Organic Letters

Synthesis of (1→4)-Linked 2-Deoxy-2-Fluoroglucose Oligomers I

Shin Sugiyama, Wasim Haque, and James Diakur*

Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB Canada, T6G 2N8

Supporting Information

EXPERIMENTAL SECTION

General Methods:

^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer or a Varian Unity 500 spectrometer in $CDCl_3$ solution unless otherwise noted. The residual $CHCl_3$ proton was set at 7.27 ppm, and used as the internal standard. Glycosylation reactions reported herein are unoptimized. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} (EM Science) and visualization was accomplished by charring with 5% methanolic sulfuric acid. Column chromatography was performed using EM Science 9385 silica gel (40 - 63μ).

4-Chlorophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-1-thio-α-D-glucopyranoside 3a. To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose **1** (3.5 g, 8.05 mmol) in dry CH_2Cl_2 (100 mL) was added 4-chlorothiophenol (1.8 g, 12.45 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was cooled to –10 °C under argon, and a solution of BF_3·Et_2O (10 mL, 79 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 72 h. (Note, this reaction proceeds slowly and longer reaction times lead to the formation of some **3b** (~ 15% after 10 days)). The reaction mixture was then cooled to 5 °C, and cold saturated aqueous $NaHCO_3$ was slowly added. After vigorous stirring, the layers were separated and the organic layer washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered and concentrated. Column chromatography using hexane:ethyl acetate (3:1) gave 2.9 g (67%) of **3a**.

R_f = 0.31 (hexane:ethyl acetate = 2:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 (d, 2H, J = 8.3 Hz, aromatic), 7.31 (d, 2H, J = 8.3 Hz, aromatic), 5.72 (d, 1H, $J_{1,2}$ = 5.9 Hz, H-1), 5.45 (dt, 1H, $J_{3,F}$ = 11.7 Hz, $J_{3,2}$ = $J_{3,4}$ = 9.5 Hz, H-3), 5.04 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, H-4), 4.83 (ddd, 1H, $J_{2,F}$ = 49.8 Hz, $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 5.9 Hz, H-2), 4.57 (ddd, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6a}$ = 5.1 Hz, $J_{5,6b}$ = 1.0 Hz, H-5), 4.29 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{6a,5}$ = 5.1 Hz, H-6a), 4.08 (dd, 1H, $J_{6b,6a}$ = 12.5 Hz, $J_{6b,5}$ = 1.0 Hz, H-6b), 2.10 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$).

4-Chlorophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 3b. To a solution of crude bromide **2** (~ 15 mmol) in $CHCl_3$ (150 mL), was added a solution of tetrabutylammonium chloride (840 mg, 3 mmol) in H_2O (20 mL) followed by 4-chlorothiophenol (3.28 g, 22.7 mmol). The mixture was cooled in an ice-water bath and a solution of KOH (1.7 g, 30.3 mmol) in H_2O (20 mL) was added dropwise over a period of 15 min. After the addition was complete, the mixture was stirred overnight at room temperature. The organic phase was separated, washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was purified by column

chromatography, and elution with hexane:ethyl acetate (2:1) provided the thioglycoside **3b** as an oil. (Yield; 6.0 g, 91 %).

R_f = 0.41 (hexane:ethyl acetate = 3: 2)

m.p. 143 °C

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 2H, *J* = 8.3 Hz, aromatic), 7.33 (d, 2H, *J* = 8.3 Hz, aromatic), 5.32 (ddd, 1H, $J_{3,F}$ = 14.2 Hz, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 9.3 Hz, H-3), 4.94 (t, 1H, $J_{4,3} = J_{4,5}$ = 9.8 Hz, H-4), 4.65 (dd, 1H, $J_{1,2}$ = 9.3 Hz, $J_{1,F}$ = 1.0 Hz, H-1), 4.21 (dd, 1H, $J_{6a,\ 6b}$ = 12.2 Hz, $J_{6a,5}$ = 2.9 Hz, H-6a), 4.18 (dd, 1H, $J_{6b,\ 6a}$ = 12.2 Hz, $J_{6b,5}$ = 4.9 Hz, H-6b), 4.15 (dt, 1H, $J_{2,F}$ = 49.3 Hz, $J_{2,3} = J_{2,1}$ = 9.3 Hz, H-2), 3.73 (ddd, 1H, $J_{5,\ 4}$ = 9.8 Hz, $J_{5,\ 6b}$ = 4.9 Hz, $J_{5,6a}$ = 2.9 Hz, H-5), 2.09 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$).

