Organic LETTERS

Letter

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Triacetonide of Glucoheptonic Acid in the Scalable Syntheses of D-Gulose, 6-Deoxy-D-gulose, L-Glucose, 6-Deoxy-L-glucose, and Related Sugars

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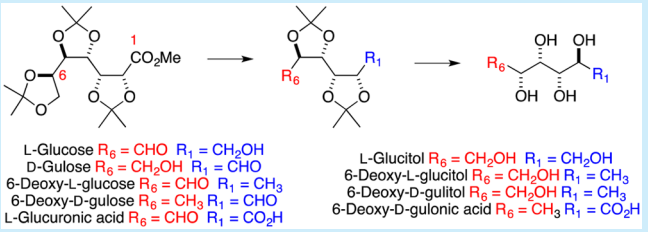
Supporting Information

ABSTRACT: Ease of separation of petrol-soluble acetonides derived from the triacetonide of methyl glucoheptonate allows scalable syntheses of rare sugars containing the L-gluco or D-gulo structural motif with any oxidation level at the C6 or C1 position of the hexose, usually without chromatography: *meso*-D-glycero-D-guloheptitol available in two steps is an ideal entry point for the study of the biotechnological production of heptoses.



Sodium glucoheptonate **1** >98% pure, prepared from the Kiliani reaction of sodium cyanide with glucose,[1] is one of the cheapest bulk carbohydrates available. On a 100 g scale, **1** may be converted in a morning to the pure triacetonide methyl ester **2** by a procedure that involves extraction of the crude product with cyclohexane as the only purification step (Scheme 1). The value of **2** in the preparation of rare sugars has been demonstrated by large-scale syntheses of L-glucose **4** and L-glucuronic acid **6**: selective deprotection of the terminal acetonide in **2**, followed by $LiAlH_4$ reduction of **2a**, and periodate cleavage gave aldehyde **3**; acid hydrolysis of **3** gave L-glucose **4** in 80% yield from the triacetonide with purification only by solvent extraction and crystallization.[2] Partial hydrolysis of **2** and subsequent oxidation with periodate afforded the stable aldehyde **5**, which with trifluoroacetic acid hydrolysis gave L-glucuronic acid **6**, isolated as the crystalline lactone in 78% yield from **2**.[2] This paper describes the synthesis of a wide range of rare sugars via intermediate acetonides derived from **2**, all easily accessible in multigram quantities with any oxidation level at C1 or C6 of the sugar.

For the synthesis of D-gulose **9**, treatment of **5** on a multigram scale with sodium borohydride in methanol at 0 °C gave completely regioselective reduction of the aldehyde to provide alcohol **7** (96%); there was no reduction of the ester group (Scheme 1). Further reduction with DIBAL-H afforded the D-gulose derivative **8** with C1 and C6 unprotected (86%). One-step DIBAL-H reduction of **5** directly to **8** did not give a clean product. Removal of the acetonides in **8** by acid ion-exchange resin gave D-gulose **9**[3] in quantitative yield (71% from triacetonide **2**). Simultaneous reduction of both the aldehyde and ester groups in **5** by $LiAlH_4$ formed the diol **10** (90%), which on treatment with acid ion-exchange resin gave L-glucitol **11** (100%) in 77% yield from the triacetonide **2**. Alditols are ideal substrates for biotechnological conversion to rare sugars: microbial oxidation of L-glucitol **11** gave D-sorbose[4] **12** in 90% yield.[5] ^{13}C and ^{1}H NMR spectra of D-gulose **9** and L-glucitol **11** were identical to those of authentic samples (see Supporting Information).

Acetonide **2** or **7** can be used for efficient syntheses of 6-deoxy sugars. Derivatives of 6-deoxy-D-gulose can be efficiently accessed by initial deoxygenation of the primary alcohol in **7** (Scheme 2). Esterification of **7** with triflic anhydide in the presence of pyridine, followed by nucleophilic substitution with sodium iodide in butanone, gave iodide **13** (81% over two steps). Hydrogenation of **13** in methanol in the presence of palladium on charcoal and triethylamine gave the crystalline diacetonide **14**, which was deprotected to afford 6-deoxy-D-gulonolactone **15**[6] (100%). Synthesis of the crystalline lactone **15** from the triacetonide **2** in 61% yield required no chromatography; the route is far more convenient than procedures from L-rhamnose[7] or D-gulonolactone.[8]

