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Convenient Large-Scale Synthesis of D-Glucaro-1,4:6,3-dilactone

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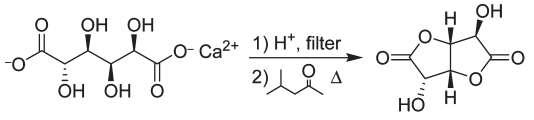
Received July 23, 2009



D-glucaro-1,4:6,3-dilactone (**1**)

Calcium D-glucarate was converted into D-glucaro-1,4:6,3-dilactone on 32-g, 1-kg, and 22-kg scale, using azeotropic distillation with methyl isobutyl ketone to drive the dehydration. The crystalline product was ≥99.5% pure by GC and NMR, and overall yield was as high as 72%.

Esters and lactones of aldaric acids are useful for the synthesis of polymers,[1−6] protein-resistant materials,[7] and nucleic acid delivery agents[8] and as chiral synthons for the production of inhibitors of HIV and *Plasmodium falciparum* proteases.[9] Aldarodilactones are particularly useful as acylating agents and cross-linkers because they are more reactive than the corresponding diesters and because they generate no byproduct when forming new ester or amide bonds. Unlike mixtures of lactone esters,[10,11] aldarodilactones such as 1,4:6,3-mannarodilactone and 1,4:6,3-glucarodilactone (**1**) are crystalline solids that can be stored indefinitely at room temperature and dispensed in known stoichiometric amounts.

We sought a method to convert commercially available calcium D-glucarate into **1** on a large scale. In contrast to the relative ease of formation of mannarodilactone,[2b,4b,6,8a,12,13] the synthesis of **1** is somewhat difficult, requiring the heating of a molten solid under vacuum[10,13,14] or repeated azeotroping from dioxane.[2] While these methods are satisfactory for laboratory-scale synthesis, the need for high vacuum, the need for high surface area and efficient heat transfer within a molten solid, difficulties in product recovery from large-scale equipment, and concern over the use of dioxane precluded their scale-up. In the end, we developed a method consisting of acidification of calcium D-glucarate in aqueous acetone, addition of methyl isobutyl ketone (MiBK, 4-methyl-2-pentanone), distillation of the acetone and azeotropic removal of water, and crystallization of **1** from the reaction mixture upon cooling (Scheme 1). Each element of this procedure is important to providing **1** in high yield and high purity.

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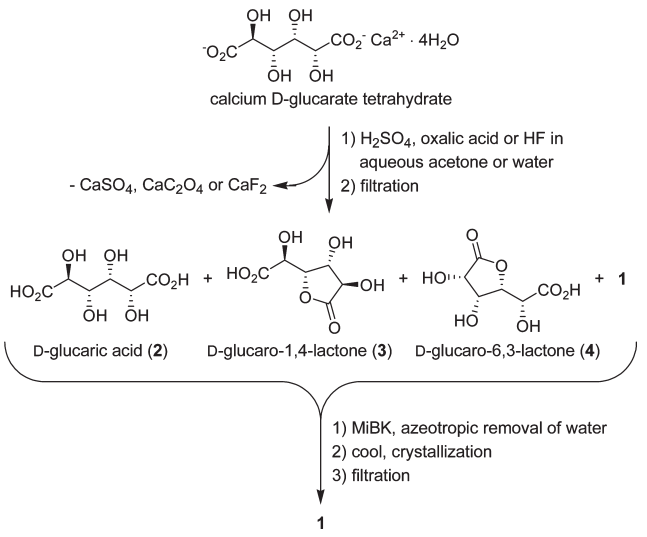
DOI: 10.1021/jo9015985 Published on Web 09/24/2009

SCHEME 1. Synthesis of 1



We examined several acids for the acidification of calcium D-glucarate. Key to success was the essentially quantitative precipitation of calcium salt byproduct while keeping glucaric acid and its monolactones in solution. Oxalic acid was the preferred acid for acidifying calcium D-glucarate in water since the solubility of calcium oxalate is only about 50 μM. However, oxalic acid is more expensive than common mineral acids. Hydrofluoric acid was also used satisfactorily to acidify calcium glucarate in water and in 9:1 (v/v) acetone−water. However, hydrofluoric acid poses significant safety risks and is even more expensive than oxalic acid. Furthermore, the byproduct, calcium fluoride, is somewhat soluble in water (0.2−0.3 mM).

