

Supporting Information

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Practical and General Palladium-Catalyzed Synthesis of Ketones from Internal Olefins**

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Supporting Information

General procedure:

All olefin oxidation reactions were carried out under aerobic conditions. Commercial reagents were obtained from Aldrich and used without further purification.

^1H and ^{13}C NMR spectra were recorded on a Varian 500 Mhz spectrometer and High resolution mass spectra were provided by the California Institute of Technology Mass Spectrometry Facility using JEOL JMS-600H High Resolution Mass Spectrometer.

Gas chromatography data was obtained using an Agilent 6850 FID gas chromatography system equipped with a HP-5 (5%-phenyl)-methylpolysiloxane capillary column (Agilent). Response factors were collected for 4-octanone, 3-octanone, 2-octanone, cyclohexanone, dodecene, 2-dodecanone and lauric aldehyde following literature procedures.¹

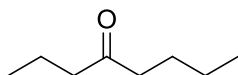
General Procedure 1 (Table 1): The corresponding palladium complex (0.01 mmol, 5 mol%) and benzoquinone (21.6 mg, 0.2 mmol, 1 equiv) were charged in a resealable 4-mL vial under air. The corresponding solvent mixture was then added, followed by the addition of aqueous HBF_4 . After the addition of *trans*-4-octene (22.4 mg, 0.2 mmol), the homogenous reaction mixture was stirred for 16 h at room temperature. The crude reaction mixture was then partitioned using a mixture of ether and water (10 mL each), tridecane was added as a standard, and an aliquot of the organic phase was submitted to GC-analysis to determine the yield of 4-octanone, 3-octanone, 2-octanone.

¹ Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740.

General Procedure 2 (Table 2 and Scheme 2): Palladium acetate (11.5 mg, 0.05 mmol, 5 mol%) and benzoquinone (108 mg, 1.00 mmol) were charged in a resealable 20-mL vial under air. A mixture of DMA (2.2 mL), MeCN (2.2 mL) and water (0.63 mL) was added, followed by the addition of aqueous HBF₄ (0.18 mL, 48% in water, 1.38 mmol). After the addition of the corresponding substrate (1.00 mmol), the homogenous reaction mixture was stirred for 16 h at room temperature. The crude reaction mixture was then diluted with brine (30 mL) and ether (30 mL), the phases were separated and the aqueous phase was further extracted (2x) with ether. The combined organic phases were then dried over Na₂SO₄, filtered, and evaporated in vacuo. In some cases, NMR-analysis of the crude mixture was performed to determine the regioselectivity of the process. The crude product was then further purified by column chromatography on silica gel using pentane/ether as eluent.

General Procedure 3 (Scheme 3): Palladium acetate (11.5 mg, 0.05 mmol, 5 mol%), benzoquinone (10.8 mg, 0.10 mmol, 10 mol%) and Fe(phtalocyanin) (28.4 mg, 0.05 mmol, 5 mol%) were charged in a resealable 20-mL vial under air. A mixture of DMA (2.2 mL), MeCN (2.2 mL) and water (0.63 mL) was added, followed by the addition of aqueous HBF₄ (0.18 mL, 48% in water, 1.38 mmol). The mixture was then purged during 2 min using an oxygen balloon, and after the addition of the corresponding substrate (1 mmol), the homogenous reaction mixture was stirred for 16 h at room temperature under an atmospheric pressure of oxygen (balloon). The crude reaction mixture was then diluted with brine (30 mL) and ether (30 mL), the phases were separated and the aqueous phase was further extracted (2x) with ether. The combined organic phases were then dried over Na₂SO₄, filtered, and evaporated in vacuo. In some cases, NMR-analysis of the crude mixture was performed to determine the regioselectivity of the process. The crude product was then further purified by column chromatography on silica gel using pentane/ether as eluent.

octan-4-one (Table 2, Entry 1)

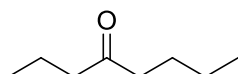


Was obtained as a clear oil (100 mg, 0.78 mmol, 78%) following the general procedure 2. The yield obtained by GC-analysis of the crude was 87%. The difference is attributed to the high volatility of the compound.

$^1\text{H NMR}$: δ 2.35 (q, $J = 7.0$ Hz, 4H), 1.62 – 1.47 (m, 4H), 1.33 – 1.22 (m, 2H), 0.87 (td, $J = 7.4, 3.3$ Hz, 6H). $^{13}\text{C NMR}$: δ 211.5, 44.7, 42.5, 25.9, 22.3, 17.3, 13.8, 13.7.

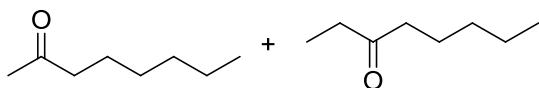
Spectral data were in accordance with a commercial sample.

octan-4-one (Table 2, Entry 2)



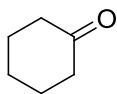
Cis-4-octene was reacted following the general procedure 2. The mixture of crude products was analyzed by GC using tridecane as a standard. Yields of products: 3% 2-octanone, 3% 3-octanone, 70% 4-octanone.

octan-2-one and octan-3-one (Table 2, Entry 3)



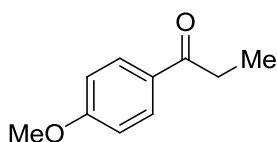
Trans-2-octene was reacted following the general procedure 2. The mixture of crude products was analyzed by GC using tridecane as a standard. Yields of products: 62% 2-octanone, 25% 3-octanone, 3% 4-octanone.

cyclohexanone (Table 2, Entry 4)



Cyclohexene was reacted following the general procedure 2. The mixture of crude products was analyzed by GC using tridecane as a standard. 75% yield was obtained. Around 9% cyclohexenone was observed by NMR spectroscopy using mesitylene as an internal standard.

1-(4-methoxyphenyl)propan-1-one (Table 2, Entry 5)

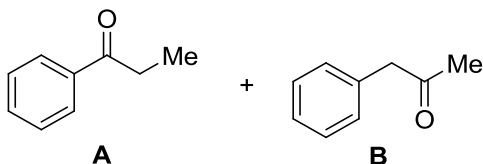


Was obtained as a solid (137 mg, 0.84 mmol, 84%) following the general procedure 2.

^1H NMR: δ 7.92 (d, $J = 9.0$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 3.83 (s, 3H), 2.92 (q, $J = 7.3$ Hz, 2H), 1.18 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR: δ 199.4, 163.3, 130.2, 130.0, 113.6, 55.4, 31.4, 8.4.

Values were in accordance with a commercial sample.

Propiophenone and phenyl acetone (Table 2, Entry 6)



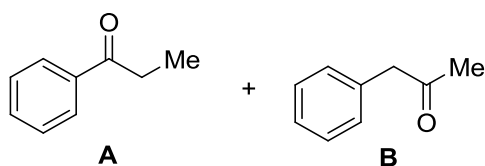
Were obtained from *trans*- β -methyl styrene following a modified general procedure 2 using MeCN/H₂O (4.4 mL/0.63 mL) as the solvent. Crude ratio by NMR was 1:1. The products could be separated by column chromatography, giving two clear oils (A: 62 mg, 0.46 mmol, 46% and B: 60 mg, 0.45 mmol, 45%).

A: ¹H NMR: 7.98 – 7.94 (m, 2H), 7.57 – 7.52 (m, 1H), 7.48 – 7.43 (m, 2H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ¹³C NMR: δ 200.8, 136.9, 132.9, 128.5, 128.0, 31.8, 8.2.

B: ¹H NMR: δ 7.36 – 7.32 (m, 2H), 7.30 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 3.70 (s, 2H), 2.15 (s, 3H). ¹³C NMR: δ 206.3, 134.2, 129.4, 128.8, 127.1, 51.0, 29.3.

Values were in accordance with a commercial sample.

Propiophenone and phenyl acetone (Table 2, Entry 7)



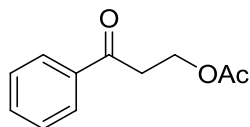
Were obtained from *cis*- β -methyl styrene following a modified general procedure 2 using MeCN/H₂O (4.4 mL/0.63 mL) as the solvent. Crude ratio by NMR was 1.4:1 (A:B). The products could be separated by column chromatography, giving two clear oils (A: 75 mg, 0.56 mmol, 56% and B: 47 mg, 0.35 mmol, 35%).

A: ¹H NMR: 7.98 – 7.94 (m, 2H), 7.57 – 7.52 (m, 1H), 7.48 – 7.43 (m, 2H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ¹³C NMR: δ 200.8, 136.9, 132.9, 128.5, 128.0, 31.8, 8.2.

B: ¹H NMR: δ 7.36 – 7.32 (m, 2H), 7.30 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 3.70 (s, 2H), 2.15 (s, 3H). ¹³C NMR: δ 206.3, 134.2, 129.4, 128.8, 127.1, 51.0, 29.3.

Values were in accordance with a commercial sample.

3-oxo-3-phenylpropyl acetate (Table 2, Entry 8)

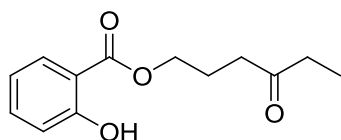


Was obtained as a clear oil (153 mg, 0.80 mmol, 80%) following a modified general procedure 2 using MeCN/H₂O (4.4 mL/0.63 mL) as the solvent and 10 mol% palladium acetate.

¹H NMR: δ 7.97 – 7.93 (m, 2H), 7.60 – 7.55 (m, 1H), 7.49 – 7.44 (m, 2H), 4.51 (t, *J* = 6.4 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.02 (s, 3H). ¹³C NMR: δ 197.0, 171.0, 136.5, 133.4, 128.7, 128.0, 59.6, 37.3, 20.9.

Values are in accordance with literature.²

4-oxohexyl 2-hydroxybenzoate (Table 2, Entry 9)

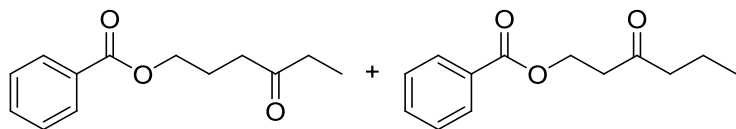


Was obtained as an oil (176 mg, 0.75 mmol, 75%) following the general procedure 2. Crude NMR analysis showed the formation of a 4:1 mixture of regioisomers. Only the major product was isolated by column chromatography.

