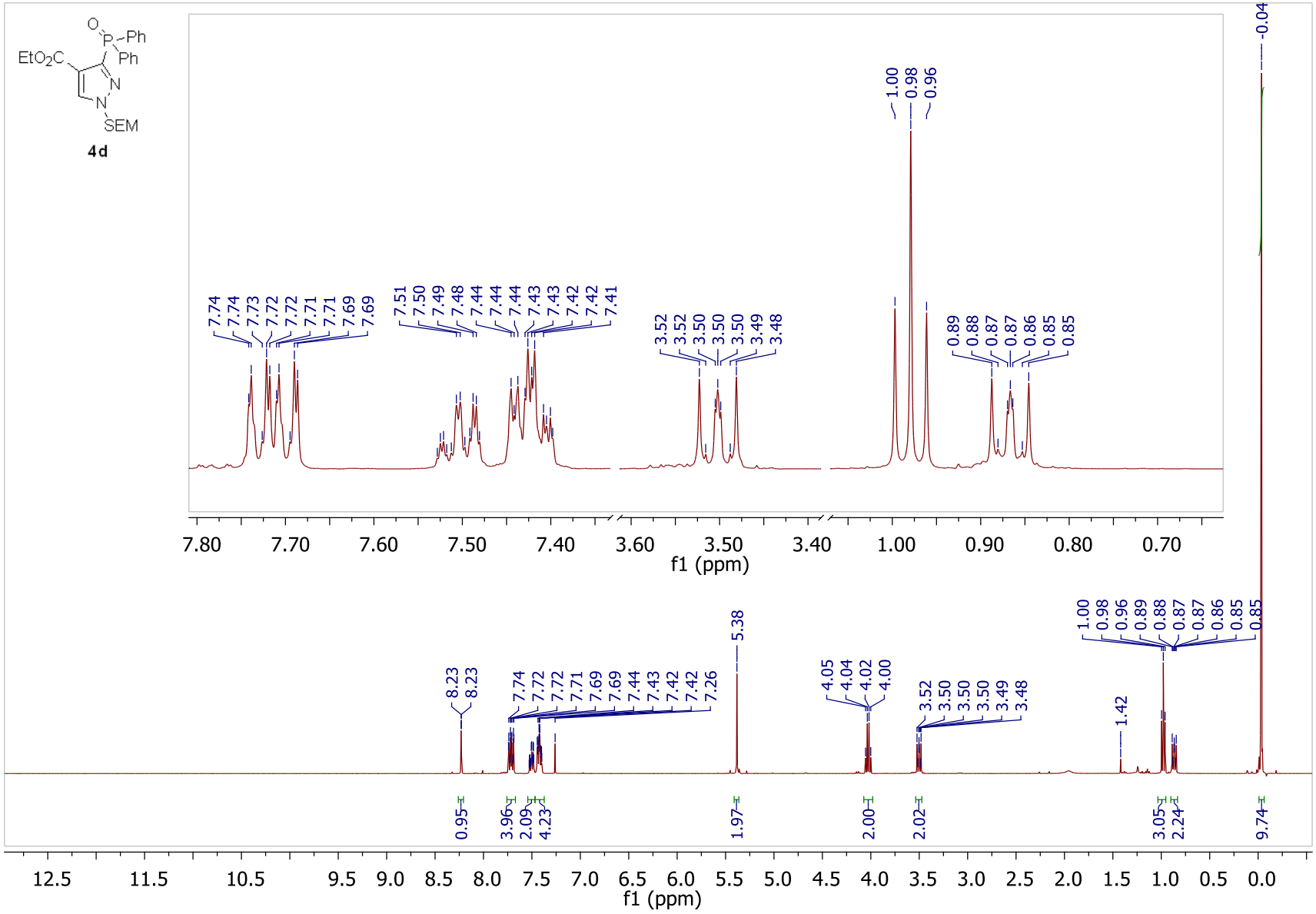

EtOOC
O
P
N
N
SEM
iPrO
iPrO
4a (29%)
-1.34
162.09
141.63
141.49
135.27
133.21
121.75
121.60
80.56
72.46
72.41
67.00
60.84
24.14
24.09
23.76
23.71
18.02
14.40
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

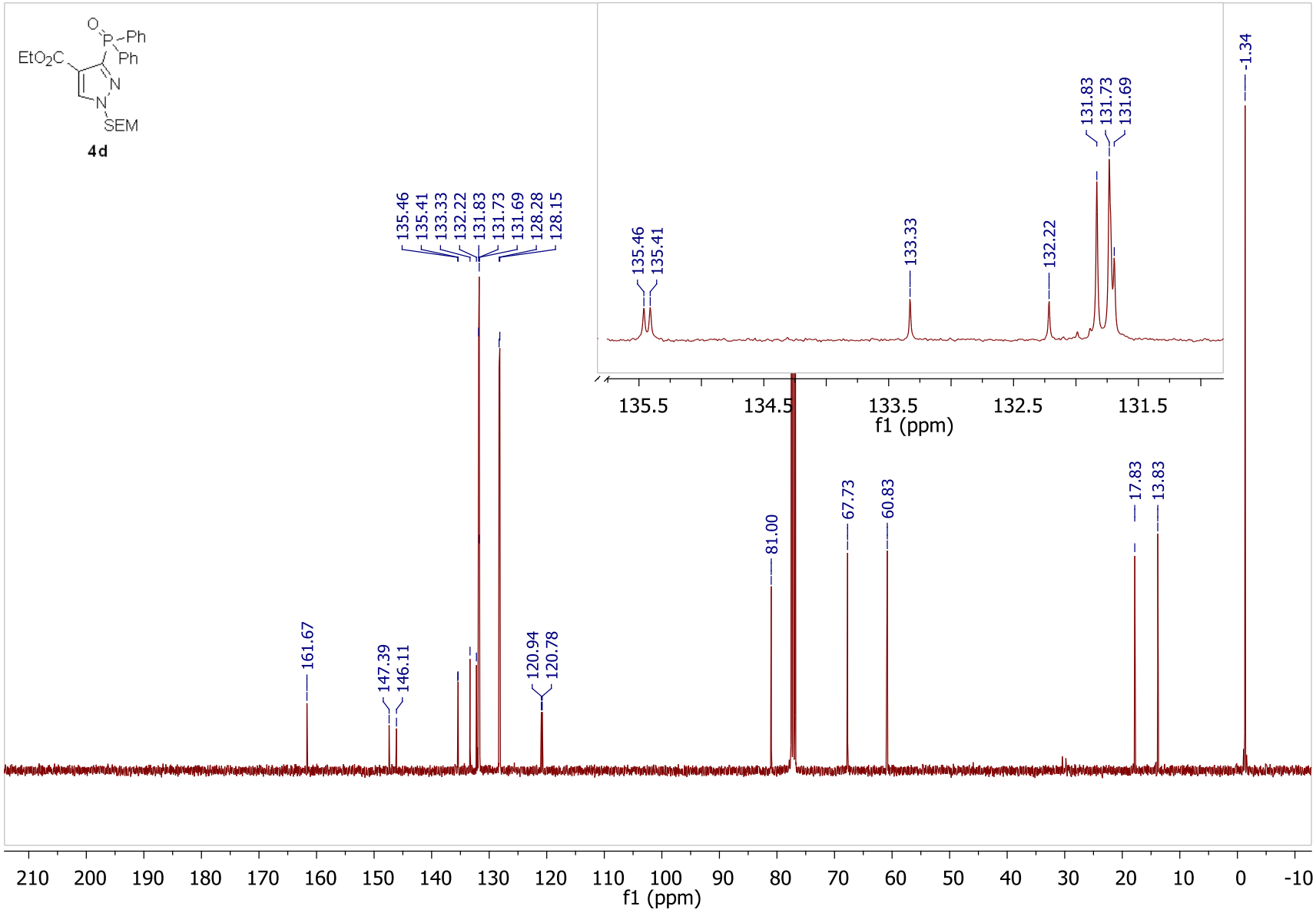

EtOOC
Ph
P
O
EtO
N
N
SEM
4b
f1 (ppm)
f1 (ppm)

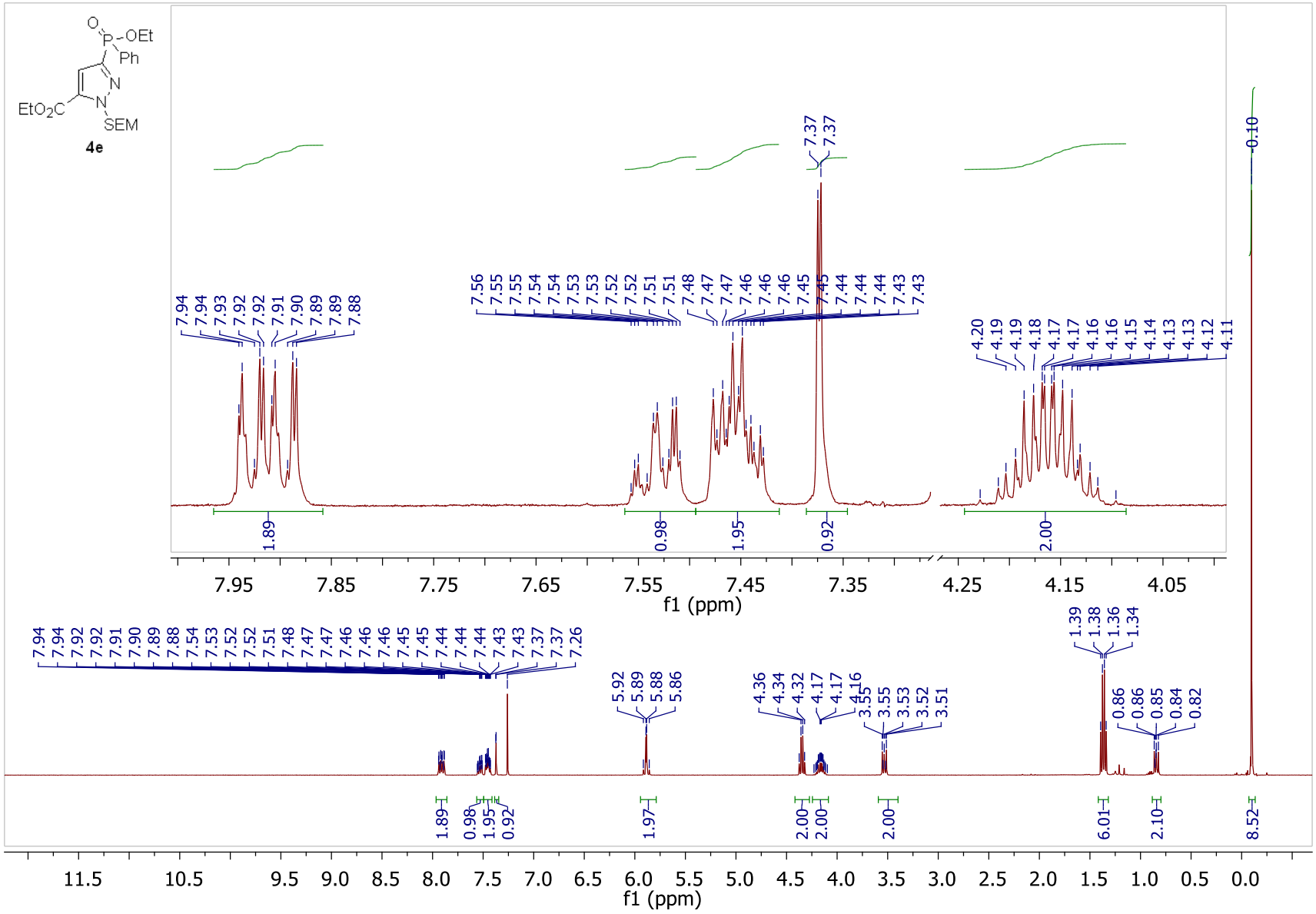

EtOOC
O
Ph
P
EtO
N
N
SEM
4b
132.66
132.63
131.85
131.74
131.68
128.33
128.19
141.37
141.25
135.78
134.40
130.13
122.01
121.87
-1.43
142
140
138
136
134
132
130
128
126
124
122
f1 (ppm)
141.37
141.25
135.78
134.40
132.66
132.63
131.85
131.74
131.68
130.13
128.33
128.19
66.81
62.27
62.21
60.85
17.79
16.39
16.32
14.23
162.02
122.01
121.87
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

