# **EXPERIMENTALS**

# MATERIALS AND TECHNIQUES

All materials, reagents and solvents were purchased from Alfa Aesar, Carbosynth, Sigma-Aldrich or TCI chemicals and used without further purification. All solvents were HPLC-grade. The dry solvents were obtained from Innovative Technology PS-MD-05 Pure-solv solvent purification system, except for pyridine, which was dried over 4Å molecular sieves.

Reactions requiring anhydrous conditions were carried out in oven-dried glassware under inert atmosphere, either using argon or nitrogen. Ambient temperature (r.t.) varied between 22 to 27 °C. Solvents were removed by concentration in vacuo at 40 °C. All reactions were monitored by thin-layer chromatography (TLC), performed on Merck aluminum plates pre-coated with 0.25 mm silica gel 60 F254. Compounds were visualized under UV irradiation and/or heating after applying a solution of Ce(SO<sub>4</sub>)<sub>2</sub> (2.5 g) and (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub> (6.25 g) in 10% aqueous H<sub>2</sub>SO<sub>4</sub> (250 mL) or vanilin (15g) in 10% ethanolic H<sub>2</sub>SO<sub>4</sub> (250 mL).

Column chromatography was performed using Davisil silica gel 60 (40-63  $\mu$ m, pre-neutralized from the manufacturer to pH 6.0-8.0) with specified solvents given as volume-ratio. Solvents was HPLC-grade, with exception of petroleum ether (b.p. 40-65 °C) and heptane, these were technical-grade.

NMR spectra were recorded on 500 MHz Avance III HD equipped with a cryogenically cooled 5 mmobserve-probe optimized for <sup>13</sup>C *or* 500 MHz Avance III HD equipped with a broadband-probe. Samples were dissolved in appropriate deuterated solvent and recorded at 298 K. <sup>13</sup>C NMR spectra were <sup>1</sup>H decoupled. Chemical shifts ( $\delta$ ) are reported in ppm downfield from TMS ( $\delta = 0$ ) using the solvent resonance as the internal standard, e.g. CDCl<sub>3</sub>: <sup>1</sup>H 7.26 ppm, <sup>13</sup>C 77.16 ppm. Coupling constants (*J*) are reported in Hertz (Hz), and the field is indicated in each case. Multiplicities are reported as singlet (s), doublet (d), triplet (t) and multiplet (m).

High-resolution mass spectroscopy (HRMS) was recorded on a SolariX XR 7 T ESI/MALDI-FT-ICR-MS instrument and data handled with the DataAnalysis ver 4.0 SP 4. ESI samples were dissolved in  $CH_3CN$  or mixtures hereof and  $H_2O$  with 0.1 % HCOOH. MALDI samples were dissolved  $CH_2Cl_2$  and applied with dithranol as matrix.

## SYNTHESIS

AcO AcO OAc

# 2,4,6-tri-O-acetyl-D-erythro-hex-2-enono-1,5-lactone (3)

Following the procedure of C. Pedersen<sup>1</sup>; D-glucono- $\delta$ -lactone (1.00 g) was suspended in 8 mL acetic anhydride at 23 °C and stirred for one hour. The resulting mixture was then cooled in an icebath to 0 °C before 0.80 mL trimethylamine was added slowly; the reaction mixture was allowed to reach 23 °C over the

next four hours. Hereafter, the mixture is concentrated, dissolved in ethyl acetate and washed twice with saturated NaHCO<sub>3</sub>, H<sub>2</sub>O and brine, the organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by column chromatography (1:3, diethyl ether/petroleum ether) to yield compound **1** (1.268 g, 79 %).

<u>This work:</u> Example 1: D-glucono- $\delta$ -lactone (10.00-10.14 g) was suspended in acetic anhydride (27.5-26.5 mL, 5.5 eq) together with iodine (21-12.6 mg, 0.15-0.087 mol%) and stirred overnight at 23 °C or for two hours at 50°C. The resulting clear mixture was added NaOAc (5.51 g, 1.2 eq) and heated to 60 °C, after 2.5-3.2 hours <sup>1</sup>H NMR indicates >95% conversion. The reaction mixture was then concentrated, dissolved in either EtOAc or Et<sub>2</sub>O, filtered and concentrated to yield yellow syrup, used further as is.

Example 2: D-glucono- $\delta$ -lactone (10.06 g) was suspended in acetic anhydride (22 mL, 4.2 eq) together with  $H_2SO_4$  (95%, ~30  $\mu$ L, 1 mol%) and stirred 22 °C and raised to 80 °C. After 10 minutes the reaction was complete and to the resulting clear mixture was added NaOAc (340 mg, 7.3 mol%) and heated to 90 °C, after 4.5 hours <sup>1</sup>H NMR indicates >95% conversion. The reaction mixture was used further as is.

<sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.44 (d,  $J_{3,4}^3$  = 4.2 Hz, 1H, H3), 5.62 (dd,  $J_{4,5}^3$  = 5.8 Hz, 1H, H4), 4.76 (m, 1H, H5), 4.39 (dd,  $J_{6a,6b}^2$  = 12.4 Hz,  $J_{3,6a}^3$  = 4.9 Hz, 1H, H6a), 4.30 (dd,  $J_{5,6b}^3$  = 4.4 Hz, 1H, H6b), 2.26 (s, 3H, CH<sub>3</sub><sup>OAc</sup>), 2.13 (s, 3H, CH<sub>3</sub><sup>OAc</sup>), 2.10 (s, 3H, CH<sub>3</sub><sup>OAc</sup>). <sup>13</sup>**C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.5/ 169.8/ 168.3 (3C, CO<sup>Ac</sup>), 157.3 (C1), 139.8 (C2), 126.2 (C3), 78.0 (C5), 64.3 (C4), 62.1 (C6), 20.8/ 20.8/ 20.5 (3C, CH<sub>3</sub><sup>Ac</sup>). Identical to reported <sup>1</sup>H NMR<sup>2</sup> and <sup>13</sup>C NMR<sup>1</sup> spectra.



# Methyl 5-(hydroxymethyl)furan-2-carboxylate (2)

Example 1: To a solution of 4 mL MeOH and **4** (147 mg, 0.51 mmol) at 22 °C, was added acetyl chloride (20  $\mu$ L, 0.5 eq). After stirring overnight TLC indicated full conversion, the reaction mixture was added silica and concentrated on this, purified by column chromatography (1:6 $\rightarrow$ 1:5 acetone/toluene) to yield compound **2** as yellowish oil (44.2 mg, 55 %)

Example 2: Using the above-mentioned procedures, D-glucono- $\delta$ -lactone (1.01 g), acetic anhydride (8 mL), iodine (6.8 mg) and NaOAc (533 mg). The crude syrup was dissolved in 10 mL MeOH and to this acetyl chloride (50  $\mu$ L, 0.12 eq) was added. After stirring for 3 days TLC indicated full conversion, the reaction mixture was concentrated and purified by column chromatography (1:6 acetone/toluene) to yield compound **2** as yellowish oil (612 mg, 69 %).

Example 3: Using the above-mentioned procedures, D-glucono- $\delta$ -lactone (10.03 g), acetic anhydride (70 mL), iodine (25 mg) and NaOAc (5.50 g). The crude syrup was dissolved in 50 mL MeOH and to this acetyl chloride (0.40 mL, 0.10 eq) was added. After stirring for 20 hours at 23 °C, the temperature was raised to 50 °C and TLC indicated full conversion after 24 hours at this temperature. The reaction mixture was concentrated and purified by vacuum distillation to yield compound **2** as yellow oil (4.997 g, 57 %).

Example 4: Using the above-mentioned procedures, D-glucono- $\delta$ -lactone (100.2 g), acetic anhydride (285 mL), H<sub>2</sub>SO<sub>4</sub> (96 %, 1 drop) and NaOAc (55 g). The crude syrup was dissolved in 200 mL MeOH and to this acetyl chloride (10 mL) was added. After stirring for 4 days at 23 °C, the reaction mixture was concentrated and purified by vacuum distillation to yield compound **2** as yellow oil (37.8 g, 43 %).

Example 5: Likewise, the following experiment demonstrates the versatility of acids that can be used for the transformation of a crude mixture of **3** into HMMF **2** (Table 1).

Table 1. Starting directly from D-glucono- $\delta$ -lactone (10 g), acetic anhydride (27 mL), iodine (21 mg) and NaOAc (5.5 g). The crude syrup of **4** was dissolved to 55 mL in MeOH and divided into 5 separate reaction

vessels. Loading Reaction time<sup>b</sup> Entry<sup>a</sup> Yield Acid (mol%) (days) 1  $H_2SO_4$ 10 3 47 2 HCId 10 4 44 3 IR-120 (H) 300 % <sup>w</sup>/<sub>w</sub> >10 <sup>e</sup>40 4 BF<sub>3</sub>·Et<sub>2</sub>O 10+50<sup>f</sup> 6 39 5 HBr<sup>g</sup> 10 4 34

a) All reactions were run at 22 °C; b) Based on daily TLC analysis; c) Calculated as 1/5 of the starting D-glucono- $\delta$ -lactone; d) generated *in situ* from AcCl; e) additional 5-(hydroxymethyl)furan-2-carboxylic acid (249mg, 16%) isolated; f) after five days additional 50 mol% catalyst added; g) as HBr (33 %) in AcOH.

**bp** 121-124 °C (2.1-2.4\*10<sup>-1</sup> mbar), <sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (d, <sup>3</sup>*J* = 3.5 Hz, 1H, H3), 6.41 (dt, *J* = 0.8 Hz, 1H, H4), 4.68 (d, *J*<sup>3</sup><sub>CH2,OH</sub> = 6.2 Hz, 2H, 5-methylene), 3.89 (s, 3H, CH<sub>3</sub><sup>ester</sup>), 2.14 (t, 1H, OH). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  159.3 (CO<sup>ester</sup>), 158.4 (C5), 144.2 (C2), 119.0 (C3), 109.6 (C4), 57.7 (5-methylene), 52.1 (CH<sub>3</sub><sup>ester</sup>). Identical to reported <sup>1</sup>H NMR<sup>3,4</sup> and <sup>13</sup>C NMR<sup>3</sup> spectra.

