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Hybrid Fluorinated and Hydrogenated Double-Chain Surfactants for Handling Membrane Proteins

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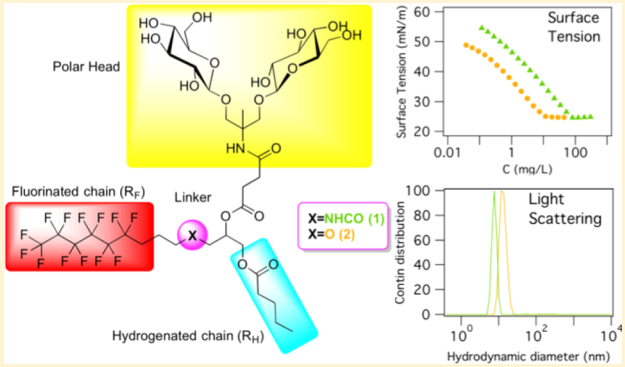
Supporting Information

ABSTRACT: Two hybrid fluorinated double-chain surfactants with a diglucosylated polar head were synthesized. The apolar domain consists of a perfluorohexyl main chain and a butyl hydrogenated branch as a side chain. They were found to self-assemble into small micelles at low critical micellar concentrations, demonstrating that the short branch increases the overall hydrophobicity while keeping the length of the apolar domain short. They were both able to keep the membrane protein bacteriorhodopsin stable, one of them for at least 3 months.



Detergents are used as solubilizing agents for the extraction, purification, and further downstream characterization of integral membrane proteins.[1] However, many of them lose their native structure and function in the presence of detergent, often irreversibly. Hence, recent years have witnessed increasing efforts at developing alternative, gentler solubilizing agents that could substitute for classical detergents without interfering with membrane protein structure and activity. There are currently several approaches including heterogeneous systems such as bicelles,[2] nanodiscs,[3] and polymers.[4−6] Among the homogeneous systems, i.e., chemically well-defined detergent-like molecules, one can cite maltoside−neopentyl glycols,[7] cyclic-based maltosides derivatives,[8] as well as tripod derivatives.[9]

Fluorinated surfactants are believed to provide a mild solubilizing environment for membrane proteins.[10,11] Indeed, fluorinated alkyl chains are considerably bulkier than fully hydrogenated ones and thus insert less easily between protein transmembrane helices. In addition, van der Waals interactions between fluorocarbons and hydrocarbons are weaker than those among hydrocarbons, thereby preserving native interactions and avoiding delipidation. As a consequence, fluorinated surfactants do not to exert detergent activity and, thus, do not allow direct membrane solubilization and protein extraction excepted in rare cases.[12,13]

According to the packing parameter theory,[14,15] micelle size and shape are a function of the geometry of the detergent itself, which in turn alter protein/detergent complex composition and stability as experienced for fluorinated surfactants.[16] As shown for alkyl maltosides, decreasing the length of the aliphatic chain leads to micelles and protein/detergent complexes of smaller sizes,[17] and adding a small aliphatic branch close to the head increased hydrophobicity without affecting the size of the micelles.[18] Therefore, increasing the overall hydrophobicity of the surfactant while keeping the length of the apolar domain short is a means for obtaining small, nondenaturing micelles, essential for membrane protein structural investigations.

In this work, we have synthesized two hybrid double-chain surfactants **1** and **2** that possess a diglucose-based polar headgroup and a six-carbon perfluorinated chain with a branched hydrogenated chain. The aim was to combine both properties of hydrogenated and fluorinated chains and to increase the hydrophobicity of the surfactants. Previously designed hybrid surfactants exhibit potentially interesting properties for membrane proteins solubilization as they form small micelles with long lifetime,[19] in which hydrophobic molecules can be solubilized.[20] Due to the low critical micellar concentration (CMC) of fluorocarbon surfactants compared to their hydrogenated analogues,[21] we used a six-carbon perfluorinated chain. Indeed, related glycosylated fluorinated surfactants with the same chain exhibit CMCs in the 0.1−1.0 mM range.[21−23] The linker between the fluorinated chain and the polar headgroup is either an amide bond for compound **1** or an ether bond for

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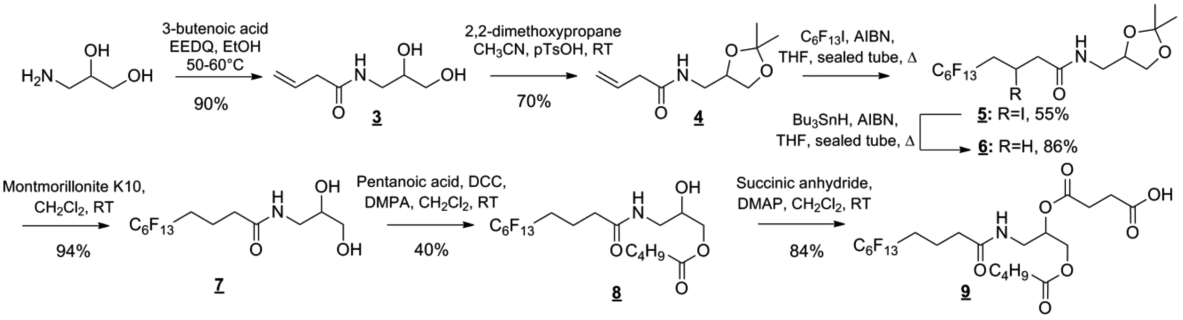
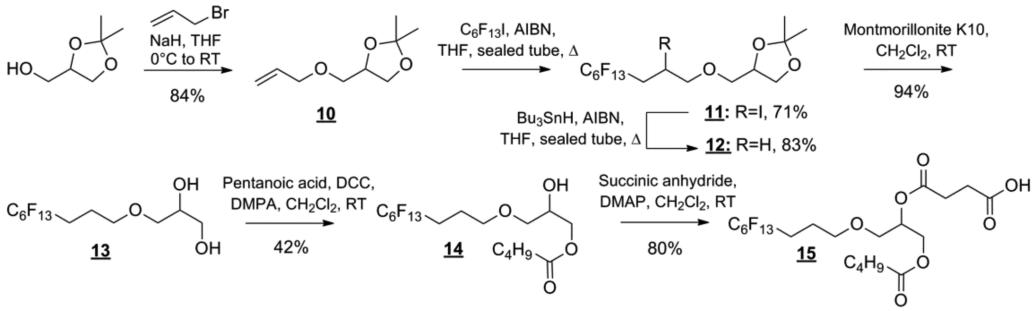
Scheme 1. Synthesis of the Amide-Based Double-Chain Intermediate 9



