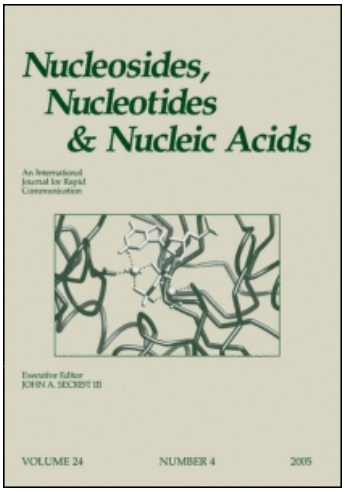

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Synthesis of AZT-α-Borano-5'-Diphospho-Hexoses

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SYNTHESIS OF AZT-α-BORANO-5'-DIPHOSPHO-HEXOSES

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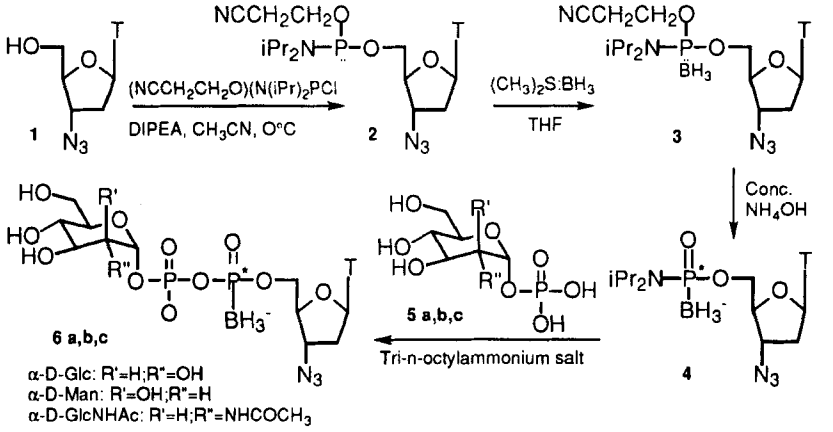
ABSTRACT : 3'-Azido-3'-deoxythymidine-α-borano-5'-diphospho-hexoses have been synthesized. Their diastereoisomers were separated by HPLC.

3'-Azido-3'-deoxythymidine (AZT) was the first drug in clinical use for the treatment of infection with the human immunodeficiency virus (HIV)[1], the etiologic agent of the acquired immunodeficiency syndrome (AIDS)[2]. More than ten years ago, Schinazi et al.[3] prepared various 5'-diphosphohexoses AZT, and many of these compounds had antiviral, including anti-HIV, activity. In this proceeding, we reported the synthesis and the evaluation of anti-HIV effects in HIV-1-LAI-infected peripheral blood mononuclear cells (PMBC) of the 5'-α-boranophosphate analogs.

Most of the chemical synthesis of sugar diphosphate nucleosides involve the coupling of a glycosyl phosphate with an activated nucleoside monophosphate (NMP)[4a,b]. The AZT α-borano-5'-diphospho-hexoses **6a,b,c** were prepared according to the following scheme: AZT **1** was phosphitylated giving **2.** Compound **2** was then oxidised into the AZT boranophosphate cyanoethylester **3** by reaction with an excess of dimethyl sulfide-borane[5]. Compound **3** reacted with conc. NH_4OH, hydrolysing the cyanoethyl group to give **4**. Reaction of **4** with trioctylammonium salt glycosyls phosphate respectively (α-D-glucose 1-P **5a**, α-D-mannose 1-P **5b** and α-D-N-acetyl-glucosamine 1-P **5c**) afforded the corresponding title compounds **6a,b,c**. The boron-modified P-diastereoisomers of **6a,b,c** were separated in 1:1 ratio by RP-HPLC on a C_{18} column eluted by a 0.01M solution of triethylammonium acetate containing 5 to 25% of acetonitrile, to give for the

mannose couple, as an example, **6b-1** (7.18 min) and **6b-2** (8.20 min) are the faster and slower eluting diastereoisomers, respectively.



Molecules were tested towards phytohemagglutinin (PHA)-P-activated PBMC infected with 100 TCID50 of the lymphotropic reference HIV-1-LAI strain. HIV replication was assessed by the dosage of reverse transcriptase (RT) activity in cell culture supernatants. Cells were one-hour pre-treated and maintained all along the culture.

None of the six tested AZT derivatives demonstrated higher antiviral activity than AZT.. The closest antiviral activity was observed with compound **6a-1** (ED50 **6a-1**: 75 nM *vs.* ED50 AZT 3 nM). Nevertheless, these molecules are of interest because 1) unlike other nucleotides, they may cross the plasma membrane, and 2) they are able to liberate α-borano AZTMP and AZTDP inside the cells and, as a consequence, the two first steps of phosphorylation, probably the most limiting for dideoxynucleoside efficiency, are avoided.

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