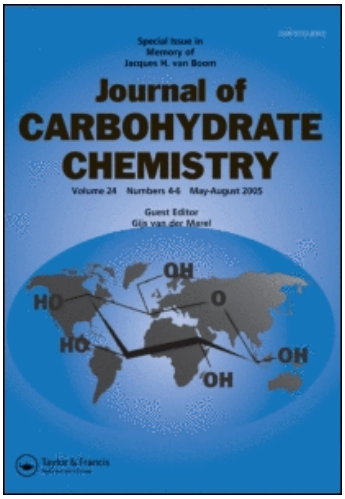

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4-AcNH-TEMPO-CATALYZED OXIDATION OF ALDOSES TO ALDARIC ACIDS USING CHLORINE OR BROMINE AS TERMINAL OXIDANTS

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ABSTRACT

The 4-AcNH-TEMPO-catalyzed oxidation of D-glucose to D-glucaric acid using elemental chlorine or bromine as the terminal oxidant is reported. The pH and temperature of the reactions were closely controlled to be between 0–5 °C and pH 11.5, respectively. Spectroscopically (^{1}H NMR) determined yields of glucarate were greater than 90%; yields of crystalline monopotassium D-glucarate (or disodium D-glucarate), isolated and purified by precipitation, were between 70 and 85%. Oxidations of mannose to mannaric acid and galactose to mucic acid were also demonstrated.

INTRODUCTION

A large body of work has been concentrated on the utilization of carbohydrates towards the goal of making renewable resources an integral component in the production of chemicals.[1] Not only is the promise of tapping a renewable resource of materials of greatest economic interest but sugar-based polymers have been, for instance, shown to be biocompatible and biodegradable.[2–4] This appealing combination of advantages of sugar-based materials is, however, often offset by the unavailability of economical processes for the production of sugar-based raw materials.[5] The transformation of

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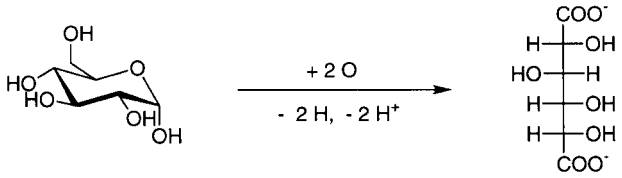
D-glucose into useful building blocks has been widely investigated.[5] However, its broader industrial use is hampered by problems of reaction selectivity and product isolation difficulties.

D-Glucaric acid, in fact, carbohydrate diacids in general.[6] are particularly promising raw materials for the formation of biodegradable detergents, metal complexation agents,[7] biodegradable polymers for high tensile strength fibers,[6,8–10] films, adhesives and plant fertilizers.[11] Glucaric acid has also been shown to have antitumor and chemopreventive properties,[12–14] cholesterol-lowering effects,[15] and is a viable chelating agent for ^{99m}Tc for the radio-imaging of tumors[16] or the early detection of myocardial infarction.[17]

D-Glucaric acid is generally made by oxidation of D-glucose, molasses or starch (Scheme 1).[5,18] The classic methods involve strong oxidants such as HNO_3 or NO_2 (N_2O_4).[19–22] These methods are generally characterized by low specificity of the oxidation, therefore requiring economically inefficient separation steps for the isolation of the glucaric acid or its salts. However, the use of the cheap oxidant HNO_3 is appealing enough that the optimization of the process is still pursued.[23,24] Other commonly used carbohydrate oxidation methods involve precious metal catalysts (Pt, Rh, Ru) or require methodologies hampering their facile use in an industrial setting.[25–27]