Scheme 2. Synthesis of the Ether-Based Double-Chain Intermediate 15

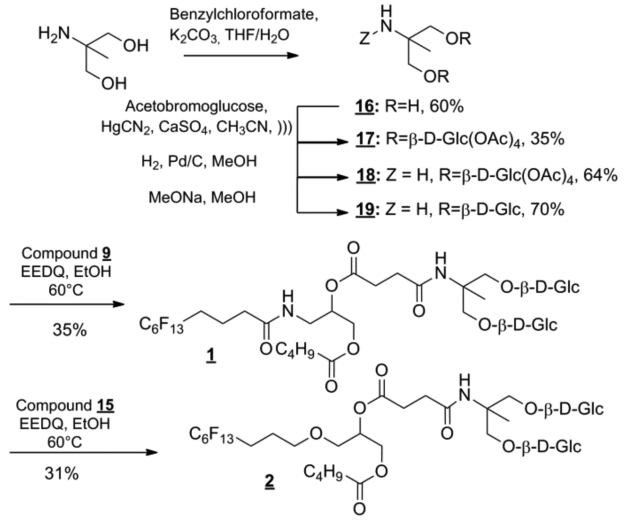


compound **2**, which allowed study of their effect on the overall hydrophobicity of the surfactant and made the synthetic route more flexible for further functionalization. Zhang et al. demonstrated with a series of branch-chained maltoside detergents that adding two carbons on the branch had a similar effect on the CMC as extending the main chain by one carbon.[18] We therefore used a butyl-hydrogenated branch as a side chain so as to maintain sufficient water solubility and to mimic the addition of two carbons in the main chain. We report herein their synthesis and their micellar and biochemical properties.

The convergent synthetic route for the synthesis of the double-chain surfactants **1** and **2** is based on three key steps: (i) synthesis of the apolar double-chain intermediates through radical addition of 1-iodoperfluorohexane onto butenoic acid based derivatives (Schemes 1 and 2); (ii) synthesis of the diglucose polar headgroup from aminopropanediol (Scheme 3); and (iii) its condensation onto the apolar double-chain intermediates (Scheme 3).

Condensation of 3-butenoic acid onto 3-aminopropane-1,2-diol was achieved using 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoleine (EEDQ) in ethanol to afford compound **3** in 90% yield. The two hydroxyl groups of compound **3** were next protected by reaction with 2,2-dimethoxypropane in CH_3CN to lead to compound **4**. The connection of the fluorinated chain onto the olefin was achieved by radical addition of 1-iodoperfluorohexane onto compound **4** in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN) as radical initiator.[24,22] The reaction monitored by ^1H NMR showed the disappearance of vinylic protons and the presence of a characteristic multiplet assigned to CHI at ∼4.70 ppm. After flash chromatography purification, compound **5** was obtained in 55% yield. In our hands, several attempts at condensating 1-iodoperfluorohexane onto compound **3** failed, likely due to the presence of free hydroxyl groups. The reduction of C−I bond was next carried out using tributyltin hydride (Bu_3SnH) in the presence of a catalytic amount of AIBN as radical

Scheme 3. Synthesis of the Diglucose-Polar Head Group 19 and Condensation onto the Double-Chain Intermediates 9 and 15



initiator leading to compound **6** in 86% yield. Hydrolysis of the 1,3-acetonide under mild acidic conditions yielded the dihydroxy derivative **7**, which was next put in reaction with 1.2 equiv of pentanoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give compound **8** in 40% yield. Due to the slight excess of pentanoic acid, formation of the diester derivative was also observed in low yield. Succinic anhydride was finally grafted onto compound **8** under basic condition leading to compound **9** in 84% yield.

Based on the work by Huang et al.,[25] a related synthetic strategy was used for the synthesis of the ether derivative. The commecially available racemic 1,2-isopropylideneglycerol was used as starting material and was transformed to its alkoxide

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derivative in the presence of sodium hydride in dry THF, which was then added to allyl bromine to give compound **10** in 84% yield. The connection of the fluorinated chain onto the olefine **10** was next achieved by radical addition of 1-iodoperfluorohexane followed by reduction of the C−I bond leading to compound **12** in 59% yield in two steps. Hydrolysis of the 1,3 acetonide and subsequent condensation of pentanoic acid led to compound **14**. The remaning free hydroxyl goup was finally condensated with succinic anhydride leading to compound **15**.

The polar headgroup was prepared from aminopropanediol, whose amino group was first protected as a benzyloxycarbonyl group to give compound **16**. The free hydroxyl group was next put in reaction with an excess of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of $HgCN_2$ under ultrasound activation. After purification by flash chromatography, compound **17** was obtained in 35% yield. Removal of the benzyloxycarbonyl group was achieved by hydrogenolysis in the presence of palladium over carbon to afford compound **18** in 64% yield, and then the acetyl groups were removed under Zemplén conditions to afford the polar headgroup **19**. The polar head was used without any purification and directly condensated onto compounds **9** and **15** in the presence of EEDQ to give after purification compounds **1** and **2** in 35% and 31% yield, respectively.

From the surface tension curves, the CMC and the limit surface tension attained at the CMC (γ_{CMC}) are directly obtained (Figure 1). Compound **1** exhibits a CMC of ∼0.08

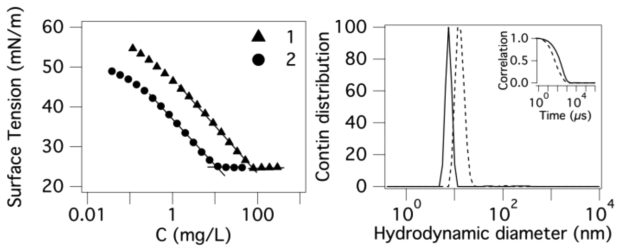

Figure 1. Plots of surface tension vs concentration for compounds **1** and **2** at 25 °C (left). Hydrodynamic diameter distribution plots for compounds **1** (full line) and **2** (dash line) at 1 g/L (right). Inset shows autocorrelation functions.

mM, while that of **2** appears to be 8 times lower with a value of ∼0.01 mM (Table 1). These low values, compared to those of single chain perfluorohexane-based surfactants, such as the commercial octylfluorinated maltoside F_6OM (∼0.70 mM)[23] or our structurally related F_6DigluM (0.38 mM)[26] and F_6H_3DigluM (0.79 mM)[27] derivatives, are indicative of a significant contribution of the butyl branch on the overall hydrophobicity in agreement with the findings by Zhang et al., who demonstrated that adding two carbons on the branch had a similar effect on the CMC as extending the main chain by one carbon.[18] Moreover, the nature of the linker between the fluorinated chain and the polar head also has an effect with a lower CMC value for the ether derivative compared to the amide one. Both compounds **1** and **2** revealed close values of surface excess (Γ) of ∼2.15 and 1.97 × 10^{-12} mol/mm^2, which correspond to surface areas (A_{min}) of ∼77 and 85 Å^2, respectively (Table 1). These values are comparable to those reported for the single-chain structurally related F_6DigluM (∼2.24 × 10^{-12} mol/mm^2) and F_6H_3DigluM (∼1.7 × 10^{-12} mol/mm^2), suggesting only a slight effect of the second

