Note

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 18 Apr 2017

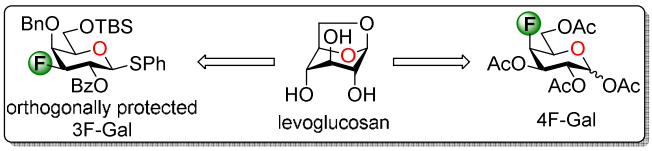
Synthesis of protected 3-deoxy-3-fluoro and 4-deoxy-4-fluoro-D-galactopyranosides from levoglucosan

Danny Lainé, Vincent Denavit and Denis Giguère*

PROTEO, RQRM, Département de Chimie, 1045 av. De la Médecine, Université Laval, Québec City, Qc, Canada G1V 0A6

Abstract

Fluorinated carbohydrates are invaluable tools to study various biochemical processes. Herein, we describe a new strategy to access orthogonally protected 3-deoxy-3-fluoro-galactopyranose and acetylated 4-deoxy-4-fluoro-galactopyranose. Starting from inexpensive levoglucosan, most reactions were performed on gram scale, allowed excellent regio- and stereocontrol with a minimal use of protection/deprotection cycles. Hence, we developed practical alternatives to the decade-long reported method to access both 3-deoxy-3-fluoro- and 4-deoxy-4-fluoro-galactopyranose.



Carbohydrates bearing a fluorine atom in replacement of a hydroxyl group have found applications in biochemical investigations (lectin-carbohydrate interactions, mechanistic probes, etc.)[1] and radiolabeling.[2] More recently, fluorinated carbohydrates were used to investigate the intramolecular hydrogen bonding properties of CHF and CF_2 groups[3] and

an innovative logP determination method was developed to show the influence of deoxy-fluorination on carbohydrate lipophilicity.[4]

The synthesis of fluorinated carbohydrates is hampered by the many hydroxyl groups' protection/deprotection steps and the low nucleophilicity of fluoride ions. Additionally, chemical processes are often tedious and time consuming due to fluorinating reagents-driven side reactions (namely eliminations). Importantly, the deoxyfluorination reaction is widely used in carbohydrate chemistry and usually occurs with inversion of configuration. Diethylaminosulfur trifluoride (DAST) is a common reagent for the preparation of fluorinated carbohydrates and its application on a wide range of substrates is well-documented.[5] As part of our program related to the synthesis of fluorinated galactosyl residues, our attention was turned towards the synthesis of 3-deoxy-3-fluoro and 4-deoxy-4-fluoro-galactopyranoses, as these motifs represent relevant glycomimetics. Remarkably, 3-deoxy-3-fluoro-galactopyranoses have been used as molecular probes,[6] involved in glycoside hydrolysis studies[7] and complex oligosaccharide syntheses.[6c–e, h] Despite their importance, no methods are currently available for the preparation of orthogonally protected 3-deoxy-3-fluoro-galactopyranoses. Hence, there is a major need to develop an efficient synthetic path to access 3-fluorinated galactopyranoside building blocks with orthogonal protecting groups at the *O*-2, *O*-4, and *O*-6 positions. As for 4-deoxy-4-fluoro-galactopyranoses, they are invaluable probes used over the years to study various biochemical processes.[8]

Figure 1 shows the synthetic strategies used to access 3-deoxy-3-fluoro and 4-deoxy-4-fluoro-galactopyranoses. The first synthesis of 3-deoxy-3-fluoro-galactopyranose was reported in the late 60s and used 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose **1** as an expensive starting material (**Figure 1a**).[9] Optimization of this process was proposed a few years later,[10] but a more convenient access to the gulofuranose framework was described starting from glucose **2**, requiring hydroxyl inversion at C-4 and fluorine installation with retention of configuration at C-3.[11] To the best of our knowledge, this is

the only known synthetic route to access 3-deoxy-3-fluoro-galactopyranose derivatives;[12] attempt to develop a new synthetic path proved to be unsuccessful (deoxyfluorination of methyl 2,4,6-tri-*O*-benzyl-α-D-gulopyranoside resulted in complex mixtures).[13]

Two distinct approaches were reported regarding the preparation of 4-deoxy-4-fluoro-galactopyranoses (**Figure 1b**). The first one involved a selective trityl protection of the *O*-6 hydroxyl group of methyl glucoside (**3**), followed by selective nucleophilic deoxyfluorination using DAST.[14] This approach was not reproducible on large scale in our hands and generated numerous side products. The second approach involved a one-pot selective 1,2,3,6-protection of glucopyranose (**4**), followed by the aforementioned DAST-mediated deoxyfluorination.[15] This transformation was also carried out through activation of the free *O*-4 hydroxyl group of compound **4** as either a triflate,[16] tosylate[17] or mesylate,[18] prior nucleophilic fluorination using TBAF (tetrabutylammonium fluoride). It is worth mentioning that TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate) [19] and Amberlyst A-26 resin (F^- form)[13, 20] have also been used as fluorinating reagents in this context. The one-pot selective 1,2,3,6-protection of glucopyranose is quite difficult to achieve[16, 21] thus, the most common approach to these motifs are from *i*) an inversion of the C-4 hydroxyl group of a selectively protected galactosyl derivative **5**[22] or *ii*) a selective benzylidene opening from compound **6**.[11b, 23] In a nutshell, the preparation of 4-deoxy-4-fluoro-galactopyranoses is lengthy and affected by many protection/deprotection steps. Also, the group of Liang recently reported that transformation of intermediate **4** (with benzyl ether as protecting group (PG)) into 4-deoxy-4-fluoro-galactopyranoses was not possible using DAST since an unexpected furanoside by-product was isolated instead.[24] Consequently, the discovery of new synthetic routes to access 3- and 4-fluorinated galactosyl derivatives is thus deemed necessary.

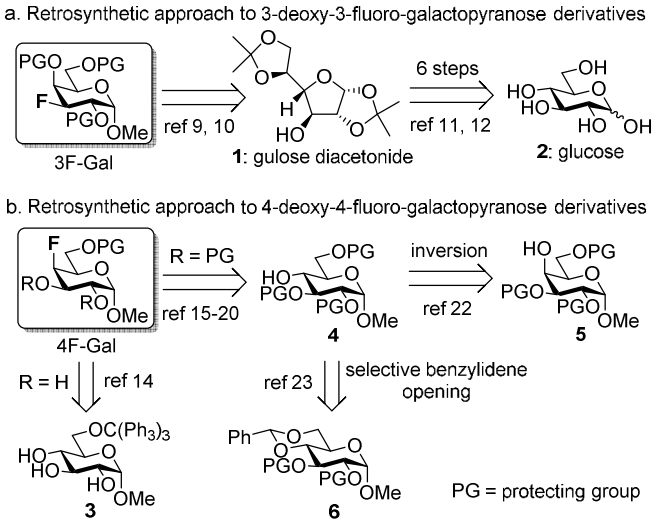


Figure 1. Retrosynthetic approaches to a) 3-deoxy-3-fluoro-galactopyranoses and b) 4-deoxy-4-fluoro-galactopyranoses

