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Synthesis of difluorinated carbocyclic analogues of 5-deoxypentofuranoses

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ABSTRACT

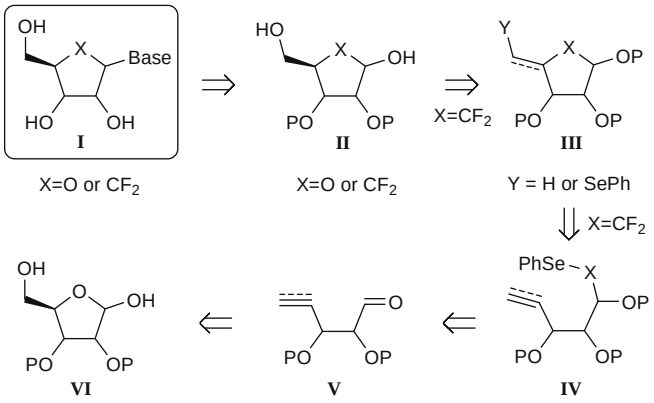
The synthesis of difluorinated carbocyclic analogues of 5-deoxypentofuranoses is described. The sequence involves an addition of $PhSeCF_2TMS$ to carbohydrate-derived aldehydes followed by a radical cyclization, and provides a secure strategy for a future synthesis of pentofuranoses and nucleoside analogues.

In recent years, carbocyclic nucleosides (**I**, X = CH_2, Scheme 1) have acquired a growing importance in the field of drug discovery. Their greater metabolic stability indeed imparts to these molecules superior therapeutical properties compared to their natural counterparts possessing a standard sugar backbone (**I**, X = O, Scheme 1).[1] As powerful antiviral (mainly against HIV, hepatitis B, and herpes viruses) and antitumoral properties are exhibited by several nucleosides (azidothymidine and gemcitabine) and carbonucleosides (entecavir, abacavir, and aristeromycin), the need for new analogues with greater activities and/or lowered side effects has thus increased.

If the fluorination of various positions on the pentose backbone has been widely studied,[2] the synthesis of CF_2-carbocyclic nucleosides, in which the intracyclic oxygen atom is replaced by a CF_2 group, is only scarcely described.[3,4] The stereoelectronic properties of the fluorine atom (strong electronegativity and small size) might nevertheless reasonably impart to these surrogates better mimicking abilities than the apolar CH_2 group.[2b] Our current interest in the synthesis of CF_2-glycosides prompted us to devise a synthetic plan for the preparation of fluorocarbocyclic analogues **II** (X = CF_2) of various pentoses using a general strategy.[5]

Our approach, as displayed in Scheme 1, is based on the use of difluorocyclopentane **III** as the key intermediate. Compounds of type **III**, which feature an exocyclic double bond or a phenylselanylmethyl moiety at C-5, might indeed be obtained through a 5-*exo* radical cyclization of a difluoromethyl radical onto a double or triple bond, through an atom-transfer or reductive process. The radical precursor **IV** would be readily prepared by addition of $PhSeCF_2TMS$ on the pentose-derived aldehyde **V**. Overall, the process would thus provide, in a limited number of steps, the corresponding CF_2 surrogate **II** of the starting carbohydrate **VI**. We wish to present herein our preliminary efforts and results in this area, which allowed the preparation of several CF_2-carbocyclic analogues of 5-deoxypentoses.

Our first study was based on the reductive cyclization of the difluoromethyl radical onto a terminal double bond. Aldehyde **1** was thus prepared according to a literature procedure[6a] and the addition of $PhSeCF_2TMS$ was examined. The use of easily enolizable α-chiral aldehydes for the fluoride-promoted addition of $PhSeCF_2TMS$ or $PhSCF_2TMS$ is poorly documented.[7] Among the different methods reported in the literature for the addition to aromatic aldehydes (TBAF as a fluoride source,[7a] $Cu(OAc)_2$/dppe as a



Scheme 1. Retrosynthetic scheme.

