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Carbon-branched carbohydrate chirons: synthesis of C-3 and C-4-branched sugar lactones derived from D-erythronolactone

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ABSTRACT

Two carbon chain extensions using a Wittig reaction on both a 1-deoxy ribulose derivative and a C-2-branched erythrose derivative are reported. Subsequent dihydroxylation resulted in the synthesis of C-3 and C-4 methyl-branched sugar lactones, the useful synthetic building blocks. Control of the stereoselectivity of both the Wittig reaction and the dihydroxylation is investigated, and 3-*C*-methyl and 4-*C*-methyl D-altrono-1,4-lactones and D-glucono-1,4-lactone and 4-*C*-hydroxymethyl-D-altrono-1,4-lactone were synthesised.

1. Introduction

The discovery of many branched chain sugars in a variety of antibiotics has prompted much research into their synthesis and biological activity.[1] For example, 3-*C*-methyl-D-mannose **1** (Fig. 1) has been found to be one of the three sugars in the trisaccharide-repeating unit from the outer membrane of *Helicobacter pylori*. This bacterium is thought to be the major cause of chronic gastritis, gastric and duodenal ulcers and has been linked to the development of gastric cancer.[2] A derivative of 3-*C*-methyl-L-mannose is one of the sugars in the pentasaccharide hapten of *Mycobacterium avium serovar* 19.[3] Another 3-*C*-methyl-branched sugar, L-olivomycose **2**, has been found to be present in the trisaccharide unit of several antitumour antibiotics of the aureolic acid group.[4] Additionally, moenuronic acid **3**, a 4-*C*-methyl-branched sugar, is found in moenomycin A, a trans-glycosylation inhibitor.[5]

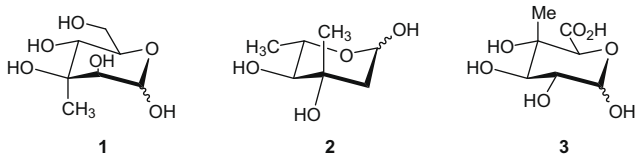

Figure 1.

Carbohydrates are readily available and are an extensive family of chirons for use in synthesis.[6] In contrast, few C-branched sugar building blocks are easily accessible and therefore there are only a small number of examples of their use in synthesis.[7] Several methods for the synthesis of branched chain sugars, including addition to a carbonyl functionality,[8] crossed aldol and other condensation reactions,[9] the Petersen olefination,[4] the Kiliani ascension of 2-C-substituted carbohydrates[10] and the Wittig reaction,[2a,8c,11] have been employed in the synthesis of C-3 and C-4-branched sugars. Recent biological studies on branched mannose derivatives have shown that this class of compounds could have potential therapeutic utility.[12]

The Wittig reaction has been previously used to introduce branch points into sugars by the addition of the phosphorous ylid to a ketone functionality on the carbohydrate backbone.[8c] This paper demonstrates that the Wittig-dihydroxylation reaction sequence can be applied to sugar lactols to simultaneously effect a two carbon chain extension and introduce a branch point. This could be carried out with 1-deoxy-sugars, sugars already containing a branching point or alternatively with straight chain sugars and a substituted Wittig reagent. In this fashion, after dihydroxylation and subsequent ring closure, sugar lactones branched at the C-2, C-3 and/or C-4 positions could be synthesised (Scheme 1).

The formation of both *E*- and *Z*-alkenes followed by the *syn* stereospecific dihydroxylation would give rise to 4 possible esters which on ring closure would allow access to four δ-lactones (Scheme 2). The formation of the *E*-alkene should lead to the generation of *gluco* and *altro* lactones whereas the *Z*-alkene should give rise to the *allo* and *manno* lactones. Therefore, by stereo control of both the Wittig and the dihydroxylation reactions all four products would be accessible in both series leading to four possible C-3-branched lactones and four possible C-4-branched lactones. Application of this methodology to the corresponding starting

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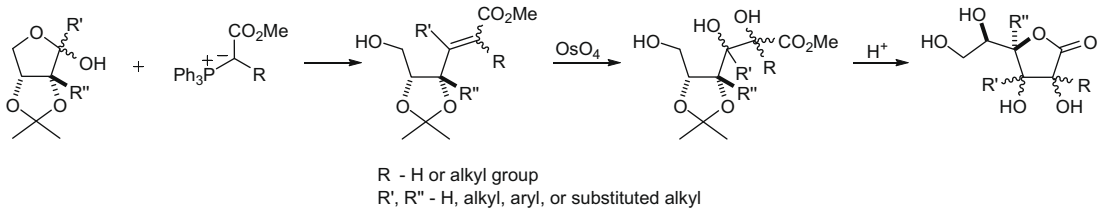


Scheme 1.

materials derived from threose would give access to the remaining four sugar lactones, that is, *gulo*, *ido*, *galacto* and *talo*.

2. Results and discussion

The two readily available D-erythrose derivatives **4** and **5** (Fig. 2) are convenient starting materials to test the synthetic pathway. Initially the Wittig reaction was carried out on 1-deoxy ribulose **5**,[13] obtained by the reaction of methyl magnesium bromide with 2,3-*O*-isopropylidene-D-erythronolactone, and the ylid and lactol were heated at 40 °C for 48 h (Scheme 3). After this time a mixture of *E*- and *Z*-alkenes **6** was formed in 94% yield, in a 6:1 *E*/*Z* ratio. If the reaction mixture was allowed to remain at 40 °C then a second product **7**, arising from an intramolecular Michael addition reaction, began to form. Interestingly the Michael addition product **7** was found to be unstable and on standing in $CDCl_3$ the formation of an additional product was observed. This was identified, by NOE experiments, as the epimer at C-3 arising from a reverse Michael reaction in the slightly acidic conditions followed by closure on the opposite face of the alkene.

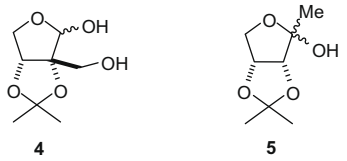
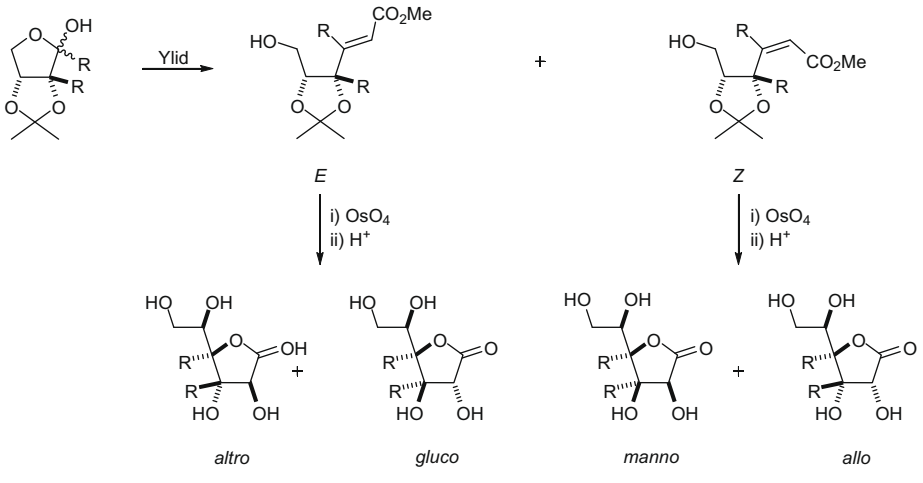


Figure 2.

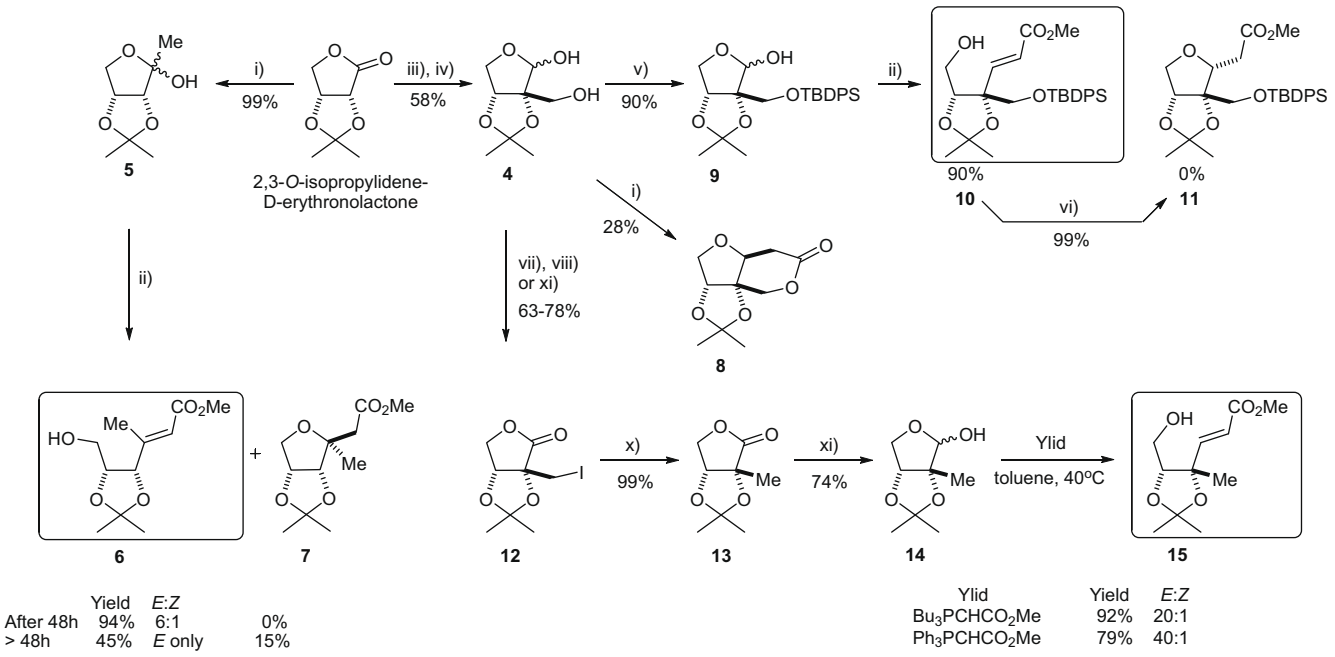
The 2-*C*-hydroxymethyl derivative **4** was synthesised from D-erythronolactone via reduction to the lactol followed by a Ho Aldol reaction.[9c] The subsequent Wittig reaction, however, yielded only the fused ring compound **8** (Scheme 2). This could arise from an intramolecular Michael reaction of the C-5 hydroxyl group with the α,β-unsaturated ester, followed by an intramolecular condensation reaction of the neopentyl hydroxyl group with the ester group to give the lactone. In order to prevent the latter of the two intramolecular reactions from occurring two options were investigated; either selectively protecting the neopentyl hydroxyl group with *tert*butyldiphenylsilyl chloride to give **9** (Scheme 3), or alternatively reducing the side chain to a methyl group to give **13**. The reduction of the side chain was achieved by bromine oxidation of the lactol **4**, this reaction proceeded smoothly to give the lactone in 87% yield. This is in direct contrast to work by Pedersen et al. who report the difficulty in oxidising a 2-*C*-methyl-erythrose derivative in this fashion.[14] The hydroxymethyl branch was then either activated as the trifluoromethanesulfonate ester and displaced with iodide or reacted directly with triphenylphosphine and iodine to give iodide **12**, subsequent reduction with hydrogen and palladium gave the 2-*C*-methyl-branched lactone **13**. This was then reduced, with di*iso*butylaluminium hydride, to give the desired lactol **14** in good yield.

