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Studies on Inversion of Configuration in the Synthesis of Iminosugars

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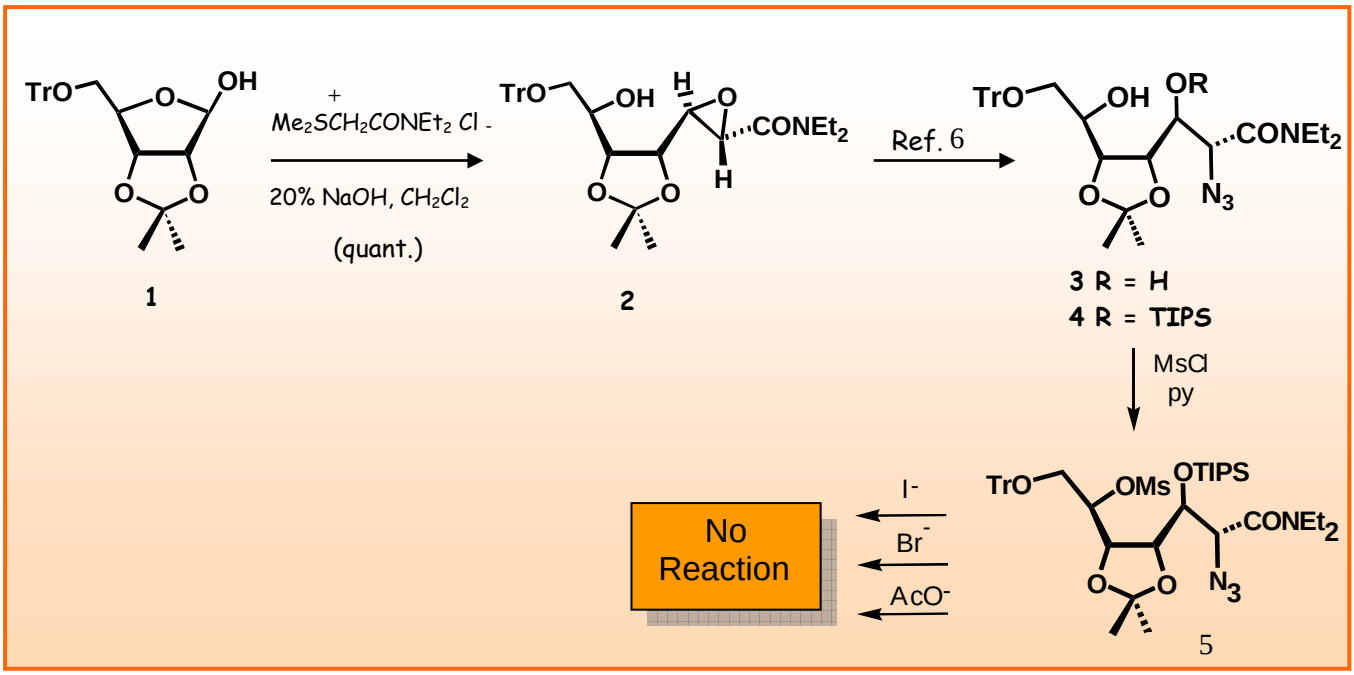
[A037]

