α,ω-Difunctional Perfluorinated Spacer Arms for Polymeric Material Derivatization

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Introduction

In recent years, the perfluorinated organic compounds have received extensive interest in various fields due to their unique physiological and physical properties.[1] Many active pharmaceutical and agrochemical derivatives include fluoroalkene or fluoro ketone motifs.[2] Fluorine-containing polymers show enhanced thermal stability, flame retardance, and resistance to chemicals and light.[3] They are also of specific interest as biomaterials because of the biological inertness imparted by fluorine.[4] At the very least, fluorinated labels are useful analytical tools in chromatography[5] and spectroscopy.[6,7] In this paper, we focus on the design and preparation of original α,ω-difunctional perfluorinated molecules as dual-acting reagents for both polymer surface derivatization and quantitative analysis of the resulting modified materials.

As part of a general program aimed at developing new biomaterials, we became interested in the biocompatibilization of microporous track-etched membranes made from synthetic polyesters by tailored chemical modifications of their surface.[8] Our strategy is based on the covalent attachment of selected biological signals that will be recognized by specific receptors of mammalian cells, thus mediating the desired biological responses.[8] The bioactive molecules of interest are naturally-occurring polypeptides or synthetic peptidomimetics; for steric reasons, their fixation on the polymer surfaces makes use of appropriate spacer arms, *i.e.*, α,ω-difunctional molecules able to react with the biomolecules at one termination and with the polymer surface at the other termination. Our selected structures for such links are disclosed in Scheme 1; their design results from several considerations, as follows.

(i) The usable anchoring points on polyesters are the surface-displayed chain ends, *i.e.*, carboxyl- and hydroxyl functions for which respective reactivities have been established.[7,8] On the other hand, our bioactive molecules offer primary amines (peptide terminal functions) or phenols (peptidomimetic templates) as anchoring points. Therefore, the coupling reactions we considered were Williamson etherification, amide bond formation, and isocyanate quenching with oxygen or nitrogen nucleophiles. Accordingly, the spacer arms were equipped with sufonate (Scheme 1, **1**; X = OSO_2R''), amine (**1** and **2**; R = R′ = H), or isocyanate termini (**2**; R, R′ = =C=O).

(ii) The quantification of molecules displayed on derivatized polymer surfaces remains a crucial problem in materials chemistry. The utility of X-ray photoelectron spectroscopy (XPS) in this context is well substantiated.[9] Moreover, the analytical achievements of this method are significantly more accurate when the fixed molecules contain an elemental tag which is not present in the native polymer. Fluorine, with its high photoelectric cross-section, is the most often used label for XPS characterization of polymer surfaces.[10] Thus, the spacer arms **1** and **2** were constructed around a perfluorinated building block. Another advantage of the fluoroalkyl motif is its established inertness and nontoxicity when grafted on polyesters.[11]

(iii) The chemical linkages involved in the spacer arms were designed to be stable in biological fluids (ether bonds).

(iv) Finally, the length of the spacers (15−25 Å) was chosen to be large enough to allow the development of macromolecular interactions, essential to the recognition of a biological signal.

In this paper, we will describe the synthesis of α,ω-difunctional perfluorinated spacer arms using 2,2′,3,3′,4,4′,5,5′-octafluorohexane-1,6-diol[12] and 3-bromopropylamine as starting materials (n = 4 and m = 2 in Scheme 1). Some aspects of the reactivity of perfluorinated alcohols and derivatives will be discussed.

Results and Discussion

Effective routes have been developed to introduce perfluoroalkyl groups and fluorine atoms into target molecules.[13] An attractive alternative approach is to use commercially available fluorinated intermediates which