4-Chlorophenyl 2-deoxy-2-fluoro-1-thio-α-D-glucopyranoside 4a. Compound **3a** (2.9 g, 6.7 mmol) was de-*O*-acetylated in dry MeOH (25 mL) with a catalytic amount of NaOMe at room temperature overnight. The solution was neutralized with Amberlite IR-120 (H^+) resin and filtered. The filtrate was evaporated to give compound **4a** (2.0 g, quantitative) as a colorless solid. This triol was used directly in the next reaction.

R_f = 0.6 (chloroform:methanol = 4:1)

4-Chlorophenyl 2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 4b. Compound **3b** (6.0 g) was de-*O*-acetylated in dry MeOH (50 mL) with a catalytic amount of NaOMe at room temperature for 2 hr. The solution was neutralized with Amberlite IR-120 (H^+) resin and filtered. The filtrate was evaporated to give compound **4** (4.2 g, quantitative) as a colorless solid.

R_f = 0.6 (chloroform:methanol = 4:1)

4-Chlorophenyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-1-thio-α-D-glucopyranoside 5a. Compound **4a** (1.0 g, 3.24 mmol) was benzylidenated in CH_3CN (30 mL) with α,α-dimethoxytoluene (745 mg, 4.9 mmol) in the presence of a catalytic amount (5%) of *p*-TsOH monohydrate at room temperature overnight. The mixture was neutralized with triethylamine and evaporated to dryness. Column chromatography using hexane:ethyl acetate (3:1) gave 920 mg (75 % yield) of **5a**.

R_f = 0.48 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-7.25 (m, 9H, aromatic), 5.73 (dd, 1H, $J_{1,2}$ = 6.1 Hz, $J_{1,F}$ = 1.5 Hz, H-1), 5.56 (s, 1H, benzylidene), 4.77 (ddd, 1H, $J_{2,F}$ = 49.7 Hz, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 6.1 Hz, H-2), 4.37 (td, 1H, $J_{5,4} = J_{5,6b}$ = 9.7 Hz, $J_{5,6a}$ = 5.2 Hz, H-5), 4.29 (dd, 1H, $J_{6a,6b}$ = 10.4 Hz, $J_{6a,5}$ = 4.9 Hz, H-6a), 4.20 (dt, 1H, $J_{3,F}$ = 12.2 Hz, $J_{3,2} = J_{3,4}$ = 9.5 Hz, H-3), 3.78 (t, 1H, $J_{6b,5} = J_{6b,6a}$ = 10.2 Hz, H-6b), 3.57 (t, 1H, $J_{4,3} = J_{4,5}$ = 9.5 Hz, H-4).

4-Chlorophenyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 5b. Compound **4b** (4.1 g, 13.3 mmol) was benzylidenated in CH_3CN (60 mL) with α,α-dimethoxytoluene (2.4 g, 15.8 mmol) in the presence of a catalytic amount of *p*-TsOH monohydrate at room temperature for 3 h. The mixture was neutralized with triethylamine and evaporated to dryness. The residue was treated with EtOH (40 mL) and kept at 7 °C for 1 h. Crystalline **5b** was collected by filtration and the concentration of the filtrate gave an additional **5b** for a combined yield of 4.0 g (76 %).

R_f = 0.45 (hexane:ethyl acetate = 3:1)

m.p. 187-188 °C

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.20 (m, 9H, aromatic), 5.52 (s, 1H, benzylidene), 4.70 (dd, 1H, $J_{1,2}$ = 9.8 Hz, $J_{1,F}$ = 2.4 Hz, H-1), 4.40 (dd, 1H, $J_{6a,6b}$ = 9.8 Hz, $J_{6a,5}$ = 4.9 Hz, H-6a), 4.15 (ddd, 1H, $J_{2,F}$ = 48.8 Hz, $J_{2,1}$ = 9.8 Hz, $J_{2,3}$ = 8.3 Hz, H-2), 4.05 (ddd, 1H, $J_{3,F}$ = 15.1 Hz, $J_{3,4}$ = 9.3 Hz, $J_{3,2}$ = 8.3 Hz, H-3), 3.75 (t, 1H, $J_{6b,5}$ = $J_{6b,6a}$ = 8.3 Hz, H-6b), 3.52 (ddd, 1H, $J_{5,6b}$ = 9.8 Hz, $J_{5,4}$ = 9.3 Hz, $J_{5,6a}$ = 4.9 Hz, H-5), 3.47 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.3 Hz, H-4).

