



Supporting Information

for

Iodine-mediated hydration of alkynes on keto-functionalized scaffolds: mechanistic insight and the regiospecific hydration of internal alkynes

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Synthetic and analytical details for all compounds

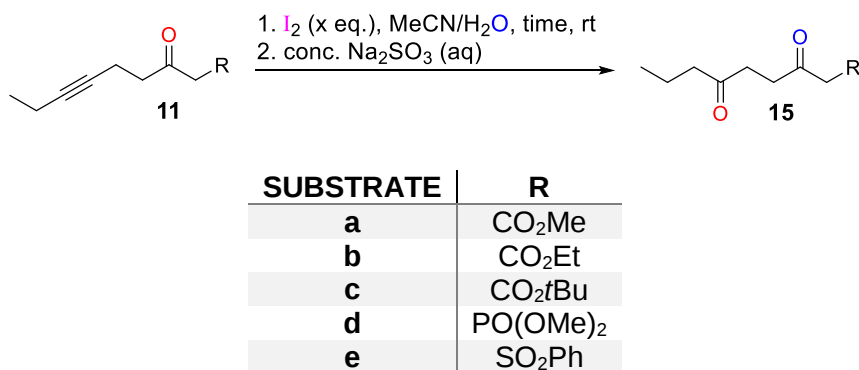
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I. General experimental:

Solvents used in reactions requiring air-free/dry conditions were obtained from a MBraun Manual Solvent Purification System and stored over 4 Å molecular sieves under nitrogen prior to use. Otherwise, unless noted, solvents for procedures performed under ambient conditions were obtained and used as is from commercial sources. Chromatography was performed with Selecto Scientific Si gel (particle size 100–200 µm). NMR spectra were recorded on a Agilent MR400DD2 spectrometer, with a multinuclear probe with two RF channels and variable temperature capability (¹H NMR: 400 MHz, ¹³C NMR: 101 MHz). For NMR, the solvent was CDCl₃ and signals are reported in parts per million (ppm) relative to residual CHCl₃. Signals are described with multiplicity, singlet (s), doublet (d), triplet (t), triplet of doublet (td), quartet (q), sextet (sx) and multiplet (m); coupling constants (*J*; Hz) and integration. The accurate mass was acquired at Georgia State University Mass Spectrometry Facility using Waters QToF micro mass spectrometer with an ESI source in a negative mode. The accurate mass was measured in the presence of an internal standard.

II. Iodine-mediated hydration:



Scheme S1: Iodine-mediated hydration of the keto alkyne scaffolds

a. Representative procedure

Methyl 3,6-dioxononanoate (15a)

A vial equipped with a stirring bar was charged with methyl 3-oxonon-6-ynoate (**11a**, 91.1 mg, 0.5 mmol) dissolved in acetonitrile (10 mL) followed by the addition of iodine (253.8 mg,

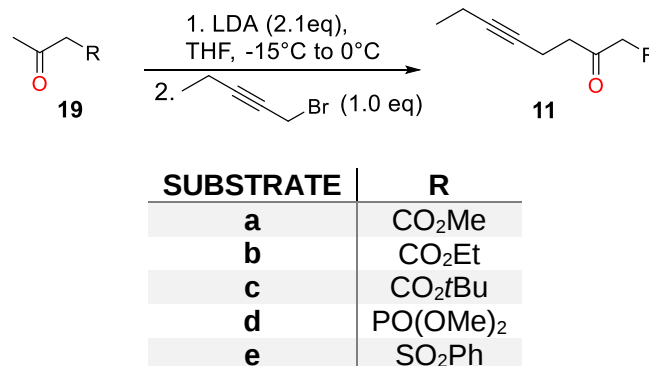
1.0 mmol). The reaction mixture was stirred under ambient atmosphere at room temperature and monitored by TLC. Upon completion, after 1.0 hours, the reaction was quenched with concentrated aqueous sodium sulfite (5 mL) with vigorous stirring for thirty minutes. The resulting yellow suspension was extracted three times with ethyl acetate (10 mL). The combined ethyl acetate extract was washed with DI water (10 mL) followed by brine (10 mL) and, dried with sodium sulfate. The dried organic extract was concentrated under vacuum and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes followed by 15% ethyl acetate in hexanes) to provide **15a** as pale yellow oil (80.1 mg, 80%). **¹H NMR** (400 MHz, CDCl₃) δ 3.72 (s, 3H), 3.50 (s, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 1.59 (sx, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ-209.0, 201.5, 167.5, 52.3, 49.1, 44.6, 36.3, 36.1, 17.3, 13.7; **HRMS** (ESI, negative ion mode) *m/z*: [M - H]⁻ calculated for C₁₀H₁₅O₄: 199.0970; Found: 199.0960.

Ethyl 3,6-dioxononanoate (15b). Synthesized from ethyl 3-oxonon-6-ynoate **11b** according to the procedure for **15a**, reaction time: 1.5 h; purification with 10% ethyl acetate in hexanes followed by 15% ethyl acetate in hexanes, orange oil, (90.5 mg, 85%). **¹H NMR** (400 MHz, CDCl₃) δ 4.15 (q, *J* = 7.4 Hz, 2H), 3.47 (s, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.58 (sx, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 208.9, 201.6, 167.1, 61.3, 49.3, 44.6, 36.3, 36.0, 17.2, 14.0, 13.6 **HRMS** (ESI, negative ion mode) *m/z*: [M - H]⁻ calculated for C₁₁H₁₇O₄: 213.1127; Found: 213.1119.

1-(Dimethylphosphoryl)octane-2,5-dione (15d) Synthesized from dimethyl (2-oxooct-5-yn-1-yl)phosphonate **11d** according to the procedure for **15a**, reaction time: 22 h; purification with 100% ethyl acetate, orange oil, (85.6 mg, 68%). **¹H NMR** (400 MHz, CDCl₃) δ 3.75 (d, ³J_{H-P} = 11.3 Hz, 6H), 3.12 (d, ²J_{H-P} = 22.7 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 2.65 (t, J = 6.1 Hz, 2H), 2.39 (t, J = 7.4 Hz, 2H), 1.56 (sx, J = 7.4 Hz, 2H), 0.86 (t, J = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 209.1, 200.6 (d, J_{C-P} = 6.2 Hz), 53.0 (d, J_{C-P} = 6.5 Hz), 44.5, 41.2 (d, J_{C-P} = 128.9 Hz), 37.5 (d, J_{C-P} = 1.8 Hz), 36.0, 17.2, 13.6; **HRMS** (ESI, negative ion mode) *m/z*: [M - H]⁻ calculated for C₁₀H₁₈O₅P: 249.0892; Found: 249.0883.

1-(Phenylsulfonyl)octane-2,5-dione (15e). Synthesized from 1-(phenylsulfonyl)oct-5-yn-2-one **11e** according to the procedure for **15a**, reaction time: 3.5 h; purification with 20% ethyl acetate in hexanes, orange oil, (100.3 mg, 71%). **¹H NMR** (400 MHz, CDCl₃) δ 7.88 (d, J = 7.9 Hz, 2H), 7.65 (tt, J = 7.4, 1.5 Hz, 1H), 7.55 (tt, J = 7.9, 1.5 Hz, 2H), 4.21 (s, 2H), 2.92 (t, J = 5.8 Hz, 2H), 2.69 (t, J = 5.8 Hz, 2H), 2.37 (t, J = 7.3 Hz, 2H), 1.55 (sx, J = 7.4 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 208.6, 197.1, 138.8, 134.2, 129.3, 128.2, 67.2, 44.4, 37.7, 36.3, 17.2, 13.6; **HRMS** (ESI, negative ion mode) *m/z*: [M - H]⁻ calculated for C₁₄H₁₇O₄S: 281.0848; Found: 281.0846.

III. Synthesis of the keto alkyne scaffolds:



Scheme S1: Synthesis of the keto alkyne scaffolds

a. Representative procedure

Methyl 3-oxonon-6-ynoate (11a)

An oven-dried round bottomed flask equipped with a stirring bar and nitrogen-inlet was charged with freshly distilled diisopropylamine (2.54 mL, 17.4 mmol) in dry THF (25.5 mL). The solution was cooled with an ice-water bath (0 °C) and treated with a drop-wise addition of *n*-butyllithium (2.5 M hexanes solution, 6.36 mL, 17.4 mmol). After 30 minutes, the resulting transparent, yellow solution was cooled with an ice-salt water bath (−15 °C) and methyl 3-oxobutanoate (0.82 mL, 7.57 mmol) was added drop-wise. The resulting solution had an intense orange-brown color. After 45 minutes, the reaction mixture was treated with drop-wise addition of 1-bromopent-2-yne (0.72 mL, 7.64 mmol). The reaction mixture was stirred overnight and allowed to warm to room temperature. The reaction was quenched with an aqueous solution of saturated ammonium chloride (10 mL) and extracted twice with ethyl acetate (50 mL). The combined organic extract was washed once with deionized (DI) water (10 mL) followed by brine (10 mL), and dried with sodium sulfate. The dried organic extract was concentrated under vacuum and the crude orange product was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide **11a**, yellow oil, (745.0 mg, 54%). Compound **11a** is known [1]. ¹H NMR (400

MHz, CDCl₃) δ 3.72 (s, 3H), 3.47 (s, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.43 (tt, J = 7.3, 2.4 Hz, 2H), 2.11 (qt, J = 7.5, 2.4 Hz, 2H), 1.07 (t, J = 7.5 Hz 3H); ¹³C NMR (101 MHz, CDCl₃) δ 201.0, 167.4, 89.4, 82.6, 52.4, 48.9, 42.3, 14.1, 13.3, 12.3.

Ethyl 3-oxonon-6-ynoate (11b). Synthesized from ethyl acetoacetate according to the procedure for **11a**; purification with 10% ethyl acetate in hexanes, yellow oil, (1.02 g, 52% based on 10 mmol ethyl acetoacetate). ¹H NMR (400 MHz, CDCl₃) δ 4.19 (q, J = 7.1 Hz, 3H), 3.45 (s, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.42 (t, J = 7.3, 2.4 Hz, 2H), 2.12 (qt, J = 7.5, 2.4 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 201.1, 166.9, 89.7, 82.5, 61.4, 49.3, 42.3, 14.1, 14.1, 13.3, 12.3; HRMS (ESI, negative ion mode) m/z : [M - H]⁻ calculated for C₁₁H₁₅O₃: 195.1021; Found: 195.1028.

tert-Butyl 3-oxonon-6-ynoate (11c). Synthesized from *tert*-butyl acetoacetate according to the procedure for **11a**; purification with 5% ethyl acetate in hexanes, yellow oil, (795.0 mg, 35% based on 10 mmol of *tert*-butyl acetoacetate). ¹H NMR (400 MHz, CDCl₃) δ 3.35 (s, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.41 (tt, J = 7.3, 2.4 Hz, 2H), 2.11 (qt, J = 7.5, 2.4 Hz, 2H), 1.45 (s, 9H), 1.07 (t, J = 7.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 201.6, 166.2, 82.4, 82.0, 50.6, 42.3, 27.9, 14.1, 13.2, 12.3; HRMS (ESI, negative ion mode) m/z : [M - H]⁻ calculated for C₁₃H₁₉O₃: 223.1334; Found: 223.1334.

Dimethyl (2-oxooct-5-yn-1-yl)phosphonate (11d). Synthesized from dimethyl (2-oxopropyl)phosphonate according to the procedure for **11a**; purification with 60% ethyl acetate in hexanes, orange oil, (566.0 mg, 48% based on 5 mmol of dimethyl (2-

oxopropyl)phosphonate). **¹H NMR** (400 MHz, CDCl₃) δ 3.74 (d, ³J_{H-P} = 11.2 Hz, 6H), 3.07 (d, ²J_{H-P} = 22.7 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.37 (tt, J = 7.2, 2.4 Hz, 2H), 2.08 (qt, J = 7.5, 2.4 Hz, 2H), 1.04 (t, J = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 200.2 (d, ²J_{H-P} = 6.5 Hz), 82.4, 77.3, 53.0 (d, ²J_{H-P} = 6.5 Hz), 43.4 (d, ³J_{H-P} = 1.4 Hz), 41.9 & 40.6 (d, J = 128.3 Hz), 14.1, 13.2, 12.3; **HRMS** (ESI, negative ion mode) *m/z*: [M - H]⁻ calculated for C₁₀H₁₆O₄P: 231.0786; Found: 231.0788.

1-(Phenylsulfonyl)oct-5-yn-2-one (11e). Synthesized from phenylsulfonylacetone according to the procedure for **11a**; purification with 20% ethyl acetate in hexanes followed by 30% ethyl acetate in hexanes, beige solid, (1.09 g, 41% based on 10 mmol phenylsulfonylacetone). **Mp** 58.4–60.8 °C, **¹H NMR** (400 MHz, CDCl₃) δ 7.87 (d, J = 7.7 Hz, 2H), 7.67 (t, J = 7.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 2H), 4.17 (s, 2H), 2.90 (t, J = 7.1 Hz, 2H), 2.39 (tt, J = 7.1, 2.4 Hz, 2H), 2.10 (qt, J = 7.5, 2.4 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 196.6, 138.5, 134.3, 129.3, 128.3, 82.8, 76.9, 66.9, 43.6, 14.1, 13.2, 12.3; **HRMS** (ESI, negative ion mode) *m/z*: [M - H]⁻ calculated for C₁₄H₁₅O₃S: 263.0742; Found: 264.0744.

