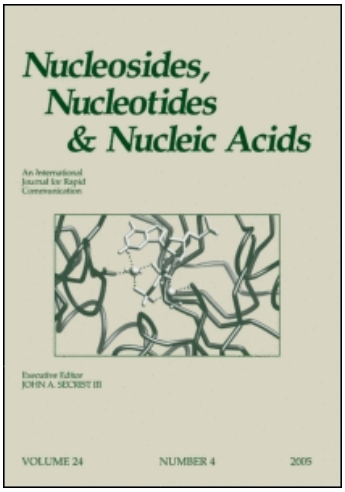

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SYNTHESIS AND ANTIVIRAL EVALUATION OF 3'-BRANCHED NUCLEOSIDE ANALOGUES

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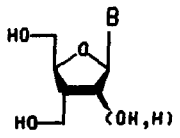
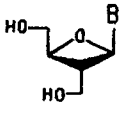
A common structural feature shared by the representative nucleoside analogues active against HIV is the lack of hydroxyl substituents at the positions C-2' and C-3' of the furanose ring.[1] These analogues, which include AZT ,ddI, D4T, ddC, 3'-FddT, are first converted to their 5'-O-triphosphates, which then exert their biological effect either as reverse transcriptase (RT) inhibitors or chain terminators or both.[2]

We reasoned, that introduction of a methylene spacer between C-3' and the hydroxyl group might cause the resulting 3'-deoxy-3'-C-hydroxymethyl nucleoside analogues I to act as RT inhibitors or chain terminators. The spatial orientation of the hydroxyl groups in these compounds may also be similar to those in the oxetanocins (II) which have a broad spectrum antiviral activity,[3] and the acycylic anti-herpes nucleoside analogues like DHPG (III).[4] Few 3'-deoxy-3'-C-hydroxymethyl nucleoside analogues are mentioned in the literature,[5] no data on their anti-viral activity is available.[6] We report here on a series of 3'-deoxy-3'-C-hydroxymethyl analogues of natural ribonucleosides and 2'-deoxyribonucleosides.



I



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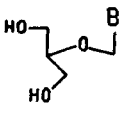
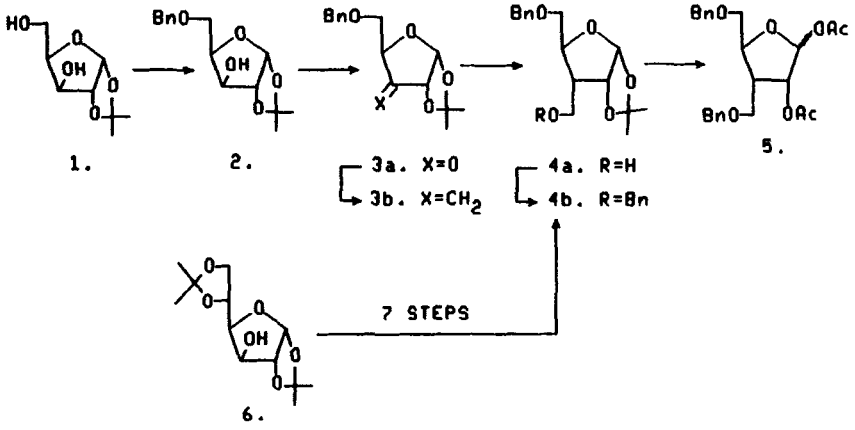


