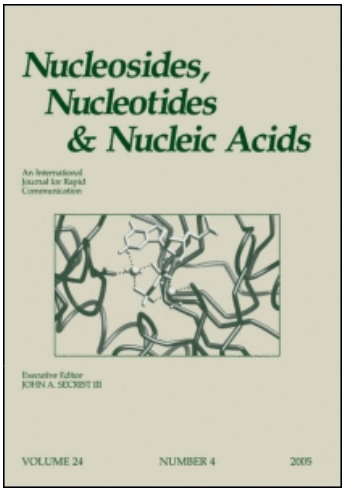

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Synthesis of Pyranose Nucleosides

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SYNTHESIS OF PYRANOSE NUCLEOSIDES

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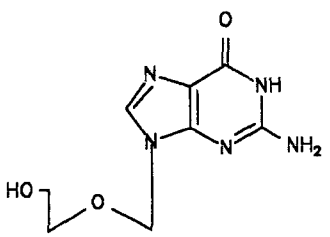
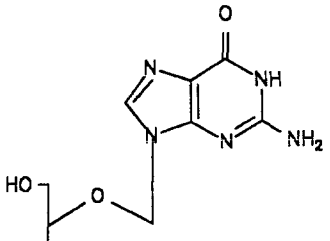
Abstract. The synthesis of pyrimidine nucleosides with a 2,3,4-trideoxy-D-glycero-hex-3-enopyranose, 2,3,4-trideoxy-D-glycero-hexopyranose, 2-deoxy-D-erythro-pentopyranose and 2-deoxy-2-fluoro-D-arabino-pentopyranose sugar moiety are described.

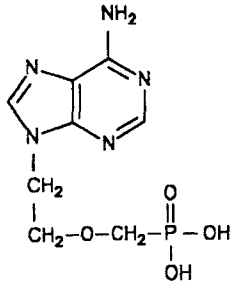
A milestone in the development of antiviral compounds was the discovery of the antiviral activity of acyclovir (ACV).[1] The fact that a simple acyclic nucleoside analogue can suppress the multiplication of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), without untoward effects to the host cells, stimulated different research groups to synthesize analogous sugar-modified nucleosides. Among the prominent compounds resulting from this research are 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG, ganciclovir)[2-4] [currently used for the treatment of cytomegalovirus (CMV) infections in immunocompromised patients] and the phosphonate analogues PMEA [9-((2-phosphonylmethoxy)ethyl)adenine] and HPMPC [1-((3-hydroxy-2-phosphonylmethoxy)-propyl)cytosine]. PMEA is a potent and selective inhibitor of human



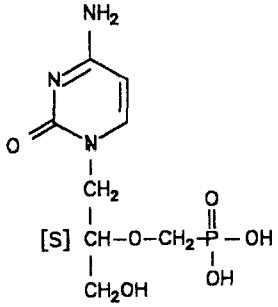
ACV



DHPG



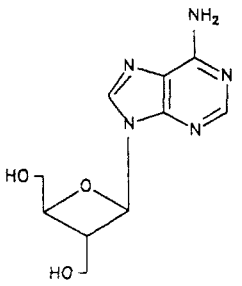
PMEA



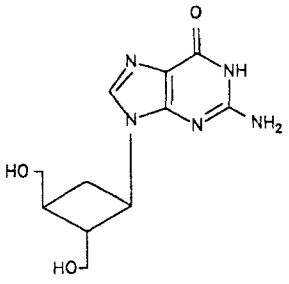
HPMPC

immunodeficiency virus (HIV)[5], whereas HPMPC is a potent and selective anti-CMV[6] compound. DHPG and ACV can be considered as acyclic analogues of nucleosides, while PMEA and HPMPC are acyclic analogues of nucleoside monophosphates.

One of the main directions in which research on antiviral nucleosides has evolved during the last years is toward "small-ring nucleosides". The discovery of the (relatively poor) anti-HSV and anti-HIV activity of the natural compound oxetanocin A[7], has prompted the synthesis of oxetanocin derivatives. This led to the identification of bis(hydroxymethyl)cyclobutylguanine (BHCG)[8] as a broad-spectrum antiviral agent (HIV, HSV).