IV. C/H Correlation spectrum for 9

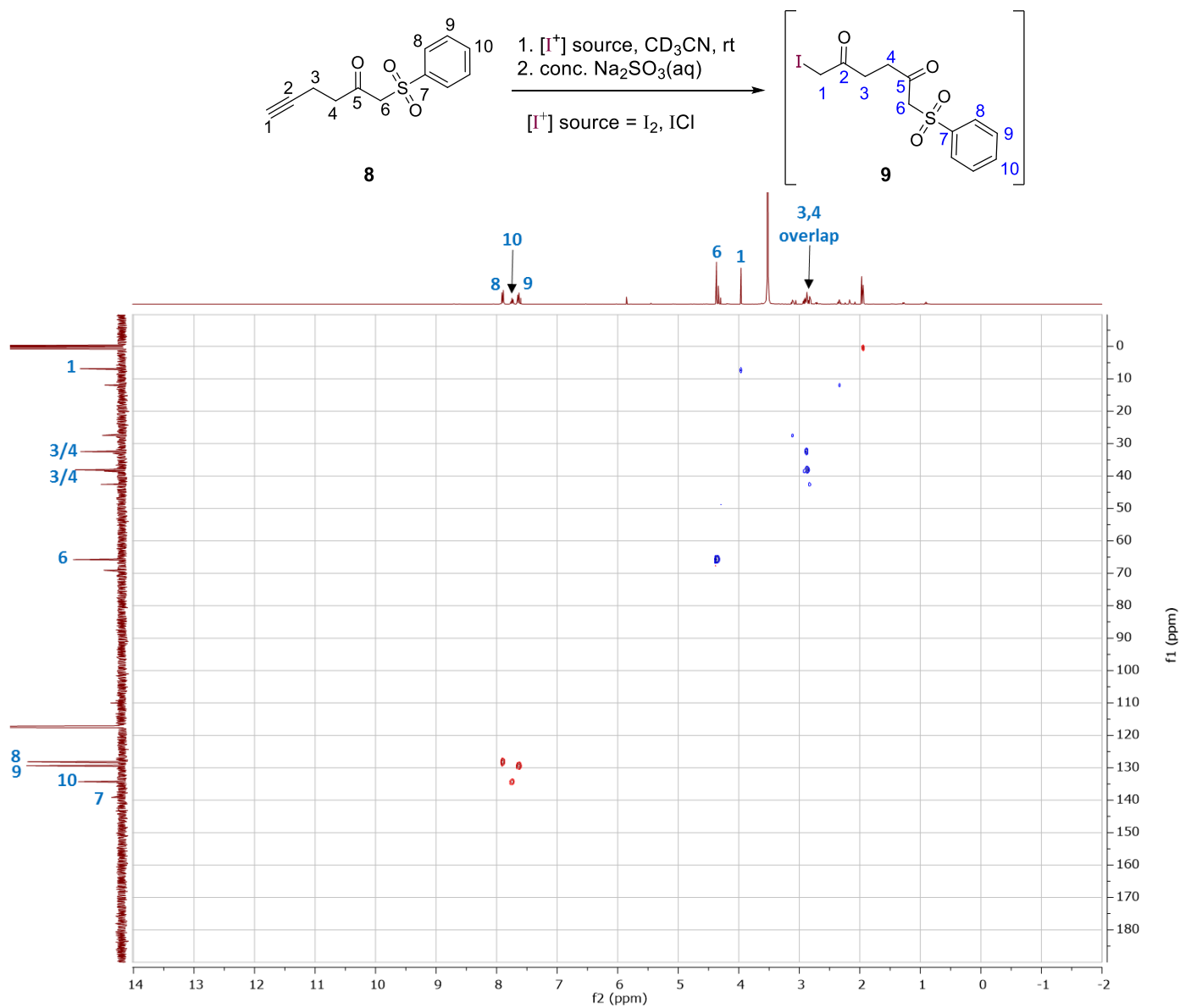


Figure S1: HSQC C/H Correlation spectra for α -iodo intermediate **9** in CD₃CN.

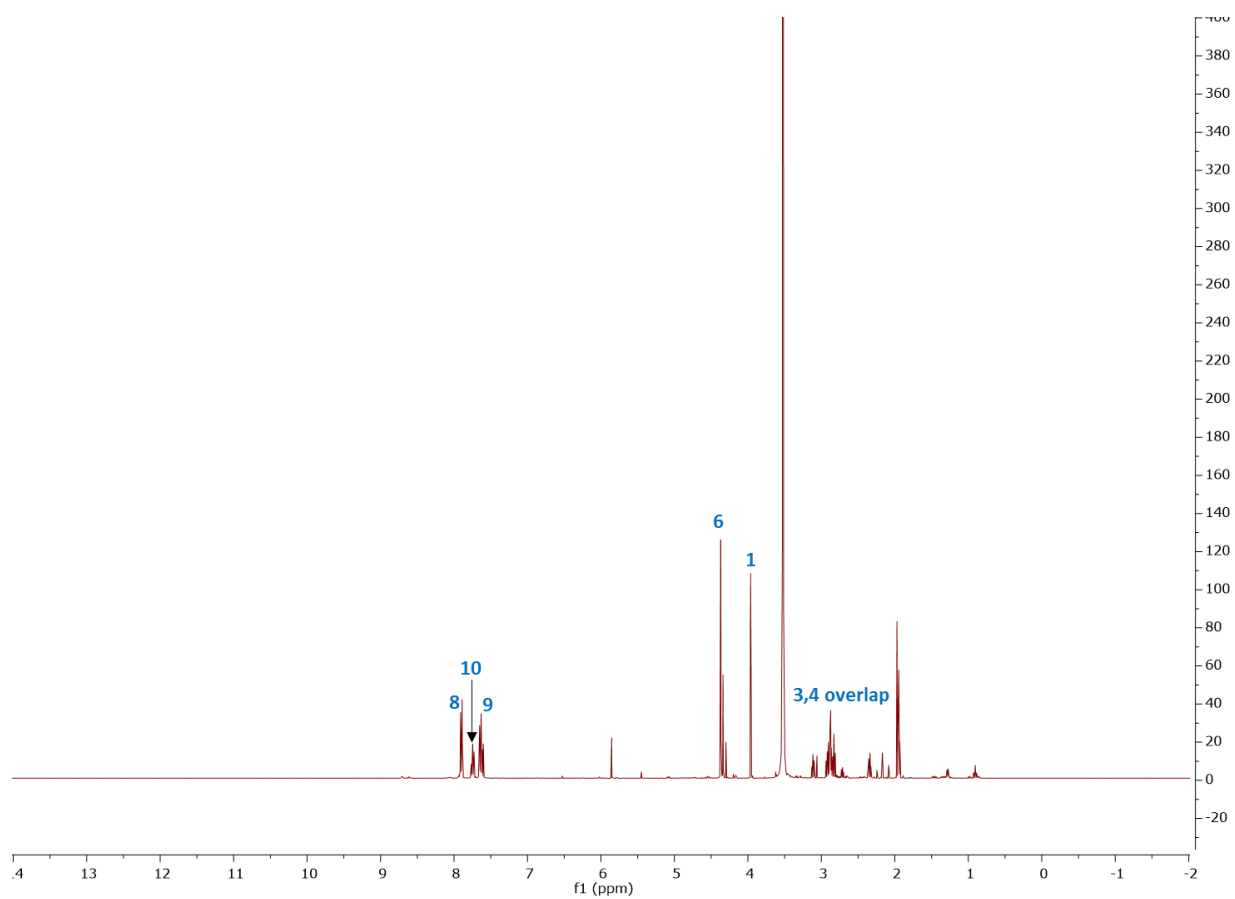


Figure S2: ^1H NMR Spectrum for α -iodo intermediate **9** in CD_3CN

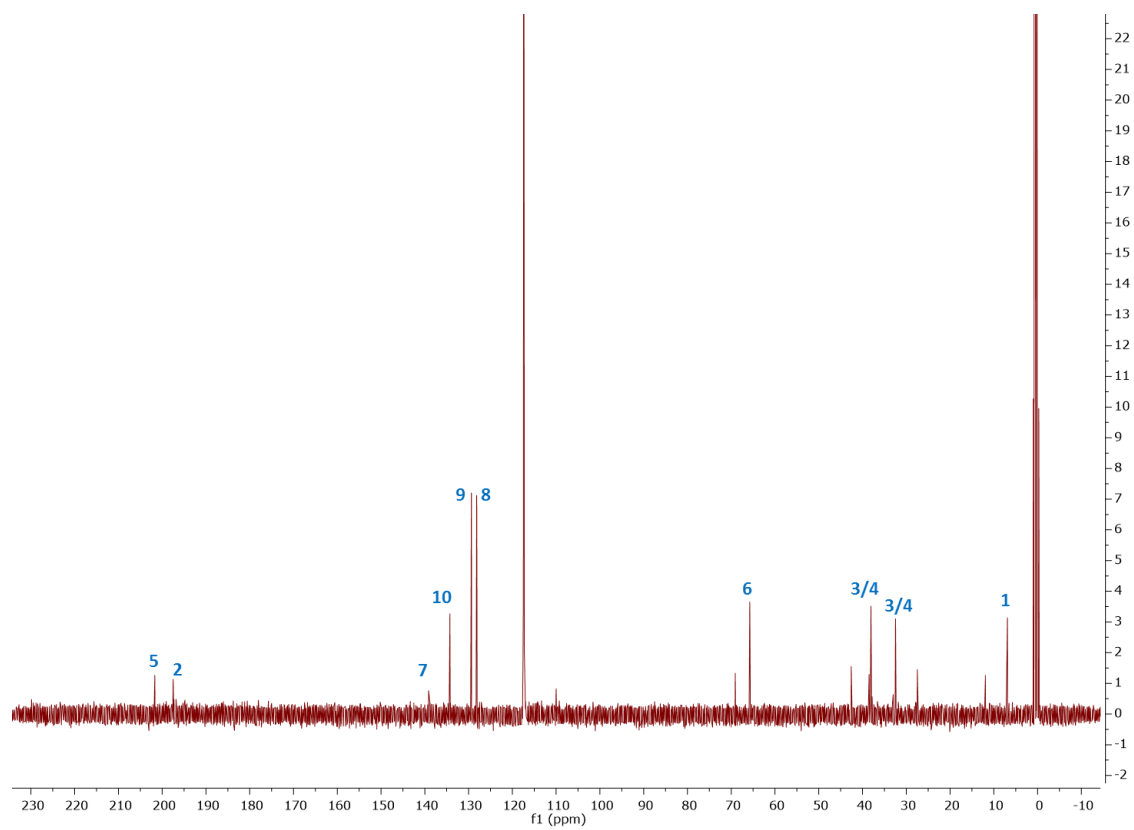
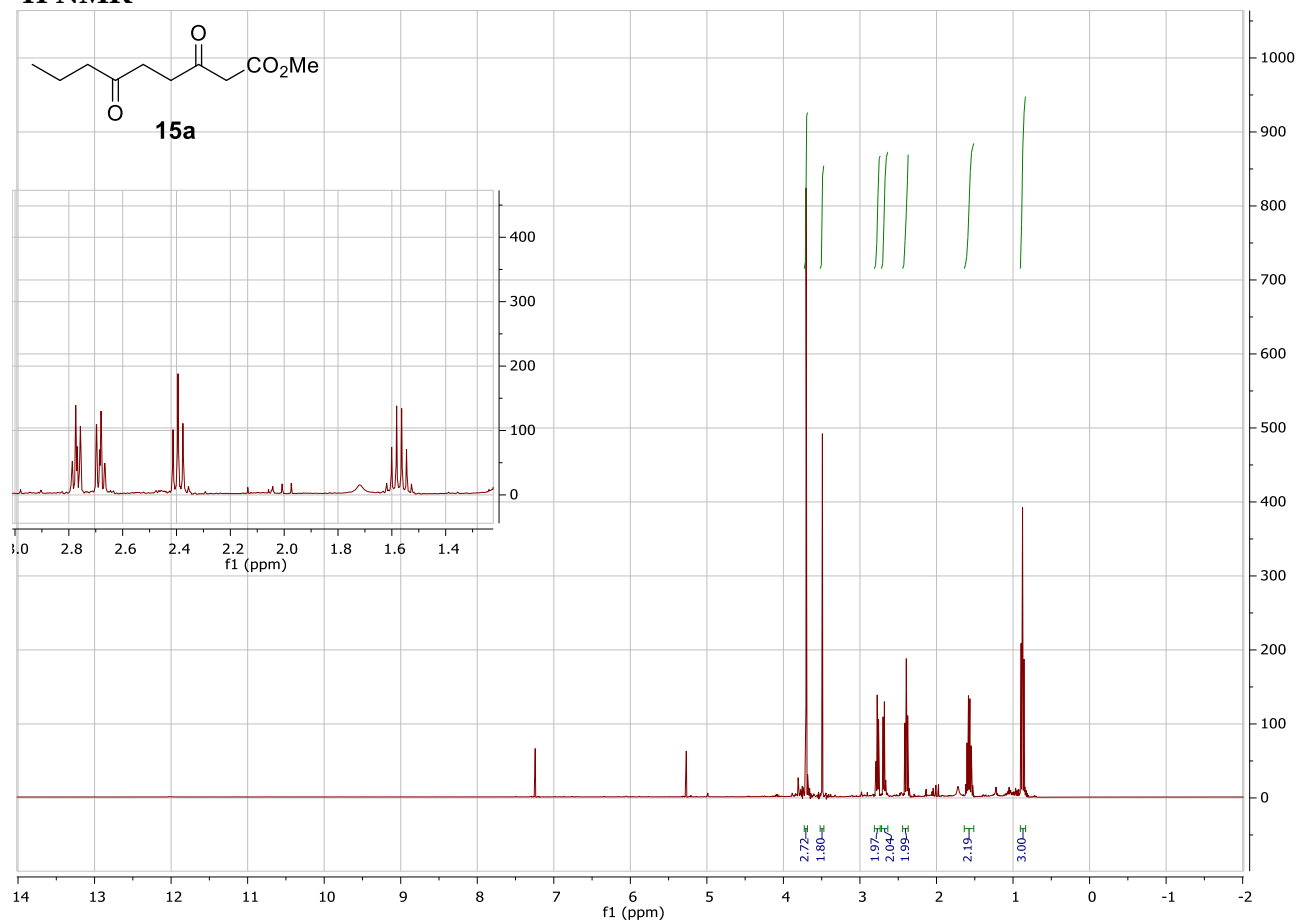


