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Straightforward Synthesis of Fluorinated Amphiphilic Thiols

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Dedicated to the memory of Prof. Giuseppe Capozzi

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C8-perfluoroalkyl thiols bearing a polyoxyethylene chain of variable length were prepared in good yields following a straightforward synthetic strategy. These thiols are soluble in organic solvents of different polarities from chloroform to methanol. The thiol with a PEG550 chain shows very good solubility in water.

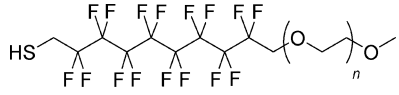
Introduction

Thiols are the most used ligands to form self-assembled monolayers (SAMs).[1] Relatively few investigations have been so far reported on perfluorocarbon monolayers on 2D surfaces,[2] and to the best of our knowledge, only two examples describe the use of fluorinated thiols for self-assembled monolayers on 3D surfaces.[3] In these latter cases, commercially available 1*H*,1*H*,2*H*,2*H*-perfluorodecanethiol was used for the passivation of the gold surface and the resulting fluorocarbon-stabilized gold nanoparticles are soluble only in fluorocarbon media.

Highly fluorinated amphiphiles[4] have diversified uses in material science[5,6] as well as emerging applications in the biomedical field.[7,8] They are characterized by a hydrophilic portion that contrasts the high hydrophobicity of the perfluorocarbon region, which thus imparts solubility in polar solvents. The resulting amphiphilicity constitutes a powerful driving force for self-organization of fluorinated amphiphiles. Moreover, in addition to the extreme hydrophobicity, F chains have a pronounced lipophobic effect, and the combination of these two characters promotes phase separation and ordering among fluorinated components in mixed molecular systems containing fluorinated and hydrogenated amphiphiles.

Despite their interesting potential applications, reports on highly fluorinated thiols are rare and not one deals with amphiphilic fluorinated thiols. This is probably related to (i) the limited number of commercially available fluorinated thiols, (ii) the well-known low solubility of perfluorinated compounds in organic solvents as the length of the perfluoroalkyl chain increases[9] and (iii) the peculiar chemistry of highly fluorinated compounds as a result of the withdrawing effect of the fluorinated chain, which makes even classical nucleophilic substitutions on the carbon atom linked to the fluorinated chain difficult.[10]

In the search for soluble perfluorinated thiols (even in polar solvents) for subsequent use as passivating agents for gold nanoparticles and surfaces, we thought that amphiphilic fluorinated thiols may represent interesting candidates. Herein, we report a straightforward synthesis of four highly fluorinated thiols **1a**–**d** characterized by a perfluorinated chain close to the sulfur atom and by a poly(oxyethylene) portion of increasing length to enhance their solubility in polar solvents (Figure 1).



1a: *n* = 3
1b: *n* = 4
1c: *n* = 6
1d: *n* = 12–13

Figure 1. Thiols **1a**–**d**.

Results and Discussion

In our synthetic approach, we had to consider that perfluorocarbon derivatives have peculiar chemical properties and unusual reactivities. This is self evident in their very low solubility in common organic solvents and in the low nucleophilicity of carbon atoms (or heteroatoms) next to fluorocarbon chains. The target molecule, TM in Scheme 1,

