A ~~short~~ synthesis of 2,3,4-trideoxy-2,3,4-trifluoroglucose

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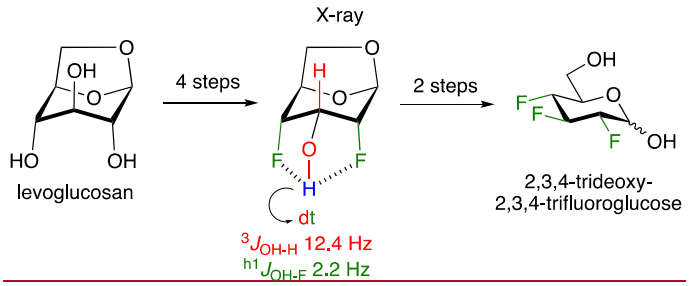

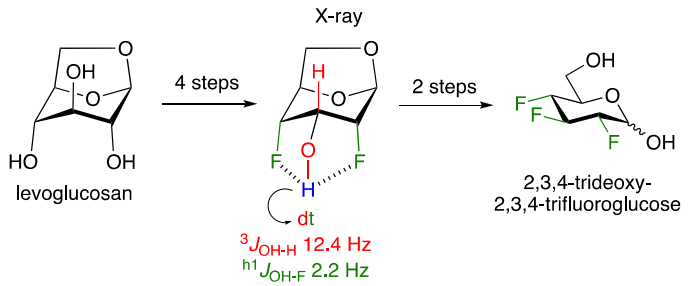

ABSTRACT

There is an increasing interest in investigating how polyfluorination of carbohydrates modifies their physical and biological properties. An example that has caught much attention is 2,3,4-trideoxy-2,3,4-trifluoroglucose~~, in which all stereogenic (non-anomeric) alcohol groups are replaced by fluorines~~. Four syntheses of this compound have ~~already~~ been reported, which are either low yielding, or long (13 or more steps). ~~Here w~~We report a 6-step synthesis of 2,3,4-trideoxy-2,3,4-trifluoroglucose starting from levoglucosan~~. In addition, we report a~~. The solution-phase structure of an intermediate, 1,6-anhydro-2,4-dideoxy-2,4-difluoroallose, features a rare example of a bifurcated F···HO···F hydrogen bond, and is compared to ~~in solution between the alcohol and two organofluorine groups of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-allose, and~~ its crystal structure ~~is described and compared to that of its C-3 (glucose) stereomer~~.

The synthesis of compounds containing multiple stereogenic CHF centers has become a topic of great interest. Seminal work has emanated from the O'Hagan group, first with acyclic multivicinal fluorinated alkane chains,[1-2] later with cyclic examples with 1,2,3,4,5,6-hexafluorinated cyclohexane as highlight.[3-5] Next to alkane fluorination, investigations have also focused on replacing multiple heteroatoms with fluorines. A notable example is the synthesis of a polyfluorinated analogue of the natural product danicalipin A by the Carreira group, in which the organochlorine groups were replaced by organofluorines.[6] Carbohydrate deoxyfluorination, in which alcohol groups are replaced by fluorines, is well-investigated.[7-9] Starting from levoglucosan (1,6-anhydroglucose), the group of Cerny already produced dideoxy-difluorinated carbohydrates in the early seventies.[10-11] The first systematic biological activity and anomeric reactivity studies of dideoxy-difluorinated carbohydrates were reported

by Withers et al.[12,13] The first syntheses of 2,3,4-trideoxy-2,3,4-trifluorinated carbohydrate derivatives (glucose and galactose) were reported by Lukacs in 1989,[14] but it is again the O'Hagan group who first synthesized, using a different synthetic strategy, fully deprotected 2,3,4-trideoxy-2,3,4-trifluoroglucose **1** (Chart 1).[15-16] Very recently, Giguère et al published an impressive synthetic effort achieving the synthesis of many 2,3,4-trifluorinated carbohydrates, as well as a 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorinated glycoside.[17]

Investigations of how such fluorination motifs modify physical and biological properties of carbohydrates are of great interest. In addition, deoxyfluorination of carbohydrates has great potential for NMR-based investigations of protein-carbohydrate interactions.[18-20] O'Hagan showed that the exchange of **1** through erythrocyte membranes was slightly slower than that of glucose[15] (and much slower than the corresponding hexafluorinated analogue).[21-22] We have shown that the lipophilicity of **1** is about three orders of magnitude higher than that of glucose.[23] This was confirmed by the Giguere group,[17] who additionally demonstrated the influence of sugar trifluorination stereochemistry on the lipophilicity.

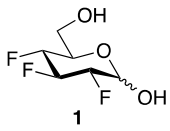

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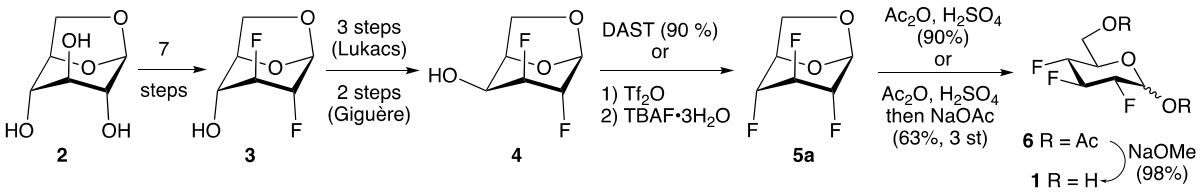
Chart 1. 2,3,4-Trideoxy-2,3,4-trifluoroglucose **1**.

The synthesis of polyfluorinated substrates is a challenging undertaking, especially towards upscaling to produce sufficient quantities. Hence, improving the pioneering syntheses of key molecules has been a focus. The original synthesis of *all-cis* 1,2,3,4,5,6-

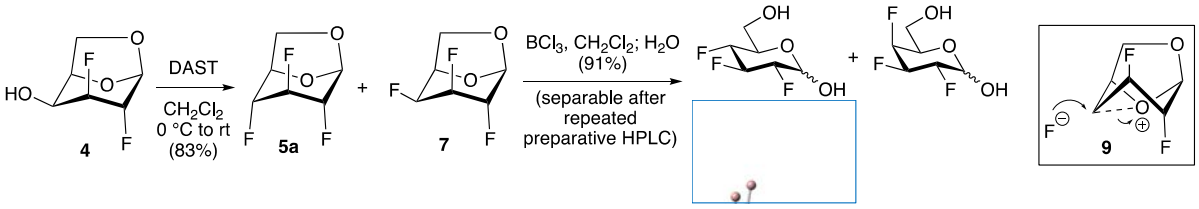
hexafluorocyclohexane has been superseded by Glorius' stereoselective reduction of hexafluorobenzene.[24] Instead of the original de novo approaches to 2,3,4-trideoxy-2,3,4-trifluoroglucose **1**,[15-16] and based on the Lukacs synthesis of 1,6-di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoroglucose **6** (Scheme 1),[14] Giguère's team achieved a scaleable synthesis of **1** (Scheme 1).[17] In both cases, the 4-OH group of **3** was inverted after conversion to the corresponding triflate, using NaOBz (Lukacs), and by a Lattrell-Dax reaction (Giguère), to arrive at the corresponding difluorinated galactosan **4**. The subsequent deoxyfluorination reaction was achieved by DAST (Lukacs) or by a 2-step fluoride displacement (Giguère). Finally, acetolysis to cleave the 1,6-anhydrobridge and deprotection gave **1** in 13 overall steps.



Scheme 1. The Lukacs[14]/Giguere[17] Synthesis of **1** Starting from Levoglucosan.

