

# **Enantioselective N-Heterocyclic Carbene Catalyzed $\beta$ -Hydroxylation of Enals Using Nitroarenes: An Atom Transfer Reaction that Proceeds via Single Electron Transfer**

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## Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Carbon tetrachloride was purchased from Aldrich and stored over 3Å molecular sieves. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Tetrahydrofuran was degassed with argon and passed through one column of neutral alumina. Methanol was purchased from Fisher Scientific and dried with activated 3Å molecular sieves. Sodium acetate was purchased from Aldrich. Column chromatography was performed on SiliCycle®SilicaFlash® P60, 40-63µm 60A. Thin layer chromatography was performed on SiliCycle® 250µm 60A plates. Visualization was accomplished with UV light or KMnO<sub>4</sub> stain followed by heating.

<sup>1</sup>H NMR spectra were recorded on Varian 400 MHz spectrometers at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from CDCl<sub>3</sub> (7.26 ppm) or acetone-D<sub>6</sub> (2.03 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). <sup>13</sup>C NMR were recorded on Varian 400 MHz spectrometers (at 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from CDCl<sub>3</sub> (77.36 ppm) or acetone-D<sub>6</sub> (205.87, 30.6 ppm). Mass spectra were recorded on an Agilent 6130 Quadrupole LC/MS.

Aldehydes were either purchased from Aldrich or prepared via known literature procedures. Nitroarenes were purchased from Aldrich.

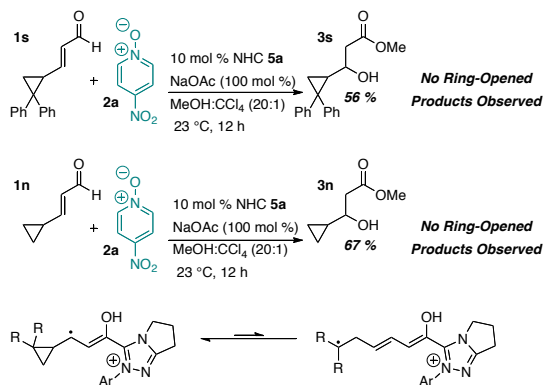
## General Procedure for the $\beta$ -Hydroxylation of Enals

To an oven dried screw cap vial charged with a magnetic stirbar was added triazolium salt **5f** (25 mg, 0.04 mmol), NaOAc (33 mg, 0.4 mmol), 4-nitropyridine N-oxide (84 mg, 0.6 mmol) and 2.0 mL of a 20:1 Carbon tetrachloride:methanol mixture followed by *trans*-cinnamaldehyde (53  $\mu$ L, 0.4 mmol). The cap was then screwed on and the reaction was allowed to stir at room temperature for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified by silica gel chromatography (6:4 hexanes:ether) to yield 32 mg (45 %) (*R*)-methyl 3-hydroxy-3-phenylpropanoate as a colorless oil.

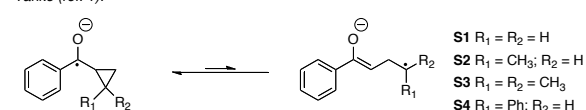
## Experiments to Probe Mechanism

### •Cyclopropyl carbinyl radical probe:

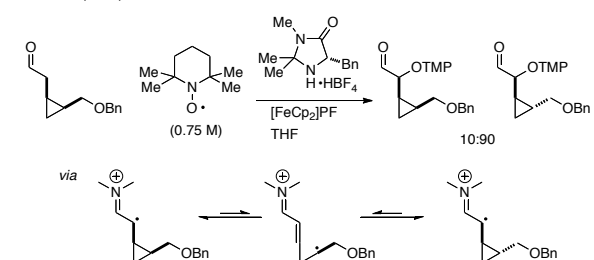
Two cyclopropane containing substrates were examined in an attempt to observe ring-opening products formed via the putative cyclopropylcarbinyl radical cation intermediate (**IIIa** in Scheme 1). However, these results should be analyzed with caution. Cyclopropyl ketyls have been demonstrated to favor the ring-closed form.<sup>1</sup> Furthermore, MacMillan has demonstrated that SOMO-mediated trapping of cyclopropane containing enamines also favors the ring-closed form, and has documented that they undergo reversible ring-opening.<sup>2</sup> The latter is particularly germane since it involves a radical cation and is likely most similar to the radical cation involved in this transformation.



•Tanko (ref. 1):

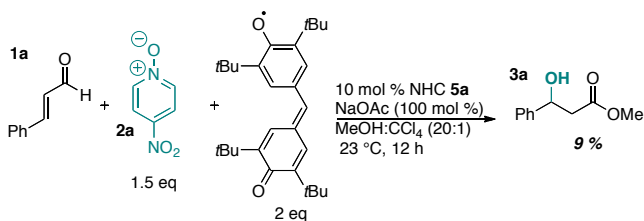


•MacMillan (ref. 2):



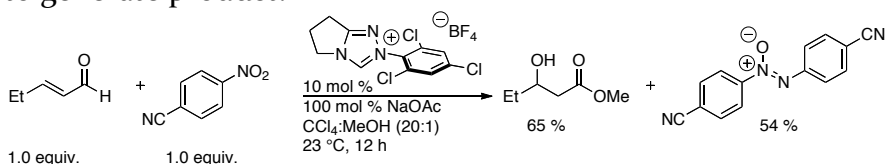
### •Galvinoxyl trap:

The use of galvinoxyl in this reaction leads to 9% yield of product with the remainder of the mass balance found in methyl cinnamate. A control experiment revealed that galvinoxyl is not a competent oxidant in the absence of the nitropyridine N-oxide.

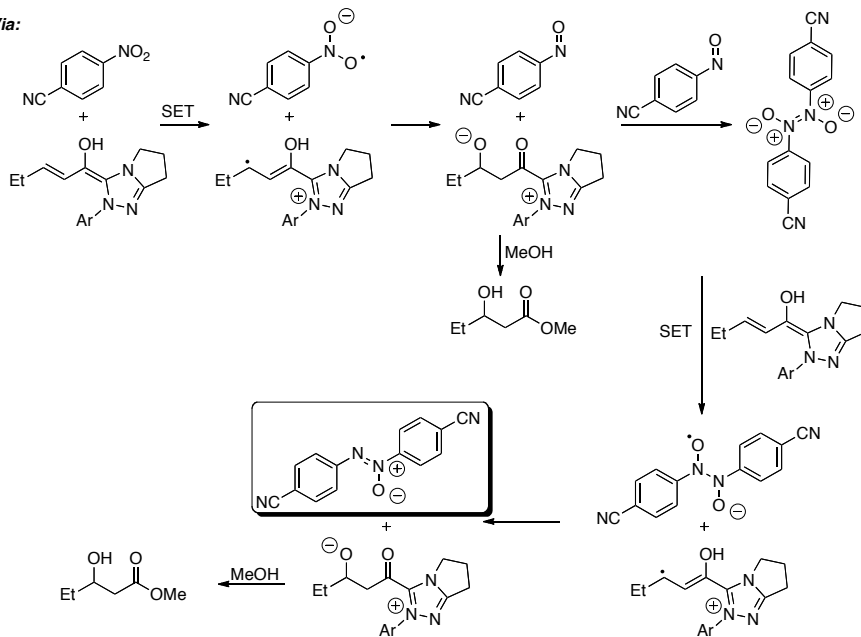


•*Isolation of the reduced nitroarene by-product:*

In several instances, we have observed nitrosoarenes formed from partial reduction of the nitroarene. In an effort to quantify this by-product, we used 4-cyano-nitrobenzene whose products of reduction have been previously characterized.<sup>3</sup> In the event, the reaction generated the diazene-N-oxide in 54% yield. This implies that the nitroso dimer (diazene dioxide) is a competent oxidant as well and substoichiometric amounts of nitroarene may be occasionally sufficient to generate product.



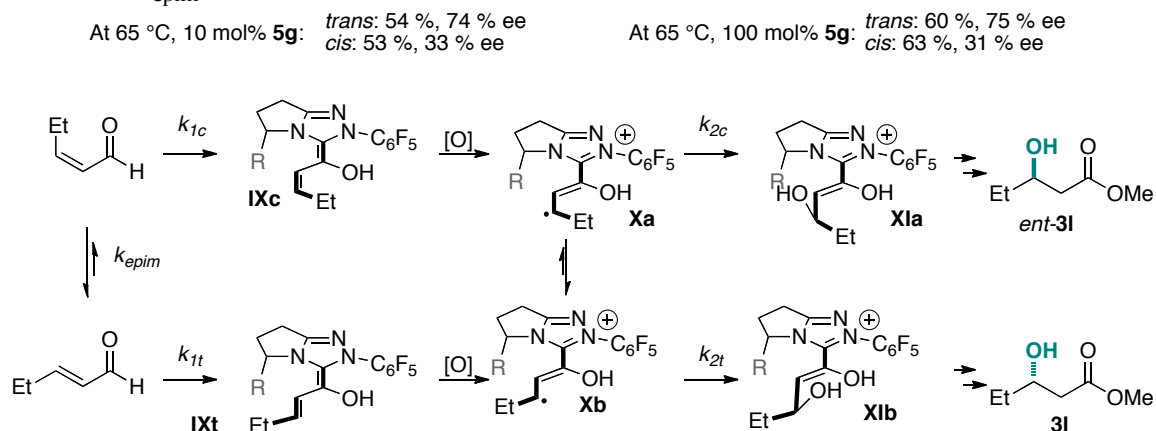
Via:



•*Cis and trans enals as probes of radical intermediates:*

As described in Scheme 3 in the manuscript, cis and trans pentenal (**11**) deliver the opposite major enantiomer at ambient temperature but the same major enantiomer at 65 °C. We further note that a reaction conducted with stoichiometric catalyst results in identical yields and enantioselectivities to that conducted with 10 mol% catalyst. These results argue that there is enantioconvergence at elevated temperatures, most likely due to the interception

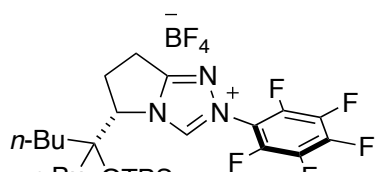
of a common intermediate, radical cation **Xb**. There is some background cis/trans isomerization of the enal under the reaction conditions even at ambient temperatures (at a rate of  $k_{epim}$ , illustrated graphically below). Formation of the Breslow intermediate from the aldehyde proceeds at a rate of  $k_{1c}$  and  $k_{1t}$  and is presumably first order in catalyst for both steps. The fact that identical selectivities are observed with both catalytic and stoichiometric NHC means the rates of enal isomerization ( $k_{epim}$ ) is irrelevant to the stereochemical outcome of the reaction. That is, if the interconversion of **Xa** and **Xb** was not occurring, acceleration of  $k_{1c} \cdot [\text{catalyst}]$  against  $k_{1t} \cdot [\text{catalyst}]$  would lead to different selectivities assuming a constant  $k_{epim}$ .



### Synthesis and Characterization of Triazolium Salts

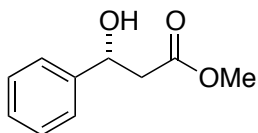
Triazolium Salt (**5d**): To a flame-dried flask with magnetic stir bar was added (*S*)-5-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidin-2-one (2.28 mg, 6.0 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (30 mL) and trimethyloxonium tetrafluoroborate (883 mg, 6.0 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 5 hours). Pentafluorophenyl hydrazine (1.18 g, 6.0 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 18 hours at which point dichloromethane was removed *in vacuo*. The resulting yellow oil was then dissolved in acetonitrile (30 mL) and trimethylorthoformate (4 mL). This solution was refluxed in an oil bath for 24 hours. After 24 hours the solvent was removed *in vacuo* and the desired product was recrystallized in EtOAc to yield triazolium salt (**5d**) (1.3 g, 33 %) as a white solid.  $[\alpha]_D^{21} = -112.8$  ( $c = 0.010$  g/ml, acetone);  $^1\text{H-NMR}$  (400 MHz; acetone- $d_6$ ):  $\delta$  9.98 (s, 1H), 7.62 (t,  $J = 3.4$  Hz, 2H), 7.51-7.43 (m, 6H), 7.36 (d,  $J = 6.7$  Hz, 2H), 6.36 (dd,  $J = 9.2, 2.3$  Hz, 1H), 3.43-3.32 (m, 1H), 3.12-3.03 (m, 2H), 1.99-1.89 (m, 1H), 0.94 (s, 9H), -0.23 (s, 3H), -0.31 (s, 3H).  $^{13}\text{C-NMR}$  (101 MHz;

acetone):  $\delta$  165.0, 143.7, 139.91, 139.86, 129.4, 129.06, 128.93, 128.56, 128.45, 82.5, 25.6, 20.6, 18.4, -4.0; **IR** (ATR, neat) 2955, 2931, 1529, 1070  $\text{cm}^{-1}$ ; **LRMS** (ESI + APCI)  $m/z$  [M+H] calcd 572.2, found 572.2

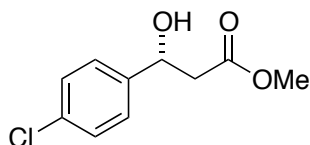


**Triazolium Salt (5g):** (*S*)-5-(5-hydroxynonan-5-yl)pyrrolidin-2-one (1.5 g, 6.5 mmol, 1 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (80 mL) and cooled to 0 °C in an ice bath. Trifluoromethanesulfonic acid tert-butyldimethylsilyl ester (3.4 mL, 15 mmol, 2.33 equiv) and 2,6-lutidine (3.2 mL, 20 mmol, 3 equiv) were added dropwise to the cooled solution. The solution was allowed to stir at 0 °C for 1.5 hours and then allowed to warm to room temperature and stir for 12 hours. After 12 hours the reaction was cooled to 0 °C and quenched with 80 mL saturated ammonium chloride and extracted 3 x 80 mL EtOAc, dried over sodium sulfate, and concentrated *in vacuo* to quantitatively yield (*S*)-5-(5-((*tert*-butyldimethylsilyl)oxy)nonan-5-yl)pyrrolidin-2-one as a colorless oil. To a flame-dried flask with magnetic stir bar was added crude (*S*)-5-(5(*S*)-5-(5-((*tert*-butyldimethylsilyl)oxy)nonan-5-yl)pyrrolidin-2-one (2.23 g, 6.5 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (25 mL) and trimethyloxonium tetrafluoroborate (961 mg, 6.5 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). Pentafluorophenyl hydrazine (1.28 mg, 6.5 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 12 hours at which point dichloromethane was removed *in vacuo*. The resulting yellow oil was then dissolved in acetonitrile (25 mL) and trimethylorthoformate (8 mL). This solution was refluxed in an oil bath for 24 hours. After 24 hours the solvent was removed *in vacuo* and the desired product was recrystallized from EtOAc to yield triazolium (**5g**) (675 mg, 16 %) as a white solid.  $[\alpha]_{\text{D}}^{21} = -47.6$  ( $c = 0.010$  g/mL, acetone);  **$^1\text{H-NMR}$**  (400 MHz; acetone- $d_6$ ):  $\delta$  10.46 (s, 1H), 5.26 (dd,  $J = 8.4, 5.8$  Hz, 1H), 3.20-3.02 (m, 2H), 2.80 (d,  $J = 13.5$  Hz, 2H), 1.94-1.76 (m, 4H), 1.52-1.34 (m, 8H), 0.95-0.89 (m, 6H), 0.79 (s, 9H), 0.22 (s, 3H), 0.09 (s, 3H).  **$^{13}\text{C-NMR}$**  (101 MHz; acetone):  $\delta$  165.1, 143.8, 79.2, 69.8, 37.1, 36.1, 25.93, 25.75, 25.3, 22.9, 22.6, 21.6, 18.1, 13.34, 13.22, -2.47, -2.60; **IR** (ATR, neat) 2957, 2931, 2860, 1600, 1543, 1069, 1003, 836, 775  $\text{cm}^{-1}$ ; **LRMS** (ESI + APCI)  $m/z$  [M+H] calcd 532.3, found 532.3

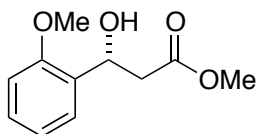
## Compound Characterization



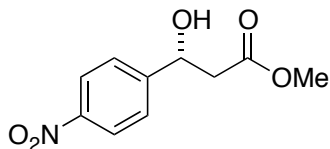
(*R*)-methyl 3-hydroxy-3-phenylpropanoate (**3a**): Colorless Oil. 45 % yield 92 % ee;  $R_f=0.29$  (1:1 hexanes:ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 6.5 min, minor: 7.3 min; **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.36-7.26 (m, 5H), 5.11 (dd,  $J = 9.0, 3.9$  Hz, 1H), 3.69 (s, 3H), 3.35 (bs, 1H), 2.73 (td,  $J = 14.3, 7.8$  Hz, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.7, 142.6, 128.5, 127.8, 125.6, 70.3, 51.9, 43.2. Spectra matched that of the previously reported compound.<sup>4</sup>



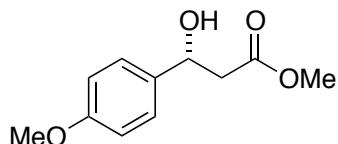
(*R*)-methyl 3-(4-chlorophenyl)-3-hydroxypropanoate (**3b**): Colorless Oil. 57 % yield, 90 % ee.  $R_f=0.29$  (1:1 hexanes:ether); **HPLC analysis**: Chiralcel OJ-H column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 35.6 min, minor: 38.9. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.33-7.28 (m, 4H), 5.10 (ddd,  $J = 8.0, 4.6, 3.5$  Hz, 1H), 3.71 (s, 3H), 3.27 (d,  $J = 3.5$  Hz, 1H), 2.71-2.69 (m, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.6, 140.9, 133.5, 128.7, 127.0, 69.6, 51.9, 42.9. Spectra matched that of the previously reported compound.<sup>5</sup>



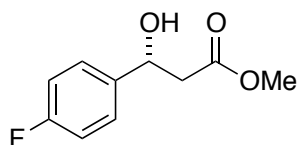
(*R*)-methyl 3-hydroxy-3-(2-methoxyphenyl)propanoate (**3c**): Colorless Oil. 44 % yield, 80 % ee.  $R_f=0.27$  (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 9.3 min, minor: 10.3 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.41 (dd,  $J = 7.5, 1.6$  Hz, 1H), 7.25 (td,  $J = 7.8, 1.9$  Hz, 1H), 6.96 (td,  $J = 7.5, 0.9$  Hz, 1H), 6.86 (d,  $J = 8.2$  Hz, 1H), 5.35 (dt,  $J = 9.0, 4.4$  Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.38 (d,  $J = 5.3$  Hz, 1H), 2.85-2.67 (m, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  173.0, 156.0, 130.4, 128.6, 126.5, 120.8, 110.3, 66.6, 55.2, 51.7, 41.5. Spectra matched that of the previously reported compound.<sup>6</sup>



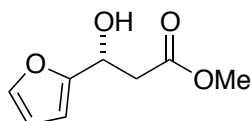
(*R*)-methyl 3-hydroxy-3-(4-nitrophenyl)propanoate (**3d**): Pale Yellow Solid. 20 % yield, 80 % ee.  $R_f=0.23$  (1:1 hexanes:ether); **HPLC analysis**: Chiralcel OJ-H column, 93:7 Hexanes:*iso*-propanol, 1.0mL/min. Major: 41.4 min, minor: 44.7. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  8.20 (d,  $J = 8.8$  Hz, 2H), 7.55 (d,  $J = 8.8$  Hz, 2H), 5.22 (dt,  $J = 8.2, 4.1$  Hz, 1H), 3.73 (s, 3H), 3.54 (d,  $J = 3.7$  Hz, 1H), 2.77-2.67 (m, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.3, 149.5, 126.4, 123.8, 69.3, 52.1, 42.7. Spectra matched that of the previously reported compound.<sup>7</sup>



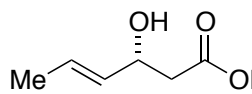
(*R*)-methyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (**3e**): 41 % yield, 92 % ee.  $R_f=0.25$  (1:1 Hexanes:Ether); **HPLC analysis**: Chiralcel OB-H column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 10.6 min, minor: 14.5 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.27 (d,  $J = 8.6$  Hz, 2H), 6.86 (d,  $J = 8.6$  Hz, 2H), 5.06 (dd,  $J = 9.2, 3.7$  Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.07 (bs, 1H), 2.78-2.63 (m, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.7, 159.2, 134.7, 126.9, 113.9, 69.9, 55.2, 51.8, 43.1. Spectra matched that of the previously reported compound.<sup>8</sup>



(*R*)-methyl 3-(4-fluorophenyl)-3-hydroxypropanoate (**3f**): Colorless Oil. 46 % yield, 91 % ee.  $R_f=0.28$  (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 19.2 min, minor: 18.5. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.35-7.31 (m, 2H), 7.04-7.00 (m, 2H), 5.10 (dt,  $J = 8.3, 3.9$  Hz, 1H), 3.71 (s, 3H), 3.27 (d,  $J = 3.9$  Hz, 1H), 2.76-2.64 (m, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.6, 162.3 ( $J=245.7$  Hz, C), 138.2 ( $J=3.0$  Hz, C), 127.3 ( $J=8.2$  Hz, CH), 115.4 ( $J=21.4$  Hz, CH), 69.6, 51.9, 43.1. Spectra matched that of the previously reported compound.<sup>9</sup>



