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Stereospecific Synthesis of a Pentopyranosyl Analogue of D4T Monophosphate

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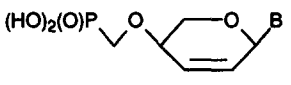
Abstract: The synthesis of a pentopyranosyl analogue of d4T monophosphate is described. In order to obtain selectively the 1,4-*cis* substituted nucleoside, a new pathway was devised with the following sequence: i) Glycosylation of peracetylated D-xylose with thymine, ii) introduction of the double bond between the 2' and 3' positions, iii) inversion of the 4'-OH under Mitsunobu conditions, and iv) introduction of the phosphonomethyl moiety.

The potent anti-HIV activity of AZT (3'-azido-3'-deoxythymidine), ddI (2',3'-dideoxyinosine) and d4T (2',3'-dideoxy-2',3'-didehydrothymidine) has led to the synthesis of a great number of 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydropentofuranosyl nucleosides[1]. The transformation of these nucleoside analogues to the triphosphates, in order to interact with the reverse transcriptase, seems to be a prerequisite for anti-HIV activity. A useful strategy to overcome the first phosphorylation step is to synthesize nucleoside phosphonates. This has been demonstrated by the synthesis of phosphonates of acyclic nucleosides[2] and furanosyl nucleosides[3]. In both examples, a phosphonomethyloxy moiety and a methylphosphate function were proven to be isosteric and isoelectronic.

Little efforts, however, have been directed towards the synthesis of saturated and unsaturated di- and trideoxypyranosyl nucleosides[4,5,6], and no phosphonate analogues of these compounds were synthesized. Therefore, we became interested in the synthesis of 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydropentopyranosyl nucleosides carrying a phosphonomethyl moiety at the O-4' position and in a 1,4-*cis* relation with the heterocyclic base (**1**). The potential activity of such compounds was further supported by our findings that 1,5-anhydrohexitol nucleosides of formula **2**, where the relation between the base and the oxygen atom to be phosphorylated is also 1,4-*cis*, show antiviral activity[7]. In this preliminary account, we report on the synthesis of the 2',3'-dideoxy-2',3'-didehydropentopyranosyl thymine derivative.



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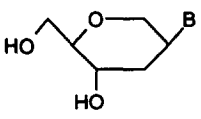
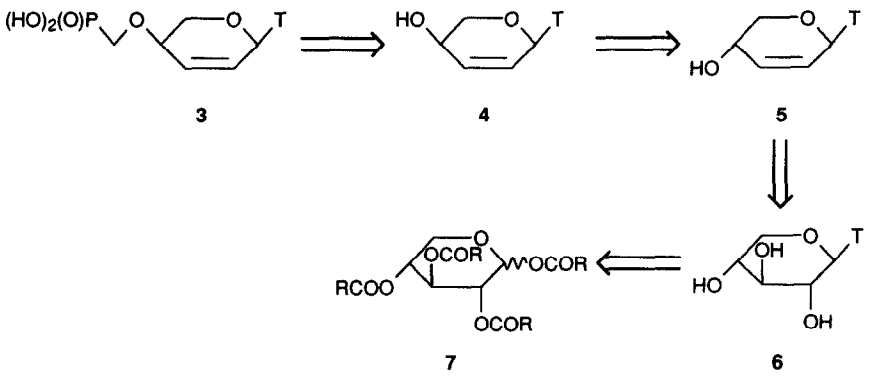