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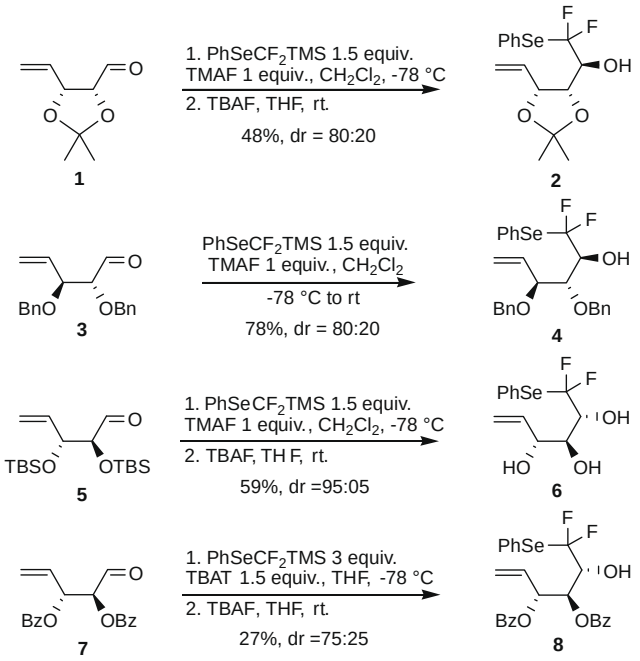
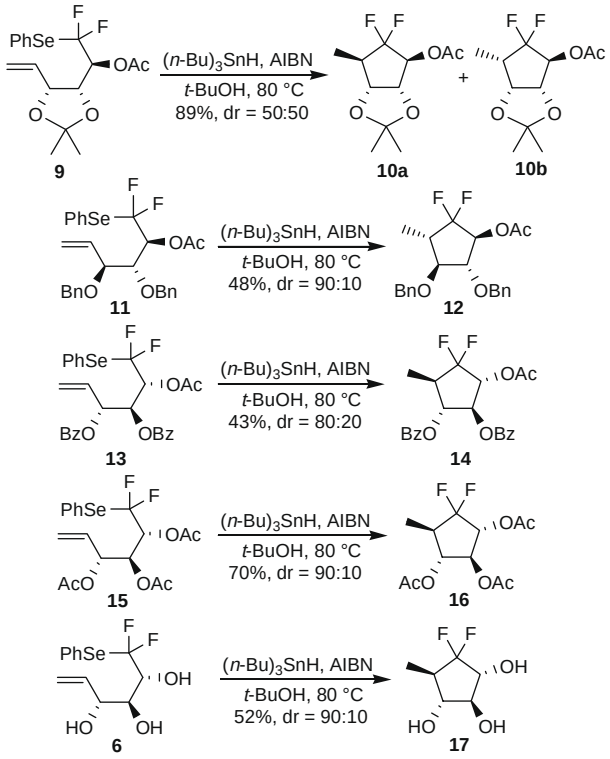


Scheme 2. Addition of $PhSeCF_2TMS$ to carbohydrate-derived aldehydes.

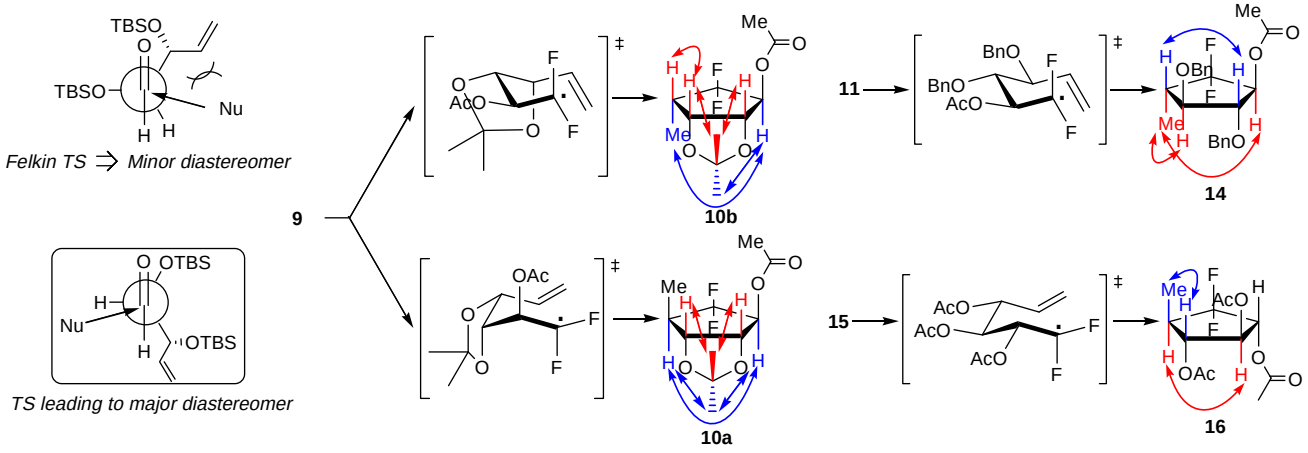


Scheme 3. Synthesis of the 5-deoxypentose CF_2-carbocyclic analogues.

