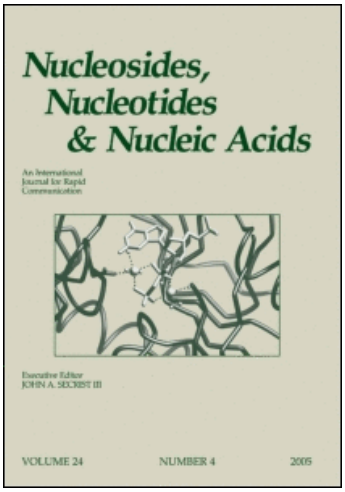

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES

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ABSTRACT

Synthesis and antiviral activity of methylenedifluorocyclopropane analogues **8a**, **8b** and **9a**, **9b** are described.

In the last two years we have accumulated a wealth of information (1–11) on chemistry and antiviral activity of methylenecyclopropane analogues **1** and **2**. Very recent studies of structure-activity relationships of this group of compounds indicated that interchange of base and hydroxymethyl groups (12) (compounds **3** and **4**) or expansion of the cyclopropane ring (13) (compounds **5** and **6**) abolished the antiviral activity of **1** (B = adenine). Replacement of the remaining double bond in **1** or **2** with an additional cyclopropane ring afforded adenine and guanine spiropentane analogues **7** (four isomers each) with a diminished antiviral potency (14). Therefore, we have focused our efforts on compounds with a preserved methylenecyclopropane system. Because substitution of hydrogen with fluorine led in many cases to biologically active analogues (15), we have now synthesized methylenedifluorocyclopropanes **8a**, **8b** and **9a**, **9b**.

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Chart 1

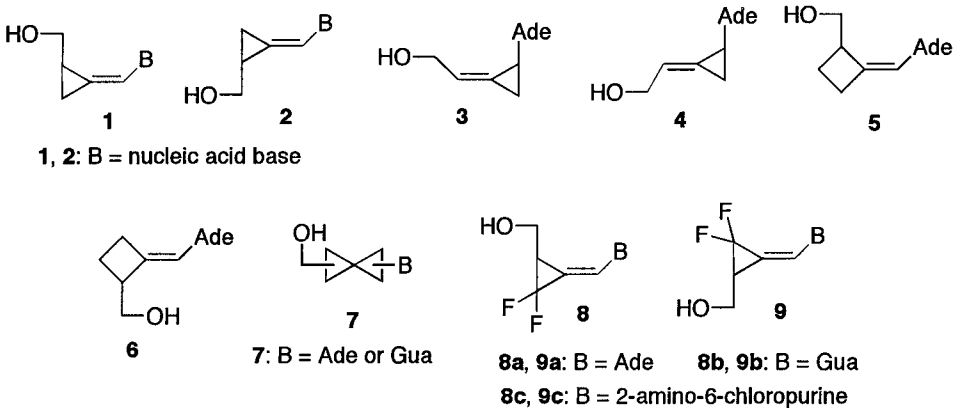
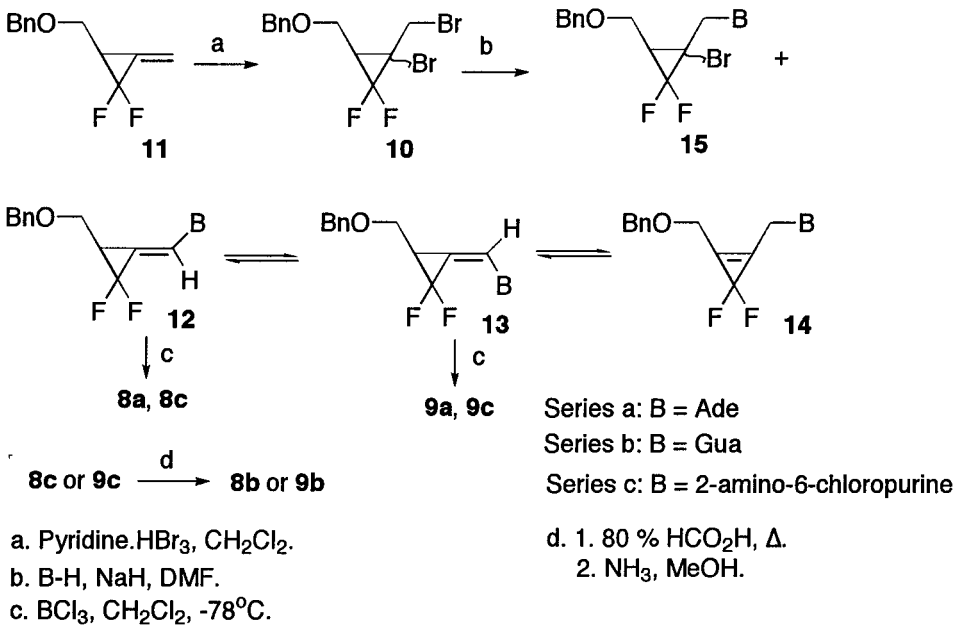


Chart 1.

The key reagent **10** for alkylation-elimination procedure (1) with nucleic acid bases was obtained by addition of bromine (using pyridinium hydrobromide perbromide) to the known (16) methylenedifluorocyclopropane **11**. Reaction of **10** with sodium salt of adenine in DMF for 16 h at room temperature afforded a mixture of three products which were separated by column chromatography on silica gel: *Cis*-isomer (17) **12a** (21%), *trans*-isomer **13a** (7%) and cyclopropene **14a** (25%).



Scheme 1.

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Deprotection of **12a** and **13a** using BCl_3 afforded target analogues **8a** and **9a** in 75 and 77% yield, respectively. In a similar fashion, alkylation-elimination procedure of **11** with 2-amino-6-chloropurine gave compounds **12c**, **13c** and **14c**. The product of a simple alkylation, compound **15b**, was also isolated. After deprotection of **12c** and **13c**, analogues **8c** and **9c** were obtained. Hydrolysis (1) of **8c** and **9c** furnished guanine analogues **8b** and **9b**. Structures of all new compounds were confirmed by ^{1}H, ^{13}C and ^{19}F NMR, UV and mass spectra including nuclear Overhauser effect (NOE) data for analogues **8a** and **9a**.

Kinetic studies of cyclopropene-methylenecyclopropane rearangement (19,20) with compounds **12c**, **13c** and **14c** under base catalysis /1,5-diazabicyclo [4.3.0]non-5-ene (DBN), acetonitrile, room temperature/ by HPLC have provided a strong evidence that composition of the products of alkylation-elimination procedure is thermodynamically controlled.

Compound **8a** inhibited the replication of human cytomegalovirus (HCMV) in human foreskin fibroblast (HFF) culture with EC_{50} 21 μM and it was non-cytotoxic ($IC_{50} > 100\mu$M) in HFF and KB cells. Against HSV-1 in BSC-1 cells (ELISA assay), EC_{50} was 70 μM. Interestingly, it was less potent than synadenol (1) (**1**, B = adenine) but more effective than the corresponding saturated difluorocyclopropane analogue (21). Compounds **8b**, **9a** and **9b** were without effect ($EC_{50} >$ 100 μM). None of the analogues was effective against HIV-1. Other antiviral tests are being continued.

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