

# Total Syntheses of Paraconic Acids and 1,10-*seco*-Guaianolides via Barbier Allylation/Translactonization Cascade of 3-(Bromomethyl)-2(5*H*)-furanone

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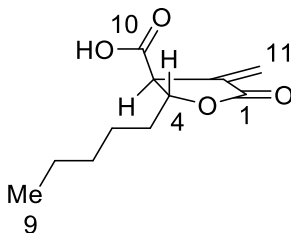
## a) General information

NMR spectra were recorded on AMX-300, AMX-400 and AMX-500 Bruker Avance spectrometers at 298 K with  $\text{CDCl}_3$  as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to chloroform ( $^1\text{H}$ ,  $\delta$  7.26;  $^{13}\text{C}$ ,  $\delta$  77.16) unless otherwise stated. Data for  $^1\text{H}$  NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. High-resolution mass spectra (HRMS) were obtained on a Xevo G2 ToF spectrometer (Ionization mode: ESI positive polarity; Mobile phase: MeOH 100  $\mu\text{l}/\text{min}$ ). Analytical thin layer chromatography (TLC) was performed using 0.25 mm silica gel 60-F<sub>254</sub> plates from Merck, using 250nm UV light as the visualizing agent and a solution of phosphomolybdic acid or  $\text{KMnO}_4$  and heat as developing stain. Flash chromatography was performed using 200-400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. The enantiomeric excess (*ee*) was determined by HPLC analysis. Chiral HPLC analysis was performed on Waters Acquity UPC2 with column OJ-H. All reagents were used as supplied by Aldrich, Fluka, Acros or Strem and used without further purification unless otherwise noted. All reactions were carried out in oven-dried glassware under nitrogen atmosphere unless otherwise noted. For reactions that require heating, oil bath was used as heating source.

## b) Data comparisons of synthetic and natural 6, 19, 20

**Table S1.** Comparison of natural and synthetic methylenolactocin (**6**)<sup>1</sup>

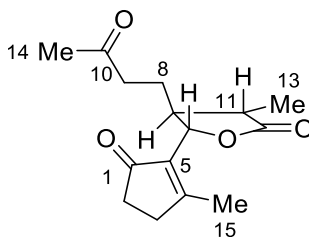
	Natural	Synthetic	Natural	Synthetic
	<sup>1</sup> H NMR (270 MHz, CDCl <sub>3</sub> )	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> )	<sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> )	<sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> )
1	-	-	168.6	168.3
2	-	-	132.5	132.7
3	3.65 (dt, 5.6, 2.9)	3.63 (dt, 5.7, 2.8)	49.6	49.5
4	4.83 (dt, 5.6, 5.4)	4.81 (dt, 7.3, 5.7)	79.1	79.0
5	1.72	1.79 - 1.71 (m)	35.7	35.9
6	1.36	1.34 - 1.31 (m)	31.3	31.5
7	1.36	1.34 - 1.31 (m)	24.4	24.6
8	1.36	1.34 - 1.31 (m)	22.4	22.6
9	0.9	0.91- 0.88 (m)	13.9	14.1
10	-	-	174.3	173.0
11a	6.47 (d, 2,9)	6.46 (d, 3.1)	126.1	125.9
11b	6.04 (d, 2,9)	6.02 (d, 2.7)		



<sup>1</sup> Chen, W. Q.; Yang, Q.; Zhou, T.; Tian, Q. S.; Zhang, G. Z., *Org. Lett.* **2015**, *17*, 5236-5239.

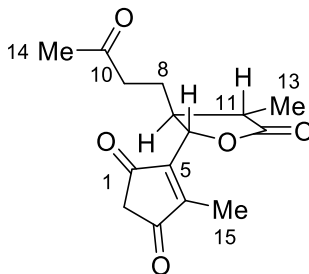
**Table S2.** Comparison of natural and synthetic **19** <sup>2</sup>

	Natural	Synthetic	Natural	Synthetic
	<sup>1</sup> H NMR (500 MHz, CDCl <sub>3</sub> )	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> )	<sup>13</sup> C NMR (125 MHz, CDCl <sub>3</sub> )	<sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> )
1	-	-	207.0	207.2
2	2.43(m)	2.43 (m)	34.4	34.6
3	2.61(m)	2.63 (m)	32.4	32.5
4	-	-	176.6	176.8
5	-	-	135.6	135.8
6	4.81(d, 9.5)	4.81 (d, 9.4)	76.2	76.4
7	2.51(m)	2.49 (dt, 8.8, 2.2)	46.2	46.4
8	1.82(m)	1.80 (m)	25.3	25.5
	1.73(m)	1.73 (m)	-	-
9	2.49(m)	2.46 (m)	40.4	40.6
10	-	-	207.2	207.4
11	2.35(dd, 11.0, 7.0)	2.36 (m)	41.6	41.8
12	-	-	178.3	178.5
13	1.35(d, 7.0)	1.34 (d, 7.0)	14.5	14.5
14	2.11(s)	2.10 (s)	29.9	30.0
15	2.17(s)	2.17 (s)	17.8	18.0

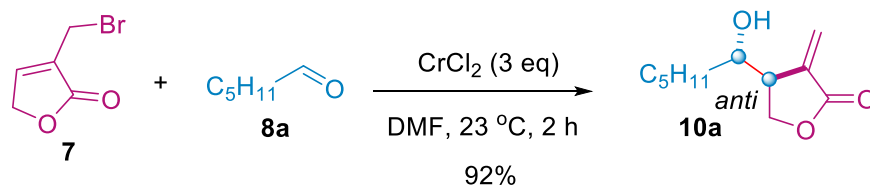
<sup>2</sup> Ahmed, A. A.; Gati, T.; Hussein, T. A.; Ali, A. T.; Tzakou, O. A.; Couladis, M. A.; Mabry, T. J.; Toth, G. *Tetrahedron* **2003**, 59, 3729-3735.

**Table S3.** Comparison of natural and synthetic **20**<sup>3</sup>

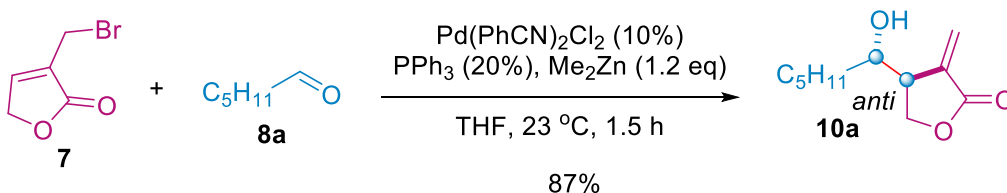
	Natural	Synthetic	Natural	Synthetic
	<sup>1</sup> H NMR (500 MHz, CDCl <sub>3</sub> )	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> )	<sup>13</sup> C NMR (125 MHz, CDCl <sub>3</sub> )	<sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> )
1	-	-	198.5	198.5
2	2.96 (d, 2.5)	2.97 (m)	41.2	41.2
3	-	-	199.4	199.4
4	-	-	158.6	158.6
5	-	-	152.9	152.9
6	5.06 (d, 9.0)	5.06 (d, 8.9)	75.5	75.5
7	2.29 (m)	2.32 (m)	47.8	47.8
8	1.86 (m)	1.84 (m)	25.4	25.4
	1.83 (m)	1.82 (m)	-	-
9	2.51 (m)	2.51 (m)	40.3	40.3
	2.49 (m)	2.49 (m)	-	-
10	-	-	207.0	206.9
11	2.43 (dq, 10.5, 7.0)	2.46 (m)	41.4	41.4
12	-	-	177.7	177.7
13	1.35 (d, 7.5)	1.33 (d, 7.0)	15.2	15.2
14	2.13 (s)	2.13 (s)	30.1	30.1
15	2.12 (s)	2.12 (s)	9.7	9.7

<sup>3</sup> Ortet, R.; Prado, S.; Mouray, E.; Thomas, O. P. *Phytochemistry*, **2008**, 69, 2961-2965.

### c) Experimental procedures for Scheme 1

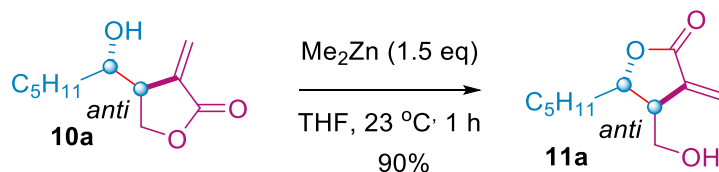


$\text{CrCl}_2$  (31 mg, 0.26 mmol, 3 equiv) was added to a solution of bromolactone **7** (15 mg, 0.085 mmol, 1.0 equiv) and hexanal **8a** (12 mg, 0.12 mmol, 1.5 equiv) in DMF (2 mL) at room temperature. The mixture was stirred for 2 hours and diluted with EtOAc. The resultant solution was washed with saturated  $\text{NH}_4\text{Cl}$  (aq.), brine, dried over  $\text{Na}_2\text{SO}_4$  and filtered. Evaporation of the solvent under reduced pressure followed by flash chromatography (90/10 pentane/ EtOAc to 75/25 pentane/EtOAc), yield **10a** (15.5 mg, 92%) as a colourless oil. The spectroscopic data of **10a** are in accordance with the literature values reported.<sup>4</sup>

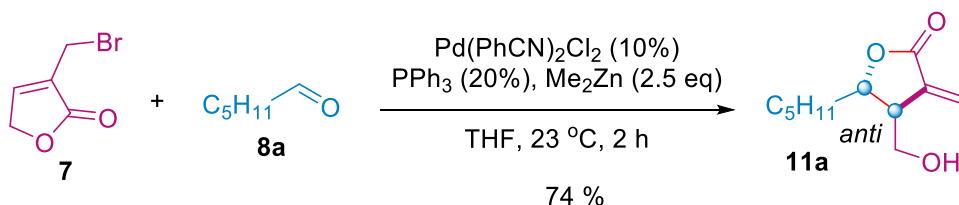


A solution of  $\text{Pd}(\text{PhCN})_2\text{Cl}_2$  (3.3 mg, 0.0085 mmol, 0.1 equiv) and  $\text{PPh}_3$  (4.4 mg, 0.017 mmol, 0.2 equiv) in THF (1 mL) was stirred at room temperature. After 30 minutes, the bromolactone **7** (15 mg, 0.085 mmol, 1.0 equiv), aldehyde **8a** (12 mg, 0.12 mmol, 1.5 equiv) and  $\text{Me}_2\text{Zn}$  (0.085 mL, 1.2 M solution in toluene, 1.5 equiv) were added to the above solution. The mixture was stirred at room temperature for 1.5 h, and then quenched with saturated  $\text{NH}_4\text{Cl}$  (aq.). The resultant solution was extracted with EtOAc, the organic layer was combined, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent under reduced pressure followed by flash chromatography (90/10 pentane/ EtOAc to 75/25 pentane/EtOAc) yield **10a** (14.6 mg, 87%) as a colourless oil.

<sup>4</sup> Hodgson, D. M.; Talbot, E. P.; Clark, B. P. *Org. Lett.* **2011**, 13, 2594-2597.



To a solution of **10a** (15 mg, 0.076 mmol, 1.0 equiv) in THF (1 mL),  $\text{Me}_2\text{Zn}$  (0.1 mL, 0.1 mmol, 1.2 M in toluene) was added. The mixture was stirred at room temperature for 1 hour and then diluted with EtOAc, the resultant solution was extracted with EtOAc, the organic layer was combined, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent under reduced pressure followed by flash chromatography (90/10 pentane/ EtOAc to 50/50 pentane/EtOAc) yield **11a** (13.5 mg, 90%) as a colourless oil. The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3o**, only with the structure corrected.



## General procedure

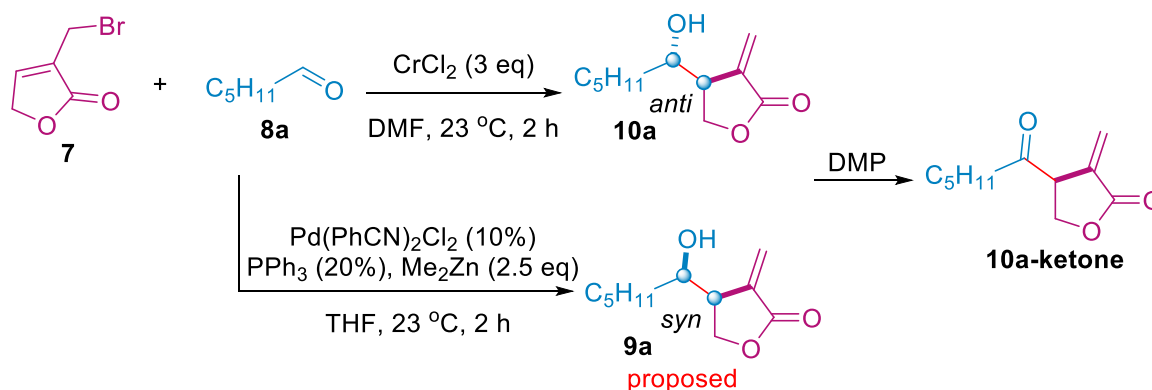
$\text{Pd(PhCN)}_2\text{Cl}_2$  (0.01 mmol, 0.1 equiv),  $\text{PPh}_3$  (0.02 mmol, 0.2 equiv) were added in dried round bottom flask and dissolved in solvent (1 mL, toluene for aromatic aldehydes, THF for aliphatic aldehydes). The reaction mixture was stirred at 23 °C for 30 min, then the bromolactone (18 mg, 0.1 mmol, 1 equiv) in solvent (0.2 mL), aldehydes (0.15 mmol, 1.5 equiv) in solvent (0.2 mL) and  $\text{Me}_2\text{Zn}$  (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) were added sequentially. The mixture was stirred at 23 °C for 4~6 hours and once TLC analysis showed full conversion, quenched with saturated  $\text{NH}_4\text{Cl}$  (aq.). The resultant solution was extracted with EtOAc, the organic layer was combined, washed with brine and dried

<sup>5</sup> Zhang, F. H.; Yang, Y. X.; Xie, L. G.; Xu, X. H. *Chem. Commun.* **2013**, 49, 4697-4699. **11a** was also reported in the following papers: Roy, S. C.; Maiti, G. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 403-404; Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, 63, 2829-2834; Hon, Y. S.; Hsieh, C. H.; Liu, Y. W. *Tetrahedron*, **2005**, 61, 2713-2723; Hodgson, D. M.; Talbot, E. P.; Clark, B. P. *Org. Lett.* **2011**, 13, 2594-2597.

over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum. The crude product was purified by column chromatography (pentane/ethyl acetate).

Following general procedure, a solution of hexanal (17.1 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2 M solution in toluene, 0.25 mmol, 2.5 equiv) in THF (2 mL) was stirred at 23 °C for 4 hours to give the desired **11a** as a yellow oil (15 mg, 74%). R<sub>f</sub> = 0.45 (3/1 pentane/ EtOAc).

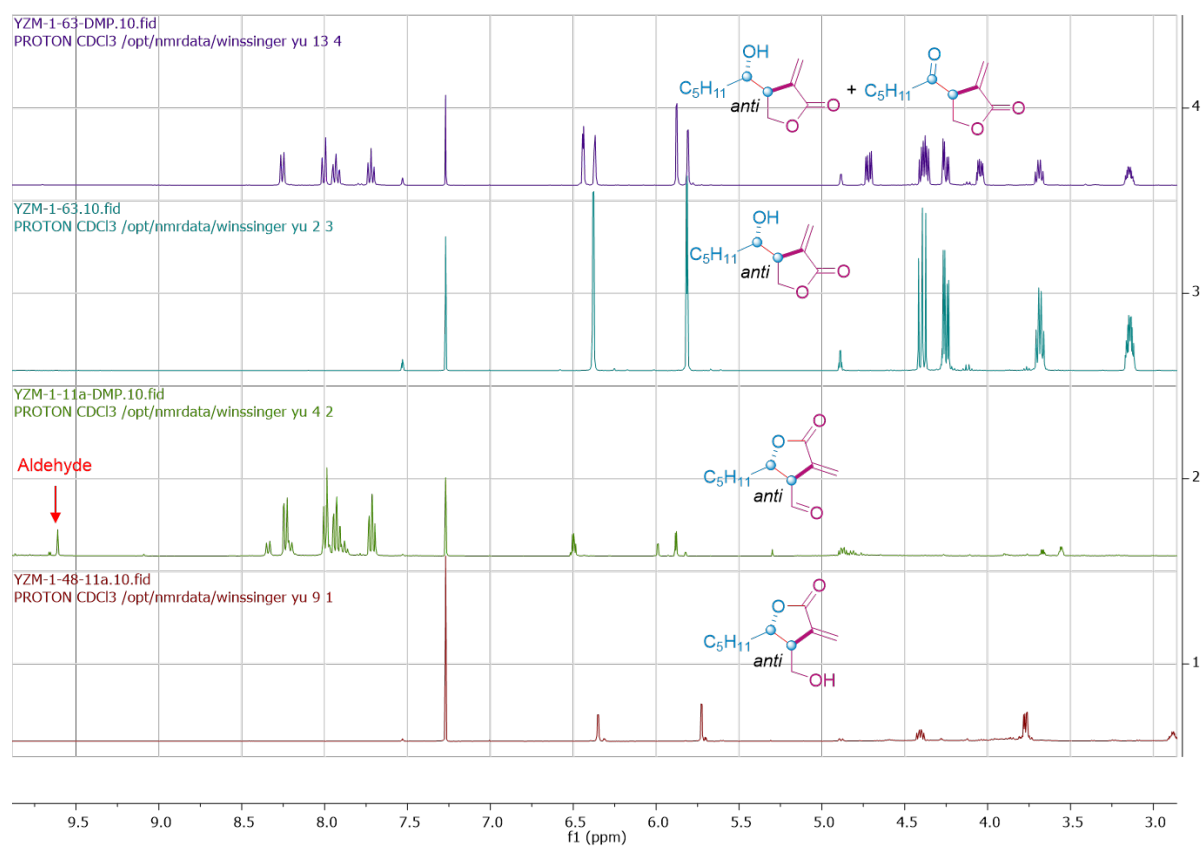
### Control experiment for DMP-oxidation of *anti*-**10a** and proposed *syn*-**9a**



**Scheme S1**, DMP-oxidation of *anti*-**10a** and proposed *syn*-**9a**.

The literature reported the preparation of *syn*-**9a**,<sup>5</sup> so we hypothesized that if **9a** and **10a** were oxidized with DMP, the same product **10a-ketone** would be obtained (**Scheme S1**). So a control experiment was conducted and the reaction was monitored by crude <sup>1</sup>H-NMR (**Figure S1**). The crude NMR clearly showed the difference between these two oxidation reactions. Of note, the appearance of an aldehyde indicated the presence of primary alcohol within **9a**.

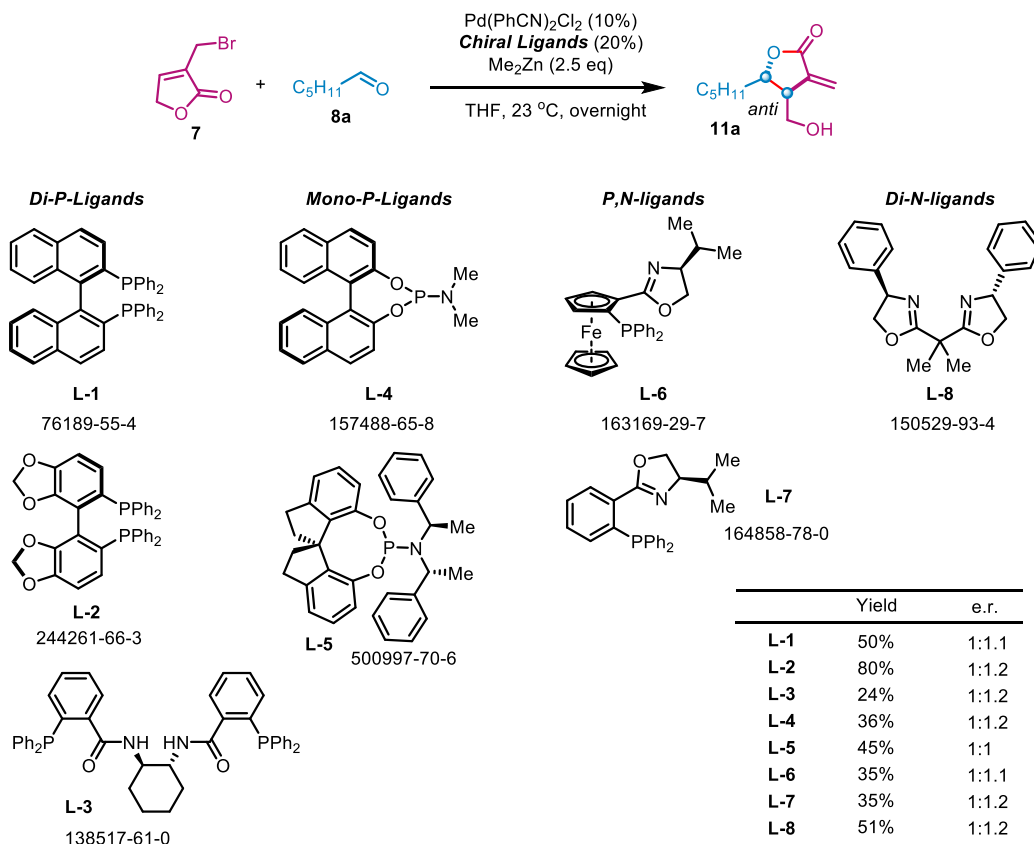




**Figure S1,** <sup>1</sup>H-NMR comparison.

## Attempt for stereoselective synthesis of *anti*-11a

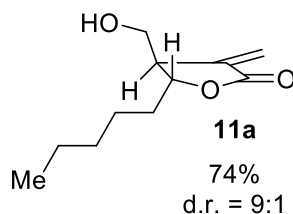
Various chiral ligands have been tested for the stereoselective synthesis of *anti*-11a. However, only poor stereoselectivity was observed from all attempts (**Figure S2**).



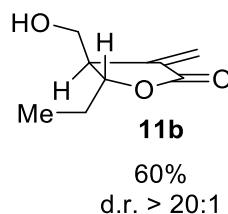
**Figure S2**, Attempt for stereoselective synthesis of *anti*-11a.

All reactions were taken based on **General procedure** with a replacement of ligand from  $\text{PPh}_3$  to **L1-L8**. As shown in **Figure S2**, the yields were determined with crude  $^1\text{H-NMR}$  with  $\text{CHBr}_3$  as internal standard. The *e.r.* was determined from crude  $^1\text{H-NMR}$  by deriving **11a** as its (*R*)-camphorsulfonate. Reaction with **L-3** resulted in uncompleted transactonization which didn't influence the determination of yield and *e.r.*.

#### d) Experimental procedures for Scheme 2



Following general procedure, reaction time: 2 h. Synthesis of **11a** has been described in section e and analytical data was consistent with the literature.<sup>5</sup>



Following general procedure, a solution of propionaldehyde (7.1 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in THF (2 mL) was stirred at 23 °C for 5 hours to give the **11b** as a colourless oil (9 mg, 60%).

#### Data of **11b**

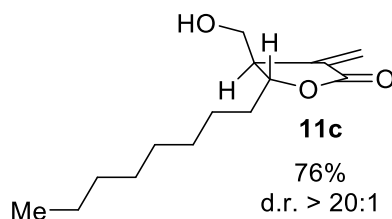
Colourless oil;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.34 (d, *J* = 2.6 Hz, 1H), 5.72 (d, *J* = 2.3 Hz, 1H), 4.35 (ddd, *J* = 6.9, 5.7, 4.3 Hz, 1H), 3.76 (dd, *J* = 6.4, 1.8 Hz, 2H), 2.88 (tdt, *J* = 6.7, 4.5, 2.5 Hz, 1H), 1.85 - 1.69 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H) ppm;

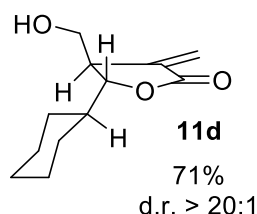
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.2, 136.4, 123.6, 82.0, 64.1, 46.5, 29.1, 9.4 ppm;

HRMS (ESI) *m/z*: [M + H]<sup>+</sup> calculated for C<sub>8</sub>H<sub>13</sub>O<sub>3</sub> 157.0865; found 157.0867;

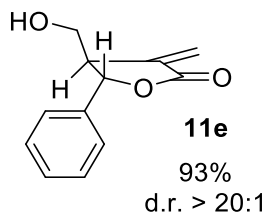
TLC: R<sub>f</sub> = 0.43 (3/1 pentane/ EtOAc).



Following general procedure, a solution of nonanal (21.3 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2 M solution in toluene, 0.25 mmol, 2.5 equiv) in THF (2 mL) was stirred at 23 °C for 4 hours to give the desired **11c** as a colourless oil (18 mg, 76%). The analytical data was consistent with the literature.<sup>6</sup>



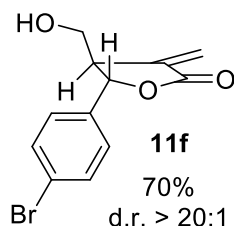
Following general procedure, a solution of cyclohexanecarboxaldehyde (17.1 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in THF (2 mL) was stirred at 23 °C for 6 hours to give the desired **11d** as a yellow oil (15 mg, 71%). R<sub>f</sub> = 0.40 (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3m**, only with the structure corrected.



