

**TRIPHOSGENE-AMINE BASE PROMOTED CHLORINATION OF UNACTIVATED
ALIPHATIC ALCOHOLS**

Andrés Villalpando, Caitlan E. Ayala, Christopher B. Watson, and Rendy Kartika*

Department of Chemistry
232 Choppin Hall
Louisiana State University
Baton Rouge, Louisiana 70803, USA

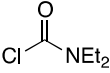
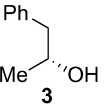
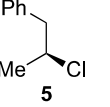
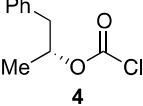
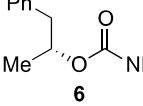
email: rkartika@lsu.edu

SUPPORTING INFORMATION

| | |
|--|------|
| 1. GC-MS Studies..... | S-2 |
| 2. ¹ H and ¹³ C NMR Spectra..... | S-22 |

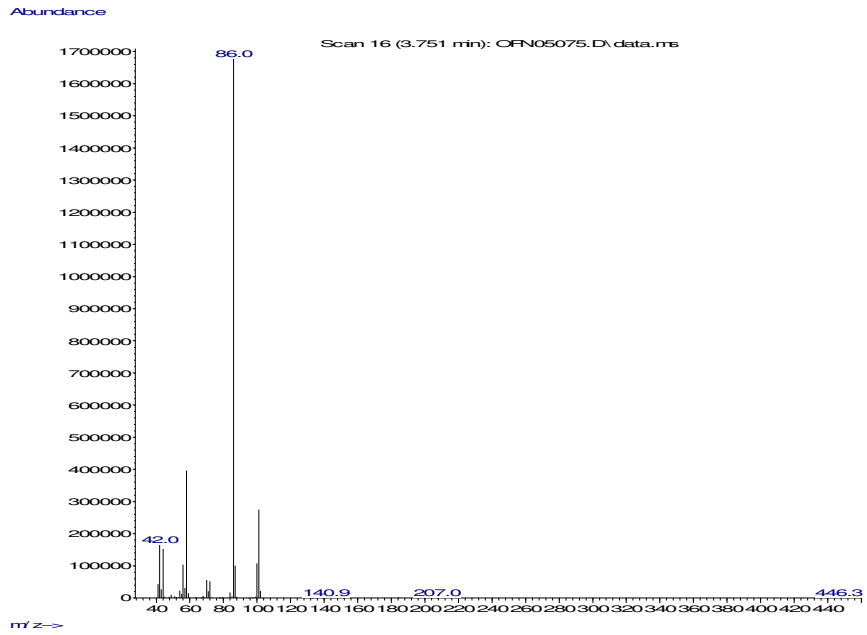
Gas Chromatography – Mass Spectrometry Study

The following table indicates the relevant peaks in the GC-MS studies. The table lists retention time and the corresponding compounds for each peak. Mass spectra of each compound are also included.

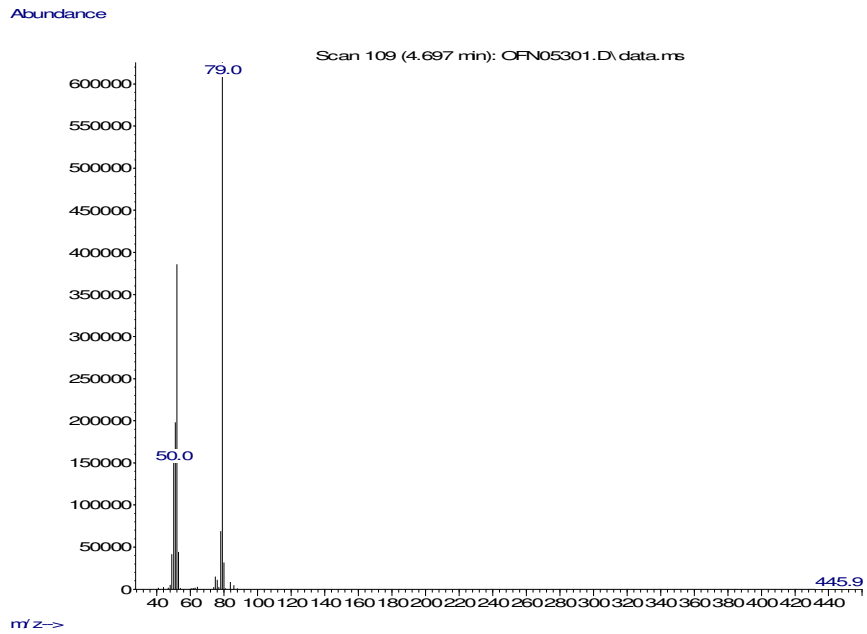
| Retention Time (min) | Compounds |
|----------------------|---|
| 3.75 | Et ₃ N |
| 4.69 | Pyridine |
| 5.18 | Toluene |
| 9.57 ^a |  |
| 11.67 |  3 |
| 11.99 |  5 |
| 14.31 |  4 |
| 18.27 |  6 |

^a Discussion on the formation of diethylcarbamoyl chloride, see: Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T.; Kartika, R. *Org. Lett.* **2012**, *14*, 3676-3679.

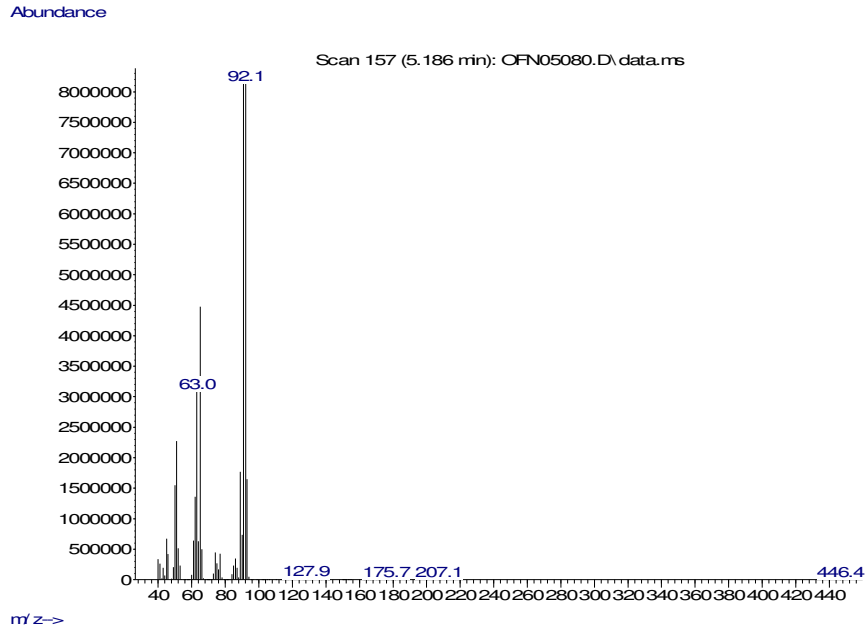
Retention time: 3.75 minutes (triethylamine)



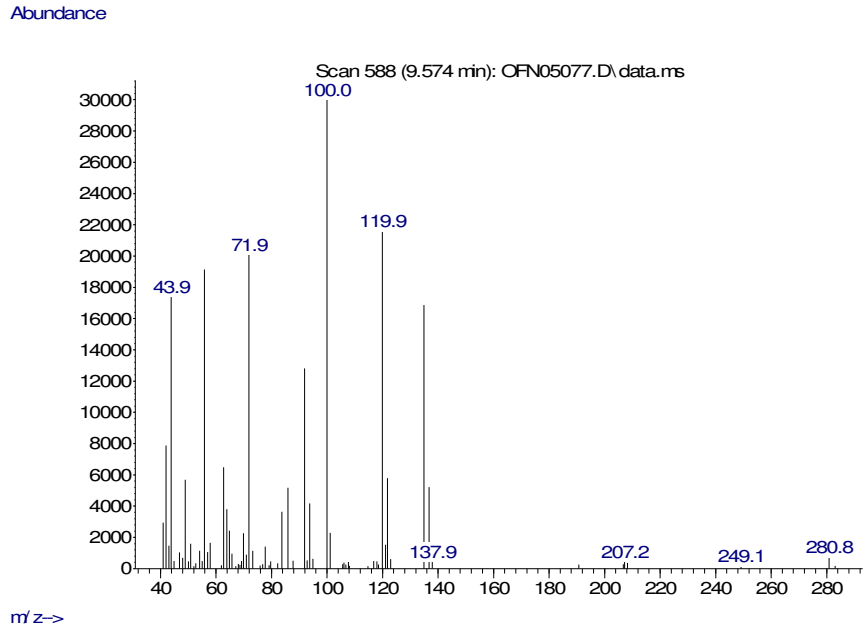
Retention time: 4.69 minutes (pyridine)



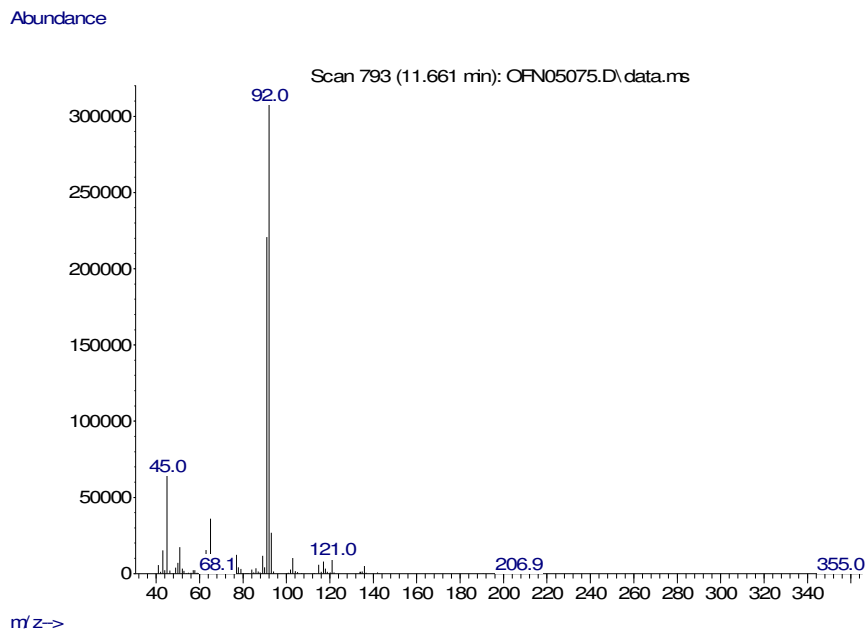
Retention time: 5.18 minutes (toluene)



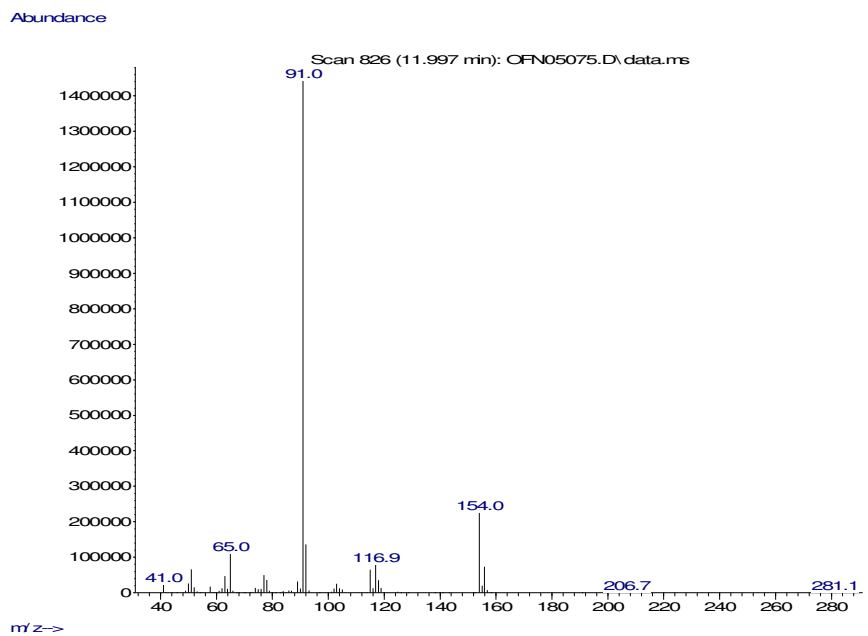
Retention time: 9.57 minutes (diethylcarbamic chloride)



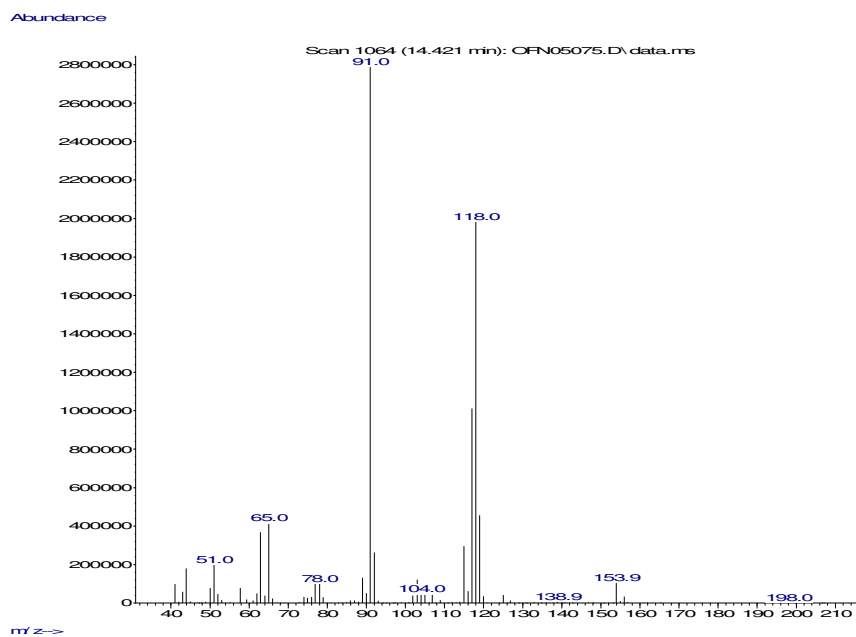
Retention time: 11.67 minutes ((R)-1-phenylpropan-2-ol 3)



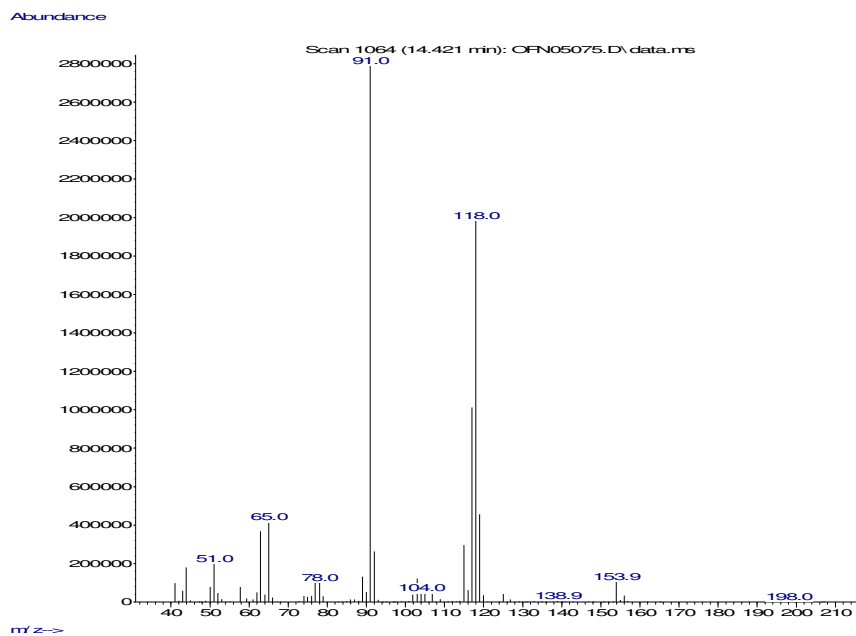
Retention time: 11.99 minutes ((S)-(2-chloropropyl)benzene 5)



Retention time: 14.31 minutes ((R)-1-phenylpropan-2-yl carbonochloridate 4)



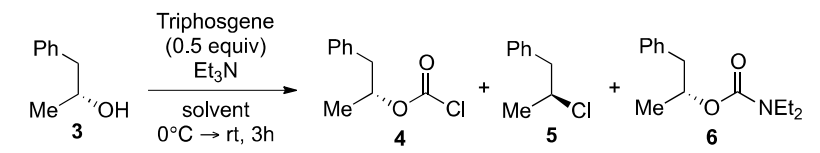
Retention time: 18.27 minutes ((R)-1-phenylpropan-2-yl diethylcarbamate 6)



GC-MS Study #1: Effect of Triethylamine Equivalence in the Triphosgene-Amine Base Chlorination Reaction.

Protocol: Alcohol **3** (68.1 mg, 0.50 mmol) was dissolved in 3.75 mL of CH₂Cl₂ (entries 1-5) or toluene (entries 6-10) inside a pressure vessel. The indicated amount of triethylamine was added to the solution and allowed to stir for 5 minutes. Triphosgene (74.2 mg, 0.25 mmol) was added to the reaction mixture. The vessel was sealed, and the reaction was allowed to stir at room temperature. After stirring for 3 hours, a small aliquot was taken out and diluted with CH₂Cl₂. The sample was then directly injected to the GC-MS instrument without further workup.

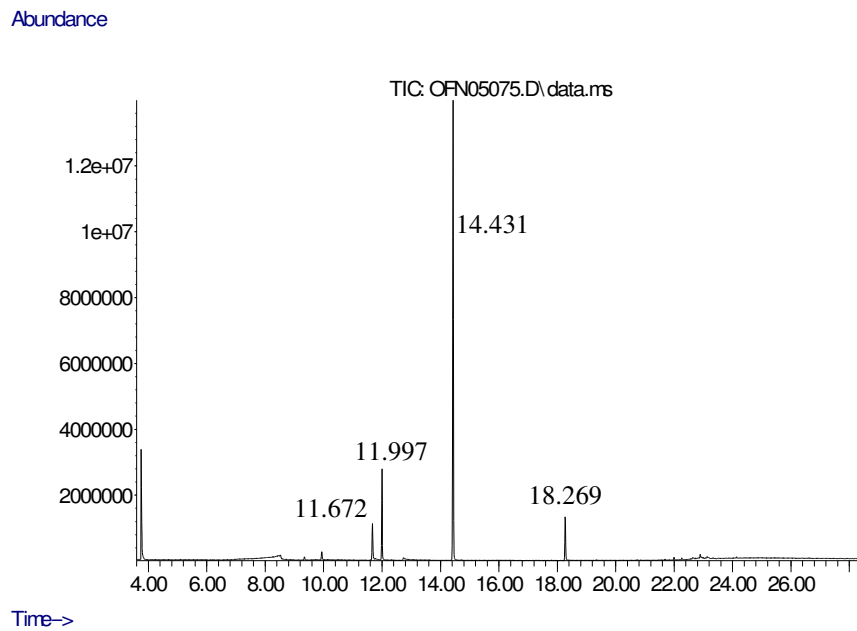
Table 1. Optimization Study with Varying the amount of Triethylamine



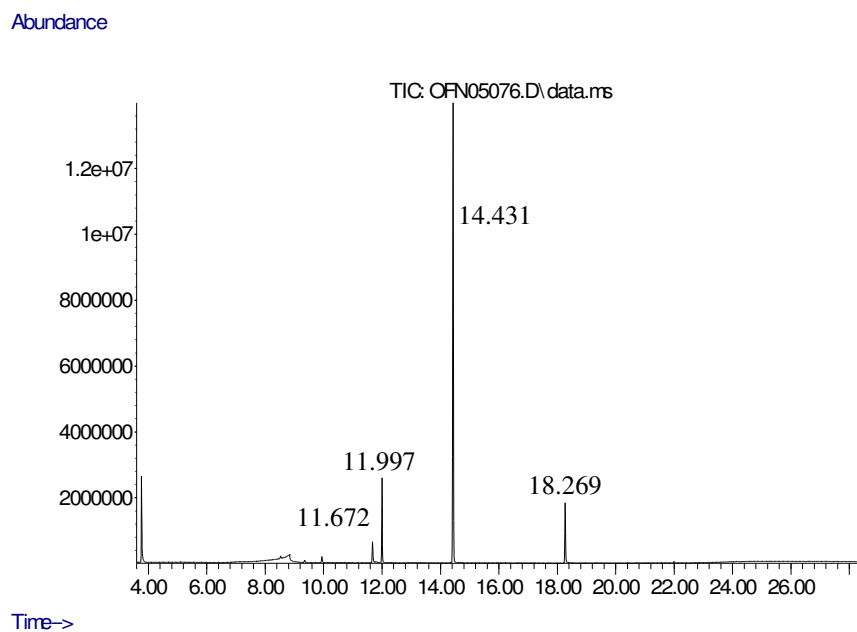
| entry | equiv Et ₃ N | solvent | yield 3 ^(a) | yield 4 ^(a) | yield 5 ^(a) | yield 6 ^(a) |
|-------|-------------------------|---------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| 1 | 1.00 | CH ₂ Cl ₂ | 6% | 73% | 14% | 7% |
| 2 | 1.25 | CH ₂ Cl ₂ | 3% | 75% | 13% | 9% |
| 3 | 1.50 | CH ₂ Cl ₂ | 2% | 45% | 27% | 27% |
| 4 | 1.75 | CH ₂ Cl ₂ | 1% | 16% | 44% | 39% |
| 5 | 2.00 | CH ₂ Cl ₂ | 0% | 3% | 51% | 46% |
| 6 | 1.00 | toluene | 11% | 86% | 3% | 0% |
| 7 | 1.25 | toluene | 3% | 87% | 5% | 5% |
| 8 | 1.50 | toluene | 2% | 87% | 6% | 5% |
| 9 | 1.75 | toluene | 1% | 54% | 18% | 27% |
| 10 | 2.00 | toluene | 2% | 65% | 21% | 13% |

^a Yields were determined by GC-MS analysis of the crude mixtures assuming that these compounds elicited identical GC responses.

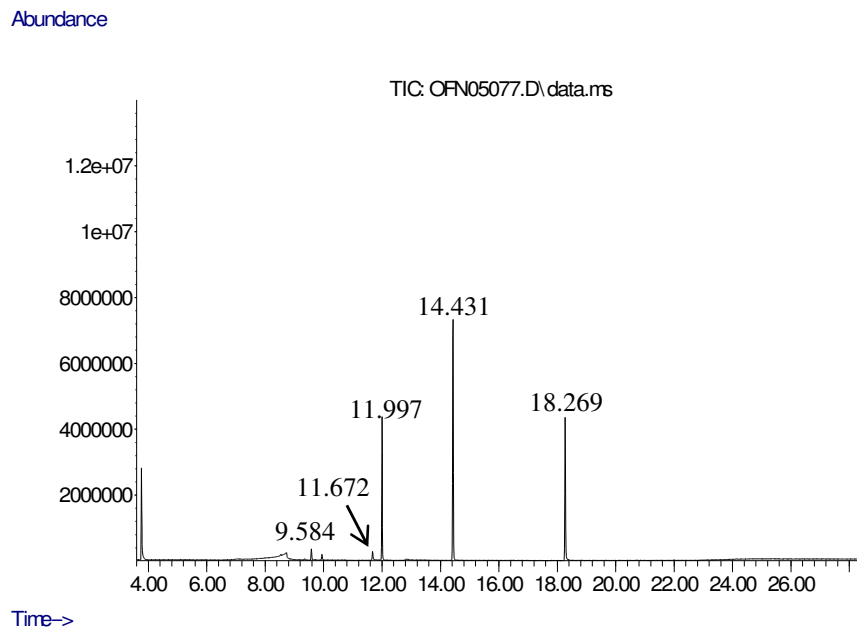
Entry 1: CH₂Cl₂, 1.00 equivalent of triethylamine (70 μL, 0.50 mmol)



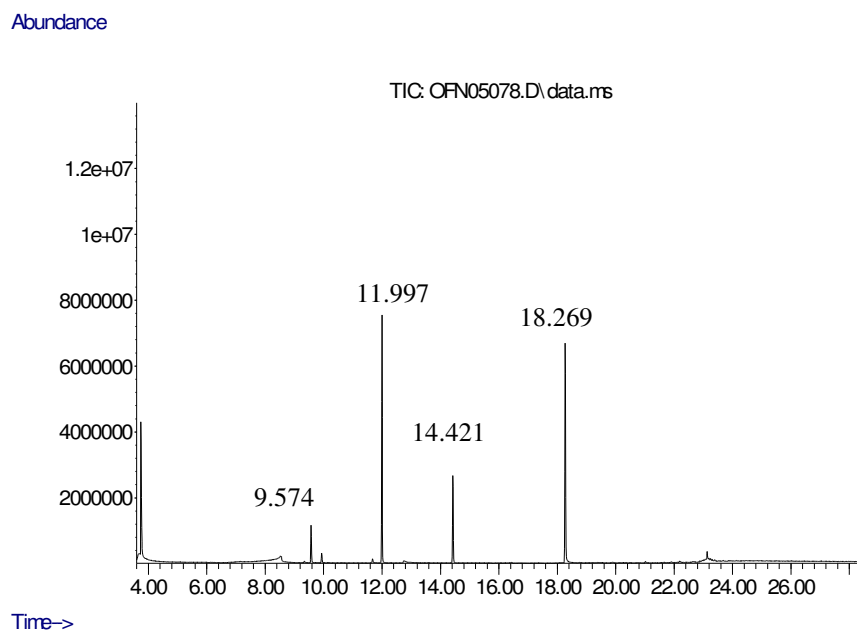
Entry 2: CH₂Cl₂, 1.25 equivalent of triethylamine (87 μL, 0.63 mmol)



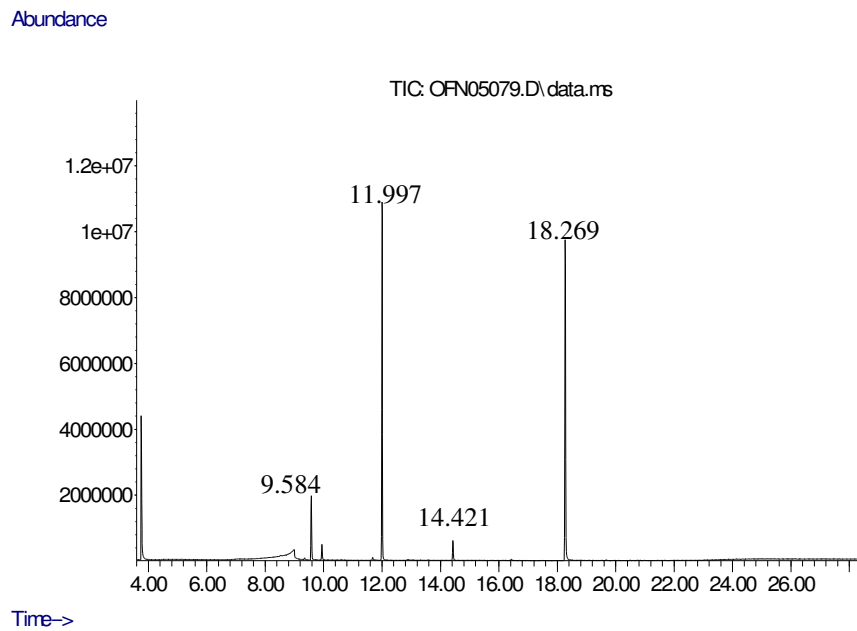
Entry 3: CH₂Cl₂, 1.50 equivalent of triethylamine (105 μL, 0.75 mmol)



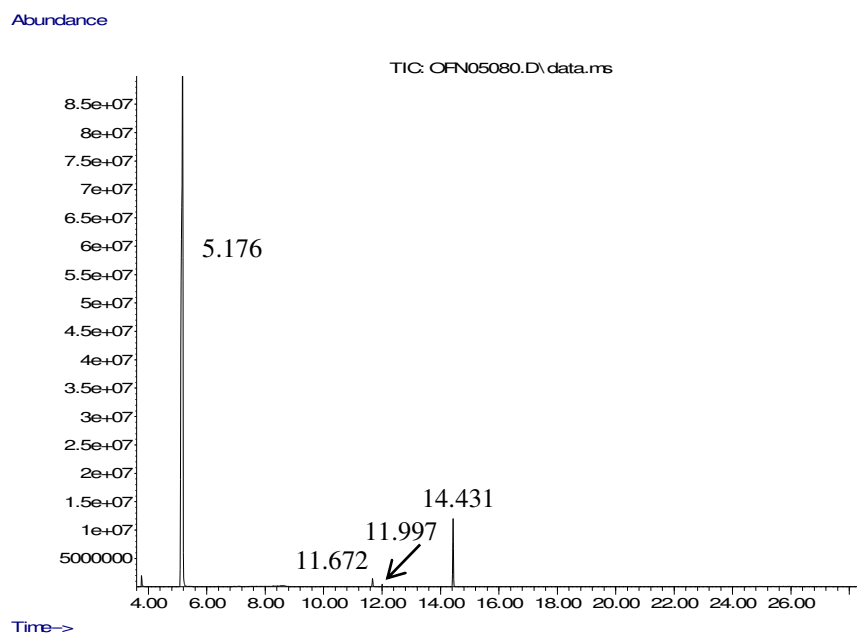
Entry 4: CH₂Cl₂, 1.75 equivalent of triethylamine (122 μL, 0.88 mmol)



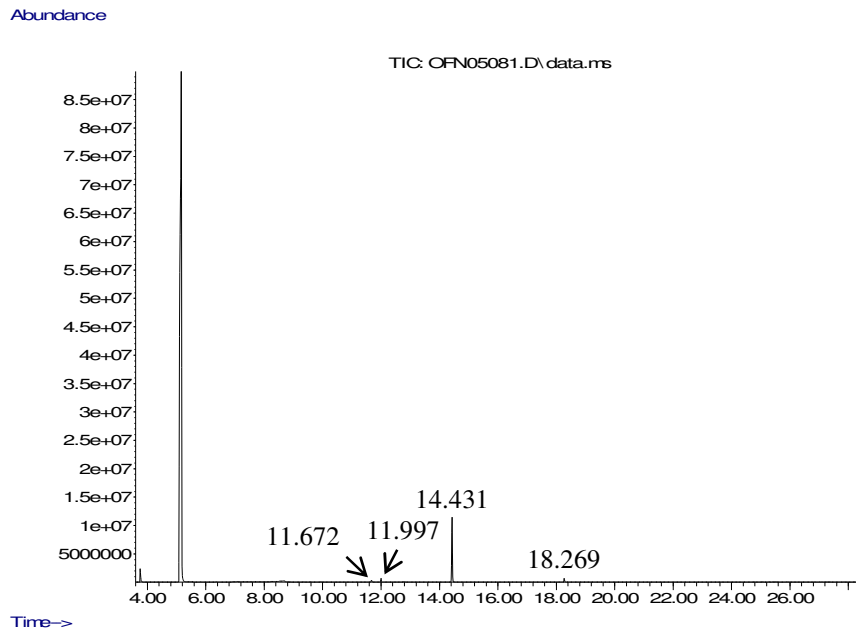
Entry 5: CH₂Cl₂, 2.00 equivalent of triethylamine (139 μL, 1.00 mmol)



