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Carbon-branched carbohydrate chirons: practical access to both enantiomers of 2-*C*-methyl-ribono-1,4-lactone and 2-*C*-methyl-arabinonolactone

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ABSTRACT

Readily crystallized 2-*C*-methyl-D-ribono-1,4-lactone is formed in a one-pot procedure from D-glucose without any protecting groups by treatment with dimethylamine to give an Amadori ketose and then with aqueous calcium hydroxide in yields of approximately 25%; 2-*C*-methyl-L-ribono-1,4-lactone is similarly produced from L-glucose. 3,4-*O*-Isopropylidene-2-*C*-methyl-D-arabinono-1,5-lactone and 2-*C*-methyl-D-arabinono-1,4-lactone were prepared in a combined 60% yield by the Kiliani reaction of sodium cyanide with a protected 1-deoxy-D-ribulose derived from D-erythronolactone; the enantiomeric arabinonolactones are similarly available from L-erythronolactone.

1. Introduction

Monosaccharides provide the most diverse family of constituents of the chiral pool for the synthesis of highly functionalized homochiral targets, all of which have linear carbon chains.[1] The lack of availability of *C*-branched carbohydrate starting materials has meant that there are only a few examples of their use as chirons.[2] 2-*C*-Methyl-D-ribono-1,4-lactone **3**, obtained in low yield by calcium oxide treatment of fructose in water, has been used in the synthesis of branched 2′-[3] and 4′-[4] C-nucleosides, 4-*C*-methylpentuloses,[5] and branched imino sugars.[6] Even so, the difficulty of this preparation means that most studies of bioactive 2′-*C*-methyl nucleosides have been made by lengthy sequences from unbranched sugars.[7]

This paper illustrates the convenient synthesis of two epimeric saccharinic acid lactones **3** and **7**. A practical synthesis of 2-*C*-methyl-D-ribonolactone **3** from glucose **1** involves an initial Amadori reaction with dimethylamine to give the aminofructose **2** followed by treatment with calcium oxide in water; direct crystallization of **3** allows the isolation of large amounts of product without any chromatography (Scheme 1). L-Glucose **1L** may be converted to the enantiomer **3L**. The protected 2-*C*-methyl-arabinono-1,5- **6** and unprotected 2-*C*-methyl-arabinono-1,4- **7** lactones can be obtained from D-erythronolactone **4** by conversion to the protected deoxyribulose **5** followed by treatment with sodium cyanide; L-erythronolactone **4L** is equally available to allow the preparation of **6L** and **7L**. The arabinonolactones **6** and **7** have been used in syntheses of 2′-*C*-methyl nucleosides[8] and carbon-branched ketoses.[5]

2. Results and discussion

2.1. Synthesis of 2-*C*-methyl-D-ribono-1,4-lactone 3 and 2-*C*-methyl-L-ribono-1,4-lactone 3L from D-glucose 1 and L-glucose 1L by the treatment of Amadori ketoses with calcium hydroxide

D-Glucose **1** on heating with calcium oxide in water for 1 h gave 2-*C*-methyl ribono-1,4-lactone **3** in approximately 0.5% yield; over 50 other products were also identified.[9] Base treatment of monosaccharides induces a wide range of reversible aldol, epimerization and dehydration reactions as well as Lobry de Bruyn rearrangements.[10] The most readily isolated compounds are saccharinic acids which are crystallized relatively easily; furthermore, their carboxylate salts are inert to further base catalyzed reactions.[11] Fructose **8** with calcium hydroxide under carefully controlled conditions of temperature and time allowed the isolation of **3** in a yield of around 10% in about 8–10 weeks;[12] if the reaction mixture is heated to avoid the long period of standing at room temperature the yield obtained by this method is much lower.

A pathway for the isomerization of fructose **8** is shown in Scheme 2.[13] Fructose can form either of two ene diols **9** or **10**, both of which may be stabilized by calcium ions. The loss of the proton at the C-3 OH of **9** and the OH at C-1 would give the enol **12**; alternatively, dehydration by loss of the C-2 hydroxyl proton could form the Favorskii intermediate **13**. Either the enol **12** or the

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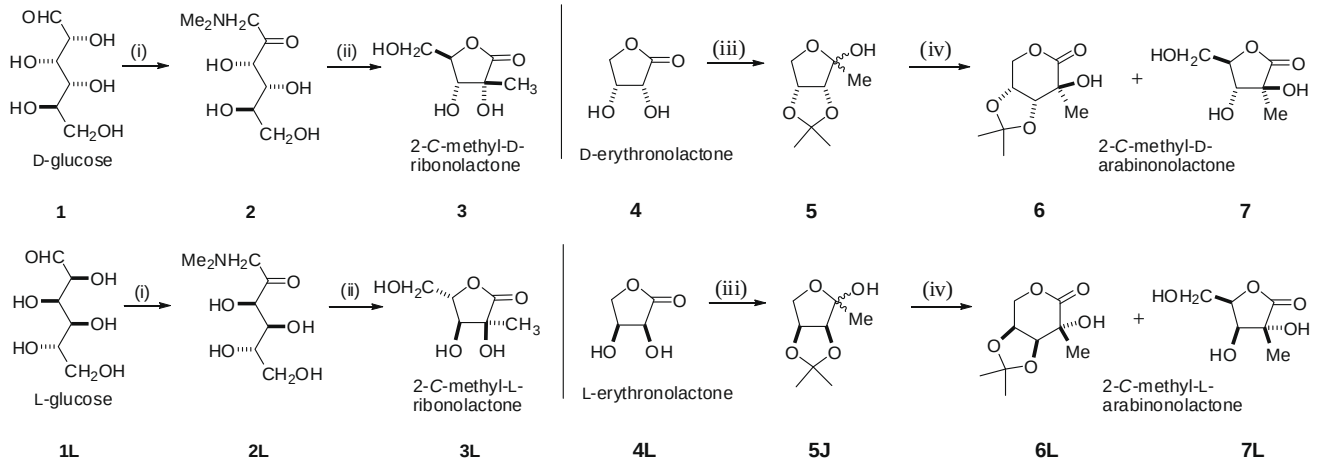
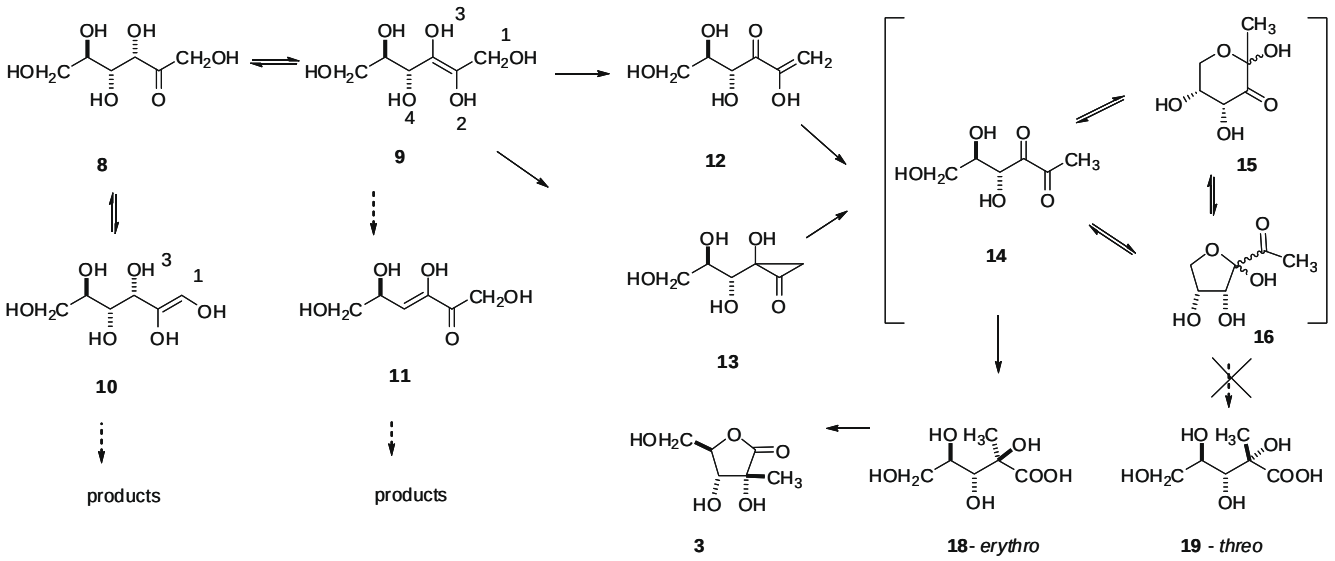