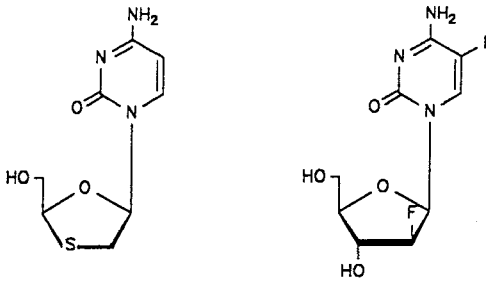
Oxetanocin A



DHCG

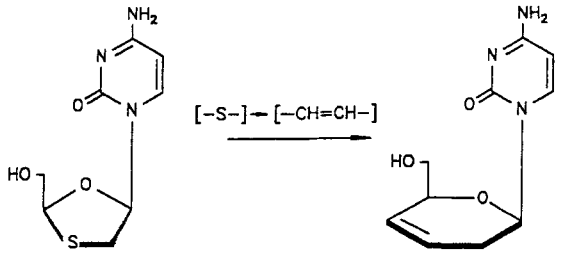
A series of nucleoside analogues from which, till now, no congener has been accredited with significant antiviral activity are those containing a pyranose sugar moiety. The structural modifications which can be carried out at the pyranose sugar are, in fact, unlimited. We started our research with two lead components, i.e. 2-(S)-hydroxymethyl-5-(R)-(cytosin-1-yl)-1,3-oxathiolane and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine. The first compound, known as

NGPB-21[9], was reported as having anti-HIV-1 activity [minimum inhibitory concentration (MIC): 1 μg/ml]. The second compound, FIAC[10], is a potent anti-herpes agent.

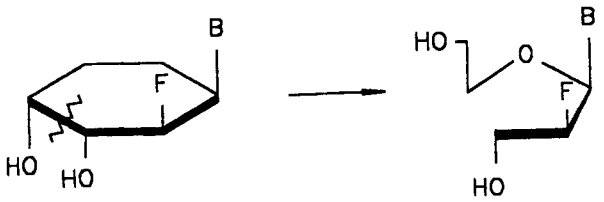


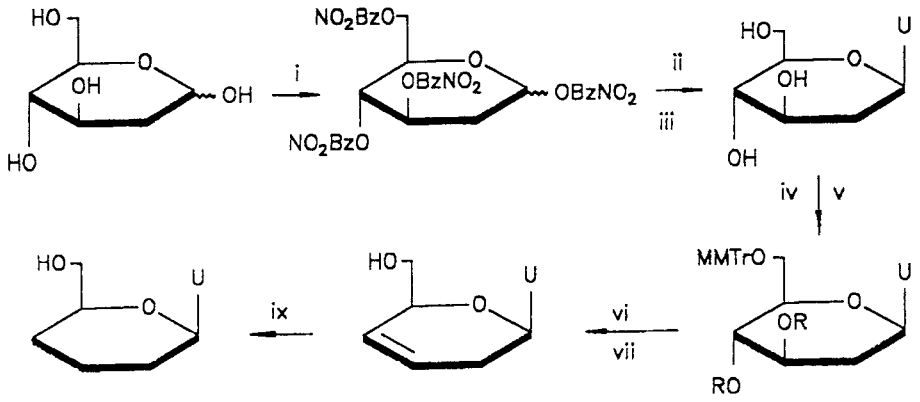
NGPB–21 FIAC

One of the oldest isosteric replacements in medicinal chemistry is the replacement of a sulfur atom by a vinyl function.[11] Indeed, the covalent bond length of a C-S-C bond is situated between the length of a C-O-C bond and the length of a C-C=C-C bond. Starting from NGPB-21, 1-(2,3,4-trideoxy-β-D-glycero-hex-3-enopyranosyl)cytosine could be expected to possess anti-HIV activity.