Both the lactols **10** and **14** were subjected to the same conditions for the Wittig reaction as described earlier to generate the *E*-alkenes **10** and **15** in excellent yields (90% and 92%, respectively). Again, as in the case of the 1-deoxy ribulose **5**, the major product was the *E*-alkene, and much greater selectivity was observed with the aldose rather than the ketose system. No Michael reaction product was seen in either case. Reaction with an alternative ylid Ph_3PCHCO_2Me was seen to be slower and again only the *E*-alkene was observed. Interestingly when the reaction was performed under anhydrous conditions the major product formed was that arising from Michael addition.

Dihydroxylation reactions proceed *syn* stereospecifically to generate *cis*-diols. Therefore it was expected that two products would



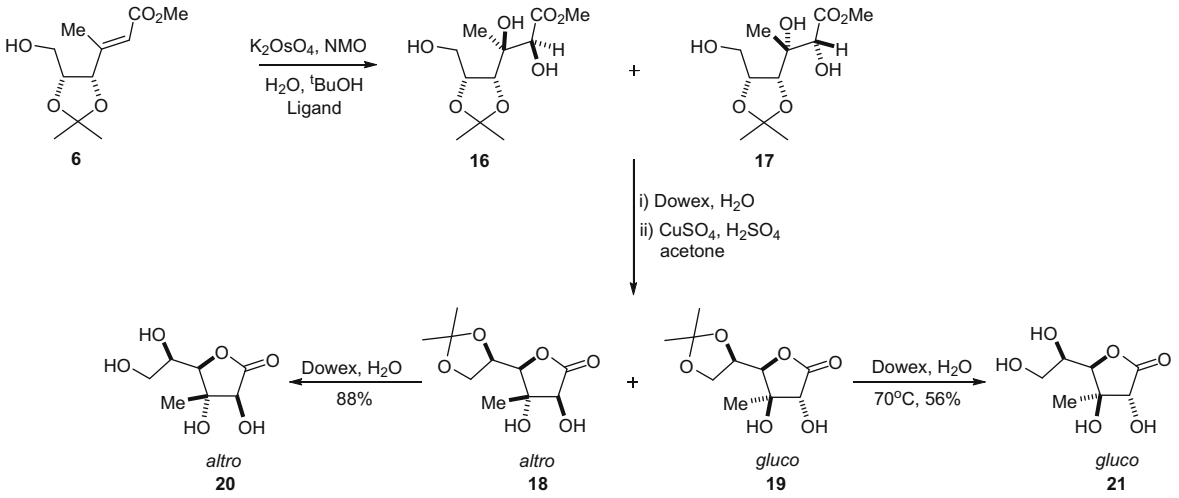
Scheme 2.



Scheme 3. Reagents and conditions: (i) MeMgBr, THF, −78 °C; (ii) Bu_3PCHCO_2Me, toluene, 40 °C; (iii) DIBALH, DCM, −78 °C; (iv) CH_2O, K_2CO_3, MeOH, 70 °C; (v) TBDPSCl, TEA, DMAP, DCM; (vi) NaOMe, MeOH; (vii) Br_2, K_2CO_3, H_2O, 0 °C; (viii) Tf_2O, Pyr., DCM, −30 to −10 °C; then Bu_4NI, THF; (ix) I_2, PPh_3, imidazole, toluene, 85 °C; (x) H_2, Pd, TEA, EtOH; (xi) DIBALH, DCM, −78 °C.

be formed from the *E*-alkenes **6** and **10**. Standard Upjohn conditions[15] (potassium osmate and 4-methylmorpholine-N-oxide (NMO)) were applied to the 1-deoxy ribulose system **6** and the reaction was seen to proceed in a very poor yield giving only 16% of a single product, later found to be **17**. Modified Sharpless conditions[16] were next investigated and alkene **6** was reacted with potassium osmate, NMO and $(DHQ)_2PHAL$ (Scheme 4). The yield of the reaction was improved to a total of 46% and two products were observed in a 1:3 ratio (**16**:**17**). It has been shown in the literature[17] that dihydroxylations may show a pH dependency and addition of certain acids can increase the rate of reactivity and alter the selectivity of the reaction, therefore a number of acids were investigated. In the case of L-malic acid (Table 1) although the reaction proceeded at a faster rate there was little change in both the yields and selectivity. Addition of citric and L-tartaric acid, however, greatly increased both the overall yield and the rate of the reaction. Interestingly the selectivity of the reaction was reversed with both of these reactions favouring the formation of triol **16** (Table 1). As L-tartaric acid is chiral it was wondered whether use of the enantiomeric D-tartaric acid would reverse the selectivity but maintain the high yields. This, however, was not seen to be the case. The reaction with D-tartaric acid was high yielding but again gave triol **16** as the major product, with the selectivity only slightly decreasing from 6:1 to 4:1.

Separation of the two triols by column chromatography was difficult and therefore the mixture was treated with acidic resin to deprotect the acetonide-protecting group and effect ring closure to the lactone. The mixture of lactones was then reprotected with anhydrous copper sulfate, acetone and catalytic sulfuric acid to give both the altronolactone **18** and the gluconolactone **19** (Scheme 4) which could be cleanly isolated and the stereochemistry firmly determined. Subsequent deprotection using Dowex (H^+)



Scheme 4.

Table 1
Ratios determined by integration in ^{1}H NMR

Ligand	Yield of **16** (%)	Yield of **17** (%)
$(DHQ)_2PHAL$ (2 mol %), 72 h	14	32
L-Malic acid (0.5 equiv), 18 h	9	28
Citric acid (0.5 equiv), 18 h[a]	42	15
Citric acid (0.75 equiv), 18 h	63	21
L-Tartaric acid (0.5 equiv), 18 h	61	10
L-Tartaric acid (0.75 equiv), 18 h	56	13
D-Tartaric acid (0.5 equiv), 18 h	55	14

[a] 38% starting material was recovered from this reaction.

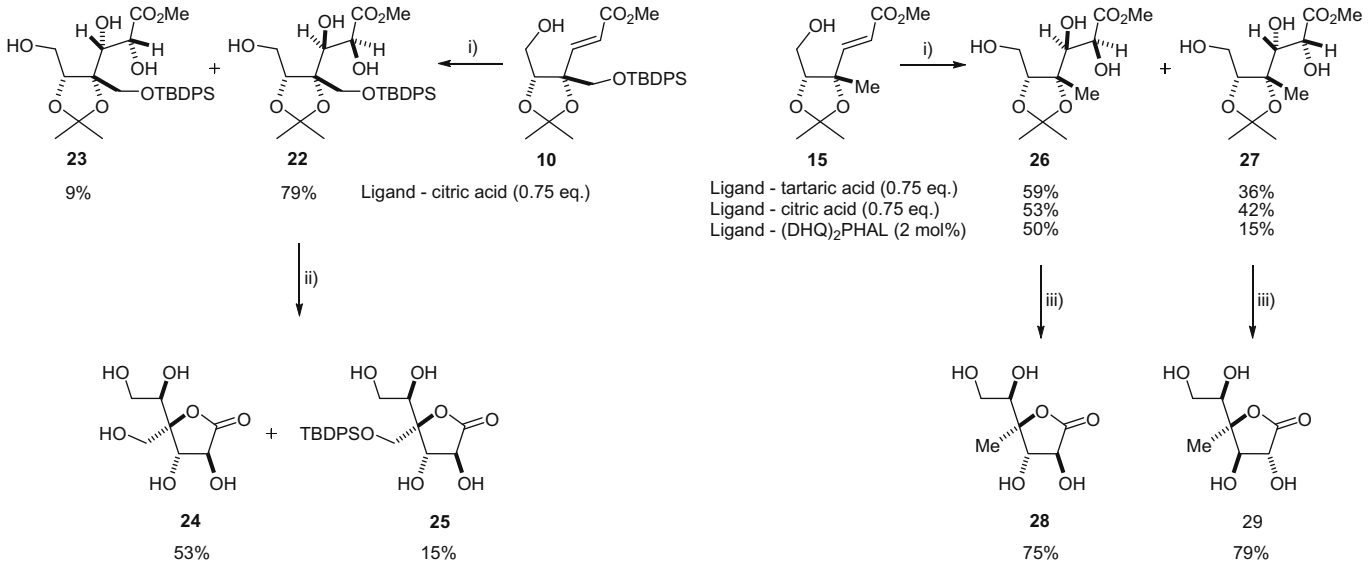
resin in water gave the fully deprotected altronolactone **20** and gluconolactone **21**.

The same reaction conditions were applied to the 2-*C*-hydroxymethyl-branched system **10** and the 2-*C*-methyl-branched system **15** (Scheme 5). In the case of **10** the acid which gave both the best yield and the greatest stereoselectivity was found to be citric acid. Additionally the triols were separable, giving the major product **22** in 79% yield and the minor product **23** in 9% yield. The stereochemistry of the major product **22** was at this point unknown, however, deprotection and ring closure to the lactone in acidic conditions gave both the fully and partially deprotected products **24** and **25** (Scheme 5), the stereochemistries of which were confirmed by NOE experiments to again be *altro*. For the case of the 2-*C*-methyl-branched system **15** less selectivity was shown with L-tartaric and citric acid giving a 5:3 or 5:4 ratio of products, respectively. The *altro* **26** was found to again be the favoured product. Interestingly, when using $(DHQ)_2PHAL$ as the ligand the selectivity remained in favour of the *altro* product **26**.

In summary, chain extension of branched sugar lactols by use of the Wittig reaction and subsequent dihydroxylation has provided access to C-3 and C-4-branched sugar lactones. The *E*-alkene was selectively formed in high yield and the subsequent dihydroxylation reactions in the presence of citric or tartaric acid proceeded in good yield. In both cases the predominant isomer was the *altro* rather than the *gluco* isomer arising from the formation of the *E*-alkene in the Wittig reaction followed by dihydroxylation predominantly on the upper face of the α,β-unsaturated ester. For the C-2-substituted systems, when the size of the C-2 substituent was reduced, from a silyl-protected hydroxymethyl group to a methyl group, the selectivity of the dihydroxylation reaction decreased allowing easier access to the *gluco* isomer. Acidic conditions were used to simultaneously deprotect and close the compounds to the desired C-3 and C-4-branched lactones. Recently, chemically synthesised 2-*C*-methyl-pentoses and 2-*C*-methyl-hexoses have been modified by the biotechnology of Izumoring[18] to 4-*C*-methyl-pentoses[19] and 5-*C*-methyl-hexoses.[20] A similar synergy of chemistry and biotechnology may allow the hexoses reported herein to be transformed into a wide range of 3-*C*- and 4-*C*-methyl-carbohydrates.

