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Synthesis of novel fluorous surfactants for microdroplet stabilisation in fluorous oil streams

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ABSTRACT

The synthesis of a number of potential fluorous surfactants, prepared with a view to stabilising microdroplets in microfluidic systems is described. The surfactants comprised compounds with both perfluoropolyether (PFPE) and perfluoroalkyl (PFA) tails with three classes of hydrophilic head group, including crown ethers and hexaethylene glycol. Hydrophilic head groups and alkyl fluorous-based tails were coupled together via amide, ester and ether linkages to afford the fluorous surfactant candidates in good yields. The resulting molecules show promise in forming and stabilising both aqueous and non-aqueous microdroplets in fluorous oil streams within poly(dimethylsiloxane) (PDMS) devices to a greater degree than the pseudosurfactants commonly employed in microdroplet research.

1. Introduction

Microdroplets within microfluidic environments are receiving considerable attention as a route towards miniaturisation of many biological and chemical systems, with concomitant benefits such as a reduction in the amounts of sample required, increased reaction efficiency in small volumes and increased throughput for large screens [1,2].

Microdroplet formation requires a droplet phase flowing within an immiscible carrier phase [3,4]. Fluorous oils [5] are increasingly used as a carrier phase for aqueous droplets due to the high degree of immiscibility between the two phases [6–9]. Aqueous droplets are easy to form in such an environment at a wide variety of flow rates. Further, fluorous oils permit the formation of non-aqueous droplet environments due to the low fluorophilicity of common organic solvents [11,12]. Any biologically or chemically active contents of the droplets will also have lower partition coefficients in fluorous oils relative to hydrocarbon oils. Therefore, fluorous oils represent a more suitable carrier phase for such droplets, permitting a wide degree of biological screening or synthetic chemical reactions within droplets.

However, because such droplets are only metastable – that is, they are prone to coalescence on contact with each other, they require careful control of the various interfacial or surface tensions within a microfluidic device to ensure successful droplet creation and stabilisation. While the surfaces within the device play an important role in droplet formation [13], the interfacial tension between organic or aqueous microdroplets within a stream of fluorous oil (and thus their stability with respect to coalescence) may only be altered by the addition of fluorous surfactants. It is only relatively recently that surfactants to stabilise such a microfluidic environment have received attention [11,10].

Synthesis of fluorosurfactants is a non-trivial exercise due to the amphiphilic nature of the molecules produced, requiring specialised fluorous phase purification [14]. This paper presents the synthesis of 13 novel fluorosurfactant molecules as part of investigations towards the use of microdroplets as reactors for chemical and biological transformations, particularly regarding the possibility of creating and stabilising microdroplets of common organic solvents for use in chemical synthesis. The performance of these surfactants for creation and stabilisation of both aqueous and non-aqueous microdroplets is introduced.

2. Surfactant molecule design

A surfactant for a general oil–water emulsion comprises three elements: a hydrophobic portion which will remain dissolved in the oil phase, a hydrophilic portion, which will dissolve at least partly into the aqueous phase, and a linker between the two [15]. For a fluorous oil–water emulsion, the hydrophobic portion of the required surfactant will be a fluorocarbon. To maximise the use of these surfactants in creating both aqueous and organic droplets, a variety of head groups need to be created with variations in their

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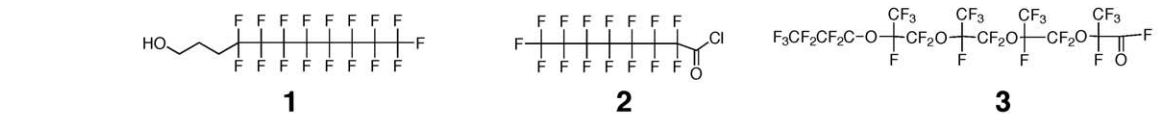
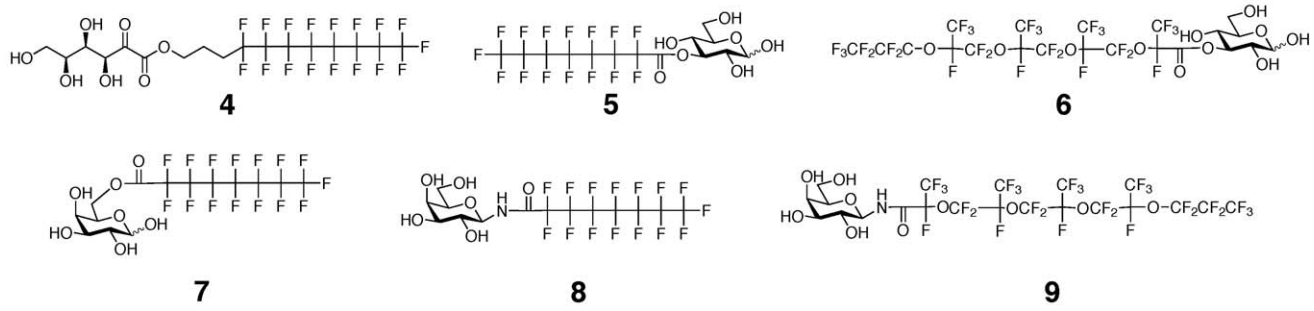
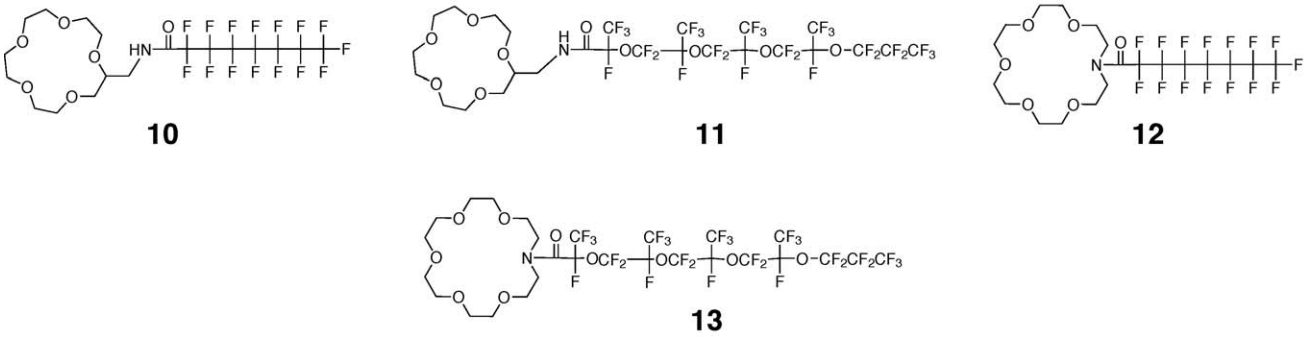


