280: Synthesis of Phosphono and Phosphate Derivatives of Hydroxyimino-D-alditols as New Potential Antifungal Agents

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In search for new effective antifungals we focus on two enzymes involved in biosynthesis of the fungal cell wall. The first enzyme is glucosamine-6-phosphate synthase (GlmS), which catalyzes transformation of D-fructose-6-phosphate (Fru-6P) to D-glucosamine-6-phosphate (GlcN-6P) in the chitin biosynthesis pathway. The second enzyme is phosphomannose isomerase (PMI) reported to play a crucial role in biosynthesis of many mannosylated structures, including cell wall components of fungi. PMI is aldose-ketose isomerase and catalyzes reversible isomerization of D-manno-6-phosphate (Man-6P) to D-fructose-6-phosphate (Fru-6P). Both enzymes are proposed as the targets for antifungal chemotherapy and a search for their selective inhibitors is continued.

Mechanisms of the reactions catalyzed by both enzymes are known and similar. The reaction performed by GlmS is believed to proceed through the formation of an imine intermediate **1**, whereas the reaction catalyzed by PMI proceeds *via* a *cis*-endiol intermediate **2** (Fig.1).

In search of mimetics of intermediates **1** and **2** we synthesize phosphono and phosphate derivatives of the hydroxyimino-D-glucitols ($\mathbf{3_{a\text{-}c}}$–$\mathbf{6_{a\text{-}c}}$). Similarity in the structures of the planed compounds to intermediates **1** and **2** allow us to assume that they can be the potential inhibitors of the both enzymes. Dimethyl and diethyl ester analogs ($\mathbf{3_{b,c}}$–$\mathbf{6_{b,c}}$) will have more lipophilic character, which make them easier to penetrate through the cytoplasmic cell membrane. It was proved that similar esters are hydrolyzed inside a cell. Here, the completed stages of our syntheses are presented.

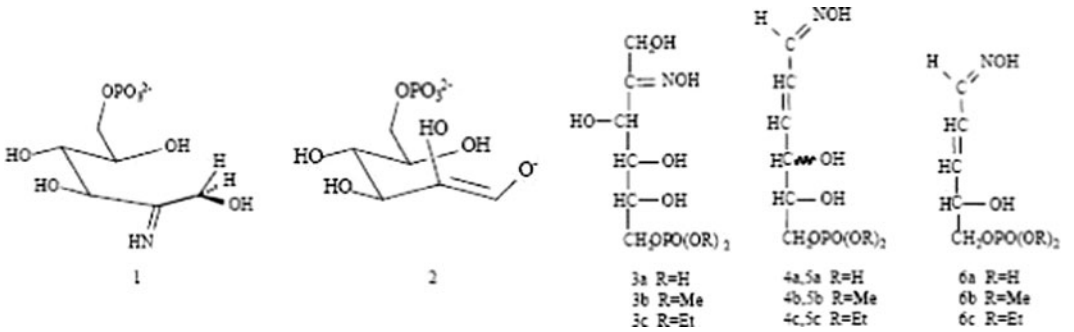

Fig.1

281: Convergent Approach to Glycoalkaloids: Syntheses of Solasonine and 25(*R*)-Solanine

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Steriodal glycoalkaloids are rich in Solanaceae family including important agricutural crop plants such as potato, tomato and eggplant. According to the aglycon skeleton, they are classified into two basic types: the spirosolans and solanidans, which contain oxa-azaspirodecane and indolizidine subunit, respectively. The studies have shown that glycoalkaloids display various biological activities such as antitumor, antiheptatoxicity and molluscicide. A cream containing solansodine glycosides mainly composed by solamargine and solasonine has been marketed as "Curaderm" for solar keratosis. So far the syntheses of glycoalkaloids have been sporatically documented. Herein, we take solasonine and 25(*R*)-solanine as a representative of