3. Experimental

All commercial reagents were used as supplied. Tetrahydrofuran and *N*,*N*-dimethylformamide were purchased dry from the Aldrich chemical company in sure-seal bottles. Pyridine was purchased dry from the Sigma–Aldrich chemical company in sure-seal bottles. All other solvents were used as supplied (analytical or HPLC grade), without prior purification. The reactions were performed under an atmosphere of nitrogen or argon, unless stated otherwise. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. The sheets were visualised using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. The concentrations are quoted in g 100 mL^{-1}. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl or Ge plates (thin film). Only the characteristic peaks are quoted. Low resolution mass spectra (*m*/*z*) were recorded on VG MassLab 20–250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high resolution mass spectra (HRMS *m*/*z*) on a Micromass Autospec 500 OAT spectrometer. The techniques used were electrospray (ESI), chemical ionisation (CI NH_3), or atmospheric pressure chemical ionisation (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) and Bruker DPX 400 and DQX 400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in hertz. Residual signals from the solvents were used as an internal reference.



Scheme 5. Reagents and conditions: (i) K_2OsO_4, NMO, H_2O, ^{t}BuOH, ligand; (ii) TFA, H_2O, dioxane; (iii) Dowex (50W X8, H^+), H_2O.

3.1. 1-Deoxy-3,4-*O*-isopropylidene-D-*erythro*-pentulofuranose 5

2,3-*O*-Isopropylidene-D-erythronolactone (16.72 g, 0.106 mol) was dissolved in dry tetrahydrofuran (400 mL), the solution was cooled to −78 °C and methyl magnesium bromide (3 M solution in ether, 39 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min after which time ammonium chloride (satd aq, 30 mL) was added and the reaction mixture was 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 (magnesium sulfate) and concentrated under reduced pressure to give the ketose **5** as a (8:1) mixture of anomers (18.2 g, 99%) which was used without further purification. Mp: 82–85 °C [lit.[21] 87–89 °C]; ν_{max} (thin film): 3423 (m, br, OH); NMR data for major anomer: δ_H ($CDCl_3$, 400 MHz): 1.31 (3H, s, OCHCH_3), 1.46 (3H, s, OCHCH_3), 1.51 (3H, s, CH_3), 3.89 (1H, d, H5, *J* 10.2), 3.97–4.00 (1H, dd, H5′, *J* 3.8, 10.3), 4.38 (1H, d, H3, *J* 6.0), 4.82–4.85 (1H, m, H4); δ_C ($CDCl_3$, 100 MHz): 22.3 (CH_3), 25.0 (OCHCH_3), 26.3 (OCHCH_3), 70.9 (C5), 80.8 (C4), 85.0 (C3), 105.9 (C2), 112.3 (O$CH(CH_3)_2$); *m/z* (ESI−ve): 173 ($[M-H]^-$, 100%).

3.2. (4*S*,5*R*,*E*)-Methyl 6-hydroxy-4,5-*O*-isopropylidene-3-methyl-hex-2-enoate 6 and (4*S*,5*R*,*Z*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-3-methyl-hex-2-enoate and methyl 3,6-anhydro-2-deoxy 4,5-*O*-isopropylidene-3-*C*-methyl-D-*ribo*-hexanoate 7

$[Bu_3PCH_2CO_2Me]^+Br^-$ (2.40 g, 6.77 mmol) was dissolved in dichloromethane (30 mL) and shaken with sodium hydroxide (1 M aq, 30 mL) for 5 min. The organic layer was washed with brine (2 × 20 mL), dried (magnesium sulfate) and the solvents were concentrated in vacuo. A solution of 1-deoxy-3,4-isopropylidine-D-*erythro*-pentolofuranose **5** (471 mg, 2.71 mmol) in toluene (5.5 mL) was added to the residue and the reaction mixture was stirred at 40 °C for 48 h. TLC analysis (ethyl acetate/cyclohexane 1:1) showed the formation of two UV active products (R_f 0.42 and 0.38). Purification by flash column chromatography (ethyl acetate/cyclohexane 1:4→1:1) afforded (4*S*,5*R*,*Z*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-3-methyl hex-2-enoate (R_f 0.42, 89 mg, 14%) and (4*S*,5*R*,*E*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-3-methyl hex-2-enoate **6** (R_f 0.38, 497 mg, 80%) as colourless oils. If the reaction mixture was allowed to remain at 40 °C for greater than 48 h a third product, a pale yellow oil, was obtained which was found to be methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-3-*C*-methyl-D-*ribo*-hexanoate **7**.

3.2.1. Data for (4*S*,5*R*,*E*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-3-methyl-hex-2-enoate 6

HRMS (ESI+ve) found: 253.1046 $[M+Na]^+$; $C_{11}H_{18}O_5Na$ requires: 253.1046; $[\alpha]_D^{17} = +41.7$ (*c* 1.28, $CHCl_3$); ν_{max} (thin film): 3423 (s, br, OH), 1719 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.31, 1.45 (2 × 3H, s, CH_3C), 2.05 (3H, a-d, Me, *J* 1.3), 2.52 (1H, br, s, OH), 3.29–3.33 (1H, dd, H6, *J* 4.8, 11.4), 3.33–3.38 (1H, dd, H6′, *J* 7.7, 11.4), 3.62 (3H, s, OMe), 4.28–4.33 (1H, ddd, H5, *J* 4.9, 6.9, 7.5), 4.58–4.61 (1H, a-dd, H4, *J* 1.1, 6.7), 5.96–5.97 (1H, a-dd, H2, *J* 1.3, 2.7); δ_C ($CDCl_3$, 100 MHz): 21.0 (Me), 27.8, 25.9 (CH_3C), 51.1 (OMe), 61.7 (C6), 78.2 (C5), 82.9 (C4), 109.3 (CH_3C), 115.8 (C2), 157.7 (C3), 166.7 (C=O); *m/z* (ESI−ve): 229 ($[M-H]^-$, 70%).

3.2.2. Data for (4*S*,5*R*, *Z*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-3-methyl-hex-2-enoate

HRMS (ESI+ve) found: 253.1046 $[M+Na]^+$; $C_{11}H_{18}O_5Na$ requires: 253.1046; $[\alpha]_D^{21} = +45.7$ (*c* 0.6, $CHCl_3$); ν_{max} (thin film): 3444 (s, br, OH), 1644 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.40, 1.54 (2 × 3H, s, CH_3C), 1.98 (3H, s, Me), 3.42–3.47 (1H, dd, H6, *J* 5.9, 11.7), 3.57–3.61 (1H, dd, H6′, *J* 3.7, 11.7), 3.69 (3H, s, OMe), 4.66–4.70 (1H, ddd, H5, *J* 3.7, 5.8, 8.0), 5.67 (1H, d, H4, *J* 8.0), 5.84–5.85 (1H, a-dd, H2, *J* 1.4, 2.9); δ_C ($CDCl_3$, 100 MHz): 22.1, 22.2 (CH_3C), 26.5 (Me), 51.3 (OMe), 61.5 (C6), 76.2 (C4), 78.7 (C5), 108.6 (CH_3C), 117.0 (C2), 159.0 (C3), 166.4 (C=O); *m/z* (ESI+ve): 280 ($[M+MeOH+NH_4]^+$, 100%).

3.2.3. Data for methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-3-*C*-methyl-D-ribo-hexanoate 7

HRMS (ESI+ve) found: 253.1049 $[M+Na]^+$; $C_{11}H_{18}O_5Na$ requires: 253.1046; $[\alpha]_D^{15} = -17.8$ (*c* 1.13, $CHCl_3$); ν_{max} (thin film): 3454 (m, br, OH), 1740 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.33 (3H, s, $C(CH_3)_2$), 1.41 (3H, s, CH_3), 1.52 (3H, s, CH_3C), 2.42 (2H, a-s, H2, H2′), 3.68 (3H, s, OMe), 3.78–3.81 (1H, dd, H6, *J* 4.2, 11.0), 3.93 (1H, d, H6′, *J* 10.9), 4.58 (1H, d, H4, *J* 6.2), 4.84–4.87 (1H, ddd, H5, *J* 0.7, 4.2, 6.0); δ_C ($CDCl_3$, 100 MHz): 20.2 (CH_3), 26.2, 26.8 (CH_3C), 41.0 (C2), 51.8 (OMe), 71.0 (C6), 81.7 (C5), 83.5 (C3), 84.6 (C4), 112.5 (CH_3C), 170.6 (C=O); *m/z* (ESI+ve): 253 ($[M+Na]^+$,100%).

3.3. Methyl 4,5-*O*-isopropylidene-3-*C*-methyl-D-altronoate 16 and methyl 4,5-*O*-isopropylidene-3-*C*-methyl-D-gluconate, 17

Alkene **6** (59 mg, 0.26 mmol) was dissolved in *tert*-butyl alcohol (0.95 mL) and water (0.95 mL), stirring under an atmosphere of argon. Citric acid (40 mg, 0.19 mmol) was added and allowed to dissolve before the addition of potassium osmate dihydrate (1 mg, 2.6 μmol) and 4-methylmorpholine N-oxide (33 mg, 0.28 mmol). The suspension was stirred at room temperature for 16 h. After this time, TLC analysis (ethyl acetate) showed complete consumption of the starting material (R_f 0.64) and the formation of two products (R_f 0.43 and 0.34). The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (ethyl acetate) to afford methyl 4,5-*O*-isopropylidene-3-*C*-methyl-D-gluconoate **17** (14 mg, 21%) and methyl 4,5-*O*-isopropylidene-3-*C*-methyl-D-altronoate **16** (43 mg, 63%), both as colourless oils.

3.3.1. Data for methyl 4,5-*O*-isopropylidene-3-*C*-methyl-D-altronoate 16 (major product, R_f 0.43)

$C_{11}H_{20}O_7$ requires: C, 49.49; H, 7.63. Found: C, 49.00; H, 8.11; HRMS (ESI+ve) found: 287.1111 $[M+Na]^+$; $C_{11}H_{20}O_7Na$ requires: 287.1101; $[\alpha]_D^{17} = +17.8$ (*c* 1.65, acetone); ν_{max} (thin film): 3418 (s, br, OH), 1738 (s, C=O); δ_H (acetone-d_6, 400 MHz): 1.31, 1.32 (2 × 3H, s, CH_3C), 1.41 (3H, s, Me), 3.57–3.62 (1H, m, H6), 3.70 (3H, s, OMe), 3.90–4.00 (1H, m, H6′), 4.15 (1H, d, H2, *J* 8.0), 4.24 (1H, s, 6-OH), 4.35 (1H, m, H4, H5) 4.41 (1H, d, 2-OH, *J* 8.2), 4.44 (1H, s, 3-OH); δ_C (acetone-d_6, 100 MHz): 20.2 (Me), 27.2, 27.0 (CH_3C), 51.5 (OMe), 61.1 (C6), 75.0 (C3), 76.2 (C5), 78.7 (C4), 79.0 (C2), 107.4 (CH_3C), 172.7 (C=O); *m/z* (ESI−ve): 263 ($[M-H]^-$, 100%).