III

B = Purine, Pyrimidine B = Adenine, Guanine B = Guanine

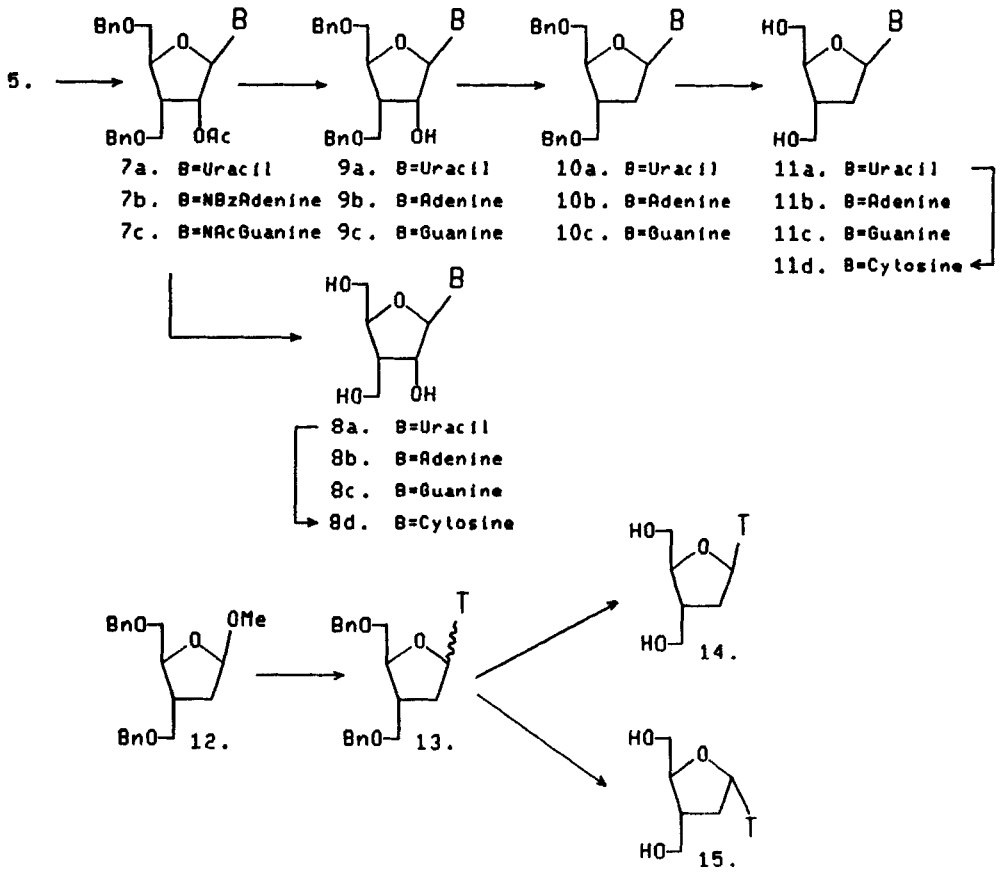
Our synthesis begun with elaboration of a suitably protected xylofuranose or glucofuranose. 1,2-O-isopropylidene-D-xylofuranose **1** was monobenzylated through a cyclic stannate to afford **2**, oxidation followed by reaction with methylenetriphenylphosphorane gave methylenefuranose **3b**. Hydroboration of **3b** yielded the 3-α-C-hydroxymethyl isomer **4a**, which was benzylated to afford the known dibenzyl acetonide **4b**. The acetonide moiety in **4b** was removed by acid hydrolysis followed by acetylation to form the key furanose synthon **5** as an anomeric mixture. Alternatively, a literature approach[7] from 1,2:5,6-di-O-isopropylidene-D-glucofuranose **6** was followed, to give the same dibenzyl acetonide **4b**.



The furanose synthon **5** was coupled with appropriate nucleic bases under Vorbruggen conditions;[8] the resulting 1-β-products **7a-c** were then deprotected to the desired analogues of ribonucleosides **8a-c**. The cytosine analogue **8d** was prepared from the uracil analogue **7a** by deprotection, acetylation, and amination,[9] which proceeds with deacetylation.

The 2'-deoxyribonucleoside analogues were prepared by selective 2'-deprotection of the nucleoside products **7**, followed by 2'-deoxygenation (Barton-McCombie).[10,11] Deprotection of the resulting 2',3'-dideoxy-3'-C-hydroxymethyl products **10a-c** led to the 2'-deoxyribonucleoside analogues **11a-c**. The 2'-deoxyuridine analogue **11a** was acetylated and treated with Lawessons's reagent. Subsequent ammonolysis in methanol at elevated temperature afforded the 2'-deoxycytidine analogue **11d**.

The β-thymidine analogue **14** and its α-isomer **15** were prepared by a coupling of the known methyl furanoside **12** with thymine under Vorbruggen conditions. The resulting mixture of anomers **13** was subjected to the transfer hydrogenolysis conditions and free nucleoside analogues **14** and **15** were separated by HPLC.



The 3'-deoxy-3'-C-hydroxymethyl ribonucleoside and 2'-deoxyribonucleoside analogues were evaluated for in vitro inhibition of different pathogenic viruses. Several of the analogues (**8d, 11b, 11c**) showed activity against HIV, but only 1-(2,3-Dideoxy-3-C-hydroxymethyl-β-D-threo-pentofuranosyl)cytosine (**11d**) had a high level of viral inhibitory activity against HIV, and a broad range of DNA viruses (Table 1).

Table 1

Virus	MULV	HIV	HSV-1	HSV-2	HCMV	VZV	EBV
ED_{50} ug/mL	0.06[b]	0.02[c]	0.1[d]	0.5[d]	0.07[d]	0.9[d]	0.8
TC_{50}[a] ug/mL	>100[b]	8.5[c]	>100	>100	>100	37	35

a. Concentration affecting death of 50% of cells.
b. XC Method.
c. XTT Method.
d. Plaque reduction.

In a systemic HSV-1 infection in mice however compound **11d** was only slightly protective at 250 mg/kg/day. Most of the material appears to be rapidly excreted unchanged in the urine.

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