

# Novel Synthesis of the Glycosidase Inhibitor Deoxymannojirimycin and of a Synthetic Precursor *D*-lyxo-Hexos-5-ulose

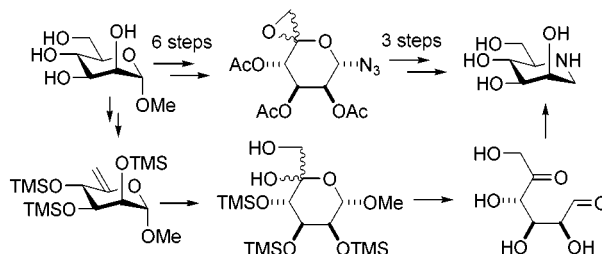
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## ABSTRACT



The synthesis of *D*-lyxo-hexos-5-ulose (5-ketomannose, 1,5-dicarbonyl sugar), a synthetic precursor to the glycoprocessing inhibitor deoxymannojirimycin, was carried out by an in situ epoxidation and hydrolysis of a trimethylsilyl-protected 6-deoxyhex-5-enopyranoside followed by facile removal of the protecting groups. A novel nine-step synthesis of deoxymannojirimycin has also been achieved from methyl  $\alpha$ -*D*-mannopyranoside; this involved methanolysis of epoxides derived from an acetylated 1-azido-6-deoxyhex-5-enopyranoside followed by deprotection and catalytic hydrogenation.

Deoxynojirimycin (**1**) and deoxymannojirimycin (**2**) are natural products that have been isolated from a variety of sources and are among the most promising lead compounds for treatment of HIV infection, diabetes, and other metabolic disorders.<sup>1</sup> These and related compounds have attracted considerable attention from synthetic<sup>2</sup> and medicinal chemists, biologists, and clinical researchers in recent years as a result of their potent inhibition of glycoprotein- and glycolipid-processing enzymes such as glycosidases and glycosyltransferases. *N*-Butyldeoxynojirimycin, for example, currently in clinical trials as a potential therapy for Gaucher disease, is an inhibitor of glucosidase I<sup>3</sup> and ceramide glycosyltransferase.<sup>4</sup> The mechanism of action of these aza-sugars seems to arise from their resemblance with the transition state structure of the glycosidic cleavage or

glycosyltransferase reaction. There is also evidence that the anti-HIV-1 activity displayed by some of these molecules may be due to inhibition by the aza-sugars at novel and as

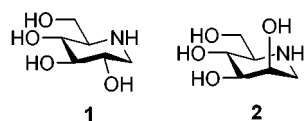
(2) For some recent syntheses of **1** and **2**, see: (a) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 5819. (b) Pistia, G.; Hollingsworth, R. I. *Carbohydr. Res.* **2000**, *328*, 467. (c) Lindström, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173. (d) Asano, K.; Hagoki, T.; Iwama, S.; Katsumura, S. *Chem. Commun.* **1999**, 41. (e) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401. (f) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (g) Schaller, C.; Vogel, P.; Jäger, V. *Carbohydr. Res.* **1998**, *314*, 25. (h) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931. (i) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741. (j) Martín, R.; Moyano, A.; Pericàs, Riera, A. *Org. Lett.* **2000**, *2*, 93. (k) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427.

(3) Schweden, J.; Borgmann, C.; Legler, G.; Bause, E. *Arch. Biochim. Biophys.* **1986**, *248*, 335.

(4) Platt, F. M.; Neises, G. R.; Karlsson, G. B.; Dwek, R. A.; Butters, T. D. *J. Biol. Chem.* **1994**, *269*, 27108.

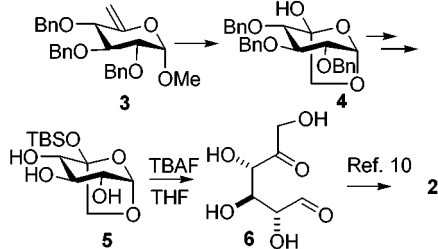
(1) (a) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, 135. (b) Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199 and references therein.

yet undetermined sites of action.<sup>5</sup> Herein we describe a novel route to deoxymannojirimycin and a new synthesis of one of its precursors, *D*-lyxo-hexos-5-ulose.



