Protective group strategies in carbohydrate and peptide chemistry

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CHAPTER

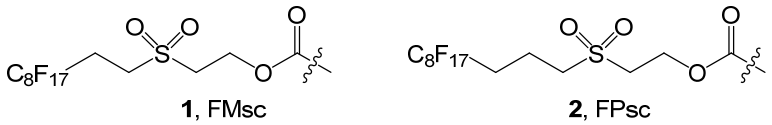
3

([1*H*,1*H*,2*H*,2*H*,3*H*,3*H*]-perfluoroundecyl)sulfonylethoxycarbonyl (FPsc): a fluorous hydroxyl protecting group in carbohydrate chemistry[1]

Introduction:

In 1997, Curran and coworkers reported fluorous solid phase extraction (FSPE) as a new purification method in synthetic organic chemistry.[2] FSPE involves the chromatographic separation of fluorous and non-fluorous components from a mixture by the use of a fluorous solid phase in combination with fluorophilic solvents.[3] Silica gel functionalized with a perfluoroalkyl chain is typically used as a fluorous solid phase in combination with methanol, acetonitrile or tetrahedrofuran as fluorophilic solvents and water as a fluorophobic solvent.[4] FSPE can be executed with the aid of both low- and high-pressure techniques.[5]

Figure 1: The FMsc and the FPsc protecting group.



1, FMsc **2**, FPsc

In recent times the application of FSPE in synthetic organic chemistry is greatly stimulated by the development of numerous fluorous reagents such as catalysts,[6] chiral auxiliaries[7] and scavengers.[8] A variety of fluorous protective groups, serving the dual purpose of protective group and purification handle in FSPE, have also been reported. Fluorous protecting groups for many relevant functional groups, such as amino[9] and hydroxyl functions[10] have been developed. Generally a fluorous protective group is obtained by the appendage of a perfluoroalkyl moiety to the core of a known protective group such as the benzyl,[11] benzyloxycarbonyl,[12] *tert*-butyl,[13] *tert*-butyloxycarbonyl,[14] trityl[15] and benzylidene[16] group. Most commonly, an ethylene spacer is incorporated to isolate the electron withdrawing effect of the fluorous tail, which can undesirably alter the properties of the protecting group.[12]

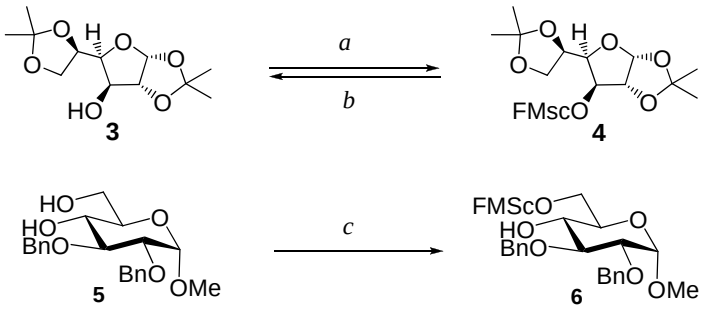
A few years ago, the [1*H*,1*H*,2*H*,2*H*]-perfluorodecylsulfonylethoxycarbonyl (FMsc, **1**, Figure 1) group was introduced as a fluorous version of the methylsulfonylethoxycarbonyl (Msc) protective group for amines.[17] The FMsc group was used as a purification handle for oligopeptides, assembled by Fmoc-based solid phase peptide synthesis (SPPS). The FMsc group could be introduced at the amino terminus of a target oligopeptide at the final stage of the SPPS. Cleavage from the solid support and purification of the resulting mixture by fluorous HPLC (FHPLC) effected separation of the fluorous target oligopeptide and non-fluorous deletion sequences. Removal of the FMsc group using mild basic conditions afforded the pure oligopeptide. This result together with the successful application of the (Msc) group for the protection of hydroxyl functions, as described in chapter 2, was an incentive to explore the use of fluorous Msc-based protective groups in carbohydrate chemistry. The outcome of this study, showing the favorable properties of the [1*H*,1*H*,2*H*,2*H*,3*H*,3*H*]-perfluoroundecylsulfonylethoxycarbonyl (FPsc) group **2** is outlined in the present chapter.

Results and discussion:

The assessment of the optimal conditions for the introduction of the methylsulfonylethoxycarbonyl (Msc) group is described in chapter 2. It turned out that pyridine as base and DCM as solvent were most efficient. Whether these conditions are also suitable for the introduction of the FMsc group (**1**) was checked by the treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **3** with 2 equivalents of [1*H*,1*H*,2*H*,2*H*]-perfluorodecylsulfonylethoxycarbonyl chloride (FMsc-Cl) and 3 equivalents of pyridine in DCM (Scheme 1). After 4 hours the reaction was complete and glucofuranose **4** was isolated in 95% yield. Next, the FMsc group could be introduced regioselectively at the primary C6-OH of diol **5** using the same conditions, albeit at lower temperature (-20 ^{o}C), to give alcohol **6** in 95% yield.

The optimal condition for the removal of the Msc group, *i.e.* 0.1 eq. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), (see Chapter 2), also proved to be appropriate for the cleavage of the FMsc group, although removal of the latter carbonate proved to be significantly faster. Subjection of compound **4** to these conditions for 1 minute gave the expected alcohol **3** in 98% yield.

Scheme 1: Installation and cleavage of the FMsc group.

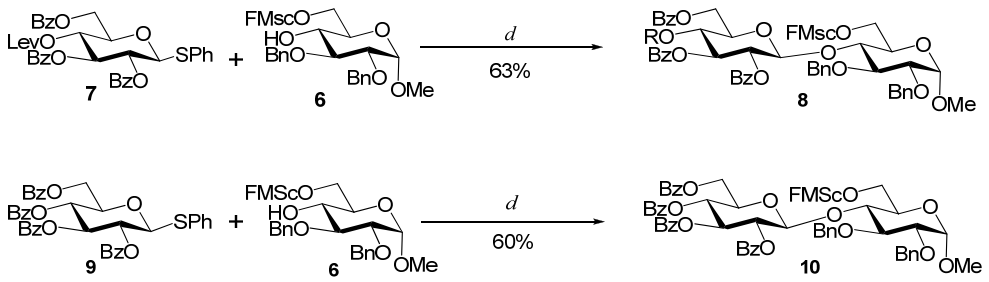


Reagents and conditions; *a*) FMS-Cl, pyr, DCM, 0 ºC-RT, 4h, 95%; *b*) DBU, dioxane, 1 min, 98%; *c*) FMS-Cl, pyr, DCM, -20 ºC-RT, 4h, 95%.

Next, the feasibility of the FMsc-protective group in *N*-iodosuccinimide (NIS) and trimethylsilyltriflate (TMSOTf) mediated glycosylation reactions was investigated. In the

first example, the FMsc-protected methyl glucoside **6** was condensed with thioglucoside **7** to provide disaccharide **8** (Scheme 2). TLC analysis of the crude reaction mixture showed the presence of a main product together with side products, probably derived from the donor. Purification by FSPE using a gradient of acetonitrile in water (50% to 100%) provided disaccharide **8**. Although TLC analysis of the combined fractions after FSPE showed the presence of one product, subsequent evaporation of the solvents caused the formation of an unwanted non-fluorous side product. A second FSPE purification gave the same result and ensuing purification by silica gel column chromatography afforded disaccharide **8** in 63% overall yield. In the second glycosylation event, FMsc-protected methyl glucoside **6** was coupled via the same procedure with perbenzoylated *S*-phenyl glucoside **9** to provide disaccharide **10** (Scheme 2). Disaccharide **10** was purified by FSPE to afford the fluorous product **8** in 80% yield. Unfortunately, again a non-fluorous side product was generated during the evaporation of the solvents. Homogeneous disaccharide **10** was obtained by silica gel column chromatography in 60% yield.

Scheme 2: Glycosylation reactions using acceptors containing the FMsc group.



