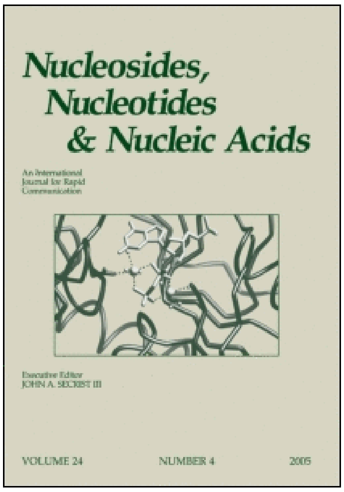

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Revisited 3'-Deoxy-3'-*C*-Methyl-β-D-Ribonucleoside Series

Mohamed Aljarah[a]; Sarah Couturier[a]; Gilles Gosselin[a]; Christophe Mathé[a]; Christian Périgaud[a]
[a] UMR 5625 CNRS-UM II, Université Montpellier II, Montpellier, France

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REVISITED 3′-DEOXY-3′-*C*-METHYL-*β*-D-RIBONUCLEOSIDE SERIES

Mohamed Aljarah, Sarah Couturier, Gilles Gosselin, Christophe Mathé, and Christian Périgaud □ *UMR 5625 CNRS-UM II, Université Montpellier II, Montpellier, France*

□ *The synthesis of some 3′-deoxy-3′-C-methylnucleoside analogues bearing naturally occuring nucleic acid bases was achieved from the preparation of a suitable peracylated 3-deoxy-3-C-methyl sugar using a stereoselective pathway. In addition, examples of chemical modifications at the 2′ position are presented.*

Keywords Nucleoside; stereoselective synthesis; glycosylation

INTRODUCTION

Nucleoside analogues represent an important class of chemotherapeutic agents.[1] Nowadays, several nucleoside analogues have been approved for the treatment of various viral infections such as herpes viruses, human immunodeficiency virus (HIV) and hepatitis B virus. In order to discover new series of nucleoside analogue able to interfere with cellular and viral proliferation, different chemical modifications of both the base and/or the sugar moiety of natural nucleosides may be attempted. In the course of our ongoing research, we have synthetized hitherto unknown 3′-*C*-branched nucleoside analogues from a sugar precursor incorporating a methyl group on the 3′ position.

SYNTHESIS OF THE SUGAR PRECURSOR

The preparation of the osidic precursor required introduction of a methyl group on the position 3 of the sugar moiety. In the first synthetic pathway, this introduction involved reduction of an exocyclic methylene

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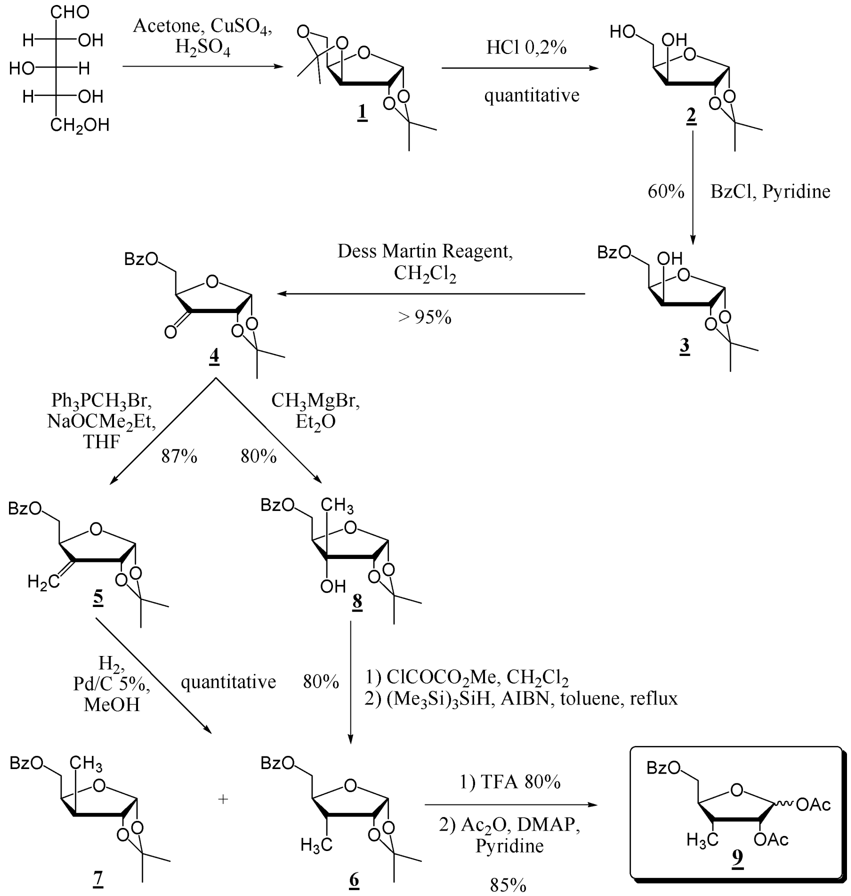
Address correspondence to Christian Périgaud, UMR 5625 CNRS-UM II, Case courrier 008, Place E. Bataillon, Université Montpellier II, 34095 Montpellier cedex 5, France. E-mail: perigaud@univ-montp2.fr



