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Synthesis of vicinal dideoxy-difluorinated galactoses

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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 D-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] ^{18}F imaging[5, 6] and mechanism-based inhibitor design.[7-9] New ^{19}F NMR based developments allow for detailed study of protein-carbohydrate interactions.[3, 10, 11]

Interesπt 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 (IC_{50} 34-38 μM) antiproliferative activity against a panel of cancer cell lines.[17]

Our group has synthesised vicinal tetrafluorinated sugar derivativatives including 2,3-dideoxy-2,2,3,3-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 Gal*p*-UDP and Gal*f*-UDP substrates.[20,21] Examples of vicinally dideoxy-difluorinated sugar derivatives include the 3,4-dideoxy-3,4-difluoro-D-glucopyranose **10**[22] and its -*N*-acetyl glucosamine analogue **11**,[23] as well as the *N*-acetyl-galactosamine **12**[23] and 2,3-dideoxy-2,3-difluoro-D-glucopyranose **13**.[24]

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

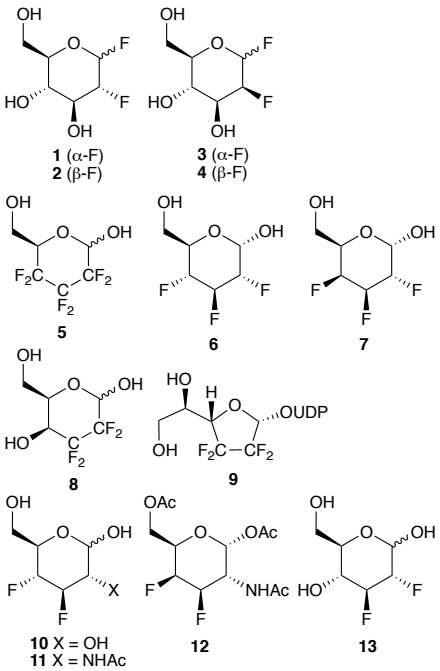

Figure 1.

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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:XXXXX

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.[15]

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 D-galactal with CF_3OF, XeF_2, or selectFluor, leading to **14b**[26-30] and **14c** (as the α-anomer).[31] Deprotected 1,2-dideoxy-1,2-difluorogalactopyranose **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**).

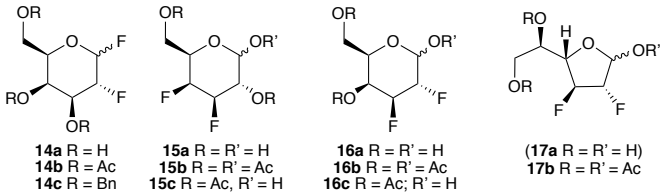
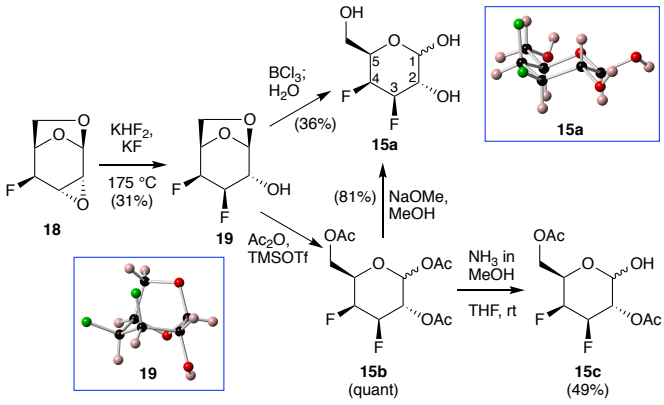


Figure 2. Vicinal dideoxy-difluorinated galactoses.

Results and discussion

The synthesis of 3,4-dideoxy-3,4-difluorogalactose **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]

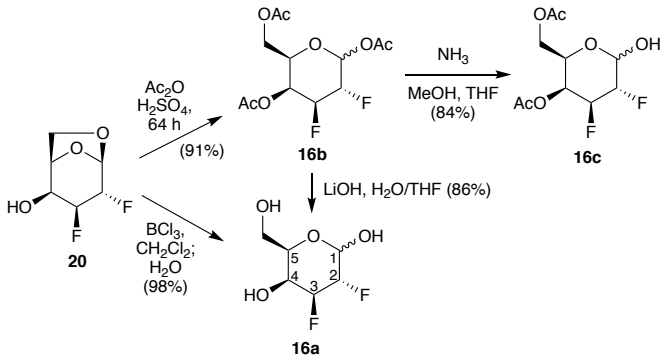
Fluoride-mediated epoxide opening of **18**, which as expected occurred regioselectively at the 3-position following the Fürst-Plattner rule (chair-like transition state),[34] was slow and required execution in a sealed tube due to the volatility of the starting material. Presumably the electron withdrawing 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] $^3J_{F3\text{-}H4}$ value of 24 Hz, and the diaxial disposition of the newly formed C2-C3 fluorohydrin by the smaller $^3J_{F3\text{-}H2}$ value of 10 Hz and the large[39] $^2J_{F3\text{-}C2}$ 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 BCl_3 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. Pleasingly, a crystal structure of the fully deprotected **15a** could be obtained, nicely showing a $^4C_1$ chair conformation. NMR analysis of **15a** in solution (acetone-d_6) shows that the $^4C_1$ chair conformation is retained: H2 and H3 display a 9.6 Hz coupling constant, indicating a ~180° dihedral angle and a 2.9 Hz value is observed for coupling between H3 and H4, corresponding to a ~60° dihedral angle. The coupling constants of 4F with H3 and H5, both measuring about 28 Hz, as well as these of F3 with H2 and H4, respectively 16 and 7 Hz, show their respective axial and equatorial dispositions. The vicinal C-F coupling constants are also diagnostic: $^3J_{C2\text{-}F4}$ is a small 2.4 Hz, while $^3J_{C1\text{-}F3}$ and $^3J_{C5\text{-}F3}$ are much larger (5.3 and 11.4 Hz), which is consistent with an axial F4 and equatorial F3. The corresponding $^3J_{C2\text{-}F4}$ value for the glucose derivative **10** is a much larger 7.7 Hz (equatorial F4).[22] Interestingly, the larger $^3J_{H2\text{-}H3}$ value of the difluorogalactose **15a** (9.6 Hz for the β-anomer, acetone-d_6) compared to that of the difluoroglucose **10a** (8.8 Hz for the β-anomer, acetone-d_6)[22] is consistent with the "β-effect" as proposed by Altona and Haasnoot,[42] in which the $^3J_{H\text{-}H}$ value between two antiperiplanar hydrogens is larger when one of these hydrogens itself is antiperiplanar with an electron withdrawing group (as is the case with F4 in **15a**). Crich *et al.* have shown that this $^3J_{H2\text{-}H3}$ coupling constant difference is consistent for a large set of glucose/galacto configured derivatives.[43]



Scheme 1. Synthesis of 3,4-dideoxy-3,4-difluorogalactose (CCDC **15a** 1879612; CCDC **19** 1879613.

The 2,3-dideoxy-2,3-difluorinated galactopyranose **16a** and its peracetylated derivative **16b** could be accessed *via* two different ways from the difluorinated 1,6-anhydro galactosan derivative **20** (Scheme 2), which was synthesised in 11 steps from levoglucosan according to Sarda *et al.*[15, 44] At first, it was found that the 1,6 anhydro bridge on **20** could be cleaved under acetolysis conditions to give the peracetylated 2,3-difluorogalactopyranse **16b** in excellent yield, although a long reaction time is required (64 h) due to the electron withdrawing effect of the fluorine atoms. Subsequent acetate hydrolysis using LiOH proceeded cleanly to afford the free sugar **16a**. Alternatively, the reducing sugar **16a** could be directly obtained from **20** using BCl_3-mediated opening, followed by hydrolysis of the anomeric chloride, which, in contrast to the anhydro bridge-opening of **19** (cf Scheme 1), now proceeded in excellent yield in a much shorter reaction time (2 h). Finally, selective anomeric

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**.