As part of a research programme investigating GLUT-1 mediated erythrocyte membrane exchange of fluorinated carbohydrates,[25] we required **1** in >100 mg quantities. However, in our hands the DAST-mediated deoxyfluorination according to Lukacs[14] led to an inseparable mixture of trifluorinated levoglucosan **5a** and levogalactosan **7** (Scheme 2), in a 7:3 ratio. Slower addition of DAST at 0 °C did lead to a much improved 97:3 ratio, but in a much

lower 50% yield (not shown). Combined with the unattractive length of this synthesis, investigations were subsequently initiated towards a shorter route for **1**.

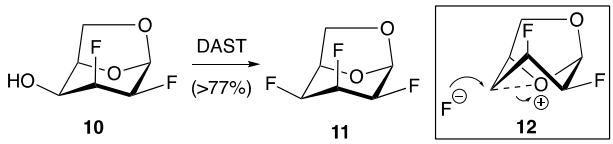


Scheme 2. Unselective Deoxyfluorination of **4**. Thermal ellipsoids drawn at the 50% probability level.

The formation of the galactose isomer can be understood by a 2-step mechanism in which expulsion of the leaving group is aided by neighboring group participation of the endocyclic oxygen to form an intermediate akin to **9**. Subsequent fluoride attack then leads to the formation of the C-4 stereocenter with retention of configuration. The participation of 1,6-anhydrosugar endocyclic oxygens in nucleophilic substitution reactions has been investigated by the group of Karban.[26] We have not observed fluoride attack at C-5 leading to a ring-contracted product, which is not unprecedented for retentive 4-OH deoxyfluorinations.[26] For such cases, the involvement of an S_Ni mechanism has also been suggested as a possible explanation.[26]

Interestingly, the equivalent DAST-mediated deoxyfluorination of 1,6-anhydro-2,3-difluorolevotalosan **10** (Scheme 3) was reported to occur with a clean retention of configuration,[17] despite the presence of the antiperiplanar C2–F bond with the endocyclic

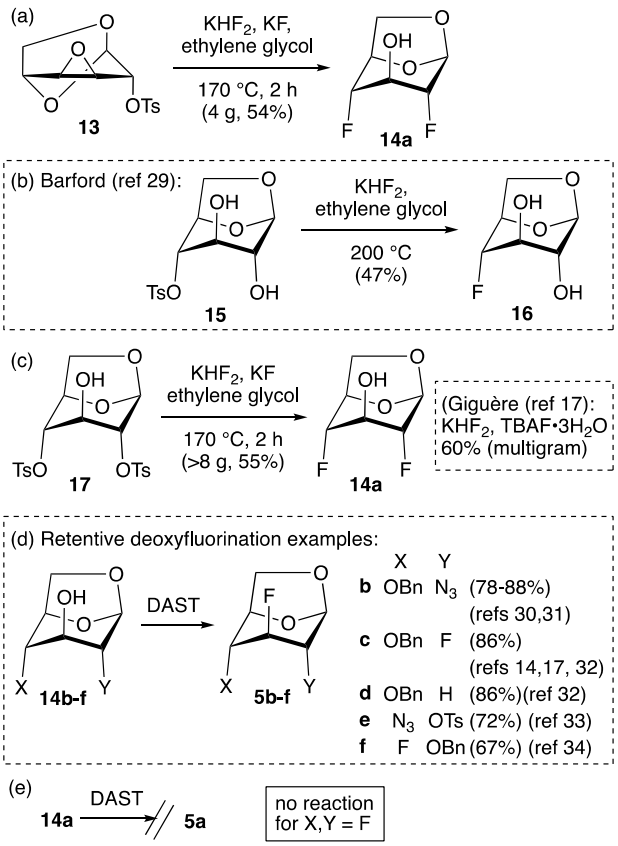
oxygen. In such a case, this could be expected to cause a reduction of the oxygen polarizability and thus its capacity for anchimeric assistance to form an epoxonium-like intermediate **12**. However, this reaction was conducted at 100 °C in a microwave oven which may have forced this process to dominate.



Scheme 3. Deoxyfluorination of 1,6-Anhydro-2,3-dideoxy-2,3-difluorotalose **10**.[17]

To open the 1,6-anhydrobridge, the mixture of **5a** and **7** was treated with BCl_3. To our delight, this conversion proceeds in excellent yield to give a mixture of the target compound **1** and 2,3,4-trideoxy-2,3,4-trifluorogalactose **8**. These are separable albeit only via multiple preparative HPLC runs. Recrystallisation of each pyranose followed by X-ray analysis allowed unambiguous confirmation of their relative stereochemistry, and the structure of **1**, also reported by O'Hagan (CSD code: CUTVIX),[15] is shown side-by-side to the novel structure of **8**.

In designing a new, shorter synthesis which also would circumvent unselective deoxyfluorination, we were attracted by a publication from Pacak et al, who reported that treatment of **13** (Scheme 4a),[27-28] with KHF_2 in ethylene glycol leads to the difluorinated **14a** as the only isolable product in 5% yield (not shown).[10-11] Pleasingly, optimization of this reaction, which involved the addition of KF and working under more concentrated conditions, improved this to a 54% yield of **14a** on multigram scale. Lower yields were obtained under rigorous exclusion of moisture.



Scheme 4. Synthesis of the 2,4-Dideoxy-2,4-difluorolevoglucosan **14a**, and its Unsuccessful Deoxyfluorination to **5a**.

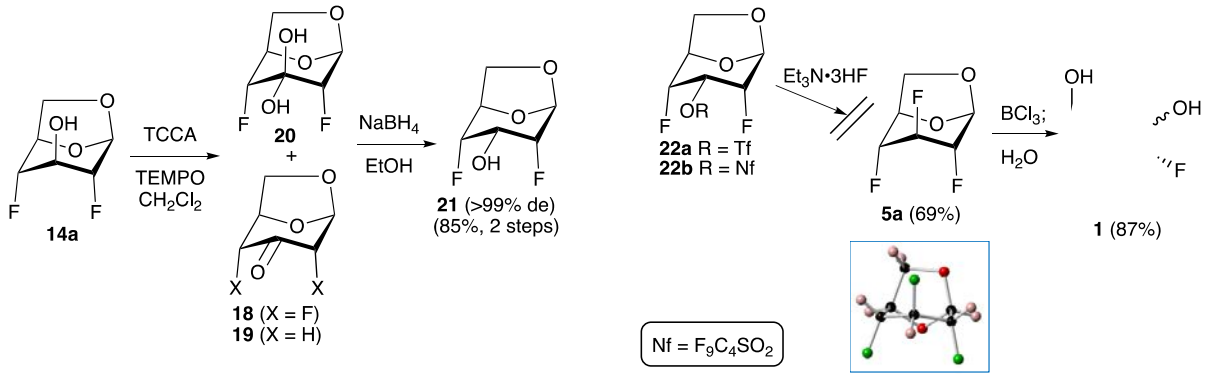
Then, inspired by a report by Barford et al,[29] who achieved fluoride introduction starting from tosylate **15** by in-situ epoxide formation under essentially the same conditions (Scheme 4b), this process was successfully repeated from known ditosylate **17** (Scheme 4c), which was obtained from levoglucosan **2** in 82% yield (not shown),[27-28] to give **14a** in 55% yield. While this manuscript was in preparation, this remarkable transformation was reported by Giguère,[17] who used 8 equiv of TBAF•$3H_2O$ as the extra fluoride source, in neat conditions at 180 °C, to obtain a slightly higher yield of 60% (multigram scale).

Finally, the plan called for direct deoxyfluorination of **14a** to give the desired **5a**. Deoxyfluorination of 3-OH groups of 1,6-anhydroglucose derivatives with retention of

configuration is well-precedented (cf examples **14b-f**, Scheme 4d),[14, 17, 30-34] which has been also been explained by neighboring group participation, now with a suitable group at the C-2 or C-4 position. This mechanism is not expected to take place with antiperiplanar fluorine substituents; however, should an S_Ni mechanism take place, the retentive deoxyfluorination of **14a** may be successful. Unfortunately, we have not been able to find conditions to form **5a** in this way (Scheme 4e), with ^{19}F NMR analysis indicating that the 3-OH group does not react with DAST.

