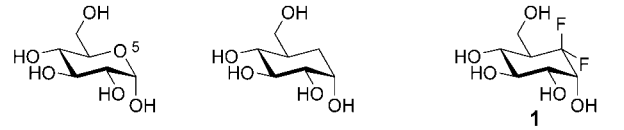
Carbohydrate Chemistry

Synthesis of *gem*-Difluorocarba-D-glucose: A Step Further in Sugar Mimesis**

Aurélie Deleuze, Candice Menozzi, Matthieu Sollogoub, and Pierre Sinaÿ**

Chemical modifications of carbohydrates have been used extensively to understand the origin of the specificity in the recognition processes by sugar-binding proteins in aqueous solution. A classical example is the work by Lemieux, wherein chemoselective removal of hydroxyl groups from oligosaccharides led to the concept of key polar interactions.[1] Along the same lines, the replacement of the endocyclic oxygen atom by a methylene group has provided hydrolytically stable glycoside mimetics called carbasugars, whose biochemical properties have been studied (Figure 1).[2–8] Such a replacement has the inherent disadvantage to suppress any possible hydrogen bond formation that involved this electronegative atom. This drawback clearly appeared in the case of carbalactoside, a close mimic of lactoside, which is no longer recognised by a β-galactosidase.[9] A model has shown that the endocyclic oxygen atom (O-5) of the D-galactose moiety is involved in the interaction with hydrogen-donating groups of the active site of the enzyme.[10] One way to circumvent this problem and to enlarge the probing spectrum of carbasugars is to replace the oxygen atom by other hydrogen-bond acceptors. Ideally, to fully understand the role of the endocyclic oxygen requires the two lone pairs to be discriminated so that they can be probed to see which of them, if any, is involved in hydrogen bonding in the active site of the enzyme. Fluorine atoms are not as strong hydrogen-bond acceptors as oxygen, but they still exhibit this property,[11–13] and more interestingly they have been used as reporter groups of the active site of enzymes through ^{19}F NMR spectroscopy.[14] It is therefore foreseeable that



α-D-glucopyranose | 5α-carba-α-D-glucopyranose | 5α-*gem*-difluorocarba-α-D-glucopyranose

Figure 1. Glucopyranose and its carbocyclic congeners.

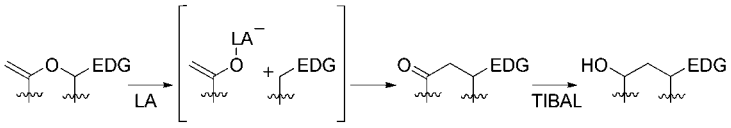
[*] A. Deleuze, C. Menozzi, Dr. M. Sollogoub, Prof. P. Sinaÿ
Département de Chimie
Ecole Normale Supérieure
UMR 8642: CNRS-ENS-UPMC Paris 6
24 rue Lhomond
75231 Paris Cedex 05 (France)
Fax: (+33) 1-4432-3397
E-mail: matthieu.sollogoub@ens.fr
pierre.sinay@ens.fr

[**] The authors would like to thank Dr. Corinne Aubert for useful discussions about cobalt.

  DOI: 10.1002/ange.200461244

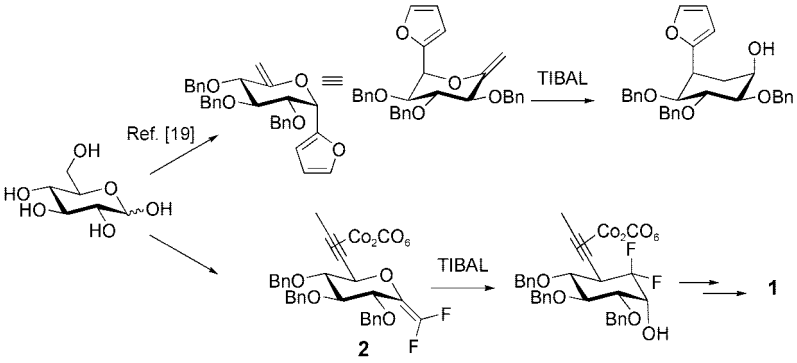
replacement of the endocyclic CH_2 group by a CF_2 moiety in a carbasugar would constitute a step further in the utilization of this family of sugar mimetics by enhancing their ability to be accepted by enzymes involving O-5 and allowing the study of their complexation by NMR spectroscopy.