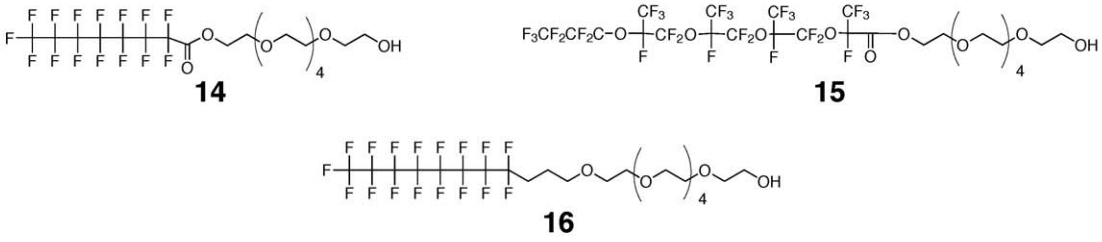
(a) Fluorous tails used in surfactant synthesis.



(b) Surfactants with carbohydrate head groups.



(c) Surfactants with crown ether head groups.



(d) Surfactants with hexaethylene glycol head groups.

Fig. 1. (a) The fluorous tails used in surfactant synthesis **1–3**, and (b–d) the fluorosurfactant molecules **4–16**.

ability to hydrogen bond, their van der Waals potential, and their chemical similarity to common organic solvents (via assessment of relative solubility parameters [16]). These surfactants need to be simple enough to synthesise but robust enough such that they will not degrade on use.

The typical performance for a hydrocarbon surfactant is to lower the interfacial tension to around 20–25 mN/m. A solution of the common hydrocarbon surfactant Span 80 in dodecane was found to have a γ_{cmc} of 22.4 mN/m and a CMC of 1.9×10^{-5} M [17], although γ_{cmc} will be strongly dependant on the nature of the oil phase.

Fluorous surfactants have generally been found to be more effective than hydrocarbon surfactants of comparable properties (identical chain lengths and head groups), with lower γ_{cmc} values and lower CMCs [18,19]. This has been rationalised as being due to the greater free energy difference of transferring a $-CF_2-$ group from the bulk state to a micellar environment relative to that of a $-CH_2-$ group [19]. It is estimated that the γ_{cmc} of a fluorinated surfactant is close to that of a hydrocarbon surfactant with 1.5 times the chain length.

There are a number of reports describing the synthesis of fluorosurfactants [20–24]. These compounds are generally synthesised by the conjugation of a perfluoroalkyl chain to a variety of hydrophilic head groups via a variety of chemical linkers. Examples of polar head groups include polyethers, [25,26], polyoxyethylenes [27], amines [28,29] and carbonyl or sulfonyl groups [30,19]. However, to our knowledge, there are currently no commercially available fluorosurfactants and, as such, synthesis of candidate fluorosurfactants for more stable microdroplet creation is necessary. For the purposes of this study, novel surfactants were

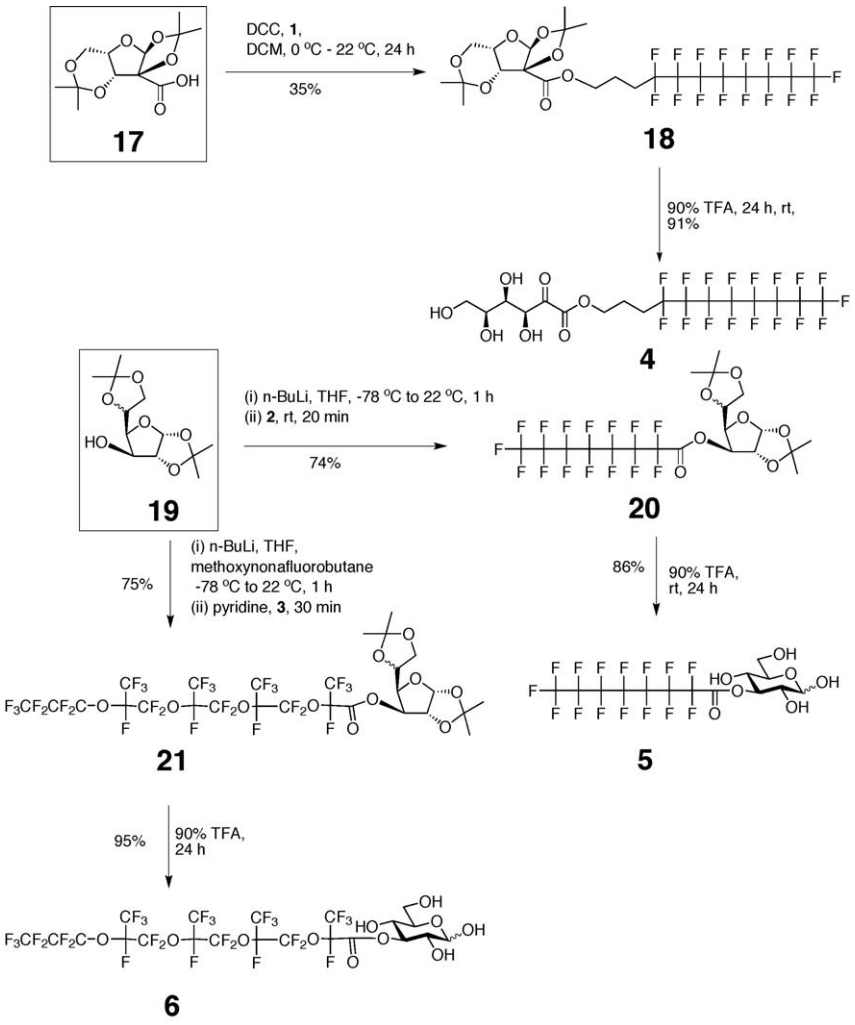


Fig. 2. Synthetic schemes for the formation of fluorosurfactants with carbohydrate head groups (**4**–**6**).

designed to tailor the affinity for stabilising both aqueous and non-aqueous microdroplets.

2.1. Selection of fluorous tails for surfactant molecules

Fluorinert FC-77 (3 M), comprising several low molecular weight fluorous ethers,[2] is frequently used as the fluorous oil phase in microdroplet devices [8]. As such, it was anticipated that simple perfluoroalkyl (PFA) or perfluoroalkyl polyether (PFPE)-based compounds would be a suitable starting point for the compounds possessing surfactant properties due to their structural similarity with the oil phase.

Surfactants were designed to include three different fluorous tails. These include two different PFA chains; a (perfluorooctanoyl)-propan-1-ol **1** and a perfluorooctanoyl **2**, and a PFPE chain of defined molecular weight containing four repeating units **3** (Fig. 1a). These three fluorous chains terminate in alcohol, acid chloride and acid fluoride functionalities, thus permitting conjugation to suitable polar head groups.

