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Syntheses of new azepane derivatives from monosaccharides

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ABSTRACT.-

Synthetic routes to polyhydroxy azepanes from monosaccharides are described. The stereoselective formation of *trans* epoxyamides and regioselective epoxyde opening led to azido derivatives that could be transformed in azepanic structures. An anomalous result was obtained in the hydrogenation in MeOH with Pd/C of the azido derivative obtained from D-mannose.

INTRODUCTION.-

Iminosugars have received considerable attention in carbohydrates and non-carbohydrates research groups because of their remarkable biological activities.

In recent years, new iminosugars with structures of **polyhydroxyazepane** have proved their utility as glycosidases inhibitors and as potential therapeutic agents.[1] These compounds have been also named **polyhydroxyperhydroazepines** or **seven-membered iminocyclitols**.

We are interested in obtaining those structures that contain an hydroxymethyl arm, (Fig. 1) because they mimic better the sugar structures. We have planned diverse syntheses starting from 2,3-epoxyamides, which are readily obtained from monosaccharides. The methodology to be applied, assumes a completely regioselective epoxide opening with nitrogen nucleophiles. This methodology has been developed by our group in the last years,[2,3,4] and leads to iminocompounds with different ring sizes.

The deprotected derivatives will be tested in order to study their biological activities.

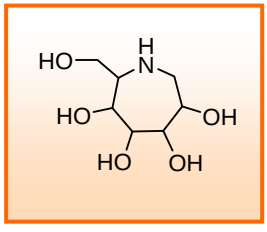


Figure 1

RESULTS AND DISCUSSION

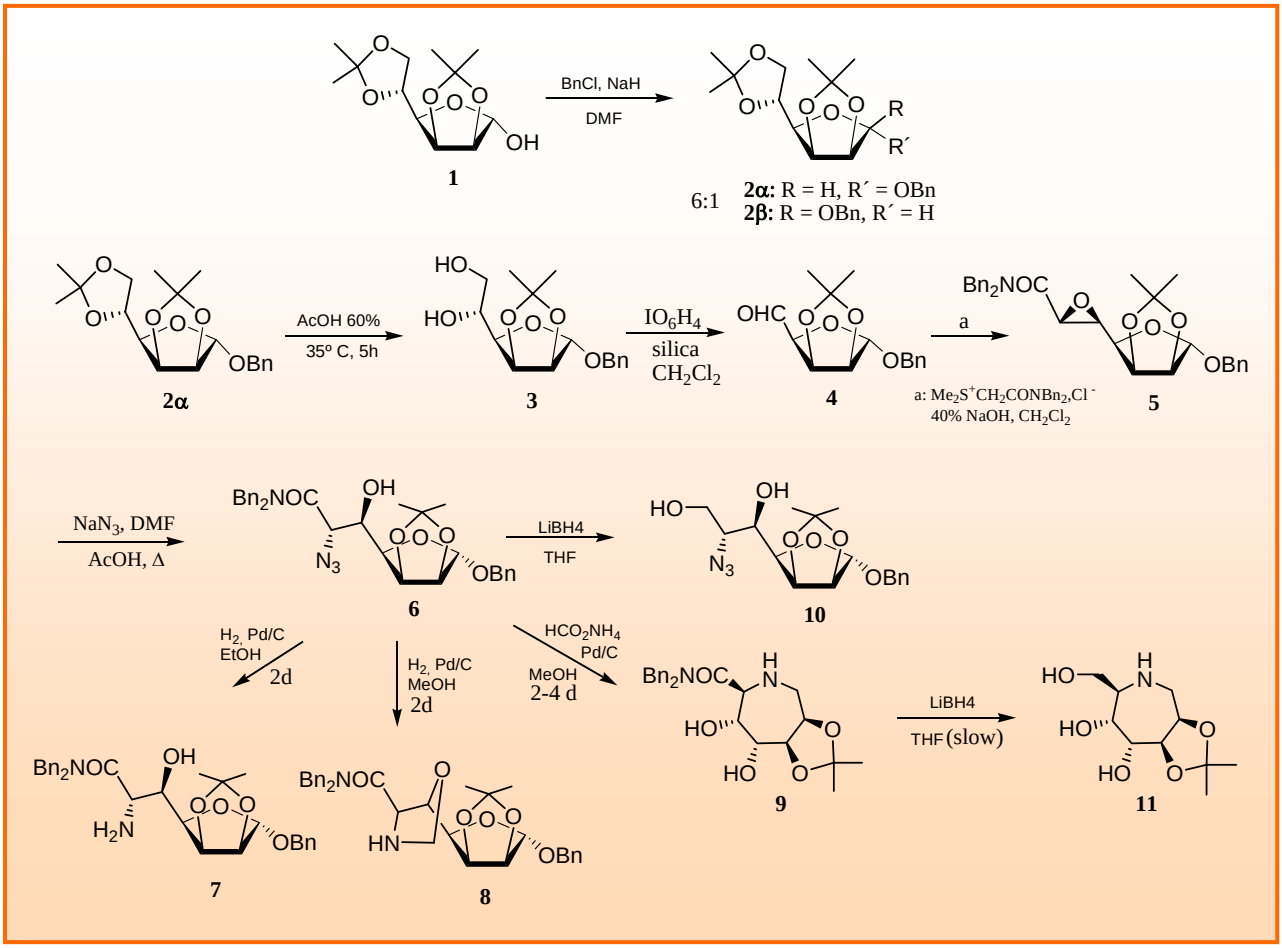
One of the synthetic strategies begins with the known D-mannose derivative **1**[5] (Scheme 1). Anomeric *O*-alkylation with benzyl chloride afforded a mixture 6:1 of benzyl glycosides[6] **2α** and **2β** that were separated by chromatography. The following steps of the synthetic route were accomplished with both isomers, separately. Regioselective deprotection of an isopropylidene group in the major compound **2α** followed by glycol cleavage afforded aldehyde **4**. This compound reacted with the amide-stabilized sulphur ylide, generated *in situ* (two phases media)[7] giving epoxyamide **5** as unique product. Absolute configuration was tentatively assigned by comparison with other epoxyamides previously studied.[8] Epoxide ring opening with NaN_3 gave the azido derivative **6** which was reduced by several methods.

