

*Supporting Information*  
for  
**Convenient Large-Scale Synthesis of D-Glucaro-1,4:6,3 dilactone**

**Troy C. Gehret, A. Stephen Frobese, James S. Zerbe and H. Keith Chenault\***

Central Research & Development, E. I. DuPont de Nemours & Co., Experimental Station,  
Wilmington, Delaware 19880

phone: 302-695-7861; e-mail: [h-keith.chenault@usa.dupont.com](mailto:h-keith.chenault@usa.dupont.com)

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## Materials and Methods:

Calcium D-glucarate tetrahydrate (D-saccharic acid, calcium salt), sulfuric acid, acetone and methyl isobutyl ketone (MiBK) were reagent grade and were used without further purification.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained at nominal resonance frequencies of 500 and 126 MHz, respectively, using acetone- $d_6$  as the solvent. Chemical shifts ( $\delta$ ) relative to tetramethylsilane were determined using residual acetone- $d_5$  ( $\delta_{\text{H}}$  2.06,  $\delta_{\text{C}}$  29.8) as the reference.  $^1\text{H}$  and  $^{13}\text{C}$  NMR peak assignments were determined by a combination of Heteronuclear Multiple Quantum Coherence (HMQC) and Heteronuclear Multiple Bond Coherence (HMBC) 2-dimensional NMR experiments. Capillary GC analysis was performed on a J&W DB-17MS column (length 30 m, inner diameter 0.32 mm, film thickness 0.25  $\mu\text{m}$ ) with helium at 35  $\text{cm sec}^{-1}$  as the carrier gas; injector/detector temperature 300  $^{\circ}\text{C}$ ; oven temperature 120-150  $^{\circ}\text{C}$  at 5  $^{\circ}\text{C}/\text{min}$ , 150-170  $^{\circ}\text{C}$  at 20  $^{\circ}\text{C}/\text{min}$ , hold 3 min, 170-300  $^{\circ}\text{C}$  at 20  $^{\circ}\text{C}/\text{min}$ , hold 3.5 min. Before GC analysis, samples were exhaustively silylated by combining under nitrogen about 5 mg of sample, 1 mL of anhydrous *N,N*-dimethylacetamide, about 5 mg of xylitol as internal standard and 0.1-0.2 mL of a 4:1 v/v mixture of *N,O*-bis(trimethylsilyl)trifluoroacetamide and chlorotrimethylsilane and allowing the derivatization reaction to sit at room temperature for 30 min.

## Experimental Procedures

**Synthesis of 1 by sparging with dry nitrogen (160-g scale).** Sulfuric acid (50.0 g, 0.500 mole) was added over a period of 30 min to a stirred suspension of calcium D-glucarate tetrahydrate (160.15 g, 0.500 mole) in 500 mL of 95:5 (v/v) acetone-water. The stirred mixture was heated at reflux for 4 h, allowed to cool to room temperature, stirred at room temperature for 1-2 h, and then filtered with suction to remove the precipitated calcium sulfate. At no time did the reaction become homogeneous. The precipitate was washed three times with 150 mL of 95:5 acetone-water.

Acetone was removed from the combined filtrate and washings by distilling under reduced pressure (pot temperature 30  $^{\circ}\text{C}$ ). The concentrated aqueous solution was stirred mechanically with a stream of dry nitrogen passing through the solution. The solution was then heated with continued stirring and nitrogen sparging to 120-130  $^{\circ}\text{C}$  for 2-2.5 hours. Stirring and sparging was discontinued, and the reaction mixture was allowed to cool to room temperature. The glassy

product (94% yield, 94-96% pure) was further purified by recrystallization from methyl ethyl ketone-toluene, 99.0% purity in 71% overall yield.

**Synthesis of 1 by azeotropic distillation with MiBK (22-kg scale).** A 50-gallon reactor was charged with 51.36 kg of acetone and 22.05 kg of calcium D-glucarate tetrahydrate over a period of 1 h, the charge port and funnel being rinsed through to the reactor with 1.82 kg of deionized water. Sulfuric acid (6.91 kg) was charged to a stainless steel bomb and pumped from there into the reactor over a period of 1 h, during which time the pot temperature rose from 22.8 to 27.8 °C. The bomb and transfer lines were rinsed through to the reactor with 1.59 kg of deionized water. The mixture was stirred overnight (19 h) at ambient temperature, under nitrogen.

