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Straightforward Preparation of Functionalized α-CF_2-Galactosides through an Oxygen to Carbon Acyl Migration

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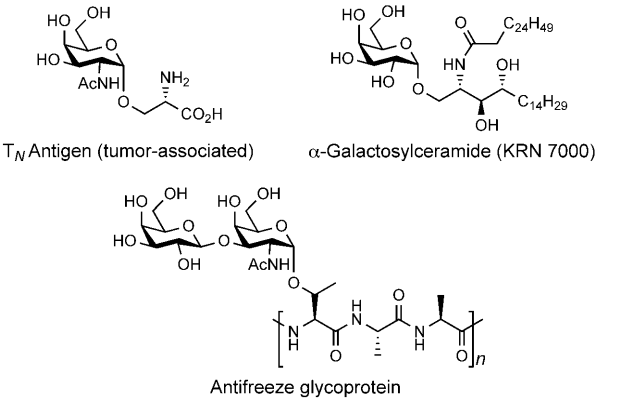
A high number of O-glycoconjugates of therapeutic interest feature an α-galactose or 2-deoxy-2-acetamido-α-galactose unit in their structure, often serving as the link between the aglycon and the glycosidic parts.[1] For example, this motif is found in tumor-associated antigens, antifreeze glycoproteins (AFGP) or in immunoregulative α-galactosylceramides. This last family of glycosphingolipids (agelasphins) exhibit strong in vivo activities against infectious diseases and tumor metastases, which were found to be related to their immunoregulative properties.[2–4]



In 2004, the Franck group reported the synthesis of the CH_2 analogue of the α-galactosylceramide KRN 7000.[5] Besides the remarkable synthetic achievement of this work, the results obtained in terms of immunostimulation were groundbreaking: α-CH_2-GalCer displayed a 1000-fold more potent antimalaria activity and a 100-fold more potent antimetastatic activity than the parent O-glycosidic molecule. Although there was no evidence that this enhancement of bioactivity was due to the hydrolytic stability of this analogue, the relevance of testing C-glycosidic surrogates of O-glycoconjugate-based drugs was thus established.[6]

Our group has been investigating for many years the synthesis of fluorinated C-glycosides, in which the glycosidic link is replaced by a CF_2 moiety.[7] The electronic properties of this group were expected to impart improved mimicking abilities to these surrogates, relative to classical C-glycosides. The incorporation of fluorine atoms into drug candidates has become more and more frequent in the past two or three decades.[8] The unique properties of the fluorine atom undoubtedly account for this trend, because its introduction into a biologically active molecule might allow alterations of crucial biological functions within limited structural modifications.[9] The synthesis of CF_2-glycopyranosides, which combine the hydrolytic stability of C-glycosidic carbohydrate analogues with these properties, was pioneered by Motherwell and co-workers and further investigated by other groups.[10] Our team aimed to provide methodologies that applied this synthesis to several carbohydrate series (glucose, mannose, and galactose) and for any pseudo-anomeric center configuration (α or β). In this context, disclosing an efficient methodology for the synthesis of CF_2 analogues of α-galactosides was thus a very attractive challenge due to the many applications one could think of for these surrogates. To the best of our knowledge, the only reported example of such an analogue is an aryl-α-CF_2-D-galactoside, a compound that was therefore not suitable for the preparation of functionalized α-galactoconjugate mimetics.[10k]

Our approach relies on the introduction of a fluorinated moiety that would feature an appropriate functional group to introduce the desired side chain (Scheme 1). A sequence involving a radical addition to galactal **1** followed by a stereoselective reduction of the resulting 2-oxogalactoside was envisioned to provide such an intermediate. If the efficiency of the radical addition was previously established, disclosing a stereoselective reduction reaction and an efficient functionalization methodology were still issues to be addressed.[7d] Herein, we are pleased to report a solution to both problems due to a new reduction method that enables the preparation of fluorinated α-C-galactosides through an original reductive acyl-chain transfer from O-2 to C-1′. This last

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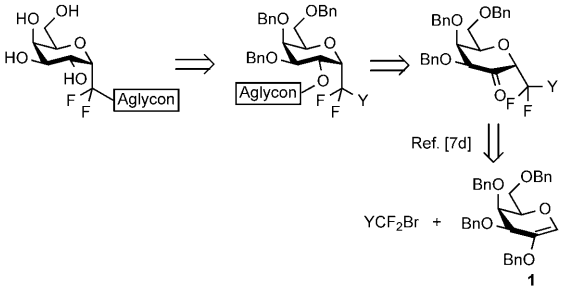
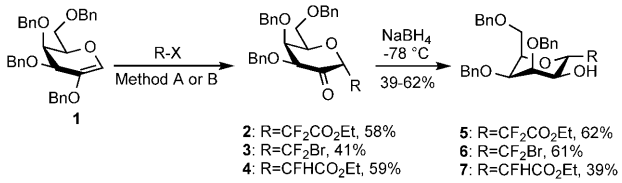


Scheme 1. Our approach to functionalized α-CF_2-galactosides. Bn = benzyl; Y = Br, CO_2Et.