Hence, it was decided to first effect 3-OH inversion (Scheme 5). Oxidation of **14a** gave a mixture of the ketone **18** and its hydrate **20**, which was immediately followed by borohydride reduction. While reduction of the corresponding (nonfluorinated) 2,4-dideoxy pyranulose **19** under similar conditions resulted in an 56:44 ratio of equatorial/axial attack,[35] reduction of **18** gave predominantly the desired axial attack to give the levoallosan derivative **21**. Axial attack is sterically hindered by the anhydro bridge, but for **18**, borohydride attack is also hindered by the two axial fluorine groups. Unsurprisingly, reaction with the bulky L-selectride, which selectively reduces cyclohexanones with an axial α-fluorine through axial attack,[36] was extremely sluggish. With $NaBH_4$ in Et_2O, the reaction was not fully selective, and 4-15% of levoglucosan **14a** was formed (not shown). This was separable from **21**, but given **14a** does not react under deoxyfluorination conditions, separation is not necessary at this stage. However, reduction with $NaBH_4$ in EtOH[37] did lead to virtually complete selectivity, leading to **21** in excellent yield. DAST mediated deoxyfluorination of **21** only led to trace amounts of **5a**, while fluoride substitution of triflate **22a** with Et_3N•3HF also did not lead to appreciable conversions. Pleasingly, successful conversion to give **5a** was achieved with the use of nonafluorobutyl sulfonyl fluoride (NfF)[38] in the presence of Et_3N•3HF as external fluoride source, which proceeds via the corresponding nonaflate **22b**. Given the volatility of **5a**, for which a crystal structure could be obtained, this reaction required execution in a sealed tube.

Finally, BCl_3-mediated opening of the 1,6-anhydro bridge gave the desired **1** in excellent yield.



Scheme 5. Successful Synthesis of 2,3,4-Trideoxy-2,3,4-trifluoroglucose **1**. Thermal Ellipsoids Drawn at the 50% Probability Level. One out of 4 Conformations Shown for **21**.

The ^{1}H NMR spectrum of **21** ($CDCl_3$) displays a very defined doublets of triplets for the alcohol group (Figure 1). Fluorine decoupling simplifies the signal to a 12.4 Hz doublet ($^3J_{H3\text{-}OH}$), a magnitude consistent with an antiperiplanar alignment, and the triplet was assigned as $^{h1}J_{OH\cdots F}$ couplings to F-2 and F-4, each measuring ±2.2 Hz. Hence, this indicates that in solution, the O–H bond is positioned in between the two C–F bonds, with hydrogen bonding to the fluorine atoms, possibly as a so-called “bifurcated hydrogen bond”. While it has been calculated that there is no enthalpic advantage to form such a three-center interaction, it has been suggested that this type of interaction ‘would become favorable if both acceptors occurred in the same molecule, and were rigidly held in the proper arrangement’.[39] Density Functional Theory calculations (IEF-PCM/B97-D3^{BJ}/6-311++G(2d,p) level of theory in

chloroform, see Supporting Information) showed this conformation as the only one being populated (99%), with two OH···F distances (values around 2.45 Å) shorter than the sum of the H and F van der Waals radii (2.57 Å), and typical of hydrogen-bond interaction. The interaction energies ($E^{(2)}_{n\rightarrow\sigma^*}$) computed from NBO analysis[40] indicated very weak charge transfers (0.67 and 0.63 kJ mol^{-1}) from the fluorine atoms lone pairs to the hydroxyl antibonding orbital, in line with values previously encountered in such OH···F interactions.[41] In addition, calculation of coupling constants within this IMHB conformer lead to $^{3}J_{H,OH}$ value of 13.5 Hz, and two $^{h1}J_{OH\cdots F}$ values of -1.6 Hz and -1.4 Hz, close to the experimental values (12.4 Hz and ±2.2 Hz), whereas the non-IMHB conformers exhibit couplings very far from the experimental data. To the best of our knowledge, there are very few examples involving an alcohol (phenol) donor and two C–F acceptors, either intermolecular (*syn*-2,4-difluoroadamantane),[42] or intramolecular (*eg* 2-(trifluoromethyl)phenol).[43] We believe there also is only one example of a 5-membered $^{h1}J_{OH\cdots F}$ coupling in the literature (4.6 Hz), reported by Bernet also on a 1,6-anhydrosugar derivative.[44]

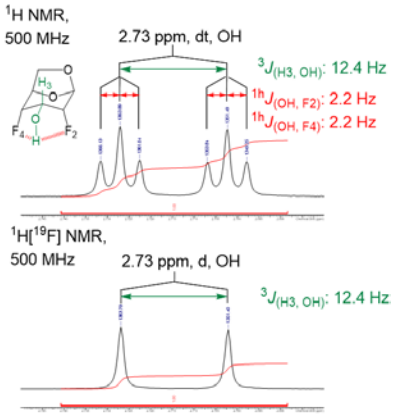


Figure 1. Coupling Constants of the Alcohol Hydrogen Before and After Fluorine Decoupling.

The weak OH•••F hydrogen bond[45-47]does not play an important role in the overall combination of interactions that determine crystal packings. The known crystal structure of **14a** (CSD code ADFGLP) has attracted interest in that its crystal packing does not include any intermolecular hydrogen bonding between the alcohol group and the fluorine atoms, despite the availability of two C–F acceptors in a small molecule.[48] In this context, we were delighted to be able to obtain single crystals of **21** (Scheme 5). Its unit cell is quite complex, containing 8 independent molecules, which differ in their OH orientation, including structures with either an antiperiplanar (as shown in Scheme 5) or a synperiplanar orientation between the O-H and alcohol C-H bonds. Like in **14a**, the packing is clearly dominated by intermolecular hydrogen bonding in which two different chains can be distinguished (see Supporting Information for details), and not by intramolecular OH•••F hydrogen bonding.

In conclusion, we have achieved a short, 6-step synthesis of 2,3,4-trideoxy-2,3,4-trifluoroglucose **1** from levoglucosan in 24% overall yield. The key transformations involved a selective difluorination of 2,4-di-*O*-tosyl levoglucosan **17**, and the deoxyfluorination of 2,4-dideoxy-2,4-difluorolevoallosan **21**. A rare F•••OH•••F bifurcated hydrogen bond was observed in solution for **21**, but although this particular conformation was also present in the crystalline state, the crystal packing of this compound is clearly dominated by intermolecular O–H•••O hydrogen bonding.

EXPERIMENTAL SECTION

Computational details. To provide further evidence of the occurrence of a bifurcated hydrogen-bond in **21**, Density Functional Theory calculations have been performed by using the A.03 version of the Gaussian 16 program.[49] Following the methodology used in our

previous work on the levoglucosan series,[41] the geometries of the various structures have been optimized at the IEF-PCM/B97-D3^{BJ}/6-311++G(2d,p) level of theory in chloroform. Frequency calculation of the various energetic minima were then carried out at the same level of theory, allowing the calculations of the corresponding Gibbs free energies, and of the Boltzmann distribution.