A number of oxoammonium oxidations of alcohol groups to aldehyde moieties have been developed and refined in recent years.[28,29] Oxoammonium salts can be used as stoichiometric oxidants or they can be generated in situ from the corresponding nitroxyl radical by an appropriate co-oxidant (referred to in the remainder of this report as the terminal oxidant).[30–32] Nitroxide-mediated oxidation reactions using hypohalites as terminal oxidants have proved to be particularly suited for the oxidation of mono- and polysaccharides. This method selectively oxidizes, in a homogenous system, primary alcohols and aldehyde groups *in the presence of a number of secondary alcohol groups* to carboxylates.[32–39] Oxidations utilizing solid phase-bound nitroxide catalysts have also been reported.[40,41] The oxidation of glucose to glucaric acid using hypohalites and 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (4-AcNH-TEMPO) was reported by us recently.[42]

Halogens dissolved in aqueous solutions of high pH disproportionate to generate hypohalites and halogenides.[43] This prompted the question whether elemental chlorine or bromine could be used as the terminal oxidant in the oxidation of D-glucose catalyzed by a nitroxide/bromide catalysts/co-catalyst system at high pH.[44] We report here the successful results of this investigation. Optimized reaction conditions allow for the isolation of glucaric acid salts in good yields.



Scheme 1. Net reaction for the conversion of glucose to glucaric acid.

RESULTS AND DISCUSSION

The Oxidation of Glucose Using Chlorine Gas

Chlorine gas bubbled through an aqueous solution of D-glucose at high pH (NaOH or KOH) containing catalytic amounts of 4-AcNH-TEMPO/bromide (0.01 equiv/0.1 equiv; for the role of bromide in these oxidations see below) immediately oxidizes the aldose as evidenced by the disappearance of the glucose as analyzed by ^{1}H NMR. The pH of the solution drops rapidly. Continuous titrations of the reaction mixture with concentrated base must be utilized to maintain a pH of 11 throughout the reaction. Any pH lower than 11 results in an incomplete reaction accompanied by the appearance of a large portion of side products. The solution warms due to the exothermic nature of the dissolution/disproportionation reaction of the chlorine and/or oxidation of the substrate and requires continuous external cooling to 0–5 °C. The higher the reaction temperature, the more tartaric and oxalic acid is formed as side products (see also below).[20,39] However, even in cases in which extensive decomposition is observed, the isolated glucarates are colorless. The isolation of the products is accomplished by precipitation following concentration, pH-adjustment or the addition of a non-solvent (EtOH), providing up to 80% isolated yield.[21] The apparatus used in the reaction is shown schematically in Figure 1.

Up to 6 weight % sugar solutions (using KOH as a base) have proven to provide ideal conditions. Higher sugar loads (up to 12 weight %) resulted in an incomplete and slower reaction, although the isolation of the potassium glucarate by precipitation was facilitated. Only traces of glucaric acid can be detected in the mother liquor by NMR. However, the crude product contains considerable amounts of bromides, necessitating a recrystallization step to obtain halide-free glucarate.

The progress of the reaction can be measured by observing the disappearance of the starting material by ^{1}H or ^{13}C NMR or by observing no further change in pH. At the endpoint of the reaction, the reaction mixture is purged with nitrogen or air. ^{1}H and ^{13}C NMR spectra of the crude mixture indicate good spectroscopic yields of potassium

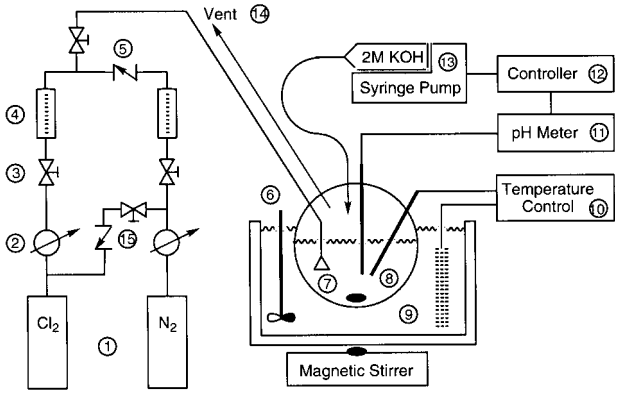


Figure 1. Schematic representation of the oxidation apparatus using chlorine or chlorine/nitrogen mixtures as terminal oxident. The numbers refer to the description of the components in the experimental section.

glucarate. The only side products visible by NMR are traces of tartaric and oxalic acids (< 10%). Using NaOH as a base, amorphous disodium glucarate can be made following the same reaction conditions as described for the potassium salt but the work-up conditions vary (see EXPERIMENTAL).