3.3.2. Data for methyl 4,5-*O*-isopropylidene-3-C-methyl-D-gluconate 17 (minor product R_f 0.34)

$C_{11}H_{20}O_7$ requires: C, 49.49; H, 7.63. Found: C, 49.00; H, 8.11; HRMS (ESI+ve) found: 287.1111 $[M+Na]^+$; $C_{11}H_{20}O_7Na$ requires: 287.1101; $[\alpha]_D^{18} = +19.6$ (*c* 0.55, acetone); ν_{max} (thin film): 3418 (s, br, OH), 1738 (s, C=O); δ_H (acetone-d_6, 400 MHz): 1.30, 1.41 (3H, s, CH_3C), 1.33 (3H, s, Me), 2.82, 2.85 (2H, 2 × s, O-H), 3.57–3.62 (1H, m, H6), 3.67–3.73 (1H, m, H6′), 3.75 (3H, s, OMe), 4.12 (1H, m, H5), 4.26 (1H, dd, H4, *J* 1.2, 5.5), 4.48 (1H, a-d, H2, *J* 5.1), 4.43–4.51 (1H, m, OH); δ_C (acetone-d_6, 100 MHz): 23.3 (Me), 27.7, 26.0 (CH_3C), 52.4 (OMe), 62.6 (C6), 74.2 (C3), 76.23 (C5), 78.9 (C4), 79.0 (C2), 108.0 (CH_3C), 166.7 (C=O); *m/z* (ESI−ve): 263 ($[M-H]^-$, 100%).

3.4. 5,6-*O*-Isopropylidene-3-*C*-methyl-D-glucono-1,4-lactone 19 and 5,6-*O*-isopropylidene-3-*C*-methyl-D-altrono-1,4-lactone 18

A mixture of methyl 4,5-*O*-isopropylidene-3-*C*-methyl-altronate **16** and methyl 4,5-*O*-isopropylidene-3-*C*-methyl-gluconate **17**, in a 4:3 ratio (135 mg, 0.51 mmol) was dissolved in water (4 mL) and stirred with Dowex® (50W X8, H^+) resin (100 mg) for 48 h. After this time, the resin was filtered away, and the solution was concentrated in vacuo to give a colourless oil (98 mg, 100%). The crude mixture of 3-*C*-methyl-D-glucono/altrono-1,5-lactone and 3-*C*-methyl-D-glucono/altrono-1,4-lactone was used without further purification. This crude was treated with acetone (2 mL), anhydrous copper sulfate (163 mg, 1.02 mmol) and a catalytic quantity of concentrated sulfuric acid. TLC analysis (ethyl acetate) after 48 h revealed complete consumption of the starting material (R_f 0.0→0.15) and the presence of two major products (R_f 0.71, 0.59). The reaction mixture was neutralised with excess sodium carbonate and the salts were filtered away through a pad of Celite®. The filtrate was concentrated in vacuo to leave an oily residue (124 mg). Purification by flash column chromatography (ethyl acetate/cyclohexane 2:1) afforded 5,6-*O*-isopropylidene-3-*C*-methyl-D-glucono-1,4-lactone **19** (24 mg, 25%, R_f 0.71) and 5,6-*O*-isopropylidene-3-*C*-methyl-D-altrono-1,4-lactone **18** (53 mg, 54%, R_f 0.59).

3.4.1. Data for 5,6-*O*-isopropylidene-3-C-methyl-D-glucono-1,4-lactone 19 (minor product, R_f 0.71)

HRMS (ESI−ve) found: 249.0970 $[M+OH]^-$; $C_{10}H_{17}O_7$ requires: 249.0969; $[\alpha]_D^{21} = +74.7$ (*c* 0.25, acetone); ν_{max} (thin film): 3452 (s, br, OH), 1772 (s, C=O); δ_H (acetone-d_6, 400 MHz): 1.32, 1.39 (2 × 3H, s, CH_3C), 1.47 (3H, s, CH_3), 3.88 (1H, d, H2, *J* 5.0), 3.92–3.95 (1H, dd, H6, *J* 5.8, 8.6), 4.07–4.11 (1H, dd, H6′, *J* 6.5, 8.6), 4.33 (1H, d, H4, *J* 6.3), 4.47 (1H, a-q, H5, *J* 6.2), 4.59 (1H, s, 3-OH), 5.62 (1H, d, 2-OH, *J* 5.1); δ_C (acetone-d_6, 100 MHz): 23.3 (*C*H_3C), 25.6 (CH_3), 27.0 (C(*C*H_3)$_2$), 66.9 (C6), 73.6 (C5), 76.8 (C3), 77.1 (C2), 85.8 (C4), 109.6 (*C*(CH_3)$_2$), 175.4 (C=O); *m/z* (ESI−ve): 463 ($[2M-H]^-$, 20%), 291 ($[M+OCOCH_3]^-$, 45%), 249 ($[M+OH]^-$, 50%), 231 ($[M-H]^-$, 73%), 203 (100%).

3.4.2. Data for 5,6-*O*-isopropylidene-3-C-methyl-D-altrono-1,4-lactone 18 (major product, R_f 0.59)

HRMS (ESI−ve) found: 231.0860 $[M-H]^-$; $C_{10}H_{15}O_6$ requires: 231.0863; $[\alpha]_D^{19} = +50.4$ (*c* 0.46, acetone); ν_{max} (thin film): 3420 (s, br, OH), 1788 (s, C=O); δ_H (acetone-d_6, 400 MHz): 1.28 (3H, s, CH_3); 1.33 (3H, s, C(CH_3)$_2$), 1.42 (3H, s, C(CH_3)$_2$), 3.86–3.92 (1H, dd, H6, *J* 5.2, 8.5), 4.10–4.14 (1H, dd, H6′, *J* 6.2, 8.6), 4.19 (1H, d, H4, *J* 7.4), 4.28–4.33 (1H, ddd, H5, *J* 5.3, 6.2, 7.3), 4.41 (1H, d, H2, *J* 5.7), 4.44 (1H, s, 3-OH), 5.24 (1H, d, 2-OH, *J* 5.8); δ_C (acetone-d_6, 100 MHz): 16.2 (CH_3), 25.5, 27.0 (C(CH_3)$_2$), 67.1 (C6), 74.4 (C5), 76.7 (C2), 78.1 (C3), 83.6 (C4), 110.1 (*C*(CH_3)$_2$), 174.3 (C=O); *m/z* (ESI−ve): 231 ($[M-H]^-$, 100%).

3.5. 3-*C*-Methyl-D-altrono-1,4-lactone 20

Protected altronolactone **18** (28 mg, 0.12 mmol) was dissolved in water (0.5 mL), and Dowex® (50W X8, H^+) was added. The reaction mixture was stirred at room temperature for 16 h, after which time TLC (ethyl acetate) showed the formation of one major product (R_f 0.1) and a small amount of unreacted starting material (R_f 0.59). After 72 h the reaction mixture was filtered and concentrated in vacuo and purified by column chromatography (20% methanol in ethyl acetate) to give 3-*C*-methyl-D-altrono-1,4-lactone **23** as a colourless oil (21 mg, 88%). HRMS (ESI+ve) found: 215.0526 $[M+Na]^+$; $C_7H_{12}NaO_6$ requires: 215.0526; $[\alpha]_D^{22} = +63.3$ (*c* 0.15, MeOH); ν_{max} (thin film): 3385 (s, br, OH), 1782 (m, C=O); δ_H (D_2O, 500 MHz): δ_H (D_2O, 500 MHz): 1.31 (3H, s, Me-4), 3.67–3.70 (1H, dd, H6, *J* 5.6, 12.2), 3.77–3.80 (1H, dd, H6′, *J* 2.8, 12.3), 3.90–3.93 (1H, ddd, H5, *J* 2.8, 5.6, 9.2), 4.25 (1H, d, H4, *J* 9.1), 4.64 (1H, s, H2); δ_C (D_2O, 125.7 MHz): 14.5 (CH_3), 63.4 (C6), 69.7 (C5), 76.3 (C2), 78.7 (C3), 80.5 (C4), 176.5 (C=O); *m/z* (ESI−ve): 191 ($[M-H]^-$, 100%).

3.6. 3-*C*-Methyl-D-glucono-1,4-lactone 21

Protected gluconolactone **19** (16 mg, 0.07 mmol) was dissolved in water (1 mL), and Dowex® (50W X8, H^+) was added. The reaction mixture was stirred at room temperature for 48 h, after which time TLC (ethyl acetate) showed the formation of one product (R_f 0.0) and unreacted starting material (R_f 0.71). The reaction mixture was heated to 70 °C and after a further 3 h the reaction mixture was filtered and concentrated in vacuo and purified by column chromatography (10% isopropanol in ethyl acetate) to give 3-*C*-methyl-D-glucono-1,4-lactone **21** as a colourless oil (7 mg, 56%). HRMS (ESI+ve) found: 215.0533 $[M+Na]^+$; $C_7H_{12}NaO_6$ requires: 215.0526; $[\alpha]_D^{20} = +47.1$ (*c* 0.48, H_2O); ν_{max} (thin film): 3148 (s, br, OH), 1772 (s, C=O); δ_H (500 MHz, D_2O): 1.35 (3H, s, CH_3), 3.67 (1H, dd, H6, *J* 3.4, 12.1), 3.75 (1H, dd, H6′, *J* 5.8, 12.1), 4.00 (1H, ddd, H5, *J* 3.4, 5.9, 6.9), 4.29 (1H, d, H4, *J* 7.1), 4.40 (1H, s, H2); δ_C (125 MHz, D_2O): 19.8 (CH_3), 62.6 (C6), 69.9 (C5), 74.7 (C2), 76.7 (C3), 84.5 (C4), 176.8 (C1); *m/z* (ESI−ve): 191 ($[M-H]^-$, 100%).

3.7. 2,3-*O*-Isopropylidene-D-erythrofuranose

2,3-*O*-Isopropylidene-D-erythronolactone (1.02 g, 6.46 mmol) was dissolved in dichloromethane (25 mL) and cooled to −78 °C. Di*iso*butylaluminium hydride (1.7 M in toluene, 4.2 mL, 7.1 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 2 h after which time IR analysis still showed the presence of a small carbonyl peak. Further, di*iso*butylaluminium hydride (2 mL) was added dropwise and the reaction mixture was stirred further for an hour. IR analysis showed the complete disappearance of the carbonyl group. (TLC analysis (ethyl acetate/cyclohexane, 1:1) showed that the product co-spotted with the starting material (R_f 0.43)). The reaction was quenched with methanol and the reaction mixture was allowed to warm to room temperature. Ethyl acetate (2 mL) was added followed by potassium dihydrogen orthophosphate (6.5 g) and sodium hydrogencarbonate (satd, aq, 10 mL). The mixture was dried (magnesium sulfate), filtered through Celite and concentrated under reduced pressure to give the crude lactol (1.02 g, 99%), a colourless oil, as a 7:1 mixture of anomers, which was used without further purification. HRMS (ESI+ve) found: 183.0628 $[M+Na]^+$; $C_7H_{12}NaO_4$ requires: 183.0628; $[\alpha]_D^{20} = -70.8$ (*c* 1.005, $CHCl_3$); ν_{max} (thin film): 3419 (s, br, OH); δ_H ($CDCl_3$, 400 MHz) (data given for major anomer): 1.29 (3H, s, CH_3C), 1.44 (3H, s, CH_3C), 3.94 (1H, br, s, OH), 3.98 (1H, d, H4, *J* 10.4), 4.02–4.05 (1H, dd, H4′, *J* 3.4, 10.4), 4.54 (1H, d, H2, *J* 5.8), 4.80–4.82 (1H, dd, H3, *J* 3.4, 5.8), 5.36 (1H, s, H1); δ_C ($CDCl_3$, 100 MHz): 24.7 (*C*H_3C), 26.1 (*C*H_3C), 71.8 (C4), 79.9 (C3), 85.1 (C2), 101.6 (C1), 112.3 (CH_3*C*); *m/z* (ESI+ve): 183 ($[M+Na]^+$, 100%).