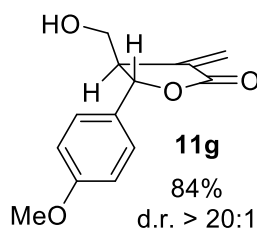
Following general procedure, a solution of benzaldehyde (16.2 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub>

<sup>6</sup> Makowski, K.; Mir, J.F.; Mera, P., Ariza; X., Asins; G., Hegardt; F.G., Herrero, L.; García, J. Serra, D. *Eur. J. Med. Chem.* **2017**, *131*, 207-221.

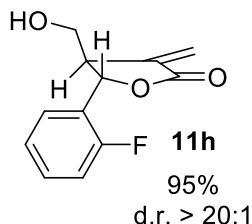
(6 mg, 0.02 mmol, 0.2 equiv) and  $\text{Me}_2\text{Zn}$  (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for 4 hours to give the desired **11e** as a yellow oil (20 mg, 93%).  $R_f = 0.45$  (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3a**, only with the structure corrected.



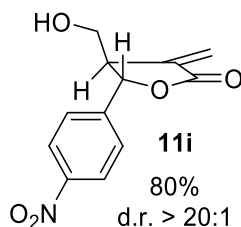
Following general procedure, a solution of 4-bromobenzaldehyde (28.3 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv),  $\text{Pd}(\text{PhCN})_2\text{Cl}_2$  (4 mg, 0.01 mmol, 0.1 equiv),  $\text{PPh}_3$  (6 mg, 0.02 mmol, 0.2 equiv) and  $\text{Me}_2\text{Zn}$  (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for 4 hours to give the desired **11f** as a yellow oil (20 mg, 70%).  $R_f = 0.40$  (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3d**, only with the structure corrected.



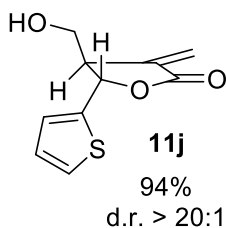
Following general procedure, a solution of 4-methoxybenzaldehyde (20.8 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv),  $\text{Pd}(\text{PhCN})_2\text{Cl}_2$  (4 mg, 0.01 mmol, 0.1 equiv),  $\text{PPh}_3$  (6 mg, 0.02 mmol, 0.2 equiv) and  $\text{Me}_2\text{Zn}$  (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for 4 hours to give the desired **11g** as a yellow oil (19 mg, 84%).  $R_f = 0.38$  (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3f**, only with the structure corrected.



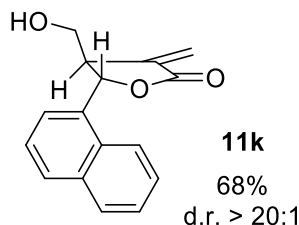
Following general procedure, a solution of 2-fluorobenzaldehyde (19.0 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for 4 hours to give the desired **11h** as a yellow oil (22 mg, 95%). R<sub>f</sub> = 0.40 (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3b**, only with the structure corrected.



Following general procedure, a solution of 4-nitrobenzaldehyde (23.1 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for hours to give the desired **11i** as a yellow oil (19 mg, 80%). R<sub>f</sub> = 0.40 (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3h**, only with the structure corrected.



Following general procedure, a solution of 2-thiophenecarboxaldehyde (17.1 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for 6 hours to give the desired **11j** as a yellow oil (20 mg, 94%). R<sub>f</sub> = 0.5 (3/1 pentane/ EtOAc). The analytical data was consistent with the literature,<sup>5</sup> matched with the compound **3k**, only with the structure corrected.



Following general procedure, a solution of 1-naphthaldehyde (23.8 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in toluene (2 mL) was stirred at 23 °C for 5 hours to give the desired **11k** as a yellow oil (18 mg, 68%).

#### Data of **11k**

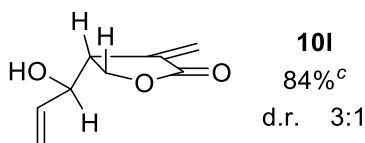
Yellow oil;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15 - 8.09 (m, 1H), 7.94 - 7.88 (m, 1H), 7.87 - 7.81 (m, 1H), 7.60 - 7.51 (m, 2H), 7.50 - 7.41 (m, 2H), 6.43 (d, *J* = 2.2 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 5.71 (d, *J* = 1.9 Hz, 1H), 4.06 - 3.87 (m, 2H), 3.30 (dddt, *J* = 7.0, 5.3, 3.4, 1.7 Hz, 1H) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.6, 135.4, 135.1, 134.0, 129.9, 129.2, 126.9, 126.2, 125.5, 124.8, 122.8, 122.7, 78.2, 64.1, 49.9 ppm;

HRMS (ESI) *m/z*: [M + Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>14</sub>O<sub>3</sub>Na 277.0841; found 277.0830;

TLC: R<sub>f</sub> = 0.48 (3/1 pentane/ EtOAc).



Following general procedure, a solution of acrolein (8.5 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in THF (2 mL) was stirred at 23 °C for overnight to give the desired **10l** as a colourless oil (13 mg, 84%).

#### Data of **10l**

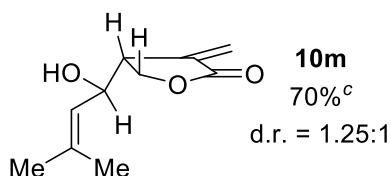
Colourless oil;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.39 (t, *J* = 2.7 Hz, 1.3H), 5.91 - 5.73 (m, 2.6H), 5.42 - 5.28 (m, 3.0H), 4.43 - 4.33 (m, 1.7H), 4.31 - 4.20 (m, 2.4H), 3.25 (dtd, *J* = 8.2, 4.2, 2.1 Hz, 1H), 3.22 - 3.16 (m, 0.3H) ppm;

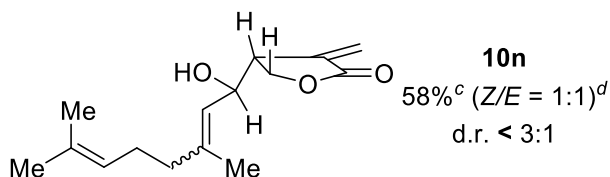
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.6, 136.9, 136.4, 134.8, 124.9, 124.4, 118.6, 118.4, 77.4, 74.7, 74.1, 67.3, 67.0, 44.0, 43.9 ppm;

HRMS (ESI) *m/z*: [M + Na]<sup>+</sup> calculated for C<sub>8</sub>H<sub>10</sub>O<sub>3</sub>Na 177.0528; found 177.0908;

TLC: R<sub>f</sub> = 0.40 (3/1 pentane/ EtOAc).



Following general procedure, a solution of 3-methylcrotonal (15.0 mg, 0.15 mmol, 1.5 equiv), bromolactone **7** (18 mg, 0.1 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (4 mg, 0.01 mmol, 0.1 equiv), PPh<sub>3</sub> (6 mg, 0.02 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (0.3 mL, 1.2M solution in toluene, 0.25 mmol, 2.5 equiv) in THF (2 mL) was stirred at 23 °C for overnight to give the desired **10n** as a colourless oil (13 mg, 70%). The spectroscopic data of **10n** are in accordance with the literature values reported.<sup>4</sup>





Following general procedure, a solution of citral (686  $\mu$ L, 4.0 mmol, 2.0 equiv), bromolactone **7** (352 mg, 2.0 mmol, 1 equiv), Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (77 mg, 0.2 mmol, 0.1 equiv), PPh<sub>3</sub> (105 mg, 0.4 mmol, 0.2 equiv) and Me<sub>2</sub>Zn (5.6 mL, 1.2 M solution in toluene, 5.0 mmol, 2.5 equiv) in THF (10 mL) was stirred at 23 °C for overnight to give the desired **10n** as a colourless oil (292 mg, 58%).

#### Data of **10n**

Colourless oil;

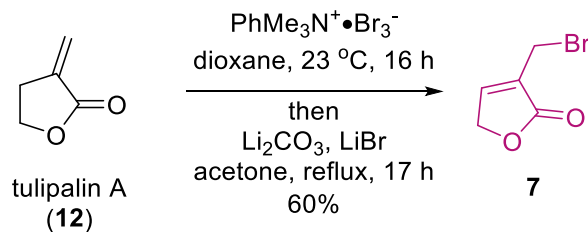
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.34 (d,  $J$  = 2.4 Hz, 1H), 6.31 (t,  $J$  = 3.1 Hz, 1H), 5.89 (dd,  $J$  = 3.1, 2.2 Hz, 0.9H), 5.74 - 5.69 (m, 1.2H), 5.19 (dddd,  $J$  = 11.5, 8.9, 5.3, 1.5 Hz, 2.2H), 5.13 - 5.00 (m, 2.8H), 4.76 (p,  $J$  = 2.1 Hz, 0.6H), 4.47 - 4.36 (m, 4.2H), 4.30 (ddd,  $J$  = 9.6, 8.1, 3.5 Hz, 1.2H), 4.12 (ddd,  $J$  = 11.4, 9.6, 4.0 Hz, 1.0H), 3.88 - 3.67 (m, 0.6H), 3.15 (dqt,  $J$  = 12.5, 5.0, 2.2 Hz, 1.9H), 1.80 - 1.75 (m, 3.0H), 1.70 - 1.66 (m, 9.0H), 1.60 (t,  $J$  = 1.8 Hz, 9.0H) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.0, 170.8, 145.0, 142.7, 135.6, 134.8, 133.3, 132.3, 132.3, 124.7, 124.4, 124.4, 124.3, 123.9, 123.6, 123.6, 123.6, 123.5, 77.4, 70.1, 69.8, 69.8, 69.4, 69.3, 68.0, 68.0, 67.5, 67.4, 44.9, 44.7, 44.6, 44.5, 39.8, 32.5, 32.5, 26.3, 25.8, 25.8, 23.6, 23.6, 17.9, 17.9, 17.1 ppm;

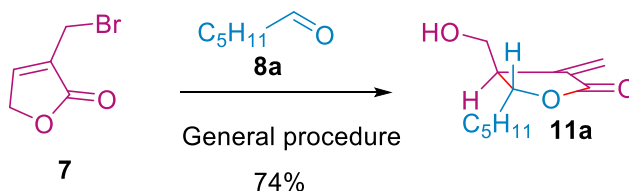
HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> calculated for C<sub>14</sub>H<sub>21</sub>O<sub>3</sub> 237.1491; found 237.1472;

TLC: R<sub>f</sub> = 0.38 (3/1 pentane/ EtOAc).

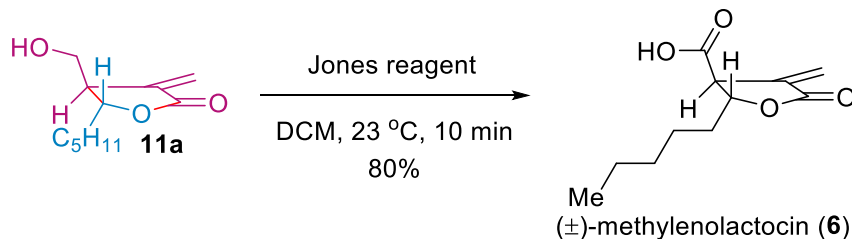
## e) Experimental procedures for Scheme 3



3-(Bromomethyl)-2(5*H*)-furanone **7** was prepared from commercially available tulipalin A (**12**) according to previously reported procedures.<sup>7</sup>



Synthesis of **11a** from **7** has been described in Experimental procedures for **Scheme 2**.



A solution of primary alcohol **11a** (20 mg, 1.0 mmol, 1.0 equiv) in acetone (2 mL) was treated with fresh prepared Jones reagent until a persistent orange colour was observed. The mixture was stirred at room temperature for 10 minutes. Then the reaction was quenched by *i*-PrOH (3 drops). The mixture was diluted with H<sub>2</sub>O (3 mL) and extracted with DCM, the organic layer was combined and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduce pressure and purified by silica gel chromatography (50/50 pentane/EtOAc to 100% EtOAc) to provide (±)-methylenolactocin **6** (17 mg, 80%) as a yellow oil.

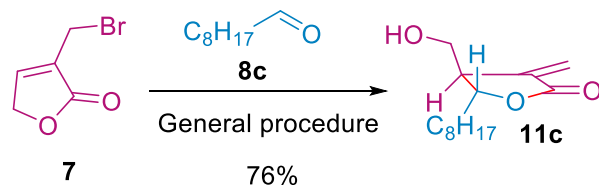
### Data of **6**

<sup>7</sup> Fuchs, M.; Schober, M.; Orthaber, A.; Faber, K. *Adv. Synth. Catal.* **2013**, 355, 2499-2505.

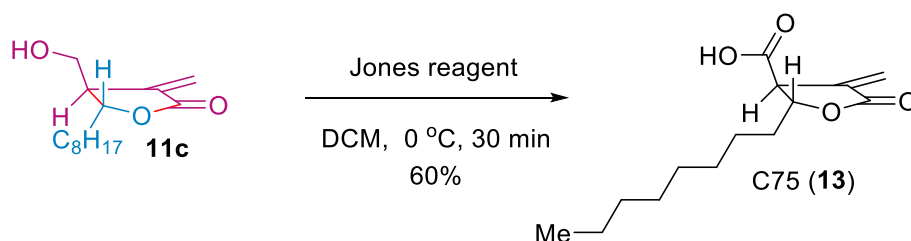
$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR see **Table S1**;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{11}\text{H}_{17}\text{O}_4$  213.1127; found 213.1450;

TLC:  $R_f$  = 0.30 (1/1 pentane/ EtOAc).



Synthesis of **11a** from **7** has been described in Experimental procedures for **Figure 2**.



A solution of the **11c** (24 mg, 1.0 mmol, 1.0 equiv) in acetone (3 mL) was treated with freshly prepared Jones reagent at 0 °C until a persistent orange colour was observed. After 30 minutes of stirring at 0 °C, *i*-PrOH (3 drops) was added to destroy the excess reagent. The reaction mixture was diluted with  $\text{H}_2\text{O}$  (3 mL) and acetone was removed under reduced pressure. The residue was extracted with DCM, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent under reduced pressure and followed by a short column of silica gel (75/25 pentane/ EtOAc to 100% EtOAc) to give **C75** (15 mg, 60%) as a white solid.

#### Data of **C75**

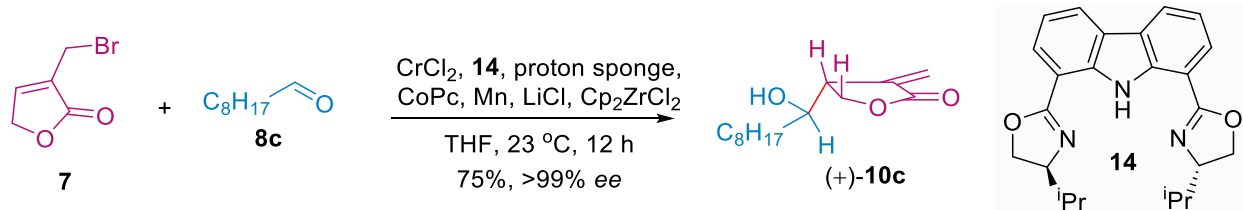
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.46 (d,  $J$  = 3.0 Hz, 1H), 6.02 (d,  $J$  = 2.7 Hz, 1H), 4.81 (dt,  $J$  = 7.3, 5.7 Hz, 1H), 3.62 (dt,  $J$  = 5.7, 2.8 Hz, 1H), 1.80 - 1.67 (m, 2H), 1.34 - 1.21 (m, 12H), 0.91 - 0.85 (m, 3H) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.5, 168.4, 132.6, 126.0, 79.0, 49.6, 35.9, 31.9, 29.5, 29.3, 29.3, 24.9, 22.8, 14.2 ppm;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{14}\text{H}_{23}\text{O}_4$  255.1596; found 255.1610;

TLC:  $R_f$  = 0.30 (1/1 pentane/ EtOAc).

The synthetic material matched the data reported.<sup>8</sup>



To a mixture of  $\text{CrCl}_2$  (4 mg, 0.03 mmol, 0.3 equiv), proton sponge (4 mg, 0.02 mmol, 0.2 equiv) and ligand **14** (12 mg, 0.03 mmol, 0.3 equiv) was added THF (2 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 hours, charged with cobalt phthalocyanine (0.3 mg, 0.0005 mmol, 0.005 equiv),  $\text{Zr}(\text{Cp})_2\text{Cl}_2$  (29 mg, 0.1 mmol, 1.0 equiv), LiCl (5 mg, 0.1 mmol, 1.0 equiv) and manganese powder (11 mg, 0.2 mmol, 2.0 equiv). Then bromolactone **7** (18 mg, 0.1 mmol, 1.0 equiv) and aldehyde **8c** (28 mg, 0.2 mmol, 2.0 equiv) were added in succession. The resulting mixture was stirred at room temperature for overnight, TLC monitored full conversion. the resultant solution was extracted with EtOAc, the organic layer was combined, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford (+)-**10c** (18 mg, 75%) as a colourless oil.

Racemic **10c** cannot be separated on chiral-HPLC with various columns under different conditions. A benzoyl group was installed on free alcohol and used for the determination of *ee*.

#### Data of (+)-**10c**

Colourless oil;  $[\alpha]_{\text{D}}^{25} = +15.0$  (c 0.4,  $\text{CHCl}_3$ ).

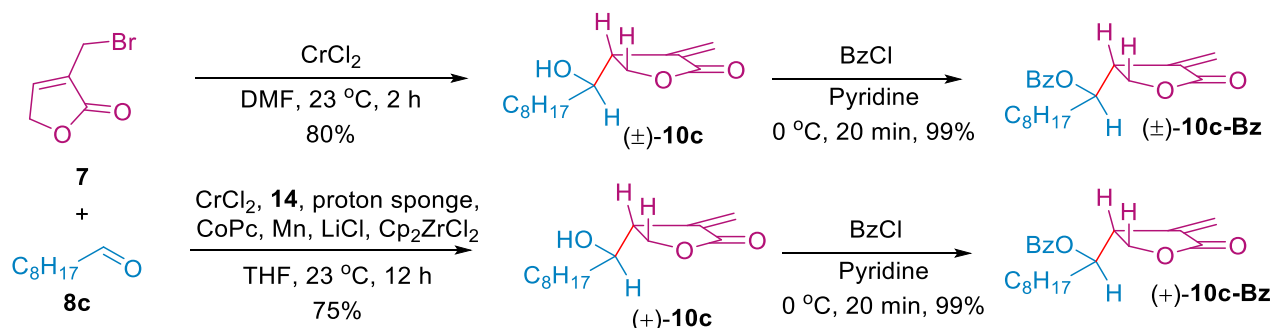
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.4 (d,  $J = 2.4$  Hz, 1H), 5.8 (dd,  $J = 2.1, 0.6$  Hz, 1H), 4.4 (dd,  $J = 9.4, 8.1$  Hz, 1H), 4.2 (dd,  $J = 9.4, 3.8$  Hz, 1H), 3.7 (q,  $J = 6.1$  Hz, 1H), 3.1 (dtd,  $J = 8.1, 3.9, 1.8$  Hz, 1H), 1.5 - 1.4 (m, 2H), 1.3 - 1.2 (m, 15H), 0.9 - 0.9 (m, 3H) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  124.7, 77.4, 73.4, 68.0, 60.6, 44.7, 33.7, 32.0, 29.6, 29.6, 29.3, 25.8, 22.8, 14.2 ppm;

<sup>8</sup> Kuhajda, F. P., Pizer, E. S., Li, J. N., Mani, N. S., Frehywot, G. L., Townsend, C. A. *PNAS*, **2000**, 97, 3450-3454.

HRMS (ESI)  $m/z$ :  $[M + H]^+$  calculated for  $C_{14}H_{25}O_3$  241.1804; found 241.1805;

TLC:  $R_f$  = 0.50 (3/1 pentane/ EtOAc).



Racemic **10c-Bz** was prepared from excess  $CrCl_2$  treatment followed by Bz protection.

To a solution of  $(\pm)$ -**10c** (1 mg, 0.0042 mmol, 1.0 equiv) in pyridine (0.5 mL) at ice-bath was added  $BzCl$  (0.7 mg, 0.005 mmol, 1.2 equiv). The mixture was stirred at this temperature for 20 minutes and TLC check full conversion. Quenched with sat.  $NH_4Cl$  and removed the pyridine under pressure. The residue was redissolved in EtOAc, washed with brine and dried over  $Na_2SO_4$ , purified by chromatography (90/10 pentane/ EtOAc), get the pure compound  $(\pm)$ -**10c-Bz** (1.5 mg, 99%) as a colorless oil.

#### Data of $(\pm)$ -**10c-Bz**

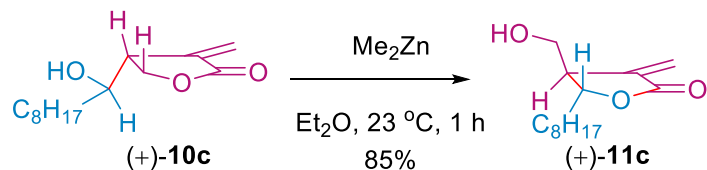
$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.99 (dd,  $J$  = 8.3, 1.4 Hz, 2H), 7.57 (d,  $J$  = 7.5 Hz, 1H), 7.45 (dd,  $J$  = 8.4, 7.1 Hz, 2H), 6.41 (d,  $J$  = 2.2 Hz, 1H), 5.78 (d,  $J$  = 2.0 Hz, 1H), 5.30 (ddd,  $J$  = 9.1, 5.0, 4.0 Hz, 1H), 4.67 - 4.28 (m, 2H), 1.81 - 1.71 (m, 1H), 1.66 - 1.57 (m, 1H), 1.40 - 1.17 (m, 12H), 0.95 - 0.79 (m, 3H) ppm;

$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  170.3, 166.1, 134.5, 133.5, 129.8, 128.7, 124.9, 75.6, 67.6, 42.1, 31.9, 30.1, 29.4, 29.4, 29.2, 25.6, 22.7, 14.2. ppm;

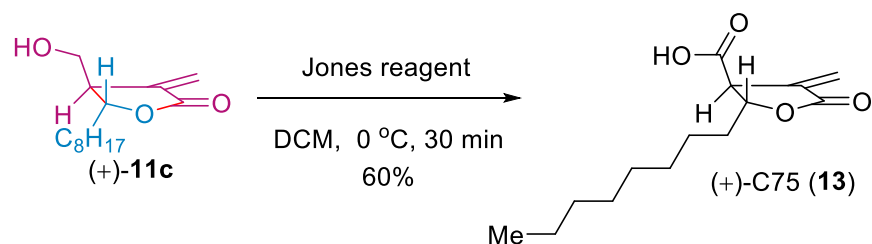
HRMS (ESI)  $m/z$ :  $[M + H]^+$  calculated for  $C_{21}H_{29}O_4$  345.2066; found 345.2065;

TLC:  $R_f$  = 0.50 (10/1 pentane/ EtOAc).

Conditions for chiral-HPLC, chiral stationary column: OJ-H, mobile phase: *n*-hexane/*i*-PrOH = 99:1, 1.0 mL/min, 215 nm, 30 °C,  $t_R$  (major) = 26.26 min,  $t_R$  (minor) = 29.89 min. Only one peak could be detected with **(+)-10c-Bz**. The result indicated >99% *ee*. See section g for detail.

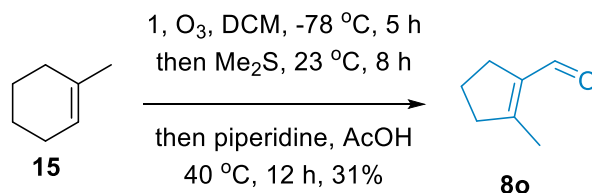


To a solution of (+)-**10c** (10 mg, 0.04 mmol, 1.0 equiv) in ether (1 mL),  $\text{Me}_2\text{Zn}$  (52  $\mu\text{L}$ , 0.06 mmol, 1.5 equiv) was added. The mixture was stirred at room temperature for 1 hour then diluted with EtOAc, the resultant solution was washed with saturated  $\text{NH}_4\text{Cl}$  (aq.), brine, dried over  $\text{Na}_2\text{SO}_4$  and filtered. Evaporation of the solvent under reduced pressure followed by flash chromatography (90/10 pentane/ EtOAc to 50/50 pentane/EtOAc), yield (+)-**11c**<sup>6</sup> (8.5 mg, 85%) as a yellow oil.



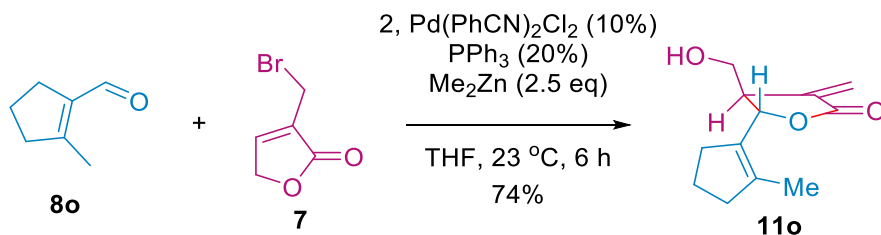
Same procedure has been used for the asymmetric synthesis of (+)-**C75** as synthesis of racemic **13** from **11c**,  $[\alpha]_{\text{D}}^{25} = +6.2$  (c 0.025,  $\text{CHCl}_3$ ).