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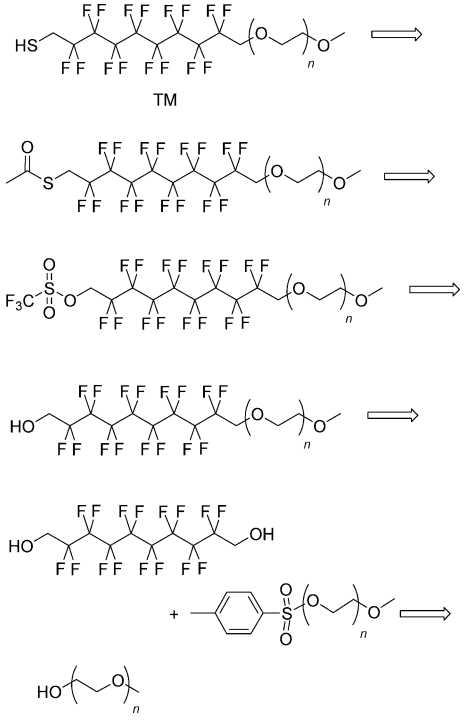
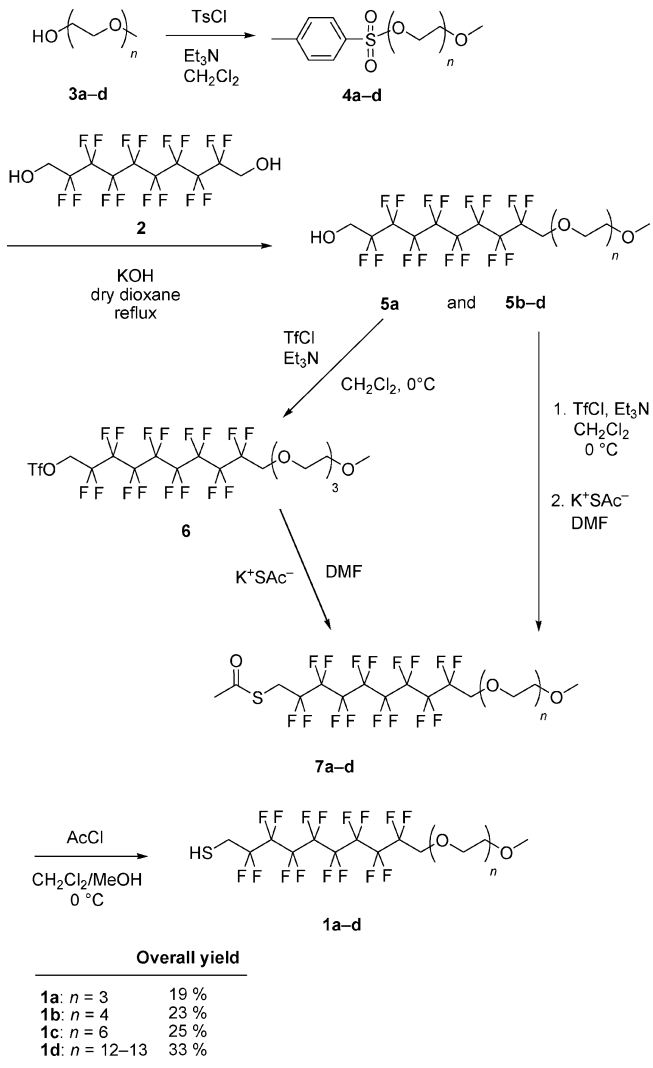
can be formed by acid or basic cleavage of the thiol protecting group. The introduction of the thioester group can be realized by an S_N2 transformation with potassium thioacetate on the triflate intermediate, which, in turn, can be obtained by FGI (functional group interchange) of the alcohol precursor by using trifluoromethanesulfonyl chloride. The amphiphilic alcohol can be obtained by connection of the commercial starting material 1*H*,1*H*,10*H*,10*H*-1,10-perfluorodecanediol (**2**) with the activated polyethylene glycol (PEG) chain. This connection step may be achieved in different ways. We first investigated the reaction with the monoprotected fluorinated diol, which implies the monoprotection step, the connection reaction and then the removal of the OH protecting group. However, preliminary experiments, under different experimental conditions, showed that this strategy is not convenient, as the monoprotection with benzyl chloride occurs with a low yield (22%), because of the formation of high quantities of diprotected diol (48%), and low conversion. Thus, the retrosynthesis is based on the monosubstitution of the fluorinated diol with 4-toluenesulfonyl-PEG. The latter is formed from commercially available short monomethylated PEG chains (n = 3, 4, 12–13). The hexa-PEG monomethyl ether is obtained from the commercially available hexa-PEG-diol by using standard procedures.



Scheme 1. Retrosynthetic analysis for thiols **1a**–**d**.

Syntheses of thiols **1a**–**d** are reported in Scheme 2. In the case of thiol **1a**, tosylate **4a** was prepared by reaction of triethylene glycol monomethyl ether (**3a**) with 4-tosylchloride and triethylamine in dichloromethane in 89% yield. The nucleophilic substitution of the anion of diol **2** on the tosylate was carried out under strong basic conditions and under reflux in dry dioxane in order to improve the nucleophilicity of the alcohol; the reaction takes place with a 75% conversion, and monosubstituted product **5a** was isolated in good yield (44%). Monoadducts **5b**–**d** were isolated, after column chromatography, in 65, 54 and 59% yield, respectively.[11] This result supports the choice to carry out the new C–O connection on the unprotected fluorinated diol to avoid the monoprotection step and cleavage of the OH protecting group.



Overall yield	
1a: n = 3	19 %
1b: n = 4	23 %
1c: n = 6	25 %
1d: n = 12–13	33 %

Scheme 2. Synthesis of thiols **1a**–**d**.

Beside this connection strategy,[12] we attempted different approaches to the formation of the linkage between the fluorinated hydrocarbon and the PEG chain. For example, we explored the transformation of the fluorinated alcohol into the corresponding carboxylic acid, which could be used for amide formation with a PEG-amine. Alternatively, we investigated the reaction of the fluorinated alcohol with *p*-nitrophenylchloroformate for subsequent reaction with PEG-OH. However, these and other approaches failed.[13]

Alcohol **5a** was converted into the good leaving group triflate with triflic chloride and triethylamine.[14] The triflate was obtained in quantitative yield and used without purification. Nucleophilic substitution on triflate **6** with potas-

sium thioacetate was carried out in *N*,*N*′-dimethylformamide and by avoiding light exposure. Product **7a** was recovered in good yield (54%) after column chromatography. The thiol protecting group was removed with HCl generated in situ from AcCl and MeOH in dichloromethane[15] to give thiol **1a** in quantitative yield.