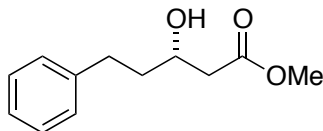
(*R*)-methyl 3-(furan-2-yl)-3-hydroxypropanoate (**3g**): Colorless Oil. 56 % yield, 84 % ee.  $R_f=0.27$  (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 9.6 min, minor: 5.6 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.37 (dd,  $J = 1.8, 0.8$  Hz, 1H), 6.33 (dd,  $J = 3.3, 1.8$  Hz, 1H), 6.28 (dt,  $J = 3.3, 0.8$  Hz, 1H), 5.14 (dd,  $J = 8.5, 4.1$  Hz, 1H), 3.73 (s, 3H), 3.09 (s, 1H), 2.88 (qd,  $J = 15.9, 6.3$  Hz, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.3, 154.6, 142.2, 110.2, 106.3, 64.2, 51.9, 39.6. Spectra matched that of the previously reported compound.<sup>8</sup>



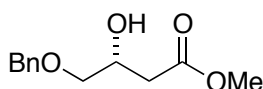
(*R,E*)-methyl 3-hydroxyhex-4-enoate (**3h**): Colorless Oil. 46 % yield, 85 % ee.  $R_f=0.32$  (1:1 hexanes:ether); **GC analysis**: Varian BDM column, 70 °C 3.0 mL/min. Major: 35.6 min, minor: 39.7 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  5.77-5.68 (m, 1H), 5.49 (ddq,  $J = 15.3, 6.6, 1.6$  Hz, 1H), 4.47 (q,  $J = 6.6$  Hz, 1H), 3.69 (s, 3H), 2.53-2.51 (m, 2H), 1.68 (dt,  $J = 6.6, 0.8$  Hz, 3H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.7, 131.7, 127.5, 68.9, 51.7, 41.3, 17.6. Spectra matched that of the previously reported compound.<sup>10</sup>



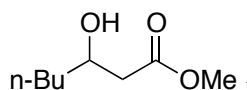
## Supporting Information



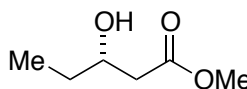
(*S*)-methyl 3-hydroxy-5-phenylpentanoate (**3i**): Colorless Oil. 58 % yield, 80 % ee (Note: reaction was ran in a 20:1 mixture of trifluorotoluene:methanol).  $R_f=0.23$  (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 7.1 min, minor: 7.9 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.31-7.17 (m, 4H), 4.02 (tt,  $J = 8.4, 4.1$  Hz, 1H), 3.71 (s, 3H), 2.99 (s, 1H), 2.83 (ddd,  $J = 14.1, 9.3, 5.2$  Hz, 1H), 2.70 (ddd,  $J = 13.8, 9.4, 7.0$  Hz, 1H), 2.55-2.42 (m, 2H), 1.90-1.81 (m, 1H), 1.74 (dddd,  $J = 13.8, 9.6, 6.9, 4.2$  Hz, 1H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  173.3, 141.7, 128.42, 128.40, 125.9, 67.2, 51.8, 41.1, 38.1, 31.7. Spectra matched that of the previously reported compound.<sup>11</sup>



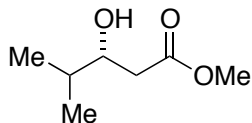
(*R*)-methyl 4-(benzyloxy)-3-hydroxybutanoate (**3j**): Colorless Oil. 71 % yield, 81 % ee.  $R_f=0.31$  (1:1 hexanes:ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes:*iso*-propanol, 1.0 mL/min. Major: 9.4 min, minor: 8.5 min.; **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.37-7.28 (m, 5H), 4.56 (s, 2H), 4.27-4.21 (m, 1H), 3.69 (s, 3H), 3.50 (qd,  $J = 9.8, 5.2$  Hz, 2H), 2.79 (bs, 1H), 2.56 (d,  $J = 6.3$  Hz, 2H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  172.5, 137.8, 128.4, 127.78, 127.70, 73.4, 73.1, 67.2, 51.8, 38.0. Spectra matched that of the previously reported compound. Absolute configuration was compared to that of the known compound.<sup>12</sup> All other absolute configurations were assigned via correlation.



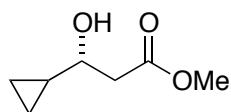
methyl 3-hydroxyheptanoate (**3k**): Colorless Oil.  $R_f = 0.25$  (1:1 hexanes:ether) **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  4.03-3.97 (m, 1H), 3.71 (s, 2H), 2.52 (dd,  $J = 16.5, 3.1$  Hz, 1H), 2.65 (bs, 1H), 2.41 (dd,  $J = 16.4, 9.0$  Hz, 1H), 1.54-1.19 (m, 7H), 0.90 (dd,  $J = 8.3, 5.5$  Hz, 3H). **<sup>13</sup>C NMR** (101 MHz; cdcl<sub>3</sub>):  $\delta$  173.5, 68.0, 51.7, 41.1, 36.2, 27.6, 22.6, 14.0 Spectra matched that of previously reported compound.<sup>13</sup>



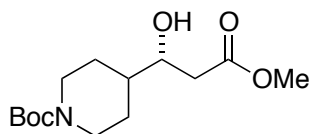
(*S*)-methyl 3-hydroxypentanoate (**3l**): Colorless Oil. 65 % yield, 86 % ee;  $R_f=0.26$  (1:1 hexanes:ether); **GC analysis**: Varian BDM column, 70 °C, 1.0 mL/min. Major: 28.6 min, minor: 31.9 min; **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>):  $\delta$  3.91 (ddd,  $J = 12.6, 9.0, 3.4$  Hz, 1H), 3.71 (s, 3H), 3.10 (bs, 1H), 2.51-2.35 (m, 2H), 1.58-1.41 (m, 2H), 0.93 (t,  $J = 7.4$  Hz, 3H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>):  $\delta$  173.4, 69.3, 51.7, 40.6, 29.4, 9.8. Spectra matched that of the previously reported compound.<sup>14</sup>



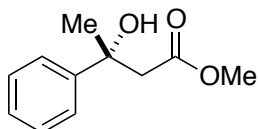
(*R*)-methyl 3-hydroxy-4-methylpentanoate (**3m**): Colorless Oil. 73 % yield, 88 % ee.  $R_f=0.28$  (1:1 hexanes:ether); **GC analysis**: Varian BDM column, 80 °C, 1.5 mL/min. Major: 18.9 min, minor: 20.3 min; **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>): δ 3.78 (ddd,  $J = 9.3, 6.0, 3.1$  Hz, 1H), 3.72 (s, 3H), 2.80 (bs, 1H), 2.54-2.38 (m, 2H), 1.71 (dq,  $J = 13.1, 6.6$  Hz, 1H), 0.94 (dd,  $J = 11.3, 6.8$  Hz, 6H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>): δ 173.9, 72.7, 51.7, 38.2, 33.1, 18.3, 17.7. Spectra matched that of the previously reported compound.<sup>15</sup>



(*R*)-methyl 3-cyclopropyl-3-hydroxypropanoate (**3n**): Colorless Oil. 61 % yield, 80 % ee.  $R_f=0.23$  (1:1 hexanes:ether) **HPLC analysis**: Chiralpak IB column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 5.1 min, minor: 4.7 min (Note: ee was obtained using the benzyl ether of compound **3e**); **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>): δ 3.71 (s, 3H), 3.32 (td,  $J = 8.4, 3.9$  Hz, 1H), 2.71 (bs, 1H), 2.68-2.56 (m, 2H), 0.99-0.90 (m, 1H), 0.59-0.47 (m, 2H), 0.39 (dq,  $J = 9.3, 4.6$  Hz, 1H), 0.22 (dq,  $J = 9.2, 4.6$  Hz, 1H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>): δ 173.0, 72.7, 51.7, 41.2, 16.8, 3.1, 2.2. Spectra matched that of the previously reported compound.<sup>16</sup>



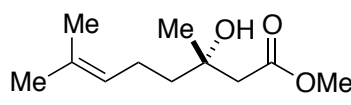
(*R*)-*tert*-butyl 4-(1-hydroxy-3-methoxy-3-oxopropyl)piperidine-1-carboxylate (**3o**): Colorless Oil. 74 % yield, 84 % ee.  $R_f=0.40$  (100 % ether); **HPLC analysis**: Chiralcel OC column, 90:10 hexanes:*iso*-propanol, 1.0 mL/min. Major: 34.2 min, minor: 39.7 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>): δ 4.15-4.12 (m, 2H), 3.79 (ddd,  $J = 9.2, 6.4, 2.8$  Hz, 1H), 3.71 (s, 3H), 2.98 (bs, 1H), 2.65 (t,  $J = 12.9$  Hz, 2H), 2.53 (dd,  $J = 16.4, 2.8$  Hz, 1H), 2.42 (dd,  $J = 16.4, 9.4$  Hz, 1H), 1.83 (dt,  $J = 13.2, 2.5$  Hz, 1H), 1.60-1.55 (m, 1H), 1.50 (m,  $J = 3.5$  Hz, 1H), 1.44 (s, 9H), 1.28-1.16 (m, 2H). **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>): δ 173.6, 154.8, 79.4, 71.2, 41.4, 38.2, 28.4, 27.9 IR (ATR neat): 3458, 2976, 1775, 1693, 1433, 1162; **LRMS** (ESI + APCI)  $m/z$  [M+H] calcd. 288.1, found 288.1 [ $\alpha$ ]<sub>D</sub><sup>21</sup> = -7.6 ( $c = 0.010$  g/ml, MeOH)

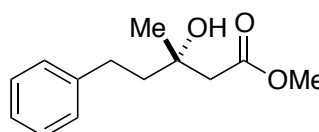


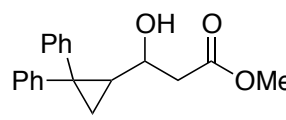
(*R*)-methyl 3-hydroxy-3-phenylbutanoate (**3p**): Colorless Oil. 36 % yield, 28 % ee.  $R_f=0.26$  (7:3 Hexanes:Ether); **HPLC analysis**: Chiralcel OJ-H column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 11.2 min. minor: 13.3 min. **<sup>1</sup>H-NMR** (400 MHz; CDCl<sub>3</sub>): δ 7.46-7.24 (m, 5H), 4.31 (s, 1H), 3.61 (s, 3H), 2.90 (dd,  $J = 75.0, 16.0$  Hz, 2H), 1.55 (s, 3H); **<sup>13</sup>C-NMR** (101 MHz; CDCl<sub>3</sub>): δ 173.1, 128.3, 125.3,

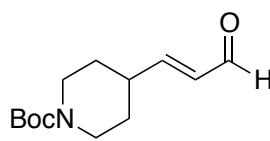
## Supporting Information

124.4, 72.7, 51.7, 46.2, 30.6. Spectra matched that of the previously reported compound.<sup>17</sup>

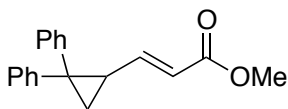
  
(*S*)-methyl 3-hydroxy-3,7-dimethyloct-6-enoate (**3q**): Colorless Oil. 40 % yield, 63 % ee.  $R_f=0.41$  (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 99:1 hexanes:*iso*-propanol, 1.0 mL/min. Major: 5.6 min, minor: 6.0 min. <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): 5.10-5.06 (m, 1H), 3.70 (s, 3H), 3.40 (bs, 1H), 2.48 (q,  $J = 15.9$  Hz, 2H), 2.07-2.01 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.52 (td,  $J = 8.4, 4.2$  Hz, 2H), 1.23 (s, 3H); <sup>13</sup>C-NMR (101 MHz; CDCl<sub>3</sub>):  $\delta$  173.4, 131.8, 124.0, 70.9, 51.6, 44.7, 41.8, 26.6, 25.6, 22.6, 17.6. Spectra matched that of the previously reported compound.<sup>12</sup>

  
(*S*)-methyl 3-hydroxy-3-methyl-5-phenylpentanoate (**3r**): Colorless Oil. 32 % yield, 46 % ee.  $R_f=0.33$  (7:3 hexanes:ether); **HPLC analysis**: Chiralpak IB column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 11.8 min, minor: 12.6 min. <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.30-7.16 (m, 5H), 3.72 (s, 3H), 3.54 (bs, 1H), 2.75-2.69 (m, 2H), 2.55 (q,  $J = 15.8$  Hz, 2H), 1.86-1.80 (m, 2H), 1.32 (s, 3H); <sup>13</sup>C-NMR (101 MHz; CDCl<sub>3</sub>):  $\delta$  173.4, 142.2, 128.40, 128.31, 125.8, 70.8, 51.7, 44.8, 43.8, 30.3, 26.7. Spectra matched that of the previously reported compound.<sup>17</sup>

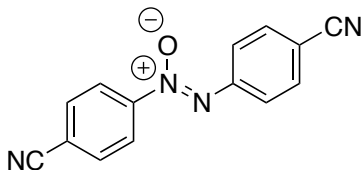
  
methyl 3-(2,2-diphenylcyclopropyl)-3-hydroxypropanoate (**3s**): Colorless Oil.  $R_f = 0.30$  (1:1 hexanes:ether) <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.49 (d,  $J = 7.2$  Hz, 2H), 7.32-7.21 (m, 7H), 7.15-7.12 (m, 1H), 3.67 (s, 3H), 3.24 (ddd,  $J = 9.6, 7.7, 4.7$  Hz, 1H), 2.79 (bs, 1H), 2.68-2.59 (m, 2H), 1.83 (td,  $J = 9.2, 6.4$  Hz, 1H), 1.26 (dt,  $J = 8.5, 4.1$  Hz, 2H). <sup>13</sup>C-NMR (101 MHz; CDCl<sub>3</sub>):  $\delta$  173.0, 146.1, 140.9, 130.3, 128.5, 128.25, 128.14, 126.8, 126.1, 69.2, 51.7, 40.9, 36.6, 31.3, 16.9 **IR** (ATR neat) 3415, 3026, 3001, 2952, 1732, 1604, 1497, 1437, 698; **LRMS** (ESI + APCI)  $m/z$  [M+H] calcd. .297.1, found 297.1

  
(*E*)-*tert*-butyl 4-(3-oxoprop-1-en-1-yl)piperidine-1-carboxylate (**10**): Colorless Oil.  $R_f=0.31$  (1:1 hexanes:ether); <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  9.51

(d,  $J = 7.7$  Hz, 1H), 6.75 (dd,  $J = 15.8, 6.4$  Hz, 1H), 6.09 (ddd,  $J = 15.8, 7.7, 1.4$  Hz, 1H), 4.15 (d,  $J = 13.3$  Hz, 2H), 2.82-2.75 (m, 2H), 2.46-2.38 (m, 1H), 1.77 (dd,  $J = 12.7, 1.4$  Hz, 2H), 1.46 (s, 9H), 1.38 (qd,  $J = 12.5, 4.4$  Hz, 2H);  $^{13}\text{C-NMR}$  (101 MHz;  $\text{CDCl}_3$ ):  $\delta$  193.9, 160.7, 154.6, 131.3, 79.7, 43.3, 39.1, 30.4, 28.4; **IR** (ATR neat): 3012, 2980, 2796, 1689, 1623, 1429, 1173; **LRMS** (ESI + APCI)  $m/z$   $[\text{M}+\text{H}]$  calcd. 238.2, found 238.2

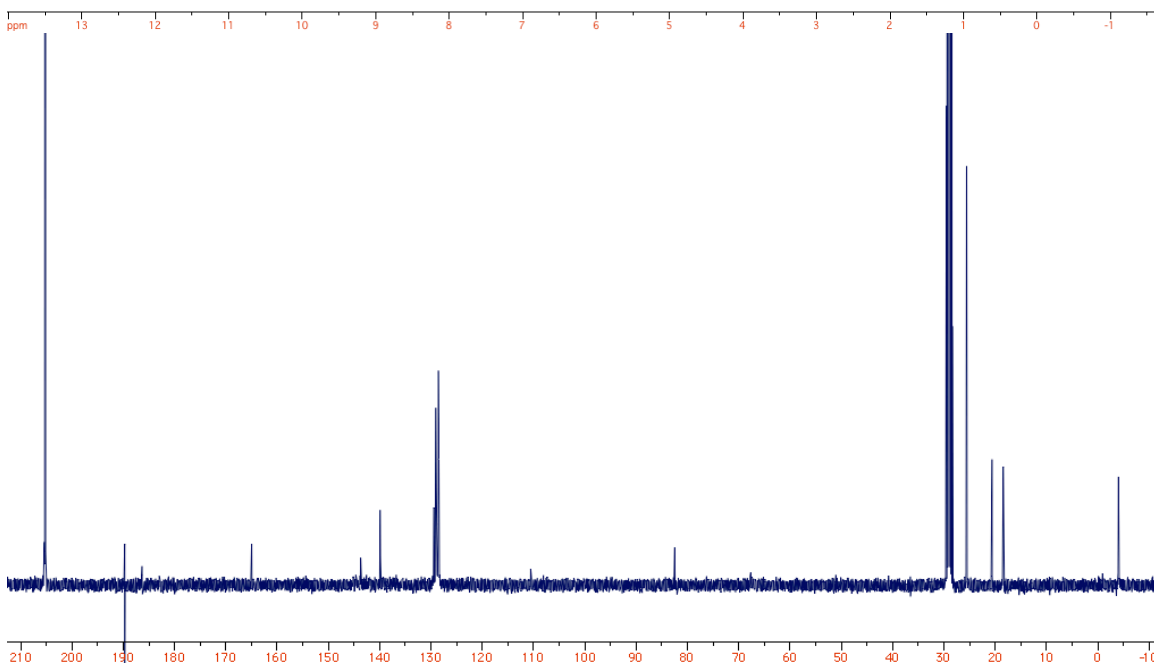
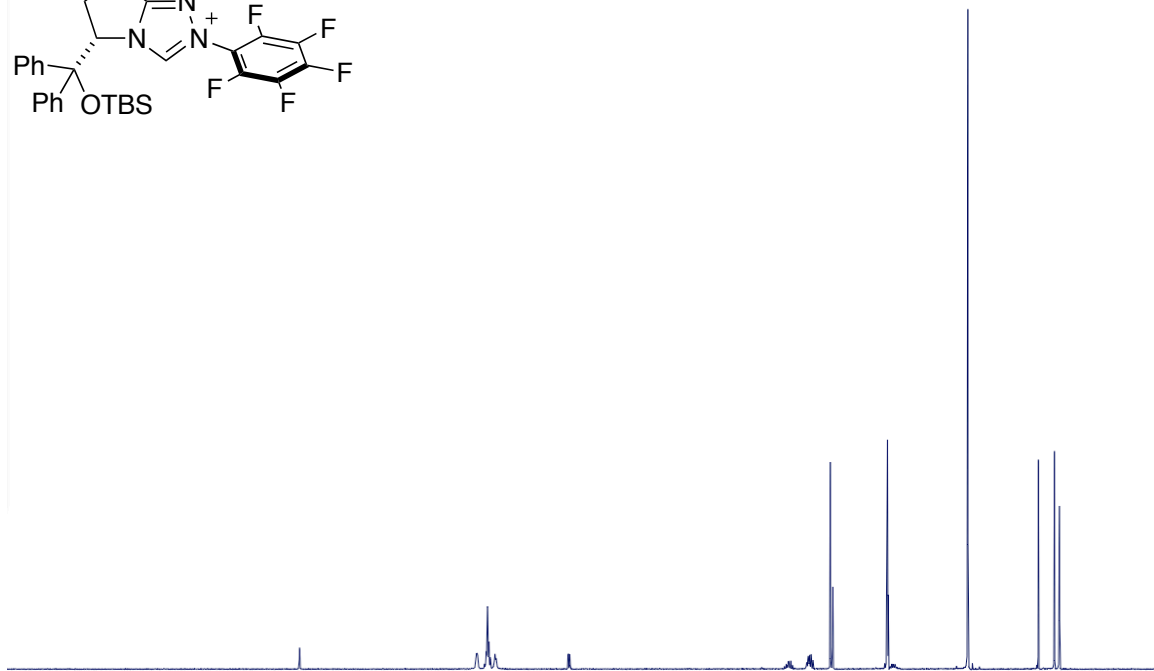
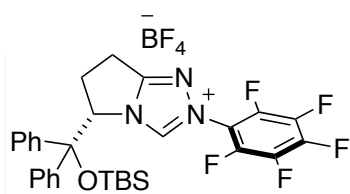