HO

## 5-(hydroxymethyl)furoic acid (3)

*Example 1;* D-glucono- $\delta$ -lactone (20.5 g, 115 mmol) was suspended in acetic anhydride (56 mL, 0.59 mol) together with freshly washed Amberlite<sup>®</sup> IR-120 (H) and stirred for 30 minutes at 60 °C. The resulting clear

mixture was filtered and NaOAc (10.7 g, 131 mmol) was added at 60 °C, stirred overnight at 40 °C and heated to 60 °C, after 3 hours <sup>1</sup>H NMR indicates >95% conversion. The reaction mixture was cooled to room temperature, filtered and everything washed twice with 25 mL toluene then concentrated, this was suspended in 25 mL toluene, filtered, washed twice with 10 mL toluene and concentrated again to yield yellow syrup of compound **4**. This was dissolved in 70 mL MeOH together with AcCl (0.82 mL, 11.5 mmol) and refluxed until TLC indicated full conversion. The mixture was cooled and 0.8 M HCl (22 mL) was added to the solution, this mixture was refluxed for 30 minutes and 10 mL of H<sub>2</sub>O/MeOH mixture was distilled off. The mixture was further concentrated to give a black solid that was crystalized from acetone and filtered twice to give a combined yield of 4.50 g (28 %) 5-(hydroxymethyl)furoic acid (HMFA) **3**, as off-white crystals.

<sup>1</sup>**H NMR** (500 MHz, MeOD)  $\delta$  7.12 (d, *J* = 3.5 Hz, 1H, H3), 6.43 (d, *J* = 3.5 Hz, 1H, H4), 4.54 (s, 2H, 5-methylene). <sup>13</sup>**C NMR** (126 MHz, MeOD)  $\delta$  = 161.8 (C1<sup>co</sup>), 160.5 (C5), 145.5 (C2), 120.0 (C3), 110.3 (C4), 57.4 (5-methylene). Identical to reported NMR spectra.<sup>5</sup>



Ethyl 5-(hydroxymethyl)furan-2-carboxylate (5)

A crude syrup of **4** (1.180 g) was dissolved in 10 mL Absolut EtOH and to the resulting mixture was added AcCl (58  $\mu$ L, 0.2 eq) at 22 °C. After 3 days, TLC analysis indicated full conversion of the starting material and the reaction mixture was concentrated, dissolved in acetone and concentrated on silica. This material was purified by column chromatography (1:5 $\rightarrow$ 1:3 $\rightarrow$ 4:6 acetone/toluene) to give the title compound **5** (240 mg, 34 %). Besides **5**, the following was also isolated, 5-(hydroxymethyl)furan-2-carboxylic acid (98 mg, 17 %), 2,4-di-O-acetyl-D-erythro-hex-2-enono-1,5-lactone (26 mg, 2.6 %) and 2-O-acetyl-D-erythro-hex-2-enono-1,5-lactone (56 mg, 6.6 %).

<sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.11 (d, *J* = 3.5 Hz, 1H, H3), 6.40 (d, *J* = 3.5 Hz, 1H, H4), 4.67 (s, 2H, 5-methylene), 4.35 (q, *J* = 7.1 Hz, 2H, H1<sup>Et</sup>), 2.24 (br s, 1H, HO<sup>methylene</sup>), 1.36 (t, *J* = 7.1 Hz, 3H, H2<sup>Et</sup>). <sup>13</sup>**C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  158.9 (C5), 158.3 (CO<sup>ester</sup>), 144.5 (C2), 118.8 (C3), 109.5 (C4), 61.2 (CH<sub>2</sub><sup>Et</sup>), 57.7 (5-methylen), 14.5 (CH<sub>3</sub><sup>Et</sup>). **HRMS** (ESP-TOF) m/z for C<sub>8</sub>H<sub>10</sub>NaO<sub>4</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 193.0471; found: 193.0478.



#### Allyl 5-(hydroxymethyl)furan-2-carboxylate (6)

A crude syrup of **4** (505 mg) was dissolved in 5.0 mL allyl alcohol and to the resulting mixture was added AcCl (60  $\mu$ L) at 22 °C. After 2 days, TLC analysis indicated full conversion of the starting material. The mixture was concentrated, dissolved in acetone and concentrated on silica. This material was purified by column chromatography (1:6 $\rightarrow$ 1:5 acetone/toluene) to give 5-(hydroxymethyl)furan-2-carboxylic acid (48 mg, 19 %) and the title compound **6** (82 mg, 25 %).