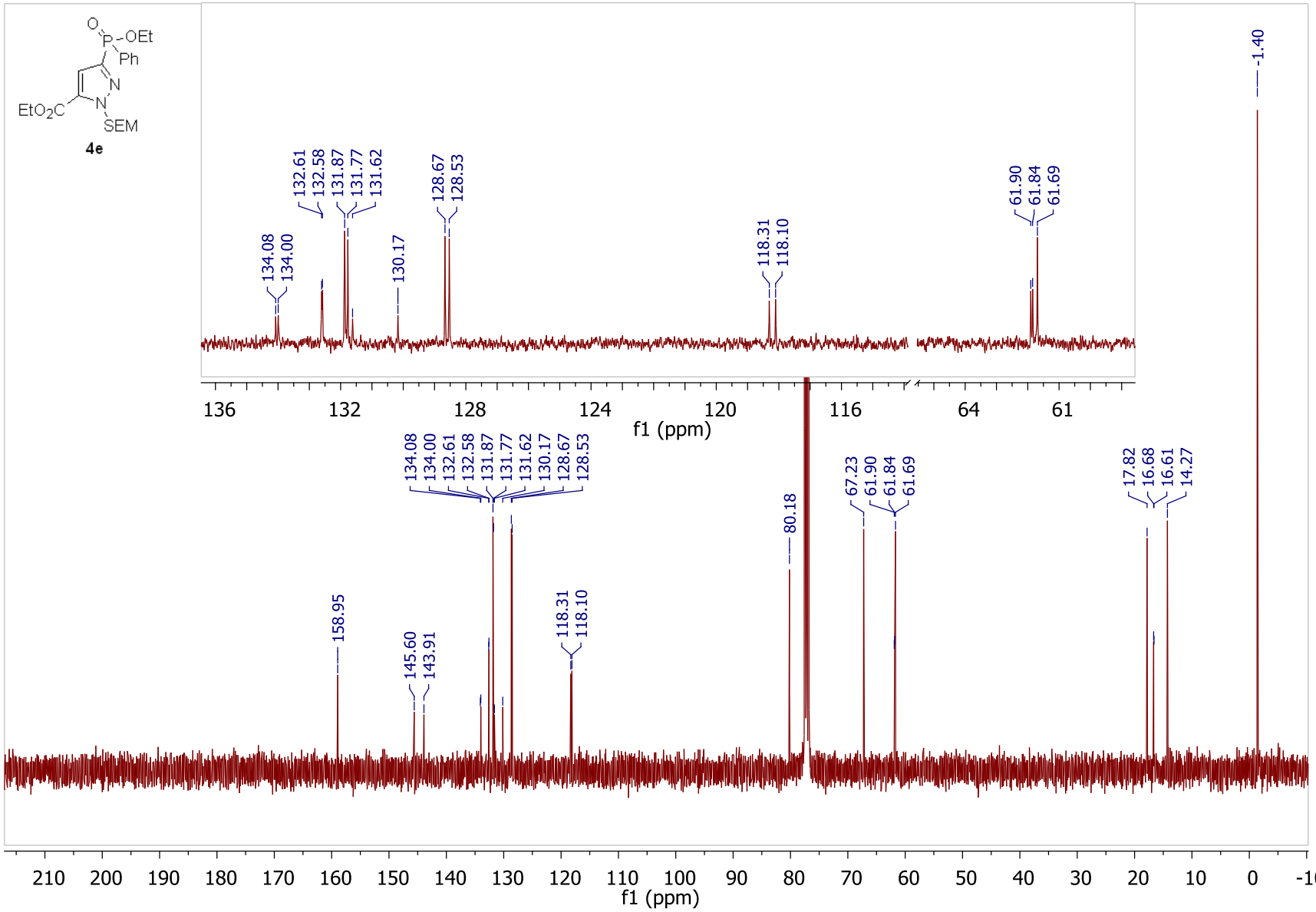

EtO2C
O
P
OEt
Ph
N
N
SEM
4c
f1 (ppm)
CHCl3

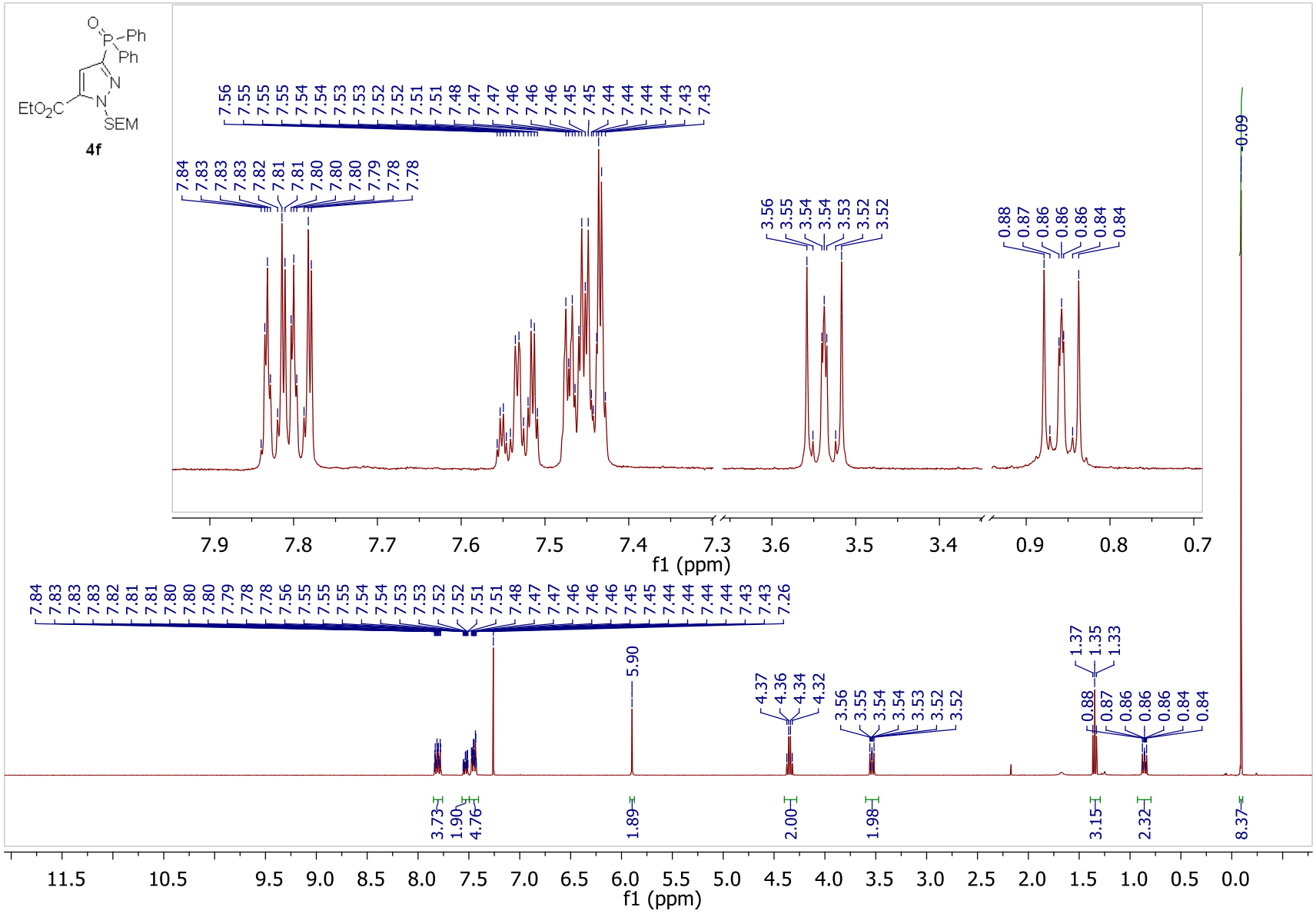

4c
135.04
134.98
132.25
131.92
131.81
130.73
128.24
128.10
120.22
120.03
-1.35
f1 (ppm)
161.56
146.47
144.84
81.12
67.73
62.16
62.10
60.78
17.88
16.67
16.60
14.20
f1 (ppm)