4-Chlorophenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-1-thio-α-D-glucopyranoside 6a. To a rapidly stirred solution of compound **5a** (900 mg, 2.27 mmol) and NaH (50 mg, 2.17 mmol) in THF (25 mL) was added BnBr (1 g, 5.85 mmol), and the mixture was stirred at 60 °C under argon for 2 h. Methanol (1 mL) was added and the mixture stirred for 15 min to destroy excess reagents. The solvents were then removed. The residue was dissolved in CH_2Cl_2 and washed with water, saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. Column chromatography using hexane:ethyl acetate (4:1) gave 800 mg (72%) of **6a**.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.50-7.20 (m, 14H, aromatic), 5.60 (dd, 1H, $J_{1,2}$ = 5.8 Hz, $J_{1,F}$ <1.0 Hz, H-1), 5.51 (s, 1H, benzylidene), 4.83 (d, 1H, J = 11.2 Hz, $CH_2C_6H_5$), 4.80 (ddd, 1H, $J_{2,F}$ = 49.4 Hz, $J_{2,3}$ = 9.0 Hz, $J_{2,1}$ = 6.0 Hz, H-2), 4.78 (d, 1H, J = 11.2 Hz, $CH_2C_6H_5$), 4.30 (td, 1H, $J_{5,4}$ = $J_{5,6b}$ = 9.6 Hz, $J_{5,6a}$ = 4.7 Hz, H-5), 4.19 (dd, 1H, $J_{6a,6a}$ = 10.4 Hz, $J_{6a,5}$ = 4.9 Hz, H-6a), 3.95 (dt, 1H, $J_{3,F}$ = 11.9 Hz, $J_{3,2}$ = $J_{3,4}$ = 9.3 Hz, H-3), 3.70 (t, 1H, $J_{6a,5}$ = $J_{6a,6b}$ = 10.2 Hz, H-6b), 3.61 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, H-4).

4-Chlorophenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 6b. To a solution of compound **5b** (3.85 g, 9.7 mmol) and BnBr (1.4 mL, 11.8 mmol) in DMF (30 mL) at 0 °C was added NaH (460 mg, 19.2 mmol) in portions. After the addition was complete, the mixture was stirred at room temperature for an additional 1 h. Methanol (3 mL) was then added and the mixture was stirred for 15 min to destroy the excess NaH. The reaction was poured into an ice water-mixture (250 mL) while stirring, and the product was extracted with CH_2Cl_2 and washed with H_2O, dried (Na_2SO_4), and concentrated. The crystalline residue was recrystallized from EtOH to give compound **6b** (4.51 g, 95%) as colorless fine needles.

R_f = 0.61 (hexane:ethyl acetate = 3:1)

m.p. 131-133 °C

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.20 (m, 14H, aromatic), 5.54 (s, 1H, benzylidene), 4.85 (d, 1H, J = 11.3 Hz, $CH_2C_6H_5$), 4.82 (d, 1H, J = 11.2 Hz, $CH_2C_6H_5$), 4.67 (dd, 1H, $J_{1,2}$ = 9.8 Hz, $J_{1,F}$ = 2.9 Hz, H-1), 4.38 (dd, 1H, $J_{6a,6b}$ = 10.3 Hz, $J_{6a,5}$ = 4.9 Hz, H-6a), 4.21 (ddd, 1H, $J_{2,F}$ = 48.3 Hz, $J_{2,1}$ = 9.8 Hz, $J_{2,3}$ = 8.3 Hz, H-2), 3.85 (ddd, 1H, $J_{3,F}$ = 14.7 Hz, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 8.3 Hz, H-3), 3.75 (t, 1H, $J_{6b,5}$ = $J_{6b,6a}$ = 10.3 Hz, H-6b), 3.58 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz, H-4), 3.48 (dt, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 4.9 Hz, H-5).