We have been interested in establishing a synthesis of multigram quantities of deoxymannojirimycin **2** as a starting material for preparing analogues for biological evaluation. 1,5-Dicarbonylsugars,<sup>6–8</sup> such as 5-ketoglucose **6** and 5-ketomannose **10**,<sup>9</sup> can be converted to **1** and **2**, respectively, by double reductive amination reactions as described by Baxter and Reitz.<sup>10</sup> Workers in our laboratory have been studying the synthetic potential of epoxides derived from 6-deoxyhex-5-enopyranosides **3** and found that they are easily hydrolyzed and ultimately give the disguised 1,5-dicarbonyl derivative **4**.<sup>11</sup> Attempts to directly remove the benzyl protecting groups from **4** to give **6**, a precursor to deoxymannojirimycin, were not successful. However, **6** was ultimately prepared after converting **4** to **5** followed by removal of the silyl protecting group (Scheme 1).<sup>11</sup>

Scheme 1



We wanted to reduce the number of protecting group manipulations used in this synthesis of ketosugars and thus investigated epoxidation–hydrolysis of the TMS protected hex-5-enopyranoside **8** with a view to establishing a convenient synthesis of **10**. It seemed reasonable to assume that the ultimate removal of the TMS groups would be more

(5) Asano, N.; Nishida, M.; Kato, A.; Kizu, H.; Matsui, K.; Shimida, Y.; Itoh, T.; Baba, M.; Watson, A. A.; Nash, R. J.; de Q. Lilley, P. M.; Watkin, D. J.; Fleet, G. W. *J. Med. Chem.* **1998**, *41*, 2565.

(6) These compounds have also been postulated as intermediates in inositol biosynthesis; see: (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.

(7) For a proposed biosynthesis of aza-sugars via 5-ketoglucose, see: (c) Hardick, D. J.; Hutchinson, D. W.; Trew, S. J.; Wellington, E. M. H. *Chem. Commun.* **1991**, 729.

(8) 1,5-Dicarbonyl sugars have recently been used for a synthesis of glycosylated deoxymannojirimycin derivatives; see: D'Andrea F.; Catelani, G.; Mariana, M.; Vecchi, B. *Tetrahedron Lett.* **2001**, *42*, 1139.

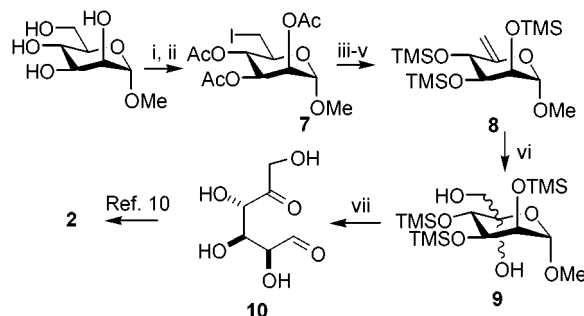
(9) 5-Ketoglucose is also known as *D*-xylo-hexos-5-ulose and 5-ketomannose as *D*-lyxo-hexos-5-ulose.

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

(11) Enright, P. M.; O'Boyle, K. M.; Murphy, P. V. *Org. Lett.* **2000**, *2*, 3929.

straightforward than removal of benzyl groups from **4**. The preparation of **8** was achieved from commercially available methyl  $\alpha$ -*D*-mannopyranoside by exchange of iodine for the hydroxyl group at C-6,<sup>12</sup> acetylation, elimination of hydrogen iodide using DBU in anhydrous toluene, and exchange of the protecting groups from acetate to TMS (Scheme 2, 46% over five steps).

Scheme 2<sup>a</sup>

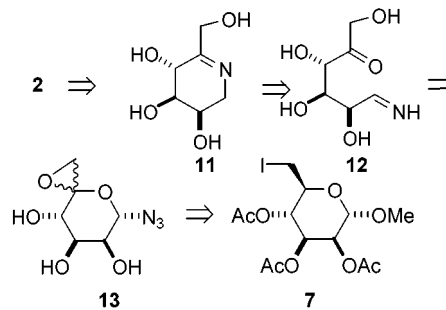


<sup>a</sup> Reagents and conditions: (i) PPh<sub>3</sub>, Im, I<sub>2</sub>, toluene, 110 °C; (ii) Ac<sub>2</sub>O, Py; (iii) DBU, toluene (anhydr), 110 °C, 50% over 3 steps; (iv) NaOMe, MeOH; (v) TMSCl, Py, 93% over two steps; (vi) 1,1,1-trifluoroacetone, Oxone, NaHCO<sub>3</sub>, Na<sub>2</sub>EDTA, CH<sub>3</sub>CN, H<sub>2</sub>O, 1 h, 71%; (vii) MeOH, 94%.