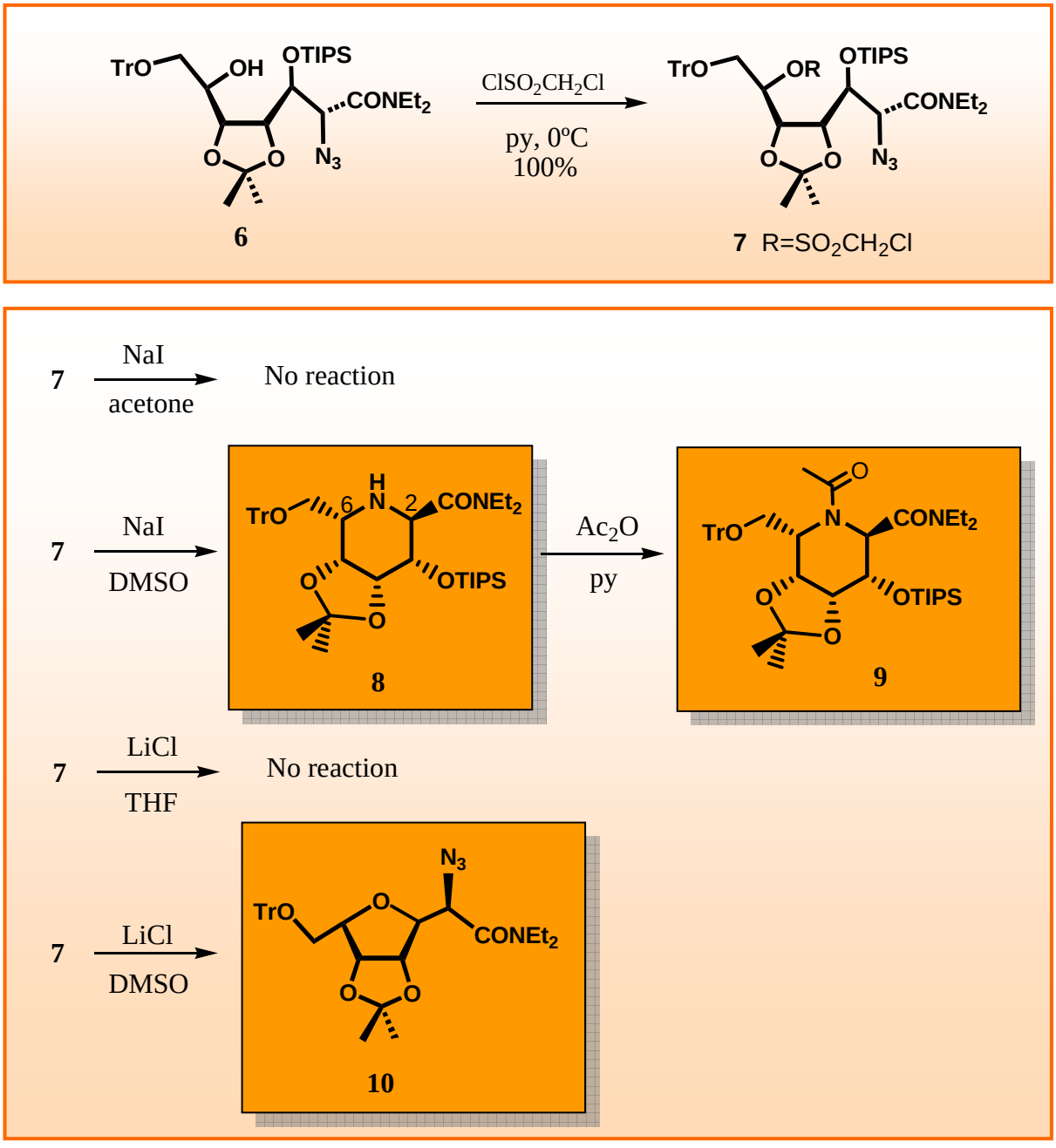
Iminosugars[1] are arousing great interest as potential therapeutic agents against HIV infection,[2] cancer,[3] diabetes[4] and other genetic or metabolic disorders.[5] In previous papers[6,7,8] we described a methodology to synthesize iminosugar derivatives with different ring sizes starting from a ribose derivative, which afforded an unique epoxyamide. The stereoselective synthesis of 2,3-epoxyamides by reaction of monosaccharides, properly functionalized, with stabilized sulfonium ylides, have been performed by our group in the last years.[9] These systems with a high degree of functionality represent new, readily available, optically active building blocks for using in synthesis.

In order to obtain iminosugars with D-configuration, we planned to change the configuration at C-6 in **3**, obtained by regioselective epoxide opening of **2**. Firstly, we had to protect selectively the hydroxyl group at C-3. The best results were obtained with TIPSOTf (triisopropyl silyl triflate) and lutidine giving **4** as the principal isomer.[6] The C-6 hydroxyl group was mesylated, giving **5**, but unfortunately could not be displaced by nucleophiles as Br^-, I^-, or AcO^-.



