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The design and synthesis of highly branched and spherically symmetric fluorinated oils and amphiles

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Abstract—A new surfactant design principle, based on concepts borrowed from protein science, is proposed. Using this principle, a class of highly branched and spherically symmetric fluorinated oils and amphiles has been designed and synthesized, for potential applications in the construction of fluorocarbon nanoparticles. The Mitsunobu reaction was employed as the key step for introducing three perfluoro-*tert*-butoxyl groups into pentaerythritol derivatives with excellent yields and extremely simple isolation procedures. Due to the symmetric arrangement of the fluorine atoms, each fluorinated oil or amphile molecule gives one sharp singlet ^{19}F NMR signal.

1. Introduction

We are interested in using fluorocarbon liquid nanoparticles, formulated as microemulsions, as multifunctional drug delivery vehicles for ^{19}F magnetic resonance image (MRI) guided targeted drug therapy.[1] To this end, we embarked on an effort to synthesize fluorinated oils (*F*-oils) and surfactants (*F*-surfactants) as modules for such nanoparticles. We choose to synthesize *F*-oils as well as *F*-surfactants because fluorocarbon microemulsions with *F*-surfactants as emulsifiers are much more stable than those with phospholipids as emulsifiers.[2] We choose to design and synthesize new *F*-oils and *F*-surfactants instead of using existing ones for two reasons. First, all fluorine atoms in an *F*-oil or an *F*-surfactant molecule should have identical chemical environment with no adjacent hydrogen atoms. This ensures that all fluorine atoms together will give one singlet ^{19}F signal, thereby maximizing signal intensity of ^{19}F MRI. This requirement rules out fluorocarbon chain molecules, such as perfluorooctyl bromide. This requirement also rules out dendrimer-type molecules that contain fluorocarbon chain segments.[3] Second, the fluorocarbon moieties of *F*-oils and *F*-surfactants should be identical (size and shape matching). The rationale, based on the molecular theory of the liquid state,[4] is that the 'cavity' vacated by an *F*-oil molecule can be filled in snuggly by an *F*-surfactant molecule and vice versa as a result of size and shape matching (note that even though *F*-oils and *F*-surfactants constitute the inner core and the outer shell of the nanoparticles, respectively, the fluorocarbon moiety of *F*-surfactants will nonetheless be in direct contact with *F*-oils at the interface of the inner core and the outer shell). Size and shape matching is achieved by appending a hydrophilic segment to the fluorocarbon moiety of an *F*-oil, thereby turning it into an *F*-surfactant. This requirement rules out macrocyclic type of molecules such as perfluoro-15-crown-5.[1c] This is because appending a hydrophilic segment to a macrocyclic *F*-oil will destroy its cyclic symmetry, thereby rendering the fluorine atoms in the resulting *F*-surfactant non-equivalent, leading to violation of the first requirement.

Here, we wish to point out that, to this date, surfactants used in pharmaceutical emulsion formulations have one common feature: their hydrophobic moieties are chain-like. The rationale is that chain-like molecules can entangle with each other (like arms), leading to stable emulsions. The paradigm of using chain-like surfactants has been practiced for decades with no rigorous proof that, as emulsifiers, chain-like surfactants are indeed superior to highly branched ones. The outcome of such a practice is dismal: currently, there is only one commercially available injectable emulsion in the US market (Diprivan®).[5] It is time to explore new paradigms for surfactant design. In our approach, the fluorocarbon moieties of *F*-oils and *F*-surfactants are highly branched. The rationale is that these branches will interdigitate with each other tightly (like fingers), leading to stable emulsions. This is based on the observation that branched side chains are often better than straight side chains at stabilizing protein molecules. The most convincing case comes from coiled-coils where exhaustive comparison of 20 natural amino acids concluded that leucine and isoleucine, two branched amino acids, are

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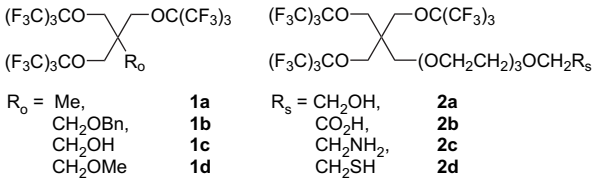


Figure 1. Structures of *F*-oils (**1a**–**1d**) and *F*-amphiles (**2a**–**2d**).

