

Triacetone 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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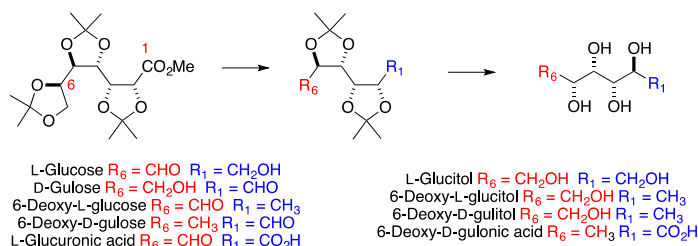
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Supporting Information Placeholder



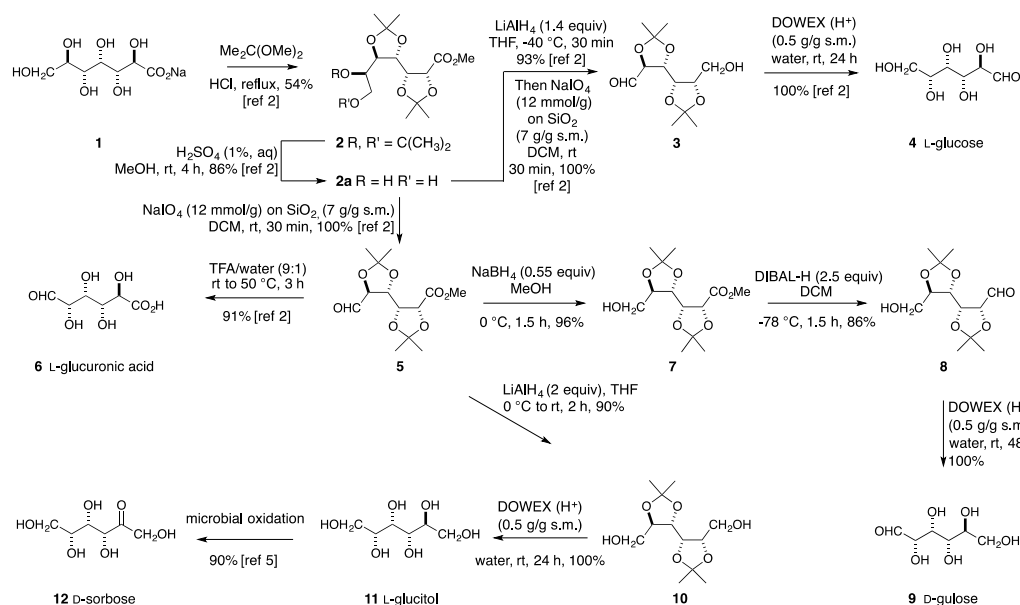
ABSTRACT: Ease of separation of petrol soluble acetonides derived from the triacetone of methyl gluco-heptonate allows scalable syntheses of rare sugars containing the L-gluco- or D-gulo- structural motif with any oxidation level at the C6 or C1 position of the hexose, usually without chromatography: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

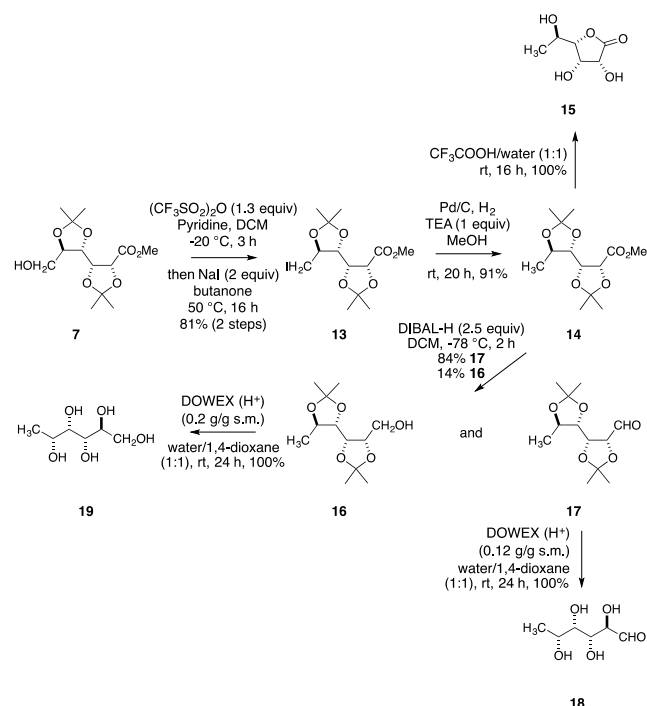
For the synthesis of D-gulose **9**, treatment of **5** on a multi-gram scale with sodium borohydride in methanol at 0 °C gave completely regioselective reduction of the aldehyde to provide the alcohol **7** (96%); there was no reduction of the ester group [Scheme 1]. Further reduction with DIBAL-H afforded 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 triacetone **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 triacetone **2**. Alditols are ideal substrates for biotechnological conversion to rare sugars: microbial oxidation of L-glucitol **11** gave D-sorbose⁴ **12** in 90% yield.⁵ ¹³C and ¹H NMR spectra of D-gulose **9** and L-glucitol **11** were identical to those of authentic samples. [see SI]

Scheme 1. L-Glucose 4, D-gulose 8, and L-glucitol 11



The acetonides **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 anhydride in the presence of pyridine, followed by nucleophilic substitution with sodium iodide in butanone, gave the 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** (100%). The 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-rhamnose⁷ or D-gulonolactone.⁸