Scheme 1. Reagents and conditions: (i) Me_2NH, AcOH, EtOH; (ii) CaO, H_2O; (iii) Me_2CO, H^+; then MeMgBr; (iv) NaCN, H_2O; then H^+, H_2O.



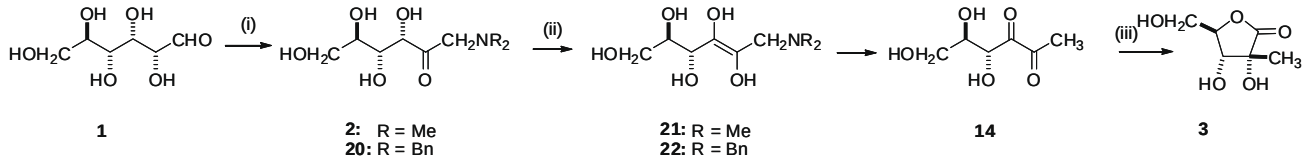
Scheme 2. Base-catalyzed isomerization of fructose **8**.

cyclopropanone **13** can then isomerize to the diketone **14**. The alternative ene diol **10** can also dehydrate with the loss of the OH group at C-3; it is therefore likely to be an advantage for the formation of diketone **14** to optimize the enol diol **9** rather than **10**. The balance between the different dehydrations is crucial to the formation of the key diketone intermediate **14**. A subsequent benzilic acid rearrangement of the diketone—in its open chain **14**, pyranose **15** or furanose **16** form—leads to the branched ribonic acid **18**, invariably isolated as its crystalline lactone **3**; *none* of the epimeric 2-*C*-methylarabinonolactone **19** is formed under these conditions.

The key steps are the conversion to (and the correct dehydration of) the ene diol **9**; it would appear likely that improving the leaving group [for example, to a mesylate] would improve the chances of diketone **14** being formed relative to competing reactions; such a modification of the C-1 CH_2OH would require a lengthy sequence involving protection and deprotection. The Amadori rearrangement is the direct conversion of an unprotected aldose with an amine to form a 1-amino-1-deoxy-ketose;[14] for example, dibenzylamine reacts with glucose **1** in methanol in the presence of acetic acid to give the Amadori ketose **20** as a crystalline material[15] in 86% yield (Scheme 3).[16]

Treatment of the Amadori product **20** with calcium hydroxide in water afforded, after acidic work-up, the branched ribono-1,4-lactone **3** in 16% yield.[17] This sequence involves an initial tautomerization to the ene diol **22**, a nitrogen equivalent of the required ene diol **9**, followed by loss of dimethylamine to form the same diketone **14** as the precursor for the benzilic acid rearrangement. The formation of an equivalent of the wrong ene diol **10** is not possible.

Although **20** was readily crystallized, its lack of solubility in water made the scale-up of the calcium oxide reaction difficult. Dimethylamine in industrial methylated spirits and acetic acid gave the corresponding Amadori dimethylamine analogue **2**, which in a one-pot reaction gave the ribono-lactone **3** via the ene diol **21** and the diketone **14**. Again *none* of the epimeric arabinono-1,4-lactone **7** was formed which was consistent with the diketone **14** being a common intermediate both in this procedure and in the isomerization of fructose **8**. The absence of epimer **7** allows the direct crystallization of pure lactone **3** with no need for any chromatographic separation. When D-galactose, the other cheap hexose, was subjected to the Amadori-calcium oxide sequence, both 2-*C*-methyl-D-lyxono-1,4-lactone and 2-*C*-methyl-D-xylono-1,4-lactone were formed which proved more difficult to sepa-



Scheme 3. Reagents and conditions: (i) $(PhCH_2)_2NH$, AcOH, EtOH or Me_2NH in MeOH; (ii) CaO, H_2O; (iii) H^+.

rate;[18] D-galactose also gives unbranched saccharinic acids easily.[19]

D-Glucose **1** was converted to the branched ribonolactone **3** by this procedure on a scalable process [157 g of **1** gave 38 g of **3**, 27%; 1260 g of **1** gave 229 g of **3**, 20%]. Additional ribonolactone **3** was present in the mother liquors and residues but further isolation of the material proved to cumbersome and not cost effective. L-Glucose **1L** [42 g] afforded 2-*C*-methyl-L-ribonolactone **3L** [10 g] in 25% yield.

