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Efficient Synthesis of Seven-Membered Iminocyclitols from Glycosylenamines.

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Abstract. Seven membered iminocyclitols are synthesized in four steps from easily available glycosylenamines (D-*gluco*, D-*galacto*, and D-*manno* configurations) through 1,6-aza-anhydrosugar derivatives. These intermediates are transformed into 2-hydroxy- and 2-unsubstituted azepanes depending on the reactants used for the cleavage of the C1-O bond. The overall yields are high.

The importance of inhibitors of glycosidases and glycosyltransferases as therapeutic agents for viral, proliferative, and metabolic diseases is being increasingly recognized.[1] Among the natural and synthetic inhibitors of these enzymes are the sugar-like alkaloids or iminocyclitols, frequently named "azasugars", a type of sugar derivative in which the endocyclic oxygen atom has been replaced by a nitrogen atom. Thus polyhydroxylated pyrrolidines, such as DMDP,[2] polyhydroxylated piperidines such as 1-deoxynojirimicin,[3] polyhydroxyindolizidines such as castanospermine,[4] the pyrrolizidine alkaloid australine,[5] and the polyhydroxy-nortropane alkaloids calistegines[6] exhibit strong and specific enzyme inhibitory activity, and are useful for treating metabolic disorders such as diabetes,[7] cancer,[8] and AIDS.[9] As a consequence of this pharmaceutical interest, in the last few years many efforts have been directed to the synthesis of these five-[10] and six-membered[2,11] iminocyclitols; however little attention has been given to the synthesis of the seven-membered ring analogs, the polyhydroxyazepanes, in spite of some bibliographic data indicating that these iminocyclitols are potent inhibitors of glycosidases[12], and some exhibit even higher inhibition potencies than the five- and six-membered counterparts. These seven-membered rings are conformationally more flexible than the five- and six-membered analogs, and hence may adopt a quasi-flattened conformation, which could lead to a favourable binding in the enzyme active site. Regarding the synthesis of polyhydroxyazepanes only a few chemical and chemoenzymatic methods have been described.[2,12] When studying the 1,4-enamino rearrangements of glycosylenamines, we observed[13] that the *N*-diethoxycarbonylvinyl per-*O*-mesylglucosylamine, under basic treatment, rearranges quantitatively to an *N*-protected 1,6-aza-anhydroglucose derivative. In this communication we use 1,6-aza-anhydrosugars (D-*gluco*, D-*galacto*, and D-*manno* configurations) for the synthesis of two types of polyhydroxyazepane (Scheme 1).

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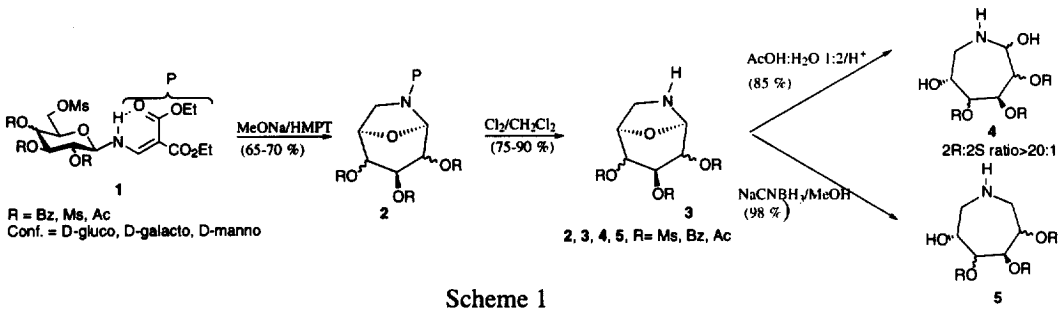
The starting 6-*O*-mesyl derivatives **1** were prepared (80-85% yield) from *N*-diethoxycarbonylvinyl-D-gluco(galacto, manno)pyranosylamines[14] by either per-*O*-mesylation with mesyl chloride or through conventional strategies[15] of partial acylation of the hydroxyl groups (HO-2, 3, and 4) and 6-*O*-mesylation.[16]