We recently reported a novel sugar-to-carbocycle rearrangement promoted by triisobutylaluminum (TIBAL)[15] or Cl_3TiO*i*Pr.[16] The proposed key step in this transformation is the opening of the ring to give a carbocationic intermediate. Indeed, this reaction is favored when this putative carbenium species can be stabilized by an electron-donating group (EDG).[17] This is generally applicable to acyclic non-sugar-derived enol ethers (Scheme 1).[18]



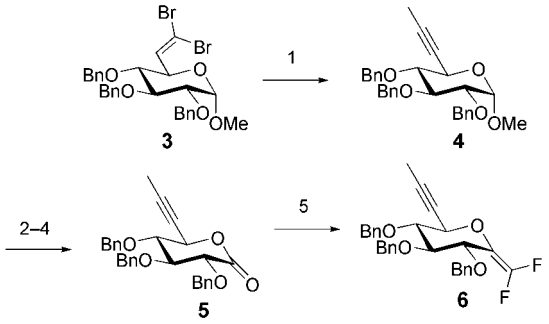
Scheme 1. General rearrangement of EDG-substituted vinyl ethers. EDG = electron-donating group, LA = Lewis acid, TIBAL = triisobutylaluminum.

As an example, we recently synthesized a carbasugar with furanyl as the EDG which was easily introduced at the anomeric centre of D-glucose through a glycosylation process. In this synthesis, the anomeric center of the carba congener is derived from the C-5 carbon atom of D-glucose.[19] Given the accessibility of ynopyranosides[20] and the recent results of Harrity and co-workers[21] who showed that dicobalt hexacarbonyl clusters[22] could act as EDGs in a similar situation, we anticipated that our TIBAL-mediated reductive rearrangement applied to the difluoroalkene **2** might provide a convenient entry to our target molecule **1** (Scheme 2).



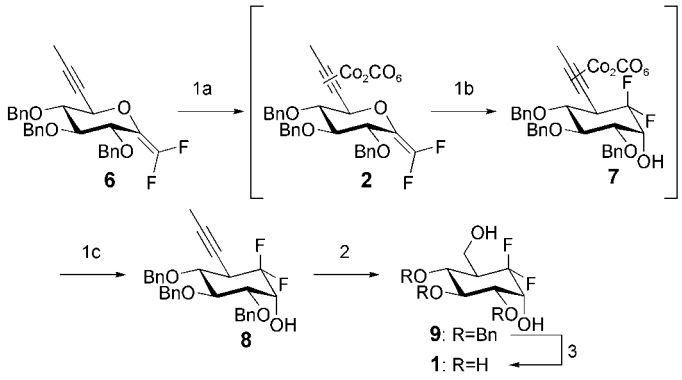
Scheme 2. Synthetic strategies for carbasugars through TIBAL-promoted rearrangements. Bn = benzyl.

Synthesis of the ynopyranose **6**, the precursor of compound **2**, is depicted in Scheme 3. The known[20] *gem*-dibromoalkene **3** was first converted into alkyne **4** through methylation of the acetylenic anion generated in situ. Acetolysis,[23] followed by hydrolysis of the generated anomeric acetate, and oxidation of the hemiacetal afforded the corresponding lactone **5**. Difluoromethylenation according to Motherwell et al.[24] provided the desired *gem*-difluoroalkene precursor **6**.



