

**A Synthesis of  $\gamma$ -Lactones Utilizing Ketoacids and  
Trimethylsulfoxonium Iodide**

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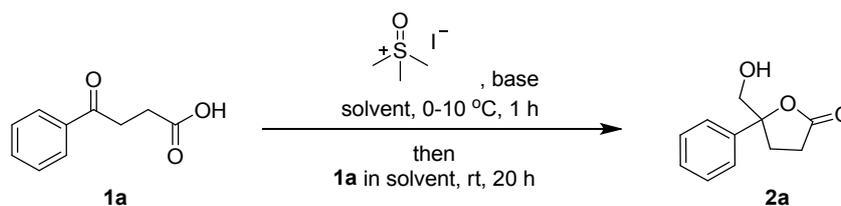
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## General Remarks

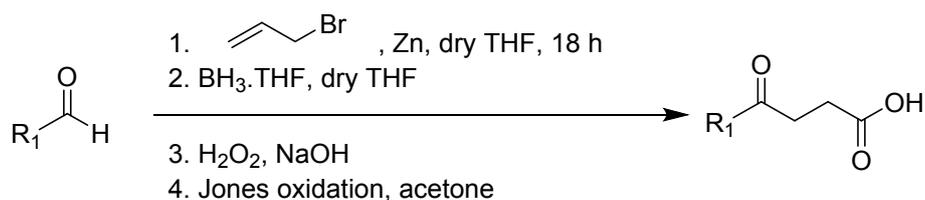
Chromatographic purification of products was accomplished using forced-flow chromatography on Merck® Kieselgel 60 F<sub>254</sub> 230-400 mesh. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F<sub>254</sub>). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde or potassium permanganate stains. Melting points were determined on a Buchi® 530 hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a Finningan® Surveyor MSQ LC-MS spectrometer. HRMS spectra were recorded on Bruker® Maxis Impact QTOF spectrometer. <sup>1</sup>H, <sup>19</sup>F and <sup>13</sup>C NMR spectra were recorded on Varian® Mercury (200 MHz, 188 MHz and 50 MHz respectively) or Bruker® (600 MHz and 150 MHz respectively), and are internally referenced to residual solvent signals. Data for <sup>1</sup>H NMR are reported as follows: chemical shift ( $\delta$  ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant and assignment. Data for <sup>19</sup>F NMR are reported in terms of chemical shift ( $\delta$  ppm) and are internally referenced to trifluoroacetic acid. Data for <sup>13</sup>C NMR are reported in terms of chemical shift ( $\delta$  ppm). Conversions of the reactions were recorded on a Shimadzu® GCMS-QP2010 Plus Gas Chromatograph Mass Spectrometer utilizing a MEGA® column (MEGA-5, F.T.: 0.25  $\mu$ m, I.D.: 0.25 mm, L: 30 m, Tmax: 350 °C, Column ID# 11475). Compounds **1a-1m** and **1r-1t** are commercially available.

### Optimization of the Reaction Conditions for the Synthesis of Lactone 2a



Entry	Base (equiv.)	Solvent (M)	Yield <sup>a</sup> (%)
1	NaH (1.2)	THF (0.2)	0
2	NaH (1.2)	CH <sub>2</sub> Cl <sub>2</sub> (0.2)	9
3	NaH (1.2)	MeCN (0.2)	traces
4	NaH (1.2)	DMSO (0.2)	55
5	K <sup>t</sup> OBu (1.2)	DMSO (0.2)	27
6	<i>n</i> -BuLi (1.2)	DMSO (0.2)	51
7	KHMDS (1.2)	DMSO (0.2)	5
8	DBU (1.2)	DMSO (0.2)	0
9	NaH (2.4)	DMSO (0.2)	68
<b>10</b>	<b>NaH (3.6)</b>	<b>DMSO (0.2)</b>	<b>76</b>
11	NaH (3.6)	DMSO (0.4)	41
12	NaH (3.6)	DMSO (0.1)	70

<sup>a</sup> Isolated Yield.

**General Procedure for the Synthesis of Ketoacids**

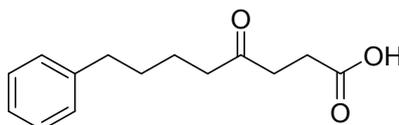
A flame dry round-bottom flask was charged with a solution of allyl bromide (4.23 g, 35.00 mmol) in anhydrous THF (20 mL) under argon atmosphere. Zinc dust (2.30 g, 35.00 mmol) was added slowly at 0 °C. The aldehyde (10.00 mmol) was dissolved in anhydrous THF (20 mL) and was added to the stirring solution. The resulting suspension was stirred for 2 h at 0 °C and then overnight at room temperature. The reaction mixture was quenched with NH<sub>4</sub>Cl (aq.) carefully at 0 °C, filtered and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was used in the next step.

A flame dry round-bottom flask was charged with a solution of crude mixture in anhydrous THF (20 mL) under argon atmosphere. A borane tetrahydrofuran complex solution 1.0 M in THF (12 mL, 12.00 mmol) was added slowly at 0 °C. The resulting suspension was stirred for 1 h at 0 °C and then overnight at room temperature. Hydrogen peroxide solution 30% (w/w) in H<sub>2</sub>O (3 mL, 30.00 mmol) was added carefully at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with aq. NaOH 1N (10 mL) carefully at 0 °C, stirred for 30 min and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was used in the next step.

The crude diol product was dissolved in acetone (20 mL) and the solution was stirred at 0 °C. Jones' reagent (2M) (17.5 mL, 35.00 mmol) was added slowly. The resulting suspension was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo*, and then was diluted with H<sub>2</sub>O (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were treated with aq. NaOH 1N (25 mL). The aqueous layer was acidified with HCl (37% w/w) (until pH=1) and

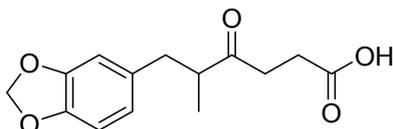
extracted with chloroform (3 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with petroleum ether:ethyl acetate (80:20-95:5) depending on the substrate.

#### 4-Oxo-8-phenyloctanoic acid (1n)

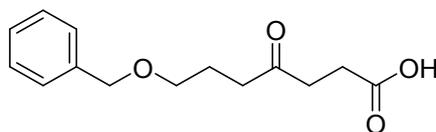


Colourless oil (1.00 g, 43%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 9.15 (1H, br s, OH), 7.31-7.15 (5H, m, ArH), 2.69-2.43 (8H, m, 4 x CH<sub>2</sub>), 1.66-1.61 (4H, m, 2 x CH<sub>2</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 208.7, 178.7, 142.0, 128.3, 128.2, 125.7, 42.4, 36.7, 35.6, 30.8, 27.7, 23.3; HRMS exact mass calculated for [M+Na]<sup>+</sup> (C<sub>14</sub>H<sub>18</sub>NaO<sub>3</sub><sup>+</sup>) requires *m/z* 257.1148, found *m/z* 257.1145.

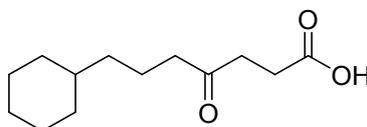
#### 6-(Benzo[d][1,3]dioxol-5-yl)-5-methyl-4-oxohexanoic acid (1o)



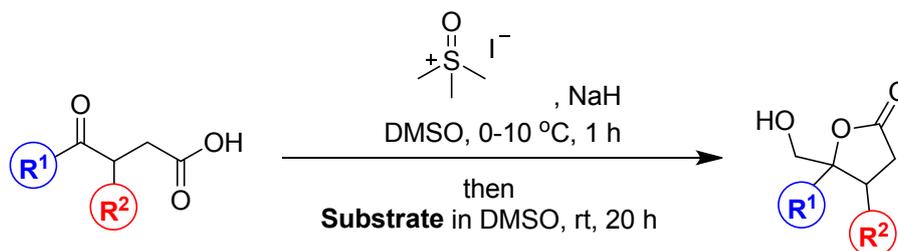
Low melting point solid (1.11 g, 42%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 9.85 (1H, br s, OH), 6.68-6.52 (3H, m, ArH), 5.87 (2H, s, OCH<sub>2</sub>), 2.92-2.40 (7H, m, 3 x CH<sub>2</sub> and CH), 1.04 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 212.1, 178.5, 147.4, 145.7, 133.0, 121.6, 109.0, 108.0, 100.6, 48.0, 38.5, 36.0, 27.5, 16.1; HRMS exact mass calculated for [M+Na]<sup>+</sup> (C<sub>14</sub>H<sub>16</sub>NaO<sub>5</sub><sup>+</sup>) requires *m/z* 287.0890, found *m/z* 287.0888.

**7-(Benzyloxy)-4-oxoheptanoic acid (1p)**

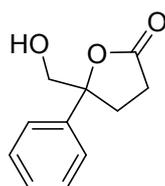
Low melting point solid (0.92 g, 37%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  10.59 (1H, br s, OH), 7.29-7.25 (5H, m, ArH), 4.45 (2H, s,  $\text{OCH}_2$ ), 3.45 (2H, t,  $J = 6.1$  Hz,  $\text{OCH}_2$ ), 2.65-2.48 (6H, m, 3 x  $\text{CH}_2$ ), 1.90-1.83 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  208.5, 177.9, 137.9, 128.1, 127.4, 127.3, 72.5, 68.9, 38.9, 36.6, 27.5, 23.5; HRMS exact mass calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{14}\text{H}_{18}\text{NaO}_4^+$ ) requires  $m/z$  273.1097, found  $m/z$  273.1095.