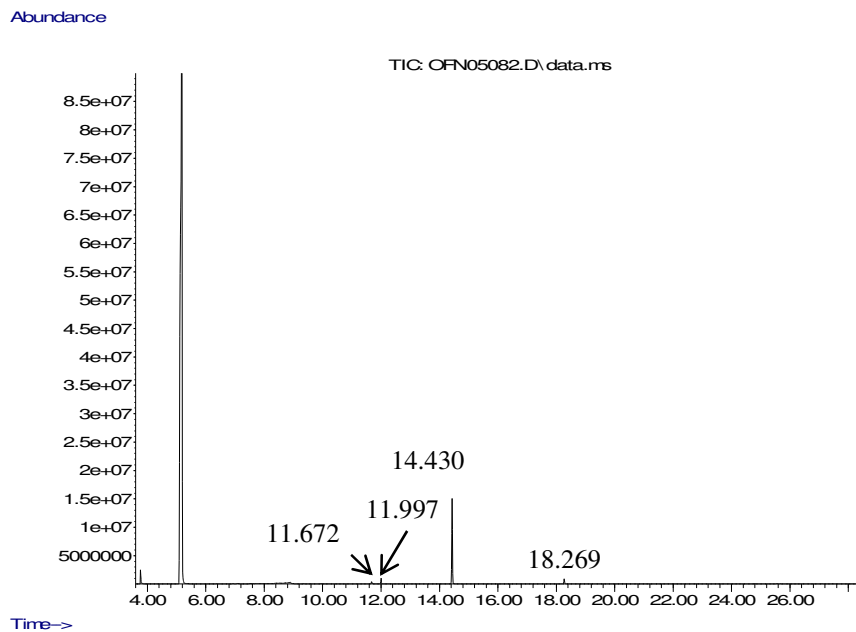
Entry 6: Toluene, 1.00 equivalent of triethylamine (70 μL, 0.50 mmol)



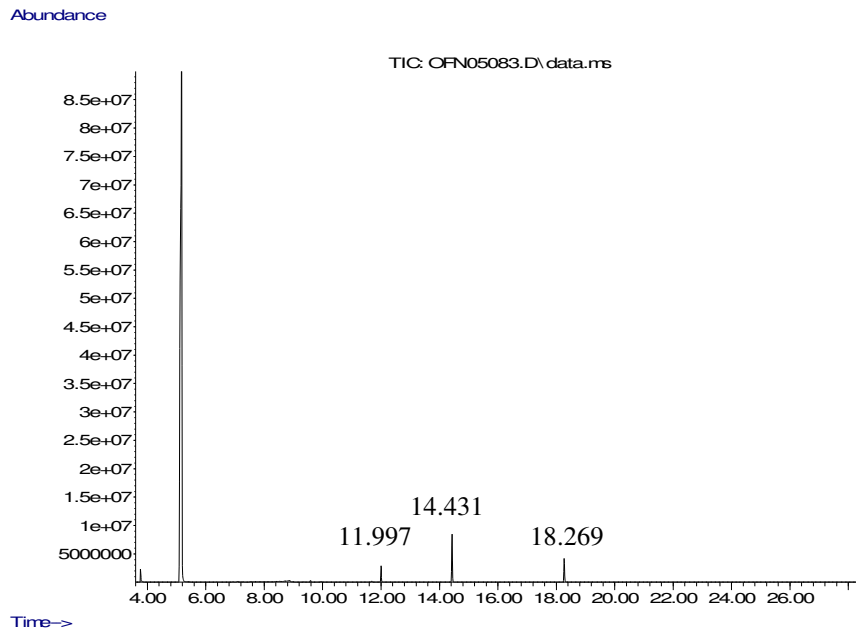
Entry 7: Toluene, 1.25 equivalent of triethylamine (87 μ L, 0.63 mmol)



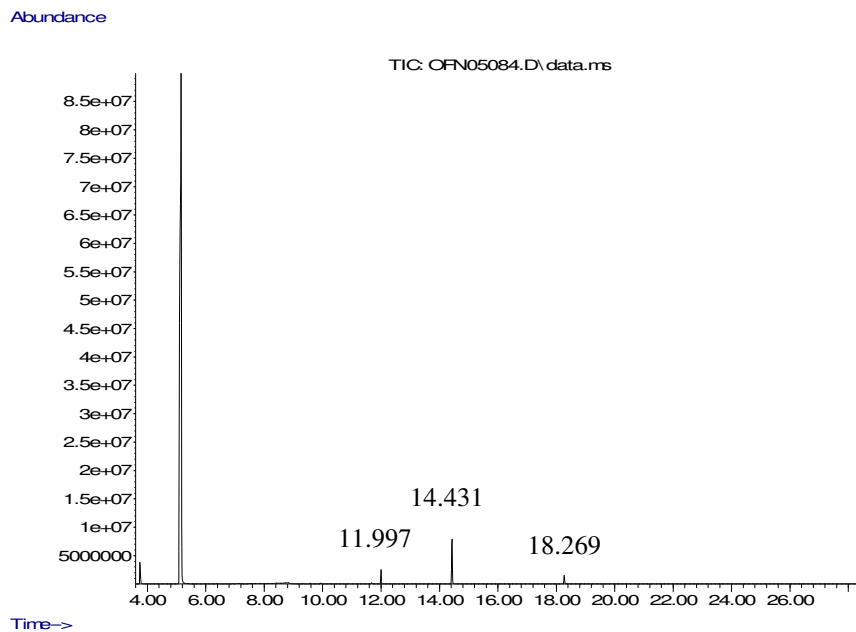
Entry 8: Toluene, 1.50 equivalent of triethylamine (105 μ L, 0.75 mmol)



Entry 9: Toluene, 1.75 equivalent of triethylamine (122 μ L, 0.88 mmol)



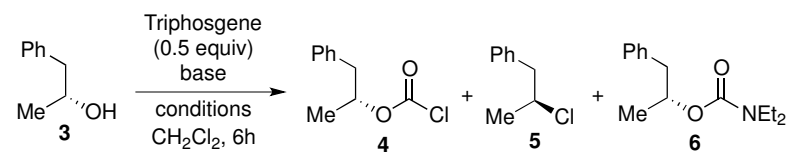
Entry 10: Toluene, 2.00 equivalent of triethylamine (139 μ L, 1.00 mmol)



GC-MS Study #2: Effect of Triethylamine-Pyridine Mixture in the Triphosgene-Amine Base Chlorination Reaction.

Protocol: Alcohol **3** (68.1 mg, 0.50 mmol) was dissolved in 3.75 mL of CH₂Cl₂ inside a pressure vessel. The indicated amount of triethylamine and pyridine was added to the solution and allowed to stir for 5 minutes. Triphosgene (74.2 mg, 0.25 mmol) was added to the reaction mixture. The vessel was sealed, and the reaction was allowed to stir either at room temperature (entries 1-4, 9-12) or in a heating bath at 40°C (entries 5-8, 13-16). After stirring for 6 hours, a small aliquot was taken out and diluted with CH₂Cl₂. The sample was then directly injected to the GC-MS instrument without further workup.

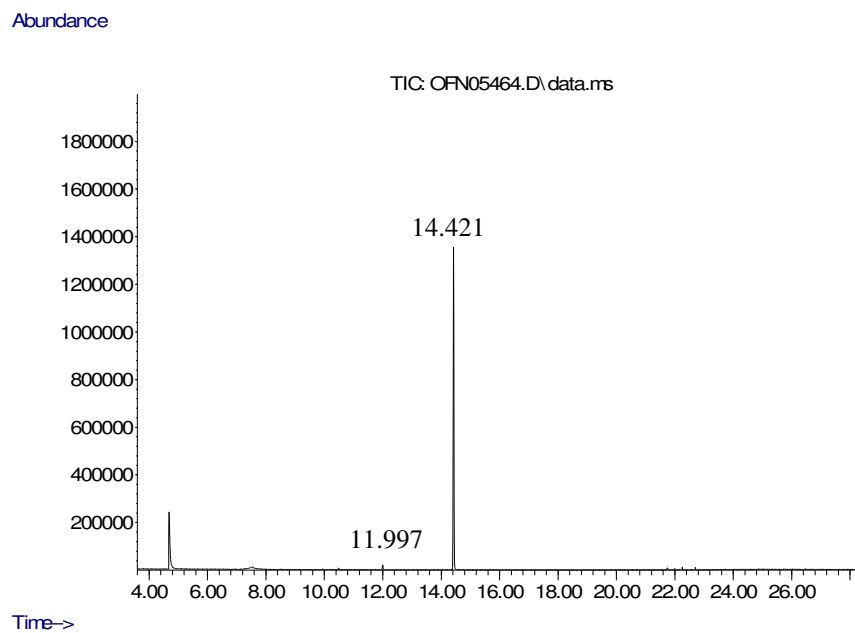
Table 2. Optimization Study with Mixed Amine Base Systems



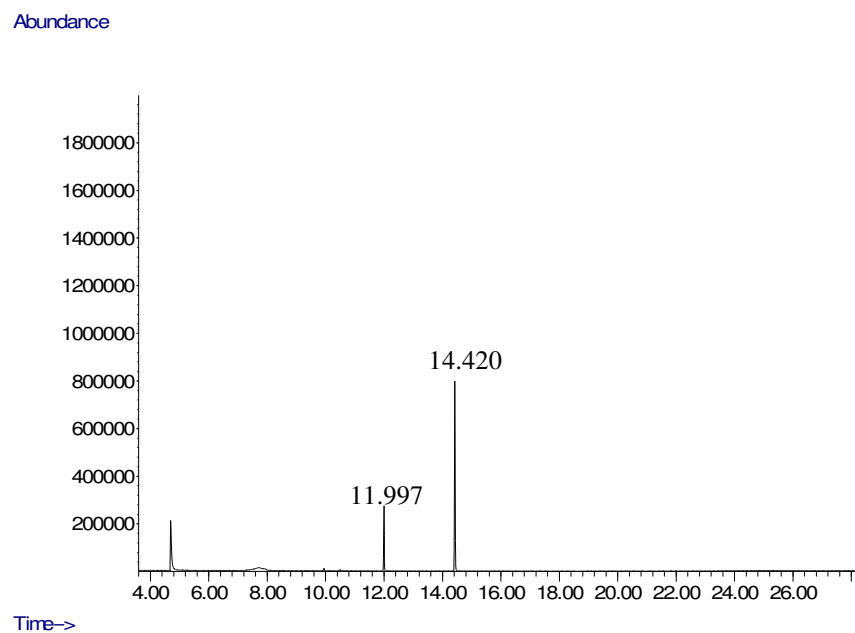
| entry | equiv Py | equiv Et ₃ N | conditions ^(a) | yield 3 ^(b) | yield 4 ^(b) | yield 5 ^(b) | yield 6 ^(b) |
|-------|----------|-------------------------|---------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| 1 | 1.2 | 0.25 | 0 °C → rt | 0% | 98% | 1% | 1% |
| 2 | 1.2 | 0.50 | 0 °C → rt | 0% | 75% | 25% | 0% |
| 3 | 1.2 | 0.75 | 0 °C → rt | 0% | 60% | 39% | 0% |
| 4 | 1.2 | 1.00 | 0 °C → rt | 0% | 50% | 50% | 0% |
| 5 | 1.2 | 0.25 | 0 °C → reflux | 0% | 34% | 66% | 0% |
| 6 | 1.2 | 0.50 | 0 °C → reflux | 0% | 9% | 90% | 1% |
| 7 | 1.2 | 0.75 | 0 °C → reflux | 0% | 0% | 100% | 0% |
| 8 | 1.2 | 1.00 | 0 °C → reflux | 0% | 1% | 90% | 9% |
| 9 | 1.0 | 0 | 0 °C → rt | 93% | 0% | 7% | 0% |
| 10 | 1.2 | 0 | 0 °C → rt | 75% | 0% | 25% | 0% |
| 11 | 1.7 | 0 | 0 °C → rt | 35% | 0% | 65% | 0% |
| 12 | 2.2 | 0 | 0 °C → rt | 28% | 0% | 72% | 0% |
| 13 | 1.0 | 0 | 0 °C → reflux | 69% | 0% | 31% | 0% |
| 14 | 1.2 | 0 | 0 °C → reflux | 0% | 44% | 56% | 0% |
| 15 | 1.7 | 0 | 0 °C → reflux | 2% | 0% | 98% | 0% |
| 16 | 2.2 | 0 | 0 °C → reflux | 0% | 0% | 100% | 0% |

^a Reagents were added at 0°C then the reaction mixture was warmed to room temperature or reflux. ^b Yields were determined by GC-MS analysis of the crude mixtures assuming that these compounds elicited identical GC responses.

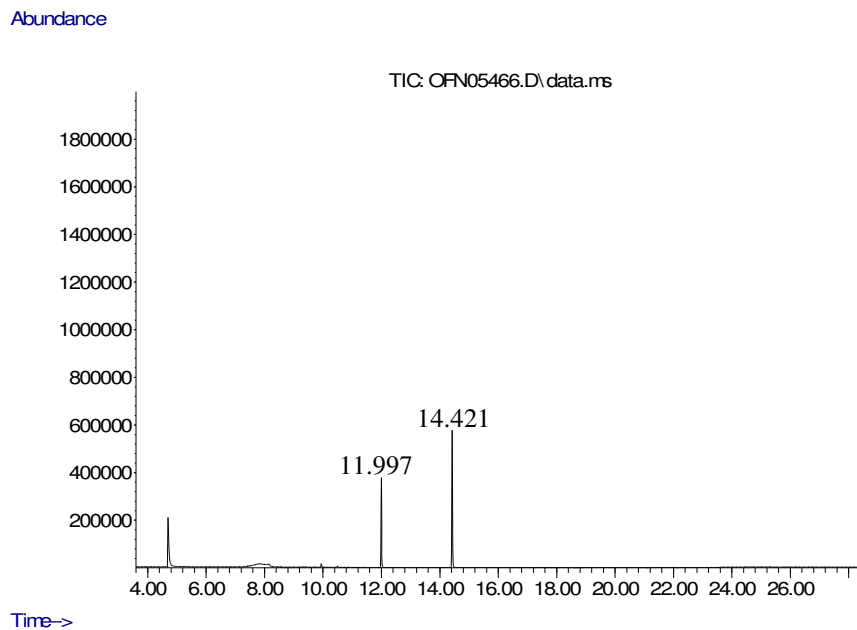
Entry 1: Room temperature, 1.2 equivalent of pyridine (48 μL , 0.60 mmol) and 0.25 equivalent of triethylamine (17 μL , 0.13 mmol)



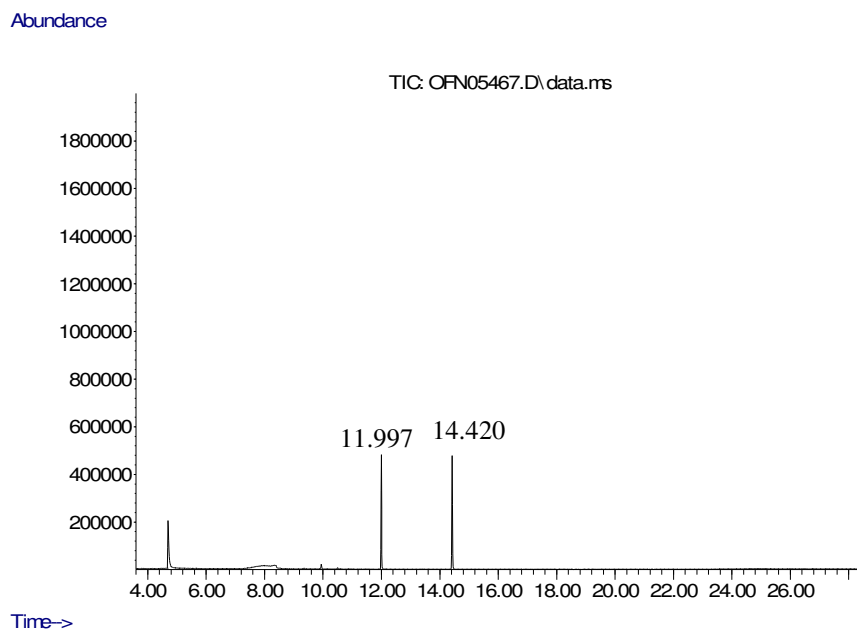
Entry 2: Room temperature, 1.2 equivalent of pyridine (48 μL , 0.60 mmol) and 0.50 equivalent of triethylamine (35 μL , 0.25 mmol)



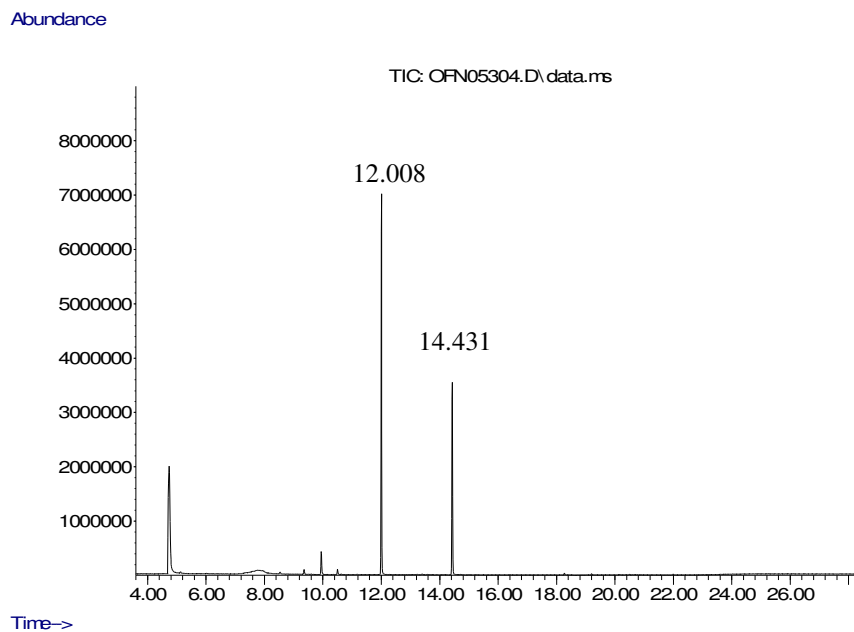
Entry 3: Room temperature, 1.2 equivalent of pyridine (48 μ L, 0.60 mmol) and 0.75 equivalent of triethylamine (52 μ L, 0.38 mmol)



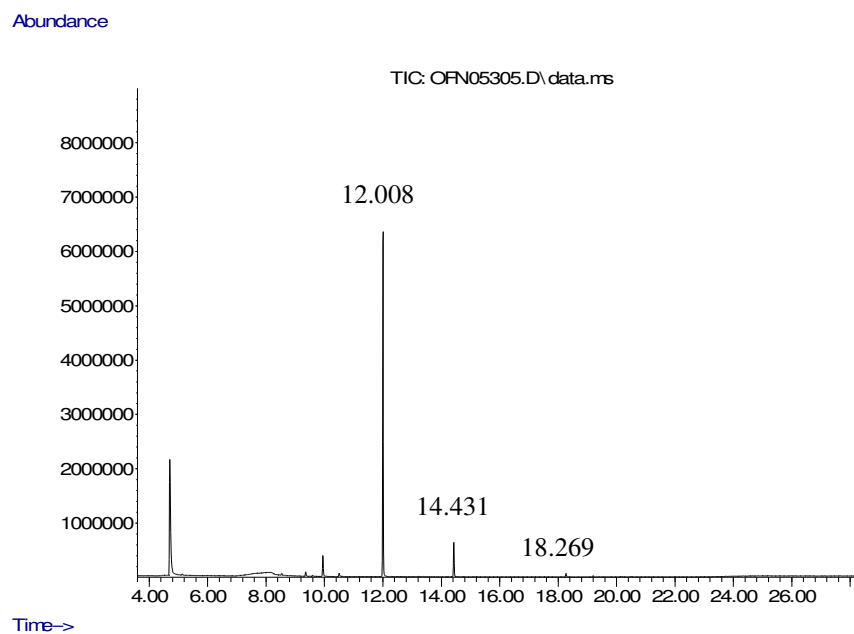
Entry 4: Room temperature, 1.2 equivalent of pyridine (48 μ L, 0.60 mmol) and 1.00 equivalent of triethylamine (52 μ L, 0.38 mmol)



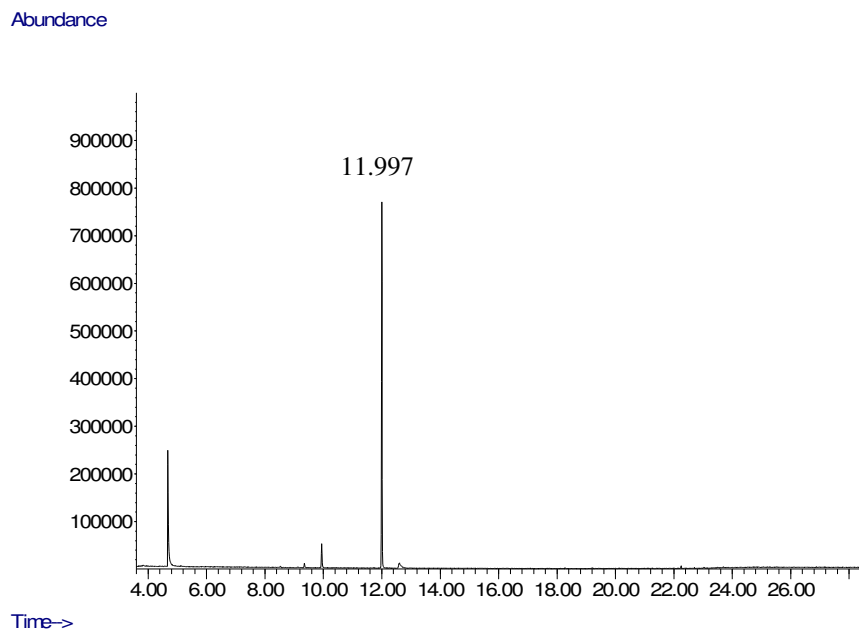
Entry 5: Reflux, 1.2 equivalent of pyridine (48 μL , 0.60 mmol) and 0.25 equivalent of triethylamine (17 μL , 0.13 mmol)



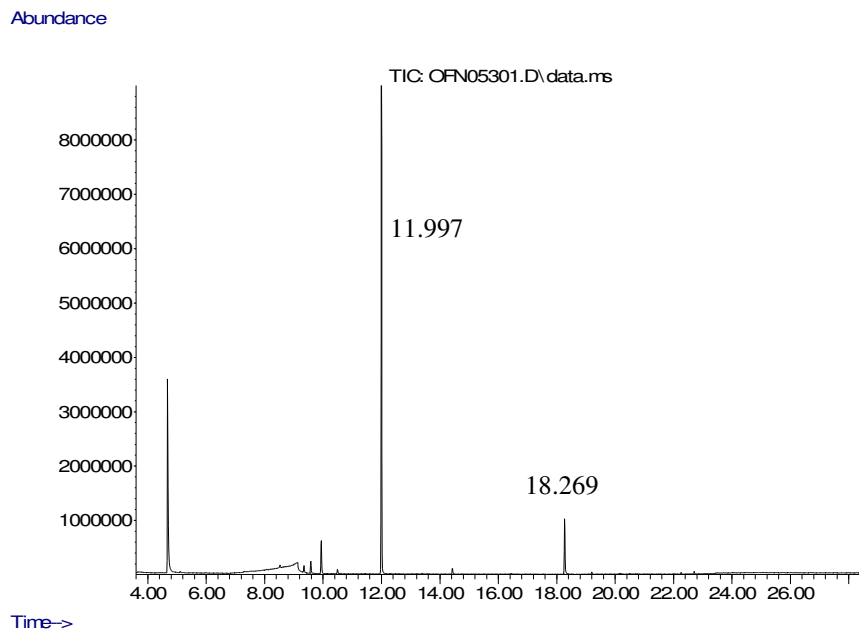
Entry 6: Reflux, 1.2 equivalent of pyridine (48 μL , 0.60 mmol) and 0.50 equivalent of triethylamine (35 μL , 0.25 mmol)



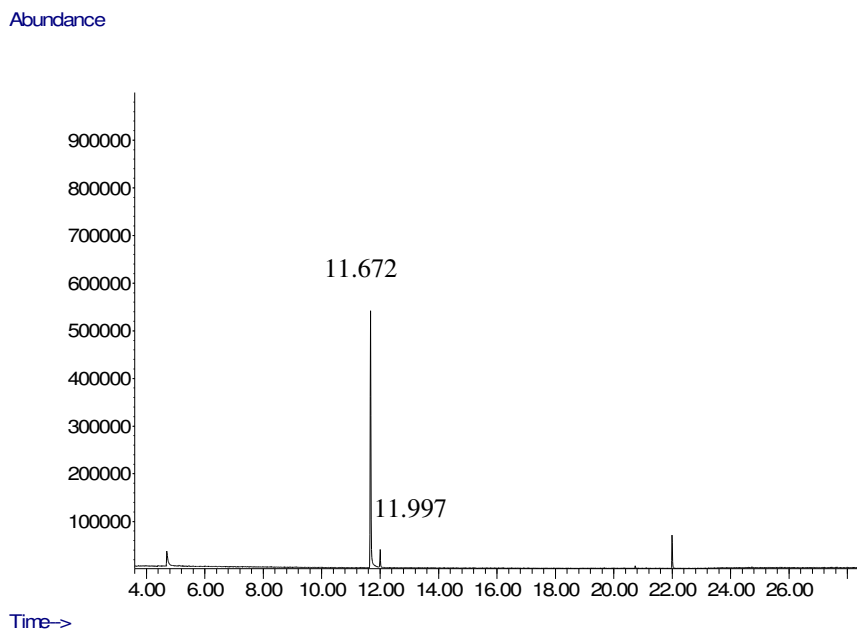
Entry 7: Reflux, 1.2 equivalent of pyridine (48 μL , 0.60 mmol) and 0.75 equivalent of triethylamine (52 μL , 0.38 mmol)



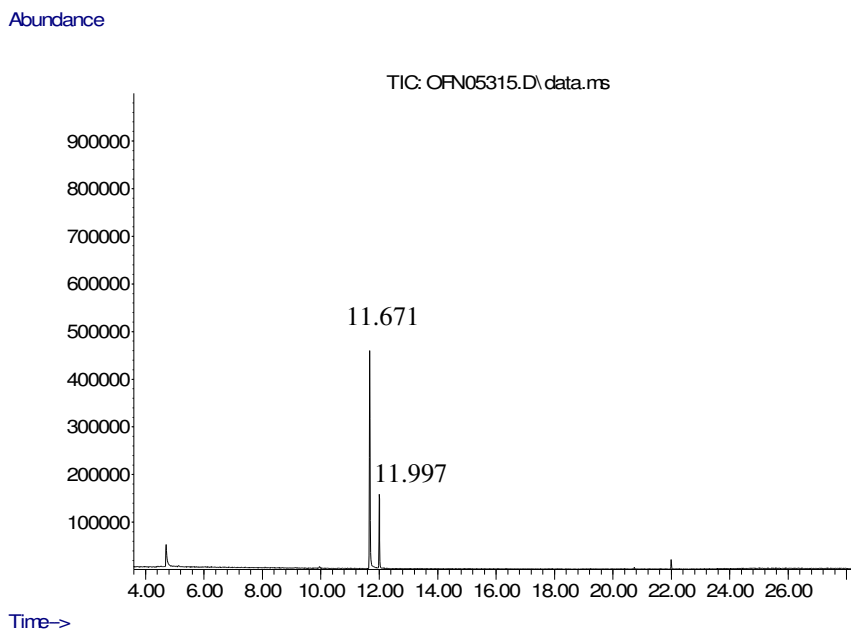
Entry 8: Reflux, 1.2 equivalent of pyridine (48 μL , 0.60 mmol) and 1.00 equivalent of triethylamine (52 μL , 0.38 mmol)



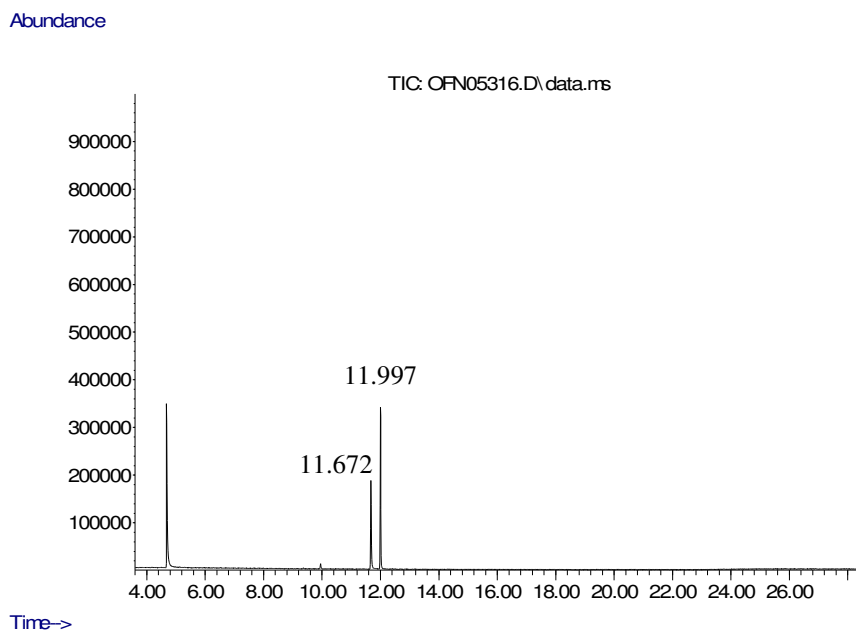
Entry 9: Room temperature, 1.0 equivalent of pyridine (40 μ L, 0.50 mmol)



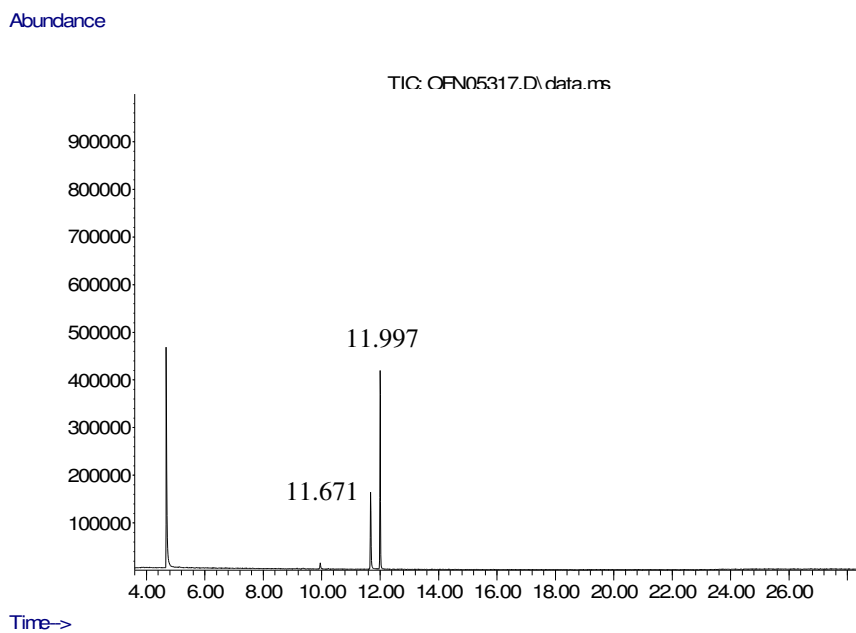
Entry 10: Room temperature, 1.2 equivalent of pyridine (48 μ L, 0.60 mmol)



