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Addition of Difluoromethyl Radicals to Glycals: A New Route to α-CF_2-D-Glycosides

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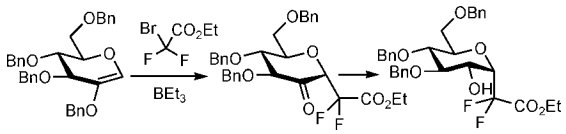
ABSTRACT



The synthesis of synthetically useful α-CF_2-glycosides by radical addition of ethyl bromodifluoroacetate onto 2-benzyloxyglycals is described. The methodology provides an access to α-*O*-glycoside mimics and, potentially, to valuable α-*O*-glycoconjugate analogues.

Among the different classes of biomolecules, *O*-glycoconjugates have acquired an increasing importance in the field of drug discovery in recent years. Their involvement in many recognition processes, such as the immune response, undoubtly accounts for this trend.[1] For example, KRN 7000, an α-galactosylceramide (α-GalCer) structurally close to natural *O*-glycolipids called agelasphins, exhibits a strong immunostimulatory activity and shows a high in vivo activity toward a wide range of diseases.[2−5] However, a major drawback of *O*-glycosides and *O*-glycoconjugates as drug development candidates resides in the low metabolic stability of the anomeric bond that erodes the bioavailability of carbohydrate-based drugs. As a consequence, the synthesis of nonhydrolyzable analogues such as CH_2-glycopyranosides has been investigated intensively, but unfortunately has scarcely ever been applied to valuable targets.[6] On the other hand, the O ↔ CF_2 transposition offers an interesting alternative to standard *C*-glycosides as it could potentially provide closer surrogates of carbohydrates thanks to the electronic properties of the CF_2 moiety.[7] Several groups have thus focused on the synthesis of CF_2-glycopyranosides as new glycomimetics.[8] The next step would be of course to produce CF_2-analogues of potent *O*-glycoconjugates such as α-galactosylceramides. This project has become a major goal,

(1) (a) *Essentials of Carbohydrate Chemistry and Biochemistry*, 2nd ed.; Lindshorst, T. K., Ed.; Wiley-VCH: Weinheim, Germany, 2002. (b) *Carbohydrate-Based Drug Discovery*; Wong, C.-H., Ed.; Wiley-VCH: Weinheim, Germany, 2003.

(2) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771.

(3) (a) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176. (b) Giaccone, G.; Punt, C. J. A.; Ando, Y.; Ruijter, R.; Nishi, N.; Peters, M.; von Blomberg, B. M. E.; Scheper, R. J.; van der Vliet, H. J. J.; van den Eertwegh, A. J. M.; Roelvink, M.; Beijnen, J.; Zwierzina, H.; Pinedo, H. M. *Clin. Cancer Res.* **2002**, *8*, 3702.

(4) (a) Grubor-Bauk, B.; Simmons, A.; Mayrhofer, G.; Speck, P. G. *J. Immunol.* **2003**, *170*, 1430. (b) Nieuwenhuis, E. E.; Matsumoto, T.; Exley, M.; Schleipman, R. A.; Glickman, J.; Bailey, D. T.; Corazza, N.; Colgan, S. P.; Onderdonk, A. B.; Blumberg, R. S. *Nat. Med.* **2002**, *8*, 588. (c) Hong, S.; Wilson, M. T.; Serizawa, I.; Wu, L.; Singh, N.; Naidenko, O. V.; Miura, T.; Haba, T.; Scherer, D. C.; Wei, J.; Kronenberg, M.; Koezuka, Y.; Van Kaer, L. *Nat. Med.* **2001**, *7*, 1052.

(5) The mechanism of action, based on a cytokine release by NKT cells, has been identified: Kronenberg, M. *Annu. Rev. Immunol.* **2005**, *23*, 877.

(6) For a review on *C*-glycoside synthesis, see: (a) Skrydstrup, T.; Vauzeilles, B.; Beau, J. M. *C*-Oligosaccharide Synthesis. In *Glycoscience*: *Chemistry and Chemical Biology*; Fraser Reid, B., Tatstuta, K., Thiem, J., Eds.; Springer: Heidelberg, Germany, 2001; Vol. 3, pp 2679. For this application of a CH_2-glyconjugate analogue, see: (b) Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *39*, 3818. (c) Schmieg, J.; Yang, G.; Franck, R. W.; Tsuji, M. *J. Exp. Med.* **2003**, *198*, 1631.

