

## Supporting Information

# Enantioselective Total Synthesis of (+)-Amphirionin-4

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### Table of Contents:

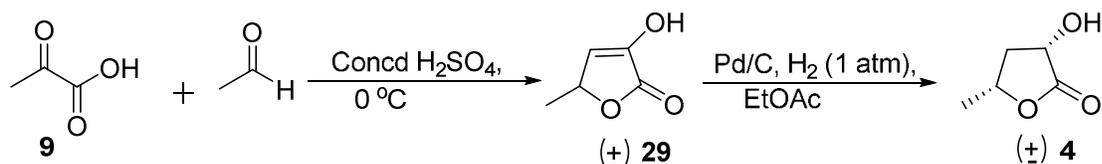
General Information.....	S1
Experimental Details.....	S2-S17
<sup>1</sup> H NMR and <sup>13</sup> C NMR Spectra of compounds.....	S18-S43
<sup>1</sup> H- <sup>1</sup> H COSY and NOESY Spectrum of Compound <b>15</b> .....	S44
Chiral HPLC Data.....	S45-S46

### General Information:

All chemical and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The following reaction solvents were distilled prior to use: Dichloromethane and toluene from calcium hydride, diethyl ether and tetrahydrofuran from Na/Benzophenone, methanol and ethanol from activated magnesium under argon. All reactions were carried out under an argon atmosphere in either flame or oven-dried (120 °C) glassware. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 Å, 250 μm thickness, F-254 indicator). Column chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature on a Bruker ARX-400 and Bruker DRX-500. Chemical shifts ( $\delta$  values) are reported in parts per million, and are referenced to the deuterated residual solvent peak. NMR data is reported as:  $\delta$  value (chemical shift, J-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet). Optical rotations were recorded on a Perkin Elmer 341 polarimeter. IR spectra were recorded on a Varian 2000 Infrared spectrophotometer and are reported as cm<sup>-1</sup>. LRMS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

## Experimental Details:

### Synthesis of Racemic Lactone 4:



To a stirred solution of concentrated  $\text{H}_2\text{SO}_4$  (30 mL) was added a mixture of pyruvic acid **9** (12 mL, 170 mmol) and acetaldehyde (19 mL, 340 mmol) dropwise over 30 min at  $0\text{ }^\circ\text{C}$ . After complete addition, the mixture was poured into a cold  $\text{H}_2\text{O}$  and extracted with  $\text{Et}_2\text{O}$  (4 $\times$ ). The combined organic extracts were washed with 1N HCl, water, saturated aqueous NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40 % EtOAc in hexane) to give **29**.

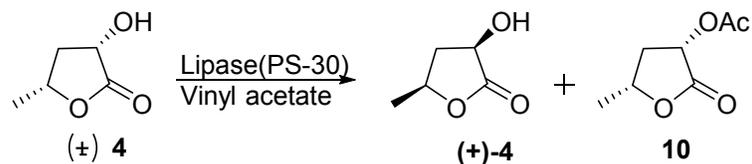
To a stirred solution of lactone **29** (3.5 g, 31 mmol) in EtOAc (20 mL) was added 10 % Pd/C (150 mg). The resulting solution was stirred at  $23\text{ }^\circ\text{C}$  under 1 atm  $\text{H}_2$  gas over 24 h. Upon completion, the mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (50 % EtOAc in hexane) to give **4** (2.87 g, 15 % yield over two steps).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.57 (dd,  $J = 11.3, 8.4$  Hz, 1H), 4.54 – 4.45 (m, 1H), 4.03 (brs, 1H), 2.70 (ddd,  $J = 12.6, 8.4, 5.1$  Hz, 1H), 1.90 – 1.80 (m, 1H), 1.43 (d,  $J = 6.2$  Hz, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.2, 73.9, 69.1, 38.8, 20.9.

IR: 3418, 2985, 2359, 1790, 1770, 1760, 1748, 1732, 1462, 1455, 1392, 1335, 1206, 1134, 1048, 1001, 946, 802, 711  $\text{cm}^{-1}$

### Synthesis of Lactones (+)-4 and 10:



To a stirred solution of alcohol **4** (0.6 g, 5.17 mmol) in THF (8 mL) were added vinyl acetate (8.4 mL, 91 mmol) and Lipase PS-30 (0.6 g) at  $23\text{ }^\circ\text{C}$  under argon atmosphere. The reaction mixture was stirred for 5h (50:50 by  $^1\text{H}$ -NMR). After this period, the reaction mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude

product was purified by silica gel column chromatography (30 % to 50 % EtOAc in hexane) to yield alcohol (+)-**4** (284 mg, 47 %) and acetate **10** (412 mg, 50 %).

Alcohol (+)-**4**;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.58 (dd,  $J = 11.2, 8.4$  Hz, 1H), 4.52 – 4.44 (m, 1H), 4.18 (brs, 1H), 2.69 (ddd,  $J = 12.9, 8.3, 5.1$  Hz, 1H), 1.89 – 1.79 (m, 1H), 1.42 (d,  $J = 6.3$  Hz, 3H).

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.3, 73.9, 69.0, 38.8, 20.9.

LRMS-ESI ( $m/z$ ): 139.2 ( $\text{M}+\text{Na}$ ) $^+$

$[\alpha]_{\text{D}}^{20} +2.8$  ( $c$  1.35,  $\text{CH}_3\text{OH}$ ); reported (Ahrens, H.; Paetow, M.; Hoppe, D. *Tetrahedron Lett.* **1992**, 33, 5327-5330)  $[\alpha]_{\text{D}}^{20} +3.6$  ( $c$  0.8,  $\text{CH}_3\text{OH}$ )

IR: 3398, 2983, 2937, 2360, 1778, 1458, 1390, 1330, 1204, 1132, 1048, 1000, 946, 878, 801, 711, 623  $\text{cm}^{-1}$

Acetate **10**;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.45 (dd,  $J = 10.9, 8.6$  Hz, 1H), 4.59 – 4.47 (m, 1H), 2.76 (ddd,  $J = 12.7, 8.5, 5.3$  Hz, 1H), 2.10 (s, 3H), 1.83 (dt,  $J = 12.5, 10.6$  Hz, 1H), 1.43 (d,  $J = 6.3$  Hz, 3H).

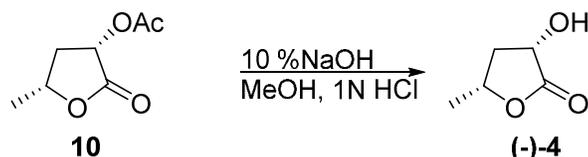
$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 172.5, 169.8, 73.6, 69.0, 36.7, 21.0, 20.6.

LRMS-ESI ( $m/z$ ): 181.2 ( $\text{M}+\text{Na}$ ) $^+$

$[\alpha]_{\text{D}}^{20} -18.45$  ( $c$  0.92,  $\text{CHCl}_3$ )

IR: 2984, 2939, 2878, 1789, 1747, 1451, 1377, 1233, 1199, 1126, 1103, 1054, 1021, 954, 939, 905, 815, 703  $\text{cm}^{-1}$

#### Synthesis of Lactone (-)-**4**:



To a stirred solution of acetate **10** (364 mg, 2.3 mmol) in MeOH (5 mL) was added aqueous NaOH (10 % solution, 5 mL) and the mixture was stirred at 23 °C for 12 h. After this period, the reaction mixture was acidified with 1N HCl solution and solvents were removed under reduced pressure. The aqueous layer was extracted with EtOAc (4 $\times$ ), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (60 % EtOAc in hexane) to give alcohol (-)-**4** (218 mg, 82 %) as a colorless oil.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.56 (dd,  $J = 11.2, 8.4$  Hz, 1H), 4.44 (tt,  $J = 11.4, 6.0$  Hz, 2H), 2.65 (ddd,  $J = 13.0, 8.3, 5.1$  Hz, 1H), 1.84 – 1.70 (m, 1H), 1.37 (d,  $J = 6.4$  Hz, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.3, 73.7, 68.9, 38.7, 20.8.

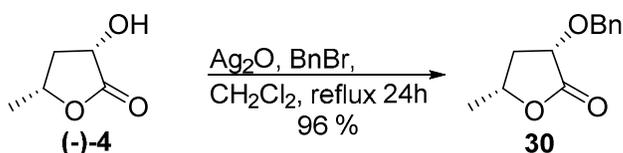
LRMS-ESI ( $m/z$ ): 139.2 ( $\text{M}+\text{Na}$ ) $^+$

$[\alpha]_{\text{D}}^{20}$  -2.3 ( $c$  1.0,  $\text{CH}_3\text{OH}$ )

IR: 3398, 2983, 2937, 2360, 1778, 1458, 1390, 1330, 1204, 1132, 1048, 1000, 946, 878, 801, 711, 623  $\text{cm}^{-1}$

Reference for compound **4**: Ahrens, H.; Paetow, M.; Hoppe, D. *Tetrahedron Lett.* **1992**, 33, 5327-5330.

### Synthesis of Lactone **30**



To a stirred solution of Lactone (-)- **4** (350 mg, 3.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) were added benzyl bromide (0.43 mL, 3.6 mmol) and silver oxide (1.0 g, 4.5 mmol) at 23 °C under argon atmosphere. The reaction mixture was stirred at reflux for 24h. Upon completion, the reaction mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (10 % EtOAc in hexane) to give **30** (599 mg, 96 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.44 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 5.00 (d,  $J$  = 11.8 Hz, 1H), 4.77 (d,  $J$  = 11.8 Hz, 1H), 4.53 – 4.43 (m, 1H), 4.30 (dd,  $J$  = 10.0, 8.2 Hz, 1H), 2.62 (ddd,  $J$  = 13.1, 8.1, 5.5 Hz, 1H), 1.90 (dt,  $J$  = 12.6, 9.8 Hz, 1H), 1.46 (d,  $J$  = 6.2 Hz, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 175.1, 137.2, 128.6, 128.1, 74.1, 73.4, 72.3, 37.3, 21.2.

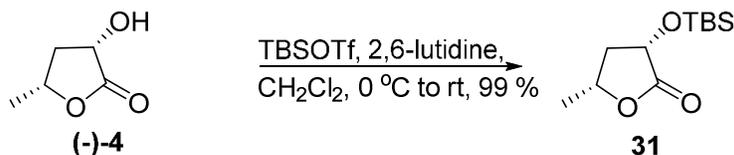
LRMS-ESI ( $m/z$ ): 229.1 ( $\text{M}+\text{Na}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ ) $^+$  calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}$ , 229.08409; found 229.08405

$[\alpha]_{\text{D}}^{20}$  +58.8 ( $c$  1.0,  $\text{CHCl}_3$ ). Chiral HPLC determined the enantiomeric excess was 92%. Conditions - Column: CHIRALPAK-IC3, Solvent: 80:20, Hexane:IPA; Temperature 23°C; Flow rate: 1 mL/min; major isomer: 14.6 min; minor isomer: 17.2 min. Please see page, S46 and S47a.

IR: 2980, 2933, 1779, 1454, 1389, 1333, 1199, 1129, 1053, 947, 740, 698  $\text{cm}^{-1}$

### Synthesis of Lactone **31**:



To a stirred solution of (-)-**4** (230 mg, 2 mmol) in dichloromethane (5 mL) were added 2,6-lutidine (0.65 ml, 6 mmol) and TBSOTf (0.65 mL, 3 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 1 h. After this period, the reaction mixture was quenched by the addition of saturated aqueous NaHCO<sub>3</sub> and extracted with dichloromethane. The extracts were washed with Saturated aqueous NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10 % EtOAc in hexane) to give **31** (454 mg, 99 %) as a white solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 4.46 – 4.34 (m, 2H), 2.56 (ddd, *J* = 12.6, 8.1, 5.3 Hz, 1H), 1.77 (dt, *J* = 12.4, 10.3 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 3.8 Hz, 9H), 0.10 (d, *J* = 17.0 Hz, 6H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 175.8, 72.6, 69.8, 40.0, 25.7, 21.1, 18.2, -4.7, -5.3.

LRMS-ESI (*m/z*): 253.2 (M+Na)<sup>+</sup>

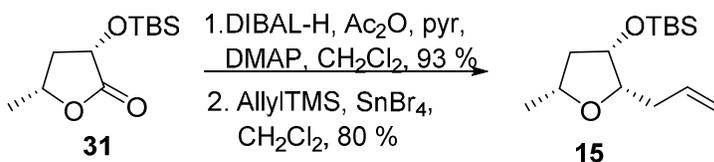
HRMS-ESI (*m/z*): (M+Na)<sup>+</sup> calcd for C<sub>11</sub>H<sub>22</sub>O<sub>3</sub>SiNa, 253.12362; found 253.12346

[α]<sub>D</sub><sup>20</sup> +16.95 (*c* 1.15, CHCl<sub>3</sub>)

Melting Point: 45-47 °C

IR: 2929, 2858, 2770, 1462, 1394, 1254, 1210, 1155, 11229, 1050, 1011, 951, 937, 899, 842, 779, 696 cm<sup>-1</sup>

### Synthesis of compound **15**:



To a stirred solution of lactone **31** (130 mg, 0.56 mmol) in dichloromethane (5 mL) at -78 °C was added DIBAL-H (0.68 ml, 0.68 mmol) under argon atmosphere and stirred at the same temperature for 2h. After this period, the reaction mixture was quenched by the addition of MeOH (1 mL) and warmed to 23 °C. Then, Saturated aqueous solution of sodium potassium tartarate was added and stirred vigorously at 23 °C for 2h until it forms white suspension. The

suspension was filtered through a plug of Celite and solvents were removed under reduced pressure.

To a crude lactol was added DMAP (7 mg, 0.056 mmol), Et<sub>3</sub>N (0.16 mL, 1.12 mmol) and Ac<sub>2</sub>O (0.08 mL, 0.84 mmol) at 0 °C under argon atmosphere and stirred for 2h. Upon completion, solvents were removed under reduced pressure and crude product was purified by silica gel column chromatography (15 % EtOAc in hexane) to give acetate **12** (140 mg, 10:1 diastereomeric ratio, 93 %) as a light yellow oil.

To a solution of acetate **12** (50 mg, 0.18 mmol) in dichloromethane (1.8 mL, 0.1 M) was added allyltrimethyl silane (0.12 mL, 0.73 mmol) at 23 °C under argon atmosphere and then cooled to -78 °C. After addition of SnBr<sub>4</sub> (96 mg, 0.22 mmol), the reaction mixture was warmed to 23 °C over 2h. Upon completion, the reaction mixture was quenched by the addition of Saturated aqueous Na<sub>2</sub>HPO<sub>4</sub> and extracted with dichloromethane. The extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. NMR analysis of the unpurified crude product showed a pair of diastereomers in an 10:1 ratio of 1,2-cis:trans diastereomers. The crude product was purified by silica gel column chromatography (70% CH<sub>2</sub>Cl<sub>2</sub> in hexane) to give **15** (38 mg, 80 %) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.22 (dt, *J* = 6.4, 3.7 Hz, 1H), 3.96-3.89 (m, 1H), 3.63 (q, *J* = 6.2 Hz, 1H), 2.42-2.32 (m, 2H), 2.26 (dt, *J* = 13.4, 6.9 Hz, 1H), 1.47 (ddd, *J* = 13.0, 6.6, 2.9 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.04 (d, *J* = 4.3 Hz, 6H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 135.9, 116.4, 83.2, 73.7, 73.5, 43.5, 34.4, 25.9, 22.2, 18.2, -4.4, -4.9.

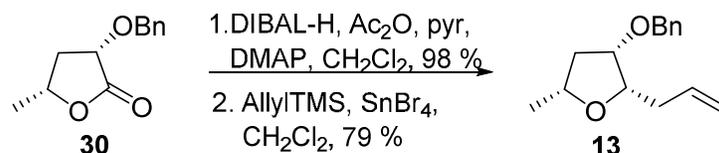
LRMS-ESI (*m/z*): 279.3 (M+Na)<sup>+</sup>

HRMS-ESI (*m/z*): (M+H)<sup>+</sup> calcd for C<sub>14</sub>H<sub>29</sub>O<sub>2</sub>Si, 257.19386; found 257.19324

[α]<sub>D</sub><sup>20</sup> -16.8 (*c* 1.0, CHCl<sub>3</sub>)

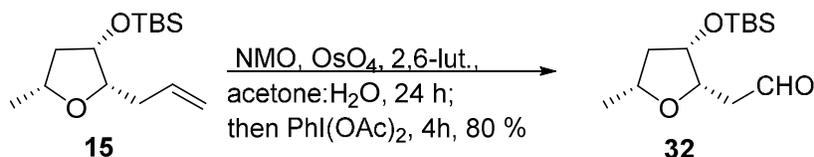
IR: 3077, 2957, 2931, 2897, 2858, 1642, 1472, 1463, 1438, 1368, 1255, 1091, 956, 912, 836, 774 cm<sup>-1</sup>

### Synthesis of compound 13:



The compound **13** was synthesized by following above procedure. NMR analysis of the unpurified crude product showed a pair of diastereomers in an 3:1 ratio of 1,2-cis:trans diastereomers.

### Synthesis of aldehyde **32**:



To a stirred solution of **15** (170 mg, 0.66 mmol) in acetone and water (10:1, 7 mL) were added 2,6-lutidine (0.15 mL, 1.33 mmol), NMO (0.116 g, 0.99 mmol) and OsO<sub>4</sub> (0.017 mL, 0.013 mmol) at 23 °C. The resulting mixture was stirred for 24 h and then PhI(OAc)<sub>2</sub> (0.32 g, 0.99 mmol) was added. After stirring for 4h, the reaction mixture was quenched by the addition of Saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with EtOAc. The extracts were washed with Saturated aqueous CuSO<sub>4</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10 % EtOAc in hexane) to give aldehyde **32** (137 mg, 80 %) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 9.79 (s, 1H), 4.34 (dt, *J* = 6.3, 4.5 Hz, 1H), 4.10 (q, *J* = 6.0 Hz, 1H), 3.95-3.89 (m, 1H), 2.74 – 2.64 (m, 2H), 2.30 (dt, *J* = 13.3, 6.8 Hz, 1H), 1.46 (ddd, *J* = 12.9, 7.3, 3.6 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 9H), -0.00 (d, *J* = 18.0 Hz, 6H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 201.3, 78.2, 74.0, 73.5, 44.3, 43.5, 25.8, 21.8, 18.1, -4.5, -5.1.

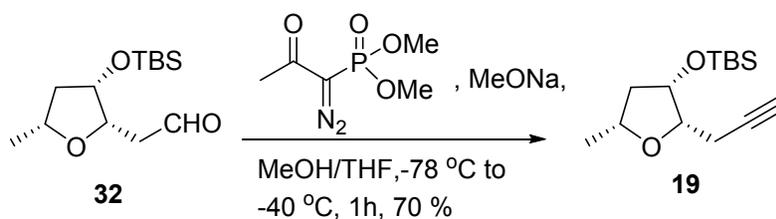
LRMS-ESI (*m/z*): 297.3 (M+K)<sup>+</sup>

HRMS-ESI (*m/z*): (M+Na)<sup>+</sup> calcd for C<sub>13</sub>H<sub>26</sub>O<sub>3</sub>SiNa, 281.15492; found 281.15468

[α]<sub>D</sub><sup>20</sup> -30.1 (*c* 1.0, CHCl<sub>3</sub>)

IR: 3431, 2956, 2931, 2858, 1726, 1372, 1256, 1089, 837, 776 cm<sup>-1</sup>

### Synthesis of alkyne **19**:



To a solution of dimethyl (1-diazo-2-oxopropyl) phosphonate (0.054 mL, 0.36 mmol) in THF (1 mL) at -78 °C was added MeONa (3.0 M in MeOH, 0.12 mL, 0.36 mmol) under argon

atmosphere and stirred for 20 min. To the resulting yellow solution aldehyde **32** (23 mg, 0.09 mmol) in THF (1 mL) was added and the reaction mixture was stirred for 1h at -40 °C. After this period the reaction mixture was quenched by the addition of Saturated aqueous NH<sub>4</sub>Cl (1 mL), and the layers were separated. The aqueous layer was extracted with EtOAc, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5 % EtOAc in hexane) to give alkyne **19** (16 mg, 70 %) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 4.29 (dt, *J* = 6.1, 3.7 Hz, 1H), 4.03 (dt, *J* = 13.6, 6.3 Hz, 1H), 3.85 – 3.78 (m, 1H), 2.56-2.46 (m, 2H), 2.32 – 2.24 (m, 1H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.52 (ddd, *J* = 13.1, 6.1, 2.7 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 5.2 Hz, 6H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 81.1, 80.9, 73.3, 72.0, 68.3, 42.1, 24.9, 21.4, 18.9, 17.2, -5.5, -6.0

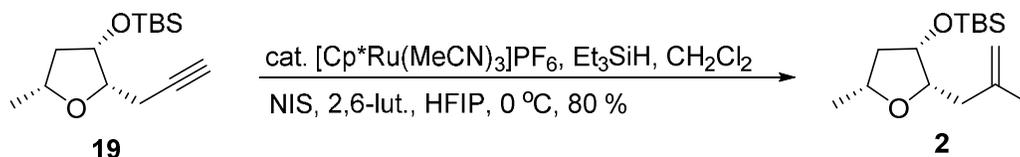
LRMS-ESI (*m/z*): 277.3 (M+Na)<sup>+</sup>

HRMS-ESI (*m/z*): (M+Na)<sup>+</sup> calcd for C<sub>14</sub>H<sub>26</sub>O<sub>2</sub>SiNa, 277.1600; found 277.1595

[α]<sub>D</sub><sup>20</sup> -29.5 (*c* 0.55, CHCl<sub>3</sub>)

IR: 3314, 2929, 2856, 2358, 1472, 1253, 1083, 978, 837, 776 cm<sup>-1</sup>

### Synthesis of vinyl iodide **2**:



To a solution of alkyne **19** (50 mg, 0.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Et<sub>3</sub>SiH (0.038 mL, 0.24 mmol) at 23 °C under argon atmosphere. After addition of [Cp<sup>\*</sup>Ru(MeCN)<sub>3</sub>]PF<sub>6</sub> (0.002 g, 0.004 mmol) at 0 °C, the reaction mixture was warmed to 23 °C and stirred for 2h. Upon completion, solvents were removed under reduced pressure and the crude product was passed through a plug of silica. To the crude product in HFIP (1 mL) was added 2,6-lutidine (0.022 mL, 0.28 mmol) at 23 °C under argon atmosphere. After addition of NIS (0.046 g, 0.3 mmol) at 0 °C, the reaction mixture was stirred for 15 min. The reaction mixture was quenched by the addition of water (0.2 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with Saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (3 % EtOAc in hexane) to give vinyl iodide **2** (60 mg, 80 %).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 6.19 – 6.16 (m, 1H), 5.79 (s, 1H), 4.28 (dt, *J* = 6.2, 4.1 Hz, 1H), 3.99 (dq, *J* = 12.9, 6.3 Hz, 1H), 3.91 (dt, *J* = 7.8, 4.5 Hz, 1H), 2.72 – 2.62 (m, 2H), 2.36 – 2.28

(m, 1H), 1.50 (ddd,  $J = 13.1, 6.7, 3.3$  Hz, 1H), 1.30 (d,  $J = 6.2$  Hz, 3H), 0.90 (s, 9H), 0.06 (d,  $J = 5.5$  Hz, 6H).

