Tetrahedron Letters, Vol.31, No.47, pp 6777-6780, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PYRROLIDINE AND PIPERIDINE AMINOSUGARS FROM DICARBONYL SUGARS IN ONE STEP. CONCISE SYNTHESIS OF 1-DEOXYNOJIRIMYCIN

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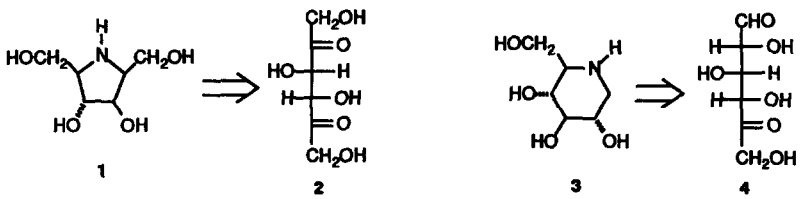
Summary: Dicarbonyl sugars are convenient substrates for the stereoselective synthesis of hydroxylated piperidines and pyrrolidines, via a double reductive amination reaction ($NaCNBH_3$, MeOH). Using this strategy, *2,5-anhydro-imino-D-glucitol* (**1**) and *1-deoxynojirimycin* (**3**) were prepared from 5-keto-D-fructose (**2**, commercially available) and 5-keto-D-glucose (**4**), respectively.

Many polyhydroxylated piperidines and pyrrolidines are powerful inhibitors of glycohydrolases, enzymes responsible for glycoprotein processing and the gastrointestinal breakdown of dietary carbohydrates.[1] These azasugars have potential therapeutic utility in the treatment of various diseases, such as diabetes, cancer, and viral infections.[2-4] Particular attention has focussed on anti-HIV activity in the AIDS area, because the proper functioning of cell-surface glycoproteins on the virus particle is essential for infectivity.[2] Therefore, it is not surprising that the synthesis of polyhydroxylated piperidines and pyrrolidines, such as 1-deoxynojirimycin (**3**),[5] has been the subject of considerable recent research.

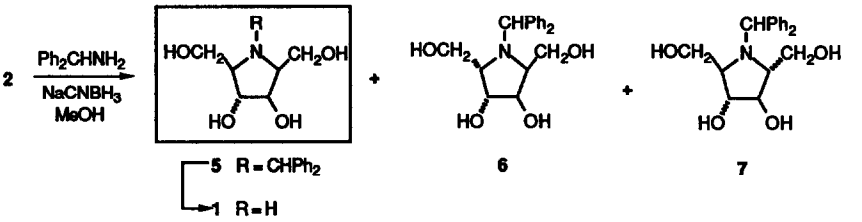
Synthetic routes to azasugars have commonly entailed azide displacement/reduction and N-alkylative cyclization with protecting-group manipulations.[5] In addition, semisynthetic methods employing an enzymatic transformation have proved useful.[5d,f,m,s] We describe here a new approach to the synthesis of polyhydroxylated piperidines and pyrrolidines that hinges on double reductive amination of appropriate dicarbonyl sugars. By this method, we achieved an efficient, stereoselective synthesis of **1** from 5-keto-D-fructose (**2**) and **3** from 5-keto-D-glucose (**4**).



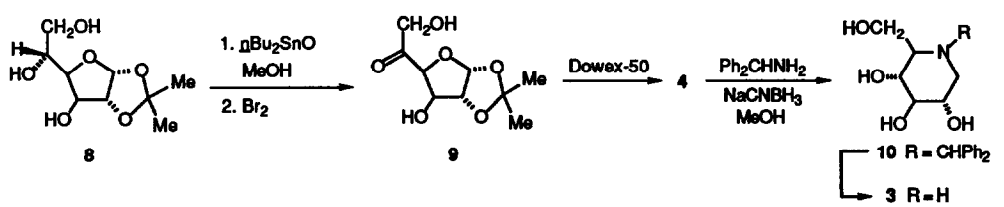
1 2 3 4

Although a variety of dicarbonyl sugars have been described, they still are a somewhat underexplored class of monosaccharides.[6] 5-Keto-D-fructose (**2**) is a commercially available representative, easily prepared by microbial oxidation of D-fructose.[7] Because of its accessibility, we initially investigated the use of **2** as a substrate in a double reductive amination protocol. After extensive experimentation (H_2 with Pd, Pt, or Ra-Ni; borohydrides) we found that **2** readily gives pyrrolidines with a variety of amines by using $NaCNBH_3$ in refluxing methanol.[10] For example, reaction with benzhydrylamine (0.85 mol-equiv) gave a mixture of pyrrolidine stereoisomers (68%),

