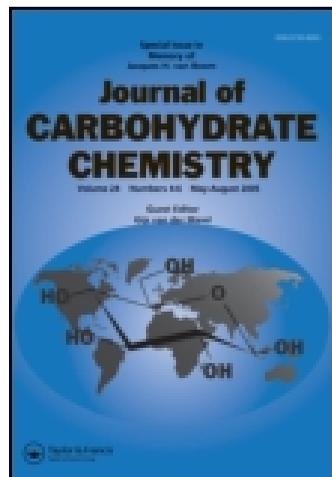


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Pentaric Acids and Derivatives from Nitric Acid–Oxidized Pentoses

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This report describes the preparation of the four stereoisomeric pentaric acids by nitric acid oxidation of D-xylose, D-arabinose, L-arabinose, and D-ribose, with xylaric, D-arabinaric, and L-arabinaric acids being made in a reactor under computer control. The pentaric acids were converted to their crystalline *N,N*-dimethylpentaramides, derivatives that proved useful for isolation of the arabinaric acids from their respective oxidation mixtures. The *N,N*-dimethylpentaramides were readily convertible to the corresponding pentaric acid disodium salts in aqueous sodium chloride. The 2,3,4-O-triacetyl-*N,N*-dimethylpentaramides of xylaric, L-arabinaric, and ribaric acid were also prepared. Ribaric acid was isolated as crystalline 1,4(5,2)-ribarolactone and further characterized by x-ray crystallography.

Keywords Nitric acid; Oxidation; Pentaric acids; Computer-controlled reaction; X-ray crystal structure

INTRODUCTION

Nitric acid oxidation of aldoses to the corresponding aldaric acids represents an old but relatively uncomplicated oxidation method.^[1–4] Such aldaric acids are

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of interest as monomer diacid starting materials for the preparation of polyhydroxypolyamides (PHPAs)^[5,6] and as useful chemical building blocks derived from renewable carbohydrates.^[7]

Synthetic polyhydroxypolyamides (PHPAs) derived from monomer aldaric acids and alkylenediamines are of importance since they are derived in part from renewable carbohydrates and readily break down in soil and serve as a source of nitrogen for plant growth.^[8,9] The stereoisomeric pentaric acids *meso*-xylaric acid (**1**), D-arabinaric acid (D-lyxaric acid) (**2**), L-arabinaric acid (L-lyxaric acid) (**3**), and *meso*-ribaric acid (**4**) (Fig 1) are among the aldaric acids of interest and the subject of this report. Since the pentaric acids are not commercially available, our first objective was to prepare representative amounts of diacids **1–3** employing a modification of the long-known aldose nitric acid method,^[1–4] which was developed in this laboratory.^[10]

A second objective was to establish a simple method to readily isolate individual pentaric acids as suitable derivatives from the corresponding oxidation reaction mixture without chromatographic purification. Among the pentaric acids, only xylaric acid (**1**) can be readily crystallized from the oxidation mixture,^[1,11] while ribaric acid can be isolated as its crystalline 1,4(5,2)-lactone (**5**).^[1,2] Consequently, a pentaric acid derivative of choice should be easily converted to the parent diacid and, while applicable to all of the pentaric acids,

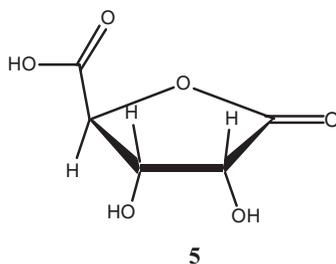
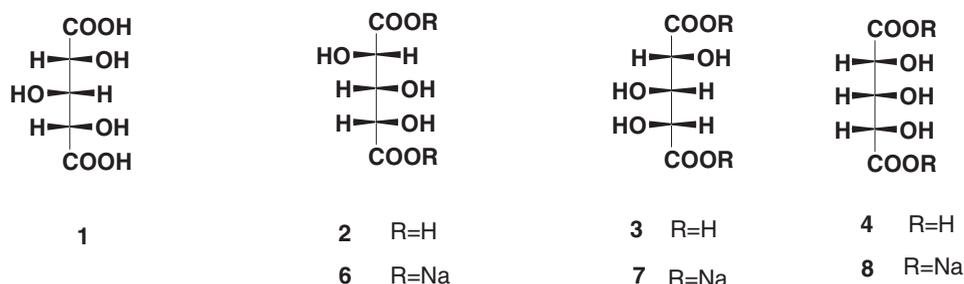


Figure 1: Stereoisomeric xylaric (**1**), D-arabinaric (**2**, D-lyxaric), L-arabinaric (**3**, L-lyxaric) and ribaric (**4**) acids, ribaro-1,4(5,2)-lactone (**5**), and disodium salts **6–8**.

would be especially important for isolation of the stereoisomeric arabinaric acids.

An additional objective of the study was to further characterize lactone **5** by way of its x-ray crystal structure.

RESULTS AND DISCUSSION

Nitric Acid Oxidations

Nitric acid oxidation of D-xylose, D-arabinose, and L-arabinose were carried out in a computer-controlled reactor under an atmosphere of oxygen in a closed 2-L reaction flask to effect a catalytic oxidation process with oxygen as the terminal oxidant. Because of its high cost and limited availability, D-ribose was only oxidized on a small scale using conventional laboratory glassware.

