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### Efficient Stereoselective Synthesis of New C-Nucleosides via Intramolecular Mitsunobu Cyclization

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## EFFICIENT STEREOSELECTIVE SYNTHESIS OF NEW C-NUCLEOSIDES VIA INTRAMOLECULAR MITSUNOBU CYCLIZATION

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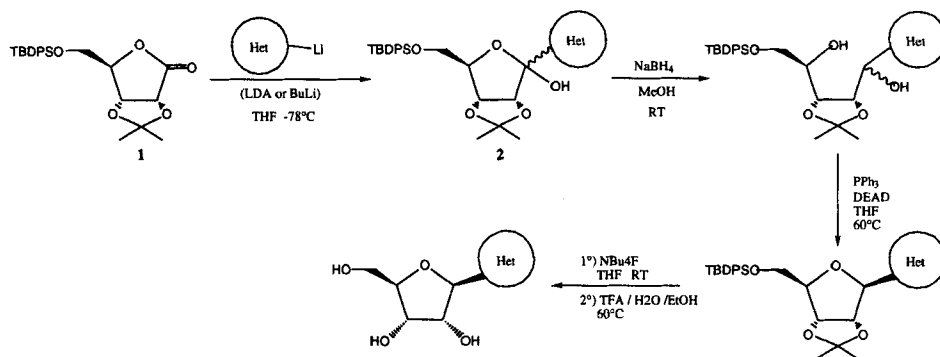
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**Abstract:** We have studied the stereoselective synthesis of new C-nucleosides by heteroarylation of the protected  $\gamma$ -ribonolactone by means of heteroaromatic systems such as indole, thiazoles, imidazoles and benzimidazoles. We have observed that the first anion addition-limiting step is very sensitive to steric factors induced by the N-protective groups in  $\alpha$ -position.

Nucleosides have attracted a wide interest in view of the importance of their biological activities. Recently, natural C-nucleosides have received a great attention since this class of molecules are well known for their potent antiviral and antitumor activities. Pseudo-uridine was isolated as the first C-nucleoside from *t*-RNA in 1957, while other natural C-nucleosides such as showdomycin, pyrazomycin, thiazofurin, formycin and pyrrolosine...etc. were isolated from fermentation broths. Furthermore, many C-nucleosides have been recently synthesized and have been shown to possess valuable biological activities.

A number of synthetic approaches to C-nucleosides have been reported. The most well known are the anionic and radical coupling reactions between sugar and base moieties. But to date, only a few examples of functionalized C-nucleosides have been reported, in particular when the reactive center of the heterocyclic moiety is adjacent to a protected or functionalized  $\alpha$ -position.

In the present work, we have studied the direct stereoselective heteroarylation of the known  $\gamma$ -ribonolactone by means of heteroaromatic systems such as indole, thiazoles, imidazoles and benzimidazoles. The synthesis required three important steps:



Heterocyclic bases:



R = Boc  
R = SO<sub>2</sub>Ph  
R = SO<sub>2</sub>NMe<sub>2</sub>

R = SO<sub>2</sub>Ph  
R = SO<sub>2</sub>NMe<sub>2</sub>

R = SO<sub>2</sub>NMe<sub>2</sub>  
R = Trityl

R = Br  
R = NH<sub>2</sub>  
R = NHBoc  
R = NMeBoc

Scheme

anionic addition of the heterocyclic lithium salt followed by reduction and intramolecular Mitsunobu cyclization as shown in the scheme.

Treatment of the protected lactone **1**, prepared in two steps from the commercially available  $\gamma$ -ribonolactone with the lithium salt of the chosen heterocyclic systems (indole, benzimidazole, imidazole and thiazoles) gave a high yield of the corresponding adducts **2**. The 1'-deoxygenation of intermediates **2** by classical conditions (Et<sub>3</sub>SiH / Lewis acid) failed. In contrast, reduction of the masked carbonyl group followed by intramolecular Mitsunobu cyclization gave a high yield of the desired  $\beta$ -anomer. We have also observed that the first anion addition-limiting step is very sensitive to steric factors induced by the N-protective groups in  $\alpha$ -position. The 2', 3', 5'-hydroxyl protecting groups and sulfamoyl group can be cleaved in one step using aq. trifluoroacetic-acid in methanol.

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- More experimental and spectral data of new compounds will be published elsewhere