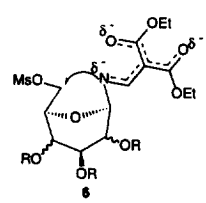


Scheme 1

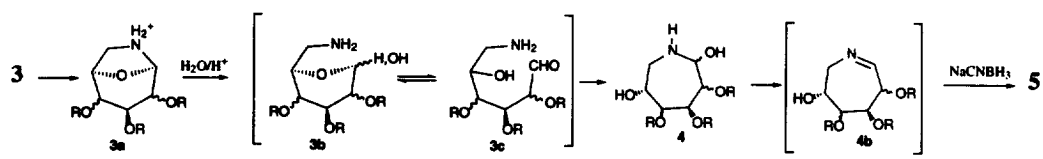
The treatment of **1** with one equivalent of sodium methoxide in HMPT gave the 1,6-aza-anhydrosugars **2** in good yield. These bicyclic sugar derivatives were crystalline compounds whose analytical and spectroscopic data (IR, ^{1}H-, and ^{13}C-NMR) confirmed the proposed structure. Thus, their ^{1}H-NMR spectra had no signals for NH and showed a singlet at 7.56-7.84 ppm for the HC= of the enamino moiety (=CHNR$_2$) instead of the doublet (=CHNHR) of compounds **1**. The signals for H-6 and C-6 were shifted upfield (0.7 and 18 ppm respectively) corresponding to substitution of the sulphonyloxy group by an enamino group.[17]

The formation of compounds **2** takes place through an intermediate amide ion **6** which is formed by attack of the methoxide ion on the NH group and is stabilized by the dialkoxycarbonylvinyl group. The nucleophilic intramolecular displacement of the 6-OMs group produces the aza-anhydrosugars **2**.

N-Deprotection with chlorine in dichloromethane[18] gave (75-95 %) the corresponding aza-anhydrosugar derivatives **3**. Recently, crude per-*O*-acetylaza-anhydrosugars related to **3** have been prepared from glycosyl azides, through glycosylimino phosphoranes, in a multistep sequence. These anhydrosugars were *N*-acylated.



When compounds **3** were left in an acid medium (AcOH: H_2O 1:2, or CH_2Cl_2:H_2O:HCl 20:1:1) for 2 h at room temperature, the hemiaminals **4**, as pairs of diastereomers, were formed (70-80 % yield). Attempts to carry out a similar reaction on compounds **2** were unsuccesful; these



Scheme 2

compounds were resistant to the acid treatment even in boiling methanol for 1 h. A possible mechanism for the formation of **4**, and also of **5**, is depicted in scheme 2. Compound **3** is protonated on the nitrogen atom (**3a**), and then undergoes the nucleophilic attack of water on C1 (sugar ring) to give the 6-amino sugar derivative

3b ⟶ **3c**. Closing the hemiaminal ring produces the azepane **4**. Structures such as **4** have been suggested as intermediates in the transformation of unprotected 6-azidoglycopyranoses into polyhydroxyazepanes.[12a] This mechanism is also supported by the fact that in compounds **2** a similar reaction does not take place, because in this case the enamino nitrogen atom is less basic than the amino group of **3**.

The NMR spectra of **4** showed that one of the pseudoanomers predominates over the other (molar ratio 2:1 to 3:1). According to Cram's rule, the major stereoisomer has the *S* configuration (C-2 of azepane ring) in the D-*gluco* and D-*galacto* (starting sugar) series and the *R* configuration in D-*manno* series. The $J_{2,3}$ values are compatible with both configurations. No mutarotation was observed when solutions of **4** in methanol or chloroform were left for 24 h at room temperature. In the case of **4** (R = Bz),[20] the major pseudoanomer (2*S*) could be crystallized with 95% of diasteromeric excess.

The iminocyclitols **5** were obtained in practically quantitative yield by reaction of **3** with sodium cyanoborohydride in methanol. The H-2 resonances of **5**[21] appeared at 3.2-3.5 ppm, whereas the same signals for **4** were at ≈ 5.7 ppm. Similar differences were observed in the signals for the resonances of C-2 (50.4 ppm for **5** and 91.5 ppm for **4**). The formation of **5** can be explained by participation of an unsaturated compound **4b** (Scheme 2) similar to the intermediate invoked in the Pd-mediated reductive amination of 6-azidogalactopyranose.[12a]

Attempts at deacylation of **5** (R=Bz) in basic medium were successful, whereas in the case of the mesyloxy derivatives **5** (R = Ms), competition between deacylation and elimination was observed, especially in the case of products coming from D-*manno* derivatives.