We aimed to develop a new synthetic route to 3-deoxy-3-fluoro and 4-deoxy-4-fluoro-galactopyranoses that could operate at a large scale, and comply with the following criteria involving: *i*) inexpensive starting materials; *ii*) satisfactory regio- and stereocontrols; *iii*) a minimal use of protection/deprotection cycles; *iv*) no tedious purifications. The intended synthetic purpose was centred around the development of a practical alternative to the known decade-long reported method.[9, 14] Furthermore, because 3-deoxy-3-fluoro-galactopyranose has found multiple applications in oligosaccharide synthesis, an orthogonally protected building block would be ideal. **Figure 2** shows our retrosynthetic analysis to orthogonally protected 3-fluoro derivative **7** and 4-fluoro derivative **8** from commercially available 1,6-anhydro-β-D-glucopyranose (levoglucosan) **12**. Fully protected compound **7** could be accessible from a chemoselective protection of 3-deoxy-3-fluoro-galactopyranose **9**. The latter is readily available from intermediate **10** through acetolysis and inversion of the *O*-4 hydroxyl group. The fluorine atom will be introduced stereoselectively through epoxide opening and functional group manipulations. Correspondingly, 4-deoxy-4-fluoro-galactopyranose **8** could be obtained *via* acetolysis and nucleophilic fluorination from intermediate **11**, readily accessible from

levoglucosan **12** by means of selective *p*-toluenesulfonylation. This strategy was preferred since the use of 1,6-anhydro core of levoglucosan avoided the preliminary protection of the *O*-6 and anomeric positions and could easily afford scalable fluorinated carbohydrates *via* simple experimental protocols.

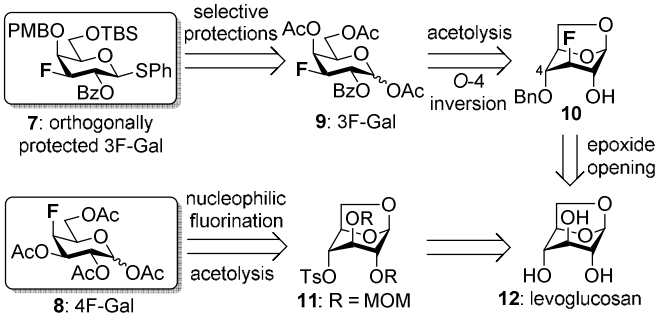
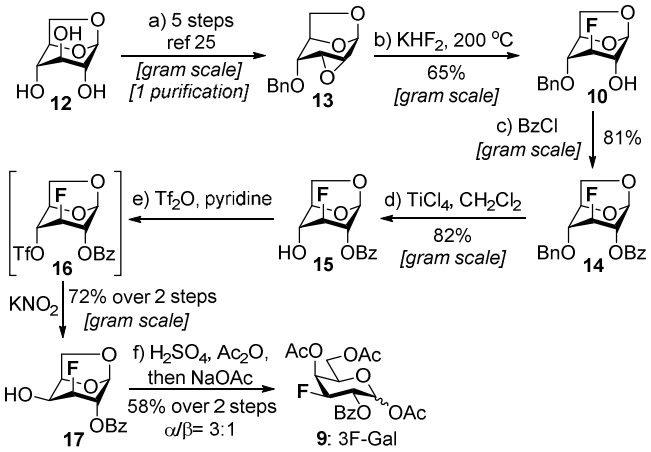


Figure 2. Retrosynthetic analysis of orthogonally protected 3-fluoro derivative **7** and 4-fluoro derivative **8** from levoglucosan **12**

The synthesis of 3-deoxy-3-fluoro-galactopyranose **7** is summarized in **Scheme 1**. Levoglucosan **12** was first converted to 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-allopyranose **13** on multi-gram scale through a known 5-step protocol requiring only one flash chromatography purification (see experimental section).[25] Fluorination of the latter was achieved *via* exposure to potassium hydrogen fluoride in ethylene glycol affording the desired 3-deoxy-3-fluoro-glucopyranose **10** in 65% yield. The rigid nature of the 1,6-anhydro core allowed a regioselective epoxide opening with the formation of only one fluorinated isomer as shown by the NMR of the crude reaction mixture.[26] Benzoylation of the free *O*-2 hydroxyl group generated compound **14** in high yield and was followed by $TiCl_4$ mediated benzyl deprotection of the 4-*O*-benzyl group.[27] Intermediate **15** was the perfect candidate for a Lattrell-Dax epimerization[28] allowing the preparation on gram scale of the desired 1,6-anhydro-galactopyranose derivative **17** *via* triflate **16**. Finally, the desired 1,4,6-tri-*O*-acetyl-2-*O*-benzoyl-3-deoxy-3-fluoro-D-galactopyranose **9** was generated from **17** through acetolysis (H_2SO_4, Ac_2O) followed by treatment with sodium

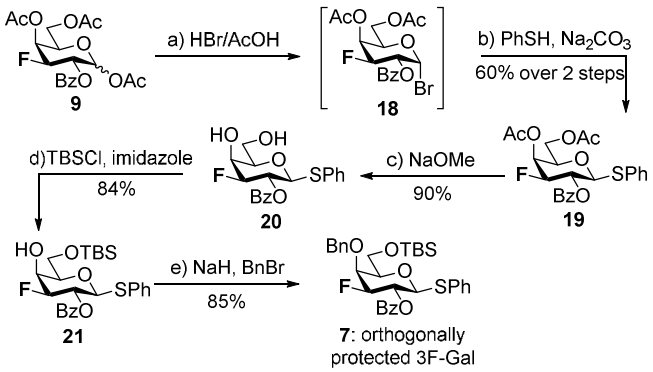
acetate (α/β = 3:1). Hence, with compound **9** in hand, the preparation of a useful orthogonally protected building block was the next task.



Scheme 1. Synthesis of 3-deoxy-3-fluoro-galactopyrane **9**: a) Reference 25; b) KHF_2 (6.1 equiv), ethylene glycol, 200 °C, 5 h, 65%; c) BzCl (3.0 equiv), pyridine, CH_2Cl_2, rt, 1 h, 81%; d) $TiCl_4$ (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 82%; e) (i) Tf_2O (2.3 equiv), pyridine, CH_2Cl_2, 0 °C to rt, 0.5 h; (ii) KNO_2 (3.0 equiv), DMF, rt, 24 h, 72% over 2 steps; f) (i) H_2SO_4 (10 equiv), Ac_2O (30 equiv), rt, 18 h; (ii) NaOAc (20 equiv), rt, 0.3 h, 58% over 2 steps, α/β = 3:1. Ac_2O = acetic anhydride, BzCl = benzoyl chloride, DMF = *N,N*-dimethylformamide, NaOAc = sodium acetate, Tf_2O = trifluoromethanesulfonic anhydride.