Catalytic hydrogenation of compound **6** in EtOH with Pd/C afforded aminoderivative **7**, surprisingly, when the hydrogenation of **6** was carried out in MeOH with Pd/C, a new product **8**, different from the normal reduction product of azido group **7** was obtained. ^{1}H-NMR, ^{13}C-NMR (Fig. 2 and 3), and HRMS were concordant with the proposal structures. The insertion of methylene in a catalytic reduction is difficult to explain, and to our knowledge, there are not similar results in the literature. However, several examples of anomalous transformations of azides under hydrogenation conditions have been reported.[9] Possibly, the high steric hindrance due to the isopropylidene group is responsible for that anormal behaviour. Catalytic hydrogenation of **6** in either EtOH or EtOAc under the same conditions, gave the amine **7.**

The benzyl glycosides were resistant in the hydrogenation conditions. Further reaction time led to mixture of compounds.

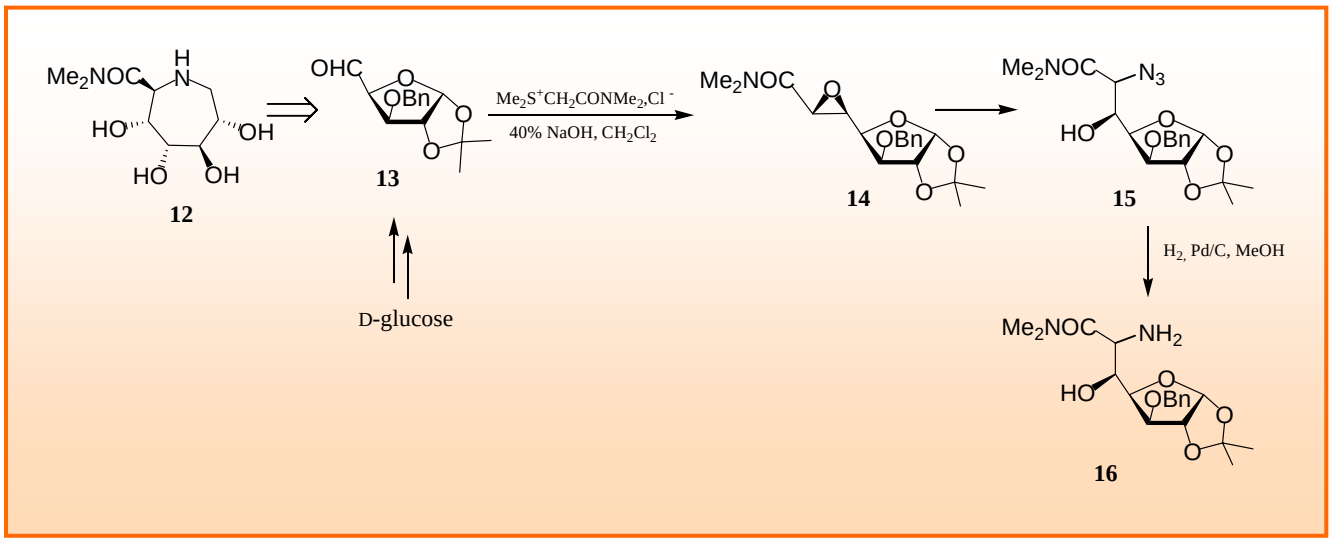
When the reaction was carried out with HCO_2NH_4 and Pd/C, the azepane derivative **9** was obtained in good yield.