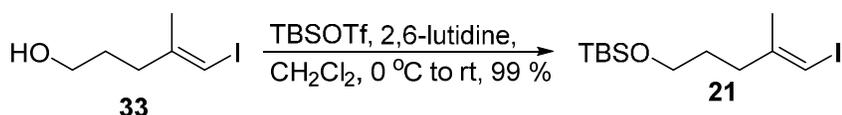
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 127.4, 108.7, 81.4, 73.9, 73.5, 46.1, 43.4, 26.0, 22.4, 18.2, -4.3, -4.8.

LRMS-ESI ( $m/z$ ): 383.4 ( $\text{M}+\text{H}$ )<sup>+</sup>

$[\alpha]_{\text{D}}^{20}$  -0.47 ( $c$  0.64,  $\text{CHCl}_3$ )

IR: 2950, 2929, 2840, 2360, 2342, 1654, 1560, 1458, 1110, 668  $\text{cm}^{-1}$

### Synthesis of vinyl iodide **21**:



To a stirred solution of **33** (2.15 g, 9.5 mmol) in dichloromethane (15 mL) were added 2,6-lutidine (3.3 ml, 28.5 mmol) and TBSOTf (3.3 mL, 14.25 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 1 h. After this period the reaction mixture was quenched by the addition of Saturated aqueous  $\text{NaHCO}_3$  and extracted with dichloromethane. The extracts were washed with Saturated aqueous  $\text{NaCl}$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (4 % EtOAc in hexane) to give **21** (3.15 g, 99 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.88 (m, 1H), 3.58 (t,  $J = 6.3$  Hz, 2H), 2.26 (td,  $J = 0.8, 7.4$  Hz, 2H), 1.84 (d,  $J = 1.1$  Hz, 3H), 1.67 – 1.62 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

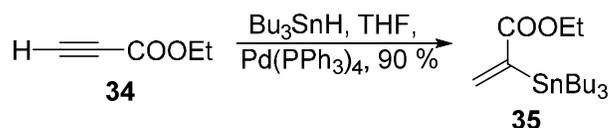
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.8, 74.8, 62.3, 36.0, 30.9, 26.1, 24.0, 18.5, -5.2.

LRMS-ESI ( $m/z$ ): 341.5 ( $\text{M}+\text{Na}$ )<sup>+</sup>

IR: 2953, 2929, 2894, 2857, 1472, 1463, 1388, 1361, 1256, 1105, 1006, 836, 813, 776, 664  $\text{cm}^{-1}$

Reference for compound **21**: Zheng, Y. F.; Oehlschlager, A. C.; Hartman, P. G. *J. Org. Chem.* **1994**, *59*, 5803–5809.

### Synthesis of compound **35**:



A degassed solution of  $\text{Bu}_3\text{SnH}$  (1.33 mL, 4.94 mmol) in THF (7 mL) was added during 1 h to a solution of ethyl propiolate **34** (0.52 mL, 5.1 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.12 g, 0.1 mmol) in THF (7

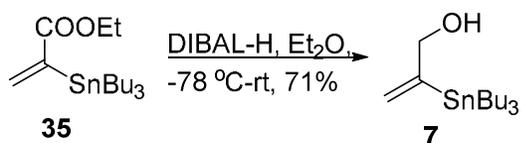
mL). The reaction mixture was stirred at 23 °C for 4 h under argon atmosphere. Upon completion, solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography (4 % EtOAc in hexane) to give **35** (1.78 g, 90 %) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 6.90 (d, *J* = 2.8 Hz, 1H), 5.91 (d, *J* = 2.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.51 – 1.47 (m, 5H), 1.32 – 1.27 (m, 10H), 0.99 – 0.95 (m, 5H), 0.88 (t, *J* = 7.4 Hz, 10H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 170.6, 146.3, 139.9, 60.7, 29.1, 27.4, 14.4, 13.8, 10.2.

IR: 2957, 2926, 2854, 2872, 2361, 1716, 1696, 1464, 1257, 1212, 1109, 1030, 963, 865 cm<sup>-1</sup>

### Synthesis of compound **7**:



A solution of **35** (1.4 g, 3.6 mmol) in ether (5 mL) was added during 1 h to a cooled (-78 °C) 1 M hexane solution of DIBAL-H (8 mL, 7.9 mmol) under argon atmosphere. After addition the reaction mixture was stirred at -78 °C for 30 min and warmed to 23 °C over 4h. After completion the reaction mixture was cooled to -20 °C and quenched by the addition of MeOH (2 mL), water (1 mL) and benzene (10 mL). The reaction mixture was warmed to 23 °C and stirred vigorously for 2h until it forms white suspension. The suspension was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (3 % EtOAc in hexane) to give **7** (0.89 g, 71 %) as a colorless oil.

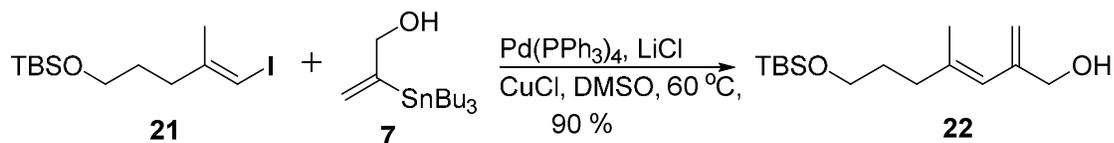
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 5.84 (d, *J* = 2.2 Hz, 1H), 5.20 – 5.17 (m, 1H), 4.19 (d, *J* = 13.2 Hz, 2H), 2.84 (brs, 1H), 1.53 – 1.42 (m, 6H), 1.28 (dq, *J* = 14.0, 7.2 Hz, 6H), 0.93 – 0.82 (m, 15H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 154.6, 122.5, 69.1, 29.2, 27.4, 13.7, 9.4.

IR: 3307, 2967, 2927, 2853, 2872, 2360, 1464, 1376, 1072, 1024, 920, 874, 668 cm<sup>-1</sup>

Reference for compounds **35** and **7**: Bellina, F.; Carpita, A.; Santis, M. D.; Rossi, R. *Tetrahedron*. **1994**, *50*, 4853-4872

### Synthesis of Diene 22:



LiCl (1.38 g, 32.4 mmol) was flame dried under high vacuum for 15 min. Upon cooling, CuCl (2.68 g, 27 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.625 g, 0.54 mmol) and DMSO (20 ml) were added, and the red color suspension was degassed for 15 min with an argon purge. To the another flask vinyl iodide **21** (1.84 g, 5.4 mmol), stannane **7** (1.88 g, 5.5 mmol) and DMSO (23 mL) were added and the mixture was degassed for 15 min with an argon purge. This mixture was cannulated to the above red color suspension and the mixture turned to green color suspension. The reaction mixture was stirred at 23 °C for 1 h, during this time the reaction mixture turned to black color suspension then heated to 60 °C for 1h. After this period, the reaction mixture was cooled, diluted with Et<sub>2</sub>O (500 mL), washed with water (200 mL) and brine (200 mL). The aqueous layer was further extracted with Et<sub>2</sub>O (2× 200 mL), washed with water(300 mL), then brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (8 % EtOAc in hexane) to give diene **22** (1.31 g, 90 %) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 5.63 (s, 1H), 5.24 (q, *J* = 1.6 Hz, 1H), 4.94 (s, 1H), 4.09 (s, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.15 – 2.09 (m, 2H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.70 – 1.63 (m, 2H), 1.50 (brs, 1H), 0.89 (s, 9H), 0.05 (s, 6H).

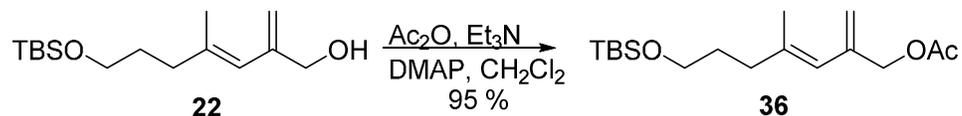
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 145.6, 141.0, 122.5, 112.6, 66.7, 62.8, 36.9, 31.2, 26.1, 18.5, 18.3, -5.1.

LRMS-ESI (*m/z*): 293.4 (M+Na)<sup>+</sup>

HRMS-ESI (*m/z*): (M+Na)<sup>+</sup> calcd for C<sub>15</sub>H<sub>30</sub>O<sub>2</sub>SiNa, 293.1913; found 293.1904

IR: 3346, 2953, 2930, 2858, 2360, 1634, 1463, 1472, 1446, 1387, 1256, 1105, 1057, 1006, 899, 836, 776 cm<sup>-1</sup>

### Synthesis of allyl acetate 36:



To a stirred solution of **22** (0.9 g, 3.33 mmol) in dichloromethane (15 mL) were added DMAP (41 mg, 0.33 mmol), acetic anhydride (0.4 mL, 4.16 mmol) and triethyl amine (0.93 mL, 6.66 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred

for 1 h. After this period, solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography (8 % EtOAc in hexane) to give **36** (0.98 g, 95 %) as a light yellow oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.59 (s, 1H), 5.21 (s, 1H), 4.98 (s, 1H), 4.52 (s, 2H), 3.59 (t,  $J$  = 6.4 Hz, 2H), 2.12 – 2.08 (m, 2H), 2.07 (s, 3H), 1.77 (s, 3H), 1.67-1.60 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H).

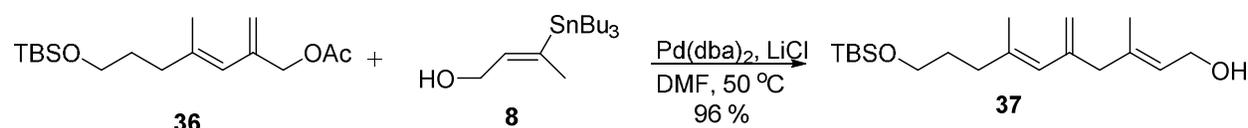
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.8, 140.9, 140.6, 122.3, 115.1, 67.4, 62.7, 36.8, 31.1, 26.1, 21.1, 18.4, 18.12, -5.2.

LRMS-ESI ( $m/z$ ): 335.2 ( $\text{M}+\text{Na}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ ) $^+$  calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_3\text{SiNa}$ , 335.2019; found 335.2009

IR: 2930, 2857, 2361, 2342, 1745, 1374, 1224, 1104, 836, 776, 668  $\text{cm}^{-1}$

### Synthesis of allyl alcohol **37**:



$\text{LiCl}$  (57mg, 1.36 mmol) was flame dried under high vacuum for 10 min. Upon cooling,  $\text{Pd}(\text{dba})_2$  (20 mg, 0.034 mmol) and  $\text{DMF}$  (1 mL) were added, and mixture was degassed for 15 min with an argon purge. To the another flask allyl acetate **36** (105 mg, 0.34 mmol), stannane **8** (121 mg, 0.34 mmol) and  $\text{DMF}$  (1.2 mL) were added and the mixture was degassed for 15 min with an argon purge. This mixture was cannulated to the above mixture and stirred at  $23\text{ }^\circ\text{C}$  for 30 min, then heated to  $50\text{ }^\circ\text{C}$  for 4h. After this period, the reaction mixture was cooled, diluted with  $\text{Et}_2\text{O}$  (30 mL), washed with water ( $2 \times 20\text{ mL}$ ), then brine ( $2 \times 20\text{ mL}$ ), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (8 %  $\text{EtOAc}$  in hexane) to give allyl alcohol **37** (105 mg, 96 %) as a light yellow oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.53 (s, 1H), 5.46 – 5.39 (m, 1H), 5.02 – 4.98 (m, 1H), 4.87 (s, 1H), 4.14 (d,  $J$  = 6.9 Hz, 2H), 3.58 (t,  $J$  = 6.6 Hz, 2H), 2.75 (s, 2H), 2.10 – 2.02 (m, 2H), 1.77 (d,  $J$  = 1.3 Hz, 3H), 1.66 – 1.62 (m, 2H), 1.61 (s, 3H), 1.40 (brs, 1H), 0.89 (s, 9H), 0.04 (s, 6H).

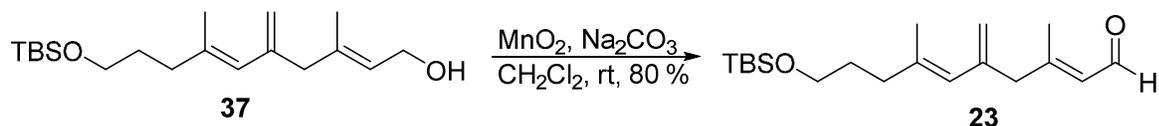
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.4, 138.5, 137.7, 125.5, 114.8, 62.9, 59.6, 48.2, 36.72, 31.3, 26.1, 18.5, 18.1, 16.0, -5.1.

LRMS-ESI ( $m/z$ ): 347.4 ( $\text{M}+\text{Na}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ ) $^+$  calcd for  $\text{C}_{19}\text{H}_{36}\text{O}_2\text{SiNa}$ , 347.2382; found 347.2374

IR: 3347, 2929, 2858, 2361, 1626, 1472, 1386, 1361, 1255, 1104, 1006, 895, 836, 776  $\text{cm}^{-1}$

### Synthesis of aldehyde **23**:



To a stirred solution of **37** (105 mg, 0.32 mmol) in dichloromethane (5 mL) were added  $\text{Na}_2\text{CO}_3$  (0.686 g, 6.47 mmol) and  $\text{MnO}_2$  (0.562 g, 6.47 mmol) at 23 °C under argon atmosphere. The reaction mixture was stirred for overnight. Upon completion, the mixture was filtered through a plug of Celite. Solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography (6 % EtOAc in hexane) to give aldehyde **23** (83 mg, 80 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.96 (d,  $J = 8.1$  Hz, 1H), 5.89 – 5.83 (m, 1H), 5.48 (s, 1H), 5.05 (s, 1H), 4.95 (s, 1H), 3.56 (t,  $J = 6.4$  Hz, 2H), 2.93 (s, 2H), 2.11 – 2.09 (m, 3H), 2.07 – 2.03 (m, 2H), 1.79 – 1.75 (m, 3H), 1.64 – 1.57 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H).

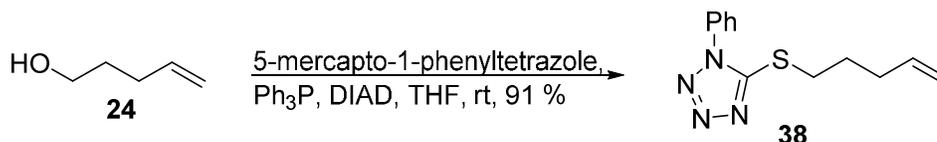
$^{13}\text{C}$  NMR (125 MHz,  $\text{CHCl}_3$ )  $\delta$ : 191.3, 161.6, 141.4, 139.8, 128.7, 124.6, 116.6, 62.7, 49.1, 36.8, 31.20, 26.0, 18.4, 18.1, 17.2, -5.2.

LRMS-ESI ( $m/z$ ): 323.5 ( $\text{M}+\text{H}$ )<sup>+</sup>

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ )<sup>+</sup> calcd for  $\text{C}_{19}\text{H}_{34}\text{O}_2\text{SiNa}$ , 345.2226; found 345.2222

IR: 3418, 2930, 2858, 2361, 1715, 1652, 1472, 1464, 1386, 1256, 1098, 836, 776  $\text{cm}^{-1}$

### Synthesis of sulfide **38**:



To a stirred solution of **24** (834 mg, 9.7 mmol) in THF (15 mL) were added  $\text{PPh}_3$  (2.7 g, 10.19 mmol), 5-mercapto-1-phenyltetrazole **25** (1.81 g, 10.19 mmol) and DIAD (2.3 mL, 11.64 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 24 h. Upon completion, solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography (8 % EtOAc in hexane) to give **38** (2.18 g, 91 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.60 – 7.49 (m, 5H), 5.81-5.73 (m, 1H), 5.08 – 4.97 (m, 2H), 3.42 – 3.34 (m, 2H), 2.25 – 2.16 (m, 2H), 1.93 (p,  $J = 7.5$  Hz, 2H).

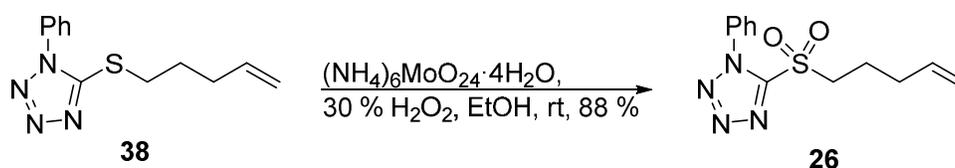
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  154.4, 136.9, 133.8, 130.2, 129.9, 123.9, 116.0, 32.7, 32.5, 28.3.

LRMS-ESI ( $m/z$ ): 269.3 ( $\text{M}+\text{Na}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{H}$ ) $^+$  calcd for  $\text{C}_{12}\text{H}_{15}\text{N}_4\text{S}$ , 247.1018; found 247.1013

IR: 3075, 2977, 2932, 2858, 2361, 2337, 1640, 1597, 1500, 1413, 1387, 1278, 1242, 1089, 1075, 1015, 991, 915, 761, 695  $\text{cm}^{-1}$

### Synthesis of sulfone **26**:



To a solution of 30 %  $\text{H}_2\text{O}_2$  (10 mL) was added hexaammonium heptamolybdate tetrahydrate (1.04 g, 0.843 mmol) and stirred for 15 min at 23 °C. This was added to sulfide **38** (2.076 g, 8.43 mmol) in EtOH (80 mL) and stirred for 24 h. Upon completion, the mixture was diluted with EtOAc and layers were separated. The organic layer was washed with water, brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc in hexane) to give sulfone **26** (2.066 g, 88 %) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CHCl}_3$ )  $\delta$ : 7.71 – 7.67 (m, 2H), 7.66 – 7.57 (m, 3H), 5.76 (ddt,  $J = 17.0$ , 10.3, 6.7 Hz, 1H), 5.14 – 5.07 (m, 2H), 3.76 – 3.71 (m, 2H), 2.28 (q,  $J = 7.2$  Hz, 2H), 2.11-2.04 (m, 2H).

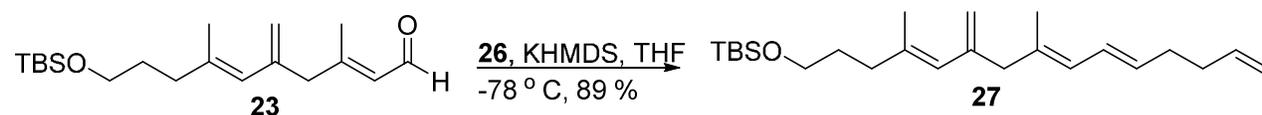
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 153.6, 135.8, 133.2, 131.6, 129.9, 125.2, 117.3, 55.4, 32.0, 21.3.

LRMS-ESI ( $m/z$ ): 301.3 ( $\text{M}+\text{Na}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ ) $^+$  calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_2\text{SNa}$ , 301.0735; found 301.0729

IR: 3079, 2918, 2362, 1642, 1596, 1498, 1460, 1340, 1152, 1047, 1015, 992, 920, 764, 689  $\text{cm}^{-1}$

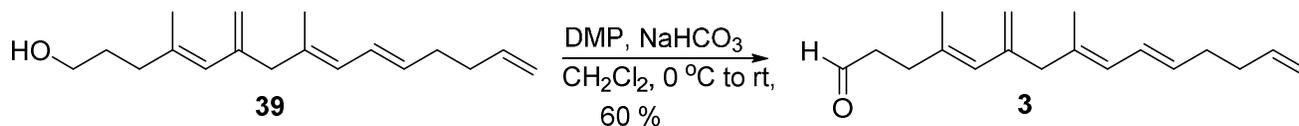
### Synthesis of compound **27**:



To a stirred solution of sulfone **26** (139 mg, 0.5 mmol) in THF (2 mL) was added KHMDS (1.4



### Synthesis of aldehyde 3:



To a stirred solution of **39** (30 mg, 0.12 mmol) in dichloromethane (2 mL) were added  $\text{NaHCO}_3$  (29 mg, 0.35 mmol) and DMP (73 mg, 0.17 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 2 h. Upon completion, the reaction mixture was quenched by the addition of Saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with dichloromethane. The extracts were washed with Saturated aqueous  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5 % EtOAc in hexane) to give **3** (18mg, 60 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.75 (t,  $J = 1.7$  Hz, 1H), 6.25 (dd,  $J = 15.1, 10.8$  Hz, 1H), 5.88 – 5.75 (m, 2H), 5.65 – 5.52 (m, 2H), 5.07 – 5.00 (m, 2H), 4.99 – 4.94 (m, 1H), 4.86 (s, 1H), 2.76 (s, 2H), 2.57 – 2.50 (m, 2H), 2.37 (t,  $J = 7.6$  Hz, 2H), 2.24 – 2.10 (m, 4H), 1.82 – 1.76 (m, 3H), 1.67 (s, 3H).

