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[A0029]

Reductions of Monosaccharide Derivative Epoxyamides to Epoxyalcohols and Regioselective Epoxide Opening

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ABSTRACT.-

Amide group reduction in monosaccharide derivative 2,3-epoxyamides were accomplished with a combination of two reagents: RedAl and $NaBH_4$, successively added at 0ºC, without affecting the epoxide group. The obtained epoxyalcohols could be regioselectively opened at the vicinal carbon to the hydroxymethyl group, by NaN_3/Me_3B without detection of another azido isomer.

INTRODUCTION.-

Our group has developed a methodology for the syntheses of **Iminoalditols** with different ring sizes. These syntheses start with epoxyamides obtained from carbohydrates and sulphur ylides.[1] The stability of amide function is good to support the diverse transformations needed in the molecules before their cyclisation to the imino derivative. In previous reports, we opened the epoxide group without reducing the amide, which was usually reduced after the conversion in the corresponding cyclic imino compound, or in the previous step to the cyclisation. Now, we are checking methods to reduce the amide before epoxide opening.

We are currently interested in **polyhydroxyazepanes** formation, because it has been proved their utility as glycosidases inhibitors and as potential therapeutic agents.[2,3]

Among the more interesting polyhydroxyazepanes, we have chosen as targets, those compounds that contain an hydroxymethyl arm, because they mimic better the sugar structures. In addition, we have planned the formation of amino derivatives. (Fig. 1)

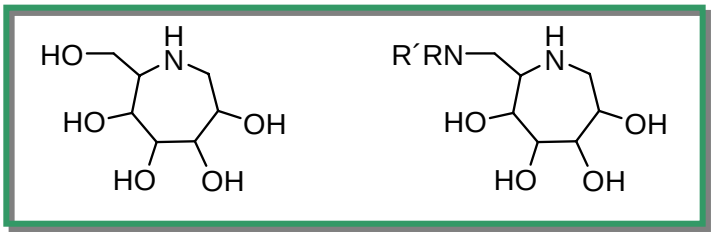
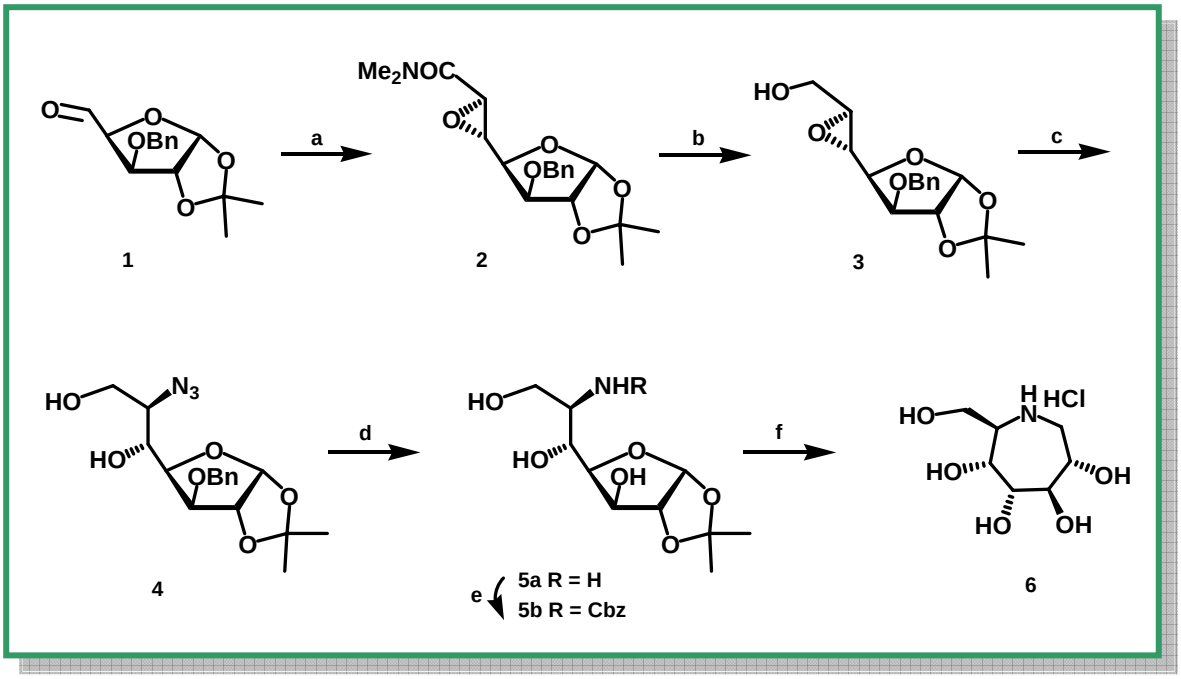