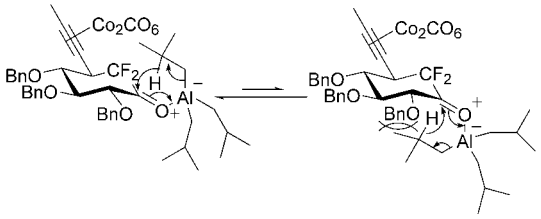
Scheme 3. Synthesis of the *gem*-difluoro-exo-glucal **6**. Reagents and conditions: 1) a) *n*BuLi (2.1 equiv), THF, −78 °C, 2 h; b) MeI (6 equiv), THF, −78 °C, 30 min; c) HMPT (4 equiv), −78 °C→RT, overnight, 75% over three steps; 2) H_2SO_4 (1 equiv), Ac_2O, 0 °C, 3 min, 75%; 3) MeONa (4 equiv), MeOH, 0 °C→RT, 2 h, 90%; 4) PCC (3 equiv), 4-Å molecular sieves (3 equiv), CH_2Cl_2, room temperature, 4 h, 74%; 5) a) HMPT (5 equiv), THF, −40 °C→RT; b) CBr_2F_2 (5 equiv), HMPT (5 equiv), THF, RT→reflux, 1 h, 95%. THF = tetrahydrofuran, HMPT = hexamethylphosphoric triamide, PCC = pyridinium chlorochromate.

As anticipated and much to our delight, the key rearrangement was performed through a two-step one-pot procedure that involved first, the complexation of the alkyne **6** by dicobalt octacarbonyl,[25] followed by the reductive TIBAL-induced rearrangement of **2**.[17] Decomplexation with CAN (ceric ammonium nitrate)[26] of the crude compound **7** afforded alcohol **8** in 75% yield over three steps and only one purification step by chromatography. The 5a-*gem*-difluorocarba-α-D-glucopyranose **1**[27] was then easily obtained by controlled reduction of the triple bond, reductive ozonolysis, and debenzylation (Scheme 4). As previously observed,[15] the rearrangement occurs with retention of configuration. The reduction of the putative transient



Scheme 4. Synthesis of the 5a-*gem*-difluorocarba-α-D-glucopyranose **1**. Reagents and conditions: 1) a) $[Co_2(CO)_8]$ (1.5 equiv), CH_2Cl_2, room temperature, 2 h; b) TIBAL (5 equiv), toluene, room temperature, 2.5 h; c) CAN (5 equiv), NEt_3 (1 equiv), acetone, 30 min, 65% over three steps; 2) a) $Pd/CaCO_3$, H_2, MeOH, room temperature, 4 h; b) O_3, CH_2Cl_2, −78 °C, 5 min; c) $NaBH_4$, CH_2Cl_2, room temperature, 1 h, 76% over three steps; 3) Pd/C, H_2, MeOH, room temperature, 1 h, 90%. CAN = ceric ammonium nitrate.

ketone is stereoselective and is classically explained by the attack of the hydride ion, which is attached to the isobutyl group, on the less-hindered face of the molecule to provide the axial hydroxyl group (Scheme 5).



Scheme 5. Stereoselectivity of the reduction of the transient ketone by TIBAL.

The reduction step described proceeds under steric control, whereas the electronic control admitted in such a case, the Ahn–Eisenstein effect,[28] gives the opposite stereoselectivity. According to this model, the most stable transition-state structure has the axial C–F[29,30] bond in the antiperiplanar position with respect to the forming H–C bond. This model implies, as shown in Figure 2, which depicts the late transition state of the reduction step, a selective attack of the hydride ion to form the equatorial hydroxyl group.

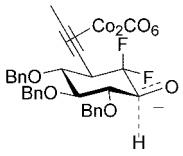
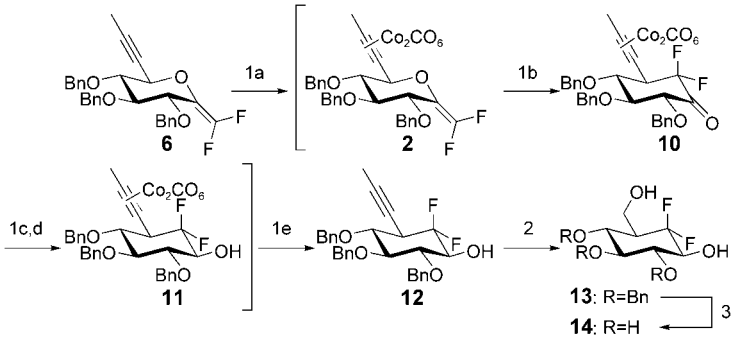


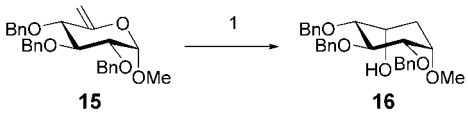
Figure 2. Anh–Eisenstein effect to obtain the axial reduction.