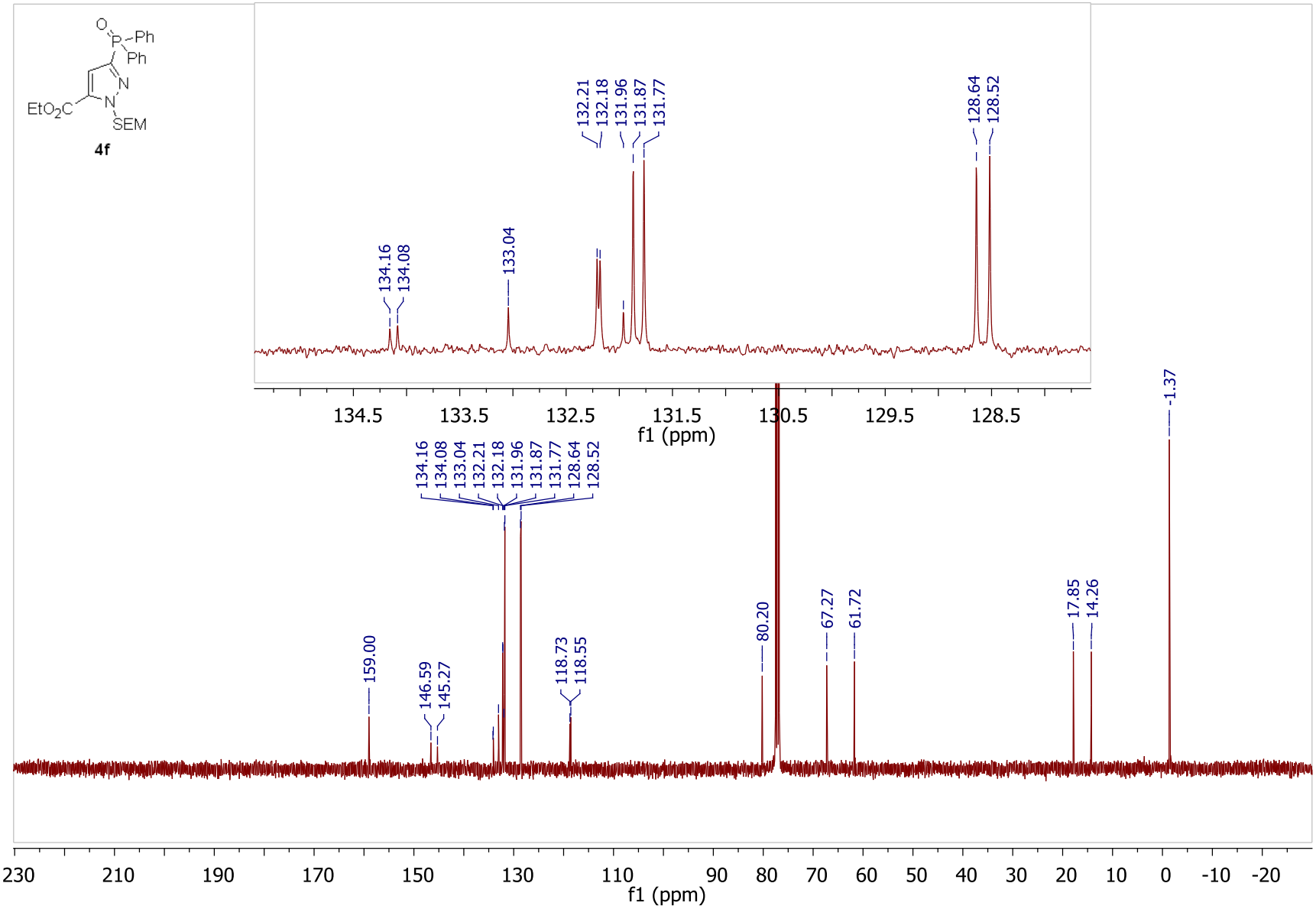

EtO2C
O
P
Ph
Ph
N
N
SEM
4d
7.74 7.74 7.73 7.72 7.72 7.71 7.71 7.69 7.69
7.51 7.50 7.49 7.48 7.44 7.44 7.44 7.43 7.43 7.42 7.42 7.41
3.52 3.52 3.50 3.50 3.50 3.49 3.48
1.00 0.98 0.96
0.89 0.88 0.87 0.87 0.86 0.85 0.85
-0.04
7.80 7.70 7.60 7.50 7.40 3.60 3.50 3.40 1.00 0.90 0.80 0.70
f1 (ppm)
8.23 8.23
7.74 7.72 7.72 7.71 7.69 7.69 7.44 7.43 7.42 7.42 7.26
5.38
4.05 4.04 4.02 4.00
3.52 3.50 3.50 3.50 3.49 3.48
1.42
1.00 0.98 0.96 0.89 0.88 0.87 0.87 0.86 0.85 0.85
0.95 3.96 2.09 4.23 1.97 2.00 2.02 3.05 2.24 9.74
12.5 11.5 10.5 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)

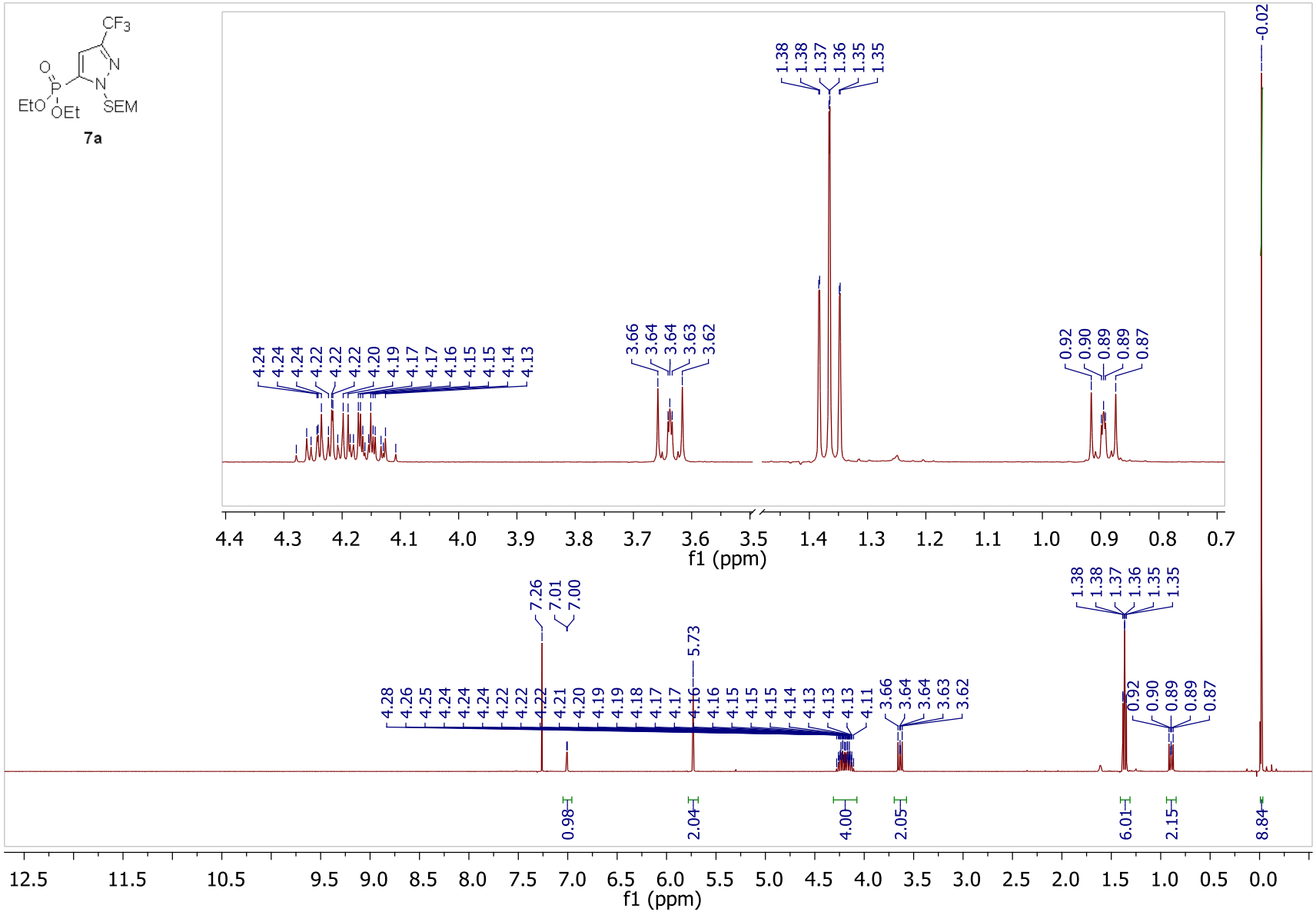

4d
135.46
135.41
133.33
132.22
131.83
131.73
131.69
128.28
128.15
161.67
147.39
146.11
120.94
120.78
81.00
67.73
60.83
17.83
13.83
-1.34
f1 (ppm)
f1 (ppm)

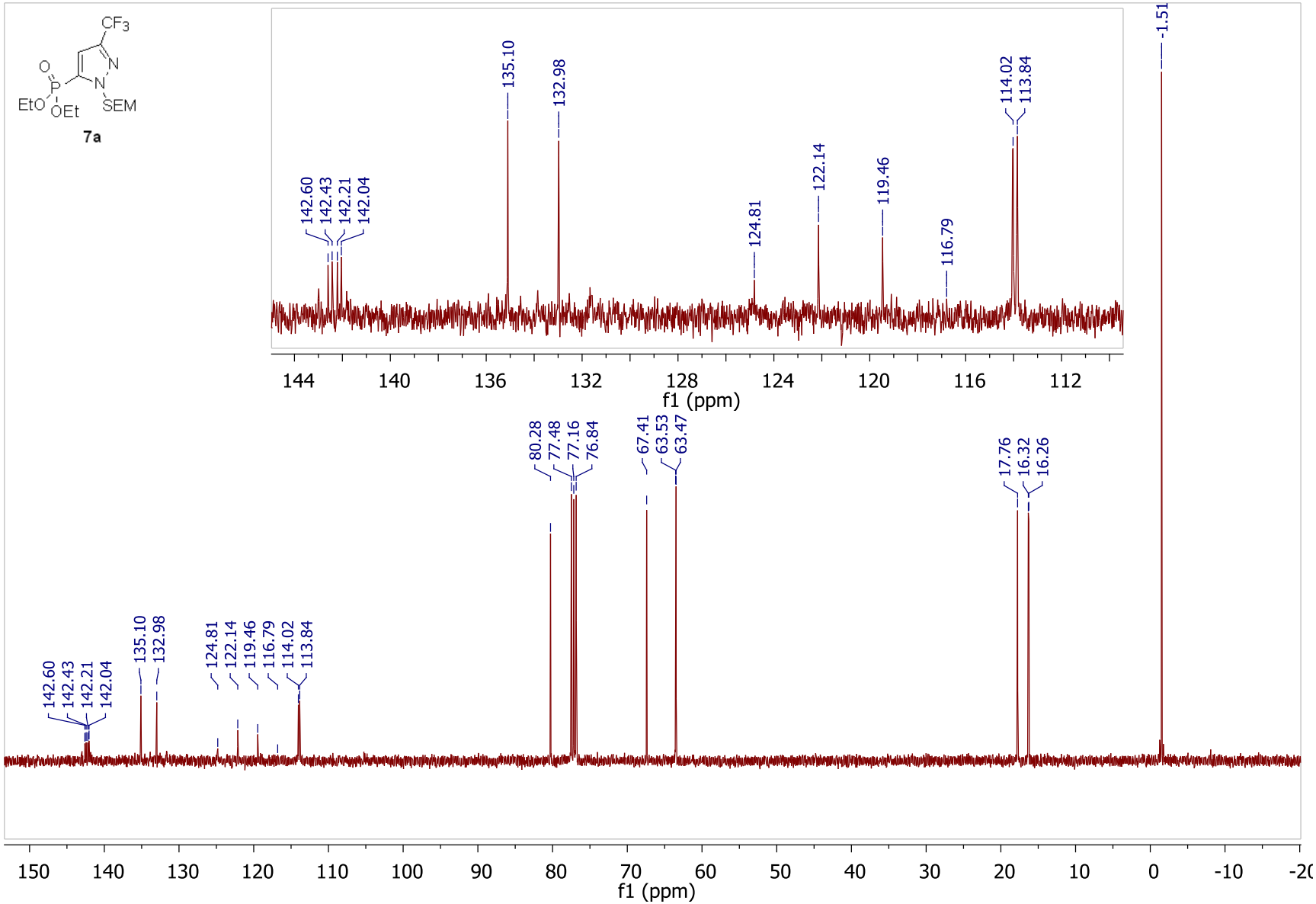

4e
f1 (ppm)
f1 (ppm)