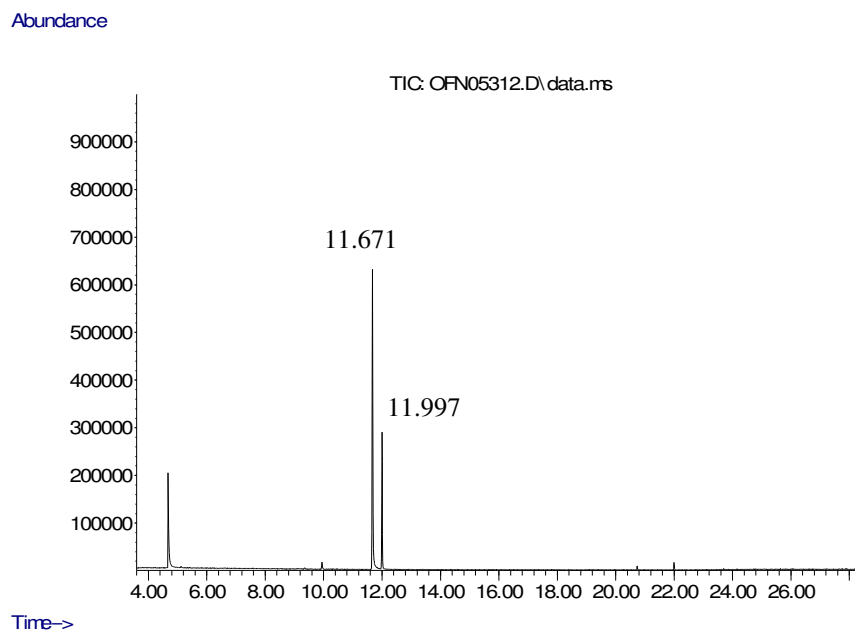
Entry 11: Room temperature, 1.7 equivalent of pyridine (48 μL , 0.60 mmol)



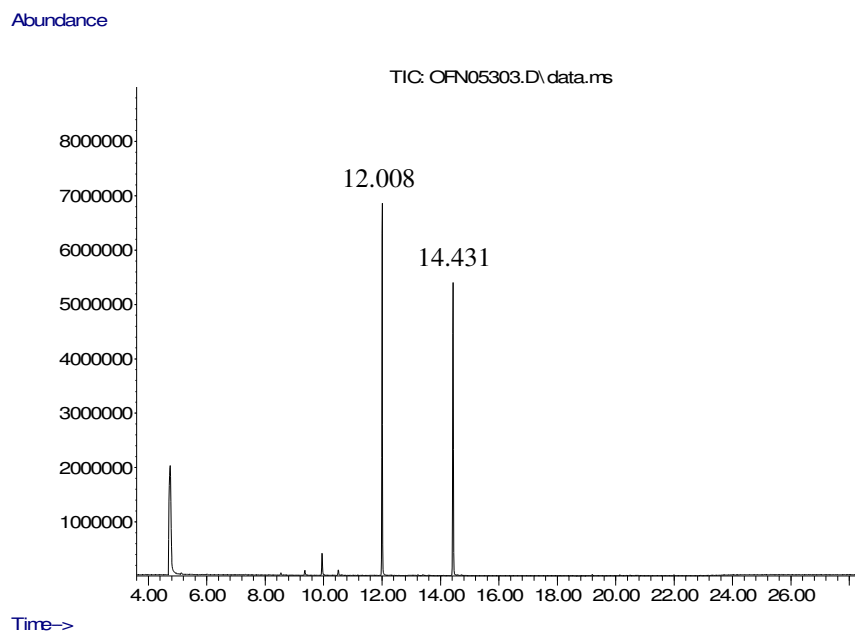
Entry 12: Room temperature, 2.2 equivalent of pyridine (89 μL , 1.10 mmol)



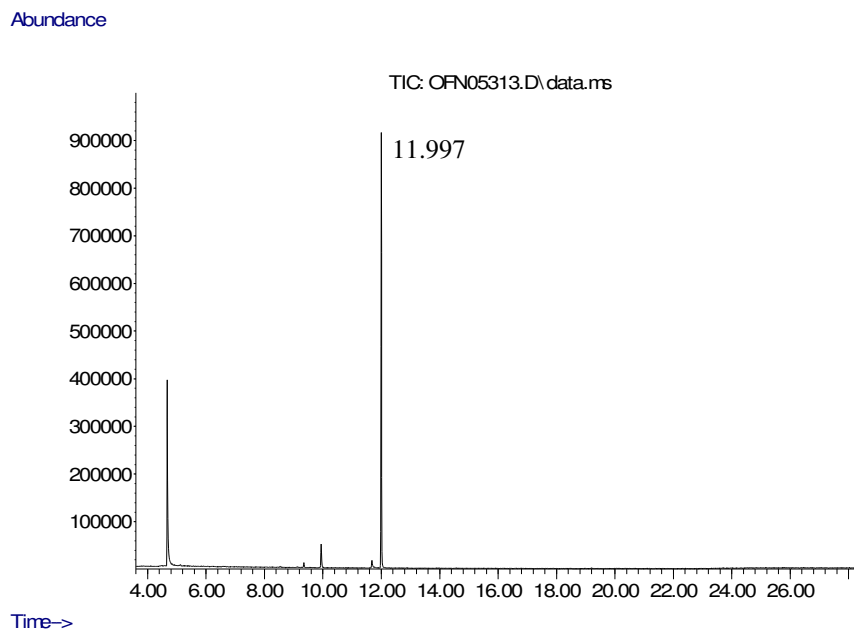
Entry 13: Reflux, 1.0 equivalent of pyridine (40 μ L, 0.50 mmol)



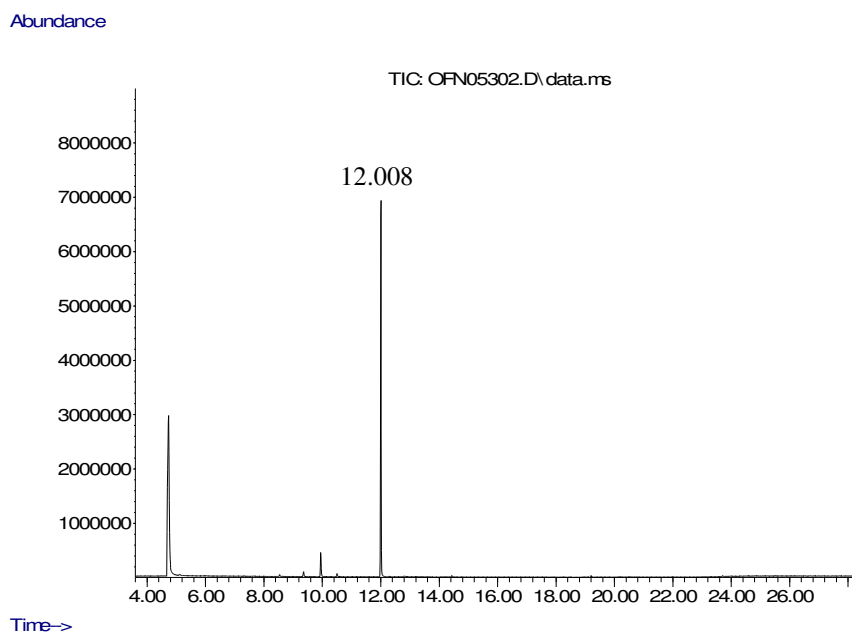
Entry 14: Reflux, 1.2 equivalent of pyridine (48 μ L, 0.60 mmol)

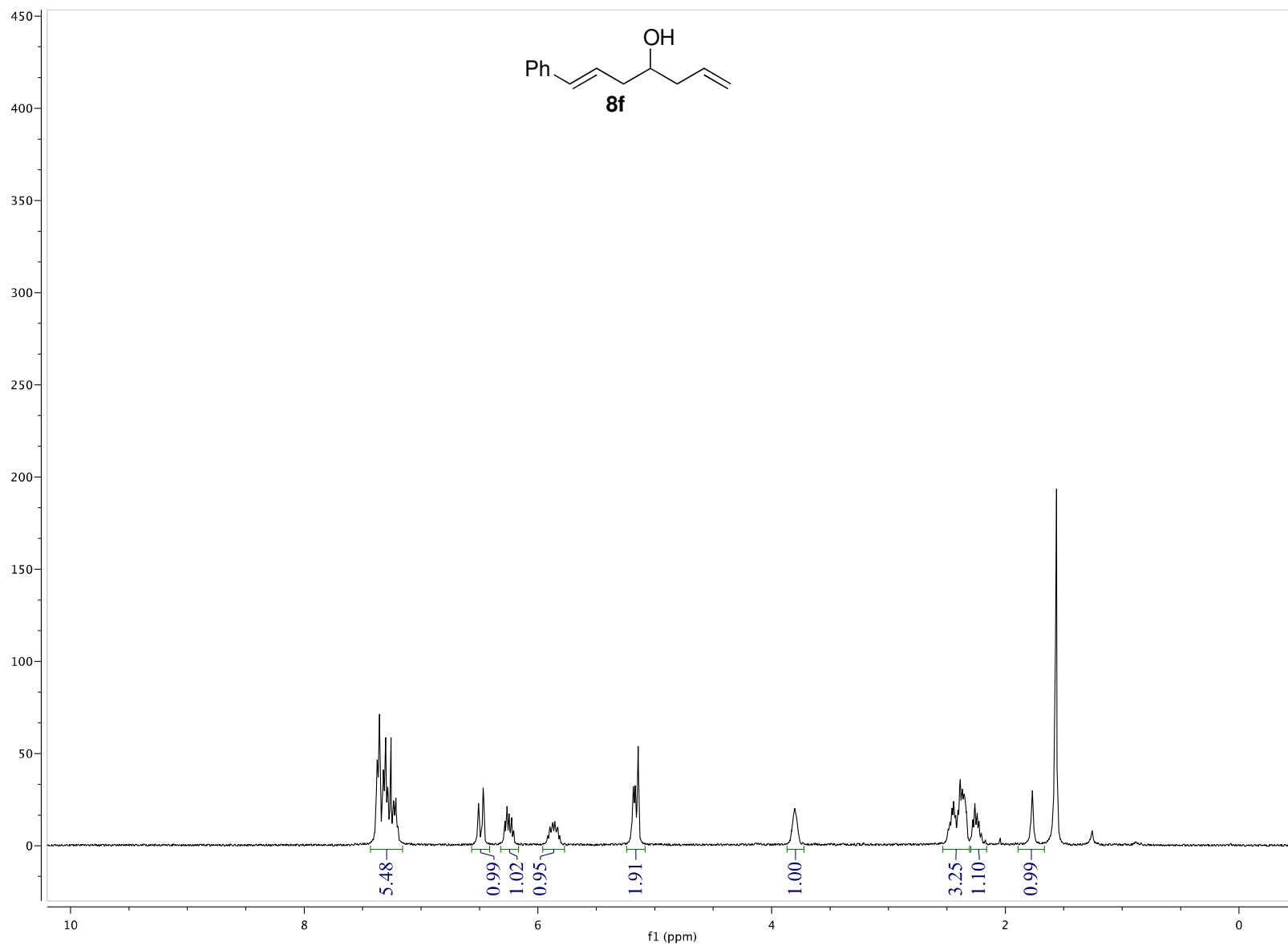


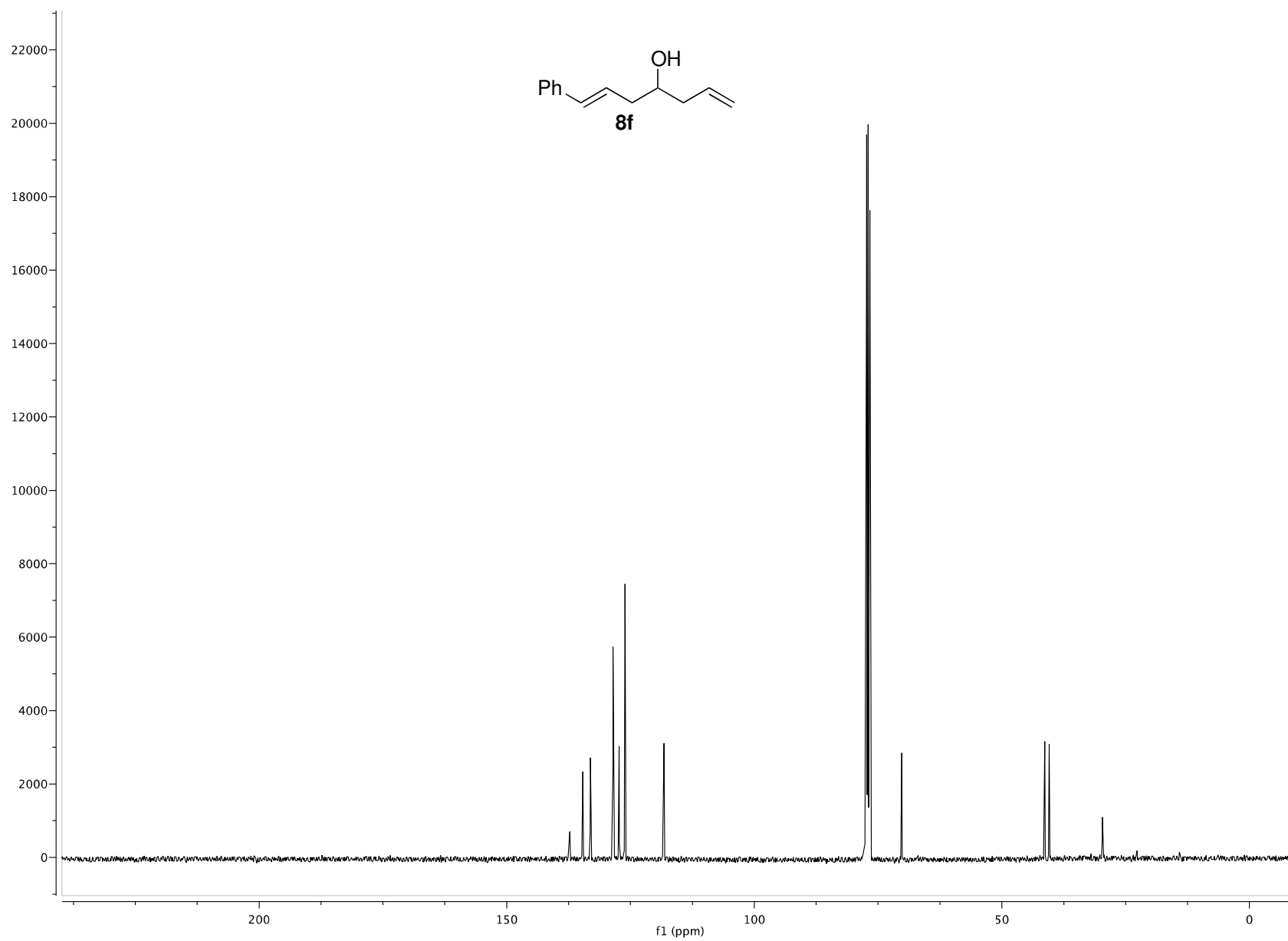
Entry 15: Room temperature, 1.7 equivalent of pyridine (48 μ L, 0.60 mmol)

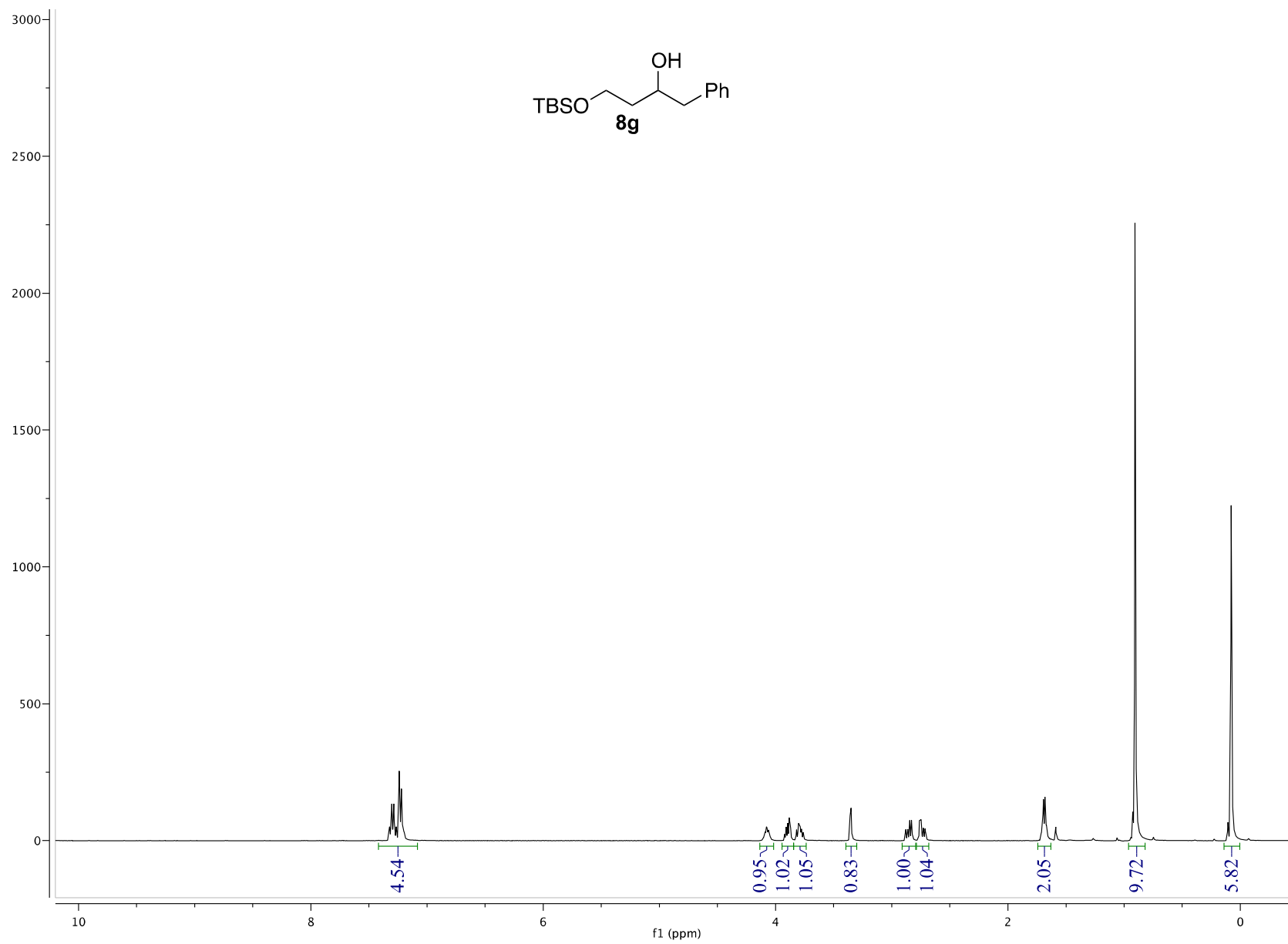
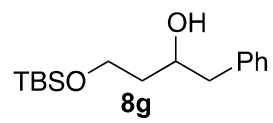


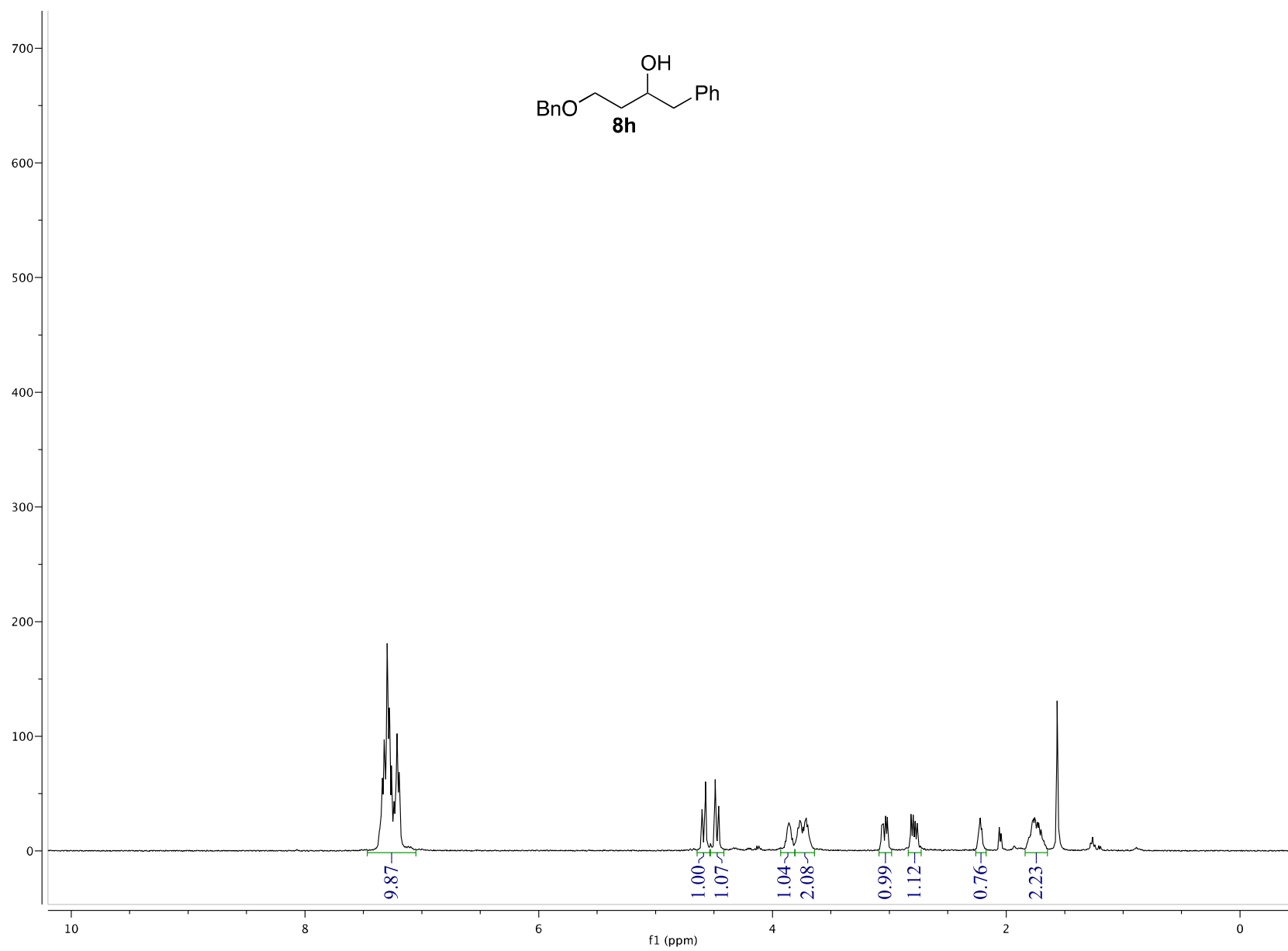
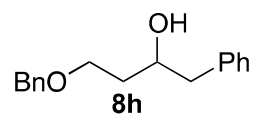
Entry 16: Room temperature, 2.2 equivalent of pyridine (89 μ L, 1.10 mmol)

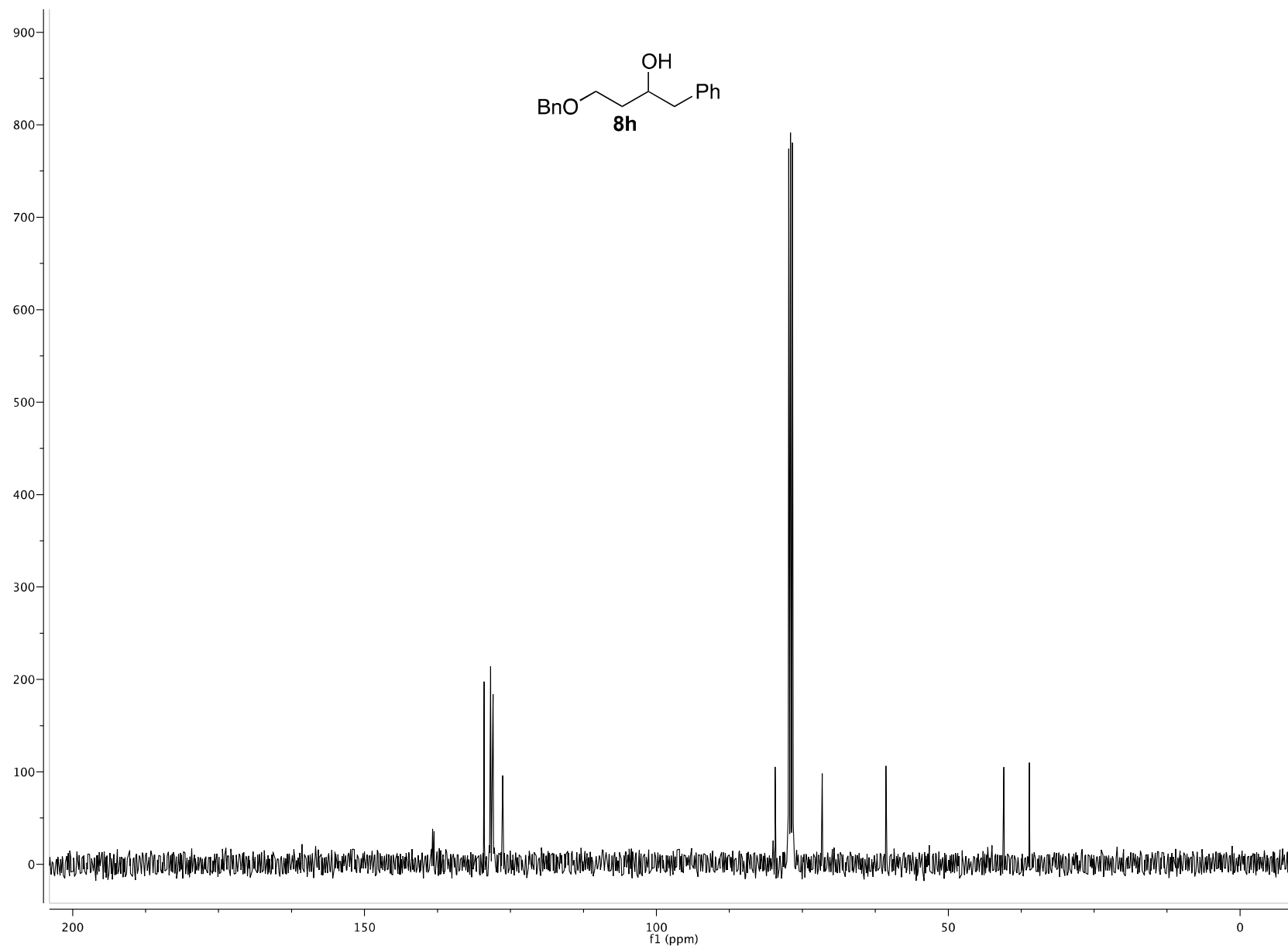


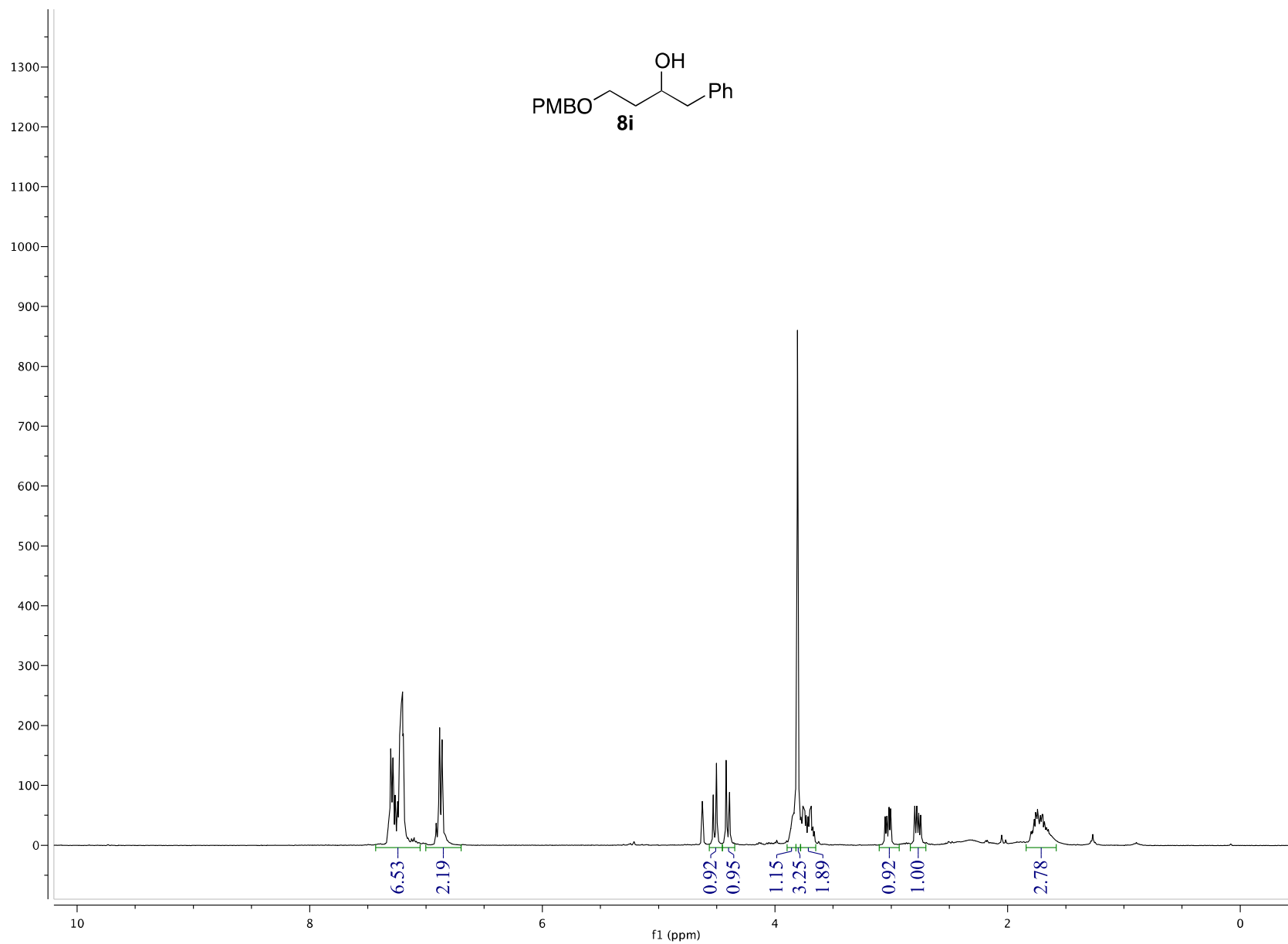
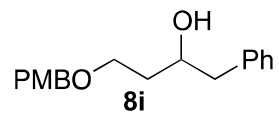