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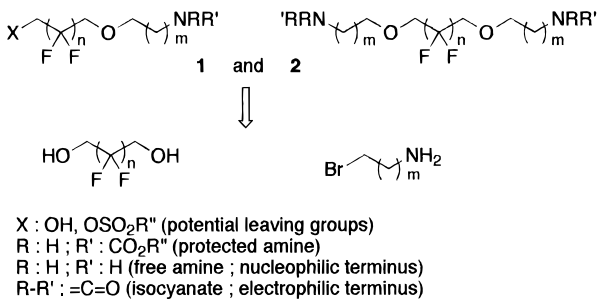
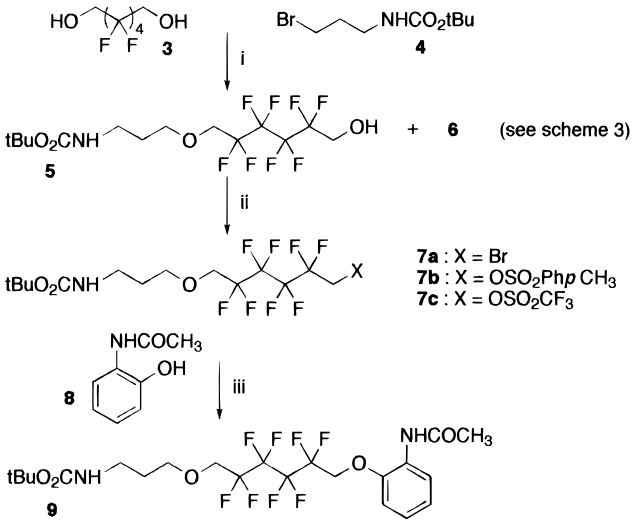
Scheme 1



Scheme 2[a]

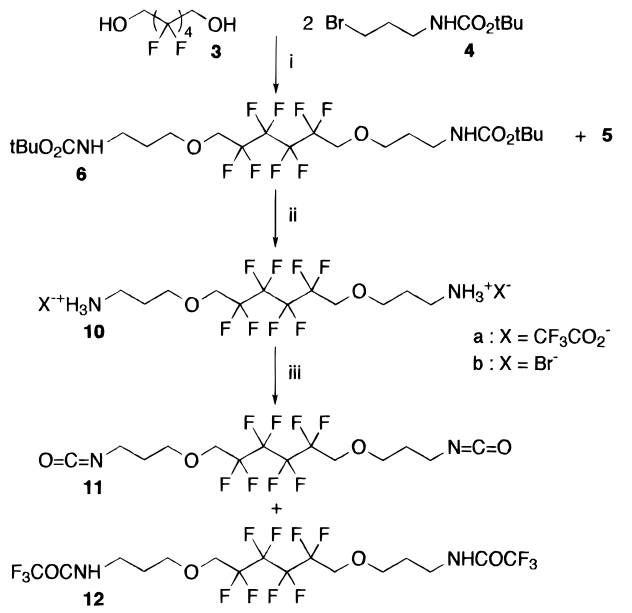


[a] Reagents and conditions: (i) NaH (1 equiv), DMF, 20 °C, 4 h; (ii) **7b**: Cl-Ts (3 equiv), pyridine, 20 °C, 24 h; **7c**: Tf_2O (1.5 equiv), pyridine (2 equiv), ether, 0−20 °C, 2 h; (iii) from **7c:8** (1 equiv), NaOH (1.25 equiv), Aliquat 336 (0.02 equiv), CH_3CN, reflux, 24 h.

would serve as precursors for further elaboration.[14] We have selected the octafluorodiol **3** as a common scaffold for the construction of the spacer arms **7** (Scheme 2) and **11** (Scheme 3). The key step is the formation of an ether linkage by alkylation of **3** (mono- or dialkylation, respectively) with the *N*-protected 3-bromopropylamine **4**.

The octafluoroalkyl moiety of the precursor **3** exerts a strong inductive and hyperconjugative effect that acts on the physical and chemical properties of the terminal hydroxyl functions. The marked influence of trifluoromethyl groups, and higher homologs, on the dissociation constants of alcohols is well established.[12,15] Moreover, the deactivating effect of perfluoroalkyl residues on the nucleophilicity of alcohols and derived alkoxides has been pointed out in several cases.[16] Amongst the methods recently described for preparing polyfluoroalkyl ethers,[17] we have adopted the classical Williamson synthesis using sodium alkoxide as the nucleophile and an alkyl bromide as the electrophile.[18]

Scheme 3[a]



[a] Reagents and conditions: (i) NaH (3 equiv), DMF, 20 °C, 3 h; (ii) **a**: CF_3CO_2H, 30 min, 20 °C; **b**: HBr 20% in HOAc, 30 min, 20 °C; (iii) **10a**: $COCl_2$ (92 equiv), toluene, 125 °C, 2 h; **10b**: $COCl_2$ (2.3 equiv), pyridine (8 equiv), CH_2Cl_2, 0 °C, 2 h.