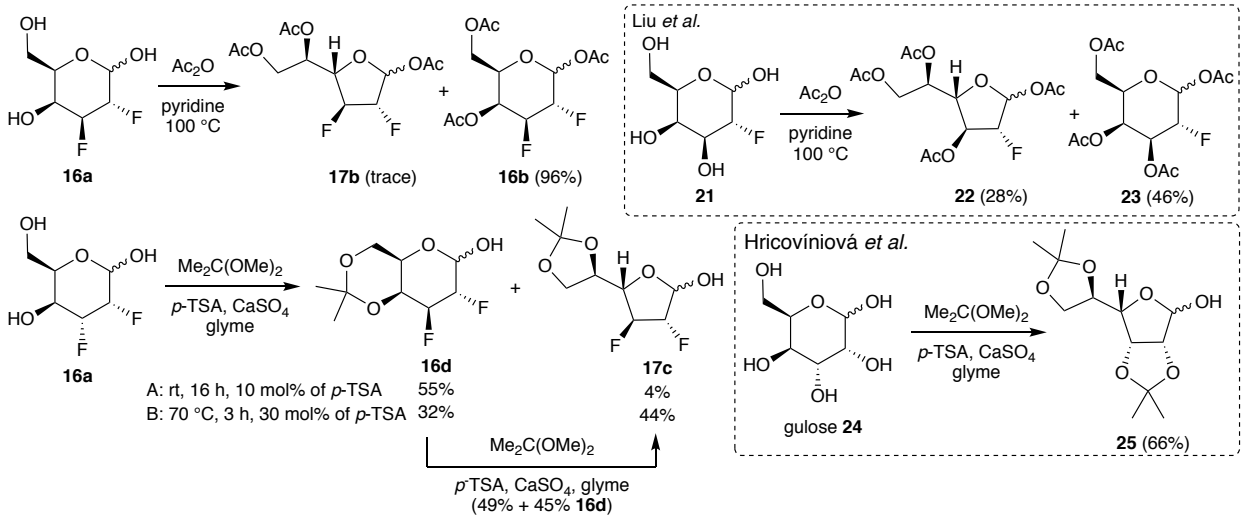
NMR analysis of **16a** (D_2O) showed the occurrence of a $^4C_1$ conformation. The vicinal H2-H3 coupling constant of 9.1–9.5 Hz indicates an antiperiplanar position, and the equatorial positions of both fluorine atoms are also evident from the large $^3J_{C4\text{-}F2}$ (8.0–8.6 Hz) and $^3J_{C1\text{-}F3}/^3J_{C5\text{-}F3}$ (10–11 and 6.0–6.7 Hz) values. The smaller magnitude of the $^3J_{H2\text{-}H3}$ coupling constant for the 2,3-difluorinated glucose derivative **13**[24] (D_2O, 8.8 Hz for both anomers) is also consistent with the Haasnoot/Altona β-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,[45-50] which unfortunately are not all applicable starting from **16a** due to the presence of the vicinal fluorine motif at C2 and C3.

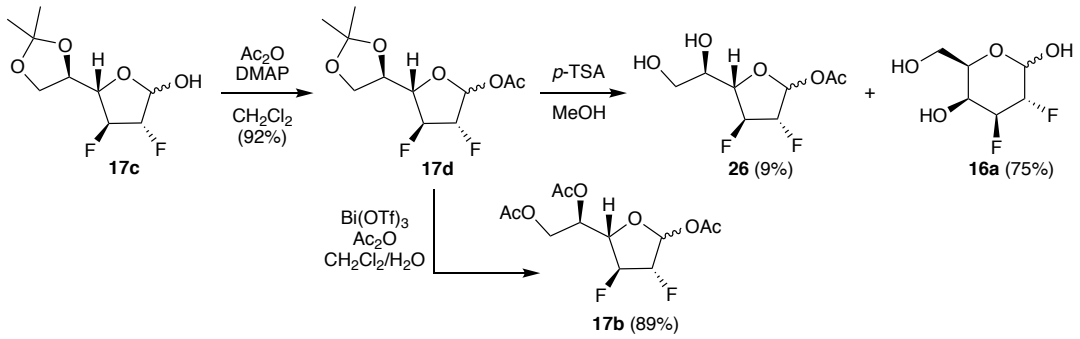
We first envisaged to obtain the furanose **17b** following an acetylation/isomerisation precedent with 2-deoxy-2-fluorogalactose **21** from Liu and co-workers (Scheme 3).[51] When applied from **16a** however, this led to the almost exclusive formation of the peracetylated pyranose **16b**, with only trace amounts of furanose product **17b** observed by ^1H 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 dimethoxypropane in glyme in the presence of $CaSO_4$ led to the formation of the gulofuranose acetal **25** in 66% yield.[52] 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 arabitol:[53] 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**.



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

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).

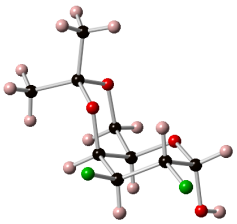


Figure 3. Crystal structure of the pyranose acetonide **16d** (CCDC 1455286).

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 corresponding acetate **17d** (Scheme 4). 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 furanose **17b** was successfully synthesized from **17d** using one-pot acetonide-to-diacetate procedure as described by Zhang *et al*.[54] This involves reaction with bismuth triflate hydrate as Lewis-acid with 3.8 equiv of Ac_2O in dichloromethane, and was reported to be suitable for similar protecting group switch on hexofuranoses. Interestingly, this reaction was initially tried with anhydrous $Bi(OTf)_3$, 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 deprotection is faster than furanose-to-pyranose rearrangement, leading to the desired 2,3-dideoxy-2,3-difluorogalactofuranosyl donor **17b** in excellent yield.

Conclusions

The synthesis of three novel vicinal dideoxy-difluorinated galactose sugar derivatives is described. 3,4-Dideoxy-3,4-difluoro-D-galactopyranose is synthesised in 6 or 7 steps from levoglucosan in per-acetylated or fully deprotected form. The first fluorination step is a retentive deoxyfluorination reaction as reported by the group of Karban,[32] and the second fluorination is a regioselective epoxide opening. The synthesis of 2,3-dideoxy-2,3-difluoro-D-galactopyranose is based on work by Sarda,[44] 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 OH5/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 triflate catalysed reaction. Both unprotected difluorinated galactopyranose derivatives were shown to exist in the $^4C_1$ 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, CH_2Cl_2 and Et_3N, 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 $KMnO_4$ (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}).

^{1}H, ^{13}C, and ^{19}F spectra were recorded in $CDCl_3$, acetone-d_6, methanol-d_4 or D_2O using a BRUKER AV400 (400, 101, 376 and 162 MHz respectively) and AV500 (500, 125, 470 and 202 MHz respectively) spectrometers. ^{1}H and ^{13}C chemical shifts (δ) are quoted in ppm relative to residual solvent peaks as appropriate. ^{19}F spectra were externally referenced to $CFCl_3$. The coupling constants (*J*) were recorded in Hertz (Hz). The coupling constants have not been averaged. Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were recorded as neat films on a Thermo Scientific Nicolet iS5 spectrometer using neat samples (solid or liquid). Electrospray mass spectra were obtained from a Waters 2700 sample manager ESI, and recorded in m/z (abundance). HRMS was obtained from a Bruker APEX III FT-ICR-MS. Samples were run in HPLC methanol or MeCN. Optical rotations were recorded on an Optical Activity POLAAR 2001 at 589 nm.