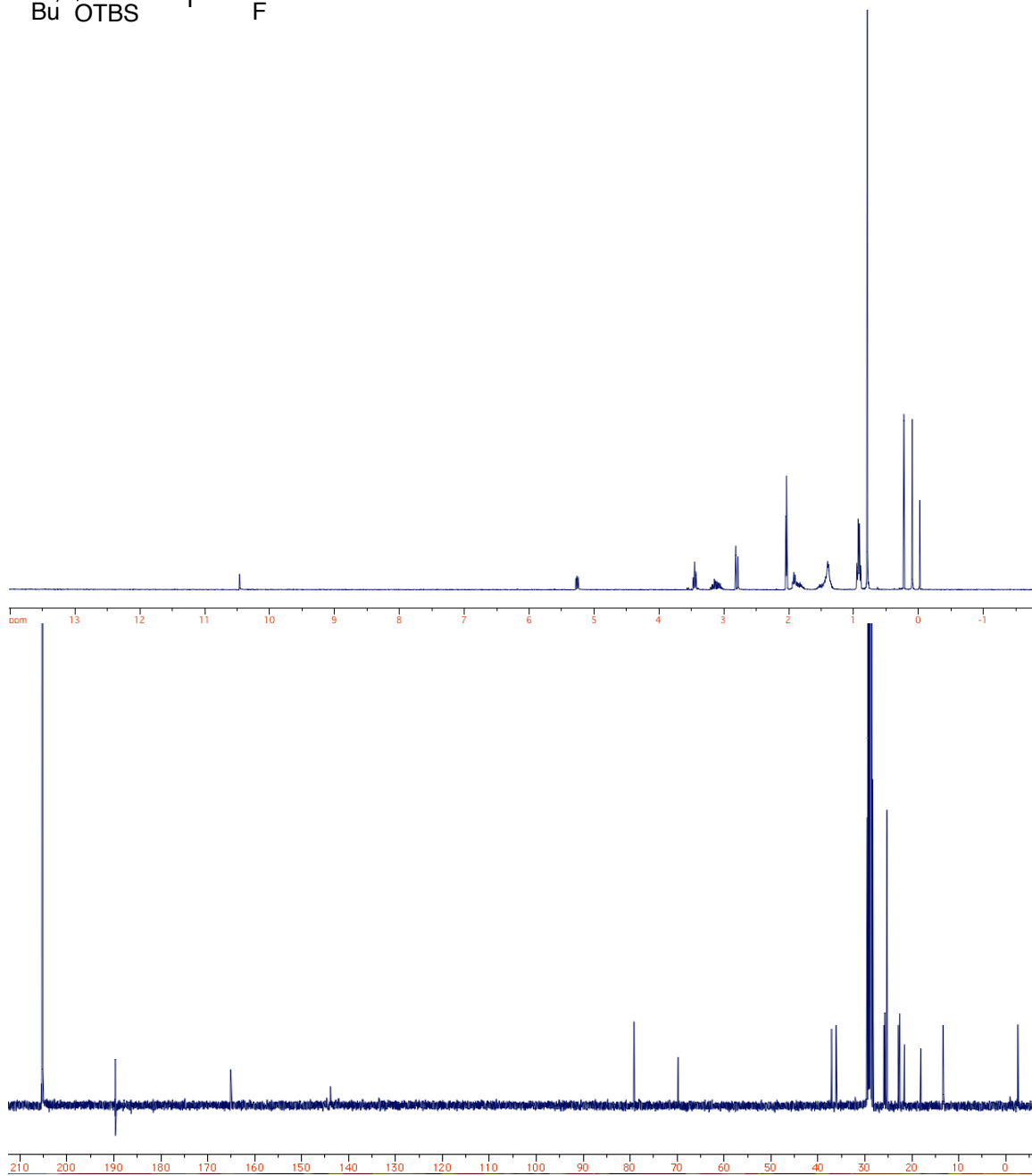
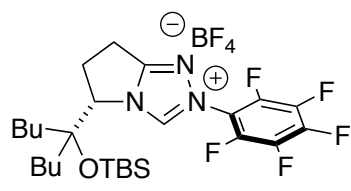
(*E*)-3-(2,2-diphenylcyclopropyl)acrylaldehyde (**1s**): White Amorphous Solid  $R_f = 0.25$  (8:2 hexanes:ether)  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  9.26 (d,  $J = 7.9$  Hz, 1H), 7.36-7.18 (m, 10H), 6.30 (dd,  $J = 15.4, 7.9$  Hz, 1H), 6.05 (dd,  $J = 15.4, 10.4$  Hz, 1H), 2.54 (ddd,  $J = 10.3, 8.5, 5.5$  Hz, 1H), 1.93 (dd,  $J = 8.5, 5.1$  Hz, 1H), 1.83 (t,  $J = 5.3$  Hz, 1H).  $^{13}\text{C-NMR}$  (101 MHz;  $\text{CDCl}_3$ ):  $\delta$  193.0, 159.8, 144.9, 140.2, 131.7, 130.4, 128.7, 128.5, 127.4, 127.3, 126.6, 30.6, 24.1 **IR**: 3056, 3025, 1681, 1629, 1494, 1446, 1177; **LRMS** (ESI + APCI)  $m/z$   $[\text{M}+\text{H}]$  calcd. 249.1, found 249.1



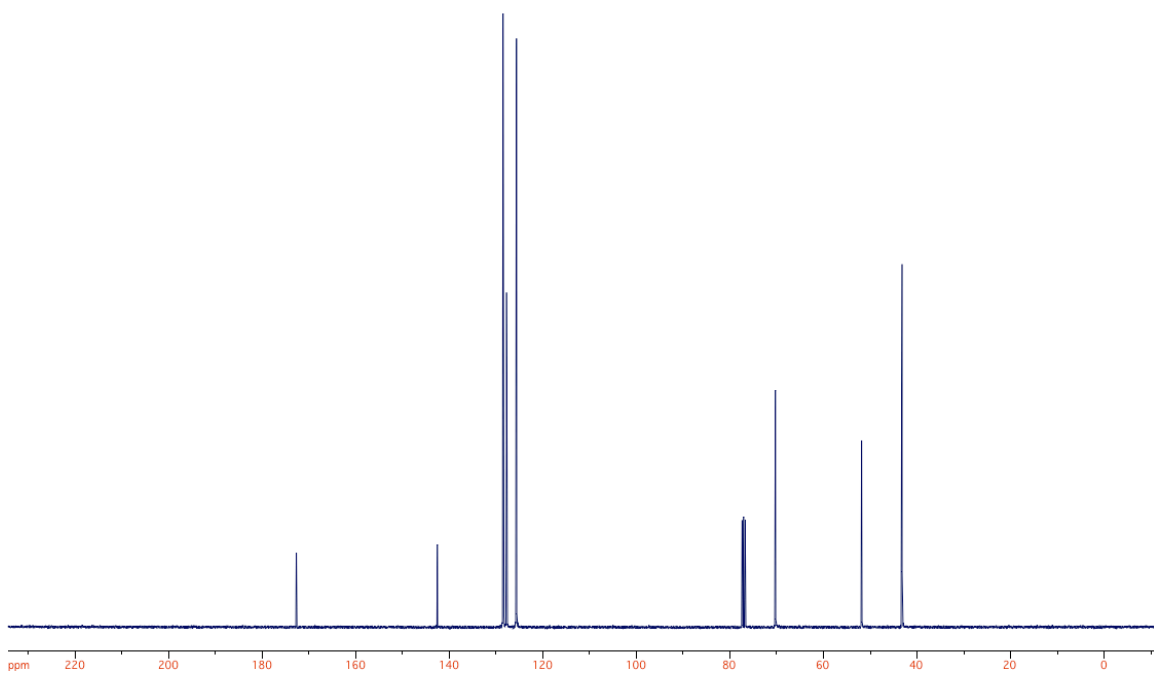
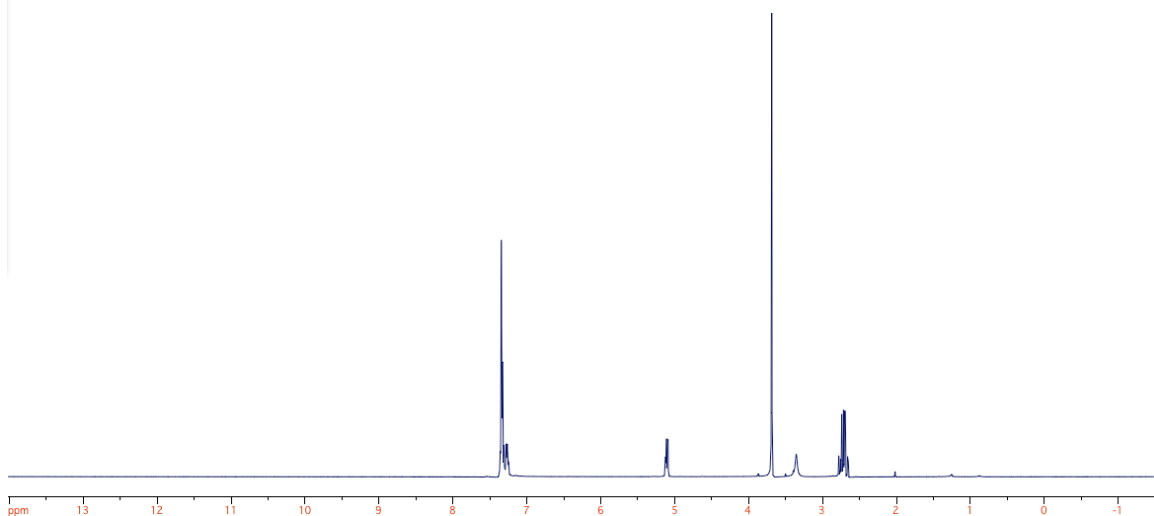
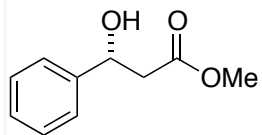
(*Z*)-1,2-bis(4-cyanophenyl)diazene oxide (**S1**): Off White Amorphous Solid.  $R_f = 0.34$  (1:1 hexanes:ether);  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  8.46 (d,  $J = 8.7$  Hz, 1H), 8.23 (d,  $J = 8.6$  Hz, 1H), 7.87 (d,  $J = 8.7$  Hz, 1H), 7.79 (d,  $J = 8.6$  Hz, 1H).  $^{13}\text{C-NMR}$  (101 MHz;  $\text{cdcl}_3$ ):  $\delta$  133.1, 132.8, 126.0, 123.4; **IR** (ATR Neat): 3104, 2224, 1600, 1490, 1459, 1344, 1311, 1291, 842. **LRMS** (ESI + APCI)  $m/z$   $[\text{M}+\text{H}]$  calcd 249.1, found 249.1 Spectra matched that of the previously reported compound.<sup>3</sup>

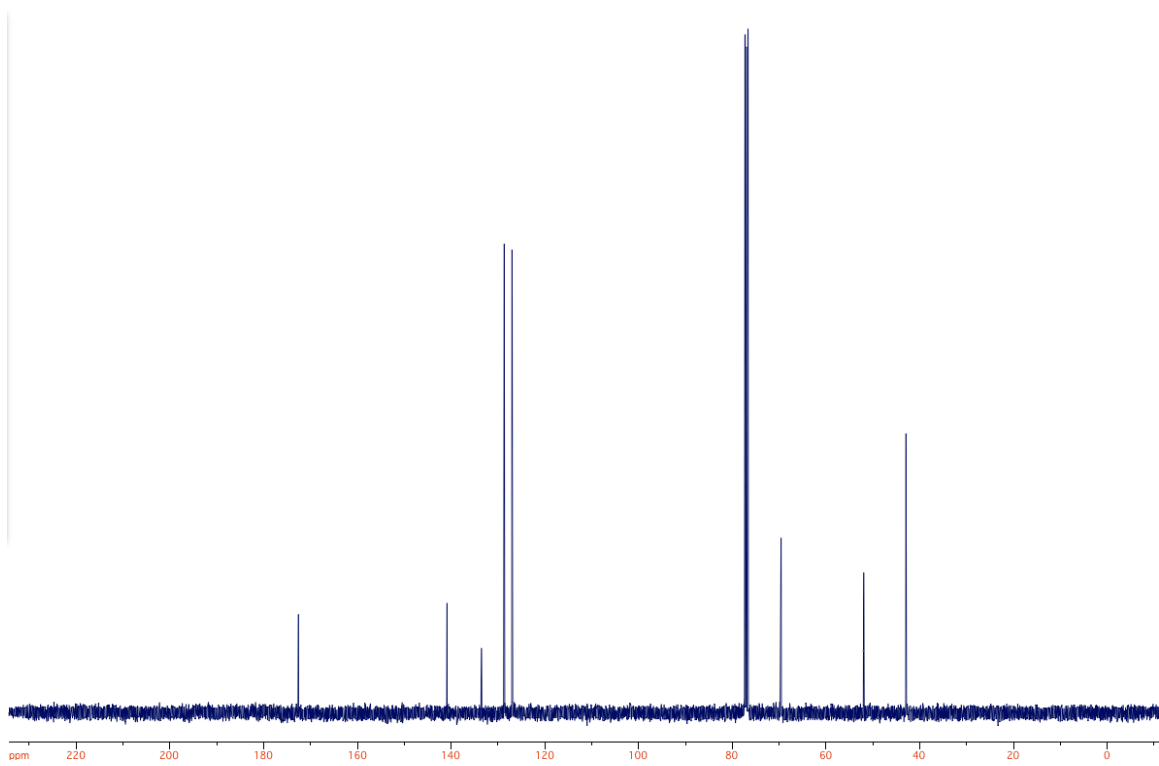
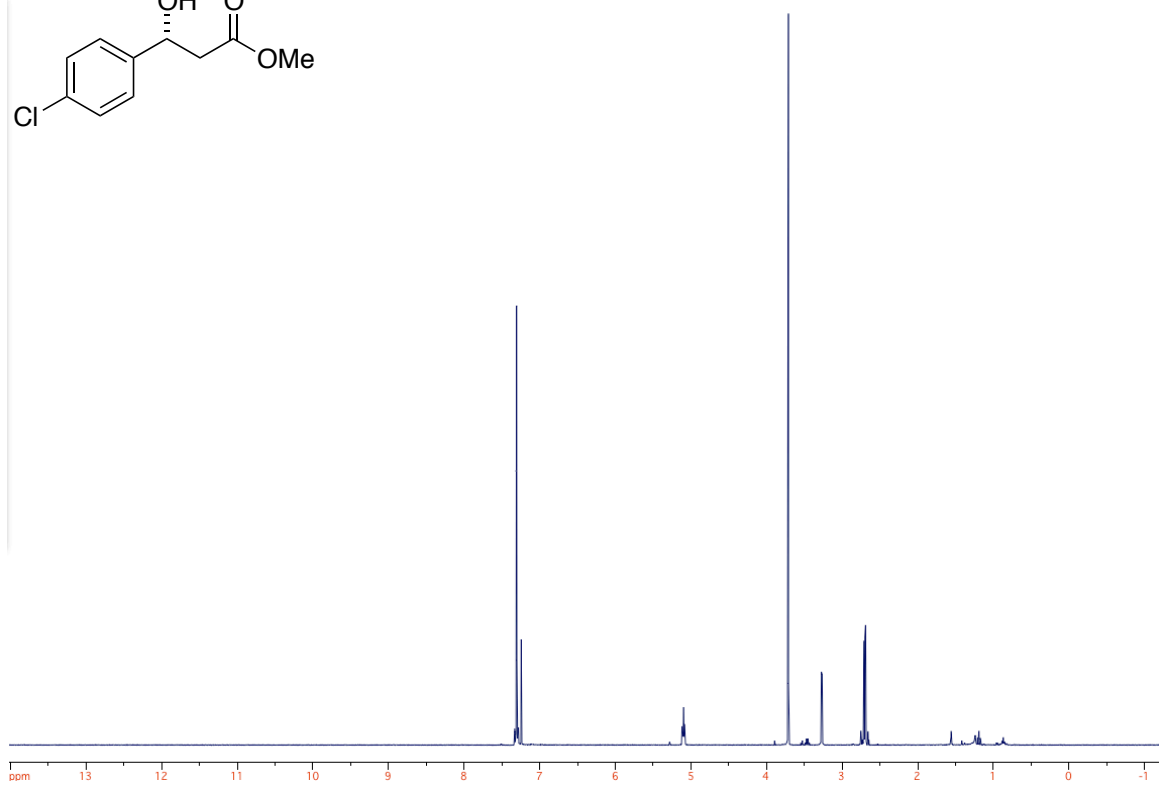
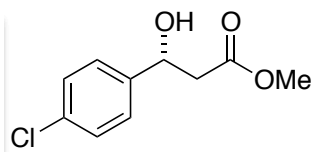
Supporting Information





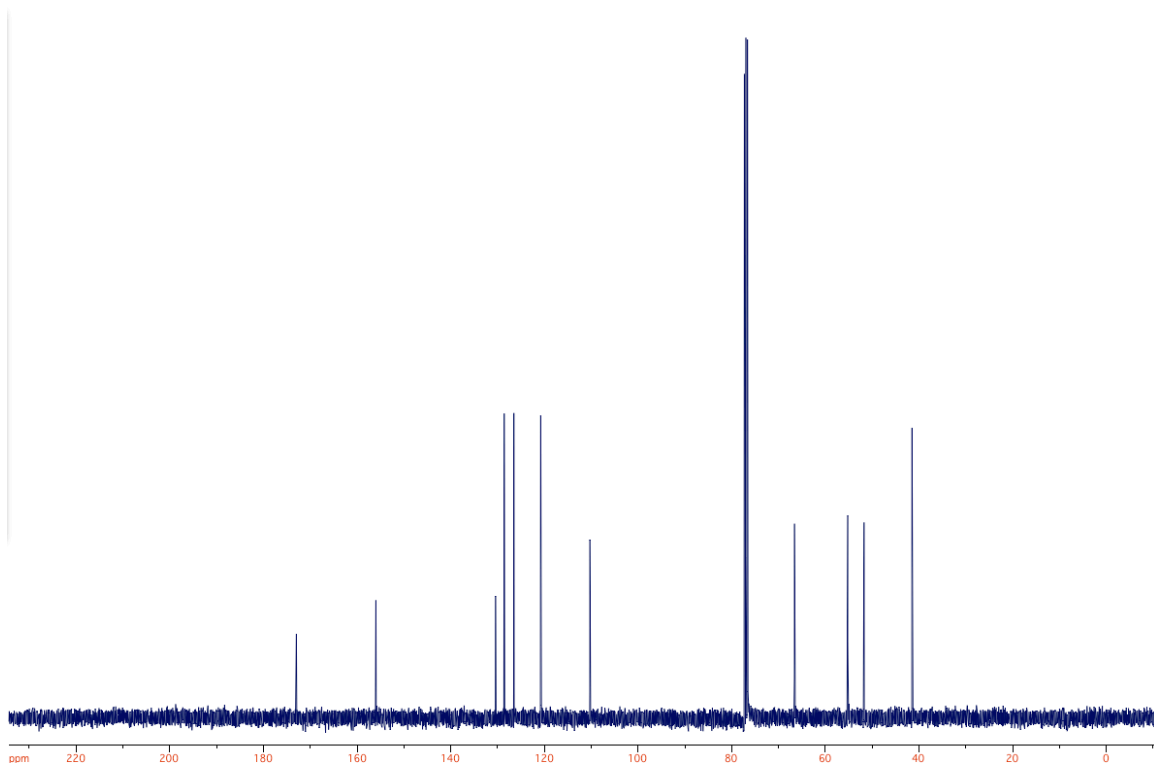
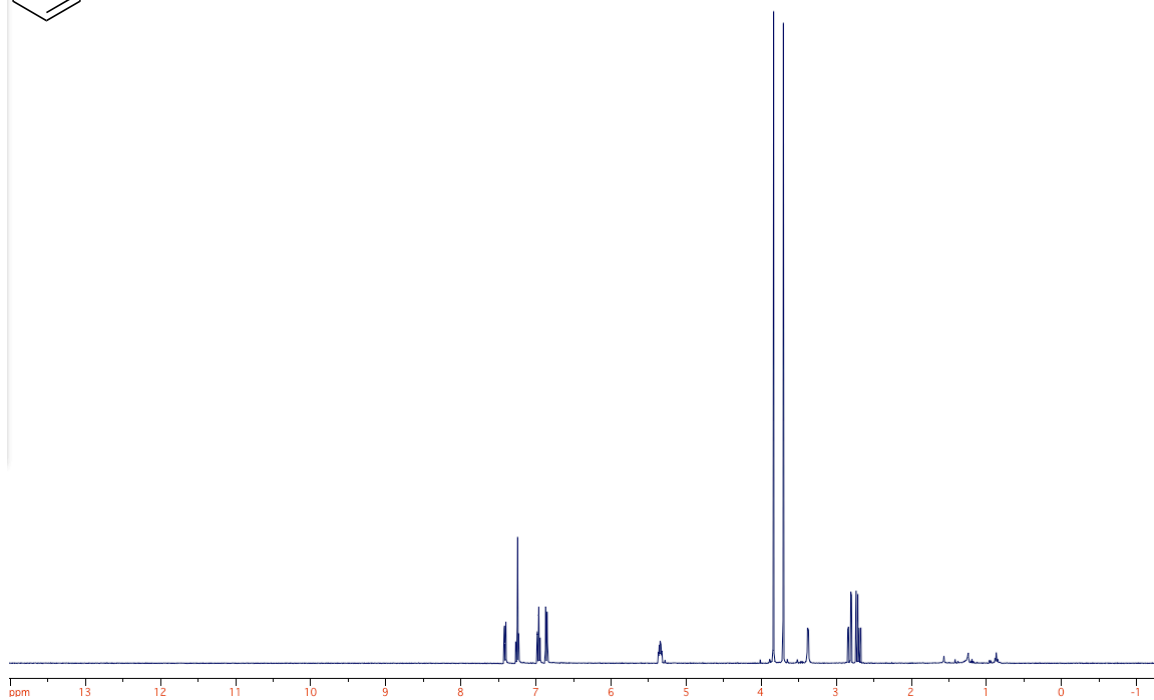
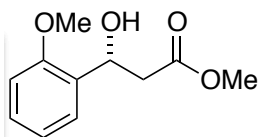
Supporting Information

