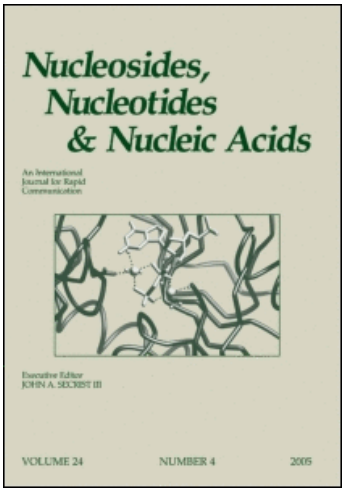

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Phosphonates Derivatives of 2',3'-Dideoxy-2',3'-didehydro-pentopyranosyl Nucleosides

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PHOSPHONATES DERIVATIVES OF 2',3'-DIDEOXY-2',3'-DIDEHYDRO-PENTOPYRANOSYL NUCLEOSIDES

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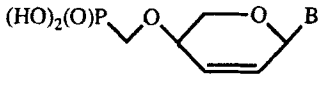
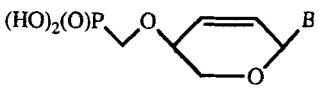
Abstract: Adenine and thymine derivatives of 2',3'-dideoxy-2',3'-didehydropento-pyranosyl nucleosides carrying a phosphonomethyl moiety at their 4'-*O*-position and in a *cis* relationship with the heterocyclic base have been synthesized.

Since the discovery of the potent anti-HIV activity of AZT, ddI and d4T, 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydropentofuranosyl nucleosides have been extensively studied as potential antivirals[1]. However, saturated and unsaturated di- and tri-deoxypyranosyl nucleosides have received little attention[2-7]. The absence of antiviral activity for most of the nucleoside analogues with a six membered ring carbohydrate moiety has been related to their poor recognizition by cellular kinases, and, hence, to the lack of the formation of their triphophates, the active metabolite interacting with the reverse transcriptase of HIV. In this activation process, the generation of the monophosphate is, in most of the cases, the limiting step. One extensively used and successful strategy to overcome this first phosphorylation is the preparation of nucleoside phosphonates. It has already been shown[8,9] that, in this respect, a phosphonomethoxy and a methylphosphate moiety act as isosteric and isoelectronic functions.

As part of our programme on the synthesis of six-membered ring nucleosides, we have now synthesized pentopyranosyl nucleosides of formula **1**, and, in the case of the adenine congener, its enantiomer **2**, where the heterocyclic base and the phosphonomethoxy moiety are in a 1,4-*cis* relationship. These compounds could be considered as ring-enlarged analogues of d4T-MP and d4A-MP, respectively, carrying a phophonomethoxy moiety as isoster of the monophosphate function. The 1,4-*cis* configuration between the base and the OH to be phosphorylated is also present in 1,5-anhydrohexitol nucleosides that have been synthesized by our group, and that show antiviral activity[10].