Glucaric acid (or its lactone) can be extracted with diethyl ether from acidic solutions.[23,45,46] Hence, direct extraction of the acid from acidified reaction mixtures is, though not explicitly demonstrated here, likely to be possible.

The Oxidation of Glucose Using Bromine

The use of elemental bromine is particularly convenient for the oxidation of aldoses in the laboratory setting. Using essentially the same reaction conditions as described above, 3.3 equiv of elemental bromine are added dropwise over several hours to the solution through a burette or, most conveniently, by means of a syringe pump. At the endpoint of the reaction, the spectroscopic yields of glucarate are approximately 90%, with tartaric acids as the major side products. Workup conditions for the bromine oxidations exclude precipitations from EtOH/water mixtures as the corresponding alkali bromides co-precipitate with the products. Thus, isolation of the oxidized carbohydrates must be achieved by pH adjustment of the reaction mixture to 3.8, eliciting the precipitation of crystalline monopotassium glucarate. Thus the use of KOH as a base is preferred over NaOH.

The Oxidation of Mannose and Galactose Using Chlorine and Bromine

The oxidation methods described are also applicable to the oxidation of mannose to mannaric and galactose to mucic acid, respectively. Isolation of mucic acid by precipitation at pH 1 affords the analytically pure material in 70% yield. Ethanol precipitation of the mannaric acid, as its disodium salt, affords a white solid which is contaminated with ~15% tartrate and ~10% of an unidentified product.[47]

The Catalyst

As the catalyst for all oxidation reactions we chose 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (4-AcNH-TEMPO) rather than the parent compound 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). 4-AcNH-TEMPO can be readily prepared, is commercially available and is less volatile and more stable than TEMPO.[29]

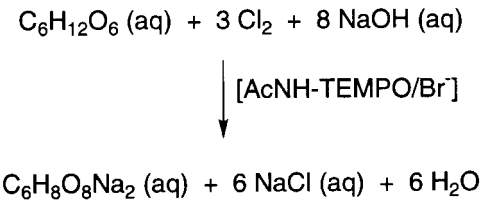
The Oxidant

The use of chlorine as an oxidant has a number of advantages over the use of bleach, in particular from an industrial point of view: Firstly, commercial hypochlorite solutions are made from chlorine and aqueous NaOH. Thus, the use of gaseous chlorine shortens the overall process by one step. Secondly, oxidations with commercial bleach

generate the sodium salt of glucaric acid in non-crystalline form. Chlorine allows the use of KOH as a base, enabling the preparation of the crystalline monopotassium salt. Thirdly, commercial bleach is a 0.7 M NaOCl solution (available chlorine 5.25%). Thus, for each mole of sugar to be oxidized, the volume of the reaction mixture increases by ~4.6 L. This necessitates the handling and evaporation of larger volumes of water which, in industrial scales, is of concern. Fourth, the side products of the process are water and NaCl or KCl. These compounds are the industrial starting materials for the synthesis of chlorine and potassium or sodium hydroxide thus allowing, at least formally, for a closed loop process generating minimal waste products.

The technical use of elemental chlorine raises concerns with respect to the possible discharge of halogenated hydrocarbons to the environment, in particular dioxins, halophenols and volatile organic compounds (VOCs) such as chloroform, methylene chloride or chloromethane.[48] However, the oxidation process described here operates at low temperatures, involves no Lewis acid catalysts and only non-aromatic substrates, all factors greatly diminishing the chance of forming unwanted or hazardous halogenated side products.