## f) Experimental procedures for Scheme 4



Compound **8o** was generated using slight modifications of previously reported protocol.<sup>9</sup>

An over-dried 500 mL two-neck round-bottom flask with 1-methylcyclohexene **15** (4.1 g, 50 mmol, 1.0 equiv), pyridine (1.2 mL, 15 mmol, 3.5 equiv), and DCM (250 mL). The reaction flask was connected to an ozone generator through plastic tubing and a glass bubbler, cooled to -78 °C over an acetone-dry ice bath. The system was purged with O<sub>2</sub> for 5 minutes, and ozone generation was initiated. The mixture was monitored by TLC and disconnection from the ozone generator immediately after complete consumption of the starting material (60~90 minutes depending on the reaction scale). The mixture was then bubbled with N<sub>2</sub> for 10 minutes, followed by the addition of dimethyl sulfide (7.35 mL, 100 mmol, 2.0 equiv), and then allowed to warm up to room temperature gradually and stirred for 8 hours. Piperidine (0.74 mL, 7.6 mmol, 0.15 equiv) and acetic acid (0.58 mL, 10 mmol, 0.2 equiv) were added to the mixture and then was heated at reflux for 16 hours. Evaporation of the solvent under reduced pressure followed by flash column chromatography, yield aldehyde **8o** as a yellow oil (1.7 g, 31%). The analysis data were matched with previous reported.



To a solution of Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (268 mg, 0.7mmol, 0.1 equiv) and PPh<sub>3</sub> (367 mg, 1.4 mmol, 0.2 equiv) in THF (20 mL) were stirred at room temperature for 30 minutes, then the

<sup>9</sup> White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813-1821.

bromolactone **7** (1.76 g, 10 mmol, 1.0 equiv) in THF (5 mL), aldehyde **8o** in THF (5 mL) and  $\text{Me}_2\text{Zn}$  (14.6 mL, 1.2 M solution in toluene, 2.5 equiv) were added. The mixture was stirred for overnight and quenched with saturated  $\text{NH}_4\text{Cl}$  (aq.), diluted with EtOAc. The resultant solution was extracted with EtOAc, the organic layer was combined, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent under reduced pressure and purified by flash column chromatography (90/10 pentane/EtOAc to 50/50 pentane/EtOAc) yielded compound **11o** as a colourless oil (1.5 g, 74%).

#### Data of **11o**

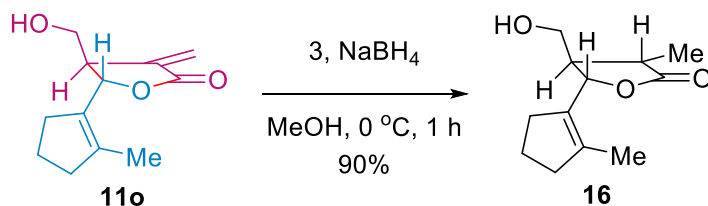
Colourless oil;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.30 (d,  $J = 2.7$  Hz, 1H), 5.72 (d,  $J = 2.4$  Hz, 1H), 5.23 (d,  $J = 5.0$  Hz, 1H), 3.81 - 3.69 (m, 2H), 2.99 - 2.92 (m, 1H), 2.35 - 2.29 (m, 3H), 2.20 (dtp,  $J = 13.3, 6.5, 2.2$  Hz, 1H), 1.80 (dtdd,  $J = 9.2, 7.9, 6.4, 2.0$  Hz, 2H), 1.73 (tt,  $J = 2.1, 1.1$  Hz, 3H) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 139.9, 136.7, 131.6, 123.0, 77.0, 63.3, 46.0, 39.0, 30.7, 21.6, 14.0 ppm;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{17}\text{O}_3$  209.1178; found 209.1177;

TLC:  $R_f = 0.40$  (3/1 pentane/ EtOAc).



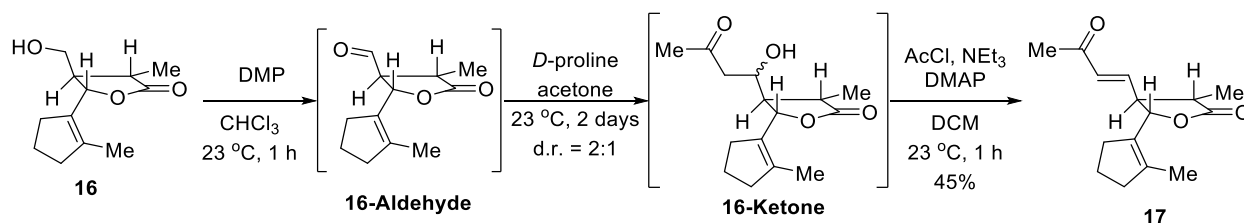
$\text{NaBH}_4$  (6 mg, 0.15 mmol, 1.5 equiv) was added to a solution of compound **11o** (21 mg, 0.1 mmol, 1.0 equiv) in MeOH (2 mL) at ice bath. After 20 minutes, quenched the reaction by addition of saturated  $\text{NH}_4\text{Cl}$  (aq.), diluted with brine and extract with DCM. Dry the organic phase and evaporate and purify the residue by flash chromatography (90/10 pentane/EtOAc to 50/50 pentane/EtOAc), yielded compound **16** as a colourless oil (19 mg, 90%).

#### Data of **16**

Colourless oil;



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.12 (d,  $J$  = 9.9 Hz, 1H), 3.77 - 3.62 (m, 2H), 2.72 (dq,  $J$  = 11.4, 7.0 Hz, 1H), 2.44 (ddp,  $J$  = 12.6, 6.0, 2.1 Hz, 1H), 2.39 - 2.33 (m, 2H), 2.33 - 2.21 (m, 1H), 2.07 (ddt,  $J$  = 11.5, 10.0, 4.0 Hz, 1H), 1.87 - 1.79 (m, 2H), 1.74 - 1.73 (m, 3H), 1.28 (d,  $J$  = 7.1 Hz, 3H) ppm;  
 $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  179.5, 140.8, 130.6, 76.5, 59.7, 49.7, 39.2, 37.3, 30.9, 21.7, 14.1, 13.9 ppm;  
 HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{19}\text{O}_3$  211.1334; found 211.1340;  
 TLC:  $R_f$  = 0.40 (3/1 pentane/ EtOAc).



Dess-Martin periodinane (64 mg, 0.15 mmol, 1.5 equiv) was added to a solution of **16** (21 mg, 0.1 mmol, 1.0 equiv) in DCM (1 mL) at room temperature. After 1 hour, stirring was stopped by which time the TLC analysis showed disappearance of starting material. The solid was filtered off and the *D*-Proline (3 mg, 0.02 mmol, 0.2 equiv), acetone (2 mL) were added to the filtrate, the mixture was stirred at room temperature for 2 days and monitored by TLC. Then the DMAP (cat.),  $\text{NEt}_3$  (139  $\mu\text{L}$ , 1 mmol, 10 equiv) and  $\text{AcCl}$  (36  $\mu\text{L}$ , 0.5 mmol, 5 equiv) were added to the solution, the mixture stirred at room temperature until the starting material had disappeared. The reaction mixture was quenched with saturated  $\text{NaHCO}_3$  (aq.), the resultant solution was extracted with EtOAc, the organic layer was combined, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (pentane/ EtOAc 10:1 to 3:1) afforded **17** as a colourless oil (17 mg, 45%).

#### Data of **17**

Colourless oil;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.58 (dd,  $J$  = 15.9, 8.0 Hz, 1H, H-8), 6.13 (dd,  $J$  = 15.9, 1.0 Hz, 1H, H-9), 4.96 (d,  $J$  = 9.8 Hz, 1H, H-6), 2.77 - 2.68 (m, 1H, H-7), 2.66 - 2.57 (m, 1H, H-11), 2.46 (dddd,  $J$  = 16.8, 7.2, 5.4, 2.9 Hz, 1H, H-3), 2.40 - 2.34 (m, 2H, H-1), 2.33 - 2.28 (m, 1H, H-3),

2.27 (s, 3H, H-14), 1.89 - 1.80 (m, 2H, H-2), 1.68 (tt,  $J = 2.1, 1.2$  Hz, 3H, H-15), 1.27 (d,  $J = 6.9$  Hz, 3H, H-13) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.3 (C-10), 177.5 (C-12), 141.845 (C-8), 133.615 (C-9), 78.1 (C-6), 51.5 (C-7), 41.6 (C-11), 39.2 (C-1), 31.1 (C-3), 27.8 (C-14), 21.7 (C-2), 14.3 (C-15), 13.3 (C-13) ppm;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{15}\text{H}_{21}\text{O}_3$  249.1491; found 249.1488;

TLC:  $R_f = 0.60$  (3/1 pentane/ EtOAc).

#### Data of **16-aldehyde**

Colorless oil;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.70 (d,  $J = 1.6$  Hz, 1H), 5.29 (d,  $J = 9.4$  Hz, 1H), 3.04 - 3.00 (m, 1H), 3.00 - 2.95 (m, 1H), 2.47 (dddt,  $J = 16.7, 9.3, 5.7, 2.0$  Hz, 1H), 2.38 (tdt,  $J = 8.0, 3.2, 1.4$  Hz, 2H), 2.35 - 2.28 (m, 1H), 1.91 - 1.82 (m, 2H), 1.72 (tt,  $J = 1.9, 1.0$  Hz, 3H), 1.36 - 1.34 (m, 3H) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.6, 176.8, 141.8, 129.4, 73.9, 59.7, 39.2, 37.4, 30.9, 21.7, 14.5, 14.2 ppm;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{17}\text{O}_3$  209.1178; found 209.1177;

TLC:  $R_f = 0.65$  (3/1 pentane/ EtOAc).

#### Data of **16-ketone**

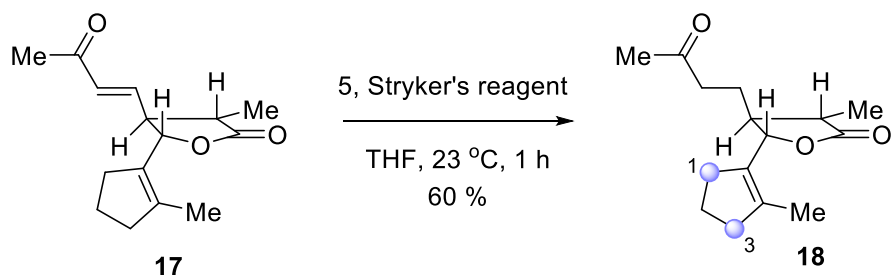
Colorless oil (2:1 diastereomers);

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.32 - 5.28 (d,  $J = 9.4$  Hz, 0.5H), 5.14 (d,  $J = 9.5$  Hz, 1H), 4.19 (dd,  $J = 9.3, 3.2$  Hz, 0.5H), 4.02 (dt,  $J = 9.3, 3.1$  Hz, 1H), 2.94 - 2.85 (m, 1H), 2.85 - 2.77 (m, 0.5H), 2.64 - 2.58 (m, 1.5H), 2.45 - 2.40 (m, 1.5H), 2.39 - 2.33 (m, 3H), 2.28 - 2.20 (m, 1.5H), 2.19 (s, 3H), 2.16 (s, 1.5H), 2.01 - 1.90 (m, 2.5H), 1.88 - 1.81 (m, 3H), 1.77 (dt,  $J = 2.1, 1.1$  Hz, 1.5H), 1.75 (dp,  $J = 2.1, 1.2$  Hz, 3H), 1.36 (d,  $J = 7.1$  Hz, 3H), 1.28 (d,  $J = 7.0$  Hz, 1.5H) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  209.4, 209.3, 179.4, 178.9, 141.3, 141.0, 131.9, 130.7, 75.9, 74.42, 65.3, 64.9, 51.9, 51.2, 48.3, 47.4, 39.2, 39.2, 37.4, 36.0, 30.9, 30.8, 30.8, 29.8, 21.8, 21.7, 16.7, 14.4, 14.2, 14.2 ppm;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{15}\text{H}_{23}\text{O}_4$  267.1596; found 267.1596;

TLC:  $R_f = 0.50$  (3/1 pentane/ EtOAc).



To a solution of ketone **17** (22 mg, 0.089 mmol, 1 equiv) in THF (1 mL), bubbled with N<sub>2</sub> for 10 minutes, followed by the addition of Stryker's reagent (35 mg, 0.018 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature. 30 minutes later, another portion of Stryker's reagent (35 mg, 0.018 mmol, 0.2 equiv) was added and stirred at the same temperature until TLC monitored the full conversion. The reaction was quenched with saturated NH<sub>4</sub>Cl (aq, 5 mL), then the organic layer was separated and extracted with DCM (10 mL  $\times$  3), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (pentane/ EtOAc 4:1 to 3:1) provided the ketone **18** as a colourless oil (13 mg, 60%).

#### Data of **18**

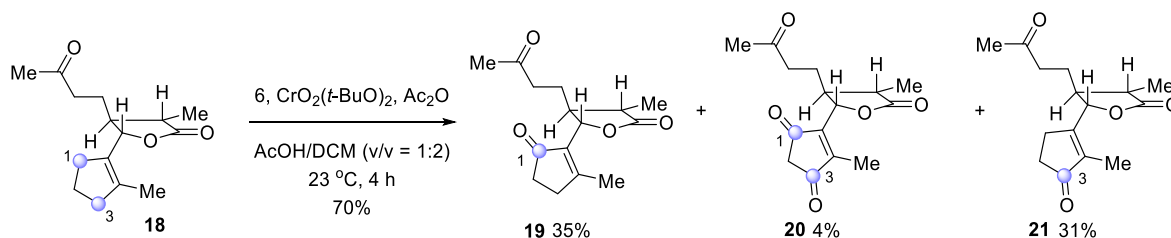
Colourless oil;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.76 (d,  $J$  = 9.8 Hz, 1H), 2.46 - 2.43 (m, 2H), 2.42 - 2.39 (m, 1H), 2.39 - 2.35 (m, 2H), 2.34 - 2.28 (m, 1H), 2.27 - 2.21 (m, 1H), 2.18 (d,  $J$  = 2.1 Hz, 1H), 2.11 (s, 3H), 2.02 - 1.95 (m, 1H), 1.88 - 1.81 (m, 3H, H-8), 1.74 (td,  $J$  = 2.0, 1.0 Hz, 3H), 1.70 - 1.66 (m, 1H), 1.29 (d,  $J$  = 7.0 Hz, 3H);

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  207.3, 178.9, 141.3, 130.96, 79.9, 46.3, 42.0, 40.5, 39.3, 31.1, 30.01, 25.0, 21.7, 14.4, 14.3;

HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> calculated for C<sub>15</sub>H<sub>23</sub>O<sub>3</sub> 251.1647; found 251.1643;

TLC: R<sub>f</sub> = 0.4 (hexane/EtOAc = 3/1).



The 1 M *t*-butyl chromate ( $\text{CrO}_2(\text{t-BuO})_2$ ) solution was freshly prepared as follows: To a solution of *t*-BuOH (1.9 mL, 20 mmol, 2 equiv) in DCM (10 mL) was added  $\text{CrO}_3$  (1 g, 10 mmol, 1 equiv). The mixture was stirred at room temperature for 30 min. The  $\text{CrO}_2(\text{t-BuO})_2$  solution was directly used for allylic oxidation.

To a stirred solution of **18** (13 mg, 0.052 mmol, 1 equiv) in DCM/AcOH (1 mL/1 mL) was added  $\text{Ac}_2\text{O}$  (49  $\mu\text{L}$ , 0.52 mmol, 10 equiv) and freshly prepared  $\text{CrO}_2(\text{t-BuO})_2$  (156  $\mu\text{L}$ , 0.16 mmol, 3 equiv). The reaction mixture was stirred at room temperature for 4 h. Then *sat. aq.*  $\text{NaHCO}_3$  was added until no bubble out. The mixture was extracted with EtOAc (10 mL  $\times$  3) and the organic layers were combined and dried over  $\text{Na}_2\text{SO}_4$ . Then filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (pentane/ EtOAc 2:1 to 1:2) provided the ketone **20** (0.5 mg, 4%) as a colourless oil, **21** (4.3 mg, 31%) as a colourless oil and **19** (4.8 mg, 35%) as a colourless oil.

#### Data of **19**

Colourless oil;

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR see **Table S2**;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{15}\text{H}_{21}\text{O}_4$  265.1440; found 265.1440;

TLC:  $R_f$  = 0.2 (Hexane/Ethyl acetate = 1/1).

#### Data of **20**

Colourless oil;

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR see **Table S3**;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{15}\text{H}_{19}\text{O}_5$  279.1233; found 279.0955;

TLC:  $R_f$  = 0.45 (Hexane/Ethyl acetate = 1/1).

#### Data of **21**

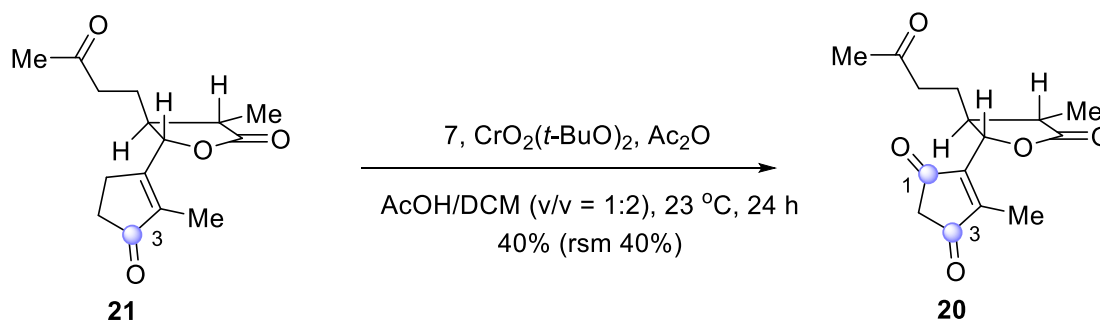
Colourless oil;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.01 (d,  $J$  = 9.6 Hz, 1H, H-6), 2.50 - 2.45 (m, 2H, H-9), 2.46 - 2.44 (m, 2H, H-2), 2.44 - 2.40 (m, 1H, H-11), 2.16 - 2.13 (m, 2H, H-1), 2.13 - 2.09 (m, 4H, H-7, H-15), 1.85 - 1.79 (m, 5H, H-8, H-14), 1.34 (d,  $J$  = 7.0 Hz, 3H, H-11) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  209.2 (C-3), 206.6 (C-10), 178.0 (C-12), 164.7 (C-4), 139.9 (C-5), 79.3 (C-6), 47.2 (C-7), 41.5 (C-11), 40.3 (C-9), 33.8 (C-2), 30.1 (C-1), 24.9 (C-15), 24.5 (C-14), 15.0 (C-13), 8.9 (C-8) ppm;

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{15}\text{H}_{21}\text{O}_4$  265.1440; found 265.1440;

TLC:  $R_f$  = 0.3 (Hexane/Ethyl acetate = 1/1).



To a stirred solution of **21** (3 mg, 0.011 mmol, 1 equiv) in DCM/AcOH (0.5 mL/0.5 mL) was added  $\text{Ac}_2\text{O}$  (20  $\mu\text{L}$ , 0.22 mmol, 20 equiv) and freshly prepared  $\text{CrO}_2(\text{t-BuO})_2$  (110  $\mu\text{L}$ , 0.11 mmol, 10 equiv). The reaction mixture was stirred at room temperature for 24 h by which time TLC indicated about 50% conversion. Then *sat. aq.*  $\text{NaHCO}_3$  was added until the evolution of gas stopped. The mixture was extracted with EtOAc (10 mL  $\times$  3) and the organic layers were combined and dried over  $\text{Na}_2\text{SO}_4$ . Then filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (pentane/ EtOAc 2:1 to 1:1) provided the ketone **20** (1.2 mg, 40%) as well as starting material **21** (1.2 mg, 40%).

## g) Chiral-HPLC of 10c

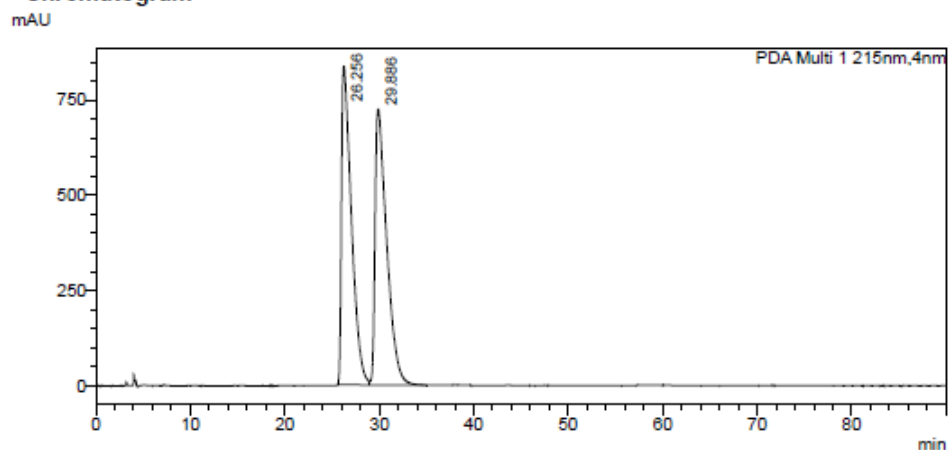
13/11/2020 10:24:30 Page 1 / 1

# SHIMADZU LabSolutions Analysis Report

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 Sample ID :  
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 Method Filename : Aqu Col2 99-1 1mL (90min).lcm  
 Batch Filename : wll-c75-bz-rac-2.lcb  
 Vial # : 1-99  
 Injection Volume : 10 uL  
 Date Acquired : 12/11/2020 15:33:36  
 Date Processed : 13/11/2020 10:08:41  
 Sample Type : Unknown  
 Acquired by : System Administrator  
 Processed by : System Administrator

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# Analysis Report

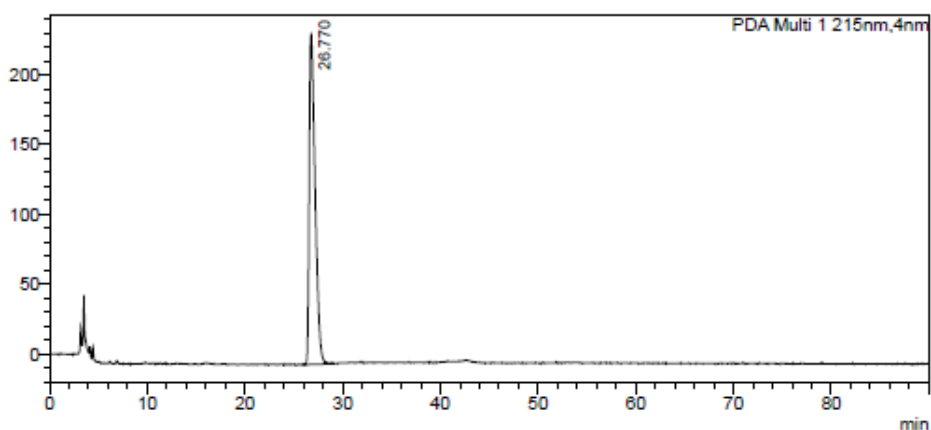
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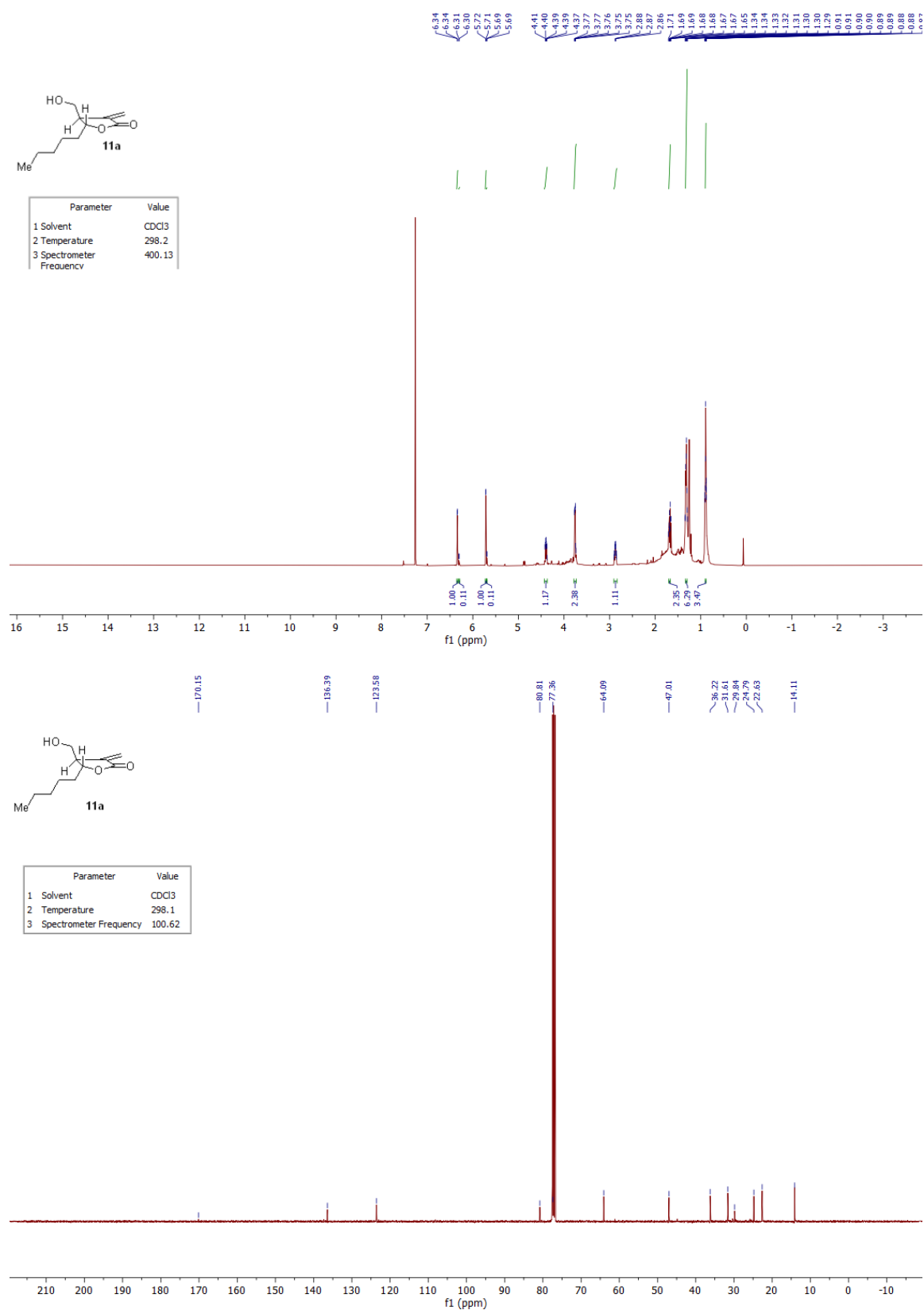