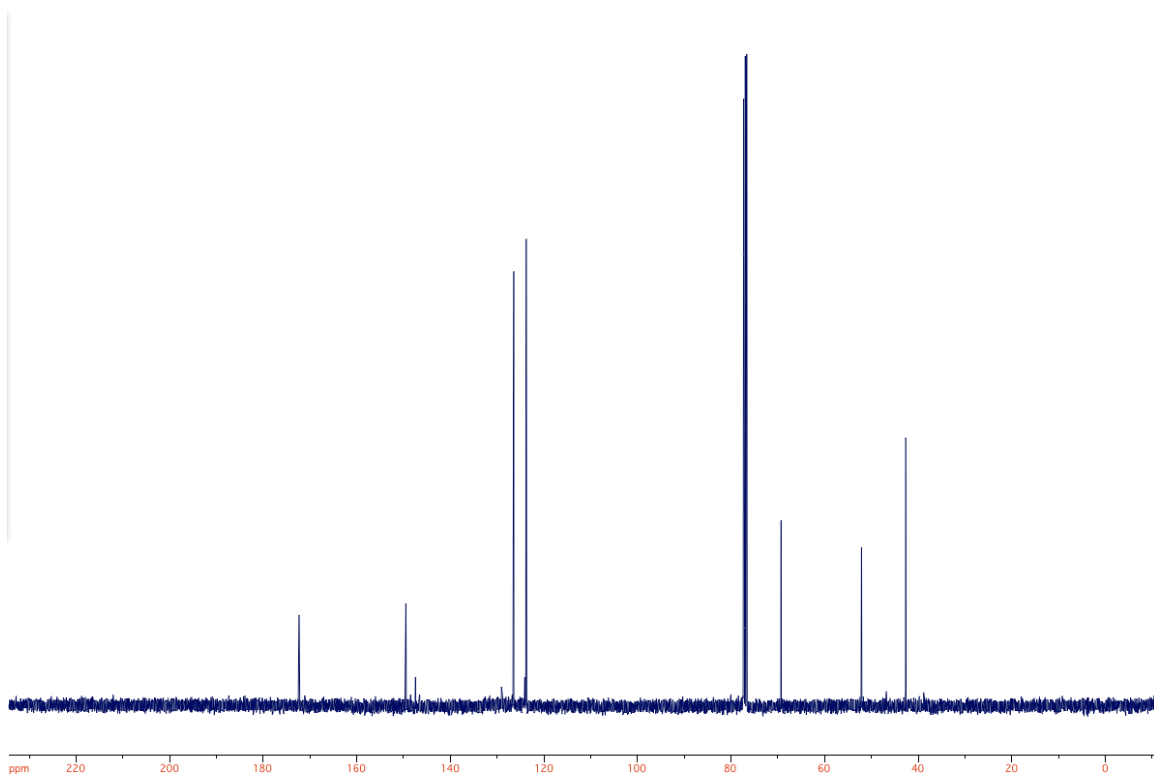
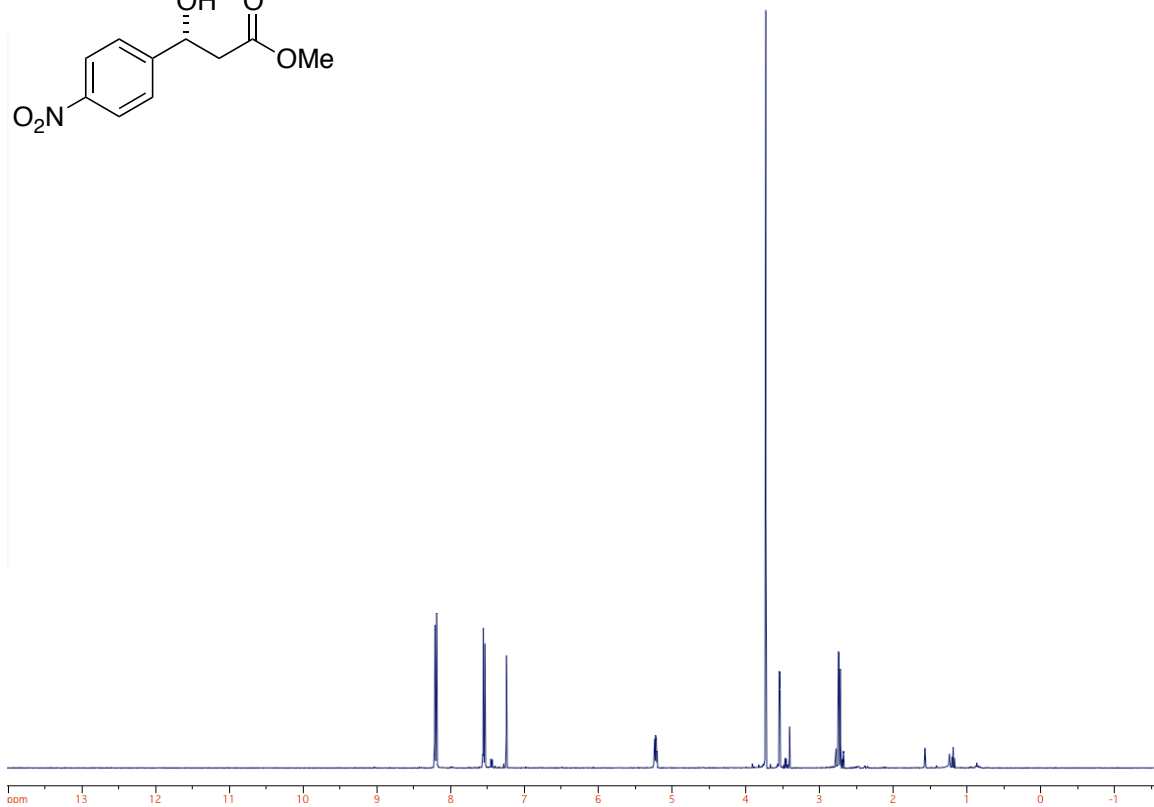
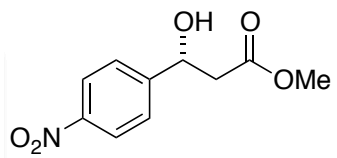




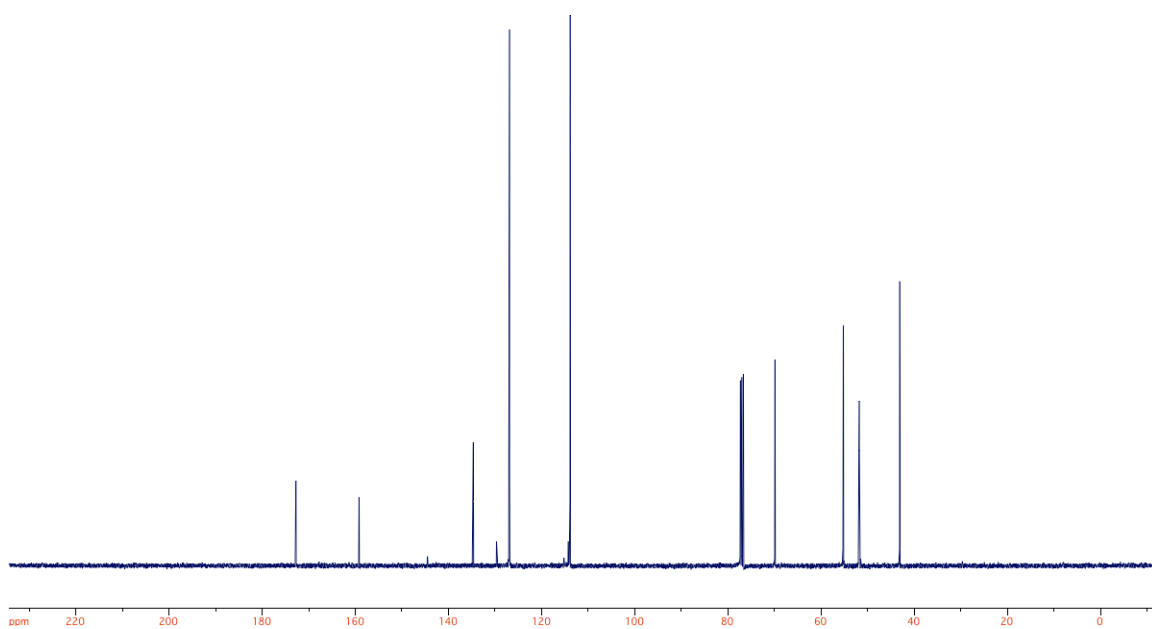
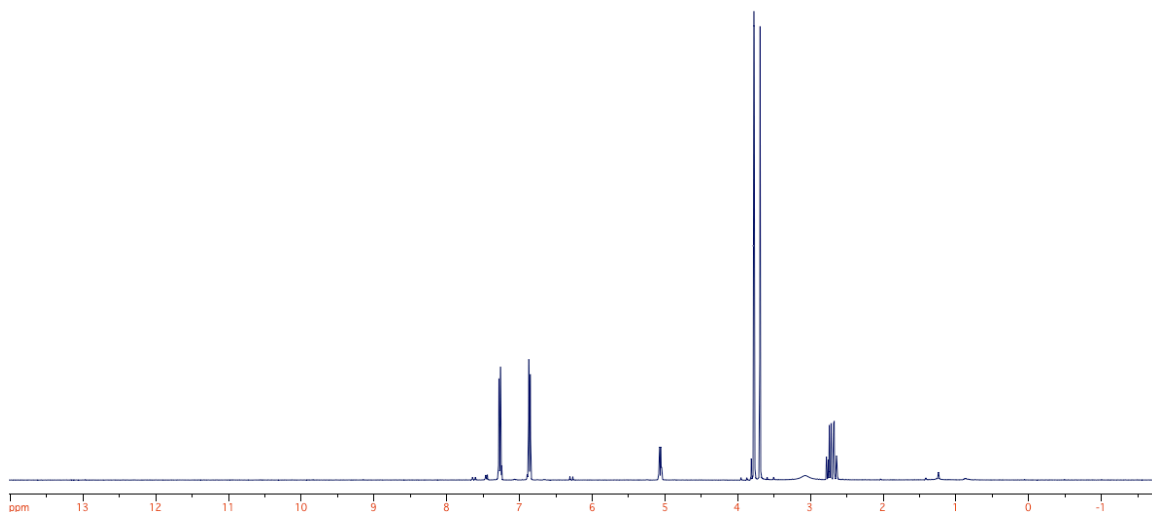
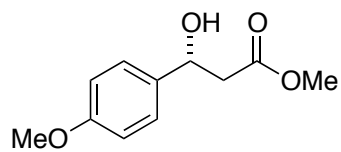


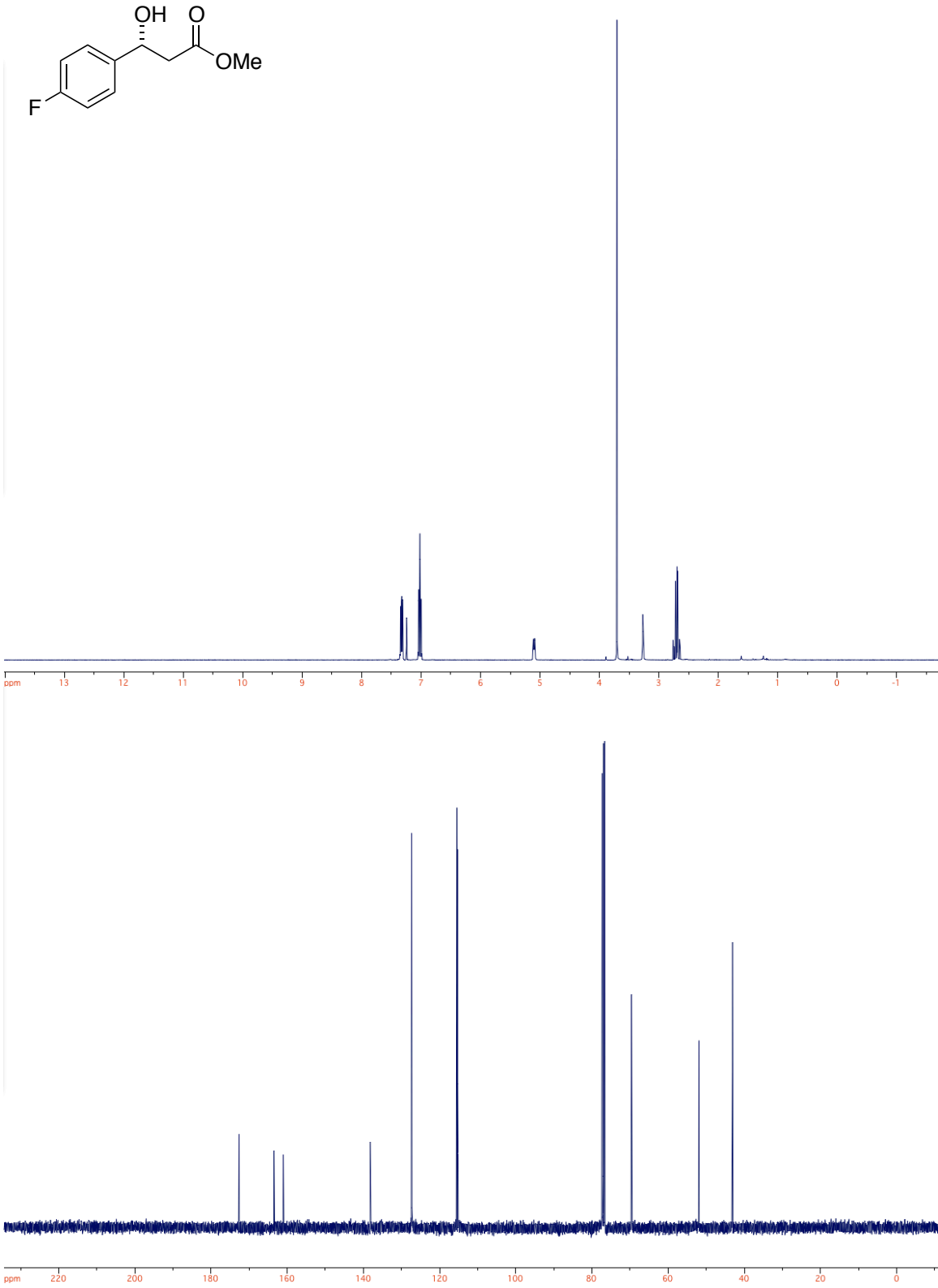
Supporting Information



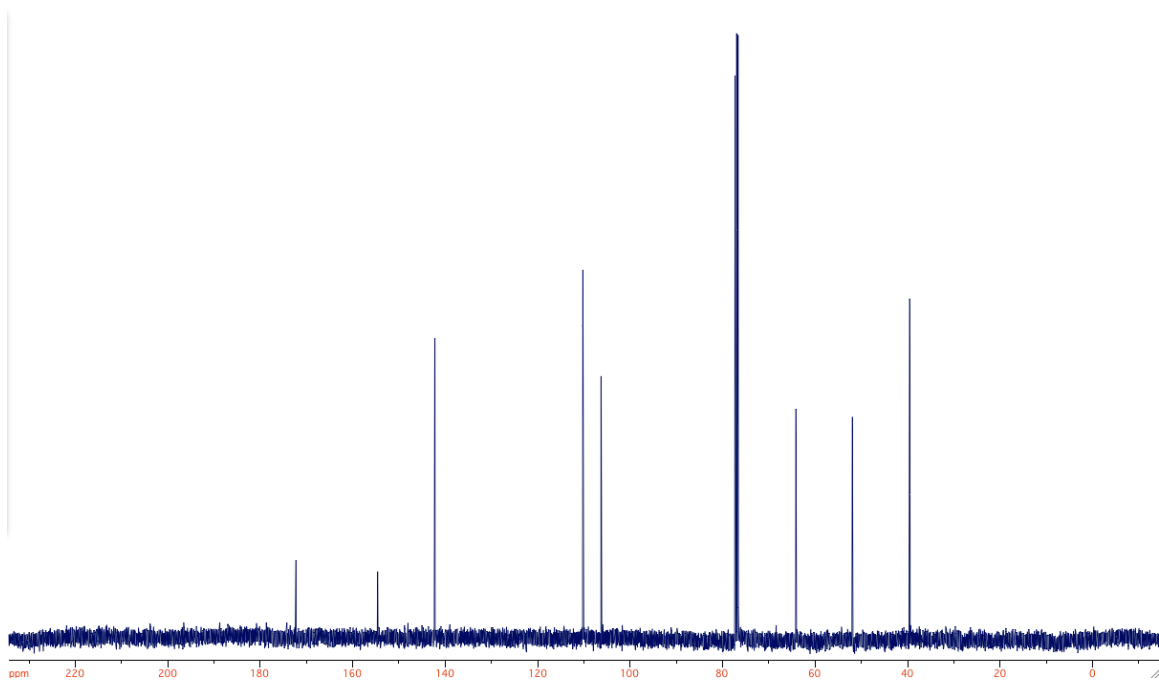
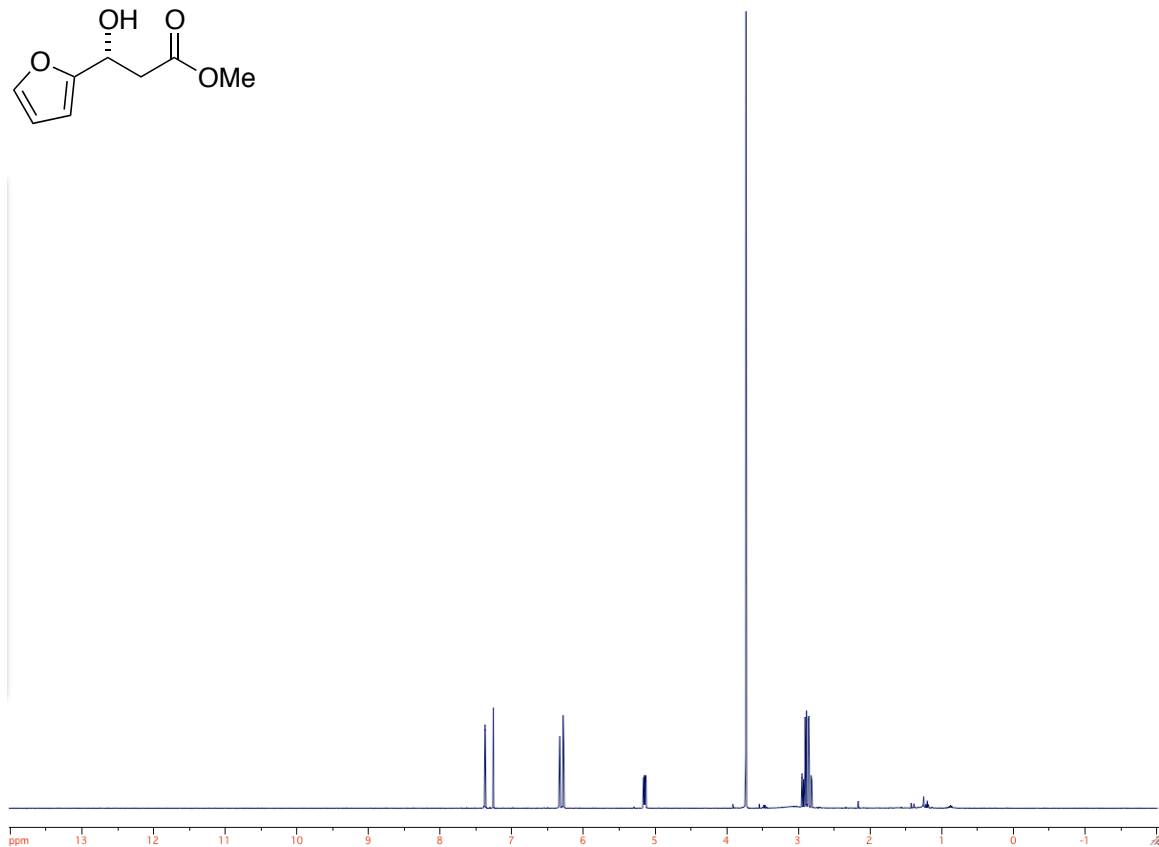
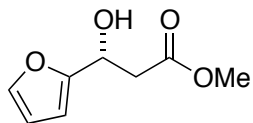