<sup>1</sup>**H NMR** (500 MHz, CDCl3)  $\delta$  7.16 (d, J = 3.4 Hz, 1H, H3), 6.42 (d, J = 3.4 Hz, 1H, H4), 6.00 (ddt, J = 17.2, 10.5, 5.8 Hz, 1H, H2<sup>All</sup>), 5.40 (dq, J = 17.2, 1.5 Hz, 1H, H3<sup>trans-H-All</sup>), 5.29 (dq, J = 10.3, 1.3 Hz, 1H, H3<sup>cis-H-All</sup>), 4.80 (dt, J = 17.2, 1.5 Hz, 1H, H3<sup>trans-H-All</sup>), 5.29 (dq, J = 10.3, 1.3 Hz, 1H, H3<sup>cis-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>cis-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 5.29 (dq, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, H3<sup>trans-H-All</sup>), 4.80 (dt, J = 10.3, 1.3 Hz, 1H, 1H), 4.80 (dt, H3<sup>trans-H-All</sup>), 4.80 (dt, H3<sup>trans-H</sup>), 4.80 (dt, H3<sup>trans-H</sup>

= 5.8, 1.4 Hz, 2H, H1<sup>All</sup>), 4.68 (d, J = 5.7 Hz, 2H, 5-methylene), 2.03 (t, J = 6.3 Hz, 1H, HO<sup>methylene</sup>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 158.5 (2C, C5, CO<sup>ester</sup>), 144.2 (C2), 131.9 (C2<sup>All</sup>), 119.1 (C3), 119.0 (C3<sup>All</sup>), 109.6 (C4), 65.7 (C1<sup>All</sup>), 57.8 (5-methylene). HRMS (ESP-TOF) m/z for C<sub>9</sub>H<sub>10</sub>NaO<sub>4</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 205.0471; found: 205.0478.



#### Butyl 5-(hydroxymethyl)furan-2-carboxylate (7)

A crude syrup of **4** (516 mg) was dissolved in 5.0 mL 1-butanol and to the resulting mixture was added AcCl (60  $\mu$ L) at 22 °C, the mixture was initially heated to allow the starting material to fully dissolve. After 2 days TLC analysis indicated full conversion of the starting material and the reaction mixture was concentrated, dissolved in acetone and concentrated on silica. This material was purified by column chromatography (1:6 $\rightarrow$ 1:5 acetone/toluene) to give the title compound **7** (133 mg, 37 %) and 5-(hydroxymethyl)furan-2-carboxylic acid (65 mg, 26 %).

<sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.11 (d, *J* = 3.5 Hz, 1H, H3), 6.41 (d, *J* = 3.4 Hz, 1H, H4), 4.67 (d, *J* = 5.3 Hz, 2H, 5-methylene), 4.30 (t, *J* = 6.7 Hz, 2H, H1<sup>nBu</sup>), 2.11 (br t, *J* = 5.3 Hz, 1H, HO<sup>methylene</sup>), 1.72 (p, *J* = 6.8 Hz, 2H, H2<sup>nBu</sup>), 1.44 (h, *J* = 7.4 Hz, 2H, H3<sup>nBu</sup>), 0.96 (t, *J* = 7.4 Hz, 3H, H4<sup>nBu</sup>). <sup>13</sup>**C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  159.0 (C5), 158.3 (CO<sup>ester</sup>), 144.5 (C2), 118.7 (C3), 109.5 (C4), 65.0 (C1<sup>nBu</sup>), 57.8 (5-methylene), 30.9 (C2<sup>nBu</sup>), 19.3 (C3<sup>nBu</sup>), 13.9 (C4<sup>nBu</sup>). **HRMS** (ESP-TOF) m/z for C<sub>10</sub>H<sub>14</sub>NaO<sub>4</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 221.0784; found: 221.0792.



#### sec-Butyl 5-(hydroxymethyl)furan-2-carboxylate (8)

A crude syrup of **4** (476 mg) was dissolved in 5.0 mL 2-butanol and to the resulting mixture was added AcCl (60  $\mu$ L) at 22 °C, the mixture was initially heated to allow the starting material to fully dissolve. After 2 days, with little conversion, the reaction mixture was heated to 70 °C overnight and TLC analysis indicated full conversion of the starting material. The mixture was concentrated, dissolved in acetone and concentrated on silica. This material was purified by column chromatography (1:6 $\rightarrow$ 1:5 acetone/toluene) to give title compound **8** (49 mg, 15 %) and 5-(hydroxymethyl)furan-2-carboxylic acid (69 mg, 29 %).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.10 (d, *J* = 3.4 Hz, 1H, H3), 6.40 (d, *J* = 3.4 Hz, 1H, H4), 5.06 (h, *J* = 6.3 Hz, 1H, H2<sup>sBu</sup>), 4.67 (s, 2H, 5-methylene), 1.77 – 1.57 (m, 2H, H3<sup>sBu</sup>), 1.31 (d, *J* = 6.3 Hz, 3H, H1<sup>sBu</sup>), 0.95 (t, *J* = 7.5 Hz, 3H, H4<sup>sBu</sup>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 158.6 (C5), 158.0 (CO<sup>ester</sup>), 144.7 (C2), 118.3 (C3), 109.4 (C4), 73.2 (C2<sup>sBu</sup>), 57.6 (5-methylene), 28.9 (C3<sup>sBu</sup>), 19.6 (C1<sup>sBu</sup>), 9.7 (C4<sup>sBu</sup>). HRMS (ESP-TOF) m/z for C<sub>10</sub>H<sub>14</sub>NaO<sub>4</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 221.0784; found: 221.0792.

