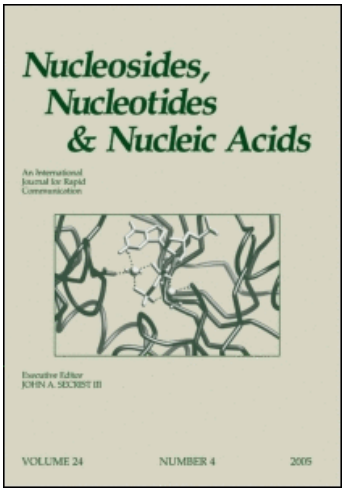

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Base-Transposed Chiral Isomeric Nucleosides

Vasu Nair[a]; Lawrence B. Zintek[a]; Pascal J. Bolon[a]; Todd B. Sells[a]
[a] Department of Chemistry, University of Iowa, Iowa City, Iowa, U.S.A.

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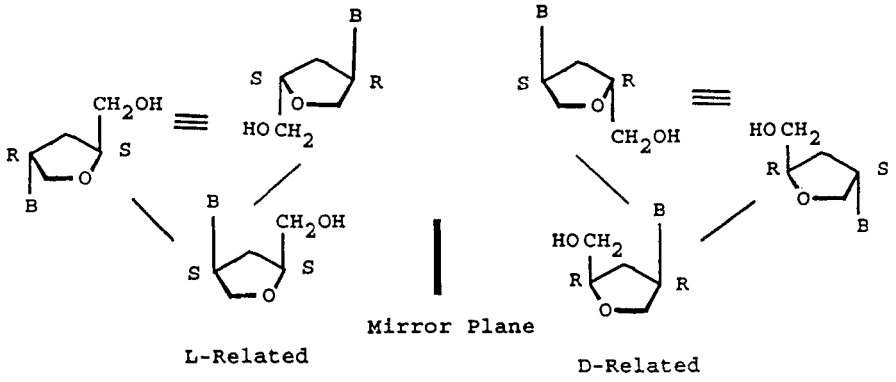
BASE-TRANSPOSED CHIRAL ISOMERIC NUCLEOSIDES

Vasu Nair,* Lawrence B. Zintek, Pascal J. Bolon and Todd B. Sells
Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, U.S.A.

Abstract: The synthesis and anti-HIV activities of a number of new analogues of base-transposed chiral isomeric nucleosides are described. Modifications of the anti-HIV active compound, (S,S)-isodideoxyadenosine, included both the base and carbohydrate regions.

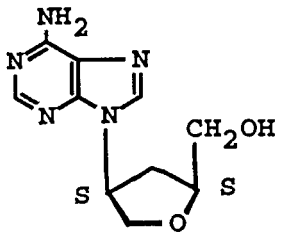
Considerable attention has been focused recently on the synthesis of novel dideoxynucleosides with the realization that compounds of this family are potential inhibitors, as their triphosphates, of HIV RT. Although numerous dideoxynucleosides have been prepared and investigated for their antiviral activity,[1-4] the search still continues for new structures that have the potential for anti-HIV activity, that are not closely related to compounds in clinical use and that would not be cross-resistant to drug-resistant strains of HIV. Recent studies in our laboratory[5-10] and elsewhere[11,12] have focused attention on the synthesis of novel isomeric dideoxynucleosides where there is transposition of the base or the -CH_2OH from the normal position to a different location in the carbohydrate component. This paper reports on progress of our work with 2'- and 3'-isomeric dideoxynucleosides of antiviral interest including new analogues of these families.