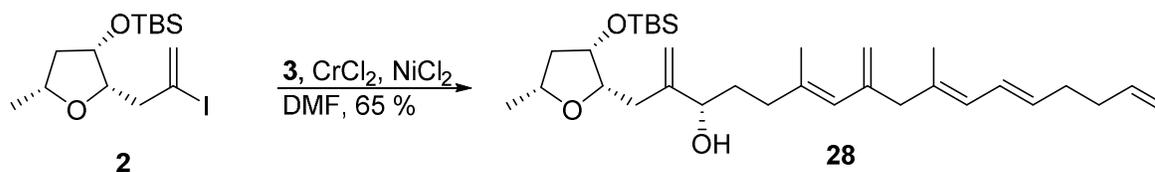
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 202.4, 143.4, 138.4, 136.3, 134.2, 132.2, 127.1, 126.7, 126.6, 115.1, 114.8, 48.3, 42.3, 33.9, 32.7, 32.5, 18.1, 16.4.

LRMS-ESI ( $m/z$ ): 281.4 ( $\text{M}+\text{Na}$ )<sup>+</sup>

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ )<sup>+</sup> calcd for  $\text{C}_{18}\text{H}_{26}\text{ONa}$ , 281.1881; found 281.1869

IR: 2926, 2361, 1728, 1641, 1447, 966, 909, 668  $\text{cm}^{-1}$

### Synthesis of compound 28:



To a stirred solution of vinyl iodide **2** (22 mg, 0.06 mmol) and aldehyde **3** (15 mg, 0.06 mmol) in DMF (1mL) were added  $\text{NiCl}_2$  (1 mg, 0.006 mmol) and  $\text{CrCl}_2$  (35mg, 0.3 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 24 h. Upon completion, the reaction mixture was quenched by the addition of Saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give the crude product in 4:1 mixture of diastereomers. The major diastereomer was purified by silica gel column chromatography (10 % EtOAc in Pentane) to give **28** (19 mg, 65 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.25 (dd,  $J = 15.1, 10.8$  Hz, 1H), 5.87 – 5.78 (m, 2H), 5.63 – 5.54 (m, 2H), 5.08 – 4.90 (m, 5H), 4.86 (brs, 1H), 4.29 – 4.24 (m, 1H), 4.01 (dq,  $J = 18.2, 5.7, 5.0$  Hz, 3H), 3.74 (ddd,  $J = 10.2, 4.1, 2.8$  Hz, 1H), 2.77 (brs, 2H), 2.51 (dd,  $J = 14.5, 10.3$  Hz, 1H), 2.32 – 2.25 (m, 1H), 2.21-2.13 (m, 5H), 2.11-2.06 (m, 1H), 2.03-1.97 (m, 1H), 1.83 – 1.76 (m, 3H), 1.76 – 1.71 (m, 1H), 1.68 (brs, 3H), 1.64-1.59 (m, 1H), 1.54 (ddd,  $J = 13.0, 6.5, 3.2$  Hz, 1H), 1.31 (d,  $J = 6.2$  Hz, 3H), 0.91 (s, 9H), 0.07 (d,  $J = 2.4$  Hz, 6H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 149.5, 143.9, 138.5, 138.4, 134.6, 131.9, 127.2, 126.5, 125.7, 114.8, 114.5, 114.2, 84.4, 75.5, 74.2, 73.8, 48.4, 43.2, 36.8, 34.7, 33.9, 32.5, 32.0, 25.9, 22.1, 18.2, 18.1, 16.4, -4.4, -4.9.

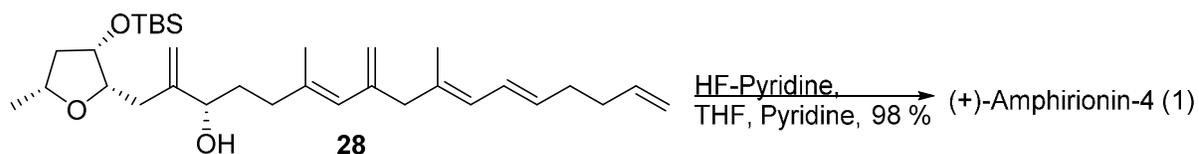
IR: 3400, 2930, 2857, 2360, 2343, 1256, 1067, 836, 775, 668  $\text{cm}^{-1}$

LRMS-ESI ( $m/z$ ): 537.4 ( $\text{M}+\text{Na}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ ) $^+$  calcd for  $\text{C}_{32}\text{H}_{54}\text{O}_3\text{SiNa}$ , 537.3740; found 537.3724

$[\alpha]_{\text{D}}^{20} +15.1$  ( $c$  0.45,  $\text{CHCl}_3$ )

#### Synthesis of (+)-Amphirionin-4 (1):



To a solution of **28** (3 mg, 0.006 mmol) in THF/Pyridine (0.4 mL/0.6 mL) in a plastic vessel was added HF. Py complex (0.3 mL) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 9h. Upon completion, the reaction mixture was quenched by the addition of Saturated aqueous  $\text{NaHCO}_3$  at 0 °C and stirred for 15 min at 23 °C. The mixture was extracted with EtOAc ( $\times 3$ ) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40 % EtOAc in Hexane) to give (+)-Amphirionin-4 (**1**) (2.3 mg, 98 %) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 6.34 (dd,  $J = 15.0, 10.8$  Hz, 1H), 5.98 (brd,  $J = 10.8$  Hz, 1H), 5.81 (brs, 1H), 5.77 (ddd,  $J = 17.0, 6.4, 3.8$  Hz, 1H), 5.58 (brdt,  $J = 14.4, 6.7$  Hz, 1H), 5.09 (brs, 1H), 5.06 (brs, 1H), 5.05 – 5.01 (m, 1H), 5.00 (brs, 1H), 4.99 – 4.96 (m, 1H), 4.92 (brs, 1H), 4.12 (dd,  $J = 5.6, 7.6$  Hz, 1H), 3.77 (dt,  $J = 6.2, 3.5$  Hz, 1H), 3.61 – 3.55 (m, 1H), 3.48 (dt,  $J = 8.6, 4.4$  Hz, 1H), 2.83 (brs, 2H), 2.63 (dd,  $J = 14.5, 8.8$  Hz, 1H), 2.27 (dd,  $J = 8.4, 5.8$  Hz, 1H), 2.25 – 2.20 (m, 2H), 2.19 – 2.13 (m, 1H), 2.13 – 2.09 (t,  $J = 6.4$  Hz, 2H), 2.08 – 2.03 (m, 2H), 1.90 – 1.86 (m, 1H), 1.84 (dd,  $J = 9.1, 5.0$  Hz, 1H), 1.81 (brd,  $J = 1.2$  Hz, 3H), 1.77 – 1.73 (m, 1H), 1.70 (brs, 3H), 1.19 (ddd,  $J = 13.5, 6.7, 2.4$  Hz, 2H), 1.14 (d,  $J = 6.2$  Hz, 3H).

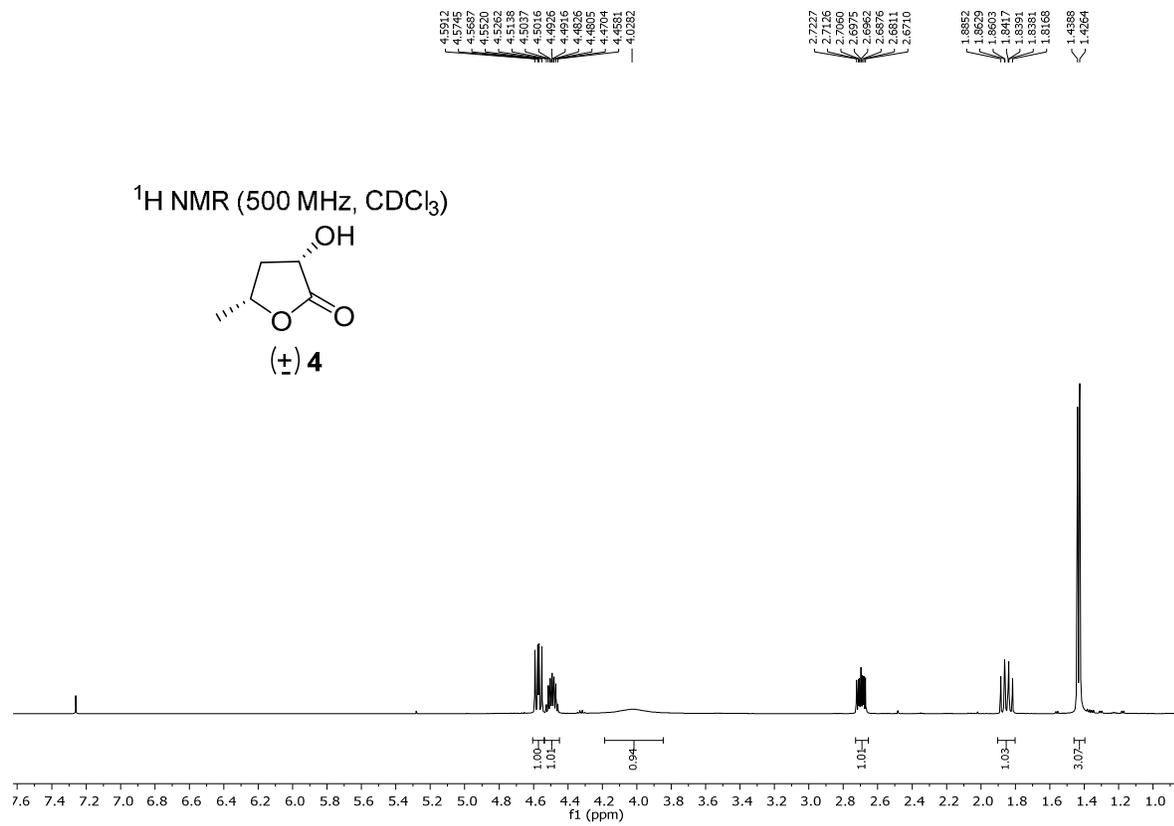
$^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 150.1, 144.3, 138.7, 138.5, 134.2, 132.1, 127.5, 127.4, 126.3, 114.9, 114.8, 112.8, 84.2, 75.2, 73.9, 73.4, 48.8, 43.2, 37.2, 35.0, 34.2, 32.8, 31.6, 22.0, 18.2, 16.4.

IR: 3394, 2925, 2853, 2359, 2340, 1560, 1458, 1377, 1076, 908, 800  $\text{cm}^{-1}$

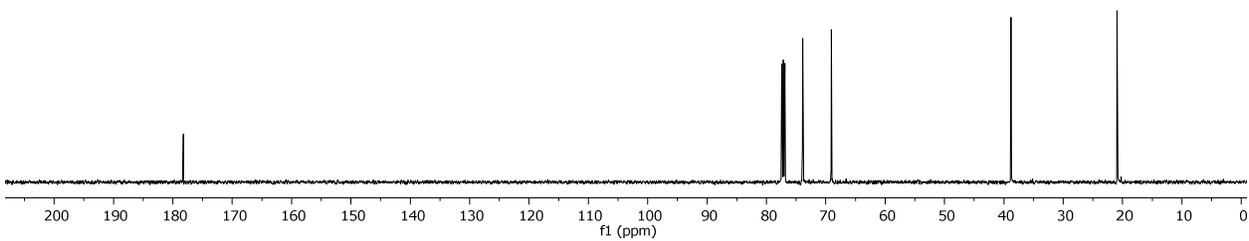
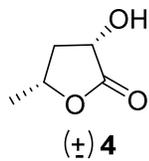
LRMS-ESI ( $m/z$ ): 423.4 ( $\text{M}+\text{Na}$ ) $^+$ , 439.4 ( $\text{M}+\text{K}$ ) $^+$

HRMS-ESI ( $m/z$ ): ( $\text{M}+\text{Na}$ ) $^+$  calcd for  $\text{C}_{26}\text{H}_{40}\text{O}_3\text{Na}$ , 423.2875; found 423.2860

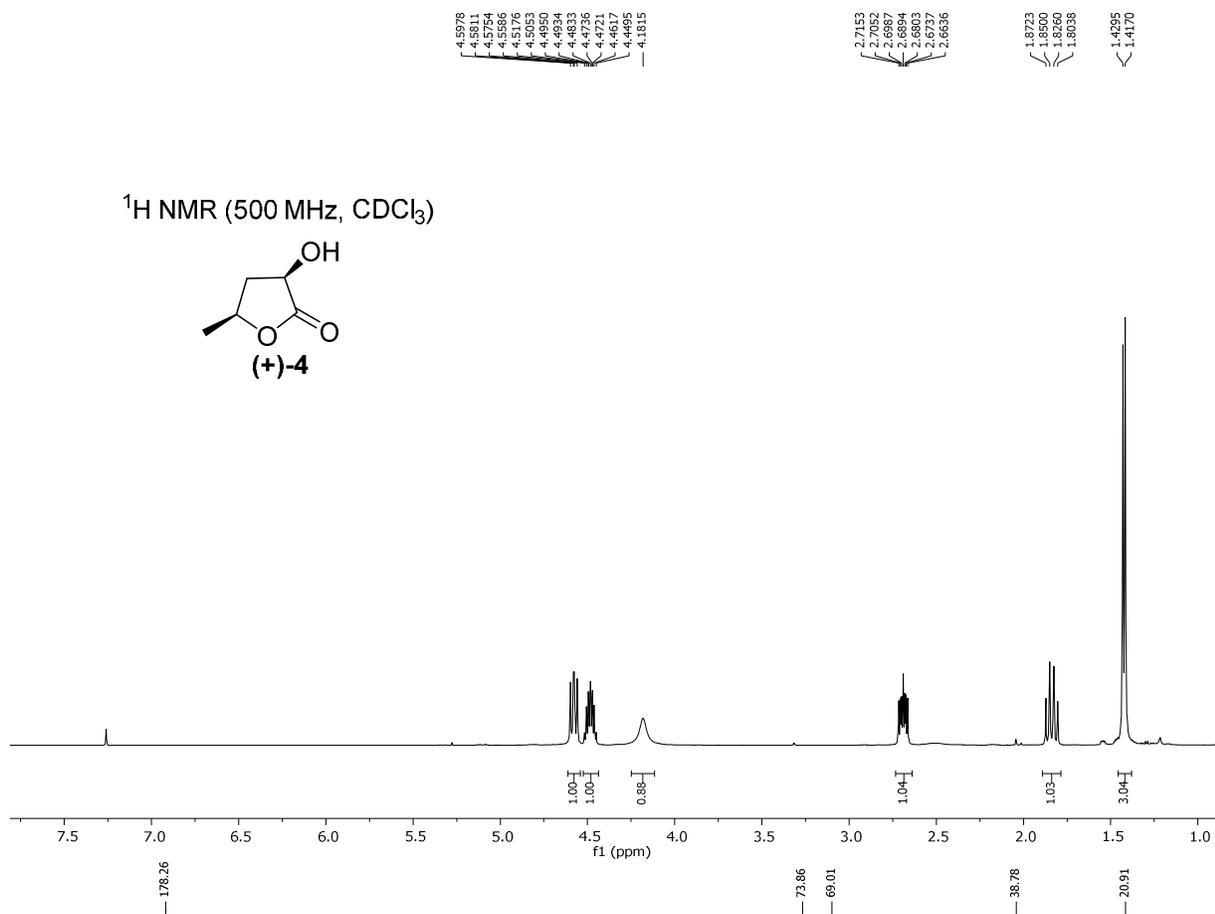
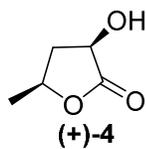
$[\alpha]_{\text{D}}^{20} +6.4$  ( $c$  0.08,  $\text{CHCl}_3$ )



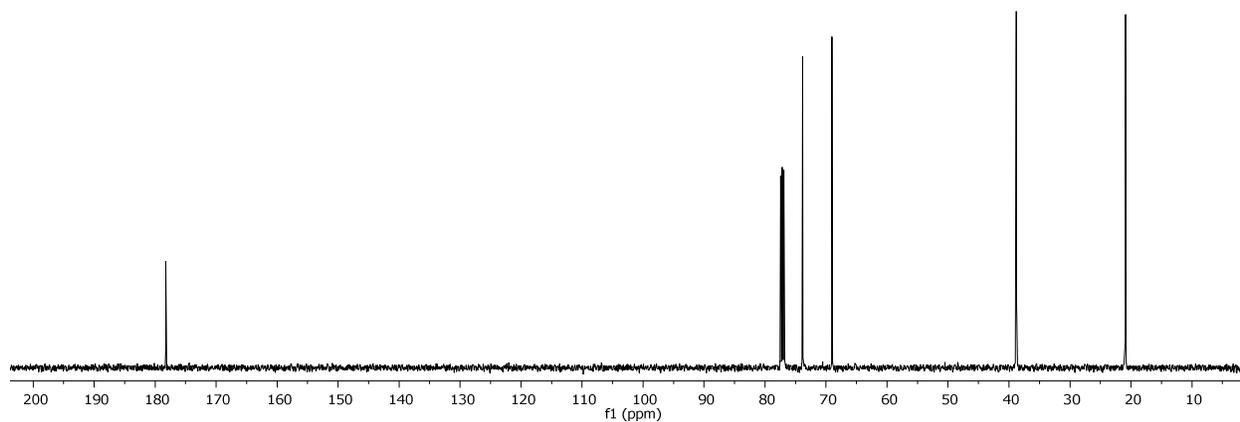
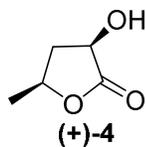
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

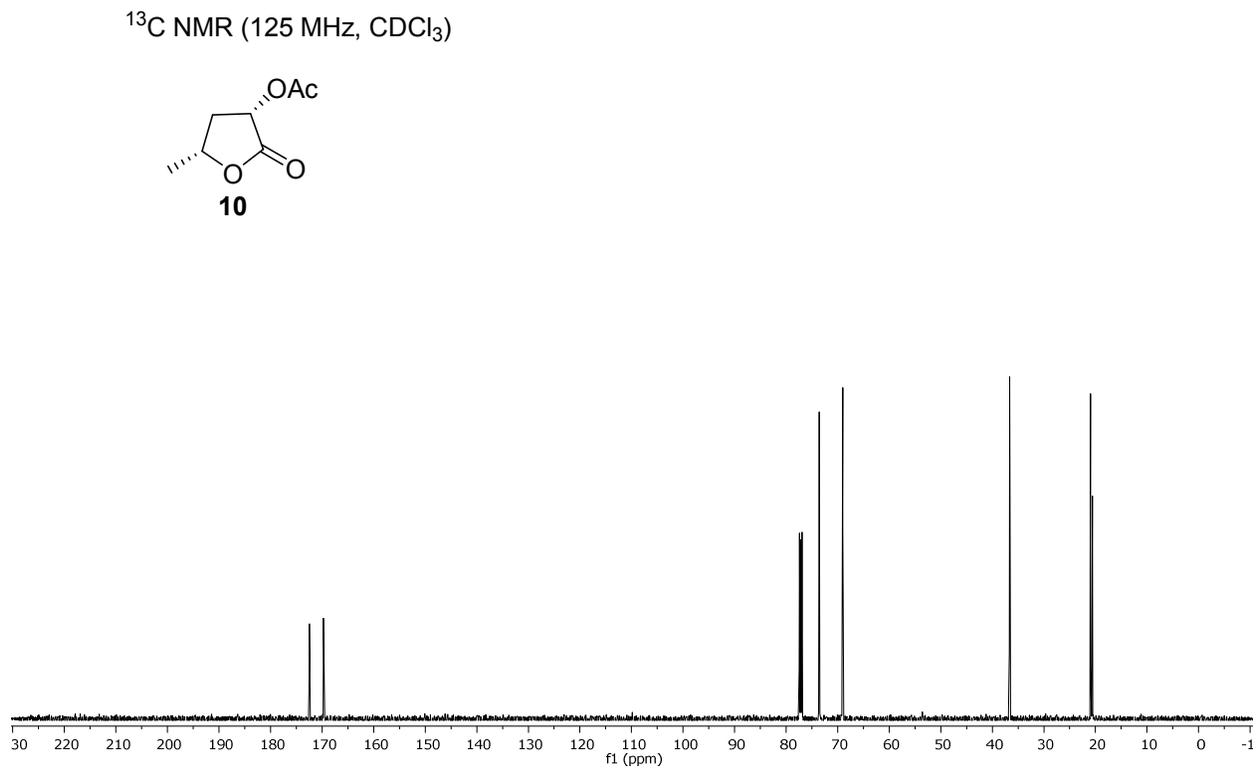
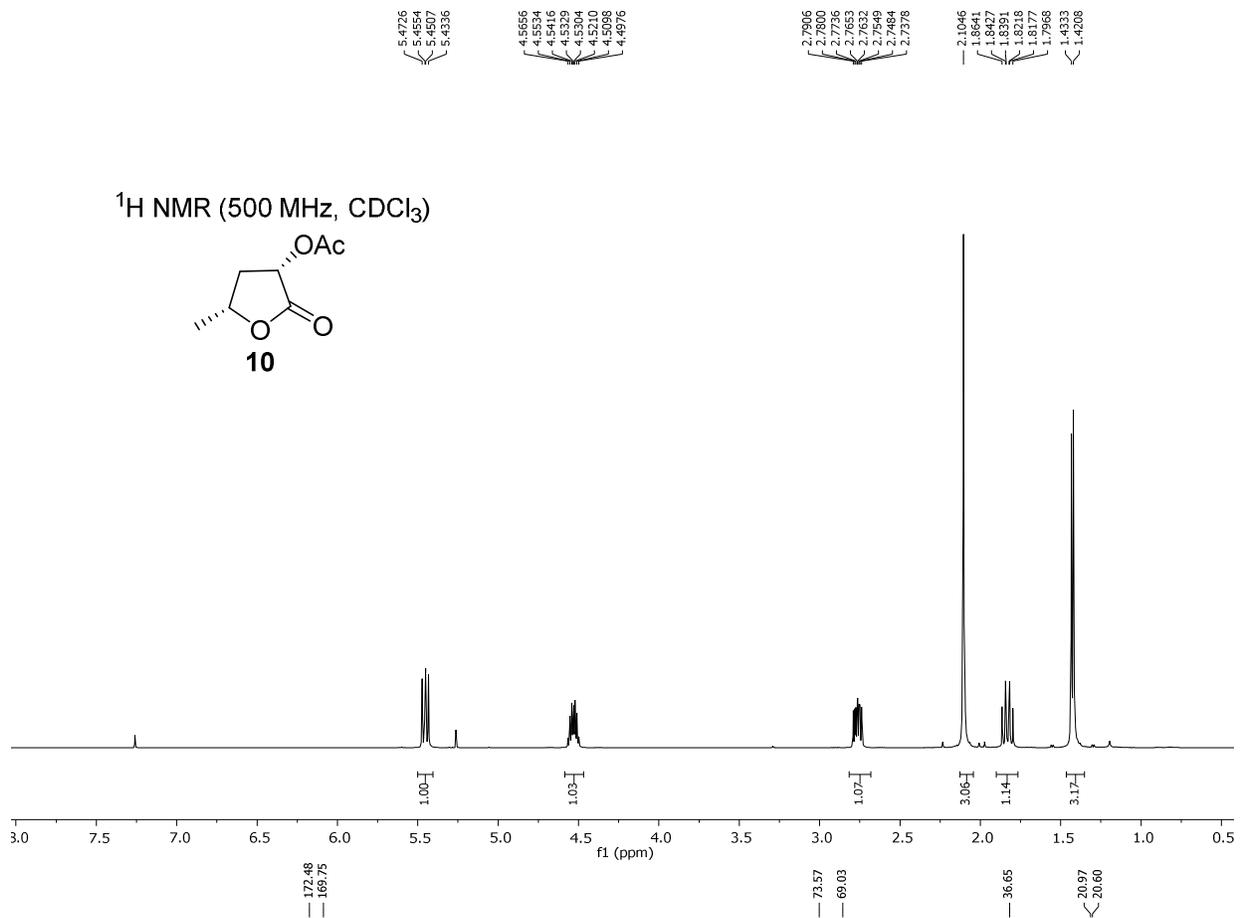


