

## Enzymatic Halocyclization of Allenic Alcohols and Carboxylates: A Biocatalytic Entry to Functionalized O-Heterocycles

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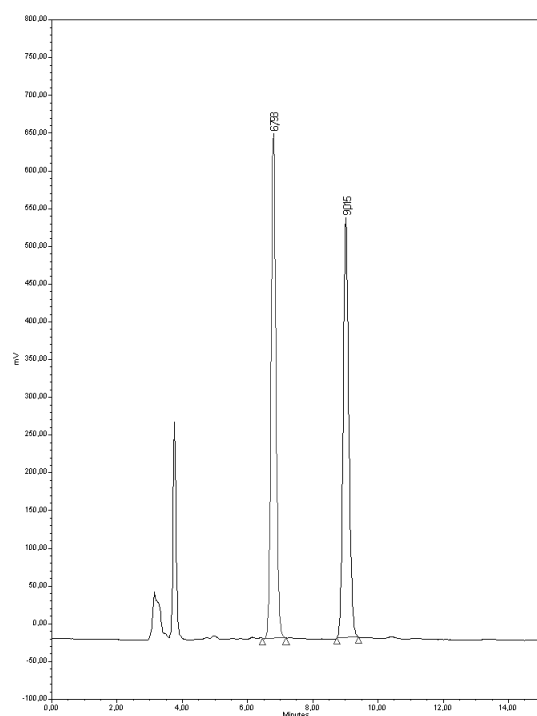
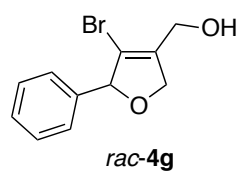
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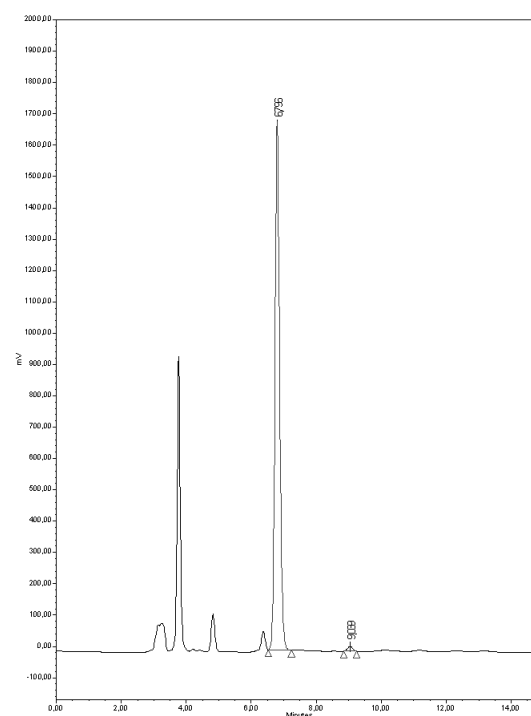
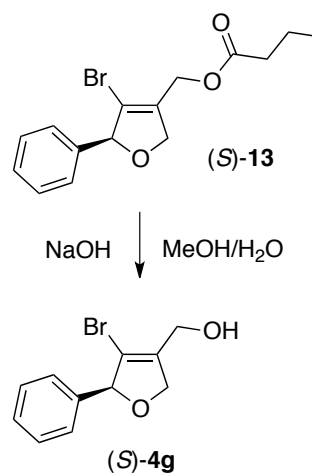
### **General remarks**

All reactions carried out under argon atmosphere were performed with dry solvents using anhydrous conditions. Anhydrous solvents were obtained from an *MBraun MB-SPS800* drying system. Commercially available reagents were used without further purification. Catalysts and cofactors were obtained from: NADH, Carbolution Chemicals GmbH; Lactoperoxidase from *Bos taurus* (*LPO*), 106 U/mg (ABTS), Bio-Research Products; Peroxidase from *Armoracia rusticana* (*HRP*), 148 U/mg (ABTS), Sigma; Peroxidase from *Glycine max* (*SBP*), 17.5 kU/mL (ABTS), Bio-Research Products; Chloroperoxidase from *Caldariomyces fumago* (*CPO*), 9.9 kU/mL (ABTS), Sigma; Glucose oxidase type II (*GOx*), 17.3 U/mg (HRP/ABTS), Sigma; Alcohol oxidase from *Pichia pastoris*, 1.1 kU/mL (HRP/ABTS), Sigma; Alcohol oxidase from *Candida boidinii*, 1.0 U/mg (HRP/ABTS), Sigma; lipase from porcine pancreas (*PPL*), MP Biomedicals. All products were purified either by column chromatography over silica gel (Macherey-Nagel MN-Kieselgel 60, 40-60  $\mu\text{m}$ , 240-400 mesh) or by recrystallization. Reactions were monitored by thin layer chromatography (TLC) carried out on precoated silica gel plates (Macherey-Nagel, TLC Silica gel 60 F<sub>254</sub>) using UV light and  $\text{KMnO}_4$ -solution or Hanessian's stain for visualization.  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were recorded at room temperature on a *Bruker Avance 400* instrument. Chemical shifts are reported in parts per million (ppm) calibrated using residual non-deuterated solvents as internal reference ( $\text{CHCl}_3$  at 7.26 ppm ( $^1\text{H}$ -NMR) and 77.16 ppm ( $^{13}\text{C}$ -NMR)). Infrared spectra were recorded on a *Bruker Alpha ECO-ATR* FT-IR-Spectrometer, absorption bands are reported in wave numbers [ $\text{cm}^{-1}$ ]. High performance liquid chromatography was performed on a *Waters* system using a *Waters 501* pump and a *Waters 2487* dual detector.

## HPLC traces



Name	Retention Time (min)	Area ( $\mu V \cdot sec$ )	% Area	Height ( $\mu V$ )	Int Type
1	6.793	6750709	50.08	666386	bb
2	9.015	6729540	49.92	551321	bb

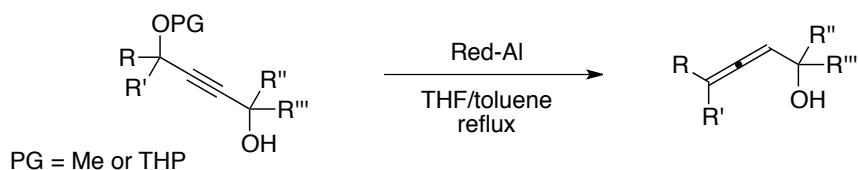


Name	Retention Time (min)	Area ( $\mu V \cdot sec$ )	% Area	Height ( $\mu V$ )	Int Type
1	6.796	17026443	99.02	1687188	bb
2	9.039	168641	0.98	15358	bb

**Supplementary Figure 1.** HPLC traces of racemic bromocyclization product **4g** and an enantio enriched sample obtained via hydrolysis of **(S)-13**.

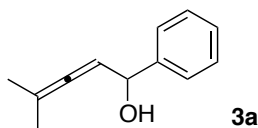
## $\alpha$ -Allenol Synthesis

### General procedure for the synthesis of the allenic alcohols (GP1)



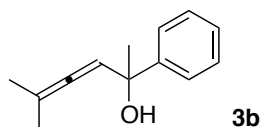
A flask was charged with a  $\delta$ -methoxy or  $\delta$ -tetrahydropyranyloxy propargylic alcohol in anhydrous THF (0.3 M). The solution was heated to reflux, before Red-Al<sup>®</sup> (1.2 eq.) was added dropwise. The mixture was stirred at reflux for 3 hours, before being carefully quenched by addition of EtOAc and aqueous NaOH solution (15 wt. %) in succession. The mixture was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, *n*-hexane/EtOAc) yielded the expected allenols.

### 4-Methyl-1-phenylpenta-2,3-dien-1-ol (**3a**)



Following the general procedure GP1, alcohol **1a** (812 mg, 4.69 mmol, 67 % yield) was obtained as a yellow oil. *R<sub>f</sub>* (*n*-hexane/EtOAc 8/1): 0.24. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 7.41-7.27 (m, 5H), 5.28 (m, 1H), 5.19 (d, *J* = 5.8 Hz, 1H), 2.16 (br s, OH), 1.75 (d, *J* = 2.8 Hz, 3H), 1.74 (d, *J* = 2.8 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 199.8, 143.6, 128.5, 127.7, 126.2, 100.1, 94.5, 72.5, 20.8, 20.7. FT-IR (neat, ATR):  $\nu$  [cm<sup>-1</sup>] = 3356 (br), 3062 (w), 3029 (w), 1968 (m), 1450 (m), 1363 (m), 1010 (s), 746 (s), 697 (s) cm<sup>-1</sup>.

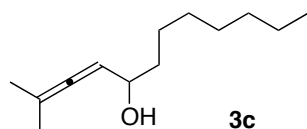
### 5-Methyl-2-phenylhexa-3,4-dien-2-ol (**3b**)



Following the general procedure GP1, alcohol **3b** (196 mg, 1.04 mmol, 40% yield) was obtained as a light yellow oil. *R<sub>f</sub>* (*n*-hexane/EtOAc 8/1) = 0.24. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 7.52 (m, 2H),

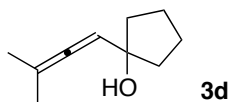
7.35 (m, 2H), 7.25 (m, 1H), 5.38 (sept,  $J = 2.8$  Hz, 1H), 2.21 (s, OH), 1.76 (dd,  $J = 5.7, 2.8$  Hz, 6H), 1.63 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 198.7, 147.8, 128.2, 126.8, 125.1, 100.4, 99.3, 73.7, 30.5, 20.7, 20.6. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3382 (br), 3059 (w), 3028 (w), 1969 (m), 1446 (s), 1364 (m), 1098 (m), 1066 (s), 767 (s), 698 (s)

### 2-Methyl-dodeca-2,3-dien-5-ol (**3c**)



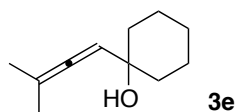
Following the general procedure GP1, alcohol **3c** (211 mg, 1.08 mmol, 43% yield) was obtained as a light yellow oil.  $R_f$  (*n*-hexane/ethyl acetate 6/1): 0.39.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.07 (dsept,  $J = 6.2, 2.9$  Hz, 1H), 4.07 (q,  $J = 6.2$  Hz, 1H), 1.71 (t,  $J = 2.9$  Hz, 6H), 1.61 (br s, OH), 1.52 (m, 2H), 1.34-1.24 (m, 10H), 0.88 (m, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 199.9, 98.7, 94.0, 70.4, 37.7, 32.0, 29.7, 29.4, 25.6, 22.8, 20.8, 14.2. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3334 (br), 2925 (s), 2855 (s), 1970 (m), 1456 (m), 1378 (m), 1363 (m), 1191 (m), 1017 (m), 989 (m).

### 1-(3-Methylbuta-1,2-dienyl)cyclopentan-1-ol (**3d**)



Following the general procedure GP1, alcohol **3d** (65 mg, 0.42 mmol, 20% yield) was obtained as light yellow oil.  $R_f$  (*n*-hexane/ethyl acetate 8/1): 0.26.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.22 (sept,  $J = 2.9$  Hz, 1H), 1.85-1.60 (m, 9H), 1.73 (d,  $J = 2.9$  Hz, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 198.4, 99.5, 97.6, 80.5, 40.6, 23.8, 20.9. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3350 (br), 2959 (s), 2871 (s), 1968 (m), 1447 (m), 1363 (m), 1189 (s), 1073 (s), 988 (s).

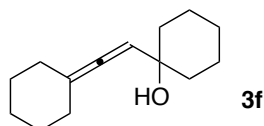
### 1-(3-Methylbuta-1,2-dienyl)cyclohexan-1-ol (**3e**)



Following the general procedure GP1, alcohol **3e** (229 mg, 1.35 mmol, 52% yield) was obtained as a light yellow oil.  $R_f$  (*n*-hexane/ethyl acetate 8/1): 0.26.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.12

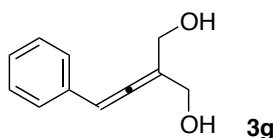
(sept,  $^5J = 2.9$  Hz, 1H), 1.72 (d,  $^5J = 2.9$  Hz, 6H), 1.66-1.32 (m, 10H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 198.4, 99.0, 98.3, 71.0, 38.4, 26.9, 25.6, 22.7, 20.6. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3356 (br), 2929 (s), 2854 (s), 1969 (m), 1447 (m), 1363 (m), 1190 (m), 1147 (m), 1056 (m), 955 (s).

#### 1-(2-Cyclohexylidenethen-1-yl)cyclohexan-1-ol (**3f**)



Following the general procedure GP1, alcohol **3f** (1.64 g, 9.41 mmol, 63% yield) was obtained as light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 8/1): 0.29.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.12 (sept,  $^5J = 2.9$  Hz, 1H), 1.72 (d,  $^5J = 2.9$  Hz, 6H), 1.66-1.32 (m, 10H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 198.4, 99.0, 98.3, 71.0, 38.4, 26.9, 25.6, 22.7, 20.6. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3356 (br), 2929 (s), 2854 (s), 1969 (m), 1447 (m), 1363 (m), 1190 (m), 1147 (m), 1056 (m), 955 (s).

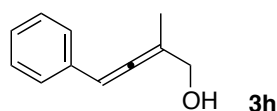
#### 2-(Hydroxymethyl)-4-phenylbuta-2,3-dien-1-ol (**3g**)



According to a previously reported protocol using phenylzinc bromide and 5-acetoxy-2,2-dimethyl-5-ethynyl-1,3-dioxane,<sup>1</sup> diol **3g** was obtained as colorless crystals (289 mg, 1.64 mmol, 82% yield). **M.p.** (chloroform): 143 °C.  $R_f$  (cyclohexane/ethyl acetate 1/1): 0.24.  $^1\text{H-NMR}$  (400 MHz,  $\text{MeOH-d}_4$ ):  $\delta$  [ppm] = 7.34-7.17 (m, 5H), 6.35 (quint,  $J = 2.1$  Hz, 1H), 4.28-4.24 (m, 4H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{MeOH-d}_4$ ):  $\delta$  [ppm] = 203.3, 135.8, 129.5, 128.0, 127.9, 109.9, 97.6, 61.4. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3263 (br), 2954 (w), 2933 (w), 2428 (w), 1953 (w), 1595 (w), 1494 (w), 1458 (w), 1413 (w), 1357 (w), 1251 (w), 1141 (w), 1062 (s), 1004 (s), 987 (m), 925 (w), 823 (w), 746 (m), 696 (s). **Elemental analysis** calcd (%) for  $\text{C}_{11}\text{H}_{12}\text{O}_2$ : C 74.98, H 6.86; found: C 74.94, H 6.95.

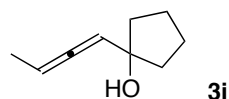
<sup>1</sup> C. Manzuna Sapu, J.-E. Bäckvall and J. Deska, *Angew. Chem. Int. Ed.* 2011, **50**, 9731.

### 2-Methyl-4-phenylbuta-2,3-dien-1-ol (**3h**)



According to a previously reported protocol using ethyl 2-methyl-4-phenylbuta-2,3-dienoate and DIBAL-H,<sup>2</sup> **3h** (122 mg, 0.77 mmol, 31% yield) was obtained as a colorless oil. *R<sub>f</sub>* (cyclohexane/ethyl acetate 6/1): 0.24. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ [ppm] = 7.36 – 7.21 (m, 5H), 6.30 (tq, <sup>5</sup>J ≈ <sup>5</sup>J' = 2.9 Hz, 1H), 4.21 (dd, <sup>2</sup>J = 13.0 Hz, <sup>5</sup>J = 2.9 Hz, 1H), 4.15 (dd, <sup>2</sup>J = 13.0 Hz, <sup>5</sup>J = 2.9 Hz, 1H), 1.88 (d, <sup>5</sup>J = 2.9 Hz, 3H), 1.63 (br s, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ [ppm] = 200.8, 134.8, 128.6, 127.0, 126.7, 104.7, 97.1, 63.9, 15.4. HRMS (ESI) calcd for C<sub>11</sub>H<sub>12</sub>NaO [M+Na]<sup>+</sup>: 183.0785, found: 183.0780.

### 1-(Buta-1,2-dienyl)cyclopentan-1-ol (**3i**)

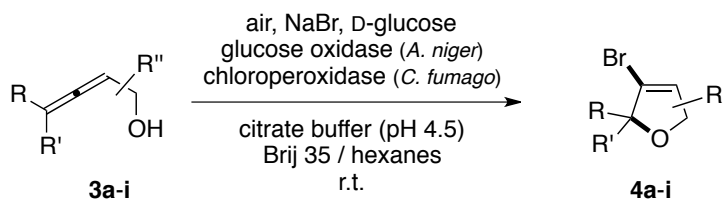


To a slurry of LiAlH<sub>4</sub> (0.126 g, 3.30 mmol) in dry diethyl ether (5 mL) at 0 °C was added 1-(3-tetrahydropyranyloxybut-1-ynyl)cyclopentan-1-ol (0.606 g, 2.50 mmol) in dry diethyl ether (3 mL) dropwise over 20 minutes. The mixture was stirred at reflux for 4 hours. The mixture was cooled down to 0 °C and the reaction was quenched by consecutive addition of H<sub>2</sub>O (1 mL), aqueous NaOH solution (1 mL, 15 wt-%) and H<sub>2</sub>O (3 mL). The mixture was stirred at r.t. for 20 minutes, before being filtered through Celite. The solid residue was washed with diethyl ether. The filtrate was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc 4:1) afforded alcohol **3i** (0.223 g, 1.58 mmol, 63 %) as a light yellow oil. *R<sub>f</sub>* (*n*-hexane/ethyl acetate 6/1): 0.25. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ [ppm] = 5.34-5.28 (m, 2H), 1.87-1.78 (m, 2H), 1.76-1.70 (m, 4H), 1.69 (dd, <sup>3</sup>J = 6.9, <sup>5</sup>J = 3.4 Hz, 3H), 1.67-1.59 (m, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ [ppm] = 201.6, 99.0, 89.7, 80.2, 40.6, 40.6, 23.8, 23.8, 14.7. FT-IR (neat, ATR): ν [cm<sup>-1</sup>] = 3353 (br), 2957 (s), 2871 (m), 1964 (m), 1439 (m), 1370 (m), 1187 (m), 1068 (s), 991 (s), 869 (s), 723 (m).

<sup>2</sup> S. Ma and W. Gao, *J. Org. Chem.* 2002, **67**, 6104.

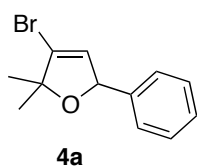
## $\alpha$ -Allenol Cyclization

### General procedure for the enzymatic halocyclization (GP2)



*n*-Hexane (10 mL) was added to a solution of Brij 35<sup>®</sup> (243 mg, 200  $\mu$ mol) in an aqueous citrate buffer (10 mL, 0.1 M, pH 4.5) to form an emulsion by vigorous stirring. Anhydrous sodium bromide (61 mg, 600  $\mu$ mol), D-(+)-glucose (72 mg, 400  $\mu$ mol), allenic alcohol or acid (200  $\mu$ mol) and chloroperoxidase from *Caldariomyces fumago* (20  $\mu$ L, 200 U, 1 U/ $\mu$ mol) were all added to the emulsion. Glucose oxidase from *Aspergillus niger* (3 mg, 50 U, 0.25 U/ $\mu$ mol) was finally added to start the reaction. The mixture was stirred vigorously for 2 - 5 hours under air (until TLC indicated conversion of the starting material). Acetonitrile (10 mL) was added to the mixture and the layers were separated. The aqueous layer was extracted with *n*-pentane (3 x 30 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The yields of halocyclization products were determined from the crude product by NMR using dimethylsulfone as internal standard. Purification by flash chromatography (SiO<sub>2</sub>, *n*-hexane/EtOAc) provided the isolated compounds.

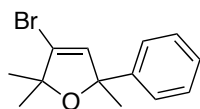
### 3-Bromo-2,2-dimethyl-5-phenyl-2,5-dihydrofuran (4a)



Following the general procedure GP2, **4a** (43 mg, 170  $\mu$ mol, 85 % yield) was obtained as a light yellow oil. *R<sub>f</sub>* (cyclohexane/ethyl acetate 6/1): 0.85. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 7.39-7.28 (m, 5H), 5.91 (d, <sup>3</sup>*J* = 1.6 Hz, 1H), 5.69 (d, <sup>3</sup>*J* = 1.6 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 140.8, 128.7, 128.3, 126.8, 126.7, 89.1, 85.3, 27.6, 26.2. FT-IR (neat, ATR):  $\nu$  [cm<sup>-1</sup>] = 3064 (w), 3030 (w), 1628 (m), 1454 (s), 1377 (m), 1361 (m), 1150 (m), 1047 (s), 852 (s), 760 (s), 696 (s).



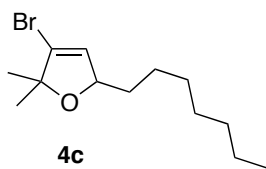
### 3-Bromo-2,2,5-trimethyl-5-phenyl-2,5-dihydrofuran (**4b**)



**4b**

Following the general procedure GP2, **4b** (45 mg, 170  $\mu$ mol, 85 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.70.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 7.44-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.27-7.22 (m, 1H), 6.11 (s, 1H), 1.66 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 146.2, 132.1, 128.4, 127.0, 125.1, 124.7, 89.1, 88.9, 30.7, 28.2, 27.1. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3060 (w), 3026 (w), 1631 (s), 1445 (m), 1377 (m), 1361 (m), 1181 (m), 1068 (m), 988 (s), 895 (s), 760 (s), 698 (s).

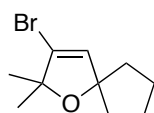
### 3-Bromo-2,2-dimethyl-5-heptyl-2,5-dihydrofuran (**4c**)



**4c**

Following the general procedure GP2, **4c** (42 mg, 153  $\mu$ mol, 77 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.88.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.28 (d,  $^3J = 1.5$  Hz, 1H), 4.69 (td,  $^3J = 6.1$ ,  $^3J' = 1.5$  Hz, 1H), 1.62-1.47 (m, 2H), 1.40-1.21 (m, 10H), 1.36 (s, 3H), 1.33 (s, 3H), 0.87 (m, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 128.6, 125.8, 88.0, 83.6, 36.7, 31.9, 29.8, 29.4, 27.9, 26.2, 25.2, 22.8, 14.2. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 2925 (s), 2855 (s), 1628 (s), 1460 (s), 1376 (m), 1360 (m), 1153 (m), 1054 (m), 892 (s), 812 (s).

### 3-Bromo-2,2-dimethyl-1-oxaspiro[4.4]non-3-ene (**4d**)

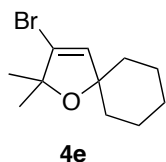


**4d**

Following the general procedure GP2, **4d** (34 mg, 148  $\mu$ mol, 74 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.70.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.78 (s, 1H), 1.85-1.55 (m, 8H), 1.34 (s, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 131.8, 124.4, 95.8, 87.7, 40.0,

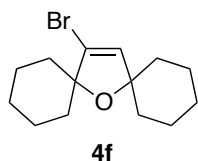
27.9, 24.4. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 2965 (s), 2928 (m), 1629 (s), 1453 (m), 1376 (m), 1360 (m), 1290 (m), 1149 (m), 1014 (m), 986 (s), 889 (s).

### 3-Bromo-2,2-dimethyl-1-oxaspiro[4.5]dec-3-ene (4e)



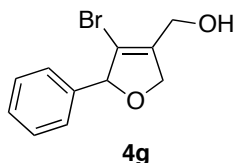
Following the general procedure GP2, **4d** (34 mg, 138  $\mu\text{mol}$ , 69 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.86.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.98 (s, 1H), 1.79-1.54 (m, 6H), 1.47-1.32 (m, 4H), 1.36 (s, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 131.8, 125.3, 88.2, 87.5, 39.1, 28.4, 25.4, 23.5. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 2930 (s), 2857 (m), 1629 (m), 1454 (m), 1376 (m), 1359 (m), 1177 (m), 1143 (m), 992 (s), 898 (s)

### 14-Bromo-7-oxadispiro[5.1.5.2]pentadec-14-ene (4f)



Following the general procedure GP2, **4f** (37 mg, 131  $\mu\text{mol}$ , 69 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.81.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.99 (s, 1H), 1.75-1.38, 20 H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 131.9, 125.4, 87.9, 87.3, 39.1, 36.3, 25.4, 25.0, 23.2, 22.0.