Table 1. Self-Aggregation Properties of Compounds 1 and 2

surfactants	**1**[a]	**2**[b]
molar mass (g/mol)	1074.8	1047.8
CMC (mM)	0.079 ± 0.020	0.011 ± 0.001
CMC (mg/L)	84.7 ± 21.3	11.1 ± 0.6
γ_{CMC} (mN/m)	24 ± 2	24 ± 2
Γ_{max}[c] × 10^{-12} (mol/mm^2)	2.15 ± 0.08	1.97 ± 0.09[a]
A_{min}[c] (Å^2)	77 ± 3	85 ± 4[a]
$\Delta G_S^{m/aq,o}$[d] (kJ/mol)	−33.4 ± 0.5	−38.4 ± 0.1
$\Delta G_S^{ad,o}$[e] (kJ/mol)	−37.2 ± 0.6	−43.0 ± 1.0
D_H (nm)[f]	7.5 ± 0.5	11.2 ± 0.6

[a]Data are averages of three experiments. [b]Data are averages of four experiments unless specified. [c]The surface excess (Γ_{max}) and the surface area per molecule (A_{min}) were estimated from the slope of the surface tension curve. [d]Gibbs free energy of micellization. [e]Free energy of adsorption. [f]Hydrodynamic diameter distribution by Contin analysis, data are averages of 10 runs.

chain on the packing at the air/water interface, in agreement with limit surface tension values.

The standard Gibbs free energies of micellization, $\Delta G_S^{m/aq,o}$, are −33.4 and −38.4 kJ/mol for **1** and **2**, respectively (Table 1). Since the incremental Gibbs energy contribution to micellization typically amounts to ∼−3 kJ/mol per methylene group,[28,29] the contribution of the ether linker compared to the amide one (−5.0 kJ/mol) corresponds roughly to the extension of the hydrocarbon chain by two methylene groups. The standard free energy of adsorption $\Delta G_S^{ad,o}$ values are −37.2 and −43.0 kJ/mol for **1** and **2**, respectively (Table 1). As the $\Delta G_S^{ad,o}$ per CH_2 group usually ranges from −3.0 to −3.5 kJ/mol at 25 °C,[28] the contribution to adsorption of the ether linker compared to the amide one (−5.8 kJ/mol) corresponds roughly to the addition of two methylene groups.

Dynamic light scattering (DLS) experiments were performed at 1 g/L, i.e., several times the CMC. Figure 1 shows that both surfactants self-organize into well-defined assemblies with apparent hydrodynamic diameters of ∼7 and ∼11 nm, respectively, suggesting the formation of rather small micelles. When compared to the popular detergent, *n*-dodecyl-β-D-maltoside (DDM) that forms globular micelles of ∼7 nm hydrodynamic diameter, its perfluorinated analogue (F_6OM) forms rodlike micelles of 30 nm hydrodynamic diameter with 60 nm maximal length.[23,30] Upon dilution, no significant difference in the Contin distribution was observed for both compounds (data not shown). The slightly larger micelles observed for compound **2** may arise from the lower polarity of the ether bond, which would make the hydrogenated chain closer to the main chain leading to a bulkier hydrophobic moiety as compared to compound **1**. Moreover, with compound **1**, stronger hydrogen bonding may occur between water molecules and the amide linker facilitating the penetration of water molecule. This would make the polar headgroup bulkier in agreement with the higher CMC and higher surface area per molecule.

To test the biochemical relevance of compounds **1** and **2**, their potential to keep the model membrane protein bacteriorhodopsin (bR) soluble and in its native form was investigated. bR is composed of seven transmembrane α-helices and binds a covalent cofactor, a retinal molecule, whose visible absorption spectrum is very sensitive to its local environment and is an excellent marker of the integrity and oligomeric state of the protein.[31] The insets of Figure 2 show the results of sucrose

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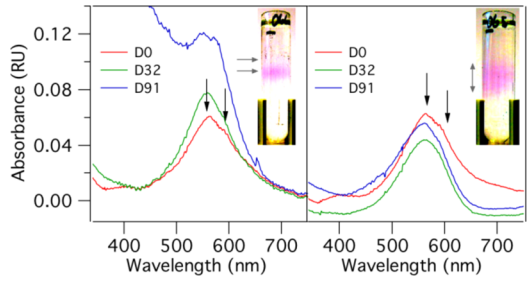

Figure 2. Spectral time course of bR in compounds **1** (left) and **2** (right). Samples incubated at 4 °C in the dark, and UV−vis spectra were recorded at the indicated time, in days. Inset: migration of bR in 10−30% sucrose gradients containing 6 mM of compounds **1** or **2**. Black arrows indicate the position of the main absorption peak and of the shoulder, and gray arrows and line indicate the position of the protein in the gradient.

gradient experiments. For bR solubilized by compound **1**, two species can be distinguished within the sharp-colored band: an upper dark purple one and a lower more pinkish one (indicated by two arrows), in agreement with the absorbance spectrum, which presents a main visible absorption peak at 555 nm with a shoulder at 570 nm (Figure 2, left panel, D0, red trace). The position and the closeness of the two species within the gradient suggest that they correspond to homogeneous monomer and dimer.[10] These species, and their relative amount, appear stable over 1 month. After 3 months, however, the spectrum shows diffusion, witness of aggregation of the protein, with the 555 and 570 nm absorbing species remaining nondenatured (Figure 2, left panel, D91, blue trace). In compound **2**, bR migrates as a broad, diffuse band. This may be related to the fact that compound **2** forms larger micelles (Figure 1) and/or reflects the presence of a mixture of different oligomeric states of the protein. Indeed, the spectrum of the collected band shows a major peak at 555 nm, with a slight shoulder around 590 nm (Figure 2, right panel), suggesting that more than one oligomeric state of the protein is present. These species are very stable over time, as the spectrum does not show any sign of neither denaturation nor aggregation after three months, which is quite remarkable. When solubilized in *n*-octyl-*β*-D-thioglucopyranoside (OTG), bR is monomeric and is completely denatured in only 3 days (not shown). The presence of higher molecular weight oligomers thus confirm that these hybrid surfactants are milder than detergents and that protein−protein interactions can be favored over surfactant−protein ones. This is particularly interesting when working with proteins composed of several subunits and/or that oligomerize.

It is interesting to note that when solubilized in compounds **1** or **2**, the protein displays a maximum of absorption in the 555−590 nm range and does not appear blue (λ_{max} = 615 nm), as when handled in fluorinated surfactants.[16,27] This suggests that compounds **1** and **2** organize so that the hydrogenated part of their hydrophobic moiety interacts with the hydrophobic domain of the protein. This is coherent with the fact that, as mentioned in the introduction, van der Waals interactions are weaker between fluoro- and hydrogenated groups than among hydrogenated ones.

We have synthesized two novel fluorinated surfactants whose apolar domain comprises a perfluorohexane group in the main chain and a butyl-hydrogenated side chain. The two compounds **1** and **2** have rather low CMCs, ∼0.08 and ∼0.01 mM, respectively, and they self-assemble into small aggregates of ∼7 and ∼11 nm hydrodynamic diameter, respectively. This demonstrates that the butyl branch significantly increases hydrophobicity while keeping the length of the apolar domain short. Compound **1** was found to form rather homogeneous complexes with the protein bacteriorhodopsin, which remained stable for a month. Complex with compound **2** was heterogeneous, but the protein remained stable for more than three months.