Lewis acid activator,[7d] etc.), the use of TMAF as a promoter led, in our hands, to the best and most reproducible results.[7c] The requirement of a two-step procedure to convert the OH/OTMS mixture initially obtained to the free alcohol **2** is the only drawback of this method (Scheme 2). The yield and the diastereoselectivity are however satisfactory and similar conditions were also applied to aldehydes **3**, **5,** and **7**.[6] Worthy of note is the fact that, for benzyl-protected aldehydes such as **3**, a warm-up to room temperature is sufficient to directly afford alcohol **4** in high yield. The TBS-protected arabinose derivative **5** led to the fully deprotected addition product **6** in appreciable yield, thanks to the two-step procedure mentioned earlier. Finally, the benzoyl-protected arabinose derivative **7** required the use of TBAT as the fluoride source to isolate the addition product **8**, unfortunately in low yield (Scheme 2).

Each major diastereomer obtained from these reactions was afterwards acetylated and engaged in a classical tin hydride-mediated radical cyclization (Scheme 3).[3a,b,8] The cyclized compounds were generally obtained within 2 h in moderate to high yields. The reaction conditions appeared compatible with all protecting groups including none, as illustrated by the successful cyclization of the unprotected arabinose derivative **8** (Scheme 3).

The relative configurations of the cyclized compounds were easily determined from NOESY NMR experiments, providing informations on the stereochemical outcome of both the $PhSeCF_2TMS$ addition and the radical cyclization (Scheme 4). The latter proceeds according to the classical Beckwith–Houk transition state.[9] A strong diastereoselectivity was therefore observed in the reaction of the xylose and arabinose derivatives **11** and **15**. On the other hand, an equimolar mixture of the two C-5 epimers **10a** and **10b** was obtained from the ribose derivative **9**. Both transition states leading to these compounds indeed suffer from at least one non-bonding 1,3-diaxial interaction (Scheme 4). More puzzling is the stereochemical outcome in the addition of $PhSeCF_2TMS$ to aldehydes **1**, **3**, **5,** and **7**, for which anti-Felkin adducts are obtained



Scheme 4. Stereoselectivity of the $PhSeCF_2TMS$ addition and of the radical cyclization.

as the major diastereomers.[10] A chelated transition state can be claimed for Cu(II)-mediated reactions,[7d] but is of course ruled out for fluoride-promoted additions. Similar results were observed in the addition of fluoroalkylsilane reagents to other carbohydrate-derived aldehydes by Portella's team.[11] The exceptional bulkiness of the postulated hypervalent fluorosilicon intermediate was invoked by the authors to explain this unusual selectivity. In the absence of relevant calculation studies regarding such reactions, a transition state similar to Portella's is therefore proposed in Scheme 4. It accounts for the observed selectivity and allows the minimization of steric interactions despite an unusual *gauche* conformation.

In summary, we have devised a general synthetic route to difluorinated carbocyclic 5-deoxypentofuranose analogues which should be applicable to the preparation of pentofuranose and nucleoside surrogates. The sequence involves an addition of $PhSeCF_2TMS$ to carbohydrate-derived aldehydes featuring a terminal double bond followed by a reductive 5-*exo*-trig radical cyclization. Several extensions of this work are currently under investigation. A similar sequence using *tert*-butanesulfinylimines derived from aldehydes **V** (Scheme 1) could for example allow us to control at will the configuration of the pseudo-anomeric center. The phenylselanyl group transfer radical cyclization of the same substrates and the reductive 5-*exo*-dig radical cyclization of similar precursors featuring a terminal triple bond are also studied. These last strategies would indeed provide access to pentofuranose and nucleoside analogues. Results in these areas will be reported in due course.

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