

PRACTICAL SYNTHESIS OF PHOSPHINIC DIPEPTIDES BY TANDEM ACTIVATION OF AMINOPHOSPHINIC AND ACRYLIC ACIDS UNDER SILYLATING CONDITIONS

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SUPPORTING INFORMATION

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Experimental Section

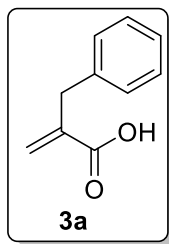
1. Synthesis and Characterization of Acrylic Acids of Type 3

General procedure for the synthesis of acrylic acids of type 3

Sodium (1.0 equiv) is slowly added and dissolved in abs. ethanol (1.4mL/mmol). Then, diethyl malonate (1.0 equiv) is added dropwise and the resulting mixture is stirred during 30 min at room temperature. Then, the respective bromide is added dropwise at room temperature and the resulting mixture is refluxed during 24 h. After removal of volatiles, H₂O is added and extractions with Et₂O (×3) are performed. The combined organic layers are dried with Na₂SO₄ and evaporated to afford the crude product which is assumed to contain only the target monoalkylated diethyl ester of type **6**. The residue is dissolved in EtOH (0.5 mL/mmol of **6**) and cooled at 0°C. At the same temperature, a solution of KOH (2.0 equiv) in EtOH (1.5 mL/mmol of **6**) is slowly added. The mixture is stirred at rt and the progress of the reaction is followed by TLC, until diethylester **6** is fully consumed (if needed, up to 1.0 equiv of KOH is gradually added). Typically, reaction time is 24h. The mixture is concentrated and the residue is diluted H₂O and Et₂O. The aqueous phase is separated, washed with Et₂O (×2), acidified with HCl 2M to pH ~1 and extracted with AcOEt (×3). The combined organic layers are dried over Na₂SO₄ and evaporated to afford diacid of type **7**. The latter is dissolved/suspended to AcOEt (1.8 mL/mmol of **7**) and Et₂NH (1.2 equiv) is added slowly at 0 °C. The temperature is raised at rt, HCHO (1.4 equiv) is added and the mixture is refluxed for 4 h. Then, the mixture is concentrated, treated with aq. NaHCO₃ 5% and washed with Et₂O (×3). The aqueous phase is acidified with HCl 2M to pH ~1 and extracted with AcOEt (×3). The combined

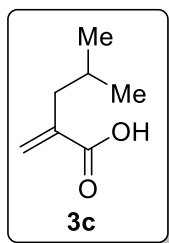
organic layers are dried over Na₂SO₄ and evaporated to afford acrylic acid of type **3** in adequately pure form to be used in the *P*-Michael reaction without further purification.

2-Benzylacrylic acid (**3a**)



Compound **3a** was prepared according to the general procedure for the synthesis of acrylic acids in a 18.7 mmol scale of diethyl malonate. The final product **3a** was obtained as a white solid in 40% (1.21 g) yield for 3 steps. M.p. 64–68 °C; ¹H NMR (200 MHz, CDCl₃) δ 7.65 – 7.30 (m, 5H), 6.66 (s, 1H), 5.78 (s, 1H), 3.89 (s, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 172.9, 139.6, 138.4, 129.1, 128.8, 128.5, 126.5, 37.5; HRMS (m/z): [M - H]⁻ calcd. for C₁₀H₉O₂⁻, 161.0608 found, 161.0603.

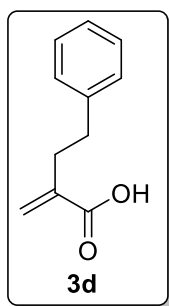
4-Methyl-2-methylenepentanoic acid (**3c**)



Compound **3c** was prepared according to the general procedure for the synthesis of acrylic acids in a 13.9 mmol scale of diethyl malonate. The final product **3c** was obtained as a light yellow oil in 60% (1.06 g) yield for 3 steps. ¹H NMR (200 MHz, CDCl₃) δ 6.32 (d, *J* = 1.2 Hz, 1H), 5.61 (d, *J* = 1.0 Hz, 1H), 2.17 (d, *J* = 7.1 Hz, 2H), 1.82 (m, 1H), 0.89

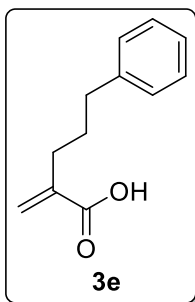
(d, $J = 6.6$ Hz, 6H); ^{13}C NMR (50 MHz, CDCl_3) δ 173.2, 139.2, 128.4, 41.0, 27.2, 22.4; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_7\text{H}_{11}\text{O}_2^-$, 127.0765 found, 127.0766.

2-Methylene-4-phenylbutanoic acid (**3d**)



Compound **3d** was prepared according to the general procedure for the synthesis of acrylic acids in a 4.2 mmol scale of diethyl malonate. The final product **3d** was obtained as a white solid in 47% (0.35 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 7.40 – 7.13 (m, 5H), 6.37 (s, 1H), 5.65 (s, 1H), 2.92 – 2.79 (m, 2H), 2.74 – 2.60 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 172.9, 141.4, 139.3, 128.6, 128.6, 128.5, 128.2, 126.2, 34.9, 33.7; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{11}\text{H}_{11}\text{O}_2^-$, 175.0765 found, 175.0765.

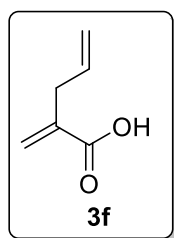
2-Methylene-5-phenylpentanoic acid (**3e**)



Compound **3e** was prepared according to the general procedure for the synthesis of acrylic acids in a 7.5 mmol scale of diethyl malonate. The final product **3e** was obtained

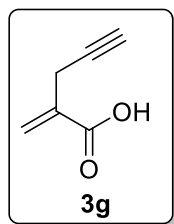
as a white solid in 44% (0.63 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 7.51 – 7.22 (m, 5H), 6.48 (d, $J = 0.8$ Hz, 1H), 5.78 (d, $J = 1.2$ Hz, 1H), 2.29 (t, $J = 7.7$ Hz, 2H), 2.50 (t, $J = 7.7$ Hz, 2H), 2.07 – 1.88 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 173.2, 142.0, 140.0, 128.5, 128.4, 127.4, 125.9, 35.4, 31.1, 30.0; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_2^-$, 189.0921 found, 189.0916.

2-Methylenepent-4-enoic acid (**3f**)



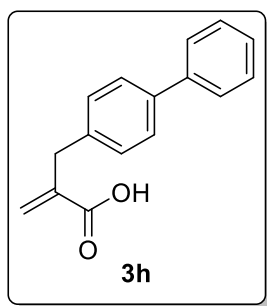
Compound **3f** was prepared according to the general procedure for the synthesis of acrylic acids in a 31 mmol scale of diethyl malonate. The final product **3f** was obtained as a light yellow oil in 24% (0.85 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 6.36 (q, $J = 1.0$ Hz, 1H), 5.98 – 5.75 (m, 1H), 5.70 (dd, $J = 2.5, 1.1$ Hz, 1H), 5.17 – 5.11 (m, 1H), 5.09 – 5.04 (m, 1H), 3.06 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 172.9, 138.5, 134.9, 128.2, 117.2, 35.5; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_6\text{H}_7\text{O}_2^-$, 111.0452 found, 111.0449.

2-Methylenepent-4-ynoic acid (**3g**)



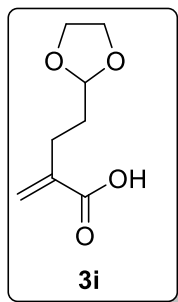
Compound **3g** was prepared according to the general procedure for the synthesis of acrylic acids in a 23 mmol scale of diethyl malonate. The final product **3g** was obtained as a light yellow thick oil in 74% (1.84 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 6.50 (d, $J = 0.9$ Hz, 1H), 6.19 (d, $J = 0.9$ Hz, 1H), 3.20 - 3.29 (m, 2H), 2.64 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ 171.8, 134.5, 129.2, 79.9, 72.4, 21.3; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_6\text{H}_5\text{O}_2^-$, 109.0295 found, 109.0292.

2-([1,1'-Biphenyl]-4-ylmethyl)acrylic acid (**3h**)



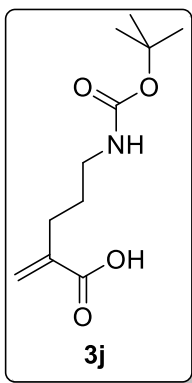
Compound **3h** was prepared according to the general procedure for the synthesis of acrylic acids in a 4.4 mmol scale of diethyl malonate. The final product **3h** was obtained as a white solid in 63% (0.66 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 7.57 – 7.02 (m, 11H), 6.34 (s, 1H), 5.57 (s, 1H), 3.59 (s, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 172.5, 141.0, 139.5, 137.7, 129.6, 129.0, 128.9, 127.4, 127.3, 127.2, 37.4; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_2^-$, 237.0921 found, 237.0923.

4-(1,3-Dioxolan-2-yl)-2-methylenebutanoic acid (**3i**)



Compound **3i** was prepared according to the general procedure for the synthesis of acrylic acids in a 5 mmol scale of diethyl malonate. The final product **3i** was obtained as a white solid in 57% (0.49 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 6.30 (s, 1H), 5.70 (q, $J = 1.3$ Hz, 1H), 4.91 (t, $J = 4.6$ Hz, 1H), 4.03 – 3.81 (m, 4H), 2.51 – 2.36 (m, 2H), 1.94 – 1.77 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 172.4, 139.5, 127.5, 103.9, 65.1, 32.5, 26.1; HRMS (m/z): $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_8\text{H}_{11}\text{O}_2^-$, 171.0663 found, 171.0659.

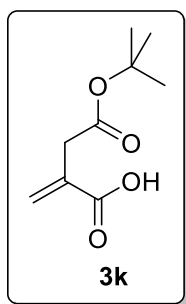
5-[(*tert*-Butoxycarbonyl)amino]-2-methylenepentanoic acid (3j)



Compound **3j** was prepared according to the general procedure for the synthesis of acrylic acids in a 7.5 mmol scale of diethyl malonate. The final product **3j** was obtained as a white solid in 47% (0.80 g) yield for 3 steps. ^1H NMR (200 MHz, CDCl_3) δ 6.27 (s, 1H), 5.64 (s, 1H), 3.11 (t, $J = 6.8$ Hz, 2H), 2.31 (t, $J = 7.8$ Hz, 2H), 1.66 (quint, $J = 7.1$ Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, CDCl_3) δ 172.0, 156.3, 139.7, 127.4, 79.5,

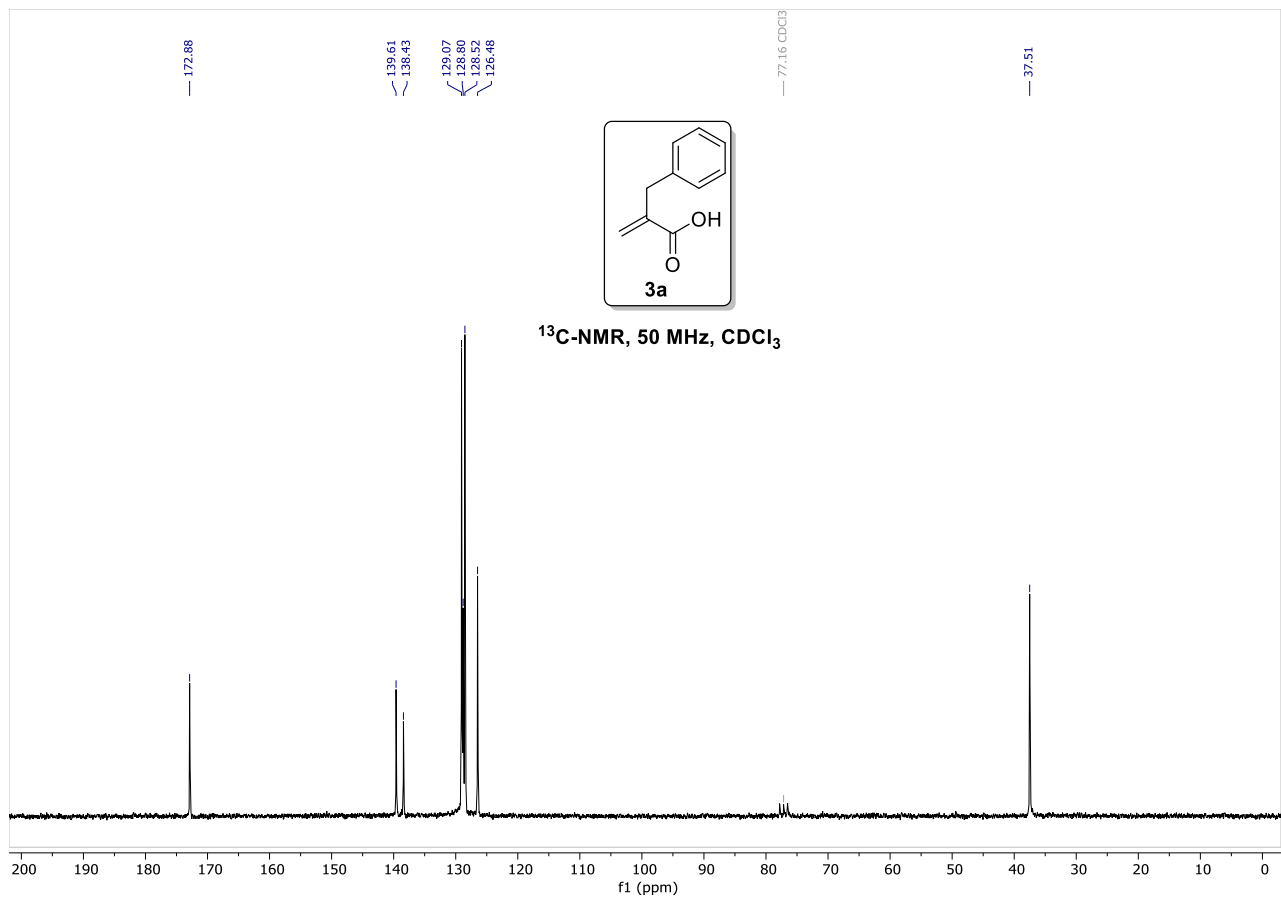
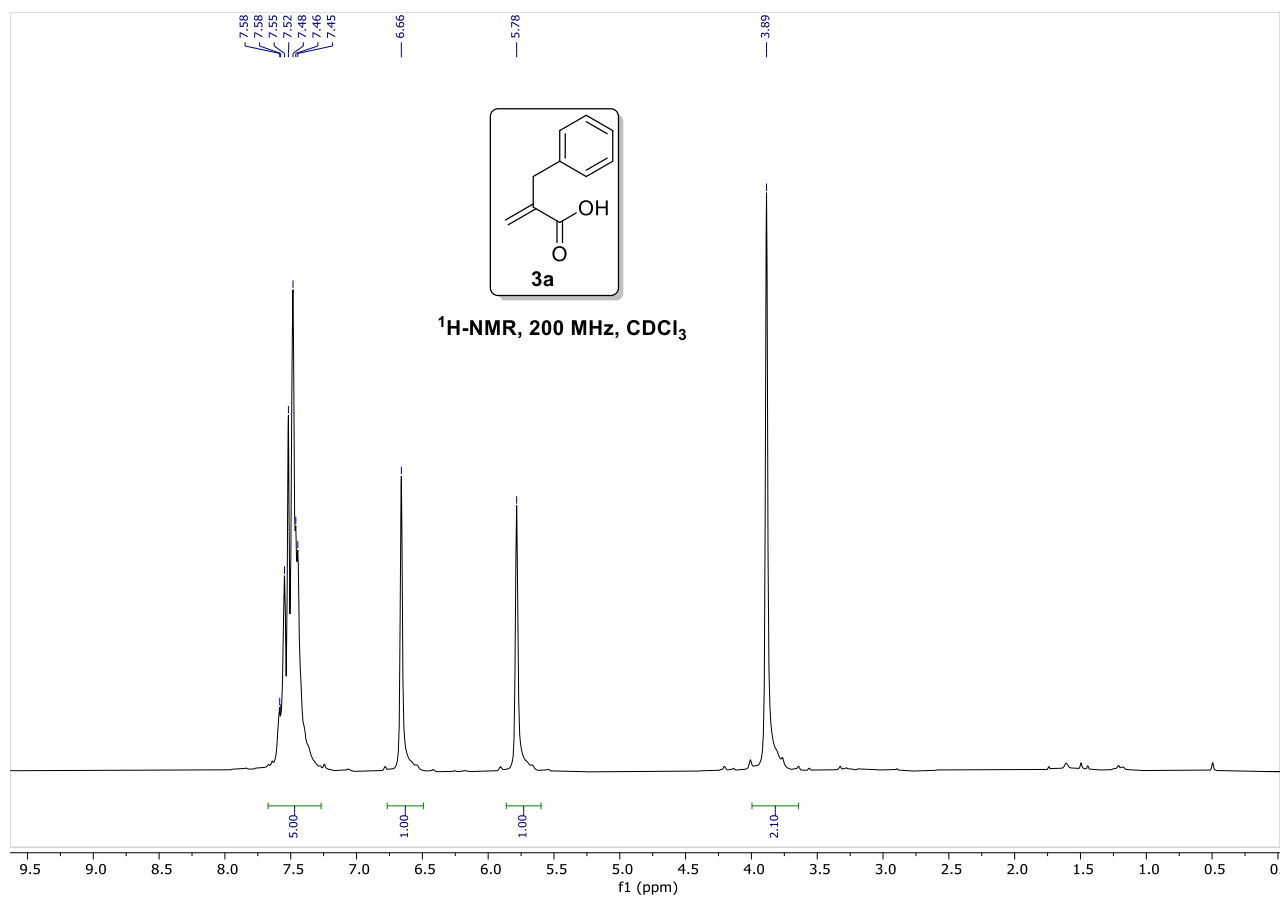
41.2, 40.2, 29.0, 28.6; HRMS (m/z): $[M - H]^-$ calcd. for $C_{11}H_{18}NO_4^-$, 228.1241 found, 228.1237.

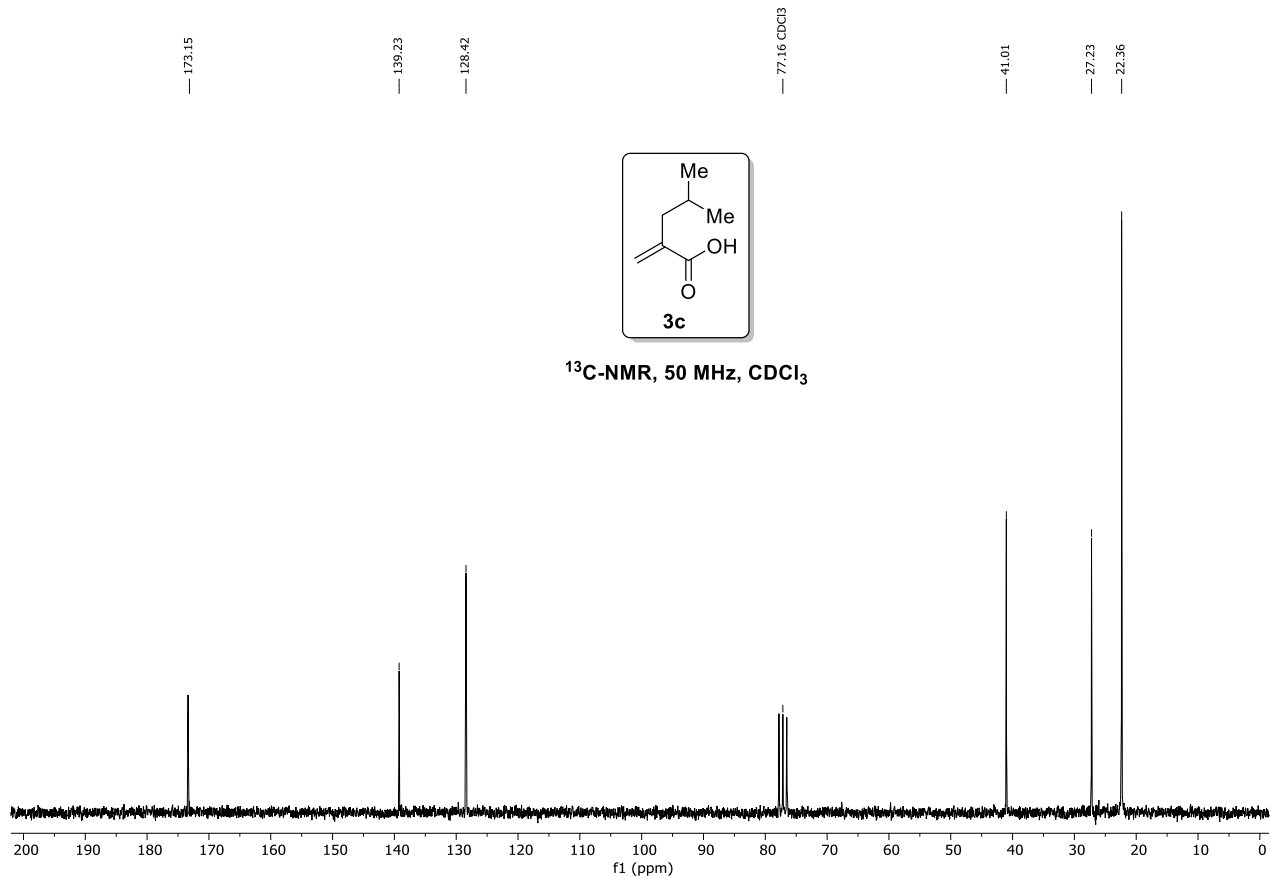
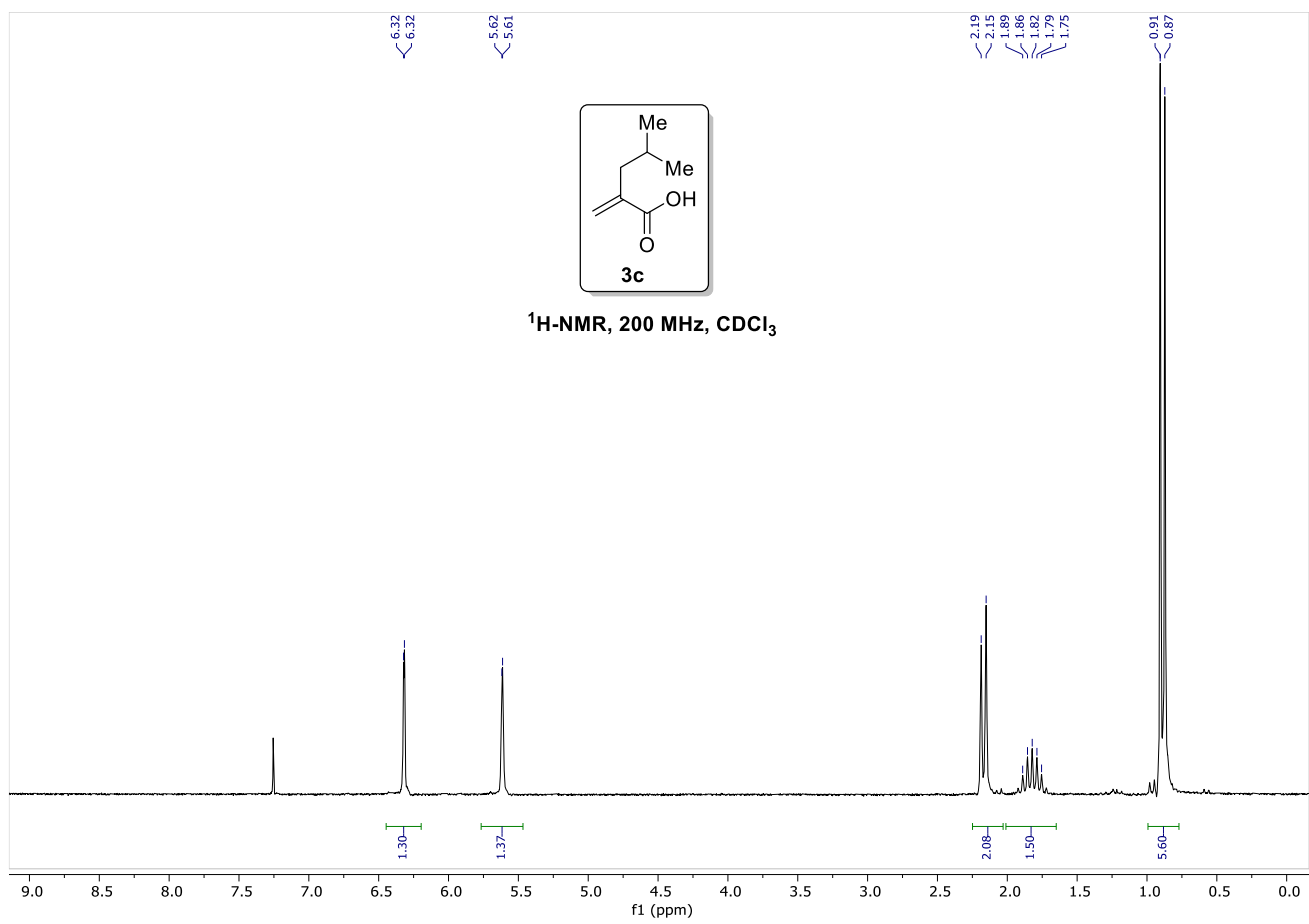
4-(*tert*-Butoxy)-2-methylene-4-oxobutanoic acid (3k)