3.8. 2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-erythrofuranose 4

2,3-*O*-Isopropylidene-D-erythrofuranose (1.617 g, 10.1 mmol) was dissolved in methanol (15 mL). Potassium carbonate (1.53 g, 11.1 mmol) and formaldehyde (37% aq, 8.3 mL) were added and the reaction was refluxed for 6 h. After this time TLC (ethyl acetate/cyclohexane, 1:1) showed the conversion of the starting material (R_f 0.57) to one major product (R_f 0.18). The reaction mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL) and the aqueous layer was further extracted with ethyl acetate (2 × 50 mL). The combined organics were dried (magnesium sulfate) and concen-

trated under reduced pressure to give the crude lactol which was purified by column chromatography (ethyl acetate/cyclohexane, 1:1) to yield 2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-D-erythrofuranose **4** (1.116 g, 58%), a colourless oil, as a 3:2 mixture of anomers. $C_8H_{14}O_5$ requires: C, 50.52, H, 7.42. Found: C, 50.00, H, 7.44; $[\alpha]_D^{20} = -51.3$ (*c* 0.91, $CHCl_3$); ν_{max} (thin film): 3424 (s, br, OH); δ_H (CD_3CN, 400 MHz) (3:2 mixture of anomers, A—major anomer): 1.38 (3H, s, CH_3C^A), 1.42 (6H, s, CH_3C^A, CH_3C^B), 1.50 (3H, s, CH_3C^B), 3.46–3.51 (1H, dd, $H4^B$, *J* 3.4, 11.0), 3.61–3.69 (2H, br, m, $H2'^B$), 3.71–3.78 (2H, br, m, $H2'^A$), 3.81 (1H, d, $H4'^B$, *J* 11.0), 3.85 (1H, d, $H4^A$, *J* 10.6), 3.97–4.00 (1H, dd, $H4'^A$, *J* 3.5, 10.5), 4.00 (1H, d, $OH1^B$, *J* 11.6), 4.45 (1H, br, s, $OH1^A$), 4.59–4.61 (2H, m, $H3^A$, $H3^B$), 4.79 (1H, d, $H1^B$, *J* 11.5), 5.21 (1H, s, $H1^A$); δ_C (CD_3CN, 100 MHz): 26.5 (CH_3C^B), 26.9 (CH_3C^B), 27.4 (2 × CH_3C^A), 62.3 ($C2'^B$), 62.5 ($C2'^A$), 67.6 ($C4^B$), 72.2 ($C4^A$), 82.4 ($C3^B$), 83.1 ($C3^A$), 89.4 ($C2^B$), 94.3 ($C2^A$), 98.5 ($C1^B$), 103.5 ($C1^A$), 113.1 (CH_3C^A), 113.4 (CH_3C^B); *m/z* (ESI−ve): 379 ($[2M-H]^-$, 15%), 249 ($[M+CH_3CO_2]^-$, 30%), 189 ($[M-H]^-$, 100%).

3.9. 3,6-Anhydro-2-deoxy-4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-D-*ribo*-hexono-1,4′-lactone 8

$[Bu_3PCH_2CO_2Me]^+Br^-$ (1.06 g, 3 mmol) was dissolved in dichloromethane (10 mL) and washed with sodium hydroxide (1 M aq, 10 mL) for 5 min. The organic layer was then washed with brine (5 mL) and the brine was re-extracted with dichloromethane (2 × 5 mL). The combined organics were dried (magnesium sulfate), filtered and concentrated in vacuo. The resulting ylid was added to a solution of 2,3-*O*-isopropylidene-2-*C*-hydroxymethyl-D-erythrofuranose **4** (228 mg, 1.2 mmol) in toluene (2.5 mL) and the reaction mixture was heated to 40 °C for 48 h. After this time TLC (ethyl acetate/cyclohexane, 1:1) showed the formation of 2 major compounds (R_f 0.67 (UV active), R_f 0.33). The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (10 mL) and washed with brine (5 mL). The organic layer was dried (magnesium sulfate), filtered and concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:6) to give the bicyclic Michael addition product **8** (R_f 0.33) as a colourless oil (71 mg, 28%). HRMS (ESI+ve) found: 237.0734 $[M+Na]^+$; $C_{10}H_{14}NaO_5$ requires: 237.0733; $[\alpha]_D^{20} = -78.3$ (*c* 0.98, CH_3CN); ν_{max} (thin film): 1763 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.39 (3H, s, CH_3C), 1.49 (3H, s, CH_3C), 2.58–2.63 (1H, dd, H2, *J* 5.5, 15.8), 2.83–2.89 (1H, dd, H2′, *J* 5.4, 15.8), 3.89–3.93 (1H, dd, H6, *J* 3.7, 11.1), 3.94–3.98 (1H, dd, H6′, *J* 1.8, 11.1), 4.34 (1H, t, H3, *J* 5.4), 4.44 (2H, a-s, H4′, H4″), 4.72–4.73 (1H, dd, H5, *J* 1.8, 3.7); δ_C (CD_3CN, 100 MHz): 26.7 (CH_3C), 27.7 (CH_3C), 35.1 (C2), 70.5 (C4′), 72.8 (C6), 82.1 (C3), 85.8 (C5), 89.2 (C4), 114.9 (CH_3C), 171.4 (C=O); *m/z* (ESI+ve): 451 ($[2M+Na]^+$, 100%).

3.10. 2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-2′-*O*-*tert*-butyldiphenylsilyl-D-erythrofuranose 9

2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-erythrofuranose **4** (703 mg, 3.7 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. Triethylamine (0.57 mL, 4.07 mmol), *tert*-butyldiphenylsilyl chloride (1.06 mL, 4.07 mmol) and dimethylaminopyridine (45 mg, 0.37 mmol) were added. The reaction mixture was stirred at room temperature for 5 h after which time TLC (ethyl acetate/cyclohexane, 1:1) showed the complete conversion of the starting material (R_f 0.33) to one major product (R_f 0.90). The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:6) to give the monosilylated compound **9** as a colourless oil (1.43 g, 90%). HRMS (ESI+ve) found: 451.1912 $[M+Na]^+$; $C_{24}H_{32}NaO_5Si$ requires: 451.1911; $[\alpha]_D^{21} = -3.5$ (*c* 0.82, CH_3CN); ν_{max} (thin film): 3442 (m, br, OH); δ_H (CD_3CN, 400 MHz) (1:1 mixture of anomers): 1.07 (9H, s, CH_3CSi), 1.31 (3H, s, CH_3C), 1.38 (3H, s, CH_3C), 1.47 (3H, s, CH_3C), 1.49 (3H, s, CH_3C), 3.54–3.57 (1H, dd, $H4^B$, *J* 3.3, 11.0), 3.81 (2H, a-s, $H2'^B$, $H2''^B$), 3.83–3.85 (1H, m, $H4'^B$), 3.84 (1H, d, $H4^A$, *J* 10.5), 3.93 (1H, d, $H2'^A$, *J* 11.2), 3.87 (1H, d, $H2'^A$, *J* 11.2), 3.97–4.01 (1H, dd, $H4'^A$, *J* 3.9, 10.4), 4.01 (1H, d, OH^B, *J* 11.7), 4.19 (1H, d, OH^A, *J* 4.4), 4.65–4.66 (2H, m, $H3^A$, $H3^B$), 4.96 (1H, d, $H1^B$, *J* 11.7), 5.25 (1H, d, $H1^A$, *J* 4.3), 7.40–7.52 (12H, m, ArH), 7.69–7.78 (8H, m, ArH); δ_C (CD_3CN, 100 MHz): 19.7 (2 × CH_3CSi), 26.9 (CH_3C), 27.2 (CH_3CSi), 27.3 (CH_3C), 28.1 (CH_3C), 28.3 (CH_3C), 64.6 ($C2'^A$), 65.1 ($C2'^B$), 68.2 ($C4^B$), 72.6 ($C4^A$), 83.1 ($C3^B$), 83.3 ($C3^A$), 89.5 ($C2^B$), 95.6 ($C2^A$), 99.1 ($C1^B$), 103.5 ($C1^A$), 113.9 (CH_3C), 114.0 (CH_3C), 128.7 (2 × ArCH), 128.8 (ArCH), 130.8 (2 × ArCH), 131.0 (ArCH), 133.6 (ArC), 133.7 (ArC), 134.0 (ArC), 134.2 (ArC), 136.4 (ArCH), 136.5 (ArCH); *m/z* (ESI−ve): 427 ($[M-H]^-$, 45%), 206 (100%).

3.11. 2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-erythrono-1,4-lactone

2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-erythrofuranose **4** (953 mg, 5.0 mmol) was dissolved in water (7.5 mL) and cooled to 0 °C and potassium carbonate (1.04 g, 7.5 mmol) was added. Bromine (0.39 mL, 7.5 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2.5 h after which time TLC (ethyl acetate/cyclohexane, 1:1) showed the complete conversion of the starting material (R_f 0.17) to one major product (R_f 0.32). The reaction was quenched with sodium thiosulfate (satd, aq) until the reaction mixture became colourless. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL), dried (magnesium sulfate) and concentrated in vacuo to give the pure lactone (823 mg, 87%) as a white crystalline solid. $C_8H_{12}O_5$ requires: C, 51.06, H, 6.43. Found: C, 50.66, H, 6.53; HRMS (ESI+ve) found: 211.0585 $[M+Na]^+$; $C_8H_{12}NaO_5$ requires: 211.0582; mp: 64–66 °C; $[\alpha]_D^{22} = -103.4$ (*c* 1.26, $CHCl_3$); ν_{max} (thin film): 3475 (m, br, OH), 1773 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.40 (3H, s, CH_3C), 1.46 (3H, s, CH_3C), 2.90 (1H, br, s, OH), 3.85–3.89 (1H, dd, H2′, *J* 1.9, 11.4), 3.99 (1H, d, H2″, *J* 11.4), 4.38–4.40 (2H, a-dd, H4, *J* 2.9, 10.7), 4.82–4.83 (1H, a-dd, H3, *J* 1.0, 2.9); δ_C ($CDCl_3$, 100 MHz): 26.2 (CH_3C), 26.9 (CH_3C), 61.6 (C2′), 70.5 (C4), 78.5 (C3), 84.6 (C2), 113.6 (CH_3C), 176.6 (C=O); *m/z* (ESI+ve): 211 ($[M+Na]^+$, 100%).

