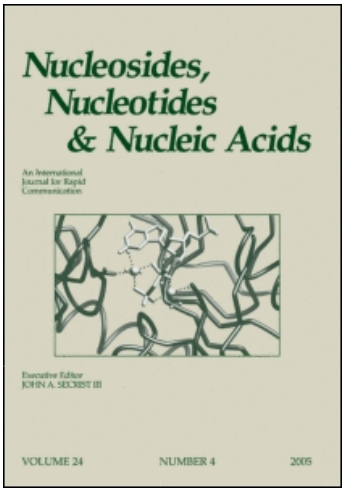

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SYNTHESIS OF NEW 3'-AMINO-2',3'-DIDEOXYNUCLEOSIDES IN FIVE STEPS STARTING FROM PERACETYLATED GLYCALS

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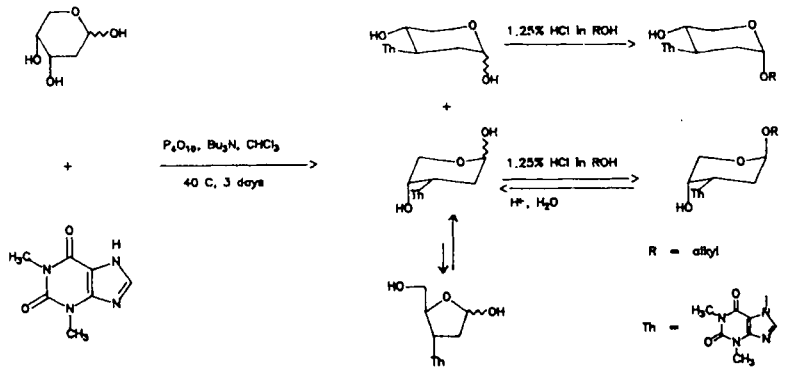
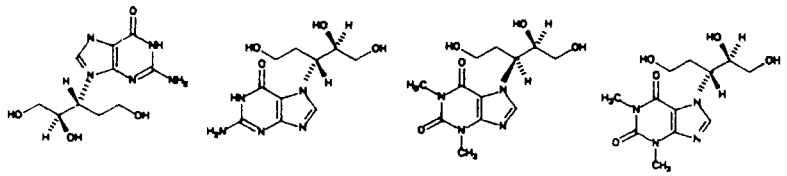
As amino sugars[1] and aminonucleosides[2] show remarkable anticancer and antiviral properties the synthetic and biological investigation in this field has become challenging.

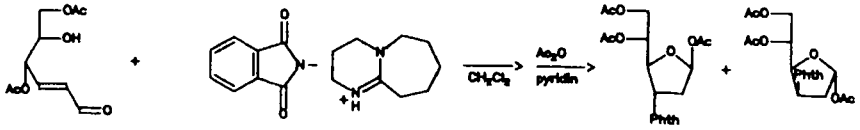
By reaction of N^6-protected adenin[3,4], N^6-protected guanin[5] and theophylline[6] with unprotected 2-deoxy-D-ribose in the presence of a phosphorus pentoxide/tributylamine reagent coupling of the purine at C-3 of the carbohydrate took place as shown in scheme I using theophylline as the nucleobase. The mechanism of this unexpected anomalously nucleoside formation which was explored by NMR of the reaction mixture showed to be a Michael type addition to the α,β-unsaturated aldehyde 4,5-dihydroxy-2-pentenal formed by ring opening of 2-deoxy-D-ribose with the phosphorus reagent.



Scheme I



Scheme II



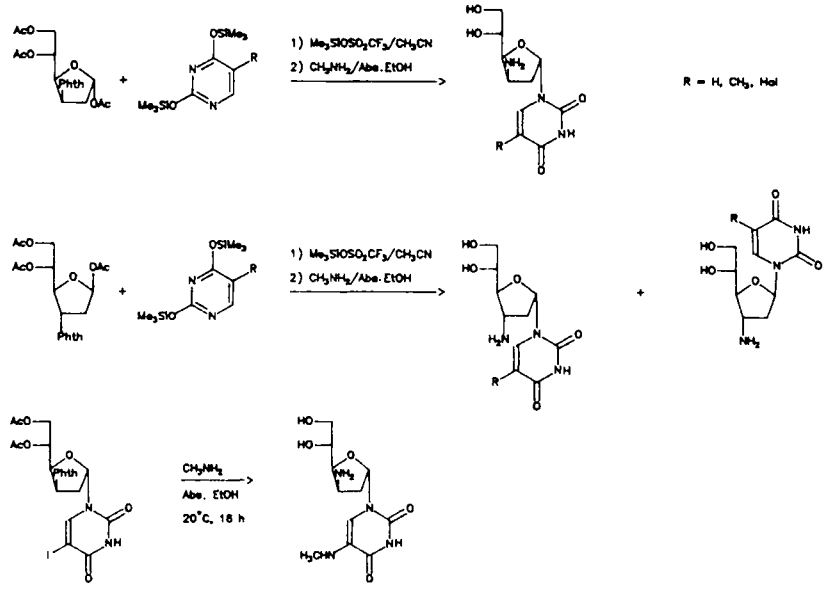
Scheme III

Reaction of different α,β-unsaturated carbohydrate aldehydes with theophylline in the presence of an organic base confirmed this reaction mechanism further as coupling of theophylline at C-3 of the carbohydrate moiety took place.