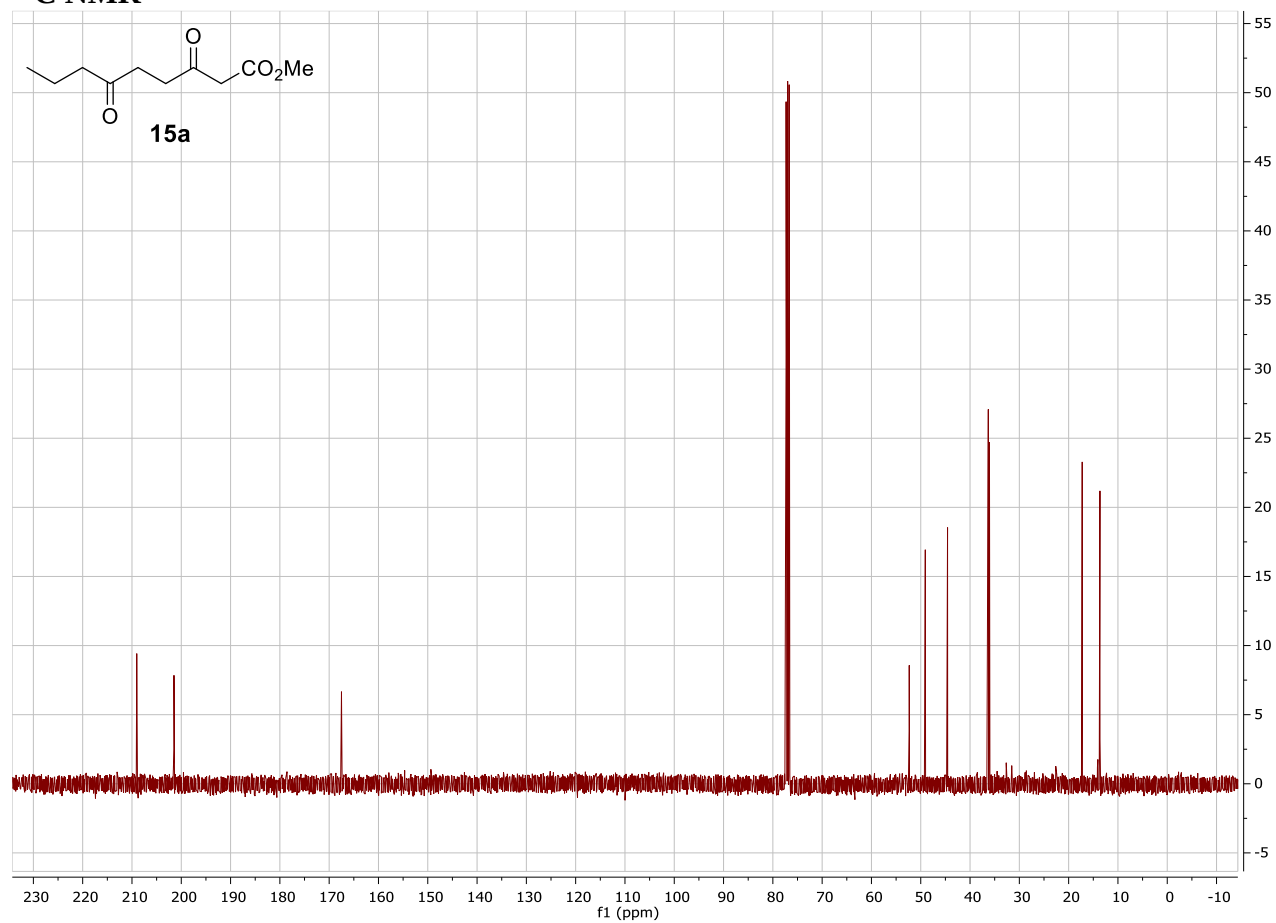
Figure S3: ^{13}C NMR for α -iodo intermediate **9** in CD_3CN

V. ^1H - and ^{13}C NMR spectra for substrates and hydration products

^1H NMR



^{13}C NMR

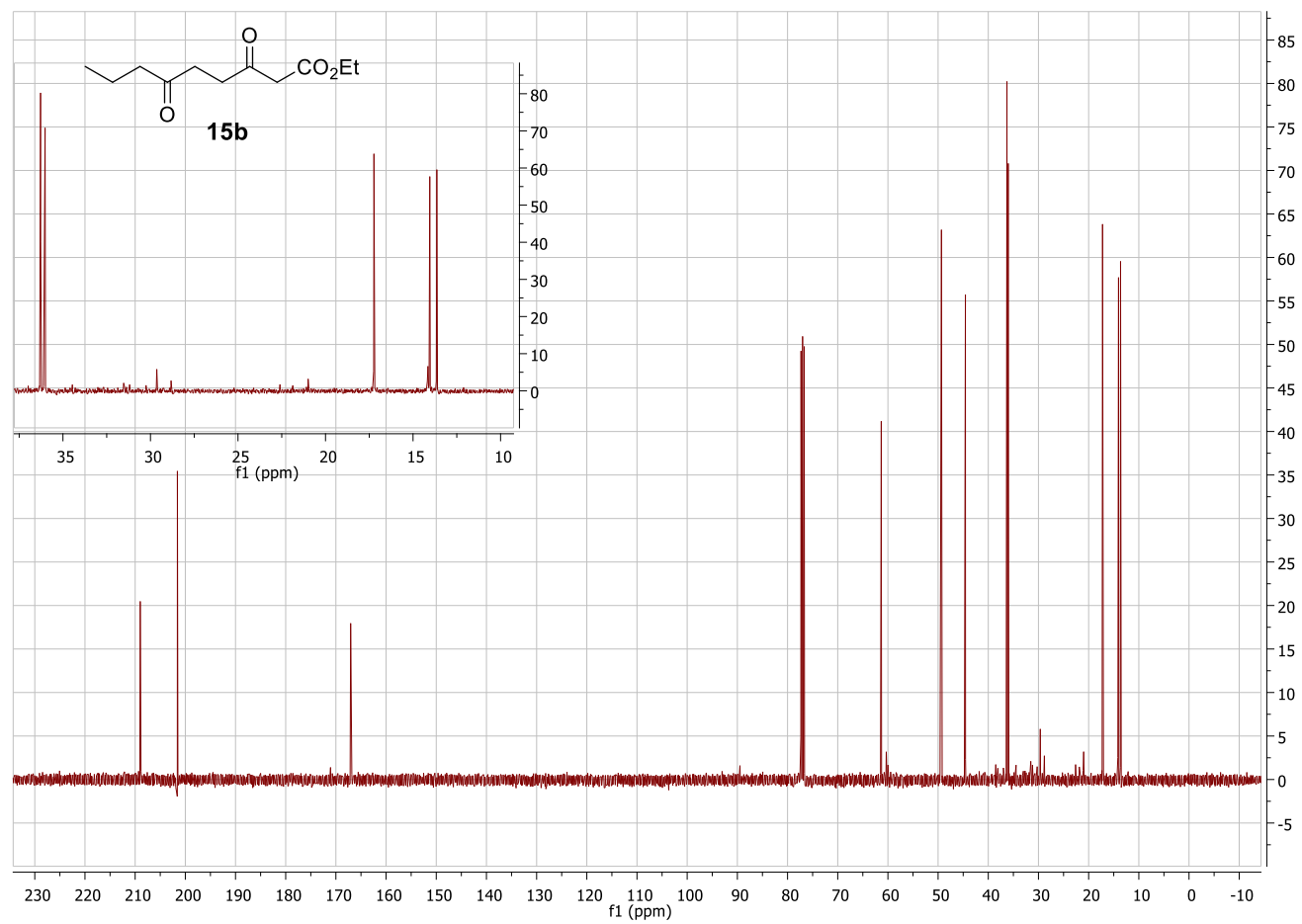


15b

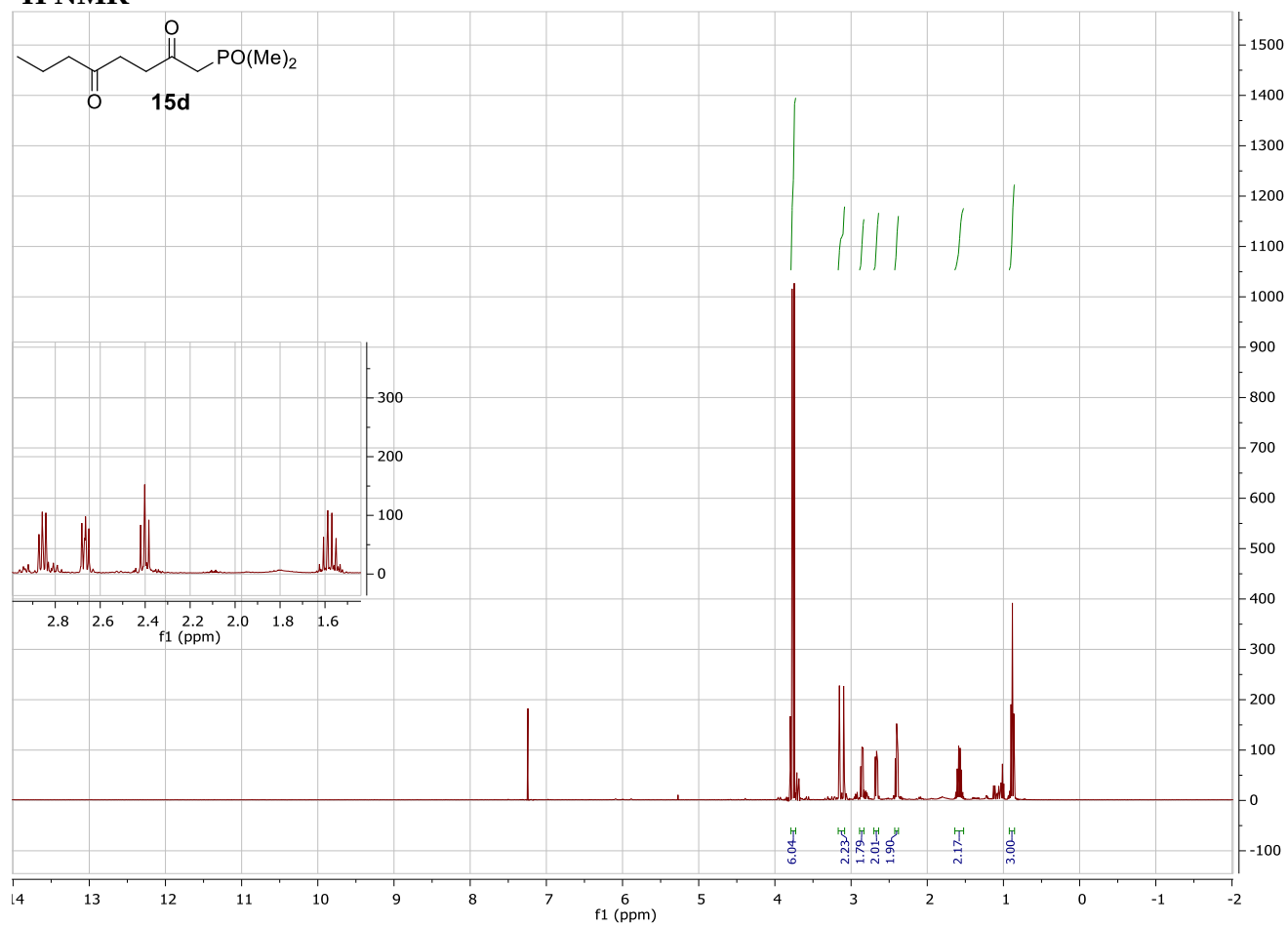
CCCC(=O)CCC(=O)CCOC(=O)CC

1H NMR spectrum (CDCl₃) of compound **15b**. The spectrum shows peaks in the aliphatic region (0-4 ppm) and a solvent peak (7.26 ppm). Integration values are provided for several peak groups: 2.00, 1.92, 2.00, 2.11, 1.76, 2.22, 3.01, 3.19, 2.00, 1.92, 2.00, 2.11, 1.76, 2.22, 3.01, 3.19.