<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)



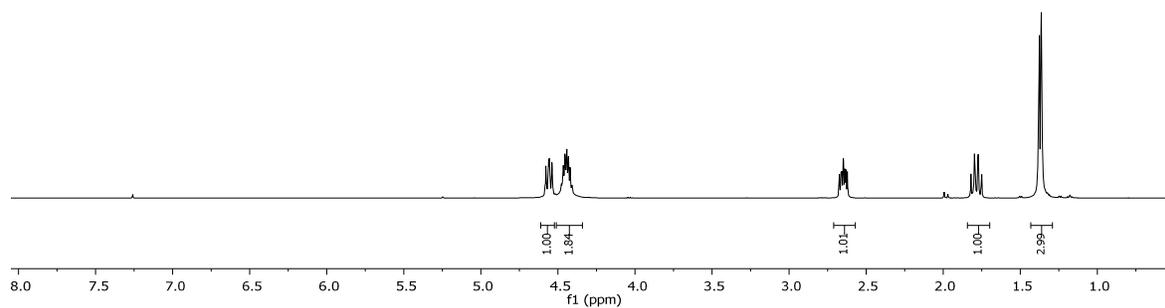
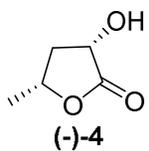


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4.4211  
4.4090

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2.6386  
2.6320  
2.6219

1.8191  
1.7971  
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1.7506  
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1.3635

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



178.25

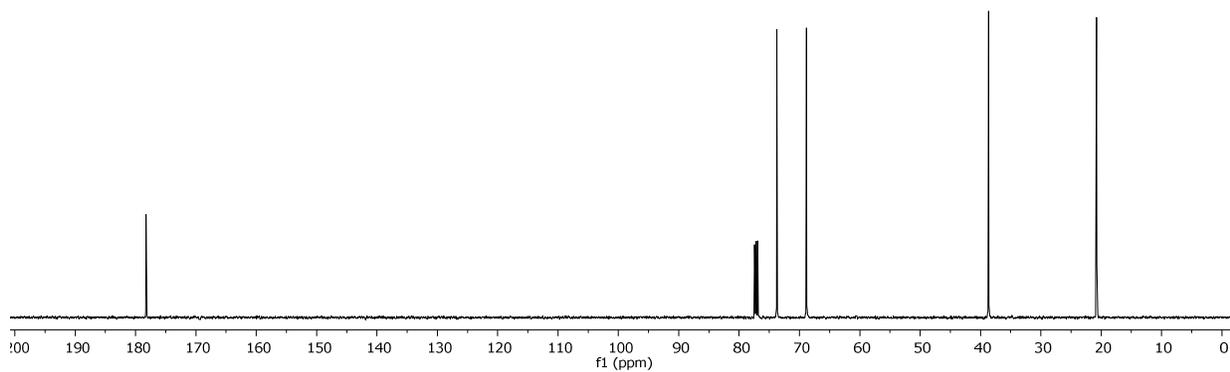
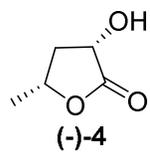
73.74

68.85

38.68

20.76

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )



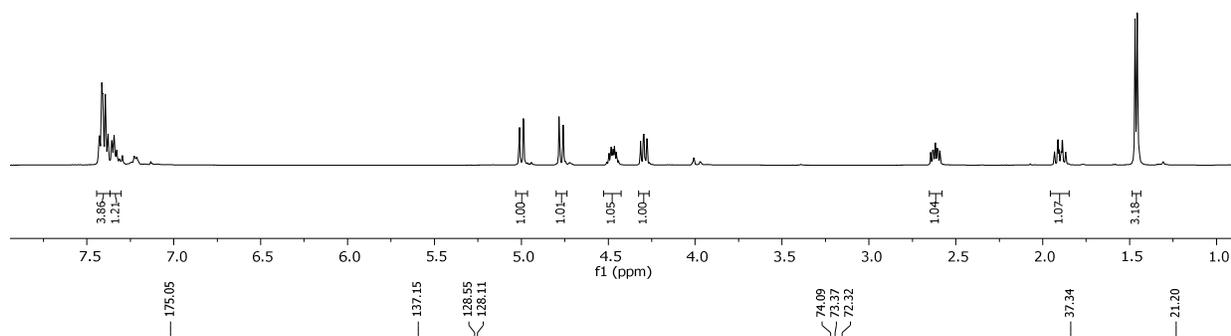
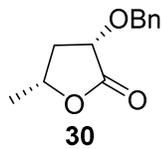
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7.3116

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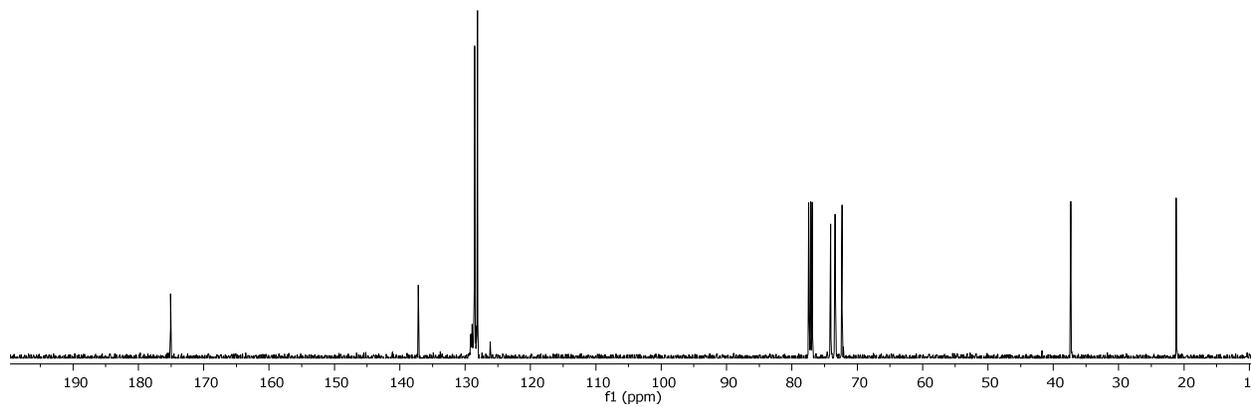
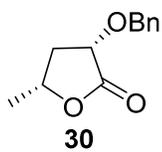
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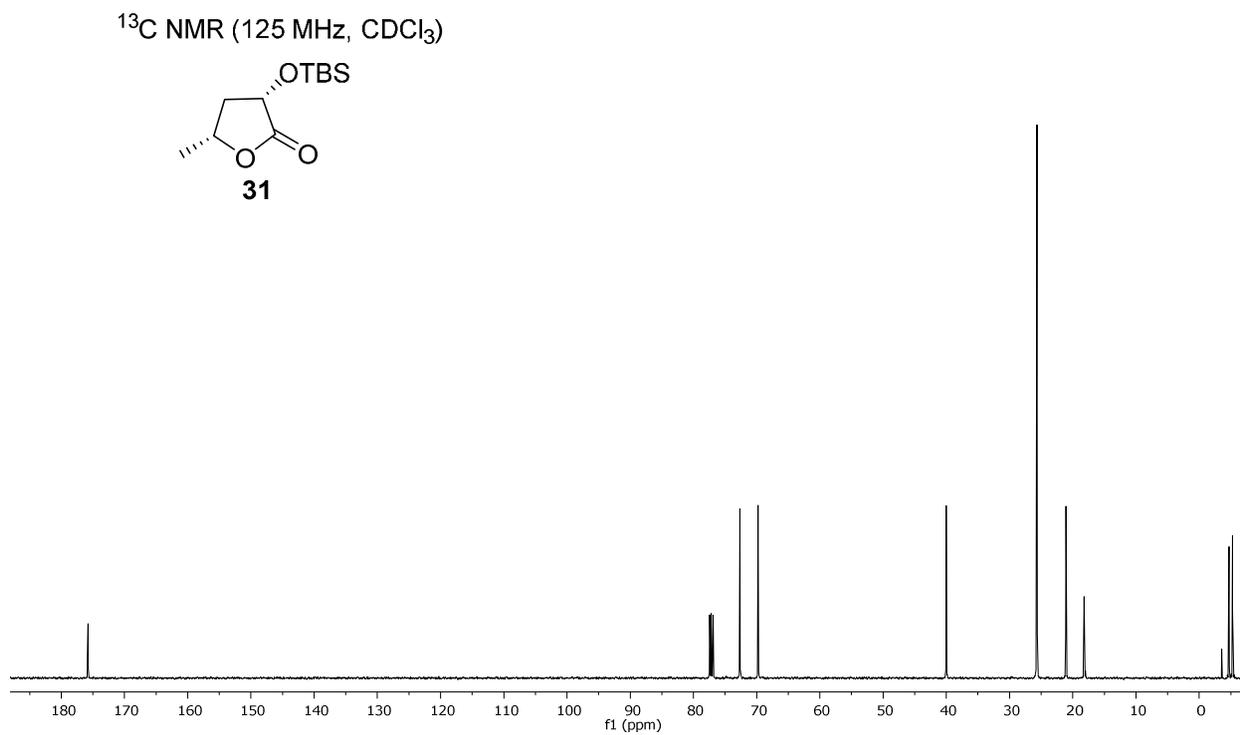
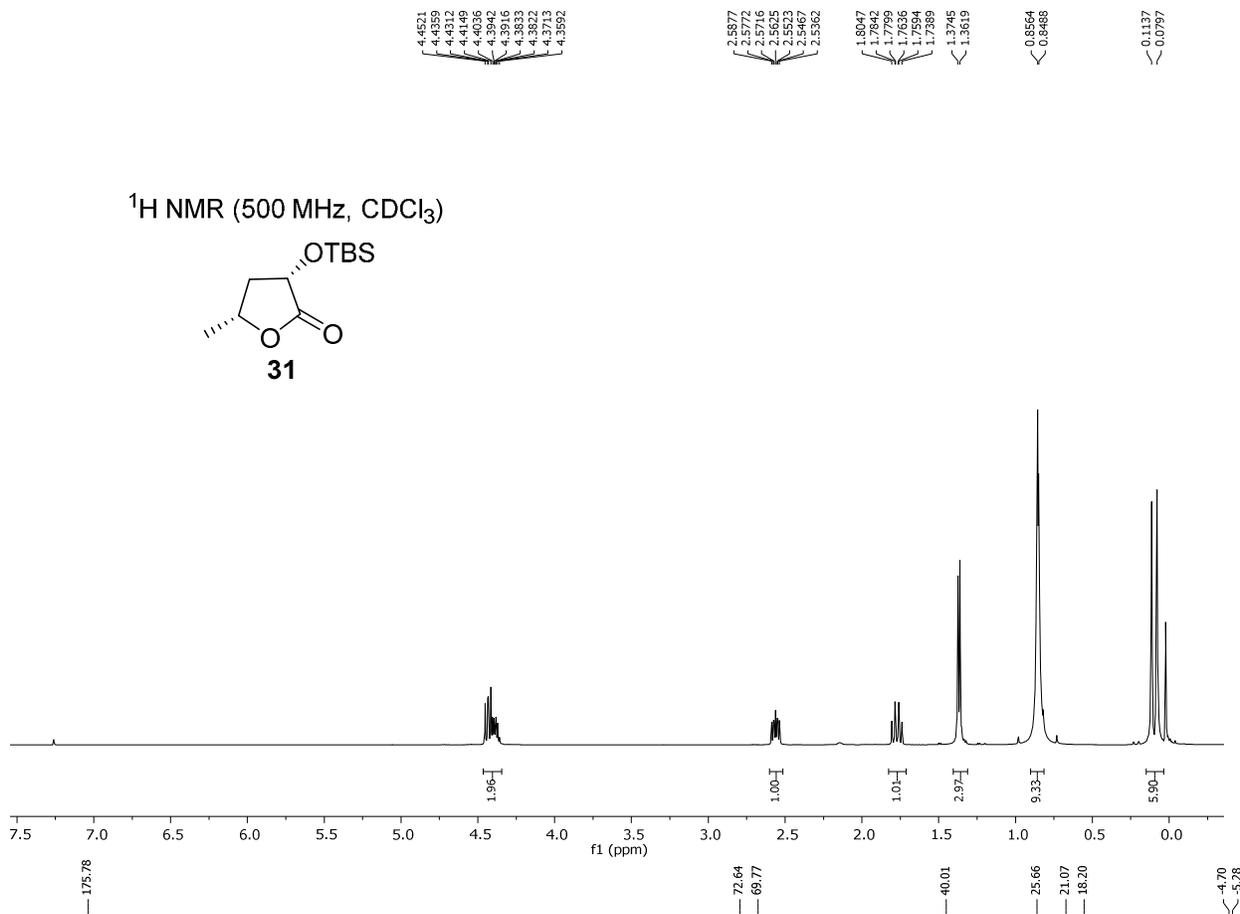
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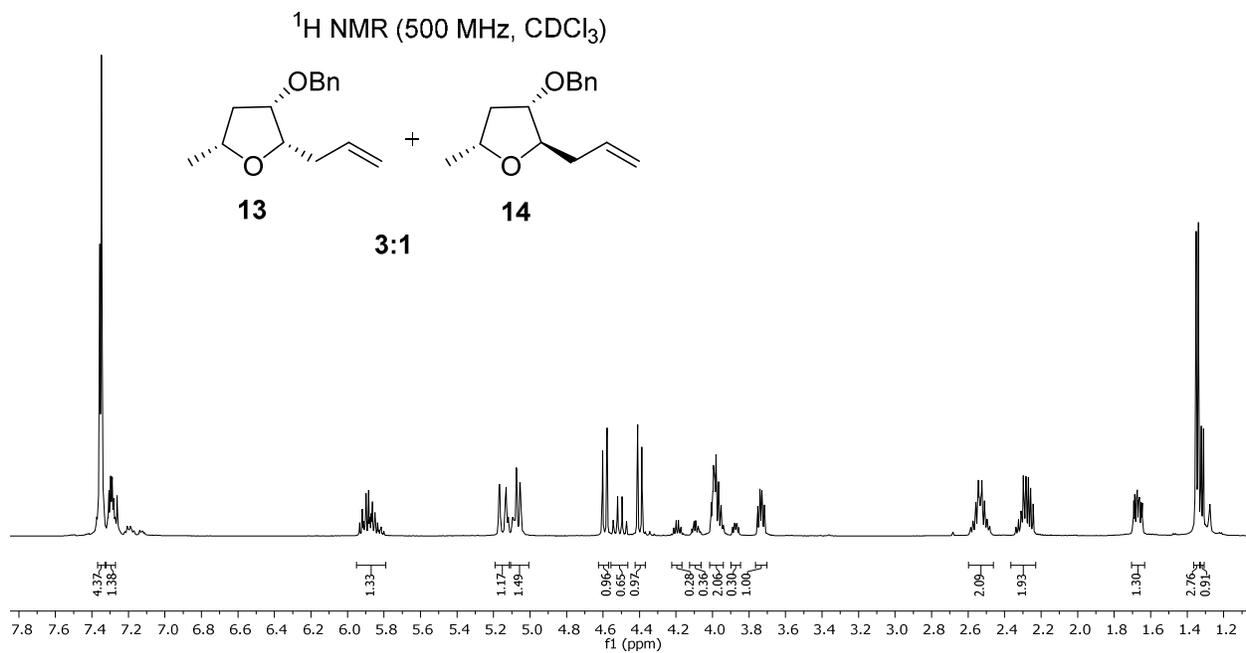
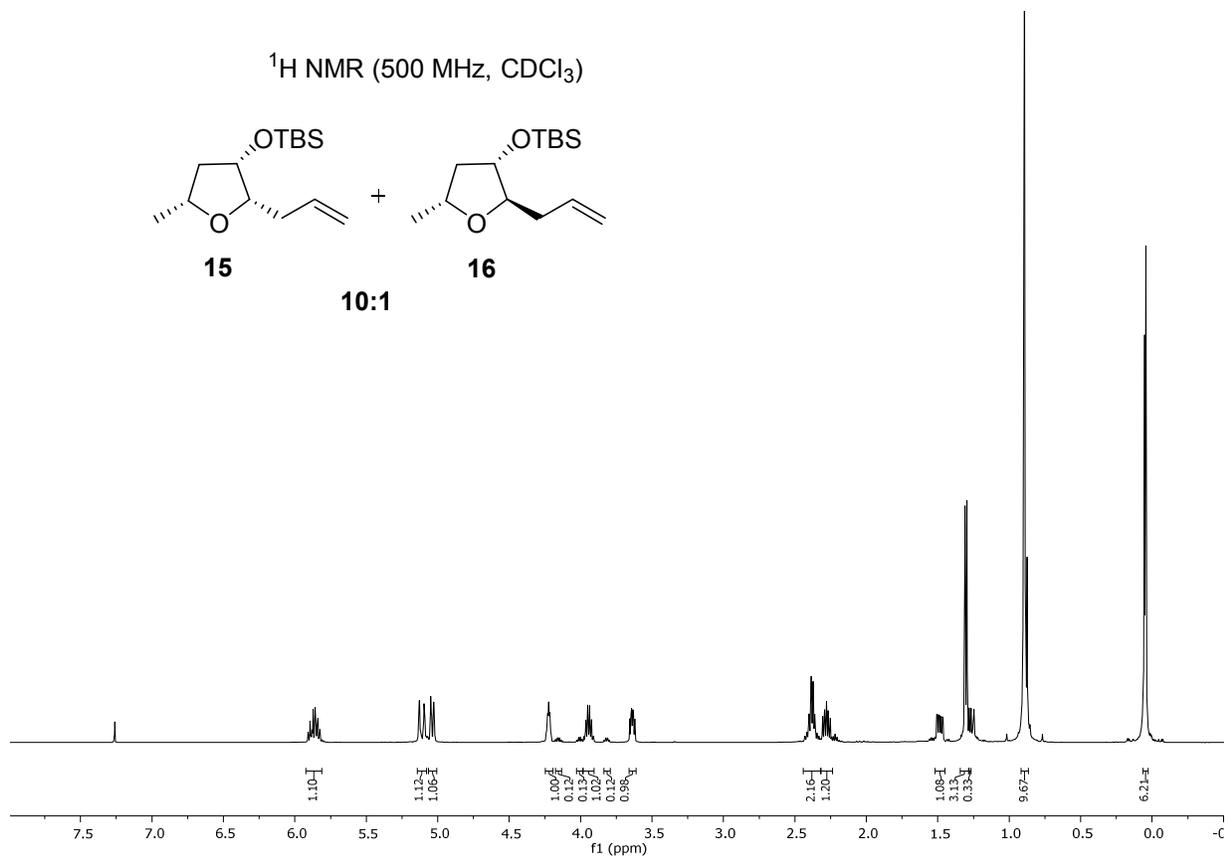
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