Thiols **1b**–**d** were synthesized by following the same pathway as that described for thiol **1a**. Tetraethylene glycol monomethyl ether was used to prepare thiol **1b**, whereas hexaethylene glycol was chosen as the starting material for the synthesis of thiol **1c**. In this case, a preliminary step of monomethylation was carried out by using NaH and iodomethane. Finally, thiol **1d** was prepared from PEG 550 monomethyl ether, which is a commercially available PEG with an average of 12–13 oxyethylene units. In contrast to the preparation of **1a**, the triflates derivatives were not isolated, and instead they were used directly in the following step for the preparation of thiols **1b**–**d**.

Structure characterization of thiols **1a**–**d** and the intermediate compounds was carried out by NMR and IR spectroscopic analysis and by MS (ESI). Particularly diagnostic is the proton chemical shift variation of the methylene group adjacent to the fluorinated chain, which strongly depends on the functional group bound to it, as shown in Figure 2.

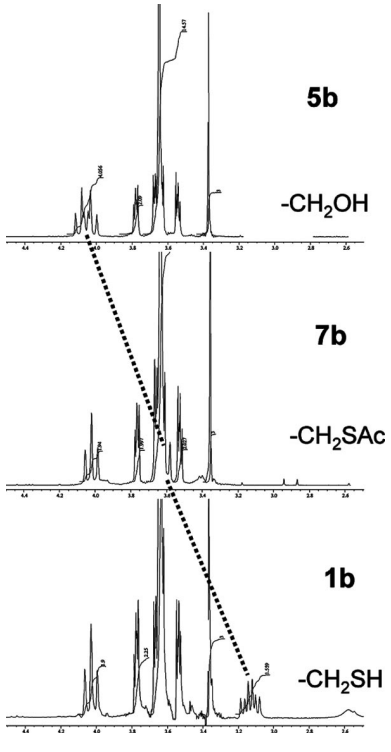


Figure 2. Portions of the ^{1}H NMR (400 MHz, $CDCl_3$) spectra showing chemical-shift variation of the CH_2 group α to the fluorinated chain in compounds **5b**, **7b** and **1b**.

Diagnostic chemical-shift variations could also be observed in the ^{19}F NMR spectra. For example, the triplet of triplets at –122 ppm pertaining to the CF_2 group next to the OH group in compound **5b** shifts to –113 ppm for the CF_2 group next to the sulfur atom in compound **7b**.

The solubility of thiols **1a**–**d** was studied in several solvents. We observed that all thiols are very soluble in chloroform, dichloromethane and ethyl acetate, as well as in polar solvents such as ethanol and methanol. However, among the four thiols, only **1d** is soluble in water, up to 0.3 M, which indicates that a rather long hydrophilic chain is needed to overwhelm the hydrophobicity of the fluorinated chain.

Conclusions

We reported easy access to a new family of amphiphilic fluorinated thiols that present very good solubility in several organic solvents. Moreover, thiol **1d**, containing a PEG 550 chain, shows very good solubility in water. This feature is particularly relevant for the use of these thiols in the preparation of new SAMs and research investigations in this field are in progress in our laboratory.

Experimental Section

General: NMR spectra were recorded with a Jeol GX-400 MHz (operating at 400 MHz for ^{1}H and at 100.5 MHz for ^{13}C), Jeol GX-270 MHz (operating at 270 MHz for ^{1}H and at 67.8 MHz for ^{13}C) or Bruker Avance 300 MHz (operating at 282 MHz for ^{19}F) by using $CDCl_3$ as deuterated solvent. ^{1}H NMR spectra were referenced to the residual protons in the deuterated solvent. Data are reported as follows: chemical shift in the δ scale; multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, br.: broad); integration; coupling constants (Hz); assignment. ^{13}C NMR spectra were referenced to the solvent chemical shift. ^{19}F NMR spectra were referenced to trifluorotoluene as external standard. Mass spectra were obtained by electrospray ionization (ESI) with an Esquire 4000 Bruker Ion Trap spectrometer. FTIR spectra were recorded by using a Thermo Nicolet Avatar 320 FTIR spectrophotometer on NaCl disks. All reagents were purchased from Aldrich and used without further purification. Dry solvents were obtained from Fluka. All other solvents were reagent grade and used as received.

