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Synthesis of D-erythroascorbic acid from D-glucose*

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ABSTRACT

Reaction of a 4:1 mixture of D-ribono- and D-arabinono-1,4-lactones with benzaldehyde and hydrochloric acid gave 59% crystalline 3,4-*O*-benzylidene-D-ribono-1,5-lactone. This acetal was oxidized with manganese dioxide in acetone to its 2-keto derivative (**6**) in 76% yield. Acid-catalyzed methanolysis of **6** gave a syrupy mixture of products, which upon tautomerization in hot methanolic sodium acetate followed by removal of sodium ions gave 78% D-erythroascorbic acid (**7**). The overall yield of **7** starting from D-glucose was 20%.

INTRODUCTION

D-*glycero*-2-Pentenono-1,4-lactone (D-erythroascorbic acid, EAA) appears to be an intermediate in the production of oxalate by phytopathogenic fungi[1]. Investigation of the metabolism of EAA (**7**) requires isotopically labeled compound, which we wish to prepare from D-glucose. We recently developed a four-step synthesis to convert D-glucose, with loss of C-1, into EAA in 11% yield[2a]. We report here a five-step method giving 20% EAA from D-glucose, again with the loss of C-1.

RESULTS AND DISCUSSION

Potassium D-arabinonate, obtained[2] by O_2-oxidation of D-glucose, was immediately converted into the calcium salt (**1**) by a modification of the method of Sperber *et al.*[3] The yield of **1**, isolated by crystallization, was 74% overall. Epimerization in hot aqueous calcium hydroxide under pressure gave a 3:7 mixture of D-ribonate (**2**) and D-arabinonate, and a 22% conversion of **1** into **2** as determined by h.p.l.c. Shereshevskii and Gyach[4] reported that other Russian workers obtained 30–35% of **2** by epimerizing **1**. Unreacted **1**, due to its low solubility in water, could be readily recovered from the reaction mixture in 50–60% yield. Three cycles of the epimerization reaction, starting with 105 g of **1**, gave crude **2** in 80% yield. Following acidification of the technical product, h.p.l.c. showed a 4:1 mixture of D-ribonolactone (**3**) and D-arabinonolactone (**4**), in agreement with Shereshevskii and Gyach[4]. The epimerization of **1** to **2** was used by Shereshevskii and Gyach[4] for the preparation of riboflavin.

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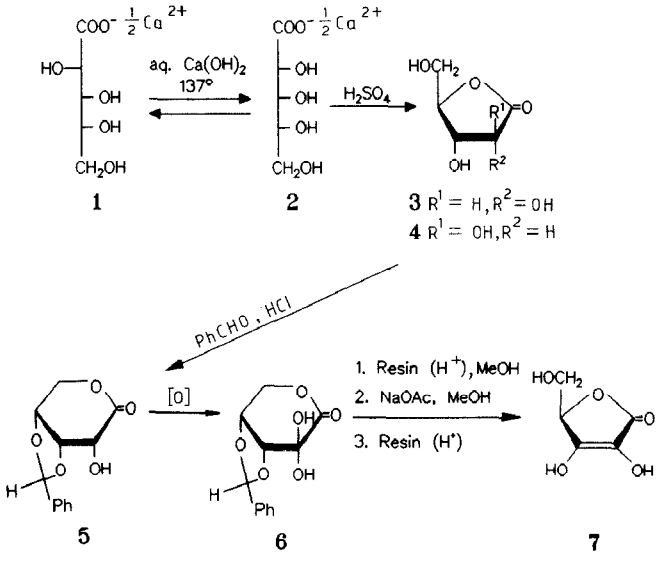


Scheme 1

Conversion into 3,4-*O*-benzylidene-D-ribono-1,5-lactone (**5**), a readily crystallized compound, enabled us to separate D-ribonolactone (**3**) from its epimeric lactone (**4**). Compound **5** also served as a key intermediate in the synthetic route to D-erythroascorbic acid (**7**) (Scheme 1). In the past[4], **3** has been separated from **4** as its crystalline 2,3-*O*-isopropylidene derivative. Here, reaction of the 4:1 mixture of **3** and **4** with benzaldehyde and concentrated hydrochloric acid[5-7] produced, as expected[4], no acetal of the D-arabinonolactone (**4**), but gave 59% (isolated) of **5** as pure crystals.