EXPERIMENTAL SECTION

Synthesis. Mercury cyanide $Hg(CN)_2$ was dried overnight on P_2O_5 under vacuum. All of the solvents were of reagent grade, distilled, and dried according to standard procedures prior to use. The progress of the reactions was monitored by thin-layer chromatography (TLC, silica plates), and the compounds were detected either by exposure to ultraviolet light (254 nm) or by spraying with a 5% sulfuric acid solution in ethanol and with a 2% ninhydrin solution in ethanol following heating at ∼150 °C. Ultrasonication was performed with a sonicator equipped with a 13 mm diameter titanium probe. Flash chromatography purification was carried out on silica gel (40−63 μm granulometry). Water was deionized with a Milli-Q water purification system (resistivity of 18.2 MΩ cm). The ^{1}H, ^{13}C, and ^{19}F NMR experiments were performed at 250, 62.86, and 235 MHz, respectively. Chemical shifts are given in ppm relative to the solvent residual peak as a heteronuclear reference for ^{1}H and ^{13}C. Abbreviations used for signal patterns are s, singlet; b, broad; d, doublet; t, triplet; q, quartet; qt, quintet; sext, sextet; m, multiplet; dd, doublet of doublet. HR-MS spectra were recorded on a mass spectrometer equipped with a TOF analyzer for ESI+ experiments.

*N-(2,3-Dihydroxypropyl)but-3-enamide (**3**).* To a solution of 3-aminopropane-1,2-diol (1.98 mL, 0.026 mol) and 3-butenoic acid (1.97 mL, 0.023 mol) in ethanol (120 mL) was added EEDQ (6.890 g, 0.028 mol) portionwise under stirring. The reaction mixture was heated at 60 °C for 18 h. After the mixture was cooled to rt, acidic resin IRC-50 was added, and the reaction mixture was filtered and concentrated in vacuo. The resulting crude compound was purified by flash chromatography (9:1 EtOAc/MeOH) to afford compound **3** (3.291 g, 90%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 6.85 (1H, t, J = 6.0 Hz); 6.00−5.79 (1H, m); 5.24−5.14 (2H, m); 4.37 (1H, m); 4.22 (1H, m); 3.74 (1H, m); 3.61−3.44 (2H, m); 3.43−3.22 (2H, m); 3.03−2.99 (2H, d, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 172.9; 130.9; 120.5; 71.2; 63.8; 42.4; 41.4. HRMS (ESI+) for $C_7H_{14}NO_3$ m/z: $[M + H]^+$ = 160.0974 (calcd); $[M + H]^+$ = 160.0974 (found).

*N-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)but-3-enamide (**4**).* To a solution of **3** (12.000 g, 0.075 mol) in CH_3CN (110 mL) were added dimethoxypropane (10.2 mL, 0.082 mol) and a catalytic amount of APTS under stirring. The reaction mixture was stirred at rt for 4 h. Et_3N was added dropwise until the pH reached ∼9, and the reaction mixture was concentrated in vacuo. The resulting crude compound was purified by flash chromatography (2:1 cyclohexane/EtOAc) to afford compound **4** (10.500 g, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.20−5.75 (2H, m); 5.36 (1H, m); 5.11 (1H, m); 4.24 (1H, m); 4.01 (1H, dd, J = 1.9 Hz, J = 6.5 Hz); 3.60 (1H, dd, J = 2.0 Hz, J = 6.4 Hz); 3.55−3.25 (2H, m); 3.04 (2H, d, J = 7.5 Hz); 1.42 (3H, s); 1.34 (3H, s). ^{13}C NMR ($CDCl_3$): 171.0; 131.3; 119.8; 109.3; 74.4; 66.7; 41.4; 26.8; 25.3. HRMS (ESI+) for $C_{10}H_{18}NO_3$ m/z: $[M + H]^+$ = 200.1287 (calcd); $[M + H]^+$ = 200.1285 (found).

*N-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-5,5,6,6,7,7,8,8,9,-9,10,10,10-tridecafluoro-3-iododecanamide) (**5**).* To a solution of **4** (0.200 g, 1.0 mmol) in anhydrous THF (5 mL) were added $C_6F_{13}I$ (0.282 mL, 1.3 mmol) and AIBN (0.099 g, 0.6 mmol) under stirring and argon atmosphere. The reaction mixture was heated at 70 °C for 18 h in a sealed tube. After being cooled to rt, the reaction mixture was concentrated in vacuo. The resulting crude compound was purified by flash chromatography (2:1 cyclohexane/EtOAc) to afford compound **5** (0.355 g, 55%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 5.90 (1H, bs); 4.70 (1H, m); 4.28 (1H, m); 4.05 (1H, dd, J = 1.9 Hz, J = 6.5 Hz); 3.79 (1H, dd, J = 2.0 Hz, J = 6.5 Hz); 3.52−3.21 (2H, m); 3.07−2.76 (4H, m); 1.46 (3H, s); 1.36 (3H, s). ^{13}C NMR ($CDCl_3$): δ 169.6;

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109.7; 74.7; 66.9; 47.5; 41.8; 40.8 (t, J = 21 Hz); 27.2; 25.2; 11.3. ^{19}F NMR ($CDCl_3$): δ −80.7 (3F); −111.7 to −115.0 (2F); −121.8 (2F); −122.8 (2F); −123.6 (2F); −126.1 (2F). HRMS (ESI+) for $C_{16}H_{18}NO_3F_{13}I$ m/z: $[M + H]^+$ = 646.0124 (calcd); $[M + H]^+$ = 646.0132 (found).

*N-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-5,5,6,6,7,7,8,8,9,-9,10,10,10-tridecafluorodecanamide (**6**).* To a solution of **5** (2.090 g, 0.0033 mol) in anhydrous THF (20 mL) were added Bu_3SnH (1.181 g, 0.0039 mol) and AIBN (0.332 g, 0.020 mol) under stirring and argon atmosphere. The reaction mixture was heated at 70 °C for 18 h in a sealed tube. After being cooled to rt, the reaction mixture was concentrated in vacuo. The resulting crude compound was purified by flash chromatography (9:1 cyclohexane/EtOAc) to afford **6** (1.473 g, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.94 (1H, bs); 4.22 (1H, m); 4.07 (1H, dd, J = 1.9 Hz, J = 6.5 Hz); 3.64 (1H, dd, J = 2.0 Hz, J = 6.3 Hz); 3.50 (1H, m); 3.25 (1H, m); 2.29 (2H, t, J = 6.9 Hz); 2.27−1.89 (4H, m); 1.41 (3H, s); 1.33 (3H, s). ^{13}C NMR ($CDCl_3$): δ 171.9; 109.6; 74.7; 66.8; 41.8; 35.2; 30.2 (t, J = 22 Hz); 26.9; 25.1; 16.6. ^{19}F NMR ($CDCl_3$): δ −81.7 (3F); −115.2 (2F); −122.8 (2F); −123.8 (2F); −124.4 (2F); −127.1 (2F). HRMS (ESI+) for $C_{16}H_{19}NO_3F_{13}$ m/z: $[M + H]^+$ = 520.1157 (calcd); $[M + H]^+$ = 520.1161 (found).