Sulfuric acid proved to be the most convenient and economical acid to use for the acidification, even though calcium sulfate is appreciably soluble in water (10−20 mM). When the acidification was performed in water alone, 2% or more of the calcium sulfate remained in the filtrate with the organic product, requiring evaporation of water, dissolution of the turbid, syrupy residue in an organic solvent, and filtration to remove the residual calcium sulfate. Thus, to drive the precipitation of calcium sulfate to completion, the acidification was conducted in aqueous acetone. The water-miscible, organic cosolvent had the additional benefit of enriching the intermediate product mixture in **1** and minimizing the amount of water to be removed during the dehydration step (Table 1). The presence of some water, however, was necessary to facilitate proton transfer and to keep the more polar D-glucaric acid and its monolactones in solution. If the acidification was performed in neat acetone, product yield was reduced by 10−20% because of precipitation of glucaric acid and its monolactones with the calcium sulfate. At least 50% (v/v) acetone was necessary to maximize precipitation of calcium sulfate, and at least 2.5−5.0% water was necessary to facilitate proton exchange and maintain solubility of all of the glucaric acid species. While 9:1 acetone−water maximized the yield of total glucaric acid species in solution after 17 h at room temperature or 2−4 h at reflux, a bit less water (2.5−5.0%) gave better overall yield of **1** after the dehydration (vide infra).

For the dehydration step, we initially examined carefully the heating of a molten mixture of D-glucaric acid and its monolactones under vacuum.[13,14] This method was found to suffer not only from incomplete conversion but also from the generation of L-*threo*- and L-*erythro*-4-deoxyhex-4-enaro-6,3-lactones[15] **5** and **6** (Table 2), presumably by thermal elimination of **1** (Scheme 2). The product, **1**, was obtained as a brown, glassy solid.

We also investigated sparging with dry nitrogen as an alternate method of driving the dehydration without incurring significant thermal decomposition of reactants or product. Acidification of calcium D-glucarate tetrahydrate with sulfuric acid in 9:1 v/v acetone−water, followed by filtration and removal of acetone under reduced pressure, gave a concentrated aqueous solution (about 67% w/w solids) containing an approximately 37:30:30:3 mol ratio of **2**, **3**, **4**, and **1**. This mixture was sparged with dry nitrogen and then heated at 110−130 °C with stirring and continued sparging for 2.5−3.5 h. The brown, glassy product (90−94% yield, 93−95% **1**) contained trace impurities of **3** (3−4%), **4** and **5** (0−1%), and an unknown (0−2%, Table 2). Crystallization from methyl ethyl ketone−toluene gave **1** of 99.0% purity in 71% overall yield.

A key feature of this synthesis was its use of a mixture of glucaric acid and monolactones as the substrate for dehydration. As water was removed, melting point depression allowed the mixture of compounds to remain a syrup even at room temperature. Syntheses of **1** with a pure monolactone or monolactone ester starting material melting from 98 to 165 °C require heating to a much higher initial temperature to melt the substrate and effect dehydration. Crystallization of **1** during the synthesis was slow enough that it often failed to solidify, even if it was formed at 80 °C.

The sparging process was quite sensitive to the flow rate and efficiency of gas dispersion. Increasing the flow rate from moderate to vigorous reduced the reaction half-life at 130 °C from approximately 45 min to about 16 min. At 100-g scale, if run at 110 or 120 °C, however, the reaction mixture did occasionally solidify, risking damage to the stirrer or reaction vessel. When the reaction was run at 130 °C for 3 h, increased levels of elimination products (7%) and color were formed. In practice, it was difficult to find the precise end point where consumption of **3** was maximized and formation of elimination products was minimized.