Oxidation of the acetal **5**. — The oxidation of **5** to its 2-keto hydrate (**6**) was best achieved using active manganese dioxide in acetone medium. The 76% yield of **6** from **5** was similar to that reported[8] for the oxidation of 3,5-*O*-benzylidene-L-*gulono*-1,4-lactone to 3,5-*O*-benzylidene-L-*xylo*-hexulosono-1,4-lactone, which was subsequently converted in one or two steps into L-ascorbic acid.

Oxidation of **5** with dimethyl sulfoxide–acetic anhydride gave only 23% of **6**, probably because of the formation of byproducts such as the *O*-acetate and the methylthiomethyl ether, arising through competitive reactions[9] of **5** with the acyloxysulfonium ion $(CH_3)_2S^+OCOCH_3$ or its transformation products. Ruthenium tetraoxide oxidation of **5** proceeded with difficulty due to the low solubility (< 15 p.p.m.) of **5** in chlorinated hydrocarbons.

The preferred oxidant, manganese dioxide, was prepared according to Mancera *et al.*[10]. Several other "active" forms of manganese dioxide, either prepared by the procedure of Carpino[11] or purchased commercially*, failed to react with **5** in acetone solution at 25°.

* The commercial product was used directly or was first washed with hot water to pH 7 and dried for 20 h at 130°.

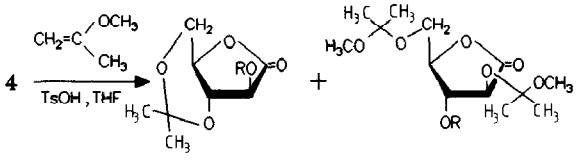
Preparation of D-*erythroascorbic acid* (**7**). — Crawford and Breitenbach[8] used aqueous acetic acid to convert 3,5-*O*-benzylidene-L-*xylo*-hexulosono-1,4-lactone directly into L-ascorbic acid in 59% isolated yield. Also, they[8] used methanolic hydrogen chloride to convert the lactone into methyl L-*xylo*-hexulosonate, which was then tautomerized to L-ascorbic acid by either acid or base catalysis. When compound **6** was treated under acidic conditions, severe decomposition occurred, and only traces of D-erythroascorbic acid (**7**) were formed as evidenced by t.l.c.

The conversion of **6** into **7** was achieved successfully by a two-stage procedure, without isolation of the intermediate products. Acid-catalyzed methanolysis of **6** at 25° in the presence of an ion-exchange resin removed the 3,4-acetal blocking group, as shown by loss of the aromatic signals in the ^{1}H-n.m.r. spectrum. The n.m.r. pattern also revealed a complex mixture of products, which presumably contained the 2-keto methyl ester and the 2-keto 1,4- and 1,5-lactones. Nevertheless, boiling the products in methanolic sodium acetate caused tautomerization of most, if not all, of the components to give D-erythroascorbic acid (**7**), which was isolated in crystalline form in 78% yield based on **6**.

The direct separation of D-ribonolactone (**3**) from D-arabinonolactone **4**, by fractional crystallization (see Experimental), provides a second pathway to EAA. The lactone **3** can be selectively oxidized at the HO-2 by chlorate[2a], or it can be protected by a 3,4-acetal group and then oxidized at the HO-2. The yield of either 2-keto derivative is 21–25% from D-glucose.

The fractional crystallization of calcium D-ribonate from the epimerization mixture is the weak preparative step in converting D-glucose into EAA. In work with isotopically labeled material, separation of the aldonates could be accomplished with a strongly acidic cation-exchange resin in the calcium form.