The 3-bromopropylamine hydrobromide was reacted with di-*tert*-butyl dicarbonate[19] to give the carbamate **4**. Equimolar amounts of diol **3**, bromide **4**, and a base were involved in the next coupling reaction (Scheme 2). The solution of **3** was first treated with the base (30 min to 1 h), and then the solution of **4** was slowly added (1 h) and the mixture was left for 3−24 h under stirring. No reaction was observed by use of K_2CO_3 as the base, in the presence of crown ether (NMR and GC analysis of the crude mixtures). But the coupling occurred well in the presence of tBuOK or NaH in DME, DMF, or DMSO solution; the ratio of the desired monoalkylated product **5** was higher with NaH than with tBuOK. Thus, we were able to obtain a 11:4:10 mixture of monoether **5**, diether **6**, and starting material **3** by reaction of the diol **3** with NaH in DMF solution at room temperature followed by quenching at 0 °C of the preformed alkoxide with the bromide **4** dissolved in DMF. Standard workup and column chromatography on neutral alumina allowed the easy separation of the three products, due to their pronounced differences in polarity: the elution order, with chloroform−2-propanol (95.5:0.5), is **6** (isolated yield of 16%), **5** (isolated yield of 44%), and **3** (isolated yield of 40%), which can be recycled. This procedure offered corrected yields of 73% in monoalkylation product and 27% in dialkylation product. The new compounds **5** and **6** were fully characterized by the usual

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spectroscopic data and elemental analysis (see Experimental Section).

Transformation of the remaining hydroxyl function of **5** into a good leaving group provided the required reactive spacer arm (Scheme 2). The perfluorinated alcohol **5** was reluctant to undergo the transformations normally observed for simple hydrocarbon alcohols. For instance, **5** was totally inert in the presence of dibromotriphenylphosphorane (Br_2PPh_3)[20] (**7a** not detected) and under the usual conditions of tosylation (Cl-Ts (1 equiv), pyr (1 equiv), CH_2Cl_2, 20 °C, 2 h). The tosyl ester **7b** was prepared by reaction of **5** with an excess of tosyl chloride in pyridine as solvent;[21] after 24 h at 20 °C, the yield of isolated product was about 60%. Unfortunately, the tosylate **7b** was poorly reactive toward nucleophilic substitutions; a similar observation was already mentioned in the case of 2,2,2-trifluoroethyl tosylate.[21b] We were unable to substitute the tosyl group of **7b** with 2-acetamidophenoxide chosen as model at bioactive peptidomimetics.

This negative result let us to consider the triflate **7c**. This was readily obtained by treatment of the precursor **5** with trifluoromethanesulfonic anhydride and pyridine in diethylether at 0 °C.[22] The triflate **7c** was indeed an efficient electrophile able to react with the phenol **8** to give the coupling product **9** (Scheme 2). A systematic screening of experimental conditions was carried out, in which the partners, **7c** and **8**, and a base (NaH, K_2CO_3, NaOH, or KOH) were mixed, in equimolar amounts, in CH_3CN or DMF, and reacted at 20 or 80 °C. Addition of a phase transfer agent ($Bu_4N^+HSO_4^-$ or Aliquat 336)[23] significantly improved the yields. The optimum conditions required KOH as base with a catalytic amount of Aliquat 336 in refluxing acetonitrile for 24 h (Scheme 2) and gave **9** in 90% yield.

Starting from the previous building blocks (**3** and **4**), the dialkylation product **6** could be obtained as major product by properly adjusting the conditions of the Williamson etherification (Scheme 3). The diol **3** in DMF solution was treated with 3 equiv of NaH at 20 °C and then with 3 equiv of bromide **4** dissolved in DMF at 0 °C. The reaction was carried out at 20 °C for 3 h. The product **6** was readily purified by column chromatography on silica gel. The α,ω-amine functions were deprotected from the di-*tert*-butyl dicarbamate **6** by reaction with trifluoroacetic acid or HBr in acetic acid, according to standard procedures of peptide synthesis.[24] The diammonium ditrifluoroacetate **10a** and dibromide **10b** were obtained, respectively (Scheme 3). The α,ω-bis-nucleophilic spacer arm **10** was finally transformed into the α,ω-bis-electrophilic spacer arm, *i.e.*, the diisocyanate **11**.