(7) For potent nonhydrolyzable CF_2-analogues of bioactive molecules, see: (a) Burke, T. R., Jr.; Lee, K. *Acc. Chem. Res.* **2003**, *36*, 426. (b) Burke, T. R., Jr.; Smyth, M. S.; Otaka, A.; Nomizu, M.; Roller, P. P.; Wolf, G.; Case, R.; Shoelson, S. E. *Biochemistry* **1994**, *33*, 6490. (c) Blackburn, G. M.; Jakeman, D. L.; Ivory, A. J.; Williamson, M. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2573 and references cited therein.

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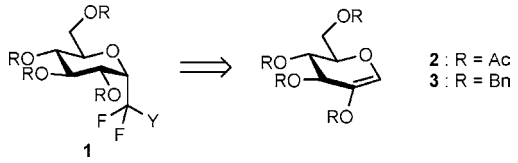
following the publication of the outstanding biological results obtained with the CH_2 analogue of KRN 7000.[6b] For such a purpose, the development of a new synthetic access to CF_2-glycopyranoside intermediates was needed and had to fulfill two major requirements.

First, the method had to lead stereoselectively to difluoromethylated analogues of α-glycosides. In the second place, the α-CF_2-glycoside obtained by such a reaction should feature appropriate functional groups in order to serve as a useful intermediate in the synthesis of α-GalCer analogues. Among the efficient CF_2-glycoside syntheses that have been developed, some methods have provided solutions only to either one problem or the other.[8b,e] We wish to present herein a new reaction for the addition of difluoromethyl radicals to glycals that leads stereoselectively to synthetically useful α-CF_2-glycosides.

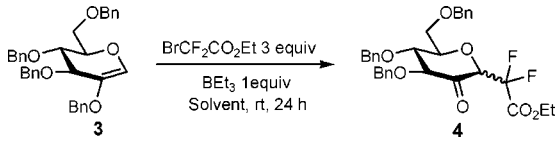
The addition of difluoromethyl radicals onto standard glycals has already been studied and exhibits a well-defined regioselectivity.[9] The addition takes place exclusively at the C-2 carbon and is therefore not suitable for CF_2-glycoside synthesis. However, we reasoned that the introduction of an alkoxy substituent at the C-2 position should direct the addition to the less hindered C-1 carbon (Scheme 1).

Scheme 1. Synthesis of α-CF_2-Glycosides from 2-Alkoxyglycals



During the early stages of this work, the group of Miethchen reported the sodium dithionite-mediated addition of bromochlorodifluoromethane to **2**, affording almost exclusively the corresponding α-CF_2-glucoside analogue **1** (Y = Cl) but with a low conversion.[8e,f] Moreover, a fluorinated synthon allowing easier functionalization than CF_2Cl was required for our purposes. The ester function of ethyl bromodifluoroacetate, an accessible and easy-to-handle fluorinated synthon, already proved suitable for further synthetic elaboration.[8h] Several initiators were tested in order to perform this addition of $BrCF_2CO_2Et$ to glycals **2** or **3**.[10] Sodium dithionite in $MeCN/H_2O$ or AIBN in refluxing benzene was not effective for this less reactive precursor. We then turned our attention to triethylborane and several attempts were made with benzylated D-glucal **3** as the starting material. The use of polar solvents appeared crucial as a low but significant conversion was observed in THF whereas only traces of product could be identified when reactions were performed in dichloromethane and toluene (Table 1). A faster reaction occurred in DMF allowing the isolation of 2-ketohexopyranoside **4** in 28% yield but a large amount of starting material was again recovered (Table 1, entry 5).

Table 1. Triethylborane-Mediated Addition of $BrCF_2CO_2Et$ to D-Glucal **3**



entry	solvent	yield (%)
1	CH_2Cl_2	traces
2	toluene	traces
3	THF	11
4	THF/H_2O	21
5	DMF	28
6	DMF	51[a]

[a] 5 equiv of $BrCF_2CO_2Et$ and 3 equiv of BEt_3 were used.

