Electronic Supporting Information (ESI)

Synthesis of Fluorinated Thomsen-Friedenreich Antigens: Direct Deoxyfluorination of αGalNAc-Threonine *tert*-Butyl Esters

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General remarks:

Solvents for moisture-sensitive reactions (toluene, MeCN, CH₂Cl₂) were distilled and dried according to standard procedures. Glycosylations were performed in flame-dried glassware under inert argon atmospheres. Reagents were purchased in the highest available commercial quality and used as supplied except where noted. Reactions were monitored by TLC with precoated silica gel 60 F254 aluminium plates (Merck KGaA, Darmstadt) using UV light as the visualizing agent and by dipping the plate into a 1:1 mixture of 1 M H₂SO₄ in EtOH and 3% 3-methoxyphenol solution in EtOH followed by heating. Flash column chromatography was performed with silica gel (0.035-0.070 mm, 60 Å) from Acros. RP-HPLC analyses were performed on a JASCO-HPLC system with a Phenomenex Luna C18(2) (250 x 4.6 mm, 5 µm) column at a flow rate of 1 mLmin-1. Mixtures of H₂O/MeCN were used as solvents. ¹H, ¹³C, ¹⁹F, and 2D NMR spectra were recorded on a Bruker AC-300 or a Bruker AM-400 spectrometer. The chemical shifts are reported in ppm relative to the signal of the deuterated solvent. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), and m (multiplet). FD-mass spectra were recorded on a Finnigan MAT-95 spectrometer. Optical rotations were measured at 546 nm and 578 nm with a Perkin-Elmer polarimeter 241.



Scheme 1: Synthesis of 3,4-Di-O-acetyl-6-deoxy-6,6-difluoro-D-galactal (13).

1,2:3,4-Di-*O*-isopropylidene- α -D-galacto-hexodialdo-1,5-pyranose (S1)¹: To a solution of oxalyl chloride (8.71 mL, 0.102 mmol) in anhyd. THF (10 mL) and anhyd. CH₂Cl₂ (10 mL) was added dimethylsulfoxide (14.43 mL, 0.203 mmol) at -60 °C. A solution of 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (12)² (11.2 g, 0.423 mmol) in anhyd. CH₂Cl₂ (10 mL) was slowly added over 5 min and the mixture was stirred at -60 °C for 10 min. Then, NEt₃ (56.90 mL, 0.406 mmol) was added over a period of 15 min and the resulting suspension was stirred for 30 min at -60 °C and slowly warmed to room temperature. After addition of water (50 mL) and extraction with CH₂Cl₂ (2 × 50 mL), the organic layer was dried with Na₂SO₄,

filtered, and concentrated in vacuo. Flash chromatography on silica gel (^cHex/EtOAc, 7:3) provided **S1** as a yellow oil (8.62 g, 0.334 mmol, 79%); $R_f = 0.33$ (^cHex/EtOAc, 7:3); ¹H-NMR (400 MHz, CDCl₃): $\delta = 9.57$ (s, 1H, 6-H), 5.63 (d, 1H, J = 4.9, 1-H), 4.63-4.53 (m, 2H, 3-H, 4-H) 4.34 (dd, 1H, J = 2.5/4.9, 2-H), 4.15 (d, 1H, J = 2.1, 5-H), 1.46, 1.39, 1.30, 1.27 (4s, 12H, CH₃).

6-Deoxy-6,6-difluoro-1,2:3,4-Di-*O***-isopropylidene-***α***-D-galactopyranose** (**S2**)³: DAST (0.85 mL, 6.91 mmol) was slowly added to a solution of aldehyde **S1** (0.81 g, 3.14 mmol) in anhyd. CH₂Cl₂ (25 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h and quenched by addition of MeOH (5 mL). The solution was washed with sat. aq NaHCO₃ (2 × 50 mL), dried (MgSO₄), and concentrated in vacuo. Flash chromato-graphy on silica gel (^cHex/EtOAc, 7:3) afforded **S2** as a yellowish amorphous solid (1.40 g, 5.00 mmol, 67%); $R_f = 0.59$ (^cHex/EtOAc, 3:1); ¹H NMR (400 MHz, CDCl₃): $\delta = 5.81$ (dt, 1H, J = 6.6/53.8, 6-H), 5.53 (dd, 1H, J = 2.0/4.9, 1-H), 4.62 (dt, 2H, J = 2.5/8.0, 3-H) 4.37-4.31 (m, 2H, 2-H, 4-H), 3.92-3.83 (m, 1H, 5-H), 1.52, 1.44, 1.33, 1.32 (4s, 12H, CH₃); ¹⁹F NMR (376.5 MHz, CDCl₃), $\delta = -131.0$ (ddd, J = 11.6/58.3/298.3, 6aF), -129.2 (dddd, J = 2.1/3.9/54.0/298.3, 6bF).

