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Synthesis of amino terminated semifluorinated long-chain alkanethiols

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Abstract

The α,ω-diiodoperfluorooctane is added to undecyl-10-en-1-ol through AIBN initiation yielding the monoadduct in good yield (1,2-dichloroethane, 52%). This is added to *N*-allylphthalimide (AIBN initiation, 1,2-dichloroethane, 81%). The resulting diiodo compound is hydrodeiodinated with Bu_3SnH (toluene, 70%) and the alcohol function is converted to thioacetate through the Mitsunobu reaction (PPh_3, DIAD, THF, 75%). The two protecting groups, phthalimide and thioacetate, are removed with hydrazine to give the expected amino terminated semifluorinated long-chain alkanethiol (ethanol, 80%). This compound has been designed in order to form mixed fluorinated self-assembled monolayers (SAMs) with semifluorinated long-chain alkanethiol giving access to a new platform system for biosensors. Similar results are reported starting from the α,ω-diiodoperfluorohexane.

Keywords: α,ω-Diiodoperfluoroalkane; Monoadduct; Amino-terminated semifluorinated long-chain alkanethiols; Mixed SAMs; Biosensors

1. Introduction

Bioaffinity sensors are important tools in a variety of fields including immunoassays, toxicology analysis, forensics, drug screening, gene expression analysis, gene identification, agrodiagnostics and pharmacogenetics [1]. Their elaboration necessitates controlled and optimised interfacial chemistry. In this field mixed self-assembled monolayers (SAMs) of long-chain alkanethiols and functional terminated ones prepared on gold surfaces are known as an interesting basis for microarray elaboration [2]. A number of terminal functions has been used, but the amino is of particular interest. It is able to couple further with biospecific receptors bearing a residual amino end group, through a X–R–X linker. In addition, the amino terminated surface can easily be biotin-derivatized, giving access to the recent field [2,3] of biotin/streptavidin platforms of high general interest through the anchoring of a broad spectrum of biotinylated molecules (e.g. oligonucleotides, DNA, peptides, proteins and carbohydrates). In such systems, the sensor surface is generally protected from the non-specific adsorption of proteins and adhesion of bacterial and mammalian cells by the presence of poly(ethylene glycol) (PEG) terminating groups [3–5].

Our aim is to elaborate such systems using fluorinated thiols in place of PEG terminated ones. Fluorine repellent character towards oil and water is well expressed by the common sentence ''nothing can stick to fluorine''. This may limit strongly the sensor extinction by fouling and the ''non-specific adsorption'' (direct adsorption of the analyte onto bare gold sites) can also be suppressed by good organisation of the fluorinated layer.

We previously reported the synthesis of semifluorinated alkanethiols [6] and studied their self-assembly at gold surfaces [7], and selected $F–(CF_2)_{8,10}–(CH_2)_{11}–SH$ as good candidates for our goal, as they formed particularly compact and defect free monolayers [7,8]. Compounds containing a fluorinated chain with 4 or 6 carbons appeared to be much less organised. Consequently, we are particularly interested in the synthesis of the amino terminated semifluorinated long-chain alkanethiols $NH_2–(CH_2)_3–(CF_2)_{6,8}–(CH_2)_{11}–SH$. The starting compounds available are the α,ω-diiodoperfluorohexane and the octane. A new strategy is also described for the thiol formation. The study of mixed self-assembled monolayers of $F–(CF_2)_{8,10}–(CH_2)_{11}–SH$ and $NH_2–(CH_2)_3–(CF_2)_{6,8}–(CH_2)_{11}–SH$ will be reported separately.

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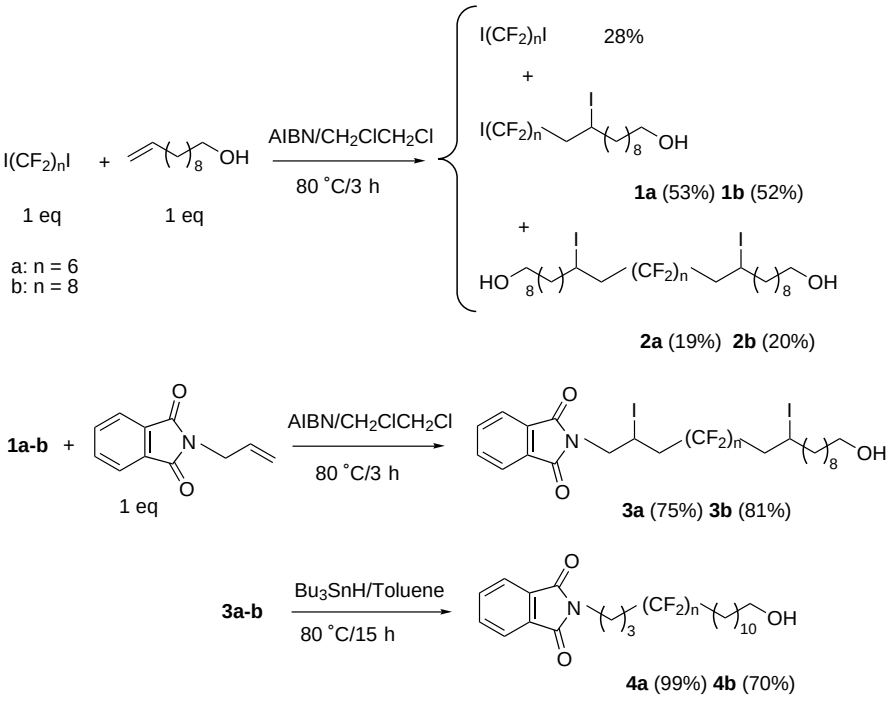