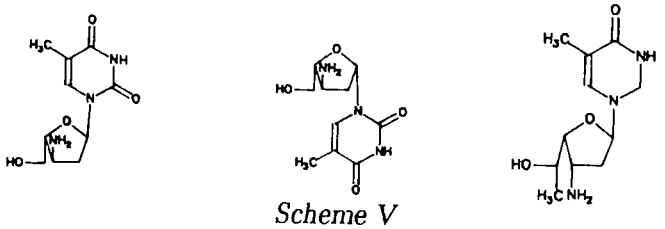
Subsequent reduction of these anomalous nucleosides with sodium-borohydride gave the corresponding alditols (scheme II) which can be considered as analogous of the anti-herpes drug acyclovir, and dyphylline used clinically to cure astma and bronchitis.

Recently we have extended this investigation using phthalimid as the nucleophile. By addition of DBU(1,8-diazabicyclo[5,4,0]undec-7-ene) phthalimide salt to the α,β-unsaturated carbohydrate aldehyde 4,6-di-*O*-acetyl-2,3-dideoxy-aldehydo-D-*erythro*-*trans*-hex-2-enose prepared by mercuric catalysed hydrolysis of peracetylated glucal an anomeric mixture of *arabino* and *ribo* isomers of 5,6-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-D-hexofuranose was obtained. Subsequent acetylation of the anomeric carbon made it possible to separate the two isomers as crystalline compounds (scheme III). Contemporary to the addition of phthalimide a base induced acetyl shift from 4-O to 5-O resulted in ring closure to give furanoses exclusively[7].

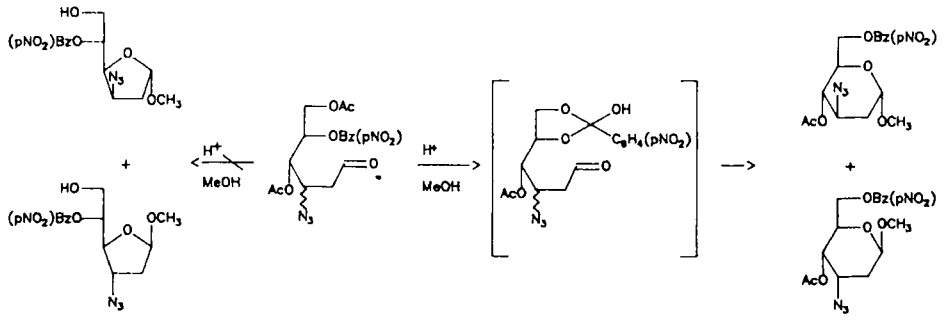
These new protected 3-amino furanoses gave us the chance to synthesize the first known examples of 3'-amino-2',3'-dideoxy nucleosides containing a hexofuranose as the carbohydrate moiety. Using the silyl



Scheme IV



Scheme V



Scheme VI

Hilbert-Johnson method with TMS-triflate as the Lewis acid followed by deprotection promoted a series of 3'-amino-2',3'-dideoxy uracil nucleosides with different configurations as shown in scheme IV. In the case of the 5-iodouracil nucleoside deprotection with 33% methylamine in absolute ethanol caused a simultaneous substitution of iodide with methylamine at C-5.

Compared to the traditional way of synthesizing 3'-amino-2',3'-dideoxy nucleosides by substitution of 3'-OH of a nucleoside with an azido group followed by reduction this new route gives the possibility to use structurally distinct α,β-unsaturated carbohydrate aldehydes producing 3'-amino-2',3'-dideoxy nucleosides with unnatural configurations which might exhibit interesting biological activities. Thus we have just prepared the first examples of α-L-*erythro* and β-L-*erythro* 3'-amino-2',3'-dideoxy-pentofuranose as well as 3'-amino-2',3',6'-trideoxy-α-L-*arabino*-hexafuranose nucleosides (scheme V).

In order to expand this investigation we tried to introduce an azido group at C'-3. As we did not succeed to provoke a contemporary acetyl shift from 4-O to 5-O of the aldehyde we decided to protect the hydroxy group at C-5 prior to addition of hydrazoic azid. Unfortunately subsequent methanolysis did not give the disired furanose isomers. Previous to deacetylation at C-4 an acetic induced benzoyl migration from 5-O to 6-O resulted in ring closure to give the pyranose isomers (scheme VI). In an other experiment using an α,β-unsaturated pentose aldehyde we likewise obtained the pyranose isomers due to benzoyl migration from 5-O to 4-O prior to ring closure.

Biological investigation and synthesis of other 3'-substituted 2',3'-dideoxy nucleosides are in progress.

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