**7-Cyclohexyl-4-oxoheptanoic acid (1q)**

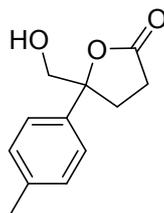
Yellow oil (1.51 g, 67%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  11.39 (1H, br s, OH), 2.66-2.50 (4H, m, 2 x  $\text{CH}_2$ ), 2.37-2.30 (2H, m,  $\text{CH}_2$ ), 1.63-1.48 (7H, m, 3 x  $\text{CH}_2$  and CH), 1.16-1.07 (6H, m, 3 x  $\text{CH}_2$ ), 0.84-0.74 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  209.1, 178.7, 42.8, 37.3, 36.7, 36.5, 33.0, 27.6, 26.5, 26.1, 20.9; HRMS exact mass calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{13}\text{H}_{22}\text{NaO}_3^+$ ) requires  $m/z$  249.1461, found  $m/z$  249.1460.

**General Procedure for the Conversion of Ketoacids to  $\gamma$ -Lactones**

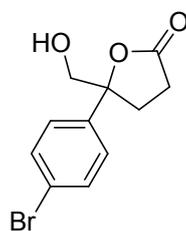
A solution of trimethylsulfoxonium iodide (660 mg, 3.00 mmol) in dry dimethylsulfoxide (3 mL) was placed in a round-bottom flask and cooled at 0 °C. Sodium hydride (60 % dispersion in mineral oil) (144 mg, 3.60 mmol) was added and the reaction mixture was left stirring at this temperature for 1 h. A solution of ketoacid (1.00 mmol) in dry dimethylsulfoxide (3 mL) was added and the reaction mixture was left for 20 h at room temperature. The crude mixture was acidified with aq. HCl (1N) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was purified using flash column chromatography (10%-40% EtOAc in Pet. Ether) to afford the desired product.

**5-(Hydroxymethyl)-5-phenyldihydrofuran-2(3H)-one (2a)<sup>1</sup>**

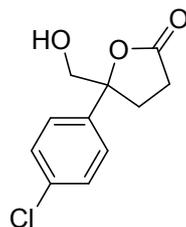
White solid (146 mg, 76%); mp 112-114 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  7.36-7.29 (5H, m, ArH), 3.86 (1H, d, *J* = 12.4 Hz, CHHOH), 3.70 (1H, d, *J* = 12.4 Hz, CHHOH), 3.16 (1H, br s, OH), 2.91-2.70 (2H, m, CH<sub>2</sub>), 2.60-2.32 (2H, m, CH<sub>2</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>)  $\delta$  177.4, 140.4, 128.5, 128.0, 124.7, 89.7, 69.2, 30.2, 29.2; MS 193 [M+H]<sup>+</sup>.

**5-(Hydroxymethyl)-5-(*p*-tolyl)dihydrofuran-2(3*H*)-one (2b)<sup>1</sup>**

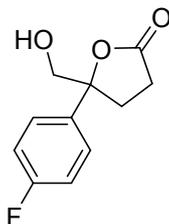
Colorless oil (128 mg, 62%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.26-7.15 (4H, m, ArH), 3.85 (1H, d, *J* = 12.4 Hz, CHHOH), 3.68 (1H, d, *J* = 12.4 Hz, CHHOH), 2.89-2.68 (3H, m, CH<sub>2</sub> and OH), 2.61-2.38 (2H, m, CH<sub>2</sub>), 2.34 (3H, s, CH<sub>3</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.4, 137.9, 137.3, 129.2, 124.6, 89.7, 69.1, 30.1, 29.2, 21.0; MS 207 [M+H]<sup>+</sup>.

**5-(4-Bromophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (2c)<sup>2</sup>**

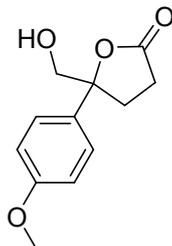
Colorless oil (177 mg, 66%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (4H, m, ArH), 3.87 (1H, d, *J* = 12.3 Hz, CHHOH), 3.70 (1H, d, *J* = 12.3 Hz, CHHOH), 3.31 (1H, br s, OH), 2.88-2.72 (2H, m, CH<sub>2</sub>), 2.61-2.32 (2H, m, CH<sub>2</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.5, 140.4, 128.5, 128.0, 124.6, 89.8, 69.2, 30.2, 29.2; MS 270 [M+H]<sup>+</sup>.

**5-(4-Chlorophenyl)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2d)<sup>3</sup>**

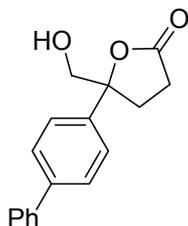
Colorless oil (156 mg, 69%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.36-7.22 (4H, m, ArH), 3.82 (1H, d, *J* = 12.3 Hz, CHHOH), 3.66 (1H, d, *J* = 12.3 Hz, CHHOH), 3.27 (1H, br s, OH), 2.85-2.67 (2H, m, CH<sub>2</sub>), 2.56-2.22 (2H, m, CH<sub>2</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.2, 139.0, 134.0, 128.7, 126.2, 89.2, 69.1, 30.2, 29.2; MS 227 [M+H]<sup>+</sup>.

**5-(4-Fluorophenyl)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2e)<sup>1</sup>**

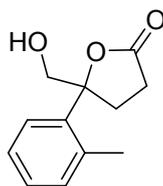
Colorless oil (124 mg, 59%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.36-7.24 (2H, m, ArH), 7.10-7.01 (2H, m, ArH), 3.83 (1H, d, *J* = 12.4 Hz, CHHOH), 3.67 (1H, d, *J* = 12.4 Hz, CHHOH), 2.89-2.69 (2H, m, CH<sub>2</sub>), 2.61-2.24 (3H, m, CH<sub>2</sub> and OH); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.0, 162.4 (d, *J* = 247.4 Hz), 136.3 (d, *J* = 3.2 Hz), 126.6 (d, *J* = 8.3 Hz), 115.6 (d, *J* = 21.6 Hz), 89.2, 69.3, 30.3, 29.2; <sup>19</sup>F (188 MHz, CDCl<sub>3</sub>): δ -58.8 (s); MS 211 [M+H]<sup>+</sup>.

**5-(Hydroxymethyl)-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one (2f)<sup>3</sup>**

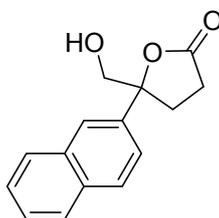
Colorless oil (93 mg, 42%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.27 (2H, d, *J* = 7.6 Hz, ArH), 6.89 (2H, d, *J* = 7.6 Hz, ArH), 3.83 (1H, d, *J* = 12.5 Hz, CHHOH), 3.79 (3H, s, OCH<sub>3</sub>), 3.65 (1H, d, *J* = 12.5 Hz, CHHOH), 2.83-2.33 (4H, m, 2 x CH<sub>2</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.4, 159.2, 132.3, 126.0, 113.9, 89.6, 69.2, 55.3, 30.1, 29.3; MS 223 [M+H]<sup>+</sup>.

**5-([1,1'-Biphenyl]-4-yl)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2g)<sup>2</sup>**

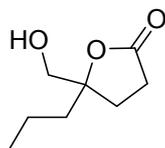
Pale yellow oil (153 mg, 57%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.88-7.80 (5H, m, ArH), 7.52-7.37 (4H, m, ArH), 3.96 (1H, d, *J* = 12.4 Hz, CHHOH), 3.82 (1H, d, *J* = 12.4 Hz, CHHOH), 2.95-2.42 (5H, m, 2 x CH<sub>2</sub> and OH); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.3, 141.0, 140.1, 139.3, 128.8, 127.5, 127.3, 127.0, 125.2, 89.6, 69.1, 30.2, 29.2; MS 269 [M+H]<sup>+</sup>.

**5-(Hydroxymethyl)-5-(*o*-tolyl)dihydrofuran-2(3*H*)-one (2h)<sup>2</sup>**

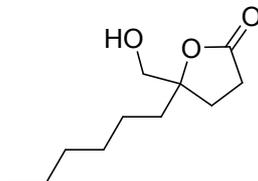
Colorless oil (45 mg, 22%); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.49-7.45 (1H, m, ArH), 7.25-7.16 (3H, m, ArH), 3.87 (2H, s, CH<sub>2</sub>OH), 3.26 (1H, br s, OH), 2.95-2.83 (2H, m, CH<sub>2</sub>), 2.56-2.44 (2H, m, CH<sub>2</sub>), 2.41 (3H, s, CH<sub>3</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.5, 138.3, 133.8, 132.3, 128.1, 126.1, 125.7, 91.0, 68.0, 30.3, 29.5, 21.4; MS 207 [M+H]<sup>+</sup>.