Acylation of **10** with phosgene followed by HCl elimination[25] gave the required diisocyanate **11**. Reaction of the trifluoroacetate salt **10a** with a large excess of phosgene in refluxing toluene for 2 h yielded a 2:1 mixture of diisocyanate **11** and ditrifluoroacetamide **12**. This amide **12** was the major product when **10a** was treated with a small excess of phosgene and pyridine (8 equiv) at 0 °C in dichloromethane. On the other hand, the same treatement applied to the dibromide salt **10b** readily afforded the diisocyanate **11** as single product ($COCl_2$ (2.3 equiv), pyridine (8 equiv), 0 °C, CH_2Cl_2). Compound **11** could be separated from the pyridinium salts by simple filtration and washing of the crude reaction mixture. The new products **11** and **12** were fully characterized as usual (see Experimental Section); **11** was also characterized as the dicarbamate after quenching with ethanol.

Conclusion

The unsymmetrical spacer arm **7c**, possessing a nucleophilic function (masked amine) at one terminus and an electrophilic function (triflate) at the other terminus, has been obtained in two steps from the octafluorohexane-1,6-diol **3**, with an overall yield of 69%. The reactivity of triflate **7c** with a phenol derivative in the Williamson etherification process has been demonstrated. The symmetrical spacer arms **10** and **11**, possessing two nucleophilic termini (amines) and two electrophilic termini (isocyanates), respectively, have been prepared from the perfluorinated synthon **3**. A two-step sequence gave **10** in 67% overall yield; a three-step sequence furnished **11** in 40% overall yield.

Our original molecules (**5**, **7**, **10**, **11**), initially designed for polymer surface derivatization, could probably find other applications as monomers for the construction of new materials. Indeed, fluorine-containing polymers exhibit interesting properties in various domains, like gas-permeable membranes, wetting-resistant resins, and medical devices.[14b,26]

Experimental Section

The solvents were dried over CaH_2 and distilled. The reagents were purchased from Acros Chimica or Fluka and used as received.

The column chromatographies were carried out with silica gel 60, 70−230 mesh ASTM supplied by Merck, and with neutral alumina (medium activity, 150 mesh) supplied by Aldrich. The TLC were done on silica gel or neutral alumina (type E) plates (Merck 60 F_{254}); product visualization was effected with UV light, iodine vapor, and a spray of permanganate solution ($KMnO_4$ (3 g), K_2CO_3 (20 g), HOAc (5 mL), water (300 mL)).

N-(*tert*-Butyloxycarbonyl)-3-bromopropylamine (4). NaOH (0.984 g, 24.6 mmol, 1.1 equiv) dissolved in water (35 mL) was placed in a round-bottomed flask. 3-Bromopropylamine hydrobromide (5 g, 22.38 mmol, 1 equiv), 2-methyl-2-propanol (25 mL) and di-*tert*-butyl dicarbonate (5.08 g, 22.38 mmol, 1 equiv) were successively added. The mixture was magnetically stirred at ambient temperature for 15−17 h. The crude solution was extracted with *n*-pentane (3 × 25 mL). The organic layer was washed with aqueous $NaHCO_3$ (2% solution, 30 mL) and then with water (30 mL), dried over $MgSO_4$, and concentrated under vacuum. Column chromatography on silica gel (50 g) using a mixture of CH_2Cl_2 and petroleum ether (40:60) for elution gave the carbamate **4** as a colorless oil (4.7 g, 88% yield): R_f = 0.35 (SiO_2; CH_2Cl_2−hexane, 40:60); ^1H NMR (300 MHz, $CDCl_3$) δ 1,44 (s, 9H), 2.03 (tt, J = 6.4 Hz, 2H), 3.29 (td, J = 6.4 Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 4.66 (br s, 1H); MS

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(EI) *m/e* 240 (M + 1, ^{81}Br, 3), 239 (M, ^{81}Br, 6), 238 (M + 1, ^{79}Br, 4), 237 (M, ^{79}Br, 7), 224 (M − CH_3, 8), 222 (M − CH_3, 8), 184 (M − C_4H_8, 58), 182 (M − C_4H_8, 63), 130 (M − CH_2CH_2Br, 11), 59 (M − C_3H_9N), 57 (C_4H_9, 100).