Once again, a one-pot procedure was developed: After reaction of the alkyne **6** with dicobalt octacarbonyl to give cluster **2**, the rearrangement was, this time, induced by $Cl_3TiOiPr$[16] to yield cyclohexanone **10**. The Lewis acid was then quenched with THF, and the ketone was reduced by means of the super hydride. The triple bond in the crude product **11** was decomplexed, and the expected equatorial alcohol **12** was obtained in 73% yield over five steps and only one purification step by column chromatography. The 5a-*gem*-difluorocarba-β-D-glucopyranose **14**[31] was then obtained as described above (Scheme 6).



Scheme 6. Synthesis of the 5a-*gem*-difluorocarba-β-D-glucopyranose **14**. Reagents and conditions: 1) a) $[Co_2(CO)_8]$ (1.5 equiv), CH_2Cl_2, room temperature, 2 h; b) $TiCl_3OiPr$ (2 equiv), CH_2Cl_2, −78 °C, 1 h; c) THF (5 equiv), −78 °C, 15 min; d) Et_3BHLi (2 equiv), CH_2Cl_2, −78 °C, 30 min; e) CAN (5 equiv), NEt_3 (1 equiv), acetone, 1 h, 73% over five steps; 2) a) Pd/$CaCO_3$, H_2, MeOH, room temperature, 1.25 h; b) O_3, CH_2Cl_2, −78 °C, 5 min; c) $NaBH_4$, CH_2Cl_2, room temperature, 1 h, 78% over three steps; 3) Pd/C, H_2, MeOH, room temperature, 1 h, 90%.

The observed stereoselectivity of this reduction process is in sharp contrast to the case in which the fluorine atoms are absent from the molecule. Indeed, when the unsaturated sugar **15**[32] was submitted to the same reaction conditions, only the axial alcohol **16**[15] was obtained in 75% yield (Scheme 7). This result supports the directing role of fluorine in the reduction of the ketone.



Scheme 7. Rearrangement and reduction of **15**. Reagents and conditions: 1) a) $TiCl_3OiPr$ (1 equiv), CH_2Cl_2, −78 °C; b) THF (5 equiv), −78 °C, 15 min; c) Et_3BHLi (2 equiv), CH_2Cl_2, −78 °C, 30 min, 73% over three steps.

In summary, we have synthesized, for the first time, two *gem*-difluorinated carba analogues of α- and β-D-glucopyranoses by using a rearrangement strategy and by taking advantage of the Anh–Eisenstein effect to obtain the β analogue. They are attractive candidates for probing the role of endocyclic oxygen atoms in carbohydrates in sugar–protein interactions. This strategy is currently being extended to other carbohydrates.