**5-(Hydroxymethyl)-5-(naphthalen-2-yl)dihydrofuran-2(3*H*)-one (2i)**

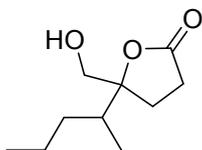
White solid (157 mg, 65%); mp 144-146 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.85-7.80 (4H, m, ArH), 7.52-7.36 (3H, m, ArH), 3.92 (1H, d, *J* = 12.5 Hz, CHHOH), 3.79 (1H, d, *J* = 12.5 Hz, CHHOH), 2.96-2.43 (4H, m, 2 x CH<sub>2</sub>); <sup>13</sup>C (50 MHz, CDCl<sub>3</sub>) δ 177.1, 137.5, 132.8, 132.7, 128.7, 128.1, 127.5, 126.7, 126.5, 123.9, 122.4, 89.6, 69.0, 30.2, 29.1; HRMS exact mass calculated for [M+H]<sup>+</sup> (C<sub>15</sub>H<sub>14</sub>O<sub>3</sub><sup>+</sup>) requires *m/z* 243.1016, found *m/z* 243.1015.

**5-(Hydroxymethyl)-5-propyldihydrofuran-2(3H)-one (2j)**

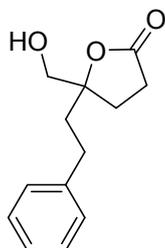
Colorless oil (76 mg, 48%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  3.73 (1H, d,  $J = 12.1$  Hz,  $\text{CHHOH}$ ), 3.51 (1H, d,  $J = 12.1$  Hz,  $\text{CHHOH}$ ), 2.75-2.45 (2H, m,  $\text{CH}_2$ ), 2.34-2.19 (1H, m,  $\text{CHH}$ ), 2.05-1.90 (1H, m,  $\text{CHH}$ ), 1.67-1.59 (1H, m,  $\text{CHH}$ ), 1.42-1.23 (3H, m,  $\text{CH}_2$  and  $\text{CHH}$ ), 0.93 (3H, t,  $J = 7.1$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  177.6, 88.9, 67.2, 38.6, 29.6, 27.4, 16.5, 14.3; HRMS exact mass calculated for  $[\text{M}+\text{H}]^+$  ( $\text{C}_8\text{H}_{14}\text{O}_3^+$ ) requires  $m/z$  159.1016, found  $m/z$  159.1013.

**5-Hexyl-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2k)**

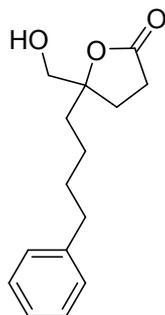
Pale yellow oil (128 mg, 64%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  3.71 (1H, d,  $J = 12.2$  Hz,  $\text{CHHOH}$ ), 3.48 (1H, d,  $J = 12.2$  Hz,  $\text{CHHOH}$ ), 2.98 (1H, br s, OH), 2.73-2.43 (2H, m,  $\text{CH}_2$ ), 2.33-2.12 (1H, m,  $\text{CHH}$ ), 2.03-1.88 (1H, m,  $\text{CHH}$ ), 1.68-1.46 (2H, m,  $\text{CH}_2$ ), 1.37-1.13 (8H, m, 4 x  $\text{CH}_2$ ), 0.85-0.83 (3H, m,  $\text{CH}_3$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  177.9, 89.2, 67.2, 36.4, 31.5, 29.7, 29.5, 27.4, 23.0, 22.5, 14.0; HRMS exact mass calculated for  $[\text{M}+\text{H}]^+$  ( $\text{C}_{11}\text{H}_{20}\text{O}_3^+$ ) requires  $m/z$  201.1485, found  $m/z$  201.1485.

**5-(Hydroxymethyl)-5-(pentan-2-yl)dihydrofuran-2(3H)-one (2l)**

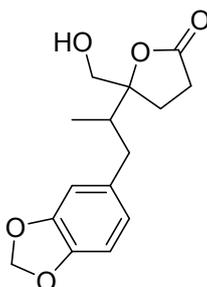
Pale yellow oil (93 mg, 50%); Mixture of diastereomers (60:40);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  3.78 (1H, d,  $J = 12.1$  Hz,  $\text{CHHOH}$ ), 3.59 (0.6H, d,  $J = 12.1$  Hz, 0.6 x  $\text{CHHOH}$ ), 3.57 (0.4H, d,  $J = 12.1$  Hz, 0.4 x  $\text{CHHOH}$ ), 2.77-2.63 (1H, m,  $\text{CHH}$ ), 2.56-2.39 (1H, m,  $\text{CHH}$ ), 2.23-1.97 (2H, m,  $\text{CH}_2$ ), 1.81 (1H, br s, OH), 1.47-1.38 (2H, m,  $\text{CHH}$  and CH), 1.22-0.99 (3H, m,  $\text{CHH}$  and  $\text{CH}_2$ ), 0.94-0.83 (6H, m, 2 x  $\text{CH}_3$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  177.8, 89.1, 67.3, 37.6, 37.4, 36.7, 29.6, 27.4, 26.5, 20.3; HRMS exact mass calculated for  $[\text{M}+\text{H}]^+$  ( $\text{C}_{10}\text{H}_{18}\text{O}_3^+$ ) requires  $m/z$  187.1329, found  $m/z$  187.1330.

**5-(Hydroxymethyl)-5-phenethyldihydrofuran-2(3H)-one (2m)<sup>2</sup>**

Colorless oil (136 mg, 62%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.15 (5H, m, ArH), 3.81 (1H, d,  $J = 12.0$  Hz,  $\text{CHHOH}$ ), 3.58 (1H, d,  $J = 12.0$  Hz,  $\text{CHHOH}$ ), 2.75-2.58 (4H, m, 2 x  $\text{CH}_2$ ), 2.40-2.25 (2H, m,  $\text{CH}_2$ ), 2.09-1.94 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  177.8, 140.8, 128.4, 128.1, 126.0, 88.7, 67.0, 38.2, 29.5, 29.3, 27.5; MS 221  $[\text{M}+\text{H}]^+$ .

**5-(Hydroxymethyl)-5-(4-phenylbutyl)dihydrofuran-2(3H)-one (2n)**

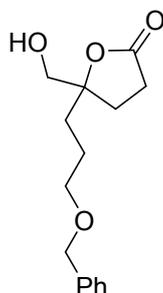
Low melting point solid (159 mg, 64%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.13 (5H, m, ArH), 3.73 (1H, d,  $J = 12.1$  Hz, CHHOH), 3.51 (1H, d,  $J = 12.1$  Hz, CHHOH), 2.79-2.45 (4H, m, 2 x  $\text{CH}_2$ ), 2.33-2.11 (2H, m, CHH and OH), 2.04-1.88 (1H, m, CHH), 1.73-1.57 (4H, m, 2 x  $\text{CH}_2$ ), 1.46-1.25 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  177.5, 142.0, 128.4, 128.3, 125.8, 88.8, 67.3, 36.2, 35.6, 31.6, 29.5, 27.4, 22.7; HRMS exact mass calculated for  $[\text{M}+\text{H}]^+$  ( $\text{C}_{15}\text{H}_{20}\text{O}_3^+$ ) requires  $m/z$  249.1485, found  $m/z$  249.1484.

**5-(1-(Benzo[d][1,3]dioxol-5-yl)propan-2-yl)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2o)**

Yellow oil (114 mg, 41%); Mixture of diastereomers (60:40);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  6.72-6.54 (3H, m, ArH), 5.91 (1.2H, s, 0.6 x  $\text{OCH}_2$ ), 5.90 (0.8H, s, 0.4 x  $\text{OCH}_2$ ), 3.91-3.80 (1H, m, CHHOH), 3.70-3.63 (2H, m, CHHOH and OH), 2.94-1.89 (7H, m, 3 x  $\text{CH}_2$  and CH), 0.82 (3H, d,  $J = 6.2$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  177.9, 177.8, 147.6, 145.8, 133.7, 133.4, 121.9, 121.8, 109.3, 109.2, 108.1, 100.8, 91.3, 66.5, 65.6, 42.1, 40.9, 37.1, 36.3, 32.9, 29.9, 29.8, 26.4, 25.2, 13.4, 13.0; HRMS

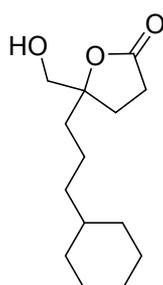
exact mass calculated for  $[M+H]^+$  ( $C_{15}H_{18}O_5^+$ ) requires  $m/z$  279.1227, found  $m/z$  279.1225.

**5-(3-(Benzyloxy)propyl)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2p)**



Pale yellow oil (172 mg, 65%);  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$  7.33-7.27 (5H, m, ArH), 4.48 (2H, s,  $OCH_2$ ), 3.71 (1H, d,  $J = 12.0$  Hz,  $CHHOH$ ), 3.56-3.45 (3H, m,  $CHHOH$  and  $OCH_2$ ), 2.75-2.46 (3H, m,  $CH_2$  and  $CHH$ ), 2.34-2.16 (2H, m,  $CHH$  and OH), 2.05-1.94 (1H, m,  $CHH$ ), 1.81-1.64 (3H, m,  $CH_2$  and  $CHH$ );  $^{13}C$  (50 MHz,  $CDCl_3$ )  $\delta$  177.5, 138.1, 128.5, 128.4, 127.6, 88.8, 73.0, 69.9, 67.0, 33.0, 29.5, 27.6, 23.5; HRMS exact mass calculated for  $[M+H]^+$  ( $C_{15}H_{20}O_4^+$ ) requires  $m/z$  265.1434, found  $m/z$  265.1430.