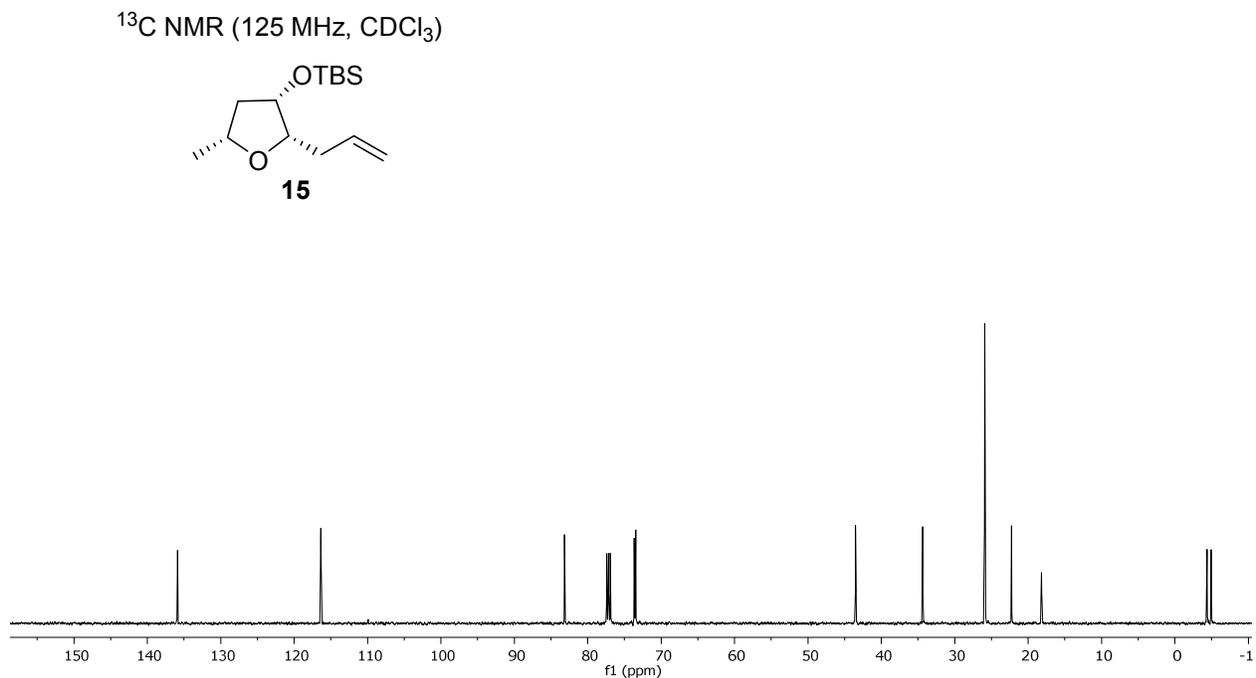
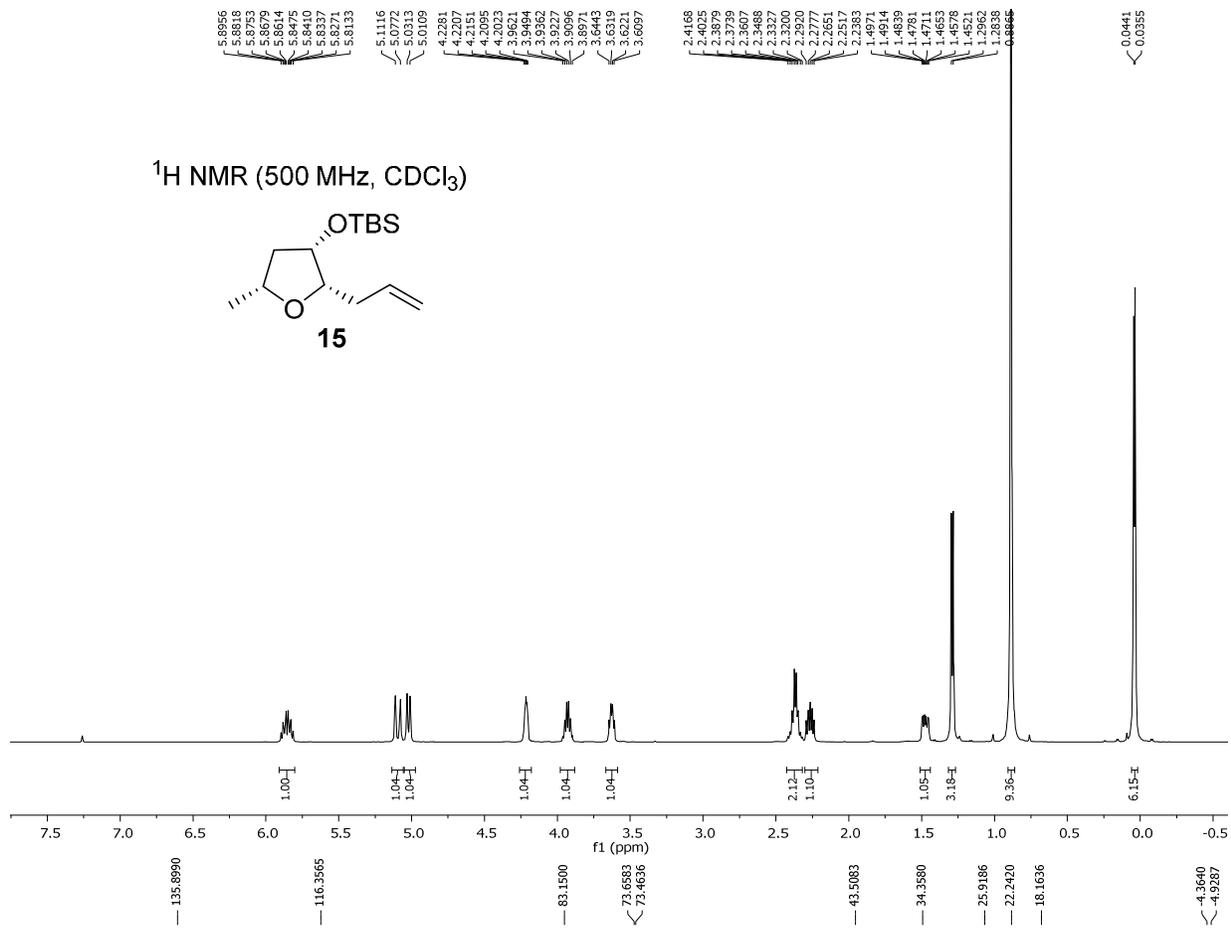


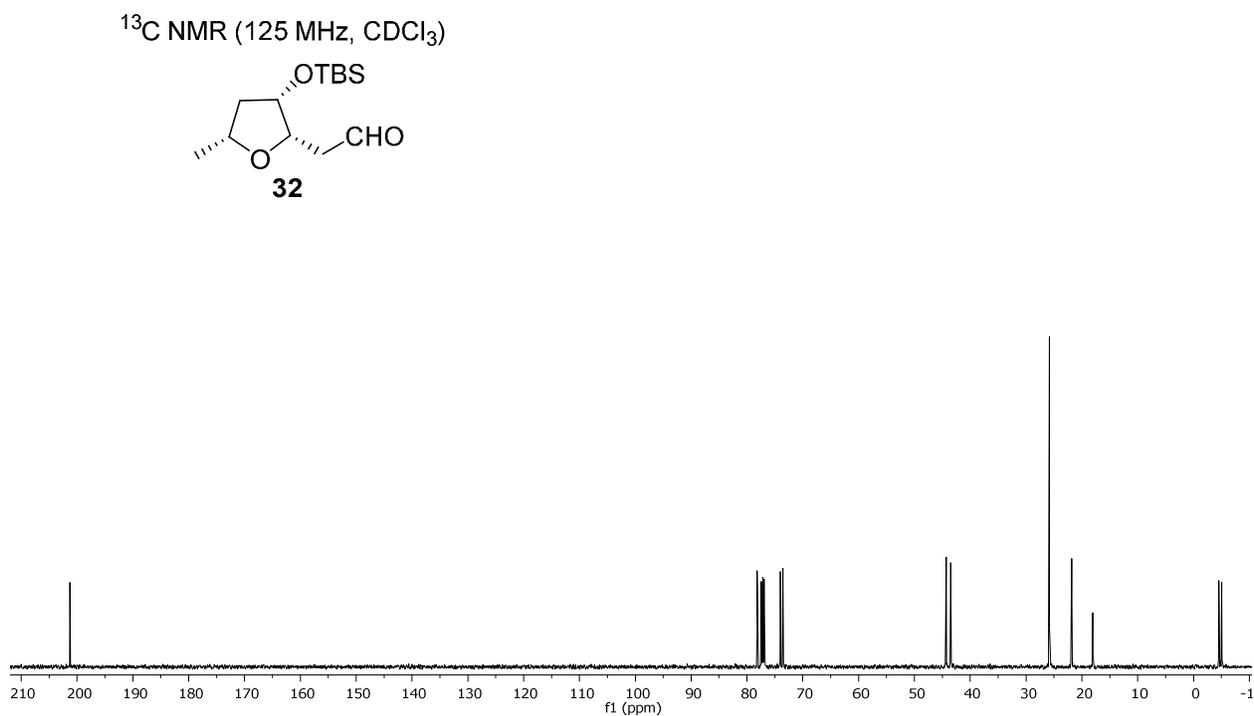
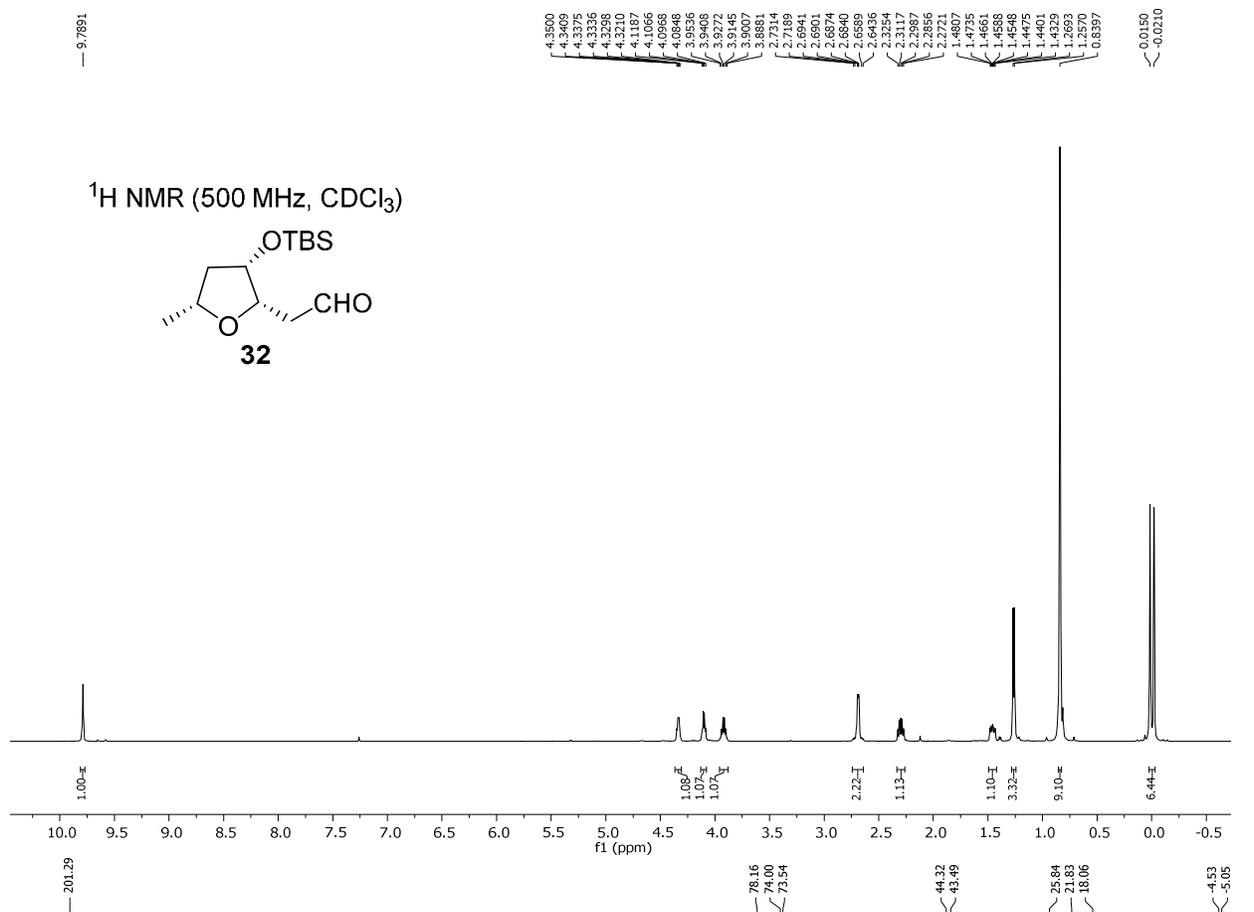
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

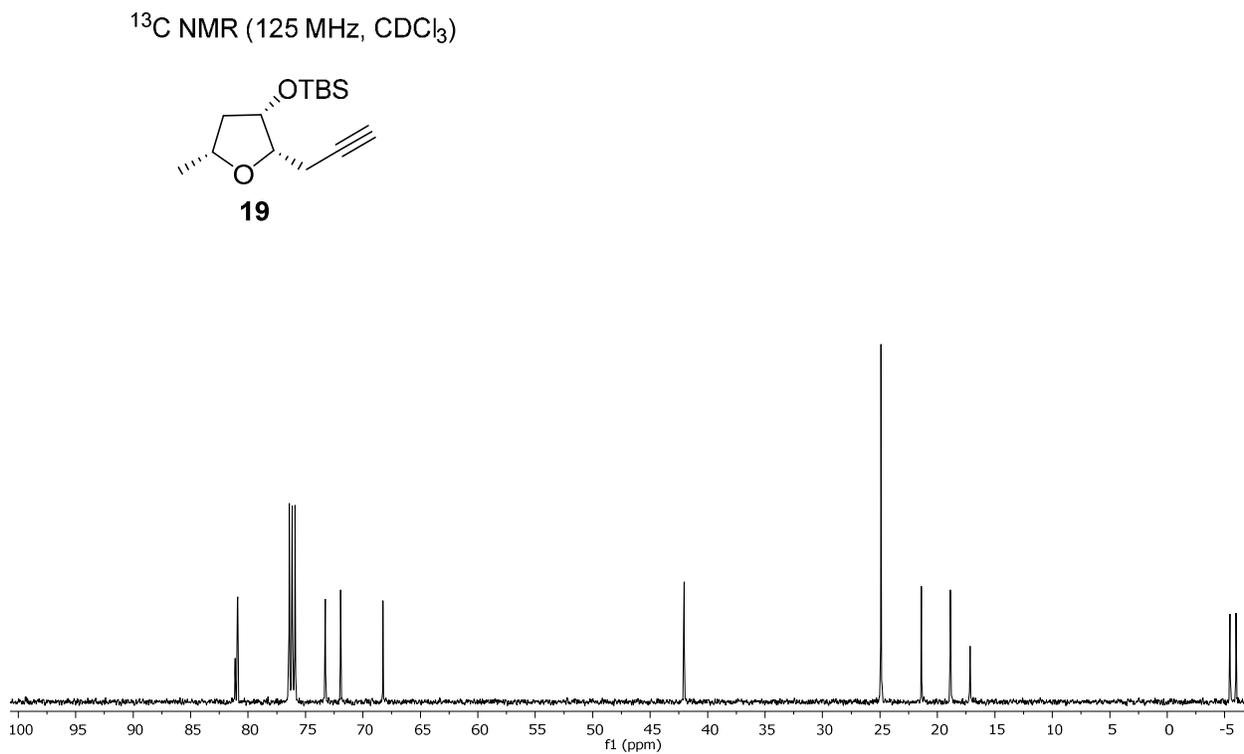
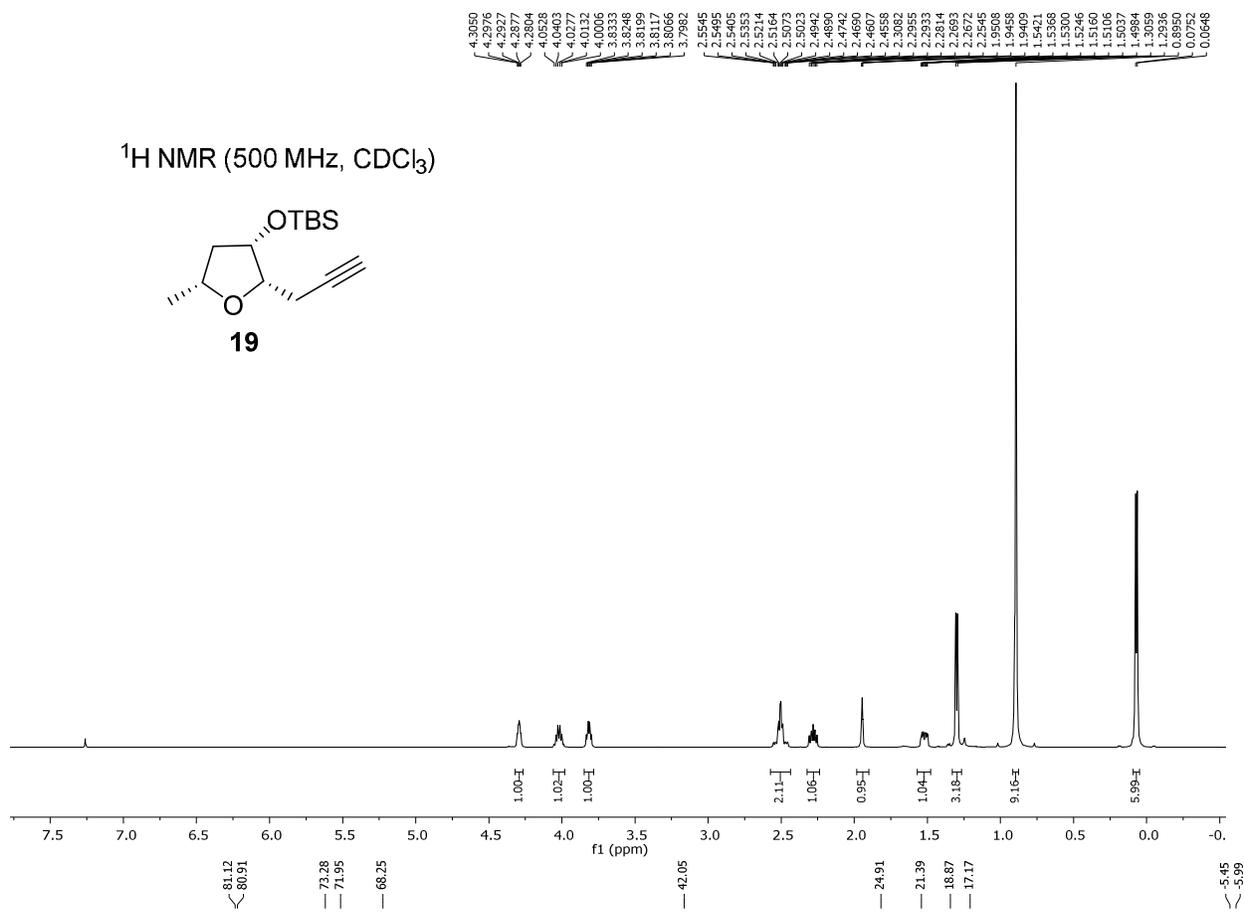


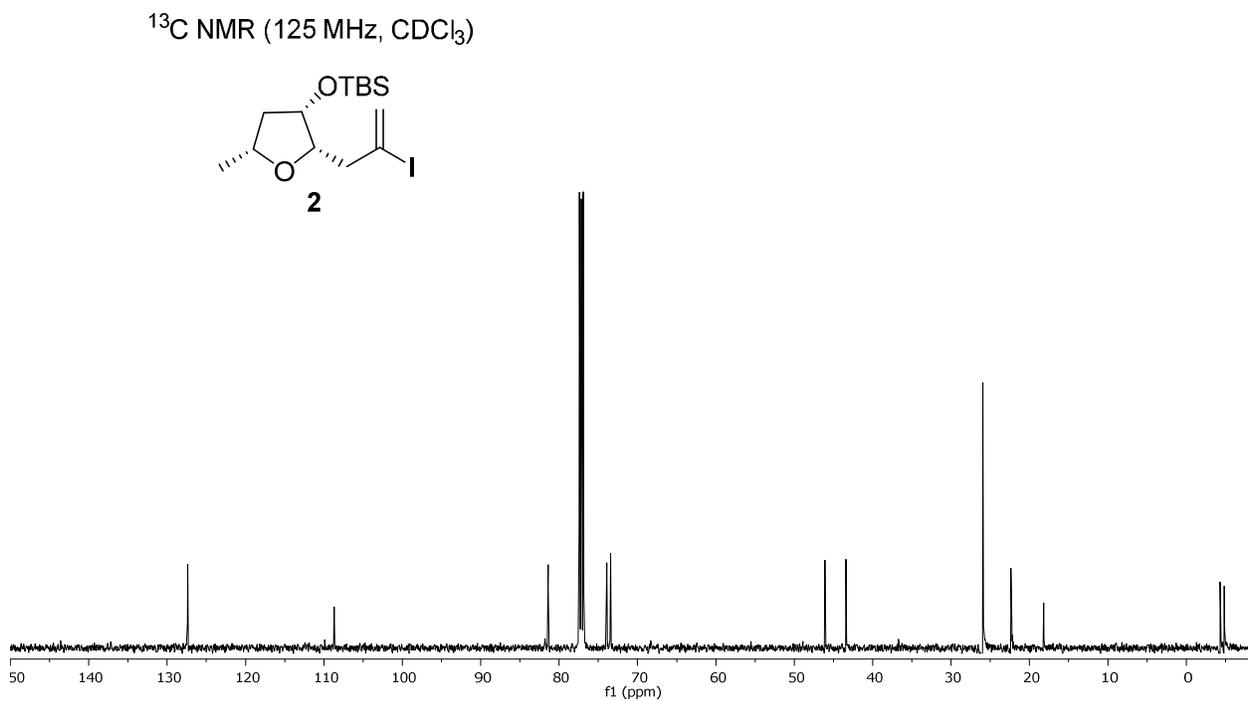
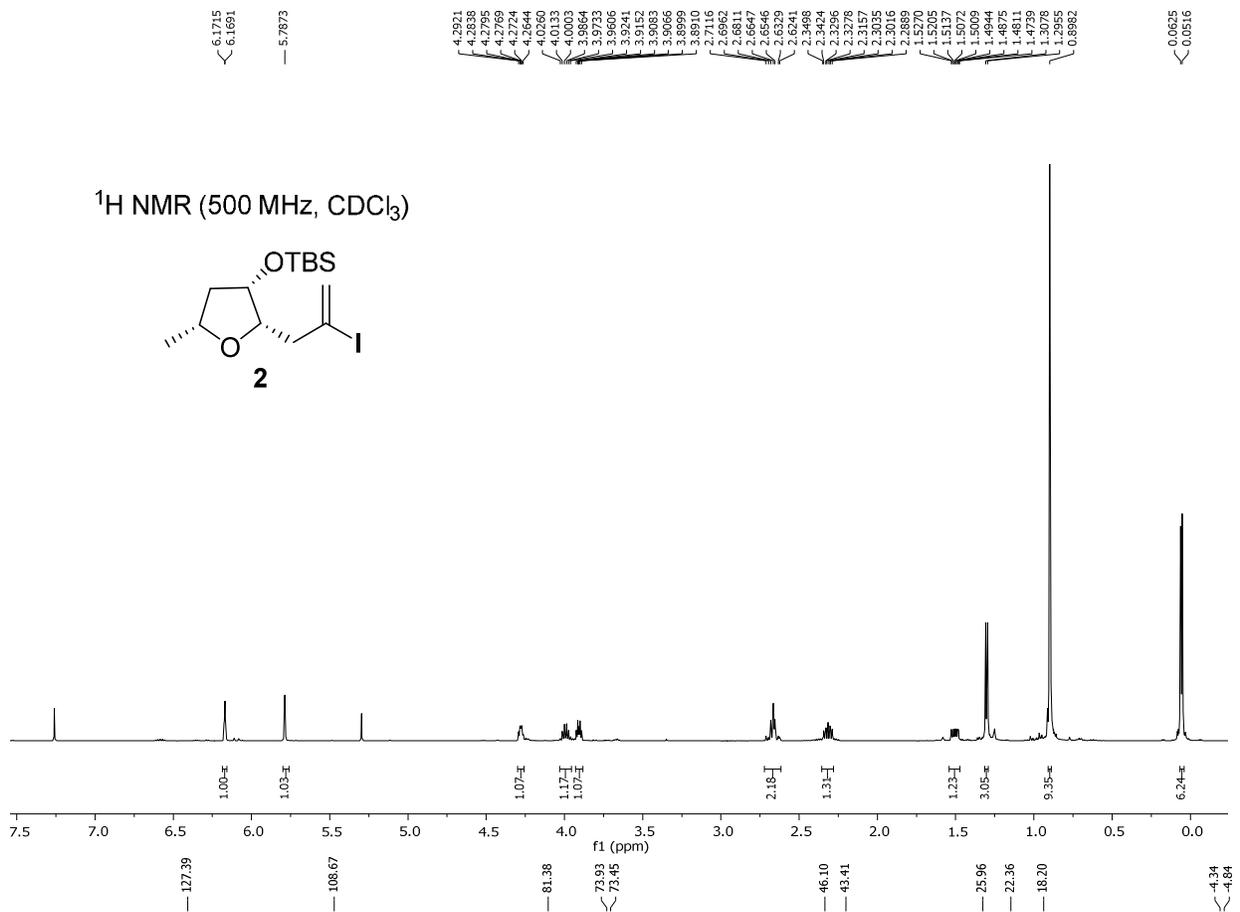