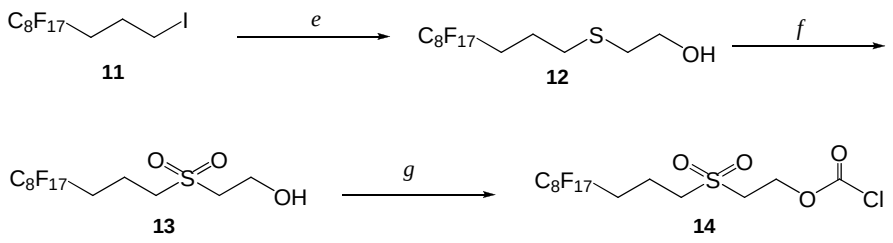
Reagents and conditions; *d*) i- NIS, TMSOTf, DCM, 0 ºC-RT, 1h; ii- FSPE.

The formation of the non-fluorous products, as described above, indicates that simple evaporation of aqueous acetonitrile can lead to partial removal of the FMsc from primary OH functions. This undesirable instability of the FMsc can be explained by the increased susceptibility of the FMsc for β-elimination by the inductive electron withdrawing effect of the perfluoroalkyl chain. It was envisaged that the

[1*H*,1*H*,2*H*,2*H*,3*H*,3*H*]-perfluoroundecylsulfonylethoxycarbonyl (FPsc, **2**, Figure 1) group, in which the distance between the sulfonyl functionality and the perfluoro moiety is increased by an additional methylene group, should be more stable.

The synthesis of [1*H*,1*H*,2*H*,2*H*,3*H*,3*H*]-perfluoroundecylsulfonylethoxycarbonyl chloride (FPsc-Cl, **14**) started from the commercially available [1*H*,1*H*,2*H*,2*H*,3*H*,3*H*]-perfluoroundecyl iodide **11** as depicted in Scheme 3.[18] The iodide was substituted with mercaptoethanol in refluxing *tert*-butylalcohol to give thioether **12** in 95% yield (Scheme 3). In the next step, compound **12** was oxidized using peracetic acid in AcOH/H_2O. The resulting sulfone **13** was isolated in 96% yield. Treatment of primary alcohol **13** with phosgene in THF gave chlorocarbonate **14**.

Scheme 3: Synthesis of FPsc-Cl.

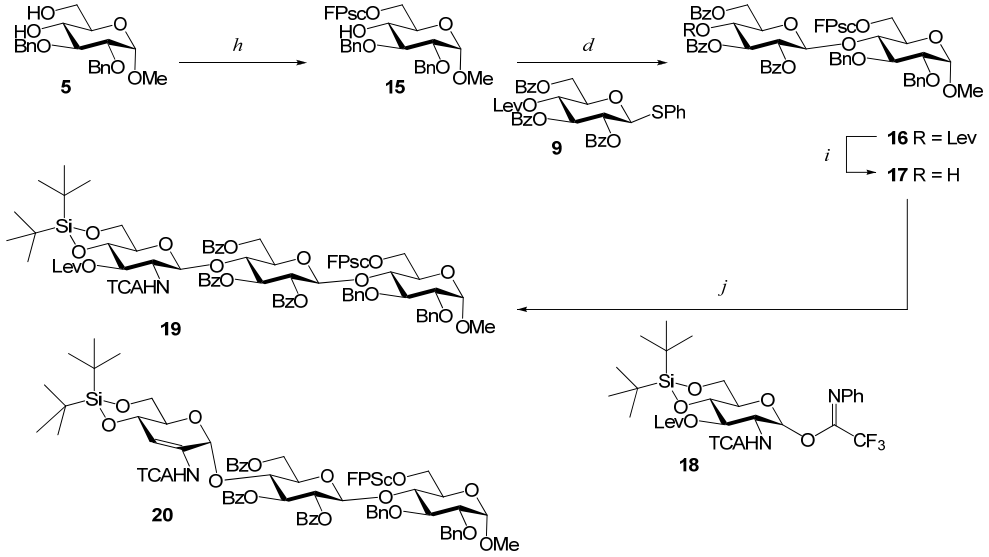


Reagents and conditions; *e*) mercaptoethanol, t-BuOH, NaOH, Reflux, 4h, 95%; *f*) AcOOH, AcOH, H_2O, EtOAc, 2h, 96%; *g*) phosgene, THF, 0 ºC, 16h, 100%.

Next, the usefulness of the FPsc group for oligosaccharide synthesis was assessed with the assembly of trisaccharide **19**.[19] First, the FPsc group was introduced selectively at the primary C6-OH of diol **5** by treatment with 1 equivalent FPsc chloride **14** at low temperature to give the acceptor glycoside **15** in 94% yield (Scheme 4). NIS/TMSOTf mediated condensation of fluorous acceptor **15** with excess of thiodonor **9** (3 equivalents), bearing a levulinoyl group at its C4-OH proceeded uneventfully. TLC analysis of the crude reaction mixture showed the presence of several products. Subsequent purification by FSPE, using a gradient of acetonitrile in water (50% to 100%) provided a single fluorous product. FPsc containing dimer **16** was isolated in excellent yield demonstrating the improved stability of the FPsc group with respect to its ethylene counterpart. The stability

of the FPsc was further substantiated by the selective removal of the levulinoyl group in **16** and ensuing purification by FSPE to afford alcohol **17** in 81% yield. Disaccharide **17** was elongated using an excess of (*N*-phenyl)trifluoro acetimidate **18**[20] (3 equivalents) and a catalytic amount of TfOH at -20 ^{o}C. After purification by FSPE, fluorous trimer **19** was isolated in 78%. It is of interest that executing the coupling of dimer **17** with **18** at 0 ^{o}C instead of -20 ^{o}C and purification by FSPE led to the isolation of a mixture of trimer **19** and a fluorous side product. After separation by silica gel chromatography, this side product was identified as FPsc protected trimer **20**, containing dehydroglucosamine. Formation of this product can be explained by β-elimination of the imidate group of donor **18**, followed by a Ferrier glycosylation on the resulting glycal.[21]

Scheme 4: Oligosaccharide synthesis using the FPsc group.



Reagents and conditions; *d*) i- NIS, TMSOTf, DCM, 0 ºC-RT, 1h; ii- FSPE, 93%; *h*) FPsc-Cl (**14**), pyr., DCM, -40 ºC-RT, 4, 94%; *i*) i- $H_2NNH_2.H_2O$, pyr./HOAc, 5 min; ii- FSPE, 94%; *j*) i- TfOH, DCM, -20 ºC-RT, 15 min; ii- FSPE, 78%

Conclusion:

In conclusion the FPsc group is a new fluorous hydroxyl-protecting group, suitable for implementation in oligosaccharide synthesis. The FPsc group can be introduced under

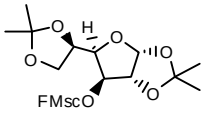
mild conditions and where necessary in a regioselective manner. It is cleaved under mild basic conditions, under which commonly used ester protecting groups stay intact. The FPsc group survives both acidic glycosylation conditions and the removal of the levulinoyl group.

Experimental:

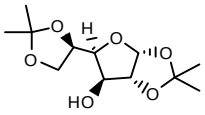
General: Dichloromethane was refluxed with P_2O_5 and distilled before use. Traces of water in donor and acceptor glycosides were removed by co-evaporation with toluene. Molecular sieves 3Å were flame dried before use. All other chemicals (Acros, Fluka, Merck, Fluorous Technologies Inc.) were used as received. Column chromatography was performed on Screening Devices silica gel 60 (0.040-0.063 mm). TLC analysis was conducted on DC-alufolien (Merck, kiesel gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with an aqueous solution of $KMnO_4$ (20%) and K_2CO_3 (10%), by spraying with 20% H_2SO_4 in ethanol or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10g/L) in 10% $H_2SO_{4\,(aq)}$ followed by charring at ~150 ºC. IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotations were measured on a Propol automatic polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV 400 (400 MHz and 100 MHz respectively), AV 500 (500 MHz and 125 MHz respectively) or DMX 600 (600 MHz and 150 MHz respectively). NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Chemical shift are relative to tetramethylsilane and are given in ppm. Coupling constants are given in Hz. All given ^{13}C spectra are proton decoupled. High resolution mass spectra were recorded on a LTQ-Orbitrap (thermo electron).