Nitric acid oxidations of aldoses are characterized by an induction period wherein the reaction mixture initially appears stable at rt but gradually warms up and then undergoes a rapid temperature increase that is accompanied by release of large amounts of gaseous, brown-colored nitrogen dioxide. In order to control the highly exothermic oxidation of the pentoses, the experimental protocols employed in this report were patterned after those described for oxidation of D-glucose to D-glucaric acid^[10] but designed for the individual sugars **1–3**. The use of a computer-controlled closed reactor for the D-glucose oxidations provided control of reaction temperature while conserving the nitric acid and using oxygen as the terminal oxidizing agent.^[12] In effect, this oxidation protocol is a catalytic reaction, with nitric acid being regenerated in situ. The emphasis in carrying out oxidations of the pentoses was to evaluate this oxidation methodology for these aldoses but without attempting to optimize oxidation conditions.

Xylose oxidation

Nitric acid removal from oxidation mixtures was typically done by concentration at reduced pressure. When the concentration step was applied to oxidation of xylose, crystalline xylaric acid (**1**) was only obtained in a yield of 33%. A shortcoming of the concentration step employed in the above example is that during the concentration step, residual nitric acid becomes more concentrated because it forms a reverse azeotrope with water, facilitating uncontrolled oxidation and production of added amounts of unwanted smaller organic acid side products. In an effort to minimize side product formation, an alternative procedure was applied to a representative D-xylose oxidation mixture. The concentration time of the nitric acid removal step was reduced, the reaction was neutralized with sodium hydroxide, and resultant sodium nitrate was separated from crude disodium xylarate, and minor coproduct organic acid sodium salts, by nanofiltration.^[10] The organic salt mixture was treated with an acid

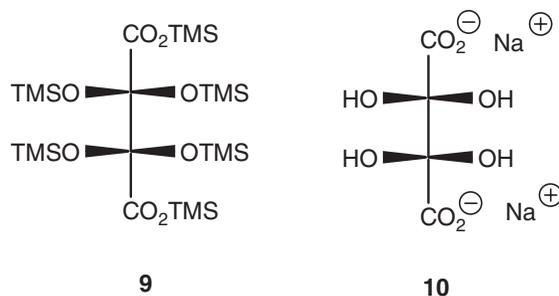


Figure 2: Per-*O*-trimethylsilyl-2,2,3,3-tetrahydroxybutanedioic acid (**9**) and disodium 2,2,3,3-tetrahydroxybutanedioate (**10**).

the exact oxidative pathway from D-xylose to **10** has not been established, **10** is clearly a disalt of the dihydrate form of diketosuccinic (dioxobutanedioic) acid formed in an overoxidation pathway. Disalt **10** (Fig. 2) has not been previously reported from oxidation of an aldopentose.

L- and *D*-arabinose oxidations

D- and L-arabinose were both oxidized using the LabMax reactor, the aqueous acid solutions concentrated to syrups and the reaction mixtures neutralized with sodium hydroxide. The target derivatives for isolation of D- and L-arabinaric acids (**2** and **3**) were corresponding disodium salts **6** and **7** by way of the water-insoluble *N,N'*-dimethyl-D- and L-arabinaramides, **12** and **13** (Fig. 3), respectfully. Notable differences in the oxidation protocols for the arabinoses compared to D-xylose oxidation stemmed from the lower water solubility of the arabinoses and the decreased reactivity of the arabinoses to nitric acid oxidation. A 62.5% D-xylose solution was added to the nitric acid and oxidation carried out at no higher than 35°C, while the arabinose solutions were added as 50% solutions and the oxidation reactor temperature raised to 50°C in order to complete the oxidations.

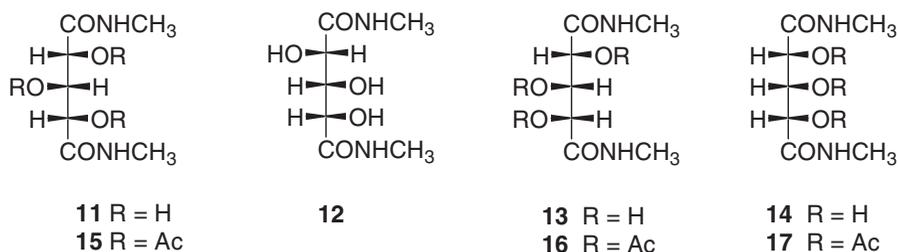
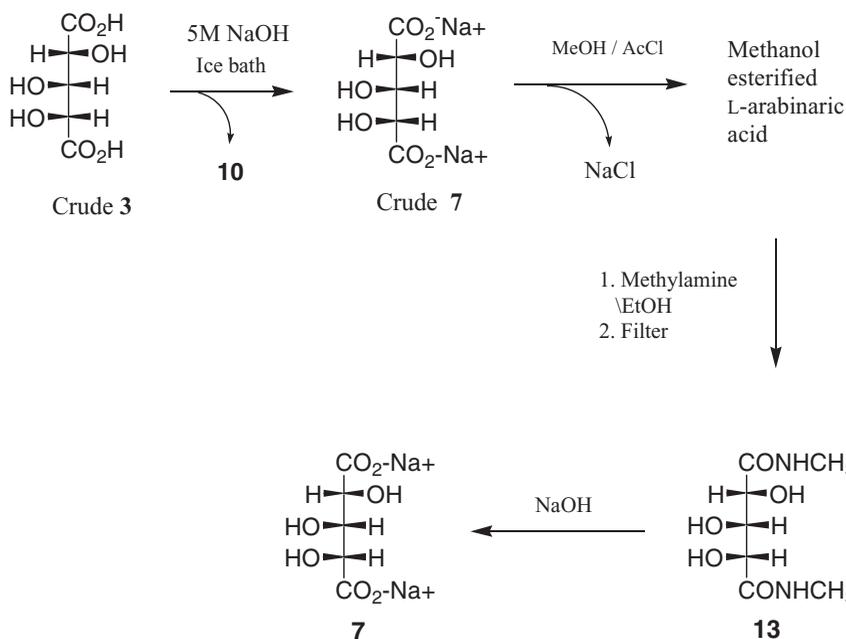


Figure 3: *N,N*-Dimethylpentaramides **11** - **14**, and 2,3,4-tri-*O*-acetyl-*N,N*-dimethylpentaramides **15** - **17**.