6.9032  
6.8977

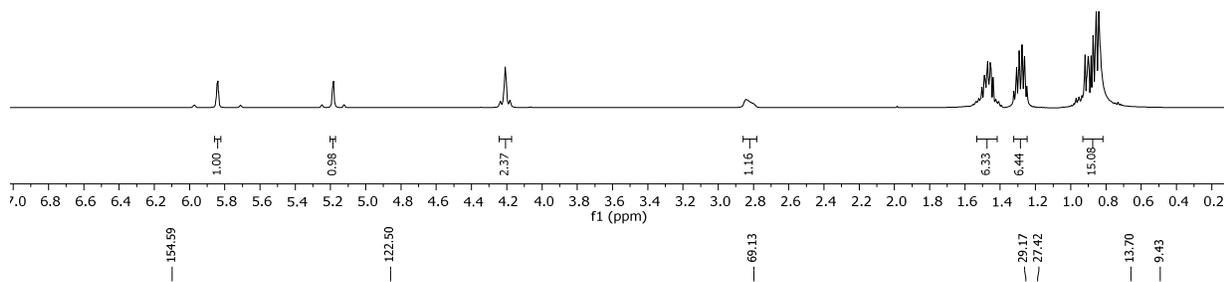
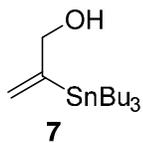
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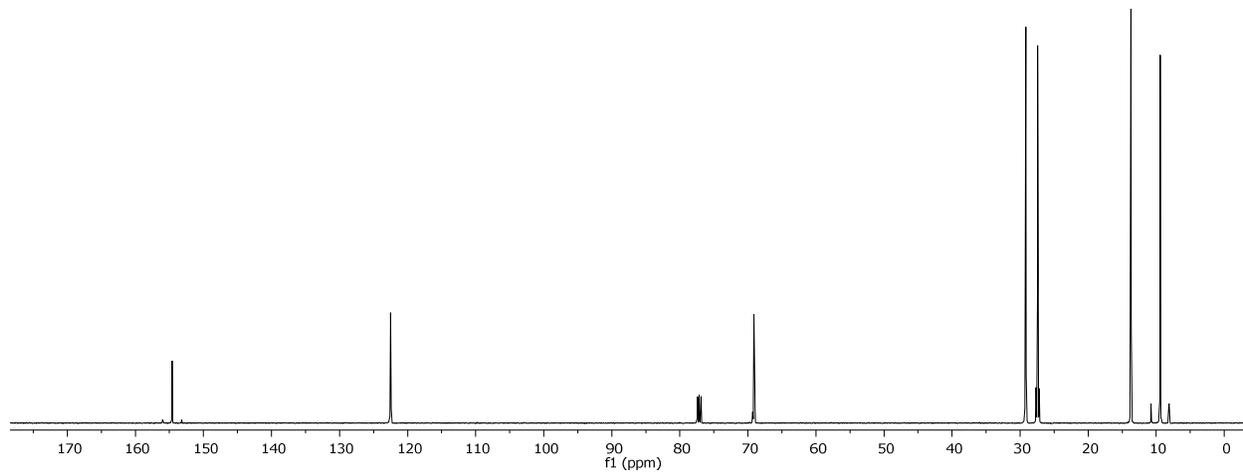
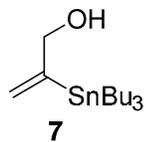
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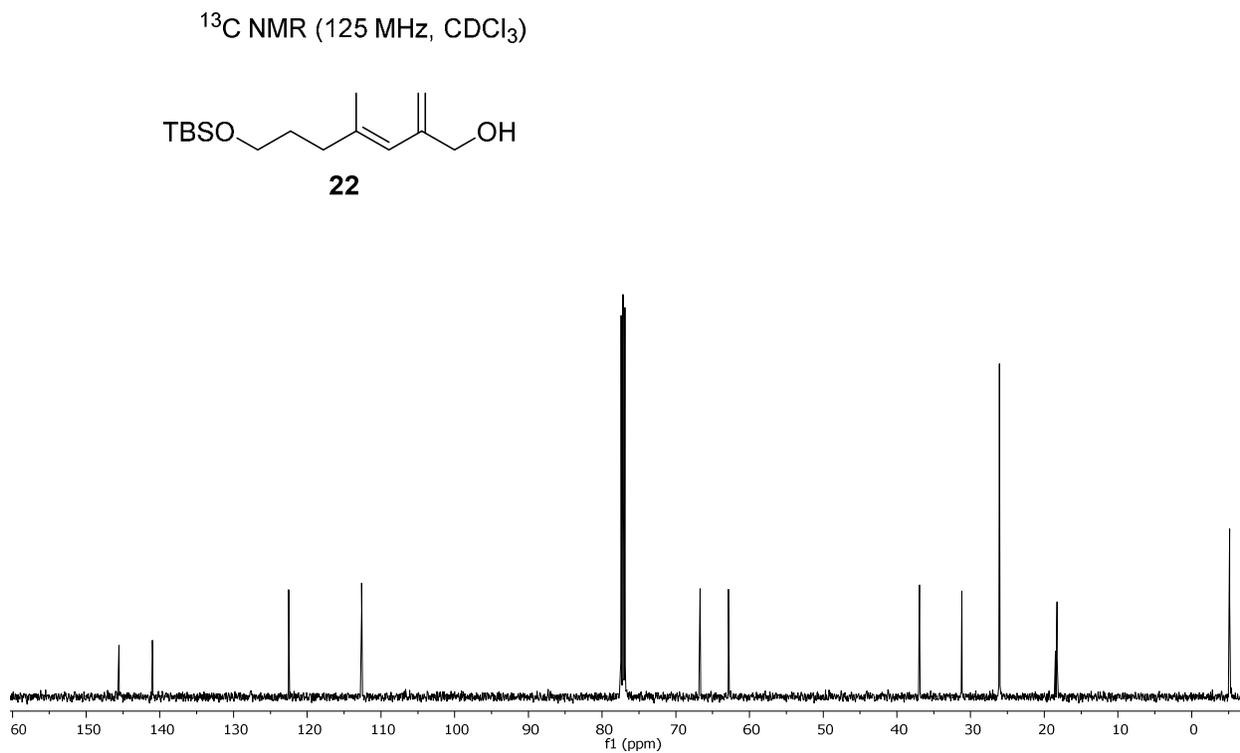
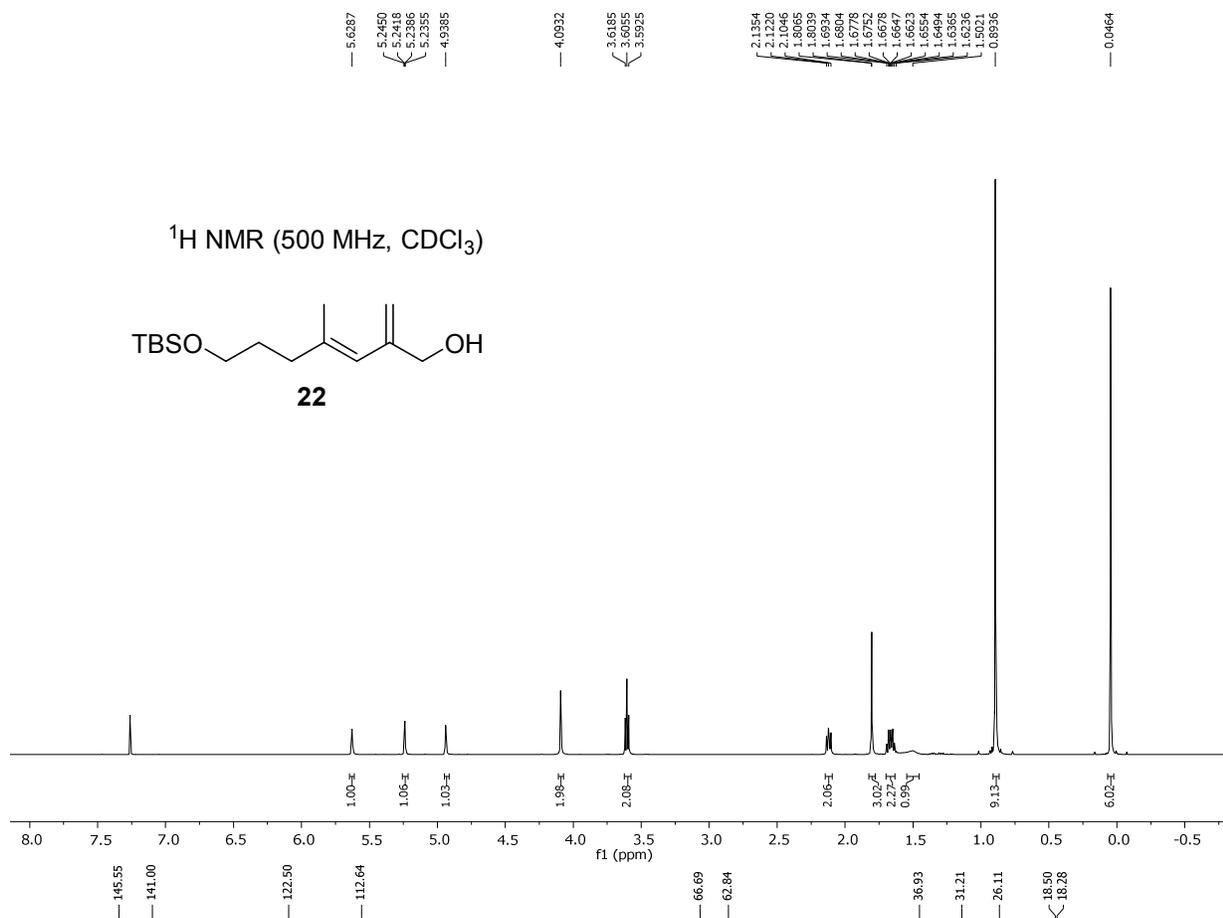
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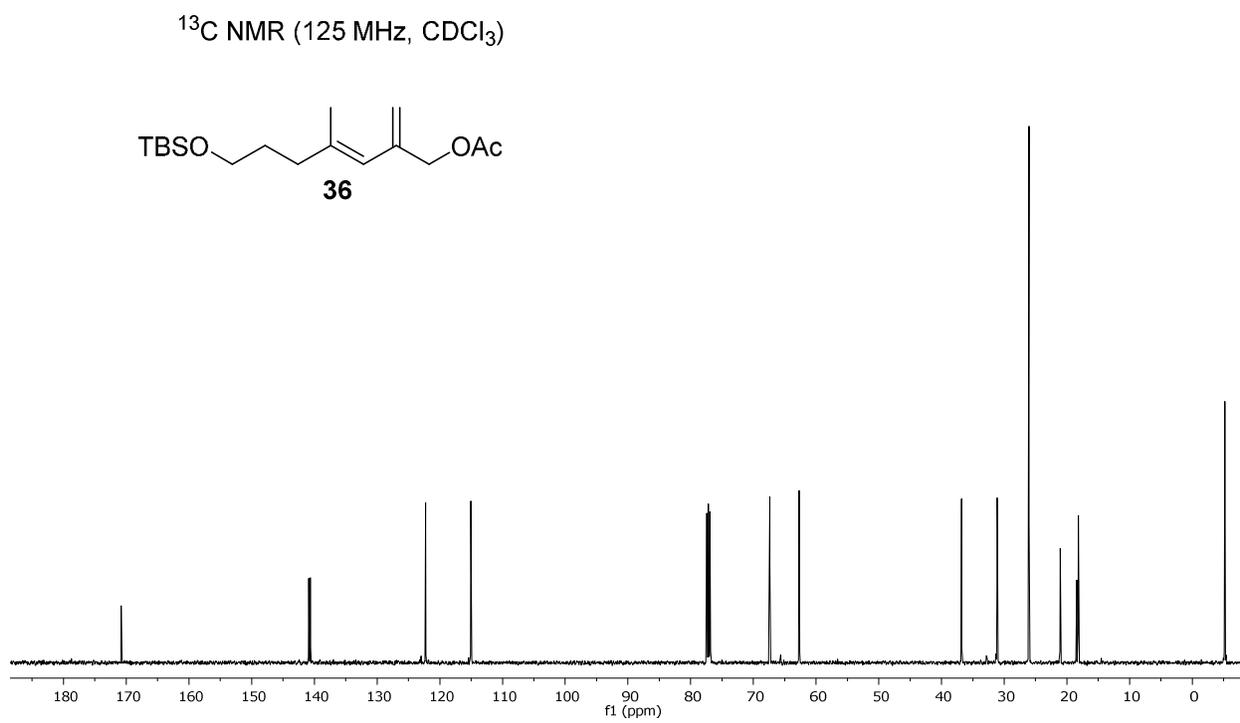
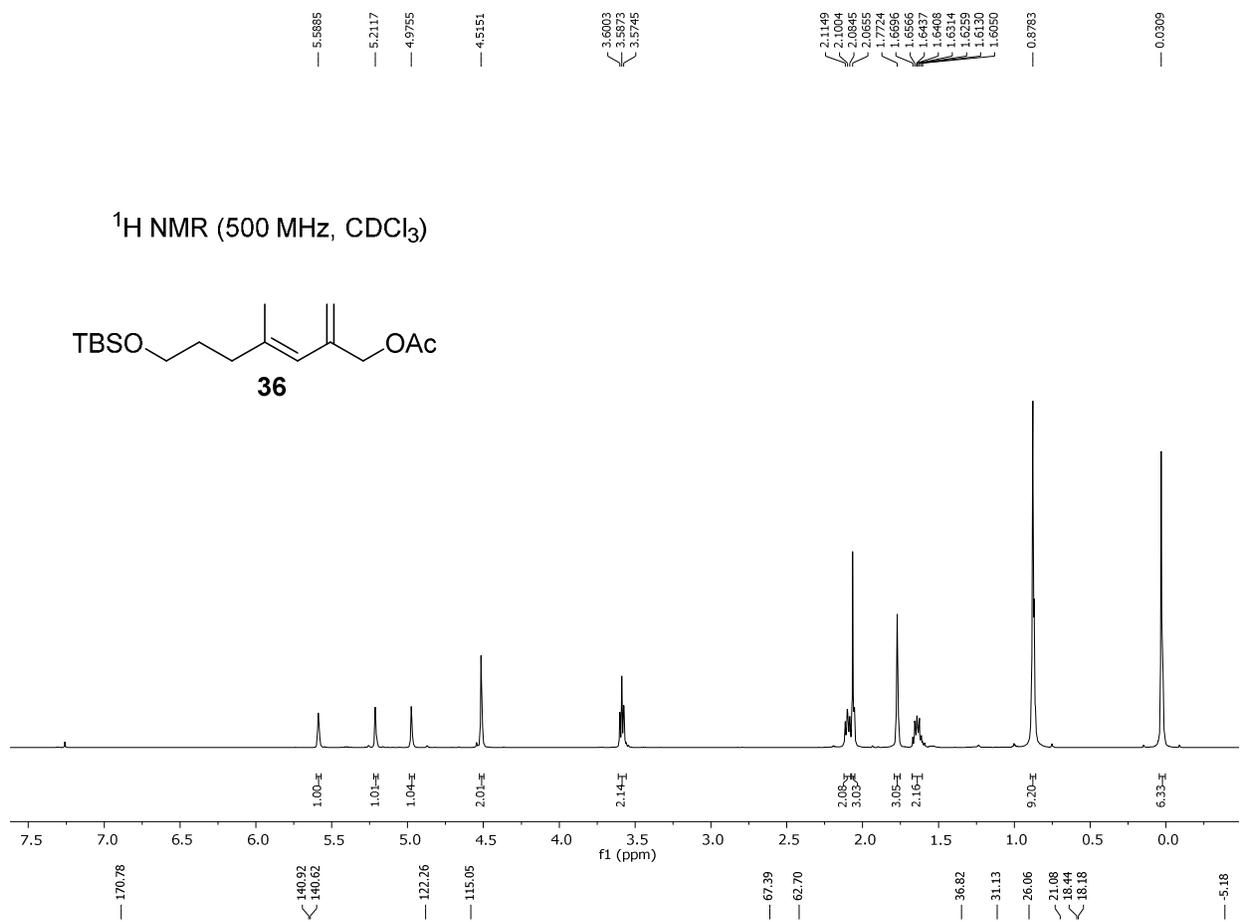
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)











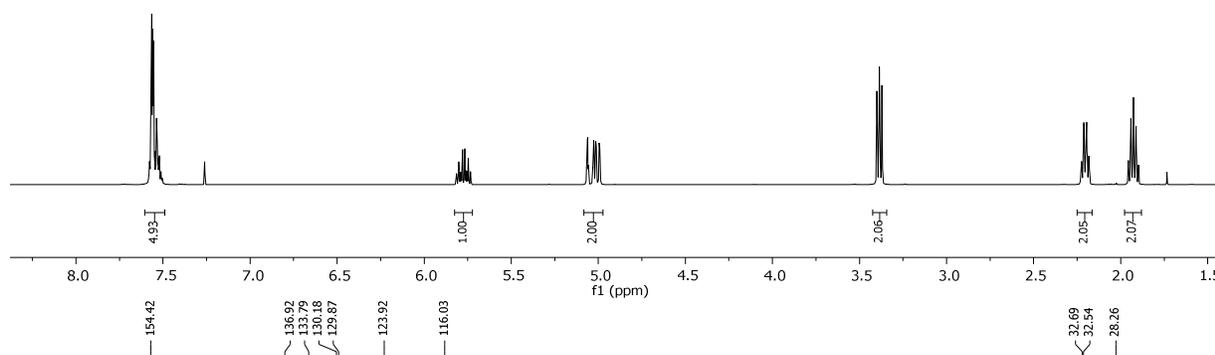
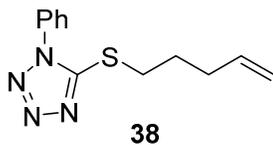
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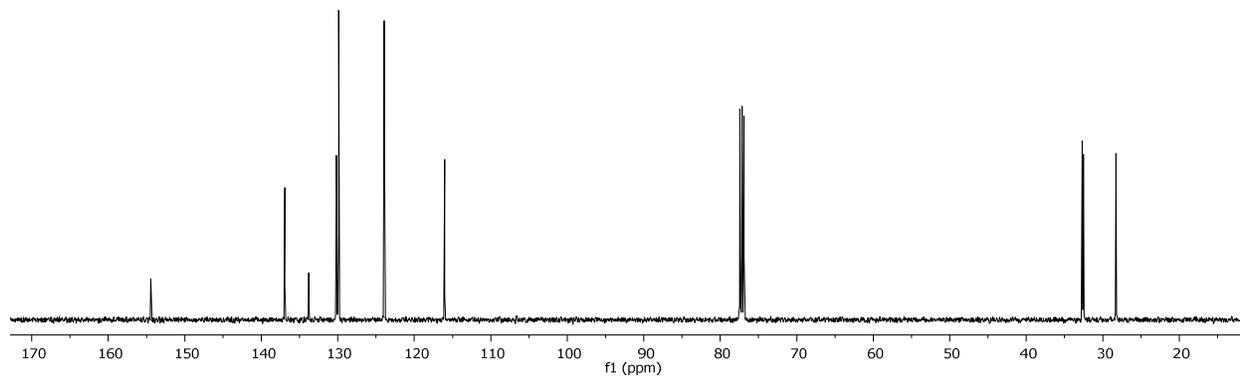
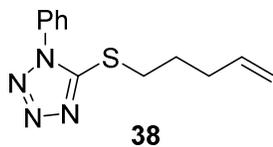
3.39999  
3.3853  
3.3706

2.2252  
2.2228  
2.2184  
2.1977  
2.1959  
2.1851  
2.1826  
2.1803  
1.9560  
1.9410  
1.9226  
1.9197  
1.8974

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

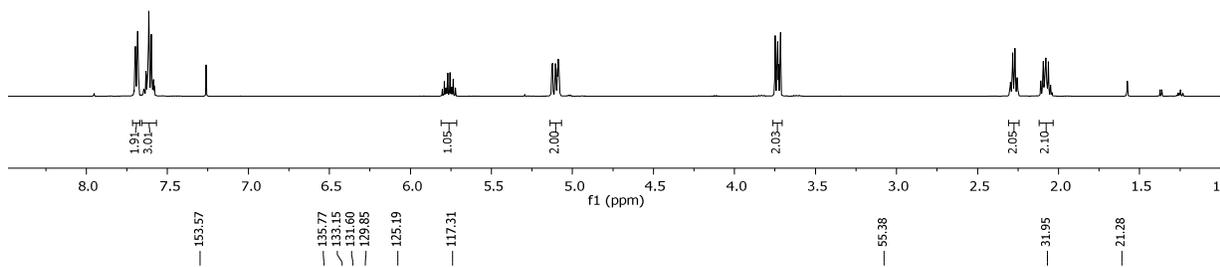
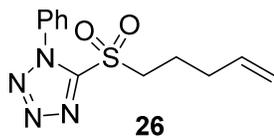