1,6-Anhydro-3,4-dideoxy-3,4-difluoro-β-D-galactopyranose 19

To a solution of 1,6:2,3-dianhydro-4-deoxy-4-fluoro-β-D-gulopyranose **18**[32] (447 mg, 3.1 mmol) in ethylene glycol (7 mL) in a sealed tube and under argon, was added KF (1.09 g, 18.8 mmol) and KHF_2 (1.40 g, 17.9 mmol). The mixture was stirred at 175 °C. After 15 h the solution was cooled to rt and a solution of sat. aq. $NaHCO_3$ (7 mL) was added dropwise, followed by extraction with Et_2O (5×70 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* and then purified by column chromatography (silica, petroleum ether/Et_2O, 1:1) to give **19** (155 mg, 0.9 mmol, 31%) as a white fluffy solid, and recovered starting material **18** (20 mg, 0.14 mmol, 4%). **R_f** 0.40 (hexane/acetone, 1:1); **mp** 134 ºC; **$[\alpha]_D^{22}$** -19.6 (*c* 1, $CHCl_3$); **IR** 3442 (br), 2958 (br), 2922 (br), 1479 (m), 1065 (s), 1038 (s) 1026 (s), 966 (s), 697 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.42 (1H, dt, *J* 5.3, 1.5 Hz, H-1), 4.88 (1H, m, *J* 49.9 Hz was observed, H-3), 4.85 (1H, ddtdd, *J* 44.3, 24.6, 4.2, 1.3, 0.5 Hz, H-4), 4.65 (1H, br. d, *J* 4.6 Hz, H-5), 4.37 (1H, br dd, *J* 7.8, 0.8 Hz, H-6endo), 4.06 – 3.97 (1H, m, H-2), 3.79 (1H, ddtt *J* 7.8, 5.0, 1.3, 0.6 Hz, H-6exo), 1.96 (1H, d, *J* 8.9 Hz, OH) ppm; **^{1}H{^{19}F} NMR** (500 MHz, $CDCl_3$): δ 5.42 (1H, t, *J* 1.6 Hz, H-1), 4.90 – 4.87 (1H, m, H-3), 4.84 (1H, br tdd, *J* 4.2, 1.3, 0.5 Hz, H-4), 4.65 (1H, tdd, J 5.0, 0.9, 0.4 Hz, H-5), 4.37 (1H, dt, *J* 7.8, 0.6 Hz, H-6endo), 4.02 (1H, dt, *J* 8.9, 1.9 Hz, H-2), 3.79 (1H, dddd, *J* 7.8, 5.1, 1.2, 0.6 Hz, H-6exo), 1.96 (1H, d, *J* 8.9 Hz, OH) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ 100.7 (C-1), 87.5 (dd, *J* 188.1, 14.3 Hz, C-4), 82.7 (dd, *J* 194.2, 16.1 Hz, C-3), 72.0 (dd, *J* 27.4, 1.0 Hz, C-5), 70.7 (dd, *J* 23.8, 2.9 Hz, C-2), 64.1 (dd, *J* 4.3, 1.7 Hz, C-6) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$): δ -203.9 (1F, ddddt, *J* 49.2, 24.9, 11.3, 4.8, 1.1 Hz, F-3), -208.5 – -208.7 (1F, m, *J* 44.4 Hz can be observed, F-4) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$): δ -203.9 (1F, d, *J* 5.0 Hz, F-3), -208.6 (1F, d, *J* 5.0 Hz, F-4) ppm; **HRMS** (ESI-) for $C_6H_7F_2O_3$ calcd. 165.0363, found 165.0369.

3,4-Dideoxy-3,4-difluoro-D-galactopyranose 15a (from 19)

To a solution of **19** (100 mg, 0.602 mmol) in CH_2Cl_2 (6.9 mL) at 0 °C was added BCl_3 (1 M in CH_2Cl_2, 2.39 mL, 2.39 mmol). The reaction was then allowed to reach rt. After 3 h sat. aq. $NaHCO_3$ (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%). **R_f** 0.20 (petroleum ether/acetone, 1:1), **R_f** 0.23 (1:1 acetone:hexane); **mp** 170-171 °C ($CHCl_3$); **$[\alpha]_D^{23}$** +67 (*c* 1, MeOH); **IR** 3407 (br), 3285 (br), 2953 (w), 1140 (s), 1079 (s), 1106 (s), 1004 (s), 799 (s), 695 (s) cm^{-1}; **^{1}H NMR** (500 MHz, acetone-d_6): (ratio α:β 2:1) δ 5.96 (1H, dd, *J* 6.9, 1.1 Hz, OH-1β), 5.80 (1H, dd, *J* 4.1, 0.9 Hz, OH-1α), 5.23 (1H , app. q, *J* 4.2 Hz, H-1α), 5.06 (1H, ddd, *J* 52.0, 8.0, 2.8 Hz, H-4α), 4.99 (1H, ddd, *J* 51.6, 6.9, 3.0 Hz, H-4β), 4.76 (1H, dddd, *J* 48.1, 27.7, 9.8, 2.9 Hz, H-3α), 4.65 (1H, d, *J* 4.4 Hz, OH-2β), 4.56 (1H, app. br t, *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, app. br dt, *J* 29.6, 7.2 Hz, H-5α), 4.05 – 4.02 (2H, m, OH-2α+OH-6β), 3.96 (1H, dd, *J* 6.6, 5.0 Hz, OH-6α), 3.94 – 3.90 (1H, m, H-2α), 3.75 – 3.60 (5H, m, H-2α+2×H-6α +2×H-6β) ppm; **^{13}C NMR** (126 MHz, acetone-d_6): (ratio α:β 2:1) δ 97.4 (d, *J* 11.4 Hz, C-1β), 93.7 (d, *J* 10.5 Hz, C-1α), 92.3 (dd, *J* 187.8, 17.6 Hz, C-3β), 90.2 (dd, *J* 186.6, 17.6 Hz, C-3α), 87.9 (dd, *J* 189.7, 16.2 Hz, C-4α), 87.1 (d, *J* 181.3, 16.2 Hz, C-4β), 72.9 (dd, *J* 17.9,*J* 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 (dd, *J* 17.6, 2.4 Hz, C-2α), 60.0 – 59.8 (m, C-6α+C6β) ppm; **^{19}F NMR** (471 MHz, acetone-d_6): (ratio α:β 2:1) δ -201.3 (1F, app dtd, *J* 47.0, 16.3, 6.8 Hz, F-3β), -206.1 – -206.3 (1F, m, F-3α), -218.3 – -219.9 (1F, m, F-4β), -222.2 (1F, dtdd, *J* 51.9, 28.3, 15.5, 0.9 Hz, F-4α) ppm; **^{19}F{^{1}H} NMR** (471 MHz, acetone-d_6): (ratio α:β 2:1) δ -201.3 (1F, d, *J* 16.3 Hz, F-3β), -206.2 (1F, d, *J* 15.5 Hz, F-3α), -219.0 (1F, d, *J* 16.3 Hz, F-4β), -222.2 (1F, d, *J* 15.5 Hz, F-4α) ppm; **HRMS (ESI+)** for $C_6H_{10}F_2NaO_4$ calcd. 207.0444, found 207.0440.

1,2,6-Tri-*O*-acetyl-3,4-dideoxy-3,4-difluoro-D-galactopyranose 15b.

