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Approaches to the synthesis of CF_2-analogues of 2-deoxy-2-aminoglycosides

Florent Poulain, Eric Leclerc *, Jean-Charles Quirion *

Université et INSA de Rouen, CNRS, UMR 6014 C.O.B.R.A.–IRCOF, 1 rue Tesnière, 76821 Mont Saint-Aignan Cedex, France

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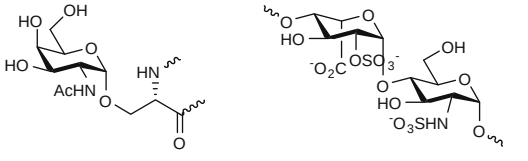
ABSTRACT

The preparation of a fluorinated *C*-glycosidic analogue of a 2-deoxy-2-acetamido-D-altrose is described. The synthetic sequence involves the addition of a difluoroenoxysilane to a D-glucal, an epoxidation of the resulting unsaturated CF_2-glycoside and a ring-opening reaction with $TMSN_3$. An Overman rearrangement of the unsaturated intermediate is also described.

A high number of natural glycoconjugates with significant biological functions feature a 2-deoxy-2-aminoglycoside moiety in their glycone group.[1,2] More generally, the majority of natural *O*-glycopeptides display a α-GalNAc/Ser or α-GalNAc/Thr core fragment.[2] The glycone and aglycone parts of all the tumour-associated antigens, which are used in the elaboration of anti-cancer vaccines, are, for example, linked by an α-2-deoxy-2-acetamido-D-galactose (α-GalNAc) residue.[1a,b] A synthetic hexasaccharide malarial toxin, used for the development of anti-malarial vaccines, features also an α-glucosamine residue.[3] Glycosylation of proteins with β-2-deoxy-2-acetamido-D-glucose (β-GlcNAc) seems on the other hand to be involved in transcriptional regulation.[4] Finally, glycosaminoglycans, which are polysaccharide compounds such as the well-known heparin, exhibit a variety of biological properties and have been exploited for the preparation of therapeutic drugs.[5] Our group has been involved for many years in the development of methodologies for the synthesis of CF_2-glycosides, a subclass of hydrolytically stable glycomimetics.[6,7] As a consequence, these numerous examples illustrating the importance of the 2-deoxy-2-aminoglycosidic link among natural glycopeptides prompted us to apply some of these methods to the synthesis of their CF_2-analogues (Fig. 1).

We recently reported the addition of the silylated difluoroketene acetal **1** to D-glucal and its application to the synthesis of α-CF_2-mannosides and pseudo-glycopeptides. An improved procedure indeed allowed us to prepare a salt-free solution of **1** which was directly used in glycosylation reactions without further purification of this sensitive material.[6c] The double bond displayed in the addition products α-**4** and β-**4**, which was first dihydroxylated for the preparation of CF_2-glycosides, could also serve for the introduction of an amino group (Scheme 1). Two sequences were planned for such a purpose: an epoxidation of the double bond followed by a ring-opening reaction with nitrogen nucleophiles, or a sigmatropic [3,3]-rearrangement of the corresponding trichloroacetimidate followed by a dihydroxylation reaction. Our investigation of these two pathways is described as follows.

The epoxidation of the addition products followed the same features as the previously described dihydroxylation reaction.[6c] The α/β mixture (6:4) of acetylated compounds **2** was totally unreactive under all the epoxidation conditions which were tested (*m*-CPBA, $V(acac)_3$/*t*-BuOOH, MnSalen/*m*-CPBA, Oxone, Oxone/Trifluoroacetone). On the other hand, deacetylation provided compounds which underwent the desired reaction using methyl(trifluoromethyl)dioxirane (generated in situ from trifluoroacetone and oxone).[8] The α/β mixture of anomers **3** was indeed successfully epoxidized to provide **5** (64% yield) as a mixture of two diastereomers in the same ratio, thus indicating that the epoxidation was probably totally diastereoselective for each anomer (Scheme 1).



α-GalNAc/Ser (T_N antigen) Major disaccharide sequence of heparin

Figure 1.

* Corresponding authors. Tel.: +33 235522901; fax: +33 235522959 (E.L.).
E-mail addresses: eric.leclerc@insa-rouen.fr (E. Leclerc), quirion@insa-rouen.fr (J.-C. Quirion).