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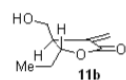
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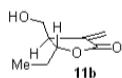
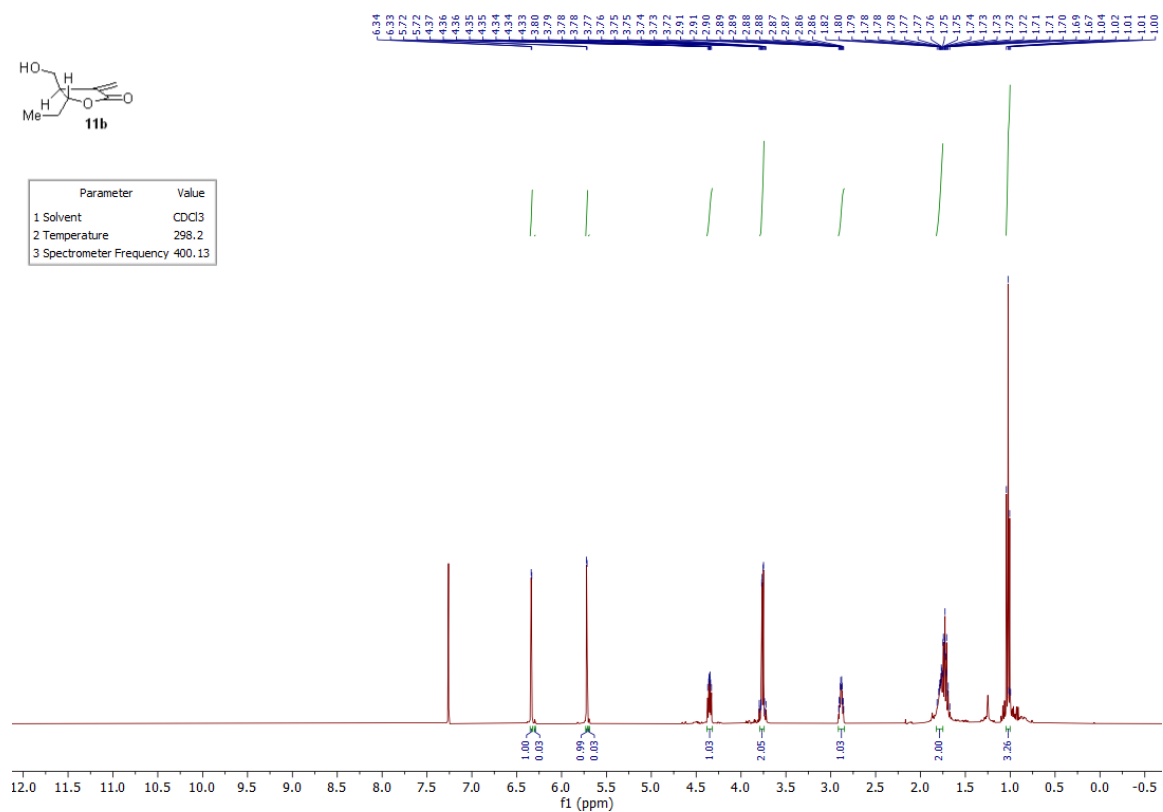
## h) $^1\text{H}$ and $^{13}\text{C}$ NMR spectra



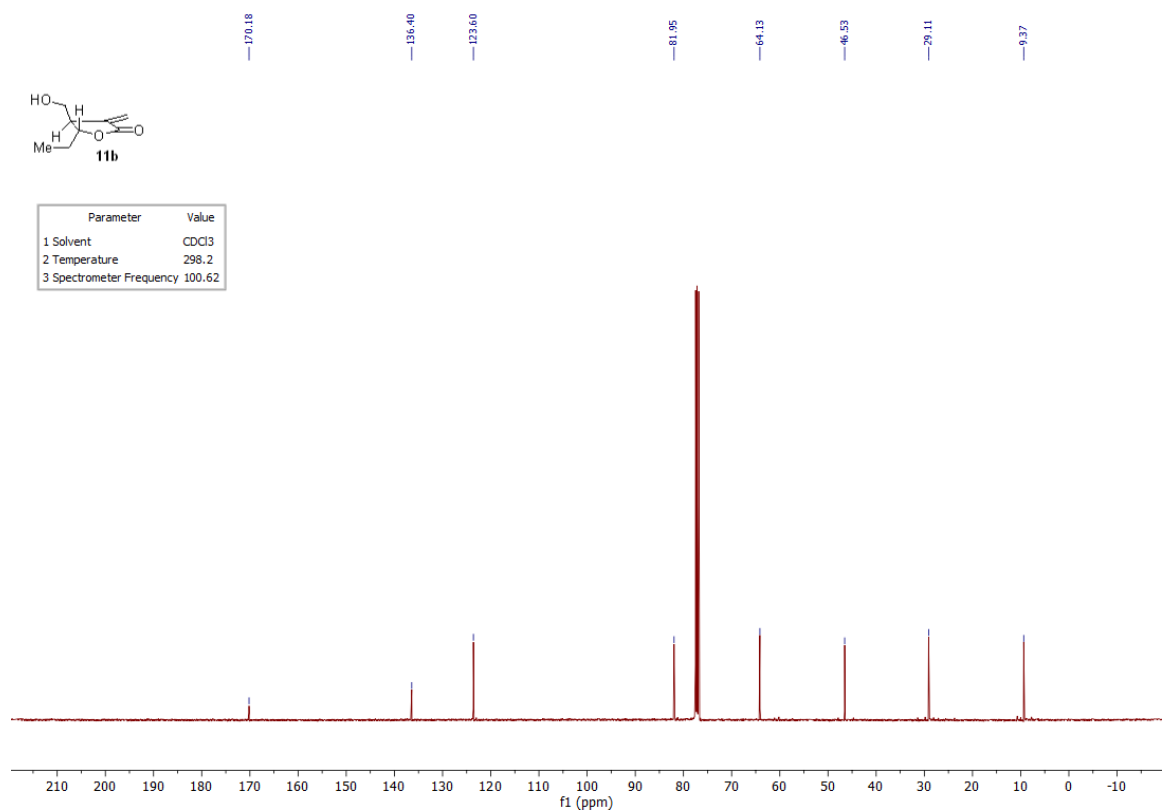




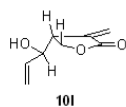
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2 Temperature	298.2
3 Spectrometer Frequency	400.13



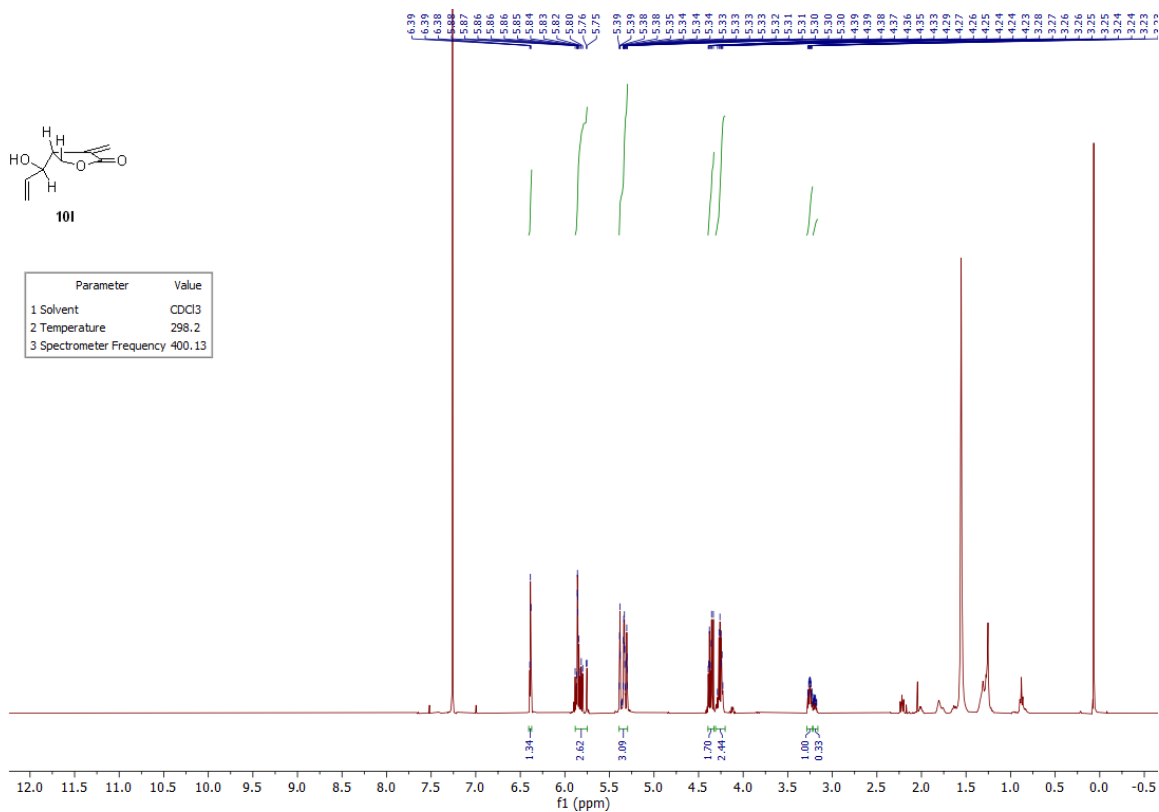
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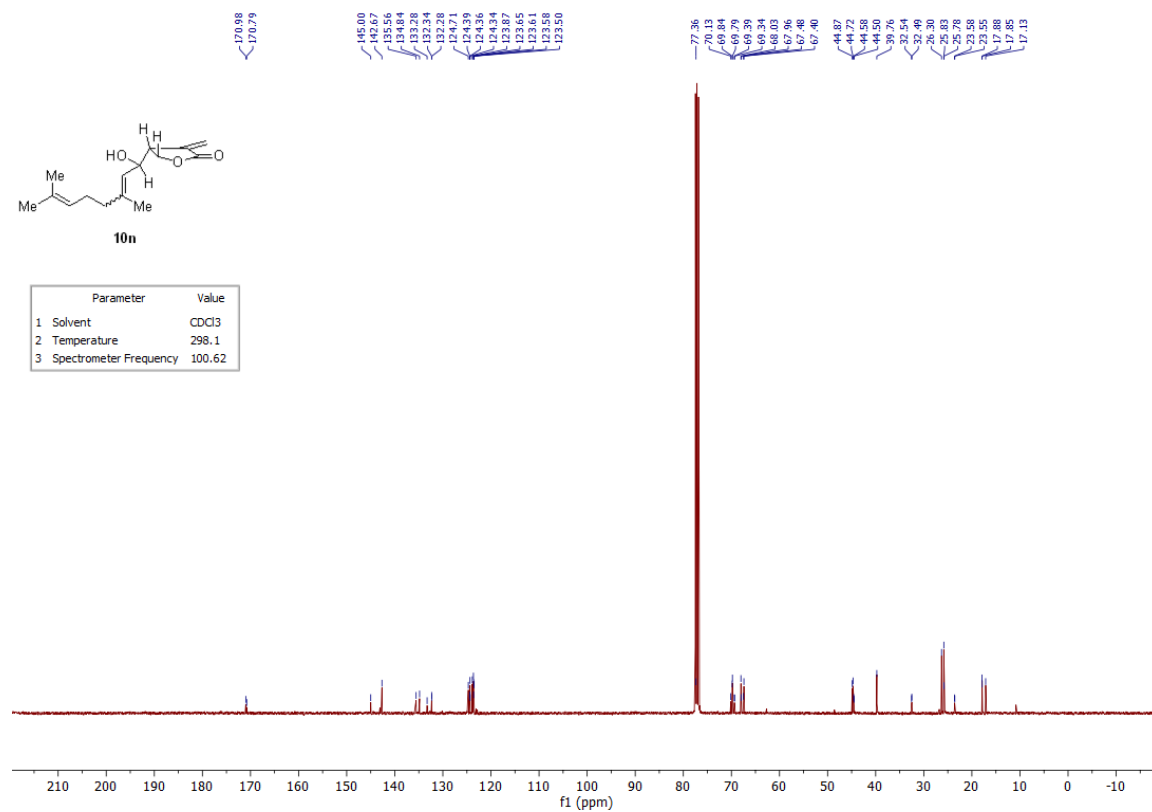
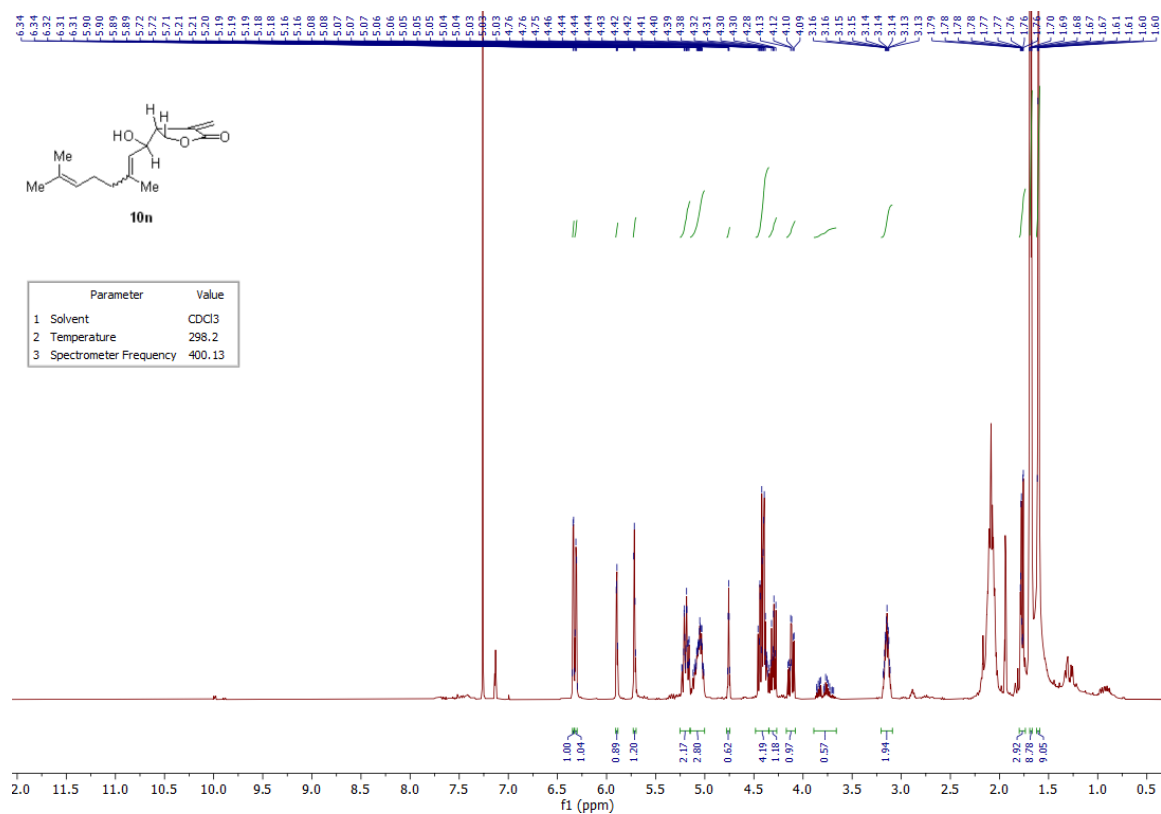


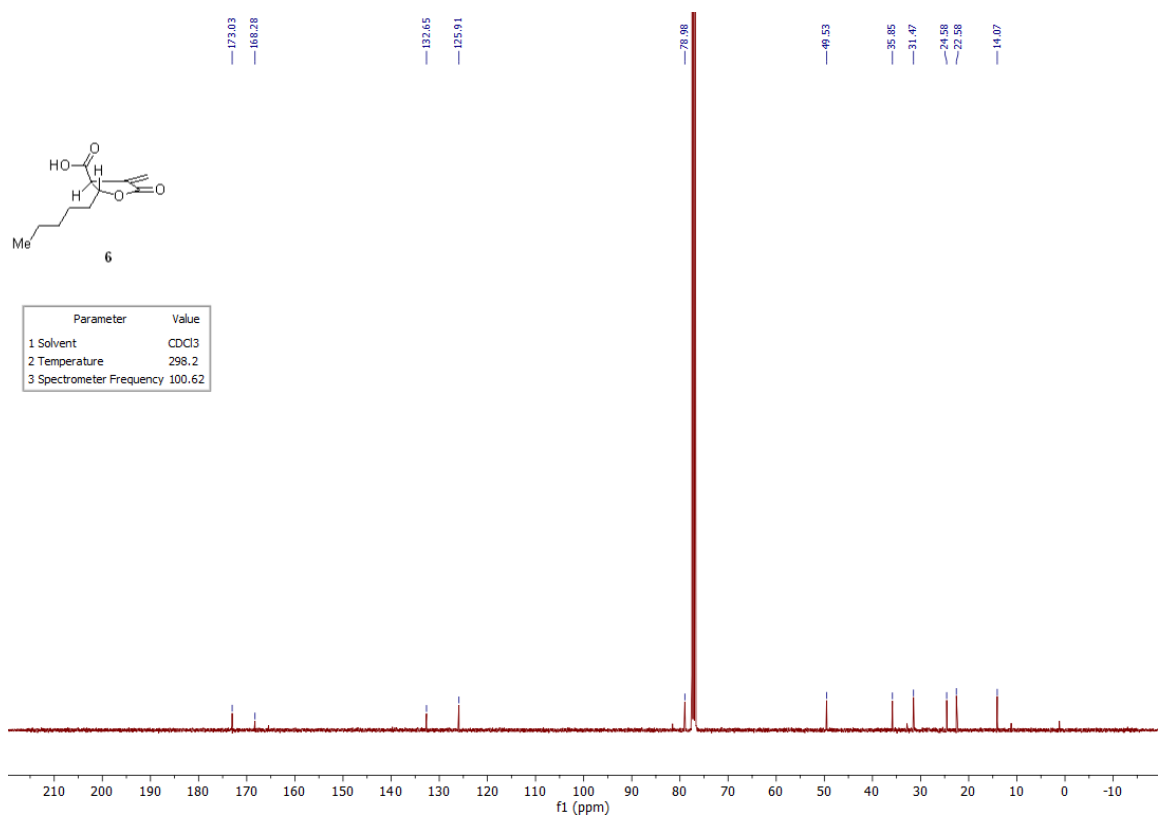
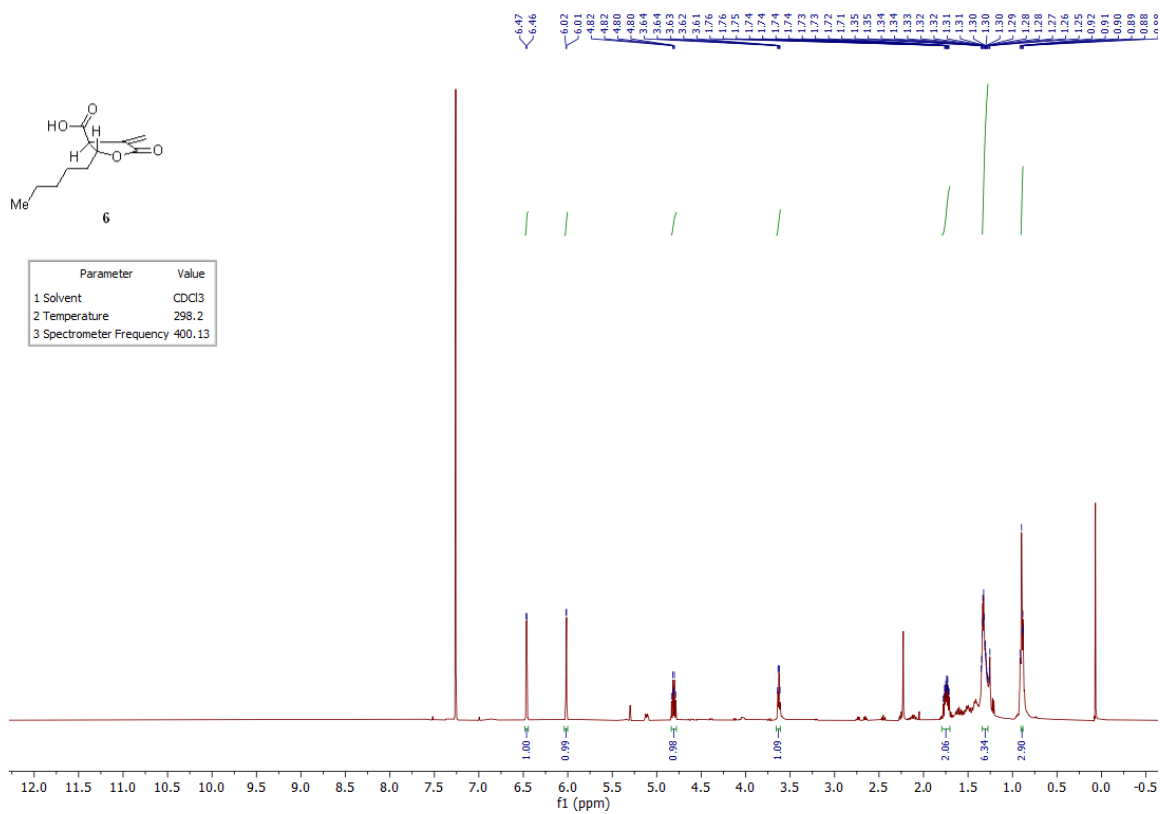


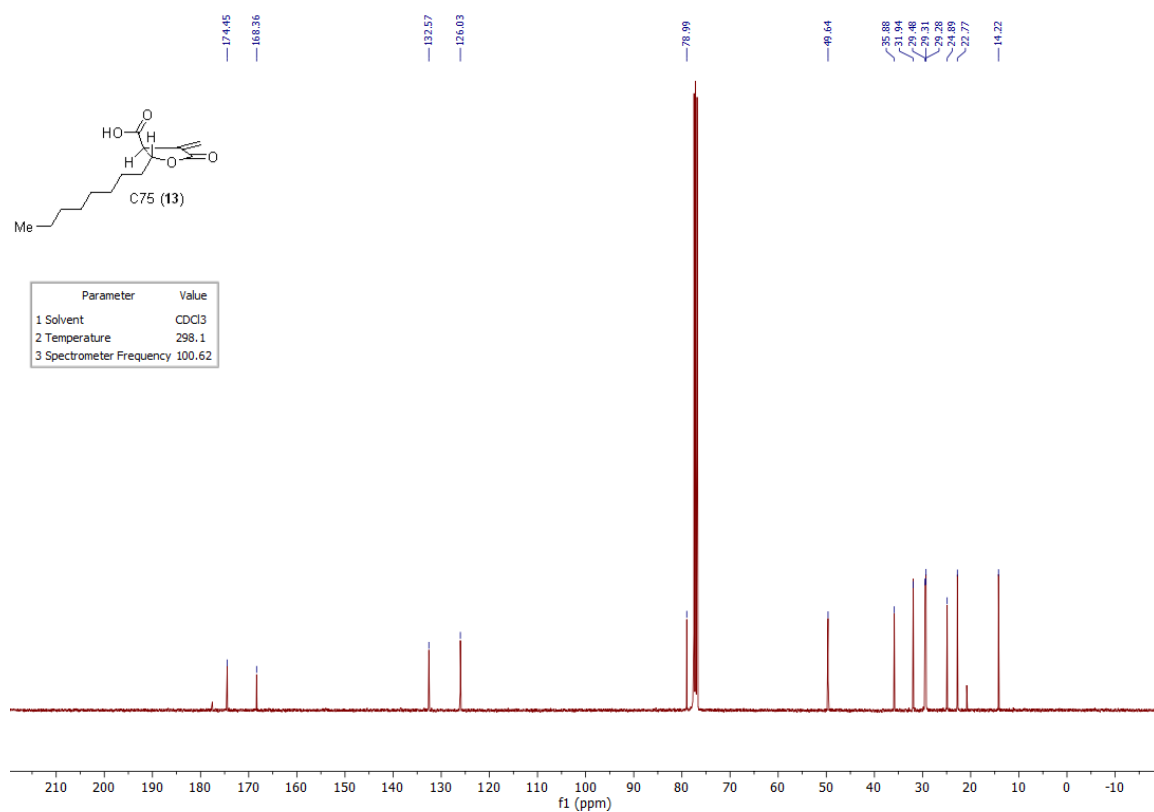
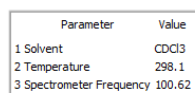
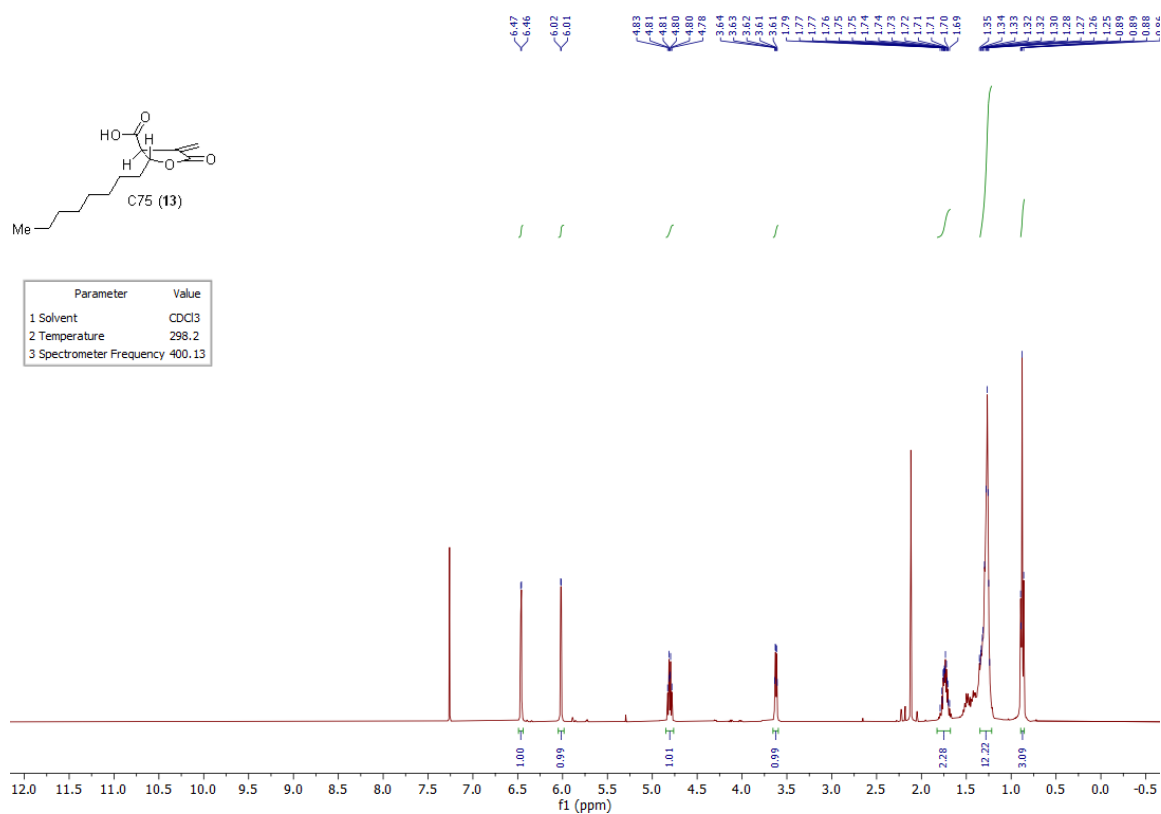
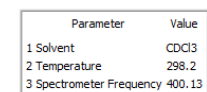