The formation of the 2-ketohexopyranoside **4** can be explained by a fragmentation of the radical resulting from the addition of $^{\bullet}CF_2CO_2Et$, thanks to the departure of a stabilized tolyl radical. This particular pathway is of course not applicable to acetylated D-glucal **2**, which moreover underwent no addition process of any type under these conditions. The need for a polar solvent is in agreement with the general behavior of fluoroalkyl radicals. Indeed, addition reactions of electronegative radicals such as $^{\bullet}CF_2CO_2Et$ to electron-rich double bonds give rise to polar transition states that are usually stabilized in polar media.[11] The reaction was eventually driven to completion by using a longer reaction time and an excess of triethylborane. Performing several additions of $BrCF_2CO_2Et$ and BEt_3 proved to be particularly efficient and 2-ketohexopyranoside **4** could be isolated in 51% yield (Table 1, entry 6). The addition of $^{\bullet}CF_2CO_2Et$ to double bonds from a stable and easily available bromodifluoroacetate is noteworthy since the few reported examples of such reactions involve the use of the less common iodide or require the painstaking synthesis of the corresponding selenide.[12] The two diastereomers **4a** and **4b** were present

(8) (a) Houlton, J. S.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron* **1993**, *49*, 8087. (b) Herpin, T. F.; Motherwell, W. B.; Weibel, J.-M. *Chem. Commun.* **1997**, 923. (c) Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Tetrahedron Lett.* **1996**, *37*, 6115. (d) Berber, H.; Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Chem. Eur. J.* **2001**, *7*, 903. (e) Wegert, A.; Miethchen, R.; Hein, M.; Reinke, H. *Synthesis* **2005**, 1850. (f) Wegert, A.; Hein, M.; Reinke, H.; Hoffmann, N.; Miethchen, R. *Carbohydr. Res.* **2006**, *341*, 2641. (g) Cuenca, A. B.; D'Hooge, F.; Gouge, V.; Castelot-Deliencourt, G.; Oulyadi, H.; Leclerc, E.; Jubault, P.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2005**, 2627. (h) Karche, N. P.; Pierry, C.; Poulain, F.; Oulyadi, H.; Leclerc, E.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2007**, 123. (i) Tony, K. A.; Denton, R. W.; Dilhas, A.; Jiménez-Barbero, J.; Mootoo, D. R. *Org. Lett.* **2007**, *9*, 1441.

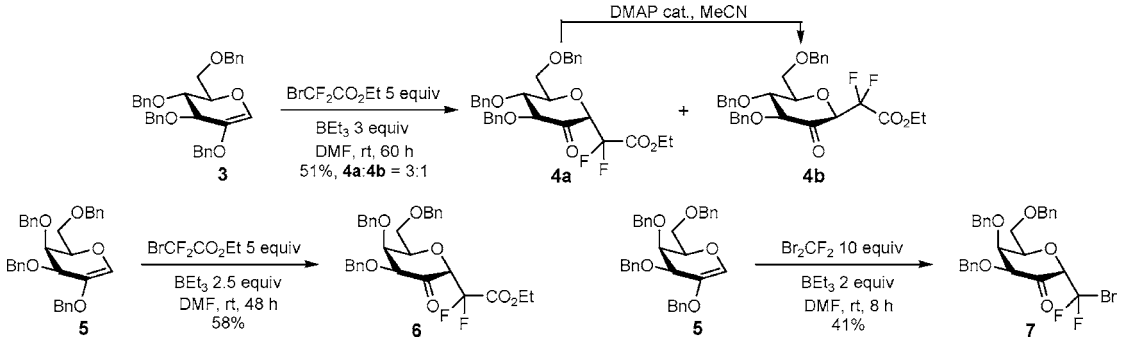
(9) (a) Miethchen, R.; Hein, M.; Reinke, H. *Eur. J. Org. Chem.* **1998**, 919. (b) Wegert, A.; Reinke, H.; Miethchen, R. *Carbohydr. Res.* **2004**, *339*, 1833.

(10) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron* **2004**, *60*, 8411.

(11) Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *96*, 1557.

(12) (a) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 5125. (b) Iseki, K.; Asada, D.; Takahashi, M.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 7399. (c) Xiao, F.; Wu, F.; Shen, Y.; Zhou, L. *J. Fluorine Chem.* **2005**, *126*, 63. (d) Murakami, S.; Ishii, H.; Fuchigami, T. *J. Fluorine Chem.* **2004**, *125*, 609.