2-[2-(2-Methoxyethoxy)ethoxy]ethyl 4-Methylbenzenesulfonate (4a): To a solution of 4-toluenesulfonyl chloride (2.39 g, 12.5 mmol) in dry dichloromethane (5 mL) was dropwise added a solution of 2-[2-(2-methoxyethoxy)ethoxy]ethanol (1.9 mL, 12.0 mmol) and triethylamine (3.38 mL, 24.0 mmol) in dry dichloromethane (2.5 mL) at 0 °C under an argon atmosphere; a white precipitate was observed. The mixture was stirred at room temperature for 18 h and then poured into water (10 mL). The solution was extracted with dichloromethane (3 × 15 mL); the organic layer was washed with HCl (6 M, 15 mL), $NaHCO_3$ (5%, 15 mL) and water (20 mL) and then dried with Na_2SO_4. The solvent was removed under reduced pressure to yield a pale-yellow oil (3.39 g). Yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3Ph), 3.35 (s, 3 H, CH_3O), 3.44–3.70 (m, 10 H, CH_2O), 4.15 (t, J = 4.62 Hz, 2 H, CH_2O), 7.33 (d, J = 8.24 Hz, 2 H, Ar), 7.82 (d, J = 8.24 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (CH_3Ph), 59.1 (CH_3O), 68.7–71.9 (CH_2O), 128.0, 129.8, 133.0, 144.8 ppm.

2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl 4-Methylbenzenesulfonate (4b): Starting from **3b** (2.00 g) and **4b** (3.31 g). Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3Ph), 3.37 (s, 3 H, CH_3O), 3.52–3.70 (m, 14 H, CH_2O), 4.16 (t, J = 4.62 Hz, 2 H,

CH_2O), 7.32 (d, J = 8.24 Hz, 2 H, Ar), 7.80 (d, J = 8.24 Hz, 2 H, Ar) ppm.

2-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]-ethanol (3c): To a suspension of NaH (0.34 g, 8.5 mmol) in distilled THF was added a solution of hexaethylene glycol (2.00 g, 7.1 mmol) in THF (8 mL) under an argon atmosphere; then CH_3I (0.53 mL, 8.5 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 12 h and then poured into water (65 mL). The aqueous phase was extracted with dichloromethane (5 × 30 mL). The organic phase was washed with water (20 mL) and dried with Na_2SO_4. After solvent removal, the crude product was purified by flash chromatography (chloroform to chloroform/methanol, 9:1) to yield a colourless oil (0.75 g). Yield: 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3O), 3.53–3.73 (m, 24 H, CH_2O) ppm.

2-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethyl 4-Methylbenzenesulfonate (4c): Starting from **3c** (0.61 g) and **4b** (0.75 g). Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3Ph), 3.37 (s, 3 H, CH_3O), 3.52–3.69 (m, 22 H, CH_2O), 4.15 (t, J = 4.76 Hz, 2 H, CH_2O), 7.32 (d, J = 8.24 Hz, 2 H, Ar), 7.80 (d, J = 8.24 Hz, 2 H, Ar) ppm.