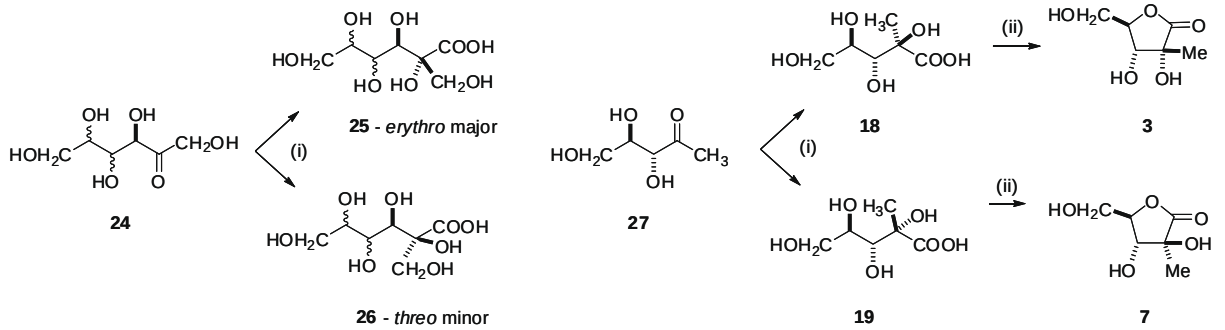
2.2. Protected 2-*C*-methyl-D-arabinono-1,5-lactone 6 and 2-*C*-methyl-D-arabinono-1,4-lactone 7 by the Kiliani extension of 1-deoxy-D-ribulose 5

The Kiliani reaction of cyanide on protected and unprotected aldoses allows easy access to a wide range of sugars,[20] including C-3 branched sugars from C-2 branched sugars.[21] The reaction of cyanide with ketoses gives branched carbohydrates;[22] in particular all four of the diastereomeric ketohexoses **24**[23] give the *erythro*-diols **25** as the major diastereomer, typically formed in a 4:1 ratio to the minor *threo*-diols **26** (Scheme 4). It might be expected that the unprotected 1-deoxy-D-ribulose **27** would give a predominance of **18** relative to **19**, and thus of the ribonolactone **3** rather than the arabinonolactone **7**.

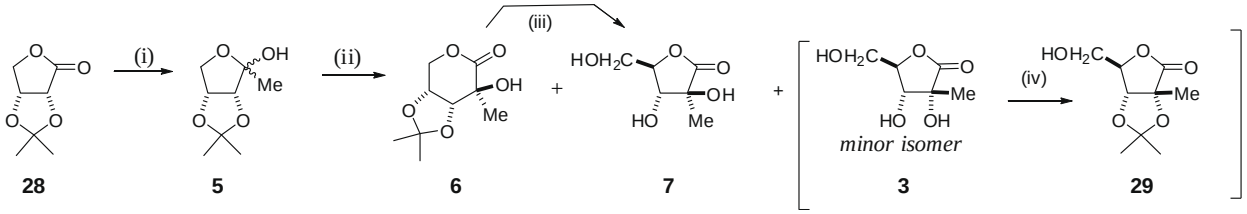
D-Erythronolactone **4**, obtained by Humphlett oxygenation of an alkaline solution of D-arabinose[24] or by hydrogen peroxide oxidation of erythrobic acid, formed a highly crystalline acetonide **28**[25] (Scheme 5). Reaction of the protected D-erythronolactone **28** with methyl magnesium bromide in THF afforded lactol **5**[26] as a mixture of anomers in 99% yield. The sensitivity of **5** to acid precluded the removal of the acetonide to give the unprotected deoxy ribulose **27** so that the Kiliani reaction was performed on the protected ribulose **5**. Treatment of **5** with aqueous sodium cyanide, followed by work-up with acid, gave the protected δ-lactone **6** (36%) together with a mixture of the deprotected γ-lactones **7**[27] and **3** (23%) in an approximate ratio of 5 to 1 and a combined yield of 59%. Changes to the concentration and/or the length of time that the reaction mixture was in contact with the Amberlite® resin caused a variation in the ratio of protected and unprotected arabinonolactone observed; however, the combined yield was consistently approximately 60%.

The protected δ-lactone **6** can easily be isolated by flash chromatography and ready crystallization, but the unprotected lactones **3** and **7** are difficult to separate from each other. A slow recrystallization of the mixture of γ-lactones afforded the pure arabinonolactone **7**; alternatively, the ribonolactone **3** may be removed from the mixture as its acetonide **29**. The isopropylidene protecting group in the 1,5-lactone **6** was removed in quantitative yield by treatment with aqueous trifluoroacetic acid to give 2-*C*-methyl-D-arabinono-1,4-lactone **7**. The structures of the protected **6**[28] and unprotected **7**[29] arabinonolactones were firmly established by X-ray crystallographic analysis.

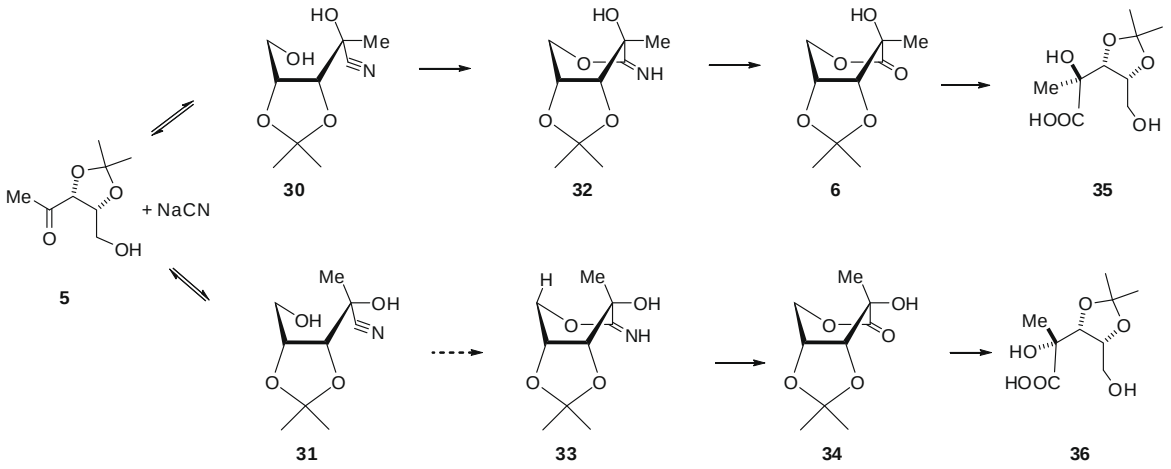
The diastereoselectivity of the Kiliani reaction may result from one of a number of reversible steps.[30] The crystal structures of 3,4-*O*-isopropylidene-1,5-lactones, including **6**, are generally in a boat conformation.[31] The protected ribulose **5** can reversibly form either cyanohydrin **30** or **31** (Scheme 6). The nitriles are then hydrolyzed by an initial cyclization to the imidates **32** and **33**, respectively, which are further hydrolyzed to the lactones **6** and **34**. Under the basic conditions of the Kiliani the lactones formed



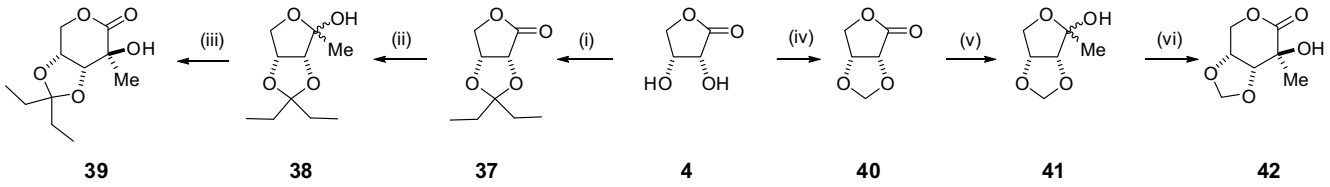
Scheme 4. Kiliani reaction on ketoses. Reagents and conditions: (i) NaCN, H_2O; (ii) H^+.