Reduction of the amide moiety in **6** and **9** was accomplished with $LiBH_4$. This reduction was faster for the tetrahydrofuran derivative **6** than for the azepane **9**, giving the primary alcohols moieties in compounds **10** or **11**, respectively.



Scheme 1. Synthesis of Azepanes from D-mannose.

In order to obtain azepane rings with a different configuration **12**, we chose aldehyde **13**[10] that was obtained from D-glucose. In a similar way epoxyamide **14** was also obtained with complete stereoselectivity and the azido group was regioselectively introduced by reaction with NaN_3 in DMF. Catalytic hydrogenation of this group in **15**, using MeOH as solvent did not give the methylene insertion product. The normal reduction product, amine **16**, was obtained. Functional group transformations in **16** will permit us to obtain the azepane **12**. (Scheme 2)



Scheme 2. Synthesis from D-glucose.

In conclusion, the stereoselective formation of epoxyamides from monosaccharide derivatives, permitted us the formation of azepane rings with different configurations. The formiate method, for azide and benzyl glycoside reductions, showed to be more efficient than the use of H_2, giving properly the azepane ring. The anomalous result obtained in the catalytic hydrogenation of the compound **6** (from D-mannose), can be attributed to their steric hindrance, since the azido compound **15** from D-gluco gave the normal reduction product.

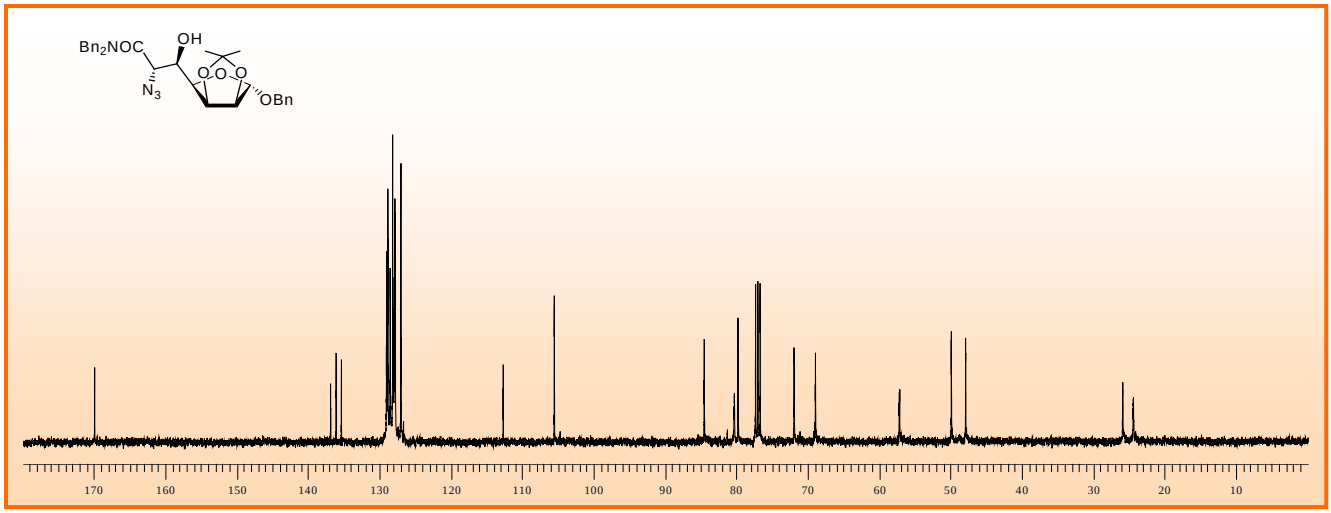


Fig 2. ^{13}C-NMR spectra ($CDCl_3$, 100 MHz) of compound **6**.