Methoxy-PEG550 4-Methylbenzenesulfonate (4d): Starting from **3d** (2.00 g) and **4d** (2.28 g). Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3Ph), 3.36 (s, 3 H, CH_3O), 3.52–3.69 (m, 42 H, CH_2O), 4.12 (t, J = 4.76 Hz, 2 H, CH_2O), 7.31 (d, J = 8.24 Hz, 2 H, Ar), 7.76 (d, J = 8.24 Hz, 2 H, Ar) ppm.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}decan-1-ol (5a): To a solution of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorodecane-1,10-diol (**2**; 2.50 g, 5.41 mmol) in dry dioxane (10 mL) was added successively **4a** (1.89 g, 5.95 mmol) and KOH powder (0.36 g, 6.49 mmol) under an argon atmosphere. The mixture was heated at reflux for 16 h and then cooled down; it was diluted with diethyl ether (15 mL) and water (15 mL); the two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and dried with Na_2SO_4. After solvent removal, the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:2 to 1:1) to yield the monosubstituted product as a clear oil (1.09 g). Conversion: 75%. Yield: 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3O), 3.54 (m, 2 H, CH_2O), 3.65 (m, 8 H, CH_2O), 3.78 (m, 2 H, CH_2O), 4.03 (m, 4 H, OCH_2CF_2) ppm. MS (ESI, CH_3OH): m/z = 609.1 [M + H]$^+$, 631.1 [M + Na]$^+$, 647.0 [M + K]$^+$.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)decan-1-ol (5b): Starting from **2** (2.50 g) and **5b** (1.53 g). Conversion: 66%. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3O), 3.54 (m, 2 H, CH_2O), 3.68 (m, 12 H, CH_2O), 3.78 (m, 2 H, CH_2O), 4.05 (m, 4 H, OCH_2CF_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.4 (m, 4 F, CF_2), –123–121.8 (m, 10 F, CF_2), –120.4 (m, 2 F, CF_2CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.7 (CH_3O), 60.1 (t, $J_{C,F}$ = 24.5 Hz, CF_2CH_2OH), 68.1 (t, $J_{C,F}$ = 24.1 Hz, CF_2CH_2O), 70.2, 70.3, 70.4, 70.5, 71.7, 72.1 (CH_2O), 110.7, 111.2, 112.7, 115.1, 115.5, 119.3 (m, CF_2) ppm. IR (film): $\tilde{\nu}$ = 3406 (s, ν_{O-H}), 2882 (s), 1650 (w), 1456 (m), 1351 (m), 1285 (m), 1212 (s, ν_{C-F}), 1149 (s), 946 (m), 855 (m), 703 (w), 654 (m) cm^{-1}. MS (ESI, CH_3OH): m/z = 675.1 [M + Na]$^+$.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}decan-1-ol (5c): Starting from **2** (0.77 g) and **5c** (0.45 g). The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:2 to ethyl acetate/methanol, 95:5). Conversion: 68%. Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3O), 3.53 (m, 2 H, CH_2O), 3.64 (m, 20 H, CH_2O), 3.78 (m, 2 H, CH_2O), 4.05 (m, 4 H, OCH_2CF_2) ppm. MS (ESI, CH_3OH): m/z = 763.2 [M + Na]$^+$.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(methoxy-PEG550)decan-1-ol (5d): Starting from **2** (4.33 g) and **5d** (3.03 g). The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1 to ethyl acetate/methanol, 1:1). Conversion: 69%. Yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3O), 3.53–3.78 (m, 46 H, CH_2O), 4.05 (m, 4 H, OCH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.7 (CH_3O), 60.3 (t, $J_{C,F}$ = 27.6 Hz, CF_2CH_2OH), 68.1 (t, $J_{C,F}$ = 25.3 Hz, CF_2CH_2O), 70.4–72.3 (CH_2O), 110.8–119.3 (m, CF_2) ppm. IR (film): $\tilde{\nu}$ = 3504 (s, ν_{O-H}), 2882 (s), 2244 (m), 1960 (m), 1692 (m), 1644 (m), 1455 (m), 1350 (s), 1145 (s, ν_{C-F}), 951 (m), 852 (m), 734 (m), 647 (m) cm^{-1}. MS (ESI, CH_3OH): m/z = 851.3, 895.3, 939.3, 983.3, 1027.3, 1071.4, 1115.4, 1159.4 [M + Na]$^+$.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}decyl Trifluoromethanesulfonate (6): To a solution of **5a** (1.09 g, 1.80 mmol) in dry dichloromethane (5 mL) was dropwise added trifluoromethanesulfonyl chloride (0.57 mL, 5.40 mmol) under an argon atmosphere; the mixture was then cooled to 0 °C, and a solution of triethylamine (2.0 mL, 14.4 mmol) in dichloromethane (2 mL) was added dropwise; a yellow precipitate was observed. The mixture was stirred at room temperature for 18 h. In order to obtain complete conversion of the reagent, successive additions of trifluoromethanesulfonyl chloride (overall 0.76 mL, 7.2 mmol) and triethylamine (overall 3.0 mL, 21.6 mmol) were carried out over 48 h. The mixture was diluted with ethyl acetate (15 mL) and water (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure to yield a yellow oil (1.26 g). Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3O), 3.54 (m, 2 H, CH_2O), 3.66 (m, 8 H, CH_2O), 3.79 (m, 2 H, CH_2O), 4.04 (t, $J_{H,F}$ = 13.91 Hz, 2 H, OCH_2CF_2), 4.82 (t, $J_{H,F}$ = 12.08 Hz, 2 H, $TfOCH_2CF_2$) ppm.

(*S*)-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}decyl) Thioacetate (7a): To a solution of **6** (1.26 g, 1.70 mmol) in dry *N*,*N*′-dimethylformamide (15 mL) was added potassium thioacetate (0.39 g, 3.40 mmol) under an argon atmosphere. The mixture was protected from light and stirred at room temperature for 4 h. Then, ethyl acetate (10 mL) and water (10 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 15 mL); the organic layer was washed with water (8 × 20 mL) and brine (20 mL) and dried with Na_2SO_4. After solvent removal, the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:2) to yield a brown oil (0.61 g). Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, $CH_3C{=}O$), 3.37 (s, 3 H, CH_3O), 3.54 (m, 2 H, CH_2O), 3.64 (m, 10 H, CH_2O, CH_2S), 3.78 (m, 2 H, CH_2O), 4.00 (t, $J_{H,F}$ = 13.91 Hz, 2 H, CH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2 (t, $J_{C,F}$ = 24.6 Hz, SCH_2CF_2), 30.2 ($CH_3C{=}O$), 59.1 (CH_3O), 68.1 (t, $J_{C,F}$ = 25.3 Hz, CF_2CH_2O), 70.1–72.3 (CH_2O), 110.7–115.6 (m, CF_2), 191.9 (C=O) ppm. IR (film): $\tilde{\nu}$ = 3413 (w), 2882 (s), 1766 (m), 1716 (s, $\nu_{C=O}$), 1456 (m), 1352 (m), 1212 (s, ν_{C-F}), 1148 (s), 958 (m), 855 (m), 702 (m) cm^{-1}. MS (ESI, CH_3OH): m/z = 689.1 [M + Na]$^+$. $C_{19}H_{22}F_{16}O_5S$ (666.41): calcd. C 34.24, H 3.33, S 4.81; found C 33.75, H 3.18, S 4.68.