IMHB interactions were analyzed through AIM topological analysis of the IEF-PCM/B97-D3^{BJ}/6-311++G(2d,p) wavefunctions with the AIM2000 program.[50] The complementary contribution of charge transfer between the acceptor lone pair(s) electrons and the σ* donor antibonding orbital was estimated through natural bond orbital (NBO) analyses.[40] The NBO method was applied at the IEF-PCM/B97-D3^{BJ}/6-311++G(2d,p) level in $CHCl_3$ to provide the corresponding interaction energies ($E^{(2)}_{n\rightarrow\sigma^*}$) evaluated from second-order perturbation theory, using the NBO 6.0 program.[51]

The spin–spin coupling constants (*J*) were then estimated from the previous optimized geometries by using the gauge-invariant atomic orbital (GIAO) method. The hybrid B97–2 functional and the pcJ-2 basis set, specifically designed for the calculation of these NMR parameters,[52] were used.

General synthesis conditions. All air/ moisture sensitive reactions were carried out under an inert atmosphere (Ar), in dried glassware. Dry CH_2Cl_2, THF, MeOH and hexane were bought from commercial suppliers, and used as received. TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F254 indicator; visualised under UV light (254 nm) and/or by staining with $KMnO_4$ (10% aq.). Flash column chromatography was performed with Sigma Aldrich 60 silica gel (40-63 micron). Preparative HPLC was carried out using a Biorad Bio-Sil D 90-10 column (250 × 22 mm at 15 mL min^{-1}). High-resolution

MS samples were analysed using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser. Samples were introduced to the mass spectrometer via a Dionex Ultimate 3000 autosampler and uHPLC pump, and eluted in five minutes at 0.6 mL min using a gradient 20% acetonitrile (0.2% formic acid) to 100% acetonitrile (0.2% formic acid) through an Acquity UPLC BEH C18 (Waters) 1.7 micron 50 × 2.1mm column. High resolution mass spectra were recorded using positive ion electrospray ionisation. ^{1}H-, ^{19}F- and ^{13}C-NMR spectra were recorded at room temperature on a Bruker Ultrashield 400 MHz or 500 MHz spectrometer. ^{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) are given in Hertz (Hz). The NMR signals were designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), spt (septet), m (multiplet), or a combination of the above. For all compounds, detailed peak assignment was performed through the combined use of HSQC and COSY NMR experiments.

-1,6-Anhydro-2,3,4-trideoxy-2,3,4-trifluoroglucose **5a** and 1,6-anhydro-2,3,4-trideoxy-2,3,4-trifluorogalactose **7** from **4** (Scheme 2).

To a solution of 1,6-anhydro-2,3-dideoxy-2,3-difluorogalactose **4**[14, 17] (100 mg, 0.60 mmol) in dry CH_2Cl_2 (2.3 mL) at 0 °C was added DAST (0.24 mL, 1.96 mmol) dropwise. The resulting mixture was stirred at rt under argon for 24 h until TLC indicated full consumption of the starting material. The reaction mixture was quenched by carefully adding sat. aq. $NaHCO_3$ (5 mL) at 0 °C, and the resulting aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were combined, dried over $MgSO_4$, filtered, and the solvent slowly evaporated under controlled reduced pressure (600 mbar). Purification by

column chromatography (pentane/CH_2Cl_2 80:20 to 50:60) afforded 92 mg (0.50 mmol, 83%) of an inseparable mixture of diastereoisomers trifluoro levoglucosan **5a** and levogalactosan **7** (*dr* 69:31) as a white solid. Selected data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 (1H, br. s, $H_{1(Glc)}$), 5.54 (1H, m, *J* = 5.1, 1.5 Hz is observed, $H_{1(Gal)}$), 5.02 (1H, m, *J* 47.7 Hz is observed, $H_{3(Gal)}$), 4.93–4.59 (5H, m), 4.57 (1H, m, *J* 44.7, 14.9, 1.5 Hz is observed, $H_{4(Glc)}$), 4.43 (1H, m, *J* 45.5, 14.9, 1.5 Hz is observed, $H_{2(Glc)}$), 4.34 (1H, br. d, *J* 8.1 Hz, $H_{6endo(Gal)}$), 3.96 (1H, br. dd, *J* 8.1, 1.0 Hz, $H_{6endo(Glc)}$), 3.74–3.89 (2H, m, $H_{6exo(Glc,Gal)}$) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -188.0 (m, *J* 45.1, 15.6, 12.1, 3.5 Hz is observed, $F_{4(Glc)}$), -191.1 (dquin, *J* 41.6, 13.8 Hz, $F_{3(Glc)}$), -193.6 (m, *J* 45.1, 3.5 Hz is observed, $F_{2(Glc)}$), -195.5 (ddd, *J* 44.6, 16.0, 8.7 Hz, $F_{4(Gal)}$), -208.8 (m, *J* 46.8, 24.3, 15.6 Hz is observed, $F_{3(Gal)}$), -209.0 (br. d, *J* 43.4 Hz, $F_{2(Gal)}$) ppm; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -188.0 (d, *J* 12.1 Hz, $F_{4(Glc)}$), -191.1 (t, *J* 12.1 Hz, $F_{3(Glc)}$), -193.6 (d, *J* 12.1 Hz, $F_{2(Glc)}$), -195.5 (d, *J* 15.6 Hz, $F_{4(Gal)}$), -208.8 (dd, *J* 15.6, 3.5 Hz, $F_{3(Gal)}$), -209.0 (d, *J* 5.2 Hz, $F_{2(Gal)}$) ppm.

-2,3,4-Trideoxy-2,3,4-trifluoro-D-glucopyranose **1** and 2,3,4-trideoxy-2,3,4-trifluoro-D-galactopyranose **8** from the mixture of **5a** and **7** (Scheme 2).

To a solution of the mixture of **5a**/**7** (89 mg, 0.53 mmol) in CH_2Cl_2 (3.6 mL) at 0 °C was added BCl_3 (1 M in CH_2Cl_2, 2.2 mL, 2.2 mmol) dropwise. The resulting mixture was stirred at rt for 2 h before being quenched with water (5 mL). The organic solvent was then removed under reduced pressure and the resulting aqueous phase was stirred for an additional 1 h at rt. The remaining water was evaporated to give a brown dense oil, which was then purified by column chromatography (pentane/acetone 90:10 to 60:40) to afford 90 mg (0.48 mmol, 91%) of a "pure" mixture of **1** and **8**. Complete separation of the two diastereoisomers could be achieved *via* repeated HPLC separations (pentane/acetone 70:30).