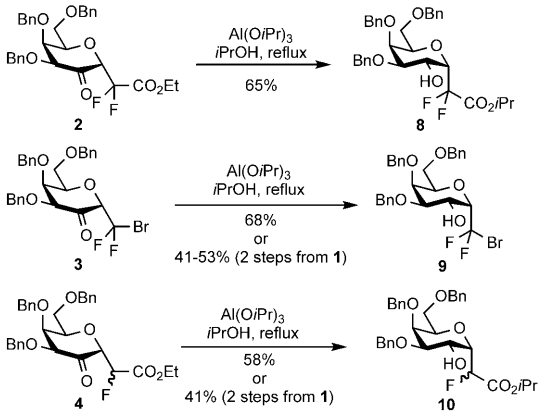
synthetic modification provides a convergent and elegant method for the preparation of analogues of α-galactose-derived glycoconjugates.

The radical addition of $BrCF_2CO_2Et$ and CF_2Br_2 to 2-benzyloxyglucal and 2-benzyloxygalactal provided 2-oxoglycosides with interesting α selectivity (Scheme 2).[7d,11] The hydride-mediated reduction of the glucose derivatives led to



Scheme 2. Radical addition onto 2-benzyloxygalactal **1** and sodium borohydride reduction of the resulting 2-oxogalactosides. Methods: A) $BrCF_2CO_2Et$ or CF_2Br_2, BEt_3, DMF, air; B) $EtOC(S)SCFHCO_2Et$, dilauroyl peroxide (DLP), 1,2-dichloroethane (DCE)/*t*BuOH, reflux. See ref. [7d].

the expected α-CF_2-D-glucoside, however, their galactose counterparts **2**–**4** behaved differently. A reversal of diastereoselectivity occurred through a major $^1C_4$ conformation, to give the α-CF_2-D-talloside analogues **5**–**7** (Scheme 2). Since the use of other hydrides (diisobutylaluminium hydride (DIBAH), L-Selectride, Et_3BHLi, and so forth) led to the same stereoselectivity, we reasoned that the diastereoselectivity issue we met with kinetically-controlled reductions could be tackled under thermodynamic control. A reversible hydride transfer would indeed favor the most stable diastereomer, which was not expected to be compound **5** because of the possibility of a strong 1,3-diaxial interaction between the C-3 and C-5 substituents. The Meerwein–Ponndorf–Verley (MPV) reduction is a well-known hydride-transfer reaction for the reversible reduction of aldehydes and ketones and was therefore chosen to challenge this assumption.[12] To our delight, the classical $Al(OiPr)_3$-mediated reaction was extremely efficient and cleanly delivered CF_2-glycosides **8**–**10** from **2**–**4** (Scheme 3). Moreover, these conditions were compatible with a direct reduction of the crude compound obtained from the radical addition, which was not the case with sodium borohydride. The two-step procedure allowed us to significantly improve the global yields,

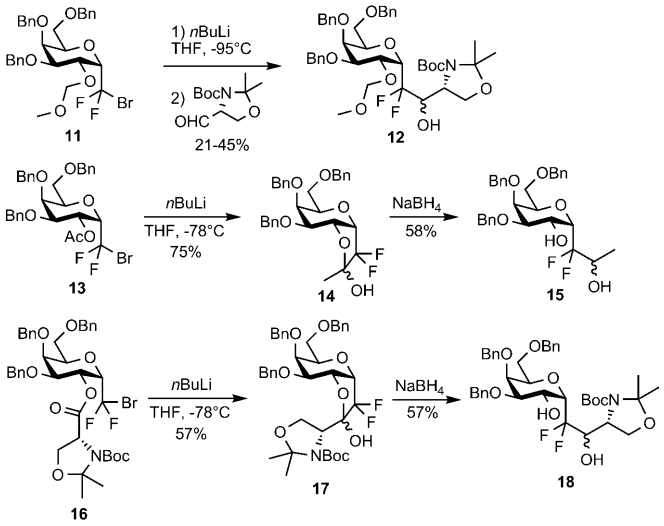


Scheme 3. Meerwein–Ponndorf–Verley reduction of **2**–**4**.

especially in the case of **3** (Scheme 3). Due the moderate stability of **3** on silica gel, when this compound undergoes chromatography immediately after the radical addition, a disappointing 41% yield is observed (Scheme 2). On the other hand, if the crude material is directly engaged in a MPV reduction, compound **9** is obtained in an appreciable 53% yield over two steps from galactal **1** (Scheme 3). A slight decrease in yield was observed when the reaction was performed on a larger scale (41% starting from 2 g of galactal).