Scheme 5. Reagents and conditions: (i) MeMgBr, THF, −78 °C, 99%; (ii) NaCN, H_2O; then Amberlite® IR 120 H^+, 59%; (iii) CF_3COOH, H_2O, 100%; (iv) Me_2CO, $CuSO_4$, conc H_2SO_4.



Scheme 6. Diastereoselectivity of the Kiliani reaction.



Scheme 7. Reagents and conditions: (i) Et_2CO, $CuSO_4$, conc H_2SO_4, 85%; (ii) MeMgBr, THF, −78 °C, 98%; (iii) NaCN, H_2O; then Amberlite® IR 120 H^+, 21%; (iv) $SOCl_2$, Me_2SO, 70%; (v) MeMgBr, THF, −78 °C, 81%; (vi) NaCN, H_2O; then Amberlite® IR 120 H^+, 15%.

the salt of the open chain acids **35** and **36**. A rationale for the preferential formation of the arabino compound **6** is that the closure of **30** to **32** [with a flagpole hydroxyl group] leads to a less sterically congested imidate than the closure of **31**–**33**, where the methyl group has an unfavorable interaction with the flagpole proton. At the end of the reaction, the acid-catalyzed closure of the salt of **35** allows the formation of the protected lactone **6**, although some hydrolysis of the acetal protecting group prior to ring closure occurs giving the unprotected arabinonolactone **7**. In contrast, closure of **36** to the more congested lactone **34** is not competitive with removal of the isopropylidene group so that only the unprotected ribono-1,4-lactone **3** is formed.

In order to avoid competitive hydrolysis of the acetonide in the closure of the open chain salt **35**, other protecting groups were briefly investigated to determine if better yields of the corresponding protected 1,5-lactones (Scheme 7) could be obtained. Treatment of erythronolactone **4** with pentanone in the presence of copper sulfate and sulfuric acid gave the non-crystalline ketal **37** (85%), which on treatment with methyl magnesium bromide gave the protected 1-deoxy ribulose **38** (98%). However, the Kiliani ascension on **38** proceeded in a low yield to give a non-crystalline lactone **39** (21%). Protection of **4** with thionyl chloride in dimethylsulfoxide gave the formaldehyde acetal **40** (70%), which gave the ribulose **41** (81%) on treatment with methyl magnesium bromide. However, reaction of **41** with sodium cyanide followed by acid work-up gave a poor yield of the protected arabinonolactone **42**[32] (15%). No advantage was found in this brief study of other protecting groups.

3. Conclusion

This paper reports a convenient and scalable synthesis of either enantiomer of 2-*C*-methyl ribono-1,4-lactone **3** from the enantiomers of glucose **1** in a one-pot procedure via an Amadori ketose and subsequent treatment with calcium oxide; the product is isolated by direct crystallization to produce hundreds of grams of material with no chromatography. The epimer 2-*C*-methyl arabinonolactone may be obtained in a protected 1,5-lactone **6** or unprotected 1,4-lactone **7** by the Kiliani cyanide extension on a protected 1-deoxyribulose **5**, easily synthesized from D-erythronolactone **4**; L-erythronolactone **4L** is equally available. The epimeric saccharinic acid lactones **3** and **7** are likely to be of value as carbohydrate chirons for enantiopure targets containing branched carbon chains.

4. Experimental

Proton nuclear magnetic resonance spectra (δ_H) were recorded on a Bruker AV400 (400 MHz) or a Bruker AVC500 (500 MHz) spectrometer and were calibrated according to the chemical shift of residual protons in the deuterated solvent. ^{13}C NMR spectra (δ_C) were recorded on a Bruker AV400 (100.6 MHz) and were calibrated according to the chemical shift of the deuterated solvent. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hertz. The following abbreviations are used to denote multiplicities: s, singlet; d, doublet; dd, double–doublet; ddd, double–double–doublet; t, triplet; a, apparent. Infrared spectra were recorded on a Bruker Tensor 27 FT IR spectrophotometer using thin films on NaCl or Ge plates and peaks are given in cm^{-1}. Low-resolution mass spectra (LRMS) were recorded on a Fisons Platform (ESI) spectrometer or a Micromass VG Autospec 500 OAT (CI(NH_3)) spectrometer. High-resolution mass spectra (HRMS) were recorded on a Micromass LCT (ESI) spectrometer, a Micromass VG Autospec 500 OAT (CI(NH_3)) spectrometer or a Micromass GCT (FI) spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm; concentrations (c) are quoted in g/100 mL. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory (Oxford). Melting points (mp) were measured on a Kofler hot-block apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with $60F_{254}$ silica from Merck,

and plates were developed by dipping in either 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or 10% sulfuric acid in EtOH with subsequent heating. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Solvents were used as supplied (HPLC grade) and commercially available reagents were used as supplied. 'JT' refers to oil jacket temperature of reactor vessels, as controlled by Julabo heater/chiller units.

4.1. 2-*C*-Methyl-D-ribono-1,4-lactone 3 and 2-*C*-methyl-L-ribono-1,4-lactone 3L