Data for 2,3,4-trideoxy-2,3,4-trifluoro-D-glucopyranose **1** (white solid): **Rf** 0.12 (pentane/EtOAc 60:40); **Mp** 98-100 °C ($CHCl_3$/acetone), lit[15] 103-105 °C ($CHCl_3$); **[α]D** +28.0 for α/β 0.30:1.00 (c 0.99, CD_3OD, 21 °C), lit[15] +40.1 for α/β 1:0.98 (c 1.15, THF-d_8, 22 °C); **IR** (neat) 3367 (m, br.), 3111 (m, br.), 2961 (m), 1032 (s), 995 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.49 (1H, br. q, *J* = 3.1 Hz, $H_{1\alpha}$), 5.09 (1H, ddddd, *J* = 55.0, 16.6, 14.0, 8.4, 7.9 Hz, $H_{3\alpha}$), 4.92 (1H, br. dd, *J* = 7.6, 3.0 Hz, $H_{1\beta}$), 4.82 (1H, dddt, 53.1, 16.5, 15.9, 8.3 Hz, $H_{3\beta}$), 4.66 (1H, m, a doublet with *J* = 50.4 Hz can observed, $H_{4\beta}$), 4.64 (1H, dddd *J* = 50.9, 15.1, 9.9, 8.3 Hz, $H_{4\alpha}$), 4.53 (1H, dddd, *J* = 49.8, 12.9, 8.9, 3.9 Hz, $H_{2\alpha}$), 4.35 (1H, dddd, *J* = 50.9, 14.5, 8.1, 7.6 Hz, $H_{2\beta}$), 4.13 (1H, ddq, *J* = 9.8, 4.4, 2.5 Hz, $H_{5\alpha}$), 4.03–3.73 (4H, m, $H_{6,6'\alpha}$ + $H_{6,6'\beta}$), 3.63–3.57 (1H, m, $H_{5\beta}$), 3.34 (1H, br. s, $OH_{1\alpha}$), 1.84 (1H, br. s, $OH_{6\alpha}$) ppm; **^{1}H{^{19}F} NMR** (500 MHz, $CDCl_3$) δ 5.49 (1H, br. d, *J* = 3.6 Hz, $H_{1\alpha}$), 5.09 (1H, t, *J* = 8.5 Hz, $H_{3\alpha}$), 4.92 (1H, d, *J* = 7.7 Hz, $H_{1\beta}$), 4.82 (1H, t, *J* = 8.3 Hz, $H_{3\beta}$), 4.67 (1H, dd, *J* = 9.8, 8.3 Hz, $H_{4\beta}$), 4.64 (1H, dd, *J* = 9.3, 8.3 Hz, $H_{4\alpha}$), 4.53 (1H, dd, *J* = 8.8, 3.8 Hz, $H_{2\alpha}$), 4.35 (1H, dd, *J* = 8.3, 7.7 Hz, $H_{2\beta}$), 4.13 (1H, ddd, *J* = 9.9, 4.2, 2.4 Hz, $H_{5\alpha}$), 4.03–3.74 (4H, m, $H_{6,6'\alpha}$ + $H_{6,6'\beta}$), 3.60 (1H, ddd, *J* = 9.8, 4.7, 2.4 Hz, $H_{5\beta}$), 3.34 (1H, br. s, $OH_{1\alpha}$), 1.84 (1H, br. s, $OH_{6\alpha}$) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -195.1– -195.4 (m, a doublet of quintets with *J* = 53.2, 13.6 Hz is observed, $F_{3\beta}$), -199.3– -199.6 (m, a doublet of triplets with *J* = 50.9, 14.4 Hz is observed, $F_{2\alpha}$ or $F_{4\alpha}$), -200.0 (dddt, *J* = 50.9, 15.9, 13.0, 2.9 Hz, $F_{2\beta}$ or $F_{4\beta}$), -200.6– -200.9 (m, a doublet of triplets with *J* = 50.7, 14.5 Hz is observed, $F_{2\beta}$ or $F_{4\beta}$), -201.0– -201.30 (m, a doublet of quintets with *J* = 54.9, 13.5 Hz is observed, $F_{3\alpha}$), -201.5 (dtd, *J* = 49.9, 13.6, 2.0 Hz, $F_{2\alpha}$ or $F_{4\alpha}$) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ -195.3 (t, *J* = 12.9 Hz, $F_{3\beta}$), -199.4 (dd, *J* = 12.9, 2.1 Hz, $F_{2\alpha}$ or $F_{4\alpha}$), -200.0 (dd, *J* = 13.6, 2.9 Hz, $F_{2\beta}$ or $F_{4\beta}$), -200.8 (dd, *J* = 12.5, 2.5 Hz, $F_{2\beta}$ or $F_{4\beta}$), -201.1 (t, *J* = 12.9 Hz, $F_{2\alpha}$ or $F_{4\alpha}$), -201.5 (dd, *J* = 12.9, 2.1 Hz, $F_{2\alpha}$ or $F_{4\alpha}$) ppm. The spectral dispersion in CD_3OD is superior: **^{1}H NMR** (500 MHz, CD_3OD) δ 5.33 (1H, q, *J* = 3.5 Hz, $H_{1\alpha}$), 4.97 (1H, dddt, *J* = 56.0, 17.0, 13.8, 8.6 Hz, $H_{3\alpha}$), 4.88 (1H,

dddt, *J* = 54.3, 16.8, 15.9, 8.4 Hz, $H_{3\beta}$), 4.82 (1H, dd, *J* = 7.7, 2.8 Hz, $H_{1\beta}$), 4.68–4.49 (2H, m, $H_{4\alpha}$ + $H_{4\beta}$), 4.49 (1H, ddddd, *J* = 50.4, 13.2, 8.9, 3.8, 0.4 Hz, $H_{2\alpha}$), 4.21 (1H, ddt, *J* = 51.5, 15.1, 8.3 Hz, $H_{2\beta}$), 4.02–3.96 (1H, m, $H_{5\alpha}$), 3.84 (1H, dq, *J* = 12.4, 2.0 Hz, $H_{6\beta}$), 3.78 (1H, dq, *J* = 12.4, 2.0 Hz, $H_{6\alpha}$), 3.73 (1H, ddd, *J* = 12.4, 4.1, 1.8 Hz, $H_{6'\alpha}$), 3.70 (1H, ddd, *J* = 12.4, 4.7, 2.0 Hz, $H_{6'\beta}$), 3.62–3.56 (1H, m, $H_{5\beta}$) ppm; **^{1}H{^{19}F} NMR** (500 MHz, CD_3OD) δ 5.33 (1H, d, *J* = 3.8 Hz, $H_{1\alpha}$), 4.96 (1H, br. t, *J* = 8.4 Hz, $H_{3\alpha}$), 4.88 (1H, t, *J* = 8.4 Hz, $H_{3\beta}$), 4.82 (1H, d, *J* = 7.7 Hz, $H_{1\beta}$), 4.59 (1H, dd, *J* = 9.8, 8.3 Hz, $H_{4\beta}$), 4.58 (1H, dd, *J* = 9.9, 8.2 Hz, $H_{4\alpha}$), 4.49 (1H, dd, *J* = 9.0, 3.8 Hz, $H_{2\alpha}$), 4.21 (1H, t, *J* = 8.1 Hz, $H_{2\beta}$), 3.99 (1H, br. ddd, *J* = 9.8, 4.1, 2.3 Hz, $H_{5\alpha}$), 3.84 (1H, dd, *J* = 12.4, 2.1 Hz, $H_{6\beta}$), 3.79 (1H, dd, *J* = 12.4, 2.1 Hz, $H_{6\alpha}$), 3.73 (1H, dd, *J* = 12.4, 4.1 Hz, $H_{6'\alpha}$), 3.70 (1H, dd, *J* = 12.4, 4.7 Hz, $H_{6'\beta}$), 3.59 (1H, ddd, *J* = 9.8, 4.7, 2.1 Hz, $H_{5\beta}$) ppm; **^{19}F NMR** (471 MHz, CD_3OD) δ -196.9– -197.2 (m, a doublet of quintets with *J* = 54.4, 13.6 Hz is observed, $F_{3\beta}$), -200.7– -201.0 (m, a doublet of triplets with *J* = 51.5, 14.3 Hz is observed, $F_{2\alpha}$ or $F_{4\alpha}$), -201.7 (dddt, *J* = 51.5, 15.7, 12.9, 2.9 Hz, $F_{2\beta}$ or $F_{4\beta}$), -202.4– -202.8 (2F, m, $F_{3\alpha}$ and $F_{2\beta}$ or $F_{4\beta}$), -203.1 (dtd, *J* = 50.0, 13.6, 2.1 Hz, $F_{2\alpha}$ or $F_{4\alpha}$) ppm.; **^{19}F{^{1}H} NMR** (471 MHz, CD_3OD) δ -197.1 (t, *J* = 12.9 Hz, $F_{3\beta}$), -200.9 (dd, *J* = 12.2, 2.1 Hz, $F_{2\alpha}$ or $F_{4\alpha}$), -201.7 (dd, *J* = 12.9, 2.9 Hz, $F_{2\beta}$ or $F_{4\beta}$), -202.6 (dd, *J* = 12.2, 2.9 Hz, $F_{2\beta}$ or $F_{4\beta}$), -202.7 (t, *J* = 12.9 Hz, $F_{3\alpha}$), -203.1 (dd, *J* = 12.9, 2.1 Hz, $F_{2\alpha}$ or $F_{4\alpha}$) ppm. To obtain a ^{13}C NMR spectrum with all carbon atoms clearly visible, acetone-*d*$_6$ was used as solvent (due to the low solubility of **1** in $CDCl_3$, we did not obtain a high-quality spectrum): **^{13}C{^{1}H} NMR** (101 MHz, acetone-*d*$_6$) δ 93.7 (ddd, *J* = 22.7, 10.3, 1.5 Hz, $C_{1\beta}$), 92.7 (dt, *J* = 185.6, 19.8 Hz, $C_{3\beta}$), 91.2 (ddd, *J* = 187.8, 17.6, 8.1 Hz, $C_{2\beta}$), 91.1 (ddd, *J* = 185.6, 20.5, 19.8 Hz, $C_{3\alpha}$), 90.0 (dd, *J* = 21.3, 10.3 Hz, $C_{1\alpha}$), 88.0 (ddd, *J* = 189.3, 14.7, 8.1 Hz, $C_{2\alpha}$), 86.9 (ddd, *J* = 184.1, 17.6, 8.1 Hz, $C_{4\beta}$), 86.9 (ddd, *J* = 182.7, 18.3, 7.3 Hz, $C_{4\alpha}$), 72.6 (dd, *J* = 23.5, 5.9 Hz, $C_{5\beta}$), 68.6 (dd, *J* = 23.5, 5.9 Hz, $C_{5\alpha}$), 60.0 (s, $C_{6\beta}$), 59.9 (s, $C_{6\alpha}$) ppm; **HRMS** (ESI-) for $C_6H_8F_3O_3$ $[M-H]^-$ Calcd. 185.0426, Found. 185.0435. The literature