3.12. (4*R*,5*R*,*E*)-Methyl 6-hydroxy-4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-4′-*O*-*tert*-butyldiphenylsilyl-hex-2-enoate 10

$[Bu_3PCH_2CO_2Me]^+Br^-$ (1.04 g, 2.9 mmol) was dissolved in dichloromethane (20 mL) and shaken with sodium hydroxide (1 M aq, 20 mL) for 5 min. The organic layer was then washed with brine (10 mL) and the brine was re-extracted with dichloromethane (2 × 10 mL). The combined organics were dried (magnesium sulfate), filtered and concentrated in vacuo. The resulting ylid was added to a solution of silyl-protected lactol **9** (499 mg, 1.17 mmol) in toluene (10 mL) and the reaction mixture was heated to 40 °C for 48 h. After this time TLC (ethyl acetate/cyclohexane, 1:4) showed the complete conversion of the starting material (R_f 0.42) to one major compound (R_f 0.32). The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (20 mL) and washed with brine (10 mL). The organic layer was dried (magnesium sulfate), filtered and concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:6) to give the *E*-alkene **10** as a colourless oil (507 mg, 90%). HRMS (ESI+ve) found: 507.2173 $[M+Na]^+$; $C_{27}H_{36}NaO_6Si$ requires: 507.2173; $[\alpha]_D^{20} = +1.9$ (*c* 1.275, CH_3CN); ν_{max} (thin film): 3490 (m, br, OH), 1726 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.06 (9H, s, CH_3CSi), 1.39

(3H, s, CH_3C), 1.49 (3H, s, CH_3C), 3.12 (1H, a-t, OH, *J* 5.4), 3.58–3.62 (1H, m, H6), 3.66–3.70 (1H, dd, H6′, *J* 5.6, 11.2), 3.72 (3H, s, OMe), 3.75 (1H, d, H4′, *J* 10.4), 3.80 (1H, d, H4″, *J* 10.4), 4.30–4.33 (1H, dd, H5, *J* 5.5, 6.5), 6.18 (1H, d, H3, *J* 15.5), 7.03 (1H, d, H2, *J* 15.5), 7.40–7.50 (6H, m, ArH), 7.69–7.73 (4H, m, ArH); δ_C (CD_3CN, 100 MHz): 19.8 (CH_3CSi), 26.8 (*C*H_3C), 27.1 (*C*H_3CSi), 28.2 (*C*H_3C), 52.1 (OMe), 62.1 (C6), 69.0 (C4′), 81.6 (C5), 85.5 (C4), 110.0 (CH_3C), 123.0 (C3), 128.7 (ArCH), 128.8 (ArCH), 130.9 (ArCH), 133.7 (ArC), 133.9 (ArC), 136.4 (ArCH), 136.5 (ArCH), 147.8 (C2), 167.1 (C=O); *m/z* (ESI+ve): 543 ($[M+MeCN+NH_4]^+$, 100%).

3.13. Methyl 3,6-anhydro-2-deoxy-4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-4′-*O*-*tert*-butyldiphenylsilyl-D-gluconate 11

Alkene **10** (79 mg, 0.16 mmol) was dissolved in methanol (1.5 mL), and sodium methoxide (10 mg, 0.18 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h after which time TLC (ethyl acetate/cyclohexane, 1:1) showed the complete conversion of the starting material (R_f 0.82) to one product (R_f 0.87). The reaction mixture was neutralised with Dowex® (50W X8, H^+) resin, filtered and concentrated in vacuo to give the Michael addition product **11** as a colourless oil (78 mg, 99%). HRMS (ESI+ve) found: 485.2346 $[M+H]^+$; $C_{27}H_{37}O_6Si$ requires: 485.2330; $[\alpha]_D^{20} = -9.8$ (*c* 1.22, $CHCl_3$); ν_{max} (thin film): 1743 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.09 (9H, s, CH_3CSi), 1.28 (3H, s, CH_3C), 1.49 (3H, s, CH_3C), 2.61–2.66 (1H, dd, H1′, *J* 4.0, 16.4), 2.67–2.73 (1H, dd, H1″, *J* 8.5, 16.4), 3.60–3.64 (1H, dd, H4, *J* 3.3, 10.7), 3.71 (3H, s, OMe), 3.75 (1H, d, H2′, *J* 10.6), 3.79 (1H, d, H2″, *J* 10.6), 4.02 (1H, d, H4′, *J* 10.7), 4.23–4.26 (1H, dd, H1, *J* 4.0, 8.5), 4.63 (1H, d, H3, *J* 3.3), 7.39–7.49 (6H, m, ArH), 7.68–7.71 (4H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 19.3 (CH_3CSi), 26.9 (*C*H_3C, *C*H_3CSi), 27.2 (*C*H_3C), 35.1 (C1′), 51.9 (OMe), 65.4 (C2′), 72.7 (C4), 79.1 (C1), 84.5 (C3), 91.7 (C2), 113.1 (CH_3C), 127.9 (ArCH), 128.0 (ArCH), 130.1 (ArCH), 132.6 (ArC), 132.9 (ArC), 135.7 (ArCH), 135.9 (ArCH), 172.1 (C=O); *m/z* (ESI+ve): 991 ($[2M+Na]^+$, 5%), 543 ($[M+MeCN+NH_4]^+$, 100%), 507 ($[M+Na]^+$, 15%).

3.14. Methyl 4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-4′-*O*-*tert*-butyldiphenylsilyl-D-altronate 22 and methyl 4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-4′-*O*-*tert*-butyldiphenylsilyl-D-gluconate 23

Alkene **10** (366 mg, 0.76 mmol) was dissolved in *tert*-butanol (2.75 mL) and water (2.75 mL), and citric acid (119 mg, 0.57 mmol) was added. Potassium osmate (3 mg, 7.6 μmol) and 4-methylmorpholine N-oxide (112 mg, 0.83 mmol) were added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture initially turned bright green which faded to almost colourless, overnight. After this time TLC (ethyl acetate/cyclohexane, 1:1) showed the conversion of the starting material (R_f 0.82) to one major (R_f 0.67) product and one minor (R_f 0.49) product. The reaction mixture was concentrated in vacuo and partitioned between ethyl acetate (20 mL) and water (10 mL), the aqueous layer was re-extracted with ethyl acetate (2 × 10 mL) and the combined organics were dried (magnesium sulfate), filtered and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:6→1:4→1:2) to give the major diol **22** (275 mg, 70%) and the minor diol **23** (21 mg, 5%) as colourless oils and a mixture of the two (50 mg, 13%, 2:1 mixture of major:minor products) giving a total combined yield of 88%.

3.14.1. Data for methyl 4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-4′-*O*-*tert*-butyldiphenylsilyl-D-altronate 22 (major product, R_f 0.67)

HRMS (ESI+ve) found: 541.2218 $[M+Na]^+$; $C_{27}H_{38}NaO_8Si$ requires: 541.2228; $[\alpha]_D^{20} = +4.8$ (*c* 1.24, CH_3CN); ν_{max} (thin film): 3473 (s, br, OH), 1741 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.07 (9H, s, CH_3CSi), 1.43 (3H, s, CH_3C), 1.46 (3H, s, CH_3C), 3.32 (1H, dd, OH6, *J* 5.8, 6.3), 3.51 (1H, d, OH2, *J* 7.2), 3.61 (3H, s, OMe), 3.78 (1H, d, OH3, *J* 7.7), 3.81–3.86 (1H, m, H6), 3.90–3.96 (1H, m, H6′), 3.94 (1H, d, H4′, *J* 11.5), 4.06–4.08 (1H, dd, H3, *J* 1.0, 7.7), 4.14 (1H, d, H4″, *J* 11.5), 4.56–4.58 (1H, dd, H2, *J* 1.0, 7.2), 4.63–4.66 (1H, dd, H5, *J* 5.2, 6.4), 7.43–7.52 (6H, m, ArH), 7.72–7.78 (4H, m, ArH); δ_C (CD_3CN, 100 MHz): 19.5 (CH_3CSi), 26.5 (*C*H_3C), 26.9 (*C*H_3CSi), 28.3 (*C*H_3C), 52.6 (OMe), 60.7 (C6), 63.0 (C4′), 70.3 (C2), 72.4 (C3), 79.0 (C5), 85.1 (C4), 108.5 (CH_3C), 128.5 (ArCH), 128.6 (ArCH), 130.6 (ArCH), 130.7 (ArCH), 133.6 (ArC), 133.7 (ArC), 136.2 (ArCH), 136.3 (ArCH), 174.8 (C=O); *m/z* (ESI−ve): 1035 ($[2M-H]^-$, 20%), 517 ($[M-H]^-$, 100%).

3.14.2. Data for methyl 4-*C*-hydroxymethyl-4,5-*O*-isopropylidene-4′-*O*-*tert*-butyldiphenylsilyl-D-gluconate 23 (minor product, R_f 0.33)

HRMS (ESI+ve) found: 541.2227 $[M+Na]^+$; $C_{27}H_{38}NaO_8Si$ requires: 541.2228; $[\alpha]_D^{20} = -15.5$ (*c* 1.255, CH_3CN); ν_{max} (thin film): 3474 (s, br, OH), 1746 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.09 (9H, s, CH_3CSi), 1.30 (3H, s, CH_3C), 1.47 (3H, s, CH_3C), 3.41 (1H, t, OH6, *J* 5.5), 3.47 (1H, d, OH2, *J* 5.7), 3.60 (1H, d, OH3, *J* 7.6), 3.73 (3H, s, OMe), 3.75 (1H, d, H4′, *J* 10.7), 3.83 (1H, d, H4″, *J* 10.5), 3.92–4.02 (2H, m, H6, H6′), 4.21–4.24 (1H, dd, H3, *J* 1.0, 7.7), 4.27 (1H, a-t, H5, *J* 4.9), 4.32 (1H, d, H2, *J* 5.7), 7.44–7.53 (6H, m, ArH), 7.69–7.72 (4H, m, ArH); δ_C (CD_3CN, 100 MHz): 19.5 (CH_3CSi), 26.4 (*C*H_3C), 27.0 (*C*H_3C, *C*H_3CSi), 52.4 (OMe), 61.0 (C6), 68.1 (C4′), 70.7 (C3), 72.3 (C2), 83.5 (C5), 85.5 (C4), 109.5 (CH_3C), 128.7 (ArCH), 130.9 (2 × ArCH), 133.2 (ArC), 133.4 (ArC), 136.3 (ArCH), 136.5 (ArCH), 173.7 (C=O); *m/z* (ESI−ve): 1035 ($[2M-H]^-$, 8%), 517 ($[M-H]^-$, 100%).

3.15. 4-*C*-Hydroxymethyl-D-altrono-1,4-lactone 24 and 4-*C*-hydroxymethyl-4′-*O*-*tert*-butyldiphenylsilyl-D-altrono-1,4-lactone 25

The major diol product **22** (71 mg, 0.14 mmol) was dissolved in water (1 mL) and dioxane (1.2 mL) and trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at room temperature for 18 h after which time TLC (ethyl acetate) showed the formation of two products (R_f 0.44, 0.05). The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography to give the silylated minor product **25** (9 mg, 15%) and the fully deprotected major product **24** (15 mg, 53%), both as colourless oils. These were both found to be the *altro* furanose products.