(*S*)-[2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)decyl] Thioacetate (7b): To a solution of **5b** (previously coevaporated with dry toluene in order to remove any trace of water; 1.15 g, 1.76 mmol) in dry dichloromethane (8 mL) was dropwise added trifluoromethanesulfonyl chloride (0.56 mL, 5.28 mmol) under an argon atmosphere; the mixture was then cooled to 0 °C, and a solution of triethylamine (1.96 mL, 14.0 mmol) in dichloromethane (3 mL) was added dropwise; a yellow precipitate was observed. The mixture was stirred at room temperature for 18 h. Another portion of trifluoromethanesulfonyl chloride (0.18 mL, 1.76 mmol) and triethylamine (1.2 mL, 8.8 mmol) was added at 0 °C. The reaction was monitored by TLC; when the reagent was completely converted, the precipitate was filtered off, the solvent was removed under reduced pressure and the residue was redissolved in *N*,*N*′-dimethylformamide under an argon atmosphere. Potassium thioacetate (0.4 g, 3.5 mmol) was added to the solution. The mixture was protected from light and stirred at room temperature for 4 h. Then, ethyl acetate (30 mL) and water (30 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 30 mL); the organic layer was washed with water (8 × 30 mL) and brine (30 mL) and dried with Na_2SO_4. After solvent removal, the crude product was purified by flash chromatography (chloroform to chloroform/methanol, 98.5:1.5) to yield a brown oil (0.54 g). Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3C=O), 3.37 (s, 3 H, CH_3O), 3.53 (m, 2 H, CH_2O), 3.64 (m, 14 H, CH_2O, CH_2S), 3.78 (m, 2 H, CH_2O), 4.03 (t, $J_{H,F}$ = 13.91 Hz, 2 H, CH_2CF_2) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 29.3 (t, $J_{C,F}$ = 23.5 Hz, SCH_2CF_2), 30.1 (CH_3C=O), 58.9 (CH_3O), 67.8 (t, $J_{C,F}$ = 25.9 Hz, CF_2CH_2O), 70.4–72.2 (CH_2O), 110.3–115.5 (m, CF_2), 191.7 (C=O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.4 (m, 2 F, CF_2), –123.0 (m, 2 F, CF_2), –123.0–121.8 (m, 8 F, CF_2), –120.4 (m, 2 F, CF_2CH_2O), –113.2 (m, 2 F, CF_2CH_2S) ppm. IR (film): $\tilde{\nu}$ = 3411 (w), 2881 (s), 1766 (m), 1716 (s, $\nu_{C=O}$), 1456 (m), 1352 (m), 1212 (s, ν_{C-F}), 1149 (s), 958 (m), 855 (m), 702 (m) cm^{-1}. MS (ESI, CH_3OH): *m*/*z* = 733.1 [M + Na]$^+$. $C_{21}H_{26}F_{16}O_6S$ (710.47): calcd. C 35.50, H 3.69, S 4.51; found C 35.03, H 3.60, S 4.45.

(*S*)-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}decyl) Thioacetate (7c): Starting from **5c** (0.45 g) and **7c** (0.30 g). The crude product was purified by flash chromatography (chloroform to chloroform/methanol, 98.5:1.5). Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3C=O), 3.37 (s, 3 H, CH_3O), 3.54 (m, 2 H, CH_2O), 3.64 (m, 22 H, CH_2O + CH_2S), 3.78 (m, 2 H, CH_2O), 4.0 (t, $J_{H,F}$ = 13.92 Hz, 2 H, CH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (t, $J_{C,F}$ = 23.7 Hz, SCH_2CF_2), 30.2 (CH_3C=O), 59.0 (CH_3O), 68.2 (t, $J_{C,F}$ = 24.5 Hz, CF_2CH_2O), 70.5–72.3 (CH_2O), 111.2–115.8 (m, CF_2), 193.7 (C=O) ppm. IR (film): $\tilde{\nu}$ = 3391 (w), 2886 (s), 1766 (m), 1716 (s, $\nu_{C=O}$), 1457 (m), 1350 (m), 1212 (s, ν_{C-F}), 1134 (s), 958 (m), 854 (m), 702 (m) cm^{-1}. MS (ESI, CH_3OH): *m*/*z* = 821.2 [M + Na]$^+$. $C_{25}H_{34}F_{16}O_8S$ (798.57): calcd. for C 37.60, H 4.29, S 4.02; found C 37.25, H 4.20, S 3.95.