Oxidation of acetal derivatives of D-*arabinono-1,4-lactone*. — Originally, we planned to synthesize D-erythroascorbic acid (**7**) from D-glucose by the oxidation of blocked derivatives of D-arabinono-1,4-lactone. We prepared the 3,5-cyclic acetal (**8**) and the 2,5-acyclic diacetal (**9**) by reaction of **4** with 2-methoxypropene in the presence of *p*-toluenesulfonic acid (Scheme 2). However, both the acetals **8** and **9** failed to undergo smooth oxidation to keto derivatives when reacted with manganese dioxide, ruthenium tetraoxide, or dimethyl sulfoxide–acetic anhydride.



8 R=H **9** R=H
8a R=Ac **9a** R=Ac

THF = tetrahydrofuran (oxolane)

Scheme 2

The yields of **8** and **9** depended on the ratio of 2-methoxypropene to D-arabino-no-1,4-lactone used in the acetalation reaction, since the formation of acetal derivatives from 2-methoxypropene is under kinetic control[12,13]. With a molar ratio of 2:1 (2-methoxypropene to **4**) the cyclic (**8**) and acyclic (**9**) acetals were isolated in 37 and 9% yield, respectively, after silica gel chromatography. With a molar ratio of 4:1 the predominant product became the acyclic acetal, and **8** and **9** were obtained in 16 and 22% yield, respectively.

The structures of **8** and **9** were determined by n.m.r. spectroscopic analysis of the compounds themselves and their acetate derivatives. In the case of **8**, two methyl signals for the isopropylidene group were observed at δ 1.43 and 1.53 in the proton spectrum, and at δ 25.1 and 27.8 in the ^{13}C spectrum, with a single acetal-carbon signal at δ 101.6. These data indicate the presence of a cyclic acetal structure in **8**.

In the case of **9**, methyl signals from isopropylidene groups were observed at δ 1.36 and 1.56 in the ^{1}H spectrum, and δ 24.2, 24.3, 24.5, and 24.8 in the ^{13}C spectrum. In addition, compound **9** showed two methoxy signals, at δ_H 3.21 and 3.37 and at δ_C 48.6 and 49.7, plus two acetal-carbon signals at δ_C 100.4 and 102.4. These results revealed that **9** contained two acyclic acetal groups.

A careful comparison of ^{1}H-n.m.r. spectra showed that upon acetylation the signal for H-2 of **8** at δ 4.29 was shifted downfield to δ 5.69 in **8a**, while the H-3 signal of **9** at δ 4.25 was shifted downfield to δ 5.38 in **9a**. The signal assignments for H-2 in **8** and H-3 in **9** were based on comparisons with the spectrum of D-arabinonolactone[14]. Thus, the cyclic acetal group in **8** was located at C-3 and C-5, and the acyclic acetal groups in **9** at C-2 and C-5. This conclusion was further supported by the ^{13}C signals of C-2 in **8a** and C-3 in **9a**, both of which exhibited significant downfield (α-C) shifts compared to the corresponding carbons in **8** and **9**, and the signals of C-1 and C-3 of **8a** and C-2 and C-4 of **9a**, which exhibited the expected upfield (β-C) shifts[15-17].

CONCLUSIONS

D-Erythroascorbic acid (**7**) can be synthesized in 20% yield by a five-step synthesis starting from D-glucose. If the method is used to prepare isotopically labeled **7**, C-2 through C-6 of D-glucose become C-1 through C-5 of **7**.