4.1.1. 2-*C*-Methyl-D-ribono-1,4-lactone 3

Dimethylamine (33% in absolute ethanol, 159 mL, 0.90 mol) was added dropwise over 0.5 h to a solution of D-glucose **1** (157 g, 0.87 mol) in industrial methylated spirits (235 mL) and acetic acid (50.3 mL, 0.87 mol) in a 2 L jacketed reactor with JT 17 °C [this step was exothermic; JT was set to 17 °C to ensure the internal temperature remained at 20 °C]. The reaction mixture was then heated (JT 75 °C) over 0.5 h, cooled to 55 °C over 0.5 h, and stirred at 55 °C for 1.5 h. TLC analysis (14:3:1:1:1, EtOH–H_2O–Py–AcOH–^{n}BuOH) showed the formation of a single major product (R_f 0.39) **2**; no glucose (R_f 0.79) remained. The solution was concentrated at 50 mbar, JT 50 °C, until bubbling ceased (1.5 h) and the brown oil was diluted with distilled water (330 mL). The reactor was evacuated and filled with nitrogen and JT was adjusted to 0 °C. Calcium oxide (73.3 g, 1.31 mol) was added in 4 portions at 10 min intervals [the reaction was exothermic; the internal temperature rose by approximately 5 °C after each addition]. Under a nitrogen atmosphere (maintained by inflated balloon), the reaction mixture was heated to JT 25 °C over 20 min and then heated to JT 40 °C over 18 h and stirred at JT 40 °C for a further 4 h. TLC analysis (14:3:1:1:1, EtOH–H_2O–Py–AcOH–^{n}BuOH) after this time indicated the absence of the Amadori ketose **2**, and the formation of a product (R_f 0.00) **3**. JT was lowered to 0 °C, and 96% sulfuric acid (88 mL, 1.65 mol) was added over 1.5 h, keeping JT at 0 °C. The pH was checked at this point to ensure it was in the range 2.4–2.7. Addition of extra sulfuric acid was occasionally necessary. Once addition was complete, JT was set to rise to 45 °C over 0.5 h and the reaction mixture stirred at JT 45 °C for 12 h. The mixture was then allowed to cool to room temperature before filtration; the reactor and filter cake were rinsed with distilled water (500 mL). TLC analysis (14:3:1:1:1, EtOH–H_2O–Py–AcOH–^{n}BuOH) of the filtrate revealed a major product (R_f 0.92). The filtrate (approx 1 L) was concentrated at 50 °C to give a brown residue which was re-dissolved in a mixture of acetone (800 mL) and water (80 mL); Fullers Earth (90 g) was added. The reaction mixture was refluxed for 0.5 h and the organic phase decanted and filtered. The solid remaining in the flask was then extracted a further three times with 10% aqueous acetone (275 mL × 3), refluxing for 5 min and decanting the acetone each time. The combined filtrates were concentrated in vacuo at 40 °C to give 109 g of a solid brown crude. Recrystallization from hot acetone gave the lactone **3** as a cream colored solid (37.5 g, 27%); mp 157–158 °C; $[\alpha]_D^{20} = +87.6$ (*c* 0.86, water); {lit.[17] mp 158–159 °C; $[\alpha]_D^{13.5} = +87.5$ (*c* 0.76, water)}; δ_H (400 MHz, CD_3OD): 1.43 (3H, s, CH_3-2), 3.73 (1H, dd, H-5 $J_{5,4}$ 4.5, $J_{5,5'}$ 12.8), 3.93 (1H, d, H-3 $J_{3,4}$ 7.8), 3.97 (1H, dd, H-5′, $J_{5',4}$ 2.4, $J_{5',5}$ 12.8), 4.32 (1H, ddd, H-4 $J_{4,5'}$ 2.4, $J_{4,5}$ 4.5, $J_{4,3}$ 7.8) δ_C (100.6 MHz, CD_3OD): 20.0 (CH_3-2), 60.0 (C-5), 72.6 (C-2), 72.6 (C-3), 83.4 (C-4), 177.0 (C-1).

4.1.2. Scale up procedure—6 L jacketed reactor for 1.25 kg glucose

D-Glucose **1** (1.26 kg, 7.00 mol); dimethylamine (33% in absolute ethanol, 1.28 L, 7.21 mol); industrial methylated spirits (1.89 L); acetic acid (405 mL, 7.01 mol); water (2.66 L); calcium oxide (589 g, 10.5 mol); 96% sulfuric acid (710 mL, 13.3 mol). The procedure was carried out as above; however, additional purification, in the form of exhaustive treatment with aqueous acetone/Fuller's Earth and a subsequent reflux with Norit activated charcoal in acetone, was required before crystallization was possible. The total mass of 2-*C*-methyl-D-ribonolactone **3** obtained was 228.7 g (20%).

4.1.3. 2-*C*-Methyl-L-ribono lactone 3L

The procedure was carried out as previously described above for the preparation of 2-*C*-methyl-L-ribonolactone **3L** using the following amounts: L-Glucose **1L** (42.4 g, 0.235 mol); dimethylamine (33% in absolute ethanol, 43.2 mL, 0.243 mol); industrial methylated spirits (64 mL); acetic acid (13.6 mL, 0.235 mol); water (89 mL); calcium oxide (19.8 g, 0.353 mol); 96% sulfuric acid (23.9 mL, 0.424 mol). After direct crystallization of lactone **3** (5.37 g), the mother liquor was concentrated, and the residue purified by column chromatography (40-60 petrol/acetone 4:1→1:1) and crystallization to give further product (4.20 g). The total yield of 2-*C*-methyl-L-ribono lactone **3L** was 9.57 g (25%); mp 158–159 °C; $[\alpha]_D^{21} = -87.6$ (*c* 0.8, water); {lit.[17] mp 160–162 °C; $[\alpha]_D^{21.5} = -87.7$ (*c* 0.6, water)}; the ^1H and ^{13}C NMR spectra were identical to those of the enantiomer **3** above.

4.1.4. 3,4-*O*-Isopropylidene-2-*C*-methyl-D-arabinono-1,5-lactone 6 and 2-*C*-methyl-D-arabinono-1,4-lactone 7

4.1.4.1. 1-Deoxy-3,4-O-isopropylidene-D-ribulose 5. Methyl magnesium bromide (3 M solution in Et_2O, 39 mL) was added dropwise to a solution of the protected D-erythronolactone **28** (16.72 g, 0.106 mol) in dry THF (400 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min after which time saturated aqueous ammonium chloride (30 mL) was added and the reaction mixture allowed to warm to room temperature. The mixture was partitioned between ethyl acetate (200 mL) and water (300 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and then the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to give the ketose **5** as a mixture of anomers (18.2 g, 99%), which was used without further purification; mp 82–85 °C [lit.[26] 87–89 °C]; ν_{max} (thin film): 3223 (OH); δ_H (400 MHz, $CDCl_3$): [a 1:5 mixture of anomers, A—major anomer] 1.32, 1.47 (5.04H, 2 × s, 2 × $C(CH_3)_2^A$), 1.36, 1.48, (0.96H, 2 × s, 2 × $C(CH_3)_2^B$), 1.52, 1.55 (3H, 2 × s, $H1^A$, $H1^B$), 2.69 (1H, s, OH), 3.62 (0.16H, dd, H-5^B, $J_{5,4}$ 4.1, $J_{5,5'}$ 11.0), 3.89–3.93 (1H, m, H-$5'^B$, H-5), 3.99 (0.84H, dd, H-$5'^A$, $J_{5,4}$ 3.8, $J_{5,5'}$ 10.3), 4.24 (0.16H, d, H-3^B, $J_{3,4}$ 6.2), 4.39 (0.84H, d, H-3^A, $J_{3,4}$ 5.9), 4.74–4.79 (0.16H, m, H-4^B), 4.84 (0.84H, dd, H-4^A, $J_{4,5}$ 3.8, $J_{4,3}$ 5.9); δ_C (100.6 MHz, $CDCl_3$): 22.3, 24.9, 26.3 (3 × CH_3^A), 21.9, 24.8, 26.1 (3 × CH_3^B), 68.4 (C-5^B), 70.9 (C-5^A), 80.1 (C-4^B), 80.8 (C-4^A), 82.0 (C-3^B), 85.0 (C-3^A), 103.0 (C-2^B), 105.9 (C-2^A), 112.4 (CMe_2^A), 113.4 (CMe_2^B); *m/z* (Cl^-): 173 $[M-H]^-$, 100%. Found: C, 55.18; H, 8.11; $C_8H_{14}O_4$ requires: C, 55.16; H, 8.10.