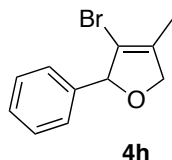
### 3-Bromo-4-(hydroxymethyl)-2-phenyl-2,5-dihydrofuran (4g)



Following the general procedure GP2, **4g** (42 mg, 165  $\mu\text{mol}$ , 82 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 9/1): 0.11.  $^1\text{H-NMR}$  (400 MHz,  $\text{MeOH-d}_4$ ):  $\delta$  [ppm] = 7.38 – 7.29 (m, 5H), 5.60 (dd,  $^4J$  = 3.6 Hz,  $^4J'$  = 5.2 Hz, 1H), 4.94 (dd,  $^4J$  = 5.2 Hz,  $^2J$  = 12.3 Hz, 1H), 4.81 (dd,  $^4J$  = 3.6 Hz,

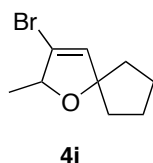
$^2J = 12.3$  Hz, 1H), 4.35 (d,  $^2J = 13.5$  Hz, 1H), 4.30 (d,  $^2J = 13.5$  Hz, 1H).  $^{13}\text{C-NMR}$  (100 MHz, MeOH- $d_4$ ):  $\delta$  [ppm] = 142.0, 140.1, 130.7, 130.4, 129.6, 116.9, 92.9, 77.9.

### 3-Bromo-4-methyl-2-phenyl-2,5-dihydrofuran (4h)



Following the general procedure GP2, **4h** (34 mg, 142  $\mu\text{mol}$ , 70 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 7/1): 0.69.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 7.48 (d,  $^3J = 8.4$  Hz, 2H), 7.35 (dd,  $^3J \approx ^3J' = 7.5$  Hz, 2H), 7.24 (t,  $^3J = 7.1$ , 1H), 6.03 (ddd,  $^3J = 10.0$  Hz,  $^3J' = 3.9$  Hz,  $^3J'' = 3.6$  Hz, 1H), 5.79 (d,  $^3J = 10.0$  Hz), 2.19-1.91 (m, 4H), 1.87-1.75 (m, 2H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 147.8, 132.2, 130.7, 128.1, 126.8, 125.4, 72.1, 39.6, 24.9, 19.2.

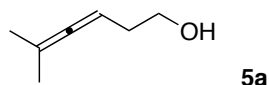
### 3-Bromo-2-methyl-1-oxaspiro[4.4]non-3-ene (4i)



Following the general procedure GP2, **4i** (8.2 mg, 38  $\mu\text{mol}$ , 69 % yield) was obtained as a light yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.73.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.86 (d,  $^4J = 2.0$  Hz, 1H), 4.75 (dq,  $J = 6.4, 2.0$  Hz, 1H), 1.86-1.47 (m, 8H), 1.33 (d,  $J = 6.4$  Hz, 3H).

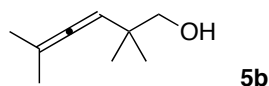
## ***β-Allenol Synthesis & Cyclization***

### **5-Methylhexa-3,4-dien-1-ol (5a)**



Ethyl 5-methylhexa-3,4-dienoate (300 mg, 1.90 mmol), dissolved in anhydrous THF (5 mL), was added dropwise to a slurry of  $\text{LiAlH}_4$  (119 mg, 3.10 mmol) in anhydrous THF (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 hours, before being quenched by consecutive addition of  $\text{H}_2\text{O}$  (1 mL), aqueous NaOH solution (1 mL, 15 wt-%) and  $\text{H}_2\text{O}$  (3 mL). The mixture was filtered through Celite and the solid residue was washed with diethyl ether. The filtrate was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc 4/1) to give alcohol **5a** (84 mg, 0.72 mmol, 38 %) as a colorless oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.22.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 4.94 (tsept,  $^3J = 6.3\text{ Hz}$ ,  $^5J = 2.9\text{ Hz}$ , 1H), 3.67 (t,  $^3J = 6.3\text{ Hz}$ , 2H), 2.20 (dt,  $^3J \approx ^3J' = 6.3\text{ Hz}$ , 2H), 1.71 (br s, OH), 1.68 (d,  $^5J = 2.9\text{ Hz}$ , 6 H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 202.7, 95.8, 85.2, 62.2, 32.6, 20.8. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3335 (br), 2930 (s), 2857 (s), 1969 (m), 1445 (m), 1363 (m), 1231 (m), 1189 (m), 1048 (s).

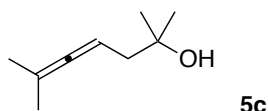
### **2,2,5-Trimethylhexa-3,4-dien-1-ol (5b)**



Following a reported procedure,<sup>3</sup> aqueous NaOH solution (50 wt. %, 0.616 g, 7.7 mmol) was added dropwise to a solution of 2,2,5-trimethylhexa-3,4-dienal (0.345 g, 2.5 mmol) in methanol (3 mL). The reaction mixture was stirred at reflux under air for 19 hours, before it was poured on ice water (6 mL). The mixture was extracted with pentane (3 x 20 mL) and the combined pentane layers were washed with  $\text{H}_2\text{O}$  (5 mL) and brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. (Allenic acid **8** can be isolated from the aqueous phase!). The resulting crude product was purified by flash chromatography (*n*-hexane/EtOAc 5/1) to afford the allenic alcohol **5b** (65 mg, 0.48 mmol, 19 %) as a yellow oil.  $R_f$  (cyclohexane/ethyl acetate 8/1): 0.27.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 4.85 (sept,  $^5J = 2.9\text{ Hz}$ , 1H), 3.33 (s, 2H), 1.71 (d,  $^5J = 2.9\text{ Hz}$ , 6H), 0.99 (s, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 200.8, 97.4, 96.5, 72.0, 37.8, 24.8, 21.0. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3398 (br), 2925 (s), 2855 (s), 1969 (w), 1458 (m), 1377 (m), 1365 (m), 1191 (m), 1076 (m), 914 (m).

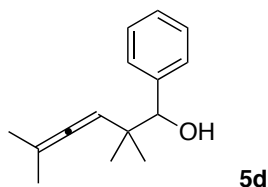
<sup>3</sup> R. S. Bly and S. U. Kooek, *J. Am. Chem. Soc.* 1969, **91**, 3292.

### 1,1,5-Trimethylhexa-3,4-dien-1-ol (**5c**)



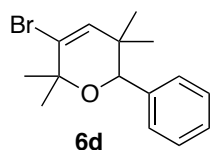
At  $-78\text{ }^{\circ}\text{C}$ , ethyl 5-methylhexa-3,4-dienoate (0.302 g, 2.0 mmol in dry THF (5 mL)) was added dropwise to a solution of methylmagnesium bromide (3.2 M in MeTHF, 1.6 mL, 5.1 mmol) in dry THF (10 mL). The reaction mixture was allowed to reach room temperature over 1 hour. The reaction was again cooled down to  $0\text{ }^{\circ}\text{C}$ , before adding aqueous saturated  $\text{NH}_4\text{Cl}$  (4 mL). The mixture was extracted with diethyl ether (3 x 15 mL). Combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc 4/1) to give allenol **5c** (109 mg, 0.80 mmol, 40 %) as a yellow oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.25.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 4.97 (tsept,  $^3J = 7.7\text{ Hz}$ ,  $^5J = 2.9\text{ Hz}$ , 1H), 2.11 (d,  $^3J = 7.7\text{ Hz}$ , 2H), 1.69 (d,  $J = 2.9\text{ Hz}$ , 6H), 1.23 (s, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 204.0, 94.6, 84.2, 70.8, 43.9, 28.9, 20.7. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3060 (w), 3026 (w), 1631 (s), 1445 (m), 1377 (m), 1361 (m), 1181 (m), 1068 (m), 988 (s), 895 (s), 760 (s), 698 (s).

### 1-Phenyl-2,2,5-trimethylhexa-3,4-dien-1-ol (**5d**)



At  $-78\text{ }^{\circ}\text{C}$ , 2,2,5-trimethylhexa-3,4-dienal (294 mg, 2.1 mmol) in anhydrous THF (10 mL) was added dropwise to a solution of phenylmagnesium bromide (1 M in THF, 5 mL, 5.0 mmol). The reaction mixture was allowed to reach room temperature over 2.5 hours. After cooling the mixture down to  $0\text{ }^{\circ}\text{C}$ , aqueous saturated  $\text{NH}_4\text{Cl}$  (5 mL) was added. The mixture was extracted with diethyl ether. The organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc 8/1) gave the desired allenol **5d** (157 mg, 0.71 mmol, 34 %) as a yellow oil.  $R_f$  (cyclohexane/ethyl acetate 8/1): 0.48.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 7.35-7.24 (m, 5H), 4.99 (dq,  $^5J \approx ^5J' = 2.9\text{ Hz}$ , 1H), 4.44 (s, 1H), 2.18 (br s, OH), 1.68 (d,  $^5J = 2.9$ , 3H), 1.66 (d,  $^5J = 2.9$ , 3H), 1.01 (s, 3H), 0.92 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 201.3, 141.1, 128.0, 127.6, 127.4, 97.4, 96.6, 81.3, 41.0, 25.6, 22.6, 20.8, 20.8. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3460 (br), 3029 (w), 1967 (m), 1452 (m), 1376 (m), 1362 (m), 1040 (m), 739 (s), 701 (s).

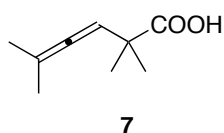
### 3-Bromo-6-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-6H-pyran (6d)



Following the general procedure GP2, **4g** (42 mg, 97  $\mu$ mol, 46 % yield) was obtained as a yellow oil.  $R_f$  (*n*-hexane/EtOAc 6/1): 0.79.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 7.38-7.26 (m, 5H), 5.94 (s, 1H), 4.54 (s, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 138.7, 138.1, 128.0, 128.0, 127.7, 127.5, 79.0, 77.6, 40.4, 29.0, 25.6, 23.9, 21.8. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3030 (w), 1638 (w), 1453 (m), 1381 (m), 1163 (m), 1058 (s), 918 (m), 832 (m), 737 (s), 699 (s).

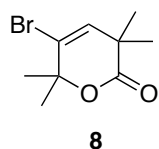
### Bromolactonization

#### 2,2,5-Trimethylpenta-3,4-dienoic acid (**7**)



The remaining combined aqueous phases from the Cannizzaro reaction yielding alcohol **5b** (see page 11) were acidified by a dropwise addition of aqueous HCl (32 %, 0.8 mL). The resulting aqueous solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give the allenic acid **7** (48 mg, 0.31 mmol, 12 %) as yellow/orange crystals, which were used without further purification.  $R_f$  (*n*-hexane/EtOAc 8/1): 0.12.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.20 (sept,  $^5J = 2.8$  Hz, 1H), 1.70 (d,  $^5J = 2.8$  Hz, 6H), 1.28 (s, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 200.5, 183.3, 99.1, 95.3, 42.8, 25.4, 20.6. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 3500-2500 (br), 3074 (w), 1971 (w), 1700 (s), 1470 (m), 1408 (m), 1364 (m), 1292 (m), 1163 (m).

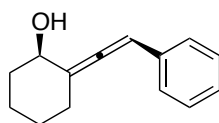
### 5-Bromo-3,3,6,6-tetramethyl-3,6-dihydro-2H-pyran-2-one (**8**)



Following the general procedure GP2, **8** (14 mg, 61  $\mu$ mol, 40 % yield) was obtained as a yellow solid.  $R_f$  (*n*-hexane/EtOAc 6/1): 0.48.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 5.88 (s, 1H), 1.62 (s, 6H), 1.37 (s, 6H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 173.8, 132.7, 122.9, 85.5, 41.2, 29.0, 28.0. **FT-IR** (neat, ATR):  $\nu$  [ $\text{cm}^{-1}$ ] = 2926 (s), 2854 (m), 1740 (s), 1464 (m), 1384 (m), 1298 (m), 1164 (m), 1127 (s).

## **Synthesis & Cyclization of Stereochemically Defined Allenols**

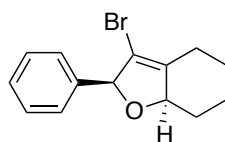
### ***syn*-2-(2-Phenylethenylidene)cyclohexanol (**11**)**



**11**

Following a reported procedure,<sup>4</sup> La(OTf)<sub>3</sub> (54 mg, 92 μmol), 2-hydroxycyclohexanone dimer (136 mg, 0.60 mmol), potassium phenylethynyl trifluoroborate (287 mg, 1.38 mmol) and 2-nitrobenzenesulfonyl hydrazide (200 mg, 0.92 mmol) were dissolved in MeCN (8 mL) and stirred for 2 h at room temperature. Et<sub>2</sub>O (50 mL) and aq. NaOH (0.5 M, 50 mL) were added, the aqueous layer was extracted with Et<sub>2</sub>O (3 x 20 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of volatiles in vacuo, column chromatography (SiO<sub>2</sub>, dichloromethane) yielded **11** (166 mg, 0.83 mmol, 90%) as colorless solid. *R<sub>f</sub>* (cyclohexane/ethyl acetate 1/1): 0.89. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): *syn*-isomer: δ [ppm] = 7.38 - 7.23 (m, 5H), 6.37 - 6.35 (m, 1H), 4.17 - 4.10 (m, 1H), 2.61 - 2.53 (m, 1H), 2.26 - 2.09 (m, 3H), 1.95 - 1.82 (m, 2H), 1.61 - 1.45 (m, 3H); *anti*-isomer (selected signals): δ [ppm] = 4.27 - 4.22 (m, 1H), 2.76 - 2.71 (m, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ [ppm] = 196.5, 135.0, 128.7, 127.1, 126.7, 112.4, 98.4, 69.5, 36.8, 30.0, 23.3, 23.9.

### ***syn*-3-Bromo-2-phenyl-2,4,5,6,7,7a-hexahydrobenzofuran (**12**)**

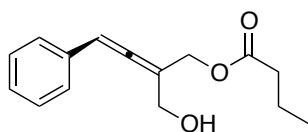


**12**

Following the general procedure GP2, **12** (50 mg, 179 μmol, 89% yield) was obtained as a colorless oil. *R<sub>f</sub>* (cyclohexane/ethyl acetate 7/1): 0.79. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): *syn*-isomer: δ [ppm] = 7.45 - 7.31 (m, 5H), 5.65 - 5.61 (m, 1H), 4.66 - 4.61 (m, 1H), 2.73 - 2.66 (m, 1H), 2.33 - 2.28 (m, 1H), 2.04 - 1.95 (m, 1H), 1.93 - 1.88 (m, 2H), 1.52 - 1.25 (m, 3H); *anti*-isomer (selected signals): δ [ppm] = 5.60 - 5.57 (m, 1H), 4.80 - 4.75 (m, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ [ppm] = 139.9, 139.6, 128.5, 128.3, 127.9, 110.9, 89.2, 84.9, 35.8, 26.1, 25.6, 23.2.

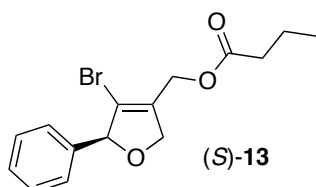
<sup>4</sup> D. A. Mundal, K. E. Lutz and R. J. Thomson, *J. Am Chem. Soc.* 2012, **134**, 5782.

**(R)-2-Hydroxymethyl-4-phenylbuta-2,3-dienyl butyrate**



Allendiol **3g** (0.2 mmol) was dissolved in dry 1,4-dioxane (1.0 ml), vinyl butyrate (127  $\mu$ l, 1.0 mmol) and crude lipase from porcine pancreas (20 mg) were added and the reaction mixture was incubated at 40°C. After the 24 h, the mixture was filtered through cotton, concentrated in vacuo and the residue was separated by column chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 9/1 to 7/3) yielding the enantioenriched monobutyrate (46.8 mg, 190  $\mu$ mol, 95%) as a colorless oil.  $[\alpha]_D^{20}$ :  $-35.6^\circ$  (c 0.5, CHCl<sub>3</sub>, 98% ee).  $R_f$  (cyclohexane/ethyl acetate 4/1): 0.53.  $^1\text{H-NMR}$  (300 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 7.22-7.33 (m 5H), 6.40 (m, 1H), 4.81 (d,  $J$  = 2.1 Hz, 2H), 4.26 (d,  $J$  = 2.2 Hz, 2H), 2.34 (t,  $J$  = 7.4 Hz, 2H), 1.66 (tq,  $J$  = 7.4 Hz, 2H), 1.28 (br s, 1H), 0.95 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C-NMR}$  (100 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 202.8, 173.8, 133.3, 128.7, 127.5, 127.1, 105.1, 98.0z, 62.0, 61.3, 36.1, 18.4, 13.7. **FT-IR** (neat, ATR):  $\nu$  [cm<sup>-1</sup>] = 3402 (br), 2964 (w), 2933 (w), 2875 (w), 1952 (w), 1732 (s), 1589 (w), 1496 (w), 1460 (w), 1415 (w), 1381 (w), 1249 (w), 1168 (s), 1024 (m), 746 (m), 692 (s). **Elemental analysis** calcd (%) for C<sub>15</sub>H<sub>18</sub>O<sub>3</sub>: C 73.15, H 7.37; found: C 73.02, H 7.51. **HPLC** (*Chiralpak IB*, *n*-hexane/isopropanol 90/10, 1.0 ml/min, 254 nm):  $t_R$  (*R*) = 6.1 min,  $t_R$  (*S*) = 7.1 min.

**(S)-(3-Bromo-2-phenyl-2,5-dihydrofuran-4-yl) butyrate (13)**

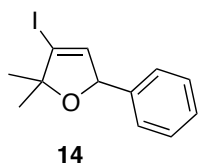


Following the general procedure GP2 using the previously obtained axially chiral butyrate, (*S*)-**13** (35.8 mg, 0.11 mmol, 55% yield) was obtained as colorless oil.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.50.  $^1\text{H-NMR}$  (400 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 7.45 - 7.31 (m, 5H), 5.69 - 5.66 (m, 1H), 4.90 (dd,  $^2J$  = 12.4 Hz,  $^4J$  = 5.8 Hz, 1H), 4.86 (s, 2H), 4.78 (dd,  $^2J$  = 12.4 Hz,  $^4J$  = 3.8 Hz, 1H), 2.39 (t,  $^3J$  = 7.3 Hz, 2H), 1.71 (tq,  $^3J \approx ^3J' = 7.3$  Hz, 2H), 1.64 (br s, 1H), 0.99 (t,  $^3J$  = 7.4 Hz, 3H).  $^{13}\text{C-NMR}$  (100 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm] = 173.3, 138.9, 133.2, 128.8, 128.5, 127.3, 118.8, 90.5, 75.9, 58.9, 35.9, 18.4, 13.7. **HPLC** (*Chiralpak IB*, *n*-hexane/isopropanol 90/10, 1.0 ml/min, 254 nm):  $t_R$  ((*S*)-**13**) = 6.8 min,  $t_R$  ((*R*)-**13**) = 9.0 min.



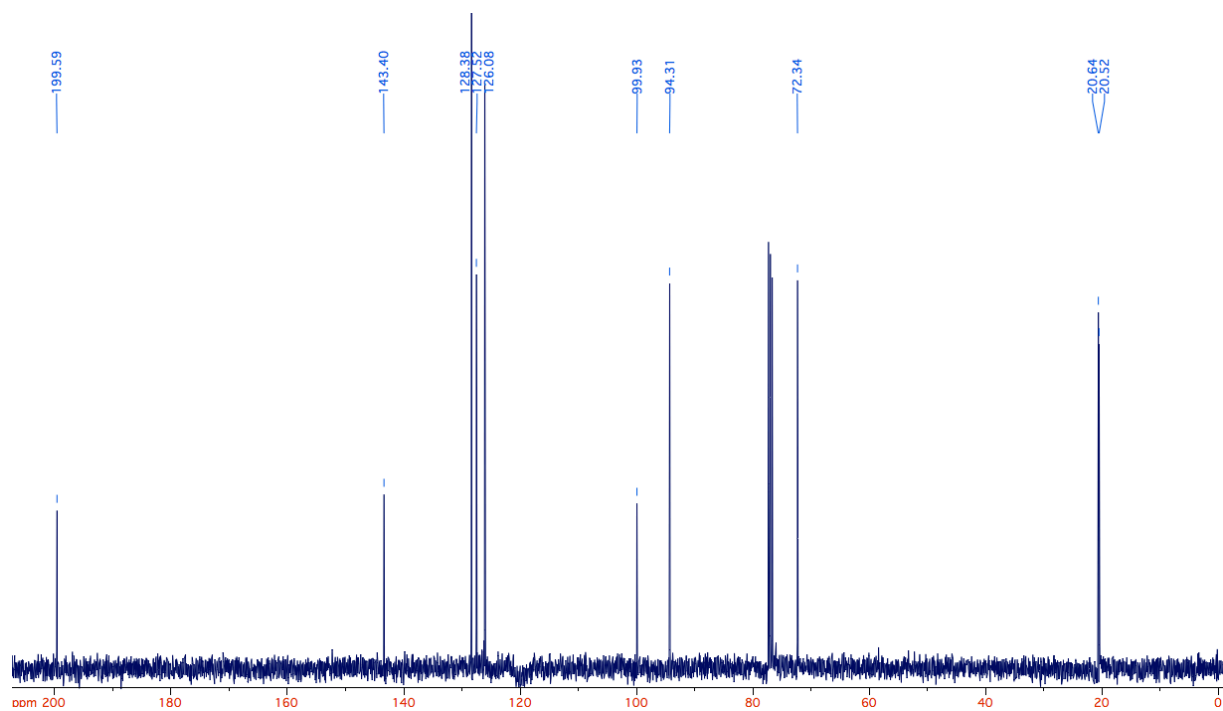
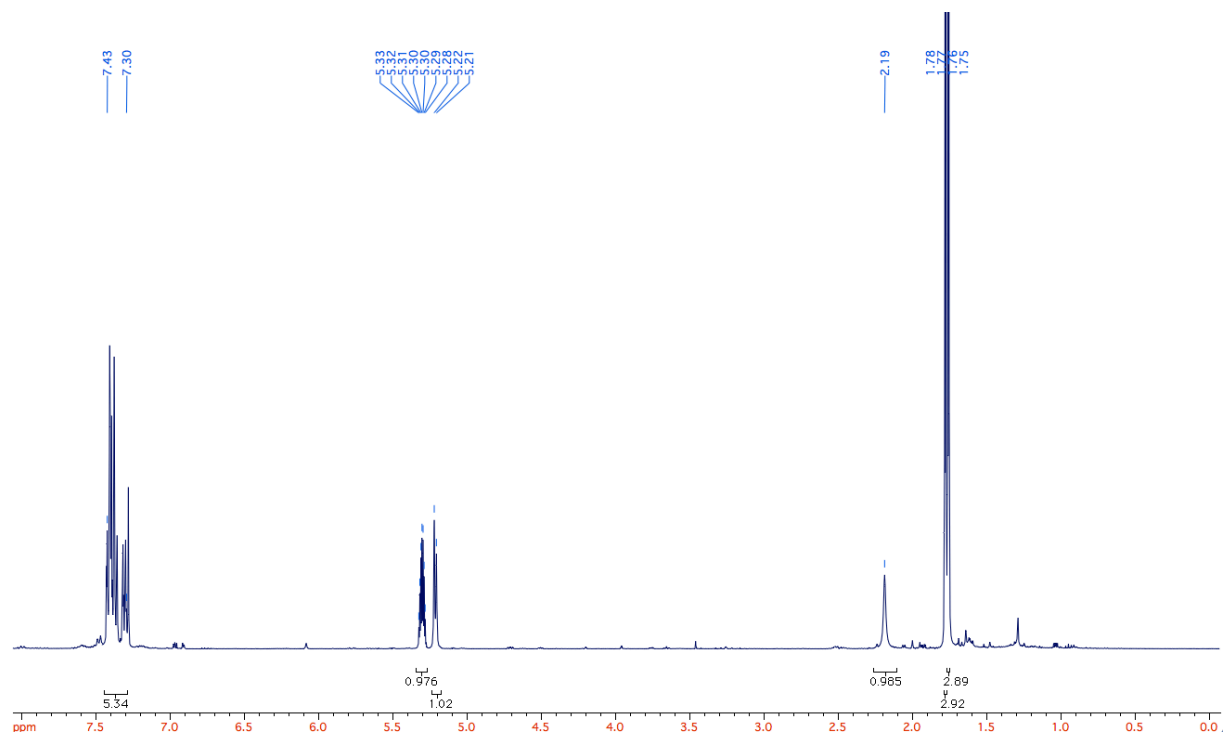
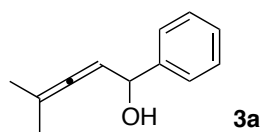
### Iodocyclization