¹H NMR: δ 10.77 (s, 1H), 7.80 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.45 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 6.97 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.87 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 4.35 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.45 (q, *J* = 7.3 Hz, 2H), 2.13 – 2.01 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H). ¹³C NMR: δ 210.1, 170.1, 161.7, 135.7, 129.8, 119.1, 117.6, 112.4, 64.6, 38.3, 36.1, 22.7, 7.8. HRMS (EI): calcd (M⁺): 236.2049; measured: 236.2046.

² *Org. Lett* **2012**, *14*, 2414.

4-oxohexyl benzoate (Table 2, Entry 10)

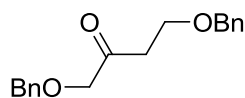


Was obtained as a clear oil (200 mg, 0.91 mmol, 91%, 4:1 mixture) following the general procedure 2.

$^1\text{H NMR}$: δ 8.04 – 7.95 (m, 2H), 7.57 – 7.50 (m, 1H), 7.46 – 7.38 (m, 2H), 4.58 (t, $J = 6.4$ Hz, 2H, minor), 4.31 (t, $J = 6.4$ Hz, 2H), 2.86 (t, $J = 6.4$ Hz, 2H, minor), 2.56 (t, $J = 7.2$ Hz, 2H), 2.44 (q, $J = 7.3$ Hz, 2H), 2.12 – 1.97 (m, 2H), 1.70 – 1.51 (m, 2H, minor), 1.04 (t, $J = 7.3$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H, minor). $^{13}\text{C NMR}$: δ 210.3, 207.9 (minor), 166.5, 166.4 (minor), 133.0 (minor), 132.9, 130.2 (minor), 129.5 (minor), 129.5, 128.3, 128.3 (minor), 64.2, 60.0 (minor), 45.1 (minor), 41.4 (minor), 38.6, 36.0, 22.9, 17.1 (minor), 13.7 (minor), 7.8.

Values are in accordance with literature.³

1,4-bis(benzyloxy)butan-2-one (Table 2, Entry 11)



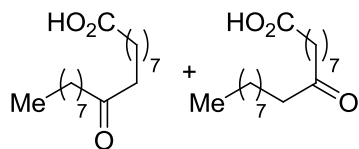
Was obtained as a clear oil (150 mg, 0.53 mmol, 53%) following a modified general procedure 2 using 10 mol% palladium acetate.

$^1\text{H NMR}$: δ 7.38 – 7.28 (m, 10H), 4.59 (s, 2H), 4.50 (s, 2H), 4.11 (s, 2H), 3.77 (t, $J = 6.2$ Hz, 2H), 2.75 (t, $J = 6.2$ Hz, 2H). $^{13}\text{C NMR}$: δ 207.0, 138.0, 137.2, 128.5, 128.4, 128.0, 127.9, 127.7, 127.7, 75.4, 73.3, 73.3, 65.0, 39.4.

³ *Org Lett* **2011**, *13*, 4308.

Values are in accordance with literature.⁴

10-oxooctadecanoic acid and 9-oxooctadecanoic acid (Table 2, Entry 12)

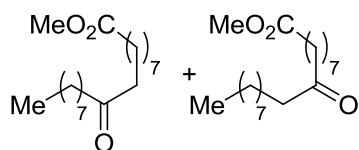


Were obtained as white solids (245 mg, 0.82 mmol, 82%, 1:1) following the general procedure 2.

¹H NMR: δ 2.37 – 2.33 (m, 6H), 1.66 – 1.49 (m, 6H), 1.35 – 1.20 (m, 18H), 0.86 (t, J = 7.0 Hz, 3H). ¹³C NMR: δ 211.8, 211.8, 180.0, 178.0, 42.8, 42.8, 42.7, 42.7, 34.0, 34.0, 31.9, 31.8, 29.4, 29.4, 29.4, 29.3, 29.2, 29.2, 29.1, 29.0, 29.0, 29.0, 28.8, 24.6, 24.6, 23.9, 23.8, 23.7, 22.7, 22.6, 14.1, 14.1. HRMS (EI): calcd C₁₈H₃₄O₃ (M⁺): 298.2508; measured: 298.2499.

Values are in accordance with literature.⁵

methyl 10-oxooctadecanoate and methyl 9-oxooctadecanoate (Table 2, Entry 13)



Were obtained as white solids (261 mg, 0.84 mmol, 84%, 1:1) following the general procedure 2.

¹H NMR: δ 3.65 (s, 3H), 2.36 (t, J = 7.5 Hz, 4H), 2.28 (t, J = 7.5 Hz, 2H), 1.60 – 1.50 (m, J = 28.6, 7.5 Hz, 6H), 1.33 – 1.19 (m, 18H), 0.86 (t, J = 7.0 Hz, 3H). ¹³C NMR: δ 211.6, 211.6, 174.2, 174.2, 51.4, 51.4, 42.8, 42.8, 42.7, 42.7, 34.0, 34.0, 31.8, 31.8, 29.4, 29.4, 29.4, 29.3,

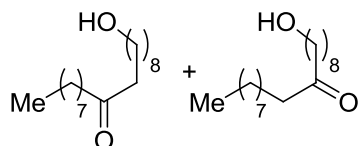
⁴ *Bull. Chem. Soc. Jap.* **1981**, *54*, 3100.

⁵ *Biosci. Biotechnol. Biochem* **2007**, *71*, 1120. *Phytochemistry* **1990**, *29*, 2323.

29.2, 29.2, 29.1, 29.0, 29.0, 28.9, 24.9, 24.8, 23.9, 23.8, 23.7, 14.1, 14.1. HRMS (EI): calcd C₁₈H₃₆O₃ (M⁺): 312.2664; measured: 312.2674.

Values are in accordance with literature.⁶

18-hydroxyoctadecan-9-one and 1-hydroxyoctadecan-9-one (Table 2, Entry 14)

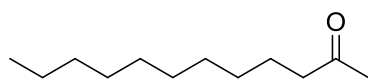


Were obtained as white solids (215 mg, 0.76 mmol, 76%, 1:1) following the general procedure 2.

¹H NMR: δ 3.62 (t, *J* = 6.6 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 4H), 1.60 – 1.40 (m, 7H), 1.36 – 1.18 (m, 20H), 0.86 (t, *J* = 7.0 Hz, 3H). ¹³C NMR: δ 211.8, 211.7, 63.0, 62.9, 42.8, 42.8, 42.8, 42.7, 32.7, 32.7, 31.8, 31.8, 29.4, 29.4, 29.4, 29.4, 29.3, 29.3, 29.3, 29.2, 29.2, 29.1, 29.1, 25.7, 25.6, 23.9, 23.8, 23.8, 22.6, 22.6, 14.1, 14.1. HRMS (EI): calcd C₁₈H₃₆O₂ (M⁺): 284.2715; measured: 284.2721.

Values are in accordance with literature.⁷

dodecan-2-one (Table 2, Entry 15)



Was obtained as a clear oil (158 mg, 0.86 mmol, 86%) following the general procedure 2. GC-analysis of the crude sample showed 97.5% selectivity for ketone formation (2.5% for the aldehyde).

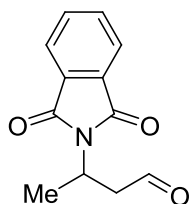
⁶ *Biosci. Biotechnol. Biochem* **2007**, *71*, 1120. *Phytochemistry* **1996**, *42*, 889.

⁷ *Tetrahedron* **1995**, *51*, 11863.

^1H NMR: δ 2.39 (t, $J = 7.5$ Hz, 2H), 2.11 (s, 3H), 1.54 (p, $J = 7.3$ Hz, 2H), 1.30 – 1.15 (m, 14H), 0.86 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR: δ 209.3, 43.8, 31.9, 29.8, 29.5, 29.4, 29.4, 29.3, 29.2, 23.8, 22.6, 14.1.

Values were in accordance with a commercial sample

3-(1,3-dioxoisindolin-2-yl)butanal (Table 2, Entry 16)

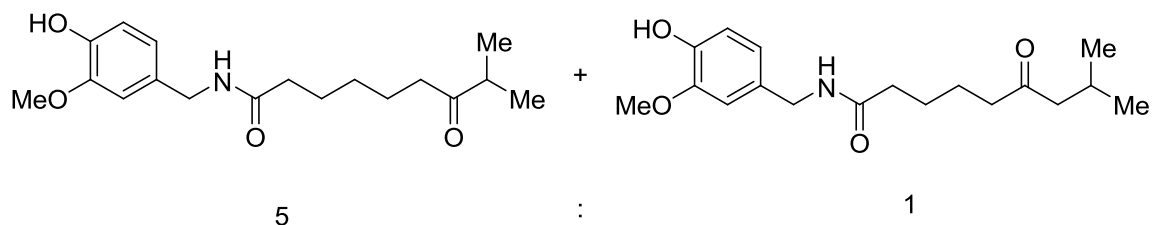


Was obtained as a white solid (188 mg, 0.87 mmol, 87%) following the general procedure 2.

^1H NMR: δ 9.74 (s, 1H), 7.80 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.70 (dd, $J = 5.5, 3.0$ Hz, 2H), 4.94 – 4.86 (m, 1H), 3.29 (ddd, $J = 18.0, 8.2, 1.4$ Hz, 1H), 3.00 (ddd, $J = 18.0, 6.2, 1.1$ Hz, 1H), 1.49 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR: δ 199.3, 168.1, 134.0, 131.8, 123.2, 47.3, 41.4, 18.8.

Values are in accordance with literature.⁸

N-(4-hydroxy-3-methoxybenzyl)-8-methyl-7-oxononanamide and N-(4-hydroxy-3-methoxybenzyl)-8-methyl-6-oxononanamide (Scheme 2)

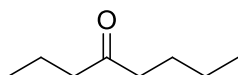


⁸ *J. Am. Chem. Soc.* **2009**, *131*, 9473.

Was obtained as a clear oil (128 mg, 0.40 mmol, 80%, 5:1) from a mixture of capsaicin and dehydrocapsaicin (TCI, 60% capsaicin) following a modified general procedure 2 on a 0.5 mmol substrate and using 10 mol% palladium acetate.

