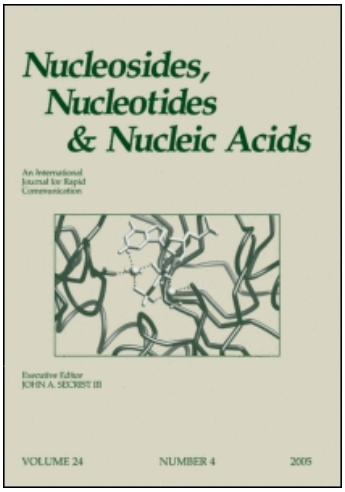

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Synthesis of Nucleosides Having Unusual Branched Sugars as Potential Antiviral Agents

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SYNTHESIS OF NUCLEOSIDES HAVING UNUSUAL BRANCHED SUGARS AS POTENTIAL ANTIVIRAL AGENTS

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ABSTRACT: Enantiomerically pure novel nucleosides having unusual branched sugars were synthesized in a stereospecific manner from a common chiral pool of (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane and evaluated for antiviral activity.

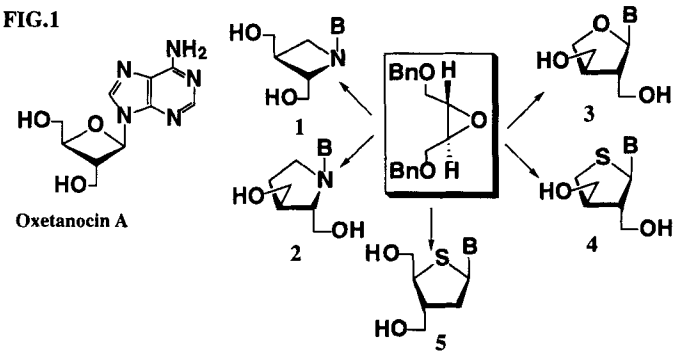
In the search for effective, selective, and nontoxic antiviral agents, a variety of strategies have been devised to design nucleoside analogs. These strategies have involved several formal modifications of the naturally occurring nucleosides, especially, alternation of the carbohydrate moiety. Since the naturally occurring purine nucleoside analog oxetanocin A and its derivatives have been found to be effective as anti-HIV-1 and anti-herpes virus agents,[1] the syntheses of different types of hydroxymethyl-branched nucleosides (the so-called ring-modified oxetanocin A analogs) have been reported. To further evaluate the structure-activity relationship of hydroxymethyl-substituted nucleosides, we have accomplished the synthesis of unusual branched sugars having bis-hydroxymethyl groups and their nucleosides (i. e. 1, 2, 3, 4, and 5). As shown in Fig.1, the synthesis of all of the branched sugars was started from (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane prepared from (+)-diethyl-L-tartrate.[2]

Synthesis of purine and/or pyrimidine nucleosides from the newly synthesized branched sugars was performed according to the general methodology.[3]

The synthesized nucleosides were evaluated *in vitro* against HSV-1 and HSV-2 in Vero cells by a plaque reduction assay and HIV-1 in MT-4 cells by an indirect immunofluorescence assay, respectively (Table 1). Compounds **1-a** and **1-g** were found to demonstrate potent anti-HIV-1 activity at approximately the same level as ddI with EC_{50} values of 0.37, 0.46, and 0.46 μg/ml, respectively.

In summary, we have developed the synthesis of novel nucleosides having unusual branched sugars as analogs of oxetanocin A. We have identified [(2'*S*, 3'*S*)-

FIG.1



bis(hydroxymethyl)azetidin-1-yl] adenine (**1-a**) and -guanine (**1-g**) as good inhibitors of HIV-1 replication.

TABLE 1 Antiviral activities against HSV-1, HSV-2, and HIV-1

Compound	EC_{50} μg/ml[a] HSV-1	HSV-2	HIV-1
1-a	33.2	34.9	0.37
1-g	5.36	6.32	0.46
1-t	>100	>100	>100
1-c	>100	>100	>100
2-a	>100	>100	>100
2-g	>100	>100	>100
2-t	>100	>100	>100
3-a	>100	>100	>100
3-t	>100	>100	>100
3-c	>100	>100	>100
4-a	>100	>100	>100
4-t	>100	>100	>100
5-a	>100	>100	>100
5-t	>100	>100	>100
ddI	ND[b]	ND	0.46
AZT	ND	ND	0.0032
acyclovir	0.32	0.39	ND

a : Concentration required to inhibit HSV-1-, HSV-2-, or HIV-1-induced cytopathic effect by 50 %.

b : Not determined.

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