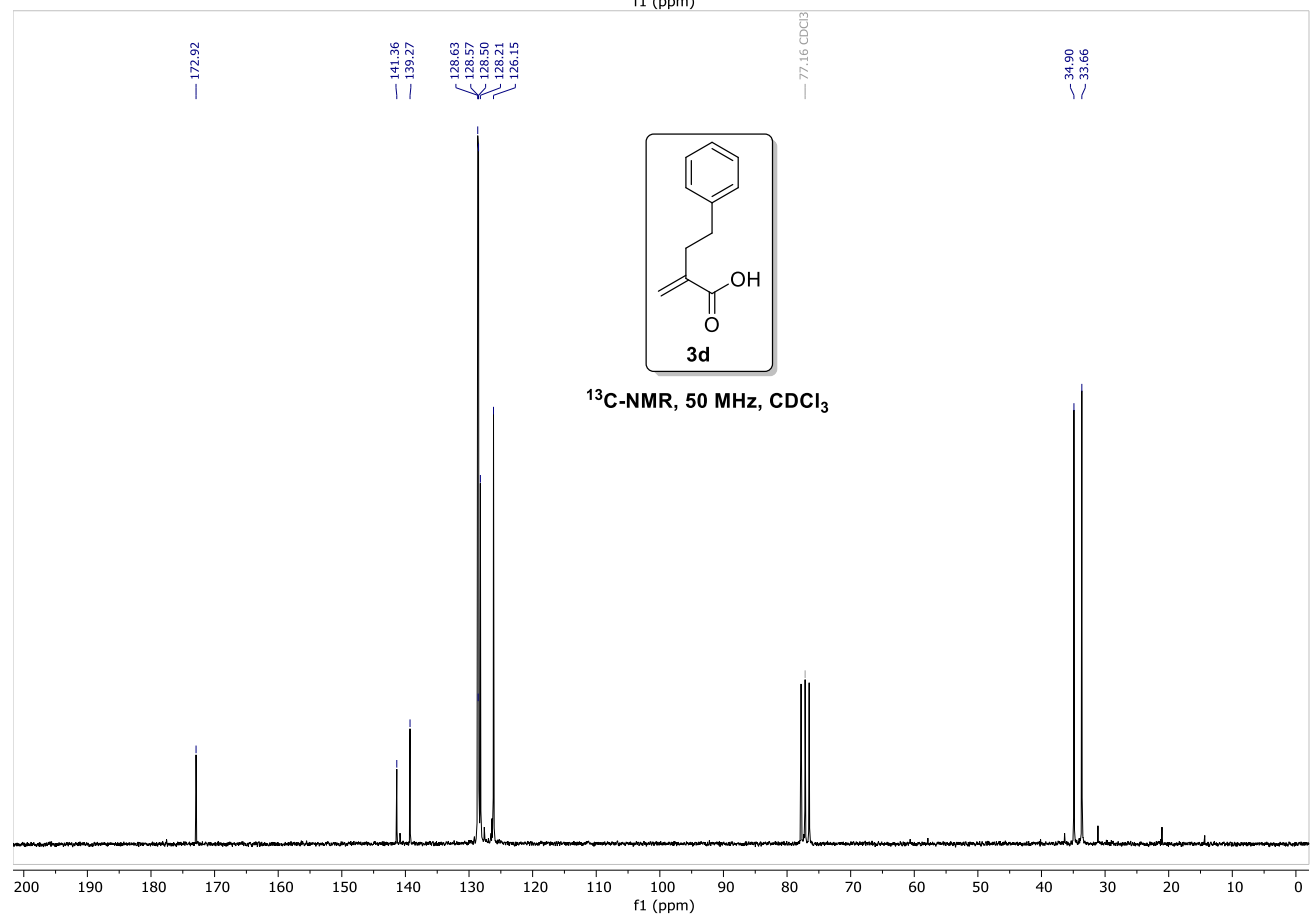
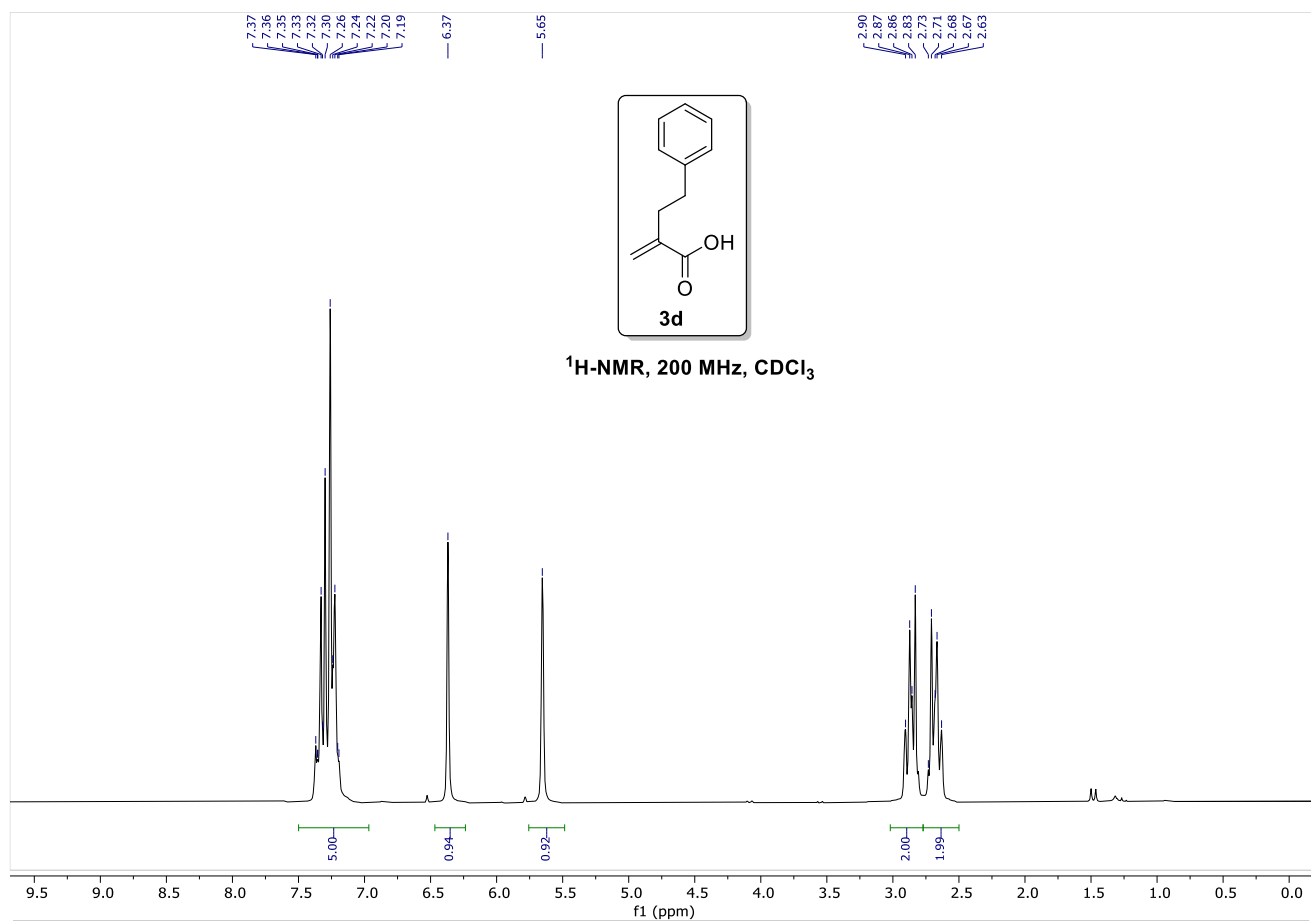


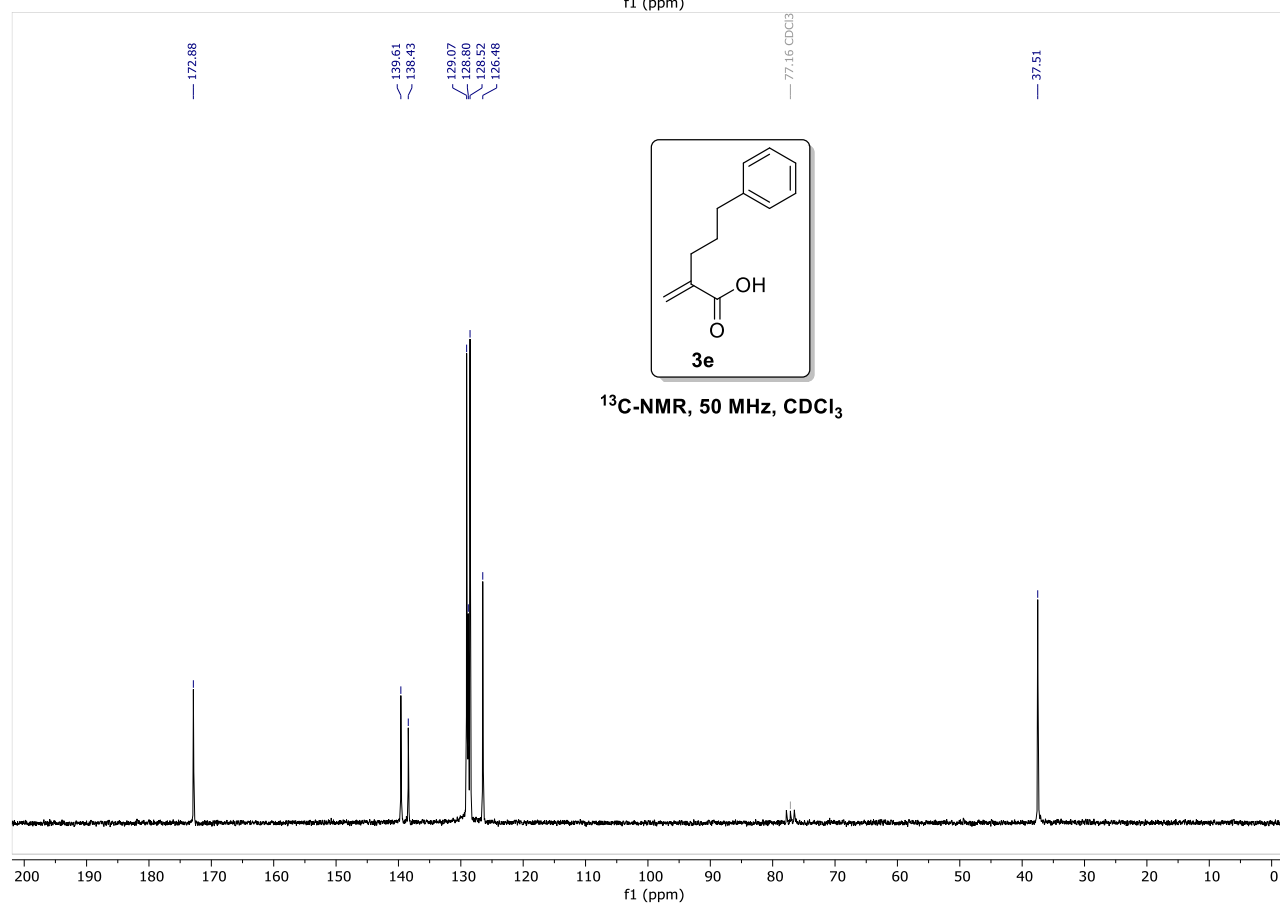
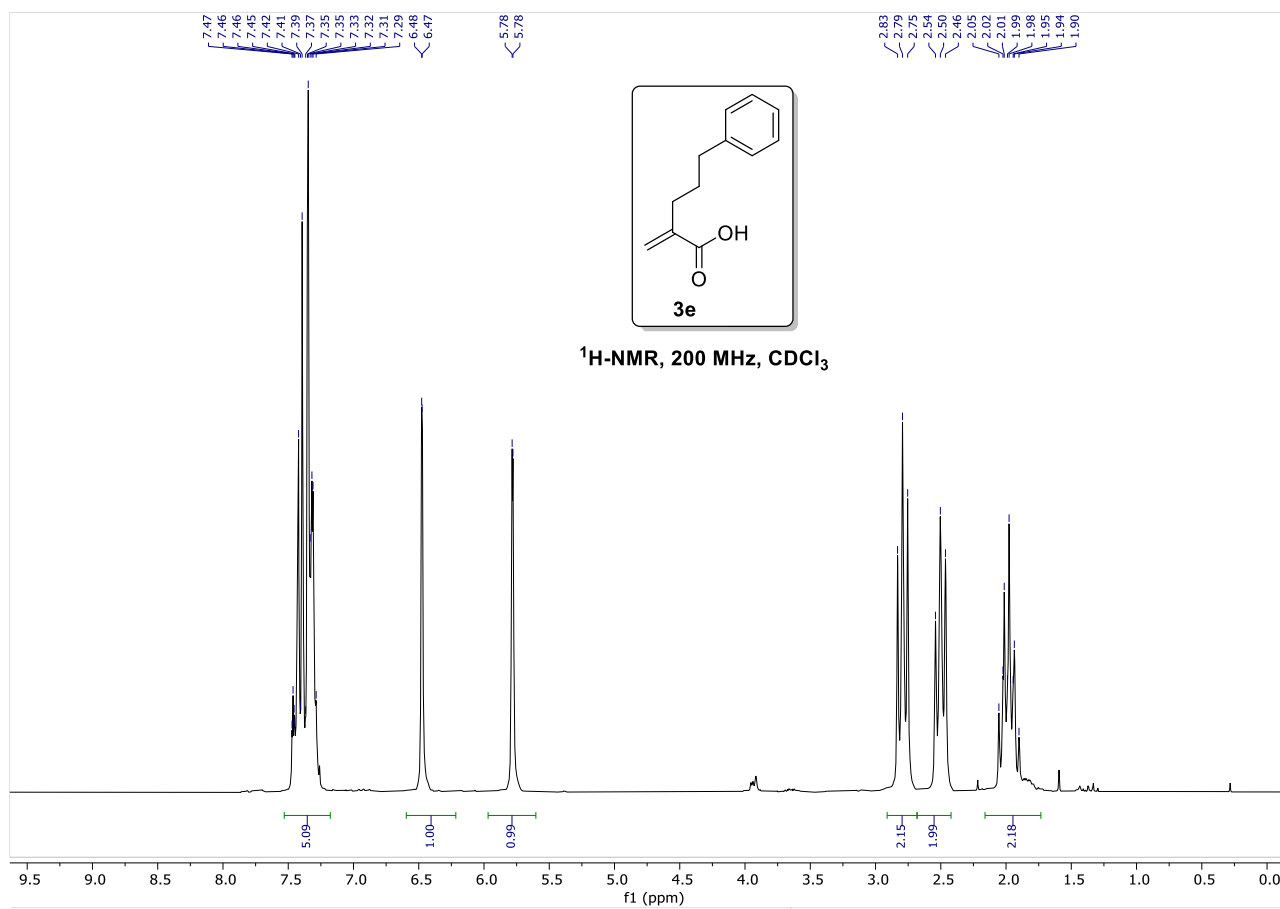
Compound **3k** was prepared according to the general procedure for the synthesis of acrylic acids in a 15 mmol scale of diethyl malonate. NaH in THF was used for the alkylation of diethylmalonate [1]. The final product **3k** was obtained as a white solid in 84% (2.34 g) yield for 3 steps. 1H NMR (200 MHz, $CDCl_3$) δ 6.42 (d, $J = 1.1$ Hz, 1H), 5.78 (q, $J = 1.1$ Hz, 1H), 3.25 (d, $J = 0.7$ Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 170.0, 134.0, 130.0, 81.3, 38.6, 27.9.; HRMS (m/z): $[M + H]^+$ calcd. for $C_9H_{15}O_4^+$, 209.0784 found, 209.0787.

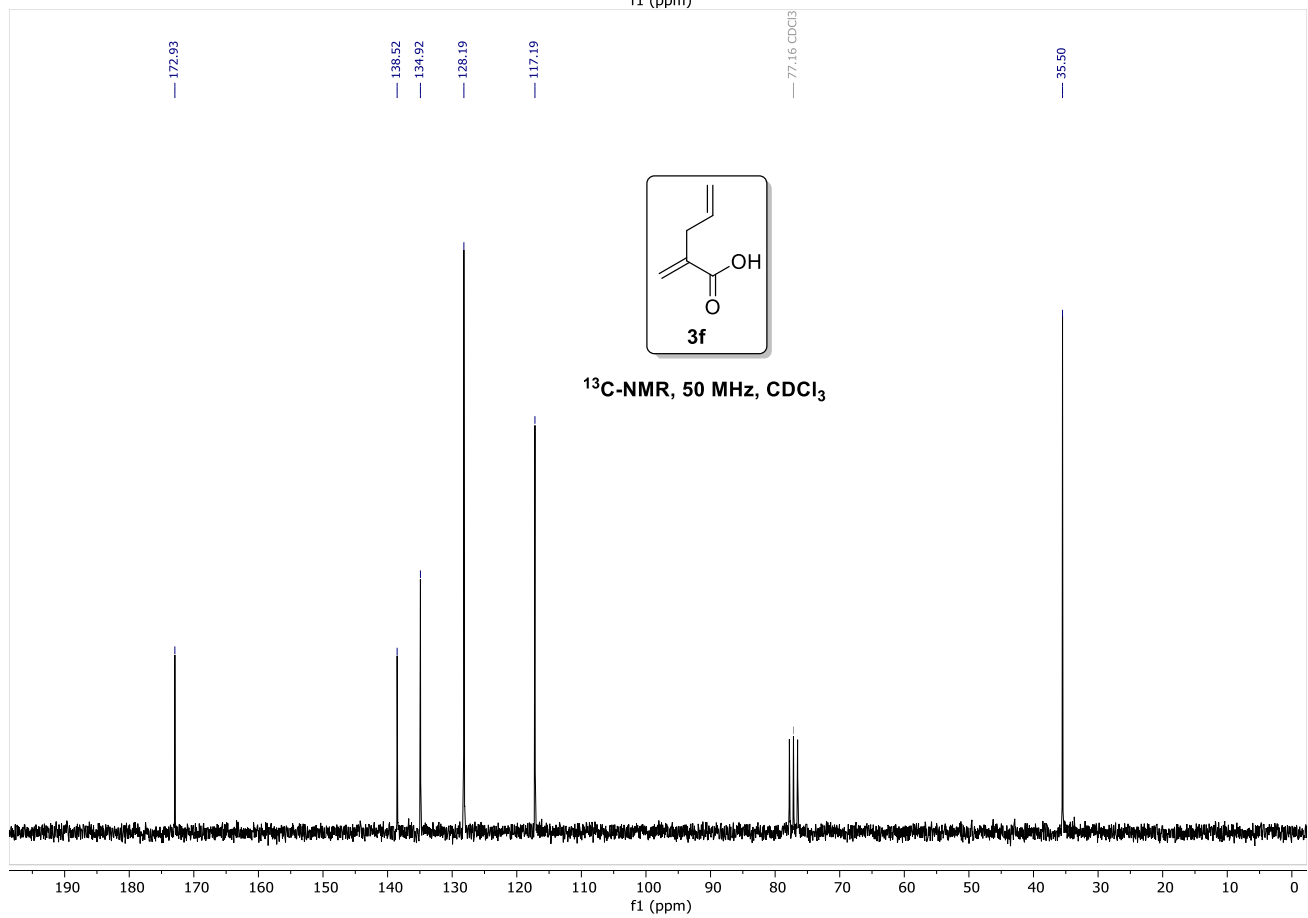
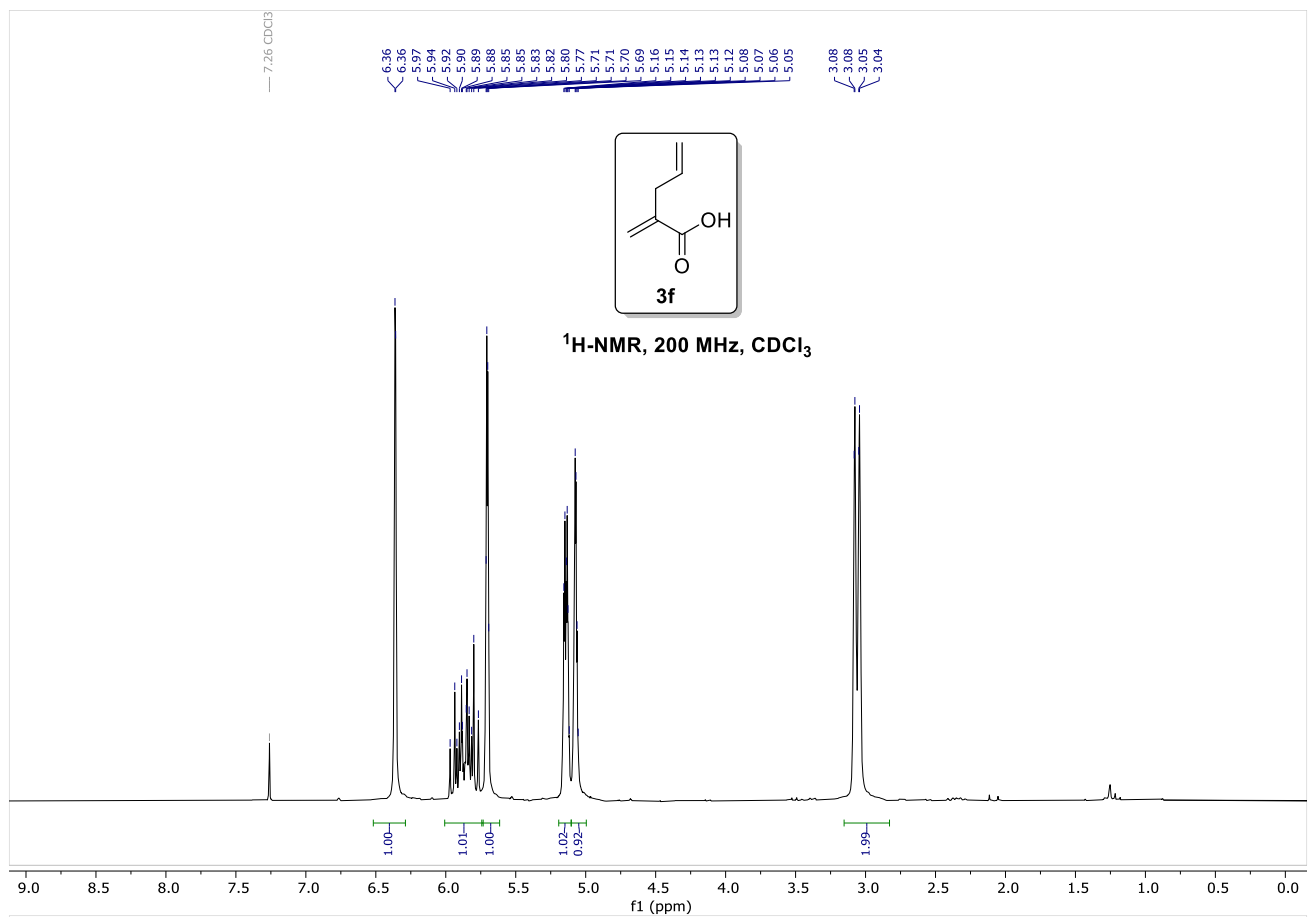
Copies of NMR spectra of compounds of type **3** and **5**

