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Kiliani reactions on ketoses: branched carbohydrate building blocks from D-tagatose and D-psicose

Raquel Soengas,[a] Ken Izumori,[b] Michela Iezzi Simone,[a] David J. Watkin,[a] Ulla P. Skytte,[c] Wim Soetaert[d] and George W. J. Fleet[a,*]

[a]*Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*
[b]*Rare Sugar Research Center, Kagawa University, Mikicho, Kagawa 761-0795 Japan*
[c]*Arla Foods Ingredients, Viby J, DK-8260 Denmark*
[d]*Department of Biochemical and Microbial Technology, Ghent University, 9000 Gent, Belgium*

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Abstract—D-Tagatose and D-psicose on treatment with sodium cyanide gave mixtures of branched sugar lactones; extraction of the crude products by acetone in the presence of acid permits direct access to branched carbohydrate diacetonides, likely to be of value as new chirons. In both cases, the major lactone products—diacetonides with a 2,3-*cis*-diol relationship—can be crystallised in around 40–50% yield from the ketohexose. A practical procedure for the conversion of 30 g of D-tagatose to give 24 g of 2,3:5,6-di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-talono-1,4-lactone is reported.

1. Introduction

Almost all readily available carbohydrate scaffolds contain linear carbon chains.[1] Although the Kiliani ascension[2] on unprotected ketoses[3,4] (to provide branched sugar building blocks) has been little investigated,[5,6] the convenient preparations of branched carbon chain diacetonides from D-fructose and L-sorbose[7] suggest that a new family of carbohydrate chirons containing branched carbon chains would be readily available from the chiral pool. D-Fructose and L-sorbose are no longer the only accessible ketohexoses.

Recent developments in biotechnology have shown that any monosaccharide can be made available cheaply in substantial quantity by environmental friendly green processes. An outstanding example of a sugar that has changed its status in a few years from rare ($5000 per lb) to common ($2.5 per lb) is D-tagatose **1**, a healthy sweetener prepared cheaply from galactose[8] and used in soft drinks and ready-to-eat cereals.[9] Izumoring[10] provides a conceptual advance in the availability of monosaccharides, demonstrating that all aldoses and ketoses might be available in substantial quantities by a combination of enzymic epimerisations with microbial oxidation–reduction procedures. A key step is the use of D-tagatose 3-epimerase for the equilibration of ketohexoses, allowing the preparation of D-psicose **5** from D-fructose.[11]

This letter reports the Kiliani reactions of D-tagatose **1** and D-psicose **5** with sodium cyanide, followed by acetonation, to give readily crystallised diacetonides **2** and **6**, respectively, as accessible branched chirons derived from sugars (Scheme 1); other acetonides formed in smaller amounts were also identified. From a practical point of view, the small amount of the *spiro-cis*-diacetonide **3** from tagatose—and the absence of any *spiro-cis*-diacetonide **7** from psicose—make these experimental procedures easier than the corresponding Kiliani reactions on fructose and sorbose.

2. Branched chirons from D-tagatose

The Kiliani reaction of cyanide with D-tagatose **1** gave a mixture of the two lactones **9** and **10** in a ratio of approximately 3:1. Extraction of this crude product with acetone in the presence of acid allowed the small amount of the diacetonide from the *spiro-cis*-diol **3** to be separated from the other products. Most of *cis*-diol fused diacetonide **2**, the major product, can then be isolated