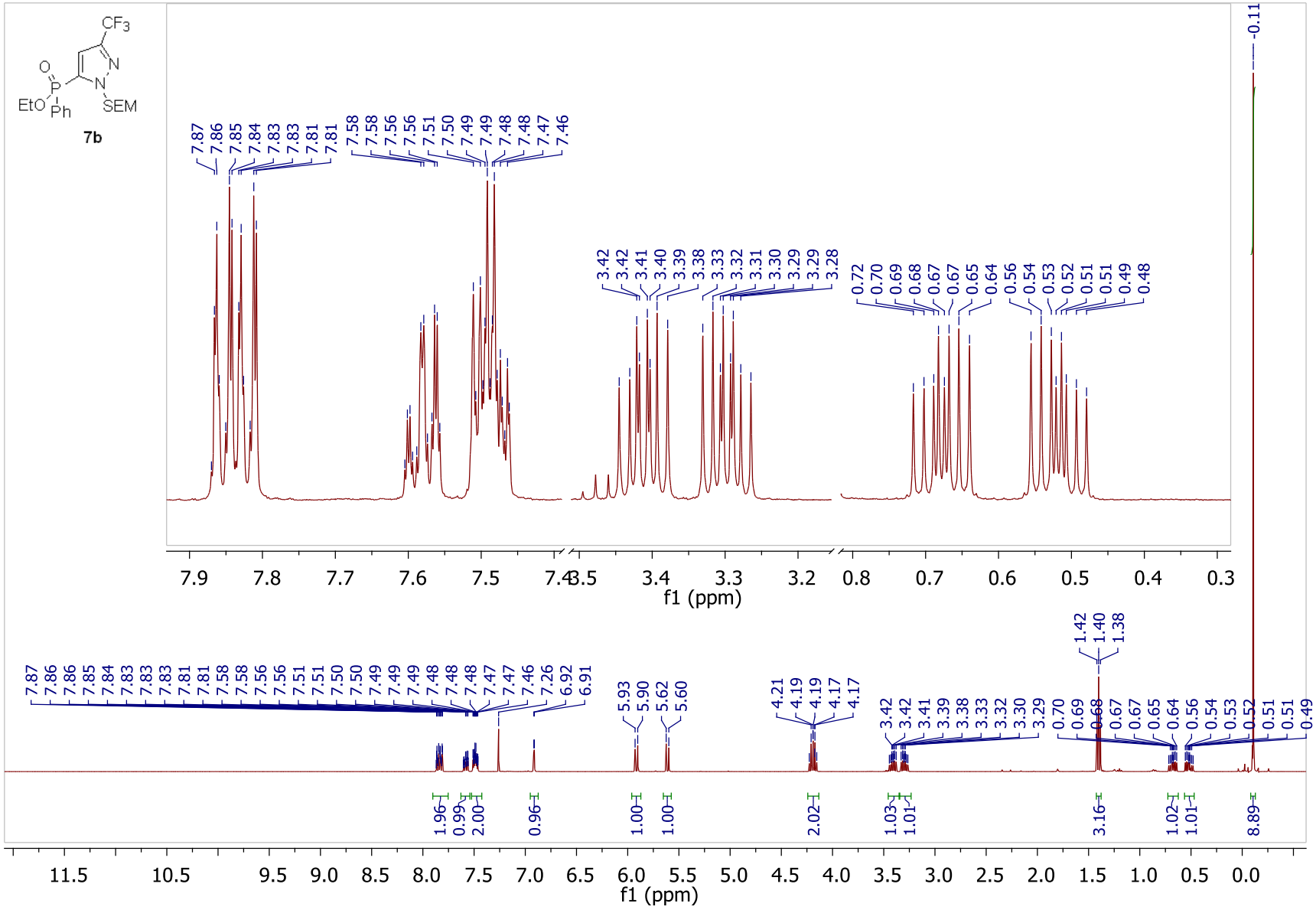

4e
O
P
OEt
Ph
N
N
SEM
EtO2C
134.08
134.00
132.61
132.58
131.87
131.77
131.62
130.17
128.67
128.53
118.31
118.10
61.90
61.84
61.69
-1.40
f1 (ppm)
158.95
145.60
143.91
80.18
67.23
17.82
16.68
16.61
14.27

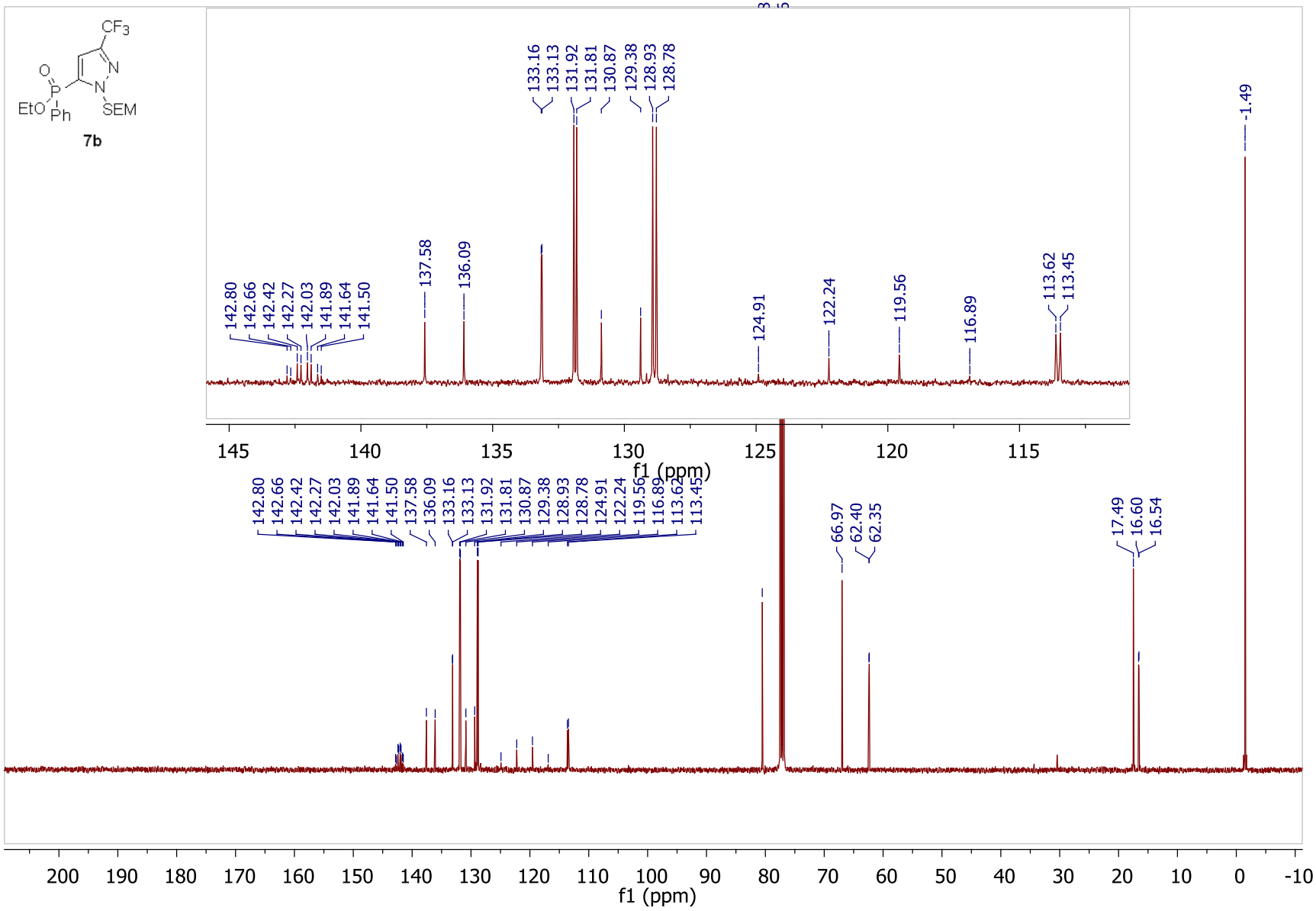

4f
f1 (ppm)
f1 (ppm)


O
P
Ph
Ph
N
N
SEM
EtO2C
4f
134.16
134.08
133.04
132.21
132.18
131.96
131.87
131.77
128.64
128.52
134.5
133.5
132.5
131.5
130.5
129.5
128.5
f1 (ppm)
159.00
146.59
145.27
118.73
118.55
80.20
67.27
61.72
17.85
14.26
-1.37
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


CF3
O
P
N
N
EtO
OEt
SEM
7a
f1 (ppm)
f1 (ppm)


CF3
O
P
N
N
EtO
OEt
SEM
7a
142.60
142.43
142.21
142.04
135.10
132.98
124.81
122.14
119.46
116.79
114.02
113.84
-1.51
80.28
77.48
77.16
76.84
67.41
63.53
63.47
17.76
16.32
16.26
f1 (ppm)


CF3
O
P
N
N
EtO
Ph
SEM
7b
f1 (ppm)
f1 (ppm)