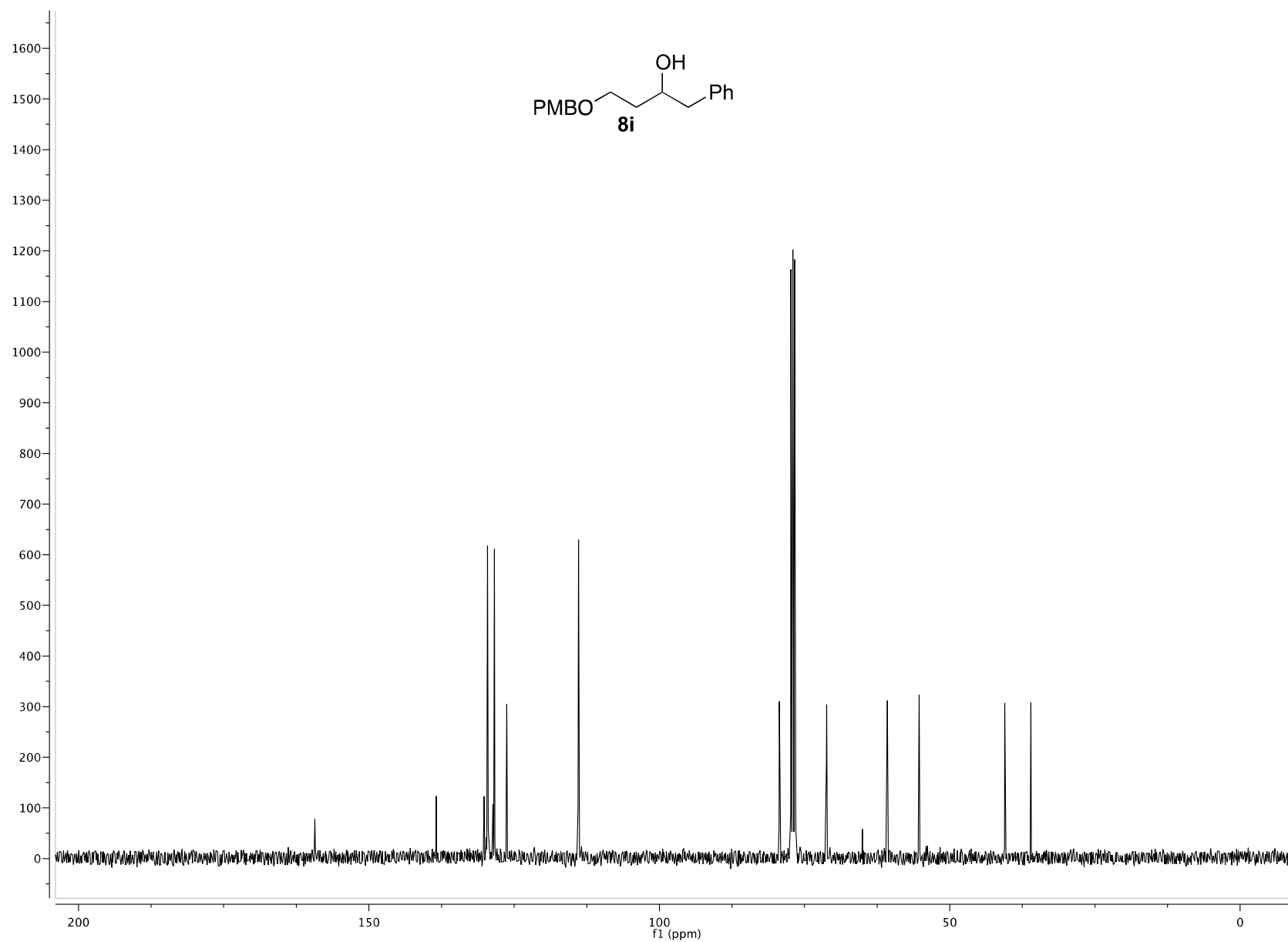


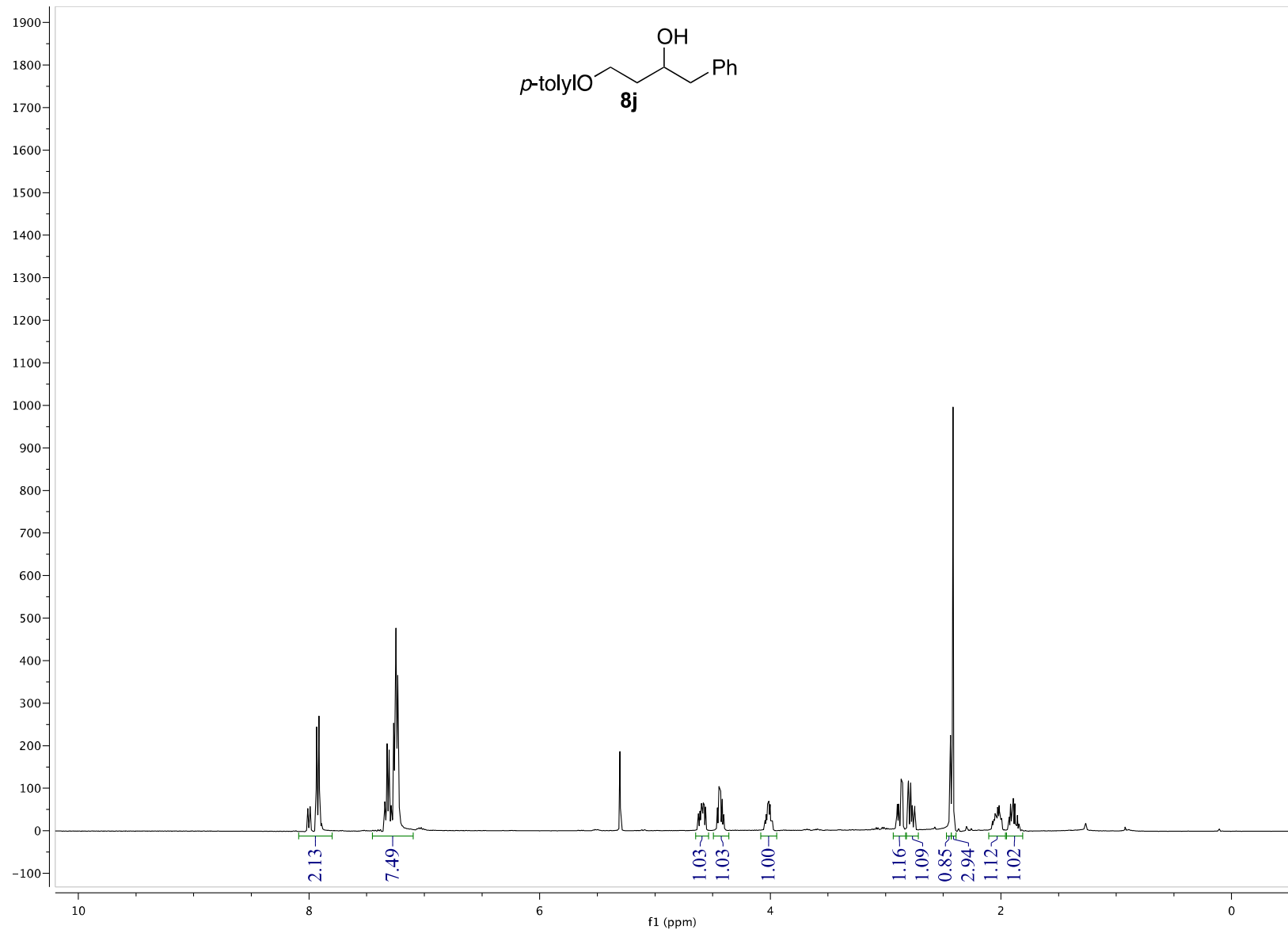


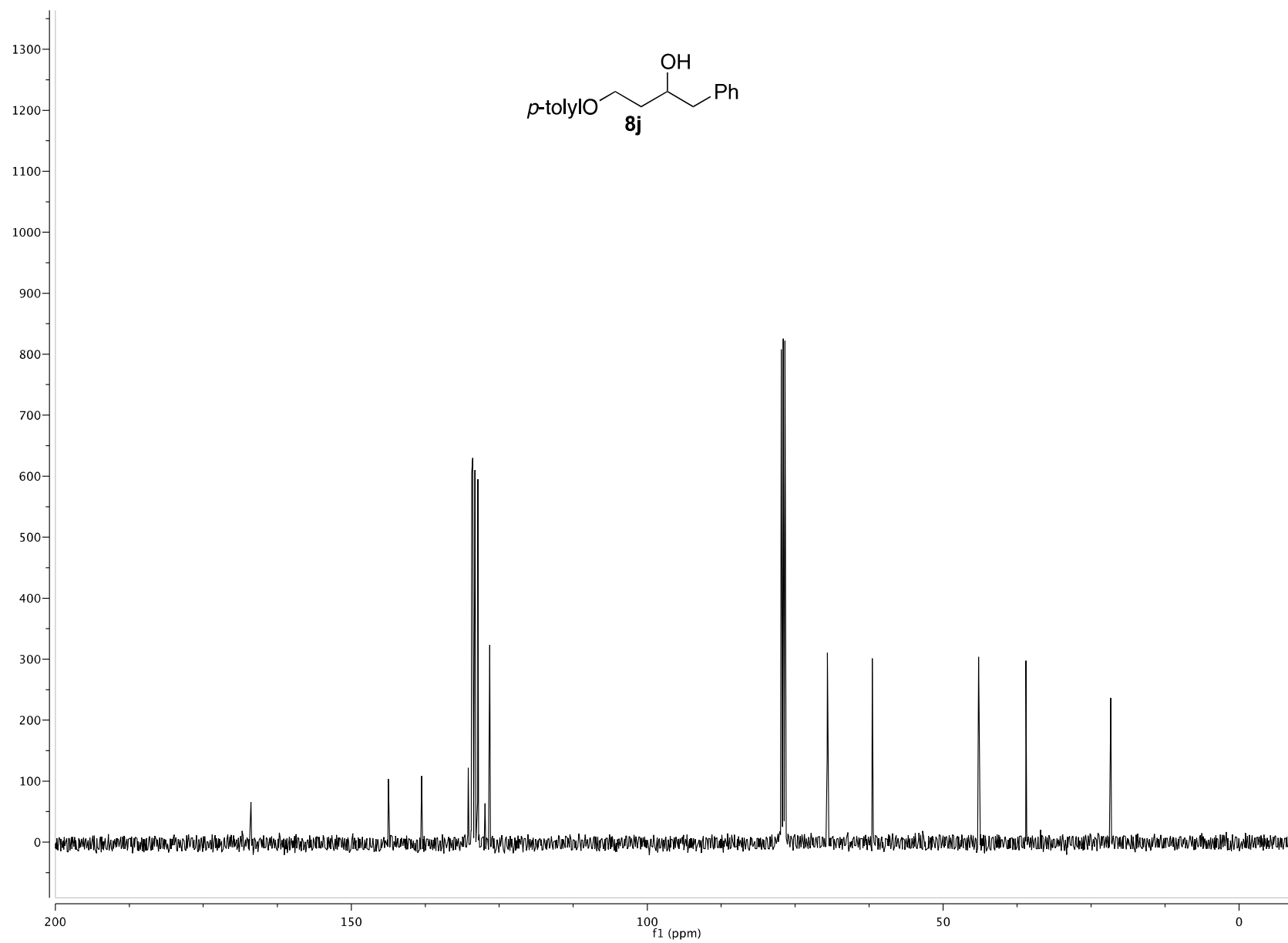


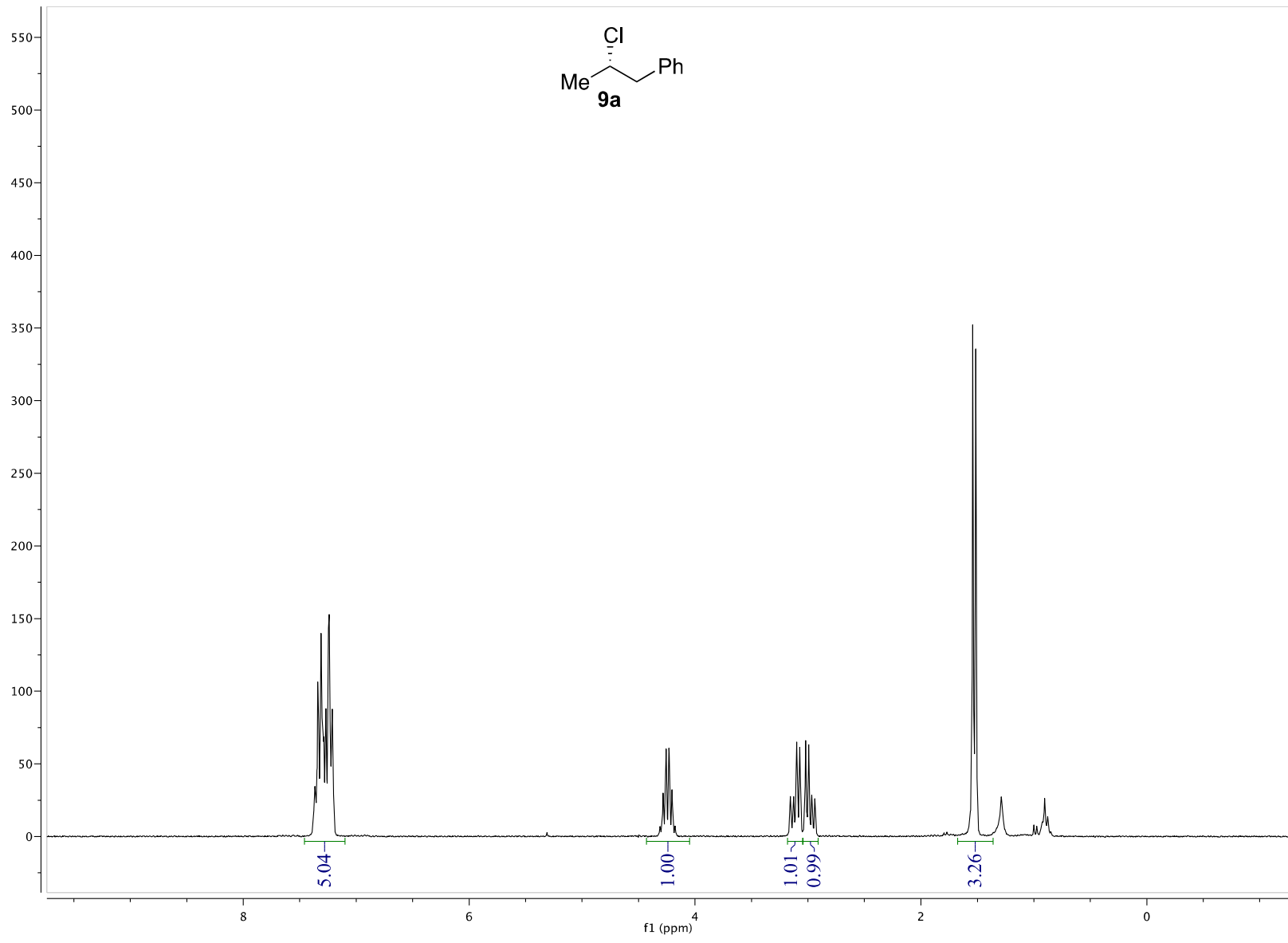


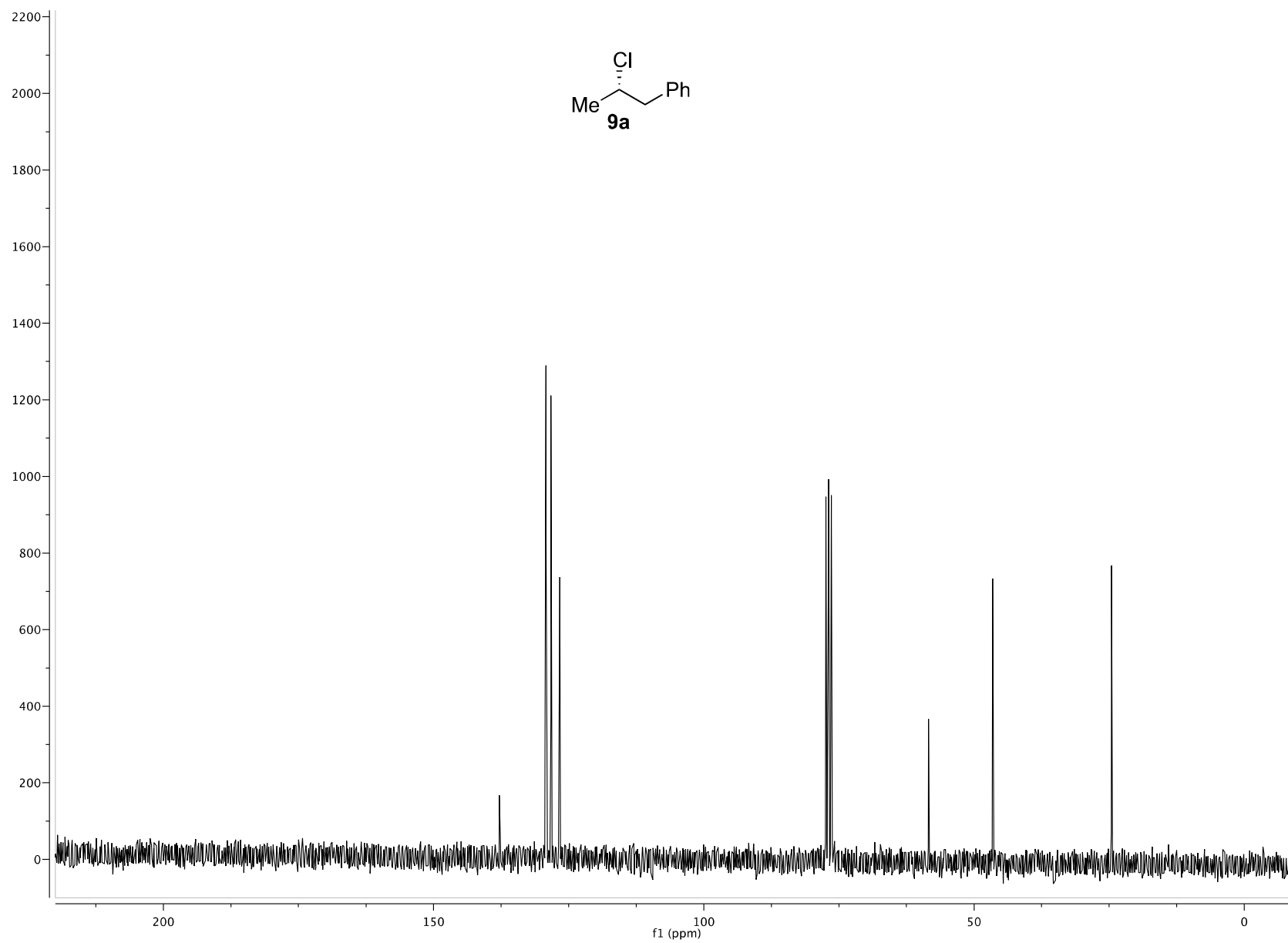


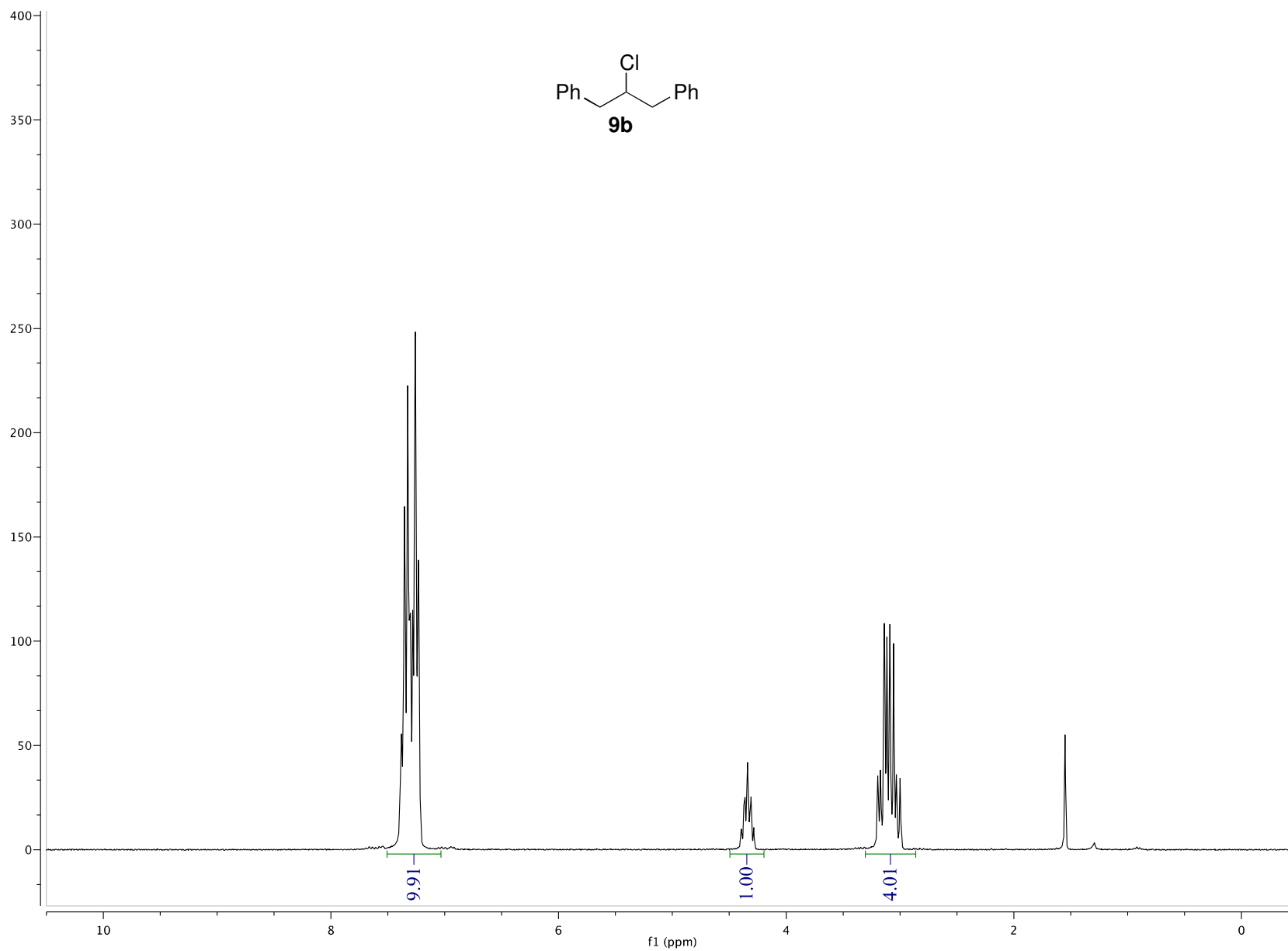


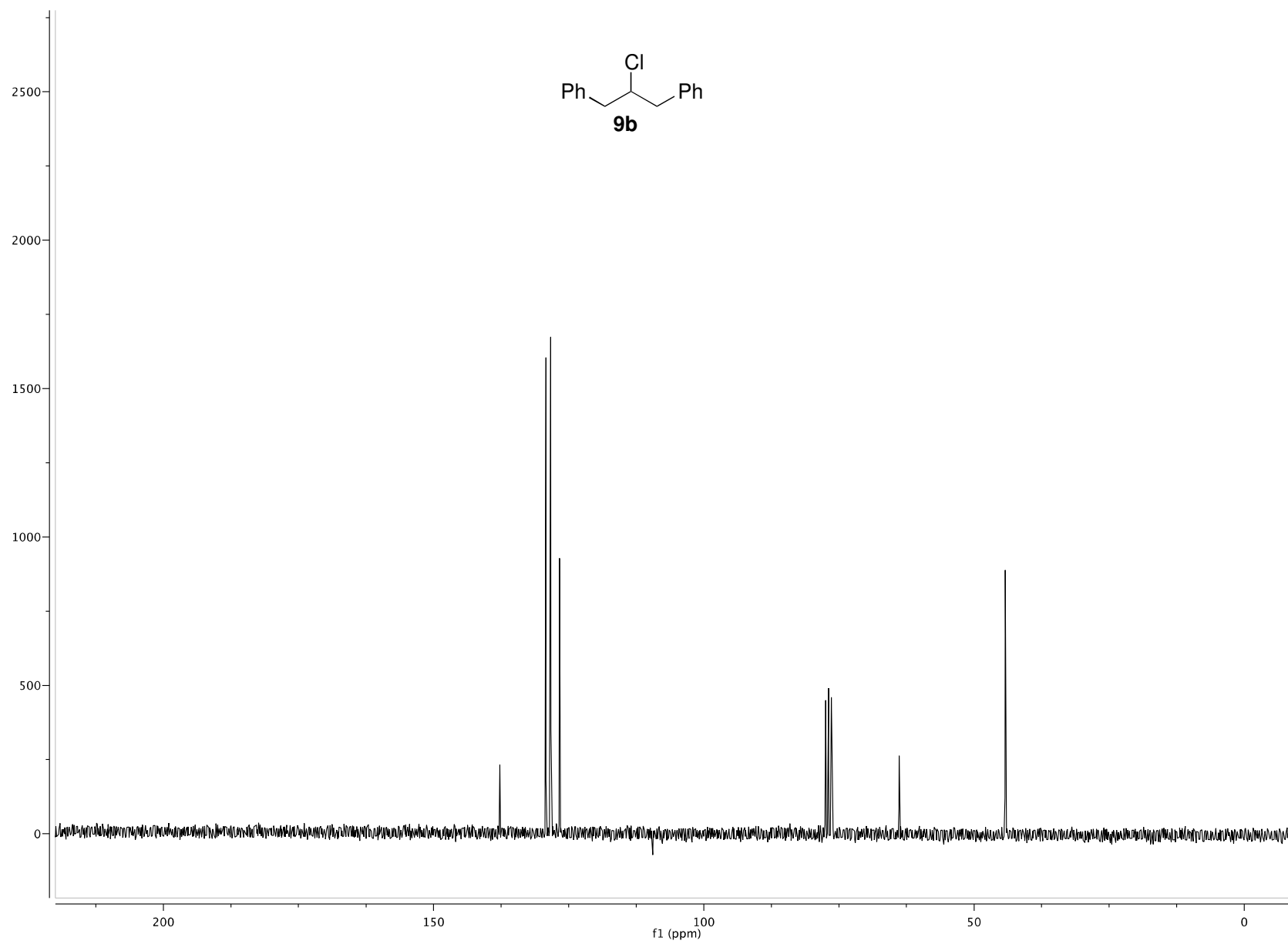


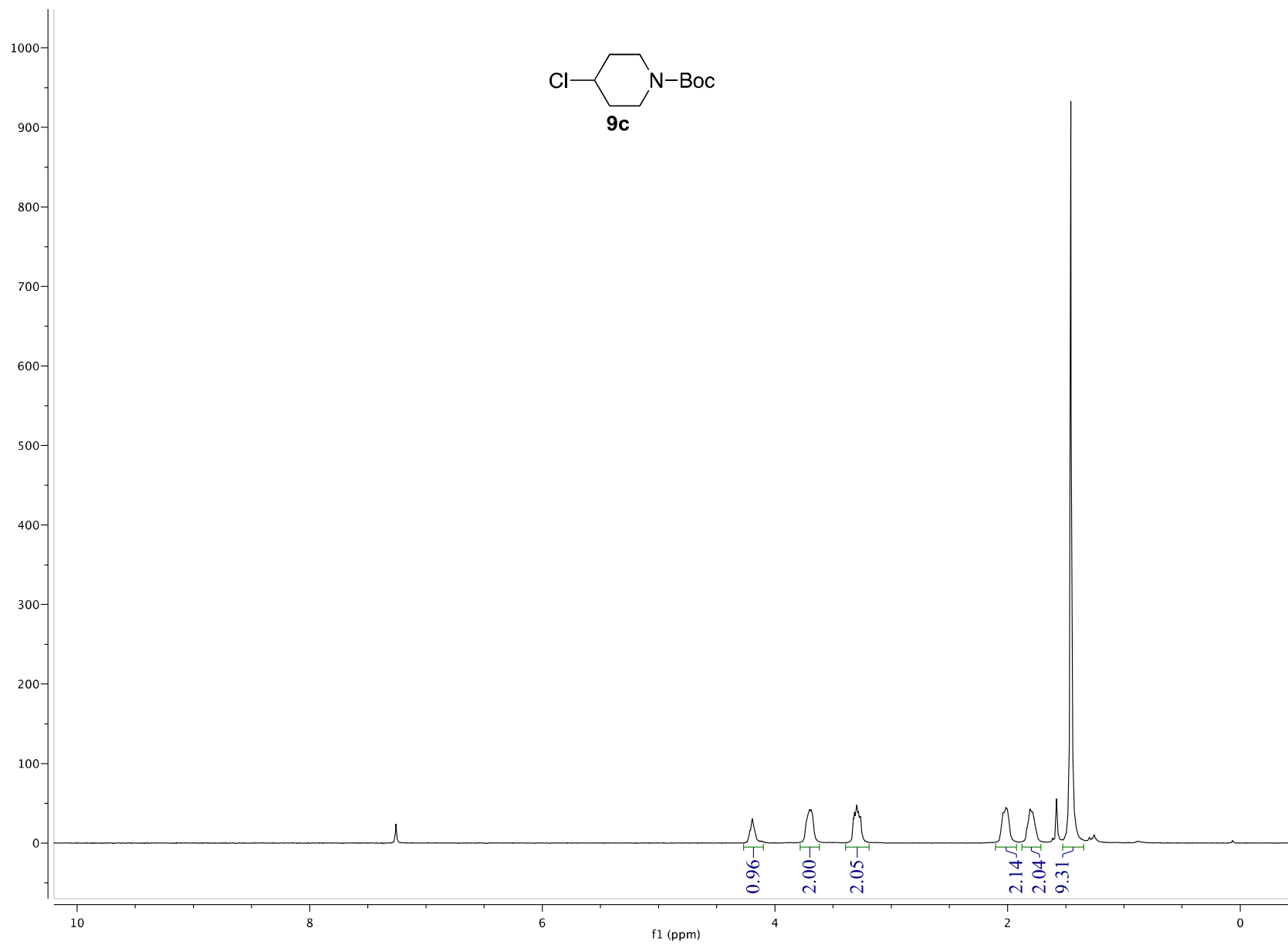


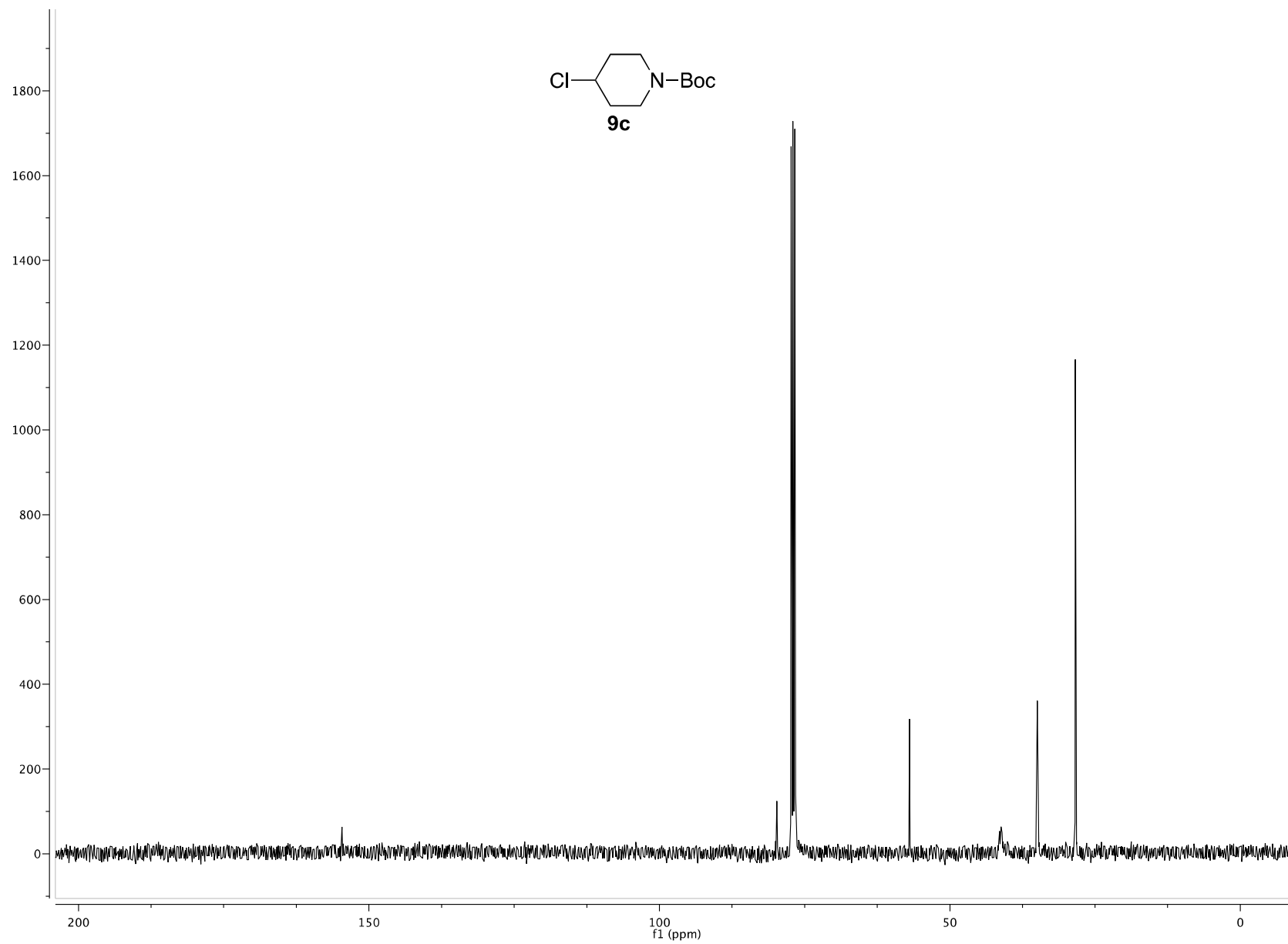


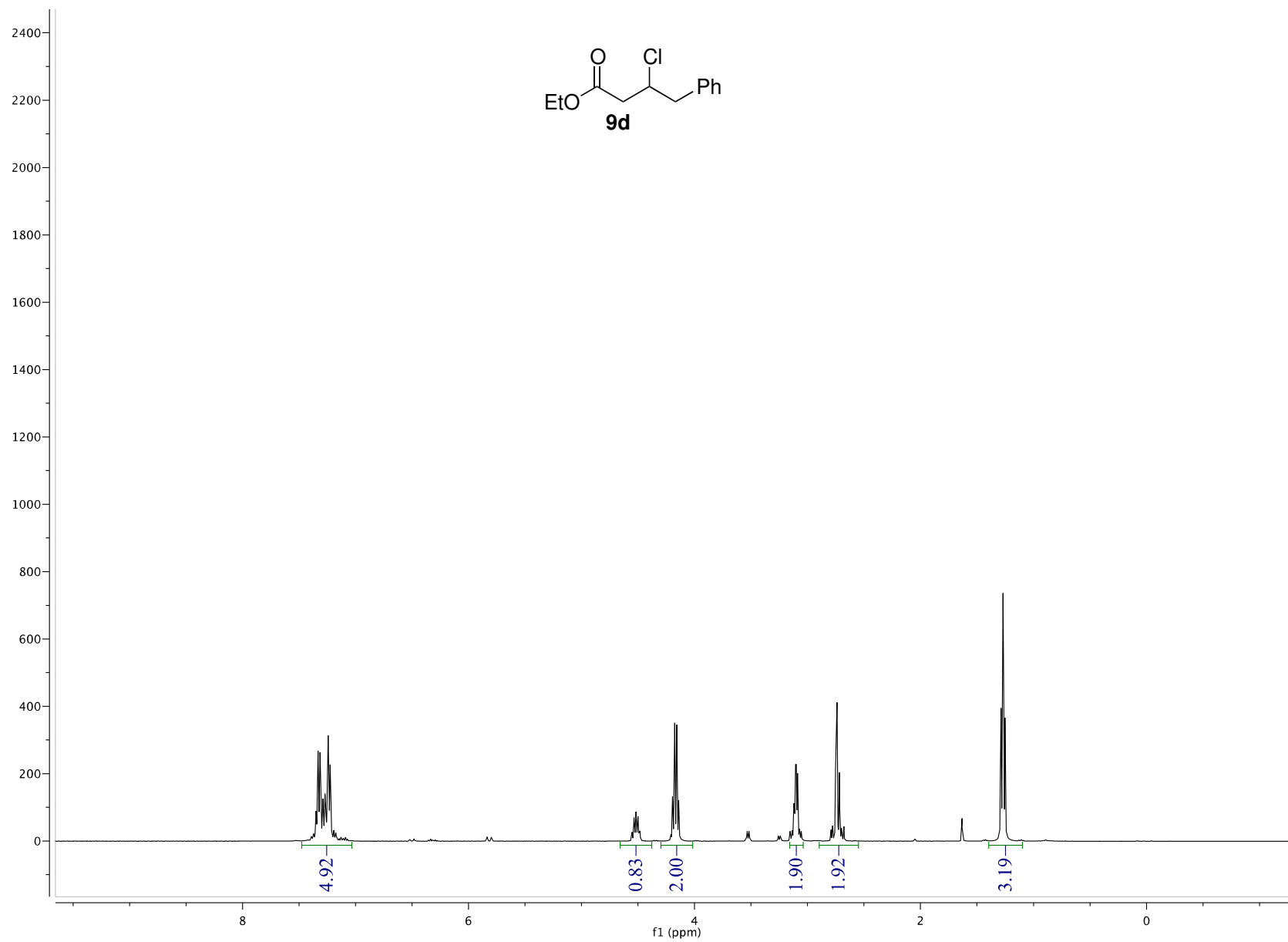