EXPERIMENTAL

General methods, and materials. — Solutions were evaporated at <40° under diminished pressure. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Specific rotations were determined in a 10-cm polarimeter tube on a Perkin–Elmer 241 polarimeter. Column chromatography was carried out at 25° on silica gel (230–400 mesh, Sigma Chemical Co.). T.l.c. was performed at 25° on aluminum sheets coated with Silica Gel 60 F_{254} (E. Merck), with detection either by viewing under short-wavelength u.v. light or by spraying with acid molybdate[18]. Both ^{1}H (400 MHz) and ^{13}C (100.6 MHz) n.m.r. spectra were recorded on a Bruker WM-400

instrument. Chemical shifts are referenced to tetramethylsilane, by calculation from the signals of the solvents used as secondary standards. High-performance anion-exchange chromatography with pulsed electrochemical detection (h.p.a.e.–p.e.d.) was done on a Dionex system equipped with a CarboPac PAI column (4 × 250 mm) and a CarboPac PA guard (3 × 25 mm). The column was developed isocratically with 150mM sodium hydroxide containing 25mM sodium acetate. All separations were carried out at ambient temperature, with a flow rate of 1 mL min^{-1}.

Active manganese dioxide was prepared according to the method of Mancera *et al.*[10] Acetone was purified by stirring with excess potassium permanganate (2 g L^{-1}) for 24 h at 25° and then distilling. 3,4-*O*-Benzylidene-D-ribono-1,5-lactone, D-ribono-1,4-lactone, ruthenium dioxide, isopropenyl methyl ether, and *p*-toluenesulfonic acid were from Aldrich Chemical Co. Methanol was reagent grade from Fisher Scientific Co.

Calcium D-*arabinonate* (**1**) *and* D-*arabinono-1,4-lactone* (**4**). — D-Glucose was oxidized[2b] to potassium D-arabinonate (m.p. 220–225°), and the potassium salt converted[2] into D-arabinono-1,4-lactone (m.p. 96–99°). Separately, calcium acetate (40.0 g, 228 mmol) was added with stirring to a hot solution of the potassium salt (92.85 g, 455 mmol) dissolved in a minimum amount of water (150 mL). Heating on the steam bath was continued for 1 h, then the mixture was cooled to 0–5° for 6 h. The colorless crystals of calcium D-arabinonate pentahydrate (**1**, $C_{10}H_{18}CaO_{12}\cdot 5H_2O$) were collected by filtration and washed with ice–water (30 mL) and ethanol (50 mL). After drying in air the material weighed 99.54 g (95%), $[\alpha]_D^{25}$ −3.3° (*c* 1.5, H_2O).

D-*Ribono-1,4-lactone* (**3**). — The method of Shereshevskii and Gyach[4] was followed, with modification. Compound **1** (104.7 g, 227 mmol), water (206 mL), and calcium hydroxide (1.01 g, 13.5 mmol) were placed in a Parr Pressure Reactor (Model 4521, Parr Instrument Co.). The mixture was heated to 137° and stirred at that temperature for 5 h. After cooling to 25°, the reaction mixture was assayed by h.p.a.e–p.e.d. Using standard curves derived from pure **3** and **4**, the reaction mixture was found to contain 63.0 g (137 mmol, 60%) of unreacted **1** and 18.5 g (50 mmol, anhydrous basis, 22% conversion) of **2**. The whole reaction mixture was treated with activated charcoal (5 g), and stirred and heated on a steam bath (20 min) while its volume was maintained by periodic additions of water. Upon cooling at 0–5° for 15 h the mixture deposited crystals of unreacted **1**. These crystals (containing 3–5% of **2**) were collected by filtration, washed with water (20 mL), and dried in air. Recovery of **1** was 64.4 g (140 mmol). The mother liquor was adjusted to pH 1.8 by adding concentrated sulfuric acid, and the precipitated calcium sulfate removed by filtration. The filtrate was evaporated to dryness under reduced pressure at 40–50°, then the residue was dissolved in methanol, and the insoluble salts again removed. The methanolic solution was evaporated under reduced pressure to give crude D-ribono-1,4-lactone (20.7 g) as a dark-brown syrup, which corresponded to a yield of 80% based on reacted **1**. The technical lactone, which was a mixture containing 20% of the D-arabinono (**4**) and 80% of the D-ribono (**3**) isomer according to h.p.l.c.–p.e.d. analysis, was used directly to prepare the benzylidene derivative (**5**).

