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Kiliani on ketoses: branched carbohydrate building blocks from D-fructose and L-sorbose

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Abstract—Protected branched sugar lactones are available via Kiliani-acetonation sequences on readily available ketoses such as D-fructose and L-sorbose. In both cases, the readily crystallized diacetonides have a 2,3-*cis*-diol relationship in the product lactone. An efficient double inversion of the configuration at C-4 and C-5 of the product from D-fructose gives access to the formal Kiliani product from L-psicose. Branched carbohydrate lactones are likely to be of significant value as chirons for homochiral targets with functionalized quaternary centres.

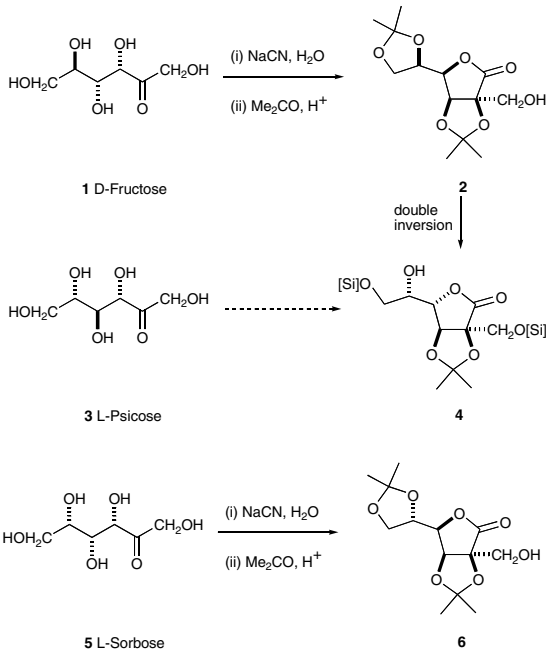
1. Introduction

Carbohydrate building blocks provide a wide range of starting materials for the enantiospecific synthesis of highly functionalized homochiral targets.[1] However, there are few, if any,[2] branched sugar chirons[3] that are easily available on a reasonable scale from cheap unprotected carbohydrates.

Although extensive studies on the Kiliani ascension[4] from an aldose to a higher sugar with a linear carbon chain have been reported,[5] the reaction on unprotected ketoses[6] (to provide branched sugars) has been little investigated. The initial work by Kiliani on the reaction of D-fructose[7] **1** and L-sorbose[8] **5** showed that the branched acids were not conveniently crystallized; further studies have been limited[9,10] and no simple protecting group chemistry of the crude products has been hitherto described. Access to simply prepared protected derivatives of branched Kiliani products would provide a new family of carbohydrate scaffolds from the chiral pool.

This letter provides experimental details for the synthesis of the two branched sugar building blocks **2** and **6** by the Kiliani reaction on D-fructose **1** and L-sorbose **5**, respectively, followed by acetonation of crude reaction mixtures (Scheme 1).

Although the yields of the two processes are moderate, the low cost of the ketoses and the ease of crystallization



Scheme 1.

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of two of the products make this a practical procedure for the generation of a series of protected branched sugar chirons. A short sequence from **2** involving a double inversion at C-4 and C-5 allows access to **4**, the formal product from a Kiliani reaction on the inaccessible sugar L-psicose **3**.

