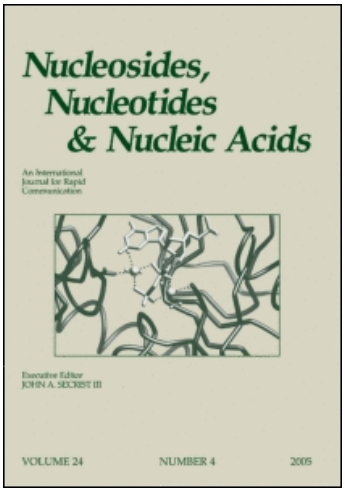

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4′-*C*-Methyl-β-D-ribofuranosyl Purine and Pyrimidine Nucleosides Revisited[†]

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ABSTRACT

In order to evaluate their antiviral properties, a series of 4′-*C*-methyl-β-D-ribofuranosyl purine and pyrimidine nucleosides has been prepared. Unfortunately, none of these 4′-branched nucleosides showed any antiviral activity or cytotoxcity when tested against HIV, HBV, and Yellow Fever virus.

Key Words: 4′-*C*-methyl-β-D-ribofuranosyl nucleosides; HIV; HBV; Yellow Fever virus.

[†]Dedicated to the memory of Martin Bryant, deceased on March 4, 2002.

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INTRODUCTION

In the search for new antiviral agents, various 4′-*C*-branched-2′-deoxynucleosides have been reported to have potent antiretroviral activity in vitro.[1] Regarding the 4′-C-methyl-β-D-ribofuranonucleoside derivatives, the synthesis of those bearing the five natural bases has been previously described but no biological data were reported.[2,3]

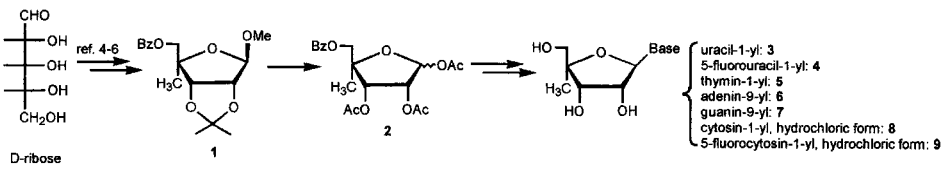
Based on these considerations, a series of 4′-*C*-methyl-β-D-ribofuranosyl purine and pyrimidine nucleosides **3**–**9** (Sch. 1) has been prepared in order to evaluate their antiviral properties.

SYNTHESIS OF THE 4′-*C*-METHYL-β-D-RIBOFURANOSYL PURINE AND PYRIMIDINE NUCLEOSIDES 3–9 (SCH. 1)

5-*O*-Benzoyl-4-*C*-methyl-1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose **1** was prepared in 8 steps according to published procedures.[4–6] Cleavage of the 2,3-*O*-isopropylidene group of **1**, followed by acetylation led to the hitherto unknown 5-*O*-benzoyl-4-*C*-methyl-1,2,3-*O*-acetyl-D-ribofuranose **2**. Condensation of **2**, under Vorbrüggen conditions, respectively with silylated uracil, 5-fluorouracil, or thymine afforded the corresponding fully acylated 4′-*C*-methyl-β-D-ribofuranosyl nucleosides. Regarding the purine nucleobases, 2 was either condensed with adenine or silylated O^6-diphenylcarbamoyl-N^2-isobutyrylguanine. Finally, treatment with saturated methanolic ammonia gave the title compounds **3**–**7**. Conversion of the uracil and 5-fluorouracil derivatives into the corresponding cytosine and 5-fluorocytosine 4′-*C*-methyl-β-D-ribofuranosyl nucleosides **8**–**9** was carried out via a treatment with Lawesson's reagent, followed by a treatment with saturated methanolic ammonia at 100°C.

ANTIVIRAL EVALUATIONS

The 4′-*C*-methyl-β-D-ribofuranosyl nucleosides **3**–**9** were evaluated for their in vitro inhibitory effects on the replication of HIV-1(IIIb) in MT-4 cell system, but none of them showed any antiviral activity or cytotoxcity (up to 100 μM, data not shown). When evaluated in anti-HBV assays in the HBV DNA-transfected



Scheme 1. Synthesis of the 4′-*C*-methyl-β-D-ribofuranonucleosides **3**–**9**.

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Hep-G2 cells (2.2.15 cells), none of the compounds tested **3**–**9** was active (up to a concentration of 10 μM) or cytotoxic (up to a concentration of 100 μM). Compounds **3**–**9** were also inactive and non-cytotoxic (up to a concentration of 100 μM) against Yellow Fever virus in BHK cell lines.

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