Scheme 2. Addition of Difluoromethyl Radicals to 2-Benzyloxy-D-glycals



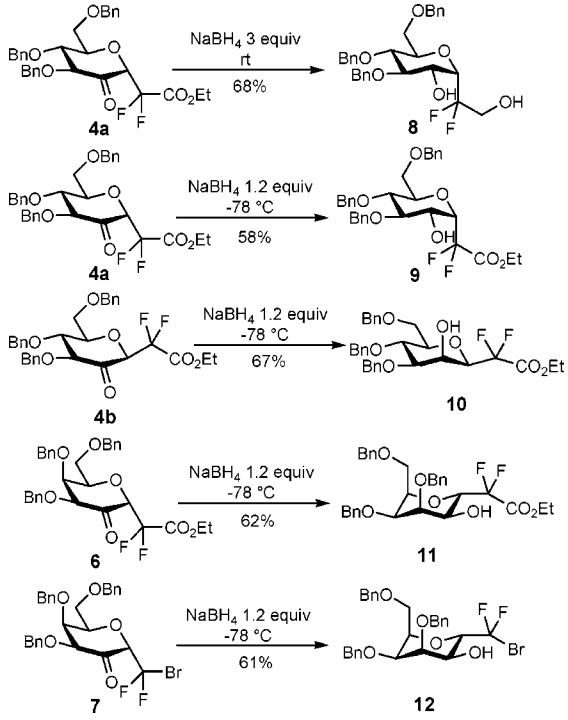
in a 3:1 ratio in the crude mixture as measured by ^{19}F NMR and were separated by column chromatography (Scheme 2).

The same procedure was succesfully applied to D-galactal **5**. The reaction proceeded this time with complete stereoselectivity. Indeed, 2-ketohexopyranoside **6** was present as a single diastereomer in the crude mixture (^{19}F NMR) and could be isolated in 59% yield. A clean and fast addition of dibromodifluoromethane was also performed and afforded 2-oxogalactoside **7** as the sole reaction product according to TLC and NMR analysis of the crude mixture. However, and despite a complete conversion of **5**, compound **7** was isolated in a disappointing 41% yield probably due to the modest stability of this compound (Scheme 2).

A reduction step was then necessary to obtain the desired CF_2-glycosides and to assess their relative configurations. A first reduction of compound **4a** under standard conditions ($NaBH_4$ in MeOH at room temperature) afforded a mixture of the desired CF_2-glycoside **9** along with a significant amount of diol **8**. The use of a 3-fold excess of sodium borohydride allowed the exclusive formation of **8** in 68% yield (Scheme 3). The selective reduction of the ketone moiety was eventually achieved by performing the reduction at −78 °C. Compounds **9**, **10**, **11**, and **12** were obtained from **4a**, **4b**, **6**, and **7** in fair yields and with complete diastereoselectivity. In each case, only one diastereomer could be detected in the ^{19}F NMR spectrum of the crude mixture (Scheme 3).

The α-D-glucoside configuration of **8** and **9** was proved thanks to HOESY and NOESY experiments performed on compound **8**. Despite diaxial coupling constants slightly lower than expected ($^3J_{ax-ax} = 7-8$ Hz), a NOE correlation between H_2 and H_4 and hOe correlations of the CF_2 moiety with H_3 and H_5 unambiguously proved this configuration and the $^4C_1$ conformation of both compounds (Figure 1). Moreover, an X-ray diffraction study performed on crystalline compound **9** later confirmed this configuration and conformation.[13] On the other hand, the assignment of a β-D-mannoside configuration to **10** was unmistakable thanks to the measurement of the different coupling constants.[14] The determination of the relative configuration of compounds **11** and **12** obtained in the galactose series was, in contrast, more puzzling. HOESY experiments showed no significant correlations between fluorine atoms and protons, and the coupling constants which could be extracted from the ^1H spectra were hardly compatible with a classical $^4C_1$ conformation. A closer examination of the ^1H spectrum of **11** revealed that the H_1-H_2, H_2-H_3, and H_3-H_4 coupling constants were consistent with an axial−axial−equatorial disposition for $H_1-H_2-H_3$. The α-D-taloside configuration ($^1C_4$ conformation) was therefore assigned to compound **11**. The same configuration and conformation was attributed to **12** due to similar ^1H NMR data.[15] The presence of the free hydroxy group in **11** provided an opportunity to perform substitution reactions with inversion of configuration at C-2 and thus obtain the desired α-D-galactoside analogues. Unfortunately, the Mitsunobu-type reactions we attempted only left unreacted starting material. Similarly, substitution