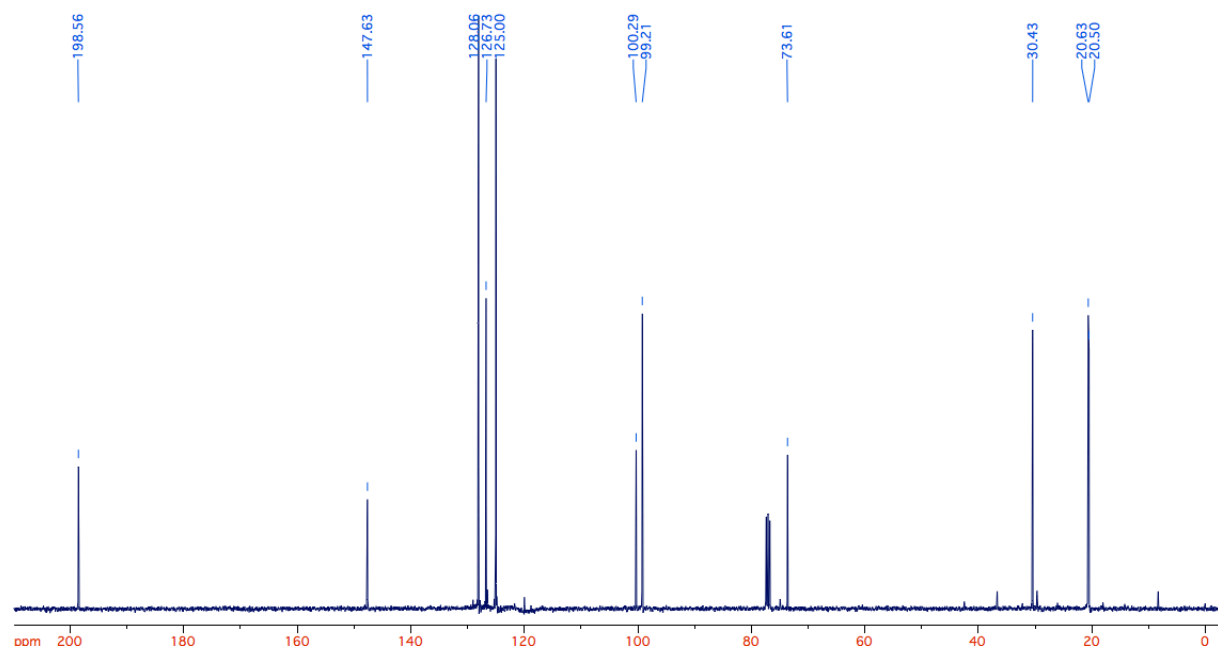
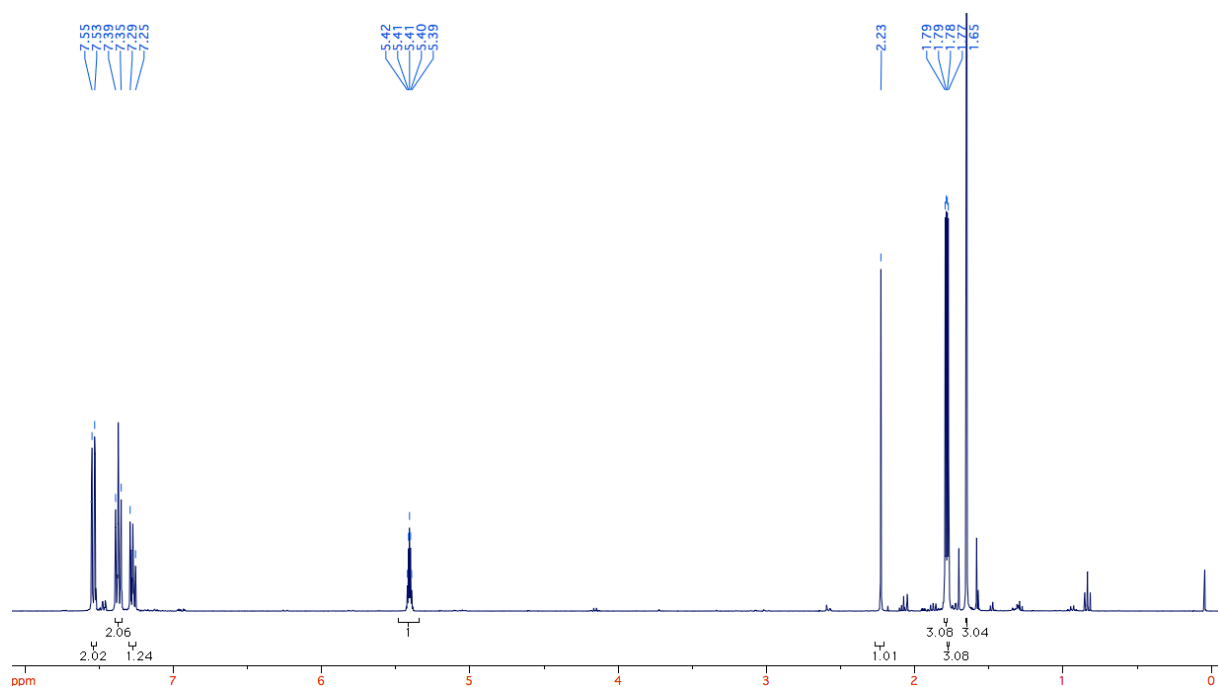
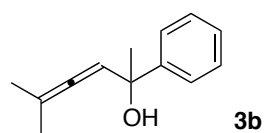
#### 3-Bromo-2,2-dimethyl-5-phenyl-2,5-dihydrofuran (**14**)

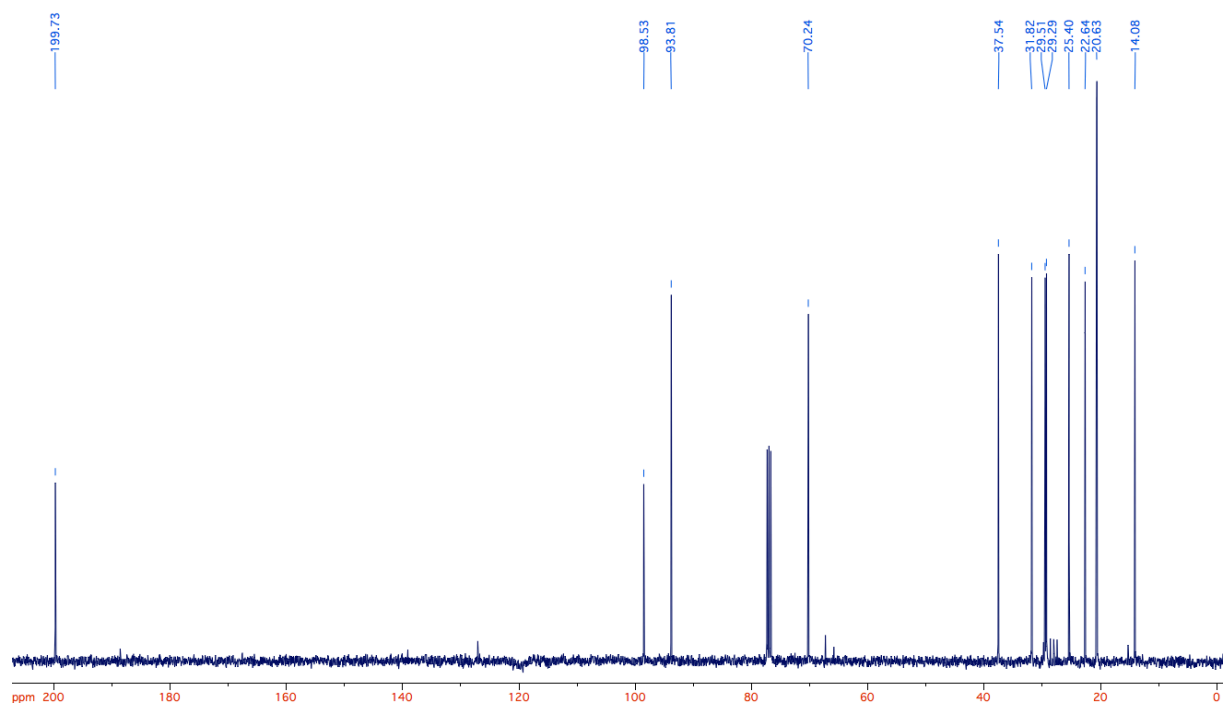
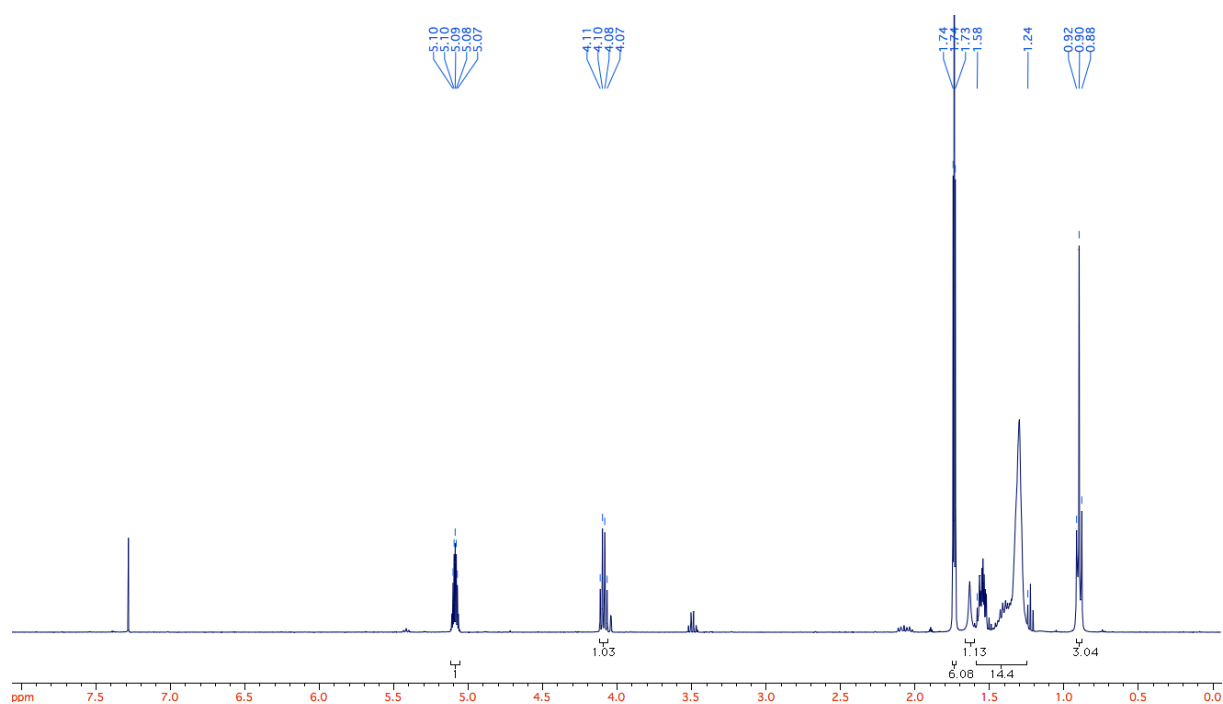
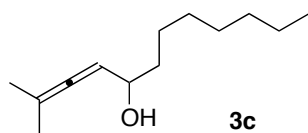


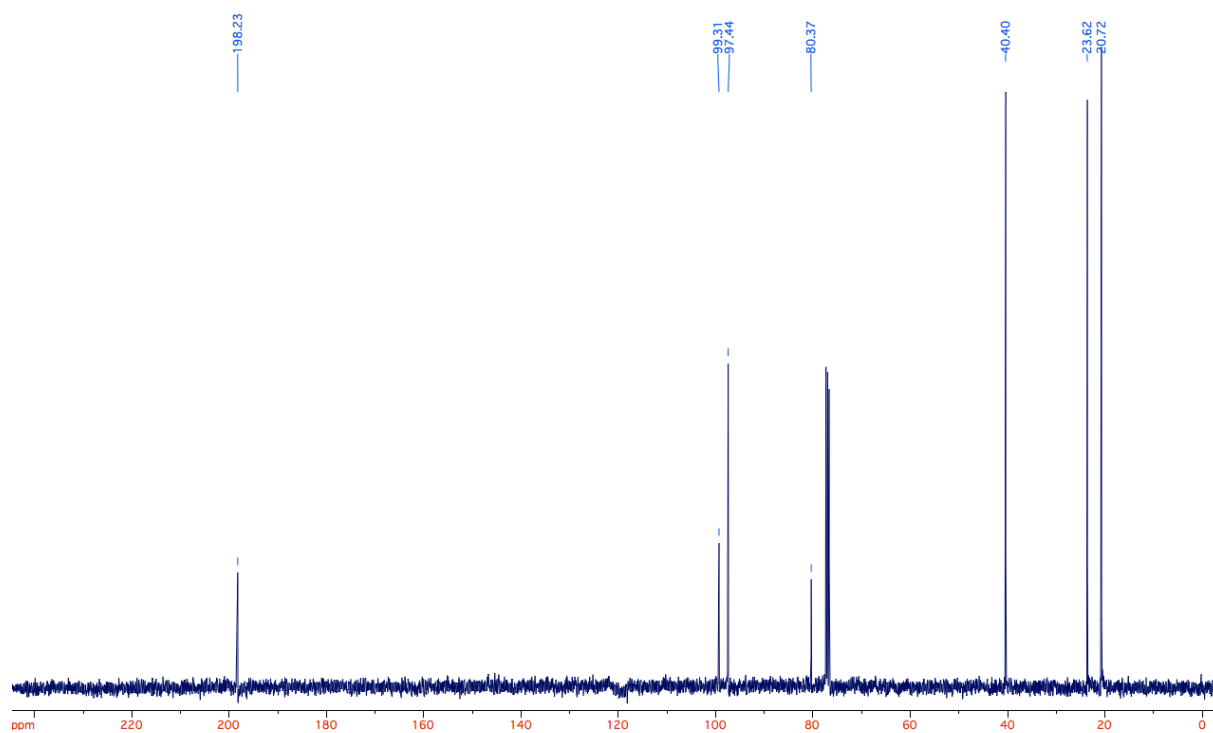
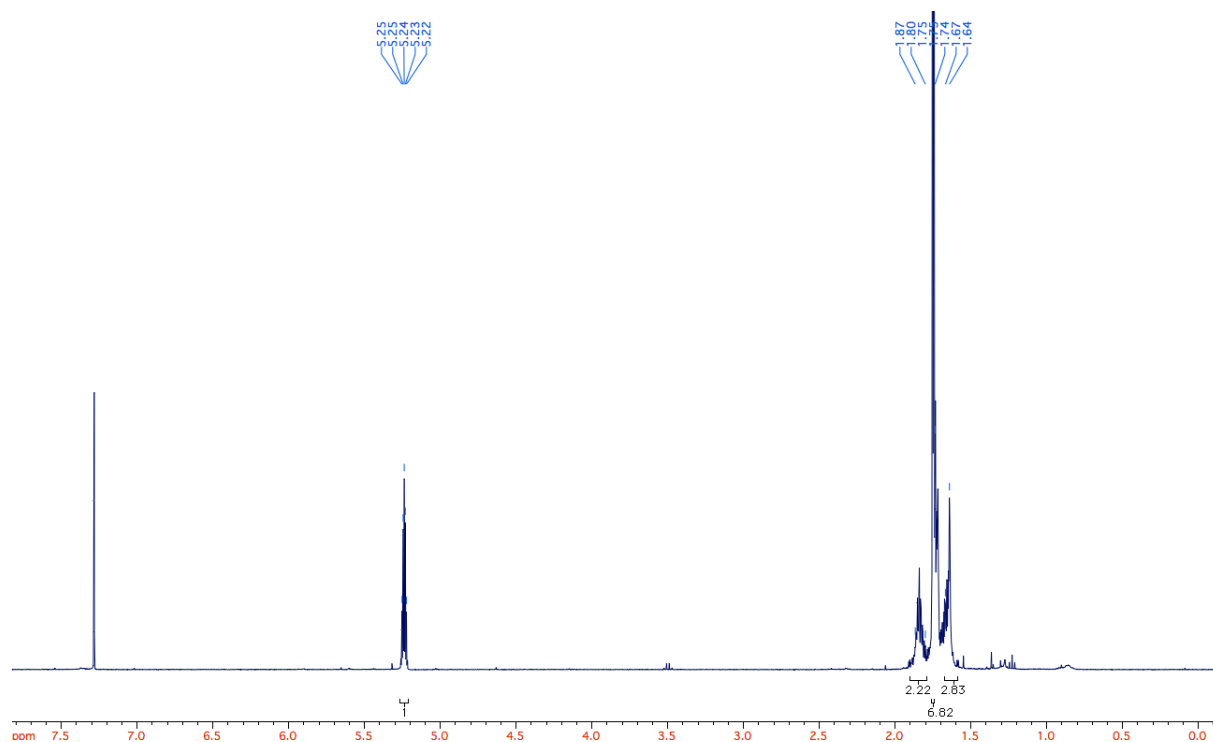
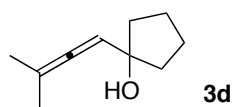
Following the general procedure GP2, **3a** (0.2 mmol) was reacted in presence of NaI instead of NaBr for one hour reaching 74% conversion as determined by  $^1\text{H-NMR}$ . As compound **14** proved to be instable during the purification workup on silica, it might be advisable to further convert the crude product after full conversion.  $R_f$  (cyclohexane/ethyl acetate 6/1): 0.85.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 7.42 - 7.30 (m, 5H), 6.11 (d,  $^3J = 1.6$  Hz, 1H), 5.73 (d,  $^3J = 1.6$  Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  [ppm] = 140.6, 136.7, 128.6, 128.1, 126.6, 100.8, 90.9, 87.2, 28.1, 26.4.

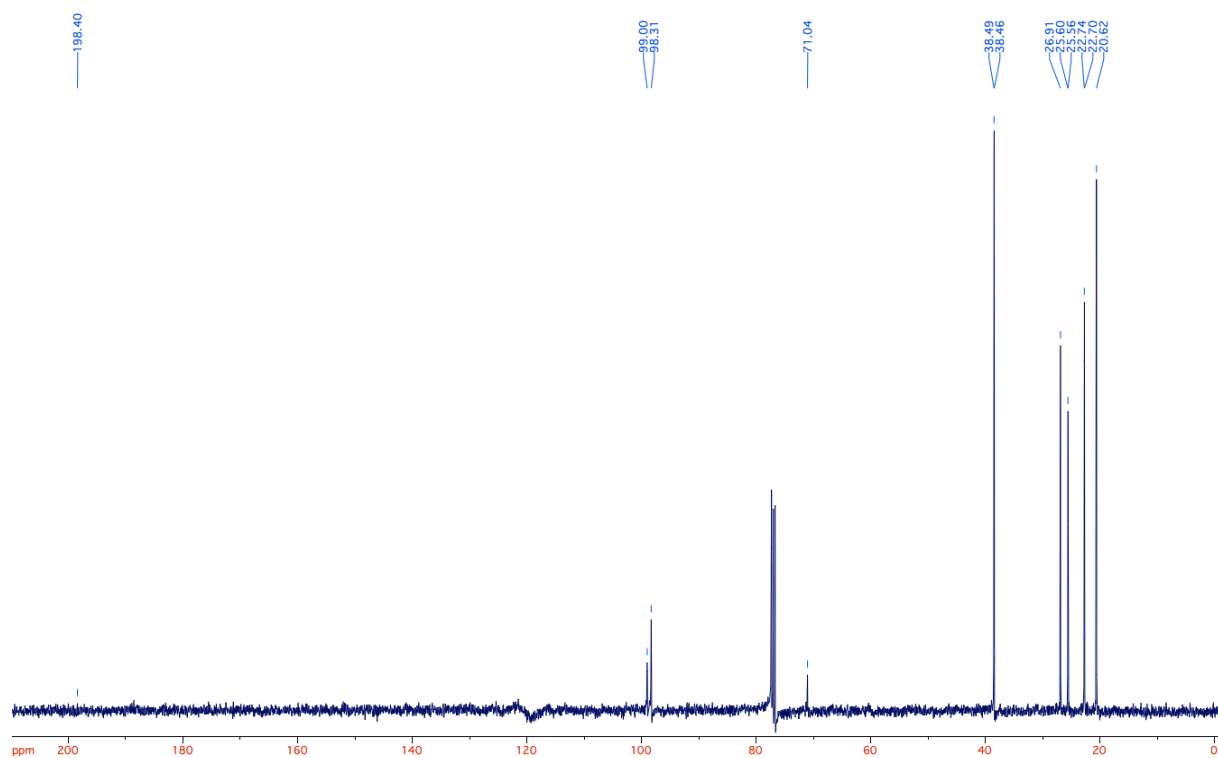
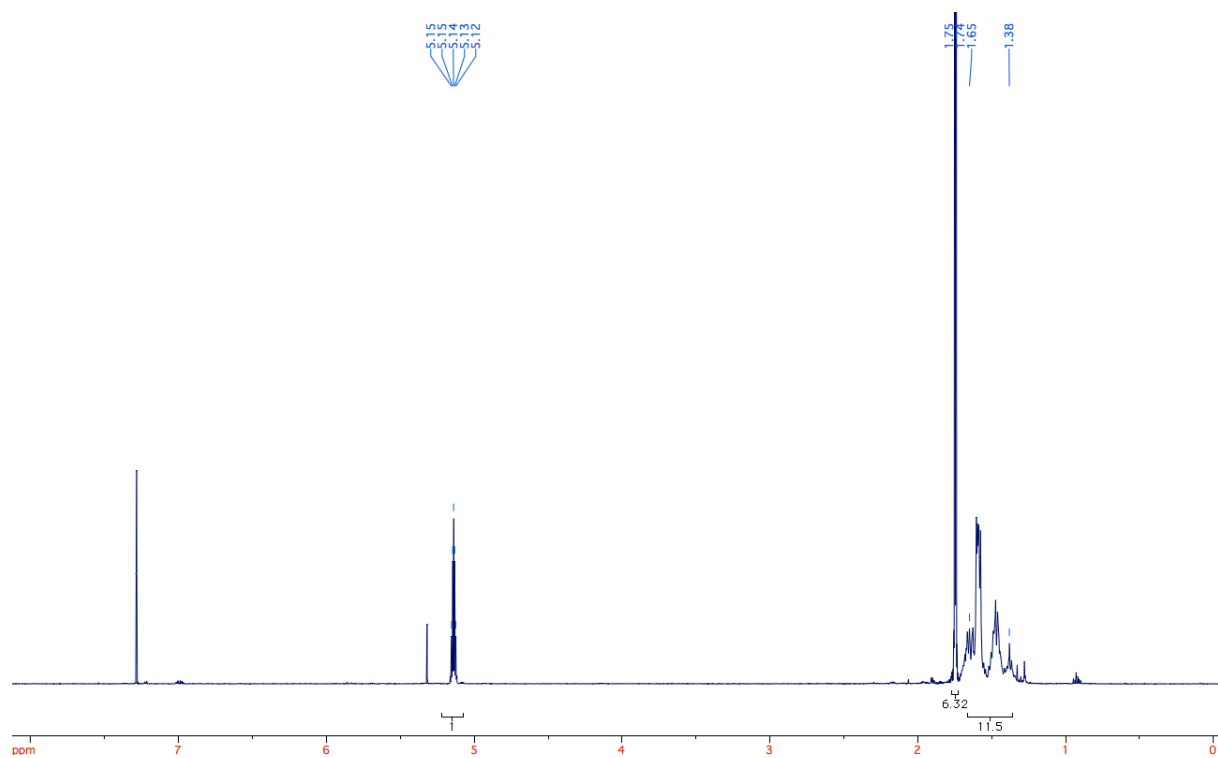
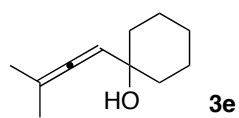
**$^1\text{H}$ - &  $^{13}\text{C}$ -NMR spectra of the compounds**