<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

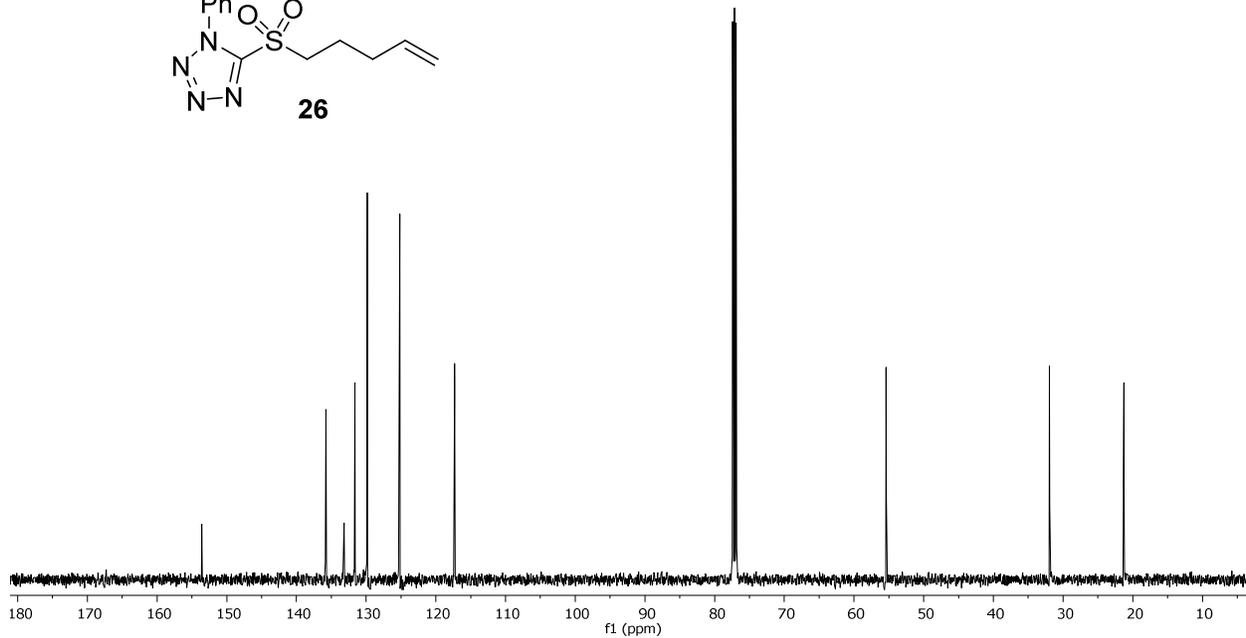
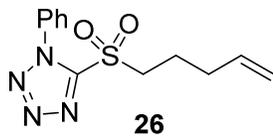


7.7055  
7.6893  
7.6856  
7.6827  
7.6826  
7.6834  
7.6798  
7.6456  
7.6395  
7.6333  
7.6332  
7.6249  
7.6206  
7.6173  
7.6137  
7.6126  
7.6093  
7.6054  
7.6008  
7.5979  
7.5886  
7.5851  
7.5837  
7.5801  
5.8035  
5.7901  
5.7839  
5.7767  
5.7695  
5.7630  
5.7588  
5.7425  
5.7354  
5.7220  
5.1293  
5.1263  
5.1232  
5.1201  
5.1149  
5.1026  
5.0996  
5.0951  
5.0921  
5.0889  
5.0857  
5.0825  
5.0822  
3.7483  
3.7386  
3.7371  
3.7337  
3.7276  
3.7166  
2.2970  
2.2827  
2.2689  
2.2650  
2.1093  
2.0946  
2.0883  
2.0841  
2.0791  
2.0746  
2.0693  
2.0653  
2.0609  
2.0402

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )



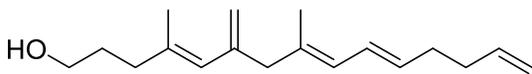


6.2837  
6.2621  
6.2536  
6.2319  
5.8658  
5.8529  
5.8453  
5.8406  
5.8171  
5.8183  
5.8120  
5.7977  
5.7918  
5.6233  
5.6106  
5.5961  
5.5874  
5.5662

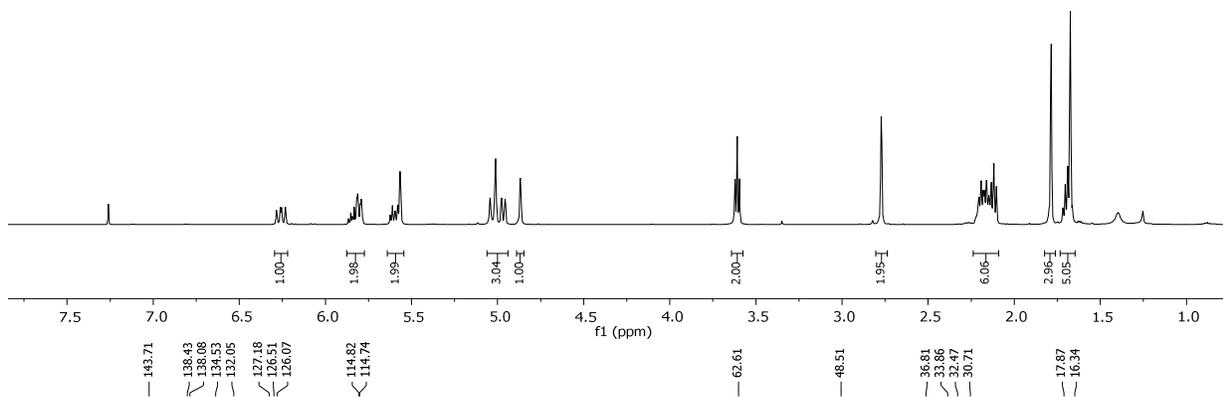
3.6221  
3.6092  
3.5963

2.7718  
2.7203  
2.2051  
2.1921  
2.1800  
2.1721  
2.1605  
2.1470  
2.1355  
2.1187  
2.1038  
1.7870  
1.7854  
1.7175  
1.7046  
1.6889  
1.6776  
1.6621

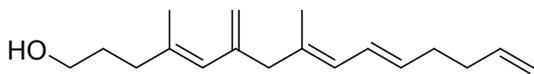
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



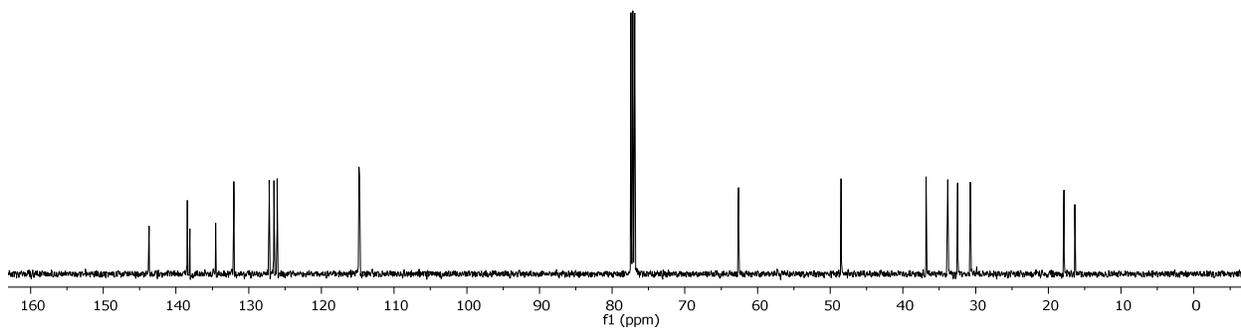
**39**

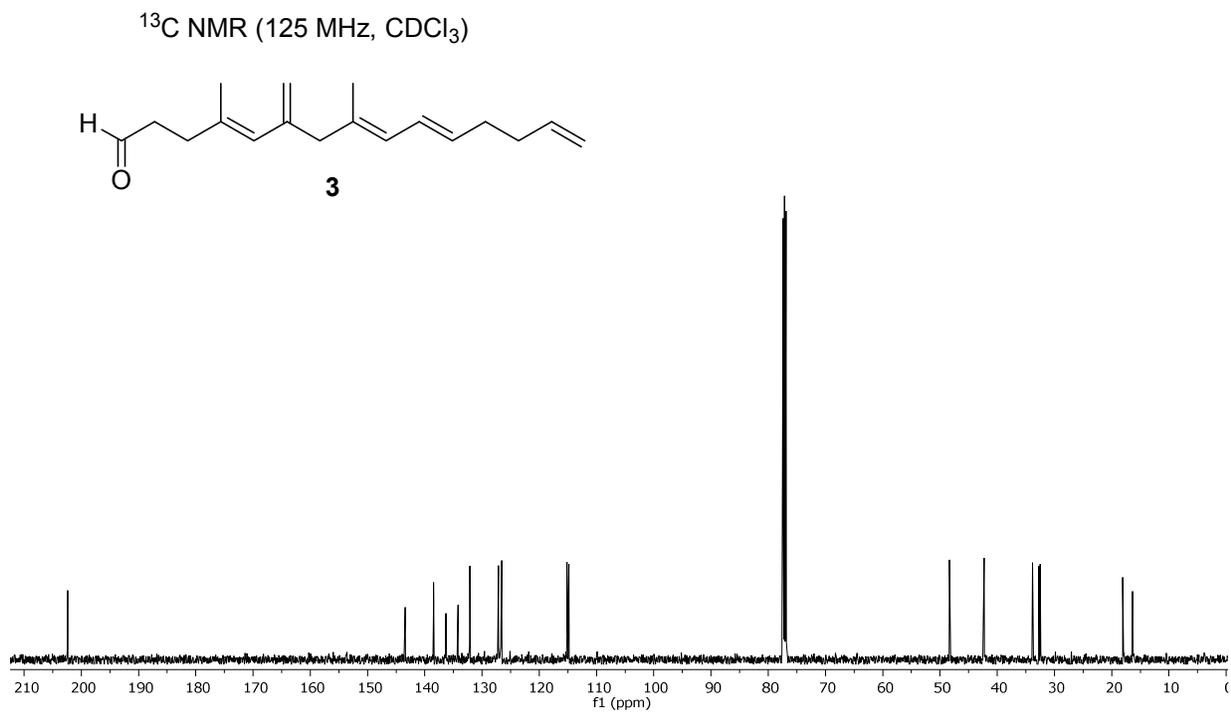
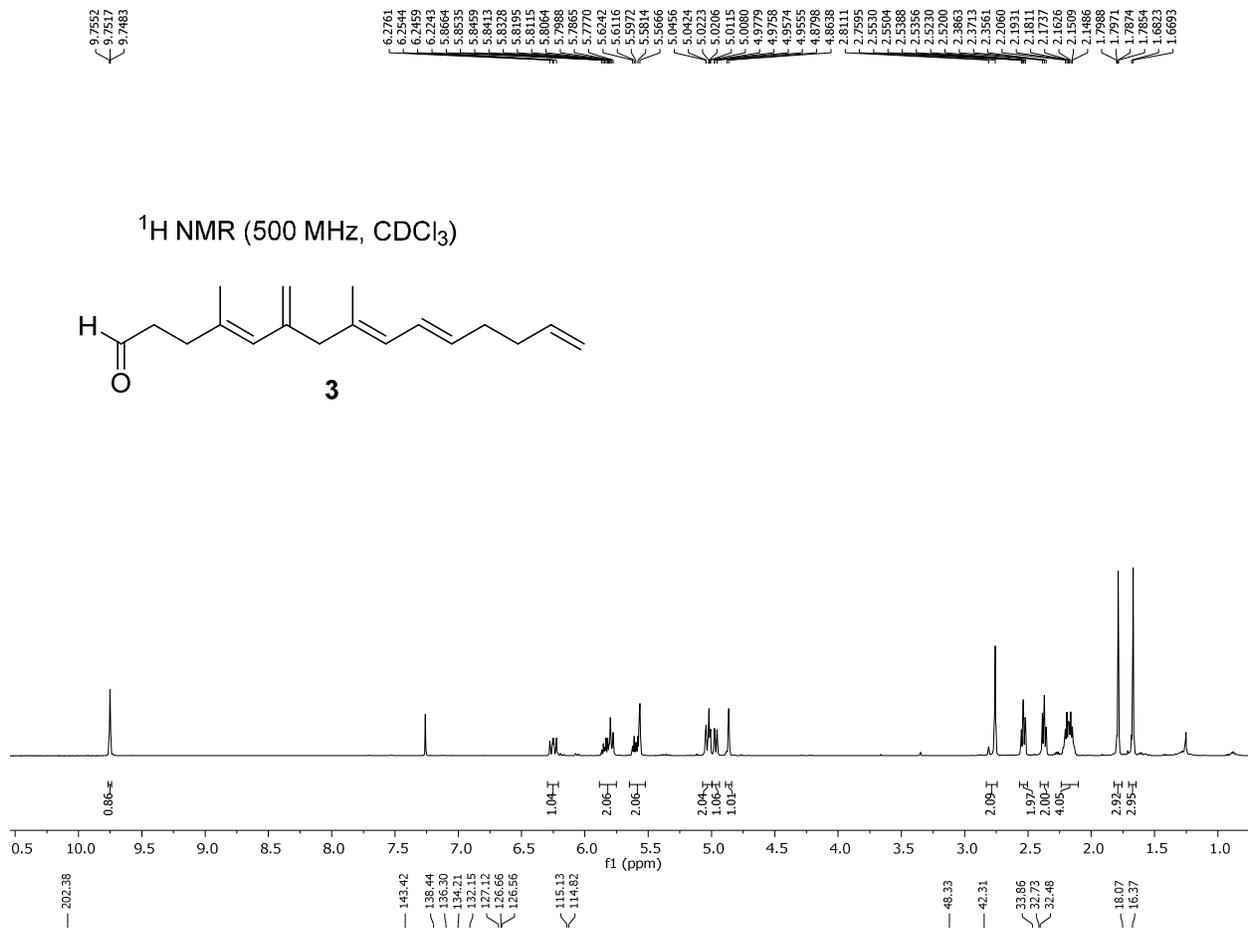


<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)



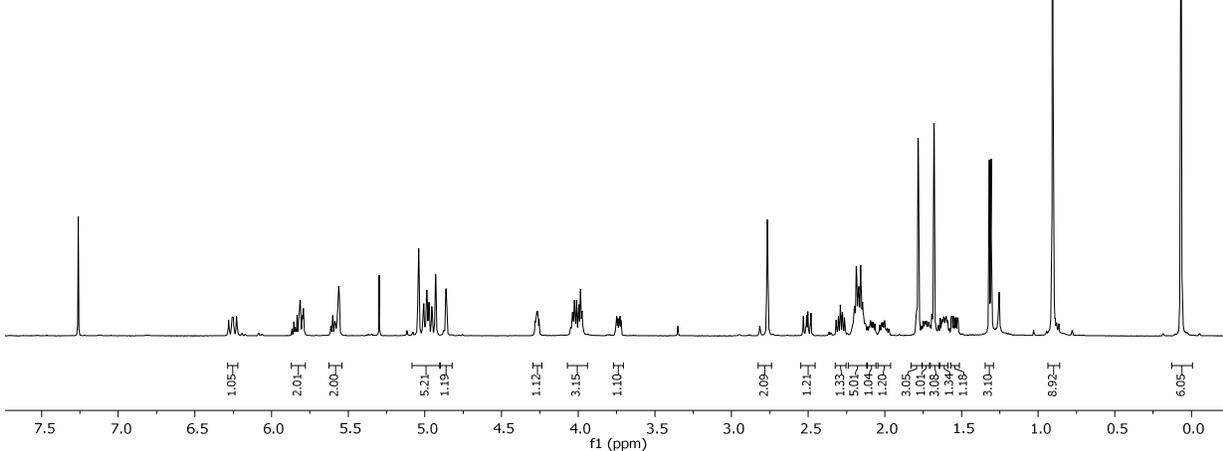
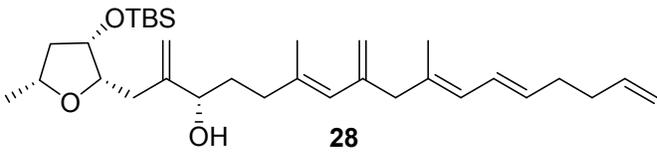
**39**





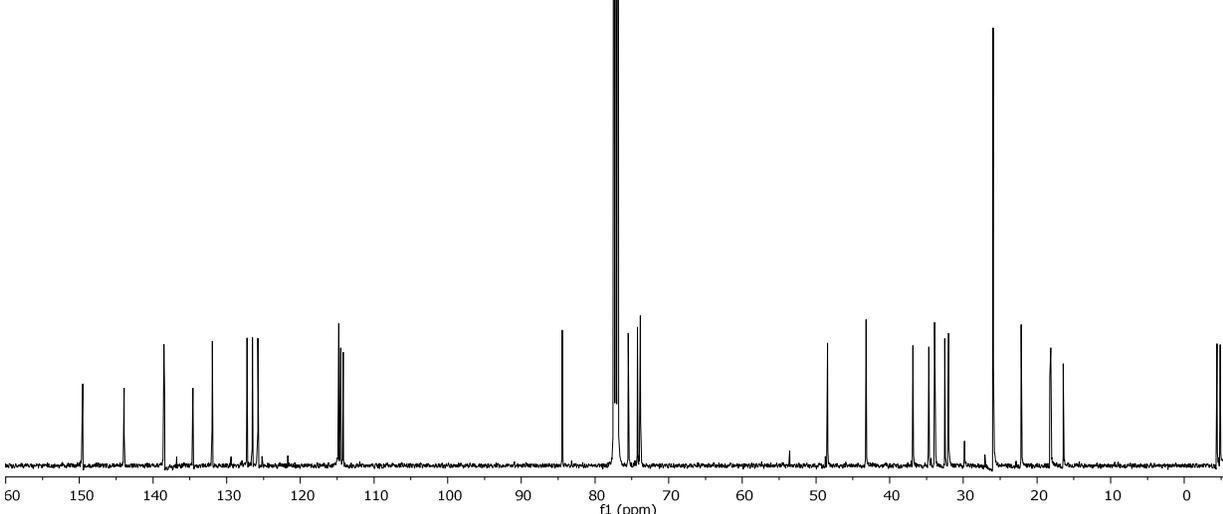
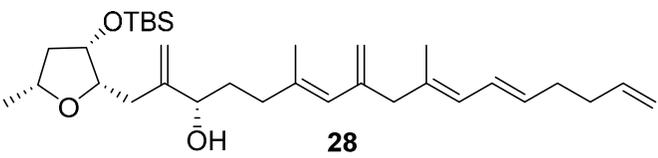
6.2793  
6.2577  
6.2491  
6.2275  
5.8174  
5.8168  
5.8137  
5.8003  
5.7928  
5.6006  
5.5696  
5.5618  
5.0440  
5.0070  
5.0040  
4.9893  
4.9876  
4.9859  
4.9796  
4.9735  
4.9525  
4.9535  
4.9303  
4.8612  
4.2740  
4.2688  
4.2671  
4.2628  
4.2530  
4.0366  
4.0241  
4.0111  
3.9966  
3.9846  
3.9747  
3.7495  
3.7465  
3.7441  
3.7348  
3.7290  
3.7264  
3.7207  
2.7655  
2.6516  
2.6130  
2.5936  
2.4821  
2.4821  
2.3168  
2.3044  
2.3021  
2.2902  
2.2782  
2.2760  
2.2665  
2.1981  
2.1859  
2.1730  
2.1711  
2.1581  
2.1443  
2.0027  
1.9357  
1.7830  
1.7810  
1.6919  
1.6794  
1.6380  
1.6252  
1.6177  
1.6114  
1.6037  
1.5981  
1.5913  
1.5662  
1.5603  
1.5537  
1.5474  
1.5407  
1.5275  
1.5272  
1.5214  
1.3193  
1.3070  
0.9057  
0.0703  
0.0656

