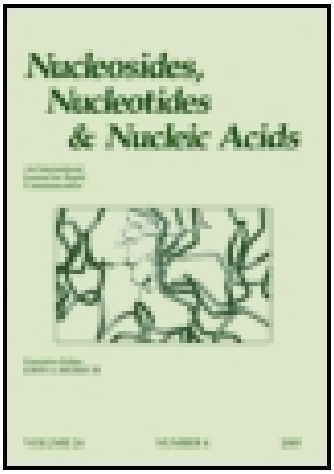

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2′-and/or 3Y-Deoxy-β-L-pentofuranosyl Nucleoside Derivatives: Stereospecific Synthesis and Antiviral Activities

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2'- AND/OR 3'-DEOXY-β-L-PENTOFURANOSYL NUCLEOSIDE DERIVATIVES: STEREOSPECIFIC SYNTHESIS AND ANTIVIRAL ACTIVITIES

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Abstract: Several L-enantiomers of nucleoside analogues were stereospecifically synthesized by a multi-step reaction from L-xylose and their antiviral properties were examined *in vitro*. Two of them, namely β-L-2',3,'-dideoxycytidine (β-L-ddC) and its 5-fluoro derivative (β-L-FddC) were found to have potent anti-human immunodeficiency virus (HIV) and significant anti-hepatitis B virus (HBV) activities in cell cultures.

Initial interest in L-nucleoside enantiomers dates from thirty years ago, when Smejkal and Sorm described the first synthesis of L-thymidine.[1] Afterwards, the mirror images of all the natural ribo- and 2'-deoxyribonucleosides were reported,[2] and more recently the potential of antisense oligonucleotides based on enantiomeric L-DNA[3] and L-RNA[4] has been discussed.

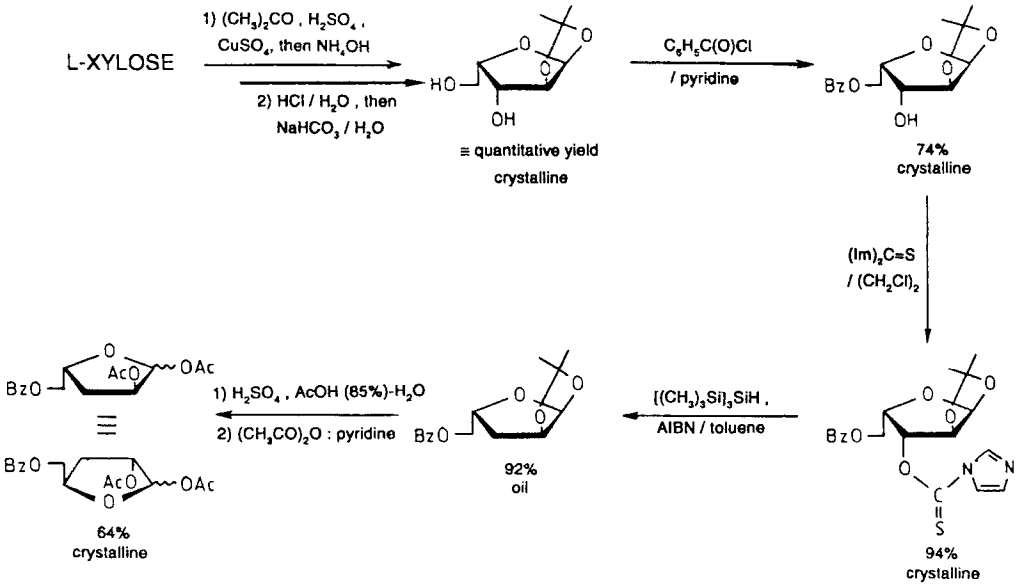
With regard to nucleoside analogues modified on the sugar or the base moiety, little attention has been given to L-enantiomers since until now it was believed that such isomers cannot be recognized by the enzymes involved in nucleic acids metabolism, and thus would not possess biological activity. However, following the pioneering works of Belleau et al.,[5] the findings that the

pure « L »-enantiomers of several promising anti-HIV and anti-HBV dioxolane[6] and oxathiolane[7] nucleoside analogues are more potent than the corresponding D-enantiomers or the racemic mixtures have led to the reconsideration of this postulate

For our part, several years ago we undertook the synthesis and the study of new series of L-nucleoside analogues.[8–13] More recently we were intrigued by the contradictory published data for β-L-dideoxycytidine, the L-enantiomer of the anti-HIV drug ddC. In 1988, Okabe et al.[14] reported that this antipode of ddC showed no activity against HIV, but three years later Mansuri et al.[15] asserted that this compound exhibited some activity against the same virus. In order to resolve the discrepancy, we decided to develop a stereospecific synthesis of the β anomer of L-ddC. Additionally, we also undertook the synthesis of its 5-fluoro derivative, as it is known from the literature[16] that introduction of a halogen in the 5-position of pyrimidine nucleosides usually preserves or enhances the biological potency of the parent compound.

