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Synthesis of D-Hexos-5-uloses by Novel in Situ Hydrolysis of Epoxides Derived from 6-Deoxyhex-5-enopyranosides

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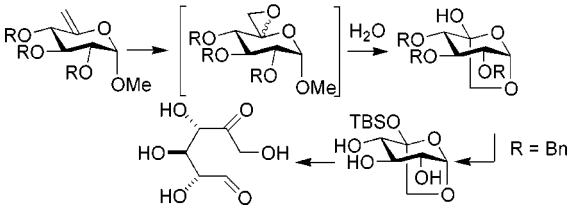
ABSTRACT

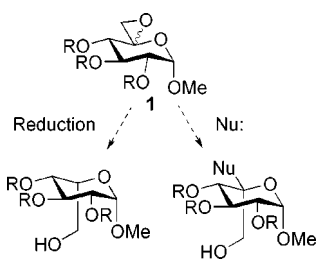


Epoxides derived from 2,3,4-tri-*O*-protected-6-deoxyhex-5-enopyranosides are hydrolyzed in situ to ultimately give novel protected-D-hexos-5-ulose derivatives (sugar 1,5-dicarbonyls, 5-ketohexoses) in moderate to high yields. The products adopt a bicyclic structure (1,6-anhydropyranos-5-ulose) in solution with the pyranose ring in $^4C_1$ conformation. The methodology has been used to prepare D-*xylo*-hexos-5-ulose (5-ketoglucose), a synthetic precursor to 1-deoxynojirimycin and a possible intermediate in the biosynthesis of inositols.

Our interest in the synthesis of novel glycosaminoglycan derivatives[1] and other carbohydrates for biological evaluation prompted us to study the synthetic potential of epoxides **1**. We envisaged that reactions of these compounds with reducing reagents or nucleophiles could proceed in a diastereoselective and/or regioselective manner to give idopyranosides and their analogues (Scheme 1). These intermediates could be further elaborated into iduronic acid glycosyl donors, novel aminoglycosides with potential as RNA binding agents,[2] or other glycomimetics.[3] Recent interest has focused on the synthetic potential of carbohydrate epoxides that are intermediates used in the preparation of oligosaccharides and other carbohydrate derivatives.[4] 6-Deoxyhex-5-enopyranosides have proven to be useful intermediates in synthesis. They can be used, for example, to prepare carbacycles by the Ferrier and other rearrangement reactions.[5] However, little work has been reported on the synthesis and reactions of their epoxides.[6] We now describe our preliminary results, which show that these epoxides are readily hydrolyzed to give novel D-hexos-5-ulose (5-ketohexose) derivatives.

Synthetic routes to the glycals **3** and **4** are well established,[7] and the sequence used for their preparation was adapted from these methods (Scheme 2). The preparation

Scheme 1



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(1) Lander, A. D. *Chem. Biol.* **1994**, *1*, 73.
(2) Alper, P. B.; Hendrix, M.; Sears, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1965.
(3) Wong, C.-H. *Acc. Chem. Res.* **1999**, *32*, 376.
(4) (a) Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (b) Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron Lett.* **1991**, 4035. (c) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183.

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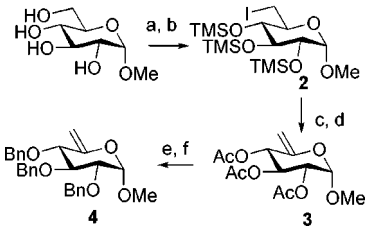
Scheme 2[a]

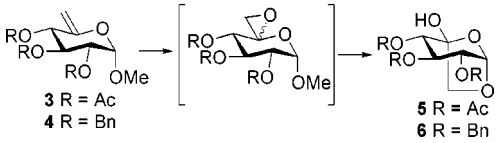


[a] Reagents and conditions: (a) PPh_3, Im, I_2, toluene, 80 °C, 3 h; (b) TMSCl, Py, 25 °C; (c) DBU, DMF, 70 °C, 3 h; (d) Ac_2O, Py; (e) NaOMe, MeOH, 25 °C, 12 h; (f) NaH, BnBr, DMF, 0 °C, 15 h.

of **3** can be carried out without purification of the intermediates. Thus, methyl 6-iodo-6-deoxy-α-D-glucopyranoside was prepared as described previously from methyl α-D-glucopyranoside[8] and then treated with excess TMSCl in pyridine to give **2**. This protected iodide was converted to glycal **3** by the elimination of hydrogen iodide[9] and exchange of the TMS groups for acetates. Deacetylation and benzylation gave **4**.[10]

D-Hexos-5-ulose derivatives **5** and **6**[11] were respectively obtained when **3** and **4** were subjected to a variety of epoxidation conditions (Table 1).