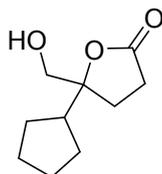
**5-(3-Cyclohexylpropyl)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2q)**



Low melting point solid (120 mg, 50%);  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$  3.73 (1H, d,  $J = 12.1$  Hz,  $CHHOH$ ), 3.50 (1H, d,  $J = 12.1$  Hz,  $CHHOH$ ), 2.78-2.44 (2H, m,  $CH_2$ ), 2.33-2.17 (1H, m,  $CHH$ ), 2.04-1.88 (1H, m,  $CHH$ ), 1.67-1.56 (6H, m, 5 x  $CHH$  and CH), 1.31-1.15 (8H, m, 8 x  $CHH$ ), 0.89-0.81 (3H, m, 3 x  $CHH$ );  $^{13}C$  (50 MHz,  $CDCl_3$ )  $\delta$  177.8, 89.2, 67.3, 37.6, 37.4, 36.7, 33.2, 29.7, 27.4, 26.6, 26.3, 20.3; HRMS

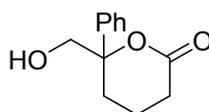
exact mass calculated for  $[M+H]^+$  ( $C_{14}H_{24}O_3^+$ ) requires  $m/z$  241.1798, found  $m/z$  241.1795.

**5-Cyclopentyl-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2r)**

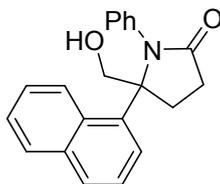


Low melting point solid (96 mg, 52%);  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$  3.79 (1H, d,  $J$  = 12.1 Hz,  $CHHOH$ ), 3.52 (1H, d,  $J$  = 12.1 Hz,  $CHHOH$ ), 2.82-2.43 (3H, m, 3 x  $CHH$ ), 2.32-1.92 (3H, m, 2 x  $CHH$  and  $CH$ ), 1.73-1.54 (5H, m, 5 x  $CHH$ ), 1.33-1.23 (3H, m,  $CH_2$  and  $OH$ );  $^{13}C$  (50 MHz,  $CDCl_3$ )  $\delta$  178.1, 91.2, 67.6, 44.8, 29.9, 26.8, 25.5, 25.4; HRMS exact mass calculated for  $[M+H]^+$  ( $C_{10}H_{16}O_3^+$ ) requires  $m/z$  185.1172, found  $m/z$  185.1170.

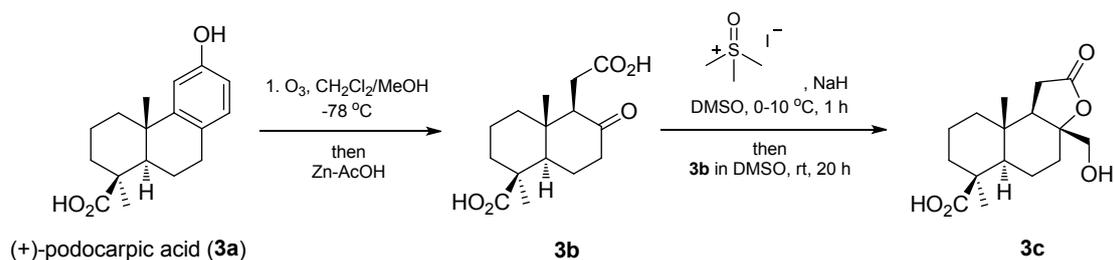
**6-(Hydroxymethyl)-6-phenyltetrahydro-2H-pyran-2-one (2s)<sup>4</sup>**



Colourless oil (109 mg, 53%);  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$  7.42-7.28 (5H, m, ArH), 3.83-3.61 (2H, m,  $CH_2OH$ ), 2.54-2.22 (5H, m, 2 x  $CH_2$  and  $OH$ ), 1.84-1.53 (2H, m,  $CH_2$ );  $^{13}C$  (50 MHz,  $CDCl_3$ )  $\delta$  171.9, 140.2, 128.8, 127.9, 125.1, 88.4, 69.9, 29.2, 27.7, 15.8; MS 207  $[M+H]^+$ .

**5-(Hydroxymethyl)-5-(naphthalen-1-yl)-1-phenylpyrrolidin-2-one (2t)**

Brown viscous oil (111 mg, 35%);  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.90-7.70 (3H, m, ArH), 7.56-7.43 (4H, m, ArH), 7.16-6.94 (5H, m, ArH), 4.22 (1H, d,  $J = 11.2$  Hz, CHHOH), 4.05 (1H, d,  $J = 11.2$  Hz, CHHOH), 2.83-2.65 (3H, m,  $\text{CH}_2$  and CHH), 2.47-2.31 (1H, m, CHH);  $^{13}\text{C}$  (50 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  177.3, 139.1, 135.6, 132.4, 132.2, 128.2, 128.1, 127.8, 127.4, 126.9, 126.0, 124.0, 71.1, 62.9, 30.8, 30.2; HRMS exact mass calculated for  $[\text{M}+\text{H}]^+$  ( $\text{C}_{21}\text{H}_{19}\text{NO}_2^+$ ) requires  $m/z$  318.1489, found  $m/z$  318.1490.

Synthesis of *epi*-(+)-Asperolide C

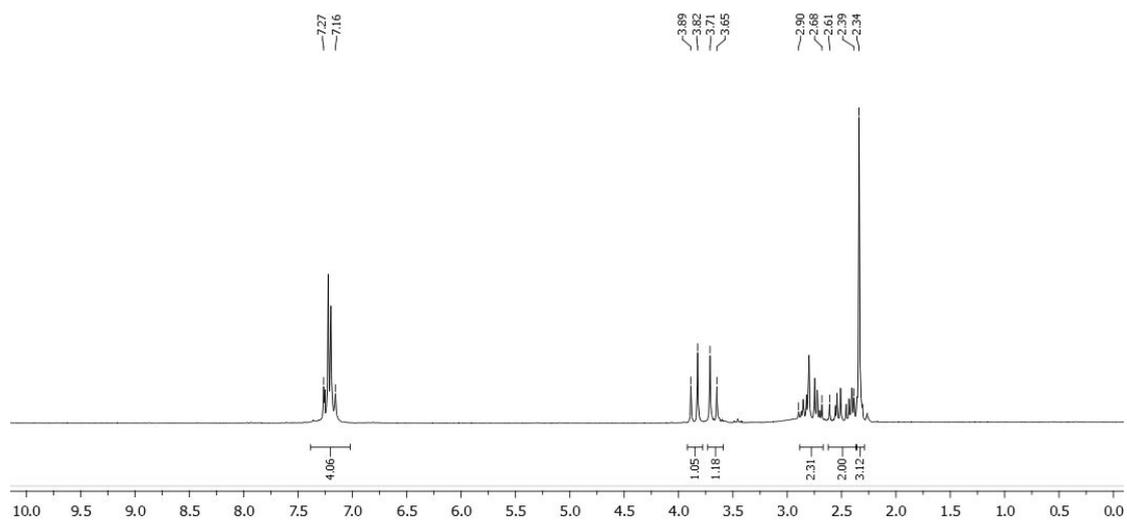
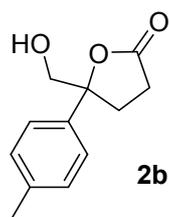
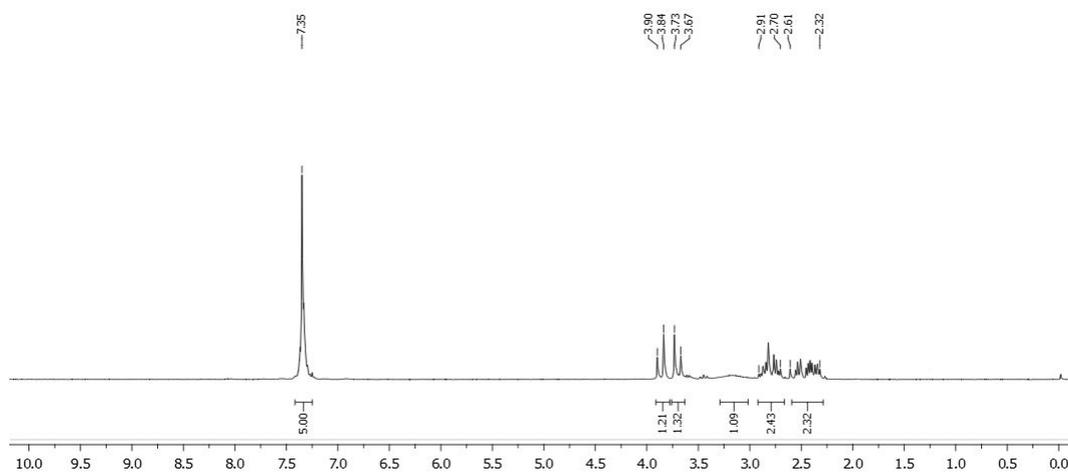
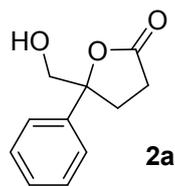
Ozone was passed through a solution of (+)-podocarpic acid **3a** (100 mg, 0.36 mmol) in dichloromethane-methanol (6 mL, 3:1) at  $-78\text{ }^{\circ}\text{C}$  for 40 min, and the resultant reaction mixture was treated with Zn-dust (0.47 g, 7.19 mmol) in acetic acid (1.0 mL). The resulting reaction mixture was left stirring for 2.5 h at room temperature. Then, it was filtered through a silica gel pad and was washed with methanol (3 x 10 mL). The filtrate was concentrated *in vacuo*, the residue was diluted with diethyl ether (20 mL) and washed with aq. KOH 10% (2 x 20 mL). The combined aqueous layers were acidified with a solution of aq. HCl 2M (pH=1). The crude reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and evaporated *in vacuo*. The crude ketoacid **3b** was used in next step without further purification. All data for crude product agrees with literature.<sup>5</sup>  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.81-2.67 (2H, m, 2 x  $\text{CHHCOOH}$ ), 2.51-2.14 (5H, m, 3 x  $\text{CHH}$  and 2 x  $\text{CH}$ ), 1.91-1.49 (4H, m, 4 x  $\text{CHH}$ ), 1.33 (3H, s,  $\text{CH}_3$ ), 1.11-1.00 (3H, m, 3 x  $\text{CHH}$ ), 0.63 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  209.6, 183.0, 179.2, 58.3, 54.0, 44.0, 42.1, 41.7, 39.1, 37.4, 28.8, 27.6, 24.6, 19.3, 13.5;  $[\alpha]_{\text{D}}^{22} = -100$  (c 0.10,  $\text{CHCl}_3$ ).