A disadvantage of 2'-fluoroarabinofuranose nucleosides, such as FIAC and FMAU, is that they are incorporated into viral as well as cellular DNA.[12] This could be the reason for the bone marrow suppression and other side effects observed at relatively low dosages of these compounds. Therefore, we synthesized the 3',4'-seco analogues of 2'-fluoroarabinofuranose nucleosides, with the aim to lower their toxicity and maintain their activity. These compounds can be prepared by scission of





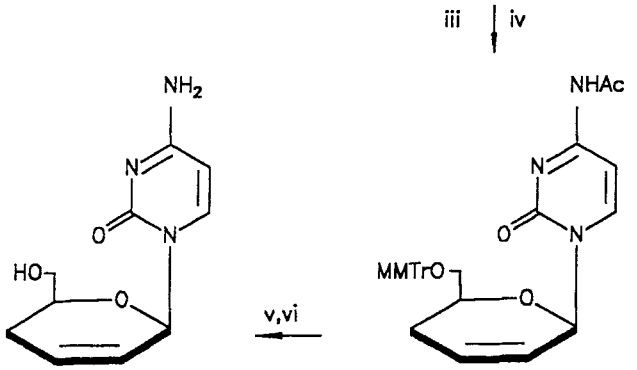
Scheme 1

i: p-NO_2benzoyl chloride, pyridine; ii: $(TMS)_2U$, TMSOTfl, $C_2H_4Cl_2$; iii: NH_3-MeOH; iv: MMTrCl, pyridine; v: H_2O, DMSO, NaOH, CS_2; $BrCH_2CH_2CN$; vi: TBTH, AIBN, toluene; vii: 98% HCOOH; ix: Raney Ni, H_2, MeOH.

the 3',4'-bond of 2'-fluoro<u>arabino</u>pyranose nucleosides. Two fundamental problems are associated with this strategy: a) a possible epimerization of the 2'-carbon atom during ring opening reactions with $NaIO_4/NaBH_4$; b) the possibility of metabolic conversion of the acyclic nucleoside to 2'-fluoroglycinic acid and further onto the extremely toxic 2'-fluoroacetic acid after cleavage of the glycosidic bond.

CHEMISTRY

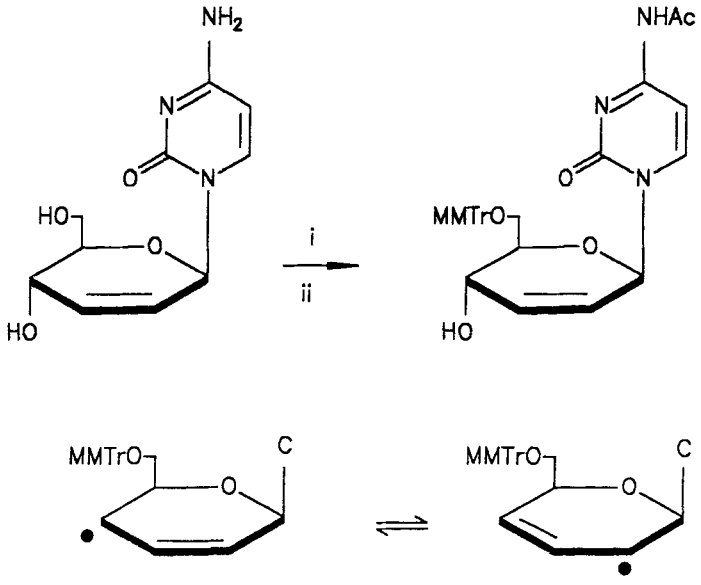
The compounds with a 3',4'-unsaturated double bond were synthesized according to Scheme 1 starting from 2-deoxy-D-glucose. The tretra(p-nitro)benzoyl derivative of 2-deoxy-D-<u>gluco</u>pyranose was condensed with the silylated bases. A mixture of the α/β-nucleosides were obtained in a ratio of 3/2. This mixture was separated and the ester groups were removed. The primary hydroxyl group was protected with a monomethoxytrityl group and the secondary hydroxyl groups were converted to xanthates by reaction with CS_2/NaOH and β-bromopropionitrile. Introduction of the double bond followed by deblocking of the 5'-hydroxyl group gave the 3',4'-unsaturated nucleoside. The unsaturated bond was reduced to obtain the fully saturated nucleoside analogues. Both α- and β-derivatives containing an uracil, thymine or cytosine base moiety were obtained using this reaction sequence.