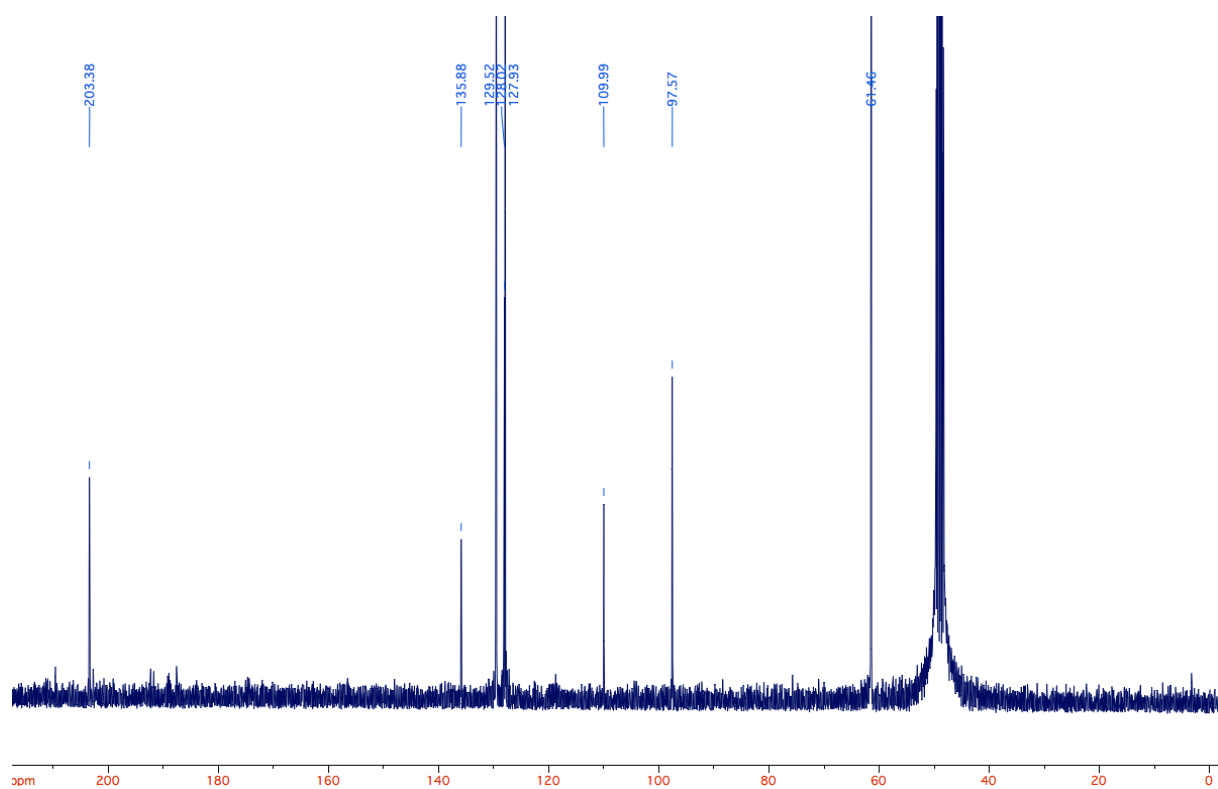
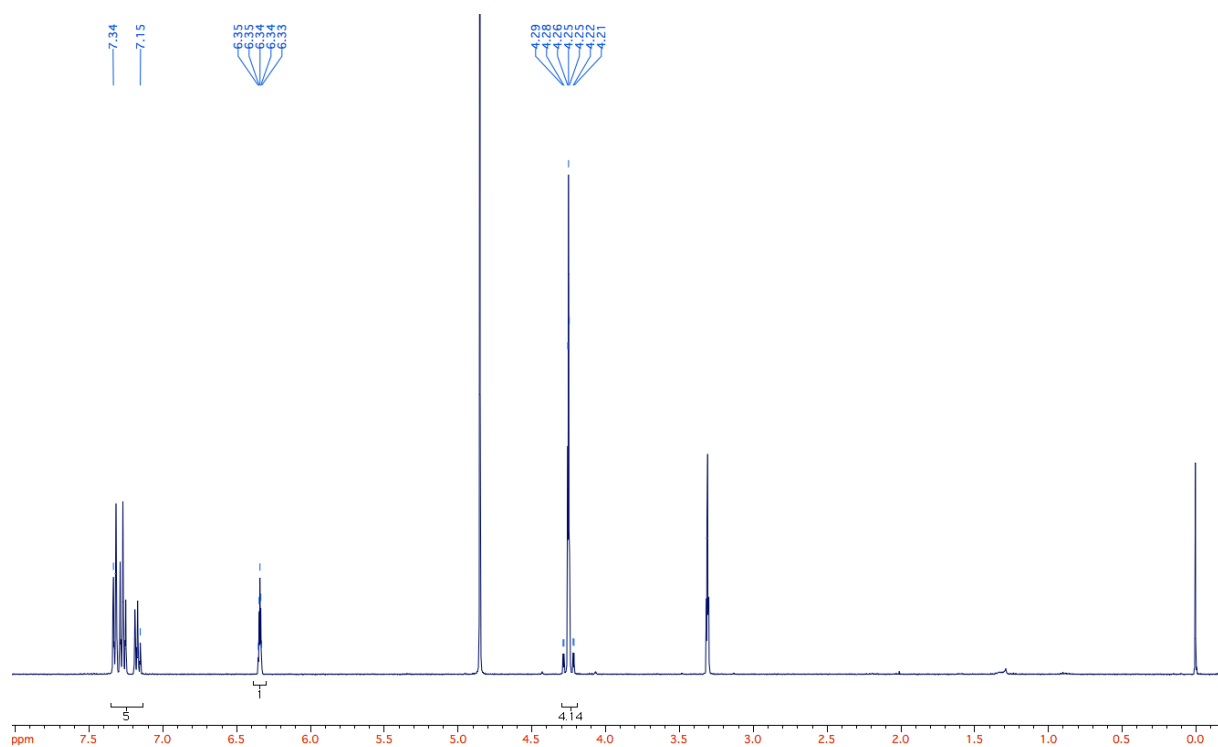
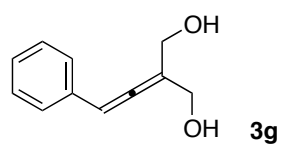


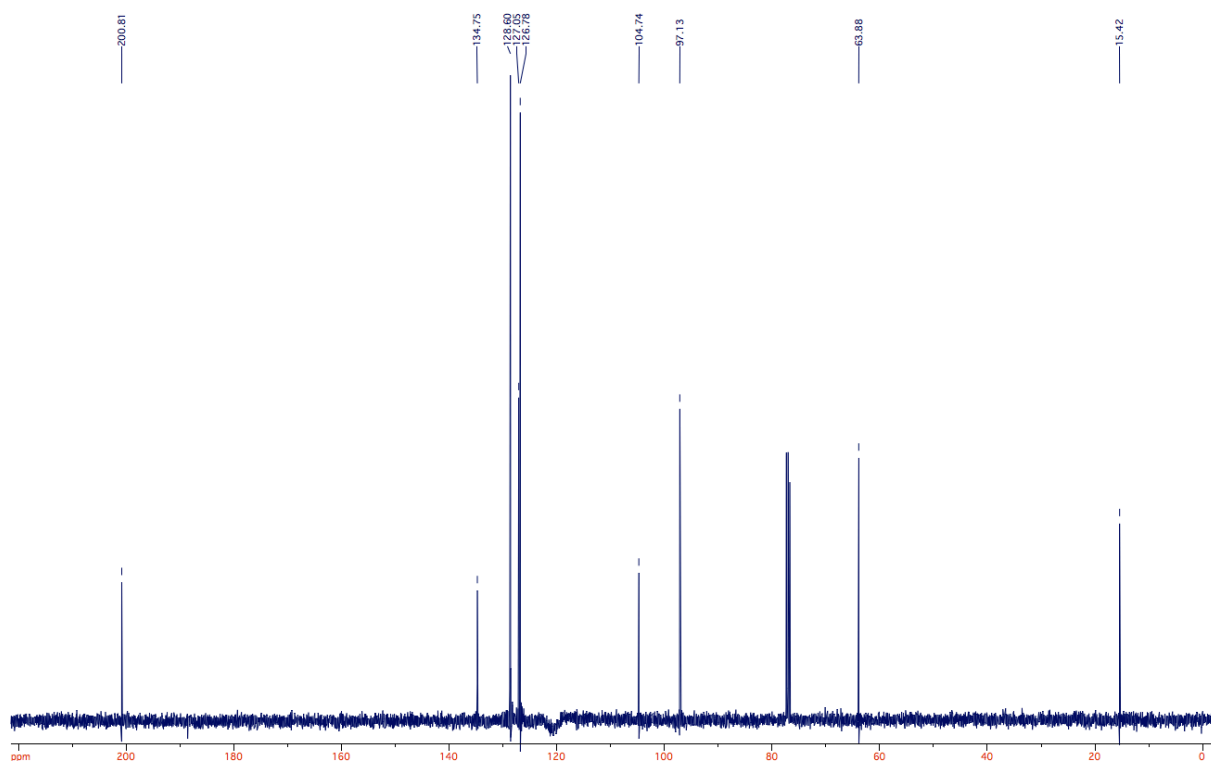
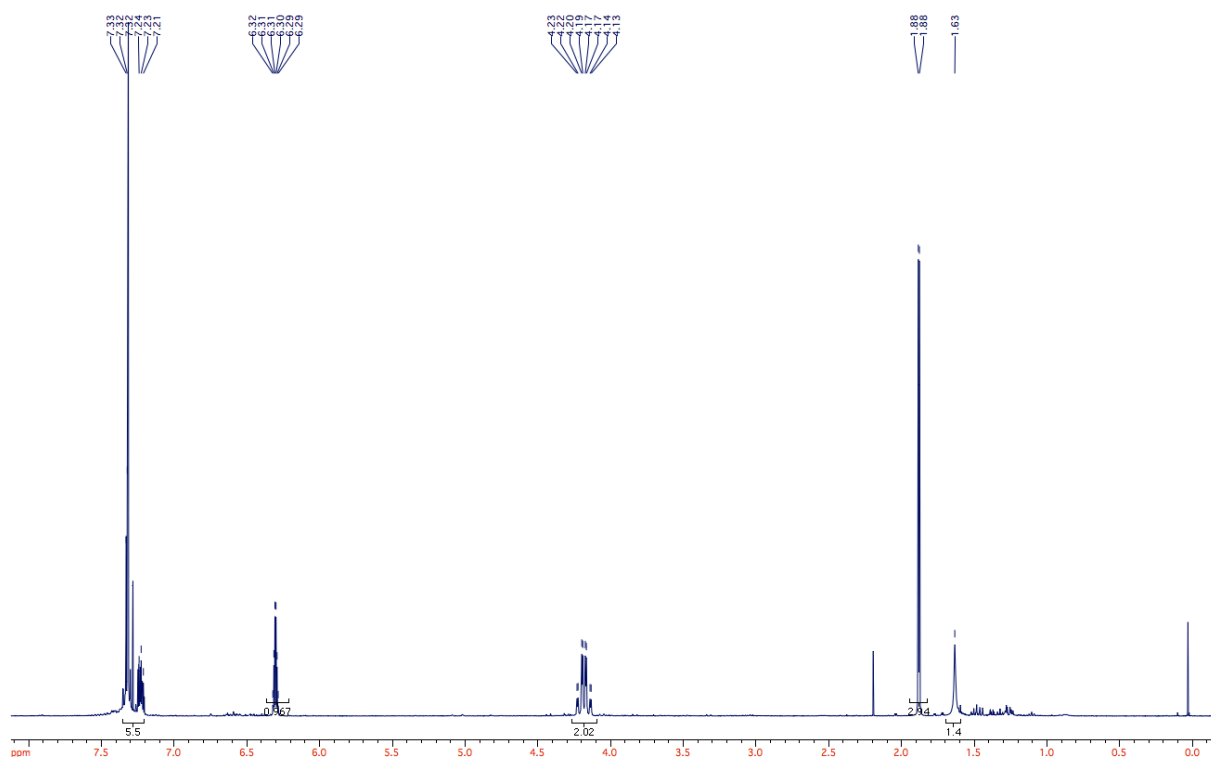
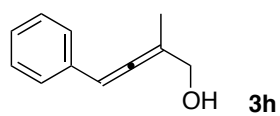




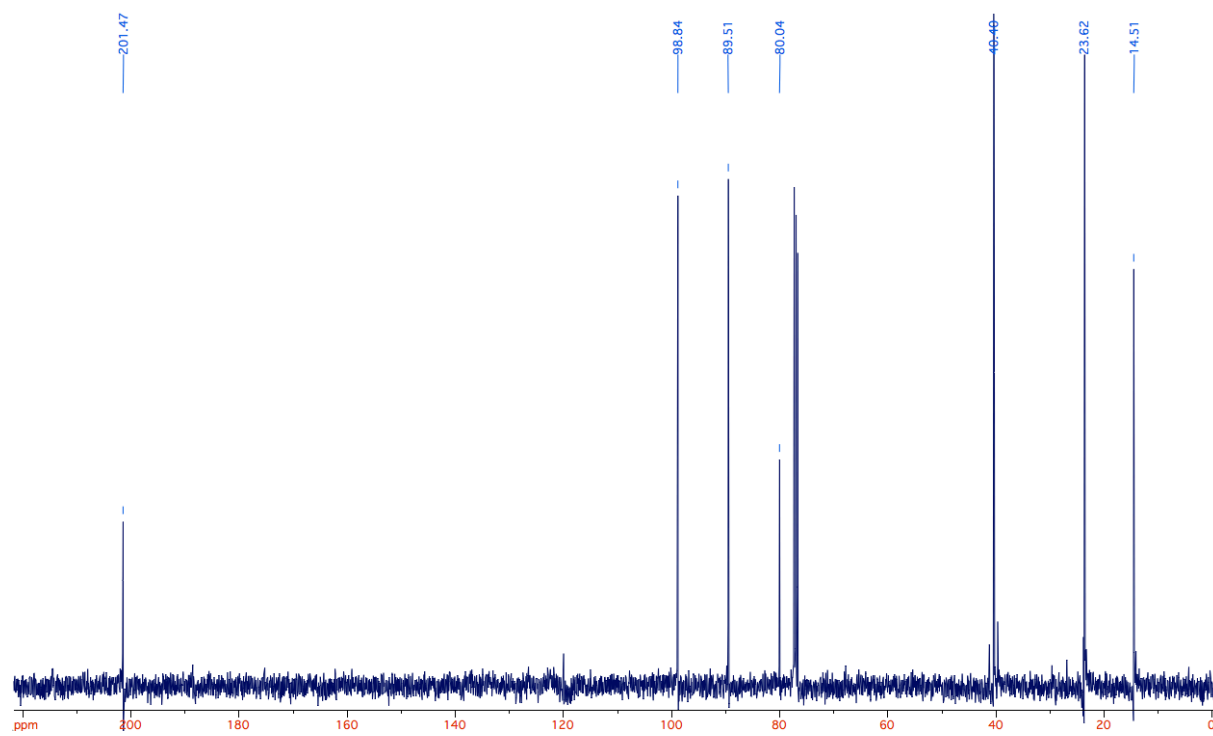
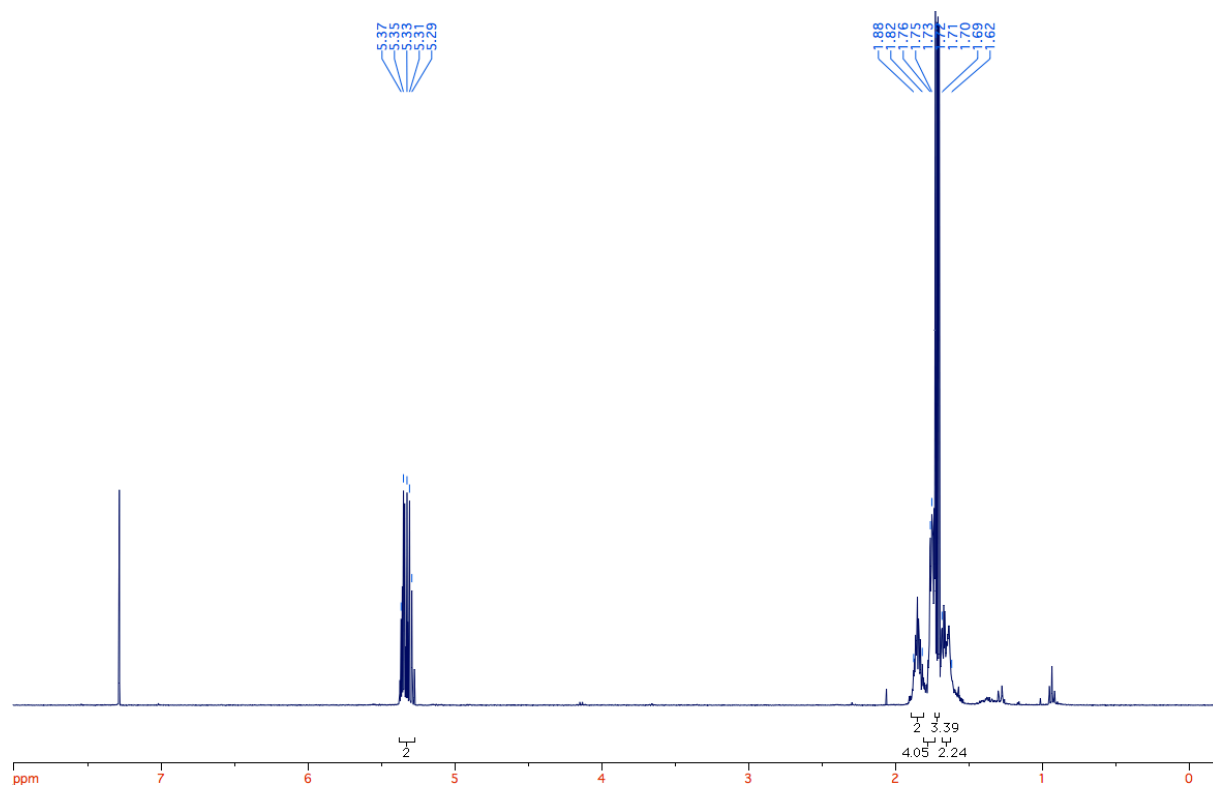
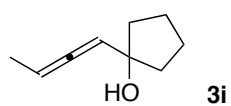


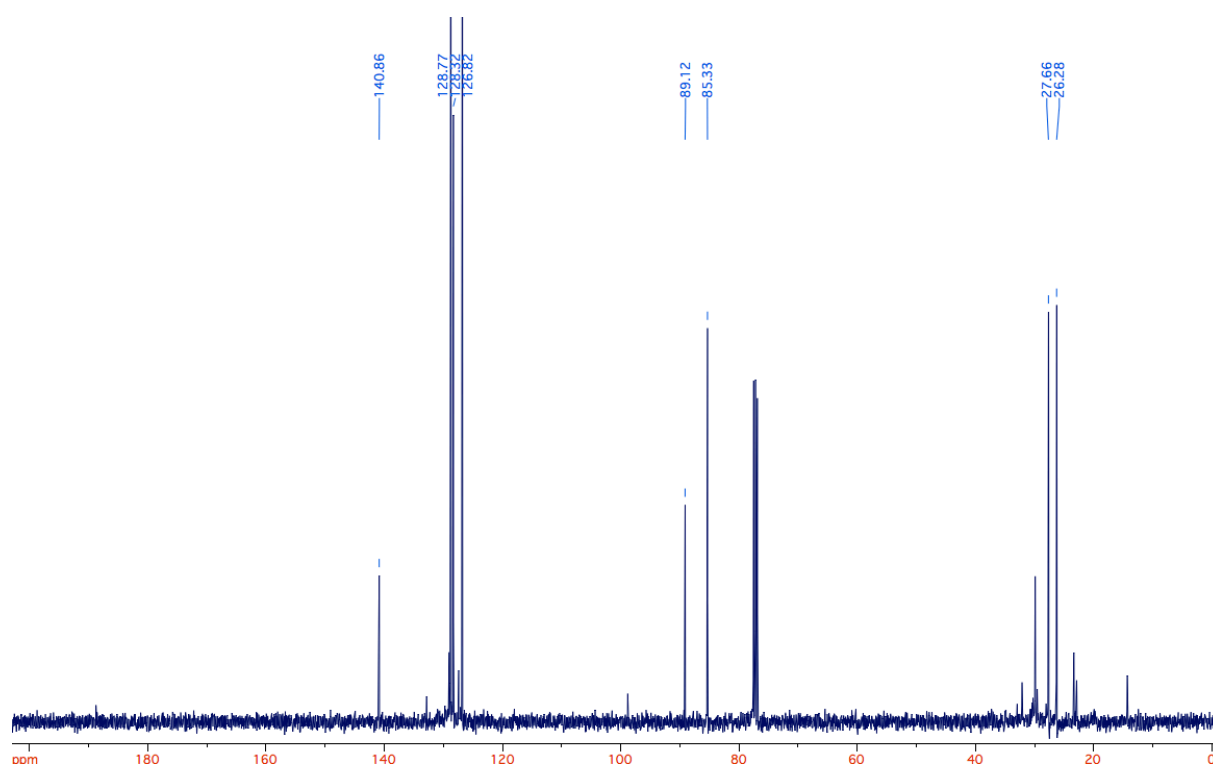
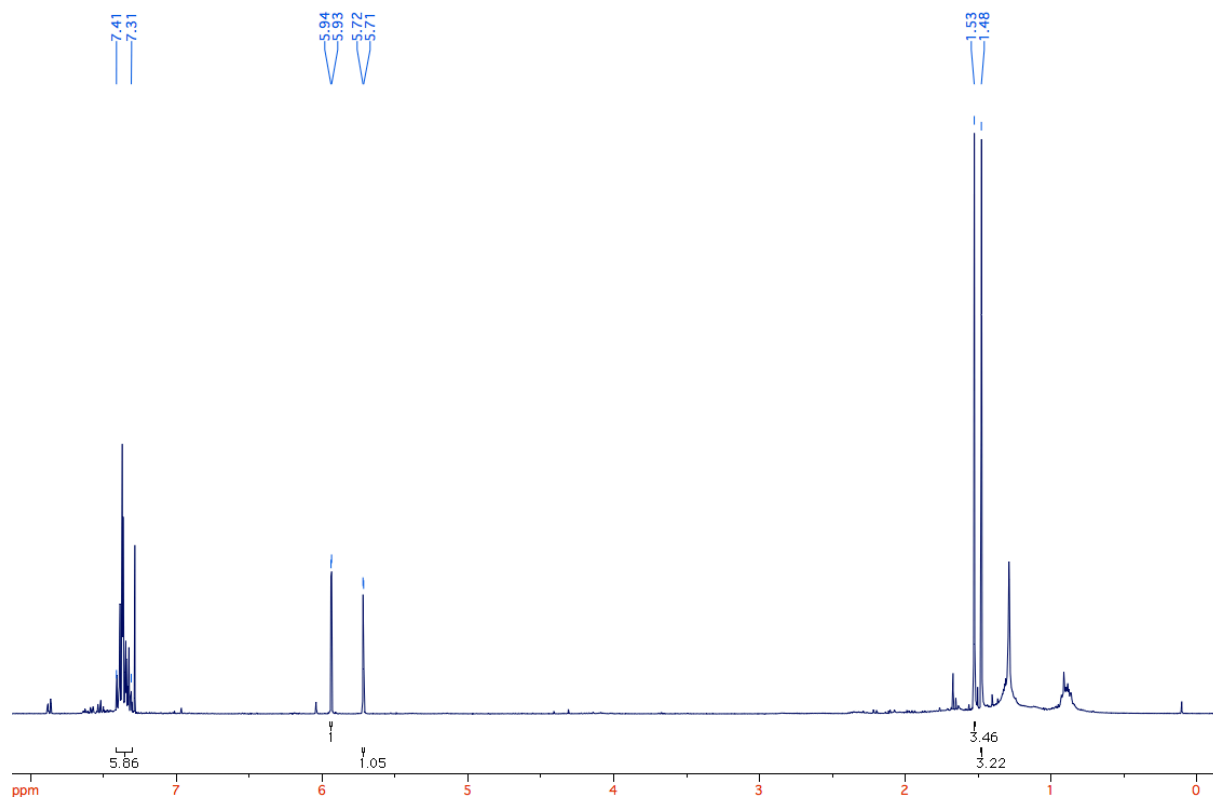
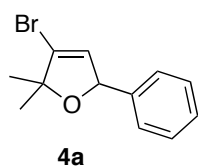