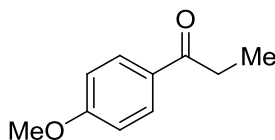
$^1\text{H NMR}$: δ 6.83 (d, $J = 8.0$ Hz, 1H), 6.78 (d, $J = 2.0$ Hz, 1H), 6.73 (dd, $J = 8.0, 1.9$ Hz, 1H), 5.96 – 5.89 (m, 2H), 4.31 (d, $J = 5.7$ Hz, 2H), 3.84 (s, 3H), 2.55 (hept, $J = 6.9$ Hz, 1H), 2.41 (t, $J = 7.3$ Hz, 2H), 2.24 (d, $J = 7.0$ Hz, 2H, minor), 2.18 (t, $J = 7.3$ Hz, 2H), 2.09 (m, 2H, minor), 1.67-1.58 (m, 2H), 1.57-1.50 (m, 2H), 1.33 – 1.24 (m, 2H), 1.05 (d, $J = 6.9$ Hz, 6H), 0.88 (d, $J = 6.6$ Hz, 6H, minor). $^{13}\text{C NMR}$: δ 215.0, 210.9 (minor), 172.8, 172.5 (minor), 146.7, 145.1, 130.3, 130.2 (minor), 120.7, 114.4, 110.7, 55.9, 51.8 (minor), 43.5, 42.8 (minor), 40.8, 39.9, 36.4, 36.4 (minor), 28.7, 25.5, 25.1 (minor), 24.6 (minor), 23.2, 23.0 (minor), 22.5 (minor), 18.2. HRMS (EI): calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_4$ (M⁺): 321.1940; found: 321.1951.

octan-4-one (Scheme 3)



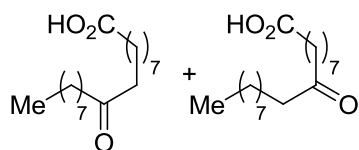
Was obtained following the general procedure 3. A yield of 83% was obtained by GC-analysis of the crude.

1-(4-methoxyphenyl)propan-1-one (Scheme 3)



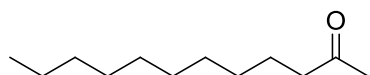
Was obtained as a solid (1.59 g, 9.7 mmol, 72%) on a 2 g-scale following general procedure 3. In that case a washing of the ethereal phase with aq. LiCl was necessary to remove DMA prior to chromatography.

10-oxooctadecanoic acid and 9-oxooctadecanoic acid (Scheme 3)



Were obtained as white solids (235 mg, 0.79 mmol, 79%, 1:1) following the general procedure 3.

dodecan-2-one (Scheme 3)

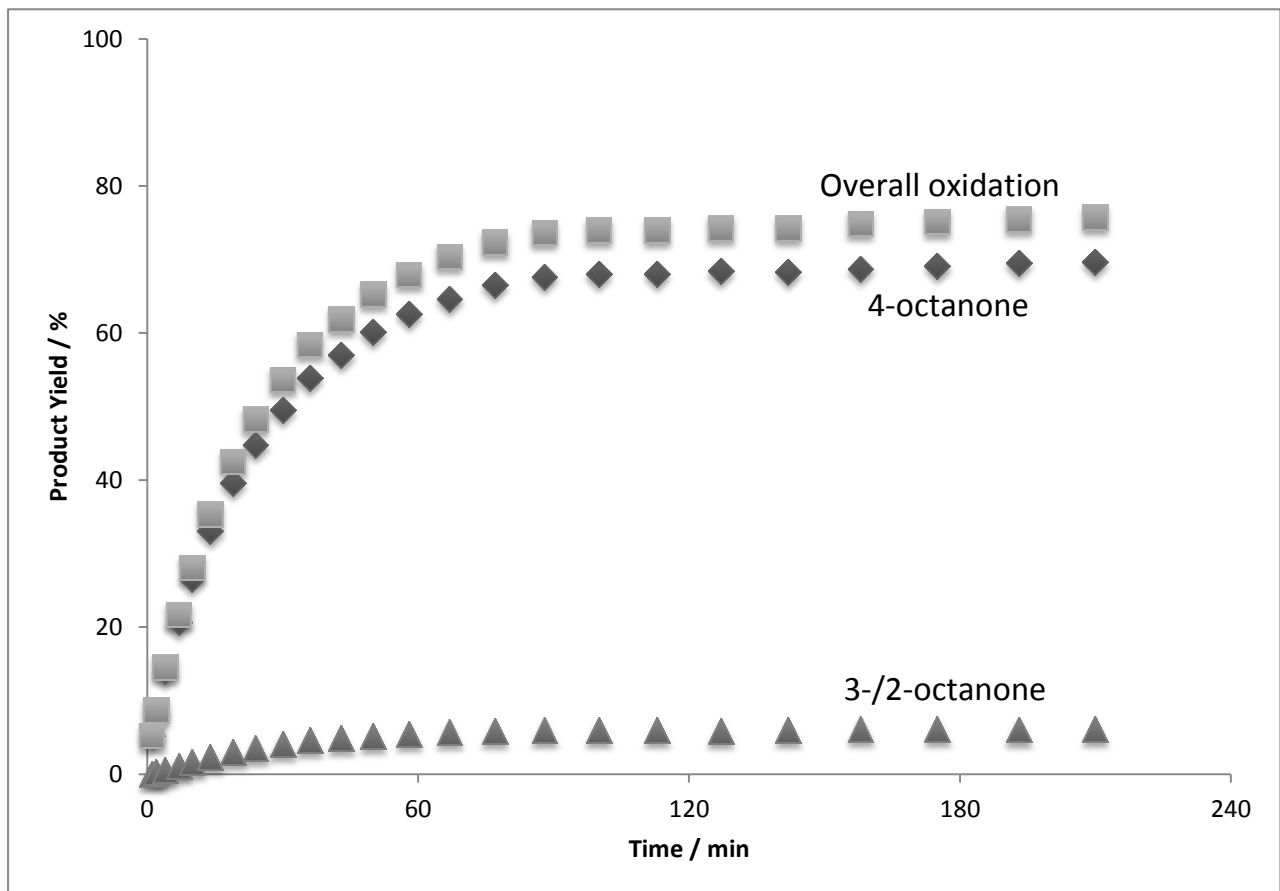
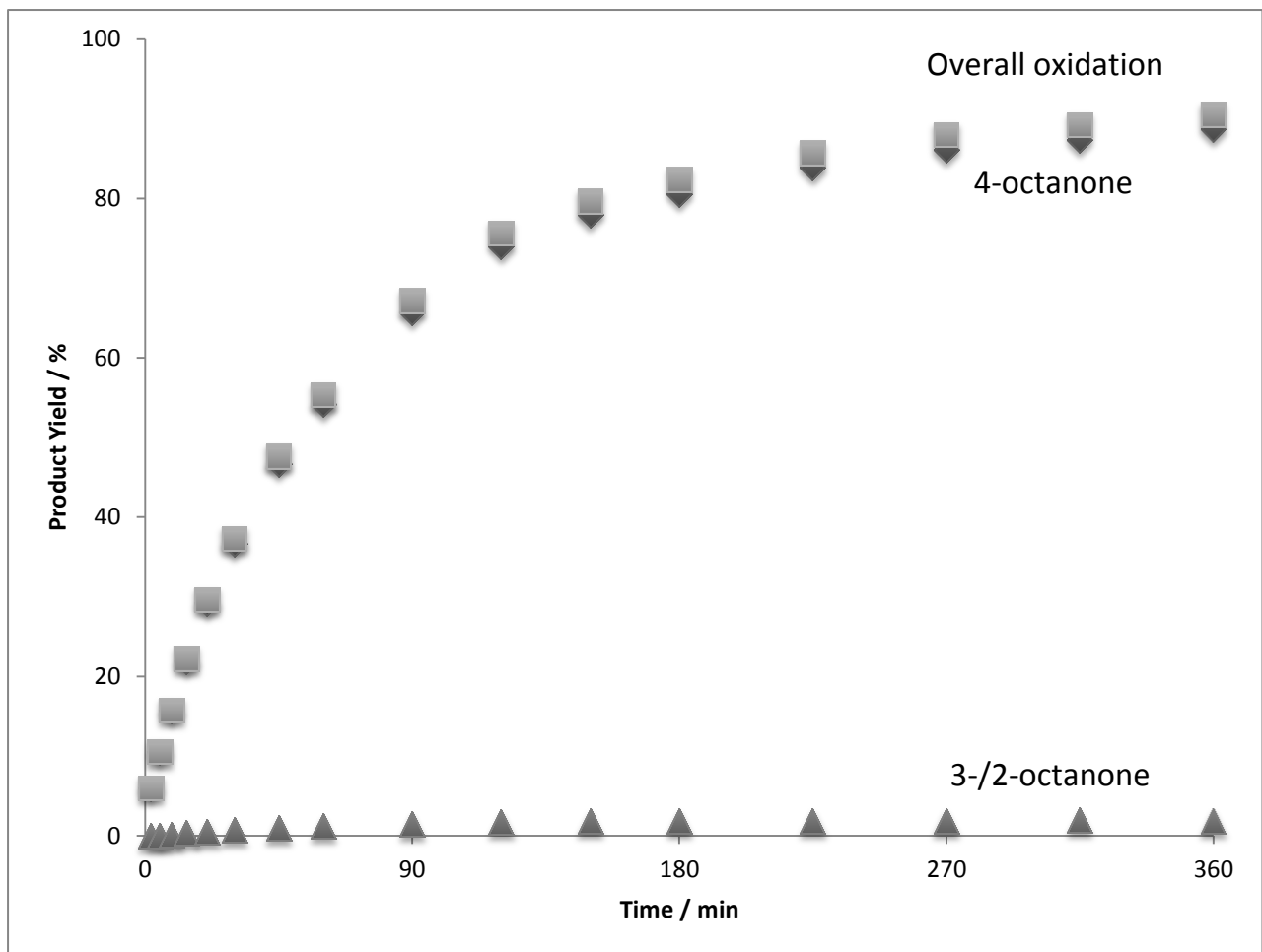


Was obtained as a clear oil (140 mg, 0.76 mmol, 76%) following the general procedure 3.