2.2. Selection of hydrophilic head groups for surfactant molecules

The fluorosurfactants designed in this study are shown in Fig. 1b–d. A variety of polar head groups were selected that could be conjugated to the aforementioned fluorous tails. These include a number of monosaccharides (Fig. 1b), crown ethers (Fig. 1c) and hexaethylene glycol (Fig. 1d). It was anticipated that these would display varied abilities to hydrogen bond with the aqueous phase when combined with the various fluorous tails. Surfactants possessing carbohydrate head groups include: **4** containing keto-L-gulonic acid, **5** and **6** containing D-glucose, **7** containing D-galactose and **8** and **9** containing D-galactos-1-amine. Two different crown ether head groups were proposed including aminomethyl 15-crown-5 in **10** and **11** and aza-18-crown-6 in **12** and **13**, while hexaethylene glycol was selected for **14**–**16**. These various polar head groups are linked via ester, amide and ether functionalities to the PFA and PFPE chains described above.

3. Results and discussion

3.1. Fluorosurfactant synthesis

The synthesis of keto-L-gulonic acid-based ester **4** started from the suitably protected precursor 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid **17** (Fig. 2). This was coupled to 3-(perfluorooctyl)propan-1-ol **1** using DCC to afford the desired ester **18** in moderate yield. Deprotection of the acetonide groups was achieved using 90% aqueous TFA to furnish the desired ester **4** in 91% yield.

The synthesis of D-glucose-based esters **5** and **6** began with commercially available di-acetone-D-glucose **19** which allowed

[2] FC-77 is a mixture of C_7F_{16} and $C_8F_{16}O$ in a batch-dependant ratio, with boiling point 100 °C and density, $\rho = 1.78$ g/cm^3.

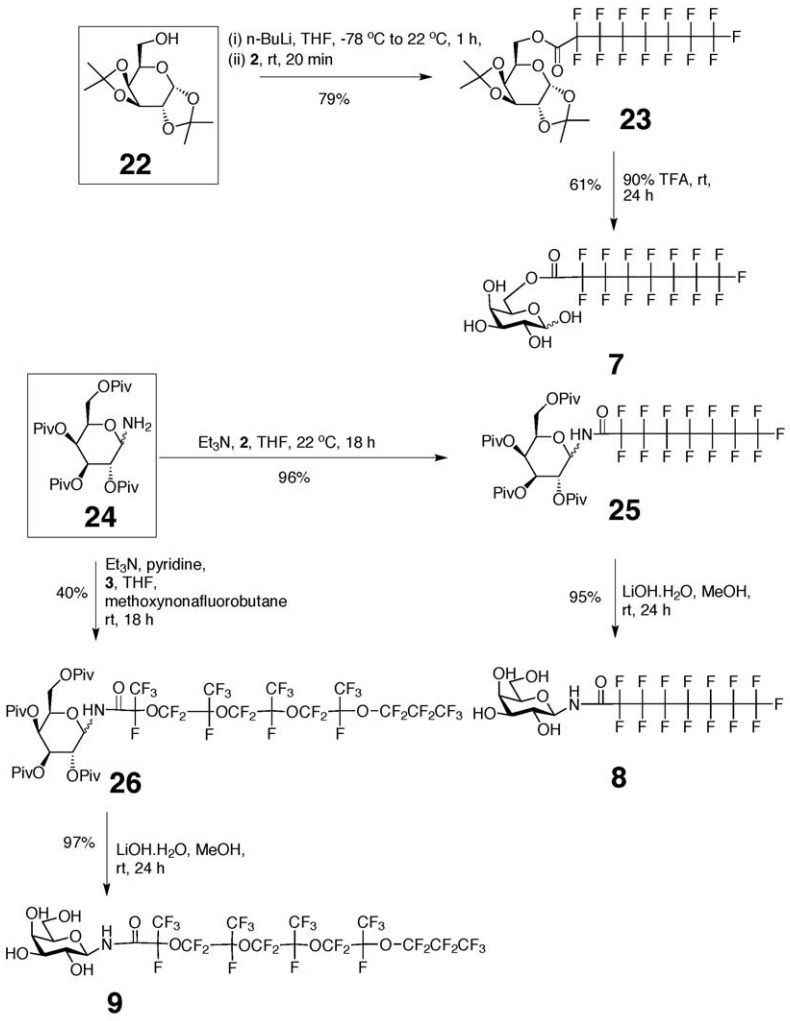


Fig. 3. Synthetic schemes for the formation of fluorosurfactants with carbohydrate head groups (**7**–**9**).

for selective acylation reactions on the C-3 alcohol (Fig. 2). Preparation of **5** involved initial esterification of **19** by deprotonation of the C-3 alcohol with *n*-butyllithium followed by the addition of perfluorooctanoyl chloride **2** to give protected ester **20** in 74% yield. Acetonide deprotection was achieved by treatment with 90% aqueous TFA followed by fluorous solid phase extraction (SPE) [14] to afford **5** as a mixture of α- and β-anomers in 86% yield.

Preparation of **6** entailed deprotonation of **19** using *n*-butyllithium in a mixture of THF and methoxynonafluorobutane (1:2, v/v) followed by the addition of perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl fluoride **3** and pyridine to afford the desired ester **21** in 75% yield. The use of methoxynonafluorobutane as the solvent was necessary to solubilise the branched fluorous chain of **3**, while pyridine was used to neutralise any excess hydrofluoric acid liberated upon formation of the ester. Acetonide deprotection was achieved by treatment with 90% aqueous TFA followed by purification by fluorous solid phase extraction [14] to afford **6** in 95% yield.

Preparation of the D-galactose-based ester **7** began from 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **22** which allowed for selective derivatisation of the C-6 hydroxyl group (Fig. 3). Deprotonation of **22** with *n*-butyllithium followed by addition of perfluorooctanoyl chloride **2** gave ester **23** in 79% yield. Treatment with 90% aqueous TFA to remove the acetonide protecting groups followed by purification by fluorous SPE furnished the D-galactose-based ester **7** as a mixture of α- and β-anomers.