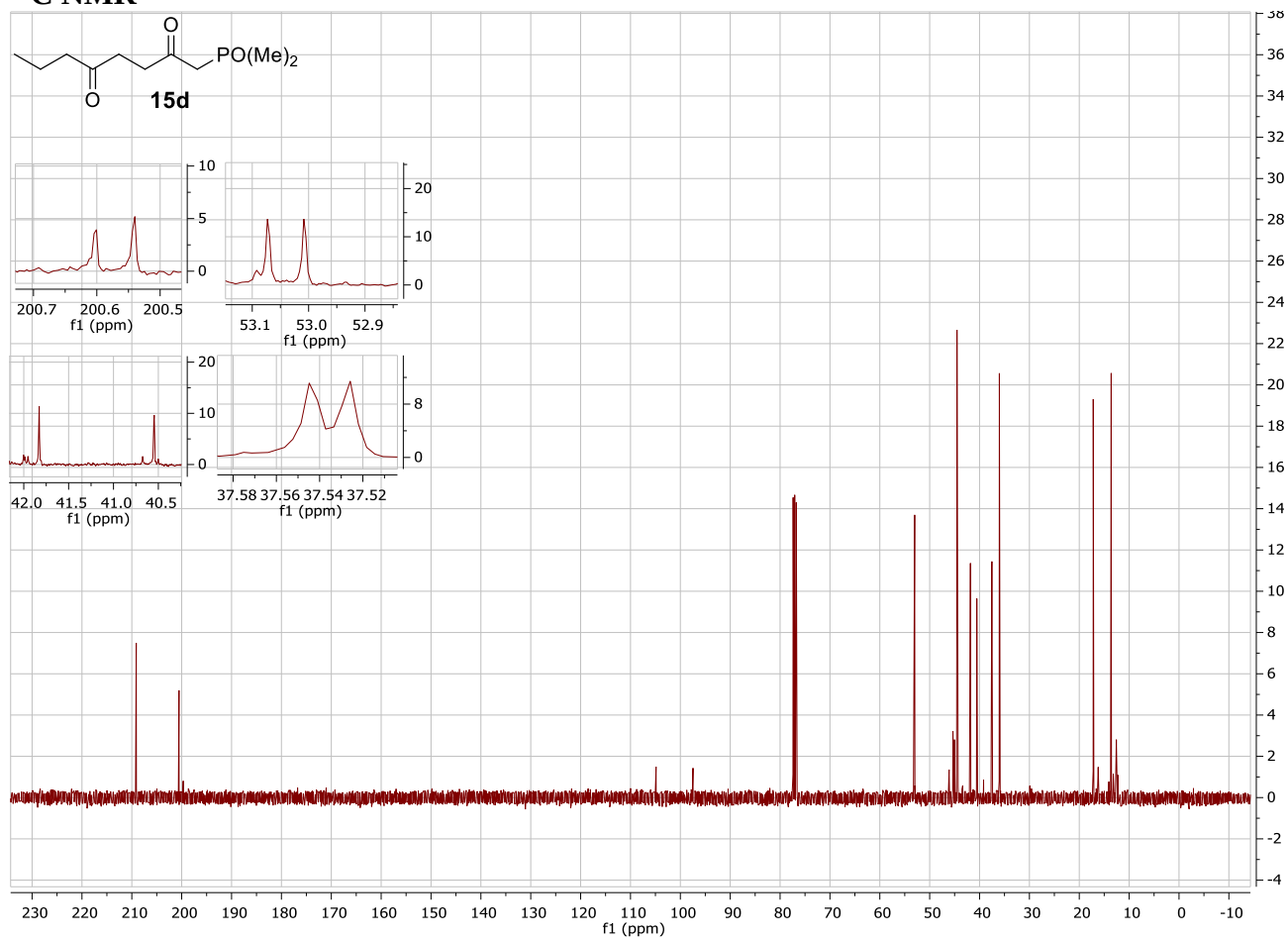
^{13}C NMR



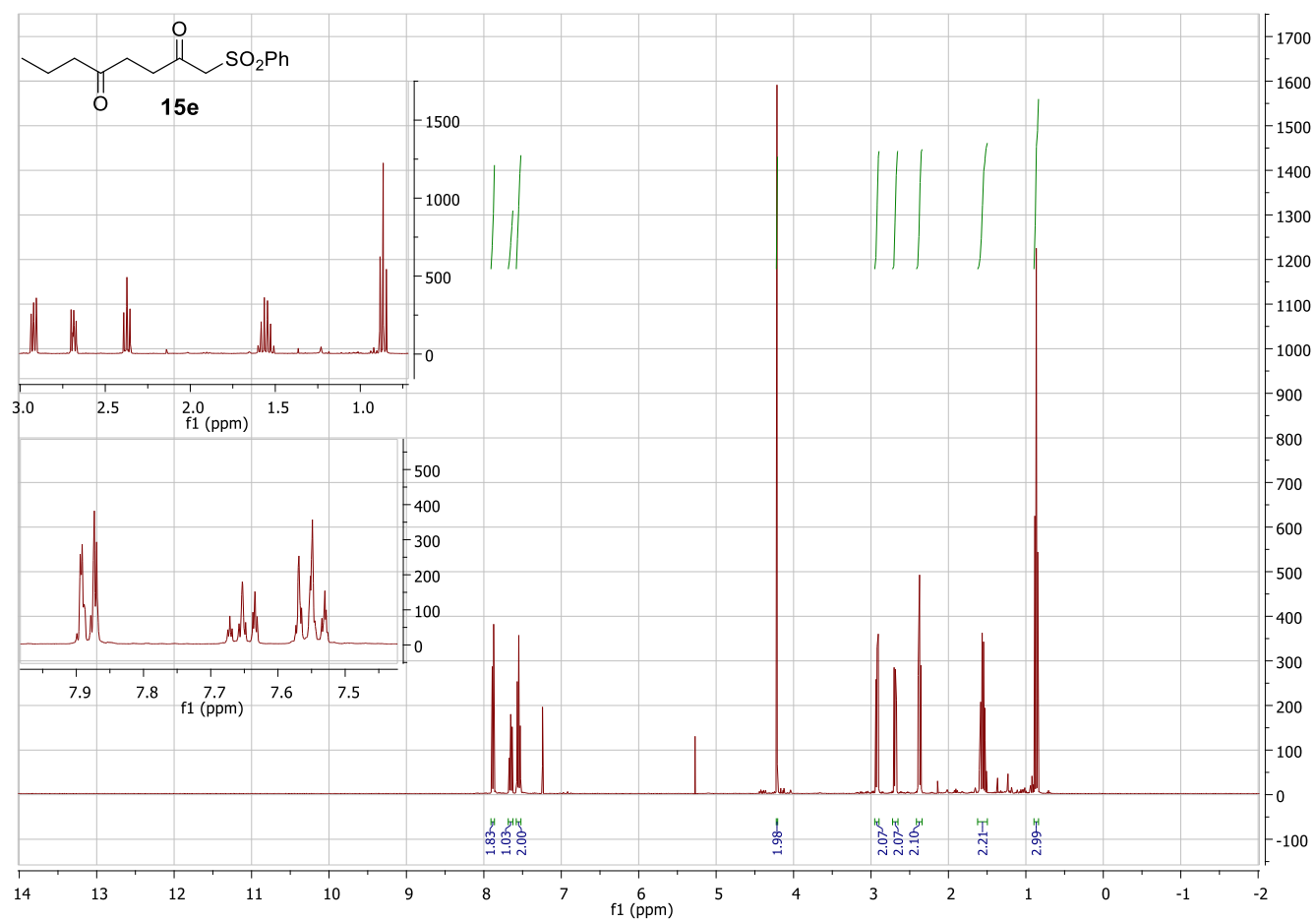
¹H NMR



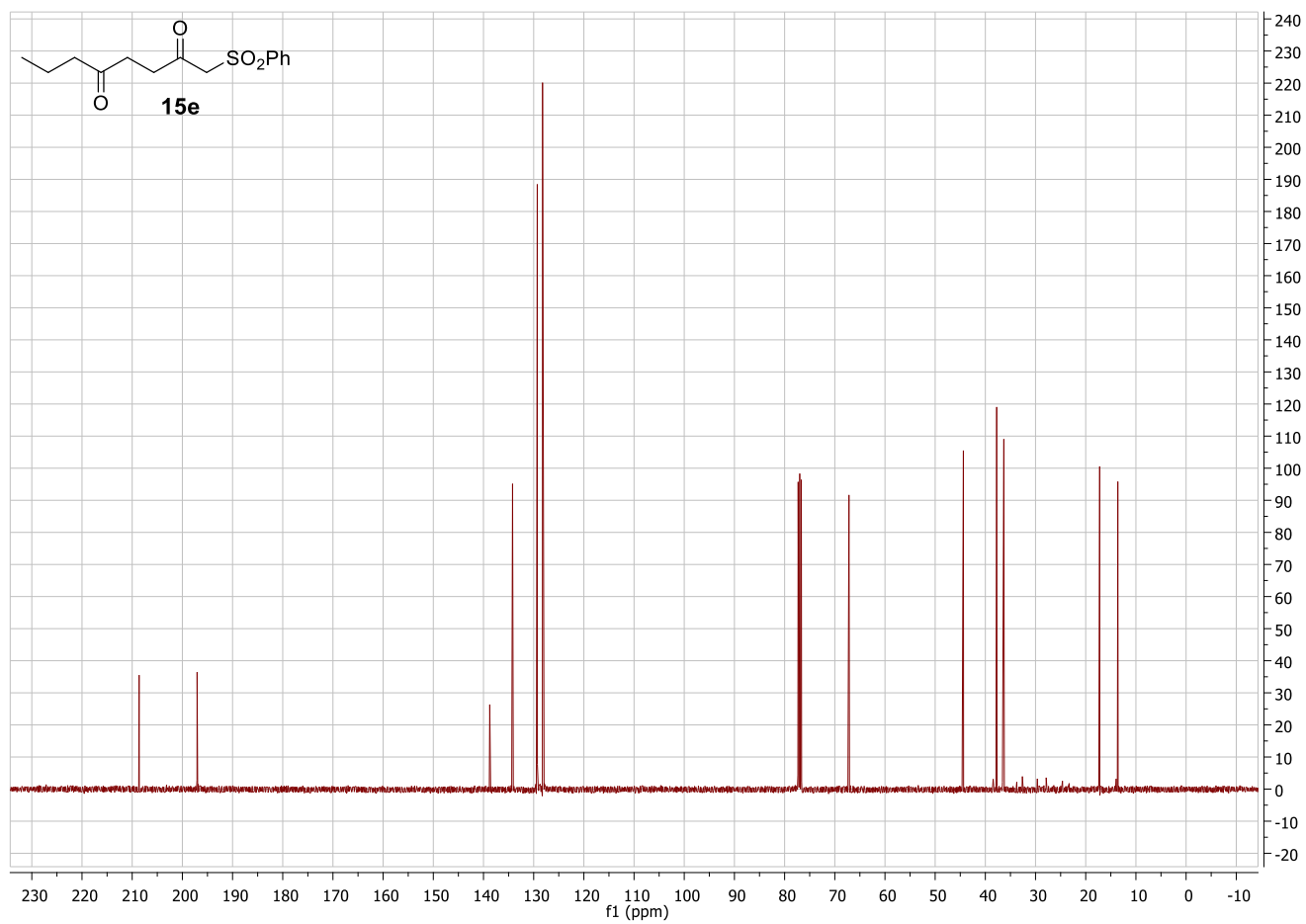
¹³C NMR



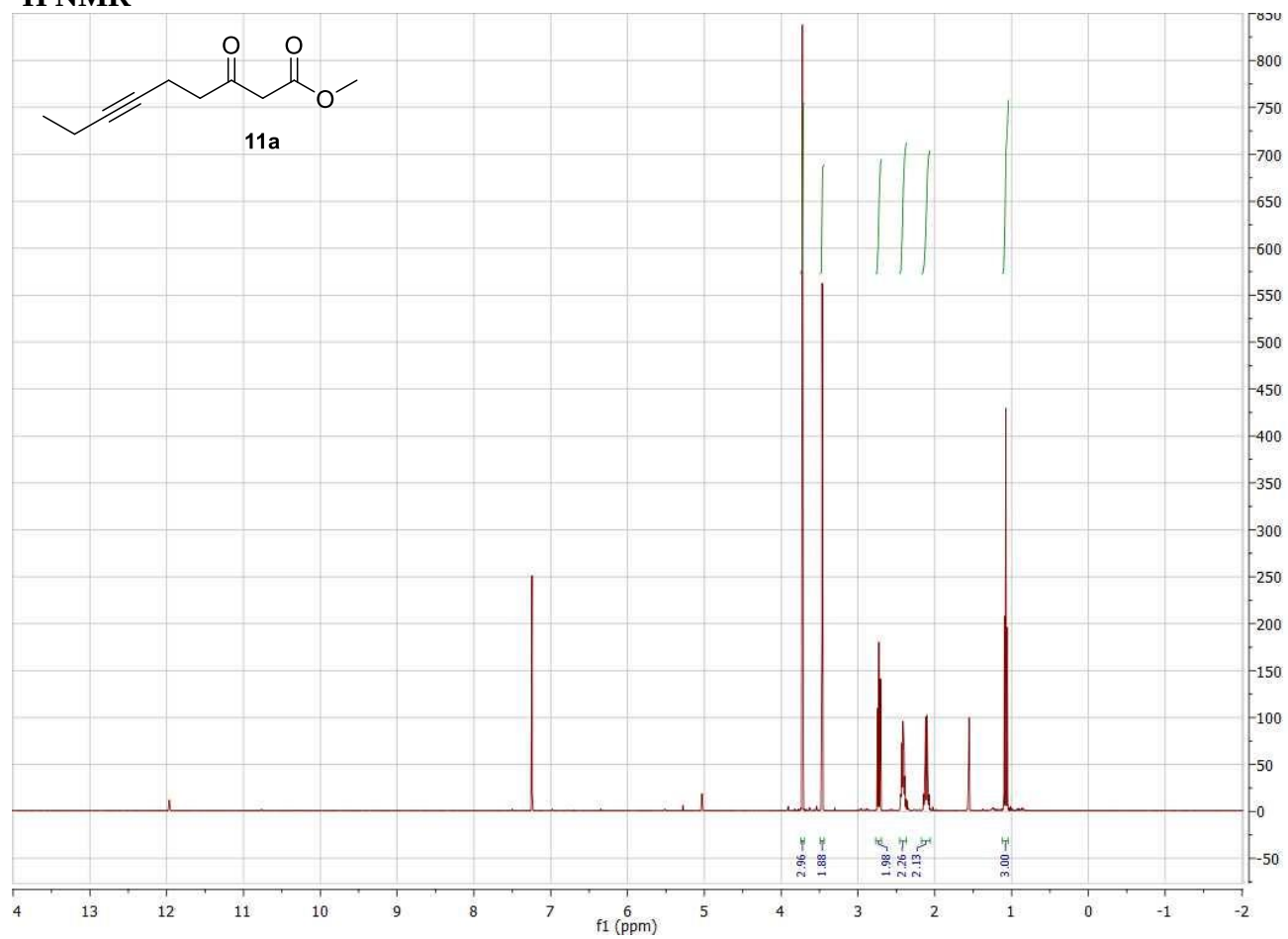