*N-(2,3-Dihydroxypropyl)-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodecanamide (**7**).* To a solution of **6** (1.128 g, 0.0022 mol) in CH_2Cl_2 (50 mL) was added Montmorillonite K10 resin (4.600 g) portionwise under stirring. The reaction mixture was stirred at rt for 1 day. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo to afford without any purification compound **7** (0.991 g, 94%) as a colorless oil. ^{1}H NMR (acetone-d_6): δ 7.37 (1H, bs); 4.07 (1H, d, J = 6.8 Hz); 3.87 (1H, t, J = 6.1 Hz); 3.66 (1H, m); 3.52−3.22 (4H, m); 2.42 (2H, t, J = 7.1 Hz); 2.42−2.18 (2H, m); 1.99−1.84 (2H, m). ^{13}C NMR (acetone-d_6): δ 173.7; 72.0; 64.4; 43.1; 34.8; 29.7 (t, J = 22 Hz); 17.1. ^{19}F NMR (acetone-d_6) δ −81.7 (3F); −114.8 (2F); −122.5 (2F); −123.5 (2F) ; −124.1 (2F); −126.8 (2F). HRMS (ESI+) for $C_{13}H_{15}NO_3F_{13}$ m/z: $[M + H]^+$ = 480.0844 (calcd); $[M + H]^+$ = 480.0847 (found).

*2-Hydroxy-3-(5,5,6,6,7,7,8,8,9,9,10,10,10tridecafluorodecanamido)propylpentanoate (**8**).* To a solution of **7** (0.963 g, 0.0020 mol) in acetone (12 mL) were successively added pentanoic acid (0.262 mL, 0.0024 mol), DCC (0.581 g, 0.0028 mol), and a catalytic amount of DMAP under stirring. The reaction mixture was stirred at rt for 10 h, and acetone (10 mL) was added. The reaction mixture was filtered out and concentrated in vacuo. The resulting crude compound was purified by flash chromatography (1:3 cyclohexane/EtOAc) to afford compound **8** (0.452 g, 40%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 6.38 (1H, t, J = 5.8 Hz); 4.10 (2H, m); 3.92(1H, m); 3.73 (1H, m); 3.52−3.18 (2H, m); 2.33 (4H, m); 2.26−1.82 (4H, m); 1.57 (2H, qt, J = 7.2 Hz); 1.32 (2H, sex, J = 7.3 Hz); 0.89 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 174.4; 173.1; 69.3; 65.8; 42.6; 35.0; 33.9; 30.1 (t, J = 23 Hz); 27.0; 22.3; 16.5; 13.7. ^{19}F NMR ($CDCl_3$): δ −80.9 (3F); −114.3 (2F); −122.0 (2F); −122.9 (2F); −123.6 (2F); −126.2 (2F). HRMS (ESI+) for $C_{18}H_{23}NO_4F_{13}$ m/z: $[M + H]^+$ = 564.1425 (calcd); $[M + H]^+$ = 564.1419 (found).

*4-Oxo-4-(1-(pentanoyloxy)-3-(5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodecanamido)propan-2-yloxy)butanoic Acid (**9**).* To a solution of **8** (0.500 g, 0.887 mmol) in anhydrous CH_2Cl_2 (5 mL) were added succinic anhydride (0.134 g, 1.331 mmol) and DMAP (0.120 g, 0.977 mmol) under stirring. The reaction mixture was stirred at rt for 4 h and then diluted with CH_2Cl_2. Aqueous HCl solution (3 N) was added dropwise until the pH reached ∼3. The reaction mixture was extracted successively with CH_2Cl_2 (1 × 10 mL) and EtOAc (2 × 15 mL). The organic layers were combined, washed with water (1 × 20 mL) and brine (1 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude compound was purified by flash chromatography (1:1 cyclohexane/EtOAc with 1% AcOH) to afford compound **9** (0.495 g, 84%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 6.29 (1H, t, J = 5.8 Hz); 5.16 (1H, m); 4.27−4.08 (2H, m); 3.71−3.25 (2H, m); 2.80−1.80 (12H, m); 1.59 (2H, qt, J = 7.2 Hz); 1.34 (2H, sex, J = 7.2 Hz); 0.91 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 176.8; 173.9; 172.8; 172.0; 71.1; 62.8; 40.0; 35.1; 33.9; 30.1 (t, J = 22 Hz); 29.2; 29.0; 27.0; 22.3; 16.5; 13.8. ^{19}F NMR ($CDCl_3$): δ −80.8 (3F); −114.3 (2F); −121.9 (2F); −122.9 (2F); −123.4 (2F); −126.2 (2F). MS (ESI+) m/z: $[M + H]^+$ = 664.2; $[M + NH_4]^+$ = 681.2; $[M + Na]^+$ = 686.2; $[M + K]^+$ = 702.2. MS (ESI-) m/z: $[M - -H]^-$ = 662.2. HRMS (ESI+) for $C_{22}H_{27}NO_7F_{13}$ m/z: $[M + H]^+$ = 664.1580 (calcd); $[M + H]^+$ = 664.1578 (found).

*4-((Allyloxy)methyl)-2,2-dimethyl-1,3-dioxolane (**10**).* To a suspension of NaH (60% dispersion in mineral oil, 0.960 g, 0.024 mol) in anhydrous THF (15 mL) was added a solution of *rac*-1,2-isopropylideneglycerol (1.500 g, 0.012 mol) and allyl bromide (2.46 mL, 0.029 mol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h and then poured onto saturated NH_4Cl. The organic phase was diluted with EtOAc (60 mL), washed with water (1 × 20 mL) and brine (1 × 20 mL), and dried over $MgSO_4$. The reaction mixture was concentrated in vacuo, and the resulting crude compound was purified by flash chromatography (1:9 cyclohexane/EtOAc) to afford compound **10** (1.730 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.81 (1H, m); 5.15 (2H, m); 4.19 (1H, qt, J = 8.1 Hz); 3.95 (3H, m); 3.66 (1H, dd, J = 1.9 Hz, J = 6.4 Hz); 3.44 (1H, dd, J = 4.0 Hz, J = 9.9 Hz); 3.36 (1H, dd, J = 4.0 Hz, J = 9.9 Hz); 1.34 (3H, s); 1.28 (3H, s). ^{13}C NMR ($CDCl_3$): δ 134.5; 117.1; 109.2; 74.7; 72.4; 71;0; 66.8; 26.7; 25.3. Despite several attempts, neither MS nor HR-MS experiments provided valid and reliable data.