(*S*)-2,2,3,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(methoxy-PEG550) Thioacetate (7d): Starting from **5d** (3.00 g) and **7d** (2.16 g). The crude product was purified by flash chromatography (chloroform to chloroform/methanol, 97:3). Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3C=O), 3.37 (s, 3 H, CH_3O), 3.54–3.78 (m, 42 H, CH_2O), 4.0 (t, $J_{H,F}$ = 13.92 Hz, 2 H, CH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2 (t, $J_{C,F}$ = 23.8 Hz, SCH_2CF_2), 30.0 (CH_3C=O), 58.9 (CH_3O), 68.1 (t, $J_{C,F}$ = 24.6 Hz, CF_2CH_2O), 70.2–72.2 (CH_2O), 110.7–115.8 (m, CF_2), 191.7 (C=O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.4 (m, 2 F, CF_2), –123.0 (m, 2 F, CF_2), –122.6–121.8 (m, 8 F, CF_2), –120.4 (m, 2 F, CF_2CH_2O), –112.8 (m, 2 F, CF_2CH_2S) ppm. IR (film): $\tilde{\nu}$ = 2873 (s), 1716 (s, $\nu_{C=O}$), 1459 (m), 1350 (m), 1294 (m), 1212 (s, ν_{C-F}), 1128 (s), 1140 (s), 954 (m), 854 (m) cm^{-1}. MS (ESI, CH_3CN): *m*/*z* = 909.2, 953.3, 997.3, 1041.3, 1085.3, 1129.3, 1173.4 [M + Na]$^+$.

2,2,3,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}decane-1-thiol (1a): To a solution of **7a** (0.616 g, 0.924 mmol) in dichloromethane (60 mL) and methanol (34 mL, 0.831 mol) was dropwise added acetyl chloride (22.6 mL, 0.318 mol) at 0 °C. The mixture was stirred at room temperature for 12 h. Another two portions of acetyl chloride (22.6 mL each) was added over 10 h, and the mixture was left to stir for 12 h. Then, dichloromethane (50 mL) and water (50 mL) were added; the phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water (6 × 40 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure to yield a yellow oil (540 mg). Yield: 94%. Overall yield from **3a**: 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (t, *J* = 8.78 Hz, 1 H, SH), 3.1 (ddt, $J_{H,F}$ = 16.84 Hz, $J_{H,H}$ = 8.78 Hz, 2 H, CH_2S), 3.36 (s, 3 H, CH_3O), 3.53 (m, 2 H, CH_2O), 3.64 (m, 8 H, CH_2O), 3.77 (m, 2 H, CH_2O), 4.03 (t, $J_{H,F}$ = 14.28 Hz, 2 H, OCH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.65 (t, $J_{C,F}$ = 25.37 Hz, CF_2CH_2S), 58.92 (CH_3O), 68.27 (t, $J_{C,F}$ = 25.37 Hz, CF_2CH_2O), 70.68 (CH_2O), 71.87 (CH_2O), 72.26 (CH_2O), 108.49 (m, CF_2), 110.82 (m, CF_2), 111.12 (m, CF_2), 115.43 (m, CF_2), 118.18 (m, CF_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.0 (m, 2 F, CF_2), –123.0 (m, 2 F, CF_2), –122.6–121.6 (m, 8 F, CF_2), –120.2 (m, 2 F, CF_2CH_2O), –113.4 (m, 2 F, CF_2CH_2S) ppm. IR (film): $\tilde{\nu}$ = 2882 (s), 2550 (w, ν_{S-H}), 1456 (m), 1352 (m), 1210 (s, ν_{C-F}), 1145 (s), 855 (m), 649 (m) cm^{-1}. MS (ESI, CH_3CN): *m*/*z* = 647.1 [M + Na]$^+$, 663.1 [M + K]$^+$.