Scheme 2: Preparation of *N,N*-dimethyl-L-arabaramide (**13**) and disodium L-arabinarate (**7**).

Both D- and L-arabinose were subjected to the same oxidation protocol and the crude arabinaric acid products treated as outlined in Scheme 2 for the L-arabinose oxidation mixture.

The crude L-arabinaric acid product was made basic with sodium hydroxide and the resulting crude disodium salt converted to a methanol-esterified product in methanol/acetyl chloride. The esterified product was then treated with methylamine/ethanol to yield *N,N*-dimethyl-L-arabaramide (**13**) as an insoluble solid. This diamide was then directly converted to solid disodium L-arabinarate (**7**, 47%) in aqueous sodium hydroxide. This same procedure was applied to a D-arabinose oxidation mixture and solid disodium D-arabinarate (**6**) isolated in 46% yield. Thus, formation of the diamide derivatives **13** and **12** proved to be an effective method to selectively remove the arabinaric acids from their respective oxidation mixtures. As with D-xylose oxidations, basification of the arabinose oxidation mixtures produced small amounts of insoluble **10** (3% to 6%).

D-Ribose oxidation

D-Ribose was oxidized on a small scale and the primary oxidation product, ribaric acid, isolated as crystalline 1,4(5,2)-ribarolactone (**5**, 49.5%).^[1,2] Lactone **5** was readily converted to disodium ribarate (**9**) in aqueous sodium hydroxide, after drying and washing with methanol isolated in >95% yield based

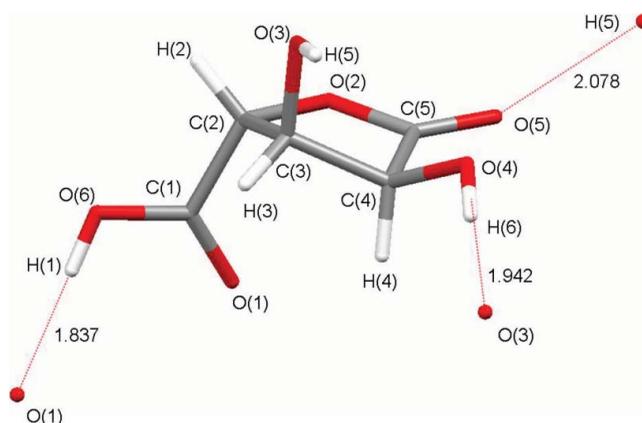


Figure 4: The geometry of 5,2-ribarolactone (**5**) showing atom labeling and hydrogen bonding (distances in angstroms) (color figure available online).

on **5**. Overall, nitric acid oxidation of the four pentoses yielded diacid solid products in the range of 46% to 50%, reasonable yields given the absence of any protecting groups on the aldoses.

1,4(5,2)-Ribaro lactone (**5**) was further characterized by x-ray crystallography, and the geometry of monoclinic crystalline **5**, with atom labeling and hydrogen bonding, is shown in Figure 4.

Monoclinic crystalline **5**, which has a crystal density of 1.761 g cm^{-3} , has one hydrogen bond acceptor [O5⋯H5-O3, 2.078 \AA , 155.41°] bonded to the hydroxyl hydrogen of an adjacent molecule. The hydroxyl group oxygen of O(4) [O4-H6⋯O3, 1.942 \AA , 167.50°] is acting as a hydrogen bond donor to the O(3) hydroxyl group of an adjacent molecule. The carboxylic acid group hydrogen (H1) is hydrogen bonded [O6-H1⋯O1, 1.873 \AA , 178.88°] to the carboxylic acid group carboxyl oxygen of an adjacent molecule. All crystal structure graphics were generated using ORTEP-3^[15] or Mercury.^[16] Crystal data and structure refinement details for 1,4(5,2)-ribarolactone (**5**) are summarized in Table 1, while full details and bond parameters are given in the supplementary information.

2,3,4-tri-*O*-acetyl-*N,N*-dimethylpentaramides **15–17**

The diacids **1–4** were further characterized as their *N,N*-dimethylpentaramides (**11–14**) and diacids **1**, **3**, and **4** as their *N,N*-dimethyl-2,3,4-tri-*O*-acetylpentaramides **15**, **16**, and **17**, respectively. These diamides are also of interest as solid-state model monomer diamide units of the corresponding polyhydroxypolyamides. The x-ray structures of all of these diamides have been determined and are the subject of the following article in this issue.