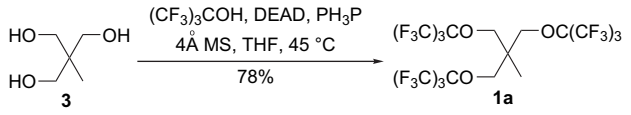
more effective at stabilizing coiled-coils than any other amino acid.[6] Tight interdigitation also occurs in fluorinated coiled-coils between branches made of the $-CF_3$ group, its bulkiness notwithstanding.[7] The importance of size and shape matching in optimizing side chain interdigitation was revealed in a study on protein interior packing.[8]

Based on these considerations, a class of highly branched *F*-oils (**1a**–**1d**) and *F*-amphiles (**2a**–**2d**) was designed (Fig. 1). As the first step toward the engineering of fluorocarbon nanoparticles, the focus of this paper is to propose a new surfactant design principle based on concepts borrowed from protein science and to explore the synthesis of *F*-oils and *F*-surfactants. Since no surface activity is measured in this work, we decided to call **2a**–**2d** ***F***-amphiles rather than *F*-surfactants. These *F*-amphiles are prototypes of *F*-surfactants that will be eventually used in fluorocarbon nanoparticle formulation. They serve the purpose of demonstrating the synthesis feasibility of amphilic molecules with a highly branched fluorocarbon moiety. Surface activities and the effectiveness of using highly branched *F*-oils and *F*-surfactants in microemulsion formulation will be evaluated in future studies.

In each *F*-oil or *F*-amphile molecule, fluorine was introduced by three symmetrically positioned perfluoro-*tert*-butoxyl groups with all 27 fluorine atoms residing on the surface of a sphere to ensure identical chemical environment for all fluorine atoms and to avoid ^{19}F–^{19}F or ^{19}F–^{1}H coupling. The stem of the hydrophilic moiety of *F*-amphiles (**2a**–**2d**) is an oligo-ethylene glycol chain. Ethylene glycol enhances aqueous solubility and is biocompatible. The oligo-ethylene glycol chain is terminated with various functional groups (–OH, –COOH, $-NH_2$, and –SH) to demonstrate synthesis feasibility and to facilitate future derivatization of these *F*-amphiles. The fluorocarbon moiety and the hydrocarbon moiety are connected through a pentaerythritol core (in the case of the *F*-oil **1a**, a derivative of pentaerythritol was used). In this work, the hydrophilic moiety of the *F*-amphiles is not branched. However, if needed, branching can certainly be introduced into the hydrophilic moiety without compromising the spherical symmetry of the fluorocarbon moiety.

2. Results and discussion

From commercially available 1,1,1-tris(hydroxymethyl)-ethane **3** and perfluoro-*tert*-butanol, *F*-oil **1a** was synthesized (Scheme 1). To introduce three perfluoro-*tert*-butoxyl groups into compound **3** in just one step, the Mitsunobu reaction was employed. This is because the three electron-withdrawing $-CF_3$ groups in perfluoro-*tert*-butanol can significantly enhance the acidity of the hydroxyl group. Thus perfluoro-*tert*-butanol is a good substrate for the Mitsunobu reaction

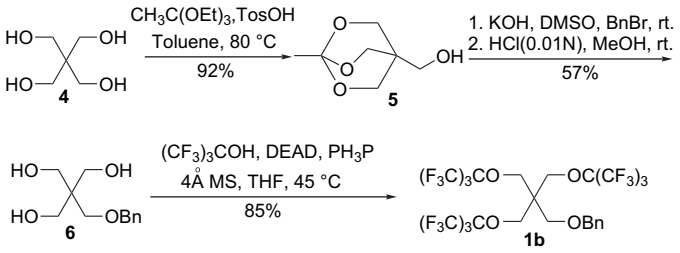


Scheme 1. Synthesis of *F*-oil **1a**.