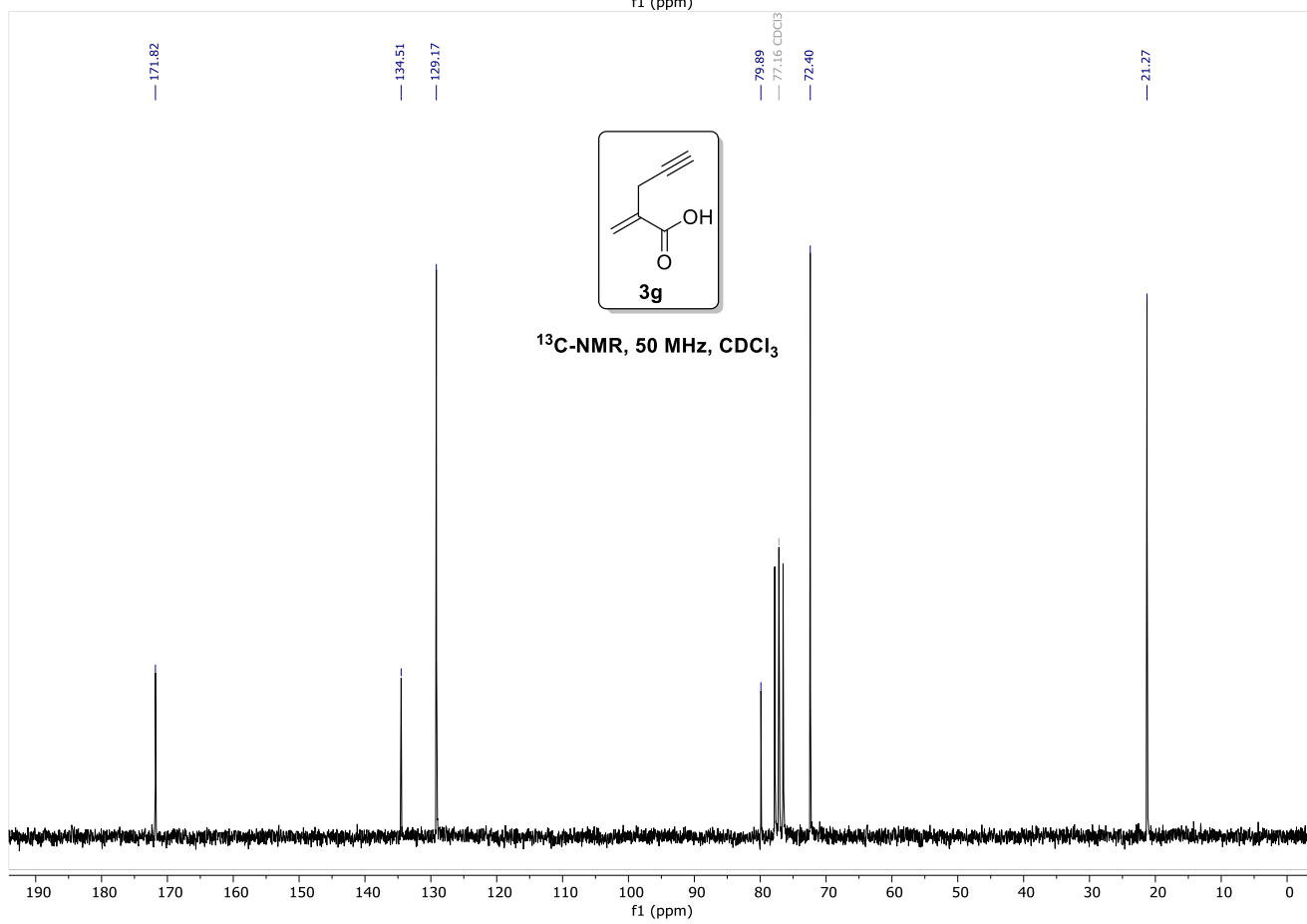
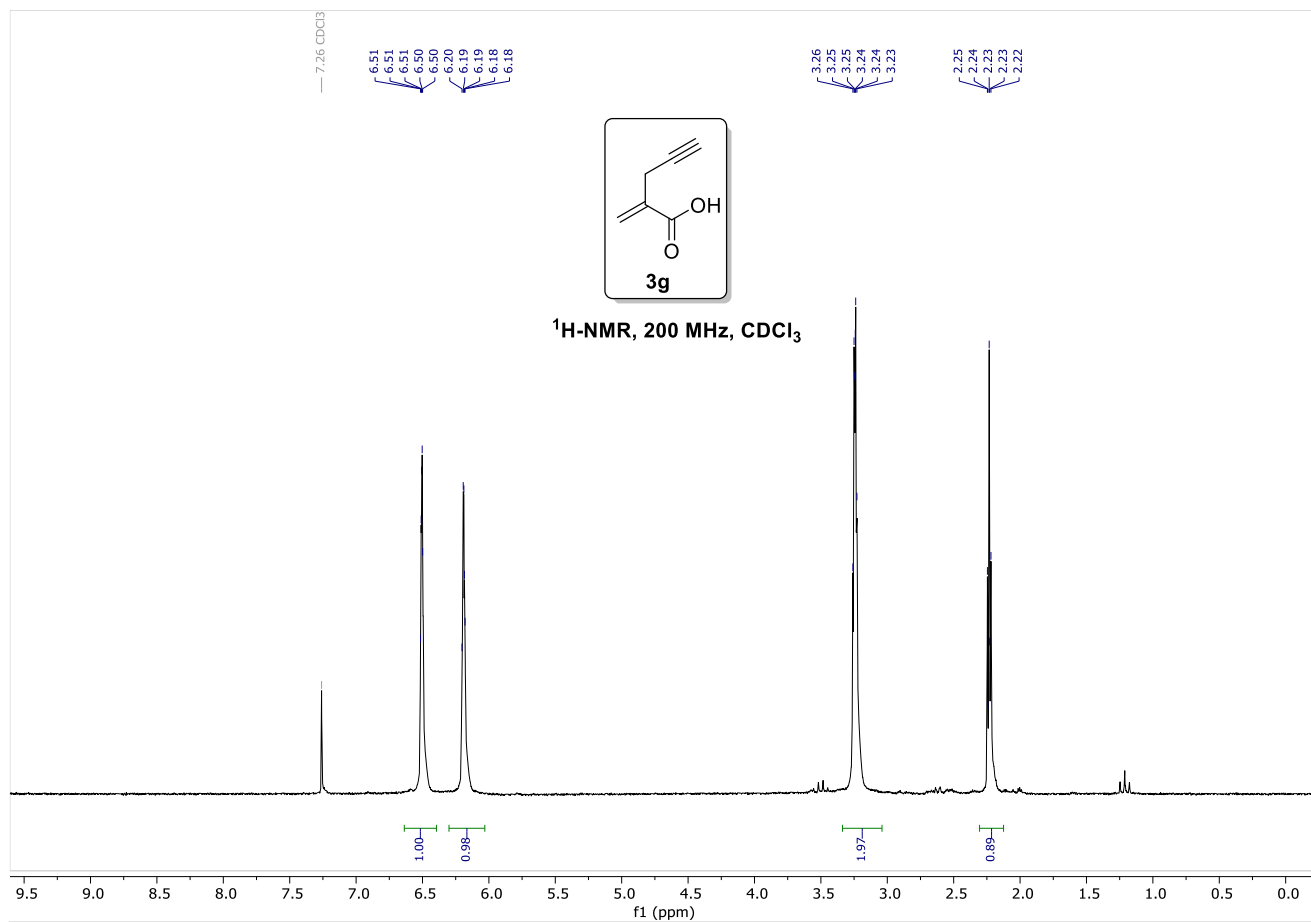


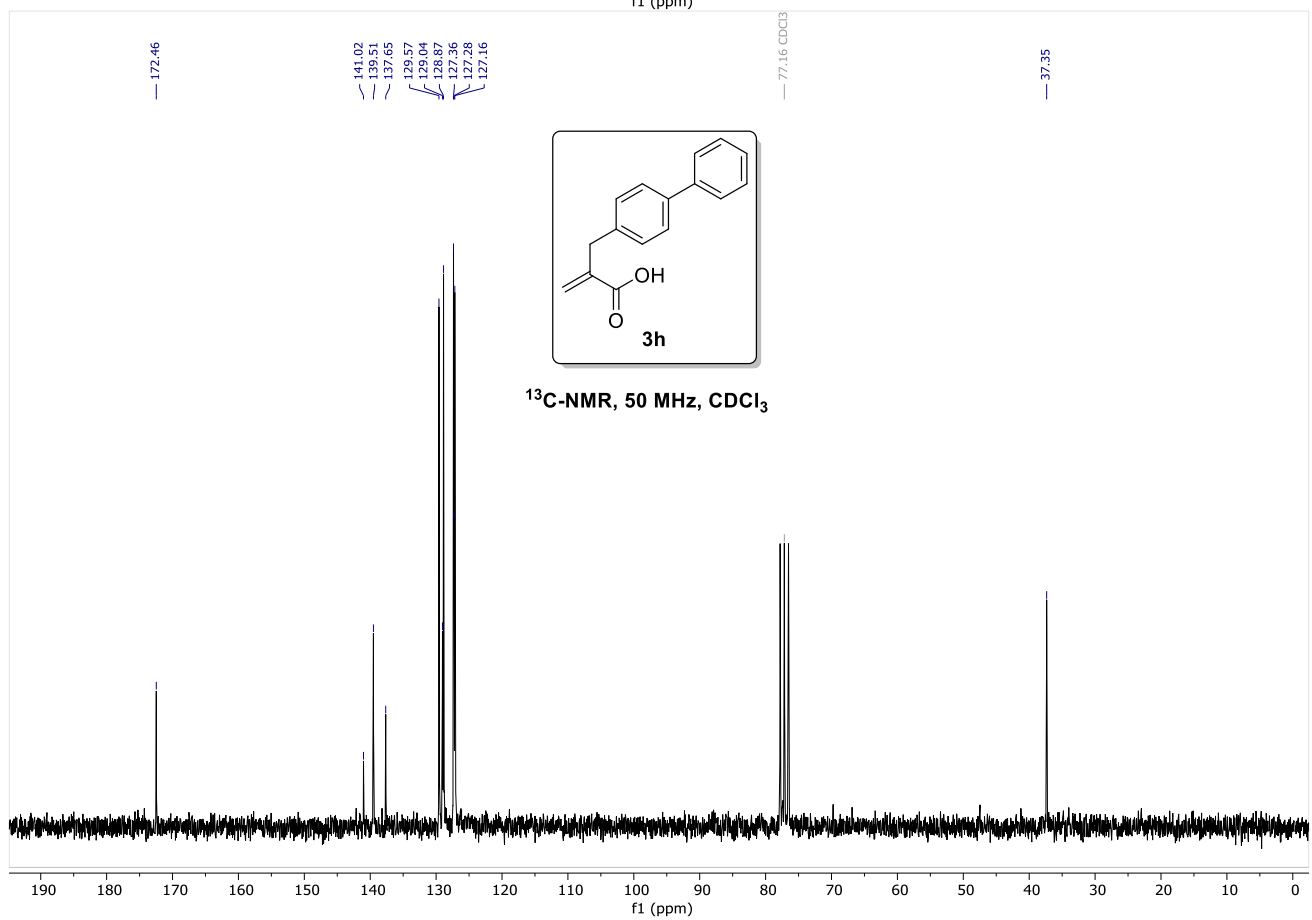
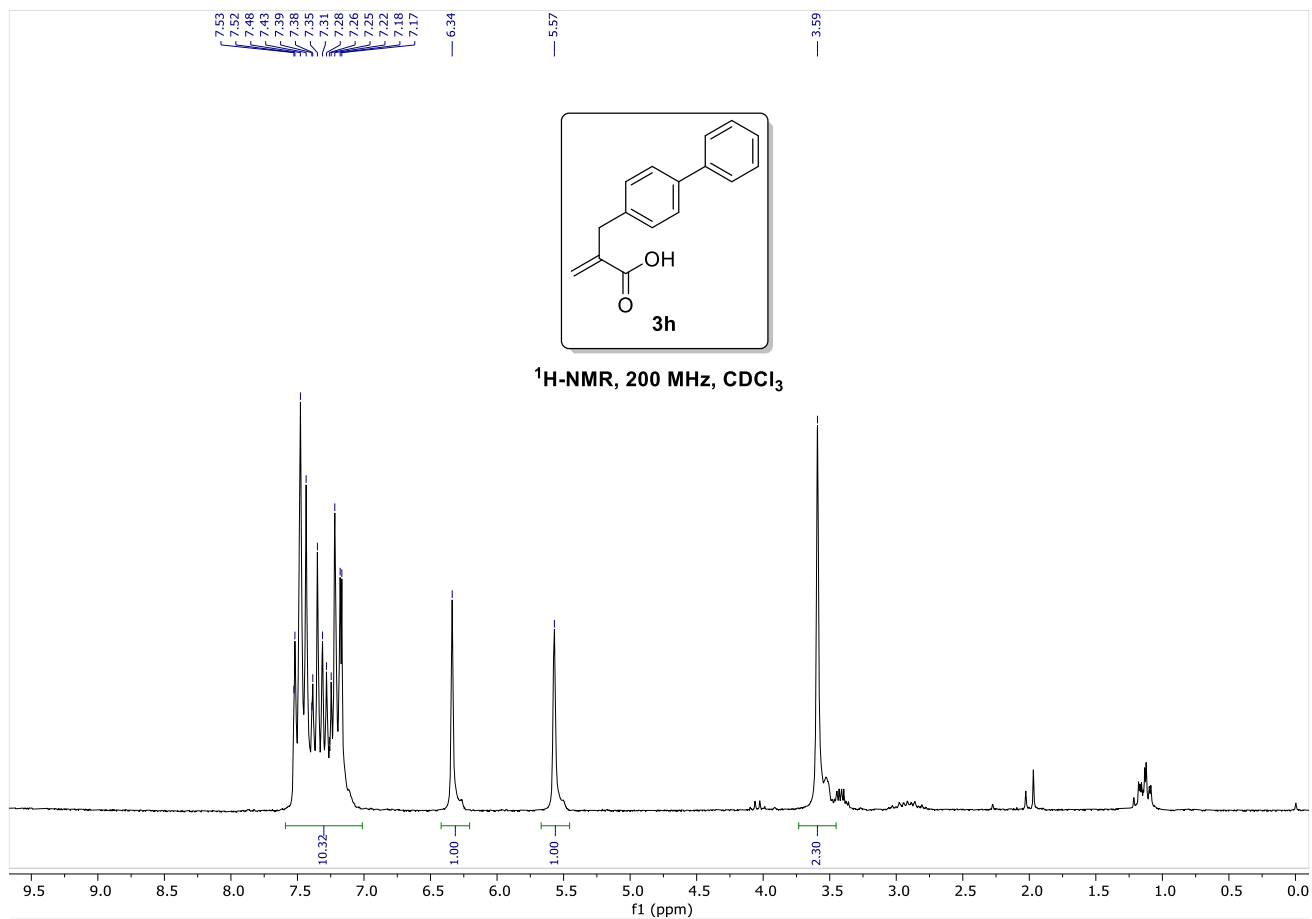


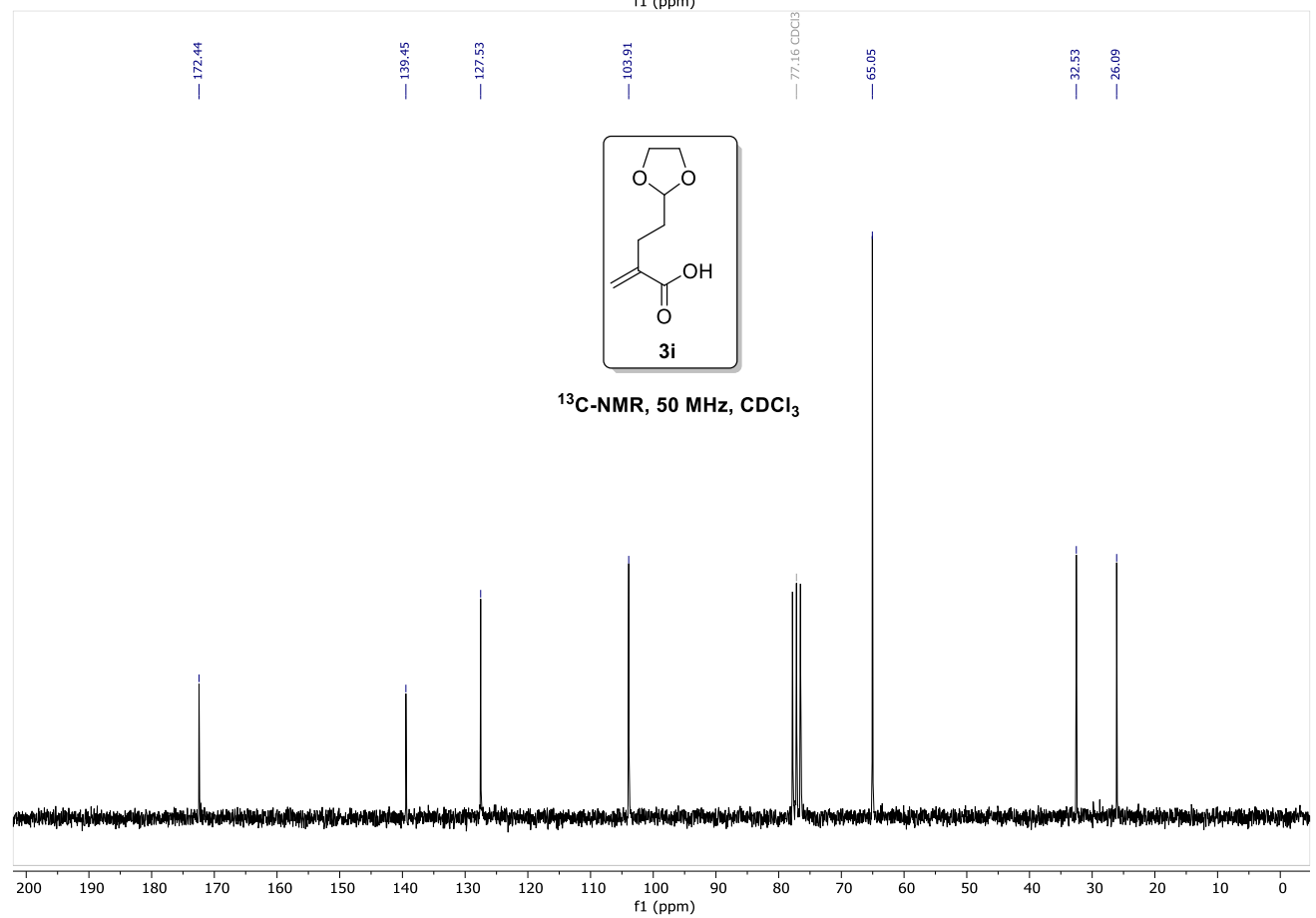
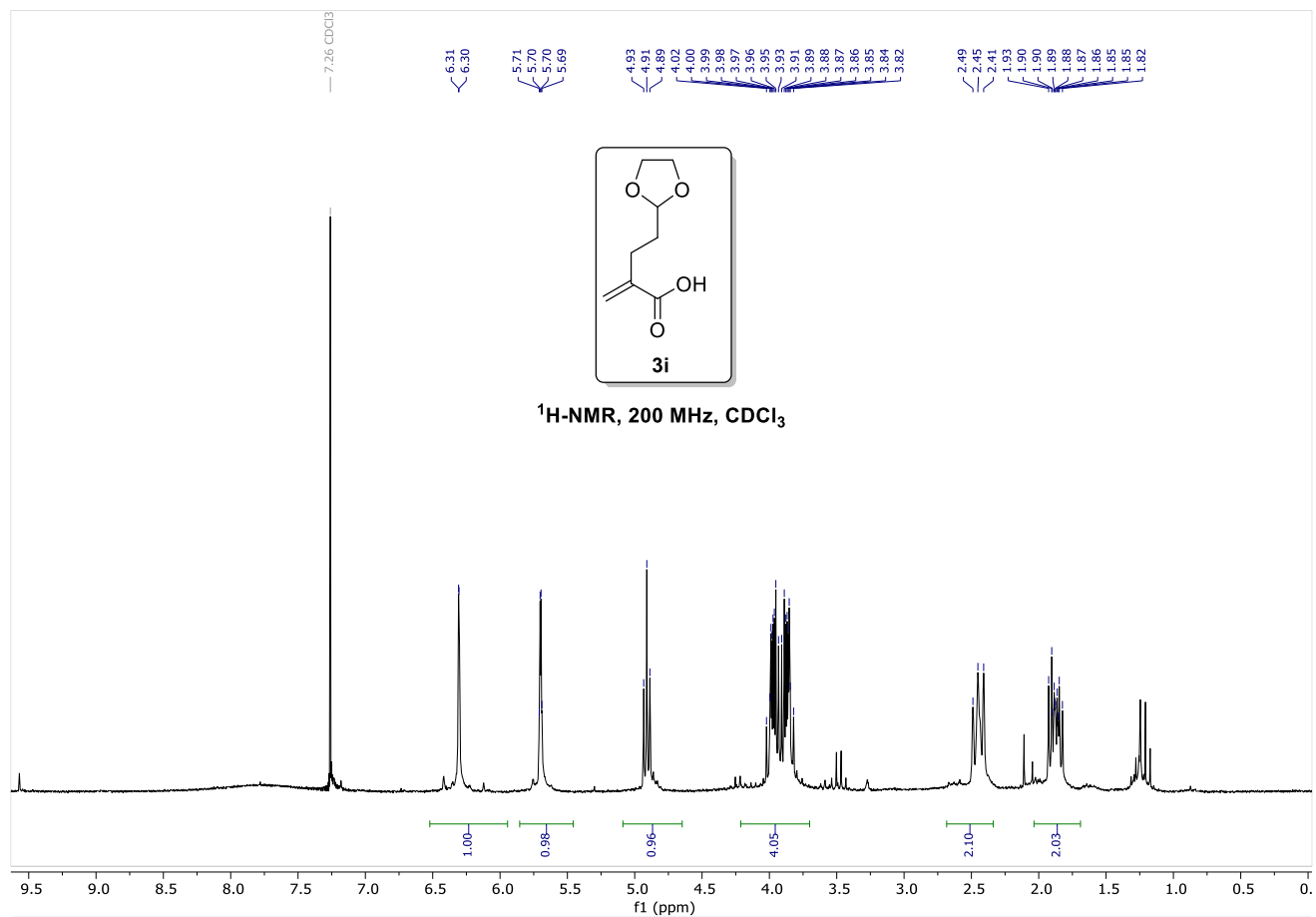


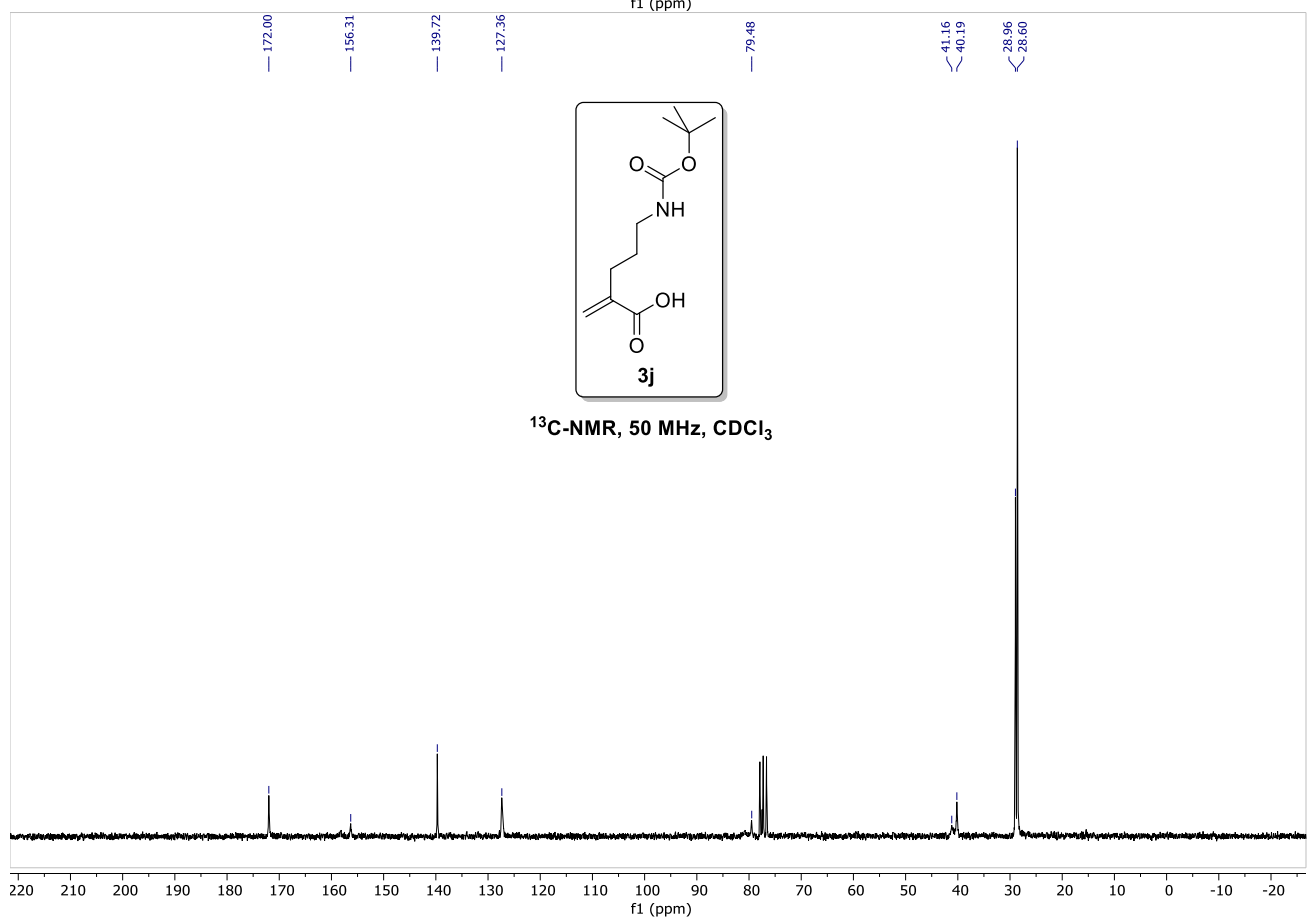
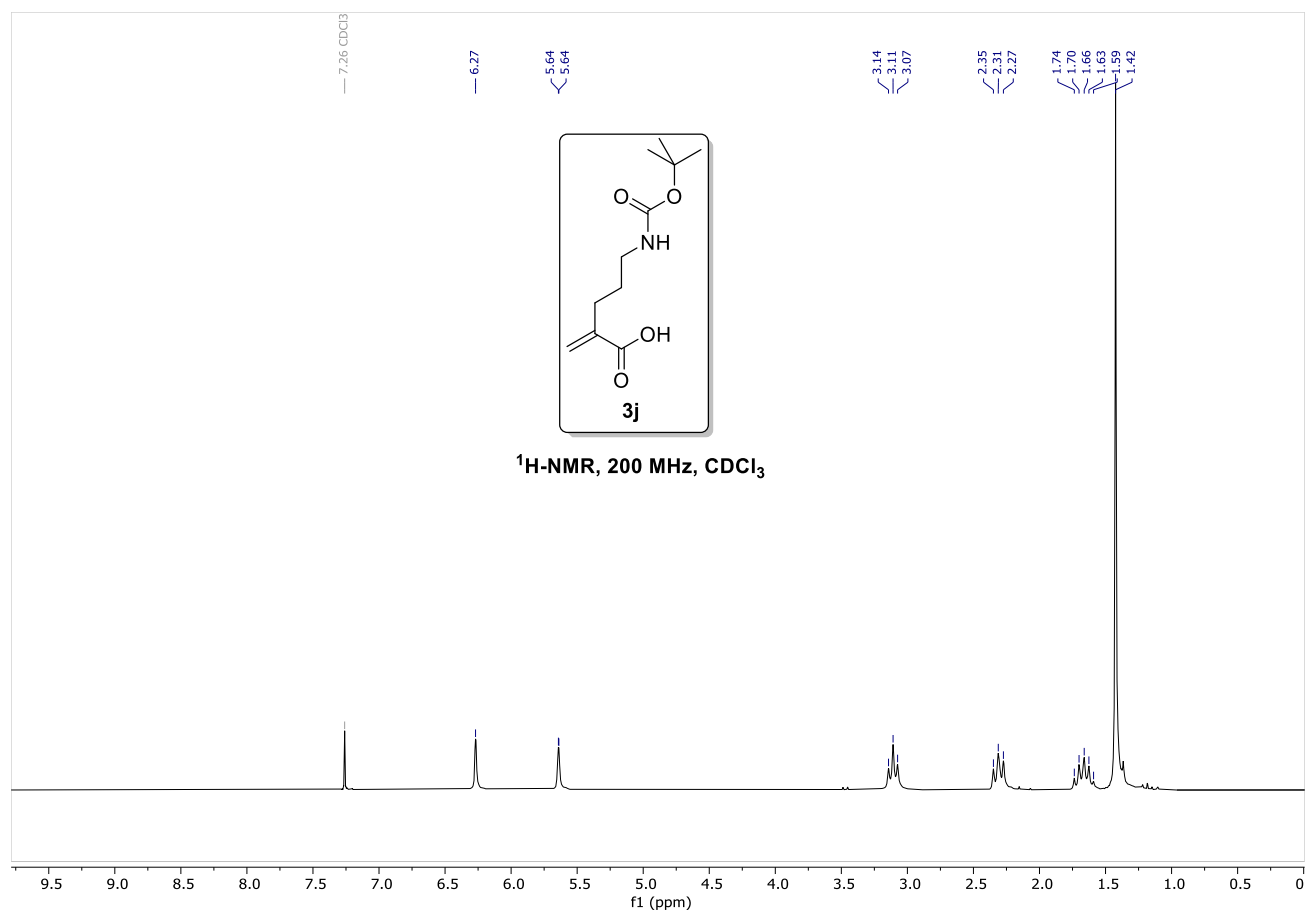