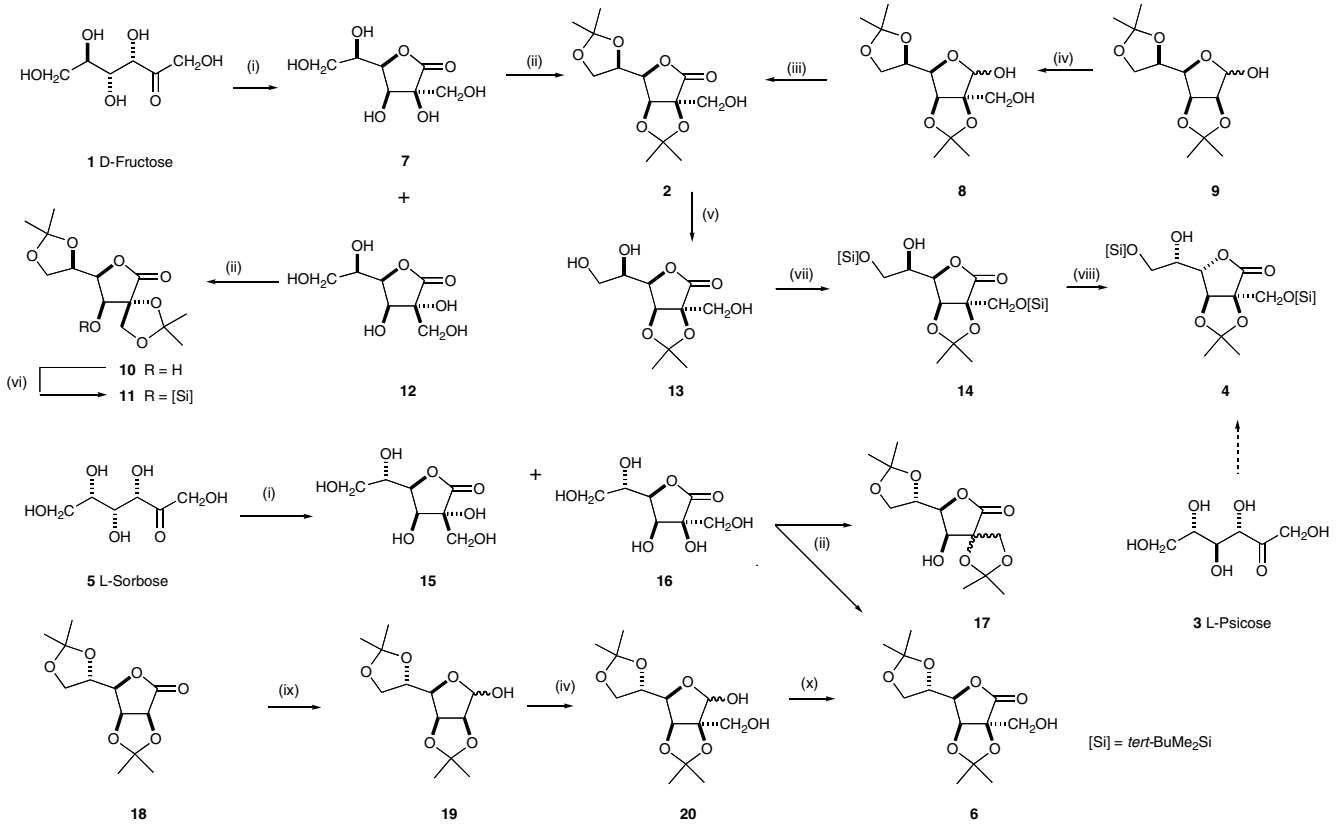
2. Synthesis

The Kiliani reaction of D-fructose **1** with aqueous sodium cyanide afforded a crude mixture of the two epimeric lactones **7** and **12** together with their open chain acids (Scheme 2). After the solvent had been removed, the residue was extracted with acetone in the presence of sulfuric acid to give a mixture that mainly consisted of the two diacetonides **2** and **10**. Although **2** and **10** are difficult to separate cleanly by flash chromatography, it is easy to crystallize the diacetonide **2**, derived from **7**, as the major product in 51% yield from the mixture. A smaller amount of the diacetonide **10**, derived from the minor isomer **12**, was isolated in 9% yield.

As a practical procedure, D-fructose **1** (10.00 g, 55.51 mmol) and sodium cyanide (3.54 g, 72.24 mmol) were stirred together in water (100 mL) at room temperature for 24 h. The reaction mixture was then refluxed until evolution of ammonia had ceased (approx 12 h). The mixture was allowed to cool at room temperature and then passed through a column of Amberlite IR-120 H^+ form and the solvent evaporated. Acetone (150 mL), concentrated sulfuric acid (2.5 mL) and anhydrous copper sulfate were added to the residue, and the resulting mixture was stirred at room temperature. After 6 h, TLC (ethyl acetate/cyclohexane 1:1) indicated the formation of a major product (R_f 0.28) and a minor one (R_f 0.31). The mixture was then neutralized with solid sodium carbonate, filtered and the solvent evaporated. The residue was shaken with dichloromethane (100 mL) and water (100 mL) and the aqueous layer was further extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated to produce a mixture which was purified by flash chromatography (ethyl acetate/cyclohexane 1:1) and crystallization of the impure fractions from ether/hexane, to yield **2**[11] (8.19 g, 51% yield) as a white crystalline solid. A minor product **10**[12] (1.44 g, 9%) was also recrystallized from ether/hexane.