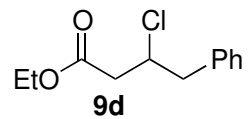


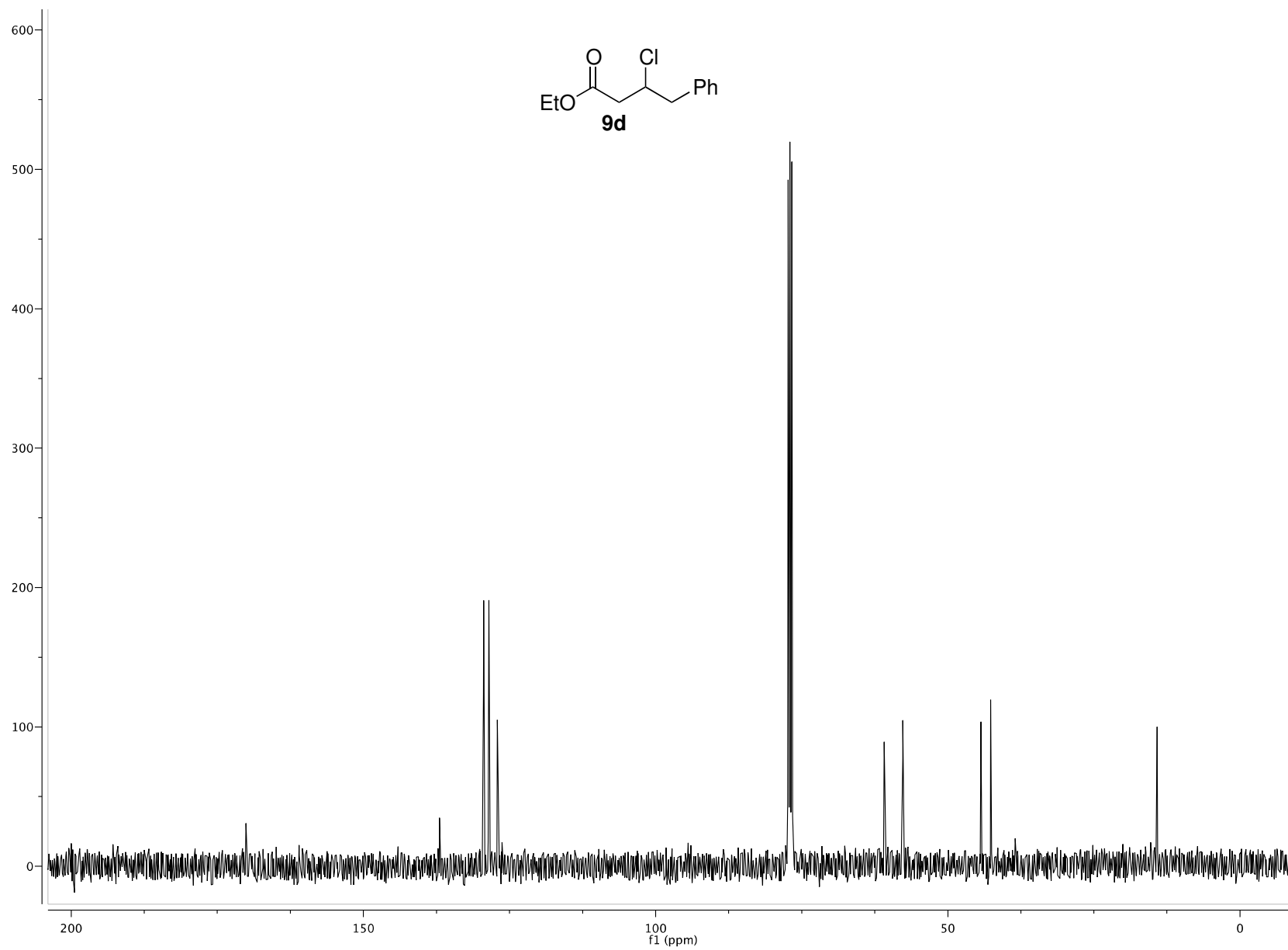


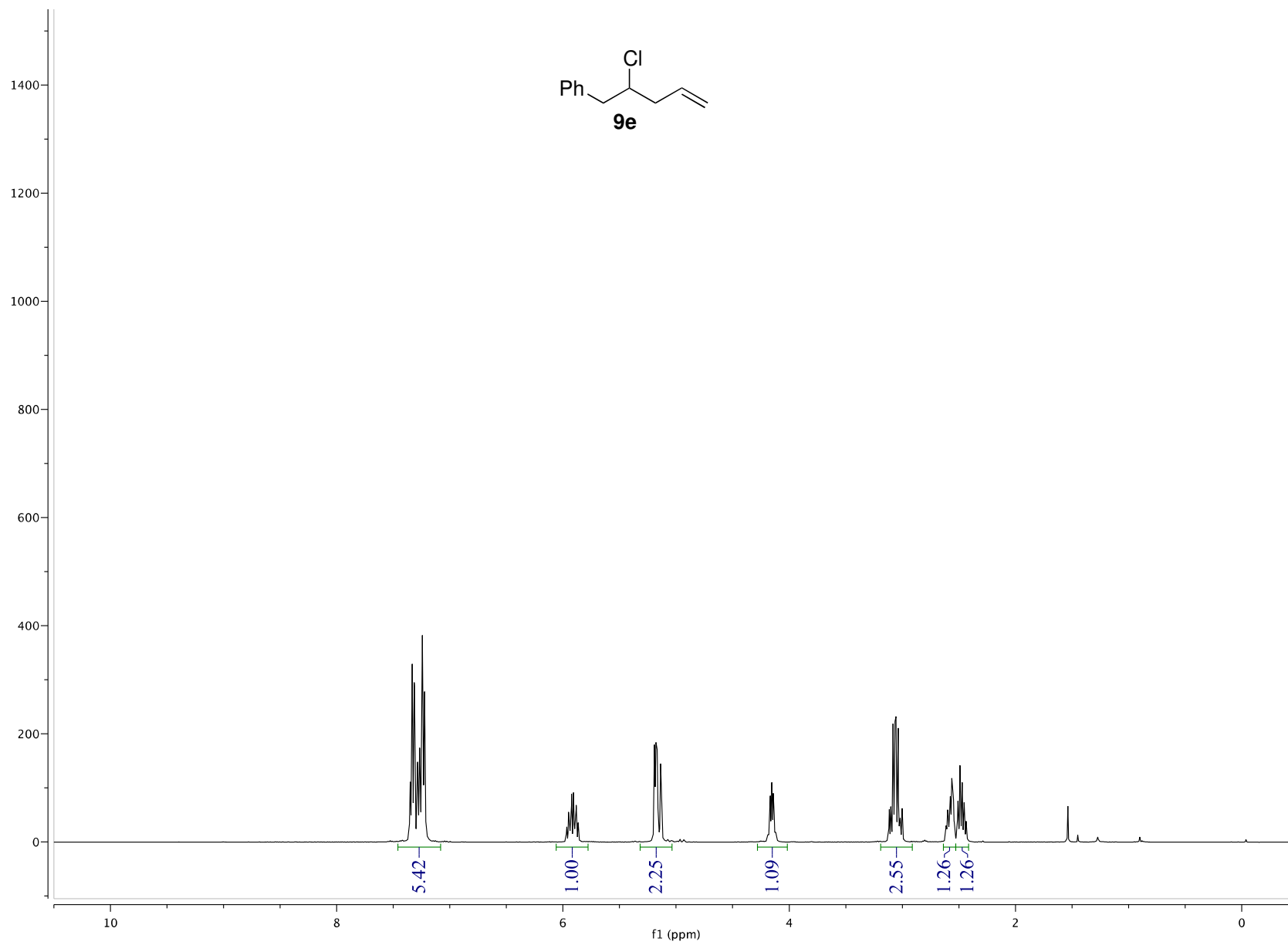
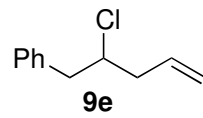


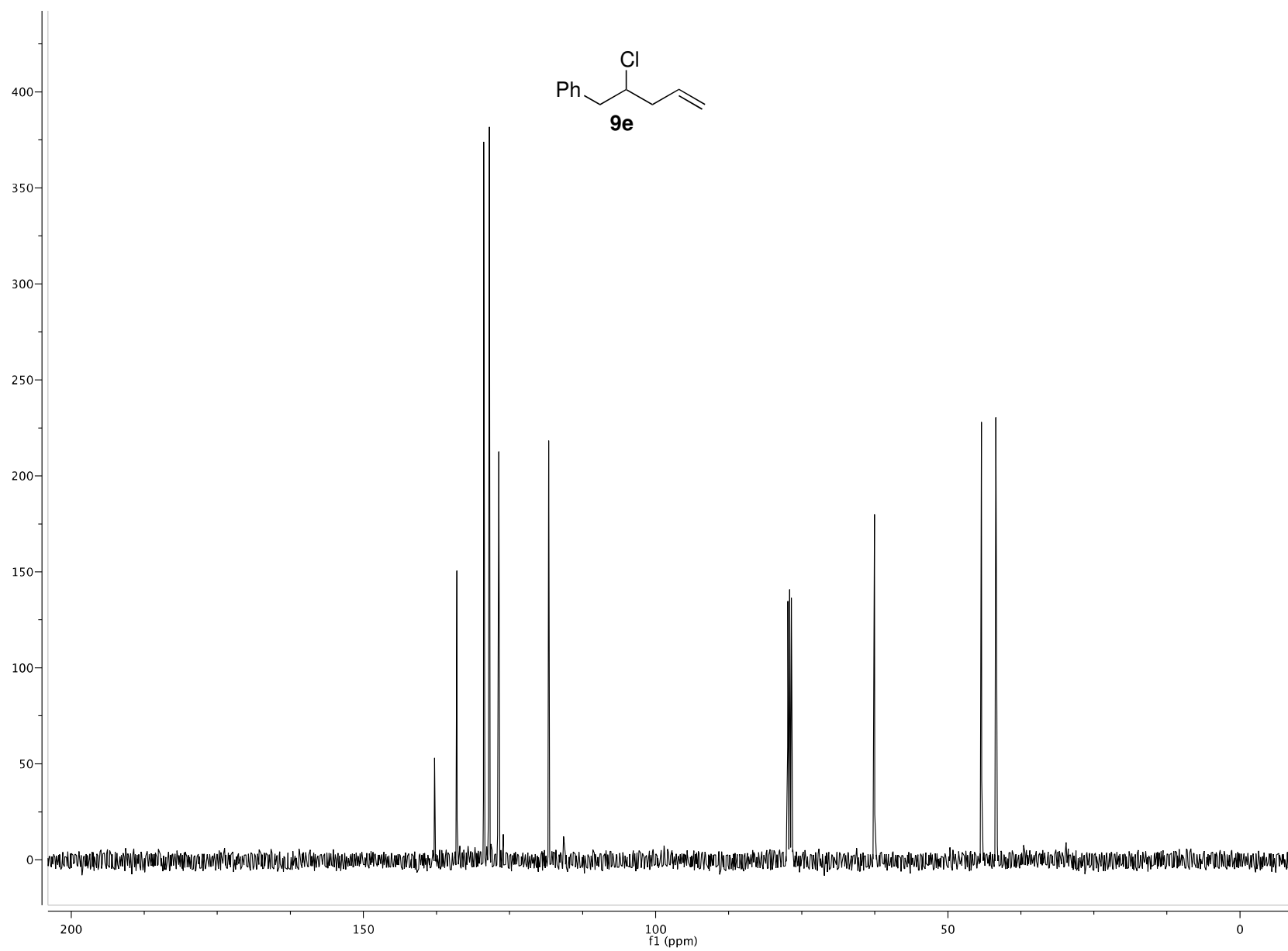


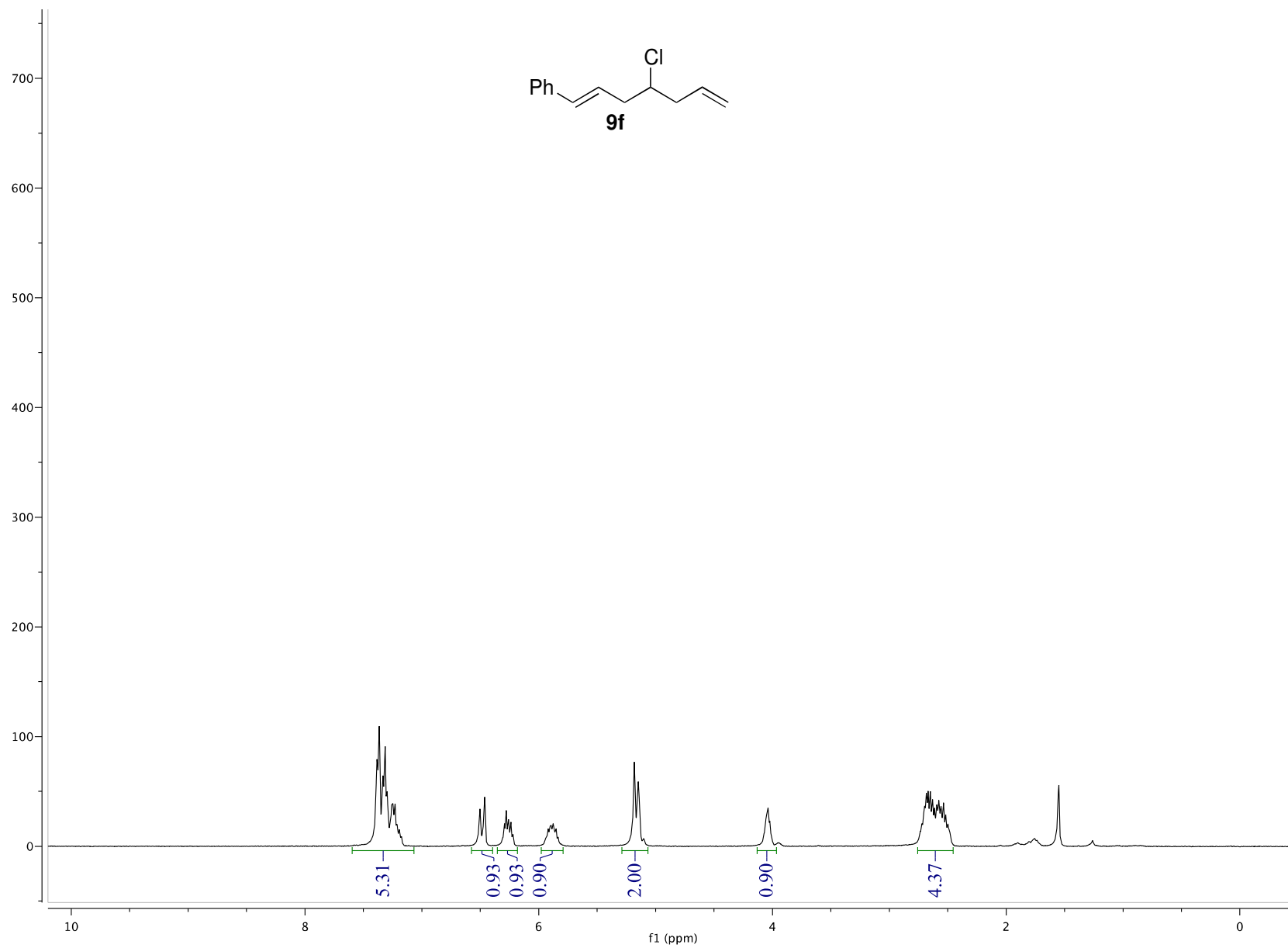
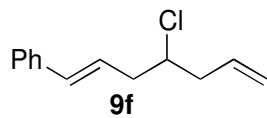


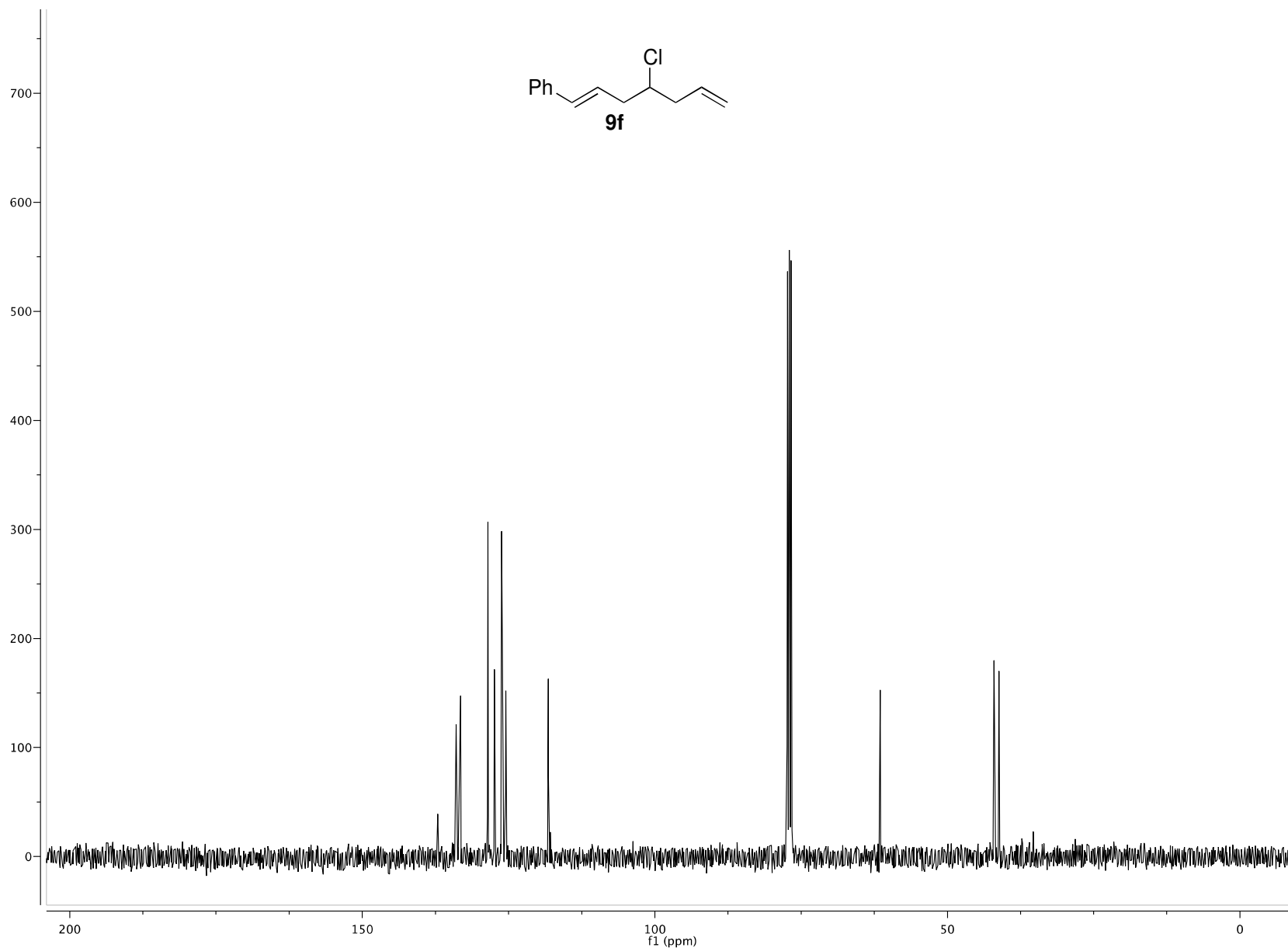


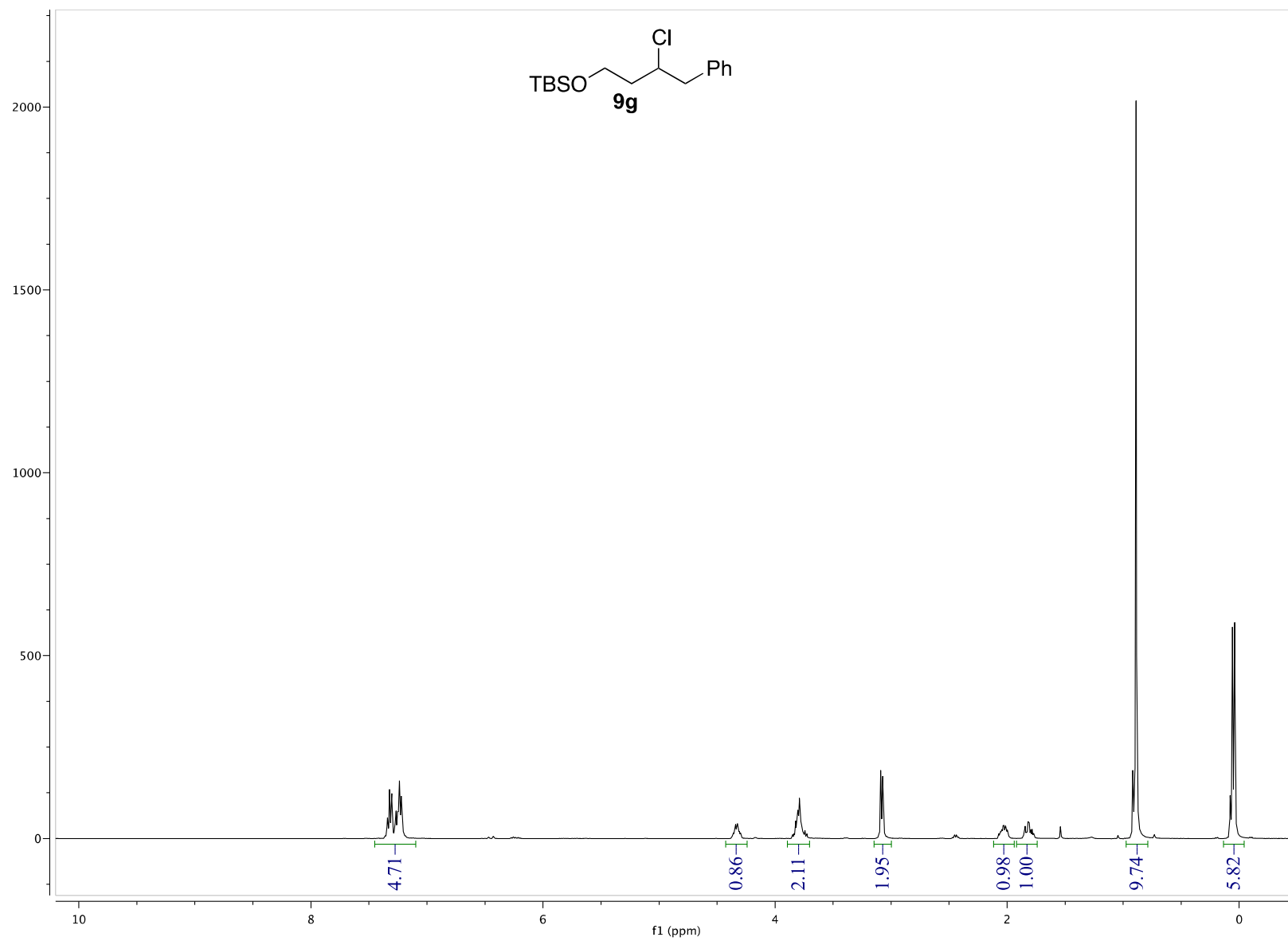


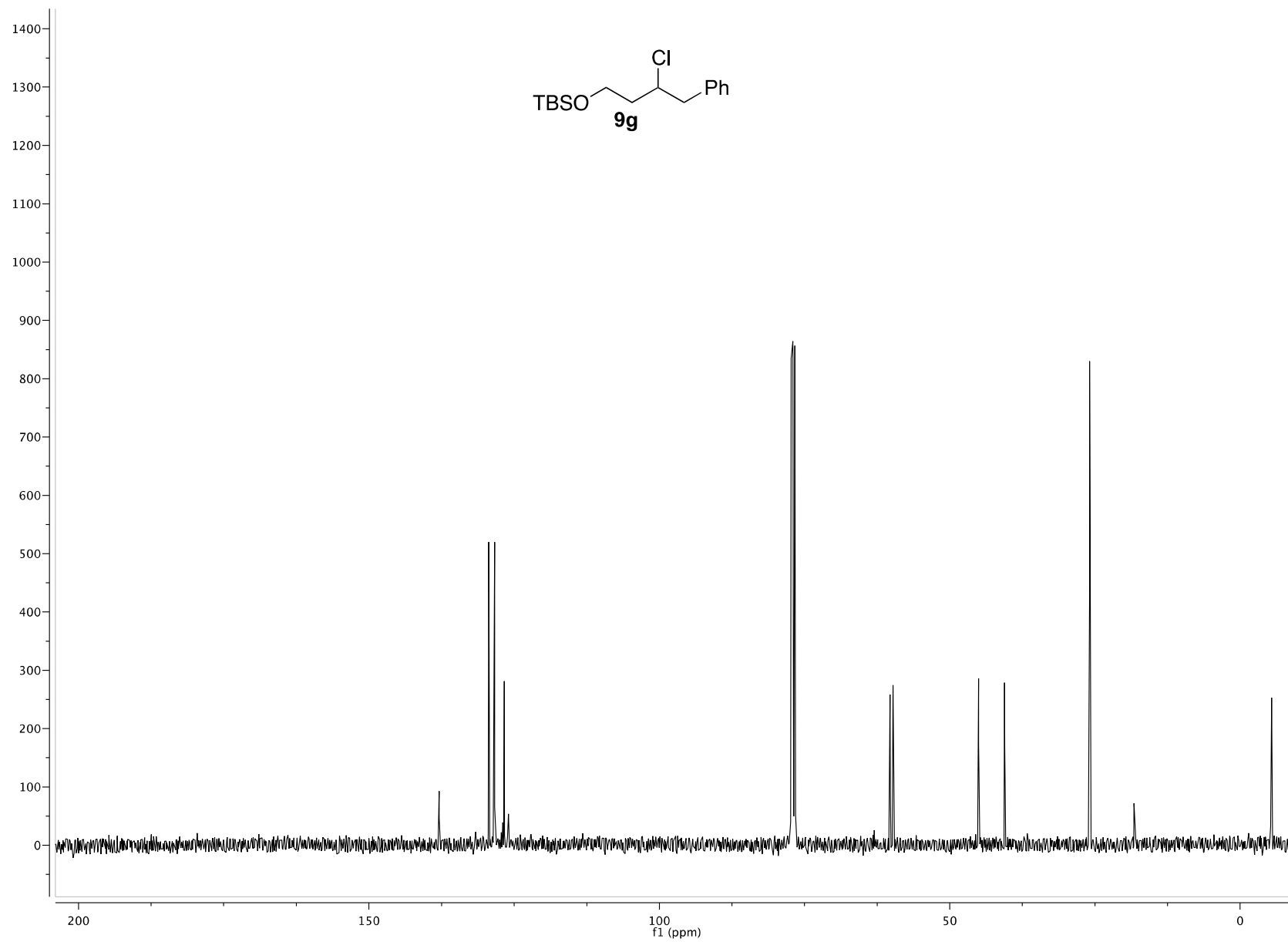
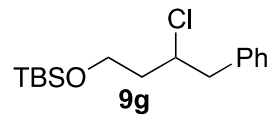


