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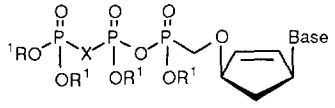
Chemoenzymatic Synthesis of Carbocyclic Nucleotide Mimics Possessing Potent Activity Against HIV-Reverse Transcriptase

C. J. Clements, S. M. Roberts, V. Merlo
Department of Chemistry, Exeter University, Stocker Rd, Exeter, Devon, EX4 4QD, UK.

The monophosphate and triphosphate carbocyclic nucleotide mimics shown below (X=O) have been found to be active inhibitors of HIV-Reverse Transcriptase; some are at least as potent as AZT. Many examples of antiviral compounds have exhibited enhanced potency for specific enantiomers: this led us to devise methods of preparation of these compounds, in optically pure form, utilising an enzyme-catalysed kinetic resolution at an early stage in the synthesis. All the aforementioned analogues display poor activity against HIV. infected cells *in vitro* . Inactivity could be due to the inability of the polar phosphorylated nucleosides to cross the lipophilic cell wall. Efforts are now being directed towards enhancing cell penetration by making less polar phosphate mimics through modifying the phosphate group (i.e. X=CH_2) whilst, hopefully, retaining biological activity. Since these analogues only remotely resemble natural nucleotides, we expect them to get less involved in the vital processes of non-infected cells and hence to show less overt toxicity than agents currently used in the clinic, e.g. AZT.



R^1=H, Et
X=O, CH_2

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A New Synthesis of 2'-Deoxypyrimidine Nucleosides Involving Sodium Cyanoborohydride.

M. R. Almond, B. E. Reitter and J. L. Rideout. Burroughs Wellcome Co., 3030 Cornwallis Rd., Research Triangle Park, N. C. 27709 U.S.A.

Since the discovery that 3'-azido-3'-deoxythymidine significantly inhibits the replication of HIV[1], a tremendous amount of effort has been directed toward the synthesis of nucleoside analogs with higher therapeutic indices. To date, three nucleoside analogs (AZT, ddI and ddC) have been approved for the treatment of AIDS. With these discoveries have come the increased demands for the production of large quantities of nucleoside precursors. Chu[2] has recently reported a new synthesis of 2'-deoxyuridine from uridine. Chu notes that 2'-deoxyuridine supplies are limited and that the compound is prohibitively expensive. In addition, several investigators have published new syntheses of thymidine[3, 4]. This poster will describe alternate syntheses of 2'-deoxyuridine and thymidine. The key step involves the dehalogenation of a 2'-halo-2'-deoxynucleoside using sodium cyanoborohydride.

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2) Huang, H. and Chu, C. K. *Syn. Comm.* **1990**, 20, 1039.
3) Murtiashaw, C. W. European Patent Application 0 351 126 A2
4) Freskos, J. N. and Senaratne, K. P. A. U.S. Patent 4,914,233, **1990**.