Synthesis of vicinal dideoxy-difluorinated galactoses

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Fluorinated carbohydrates have been employed as probes for fundamental studies of protein-carbohydrate interactions, but also in the development of mechanism-based enzyme inhibitors. There is a continuing demand for novel fluorinated carbohydrate probes. Whereas most examples so far involved monodeoxyfluorinated sugars, multiply deoxyfluorinated sugars have gained much interest. Here we report the synthesis and characterisation of novel vicinal dideoxy-difluorinated α-galactoses with fluorination at the 3,4-positions, and at the 2,3-positions, the latter in both the pyranose and furanose forms. This includes a successful pyranose-into-furanose isomerisation protocol.

Introduction

Fluorine incorporation in carbohydrates has been successfully employed for applications such as epitope mapping,1–3 stabilisation of glycosidic bonds,4 19F imaging5–6 and mechanism-based inhibitor design.7–9 New 19F NMR based developments allow for detailed study of protein-carbohydrate interactions.3,10,11

Interest in multiply deoxyfluorinated carbohydrates commenced with seminal work of Withers,1 in which he reported that 1,2-dideoxy-1,2-difluorinated glucose derivatives 1 and 2 (Figure 1) displayed a larger affinity to glycogen phosphorylase than what could be expected from the values of their respective monofluorinated derivatives. Furthermore, it was shown that the stereochemistry at the fluorinated centres was very important, as the mannose derivatives 3 and 4 displayed much lower affinity. The 1,2-dideoxy derivative (not shown) was an even poorer binder. This work led DiMagno to propose the ’polar hydrophobicity’ concept, in which he synthesised the hexafluorinated pyranose 5,12,13 and established its much faster GLUT-1 mediated erythrocyte membrane transport rate compared to glucose. Later, O’Hagan synthesised the corresponding 2,3,4-trideoxy-2,3,4-trifluoroglucose derivative 6 and showed that its transport rate is slightly slower than that of glucose.14 Other syntheses of 6 have been reported.15,16 Recently, Giguere synthesised a large number of 2,3,4-trideoxy-2,3,4-trifluorinated sugars, including the fluorinated galactose derivative 7. Its β-thionaphthyl glycoside displayed weak (IC50 34-38 μM) antiproliferative activity against a panel of cancer cell lines.17

Our group has synthesised vicinal tetrafluorinated sugar derivatives including 2,3-dideoxy-2,3,3-tetrafluoro-D-threo-hexopyranose 8,18,19 and showed that its furanosyl-UDP derivative 9 was a superior binder to UGM (galactose mutase) than the native Galp-UDP and Galf-UDP substrates.20,21 Examples of vicinally dideoxy-difluorinated sugar derivatives include the 3,4-dideoxy-3,4-difluoro-D-glucopyranose 1023 and its -N-acetyl glucosamine analogue 11,23 as well as 3,4-dideoxy-3,4-difluoro-D-glucopyranose 13.24

In addition, our group has developed methodology for fluorosugar lipophilicity measurement, which demonstrated the significant lipophilicity (logP) increases arising from sugar deoxygenations.25 Apart from the number of deoxygenations

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†Electronic Supplementary Information (ESI) available: Copies of NMR spectra of the novel compounds, crystallographic details for compounds 15a, 16d, and 19. See DOI: 10.1039/x0xx00000x. The NMR FID data is available from the Southampton repository at DOI:XXX0000
and deoxyfluorinations, lipophilicity changes depend on fluorination position and relative stereochemistry, a point which has been further nicely illustrated by Giguere with a large number of the aforementioned 2,3,4-trideoxy-2,3,4-trifluorinated sugar analogues.

In galactose, the vicinal dideoxy-difluoro motif has only been described at the 1- and 2-positions. It is synthesised through reaction of tri-O-acetyl or tri-O-benzyl protected o-galactal with CF$_3$OF, XeF$_2$, or selectFluor, leading to 14b$^{26-30}$ and 14c (as the α-anomer).$^{15}$ Deprotected 1,2-dideoxy-1,2-difuorogalactopyranose 14a has also been described (as α-anomer).$^{27}$ Here we describe the synthesis of the two other vicinal difluorinated galactose derivatives 15 and 16 (Figure 2), both as free hemiacetal and as suitably protected building blocks, eg for activation as glycosyl donor. For 16, the corresponding furanose isomer with required protection at the 5 and 6-positions was also obtained (17b).