A small portion (3.5 g) of the technical lactone was dissolved in methanol (5 mL)

and *n*-butanol (25 mL). The solution was concentrated to 15–20 mL, and seeded with D-ribono-1,4-lactone. On standing at 25° for a few days the concentrate deposited crystalline material, which was filtered off, washed with butanol, and recrystallized from methanol–ethyl acetate to give **3** (0.80 g) as colorless needles, m.p. 82–83°; $[\alpha]_D^{25}$ +18.2° (*c* 1.0, H_2O); lit.[4] m.p. 78–80°, $[\alpha]_D$ +18.4°. The mother liquor was concentrated to a syrup (2.7 g), which still gave a 50% yield of **5** when treated as described in the next paragraph.

3,4-O-Benzylidene-D-ribono-1,5-lactone (**5**). — A mixture of technical **3** (syrup, 20.7 g, 140 mmol), benzaldehyde (186 mL), and concentrated hydrochloric acid (18.6 mL) was shaken at 25° for ~30 min until the syrup dissolved. The solution was stirred for 7 h, then diethyl ether (232 mL) was added and the mixture was cooled overnight at 0°. The deposited crystals were collected by filtration and washed successively with water, 2.5% sodium hydrogencarbonate solution, water, and petroleum ether. After drying over phosphorus pentoxide the product (19.9 g) was recrystallized from acetone to give **5** (19.5 g, 59%) as colorless needles, m.p. 237–238°; $[\alpha]_D^{25}$ −174° (*c* 1.17, Me_2NCHO); lit.[7] m.p. 233–235.5°, $[\alpha]_D$ −174.1°.

3,4-O-Benzylidene-D-erythro-pentulosono-1,5-lactone hydrate (**6**). — *Method A.* To a solution of **5** (2.36 g, 10 mmol) in dimethyl sulfoxide (100 mL) at 25° was added acetic anhydride (20 mL). The solution was stirred under nitrogen for 14 h, and then poured into a mixture of 1:1 diethyl ether–ethyl acetate and ice–water. After extraction, the organic layer was collected and dried over anhydrous sodium sulfate. Evaporation under reduced pressure gave a syrup that was shown to have three components on t.l.c. (8:4:1:4 chloroform–ethyl acetate–acetone–petroleum ether). The syrup was subjected to column chromatography on silica gel with 2:1 chloroform–acetone as eluting solvent to give 1.74 g of crude product, which was the slowest-moving component on t.l.c. This material was rechromatographed on silica gel with 8:4:1:4 chloroform–ethyl acetate–acetone–petroleum ether as eluent. Compound **6** (0.55 g, 23.5%) was obtained as colorless platelets from acetone–carbon tetrachloride, m.p. 125–128°; $[\alpha]_D^{25}$ −153° (*c* 1.09, $CHCl_3$); ^{1}H-n.m.r. (acetone-d_6): δ 7.35–7.48 (m, 5 H, Ar-H), 6.43 (s, 1 H, O*H*), 5.92 (s, 1 H, O*H*), 5.79 (s, 1 H, PhC*H*), 4.87 (dd, 1 H, *J* 2.1, 12.4 Hz, H-5b), 4.74 (ddd, 1 H, *J* 0.8, 2.1, 8.0 Hz, H-4), 4.55 (d, 1 H, *J* 8.0 Hz, H-3), and 4.43 (dd, 1 H, *J* 0.8, 12.4 Hz, H-5a); ^{13}C-n.m.r. (acetone-d_6): δ 170.8 (C-1), 138.3, 130.6, 129.3, and 128.1 (6 Ar-C), 104.8 (Ph*C*H), 91.0 (C-2), 79.6 (C-3), 74.7 (C-4), and 70.0 (C-5); ^{13}C (Me_2SO-d_6): δ 169.2 (C-1), 136.0, 129.8, 128.2, and 127.0 (6 Ar-C), 102.5 (Ph*C*H), 89.6 (C-2), 78.4 (C-3), 73.2 (C-4), and 68.4 (C-5).