The structure of **10** was firmly established by X-ray crystallographic analysis[13] of the corresponding silyl ether **11**, {mp 76–78 °C, $[\alpha]_D^{21}$ +46.0 (*c*, 0.42)[14]} formed by treatment of **10** with *tert*-butyldimethyl (TBDMS) triflate in dichloromethane in the presence of 2,6-lutidine.

A beautiful series of papers by Ho exploited the crossed aldol reactions of 2,3-*O*-isopropylidene protected sugars



Scheme 2. Reagents and conditions: (i) NaCN, H_2O; (ii) Me_2CO, H_2SO_4, $CuSO_4$; (iii) Br_2, $BaCO_3$, H_2O; (iv) CH_2O, K_2CO_3, H_2O; (v) CH_3CO_2H, H_2O; (vi) $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2; (vii) TBDMSCl, pyridine, DMF; (viii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, then KOH, H_2O, dioxane; (ix) DIBAL-H, THF; (x) Br_2, $BaCO_3$, H_2O, dioxane.

with formaldehyde.[15] Thus, an identical sample of **2** was also prepared from diacetone mannose **9**[16] by an initial aldol condensation with aqueous formaldehyde to give **8** [52% yield]; subsequent oxidation of the lactol **8** with bromine water gave **2** mp 130–132 °C, $[\alpha]_D^{21}$ +34.7 (*c*, 1.0) in 86% yield. However, the direct Kiliani procedure appears to be easily scalable, requires less effort and is completed at a small fraction of the cost of starting from D-mannose.

Some chemistry of the diacetonide **2** was explored. Mild acid hydrolysis of **2** by aqueous acetic acid gave the monoacetonide **13** in quantitative yield {mp 128–132 °C, $[\alpha]_D^{24}$ +64.4 (*c*, 0.93, MeOH)}. Treatment of **13** with TBDMS chloride in DMF in the presence of pyridine gave the disilyl ether **14** [73% yield, oil, $[\alpha]_D^{21}$ +36.5 (*c*, 1.26)]. The disilyl ether **14** was treated with triflic anhydride in dichloromethane in the presence of pyridine to give the corresponding triflate which, when treated with potassium hydroxide in aqueous dioxane, afforded the alcohol **4** ($[\alpha]_D^{21}$ +13.5 (*c*, 0.73), oil)—formed by double inversion at C-5 and C-4—in 58% yield. The structure of the L-allono-lactone **4**, the formal product from a Kiliani sequence from L-psicose **3**, was firmly established by X-ray crystallographic analysis of a derivative.[17]

The Kiliani reaction on L-sorbose **5** to give the lactones **15** and **16**, with subsequent acetonation, was performed identically to that described above for D-fructose **1** to the stage of the processing of the residue of the crude mixture of diacetonides. Whereas for fructose **1** an initial flash column was necessary in the work-up, direct crystallization of the residue from L-sorbose allowed isolation of the diacetonide **6**[18] in 17% yield without chromatography; however, further work-up of the mixture of the epimeric spiro-acetonides **17**[19] is difficult.[20]

The diacetonide **6** was also prepared from the diacetonide of L-gulonolactone **18**.[21] Reduction of **18** with diisobutylaluminium hydride (DIBAL-H) in THF gave the corresponding lactol[22,23] **19** which underwent a crossed aldol reaction with aqueous formaldehyde to the branched gulose **20** mp 83–85 °C, $[\alpha]_D^{26}$ +5.0 (*c* 0.73) in 70% yield. Oxidation of the lactol **20** with bromine in aqueous dioxane in the presence of barium carbonate afforded the branched lactone **6** in 96% yield, identical in all respects with the sample of **6** made from sorbose. While the four-step route from L-gulonolactone is efficient, it competes neither in terms of cost nor time with the procedure from L-sorbose.