General method for glycosylations using NIS/TMSOTf: A solution of 1-thio-β-D-glucopyranoside (donor) and acceptor in DCM (0.05 M) was stirred over activated MS3Å for 30 minutes before *N*-iodosuccinimide (1.3 eq with respect to the donor) was added. The mixture was cooled to -40 °C followed by the addition of trimethylsilyl trifluoromethanesulfonate (0.1 eq). The mixture was allowed to warm to room temperature. The reaction mixture was quenched with triethylamine (5 eq), filtered, diluted with ETOAc and washed with $Na_2S_2O_{3\,(aq)}$. The aqueous layer was extracted with EtOAc thrice, after which the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by fluorous solid phase extraction (FSPE).

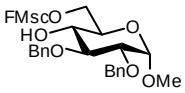
General procedure for fluorous solid phase extraction (FSPE): A FSPE Cartridge preloaded with 10 g of fluorous silica gel was eluted with DMF (20 ml), acetonitrile (30 ml) and 50% acetonitrile in H_2O (50 ml) before loading the crude product in acetonitrile (1.5 ml). The cartridge was eluted with 50% acetonitrile in H_2O (50 ml) and 70% acetonitrile in H_2O (50 ml) to wash the fluorophobic fraction. Next, fluorophilic fraction was eluted with acetonitrile (50 ml) to afford the target compound.



1,2:5,6-di-*O*-isopropylidene-3-*O*-([1H,1H,2H,2H]-perfluorodecyl)sulfonylethoxycarbonyl-α-D-glucofuranoside (4): A solution of 1,2:5,6-*O*-isopropylidene-α-D-glucofuranose **3** (0.039 g, 0.14 mmol) in DCM (1.5 ml, 0.1 M) was cooled to 0 °C before pyridine (36 µl, 0.45 mmol, 3 eq) was added. Next, ([1H,1H,2H,2H]-perfluorodecyl)sulfonylethoxycarbonyl chloride (FMsc-Cl, 10% in DCM, 0.185 g, 0.30 mmol, 2 eq) was added drop-wise at 0 °C over the span of 30 minutes. The mixture was allowed to warm to room temperature. The reaction mixture was quenched with methanol, diluted with DCM, washed with $NaHCO_{3\,(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography to afford compound **9** (0.120 g, 142 µmol, 95%). TLC (50% n-hexane in EtOAc): R_f = 0.8; $[\alpha]_D^{22}$: +10.8º (c = 0.5, DCM); IR (neat, cm^{-1}): 494, 1023, 1091, 1145, 1199, 1373, 1748; ^1H NMR (600 MHz, $CDCl_3$) δ = 1.28 (s, 3H, CH_3 isopropylidene), 1.29 (s, 3H, CH_3 isopropylidene), 1.40 (s, 3H, CH_3 isopropylidene), 1.50 (s, 3H, CH_3 isopropylidene), 2.67 (m, 2H, $RfC\underline{H}_2CH_2SO_2(CH_2)_2$-), 3.32 (m, 2H, $RfCH_2C\underline{H}_2SO_2(CH_2)_2$-), 3.40 (m, 2H, $Rf(CH_2)_2SO_2C\underline{H}_2CH_2$-), 4.02 (m, 2H, 2xH-6), 4.15 (m, 2H, H-4 and H-5), 4.55 (d, 1H, *J* = 3.6 Hz, H-3), 4.61 (m, 2H, $Rf(CH_2)_2SO_2CH_2C\underline{H}_2$-), 5.14 (d, 1H, *J* = 2.4 Hz, H-2), 5.85 (d, 1H, *J* = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 23.5 (t, *J* = 22.0 Hz, $RfC\underline{H}_2CH_2SO_2(CH_2)_2$-), 24.5 ($CH_3$ isopropylidene), 25.6 (CH_3 isopropylidene), 26.2 (CH_3 isopropylidene), 26.5 (CH_3 isopropylidene), 45.8 ($RfCH_2\underline{C}H_2SO_2(CH_2)_2$-), 52.3 ($Rf(CH_2)_2SO_2\underline{C}H_2CH_2$-), 60.8 ($Rf(CH_2)_2SO_2CH_2\underline{C}H_2$-), 66.7 (C-6), 71.8, 79.1 (C-4 and C-5), 79.8 (C-3), 82.6 (C-2), 104.5 (C-1), 109.1 (C_q isopropylidene), 112.0 (C_q isopropylidene), 152.6 (C=O FMsc); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -126.4, -123.7, -123.0, -122.2, -122.0, -114.8 (CF_2), -81.1 (CF_3); HRMS $[M+Na]^+$ calcd for $C_{25}H_{27}O_{10}SNa$ 865.09457 was found 865.09521.

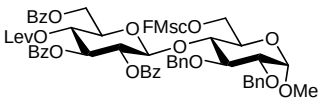


1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (Cleavage of FMsc from 4): To a solution of **4** (24 mg, 28 µmol) in dioxane (0.6 ml, 0.05 M) was added DBU (1% in dioxane, 42 µl, 2.9 µmol, 0.1 eq) and the reaction mixture was stirred for 1 minute. The reaction mixture was neutralized with $NH_4Cl_{\,(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{\,(aq)}$, $NaHCO_{3\,(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography to afford 1,2:5,6-di-*O*-isopropylidene- -α-D-glucofuranose (7.3 mg, 28 µmol, 98%)

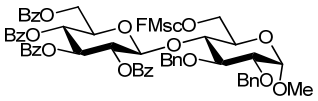


Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H]-perfluorodecyl)sulfonylethoxycarbonyl -α-D-glucopyranoside (6): A solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **5** (0.127 g, 0.34 mmol) in DCM (1 ml, 0.3 M) was cooled to -20 °C before pyridine (82 ml, 1.0 mmol, 3 eq) was added. Next, ([1H,1H,2H,2H]-perfluorodecylsulfonylethoxycarbonyl chloride (FMsc-Cl in 0.1 ml DCM, 0.419 g, 0.68 mmol, 2 eq) was added drop-wise over the span of 45 minutes. The mixture was allowed to warm to room temperature and stirring was continued for 4 hours. The reaction mixture was quenched with methanol, diluted with DCM, washed with $NaHCO_{3\,(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography to afford **6** (0.310 g, 0.32 mmol , 95%). TLC (50% EtOAc in n-hexane): R_f = 0.9; $[\alpha]_D^{22}$: +11.6º (c = 1, DCM); IR (neat, cm^{-1}): 1056, 1134,

1145, 1199, 1749; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.61-2.69 (m, 2H, RfC<u>H</u>$_2$CH$_2$SO$_2$(CH$_2$)$_2$-), 3.30 (m, 2H, RfCH$_2$C<u>H</u>$_2$SO$_2$(CH$_2$)$_2$-), 3.33 (s, 3H, CH_3 OMe), 3.37 (m, 3H, H-4 and Rf(CH$_2$)$_2$SO$_2$C<u>H</u>$_2$CH$_2$-), 3.47 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, H-2), 3.74 (m, 2H, H-3 and H-5), 4.33 (dd, 1H, *J* = 5.4 Hz, *J* = 11.4 Hz, H-6), 4.37 (dd, 1H, *J* = 1.8 Hz, *J* = 11.4 Hz, H-6), 4.55 (t, 2H, *J* = 4.8 Hz, Rf(CH$_2$)$_2$SO$_2$CH$_2$C<u>H</u>$_2$-), 4.57 (d, 1H, *J* = 3.6 Hz, H-1), 4.62 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.67 (d, 1H, *J* = 11.4 Hz, CH<u>H</u> Bn), 4.74 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.99 (d, 1H, *J* = 11.4 Hz, CH<u>H</u> Bn), 7.22-7.41 (m, 10H, H arom); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 24.0 (t, *J* = 22.5 Hz, Rf<u>C</u>H$_2$CH$_2$SO$_2$(CH$_2$-)$_2$), 46.3 (RfCH$_2$<u>C</u>H$_2$SO$_2$(CH$_2$-)$_2$), 52.8 (Rf(CH$_2$)$_2$SO$_2$<u>C</u>H$_2$CH$_2$-), 55.2 (CH_3 OMe), 61.0 (Rf(CH$_2$)$_2$SO$_2$CH$_2$<u>C</u>H$_2$-), 67.6 (C-6), 68.8 (C-3 or C-5), 69.7 (C-4), 73.2 (CH_2 Bn), 75.4 (CH_2 Bn), 79.6 (C-2), 81.0 (C-3 or C-5), 98.1 (C-1), 128.0-129.0 (CH arom), 137.8 (C_q Bn), 138.5 (C_q Bn), 154.3 (C=O FMsc); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -129.6, -126.7, -126.2, -125.4, -125.2, -117.3 (CF_2), -84.3 (CF_3); HRMS $[M+Na]^+$ calcd for $C_{34}H_{33}O_{10}F_{17}SNa$ 979.14152 was found 979.14211.