Table 1: Crystal data and structure refinement for 1,4(5,2)-ribarolactone (5)

| | | |
|-----------------------------------|---|---|
| Identification code | 1,4(5,2)-ribarolactone | |
| Empirical formula | C ₅ H ₆ O ₆ | |
| Formula weight | 162.10 | |
| Temperature | 173(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 6.2642(7) Å b = 5.3342(6) Å c = 18.317(2) Å | $\alpha = 90^\circ$, $\beta = 92.405(9)^\circ$, $\gamma = 90^\circ$. |
| Volume | 611.51(12) Å ³ | |
| Z | 4 | |
| Density (calculated) | 1.761 Mg/m ³ | |
| Absorption coefficient | 1.490 mm ⁻¹ | |
| F(000) | 336 | |
| Crystal size | 0.39 × 0.29 × 0.09 mm ³ | |
| Theta range for data collection | 4.83 to 61.24°. | |
| Index ranges | -6 < = h < = 6, -5 < = k < = 5, -20 < = l < = 20 | |
| Reflections collected | 2050 | |
| Independent reflections | 847 (R(int) = 0.0127) | |
| Completeness to theta = 61.24° | 90.1% | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.8776 and 0.5942 | |
| Refinement method | Full-matrix least-squares on F ² | |
| Data / restraints / parameters | 847 / 0 / 109 | |
| Goodness-of-fit on F ² | 1.109 | |
| Final R indices (I > 2sigma(I)) | R1 = 0.0279, wR2 = 0.0716 | |
| R indices (all data) | R1 = 0.0308, wR2 = 0.0739 | |
| Largest diff. peak and hole | 0.157 and -0.228 e.Å ⁻³ | |

EXPERIMENTAL

General Methods

Concentrations of solutions were carried out under reduced pressure. Drying of samples was carried out at reduced pressure using a Fischer Scientific Isotemp Vacuum Oven Model 280A at rt. Elemental analyses were

performed by Atlantic Microlab, Inc. (Norcross, GA). Melting points were obtained with a Fisher-Johns melting point apparatus and are reported uncorrected.

Oxidations of D-xylose, D-arabinose, and L-arabinose were performed using a Mettler Toledo RC-1 LabMax fitted with a Mettler Toledo PG5002-S Delta Range top-loading balance, ProMinent Fluid Controls Inc. Model G/4b1201TT1 liquid feed pump; Sierra 830/840/860 Series Side-Trak & Auto-Trak Mass Flow Meter and Controller flow valve; FTS Maxi Cool recirculation chiller; and appropriate gas bubbler, pressure manifold with safety valves and gauges, condenser, pH meter, stir rod, thermometer, and temperature-controlled jacketed reaction flask. The system is operator controlled through Camile TG v1.2 software, enabling temperature and pressure control within the 2-L reaction vessel. Concentration of nitric acid was carried out under reduced pressure with a system consisting of a Buchi Rotovapor R-205, Buchi Vacuum Controller V-800, Buchi Heating Bath B-490, Brinkmann Model B-169 Vacuum Aspirator, and Thermo Haake compact refrigerated circulator DC30-K20 in conjunction with a Thermo Haake EK45 immersion circulator cooling coil.

GC-MS analyses were performed on an Agilent 6890N GC interfaced to an Agilent 5973 MS detector. A Phenomenex ZB-5 GC column, 30 m \times 0.25 mm \times 0.25 μ m, composed of 5% phenyl 95% dimethylpolysiloxane, was used for all GC-MS analysis. Samples for GC-MS analyses were prepared as per-*O*-trimethylsilyl derivatives. Tri-Sil Reagent (1.0 mL) was added to dried sample (5.0 mg) in a vial (7 mL) and the mixture heated at 50°C for 60 min. The sample was cooled to rt and heptane (6 mL) added. The mixture was centrifuged, the liquid portion (3 mL) separated and diluted with heptane (3 mL), and aliquots from the resulting solution taken for GC-MS analysis. The following temperature program was employed for sample analysis: begin 32°C, + 12.5°C/min to 250°C, (hold 5 min), + 20°/min to 300°C (hold 5 min), total acquisition time of 30.10 min.

NMR spectra were recorded using a 400-MHz Varian *Unity Plus* spectrometer, at 400 MHz for proton spectra and at 100 MHz for carbon spectra. NMR spectra were processed using ACD/SpecManager 1D NMR software Version 9.13. Chemical shifts were expressed in parts per million relative to *t*-BuOH (1.203 ppm) for D₂O.

Nanofiltration was performed using reverse osmosis (RO) purified water on a unit built in-house consisting of the necessary valves, pump, tubing, pressure gauge, and fitted with a G.E. Water & Process Technologies Model DL2540F1072 nanopore filter.

High-performance liquid chromatography (HPLC), employing a refractive index (RI) detector, was performed on two Aminex HPX-87H columns in series. The first column was heated to 35°C and the second column to 85°C.

A 0.005-M H_2SO_4 eluent was heated to 70°C under an argon atmosphere and samples run isocratically at a 0.5-mL/min flow rate.

Nitric Acid Oxidations

Nitric acid oxidation of D-xylose

Nitric acid oxidation of D-xylose was carried out using the LabMax reactor. The parameters were programmed in a series of stages for the oxidation. Stage 1: The reactor vessel temperature was set at 25°C and the stirring rod speed at 200 rpm. Concentrated nitric acid (70%, 3 mol, 187 mL) was added, the vessel was closed to the atmosphere, and time set for 3 min. Stage 2: Oxygen was added to the reaction vessel to increase the pressure to 0.25 bar. Stage 3: D-xylose [181.2 g of an aqueous 62.5% solution containing sodium nitrite (1.16 g, 16.8 mmol)] was added over 120 min. Stage 4: A 1-min stabilization period was employed with no change in reaction conditions. Stage 5: The reactor temperature was raised to 35°C and the pressure raised by addition of oxygen to 0.5 bar over 60 min. Stage 6: The reaction mixture was held at 35°C and 0.5 bar of pressure for 210 min. Stage 7: The reaction mixture was cooled to 25°C over 10 min and the vessel opened to the atmosphere.