The efficient synthesis of orthogonally protected fluorinated monosaccharide building blocks could simplify the preparation of complex oligosaccharides. Consequently, the preparation of the corresponding 3-deoxy-3-fluoro thiogalactoside could be of great interest.[6c–e, h] With *O*-2 benzoate **9** in hand, functionalization of the anomeric position as thiophenol and chemoselective protections of the *O*-4 and *O*-6 hydroxyl groups could be straightforward (Scheme 2). Thus, treatment of compound **9** with 33% HBr in acetic acid resulted in formation of the α-galactosyl bromide **18**. The crude bromide product was

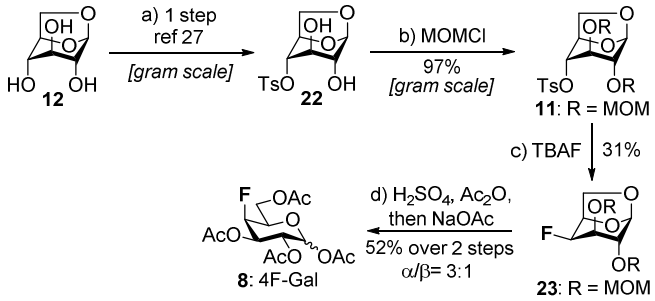
subjected to a phase transfer catalyzed nucleophilic displacements with thiophenol that occurred with complete anomeric inversion to afford the corresponding phenyl 1-thio-β-galactoside **19**. After selective de-*O*-acetylations with methanolic sodium methoxide (90% yield), diol **20** was submitted to sequential selective protections at *O*-4 and *O*-6. Hence, silylation at *O*-6 was achieved with TBSCl in 84% yield and benzylether formation at *O*-4 was then possible after treatment with NaH and benzyl bromide in 85% yield. To the best of our knowledge, compound **7** represents the first orthogonally protected phenyl 3-deoxy-3-fluoro-1-thio-β-galactoside donor and could be useful as a versatile building block towards complex oligosaccharide synthesis.



Scheme 2. Synthesis of orthogonally protected phenyl 3-deoxy-3-fluoro-1-thio-β-galactoside **7**: a) 33% HBr in AcOH, CH_2Cl_2, 0 °C to rt, 1.5 h; b) PhSH (3.0 equiv), TBAHS (1.0 equiv), EtOAc, 1 M Na_2CO_3, rt, 18 h, 60% over 2 steps; c) 1M NaOMe, MeOH, 0 °C to rt, 1.5 h, 90%; d) TBSCl (2.2 equiv), imidazole (1.5 equiv), DMF, 0 °C to rt, 3.0 h, 84%; e) NaH (2.0 equiv), BnBr (4.0 equiv), DMF, rt, 0.5 h, 85%. AcOH = acetic acid; BnBr = benzyl bromide; Bz = benzoate; PhSH = thiophenol; TBSCl = tert-butyldimethylsilyl chloride.

Levoglucosan is a useful synthetic starting material since 4-substituted derivatives can be selectively accessed in one synthetic step. The synthesis of 4-deoxy-4-fluoro-galactopyranose **8** was initiated with mono-*O*-*p*-toluenesulfonylation as previously described (**Scheme 3**).[29] Nucleophilic fluorination on tosylate **22** resulted only in

decomposition under various conditions. Thus, careful optimization led us to protect the hydroxyl groups as MOM ethers in 97% yield. Upon extensive experimentation, nucleophilic fluorination was achieved using excess TBAF in boiling THF for 3 days. Compound **23** was isolated in modest yield as an inseparable mixture, but this process was highly reproducible and could be done on large scale. The clear advantage of this new methodology is the simultaneous acetolysis and MOM ether hydrolysis under acidic conditions allowing formation of the desired 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-fluoro-D-galactopyranose **8**[8a] (α/β = 3:1).



Scheme 3. Synthesis of 4-deoxy-4-fluoro-galactopyranose **8**: a) Reference 29; b) MOMCl (10 equiv), DIPEA (11 equiv), CH_2Cl_2, 40 °C, 18 h, 97%; c) TBAF (10 equiv), THF, 66 °C, 72 h, 31%, based on 76% purity; d) (i) H_2SO_4 (10 equiv), Ac_2O (30 equiv), rt, 18 h; (ii) NaOAc (20 equiv), rt, 0.3 h, 52% over 2 steps, α/β = 3:1. Ac_2O = acetic anhydride, DIPEA = *N,N*-diisopropylethylamine, MOMCl = chloromethyl methyl ether, NaOAc = sodium acetate, TBAF = tetrabutylammonium fluoride.

New synthetic routes for the construction of 3-deoxy-3-fluoro- and 4-deoxy-4-fluoro-galactopyranoses were developed. To the best of our knowledge, these strategies are the only alternatives to the decade-long reported methods. Most reactions were performed on gram scale, allowed excellent regio- and stereocontrol and made minimal use of protection/deprotection cycles. The described strategy allowed the preparation of an orthogonally protected 3-deoxy-3-fluoro-galactopyranose building block that could be

useful in oligosaccharide synthesis. Finally, the development of new strategy to access fluorinated carbohydrates of biological interest will address the needs of the glycobiology field.

Experimental section

General information. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) was distilled from CaH2 and *N*,*N*′-dimethylformamide (DMF) from ninhydrin and kept over molecular sieves. Tetrahydrofuran (THF) was distilled from Na/benzophenone immediately before use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and charring with a solution of 3 g of PhOH and 5 ml of H_2SO_4 in EtOH, followed by heating with a heatgun. SiliaFlash® P60 40-63 μm (230 - 400 mesh) was used for flash column chromatography. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$: ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) as an internal reference. Coupling constants (*J*) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC) two-dimensional correlation spectroscopy. Infrared spectra were recorded using a Thermo Scientific Nicolet 380 FT-IR spectrometer. The absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were measured with an Agilent 6210 LC Time of Flight mass spectrometer in electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$ or ammonium adducts $[M + NH_4]^+$ were used for empirical formula confirmation.