The synthesis of amides **8** and **9** bearing a D-galactopyransylamine polar head group began from perpivaloylated derivative **24** (Fig. 3). Preparation of **8** involved deprotonation of **24** with triethylamine followed by treatment with perfluorooctanoyl chloride **2** to afford protected amide **25** as solely the β-anomer in 96% yield. Hydrolysis of the pivaloyl esters was achieved by treatment with lithium hydroxide which, after purification by fluorous SPE, gave **8** in 97% yield. In a similar manner, **9** was prepared by initial deprotonation of **24** with triethylamine in a mixture of THF and methoxynonafluorobutane (2:1, v/v). Addition of the acid fluoride **3** and pyridine gave the desired amide **26** in 40% yield. Hydrolysis of the pivaloyl esters followed by purification by fluorous SPE gave amide **9** in 97% yield.

3.2. Synthesis of surfactants with crown ether head groups

Amides **10** and **12** bearing a perfluorooctanoyl chain were synthesised in a similar manner to that described for carbohydrate-based analogue **8**. Briefly, treatment of 15-crown-5 **27** or 1-aza-18-crown-6 **28** with triethylamine and perfluorooctanoyl chloride **2** followed by purification by fluorous SPE gave **10** and **12** in 96% and 77% yield respectively (Fig. 4). Amides **11** and **13** bearing a PFPE chain were synthesised in a similar manner to that

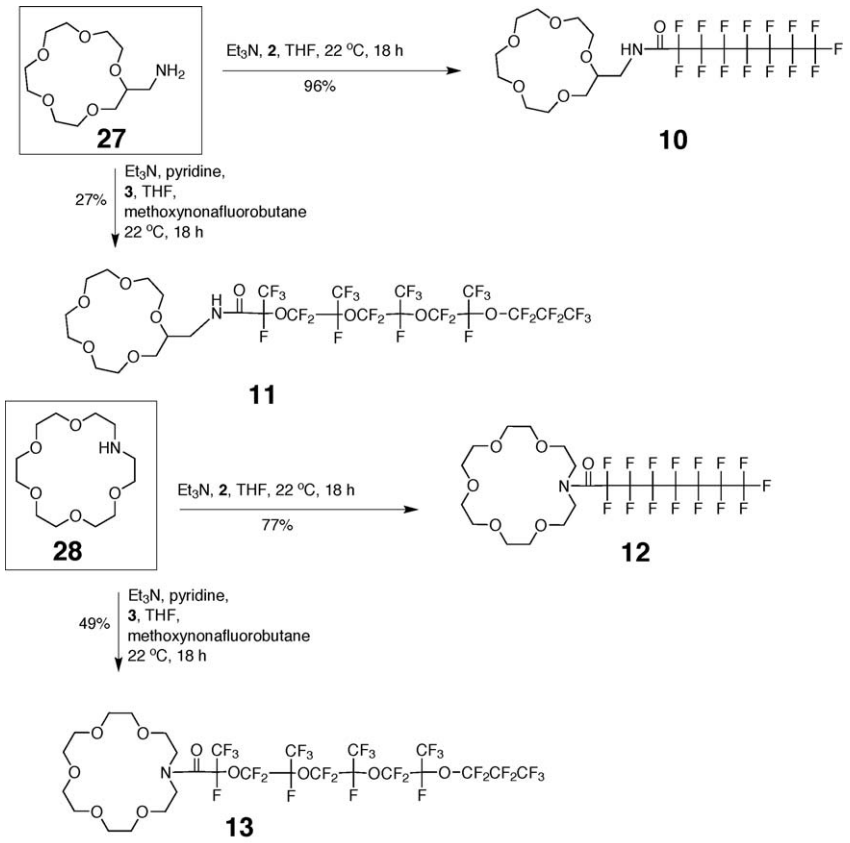


Fig. 4. The formation of fluorosurfactants with crown ether head groups (**10**–**13**).

described for **9**. This involved deprotonation of 15-crown-5 **27** or 1-aza-18-crown-6 **28** with triethylamine in a mixture of THF and methoxynonafluorobutane (2:1, v/v) followed by addition of acid fluoride **3** and pyridine to afford, after silica gel chromatography, the crown ether-based amides **11** and **13** in 27% and 49% yield respectively (Fig. 4).

3.3. Synthesis of surfactants with hexaethylene glycol head groups

In order to create molecules **14**–**16** possessing hexaethylene glycol head groups it was first necessary to achieve either monoprotection or monoactivation of a terminal hydroxyl group on the hexaethylene chain therefore allowing for selective modifications with fluorous derivatives **1**, **2** and **3**[31]. Activation of hexaethyleneglycol **29** was achieved by mono-tosylation, whereby the diol was reacted with silver (I) oxide and potassium iodide in the presence of tosyl chloride to afford **30** in 67% yield (Fig. 5). Mono-benzylation of **29** was achieved under similar conditions using benzyl bromide in place of tosyl chloride to afford **31** in 68% yield.

Ester **14** bearing a perfluorooctanoyl chain was synthesised by deprotonation of **31** with *n*-butyllithium followed by addition of perfluorooctanoyl chloride **2** to afford benzyl protected ester **32** in 63% yield (Fig. 5). Hydrogenolysis of **32** furnished ester **14** in 76% yield after fluorous SPE. In a similar manner, acid fluoride **3** and pyridine were added to a deprotonated solution of **31** in a mixture of THF and methoxynonafluorobutane (3:2, v/v) to afford **33** in 70% yield which, upon hydrogenolysis and fluorous SPE, gave the desired ester **15** in 89% yield.

Preparation of ether-linked molecule **16** involved deprotonation of 3-(perfluorooctyl)propan-1-ol **1** followed by treatment with tosylate **30** to afford the desired ether **16** in 32% yield after fluorous SPE (Fig. 5).

Having completed the synthesis of molecules **4**–**16**, their surfactant properties were assessed with respect to the stabilisation of aqueous and non-aqueous microdroplets.

3.4. Creation of aqueous and non-aqueous microdroplets using synthesised fluorosurfactants

To demonstrate that the molecules described above are suitable surfactant candidates for the production and stabilisation of microdroplets, a number of the synthesised surfactants were added to the fluorous oil phase (FC-77) to create droplets of both aqueous and organic solvents within channels in poly(dimethylsiloxane) (PDMS) microdevices (Fig. 6). Briefly, amide **11** was used at 2.5 mM concentration to create droplets of methanol within microdevices. Surfactant **15** was used at 1.6 mM concentration to produce droplets of acetonitrile. Such droplets could not be formed in the absence of surfactant, where the organic solvent coflows with the fluorous oil phase, and may even in some cases promote breakup of the oil phase to create fluorous droplets in an organic solvent carrier phase (Fig. 6a). Lastly, surfactant **15** was used at 13 μM concentration to stabilise water droplets within microdevices. Such droplets were stable upon entering the exit reservoir of the microdevice. This behaviour does not occur in the absence of surfactant, where droplets coalesce upon entering the reservoir.