Received: July 8, 2004

Keywords: carbohydrates · cyclization · fluorine · reduction · synthetic methods

[1] a) R. U. Lemieux, *Chem. Soc. Rev.* **1989**, *18*, 347–374; b) R. U. Lemieux, *Acc. Chem. Res.* **1996**, *29*, 373–380.
[2] T. Suami, S. Ogawa, *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21–90.
[3] S. Ogawa, N. Matsunaga, H. Li, M. M. Palcic, *Eur. J. Org. Chem.* **1999**, *3*, 631–642.
[4] M. Carpintero, A. Fernandez-Mayoralas, J. Jimenez-Barbero, *Eur. J. Org. Chem.* **2001**, *4*, 681–689.
[5] S. Ogawa, Y. Uematsu, S. Yoshida, N. Sasaki, T. Suami, *J. Carbohydr. Chem.* **1987**, *6*, 471–478.
[6] S. Ogawa, A. Maruyama, T. Odagiri, H. Yuasa, H. Hashimoto, *Eur. J. Org. Chem.* **2001**, *5*, 967–974.
[7] M. Carpintero, A. Bastida, E. Garcia-Junceda, J. Jimenez-Barbero, A. Fernandez-Mayoralas, *Eur. J. Org. Chem.* **2001**, *4*, 4127–4135.
[8] M. Kitaoka, S. Ogawa, H. Taniguchi, *Carbohydr. Res.* **1993**, *247*, 355–359.
[9] E. Montero, A. Garcia-Herrero, J. L. Asensio, K. Hirai, S. Ogawa, F. Santoyo-Gonzalez, F. J. Canada, J. Jimenez-Barbero, *Eur. J. Org. Chem.* **2000**, 1945–1952.
[10] J. F. Espinosa, E. Montero, A. Vian, J. L. Garcia, H. Dietrich, M. Martin-Lomas, R. R. Schmidt, A. Imberty, F. J. Canada, J. Jimenez-Barbero, *J. Am. Chem. Soc.* **1998**, *120*, 10862–10871.
[11] L. A. Curtiss, D. J. Frurip, M. Blander, *J. Am. Chem. Soc.* **1978**, *100*, 79–86.
[12] D. A. Dixon, B. E. Smart, *J. Phys. Chem.* **1991**, *95*, 1609–1612.
[13] J. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron* **1996**, *52*, 12613–12622.
[14] J. Feeney, J. E. McCormick, C. J. Bauer, B. Birdsall, C. M. Moody, B. A. Starkmann, D. W. Young, P. Francis, R. H. Havlin,