Different and interesting results were achieved with the chloromesylate derivative **7**, as it is depicted in the next scheme. Compound **7** was easily obtained in 45 mn and isolated after usual work-up without need of further purification. NMR data confirmed its structure.

Formation and reactivity of chloromesylate derivative 7



Several reactions were performed treating **7** with different nucleophiles, obtaining the following results:

1- NaI in acetone: After 48 h at room temperature, the starting material was recovered.

2- NaI in DMSO: After 48 h at room temperature, a new, more polar product was observed **8**, which was isolated and purified by column chromatography (75% yield). Spectroscopic data permitted us to elucidate the structure of **8**, with the formation of a pyrimidine ring. The last scheme shows the two proposed steps in the formation of **8**:

   i- Iodide causes azido group reduction to the amine.

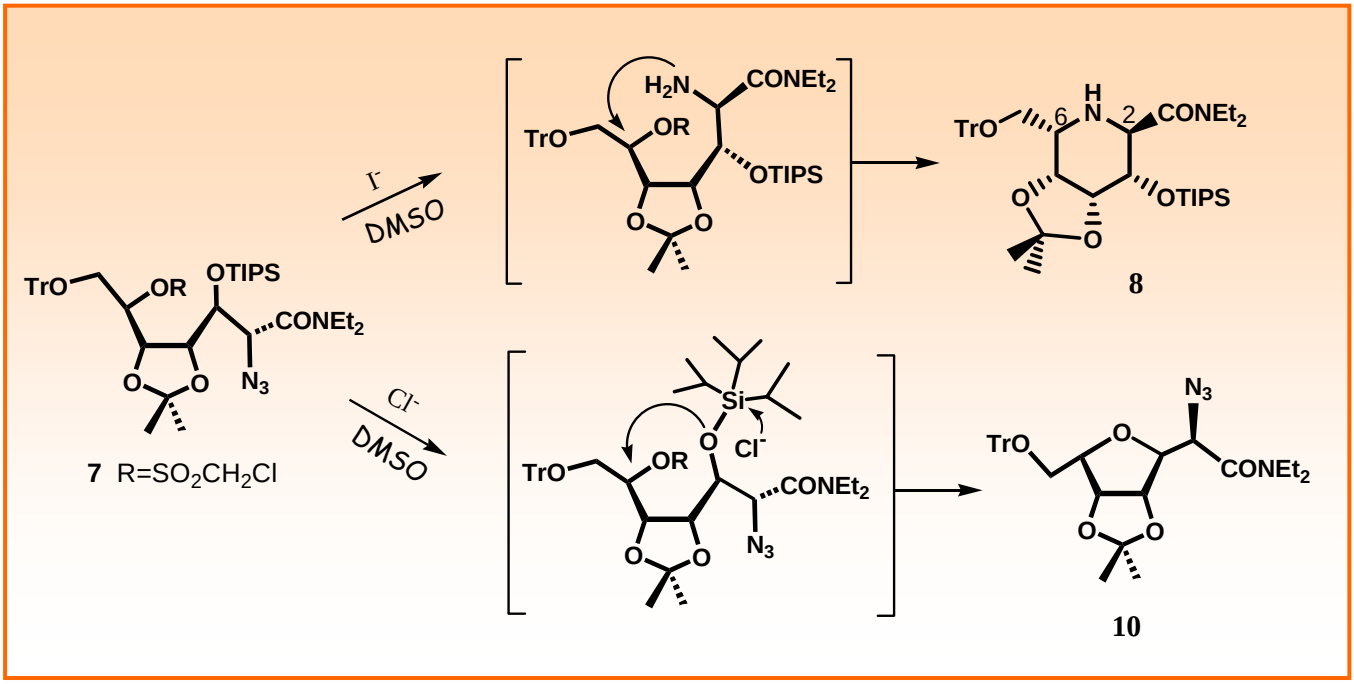
   ii- Once the amine has been formed, displaces the chloromesylate group giving the iminosugar but with L-configuration.