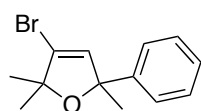




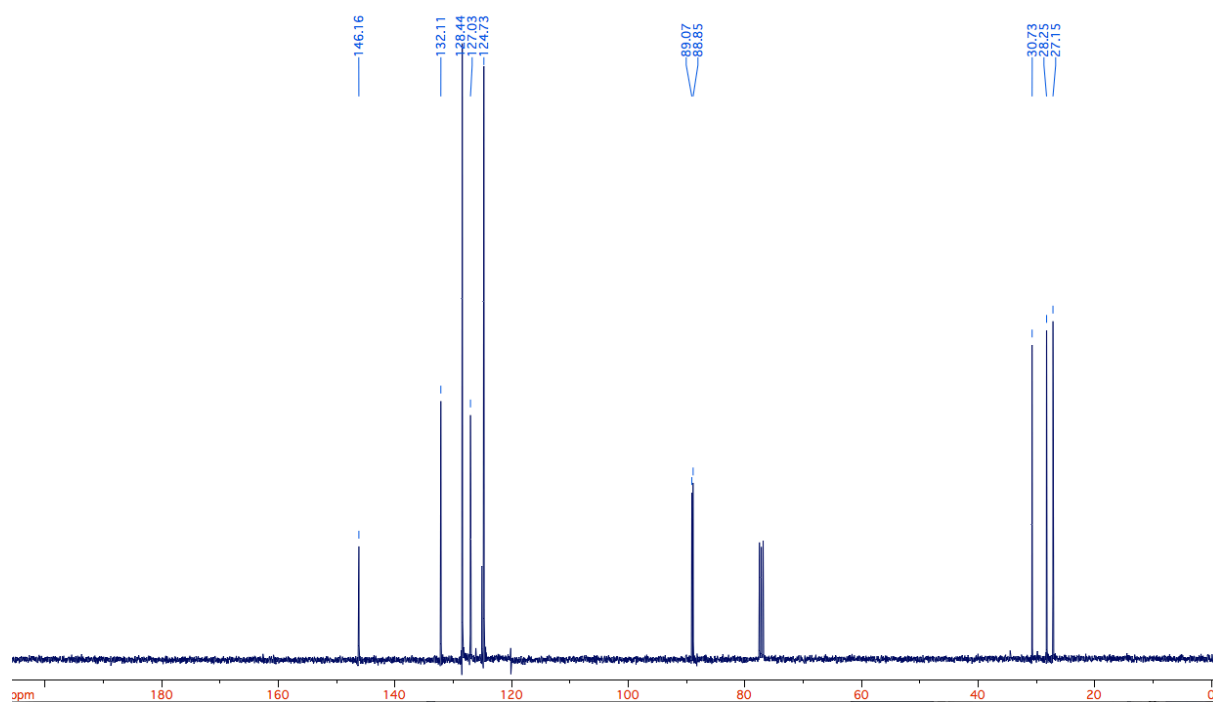
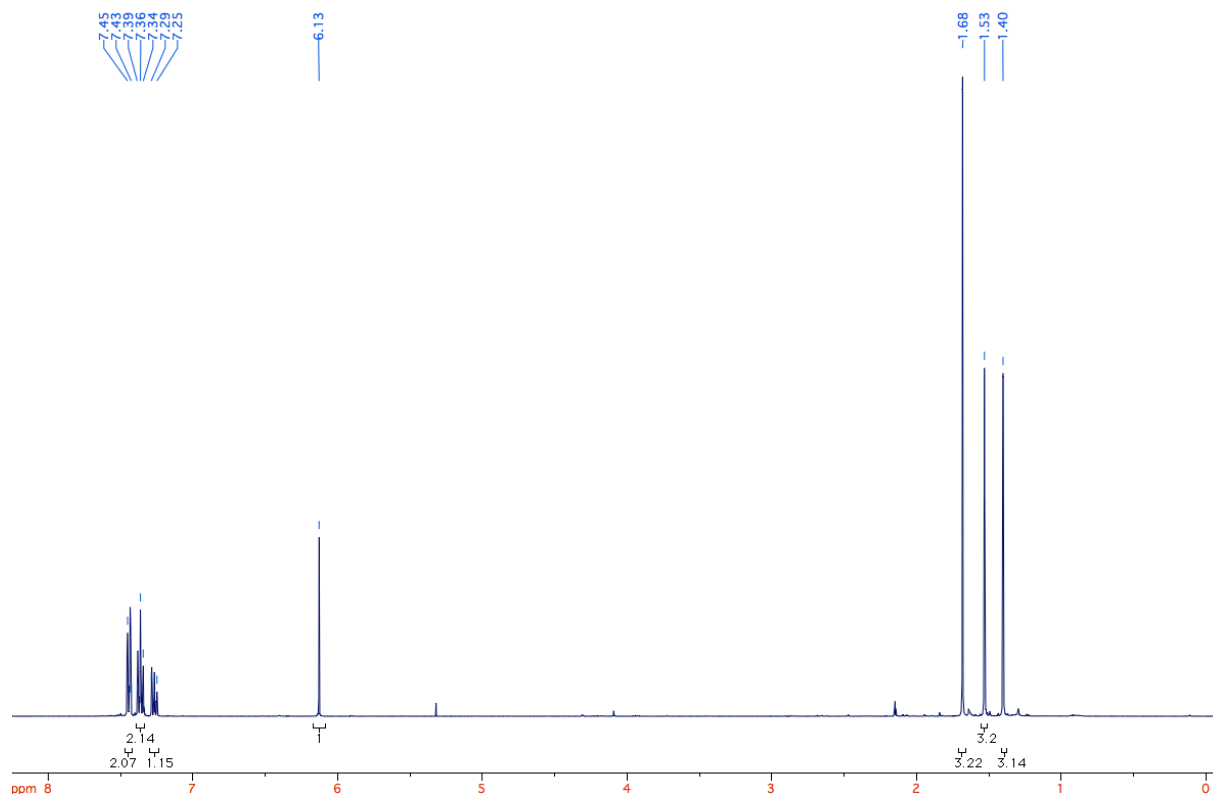


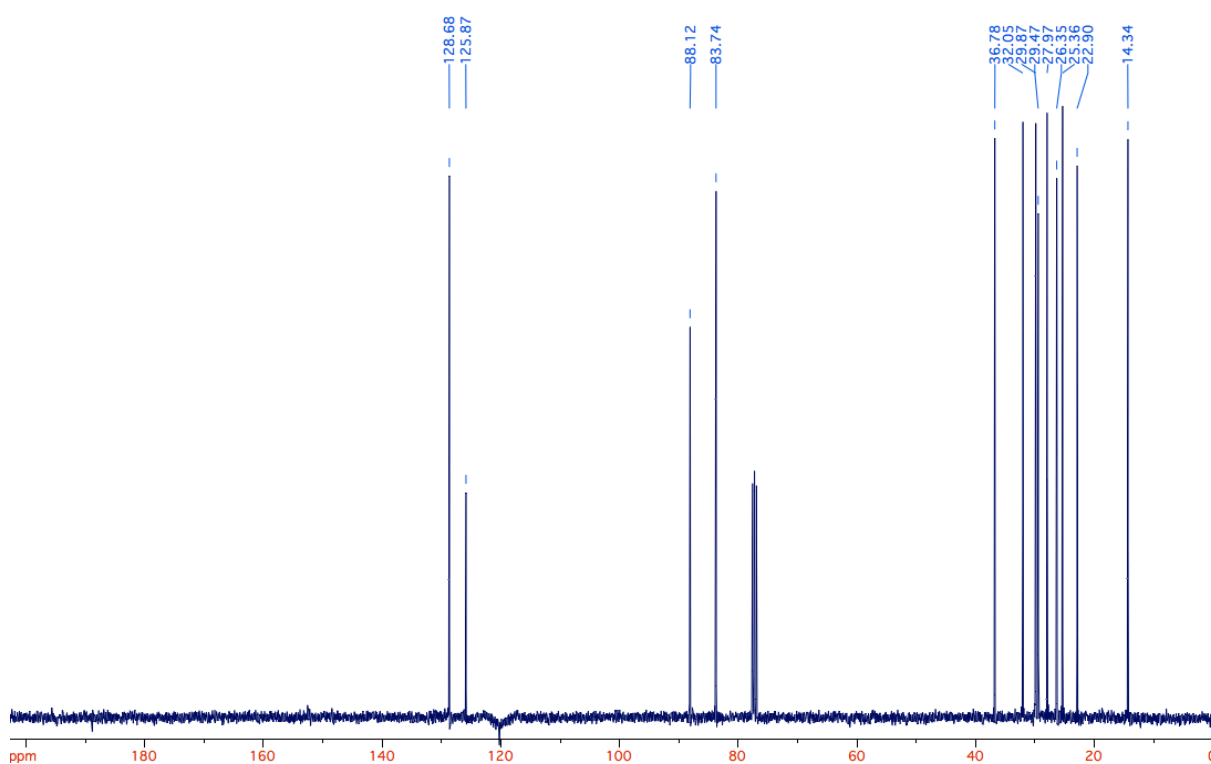
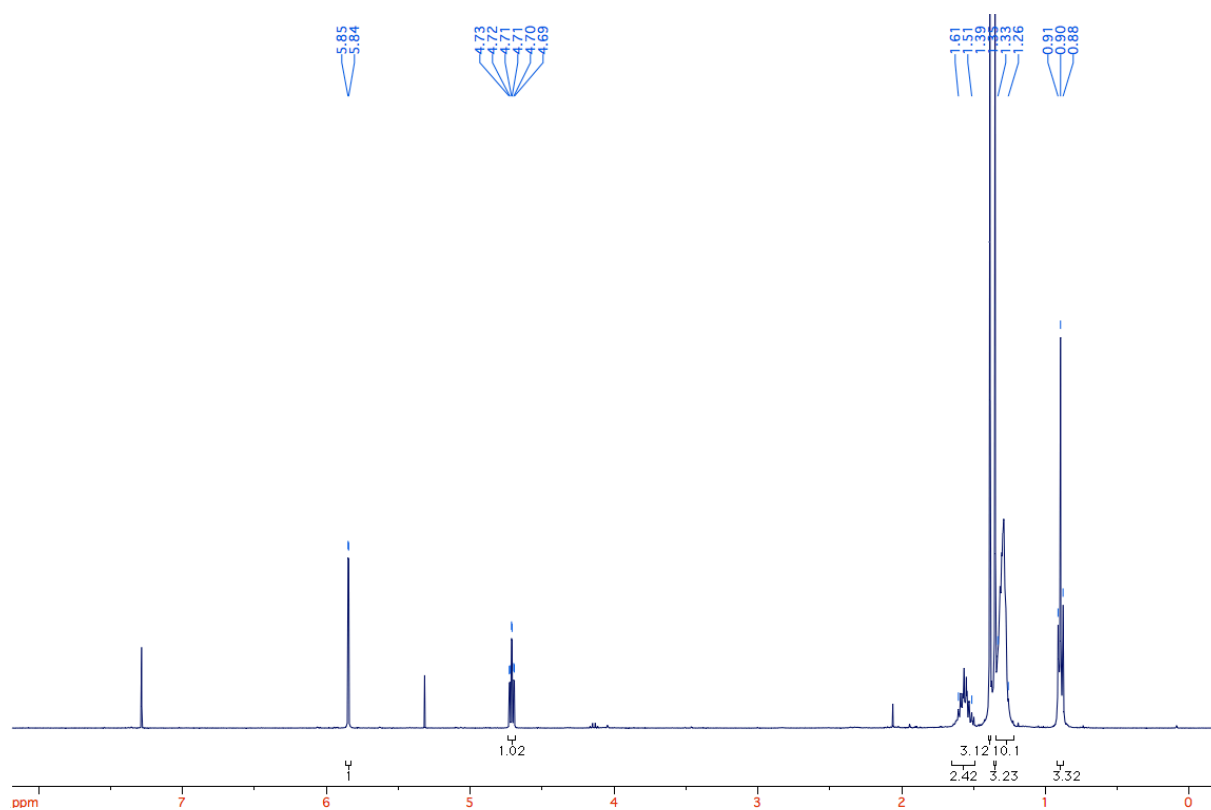
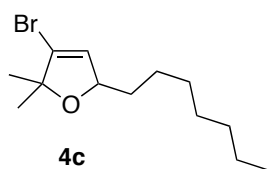


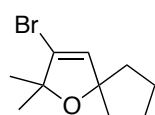




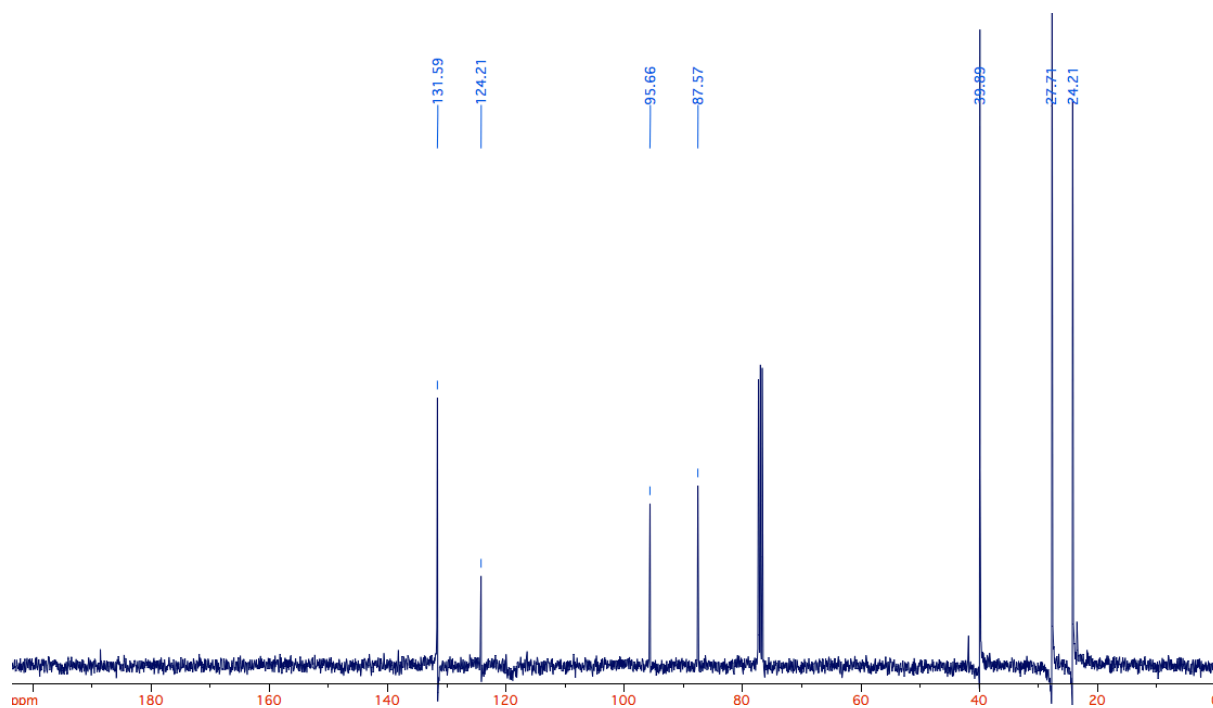
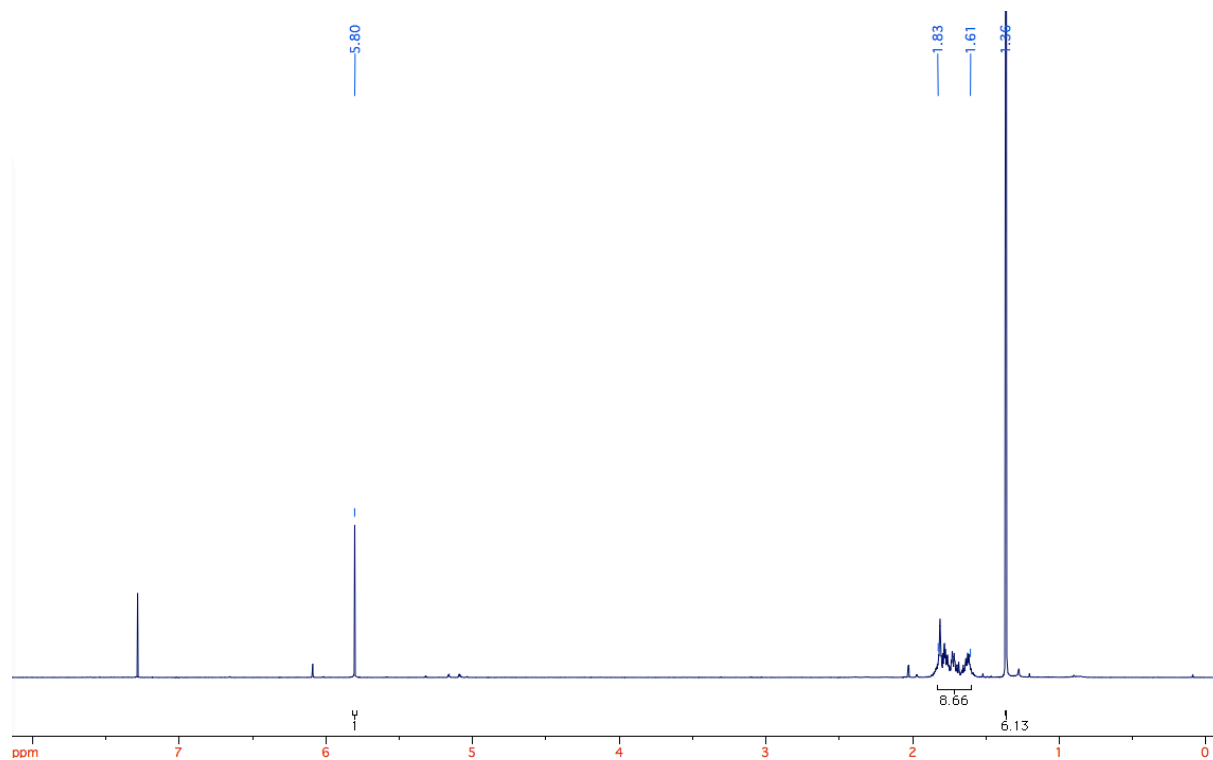
**4b**

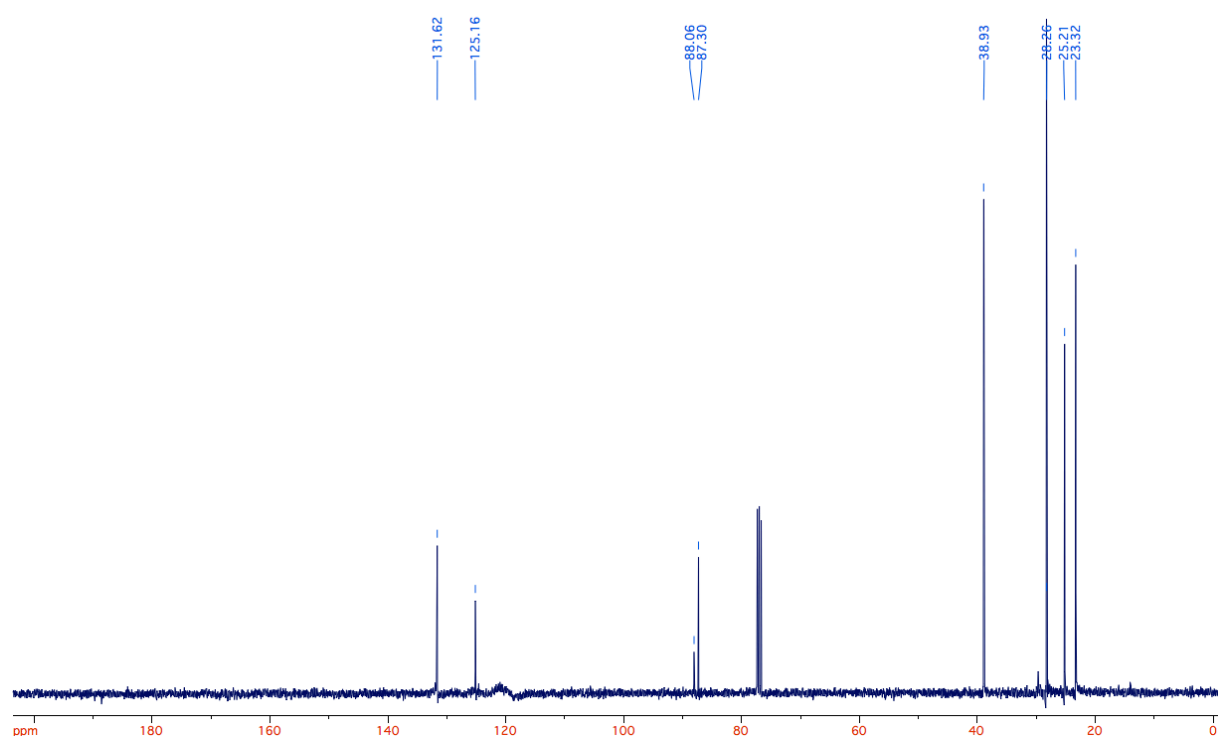
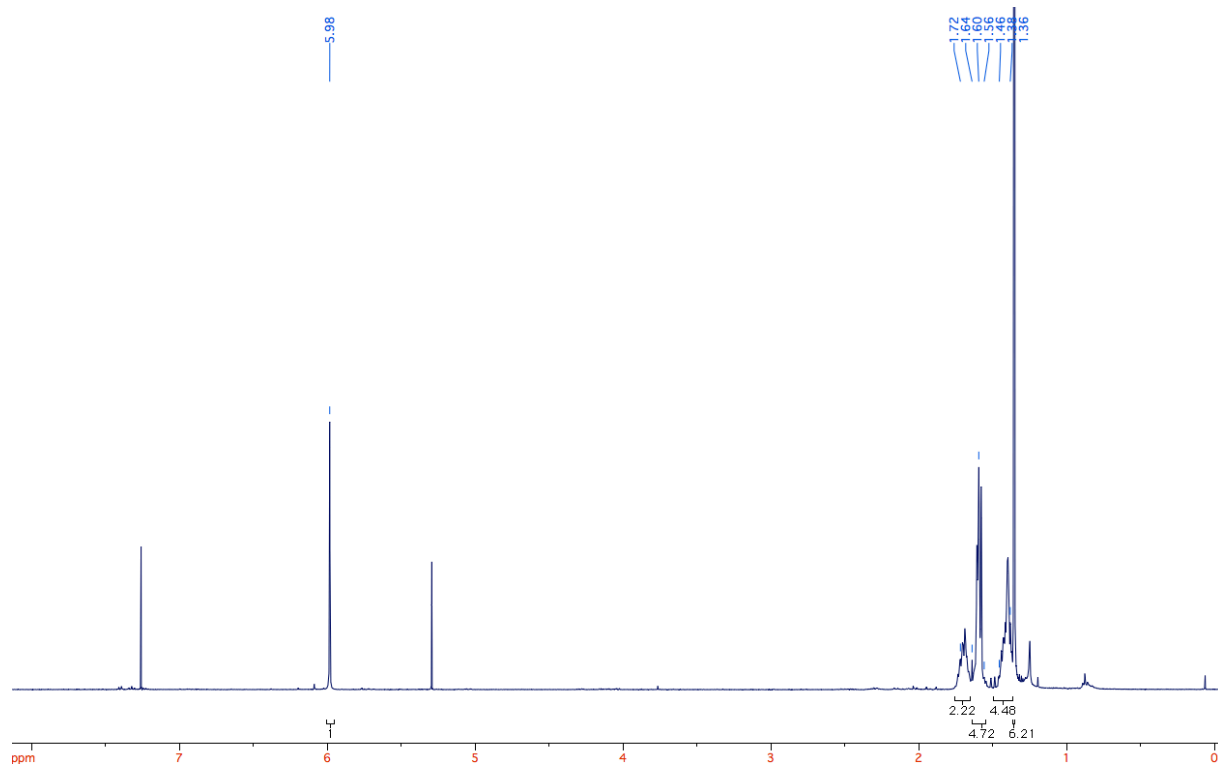
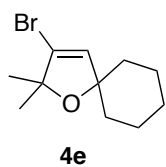