Figure 1

RESULTS AND DISCUSSION

The first synthetic scheme begins with the known D-glucose derivative **1**[4] (Scheme 1). This aldehyde reacted with the generated *in situ* sulphur ylide ($Me_2SCHCONMe_2$) to afford stereoselectively the epoxyamide **2**. Its absolute configuration was first tentatively assigned by comparison with other epoxyamides previously studied,[5] and later confirmed with the ^{1}H-NMR data of the epoxyalcohol **3**, previously synthesised by other method.[6] Epoxyamide **2** could be reduced with a previous treatment with RedAl at 0ºC in THF, followed by addition of sodium borohydride in MeOH at the same temperature.[7] This combined reduction gave the epoxialcohol **3** in 64% yield (two steps). No epoxide opening product was detected. Regioselective epoxide opening was accomplished when the epoxyalcohol was treated with NaN_3 and Me_3B, in DMF as solvent at 70ºC, for 2 d,[8] giving the azido diol **4** in high yield (97%). This azido derivative was transformed in the protected amine **5b** which can be transformed in the azepane **6** with Dhavale´s method.[9]

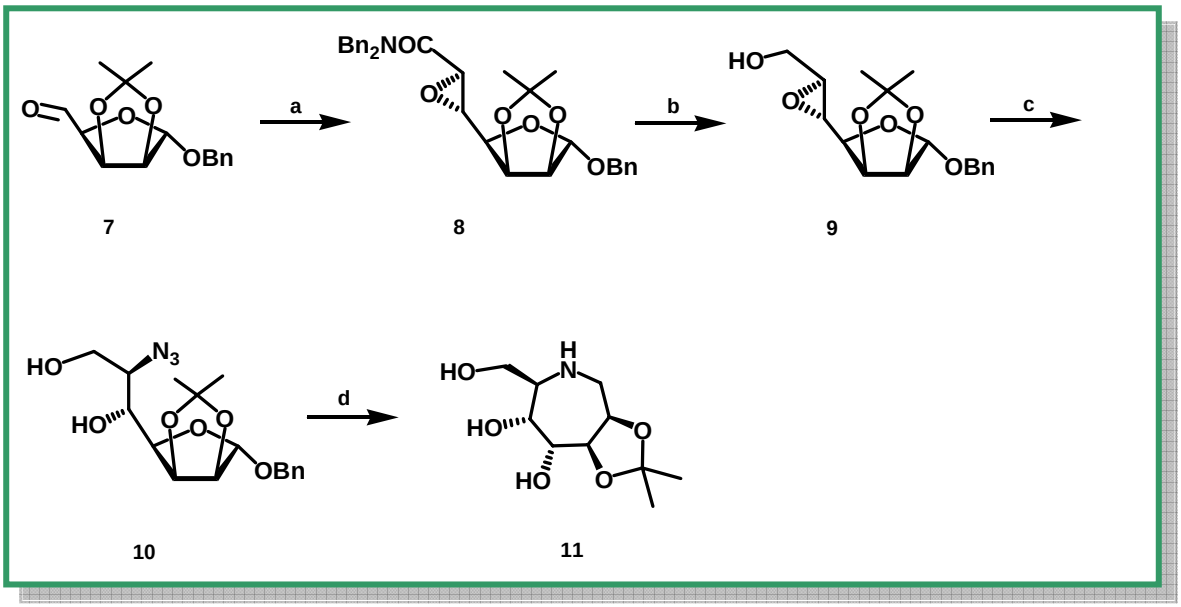


Scheme 1: Synthetic scheme with glucose derivatives.

Reagents and conditions: a) $Me_2S^+CH_2CONBn_2,Cl^-$, 40% aq. NaOH, CH_2Cl_2; b) 1. RedAl, THF, 0ºC, 2. $NaBH_4$, MeOH, 0ºC; c) NaN_3, Me_3B, DMF, 70ºC, 48h; d) NH_4HCOO, Pd/C, MeOH, Δ; e) CBzCl, MeOH:H_2O (9:1), 0 to 25 °C, f) H_2, Pd/C, MeOH:HCl (9:1), 80 psi, 24 h.[9]

In a similar fashion, the known D-mannose derivative **7,** prepared by partial hydrolysis from the di-O-isopropylidene derivative[10] followed by periodic oxidation,[4] reacted with the generated *in situ* sulphur ylide ($Me_2SCHCONBn_2$) to afford stereoselectively the epoxyamide

8. Reduction of compound **8,** in the same conditions as for the glucose derivative, with RedAl and sodium borohydride, gave the epoxyalcohol **9** but with better yield (80%, two steps). When we employed lithium borohydride as reductor, in THF, the epoxyalcohol **9** was also obtained but with a minor amount of reduced epoxide. Compound **9** was regioselectively opened with NaN_3 and Me_3B giving the azido diol **10** in 82% yield. The catalytic transfer hydrogenation of azido diol **10** with NH_4HCO_2 and Pd/C in MeOH under reflux gave directly, after 2 d, the desired azepane derivative **11** in near quantitative yield (99%).