Table 1. Epoxidation−Hydrolysis of **3** and **4**

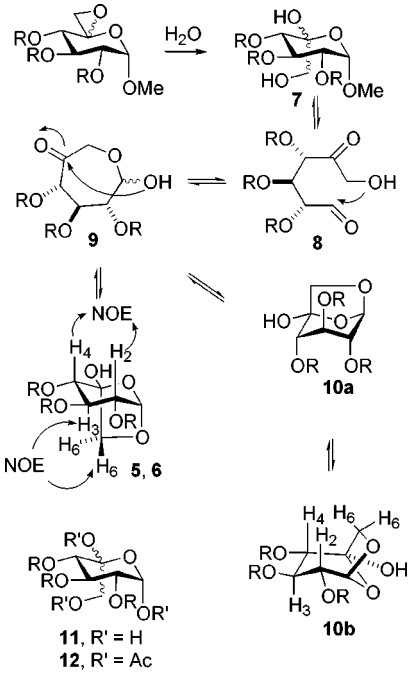


entry	R	reagents and conditions[a]	% yield
1	Bn	a	35
2	Bn	b	30
3	Bn	c	26
4	Bn	d	75−95
5	Bn	e	43
6	Bn	f	26
7	Ac	a	<10
8	Ac	b	27
9	Ac	d	12−50[b]

[a] (a) CH_3ReO_3 (0.5 mol %), pyridine (12 mol %), 30% H_2O_2 (1.5 equiv), CH_2Cl_2/H_2O; (b) MCPBA, $NaHCO_3$, CH_2Cl_2 15 h; (c) MCPBA, $ClCH_2CH_2Cl$, 4.5 h; (d) 1,1,1-trifluoroacetone, Oxone, $NaHCO_3$, Na_2EDTA, CH_3CN, H_2O; (e) acetone, KOH, Na_2EDTA, Oxone, $NaHCO_3$, CH_3CN, H_2O; (f) acetone, KOH, Oxone, Bu_4NHSO_4, phosphate buffer, benzene. [b] The yields are depleted by prolonged chromatography using silica gel.

The best reaction occurred when the benzylated glycal **4** was treated with methyl(trifluoromethyl)dioxirane, generated in situ,[12] giving **6** consistently in yields greater than 75%; this reaction can easily be carried out on a multigram scale.[13] The yields of ketohexose **6** were reduced when other conditions were employed. The formation of the products obtained can be explained by a mechanism that involves hydrolysis of the initially formed epoxide **2**, giving the hemiacetal **7** that subsequently loses methanol (Scheme 3).

Scheme 3



The high susceptibility of the epoxides to undergo reaction with water can be compared with epoxides derived from 4-deoxy-L-*threo*-hex-4-enopyranoside which have been shown to react in situ with methanol to give bis-glycosides that also can been used to prepare 5-ketohexoses.[14] Chapleur and coworkers have recently published a synthesis of a hemiacetal closely related to **7** by dihydroxylation of 2,3-di-*O*-benzyl-4-*O*-methanesulfonyl-6-deoxyhex-5-enopyranoside using $RuCl_3/NaIO_4$; they show that removal of the aglycon occurs

(5) (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779. (b) Dalko, P.; Sinay, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 773.

(6) To the best of our knowledge, only one example of synthesis of an epoxide from 6-deoxyhex-5-enopyranosides has been reported: Defaye, J. *C. R. Hebd. Seances Acad. Sci.* **1962**, *255*, 794.

(7) Semeria, D.; Phillipe, M.; Delaumeny, J.-M.; Sepulchre, A.-M.; Gero, S. D. *Synthesis* **1983**, 710.

(8) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

(9) The yield of **3** was significantly reduced if unprotected iodide was used in the elimination reaction.

(10) Glycal **3** was isolated yield in 61% yield from methyl α-D-glucopyranoside; **4** was isolated in 81% yield from **3**.

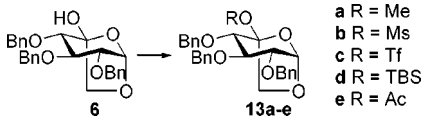
(11) The products give satisfactory ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectrometry data.