The relative effectiveness and efficiency of these surfactant molecules towards forming and stabilising both aqueous and non-aqueous microdroplets remains to be investigated in more detail, results of which will be reported in due course.

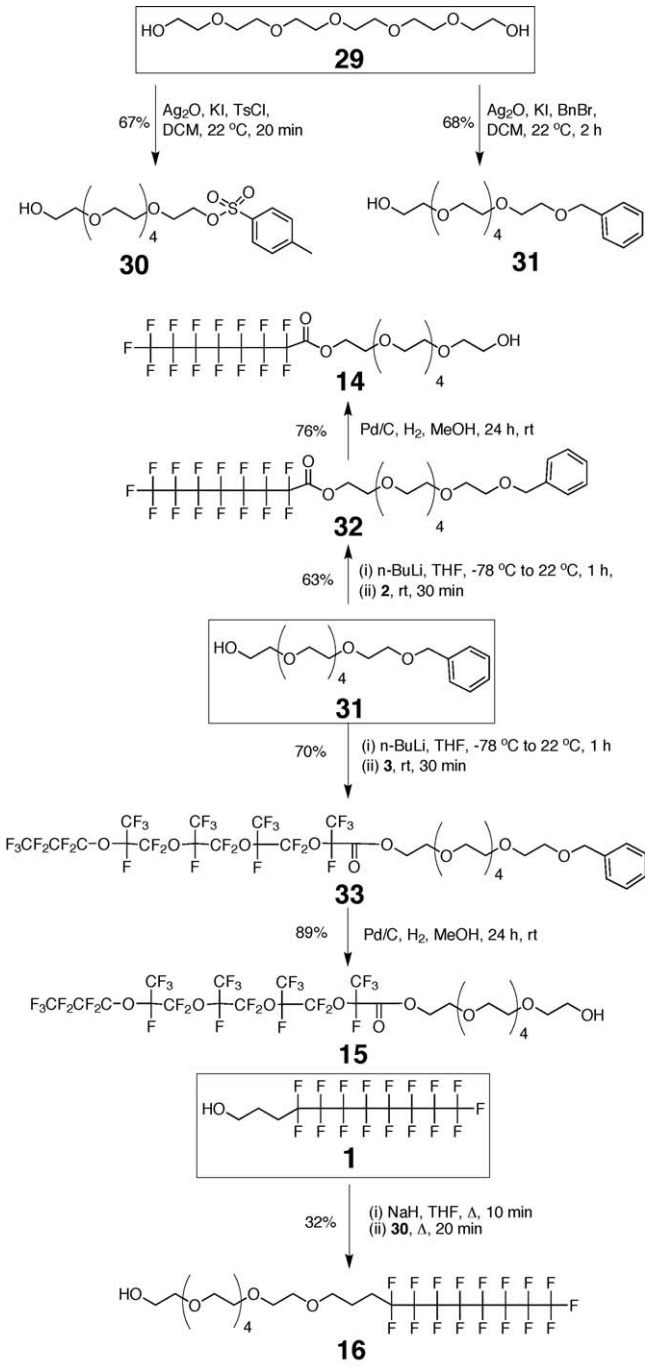


Fig. 5. The formation of fluorosurfactants with hexaethylene glycol head groups (**14**–**16**).

4. Conclusions

The synthesis of 13 potential fluorosurfactants containing a number of hydrophilic head groups and fluoroalkane tails is presented. The compounds were prepared using a variety of coupling methods to bring together the fluorous tails and hydrophilic head groups in good yields. A number of fluorosurfactants demonstrated the ability to stabilise the interface between fluorous oils and water, and also fluorous oils and organic solvents to create both aqueous and non-aqueous microdroplets in fluorous-coated PDMS devices. In the absence of surfactants such microdroplets either cannot be formed or are prone to immediate coalescence. As such, these molecules represent good candidates for further study into the production of stable microdroplets in such environments.

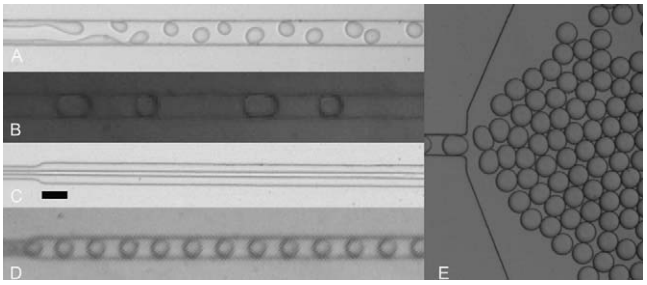


Fig. 6. Flows of water and organic solvents in fluorous-coated PDMS devices with and without fluorous surfactants using FC-77 as the fluorous oil phase. (a) Without surfactant, methanol with fluorous oil at total flow rates of 150 μl/h, produces a coflowing stream before droplets of fluorous oil are created in a stream of methanol. (b) With 2.5 mM of molecule **11** as surfactant in the oil phase, methanol droplets are created in the channel within the fluorous oil stream. (c) Without surfactant, acetonitrile coflows with fluorous oil at flow rates of 400 μl/h. (d) With 1.6 mM of molecule **15** as surfactant in the oil phase, acetonitrile droplets are created in the channel. (e) With 13 μM of molecule **15** as surfactant in the oil phase, water droplets exiting the microchannel into the larger reservoir are stabilised against coalescence. The scale bar is 50 μm. Fluids are flowing from left to right, being created at flow junctions between oil and droplet phases to the left of the region shown in the photographs.

5. Experimental

5.1. Experimental procedures for surfactant synthesis

Chemicals used in surfactant synthesis were purchased from Sigma–Aldrich Ltd. (Gillingham, UK) and Fluorochem Ltd (Derbyshire, UK) and used as received. All non-aqueous reactions were carried out in pre-dried glassware under an inert atmosphere (N_2 or Ar). Organic solvents were freshly distilled prior to use and milli-Q deionised water was used for all synthetic and microfluidic work. Analytical thin layer chromatography was carried out on commercial silica gel 60 0.25 mm plates using either UV absorption or potassium permanganate stain (3 g potassium permanganate, 20 g potassium carbonate, 5 ml of 5% sodium hydroxide, 300 ml water) for visualisation. R_f values are quoted with respect to the solvent system used to develop the plate. Column chromatography was carried out using 230–400 mesh silica gel 60. Fluorous solid phase extraction (SPE) was performed using Fluoroflash columns purchased from Fluorous Technologies, Inc. (Pittsburgh, USA). Unless otherwise stated petroleum ether refers to the fraction collected between 40 and 60 °C. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer in deuterated solvents, as indicated. ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer linked to a Bruker 5 mm dual Cryoprobe operating at 125 MHz. ^{19}F NMR were recorded using a Bruker AVANCE 400 QNP spectrometer operating at 376 MHz. All chemical shifts are quoted in parts per million (ppm) δ. Coupling constants for ^{1}H and ^{19}F NMR spectra are assigned where possible and are given in Hz. ^{1}H, ^{13}C and ^{19}F NMR signals are assigned where possible. High resolution mass spectrometry was carried out using a Micromass Quadrapole-Time of Flight (Q-TOF) spectrometer.