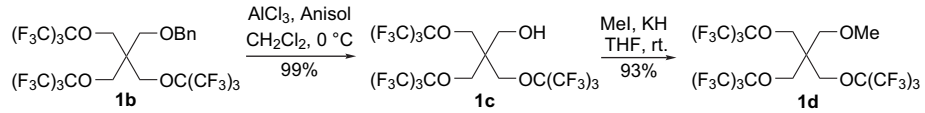
to form perfluoro-*tert*-butyl ethers.[9] Initially, treating compound **3** with DEAD and Ph_3P at 0 °C for 30 min and then with perfluoro-*tert*-butanol for 40 h led to no desired product. Elevating reaction temperature from 0 °C to room temperature or refluxing after the addition of perfluoro-*tert*-butanol also led to no desired product. As perfluoro-*tert*-butanol is a volatile substance with a low boiling point (45 °C), the reaction was then carried out in a sealed vessel at 45 °C for 30 h. To our delight, the reaction proceeded smoothly and ether **1a** was isolated with a 67% yield. When 4 Å molecular sieves were added to the reaction, the yield can be improved to 78%. Interestingly, the resulting *F*-oil **1a** can be very easily isolated from the reaction mixture: after adding water to quench the reaction at room temperature, the fluorinated ether **1a** automatically settled to the bottom of the reaction vessel due to separation of fluorous compounds from aqueous and hydrocarbon phases.[10] Thus, the product **1a** was collected through simple phase separation. Due to no or low fluorine content, all the reagents and side products remained in the reaction mixture.

Our synthesis of *F*-oil **1b** started with the modification of commercially available pentaerythritol **4** (Scheme 2).[11] In order to selectively protect one of its four hydroxyl groups, pentaerythritol **4** was first converted to the hydroxylmethyl orthoester **5**. After protecting the remaining hydroxyl group with the benzyl group, the orthoester intermediate was then hydrolyzed to give the corresponding pentaerythritol monobenzyl ether **6** with good yield on a 50 g scale. *F*-oil **1b** was then synthesized from **6** with an 85% yield using the same reaction condition and the same isolation method as that used for **1a**.

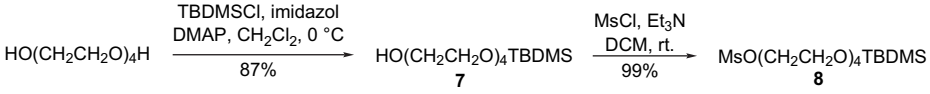
F-oils **1c** and **1d** were synthesized sequentially from *F*-oil **1b** (Scheme 3). Initial attempts to remove the benzyl group in **1b** through hydrogenolysis with either palladium on carbon or palladium hydroxide on carbon as the catalyst in methanol under a hydrogen atmosphere of 30 bars were unsuccessful. Two factors might have hampered the hydrogenolysis reaction. Firstly, the benzyl ether is surrounded with three very bulky perfluoro-*tert*-butoxyl ethers, posing significant steric barriers to the catalyst. Secondly, the highly fluorinated **1b** has limited solubility in methanol, the reaction solvent. As benzyl ether is susceptible to Lewis acid-catalyzed acidolysis, aluminum chloride was then employed to remove the benzyl group. Treatment of benzyl ether **1b** with aluminum chloride and anisol in dichloromethane gave the anticipated product **1c** with quantitative yield. Compound **1c** was also isolated from the reaction mixture through phase separation. To our surprise, no side reactions, such as cleavage of the perfluoro-*tert*-butyl ether or rearrangement of the pentaerythritol derivatives, took place to any appreciable extent during the reaction based on the quantitative yield and the ^{19}F NMR spectrum of isolated **1c** (Supplementary data). This indicates that the perfluoro-*tert*-butyl ether bond is stable under acidic conditions. This property will facilitate future



Scheme 2. Synthesis of *F*-oil **1b**.



Scheme 3. Synthesis of *F*-oils **1c** and **1d**.



Scheme 4. Modification of tetraethylene glycol.

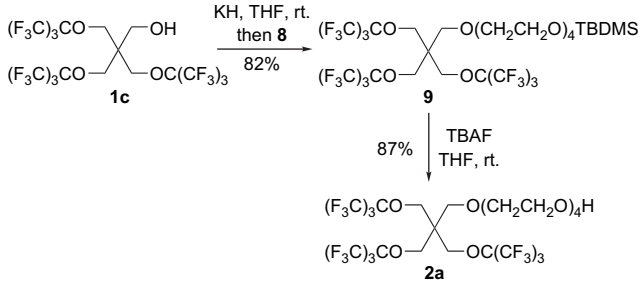
derivatization and formulation of this class of compounds. Methylation of alcohol **1c** was carried out with iodomethane and potassium hydride. After quenching the reaction with water, **1d** was isolated by simple phase separation with a 93% yield. In summary, all *F*-oils were isolated from reaction mixtures using simple phase separation (For purity, see NMR spectra of these compounds in Supplementary data).