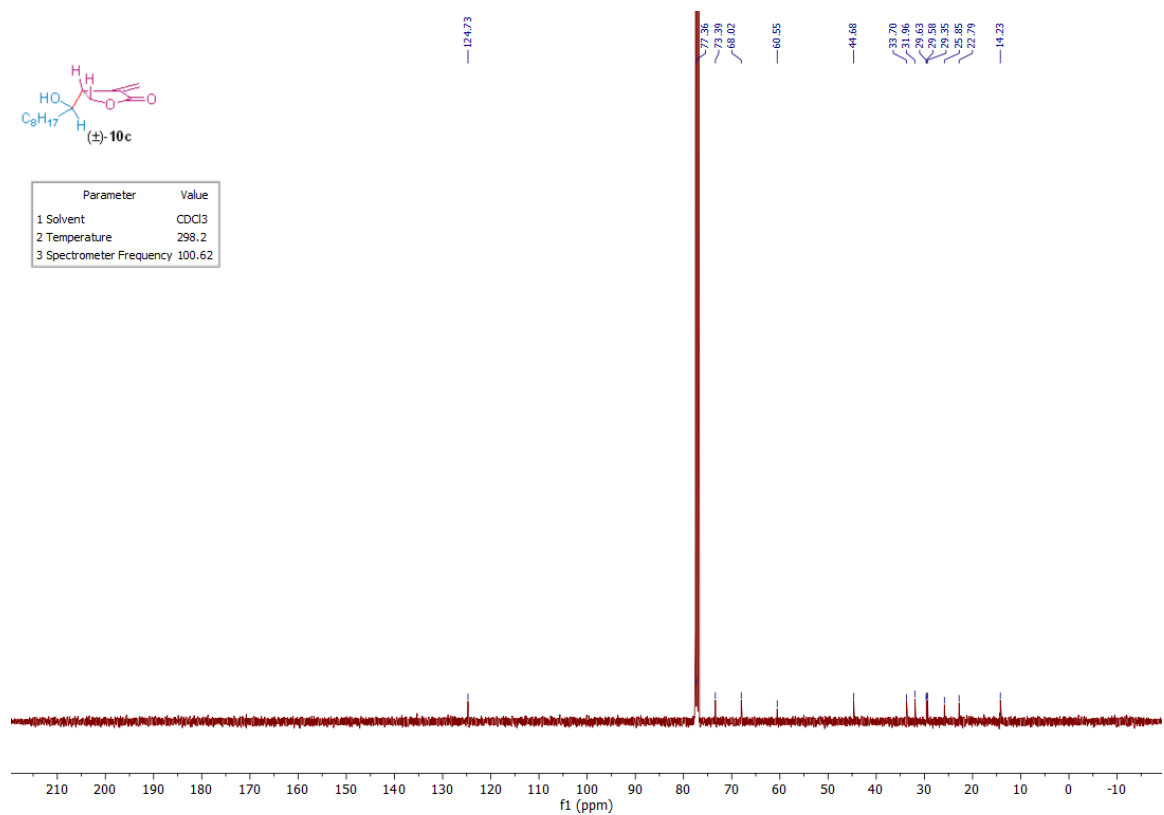
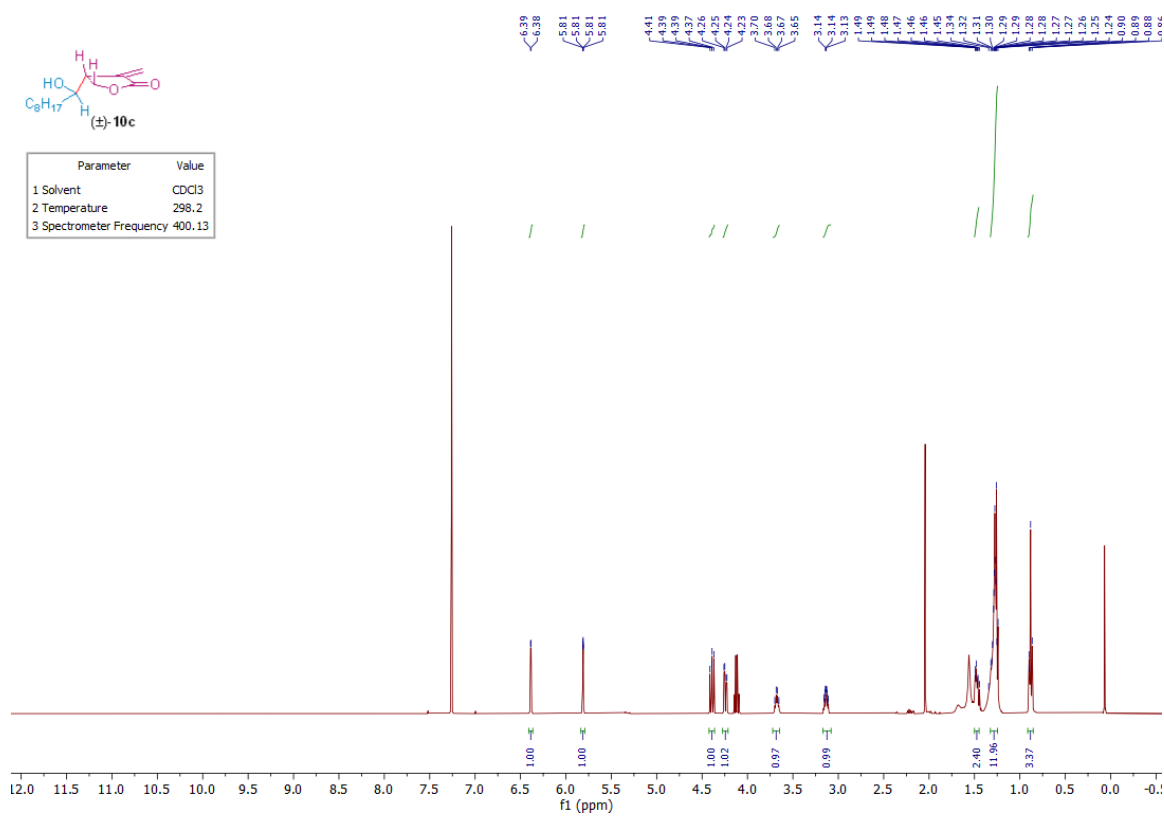
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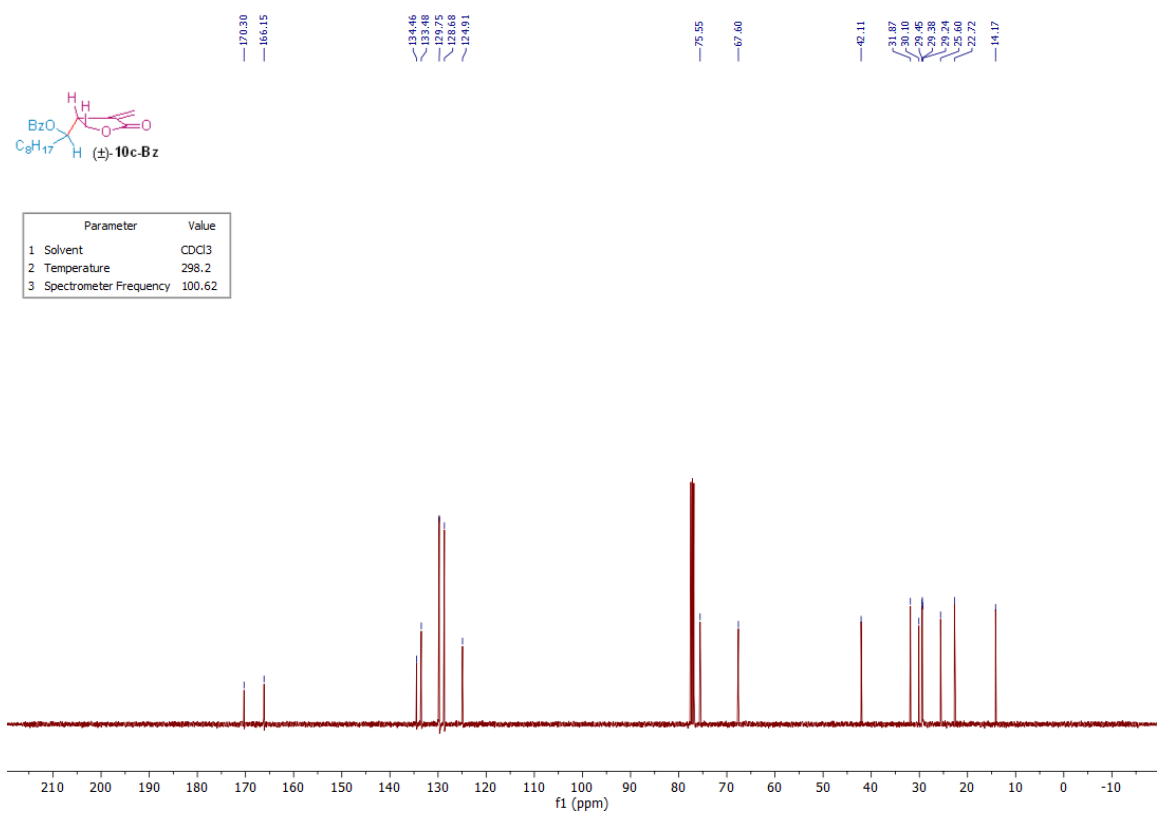
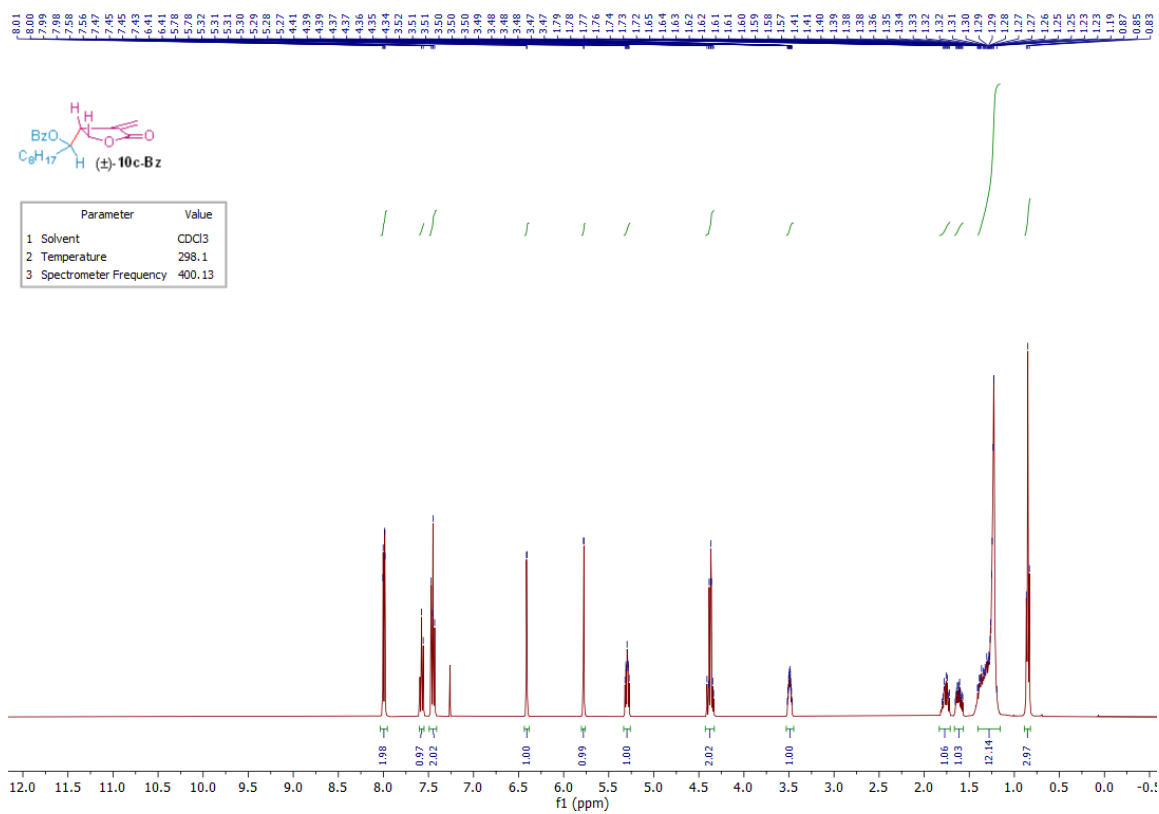




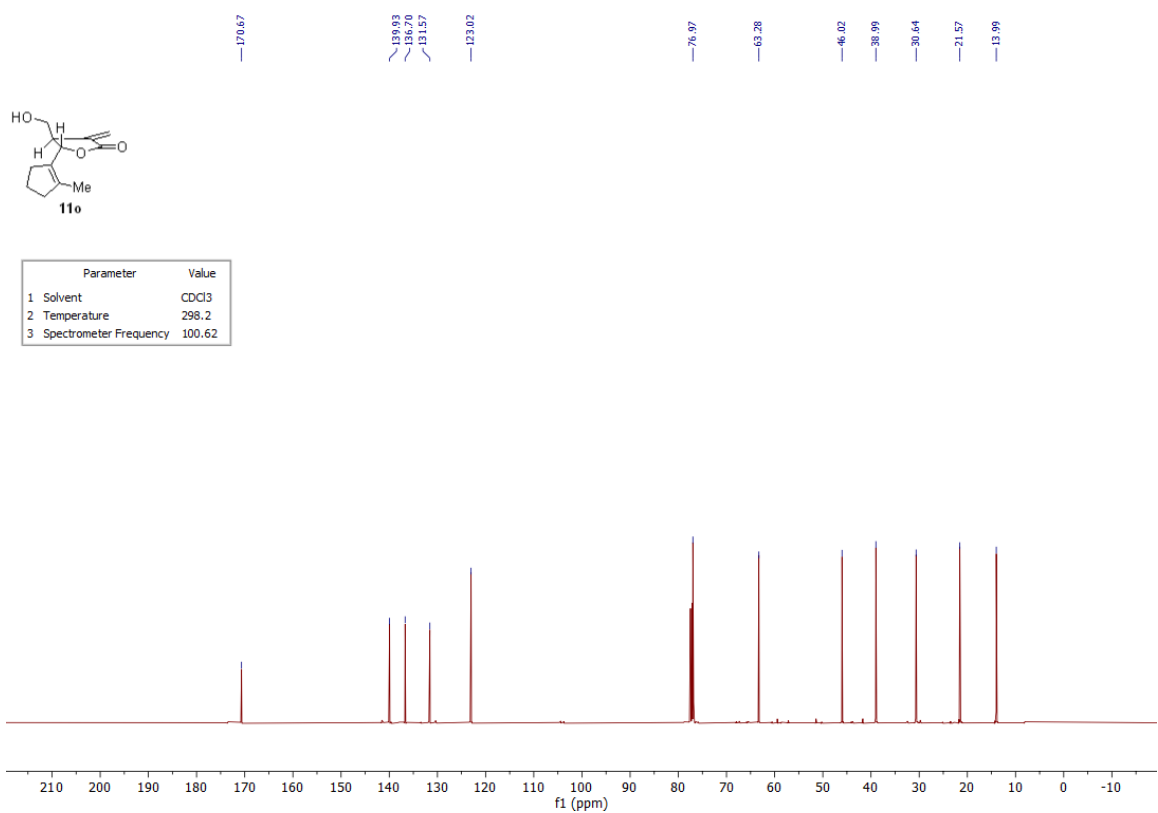
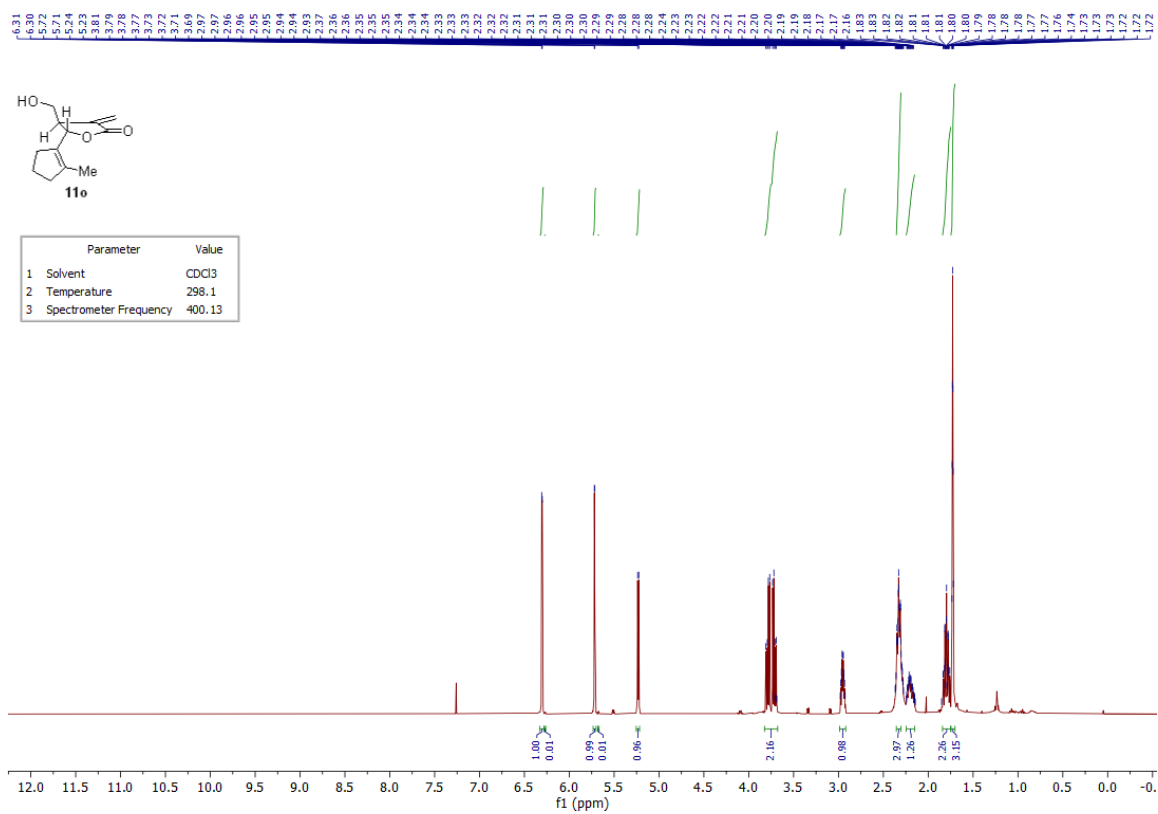


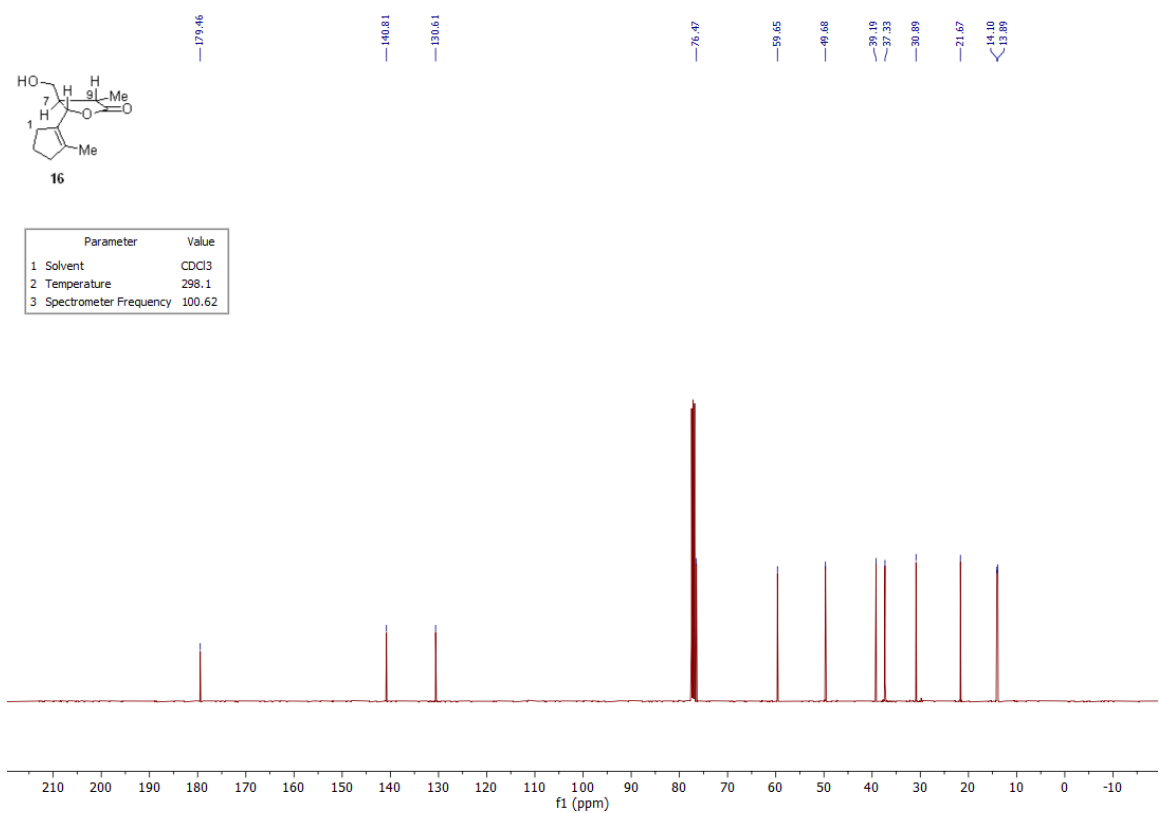
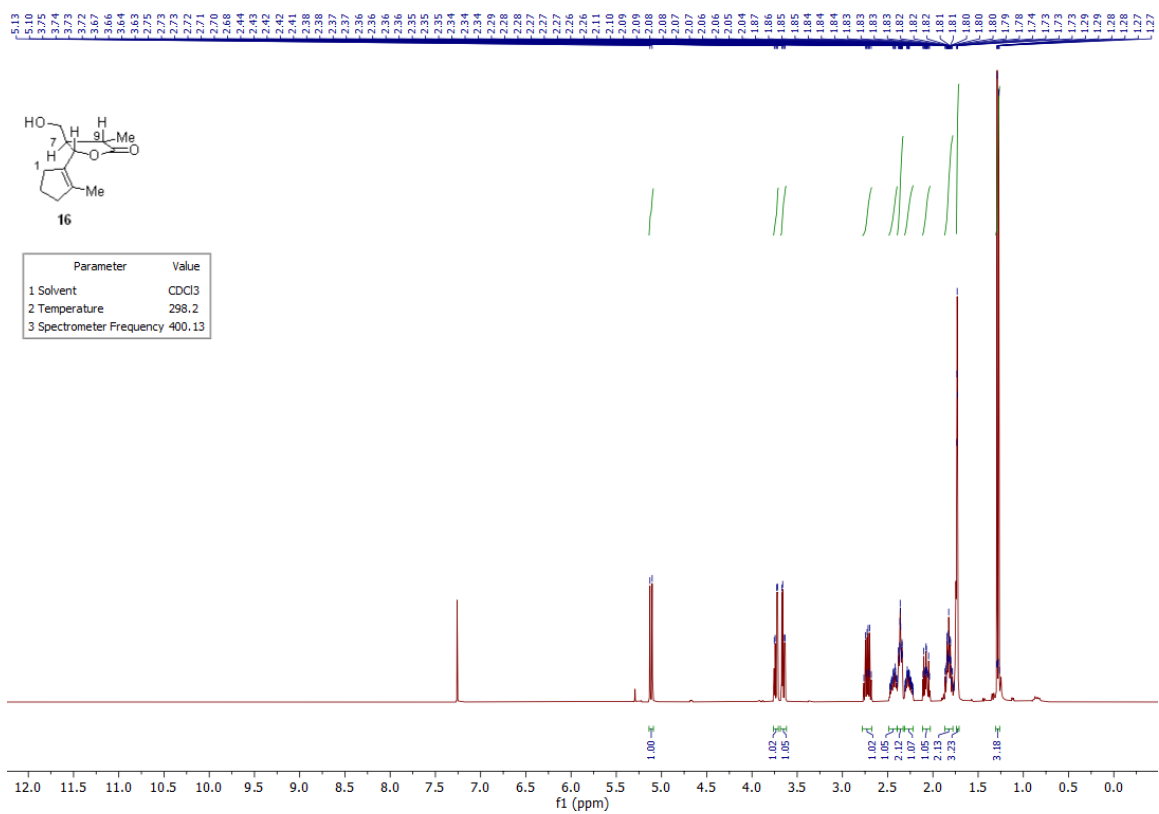