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



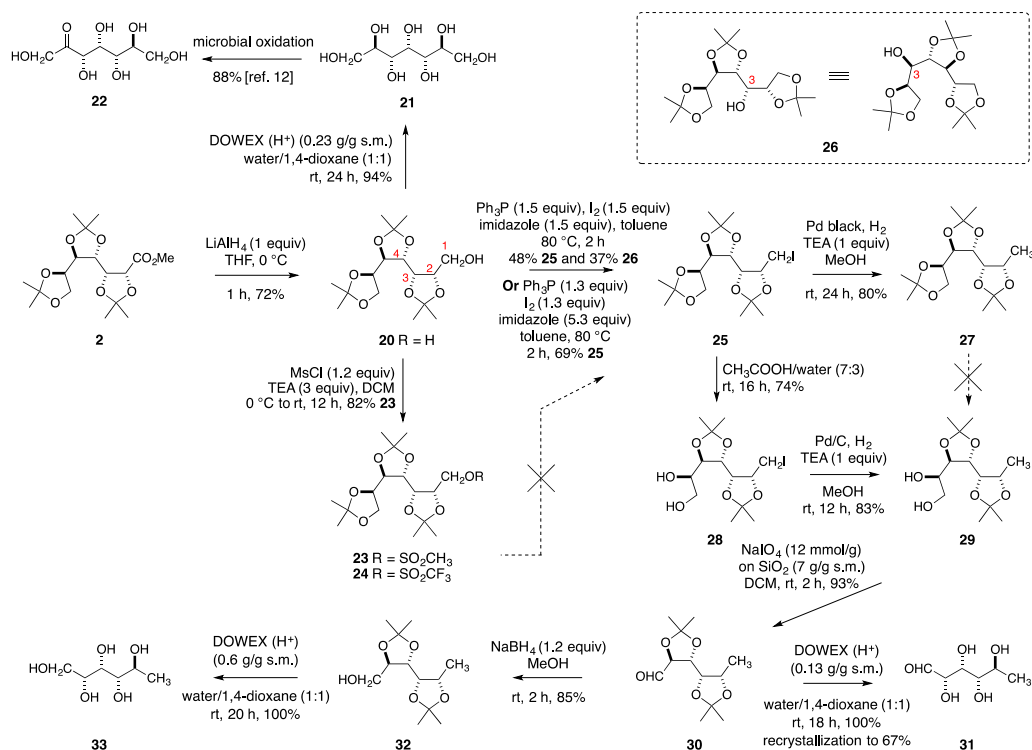
Reduction of ester **14** with DIBAL-H at -78°C gave the protected aldehyde **17** (84%) and a small amount of the alco-

hol **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-rhamnose⁷ [overall 56% yield from **2**]. Acid hydrolysis of **16** gave 6-deoxy-D-gulitol (1-deoxy-L-glucitol) **19**¹⁰.

The heptitol¹¹ 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-glucio-heptulose **22** in 88% yield, as described long ago by Hudson,¹² and provides an ideal entry point for the isomerisation of seven carbon sugars by the biotechnology of Izumoring,¹³ there is much current interest in the investigation of the synthesis and biological properties of heptuloses.¹⁴

Deoxygenation of the primary alcohol in the triacetonide **20** gave efficient syntheses of 6-deoxy-L-glucose [L-quinovose] derivatives. The 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 dichloromethane gave the 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 sulphur [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 the triflate **24** since 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 reaction¹⁶ of alcohol **20** with imidazole:triphenylphosphine:iodine in a 1:1:1 ratio gave the 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 ($\delta = 109.3$ ppm, 2

Scheme 3. *meso*-D-glycero-D-gulo-Heptitol **21**, 6-Deoxy-L-glucose [L-quinovose] **31** and 6-Deoxy-L-glucitol **33**



109.7 ppm, 109.8 ppm) indicated the presence of three five-membered rings ketals; ii) the peak of free hydroxyl group ($\delta = 2.17$ ppm) of **26** was a doublet in ¹H NMR spectrum; iii) ¹H-¹H Correlation Spectroscopy (COSY) indicated the hydroxyl group is correlated with H-3. The formation of **26** was also observed by leaving **20** in CDCl₃ for 3 weeks at room temperature. **20** and **26** are the only two possible triacetones of heptitol **21** with only five-ring ketals. The formation of **26** from **20** is acid catalysed. Accordingly, when the ratio of the Appel reactants imidazole:triphenylphosphine:iodine was changed to a 4:1:1 ratio with an excess of base, the conversion of alcohol **20** gave iodide **25** in 69% yield on an 11 g scale without the formation of **26**.

Hydrogenolysis of the iodide **25** with palladium black and triethylamine gave the methyl triacetone **27** (80%). However, no conditions for selective acid hydrolysis of **27** to the diol **29** were found. In contrast, the iodomethyl triacetone **25** with aqueous acetic acid gave the diol **28** (74%). Hydrogenolysis of **28** in methanol in the presence of palladium on charcoal and triethylamine afforded the crystalline deoxyheptitol diacetone **29** (83%). Cleavage of diol **29** with sodium periodate on silica gel in dichloromethane¹⁷ formed aldehyde **30** (93%) which on acid ion exchange resin hydrolysis gave the deoxyhexose **31** (67%), identical to a sample produced from L-rhamnose.⁷ Reduction of aldehyde **30** by sodium borohydride in methanol gave the diacetone **32** (85%) which on removal of the acetone 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 triacetone **2** without the need for any chromatography. The NMR spectra of 6-deoxy-L-glucose was identical with those of commercial available 6-deoxy-D-glucose.

Heptonic acid lactones with only acetone protection derived from Kiliani synthesis on aldoses¹⁸ or ketoses¹⁹ are well-established intermediates for the efficient synthesis of highly functionalised targets.²⁰ This paper underlines the value of

triacetones²¹ 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; the 6-deoxyalditols **19** and **33** are useful starting materials for the biotechnology of Izumoring in the synthesis of deoxyhexoses.²⁴

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data. The Supporting Information is available free of charge via Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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