F-oil **1c** serves as the starting material for the synthesis of *F*-amphiles **2a**–**2d**. The synthesis started with the modification of tetraethylene glycol (Scheme 4). Selective protection of one of the two hydroxyl groups in tetraethylene glycol with TBDMS gave the alcohol **7** with good yield (87%). Treatment of the alcohol **7** with methanesulfonyl chloride and triethylamine afforded the methanesulfonate **8** with a 99% yield.

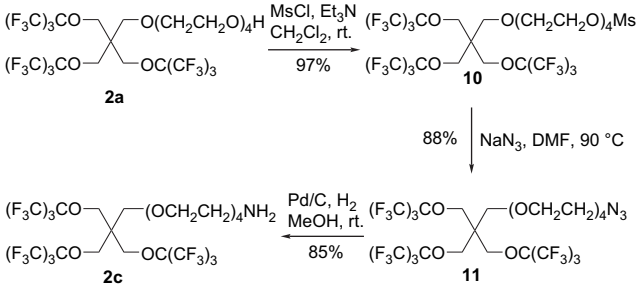
Compound **9** was then synthesized from methanesulfonate **8** and the alcohol **1c** (Scheme 5). In order to form the ether bond in compound **9**, the alcohol **1c** was treated with sodium hydride followed by methanesulfonate **8**. Product **9** was isolated by column purification with only a 40% yield. Then a much stronger base, potassium hydride, was employed as the base for this reaction. Fortunately, ether **9** was isolated with an 82% yield. Removal of the silyl protective group in compound **9** gave *F*-amphile **2a** as a viscous liquid with an 87% yield. It is noteworthy that, in contrast to *F*-oils **1a**–**1d**, compounds **9** and **2a** can neither be phase separated from the quenched reaction mixture nor be extracted from the reaction mixture (diluted by 95/5 (v/v) acetonitrile/water after concentrating under vacuum) with FC72 (perfluorohexanes). Instead, compounds **9** and **2a** were purified by flash column chromatography on silica gel.

F-amphile **2a** serves as the starting material for the synthesis of other *F*-amphiles (**2b**–**2d**). Compound **2b** was synthesized as a viscous wax with an 84% yield by Jones oxidation of the primary alcohol in compound **2a** to carboxylic acid (Scheme 6).

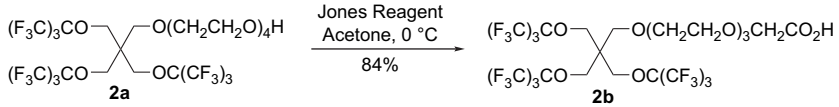
From **2a**, *F*-amphile **2c** was also synthesized (Scheme 7). After transforming the hydroxyl group in **2a** into the



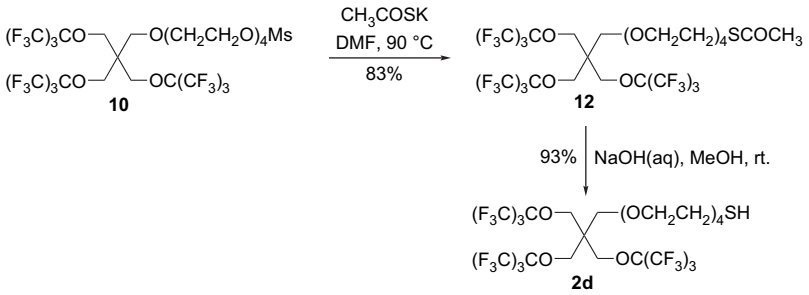
Scheme 5. Synthesis of *F*-amphile **2a**.



Scheme 7. Synthesis of *F*-amphile **2c**.



Scheme 6. Synthesis of *F*-amphile **2b**.



Scheme 8. Synthesis of *F*-amphile **2d**.

methanesulfonate **10** with a 97% yield, **10** was treated with sodium azide to give the azide **11** with an 88% yield. Hydrogenolysis of the azido group in compound **11** with palladium on carbon afforded *F*-amphile **2c** as a viscous liquid with an 85% yield.

Finally, *F*-amphile **2d** was synthesized from **10** (Scheme 8). Treatment of the methanesulfonate **10** with potassium thiolacetate afforded the thiolester **12** with an 83% yield. After hydrolysis of the thiolester **12** with sodium hydroxide, *F*-amphile **2d** was obtained as a viscous liquid with a 93% yield.

