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Synthesis of *exo*-methylenedifluorocyclopentanes as precursors of fluorinated carbasugars by 5-*exo*-dig radical cyclization

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ABSTRACT

The synthesis of polyhydroxylated 1,1-difluoro-5-methylenecyclopentanes is described. The sequence involves an addition of $PhSeCF_2TMS$ to a tartrate-derived aldehyde or its corresponding *tert*-butanesulfinylimines followed by a radical cyclization. The use of a benzyl protected substrate led to an unproductive 1,5-hydrogen transfer after cyclization but the desired compound was eventually obtained from the unprotected substrate. A hydroboration/oxidation sequence was investigated on these 1,1-difluoro-5-methylenecyclopentanes as it would provide fluorinated carbasugars, a new and promising class of glycomimetics. Unfortunately, this reaction was poorly efficient and its regioselectivity not the expected one.

Presentation of the research group:
The group entitled "Synthesis of fluorinated biomolecules" is part of the COBRA laboratory UMR-CNRS-6014 located in Mont-Sain-Aignan. The group is headed by Xavier Pannecoucke (Pr. INSA-Rouen), with 6 permanent co-workers: Jean-Philippe Bouillon (Pr. Univ-Rouen), Dominique Cahard (DR CNRS), Samuel Couve-Bonnaire (lecturer INSA-Rouen), Philippe Jubault (Pr. INSA-Rouen), Eric Leclerc (CR CNRS) and Jean-Charles Quirion (Pr. INSA-Rouen).
Our research interests are dealing with the development of new methodologies in fluorine chemistry and their application to the synthesis of fluorinated biomolecules.
Methodological studies:

Enantioselective electrophilic fluorination and trifluoromethylation (chiral reagents, organometallic catalysis and organocatalysis).
Diethylzinc/Ethyldibromofluoroacetate: an original association for the synthesis of new fluorinated scaffolds.

Fluorinated biomolecules and applications:

- Fluorinated glycomimetics (C-glycosides and carba-sugars).
- Fluoroalkene as amide bond mimic: Asymmetric synthesis of fluorinated dipeptide analogues and synthesis of alkaloid analogues.
- Fluorinated polyfunctional cyclopropanes as therapeutic agents.
- Synthesis of trifluoromethylated heterocycles from perfluoroketene dithioacetals and γ-ketothioesters, for pharmaceutical applications.

1. Introduction

The development of new nucleoside analogues remains a productive approach for the development of antitumoral or antiviral agents. Indeed, these agents may act as inhibitors of various enzymes involved in the cell or viral replication processes. Depending on their degree of phosphorylation, inhibition of thymidilate synthetase, ribonucleotide reductase or DNA polymerases may occur, these nucleoside analogues acting either as competitive inhibitors or alternate substrates [1]. The use of a

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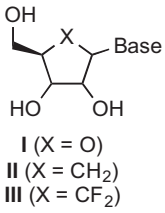
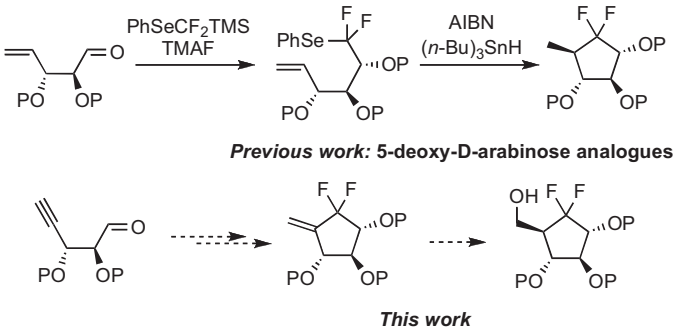


Fig. 1. Nucleoside and analogues.