Optical rotations were measured with a JASCO DIP-360 digital polarimeter, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

1,6:2,3-dianhydro-4-*O*-benzyl-β-D-allopyranose (**13**). To a stirred solution of 1,6-anhydro-4-*O*-benzyl-3-*O*-methanesulfonyl-2-*O*-(4-toluenesulfonyl)-β-D-glucopyranose (6.80 g, 14.03 mmol, 1.0 equiv) in CH_2Cl_2 (30 ml) at −18 °C, was added a solution of sodium methoxide (prepared from metalic sodium: 2.10 g, 91.20 mmol, 6.5 equiv) in methanol (70 ml). The mixture was slowly warmed up to rt over 2 h, then stirred for 20 h. The reaction was then neutralised with an aq. 10% HCl solution, and concentrated to removed the MeOH. The residue was diluted with CH_2Cl_2 (100 ml) and water (100 ml), then extracted with CH_2Cl_2 (2 × 100 ml). The combined organic phases were washed with water (200 ml) and brine (200 ml), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone/toluene, 1:9) to give a white solid (2.65 g, 10.12 mmol, 58% yield over 2 steps). The spectroscopic data derived from compound **13** match those reported in the literature.[25]

1,6-Anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (**10**). To a stirred solution of compound **13** (2.65 g, 11.321 mmol, 1.0 equiv) in ethylene glycol (95 mL) was added KHF_2 (5.39g, 69.06 mmol, 6.1 equiv). The mixture was heated under reflux (~200°C) for 5 h. After cooling, the reaction was quenched with an aqueous 5% solution of K_2CO_3 (200ml) and stirred for 5 minutes. The mixture was then extracted with CH_2Cl_2 (5 × 25 ml) and the combined organic phases were washed with water (3 × 15 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:3) to give **10** as a white amorphous solid (1.87 g, 7.36 mmol, 65% yield): R_f = 0.38 (silica, EtOAc:hexanes, 2:3); $[\alpha]_D^{25}$ = –47.1° (*c* 0.5, MeOH); IR (ATR, ZnSe) ν : 3434, 2962, 2870, 1415, 1321, 1078, 720 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ = 7.41 – 7.31 (m, 5H, Ar), 5.47 (t, *J* = 1.9 Hz, 1H, H1), 4.74 – 4.61 (m, 4H, C*H*$_2$Ph, H3, H5), 4.01 (dt, *J* = 7.7, 1.2 Hz, 1H, H6a), 3.80 (ddd, *J* = 7.7, 5.7, 2.2 Hz, 1H, H6b), 3.67 (tqd, *J* = 12.3, 1.7, 0.7 Hz, 1H, H2), 3.53 (dqd, *J* = 12.9, 1.8, 0.7 Hz, 1H, H4), 2.50 (ddd, *J* = 12.4, 2.1, 1.2 Hz,

1H, OH) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 136.9, 128.8, 128.5, 128.0 (6C, Ar), 101.4 (C1), 88.2 (d, *J* = 184.1 Hz, C3), 74.2 (d, *J* = 26.5 Hz, C4), 73.7 (C5), 71.8 (*C*H_2Ph), 67.4 (d, *J* = 23.7 Hz, C2), 65.1 (d, *J* = 4.7 Hz, C6) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ = –184.7 (dt, *J* = 44.2, 12.4 Hz, F3) ppm; HRMS calcd for $C_{13}H_{19}O_4NF^+$ $[M+NH_4]^+$ 272.1293 found 272.1300.

1,6-Anhydro-2-*O*-benzoyl-4-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (**14**). To a stirred solution of compound **10** (1.87 g, 7.359 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at 0 °C was added pyridine (25 mL) and benzoyl chloride (2.56 mL, 22.08 mmol, 3.0 equiv). The mixture was stirred at room temperature for 1 h and then quenched with a sat. aq. $NaHCO_3$ solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with an aq. 10% H_2SO_4 solution (2 × 50 mL), sat. aq. $NaHCO_3$ solution (2 × 50 mL) and brine (100 ml). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:4) to give **14** as a white amorphous solid (2.13 g, 5.94 mmol, 81% yield): R_f = 0.24 (silica, EtOAc:hexanes, 1:4): $[\alpha]_D^{25}$ = +27.6° (*c* 0.7, MeOH); IR (ATR, ZnSe) ν : 2903, 1717, 1269, 1098, 1011, 712, 698; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.10 – 8.06 (m, 2H, Ar), 7.63 – 7.55 (m, 1H, Ar), 7.46 – 7.41 (m, 2H, Ar), 7.38 – 7.29 (m, 5H, Ar), 5.59 (s, 1H, H1), 5.01 (d, *J* = 16.7 Hz, 1H, H2), 4.82 – 4.67 (m, 4H, C*H*$_2$Ph, H3, H5), 4.01 (d, *J* = 7.6 Hz, 1H, H6a), 3.82 (ddd, *J* = 7.6, 5.7, 1.8 Hz, 1H, H6b), 3.58 (d, *J* = 15.6 Hz, 1H, H4) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 165.5 (*C*OPh), 137.3, 133.7, 130.2, 129.3, 128.7, 128.6, 128.2, 128.0 (12C, Ar), 99.3 (C1), 88.2 (d, *J* = 181.1 Hz, C3), 75.1 (d, *J* = 26.2 Hz, C4), 74.3 (d, *J* = 1.4 Hz, C5), 71.9 (*C*H_2Ph), 69.4 (d, *J* = 27.8 Hz, C2), 65.5 (d, *J* = 3.2 Hz, C6) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ = –183.4 (dt, *J* = 43.8, 16.4 Hz, F3) ppm; HRMS calcd for $C_{20}H_{20}O_5F^+$ $[M+H]^+$ 359.1289 found 359.1307.

1,6-Anhydro-2-*O*-benzoyl-3-deoxy-3-fluoro-β-D-glucopyranose (**15**). To a stirred solution of compound **14** (2.11 g, 5.90 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C was added $TiCl_4$ (1 M in CH_2Cl_2, 6.5 ml, 1.1 equiv). The mixture was stirred at 0°C for 1 h and then quenched at 0°C with water (50 mL). The mixture was extracted with CH_2Cl_2 (3

× 30 mL) and the combined organic phases were washed with water (2 × 50 mL) and brine (50 ml). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give **15** as a white amorphous solid (1.29 g, 4.81 mmol, 82% yield); R_f = 0.33 (silica, EtOAc:hexanes, 1:1): $[\alpha]_D^{25}$ = +19.9° (*c* 0.6, MeOH); IR (ATR, ZnSe) ν : 3438, 2966, 2904, 1716, 1267, 1009, 713; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.06 – 8.01 (m, 2H, Ar), 7.64 – 7.58 (m, 1H, Ar), 7.50 – 7.44 (m, 2H, Ar), 5.61 (t, *J* = 1.7 Hz, 1H, H1), 5.01 (dq, *J* = 14.7, 1.4 Hz, 1H, H2), 4.75 – 4.64 (m, 2H, H3, H5), 4.19 (dt, *J* = 7.8, 1.2 Hz, 1H, H6a), 3.89 (ddd, *J* = 8.0, 5.8, 2.5 Hz, 1H, H6b), 3.85 (tq, *J* = 11.5, 1.9 Hz, 1H, H4), 2.72 (d, *J* = 11.4 Hz, 1H, OH) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 165.0 (*C*OPh), 133.9, 130.0, 129.0, 128.8 (6C, Ar), 99.3 (C1), 88.9 (d, *J* = 183.2 Hz, C3), 75.9 (C5), 68.5 (d, *J* = 28.5 Hz, C2), 67.9 (d, *J* = 27.2 Hz, C4), 65.0 (d, *J* = 4.8 Hz, C6) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ = –183.5 (dt, *J* = 43.6, 13.3 Hz, F3) ppm; HRMS calcd for $C_{13}H_{14}O_5F^+$ $[M+H]^+$ 269.0820 found 269.0824.