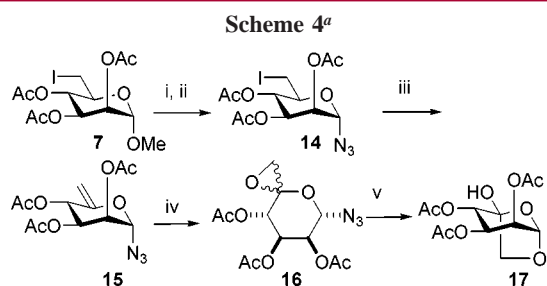
Interestingly, the hemiketal derivative **9** was isolated in 71% yield<sup>13</sup> after treatment of **8** with methyl(trifluoromethyl)-dioxirane generated in situ.<sup>14</sup> The TMS groups can be removed simply from **8** by stirring in methanol, and the desired 1,5-dicarbonyl product **10** can be isolated in good yield (94%) without a need for chromatography.<sup>15</sup>

Baxter and Reitz have previously reported a yield of 29% for conversion of **10** to **2**, using their double reductive amination strategy, suggesting alternative routes to the aza sugar **2** could be explored that might be more efficient in this case. It seemed reasonable that the imine **12** would be generated in situ during catalytic hydrogenation of epoxide **13** (or of a synthetic equivalent) and that further reduction would give **2** via the cyclic imine **11** (Scheme 3).<sup>16</sup>

Scheme 3



Thus we commenced with the synthesis of **15** (Scheme 4). The iodo-derivative **7** can be converted into **14** (83%)

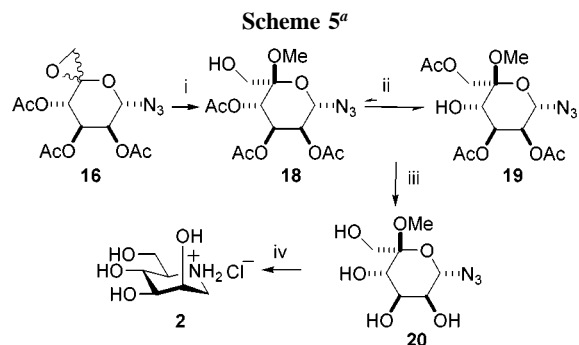


<sup>a</sup> Reagents and conditions: (i) H<sub>2</sub>SO<sub>4</sub> (cat.), Ac<sub>2</sub>O; (ii) TMSN<sub>3</sub>, SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (iii) DBU, toluene, 110 °C, 46% for 5 steps from methyl  $\alpha$ -D-mannopyranoside; (iv) 1,1,1-trifluoroacetone, Oxone, NaHCO<sub>3</sub>, Na<sub>2</sub>EDTA, CH<sub>3</sub>CN, H<sub>2</sub>O, 97%; (v) silica gel chromatography.

by an acetolysis reaction followed by reaction with trimethylsilyl azide catalyzed by tin(IV) chloride in dichloromethane. Elimination of hydrogen iodide was effected as before to give the desired 1-azido-6-deoxyhex-5-enopyranoside **15** in 50% yield. It was possible in this case to isolate a mixture of epoxides **16**<sup>17</sup> from the reaction of **15** with methyl(trifluoromethyl)dioxirane, generated in situ, despite the presence of water in the reaction mixture. However, prolonged reaction time or attempts to separate the epoxides by chromatography lead to formation of the hexos-5-ulose derivative **17**.

We decided to explore the conversion of the epoxides into a more stable intermediate suitable for completion of the synthesis before proceeding further. Thus reaction of **16** with methanol proceeded smoothly to give a single product **18**. Acetate migration occurred from the 4-OH group to the 6-OH group during attempted purification of **18** by chromatography giving **19** (98%). The acetate protecting groups were removed to give **20**.<sup>18</sup> Catalytic hydrogenation of **20** gave deoxymannojirimycin **2**, which can be isolated as the amine or as its hydrochloride salt, which after purification was

obtained in 23% yield.<sup>19</sup> All the analytical data for the salt were identical with that of a sample purchased from Sigma and with literature data reported by Fleet.<sup>20</sup> In summary, we