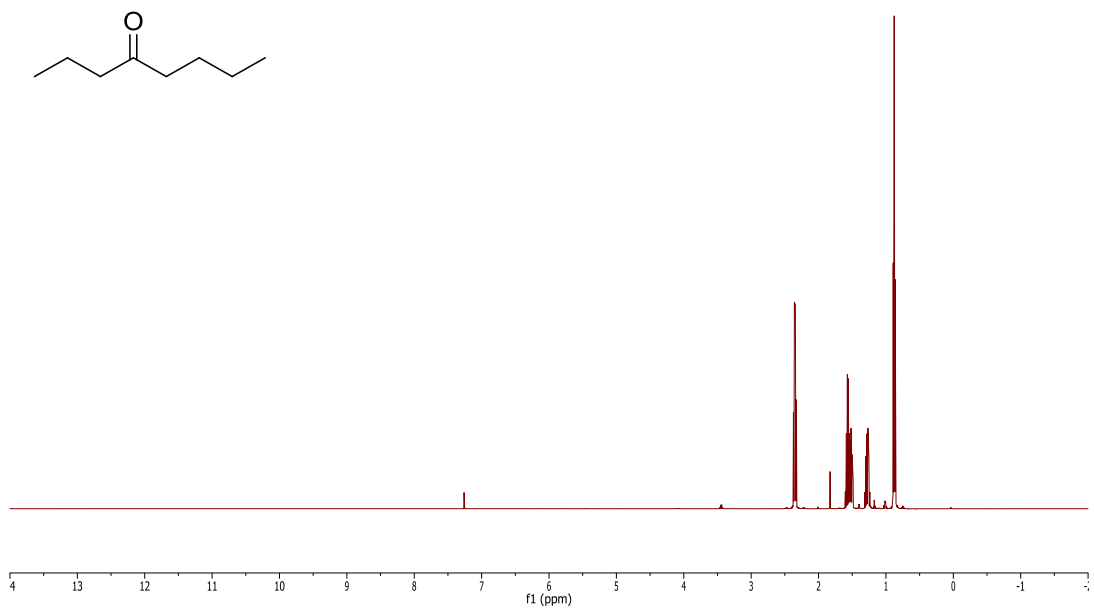
Reaction profile (Figure 1)

Each profile was generated in triplicate and the values were averaged and graphed using Microsoft Excel to produce the final curves.

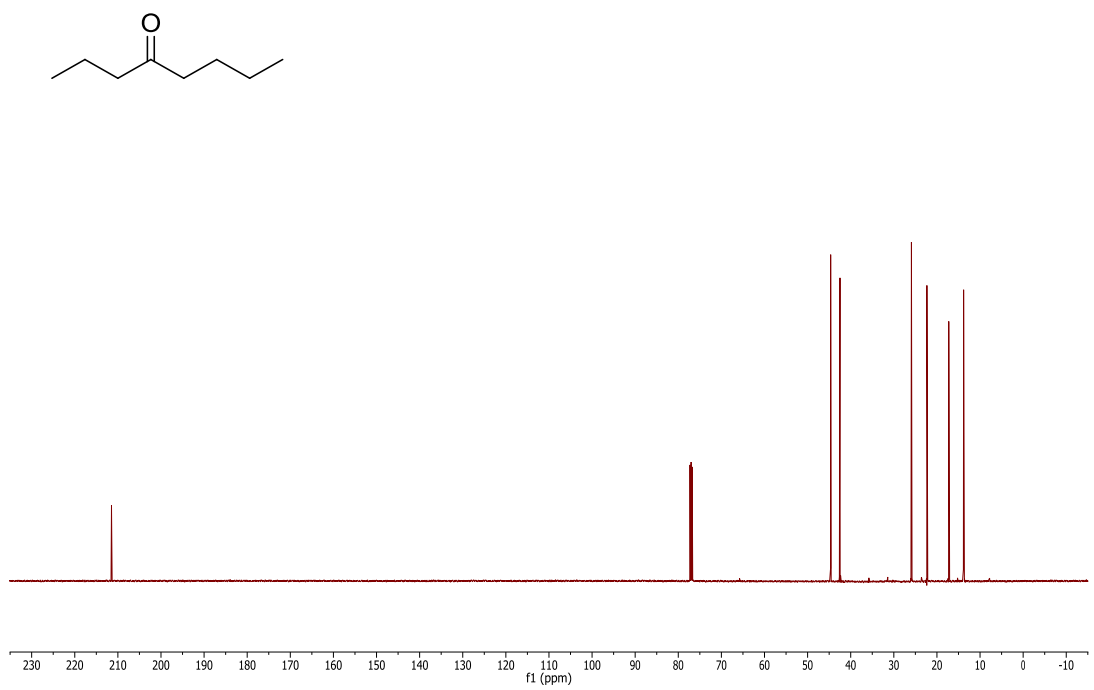
Palladium acetate (11.5 mg, 0.05 mmol, 5 mol%) and benzoquinone (108 mg, 1.00 mmol) were charged into 8-mL vials with permeable septum caps under air. 5.4 mL of a stock solution consisting of all of the liquid components was added (stock solution: 9 mL MeCN, 9 mL DMA, 2 mL H₂O, 0.72 mL HBF₄ (48% in water), 250 μL PhNO₂ (to be used as an internal standard) and 628 μL of either *trans*-4-octene or *cis*-4-octene (for **A** or **B** respectively)). Time points were taken at the given times and quenched with a 3:1 mixture of EtOAc and Et₃N, followed by analysis with GC.



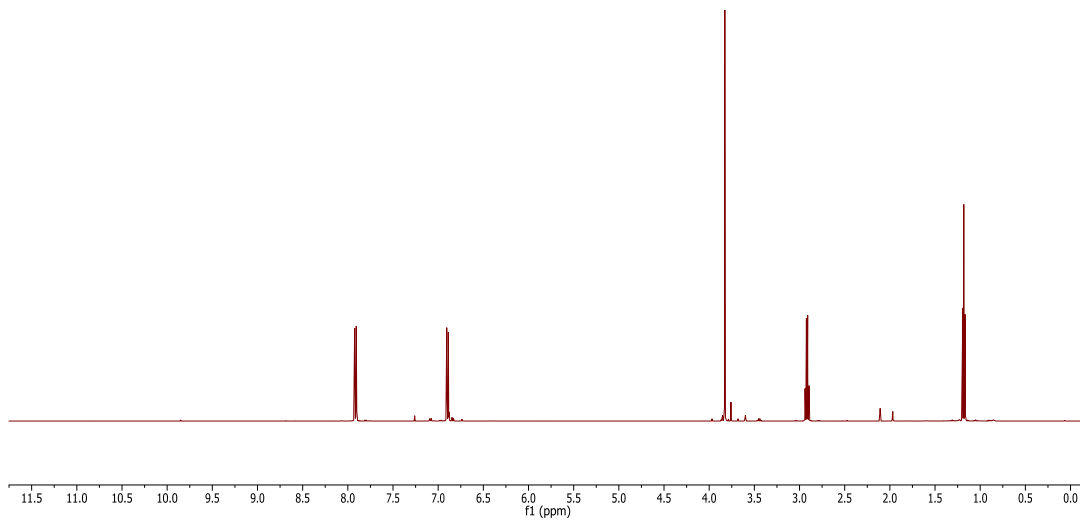
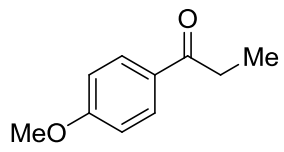
PROTON01
BM-193_CC



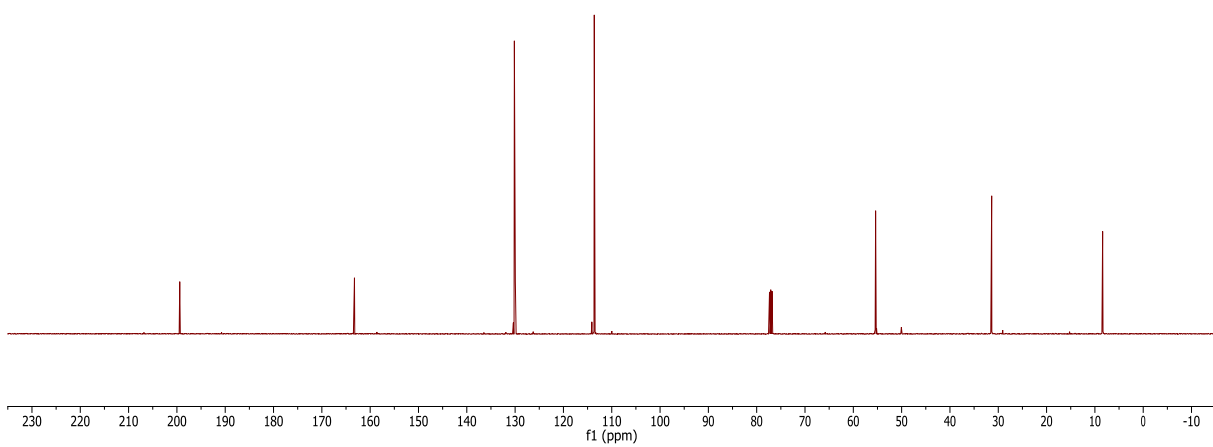
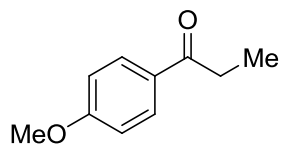
CARBON01
BM-193_CC