SCHEME 1

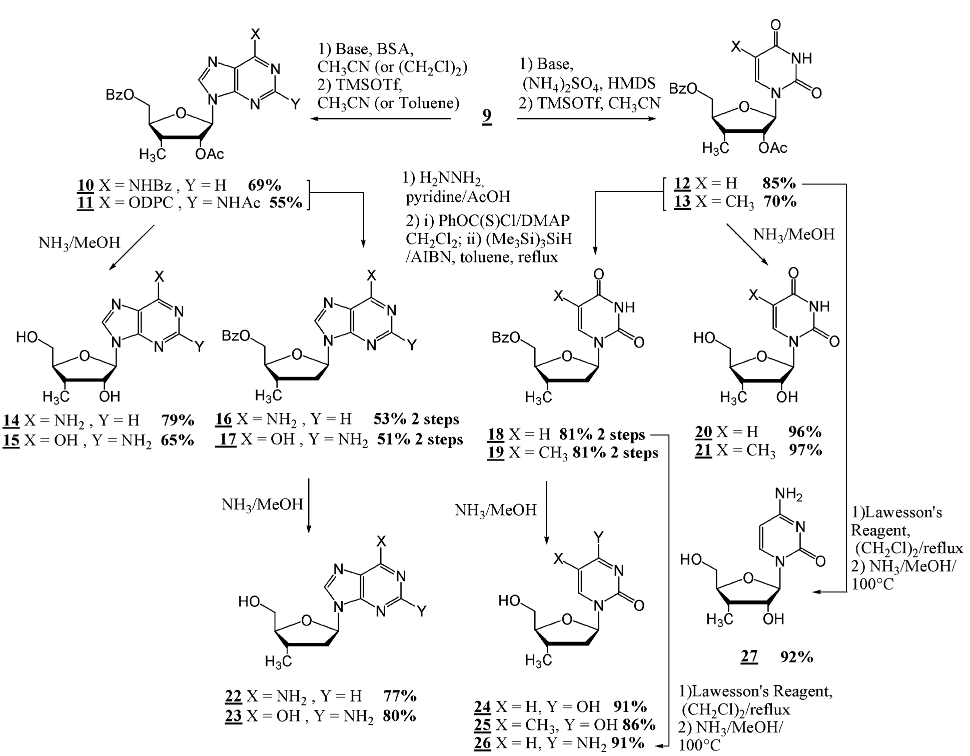
group previously obtained by a Wittig reaction on the keto sugar 4 (Scheme 1). Hydrogenation of the resulting exocyclic double bound in the presence of Pd/C was not as stereoselective as expected[2,3] and leads to the formation of two diastereoisomers 6 and 7 with a low diastereoselectivity for the desired isomer 6.

The influence of pressure, temperature, nature of the solvent and the catalyst on the stereoselectivity of the hydrogenation reaction have been investigated. Whatever the conditions used, the two diastereoisomers have been obtained with a ratio up to 80:20 in favour of the desired compound 6. Many attempts to separate these two diastereoisomers have been performed including crystallization, chromatography on silica gel, and reverse phases, without any success. In a second pathway, the methyl group has been introduced in position 3 by addition of methylmagnesium bromide on the ketosugar 4. This reaction leads only to compound 8,[4] which gives through radical deoxygenation the diastereoisomer 6 in a stereospecific way. Finally, the positions 1 and 2 have been deprotected then acetylated leading to the expected sugar precursor 9.

SYNTHESIS OF THE NUCLEOSIDE ANALOGUES

The sugar precursor 9 was glycosylated (Scheme 2) with different heterocyclic bases persilylated with *N,O*-bis(trimethylsilyl)acetamide (BSA) according to the Vorbrüggen procedure (uracil and thymine for pyrimidines,[5] *N*-6-benzoyladenine,[6] and *N*-2-acetyl-6-*O*-diphenylcarbamoyl-guanine[7] for purines).

Cleavage of the different protecting groups of compounds 10–13 give target ribonucleosides 14, 15, 20, and 21. Compounds 16–19 were obtained after regioselective deacylation and radical reductive process which upon deprotection provided the corresponding 3′-*C*-methyl-2′,3′-dideoxynucleosides 22–25. Conversion of uridine derivatives 12 and 18 to the cytidine derivatives 26 and 27 was done by conversion of the lactame function to thioamid followed by aminolysis.[8]



SCHEME 2

BIOLOGICAL EVALUATION

Evaluation of the antiviral and antitumoral activities of the 3′-deoxy-3′-*C*-methyl-nucleosides **14**, **15**, **20**, **21** as well as the 3′-*C*-methyl-2′,3′-dideoxynucleosides **22**–**25** is under investigation.

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