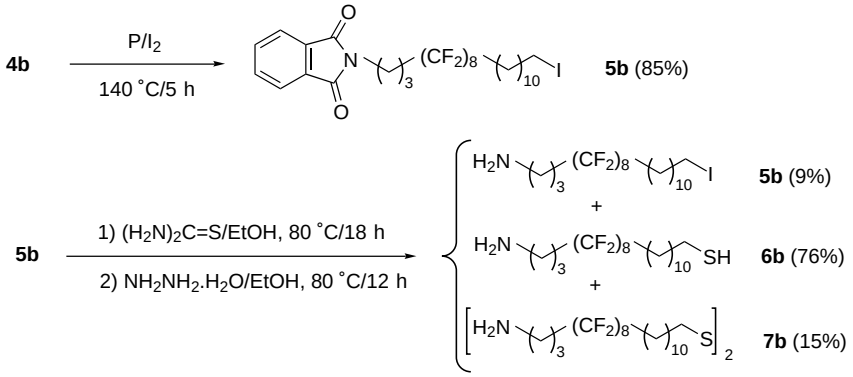
Scheme 1. Synthesis of the amino protected semifluorinated long-chain alcohols **4a**–**b**.

2. Results and discussion

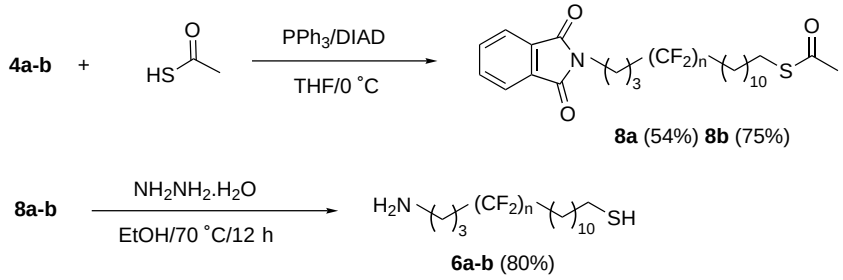
The key step in our synthetic approach involves the radical chain addition of the diiodo compound to undecyl-10-en-1-ol under conditions favouring monoadduct formation, relative to the diadduct [9]. In previous work [10] on the addition of α,ω-diiodoperfluorobutane to alkenols and alkynols, we used the Huang radical initiator system [11]. Here we discarded this initiator system because the long-chain diiodo compounds, α,ω-diiodoperfluorohexane and the octane, are very poorly soluble in the water/acetonitrile biphasic system. Consequently, we used the classical AIBN initiation with 1,2-dichloroethane as solvent. The general reaction pathway and observed yields are depicted in Scheme 1. Formation of the monoadduct was observed with significant selectivity and purification was performed by column chromatography (see Section 4).

The second step is the radical chain addition, under similar conditions, of the monoadduct to the protected allylamine. This compound was preferred to the free amine in order to eliminate side reactions [12]. High yields of the diiodides **3a**–**b** were observed (Scheme 1). Purification and identification are reported in the experimental. The diiodides **3a**–**b** were reduced using tri-*n*-butyltin hydride, yielding **4a**–**b** in good yield.

At this point the strategy was to form the thiol function from the alcohol. We initially chose [6], the conversion of the alcohol **4b** into the iodide **5b**, followed by formation of the isothiouronium salt. This salt was then converted into thiol and at the same time the amino group was deprotected, with hydrazine (Scheme 2). A mixture of the starting iodide **5b**, thiol **6b** and undesired disulfide **7b** was obtained. Separation of **6b** could not be effected, despite attempts of recrystallization and column chromatography.



Scheme 2. Synthesis of the semifluorinated long-chain aminothiol **6b** from thiourea.



Scheme 3. Synthesis of the semifluorinated long-chain aminothiols **6a–b** through the Mitsunobu reaction.

In order to circumvent these difficulties, the Mitsunobu method [13] was used (Scheme 3) starting from the alcohol **4a–b**. The resulting thioacetate **8a–b** was obtained pure by recrystallization from methanol (a key step impossible to perform for the iodide **5b** encountered in the preceding method). As in the previous route, the thioacetate **8a–b** and the amine function were deprotected with hydrazine. Aminothiols **6a–b** were obtained in good yield and in a pure state.

3. Conclusion

The synthesis of amino terminated semifluorinated long-chain alkanethiols NH_2–$(CH_2)_3$–$(CF_2)_{6,8}$–$(CH_2)_{11}$–SH has been achieved in good yield and in a highly pure state. Elaboration of mixed SAMs with the thiols F–$(CF_2)_{8,10}$–$(CH_2)_{11}$–SH, should now be possible.

4. Experimental

4.1. General experimental procedures

Daikin Co. kindly supplied 1,6-diiodoperfluorohexane and 1,8-diiodoperfluorooctane. The products were characterised by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, all at room temperature and recorded in $CDCl_3$ on a Brucker AC 250 spectrometer operating at 200 MHz for ^{1}H, at 235 MHz for ^{19}F and on a Brucker DRX 400 operating at 100 MHz for ^{13}C. All chemical shifts are reported in ppm downfield of the standard (TMS and CCl_3F). The letters s, br, t, q and m designate singlet, broad, triplet, quadruplet and multiplet, respectively. Melting points were determined in open glass capillaries using a Gallenkamp Melting Point Apparatus. Infrared spectra were recorded on a Brucker IFS 25 instrument in transmittance mode. IR data are given in cm^{-1}. Mass spectra were recorded on a Jeol DX 300 spectrometer.