* Corresponding author. E-mail: george.fleet@chem.ox.ac.uk

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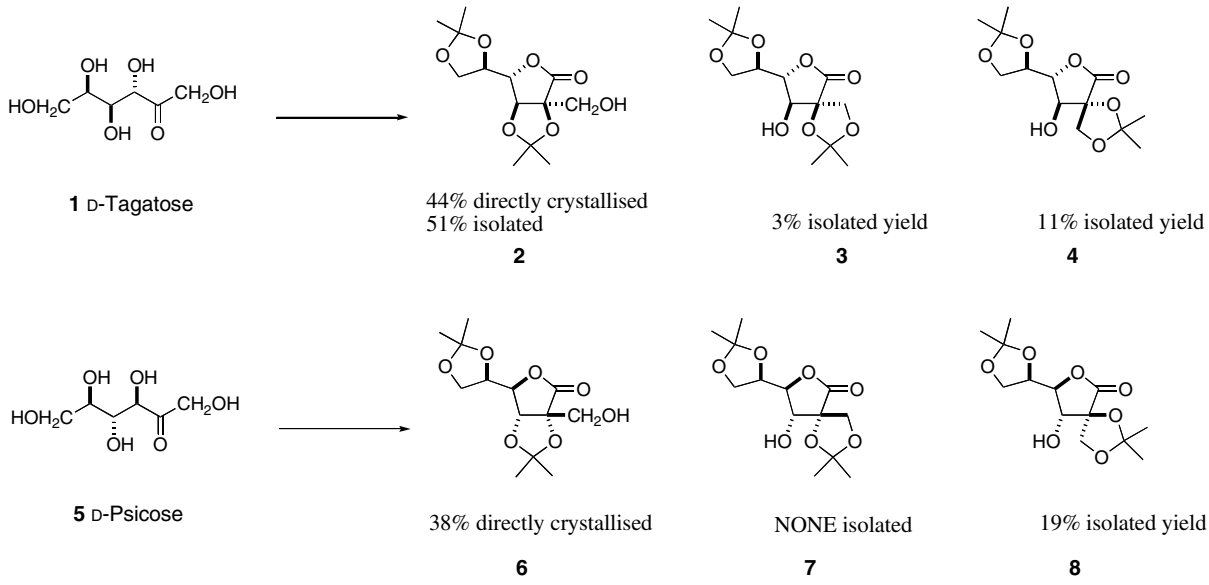
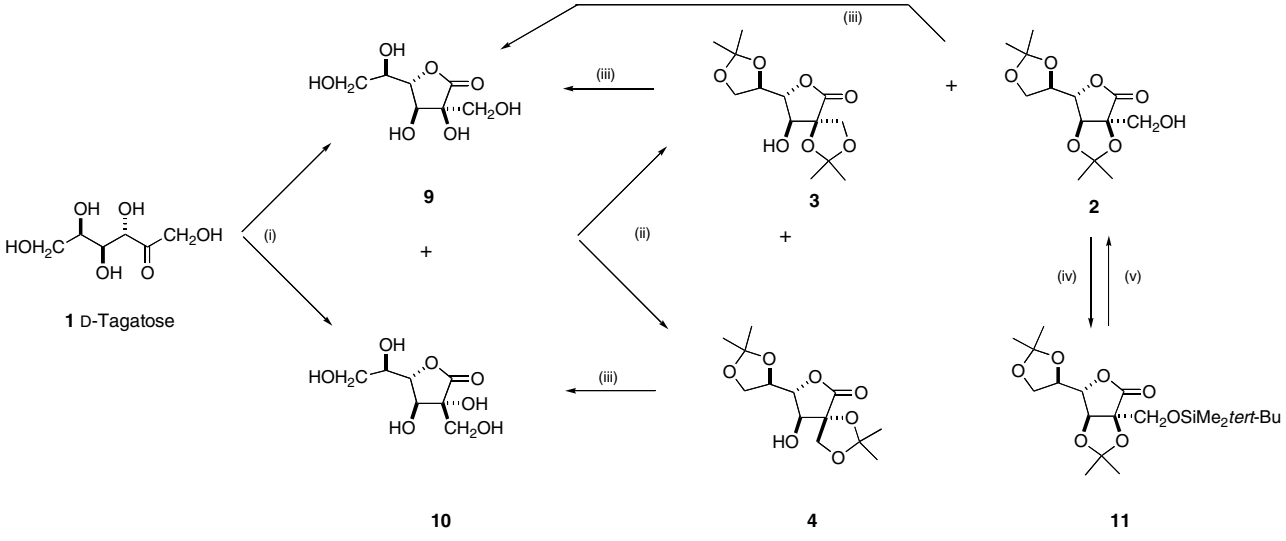