*2,2-Dimethyl-4-((4,4,5,5,6,6,7,7,8,8,9,9,9-trideca-fluoro-2iodononyl-oxy)methyl)-1,3-dioxolane (**11**).* To a solution of **10** (0.200 g, 1.16 mmol) in anhydrous THF (1 mL) were added $C_6F_{13}I$ (0.326 mL, 1.51 mmol) and AIBN (0.114 g, 0.70 mmol), under stirring and argon atmosphere in a sealed tube. The reaction mixture was heated at 70 °C for 18 h. After being cooled to rt, the reaction mixture was concentrated in vacuo. The resulting crude compound was purified by flash chromatography (9:1 cyclohexane/EtOAc) to afford compound **11** (0.509 g, 71%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 4.40−4.20 (2H, m); 4.05 (1H, m); 3.85−3.70 (3H, m); 3.57 (2H); 3.20−2.90 (1H, m); 2.80−2.60 (1H, m); 1.42 (3H, s); 1.36 (3H, s). ^{13}C NMR ($CDCl_3$): δ 109.7; 76.6; 74.7; 71.8; 66.7; 37.7; 26.8; 25.4; 14.3. ^{19}F NMR ($CDCl_3$): δ −80.7 (3F); −113.7 (m, 2F); −121.8 (2F); −122.8 (2F); −123.6 (2F); −126.1 (2F). HRMS for $C_{15}H_{17}O_3F_{13}I$ (ESI+) m/z: $[M + H]^+$ = 619.0015 (calcd); $[M + H]^+$ = 619.0019 (found).

*2,2-Dimethyl-4-((4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)-methyl)-1,3-dioxolane (**12**).* To a solution of **11** (0.717 g, 1.16 mmol) in anhydrous THF (5 mL) were added Bu_3SnH (0.326 mL, 1.51 mmol) and AIBN (0.114 g, 0.70 mmol) under stirring and argon atmosphere. The reaction mixture was heated at 70 °C for 18 h in a sealed tube. After being cooled to rt, the reaction mixture was concentrated in vacuo. The resulting crude compound was purified by flash chromatography (9:1 cyclohexane/EtOAc) to afford **12** (0.473 g, 83%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 4.25 (1H, qt), 4.05 (1H, m); 3.72 (1H, m); 3.65−3.40 (4H, m); 2.20 (2H, m); 1.90 (2H, m); 1.41 (3H, s); 1.36 (3H, s). ^{13}C NMR ($CDCl_3$): δ 109.6; 74.8; 72.0; 70.1; 66.8; 28.0 (t, J = 22 Hz); 26.8; 25.5; 20.8. ^{19}F NMR ($CDCl_3$): δ −80.8 (3F); −114.4 (m, 2F); −121.9 (2F); −122.9 (2F); −123.6 (2F); −126.2 (2F). HRMS (ESI+) for $C_{15}H_{18}O_3F_{13}$ m/z: $[M + H]^+$ = 493.1048 (calcd); $[M + H]^+$ = 493.1049 (found).

*3-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)propane-1,2-diol (**13**).* To a solution of **12** (1.443 g, 0.0029 mol) in CH_2Cl_2 (60 mL) was added Montmorillonite K10 resin (5.56 g) portionwise under stirring. The reaction mixture was stirred at rt for 1 day. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo to afford without any further purification compound **13** (1.250 g, 94%), as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.87 (1H, m); 3.77−3.41 (6H, m); 3.48 (1H, bs); 3.02 (1H, bs); 2.16 (2H, m); 1.88 (2H, m). ^{13}C NMR ($CDCl_3$): δ 72.4; 70.9; 70.1; 64.0; 27.9 (t, J = 22 Hz); 20.8. ^{19}F NMR ($CDCl_3$): δ −80.8 (3F); −114.4 (m, 2F); −121.9 (2F); −122.9 (2F); −123.4 (2F); −126.1 (2F). HRMS (ESI+) for $C_{12}H_{14}O_3F_{13}$ m/z: $[M + H]^+$ = 453.0735 (calcd); $[M + H]^+$ = 453.0740 (found).

*3-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)propane-1,2-diol (**14**).* To a solution of **13** (1.250 g, 0.0027 mol) in anhydrous CH_2Cl_2 (25 mL) were successively added pentanoic acid (0.37 mL,

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0.0033 mol), DCC (0.805 g, 0.0038 mol), and a catalytic amount of DMAP. The reaction mixture was stirred at rt for 10 h, and then CH_2Cl_2 (15 mL) was added. The resulting suspension was filtered and concentrated in vacuo. The crude compound was purified by flash chromatography (2:1 cyclohexane/EtOAc) to afford compound **14** (0.622 g, 42%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 4.25−4.02 (2H, m); 3.99 (1H, m); 3.62−3.39 (4H, m); 2.63 (1H, d, J = 4.7 Hz); 2.33 (2H, t, J = 7.7 Hz); 2.17 (2H, m); 1.87 (2H, m); 1.59 (2H, qt, J = 7.7 Hz); 1.35 (2H, sex, J = 7.3 Hz); 0.89 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 174.2; 71.8; 70.1; 69.0; 65.4; 34.1; 28.0 (t, J = 22 Hz); 27.1; 22.3; 20.8; 13.7. ^{19}F NMR ($CDCl_3$): δ −80.7 (3F); −114.4 (m, 2F); −121.9 (2F); −122.9 (2F); −123.4 (2F); −126.1 (2F). HRMS (ESI+) for $C_{17}H_{22}O_4F_{13}$ m/z: $[M + H]^+$ = 537.1311 (calcd); $[M + H]^+$ = 537.1310 (found).

*4-Oxo-4-(1-(pentanoyloxy)-3-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)propan-2-yloxy)butanoic Acid (**15**).* To a solution of **14** (0.500 g, 0.932 mmol) in anhydrous CH_2Cl_2 (5 mL) were successively added succinic anhydride (0.140 g, 1.398 mmol) and DMAP (0.125 g, 1.025 mmol). The reaction mixture was stirred at rt for 4 h. The resulting suspension was diluted in CH_2Cl_2 (5 mL), and 3 N HCl was subsequently added dropwise with until pH reached ∼4. The mixture was then extracted successively with CH_2Cl_2 (1 × 10 mL) and EtOAc (2 × 15 mL). The organic layers were combined, washed with water (1 × 20 mL) and brine (1 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude compound was purified by flash chromatography (2:1 cyclohexane/EtOAc with 1% AcOH) to afford compound **15** (0.475 g, 80%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 5.21 (1H, m); 4.36−4.08 (2H, m); 3.62−3.44 (4H, m); 2.64 (4H, m); 2.31 (2H, t, J = 7.7 Hz); 2.17 (2H, m); 1.86 (2H, m); 1.60 (2H, qt, J = 7.5 Hz); 1.33 (2H, sex, J = 7.4 Hz); 0.89 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$): δ 178.0; 173.6; 171.5; 70.7; 69.9; 69.0; 62.4; 34.0; 28.9; 27.8 (t, J = 23 Hz); 27.0; 22.2; 20.7; 13.7. ^{19}F NMR ($CDCl_3$): δ −80.9 (3F); −114.4 (m, 2F); −122.0 (2F); −122.9 (2F); −123.5 (2F); −126.2 (2F). HRMS (ESI+) for $C_{21}H_{26}O_7F_{13}$ m/z: $[M + H]^+$ = 637.1471 (calcd); $[M + H]^+$ = 637.1473 (found).