The mixture was filtered through a sparkler filter dressed with duck cloth and 40- $\mu$ m Dacron® cloth to give 37.05 kg of filtrate. The kettle and filter cake were rinsed through with a mixture of 49.77 kg of acetone and 3.27 kg of deionized water, divided into three portions. The combined filtrate and washings (95.23 kg) were adjusted to 125 kg by addition of 29.77 kg of acetone and stored in a 55-gallon polylined drum.

The cleaned 50-gallon reactor was then charged with half (62.5 kg) of the product solution from above and 59.55 kg of MiBK over a period of 32 min. The mixture was stirred and heated to reflux over the next 2 h. Over the next 7 h, 79.77 kg of acetone/water/MiBK were distilled off. The contents of the 50-gallon reactor were transferred through a line heated at 80 °C and a 200- $\mu$ m in-line filter to a 20-gallon kettle, which was cooled to 40 °C and then 32 °C. About 50 mL of the solution was removed, seeded with crystals of **1** to initiate crystallization, and then returned to the 20-gallon reactor to initiate crystallization of the product.

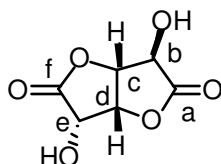
After stirring gently overnight, the material was transferred to a sparkler filter, and 6.59 kg of MiBK was used to rinse out the reactor and rinse through the filter cake. The filter cake (5.45 kg) was dried in a vacuum oven at 50 °C with a slight nitrogen purge for a day and a half to give 3.244 kg of crystalline **1** (27.1% yield), purity 99.4% by  $^1\text{H}$  NMR and 99.6% by GC.

The second half of the product solution (137.3 lb) was treated as above, except that only 77.27 kg of acetone/water/MiBK was removed. Dried **1** weighed 2.248 kg (18.8% yield) and was 99.7% pure by both  $^1\text{H}$  NMR and GC.

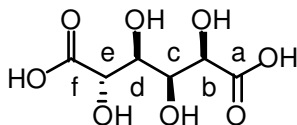
The combined mother liquors and MiBK rinses were returned to the 50-gallon reactor, stirred and heated to reflux over the next 4 hours. Over the next 4.5 hours, 45.45 kg of solvent was distilled off. The contents of the 50-gallon reactor were transferred to the 20-gallon kettle as above. An aliquot was removed, seeded with **1**, and returned to the mixture at 42 °C. After the slurry had stirred overnight, the material was transferred to a sparkler filter, and 7.95 kg of MiBK was used to rinse out the reactor and rinse through the filter cake. The filter cake was rinsed with an additional 3.18 kg of MiBK and dried in a vacuum oven to give 1.879 kg (15.6% yield) of **1** that was 99.5% pure by  $^1\text{H}$  NMR and 99.8% pure by GC.

### $^1\text{H}$ and $^{13}\text{C}$ NMR Data

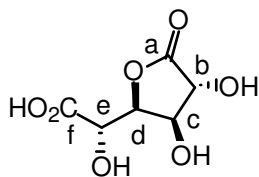
**D-Glucaro-1,4:6,3-dilactone (1).**  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  5.91 (br s, 1H, OH<sub>b</sub>), 5.43 (br d,  $J = 5.2$  Hz, 1H, OH<sub>e</sub>), 5.37 (dd,  $J = 3.6, 4.0$  Hz,  $^1J_{\text{CH}} = 170.2$  Hz, 1H, H<sub>d</sub>), 5.02 (d,  $J = 3.6$  Hz,  $^1J_{\text{CH}} = 168.4$  Hz, 1H, H<sub>c</sub>), 4.87 (d,  $J = 4.0$  Hz,  $^1J_{\text{CH}} = 144.5$  Hz, 1H, H<sub>e</sub>), 4.37 (s,  $^1J_{\text{CH}} = 156.5$  Hz, 1H, H<sub>b</sub>).  $^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  174.1 (C<sub>a</sub>), 173.8 (C<sub>f</sub>), 79.8 (C<sub>c</sub>), 79.2 (C<sub>d</sub>), 71.9 (C<sub>b</sub>), 69.9 (C<sub>e</sub>).