Isolation of xylaric acid (1)—concentration method

A D-xylose oxidation mixture, taken directly from the Mettler Toledo LabMax reactor, was concentrated to a thick syrup at 50°C. Water (200 mL) was added to dissolve the syrup and the resulting solution concentrated to a syrup. This concentration process was repeated twice; the resulting syrup was seeded with xylaric acid and then left undisturbed at rt for 3 d. Cold acetone (300 mL) was added to the semisolid mixture and the mixture stirred at rt for 12 h. The mixture was cooled (ice bath) and white solid xylaric acid was obtained by filtration. (**1**, 44.6 g, 247.5 mmol, 33.00% yield): mp 144–145°C (Lit. 145.5°C,^[1] 151–2°C,^[11] $^1\text{H NMR}$ (D_2O) δ 4.45 (d, 2H, $J = 4.33$ Hz, H-1, H-3) δ 4.22 (t, 1H, H-2); Anal. Calcd for $\text{C}_5\text{H}_8\text{O}_7$ (180.11): C, 33.34; H, 4.48. Found C, 33.31; H, 4.34.

Isolation of xylaric acid (1)—nanofiltration method

A D-xylose oxidation mixture, taken directly from the LabMax reactor, was concentrated to a thick syrup at 50°C. Water (200 mL) was added to dissolve the syrup, the solution cooled (ice bath), and sodium hydroxide (5 M) added with stirring to bring the mixture to pH 4.5. A white precipitate formed, then removed by filtration, and characterized as disodium 2,2,3,3-tetrahydroxybutanedioate (**10**, 8.39 g, 37.1 mmol, 4.94% yield), mp (dec.) 142°C. The filtrate was cooled (ice bath) and sodium hydroxide (5 M) added

with stirring to bring the solution to pH 10. The solution was concentrated under reduced pressure at 50°C to give a brown solid to which absolute ethanol (300 mL) was added and the mixture stirred at rt for 12 h. The solid was removed by filtration and dried to yield crude disodium xylarate (156.9 g) as a brown solid. The solid was dissolved in RO water (3,500 mL) and the solution subjected to nanofiltration. When the permeate volume reached 1,000 mL, RO water (1,000 mL) was added to the feedstock. The typical rate of permeate flow was 48 mL/min. After 2,000 mL of permeate had been removed, another 1,000 mL of RO water was added to the feedstock. This was repeated until 4,000 mL of RO water had been added to the feedstock. Filtration continued until the permeate flow slowed to a trickle. The retentate contained predominantly organic acid sodium salts and the permeate predominately inorganic sodium nitrate, as determined by HPLC analyses. The retentate was concentrated at 50°C to 200 mL and treated with an excess of Amberlite IR-120H⁺ resin (1.32 L, 2.5 mol, 3 h). The resin was removed by filtration and rinsed with water (500 mL), and the combined filtrate and rinse concentrated at 50°C to a thick syrup. The syrup was seeded with xylaric acid and allowed to remain undisturbed at rt for 3 d. Cold acetone (300 mL) was added to the near-solid product and the mixture stirred at rt for 12 h. The mixture was cooled (ice bath) and white solid xylaric acid was separated by filtration (**1**, 67.10 g, 372.6 mmol, 49.67% yield): mp 138–140°C (lit. 145.5°C), ¹H NMR (D₂O) δ 4.45 (d, 2H, H-1, H-3) δ 4.22 (t, 1H, H-2).

Disodium L-arabinarate (7) from nitric acid oxidation of L-arabinose

The oxidation of L-arabinose was carried out using the LabMax reactor employing a procedure patterned after that used for D-xylose oxidation. The following reaction parameters for the oxidation were programmed into the Recipe Menu accessed on the LabMax Camile TG v1.2 software in the following series of stages. Stage 1: The reactor vessel temperature was set at 25°C and the stirring rod speed at 200 rpm. Concentrated nitric acid (70%, 5.13 mol, 320 mL) was added and the vessel was closed to the atmosphere. Stage 2: Oxygen was added to the reaction vessel to increase the pressure to 0.25 bar. Stage 3: L-Arabinose [226.6 g of an aqueous 50.0% solution containing sodium nitrite (1.76 g, 25.5 mmol)] was added over 90 min. Stage 4: A 1-min stabilization period was employed with no changes in reaction conditions. Stage 5: The reactor temperature was raised to 50°C and the pressure raised by addition of oxygen to 0.5 bar over 45 min. Stage 6: The reaction was held at 50°C and 0.5 bar of pressure for 180 min. Stage 7: The reaction mixture was cooled to 25°C over 10 min and the vessel opened to the atmosphere. The L-arabinose oxidation mixture was taken directly from the LabMax reactor, concentrated to a syrup at 50°C, and dissolved in cold (ice bath) water (200 mL). Sodium hydroxide

(5 M) was added with stirring to bring the mixture to pH 4.5. A white precipitate that formed was removed by filtration and identified as disodium 2,2,3,3-tetrahydroxybutanedioate (**10**, 7.95 g, 35.2 mmol, 4.69%, mp (dec.) 142°C). The filtrate was cooled (ice bath) and sodium hydroxide (5 M) added with stirring to bring the mixture to pH 10. The solution was concentrated at 50°C to give a brown solid, which was stirred with absolute ethanol (300 mL) at rt for 12 h. The solid was removed by filtration and dried, to yield crude disodium L-arabinate (148.8 g) as a brown solid. Acetyl chloride (119 g, 1.52 mol) was added with stirring to a mixture of crude solid **3** and cold (ice bath) methanol (100 mL). The reaction mixture was stirred at rt (4 h), after which white, insoluble sodium chloride was removed by filtration. The filtrate was concentrated to a thick syrup at 40°C, which was then dissolved in methanol (100 mL). A solution of methylamine in ethanol (33% b/w, 87.0 g, 265 mL, 2.80 mol) was added dropwise to the cold (ice bath) methanol solution, and the resulting reaction mixture stirred at rt (24 h). White solid *N,N'*-dimethyl-L-arabaramide (**13**) was removed by filtration and used directly in the next step. An analytical sample of **13** was prepared by recrystallization from ethanol, mp 193°C; Anal. Calcd for C₇H₁₄N₂O₅ (206.2): C, 40.77; H, 6.84; N, 13.58. Found C, 41.07; H, 6.87; N, 13.54.