4-Chlorophenyl 3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-α-D-glucopyranoside 7a. To a stirred solution of compound **6a** (700 mg, 1.44 mmol), $NaBH_3CN$ (900 mg, 14.4 mmol) and powdered Drierite® (1.5 g) in THF (10 mL, containing a trace amount of methyl orange) at room temperature was added dropwise, a solution of saturated ethereal HCl until the evolution of the gas ceased (~ 3 mL) and the solution color remained red. The mixture was diluted with $CHCl_3$ and filtered through a Celite® pad. The filtrate was washed with saturated aqueous sodium $NaHCO_3$, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (15 mL), stirred overnight and then evaporated. The product was purified by column chromatography using hexane:ethyl acetate (4: 1) to provide 562 mg (80%) of **7a**.

R_f = 0.45 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.50-7.20 (m, 14H, aromatic), 5.65 (dd, 1H, $J_{1,2}$ = 5.8 Hz, $J_{1,F}$ <1.0 Hz, H-1), 4.97 (d, 1H, J = 11.3 Hz, $CH_2C_6H_5$), 4.82 (ddd, 1H, $J_{2,F}$ = 50.5 Hz, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 5.8 Hz, H-2), 4.71 (d, 1H, J = 11.3 Hz, $CH_2C_6H_5$), 4.60 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.42 (d, 1H, J = 11.2 Hz, $CH_2C_6H_5$), 4.35 (dt, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 4.0 Hz, H-5), 3.78 (dt, 1H, $J_{3,F}$ obscured, $J_{3,2}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.74 (m, 1H, H-6a), 3.74 (m, 1H, H-6b), 3.68 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.0 Hz, H-4), 2.45 (br s, 1H, OH).

4-Chlorophenyl 3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 7b. To a stirred solution of compound **6b** (4.2 g, 8.6 mmol), $NaBH_3CN$ (5.4 g, 86 mmol) and powdered molecular sieves 4Å (7 g) in THF (80 mL) at room temperature was added dropwise, a solution of saturated HCl in ether until the evolution of the gas ceased. The mixture was diluted with $CHCl_3$ (200 mL) and filtered through a Celite® pad. The filtrate was washed saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated. The residue was then treated with MeOH (100 mL) (caution - evolution of gas), stirred overnight and evaporated. The product was purified by column chromatography using hexane:ethyl acetate (4:1) as eluant to give **7** (4.0 g, 95%) as a crystalline solid.

R_f = 0.32 (hexane:ethyl acetate = 3:1)

m.p. 89 °C

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.52-7.20 (m, 14H, aromatic), 4.92 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.68 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.61 (dd, 1H, $J_{1,2}$ = 9.3 Hz, $J_{1,F}$ = 2.0 Hz, H-1), 4.58 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.55 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.21 (ddd, 1H, $J_{2,F}$ = 49.3 Hz, $J_{2,1}$ = 9.3 Hz, $J_{2,3}$ = 8.3 Hz, H-2), 3.78 (dd, 1H, $J_{6a,6b}$ = 10.3 Hz, $J_{6a,5}$ = 3.4 Hz, H-6a), 3.72 (d, 1H, $J_{6b,6a}$ = 10.3 Hz, $J_{6b,5}$ = 4.9 Hz, H-6b), 3.66-3.54 (m, 3H, H-3, H-4, OH), 3.51 (m, 1H, H-5).

4-Chlorophenyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-α-D-glucopyranoside 8a. Compound **7a** (365 mg, 0.75 mmol) was acetylated in 2:1 pyridine:acetic anhydride (9 mL) at room temperature overnight. The solvents were removed and the residue was dissolved in CH_2Cl_2 and then washed successively with dilute aqueous HCl, water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated. Column chromatography using chloroform as eluant gave 357 mg (90%) of **8a.**

R_f = 0.46 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30-7.05 (m, 14H, aromatic), 5.66 (d, 1H, $J_{1,2}$ = 5.9 Hz, H-1), 5.06 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz, H-4), 4.88 (d, 1H, J = 12.2 Hz, $CH_2C_6H_5$), 4.86 (ddd, 1H, $J_{2,F}$ = 49.8 Hz, $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 5.9 Hz, H-2), 4.63 (d, 1H, J = 12.2 Hz, $CH_2C_6H_5$), 4.52 (d, 1H, J = 11.8 Hz, $CH_2C_6H_5$), 4.47 (dt, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 4.4 Hz, H-5), 4.46 (d, 1H, J = 11.8 Hz, $CH_2C_6H_5$), 3.88 (dt, 1H, $J_{3,F}$ = 12.2 Hz, $J_{3,4}$ = $J_{3,5}$ = 9.3 Hz, H-3), 3.55 (d, 2H, $J_{6a,5}$ = $J_{6b,5}$ = 4.4 Hz, H-6a and H-6b), 1.93 (s, 3H, $COCH_3$).