To a solution of **19** (300 mg, 1.81 mmol) in Ac_2O (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 CH_2Cl_2 (5 mL) and then slowly neutralised with a solution of sat. aq. $NaHCO_3$. The aqueous phase was then separated and extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were washed with $NaHCO_3$ (3×20 mL), H_2O (20 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, hexane/acetone, 7:3) to give **15b** as a mixture of anomers (ratio α:β 2:15), as a pale yellow oil (560 mg, 1.81 mmol, quant.). **R_f** 0.29 (hexane/acetone, 7:3); **IR** 1750 (s), 1372 (m), 1229 (s), 1214 (s), 1077 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.41 (1H, t, *J* 4.3 Hz, H-1α), 5.65 (1H, d, *J* 8.0 Hz, H-1β), 5.46 (1H, app. tdd, *J* 10.5, 3.8, 0.9 Hz, H-2α), 5.06 (1H, ddd, *J* 50.5, 7.6, 2.6 Hz, H-4α), 4.99 (1H, ddd, *J* 50.5, 7.6, 2.7 Hz, H-4β), 4.88 (1H, dddd, *J* 47.8, 25.9, 10.3, 2.8 Hz, H-3α), 4.62 (1H, dddd, *J* 47.0, 26.0, 9.7, 2.8 Hz, H-3β), 4.32 (1H, app. ddt, *J* 11.4, 6.8, 1.1, H-6α), 4.27 (1H, dd, *J* 11.4, 6.4, H-6'α), 4.17 (1H, br, dt, *J* 27.7, 6.6 Hz, H-5α), 3.89 (1H,

dtd, *J* 25.3, 6.5, 1.3 Hz, H-5β), 2.15 (3H, s, COC$\underline{H}_3$-α), 2.14 (3H, s, COC$\underline{H}_3$-β), 2.12 (3H, s, COC$\underline{H}_3$-β), 2.10 (3H, s, COC$\underline{H}_3$-β), 2.10 (3H, s, COC$\underline{H}_3$-α), 2.09 (3H, s, COC$\underline{H}_3$-α) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.6 (s, $\underline{C}OCH_3$-α), 170.5 (s, $\underline{C}OCH_3$-β), 169.7 (s, $\underline{C}OCH_3$-α), 169.20 (s, $\underline{C}OCH_3$-β), 169.19 (s, $\underline{C}OCH_3$-β), 168.7 (s, $\underline{C}OCH_3$-α), 91.4 (s, d, *J* 11.2, C-1β), 89.9 (d, *J* 9.1 Hz, C-1α), 89.0 (dd, *J* 195.7, 18.1 Hz, C-3β), 86.5 (dd, *J* 187.4, 16.7 Hz, C-4α), 85.8 (dd, *J* 193.2, 18.0 Hz, C-3α), 85.7 (dd, *J* 187.9, 16.2 Hz, C-4β), 71.2 (dd, *J* 18.2, 6.1 Hz, C-5β), 69.2 (dd, *J* 18.4, 5.5 Hz, C-5α), 68.5 (d, *J* 19.3 Hz, C-2β), 67.2 (dd, *J* 18.8, 2.4 Hz, C-2α), 61.5 (dd, *J* 6.2, 2.2 Hz, C-6α), 61.3 (dd, *J* 5.7, 2.6 Hz, C-6β), 20.9 (s, CO$\underline{C}H_3$-α), 20.84 (s, CO$\underline{C}H_3$-α), 20.82 (s, CO$\underline{C}H_3$-β), 20.77 (s, CO$\underline{C}H_3$-β), 20.6 (s, CO$\underline{C}H_3$-α) ppm. One carbon resonance for the minor β-anomer could not be located; **^{19}F NMR** (471 MHz, $CDCl_3$): δ -201.3 – -201.6 (1F, m, *J* 46.9 Hz is observed, F-3β), -205.0 – -205.3(1F, m, *J* 47.7 Hz, is observed, F-3α), -217.8 (1F, dtd, *J* 50.3, 25.6, 14.9 Hz, F-4β), -220.0 (1F, dtdd, *J* 50.6, 27.4, 14.9, 0.9 Hz, F-4α) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$): δ -201.3 (1F, d, *J* 15.0 Hz, F-3β), -204.9 (1F, d, *J* 14.7 Hz, F-3α), -217.8 (1F, d, *J* 15.0 Hz, F-4β), -220.0 (1F, d, *J* 15.0 Hz, F-4α) ppm; **MS (ESI+):** 333 $[M+Na]^+$; **HRMS** (ESI+) for $C_{12}H_{16}F_2NaO_7$ calcd. 333.0761, found 333.0761.

3,4-Dideoxy-3,4-difluoro-D-galactopyranose 15a (from 15b)

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.

2,6-Di-*O*-acetyl-3,4-dideoxy-3,4-difluoro-D-galactopyranose 15c

To a solution of **15b** (352 mg, 1.13 mmol) in THF (14 mL) at 0 °C was added a solution of NH_3 in MeOH (7 N, 3.17 mL). After 1 h the reaction mixture was allowed to warm to rt, and stirred for 3 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica, petroleum ether/acetone, 7/3) to give title compound **15c** as a pale yellow oil (150 mg, 0.56 mmol, 49%). **R_f** 0.29 (hexane/acetone, 6:4); **$[\alpha]_D^{24}$** 108.6 (*c* 0.5, $CHCl_3$); **IR** 3435 (br), 2965 (w), 1742 (s), 1373 (m), 1229 (s), 1048 (s) cm^{-1}; **^{1}H NMR** (α-anomer only) (400 MHz, $CDCl_3$): (ratio α:β 5:1) δ 5.56 (1H, app. q, *J* 3.8 Hz, H-1α), 5.26 (1H, app. td, *J* 10.4, 3.6 Hz, H-2α), 5.03 (1H, ddd, *J* 51.0, 7.6, 2.9 Hz, H-4α), 4.95 (1H, dddd, *J* 48.2, 26.2, 10.3, 2.8 Hz, H-3α), 4.40 – 4.27 (3H, m, H-5α, H-6α), 3.10 (1H, d, *J* 2.7 Hz, OHα), 2.17 (3H, s, COC$\underline{H}_3$), 2.11 (3H, s, COC$\underline{H}_3$) ppm; **^{13}C NMR** (α-anomer only) (101 MHz, $CDCl_3$): (ratio α:β 5:1) δ 170.6 ($\underline{C}OOCH_3$), 170.2 ($\underline{C}OOCH_3$), 90.9 (d, *J* 8.8 Hz, C-1α), 86.9 (dd, *J* 186.3, 16.9 Hz, C-4α), 85.6 (dd, *J* 191.8, 18.0 Hz, C-3α), 68.9 (dd, *J* 18.3, 2.2 Hz, C-2α), 66.6 (dd, *J* 18.0, 5.5 Hz, C-5α), 61.8 (dd, *J* 5.9, 2.2 Hz, C-6α), 20.8 (COO$\underline{C}H_3$), 20.7 (COO$\underline{C}H_3$) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$): (ratio α:β 5:1) δ -201.4 (1F, m, *J* 46.8 Hz is observed, F-3β), -206.2 (1F, m, *J* 48.5 Hz is observed, F-3α), -217.8 (1F, dtd, *J* 50.3, 26.0, 26.0, 15.6 Hz, F-4β), -220.2 – -220.6 (1F, m, F-4α) ppm; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): (ratio α:β 5:1) δ -201.5 (1F, d, *J* 15.6 Hz, F-3β), -206.3 (1F, d, *J* 15.6 Hz, F-3α), -217.9 (1F, d, *J* 15.6 Hz, F-4β), -220.5 (1F, d, *J* 15.6 Hz, F-4α) ppm; **HRMS (ESI+)** for $C_{10}H_{14}F_2NaO_6$ calcd. 291.0656, found 291.0651.