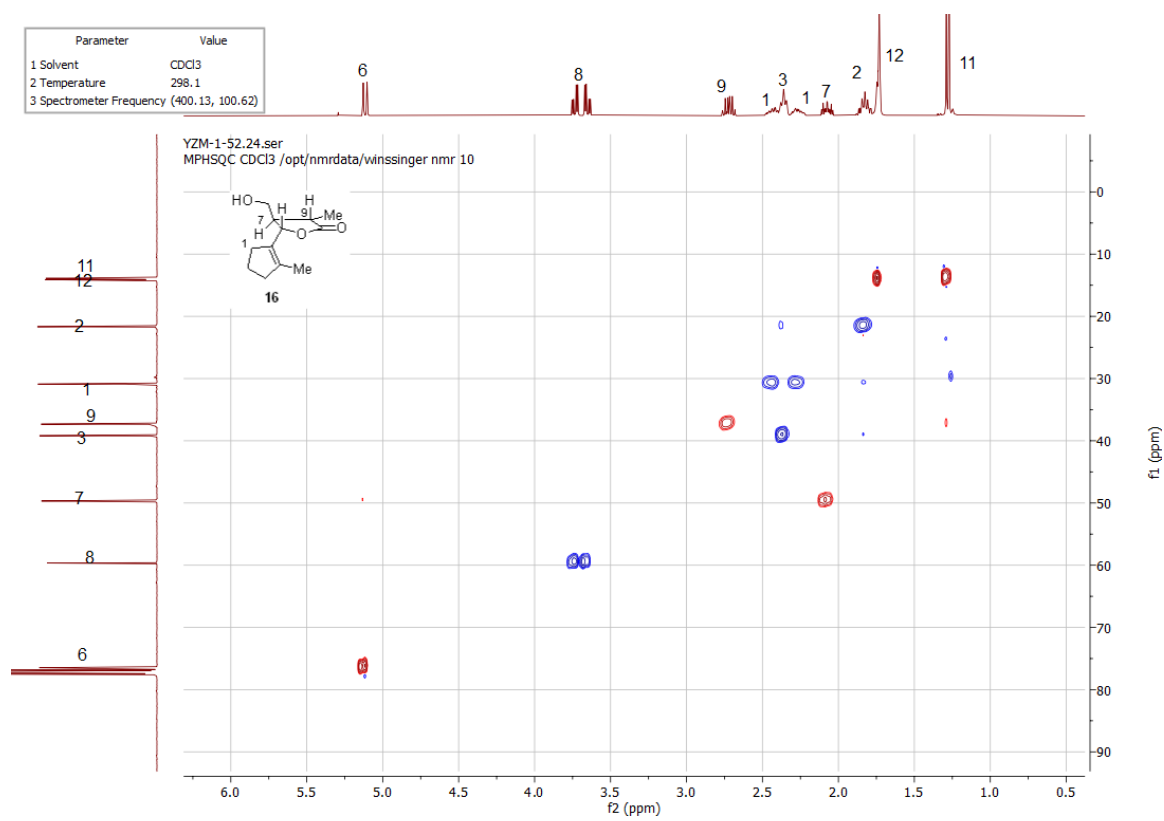
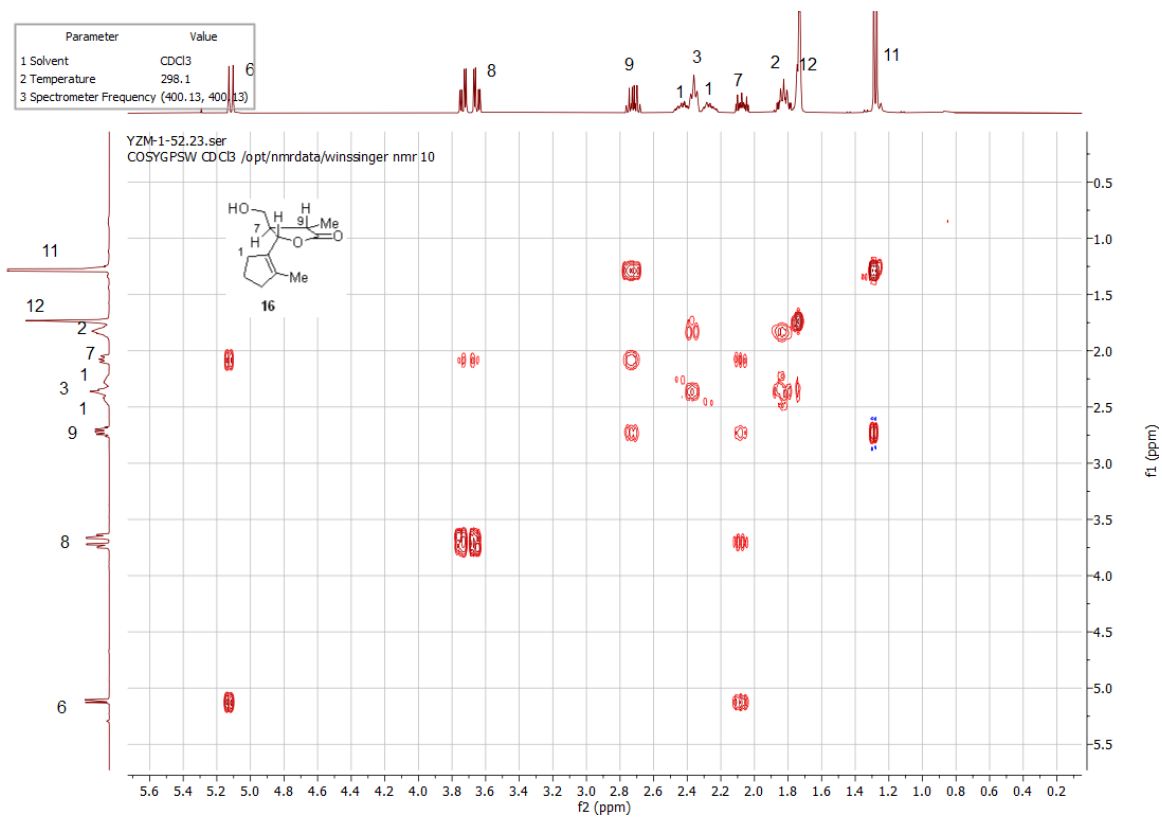


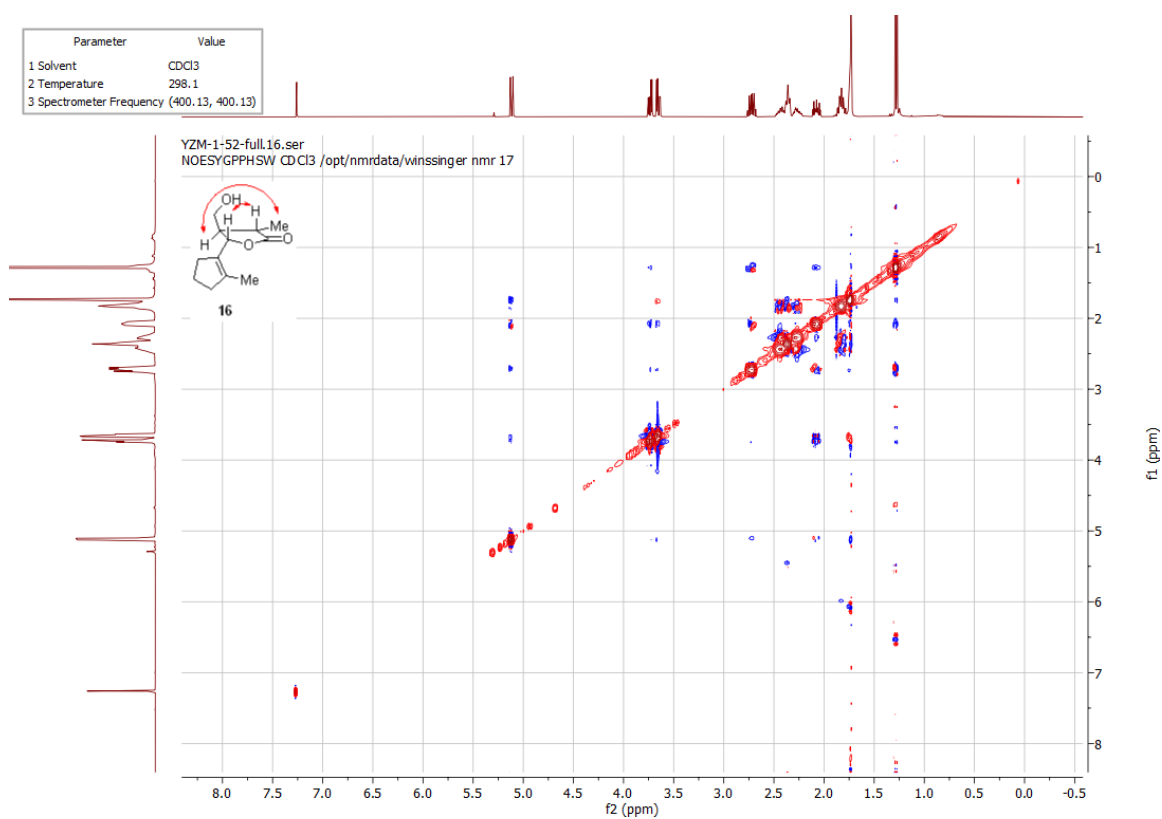
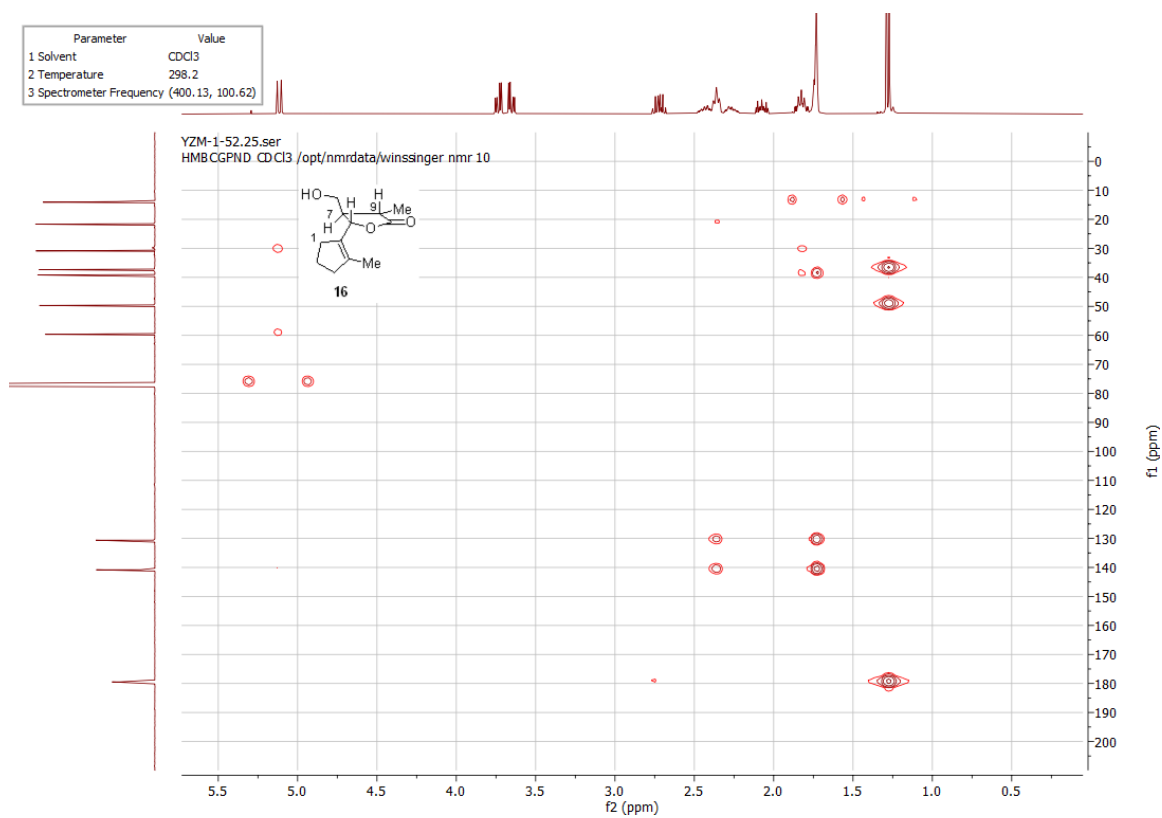


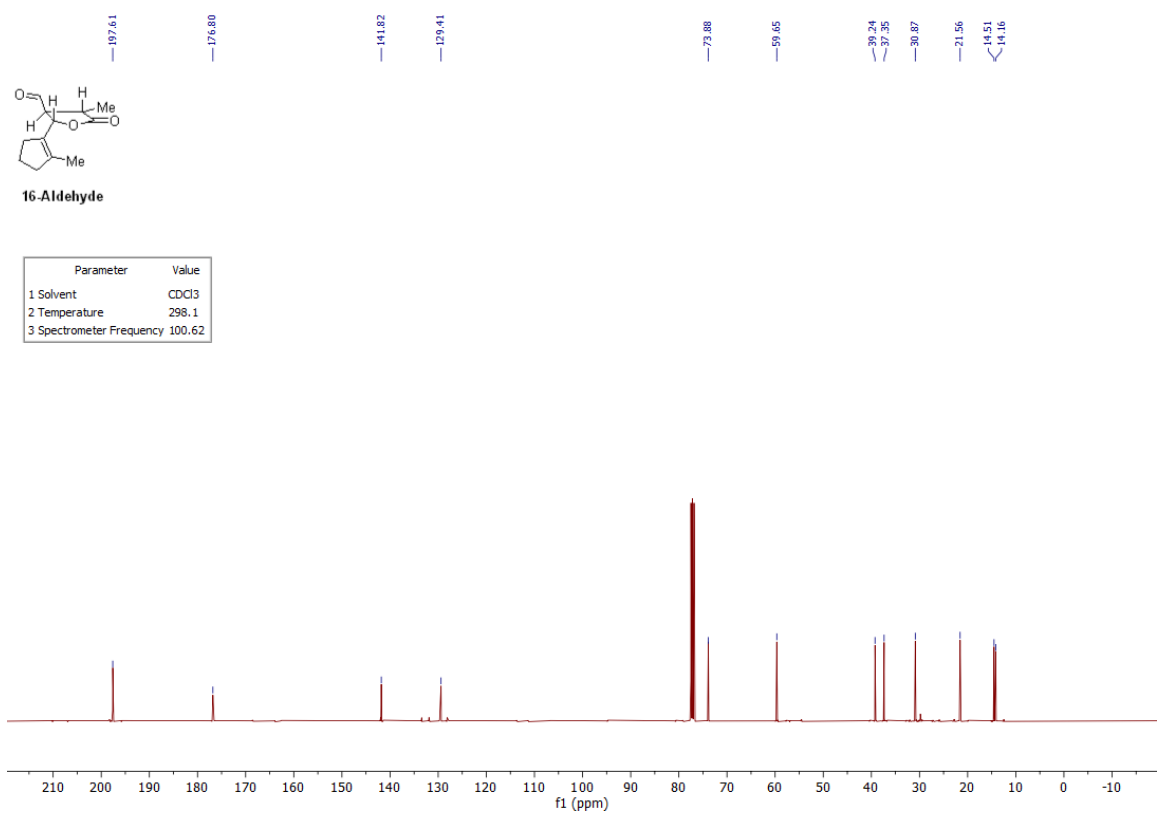
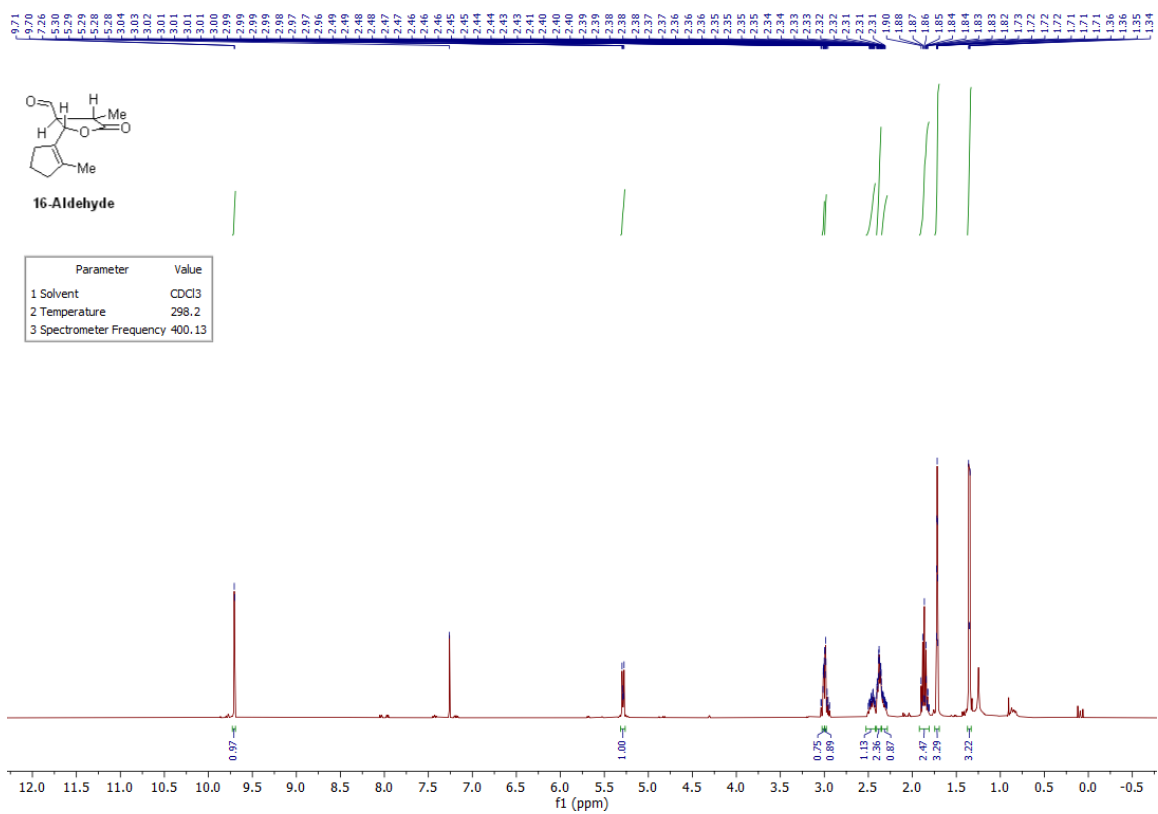


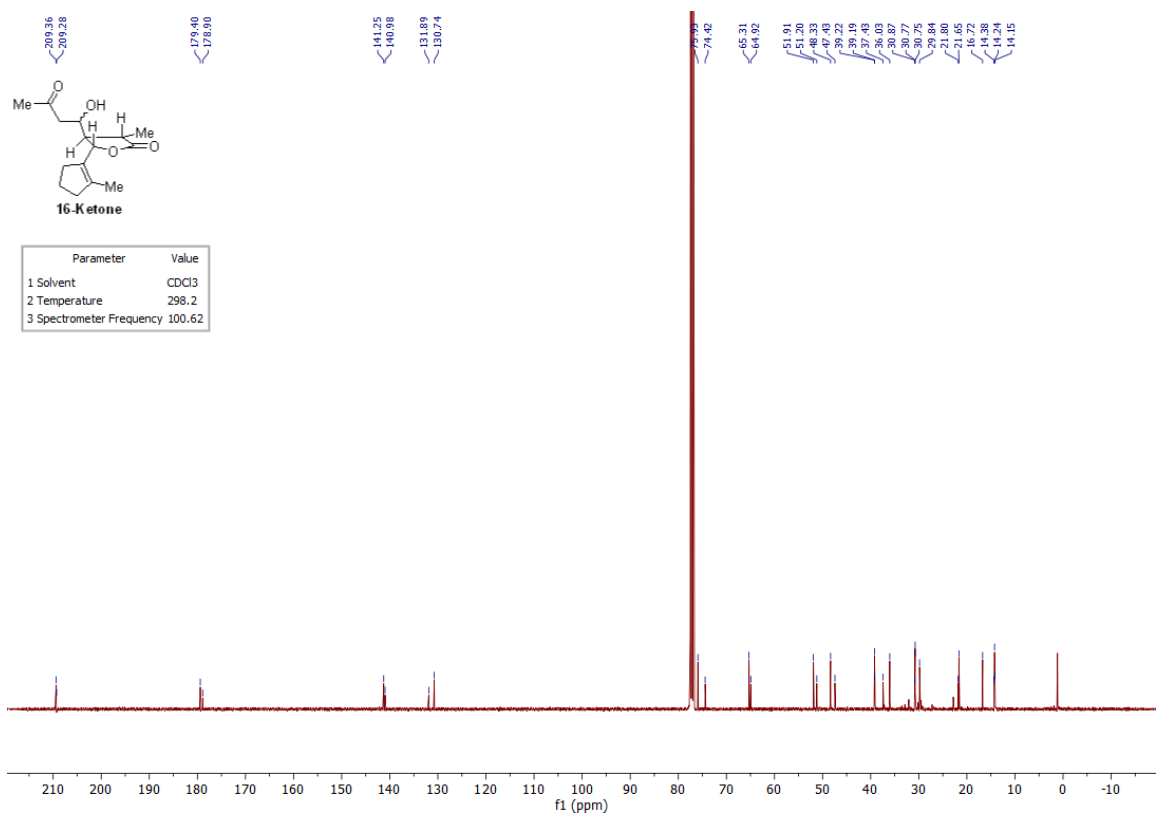
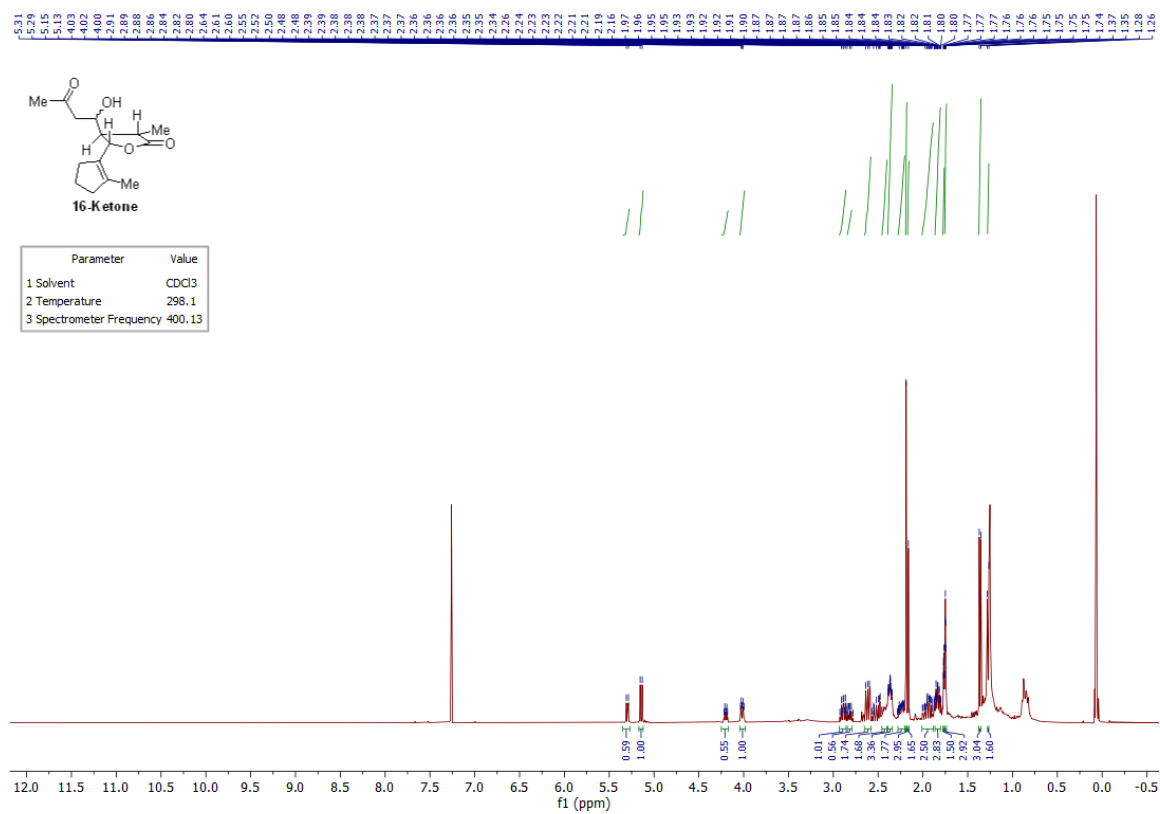