^{19}F NMR spectra of *F*-oils and *F*-amphiles were acquired. As designed, each of the *F*-oils and *F*-amphiles gave only one sharp singlet ^{19}F NMR signal with a peak width around 0.03 ppm (Fig. 2).[12] Hence, from the ^{19}F signal intensity standpoint, these *F*-oils and *F*-amphiles are ideal for ^{19}F magnetic resonance imaging applications.

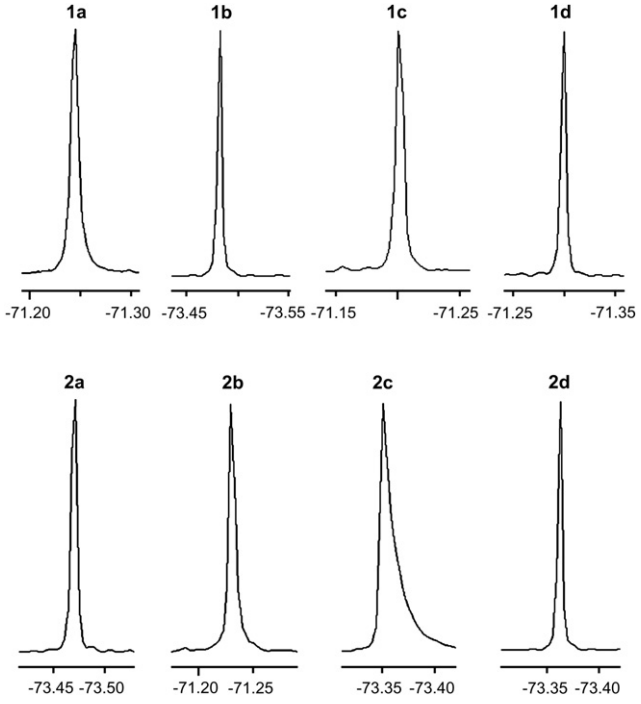


Figure 2. ^{19}F NMR (376 MHz) spectra of *F*-oils (**1a**–**1d**) and *F*-amphiles (**2a**–**2d**).

3. Conclusion

A class of highly branched and spherically symmetric fluorinated oils and amphiles has been efficiently synthesized. Three perfluoro-*tert*-butoxyl groups were simultaneously introduced into the substrates by the Mitsunobu reaction (Schemes 1 and 2) with high yields and straightforward isolation procedures (phase separation). As a result of spherical symmetry, all 27 fluorine atoms in each *F*-oil or *F*-amphile give one sharp singlet ^{19}F NMR signal.

4. Experimental

4.1. *F*-oil 1a

To a stirred suspension of 1,1,1-tris(hydroxymethyl)-ethane **3** (6.0 g, 50.0 mmol), triphenylphosphine (59.0 g, 225.1 mmol) and 4 Å molecular sieves (6 g) in tetrahydrofuran (300 mL) at 0 °C was added dropwise diethylazodicarboxylate (39.2 g, 225.1 mmol). Afterward, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 20 min. Then perfluoro-*tert*-butanol (53.2 g, 225.1 mmol) was added in one portion and the resulting mixture was stirred for 30 h at 45 °C in a sealed vessel. Water (30 mL) was added to the reaction mixture and stirred for an additional 10 min. Then the mixture was transferred to a separatory funnel and the lower phase was collected. Removal of the perfluoro-*tert*-butanol under vacuum gave the product **1a** as a clear oil (30.3 g, 78%). ^{1}H NMR (400 MHz, neat) δ 3.95 (s, 6H), 1.05 (s, 3H); ^{19}F NMR (376 MHz, neat) δ −71.25 (s); ^{13}C NMR (100.7 MHz, neat) δ 120.2 (q, J=291.8 Hz), 79.7 (m), 69.0, 41.3, 14.3; MS (CI) m/z 759 (M^+–Me, 24); HRMS (MALDI-TOF) calcd for $C_{17}H_{10}F_{27}O_3$ 775.0199, found 775.0193.

4.2. Alcohol 5

To a suspension of pentaerythritol **4** (68.0 g, 0.5 mol) in toluene (50 mL) were added triethyl orthoacetate (81.0 g, 92 mL, 0.5 mol) and *p*-toluenesulfonic acid monohydrate (300 mg). Ethanol was distilled from the mixture at 80 °C overnight. After all the ethanol had been distilled away, the bath temperature was raised to 125 °C and toluene was distilled off until the solution was homogeneous. The residue was purified by column chromatography on neutral aluminum oxide (CH_2Cl_2/MeOH=10/1) to give alcohol **5** as a white solid (73.6 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 6H), 3.44 (s, 2H), 1.44 (s, 3H).