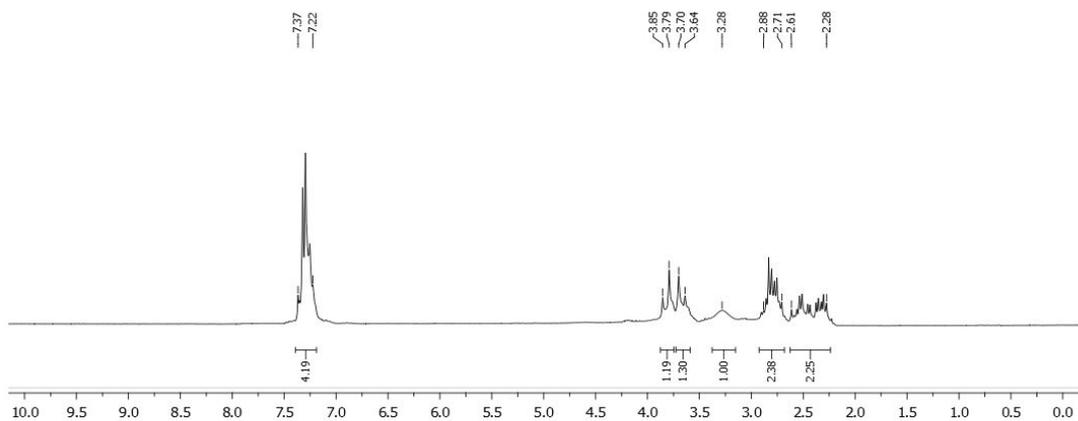
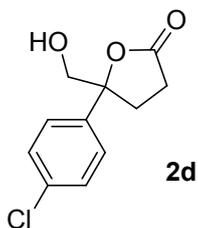
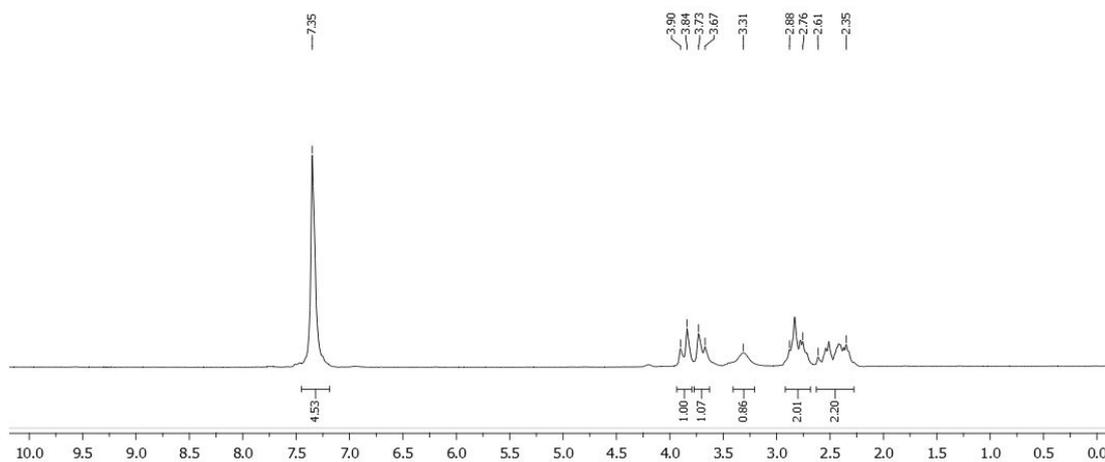
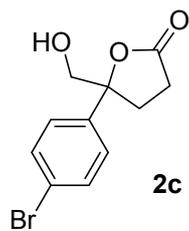
A solution of trimethylsulfoxonium iodide (0.24 g, 1.08 mmol) in dry dimethylsulfoxide (1.1 mL) was placed in a round-bottom flask and cooled at  $0\text{ }^{\circ}\text{C}$ . Sodium hydride (60 % dispersion in mineral oil) (52 mg, 1.30 mmol) was added and the reaction mixture was left stirring at this temperature for 1 h. A solution of ketoacid **3b** (0.36 mmol) in dry dimethylsulfoxide (1.1 mL) was added and the reaction mixture was left for 20 h at room temperature. The crude mixture was acidified with aq. HCl (1N) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude mixture was purified using flash column chromatography (5%-95% MeOH in  $\text{CHCl}_3$ ) to

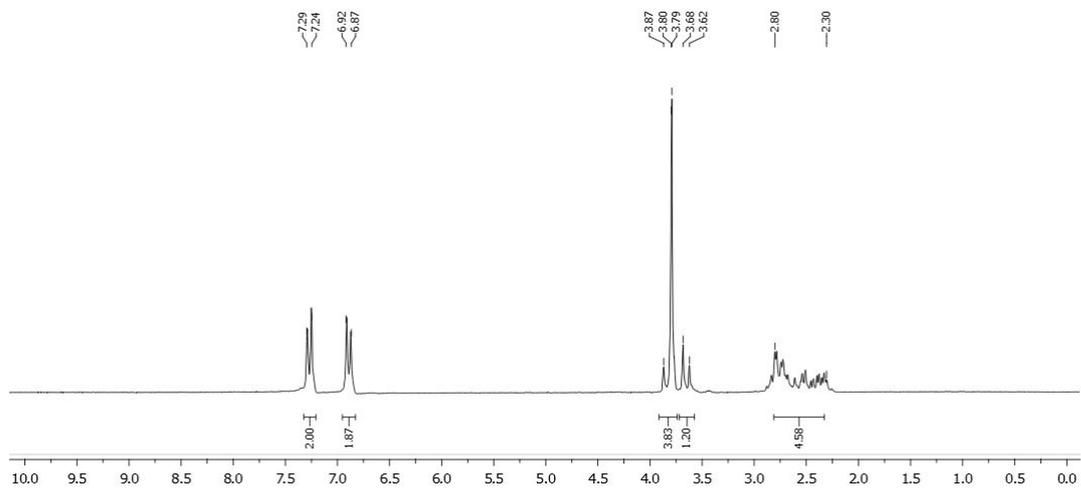
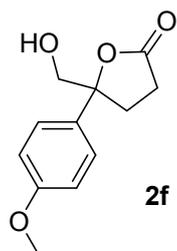
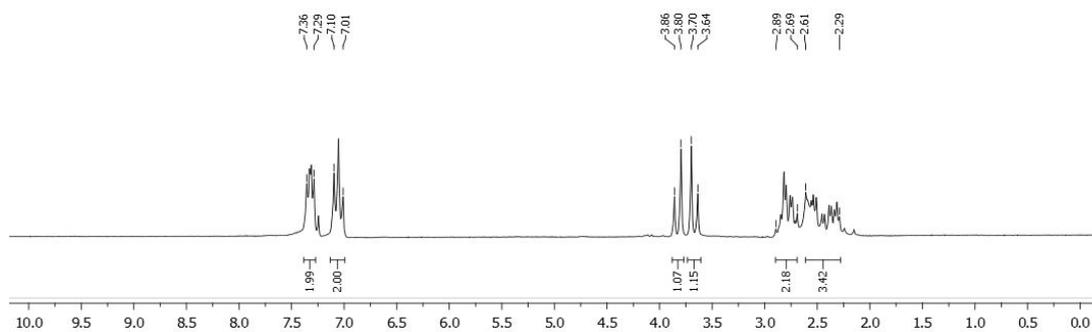
afford the desired product **3c** as a white solid (26 mg, 24%); m.p. 208-210 °C; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD and CDCl<sub>3</sub>) δ 3.68 (1H, d, *J* = 12.3 Hz, OCHH), 3.66 (1H, d, *J* = 12.3 Hz, OCHH), 2.45 (1H, tt, *J* = 12.6 and 8.9 Hz, CHH), 2.24 (1H, dd, *J* = 12.6 and 7.2 Hz, CH), 2.19 (1H, dt, *J* = 13.2 and 2.8 Hz, CHH), 2.12-2.08 (2H, m, 2 x CHH), 1.93-1.83 (2H, m, 2 x CHH), 1.54-1.50 (1H, m, CHH), 1.42-1.27 (6H, m, 5 x CHH and OH), 1.22 (3H, s, CH<sub>3</sub>), 0.99 (3H, s, CH<sub>3</sub>), 0.96-0.89 (1H, m, CH); <sup>13</sup>C (150 MHz, CD<sub>3</sub>OD and CDCl<sub>3</sub>) δ 179.4, 179.0, 94.2, 69.3, 55.5, 50.9, 46.4, 42.8, 36.1, 31.5, 29.4, 28.7, 27.0, 21.2, 19.0, 13.7; [α]<sub>D</sub><sup>22</sup> = -20 (c 0.10, MeOH); HRMS exact mass calculated for [M+H]<sup>+</sup> (C<sub>16</sub>H<sub>25</sub>O<sub>5</sub><sup>+</sup>) requires *m/z* 297.1697, found *m/z* 297.1694 and for [M-H]<sup>-</sup> (C<sub>16</sub>H<sub>23</sub>O<sub>5</sub><sup>-</sup>) requires *m/z* 295.1551, found *m/z* 295.1541.