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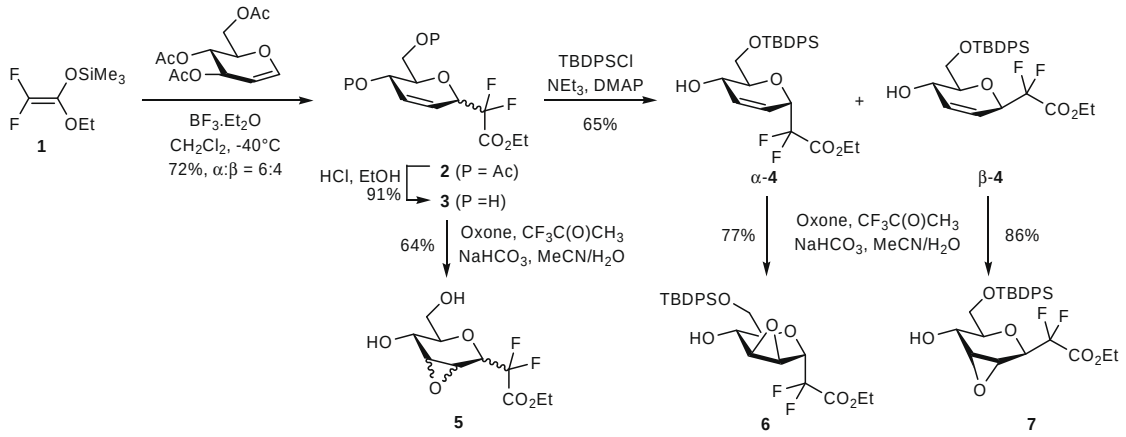
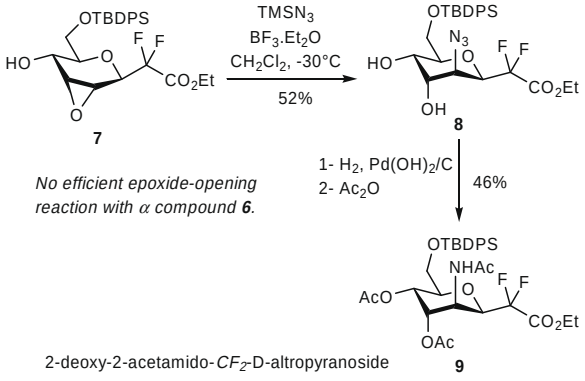


Scheme 1.

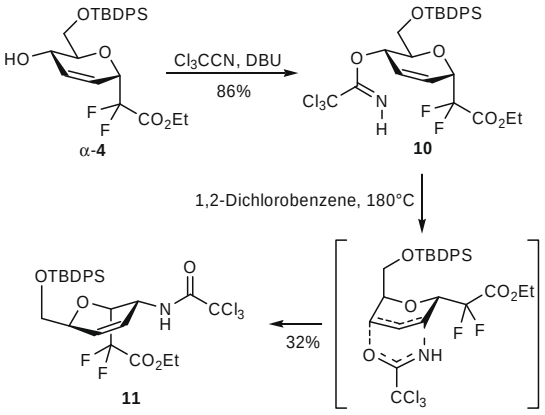
This was confirmed when submitting each anomer α-**4** or β-**4**, obtained and separated after selective silylation of the C-6 alcohol, to the same epoxidation conditions. Epoxides **6** and **7** were indeed isolated as a single diastereomer for each reaction in 77% and 86% yield, respectively (Scheme 1).[9] The lack of reactivity of the acetylated product **2** in the dihydroxylation and epoxidation reactions was attributed to the combined electron-withdrawing effects of the difluoroacetate and acetoxy groups.

The relative configurations of epoxides **6** and **7** were not determined at that stage due to the overlaps of crucial signals in the ^{1}H NMR spectra, which prevented us from collecting useful NOESY data. Ring opening reactions using nitrogen nucleophiles were then investigated, beginning with the β derivative **7**. Benzylamine and azides ($TMSN_3$, NaN_3) were tested as nucleophiles using Brönsted or Lewis acids (NH_4Cl, $BF_3{\cdot}Et_2O$, $LiClO_4$, $Yb(OTf)_3$) as additives. The best result was obtained using trimethylsilyl azide in the presence of a stoichiometric amount of $BF_3{\cdot}Et_2O$ at low temperature. These conditions yielded the 2-deoxy-2-azido-*CF*$_2$-glycoside **8** in 52% yield as a single regio- and stereoisomer (Scheme 2).[10] On the other hand, the α compound **6** was totally unreactive under these conditions and all our efforts devoted to the ring-opening of this epoxide were unsuccessful, whatever the nucleophile ($TMSN_3$, NaN_3, $BnNH_2$) and the acid ($BF_3{\cdot}Et_2O$, TMSOTf, $LiClO_4$, $AlCl_3$, $Yb(OTf)_3$, etc.) involved in the process. All these conditions either left the starting material unchanged or led to complex mixtures from which a ring-opening compound was isolated only once, although in very low yield, using $BnNH_2$ as the nucleophile in the presence of $Yb(OTf)_3$. The azido group of compound **8** was hydrogenated afterward and acetylated to yield **9**, which is, to the best of our knowledge, the first reported example of a 2-deoxy-2-acetamido-*CF*$_2$-D-glycoside (Scheme 2).