1,6-Anhydro-2-*O*-benzoyl-3-deoxy-3-fluoro-β-D-galactopyranose (**17**). To a stirred solution of compound **15** (1.08 g, 4.03 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) at 0 °C was added pyridine (3 mL) and Tf_2O (1.55 mL, 9.23 mmol, 2.3 equiv). The mixture was stirred at room temperature for 0.5 h and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (1 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Triflate **16** was used for the next step without further purification. To the crude triflate in DMF (20 ml) at room temperature was added KNO_2 (1.02 g, 12.03 mmol, 3.0 equiv). The mixture was stirred 24 h at room temperature, and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (40 mL), water (2 × 40 ml) and brine (40 ml). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **17** as a white amorphous solid (0.782 g, 2.92 mmol, 72% yield over two steps): R_f = 0.30 (silica, acetone:toluene, 5:95): $[\alpha]_D^{25}$ = +40.8° (*c* 0.2, MeOH); IR (ATR, ZnSe) ν : 3411, 2920, 2851, 1716, 1269, 1101, 708; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.08 – 8.01 (m, 2H, Ar), 7.64 – 7.57 (m, 1H, Ar), 7.52 – 7.43 (m, 2H,

Ar), 5.55 (t, *J* = 1.6 Hz, 1H, H1), 5.24 (dt, *J* = 13.4, 1.7 Hz, 1H, H2), 4.85 (ddq, *J* = 47.5, 4.6, 1.6 Hz, 1H, H3), 4.56 (t, *J* = 4.7 Hz, 1H, H5), 4.24 (d, *J* = 7.8 Hz, 1H, H6a), 4.17 (dt, *J* = 26.6, 4.4 Hz, 1H, H4), 3.77 (dd, *J* = 7.8, 5.2 Hz, 1H, H6b) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 165.0 (*C*OPh), 133.9, 130.1, 128.9, 128.7 (6C, Ar), 98.7 (C1), 88.5 (d, *J* = 179.7 Hz, C3), 74.2 (C5), 70.4 (d, *J* = 27.7 Hz, C2), 65.4 (d, *J* = 18.0 Hz, C4), 63.9 (d, *J* = 3.4 Hz, C6) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ = –204.2 (ddd, *J* = 47.6, 27.0, 13.6 Hz, F3) ppm; HRMS calcd for $C_{13}H_{13}O_5FNa^+$ [*M*+Na^+] 291.0639 found 291.0644.

1,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-3-deoxy-3-fluoro-α/β-D-galactopyranose (**9**). To a stirred solution of compound **17** (0.782 g, 2.92 mmol, 1.0 equiv) in Ac_2O (8.26 mL, 87.40 mmol, 30 equiv) at 0 °C was added H_2SO_4 (1.55 mL, 29.08 mmol, 10 equiv). The mixture was stirred at room temperature for 18 h. After this time, the mixture was cooled down to 0 °C and NaOAc (4.78 g, 58.27 mmol, 20 equiv) was added. The mixture was stirred for an additional 20 min and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were washed with water (1 × 50 mL) and brine (1 × 50 ml) and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone:toluene, 1:9) to give compound **9** (α/β, 1:3.4) as a white amorphous solid (0.694 g, 1.691 mmol, 58% yield): R_f = 0.42 (silica, acetone:toluene, 1:9); $[\alpha]_D^{25}$ = +82.2° (*c* 0.8, MeOH); IR (ATR, ZnSe) ν : 2960, 2878, 1736, 1208, 1010, 933, 710; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.05 – 7.97 (m, 4H, 2 × Arα, 2 × Arβ), 7.64 – 7.55 (m, 2H, 1 × Arα, 1 × Arβ), 7.49 – 7.42 (m, 4H, 2 × Arα, 2 × Arβ), 6.54 (t, *J* = 4.3 Hz, 1H, H1α), 5.83 (d, *J* = 8.3, 1H, H1β), 5.75 – 5.61 (m, 4H, H2α, H2β, H4α, H4β), 5.12 (ddd, *J* = 48.4, 10.2, 3.7 Hz, 1H, H3α), 4.84 (ddd, *J* = 47.4, 9.6, 3.8 Hz, 1H, H3β), 4.34 (tt, *J* = 6.6, 1.5 Hz, 1H, H5α), 4.23 (dd, *J* = 11.4, 6.4 Hz, 1H, H6aβ), 4.21 – 4.15 (m, 2H, H6aα, H6bβ), 4.11 (ddd, *J* = 11.4, 6.7, 1.3 Hz, 1H, H6bα), 4.06 (tt, *J* = 6.5, 1.6 Hz, 1H, H5β), 2.21 (s, 1H, COC*H*$_3$β), 2.20 (s, 3H, COC*H*$_3$α), 2.14 (s, 3H, COC*H*$_3$α), 2.08 (s, 1H, COC*H*$_3$β), 2.07 (s, 3H, COC*H*$_3$α), 2.06 (s, 1H, COC*H*$_3$β) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 170.6, 170.6, 170.0, 170.0, 169.2, 168.7, 165.6, 165.1 (8C, 3 × *C*OCH_3α, 3 × *C*OCH_3β, *C*OPhα, *C*OPhβ), 133.8, 133.8, 130.0, 129.9, 129.0, 128.7, 128.7 (12C, 6 × Arα, 6 × Arβ), 91.6 (d, *J* = 11.3 Hz, C1β), 90.0 (d, *J* = 9.1 Hz,

C1α), 89.0 (d, J = 195.7 Hz, C3β), 85.9 (d, J = 193.3 Hz, C3α), 71.3 (d, J = 5.8 Hz, C5β), 69.6 (d, J = 20.1 Hz, C2β), 68.8 (d, J = 5.3 Hz, C5α), 68.3 (d, J = 19.3 Hz, C2α), 67.5 (d, J = 16.9 Hz, C4α), 66.9 (d, J = 16.8 Hz, C4β), 61.4 (d, J = 2.3 Hz, C6α), 61.3 (d, J = 2.6 Hz, C6β), 20.9, 20.8 (6C, 3 × CO*C*H$_3$α, 3 × CO*C*H$_3$β) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ = –199.8 (ddd, J = 47.3, 11.6, 5.7 Hz, F3β), –203.5 (ddt, J = 48.5, 11.3, 5.7 Hz, F3α) ppm; HRMS calcd for $C_{19}H_{21}O_9FNa^+$ [M+Na]$^+$ 435.1062 found 435.1063.