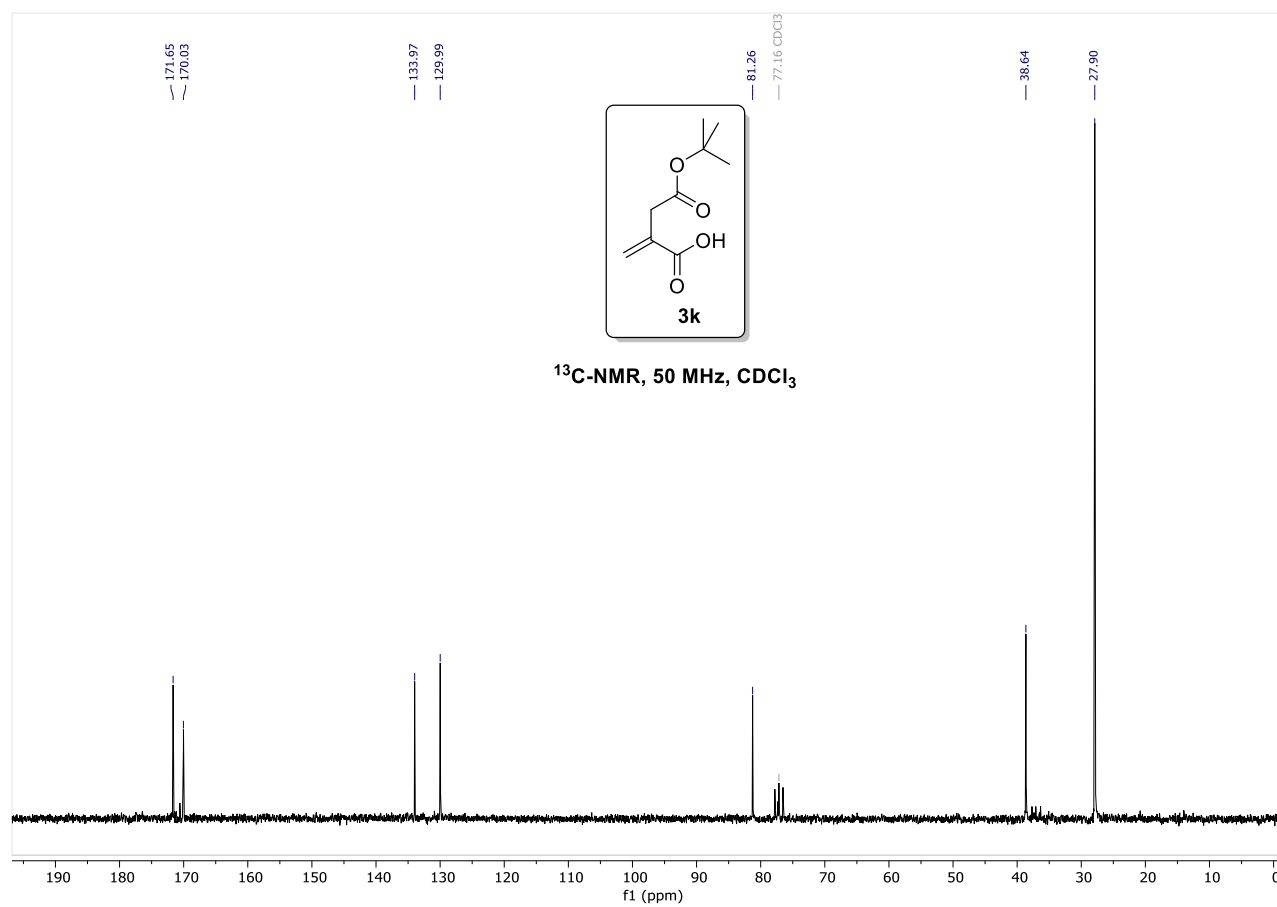
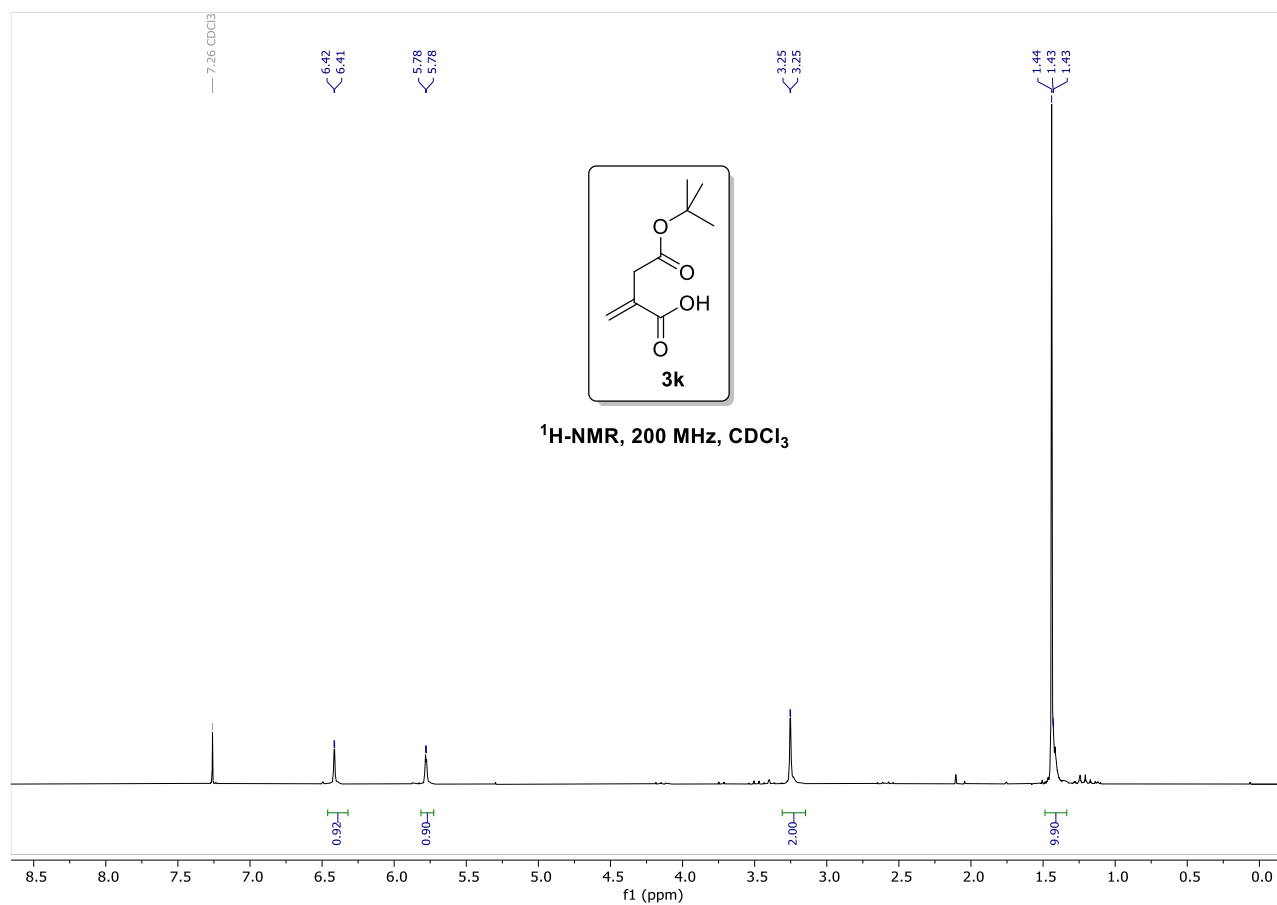


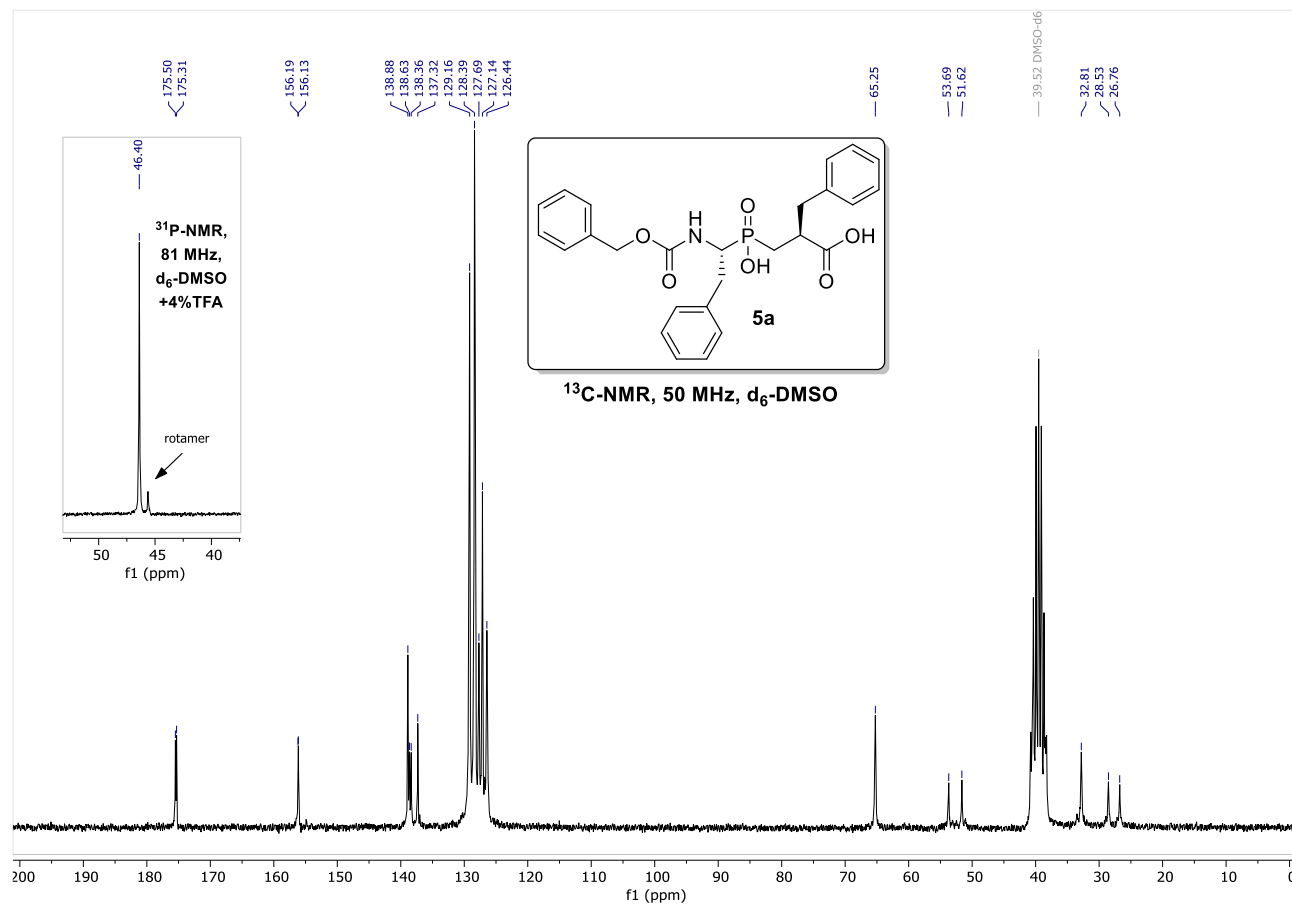
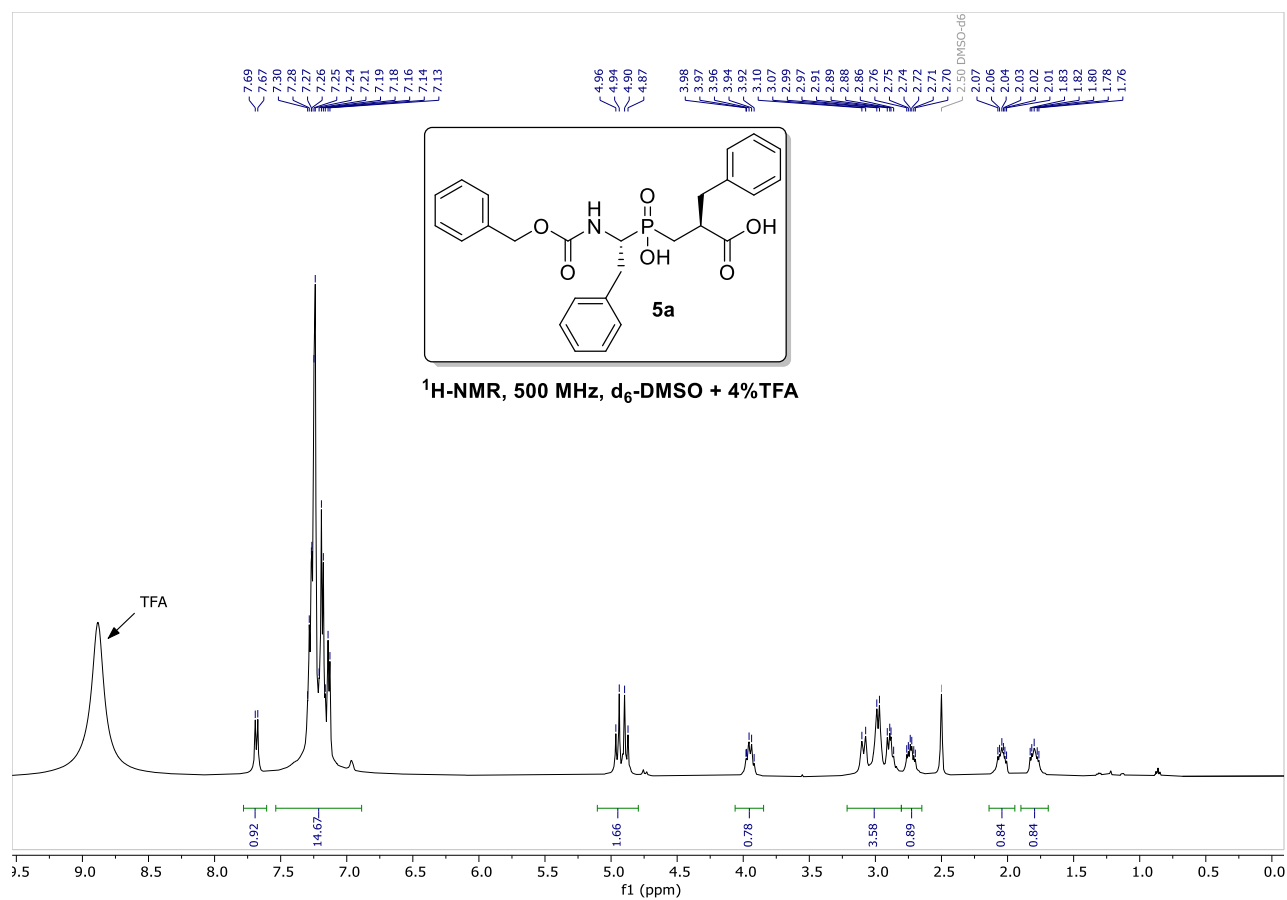


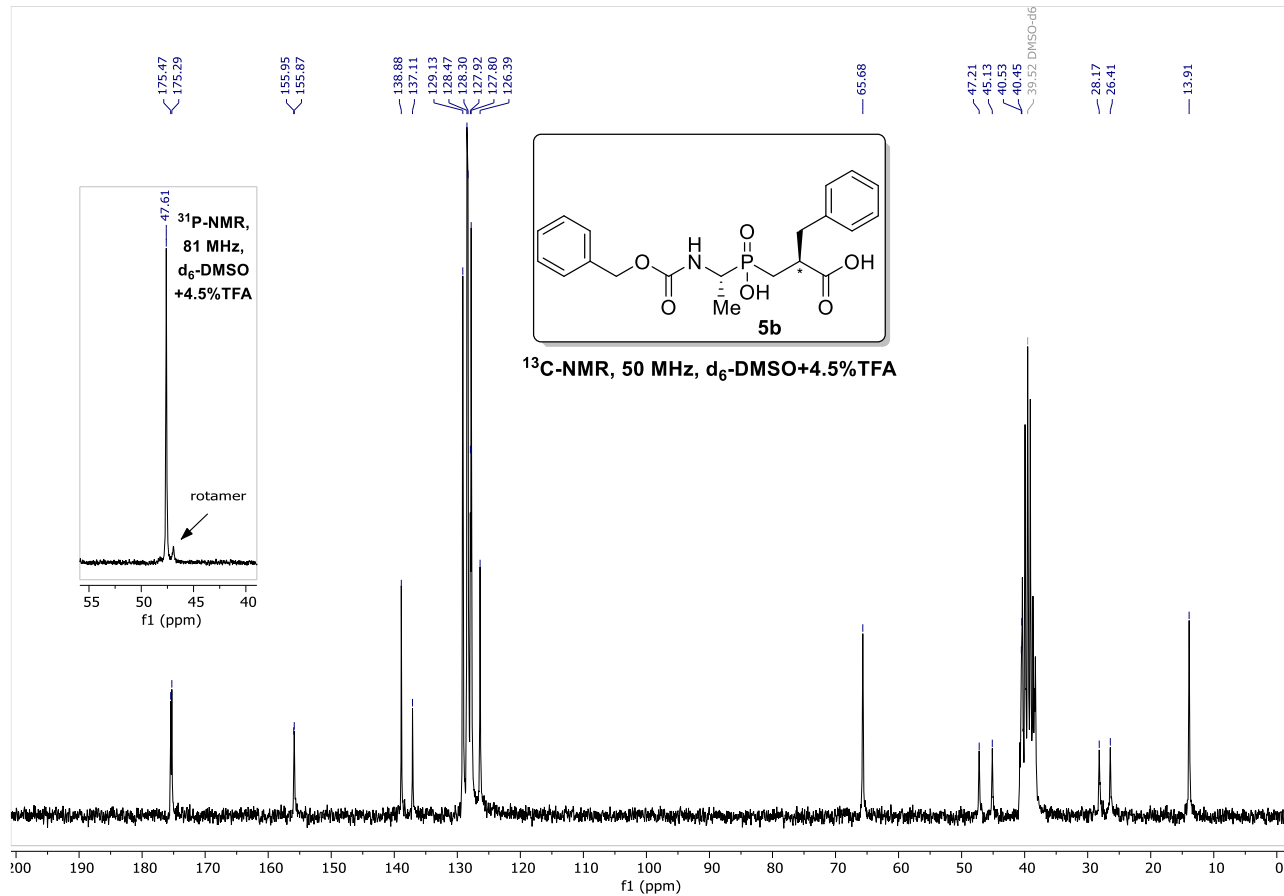
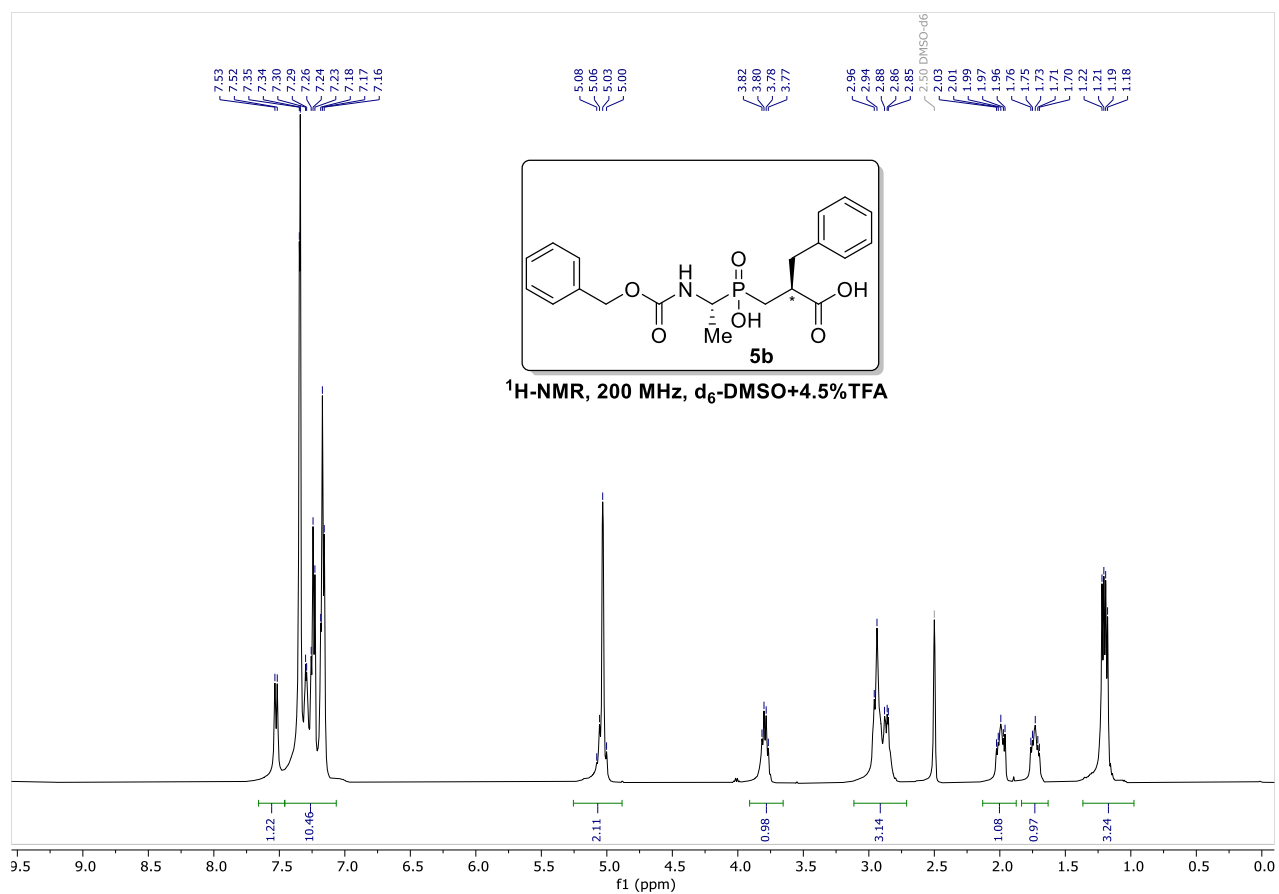