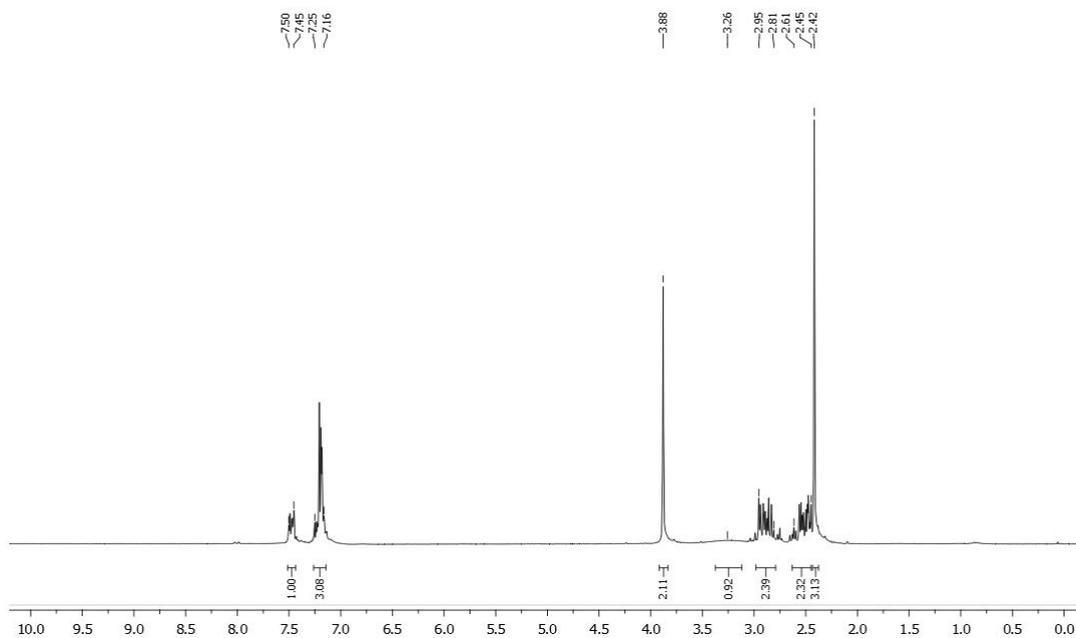
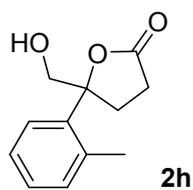
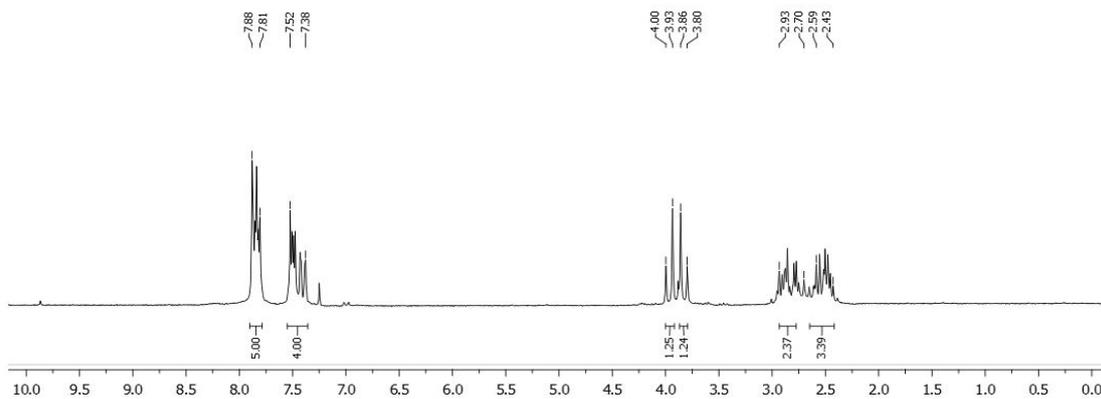
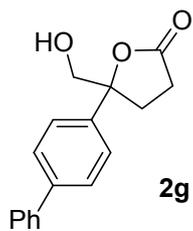
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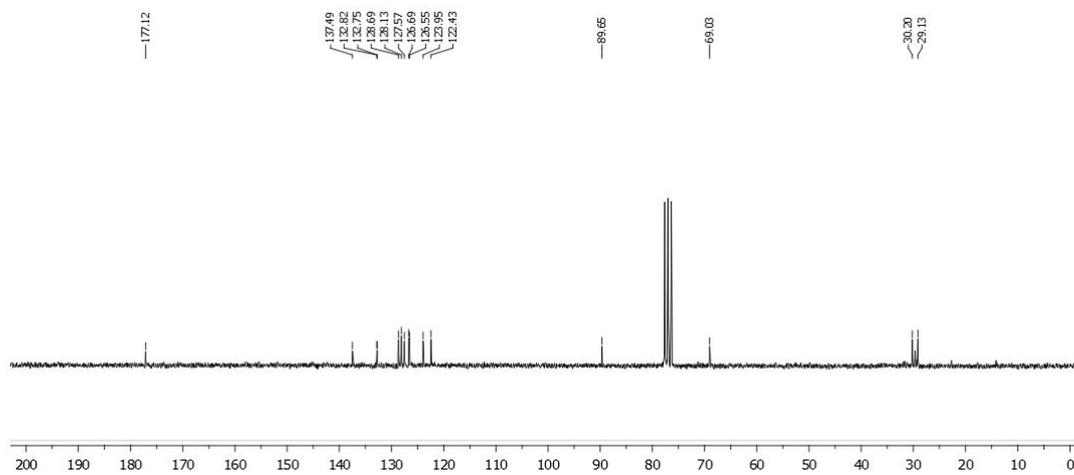
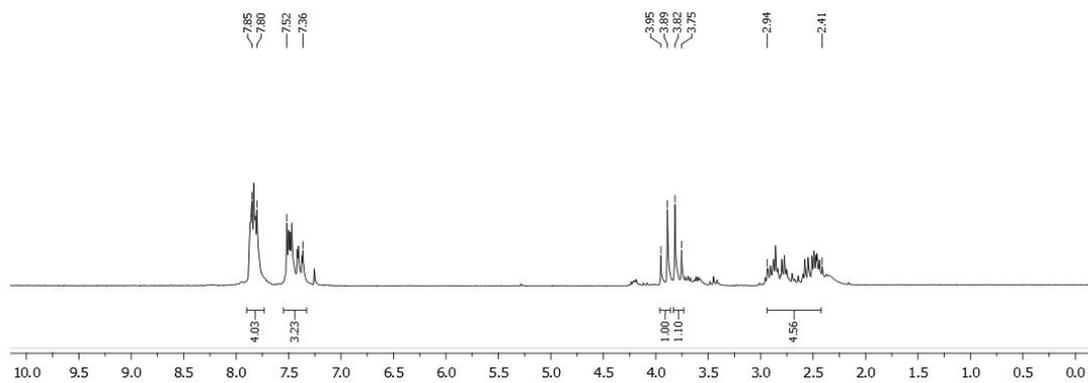
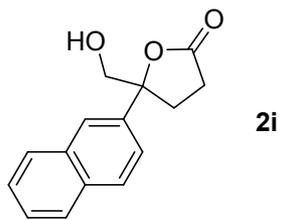
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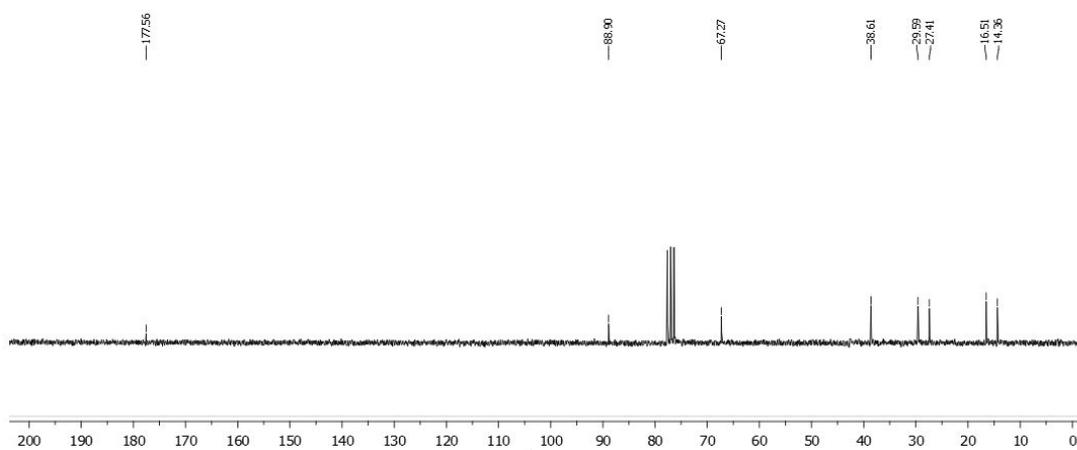
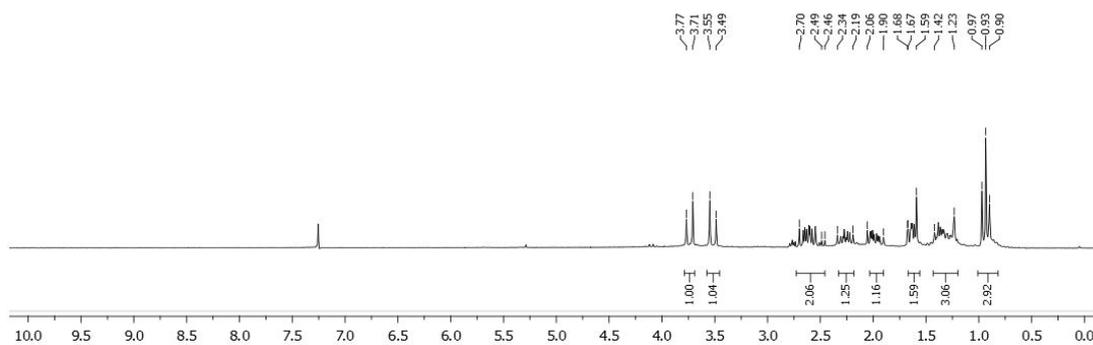
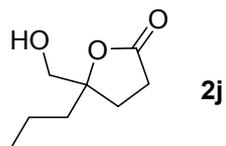