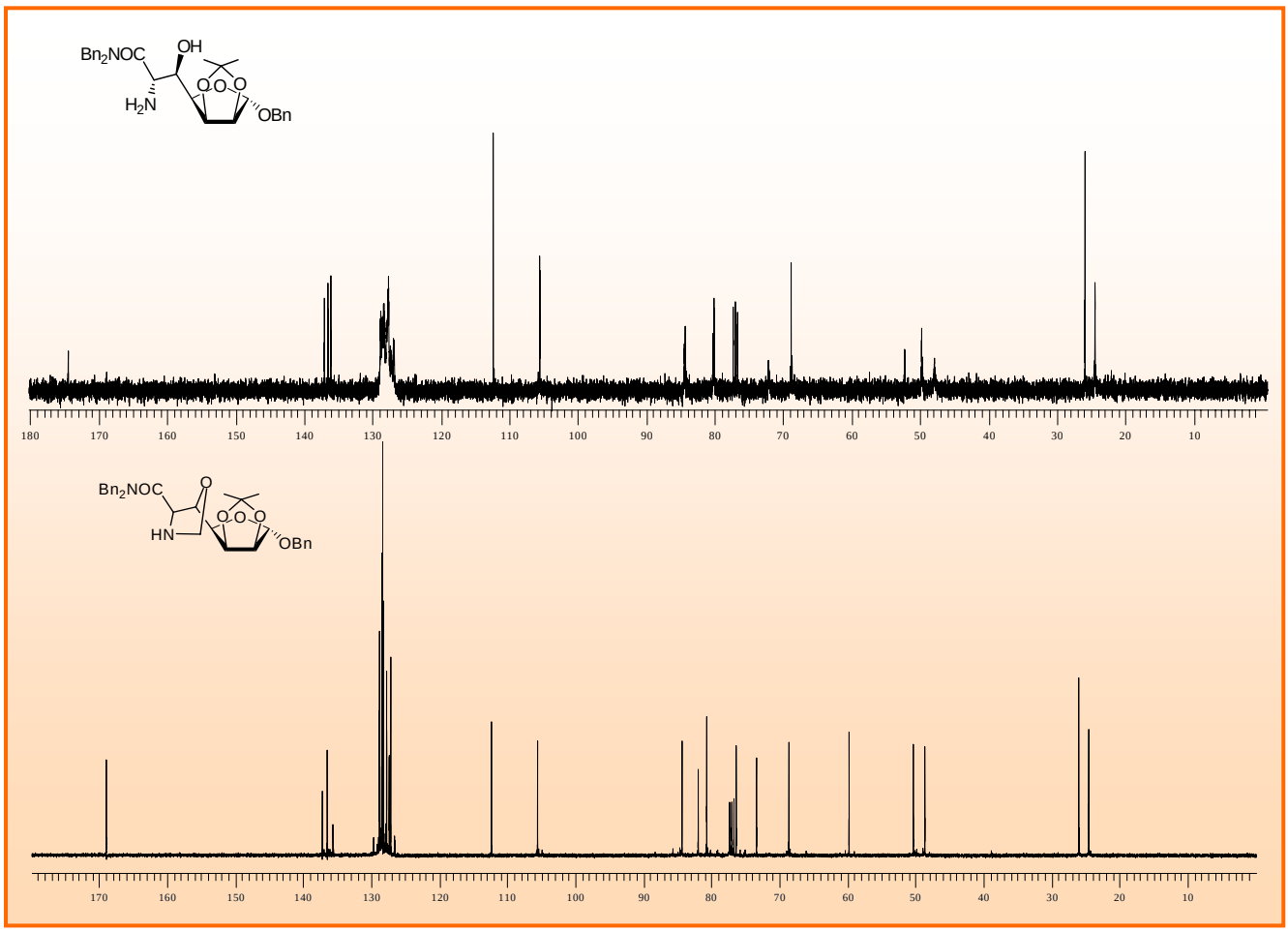


Fig 3. ^{13}C-NMR spectra ($CDCl_3$, 100 MHz) of compounds **7** and **8**.

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