The net equation of the oxidation reaction is:



Thus only three equiv of halogen are required for the oxidation of an aldose to the corresponding aldaric acid. Although the formation of 'overoxidized' products is a concern, we found that a 10–15% excess of oxidant is required for the reaction to go to completion. It has been known that the ideal temperature for the disproportionation reaction of the halogens lies between −8 °C and −5 °C. Chlorate and bromate ions begin to form at temperatures above this.[43] The kinetics of chlorate oxidations is slow.[49,50] Due to the freezing point of our solution at ~−1 °C, we must compensate for the loss of viable oxidant by using a larger than calculated amount of oxidant.

Mechanistic Considerations

The overall reaction requires a number of individual steps to proceed in a synchronized fashion (Figure 2). The mechanism is complex and not fully understood. It is known, however, that several competing pH-dependent pathways exist.[51,52] The reactions involved in the oxidation process are: ① Dissolution of the chlorine in base to disproportionate to hypochlorite and chloride. ② Hypochlorite oxidizes bromide ions to generate hypobromite, although one can shortcut the catalytic cycle by using bromine instead of chlorine generating directly hypobromite. ③ Hypobromite has been shown to oxidize the nitroxide form of the catalysts to the active nitroxammonium salt at a faster rate than hypochlorite.[51] ④ Direct oxidation of the nitroxide by chlorine has been shown

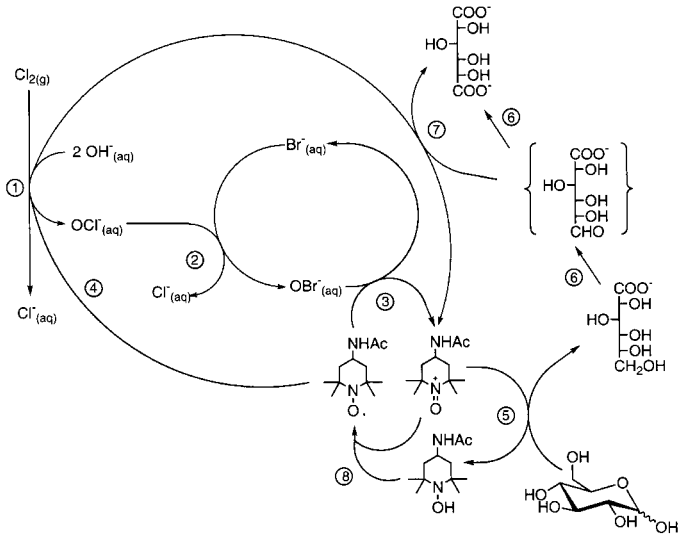


Figure 2. Schematic representation of the possible reactions involved in the oxoammonium/bromide-mediated oxidation of glucose to glucaric acid using chlorine as terminal oxidant.

to be possible in aqueous and non-aqueous solutions and cannot be excluded as an alternate oxidation pathway.[31,53] ⑤ The fastest oxidation of the substrate appears to be the oxidation of the C-1 carbon of D-glucose to form gluconolactone which converts to gluconate (see below). The nitroxonium form of the catalysts as well as hypochlorite in the absence of a catalyst are capable of performing this oxidation.[54–56] ⑥ C-6 of the