4-Chlorophenyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 8b. Compound **7b** (2.0 g, 4.1 mmol) was acetylated in pyridine (10 mL) with acetic anhydride (0.77 mL, 8.2 mmol) at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 and washed successively with dilute aqueous HCl, water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated. Column chromatography using hexane:ethyl acetate (3:1) as eluant gave 2.0 g (92%) of **8b** as an oil which solidified upon standing at room temperature.

R_f = 0.40 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.10 (m, 14H, aromatic), 4.92 (t, 1H, $J_{4,3} = J_{4,5}$ = 9.8 Hz, H-4), 4.83 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.61 (dd, 1H, $J_{1,2}$ = 9.8 Hz, $J_{1,F}$ = 2.0 Hz, H-1), 4.59 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.51 (s, 2H, $CH_2C_6H_5$), 4.25 (ddd, 1H, $J_{2,F}$ = 49.3 Hz, $J_{2,1}$ = 9.8 Hz, $J_{2,3}$ = 8.3 Hz, H-2), 3.70 (ddd, 1H, $J_{3,F}$ = 14.7 Hz, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 8.3 Hz, H-3), 3.59 (dt, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6a} = J_{5,6b}$ = 4.9 Hz, H-5), 3.54 (d, 2H, $J_{6a,5} = J_{6b,5}$ = 4.9 Hz, H-6a, H-6b), 1.89 (s, 3H, $COCH_3$).

4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl chloride 9a. To a stirred solution of phenylsulfoxide (628 mg, 3.1 mmol) in CH_2Cl_2 (2 mL) at -78 °C under argon was added dropwise, a solution of oxalyl chloride (0.18 mL, 2.1 mmol) in CH_2Cl_2 (1 mL). After 5 min, a solution of compound **8b** (550 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was then allowed to attain room temperature over a period of 2 h and then stirred at room temperature for an additional 1.5 h. To this yellow colored mixture was added cyclopentene (0.5 mL), and the solution was stirred until the yellow color disappeared. The mixture was concentrated and the residue was purified by column chromatography using hexane:ethyl acetate (7:2). Compound **9a** (400 mg, 91%) was obtained as an oil, and this material was found to be the α-anomer almost exclusively.

R_f = 0.43 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H, aromatic), 6.26 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 5.19 (t, 1H, $J_{4,3} = J_{4,5}$ = 10.4 Hz, H-4), 4.89 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.74 (ddd, 1H, $J_{2,F}$ = 49.3 Hz, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 3.9 Hz, H-2), 4.64 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.56 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.51 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.20 (ddd, 1H, $J_{5,4}$ = 10.4 Hz, $J_{5,6b}$ = 4.3 Hz, $J_{5,6a}$ = 2.8 Hz, H-5), 4.10 (ddd, 1H, $J_{3,4}$ = 10.4 Hz, $J_{3,F}$ = 10.1 Hz, $J_{3,2}$ = 9.2 Hz, H-3), 3.59 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{6a,5}$ = 2.8 Hz, H-6a) 3.52 (dd, 1H, $J_{6b,6a}$ = 11.0 Hz, $J_{6a,5}$ = 4.3 Hz, H-6b), 1.91 (s, 3H, $COCH_3$).

4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosyl chloride 9b. The procedure was identical to that described for the preparation of **9a**, except that the starting thioglycoside was **8a**. The chloride obtained was found to be a mixture of **9b**/**9a** (11:1).

Data for **9b**.

