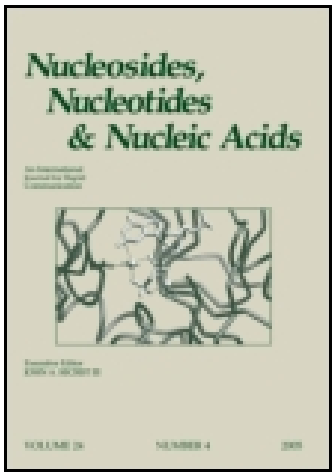

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SYNTHESIS AND STUDY OF CONFORMATIONALLY RESTRICTED 3′-DEOXY-3′,4′-EXO-METHYLENE NUCLEOSIDE ANALOGUES

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SYNTHESIS AND STUDY OF CONFORMATIONALLY RESTRICTED 3′-DEOXY-3′,4′-*EXO*-METHYLENE NUCLEOSIDE ANALOGUES

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▫ *Hitherto unknown restricted 3′-deoxy-3′,4′-exo-methylene nucleoside derivatives bearing the nucleic acid naturally occurring pyrimidine bases have been synthesized. The compounds were tested for their activity against HIV, HBV, and several RNA viruses, but they did not show significant antiviral effect.*

Keywords Nucleoside Analogues/Antiviral Agents

INTRODUCTION

Over several decades, a large number of nucleoside analogues have been synthesized and some of them have been shown to present potent antiviral or antitumoral activities. In order to discover new nucleoside derivatives endowed with biological activities, modifications of the base and/or sugar moiety of natural nucleosides can be attempted. For our part, we chose to introduce modifications on the sugar capable of restricting the dynamic equilibrium between the northern-type and southern-type geometry that normally characterize the sugar moiety of standard nucleosides in solution. In this respect, we have synthesized new conformationally locked nucleoside analogues built on a 2-oxabicyclo[3.1.0.]hexane system bearing purine and pyrimidine bases. Assuming that the conformation and puckering[1] of the glycon moiety of nucleosides play a critical role in modulating biological activity; for example, new conformationally restricted nucleoside analogues could be used to obtain further information regarding the correlation between sugar ring conformation and biological activity.