2,5-Furandicarboxylic acid, FDCA (1)

Example 1: HMMF, **2** (220 mg, 1.41 mmol, 1.0 eq) was dissolved in solution made of  $H_2O$  (15 ml) and NaOH (1.30 g, 32.43 mmol, 23.0 eq). KMnO<sub>4</sub> (512 mg, 3.24 mmol, 2.3 eq.) was added under stirring and this was continued for 30 minutes at 22 °C. The reaction mixture was filtered to remove  $Mn_2O$ , the flask and filter-cake was washed with 10 mL  $H_2O$ . Afterwards, 37 % HCl (aq.) was added to the filtrate (pH 1). The precipitate was separated by filtration, washed with water and dried to produce compound **1** (165 mg, 75 %).

Example 2: HMMF, **2** (700 mg, 4.5 mmol) as dissolved in 1,2-dichloroethane (4 mL), then  $Fe(NO_3)_3 \cdot 9H_2O$  (362 mg, 0.90 mmol), TEMPO (140 mg, 0.90 mmol) and KCI (33 mg, 0.44 mmol) was added. The flask was sealed with a rubber septum and an  $O_2$  balloon was added. The reaction progress was followed by NMR, this indicated the starting material was converted into aldehyde within one day. Full conversion into the carboxylic acid was first obtained after 7 days. The mixture was concentrated and dissolved in 0.1M NaOH, the insoluble residue was removed by filtration. The filtrate was acidified using 37 % HCl until pH $\approx$ 1. The desired product precipitated as yellow solid (23 % as mixture of 2,5-furandicarboxylic acid methyl ester and FDCA **1**, 4:1).

Example 3: Similar conditions to example 2; starting from 5.2 g of HMMF, **2** (33 mmol) resulted in a yellow solid (42 % as mixture of 2,5-furandicarboxylic acid methyl ester and FDCA **1**).

<sup>1</sup>**H NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  13.61 (br, 2H, H<sup>carboxylic acid</sup>), 7.29 (s, 2H, H3, H4). <sup>13</sup>**C NMR** (126 MHz, DMSO-d<sub>6</sub>)  $\delta$  158.88 (CO<sup>carboxylic acid</sup>), 147.01 (C2, C5), 118.40 (C3, C4). **HMRS** (ESP-TOF) m/z for C<sub>6</sub>H<sub>5</sub>O<sub>5</sub><sup>+</sup> (MH<sup>+</sup>) calculated: 157.0131, found: 157.0362; for C<sub>6</sub>H<sub>4</sub>NaO<sub>5</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 178.9951, found: 178.9963.



## Methyl 5-(chloromethyl)furan-2-carboxylate (9)

Example 1: D-glucono- $\delta$ -lactone (20.06 g, 112.6 mmol) was suspended in Ac<sub>2</sub>O (55 mL, 582 mmol) then catalytic amount of I<sub>2</sub> (23 mg, 0.09 mol%) was added and stirred for 45 minutes at 55 °C, when the solution cleared and TLC indicates full conversion. The resulting mixture was added NaOAc (11.0 g, 134 mmol) and heated to 60°C, after 3.5 hours, <sup>1</sup>H NMR indicates >95% conversion. The reaction mixture was then concentrated, dissolved in either EtOAc or Et<sub>2</sub>O, filtered and concentrated to yield yellow syrup (31.58 g), used further as is. From this crude 4, 18.03 g (~63 mmol) was dissolved in 100 mL MeOH, and AcCl (10 mL, 140 mmol) was added slowly to the mixture, through a reflux condenser, a considerable amount of heat is produced during this step. After 20 minutes TLC indicates full conversion and the reaction mixture is concentrated, and redissolved in 50 mL MeOH and stirred overnight at 22 °C. The mixture was concentrated and taken up in aqueous 37 % HCl (42 mL) and catalytic amount of H<sub>2</sub>SO<sub>4</sub> (95 %, 20 µL) was added. The reaction mixture was heated to 50 °C for 1 hour and allowed to cool before 8 g NaCl was added to the solution. This was then poured into a separation funnel and extracted eight times by 30 mL CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were washed with H<sub>2</sub>O, brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dark orange oil (7.11g). This was purified by vacuum distillation to give the product 4 (4.38 g, 40 %) as yellow oil that solidifies upon storage at 4 °C and the corresponding acid (485 mg, 4.8 %) was isolated as a colorless sublimed crystalline solid on the sides of the distillation apparatus.

Example 2: HMMF, **2** (0.90 g, 5.76 mmol, 1.0 eq) was dissolved in 5 eq. HCl (37%, aq) and heated for 1 h at 50 °C. Afterwards, the reaction mixture was quenched with 30 mL Et<sub>2</sub>O, washed twice with water (5 mL), once with brine (5 mL), dried with MgSO<sub>4</sub>, filtered and concentrated. The crude product was purified by column chromatography (1:9 acetone/toluene) to yield compound **4** as yellowish oil (0.62 g, 62 %).