Monoalkylation of Diol 3. The reaction was conducted in a flame-dried vessel under argon atmosphere. 2,2′,3,3′,4,4′,5,5′-octafluorohexane-1,6-diol (**3**) (1.1 g, 4.2 mmol, 1 equiv) dissolved in DMF (5 mL) was treated with NaH (60% oily suspension, 168 mg, 4.2 mmol, 1 equiv), under stirring, at ambient temperature for 30 min. Then, a solution of **4** (1 g, 4.2 mmol, 1 equiv) in DMF (10 mL) was added dropwise over 1 h to the ice-cooled anion of **3**. The mixture was further stirred for 3 h at 20 °C. Ethyl acetate (30 mL) was added, and the crude solution was washed twice with brine (40 mL) and then with water (40 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Column chromatography on alumina (50 g) using a mixture of $CHCl_3$ and 2-propanol (99.5:0.5) and then ethanol as successive eluents gave 6-[[3-[[*N*-(*tert*-butyloxycarbonyl)aminopropyl]oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexan-1-ol (**5**) (0.77 g, 44% yield) as a pale yellow oil: R_f = 0.35 (Al_2O_3; $CHCl_3$−iPrOH, 99.5:0.5); IR (film) ν 3599, 3449, 1708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.78 (tt, J = 6.4 and 5.8 Hz, 2H), 3.20 (td, J = 6.4 and 5.4 Hz, 2H), 3.66 (t, J = 5.8 Hz, 2H), 3.91 (t, J_{HF}= 14 Hz, 2H), 4.03 (td, J_{HF} = 14.5 Hz, J = 7 Hz, 2H), 4.78 (br t, 1H), 5.11 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.99, 29.36, 37.81, 59.92 (t, J_{CF} = 25 Hz), 67.72 (t, J_{CF} = 25 Hz), 70.99, 79.18, 111.13 (Tquint, J_{CF} = 265 and 32 Hz), 111.32 (Tquint, J_{CF} = 265 and 32 Hz), 115.34 (Tt, J_{CF} = 258 and 29 Hz), 115.57 (Tt, J_{CF} = 256 and 29 Hz), 156.31; ^{19}F NMR (188 MHz, $CDCl_3$) δ −120.0 (tt, J = 13 Hz, 2F), −122.8 (tt, J = 13 Hz, 2F), −124.3 and −124.4 (tt, J = 13 Hz, 2F and 2F); MS (FAB) *m/e* 420 (M + 1, 10), 364 (67), 320 (100). Anal. Calcd for $C_{14}H_{21}O_4NF_8$: C, 40.10; H, 5.05; N, 3.34. Found: C, 40.43; H, 4.86; N, 3.14. The first fractions of the chromatography contained the dialkylation product **6** (0.377 g, 16% yield), and the last fractions contained the unreacted alcohol **3** (0.45 g, 40% yield).

Dialkylation of Diol 3. The reaction was conducted in a flame-dried vessel, under argon atmosphere. 2,2′,3,3′,4,4′,5,5′-Octafluorohexane-1,6-diol (**3**) (1.62 g, 6.1 mmol, 1 equiv) dissolved in DMF (13 mL) was treated with NaH (60% oily suspension, 734 mg, 18.3 mmol, 3 equiv) under stirring at 20 °C. A solution of **4** (4.36 g, 18.3 mmol, 3 equiv) in DMF (13 mL) was immediatly added, dropwise, over 15 min at 0 °C. The mixture was further stirred for 3 h at 20 °C. Ethyl acetate (60 mL) was added, and the crude solution was worked up as before. Column chromatography on silica gel (75 g) using a mixture of ether and petroleum ether (60:40) as eluent gave 1,6-bis[[3-[*N*-(*tert*-butyloxycarbonyl)amino]propyl]oxy]-2,2′,3,3′,4,4′, 5,5′-octafluorohexane (**6**) (2.38 g , 67% yield) as a colorless gum: R_f = 0.1 (SiO_2; ether−petroleum ether, 60:40); R_f = 0.88 (Al_2O_3; $CHCl_3$−iPrOH, 99.5:0.5); IR (film) ν 3447, 1709 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.80 (tt, J = 6.3 and 5.7 Hz, 2H), 3.23 (td, J = 6.3 and 5.3 Hz, 2H), 3.67 (t, J = 5.9 Hz, 2H), 3.92 (t, J_{HF} = 13.9 Hz, 2H), 4.91 (br t, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.17, 29.49, 37.84, 67.84 (t, J_{CF} = 25.3 Hz), 71.11, 78.81, 111.15 (Tquint, J_{CF} = 267 and 33 Hz), 115.37 (Tt, J_{CF} = 256 and 30 Hz), 155.88; MS (FAB) *m/e* 577 (M + 1, 18), 477 (21), 421 (100). Anal. Calcd for $C_{22}H_{36}O_6N_2F_8$: C, 45.83; H, 6.29; N, 4.86. Found: C, 45.81; H, 6.27; N, 4.64.