4.1.5. 3,4-*O*-Isopropylidene-2-*C*-methyl-D-arabinono-1,5-lactone 6, 2-*C*-methyl-D-arabinono-1,4-lactone 7 and 2-*C*-methyl-D-ribono-1,4-lactone 3

The protected ketose **5** (8.70 g, 50.1 mmol) was stirred with sodium cyanide (3.20 g, 65.1 mmol) in water (60 mL) at room temperature for 48 h. The mixture was then refluxed for another 48 h. At this point, a test (Prussian blue test) for cyanide was negative. The reaction mixture was passed through an Amberlite® IR 120 (H^+) column, eluted with water (3 × column volumes) and the combined aqueous washings concentrated. TLC (ethyl acetate/cyclohexane, 1:1) of the residue showed the formation of multiple products. The residue was then purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1→5:1) to

yield 3,4-*O*-isopropylidene-2-*C*-methyl-D-arabinono-1,5-lactone **6** (3.70 g, 36%; R_f 0.70 ethyl acetate/cyclohexane, 3:1) as a white crystalline solid; mp 108–109.5 °C; $[\alpha]_D^{22} = -124.7$ (*c* 1.01, $CHCl_3$); ν_{max} (thin film): 3447 (OH), 1743 (C=O); δ_H (400 MHz, CD_3CN): 1.33, 1.35, 1.44 (9H, 3 × s, 3 × CH_3), 4.01 (1H, s, OH), 4.26 (1H, dd, H-5, $J_{5,4}$ 1.0, $J_{5,5'}$ 12.3), 4.31 (1H, d, H-3, $J_{3,4}$ 7.5), 4.57 (1H, ddd, H-4, $J_{4,5}$ 1.0, $J_{4,5'}$ 2.0, $J_{4,3}$ 7.5), 4.85 (1H, dd, H-5′, $J_{5',4}$ 2.0, $J_{5',5}$ 12.3); δ_C (100.6 MHz, CD_3CN): 21.7, 23.6, 25.9 (3 × CH_3), 68.7 (C-5), 72.2 (C-2), 72.6 (C-4), 79.4 (C-3), 109.4 (CMe_2), 171.1 (C-1); *m/z* (CI^+): 220 $[M+NH_4]^+$, 100%; HRMS (ESI^+): Found: 225.0731 $[M+Na]^+$; $C_9H_{14}NaO_5$ requires: 225.0733. Found: C, 53.48; H, 7.00; $C_9H_{14}O_5$ requires C, 53.46; H, 6.98; and an inseparable mixture of lactones 2-*C*-methyl-D-arabinono-1,4-lactone **7** and 2-*C*-methyl-D-ribono-1,4-lactone **3** (1.90 g, 23%; R_f 0.13 ethyl acetate/cyclohexane, 3:1) in an approximate ratio of 10:1 as a colorless glass. The relative amounts of the protected **6** and unprotected **7** lactones depended on the length of time the reaction mixture was in contact with the ion exchange resin but the combined yield was approximately 60%.

4.1.6. 2-*C*-Methyl-D-arabinono-1,4-lactone 7 and 2,3-*O*-isopropylidene-2-*C*-methyl-D-ribono-1,4-lactone 29

The mixture of the unprotected lactones, **3** and **7** (2.83 g, 17.5 mmol), was dissolved in acetone (50 mL) and the solution stirred under argon in the presence of copper sulfate (5.58 g, 34.9 mmol) and conc. sulfuric acid (1 drop). After 16 h, TLC (ethyl acetate) indicated the formation of a minor product (R_f 0.51) and the remaining starting material (R_f 0.22). Solid sodium carbonate was then added to the mixture until pH 6 was reached. The reaction mixture was filtered through Celite, the solvent removed, and the resulting pale yellow residue purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1) to give unchanged 2-*C*-methyl-D-arabinono-1,4-lactone **7**, (1.65 g, 58%) (recrystallized from ethyl acetate/cyclohexane); mp 65–68 °C; $[\alpha]_D^{22} = +77.5$ (*c* 1.03, H_2O) [lit.[33] 63–65 °C; [lit.[8] $[\alpha]_D^{20} = +82.5$ (*c*, 0.90, H_2O)], [lit.[27] $[\alpha]_D = +69.0$ (*c* 1.60, H_2O)]; ν_{max} (thin film): 3273 (OH), 1760 (C=O); δ_H (400 MHz, DMSO-d_6): 1.19 (3H, s, CH_3), 3.50 (1H, dd, H-5, $J_{5,4}$ 4.8, $J_{5,5'}$ 5.5), 3.72 (1H, dd, H-5′, $J_{5',4}$ 2.3, $J_{5',5}$ 5.5), 3.92–3.96 (1H, m, H-4), 3.98–4.03 (1H, m, H-3), 5.10 (1H, a-t, *J* 4.2, OH), 5.73 (1H, d, *J* 5.3, OH), 5.81 (1H, s, OH); δ_C (100.6 MHz, DMSO-d_6): 18.8 (CH_3), 60.4 (C-5), 74.3 (C-3), 75.8 (C-2), 82.5 (C-4), 178.8 (C-1); *m/z* (ESI^-): 161 $[M-H]^-$, 100%; HRMS (ESI^-): Found: 161.0455 $[M-H]^-$; $C_6H_9O_5$ requires: 161.0450 and 2,3-*O*-isopropylidene-2-*C*-methyl-D-ribono-1,4-lactone **29** (0.334 g, 11%) as a colorless oil; $[\alpha]_D^{21} = -28.1$ (*c* 1.03, $CHCl_3$) [lit.[6a] $[\alpha]_D^{19} = -35.6$ (*c* 1.40, acetone)]; ν_{max} (thin film): 3484 (OH), 1783 (C=O); δ_H (400 MHz, MeOD): 1.40, 1.41 (6H, 2 × s, 2 × $C(CH_3)_2$), 1.63 (3H, s, H2′), 3.77 (1H, dd, H-5, $J_{5,4}$ 2.8, $J_{5,5'}$ 12.4), 3.83 (1H, dd, H-5′, $J_{5',4}$ 3.10, $J_{5',5}$ 12.4), 4.53 (1H, a-t, *J* 3.9, H-4), 4.59 (1H, br s, H-3); *m/z* (ESI^-): 403 $[2M-H]^-$, 100%.

