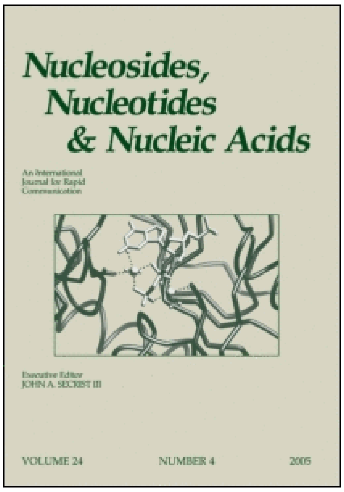

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of Isomeric Dideoxynucleosides with Partial Symmetry

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SYNTHESIS OF ISOMERIC DIDEOXYNUCLEOSIDES WITH PARTIAL SYMMETRY

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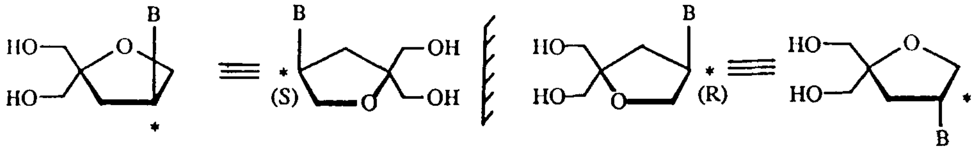
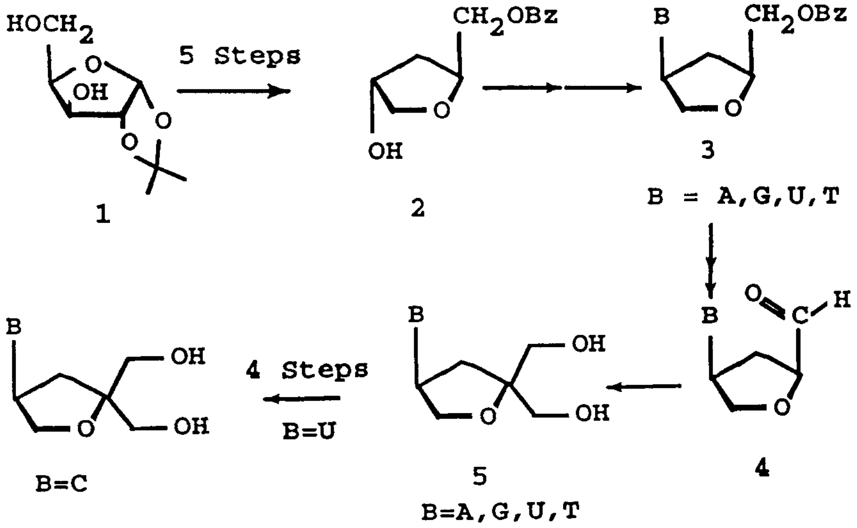
Abstract: Approaches to the synthesis of (S) and (R) enantiomers of hydroxymethylated isodideoxynucleosides have been developed. Because of the symmetry introduced at the carbon that normally bears the -CH_2OH group, these compounds have only one asymmetric center and each enantiomeric series may be viewed as being both D- and L-related.

Nucleoside and nucleotide analogues such as 3'-azido-3'-deoxythymidine (AZT), dideoxycytidine (ddC), and dideoxyinosine (ddI) have shown remarkable activity as inhibitors of the human immunodeficiency virus (HIV).[1-3] However, their toxicities, which include bone marrow toxicity, peripheral neuropathy, pancreatitis and hepatotoxicity, have posed some problems concerning their long-term usefulness. The development of resistant strains on prolonged clinical use of these compounds and their cross resistance to related nucleosides also limits their utilization. For this reason, the synthesis of new and different nucleosides is of significance in this area. Additionally, if the new nucleosides are structurally unlike the currently used antiviral agents, the probability of cross resistance would be expected to be diminished. In some recent studies, Maag, Prisbe and coworkers[4] have suggested that some 2'-deoxynucleosides bearing modifications at the 4'-α-position show anti-HIV activity in CD-4^+ (A 3.01) cell lines. Our investigations on novel isomeric dideoxynucleosides of potential anti-HIV interest[5-10] led us to the study of 2'-isomeric dideoxynucleosides bearing functionalities at the 4'-position (see Scheme 1 for generalized structures). Because of the symmetry introduced at the 4'-position, these molecules have only one asymmetric center which is at the carbon bearing the base moiety. Additionally and interestingly, each enantiomeric series may be viewed as being both D- and L-related.

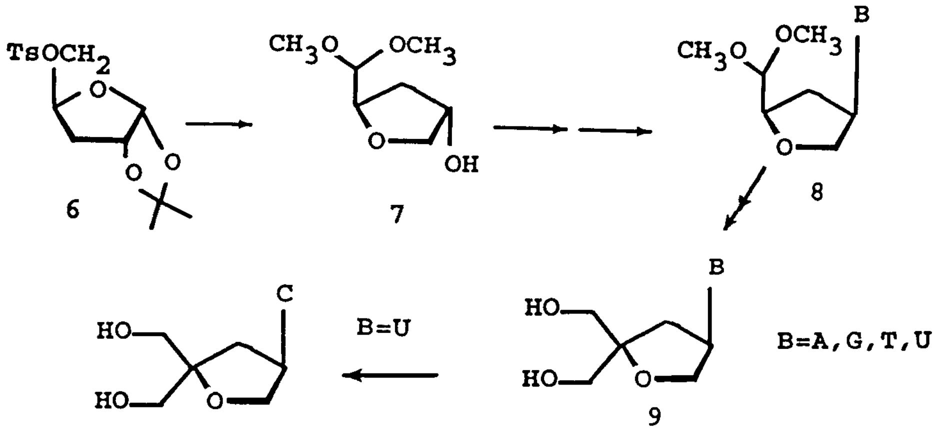


Scheme 1

Synthesis of compounds of the (S)-series was approached with the deoxy sugar **1**, prepared in a few steps from D-xylose. Compound **1** could be converted in several steps as described previously[7] to the isomeric nucleosides **3**. Oxidation of deprotected **3** to the aldehyde **4** followed by a sequential aldol condensation and Cannizzarro reaction[11] gave the desired bis-hydroxymethyl target compound **5**. The hydroxymethyl (S)-isodideoxycytidine analogue was synthesized from the corresponding isodideoxyuridine.



Synthesis of compounds of the (R)-series used the tosylate **6** as the starting compound. Treatment of **6** with methanolic acetic acid[12] gave the rearranged compound **7** which was coupled via its tosylate to the various bases to give the nucleosides **8**. Hydrolysis of **8** followed by the aldol-Cannizzarro sequence gave the target (R)-compounds **9**. As in the (S)-series, the hydroxymethyl (R)-isodideoxycytidine analogue was synthesized from the corresponding (R)-isodideoxyuridine.



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