3.15.1. Data for 4-*C*-hydroxymethyl-4′-*O*-*tert*-butyldiphenylsilyl-D-altrono-1,4-lactone 25 (minor product, R_f 0.44)

HRMS (ESI+ve) found: 469.1644 $[M+Na]^+$; $C_{23}H_{30}NaO_7Si$ requires: 469.1653; $[\alpha]_D^{20} = -9.8$ (*c* 0.97, CH_3CN); ν_{max} (thin film): 3406 (s, br, OH), 1775 (s, C=O); δ_H (CD_3CN, 400 MHz): 0.99 (9H, s, CH_3CSi), 3.27 (1H, br, s, OH6), 3.37–3.41 (1H, m, H6), 3.54–3.58 (1H, m, H6′), 3.63 (1H, d, H4′, *J* 11.1), 3.75 (1H, a-s, br, H5), 4.09 (1H, d, H4″, *J* 11.1), 4.13 (1H, d, br, OH2, *J* 4.8), 4.20 (1H, d, br, OH3, *J* 3.5), 4.52–4.55 (1H, dd, H3, *J* 2.2, 8.8), 4.73–4.76 (1H, dd, H2, *J* 3.3, 8.7), 7.37–7.53 (6H, m, ArH), 7.69–7.78 (4H, m, ArH); δ_C (CD_3CN, 100 MHz): 19.6 (CH_3CSi), 27.6 (*C*H_3CSi), 62.8 (C6), 63.6 (C4′), 72.4 (C5), 74.4 (C3), 74.5 (C2), 88.1 (C4), 128.6 (ArCH), 128.9 (ArCH), 130.4 (ArCH), 133.4 (ArC), 133.6 (ArC), 136.5 (ArCH), 137.1 (ArCH), 175.4 (C=O); *m/z* (ESI−ve): 505 ($[M+CH_3CO_2]^-$, 47%), 445 ($[M-H]^-$, 100%).

3.15.2. Data for 4-C-hydroxymethyl-D-altrono-1,4-lactone 24 (major product, R_f 0.05)

HRMS (ESI+ve) found: 231.0475 $[M+Na]^+$; $C_7H_{12}NaO_7$ requires: 231.0475; $[\alpha]_D^{20} = -11.4$ (*c* 1.13, MeOH); ν_{max} (thin film): 3357 (s,

br, OH), 1774 (s, C=O); δ_H (MeOD, 400 MHz): 3.54–3.58 (1H, dd, H6, *J* 6.6, 11.8), 3.63 (1H, d, H4′, *J* 12.4), 3.65–3.69 (1H, dd, H6′, *J* 3.5, 11.8), 3.80–3.82 (1H, dd, H5, *J* 3.5, 6.6), 4.02 (1H, d, H4″, *J* 12.3), 4.53 (1H, d, H3, *J* 8.8), 4.64 (1H, d, H2, *J* 8.8); δ_C (MeOD, 100 MHz): 61.8 (C4′), 63.1 (C6), 73.5 (C5), 75.1 (C3), 75.2 (C2), 89.2 (C4), 177.0 (C=O); *m/z* (ESI−ve): 207 ([M−H]$^-$, 100%).

3.16. 2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-2′-*O*-trifluoromethanesulfonyl-D-erythrono-1,4-lactone

2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (823 mg, 4.3 mmol) was dissolved in dichloromethane (5.5 mL) and pyridine (1.06 mL, 13.1 mmol) was added. The reaction mixture was cooled to −30 °C and triflic anhydride (1.18 mL, 7.0 mmol) was added. The reaction mixture was stirred at −30 to −10 °C for 3 h. After this time TLC (ethyl acetate/cyclohexane, 1:1) showed the complete consumption of the starting material (R_f 0.26) and the formation of one major product (R_f 0.53). The reaction mixture was diluted with dichloromethane (25 mL) and washed with hydrochloric acid (1 M, aq, 15 mL), and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (magnesium sulfate) and concentrated under reduced pressure to give the crude triflate (1.31 g, 94%) as a crystalline solid which was used without further purification. $C_9H_{11}F_3O_7S$ requires: C, 33.75, H, 3.46. Found: C, 33.92, H, 3.37; HRMS (ESI+ve) found: 343.0070 [M+Na]$^+$; $C_9H_{11}F_3NaO_7S$ requires: 343.0075; mp: 106–108 °C; $[\alpha]_D^{17} = -52.7$ (*c* 0.7, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 1.45 (3H, s, CH_3C), 1.52 (3H, s, CH_3C), 4.40–4.44 (1H, dd, H4, *J* 3.9, 11.2), 4.52 (1H, d, H4′, *J* 11.2), 4.68 (1H, d, H2′, *J* 11.0), 4.77 (1H, d, H2″, *J* 11.0), 4.91 (1H, d, H3, *J* 3.9); δ_C ($CDCl_3$, 100 MHz): 25.9 (*C*H$_3$C), 26.8 (*C*H$_3$C), 70.0 (C4), 71.1 (C2′), 77.3 (C3), 81.9 (C2), 115.0 (CH$_3$*C*), 172.3 (C=O); *m/z* (ESI+ve): 343 ([M+Na]$^+$, 100%).

3.17. 2-*C*-Iodomethyl-2,3-*O*-isopropylidene-D-erythrono-1,4-lactone 12

Method 1: Crude 2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-2′-*O*-trifluoromethanesulfonyl-D-erythrono-1,4-lactone (1.3 g, 4.06 mmol) was dissolved in tetrahydrofuran (15 mL) and tetrabutylammonium iodide (3.0 g, 8.12 mmol) was added. The reaction mixture was stirred at room temperature for 18 h in the dark after which time TLC (ethyl acetate/cyclohexane, 1:1) showed the conversion of the starting material (R_f 0.53) to one major product (R_f 0.74). The reaction mixture was concentrated under reduced pressure and the residue was taken up in ethyl acetate (30 mL) and washed with water (15 mL) and sodium thiosulfate (satd aq, 15 mL), dried (magnesium sulfate) and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate/cyclohexane, 1:6→1:3→1:1) to give the pure iodide **12** (928 mg, 77%) as a light yellow oil.

Method 2: Imidazole (1.56 g, 22.9 mmol), triphenylphosphine (3.62 g, 13.8 mmol) and iodine (3.5 g, 13.8 mmol) were added to a stirred solution of 2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (1.2 g, 6.3 mmol) in toluene (29 mL) and stirred at 85 °C for 2 h. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo and then partitioned between dichloromethane (50 mL) and saturated sodium hydrogencarbonate solution (50 mL). The resulting solution was extracted with dichloromethane (3 × 50 mL) and the combined organic layers were washed with water (2 × 50 mL), dried (magnesium sulfate), filtered and concentrated in vacuo. The resulting residue was purified by flash column chromatography (ethyl acetate/cyclohexane 6:1) to afford the 2-*C*-iodomethyl-2,3-*O*-isopropylidene-D-erythrono-1,4-lactone as a light yellow oil (1.776 g, 95%). $C_8H_{11}IO_4$ requires: C, 32.24, H, 3.72. Found: C, 32.19, H, 3.75; HRMS (FI+ve) found: 297.9712 [M]$^+$; $C_8H_{11}IO_4$ requires: 297.9702; $[\alpha]_D^{22} = -72.1$ (*c* 0.89, $CHCl_3$); ν_{max} (thin film): 1782 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.44 (3H, s, CH_3C), 1.47 (3H, s, CH_3C), 3.36 (1H, d, H2′, *J* 10.5), 3.51 (1H, d, H2″, *J* 10.6), 4.39 (1H, d, H4, *J* 10.9), 4.46–4.50 (1H, dd, H4', *J* 4.0, 11.0), 4.72 (1H, d, H3, *J* 4.0); δ_C ($CDCl_3$, 100 MHz): 1.2 (C2′), 26.5 (*C*H$_3$C), 27.0 (*C*H$_3$C), 70.8 (C4), 80.5 (C3), 80.5 (C3), 83.4 (C2), 114.3 (CH$_3$*C*), 173.4 (C=O); *m/z* (FI+ve): 298 ([M]$^+$, 100%).

3.18. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone 13

2-*C*-Iodomethyl-2,3-*O*-isopropylidene-D-erythrono-1,4-lactone **12** (928 mg, 3.1 mmol) was dissolved in ethanol (30 mL), and triethylamine (1.3 mL, 9.3 mmol) and palladium black (93 mg) were added. The reaction mixture was flushed with argon and hydrogen and was stirred at rt for 18 h after which time TLC (ethyl acetate/cyclohexane, 1:1) showed the complete conversion of the starting material (R_f 0.74) to one major product (R_f 0.60). The reaction mixture was flushed with argon, filtered through Celite and concentrated in vacuo. The residue was partitioned between dichloromethane (25 mL) and sodium thiosulfate (satd, aq, 15 mL). The aqueous layer was re-extracted with dichloromethane (2 × 5 mL) and the combined organic layers were washed with water (10 mL), dried (magnesium sulfate) and concentrated under reduced pressure to give 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone **13** (530 mg, 99%) as a light yellow oil. HRMS (CI+ve) found: 190.1076 [M+NH$_4$]$^+$; $C_8H_{16}NO_4$ requires: 190.1079; $[\alpha]_D^{20} = -95.5$ (*c*, 0.69 in $CHCl_3$); mp: 51–53 °C; ν_{max} (thin film): 1785 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.42 (3H, s, CH_3C), 1.47 (3H, s, CH_3C), 1.55 (3H, s, Me), 4.30–4.34 (1H, dd, H4, *J* 3.5, 11.1), 4.41 (1H, d, H4′, *J* 11.0), 4.48 (1H, d, H3, *J* 3.4); δ_C ($CDCl_3$, 100 MHz): 18.4 (Me), 26.5 (*C*H$_3$C), 26.9 (*C*H$_3$C), 68.9 (C4), 80.3 (C3), 81.4 (C2), 113.0 (CH$_3$*C*), 176.7 (C=O); *m/z* (CI+ve): 190 ([M+NH$_4$]$^+$, 100%).

3.19. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythronofuranose 14

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythronolactone **13** (530 mg, 3.1 mmol) was dissolved in dichloromethane (15 mL) and cooled to −78 °C. Di*iso*butylaluminium hydride (1 M in toluene, 3.2 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 3.5 h. After this time IR showed the presence of a small amount of remaining starting material and therefore a further portion of di*iso*butylaluminium hydride (0.6 mL) was added. The reaction mixture was stirred for a further 1 h after which time IR showed the complete disappearance of the carbonyl peak and the formation of an OH signal. The reaction was quenched with methanol and the reaction mixture was allowed to warm to room temperature. Ethyl acetate (2 mL), potassium dihydrogen orthophosphate (2 g) and sodium hydrogencarbonate (satd aq, 2 mL) were added and the mixture was stirred for 10 min. The mixture was dried (magnesium sulfate), filtered through Celite and concentrated in vacuo to give the crude lactol which was purified by column chromatography (ethyl acetate/cyclohexane, 1:4) to give 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrofuranose **14** as a pale yellow oil (426 mg, 74%) as a 5:8 mixture of anomers. HRMS (ESI+ve) found: 197.0784 [M+Na]$^+$; $C_8H_{14}NaO_4$ requires: 197.0790; $[\alpha]_D^{21} = -56.8$ (*c* 1.01, $CHCl_3$); ν_{max} (thin film): 3442 (s, OH); δ_H ($CDCl_3$, 400 MHz) (5:8 mixture of anomers, A—major anomer): 1.41 (3H, s, CH_3C^A), 1.45 (3H, s, Me^B), 1.46 (6H, s, CH_3C^A, CH_3C^B), 1.49 (3H, s, Me^A), 1.53 (3H, s, CH_3C^B), 2.82–2.86 (1H, br, m, OH^A), 3.55–3.59 (1H, dd, H4^B, *J* 3.4, 11.1), 3.84 (1H, d, OH^B, *J* 11.5), 3.92 (1H, d, H4^A, *J* 10.4), 3.96 (1H, d, H4′^{B}, *J* 11.1), 4.07–4.11 (1H, dd, H4′^{A}, *J* 3.5, 10.4), 4.39 (1H, d, H3^B, *J* 3.4), 4.42 (1H, d, H3^A, *J* 3.6), 4.64 (1H, d, H1^B, *J* 11.4), 5.26 (1H, d, H1^A, *J*

2.7); δ_C ($CDCl_3$, 100 MHz): 19.7 (Me^A), 21.5 (Me^B), 26.7 (CH_3C^B), 27.0 (CH_3C^B), 27.5 (CH_3C^A), 27.7 (CH_3C^A), 67.2 ($C4^B$), 71.8 ($C4^A$), 85.1 ($C3^B$), 86.1 ($C2^B$), 86.2 ($C3^A$), 91.5 ($C2^A$), 101.5 ($C1^B$), 103.4 ($C1^A$), 112.5 (CH_3C^A), 113.1 (CH_3C^B); *m/z* (ESI+ve): 197 ([M+Na]$^+$, 100%).