(12) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

(13) **Experimental procedure for preparation of 6:** Acetonitrile (70 mL), 1,1,1-trifluoroacetone (10 mL, 0.1 mol), and Na_2EDTA (50 mL of 4.0×10^{-4} M aqueous solution) were added to a cooled solution (0 °C) of **4** (4.5 g, 0.01 mol). A mixture of Oxone (30 g, 0.05 mol) and $NaHCO_3$ (6.51 g, 0.07 mol) was added in 3.04 g portions every 5 min. The reaction was then allowed to stir overnight and was poured into ice-cold water. The product was extracted with dichloromethane (3×). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was eluted from silica gel using an ethyl acetate−petroleum ether (bp 40−60 °C) gradient (1:4 to 1:1) to give **6** (4.36 g, 95%).

during silica gel chromatography and describe a 1,6-anhydroidopyranos-5-ulose structure for the product that they ultimately obtain.[15] This bicyclic structure (**5**, **6**), which has the pyranose ring in $^4C_1$ conformation and disguises the aldehyde and ketone, is also proposed for the products obtained here. It is one of a number of tautomers that are possible (Scheme 3), yet it appears to be favored exclusively by the 2,3,4-tri-*O*-protected-5-ketoglucoses. There are no spectroscopic data (NMR or IR) to support the presence of an open chain, **8**, or septanos-5-ulose structure, **9**, in an equilibrium product mixture.[16] The 1,6-anhydro-D-glucopyranos-5-ulose tautomer **10a** with its pyranose ring in $^1C_4$ conformation can be excluded on the basis of the coupling constants that are observed for the ring protons in the ^{1}H NMR spectra of the products. However, these data alone are not sufficient to confirm the idose configuration, assigned to the product (**5**, **6**); the pyran ring of the glucose tautomer could adopt a twist boat conformation, **10b**, which would also account for the coupling constants observed.[17] Thus, 2D-NOESY experiments were carried out to establish the product configuration. Cross-peaks, possible only for structures **5** and **6**, were observed between H-3 and one of the H-6 protons; they were not observed for H-2 and H-6 or for H-4 and H-6 as would have been expected for **10b**. Chemical reactions of **6** (Table 2) were also studied and rule

Table 2. Reactions of **6**



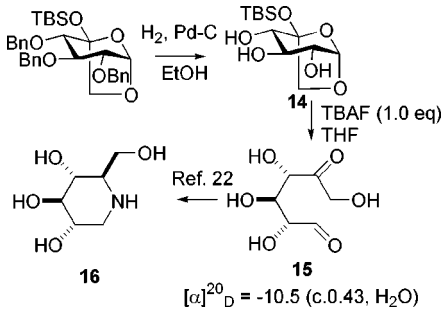
entry	R	reagents and conditions[a]	% yield
1	Me	a	78[b]
2	Ms	b	63
3	Tf	c	66[b]
4	TBS	d	48
5	Ac	e	58

[a] (a) NaH (2 equiv), MeI (2 equiv), DMF, 25 °C, 12 h; (b) MsCl (2 equiv), DMAP, Py, 2.5 h; (c) Tf_2O (2 equiv), 2,6-lutidine (4 equiv), CH_2Cl_2, −40 to 25 °C, 15 h; (d) TBSOTf (1.5 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2; (e) Ac_2O, Py, DMAP (cat.), 25 °C, 15 h. [b] Yield based on recovered starting material.

out the possibility that a hydrated form of the hexos-5-ulose **11** had been isolated.[18] Reaction of **6**, for example, in the presence of excess acetic anhydride and pyridine gave the monoacetate **13e**. The triacetate **12** would have been expected as a product had the reactant been **11**. These experiments confirm the idopyranose configuration assigned to the products.[19]

The *tert*-butyldimethylsilyl (TBS) derivative **13d** was converted to D-*xylo*-hexos-5-ulose[20] **15** after removal of benzyl groups by catalytic hydrogenation and subsequent treatment of the product with tetrabutylammonium fluoride in THF (Scheme 4).[21] D-*xylo*-Hexos-5-ulose has been used

Scheme 4



previously in synthesis of the glycosidase inhibitor 1-deoxynojirimycin **16**[22] and has also been postulated as an intermediate in the biosynthesis of inositols.[23] Protection of the free hydroxyl of **6** with the TBS group was necessary as attempts to obtain **15** directly from **5** or **6** were not successful.[24]