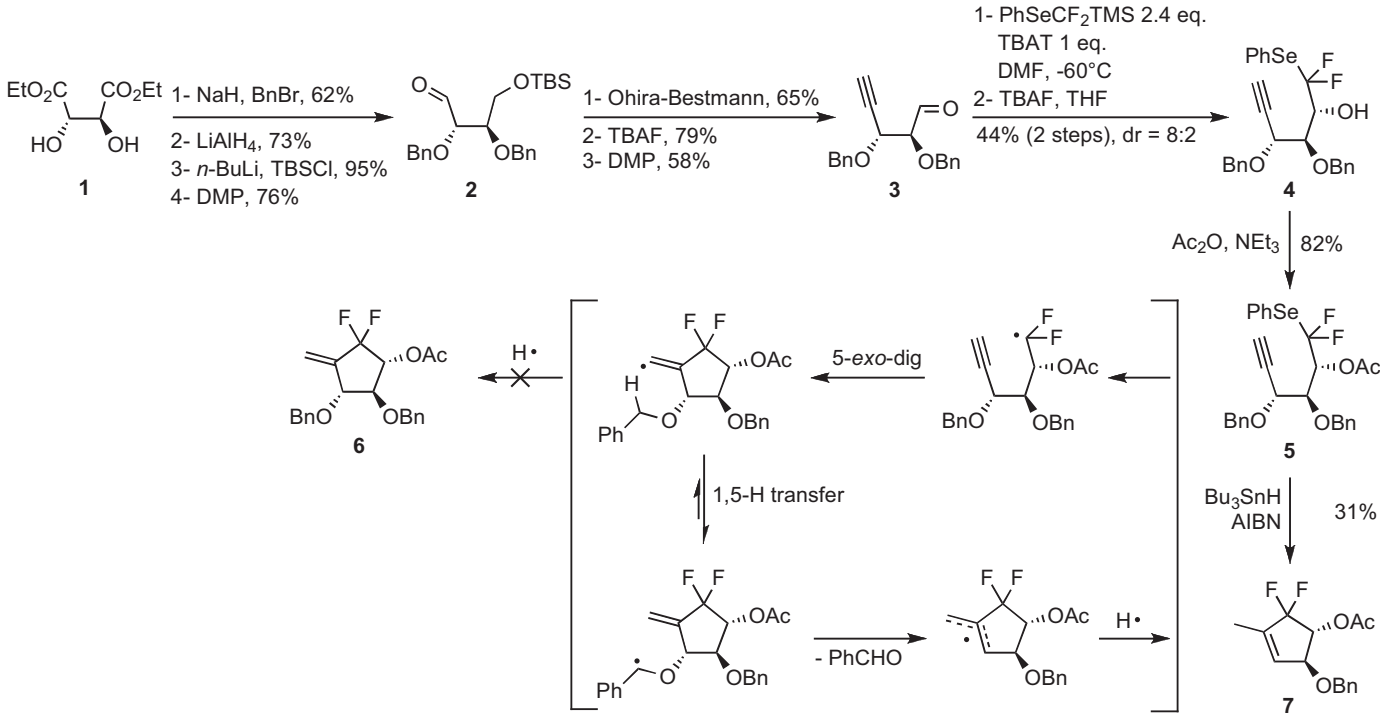
Scheme 1. General retrosynthetic scheme.

standard sugar backbone (**I**, X = O, Fig. 1) with modifications either on the base or on the substituents of the carbohydrate ring led to several powerful anticancer or antiviral drugs (5-fluorouracil, gemcitabine, azidothymidine, zalcitabine). Carbocyclic nucleosides (**II**, X = CH_2, Fig. 1) have more recently emerged in this field and several lead compounds have been discovered (entecavir, abacavir, aristeromycin) [2]. Unfortunately, all these compounds may suffer from a lack of selectivity or bioavailability (and thus from a certain toxicity) and the need for new analogues with greater activities and/or lowered side effects has therefore increased.

The fluorination of various positions on the base or on the pentose backbone has been widely studied, especially the replacement of the hydroxyl group in 2-position of the sugar backbone which is known to slow down the metabolic cleavage of the N-glycosidic bond and gave rise to efficient drugs (gemcitabine, clorofarabine) [3]. We were to our part interested in the synthesis of CF_2-carbocyclic nucleosides **III**, in which the intracyclic oxygen atom is replaced by a CF_2 group. Such compounds were indeed only scarcely described and no general method for their preparation was provided (Scheme 1) [4,5]. The stereoelectronic properties of the fluorine atom (strong electronegativity, small size) might nevertheless reasonably impart to these surrogates better mimicking abilities than the apolar CH_2 group [3b] The synthesis of fluorinated carbanucleosides obviously required a general method to prepare fluorocarbocyclic analogues of pentoses. We already reported a synthetic route to 5-deoxy-CF_2-carbasugars based on a 5-*exo*-trig reductive radical cyclization of a precursor obtained from an addition of $PhSeCF_2TMS$ to the corresponding aldehyde (Scheme 1) [6]. One of the ways to obtain exact analogues of sugars using the same strategy was to perform a 5-*exo*-dig radical cyclization on a similar substrate featuring a terminal triple bond. The resulting *exo*-methylenedifluorocyclopentane could indeed be adequately functionalized to provide the desired CF_2-carbasugar (Scheme 1). We wish to report herein the work which has been achieved using such an approach.

2. Results and discussion

The benzyl-protected ynal **3** was prepared from D-diethyltartrate **1** using modifications of the literature procedures (Scheme 2). Aldehyde **2** was obtained, according to Marshall's procedure, by benzylation, complete reduction, monoprotection with a *tert*-butyldimethylsilyl (TBS) group and oxidation with Dess–Martin periodinane (DMP) of **1** [7]. The triple bond was introduced using the Ohira–Bestmann reagent [8] and the remaining alcohol was deprotected. Aldehyde **3** was obtained after another Dess–Martin oxidation and subjected to the fluoride-promoted addition of



Scheme 2. First synthesis with a benzyl-protected substrate.