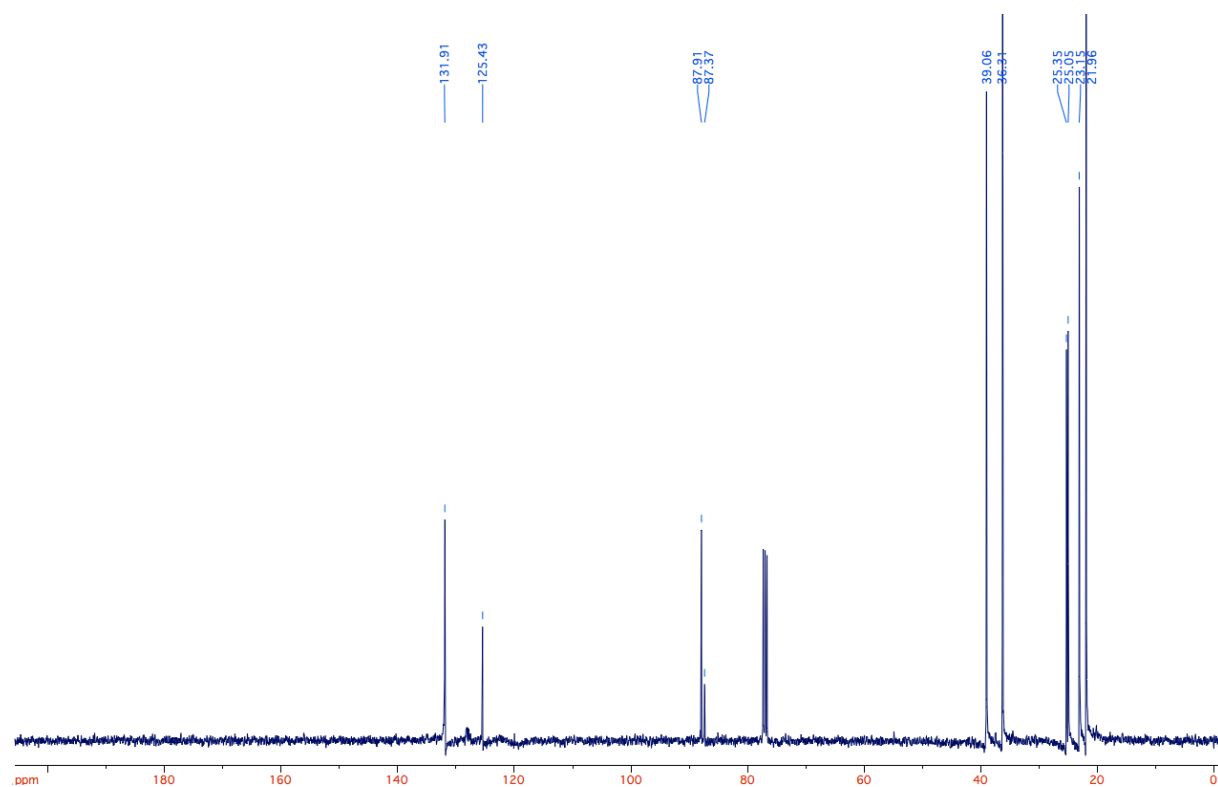
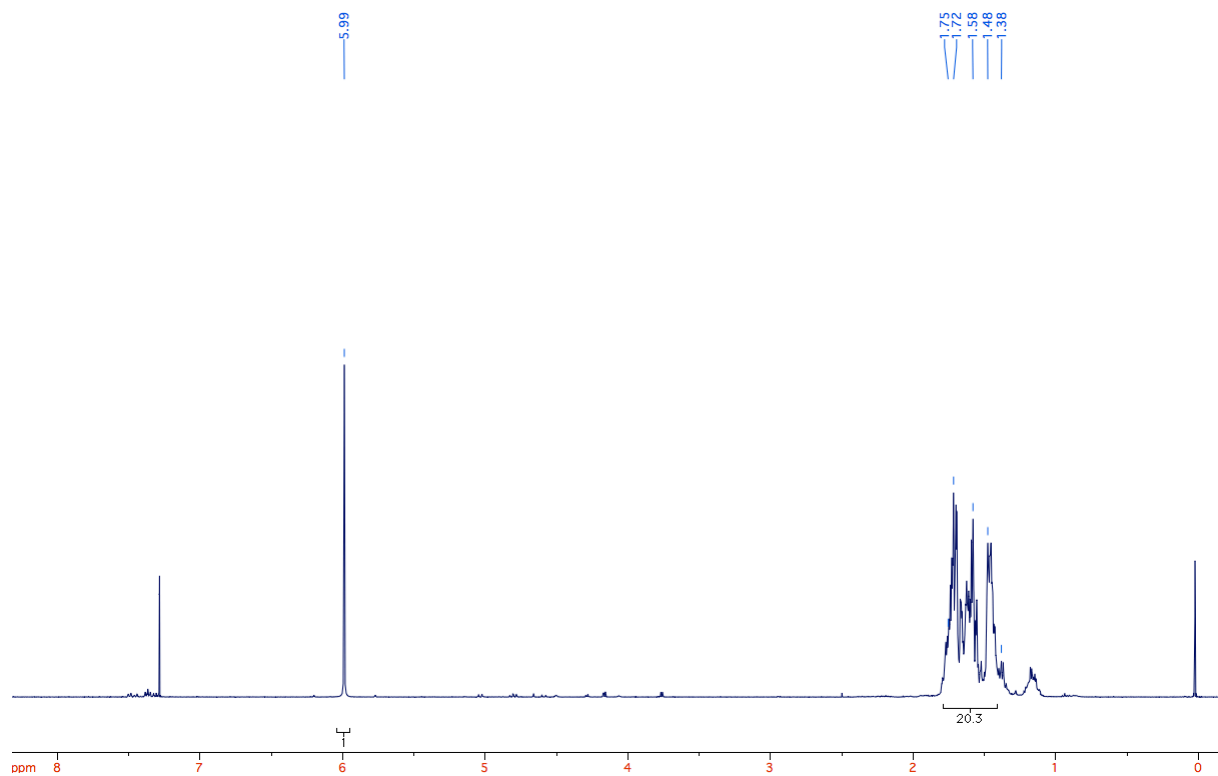
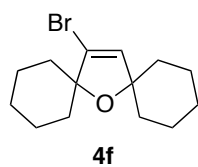


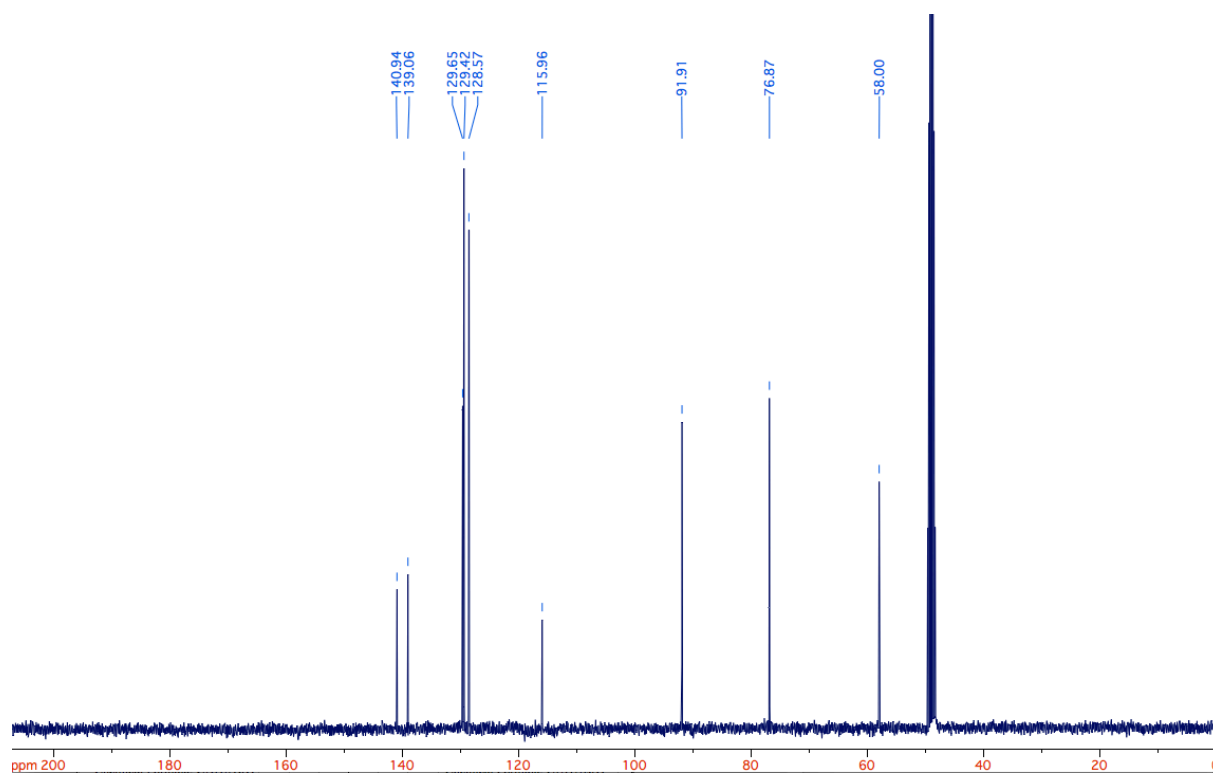
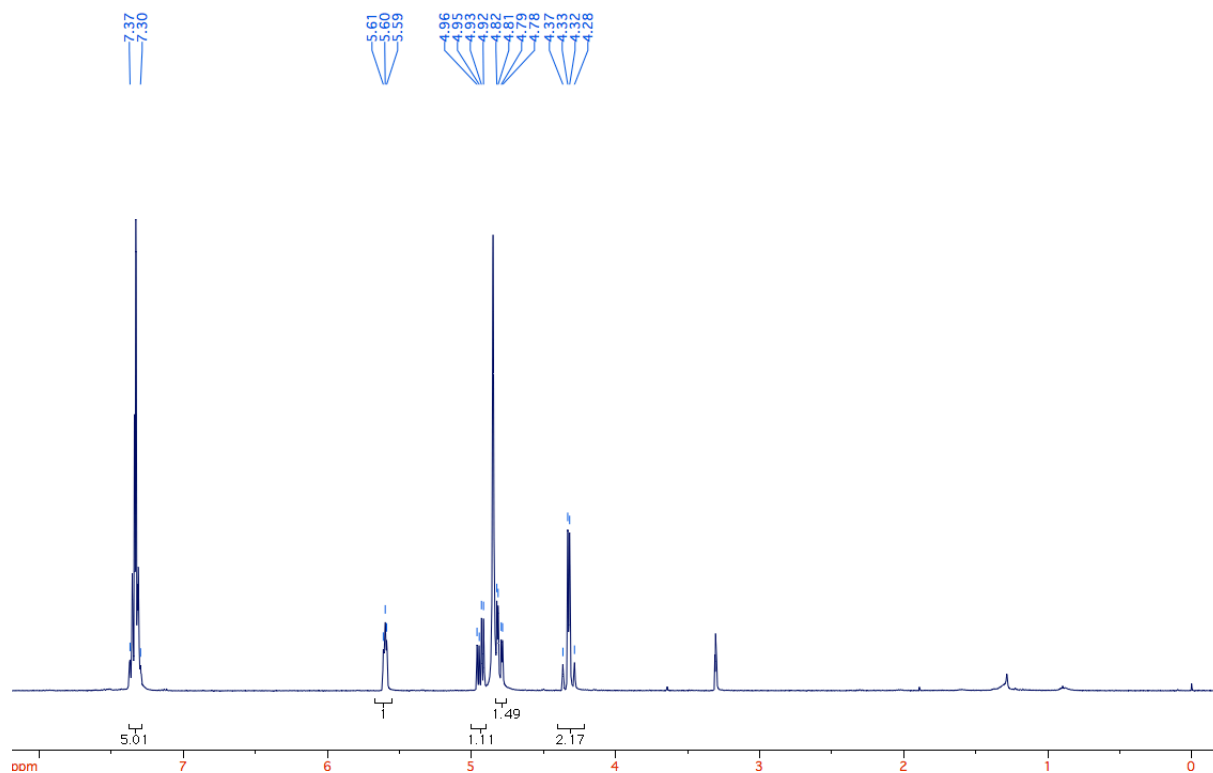
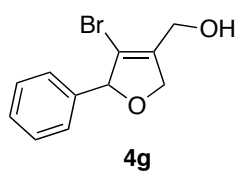


**4d**

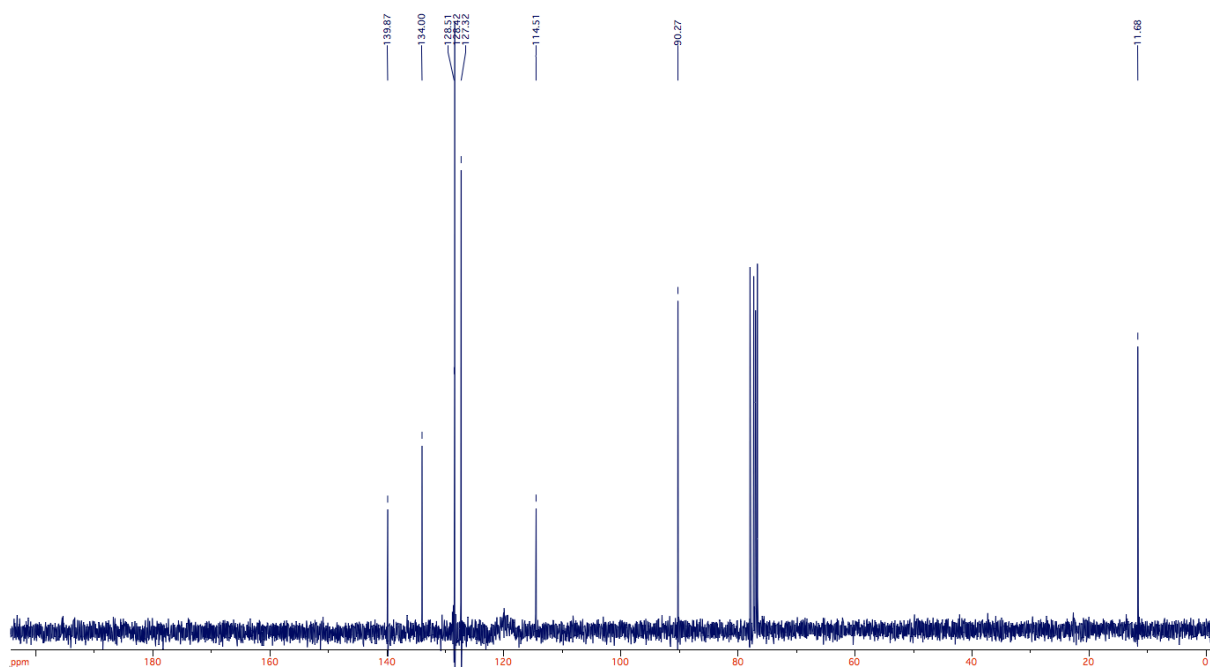
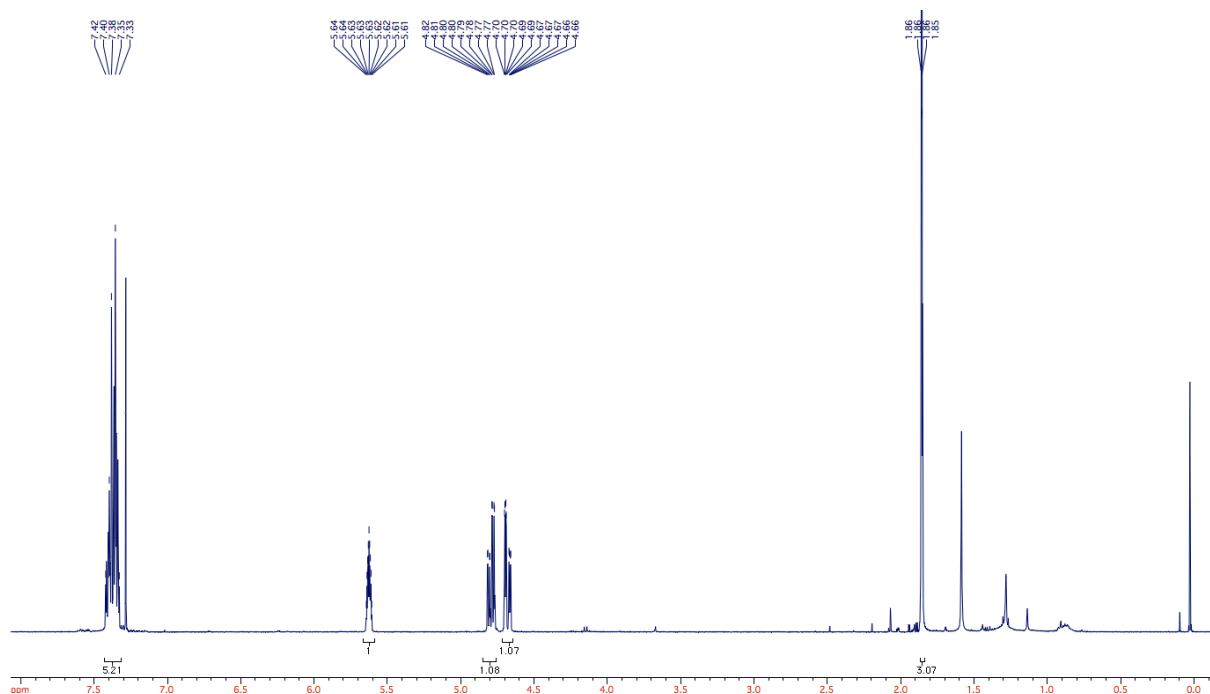
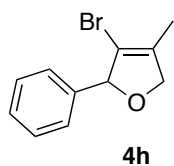


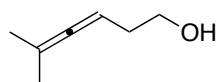




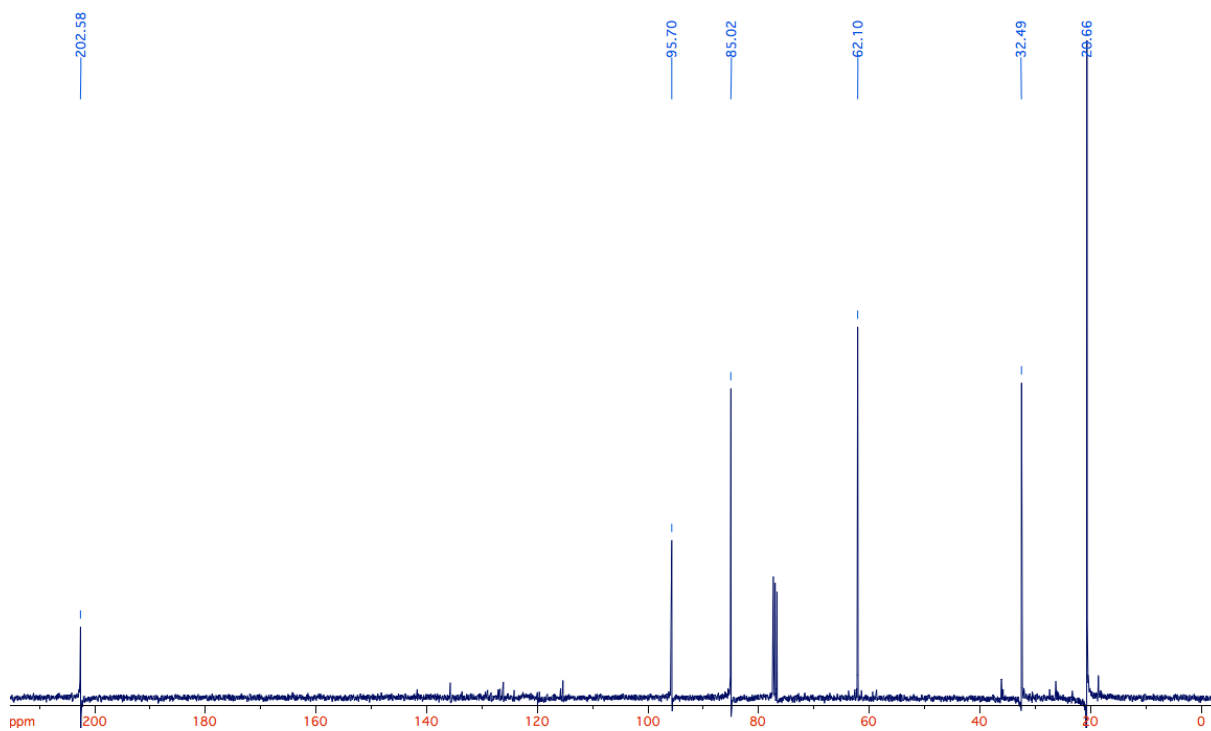
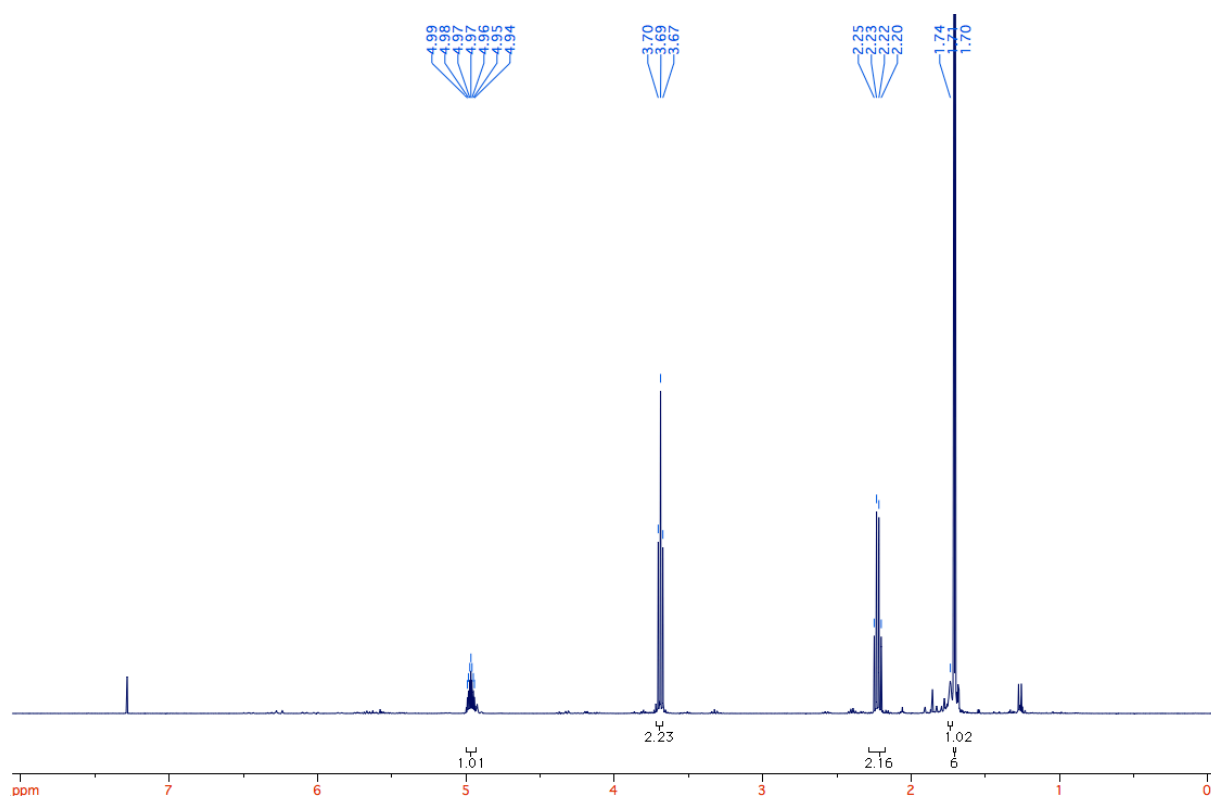


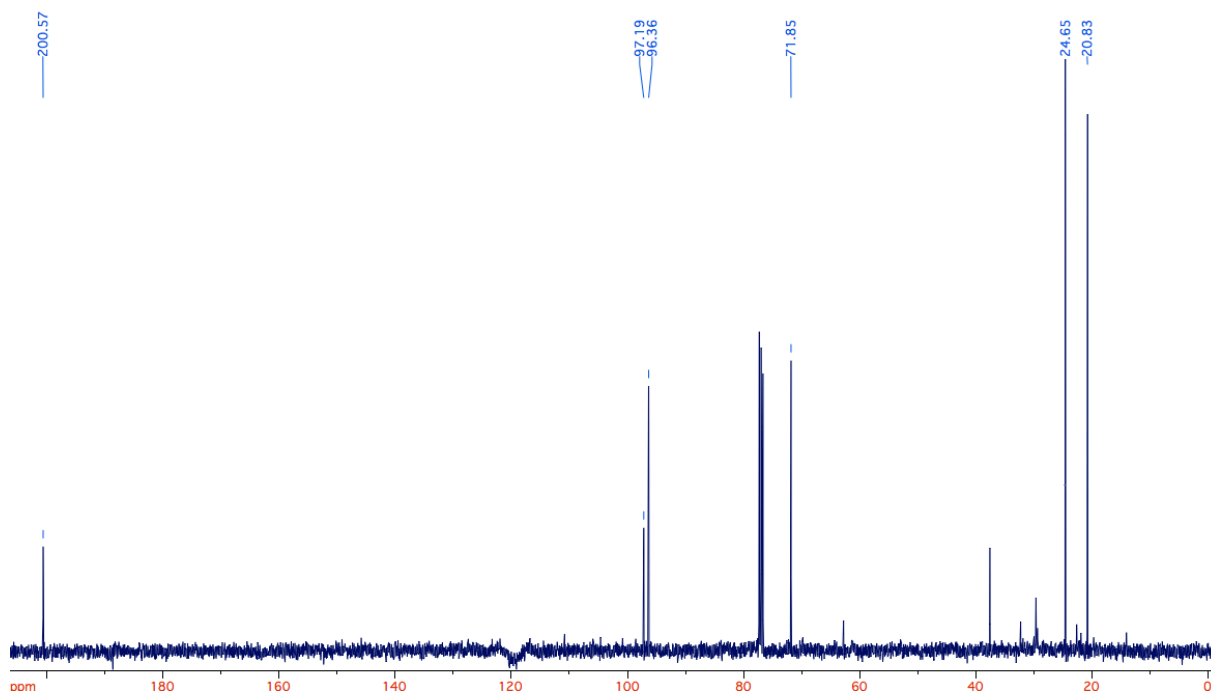
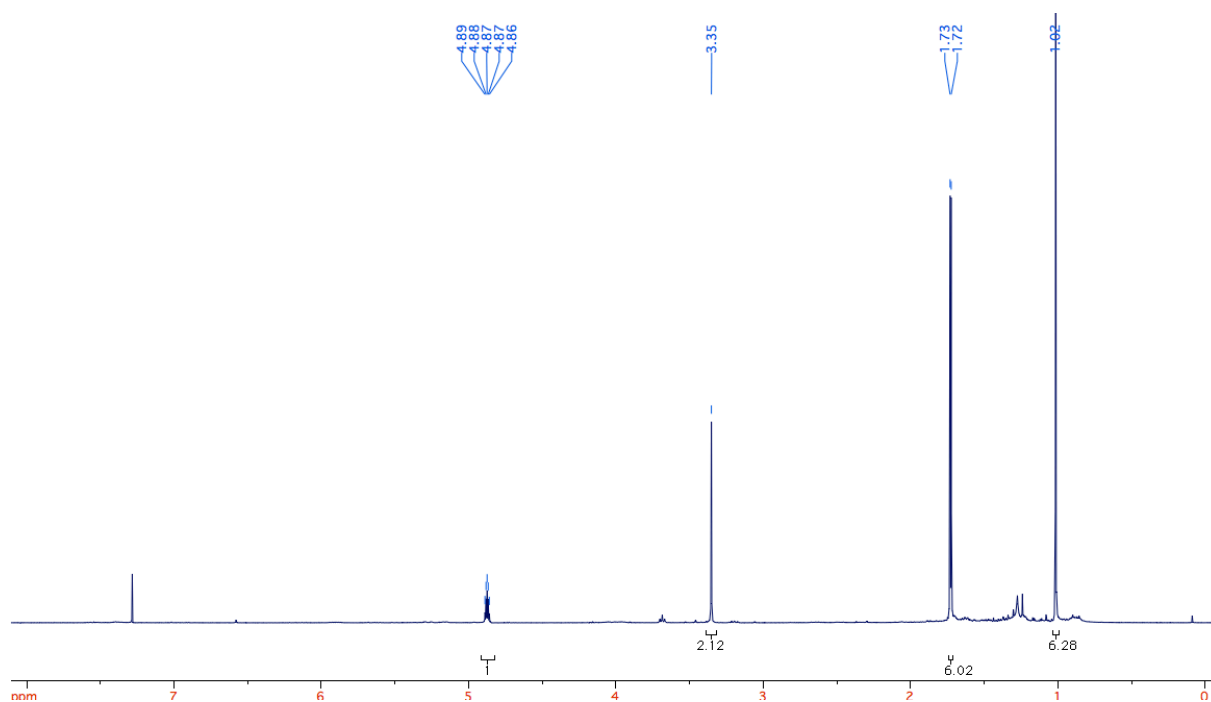
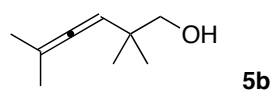