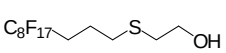


Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H]-perfluorodecyl)sulfonylethoxycarbonyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-levulinoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (8): Disaccharide **8** was prepared form acceptor **6** (0.055 g, 57.5 μmol, 1 eq) and donor **7** (0.117 g, 172.5 μmol, 3 eq) according to the general procedure for glycosylations as described above. The crude product was purified by general procedure of FSPE as described above. The side product generated during the evaporation of solvent was removed by silica gel chromatography to afford compound **8** (0.055 g, 36 μmol, 63%). TLC (33% EtOAc in toluene): R_f = 0.3; $[\alpha]_D^{22}$: +34.4º (c = 1, DCM); IR (neat, cm^{-1}): 713, 1147, 1207, 1269, 1732; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.92 (s, 3H, CH_3 Lev), 2.28-2.55 (m, 4H, 2xCH_2 Lev), 2.69 (m, 2H, RfC<u>H</u>$_2$CH$_2$SO$_2$(CH$_2$)$_2$-), 3.25 (s, 3H, CH_3 OMe), 3.34 (m, 4H, RfCH$_2$C<u>H</u>$_2$SO$_2$(CH$_2$)$_2$- and Rf(CH$_2$)$_2$SO$_2$C<u>H</u>$_2$CH$_2$-), 3.42 (dd, 1H, *J* = 3.5 Hz, *J* = 9.5 Hz, H-2), 3.73 (m, 2H, H-4 and H-5), 3.79 (m, 1H, H-5'), 3.96 (t, 1H, *J* = 9.0 Hz, H-3), 4.19 (dd, 1H, *J* = 3.0 Hz, *J* = 11.0 Hz, H-6), 4.25 (m, 2H, H-6 and H-6'), 4.34 (dd, 1H, *J* = 2.0 Hz, *J* = 12.0 Hz, H-6'), 4.41-4.45 (m, 1H, Rf(CH$_2$)$_2$SO$_2$CH$_2$CH<u>H</u>-), 4.48 (d, 1H, *J* = 3.5 Hz, H-1), 4.56 (m, 2H, Rf(CH$_2$)$_2$SO$_2$CH$_2$CH<u>H</u>- and CH<u>H</u> Bn), 4.67 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.91 (d, 1H, *J* = 11.5 Hz, CH<u>H</u> Bn), 5.02 (m, 2H, H-1' and CH<u>H</u> Bn), 5.38-5.46 (m, 2H, H-4' and H-2'), 5.68 (t, 1H, *J* = 9.5 Hz, H-3'), 7.20-8.02 (m, 25H, H arom); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.7 (MeCOCH$_2$<u>C</u>H$_2$COO), 29.3 (CH_3 Lev), 29.7 (Rf<u>C</u>H$_2$CH$_2$SO$_2$(CH$_2$)$_2$), 37.7 (MeCO<u>C</u>H$_2$CH$_2$COO), 45.9 (RfCH$_2$<u>C</u>H$_2$SO$_2$(CH$_2$)$_2$), 52.5 (Rf(CH$_2$)$_2$SO$_2$<u>C</u>H$_2$CH$_2$), 55.2 (CH_3 OMe), 60.5 (Rf(CH$_2$)$_2$SO$_2$CH$_2$<u>C</u>H$_2$), 62.2 (C-6'), 66.5 (C-6), 67.6 (C-4 or C-5), 68.5 (C-4'), 71.3 (C-5'), 71.9 (C-2'), 72.4 (C-3'), 73.4 (CH_2 Bn), 74.9 (CH_2 Bn), 78.2 (C-4 or C-5), 79.4 (C-2), 79.6 (C-3), 97.9 (C-1), 100.9 (C-1'), 126.7-133.3 (CH arom), 128.8 (C_q Bz), 137.9 (C_q Bn), 139.0 (C_q Bn), 153.8 (C=O FMsc), 165.0 (C=O Bz), 165.7 (C=O Bz), 165.9 (C=O Bz), 171.3 (C=O MeCOCH$_2$CH$_2$<u>CO</u>O), 205.5 (C=O Me<u>CO</u>CH$_2$CH$_2$COO-); ^{19}F NMR (376 MHz, ($CDCl_3$) δ = -126.4, -123.7, -123.0, -122.2, -122.0, -114.7 (CF_2), -81.1 (CF_3); HRMS $[M+Na]^+$ calcd for $C_{66}H_{62}O_{20}F_{17}S$ 1551.30977 was found 1551.30844.

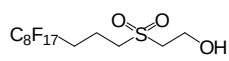


Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H]-perfluorodecyl)sulfonylethoxycarbonyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-

β-D-glucopyranosyl)-α-D-glucopyranoside (10): Disaccharide **10** was prepared from acceptor **6** (0.045 g, 47 μmol, 1 eq) and donor **9** (0.094 g, 0.141 mmol, 3 eq) according to the general procedure for glycosylations as described above. The crude product was purified by general procedure of FSPE as described above. The side product generated during the evaporation of solvent was removed by silica gel chromatography to afford compound **10** (0.043 g, 28 μmol, 60%). TLC (50% EtOAc in PE): R_f = 0.6; $[\alpha]_D^{22}$: +40.4º (c = 0.5, DCM); IR (neat, cm^{-1}): 708, 1026, 1091, 1205, 1244, 1733; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.67-2.73 (m, 2H, RfC$\underline{H}_2$CH$_2$SO$_2$(CH$_2$)$_2$-), 3.27 (s, 3H, CH$_3$ OMe), 3.38 (m, 4H, RfCH$_2$C$\underline{H}_2$SO$_2$(CH$_2$-)$_2$ and Rf(CH$_2$)$_2$SO$_2$C$\underline{H}_2$CH$_2$-), 3.44 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, H-2), 3.75 (m, 2H, H-5 and H-4), 3.94 (m, 2H, H-3 and H-5'), 4.24 (m, 3H, H-6, H-6 and H-6'), 4.37 (dd, 1H, *J* = 3.2 Hz, *J* = 12.0 Hz, H-6'), 4.41-4.47 (m, 1H, Rf(CH$_2$)$_2$SO$_2$CH$_2$CH$\underline{H}$-), 4.49 (d, 1H, *J* = 3.6 Hz, H-1), 4.55 (m, 2H, Rf(CH$_2$)$_2$SO$_2$CH$_2$CH$\underline{H}$- and CH$\underline{H}$ Bn), 4.69 (d, 1H, *J* = 12.0 Hz, CH$\underline{H}$ Bn), 4.92 (d, 1H, *J* = 11.6 Hz, CH$\underline{H}$ Bn), 5.04 (d, 1H, *J* = 11.6 Hz, CH$\underline{H}$ Bn), 5.08 (d, 1H, *J* = 8.0 Hz, H-1'), 5.52 (dd, 1H, *J* = 8.0 Hz, *J* = 9.6 Hz, H-2'), 5.64 (t, 1H, *J* = 9.6 Hz, H-4'), 5.87 (t, 1H, *J* = 9.6 Hz, H-3'), 7.19-7.98 (m, 30H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.1 (t, *J* = 22.0 Hz, Rf$\underline{C}$H$_2$CH$_2$SO$_2$(CH$_2$)$_2$-), 54.9 (RfCH$_2$$\underline{C}H_2SO_2$(CH$_2$)$_2$-), 52.6 (Rf(CH$_2$)$_2SO_2$$\underline{C}H_2$CH-$_2$), 55.3 (CH$_3$ OMe), 60.5 (Rf(CH$_2$)$_2$SO$_2$CH$_2$$\underline{C}H_2$-), 62.8 (C-6'), 66.6 (C-6), 69.4 (C-4 or C-5), 72.0 (C-4'), 72.5 (C-5'), 72.6 (C-2'), 73.0 (C-3'), 73.5 (CH$_2$ Bn), 74.9 (CH$_2$ Bn), 78.1 (C-4 or C-5), 79.4 (C-2), 79.6 (C-3), 98.0 (C-1), 101.0 (C-1'), 126.9-133.3 (CH arom), 128.7 (C$_q$ Bz), 128.8 (C$_q$ Bz), 128.9 (C$_q$ Bz), 129.6 (C$_q$ Bz), 138.0 (C$_q$ Bn), 139.0 (C$_q$ Bn), 153.9 (C=O FMsc), 165.0 (C=O Bz), 165.0 (C=O Bz), 165.7 (C=O Bz), 166.0 (C=O Bz); ^{19}F NMR (376 MHz, ($CDCl_3$) δ = -126.4, -123.4, -123.0, -122.2, -121.9, -113.9 (CF_2), -81.1 (CF_3); HRMS $[M+H]^+$ calcd for $C_{68}H_{60}O_{19}F_{17}S$ 1535.31726 was found 1535.31891, $[M+Na]^+$ calcd for $C_{68}H_{58}O_{19}F_{17}SNa$ 1557.29920 was found 1557.30047.