R_f = 0.36 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.20-7.10 (m, 10H, aromatic), 5.25 (dd, 1H, $J_{1,2}$ = 8.3 Hz, $J_{1,F}$ = 2.4 Hz, H-1), 5.10 (t, 1H, $J_{4,3} = J_{4,5}$ = 9.8 Hz, H-4), 4.86 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.62 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.53 (s, 2H, $CH_2C_6H_5$), 4.51 (dt, 1H, $J_{2,F}$ = 49.3 Hz, $J_{2,1} = J_{2,3}$ = 8.3 Hz, H-2), 3.71 (ddd, 1H, $J_{3,F}$ = 14.6 Hz, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 8.3 Hz, H-3), 3.66 (dt, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6a} = J_{5,6b}$ = 3.9 Hz, H-5), 3.55 (d, 2H, $J_{6a,5} = J_{6b,5}$ = 3.9 Hz, H-6a, H-6b), 1.90 (s, 3H, $COCH_3$).

4-Chlorophenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 10, and 4-chlorophenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 12.

Procedure A: A mixture of **7b** (78 mg, 0.19 mmol), AgOTf (62 mg, 0.24 mmol), 2,6-di-*tert*-butylpyridine (134 mg, 0.34 mmol), and Drierite® (250 mg) in CH_2Cl_2:toluene (4:1) (1 mL) was stirred at room temperature for 1 h. The solution was cooled to -78 °C under argon, and a solution of **9a** (81 mg, 0.19 mmol) in CH_2Cl_2:toluene (4:1) (1 mL)

was then added. The reaction was stirred at this temperature for 5 min, then allowed to slowly warm to room temperature. After 1 h of stirring at room temperature, the reaction was diluted with CH_2Cl_2 and filtered through Celite®. The filtrate was washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated. Column chromatography using hexane:ethyl acetate (7:1) as eluant gave **10** (36 mg, 26%), **12** (55 mg, 39%) (**10**:**12** = 40:60) along with recovered **7b** (23 mg, 30%).

Repeating this procedure using chloride **9b** gave **10**:**12** (45:55).

Procedure B: To a solution of **9a** (195 mg, 0.46 mmol) and **7** (248 mg, 0.51 mmol) in CH_3CN:toluene (1:1) (10 mL), was added a solution of AgOTf (177 mg, 0.69 mmol) and 2,6-di-*tert*-butylpyridine (159 mg, 0.83 mmol) in CH_3CN (5 mL). The reaction mixture was concentrated under water aspiration pressure at < 40 °C using a rotary evaporator. The residue was then co-evaporated with toluene (3 x 3 mL), and $CHCl_3$ was added and the mixture filtered to remove insoluble materials. The filtrate was washed with H_2O, dried (Na_2SO_4) and concentrated. Column chromatography using hexane:ethyl acetate (5:1) provided **10** (213 mg) followed by **12** (130 mg), both as oils, in a combined yield of 83 %, (**10**:**12** = 62:38).

Data for compound **10**:

R_f = 0.46 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.20 (m, 24H, aromatic), 5.68 (d, 1H, $J_{1',2'}$ = 3.9 Hz, H-1'), 5.02 (t, 1H, $J_{4',3'}$ = $J_{4',5'}$ = 9.8 Hz, H-4'), 4.88 (d, 1H, J = 9.8 Hz, $CH_2C_6H_5$), 4.84 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.70 (d, 1H, J = 9.8 Hz, $CH_2C_6H_5$), 4.65 (dd, 1H, $J_{1,2}$ = 9.8 Hz, $J_{1,F}$ = 1.0 Hz, H-1), 4.59 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.51 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.48 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.48 (ddd, 1H, $J_{2',F}$ = 49.3 Hz, $J_{2',3'}$ = 9.8 Hz, $J_{2',1'}$ = 3.9 Hz, H-2'), 4.44 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.34 (d, 1H, J = 11.7 Hz, $CH_2C_6H_5$), 4.25 (ddd, 1H, $J_{2,F}$ = 49.8 Hz, $J_{2,1}$ = 9.8 Hz, $J_{2,3}$ = 8.3 Hz, H-2), 3.94-3.78 (m, 5H, H-3, H-4, H-6a, H-3', H-5'), 3.73 (dd, 1H, $J_{6b,6a}$ = 11.2 Hz, $J_{6b,5}$ = 5.4 Hz, H-6b), 3.63 (ddd, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6b}$ = 5.4 Hz, $J_{5,6a}$ = 1.5 Hz, H-5), 3.34 (dd, 1H, $J_{6'a,6'b}$ = 10.7 Hz, $J_{6'a,5'}$ = 2.9 Hz, H-6'a), 3.30 (dd, 1H, $J_{6'b,6'a}$ = 10.7 Hz, $J_{6'b,5'}$ = 4.4 Hz, H-6'b), 1.90 (s, 3H, $COCH_3$).