1a B=Thymin-1-yl
1b B=Adenin-9-yl

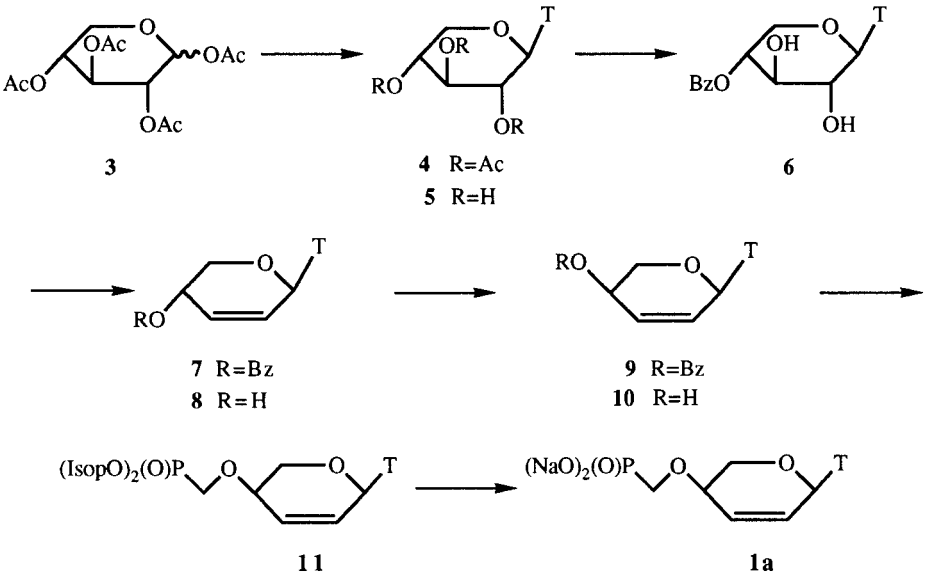


2 B=Adenin-9-yl

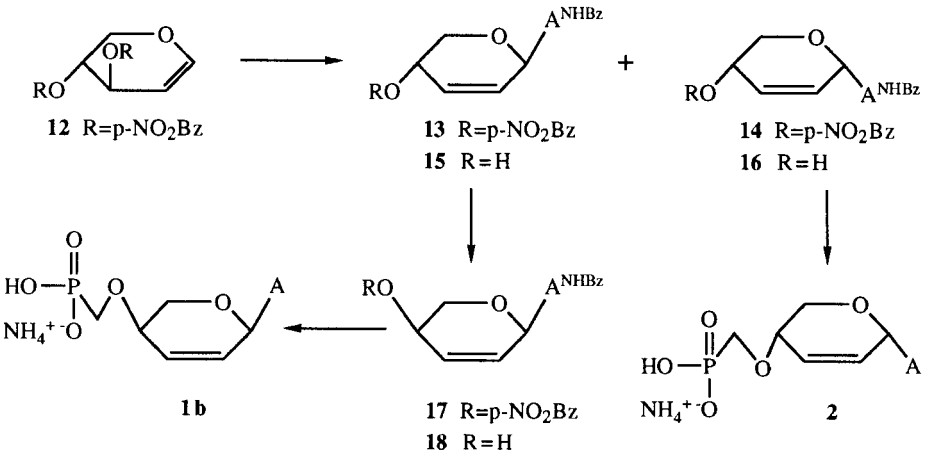
For the synthesis of the thymine derivative **1a**, a stereospecific pathway was devised starting from peracetylated D-xylose (scheme 1). Reaction of this (**3**) with silylated thymine in the presence of trimethylsilyl triflate afforded the β-D-pyranosylnucleoside (**4**), which was deacetylated by reaction with NaOMe/MeOH (**5**, 60% from **3**). Then, the 4'-OH of the xylose moiety was selectively protected by treatment with Bu_2SnO in methanol and reaction with 1.1 eq. of benzoyl chloride in dioxane/DMF (4:1) (**6**, 79% yield). The olefin **7** was obtained from the diol **6** by reaction with chlorodiphenylphosphine/iodine/imidazole (2.2:2.2:4eq./diol) in toluene/acetonitrile and treatment with Zn[11] to complete the transformation of the intermediate iodo diphenylphosphinate to the unsaturated compound. The benzoyl group was then removed by treatment with methanolic ammonia (65% of **8** from **6**). In the next step, the configuration of the stereogenic centre at the 4'-position was inverted using benzoic acid under Mitsunobu conditions[12]. After deprotection, the L-nucleoside **10** was obtained in 75% yield. No allylic rearrangement was detected. The phosphonomethyl moiety was introduced by reaction of **10** with NaH and diisopropyl[(p-tolylsulfonyl)oxy] methanephosphonate[13,14] in DMF at 40°C. The 4'-*O*-alkylated derivative **11** was deprotected by treatment with trimethylsilyl bromide and hydrolysis, to afford, after purification, the disodium salt of **1a**.

A different reaction sequence was followed for the synthesis of the adenine derivatives. Our earlier investigations have shown that 2',3'-unsaturated nucleosides can be obtained by direct condensation of di-*O*-acylated-D-xylal with heterocyclic bases in boiling DMF, without external acid catalysis[15]. Following this procedure (Scheme 2), the N-9 adenine derivatives **13** and **14** were obtained by reaction of di-*p*-NO_2-benzoyl-D-xylal with N^6-benzoyladenine. The mixture of anomers was resolved after selective deprotection of the alcohol moiety with NaOMe in MeOH:dioxane, yielding the α-D- and β-D-*glycero*-pent-2'-enosyl nucleosides **16** and **15** in 19% and 25% yield, respectively, from the xylal. The stereochemical assigment of both isomers was determined by X-Ray crystallography[15]. It should be mentioned that no appreciable amounts of 3'-substituted-1',2'-unsaturated nucleosides were detected.

The configuration of the 4'-OH center in the β-anomer **15** was inverted by reaction with *p*-nitrobenzoic acid under Mitsunobu conditions and selective deprotection, to yield



Scheme 1



Scheme 2

the 1,4-*cis*-substituted olefin **18** in 73% yield. Again, no allylic rearrangement was detected. Reaction of the alcohols **16** and **18** with NaH and diisopropyl [(p-tolylsulfonyl)-oxy]methanephosphonate afforded the 4'-*O*-alkylated derivatives which were deprotected by successive treatment with methanolic ammonia and trimethylsilyl bromide in DMF. The phosphonates derivatives were isolated as their ammonium salts **2** and **1b** (30% and 24% yield, from their respective allylic alcohols **16** and **18**). The treatment with TMSiBr had to be carried out in the presence of an excess of 2,6-lutidine[16], otherwise extensive decomposition was observed. This seems to indicate the sensitivity of the glycosidic bond in these structures to acidic conditions, and contrasts with the greater stability reported for the furanose analogue[9].

When tested for inhibitory activity against virus replication in cell culture including HIV-1, HIV-2, HSV-1, HSV-2, VZV and HCMV, the phosphonate derivatives **1** and **2** were found to be inactive at concentrations up to 100 μg/ml. Also no toxicity to the cell monolayers was observed.

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