CF3
O
P
EtO
Ph
N
N
SEM
7b
142.80
142.66
142.42
142.27
142.03
141.89
141.64
141.50
137.58
136.09
133.16
133.13
131.92
131.81
130.87
129.38
128.93
128.78
124.91
122.24
119.56
116.89
113.62
113.45
-1.49
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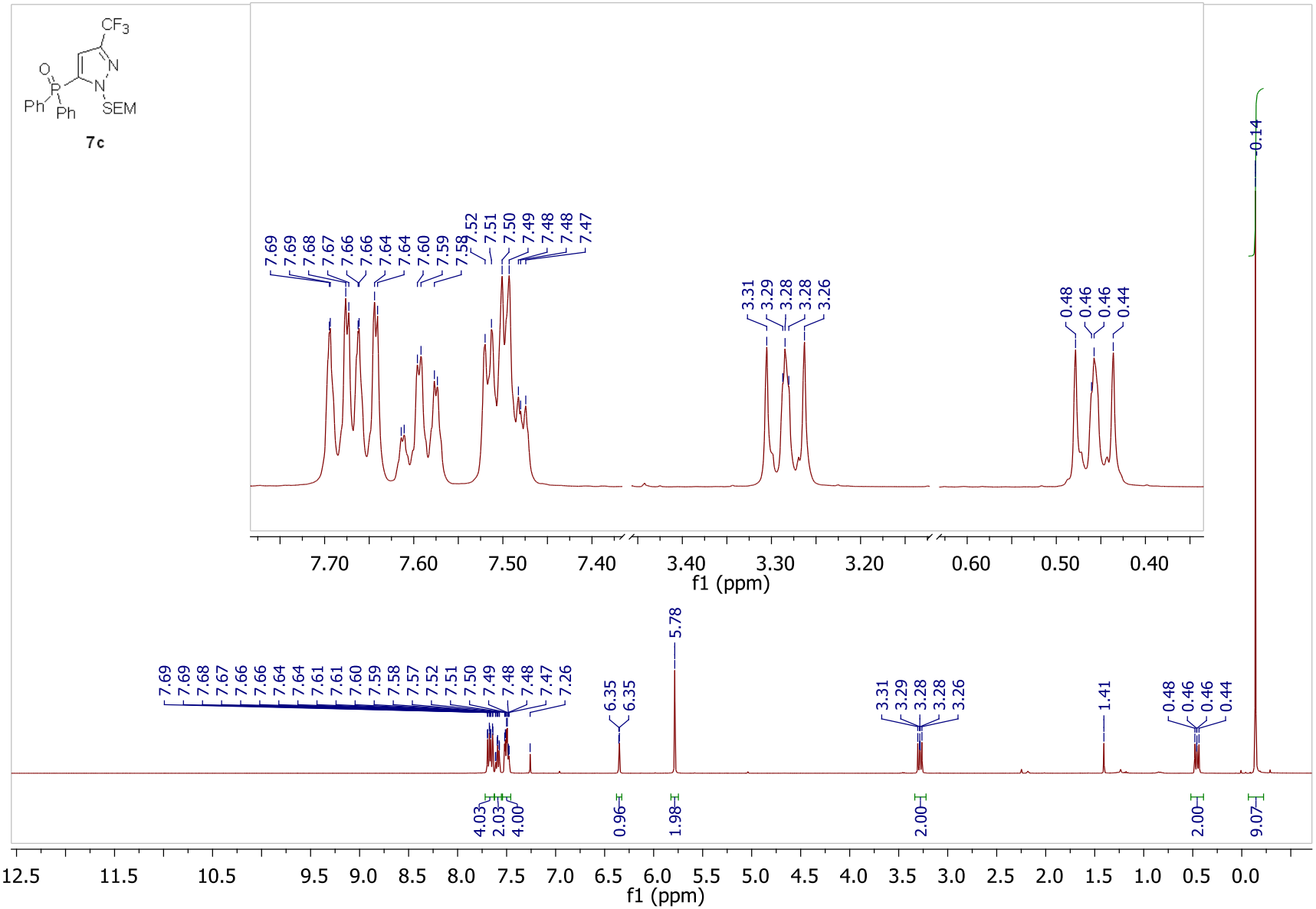
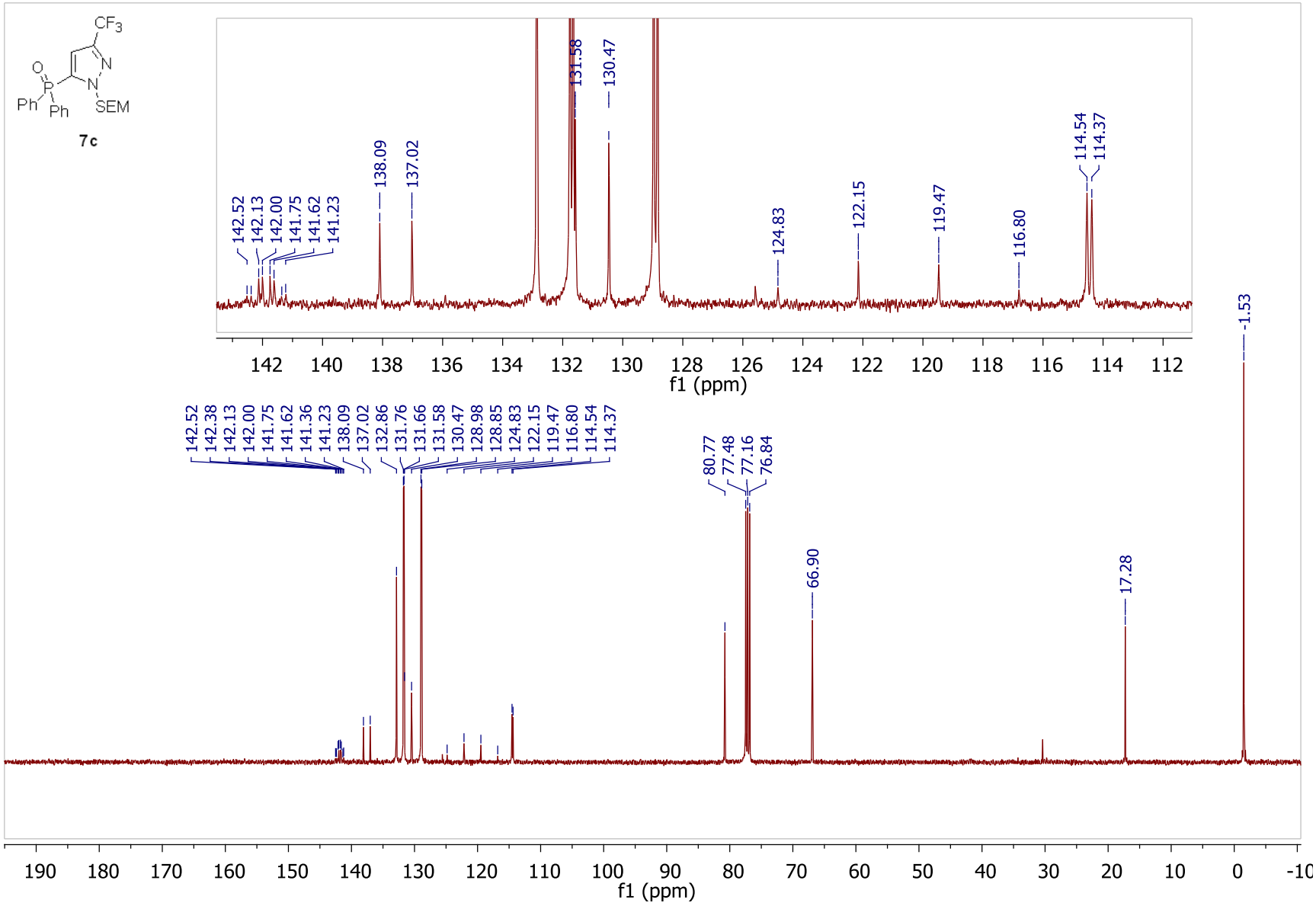
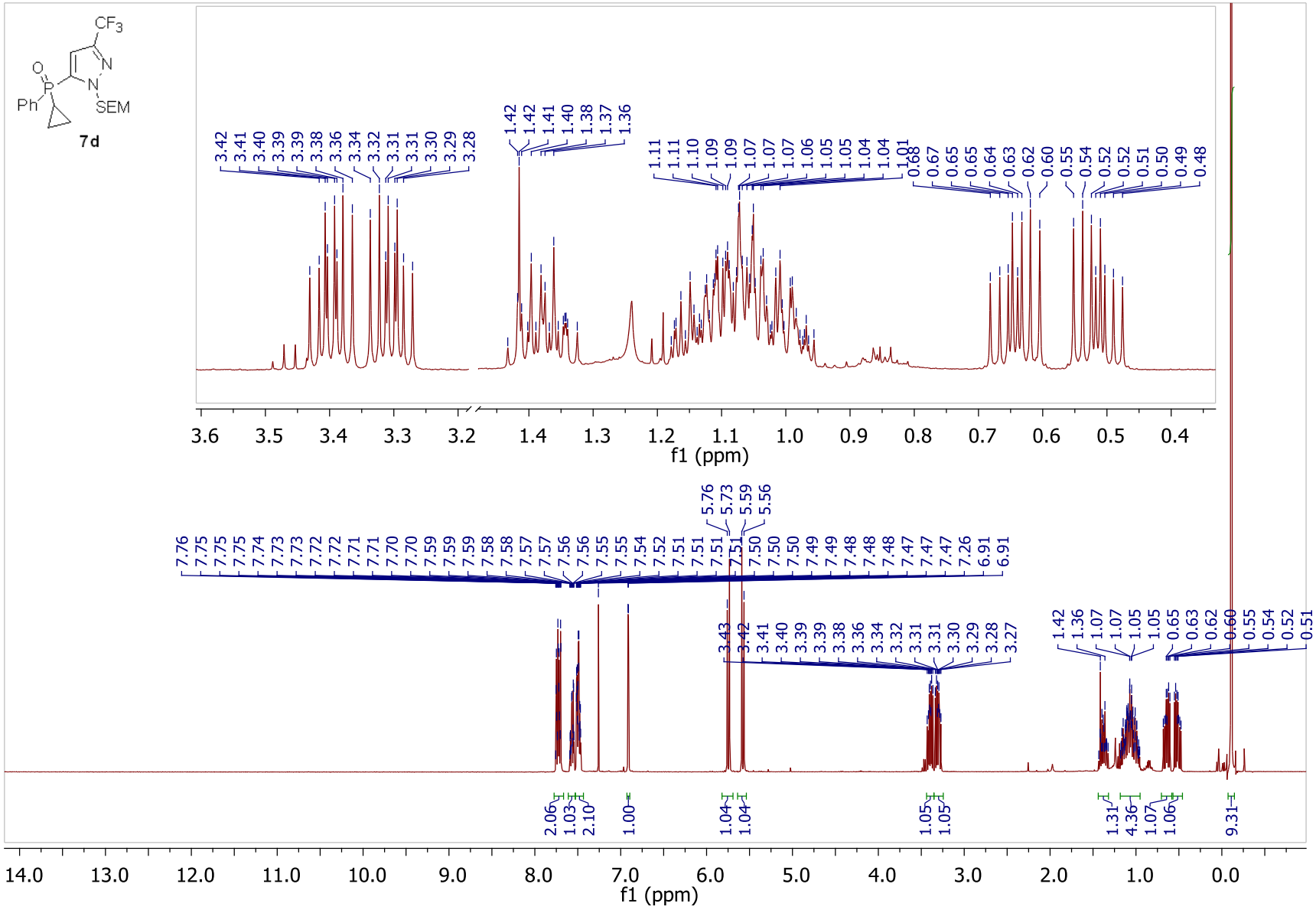
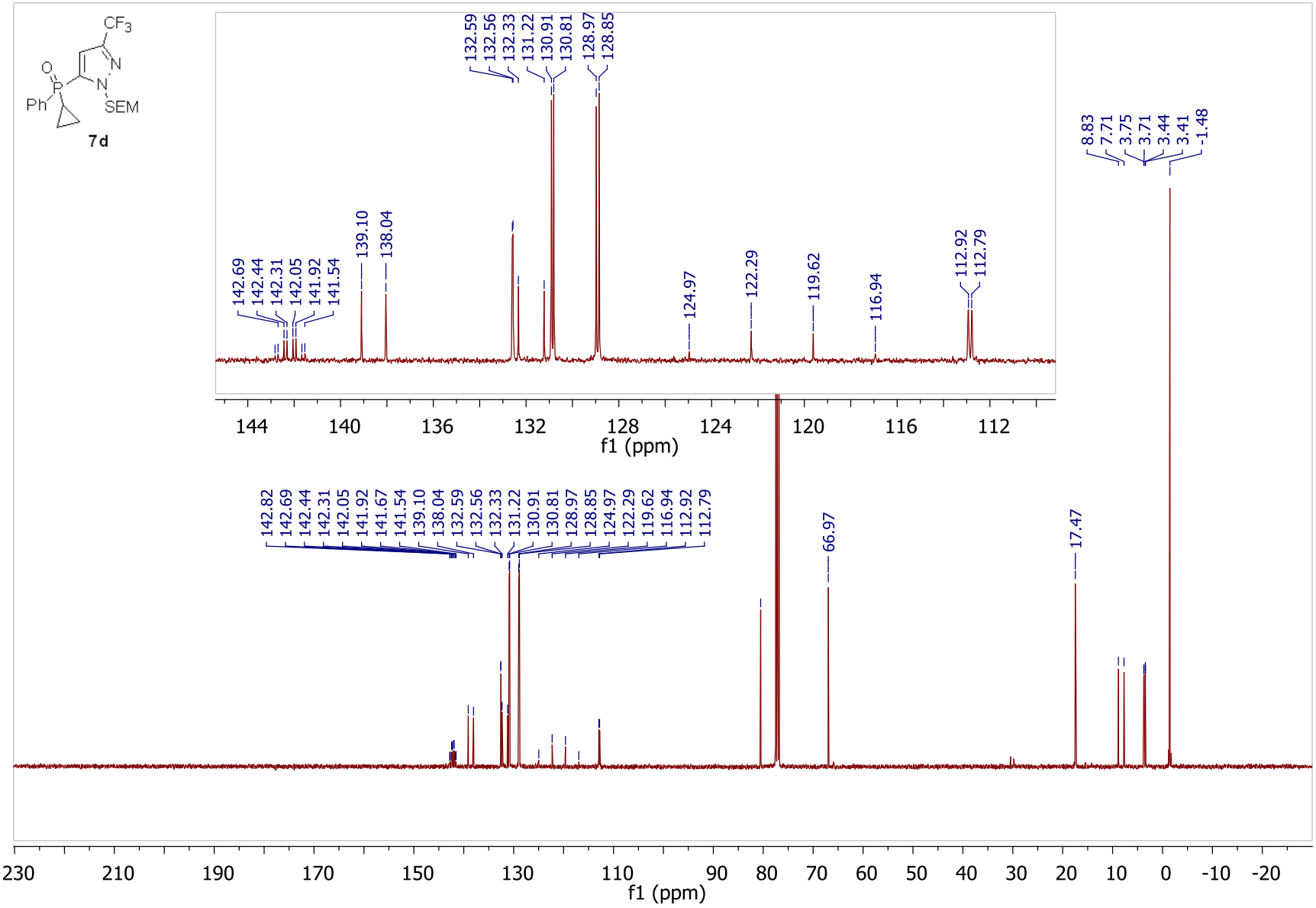
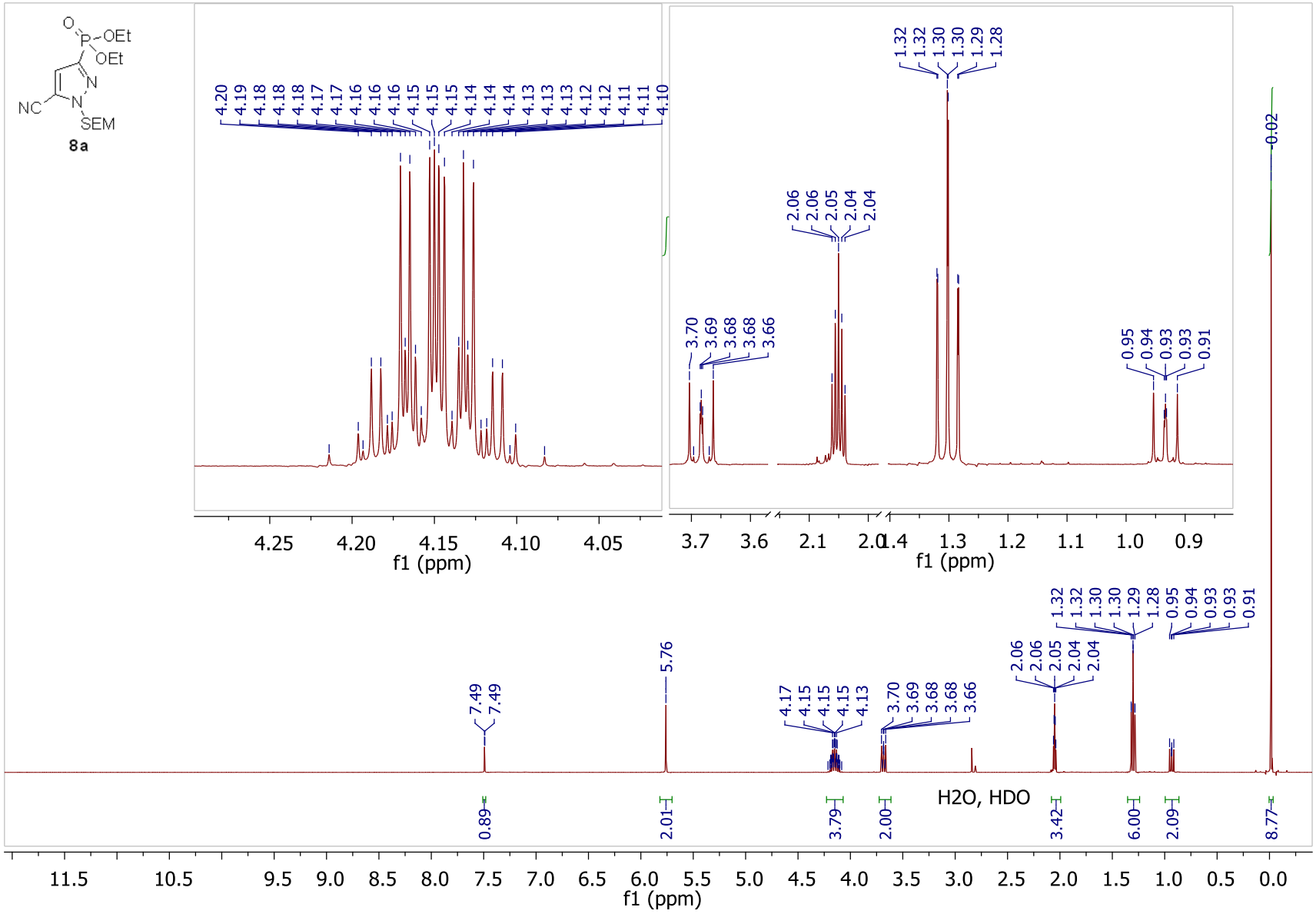
62.35
17.49
16.60
16.54
f1 (ppm)