4.3. Triol 6

Powdered KOH (123.2 g, 2.2 mol) was added to stirred dimethyl sulfoxide (750 mL) and the resulting mixture was stirred at room temperature for 10 min. Alcohol **5** (73.6 g, 460.0 mol) was added, followed quickly by benzyl bromide (94.7 g, 65.9 mL, 554.0 mmol). The reaction mixture was stirred for 2 h and then diluted with water (3000 mL) and extracted with diethyl ether. The combined extract was washed with brine and water, dried with magnesium sulfate, and concentrated to afford the 4-benzyloxymethyl-1-methyl-2,6,7-trioxa-bicyclo[2.2.2]octane intermediate as a white solid. The intermediate was dissolved in methanol (300 mL) and treated with 0.1 N HCl (600 mL). The resulting mixture was stirred at room temperature for 4 h, treated with sodium bicarbonate (42.5 g, 506.0 mmol), stirred for an additional 1 h, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/methanol=10/1) to give the triol **6** as a viscous oil (59.3 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.33 (m, 5H), 4.46 (s, 2H), 3.64 (s, 6H), 3.39 (s, 2H).

4.4. *F*-oil 1b

Same procedure as described for the synthesis of **1a**, clear oil, yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H), 4.47 (s, 2H), 4.08 (s, 6H), 3.45 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.47 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 137.3, 128.6, 128.1, 128.0, 120.3 (q, J= 292.5 Hz), 79.7 (m), 73.9, 65.6, 65.5, 46.4; MS (CI) m/z 881 (M^++1, 100), 880 (M^+); HRMS (CI) calcd for $C_{24}H_{15}F_{27}O_4$ 880.0539, found 880.0515.

4.5. *F*-oil 1c

To a stirred solution of **1b** (29.3 g, 33.2 mmol) and anisol (14.4 g, 132.9 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added aluminum chloride powder (13.3 g, 99.7 mmol) slowly. The resulting mixture was stirred at 0 °C for 1 h and then water (100 mL) was added slowly. The lower layer was collected as a clear oil of **1c** (25.9 g, 99%). ^{1}H NMR (400 MHz, acetone-d_6) δ 4.27 (s, 6H), 3.74 (s, 2H); ^{19}F NMR (376 MHz, acetone-d_6) δ −71.20 (s); ^{13}C NMR (100.7 MHz, acetone-d_6) δ 121.5 (q, J=291.8 Hz), 80.9 (m), 67.5, 58.7, 47.9; MS (CI) m/z 791 (M^++1, 100); HRMS (CI) calcd for $C_{17}H_{10}F_{27}O_4$ 791.0150, found 791.0131.

4.6. *F*-oil 1d

To a stirred solution of alcohol **1c** (7.9 g, 10.0 mmol) in tetrahydrofuran (50 mL) at 0 °C was added KH (2.4 g, 25% in mineral oil, 15 mmol). The resulting mixture was stirred at 0 °C for 10 min and then iodomethane (4.26 g, 30 mmol) was added. After stirring overnight at room temperature, water (100 mL) was added slowly to the mixture. The lower layer was collected as a clear oil of **1d** (7.5 g, 93%). ^{1}H NMR (400 MHz, acetone-d_6) δ 4.19 (s, 6H), 3.42 (s, 2H), 3.34 (s, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −71.30 (s); ^{13}C NMR (100.7 MHz, acetone-d_6) δ 121.3 (q, J= 292.6 Hz), 76.9 (m), 68.1, 66.6, 59.2, 47.4; HRMS (MALDI-TOF) calcd for $C_{18}H_{11}F_{27}NaO_4$ 827.0124, found 827.0118.

4.7. Alcohol 7

To a stirred solution of tetraethylene glycol (9.7 g, 50.0 mmol), imidazol (10.2 g, 150 mmol), and 4-dimethylaminopyridine (3.0 g) in CH_2Cl_2/dimethylformamide (450 mL/50 mL) at 0 °C was added dropwise *tert*-butylchlorodimethylsilane (9.6 g, 50 mmol) over 3 h. The resulting mixture was stirred at room temperature overnight and quenched with water (300 mL). The organic phase was collected and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over anhydrous magnesium sulfate. After concentrating under vacuum, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/methanol=10/1) to give alcohol **7** as a clear oil (13.4 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50–3.70 (m, 16H), 0.83 (s, 9H), 0.01 (s, 6H).