Reduction of ester **14** with DIBAL-H at −78 °C gave the protected aldehyde **17** (84%) and a small amount of the alcohol **16** (14%), easily separated by flash chromatography. Acid ion-exchange hydrolysis of the acetonides in **17** formed 6-deoxy-D-gulose **18**[9] (100%), identical to a sample from L-rhamnose[7]

Received: July 13, 2016

DOI: 10.1021/acs.orglett.6b02041
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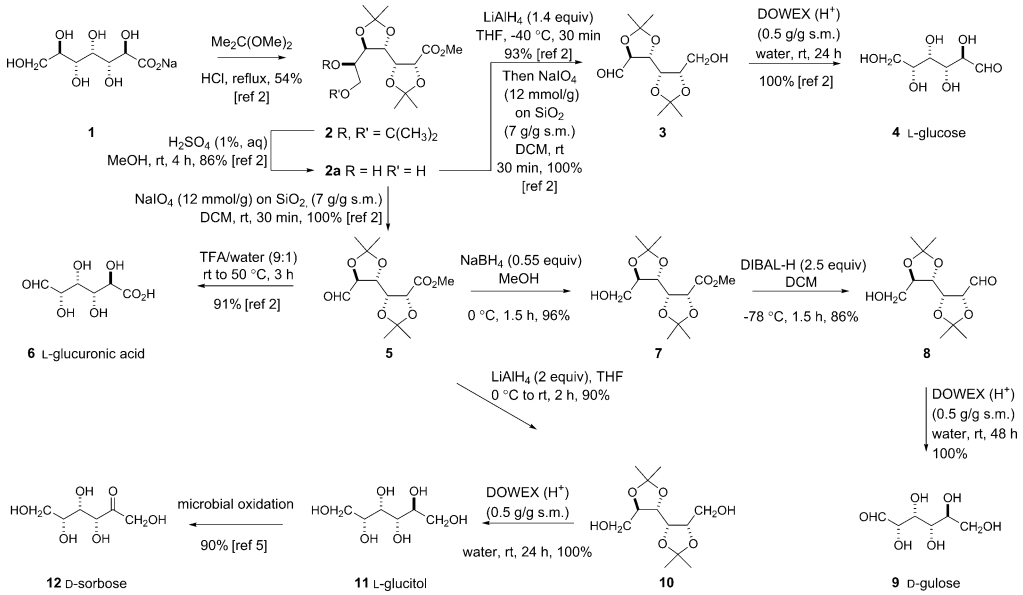
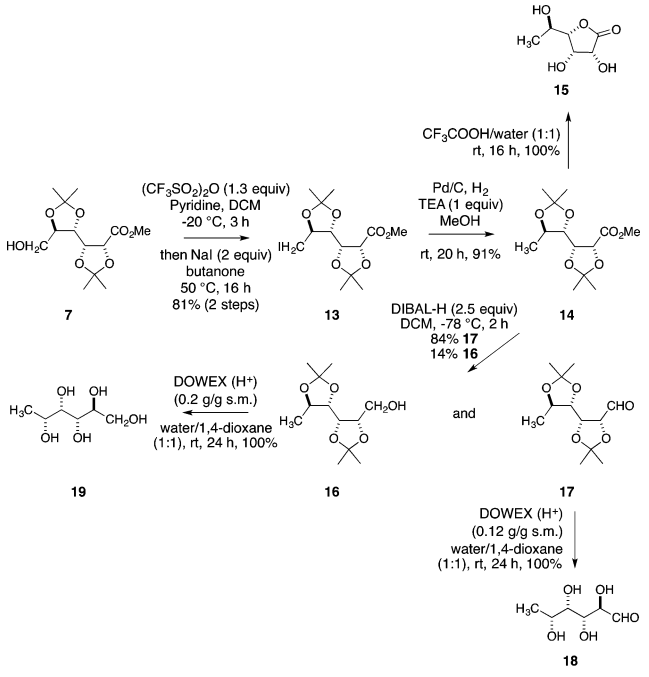
Scheme 1. L-Glucose 4, D-Gulose 8, and L-Glucitol 11