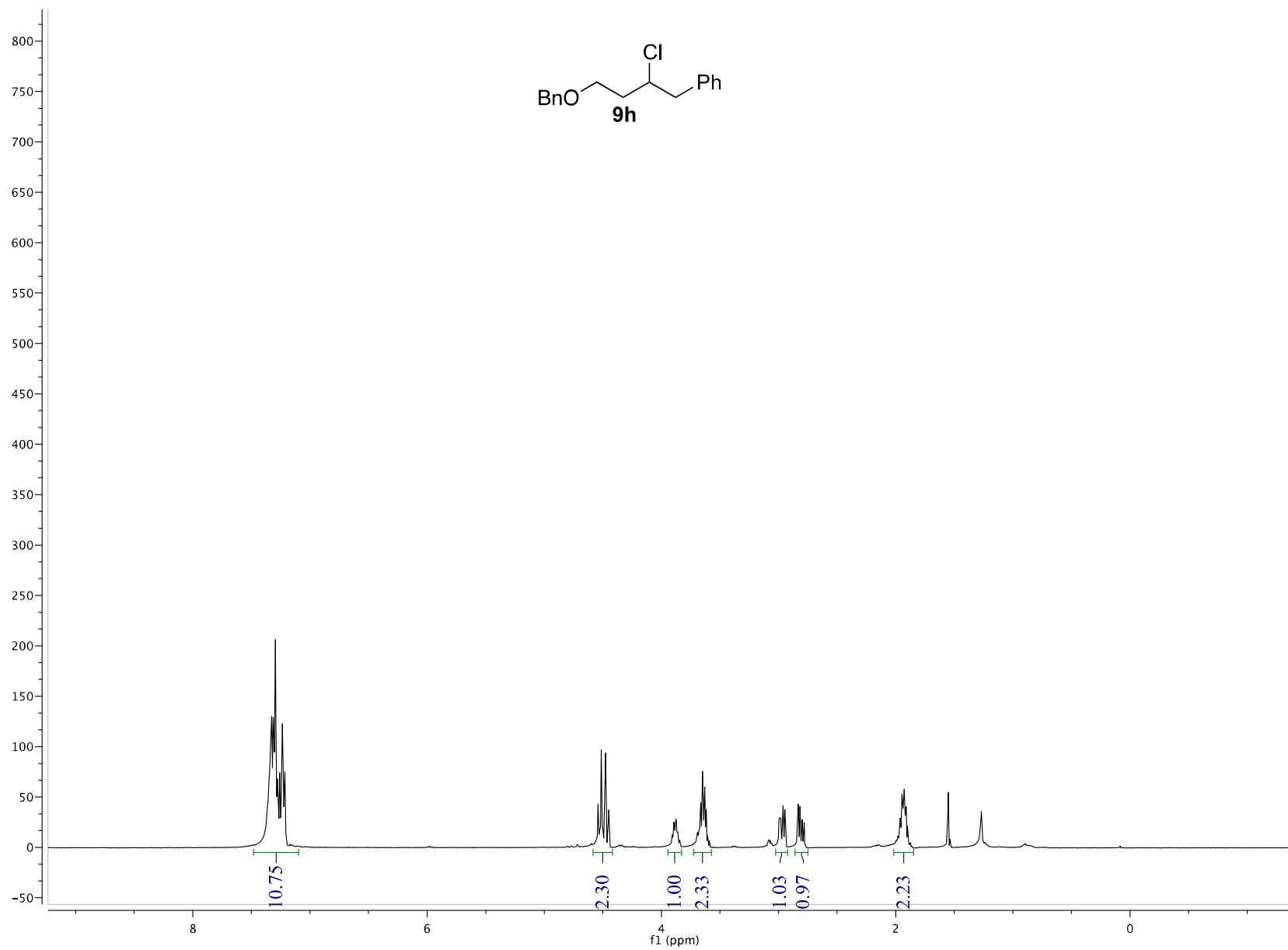
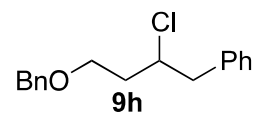


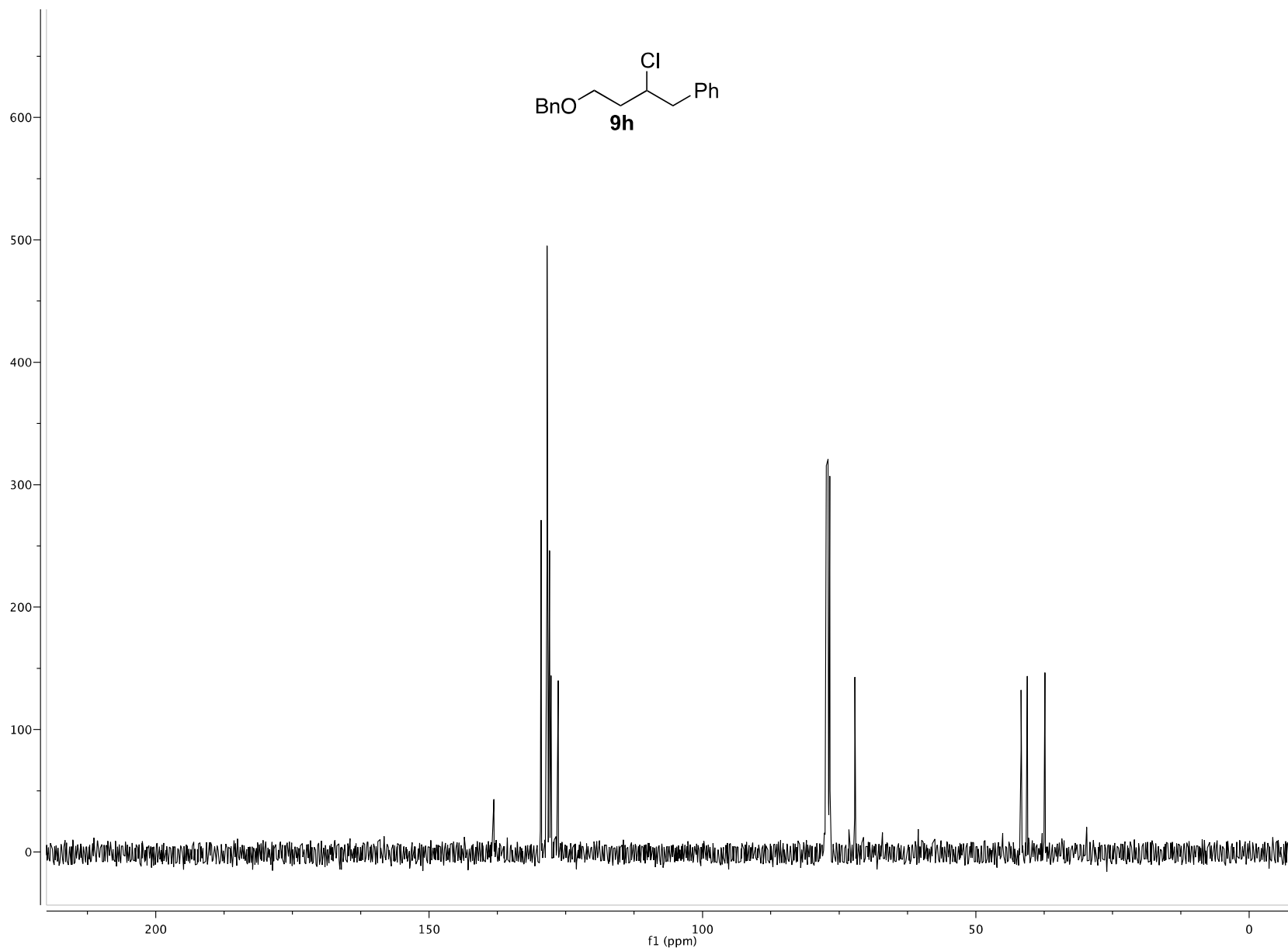


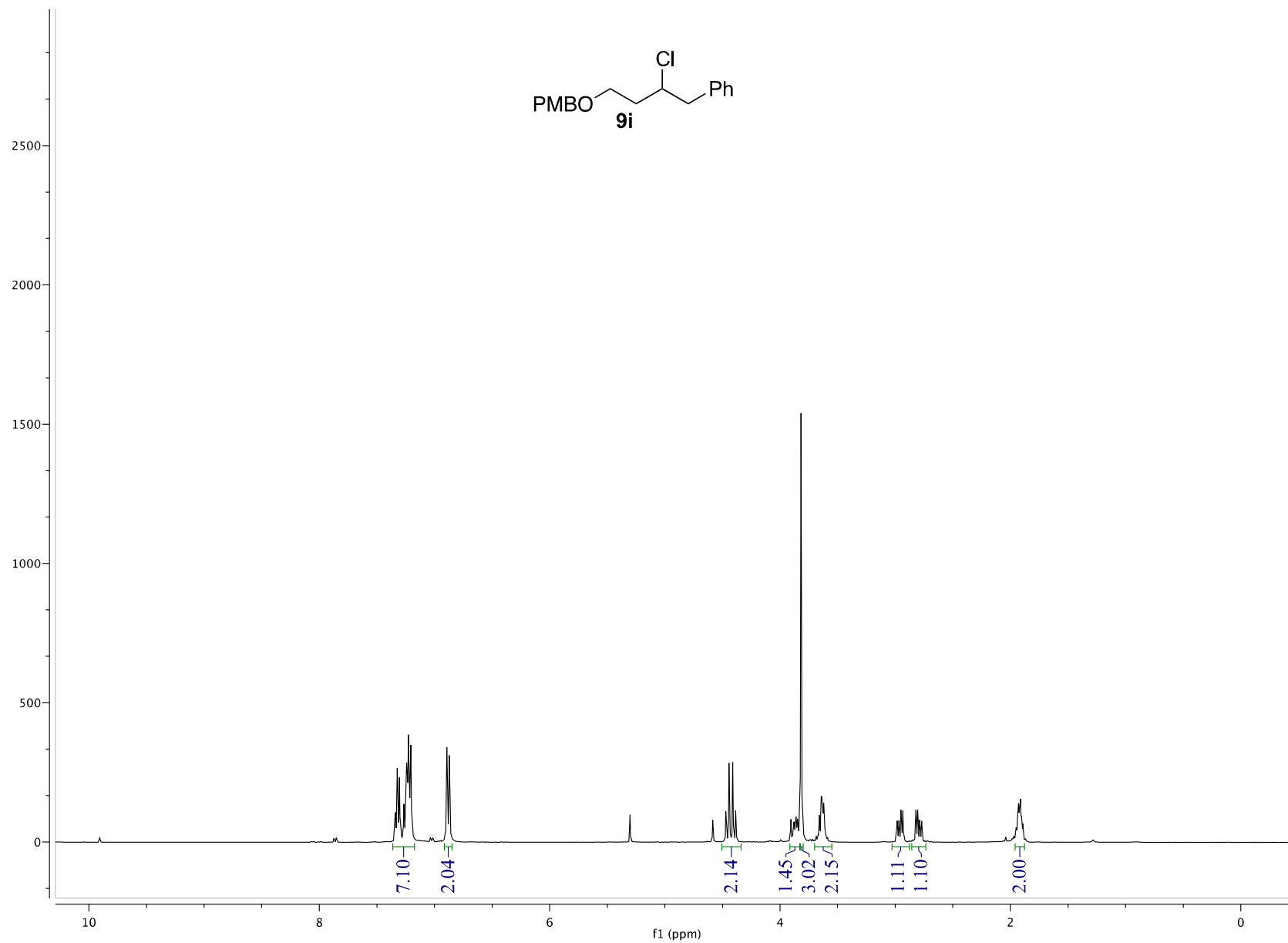
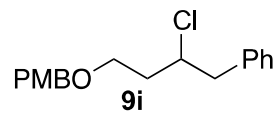


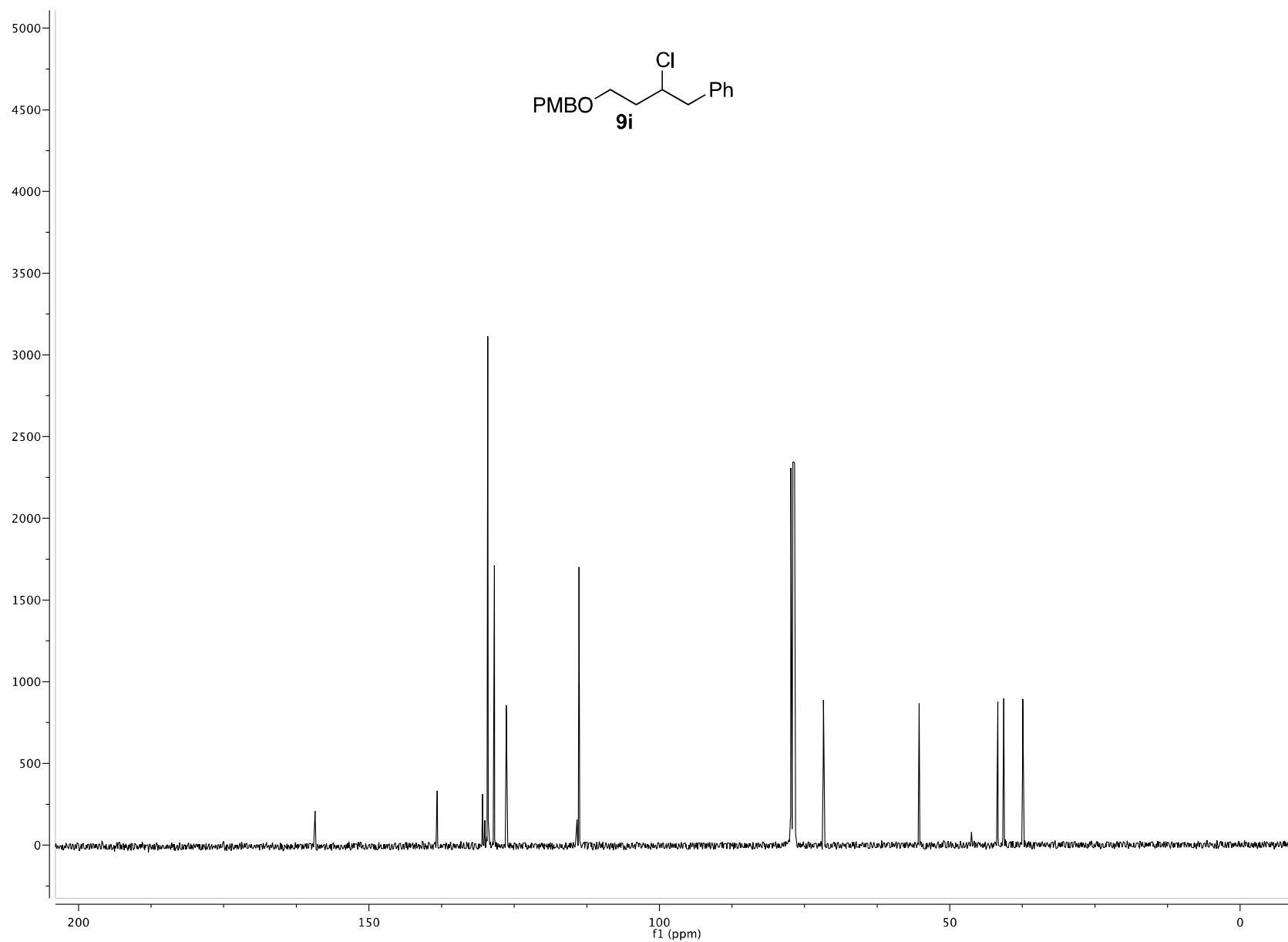


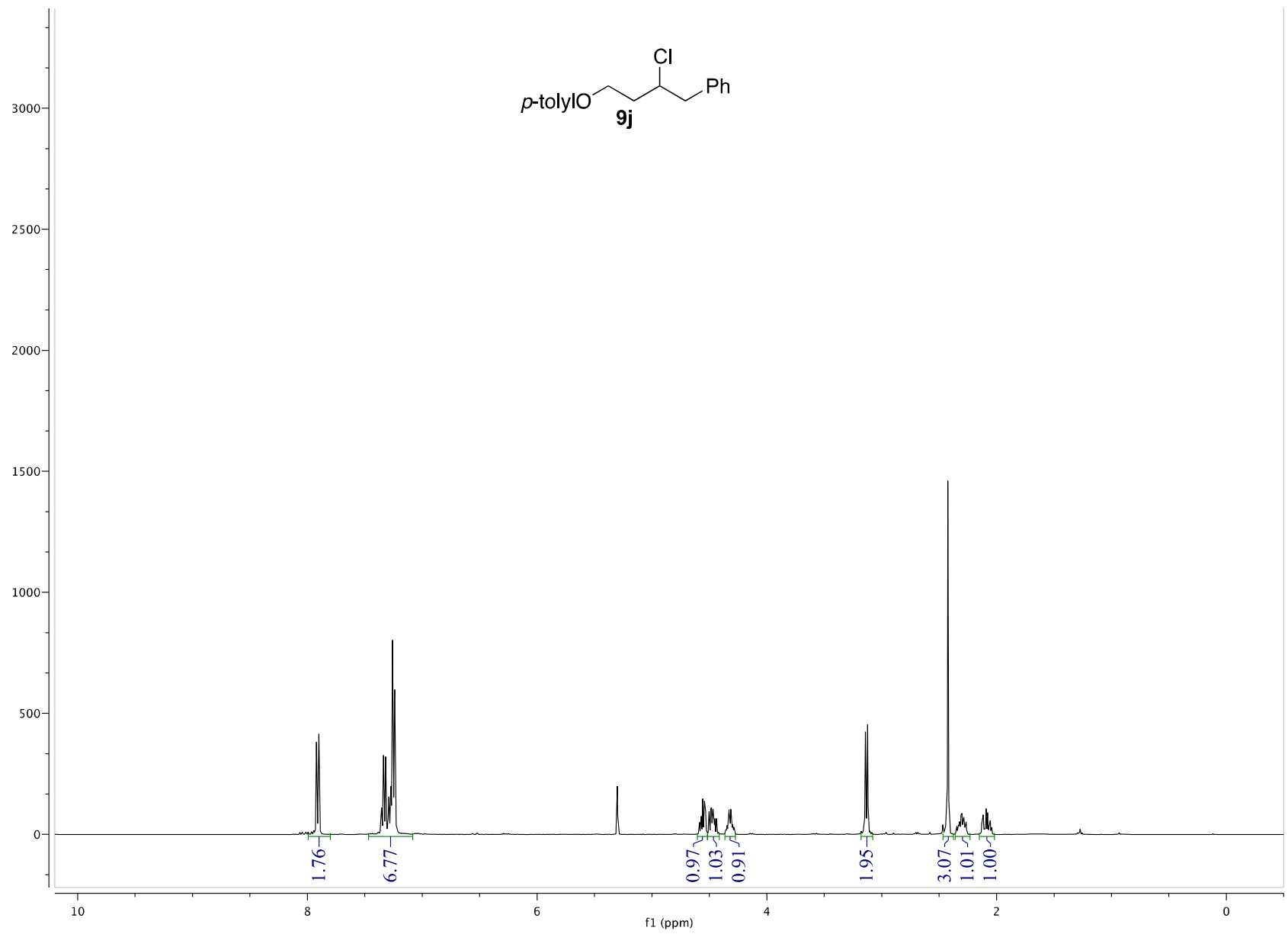
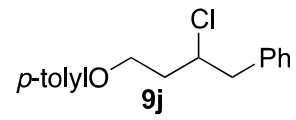


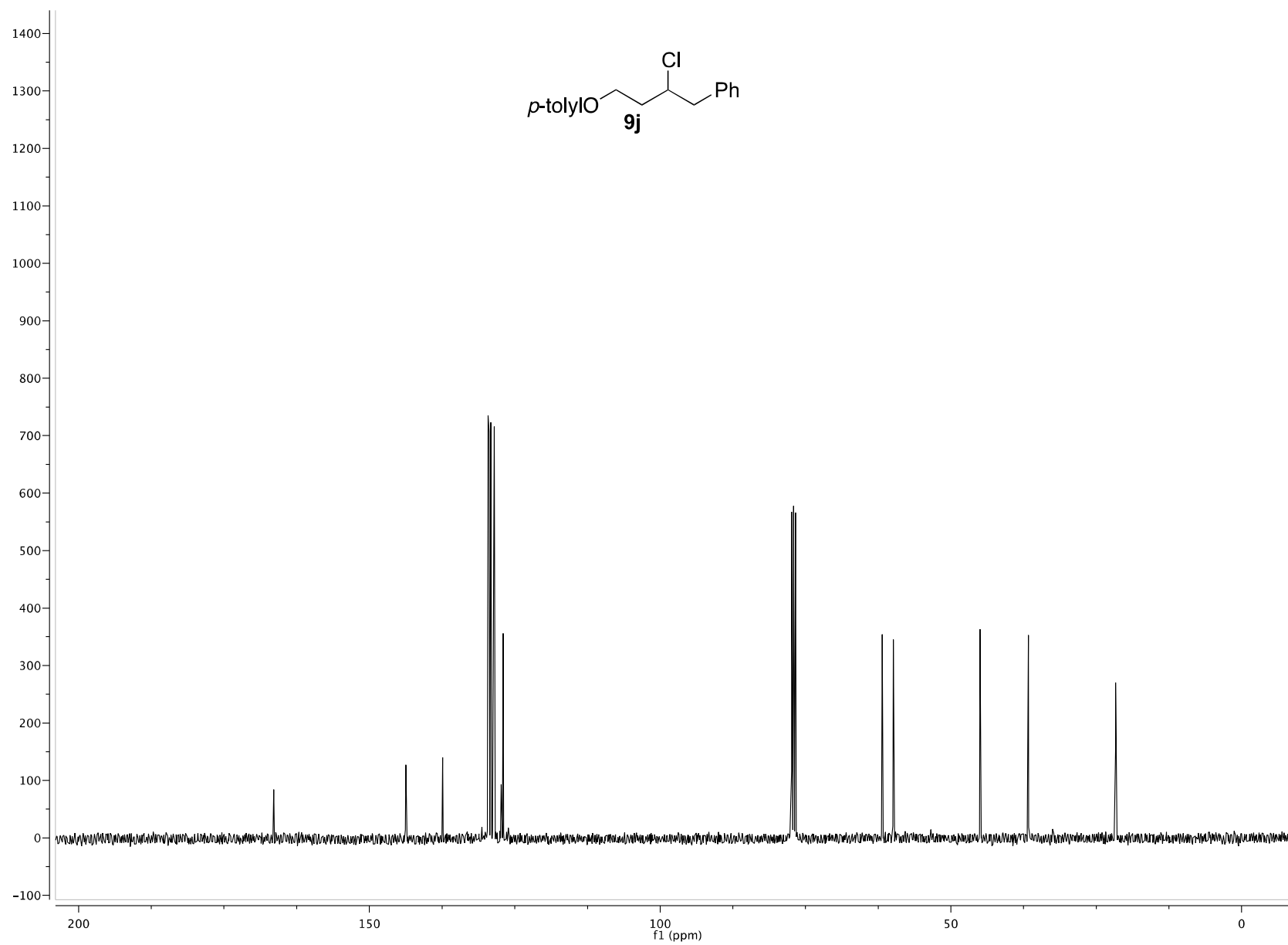


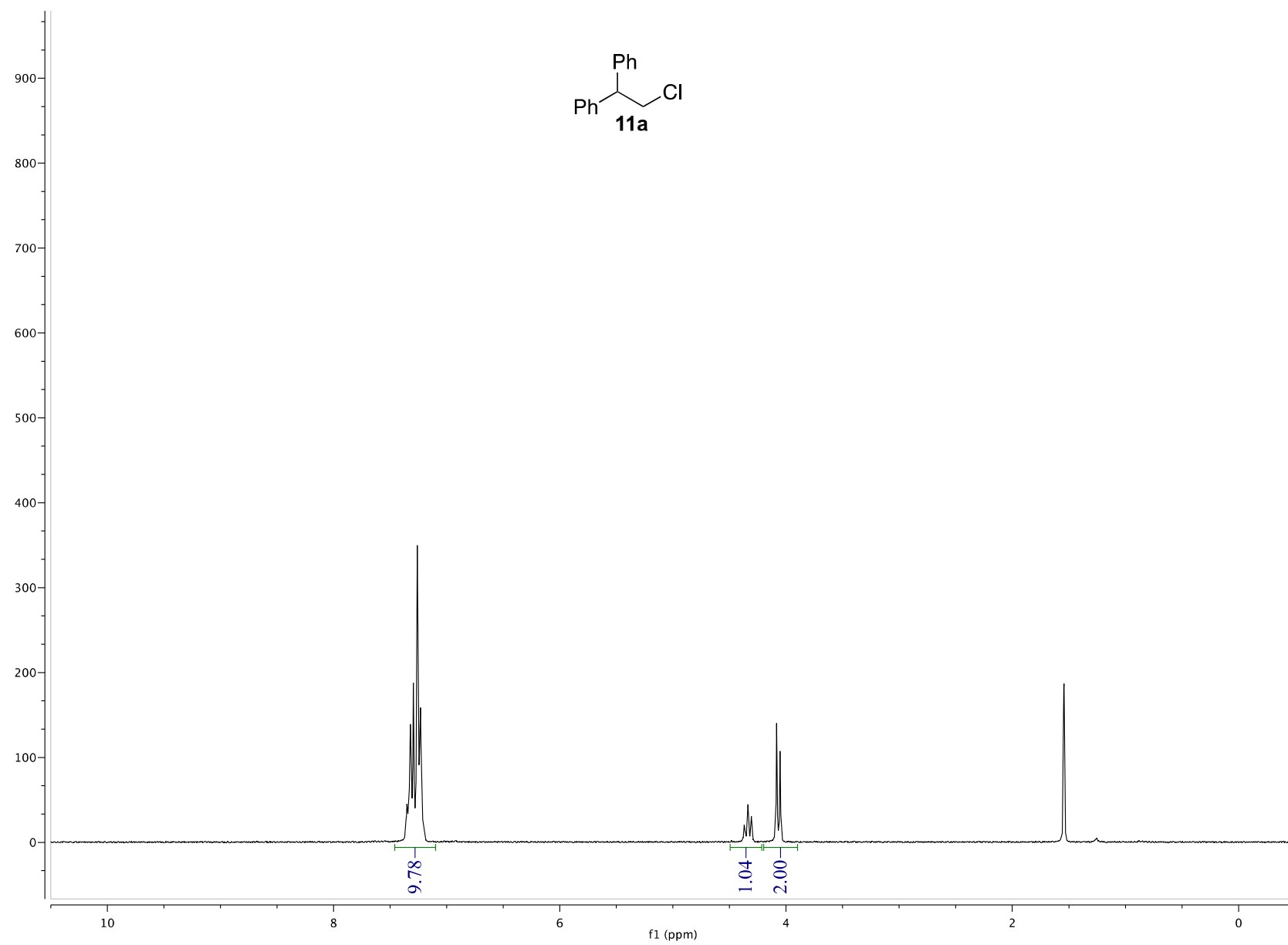
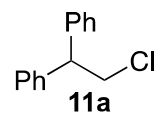