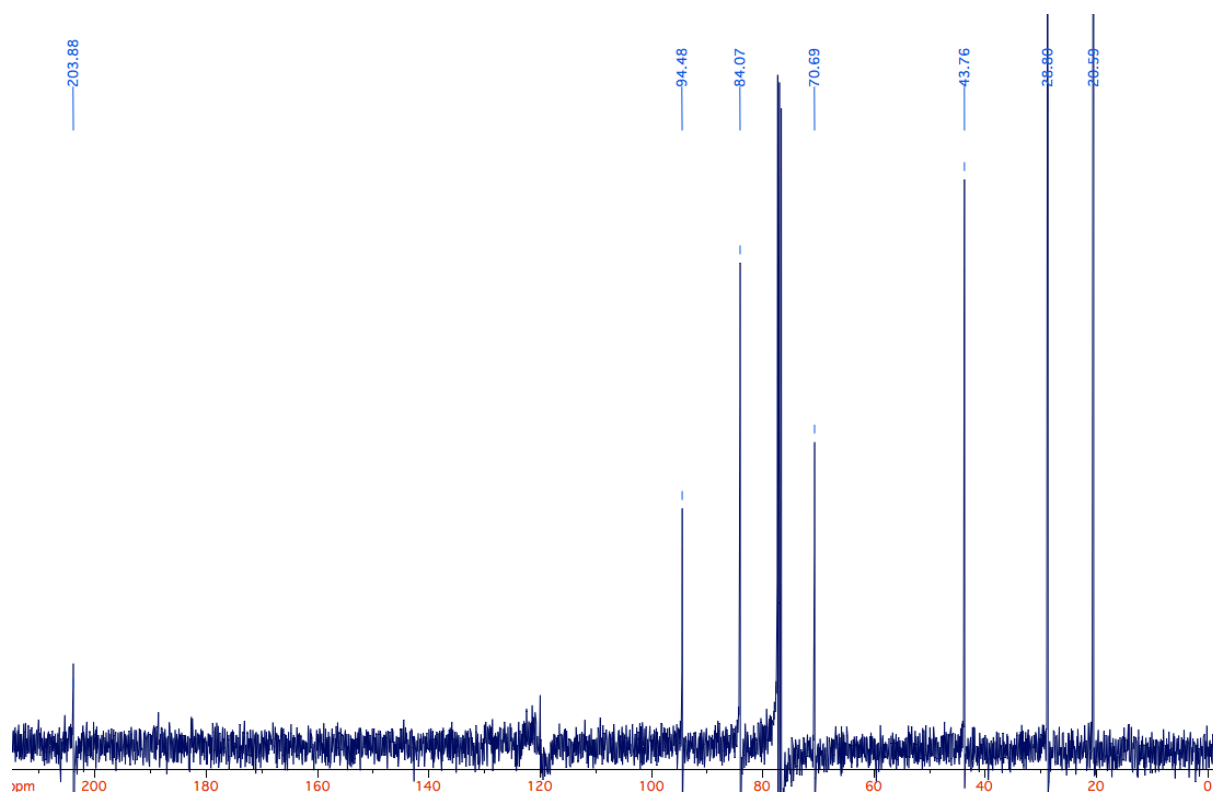
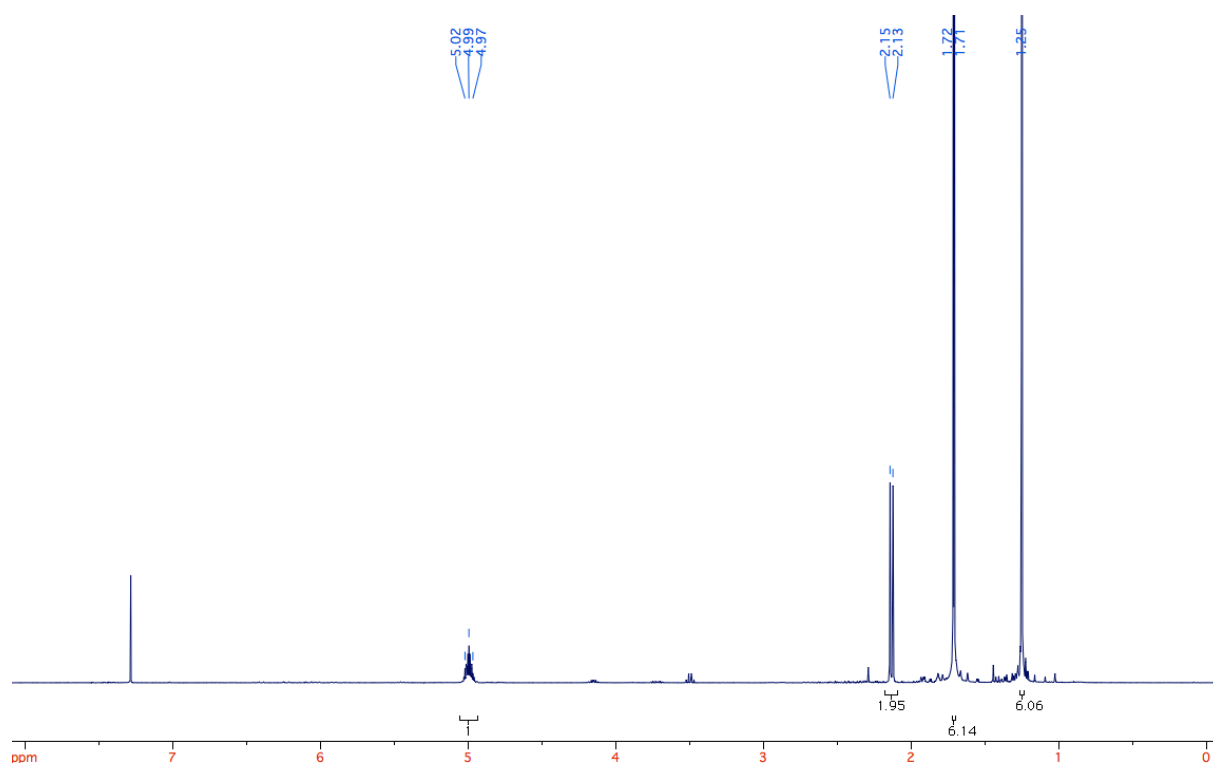
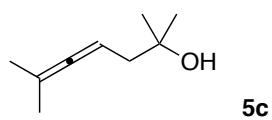


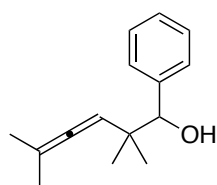


**5a**

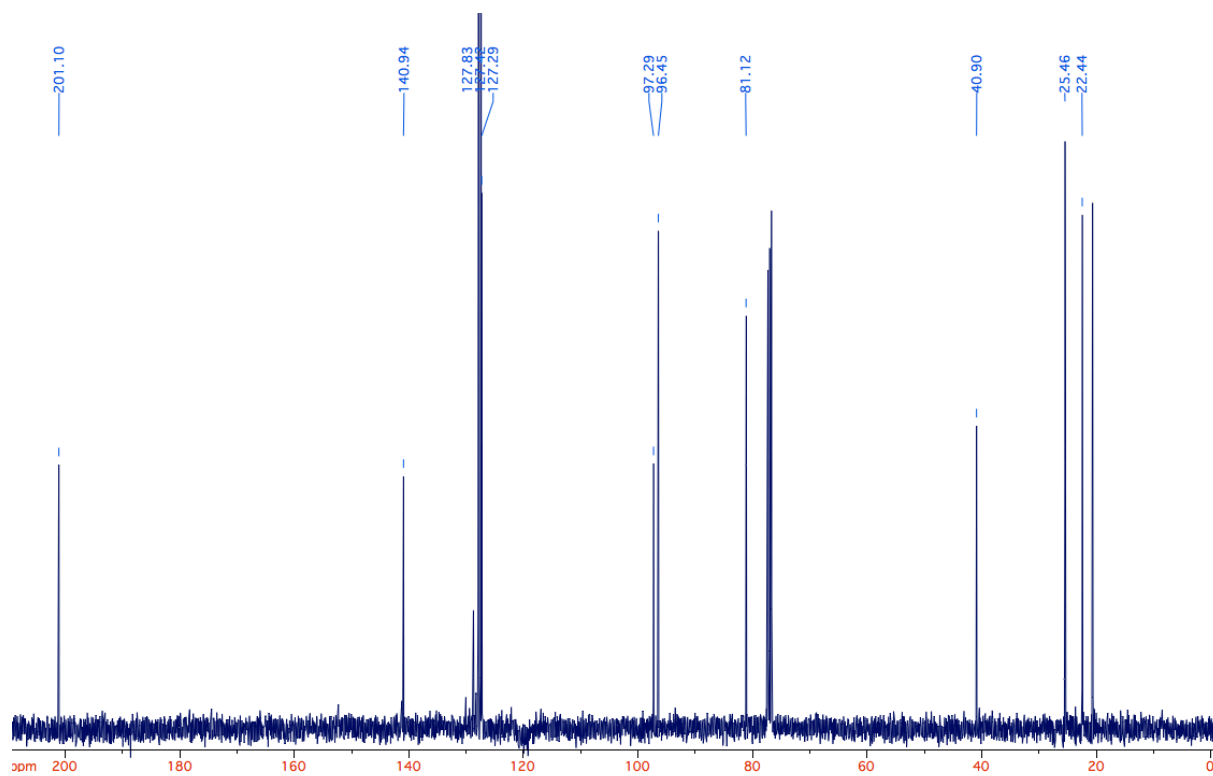
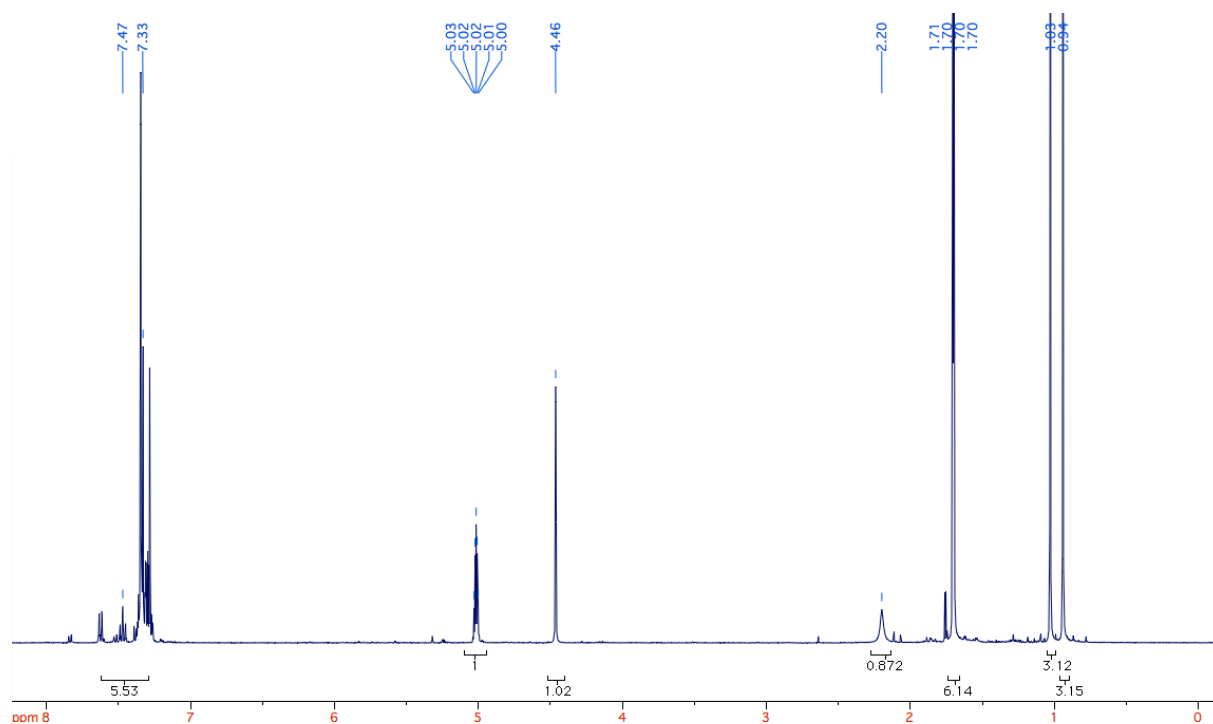


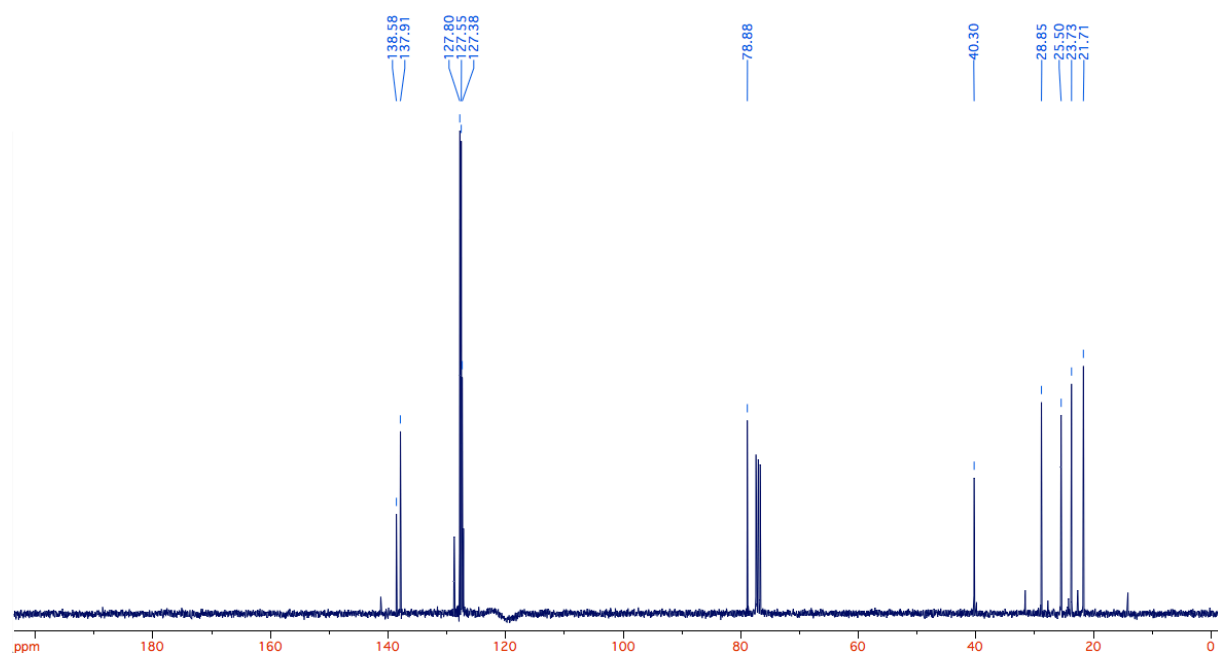
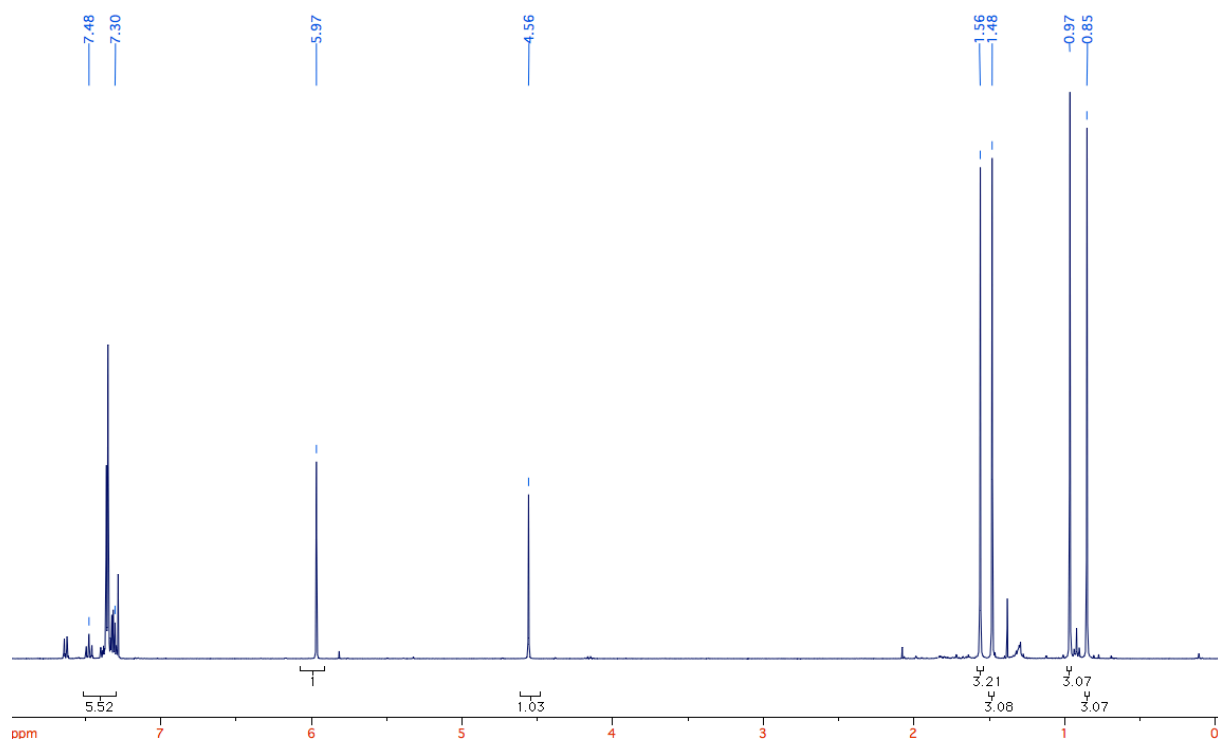
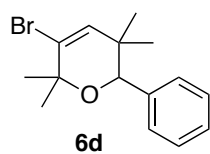


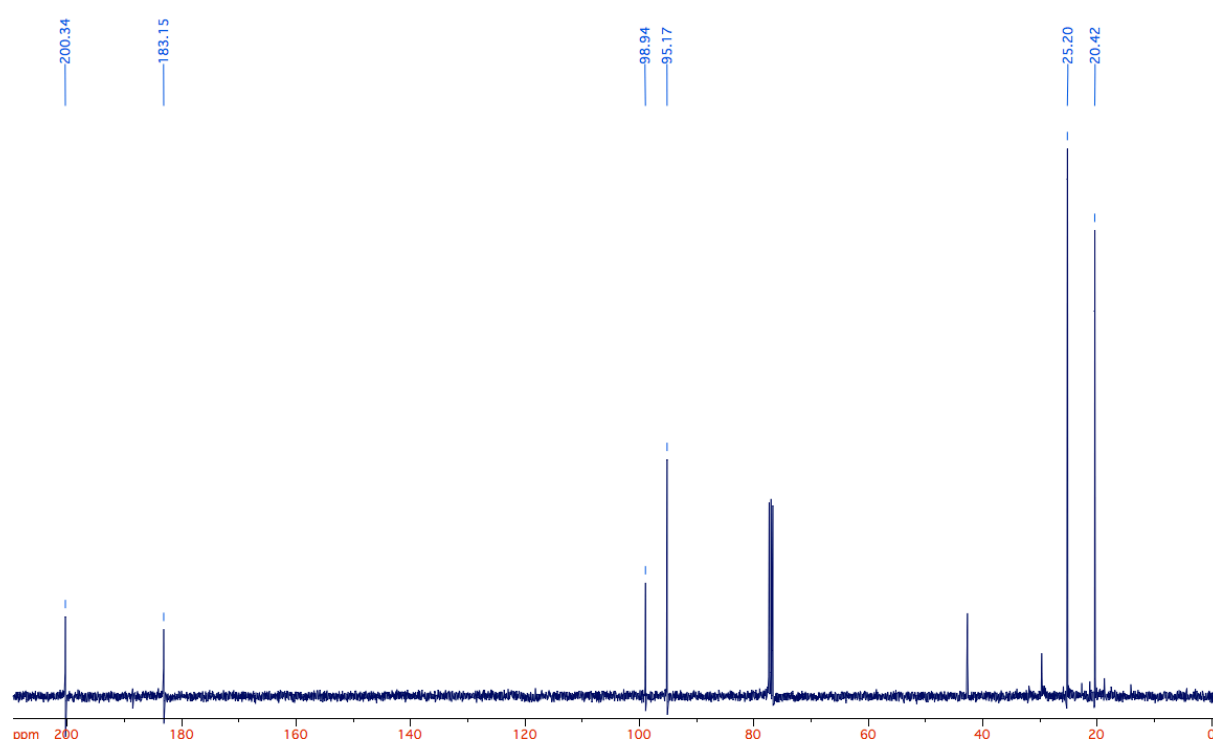
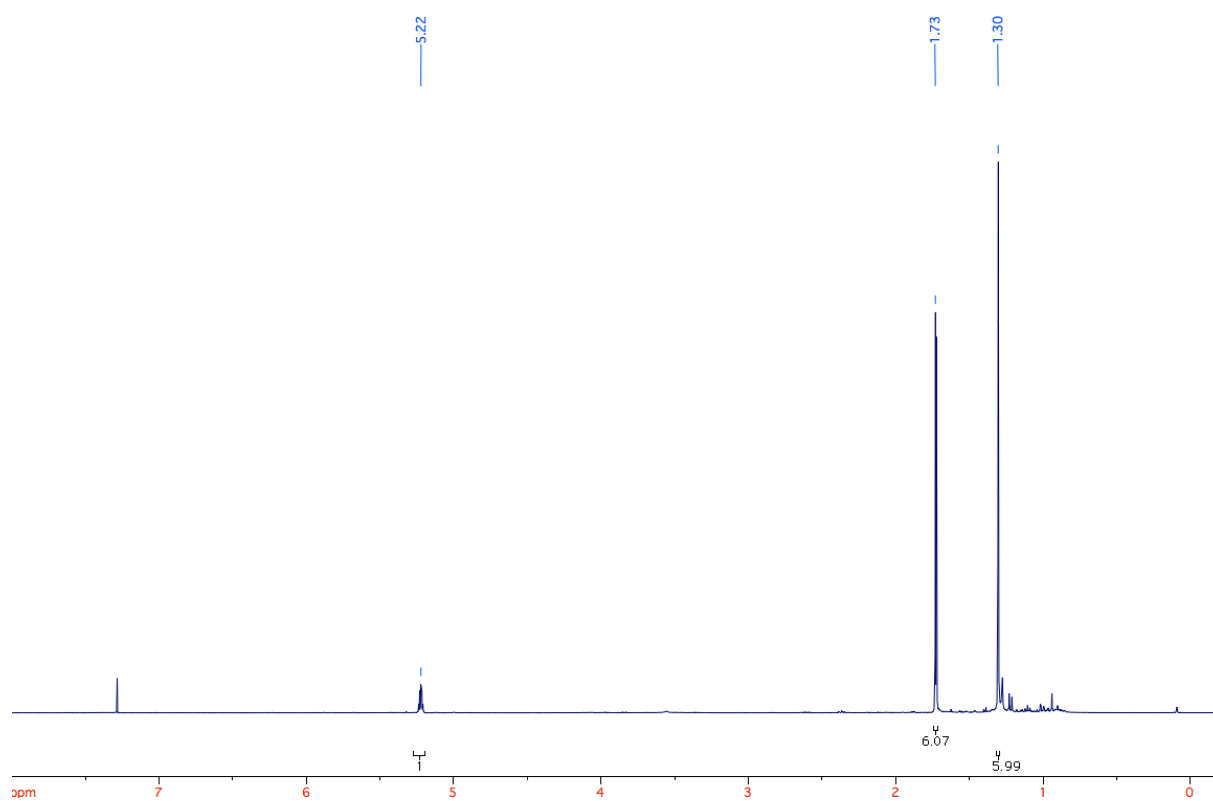
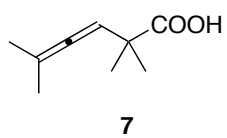