**bp** 80-82 °C (1.6-1.8\*10<sup>-1</sup> mbar), <sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.13 (d, <sup>3</sup>*J* = 3.5 Hz, 1H, H3), 6.49 (d, <sup>3</sup>*J* = 3.5 Hz, 1H, H4), 4.59 (s, 2H, CH<sub>2</sub><sup>chloromethyl</sup>), 3.90 (s, 3H, CH<sub>3</sub><sup>ester</sup>). <sup>13</sup>**C NMR** (126 MHz, CDCl<sub>3</sub>) δ = 158.9 (CO<sup>ester</sup>), 154.3 (C5), 144.9 (C2), 119.0 (C3), 111.5 (C4), 52.2 (CH<sub>3</sub><sup>ester</sup>), 36.8 (CH<sub>2</sub><sup>chloromethyl</sup>). **HRMS** (ESP-TOF) m/z for C<sub>7</sub>H<sub>7</sub>NaClO<sub>3</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 175.0156; found: 175.0156. Identical to reported NMR spectra.<sup>6</sup>



Methyl 5-(bromomethyl)furan-2-carboxylate (10)

HMMF, **2** (2.91 g, 18.64 mmol, 1.0 eq) was dissolved in 5 eq. HBr (47%, aq) and stirred for 115 hours at room temperature. The reaction mixture was diluted with 10 mL H<sub>2</sub>O and extracted three times with EtOAc (30 mL). The combined organic phases were washed twice with water (15 mL), twice with brine (15 mL), dried with MgSO<sub>4</sub>, filtered and concentrated. The crude product was purified by column chromatography (1:5 EtOAc/Heptane) to yield compound **10** as colorless oil (3.37 g, 83 %).

<sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.12 (d, <sup>3</sup>*J* = 3.4 Hz, 1H, H3), 6.49 (d, <sup>3</sup>*J* = 3.4 Hz, 1H, H4), 4.48 (s, 2H, CH<sub>2</sub><sup>bromomethyl</sup>), 3.90 (s, 3H, CH<sub>3</sub><sup>ester</sup>). <sup>13</sup>**C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  158.8 (CO<sup>ester</sup>), 154.3 (C5), 144.8 (C2), 119.0 (C3), 111.5 (C4), 52.1 (CH<sub>3</sub><sup>ester</sup>), 21.9. **HMRS** (ESP-TOF) m/z for C<sub>7</sub>H<sub>8</sub>ClO<sub>3</sub><sup>+</sup> (MH<sup>+</sup>) calculated: 218.9651, found: 218.9650; for C<sub>7</sub>H<sub>7</sub>NaBrO<sub>3</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 240.9471, found: 240.9469.



N,N,N',N'-tetrakis(methyl 2-carboxyfuran-5-methylene)-ethane-1,2-diamine (11)

HMMF **2** (3,35g, 15,28 mmol, 1,0 eq) was dissolved in 40 mL DMF together with ethylenediamine (0.26 mL, 3.8 mmol 0.25 eq), to the resulting mixture,  $Na_2CO_3$  (1.94 g, 18.3 mmol, 1.2 eq) was added in portions and the mixture was stirred at room temperature. Full conversion of the starting material was observed after 20 hours, the reaction mixture was stirred for a total of 43 hours. The reaction mixture was diluted with water (50 mL) and extracted twice with EtOAc (50 mL). The combined organic phases were washed with water (30 mL), twice with brine (30 mL), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by recrystallization from EtOAc/Heptane to yield **11** (1.36 g, 58 %).

<sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.11 (d, <sup>3</sup>*J*=3.3, 4H, H3), 6.36 (br s, 4H, H4), 3.86 (s, 12H, CH<sub>3</sub><sup>ester</sup>), 3.76 (s, 8H, 5-methylene), 2.69 (s, 4H, ethylene). <sup>13</sup>**C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 159.2 (CO<sup>ester</sup>), 157.1 (C5), 144.0 (C2), 119.0 (C3), 111.0 (C4), 52.0 (CH<sub>3</sub><sup>ester</sup>), 51.6 (ethylene), 50.7 (5-methylene). **HMRS** (ESP-TOF) m/z for C<sub>30</sub>H<sub>33</sub>O<sub>12</sub>N<sub>2</sub><sup>+</sup> (MH<sup>+</sup>) calculated: 613.2028, found: 613.20280; for C<sub>30</sub>H<sub>32</sub>NaO<sub>12</sub>N<sub>2</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 635.1847, found: 635.18514.



N,N'-(ethane-1,2-diyl)bis(5-(hydroxymethyl)furan-2-carboxamide) (12)

HMMF **2** (0.1842 g, 1.180 mmol, 1.0 eq) was dissolved in MeOH (1.5 mL). To this mixture ethylenediamine (0.790 ml, 11.80 mmol, 10 eq) was added and the mixture was stirred at room temperature for 17h. The reaction mixture was concentrated to yield crude N-(2-aminoethyl)-5-(hydroxymethyl)furan-2-carboxamide. This crude was dissolved in MeOH (1.0 mL) and 0.50 mL solution of HMMF (0.3801 g HMMF **2** in 1.03 mL MeOH) was added together with NEt<sub>3</sub> (16  $\mu$ L, 0.118 mmol, 0.1 eq). The mixture was stirred at room temperature for 18h and then at 50 °C for 25h. When TLC showed full conversion the mixture, was concentrated and purified by column chromatography (8:1 EtOAc/MeOH) to yield compound **12** (0.0943 g, 26 %).