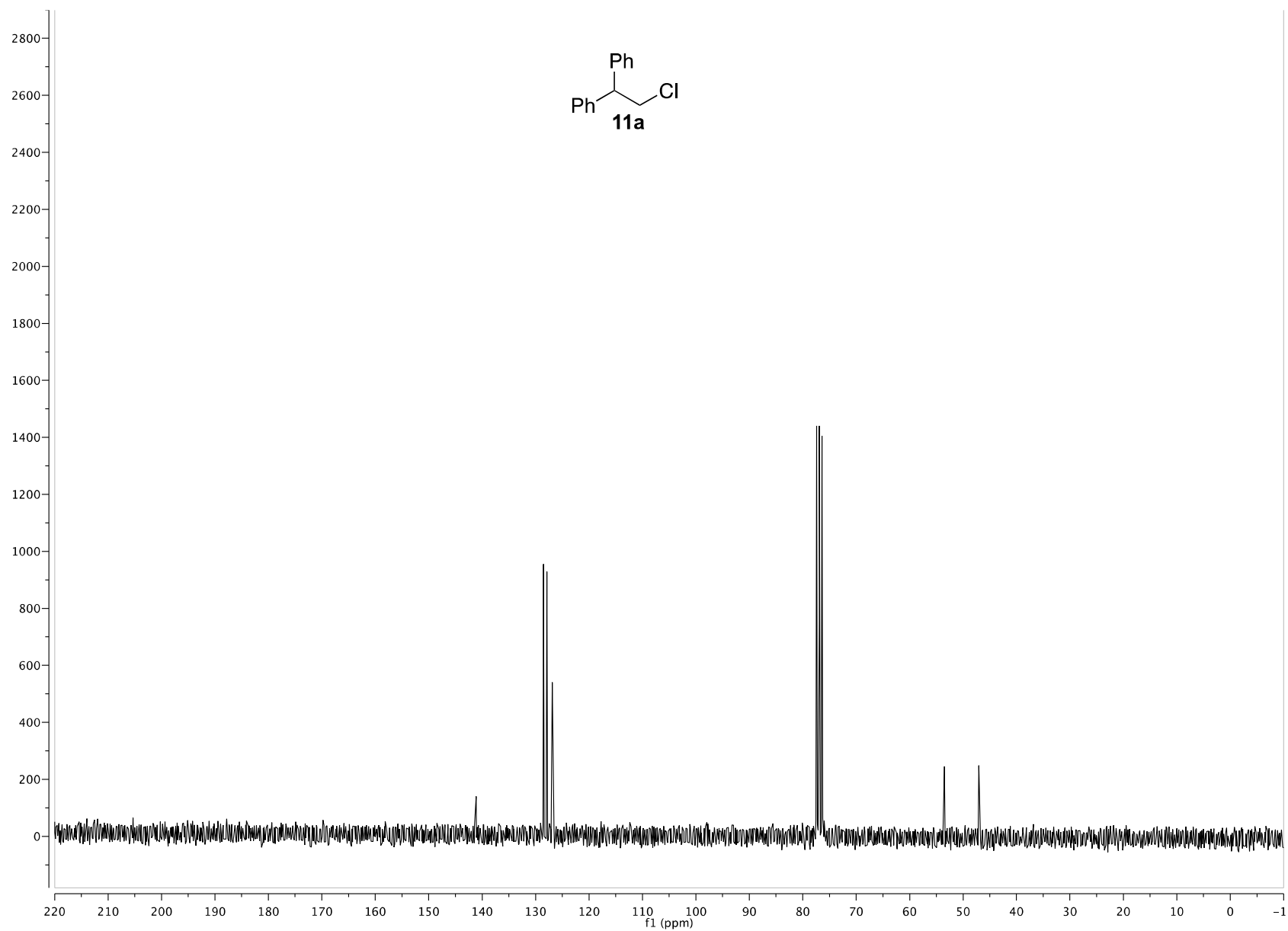


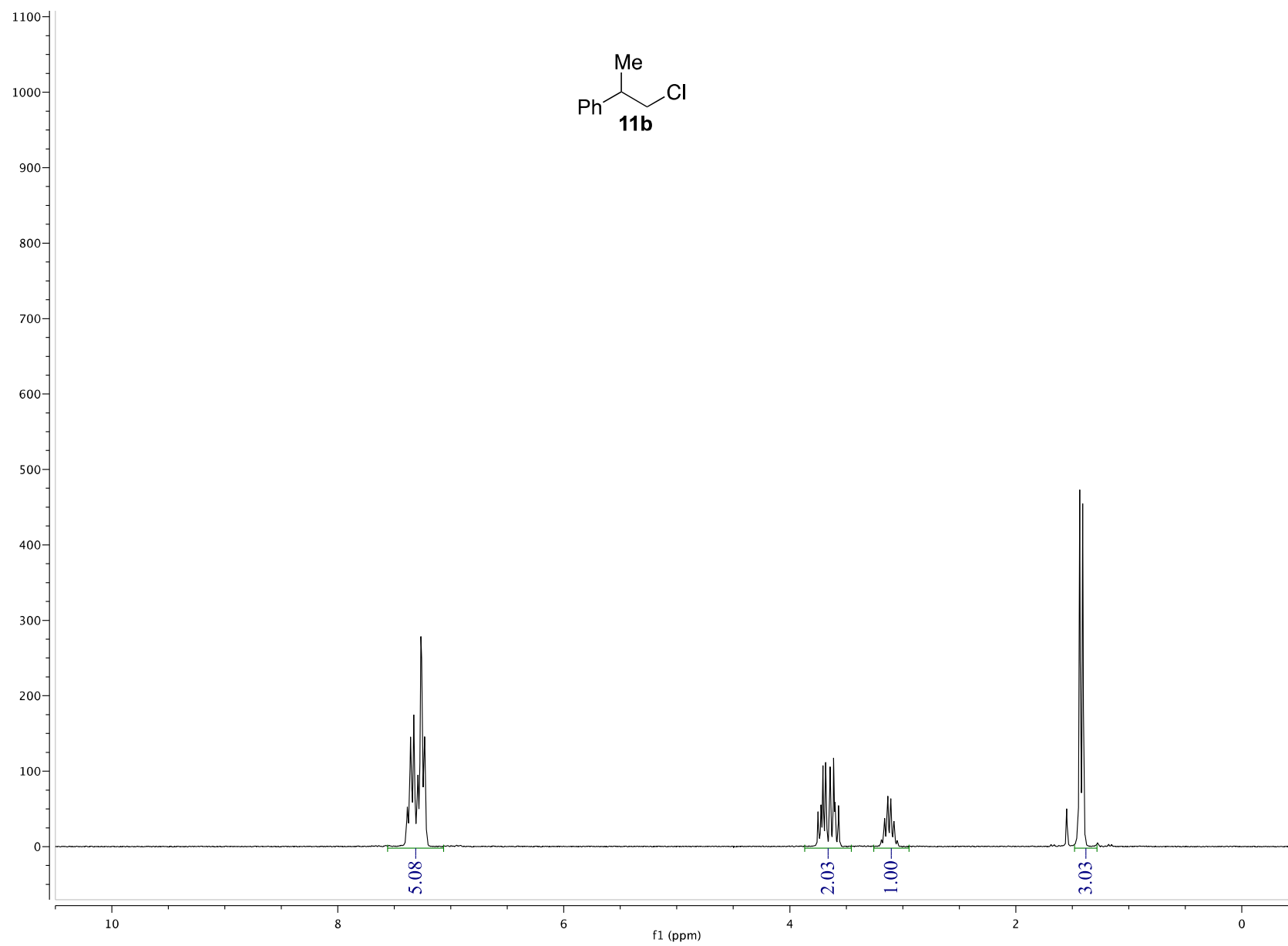


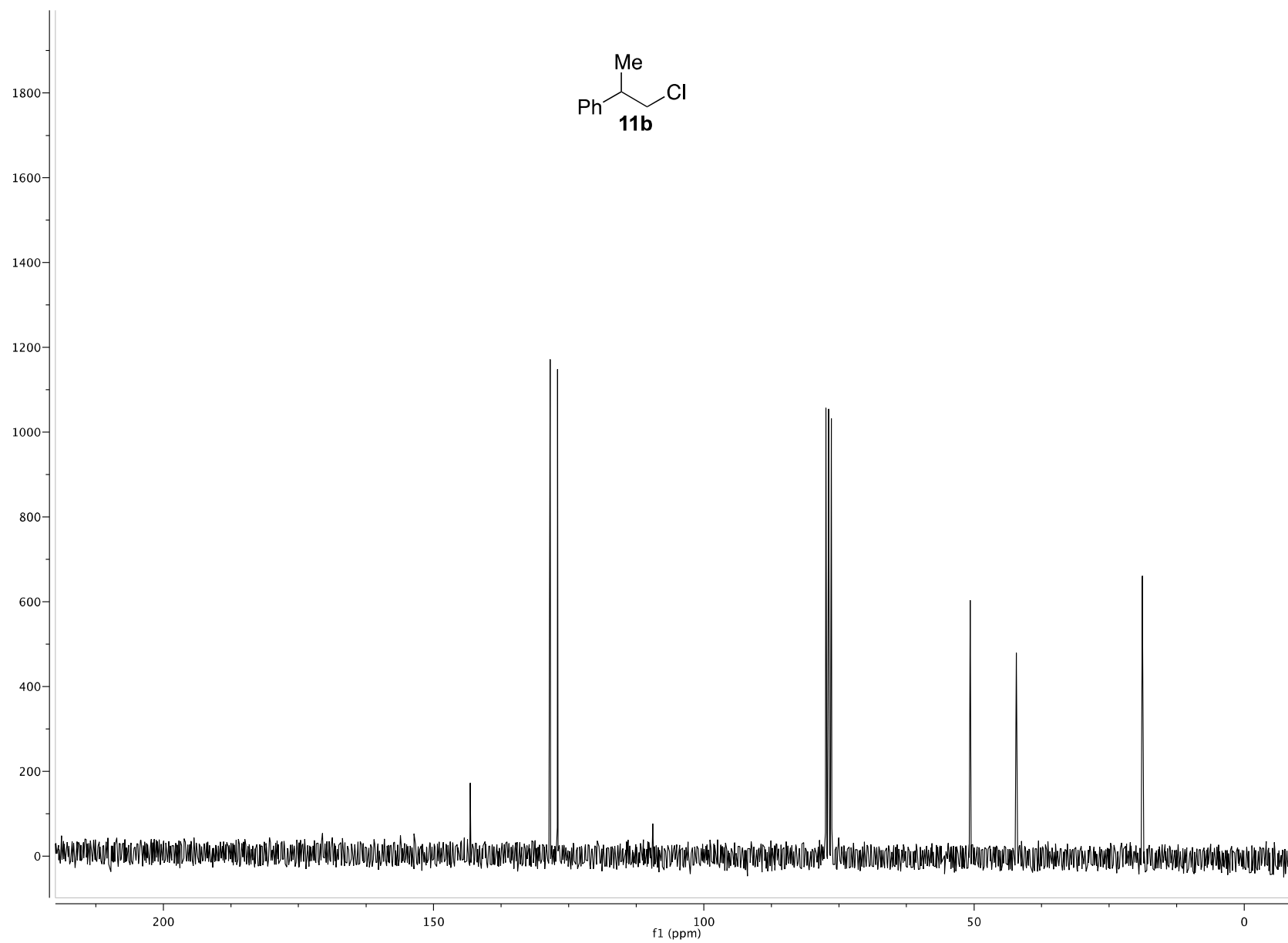


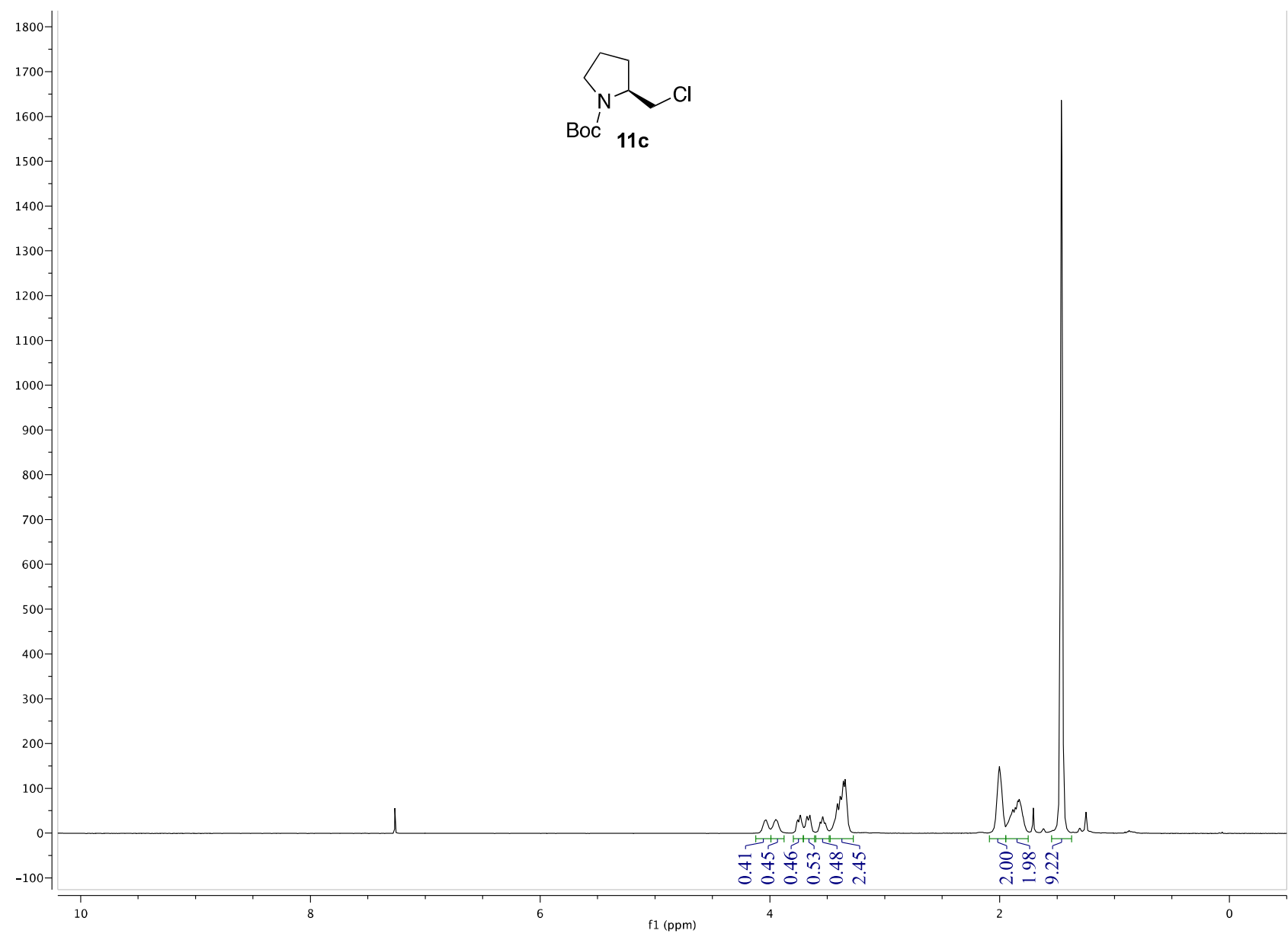
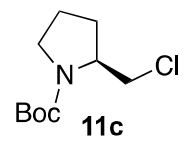


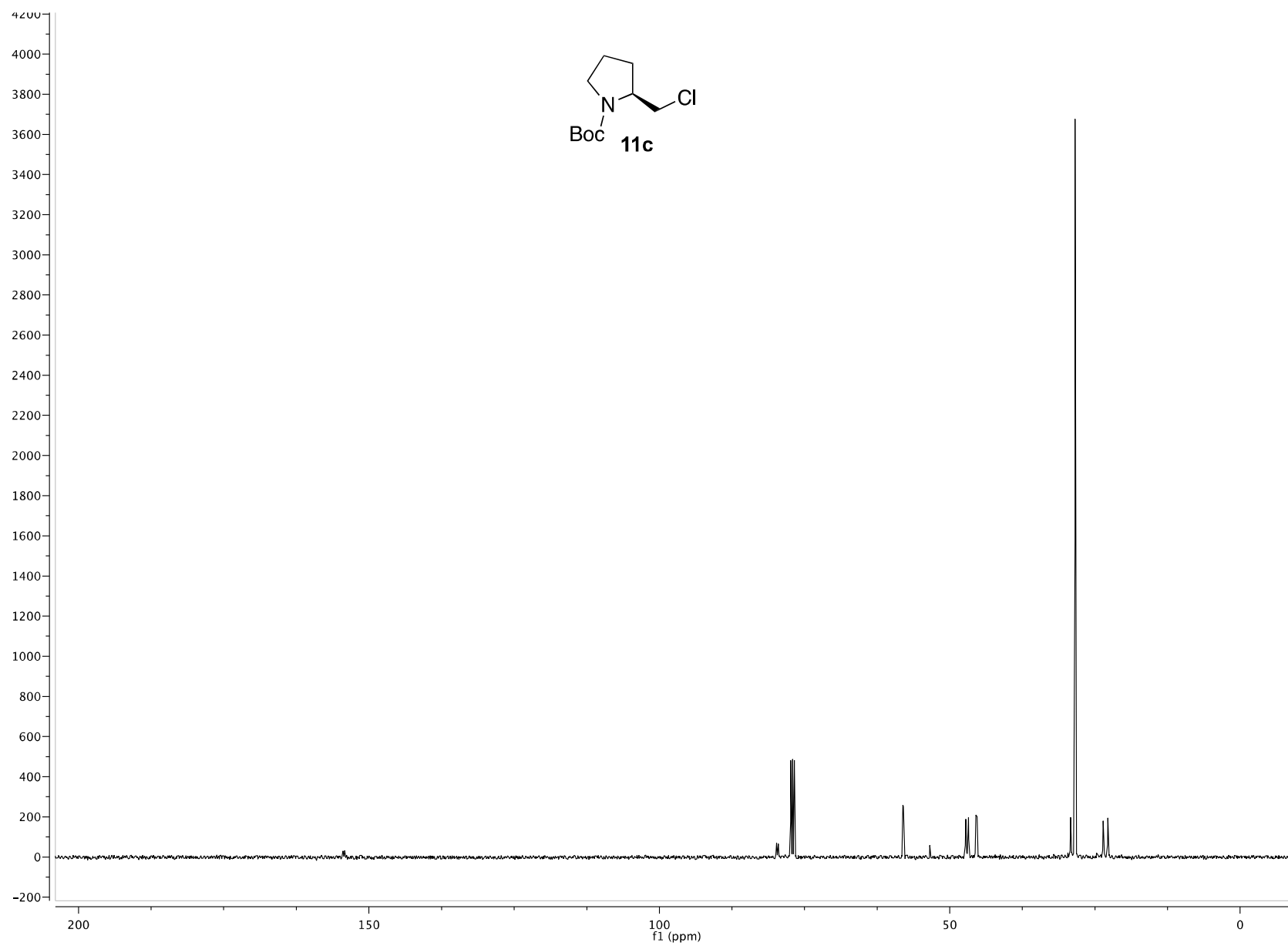


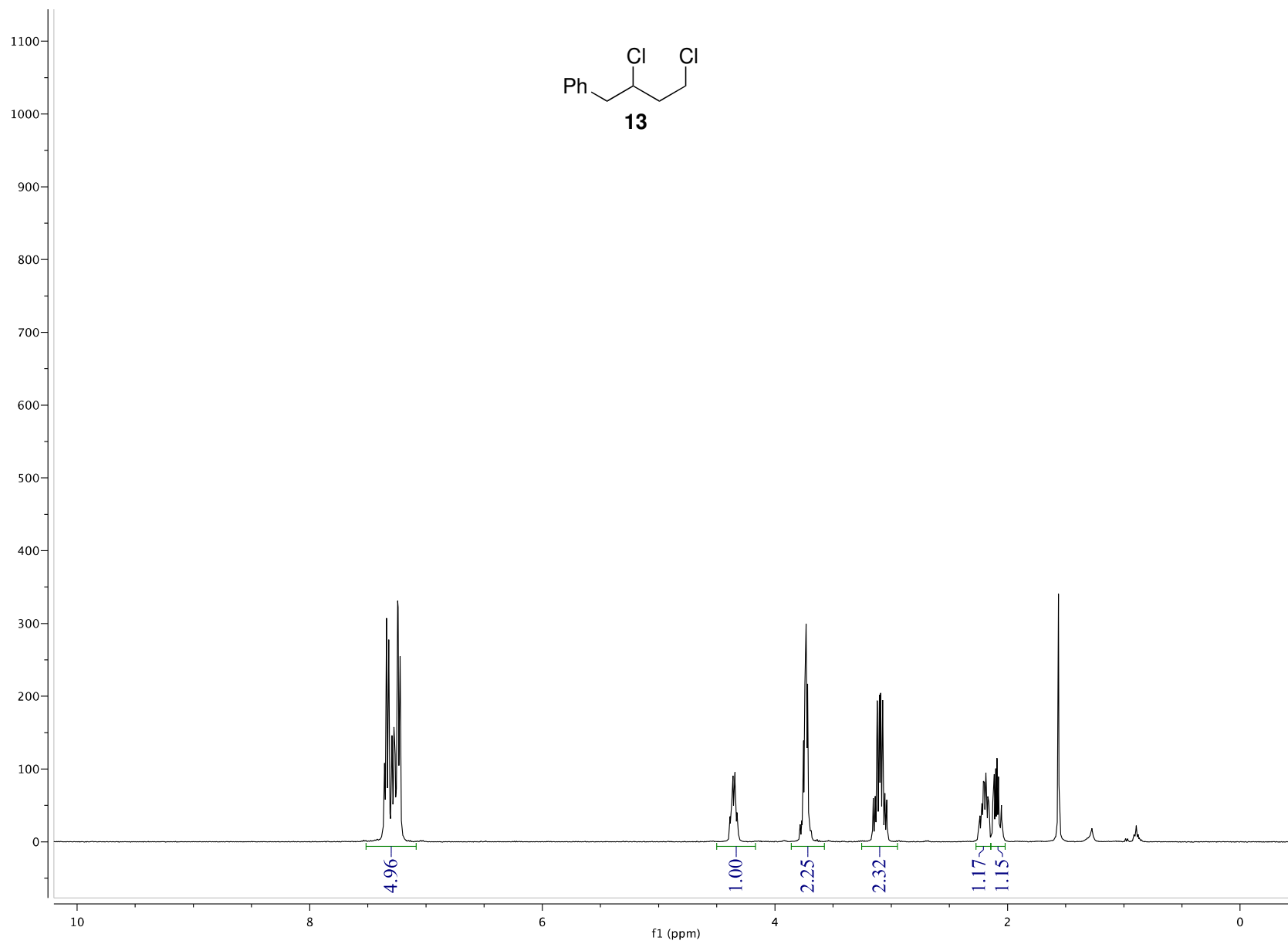
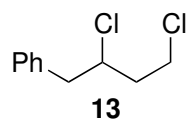




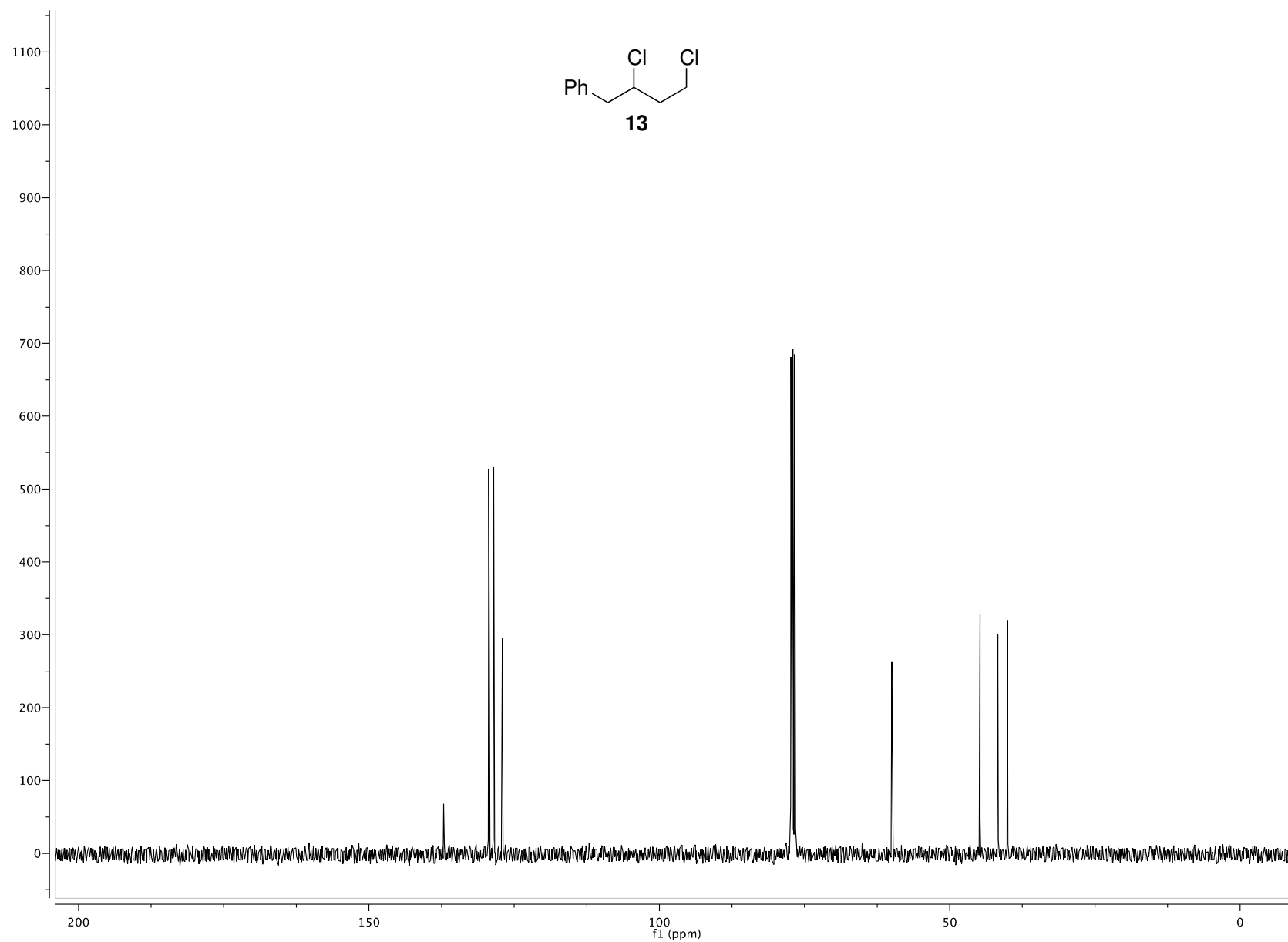


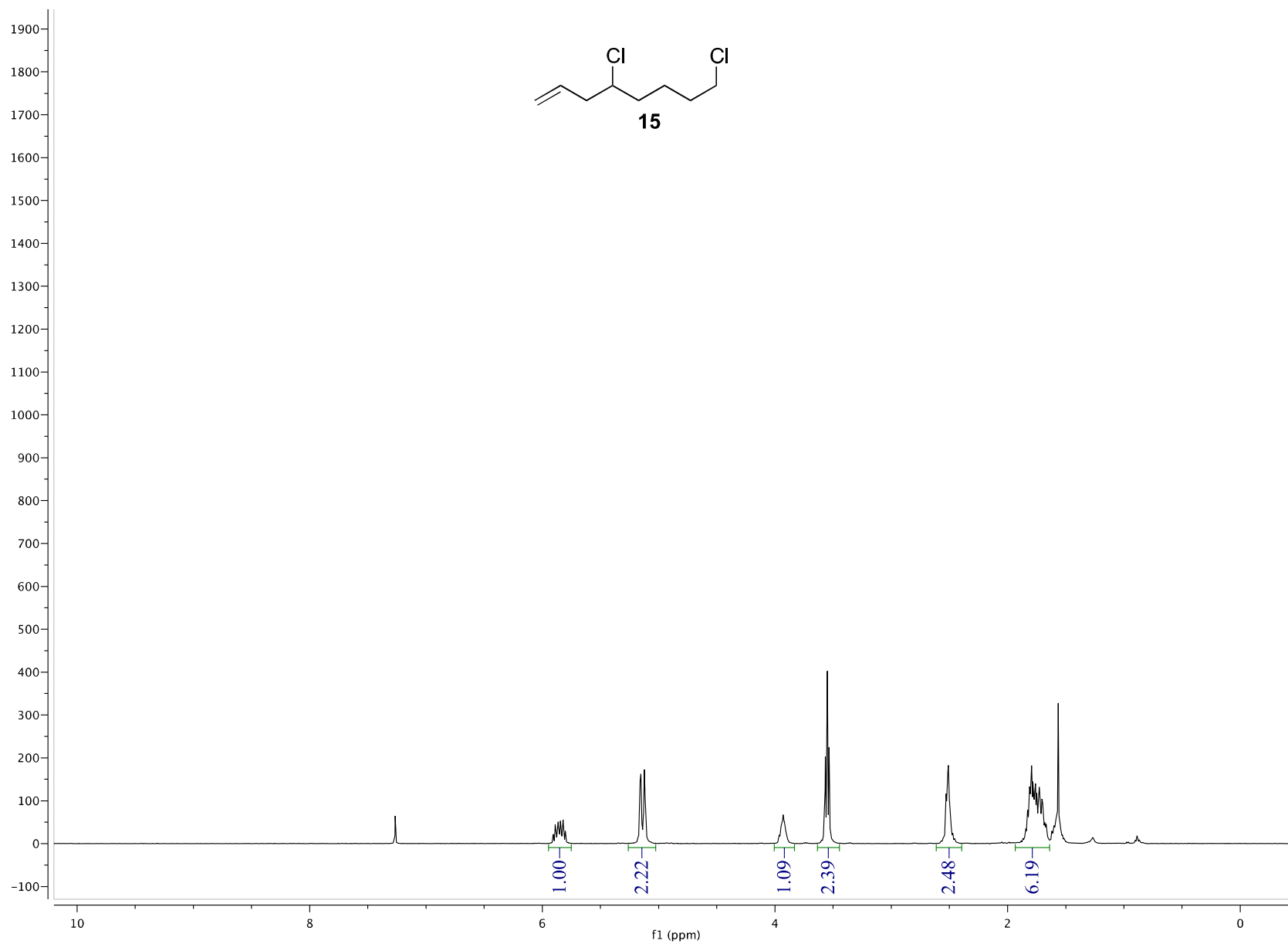
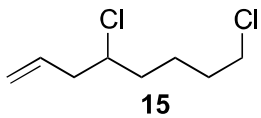




