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Fluorination of tertiary alcohols derived from di-*O*-isopropylidenehexofuranose and *O*-isopropylidenepentofuranose

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In dedication to Professor Alain Tressaud on the occasion of his 70th birthday.

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ABSTRACT

The stereo- and regioselectivity of the dehydroxyfluorination of various tertiary alcohols derived from di-*O*-isopropylidenehexofuranose and 1,2-*O*-isopropylidenepentofuranose has been studied. Reactions have been accomplished using DAST and PFPDEA (1,1,3,3,3-pentafluoropropene-diethylamine adduct) as fluorinating reagents. Dehydroxyfluorination of allylic alcohol **2a** has occurred with an inversion of configuration and allylic rearrangement leading to two ciral regioisomers **6a** and **7a**. Analogous reaction of **2b** has given allylic chiral fluoride **7b** as the only product. In case of phenylacetylene, styryl and benzylic alcohols **3a**/**3b-5a**/**5b** the single diastereoisomers **8a**/**8b-10a**/**10b** have been obtained. Additionally, the participation of 1,2-*O*-substituent effect in carbocation stabilization during fluorination have been discussed.

1. Introduction

Placing a fluorine atom into molecules, due to its steric and polar characteristic can have a remarkable effect upon the physical, chemical and biological properties [1]. This effect is especially apparent in a group of fluorinated carbohydrates and their derivatives. Their numerous applications in medicinal chemistry varies from radio labeled sugars used as sensors in medicinal imaging (e.g. [^{18}F]-2-fluoro-2-deoxy-D-glucose – FDG [2]) to building blocks for the synthesis of nucleosides with antiviral and antitumor properties (e.g. 2′,2′-difluoro-2′-deoxycytidine-*gemcitabine* [3]; 2′-fluoromethylene-2′-deoxycytidine-*tezacitabine* [4] – inhibitors of RNR) [Fig. 1].

Dehydroxyfluorination, effective with primary, secondary and tertiary alcohols, is one of the methods of introducing a fluorine into organic compounds. Regarding the direct conversion of hydroxyl groups to fluorides, numerous reagents are available [5]. Among the most useful, diethylaminosulfur trifluoride (DAST) has been employed [6]. In alternative method α-fluoroamine and α-fluoroenamine derivatives have been applied [5,7–9]. Among them Yarovenko's (diethylamine adduct of chlorotrifluoroethene) [7] and Ishikawa's (diethylamine adduct of hexafluoropropene) [8] as fluorinating reagents have been used. Application of 1,1,3,3,3-pentafluoropropene diethylamine adduct (PFPDEA) as a dehydroxyfluorination reagent has also been studied [9]. Among organic fluorine compounds, allylic and propargylic fluorides constitute an important class of chiral building blocks essential for organic synthesis [10]. A direct dehydroxyfluorination of allylic alcohols using DAST (Scheme 1) can occurred with a retention or an inversion of configuration. Additionally, transposition of the double bond has been observed [6a,10–12]. Allylic substitution has not been limited to DAST but also has occurred with other fluorinating reagents [12a]. In general, fluorination of the substituted with alkyl groups allylic alcohols leads to low regioselectivity, while phenyl or conjugated double bonds substituents increase regioselectivity [11a,13a].

While regio- and stereoselectivity during fluorination of allylic alcohols remain uncertain, several methodologies have been proposed to solve this problem [14]. Grée et al. have achieved the regio- and stereocontrol of fluorination by temporary complexation of the π-system with a transition metals [15]. Moreover, Prakesch et al. demonstrated a complete regiocontrol and good stereocontrol of dehydroxyfluorination of propargylic alcohols followed by hydrometallation or hydrogenation [15c,16]. However, still preservation of the absolute configuration at the fluorine-containing stereocenter was not complete. Furthermore, Gouverneur et al. reported for the first time enantioselective synthesis of propargylic fluorides using an electrophilic fluorine

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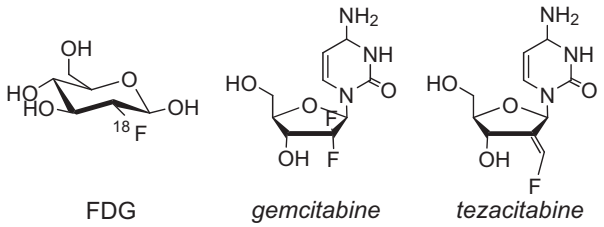


Fig. 1. Examples of fluorinated sugar derivatives.

source [17]. Starting from highly enantioenriched allenylsilanes, complete chirality transfer was achieved. Nevertheless, a disadvantage of this approach – extended and time-costly synthesis of starting materials – limits its application on larger scales (Scheme 2).