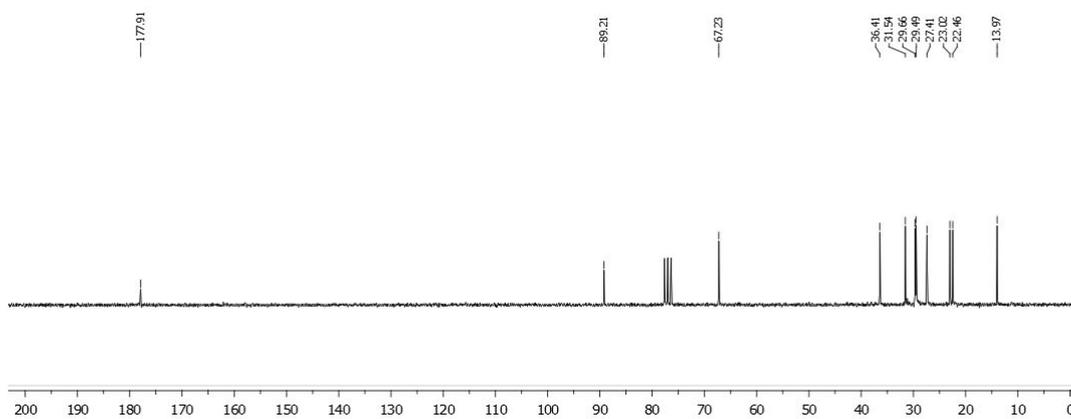
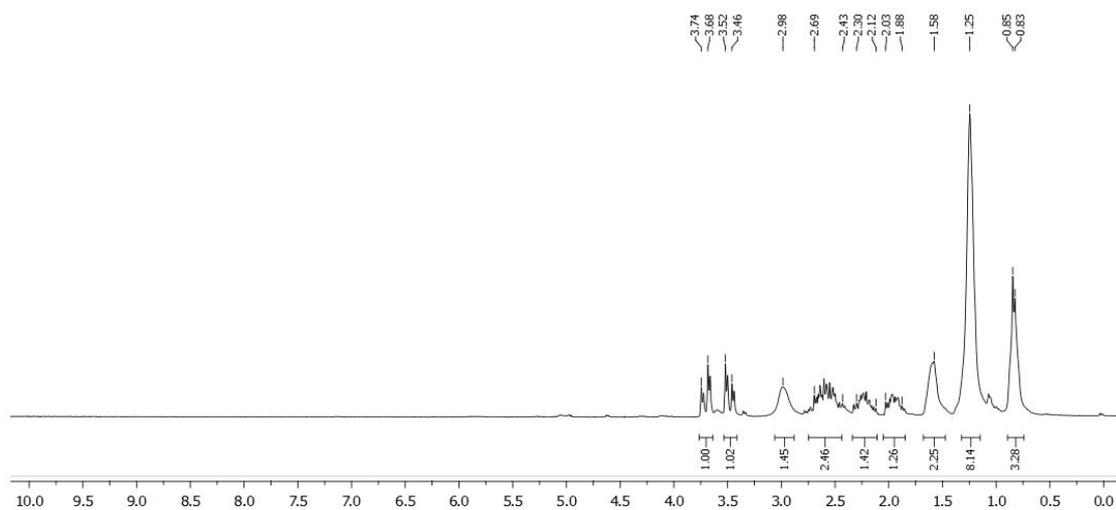
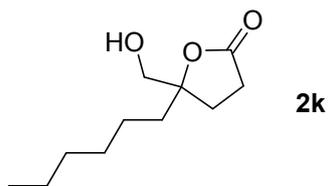


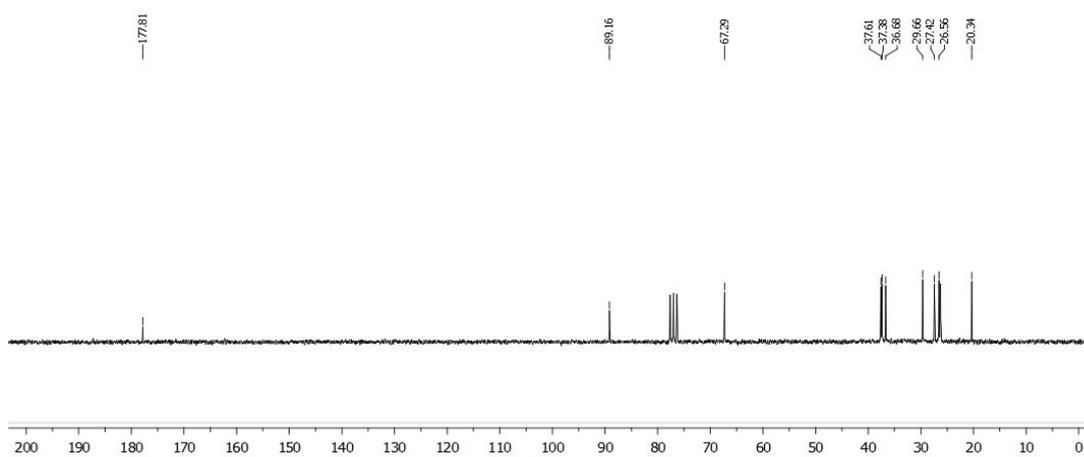
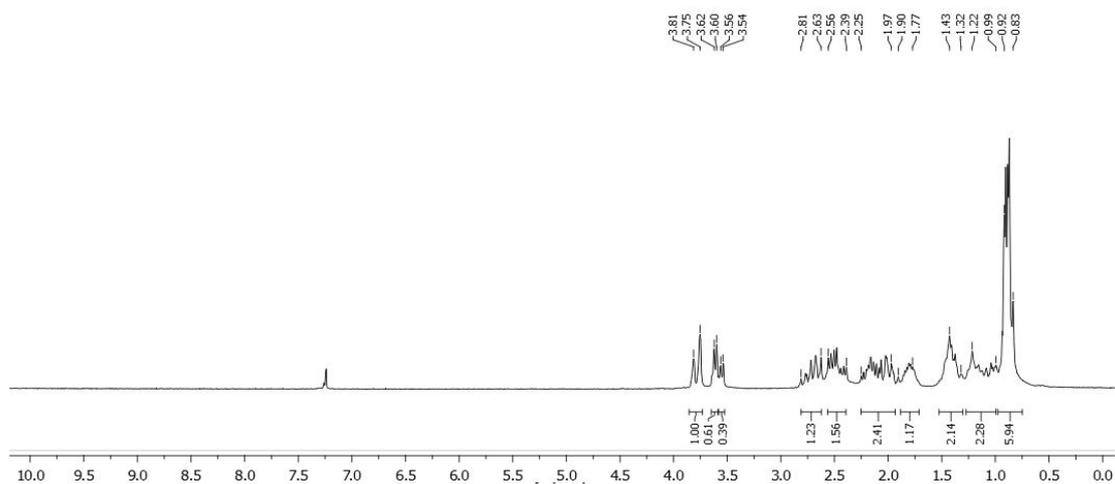
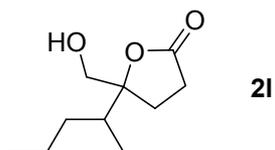