4.2. Synthesis of monoadducts $I(CF_2)_nCH_2CHI(CH_2)_9OH$ *1a* ($n = 6$) and *1b* ($n = 8$) and diadducts *2a* and *b*

α,ω-Diiodoperfluoroalkane (0.036 mol for $n = 6$ and 0.046 mol for $n = 8$), undecyl-10-en-1-ol (0.036 mol for $n = 6$ and 0.046 mol for $n = 8$) and AIBN (5%, 1.8 mmol for $n = 6$ and 2.3 mmol for $n = 8$) were dissolved in 1,2-dichloroethane (50 ml for $n = 6$ and 75 ml for $n = 8$) under dinitrogen. The mixture was heated at 70 °C for 3 h under dinitrogen. After cooling, the solvent was removed by rotary evaporation and the mixture was separated by column chromatography on silica gel (petroleum ether/diethyl ether = 90/10) affording unreacted α,ω-diiodoperfluoroalkane (28% for $n = 6$ and $n = 8$), monoadduct (53% for $n = 6$ as a colourless oil and 52% for $n = 8$ as a white wax) and diadduct (19% for $n = 6$ and 20% for $n = 8$, both as a white powder).

Assignments for 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluoro-10,17-diiodo-heptadecanol (**1a**) are as follows: ^{1}H NMR δ: 1.33 (br, (C**H**$_2$)$_6$, 12H); 1.44 (s, O**H**, 1H); 1.57 (m, C**H**$_2$CH$_2$OH, 2H); 1.81 (m, C**H**$_2$(CH$_2$)$_6$, 2H); 2.88 (m, CF$_2$C**H**$_2$, 2H); 3.66 (t, $^3J_{HH} = 6.51$ Hz, C**H**$_2$OH, 2H); 4.36 (m, C**H**I, 1H). ^{19}F NMR δ: −59.4 (s, IC**F**$_2$, 2F); −113.5 (s, ICF$_2$C**F**$_2$, 2F); A from AB −112.1, B from AB −114.9 (AB system, $^2J_{FF} = 1.2$ Hz, C**F**$_2$CH$_2$, 2F); −121.5 (s, ICF$_2$CF$_2$C**F**$_2$, 2F); −122.1 (s, C**F**$_2$CF$_2$CH$_2$, 2F); −124.1 (s, C**F**$_2$CF$_2$CF$_2$CH$_2$, 2F). ^{13}C NMR δ: 21.11 (s, C10); 26.11 (s, C3); 28.87 (s, C8); 29.68–29.86 (s, C4, C5, C6 and C7); 33.17 (s, C2); 40.68 (s, C9); 42.08 (t, $^2J_{CF} = 20.83$ Hz, C11); 63.46 (s, C1); 94.05 (tt, $^1J_{CF} = 321.3$ Hz, $^2J_{CF} = 42$ Hz, C17); 106.34–114 (tt, C13, C14, C15 and C16); 118.30 (tt, $^1J_{CF} = 258.6$ Hz, $^2J_{CF} = 31.5$ Hz, C12). IR (KBr) ν_{max}: 3361 (O–H); 2929 and 2859 (C–H); 1203 and 1146 (C–F). MS (FAB+) *m/z*: 724 ($(M)^+$, 2%).

Assignments for 12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluoro-10,19-diiodo-nonadecanol (**1b**) are as follows: ^{1}H NMR δ: 1.34 (br, (C**H**$_2$)$_6$, 12H); 1.56 (m, C**H**$_2$CH$_2$OH, 2H); 1.79 (m, C**H**$_2$(CH$_2$)$_6$, 2H); 2.88 (m, CF$_2$C**H**$_2$, 2H); 3.67 (t, $^3J_{HH} = 6.53$ Hz, C**H**$_2$OH, 2H); 4.36 (m, C**H**I, 1H). ^{19}F NMR δ: −59.5 (s, IC**F**$_2$, 2F); −113.5 (s, ICF$_2$C**F**$_2$, 2F); A from AB −112.2, B from AB −115 (AB system, $^2J_{FF} = 1.1$ Hz, C**F**$_2$CH$_2$, 2F); −121.3 (s, ICF$_2$CF$_2$C**F**$_2$, 2F); −122.1 (s, C**F**$_2$C**F**$_2$CF$_2$C**F**$_2$CF$_2$CH$_2$, 6F); −124 (s, C**F**$_2$CF$_2$CF$_2$CH$_2$, 2F). ^{13}C NMR δ: 21.39 (s, C10); 26.10 (s, C3); 28.87 (s, C8); 29.68–29.94 (s, C4, C5, C6 and C7); 33.14 (s, C2); 40.68 (s, C9); 42.06 (t, $^2J_{CF} = 20.78$ Hz, C11); 63.39 (s, C1); 93.86 (tt, $^1J_{CF} = 321.2$ Hz, $^2J_{CF} = 41.7$ Hz, C19); 105.97–114.18 (tt, C13, C14, C15, C16, C17 and C18); 118.30 (tt,

$^1J_{CF} = 258.4$ Hz, $^2J_{CF} = 31.6$ Hz, C12). IR (KBr) ν_{max}: 3333 (O–H); 2924 and 2855 (C–H); 1202 and 1147 (C–F). MS (FAB+) *m/z*: 807 ($(M + H–H_2O)^+$, 35%).