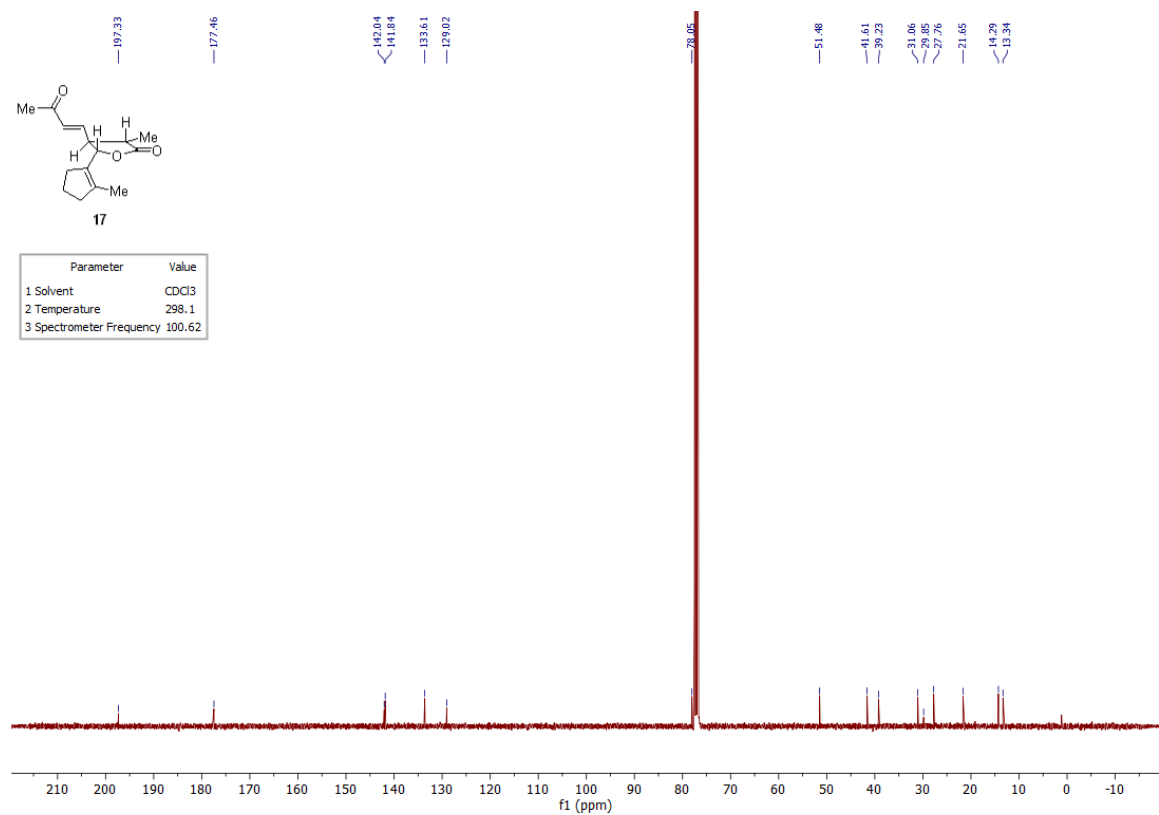
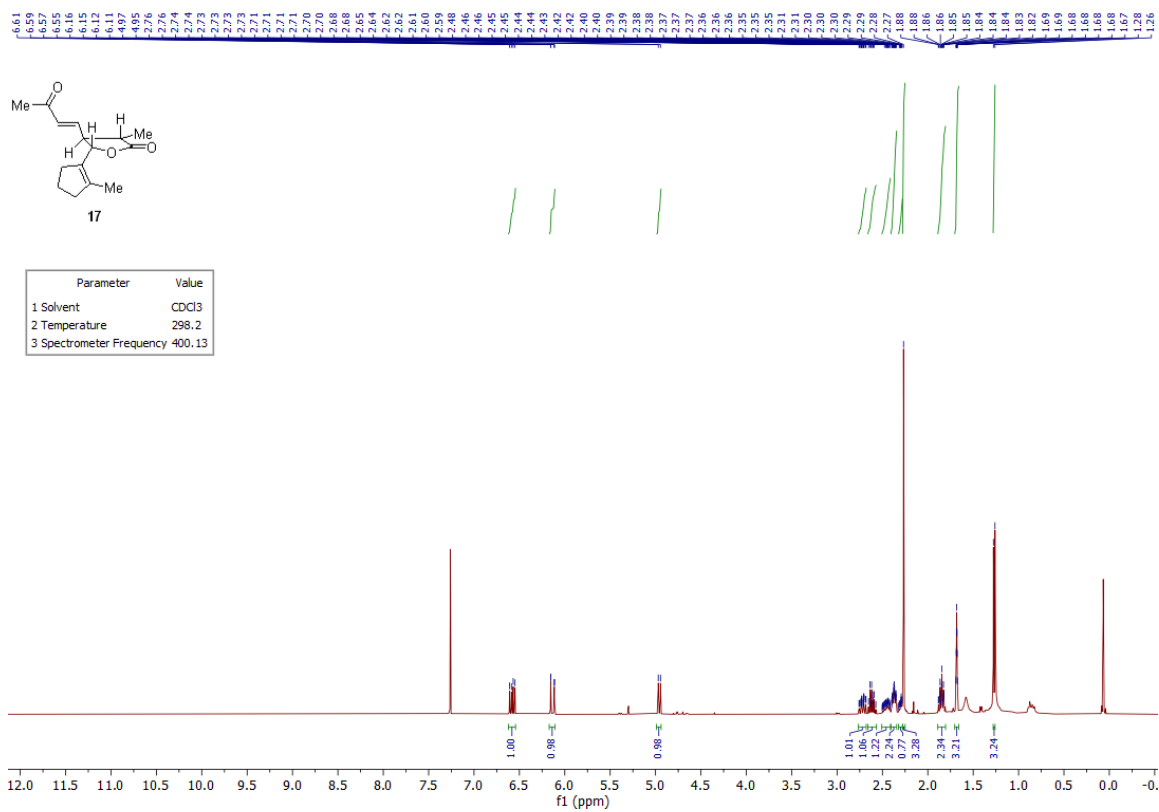


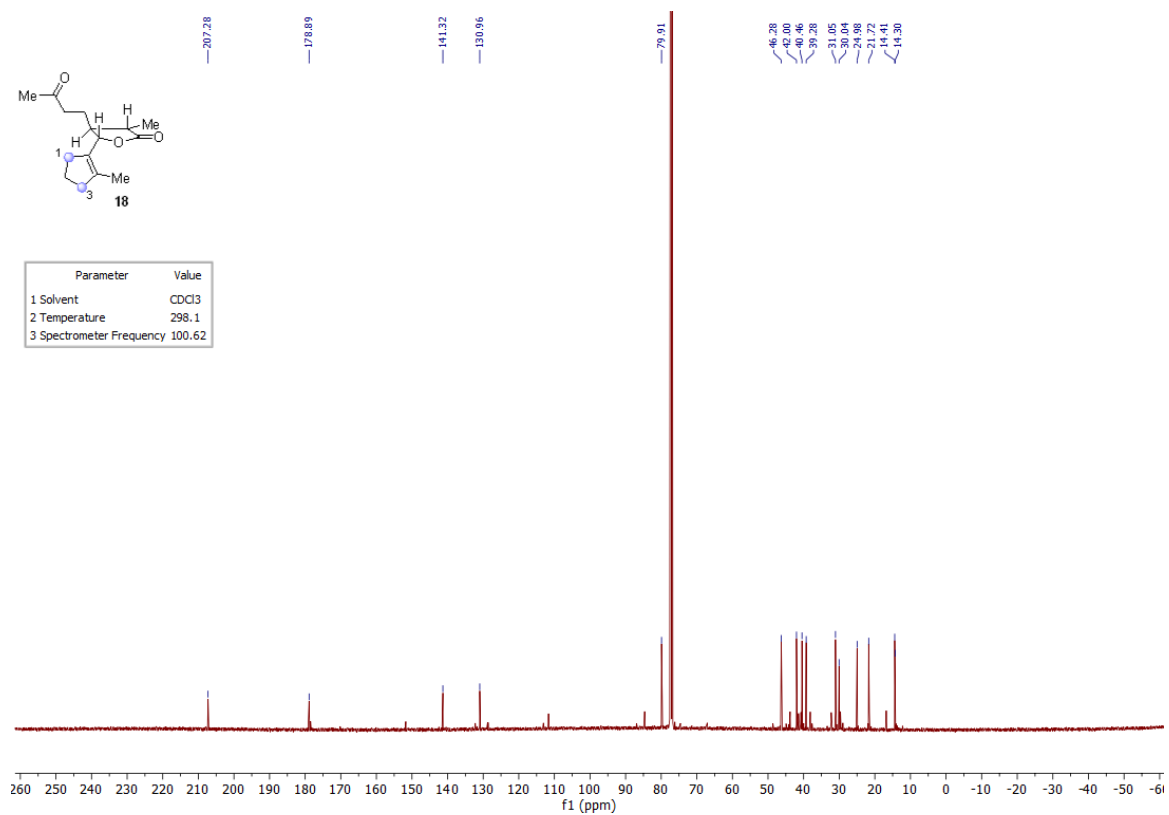
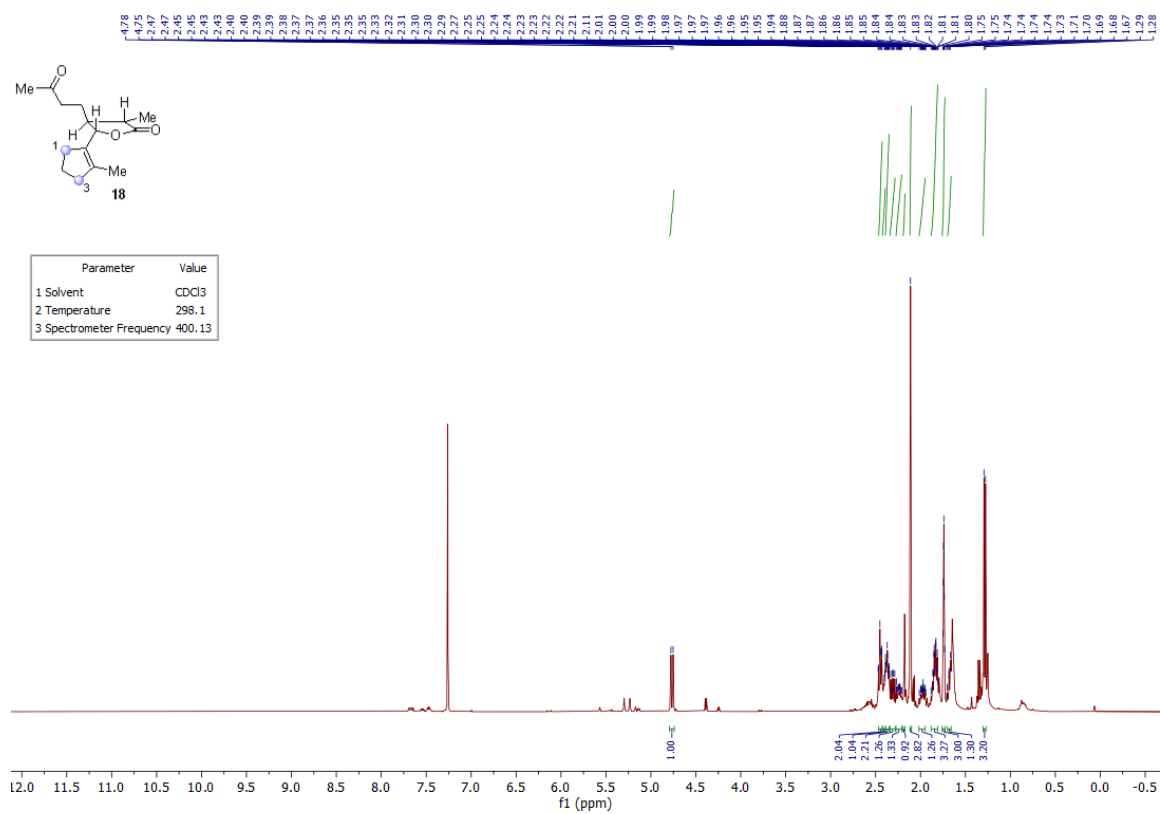




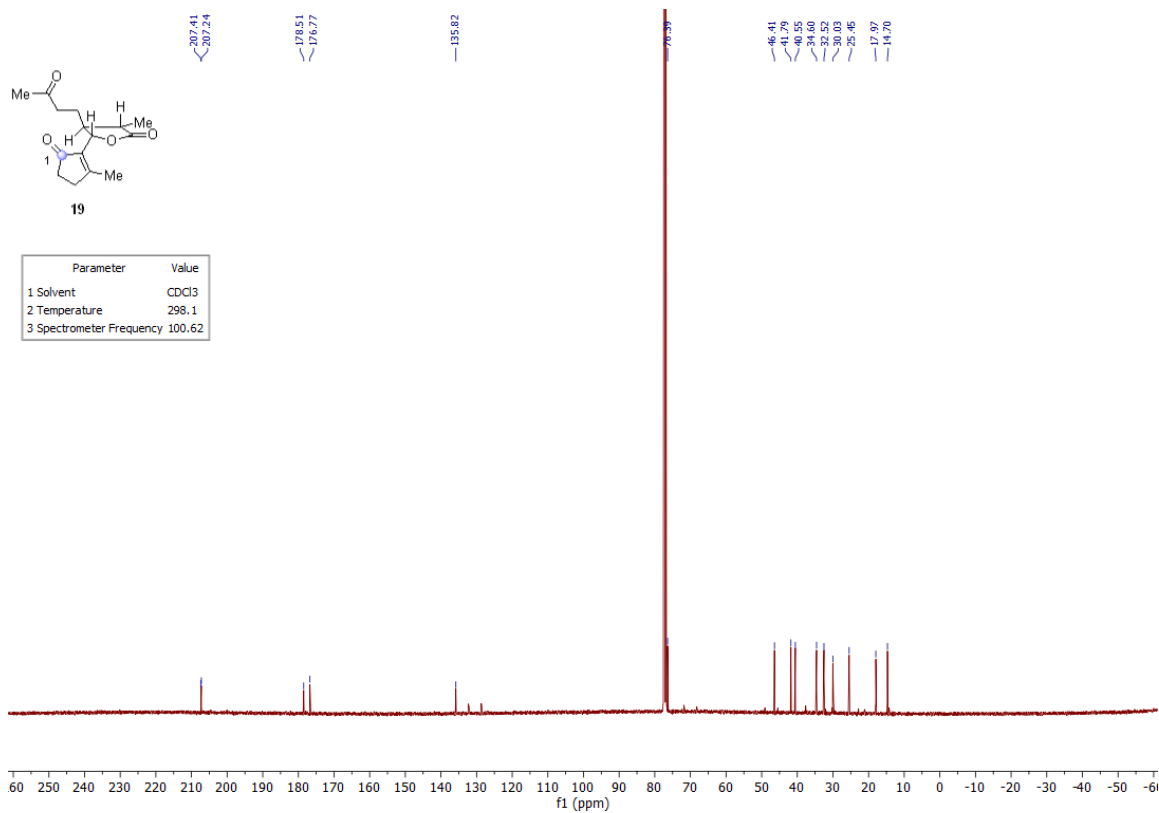
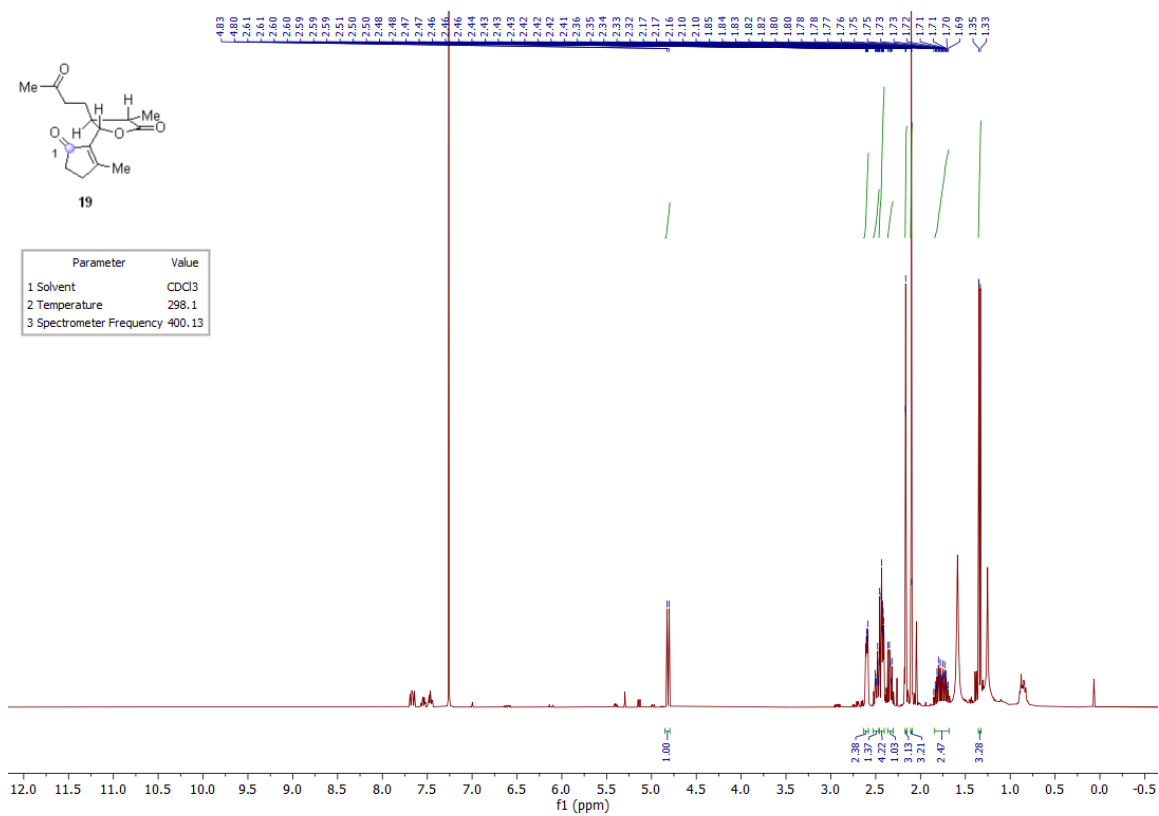


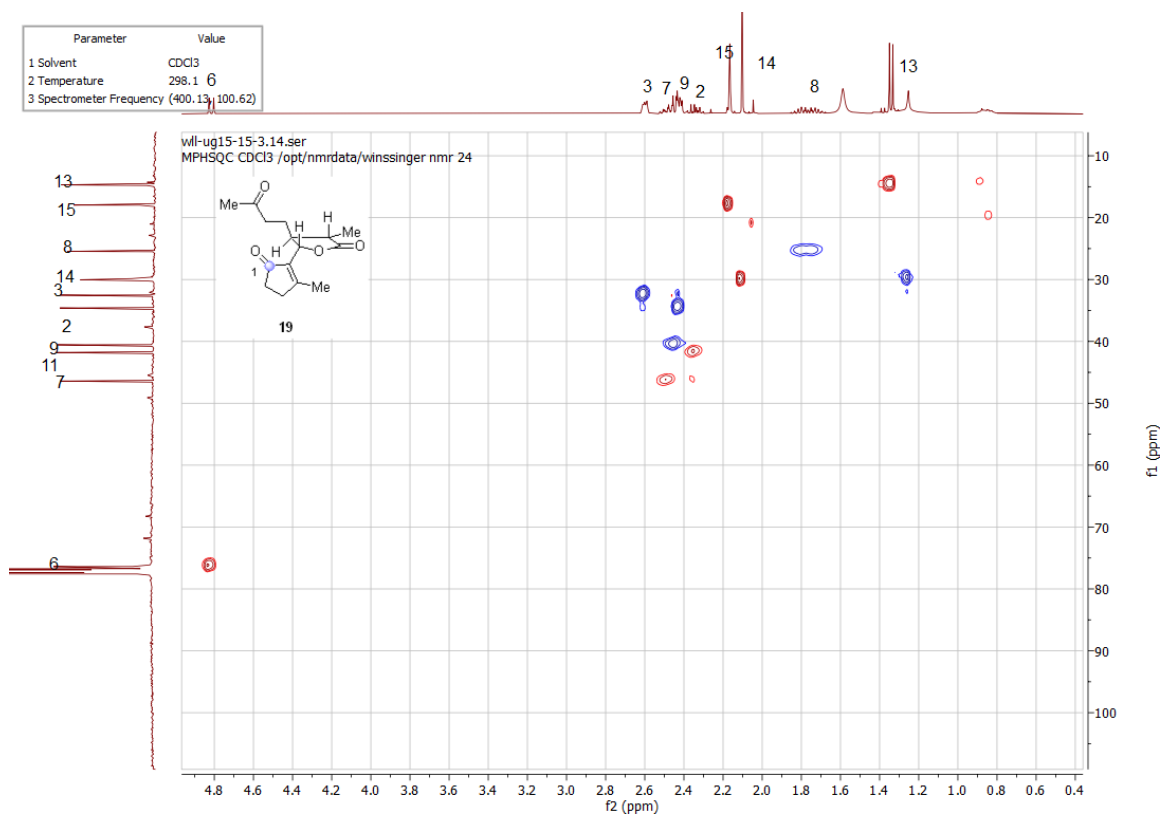
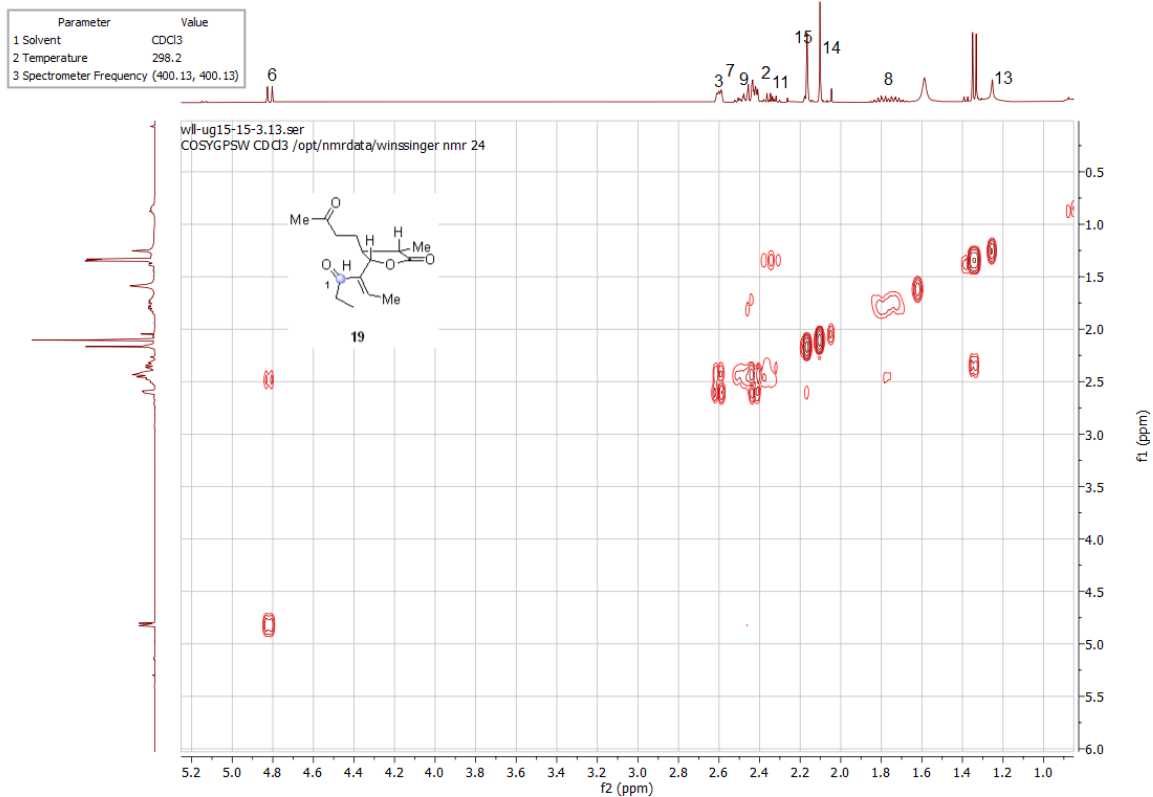