Anal. Calc. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.76. Found: C, 56.92; H, 4.87.

Method B. To a stirred mixture of **5** (236 mg, 1 mmol), ruthenium dioxide (100 mg) and benzyltriethylammonium chloride (15 mg) in chloroform (50 mL) and dioxane (50 mL) at 25° was added a solution of sodium periodate (1.3 g) in water (10 mL). After 24 h additional ruthenium dioxide (100 mg) and sodium periodate solution (1.3 g in 10 mL water) were added. After another 15 h of stirring, the reaction mixture was filtered through a bed of diatomaceous earth. The organic layer was separated, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give a yellow

syrup, which was shown to have two components on t.l.c. (8:4:1:4 chloroform–ethyl acetate–acetone–petroleum ether). The faster moving component with R_F 0.23 was the desired keto lactone (**6**). The syrup was subjected to column chromatography on silica gel using the same solvent mixture to give **6** (110 mg, 43%) in fractions (15 mL each) 8–12 and **5** (40 mg) in fractions 18–25. Analytically pure **6** was obtained by recrystallization from acetone–carbon tetrachloride.

Method C. To a suspension of active manganese dioxide[10] (4.35 g, 50 mmol) in purified acetone (300 mL) was added **5** (1.18 g, 5 mmol), and the mixture was stirred until no starting material was detectable on t.l.c. (1:1 ethyl acetate–petroleum ether). Most of the oxidant was removed by filtration through a bed of diatomaceous earth, followed by concentration to 50 mL and filtration through a bed of silica gel. The solvent was evaporated under reduced pressure to obtain crude **6** as a colorless solid. Recrystallization from acetone–carbon tetrachloride gave pure **6** (0.96 g, 76%).

D-*Erythroascorbic acid* (**7**). — To a solution of **6** (1.0 g, 4 mmol) in methanol (100 mL) was added strongly acidic ion-exchange resin (Amberlite IR-120, H^+ form, 28 g, Mallinckrodt), which had been solvent-exchanged with dry methanol over a period of several days. The slurry was stirred at 25° until no starting material was detectable on t.l.c. (1:1 ethyl acetate–petoleum ether), at which time the resin was removed by filtration. The filtrate was concentrated to dryness, and the residue dissolved in methanol (80 mL) containing anhydrous sodium acetate (2.0 g). This reaction mixture was heated at reflux for 5 min, then cooled to 25°, and acidified to pH 2 (wet pH paper) by adding Amberlite IR-120 resin (H^+ form) in methanol. The resin was removed by filtration, and the filtrate evaporated to dryness to give D-erythroascorbic acid (**7**) as a colorless solid. Compound **7** was further purified by recrystallization from acetonitrile to give colorless needles (457 mg, 78%), m.p. 161–162°; $[\alpha]_D^{25}$ +12.5° (*c* 1.0, MeOH), in agreement with the m.p. of 161° and specific rotation ($[\alpha]_D^{25}$) of +12.6° of previously prepared[2a] material. The ^{1}H-n.m.r. (MeOH-d_4) showed: δ 4.69 (dd, 1 H, *J* 2.5, 4.5 Hz, H-4), 3.94 (dd, 1 H, *J* 2.5, 12.6 Hz, H-5b), and 3.68 (dd, 1 H, *J* 4.5, 12.6 Hz, H-5a); ^{13}C-n.m.r. (MeOH-d_4): δ 173.3 (C-1), 154.0 (C-3), 119.9 (C-2), 78.5 (C-4), and 61.7 (C-5).

Anal. Calc. for $C_5H_6O_5$: C, 41.09; H, 4.10. Found: C, 40.95; H, 4.19.