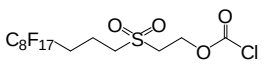


([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfidylethanol (12): NaOH (0.714 g, 17.9 mmol, 1.5 eq) and 2-mercaptoethanol (2.1 ml, 29.8 mmol, 2.5 eq) were refluxed in *t*-BuOH (40 ml) for 30 minutes. ([1H,1H,2H,2H,3H,3H]-perfluoroundecyl iodide (7.0 g, 11.9 mmol, 1 eq) was added and the mixture was refluxed for 2h. After evaporation of all volatiles, the crude product was subjected to silica gel column chromatography to give the compound **12** (6.11 g, 11.4 mmol, 95%). TLC (33% EtOAC in Toluene): R_f = 0.7; IR (neat, cm^{-1}): 528, 1197, 3341; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.94 (m, 2H, RfCH$_2$C$\underline{H}_2$CH$_2$S(CH$_2$)$_2$OH), 2.24 (m, 2H, RfC$\underline{H}_2$(CH)$_2$S(CH)$_2$OH), 2.67 (t, 2H, *J* = 7.2 Hz, Rf(CH$_2$)$_2$C$\underline{H}_2$S(CH$_2$)$_2$OH), 2.76 (t, 2H, *J* = 6.0 Hz, Rf(CH$_2$)$_3$SC$\underline{H}_2$CH$_2$OH), 3.79 (t, 2H, *J* = 6.0 Hz, Rf(CH$_2$)$_3$SCH$_2$C$\underline{H}_2$OH), 3.87 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.2 (RfCH$_2$$\underline{C}H_2CH_2$S(CH$_2$)$_2$OH), 29.6 (t, *J* = 22.0 Hz, Rf$\underline{C}$H$_2$(CH$_2$)$_2$S(CH$_2$)$_2$OH), 30.9 (Rf(CH$_2$)$_2$$\underline{C}H_2$S(CH$_2$)$_2$OH), 34.4 (Rf(CH$_2$)$_3S\underline{C}H_2CH_2$OH), 60.8 (Rf(CH$_2$)$_3SCH_2$$\underline{C}H_2$OH), 107.8-120.8 (CF); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -127.4, -124.4, -123.8, -123.0, -122.7, -115.1 (CF_2), -81.3 (CF_3); HRMS $[M+H]^+$ calcd for $C_{13}H_{12}O_1F_{17}S_1$ 539.03319 was found 539.03327.

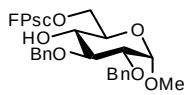


([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethanol (13): 39% AcOOH (4.9 ml, 28.4 mmol, 2.5 eq) and H_2O (2 ml) were added to a solution of **12** (6.11 g, 11.4 mmol) in ice cooled AcOH (3.8 ml). If gel formation occurred, EtOAc (5 ml) was added. The mixture was stirred for 90 minutes. The mixture was neutralized by careful addition of $NaHCO_{3\ (s)}$, extracted using large excess of

EtOAc, dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography to afford white crystalline **13** (6.21 g, 10.9 mmol, 96%). TLC (75% EtOAc in PE): R_f = 0.6; IR (neat, cm^{-1}): 506, 1115, 3475; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ = 2.18 (m, 2H, $RfCH_2C\underline{H}_2CH_2SO_2(CH_2)_2OH$), 2.42-2.56 (m, 2H, $RfC\underline{H}_2(CH_2)_2SO_2(CH_2)_2OH$), 3.29 (t, 2H, *J* = 5.6 Hz, $Rf(CH_2)_2C\underline{H}_2SO_2(CH_2)_2OH$), 3.35 (t, 2H, *J* = 7.6 Hz, $Rf(CH_2)_3SO_2C\underline{H}_2CH_2OH$), 4.03 (dt, 2H, *J* = 5.2 Hz, *J* = 5.6 Hz, $Rf(CH_2)_3SO_2CH_2C\underline{H}_2OH$), 4.26 (t, 1H, *J* = 5.2 Hz, OH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ = 13.6 ($RfCH_2\underline{C}H_2CH_2SO_2(CH_2)_2OH$), 29.0 (m, $Rf\underline{C}H_2(CH_2)_2SO_2(CH_2)_2OH$), 52.9 ($Rf(CH_2)_2\underline{C}H_2SO_2(CH_2)_2OH$), 55.3 ($Rf(CH_2)_3SO_2\underline{C}H_2CH_2OH$), 55.9 ($Rf(CH_2)_3SO_2CH_2\underline{C}H_2OH$), 111.1-121.0 (CF); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ = -127.2, -124.5, -123.7, -122.8, -122.7, -114.7 (CF_2), -81.2 (CF_3); HRMS $[M+H]^+$ calcd for $C_{13}H_{12}O_3F_{17}S_1$ 571.02302 was found 571.02302.

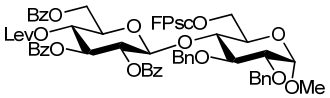


([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl chloride (14): To the solution of **13** (5.90 g, 10.4 mmol,) in freshly distilled THF (65 ml, 0.16 M) was added phosgene (20% in toluene, 9.4 ml, 18.6 mmol, 1.8 eq) at 0 ºC and the reaction mixture was stirred for 16 hours. Next the solvents and phosgene were removed *in vacuo* to give **14** (6.54 g, 10.4 mmol, 100%); IR (neat, cm^{-1}): 1139, 1769; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.26 (m, 2H, $RfCH_2C\underline{H}_2CH_2SO_2(CH_2)_2O$-), 2.36 (m, 2H, $RfC\underline{H}_2(CH_2)_2SO_2(CH_2)_2O$-), 3.18 (t, 2H, *J* = 7.2 Hz, $Rf(CH_2)_2C\underline{H}_2SO_2(CH_2)_2O$-), 3.40 (t, 2H, *J* = 5.6 Hz, $Rf(CH_2)_3SO_2C\underline{H}_2CH_2O$-), 4.76 (t, 2H, *J* = 5.6 Hz, $Rf(CH_2)_3SO_2CH_2C\underline{H}_2O$-); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.7 ($RfCH_2\underline{C}H_2CH_2SO_2(CH_2)_2O$-), 29.2 (m, $Rf\underline{C}H_2(CH_2)_2SO_2(CH_2)_2O$-), 51.8 ($Rf(CH_2)_2\underline{C}H_2SO_2(CH_2)_2O$-), 53.5 ($Rf(CH_2)_3SO_2\underline{C}H_2CH_2O$-), 64.4 ($Rf(CH_2)_3SO_2CH_2\underline{C}H_2O$-); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -126.5, -123.8, -123.1, -122.3, -122.0, -114.7 (CF_2) , -81.2 (CF_3); HRMS $[M+H]^+$ calcd for $C_{14}H_{10}O_4F_{17}S_1Na$ 654.96091 was found 654.95760.