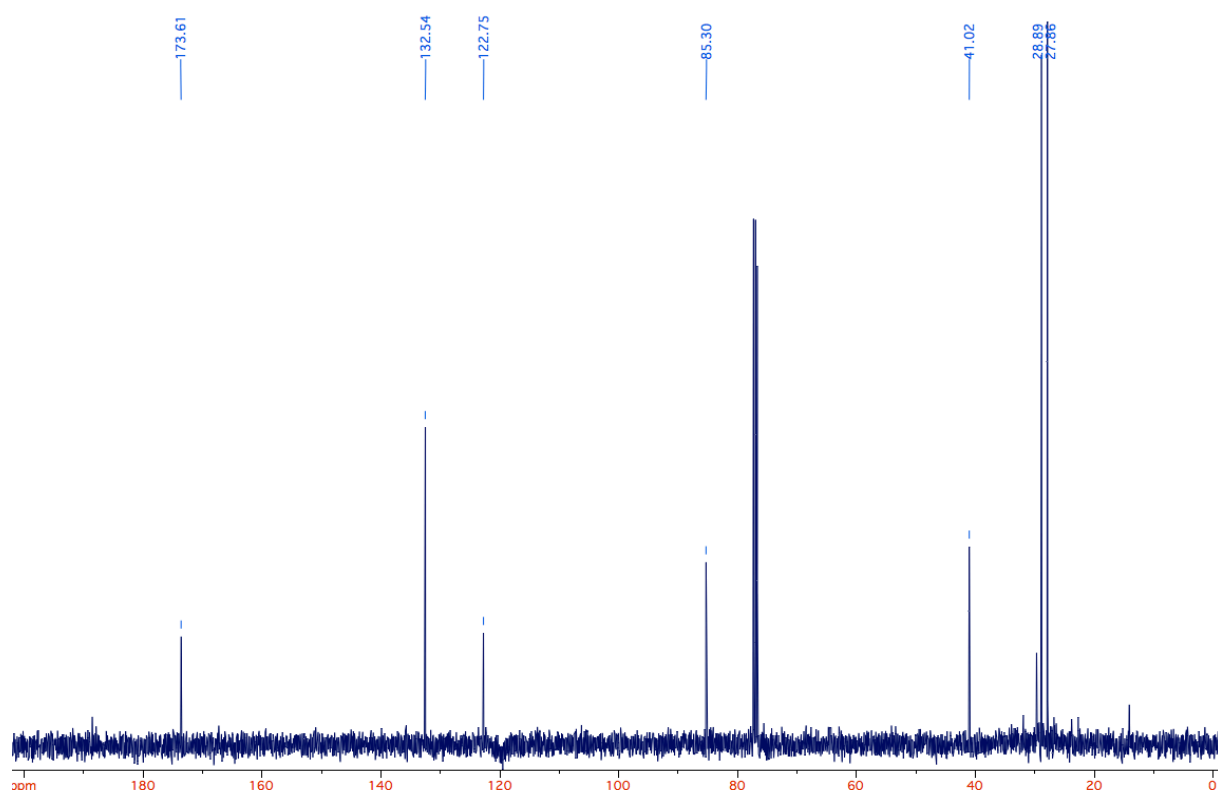
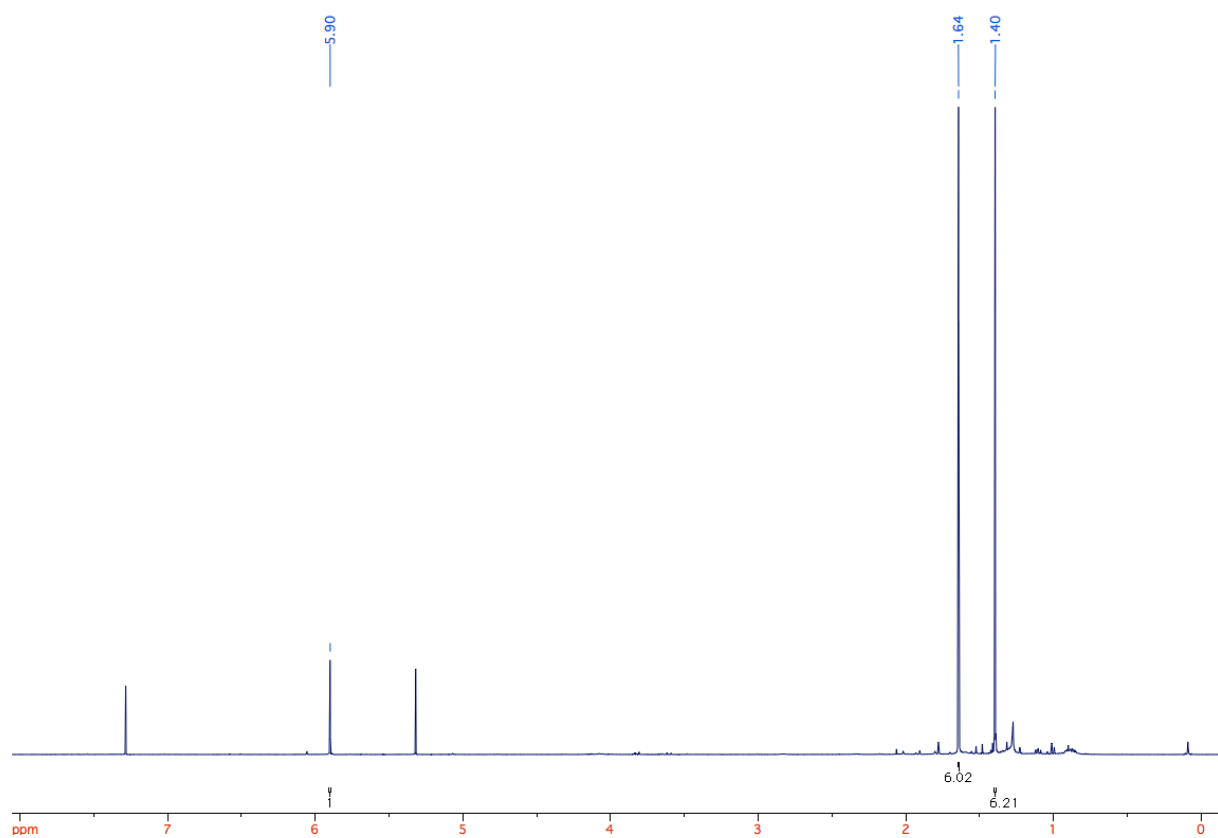
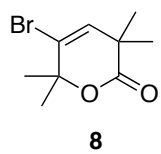


**5d**

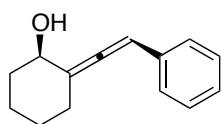




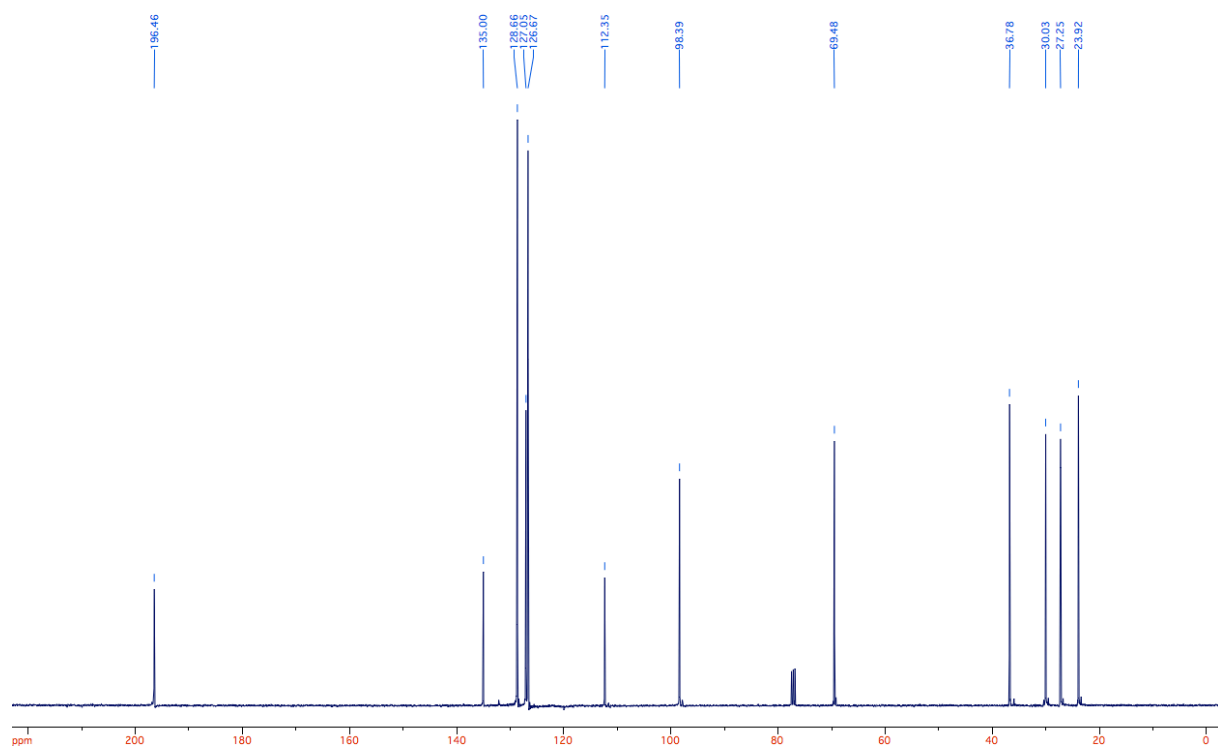
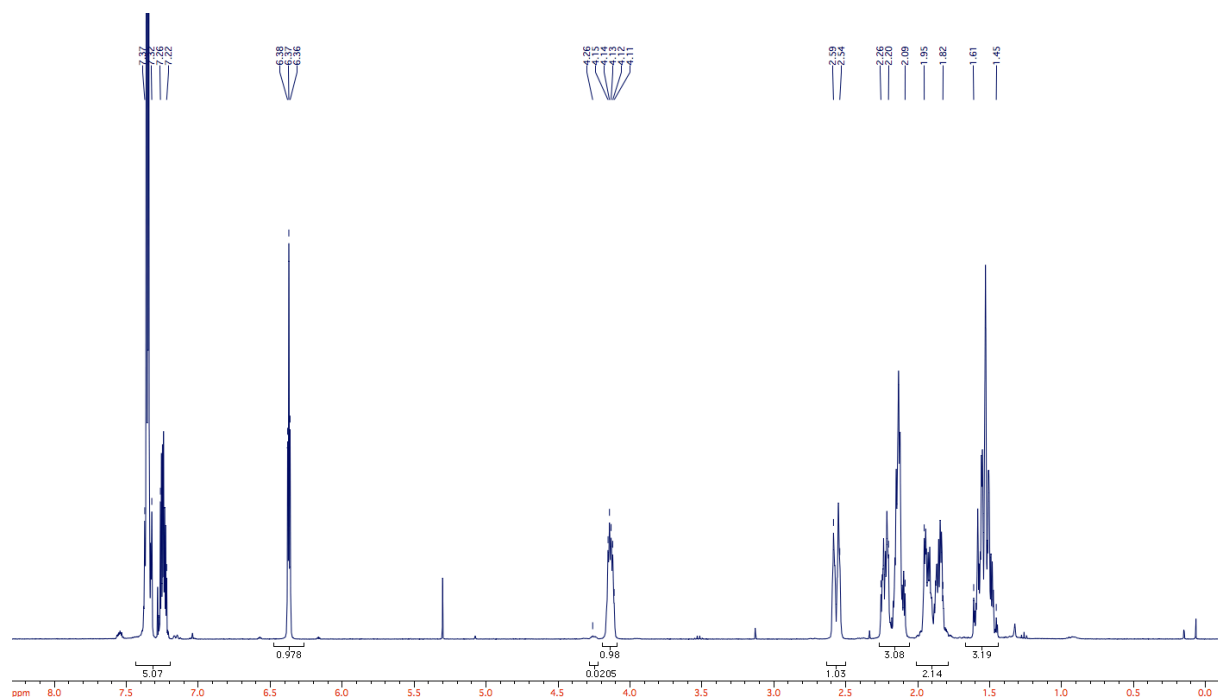


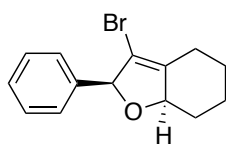




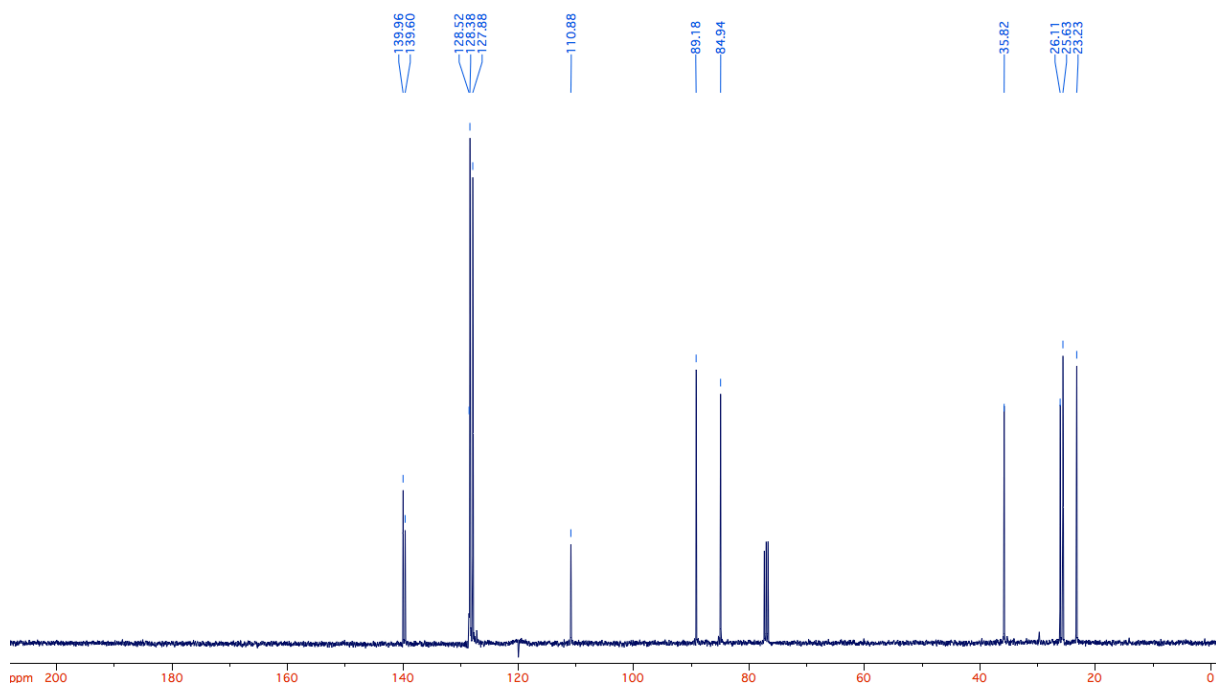
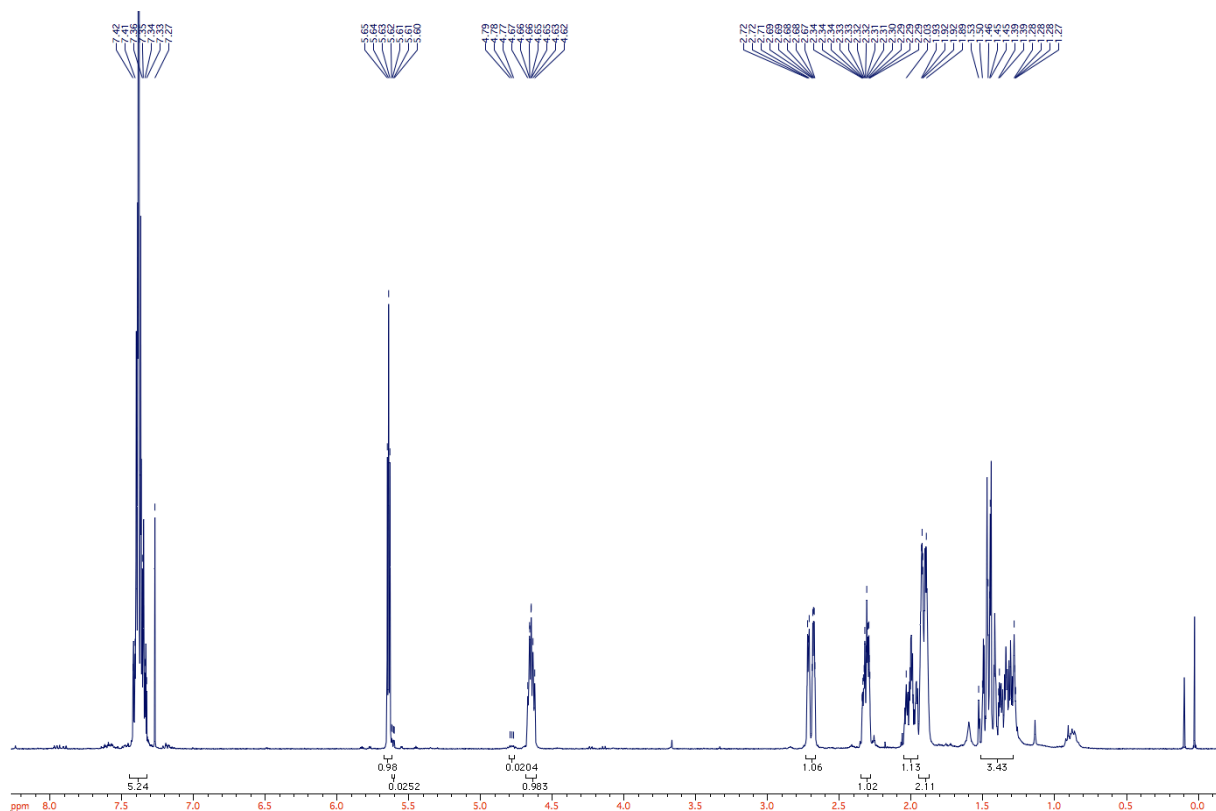


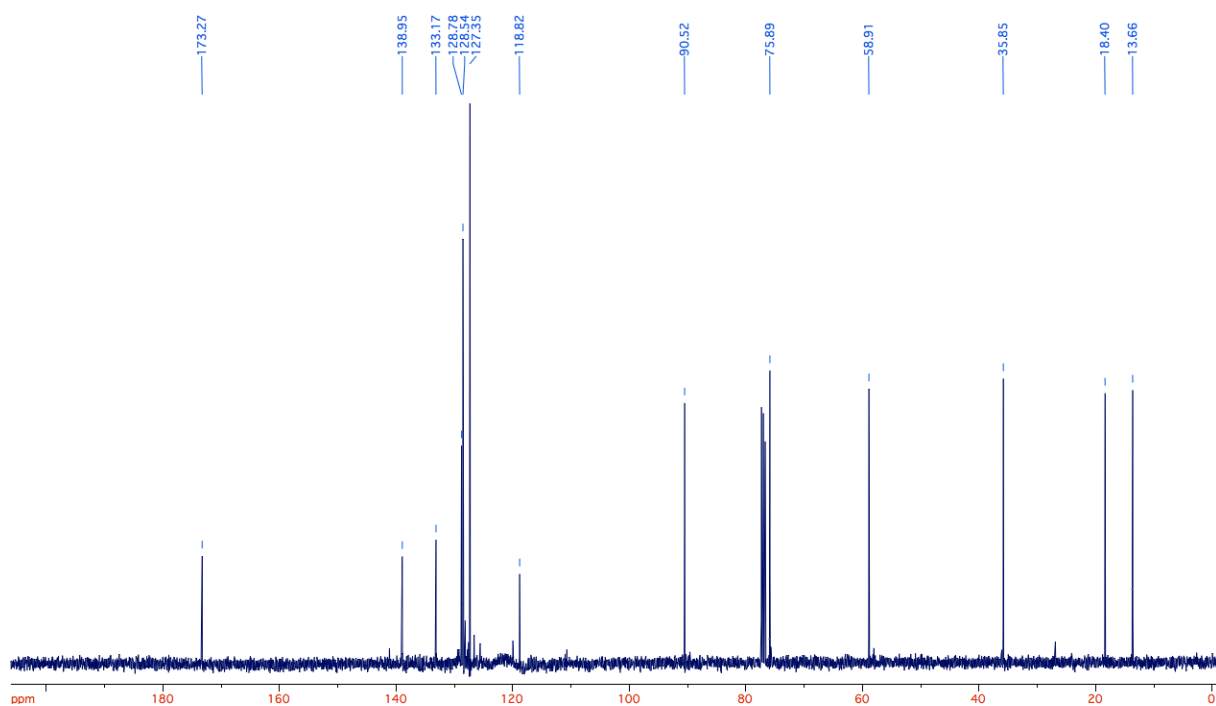
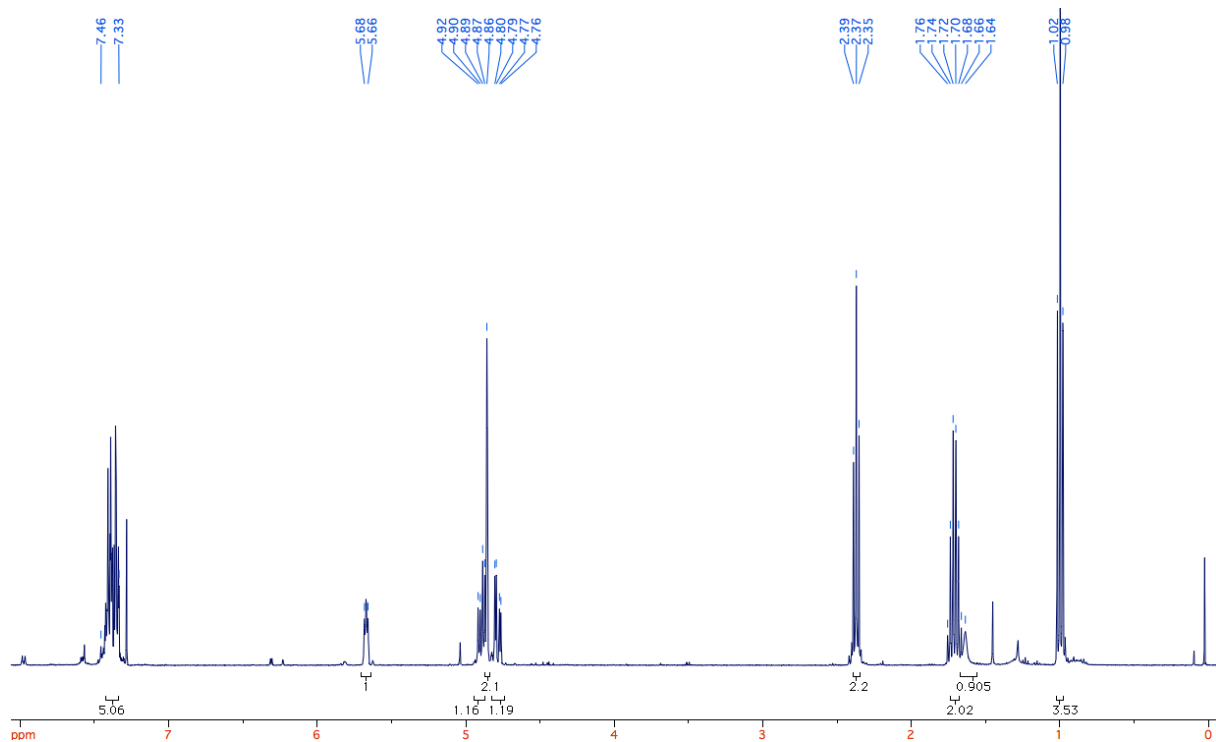
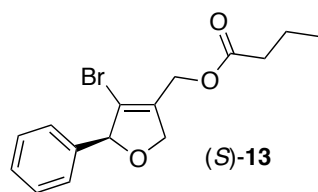
11

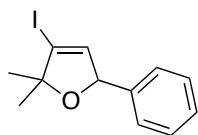




12







**14**

crude NMR after 1h (due to decomposition of **14** on silica)