Isomeric dideoxynucleosides where the base is transposed from the natural 1'-position to the 2'-position, their mirror images and their diastereoisomers are shown in Scheme 1. The focus of much of our recent work in this area has been with the (S,S)-isodideoxynucleosides. The most antivirally active compound synthesized in this series is (S,S)-isodideoxyadenosine (**1**). This compound may be viewed as belonging to the class of L-related dideoxynucleosides. Its diastereoisomer, the (S,R) compound **2**, has also been synthesized by us. Both (S,R) and (R,S) enantiomers (**3** and **4**) of the related 3'-isomeric nucleosides have also been synthesized by methodologies related to the synthesis of **1**.[6,7] Compound **1** exhibited potent anti-HIV activity against HIV-1 in MT-4 cells with

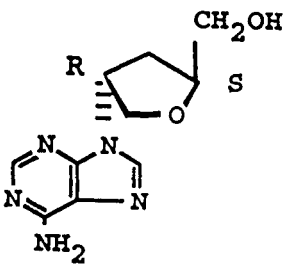


Scheme 1

relatively low toxicity. Its "glycosidic bond" is very stable with respect to hydrolytic cleavage. This compound is metabolically stable towards mammalian adenosine deaminase. The diastereoisomer of **1**, i.e. compound **2**, was inactive. The 3'-isomeric dideoxynucleoside series, **3** and **4**, showed only low antiviral activity.



1



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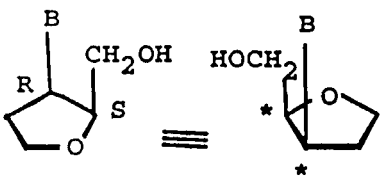

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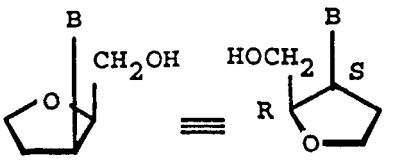

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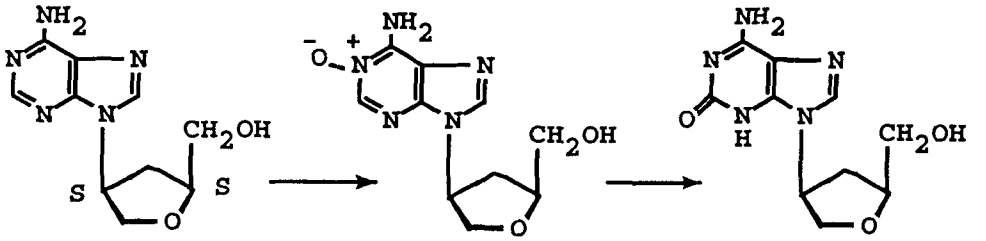
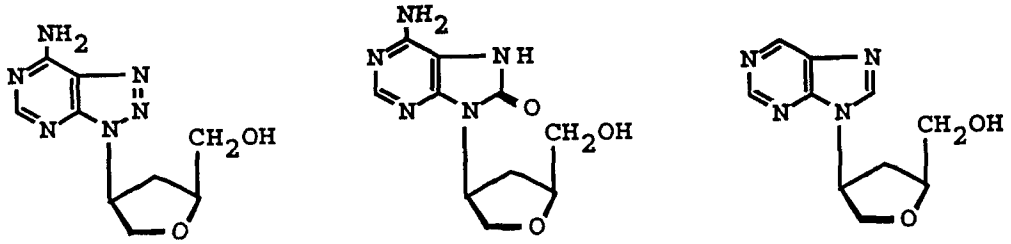


5

Scheme 2

We have also synthesized a number of derivatives of the active compound **1**. For example, the 2-hydroxy analogue of **1** (isodideoxyisoguanosine **5**) was synthesized from the photochemical rearrangement of the N-oxide of **1** (Scheme 2).

Other modifications of the base moiety of (S,S)-isodideoxyadenosine include the 8-aza analogue **6**, the 8-hydroxy compound **7**, and the deaminated analogue **8**. Anti-HIV screening indicated that these compounds were either inactive or had very low activity. The inactivity of **6** was not anticipated.



6 7 8

Modification of the carbohydrate moiety of (S,S)-isodideoxyadenosine was also carried out, including introduction of functionality at the carbon bearing the -CH_2OH (e.g. azido, hydroxymethyl) and also chain elongation of -CH_2OH. Antiviral studies of these carbohydrate modified compounds are in progress.

ACKNOWLEDGMENTS

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