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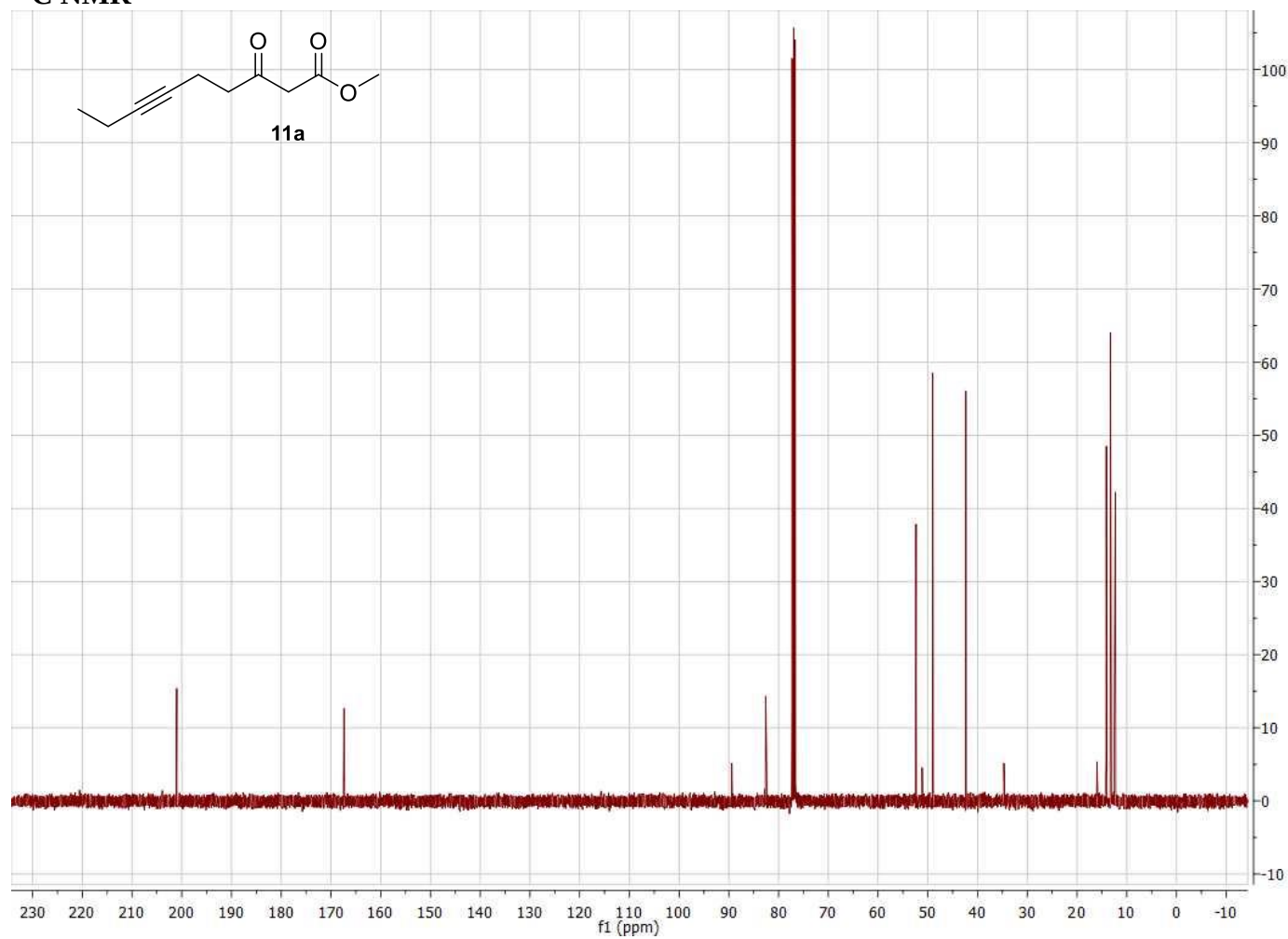
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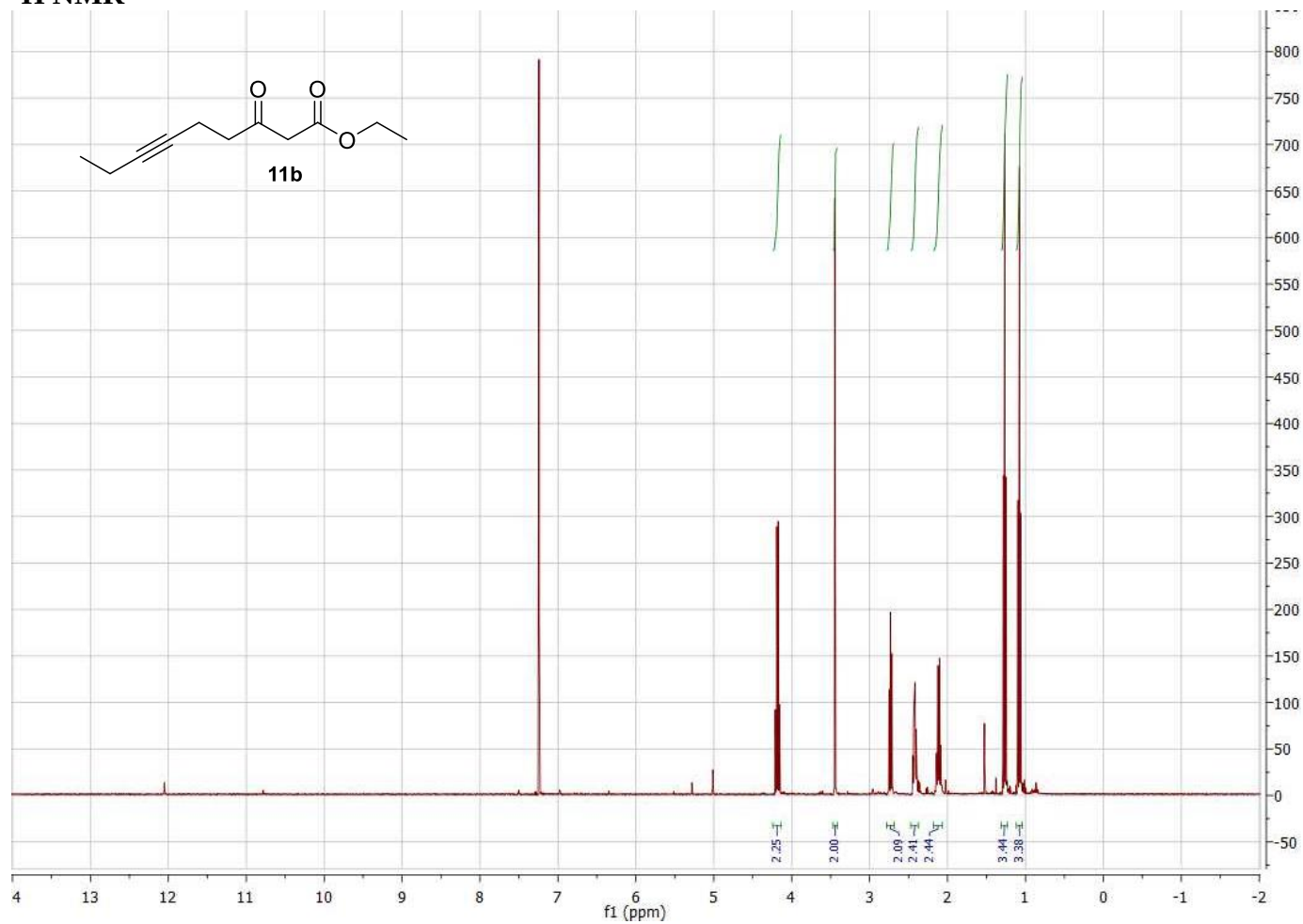
¹H NMR