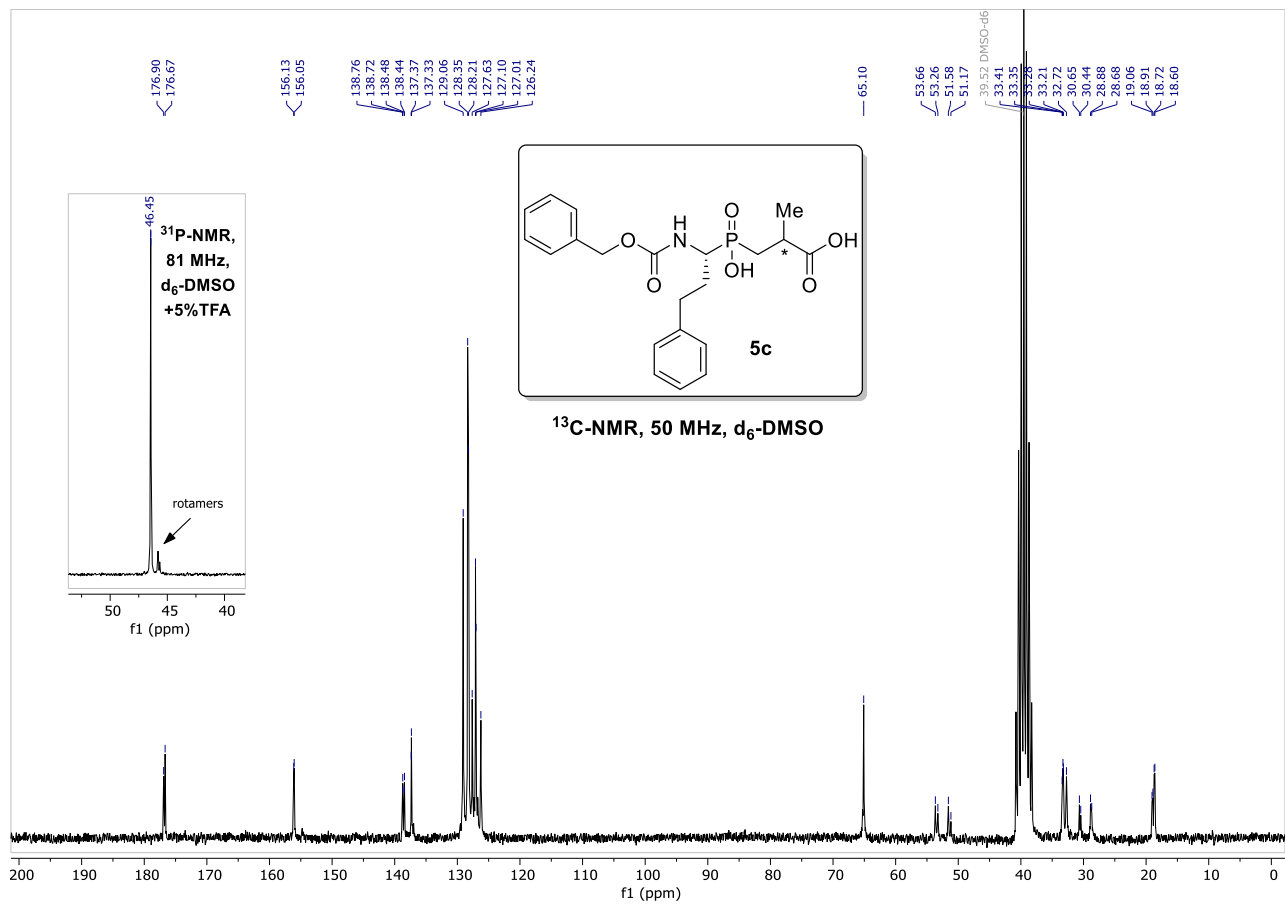
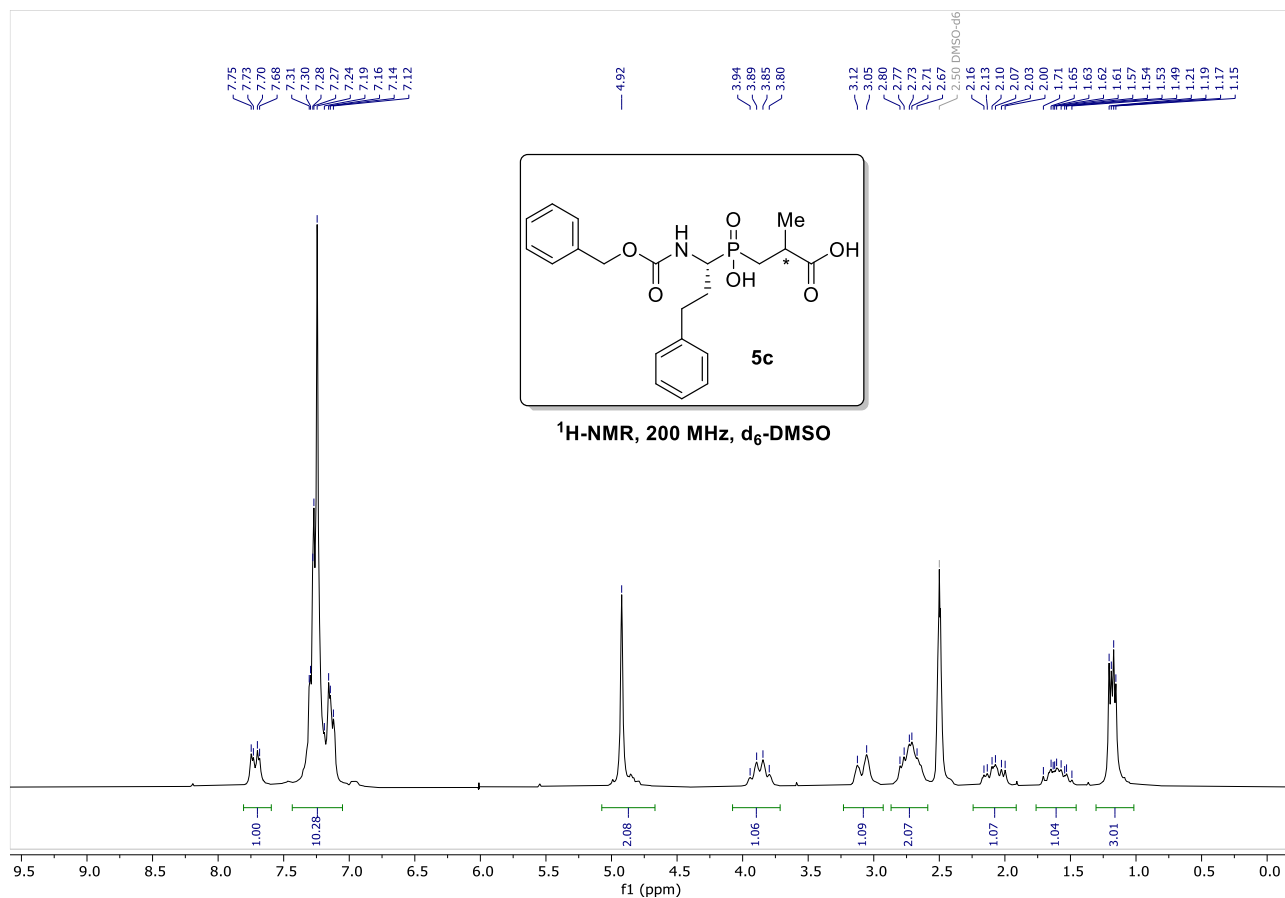


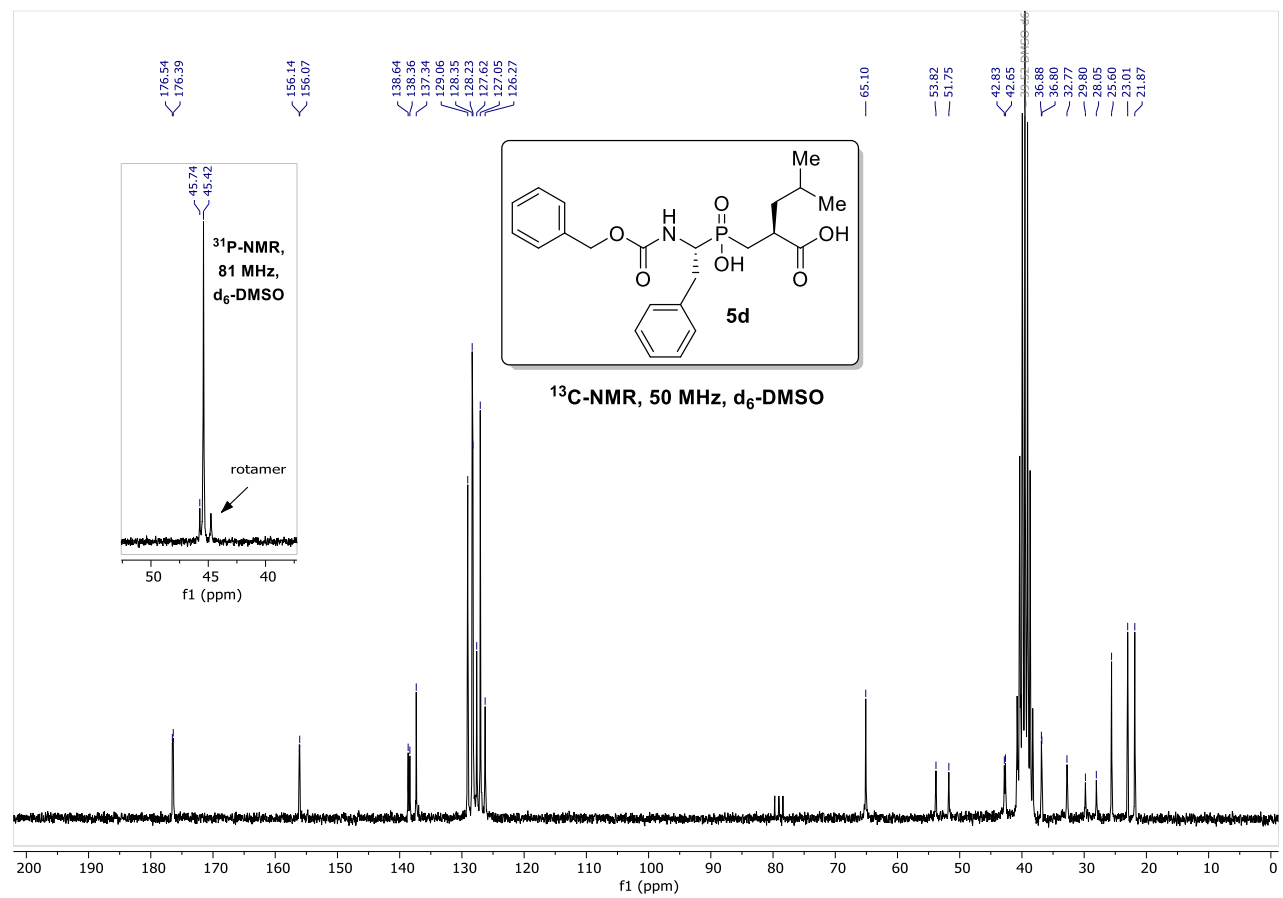
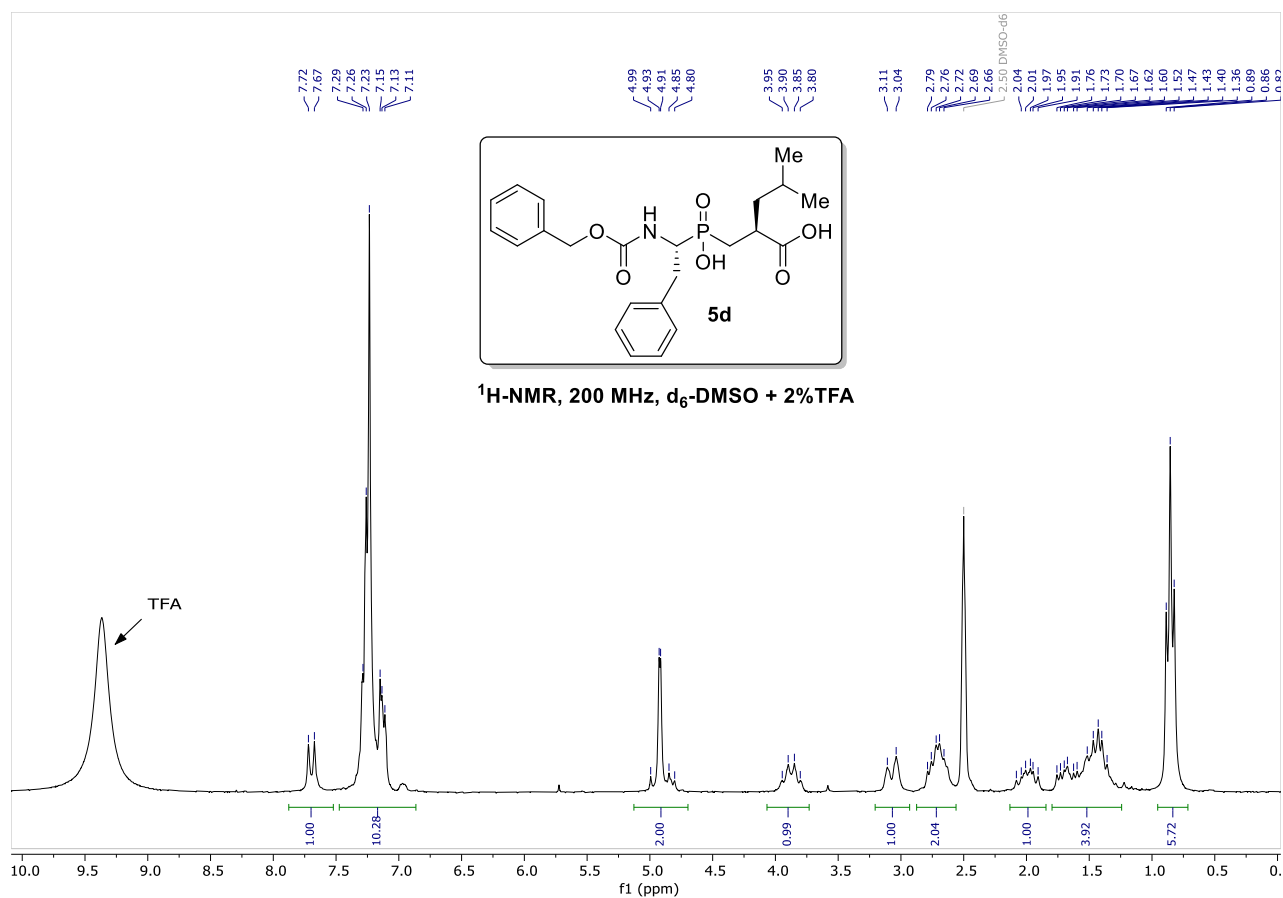


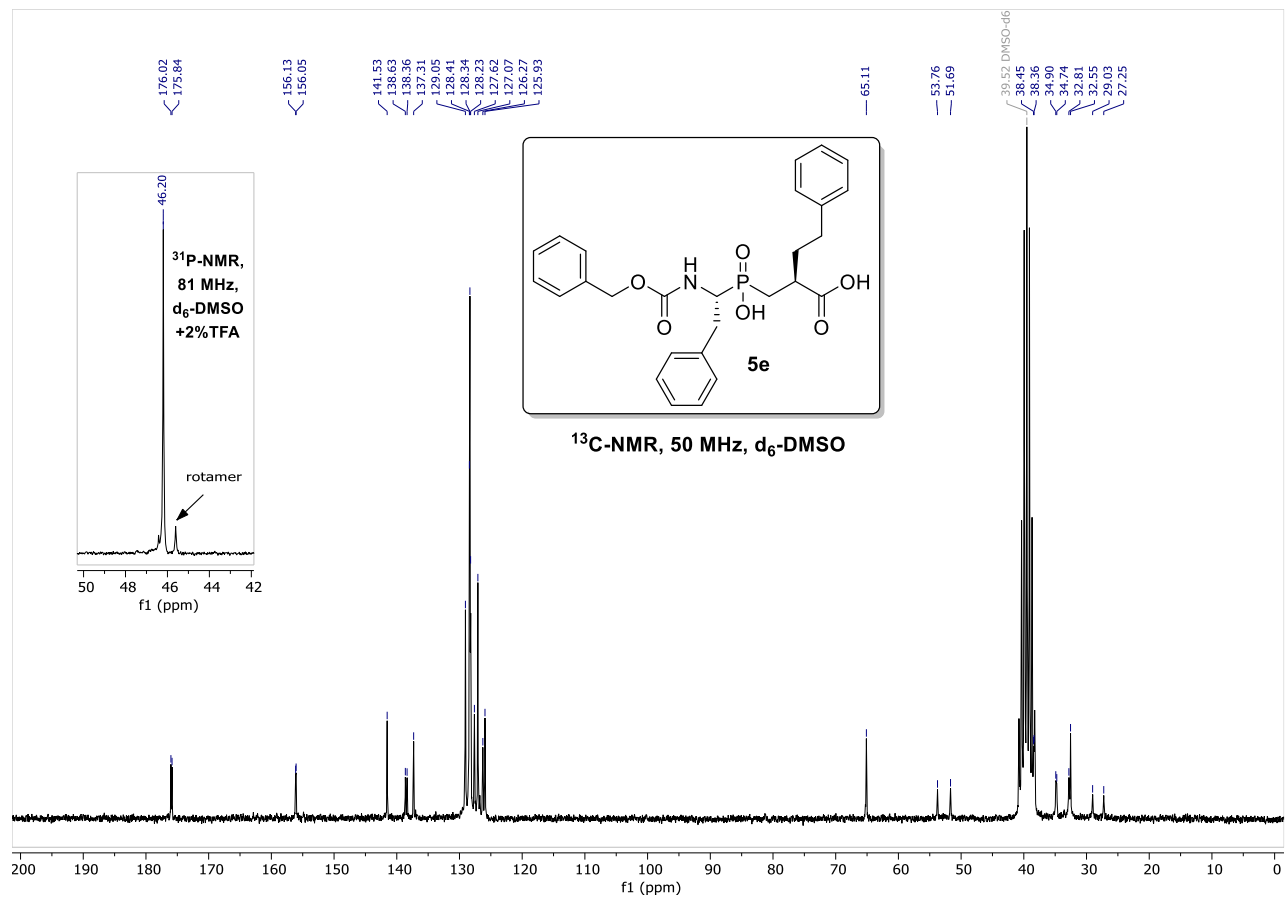
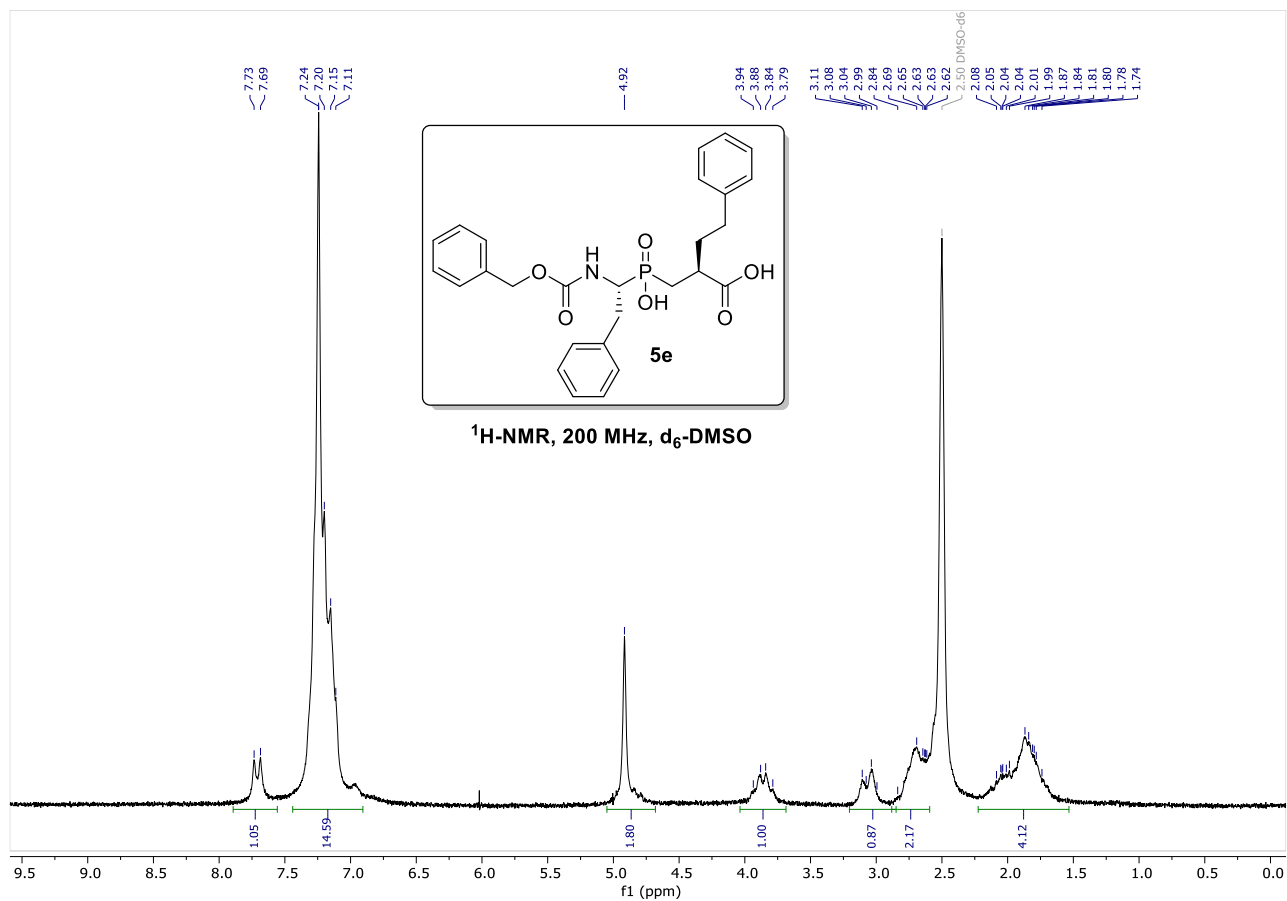


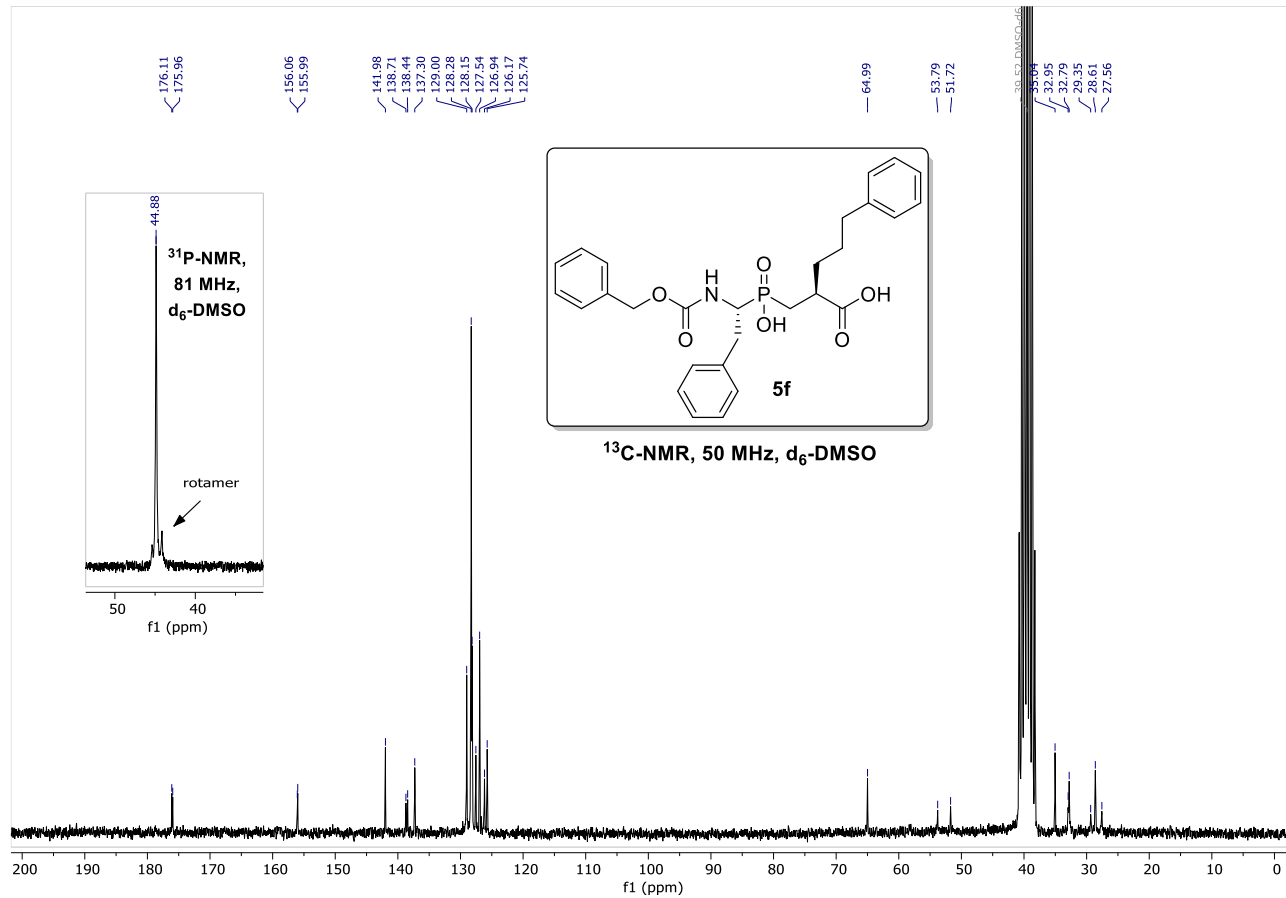
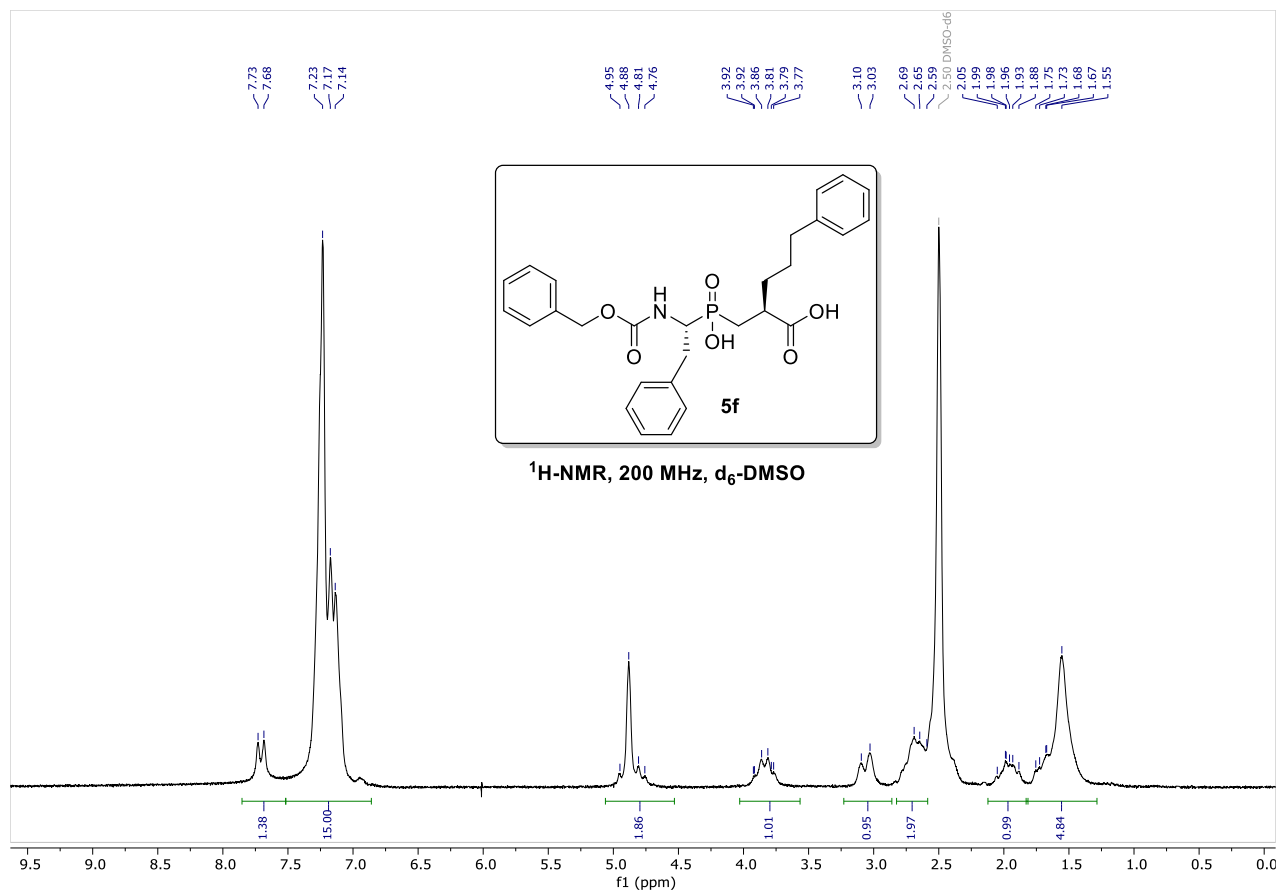