Figure 2. Vicinal dideoxy-difluorinated galactoses.

Results and discussion

The synthesis of 3,4-dideoxy-3,4-difluorgalactose 15a was envisaged from the known fluoro-epoxide 18,$^{32}$ which is accessible in two steps from the commercially available “Cerny epoxide” (1,6:3,4-dianhydro-2-O-tosyl-β-D-galactopyranose, not shown).$^{33}$

Fluoride-mediated epoxide opening of 18, which as expected occurred regioselectively at the 3-position following the Fürst-Plattner rule (chair-like transition state),$^{34}$ was slow and required execution in a sealed tube due to the volatility of the starting material. Presumably the electron withdrawing effects of the 4β-fluoro group and the anomeric acetal hampered the fluoride attack.$^{35-39}$ No product resulting from competing fluoride opening at C2 was isolated. The axial disposition of the 3-F group in 19 was evident from the large$^{40}$ $J_{F3-H2}$ value of 24 Hz, and the diaxial disposition of the newly formed C2-C3 fluorohydrin by the smaller $J_{F2-H2}$ value of 10 Hz and the large$^{19}$ $J_{F2-C2}$ Value of 24 Hz. Moreover, 19 proved to be a crystalline solid and X-ray crystallographic analysis confirmed structural assignment (see ESI for full details). Next, opening of the 1,6-anhydro bridge was achieved by BC$_3$I$_5$ to form the corresponding glycosyl chloride, which was directly hydrolysed to give 15a, albeit in low yield. A much higher-yielding procedure involved TMSOTf-catalysed acetolysis$^{41}$ to give 15b, which could then be deprotected to give 15a in 81% over 2 steps. Alternatively, selective anomeric deacetylation was achieved to give 15c in 49% yield. 

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deprotection could be achieved using methanolic ammonia in THF, leading to 16c in 84% yield.

Scheme 2. Synthesis of 2,3-dideoxy-2,3-difluorogalactose 16.

NMR analysis of 16a (D₂O) showed the occurrence of a $^3C_1$ conformation. The vicinal H2-H3 coupling constant of 9.1–9.5 Hz indicates an antiperiplanar position, and the equatorial positions of both fluorine atoms are also evident from the large $^3J_{C4,2}$ (8.0–8.6 Hz) and $^3J_{C4,3}$/$^3J_{C3,3}$ (10–11 and 6.0–6.7 Hz) values. The smaller magnitude of the $^3J_{C2,H2}$ coupling constant for the 2,3-difluorinated glucose derivative 13¹⁴ (D₂O, 8.8 Hz for both anomers) is also consistent with the Haasnoot/Altona $\beta$-effect.

The synthesis of the corresponding protected furanose isomer 17b was investigated starting from the pyranose derivatives. Many excellent pyranose-to-furanose isomerisation protocols have been reported, which unfortunately are not all applicable starting from 16a due to the presence of the vicinal fluorine motif at C2 and C3.

We first envisaged to obtain the furanose 17b following an acetylation/isomerisation precedent with 2-deoxy-2-fluorogalactose 21 from Liu and co-workers (Scheme 3). When applied from 16a however, this led to the almost exclusive formation of the peracetylated pyranose 16b, with only trace amounts of furanose product 17b observed by $^1$H and $^{19}$F NMR analysis.

A different protecting group approach towards the furanose form was inspired by the work of Hricovíniová et al., which showed that treatment of gulose 24 (featuring an axial 4-OH group) with dimethoxymethane in glyme in the presence of CaSO₄ led to the formation of the gulofuranose acetal 25 in 66% yield. Although formation of the corresponding pyranose is not specifically mentioned in the paper, it is described in the experimental procedure that the formation of another product was detected by TLC analysis. In the case of 16a, even though the absence of hydroxyl groups at C2/C3 does not allow formation of a stable [3.3.0] fused bicyclic ring (such as in 25), it was assumed that the 6-OH group of 16a would react first, resulting in the preferential formation of the 5,6-acetonide group under kinetic conditions.