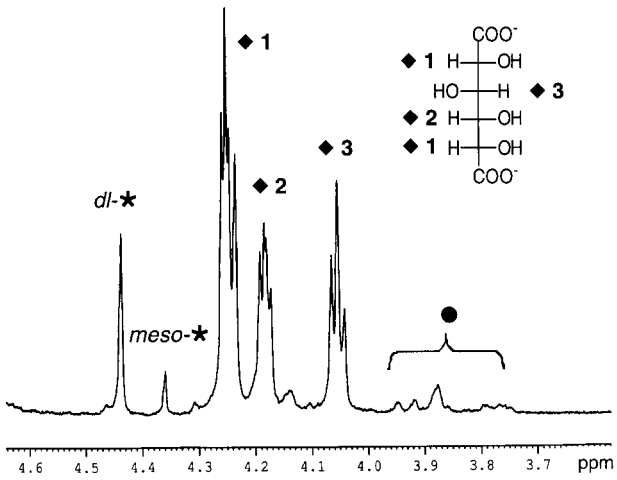


Figure 3. Typical ^{1}H NMR spectrum (400 MHz, D_2O, 25 °C) of the final crude reaction mixture of a nitroxide-mediated glucose oxidation using 3.3 equiv of bromine. For experimental details, see experimental section. ●: signals characteristics of gluconate; ◆: glucarate; ★: tartrates.[57]

gluconic acid then gets converted into a carboxylic acid (glucaric acid), presumably via an aldehyde oxidation step. However, the aldehyde (in the free aldehyde, hydrate or hemiacetal form) is never present in high enough concentrations to be detected by ^{1}HNMR (see below). The first oxidation in this step (primary alcohol to aldehyde) is likely due to the selective oxidation by oxammonium salts.[32] ⑦ Conversion of the aldehyde to the acid functionality can be performed by hypochlorite as well as chlorine gas. ⑧ Upon performing an oxidation, the oxammonium salt is reduced to a hydroxyl amine which conproportionates with another equiv of oxammonium salt to produce two equiv of nitroxide, thus closing the catalytic cycle.[32]

Figure 3 shows the stacked plot of a ^{1}H NMR of a typical bromine oxidation of glucose. Aliquots of the reaction mixture were removed at the times indicated, freeze dried and dissolved in D_2O. At the beginning of the reaction (0 min), only the peaks indicative of glucose are visible (notice, for instance, the α and β anomeric protons at $\delta = 5.15$ and 4.56 ppm, respectively, or the H-2 proton at $\delta = 3.15$ ppm). To the same degree as these signals disappear, a doublet at 4.10 ppm and a cluster of peaks centered around 3.6 ppm, attributable to the H-2 and H-6 of gluconic acid appear.[57] After 60 min, equivalent to the addition of one equiv of oxidant, the spectrum is dominated by the signals for gluconic acid. In the course of the addition of the remaining two equiv of oxidant, the gluconic acid peaks disappear as the glucaric acid peaks appear. No NMR evidence for the presumed C-6 aldehyde intermediate can be detected. Interestingly, the appearance of the major side product tartaric acid (*dl*-tartrate at 4.35 ppm and the *meso*-tartrate at 4.25 ppm) is visible from the onset of the oxidation. While we assume that tartaric acid is the 'overoxidation' product of glucaric acid, its early appearance may indicate a competing oxidation pathway of glucose directly leading to tartaric acid. The NMR data clearly show that the oxidation of glucose to glucaric acid is a two-step process (Figure 4).

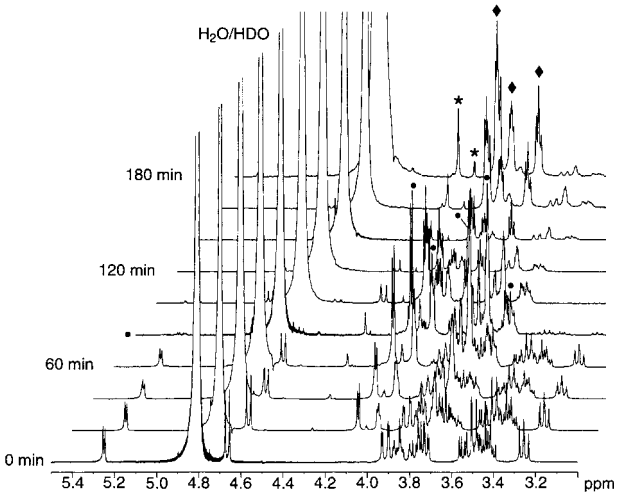


Figure 4. Stacked plot of the ^{1}H NMR (400 MHz, D_2O, 25 °C) of aliquots of a nitroxide-mediated glucose oxidation using 3.3 equiv of bromine added over 180 min; sampled at the times indicated. For experimental details, see experimental section. ●: signals characteristic of gluconate; ◆: glucarate; ★: tartrates.[57]