Data for compound **12**:

R_f = 0.44 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.20 (m, 24H, aromatic), 5.03 (t, 1H, $J_{4',3'}$ = $J_{4',5'}$ = 9.8 Hz, H-4'), 4.89 (d, 1H, J = 11.6 Hz, $CH_2C_6H_5$), 4.83 (d, 1H, J = 11.6 Hz, $CH_2C_6H_5$), 4.79 (d, 1H, J = 11.6 Hz, $CH_2C_6H_5$), 4.70-4.50 (m, 5H, H-1, H-1', 3 x $CH_2C_6H_5$), 4.35 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.32 (ddd, 1H, $J_{2',F}$ = 50.7 Hz, $J_{2',1'}$ = 9.8 Hz, $J_{2',3'}$ = 8.8 Hz, H-2'), 4.30 (d, 1H, J = 11.9 Hz, $CH_2C_6H_5$), 4.19 (ddd, 1H, $J_{2,F}$ = 51.0 Hz, $J_{2,1}$ = 9.8 Hz, $J_{2,3}$ = 8.2 Hz, H-2), 3.92 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz, H-4), 3.85 (d, 2H, $J_{6a,5}$ = $J_{6b,5}$ = 2.8 Hz, H-6a, H-6b) 3.75 (ddd, 1H, $J_{3,F}$ = 15.3 Hz, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 8.2 Hz, H-3), 3.65-3.50 (m, 2H, H-5, H-3'), 3.45-3.30 (m, 3H, H-5', H-6a', H-6b'). 1.90 (s, 3H, $COCH_3$).

4-Chlorophenyl (3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 11. Compound **10** (210 mg, 0.24 mmol) was de-*O*-acetylated in a mixture of CH_2Cl_2 (3 mL) and MeOH (3 mL) with a catalytic amount of NaOMe at room temperature for 6 h. After this time, the solution was neutralized with AcOH and concentrated. Column chromatography using hexane:ethyl acetate (3:2) provided compound **11** (185 mg, 93%) as an oil.

R_f = 0.34 (hexane:ethyl acetate = 3:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 24H, aromatic), 5.71 (d, 1H, $J_{1',2'}$ = 4.4 Hz, H-1'), 4.95 (d, 1H, *J* = 11.3 Hz, $CH_2C_6H_5$), 4.90 (d, 1H, *J* = 10.1 Hz, $CH_2C_6H_5$), 4.76-4.62 (m, 3H, H-1, 2 x $CH_2C_6H_5$), 4.60-4.12 (m, 6H, H-2, H-2', 4 x $CH_2C_6H_5$), 4.00-3.45 (m, 10H, H-3, H-4, H-5, H-6a, H-6b, H-3', H-4', H-5', H-6a', H-6b').

4-Chlorophenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 13, and 4-chlorophenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 16.

The glycosidation reaction was carried out as described for compounds **10**/**12** (Procedure B). A mixture of **9a** (95 mg, 0.22 mmol), **11** (170 mg, 0.20 mmol), AgOTf (87 mg, 0.34 mmol) and 2,6-di-*tert*-butylpyridine (77 mg, 40.2 mmol) in CH_3CN:toluene (3:2) (5 ml) was subjected to the forced reaction conditions. After work up, the products were purified by column chromatography using hexane:ethyl acetate (5:1) to provide compound **13** (115 mg) followed by **16** (97 mg) in 85% combined yield, each as a colorless foam.

As a result of the complex F-H coupling patterns displayed by the H-2 and H-3 ring protons, complete spectral assignment of the subsequent 2-FDG based oligosaccharides was extremely difficult. For the remaining compounds, the ^{1}H-NMR spectral assignments are tentative, and only the shifts of the key reporter groups are given.