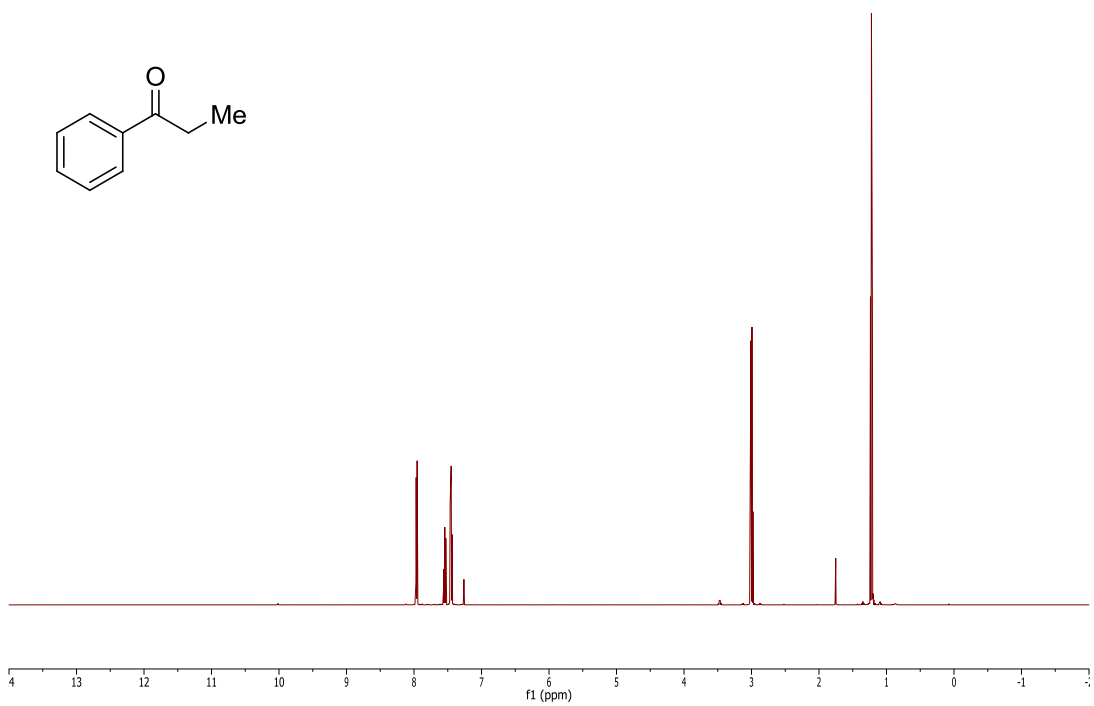
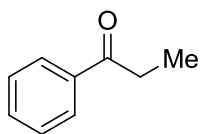
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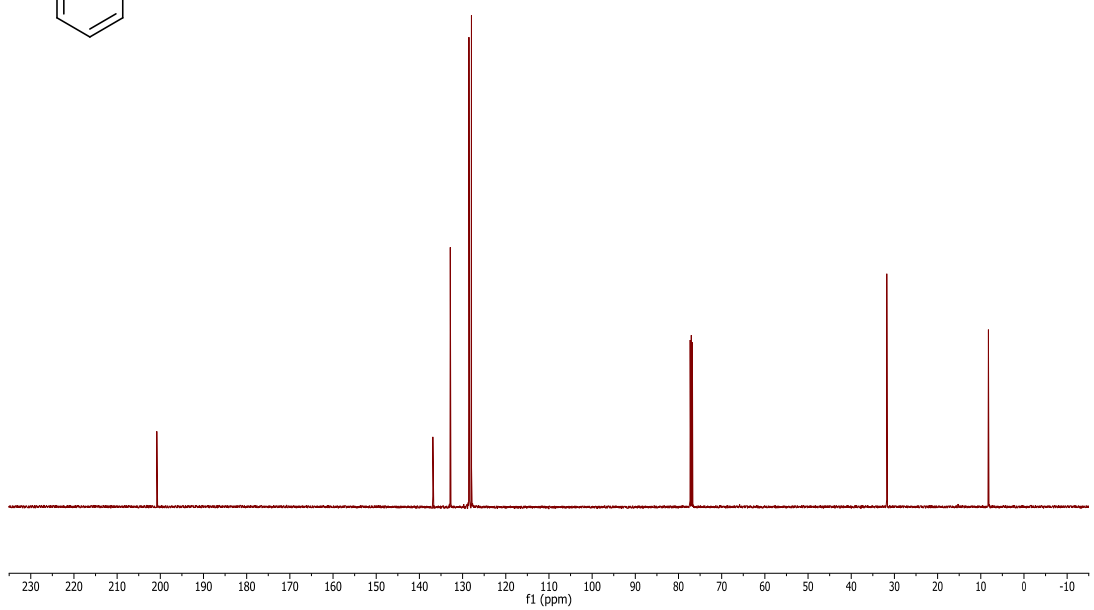
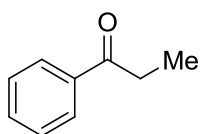
CARBON01
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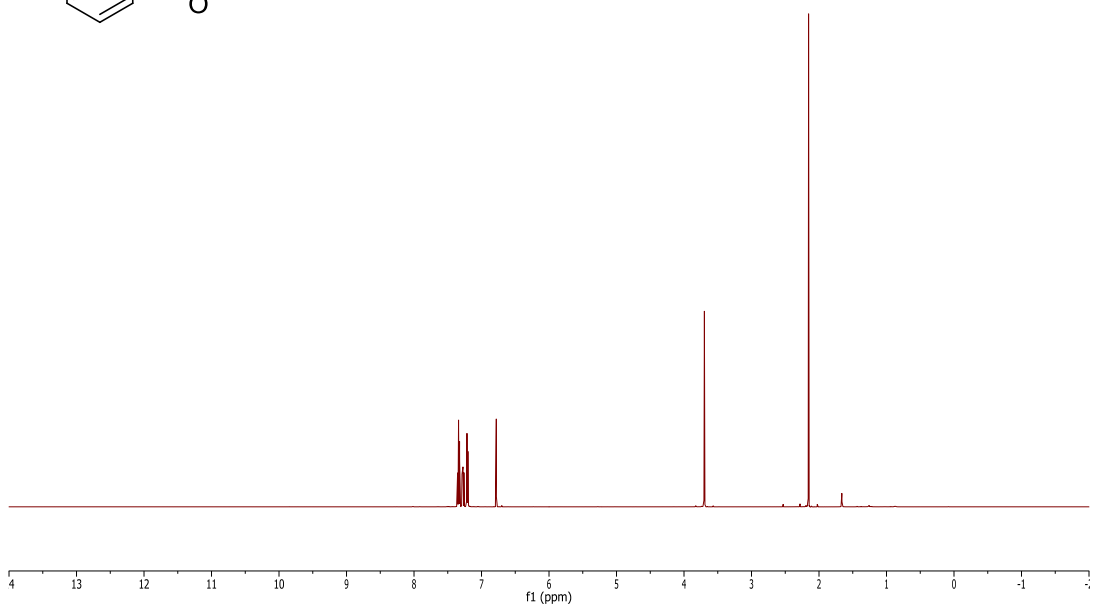
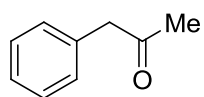
PROTON01
BM-203_CC



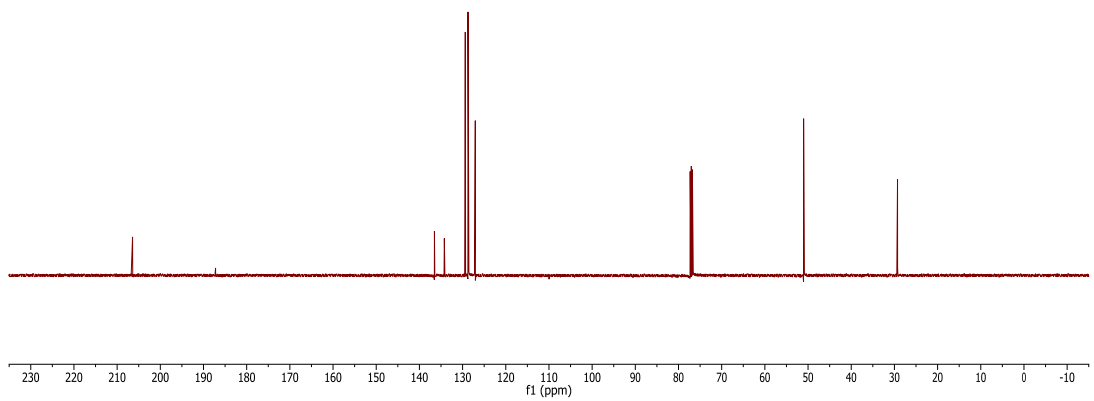
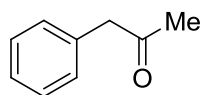
CARBON01
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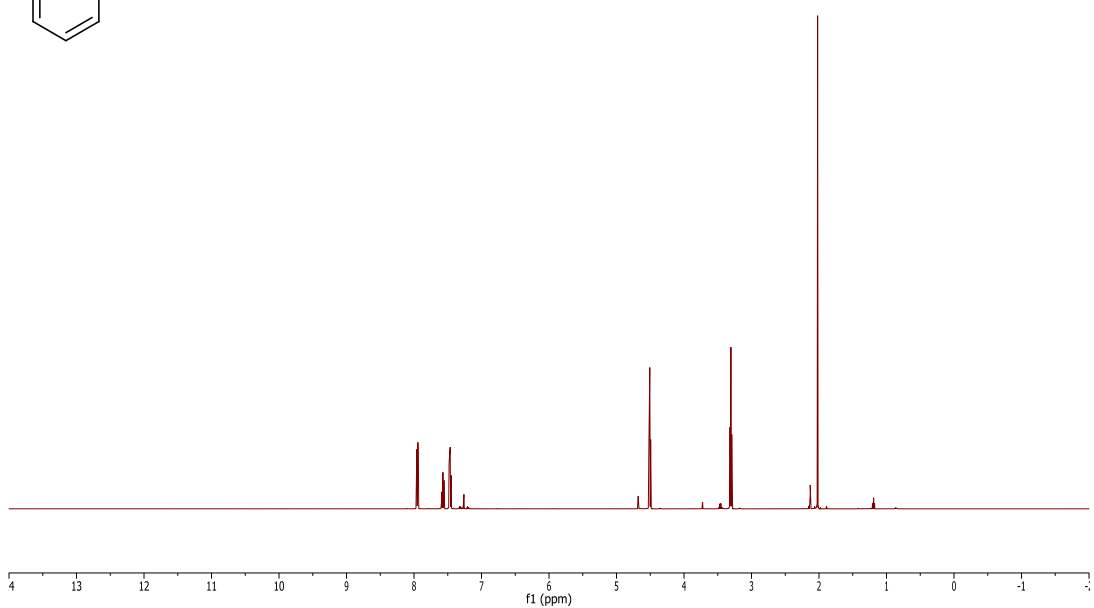
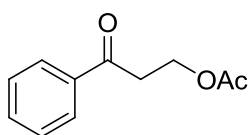
PROTON01
BM-248B_CC