4.8. Methanesulfonate 8

To a stirred solution of alcohol **7** (6.2 g, 20 mmol) and pyridine (4.8 g, 60 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added methanesulfonyl chloride (5.5 g, 24 mmol). The resulting mixture was stirred at room temperature for 2 h and quenched with water (100 mL). The organic phase was collected and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over anhydrous magnesium sulfate. After concentrating under vacuum, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give methanesulfonate **8** as a clear oil (7.7 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29–4.32 (m, 2H), 3.68–3.71 (m, 4H), 3.57–3.60 (m, 8H), 3.47–3.49 (m, 2H), 3.01 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

4.9. Compound 9

To a suspension of alcohol **1c** (15.8 g, 20.0 mmol) in tetrahydrofuran (100 mL) at 0 °C was added KH (4.8 g, 25% in mineral oil, 30 mmol) and the resulting mixture was stirred at 0 °C for an additional 10 min. Methanesulfonate **8** (11.6 g, 30 mmol) was added at 0 °C and the resulting mixture was stirred overnight at room temperature. After adding slowly 100 mL of 2 N HCl aqueous solution, the mixture was extracted with ethyl acetate and the combined organic phase was dried over anhydrous magnesium sulfate. After solvent removal under vacuum, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give compound **9** as a clear oil (17.7 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 6H), 3.71 (t, J=5.6 Hz, 2H), 3.49–3.60 (m, 14H), 3.41 (s, 2H), 0.83 (s, 9H), 0.00 (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.19 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 120.2 (q, J=292.5 Hz), 79.7 (m), 72.7, 70.8, 70.75, 70.7, 70.6, 70.3, 66.4, 65.5, 62.7, 46.2, 25.7, 18.2, −0.4, −5.6; HRMS (MALDI-TOF) calcd for $C_{31}H_{40}F_{27}O_8Si$ 1081.2063, found 1081.2058.

4.10. *F*-amphile 2a

Tetrabutylammonium fluoride (12 mL, 1 N solution in THF) was added dropwise to a stirred solution of compound **9** (10.8 g, 10.0 mmol) in tetrahydrofuran (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for

4 h and quenched with water (200 mL). After extracting the reaction mixture with ethyl acetate, the combined organic phase was dried over anhydrous magnesium sulfate. After concentrating under vacuum, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give alcohol **2a** as a clear viscous liquid (11.1 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 6H), 3.53–3.60 (m, 16H), 3.39 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.47 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 120.2 (q, J=292.6 Hz), 79.7 (m), 72.5, 70.7, 70.6, 70.5, 70.32, 70.3, 66.4, 65.9, 65.5, 61.7, 46.2; MS (CI) *m/z* 967 (M^++1, 100); HRMS (CI) calcd for $C_{25}H_{26}F_{27}O_8$ 967.1198, found 967.1174.

4.11. *F*-amphile 2b

To a stirred solution of compound **2a** (3.87 g, 4.0 mmol) in acetone (40 mL) at 0 °C was added dropwise a solution of Jones reagent (8 mL). After the addition, the resulting mixture was stirred at room temperature for 1 h and then *iso*-propanol (10 mL) was added slowly to the reaction mixture at 0 °C. After solvent removal under vacuum, the residue was dissolved in water and extracted with ether. The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/3) to give the acid **2b** as a viscous wax (3.3 g, 84%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.14 (s, 6H), 4.08 (s, 2H), 3.57–3.69 (m, 12H), 3.50 (s, 2H); ^{19}F NMR (376 MHz, CD_3OD) δ −71.23 (s); ^{13}C NMR (100.7 MHz, CD_3OD) δ 174.9, 121.6 (q, J=292.5 Hz), 80.8 (m), 72.0, 71.6, 71.57, 71.55, 71.5, 71.4, 69.7, 67.6, 67.2, 47.5; MS (CI) *m/z* 981 (M^++1, 100); HRMS (CI) calcd for $C_{25}H_{24}F_{27}O_9$ 981.0991, found 981.0989.