Phenyl 4,6-di-*O*-acetyl-2-*O*-benzoyl-3-deoxy-3-fluoro-1-thio-β-D-galactopyranoside (**19**). To a stirred solution of compound **9** (11.8 mg, 0.03 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) at 0 °C was added a 33% wt solution of HBr in AcOH (0.1 mL). The mixture was stirred at room temperature for 90 min and then quenched with a sat. aq. $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (3 × 1 mL) and the combined organic phases were washed with brine (1 × 2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude bromide **18** was used for the next step whitout further purification. To a solution of the crude bromide in EtOAc (0.2 mL) at room temperature was added tetrabutylammonium hydrogen sulfate (TBAHS) (9.7 mg, 0.03 mmol, 1 equiv), thiophenol (10 μL, 0.09 mmol, 3 equiv) and a 1 M aq. Na_2CO_3 solution (0.2 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (2 mL) was added, and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic phases were washed with brine (1 × 2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:7) to give **19** as a white amorphous solid (7.9 mg, 0.0171 mmol, 60% yield); R_f = 0.27 (silica, EtOAc/hexanes, 3:7): $[\alpha]_D^{25}$ = +15.8° (*c* 0.3, MeOH); IR (ATR, ZnSe) ν : 2920, 2850, 1733, 1451, 1215, 1028, 707; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.09 – 8.06 (m, 2H, Ar), 7.64 – 7.59 (m, 1H, Ar), 7.51 – 7.46 (m, 4H, Ar), 7.32 – 7.27 (m, 3H, Ar), 5.64 (ddd, J = 5.9, 3.7, 1.1 Hz, 1H, H4), 5.57 (ddd, J = 11.2, 10.1, 9.3 Hz, 1H, H2), 4.81 (dd, J = 10.0, 0.9 Hz, 1H, H1), 4.81 (ddd, J = 47.5, 9.3, 3.7 Hz, 1H, H3), 4.24 – 4.17 (m, 2H, H6a, H6b), 3.95 (tdd, J = 7.0, 1.8, 1.1 Hz, 1H, H5), 2.16 (s, 3H, COC*H*$_3$), 2.08 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 170.6, 170.1 (2C, *C*OCH$_3$), 165.3 (1C, *C*OPh), 133.6, 133.0, 132.4, 130.1, 129.5, 129.0, 128.6, 128.5 (12C, Ar), 89.9 (d, J = 196.9 Hz, 1C, C3), 86.2 (d, J = 7.6 Hz, 1C,

C1), 74.3 (d, J = 5.4 Hz, 1C, C5), 68.9 (d, J = 19.6 Hz, 1C, C2), 67.4 (d, J = 16.7 Hz, 1C, C4), 61.9 (d, J = 2.6 Hz, 1C, C6), 20.9, 20.8 (2C, CO*C*H$_3$) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ = –195.2 (ddd, J = 47.1, 11.1, 5.6 Hz, F3) ppm; HRMS calcd for $C_{23}H_{24}O_7SF^+$ [*M*+H]$^+$ 463.1221 found 463.1240.

Phenyl 2-*O*-benzoyl-3-deoxy-3-fluoro-1-thio-β-D-galactopyranoside (**20**). To a stirred solution of compound **19** (25.7 mg, 0.06 mmol, 1.0 equiv) in MeOH (1.4 mL) at 0 °C was added a solution of sodium methoxide (1 M in MeOH) until pH = 8–9. The mixture was slowly warmed up to room temperature over 90 min. After this time, the mixture was neutralized to pH = 7 with acid resin (Amberlite IR-120), filtered and concentrated under reduced pressure. Compound **20** was isolated as a white amorphous solid (19.0 mg, 0.05 mmol, 90% yield) and used for the next step whitout further purification: R_f = 0.20 (silica, EtOAc:hexanes, 7:3): $[\alpha]_D^{25}$ = +32.3° (*c* 0.2, MeOH); IR (NaCl film) ν : 2962, 2921, 2854, 1724, 1262, 1069, 803; ^{1}H NMR: (500 MHz, $(CD_3)_2CO$) δ = 8.10 – 8.05 (m, 2H, Ar), 7.70 – 7.65 (m, 1H, Ar), 7.57 – 7.52 (m, 2H, Ar), 7.49 – 7.46 (m, 2H, Ar), 7.31 – 7.24 (m, 3H, Ar), 5.70 (ddd, J = 11.0, 10.0, 9.3 Hz, 1H, H2), 5.07 (dd, J = 10.0, 1.0 Hz, 1H, H1), 4.95 (ddd, J = 49.1, 9.3, 3.3 Hz, 1H, H3), 4.70 (d, J = 4.8 Hz, 1H, C$_4$O*H*), 4.41 – 4.37 (m, 1H, H4), 4.08 (t, J = 5.9 Hz, 1H, C$_6$O*H*), 3.89 – 3.79 (m, 3H, H5, H6a, H6b) ppm; ^{13}C NMR: (126 MHz, $(CD_3)_2CO$) δ = 165.8 (1C, *C*OPh), 135.0, 134.3, 131.8, 130.9, 130.4, 129.8, 129.5, 128.1 (12C, Ar), 93.4 (d, J = 189.0 Hz, 1C, C3), 86.3 (d, J = 7.9 Hz, 1C, C1), 79.4 (d, J = 6.3 Hz, 1C, C5), 70.1 (d, J = 19.1 Hz, 1C, C2), 68.1 (d, J = 16.6 Hz, 1C, C4), 61.8 (d, J = 2.9 Hz, 1C, C6) ppm; ^{19}F NMR: (470 MHz, $(CD_3)_2CO$) δ = –195.5 (ddd, J = 49.6, 11.3, 7.5 Hz, F3); HRMS calcd for $C_{19}H_{20}O_5SF^+$ [*M*+H]$^+$ 379.1010 found 379.1002.