Scheme 2. 6-Deoxy-D-gulonolactone 15, 6-Deoxy-D-gulose 18, and 6-Deoxy-D-gulitol [6-Deoxy-D-glucitol] 19



(overall 56% yield from **2**). Acid hydrolysis of **16** gave 6-deoxy-D-gulitol (1-deoxy-L-glucitol) **19**.[10]

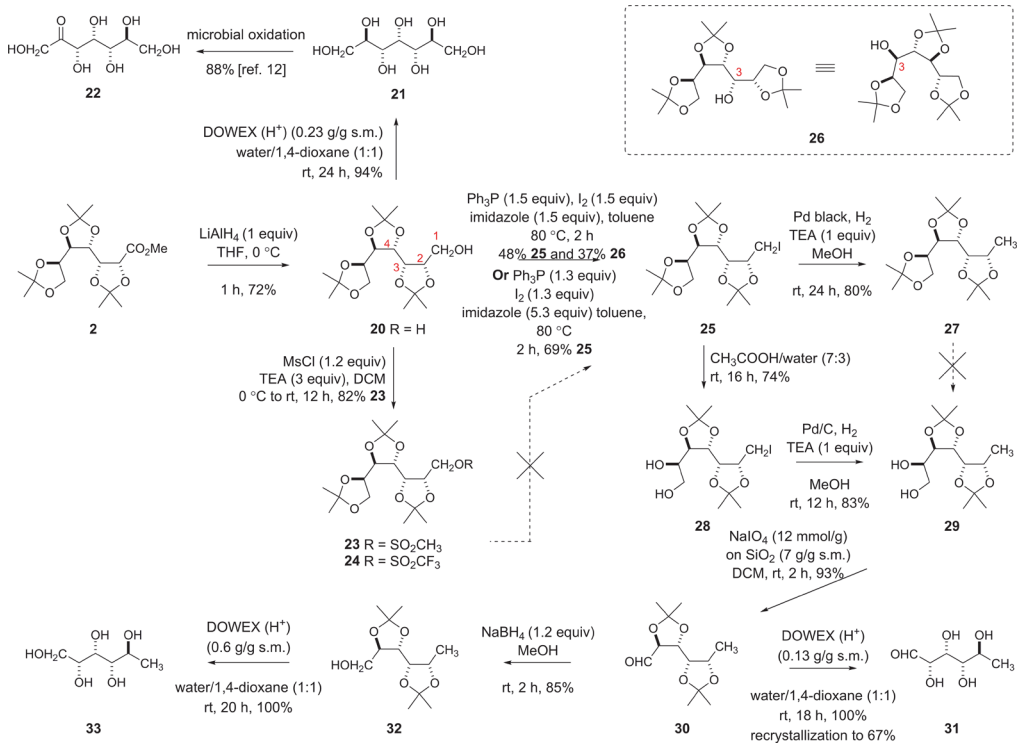
Heptitol[11] triacetonide **20** was formed in the reduction of methyl ester **2** with $LiAlH_4$ (74%) (Scheme 3). Acid ion-exchange hydrolysis of **20** formed the *meso*-heptitol **21** (94%). Microbial oxidation of **21** with *Acetobacter suboxydans* forms L-glucoheptulose **22** in 88% yield, as described long ago by Hudson,[12] and provides an ideal entry point for the isomerization of seven carbon sugars by the biotechnology of Izumori;[13] there is much current interest in the investigation of the synthesis and biological properties of heptuloses.[14]