Scheme 2: Synthetic scheme with mannose derivatives.

Reagents and conditions: a) $Me_2S^+CH_2CONBn_2,Cl^-$, 40% aq. NaOH, CH_2Cl_2; b) 1. RedAl, THF, 0ºC, 2. $NaBH_4$, MeOH, 0ºC; c) NaN_3, Me_3B, DMF, 70ºC, 48h; d) NH_4HCOO, Pd/C, MeOH, Δ.

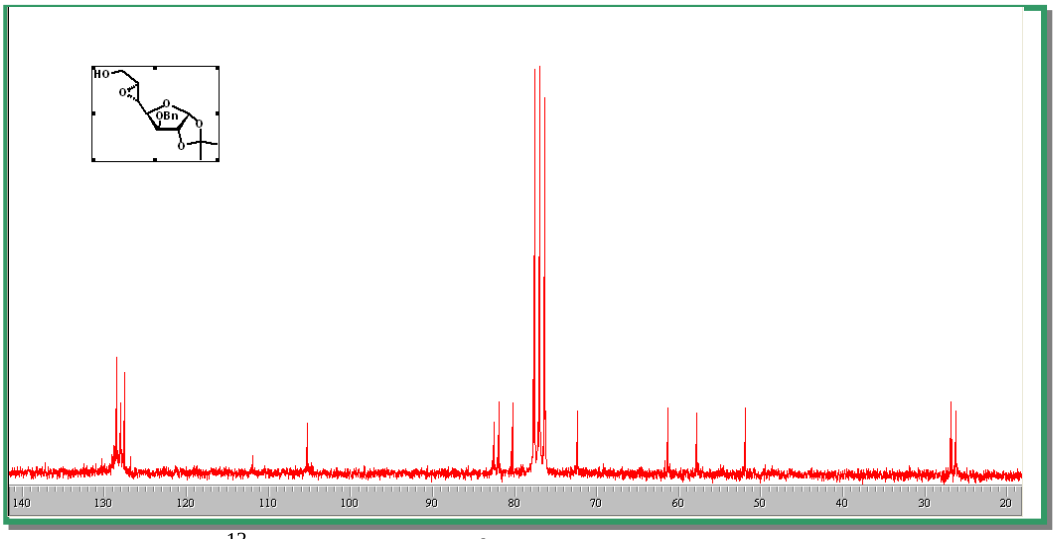


Figure 2. ^{13}C-NMR spectra of compound **3**.

In conclusion, the combination of reductors RedAl and $NaBH_4$ has been shown to be a good choice to obtain epoxyalcohols from carbohydrate derivative epoxyamides. On the other hand, the obtained epoxyalcohols could be regioselectively opened with NaN_3/Me_3B, obtaining an unique azido-isomer.

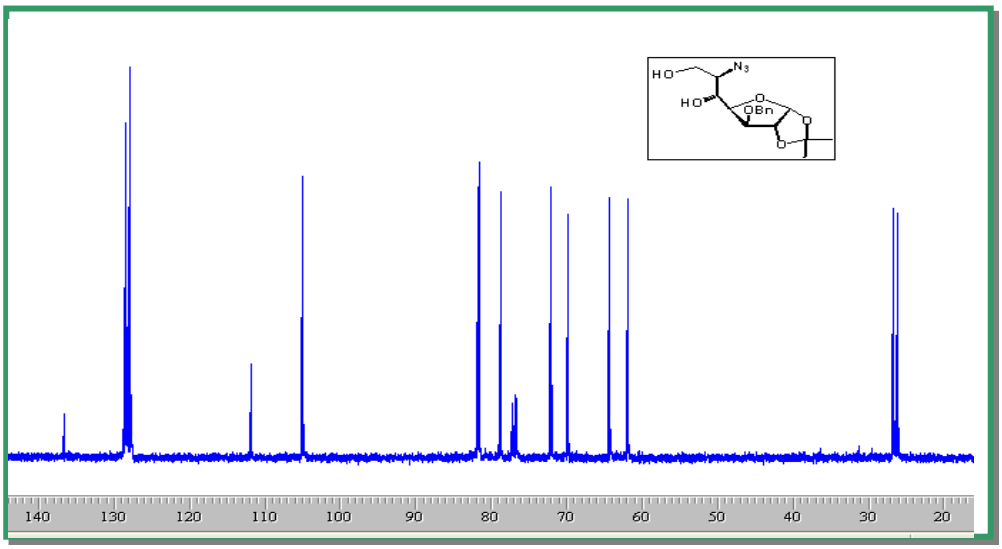


Figure 3. ^{13}C-NMR spectra of compound **4**.

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