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Graphical Abstract





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Optimized Synthesis of a Pentafluoro-*gem*-diol and Conversion to a CF_2Br Glucopyranose through Trifluoroacetate-Release and Halogenation

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ABSTRACT

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Keywords: fluorine aldol reaction halogenation glycoside pyranose Pentafluoro-*gem*-diols are substrates that enable the synthesis of valuable difluoromethylenecontaining organic molecules through the release of trifluoroacetate. Currently, only one synthetic strategy is available to assemble these important precursors. Herein, two new synthetic strategies to a complex pentafluoro-*gem*-diol are compared to the existing route, and an improved synthetic route has completed. Moreover, the first synthesis of a CF_2Br -glucopyranose was finished by a tandem trifluoroacetate-release halogenation/cyclization protocol.

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Fluorinated organic molecules have a prominent role in the pharmaceutical and agrochemical industries.^{1,2} The incorporation of fluorine can improve the pharmacokinetic properties of lead molecules, as it is known to increase metabolic stability and lipophilicity. Although there are many methods to introduce fluorine³ and trifluoromethyl groups,⁴ there are substantially fewer strategies to install a difluoromethylene group.⁵⁻⁷ The most common synthetic protocols for installing a difluoromethylene group are through the use of a difluoroenol⁸ or a difluoroenolate.9-11 Difluoroenolates are typically derived from bromodifluoroacetate with a Reformatsky reaction.⁹ In 2011, we demonstrated that difluoroenolates could be generated by the mild release of trifluoroacetate from pentafluoro-gem-diols using LiBr and Et₃N.¹² The difluoroenolates react well with aldehydes,¹² imines,¹³ and electrophilic halogenation reagents¹⁴ (Figure 1). Subsequent innovations mediated by the release of trifluoroacetate include catalytic asymmetric aldol reactions,¹⁵ integration with light-induced photoredox catalysis,16 and stereoselective additions to chiral *N*-sulfinyl imines.¹⁷ Indeed, the major advantage of using trifluoroacetate release is that it is quite mild yet compatible with many types of reagents. Even though these reports have characterized the novel reactivity of the difluoroenolates generated from trifluoroacetate release, none have been applied to the construction of more complex, difluorinated organic molecules.18



Figure 1. Generation and reactivity of difluoroenolates from the release of trifluoroacetate.

Natural products serve as a valuable resource for drug discovery.¹⁹ Moreover, a substantial portion of natural products display a sugar on their respective structures.²⁰ As part of our ongoing efforts to modify the structures of natural products for drug discovery,²¹ we aim to create tools to access derivatives of complex glycosylated natural products. The synthesis of a pentafluoro-*gem*-diol derived from glucose would not only be an important first step toward achieving this goal, but also it would demonstrate the compatibility of the pentafluoro-*gem*-diol in complex organic structures. Accordingly, we herein report an optimized synthetic route for the assembly of the requisite pentafluoro-*gem*-diol derived from glucose, as well as a single transformation, promoted by the release of trifluoroacetate, to form the first *CF*₂*Br*-glucopyranose.

Previously, our laboratory has reported that the substrates for trifluoroacetate release, 2,2,4,4-pentafluoro-3,3-dihydroxyketones, can be assembled by trifluoroacetylation of methyl ketones followed by difluorination.¹² This method is the only reported route to synthesize these types of compounds.¹²⁻¹⁸ Using this strategy, pentafluoro-*gem*-diol **1** was envisioned to arise from the methyl ketone **2** which, in turn, would be accessed from glucose (Scheme 1).



Scheme 1. Synthetic strategy for glucose-derived pentafluoro-*gem*-diol 1.

The synthesis commenced with the selective protection of the known acyclic triol 3,²² that is derived in three steps from glucose, to give the alcohol 4 (Scheme 2). Then, Swern oxidation provided the aldehyde 5 in 92% yield. Methylation with MeMgBr followed by TPAP/NMO-mediated oxidation afforded the ketone 2. Trifluoroacetylation followed by difluorination with Selectfluor[®] gave the pentafluoro *gem*-diol 1 in 43% yield over two steps, and no æpimerization of the ketone was observed during any of the synthetic transformations. Although this path provided the target 1 from the requisite aldehyde 5 in four synthetic steps, we sought to develop a shorter and more efficient route.



Scheme 2. Preparation of pentafluoro-*gem*-diol **1** by trifluoroacetylation and difluorination of methyl ketone **2**.