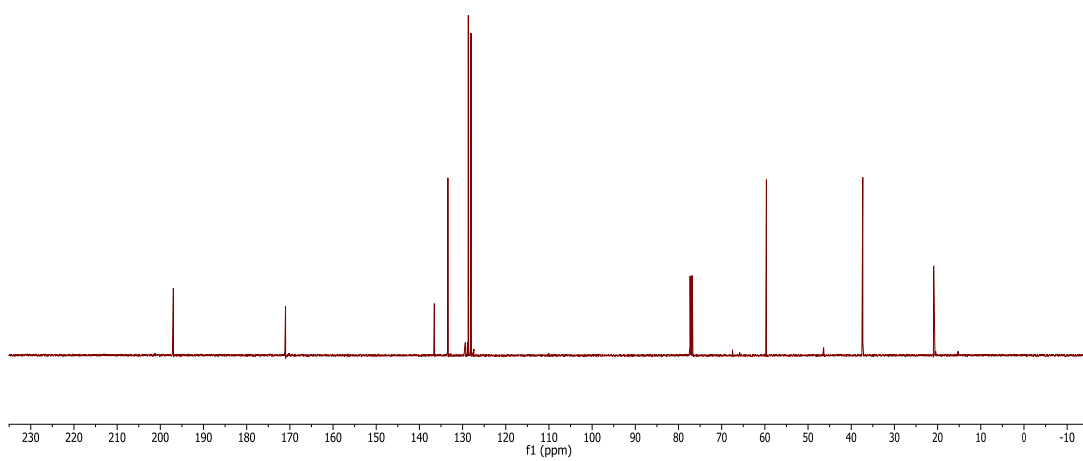
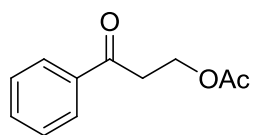
CARBON01
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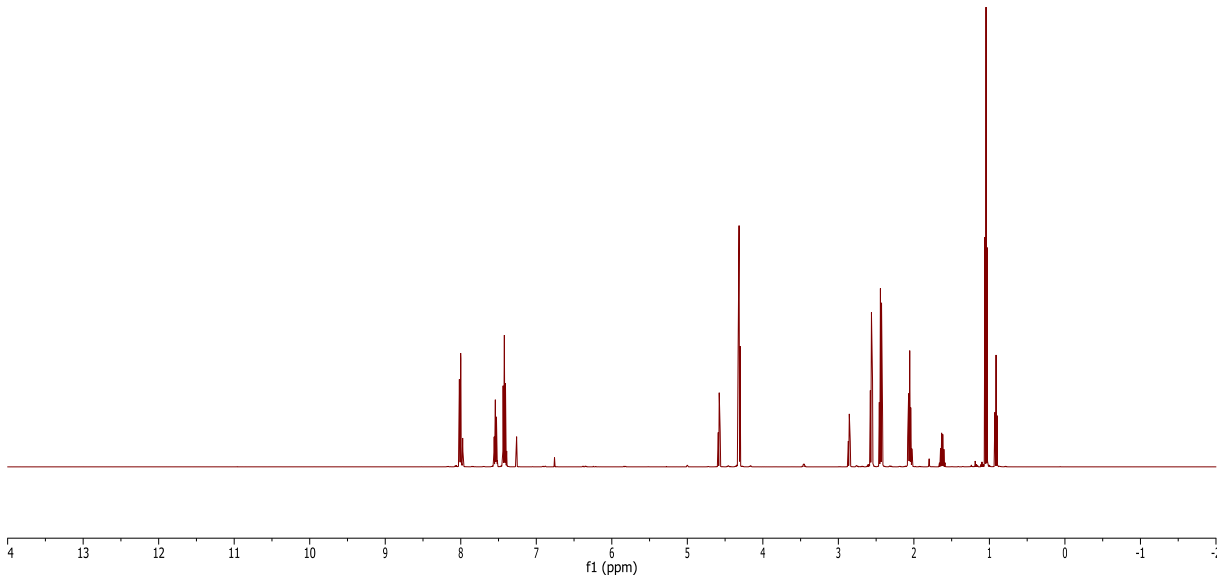
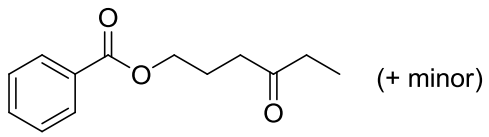
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BM-238_CC



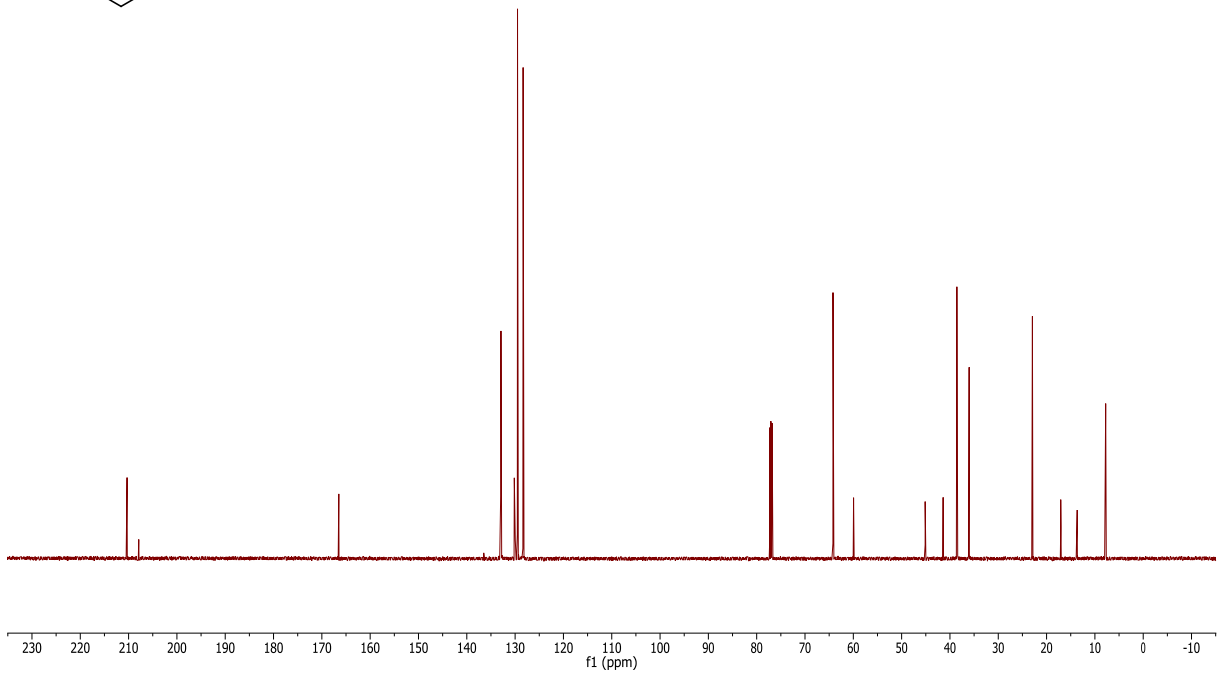
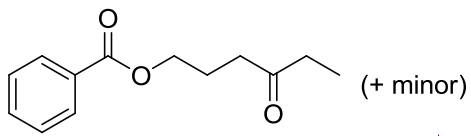
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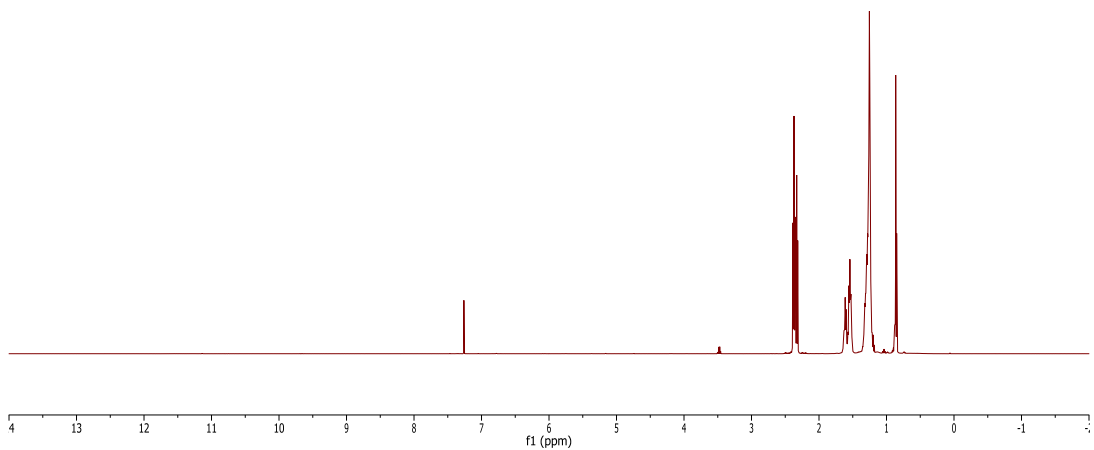
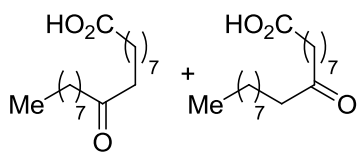
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BM-244_CC