6-Deoxy-6,6-difluoro-1,2,3,4-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **(S4)**: А solution of difluoride S2 (1.36 g, 4.87 mmol) in acetic acid (80%, 30 mL) was refluxed for 18 h. The solvent was removed in vacuo, the residue was co-evaporated with toluene (4 \times 30 mL), and dissolved in pyridine (20 mL). After addition of Ac₂O (4.57 mL, 48.65 mmol), the reaction mixture was stirred at room temperature for 12 h and concentrated in vacuo. The residue was co-evaporated with toluene (4×50 mL) and purified by flash chromatography on silica gel (^cHex/EtOAc, 2:1) to provide 6-Deoxy-6.6-difluoro-1.2.3.4-tetra-O-acetyl- α/β -Dgalactopyranose (S3)^{3c} as a yellow oil (1.70 g, 4.72 mmol, 97%). Peracetylated difluoride S3 (5.46 g, 15.16 mmol), dissolved in anhyd. CH₂Cl₂ (50 mL), was treated dropwise with HBr in glacial acetic acid (33%, 10.47 mL, 60.93 mmol) at 0 °C. After warming to room temperature, the reaction mixture was stirred for 3 d, poured on ice/water (300 mL) and neutralized at 0 °C with solid NaHCO₃ The aq phase was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic phases were washed with sat. aq NaHCO₃ (2×50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography on silica gel (^cHex/EtOAc, 2:1) afforded S4 as a yellowish amorphous solid (3.01 g, 7.74 mmol, 51%); $R_f = 0.55$ (^cHex/EtOAc, 2:1); analytical RP-HPLC (Luna, H₂O/MeCN, 80:20 (5 min) \rightarrow 30:70 (35 min) → 0:100 (20 min) → 0:100 (10 min): $R_t = 20.0$ min; $[\alpha]_D^{23} = 185.0$ (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃, COSY), $\delta = 6.69$ (d, 1H, J = 4.0, 1-H), 5.77 (ddd, 1H, J = 5.4/54.3/55.9, 6-H), 5.67-5.64 (m, 1H, 4-H), 5.36 (dd, 1H, J = 3.3/10.7, 3-H), 5.04 (dd, 1H, J = 4.0/10.7, 2-H), 4.37 (ddd, 1H, J = 2.8/7.6/10.7, 5-H), 2.13, 2.09, 1.99 (3s, 9H, CH₃).4.62; ¹³C NMR (75 MHz, CDCl₃), $\delta = 170.0$, 169.7, 169.3 (C=O), 112.3 (dd, J = 241.4/246.7, C6), 87.0 (C1), 72.3 (dd, J = 26.3/30.6, C5), 67.4 (C3), 67.4 (C2), 65.9 (dd, J = 2.4/5.5, C4), 20.7, 20.5, 20.5 (3 × CH₃-Ac); ¹⁹F NMR (376.5 MHz, CDCl₃), $\delta = -130.4$ (ddd, 1F, J = 5.2/54.2/302.3, 6aF), -129.0 (ddd, J = 10.8/55.8/302.6, 6bF); FD-MS: m/z: 309.35 [M-Br]⁺, 389.34 ([M+H]⁺.

3,4-Di-O-acetyl-6-deoxy-6,6-difluoro-D-galactal (13): To a suspension of activated zinc powder (3.66 g, 55.93 mmol; activated by successive washings with 1M HCl, water, EtOAc and Et₂O) in EtOAc (70 mL) was added N-methylimidazole (0.53mL, 6.71 mmol). The reaction mixture was heated under reflux and a solution of galactosyl bromide S4 (2.18 g, 5.59 mmol) in EtOAc (10 mL) was slowly added. After refluxing for two additional hours, the reaction mixture was cooled to room temperature, filtered through Hyflo Supercel, and the filtrate was washed with 1M HCl (2×40 mL), sat. aq NaHCO₃ (2×40 mL), dried (MgSO₄), and concentrated in vacuo. Purification by flash chromatography on silica gel (^cHex/EtOAc, 2:1) afforded 13 as a yellowish amorphous solid (1.22 g, 4.88 mmol, 87%); $R_f = 0.46$ (^cHex/EtOAc, 2:1); analytical RP-HPLC (Luna, H₂O/MeCN, 80:20 (5 min) \rightarrow 30:70 (35 min) \rightarrow 0:100 (20 min) \rightarrow 0:100 (10 min): R_t = 16.8 min; $[\alpha]_D^{23} = -39.0$ (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃, COSY), $\delta = 6.50$ (d, 1H, J = 6.3, 1-H), 5.86 (td, 1H, J = 6.0/55.5, 6-H), 5.62-5.47 (m, 2H, 4-H, 3-H), 4.75 (dt, 1H, J = 2.0/6.3, 2-H), 4.20 (dd, 1H, J = 7.6/14.2, 5-H), 2.14, 2.03 (2s, 6H, CH₃).; ¹³C NMR (75 MHz, CDCl₃), $\delta = 170.2$, 169.8 (C=O), 112.7 (t, *J* = 243.8, C6), 99.6 (C2), 73.8 (t, *J* = 27.2, C5), 63.5 (C3), 62.0 (d, *J* = 4.2, C4), 20.7, 20.6 (2 × CH₃-Ac); ¹⁹F NMR (376.5 MHz, CDCl₃), δ = -129.6 (d, J = 55.1); FD-MS: m/z: 251.29 $([M+H]^+)$.

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¹H NMR of compound 8



¹³C NMR of compound 8



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¹⁹F NMR of compound 8 (+ rotamer)



¹H NMR of compound 9



¹³C NMR of compound 9



¹⁹F NMR of compound 9



1H NMR of compound $\beta\text{--}11$



 ^{13}C NMR of compound $\beta\text{--}11$



 ^{19}F NMR of compound $\beta\text{--}11$ (+ rotamer)







¹H NMR of compound 16



¹³C NMR of compound 16



¹⁹F NMR of compound 16





RP-HPLC of compound 16

¹H NMR of compound 17



¹³C NMR of compound 17



¹H NMR of compound 18



¹³C NMR of compound 18



¹⁹F NMR of compound 18



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^{1}H NMR of compound β -19



^{13}C NMR of compound $\beta\text{--}19$



^{19}F NMR of compound $\beta\text{--}19$



RP-HPLC of compound β-19 (+ rotamer)