1,4,6-Tri-*O*-acetyl-2,3-dideoxy-2,3-difluorogalactose 16b

To a solution of **20** (627 mg, 3.77 mmol) in Ac_2O (14 mL, 148 mmol) at 0 °C was added dropwise concentrated sulfuric acid (1 mL, 18.6 mmol). After 64 h at rt the reaction was neutralised at 0 °C with a sat. aq. solution of $NaHCO_3$ (40 mL). The mixture was extracted with EtOAc (40 mL, then 2×30 mL), and the combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, petroleum ether/acetone 75:25) to give **16b** as a white solid (1.06 g, 91%, ratio α:β 4:1). **R_f** 0.35 (hexane/acetone, 7:3); **IR** (neat): 1751 (s), 1214 (s), 1082 (m), 1041 (w), 1014 (w) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.46 (1H, app. t, *J* 4.2 Hz, H-1α), 5.73 (1H, dd, *J* 8.0 , 4.1 Hz, H-1β), 5.70 – 5.64 (1H, m, H-4α), 5.61 (1H, dddd, *J* 5.2, 3.9, 2.6, 1.1 Hz, H-4β), 5.10 – 4.88 (2H, m, H-2α, H-3α), 4.87 – 4.64 (2H, m, H-2β, H-3β), 4.25 (1H, tt, *J* 6.7, 1.2 Hz, H-5α), 4.16 (1H, dd, *J* 11.4, 6.4 Hz, H-6β), 4.12 (1H, dd, *J* 11.4, 6.6 Hz, H-6α), 4.12 – 4.06 (1H, m, H-6'β), 4.06 (1H, ddd, *J* 11.3, 6.8, 1.1 Hz, H-6'α), 3.99 (1H, tdd, *J* 6.5, 1.7, 1.3 Hz, H-5β), 2.19 (3H, s, COC$\underline{H}_3$-β), 2.17 (3H, s, COC$\underline{H}_3$-α), 2.16 (3H, s, COC$\underline{H}_3$-β), 2.16 (3H, s, COC$\underline{H}_3$-α), 2.05 (3H, s, COC$\underline{H}_3$-β), 2.05 (3H, s, COC$\underline{H}_3$-α) ppm; **^{1}H{^{19}F} NMR** (500 MHz, $CDCl_3$): δ 6.46 (1H, d, *J* 4.0 Hz, H-1α), 5.73 (1H, d, *J* 7.8 Hz, H-1β), 5.67 (1H, dd, *J* 3.7, 1.3 Hz, H-4α), 5.61 (1H, dd, *J* 3.9, 1.1 Hz, H-4β), 5.02 (1H, dd, *J* 9.4, 3.8 Hz, H-3α), 4.96 (1H, dd, *J* 9.5, 4.2 Hz, H-2α), 4.79 (1H, dd, *J* 9.1, 4.0 Hz, H-3β), 4.73 (1H, dd, *J* 9.1, 7.9 Hz, H-2β), 4.25 (1H, td, *J* 6.7, 1.3 Hz, H-5α), 4.16 (1H, dd, *J* 11.4, 6.4 Hz, H-6β), 4.12 (1H, dd, *J* 11.4, 6.6 Hz, H-6α), 4.12 – 4.06 (1H, dd, *J* 11.5, 6.6 Hz, H-6'β), 4.06 (1H, dd, *J* 11.4, 6.7 Hz, H-6'α), 3.99 (1H, td, *J* 6.5, 1.2 Hz, H-5β), 2.19 (3H, s, COC$\underline{H}_3$-β), 2.17 (3H, s, COC$\underline{H}_3$-β), 2.16 (3H, s, COC$\underline{H}_3$-β), 2.16 (3H, s, COC$\underline{H}_3$-β), 2.05 (3H, s, COC$\underline{H}_3$-β), 2.05 (3H, s, COC$\underline{H}_3$-β) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.3 ($\underline{C}OCH_3$-α+β), 169.58 ($\underline{C}OCH_3$-α), 169.55 ($\underline{C}OCH_3$- β), 168.8 ($\underline{C}OCH_3$-β), 168.6 ($\underline{C}OCH_3$-α), 90.8 (dd, *J* 24.6 , 11.4 Hz, C-1β), 89.1 (dd, *J* 22.7 , 9.5 Hz, C-1α), 88.7 (dd, *J* 194.4 , 19.1 Hz, C_2β or C_3β), 87.8 (dd, *J* 188.5 , 20.5 Hz, C_2β or C_3β), 86.2 (dd, *J* 192.2 , 19.1 Hz, C-2α), 85.1 (dd, *J* 191.1 , *J* 19.4 Hz, C-3α), 71.0 (d, *J* 5.9 Hz, C-5β), 68.5 (d, *J* 5.1 Hz, C-5α), 67.7 (dd, *J* 16.9 , 8.1 Hz, C-4α), 67.2 (dd, *J* 17.2 , 8.4 Hz, C-4β), 60.9 (d, *J* 2.2 Hz, C-6α), 60.8 (d, *J* 2.2 Hz, C-6β), 20.7 ($\underline{C}OCH_{30}$-α+β), 20.56 ($\underline{C}OCH_3$-α+β), 20.45 ($\underline{C}OCH_3$-α+β) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$): δ -200.8 (1F, m, Fβ), -204.8 – -205.1 (1F, m, *J* 48.6 Hz is observed, Fα), -208.2 (1F, dtdd, *J* 51.9, 13.9, 4.3, 2.5 Hz, Fβ), -209.6 – -209.9 (1F, m, Fα) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$): δ -200.8 (1F, d, *J* 13.9 Hz, Fβ), -205.0 (1F, d, *J* 13.6 Hz, Fα), -208.2 (1F, d, *J* 13.9 Hz, Fβ), -209.8 (1F, d, *J* 13.6 Hz, Fα) ppm; **MS (ESI+)** 333 $[M+Na]^+$; **HRMS** (ESI+) for $C_{12}H_{16}F_2NaO_7$ $[M+Na]^+$ cacld 333.0761, found 333.0754.

2,3-Dideoxy-2,3-difluorogalactose 16a (from 20)

To a solution of **20** (3.10 g, 18.7 mmol) in CH_2Cl_2 at 0 °C was added dropwise BCl_3 (1 M in CH_2Cl_2, 37.3 mL, 37.3 mmol), over a period of 30 min. The mixture was stirred at 0 °C for 30 min,

allowed to warm up to rt and stirred for 3.5 h. Water (100 mL) was added, and the resulting biphasic mixture was stirred for 5-10 min, before concentrating *in vacuo* and purification by column chromatography (silica, CH_2Cl_2/MeOH, 9:1) to afford **16a** as a colourless oil (3.38 g, 18.4 mmol, 98%).