NMR data are reported in $CDCl_3$ (^{1}H NMR without *J* values); otherwise the data above are consistent with the literature.[15]

Data for 2,3,4-trideoxy-2,3,4-trifluoro-D-galactopyranose **8** (while solid): **Rf** 0.12 (pentane/EtOAc 60:40); **Mp** 114-116 °C ($CHCl_3$/acetone); **$[\alpha]_D$** +62.4 for (c 0.21, CD_3OD, 21 °C; sample equilibrated for 48h, α/β 1.00:0.64 at time of measurement), lit[17] +58.9 for (c 0.6, MeOH, 25 °C); **IR** (neat) 3362 (w, br.), 3134 (w, br.), 2961 (w), 1159 (m), 1059 (s) cm^{-1}; **^{1}H NMR** (500 MHz, acetone-*d*$_6$) δ 6.46 (1H, br. d, *J* = 7.2 Hz, $OH_{1\beta}$), 6.28 (1H, br. d, *J* = 4.5 Hz, $OH_{1\alpha}$), 5.47 (1H, q, *J* = 4.4 Hz, $H_{1\alpha}$), 5.18 (1H, ddddd, *J* = 51.4, 7.6, 3.7, 3.0, 0.7 Hz, $H_{4\alpha}$), 5.19–5.04 (1H, m, $H_{4\beta}$), 5.13–4.87 (3H, m, $H_{3\alpha}$ + $H_{3\beta}$ + $H_{1\beta}$), 4.86–4.70 (1H, m, a doublet with *J* = 51.2 Hz is observed, $H_{2\alpha}$), 4.47 (1H, ddddd, *J* = 52.6, 13.2, 9.1, 7.7, 1.2 Hz, $H_{2\beta}$), 4.22–4.11 (2H, m, $OH_{6\beta}$ + $H_{5\alpha}$), 4.11 (1H, dd, *J* = 6.5, 5.1 Hz, $OH_{6\alpha}$), 3.78 (1H, dddd, *J* = 27.0, 7.5, 5.4, 1.8 Hz, $H_{5\beta}$), 3.73–3.61 (4H, m, $H_{6,6'\alpha}$ + $H_{6,6'\beta}$) ppm; **^{1}H{^{19}F} NMR** (500 MHz, acetone-*d*$_6$) δ 6.46 (1H, d, *J* = 7.1 Hz, $OH_{1\beta}$), 6.28 (1H, br. dd, *J* = 4.5, 0.6 Hz, $OH_{1\alpha}$), 5.47 (1H, t, *J* = 4.2 Hz, $H_{1\alpha}$), 5.18 (1H, br. d, *J* = 3.0 Hz, $H_{4\alpha}$), 5.11 (1H, br. d, *J* = 3.4 Hz, $H_{4\beta}$), 5.08 (1H, dd, *J* = 9.5, 2.9 Hz, $H_{3\alpha}$), 4.97 (1H, dd, *J* = 9.2, 3.2 Hz, $H_{3\beta}$), 4.88 (1H, t, *J* = 7.4 Hz, $H_{1\beta}$), 4.78 (1H, br. dd, *J* = 9.6, 3.8 Hz, $H_{2\alpha}$), 4.47 (1H, dd, *J* = 9.2, 7.7 Hz, $H_{2\beta}$), 4.19 (1H, br. dd, *J* = 6.1, 5.4 Hz, $OH_{6\beta}$), 4.16 (1H, br. t, *J* = 6.9 Hz, $H_{5\alpha}$), 4.10 (1H, dd, *J* = 6.4, 5.1 Hz, $OH_{6\alpha}$), 3.78 (1H, dd, *J* = 7.7, 6.0 Hz, $H_{5\beta}$), 3.75–3.61 (4H, m, $H_{6,6'\alpha}$ + $H_{6,6'\beta}$) ppm; **^{13}C{^{1}H} NMR** (101 MHz, acetone-*d*$_6$) δ 94.1 (dd, *J* = 22.7, 10.3 Hz, $C_{1\beta}$), 90.9 (dd, *J* = 184.9, 18.3 Hz, $C_{2\beta}$), 90.5 (dd, *J* = 20.5, 9.5 Hz, $C_{1\alpha}$), 89.8 (ddd, *J* = 188.5, 19.1, 17.6 Hz, $C_{3\beta}$), 87.9 (ddd, *J* = 181.2, 16.1, 8.8 Hz, $C_{4\alpha}$), 87.4 (ddd, *J* = 187.8, 19.1, 17.6 Hz, $C_{3\alpha}$), 87.1 (ddd, *J* = 181.9, 16.1, 8.8 Hz, $C_{4\beta}$), 87.0 (ddd, *J* = 187.8, 17.6, 2.2 Hz, $C_{2\alpha}$), 72.6 (dd, *J* = 17.6, 5.1 Hz, $C_{5\beta}$), 68.7 (ddd, *J* = 19.1, 3.7, 1.5 Hz, $C_{5\alpha}$), 59.3 – 59.0 (m, $C_{6\alpha}$ + $C_{6\beta}$) ppm; **^{19}F NMR** (471 MHz, acetone-*d*$_6$) δ -202.7 (dqd, *J* = 47.7, 14.1, 6.4 Hz, $F_{3\beta}$), -207.7 (dtt, *J* = 52.2, 13.8, 3.6 Hz, $F_{2\beta}$ or $F_{4\beta}$), -207.9 – -208.1 (m, a doublet with *J* = 48.6 Hz is observed, $F_{3\alpha}$), -

208.7 (dddd, J = 51.5, 13.6, 12.2, 3.6 Hz, $F_{2\alpha}$ or $F_{4\alpha}$), -219.5– -219.8 (m, a doublet of triplets of doublets with J = 51.0, 26.5, 15.7 Hz is observed, $F_{2\beta}$ or $F_{4\beta}$), -222.3– -222.6 (m, a doublet of triplets of doublets with J = 52.2, 28.6, 15.1 Hz is observed, $F_{2\alpha}$ or $F_{4\alpha}$) ppm; **^{19}F{^{1}H} NMR** (471 MHz, acetone-d_6) δ -202.7 (dd, J = 15.0, 13.6 Hz, $F_{3\beta}$), -207.7 (d, J = 14.3 Hz, $F_{2\beta}$ or $F_{4\beta}$), -208.0 (dd, J = 15.0, 13.6 Hz, $F_{3\alpha}$), -208.7 (d, J = 13.6 Hz, $F_{2\alpha}$ or $F_{4\alpha}$), -219.7 (d, J = 15.0 Hz, $F_{2\beta}$ or $F_{4\beta}$), -222.5 (d, J = 15.0 Hz, $F_{2\alpha}$ or $F_{4\alpha}$) ppm. NMR data match those previously reported.[17]

-1,6-Anhydro-2,4-dideoxy-2,4-difluoroglucose **14a** from **13** (Scheme 4).