<sup>a</sup> Reagents and conditions: (i) MeOH; silica gel chromatography; (ii) silica gel chromatography, 98% from **16**; (iii) NaOMe, MeOH; (iv) Pd-C, H<sub>2</sub>, MeOH then HCl, Et<sub>2</sub>O, yield of **20** estimated to be ~60% in crude product, yield is 23% after purification by chromatography.

have developed a new synthesis of 5-ketomannose from TMS-protected 6-deoxyhex-5-enopyranosides; this methodology should be applicable to the synthesis of a range of other 1,5-dicarbonyl derivatives. It has also been shown that epoxides prepared from 1-azido-6-deoxyhex-5-enopyranosides can be used in the synthesis of deoxymannojirimycin. The sequence is being further optimized so that it will be useful for preparation of multigram quantities of the desired product and its derivatives. The efficiency of this route can be compared with the overall yields possible by the Baxter and Reitz method. They used methyl 2,3-di-*O*-isopropylidene- $\alpha$ -D-mannofuranoside as a starting material and converted this to **10** by selective oxidation at C-5 followed by hydrolysis of the isopropylidene group and methyl glycoside in 75% overall yield; Barton and co-workers have more recently described a synthesis of the mannofuranoside in one pot from D-mannose in 83% yield.<sup>21</sup> This route would thus provide **10** in 63% yield over three steps and deoxymannojirimycin in 18% yield over five steps from D-mannose. The routes described herein provides **10** in 31% yield over seven steps and **2** in 9% yield<sup>22</sup> over nine steps. Although the strategy is not yet as potent as that of Baxter and Reitz, there could be advantages in some cases of using 1-azido-6-deoxyhex-5-enopyranosides as intermediates. This may include synthesis of oligosaccharides that incorporate an aza-sugar component or for the synthesis of oligosaccharides incorporating aza-C-disaccharides. The route is thus being

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

(13) Prolonged reaction times lead to depleted yields of product. We had not observed these hemiketals previously from these reactions; see ref 11. Related hemiketals have been observed by other workers; see: Taillefumier, C.; Lakhri, M.; Chapleur, Y. *Synlett* **1999**, 697.

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

(15) The <sup>1</sup>H and <sup>13</sup>C NMR data are identical with those previously reported. These spectra are complex as a result of the presence of a number of interconverting isomers that have been studied in detail previously; see: Kiely, D. E.; Harry-O'Kuru, R. E.; Morris, P. E., Jr.; Morton, D. W.; Riordan, J. M. *J. Carbohydr. Chem.* **1997**, *16*, 1159.

(16) A cyclic imine was first used by Paulsen in a synthesis of **1**; see: Paulsen, H.; Sangster, I.; Heyns, K. *Chem. Ber.* **1967**, *100*, 802.

(17) A 1.4:1 mixture of epoxides was obtained. The oxygen atom of the oxirane ring is believed to be *trans* to the pyranose oxygen in the major stereoisomer; this is based on chemical shift and NOE data.

(18) From analysis of coupling constants in the <sup>1</sup>H NMR spectrum the pyranose ring has a <sup>1</sup>C<sub>4</sub> conformation. Some epimerization of the  $\alpha$ -azide (azide in equatorial orientation) to the  $\beta$ -azide can be observed during prolonged reaction times, which occur if more dilute concentrations of sodium methoxide are used. The epimerization can be avoided by reducing the reaction time by increasing methoxide concentration. See Supplementary Information for details. It appears advantageous to use the pure  $\alpha$ -azide in the final step rather than an  $\alpha/\beta$  mixture as reduction of  $\beta$ -isomer (azide in axial orientation) is much slower.

(19) NMR analysis of the crude product did not indicate that the C-5 epimer was present in the reaction mixture.

(20) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron Lett.* **1989**, *30*, 327.

(21) Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2123-2136.

(22) The yield is given after purification of **2** using chromatography; this requires further optimization as NMR indicates that the major product in the crude reaction mixture is **2**, estimated to be 60%. We are also investigating the possibility of carrying out the final three steps in a single pot.

investigated for its potential in the synthesis of deoxynojirimycin and other important aza-sugars. This work and the biological activity of analogues will be reported in due course.

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**Supporting Information Available:** Descriptions of experimental procedures, analytical and spectroscopic data, and selected  $^1\text{H}$  and  $^{13}\text{C}$  spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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