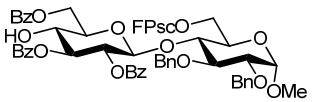


Methyl 2,3,-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl-α-D-glucopyranoside (15): A solution of **5** (0.153 g, 0.41 mmol) in DCM (1.4 ml, 0.3 M) was cooled to -40 ºC before pyridine (0.1 ml, 1.22 mmol, 3 eq) was added. Next, ([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl chloride (FPsc-Cl in 0.1 ml DCM, 0.387 g, 0.61 mmol, 1.5 eq) was added drop-wise over the span of 45 minutes. The reaction mixture was allowed to warm to room temperature and the stirring was continued for 4 hours. The reaction mixture was quenched with methanol, diluted with DCM, washed with $NaHCO_{3\,(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated and the crude product was purified by silica gel column chromatography to afford **15** (0.372 g, 0.38 mmol, 94%). TLC (5% Et_2O in DCM): R_f = 0.8; $[\alpha]_D^{22}$: +20.2º (c = 1, DCM); IR (neat, cm^{-1}): 734, 1200, 1748, 2927; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.14-2.21 (m, 2H, $RfCH_2C\underline{H}_2CH_2SO_2(CH_2)_2$-), 2.23-2.34 (m, 2H, $RfC\underline{H}_2(CH_2)_2SO_2(CH_2)_2$-), 2.72 (s, 1H, C4-OH), 3.09 (t, 2H, *J* = 7.6 Hz, $Rf(CH_2)_2C\underline{H}_2SO_2(CH_2$-$)_2$), 3.29 (t, 2H, *J* = 5.6 Hz, $Rf(CH_2)_3SO_2C\underline{H}_2CH_2$-), 3.36 (s, 3H, CH_3 OMe), 3.44 (t, 1H, *J* = 10.0 Hz, H-4), 3.49 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, H-2), 3.73-3.80 (m, 2H, H-3 and H-5), 4.37 (m, 2H, 2xH-6), 4.51 (t, 2H, *J* = 6.0 Hz, $Rf(CH_2)_3SO_2CH_2C\underline{H}_2$-), 4.61 (d, 1H, *J* = 3.2 Hz, H-1), 4.64 (d, 1H, *J* = 12.4 Hz, CH<u>H</u> Bn), 4.74 (m, 2H, 2xCH<u>H</u> Bn), 4.99 (d, 1H, *J* = 11.2 Hz, CH<u>H</u> Bn), 7.26-7.35 (m, 10H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.4 ($RfCH_2\underline{C}H_2CH_2SO_2(CH_2)_2$-), 29.3 (t, *J* = 22.0 Hz, $Rf\underline{C}H_2(CH_2)_2SO_2(CH_2)_{2}$-), 52.0 ($Rf(CH_2)_2\underline{C}H_2SO_2(CH_2)_2$-),

52.9 (Rf$(CH_2)_3SO_2\underline{C}H_2CH_2$-), 55.1 ($CH_3$ OMe), 61.0 (Rf$(CH_2)_3SO_2CH_2\underline{C}H_2$-), 67.3 (C-6), 68.9 (C-5), 69.6 (C-4), 73.0 (CH_2 Bn), 75.3 (CH_2 Bn), 79.5 (C-2), 81.0 (C-3), 98.0 (C-1), 108.3-118.4 (CF), 127.4-128.4 (CH arom), 137.8 (C_q Bn), 138.6 (C_q Bn), 154.3 (C=O FPsc); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -126.4, -123.7, -123.0, -122.2, -122.0, -114.8 (CF_2), -81.1 (CF_3); HRMS $[M+Na]^+$ calcd for $C_{35}H_{35}O_{10}F_{17}SNa$ 993.15717 was found 993.15814.

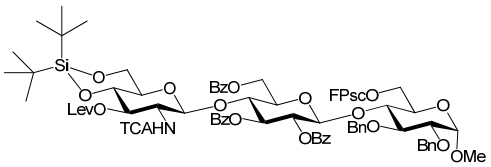


Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-levulinoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (16): Disaccharide **16** was prepared from acceptor **15** (0.31 g, 0.39 mmol, 1 eq) and donor **9** (0.57 g, 0.84 mmol, 2.6 eq) according to the general procedure for glycosylations as described above. The crude product was purified by general procedure of FSPE as described above to afford compound **16** (0.46 g, 0.30 mmol, 93%). TLC (5% Methanol in DCM): R_f = 0.85; $[\alpha]_D^{22}$: +24.4° (c = 0.5, DCM); IR (neat, cm^{-1}): 710, 1203, 1722; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.90 (s, 3H, CH_3 Lev), 2.15-2.21 (m, 2H, Rf$CH_2\underline{C}H_2CH_2SO_2(CH_2)_2$-), 2.25-2.43 (m, 4H, 2x$CH_2$ Lev), 2.49 (m, 2H, Rf$\underline{C}H_2(CH_2)_2SO_2(CH_2)_2$-), 3.18 (t, 2H, *J* = 7.6 Hz, Rf$(CH_2)_2\underline{C}H_2SO_2(CH_2)_2$-), 3.25 (s, 3H, CH_3 OMe), 3.26-3.32 (m, 1H, Rf$(CH_2)_3SO_2CH\underline{H}CH_2$-), 3.38 (m, 1H, Rf$(CH_2)_3SO_2CH\underline{H}CH_2$-), 3.42 (dd, 1H, *J* = 4.8 Hz, *J* = 11.6 Hz, H-2), 3.72 (m, 1H, H-5), 3.79 (t, 1H, *J* = 8.8 Hz, H-4), 3.91 (m, 1H, H-5'), 3.97 (t, 1H, *J* = 9.2 Hz, H-3), 4.22 (m, 1H, H-6), 4.26-4.32 (m, 2H, H-6 and H-6'), 4.38 (dd, 1H, *J* = 2.0 Hz, *J* = 12.0 Hz, H-6'), 4.41-4.47 (m, 1H, Rf$(CH_2)_3SO_2CH_2CH\underline{H}$-), 4.50 (d, 1H, *J* = 3.6 Hz, H-1), 4.52-4.58 (m, 2H, Rf$(CH_2)_3SO_2CH_2CH\underline{H}$- and C$\underline{H}$ Bn), 4.69 (d, 1H, *J* = 12.0 Hz, C$\underline{H}$ Bn), 4.90 (d, 1H, *J* = 11.6 Hz, C$\underline{H}$ Bn), 5.06 (m, 2H, H-1' and C$\underline{H}$ Bn), 5.41-5.49 (m, 2H, H-4' and H-2'), 5.72 (t, 1H, *J* = 9.6 Hz, H-3'), 7.17-8.04 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.5 (Rf$CH_2\underline{C}H_2CH_2SO_2(CH_2)_2$-), 27.6 (MeCOC$H_2\underline{C}H_2$COO-), 29.1 ($CH_3$ Lev), 29.3 (t, *J* = 22.0 Hz, Rf$\underline{C}H_2(CH_2)_2SO_2(CH_2)_2$-), 37.6 (MeCO$\underline{C}H_2CH_2$COO-), 51.7 (Rf$(CH_2)_2\underline{C}H_2SO_2(CH_2)_2$-), 52.7 (Rf$(CH_2)_3SO_2\underline{C}H_2CH_2$-), 55.2 ($CH_3$ OMe), 60.5 (Rf$(CH_2)_3SO_2CH_2\underline{C}H_2$-), 62.2 (C-6'), 66.3 (C-6), 67.6 (C-5), 68.5 (C-4'), 71.6 (C-5'), 72.1 (C-2'), 72.9 (C-3'), 79.3 (CH_2 Bn), 74.9 (CH_2 Bn), 78.0 (C-4), 79.4 (C-2), 79.4 (C-3), 97.9 (C-1), 100.7 (C-1'), 108.0-120.4 (CF), 127.9-133.3 (CH arom), 128.8 (C_q Bz), 137.8 (C_q Bn), 138.9 (C_q Bn), 153.9 (C=O FPsc), 164.9 (C=O Bz), 165.7 (C=O Bz), 165.9 (C=O Bz), 171.3 (C=O MeCOC$H_2CH_2\underline{CO}$O-), 205.5 (C=O Me$\underline{CO}CH_2CH_2$COO-); ^{19}F NMR (376 MHz, ($CDCl_3$) δ = -126.4, -123.7, -123.0, -122.2, -122.0, -114.7 (CF_2), -81.1 (CF_3); HRMS $[M+H]^+$ calcd for $C_{67}H_{64}O_{20}F_{17}S$ 1543.34347 was found 1543.34541.