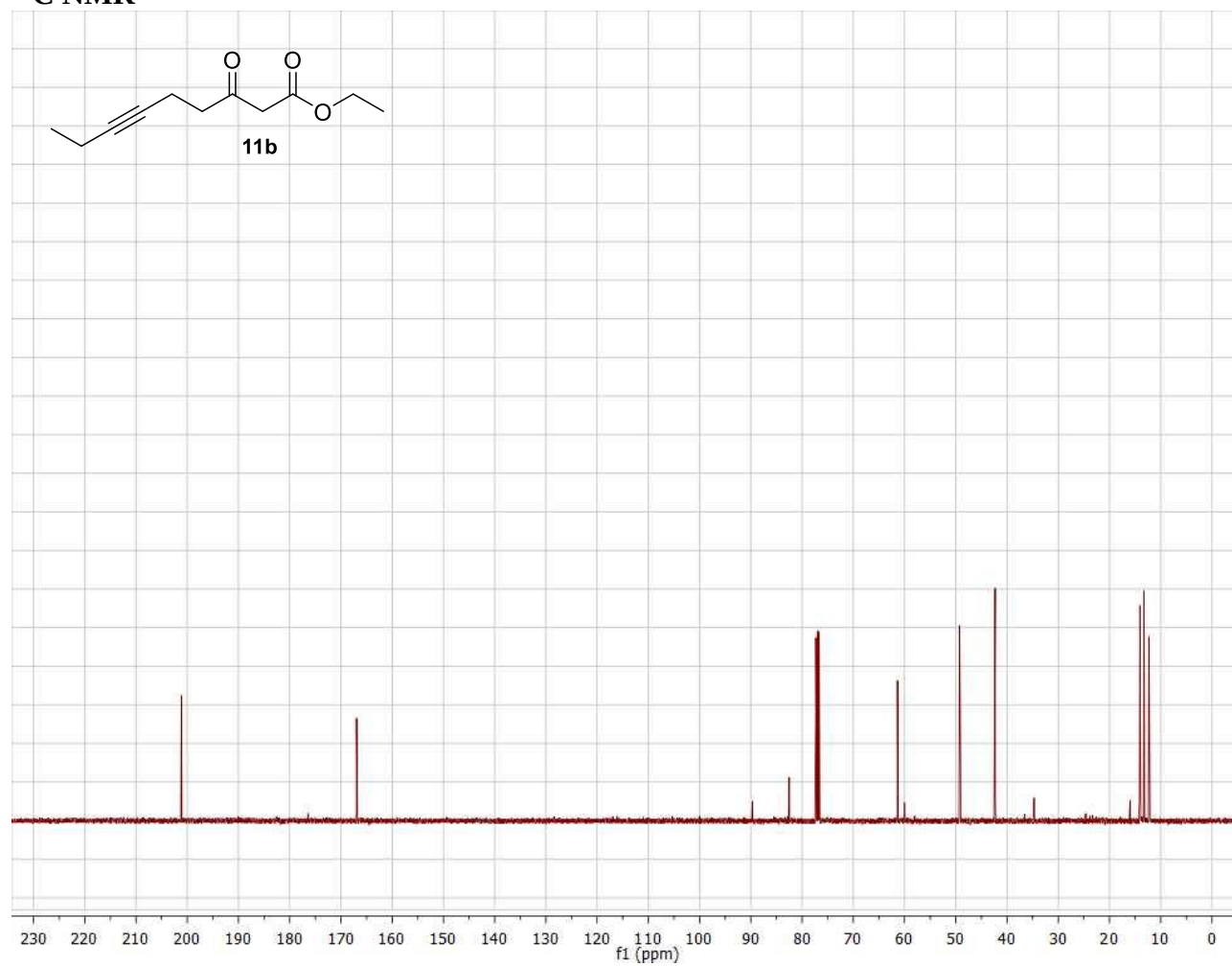
^{13}C NMR



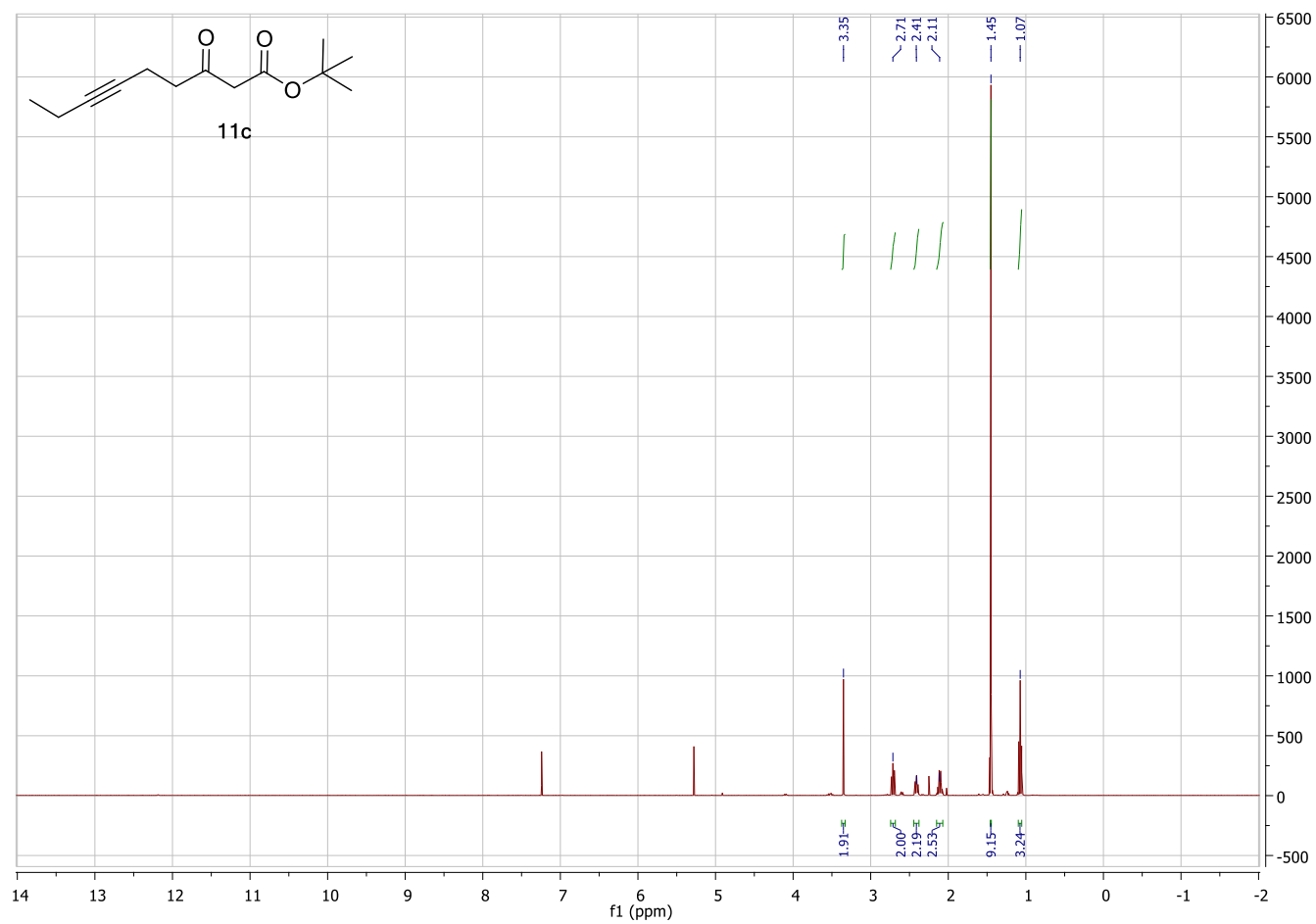
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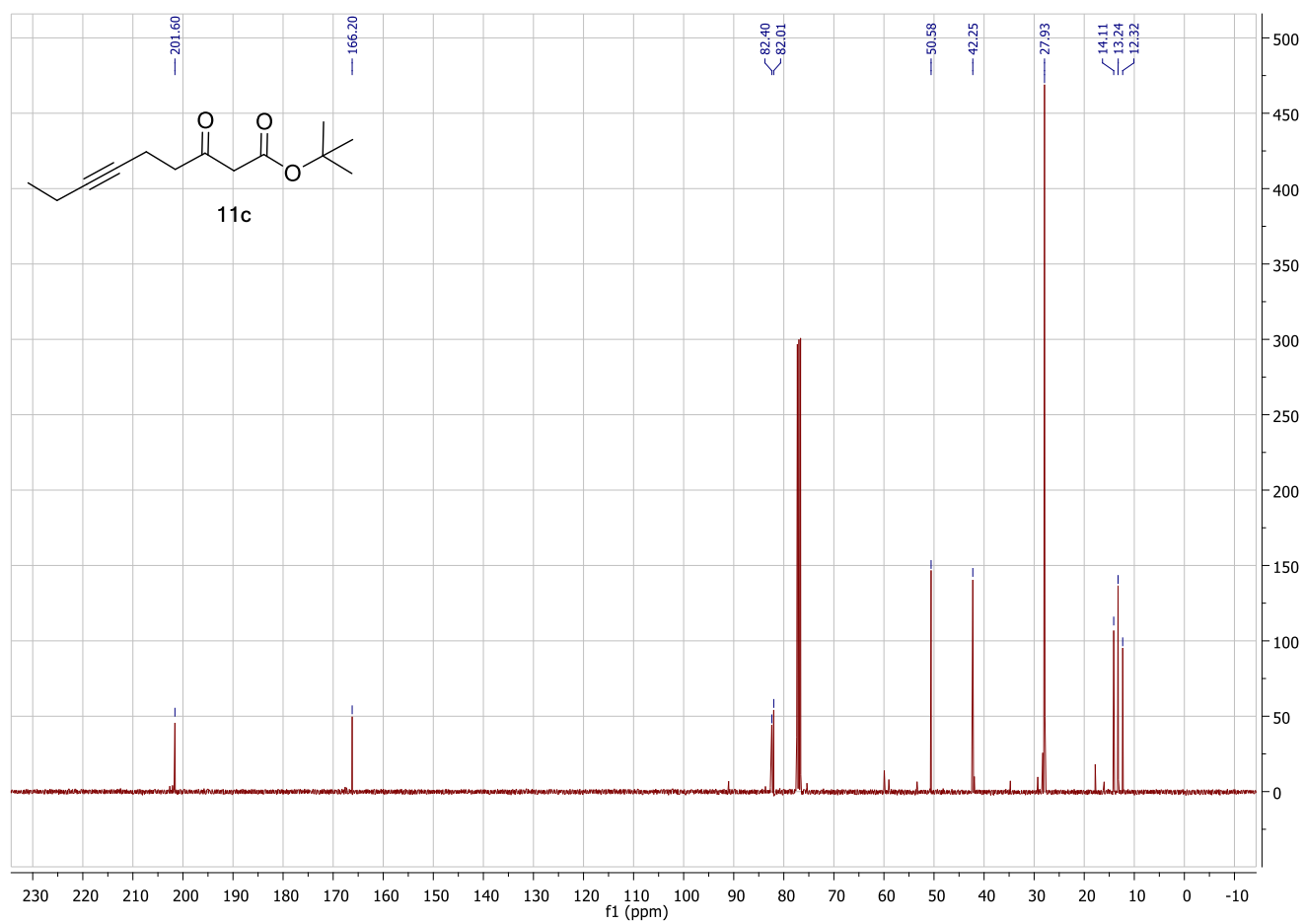
^{13}C NMR