3. Conclusion

This letter provides an indication of the potential ease of access to protected branched sugar chirons; both from fructose and from sorbose easily crystallized branched diacetonides can be isolated. Such carbohydrate building blocks are not restricted to those available from the Kiliani-acetonation procedure on D-fructose and L-sorbose. The Ferrier–Kiliani combination of microbial oxidation of alditols combined with cyanohydrin formation and acetonation,[24] and the microbial oxidation–enzyme catalyzed epimerizations reported by Izumori and co-workers,[25] may provide a powerful armory for the synthesis of new densely functionalized homochiral targets.

Acknowledgements

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11. Selected data for 2-*C*-hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone **2**: mp 128–130 °C; $[\alpha]_D^{21}$ +34.7 (*c*, 1.0, $CHCl_3$); δ_H (d_6-acetone): 1.35, 1.41, 1.42 (4 × s, 12H, 4 × –CH_3), 3.89–4.03 (m, 3H, H_6, $H_{2'}$, $H_{2''}$, 4.15 (dd, 1H, $J_{6,6'}$ 8.9 Hz, $J_{6',5}$ 6.2 Hz, $H_{6'}$, 4.41–4.46 (m, 1H, H_5), 4.50 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 7.0 Hz, H_4), 4.69 (dd, 1H, $J_{2',OH}$ 4.8 Hz, $J_{2'',OH}$ 6.1 Hz, –OH), 4.92 (d, 1H, $J_{3,4}$ 3.4 Hz, H_3); δ_C ($CDCl_3$): 26.99, 26.16, 26.76 (4 × –CH_3), 61.43, 66.24 (2 × –CH_2–), 72.42, 78.45, 78.70 (3 × –CH–), 86.00, 109.73, 113.79 (3 × –C–), 175.69 (–C═O).
12. Selected data for 2-*C*-hydroxymethyl-2,2′:5,6-di-*O*-isopropylidene-D-glucono-1,4-lactone **10**: mp 102–104 °C; $[\alpha]_D^{21}$ +67.7 (*c*, 1.56, $CHCl_3$); δ_H ($CDCl_3$): 1.37, 1.45, 1.46 (3 × s, 12H, 4 × –CH_3), 2.65 (d, 1H, $J_{OH,3}$ 3.1 Hz, –OH), 4.05 (dd, 1H, $J_{6,6'}$ 8.9 Hz, $J_{6',5}$ 4.1 Hz, $H_{6'}$), 4.20–4.25 (m,

2H, H_6, H_3), 4.30 (d, 1H, $J_{2',2''}$ 9.6 Hz, $H_{2''}$, 4.30–4.35 (m, 1H, H_5), 4.44 (d, 1H, $J_{3,4}$ 3.4 Hz, H_4), 4.47 (d, 1H, $J_{2',2''}$ 9.6 Hz, $H_{2'}$); δ_C ($CDCl_3$): 24.96, 25.28, 26.34, 26.81 ($4\times$–CH_3), 65.39, 67.37 ($2\times$–CH_2–), 72.69, 72.96, 81.35 ($3\times$–CH–), 82.66, 110.14, 112.73 ($3\times$–C–), 173.94 (–C=O).

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18. Selected data for 2-*C*-hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone **6**: mp 128–129 °C {lit. [19] 132–133 °C}; $[\alpha]_D^{23.5}$ +57.9 (*c* 1.14, $CHCl_3$); δ_H ($CDCl_3$) 1.39, 1.39, 1.46, 1.47 ($4\times$ s, 12H, $4\times C\mathit{H}_3$), 3.81–3.86 (m, 1H, H-6), 3.90 (d, 1H, H-2′, $J_{2',2''}$ 11.4 Hz), 4.01 (d, 1H, H-2″, $J_{2'',2'}$ 11.4 Hz), 4.19–4.23 (m, 1H, H-6′), 4.41–4.48 (m, 2H, H-4, H-5), 4.70 (d, 1H, H-3, $J_{3,4}$ 2.9 Hz); δ_C ($CDCl_3$) 25.52, 26.32, 26.63, 26.85 ($4\times C\mathit{H}_3$), 61.57 (C-2′), 65.11 (C-6), 74.98 (C-5), 78.72 (C-3), 81.15 (C-4), 86.14 (C-2), 110.46, 114.18 ($2\times C(CH_3)_2$), 175.49 (C-1).
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