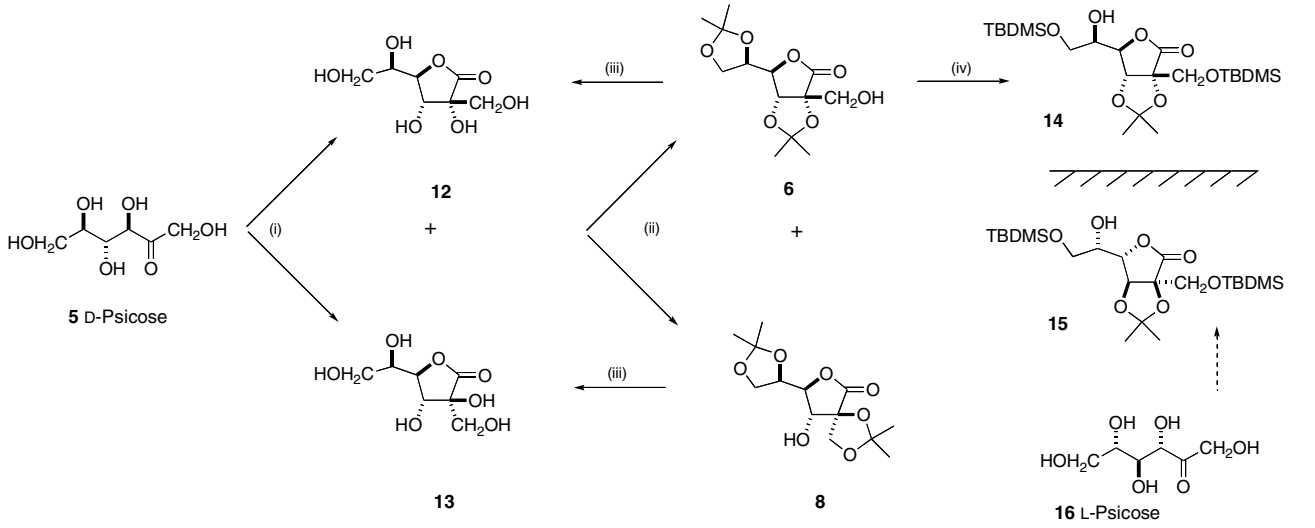
Scheme 1. Products from Kiliani ascension–acetonation of tagatose and psicose.



Scheme 2. Reagents and conditions: (i) NaCN, H_2O; then H^+/H_2O; (ii) Me_2CO, H_2SO_4, $CuSO_4$; (iii) CF_3CO_2H, H_2O; (iv) *tert*-$BuMe_2SiCl$, imidazole, DMF; (v) *n*-Bu_4NF, THF.

by crystallisation. Removal of the remaining **2** as its primary *tert*-butyldimethylsilyl (TBDMS) ether from the mixture of diacetonides allows the isolation of moderate amounts of the pure *trans-spiro*-diacetonide **4** with the more hindered secondary alcohol free. The following provides a practical procedure for the Kiliani reaction of tagatose on a moderate scale (Scheme 2).

A solution of D-tagatose **1** (30.00 g, 0.17 mol) and sodium cyanide (10.62 g, 0.22 mol) in water (300 mL) was stirred at room temperature for 24 h and then refluxed until evolution of ammonia had ceased (approx 12 h). The reaction mixture was allowed to cool to room temperature and passed through a column of Amberlite IR-120 H^+. The solvent was removed and the resulting residue of lactones **9** and **10** (33.63 g) treated with acetone (450 mL), concentrated sulfuric acid (9 mL) and copper sulfate (10.00 g). The reaction mixture was stirred at room temperature for 6 h when TLC (ethyl acetate/cyclohexane 1:1) indicated the formation of a major product (R_f 0.29) and a minor one (R_f 0.32). The mixture was then neutralised with solid sodium carbonate, filtered and the solvent evaporated. The residue was shaken with dichloromethane (300 mL) and water (300 mL); the aqueous layer was further extracted with dichloromethane (2×100 mL). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated to produce a mixture of diacetonides, which was separated by flash chromatography (ethyl acetate/cyclohexane 2:3→1:1), to yield the *cis*-diol *spiro*-diacetonide **3**[12] (1.52 g, 3%) and a 5:2 mixture (^1H NMR; integration of H-3 in **2** and H-2 in **4**) of the *cis*-fused diacetonide **2** and the *trans*-diol *spiro*-diacetonide **4** (31.31 g) (combined yield of diacetonides (32.8 g) is 68% from tagatose). The *cis*-fused diacetonide **2**[13] (21.01 g, 44%) was directly crystallised from the mixture