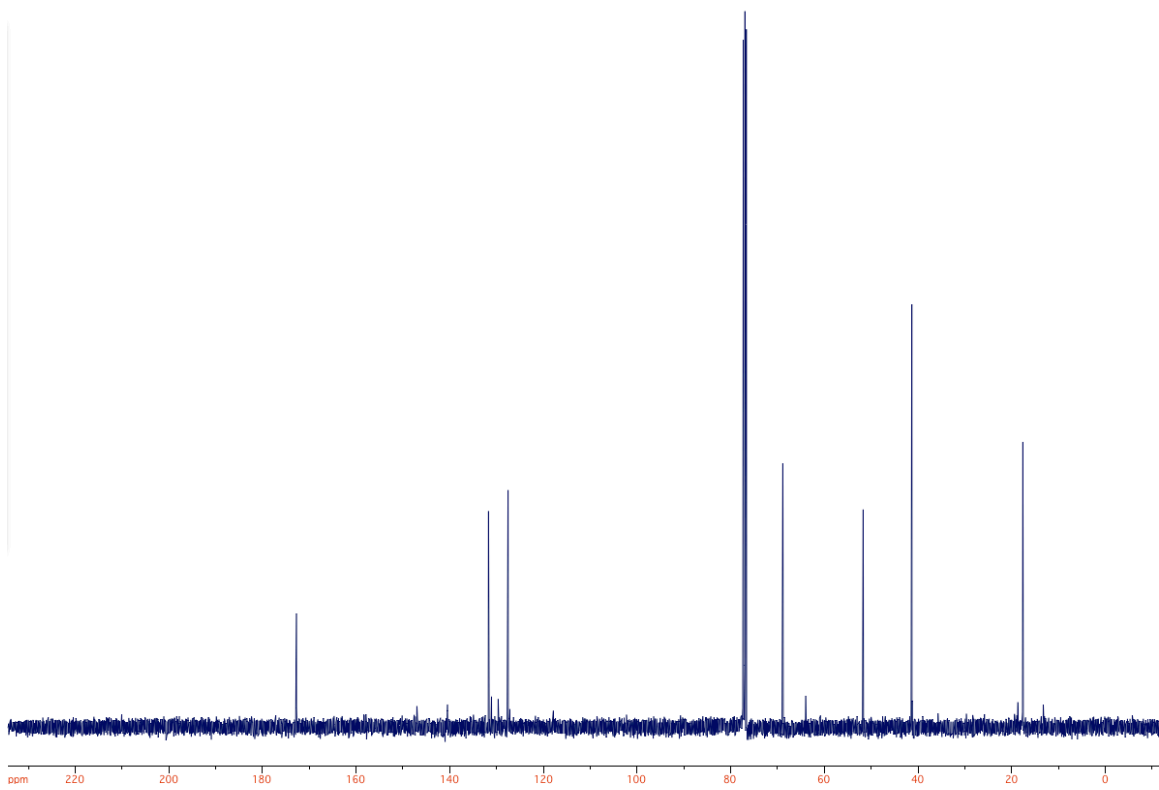
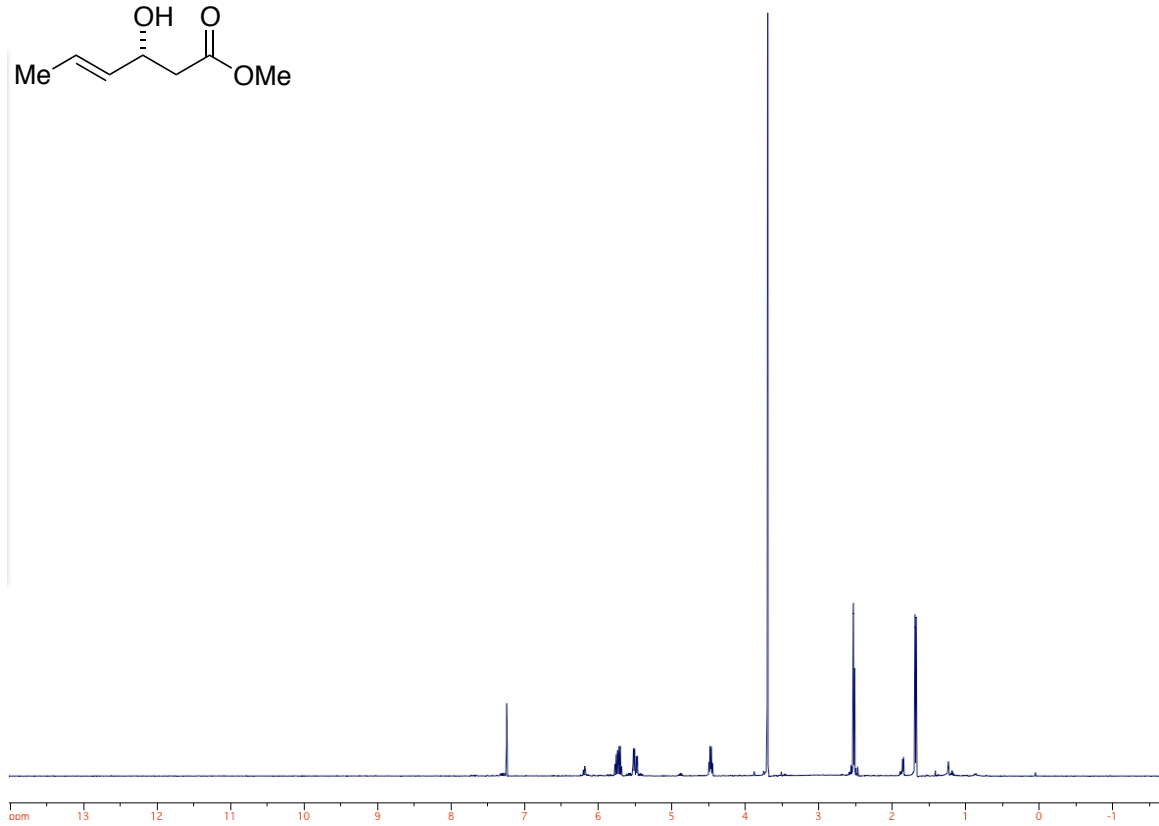
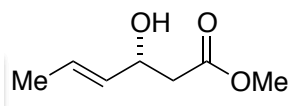
Supporting Information



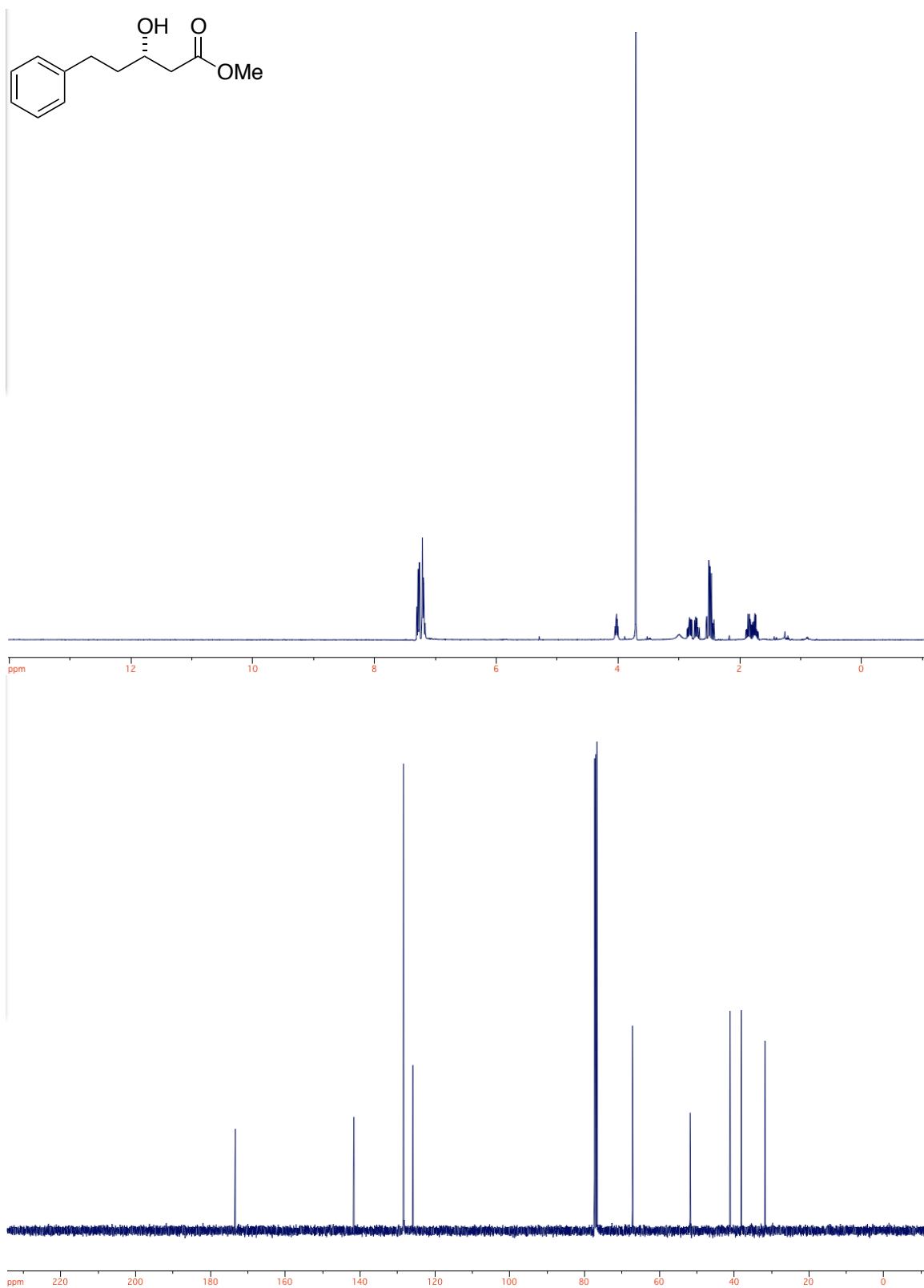


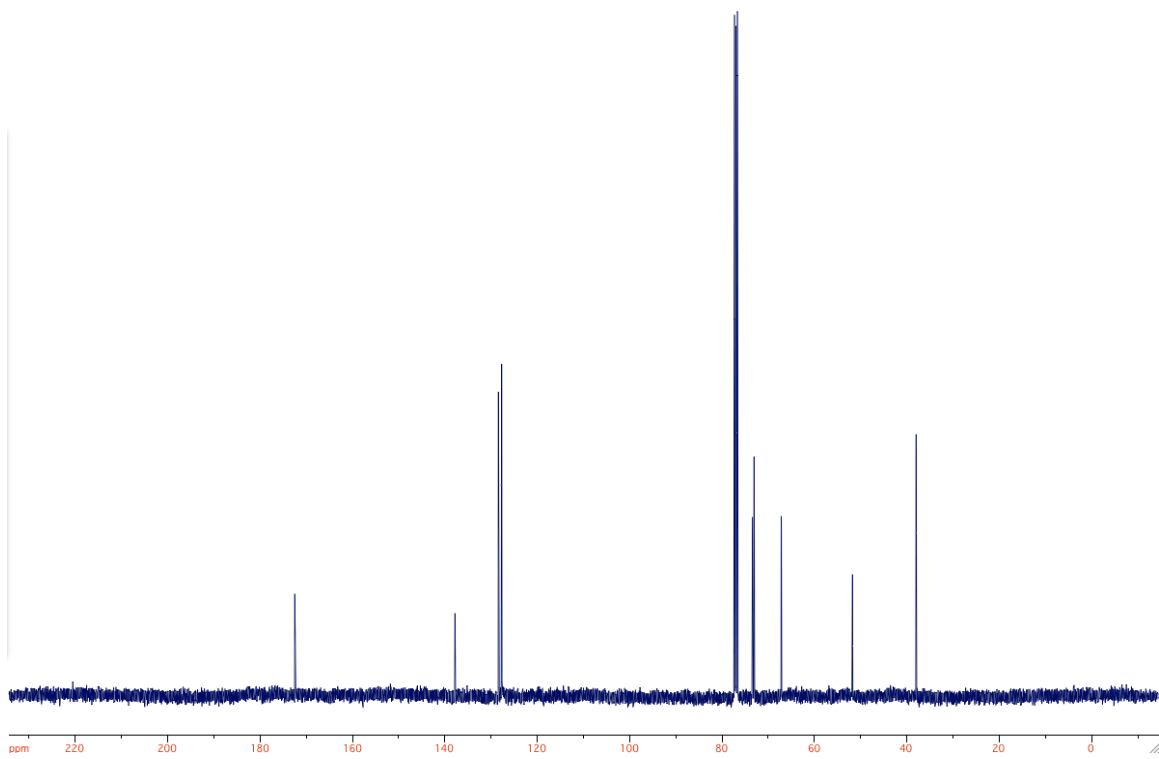
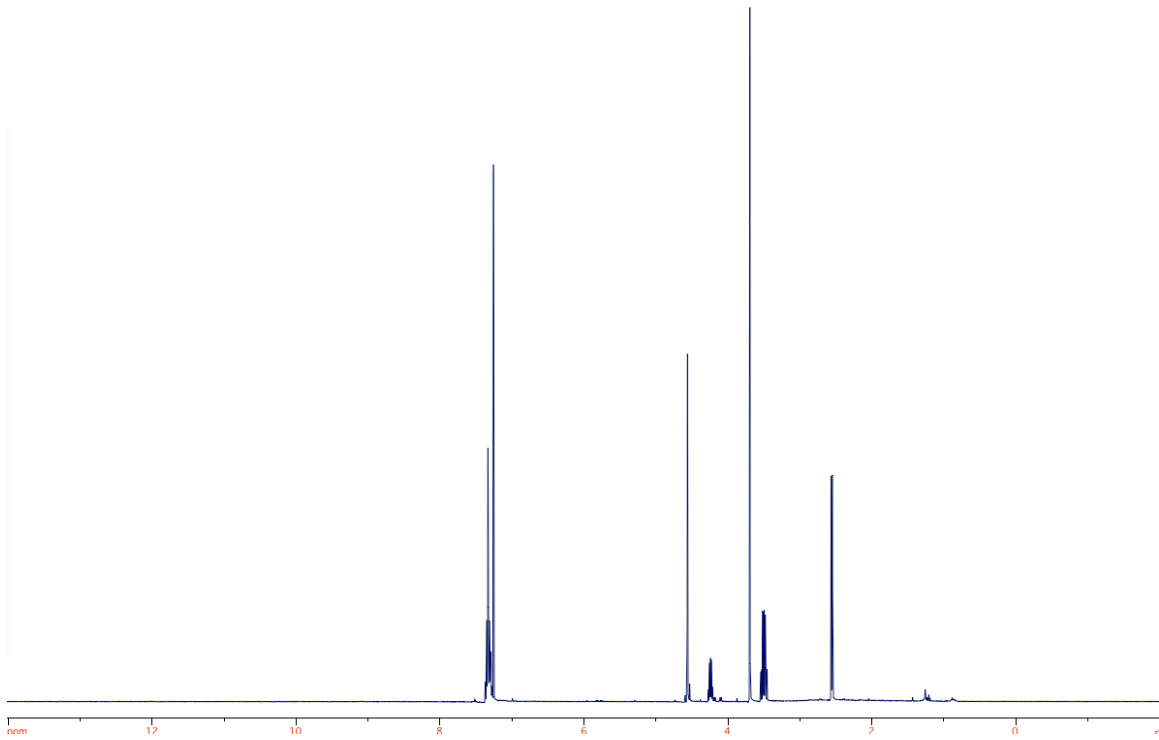
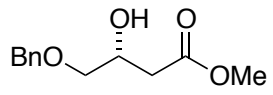
Supporting Information