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

To a solution of **16b** (1.06 g, 3.42 mmol) in a mixture of THF (30 mL) and H_2O (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, CH_2Cl_2/MeOH, 90:10) to give **16a** as a colourless oil (540 mg, 2.93 mmol, 86%). **R_f** 0.11 (hexane/acetone, 1:1)**; $[\alpha]_D^{20}$** +81.4 (*c* 1, MeOH); **IR** (neat) 3379 (m br), 2917 (w), 2496 (m), 1029 (s) cm^{-1}; **^{1}H NMR** (500 MHz, D_2O): (ratio α:β 1:1) δ 5.51(1H, br. t, *J* 4.3 Hz, H-1α), 5.10 – 4.77 (4H, m, H-1β, H-2α, H-3α, H-2β), 4.58 (1H, dddd, *J* 52.4, 13.6, 9.2, 7.7 Hz, H-2β), 4.35 – 4.30 (1H, m, H-4α), 4.29 – 4.22 (1H, m, H-4β), 4.17 – 4.09 (1H, m, H-5α), 3.83 – 3.69 (5H, m, H-5β, H-6α+ β, H-6'α+β) ppm; **^{1}H{^{19}F} NMR** (ratio α:β 1:1): δ 5.51 (1H, d, *J* 4.1 Hz, H-1α), 4.98 (1H, dd, *J* 9.6, 3.6 Hz, H-3α), 4.91 (1H, dd, *J* 9.5, 4.1 Hz, H-2α), 4.87 (1H, d, *J* 7.7 Hz, H-1β), 4.85 (1H, dd, *J* 9.1, 3.7 Hz, H-3β), 4.58 (1H, dd, *J* 9.1, 7.7 Hz, H-2β), 4.32 (1H, dd, *J* 3.6, 1.1 Hz, H-4α), 4.26 (1H, dd, *J* 3.7, 0.9 Hz, H-4β), 4.13 (1H, app. td, *J* 6.2, 1.1 Hz, H-5α), 3.78 (1H, dd, *J* 12.0, 8.5 Hz, H-6α), 3.78 – 3.71 (4H, m, H-5β, H-6β, H-6'α+β) ppm; **^{13}C NMR** (126 MHz, D_2O): (ratio α:β 1:1) δ 93.5 (dd, *J* 23.2, *J* 11.1 Hz, C-1β), 91.1 (dd, *J* 184.7, 17.5 Hz, C-3β), 90.7 (dd, *J* 181.7, 18.4 Hz, C-2β), 90.1 (dd, *J* 20.7, 9.8 Hz, C-1α), 89.0 (dd, *J* 183.0, 17.5 Hz, C-3α), 87.2 (dd, *J* 184.5, 17.9 Hz, C-2α), 73.9 (d, *J* 6.7, C-5β), 69.7 (dd, *J* 6.0, 1.0 Hz, C-5α), 68.0 (dd, *J* 16.9, 8.1 Hz, C-4α), 67.4 (dd, *J* 16.7, 8.6 Hz, C-4β), 60.6 (d, *J* 2.6 Hz, C-6α), 60.4 (d, *J* 3.3 Hz, C-6β) ppm; **^{19}F NMR** (376 MHz, D_2O): (ratio α:β 1:1) δ -200.4 (1F, app. dtd, *J* 48.5, 13.9, 5.2 Hz, F-2β or F-3β), -204.5 (1F, m, *J* 52.0 Hz is observed, F-2α or F-3α), -208.4 (1F, app. dtt, *J* 52.0, 14.7, 3.5 Hz, F-2β or F-3β), -208.8 (1F, m, F-2α or F-3α) ppm; **^{19}F{^{1}H} NMR** (471 MHz, D_2O): (ratio α:β 1:1) δ -200.3 (1F, d, *J* 14.3 Hz, F-2β or F-3β), -204.4 (1F, d, *J* 14.7 Hz, F-2α or F-3α), -208.3 (1F, d, *J* 14.3 Hz, F-2β or F-3β), -208.6 (1F, d, *J* 14.7 Hz, F-2α or F-3α) ppm **HRMS (ESI+)** for $C_6H_{10}F_2NaO_4$ $[M+Na]^+$ calcd. 207.0444, found. 207.0436.

4,6-Di-*O*-Acetyl-2,3-dideoxy-2,3-difluorogalactose 16c

To a solution of **16b** (483 mg, 1.56 mmol) in THF at 0 °C was added a solution of NH_3 in MeOH (7 M, 4.5 mL, 31 mmol). The mixture was stirred at 0 °C for 1 h, then at rt for 6 h, before concentrating the solvent *in vacuo* and purification by column chromatography (silica, petroleum ether/acetone, 7:3 to 6:4) afforded **16c** as a viscous oil (350 mg, 1.30 mmol, 84%). **R_f** 0.38 (α), 0.35 (β) (hexane/acetone, 1:1); **$[\alpha]_D^{24}$** +97.3 (*c* 1, $CDCl_3$); **IR** (neat) 3427 (m, br.), 1740 (s), 1373 (m), 1223 (s), 1049 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) (ratio α:β 3:1) δ 5.65 (1H, br dtd, *J* 7.2, 4.1, 1.3 Hz, H-4α), 5.59 (1H, dddd, *J* 5.2, 3.9, 2.6, 1.1 Hz, H-4β), 5.55 (1H, q, *J* 3.7 Hz, H-1α), 5.08 (1H, dddd, *J* 49.0, 11.9, 9.4, 3.9 Hz, H-3α), 4.87 – 4.83 (1H, br m, H-1β), 4.84 (1H, dddd, *J* 50.7, 11.8, 9.4, 3.8 Hz, H-3α), 4.74 (1H, dddd, *J* 47.8, 13.1, 9.0, 3.9 Hz, H-3β), 4.57 (1H, dddd, *J* 51.8, 13.1, 9.0, 7.7 Hz, H-2β), 4.43 (1H, tt, *J* 6.5, 1.3 Hz, H-5α), 4.18 (1H, br dd, *J* 11.3, 6.2 Hz, H-6β), 4.15 (1H, dd, *J* 11.4, 6.1 Hz, H-6α), 4.13 (1H, ddd, *J* 11.7, 6.9, 1.0 Hz, H-6β'), 4.08 (1H, ddd, *J* 11.4, 6.9, 1.0 Hz, H-6α'), 3.90 (1H, tt, *J* 6.5, 1.4 Hz, H-5β), 3.53 (1H, br s, OH-1β), 3.10 (1H, d, *J* 3.2 Hz, OH-1α), 2.16 (3H, s, $COCH_3$-β), 2.15 (3H, s, $COCH_3$-α), 2.07 (6H, br s, $COCH_3$-α+β); **^{1}H{^{19}F} NMR** (500 MHz, $CDCl_3$): (ratio α:β 3:1) δ 5.65 (1H, dd, *J* 3.9, 1.3 Hz, H-4α), 5.59 (1H, dd, *J* 4.0, 1.1 Hz, H-4β), 5.55 (1H, t, *J* 3.4 Hz, H-1α), 5.07 (1H, dd, *J* 9.3, 3.9 Hz, H-3α), 4.84 (1H, br dd, *J* 9.5, 3.7 Hz, H-1β + H-3α), 4.74 (1H, dd, *J* 9.1, 4.0 Hz, H-3β), 4.57 (1H, dd, *J* 9.1, 7.6 Hz, H-2β), 4.43 (1H, dddd, *J* 6.9, 6.1, 1.3, 0.5 Hz, H-5α), 4.18 (1H, dd, *J* 11.4, 6.2 Hz, H-6β), 4.15 (1H, dd, *J* 11.3, 6.1 Hz, H-6α), 4.13 (1H, dd, *J* 11.5, 6.7 Hz, H-6β'), 4.08 (1H, dd, *J* 11.4, 6.9 Hz, H-6α'), 3.90 (1H, td, *J* 6.5, 1.1 Hz, H-5β), 3.53 (1H, br s, OH-1β), 3.10 (1H, d, *J* 3.2 Hz, OH-1α), 2.16 (3H, s, $COCH_3$-β), 2.15 (3H, s, $COCH_3$-α), 2.07 (6H, br s, $COCH_3$-α+β) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): (ratio α:β 3:1) δ 170.7 ($COCH_3$-α and β), 169.94 ($COCH_3$-α), 169.90 ($COCH_3$-β), 94.5 (dd, *J* 23.4, 10.7 Hz, C-1β), 91.2 (dd, *J* 21.3, 9.7 Hz, C-1α), 90.4 (dd, *J* 186.4, 19.1 Hz, C-2β), 88.9 (dd, *J* 193.8, 19.1 Hz, C-3β), 86.8 (dd, *J* 189.3, 18.6 Hz, C-2α), 86.2 (dd, *J* 191.2, 19.1 Hz, C-3α), 70.5 (d, *J* 6.4 Hz, C-5β), 68.7 (dd, *J* 16.9, 8.1 Hz, C-4α), 67.7 (dd, *J* 16.8, 8.5 Hz, C-4β), 66.6 (d, *J* 5.0 Hz, C-5α), 61.8 (d, *J* 1.7 Hz, C-6α), 61.6 (d, *J* 2.6 Hz, C-6β), 20.86 ($CO\underline{C}H_3$-α), 20.84 ($CO\underline{C}H_3$-β), 20.72 ($CO\underline{C}H_3$-α), 20.69 ($CO\underline{C}H_3$-β) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) (ratio α:β 3:1): δ -201.0 (1F, app. dtd, *J* 48.1, 13.6, 5.5 Hz, F-3β), -206.8 (1F, m, *J* 49.3 can be observed, F-3α), -207.0 (1F, app. dtdd, *J* 52.2 13.9, 3.9, 2.5 Hz, F-2β), -208.1 (1F, dddd, *J* 50.4, 13.6, 11.8, 3.2 Hz, F-2α) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) (ratio α:β 3:1): δ -201.0 (1F, d, *J* 14.0 Hz, F-3β), -206.8 (1F, d, *J* 14.0 Hz, F-3α), -207.0 (1F, d, *J* 14.0 Hz, F-2β), -208.1 (1F, d, *J* 14.0 Hz, F-2α) ppm; **MS (ESI+)** (m/z) 291 $[M+Na]^+$; **HRMS (ESI+)** for $C_{10}H_{14}F_2NaO_6$ $[M+Na]^+$ calcd. 291.0656, found 291.0646.