A sample of 2-*C*-methyl-D-arabinono-1,4-lactone **7**, (100%) was also prepared by hydrolysis of the protected lactone **6** (101 mg, 0.5 mmol) in water (1.5 mL), 1,4-dioxane (0.7 mL), and trifluoroacetic acid (2 mL). The reaction mixture was stirred for 18 h at room temperature after which time TLC (ethyl acetate/cyclohexane, 3:1) showed complete conversion of the starting material **6** (R_f 0.70) to the deprotected lactone **7** (R_f 0.13), identical to the material described above.

4.1.7. 2,3-*O*-Isopentylidene-D-erythronolactone 37

Copper sulfate (1.39 g, 8.68 mmol) and concentrated sulfuric acid (0.2 mL) were added to a solution of D-erythronolactone **4** (512 mg, 4.34 mmol) in 3-pentanone (11 mL). The reaction mixture was stirred at room temperature for 18 h after which time TLC (ethyl acetate/cyclohexane, 3:1) showed the formation of one major product (R_f 0.83) and a small amount of unreacted starting material (R_f 0.07). The solution was neutralized with solid sodium carbonate, filtered through Celite, and the filtrate concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:1) to give the pentylidene derivative **37** as a light yellow oil (686 mg, 85%); $[\alpha]_D^{23} = -113.0$ (*c* 1.0, $CHCl_3$); ν_{max} (thin film): 1784 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (3H, t, CH_3, *J* 7.5), 0.90 (3H, t, CH_3, *J* 7.5), 1.61–1.67 (2H, q, CH_2, *J* 7.5), 1.66–1.71 (2H, q, CH_2, *J* 7.5), 4.38–4.41 (1H, dd, H-4, $J_{4,3}$ 3.8, $J_{4,4'}$ 11.0), 4.46 (1H, d, H-4′, $J_{4',4}$ 11.0), 4.76 (1H, d, H-2, $J_{2,3}$ 5.8), 4.88–4.90 (1H, dd, H-3, $J_{3,4}$ 3.9, $J_{3,2}$ 5.8); δ_C (100.6 MHz, $CDCl_3$): 7.2 (CH_3), 8.1 (CH_3), 29.2 (CH_2), 29.7 (CH_2), 70.4 (C-4), 74.8 (C-2), 75.7 (C-3), 118.1 (CH_3C), 173.9 (C=O); *m/z* (TOF MS CI^+): 204 $[M+NH_4]^+$, 100%; 187 $[M+H]^+$, 10%; HRMS (TOF MS CI^+): Found: 204.1244 $[M+NH_4]^+$; $C_9H_{18}NO_4$ requires: 204.1236. Found: C, 58.00, H, 7.44; $C_9H_{14}O_4$ requires: C, 58.05, H, 7.58.

4.1.8. 1-Deoxy-3,4-*O*-isopentylidene-D-ribulose 38

Methyl magnesium bromide (3 M in ether, 0.99 mL, 2.96 mmol) was added to a solution of the protected D-erythronolactone **37** (500 mg, 2.69 mmol) in dry THF (11 mL) at −78 °C; after 1 h, three further portions of methyl magnesium bromide (0.18 mL, 0.54 mmol) were added at 20 min intervals. After 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (1 mL) and partitioned between ethyl acetate (30 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the lactols **38** (530 mg, 98%) as a 1:4 mixture of anomers, as a colorless oil; ν_{max} (thin film): 3418 (OH); δ_H (400 MHz, $CDCl_3$): [A—major anomer] 0.86–1.00 (6H, m, CH_3), 1.36 (0.6H, s, Me^B), 1.56 (2.4H, s, Me^A), 1.56–1.74 (4H, m, CH_2), 3.60–3.64 (0.2H, dd, H-5^B, $J_{5,4}$ 4.2, $J_{5,5'}$ 10.9), 3.93 (0.8H, d, H-5^A, $J_{5,5'}$ 10.2), 3.94 (0.2H, d, H-$5'^B$, $J_{5',5}$ 10.9), 3.99–4.03 (0.8H, dd, H-$5'^A$, $J_{5',4}$ 3.9, $J_{5',5}$ 10.2), 4.25 (0.2H, d, H-3^B, $J_{3,4}$ 6.3), 4.40 (0.8H, d, H-3^A, $J_{3,4}$ 5.9), 4.71–4.80 (0.2H, m, H-4^B), 4.85–4.88 (0.8H, dd, H-4^A, $J_{4,5'}$ 3.9, $J_{4,3}$ 5.9); δ_C (100.6 MHz, $CDCl_3$): 7.6 ($CH_3{}^A$, $CH_3{}^B$), 7.8 ($CH_3{}^B$), 8.4 ($CH_3{}^A$), 21.8 (Me^B), 22.4 (Me^A), 28.8 ($CH_2{}^B$), 29.0 ($CH_2{}^A$, $CH_2{}^B$), 29.3 ($CH_2{}^A$), 68.8 (C-5^B), 71.4 (C-5^A), 80.3 (C-4^B), 81.1 (C-4^A), 82.2 (C-3^B), 85.2 (C-3^A), 103.4 (C-2^B), 106.0 (C-2^A), 116.7 ($(CH_3CH_2)_2C^A$), 117.5 ($(CH_3CH_2)_2C^B$); *m/z* (ESI^-): 201 $[M-H]^+$, 100%; HRMS (ESI^-): Found: 201.1129 $[M-H]^+$; $C_{10}H_{17}O_4$ requires: 201.1121.