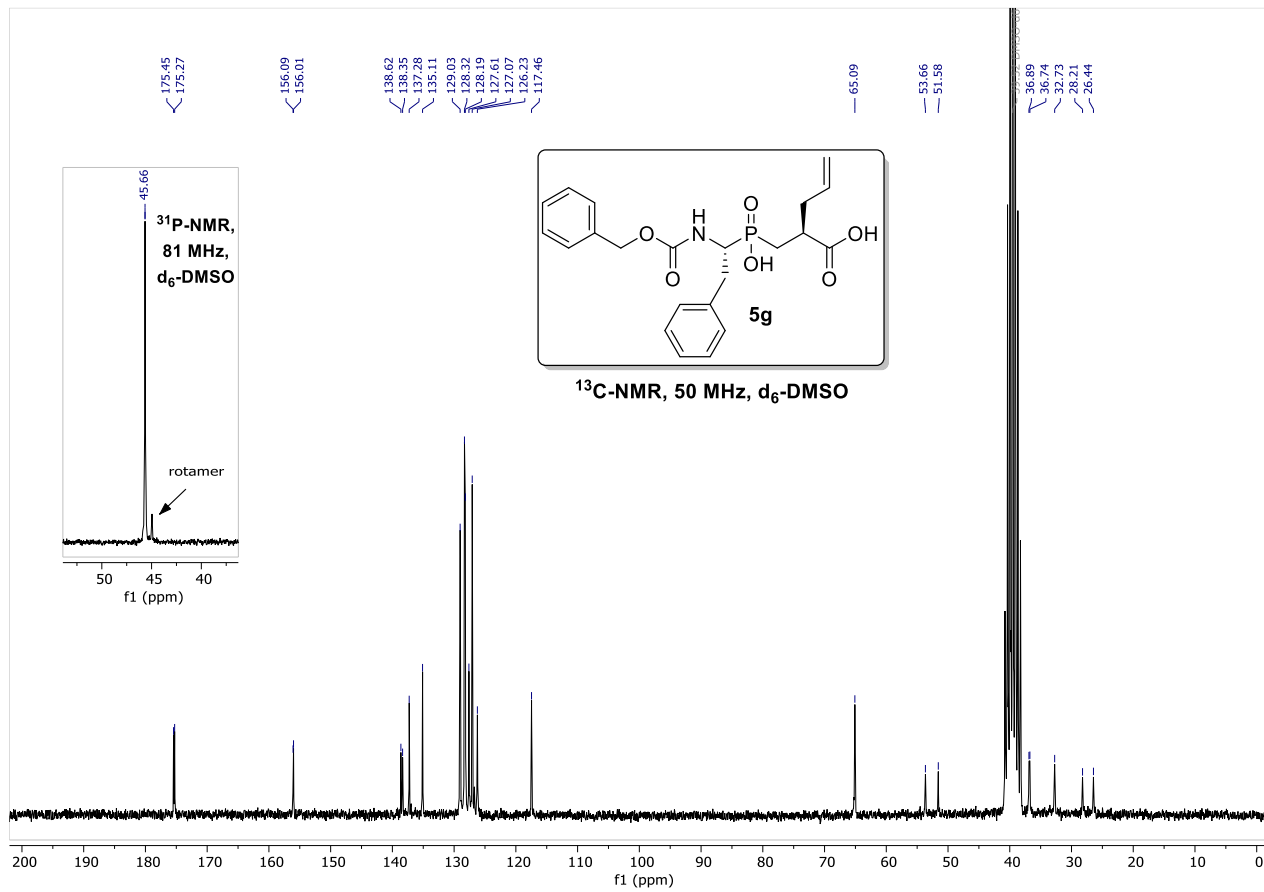
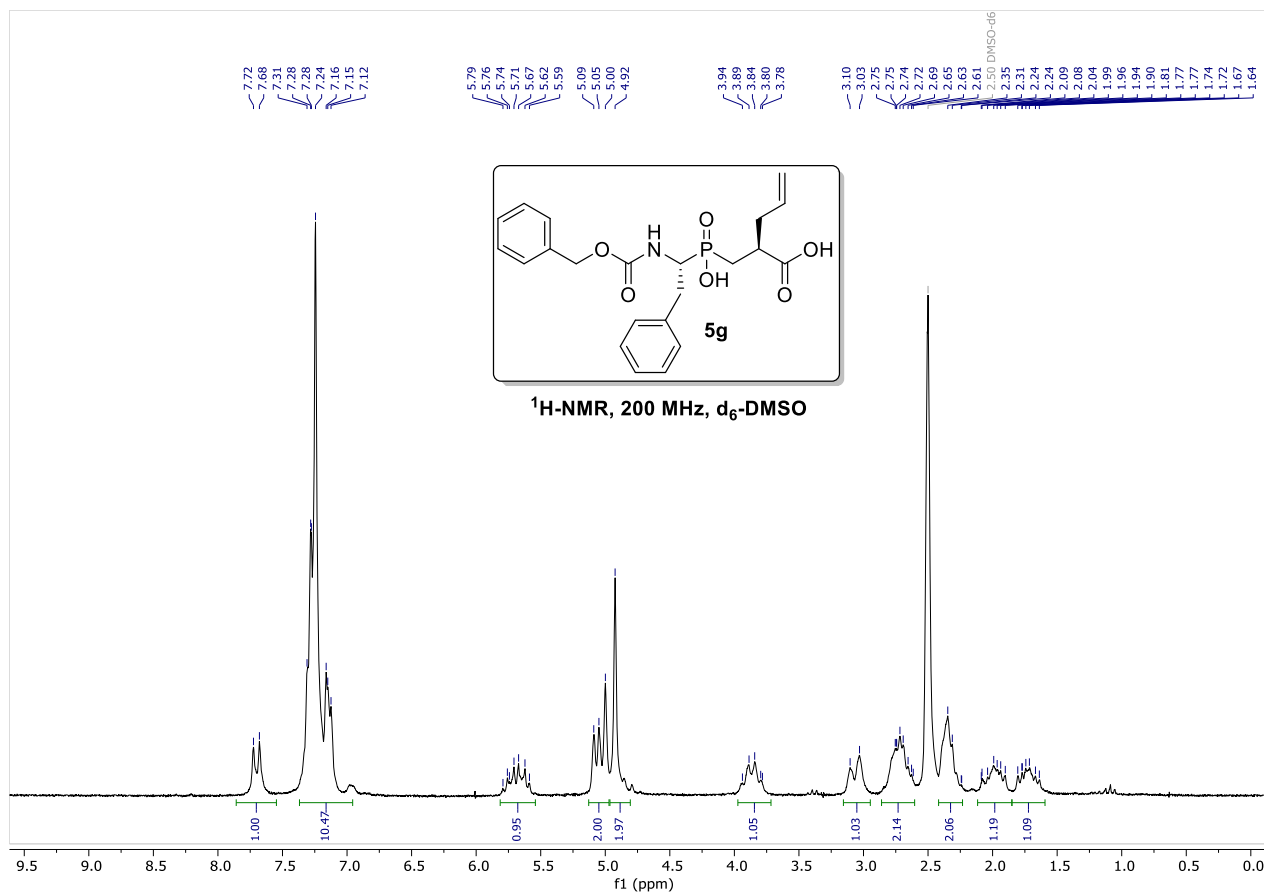


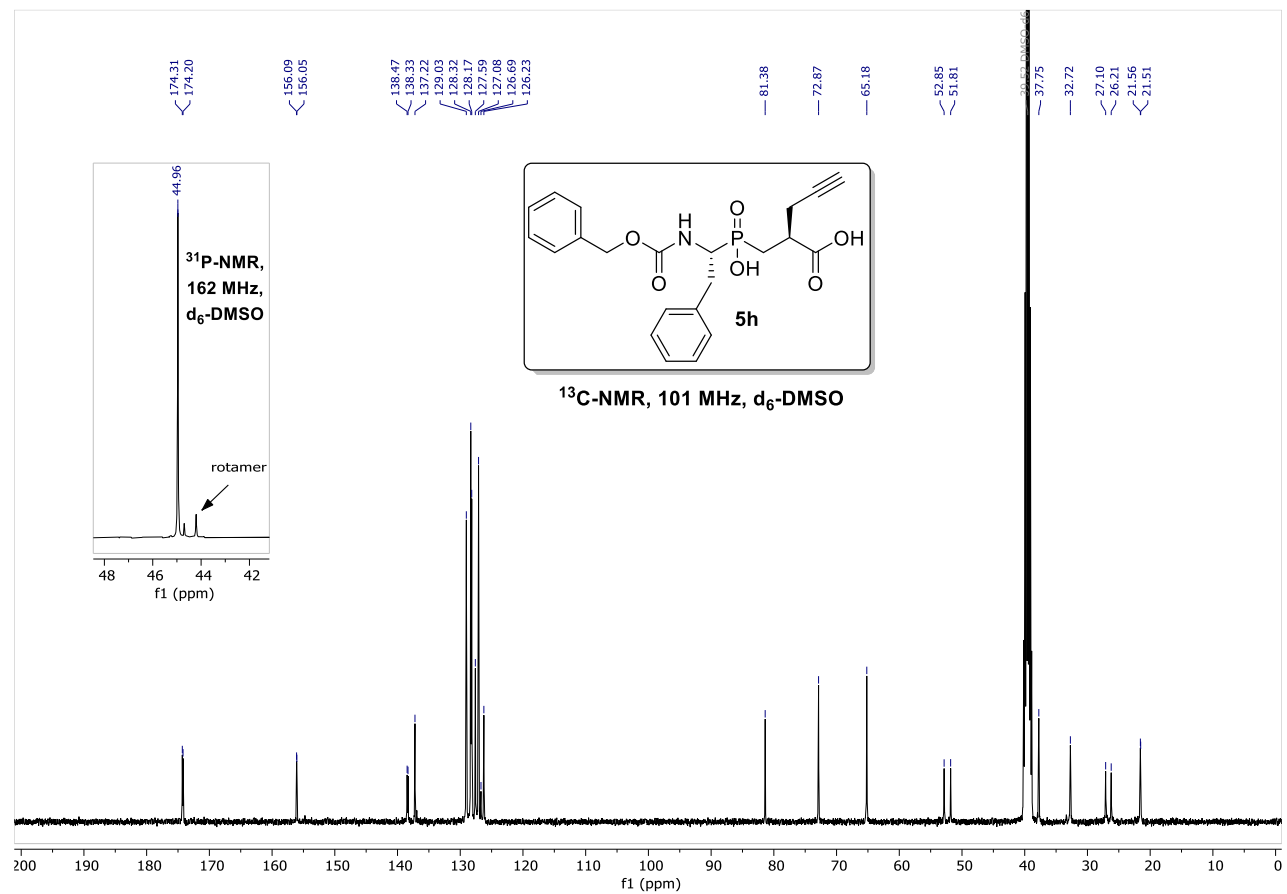
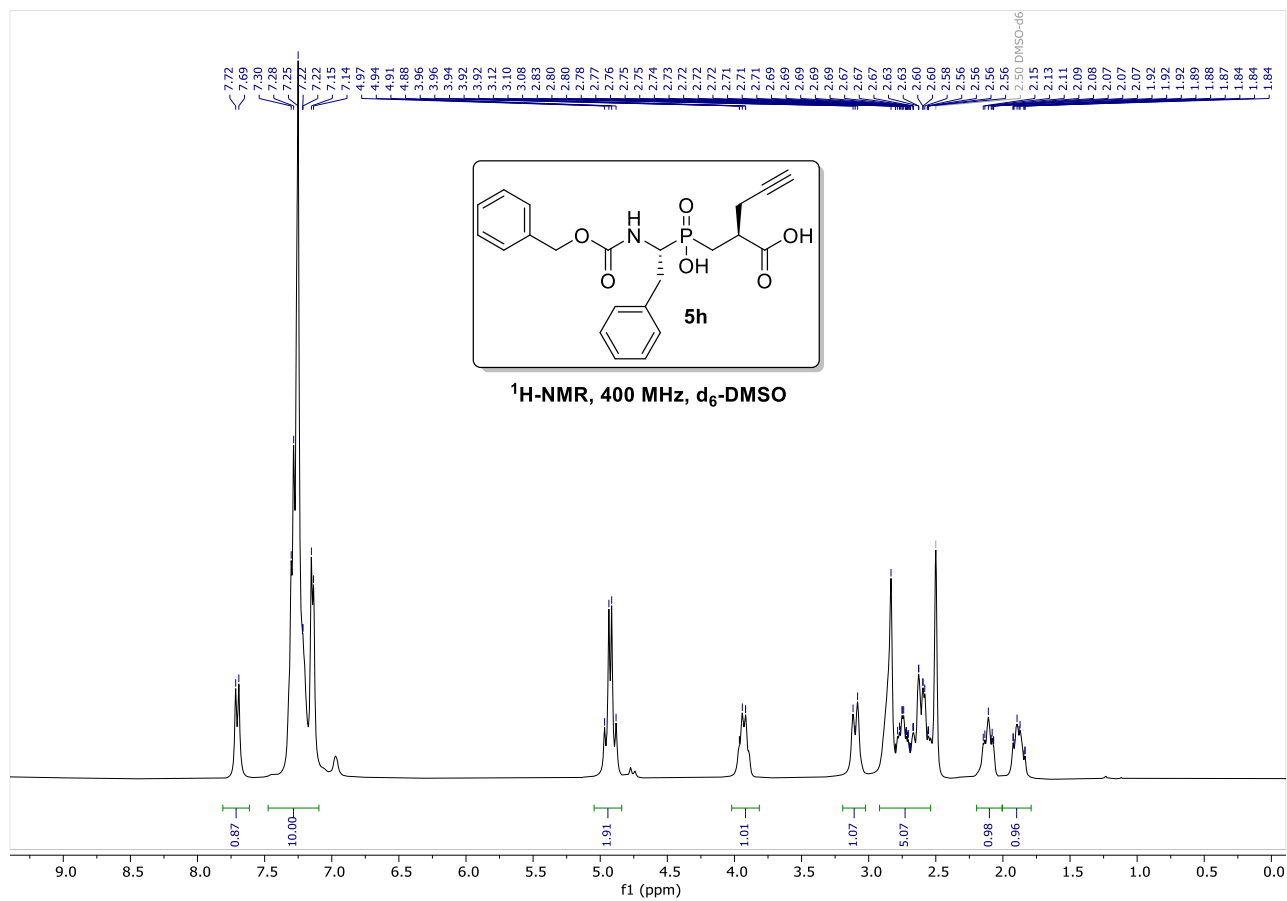


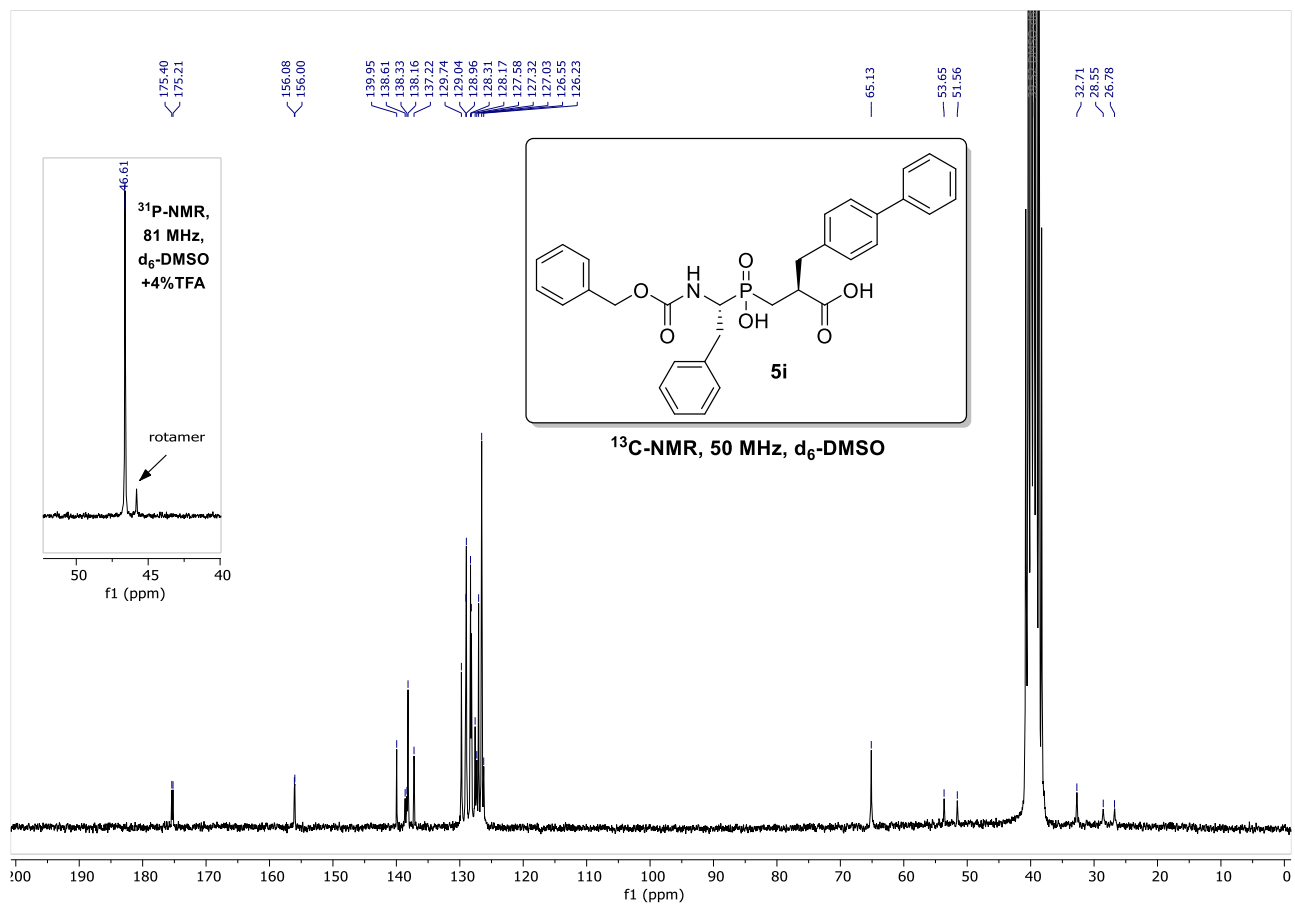
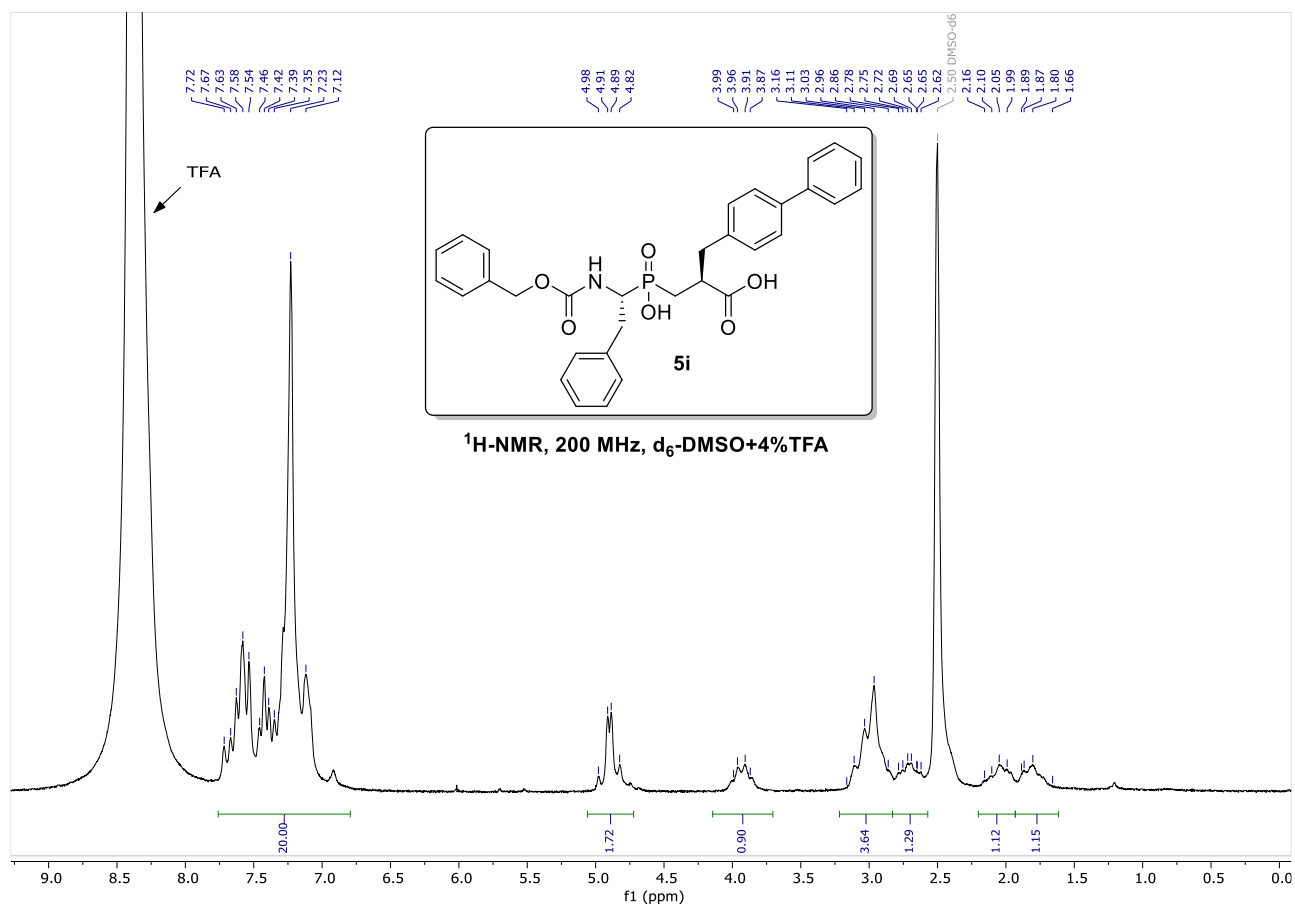