Scheme 3. Reagents and conditions: (i) NaCN, H_2O; then H^+/H_2O; (ii) Me_2CO, H_2SO_4, $CuSO_4$; (iii) CF_3CO_2H, H_2O; (iv) CH_3CO_2H, H_2O; then *tert*-$BuMe_2SiCl$, imidazole, DMF.

from ether/hexane. Evaporation of the mother liquors afforded a 1:3 mixture of **2** and *trans*-diol *spiro*-diacetonide **4** (10.06 g). The structure of the *spiro*-**3**[14] and *cis*-fused **2**[15] diacetonides were firmly established by X-ray crystallographic analysis.

Pure *trans*-diacetonide **4** (which contains a hindered secondary alcohol) may be isolated from the mixture by removal of **2** (which contains a primary alcohol) as its *tert*-butyldimethylsilyl (TBDMS) ether **11**. Thus, TBDMS chloride (6.65 g, 44.10 mmol) was added to the mixture of **2** and **4** (10.06 g, 35.62 mmol) in the presence of imidazole (6.00 g, 85.00 mmol) in dry DMF (100 mL) at −20 °C, and the resulting reaction mixture was stirred at this temperature for 4 h. The solvent was then evaporated and the residue was shaken with chloroform (200 mL) and water (3 × 150 mL); the organic layer was dried (magnesium sulfate) and the solvent removed to give a residue, which was separated by flash chromatography (ethyl acetate/cyclohexane 1:4→1:1), to give the primary silyl ether **11**[16] (4.93 g) as a colourless oil and the *trans-spiro* compound **4**[17] (5.39 g, 11% based on tagatose) as a white solid. Removal of the TBDMS ether from **11** by tetra-*n*-butylammonium fluoride in THF gave a further quantity of the *cis*-fused acetonide **2** (3.25 g, 7.0% from tagatose). Thus the final isolated yields of the acetonides **3**, **2** and **4** from D-tagatose **1** were 3%, 51% and 11%, respectively.

Treatment of both the *cis*-fused **2** and *cis*-spiro **3** diacetonides with aqueous trifluoroacetic acid (TFA) gave the deprotected branched talono-lactone **9**;[18] a pure sample of the isomeric deprotected branched galactono-lactone **10**[19] was obtained by reaction of the *trans*-spiro **4** with aqueous TFA.

3. Branched chirons from D-psicose

A similar procedure was adopted for the Kiliani reaction of D-psicose **5** with sodium cyanide (Scheme 3), which gave a crude product mixture of the lactones **12** and **13**. Extraction of the crude mixture of lactones with acetone in the presence of copper sulfate and sulfuric acid gave a mixture of only *two* diacetonides **6** and **8** in an approximate ratio of 2:1 (56% and 28% yield, respectively) in a combined yield of 84%. There was no evidence of the formation of the *spiro-cis*-diacetonide **7**. The major product **6**[20] could be directly crystallised from the crude extract (ether/hexane) in 38% yield, leaving a residue in which the ratio of **6**–**8** was 1:3. There was no need for any chromatography in the isolation of **6** by this procedure.

A pure sample of the *spiro-trans*-diacetonide **8**[21] (19% yield) could be isolated by removal of **6** as its TBDMS ether; however, the selectivity between the alcohols **6** and **8** in the silylation reaction makes this an inefficient isolation procedure. Further studies on a practical procedure for the isolation of the acetonides **6** and **8** on a larger scale are in progress.