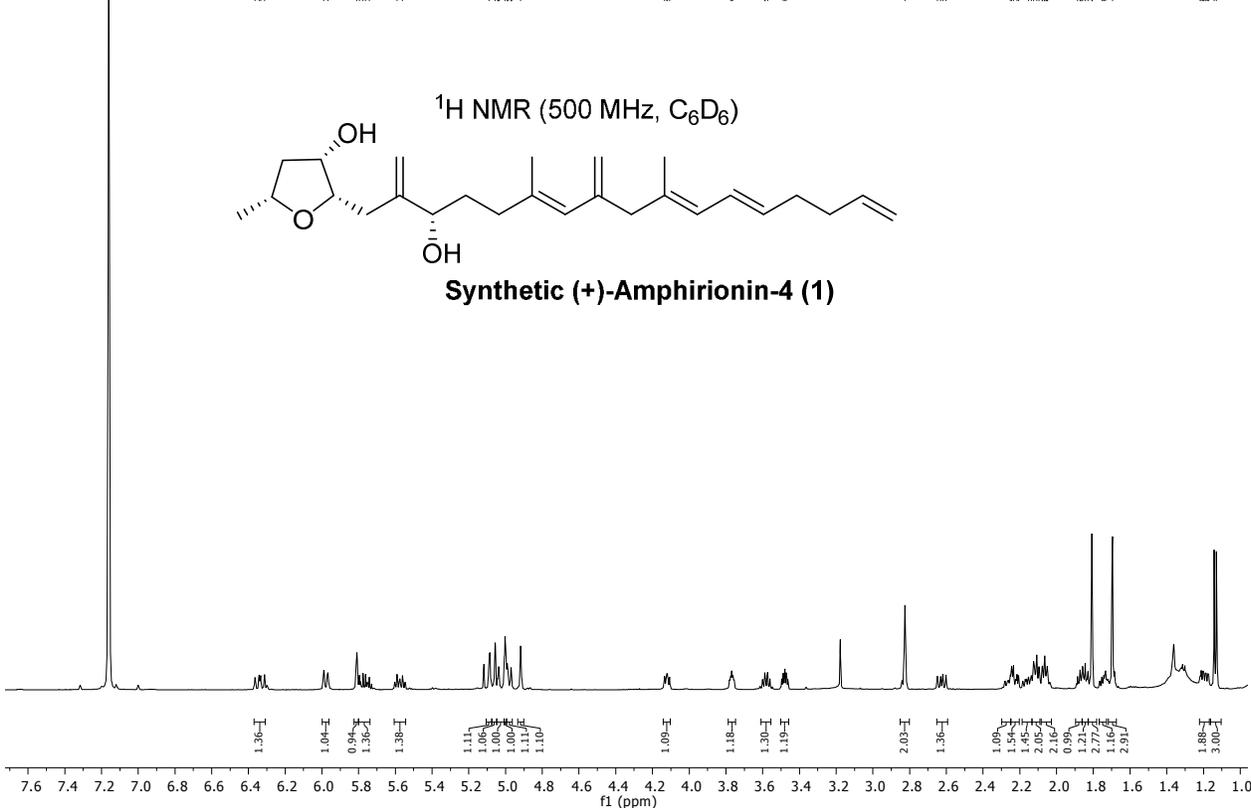
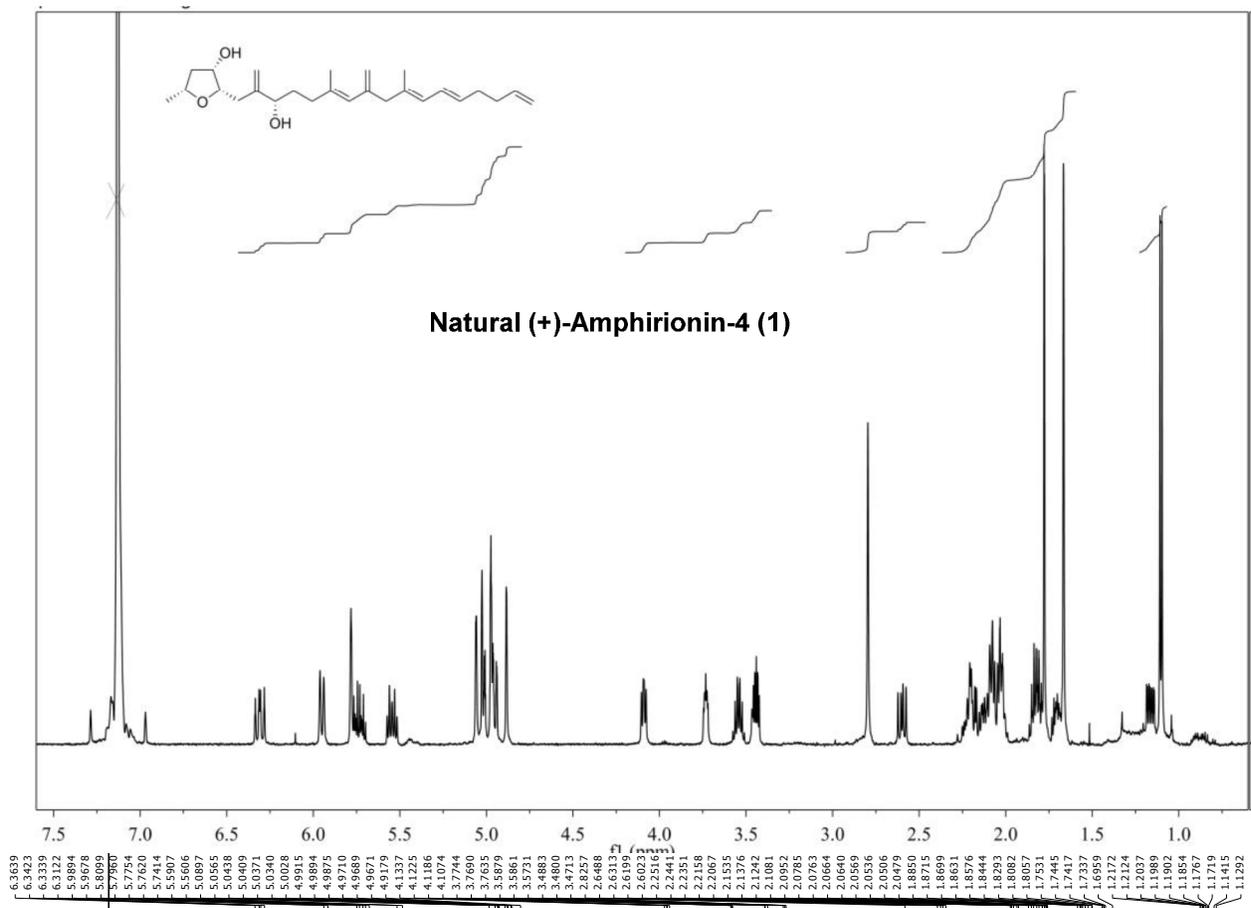
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

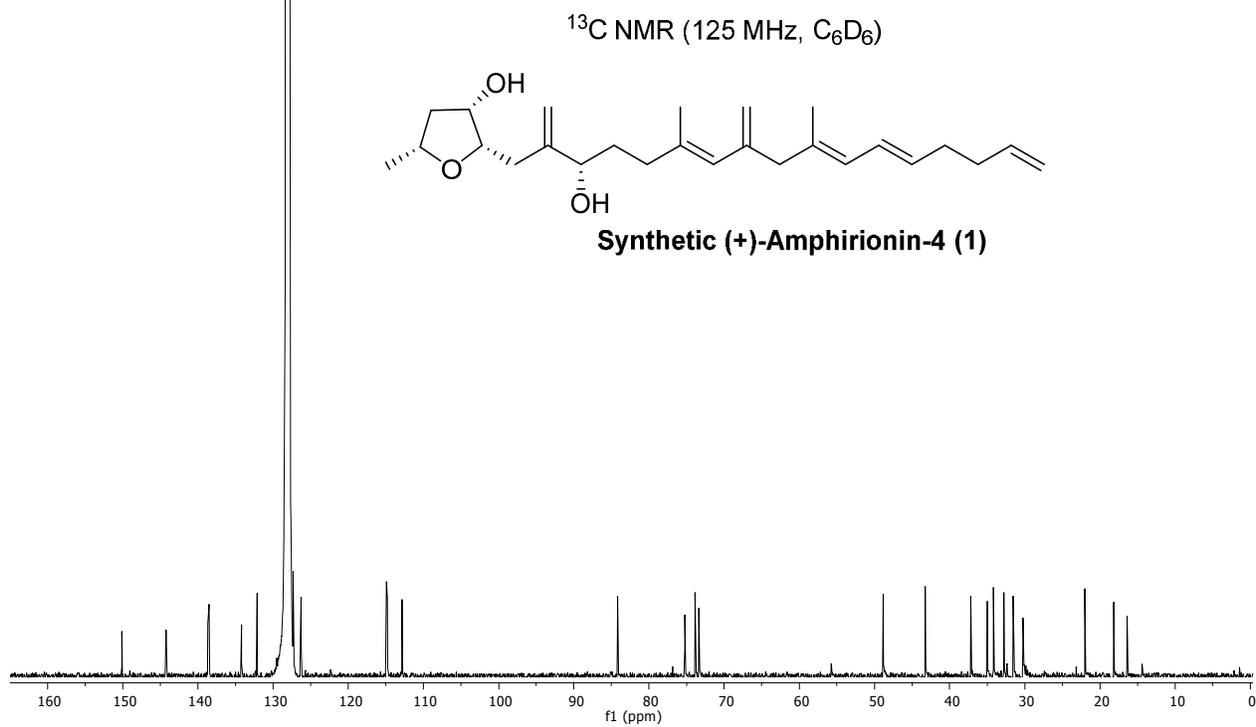
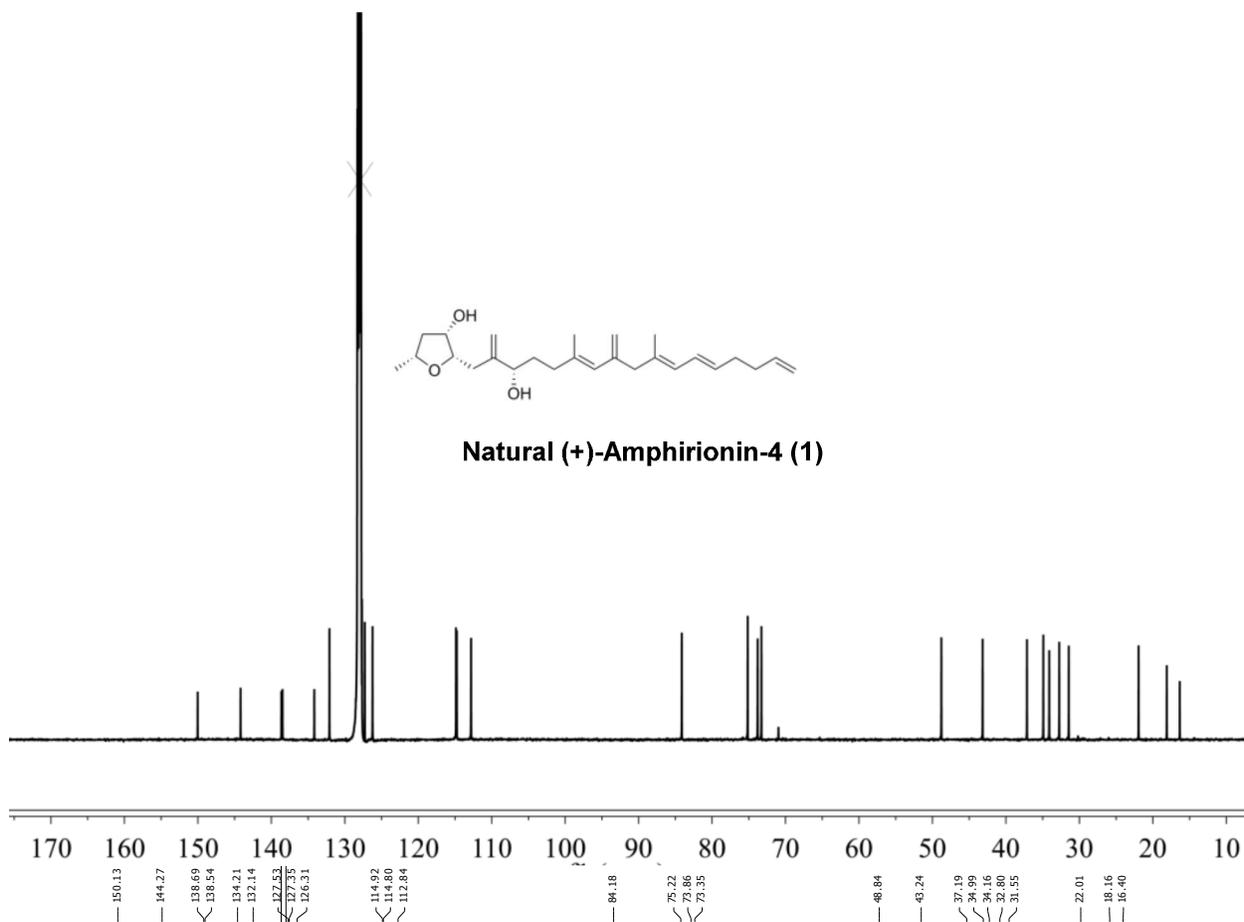


149.54  
143.92  
138.51  
138.44  
134.60  
131.94  
127.21  
126.49  
125.74  
114.76  
114.59  
114.19  
84.41  
75.77  
74.24  
73.84  
48.44  
43.19  
36.84  
34.69  
33.58  
32.52  
32.01  
25.93  
22.14  
18.24  
18.11  
16.43  
4.42  
4.86

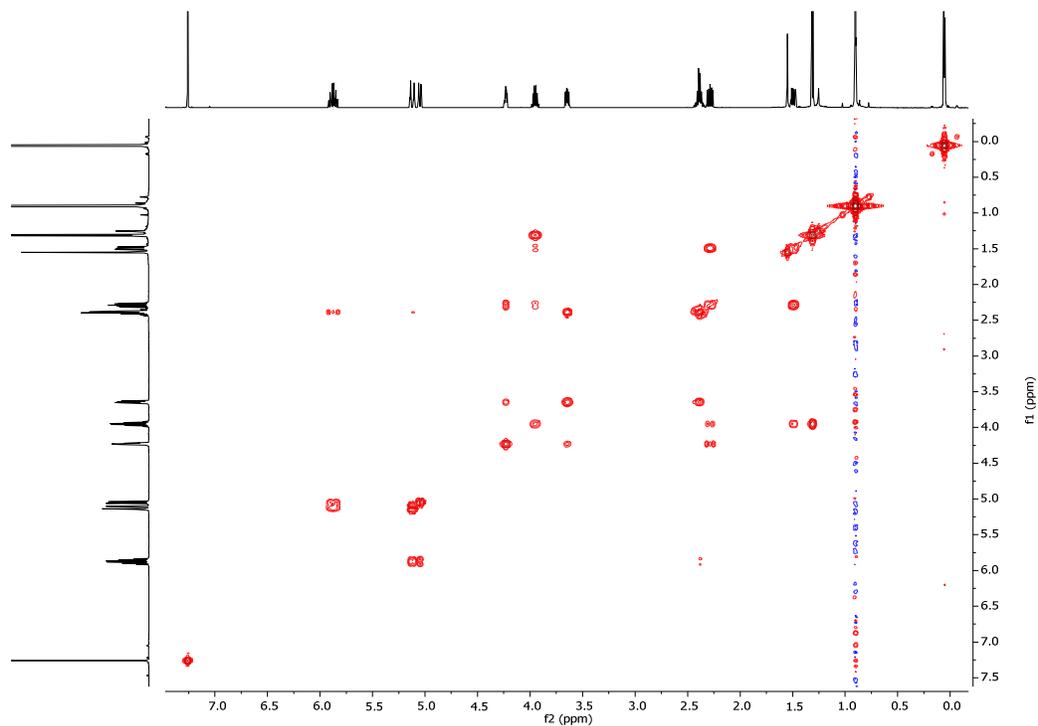
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)



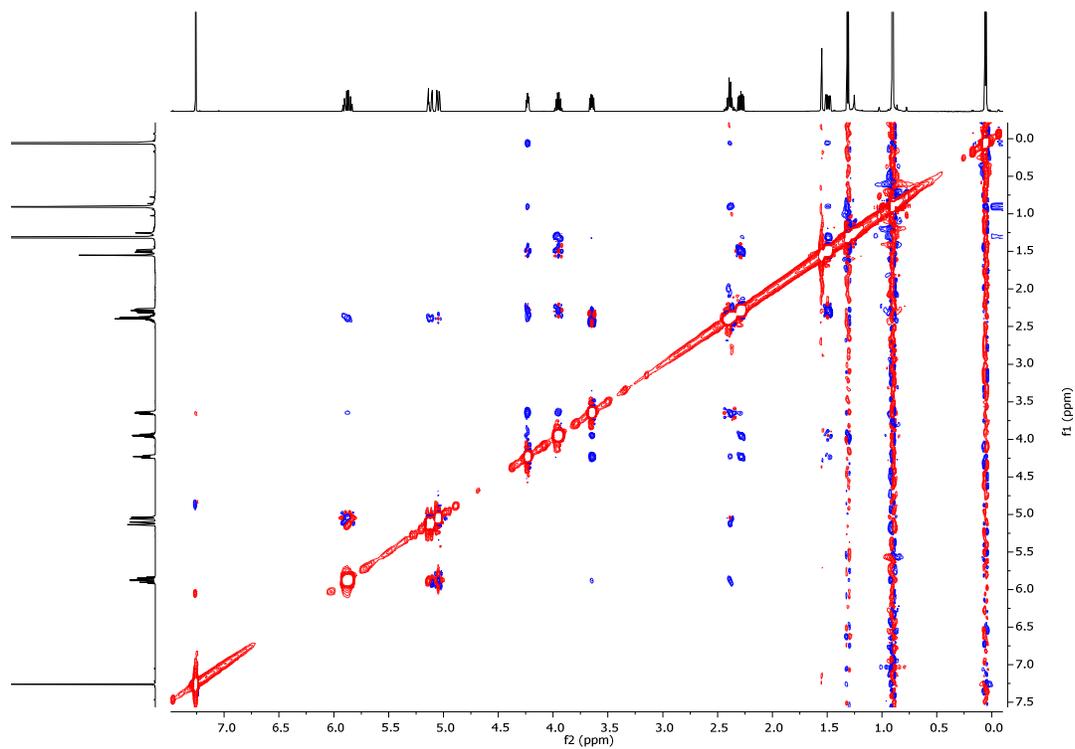




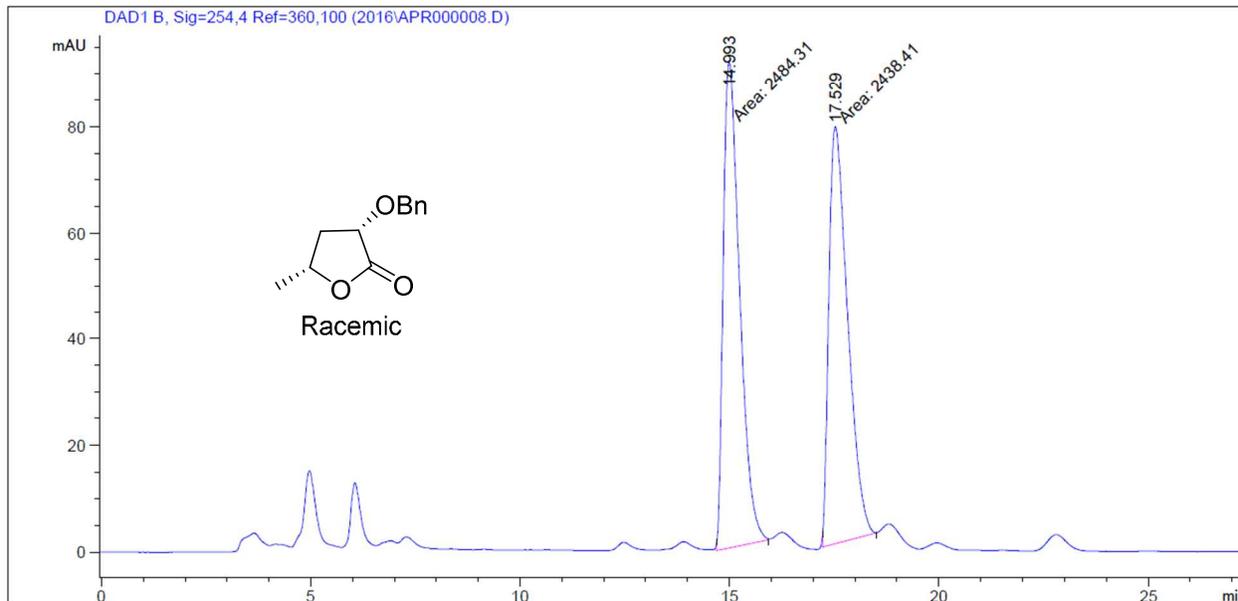
$^1\text{H}$ - $^1\text{H}$  COSY Spectrum of Compound **15** (500 MHz,  $\text{CDCl}_3$ )



NOESY Spectrum of Compound **15** (500 MHz,  $\text{CDCl}_3$ )



# Chiral HPLC



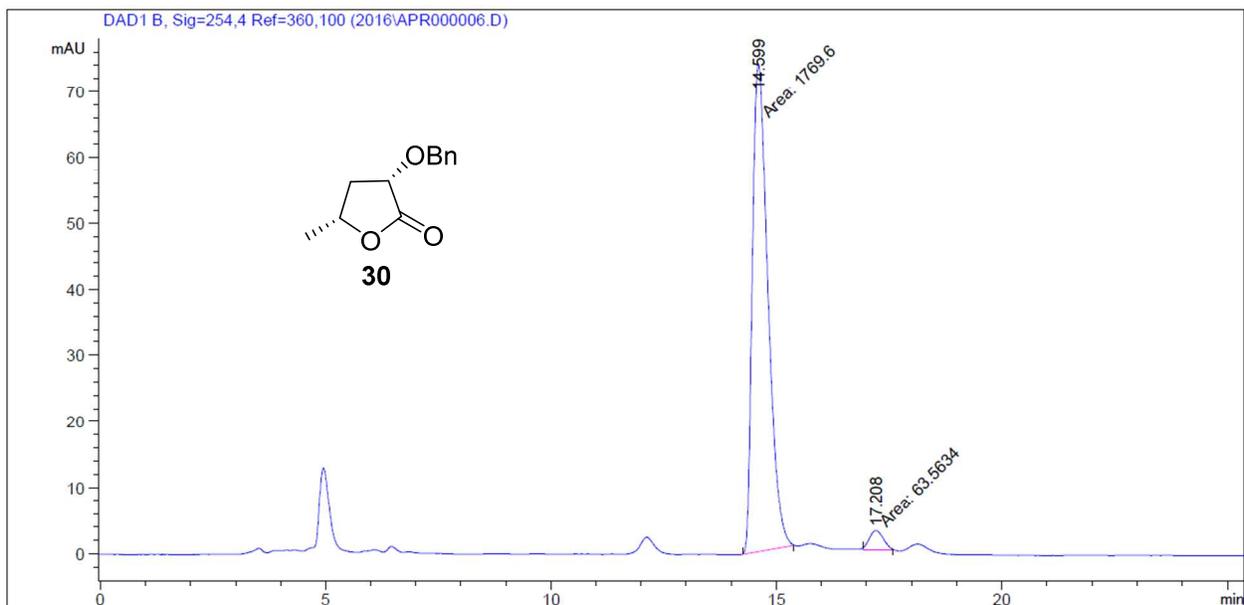
=====  
 Area Percent Report  
 =====

Sorted By : Signal  
 Multiplier: : 1.0000  
 Dilution: : 1.0000  
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.993	MM	0.4521	2484.31494	91.59061	50.4662
2	17.529	MM	0.5183	2438.41357	78.40591	49.5338

Totals : 4922.72852 169.99651



=====  
 Area Percent Report  
 =====

Sorted By : Signal  
 Multiplier: : 1.0000  
 Dilution: : 1.0000  
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.599	MM	0.3991	1769.59985	73.90331	96.5326
2	17.208	MM	0.3630	63.56343	2.91843	3.4674

Totals : 1833.16328 76.82174