5.1.1. Synthesis of (2R,3S,4R,5S)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl 2,3,4-trihydroxy-5-(hydroxymethyl)tetrahydrofuran-3-carboxylate (4)

DCC (1.08 g, 5.23 mmol) in anhydrous dichloromethane (4 ml) was added dropwise to a mixture of 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid monohydrate **17** (1.53 g, 5.23 mmol), 3-(perfluorooctyl)propan-1-ol **1** (1 g, 2.09 mmol) and pyridine (0.44 ml, 5.23 mmol) in dichloromethane (10 ml) at 0 °C. The

reaction was stirred at 22 °C for 24 h before filtering through a small plug of celite and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 10:3, v/v petroleum ether/ethyl acetate) gave the desired ester **18** as a pale yellow oil (0.53 g, 35%).

Ester **18** (90 mg, 0.12 mmol) was dissolved in 90 % TFA (1 ml) and the reaction stirred at rt for 24 h. The solution was concentrated *in vacuo* and resuspended in ethyl acetate (15 ml). The organic fraction were washed with water, brine, dried (Na_2SO_4) and the solvent removed *in vacuo*, giving the desired tetraol **4** as a white solid (73 mg, 91%).

NMR: ^{1}H (400 MHz, MeOD) δ 1.95–2.10 (m, J = 6.0 Hz, 2H, CH_2), 2.23–2.39 (m, J = 8.0 Hz, 2H, CH_2), 3.48–3.71 (m, J = 2.0, 4.0, 6.0 Hz, 5H), 4.22–4.34 (m, J = 6.0 Hz, 2H, CH_2) ppm. ^{19}F (376 MHz, MeOD) δ −78.7 (td, J = 2.0, 10.0 Hz, CF_3), −111.6 (m, J = 13.0 Hz, CH_2CF_2), −119.0 (m, CF_2), - 112.0 (m, CF_2), −120.0 (m, CF_2), −120.8 (m, CF_2), −123.6 (m, J = 6.0 Hz, CF_2) ppm.

HRMS: for $C_{17}H_{15}O_7F_{17}Na$ calcd 677.0439, found 677.0419.

5.1.2. Synthesis of 2-(1,2-dihydroxyethyl)-4,5-dihydroxytetrahydrofuran-3-yl 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoate (5)

n-Butyllithium (1.26 ml of a 1.6 M solution in hexanes, 2.02 mmol) was added dropwise over a period of 10 min to a solution of di-acetone-D-glucose **19** (500 mg, 1.92 mmol) in THF (10 ml) at −78 °C. The reaction was stirred at 22 °C for 1 h before the dropwise addition of perfluorooctanoyl chloride **2** (2.08 g, 4.80 mmol). The reaction was stirred at 22 °C for 15 min before the solvent was removed *in vacuo* at 30 °C. Purification by column chromatography (eluent: 8:1, v/v petroleum ether/ethyl acetate) gave the desired ester **20** as a colourless oil (930 mg, 74%).

Ester **20** (100 mg, 0.16 mmol) was dissolved in 90% TFA (1 ml) and the reaction stirred at 22 °C for 24 h. The solution was evaporated and the resulting residue purified by fluorous SPE (dissolved in MeOH and applied to a 2 ml cartridge) to give the desired tetraol **5** as a cream oil as a mixture of α- and β-anomers (75 mg, 86%).

NMR: ^{1}H (400 MHz, MeOD) (mixture of α- and β-anomers) δ 3.40 (m, 2H), 3.58 (m, 3H), 3.67 (dd, J = 6.0, 12.0 Hz, 1H), 3.72 (dd, J = 5.0, 12.0 Hz, 1H), 3.78 (dd, J = 2.5, 12.0 Hz, 1H), 3.84 (dd, J = 2.0, 12.0 Hz, 2H), 4.56 (d, J = 8.0 Hz, 1H), 5.09 (t, J = 9.5 Hz, 1H), 5.14 (d, J = 3.5 Hz, 1H), 5.38 (t, J = 9.0 Hz, 1H) ppm. ^{13}C (125 MHz, MeOD) (mixture of α- and β-anomers) δ 62.1 (s, CH_2), 62.2 (s, CH_2), 69.2 (s, CH), 69.2 (s, CH), 71.6 (s, CH), 72.9 (s, CH), 74.0 (s, CH), 77.8 (s, CH), 82.3 (s, CH), 83.8 (s, CH), 94.0 (s, CHOH), 98.2 (s, CHOH), 101.2, 109.5 (m, CF), 111.8 (m, CF), 114.2 (m, CF), 116.9 (m, CF), 118.8 (m, CF) 210.1 (s, –COO–) ppm. ^{19}F (376 MHz, MeOD) δ −81.8 (m, CF_3), −119.1 (m, CF_2CO), −121.9 (m, CF), −122.1 (m, CF), −122.6 (m, CF), −123.1 (m, CF), −126.7 (m, CF) ppm.

HRMS: for $C_{14}H_{11}O_7F_{15}Na$ calcd 599.0157, found 599.0158.

5.1.3. Synthesis of (2S,5S,8S,11S)-2-(1,2-dihydroxyethyl)-4,5-dihydroxytetrahydrofuran-3-yl 2,4,4,5,7,7,8,10,10,11,13,13,14,14,14-pentadecafluoro-2,5,8,11-tetrakis(trifluoromethyl)-3,6,9,12-tetraoxatetradecan-1-oate (6)

n-Butyllithium (1.26 ml of a 1.6 M solution in hexanes, 2.02 mmol) was added dropwise over a period of 10 min to a solution of di-acetone-D-glucose **19** (500 mg, 1.92 mmol) in THF (6 ml) and methoxynonafluorobutane (4 ml) at −78 °C. The reaction was stirred at 22 °C for 1 h before the dropwise addition of pyridine (0.39 ml, 4.80 mmol) and perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl fluoride **3** (3.98 g, 4.80 mmol). The reaction was stirred at 22 °C for 30 min before the solvent was removed *in vacuo* at 30 °C. Purification by column chromatography (eluent: 8:1, v/v petroleum ether/ethyl acetate) gave the desired ester **21** as a colourless oil (1.54 g, 75%).