The structure of **6** was firmly established by removal of the side chain acetonide with aqueous acetic acid followed by silylation of both primary alcohols by TBDMS chloride in DMF in the presence of imidazole to give the bis-TBDMS ether **14** (71% overall yield). The silyl ether **14**, $[\alpha]_D^{21}$ −13.2 (*c* 1.1, $CHCl_3$) had identical ^{13}C and ^1H NMR and infrared spectra to those of its enantiomer **15**, $[\alpha]_D^{21}$ +13.5 (*c* 0.75, $CHCl_3$),[7] the formal product from a similar procedure starting from L-psicose **16**. Treatment of the *cis*-diol **6** and *trans*-diol **8** diacetonides with aqueous trifluoroacetic acid (TFA) gave, respectively, pure samples of the unprotected branched *allono*-**12**[22] and *altrono*-**13**[23] lactones.

4. Summary

The amounts of the *spiro-cis*-diol diacetonides derived from tagatose and psicose in which the carbon side chain at C-4 of the lactones is *trans*- to the new *cis*-diol

unit are very much less than the corresponding materials obtained in the Kiliani reactions of fructose and sorbose where the side chain is *cis*. This makes the isolation of the major products more convenient. There may be relatively unfavourable steric repulsions when the *cis*-diol acetonide and the C5, C6 side chain are on the same side of the lactone ring; this is the case with the products from fructose and sorbose, where such interactions may cause greater production of the *cis-spiro* acetonides.

All the ketohexoses undergo efficient cyanohydrin extensions and form at least some readily crystallised diacetonides. The chirons described in this paper produce branched THF derived scaffolds for a new class of sugar amino acid.[24]