The different NMR data which were collected unambiguously proved the β-altrose configuration of compound **8** as well as the regioselectivity of the ring-opening reaction. The β-configuration was confirmed by a NOESY correlation between H-1 and H-5, and the different coupling constants were in favour of this relative configuration.[11] The regioselectivity of the epoxide opening was proved by a scalar coupling between H-3 and an OH group, as indicated by a COSY correlation between these two protons. The relative configuration of epoxide **7**, as displayed in Scheme 1, has been deduced from this study. The regio- and stereoselectivity of the reaction leading to **8** is consistent with a *trans* diaxial opening of epoxide **7**. If the electron-withdrawing effect of the difluorinated substituent should destabilize the apparition of a positive charge on C-2, this well-known ring-opening pathway for cyclohexene oxides seems nevertheless favoured.[12] The stereoselectivity of the reaction leading to **7** is consistent with an epoxidation *anti* to the difluoroacetate group, the largest substituent α to the double bond. A hydrogen bonding of the dimethyldioxirane reagent with a free hydroxy group has been invoked in the literature to explain a *syn* epoxidation of a cyclohex-2-en-1-ol.[13] Although, in our case, this model would of course lead to the same product **7**, the H-bonding between the OH group and methyl(trifluoromethyl)dioxirane in a protic medium is not likely. As epoxide **6** remained poorly reactive towards the addition of nitrogen nucleophiles, the relative configuration displayed in Scheme 1 could not be deduced from a ring-opening product and has only been postulated. An epoxidation *anti* to the CF_2CO_2Et and OH groups appeared as



Scheme 2.



Scheme 3.

the most reasonable pathway since, as explained above, a steric discrimination is more likely under these conditions than the H-bonding approach.

A second strategy was developed which is based on the Overman sigmatropic [3,3]-rearrangement of a trichloroacetimidate derived from **4**. This reaction has been quite developed for the synthesis of classical 2-deoxy-2-amino-D-glycosides.[14] Trichloroacetimidate **10** was thus prepared using standard conditions, and several attempts were made to promote the sigmatropic rearrangement (Scheme 3). It was already known from previous reports that compounds with the glucose configuration required higher temperatures than their galactose counterparts for the rearrangement to occur. For stereoelectronic reasons, a pseudo-axial arrangement of the trichloroacetimidate moiety in the transition state is indeed necessary for this reaction. In the glucose series, this can be achieved only by reaching a pseudo-chair conformation of higher-energy (Scheme 3). High temperatures are thus required and the best results were obtained in refluxing 1,2-dichlorobenzene with a catalytic amount of potassium carbonate, yielding trichloroacetamide **11** in 32% yield (Scheme 3).[15]

The next step was thus to functionalize the remaining double bond in order to access to the desired 2-amino-CF_2-glycoside. The dihydroxylation of related compounds was well documented and was expected to occur *anti* to the trichloroacetamide group to deliver preferentially the 2-deoxy-2-amino-D-galactose analogue.[14b,c] To our disappointment, compound **11** remained totally unreactive under all the conditions which were tested (cat. OsO_4/NMO or stoichiometric OsO_4 in different solvent systems, at room temperature or at 60 °C). This lack of reactivity of the double bond was attributed to the combined strong electron-withdrawing effects of the trichloroacetamide group and, to a lesser extent, of the difluoroacetate group. Unfortunately, our attempts to deprotect the trichloroacetamide moiety affected also the highly reactive difluoroacetate and raised many compatibility problems. The epoxidation reaction of **11** was not examined but the synthesis of the desired 2-deoxy-2-amino-CF_2-glycoside would anyway involve a difficult opening of the resulting epoxide with oxygen nucleophiles. Combined with the low yield obtained for the rearrangement, this approach was thus too compromised to be further investigated.

In conclusion, we applied our recently developed difluoroenoxysilane addition reaction to the synthesis of 2-deoxy-2-aminoglycoside analogues. A CF_2-analogue of 2-deoxy-2-acetamido-D-altrose, first example of a CF_2-aminopyranoside, has been synthesized through an epoxidation/azidation sequence performed on the addition product β-**4**. Another approach, based on the Overman rearrangement of the trichloroacetimidate derived from α-**4**, was also investigated. The expected product **11** was obtained but unfortunately could not be converted to the corresponding CF_2-aminopyranoside using a dihydroxylation reaction. However, these strategies remain reasonable approaches for the synthesis of the CF_2-analogues of these valuable carbohydrate derivatives. Our efforts will now focus on the preparation of surrogates to 2-deoxy-2-aminoglycosides of biological importance, such as α-GalNAc and β-GlcNAc.