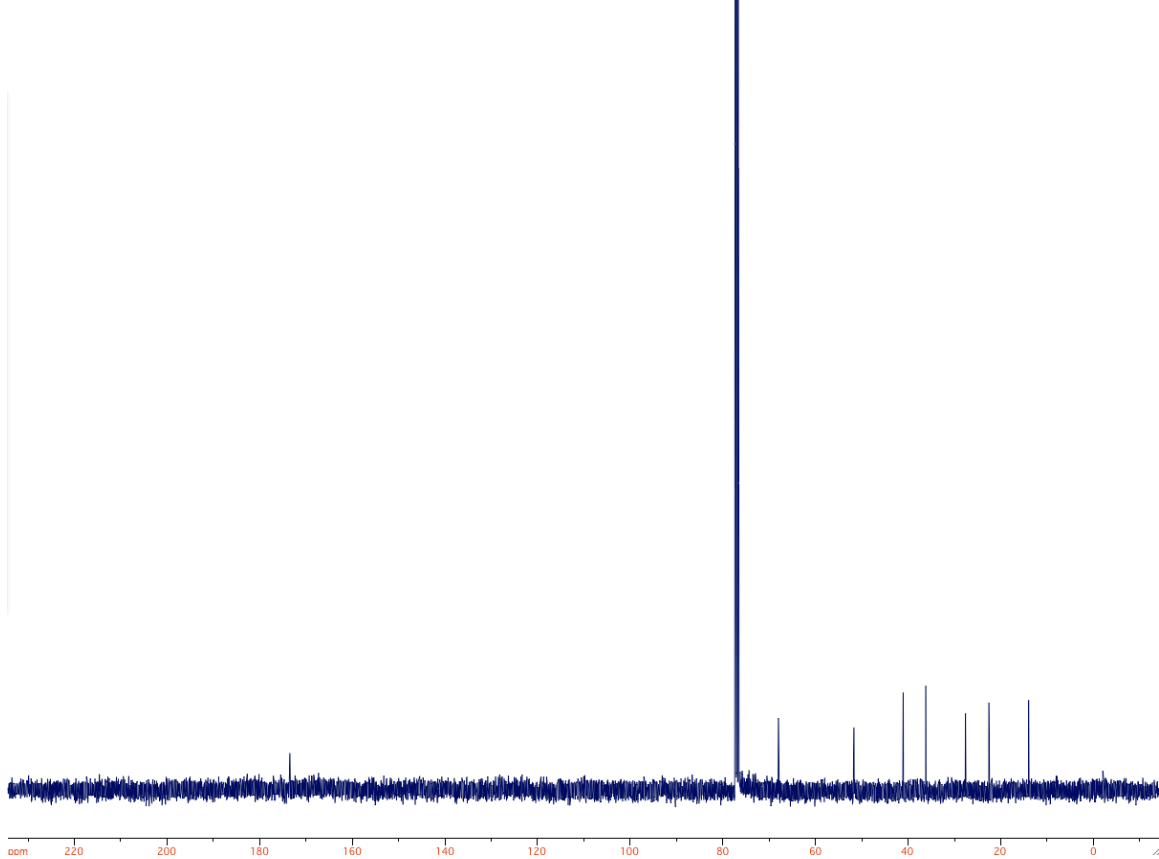
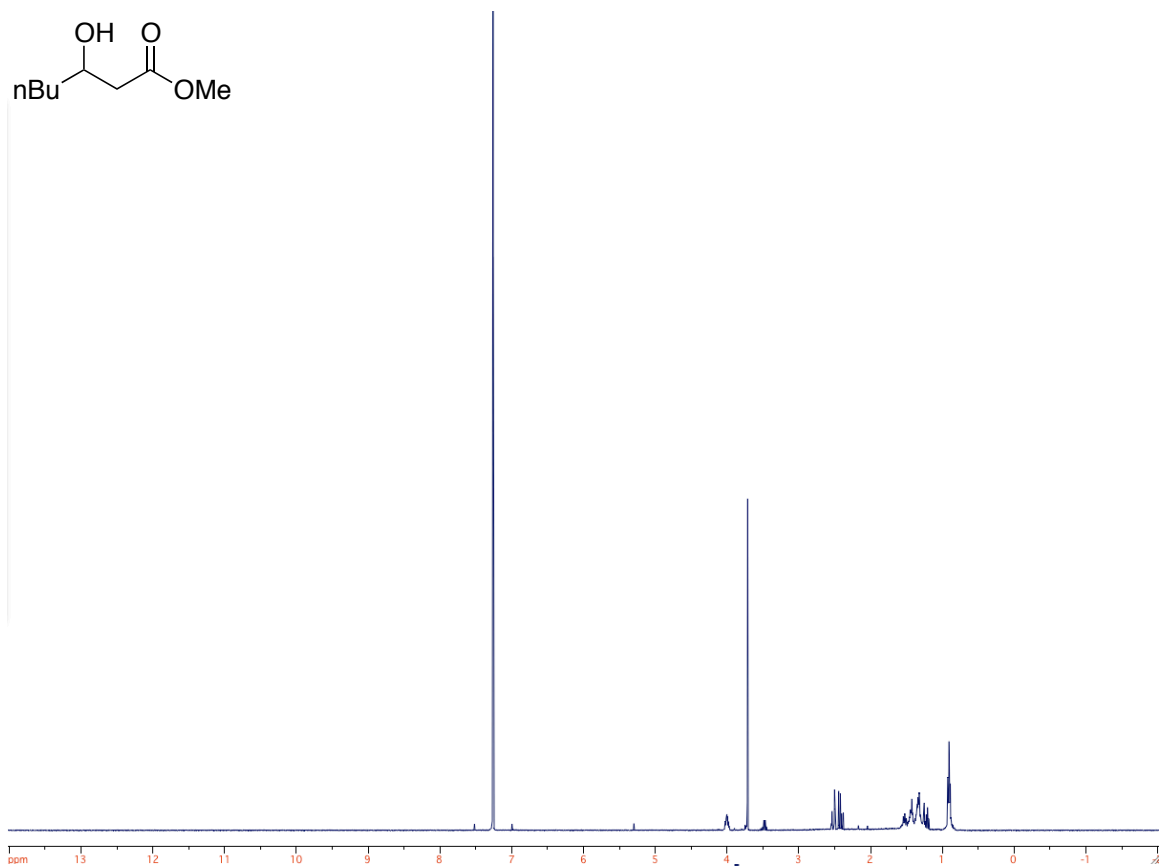
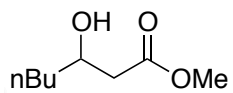
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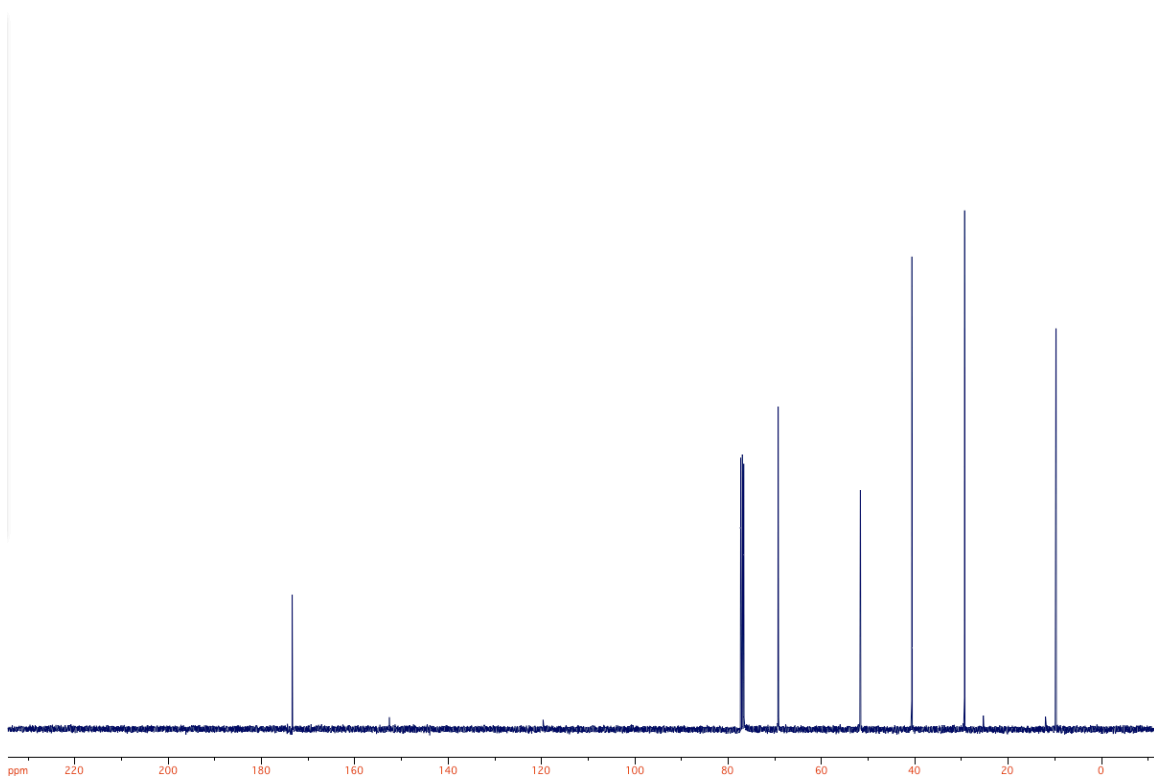
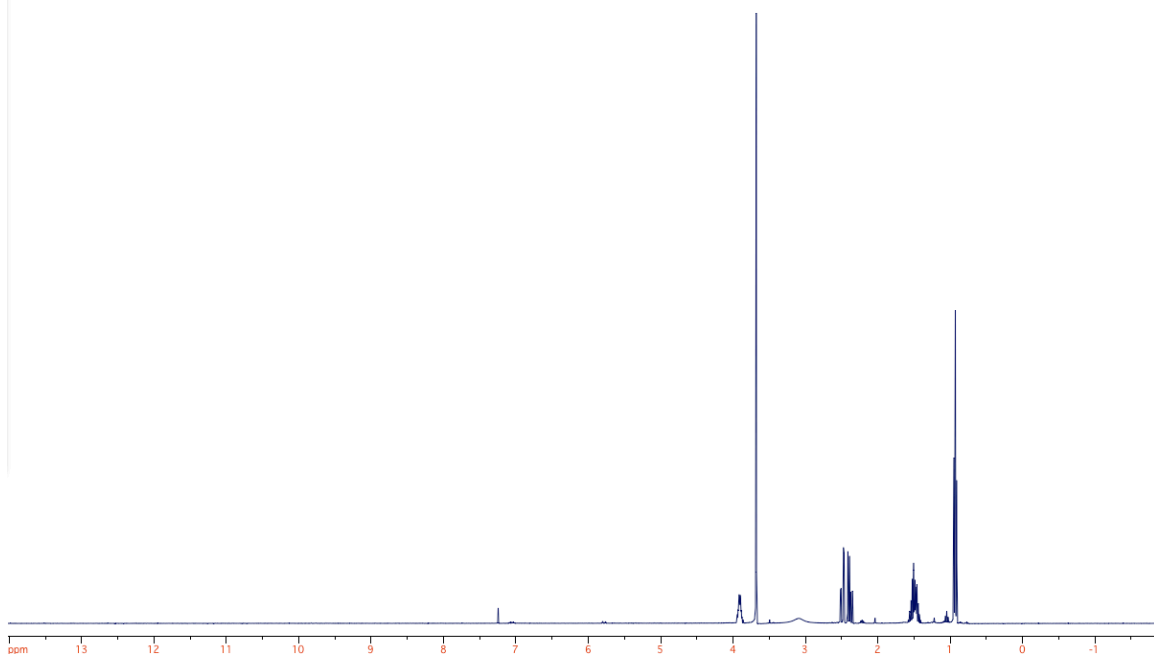
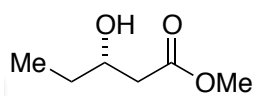




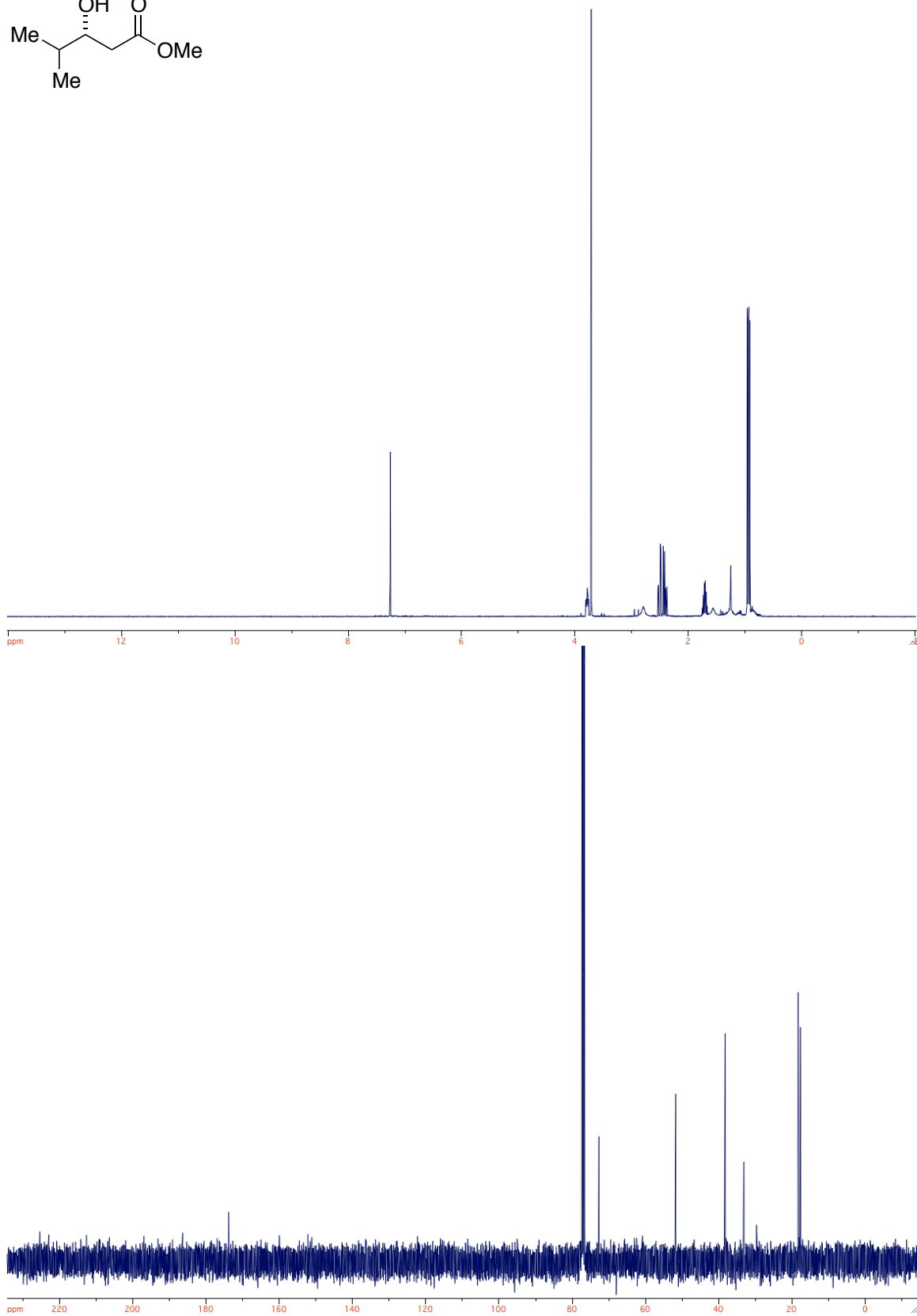
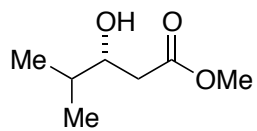


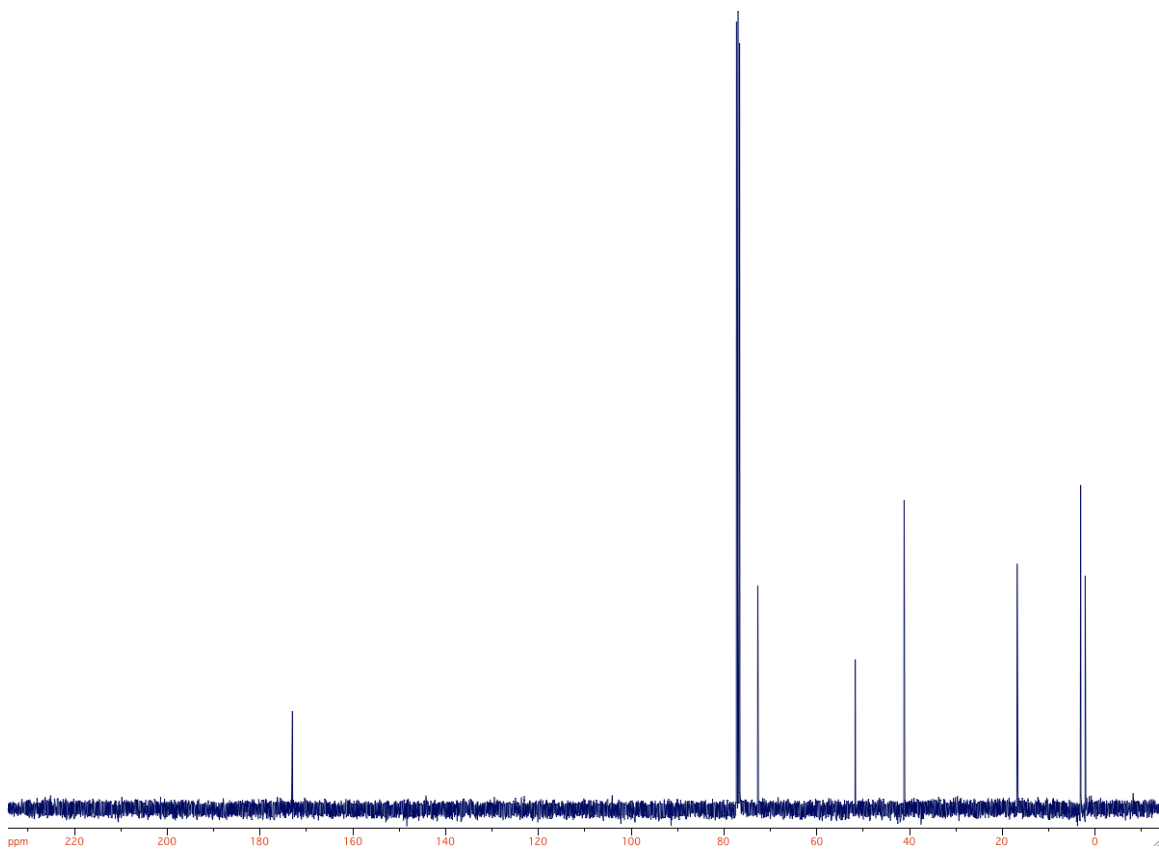
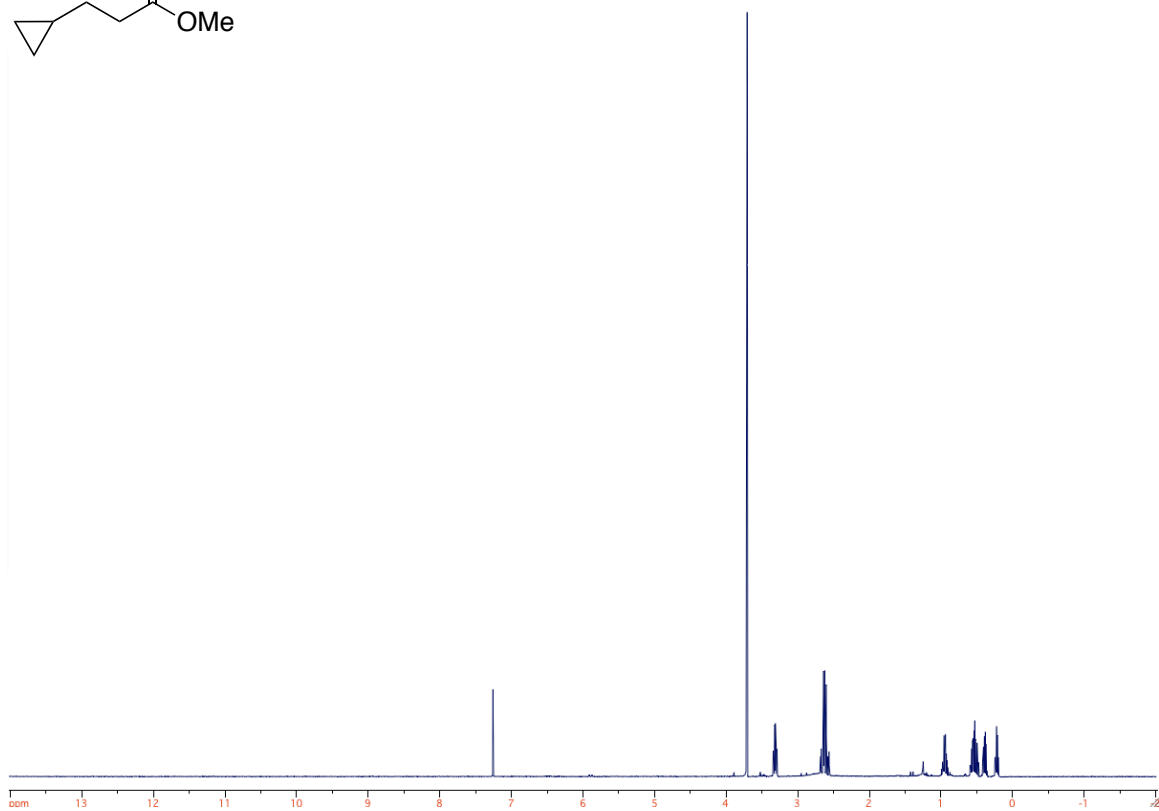
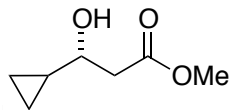
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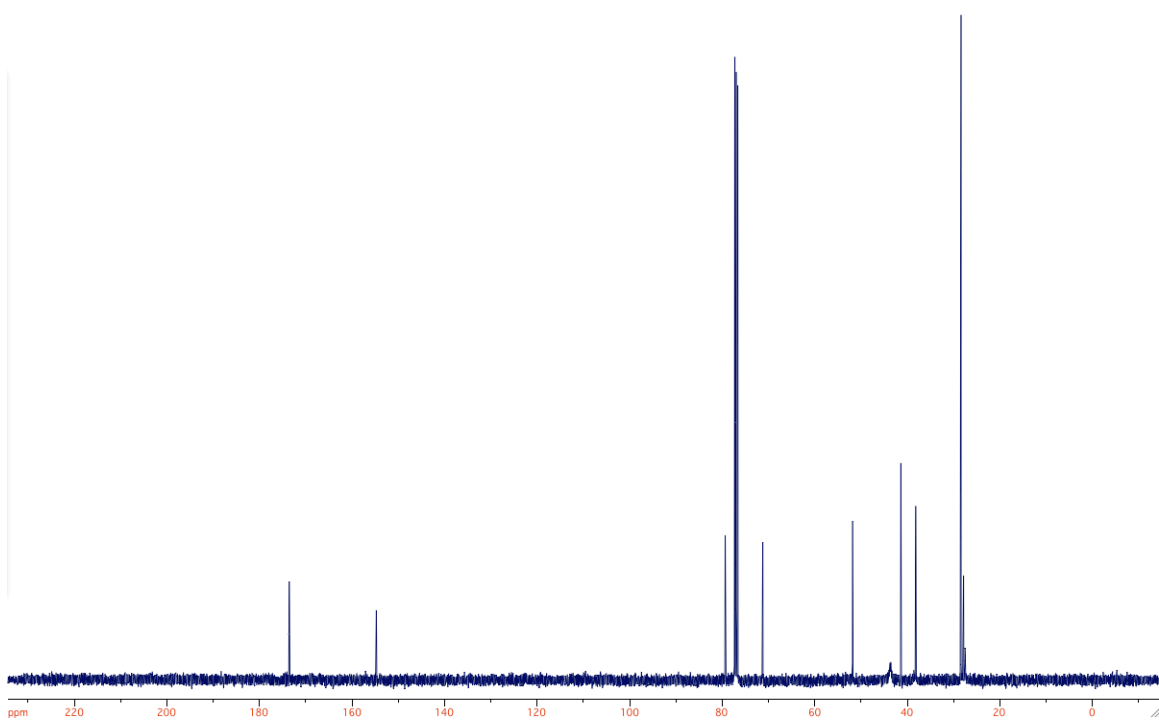
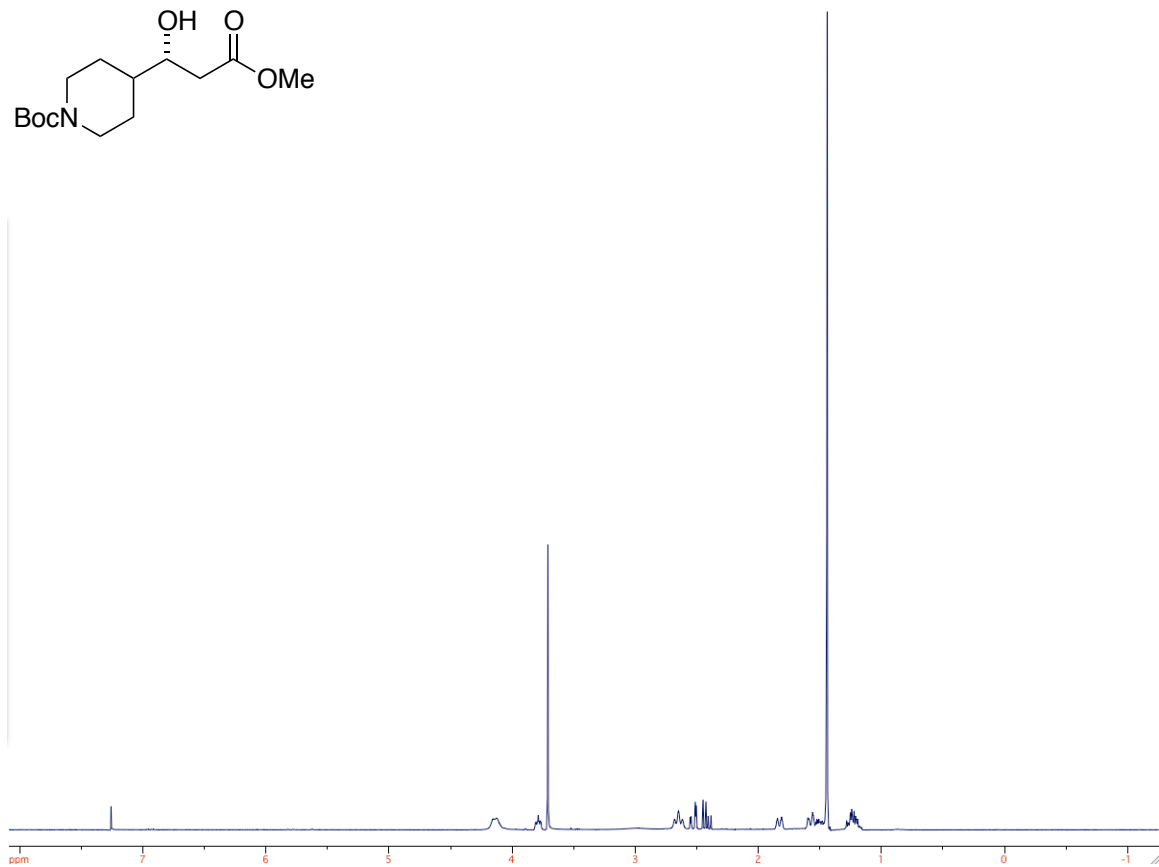
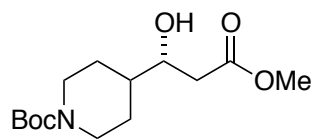