Key to discovering the current azeotropic method was the observation that recrystallizing crude **1** from MiBK generated a higher level of **1** in both the crystallized solid and the mother liquor than was present initially. Although a number of solvents were screened, including propyl acetate (bp 102 °C), diethyl ketone (bp 102 °C), cyclopentanone (bp 131 °C), cyclohexanone (bp 155 °C), glyme (bp 85 °C), dioxane (bp 102 °C), 1,2-diethoxyethane (bp 121 °C), and diglyme (bp 162 °C), MiBK (bp 118 °C) was unique in its ability to keep all of the various glucaric acid species in solution, facilitate azeotropic removal of water, minimize the formation of elimination products, and allow the crystallization of **1** in reasonable yield, purity, and color upon

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TABLE 1. Acidification of Calcium D-Glucarate Tetrahydrate

				composition (mol %)[b]			
solvent, acetone:water	temp	time (h)	yield (%)[a]	**1**	**2**	**3**	**4**
0:100	ambient	72	100	12	25	31	32
70:30	ambient	17	98	18	8	33	41
80:20	ambient	17	91	26	12	32	30
90:10	ambient	17	100	30	5	27	38
100:0	ambient	17	81	68	0	14	18
100:0	reflux	4	87	52	3	24	21
90:10	reflux	1	96	54	1	19	26
90:10	reflux	2	99	45	2	23	30
90:10	reflux	4	100	15	14	32	39

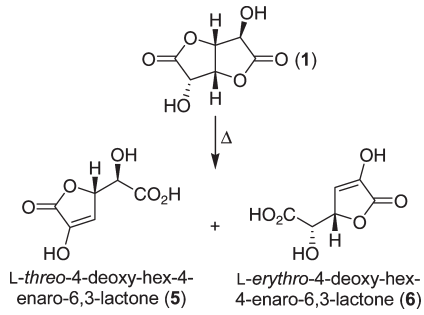
[a]Isolated yield. [b]Determined by ^{1}H or ^{13}C NMR after acidification with 1 mol equiv of sulfuric acid and removal of solvent at 20−40 °C.

TABLE 2. Scouting Synthesis of 1 by Various Methods[a]

					product composition (mol %)[c]				
method	temp (°C)	time (h)	scale (mol)	yield (%)[b]	**1**	**3**	**4**	**5**	**6**
vacuum melt	90	3.0	0.05	87	97.0	0.0	1.5	1.1	0.4
vacuum melt	95	2.25	0.05	87	94.7	0.0	4.3	0.7	0.3
vacuum melt	130	1.0	0.05	76	59[d]	0	0	14	6
sparging	110	3.0	0.50	91	94.0[e]	0.0	2.1	0.4	0.0
sparging	120	3.5	0.50	90	94.7[f]	0.0	0.2	0.3	0.0
sparging	130	2.5	0.156	94	93.2[g]	0.0	3.4	1.1	0.5
azeotroping[h]	120	−	0.10	50	99.5	0.2	0.2	0.1	0.0
azeotroping[i]	120	−	0.10	62	99.7	0.1	0.1	0.1	0.0
azeotroping[j]	120	−	0.10	71	99.5[k]	0.1	0.1	0.0	0.0

[a]Calcium D-glucarate tetrahydrate (1 M in 9:1 v/v acetone:water) was acidified with 1 mol equiv of sulfuric acid at ambient temperature for 2−6 h, filtered, and (a) stripped of solvent by rotary evaporation before being heated at 1 Torr (vacuum melt), (b) concentrated under reduced pressure to remove acetone before being heated and sparged with nitrogen (sparging), or (c) diluted with 1 volume of acetone−water and 2.5 volumes of MiBK before being concentrated by distillation (azeotroping). [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Product also contained 20% of an unknown and 1% of 3-hydroxy-2*H*-pyran-2-one. [e]Product also contained 3.5% of unknown impurities. [f]Product also contained 4.8% of unknown impurities. [g]Product also contained 1.8% of unknown impurities. [h]Acidification of calcium D-glucarate was conducted at reflux for 3 h. [i]Calcium D-glucarate was acidified in 95:5 v/v acetone:water at reflux for 4 h. [j]Calcium D-glucarate was acidified in 97.5:2.5 v/v acetone:water at reflux for 4 h. [k]Product also contained 0.3% of an unknown impurity.

SCHEME 2. Thermal Decomposition of 1



L-*threo*-4-deoxy-hex-4-enaro-6,3-lactone (**5**)

L-*erythro*-4-deoxy-hex-4-enaro-6,3-lactone (**6**)

cooling of the reaction mixture. Somewhat surprisingly, the use of MiBK also resulted in essentially no acetal formation as the dehydration proceeded.