Assignments for 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluoro-10,19-diiodo-octacosan-1,28-diol (**2a**) are as follows: ^{1}H NMR δ: 1.32 (br, $(CH_2)_6$, 24H); 1.56 (m, CH_2CH_2OH, 4H); 1.7 (s, OH, 1H); 1.8 (m, $CH_2(CH_2)_6$, 4H); 2.87 (m, CF_2CH_2, 4H); 3.64 (t, $^3J_{HH} = 6.51$ Hz, CH_2OH, 4H); 4.34 (m, CHI, 2H). ^{19}F NMR δ: A from AB −112.2, B from AB −115 (AB system, $^2J_{FF} = 1.2$ Hz, CF_2CH_2, 4F); −122.1 (s, $CF_2CF_2CH_2$, 4F); −124.1 (s, $CF_2CF_2CF_2CH_2$, 4F). ^{13}C NMR δ: 21.57 (s, C10 and C19); 26.11 (s, C3 and C26); 28.87 (s, C8 and C21); 29.68–29.93 (s, C4, C5, C6, C7, C22, C23, C24 and C25); 33.13 (s, C2 and C27); 40.68 (s, C9 and C20); 42.09 (t, $^2J_{CF} = 20.84$ Hz, C11 and C18); 63.35 (s, C1 and C28); 108.42–114.47 (tt, C13, C14, C15 and C16); 118.30 (tt, $^1J_{CF} = 258.2$ Hz, $^2J_{CF} = 31.7$ Hz, C12 and C17). IR (KBr) ν_{max}: 3440 (O–H); 2929 and 2859 (C–H); 1200 (C–F). MS (FAB+) *m/z*: 895 ($(M + H)^+$, 18%).

Assignments for 12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluoro-10,21-diiodo-triacontan-1,30-diol (**2b**) are as follows: mp 70.5–71 °C. ^{1}H NMR δ: 1.34 (br, $(CH_2)_6$, 24H); 1.58 (m, CH_2CH_2OH, 4H); 1.82 (m, $CH_2(CH_2)_6$, 4H); 2.88 (m, CF_2CH_2, 4H); 3.67 (t, $^3J_{HH} = 6.51$ Hz, CH_2OH, 4H); 4.36 (m, CHI, 2H). ^{19}F NMR δ: A from AB −112.2, B from AB −115 (AB system, $^2J_{FF} = 1.2$ Hz, CF_2CH_2, 4F); −122 (s, $CF_2CF_2CH_2$, 4F); −122.3 (s, $CF_2CF_2CF_2CH_2$, 4F); −124.1 (s, CF_2-$CF_2CF_2CF_2CH_2$, 4F). ^{13}C NMR δ: 21.40 (s, C10 and C21); 26.08 (s, C3 and C28); 28.84 (s, C8 and C23); 29.66–29.91 (s, C4, C5, C6, C7, C24, C25, C26 and C27); 33.11 (s, C2 and C29); 40.66 (s, C9 and C22); 42.04 (t, $^2J_{CF} = 20.8$ Hz, C11 and C20); 63.35 (s, C1 and C30); 108.01–114.45 (tt, C13, C14, C15, C16, C17 and C18); 118.28 (tt, $^1J_{CF} = 258.3$ Hz, $^2J_{CF} = 31.5$ Hz, C12 and C19). IR (KBr) ν_{max}: 3321 (O–H); 2924 and 2855 (C–H); 1195 (C–F). MS (FAB+) *m/z*: 995 ($(M + H)^+$, 17%).

4.3. Synthesis of diiodo compounds *3a* and *b*

Monoadduct **1a–b** (0.018 mol for $n = 6$ and 0.023 mol for $n = 8$), *N*-allylphthalimide (0.018 mol for $n = 6$ and 0.023 mol for $n = 8$) and AIBN (10%, 1.8 mmol for $n = 6$ and 2.3 mmol for $n = 8$) were dissolved in 1,2-dichloroethane (50 ml for $n = 6$ and 75 ml for $n = 8$) under nitrogen. The mixture was heated at 70 °C for 3 h under dinitrogen. After cooling, the solvent was removed by rotary evaporation affording the crude product which was purified by column chromatography on silica gel (petroleum ether/diethyl ether = 80/20). The difunctional compound **3a–b** was obtained in the pure state as a colourless oil with 75% yield for $n = 6$ (**3a**) and as a white wax with 81% yield for $n = 8$ (**3b**).

Assignments for 2-(4,4,5,5,6,6,7,7,8,8,9,9-dodecafluoro-20-hydroxy-2,11-diiodo-eicosyl)-isoindole-1,3-dione (**3a**) are as follows: ^{1}H NMR δ: 1.33 (br, $(CH_2)_6$, 12H); 1.57 (m, CH_2CH_2OH, 2H); 1.81 (m, $CH_2(CH_2)_6$, 2H); 2.87 (m, $CH_2(CF_2)_6CH_2$, 4H); 3.66 (t, $^3J_{HH} = 6.51$ Hz, CH_2OH, 2H); 4.09 (m, NCH_2, 2H); 4.35 (m, CF_2CH_2CHI, 1H); 4.74 (m, NCH_2CHI, 1H); 7.86 (m, C_6H_4, 4H). ^{19}F NMR δ: A from AB −112.3, B from AB −114.1 (AB system, $^2J_{FF} = 1.1$ Hz, $NCH_2CHICH_2CF_2$, 2F); A from AB −112.4, B from AB −114.9 (AB system, $^2J_{FF} = 1.1$ Hz, CF_2CH_2CHI, 2F); −122.1 (s, $CF_2CF_2CH_2$, 4F); −124 (s, $CH_2CF_2CF_2CF_2$, 2F); −124.1 (s, $CF_2CF_2CF_2CH_2$, 2F). ^{13}C NMR δ: 13.79 (s, C2′); 21.56 (s, C11′); 26.11 (s, C18′); 28.87 (s, C13′); 29.68–29.93 (s, C14′, C15′, C16′ and C17′); 33.17 (s, C19′); 40.01 (t, $^2J_{CF} = 21.29$ Hz, C3′); 40.69 (s, C12′); 42.10 (t, $^2J_{CF} = 20.84$ Hz, C10′); 46.25 (s, C1′); 63.45 (s, C20′); 108.07–114.51 (tt, C5′, C6′, C7′ and C8′); 114.82–121.17 (tt, C4′ and C9′); 124.15 (s, C4 and C7); 131.98 (s, C5 and C6); 134.86 (s, C3a and C7a); 168.09 (s, C1 and C3). IR (KBr) ν_{max}: 3428 (O–H); 2929 and 2858 (C–H); 1718 (O=CNC=O); 1197 (C–F). MS (FAB+) *m/z*: 912 ($(M + H)^+$, 5%).