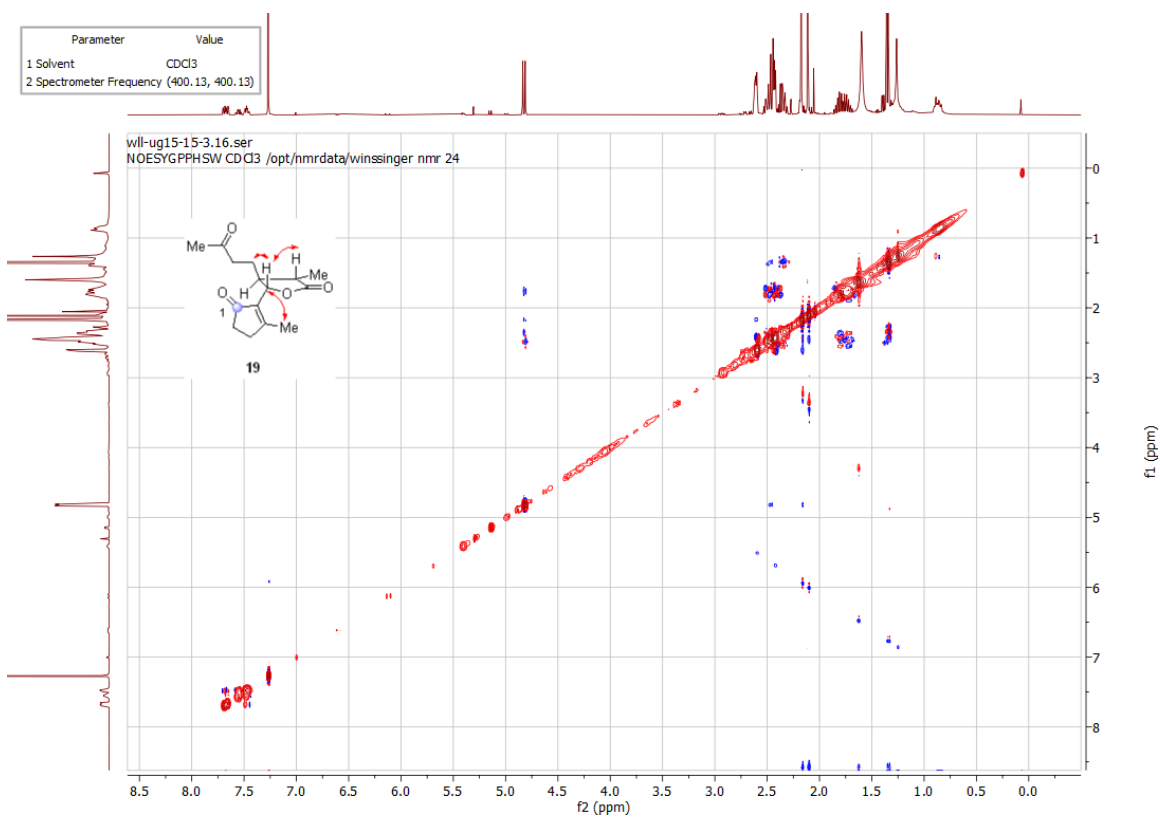
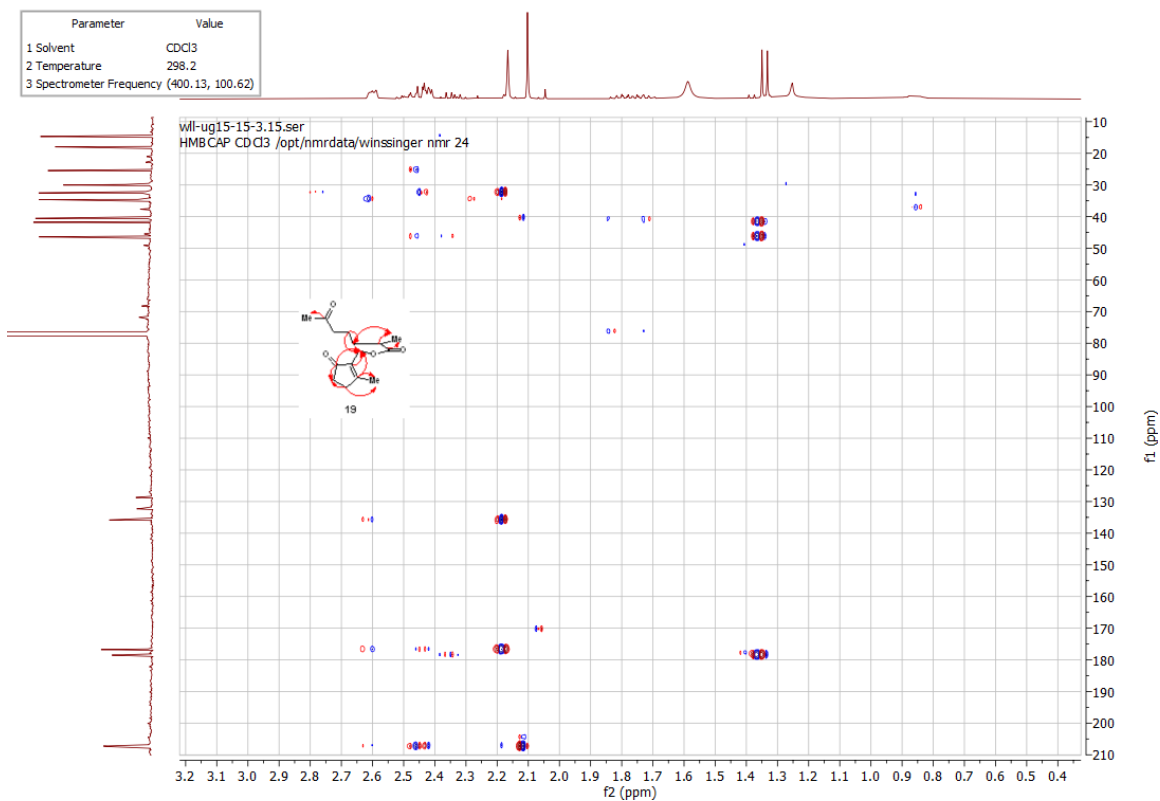


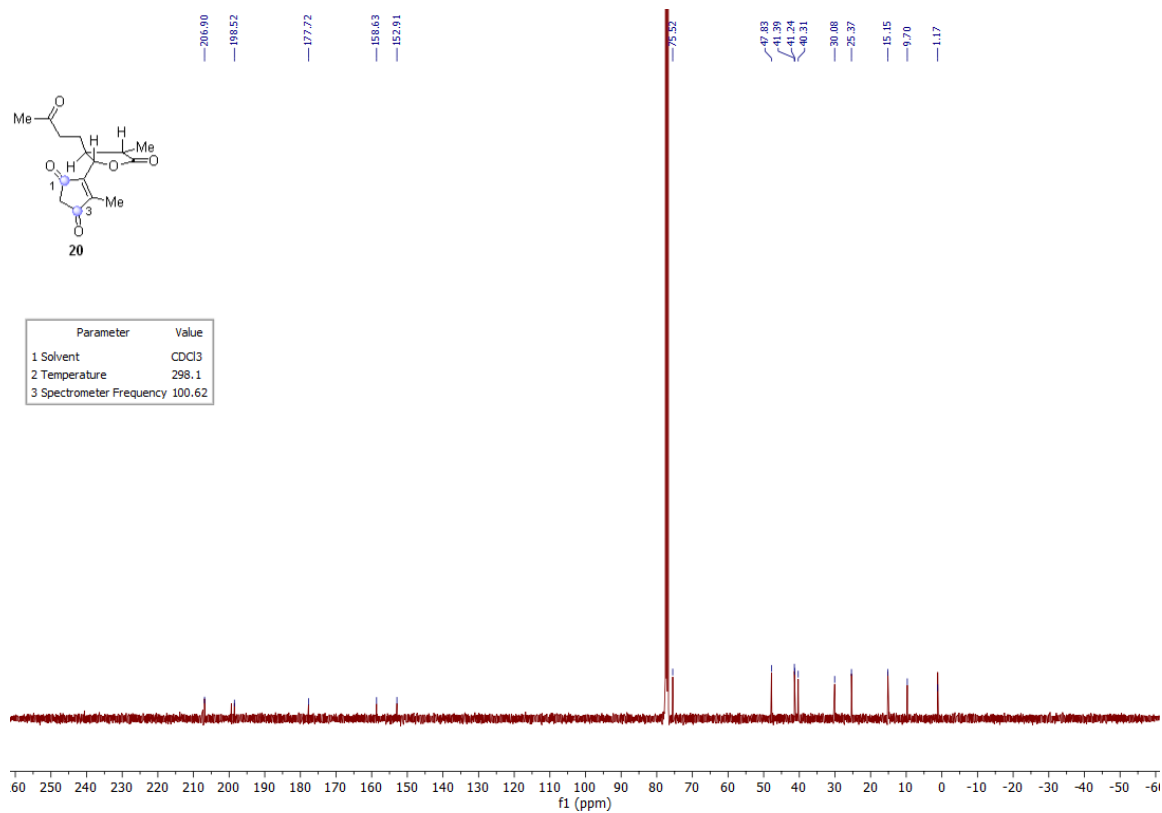
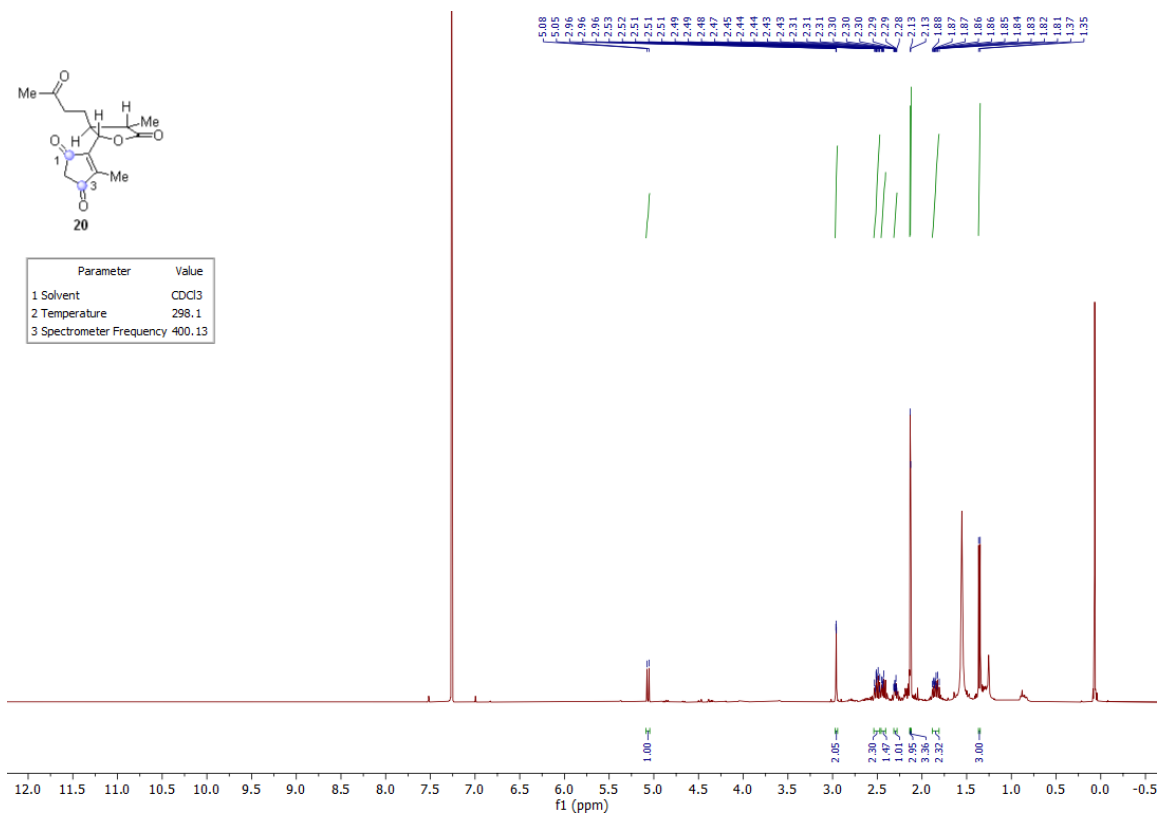


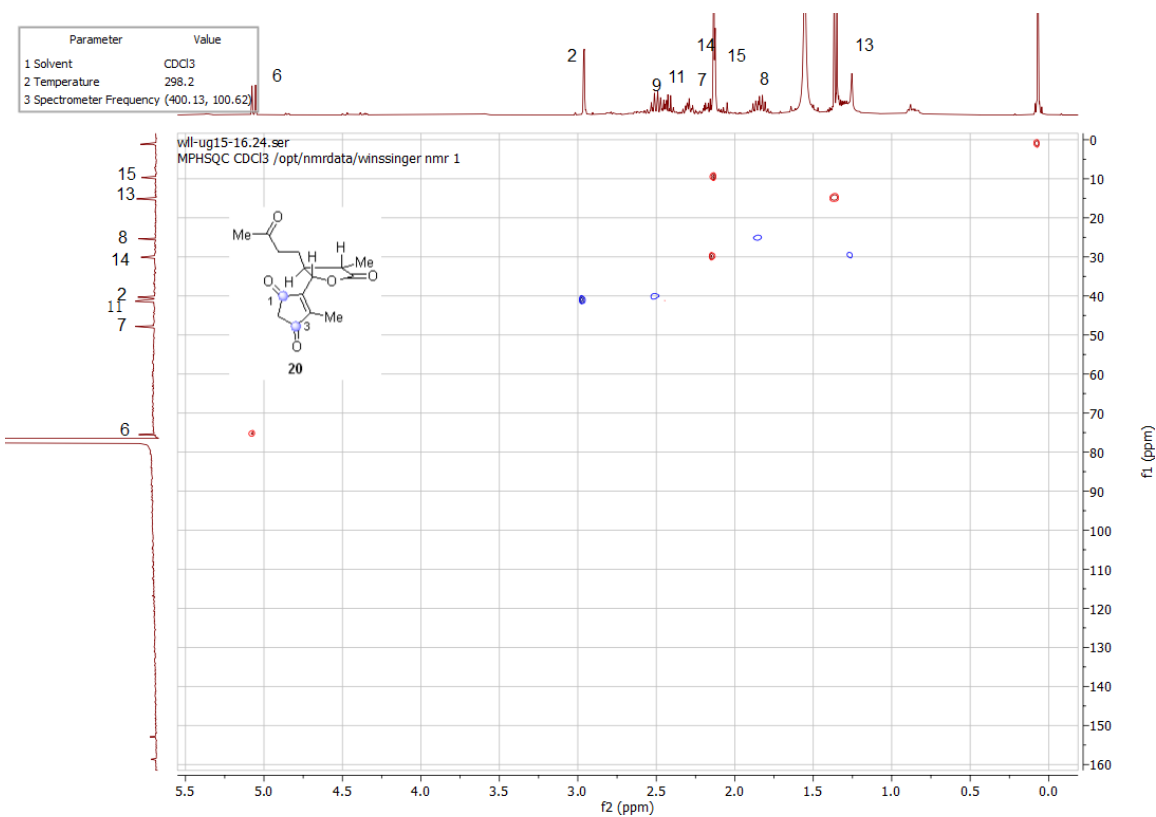
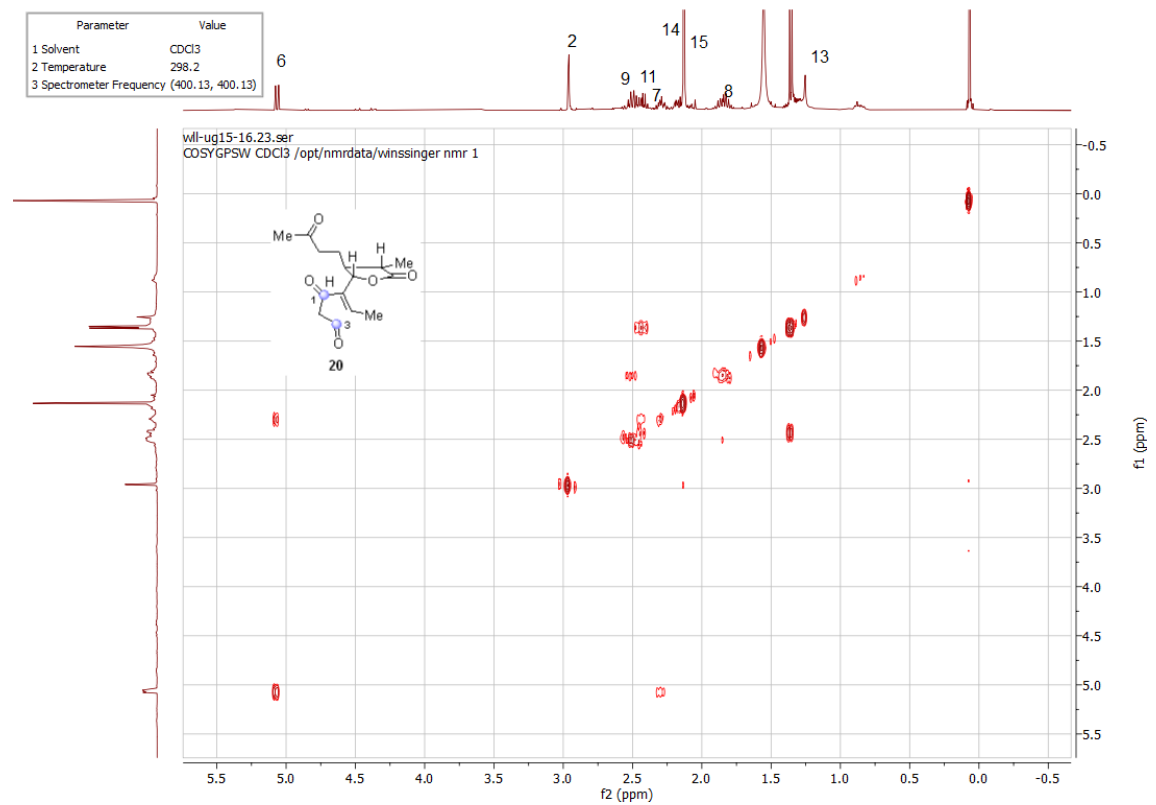


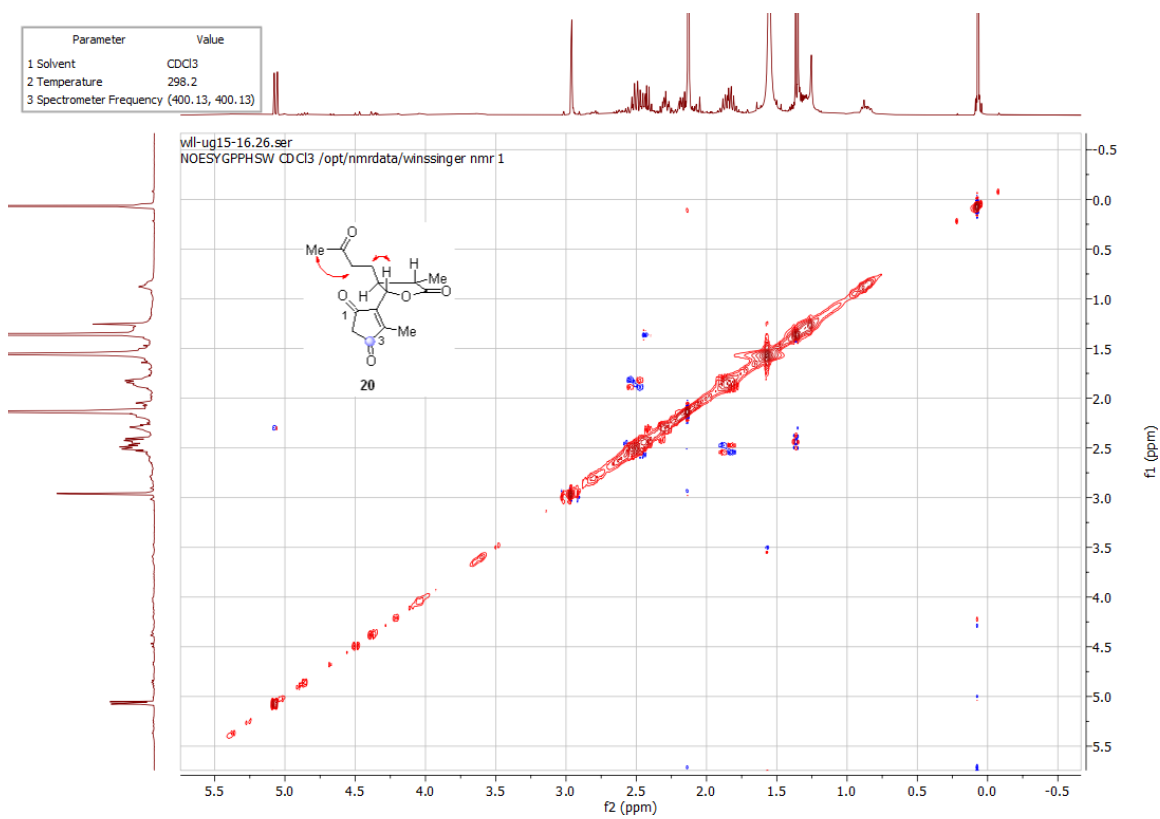
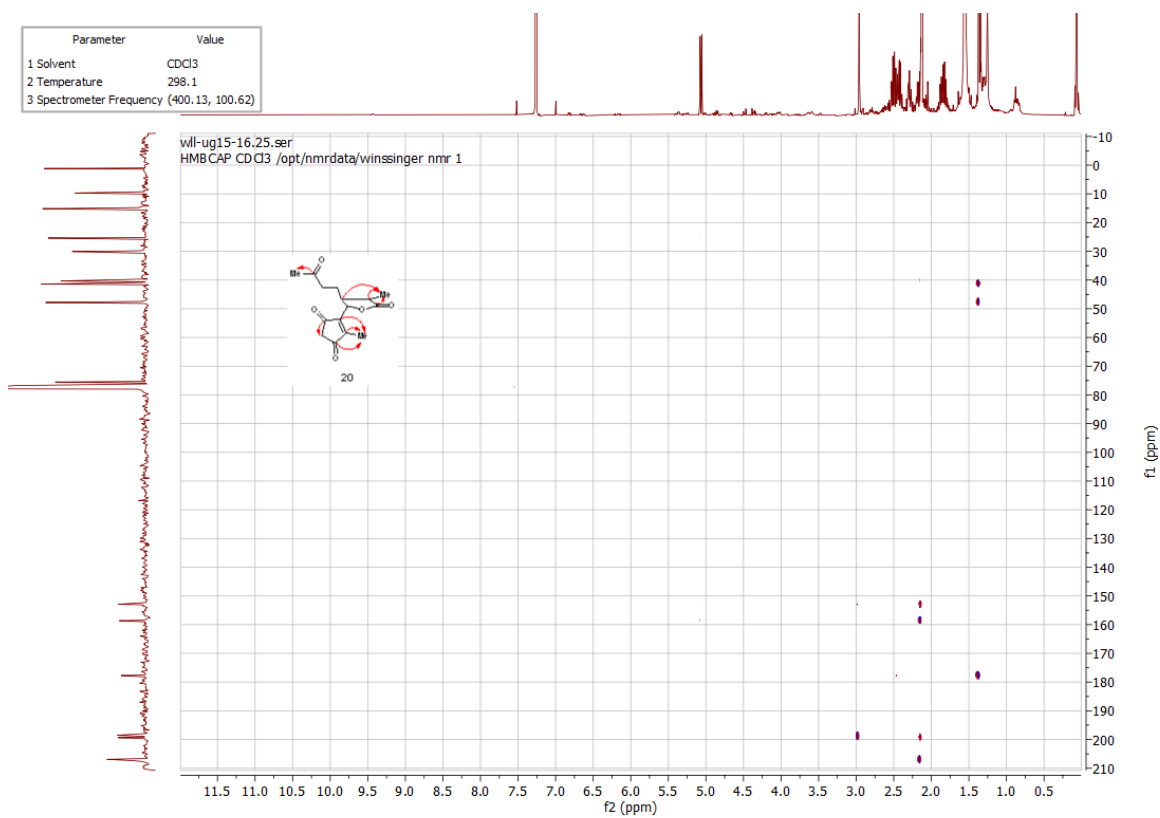














**21**

Chemical structure of compound **21** is shown. The structure is a substituted cyclopentane derivative with a methyl group, a methyl ester, and a methyl ketone group.

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) of compound **21** is displayed. The x-axis represents the chemical shift in ppm (f1), ranging from 12.0 to -0.5. The spectrum shows several peaks, with integration values provided below the baseline.

Parameter	Value
1 Solvent	CDCl <sub>3</sub>
2 Temperature	298.1
3 Spectrometer Frequency	400.13

Integration values (from left to right): 1.00, 1.15, 1.16, 1.80, 2.14, 0.96, 3.04, 2.04, 3.18, 3.35.

Chemical shift values (ppm) are listed on the right side of the spectrum, ranging from 5.02 to -1.72.



**21**

CC(=O)O[C@H]1C[C@@H](C)C(=O)N1C

Chemical structure of compound 21, a substituted pyrrolidine derivative, is shown. The structure includes a pyrrolidine ring with a methyl group at position 3, a carbonyl group at position 2, and a side chain at position 4 consisting of a methylene group, a chiral center with a methyl group and a hydroxyl group, and a carboxylic acid group.

1 Solvent CDCl<sub>3</sub>  
2 Temperature 298.1  
3 Spectrometer Frequency 100.62

Peak list (ppm): 206.19, 206.63, 177.97, 164.66, 139.94, 79.29, 47.20, 41.51, 39.85, 38.28, 33.12, 30.12, 24.91, 24.48, 15.01, 8.91.

Figure S10: <sup>13</sup>C NMR spectrum of compound 21 in CDCl<sub>3</sub>. The x-axis represents the chemical shift in ppm (f1), ranging from 60 to -60. The y-axis represents the intensity. The spectrum shows several peaks corresponding to the carbon atoms in the molecule, with the most prominent peak at 79.29 ppm, likely representing the solvent CDCl<sub>3</sub>.