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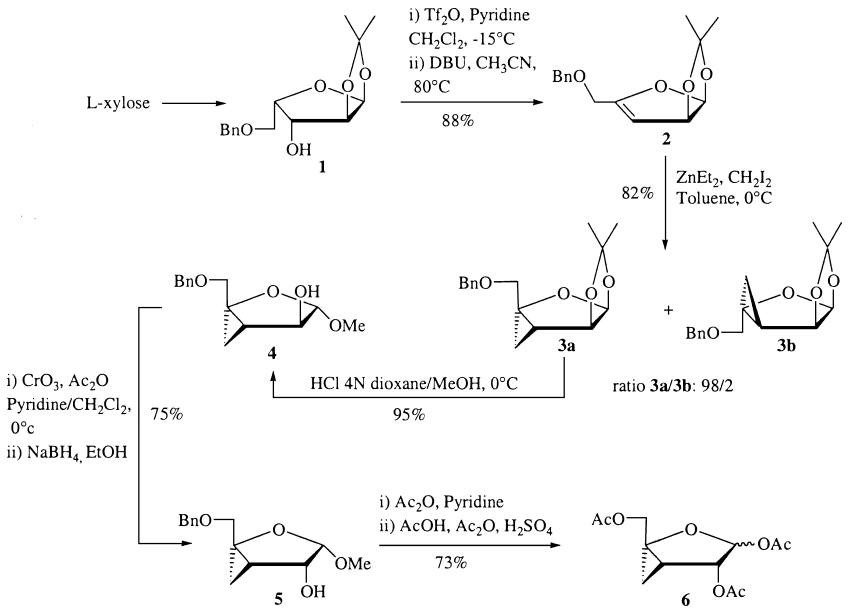
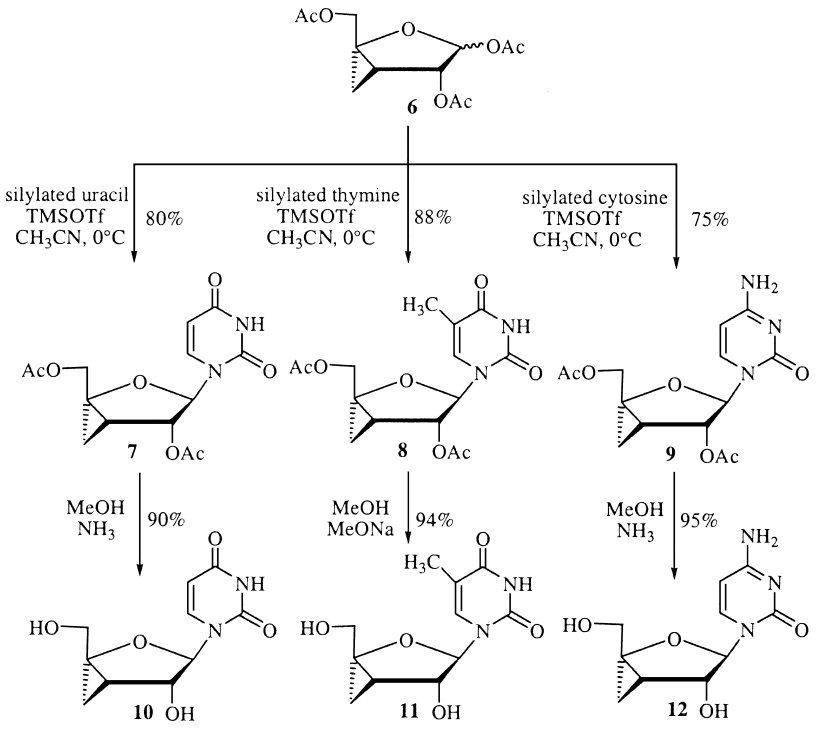


SCHEME 1 Synthesis of the sugar precursor 6.



SCHEME 2 Synthesis of the target nucleosides 10–12.

SYNTHESIS

The synthesis of compound **1** was achieved from L-xylose in 3 steps using a procedure previously established for D-xylose.[2] The cyclopropanation of compound **2** was accomplished via a Simmons-Smith reaction following Furukawa's procedure[3] to afford a mixture of compounds **3a** and **3b** (ratio **3a**/**3b**: 98/2). Separation of compounds **3a** and **3b** was readily achieved on silica gel column chromatography. Structural assignments of **3a** and **3b** were based upon ^{1}H NMR spectra and NOE effects. After cleavage of the isopropylidene group, an oxidation-reduction process gave stereospecifically compound **5**, which was finally converted into the sugar precursor **6**, obtained as a mixture of β- and α-anomers (ratio α/β: 9/91) with an 20% overall yield from L-xylose (Scheme 1).

Coupling reactions of sugar **6** with silylated bases (uracil, thymine, and cytosine) provided acetylated nucleosides **7–9** (Scheme 2). The deprotection of **7–9** afforded the target restricted 3′-deoxy-3′,4′-*exo*-methylene pyrimidine nucleoside analogues **10–12**.

Structural assignments for all the compounds were based upon their elemental analysis and physicochemical properties (melting point, ^{1}H NMR, ^{13}C NMR, UV, mass spectra, and optical rotation).

CONFORMATIONAL ANALYSIS

We used the program Pseurot[4] for the determination of the conformation of the furanose ring taking compound **11** as a model. After determination of parameters A and B using ΦHH = Aνj + B, a convergence was obtained toward a south-type conformation with P = 158° and ν_{max} = 23.9° (x [south = 0.69]) and north-type conformation with P = −26.5° and ν_{max} = 21.6°.

BIOLOGICAL EVALUATIONS

The nucleoside analogues **10–12** were tested for their in vitro inhibitory effects on the replication of HIV, HBV, and several RNA viruses. None of these compounds showed significant antiviral activity.

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