CONCLUSION

We have demonstrated that the nitroxide-mediated oxidation of aldoses to the corresponding aldaric acids using chlorine gas or elemental bromine as terminal oxidant is, under tight reaction control, a convenient and high yielding reaction. The bromine oxidation method appears to be particularly suited for the synthesis of aldaric acids and their salts in a standard research laboratory. The chlorine oxidation method is, due to its process in aqueous solution, use of an economical oxidant and a readily available catalysts/co-catalysts system, most suited for commercial development.[58] This oxidation process should also be applicable to the oxidation of oligo- and polysaccharides (cellulose, starch, dextrans, amylopectin, etc.).

EXPERIMENTAL

General Methods. The oxidation catalyst 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (4-AcNH-TEMPO) was prepared as reported[29] but is also commerically available from Acros Organics or Aldrich. All other chemicals were purchased from chemical supply houses (Fluka, Aldrich) and were used as received. ^{1}H and ^{13}C NMR spectra in D_2O were recorded at ambient temperature on a Bruker DRX-400 after either freeze-drying the sample or using a water suppression pulse sequence.

Oxidation Apparatus. The gas delivery system was constructed from stainless steel (SS316) or monel: 1—lecture bottles, needle valves; 2—pressure gauge; 3—needle valve; 4—flow meters; 5—check valve; 6—mechanical stirrer to ensure efficient cooling; 7—medium glass frit; 8—four-neck round bottom flask; 9—^{i}PrOH/H_2O cooling bath; 10—Immersion cooler with temperature controller; 11—pH meter; 12—home-built interface monitoring the output of the pH meter in mV and activating the syringe pump above/below a preset value (control ±0.2 pH units); 13—Syringe pump loaded with a polyethylene syringe filled with 7.5 M aqueous NaOH/KOH (components 11–13 fulfil the role of an autotitrator); 14—vent with KOH scrubber; 15—needle valve/check valve combination to allow for a nitrogen flush of the chlorine lines (Figure 1).

Sodium Glucarate by Cl_2-Oxidation of Glucose. D-Glucose (2 g, 11.1 mmol), 4-AcNH-TEMPO (0.040 g, 0.013 mmol) and KBr (0.3 g, 2.5 mmol) were dissolved in water (50 mL) and added to the reaction vessel (250 mL four-neck round bottom flask) cooled to 0–5 °C. The pH of the solution was adjusted to pH 11.5 with a 7.5 M NaOH solution. Under stirring, Cl_2 gas (Cl_2–N_2 mixtures were also successfully used) was bubbled through a fine glass frit into the solution at a rate such that the reaction mixture temperature never rose above 5 °C. Throughout the reaction, the pH was maintained between pH 11.4 and 11.7 by automated titration with 7.5 M NaOH. The reaction was monitored by recording the ^{1}H NMR of aliquots of the reaction mixture. The endpoint of the reaction was reached once all starting material was consumed or the calculated amount of base was used. To remove excess Cl_2, the reaction mixture was purged with N_2. A ^{1}H NMR spectrum of the crude reaction mixture showed that $\geq 97\%$ of the starting D-glucose was converted to disodium D-glucarate and a discernible amount of side products (mainly sodium tartrate). The product was isolated

by additon of concd aqueous HCl to the cold mixture (final pH 8). The solution was then concentrated under vacuum to about 20 mL and sodium glucarate was precipitated with EtOH (70 mL). The crude gummy precipitate was dissolved in water (20 mL) and the precipitation operation repeated. The resulting gum was washed with a mixture of ethanol/water (4:1) and dried at 40 °C under reduced pressure. Yield: 2.73 g (95%). The material contains up to 7% tartaric acids and up to 3% by weight halide. Adjusted yield of disodium glucarate: 85%.