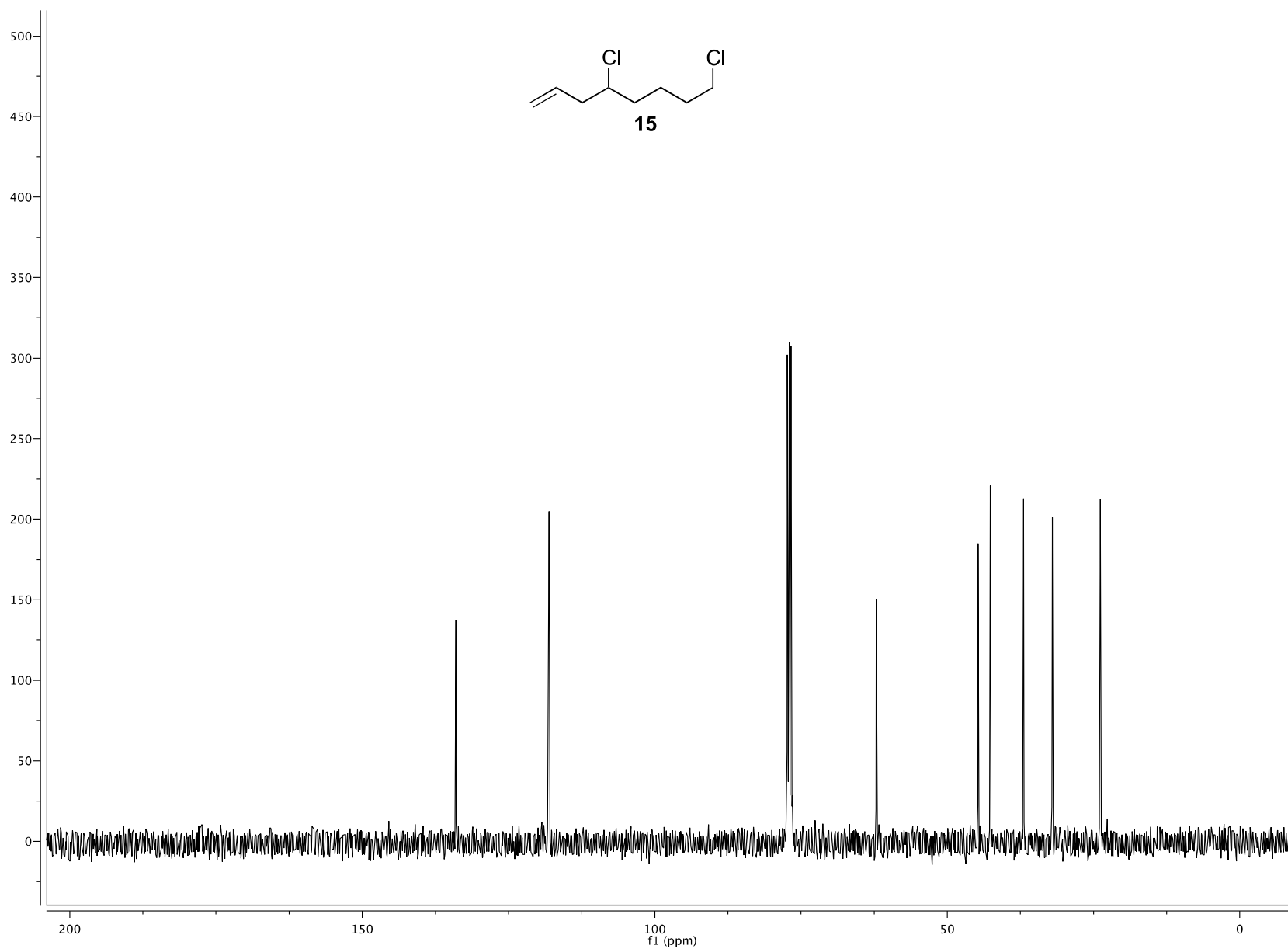
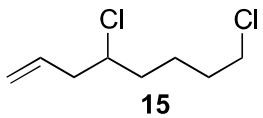


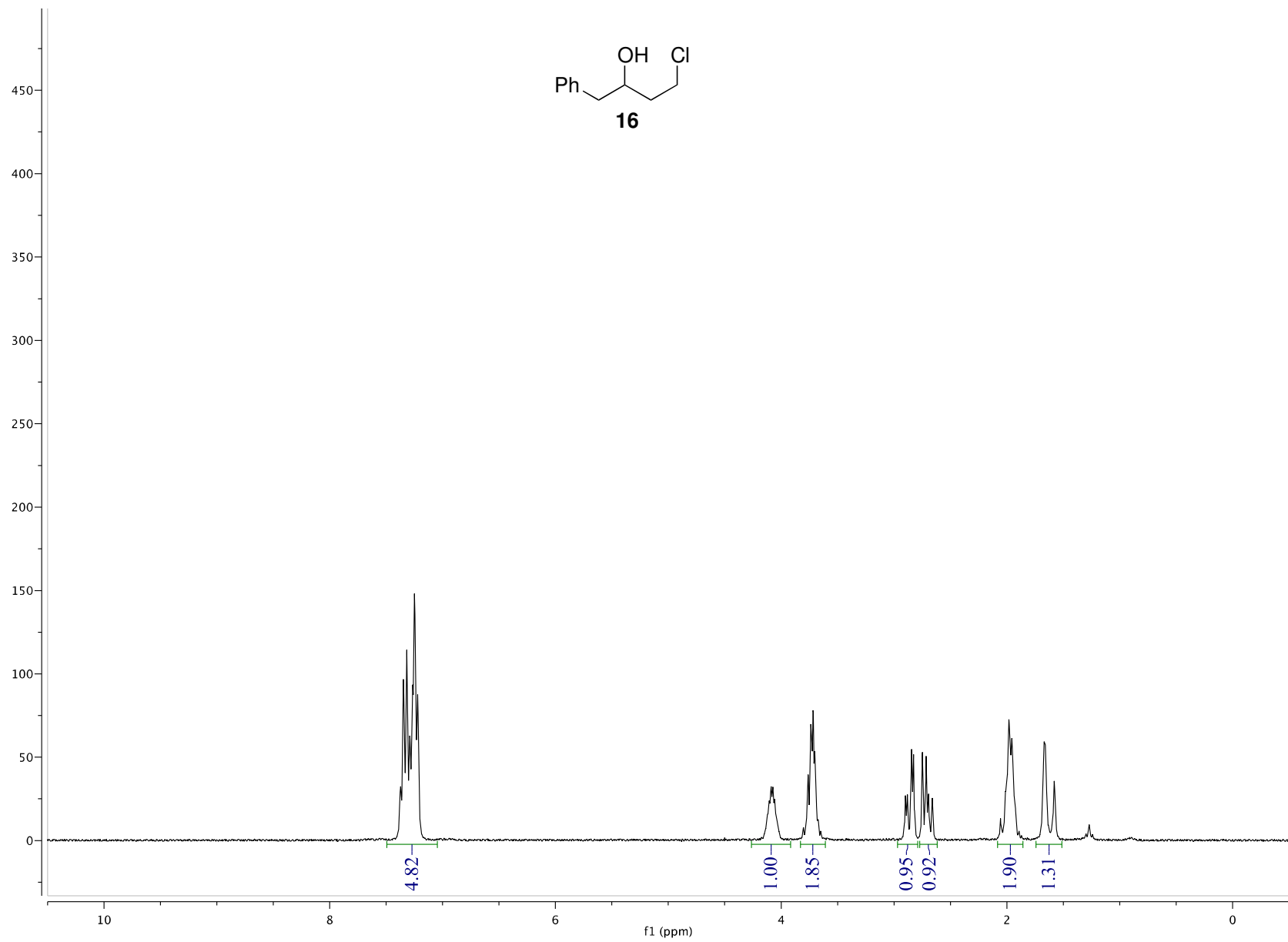
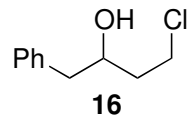
S-58



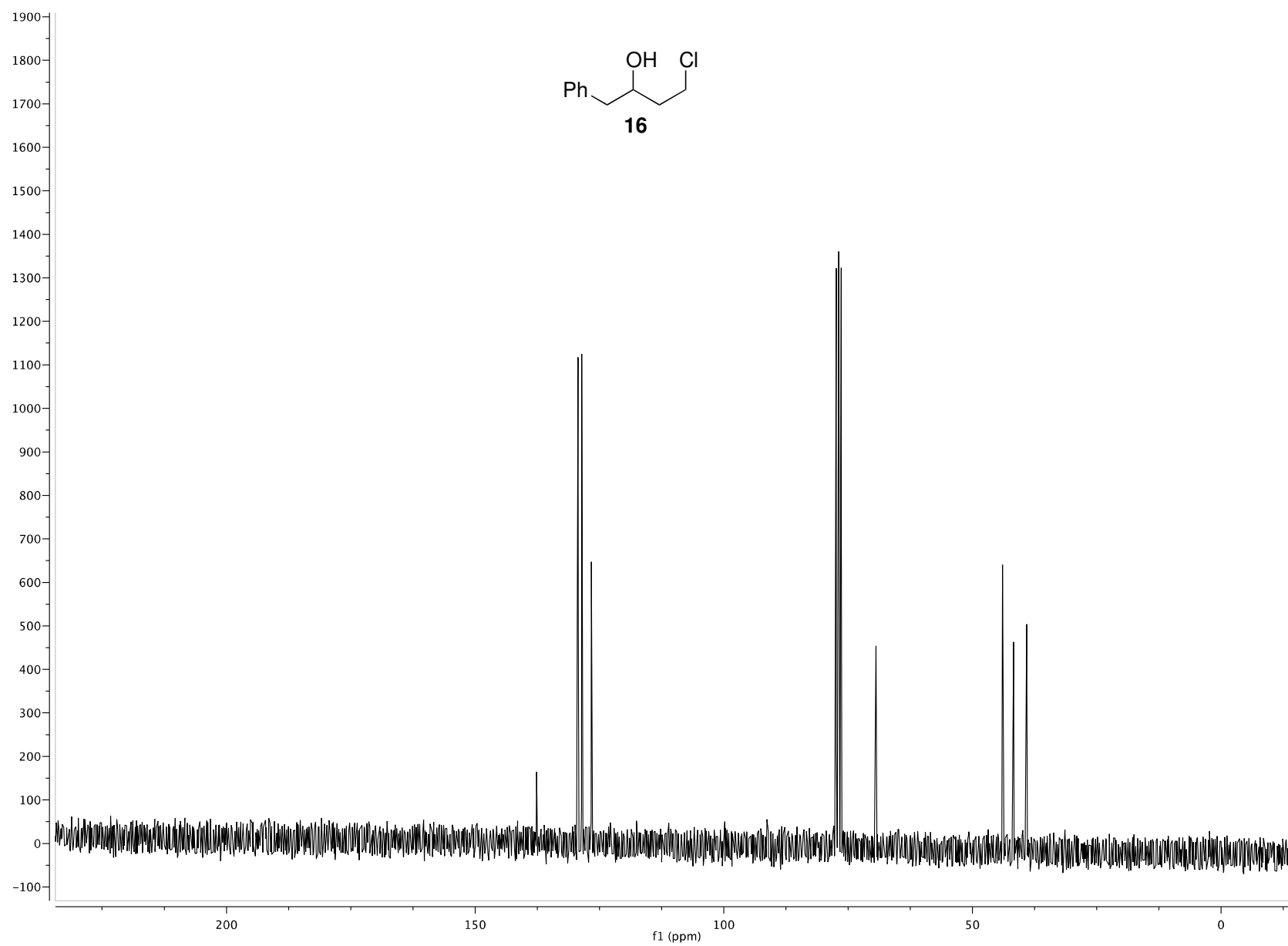


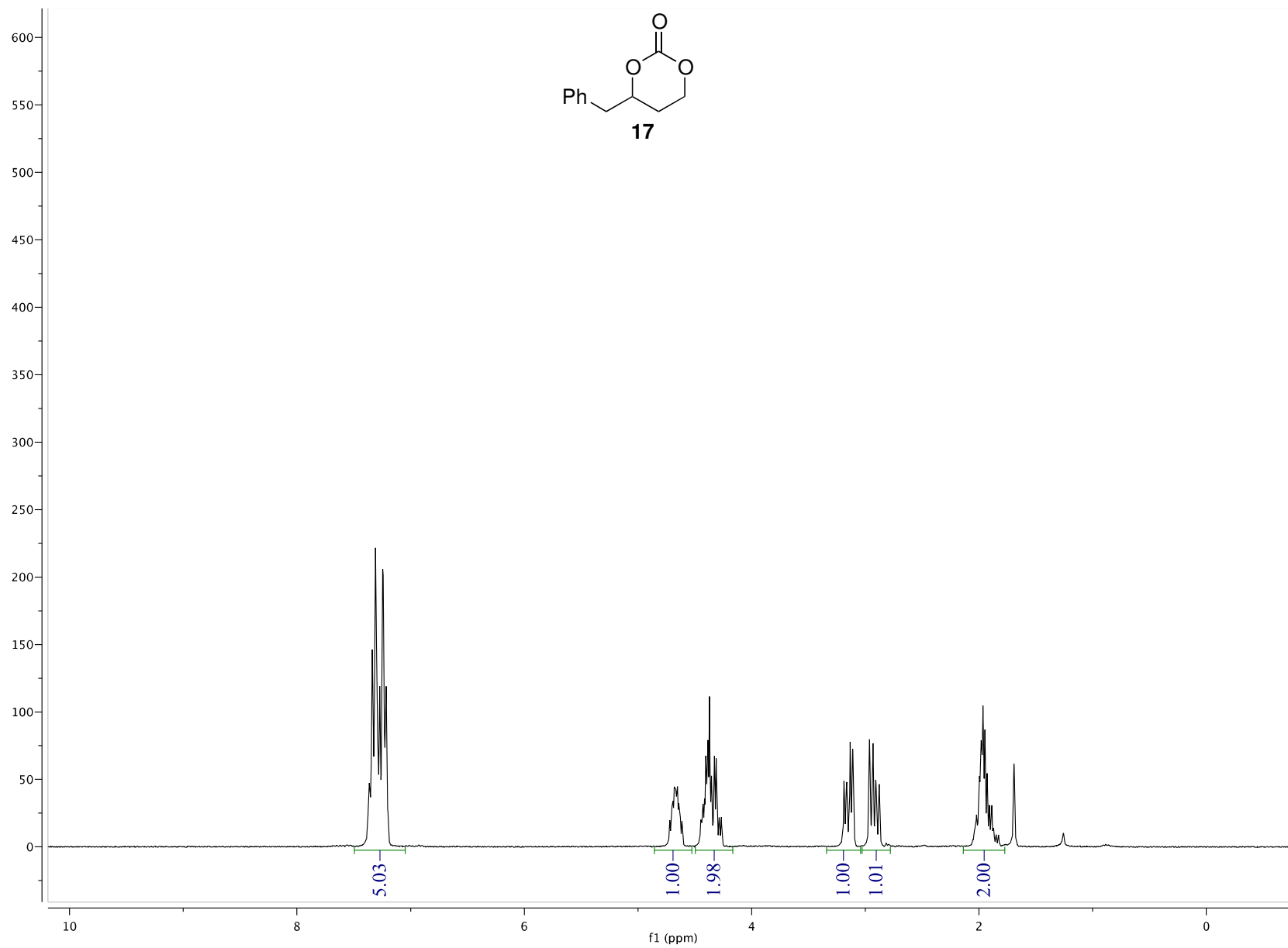
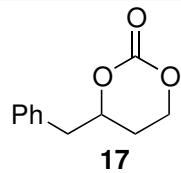
S-60

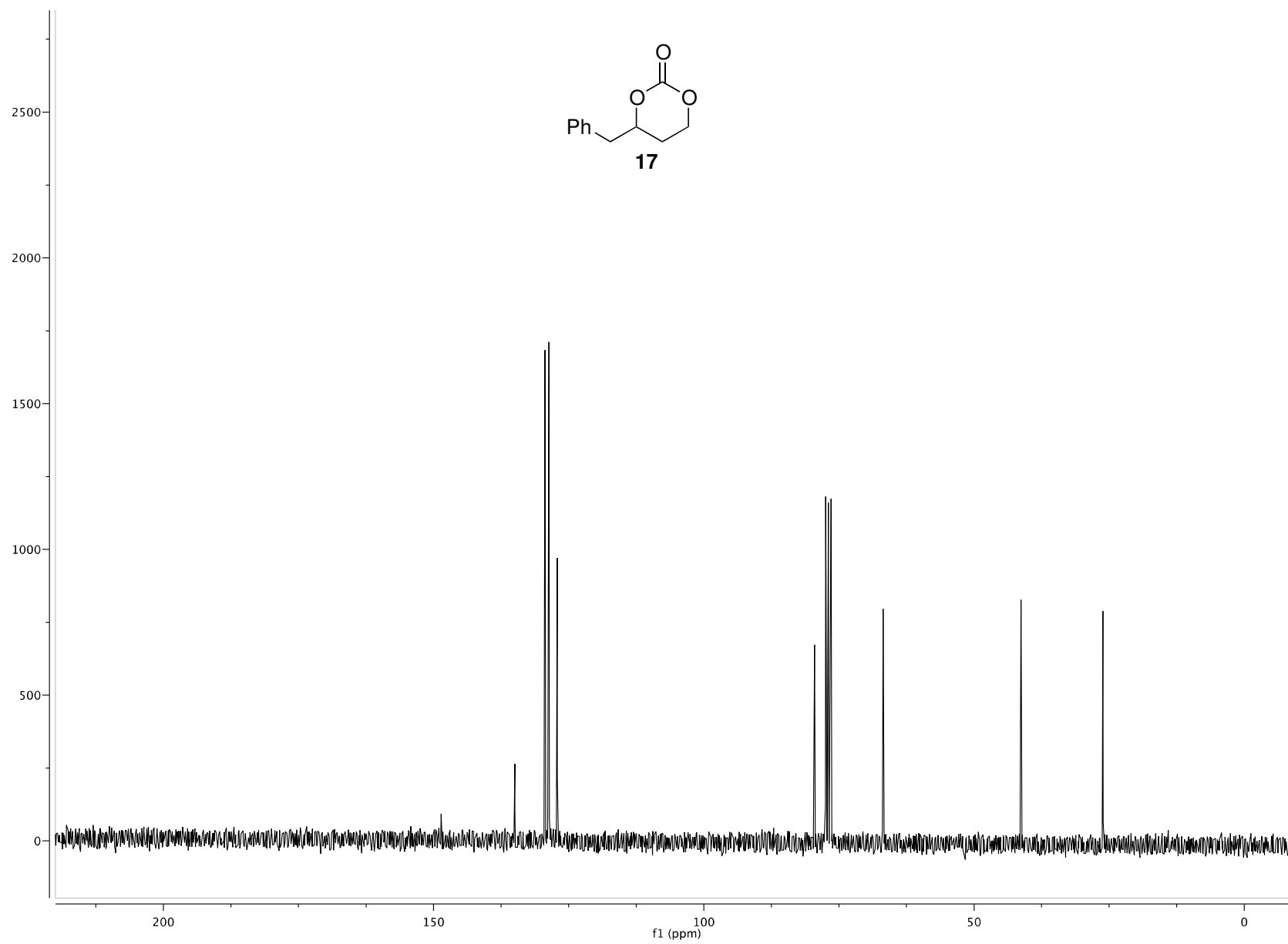


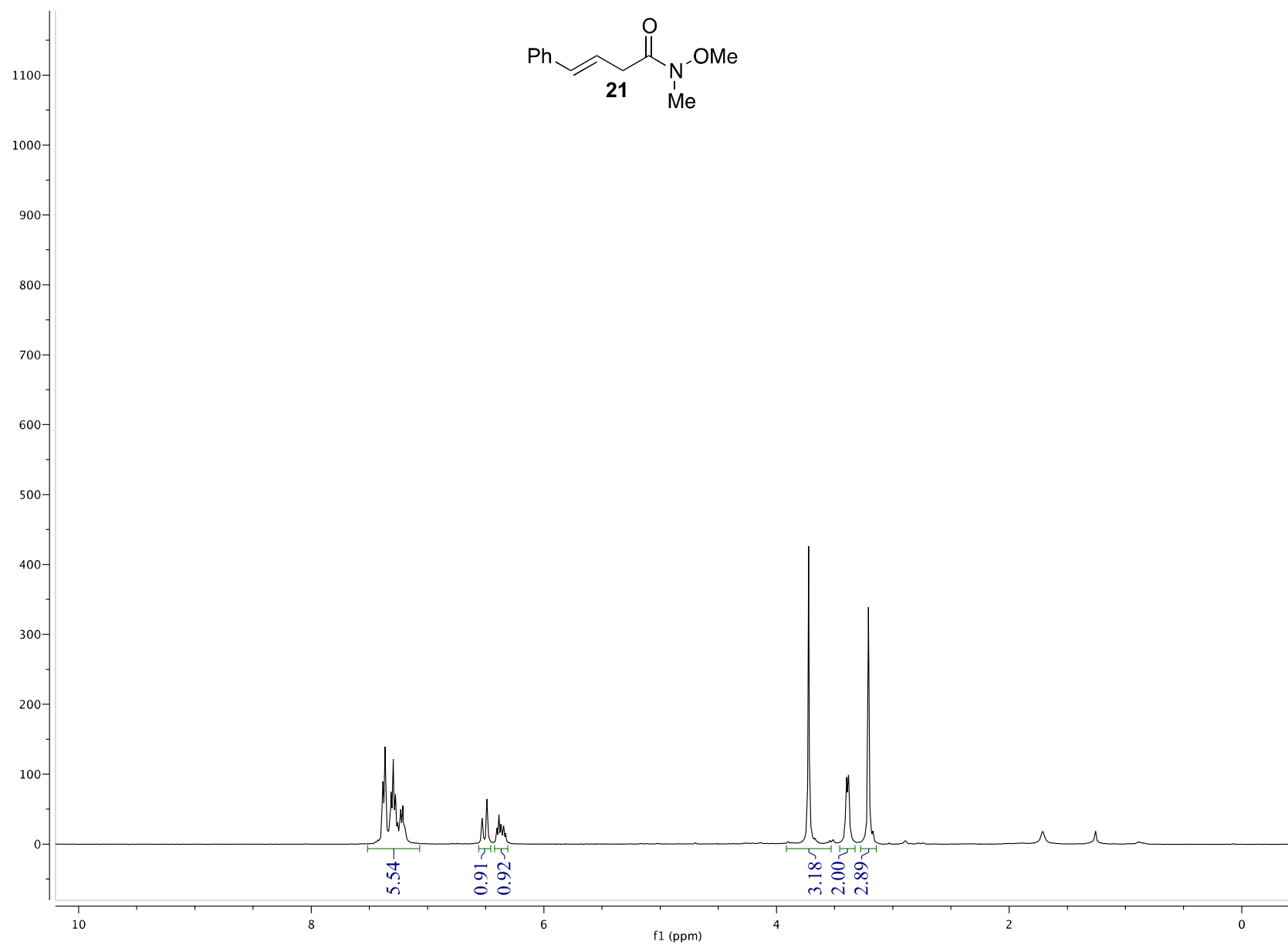
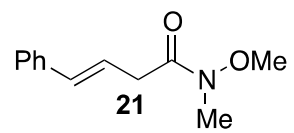


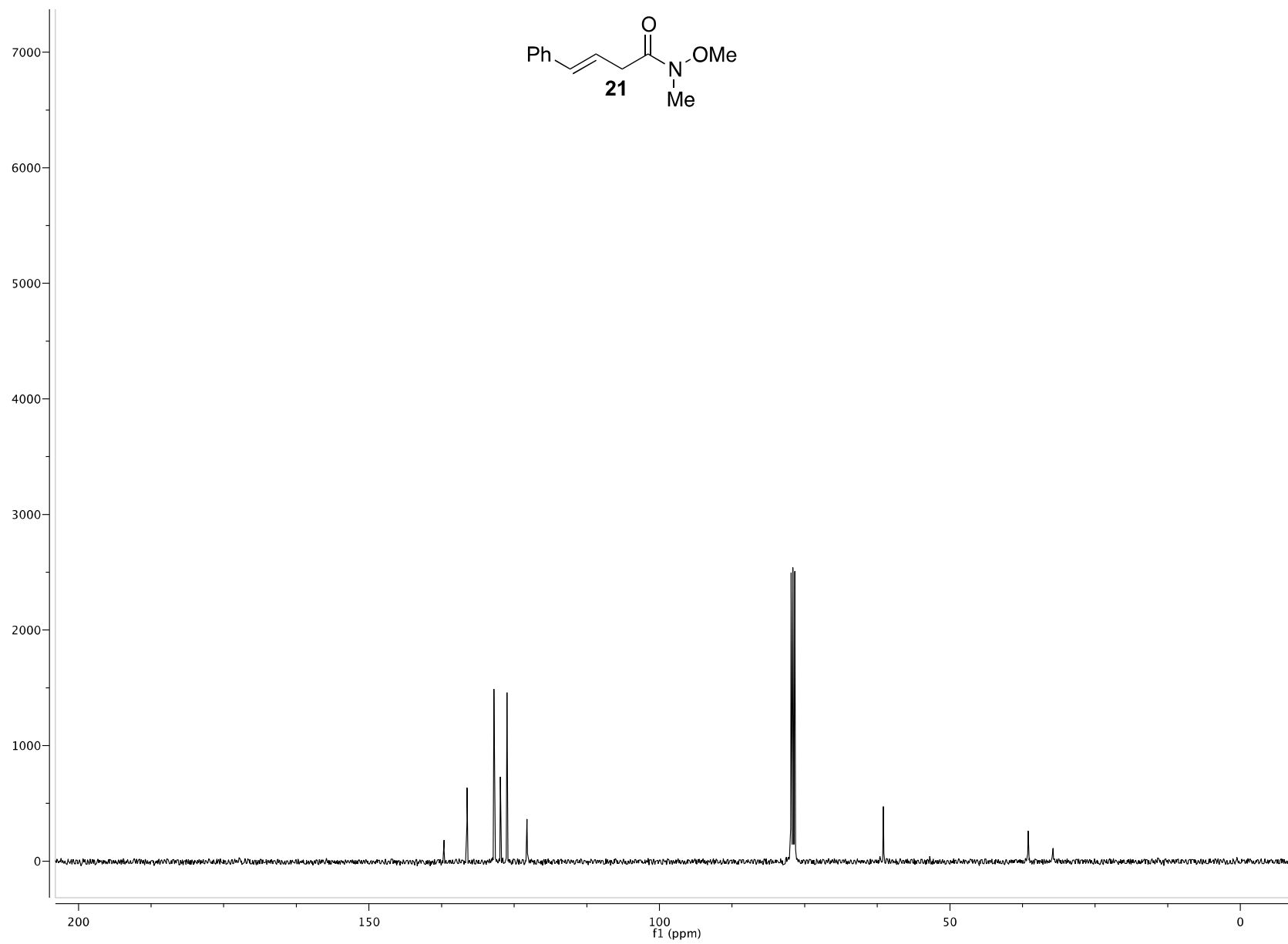
S-62

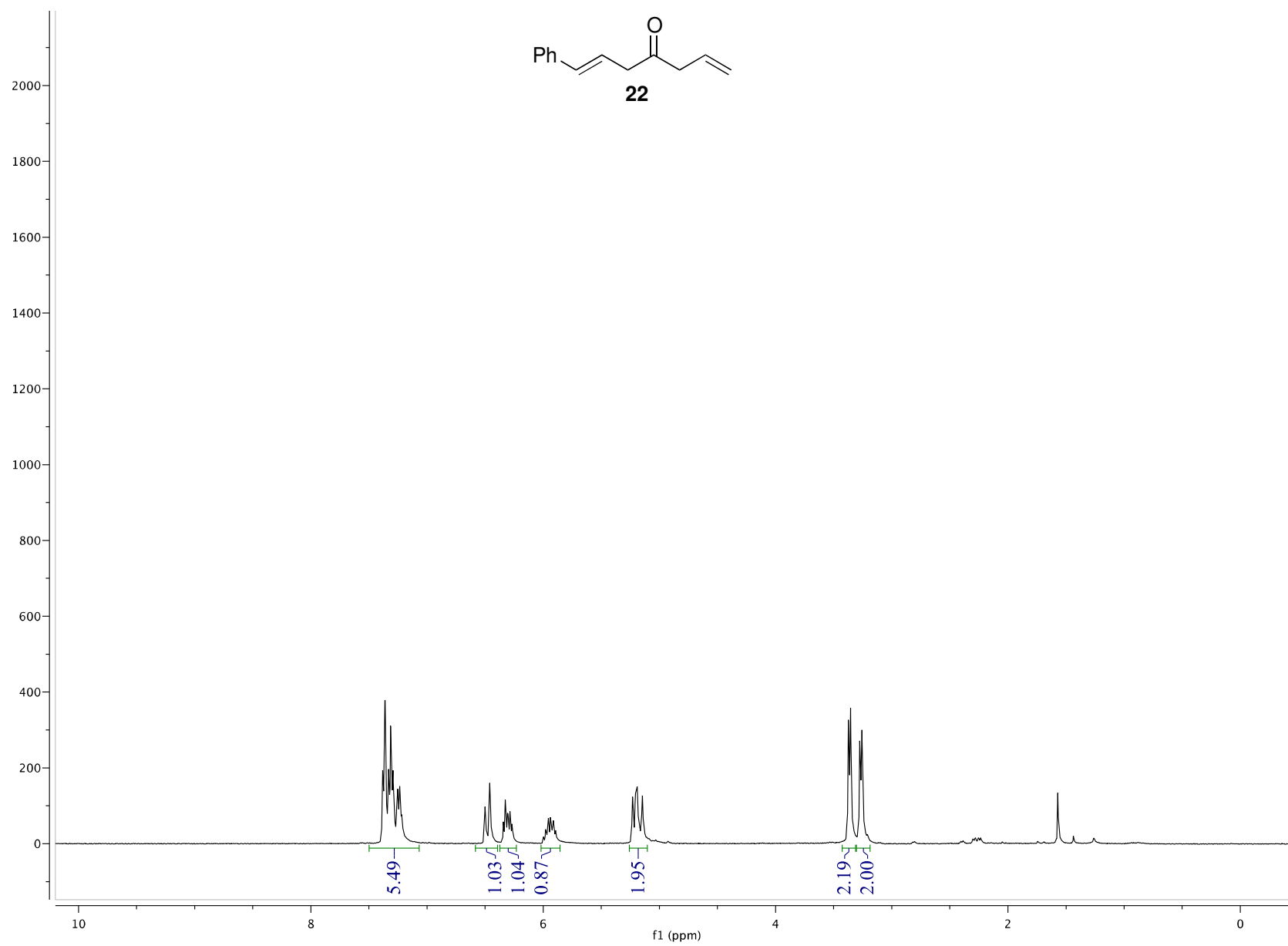
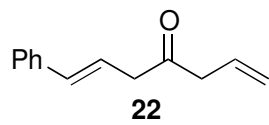












S-68