<sup>1</sup>**H NMR** (500 MHz, DMSO)  $\delta$  = 8.38 (t, <sup>3</sup>*J*=5.4, 2H, NH<sup>amide</sup>), 7.01 (d, <sup>3</sup>*J*=3.3, 2H, H3), 6.41 (d, <sup>3</sup>*J*=3.3, 2H, H4), 5.36 (t, <sup>3</sup>*J*=5.8, 2H, HO<sup>5-methylene</sup>), 4.43 (d, <sup>3</sup>*J*=5.7, 4H, 5-methylene), 3.35 (d, <sup>3</sup>*J*=5.6, 4H, ethylene). <sup>13</sup>**C NMR** (126 MHz, DMSO)  $\delta$  = 158.0, 157.5 (CO<sup>amide</sup>, C5), 146.9 (C2), 113.9 (C3), 108.7 (C4), 55.8 (5-methylene), 38.4 (ethylene). **HMRS** (MALDI-TOF) m/z for C<sub>14</sub>H<sub>16</sub>NaO<sub>6</sub>N<sub>2</sub><sup>+</sup> (MNa<sup>+</sup>) calculated: 331.0901, found: 331.08974.

#### COLLECTED DATA FROM MONITORING KINETICS BY NMR



Scheme S1. Conversion of peracetylated gluconolactone 13 into the mono-eliminated intermediate 4.

**Base catalyzed elimination** (Part 1) Per acetylated gluconolactone **13** (0.0338 g, 0.0976 mmol, 1.0 eq), NaOAc (0.0097 g, 0.1182 mmol, 1.2 eq), and mesitylene (1.4  $\mu$ L, 0.0101 mmol, 0.1 eq) were added together to a NMR tube and dissolved in AcOD-d<sub>3</sub> (0.50 mL). The mixture was sonicated at 50 <sup>o</sup>C (temperature fluctuated) and <sup>1</sup>H NMR was recorded at the appropriate times.

Based on these experimental data on the conversion from compound 13 to 4, this these both fits a first-order reaction kinetics. The results are shown below.



Figure S1. Conversion of peracetylated gluconolactone 13 (Green curve – corresponds to compound 13 and equation Y1') into the mono-eliminated intermediate 4 (Red curve – corresponds to compound 4 and equation Y').

# $\mathbf{Y}' = \mathbf{B} + \mathbf{F}^* \exp(-\mathbf{t}^* \mathbf{G})$

B=6.205e+4; F=-6.243e+4; G=0.006155; Error: 0.0002747

# $Y1' = B + F^* exp(-t^*G)$

B=-3328; F=7.813e+4; G=0.005037; Error: 0.0002367



6.65 6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 fl (ppm)

t, min	I <sub>1</sub>	Γ <sub>1</sub>	l <sub>2</sub>	ľ <sub>2</sub>
0	263.58	-374.82	71619.40	73728.88
10	4326.05	3351.36	69429.68	70059.80
20	7078.50	6855.12	66707.73	66563.60
30	9931.82	10149.74	64145.66	63232.13
50	15294.05	16160.75	58779.22	57032.70
80	21429.22	23897.50	49759.46	48786.55
110	29811.74	30329.88	43627.83	41651.96
140	35992.00	35677.79	35902.65	35479.09
200	45869.08	43820.73	21136.95	25517.46
290	51034.01	51573.87	14792.96	15067.64
380	58655.09	56029.57	8704.60	8299.61
470	59214.94	58590.24	3774.28	3916.17
560	57223.51	60061.85	2032.29	1077.15

**t** – total time of sonication.  $I_1$ ,  $I'_1$  – measured and calculated (by equation) intensity of the peaks for **4**.  $I_2$ ,  $I'_2$  – measured and calculated (by equation) intensity of the peaks for **13**.



Scheme S2. By extending the observation for the conversion of above we were able to observe the conversion of mono-eliminated intermediate 4 into the pyranone side-product 14.

**Base catalyzed elimination** (Part 2) The double eliminated side-product 14 was observed in the same experiment. This was followed by extending the observation period. However, two side-products was observed, where only one was identified as 14.

The conversion of 4 fits best a first-order reaction, while side-product 14 is zero-order. However compound **B** does not fit any order of reaction, but appear to reach a steady-state.



Figure S2. By extending the observation for the conversion of above we were able to observe the conversion of mono-eliminated intermediate 4 (Red curve – corresponds to 4 and equation Y') into the pyranone side-product 14 (Yellow curve - corresponds to side-product 14 and equation Y1) and unknown side-product B (Green curve – corresponds to side-product B and equation Y2').