To a solution of **13**[27-28] (4.04 g, 13.5 mmol) in ethylene glycol (34 mL) were added KHF_2 (6.34 g, 81.2 mmol) and KF (4.72 g, 81.4 mmol). The resulting mixture was stirred for 2 h in a setup let open to the air at 170 °C before being allowed to cool down and loaded onto a silica gel column ($CHCl_3$/acetone 70:30), which afforded pure 2,4-difluoro levoglucosan **14a** (1.21 g, 7.29 mmol, 54%) as slightly orange crystals. **Rf** 0.38 (petroleum ether/acetone 70:30). **Mp** 96-98 °C (chloroform/acetone), lit[53] 99-100 °C (no solvent given); **[α]$_D$** -63.0 (c 0.82, water, 21 °C), lit[11] -62 (c 0.82, water, 20 °C); **IR** (neat) 3454 (w, br.), 2961 (w), 1038 (s), 1016 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.61 (1H, br. dt, J = 3.8, 1.4 Hz, H_1), 4.78 (1H, br. ddq, J = 12.9, 5.7, 1.3 Hz, H_5), 4.45 (1H, m, J = 46.4 Hz is observed, H_4), 4.30 (1H, br. dquin, J = 46.4, 1.3 Hz, H_2), 4.11 (1H, m, J = 18.0 Hz can be extracted, H_3), 4.04 (1H, dt, J = 7.8, 0.9 Hz, H_{6endo}), 3.80 (1H, m, H_{6exo}), 2.30 (1H, br. d, J = 6.1 Hz, OH_3) ppm; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 99.3 (d, J = 28.6 Hz, C_1), 89.9 (dd, J = 181.9, 5.1 Hz, C_4), 88.0 (dd, J = 184.1, 4.4 Hz, C_2), 74.3 (d, J = 22.7 Hz, C_5), 69.5 (dd, J = 29.3, 27.9 Hz, C_3), 64.7 (d, J = 9.5 Hz, C_6) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -183.3 (m, J = 46.3, 17.3, 12.8, 4.1, 0.9 Hz, F_4), -188.4 (ddd, J = 46.5, 18.4, 3.9 Hz, F_2) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ

-183.3 (s, F_4), -188.4 (s, F_2) ppm; **HRMS** (CI) for $C_6H_9F_2O_3$ $[M+H]^+$ Calcd. 167.05143, Found 167.05391. NMR data match those previously reported.[17]

-1,6-Anhydro-2,4-dideoxy-2,4-difluoroglucose **14a** from **17** (Scheme 4).

Following the same procedure as described just above, 2,4-di-*O*-tosyl levoglucosan **17**[27-28] (8.36 g, 17.8 mmol) was converted into 2,4-difluoro levoglucosan **14a** (1.51 g, 9.09 mmol, 55%), obtained pure as a white solid after column chromatography (CH_2Cl_2/EtOAc 60:40).

-1,6-Anhydro-2,4-dideoxy-2,4-difluoroallose **21** (Scheme 5).

To a round-bottom flask were added 2,4-difluoro levoglucosan **14a** (790 mg, 4.76 mmol) and anhydrous CH_2Cl_2 (78.3 mL). The resulting solution was cooled to 0 °C, followed by the addition of TCCA (2.19 g, 9.42 mmol) and TEMPO (40 mg, 0.256 mmol). The reaction mixture was stirred at room temperature for 2 h, and monitored by TLC analysis. Upon completion, the mixture was filtered over Celite, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was eluted over a pad of silica gel (acetone/CH_2Cl_2 10/90-20/80) to afford a mixture of the 3-uloside **18** and its hydrate form **20**. Following a modified literature procedure,[37] this mixture (~4.76 mmol) was dissolved in EtOH (reagent grade, 25 mL), followed by slow addition of a solution of $NaBH_4$ (540 mg, 14.27 mmol) in EtOH (25 mL). The reaction mixture was stirred at room temperature for 2 h, and then monitored by $^{19}F\{^1H\}$ NMR analysis. Upon completion, acetic acid (1 mL) was slowly added to the reaction mixture, and the solvent was then removed by evaporation under reduced pressure. The residue was diluted with water (100 mL), and extracted with EtOAc (100 mL × 7). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. $^{19}F\{^1H\}$

NMR analysis of the crude mixture indicated that reduction of the ketone was highly diastereoselective (*de* ≈99%, see Supporting Information). The crude mixture was purified by flash chromatography (acetone/CH_2Cl_2 10/90) to afford the desired product **21** (670 mg, 4.03 mmol, 85%) as a white solid. An analytical sample of pure **21** was obtained by HPLC (CH_2Cl_2/EtOAc 70:30), as a white solid. **Rf** 0.70 (CH_2Cl_2/acetone 70:30); **Mp** 108-110 °C (hexane/CH_2Cl_2), lit[37] 113-115 °C (EtOAc); **[α]D** -69.0 (c 1.06, MeOH, 24 °C), lit[37] -85 (c 0.6, $CHCl_3$, 23-25 °C); **IR** (neat) 3265 (m, br.), 2989 (w), 2915 (w), 1339 (m), 1033 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.67 (1H, br. t, *J* =2.1 Hz, H_1), 4.90–4.83 (1H, m, H_5), 4.68 (1H, m, *J* =48.5 Hz is observed, H_4), 4.57 (1H, m, *J* =49.8 Hz is observed, H_2), 3.92–3.75 (1H, m, H_{6exo}), 3.84 (1H, m, *J* = 12.4, 4.2 Hz is observed, H_3), 3.72 (1H, br. dt, *J* =8.4, 1.1 Hz, H_{6endo}), 2.73 (1H, dt, *J* = 12.4, 2.3 Hz, OH_3) ppm; **^{1}H{^{19}F} NMR** (500 MHz, $CDCl_3$) δ 5.67 (1H, d, *J* = 2.6 Hz, H_1), 4.87 (1H, m, H_5), 4.68 (1H, br. t, *J* = 3.4 Hz, H_4), 4.57 (1H, ddd, *J* = 4.1, 2.8, 1.1 Hz, H_2), 3.84 (1H, dt, *J* = 12.1, 4.1 Hz, H_3), 3.83 (1H, dd, *J* = 8.6, 5.6 Hz, H_{6exo}), 3.72 (1H, dd, *J* = 8.4, 1.0 Hz, H_{6endo}), 2.73 (1H, d, *J* = 12.4 Hz, OH_3) ppm; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 98.5 (d, *J* = 24.2 Hz, C_1), 88.0 (d, *J* = 184.9 Hz, C_2), 86.5 (d, *J* = 184.9 Hz, C_4), 73.6 (d, *J* = 19.1 Hz, C_5), 63.7 (d, *J* = 6.6 Hz, C_6), 62.8 (t, *J* = 18.3 Hz, C_3) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -204.8 (m, F_4), -207.0 (br. dddt, *J* = 49.9, 25.6, 8.9, 2.3 Hz, F_2) ppm; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ -204.8 (d, *J* = 9.3 Hz, F_4), -207.0 (d, *J* = 9.3 Hz, F_2) ppm; **HRMS** (CI) for $C_6H_9F_2O_3$ $[M+H]^+$ Calcd. 167.05143, Found 167.05425.