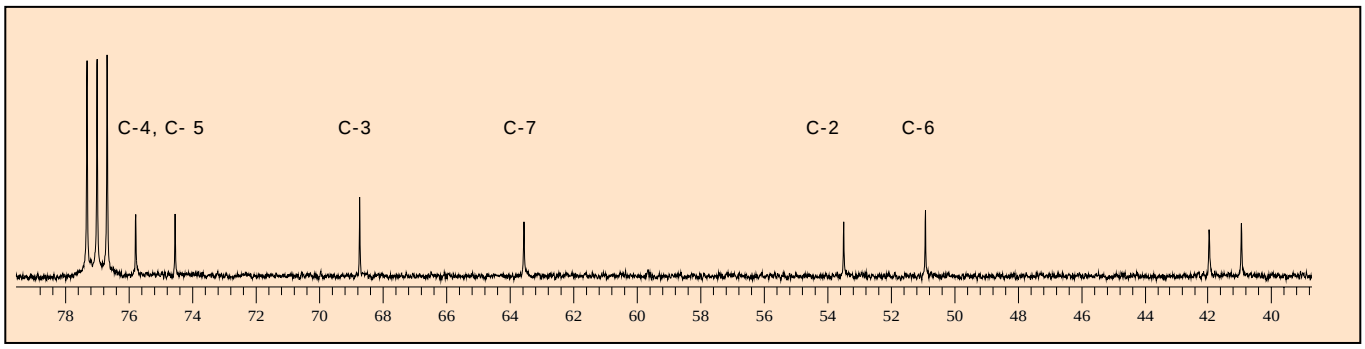
   Acetylation of **8** confirmed its structure.

3- LiCl in THF: The starting material was recovered.

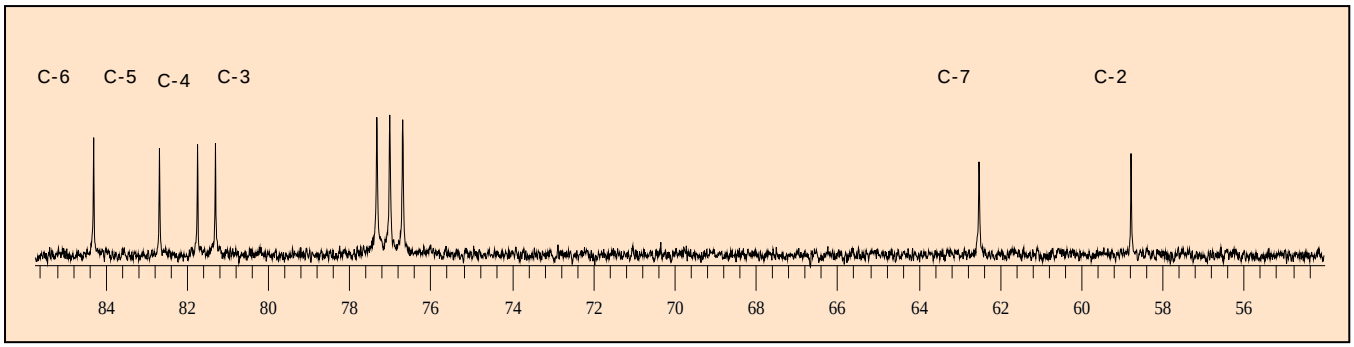
4- LiCl in DMSO: After 30 h at room temperature, a new, more polar product was observed (**10**), which was isolated and purified by column chromatography. NMR data showed the disappearance of the silyl group and the formation of a furanose ring.

Formation of compounds 8 and 10





^{13}C-NMR ($CDCl_3$, 100 MHz) of compound ***8***



^{13}C-NMR ($CDCl_3$, 100 MHz) of compound ***10***

These results confirmed us the importance of the solvent in these displacements, it being DMSO the solvent that permits a better reactivity. The failed attempts of direct substitution on C-6 can be due to the large steric hindrance of the trityl group.

Acknowledgments

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