Ester **21** (200 mg, 0.19 mmol) was dissolved in 90% TFA (2 ml) and the reaction stirred at 22 °C for 20 h. The solution was evaporated and the resulting residue purified by fluorous SPE (dissolved in MeOH and applied to a 2 ml cartridge) to give the desired tetraol **6** as a cream oil as a mixture of diastereoisomers (180 mg, 95%).

NMR: ^{1}H (400 MHz, MeOD) δ (mixture of anomers) 3.47–3.58 (m, 2H), 3.64–3.85 (m, 2H), 4.10–4.15 (m, 1H), 4.45–4.70 (m, 2H), 5.13 (m, J_{CH} = 4.0, 9.5 Hz, 1H), 5.38 (t, J_{CH} = 9.5 Hz, 1H) ppm. ^{13}C (125 MHz, MeOD) δ 60.7 (s, CH_2), 66.3 (s, CH_2), multiple peaks between 67.8 and 82.3 (all s, CHOH & CH), 92.6 (s, CHOH), 96.8 (s, CHOH), 99.5 (m, CF), 101.0 (m, CF), 103.5 (m, CF), 106.5 (m, CF), 108.5 (m, CF), 113.5 (m, CF_2), 115.9 (m, CF_2), 118.4 (m, CF_2), 120.9 (m, CF_2), 157.0 (m, CF_3), 158.0 (m, –COO–) ppm. ^{19}F (376 MHz, MeOD) δ −77.1 (m, CF_3), −82.6 (m, $COCF_2$), −119.9 (m, CF_2), −120.0 (s, CF_2), −122.9 (s, CF_2), −123.9 (m, CF_2), −127.5 (m, CF_2) ppm.

HRMS: for $C_{21}H_{11}O_{11}F_{29}Na$ calcd 1012.9731, found 1012.9774.

5.1.4. Synthesis of ((3R,4S,5R,6S)-3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-yl)methyl 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoate (7)

n-Butyllithium (1.26 ml of a 1.6 M solution in hexanes, 2.02 mmol) was added dropwise over a period of 10 min to a solution of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **22** (500 mg, 1.92 mmol) in THF (10 ml) at −78 °C. The reaction was stirred at 22 °C for 1 h before the dropwise addition of perfluorooctanoyl chloride **2** (2.08 g, 4.80 mmol). The solution was stirred at 22 °C for 20 min before the solvent was removed *in vacuo* at 30 °C. Purification by column chromatography (eluent: 8:1, v/v petroleum ether/ethyl acetate) gave the desired ester **23** as a white solid (1.00 g, 79%).

Ester **23** (240 mg, 0.37 mmol) was dissolved in 90% TFA (2.4 ml) and the reaction stirred at 22 °C for 20 h. The solution was evaporated and the resulting residue purified by fluorous solid phase extraction (dissolved in MeOH and applied to a 2 ml cartridge) to give the desired tetraol **7** as a mixture of α- and β-anomers as a white solid (130 mg, 61%).

NMR: ^{1}H (400 MHz, MeOD) δ 3.40–5.25 ppm multiple peaks arising from α- and β-anomers. ^{13}C (125 MHz, MeOD) δ between 59.0 and 104.0 multiple peaks arising from α- and β-anomers, 105.7 (m, CF), 108.0 (m, CF), 110.5 (m, CF), 112.3 (m, CF), 113.3 (m, CF), 115.8 (m, CF), 118.0 (m, CF), 157.3 (m, –OCO–) ppm. ^{19}F (376 MHz, MeOD) δ −77.1 (m, CF_3), −82.8 (m, $COCF_2$), −120.0 (m, CF_2), −120.0 (s, CF_2), −122.9 (s, CF_2), −123.9 (m, CF_2), −127.5 (m, CF_2) ppm.

HRMS: for $C_{14}H_{11}O_{11}F_{15}Na$ calcd 599.0147, found 599.0147.

5.1.5. Synthesis of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)octanamide (8)

Triethylamine (0.27 ml, 1.94 mmol) was added dropwise to a solution of 2,3,4,6-tetra-*O*-pivaloyl-D-galactopyransylamine **24** (500 mg, 0.97 mmol) in THF (7 ml). The solution was cooled to 0 °C and perfluorooctanoyl chloride **2** (420 mg, 0.97 mmol) was added dropwise over 15 min. The reaction was stirred at 0 °C for 1.5 h and at 22 °C for a further 18 h. The reaction was quenched with saturated aqueous ammonium chloride solution (5 ml) before the aqueous fraction was extracted with chloroform (3× 5 ml). The combined organic fractions were washed with water, brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 8:1, v/v, petroleum ether/ethyl acetate) gave the desired amide **25** as a white foam (0.85 g, 96%).

To a solution of tetrapivolate **25** (150 mg, 0.17 mmol) in MeOH (3.5 ml) was added lithium hydroxide monohydrate (17.3 mg, 0.41 mmol). The reaction was stirred at 22 °C for 48 h before

Dowex 50W-X8(H^+) (0.52 g) was added and stirring continued for a further 10 min. After the resin was filtered off the filtrate was evaporated to give a residue, which was purified by fluorous SPE (dissolved in MeOH and applied to a 2 ml cartridge) to give the desired tetraol **8** as a cream oil (90 mg, 95%).

NMR: ^{1}H (400 MHz, MeOD) δ 3.53 (dd, J = 3.5, 9.5 Hz, 1H, CHOH), 3.60–3.78 (m, CHOH, CH_2, 4H), 3.90 (m, 3.5 Hz, C*H* (CH_2OH)OC, 1H), 4.95 (d, J = 9.0 Hz, CHNH, 1H) ppm. ^{13}C (125 MHz, MeOD) δ 62.4 (s, CH_2), 70.4 (s, CHOH), 70.8 (s, CHOH), 75.7 (s, CHOH), 78.8 (s, CHOH), 82.0 (s, CHOH), 110.2 (m, CF), 112.0 (m, CF), 114.0 (m, CF), 117.4 (t, $^1J_{CF}$ = 13.0 Hz, CF_2), 119.6 (t, $^1J_{CF}$ = 13.0 Hz, CF_2), 121.9 (t, $^1J_{CF}$ = 13.0 Hz, CF_2), 159.5 (t, $^2J_{CF}$ = 10.5 Hz, *C* OCF_2) ppm. ^{19}F (376 MHz, MeOD) δ −81.9 (tt, $^3J_{FF}$ = 10.0 Hz, $^4J_{FF}$ = 2.5 Hz, CF_3), −120.3 (m, J = 10.5 Hz, CF_2), −121.9 (m, CF_2), −122.5 (m, CF_2), −122.9 (m, CF_2), −123.2 (m, CF_2), −126.8 (m, CF_2) ppm.