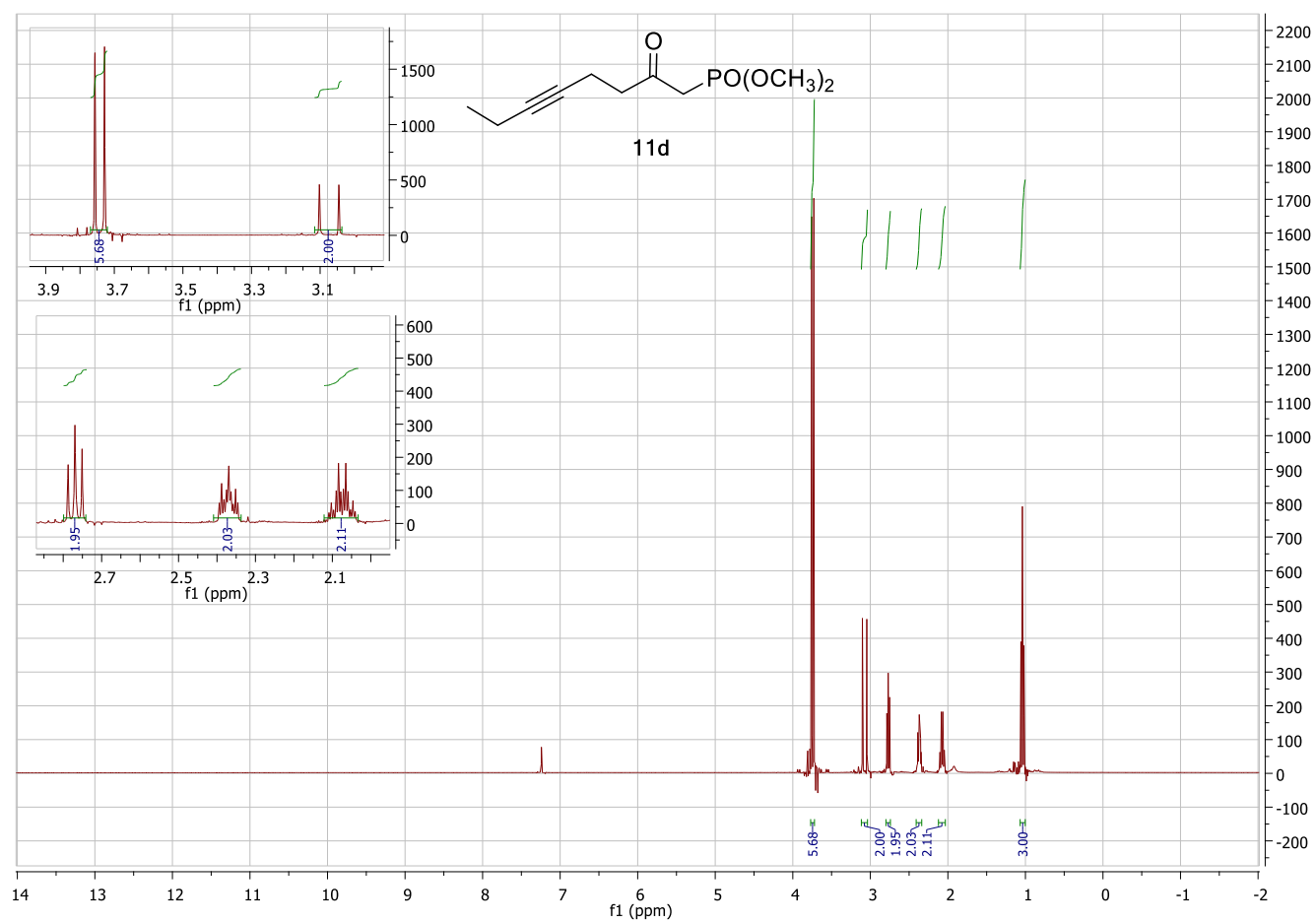
¹H NMR



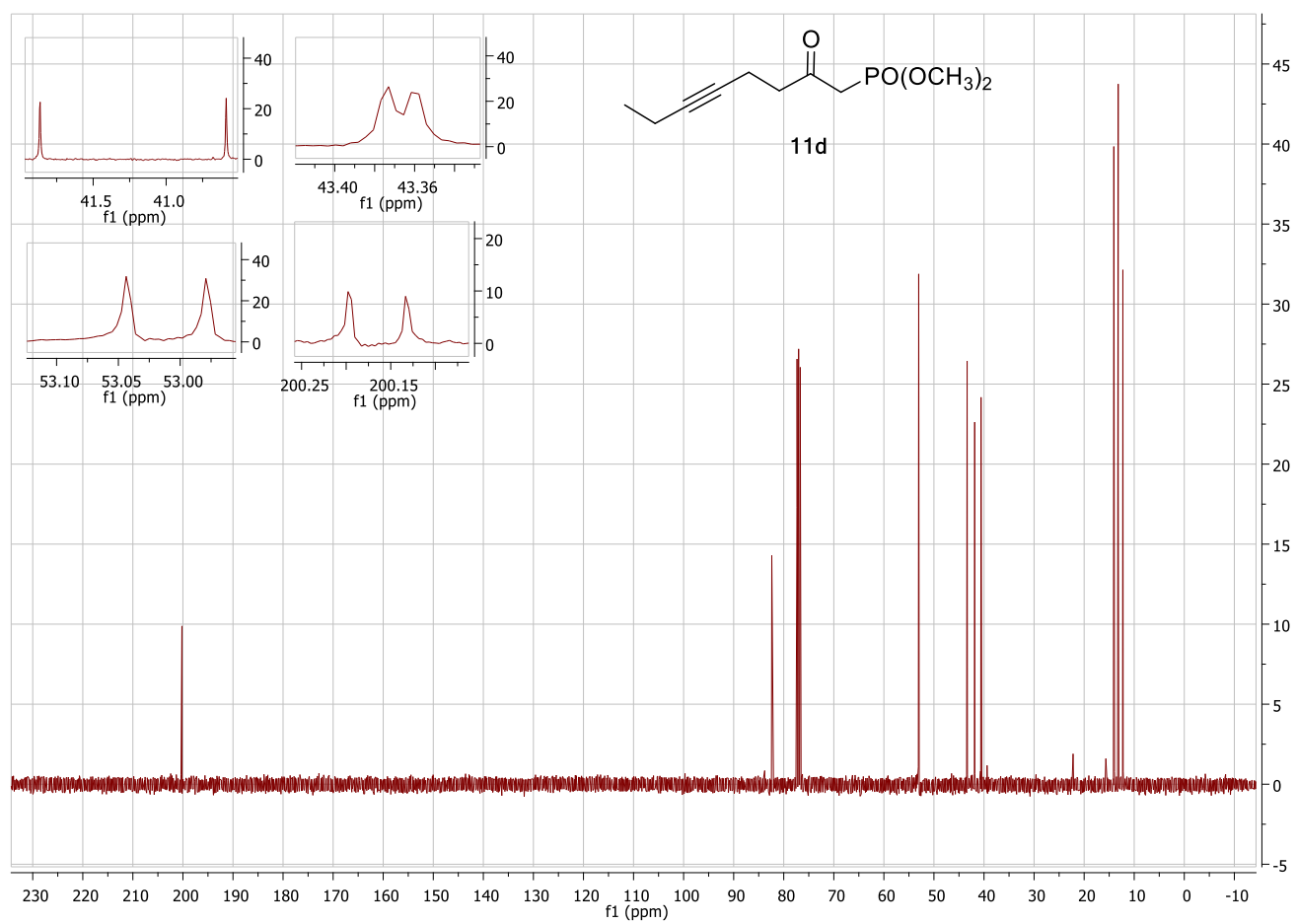
¹³C NMR



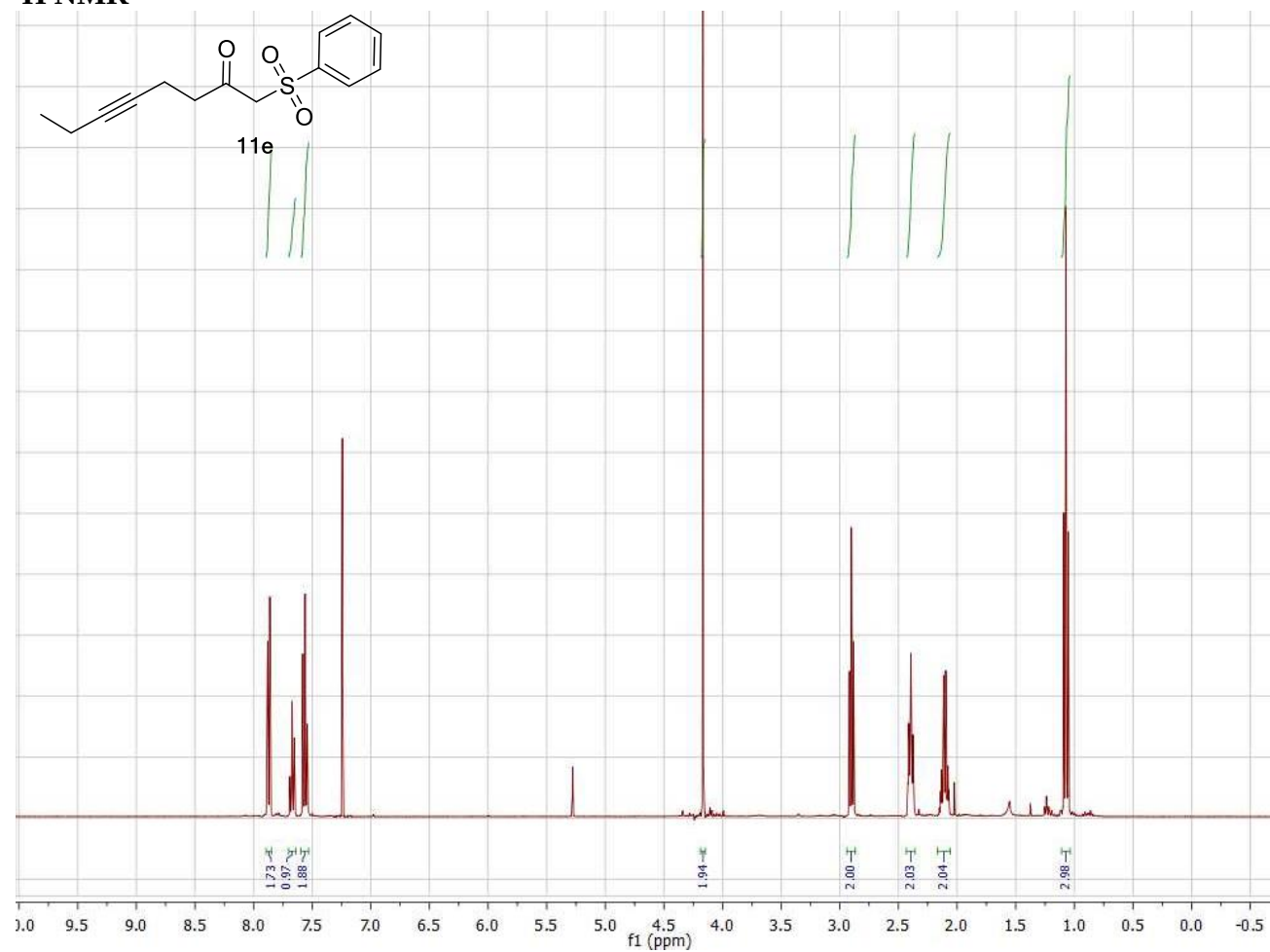
¹H NMR



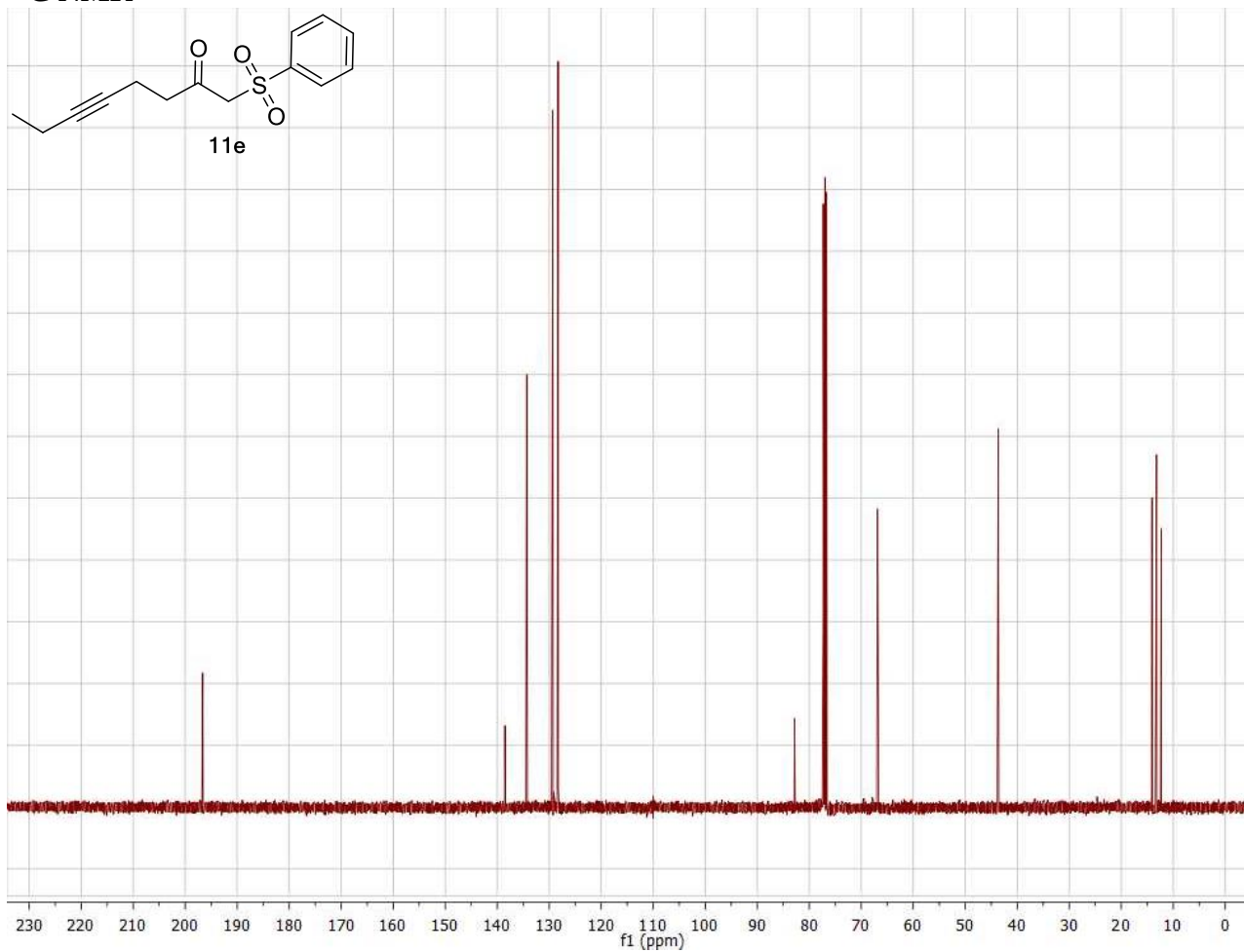
¹³C NMR



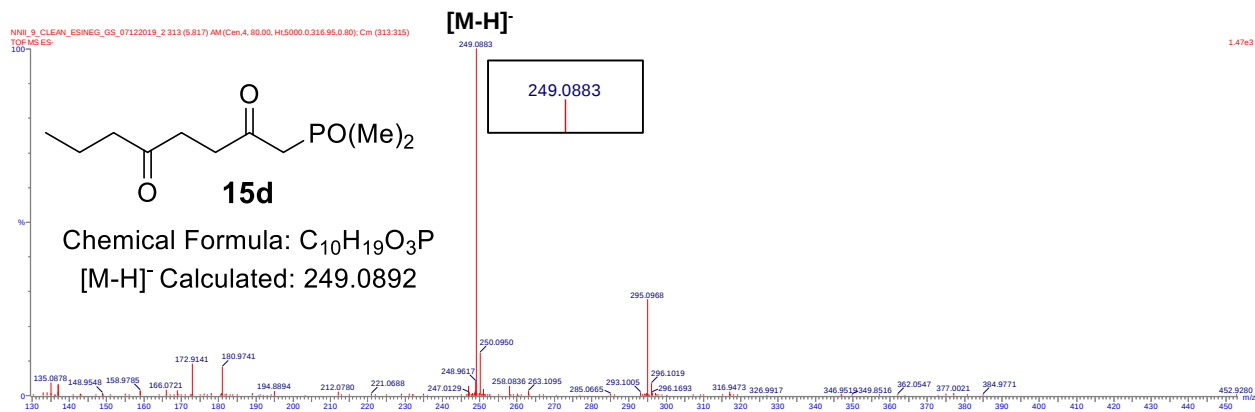
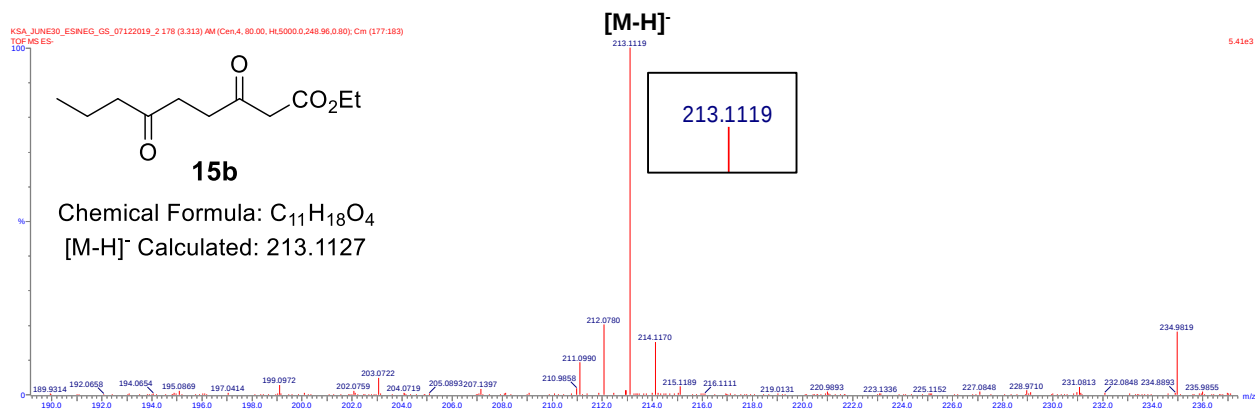
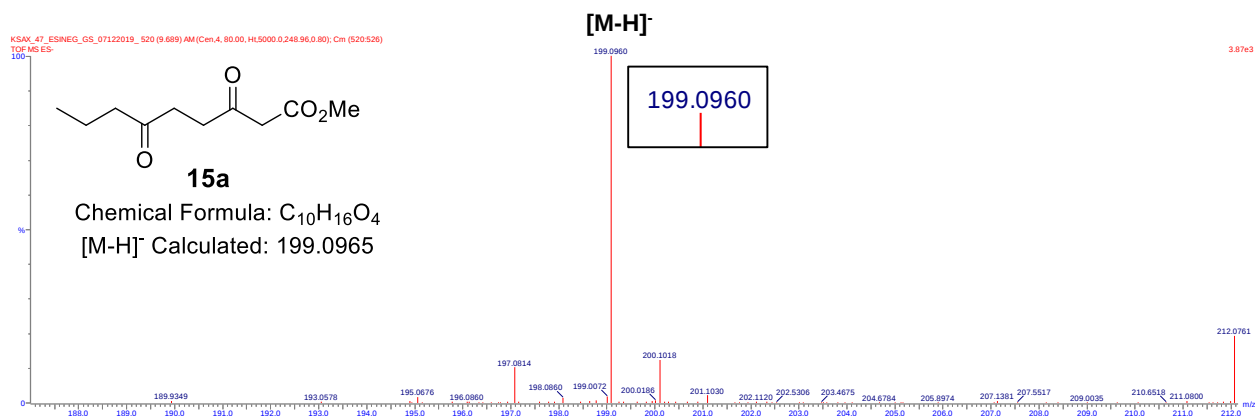
^1H NMR

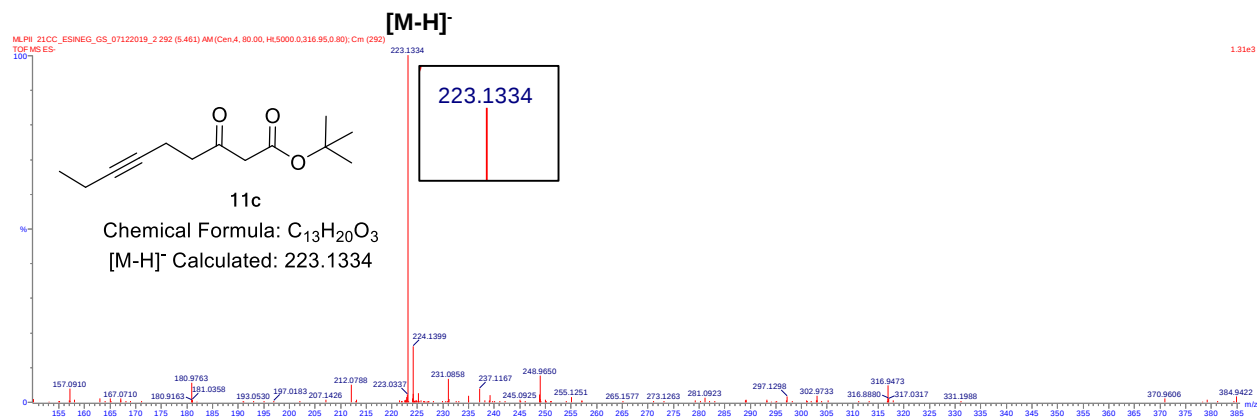