Acknowledgements

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12. 2,2′:5,6-Di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-*talono*-1,4-lactone **3**: mp 130–132 °C (diethyl ether/cyclohexane); $[\alpha]_D^{20}$ +10.2 (*c* 1.2, chloroform); ν_{max} (NaCl): 3377 (–OH), 1776 (–C=O) cm^{-1}; δ_H ($CDCl_3$): 1.33, 1.38, 1.39, 1.46 (4 × s, 12H, 2 × –C(CH_3)$_2$), 3.88 (d, 1H, $J_{2',2''}$ 12.0 Hz, H2′), 4.05 (dd, 1H, $J_{6,6'}$ 8.5 Hz, $J_{6',5}$ 8.2 Hz, H6′), 4.10 (d, 1H, $J_{2',2''}$ 12.0 Hz, H2′); 4.18 (dd, 1H, $J_{6,6'}$ 8.5 Hz, $J_{6,5}$ 7.0 Hz, H6), 4.26 (s, 1H, H3), 4.31–4.36 (m, 2H, H4, H5), 4.88 (br s, 1H, –OH); δ_C ($CDCl_3$): 20.3, 25.2, 25.7, 28.8 (2 × –C(CH_3)$_2$), 62.2 (C-2′), 65.7 (C-6), 68.7 (C-2), 74.7 (C-5), 75.6 (C-3), 81.0 (C-4), 98.7, 111.5 (2 × –C(CH_3)$_2$), 175.1 (C-1); *m/z* (NH_3, ES+): 289 $(M+H)^+$, HRMS calcd for $C_{13}H_{20}O_7$ [$(M+H)^+$] 289.1287; found 289.1290.
13. 2,3:5,6-Di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-*talono*-1,4-lactone **2**: mp 109–111 °C (diethyl ether/cyclohexane); $[\alpha]_D^{20}$ −26.9 (*c* 1.4, chloroform); ν_{max} (NaCl): 3454 (–OH), 1787 (–C=O) cm^{-1}; δ_H ($CDCl_3$): 1.33, 1.36, 1.46, 1.47 (4 × s, 12H, 2 × –C(CH_3)$_2$), 2.24–2.30 (m, 1H, –OH), 3.96–4.00 (m, 3H, H6, H2′, H2″), 4.14 (dd, 1H, $J_{6,6'}$ 8.4 Hz, $J_{6',5}$ 6.9 Hz, H6′), 4.32–4.36 (m, 1H, H5), 4.52 (d, 1H, $J_{4,5}$ 0.7 Hz, H4), 4.76 (s, 1H, H3); δ_C ($CDCl_3$): 25.3, 25.4, 26.6, 26.9 (2 × –C(CH_3)$_2$), 60.1 (C-2′), 65.2 (C-6), 75.1 (C-5), 79.3 (C-3), 81.7 (C-4), 85.6 (C-2), 110.5, 113.4 (2 × –C(CH_3)$_2$), 174.5 (C-1); *m/z* (NH_3, ES+): 289 $(M+H)^+$; Found: C 54.17, H 7.00; $C_{13}H_{20}O_7$ requires C 54.16, H 6.99.
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16. 2-*C*-*tert*-Butyldimethylsilyloxymethyl-2,3:5,6-di-*O*-isopropylidene-D-*talono*-1,4-lactone **11**: $[\alpha]_D^{20}$ −5.5 (*c* 2.0, chloroform); ν_{max} (NaCl): 1790 (–C=O) cm^{-1}; δ_H ($CDCl_3$): 0.09, 0.10 (2 × s, 6H, –Si(CH_3)$_2$), 0.92 (s, 9H, –SiC(CH_3)$_3$), 1.36, 1.44, 1.46 (3 × s, 12H, 2 × –C(CH_3)$_2$), 3.91–3.97 (m, 2H, H6, H2″), 4.03 (d, 1H, $J_{2',2''}$ 11.2 Hz, H2′), 4.13 (dd, 1H, $J_{6,6'}$ 12.0 Hz, $J_{6',5}$ 6.8 Hz, H6′), 4.30–4.35 (m, 1H, H5), 4.48 (d, 1H, $J_{4,5}$ 2.8 Hz, H4), 