2

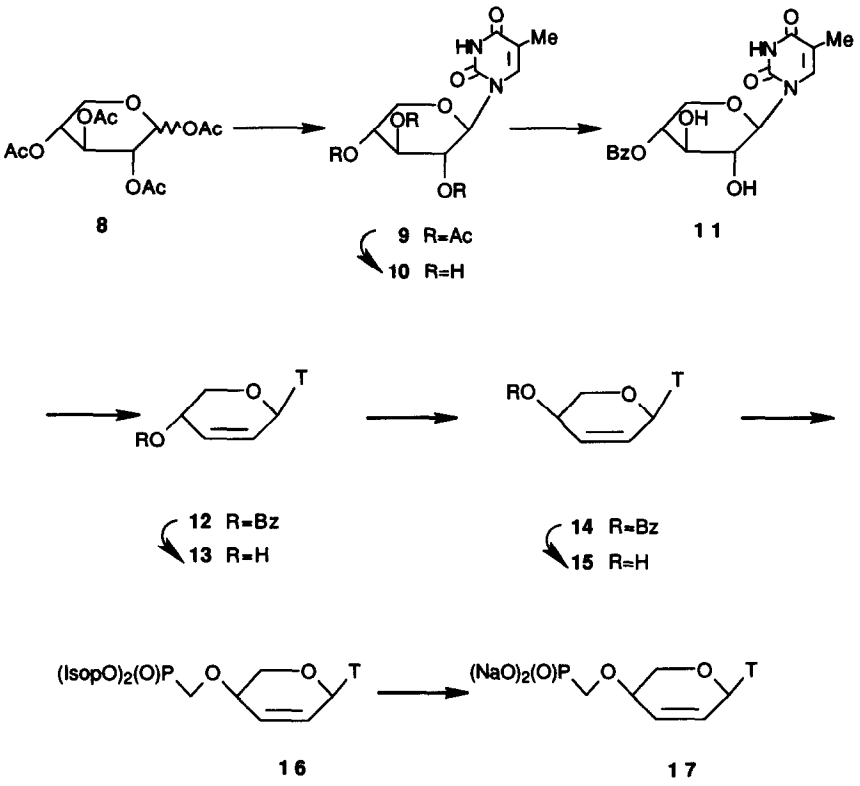
2',3'-Unsaturated pyranosyl nucleosides have been mostly obtained by condensation of glycals with heterocyclic bases in the presence of acids[8]. However, this method affords mixtures of α and β- anomers and, in some cases, considerable amounts of the 3'-substituted 1',2'-unsaturated derivatives are obtained. A recent report describes[9] that the reaction of diacetyl D-xylal with persilylated thymine using perchlorate as catalyst affords exclusively the α-anomer. Therefore, we prefered to use a strategy that would lead exclusively to the target 1,4-*cis* substituted nucleosides.

In a retrosynthetic analysis (scheme 1), the desired phosphonate derivative **3** could be obtained from its alcohol precursor **4**. This actually belongs to the L-series but could be prepared from its D-analogue **5** by inversion of configuration at the 4'-position under Mitsunobu conditions[10]. To assure the β-configuration in the synthesis of **5**, we decided to introduce the heterocyclic base in a 2-*O*-acylated pyranose derivative, so that anchimeric assistance of the 2-*O*-acyl function would lead exclusively to the β-nucleoside **6**. Introduction of the double bond between the 2' and 3' positions could then be carried out on appropriately protected **6**. Although there are several methods available for the generation of a double bond in pyranoses[11], they have not been applied to a pyranosyl nucleoside. The triphenylphosphine/iodine/imidazole system[12] gave the best results in our hands. The selective protection of the 4'-OH in **6** was carried out by treatment with Bu_2SnO and benzoyl chloride, following a slight modification of the method described for methyl glycosides[13].



Scheme 1

Thus, treatment of peracetylated D-xylose (scheme 2) with silylated thymine in the presence of trimethylsilyl triflate following Vorbrüggen procedure[14] afforded the β-D-pyranosyl nucleoside **9** in 70% yield, which was deacetylated by reaction with NaOMe/MeOH (**10**, 85%). Selective protection of the 4'-OH of **10** was carried out by treatment with Bu_2SnO in boiling methanol and reaction with 1.1 eq. of benzoyl chloride in dioxane/DMF (4:1) at room temperature to furnish **11** (79% yield). Treatment of **11** with chlorodiphenylphosphine/iodine/ imidazole (2.2:2.2:4eq./diol)[12b] in toluene/acetonitrile, followed by reaction "in situ" with Zn led to the unsaturated nucleoside **12**, which was debenzoylated by treatment with ammonia in methanol (65% yield from **11**). The addition of Zn was necessary for the complete transformation of the intermediate iodo diphenylphosphinate to the final product [12b].