In conclusion, a new, short, experimentally easy, and high-yielding method for the syntheses of two types of chiral polyhydroxyazepane from glycosylenamines is reported. The chirality is defined by the configuration of the sugar. The dialkoxycarbonylvinyl group is used to protect the amino function and to stabilize the intermediate anion **6**.

The scope of the method is currently being studied in our laboratory.

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16. All new compounds had satisfactory analytical and spectroscopic (^{1}H- and ^{13}C- NMR) data.
17. *Selected data* for 1,6-anhydro-2,3,4-tri-*O*-benzoyl-*N*-(2,2-diethoxycarbonylvinyl)-β-D-glucopyranosylamine (**2**, R= Bz) as example. Mp 166-168 °C; $[\alpha]_D^{26}$ -69° (*c* 1.0 dichloromethane); IR ν_{max} 2961, 1717, 1699, 1602, 1364, 1262, 1088, 1026, 710 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.17-7.27 (m, 15 H, 3 Ph), 7.84 (s, 1 H, HC=), 5.65 (bs, 1 H, H-1), 5.54 (b signal, 1 H, $J_{3,4}$ =0.3, H-3), 5.14 (bd, 1 H, $J_{2,3}$ =1.3, H-2), 5.08 (b signal, 1 H, $J_{4,5}$ =0.3, H-4), 4.99 (bd, 1 H, $J_{5,6b}$ =6.4, H-5), 4.31-4.18 (m, 4 H, 2 CH_2CH_3), 3.82 (d, 1 H, $J_{6a,6b}$ =10.9, H-6a), 3.70 (dd, 1 H, H-6b), 1.33-1.26 (m, 6 H, 2 CH_2CH_3); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 166.4, 166.2, 165.1, 165.0, 164.5 (5 CO), 144.6 (HC=), 133.7-127.8 (18 C, 3 Ph), 97.8 (=C), 89.4 (C-1), 75.7 (C-5), 69.6 (C-4), 68.8 (2 C, C-2, C-3), 60.9, 60.3 (2 CH_2CH_3), 48.1 (C-6), 14.3, 14.1 (2 CH_2CH_3).
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20. Selected data for 2*S*,3*R*,4*S*,5*R*,6*R*-3,4,5-tribenzoyloxy-2,6-dihydroxyazepane (**4**, R = Bz) ^{1}H-NMR (500 MHz, CD_3OD) δ 7.96-7.30 (m, 15 H, 3 Ph), 6.21 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ =10.0, H-4), 5.68 (d, 1 H, $J_{2,3}$=3.5, H-2), 5.46 (t, 1 H, $J_{5,6}$ =10.0, H-5), 5.32 (dd, 1 H, H-3), 4.58 (m, 1 H, H-6), 3.34-3.19 (m, 2 H, H-7a, H-7b); ^{13}C-NMR (125.7 MHz, CD_3OD) δ 167.4, 167.3, 167.1 (3 CO), 135.1-129.6 (18 C, 3 Ph), 91.5 (C-2), 73.5 (C-3), 72.2 (C-5), 71.3 (C-4), 67.1 (C-6), 41.6 (C-7).
21. 3*S*,4*R*,5*R*,6*R*-3,4,5-tribenzoyloxy-6-hydroxyazepane (**5**, R = Bz) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.03-7.19 (m, 15 H, 3 Ph), 6.29 (dd, 1 H, $J_{3,4}$ =6.5, $J_{4,5}$ =9.6, H-4), 5.62 (dd, 1 H, $J_{5,6}$=1.1, H-5), 5.47 (m, 1 H, H-3), 4.30 (m, 1 H, H-6), 3.51 (dd, 1 H, $J_{2a,2b}$ =15.0, $J_{2a,3}$ =4.1, H-2a), 3.36 (dd, 1 H, $J_{6,7a}$ =4.1, $J_{7a,7b}$ =14.1, H-7a), 3.24 (dd, 1 H, $J_{2b,3}$ =3.8, H-2b), 3.08 (dd, 1 H, $J_{6,7b}$ =2.4, H-7b), 2.71 (bs, 1 H, OH); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 165.7 (CO), 165.6 (2 CO), 133.3-125.2 (18 C, 3 Ph), 75.0 (C-3), 74.7 (C-5), 72.0 (C-4), 70.6 (C-6), 52.9 (C-7), 50.4 (C-2).