4.74 (s, 1H, H3); δ_C ($CDCl_3$): −5.7, −5.4 (2 × –Si(CH_3)$_2$), 10.3 (–SiC(CH_3)$_3$), 25.5, 25.6, 26.5, 27.2 (2 × –C(CH_3)$_2$), 25.8 (–SiC(CH_3)$_3$), 60.8 (C-2′), 65.3 (C-6), 75.4 (C-5), 79.1 (C-3), 81.9 (C-4), 86.3 (C-2), 110.4, 113.5 (2 × –C(CH_3)$_2$), 174.3 (C-1); *m/z* (NH_3, ES+): 403 $(M+H)^+$, HRMS calcd for $C_{19}H_{34}O_7Si$ [$(M+H)^+$] 403.2152; found 403.2154.
17. 2,2′:5,6-Di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-*galactono*-1,4-lactone **4**: mp 126–128 °C (diethyl ether/cyclohexane); $[\alpha]_D^{20}$ −53.7 (*c* 1.8, chloroform); ν_{max} (NaCl): 3443 (–OH), 1790 (–C=O) cm^{-1}; δ_H ($CDCl_3$): 1.39, 1.43, 1.52, 1.59 (4 × s, 12H, 2 × –C(CH_3)$_2$), 2.69 (br s, 1H, –OH), 3.99–4.03 (m, 3H, H4, H6′, H2″), 4.14 (dd, 1H, $J_{6,5}$ 6.8 Hz, $J_{6,6'}$ 8.6 Hz, H6), 4.36–4.40 (m, 1H, H5), 4.51 (dd, 1H, $J_{3,OH}$ 3.8 Hz, $J_{3,4}$ 8.2 Hz, H3), 4.61 (d, 1H, $J_{2',2''}$ 8.7 Hz, H2′); δ_C ($CDCl_3$): 25.3, 26.0, 26.3 (2 × –C(CH_3)$_2$), 64.8 (C-2′), 65.5 (C-6), 72.4 (C-3), 73.7 (C-5), 79.6 (C-4), 83.7 (C-2), 110.2, 112.3 (2 × –C(CH_3)$_2$), 173.8 (C-1); *m/z* (NH_3, ES+): 289 $(M+H)^+$; Found: C 54.18, H 7.00; $C_{13}H_{20}O_7$ requires C 54.16, H 6.99.
18. 2-*C*-Hydroxymethyl-D-*talono*-1,4-lactone **9**, oil, $[\alpha]_D^{21}$ −49.0 (*c* 3.1, in water); ν_{max} (Ge IR plate): 3565 (–OH), 1769 (–C=O) cm^{-1}; δ_H (D_2O): 3.71 (d, 1H, $J_{2',2''}$ 11.6 Hz, H2′), 3.72–3.76 (m, 2H, H6, H6′), 3.82 (d, 1H, $J_{2',2''}$ 11.6 Hz, H2″), 3.94–3.97 (m, 1H, H5), 4.43–4.49 (m, 2H, H4, H3); δ_C (D_2O): 61.2 (C-6), 62.9 (C-2′), 68.1, 70.1 (C-3, C-5), 75.7 (C-2), 82.8 (C-4), 176.8 (C-1); *m/z* (NH_3, ES−): 225 $(M-H+NH_4)^+$; HRMS calcd for $C_7H_{11}O_7$ [$(M-H)^+$] 207.0501; found 207.0505.
19. 2-*C*-Hydroxymethyl-D-*galactono*-1,4-lactone **10**, oil, $[\alpha]_D^{21}$ −46.9 (*c* 1.1, water); ν_{max} (Ge IR plate): 3563(–OH), 1768 (–C=O) cm^{-1}; δ_H (D_2O): 3.71–3.75 (m, 2H, H6, H6′), 3.79 (d, 1H, $J_{2',2''}$ 11.8 Hz, H2′), 3.89–3.92 (m, 1H, H5), 4.00 (d, 1H, $J_{2',2''}$ 11.6 Hz, H2″), 4.41 (dd, 1H, $J_{3,4}$ 8.3 Hz, $J_{4,5}$ 2.7 Hz, H4), 4.51 (d, 1H, $J_{3,4}$ 8.3 Hz, H3); δ_C (D_2O): 61.9 (C-6), 62.7 (C-2′), 70.0, 74.5 (C-3, C-5), 78.7 (C-2), 81.5 (C-4), 178.3 (C-1); *m/z* (NH_3, ES−): 225 $(M-H+NH_4)^+$;