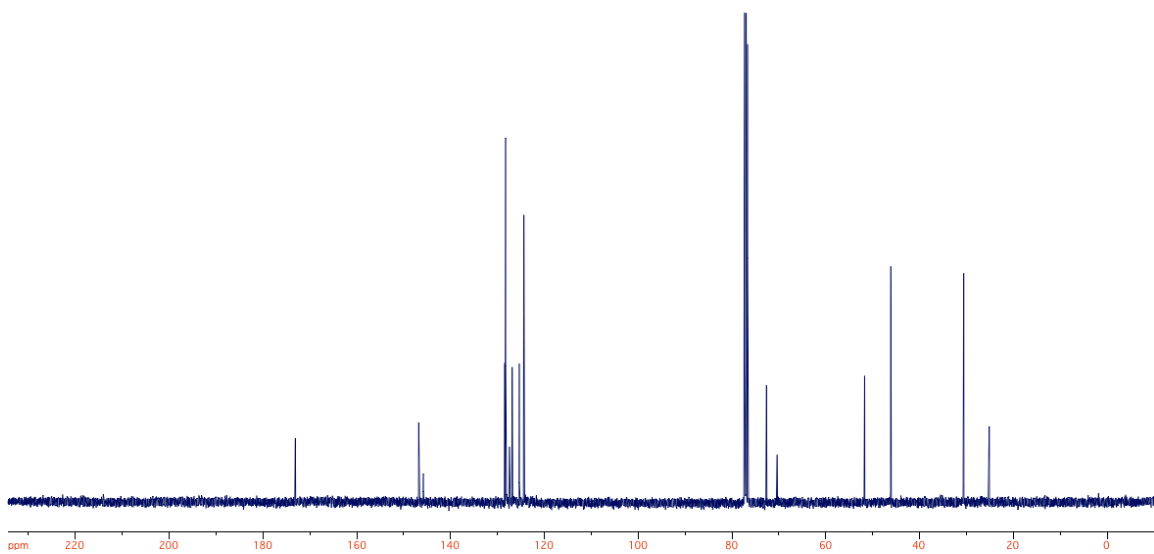
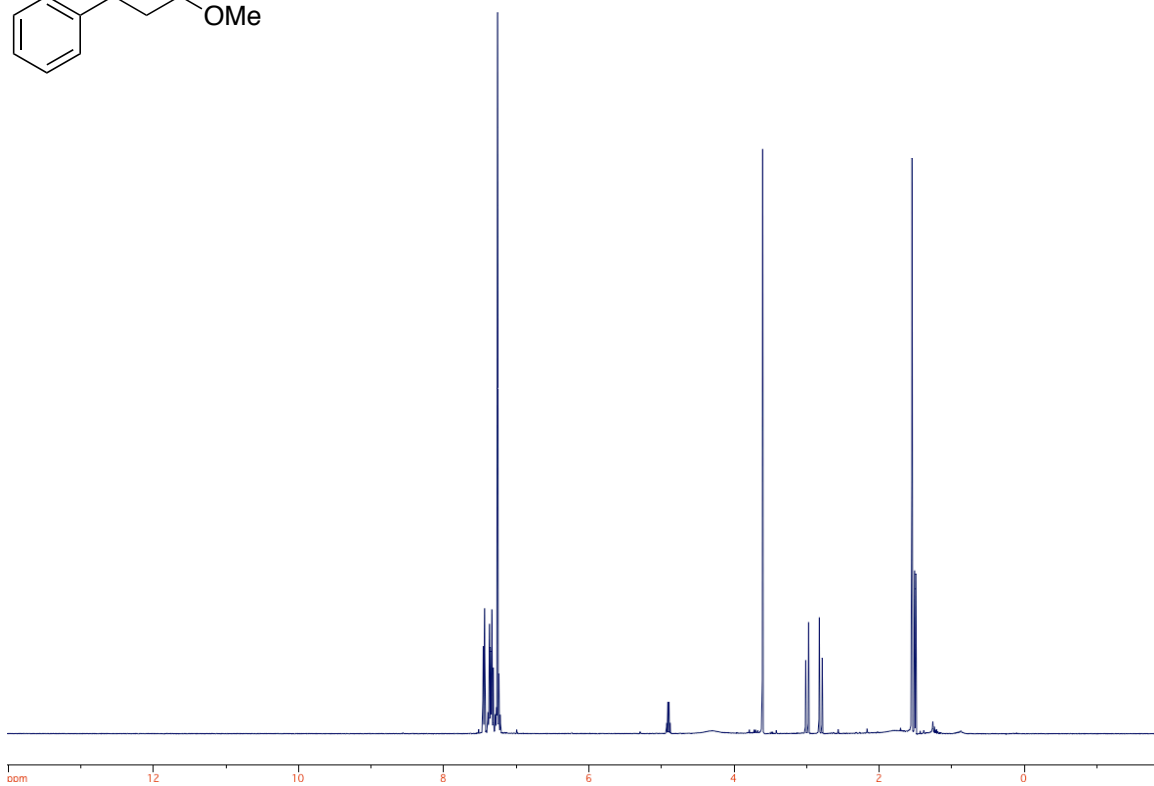
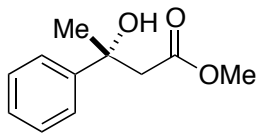
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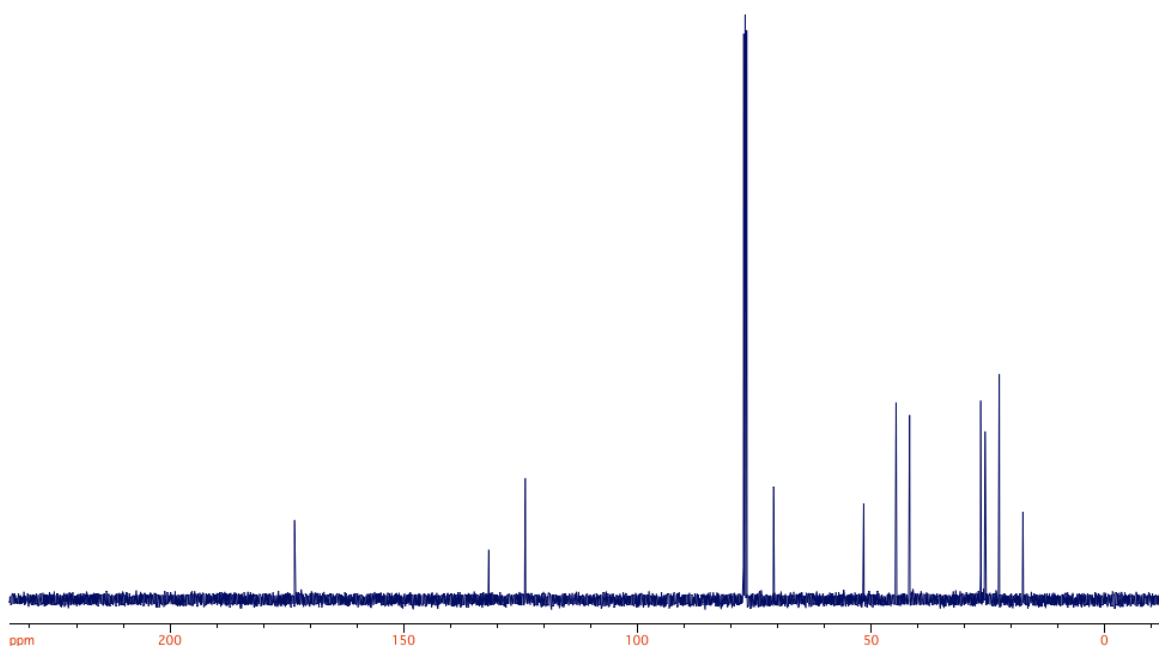
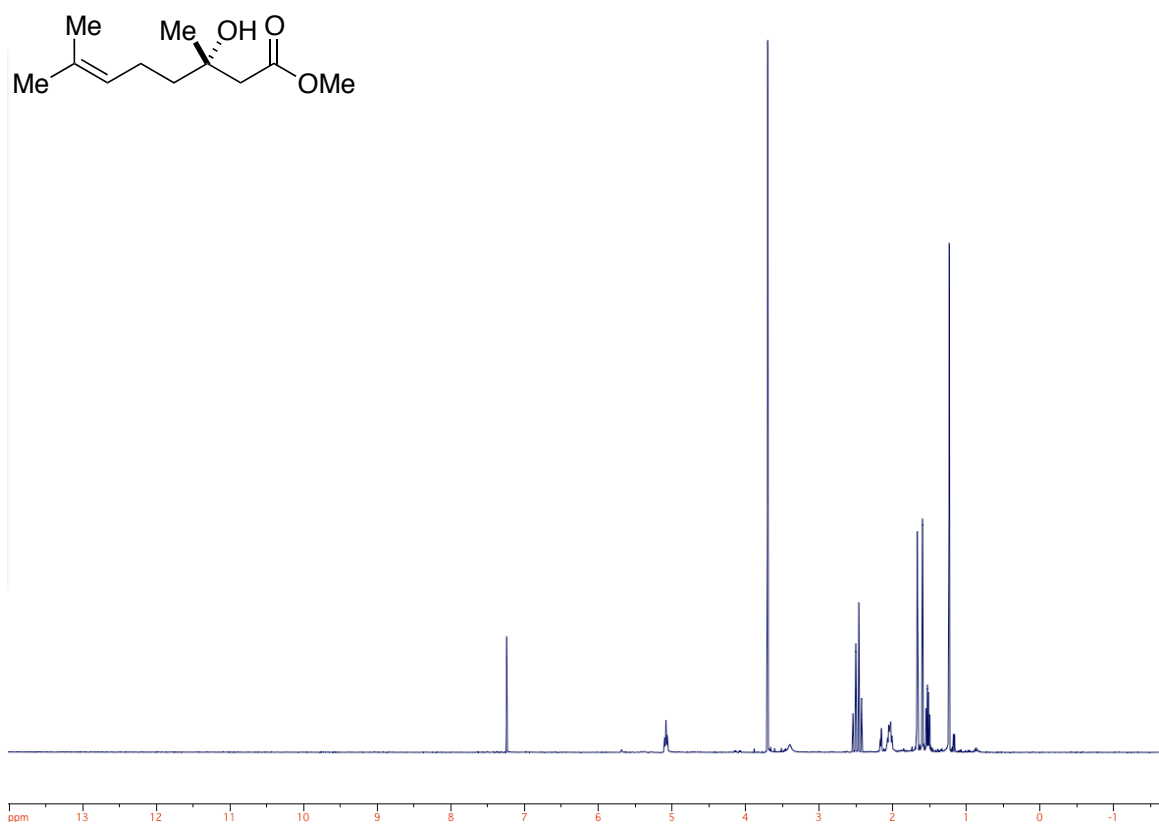