Assignments for 2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-hexadecafluoro-22-hydroxy-2,13-diiodo-docosyl)-isoindole-1,3-dione (**3b**) are as follows: ^{1}H NMR δ: 1.34 (br, $(CH_2)_6$, 12H); 1.59 (m, CH_2CH_2OH, 2H); 1.64 (s, OH, 1H); 1.79 (m, $CH_2(CH_2)_6$, 2H); 2.88 (m, $CH_2(CF_2)_6CH_2$, 4H); 3.67 (t, $^3J_{HH} = 6.48$ Hz, CH_2OH, 2H); 4.09 (m, NCH_2, 2H); 4.36 (m, CF_2CH_2CHI, 1H); 4.74 (m, NCH_2CHI, 1H); 7.86 (m, C_6H_4, 4H). ^{19}F NMR δ: A from AB −112.4, B from AB −114.1 (AB system, $^2J_{FF} = 1.1$ Hz, $NCH_2CHICH_2CF_2$, 2F); A from AB −112.4, B from AB −115 (AB system, $^2J_{FF} = 1.1$ Hz, CF_2CH_2CHI, 2F); −122 (s, $CF_2CF_2CH_2$, 4F); −122.3 (s, $CF_2CF_2CF_2CH_2$, 4F); −123.9 (s, CH_2-$CF_2CF_2CF_2CF_2$, 2F); −124.1 (s, $CF_2CF_2CF_2CF_2CH_2$, 2F). ^{13}C NMR δ: 13.67 (s, C2′); 21.45 (s, C13′); 26.11 (s, C20′); 28.87 (s, C15′); 29.68–29.93 (s, C16′, C17′, C18′ and C19′); 33.16 (s, C21′); 39.93 (t, $^2J_{CF} = 21.33$ Hz, C3′); 40.68 (s, C14′); 42.05 (t, $^2J_{CF} = 20.73$ Hz, C12′); 46.24 (s, C1′); 63.42 (s, C22′); 108.37–114.57 (tt, C5′, C6′, C7′, C8′, C9′ and C10′); 115.30–121.18 (tt, C4′ and C11′); 124.15 (s, C4 and C7); 131.97 (s, C5 and C6); 134.86 (s, C3a and C7a); 168.09 (s, C1 and C3). IR (KBr) ν_{max}: 3340 (O–H); 2924 and 2855 (C–H); 1713 (O=CNC=O); 1198 and 1073 (C–F). MS (FAB+) *m/z*: 1012 ($(M + H)^+$, 15%).

4.4. Reduction of the iodide functions in *3a–b* by tri-n-butyltin hydride, formation of the reduced difunctional compounds *4a–b*

Compounds **3a–b** (0.014 mol for **3a** and 0.015 mol for **3b**) and 10% of AIBN (1.4 mmol for **3a** and 1.5 mmol for **3b**) were dissolved in 30 ml of toluene under a dinitrogen atmosphere, followed by a dropwise addition of Bu_3SnH (200%, 0.028 mol for **3a** and 0.03 mol for **3b**) through a septum. The mixture was heated for 18 h at 70 °C under stirring. After cooling, toluene was evaporated under vacuum, and then the mixture was redissolved in diethyl

ether, washed two times with water and two times with brine. The ethereal layer was dried with sodium sulfate and filtered. The required amount of KF (0.028 mol for **3a** and 0.03 mol for **3b**) was dispersed in the ethereal solution and kept 12 h under stirring, in order to transform the tri-*n*-butyltin iodide formed into tri-*n*-butyltin fluoride, insoluble in diethyl ether. The solution was filtered and the filtrate was evaporated under reduced pressure. The reduced product was obtained in the pure state as a white powder (99% for **4a** and 70% for **4b**).

Assignments for 2-(4,4,5,5,6,6,7,7,8,8,9,9-dodecafluoro-20-hydroxy-eicosyl)-isoindole-1,3-dione (**4a**) are as follows: mp 77.7–78 °C. ^{1}H NMR δ: 1.32 (br, (C**H**$_2$)$_8$, 16H); 1.59 (m, NCH$_2$C**H**$_2$, C**H**$_2$CH$_2$OH, 4H); 1.7 (s, O**H**, 1H); 2.06 (m, C**H**$_2$(CF$_2$)$_6$C**H**$_2$, 4H); 3.66 (q, $^3J_{HH} = {}^3J_{HOH} = 5.97$ Hz, C**H**$_2$OH, 2H); 3.8 (t, $^3J_{HH} = 6.79$ Hz, NC**H**$_2$, 2H); 7.83 (m, C$_6$**H**$_4$, 4H). ^{19}F NMR δ: −114.9 (s, CH$_2$C**F**$_2$, C**F**$_2$CH$_2$, 4F); −122.4 (s, C**F**$_2$CF$_2$CH$_2$, 4F); −124 (s, CH$_2$CF$_2$CF$_2$C**F**$_2$, 2F); −124.2 (s, C**F**$_2$CF$_2$CF$_2$CH$_2$, 2F). ^{13}C NMR δ: 14 (s, C2′); 20.49 (s, C11′), 26.13 (s, C18′); 29.13 (t, $^2J_{CF} = 22.64$ Hz, C3′); 29.48–29.94 (s, C12′, C13′, C14′, C15′, C16′ and C17′); 31.33 (t, $^2J_{CF} = 22.39$ Hz, C10′); 33.18 (s, C19′); 37.44 (s, C1′); 63.4 (s, C20′); 108.62–114.63 (tt, C5′, C6′, C7′ and C8′); 115.62–121.81 (tt, C4′ and C9′); 123.81 (s, C4 and C7); 132.31 (s, C5 and C6); 134.54 (s, C3a and C7a); 168.64 (s, C1 and C3). IR (KBr) ν_{max}: 3469 (O–H); 2927 (C–H); 1701 (O=CNC=O); 1185 and 1057 (C–F). MS (FAB+) *m/z*: 660 ($(M + H)^+$, 2%).