4.12. Methanesulfonate 10

To a stirred solution of compound **2a** (11.6 g, 12 mmol) and triethylamine (7.3 g, 72 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added methanesulfonyl chloride (4.2 g, 36 mmol). The resulting mixture was stirred at room temperature overnight and quenched with water (100 mL). The organic phase was collected and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over anhydrous magnesium sulfate. After concentrating under vacuum, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give methanesulfonate **10** as a clear oil (12.0 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (m, 2H), 4.04 (s, 6H), 3.73–3.76 (m, 2H), 3.53–3.67 (m, 12H), 3.43 (s, 2H), 3.04 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.37 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 120.1 (q, J=292.6 Hz), 79.6 (m), 70.7, 70.6, 70.5, 70.2, 69.2, 69.1, 69.0, 66.3, 65.4, 63.5, 46.2, 37.5; MS (MALDI-TOF) *m/z* 1067 (M^++Na, 100); HRMS (MALDI-TOF) calcd for $C_{26}H_{27}F_{27}O_{10}SNa$ 1067.0791, found 1067.0786.

4.13. Azide 11

To a stirred solution of methanesulfonate **10** (11.8 g, 11.3 mmol) in dimethylformamide (60 mL) was added sodium azide (1.6 g, 25.0 mmol) and the resulting mixture was stirred at 90 °C overnight. After removal of solvent, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give azide **11** as a clear oil (9.9 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 6H), 3.56–3.68 (m, 14H), 3.44 (s, 2H), 3.38 (t, J=5.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.57 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 120.3 (q, J=292.5 Hz), 79.8 (m), 71.0, 70.9, 70.87, 70.85, 70.8, 70.5, 70.3, 66.6, 65.7, 50.9, 46.2; MS (CI) *m/z* 992 (M^++1, 100); HRMS (CI) calcd for $C_{25}H_{25}F_{27}N_3O_7$ 992.1261, found 992.1263.

4.14. *F*-amphile 2c

A suspension of palladium on carbon (1.0 g, 10% Pd) in methanol (100 mL) was stirred under vacuum for 5 min and then stirred under an atmosphere of hydrogen for 10 min. A solution of azide **11** (9.9 g, 9.9 mmol) was added to the suspension and the resulting mixture was stirred under an atmosphere of hydrogen overnight. After filtration, the solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/methanol=1/10) to give amine **2c** as a clear viscous liquid (8.1 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 6H), 3.37–3.56 (m, 16H), 2.79 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.35 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 119.7 (q, J=293.3 Hz), 78.9 (m), 72.8, 70.2, 70.0, 69.7, 69.6, 65.8, 65.0, 45.7, 41.1; MS (CI) *m/z* 966 (M^++1, 100); HRMS (CI) calcd for $C_{25}H_{27}F_{27}NO_7$ 966.1356, found 966.1353.

4.15. Thiolester 12

To a stirred solution of methanesulfonate **10** (7.5 g, 7.0 mmol) in dimethylformamide (50 mL) was added potassium thiolacetate (1.7 g, 15.0 mmol) and the resulting mixture was stirred at 90 °C overnight. After solvent removal, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give thiolester **12** as a clear oil (5.9 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 6H), 3.54–3.60 (m, 14H), 3.42 (s, 2H), 3.06 (t, J=6.8 Hz, 2H), 2.29 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.33 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 195.4, 120.1 (q, J=292.6 Hz), 79.6 (m), 70.7, 70.6, 70.54, 70.5, 70.3, 69.8, 66.3, 65.5, 46.2, 30.3, 28.7; MS (MALDI-TOF) *m/z* 1047 (M^++Na, 100); HRMS (MALDI-TOF) calcd for $C_{27}H_{27}F_{27}NaO_8S$ 1047.0893, found 1047.0920.

4.16. *F*-amphile 2d

To a solution of thiolester **12** (4.7 g, 4.6 mmol) in methanol (30 mL) was added 1 N sodium hydroxide solution (15 mL) and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was acidified with 2 N HCl aqueous solution (8 mL) and the solvent was then removed under vacuum. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate=1/1) to give thiol **2d** as a clear viscous liquid (4.2 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 6H), 3.51–3.59 (m, 14H), 3.41 (s, 2H), 3.65 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.36 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 120.1 (q, J=293.3 Hz), 79.6 (m), 72.9, 70.8, 70.6, 70.5, 70.3, 70.3, 70.2, 66.3, 65.5, 46.2, 24.2; MS (CI) *m/z* 983 (M^++1, 100); HRMS (CI) calcd for $C_{25}H_{26}F_{27}O_7S$ 983.0968, found 983.0971.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.004.

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