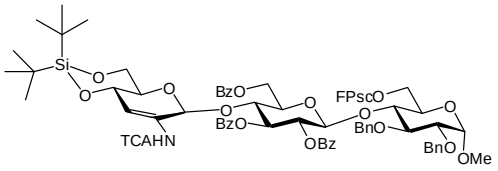
Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl-4-*O*-(2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (17): To a solution of **16** (0.44 g, 0.29 mmol) in pyridine (2.4 ml, 0.1 M) and acetic acid (0.6 ml) was added hydrazine hydrate (72 µl, 1.49 mmol, 5 eq) and the mixture was stirred for 5 minutes, quenched with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3\ (aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated. . The crude product was purified by general procedure of FSPE as described above to afford compound **16** (0.332 g, 0.23 mmol, 81%). TLC (40% Toluene in EtOAc): R_f = 0.6; $[\alpha]_D^{22}$: +44.0° (c = 1.0, DCM); IR (neat, cm^{-1}): 1044, 1246, 1719, 3395; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.20 (m, 2H, Rf$CH_2\underline{C}H_2CH_2SO_2(CH_2)_2$-), 2.26-2.33 (m, 2H, Rf$\underline{C}H_2(CH_2)_2SO_2(CH_2)_2$-),

3.14-3.21 (m, 2H, Rf(CH_2)$_2$C<u>H</u>$_2$SO$_2$(CH_2)$_2$-), 3.28 (m, 4H, CH_3 OMe and Rf(CH_2)$_3$SO$_2$CH<u>H</u>CH_2-), 3.40 (m, 1H, Rf(CH_2)$_3$SO$_2$CH<u>H</u>CH_2-), 3.45 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz, H-2) , 3.52 (d, 1H, *J* = 4.8 Hz, C4'-OH), 3.69-3.84 (m, 4H, H-5, H-5', H-4 and H-4'), 3.96 (t, 1H, *J* = 9.2 Hz, H-3), 4.20 (d, 1H, *J* = 11.2 Hz, H-6'), 4.30 (dd, 1H, *J* = 2.8 Hz, *J* = 9.6 Hz, H-6'), 4.39-4.50 (m, 3H, H-6, H-1 and Rf(CH_2)$_3$SO$_2$CH$_2$CH<u>H</u>-), 4.54-4.65 (m, 3H, H-6, Rf(CH_2)$_3$SO$_2$CH$_2$CH<u>H</u>-, and CH<u>H</u> Bn), 4.69 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.88 (d, 1H, *J* = 11.6 Hz, CH<u>H</u> Bn), 4.99 (d, 1H, *J* = 8.0 Hz, H-1'), 5.13 (d, 1H, *J* = 11.6 Hz, CH<u>H</u> Bn), 5.42 (t, 1H, *J* = 9.6 Hz, H-3'), 5.55 (t, 1H, *J* = 9.2 Hz, H-2'), 7.19-8.00 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.4 (RfCH$_2$<u>C</u>H$_2$CH$_2$SO$_2$(CH_2)$_2$-), 29.4 (t, *J* = 22.0 Hz, Rf<u>C</u>H$_2$(CH_2)$_2$SO$_2$(CH_2)$_2$-), 51.7 (Rf(CH_2)$_2$<u>C</u>H$_2$SO$_2$(CH_2)$_2$-), 52.8 (Rf(CH_2)$_3$SO$_2$<u>C</u>H$_2$CH$_2$-), 55.2 (CH_3 OMe), 60.4 (Rf(CH_2)$_3$SO$_2$CH$_2$<u>C</u>H$_2$-), 63.0 (C-6'), 66.4 (C-6), 67.7 (C-5), 69.0 (C-4'), 72.1 (C-2'), 73.4 (CH_2 Bn), 74.4 (C-5'), 75.0 (CH_2 Bn), 75.8 (C-3'), 78.2 (C-4), 79.1 (C-2), 79.6 (C-3), 98.0 (C-1), 100.9 (C-1'), 108.1-120.4 (CF), 126.9-133.3 (CH arom), 128.8 (C_q Bz), 128.9 (C_q Bz), 129.4 (C_q Bz), 137.9 (C_q Bn), 139.1 (C_q Bn), 154.0 (C=O FPsc), 165.1 (C=O Bz), 166.8 (C=O Bz), 167.0 (C=O Bz); ^{19}F NMR (376 MHz, ($CDCl_3$) δ = -126.5, -123.7, -123.1, -122.3, -122.0, -114.7 (CF_2) , -81.1 (CF_3); HRMS $[M+H]^+$ calcd for $C_{67}H_{58}O_{18}F_{17}S$ 1445.30724 was found 1445.30859, $[M+Na]^+$ calcd for $C_{62}H_{57}O_{18}F_{17}SNa$ 1467.28864 was found 1467.28959.



Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl-4-*O*-[2,3,6-tri-*O*-benzoyl-4-*O*-{2-deoxy-4,6-*O*-di-*tert*-butylsilyl-3-*O*-levulinoyl-2-*N*-trichloroacetamido-β-D-glucopyranosyl}-β-D-glucopyranosyl]-α-D-glucopyranoside (19): To the solution of **17** (0.288 g, 0.20 mmol) and **18** (0.394 mg, 0.60 mmol, 3 eq) in DCM (2 ml) was added triflic acid (5% in DCM, 67 µl, 0.02 mmol, 0.1 eq) at -20 ºC and the mixture was stirred at same temperature for 15 minutes before TLC showed complete disappearance of the acceptor. The mixture was diluted with EtOAc and washed with $NaHCO_{3\,(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated and purified by FPSE to give **19** (0.312 mg, 0.16 mmol, 78%). TLC (50% Toluene in EtOAc): R_f = 0.65; $[\alpha]_D^{22}$: +2.6º (c = 1.0, DCM); IR (neat, cm^{-1}): 710, 1069, 1728; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.76 (s, 9H, 3xCH_3 TBDS), 0.84 (s, 9H, 3xCH_3 TBDS), 2.11 (s, 3H, CH_3 Lev), 2.13-2.25 (m, 3H, RfCH$_2$C<u>H</u>$_2$CH$_2$SO$_2$(CH_2)$_2$-) and MeCOC<u>H</u>HCH$_2$COO-), 2.49 (m, 1H, H-6''), 2.51-2.58 (m, 3H, MeCOCH$_2$C<u>H</u>$_2$COO- and MeCOC<u>H</u>HCH$_2$COO-), 2.67 (m, 2H, RfC<u>H</u>$_2$(CH_2)$_2$SO$_2$(CH_2)$_2$-), 2.75-2.81(m, 1H, H-5''), 3.24 (m, 5H, CH_3 OMe, Rf(CH_2)$_2$C<u>H</u>HSO$_2$(CH_2)$_2$- and Rf(CH_2)$_3$SO$_2$CH<u>H</u>CH_2-), 3.35-3.46 (m, 4H, H-2, H-4'', H-6'' and Rf(CH_2)$_3$SO$_2$CH<u>H</u>CH_2-), 3.57 (m, 1H, Rf(CH_2)$_3$SO$_2$CH<u>H</u>CH_2-), 3.63 (m, 1H, H-5), 3.80 (m, 1H, H-2''), 3.85-3.92 (m, 3H, H-3, H-4 and H-4'), 4.00 (m, 1H, H-5'), 4.06 (d, 1H, *J* = 10.4 Hz, H-6), 4.12 (d, 1H, *J* = 12.4 Hz, H-6'), 4.23 (d, 1H, *J* = 8.4 Hz, H-1''), 4.38 (dd, 1H, *J* = 2.8 Hz, *J* = 11.6 Hz, H-6), 4.46 (d, 1H, *J* = 3.6 Hz, H-1), 4.51-4.57 (m, 2H, CH<u>H</u> Bn and Rf(CH_2)$_3$SO$_2$CH$_2$CH<u>H</u>-), 4.68-4.76 (m, 2H, Rf(CH_2)$_3$SO$_2$CH$_2$CH<u>H</u>- and CH<u>H</u> Bn), 4.84 (m, 3H, H-6', H-3'' and CH<u>H</u> Bn), 4.97 (d, 1H, *J* = 8.0 Hz, H-1'), 5.17 (d, 1H, *J* = 11.6 Hz, CH<u>H</u> Bn), 5.44 (dd, 1H, *J* = 8.4 Hz, *J* = 10.0 Hz, H-2'), 5.73 (t, 1H, *J* = 9.6 Hz, H-3'), 7.12-8.04 (m, 26H, H arom and NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.5 (RfCH$_2$<u>C</u>H$_2$CH$_2$SO$_2$(CH_2)$_2$-), 19.5 (C_q TBDS), 22.2 (C_q TBDS), 26.6 (3xCH_3 TBDS), 27.0 (3xCH_3 TBDS), 27.8 (MeCOCH$_2$<u>C</u>H$_2$COO-), 29.1 (t, *J* = 22.0 Hz, Rf<u>C</u>H$_2$(CH_2)$_2$SO$_2$(CH_2)$_2$-),