Scheme 2

The configuration of the stereogenic center at the 4'-position was inverted using benzoic acid under Mitsunobu conditions. Thus, treatment of a solution of **13** and Ph_3P (1.5 eq.) in THF with a solution of benzoic acid (1.5 eq.) and DEAD (1.5 eq.) afforded the benzoate **14**, which was deprotected (75% from **13**). ^{1}H-NMR spin decoupling experiments on **15** demonstrated that no allylic rearrangement had occurred in this reaction, the product of inverted configuration at C-4' being the only one isolated.[15] Reaction of the allylic alcohol **15** with NaH and diisopropyl [(p-tolylsulfonyl)oxy]methanephosphonate[16] in DMF at 40°C for 3 days afforded the 4'-*O*-alkylated derivative **16** in moderate yield (25%). The deprotected phosphonate nucleoside **17**[17] was obtained by treatment of **16** with trimethylsilyl bromide and then purified by chromatography over Sephadex DEAD A25 eluting with a gradient H_2O-0.1M ammonium hydrogen carbonate, followed by transformation into the disodium salt **17**.

The phosphonate **17** was tested at concentrations up to 100 μg/mL for inhibition of virus replication in cell culture. No activity was found against HIV-1 or HIV-2 in CEM cells. Also, no toxicity to the cell monolayers was observed. The lack of activity of this phosphonate could be due to poor cellular uptake, or inefficient intracellular metabolism to the diphosphate, or the inactivity of this diphosphate against the reverse transcriptase of HIV, the target enzyme. Further investigations are required to clarify this issue.

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15. NMR data for **15**: δ_H (300 MHz, DMSO-d_6): 11.4 (br s, NH-3), 7.46 (s, H-6), 6.26 (m, H-3'), 6.13 (dd, H-1'), 5.76 (dd, $J_{2',3'}$=9.3, $J_{1',2'}$=0-2 Hz, H-2'), 5.21 (br s, OH-4'), 3.93 (m, H-4'), 3.81 (dd, $J_{4',5'b}$=3.6 Hz), 3.61 (dd, Jab=11.8, $J_{4',5'a}$=3.9 Hz, H-5'a), 1.78 (s, CH_3); δ_C (75 MHz, DMSO-d_6): 164.0 (C-4), 150.7 (C-2), 134.7, 137.2 (C-6, C-3'), 126.3 (C-2'), 109.2 (C-5), 76.8 (C-1'), 67.8 (C-4'), 60.3 (C-5'), 12.1 (CH_3).
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17. Selected data for **17**:UV (H_2O) λ max: 266 (ε=9300). δ_H (200 MHz, D_2O): 7.60 (s, H-6), 6.53 (m, H-3'), 6.30 (dd, H-1'), 5.97 (dd, $J_{2',3'}$=10.6, $J_{1',2'}$=1.3 Hz, H-2'), 4.07 (m, H-4', H-5'), 3.75 (m, P(O)CH_2), 1.89 (s, CH_3); δ_C (50 MHz, D_2O): 169.1 (C-4), 153.6 (C-2), 140.4 (C-6), 132.5, 129.0 (C-2', C-3'), 112.9 (C-5), 79.8 (C-1'), 71.3 (C-4'), 66.7 ($J_{C,P}$=155 Hz, OCH_2P), 66.6 (C-5'), 12.8 (CH_3). HRMS (-LSIMS, glycerol) calcd. for $C_{11}H_{14}N_2O_7P$ (M-H) 317.0538, found 317.0545.

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