Assignments for 2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-hexadecafluoro-22-hydroxy-docosyl)-isoindole-1,3-dione (**4b**) are as follows: mp 101.3–102.6 °C. ^{1}H NMR δ: 1.32 (br, (C**H**$_2$)$_8$, 16H); 1.61 (m, NCH$_2$C**H**$_2$, C**H**$_2$CH$_2$OH, 4H); 1.63 (s, O**H**, 1H); 2.07 (m, C**H**$_2$(CF$_2$)$_6$C**H**$_2$, 4H); 3.67 (q, $^3J_{HH} = {}^3J_{HOH} = 6.16$ Hz, C**H**$_2$OH, 2H); 3.81 (t, $^3J_{HH} = 6.8$ Hz, NC**H**$_2$, 2H); 7.83 (m, C$_6$H$_4$, 4H). ^{19}F NMR δ: −114.8 (s, CH$_2$C**F**$_2$, C**F**$_2$CH$_2$, 4F); −122.2 (s, C**F**$_2$C**F**$_2$-CF$_2$CH$_2$, 8F); −123.8 (s, CH$_2$CF$_2$CF$_2$C**F**$_2$, 2F); −124 (s, C**F**$_2$CF$_2$CF$_2$CH$_2$, 2F). ^{13}C NMR δ: 14.03 (s, C2′); 20.48 (s, C13′); 26.12 (s, C20′); 29.09 (t, $^2J_{CF} = 22.6$ Hz, C3′); 29.48–29.93 (s, C14′, C15′, C16′, C17′, C18′ and C19′); 31.30 (t, $^2J_{CF} = 22.35$ Hz, C12′); 33.18 (s, C21′); 37.42 (s, C1′); 63.43 (s, C22′); 108.90–114.04 (tt, C5′, C6′, C7′, C8′, C9′ and C10′); 115.95–121.4 (tt, C4′ and C11′); 123.81 (s, C4 and C7); 132.32 (s, C5 and C6); 134.54 (s, C3a and C7a); 168.63 (s, C1 and C3). IR (KBr) ν_{max}: 3452 (O–H); 2925 and 2856 (C–H); 1712 (O=CNC=O); 1147 and 1055 (C–F). MS (FAB+) *m/z*: 760 ($(M + H)^+$, 6%).

4.5. Conversion of the alcohol *4b* into the iodide *5b*

The alcohol **4b** (4.48 mmol), red phosphorus (30%, 1.49 mmol) and iodine (50%, 2.24 mmol) were introduced into an Erlenmeyer flask equipped with a reflux condenser and a magnetic stirrer, and heated at 140 °C for 5 h. The reaction mixture was cooled to room temperature and the solid product treated three times with dichloromethane (3 × 50 ml) to extract the iodide compound. The combined organic extracts were filtered and washed with water (2 × 50 ml) and with saturated aqueous NaCl (2 × 50 ml). The organic solution was dried over sodium sulfate and freed from solvent on a rotary evaporator. The crude iodide obtained as a yellow paste was recrystallized in heptane to give compound **5b** as a white powder with a 85% yield.

Assignments for 2-(4,4,5,5,6,6,7,7,8,8,9,9-dodecafluoro-20-iodo-eicosyl)-isoindole-1,3-dione (**5b**) are as follows: ^{1}H NMR δ: 1.29 (br, (C**H**$_2$)$_7$, NCH$_2$C**H**$_2$, 16H); 1.61 (m, CF$_2$CH$_2$C**H**$_2$, 2H); 1.84 (m, C**H**$_2$CH$_2$I, 2H); 2.07 (m, C**H**$_2$(CF$_2$)$_8$C**H**$_2$, 4H); 3.21 (t, $^3J_{HH} = 7$ Hz, C**H**$_2$I, 2H); 3.81 (t, $^3J_{HH} = 6.8$ Hz, NC**H**$_2$, 2H); 7.83 (m, C$_6$**H**$_4$, 4H). ^{19}F NMR δ: −114.7 (s, CH$_2$C**F**$_2$, C**F**$_2$CH$_2$, 4F); −122.2 (s, C**F**$_2$CF$_2$CH$_2$, 4F); −123.8 (s, CH$_2$CF$_2$CF$_2$C**F**$_2$, 2F); −124 (s, C**F**$_2$CF$_2$CF$_2$CH$_2$, 2F). MS (FAB+) *m/z*: 870 ($(M + H)^+$, 30%); 742 ($(M - I)^+$, 25%).

4.6. Formation of the thiol *6b* starting from the iodide compound *5b*

In a three-necked round bottomed flask containing ethanol (20 ml) and the iodide **5b** (3.81 mmol), 1.5 eq of thiourea (5.71 mmol) was added and heated under reflux for 18 h. After cooling to room temperature the reaction flask was degassed under dinitrogen and 5 eq of hydrazine hydrate (19 mmol) were added dropwise through a septum. The addition completed, the mixture was refluxed for 12 h. Then HCl (0.1 M, 10 ml) was added at room temperature. The solution was filtered to eliminate the resulting phthalylhydrazide. The mixture was extracted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and the solvent removed under reduced pressure to give a yellow powder containing three products: the starting iodide **5b**, the expected thiol **6b** and the corresponding disulfide **7b** in a molar ratio 76/9/15, respectively. At this step, several purification tests proved unsuccessful (recrystallization and chromatography). The three products were identified as a mixture and by comparison with spectroscopic data of similar compounds. **5b** assignments have been reported in Section 4.5 and **6b** assignments are reported in Section 4.8.