Tosylation of Compounds 5. Alcohol **5** (174 mg, 0.415 mmol, 1 equiv) dissolved in pyridine (1 mL) was treated at 0 °C with tosyl chloride (237 mg, 1.24 mmol, 3 equiv). The mixture was stirred for 1 h at 0 °C and 23 h at 20 °C. Diethyl ether was added (20 mL), and the solution was washed successively with 1.5 M HCl (2 × 20 mL), 3% $NaHCO_3$ (2 × 20 mL), and water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacum to give 6-[[3-[*N*-(*tert*-butyloxycarbonyl)amino]propyl]oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexyl 1-tosylate **7b** as a yellow oil (0.143 g, 60% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.78 (tt, J = 6.1 Hz, 2H), 2.47 (s, 3H), 3.22 (td, J = 6.1 Hz, 2H), 3.65 (t, J = 6.1 Hz, 2H), 3.89 (t, J_{HF} = 13.7 Hz, 2H), 4.45 (t, J_{HF} = 13 Hz, 2H), 4.93 (br t, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H).

Triflation of Compound 5. The reaction was conducted in a flame-dried vessel, under argon atmosphere. Alcohol **5** (0.464 g, 1.11 mmol, 1 equiv) dissolved in ether (10 mL) was treated at 0 °C with pyridine (180 μL, 2.22 mmol, 2 equiv) and trifluoromethanesulfonic anhydride (280 μL, 1.66 mmol, 1.5 equiv). The mixture was stirred for 15 min at 0 °C and 2 h at 20 °C. Filtration and concentration under vacuum gave 6-[[3-[*N*-(*tert*-butyloxycarbonyl)aminopropyl]oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexyl 1-triflate (**7c**) as a pale yellow oil (0.477 g, 94% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.80 (tt, J = 6.1 Hz, 2H), 3.23 (td, J = 6.1 Hz, 2H), 3.67 (t, J = 6.1 Hz, 2H), 3.94 (t, J_{HF} = 13.8 Hz, 2H), 4.67 (br t, 1H), 4.82 (t, J_{HF} = 12.6 Hz, 2H).

Coupling of Triflate 7c. The reaction was conducted in a flame-dried vessel, under argon atmosphere. A mixture of **7c** (98 mg, 0.177 mmol, 1 equiv), 2-acetamidophenol **8** (28 mg, 0.177 mmol, 1 equiv), KOH (12.5 mg, 0.22 mmol, 1.25 equiv), and Aliquat 336 (1.4 mg, 0.00355 mmol, 0.02 equiv) in acetonitrile (1.5 mL) was refluxed for 24 h. Filtration on Celite, concentration, and column chromatography on silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (60:40) as eluant gave de-O-alkylated acetamidophenol **9** as a gum (89 mg, 90% yield): R_f = 0.10 (SiO_2, CH_2Cl_2); IR (film) ν 3418, 1709, 1646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.80 (tt, J = 6.2 and 5.9 Hz, 2H), 2.22 (s, 3H), 3.21 (td, J = 6.2 Hz, 2H), 3.67 (t, J = 5.9 Hz, 2H), 3.93 (t, J_{HF} = 13.7 Hz, 2H), 4.74 (br t, 1H), 4.82 (t, J_{HF} = 12.5 Hz, 2H), 7.20 (dd, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.38 (dd, 1H), 7.37 (s, 1H), 8.22 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.25, 29.60, 29.70, 37.91, 67.86, 68.36 (t, J_{CF} = 25.5 Hz), 71.23 (t, J_{CF} = 27.7 Hz), 79.00, 110.7 (Tquint), 112.3 (Tquint), 114.6 (Tt), 115.3 (Tt), 121.4, 124.1, 125.3, 129.0, 130.3, 155.9, 156.0, 168.2; MS (FAB) *m/e* 552 (M, 3), 496 (63), 452 (100).

