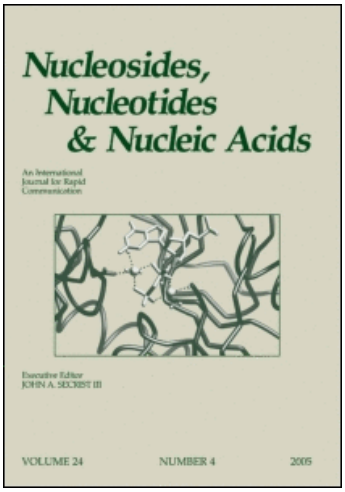

Nucleosides, Nucleotides and Nucleic Acids

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

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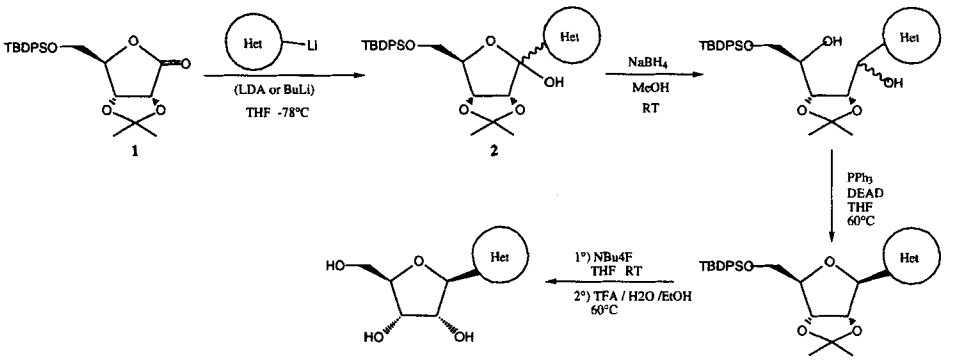
Abstract: We have studied the stereoselective synthesis of new C-nucleosides by heteroarylation of the protected γ-ribonolactone by means of heteroaromatic systems such as indole, thiazoles, imidazoles and benzimidazoles. We have observed that the first anion addition-limiting step is very sensitive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

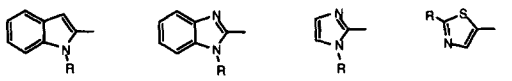
Nucleosides have attracted a wide interest in view of the importance of their biological activities. Recently, natural C-nucleosides have received a great attention since this class of molecules are well known for their potent antiviral and antitumor activities. Pseudo-uridine was isolated as the first 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 posses 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 particularly when the reactive center of the heterocyclic moiety is adjacent to a protected or functionalized α-position.

In the present work, we have studied the direct stereoselective heteroarylation of the known γ-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_2Ph
R = SO_2NMe_2

R = SO_2Ph
R = SO_2NMe_2

R = SO_2NMe_2
R = Trityl

R = Br
R = NH_2
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 γ-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_3SiH / Lewis acid) failed. In contrast, reduction of the masked carbonyl group followed by intramolecular Mitsunobu cyclization gave a high yield of the desired β-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 α-position. The 2', 3', 5'-hydroxyl protecting groups and sulfamoyl group can be cleaved in one step using aq. trifluroacetic-acid in methanol.

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More experimental and spectral data of new compounds will be published elsewere