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9. To a solution of β-**4** (245 mg, 0.50 mmol) in acetonitrile (8 mL) cooled at 0 °C were added a solution of EDTA (0.0004 M in water, 4 mL) and trifluoroacetone (3.5 mmol). A mixture of $NaHCO_3$ (0.8 g, 9.5 mmol) and oxone (1.8 g, 2.93 mmol) was added at 0 °C in small portions over 4 h. The slurry was vigorously stirred at 0 °C until complete consumption of the starting material, and then concentrated under reduced pressure to remove acetonitrile. The concentrate was dissolved in a minimal amount of water and AcOEt (10 mL). The aqueous layer was extracted with AcOEt (2 × 10 mL). The organic layers were combined and washed with brine (15 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography over silica gel (cyclohexane/AcOEt 85:15) afforded **7** as a colourless oil (220 mg, 86% yield): R_f = 0.30 (cyclohexane/AcOEt 8:2); $[\alpha]_D$ +1.59 (*c* 0.39, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.68–7.62 (m, 4H), 7.49–7.36 (m, 6H), 4.38–4.20 (m, 3H), 4.15–4.08 (m, 1H), 3.87–3.77 (m, 2H), 3.76 (d, *J* = 4.1 Hz, 1H), 3.59 (dd, *J* = 4.1 Hz, *J* = 1.3 Hz, 1H), 3.50–3.45 (m, 1H), 2.58 (d, *J* = 6.4 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H); ^{19}F NMR (282.5 MHz; $CDCl_3$) δ −113.3 (dd, *J* = 271.5 Hz, *J* = 7.5 Hz, 1F), −120.3 (dd, *J* = 271.5 Hz, *J* = 14.0 Hz, 1F); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ 135.9, 130.3, 128.2, 112.9 (t, *J* = 254.7 Hz), 74.2, 73.8 (t, *J* = 28.8 Hz), 66.8, 64.3, 60.9, 54.5 (2C), 27.0, 14.5; IR (neat) ν_{max} 3436.1, 2930.8, 2857, 1762.2 cm^{-1}; MS (ESI+) *m/z* = 529 ([M+Na]$^+$); Anal. Calcd for $C_{26}H_{32}F_2O_6Si$: C, 61.64; H, 6.37. Found: C, 61.59; H, 6.43.
10. To a solution of **7** (130 mg, 0.26 mmol) in dichloromethane (3 mL) cooled at −30 °C were added $TMSN_3$ (0.8 mL, 6 mmol) and $BF_3{\cdot}Et_2O$ (36 μL, 0.28 mmol). The solution was allowed to warm up to 10 °C over 4 h. After complete conversion of the starting material (TLC monitoring), a saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the mixture was extracted with AcOEt (3 × 5 mL). The combined organic extracts were washed with brine (8 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography over silica gel (cyclohexane/ethyl acetate 80:20, 1% triethylamine) afforded **8** as a colourless oil (73 mg, 0.135 mmol, 52% yield): R_f = 0.20 (cyclohexane/AcOEt 8:2); $[\alpha]_D$ −8.25 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.68–7.63 (m, 4H), 7.50–7.38 (m, 6H), 4.38 (br s, 1H), 4.28 (dd, *J* = 2.7 Hz, *J* = 8.3, 1H), 4.22 (br s, 1H), 4.02–3.95 (m, 2H), 3.88 (s, 1H), 3.82–3.75 (m, 4H), 2.78 (d, *J* = 1.3 Hz, 1H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 9H); ^{19}F NMR (282.5 MHz; $CDCl_3$) δ −114.52 (ddd, *J* = 245.7 Hz, *J* = 7.5 Hz, *J* = 2.1 Hz, 1F), -130.34 (d, *J* = 245.7 Hz, 1F); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ 135.7, 132.2, 130.3, 128.1, 120.9 (t, *J* = 250.1 Hz), 77.6, 72.7 (dd, *J* = 17.7 Hz, *J* = 36.6 Hz), 70.7, 69.1, 66.8, 66.3, 60.1, 26.9, 19.2, 15.2; IR (neat) ν_{max} 3448.2, 2931.6, 2858.5, 2130.9, 1762 cm^{-1}; MS (IC+) *m/z* = 567 ([M+NH$_4$]$^+$); Anal. Calcd for $C_{26}H_{33}F_2N_3O_6Si$: C, 56.82; H, 6.05; N, 7.64. Found: C, 56.86; H, 6.05; N, 7.58.
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