Hence, 16a was treated under the Hricovíniová conditions (A). After 16 h, analysis by TLC indicated the formation of two products, with a very distinct retention factor, which after separation by column chromatography were identified as the pyranose derivative 16c as the major product, and the desired galactofuranose 17c as minor product. Optimisation was achieved by using similar kinetic acetal formation conditions that our group had developed for the selective protection of arabinol; the reaction temperature was increased to allow faster dissolution of 16a, an increased catalyst loading was used to accelerate the reaction, and neutralisation of the acid catalyst after reaction was carried out at the elevated temperature. Indeed, reaction was now complete in a much-reduced reaction time, giving the furanose 17c as the major product in 44% yield next to the pyranose derivative 16d in 32% yield. Interestingly, when treated in the same reaction conditions, it was found that isomerisation of the pyranose acetal 16d can be initiated, to reach a roughly 1:1 mixture of ring isomers of 16d and 17c.

Scheme 3. Synthesis of the galactofuranose 17.
Both products could be assigned by NMR analysis. Thus, in the case of the furanose derivative, a correlation point can be observed in the HMBC spectrum between H-1 and C-4 (for the major anomer), indicative of a 5-membered sugar ring. Conversely, in the case of the pyranose, a correlation point can be observed in the HMBC spectrum between H-1 and C-5 (for the major anomer), confirming the 6-membered ring composition. In addition, 16d proved crystalline, and single crystal X-ray analysis confirmed its structure (Figure 3).

![Figure 3. Crystal structure of the pyranose acetonide 16d (CCDC 1455286).](image)

Next, an acetonide to acetyl protecting group swap, in order to allow a wider range of glycosylation conditions, was attempted. To avoid ring isomerisation to the more stable pyranose form, the anomeric hemiacetal group was first converted to the anomeric hemiacetal group was first converted to the 1,2-epoxide hemiacetal group using p-TSA in a MeOH-pyridine acetylation procedure as described by Zhang et al.26 Unfortunately, subsequent removal of the acetonide protecting group using p-TSA was accompanied by isomerisation to the pyranose 16a instead of the desired furanose 26. Treatment of 17d with aqueous AcOH at 55 °C for 2 h led to recovery of the starting material (not shown). However, the target pyranose 17b was successfully synthesized from 17d using one-pot acetonide-to-diactate procedure as described by Zhang et al.26 This involves reaction with bismuth trflate hydrate as Lewis-acid with 3.8 equiv of Ac₂O in dichloromethane, and was reported to be suitable for similar protecting group switch on hexofuranoses. Interestingly, this reaction was initially tried with anhydrous Bi(O(Tf)₂), but full conversion was only achieved by adding a few drops of water to the reaction mixture. Pleasingly, under these conditions, diol acetylation after acetonide deprediction is faster than furanose-to-pyranose rearrangement, leading to the desired 2,3-dideoxy-2,3-difluorogalactofuranosyl donor 17b in excellent yield.

Scheme 4. Protecting group switch to obtain tri-O-acetyl-2,3-dideoxy-2,3-difluorofuranose 17b.

Conclusions

The synthesis of three novel vicinal dideoxy-difluorinated galactose sugar derivatives is described. 3,4-Dideoxy-3,4-difluoro-β-galactopyranose is synthesised in 6 or 7 steps from levoglucosan in per-acetylated or fully deprotected form. The first fluorination step is a retentive deoxylfluorination reaction as reported by the group of Karban,28 and the second fluorination is a regioselective epoxide opening. The synthesis of 2,3-dideoxy-2,3-difluoro-β-galactopyranose is based on work by Sarda et al.,24 and it was shown that a pyranose-into-furanose isomerisation protocol based on acetonide formation allowed access to the corresponding furanose form in good yields. A key finding was that replacement of the acetonide at OHS/OH6 by a more stable acetate protecting group (for glycosylation purposes) could be achieved without re-isomerisation side reaction back to the pyranose form, using a bismuth trflate catalysed reaction. Both unprotected difluorinated galactopyranose derivatives were shown to exist in the 4C1 conformation, and NMR-based analysis allows to conclude that this conformation is retained in the solution phase.