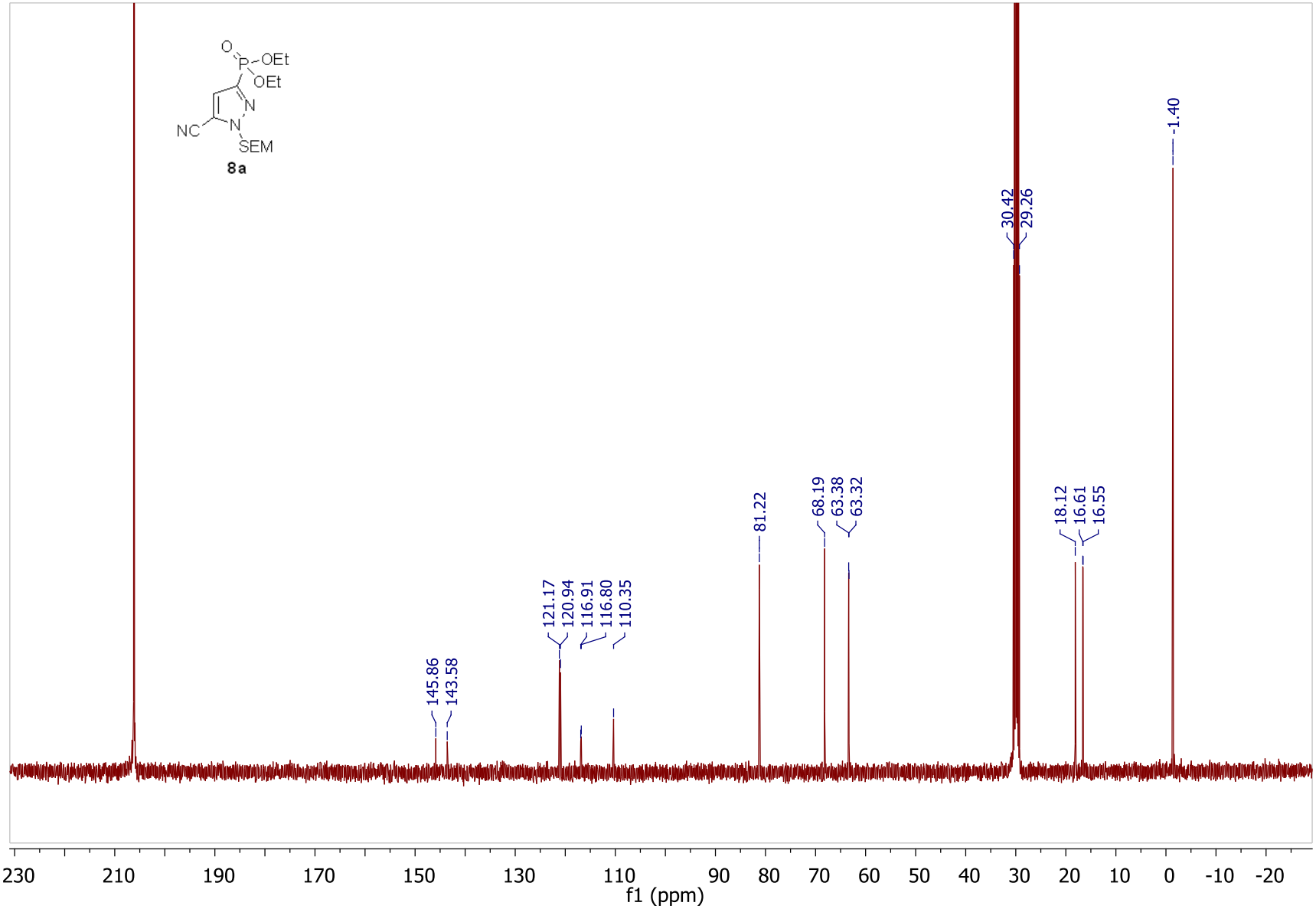

CF3
O
P
Ph
Ph
N
N
SEM
7c
7.69 7.69 7.68 7.67 7.66 7.66 7.64 7.64 7.60 7.59 7.58 7.52 7.51 7.50 7.49 7.48 7.48 7.47
3.31 3.29 3.28 3.28 3.26
0.48 0.46 0.46 0.44
0.14
7.70 7.60 7.50 7.40 3.40 3.30 3.20 0.60 0.50 0.40
f1 (ppm)
7.69 7.69 7.68 7.67 7.66 7.66 7.64 7.64 7.61 7.61 7.60 7.59 7.58 7.57 7.52 7.51 7.50 7.49 7.48 7.48 7.47 7.26
6.35 6.35
5.78
3.31 3.29 3.28 3.28 3.26
1.41
0.48 0.46 0.46 0.44
4.03 2.03 4.00 0.96 1.98 2.00 2.00 9.07
12.5 11.5 10.5 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)