**Y' = B+F\*exp(-X\*G)** B=-1.152e+4; F=8.203e+4; G=0.0003115; Error: 0.00005337

**Y1' = A+B\*X** A=-2205; B=11.41; Error: 1560

# $Y2' = B + F^* exp(-X^*G)$

B=1.279e+4; F=-1.370e+4; G=0.001636;	
Error: 0.0002478	

t, min	I <sub>1</sub>	$\Gamma_1$	I <sub>2</sub>	$\Gamma_2$	I <sub>3</sub>	Γ <sub>3</sub>
560	56521.756	57385.268	2452.899	1989.482	7161.483	7306.824
650	54674.496	55480.213	3774.861	3759.096	7977.833	8057.036
740	54657.408	53627.832	4978.476	5436.225	8682.856	8704.544
860	52359.339	51237.415	6792.996	7536.847	9516.463	9432.144
1040	47709.602	47815.247	10452.819	10418.895	10841.135	10287.782
1130	45939.506	46174.796	12198.292	11747.96	10937.974	10629.9
1310	43233.338	43028.712	15127.734	14201.335	11221.521	11180.039
1490	40230.808	40054.197	16473.468	16404.969	11505.628	11589.861
1610	38974.878	38161.861	16852.8	17747.977	10801.011	11803.198
1970	32031.247	32891.388	21240.696	21245.613	12069.97	12240.968
2150	29186.227	30469.702	22882.17	22732.172	12169.399	12380.19
2510	25406.582	26015.32	25313.184	25266.721	12696.296	12561.161
2700	25275.002	23858.238	26347.368	26400.472	13213.521	12621.442

**t** – total time of sonication.  $\mathbf{I}_1, \mathbf{I}_1 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for **4.**  $\mathbf{I}_2$ ,  $\mathbf{I}_2 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{m}$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{I}_3$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{I}_3$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{I}_3$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{I}_3$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{I}_3$  measured and calculated (by equation) intensity of the peaks for side-product **14.**  $\mathbf{I}_3, \mathbf{I}_3 - \mathbf{I}_3$  measured and calculated (by equation) intensi

In the graphs below, compound 4 and 14 corresponds to the number 9 and A, respectively.











Acid catalysed HMMF formation: Compound 4 (0.0280 g, 0.0978 mmol, 1.0 eq), AcCl (0.75  $\mu$ L, 0.0106 mmol, 0.1 eq), and mesitylene (1.4  $\mu$ L, 0.0101 mmol, 0.1 eq) were added together to a NMR-tube and dissolved in MeOD-d<sub>3</sub> (0.50 mL). The mixture was sonicated at 50 °C (temperature fluctuated) and <sup>1</sup>H NMR was recorded at the reported times. Results are shown below.



Scheme S4. Formation of HMMF 2 (Red curve – corresponds to HMMF 2 and equation Y') from mono-eliminated intermediate 4 (Yellow curve – corresponds to compound 4 and equation Y1') in deuterated methanol.

**Y' = B+F\*exp(-X\*G)** B=1.195e+5; F=-1.203e+5; G=0.008519; Error: 0.0004071

**Y1' = B+F\*exp(-X\*G)** B=7015; F=1.391e+5; G=0.03877; Error: 0.002301



t, min	l <sub>3</sub>	l <sub>3</sub> ′	I <sub>4</sub>	I <sub>4</sub> ′
0	857.917	-880.294	151431.3	146143.3
10	7922.238	8946.225	92936.028	101430.43
20	16408.506	17970.296	68993.84	71087.307
40	33261.792	33867.86	39617.734	36521.955
60	48237.091	47275.001	27490.502	20603.657
90	66604.24	63552.606	14414.081	11261.644
120	73014.612	76159.234	10136.739	8342.04
150	83629.848	85922.775	7653.905	7429.593
180	97320.493	93484.41	4719.231	7144.432
240	103510.86	103876.3	3538.251	7027.46
280	107780.9	108374.09	3077.686	7017.484

t – total time of sonication.

 $I_{3,}$   $I'_{3}$  – measured and calculated (by equation) intensity of the peaks for HMMF 2.

 $I_{4,}$   $I'_{4}$  – measured and calculated (by equation) intensity of the peaks for compound 4.

In the graphs below, HMMF 2 and compound 4 corresponds to the numbers 1 and 9 respectively.







Based on the obtained data, the consumption of compound **4** fits best a first-order reaction. The HMMF **2** formation does not fits any order of reaction. This suggests that formation of HMMF from compound **4** goes through one or more intermediates states with different order of reaction. After full conversion of the starting material, a formation of a side-product corresponding to the deacetylated 2-*H*-pyranone derivative of **14**, in a ratio with HMMF **2** of 1:4.5 (2-*H*-pyranone/**2**) was observed. This suggests that the formation pyranone is present under acidic conditions, similar to how **14** was observed under the basic elimination conditions (part 2 above) and probably account for most loss of yield in these reactions.

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1.00-[

7.0

7.5

8.0

13C NMR (126 MHz, CDC)

.0 8.5













90 80 f1 (ppm) 



90 80 f1 (ppm) 