Assignments for **7b** are as follows: ^{1}H NMR δ: 1.3 (br, (C**H**$_2$)$_7$, NCH$_2$C**H**$_2$, 32H); 1.63 (m, CF$_2$CH$_2$C**H**$_2$, 4H); 1.76 (m, C**H**$_2$CH$_2$S, 4H); 2.12 (m, C**H**$_2$(CF$_2$)$_8$C**H**$_2$, 8H); 2.7 (t, $^3J_{HH} = 7.3$ Hz, C**H**$_2$S, 4H); 2.82 (t, $^3J_{HH} = 6.9$ Hz, H$_2$NC**H**$_2$, 4H). ^{19}F NMR δ: −114.8 (s, CH$_2$C**F**$_2$, C**F**$_2$CH$_2$, 4F); −122.2 (s, C**F**$_2$C**F**$_2$CF$_2$CH$_2$, 8F); −124 (s, C**F**$_2$-CF$_2$CF$_2$CF$_2$CH$_2$, 4F).

4.7. Conversion of alcohols *4a–b* into thiolacetates *8a–b* using the Mitsunobu reaction

To a solution of triphenylphosphine in anhydrous THF (0.0278 mol in 75 ml for **4a** and 0.02 mol in 50 ml for **4b**) diisopropyl azodicarboxylate (DIAD, 0.0278 mol for **4a** and

0.02 mol for **4b**) was added at 0 °C under a dinitrogen atmosphere. After observation of a white fine precipitate, a mixture of alcohol (0.0139 mol of **4a** and 0.010 mol of **4b**) and thiolacetic acid (0.0278 mol with **4a** and 0.02 mol with **4b**) in THF (50 ml) was added dropwise to the initial solution over a time of 15 min. After 1 h at 0 °C, the mixture turned yellow and was stirred at room temperature for 12 h. The solvent was removed by rotary evaporation and the mixture was extracted with diethyl ether (70 ml). The organic layer was washed with water (2 × 30 ml) and brine (2 × 30 ml), and then dried over sodium sulfate. Removal of the solvent afforded the crude product, which was purified by recrystallization in methanol. The thiolacetates were obtained in the pure state as white powders with a 54% yield for **8a** and 75% yield for **8b**.

Assignments for thioacetic acid 20-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-12,12,13,13,14,14,15,15,16,16,17,17-dodecafluoro-eicosyl ester (**8a**) are as follows: mp 67.5–68.3 °C. ^{1}H NMR δ: 1.3 (br, $(CH_2)_8$, 16H); 1.59 (m, NCH_2CH_2, CH_2CH_2S, 4H); 1.65 (s, OH, 1H); 2.06 (m, $CH_2(CF_2)_6CH_2$, 4H); 2.34 (s, $CH_3C{=}O$, 3H); 2.88 (t, $^3J_{HH} = 7.2$ Hz, $CH_2SC{=}O$, 2H); 3.8 (t, $^3J_{HH} = 6.81$ Hz, NCH_2, 2H); 7.82 (m, C_6H_4, 4H). ^{19}F NMR δ: −114.8 (s, CH_2CF_2, CF_2CH_2, 4F); −122.3 (s, $CF_2CF_2CH_2$, 4F); −124 (s, $CH_2CF_2CF_2CF_2$, 2F); −124.2 (s, $CF_2CF_2CF_2CH_2$, 2F). ^{13}C NMR δ: 20.38 (s, C19); 20.5 (s, C10); 29.14 (t, $^2J_{CF} = 22.75$ Hz, C18); 29.18 (s, CH_3); 29.47–29.88 (s, C2, C3, C4, C5, C6, C7, C8 and C9); 31.01 (s, C1); 31.34 (t, $^2J_{CF} = 22.36$ Hz, C11); 37.44 (s, C20); 108.47–114.61 (tt, C13, C14, C15 and C16); 115.62–121.39 (tt, C12 and C17); 123.8 (s, C4′ and C7′); 132.33 (s, C5′ and C6′); 134.52 (s, C3a and C7a); 168.61 (s, C1′ and C3′); 196.48 (s, $C{=}OCH_3$). IR (KBr) ν_{max}: 2921 and 2850 (C–H); 1695 (C=O); 1130 (C–F). MS (FAB+) *m/z*: 718 ($(M + H)^+$, 10%).