Experimental section

Chemical reagents were obtained from commercial sources and used without further purification, unless stated otherwise. All air/moisture sensitive reactions were carried out under inert atmosphere (Ar) in flame-dried glassware. Anhydrous bottles of THF (tetrahydrofuran), toluene, CH₂Cl₂ and Et₂N, bought from commercial sources, were used for the reactions. When appropriate, other reagents and solvents were purified by standard techniques. Reactions were monitored by TLC (MERCK Kieselgel 60 F254, aluminium sheet), visualised under UV light (254 nm), and by staining with KMnO₄ (10% aq.) or vanillin. Column chromatography was performed on silica gel (MERCK Geduran 60 Å, particle size 40-63 μm). All reported solvent mixtures are volume measures. Normal phase preparative HPLC was carried out using Biorad Bio-Sil D 90-10 columns (250 × 10 mm at 10 mL·min⁻¹ and 1250 × 22 mm at 20 mL·min⁻¹). Reverse phase
preparative HPLC was carried out using a Waters XSelect C18 column (19 × 250 mm at 17 mL.min⁻¹). Size exclusion chromatography was carried out on a GE healthcare column (XK16 model), packed with Sephadex LH-20 (MeOH used as mobile phase). The column was connected to an AKTA apparatus (1.5 mL.min⁻¹).

¹H, ¹³C, and ¹⁹F spectra were recorded in CDCl₃, acetone-d₆, methanol-d₄ or D₂O using a BRUKER AV400 (400, 101, 376 and 162 MHz respectively) and AV500 (500, 125, 470 and 202 MHz respectively) spectrometers. ¹H and ¹³C chemical shifts (δ) are quoted in ppm relative to residual solvent peaks as appropriate.

¹³C NMR (500 MHz, acetone-d₆): (α:β:γ:δ) 143.9, 117.7, 144.8, 133.7 ppm; ¹⁹F NMR (471 MHz, acetone-d₆): δ -203.9 (1F, ddd, J = 4.0, 7.5, 1.0 Hz, F-3); -208.6 (1F, d, J = 50.0 Hz, F-4) ppm; HRMS (ESI-) for C₃H₅F₂O₂ calcld. 165.0363, found 165.0369.

3,4-Dideoxy-3,4-difluoro-o-galactopyranos-15a (from 19)
To a solution of 19 (100 mg, 0.602 mmol) in CH₂Cl₂ (6.9 mL) at 0 °C was added BCls (1 M in CH₂Cl₂, 2.39 mL, 2.39 mmol). The reaction was then allowed to reach rt. After 3 h sat. aq. NaHCO₃ (20 mL) was added at 0 °C. After 30 min the reaction was concentrated. The crude residue was then purified by column chromatography (silica, petroleum ether/acetone, 1:1) to give 15a as a white solid (40 mg, 0.22 mol, 36%). R₉ 0.20 (petroleum ether/acetone, 1:1, R₉ 0.23 (1:1 acetone:hexane); mp 170-171 °C (CHCl₃). [α]D²³ +67 (c 1, MeOH); IR 3407 (br), 3285 (br), 2953 (w), 1140 (s), 1079 (s), 1104 (s), 799 (s), 695 (s) cm⁻¹; ¹H NMR (500 MHz, acetone-d₆): (α:β:γ:δ) 5.96 (1H, dd, J = 6.9, 1.1 Hz, OH-1’); 5.80 (1H, dd, J = 4.1, 0.9 Hz, OH-1x); 5.23 (1H, q, J = 4.2 Hz, H-1cα); 5.06 (1H, dd, J = 52.0, 8.2 Hz, H-4x); 4.99 (1H, ddd, J = 51.6, 6.9, 3.0 Hz, H-4β); 4.76 (1H, ddd, J = 48.1, 27.7, 9.8, 2.9 Hz, H-3α); 4.65 (1H, d, J = 14.4, H-2β); 4.56 (1H, abr. br, J = 7.7, 6.9 Hz, H-1β); 4.58 (2H, dddd, J = 46.9, 27.9, 9.6, 2.9 Hz, H-3β); 4.09 (1H, abr. br, J = 29.6, 7.2 Hz, H-5α); 4.05 – 4.02 (2H, m, OH-2x+OH-2α+2x-H6α+2x-H6β) ppm; ¹³C NMR (126 MHz, acetone-d₆): (α:β:γ:δ) 97.4 (d, J = 11.4 Hz, C-1’); 93.7 (d, J = 10.5 Hz, C-1x); 92.3 (d, J = 187.8, 17.6 Hz, C-3); 90.2 (d, J = 186.6, 17.6 Hz, C-3x); 89.7 (dd, J = 189.7, 16.2 Hz, C-4x); 81.7 (d, J = 181.3, 16.2 Hz, C-4β); 72.9 (dd, J = 17.9J, 6.0 Hz, C-5β); 71.7 (d, J = 16.7 Hz, C-2β); 69.4 (dd, J = 18.1, 5.3 Hz, C-5α); 68.2 (d, J = 17.6, 2.4 Hz, C-2x); 60.0 – 59.8 (m, C-6x+C6α) ppm; ¹⁹F NMR (471 MHz, acetone-d₆): (α:β:γ:δ) 23.9 (1F, d, J = 11.4 Hz, F-1β); 23.8 (1F, d, J = 11.4 Hz, F-1x); 23.6 (1F, d, J = 11.4 Hz, F-1); 23.5 (1F, d, J = 11.4 Hz, F-1a) ppm; HRMS (ESI+) for C₃H₅F₂O₂ calcld. 207.0444, found 207.0440.