Monopotassium Glucarate by Cl_2-Oxidation of Glucose. The oxidation was carried out in the same manner as described above using KOH rather than NaOH. The pH of the final solution was adjusted to 3.8 using concd aqueous HCl and the monopotassium glucarate was allowed to precipitate at 0 °C giving after filtration and drying, 1.56 g of halide-free material (56% yield). Concentration of the mother liquor and re-adjustment of the pH to 3.8, followed by a filtration afforded an additional 0.56 g of material with a positive chloride analysis. The combined yield was 2.12 g (77% yield). Analysis showed an average of 10% KCl (70% calculated potassium glucarate yield). The ^{1}H NMR of the mother liquor shows significant residual amounts of glucarate present.

Mucic Acid by Cl_2-Oxidation of Galactose. The oxidation was carried out using galactose (2 g) in the same manner as described for the glucose oxidation in NaOH. The pH of the reaction mixture was adjusted using concd HCl to pH 1. Mucic acid precipitated and was isolated by filtration to give, after drying under vacuum at 40 °C, 1.6 g of chloride-free material (70% yield). ^{1}H NMR spectra of the mother liquor showed the presence of residual mucic acid.

Monopotassium Glucarate by Br_2-Oxidation of Glucose. A stirred mixture of D-glucose (3 g) and 4-acetylamino-TEMPO (40 mg) in 50 mL of water was cooled to 0 °C. The pH was adjusted to pH 11.5 with a 7.5 M KOH solution. To a burette containing water (5 mL—the water layer prevents the loss of gaseous bromine) was added bromine (8.8 g, 3.0–3.1 mL, 3.4 equiv). Bromine was added drop-wise at a rate allowing for the disappearance of the droplets of bromine at the bottom of the reactor before further addition of bromine. The pH of the reaction was controlled at pH 11.5 with a 7.5 M KOH solution. The reaction was completed once the entire amount of bromine was added and the reaction mixture showed a negative iodide/starch paper test. The solution was acidified with concd HCl to pH 3.8. After stirring the chilled mixture for 60 min, the thick white precipitate was filtered yielding, after drying at 40 °C under vacuum, 2.8 g of product (70% yield). The material showed a negative halide analysis and conforms to literature spectroscopic data.[57] A second crop of monopotassium glucarate (~0.5 g) could be obtained from the mother liquor by concentration under vacuum at 40 °C to about 20 mL and re-adjustment of the pH to 3.8. However, this material contained chloride.

Mucic Acid by Br_2-Oxidation of Galactose. The oxidation was carried out with galactose (2 g) in the same manner as described above for the Br_2-oxidation of glucose but using NaOH as a base. The ^{1}H NMR spectrum of the crude mixture showed mucic acid in high yield and tartaric acid as main by-product, no residual galactose and only traces (if any) of galactonic acid. Workup as described above. Isolated yields varied from

1.5–1.8 g (60 to 80% yields). ^{1}H NMR and ^{13}C NMR spectra of the sample were identical to those of commercial samples. The samples showed negative halide analyses.

Disodium Mannarate by Cl_2- or Br_2-Oxidation of Mannose. The oxidations were carried out in the same manner as described for the glucose oxidations in NaOH. The crude product was isolated in the same manner as described for sodium glucarate. The ^{1}H NMR of the gummy product indicated the presence of 15% tartrates and ~10% of an unidentified material (400 MHz ^{1}H NMR, D_2O: doublets at $\delta = 3.90$, 4.23 and 4.45, $J = 4$Hz, 1:1:1 ratio).

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