5,6-Di-*O*-isopropylidene-2,3-dideoxy-2,3-difluoro-D-galactofuranose 17c and 4,6-di-*O*-isopropylidene-2,3-dideoxy-2,3-difluoro-D-galactopyranose 16d (from 16a).

To a solution of **16a** (636 mg, 3.45 mmol) in glyme (42 mL) at rt was added $CaSO_4$ (dried under vacuum prior to use, 941 mg, 6.91 mmol), 2,2-dimethoxypropane (2.14 mL, 17.27 mmol) and *p*-TSA (177 mg, 1.04 mmol) in this order. The mixture was heated to 70 °C. After 3 h a sat. aq. solution of $NaHCO_3$ (20 mL) was added at that temperature. The resulting mixture was filtered over cotton wool, and extracted with EtOAc (60 mL then 2×30 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and then purified by column chromatography (silica, petroleum ether/acetone 85:15 to 5:5) gave first the furanose acetal **17c** as a pale yellow oil (338 mg, 1.51 mmol, 44%) and the pyranose acetal **16d** as a viscous yellow oil (283 mg, 1.10 mmol, 32%).

Data for 2,3-F_2-galactopyranose acetal **16d**: **R_f** 0.34 (hexane/acetone, 1:1); **$[\alpha]_D^{24}$** +107.7 (*c* 1, $CDCl_3$); **IR** (neat) 3412 (m br), 2995 (w br), 1385 (m), 1066 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): (ratio α:β 7:1) δ 5.58 (1H, t, *J* 3.95 Hz, H-1α), 5.11 – 4.90 (2H, m, H-2α, H-3α), 4.81 – 4.53 (3H, m, H-1β, H-2β, H-3β), 4.53

– 4.48 (1H, m, H-4α), 4.44 (1H, dddd, *J* 5.0, 3.8, 2.5, 1.2 Hz, H-4β), 4.12 (1H, dd, *J* 13.1, 1.9 Hz, H-6α), 4.10 (1H, dd, *J* 12.9, 2.1 Hz, H-6β), 3.98 (1H, dt, *J* 13.0, 1.9 Hz, H-6'β), 3.91 (1H, dt, *J* 13.0, 1.9 Hz, H-6'α), 3.87 – 3.83 (1H, m, H-5α), 3.43 – 3.41 (1H, m, H-5β), 3.29 (1H, d, *J* 2.6 Hz, OH), 1.52 – 1.46 (6H, m, C(CH$_3$)$_2$-β), 1.50 (3H, s. C(CH$_3$)$_2$-α), 1.48 (3H, s, C(CH$_3$)$_2$-α) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): (ratio α:β 7:1) δ 99.3 (C(CH$_3$)$_2$-β), 99.0 (C(CH$_3$)$_2$-α), 94.3 (dd, *J* 23.4, 10.3 Hz, C-1β), 91.4 (dd, *J* 21.6, 9.2 Hz, C-1α), 90.0 (dd, 184.9, 18.3 Hz, C-2β or C-3β), 89.5 (dd, *J* 193.7, 18.3 Hz, C-2β or C-3β), 86.51 (dd, *J* 190.7, 18.3 Hz, C-2α or C-3α), 86.46 (dd, *J* 187.1, 17.6 Hz, C-2α or C-3α), 68.2 (dd, *J* 16.1, 8.1 Hz, C-4α), 67.7 (dd, *J* 16.1, 8.1 Hz, C-4β), 65.6 (d, *J* 6.6 Hz, C-5β), 62.3 (C-6α), 62.2 (C-6β), 61.9 (d, *J* 5.9 Hz, C-5α), 29.2 (C(CH$_3$)$_2$-α), 28.9 (C(CH$_3$)$_2$-β), 18.3 (C(CH$_3$)$_2$-β), 18.2 (C(CH$_3$)$_2$-α) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$): (ratio α:β 7:1) δ -205.5 – -206.3 (1F, m, F-2β or F-3β), -207.6 – -208.8 (1F, m, F-2β or F-3β), -208.9 – -210.1 (1F, m, F-2α or F-3α), -211.1 – -212.1 (1F, m, F-2α or F-3α) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$): (ratio α:β 7:1) δ -205.7 (1F, d, *J* 13.9 Hz, F-2β or F-3β), -208.0 (1F, d, *J* 14.0 Hz, F-2β or F-3β), -209.4 (1F, d, *J* 13.6 Hz, F-2α or F-3α), -211.4 (1F, d, *J* 13.6 Hz, F-2α or F-3α) ppm; **MS (ESI+)** (m/z) 247 $[M+Na]^+$; **HRMS (ESI+)** for $C_9H_{14}F_2NaO_4$ $[M+Na]^+$ calcd. 247.0757, found 247.0758.

Data for 2,3-F$_2$-galactofuranose acetal **17c**: **$[\alpha]_D$** This compound could not be obtained in suitable purity. **R_f** 0.45 (hexane/acetone, 1:1); **IR** (neat) 3420 (m br), 2991 (m br), 2349 (m), 1221 (m), 1054 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): (ratio *minor*/*major* 2:5) δ 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, ddt, *J* 54.6, 16.3, 4.4 Hz, H-3 *minor*), 5.09 (1H, dddd, 49.3, 14.0, 1.1, 0.5 Hz, H-2 *major*), 5.08 (1H, ddt, *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, ddd, *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, ddd, *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, d, *J* 10.0 Hz, OH *major*), 3.03 (1H, d, *J* 3.5 Hz, OH *minor*), 1.49 (3H, d, *J* 0.6 Hz C(CH$_3$)$_2$ *minor*), 1.47 (3H, d, *J* 0.6 Hz C(CH$_3$)$_2$ *major*), 1.41 (3H, d, *J* 0.6 Hz C(CH$_3$)$_2$ *minor*), 1.39 (3H, d, *J* 0.6 Hz C(CH$_3$)$_2$ *major*) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): (ratio *minor*/*major* 2:5) δ 110.4 (C(CH$_3$)$_2$ *minor*), 110.3 (C(CH$_3$)$_2$ *major*), 100.0 (dd, *J* 35.9, 5.1 Hz, C-1 *major*), 97.9 (dd, *J* 181.2, 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 (d, *J* 5.9 Hz, C-5 *minor*), 74.7 (d, *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; **^{19}F NMR** (376 MHz, $CDCl_3$): (ratio *minor*/*major* 2:5) δ -193.9 (1F, dddd, *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, ddd, *J* 52.0, 16.0, 7.2 Hz, F-2 *minor*) ppm; **^{19}F{^{1}H} NMR** (476 MHz, $CDCl_3$): (ratio *minor*/*major* 2:5) δ -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 $C_9H_{14}F_2NaO_4$ $[M+Na]^+$ calcd. 247.0757, found 247.0758.