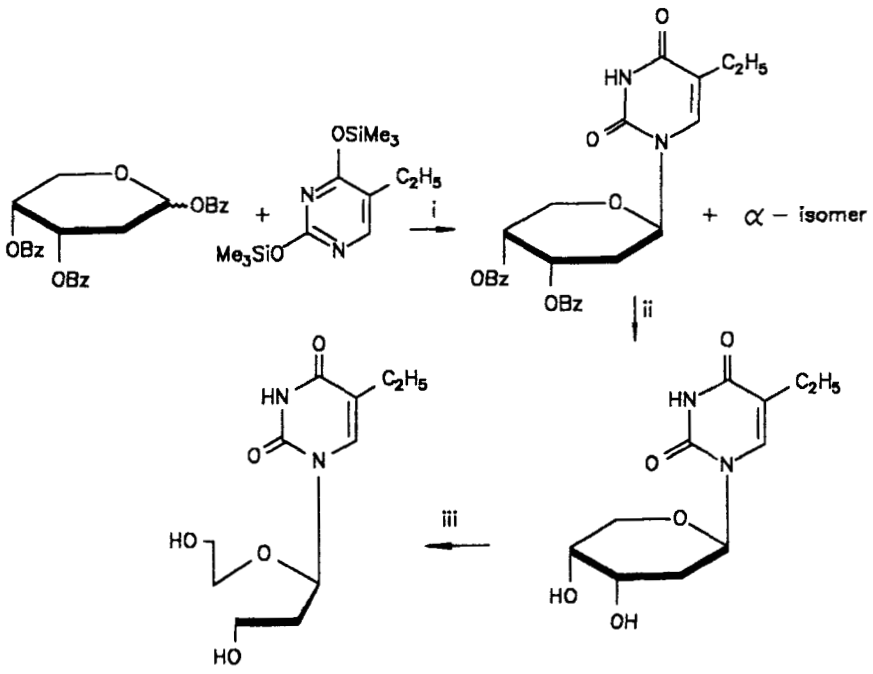


Scheme 2

i: Ac_2O, ETOH; ii: MMTrCl, pyridine; iii: $\phi OC(S)Cl$, DMAP, CH_3CN; iv: TBTH, AIBN, toluene; v: NH_3-MeOH; vii: HOAc 80%.

The 2',3'-unsaturated nucleoside analogues containing a cytosine base moiety were obtained as described in Scheme 2. The starting material could be synthesized from tri-O-acetylglucal and silylated N-benzoylcytosine. During the radicalar removal of the 4'-hydroxyl group, the double bond partially migrated to the 3',4'-position, thus affording a mixture of the 2',3'- and 3',4'-unsaturated compounds in the ratio of 4/1.