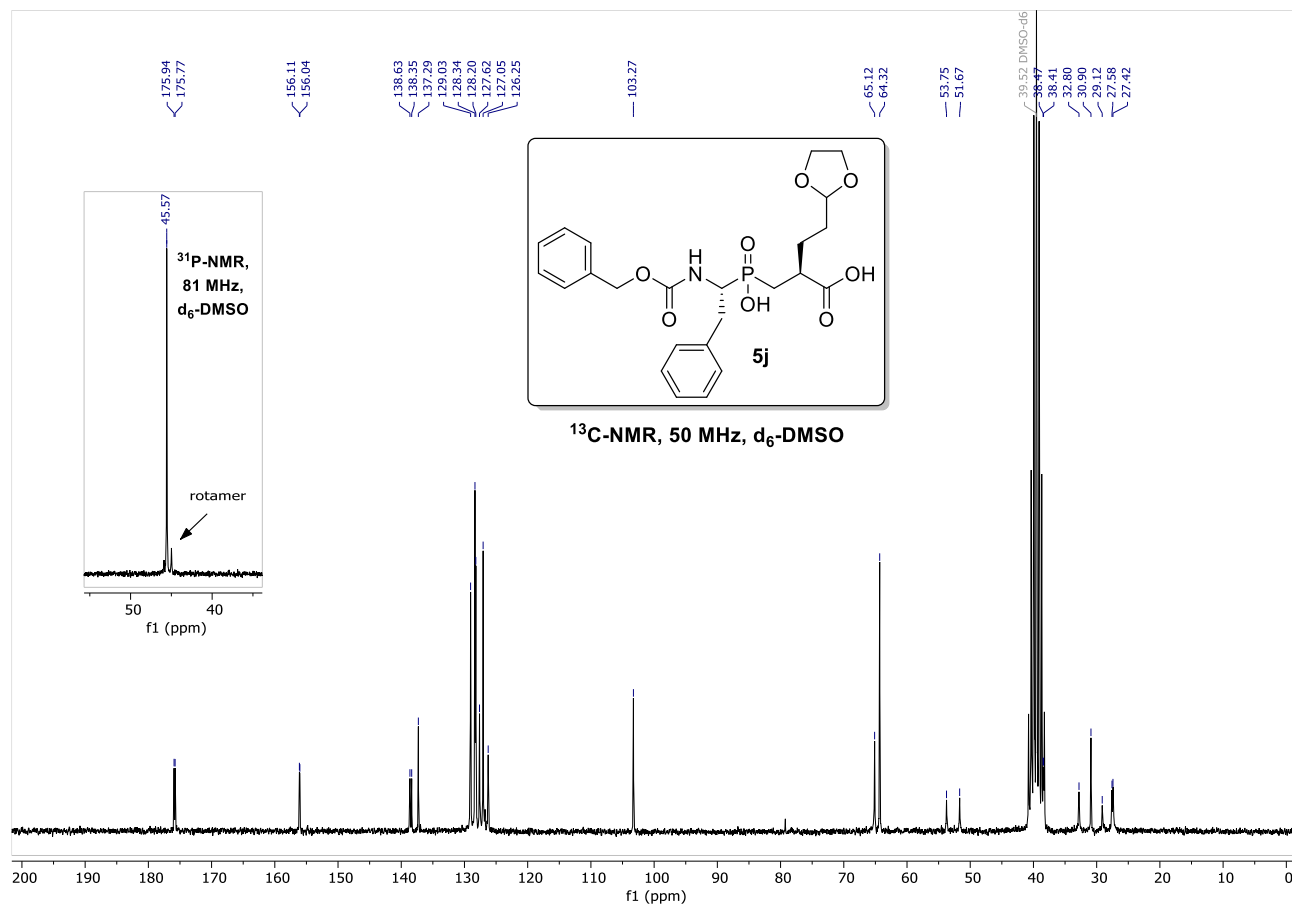
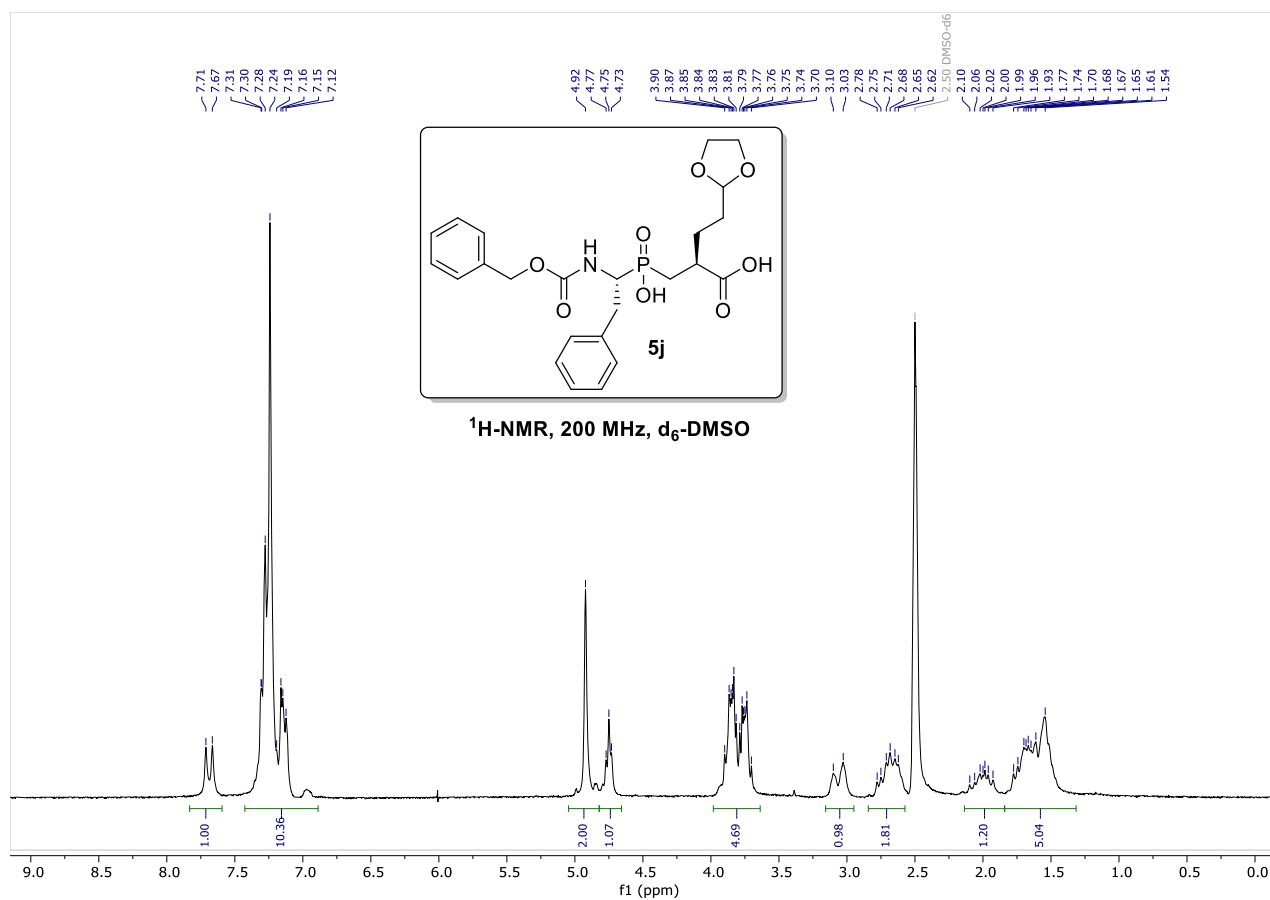


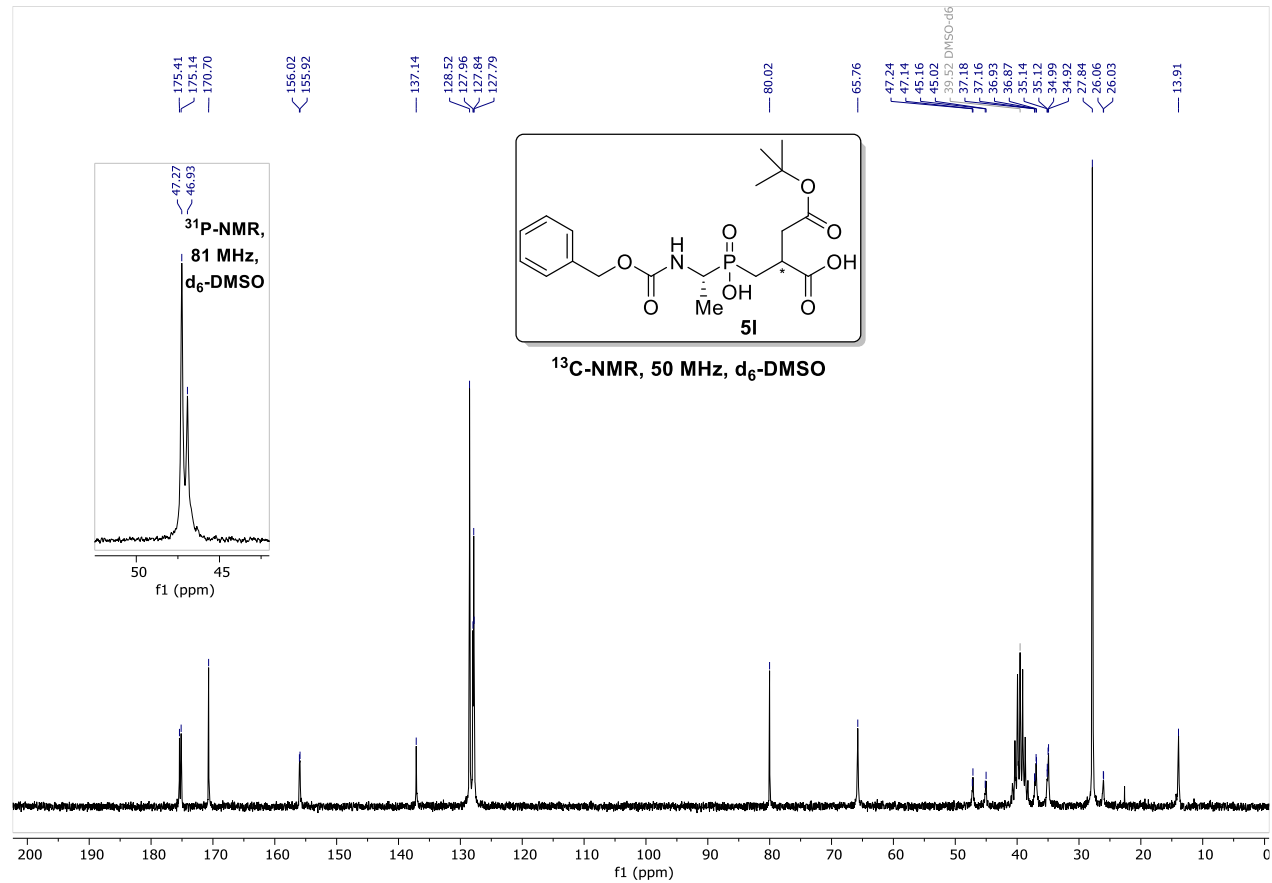
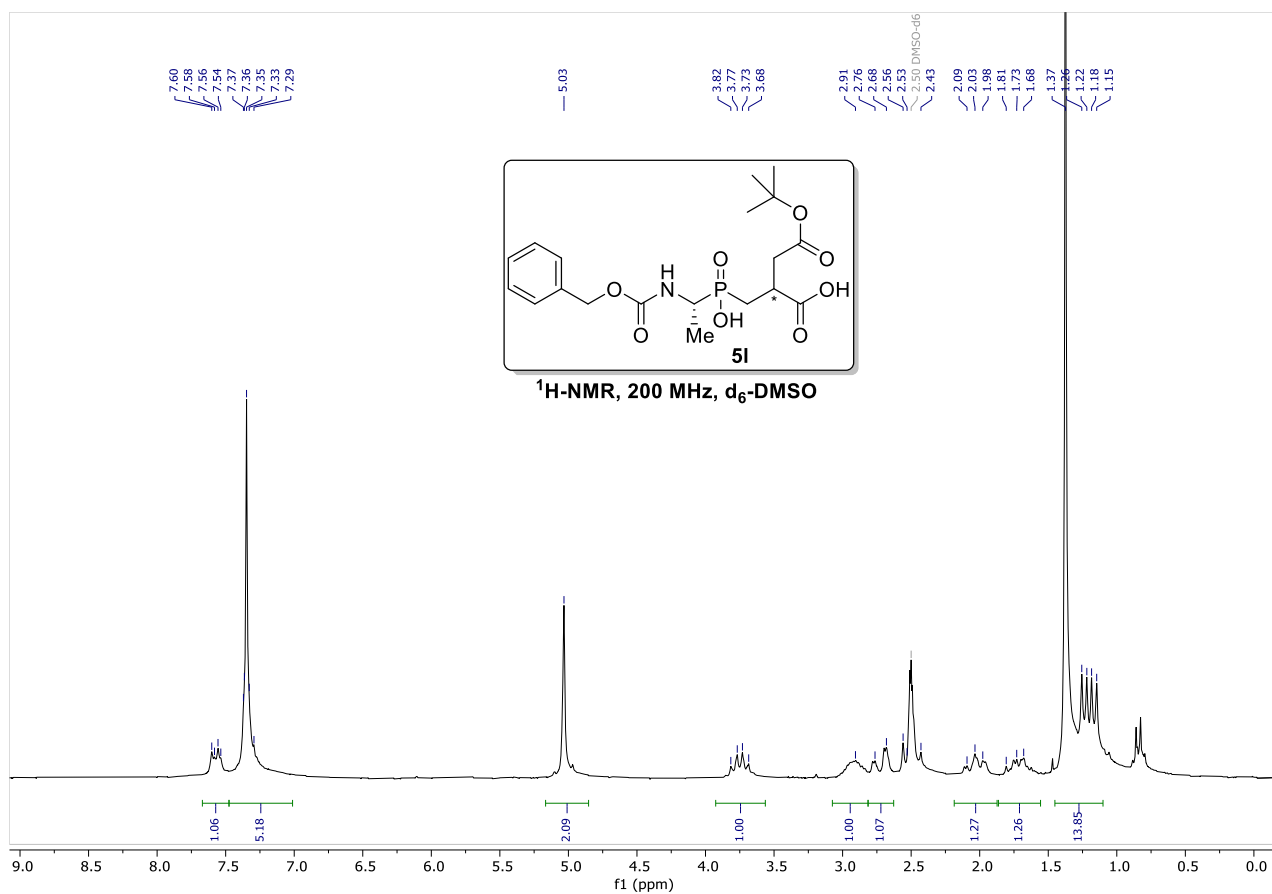


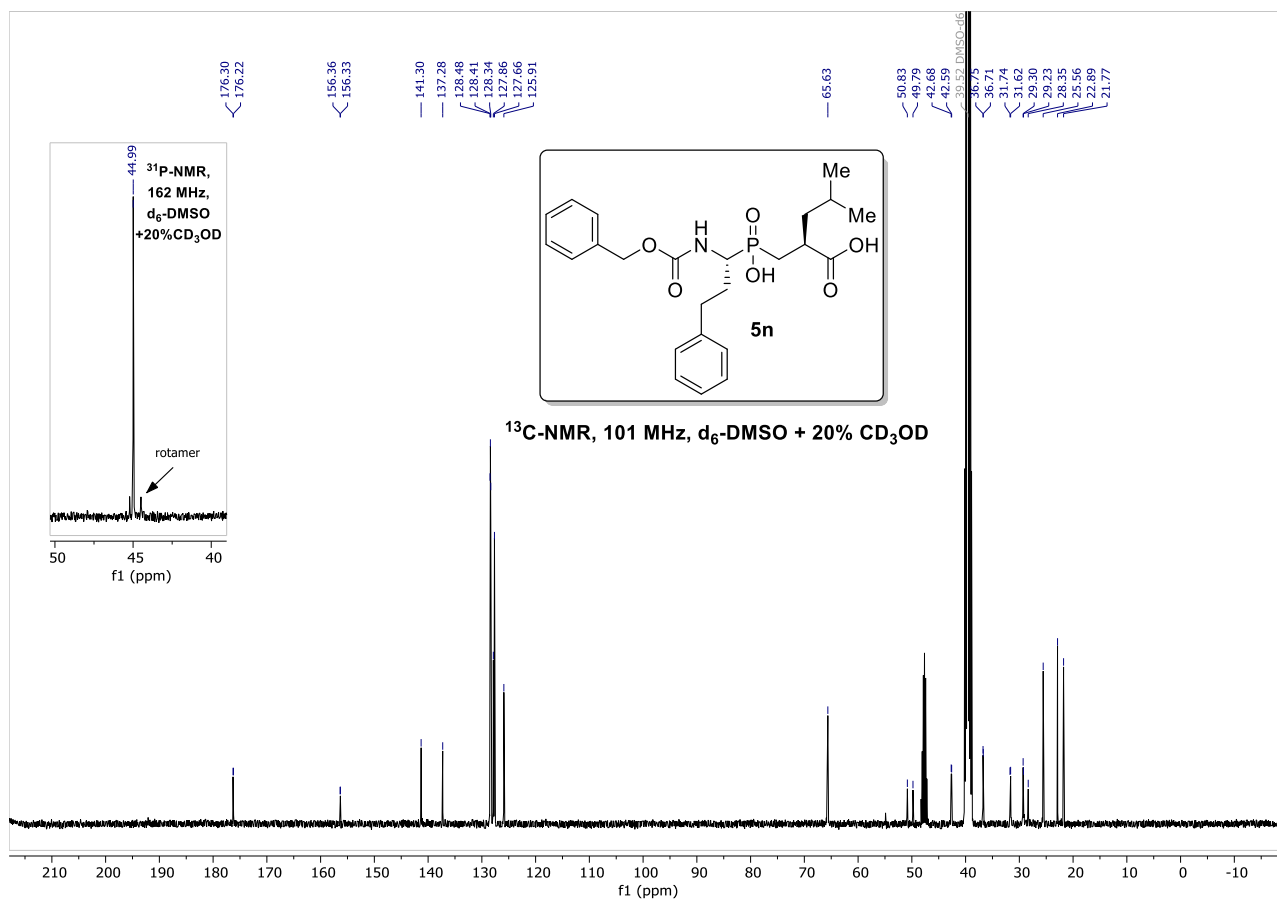
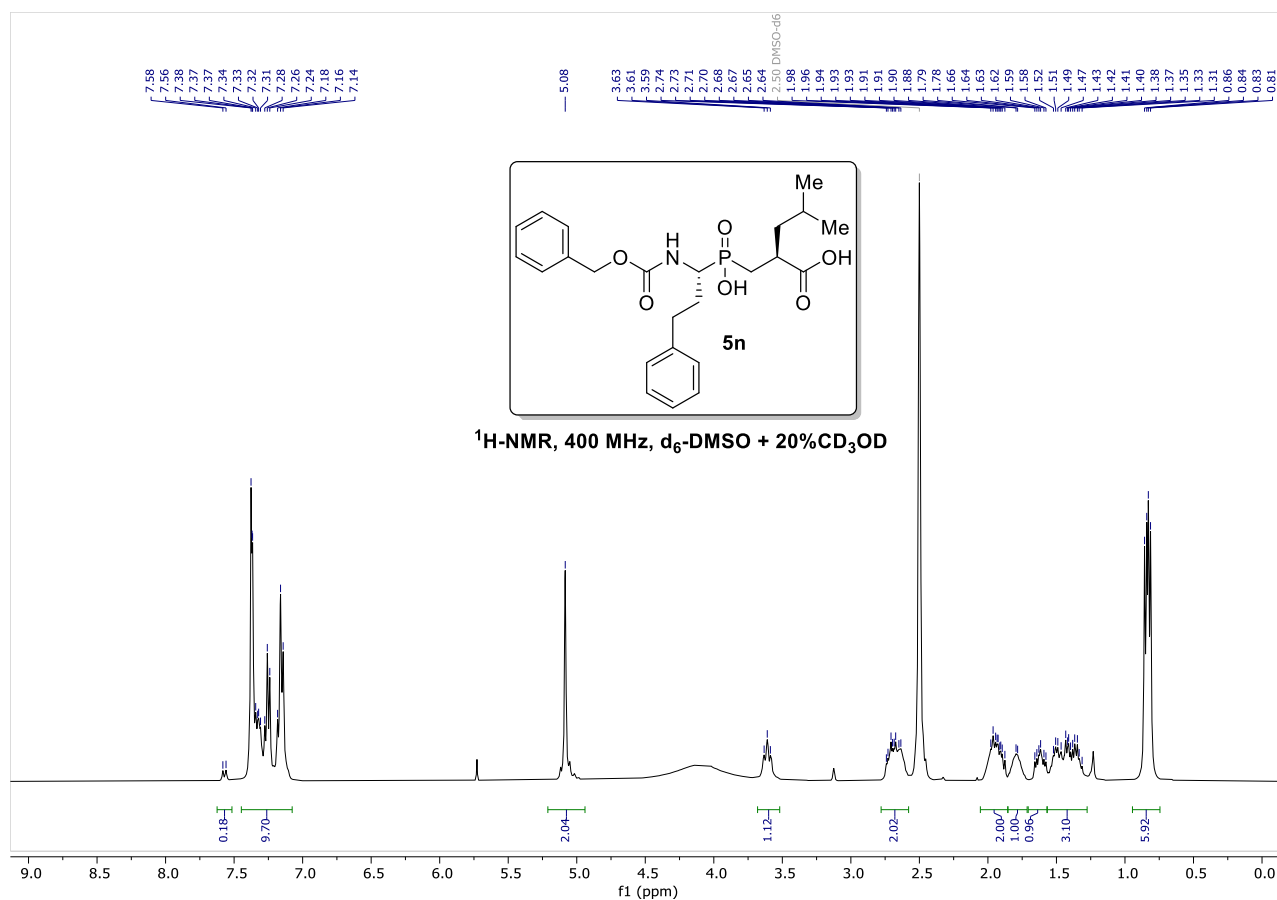


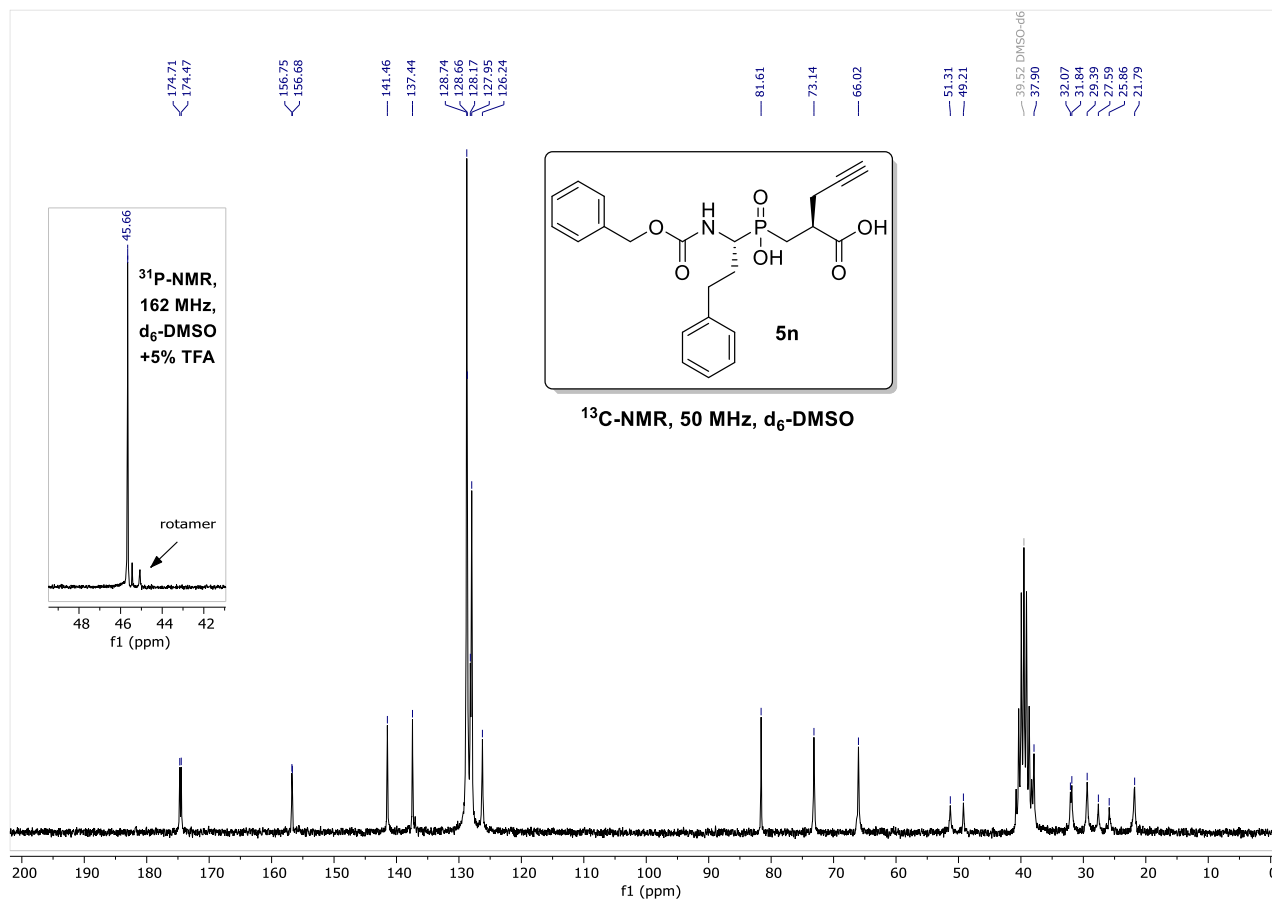
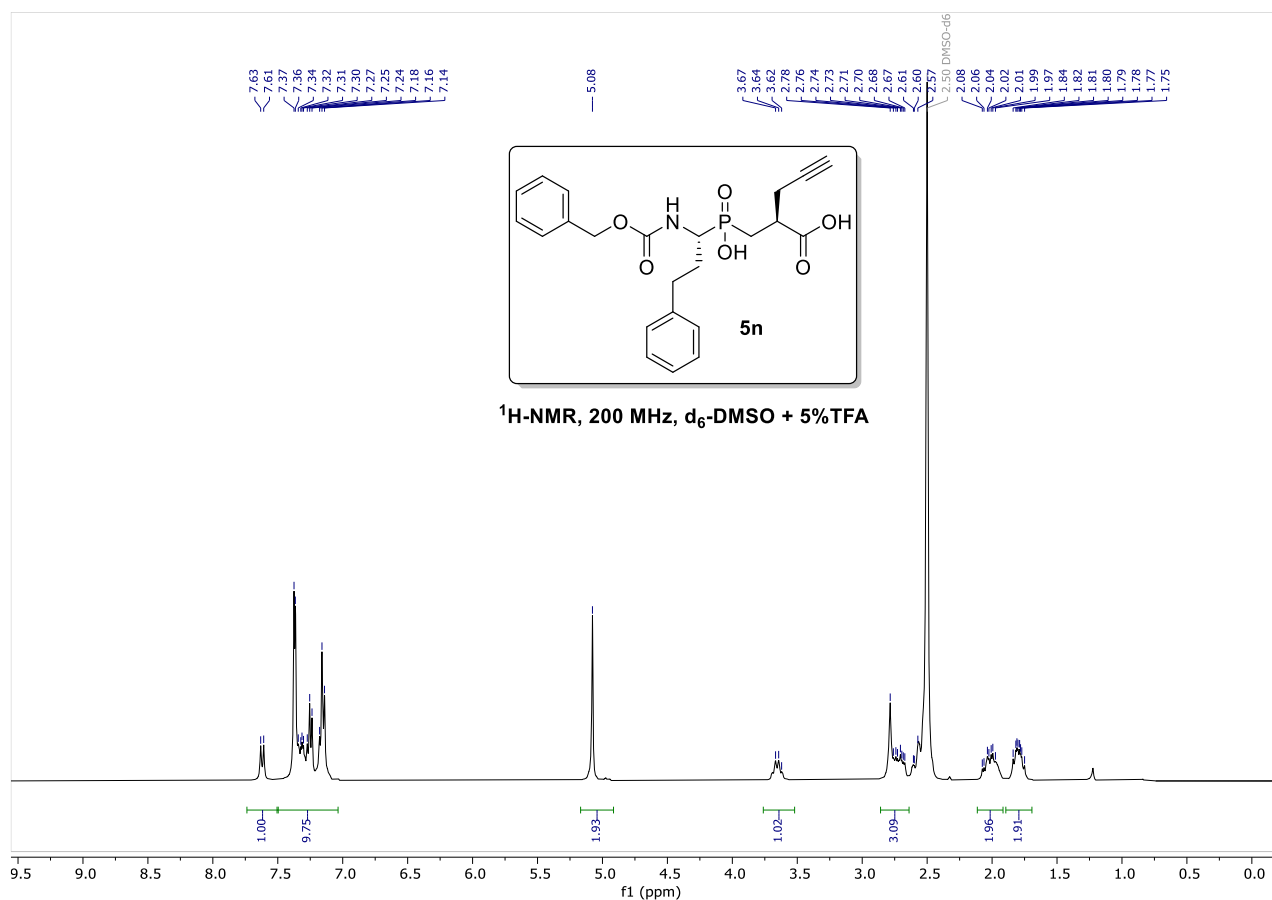