5,6-Di-*O*-isopropylidene-2,3-dideoxy-2,3-difluoro-D-galactofuranose 17c (from 16d)

Galactopyranose acetal **16d** (1.86 g, 8.30 mmol) was subjected to the same conditions as above to give, after column chromatography, the furanose acetal **17c** as a pale yellow oil (905, 4.04 mmol, 49%, combined yield of 60% over 2 steps), alongside with the recovered starting material **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-D-galactofuranose 17d

To a solution of **17c** (469 mg, 2.09 mmol) in CH_2Cl_2 (10 mL) at 0 °C was successively added DMAP (38 mg, 0.31 mmol, 15 mol %) and Ac_2O (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_2Cl_2 (10 mL), dried over $MgSO_4$, and concentrated. Filtration over a pad of silica gel (petroleum ether/acetone 8:2) gave the protected intermediate **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/acetone, 7:3); **^{1}H NMR** (selected peaks, *major* anomer only) (400 MHz, $CDCl_3$): δ 6.36 (1H, d, *J* 10.5 Hz, H-1), 5.14 (1H, br. dd, *J* 48.7, 13.0 Hz, H-2), 5.11 (br. ddd, *J* 51.8, 19.6, 3.42 Hz, H-3), 4.40 (1H, br. dt, *J* 15.9, 4.7 Hz, H-4), 4.38 – 4.33 (1H, m, H-5), 4.09 (1H, dd, *J* 9.0, 6.9 Hz, H-6), 3.89 (1H, dd, *J* 9.0, 5.4 Hz, H-6'), 2.13 (3H, s, COCH$_3$), 1.46 (3H, s, C(CH$_3$)$_2$), 1.38 (3H, s, C(CH$_3$)$_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.1 (COCH$_3$), 110.2 (C(CH$_3$)$_2$), 98.6 (dd, *J* 37.4, 4.4 Hz, C-1), 97.0 (dd, *J* 183.4, 29.3 Hz, C-2 or C-3), 94.1 (dd, *J* 185.6, 30.8 Hz, C-3 or C-2), 84.3 (dd, *J* 27.1, 2.2 Hz, C-4), 74.0 (d, *J* 5.1 Hz, C-5), 65.1 (d, *J* 2.2 Hz, C-6), 26.2 ((C(CH$_3$)$_2$), 25.0 ((C(CH$_3$)$_2$) ppm **^{19}F NMR** (376 MHz, $CDCl_3$): δ -192.8 (1F, dddd, *J* 51.6, 24.7, 13.9, 8.7 Hz, F-3 *major*), -195.0 (1F, ddt, *J* 48.5, 19.1, 8.7 Hz, F-2 *major*), -202.5 (1F, dtd, *J* 55.9, 19.3, 6.9 Hz, F-2 *minor* or F-3 *minor*), -208.4 (1F, m, F-2 *minor* or F-3 *minor*) ppm **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): δ -192.8 (1F, d, *J* 8.7 Hz, F-3 *major*), -194.8 (1F, d, *J* 8.7 Hz, F-2 *major*), -202.5 (1F, d, *J* 7.6 Hz, F-2 *minor* or F-3 *minor*), -208.4 (1F, d, *J* 7.6 Hz, F-2 *minor* or F-3 *minor*) ppm; **HRMS** (ESI+) for $C_{11}H_{16}F_2NaO_5$ $[M+Na]^+$ calcd 289.0863, found 289.0854.

1,5,6-Tri-*O*-acetyl-2,3-dideoxy-2,3-difluoro-D-galactofuranose 17b

Compound **17d** (480 mg, 1.80 mmol) was dissolved in CH_2Cl_2 (8 mL), after which Ac_2O (641 µL, 6.83 mmol), $Bi(OTf)_3$ (45 mg, 0.068 mmol, 3.8 mol%) and H_2O (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/acetone, 8:2) afforded

17b as a yellow oil (500 mg, 1.61 mmol, 89%, *minor*/*major* 1:9). **IR** (neat) 2951 (w), 1743 (s), 1370 (m), 1216 (s), 1017 (m, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.36 (1H, d, *J* 10.8 Hz, H-1 *major*), 6.29 (1H, d, *J* 3.9 Hz, H-1 *minor*), 5.38 (1H, dt, *J* 6.7, 4.2 Hz, H-5 *major*), 5.35 – 5.16 (3H, m, H-2 *minor*, H-3 *minor*, H-5 *minor*), 5.10 (1H, dd, *J* 48.4, 12.5 Hz, H-3 *major*), 5.07 (1H, dddt, *J* 50.9, 17.6, 3.7, 1.1 Hz, H-2 *major*), 4.53 (1H, dt, *J* 24.7, 3.7 Hz, H-4 *major*), 4.36 – 4.18 (2H, m, H-4 *minor*, H-6 *minor*), 4.31 (1H, dd, *J* 12.0, 4.4 Hz, H-6 *major*), 4.21 (1H, dd, *J* 11.7, 6.7 Hz, H-6' *major*), 4.13 (1H, dd, *J* 12.2, 6.1 Hz, H-6' *minor*), 2.14 (3H, s, $COCH_3$ *minor*), 2.11 (3H, s, $COCH_3$ *major*), 2.10 (3H, s, $COCH_3$ *minor*), 2.09 (3H, s, $COCH_3$ *major*), 2.07 (3H, s, $COCH_3$ *minor*), 2.05 (3H, s, $COCH_3$ *major*) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ ppm 170.41 ($COCH_3$ *major*), 170.38 ($COCH_3$ *minor*), 170.3 ($COCH_3$ *major*), 169.9 ($COCH_3$ *minor*), 169.1 ($COCH_3$ *minor*), 169.0 ($COCH_3$ *major*), 98.6 (dd, *J* 37.4, 3.7 Hz, C-1 *major*), 96.5 (dd, *J* 183.4, 29.3 Hz, C-3 *major*), 94.1 (dd, *J* 185.6, 31.5 Hz, C-2 *major*), 93.6 (dd, *J* 189.3, 24.2 Hz, C-2 *minor* or C-3 *minor*), 92.4 (dd, *J* 17.6, 9.5 Hz, C-1 *minor*), 92.0 (dd, *J* 203.2, 24.2 Hz, C-2 *minor* or C-3 *minor*), 83.2 (dd, *J* 28.6, 1.5 Hz, C-4 *major*), 78.9 (dd, *J* 27.5, 8.4 Hz, C-4 *minor*), 70.3 (d, *J* 5.1 Hz, C-5 *minor*), 68.9 (d, *J* 6.6 Hz, C-5 *major*), 62.2 (C-6 *major*), 61.9 (C-6 *minor*), 20.93 ($COCH_3$ *minor*), 20.87 ($COCH_3$ *major*), 20.72 ($COCH_3$ *minor*), 20.67 ($COCH_3$ *major*), 20.66 ($COCH_3$ *major*), 20.61 ($COCH_3$ *minor*) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -192.0 (1F, dddd, *J* 51.2, 25.1, 13.0, 9.5 Hz, F-2 *major*), -196.1 (1F, ddt, *J* 48.6, 17.3, 9.5 Hz, F-3 *major*), -200.1 – -200.8 (1F, m, F-2 *minor* or F-3 *minor*), -207.0 – -209.4 (1F, m, F-2 *minor* or F-3 *minor*) ppm **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): δ -191.9 (1F, d, *J* 6.94 Hz, F-2 *major*), -196.0 (1F, d, *J* 6.9 Hz, F-3 *major*), -200.4 (1F, d, *J* 6.9 Hz, F-2 *minor* or F-3 *minor*), -208.1 (1F, d, *J* 6.9 Hz, F-2 *minor* or F-3 *minor*) ppm; **MS (ESI+)** (m/z) 333 $[M+Na]^+$; **HRMS (ESI+)** for $C_{12}H_{16}F_2NaO_7$ $[M+Na]^+$ calcd 333.0761, found 333.0755.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This project has been funded by the Industrial Biotechnology Catalyst (Innovate UK, BBSRC, EPSRC, BB/M028941/1) to support the translation, development and commercialization of innovative Industrial Biotechnology processes. We also thank the EPSRC (core capability EP/K039466/1) for funding.

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