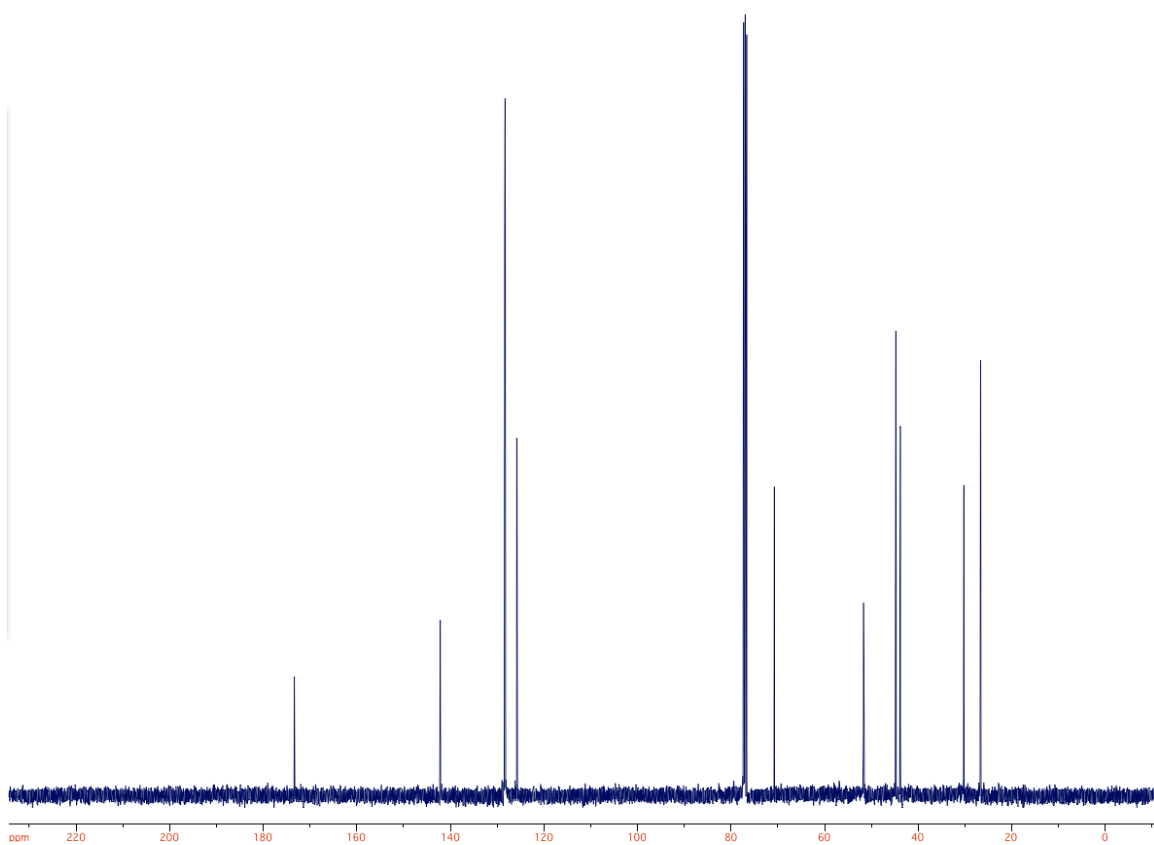
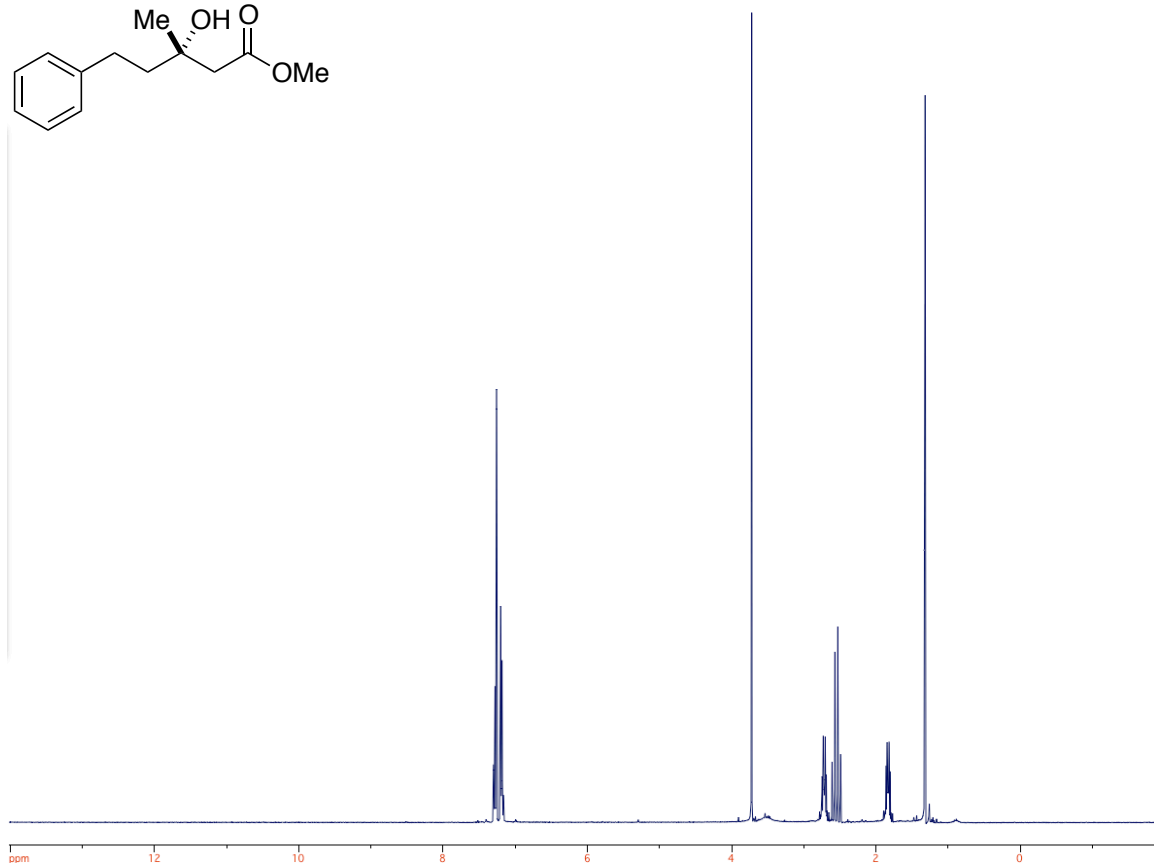
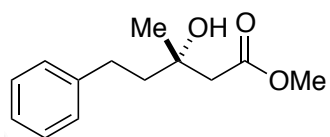
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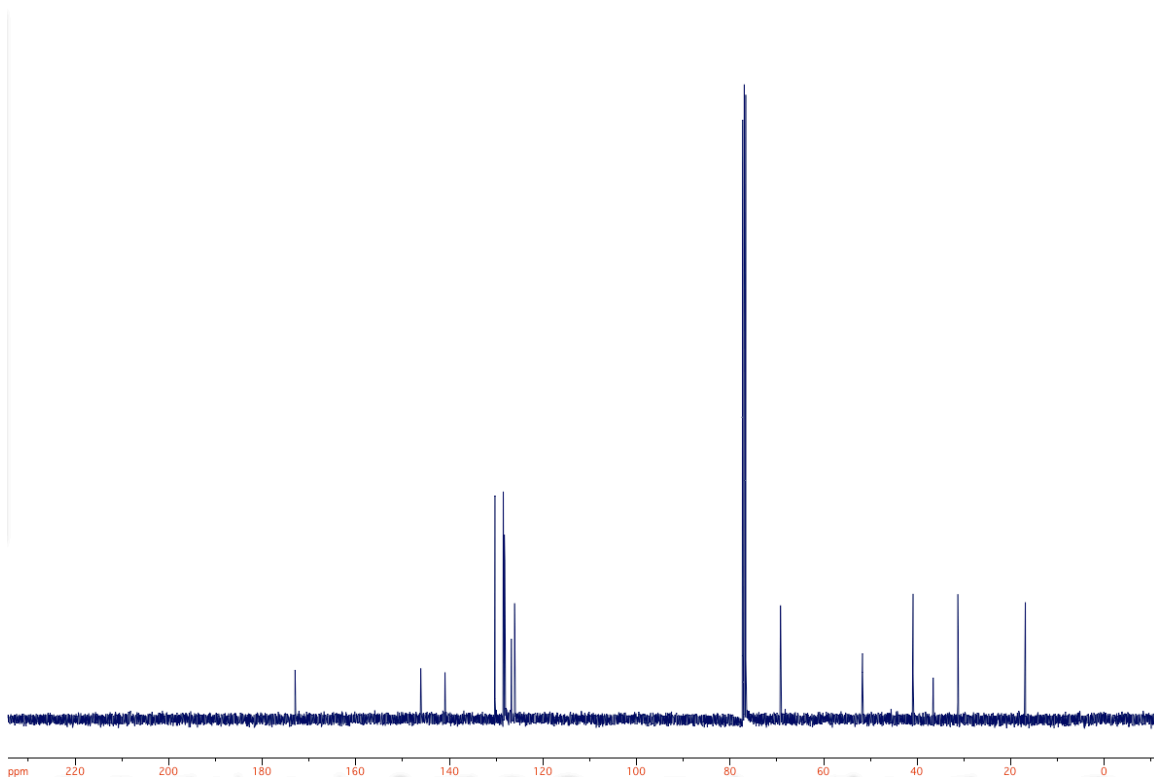
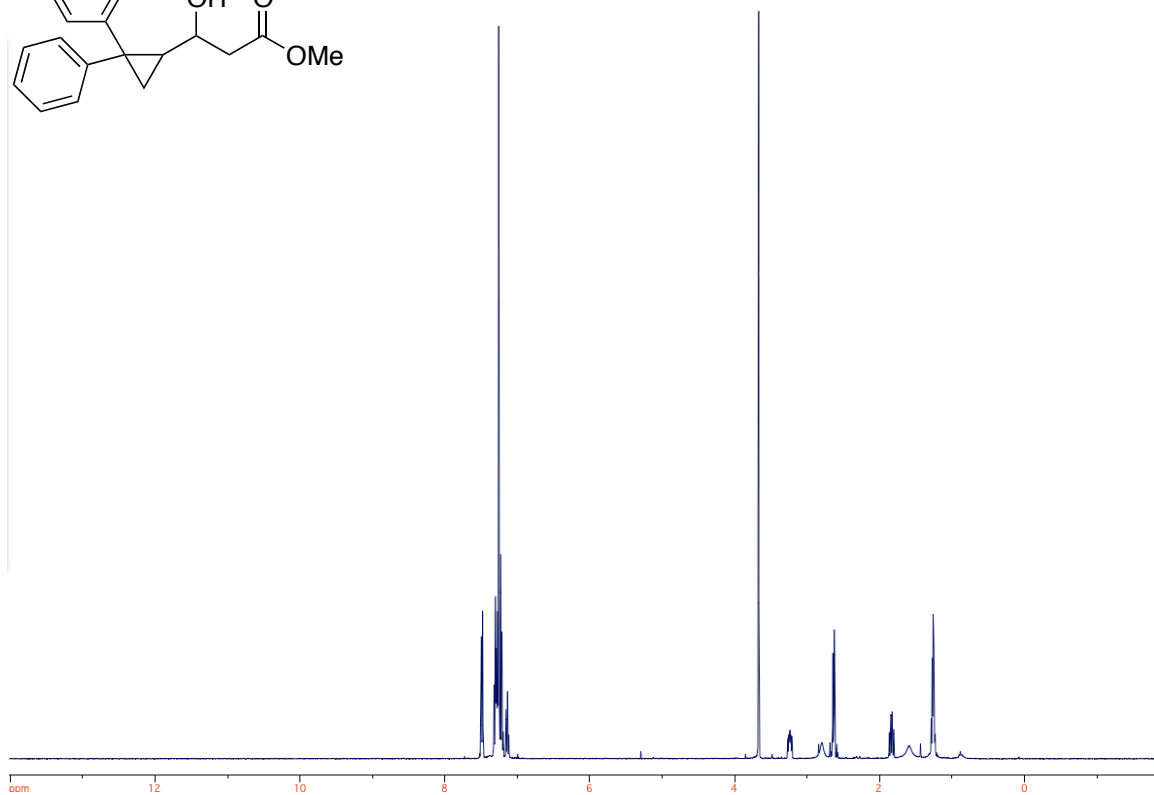
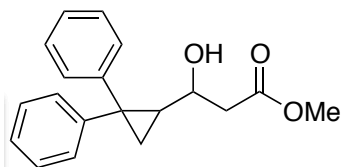
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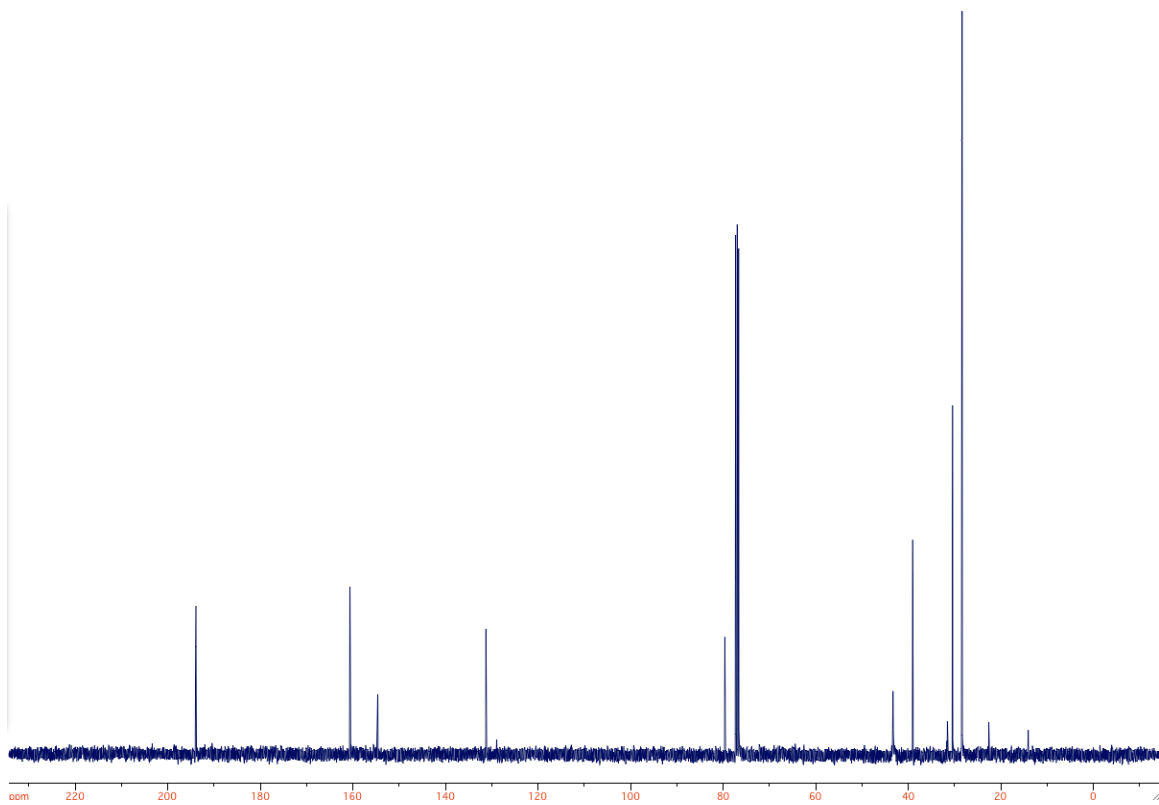
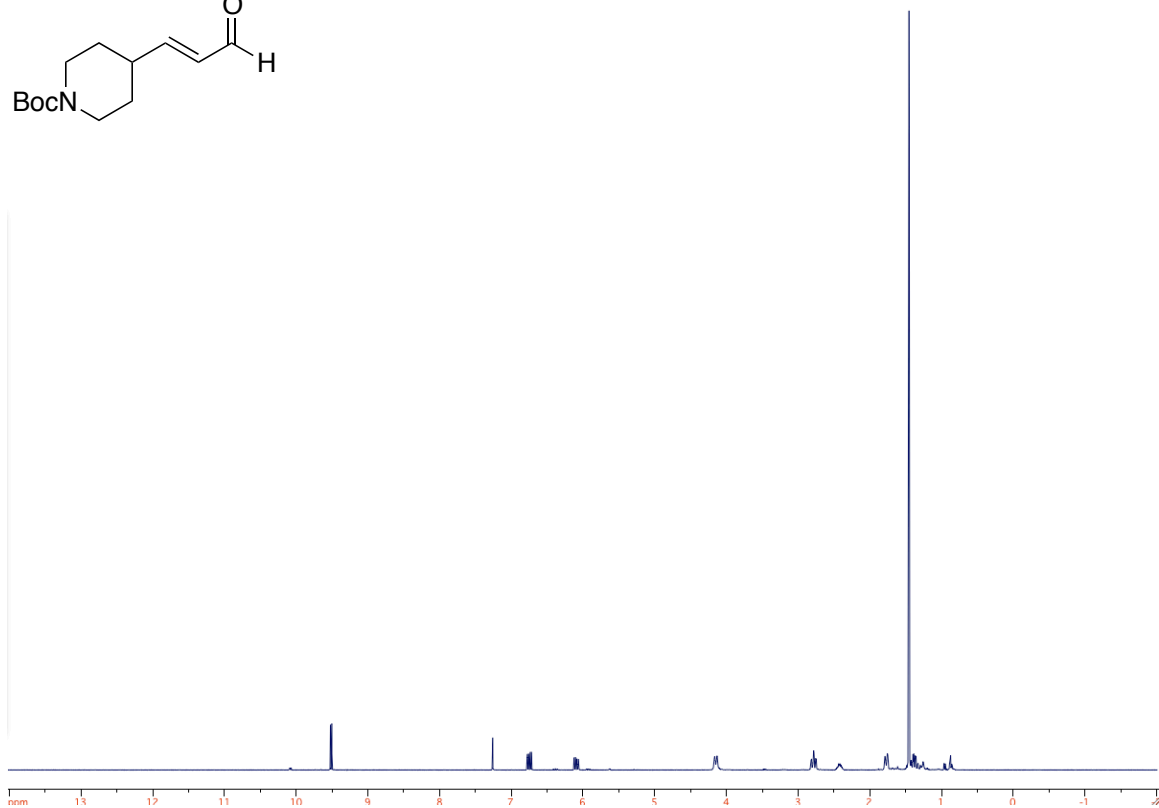
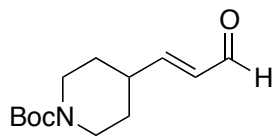




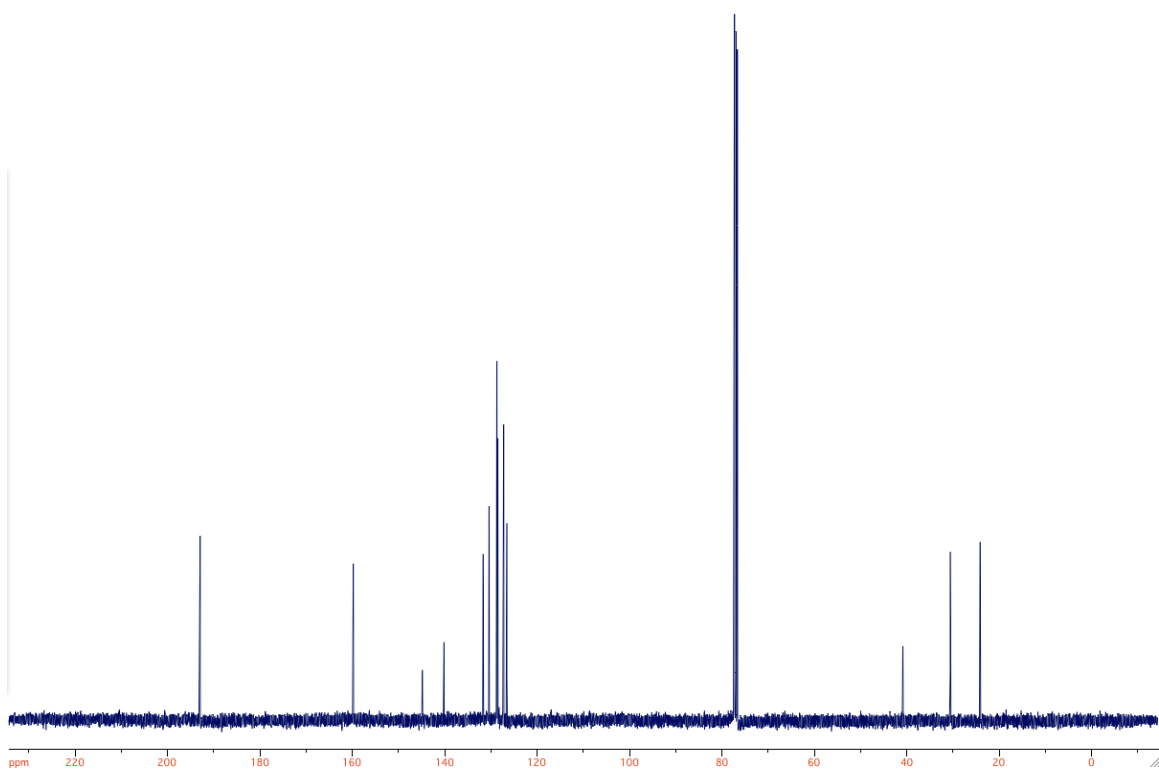
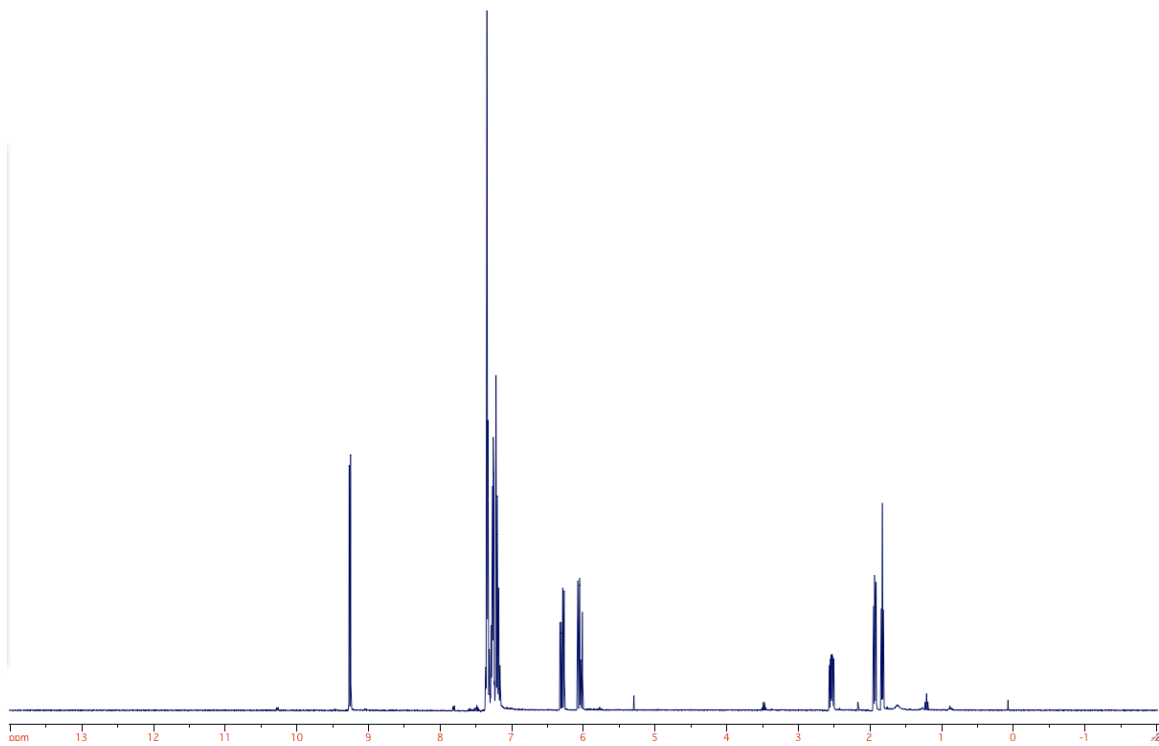


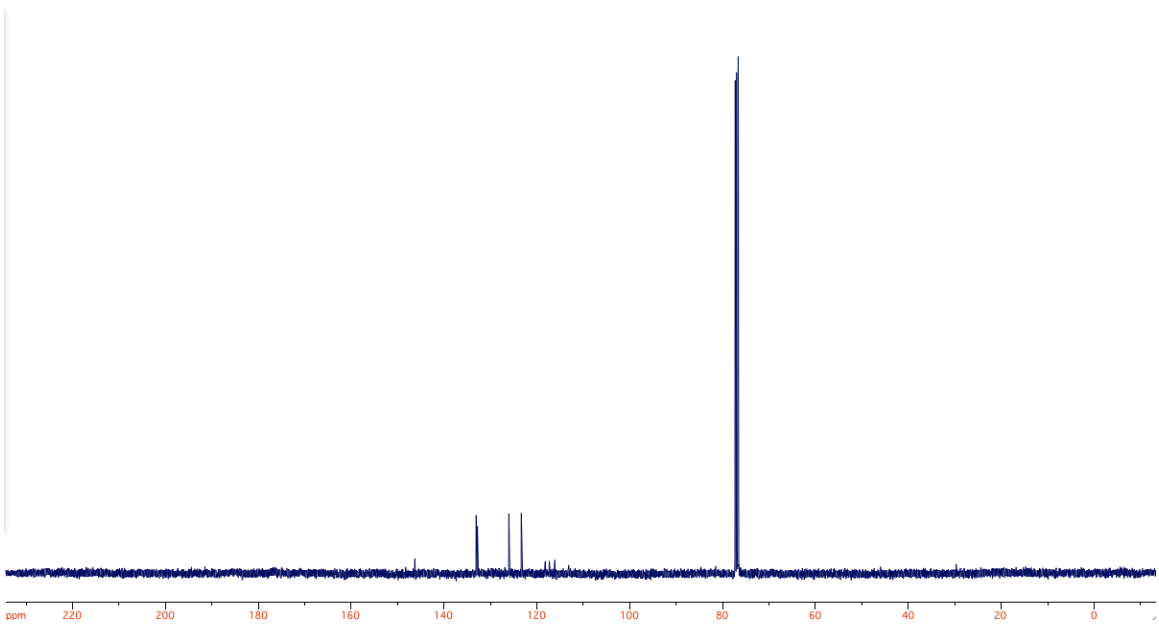
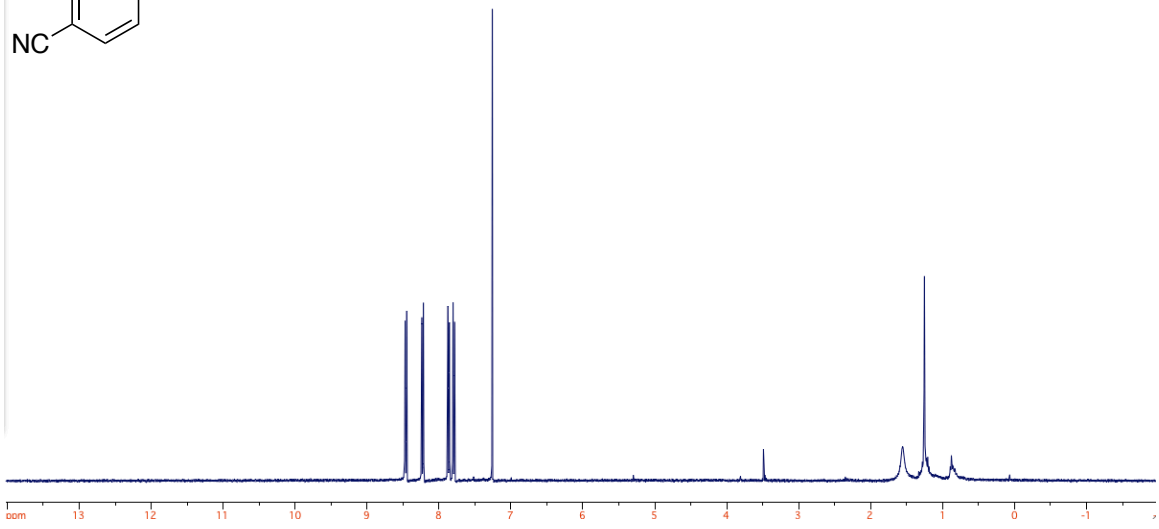
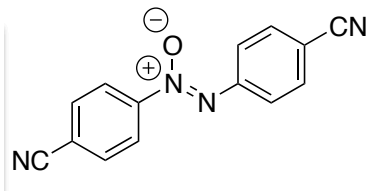
Supporting Information





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- <sup>1</sup> Tanko, J. M.; Drumright, R. E. *J. Am. Chem. Soc.* **1990**, *112*, 5362.
- <sup>2</sup> Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012.
- <sup>3</sup> Sakai, N.; Fujii, K.; Nabeshima, S.; Ikeda, R.; Konakahara, T. *Chem. Commun.* **2010**, *46*, 3173.
- <sup>4</sup> Denmark, S. E.; Eklov, B. M.; Yao, P. J.; Eastgate, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 11770.
- <sup>5</sup> Xu, Q.; Gu, X.; Liu, S.; Dou, Q.; Shi, M. *J. Org. Chem.* **2007**, *72*, 2240.
- <sup>6</sup> Raders, S. M.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 5417.
- <sup>7</sup> Watanabe, Y.; Washio, T.; Krishnamurthi, J.; Anada, M.; Hashimoto, S. *Chem. Commun.* **2012**, *48*, 6969.
- <sup>8</sup> Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.
- <sup>9</sup> Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2501.
- <sup>10</sup> Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.
- <sup>11</sup> Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774.
- <sup>12</sup> Jiang, H.; Gschwend, B.; Albrecht, L.; Jørgensen, K. A. *Org. Lett.* **2010**, *12*, 5052.
- <sup>13</sup> Denmark, S. E.; Ahmad, M. *J. Org. Chem.* **2007**, *72*, 9630.
- <sup>14</sup> Lee, J.-C.-H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544.
- <sup>15</sup> Yamaguchi, S.; Muro, S.; Kobayashi, M.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2003**, *68*, 6274.
- <sup>16</sup> Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 46556.
- <sup>17</sup> Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235.