1,6-Bis[(3-aminopropyl)oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexane (10). Bis-Boc compound **6** (170 mg, 0.295 mmol) was treated with trifluoroacetic acid (2 mL) for 30 min at ambient temperature. Evaporation under vacuum gave the bis-trifluoroacetate salt **10a** (178 mg, 100% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.82 (tt, J = 6 and 7 Hz, 2H), 2.83 (br t, 2H), 3.64 (t, J = 6 Hz, 2H), 4.07 (t, J_{HF} = 14.7 Hz, 2H), 7.93 (br s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.09, 36.11, 66.71 (t, J_{CF} = 24.6 Hz), 68.92, 110.99 (Tquint, J_{CF} = 266 and 33.5 Hz), 115.83 (Tt, J_{CF} = 257 and 30.5 Hz), 117.0 (Q, J = 297 Hz), 158.51 (q, J = 32.2 Hz).

Bis-Boc compound **6** (126 mg, 0.22 mmol) was treated with a solution of HBr in HOAc (30% concentration, 2 mL) for 30 min at 20 °C. Coevaporation under vacuum with toluene (2 × 10 mL) gave a gum which solidified by trituration with ether (5 mL) to furnish the dibromide salt **10b** (112 mg, 89% yield) as a hygroscopic white solid.

Reaction of Compounds 10b with Phosgene. The dibromide salt **10b** (106 mg, 0.197 mmol, 1 equiv) dissolved in CH_2Cl_2 (2 mL) was treated at 0 °C with pyridine (127.5 μL, 1.576 mmol, 8 equiv) and phosgene (1.93 M solution in toluene, 265 μL, 0.512 mmol, 2.3 equiv). The mixture was stirred for 2 h at 20 °C and then filtered and washed with 0.5 N aqueous HCl (2 × 5 mL) and water (1 × 5 mL). Drying over $MgSO_4$ and concentration under vacuum gave 1,6-bis[(3-isocyanatopropyl)-oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexane **11** (56 mg, 66% yield) as a pale yellow oil: IR (CH_2Cl_2) ν 2282 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (tt, J = 6.2 Hz, 2H), 3.40 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.0 Hz, 2H), 4.09 (t, J_{HF} = 14.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.32, 39.9, 66.79 (t, J_{CF} = 24.8 Hz), 68.80, 110.99 (Tquint, J_{CF} = 264.5 and 33.2 Hz), 115.87 (Tt, J_{CF} = 255.1 and 30.8 Hz), 121.52. Dissolution of **11** in ethanol and concentration gave 1,6-bis[[3-[*N*-(ethyloxycarbonyl)amino]propyl]oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H), 3.95 (q, 2H), see **6** for the other signals; MS (EI) *m/e* 550.

Reaction of Compound 10a with Phosgene. The bis-trifluoroacetate salt **10a** (178 mg, 0.295 mmol) was treated as above. Column chromatography on silica gel (4 g) with a mixture of petroleum ether and ethyl acetate (70:30) as eluent gave 1,6-bis[[1-[*N*-(trifluoroacetyl)amino]propyl]oxy]-2,2′,3,3′,4,4′,5,5′-octafluorohexane (**12**) as a colorless oil (87 mg, 52% yield): R_f = 0.30; IR (CH_2Cl_2) ν 3420, 1725 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.75 (tt, J = 6.5 and 6.3 Hz, 2H), 3.23 (td, J = 6.7 and 6.3 Hz, 2H), 3.59 (t, J = 6.1 Hz, 2H), 4.05 (t, J_{HF} = 14.6 Hz, 2H), 9.38 (br t, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.23, 36.27,

66.76 (t, J_{CF} = 24.7 Hz), 69.47, 110.95 (Tquint, J_{CF} = 266 and 33 Hz), 115.81 (Tt, J_{CF} = 257 and 30.6 Hz), 115.88 (q, J = 288 Hz), 156.21 (q, J = 36 Hz); MS (FAB) m/e 569 (M + 1, 48), 473 (M + 1− $COCF_3$, 8), 454 (7), 307 (9), 289 (11), 154 ($CF_3CONH(CH_2)_3$, 100).

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Supporting Information Available: ^{1}H NMR spectra of **4**−**6**, **7b**,**c**, **9**, **10a**, **11**, and **12** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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