Scheme 3. Synthesis of α-CF_2-Glucosides and Talosides



(13) CCDC-641689 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

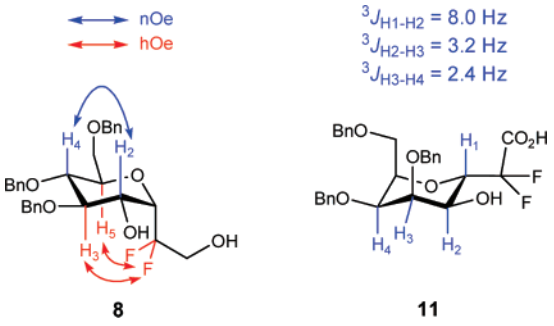


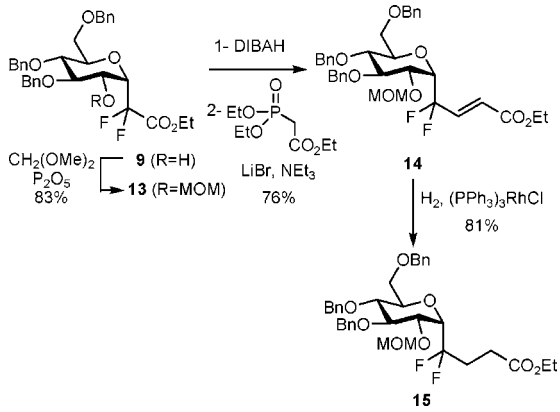
Figure 1. Configurations and conformations of the α-CF_2-glycosides.

reactions of the triflate derived from **11** did not afford the desired α-D-galactoside.

The discrepancy between the favored conformations of the glucose derivative **9** and of the galactose derivative **11** prompted us to take a closer look at their precursors **4a** and **6** through epimerization studies. It was found that, under slightly basic conditions, the glucose derivative **4a** could be converted to a 4:1 mixture of **4b** and **4a** whereas galactose derivative **6** was either left unchanged or degraded under basic conditions (Scheme 2). It was deduced from these results that the conformations of **4a** and **6** were also dissimilar. The strong steric repulsions induced by the CF_2-CO_2Et group were certainly dramatically increased in the galactose series and give rise to these unusual conformations.[16]

Finally, the relevance of the ester function for C−C bond formation was illustrated by the synthesis of compound **15** through an olefination/hydrogenation sequence inspired from syntheses of CH_2-analogues of glycosylserine.[17] The ester function of MOM-protected **13** was reduced and the resulting hemiketal was directly subjected to a Horner−Wadsworth−Emmons reaction with triethyl phosphonoacetate to afford **14** in 76% overall yield. Homogeneous hydrogenation allowed the isolation of CF_2-glycoside **15** in 81% yield (Scheme 4).

Scheme 4. Side-Chain Elongation



In conclusion, we have reported an original methodology for the preparation of synthetically useful α-CF_2-glycosides based on the radical addition of $BrCF_2CO_2Et$ or CF_2Br_2 to glycals. The presence of the ester function in the final compounds allows further synthetic elaboration toward the preparation of *O*-glycoconjugate analogues. The ketone function in compounds **4**, **6**, and **7** is also valuable for the synthesis of 2-deoxy-2-aminoglycoside analogues via reductive amination reactions. These two research areas, along with the scope and limitations of this radical addition reaction, are currently under investigation.

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Supporting Information Available: Complete experimental details and compound characterization data, as well as copies of ^1H, ^{19}F, and ^{13}C spectra, NOESY and HOESY spectra for **8**, and a CIF file for the X-ray diffraction study of **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The stereoselective reduction of α- and β-2-keto-D-*arabino*-hexopyranosides is well documented: (a) Lichtenthaler, F. W.; Lergenmüller, M.; Peters, S.; Varga, Z. *Tetrahedron*: *Asymmetry* **2003**, *14*, 727. (b) Lichtenthaler, F. W.; Lergenmüller, M.; Schwidetzky, S. *Eur. J. Org. Chem.* **2003**, 3094.

(15) A similar stereochemical outcome for the reduction of other 2-oxogalactosides has been described: Cipolla, L.; La Ferla, B.; Lay, L.; Peri, F.; Nicotra, F. *Tetrahedron*: *Asymmetry* **2000**, *11*, 295.

(16) A similar situation was already observed with another methodology. See ref 8h.

(17) (a) Debenham, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9897. (b) Bertozzi, C. R.; Hoeprich, P. D., Jr.; Bednarski, M. D. *J. Org. Chem.* **1992**, *57*, 6092.