Aqueous sodium hydroxide (2 M, 0.760 mmol, 380.1 mL) was added at rt to solid **13**, the reaction mixture was stirred for 3 d and concentrated at 40°C, and the resultant solid stirred with absolute ethanol (300 mL). The solid was removed by filtration and the stirring/filtration process with ethanol was repeated three times to give a final white amorphous solid of disodium L-arabinate (**7**, 79.9 g, 356.5 mmol, 47.5%); [α]²⁰D -3.68 (*c* 0.217, water); ¹H NMR (D₂O) δ 4.15 (d, 1H, *J* = 1.47 Hz) δ 4.03 (d, 1H) δ 3.99 (d, 1H). ¹³C NMR (D₂O): 180.60, 180.05, 74.20, 74.16, 72.94 ppm. GC-MS of salt **7** as its per-O-TMS derivative (ESI) *m/z* Calcd for [M - 15, C₁₉H₄₅O₇Si₅⁺] 525.2. Found 525. The ¹H NMR spectrum of **7** supported a single disalt structure with no evidence of epimerized product(s).

Disodium D-arabinate (6) from nitric acid oxidation of D-arabinose

The oxidation of D-arabinose was carried out in the LabMax reactor using the procedure described for oxidation of L-arabinose. The D-arabinose oxidation mixture was taken directly from the LabMax reactor, concentrated to a syrup at 50°C, and dissolved in cold (ice bath) water (200 mL). Sodium hydroxide (5 M) was added with stirring to bring the mixture to pH 4.5. White solid disodium 2,2,3,3-tetrahydroxybutanedioate (6.25 g, 27.7 mmol, 3.69%, mp (dec.) 142°C) precipitated and was then removed by filtration. The filtrate was cooled (ice bath) and sodium hydroxide (5 M) added with stirring to bring the mixture to pH 10. The solution was concentrated at 50°C to give a brown solid, which was stirred with absolute ethanol (300 mL) at rt for 12 h. The solid was removed by filtration and dried to yield crude disodium D-arabinate as

a brown solid (142.45 g). Acetyl chloride (119 g, 1.52 mol) was added with stirring to a mixture of crude solid disodium D-arabinate and cold (ice bath) methanol (100 mL). The reaction mixture was stirred at rt for 4 h, white insoluble sodium chloride was removed by filtration, and the filtrate concentrated to a thick syrup at 40°C. The syrup was dissolved in methanol (100 mL), a solution of methylamine in ethanol (33% b/w, 87.0 g, 265 mL, 2.80 mol) was added dropwise to the cold (ice bath) solution, and the resulting reaction mixture stirred at rt (24 h). White solid *N,N'*-dimethyl-D-arabaramide (**12**) was removed by filtration and used directly in the next step. An analytical sample of **12** was prepared by recrystallization from ethanol, mp 195°C; Anal. Calcd for C₇H₁₄N₂O₅ (206.2): C, 40.77; H, 6.84; N, 13.58. Found C, 40.91; H, 6.70; N, 13.35.

Aqueous sodium hydroxide (2M, 0.760 mmol, 380 mL) was added at rt to solid **12**, the reaction mixture was stirred for 3 d and concentrated at 40°C, and the resultant solid was stirred with absolute ethanol (300 mL) and then removed by filtration. The ethanol stirring/filtration processes were repeated three times to give a final white amorphous solid of disodium D-arabinate (**6**), 77.3 g, 345.2 mmol, 46.02%; [α]²⁰D 4.46 (*c* 0.213, water); ¹H NMR (D₂O) δ 4.15 (d, 1H, *J* = 1.47 Hz) δ 4.03 (d, 1H) δ 3.99 (d, 1H). ¹³C NMR (D₂O): 180.60, 180.05, 74.20, 74.16, 72.94 ppm. GC-MS of salt **6** as its per-O-TMS derivative (ESI) *m/z* Calcd for [M - 15, C₁₉H₄₅O₇Si₅⁺] 525.2. Found 525. The ¹H NMR spectrum of **6** supported a single disalt structure with no evidence of epimerized product(s).

Ribaro-5,2(1,4)-lactone (5)—nitric acid oxidation of D-ribose

Solid D-ribose (30.4 g, 202.3 mmol) and solid sodium nitrite (<1 mg) were added to nitric acid (70%, 75 mL, 1.80 mol) in a 500-mL round-bottom flask. The flask was immediately fitted with a water-cooled Liebig condenser and the resulting solution warmed with stirring in an oil bath (65°C, 4 h). Within 1 min the solution warmed to boiling and brown gases violently evolved. At the end of the reaction process the resulting solution was concentrated under reduced pressure to yield a white solid, which was dissolved in water (100 mL) and the solution concentrated to dryness. The dissolution/concentration processes were then repeated twice. The solid product was triturated by stirring with ethyl ether (300 mL, 1 h), to remove nitric acid,^[17] and then isolated by filtration.