W. D. Arnold, E. Oldfield, *J. Am. Chem. Soc.* **1996**, *118*, 8700 – 8706.
[15] S. K. Das, J.-M. Mallet, P. Sinaÿ, *Angew. Chem.* **1997**, *109*, 513 – 516; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 493 – 496.
[16] M. Sollogoub, J.-M. Mallet, P. Sinaÿ, *Tetrahedron Lett.* **1998**, *39*, 3471 – 3472.
[17] M. Sollogoub, J.-M. Mallet, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 370 – 372; *Angew. Chem. Int. Ed.* **2000**, *39*, 362 – 364.
[18] B. du Roizel, M. Sollogoub, A. J. Pearce, P. Sinaÿ, *Chem. Commun.* **2000**, 1507 – 1508.
[19] M. Sollogoub, A. J. Pearce, A. Herault, P. Sinaÿ, *Tetrahedron: Asymmetry* **2000**, *11*, 283 – 294.
[20] D. Rouzaud, P. Sinaÿ, *J. Chem. Soc. Chem. Commun.* **1983**, 1353 – 1354.
[21] D. R. Carbury, S. Reigner, J. W. Myatt, N. D. Miller, J. P. A. Harrity, *Angew. Chem.* **2002**, *114*, 2699 – 2701; *Angew. Chem. Int. Ed.* **2002**, *41*, 2584 – 2587.
[22] K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207 – 214.
[23] J. M. Aurrecoechea, B. Lopez, M. Arrate, *J. Org. Chem.* **2000**, *65*, 6493 – 6501.
[24] W. B. Motherwell, M. J. Tozer, B. C. Ross, *J. Chem. Soc. Chem. Commun.* **1989**, 1437 – 1439.
[25] K. M. Nicholas, M. Mulvaney, M. Bayer, *J. Am. Chem. Soc.* **1980**, *102*, 2508 – 2510.
[26] D. Seyferth, A. T. Wehman, *J. Am. Chem. Soc.* **1970**, *92*, 5520 – 5522.
[27] **1**: $[\alpha]_D^{20} = +2.4$ ($c = 0.9$, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS): $\delta = 4.18$ (dd, $^3J(5,6) = 4.8$, $^3J(6,6') = 11.6$ Hz, 1H; H-6), 4.14 (dd, $^3J(5,6') = 4.4$, $^3J(6,6') = 11.6$ Hz, 1H; H-6′), 4.05 (ddd, $^3J(1,2) = {}^3J(1,F_{eq}) = 3.9$, $^3J(1,F_{ax}) = 7.8$ Hz, 1H; H-1), 3.83 (t, $^3J(3,4) = {}^3J(3,2) = 9.4$ Hz, 1H; H-3), 3.64–3.59 (m, 1H; H-2), 3.61 (t, $^3J(3,4) = {}^3J(4,5) = 10.1$ Hz, 1H; H-4), 2.50 ppm (ddq, $^3J(5,6) = {}^3J(5,F_{eq}) = 4.2$, $^3J(5,F_{ax}) = 30.7$, $^3J(5,4) = 11.0$ Hz, 1H; H-5); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): $\delta = 124.1$ (dd, $^1J(C,F) = 240.8$, $^1J(C,F) = 251.8$ Hz; CF_2), 75.6 (s; C-3), 73.5 (dd, $^2J(C,F) = 22.1$, $^2J(C,F) = 32.3$ Hz; C-1), 72.1 (d, $^3J(C,F) = 11.0$ Hz; C-2 or C-4), 72.0 (d, $^3J(C,F) = 9.0$ Hz; C-2 or C-4), 58.7 (t, $^3J(C,F) = 2.9$ Hz; C-6), 46.5 ppm (t, $^2J(C,F) = 20.0$ Hz; C-5). ^{19}F NMR (235 MHz, CD_3OD, 25 °C): $\delta = -110.3$ (d, $^2J(F,F) = 256.5$ Hz; F_{eq}), −115.7 ppm (ddd, $^2J(F,F) = 256.5$, $^3J(F,H\text{-}5) = 30.6$, $^3J(F,H\text{-}1) = 3.5$ Hz; F_{ax}); DCI-MS (desorption chemical ionization; NH_3): m/z: 232 $[M+NH_3+H]^+$, 215 $[M+H]^+$; HRMS (DCI, NH_3): calcd for $C_7H_{13}O_5F_2$: 215.0731; found: 215.0726.
[28] N. T. Anh, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61 – 70.
[29] S. S. Wong, M. N. Paddon-Row, *J. Chem. Soc. Chem. Commun.* **1990**, 456 – 458.
[30] C. F. Bridge, D. O'Hagan, K. A. Reynolds, K. K. Wallace, *J. Chem. Soc. Chem. Commun.* **1995**, 2329 – 2330.
[31] **14**: $[\alpha]_D^{20} = +1.0$ ($c = 1.2$, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS): $\delta = 4.18$ (dd, $^3J(5,6) = 4.6$, $^3J(6,6') = 12.0$ Hz, 1H; H-6), 4.15 (dd, $^3J(5,6') = 4.6$, $^3J(6,6') = 12.0$ Hz, 1H; H-6′), 3.80–3.71 (m, 1H; H-2), 3.68–3.62 (m, 1H; H-4), 3.53–3.48 (m, 2H; H-1, H-3), 2.12 ppm (ddq, $^3J(5,6) = {}^3J(5,F_{eq}) = 4.2$, $^3J(5,F_{ax}) = 28.6$, $^3J(5,4) = 11.6$ Hz, 1H; H-5); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): $\delta = 122.8$ (dd, $^1J(C,F) = 245.4$; $^1J(C,F) = 248.9$ Hz; CF_2), 78.2 (d, $^4J(C,F) = 1.2$ Hz; C-3), 75.2 (t, $^2J(C,F) = 20.3$ Hz; C-1), 73.2 (d, $^3J(C,F) = 9.5$ Hz; C-2 or C-4), 71.7 (d, $^3J(C,F) = 10.2$ Hz; C-2 or C-4), 58.6 (t, $^3J(C,F) = 3.1$ Hz; C-6), 49.0 ppm (t, $^2J(C,F) = 20.0$ Hz; C-5). ^{19}F NMR (235 MHz, CD_3OD, 25 °C): $\delta = -110.3$ (d, $^2J(F,F) = 260.0$ Hz; F_{eq}), −126.1 ppm (ddd, $^2J(F,F) = 260.0$, $^3J(F,H\text{-}5) = 28.2$, $^3J(F,H\text{-}1) = 21.2$ Hz; F_{ax}); DCI-MS (NH_3): m/z: 232 $[M+NH_3+H]^+$; HRMS (DCI, NH_3): calcd for $C_7H_{16}O_5NF_2$: 232.0997; found 232.0999.
[32] T. Iimori, H. Takahashi, S. Ikegami, *Tetrahedron Lett.* **1996**, *37*, 649 – 652.