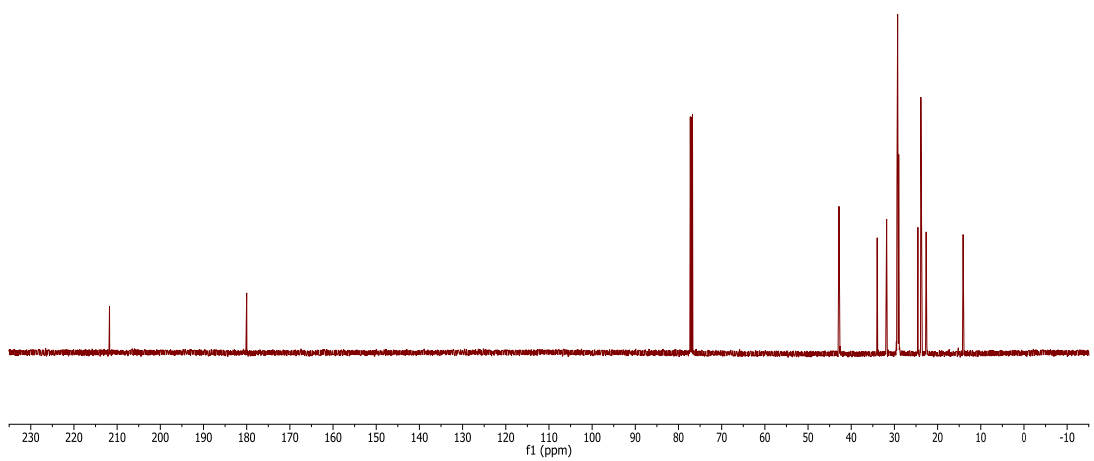
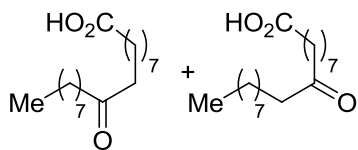
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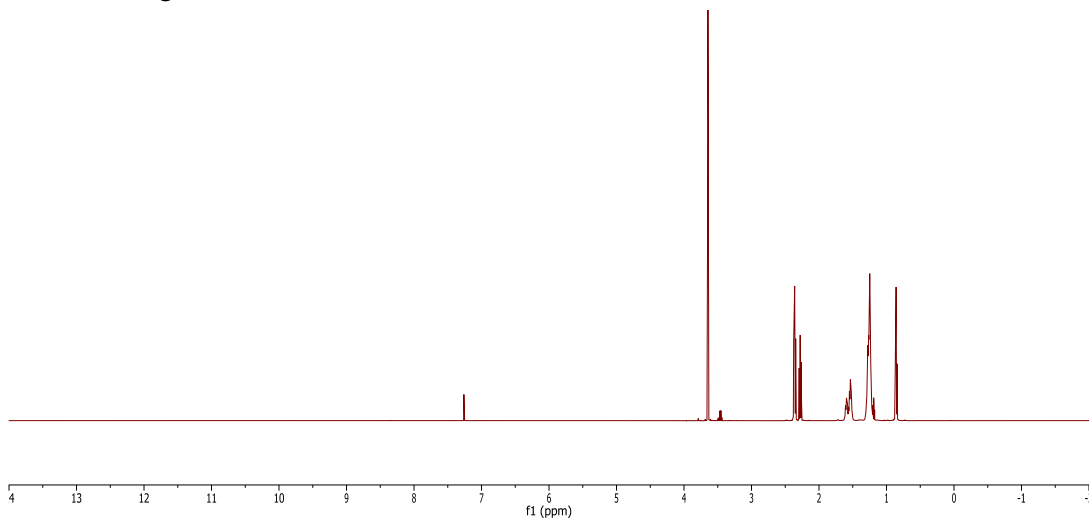
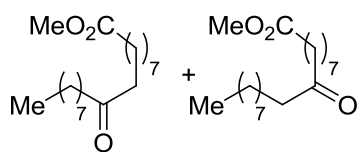
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BM-207A_CC



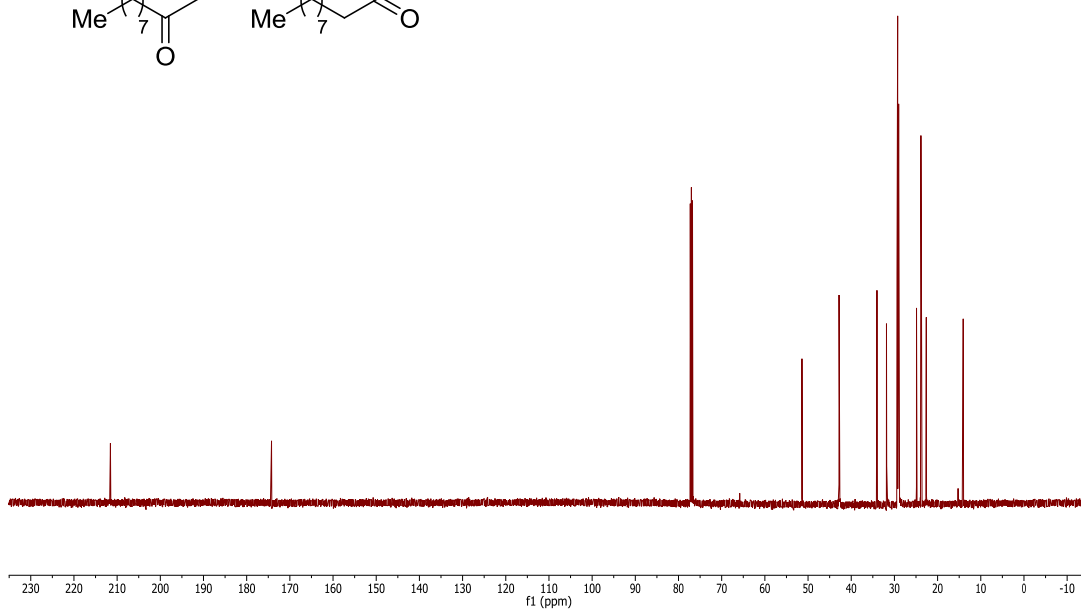
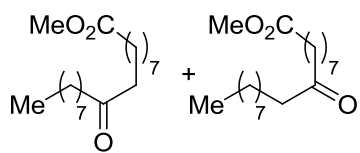
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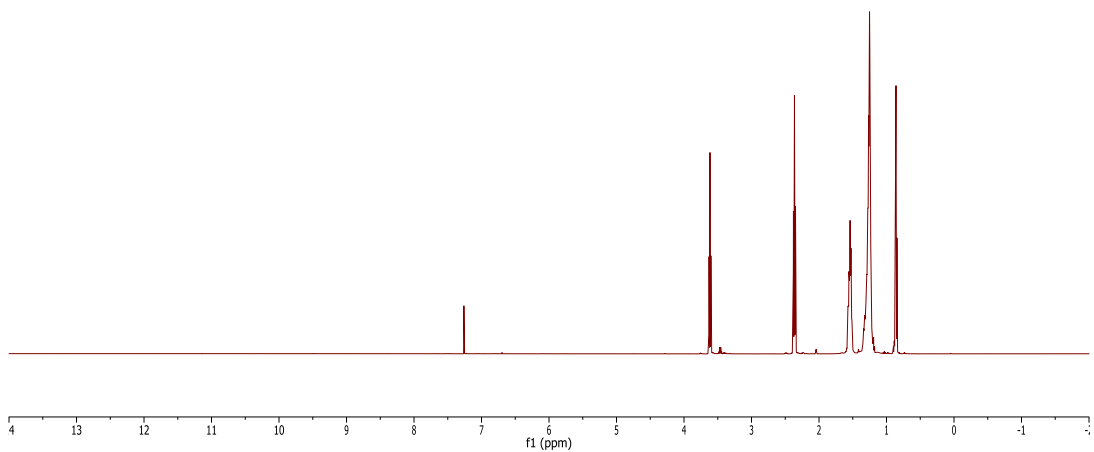
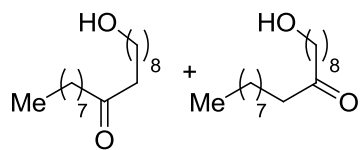
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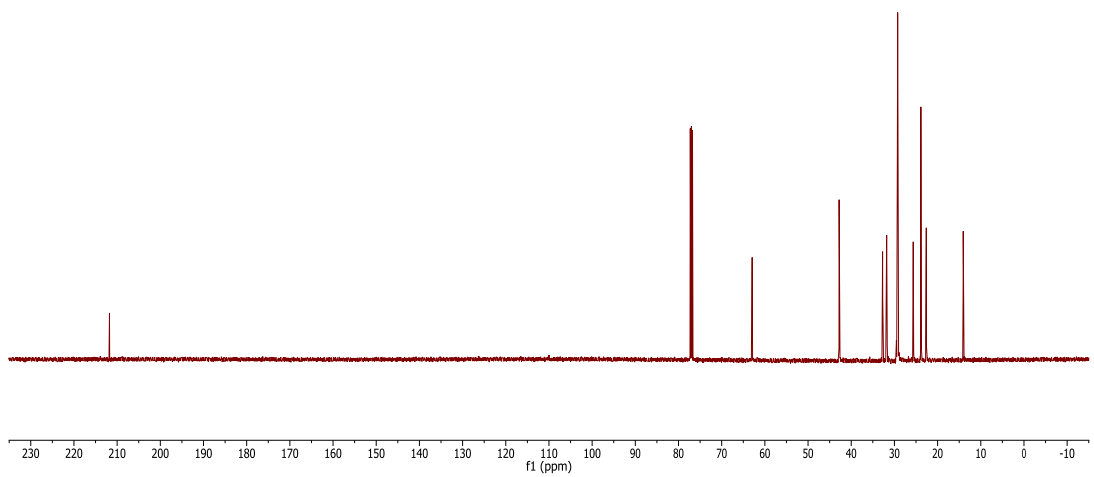
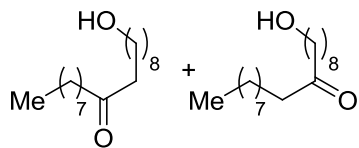
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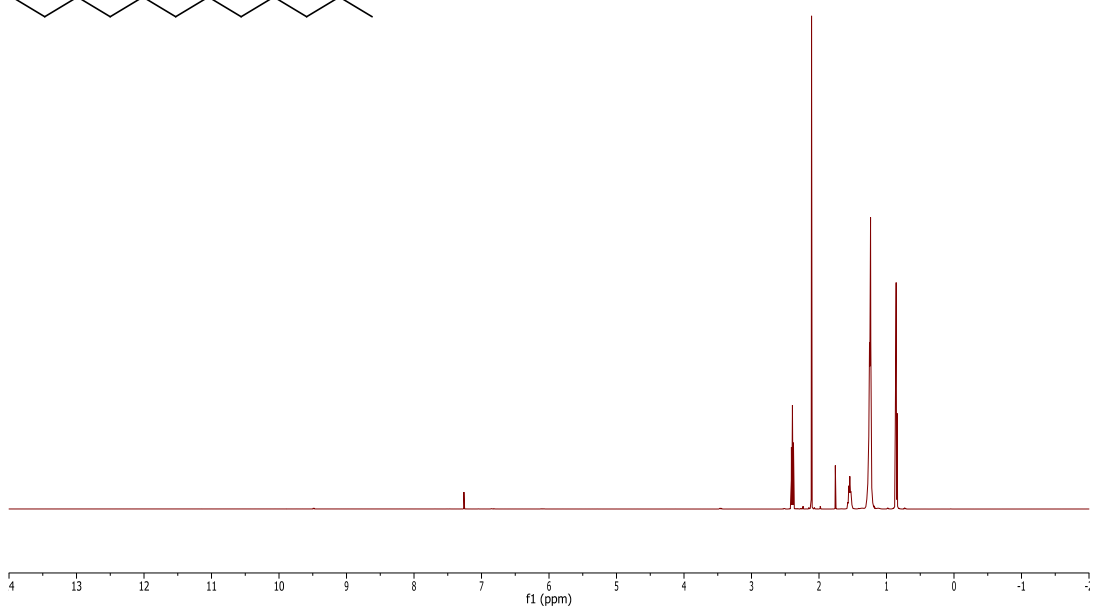
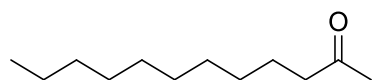
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BM-215_CC