29.6 (CH_3 Lev), 37.9 (MeCO<u>C</u>H_2CH_2COO-), 50.5 (RfC$(CH_2)_2$<u>C</u>$H_2SO_2(CH_2)_2$-), 53.3 (Rf$(CH_2)_3SO_2$<u>C</u>H_2CH_2-), 55.3 (CH_3 OMe), 55.4 (C-4''), 60.2 (Rf$(CH_2)_3SO_2CH_2$<u>C</u>H_2-), 62.1 (C-6'), 64.7 (C-6''), 66.0 (C-6), 67.6 (C-5), 70.6 (C-5''), 71.9 (C-2'), 72.6 (C-3'), 72.6 (C-4), 73.6 (CH_2 Bn), 73.9 (C-3''), 74.4 (C-5'), 75.0 (CH_2 Bn), 75.7 (C-3), 78.7 (C-4' and C-2), 79.6 (C-2''), 92.2 (CCl_3), 98.3 (C-1), 100.8 (C-1''), 101.1 (C-1'), 108.3-118.5 (CF), 127.0-133.7 (CH arom), 128.4 (C_q Bz), 128.6 (C_q Bz), 128.7 (C_q Bz), 137.9 (C_q Bn), 139.2 (C_q Bn), 154.0 (C=O FPsc), 162.3 (C=O TCA), 165.2 (C=O Bz), 165.4 (C=O Bz), 166.8 (C=O Bz), 172.2 (C=O MeCOCH_2CH_2<u>CO</u>O-), 205.5 (C=O Me<u>CO</u>CH_2CH_2COO-); ^{19}F NMR (376 MHz, ($CDCl_3$) δ = -126.4, -123.7, -123.0, -122.2, -122.0, -114.6 (CF_2) , -81.1 (CF_3); HRMS $[M+H]^+$ calcd for $C_{83}H_{89}NO_{25}Cl_3F_{17}SSi$ 1988.40805 was found 1988.40959.



Methyl 2,3-di-*O*-benzyl-6-*O*-([1H,1H,2H,2H,3H,3H]-perfluoroundecyl)sulfonylethoxycarbonyl-4-*O*-[2,3,6-tri-*O*-benzoyl-4-*O*-{2,3-dideoxy-4,6-*O*-di-*tert*-butylsilyl-2-*N*-trichloroacetamido-*erythro*-hex-2-eno-pyranosyl}-β-D-glucopyranosyl]-α-D-glucopyranoside (20): When the synthesis of **19** was carried at 0 ºC, two fluorous products were obtained after FSPE. **19** was separated from **20** (14%) by silica gel column chromatography. TLC (50% Toluene in EtOAc): R_f = 0.75; $[\alpha]_D^{22}$: +52.8º (c = 0.8, DCM); IR (neat, cm^{-1}): 731, 1264; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (s, 9H, 3xCH_3 TBDS), 0.99 (s, 9H, 3xCH_3 TBDS), 2.11-2.35 (m, 4H, RfCH_2<u>C</u>$H_2CH_2SO_2(CH_2)_2$- and RfC<u>H</u>$_2(CH_2)_2SO_2(CH_2)_2$-), 3.07 (t, 2H, *J* = 7.6 Hz, Rf$(CH_2)_2$<u>C</u>$H_2SO_2(CH_2)_2$-), 3.19-3.26 (m, 5H, CH_3 OMe, Rf$(CH_2)_3SO_2$<u>C</u>H_2CH_2-), 3.41 (dd, 1H, *J* = 3.6 Hz, *J* = 9.2 Hz, H-2), 3.68 (m, 5H, H-4, H-5, H-6'', H-5', H-5''), 3.97 (t, 1H, *J* = 9.2 Hz, H-3), 4.03-4.11 (m, 2H, H-6 and H-6'), 4.16 (dd, 1H, *J* = 3.6 Hz, *J* = 11.6 Hz, H-6''), 4.23 (dd, 1H, *J* = 3.2 Hz, *J* = 11.6 Hz, H-6), 4.30 (t, 1H, *J* = 9.2 Hz, H-4'), 4.34-4.47 (m, 3H, H-4'' and Rf$(CH_2)_3SO_2CH_2$<u>C</u>H_2-), 4.49 (d, 1H, *J* = 3.6 Hz, H-1), 4.52 (d, 1H, *J* = 12.4 Hz, CH<u>H</u> Bn), 4.65 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.70 (dd, 1H, *J* = 3.0 Hz, *J* = 12.0 Hz, H-6'), 4.90 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.97-5.08 (m, 3H, ‚H-1', H-1'' and CH<u>H</u> Bn), 5.38 (dd, 1H, *J* = 8.0 Hz, *J* = 9.6 Hz, H-2'), 5.61 (t, 1H, *J* = 9.6 Hz, H-3'), 6.86 (s, 1H, H-3''), 7.15-8.06 (m, 26H, H arom and NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6 (RfCH_2<u>C</u>$H_2CH_2SO_2(CH_2)_2$-), 20.0 (C_q TBDS), 22.3 (C_q TBDS), 26.8 (3xCH_3 TBDS), 27.3 (3xCH_3 TBDS), 29.5 (t, *J* = 22.0 Hz, Rf<u>C</u>$H_2(CH_2)_2SO_2(CH_2)_2$-), 52.0 (RfC$(CH_2)_2$<u>C</u>$H_2SO_2(CH_2)_2$-), 52.8 (Rf$(CH_2)_3SO_2$<u>C</u>H_2CH_2-), 55.3 (CH_3 OMe), 60.2 (Rf$(CH_2)_3SO_2CH_2$<u>C</u>H_2-), 62.5 (C-6), 66.1 (C-6''), 66.6 (C-6'), 67.7, 68.5, 72.9, 77.4 (C-4, C-5, C-5' and C-5''), 69.5 (C-4''), 71.2 (C-4'), 72.6 (C-2'), 73.3 (CH_2 Bn), 74.6 (CH_2 Bn), 76.4 (C-3'), 78.9 (C-3), 79.6 (C-2), 92.2 (CCl_3), 92.6 (C-1''), 98.0 (C-1), 99.6 (C-1'), 118.2 (C-3''), 120.9 (C-2''), 126.5-134.0 (CH arom), 128.4 (C_q Bz), 128.6 (C_q Bz), 128.7 (C_q Bz), 137.9 (C_q Bn), 138.9 (C_q Bn), 153.9 (C=O FPsc), 159.9 (C=O TCA), 165.1 (C=O Bz), 165.8 (C=O Bz), 166.6 (C=O Bz); HRMS $[M+Na]^+$ calcd for $C_{78}H_{81}NO_{22}Cl_3F_{17}SSi$ 1894.34265 was found 1894.34094.

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