Indium-mediated difluoroallylation of aldehydes is mild reaction that installs a difluorinated group.²³ This chemistry has been aptly applied to synthesis of difluorinated sugar nucleosides by Qing and coworkers.²⁴ Accordingly, the aldehyde 5 was smoothly difluoroallylated with indium in DMF at 100 °C to give the difluoroalcohol 6 as an inseparable mixture of diasteromers (Scheme 3). The high temperature was necessary to obtain a good conversion. Oxidation of 6 with Dess-Martin periodinane produced the ketone 7 in 88%. Ozonolysis of the terminal olefin of 7 was attempted to generate the difluoroaldehyde 8; however, a complex mixture was observed in the ¹H, ¹⁹F and ¹³C NMR spectra. Although difluoroaldehydes are known in the literature to exist in equilibrium with the hydrate form, the free difluoroaldehyde is usually observed.²⁴ Unfortunately, some difluoroaldehydes exclusively form multimers (i.e., polymerize with other hydrates) and these complex mixtures are characterized as other derivatives.²⁴ In the case of 8, the reaction mixture from 7 was reduced to the respective diol 9 using LiBH₄.²⁵ Although this transformation validated the formation of the difluoroaldehyde 8, this synthetic route was abandoned for a new strategy.



Scheme 3. Preparation of difluoroaldehyde 8 by an indium-mediated difluoroallylation of aldehyde 5.

The third and final approach was inspired from the reported addition of lithium-based pentafluoroenolates to aldehydes.²⁶ Specifically, treatment of hexafluoroisopropanol (HFIP) with 2 equivalents of n-BuLi generates a perfluoroenolate that adds smoothly to aldehydes. These unique pentafluorinated products were studied by Guerrero, and it was reported that base-mediated decomposition produces difluoroacetic acids by fluoroform release.²⁷ We aimed to exploit this class of compound, in a different fashion, by oxidizing the secondary alcohol to a ketone to produce the desired pentafluoro-gem-diol with an adjacent ketone. Accordingly, the pentafluoroenolate was added to 2naphthaldehyde to generate the fluorinated substrate 10. Then, compound **10** was treated with nine different oxidants to identify conditions that would provide the gem-diol 11^{12} in good yield (Table 1). DCC/DMSO, PDC, and TEMPO/NaOCl produced 11 in low yields (i.e., 33-45% based on ¹⁹F NMR). Dess-Martin periodinane gave the product 11 in 63% yield, and TPAP/NMO provided the highest yield of 11 at 90% after 24 h. These data validate the potential of oxidation to the gem-diol and represent a new route to access these types of fluorinated molecules.

Table 1. Oxidation of pentafluoroalcohol 10.



Commencing from aldehyde 5, addition of the pentafluoroenolate generated from HFIP provided the alcohol 12 in an optimized yield of 52% (Scheme 4). Temperature control was critical for obtaining good yields during this transformation, as holding the reaction mixture at -40 °C for 15 min, during the warming process, provided the highest conversion to the product 12. Based on the previous studies with compound 10, the oxidation of 12 to the pentafluoro-gem-diol 1 was initially conducted with TPAP/NMO (see Table 1), but Dess-Martin periodinane gave a near quantitative conversion to 1 at 95% isolated yield.²⁸ This route was a substantial improvement over the aforementioned four-step synthesis of 1 from 5, as the substrate 1 was procured in only two synthetic steps. In order to demonstrate that the complex pentafluoro-gem-diol 1 participates in trifluoroacetate-release mediated additions, the substrate 1 was treated with LiBr, Et₃N, and Selectfluor[®] for 1 h to promote the release of trifluoroacetate and halogenation.¹⁴ Remarkably, the CF_2Br -glucopyranose 13 was obtained as a single diastereomer

in 41% yield from a tandem cascade of the release of trifluoroacetate, halogenation, acetonide cleavage, and cyclization. Assignment of the relative stereochemical configuration was accomplished by COSY, HMQC, HMBC, NOESY, and ${}^{1}\text{H}{-}^{19}\text{F}$ 2D HOESY NMR data (see Scheme 4). The utility of ${}^{1}\text{H}{-}^{19}\text{F}$ 2D HOESY experiments in assigning stereochemical configuration of centers on cyclic structures has been elegantly described by Crich and coworkers,²⁹ and the data for **13** was in excellent agreement with this precedent.



Scheme 4. Optimized synthesis of pentafluoro-*gem*-diol 1 and conversion to CF_2Br -glucopyranose 13 with a depiction of the NOESY and ¹H⁻¹⁹F HOESY data.

In conclusion, three synthetic routes to prepare complex pentafluoro-*gem*-diols have been presented. The optimal route requires an aldehyde and only two synthetic steps to assemble the pentafluoro-*gem*-diol. This work offers an improved alternative to the only reported method¹² for the preparation of these structures. These substrates are versatile intermediates for assembling difluorinated organic structures through the use of trifluoroacetate release. The CF_2Br -glucopyranose was obtained through a novel, tandem trifluoroacetate-release halogenation, deprotection, and cyclization reaction. The reaction not only demonstrates the importance of complex pentafluoro-*gem*-diols but also extends the scope of trifluoroacetate release.

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Supplementary Material

Full experiment details and spectroscopic data (PDF).

Highlights

- A complex glucose-derived pentafluoro-gem-diol is synthesized. •
- Accepter A tandem trifluoroacetate-release halogenation/cyclization is executed. •