Phenyl 2-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyloxy)-3-deoxy-3-fluoro-1-thio-β-D-galactopyranoside (**21**). To a stirred solution of compound **20** (11.1 mg, 0.03 mmol, 1.0 equiv) in DMF (1 mL) at 0 °C was added imidazole (3.0 mg, 0.04 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl chloride (9.6 mg, 0.06 mmol, 2.2 equiv). The mixture was stirred at room temperature for 4.5 h and then quenched with sat. aq. NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 × 1 mL) and the combined organic phases

were washed with brine (1 × 2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:4) to give **21** as a white amorphous solid (12 mg, 0.02 mmol, 84% yield); R_f = 0.35 (silica, EtOAc:hexanes, 1:4): $[\alpha]_D^{25}$ = +20.4° (*c* 0.6, MeOH); IR (NaCl film) ν : 2979, 2928, 2869, 1731, 1261, 1142, 708; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.11 – 8.03 (m, 2H, Ar), 7.67 – 7.55 (m, 1H, Ar), 7.53 – 7.42 (m, 4H, Ar), 7.30 – 7.26 (m, 3H, Ar), 5.64 (ddd, *J* = 11.3, 10.0, 9.1 Hz, 1H, H2), 4.79 (dd, *J* = 10.0, 1.0 Hz, 1H, H1), 4.70 (ddd, *J* = 48.7, 9.2, 3.2 Hz, 1H, H3), 4.37 (dt, *J* = 6.5, 3.0 Hz, 1H, H4), 4.00 (dd, *J* = 10.4, 6.1 Hz, 1H, H6a), 3.93 (ddd, *J* = 10.4, 5.0, 1.3 Hz, 1H, H6b), 3.60 (dd, *J* = 6.1, 5.1 Hz, 1H, H5), 2.73 (d, *J* = 3.4 Hz, 1H, $C_4O\mathit{H}$), 0.92 (s, 9H, $SiC(C\mathit{H}_3)_3$), 0.12 (s, 3H, $Si(C\mathit{H}_3)_2$), 0.11 (s, 3H, $Si(C\mathit{H}_3)_2$) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 165.3 (1C, *C*OPh), 133.4, 132.8, 132.7, 130.1, 129.8, 129.0, 128.6, 128.1 (12C, Ar), 92.8 (d, *J* = 190.8 Hz, 1C, C3), 86.2 (d, *J* = 7.7 Hz, 1C, C1), 77.5 (d, *J* = 6.0 Hz, 1C, C5), 69.0 (d, *J* = 19.5 Hz, 1C, C2), 67.9 (d, *J* = 16.7 Hz, 1C, C4), 62.4 (d, *J* = 2.8 Hz, 1C, C6), 26.0 (3C, $SiC(\mathit{C}H_3)_3$), 18.4 (1C, $Si\mathit{C}(CH_3)_3$), –5.3, (2C, $Si(\mathit{C}H_3)_2$) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ –194.5 (ddd, *J* = 48.8, 11.4, 7.0 Hz, F3); HRMS calcd for $C_{25}H_{34}O_5SFSi^+$ $[M+H]^+$ 493.1875 found 493.1867.

Phenyl 2-*O*-benzoyl-4-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyloxy)-3-deoxy-3-fluoro-1-thio-β-D-galactopyranoside (**7**). To a stirred solution of compound **21** (11 mg, 0.02 mmol, 1.0 equiv) in DMF (1 mL) at room temperature was added NaH (1.8 mg, 0.04, 2 equiv) and benzyl bromide (11 μL, 0.09 mmol, 4 equiv). The mixture was stirred at room temperature for 45 min. The reaction was then quenched with sat. aq. NH_4Cl solution (2 mL), and extracted with EtOAc (3 × 1 mL). The combined organic phases were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:9) to give **7** as a white amorphous solid (11 mg, 0.02 mmol, 85% yield): R_f = 0.34 (silica, EtOAc/hexanes, 1:9); $[\alpha]_D^{25}$ = +3.34° (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν : 2925, 2852, 1719, 1258, 1115, 854, 706; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.13 – 7.98 (m, 2H, Ar), 7.65 – 7.55 (m, 1H, Ar), 7.51 – 7.42 (m, 4H, Ar), 7.34 (d, *J* = 5.1 Hz, 4H, Ar), 7.31 – 7.27 (m, 1H, Ar), 7.25 – 7.19 (m, 3H, Ar), 5.71 (q, *J* = 9.9 Hz, 1H, H2),

4.79 (d, *J* = 9.9 Hz, 1H, H1), 4.78 (ddd, *J* = 48.7, 9.3, 3.0 Hz, 1H, H3), 4.78 (ABq, *J* = 166.0, 11.5 Hz, 2H, OC*H*$_2$Ph), 4.15 (dd, *J* = 7.1, 3.0 Hz, 1H, H4), 3.88 – 3.77 (m, 2H, H6a, H6b), 3.59 (dd, *J* = 7.1, 5.9 Hz, 1H, H5), 0.91 (s, 9H, SiC(C*H*$_3$)$_3$), 0.07 (s, 3H, Si(C*H*$_3$)$_2$), 0.07 (s, 3H, Si(C*H*$_3$)$_2$) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 165.3 (1C, *C*OPh), 138.5, 133.2, 133.1, 132.7, 130.4, 130.1, 128.9, 128.5, 128.4, 128.0, 127.9, 127.8 (18C, Ar), 94.2 (d, *J* = 194.2 Hz, 1C, C3), 86.2 (d, *J* = 7.5 Hz, 1C, C1), 78.8 (d, *J* = 6.7 Hz, 1C, C5), 75.0 (d, *J* = 3.8 Hz, 1C, O*C*H$_2$Ph), 74.3 (d, *J* = 15.2 Hz, 1C, C4), 69.9 (d, *J* = 19.0 Hz, 1C, C2), 61.6 (d, *J* = 2.4 Hz, 1C, C6), 26.1 (3C, SiC(*C*H$_3$)$_3$), 18.4 (1C, Si*C*(CH$_3$)$_3$), –5.2, –5.3 (2C, Si(*C*H$_3$)$_2$) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ –192.6 (dt, *J* = 48.8, 8.8 Hz, F3); HRMS calcd for $C_{32}H_{39}O_5SFSiNa^+$ [*M*+Na]$^+$ 605.2164 found 605.2164.

1,6-Anhydro-2,3-di-*O*-methoxymethyl-4-*O*-(4-toluenesulfonyl)-β-D-glucopyranose (**11**). To a stirred solution of compound **22**[29] (2.09 g, 6.61 mmol, 1.0 equiv) in CH_2Cl_2 (70.0 ml) was added *N,N*-diisopropylethylamine (12.7 ml, 72.57 mmol, 11 equiv) and chloromethyl methyl ether (5.0 ml, 65.83 mmol, 10 equiv). The mixture was stirred at 40 °C for 18 h and then quenched with water (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ solution (100 mL), water (100 ml) and brine (100 ml), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give **11** as a colorless oil (2.59 g, 6.40 mmol, 97% yield); R_f = 0.35 (silica, EtOAc:hexanes, 1:1): $[\alpha]_D^{25}$ = –43.1° (*c* 1.0, $CHCl_3$); IR (ATR, ZnSe) ν : 2951, 2897, 1359, 1175, 1035, 956, 814; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.1 Hz, 2H, Ar), 7.34 (d, *J* = 8.4 Hz, 2H, Ar), 5.44 (s, 1H, H1), 4.63 (s, 2H, OC*H*$_2$OCH$_3$), 4.57 (s, 2H, OC*H*$_2$OCH$_3$), 4.54 (d, *J* = 5.6 Hz, 1H, H5), 4.42 (s, 1H, H4), 4.03 (d, *J* = 7.6 Hz, 1H, H6), 3.85 – 3.82 (m, 1H, H3), 3.72 – 3.68 (m, 1H, H6), 3.49 (s, 1H, H2), 3.36 (s, 3H, OCH$_2$OC*H*$_3$), 3.31 (s, 3H, OCH$_2$OC*H*$_3$), 2.44 (s, 3H, ArC*H*$_3$) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 145.3, 133.7, 130.0, 128.0 (6C, Ar), 100.8 (1C, C1), 96.2, 96.1 (2C, O*C*H$_2$OCH$_3$), 77.0 (1C, C4), 74.0 (1C, C5), 73.42 (1C, C3), 73.35 (1C, C2), 64.9 (1C, C6), 56.0, 55.8 (2C, OCH$_2$O*C*H$_3$),