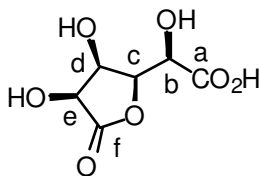
**D-Glucaric Acid (2).**  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  4.42 (d,  $J = 3.0$  Hz, 1H, H<sub>b</sub>), 4.28 (d,  $J = 6.0$  Hz, 1H, H<sub>e</sub>), 4.21 (dd,  $J = 3.0, 3.8$  Hz, 1H, H<sub>c</sub>), 4.05 (dd,  $J = 3.8, 6.0$  Hz, 1H, H<sub>d</sub>).  $^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  174.3 (C<sub>f</sub>), 174.1 (C<sub>a</sub>), 72.7 (C<sub>d</sub>), 71.3 (C<sub>b</sub>), 70.7 (C<sub>e</sub>), 70.0 (C<sub>c</sub>).



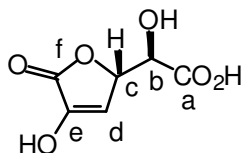
**D-Glucaro-1,4-lactone (3).**  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  4.92 (dd,  $J = 3.0, 7.5$  Hz, 1H, H<sub>d</sub>), 4.62 (d,  $J = 7.7$  Hz, 1H, H<sub>b</sub>), 4.55 (dd,  $J = 7.5, 7.8$  Hz, 1H, H<sub>c</sub>), 4.49 (d,  $J = 3.0$  Hz, 1H, H<sub>e</sub>).  $^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  175.3 (C<sub>a</sub>), 172.33 (C<sub>f</sub>), 79.8 (C<sub>d</sub>), 73.6 (C<sub>b</sub>), 75.4 (C<sub>c</sub>), 70.9 (C<sub>e</sub>).



**D-Glucaro-6,3-lactone (4).**  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  4.67 (dd,  $J = 3.6, 5.6$  Hz, 1H,  $\text{H}_c$ ), 4.65 (dd,  $J = 3.6, 4.8$  Hz, 1H,  $\text{H}_d$ ), 4.61 (d,  $J = 5.6$  Hz, 1H,  $\text{H}_b$ ), 4.56 (d,  $J = 4.8$  Hz, 1H,  $\text{H}_e$ ).  $^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  175.6 ( $\text{C}_f$ ), 172.08 ( $\text{C}_a$ ), 80.0 ( $\text{C}_c$ ), 71.1 ( $\text{C}_e$ ), 71.1 ( $\text{C}_d$ ), 70.4 ( $\text{C}_b$ ).



**L-threo-4-Deoxy-hex-4-enaro-6,3-lactone (5).**  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  6.25 (d,  $J = 2.1$  Hz, 1H,  $\text{H}_d$ ), 5.29 (t,  $J = 2.3$  Hz, 1H,  $\text{H}_c$ ), 4.44 (d,  $J = 2.6$  Hz, 1H,  $\text{H}_b$ ).  $^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  172.7 ( $\text{C}_a$ ), 169.4 ( $\text{C}_f$ ), 144.9 ( $\text{C}_e$ ), 117.6 ( $\text{C}_d$ ), 79.7 ( $\text{C}_c$ ), 70.6 ( $\text{C}_b$ ).



**4-Deoxy-L-erythro-hex-4-enaro-6,3-lactone (6).**  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  6.11 (d,  $J = 2.1$  Hz, 1H,  $\text{H}_c$ ), 5.21 (dd,  $J = 2.1, 3.7$  Hz, 1H,  $\text{H}_d$ ), 4.52 (d,  $J = 3.7$  Hz, 1H,  $\text{H}_e$ ).