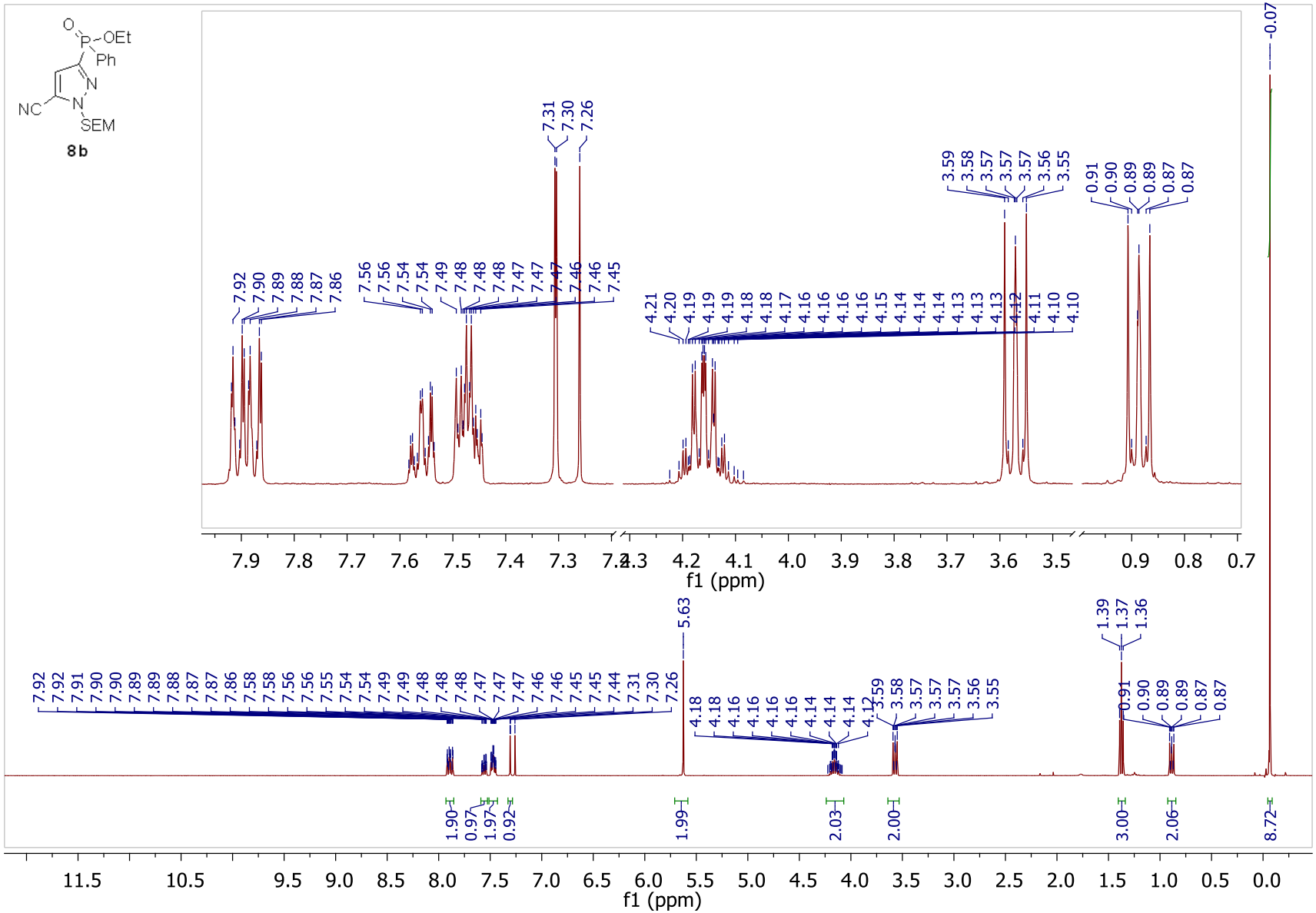

CF3
O
P
Ph
Ph
N
N
SEM
7c
142.52
142.13
142.00
141.75
141.62
141.23
138.09
137.02
131.58
130.47
124.83
122.15
119.47
116.80
114.54
114.37
142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
f1 (ppm)
142.52
142.38
142.13
142.00
141.75
141.62
141.36
141.23
138.09
137.02
132.86
131.76
131.66
131.58
130.47
128.98
128.85
124.83
122.15
119.47
116.80
114.54
114.37
80.77
77.48
77.16
76.84
66.90
17.28
-1.53
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

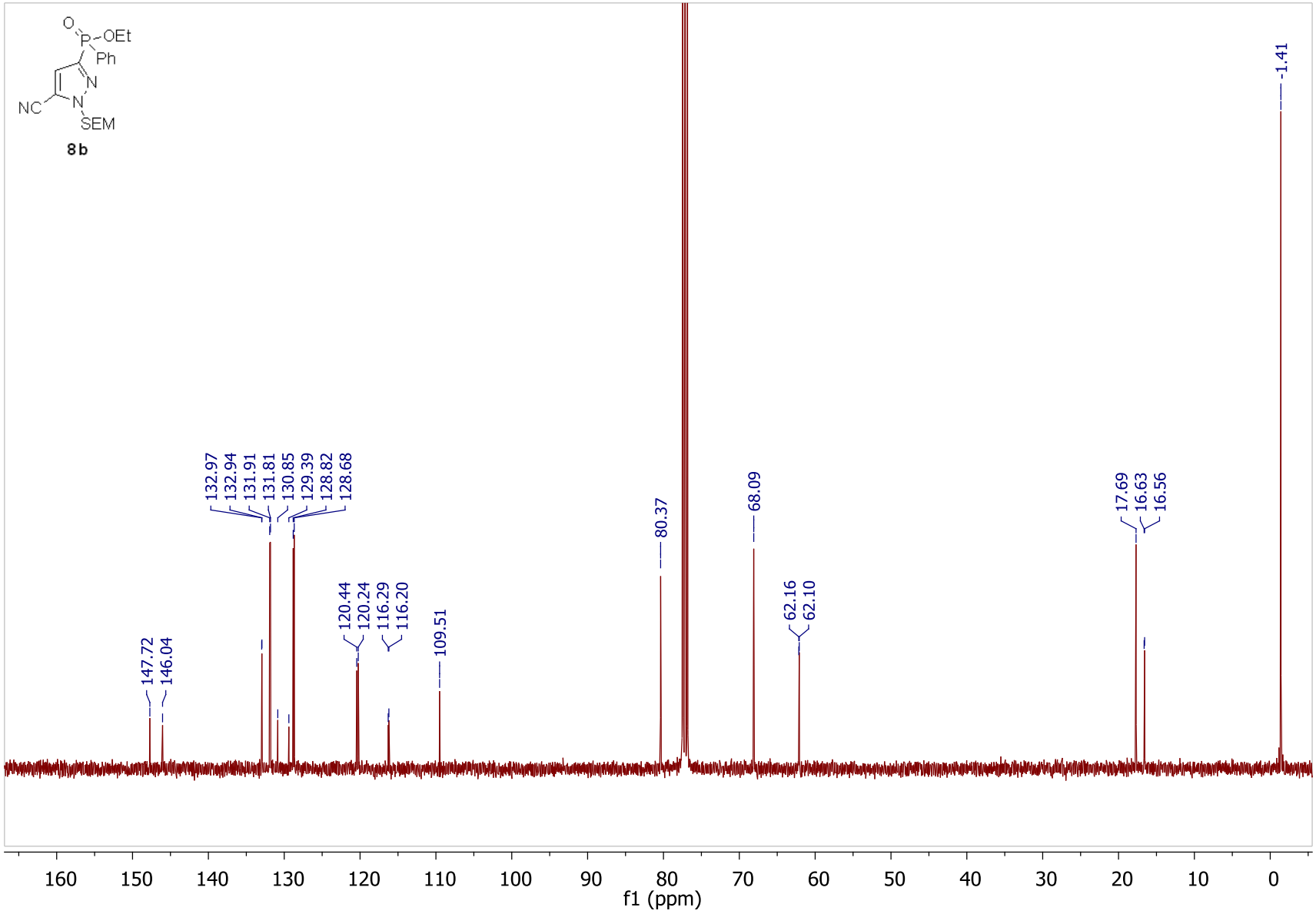

CF3
O
P
Ph
N
N
SEM
7d
3.42 3.41 3.40 3.39 3.39 3.38 3.36 3.34 3.32 3.31 3.31 3.30 3.29 3.28
1.42 1.42 1.41 1.40 1.38 1.37 1.36
1.11 1.11 1.10 1.09 1.09 1.07 1.07 1.07 1.06 1.05 1.05 1.04 1.04 1.01 0.68 0.67 0.65 0.65 0.64 0.63 0.62 0.60 0.55 0.54 0.52 0.52 0.51 0.50 0.49 0.48
3.6 3.5 3.4 3.3 3.2 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4
f1 (ppm)
5.76 5.73 5.59 5.56
7.76 7.75 7.75 7.75 7.74 7.73 7.73 7.72 7.72 7.71 7.71 7.70 7.70 7.59 7.59 7.59 7.58 7.58 7.57 7.57 7.56 7.56 7.55 7.55 7.54 7.52 7.51 7.51 7.51 7.51 7.50 7.50 7.49 7.49 7.48 7.48 7.48 7.47 7.47 7.47 7.26 6.91 6.91
3.43 3.42 3.41 3.40 3.39 3.39 3.38 3.36 3.34 3.32 3.31 3.31 3.30 3.29 3.28 3.27
1.42 1.36 1.07 1.07 1.05 1.05 0.65 0.63 0.62 0.60 0.55 0.54 0.52 0.51
2.06 1.03 2.10 1.00 1.04 1.04 1.05 1.05 1.31 4.36 1.07 1.06 9.31
14.0 13.0 12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