*Benzyl 1,3-Dihydroxy-2-methylpropan-2-ylcarbamate (**16**).* To a solution of aminopropanediol (5.000 g, 0.0476 mol) in a 1:1 (v/v) THF/H_2O mixture (70 mL) were successively added K_2CO_3 (13.120 g, 0.0951 mol) and benzyl chloroformate (8.16 mL, 0.057 mol) at 0 °C under stirring. The reaction mixture was stirred at rt for 3 h. Aqueous 3 N HCl was added dropwise until pH reached ∼3. The reaction mixture was extracted with EtOAc (2 × 40 mL). The organic layers were combined, washed with water (1 × 40 mL) and brine (1 × 40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude compound was purified by flash chromatography (1:4 cyclohexane/EtOAc) to afford compound **16** (6.828 g, 60%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 7.26 (5H, m); 5.45 (1H, bs); 4.97 (2H, s); 3.93 (2H, bs); 3.60 (4H, dd, J = 11.3 Hz, J = 13.0 Hz); 1.09 (3H, s).^{13}C NMR ($CDCl_3$): δ 156.6; 136.2; 128.7; 128.3; 128.2; 67.4; 66.9; 57.2; 19.8. HRMS (ESI+) for $C_{12}H_{18}NO_4$ m/z: $[M + H]^+$ = 240.1236 (calcd); $[M + H]^+$ = 240.1235 (found).

*Benzyl (1,3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyl)-oxymethyl)-2-methylpropan-2-yl)carbamate (**17**).* To a solution of **16** (3.510 g, 0.015 mol) in CH_3CN (30 mL) were successively added $HgCN_2$ (14.850 g, 28.44 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (24.160 g, 0.059 mol) at 0 °C under stirring in the presence of $CaSO_4$. The reaction mixture was stirred for 15 min under sonication (pulse 1 s/1 s), filtered through a pad of Celite, and concentrated in vacuo. The residue was solubilized in EtOAc, and the organic layer was successively washed with aqueous solutions of saturated $NaHCO_3$ (1 × 70 mL), KI 10% (2 × 50 mL), saturated $Na_2S_2O_3$ (2 × 50 mL), and brine (1 × 50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude compound was purified by flash chromatography (4:6 cyclohexane/EtOAc) to afford compound **17** (4.720 g, 35%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 7.30 (5H, m); 5.30−4.70 (11H, m); 4.41 (2H, d, J = 7.7 Hz); 4.15 (4H, m); 3.65 (2H, m); 3.53 (2H, m); 3.32 (2H, m); 2.06−1.92 (24H, m); 1.20 (3H, s). ^{13}C NMR ($CDCl_3$): δ 170.8; 170.3; 169.5; 169.3; 136.4; 128.7; 128.3; 101.3; 73.0; 72.7; 72.0; 71.4; 68.4; 66.5; 61.9; 55.5; 20.7; 18.8. HRMS (ESI+) for $C_{40}H_{54}NO_{22}$ m/z: $[M + H]^+$ = 900.3137 (calcd); $[M + H]^+$ = 900.3147 (found).

*2-Amino-2-methylpropane-1,3-bis(2′,3′,4′,6′-tetra-O-acetylβ-D-glucopyranosyl)oxymethyl) (**18**).* To a solution of **17** (4.720 g, 5.3 mmol) in MeOH (50 mL), palladium over carbon (10%, 0.470g) was added portionwise at 0 °C under stirring. The reaction mixture was stirred under hydrogen atmosphere (8 bar) for 18 h. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo to afford the crude compound **18** (2.599 g, 64%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 5.30−4.89 (7H, m); 4.41 (2H, d, J = 7.7 Hz); 4.25 (2H, m); 4.10 (2H, m); 3.65 (2H, m); 3.53 (2H, m); 3.32 (2H, m); 2.06−1.92 (24H, m); 0.98 (3H, s). ^{13}C NMR ($CDCl_3$): δ 170.6; 170.2; 169.3; 101.2; 75.9; 75.3; 72.6; 71.8; 71.4; 68.4; 61.9; 52.5; 22.0; 20.8. MS (ESI+) m/z: $[M + H]^+$ = 766.4; $[M + Na]^+$ = 788.3. Crude compound **18** was used directly in the next step without any purification.

*2-Amino-2-methylpropane-1,3-bis(β-D-glucopyranosyl)-oxymethyl) (**19**).* To a solution of **18** (2.250 g, 2.9 mmol) in MeOH (100 mL) was added a catalytic amount of MeONa portionwise under stirring. The reaction mixture was stirred at rt for 18 h. Acidic resin IRC50 was added to the reaction mixture. The reaction mixture was filtered and concentrated in vacuo to afford the crude compound **19** (0.883 g, 70%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 5.15 (8H, bs); 4.15 (2H, t, J = 7.4 Hz); 3.83−3.32 (10H, m); 3.21−2.93 (8H, m); 1.14 (3H, s). ^{13}C NMR (DMSO-d_6): δ 103.9; 77.1; 76.2; 73.6; 71.8; 70.1; 61.0 (CH); 55.3; 19.5. HRMS (ESI+) for $C_{16}H_{32}NO_{12}$ m/z: $[M + H]^+$ = 430.1919 (calcd); $[M + H]^+$ = 430.1920 (found). Crude compound **19** was used directly in the next step without any purification.

*2-(4-(2-Methyl-1,3-bis(β-D-glucopyranosyl)oxymethyl)-3-(5,5,-6,6,7,7,8,8,9,9,10,10,10)-tridecafluorodecanamido)-propylpentanoate (**1**).* To a solution of **9** (0.480 g, 0.723 mmol) in anhydrous EtOH (5 mL) were successively added **19** (0.342 g, 0.796 mmol) and EEDQ (0.215 g, 0.868 mmol) under stirring. The reaction was heated at 60 °C for 18 h. After being cooled to rt, the mixture was concentrated in vacuo. The crude compound was purified by flash chromatography (7:2:1 EtOAc/MeOH/H_2O) to afford compound **1** (0.271 g, 35%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 8.03 (1H, t, J = 5.6 Hz); 7.27 (1H, m); 5.16−4.83 (6H, m); 4.50 (2H, m); 4.16−3.26 (15H, m); 3.26−2.84 (8H, m); 2.47−2.06 (10H, m); 1.77 (2H, m); 1.50 (2H, qt, J = 7.4 Hz); 1.10 (5H, m); 0.87 (3H, t, J = 4.7 Hz). ^{13}C NMR (DMSO-d_6): δ 172.7; 172.1; 171.3; 170.2; 103.8; 76.6; 76.2; 73.2; 71.2; 70.0; 62.3; 61.6; 56.2; 38.9; 33.5; 32.7; 30.2; 28.8 (t, J = 22 Hz); 26.2; 21.3; 18.4; 16.0; 13.6. ^{19}F NMR (DMSO-d_6): δ −80.1 (3F); −113.4 (2F); −121.7 (2F); −122.5 (2F); −123.1 (2F); −125.7 (2F). MS (ESI+) m/z: $[M + H]^+$ = 1075.4; $[M + Na]^+$ = 1097.4. HRMS (ESI+) for $C_{38}H_{59}N_3O_{18}F_{13}$ m/z: $[M + NH_4]^+$ = 1092.3581 (calcd); $[M + NH_4]^+$ = 1092. 3568 (found).