Assignments for thioacetic acid 22-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluoro-docosyl ester (**8b**) are as follows: mp 79–79.5 °C. ^{1}H NMR δ: 1.29 (br, $(CH_2)_8$, 16H); 1.61 (m, NCH_2CH_2, CH_2CH_2S, 4H); 2.07 (m, $CH_2(CF_2)_6CH_2$, 4H); 2.34 (s, $CH_3C{=}O$, 3H); 2.88 (t, $^3J_{HH} = 7.2$ Hz, $CH_2SC{=}O$, 2H); 3.81 (t, $^3J_{HH} = 6.73$ Hz, NCH_2, 2H); 7.86 (m, C_6H_4, 4H). ^{19}F NMR δ: −114.9 (s, CH_2CF_2, CF_2CH_2, 4F); −122.3 (s, $CF_2CF_2CF_2CH_2$, 8F); −123.9 (s, $CH_2CF_2CF_2CF_2$, 2F); −124.1 (s, $CF_2CF_2CF_2CH_2$, 2F). ^{13}C NMR δ: 20.03 (s, C21); 20.08 (s, C10); 28.76 (t, $^2J_{CF} = 22.72$ Hz, C20); 28.76 (s, CH_3); 29.04–29.47 (s, C2, C3, C4, C5, C6, C7, C8 and C9); 30.53 (s, C1); 30.92 (t, $^2J_{CF} = 22.3$ Hz, C11); 37.01 (s, C22); 107.43–114.91 (tt, C13, C14, C15, C16, C17 and C18); 115.56–122.36 (tt, C12 and C19); 123.36 (s, C4′ and C7′); 131.96 (s, C5′ and C6′); 134.08 (s, C3a and C7a); 168.15 (s, C1′ and C3′); 195.92 (s, $C{=}OCH_3$). IR (KBr) ν_{max}: 2928 and 2857 (C–H); 1709 (C=O); 1148 and 1200 (C–F). MS (FAB+) *m/z*: 818 ($(M + H)^+$, 8%).

*4.8. Deprotection of amino and thiol functions of **8a** and **b** to afford compounds **6a** and **b***

The thioacetate (6.44 mmol for **8a** and 3.67 mmol for **8b**) was dissolved in ethanol (125 ml for **5a** and 75 ml for **5b**) under dinitrogen and hydrazine hydrate (0.032 mol for **8a** and 0.018 mol for **8b**) was added dropwise through a septum. After addition, the mixture was heated at reflux with stirring for 12 h. After cooling the phthalylhydrazide precipitate was filtered. An ethanolic solution (25 ml) of sodium hydroxide (6.44 mmol for **8a** and 3.67 mmol for **8b**) was added to the filtrate. The product was extracted by adding diethyl ether (100 ml) and water. The ethereal layer was washed three times with water (3 × 30 ml) and with brine (3 × 30 ml) and dried over sodium sulfate. The solvent was removed by rotary evaporation. Aminoperfluoroalkane thiols **6a** and **b** were obtained in the pure state as a white powder with a yield of 80%.

Assignments for 20-amino-12,12,13,13,14,14,15,15,16,16,17,17-dodecafluoro-eicosane-1-thiol (**6a**) are as follows: mp 77–78.5 °C. ^{1}H NMR δ: 1.29 (br, $(CH_2)_8$, 16H); 1.59 (m, CH_2CH_2S, 2H); 1.76 (m, NCH_2CH_2, 2H); 2.1 (m, $CH_2(CF_2)_6CH_2$, 4H); 2.51 (q, $^3J_{HH} = {}^3J_{HSH} = 6.79$ Hz, CH_2SH, 2H); 2.79 (t, $^3J_{HH} = 6.91$ Hz, CH_2NH_2, 2H); ^{19}F NMR δ: −114.8 (s, CH_2CF_2, CF_2CH_2, 4F); −122.3 (s, $CF_2CF_2CH_2$, 4F); −124.1 (s, $CF_2CF_2CF_2CH_2$, 4F). ^{13}C NMR δ: 20.48 (s, C10); 24.54 (s, C19); 24.99 (s, C1); 28.73 (s, C3); 29.86 (t, $^2J_{CF} = 21.82$ Hz, C18); 29.42–29.83 (s, C4, C5, C6, C7, C8 and C9); 31.31 (t, $^2J_{CF} = 22.36$ Hz, C11); 34.42 (s, C2); 41.68 (s, C20); 108.26–114.99 (tt, C13, C14, C15 and C16); 116.03–121.7 (tt, C12 and C17). IR (KBr) ν_{max}: 3365 (N–H); 2922 (C–H); 1136 (C–F). MS (FAB+) *m/z*: 546 ($(M + H)^+$, 15%).

Assignments for 22-amino-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluoro-docosane-1-thiol (**6b**) are as follows: mp 102.5–103.9 °C. ^{1}H NMR δ: 1.31 (br, $(CH_2)_8$, 16H); 1.62 (m, CH_2CH_2S, 2H); 1.78 (m, NCH_2CH_2, 2H); 2.08 (m, $CH_2(CF_2)_6CH_2$, 4H); 2.55 (q, $^3J_{HH} = {}^3J_{HSH} = 7.28$ Hz, CH_2SH, 2H); 2.83 (t, $^3J_{HH} = 6.89$ Hz, CH_2NH_2, 2H); ^{19}F NMR δ: −114.8 (s, CH_2CF_2, CF_2CH_2, 4F); −122.2 (s, $CF_2CF_2CF_2CH_2$, 8F); −124 (s, $CF_2CF_2CF_2CF_2CH_2$, 4F). ^{13}C NMR δ: 20.49 (s, C10); 24.58 (s, C21); 25.06 (s, C1); 28.76 (s, C3); 28.85 (t, $^2J_{CF} = 22.49$ Hz, C20); 29.45–29.86 (s, C4, C5, C6, C7, C8 and C9); 31.30 (t, $^2J_{CF} = 22.47$ Hz, C11); 34.44 (s, C2); 41.73 (s, C22); 108.27–114.41 (tt, C13, C14, C15, C16, C17 and C18); 114.87–121.05 (tt, C12 and C19). IR (KBr) ν_{max}: 3442 (N–H); 2928 and 2856 (C–H); 1151 and 1209 (C–F). MS (FAB+) *m/z*: 646 ($(M + H)^+$, 58%). Anal. Calcd. for $C_{22}H_{31}F_{12}NS$: C, 40.93%; H, 4.84%; F, 47.09%; N, 2.17%; S, 4.97%. Found: C, 41.44%; H, 5.07%; F, 46.72%; N, 2.01%; S, 5.17%.

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