In summary, we have described a new route to 5-ketoglucose and some of its novel protected derivatives.[25] The methodology could, in principle, have potential for a general synthesis of 5-ketohexoses or other 1,5-dicarbonyl derivatives. Reaction, for example, of the mannose derivative **17** gives 2,3,4-tri-*O*-benzyl-1,6-anhydro-L-gulopyranos-5-ulose **18** (Scheme 5). Work is currently underway to explore the biological properties and synthetic potential of novel hexos-

(14) Barili, P. L.; Berti, G.; Catelini, G.; D'Andrea, F.; De Rensis, F. *Tetrahedron* **1997**, 8665.

(15) Taillefumier, C.; Lakhrissi, M.; Chapleur, Y. *Synlett* **1999**, 697.

(16) ^{1}H NMR spectra were recorded for **5** and **6** in $CDCl_3$, and IR spectra were obtained for liquid film for **5** and by KBr disk and $CHCl_3$ methods for **6**.

(17) Monte Carlo conformational searches (SUMM method, amber Force Field) using Macromodel 6.0 were performed on tautomer **10** (R = Bn and R = H). For the benzylated compound, there were 70 structures found within 3.0 kcal mol^{-1} of the global minimum. All except one had $^1C_4$ conformations for the pyranose ring. For the unprotected derivative, 15 of 24 low-energy structures within 3 kcal mol^{-1} of the global minimum had a twist-boat conformation. Thus, we wanted to rule out any possibility that the product isolated adopts a twist boat, **10b**, even though these calculations indicated a $^1C_4$ conformation should be favored for the pyranose ring of the protected compound.

(18) Detailed studies on equilibrium product mixtures in aqueous solution of unprotected hexos-5-uloses have been carried out. See: (a) Kiely, D. E.; Harry-O'Kuru, R. E.; Morris, P. E., Jr.; Morton, D. W.; Riordan, J. M. *J. Carbohydr. Chem.* **1997**, *16*, 1159. (b) Riordan, J. M.; Morris, P. E., Jr.; Kiely, D. E. *J. Carbohydr. Chem.* **1993**, *12*, 865.

(19) Compounds **13a**−**e** have the idose configuration as confirmed by NMR.

(20) The compound has NMR data in good agreement with that already reported; see refs 18b and 22.

(21) The use of more than 1 equiv of TBAF leads to formation of unidentified products.

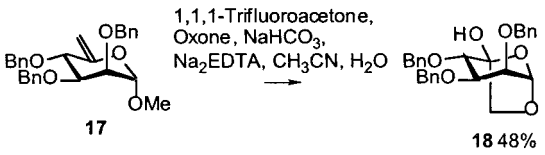
(22) Baxter, E.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175.

(23) (a) Wong, Y.-H. H.; Sherman, W. R. *J. Biol. Chem.* **1981**, *256*, 7077. (b) Eisenberg, F., Jr.; Maeda, T. In *Inositols and Phosphoinositides*; Bleasdale, J. E., Eichberg, J., Hauser, G., Eds.; Humana: New Jersey, 1985; p 3.

(24) Compound **5** when treated with sodium methoxide in methanol gave an intractable product mixture. Catalytic hydrogenation of **6** using Pd−C, H_2 in ethanol gave a complex mixture, which did not contain **15**.

(25) For previous syntheses of **15** and some of its other protected derivatives, see refs 14 and 22 and (a) Heusinger, H. *Carbohydr. Res.* **1988** *181*, 67−76. (b) Kiely, D. E.; Fletcher, H. G., Jr. *J. Org. Chem.* **1969**, *34*, 1386. (c) Helferich, B.; Bigelow, N. M. *Z. Physiol. Chem.* **1931**, 200. (d) Blattner, R.; Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1523. (e) Ferrier, R. J.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1528.

Scheme 5



17 **18** 48%

5-uloses that adopt the bicyclic structure. Isolation of the epoxides and continuing investigation of their synthetic potential is in progress.[26]

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Supporting Information Available: Details of the preparation of **3** and **4**. NMR, IR, $[\alpha]_D$, and HRMS data for **5**, **6**, **13a**−**e**, and **18**. ^{1}H NMR and ^{13}C NMR spectra for **15** and 2D-NOESY spectra for **5**, **6**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) There is evidence (NMR and MS) to support epoxide formation in the reactions. They have not as yet been purified sufficiently for publication purposes.