1,2,6-Tri-O-acetyl-3,4-dideoxy-3,4-difluoro-o-galactopyranos-15b (from 19)
To a solution of 19 (300 mg, 1.81 mmol) in Ac₂O (2.7 mL) at 0 °C was added TMSOTf (0.07 mL, 0.36 mmol). After 30 min the reaction mixture was warmed up to rt. After an additional 2 h the mixture was diluted with CH₂Cl₂ (5 mL) and then slowly neutralised with a solution of sat. aq. NaHCO₃. The aqueous phase was then separated and extracted with CH₂Cl₂ (3×20 mL), the combined organic phases were washed with NaHCO₃ (3×20 mL), H₂O (20 mL), dried over MgSO₄, filtered, concentrated in vacuo and purified by column chromatography (silica, hexane/acetonitrile, 7:3) to give 15b as a mixture of anomers (α:β:γ:δ, as a pale yellow oil (565 mg, 1.81 mmol, quant.). R₉ 0.29 (hexane/acetonitrile, 7:3); IR 1750 (s), 1372 (m), 1229 (s), 1214 (t), 1077 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 4.11 (1H, t, J = 4.3 Hz, H-1α), 5.65 (1H, d, J = 8.0 Hz, H-1β), 5.46 (1H, abr. tdd, J = 10.5, 3.8, 0.9 Hz, H-2α); 5.06 (1H, dd, J = 50.5, 7.6, 2.6 Hz, H-4x); 4.99 (1H, ddd, J = 47.8, 25.9, 10.3, 2.8 Hz, H-3α); 4.62 (1H, dddd, J = 27.6, 20.0, 9.7, 2.8 Hz, H-3β); 3.42 (1H, abr. ddt, J = 11.4, 6.8, 1.1, H-6xα); 4.27 (1H, dd, J = 11.4, 6.4, H-6xβ) ppm; ¹³C NMR (126 MHz, CDCl₃): δ 237.7, 172.5, 118.1, 61.7, 59.3, 43.8, 40.9, 38.9, 36.6, 23.8, 21.7 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ -203.9 (1F, d, J = 4.5 Hz, F-3); -208.6 (1F, s, J = 44.4 Hz, F-4) ppm; HRMS (ESI-) for C₅H₆F₂O₂ calcld. 165.0363, found 165.0369.
To a solution of 15b (200 mg, 0.64 mmol) in MeOH was added MeONa (25% wt, 0.03 mL, 0.15 mmol). After 3 h the reaction was neutralised to pH 7 using Amberlite® IR120 hydrogen form resin, filtered, and concentrated. The crude residue was purified by column chromatography (50% acetone in hexane) to give first the partially deprotected 6-O-acetyl product (14 mg, 0.06 mmol, 10%) and then the fully deprotected product 15a (96 mg, 0.52 mmol, 81%) as a white solid.
To a solution of 16b (1.06 g, 3.42 mmol) in a mixture of THF (30 mL) and H2O (2.5 mL) at rt was added LiOH (370 mg, 15.5 mmol). The reaction was stirred for 1 h, during which an emulsion was observed. The solvent was concentrated in vacuo and purified by column chromatography (silica, CH2Cl2/MeOH, 9:1) to afford 16a as a colourless oil (3.54 g, 29.3% yield, 98%).