The analytical data clearly indicated that **6** and **9** were diastereomers and therefore that **9** was the desired α-CF_2-D-galactoside. The saponification of ethyl esters **5** and **7** and isopropyl esters **8** and **10** led to carboxylic acids with different NMR data, to give the same conclusion. An X-ray diffraction study on **9** eventually confirmed the C-2 configuration.[13] To our surprise, and unlike the results obtained by Jiménez-Barbero and Vogel for a fully deprotected α-CF_2-galactoside, this benzylated derivative crystallized under a $^1C_4$ chair conformation.[10k] The conformational flexibility of this compound in solution was however demonstrated by the sole H-3/H-5 NOESY correlation. This NMR data is indeed only compatible with a $^1S_3$-skew-boat or a $^4C_1$-chair conformation and the $^1C_4$-chair conformation is therefore exclusive only in the solid state.

Having in hand several fluorinated α-*C*-galactosides, the next step was to explore further synthetic modifications that would enable future preparations of α-GalCer analogues. The CF_2Br group of **9** appeared suitable to introduce aglycon moieties through a Br/Li exchange, followed by a nucleophilic addition on the appropriate electrophile. However, we were worried about the thermal stability of the corresponding CF_2Li compound due to its carbenoid nature. This prediction was confirmed by the poor results obtained from many attempts to perform a Br/Li exchange on **11**, followed by an intermolecular addition (Scheme 4). Low and irreproducible yields of addition products **12** were indeed obtained when the CF_2Li compound was allowed to react with Garner's aldehyde. On the other hand, a trapping of the lithium species with an internal electrophile attached to O-2 ap-



Scheme 4. Br/Li exchange and intramolecular trapping with an electrophile. Boc = *tert*-butoxycarbonyl.

peared as a method of choice to circumvent the potential problem of stability. To challenge this intramolecular strategy, acetate **13** was thus prepared from **9** by using a standard acetylation procedure (Ac_2O/NEt_3). We were pleased to see that a Br/Li exchange on **13** indeed resulted in the immediate trapping of the lithium species by the neighboring acetate to afford the stable hemiketal species **14** in 75% yield.[14] A reduction of this intermediate provided the alcohol **15** in 68% yield and the global transformation can be analyzed as a formal addition of the lithiated anion of **9** to acetaldehyde. This reductive migration of an ester from O-2 to C-1′ appeared to be a good approach to O-glycoconjugate analogues, if a highly functionalized ester was introduced at the 2-position of **9**. Ester **16** was thus prepared from **9** and from the corresponding D-serine-derived acid (through an *N*,*N*′-diisopropylcarbodiimide (DIPC)-mediated coupling, 85% yield) to challenge this hypothesis. To our delight, a Br/Li exchange with *n*BuLi at −78 °C provided hemiketal **17** in 57% yield, which could be reduced to the desired α-C-galactoside **18** in 57% yield. If the intermolecular trapping of the lithiated anion at low temperature can still be investigated, this last intramolecular strategy appears much more preferable for the synthesis of highly functionalized glycoconjugate analogues. The high chemical and configurational stability of α-aminoesters and acids compared with α-aminoaldehydes is indeed appreciable for the preparation of the aglyconic moiety.

An efficient synthesis of fluorinated α-C-galactosides has thus been described. The method involves an addition of difluoromethyl radicals to 2-benzyloxygalactal, followed by a Meerwein–Ponndorf–Verley reduction of the resulting 2-ketohexopyranosides. An efficient synthetic modification of these compounds, through a Br/Li exchange, followed by an intramolecular trapping of the resulting lithium species by the neighboring ester group on O-2, has also been disclosed. This sequence is desirable for the future syntheses of O-glycoconjugate analogues because it would allow the introduction of various aglycon moieties in the pseudo-anomeric position through a simple, mild, and convergent process. The synthesis of difluorinated α-*C*-galactosylceramides and a thorough conformational study of α-CF_2-galactosides are currently under investigation. Results in these areas will be reported in due course.

Experimental Section

Representative procedure for the reductive acyl chain transfer: *n*BuLi (1.53 M in hexane, 0.337 mL, 0.52 mmol) was added dropwise to a solution of acetate **13** (0.260 g, 0.43 mmol; obtained by acetylation of **9** using Ac_2O/NEt_3/cat. 4-dimethylaminopyridine (DMAP)) in THF (5 mL) at −78 °C under an argon atmosphere. The mixture was stirred for 1 h at −78 °C then quenched with 1 M HCl (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated. Chromatography on a flash purification system (3–30% EtOAc in cyclohexane) gave intermediate **14** as a colorless oil (0.171 g, 75%). The two diastereomers could not be separated at this stage. $NaBH_4$ (0.019 g, 0.50 mmol) was added to a solution of **14** (0.171 g, 0.32 mmol) in MeOH (5 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C, at which point TLC monitoring showed complete conversion of **14** (eluent: cyclohexane/EtOAc 70:30). The mixture was then warmed up to RT, quenched with sat. NH_4Cl and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Chromatography on a flash purification system (7–60% EtOAc in cyclohexane) gave **15** as a colorless oil (0.098 g, 58%).

Acknowledgements

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Keywords: fluorine · glycoconjugates · organolithium · radical reactions · reduction

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