Data for compound **13**:

R_f = 0.43 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 34H, aromatic), 5.76 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1'), 5.66 (d, 1H, $J_{1'',2''}$ = 4.0 Hz, H-1''), 5.10 (t, 1H, $J_{4'',3''} = J_{4'',5''}$ = 9.8 Hz, H-4''), 1.90 (s, 3H, $COCH_3$).

Data for compound **16**:

R_f = 0.39 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 34H, aromatic), 5.74 (d, 1H, $J_{1',2'}$ = 4.3 Hz, H-1'), 5.01 (t, 1H, $J_{4'',3''} = J_{4'',5''}$ = 9.6 Hz, H-4''), 1.90 (s, 3H, $COCH_3$).

(4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl chloride 14. To a stirred solution of phenylsulfoxide (32.3 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at – 78 °C under argon was slowly added, a solution of oxalyl chloride (13.5 mg, 0.11 mmol) in CH_2Cl_2 (1 mL). After 5 min, a solution of compound **13** (65 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was then allowed to attain room temperature over a period of 1.5 h. Cyclopentene (0.5 mL) was slowly added to the yellow colored solution until it became colorless. The mixture was concentrated and the residue was purified by column chromatography using hexane:ethyl acetate (3:1) to give compound **14** (48 mg, 81%) as a foam.

R_f = 0.37 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40-7.20 (m, 30H, aromatic), 6.23 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 5.74 (d, 1H, $J_{1',2'}$ = 4.4 Hz, H-1'), 5.62 (d, 1H, $J_{1'',2''}$ = 3.9 Hz, H-1''), 5.07 (t, 1H, $J_{4'',3''} = J_{4'',5''}$ = 9.8 Hz, H-4''), 1.90 (s, 3H, $COCH_3$).

4-Chlorophenyl (3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 15. Compound **13** (50 mg, 0.04 mmol) was de-*O*-acetylated in a mixture of CH_2Cl_2 (2 mL) and MeOH (2 mL) with a catalytic amount of NaOMe at room temperature for 6 h. The solution was then neutralized with AcOH and concentrated. Column chromatography using hexane:ethyl acetate (3:1) provided compound **15** (47 mg, 97%) as a colorless foam.

R_f = 0.35 (hexane:ethyl acetate = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.20 (m, 34H, aromatic), 5.73 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1'), 5.63 (d, 1H, $J_{1'',2''}$ = 4.0 Hz, H-1'').

4-Chlorophenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3, 6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 17, and 4-chlorophenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-(3, 6-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside 18. A mixture of **14** (32 mg, 0.03 mmol), **15** (42 mg, 0.03 mmol), AgOTf (11 mg, 0.04 mmol) and 2,6-di-*tert*-butylpyridine (10 mg, 0.05 mmol) in CH_3CN (3 mL) and toluene (2 mL) was treated according to Procedure B. After work up, the resulting residue was purified by column chromatography using hexane:ethyl acetate (3:1) provided 35 mg of foam which was homogeneous by TLC (hexane:ethyl acetate 3:1). However, ^{1}H NMR revealed that the product obtained was a mixture of compounds **17** and **18**. The mixture was then separated by column chromatography using toluene-ethyl acetate (15:1) as eluant.

Data for compound **17**:

R_f = 0.28 (toluene:ethyl acetate = 15:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.10 (m, 64H, aromatic), 5.79 (d, 1H, *J* = 3.9 Hz, α anomeric proton), 5.76 (d, 2H, overlap of two α anomeric protons), 5.71 (d, 1H, *J* = 3.9 Hz, α anomeric proton), 5.64 (d, 1H, *J* = 3.9 Hz, α anomeric proton), 5.09 (t, 1H, $J_{4'''',3''''} = J_{4'''',5''''}$ = 9.8 Hz, H-4'''''), 1.90 (s, 3H, $COCH_3$).

Data for compound **18**:

R_f = 0.23 (toluene:ethyl acetate = 15:1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.10 (m, 64H, aromatic), 5.79 (d, 1H, *J* = 3.9 Hz, α anomeric proton), 5.76 (d, 1H, *J* = 3.9 Hz, α anomeric proton), 5.64 (m, 2H, overlap of two α anomeric protons), 5.08 (t, 1H, $J_{4'''',3''''} = J_{4'''',5''''}$ = 9.8 Hz, H-4'''''), 1.90 (s, 3H, $COCH_3$).