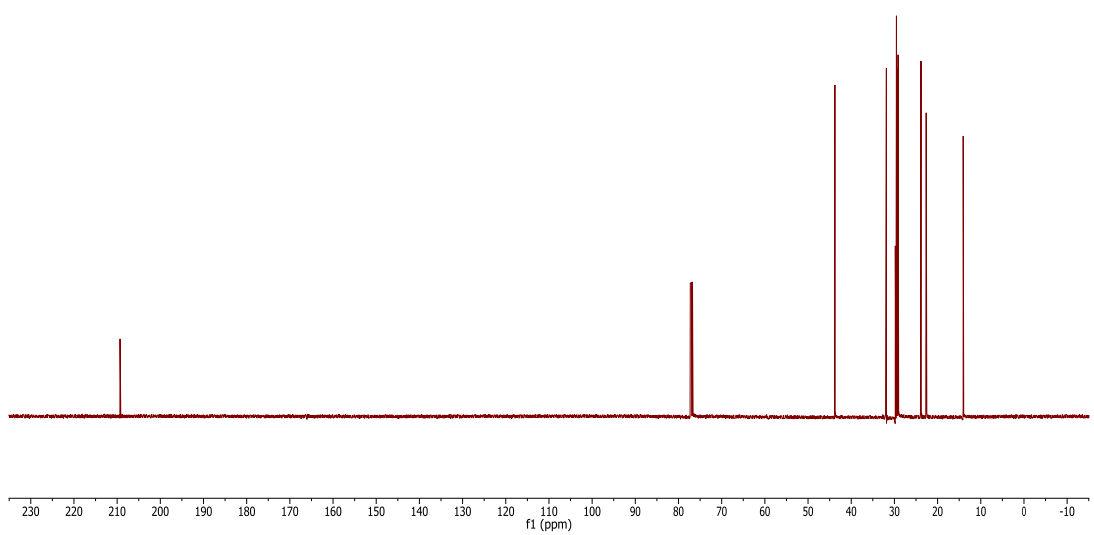
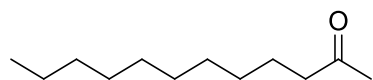
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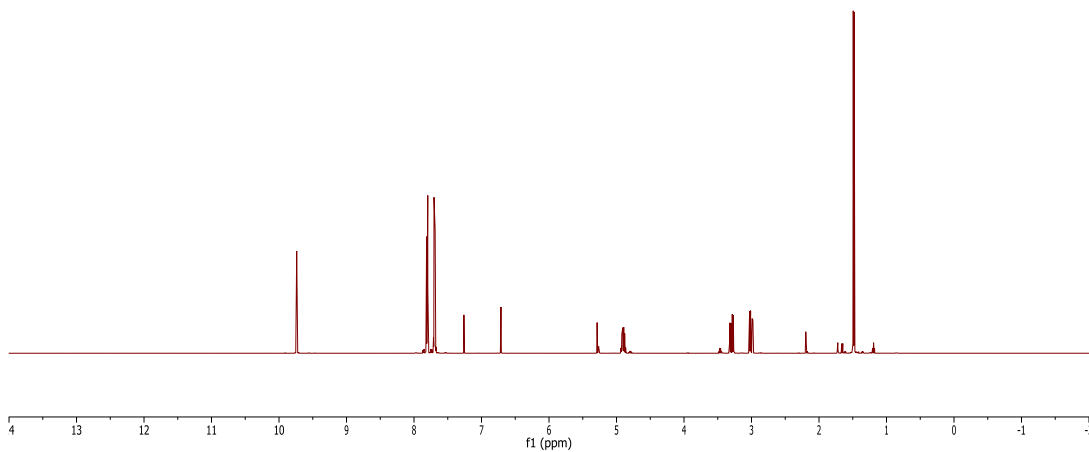
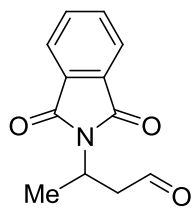
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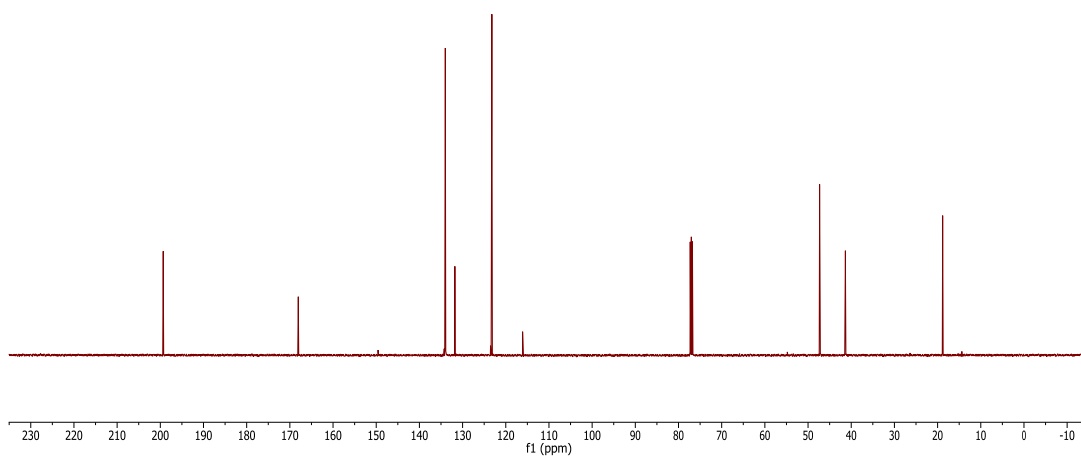
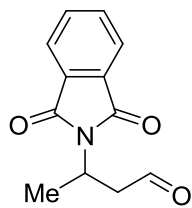
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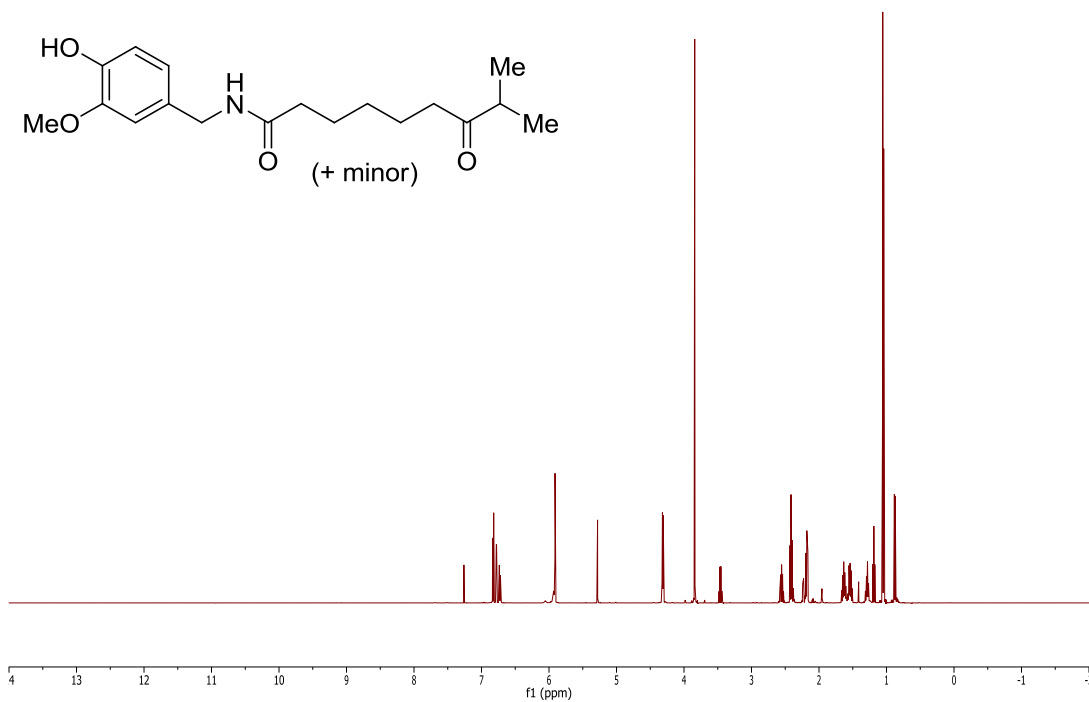
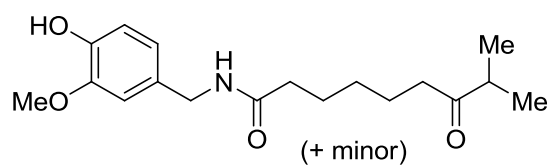
PROTON01
BM-242_CC



CARBON01
BM-242_CC



PROTON01
BM-247_CC
b



CARBON01
BM-247_CC