*2-(4-(2-Methyl-1,3-bis(β-D-glucopyranosyl)oxymethyl)-3-(4,4,5,5,-6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)propyl Pentanoate (**2**).* To a solution of **15** (0.530 g, 0.830 mmol) in anhydrous EtOH (5 mL) were successively added amine **19** (0394 g, 0.916 mmol) and EEDQ (0.248 g, 0.999 mmol). The reaction was heated at 60 °C under stirring for 18 h. After being cooled to rt, the mixture was concentrated in vacuo. The resulting crude compound was purified by flash chromatography (7:2:1 EtOAc/MeOH/H_2O) to afford compound **2** (0.269 g, 31%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 7.26 (1H, bs); 5.19−4.92 (7H, m); 4.50 (2H, m); 4.29−4.08 (4H, m); 3.96−3.38 (12H, m); 3.25−2.91 (8H, m); 2.40−2.13 (8H, m); 1.76 (2H, m); 1.50 (2H, qt, J = 7.4 Hz); 1.29 (2H, m, J = 7.3 Hz); 1.26 (3H, s); 0.87 (3H, t, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6): δ 172.7; 172.0; 170.8; 103.8; 76.8; 76.6; 73.5; 71.5; 70.4; 69.4; 68.7; 62.4; 61.5; 56.2; 33.0; 30.4; 28.9; 26.5; 21.6; 20.2; 18.7; 13.6. ^{19}F NMR (DMSO-d_6) δ −80.8 (3F); −113.9 (m, 2F); −122.2 (2F); −123.2 (2F); −123.6 (2F); −126.3 (2F). MS (ESI+) m/z: $[M + H]^+$ = 1048.4; $[M + Na]^+$ = 1070.4. HRMS (ESI+) for $C_{37}H_{58}N_2O_{18}F_{13}$ m/z: $[M + NH_4]^+$ = 1065.3472 (calcd); $[M + NH_4]^+$ = 1065.3460 (found).

Surface Tension Measurements. The surface activity of the surfactants in solution at the air/water interface was determined by the

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Wilhelmy plate technique. Briefly, the stock surfactant solution was prepared 12−24 h prior to the measurements using Milli-Q water at 3−5 times the CMC. Twenty milliliters of the stock solution was transferred into a glass trough. Surface tensions were determined by dilution of the solution. In a typical experiment, 50−70 concentration steps were used with ∼20 min between each concentration step. The platinum plate was cleaned by flaming before experiments. The glassware was cleaned with sulfochromic solution and rinsed with Milli-Q water. All measurements were performed at (25 ± 0.5)°C.

Surface tension data were treated in terms of the Gibbs adsorption equation to determine the surface excess (Γ_{max}) as $\Gamma_{max} = -\frac{1}{RT}\frac{d\gamma}{d \ln C}$, and the surface area per molecule (A_{min}) at the air/water interface from the slope of the surface tension curve as $A_{min} = \frac{1}{N_A \Gamma_{max}}$

From the CMC, the mole fraction partition coefficient of surfactant (S) from the aqueous (aq) into the micellar (m) phase is calculated as $K_S^{m/aq} \equiv \frac{X_S^m}{X_S^{aq}} = \frac{55.5M}{CMC}$

Here, $X_S^m = 1$ and $X_S^{aq} = c_S^{aq}/(c_w + c_S^{aq})$ denote the mole fractions of surfactant in the micellar and the aqueous phases, respectively, with c_S^{aq} being the concentration of surfactant monomers in the aqueous phase and $c_w = 55.5$ M the water concentration. Then, the standard molar Gibbs free energy change accompanying micelle formation takes the form $\Delta G_S^{m/aq,\circ} = -RT \ln K_S^{m/aq} = RT \ln \frac{CMC}{55.5M}$

The standard free energy of adsorption was calculated as $\Delta G_S^{ad,\circ} = \Delta G_S^{m/aq,\circ} - \pi_{CMC} A_{min}$ with $\Delta G_S^{m/aq,\circ}$ obtained from the CMC and $\pi_{CMC} = \gamma_{water} - \gamma_{CMC}$, the maximum excess surface pressure at the CMC.

Dynamic Light Scattering. Hydrodynamic particle size distributions were determined by using a He−Ne laser (λ 633 nm, 4.0 mW). The surfactant solution was prepared at 1 g/L 24 h prior to measurements using Milli-Q water. The solution was vortexed for a few minutes and then incubated at room temperature for 24 h. The surfactant solution was passed through a 0.45-μm filter before being transferred into a 45-μL low-volume quartz batch cuvette. The time-dependent correlation function of the scattered light intensity was measured at an angle of 173° (backscattering detection). The hydrodynamic diameter (D_H) of the particles was estimated from their diffusion coefficient (D) using the Stokes−Einstein equation, $D = k_B T/3\pi\eta D_H$, where k_B is the Boltzmann's constant, T absolute temperature, and η the viscosity of the solvent. Contin analysis was used for evaluating autocorrelation functions. All measurements were performed at 25 ± 0.5 °C.

Biochemistry. Purified purple membrane was solubilized 36 h at 4 °C with 52 mM OTG at a membrane concentration of 1.5 g/L in 20 mM sodium phosphate buffer, pH 6.8. Samples were diluted to reach a final OTG concentration of 15 mM, supplemented with 3.6 mM of the surfactant to be tested and incubated 15 min prior to being loaded onto a 10−30% (w/w) sucrose gradient containing 20 mM sodium phosphate buffer pH 6.8 and 6 mM of the same surfactant. Gradients were centrifuged for 4 h at 55000 rpm (200000g) in the TLS 55 rotor of a TL100 ultracentrifuge (Beckman). The bands containing the colored proteins were collected with a syringe, and protein samples were kept at 4 °C in the dark for UV−vis spectrophotometry monitoring.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02137.

^{1}H and ^{13}C NMR spectra of compounds **3**−**4**, **10**, and **16**−**19**; ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds **1**−**2**, **5**−**9**, and **11**−**15**; mass spectrometry data of compounds **1**−**19** (PDF)

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Notes

The authors declare no competing financial interest.

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