4.1.9. 3,4-*O*-Isopentylidene-2-*C*-methyl-D-arabinono-1,5-lactone 39

Sodium cyanide (348 mg, 7.09 mmol) was added to a solution of the lactols **38** (1.10 g, 5.46 mmol) in water (40 mL) and dioxane (40 mL). The reaction mixture was stirred for 54 h, refluxed for 36 h and then passed down an Amberlite® IR 120 (H^+) column and eluted with water (3 column volumes). The solvent was removed in vacuo and the residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:4→10% methanol in ethyl acetate) to give the protected lactone **39** (248 mg, 21%; R_f 0.53 ethyl acetate/cyclohexane, 3:1), oil; ν_{max} (thin film): 3416 (OH), 1739 (C=O); δ_H (400 MHz, $CDCl_3$): 0.82 (3H, t, CH_3, *J* 7.5), 0.88 (3H, t, CH_3, *J* 7.5), 1.56–1.68 (4H, m, CH_2), 4.29 (1H, d, H-3, $J_{3,4}$ 7.6), 4.37 (1H, d, H-5, $J_{5,5'}$ 12.2), 4.50–4.52 (1H, a-dd, H-4, *J* 1.0, $J_{4,3}$ 7.5), 4.88–4.91 (1H, dd, H-5′, $J_{5',4}$ 2.1, $J_{5',5}$ 12.2); δ_C (100.6 MHz, $CDCl_3$,): 6.9 (CH_3), 8.6 (CH_3), 22.1 (Me), 28.1 (CH_2), 28.6 (CH_2), 68.9 (C-5), 71.7 (C-2), 72.2 (C-4), 78.9 (C-3), 113.5 (CH_3CH_2C), 172.0 (C=O).

The unprotected lactone **7** was also obtained (174 mg, 20%; R_f 0.03 ethyl acetate/cyclohexane, 3:1), identical to the material prepared above.

4.1.10. 2,3-*O*-Methylidene-D-erythrono-1,4-lactone 40

Thionyl chloride (0.68 mL, 9.32 mmol) was added over 30 min to a stirred solution of D-erythronolactone **4** (1.0 g, 8.47 mmol) in DMSO (4.1 mL, 84.7 mmol) at room temperature. The reaction mixture was heated at 65 °C for 2 h and then allowed to cool to room temperature. Water (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 20 mL); the combined organic extracts were dried (magnesium sulfate) and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:3→ethyl acetate) to give the protected lactone **40** as a crystalline solid (0.77 g, 70%); mp 39–41 °C; $[\alpha]_D^{21} = -120$ (*c* 1.01, $CHCl_3$); ν_{max} (thin film): 3419 (OH), 1778 (C=O); δ_H (400 MHz, $CDCl_3$): 4.37 (1H, d, H-4, $J_{4,4'}$ 10.8), 4.45–4.46 (1H, m, H-4′), 4.73–4.76 (2H, m, H-2, H-3), 4.92 (1H, s, OCH_2O), 4.97 (1H, s, OCH_2O); δ_C (100.6 MHz, $CDCl_3$): 71.2 (C-4), 74.1, 75.4 (C-2 and C-3), 96.6 (OCH_2O), 173.5 (C-1); HRMS (FI): Found: 130.0260 [M·]; $C_5H_6O_4$ requires: 130.0266.

4.1.11. 1-Deoxy-3,4-*O*-methylidene-D-ribulose 41

Methyl magnesium bromide (3 M solution in ether, 1.80 mL) was added dropwise to a stirred solution of lactone **40** (0.65 g, 5.00 mmol) in THF (6 mL) at −70 °C and stirred at this temperature for 1 h. Saturated aqueous ammonium chloride (6 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was partitioned between ethyl acetate (20 mL) and water (20 mL) and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. Column chromatography (ethyl acetate/cyclohexane, 1:3→1:1) gave the lactols **41** as a colorless amorphous solid (0.59 g, 81%); $[\alpha]_D^{21} = -61$ (*c* 1.0, $CHCl_3$); ν_{max} (thin film): 3100 (OH); δ_H (400 MHz, $CDCl_3$): [1:6 mixture of anomers, A—major anomer] 1.35 (0.42H, s, Me^B), 1.54 (2.58H, s, Me^A), 3.72 (0.14H, dd, H-4^B, $J_{4,3}$ 4.6, $J_{4,4'}$ 11.2), 3.97 (0.86H, d, H-4^A, $J_{4,4'}$ 10.6), 3.98 (0.14H, dd, H-$4'^B$, $J_{4',3}$ 1.5, $J_{4',4}$ 11.2), 4.08 (0.86H, dd, H-$4'^A$, $J_{4',3}$ 4.1, $J_{4',4}$ 10.6), 4.18 (0.14H, d, H-2^B, $J_{2,3}$ 6.1), 4.34 (0.86H, d, H-2^A, $J_{2,3}$ 5.8), 4.76–4.77 (0.14H, ddd, H-3^B, $J_{3,4'}$ 1.5, $J_{3,4}$ 4.6, $J_{3,2}$ 6.1), 4.82 (0.86H, dd, H-3^A, $J_{3,4'}$ 4.1, $J_{3,2}$ 5.8), 4.95 (0.86H, s, OCH_2O^A), 4.96 (0.86H, s, OCH_2O^A), 5.01 (0.14H, s, OCH_2O^B), 5.16 (0.14H, s, OCH_2O^B); δ_C (100.6 MHz, $CDCl_3$): 21.9 (Me^B), 22.2 (Me^A), 68.5 (C-4^B), 71.2 (C-4^A), 80.0 (C-3^B), 80.3 (C-3^A), 81.6 (C-2^B), 84.0 (C-2^A), 96.0 (OCH_2O^A), 96.8 (OCH_2O^B), 103.6 (C-1^B), 105.5 (C-1^A); HRMS (FI): Found: 147.0652 $[M+H]^+$; $C_6H_{11}O_4$ requires: 147.0657.

4.1.12. 3,4-*O*-Methylidene-2-*C*-methyl-D-arabinono-1,5-lactone 42

Sodium cyanide (0.25 g, 5.07 mmol) was added to a stirred suspension of the protected 1-deoxy ribulose **41** (0.57 g, 3.90 mmol) in H_2O (6 mL) and the reaction mixture was stirred at room temperature for 18 h and then refluxed for 48 h. The reaction mixture was allowed to cool to room temperature and then passed through Amberlite® IR 120 ion exchange resin. The mixture was concentrated in vacuo and subjected to column chromatography (ethyl acetate/cyclohexane, 1:3→1:1) to afford the title compound **42** as a crystalline solid (0.10 g, 15%); mp 100–102 °C (from ethyl acetate/cyclohexane); $[\alpha]_D^{21} = -126$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.67 (3H, s, Me), 3.04 (1H, s, OH), 4.25 (1H, d, H-3 $J_{3,4}$ 7.9), 4.46–4.50 (2H, m, H-4, H-5), 4.82 (1H, s, OCH_2O), 4.97 (1H, dd, H-5′, $J_{5',4}$ 1.9, $J_{5',5}$ 12.0), 5.17 (1H, s, OCH_2O); δ_C (100.6 MHz, $CDCl_3$): 22.1 (Me), 68.7 (C-5), 71.5 (C-4), 72.2 (C-3), 78.8 (C-2), 94.9 (OCH_2O), 171.4 (C=O); HRMS (ESI^+): Found: 197.0421 $[M+Na]^+$; $C_7H_{10}O_5Na$ requires: 197.0420.

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