2,2,3,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)decane-1-thiol (1b): Starting from **7b** (0.23 g) and **1b** (0.20 g). Yield: 95%. Overall yield from **3b**: 23%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (t, *J* = 9.15 Hz, 1 H, SH), 3.15 (ddt, $J_{H,F}$ = 16.84 Hz, $J_{H,H}$ = 9.15 Hz, 2 H, CH_2S), 3.37 (s, 3 H, CH_3O), 3.55 (m, 2 H, CH_2O), 3.64 (m, 12 H, CH_2O), 3.77 (m, 2 H, CH_2O), 4.03 (t, $J_{H,F}$ = 13.92 Hz, 2 H, OCH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.69 (t, $J_{C,F}$ = 25.37 Hz, CF_2CH_2S), 58.99 (CH_3O), 68.29 (t, $J_{C,F}$ = 24.60 Hz, CF_2CH_2O), 70.56 (CH_2O), 71.89 (CH_2O), 72.31 (CH_2O), 108.44 (m, CF_2), 110.87 (m, CF_2), 111.12 (m, CF_2), 115.61 (m, CF_2), 118.17 (m, CF_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.2 (m, 2 F, CF_2), –123.2 (m, 2 F, CF_2), –122.6–121.8 (m, 8 F, CF_2), –120.4 (m, 2 F, CF_2CH_2O), –113.6 (m, 2 F, CF_2CH_2S) ppm. IR (film): $\tilde{\nu}$ = 2882 (s), 2550 (w, ν_{S-H}), 1456 (m), 1352 (m), 1220 (s, ν_{C-F}), 1144 (s), 855 (m), 648 (m) cm^{-1}. MS (ESI, CH_3CN): *m*/*z* = 691.1 [M + Na]$^+$, 707.1 [M + K]$^+$.

2,2,3,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}decane-1-thiol (1c): Starting from **7c** (0.30 g) and **1c** (0.27 g). Yield: 94%. Overall yield from **3c**: 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (t, *J* = 9.15 Hz, 1 H, SH), 3.11 (ddt, $J_{H,F}$ = 16.84 Hz, $J_{H,H}$ = 9.16 Hz, 2 H, CH_2S), 3.37 (s, 3 H, CH_3O), 3.52 (m, 2 H, CH_2O), 3.62 (m, 20 H, CH_2O), 3.75 (m, 2 H, CH_2O), 4.01 (t, $J_{H,F}$ = 13.92 Hz, 2 H, OCH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.62 (t, $J_{C,F}$ = 26.13 Hz, CF_2CH_2S), 58.90 (CH_3O), 68.24 (t, $J_{C,F}$ = 24.59 Hz, CF_2CH_2O), 70.50 (CH_2O), 71.86 (CH_2O), 72.25 (CH_2O), 108.43 (m, CF_2), 110.82 (m, CF_2), 111.13 (m, CF_2), 115.40 (m, CF_2), 118.24 (m, CF_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.2 (m, 2 F, CF_2), –123.2 (m, 2 F, CF_2), –122.6–121.8 (m, 8 F, CF_2),

–120.4 (m, 2 F, CF_2CH_2O), –113.6 (m, 2 F, CF_2CH_2S) ppm. IR (film): $\tilde{\nu}$ = 2881 (s), 2550 (w, ν_{S-H}), 1456 (m), 1351 (m), 1211 (s, ν_{C-F}), 1149 (s), 855 (m) cm^{-1}. MS (ESI, CH_3CN): *m/z* = 778.2 [M + Na]$^+$, 794.1 [M + K]$^+$.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(methoxy-PEG550)decan-1-thiol (1d): Starting from **7d** (2.17 g) and **1d** (2.00 g). Yield: 92%. Overall yield from **3d**: 33%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (t, J = 8.9 Hz, 1 H, SH), 3.11 (ddt, $J_{H,F}$ = 16.84 Hz, $J_{H,H}$ = 8.9 Hz, 2 H, CH_2S), 3.37 (s, 3 H, CH_3O), 3.53–3.77 (m, 44 H, CH_2O), 4.02 (t, $J_{H,F}$ = 14.28 Hz, 2 H, OCH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.65 (t, $J_{C,F}$ = 24.6 Hz, CF_2CH_2S), 58.96 (CH_3O), 68.24 (t, $J_{C,F}$ = 25.37 Hz, CF_2CH_2O), 70.49 (CH_2O), 71.86–72.25 (CH_2O), 108.43 (m, CF_2), 110.75 (m, CF_2), 111.41 (m, CF_2), 115.56 (m, CF_2), 115.70 (m, CF_2), 118.15 (m, CF_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.0 (m, 2 F, CF_2), –123.2 (m, 2 F, CF_2), –122.6–121.8 (m, 8 F, CF_2), –120.4 (m, 2 F, CF_2CH_2O), –113.6 (m, 2 F, CF_2CH_2S) ppm. IR (film): $\tilde{\nu}$ = 3523 (s), 2876 (s), 2550 (w, ν_{S-H}), 1644 (m), 1456 (m), 1350 (s), 1212 (s, ν_{C-F}), 1147 (s), 951 (m), 852 (m), 702 (w), 643 (m) cm^{-1}.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **7a**–**d** and **1a**–**d**; ^{19}F NMR spectrum of **7d**.

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