2,3-Dideoxy-2,3-difluorogalactose 16a (from 16b)

The reaction was stirred for 16 h, during which an emulsion was observed. The solvent was concentrated in vacuo and purified by column chromatography (silica, CH2Cl2/MeOH, 9:1) to afford 16a as a colourless oil (3.54 g, 29.3% yield, 98%).

To a solution of 16a (1.06 g, 3.42 mmol) in THF at 0 °C was added dimethoxypropane (2.14 mL, 17.27 mmol) and TSA (177 mg, 1.04 mmol) in this order. The mixture was added, before concentrating in vacuo to afford 2,3-Dideoxy-2,3-difluorogalactose 16a as a colourless oil (3.38 g, 18.4 mmol, 98%).
Data for 2,3,4-lacto-galactofuranosan acetal

\textit{17c: [a]}. This compound could not be obtained in suitable purity. \textit{Rf} 0.45 (hexane/acetonitrile, 1:1); IR (neat) 3420 (br), 2991 (br), 2349 (m), 1221 (m), 1054 (s) cm\(^{-1};\) \textit{1H} NMR (500 MHz, CDCl\(_3\)) (ratio major/minor 2.5) \(\delta 5.58\) (1H, dd, J 10.6, 3.1 Hz, H-1 major), 5.39 (1H, dt, J 10.0, 4.3 Hz, H-1 minor), 5.25 (1H, dt, J 5.46, 16.3, 4.4 Hz, H-3 minor), 5.09 (1H, dd, J 49.3, 14.9, 1.1, 0.5 Hz, H-2 major), 5.08 (1H, dd, J 51.6, 20.6, 4.3 Hz, H-2 minor), 4.98 (1H, J 51.6, 20.3, 4.6, 1.1 Hz, H-3 major), 4.40 (1H, dd, J 22.6, 5.7, 5.7 Hz, H-4 major), 4.33 (1H, dt, J 6.7, 5.6 Hz, H-5 major), 4.31 (1H, J 6.6, 3.7 Hz, H-5 minor), 4.14 (1H, dd, J 24.0, 4.2, 3.8 Hz, H-4 minor), 4.11 (1H, dd, J 8.7, 6.7 Hz, H-6 major), 4.09 (1H, dd, J 8.4, 6.5 Hz, H-6 minor), 3.95 – 3.86 (1H, m, H-6’ minor), 3.89 (1H, dd, J 8.7, 5.8 Hz, H-6’ major), 3.82 (1H, dd, J 10.0 Hz, OH major), 3.03 (1H, d, J 3.5 Hz, OH minor), 1.49 (3H, d, J 6.0 Hz C(CH\(_3\))\(_3\) minor), 1.47 (3H, d, J 0.6 Hz C(CH\(_3\))\(_2\) minor), 1.41 (3H, d, J 0.6 Hz C(CH\(_3\))\(_2\) minor), 1.39 (3H, d, J 0.6 Hz C(CH\(_3\))\(_2\) minor) ppm; \textit{13C} NMR (100 MHz, CDCl\(_3\)) (ratio major/minor 2.5) \(\delta 110.4\) (C(CH\(_3\))\(_3\) minor), 110.3 (C(CH\(_3\))\(_3\) major), 100.0 (dd, J 39.5, 25.4 Hz, C-2 minor), 97.9 (dd, J 182.1, 27.1 Hz, C-2 major), 95.3 (dd, J 19.1 Hz, J 8.1 Hz, C-1 minor), 94.91 (dd, J 185.6, 25.7 Hz, C-3 minor), 94.89 (dd, J 185.6, 30.1 Hz, C-3 major), 93.6 (dd, J 195.1, 24.9 Hz, C-2 minor), 82.8 (dd, J 27.1, 2.9 Hz, C-4 major), 79.0 (dd, J 26.4, 7.3 Hz, C-4 minor), 75.2 (dd, J 5.9, 5.9 Hz, C-5 minor), 74.7 (dd, J 5.1 Hz, C-5 major), 65.2 (C-6 minor and major), 26.3 (C(CH\(_3\))\(_2\) major), 26.1 (C(CH\(_3\))\(_2\) minor), 25.3 (C(CH\(_3\))\(_2\) minor), 25.0 (C(CH\(_3\))\(_2\) major) ppm; \textit{19F} NMR (376 MHz, CDCl\(_3\)) (ratio major/minor 2.5) \(\delta -193.9\) (1F, ddd, J 51.4, 21.9, 14.3, 7.9 Hz, F-3 major), -195.6 (1F, ddt, J 49.0, 19.5, 8.1 Hz, F-2 major), 196.0 – 196.9 (1F, m, F3 minor), -208.4 (1F, dd, J 52.0, 16.0, 7.2 Hz, F-2 minor) ppm; \textit{19F} NMR (476 MHz, CDCl\(_3\)) (ratio major/minor 2.5) \(\delta -193.9\) (1F, d, J 7.9 Hz, F-3 major), -195.6 (1F, d, J 8.1 Hz F-2 major) -196.1 (1F, d, J 7.2 Hz F-3 minor), -208.4 (1F, d, J 7.2 Hz F-2 minor) ppm; MS (ESI\(^+\)) (m/z) 247 [M+Na]\(^+\); HRMS (ESI\(^+\)) for C\(_{12}\)H\(_{16}\)F\(_{2}\)NaO\(_3\) [M+Na]\(^+\) calcld. 247.0757, found 247.0758.