21.8 (1C, Ar*C*H$_3$) ppm; HRMS calcd for $C_{34}H_{52}O_{18}NS_2^+$ [2*M*+NH$_4$]$^+$ 826.2620 found 826.2600.

1,6-Anhydro-4-deoxy-4-fluoro-2,3-di-*O*-methoxymethyl-β-D-galactopyranose (**23**). Compound **11** (2.21 g, 5.46 mmol, 1.0 equiv) was stirred in tetrabutylammonium fluoride (1 M in THF, 55 ml, 10 equiv) under reflux for 72 h. After this time, water (50 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic phases were washed with sat. aq. $NaHCO_3$ solution (1 × 100 mL) and brine (1 × 100 ml), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc:hexanes, 2:3) to give **23** as a white amorphous solid (0.433 g, 31% yield, 76% purity). The inseparable mixture containing the desired fluoro product **23** was used for the next step without further purification. R_f = 0.51 (silica, EtOAc:hexanes, 2:3); ^{19}F NMR: (470 MHz, $CDCl_3$) δ –205.78 (dt, *J* = 44.8, 5.3 Hz, F4); HRMS calcd for $C_{10}H_{17}O_6FNa^+$ [*M*+Na]$^+$ 275.0901 found 275.0897.

1,2,3,6-Tetra-*O*-acetyl-4-deoxy-4-fluoro-α/β-D-galactopyranose (**8**). To a stirred solution of the mixture containing compound **23** (0.433 g, 1.0 equiv) in Ac_2O (4.9 mL, 51.84 mmol, 30 equiv) at 0 °C was added H_2SO_4 (0.92 mL, 17.26 mmol, 10 equiv). The mixture was stirred at room temperature for 18 h. After this time, the mixture was cooled down to 0 °C and NaOAc (2.81 g, 34.26 mmol, 20 equiv) was added. The mixture was stirred for an additional 20 min and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with water (1 × 30 mL) and brine (1 × 30 ml) and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, AcOEt:hexanes 1:1) to give compound **8** (α/β, 1:3.7) as a yellow oil, (0.313 g, 0.89 mmol, 52% yield): R_f = 0.43 (silica, AcOEt:hexanes 1:1); $[\alpha]_D^{25}$ = +66.7° (*c* 0.2, $CHCl_3$); IR (ATR, ZnSe) ν : 2921, 2850, 1741, 1371, 1208, 1070, 938; ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 6.39 (d, *J* = 3.6 Hz, 1H, H1α), 5.70 (dd, *J* = 8.3, 0.9 Hz, 1H, H1β), 5.42 – 5.38 (m, 2H, H2α, H2β), 5.28 (ddd, *J* = 26.6, 10.9, 2.5 Hz, 1H, H3α), 5.00 (ddd, *J* = 27.4, 10.5, 2.7 Hz, 1H, H3β), 4.97 (dd, *J* = 50.2, 2.5 Hz, 1H, H4α), 4.89

(dd, J = 50.0, 2.7 Hz, 1H, H4β), 4.34 – 4.14 (m, 6H, 1 × H5α, 1 × H6aα, 1 × H6bα, 1 × H6aβ, 1 × H6bβ), 3.95 (dt, J = 26.1, 6.5 Hz, 1H, H5β), 2.15 (s, 3H, COCH_3α), 2.14 (s, 3H, COCH_3α), 2.12 (s, 3H, COCH_3β), 2.12 (s, 3H, COCH_3β), 2.09 (s, 3H, COCH_3α), 2.08 (s, 3H, COCH_3β), 2.05 (s, 3H, COCH_3β), 2.03 (s, 3H, COCH_3α) ppm; ^{13}C NMR: (126 MHz, $CDCl_3$) δ = 170.6, 170.54, 170.52, 170.4, 169.8, 169.3, 169.2, 168.9 (8C, 4 × COCH$_3$α, 4 × COCH$_3$β), 92.0 (1C, C1β), 89.7 (1C, C1α), 86.5 (d, J = 185.9 Hz, 1C, C4α), 85.7 (d, J = 187.2 Hz, 1C, C4β), 72.0 (d, J = 18.0 Hz, 1C, C5β), 71.5 (d, J = 18.0 Hz, 1C, C3β), 69.2 (d, J = 18.2 Hz, 1C, C5α), 68.0 (d, J = 17.6 Hz, 1C, C3α), 67.8 (d, J = 1.1 Hz, 1C, C2β), 66.3 (d, J = 2.4 Hz, C2α), 61.5 (d, J = 6.3 Hz, 1C, C6α), 61.4 (d, J = 6.0 Hz, 1C, C6β), 21.02, 20.96, 20.94, 20.89, 20.87, 20.84, 20.76, 20.66 (8C, 4 × COCH$_3$α, 4 × COCH$_3$β) ppm; ^{19}F NMR: (470 MHz, $CDCl_3$) δ –217.07 (dt, J = 50.1, 27.2 Hz, F4β), –219.23 (ddd, J = 50.4, 30.3, 26.5 Hz, F4α) ppm; HRMS calcd for $C_{14}H_{23}O_9NF^+$ [M+NH_4]$^+$ 368.1351 found 368.1369.

Associated content

Supporting information

Copies of ^{1}H, ^{13}C ^{19}F, COSY and HSQC NMR spectra for new compounds.

Author information

Corresponding Author

E-mail: denis.giguere@chm.ulaval.ca

Notes

The authors declare no competing financial interest.

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds de Recherche du Québec – Nature et Technologies and the Université Laval. D.L. thanks the Bourse de la Fondation Georges-Élie-Amyot and

PROTEO for a postgraduate fellowship. Finally, the authors would like to thank Dr. Yoann M. Chabre for proof reading of this article and Dr. Jean-François Paquin for useful discussion.

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