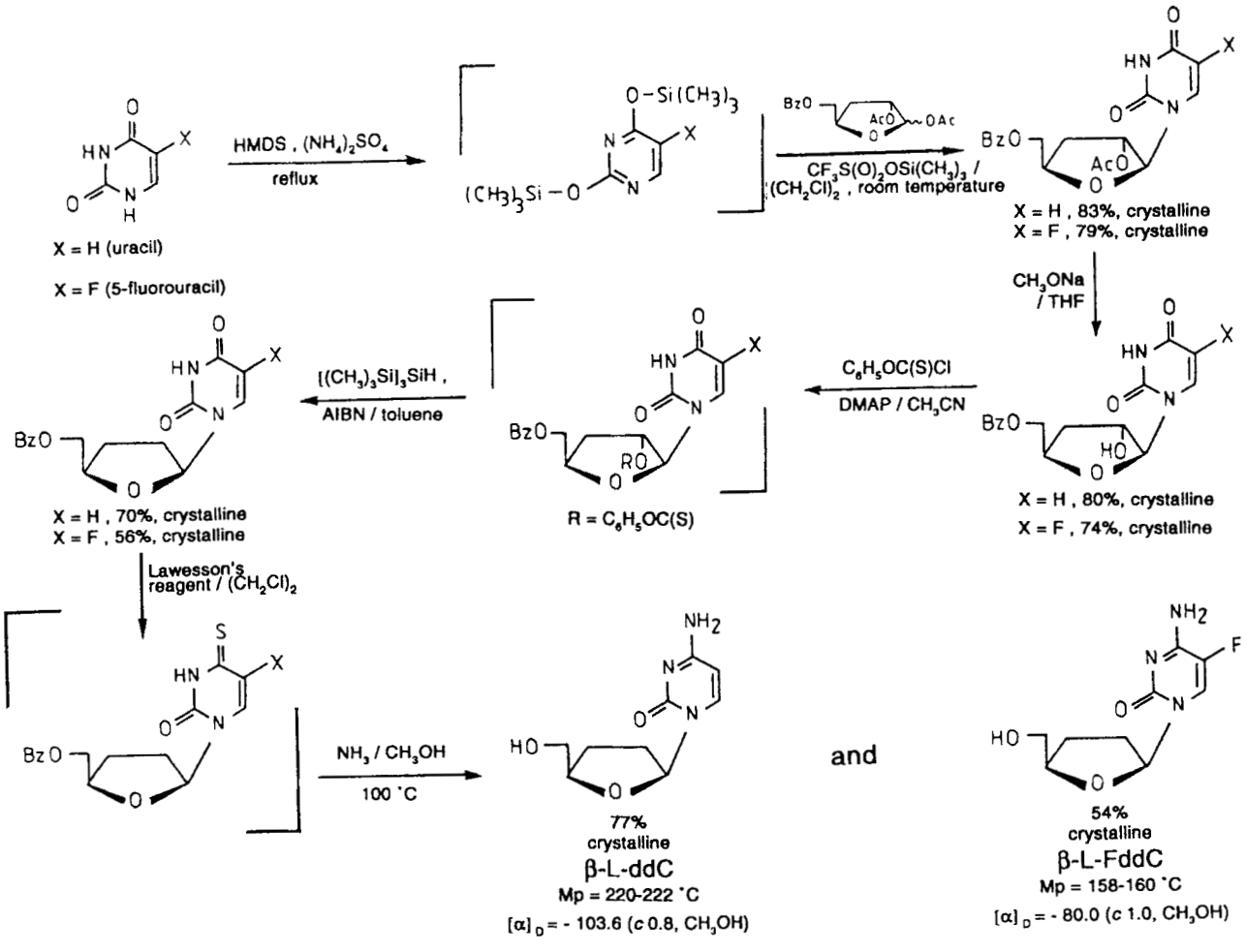
From a synthetic view point, starting from L-xylose, we first prepared in several steps and in good yield a fully acylated L-sugar, hitherto unknown and already deoxygenated in its 3 position (Scheme 1). This sugar was condensed with silylated uracil and silylated 5-fluorouracil to give the corresponding fully protected nucleosides. These compounds were selectively deacylated at their 2' position, and then subjected to a deoxygenative hydrogenolysis. Finally, pure β-L-ddC and β-L-FddC were obtained as crystalline compounds *via* the intermediacy of their thioamide derivatives (Scheme 2).

The newly synthesized β-L-ddC and β-L-FddC were studied in detail and compared to their D-enantiomers and to AZT.[17–20] From these studies the anti-HIV properties of β-L-ddC were confirmed and its antiviral activity was extended to HBV. More important, in all cases β-L-FddC exhibited better antiviral activities, and the main results regarding this compound are summarized below: i) β-L-FddC has potent antiretroviral (HIV-1, HIV-2, SIV) activities in cell culture systems including lymphocytes and macrophages; ii) it has significant



-Scheme 1-

anti-HBV activity in HBV transfected human liver cells but it is devoid of effect against other DNA and RNA viruses; iii) this compound, which is more active and selective than its D-enantiomer, shows minor toxicity (lymphocytes, bone marrow cells) and no inhibitory effect on DNA mitochondrial content; iv) β-L-FddC is not cross-resistant with AZT and with the non-nucleoside reverse transcriptase inhibitor nevirapine, but it shows cross-resistance with the « L » oxathiolane enantiomers 3TC and FTC; v) its triphosphate inhibits HIV-1 reverse transcriptase and woodchuck hepatitis virus DNA polymerase at micromolar concentrations whereas it does not inhibit cellular DNA polymerases (α, β) at concentrations up to 100 μM. Furthermore, we have found than the antiviral activity of β-L-FddC is reversed by 2'-deoxycytidine and that this compound has synergistic effects with AZT when evaluated in combination on cell-to-cell infection from different patient'cells to activated normal lymphocytes.



-Scheme 2-

In conclusion, the data so far presented suggest that further preclinical development of β-L-FddC seems warranted to determine its benefit for the treatment of infections caused by HIV and HBV. Moreover, it is noteworthy that during the completion of our work, three other groups also reported the synthesis and biological activities of β-L-FddC.[21–23] The results of their antiviral evaluation are consistent with our findings. Thus, the striking properties of β-L-FddC, and to a lesser extent those of β-L-ddC, provide a strong rationale for studying the L-enantiomers of other nucleoside analogues. Work is in progress in our laboratory on this topic.

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