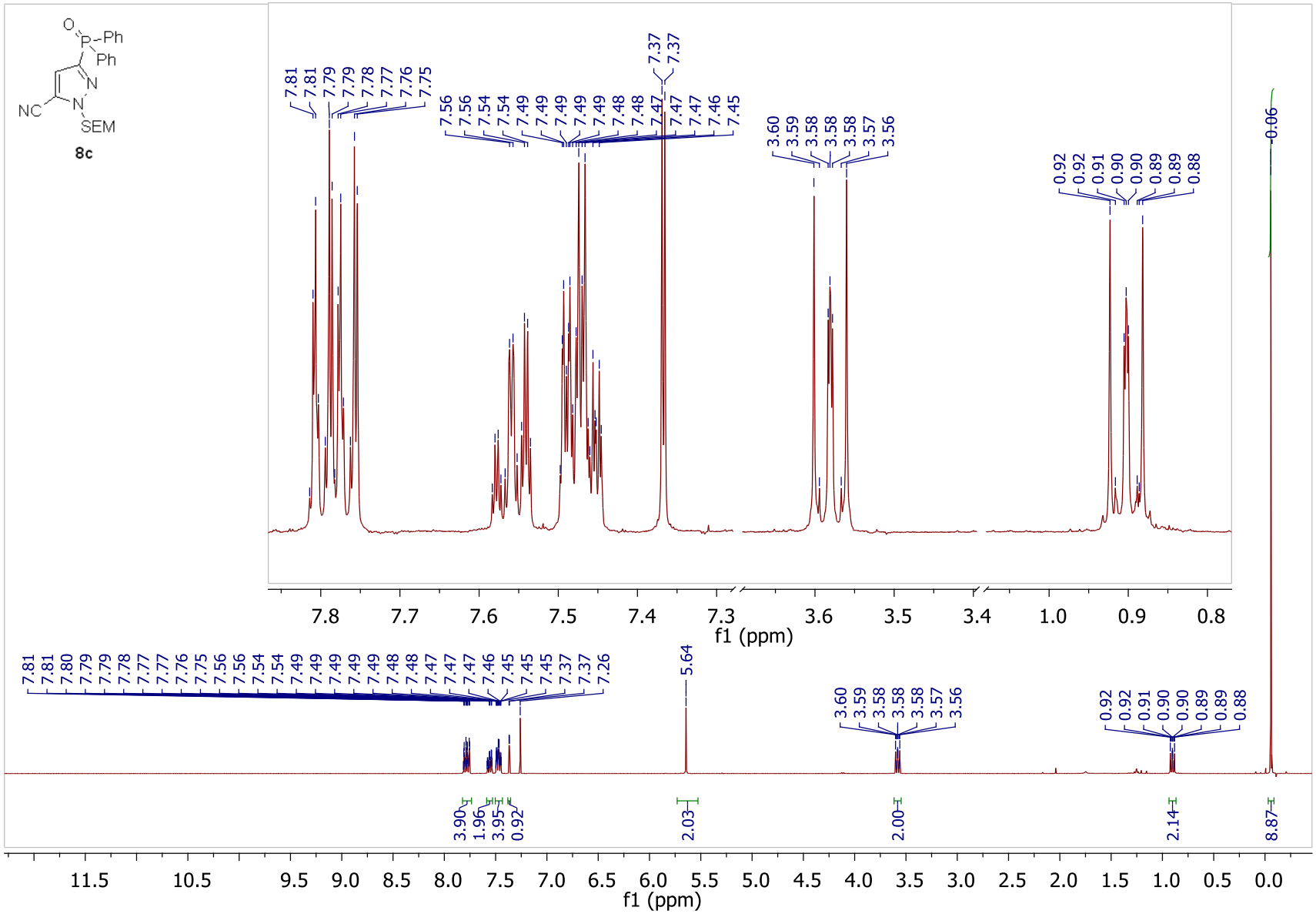

CF3
O
P
Ph
N
N
SEM
7d
132.59
132.56
132.33
131.22
130.91
130.81
128.97
128.85
142.69
142.44
142.31
142.05
141.92
141.54
139.10
138.04
124.97
122.29
119.62
116.94
112.92
112.79
8.83
7.71
3.75
3.71
3.44
3.41
-1.48
144
140
136
132
128
124
120
116
112
f1 (ppm)
142.82
142.69
142.44
142.31
142.05
141.92
141.67
141.54
139.10
138.04
132.59
132.56
132.33
131.22
130.91
130.81
128.97
128.85
124.97
122.29
119.62
116.94
112.92
112.79
66.97
17.47
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

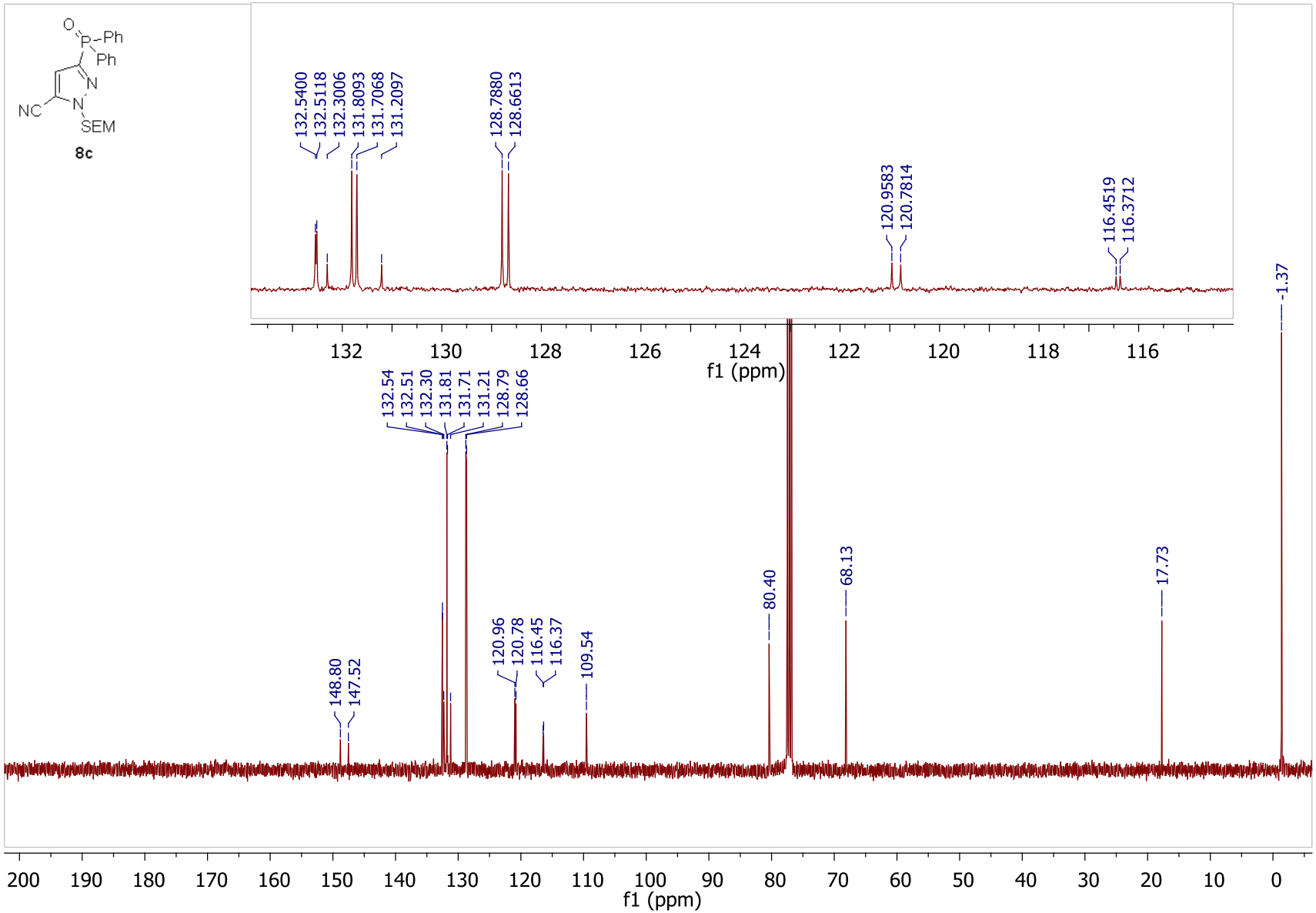

O
P
OEt
OEt
N
N
NC
SEM
8a
4.20 4.19 4.18 4.18 4.18 4.17 4.17 4.16 4.16 4.16 4.15 4.15 4.15 4.14 4.14 4.14 4.13 4.13 4.13 4.12 4.12 4.11 4.11 4.10
3.70 3.69 3.68 3.68 3.66
2.06 2.06 2.05 2.04 2.04
1.32 1.32 1.30 1.30 1.29 1.28
0.95 0.94 0.93 0.93 0.91
0.02
4.25 4.20 4.15 4.10 4.05
f1 (ppm)
3.7 3.6 2.1 2.0 1.4 1.3 1.2 1.1 1.0 0.9
f1 (ppm)
7.49 7.49
5.76
4.17 4.15 4.15 4.15 4.13
3.70 3.69 3.68 3.68 3.66
2.06 2.06 2.05 2.04 2.04
1.32 1.32 1.30 1.30 1.29 1.28
0.95 0.94 0.93 0.93 0.91
H2O, HDO
0.89
2.01
3.79
2.00
3.42
6.00
2.09
8.77
11.5 10.5 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
P
OEt
OEt
N
N
NC
SEM
8a
145.86
143.58
121.17
120.94
116.91
116.80
110.35
81.22
68.19
63.38
63.32
30.42
29.26
18.12
16.61
16.55
-1.40
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


O
P
OEt
Ph
N
N
NC
SEM
8b
7.92 7.90 7.89 7.88 7.87 7.86
7.56 7.56 7.54 7.54 7.49 7.48 7.48 7.47 7.47 7.47 7.46 7.46 7.45
7.31 7.30 7.26
4.21 4.20 4.19 4.19 4.19 4.18 4.18 4.17 4.16 4.16 4.16 4.15 4.14 4.14 4.14 4.13 4.13 4.13 4.12 4.11 4.10 4.10
3.59 3.58 3.57 3.57 3.57 3.56 3.55
0.91 0.90 0.89 0.89 0.87 0.87
-0.07
f1 (ppm)
5.63
1.39 1.37 1.36
1.90 0.97 1.97 0.92 1.99 2.03 2.00 3.00 2.06 8.72
f1 (ppm)


O
P
OEt
Ph
N
N
NC
SEM
8b
147.72
146.04
132.97
132.94
131.91
131.81
130.85
129.39
128.82
128.68
120.44
120.24
116.29
116.20
109.51
80.37
68.09
62.16
62.10
17.69
16.63
16.56
-1.41
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
P
Ph
Ph
N
N
NC
SEM
8c
7.81 7.81 7.79 7.79 7.78 7.77 7.76 7.75
7.56 7.56 7.54 7.54 7.49 7.49 7.49 7.49 7.48 7.48 7.47 7.47 7.47 7.46 7.45
7.37 7.37
3.60 3.59 3.58 3.58 3.58 3.57 3.56
0.92 0.92 0.91 0.90 0.90 0.89 0.89 0.88
0.06
7.8 7.7 7.6 7.5 7.4 7.3 3.6 3.5 3.4 1.0 0.9 0.8
f1 (ppm)
7.81 7.81 7.80 7.79 7.79 7.78 7.77 7.77 7.76 7.75 7.56 7.56 7.54 7.54 7.49 7.49 7.49 7.49 7.49 7.48 7.48 7.47 7.47 7.47 7.46 7.45 7.45 7.45 7.37 7.37 7.26
5.64
3.60 3.59 3.58 3.58 3.58 3.57 3.56
0.92 0.92 0.91 0.90 0.90 0.89 0.89 0.88
3.90 1.96 3.95 0.92 2.03 2.00 2.14 8.87
11.5 10.5 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
P
Ph
Ph
N
N
NC
SEM
8c
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132.3006
131.8093
131.7068
131.2097
128.7880
128.6613
120.9583
120.7814
116.4519
116.3712
132
130
128
126
124
122
120
118
116
f1 (ppm)
132.54
132.51
132.30
131.81
131.71
131.21
128.79
128.66
148.80
147.52
120.96
120.78
116.45
116.37
109.54
80.40
68.13
17.73
-1.37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)