- 1,6-Anhydro-3-*O*-trifluoromethanesulfonyl-2,4-dideoxy-2,4-difluoroallose **22a** (Scheme 5).

To a solution of a 8:92 mixture of **14a**/**21** (205 mg, 1.23 mmol, 1.13 mmol of **21**) in dry CH_2Cl_2 (3.2 mL) at 0 °C was added pyridine (0.12 mL, 1.48 mmol). Stirring was continued at 0 °C for 10 min before Tf_2O (0.21 mL, 1.26 mmol) was added. The resulting mixture was

allowed to warm to rt and stirred for an additional hour before being filtered through a pad of silica. Solvent was removed under vacuum and the resulting orange oil purified by column chromatography (hexane/CH_2Cl_2 80:20 to 60:40) which afforded 218 mg (0.73 mmol, 65%) of compound **22a** as a white solid. **Rf** 0.24 (pentane/ CH_2Cl_2 50:50). **Mp** 108-110 °C (pentane/CH_2Cl_2); **[α]D** -50.2 (c 0.52, $CHCl_3$, 22 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.71 (1H, br. t, *J* 2.2 Hz, H_1), 4.95–4.91 (1H, m, H_5), 4.90 (1H, m, *J* 24.3, 3.9 Hz is observed, H_3), 4.87 (1H, m, *J* 50.9 Hz is observed, H_4), 4.75 (1H, m, *J* 50.3 Hz is observed, H_2), 3.88 (1H, m, *J* 8.6, 5.1, 2.2 Hz is observed, H_{6exo}), 3.80 (1H, br. dt, *J* 8.9, 1.0 Hz, H_{6endo}) ppm; **^{1}H{^{19}F} NMR** (500 MHz, $CDCl_3$) δ 5.71 (1H, d, *J* 2.8 Hz, H_1), 4.94 (1H, br. dd, *J* 4.8, 2.7 Hz, H_5), 4.90 (1H, t, *J* 3.8 Hz, H_3), 4.88–4.84 (1H, m, H_4), 4.76 (1H, m, *J* 3.9, 2.6, 1.4 Hz is observed, H_2), 3.88 (1H, dd, *J* 8.8, 5.6 Hz, H_{6exo}), 3.80 (1H, dd, *J* 8.8, 0.9 Hz, H_{6endo}) ppm; **^{13}C{^{1}H) NMR** (101 MHz, $CDCl_3$) δ 118.3 (q, *J* 319.1 Hz, CF_3), 98.4 (d, *J* 23.5 Hz, C_1), 85.6 (d, *J* 195.1 Hz, C_4), 84.3 (d, *J* 197.3 Hz, C_2), 75.7 (t, *J* 16.9 Hz, C_3), 73.9 (d, *J* 19.1 Hz, C_5), 63.7 (d, *J* 5.9 Hz, C_6) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.04 (s, CF_3), -202.1– -202.5 (m), -204.2 (ddd, *J* 50.3, 24.3, 10.4 Hz) ppm; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -75.0 (s, CF_3), -202.3 (d, *J* 10.4 Hz), -204.2 (d, *J* 10.4 Hz) ppm; **HRMS** (CI) for $C_7H_8F_5O_5S$ $[M+H]^+$ Calcd. 299.00071, Found 299.00012.

-1,6-Anhydro-2,3,4-trideoxy-2,3,4-trifluoroglucose **5a** from **21** (Scheme 5).

To a solution of **21** containing 4% of **14a** (335 mg, 2.02 mmol, 1.94 mmol of **21**) in anhydrous THF (5.7 mL) in a sealed tube reactor was added triethylamine (1.62 mL, 11.6 mmol, 5.8 equiv), Et_3N•3HF (0.63 mL, 3.86 mmol), and NfF (0.65 mL, 3.92 mmol). The resulting mixture was stirred at 90 °C for 4 days before being quenched with sat. aq. $NaHCO_3$ (17 mL). The layers were separated and the aqueous phase was diluted with water (20 mL) to

dissolve the large amount of salts formed during quenching, and extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under vacuum. Purification by column chromatography (pentane/DCM 90:10 to 50:50) afforded **5a** (222 mg, 1.34 mmol, 69%) as a white solid, as well as unreacted **14a** (10 mg). **Rf** 0.64 (pentane/EtOAc 80:20); **Mp** 66-68 °C (hexane/CH_2Cl_2); **$[\alpha]_D$** -53.8 (c 1.30, $CHCl_3$, 24 °C), lit[14] -56.0 (c 1.32, $CHCl_3$, 22 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 (1H, br. s, H_1), 4.85–4.78 (1H, m, H_5), 4.83 (1H, dtquin, *J* = 42.5, 15.2, 1.7 Hz, H_3), 4.57 (1H, ddd, *J* = 44.7, 14.9, 1.2 Hz, H_4), 4.43 (1H, ddd, *J* = 45.5, 15.2, 1.2 Hz, H_2), 3.97 (1H, dd, *J* = 8.1, 1.0 Hz, H_{6endo}), 3.90–3.78 (1H, m, H_{6exo}) ppm; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 98.6 (dd, *J* = 28.6, 2.2 Hz, C_1), 87.2 (dt, *J* = 178.3, 33.7 Hz, C_3), 86.4 (ddd, *J* = 182.7, 31.5, 4.4 Hz, C_4), 84.5 (ddd, *J* = 182.7, 27.9, 3.7 Hz, C_2), 73.5 (dd, *J* = 21.6, 1.8 Hz, C_5), 64.1 (dd, *J* = 9.2, 2.6 Hz, C_6) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -188.0 (ddtd, *J* = 44.8, 15.7, 10.9, 4.3 Hz, F_4), -191.1 (dquin, *J* = 42.4, 14.1 Hz, F_3), -193.6 (m, *J* = 45.1 Hz is observed, F_2) ppm; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -188.0 (d, *J* = 12.1 Hz, F_4), -191.1 (t, *J* = 12.1 Hz, F_3), -193.6 (1F, d, *J* = 12.1 Hz, F_2) ppm. ^{13}C NMR matches the literature data (pyridine d_5).[14]

-2,3,4-Trideoxy-2,3,4-trifluoro-D-glucopyranose **1** from pure **5a** (Scheme 5).

To a solution of trifluoro levoglucosan **5a** (124 mg, 0.74 mmol) in CH_2Cl_2 (5.1 mL) at 0 °C was added BCl_3 (1 M in CH_2Cl_2, 3.1 mL, 3.1 mmol) dropwise. The resulting mixture was stirred at rt for 2 h before being quenched with water (7 mL). DCM was then removed under reduced pressure and the resulting aqueous phase was stirred for an additional 1 h at rt. The remaining water was evaporated to give a brown dense oil, which was then purified by column chromatography (pentane/acetone 90:10 to 60:40) to afford 119 mg of trifluoroglucose **1** (0.64 mmol, 87%) as a dense clear oil which solidified upon standing.

Supporting Information: Copies of NMR spectra, ratio determination for the DAST reaction of **4** and reduction of **18**, tables with the relative Gibbs energy and populations of the energetic minima of **21** and discussion about the coupling constant analysis, CIF files and X-ray data of compounds **1**, **5a**, **8**, and **21**, and crystal packing discussion for **14a** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org/. The raw NMR data files are available free of charge at http://dx.doi.org/xxxxxxxxxxxxxxx

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