The trituration/filtration process was repeated five times and after each filtration step the filtrate was tested for acidity using pH paper, the fifth filtrate having a neutral pH. The white solid was dried under vacuum overnight to yield ribaro-5,2(1,4)-lactone (**5**), 16.3 g, 100 mmol, 49.5% yield. ¹H NMR (D₂O) δ 5.01 (s, 1H) δ 4.66 (d, 1H) δ 4.62 (d, 1H), mp 163–166°C, lit mp 170–171°C.^[1] Anal. Calcd for C₅H₆O₆ (162.10): C, 37.05; H, 3.73. Found C, 36.87; H, 3.71.

Disodium ribarate (8)

Aqueous sodium hydroxide (5 M, 30.0 mL, 150 mmol) was added dropwise, with stirring at rt to a solution of ribaric-5,2(1,4)-lactone (**5**, 10.0 g, 61.8 mmol) in water (50 mL). The solution was stirred at rt for 12 h and then concentrated at 35°C to a white solid. The solid was washed by stirring with methanol (100 mL, 1 h), the white solid isolated by filtration, and the methanol wash procedure repeated three times. The resulting white solid was dried to yield disodium ribarate (**8**, 13.2 g, 59.1 mmol, 95.65%). ¹H NMR (D₂O) δ 4.062 (s, H_{2,3,4}). ¹³C NMR (D₂O): 179.84, 75.42, 74.03 ppm. GC-MS of **7** as its per-O-TMS derivative (ESI) *m/z* Calcd for C₂₀H₄₈O₇Si₅ [M – 15, C₁₉H₄₅O₇Si₅]⁺ 525.2. Found 525. The ¹H NMR spectrum of **8** supported a single disalt structure with no evidence of epimerized product(s).

Disodium 2,2,3,3-tetrahydroxybutanedioate (10)

Disalt **10** was prepared by a modified procedure described by Burnett et al.^[13] and based on the early reports of Fenton.^[18,19] Glacial acetic acid (1 mL) dissolved in cold (ice bath) water (1 mL) was added to a solution of dihydroxyfumaric acid (0.19 g, 1.30 mmol) in water (5 mL). Bromine (0.28 g, 1.73 mmol) was added dropwise with stirring to cold (ice bath) glacial acetic acid (1.5 mL) and the bromine/glacial acetic acid solution was added dropwise over 3 h to the cooled dihydroxyfumaric acid/acetic acid solution. Solid sodium bicarbonate was added until bubble formation stopped and a precipitate that formed was removed by filtration. The solid was washed with acetone (3 × 2 mL), isolated by filtration, and dried to give disodium 2,2,3,3-tetrahydroxybutanedioate dihydrate (**10**, 0.24 g, 0.92 mmol, 70.4%): mp (dec.) 142°C. Anal. Calcd for C₄H₈Na₂O₁₀ (262.08): C, 18.33; H, 3.08. Found C, 18.12; H, 3.07.

N,N'-dimethylxylaramide (11)

Acetyl chloride (0.34 g, 2.85 mmol) was added to a solution of xylaric acid (**1**, 2.06 g, 11.4 mmol) in cold methanol (10 mL) and the solution stirred for 3 h. The reaction mixture was concentrated to a syrup and the syrup was dissolved in cold (ice bath) methanol (15 mL) to which methylamine 10.5 M (5.21 g, 0.17 mmol) in ethanol was added dropwise. The solution was stirred for 3 h and a white solid was removed by filtration and rinsed with cold methanol (2 × 5 mL); yield *N,N'*-dimethylxylaramide (**11**, 1.74 g, 8.43 mmol, 73.8%): mp 191–194°C; ¹H NMR (D₂O) δ 4.266–4.256 (d, 2H, *J* = 3.66 Hz), 4.097–4.079 (t, 1H), 2.749 (s, 6H); ¹³C NMR (D₂O): 175.55, 73.34, 26.58 ppm. Analytical-grade crystals of **11** were obtained by dissolving the white solid in water and allowing the water to slowly evaporate. Anal. Calcd for C₇H₁₄N₂O₅ (206.2): C, 40.77; H, 6.84; N, 13.59. Found C, 40.69; H, 6.84; N, 13.40.

2,3,4-Tri-O-acetyl-N,N'-dimethylxylaramide (15)

Acetic anhydride (5.0 mL, 52.9 mmol) was added to **11** (0.24 g, 1.18 mmol) in pyridine (4 mL) and the solution warmed at 50°C for 3 h. Cold water (7 mL) was added with stirring to the reaction mixture and the mixture extracted with chloroform (3 × 4 mL). The chloroform solutions were combined and concentrated under a stream of nitrogen and then dried at reduced pressure overnight to yield crystalline 2,3,4-tri-*O*-acetyl-*N,N'*-dimethylxylaramide (**15**, 0.27 g, 0.58 mmol, 85.3%): mp 171°C; ¹H NMR (CDCl₃) δ 6.26 (s, 2H), 5.70 (t, 1H, *J* = 5.11 Hz), 5.40–5.38 (d, 2H, *J* = 5.53 Hz), 2.81 (s, 3H), 2.80 (s, 3H), 2.16 (s, 6H), 2.05 (s, 3H); ¹³C NMR (CDCl₃): 169.44, 166.85, 71.86, 70.43, 26.15, 20.65, 20.43 ppm. Analytical-grade crystals of **15** were obtained by dissolving the crystalline product described in water and allowing acetone to diffuse into the aqueous solution. Anal. Calcd for C₁₃H₂₀N₂O₈ (332.31): C, 46.99; H, 6.07; N, 8.43. Found C, 46.93; H, 6.12; N, 8.33.