5,6-Di-O-isopropylidene-2,3-dideoxy-2,3-difluoro-o-
galactofuranosan 17c (from 16d)

Galactopyranosac acetel \textit{16d} (1.86 g, 8.30 mmol) was subjected to the same conditions as above to give, after column chromatography, the furanosac acetel \textit{17c} as a pale yellow oil (905, 4.04 mmol, 49%, combined yield of 60% over 2 steps), alongside with the recovered starting material \textit{16c} (837 mg, 3.73 mmol, 45%, combined yield of 20% over 2 steps).

1-O-Acetyl-5,6-di-O-isopropylidene-2,3-dideoxy-2,3-difluoro-o-
galactofuranosan 17d

To a solution of \textit{17c} (469 mg, 2.09 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at 0 °C was successively added DMAP (38 mg, 0.31 mmol, 15 mol%) and Ac\(_2\)O (275 µL, 2.93 mmol). The mixture was stirred at rt for 3 h, before quenching with a sat. aq. solution of NaHCO\(_3\) (10 mL). Phases were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (10 mL), dried over MgSO\(_4\), and concentrated. Filtration over a pad of silica gel (petroleum ether/acetonitrile, 8:2) gave the protected intermediate \textit{17d} as a colourless oil (516 mg, 1.93 mmol, 92%, ratio minor/major 1:10), which was directly submitted to the next reaction. \(R_f\) 0.40 (hexane/acetonitrile, 7:3); \textit{1H} NMR (selected peaks, major anomer only) (400 MHz, CDCl\(_3\)) (ESI\(^+\)) for \textit{m/z} 247.0757, found 247.0758.

1,5,6-Tri-O-acetyl-2,3-dideoxy-2,3-difluoro-o-galactofuranosan 17b

Compound \textit{17d} (480 mg, 1.80 mmol) was dissolved in CH\(_2\)Cl\(_2\) (8 mL), after which Ac\(_2\)O (641 µL, 6.83 mmol), Bi(Otf)_3 (45 mg, 0.068 mmol, 3.8 mol%) and H\(_2\)O (40 µL, 2.29 mmol) were added in this order. The reaction was stirred at rt for 2 h. The reaction was quenched with a sat. aq. solution of NaHCO\(_3\) (10 mL). The phases were separated and the organic layer was washed with a sat. aq. solution of NaHCO\(_3\) (1×10 mL). The combined aqueous layers were then extracted with DCM (110 mL). The combined organic layers were combined, dried over MgSO\(_4\), and concentrated in vacuo and then purified by column chromatography (silica, petroleum ether/acetonitrile, 8:2) afforded

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**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**