3.20. (4*S*,5*R*,*E*)-Methyl 6-hydroxy-4,5-*O*-isopropylidene-4-*C*-methyl-hex-2-enoate 15 and (4*S*,5*R*,*Z*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-4-*C*-methyl-hex-2-enoate

$[Bu_3PCH_2CO_2Me]^+Br^-$ (418 mg, 1.18 mmol) was dissolved in dichloromethane (20 mL) and shaken with sodium hydroxide (1 M aq, 10 mL) for 5 min. The organic layer was then washed with brine (10 mL) and the brine was re-extracted with dichloromethane (2 × 5 mL). The combined organics were dried (magnesium sulfate), filtered and concentrated in vacuo. The resulting ylid was added to a solution of silyl-protected lactol (82 mg, 0.47 mmol) in toluene (4 mL) and the reaction mixture was heated to 40 °C for 96 h. After this time TLC (ethyl acetate/cyclohexane, 1:1) showed the complete conversion of the starting material (R_f 0.59) to one major compound (R_f 0.55). The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (20 mL) and washed with brine (10 mL). The organic layer was dried (magnesium sulfate), filtered and concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:6) to give an inseparable mixture of *E*-alkene **15** and *Z*-alkene as a colourless oil (97 mg, 89%, *E*:*Z*, 20:1).

3.20.1. Data for (4*S*,5*R*,*E*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-4-C-methyl-hex-2-enoate 15

δ_H ($CDCl_3$, 400 MHz): 1.40 (3H, s, CH_3C), 1.41 (3H, s, CH_3C), 1.47 (3H, s, Me), 2.66–2.68 (1H, t, OH, *J* 5.2), 3.59–3.68 (2H, m, H6, H6′), 3.72 (3H, s, OMe), 4.03–4.06 (1H, dd, H5, *J* 5.2, 6.5), 6.06 (1H, d, H3, *J* 15.5), 6.82 (1H, d, H2, *J* 15.5); δ_C ($CDCl_3$, 100 MHz): 25.3 (*C*H_3C), 26.5 (*C*H_3C), 27.9 (Me), 51.7 (OMe), 61.4 (C6), 81.3 (C4), 84.5 (C5), 109.1 (CH_3*C*), 120.6 (C3), 148.9 (C2), 166.9 (C=O).

3.20.2. Data for (4*S*,5*R*,*Z*)-methyl 6-hydroxy-4,5-*O*-isopropylidene-4-*C*-methyl-hex-2-enoate

δ_H ($CDCl_3$, 400 MHz): 1.38 (6H, s, 2 × Me), 1.40 (3H, s, Me), 2.74–2.77 (1H, dd, OH, *J* 5.4, 7.0), 3.59–3.68 (2H, m, H6, H6′), 3.70 (3H, s, OMe), 4.19–4.22 (1H, dd, H5, *J* 5.1, 7.4), 5.79 (1H, d, H3, *J* 12.8), 6.13 (1H, d, H2, *J* 12.8); δ_C ($CDCl_3$, 100 MHz): 25.5 (CH_3C), 26.5 (*C*H_3C), 28.7 (Me), 51.7 (OMe), 61.7 (C6), 83.2 (C4), 84.2 (C5), 108.8 (CH_3*C*), 120.2 (C3), 146.3 (C2), 167.0 (C=O).

3.21. Methyl 4-*C*-methyl-4,5-*O*-isopropylidene-D-altronate 26 and methyl 4-*C*-methyl-4,5-*O*-isopropylidene-D-gluconate 27

Alkene **15** (40 mg, 0.18 mmol) was dissolved in *tert*-butanol (0.65 mL) and water (0.65 mL), and L-(+)-tartaric acid (20 mg, 0.14 mmol) was added. Potassium osmate (1 mg, μmol) and 4-methylmorpholine N-oxide (23 mg, 0.20 mmol) were added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture initially turned bright green which faded to almost colourless, overnight. After this time TLC (ethyl acetate) showed the conversion of the starting material (R_f 0.62) to one major (R_f 0.35) product and one minor (R_f 0.25) product. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate) to give the major diol **26** (20 mg, 44%) and the minor diol **27** (13 mg, 29%) as a colourless oil and a mixture of the two (10 mg, 22%, 2:1) giving a total combined yield of 95%.

3.21.1. Data for methyl 4-*C*-methyl-4,5-*O*-isopropylidene-D-altronate 26 (major product, R_f 0.35)

HRMS (ESI−ve) found: 263.11356 [M−H]$^+$; $C_{11}H_{19}O_7$ requires: 263.11363; $[\alpha]_D^{25} = -4.5$ (*c*, 0.605 in $CHCl_3$), $[\alpha]_D^{25} = -11.3$ (*c* 0.15, $CHCl_3$); ν_{max} (thin film): 3442 (s, br, OH), 1741 (s, C=O); δ_H ($CHCl_3$, 400 MHz): 1.40 (3H, s, CH_3C), 1.41 (3H, s, Me-4), 1.45 (3H, s, CH_3C), 2.83–2.87 (1H, m, 6-OH), 3.26 (1H, d, 2-OH, *J* 4.4), 3.32 (1H, d, 3-OH, *J* 9.1), 3.85 (3H, s, OMe), 3.90–3.96 (3H, m, H5, H6, H6′), 4.05–4.07 (1H, dd, H3, *J* 0.8, 9.1), 4.66–4.68 (1H, dd, H2, *J* 0.8, 4.4); δ_C ($CHCl_3$, 100.6 MHz): 19.4 (Me-4), 26.4 ((CH_3)$_2$C), 28.1 ((CH_3)$_2$C), 53.2 (C6), 69.0 (C2), 70.9 (C3), 82.3 (C4), 83.8 (C5), 108.1 ((CH_3)$_2$*C*), 175.0 (C=O); *m/z* (ESI−ve): 263 ([M−H]$^+$, 100%), 527 ([2M−H]$^+$, 15%).

3.21.2. Data for methyl 4-*C*-methyl-4,5-*O*-isopropylidene-D-gluconate 27 (minor product, R_f 0.25)

HRMS (ESI−ve) found: 263.11353 [M−H]$^-$; $C_{11}H_{19}O_7$ requires: 263.11363; $[\alpha]_D^{25} = -16.3$ (*c* 0.3, $CHCl_3$); ν_{max} (thin film): 3447 (s, br, OH), 1759 (s, C=O); δ_H ($CDCl_3$,400 MHz): 1.46 (3H, s, Me-4), 1.55 (3H, s, CH_3C), 1.64 (3H, s, CH_3C), 2.42 (1H, t, 6-OH, *J* 5.2), 3.23 (1H, d, 3-OH, *J* 8.1), 3.55 (1H, d, 2-OH, *J* 3.9), 3.83 (3H, s, OMe), 3.87–3.90 (1H, dd, H3, *J* 1.0, 8.1), 3.97–4.07 (2H, m, H6, H6′), 4.06–4.10 (1H, m, H5), 4.49–4.51 (1H, dd, H2, *J* 1.1, 3.8); δ_C ($CDCl_3$, 100.6 MHz): 23.8 (Me-4), 26.1 ((CH_3)$_2$C), 27.1 ((CH_3)$_2$C), 52.8 (OMe), 60.2 (C6), 72.0 (C3), 72.1 (C2), 83.7 (C4), 85.0 (C5), 109.1 ((CH_3)$_2$*C*), 172.9 (C=O); *m/z* (ESI−ve): 263 ([M−H]$^-$, 87%), 527 ([2M−H]$^+$, 15%).

3.22. 4-*C*-Methyl-D-altrono-1,4-lactone 28

Methyl 4-*C*-methyl-4,5-*O*-isopropylidene-D-altronate **26** (119 mg, 0.45 mmol) was dissolved in water (3.6 mL) and stirred with Dowex® (50W X8, H^+) resin (90 mg) for 48 h. After this time, the reaction mixture was filtered, and the solution was concentrated in vacuo to give 4-*C*-methyl-D-altrono-1,4-lactone **28** as a colourless oil (86 mg, 75%). HRMS (ESI+ve) found: 215.0530 [M+Na]$^+$; $C_7H_{12}NaO_6$ requires: 215.0526; $[\alpha]_D^{25} = -2.8$ (*c* 1.09, MeOH); ν_{max} (thin film): 3383 (s, br, OH), 1774 (s, C=O); δ_H (MeOD, 400 MHz): 2.39 (3H, s, Me), 4.67 (1H, dd, H6, *J* 2.1, 10.8), 4.72–4.81 (2H, m, H5, H6′), 4.97 (1H, d, H3, *J* 8.3), 5.62 (1H, d, H2, *J* 8.3); δ_C (MeOD, 100 MHz): 22.9 (Me), 63.6 (C6), 75.0 (C2), 78.1 (C5), 82.7 (C3), 86.7 (C4), 176.8 (C=O).

3.23. 4-*C*-Methyl-D-glucono-1,4-lactone 29

The gluconate product **27** (80 mg, 0.30 mmol) was dissolved in water (2.4 mL) and stirred with Dowex® (50W X8, H^+) resin (60 mg) for 48 h. After this time, the reaction mixture was filtered, and the solution was concentrated in vacuo to give 4-*C*-methyl-D-glucono-1,4-lactone **29** as a white crystalline solid (60 mg, 79%) HRMS (ESI+ve) found: 215.0527 [M+Na]$^+$; $C_7H_{12}NaO_6$ requires: 215.0526; mp: 121–124 °C; $[\alpha]_D^{25} = +22.2$ (*c* 0.34, MeOH); ν_{max} (thin film): 3356 (s, br, OH), 1771 (s, C=O); δ_H (MeOD, 400 MHz): 2.39 (3H, s, Me), 4.58 (1H, dd, H6, *J* 7.1, 12.1), 4.68–4.73 (2H, m, H5, H6′), 5.39 (1H, d, H2, *J* 9.3), 5.43 (1H, d, H3, *J* 9.3); δ_C (MeOD, 100 MHz): 17.8 (Me), 63.2 (C6), 74.1 (C3), 74.3 (C2), 76.3 (C5), 87.1 (C4), 176.0 (C=O); *m/z* (ESI−ve): 383 ([2M−H]$^-$, 100%), 191 ([M−H]$^-$, 55%).

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