*3,5-*O*-Isopropylidene-*D*-arabinono-1,4-lactone* (**8**) *and 2,5-di-*O*-(1-methoxy-1-methylethyl)-*D*-arabinono-1,4-lactone* (**9**) *and their acetyl derivatives* (**8a** *and* **9a**). — A solution of **4** (444 mg, 3 mmol) in dry tetrahydrofuran (10 mL) containing Drierite powder (150 mg) was maintained at 0–5° for 30 min, and isopropenyl methyl ether (0.6 mL, 6 mmol) and *p*-toluenesulfonic acid (3 mg) were added. The mixture was stirred at 0–5° until t.l.c. indicated that all the starting material (**4**) had disappeared (~5 h), at which time anhydrous pyridine (0.2 mL) was added. Stirring was continued overnight at 25°, then the Drierite was removed by filtration through a bed of silica gel, and the residue washed with 3:1 chloroform–acetone. The filtrate was evaporated under reduced pressure to give a syrup (0.66 g), which was subjected to flash-column chromatography on silica gel eluted successively with 4:1:5 and 4:1:2 chloroform–acetone–petroleum ether to afford **9** (80 mg, 9%) and **8** (210 mg, 37%), from fractions (20 mL each) 16–24 and 62–80, respectively.

Compound **8** was recrystallized from chloroform–acetone–petroleum ether to give colorless crystals, m.p. 192–194°; $[\alpha]_D^{25}$ +126.3° (*c* 0.4, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 4.87 (dd, 1 H, *J* 8.2, 8.2 Hz, H-3), 4.44 (ddd, 1 H, *J* 8.2, 2.0, 2.0 Hz, H-4), 4.29 (d, 1 H, *J* 8.2 Hz, H-2), 3.86 (dd, 1 H, *J* 11.5, 2.0 Hz, H-5b), 3.64 (dd, 1 H, *J* 11.5, 2.0 Hz, H-5a), 2.83 (s, 1 H, D_2O exchangeable, O*H*), 1.53, and 1.43 (2 s, 6 H, CCH_3); ^{13}C-n.m.r. ($CDCl_3$): δ 174.5 (C-1), 101.6 (acetal-C), 78.9 (C-4), 74.7 (C-3), 71.4 (C-2), 57.5 (C-5), 27.8, and 25.1 (2 C*C*H_3).

Anal. Calc. for $C_8H_{12}O_5$: C, 51.06; H, 6.38. Found: C, 50.71; H, 6.51.

To a solution of **8** (94 mg, 0.5 mmol) in pyridine (1.0 mL) was added acetic anhydride (0.5 mL). The mixture was allowed to stand for 6 h at 25°, then poured into ice–water. The precipitate was collected by filtration, washed with water, and dried over phosphorus pentoxide in vacuum. The dry solid (94 mg), m.p. 222–223°; $[\alpha]_D^{25}$ +113° (*c* 1.0, $CHCl_3$), was recrystallized from acetone–petroleum ether to give colorless crystals of **8a**, m.p. 229–230°; $[\alpha]_D^{25}$ +111.4° (*c* 0.98, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 5.69 (d, 1 H, *J* 8.3 Hz, H-2), 5.04 (dd, 1 H, *J* 8.3, 8.3 Hz, H-3), 4.37 (ddd, 1 H, *J* 8.3, 1.8, 1.8 Hz, H-4), 3.87 (dd, 1 H, *J* 11.5, 1.8 Hz, H-5b), 3.64 (dd, 1 H, *J* 11.5, 1.8 Hz, H-5a), 2.22 (s, 3 H, CH_3CO), 1.42, and 1.35 (2 s, 6 H, CCH_3); ^{13}C-n.m.r. ($CDCl_3$): δ 169.2 (C-1 and CH_3*C*O), 101.4 (acetal-C), 78.6 (C-4), 74.2 (C-2), 68.8 (C-3), 57.7 (C-5), 27.1 and 24.9 (C*C*H_3), and 20.5 (*C*H_3CO).