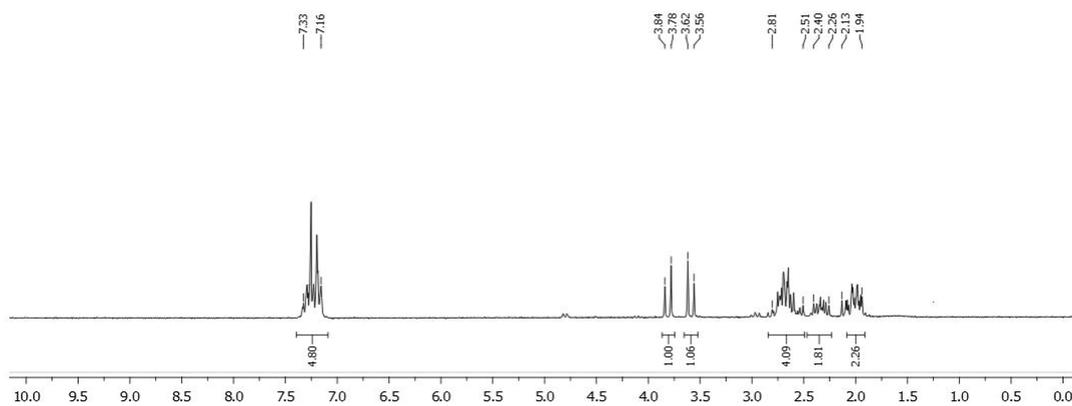
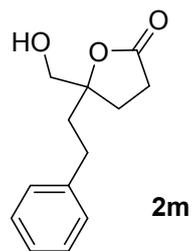


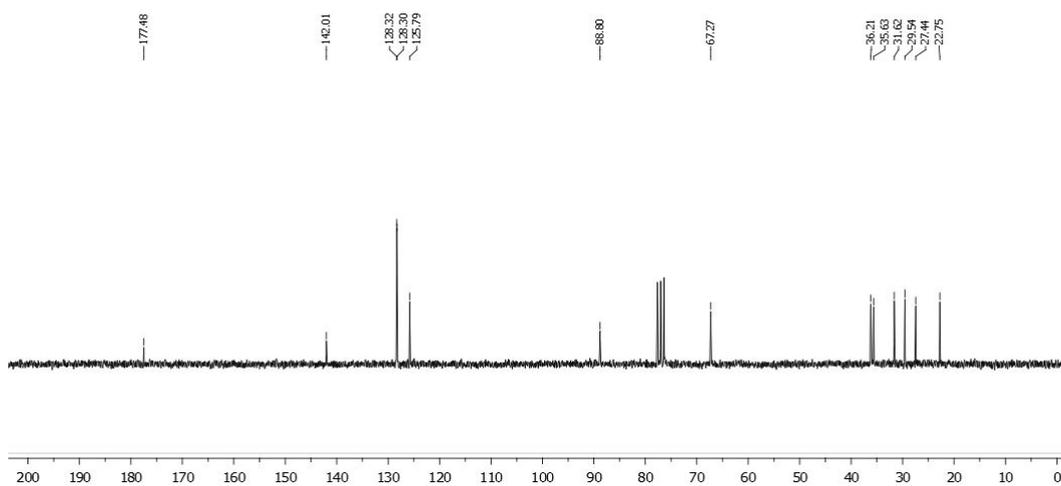
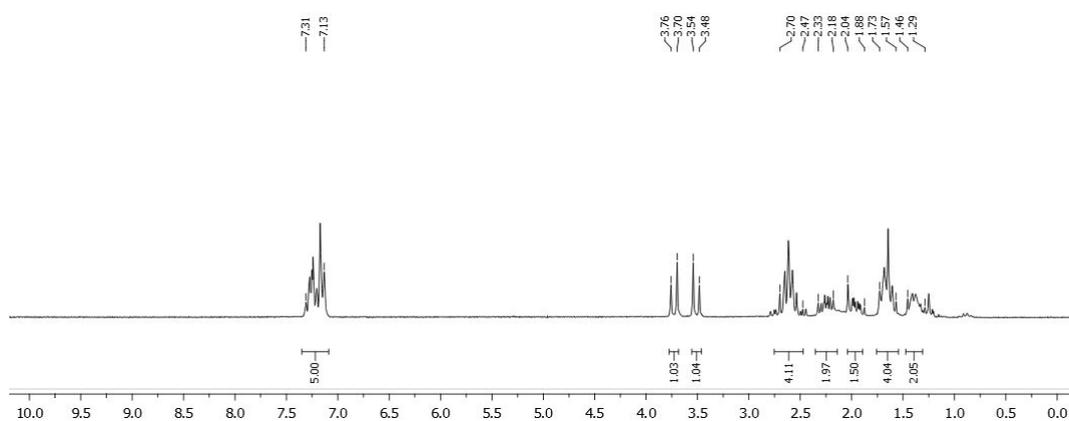
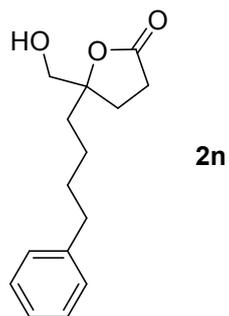




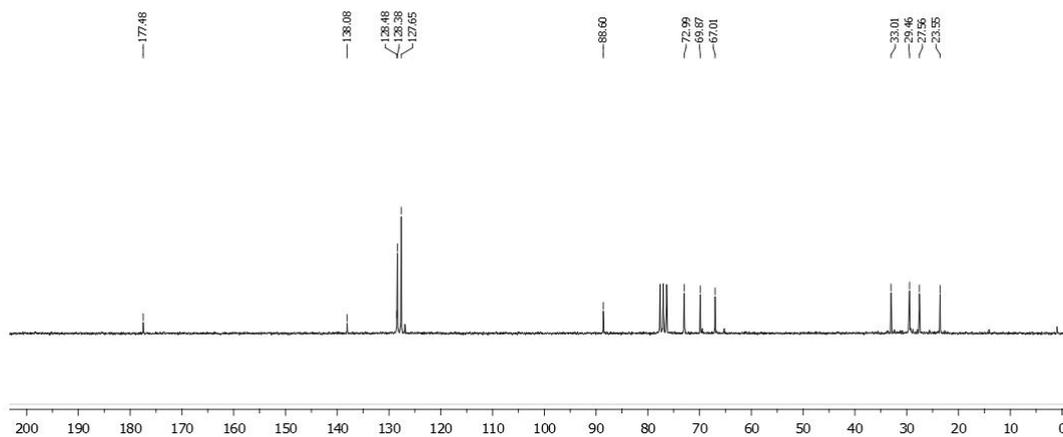
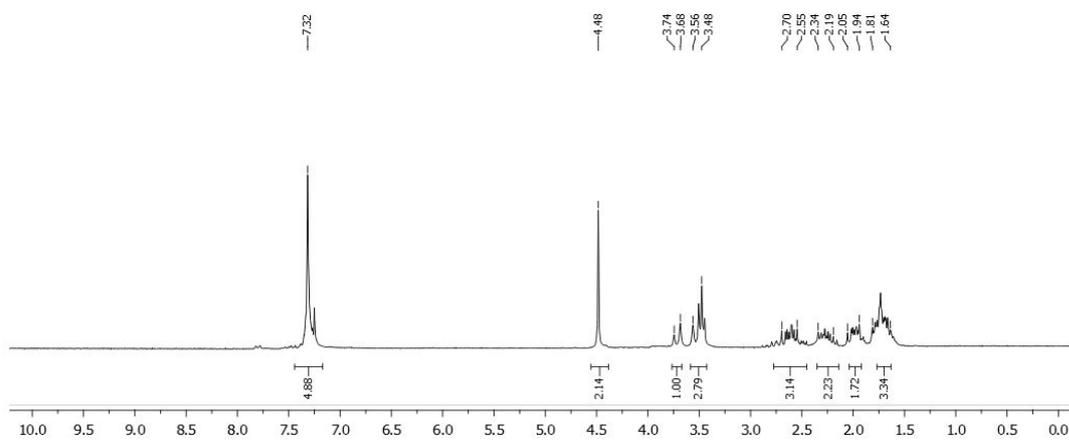
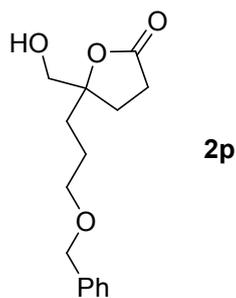


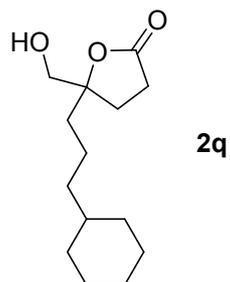










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