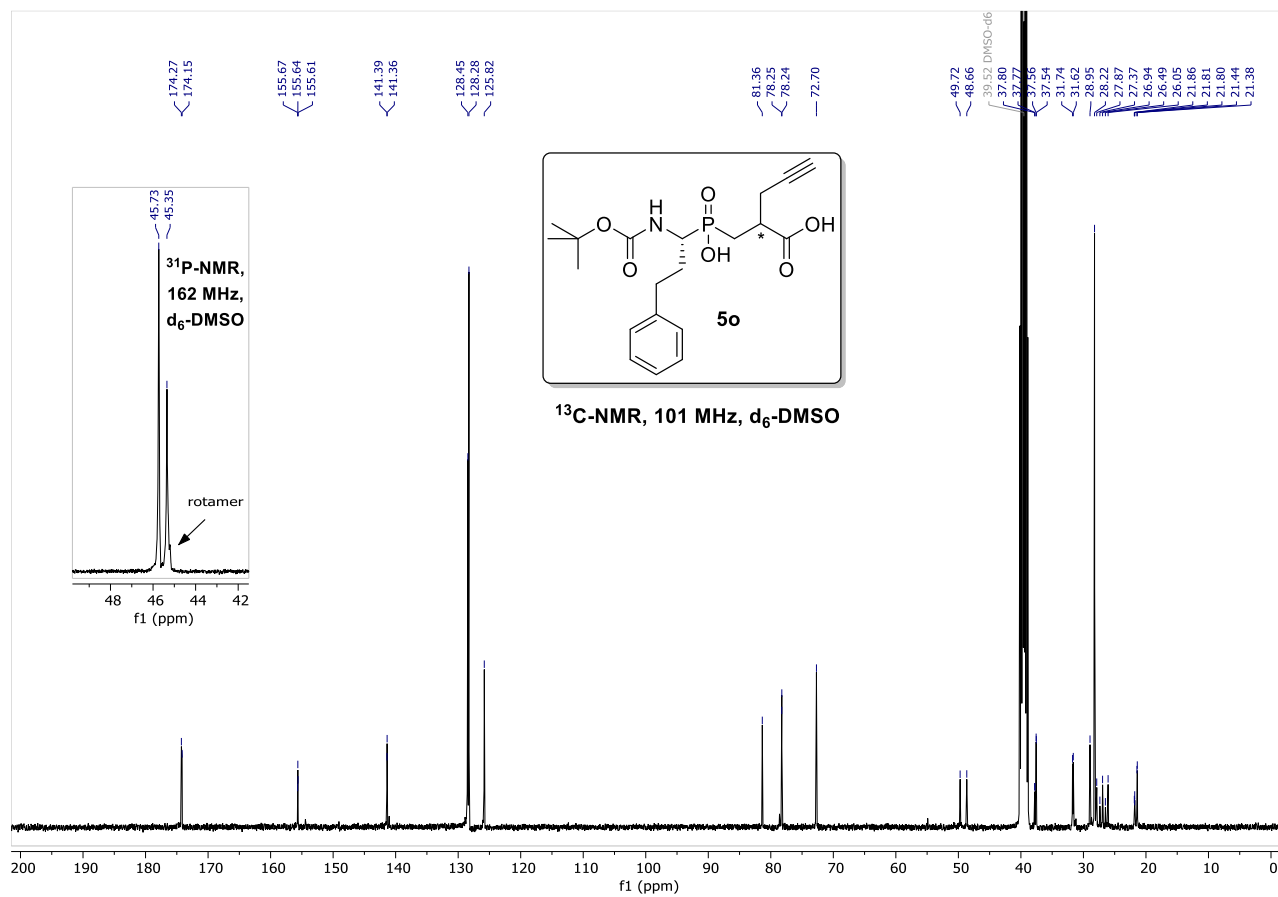
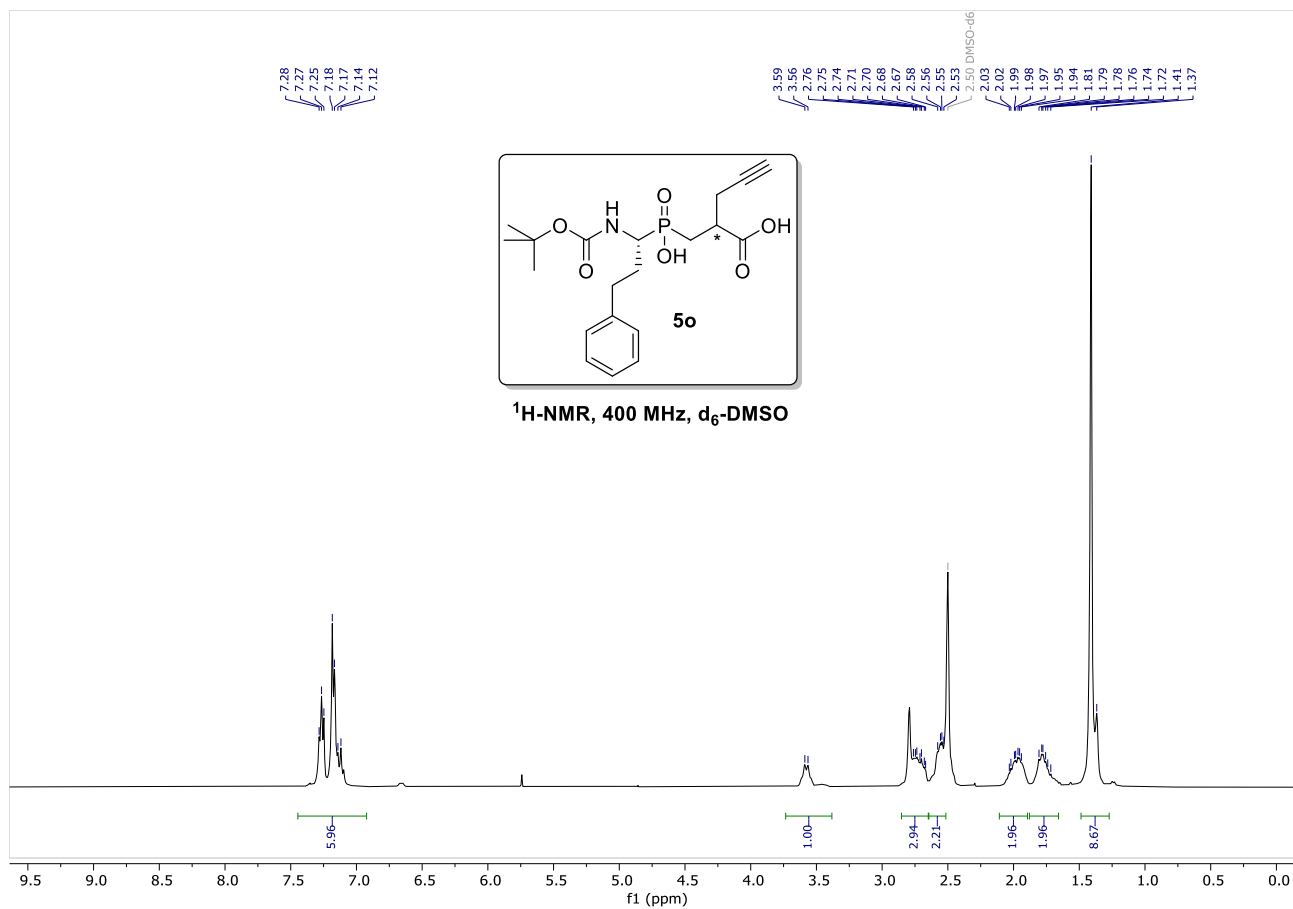


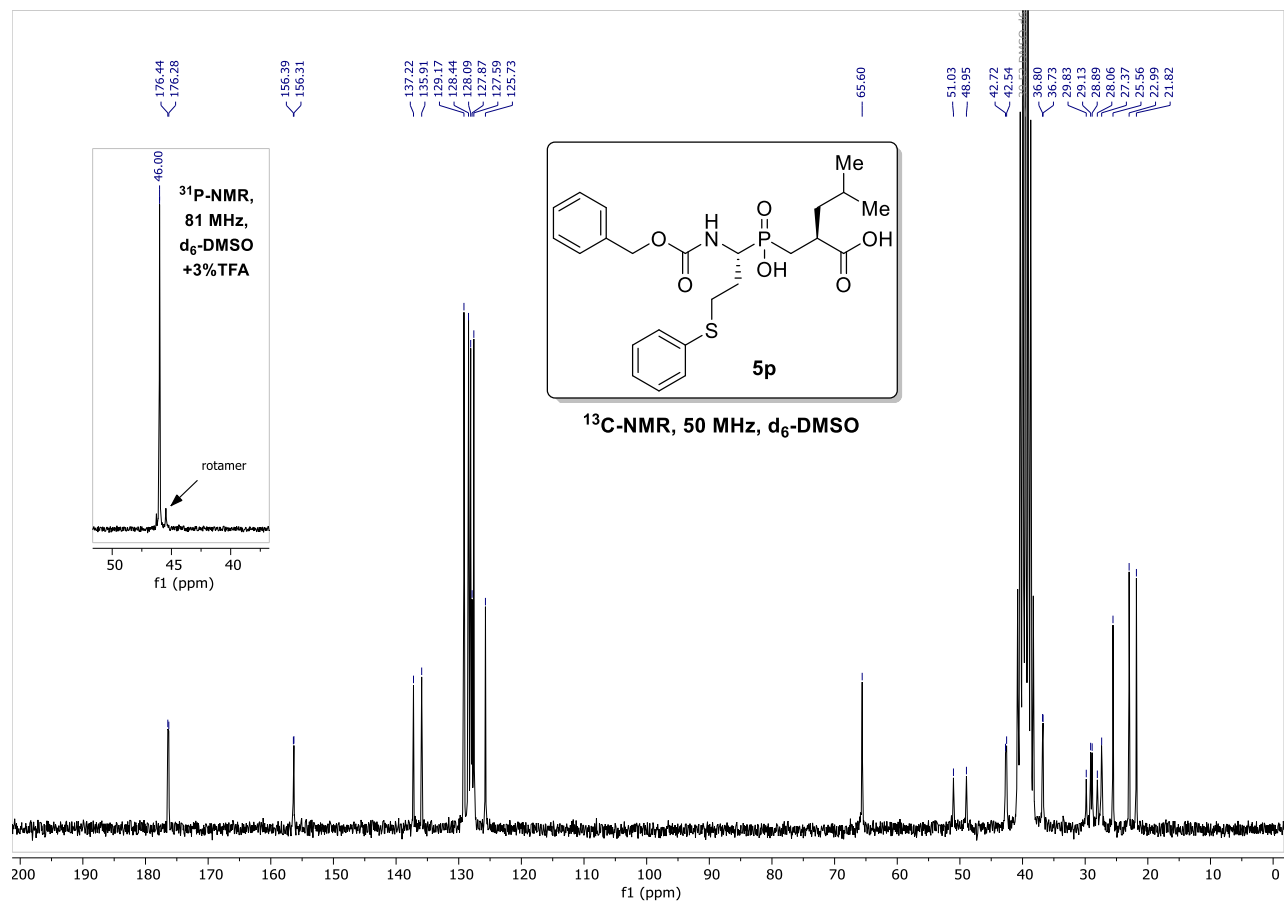
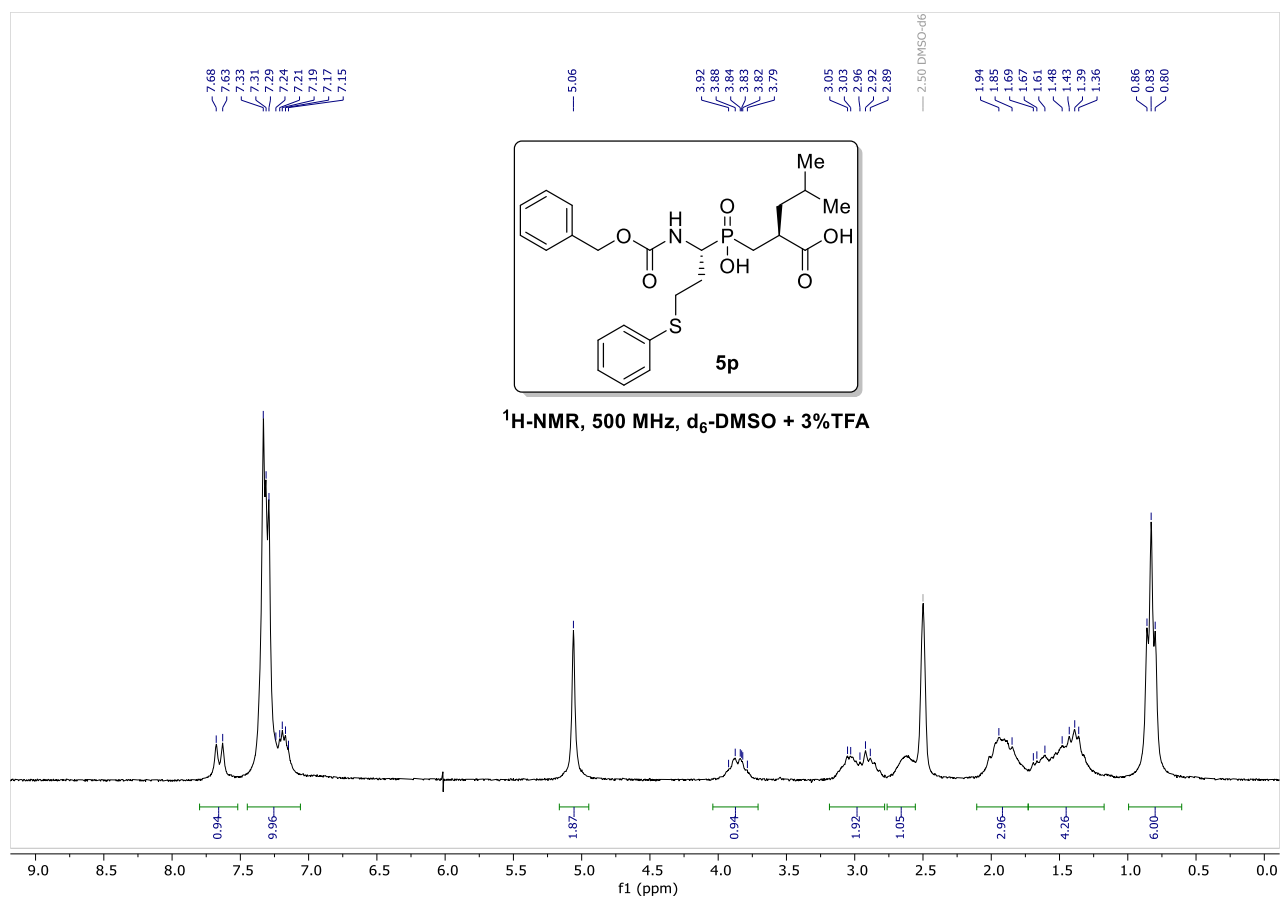


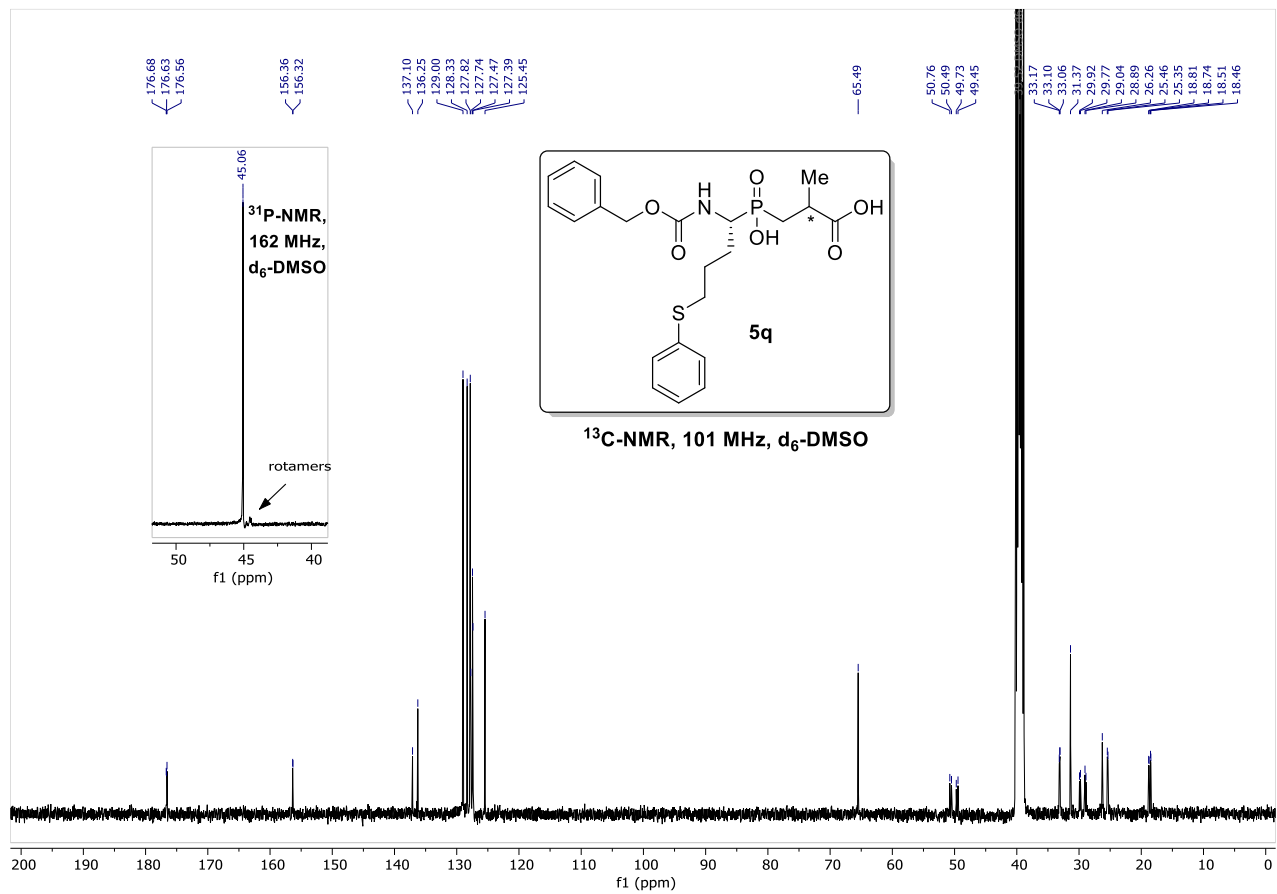
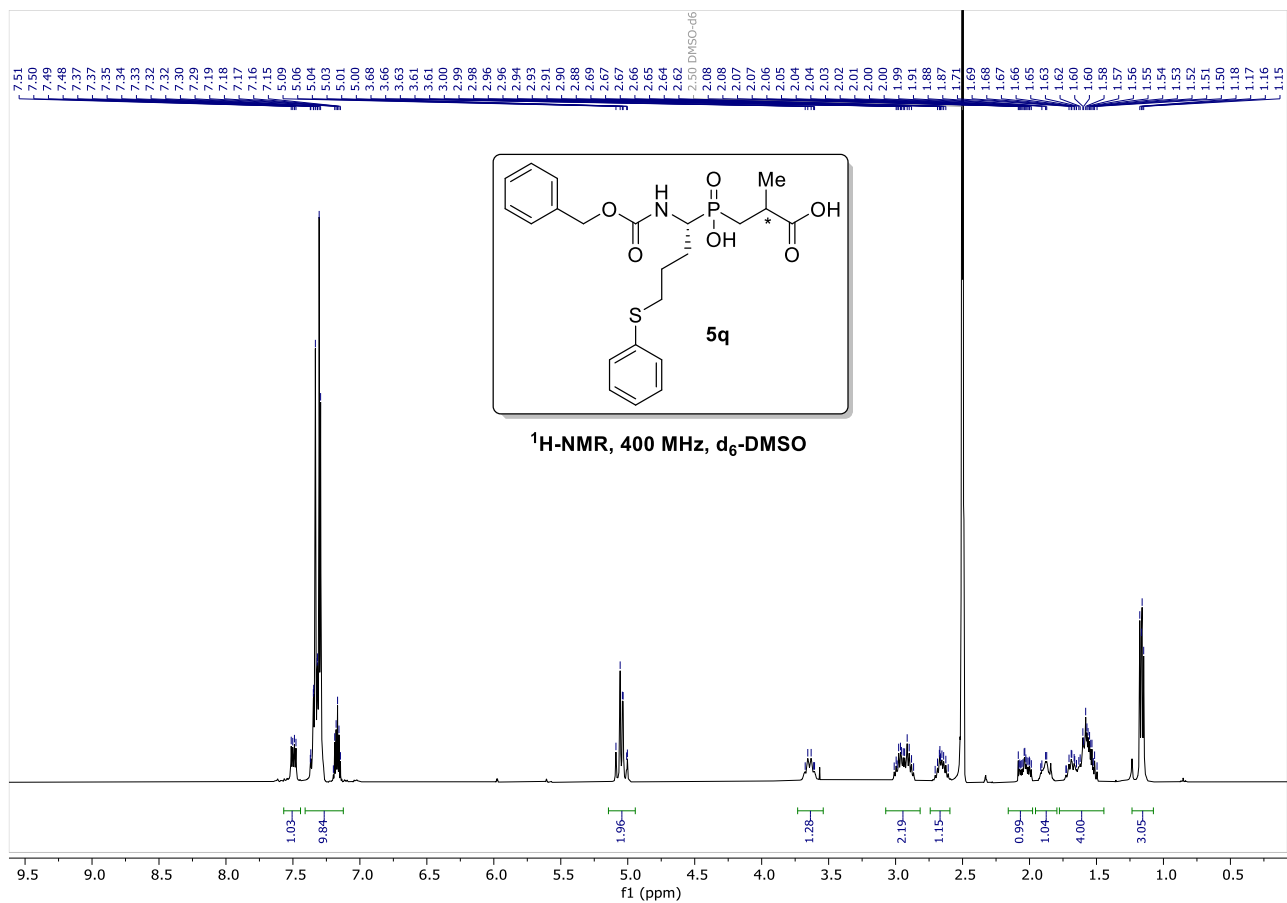












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