Compound **9** was recrystallized from diethyl ether–petroleum ether to give colorless crystals, m.p. 133–134°; $[\alpha]_D^{25}$ +11.6° (*c* 0.32, $CHCl_3$); $[\alpha]_D^{25}$ +11.2° (*c* 0.82, MeOH); ^{1}H-n.m.r. ($CDCl_3$): δ 4.55 (d, 1 H, *J* 5.7 Hz, H-2), 4.25 (m, 2 H, H-3,4), 3.77 (dd, 1 H, *J* 11.2, 2.4 Hz, H-5b), 3.64 (dd, 1 H, *J* 11.2, 4.5 Hz, H-5a), 3.50 (s, 1 H, D_2O exchangeable, O*H*), 3.37, 3.21 (2 s, 6 H, OCH_3), 1.50, and 1.36 (2 s, 12 H, CCH_3); ^{13}C-n.m.r. ($CDCl_3$): δ 171.8 (C-1), 102.4 and 100.4 (acetal-C), 78.7 (C-4), 74.7 (C-3), 73.6 (C-2), 59.2 (C-5), 49.7 and 48.6 (O*C*H_3), 24.8, 24.5, 24.3, and 24.2 (4 C*C*H_3).

Anal. Calc. for $C_{13}H_{24}O_7 \cdot 0.5\ H_2O$: C, 51.83; H, 8.31. Found: C, 51.82; H, 7.96.

To a solution of **9** (292 mg, 1 mmol) in pyridine (2.0 mL) was added acetic anhydride (0.7 mL), and the mixture was allowed to stand at 25° until monitoring by t.l.c. showed that acetylation was complete (~4 h). The acetate derivative was isolated by extractive workup, using diethyl ether. Evaporation of the ether gave a syrup (0.36 g), which was subjected to flash-column chromatography on silica gel eluted with 4:1:5 chloroform–acetone–petroleum ether to afford pure **9a** (0.28 g, 84%) from fractions 5–8. The acetate **9a** crystallized on standing overnight at 4°. The colorless needles had m.p. 62–63°; $[\alpha]_D^{25}$ −6.4° (*c* 1.04, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): 5.38 (dd, 1 H, *J* 5.7, 5.7 Hz, H-3), 4.66 (d, 1 H, *J* 5.7 Hz, H-2), 4.36 (ddd, 1 H, *J* 5.7, 4.5, 2.4 Hz, H-4), 3.70 (dd, 1 H, *J* 11.0, 2.4 Hz, H-5b), 3.62 (dd, 1 H, *J* 11.0, 4.5 Hz, H-5a), 3.30, 3.21 (2 s, 6 H, OCH_3), 2.12 (s, 3 H, CH_3CO), 1.45, 1.36, 1.35, and 1.34 (4 s, 12 H, CCH_3); ^{13}C-n.m.r. ($CDCl_3$): 172.3 (C-1), 169.8 (CH_3*C*O), 102.2 and 100.4 (acetal-C), 79.9 (C-3), 74.9 (C-4), 70.6 (C-2), 60.0 (C-5), 49.3 and 48.7 (O*C*H_3), 25.3, 24.7, 24.2, 24.1 (4 C*C*H_3), and 20.7 (*C*H_3CO).

NOTE ADDED AT PROOF

Methanolysis of **6** in the presence of a strongly acidic cation-exchange resin (H^+) at 25° was used to produce **7**. The methanol used in this stage should contain 0.5% water to insure removal of the benzylidene group. If the methanol was dry, the reaction gave mainly the methyl ester of 3,4-*O*-benzylidene-D-*erythro*-2-pentulosonic acid, m.p. 184–185°, $[\alpha]_D^{25}$ −75° (*c* 0.17, MeOH), which was identified by elemental analysis and ^{1}H- and ^{13}C-n.m.r.

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