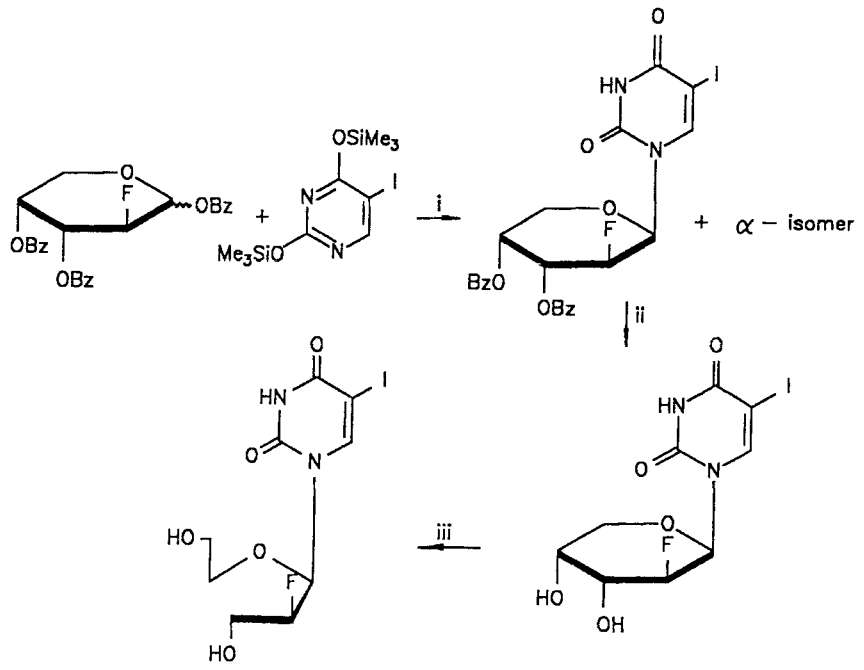




Scheme 3

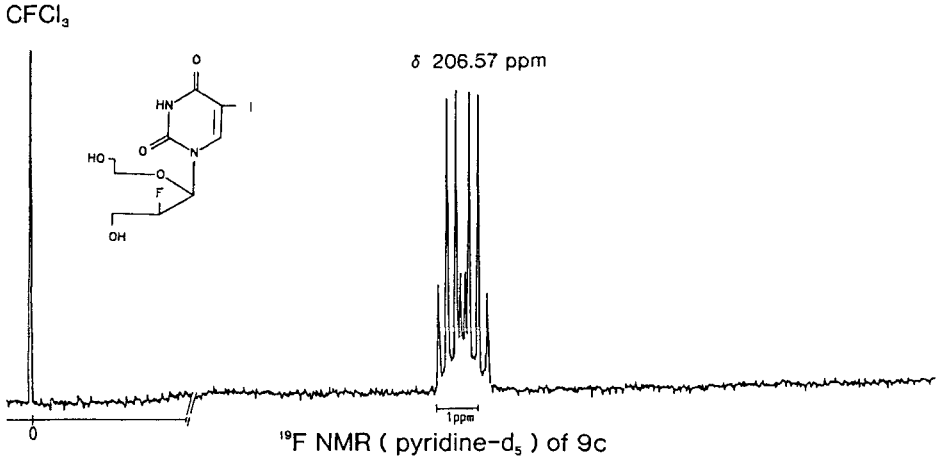
i: TMSOTf1.1.2 equiv, $C_2H_4Cl_2$, R.T.; ii: NH_3-MeOH; iii: $NaIO_4$-$NaBH_4$.

Condensation of 1,3,4-tri-O-benzoyl-2-deoxy-D-ribopyranose with silylated bases (thymine, uracil, 5-fluorouracil, 5-iodouracil, 5-ethyluracil, N^4-benzoylcytosine) in dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf1) gave the corresponding nucleosides in over 90% yield in an α/β ratio of approximately 75/25, as shown in Scheme 3 (with 5-ethyluracil serving as the base moiety). Starting from the pure α-nucleoside an anomerization can be performed by stirring the compound in acetonitrile in the presence of TMSOTf1. An equilibration was reached after formation of 20-30% of the β-isomer. Reaction of the purine base (N^6-benzoyladenine and N^2-acetyl-O^6-diphenylcarbamoylguanine) with trimethylsilyl perchlorate as catalyst was carried out at reflux temperature (yield: approximately 60%). Debenzoylation was carried out with ammonia in methanol. Periodate cleavage, followed by sodium borohydride reduction, provided the corresponding acyclic nucleosides.



Scheme 4

i: TMSOTfl, $C_2H_4Cl_2$, reflux; ii: NH_3-MeOH; iii: $NaIO_4$-$NaBH_4$.



The compound with the adenine base moiety, 9-(2-deoxy-β-D-ribopyranosyl)adenine, was synthesized previously by different research groups. The assignment of the anomeric configuration[13] was based on a study of the splitting pattern of the protons in the ^1H NMR spectrum. This spectrum could be explained by assuming a distorted 1C conformation for the α-isomer with the C-5' methylene group occupying a position coplanar or approaching coplanarity with the ring oxygen atom and the carbon atom C-4'. However, the spectrum which has previous been described for the α-isomer corresponds to the nucleoside with the β-configuration. This was proven by X-ray analysis. The molecule adopts a slightly flattened C1 chair conformation.

2'-Deoxy-2'-fluoro-β-arabinopyranosyl nucleosides were synthesized by condensation of 1,3,4-tri-O-benzoyl-2-deoxy-2-fluoro-D-arabi-nopyranose with the appropriate silylated bases in the presence of trimethylsilyl triflate as shown in Scheme 4 with 5-iodouracil as example. Here again, the α-isomer predominates (α/β 4:3). The anomeric configuration was assigned by X-ray crystallographic analysis.
After deprotection, the 3',4'-bond was opened by reaction with periodate. Opening of this bond was more difficult than opening of the non-fluorinated analogues and required 6-hr reaction time at 60°C. This longer reaction time could have facilitated epimerization at C-2' during the reaction itself or during the subsequent reaction with $NaBH_4$. However, both the ^{13}C NMR spectrum and the ^{19}F NMR spectrum provided proof that the isolated compounds were essentially pure.

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