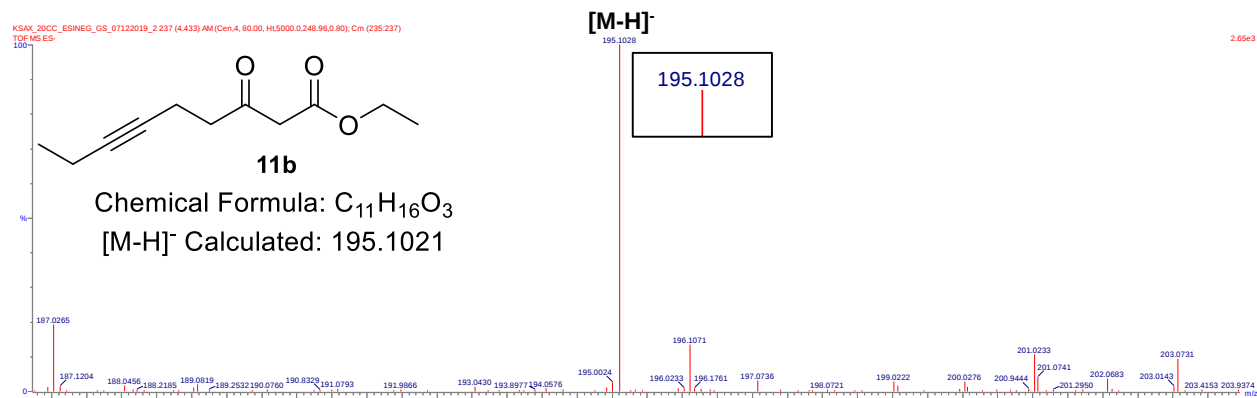
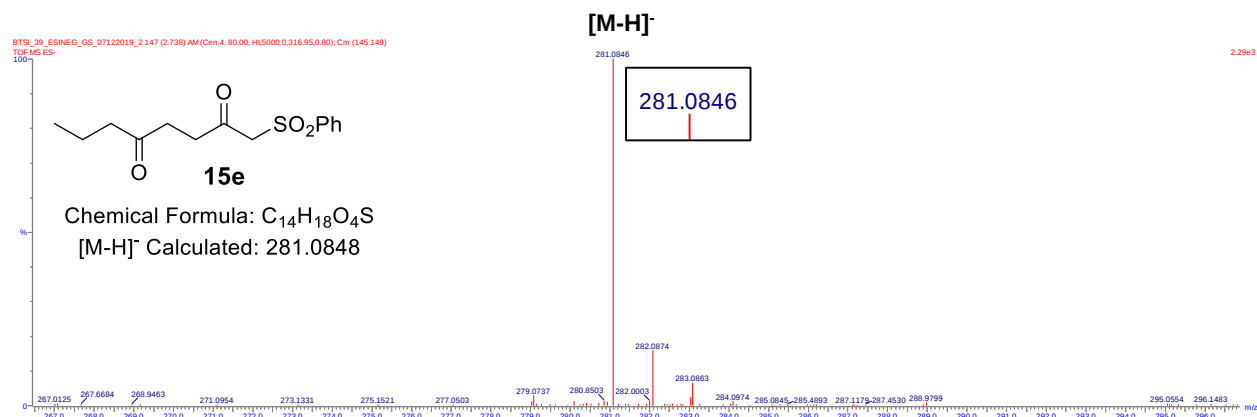


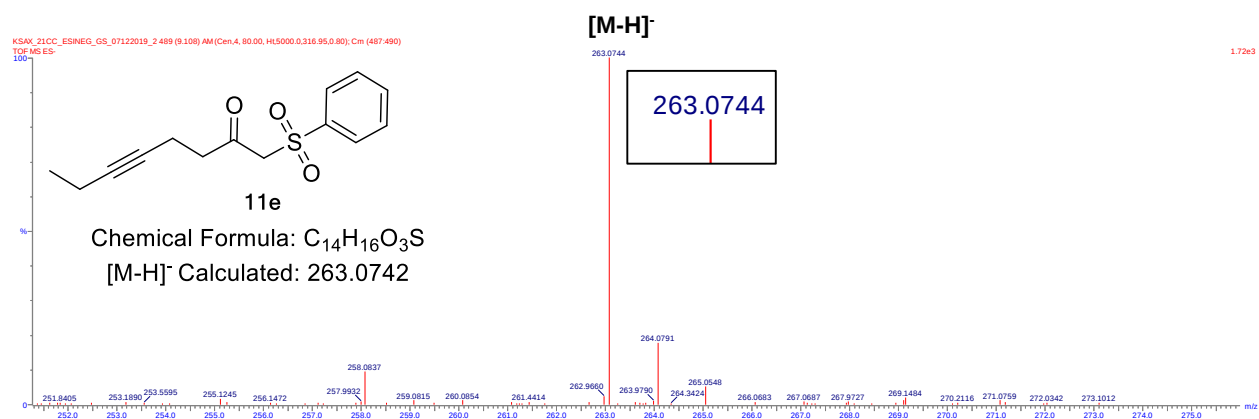
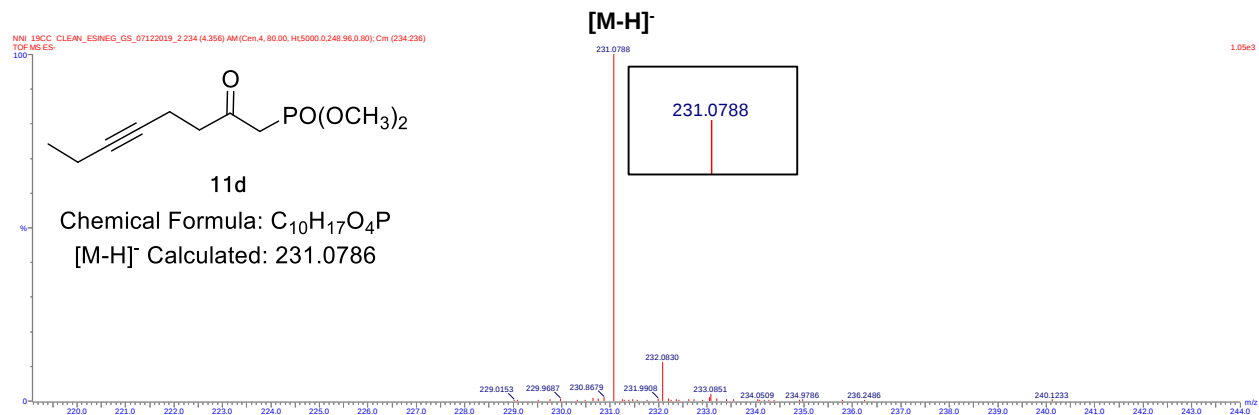
^{13}C NMR



VI. High resolution mass spectra (negative ion mode)







References

1. Achmatowicz, O., Jr.; Cynkowski, T.; Bukowski, P. *Polish Journal of Chemistry* **1983**, 57 (7-8-9), 1047-50.