highly enriched in 2,5-anhydro-imino-D-glucitol (**5**). There are three stereoisomers that can form in the reaction: D-glucitol **5**, L-iditol **6**, and D-mannitol **7**. If reductive amination on both ketones were to proceed stereorandomly, then a 2:1:1 ratio of **5**:**6**:**7** would be observed. Instead, we found an 86:8:6 mixture of **5**:**6**:**7**, from which pure **5** (and **7**) were readily isolated.[11] The significant stereocontrol and the unexpected preference for glucitol isomer **5** can be attributed to a moderate threo/erythro stereoselectivity in the first reductive amination, on an acyclic ketone, followed by high cis stereoselectivity in reduction of the cyclic imine, via assistance by the neighboring ring hydroxyl group.[13] Removal of the benzhydryl group from **5** gave **1** [20% $Pd(OH)_2/C$, H_2; 91%], a new imino sugar which comprises part of the carbon skeleton of the alexine pyrrolizidine alkaloids.[14]

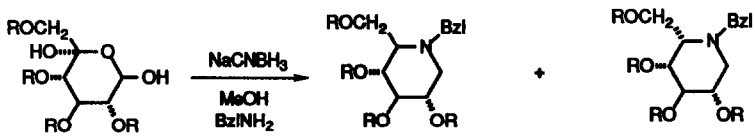


With success in forming the pyrrolidine ring, we sought to extend our method to the synthesis of piperidines, such as 1-deoxynojirimycin (**3**), from 5-keto-D-glucose (**4**).[15] We reasoned that this reaction might even be more stereoselective since the first reductive amination would presumably involve the more reactive aldehyde carbonyl, and the second, stereodetermining reduction of the cyclic imine would be subject to strong stereocontrol (via internal delivery of hydride). Koebernick at Bayer has demonstrated the special stereocontrol available upon reduction of imines with borohydride sources, compared with noble metal hydrogenations.[5f] In his work, an amino sorbose derivative (i.e. the product of the first reductive amination of **4**) reduced with $Me_2NH{\cdot}BH_3$ to give the deoxynojirimycin (glucitol) stereoisomer, with only traces of the other (iditol) reduction product.[5f] Ketoaldose **4** had been described in the literature, but had not been completely characterized or employed as a precursor to azasugars. We improved on the reported synthesis of **4** by combining the highly selective oxidation[16] of readily available **8** to **9** with the deketalization used in the synthesis of **4** by Kiely and Fletcher.[15b,18] Reductive amination of **4** with benzhydrylamine ($NaCNBH_3$, MeOH; 0.8 mol-equiv of amine; 0°C) gave a mixture of 1-deoxynojirimycin derivative **10** and the L-iditol diastereomer in a ratio of 96:4 (74% after chromatography).[19] Deprotection by hydrogenolysis [20% $Pd(OH)_2$, H_2; 90%] followed by ion-exchange on Dowex 50W-X8 resin and recrystallization gave 1-deoxynojirimycin (**3**), identical to the natural product.[20] From **4**, the two-step yield for preparation of **3** is 67%.



We attribute the high stereoselectivity in the formation of **10** to hydroxyl-directed hydride delivery, as in the reaction of **2**. In order to probe this point, we prepared diols **11** and **12**,[21] which are hydrates of acylated **4**, in equilibrium with the unhydrated open-chain forms in $CDCl_3$ (20-30% acyclic form, 400 MHz ^1H NMR).

Reductive aminations with benzylamine, under the same conditions as those employed for **4**, proved much more problematic, as sugars **11** and **12** underwent considerable decomposition even at 0°C. Only under carefully controlled conditions (-78°C, 1 h, gradual warming) were tractable products obtained. Two stereoisomers were isolated in mixtures of 1:1 for **13** and **14**, and 1:2 for **15** and **16**. Not only were these reactions stereorandom, but the combined yields of the products were low (27% for **13/14** and 30% for **15/16**). A similar result was obtained upon reaction of **11** with benzhydrylamine. These experiments clearly establish the special role of the free hydroxyls in **4** (and also in **2**) in facilitating a stereoselective and efficient reductive amination reaction.



