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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

Pentafluoro-*gem*-diols are substrates that enable the synthesis of valuable difluoromethylene-containing 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.

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 fluorine[3] 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 difluoroenol[8] 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 Et_3N.[12] The difluoroenolates react well with aldehydes,[12] imines,[13] and electrophilic halogenation reagents[14] (Fig. 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]

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_2Br*-glucopyranose.

Previously, our laboratory has reported that the substrates for trifluoroacetate release, 2,2,4,4,4-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).

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

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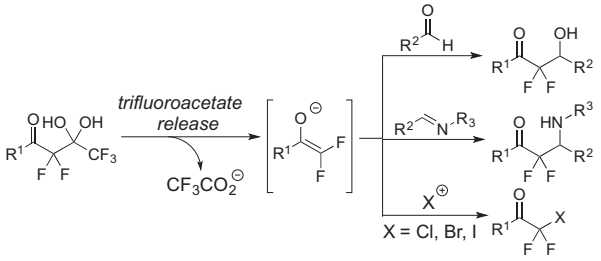
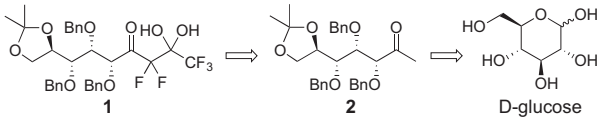


Figure 1. Generation and reactivity of difluoroenolates from the release of trifluoroacetate.

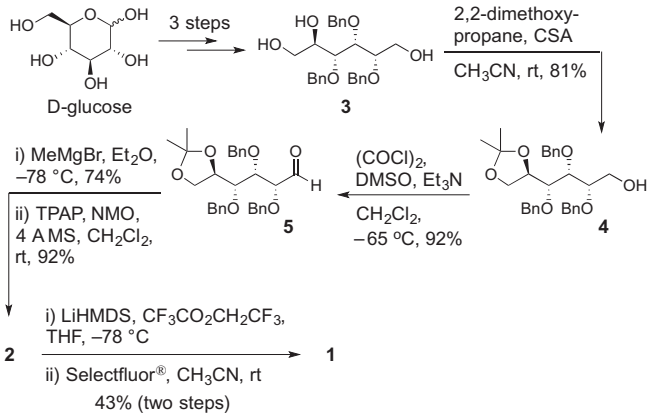
by TPAP/NMO-mediated oxidation afforded the ketone **2**. Trifluoroacetylation followed by difluorination with Selectfluor® gave the pentafluoro *gem*-diol **1** in 43% yield over two steps, and no α-epimerization of the ketone was observed during any of the synthetic transformations. Although this path provided the target **1** from the requisite aldehyde **5** in four synthetic steps, we sought to develop a shorter and more efficient route.

Indium-mediated difluoroallylation of aldehydes is a mild reaction that installs a difluorinated group.[23] This chemistry has been aptly applied to synthesis of difluorinated sugar nucleosides by Qing and co-workers.[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 ^{1}H, ^{19}F and ^{13}C 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 $LiBH_4$.[25] Although this transformation validated the formation of the difluoroaldehyde **8**, this synthetic route was abandoned for a new strategy.

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 equiv 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 2-naphthaldehyde 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 ^{19}F NMR). Dess–Martin periodinane gave the product **11** in 63% yield, and TPAP/NMO provided the highest yield of **11** at 90% after



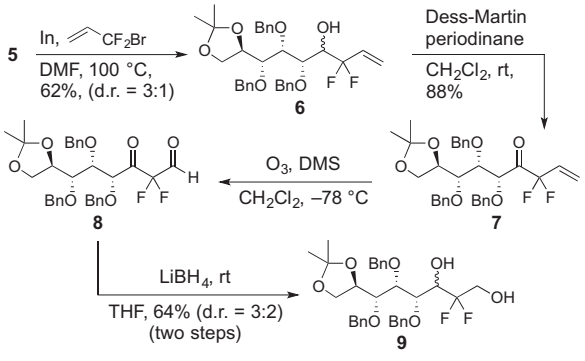
Scheme 1. Synthetic strategy for glucose-derived pentafluoro-*gem*-diol **1**.



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

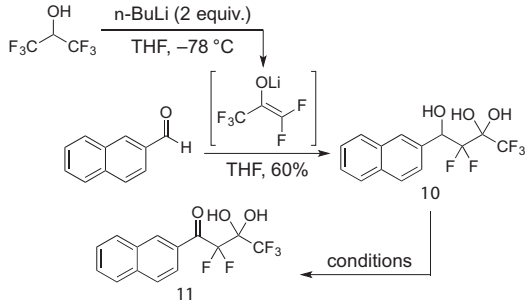
24 h. These data validate the potential of oxidation to the *gem*-diol and represent a new route to access these types of fluorinated molecules.

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 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, Et_3N, 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}H–^{19}F 2D HOESY NMR data (see Scheme 4). The utility of ^{1}H–^{19}F 2D HOESY experiments in assigning stereochemical configuration of centers on cyclic structures has been elegantly described by Crich and co-workers,[29] and the data for **13** were in excellent agreement with this precedent.



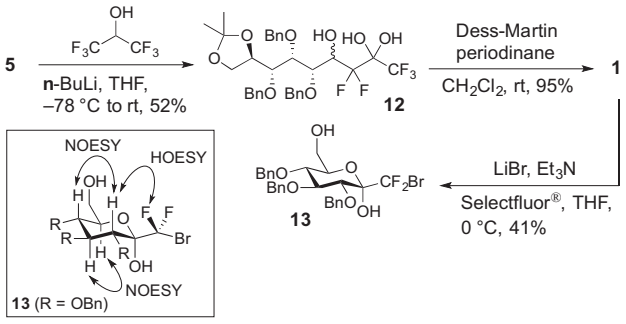
Scheme 3. Preparation of difluoroaldehyde **8** by an indium-mediated difluoroallylation of aldehyde **5**.

Table 1
Oxidation of pentafluoroalcohol **10**



Entry	Conditions	Yield[a] (%)
1	DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to 0 °C	0
2	PDC, DMF, rt, 16 h	35
3	DCC, DMSO, AcOH, rt, 24 h	33
4	DCC, DMSO, TFA, rt, 24 h	45
5	Oxone, THF, H_2O, rt, 24 h	0
6	TEMPO, NaOCl, NaBr, THF, H_2O, 5 h	34
7	Dess–Martin periodinane, CH_2Cl_2, rt, 24 h,	63
8	TPAP, NMO, 4 Å MS, CH_3CN, rt, 24 h	90

[a] Yield determined by ^{19}F NMR.



Scheme 4. Optimized synthesis of pentafluoro-*gem*-diol **1** and conversion to *CF_2Br*-glucopyranose **13** with a depiction of the NOESY and ^1H–^{19}F 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 method[12] 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 data

Supplementary data (experiment details and spectroscopic data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.064.

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