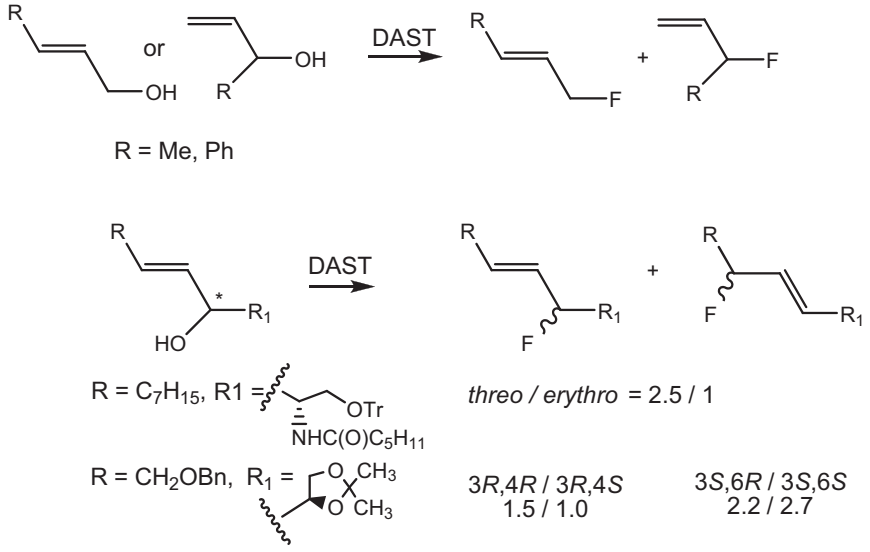
Recently, Jiang et al. reported successful synthesis of chiral propargylic or secondary allylic fluorides with enantioselectivity up to 99% ee [18]. This method involved organocatalytic α-fluorination of aldehyde and next homologation of the intermediate to obtain chiral fluorides (Scheme 2). Also, Grée et al. reported an alternative method for fluorination dienic alcohols that are complexed with iron tricarbonyl leading to nonracemic products [15a]. However, fluorination of chiral secondary dienyl alcohol complexes occurs with retention of configuration for one enantiomer and with partial racemisation for the opposite one. Although the influence of the structural features of the starting allylic alcohols on the stereo- and regioselectivity of fluorination has been extensively studied, there is a need for alternative, efficient methodology for obtaining optically active alcohols. This possibility could be achieved by applying carbohydrates as chiral tools or blocks in an organic synthesis. In a search for novel inhibitors of ribonucleoside reductases [19], we attempted the synthesis of 2′-fluoro-2′-vinyl-2′-deoxycytidine as a Tezacitabine [4] analogues. In our approach, first we studied fluorination, using PFPDEA and DAST, with carbohydrate precursors. In this paper we report the results of our studies concerning the dehydroxyfluorination of tertiary alcohols derived from *O*-isopropylidenehexo- and -pentofuranose compounds, additionally modified at C-3 with the vinyl, phenyl, styryl or phenylacetylene substituents. Resulting stereocontrol strongly affected by neighboring 1,2-*O*-isopropylidene groups in rigid pentofuranose rings would be also discussed.

2. Results and discussion

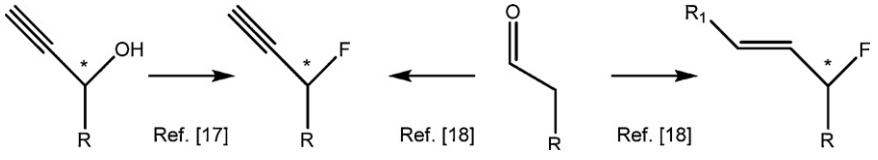
Our synthesis were started from easily to handle diacetone glucose and 5-*O*-benzyl-1,2-*O*-isopropylidenexylofuranose derivatives. Treatment of 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose-3-ulose **1a** [20] and 5-*O*-benzyl-3-oxo-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose **1b** [21] with different Grignard reagents or addition of lithium acetylide yield two series of tertiary alcohols (Scheme 3). Treatment of ketones **1a** and **1b** with vinyl magnesium bromide gave **2a** [22] and **2b** with 59% and 52% yields, respectively.

Next, the prepared tertiary allylic alcohol **2a** was examined towards dehydroxyfluorination. Reaction of pentafluoropropene diethyl amine adduct [PFPDEA, RT (48 h)] prepared in our laboratory [9] with **2a** gave, after isolation, only two products **6a** and **7a** with 31% and 34% yields, respectively (Scheme 4). Corresponding reaction of **2a** with DAST [−78 °C (1 h), RT (1 h)] gave only **6a**/**7a** with 1.6/1 ratio and lower yield (26%/16%).

The signals in ^{19}F NMR spectra for **6a** appeared at δ −181.3 (ddd, ^{3}J = 31.5, 21.6, 11.5 Hz) whereas for product **7a** they were located at δ −214.6 (tddd, ^{2}J = 46.7 Hz, ^{3}J = 13.2 Hz, ^{5}J = 5.4, 2.5 Hz). The larger values of coupling constants in **6a** observed for fluorine and vicinal hydrogen atom H-4 (*trans*, ^{3}J = 31.5 Hz) as well as smaller coupling constants between fluorine and H-2 (*cis*, ^{3}J = 11.5 Hz) supported the stereochemical assignment at C-3 as being 3*R* [23].



Scheme 1.



Scheme 2.