HRMS calcd for $C_7H_{11}O_7$ [$(M-H)^+$] 207.0501; found 207.0504.

20. 2,3:5,6-Di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-*allono*-1,4-lactone **6**: mp 132–134 °C; $[\alpha]_D^{20}$ −23.6 (*c* 1.0, chloroform); ν_{max} (NaCl): 3198 (–OH), 1781 (–C═O) cm^{-1}; δ_H ($CDCl_3$): 1.36, 1.45, 1.47, 1.50 (4 × s, 12H, 2 × –C(CH_3)$_2$), 2.20 (dd, 1H, $J_{OH,2''}$ 8.7 Hz, $J_{OH,2'}$ 4.0 Hz, –OH), 3.92–4.04 (m, 3H, H6, H2′, H2″), 4.17 (dd, 1H, $J_{6,6'}$ 9.0 Hz, $J_{6',5}$ 6.8 Hz, H6′), 4.30–4.35 (m, 1H, H5), 4.43 (d, 1H, $J_{4,5}$ 5.8 Hz, H4), 4.80 (s, 1H, H3); δ_C ($CDCl_3$): 24.6, 26.3, 26.6, 26.9 (2 × –C(CH_3)$_2$), 61.3 (C-2′), 66.1 (C-6), 73.9 (C-5), 78.5 (C-3), 83.6 (C-4), 85.4 (C-2), 110.6, 113.5 (2 × –C(CH_3)$_2$), 174.6 (C-1); *m/z* (NH_3, ES−): 287 $(M-H)^+$; Found: C 54.33, H 7.10; $C_{13}H_{20}O_7$ requires C 54.16, H 6.99.
21. 2,2′:5,6-Di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-*altrono*-1,4-lactone **8**: mp 108–110 °C (diethyl ether/cyclohexane); $[\alpha]_D^{19}$ +4.5 (*c* 1, chloroform); ν_{max} (NaCl): 3454 (–OH), 1791 (–C═O) cm^{-1}; δ_H ($CDCl_3$): 1.39, 1.43, 1.52, 1.59 (4 × s, 12H, 2 × –C(CH_3)$_2$), 2.69 (br s, 1H, –OH), 3.99–4.03 (m, 3H, H4, H6′, H2″), 4.14 (dd, 1H, $J_{6,5}$ 6.8 Hz, $J_{6,6'}$ 8.6 Hz, H6), 4.36–4.40 (m, 1H, H5), 4.51 (dd, 1H, $J_{3,OH}$ 3.8 Hz, $J_{3,4}$ 8.2 Hz, H3), 4.61 (d, 1H, $J_{2',2''}$ 8.7 Hz, H2′); δ_C ($CDCl_3$): 25.3, 26.0, 26.3 (2 × –C(CH_3)$_2$), 64.8 (C-2′), 65.5 (C-6), 72.4 (C-3), 73.7 (C-5), 79.6 (C-4), 83.7 (C-2), 110.2, 112.3 (2 × –C(CH_3)$_2$), 173.8 (C-1); *m/z* (NH_3, ES+): 289 $(M+H)^+$; Found: C 54.37, H 7.19; $C_{13}H_{20}O_7$ requires C 54.16, H 6.99.
22. 2-*C*-Hydroxymethyl-D-*allono*-1,4-lactone **12**: $[\alpha]_D^{19}$ +36.3 (*c* 1.2, water); ν_{max} (Ge IR plate): 3384 (–OH), 1770 (–C═O) cm^{-1}; δ_H (D_2O): 3.65–3.78 (m, 3H, H6, H6′, H2′), 3.80 (d, 1H, $J_{2',2''}$ 8.0 Hz, H2″), 4.10–4.14 (m, 1H, H5), 4.44 (dd, 1H, $J_{3,4}$ 7.0 Hz, $J_{4,5}$ 4.0 Hz, H4), 4.52 (d, 1H, $J_{3,4}$ 7.0 Hz, H3); δ_C (D_2O): 61.4 (C-6), 62.2 (C-2′), 67.5, 70.8 (C-3, C-5), 75.9 (C-2), 83.2 (C-4), 176.9 (C-1); *m/z* (NH_3, ES−): 207 $(M-H)^+$; HRMS calcd for $C_7H_{11}O_7$ [$(M-H)^+$] 207.0501; found 207.0509.
23. 2-*C*-Hydroxymethyl-D-*altrono*-1,4-lactone **13**: $[\alpha]_D^{20}$ +32.8 (*c* 2.0, water); ν_{max} (Ge IR plate): 3418 (–OH), 1769 (–C═O) cm^{-1}; δ_H (D_2O): 3.45 (d, 1H, $J_{6,5}$ 7.2 Hz, $J_{6,6'}$ 11.8 Hz, H6), 3.53–3.59 (m, 2H, H6′, H2′), 3.79 (d, 1H, $J_{2',2''}$ 11.5 Hz, H2″), 3.90–3.93 (m, 1H, H5), 4.22 (dd, 1H, $J_{3,4}$ 7.9 Hz, $J_{4,5}$ 3.5 Hz, H4), 4.35 (d, 1H, $J_{3,4}$ 7.9 Hz, H3); δ_C (D_2O): 62.0, 62.1 (C-6, C-2′), 71.1, 73.9 (C-3, C-5), 79.0 (C-2), 81.9 (C-4), 178.3 (C-1); *m/z* (NH_3, ES−): 207 $(M-H)^+$; HRMS calcd for $C_7H_{11}O_7$ [$(M-H)^+$] 207.0501; found 207.0506.
24. Simone, M. I.; Soengas, R.; Newton, C. R.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **2005**, *46*, following paper, doi:10.1016/j.tetlet.2005.06.029.