Deoxygenation of the primary alcohol in triacetonide **20** gave efficient syntheses of 6-deoxy-L-glucose (L-quinovose) derivatives. Triflate ester **24** derived from **20** was unstable, and it was not possible to convert **2** to the corresponding iodide **25** by an analogous protocol used for **7** to **13**. Reaction of **20** with mesyl chloride and triethylamine in DCM gave mesylate **23** (82%); all attempts at nucleophilic displacement of the primary mesylate in **23** failed: **23** was recovered unchanged on heating overnight with sodium iodide in acetone at reflux or in DMF at 100 °C; reduction of **23** with $LiAlH_4$ resulted in nucleophilic attack on sulfur (rather than carbon) to give **20**. Although S_N reactions in carbohydrate chemistry are difficult due to the presence of β-oxygen substituents,[15] iodides are almost always formed in good yields by displacement of primary mesylates. Additional steric hindrance to nucleophilic attack may be due to the *cis* relationship in the C2−C3 ketal between the ketal at C4−C5 and the leaving group at C1. This would also explain the instability of triflate **24** because the ketal oxygen at C4 might act as an internal nucleophile on the leaving group at C1. For the introduction of an iodide at C1, it is necessary to have the iodide present during the activation of the leaving group at C1. Appel reaction[16] of alcohol **20** with imidazole/triphenylphosphine/iodine in a 1:1:1 ratio gave iodide **25** (48%) together with another acetonide **26** (37%). The structure of **26** was confirmed by NMR spectra with $CDCl_3$ as solvent: (i) three quaternary carbon signals (δ = 109.3, 109.7, 109.8 ppm) indicated the presence of three five-membered-ring ketals; (ii) the peak of free hydroxyl group (δ = 2.17 ppm) of **26** was a doublet in ^{1}H NMR spectrum; (iii) ^{1}H−^{1}H correlation spectroscopy indicated the hydroxyl group is correlated with H-3. Formation of **26** was also observed by leaving **20** in $CDCl_3$ for 3 weeks at room temperature. **20** and **26** are the only two possible triacetonides of heptitol **21** with only five-ring ketals. Formation of **26** from **20** is acid-catalyzed. Accordingly, when the Appel reactant ratio of imidazole/triphenylphosphine/iodine was changed to a 4:1:1 with an excess of base, conversion of alcohol **20** gave iodide **25** in 69% yield on an 11 g scale without the formation of **26**.

Hydrogenolysis of iodide **25** with palladium black and triethylamine gave the methyl triacetonide **27** (80%). However, no conditions for selective acid hydrolysis of **27** to the diol **29** were found. In contrast, the iodomethyl triacetonide **25** with aqueous acetic acid gave diol **28** (74%). Hydrogenolysis of **28** in methanol in the presence of palladium on charcoal and

DOI: 10.1021/acs.orglett.6b02041
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. *meso*-D-Glycero-D-guloheptitol 21, 6-Deoxy-L-glucose [L-Quinovose] 31, and 6-Deoxy-L-glucitol 33



triethylamine afforded the crystalline deoxyheptitol diacetonide **29** (83%). Cleavage of diol **29** with sodium periodate on silica gel in DCM[17] formed aldehyde **30** (93%), which on acid ion-exchange resin hydrolysis gave deoxyhexose **31** (67%), identical to a sample produced from L-rhamnose.[7] Reduction of aldehyde **30** by sodium borohydride in methanol gave diacetonide **32** (85%), which on removal of the acetonide protecting groups by acid hydrolysis formed 6-deoxyalditol **33** (100%). 6-Deoxy-L-glucose **31** and 6-deoxy-L-glucitol **33** were formed in overall yields of 19 and 24%, respectively, from the heptonate triacetonide **2** without the need for any chromatography. The NMR spectra of 6-deoxy-L-glucose were identical to those of commercially available 6-deoxy-D-glucose.

Heptonic acid lactones with only acetonide protection derived from Kiliani synthesis on aldoses[18] or ketoses[19] are well-established intermediates for the efficient synthesis of highly functionalized targets.[20] This paper underlines the value of triacetonides[21] derived from seven carbon sugars; **2** is a divergent intermediate for access to rare sugars possessing either a D-gulo or L-gluco structural motif with any oxidation level at C1 or C6. This approach, which may be general for heptonates, increases chemical and biotechnological procedures for easy access to rare sugars.[22] L-Rhamnose, a cheap 6-deoxyhexose, provides an alternative strategy for the synthesis of many of its diastereomers and derivatives.[7,23] In particular, microbial oxidations of alditols to ketoses usually give high-yield regioselective reactions to a pure ketose; 6-deoxyalditols **19** and **33** are useful starting materials for the biotechnology of Izumori in the synthesis of deoxyhexoses.[24]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02041.

Experimental procedures and full spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Leverhulme Trust (G.W.J.F.) and Xunta de Galicia (Project GRC2014/040). We are grateful to Carbosynth for samples of authentic sugars for comparison purposes.

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DOI: 10.1021/acs.orglett.6b02041
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DOI: 10.1021/acs.orglett.6b02041
Org. Lett. XXXX, XXX, XXX−XXX