As the azeotropic synthesis of **1** with MiBK was optimized, several facts came to light. First, the yield of **1** was maximized by maintaining all of the glucaric acid species homogeneous in solution during the course of acidification and azeotropic dehydration. Because D-glucaric acid and its monolactones are poorly soluble in MiBK, operating in neat MiBK was unfeasible. Conducting the initial acidification of calcium D-glucarate in neat MiBK resulted in about 70% of the glucarate species being lost as a deposit on the precipitated calcium sulfate. Even at dilute initial concentrations, glucaric acid and monolactones separated from solution, pulling **1** out with them. Upon heating, the syrupy deposit of glucarate species remained stuck to the walls of the flask, where it tended to decompose thermally and reduce the overall yield of **1**. Thus, a mixture of MiBK and acetone was required to keep all of the glucaric acid species homogeneous in solution.

However, when MiBK was added to a mixture of glucaric acid and its monolactones in 9:1 acetone−water (produced by the acidification described above), an aqueous layer in which the polar glucarate compounds dissolved selectively phase-separated. As water was removed azeotropically, the glucarate species in the aqueous phase failed to return to bulk solution and were lost as a dark syrupy deposit on the walls of the reaction vessel. Thus, although a certain amount of water was advantageous to maximize the yield of the acidification step, it became problematic in the azeotropic dehydration step conducted with MiBK and was therefore kept at a minimum. We examined the ability of quaternary solvent systems (adding an additional organic cosolvent to MiBK−acetone−water) and an extensive range of surfactants[16] to maintain a single liquid phase throughout the reaction, all without success.

In practice, the best overall yields of highly pure GDL were obtained by removing the solvent in two steps, cooling the mixture, and collecting a crop of crystalline GDL after each distillation. The mother liquor could ultimately be recycled to maximize the yield if the process was practiced repeatedly.

(16) PEG, PEG-PPG random copolymers, Pluronics, sorbitan esters, Tween and Brij surfactants, SDS, and tetraalkylammonium salts.

Experimental Section

Synthesis of 1 (1-kg scale). Sulfuric acid (312.5 g, 3.122 mol) was added over a period of 30 min to a stirred suspension of calcium D-glucarate tetrahydrate (1000 g, 3.122 mol) in 3.1 L of 95:5 (v/v) acetone−water. The stirred mixture was heated at reflux for 4 h, cooled 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 1.0 L of 95:5 acetone−water.

Since some of the acetone was lost by evaporation during filtration, the filtrate and washings were combined and adjusted to 6.2 L by addition of acetone (about 1.6 L). MiBK (6.75 L) was added to the solution, which was stirred and heated (pot 65−95 °C) so as to remove 6.2 L of acetone containing some water and MiBK by fractional distillation (still head 56−85 °C). Distillation continued until the pot temperature reached 115−119 °C, at which point distillation was discontinued, and the reaction was heated at reflux for 30 min. Then, distillation was resumed until a total of 8.56 L had been removed from the original reaction volume.

The reaction mixture was filtered hot to separate the solution from about 30 g of a brown oil that adhered to the surface of the glass reaction vessel. The reaction filtrate was allowed to cool with stirring under a blanket of dry nitrogen. The solution was seeded with 0.5−0.6 g of **1** and cooled to room temperature. Once the mixture had reached room temperature, crystallization was allowed to continue for 2−3 h or overnight. The white, crystalline **1** was collected by filtration, rinsed with one 750-mL portion of MiBK, and dried under a stream of nitrogen and then under vacuum: yield 250−270 g (46−50%), purity 99.5% by ^{1}H NMR, 99.8% by GC.

The mother liquor from the first crystallization (about 4.7 L) was further concentrated to 1.9 L by distillation. The concentrated mother liquor was filtered hot, cooled with stirring under a blanket of dry nitrogen as before, and seeded with 0.3 g of **1**. Once the mixture had reached room temperature, crystallization was allowed to continue for 2−3 h or overnight. The white, crystalline **1** was collected by filtration, rinsed with one 375-mL portion of MiBK, and dried under a stream of nitrogen and then under vacuum: yield 125 g (23%), purity 99.6% by ^{1}H NMR, 99.9% by GC.

Supporting Information Available: General experimental methods, synthesis of **1** by sparging with nitrogen (160-g scale) and by azeotroping with MiBK (22-kg scale), and ^{1}H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.