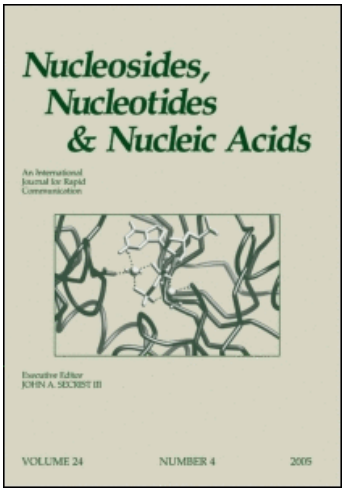

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Methylenecyclopropane Analogues of Nucleosides: Synthesis, Absolute Configuration, and Enantioselectivity of Antiviral Effect of (*R*)-(-)- and (*S*)-( )-Synadenol

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METHYLENECYCLOPROPANE ANALOGUES OF NUCLEOSIDES: SYNTHESIS, ABSOLUTE CONFIGURATION, AND ENANTIOSELECTIVITY OF ANTIVIRAL EFFECT OF (*R*)-(-)- AND (*S*)-(+)-SYNADENOL

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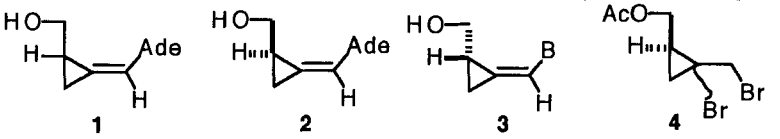
ABSTRACT. Synthesis, absolute configuration and antiviral activity of enantiomeric antiviral agents (*R*)-(-)- and (*S*)-(+)-synadenol (**2** and **3a**) are described.

Recently, we have described a new class of nucleoside analogues comprising a methylenecyclopropane moiety and exhibiting a broad-spectrum antiviral activity[1-5]. Purine analogues **1a - 1d** are of particular interest in view of their potent in vivo activity in a mouse model of cytomegalovirus (CMV) infection[6]. The biological activity has been investigated with racemic mixtures of these analogues. Therefore, availability of enantiomers and investigation of enantioselectivity of the antiviral effect have become of prime importance. We now wish to report synthesis and biological investigation of (*R*)-(-)- and (*S*)-(+)-synadenol (**2** and **3a**). Deamination of racemic **1a** by adenosine deaminase afforded (-)-synadenol (**2**, $[\alpha]_D^{25}$ -120°, c 0.1, MeOH) and (+)-synhypoxanthol (**3b**, $[\alpha]_D^{25}$ 112.5°). The latter was converted to (+)-synadenol (**3a**, $[\alpha]_D^{25}$ 123°) by the procedure described for the synthesis of (*S*)-adenallene[7]. More convenient is alkylation of adenine with agent **4** derived from the known[8] *R*-methylenecyclopropanecarboxylic acid according to the procedure[1,5] elaborated for racemic compound **1a**. This method is also

generally suitable for synthesis of other enantiomeric methylenecyclopropane analogues. The obtained (*R*)-synadenol was identical (chiral HPLC) with the (-)-enantiomer **2** from enzymic deamination. The *R* configuration of the (-)-enantiomer was also confirmed by X-ray diffraction. These results have also shown that the previous assignment of *S*



1a: B = Ade, **1b**: B = Gua, **1c**: B = 2-amino-6-methoxypurine,
1d: B = 2-amino-6-cyclopropylaminopurine, **3a**: B = Ade, **3b**: B = hypoxanthine

configuration to (-)-synadenol (**2**) is erroneous[9]. Biological assays revealed significant differences in enantioselectivity of antiviral effect. Virtually no enantioselectivity was observed against HCMV, VZV and HBV. Some preference for the *S*-enantiomer **3a** was seen in HSV-1 and HSV-2 assays where **1a** is only a moderate inhibitor[1]. The *R*-enantiomer was strongly favored in cultures infected with EBV and HIV-1. It is possible that these differences reflect varying mechanisms of action of synadenol (**1a**) in cell cultures infected with particular viruses. A full account of these results will be published elsewhere[10].

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