2,3,4-Tri-O-acetyl-N,N'-dimethyl L-arabinaramide (16)

Acetic anhydride (5.0 mL, 52.9 mmol) was added dropwise to *N,N'*-dimethyl-L-arabinaramide (**13**, 0.35 g, 1.69 mmol) in pyridine (4 mL) and the solution warmed to 50°C for 3 h. Cold (ice bath) water (7 mL) was added dropwise to the solution and the mixture concentrated under a stream of nitrogen and then at reduced pressure overnight. The resulting solid was stirred with water (1.5 mL) for 30 min, isolated by filtration, and dried to yield 2,3,4-tri-*O*-acetyl-*N,N'*-dimethyl-L-arabinaramide (**16**, 0.35 g, 1.06 mmol, 62.74%): mp 209–210°C; ¹H NMR (CDCl₃) δ 6.74 (s, 1H), 6.46 (s, 1H), 5.67–5.64 (d, 1H), 5.48–5.46 (d, *J* = 7.99 Hz, 1H), 5.35–5.34 (d, 1H, *J* = 4.79 Hz), 2.85–2.83 (q, 6H), 2.21 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H); ¹³C NMR (CDCl₃): 169.48, 169.27, 168.65, 166.91, 166.81, 71.71, 70.57, 70.50, 26.18, 26.09. Analytical-grade crystals of **16** were obtained by dissolving the crystalline product in warm methanol and allowing the diffusion of acetone into the methanol solution. Anal. Calcd for C₁₃H₂₀N₂O₈ (332.31): C, 46.99; H, 6.07; N, 8.43. Found C, 47.03; H, 6.07; N, 8.41.

N,N'-Dimethylribaramide (14)

Acetyl chloride (4.61 mL, 5.09 g, 64.8 mmol) was added to a solution of disodium ribarate (**8**, 4.84 g, 21.6 mmol) in cold (ice bath) methanol (30 mL) and the reaction mixture stirred for 3 h. A white solid was removed by filtration, the filtrate was concentrated, and the syrupy residue dissolved in cold (ice bath) methanol (10 mL). Methylamine (10.5 M, 11.0 mL, 86.4 mmol) in ethanol was added dropwise to the methanol solution and the reaction mixture stirred overnight at rt. A white solid was removed by filtration, dried at reduced pressure overnight, stirred with methanol (5 mL), separated by filtration, rinsed with methanol (2 × 1 mL), and dried to yield *N,N'*-dimethylribaramide (**14**,

1.58 g, 7.67 mmol, 35.5%): mp 165–168°C; ^1H NMR (D_2O) δ 4.233 (d, 1H, $J = 5.13$ Hz), 4.112 (t, 2H, $J = 5.13$ Hz), 2.73 (s, 6H); ^{13}C NMR (D_2O): 175.48, 74.37, 73.04, 26.55 ppm. Evaporation of water from an aqueous solution of **14** gave analytical-grade product. Anal. Calcd for $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_5$ (206.2): C, 40.77; H, 6.84; N, 13.59. Found C, 40.86; H, 6.83; N, 13.58.

2,3,4-Tri-O-acetyl-N,N'-dimethylribaramide (17)

Acetic anhydride (11.8 mL, 125 mmol) was added dropwise to *N,N'*-dimethylribaramide (**14**, 1.25 g, 6.23 mmol) in pyridine (5 mL) and the solution stirred overnight. Cold (ice bath) water (15 mL) was added dropwise and the mixture stirred for 30 min. The solvent was removed under a stream of nitrogen, the residue dissolved in water (3 mL), and the aqueous solution extracted with chloroform (3×10 mL). The chloroform extracts were combined, concentrated under a stream of nitrogen, and dried at reduced pressure overnight to yield 2,3,4-tri-*O*-acetyl-*N,N'*-dimethylribaramide (**17**, 2.05 g, 6.16 mmol, 79.9%): mp 166–169°C; ^1H NMR (CDCl_3) δ 6.33 (s, 2H), 5.66 (t, 1H, $J = 5.86$ Hz), 5.45 (d, 2H, $J = 5.86$ Hz), 2.81 (s, 3H), 2.80 (s, 3H), 2.13 (s, 6H), 2.03 (s, 3H); ^{13}C NMR (CDCl_3): 169.23, 166.73, 71.18, 70.65, 26.11, 20.68 ppm. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_{11}$ (332.31): C, 46.99; H, 6.07; N, 8.43. Found C, 47.17; H, 5.97; N, 8.54.

Crystal Structure Analysis

A suitable crystal of 1,4(5,2)-ribarolactone (**5**) was coated with Paratone N oil, suspended in a small fiber loop, and placed in a cooled nitrogen gas stream at 173 K on a Bruker D8 APEX II CCD sealed tube diffractometer with graphite monochromated CuK_α (1.54178 Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10-s frame exposures and 0.5° frame widths. Data collection, indexing, and initial cell refinements were all carried out using APEX II^[20] software. Frame integration and final cell refinements were done using SAINT^[21] software.

The structure was solved using direct methods and difference Fourier techniques (SHELXTL, V6.12).^[22] Hydrogen atoms were placed in their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic U_{ij} related to the atom's ridded upon except for the hydrogens on O2 and O3 that were located in a diff map and refined. All nonhydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from the *International Tables for X-ray Crystallography*.^[23] Structure solution, refinement, graphics, and generation of publication materials were performed by using SHELXTL, v6.12 software. Additional details of data collection and structure refinement are given in Table 1.

Supplementary Information

The Supplementary Tables give crystal data and refinement details, bond lengths, bond angles, selected torsion angles, and H-bonding details for **1–7**. Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Center, CCDC Nos. 865172-865178 for compound **5**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1 EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: <http://www.ccdc.ac.uk>). ¹H NMR spectra of compounds prepared are included as additional supplementary information.

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