11 R = Ac
12 R = Bz

13 R = Ac
15 R = Bz

14 R = Ac
16 R = Bz

Tsuda and colleagues prepared nojirimycin from **9**, but they formed the C-N bond at C5 first (before the C-N bond at C1) by reduction of an oxime derived from **9** with aluminum hydride reagents,[5o] a modification of the original work of Inouye and co-workers.[5b] Reduction of the oxime was not very stereoselective and was dependent on the oxime geometry; there were mixtures of products that were eventually resolved through a chemical process.[5o] These results underscore the advantage of using **4** en route to **3**, presumably because the C1-N bond forms first in reaction of **4**, with the key stereodetermining step being reduction of the subsequent, cyclic imine intermediate.

Our protocol allows for the direct preparation of glycohydrolase inhibitors with a minimum of protecting-group manipulations. Varying the amine component in the reaction provides N-substituted aminosugars directly.[22]

Acknowledgement. We appreciate the advice and encouragement of Dr. Bruce E. Maryanoff.

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11. The benzhydryl group allowed for complete partitioning into $CHCl_3$ during extraction. This gave 64% of a 92:8 mixture of **5** and **6**, and 4% of pure **7**. Homogeneous **5** was obtained by recrystallization of the **5**:**6** mixture (65%). On a large scale, 800 g of crude **5** was obtained after the reaction workup, from which 90 g of pure **5** crystallized out directly. During a preparation starting with 50 g of **2**, over 600 mg of pure **7**[12] was also obtained by chromatography. Isomer assignments were based on ^{13}C NMR spectra; glucitol **5** was easy to identify because it has six unique sugar-derived carbon resonances. ^{13}C NMR data for the aliphatic carbons ($CDCl_3$) for **5**: δ 59.7, 60.7 (C1,6); 61.7, 66.3 (C2,5); 71.2 (C'N); 75.5, 75.7 (C3,4); **6**: δ 58.4 (C1,6); 61.3 (C2,5); 68.7 (C'N); 75.8 (C3,4); **7**: δ 62.4 (C1,6); 68.0 (C2,5); 70.5 (C'N); 80.9 (C3,4). M.p. (corrected): **5**, 152.5-154.5°C ; **7**, 172-179°C (dec.). $[\alpha]_D^{22}$ for **5**: +25.8° (c 1.2, MeOH); **7**: +130.9° (c 0.3, MeOH).
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13. (a) Although **2** is sparingly soluble in MeOH, a ^{13}C NMR in that solvent (100 MHz, 25°C) revealed the presence of 10-20% acyclic form which could be siphoned off as the reaction proceeds. (b) Internal delivery of hydride directed by a proximal hydroxyl group has been seen with $NaBH(OAc)_3$: Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. The use of this reagent in several solvents failed to produce pyrrolidine products upon reaction of **2** with amines.
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18. Spectral properties and analytical data have not been presented for **4** in the literature, with the exception of a passing mention of the ^1H NMR spectrum (footnote 21 in Kiely, D. E.; Talhouk, J. W.; Riordan, J. M.; Gray K. *J. Carbohydr. Chem.* **1983**, *2*, 427). In agreement with these authors we observed 70-80% of the β-pyranose form in D_2O (400 MHz), along with several other forms interconvertible by mutarotation and ring closing and opening. Compound **4** is stable to storage at 0°C for at least a month.
19. Reversed-phase HPLC was required to properly quantitate the glucitol:iditol ratio in this reaction. This reaction has been carried out on a multi-gram scale.
20. The 400-MHz ^1H NMR and melting point of our sample of **3** was identical to that of an authentic sample (Sigma Chemical Company). The ion exchange treatment was required to make the chemical shifts in the ^1H NMR exactly coincide with those in the natural product, possibly due to a small amount of palladium complexation with **3** in the hydrogenolysis reaction.
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22. The example with benzhydrylamine described in this paper has now been supplemented with a variety of other cases which will be reported in a full account of our work.

(Received in USA 27 August 1990)