HRMS: for $C_{14}H_{12}NO_6F_{15}Na$ calcd 598.0317, found 598.0389.

5.1.6. Synthesis of (2R,5R,8R,11R)-2,4,4,5,7,7,8,10,10,11,13,13,14,14,14-pentadecafluoro-2,5,8,11-tetrakis(trifluoromethyl)-N-((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-3,6,9,12-tetraoxatetradecan-1-amide (9)

Triethylamine (0.27 ml, 1.94 mmol) was added dropwise to a solution of 2,3,4,6-tetra-*O*-pivaloyl-D-galactopyransylamine **24** (500 mg, 0.97 mmol) in THF (5 ml) and methoxynonafluorobutane (2.5 ml). The solution was cooled to 0 °C and pyridine (0.08 ml, 0.97 mmol) and perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl fluoride **3** (804 mg, 0.97 mmol) was added dropwise over 15 min. The reaction was stirred at 0 °C for 1.5 h and at 22 °C for a further 18 h. The reaction was diluted with dichloromethane (20 ml), the organic fraction washed with saturated aqueous ammonium chloride solution (25 ml), water (25 ml), brine (25 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 8:1, v/v, petroleum ether/ethyl acetate) gave the desired amide **26** as a colourless oil (0.50 g, 40%).

To a solution of tetrapivolate **26** (210 mg, 0.17 mmol) in MeOH (3.5 ml) was added lithium hydroxide monohydrate (17.3 mg, 0.41 mmol). The reaction was stirred at 22 °C for 48 h before Dowex 50W-X8(H^+) (0.52 g) was added and stirring continued for a further 10 min. After the resin was filtered off the filtrate was evaporated to give a residue, which was purified by fluorous SPE (dissolved in MeOH and applied to a 2 ml cartridge) to give the desired *tetraol* **9** as a mixture of diastereoisomers (150 mg, 97%).

NMR: ^{1}H (400 MHz, MeOD) mixture of diastereoisomers δ 3.52 (ddd, J = 1.5, 3.5, 9.5 Hz, CHOH, 1H), 3.58–3.75 (m, CHOH, CH_2, 4H), 3.92 (ddd, J = 0.5, 3.5, 8.0 Hz, C*H* (CH_2OH)OC, 1H), 4.95 (dd, J = 4.0, 9.0 Hz, CHNH, 1H) ppm. ^{13}C (125 MHz, MeOD) mixture of diastereoisomers δ 62.1 (s, CH_2), 62.1 (s, CH_2), 62.3 (s, CH_2), 70.3 (s, CHOH), 70.4 (s, CHOH), 70.8 (s, CHOH), 70.9 (s, CHOH), 70.9 (s, CHOH), 75.8 (s, CHOH), 75.8 (s, CHOH), 78.6 (s, CHOH), 78.8 (s, CHOH), 82.1 (s, CHOH), 82.2 (s, CHOH), 102.8 (m, CF), 105.1 (m, CF), 107.7 (m, CF), 114.7 (m, CF), 117.2 (m, CF), 119.3 (m, CF), 122.1 (m, CF), 160.0 (m, CO) ppm. ^{19}F (376 MHz, MeOD) δ −80.9 (m, CF_3), −82.5 (s, CF), −83.4 (t, J = 2.5 Hz, CF), −130.5 (s, CF), −133.5 to −134.0 (m, CF), −145.0 to −146.0 (m, CF) ppm.

HRMS: for $C_{21}H_{12}NO_{10}F_{29}Na$ calcd 1011.9890, found 1011.9863.

5.1.7. Synthesis of N-((1,4,7,10,13-pentaoxacyclopentadecan-2-yl)methyl)-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanamide (10)

Triethylamine (0.49 ml, 3.54 mmol) was added dropwise to a solution of aminomethyl 15-crown-5 **27** (0.44 ml, 1.77 mmol) in THF (7 ml). The solution was cooled to 0 °C and perfluorooctanoyl chloride **2** (766 mg, 1.77 mmol) was added dropwise over 15 min. The reaction was stirred at 0 °C for 1.5 h and at 22 °C for a further 18 h. The reaction was diluted with chloroform (20 ml), the organic fraction washed with saturated aqueous ammonium chloride solution (25 ml), water (25 ml), brine (25 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 95:5, v/v chloroform/methanol) gave the desired amide **10** as a yellow oil (1.10 g, 96%).

NMR: ^{1}H (400 MHz, $CDCl_3$) δ 3.30–3.38 (m, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, –NHCH_2–), 3.46–3.73 (m, $^3J_{HH}$ = 6.0 Hz, 20H, CH_2), 3.86 (m, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, –NHCH_2–), 7.47 (br s, 1H, NH) ppm. ^{13}C (125 MHz, $CDCl_3$) δ 42.3 (s, –$NHCH_2$–), multiple peaks between 69.5 and 72.0 (all s), CH_2), 76.4 (s, –$NHCH_2$*C* H–), 77.2 (s, –$NHCH_2$*C* H–), 105.7–107.1 (m, J_{CF} = 28.0, 129.0 Hz, CF_2), 107.7–109.2 (m, J_{CF} = 127.0 Hz, CF_2), 109.8–111.4 (m, J_{CF} = 127.5 Hz, CF_2), 112.0–113.8 (m, J_{CF} = 38.0, 126.5, 133 Hz, CF_2), 115.8 (t, $^1J_{CF}$ = 131.5 Hz, CF_2), 118.1 (t, $^1J_{CF}$ = 131.5 Hz, CF_2), 120.4 (t, $^1J_{CF}$ = 131.5 Hz, CF_3), 157.1 (t, $^1J_{CF}$ = 102.5 Hz, –$CONH_2$–) ppm. ^{19}F (376 MHz, $CDCl_3$) δ −81.4 (m, CF_3), −120.1 (t, $^3J_{FF}$ = 14.0 Hz, CF_2NH), −122.1 (m, CF_2), −122.5 (m, CF_2), −123.0 (m, CF_2), −123.2 (m, CF_2), −126.7 (m, CF_2) ppm.

HRMS: for $C_{19}H_{23}NO_6F_{29}$ calcd 646.1284, found 646.1294.

5.1.8. Synthesis of (2R,5R,8R,11R)-N-((1,4,7,10,13-pentaoxacyclopentadecan-2-yl)methyl)-2,4,4,5,7,7,8,10,10,11,13,13,14,14,14-pentadecafluoro-2,5,8,11-tetrakis(trifluoromethyl)-3,6,9,12-tetraoxatetradecan-1-amide (11)

Triethylamine (0.41 ml, 2.90 mmol) was added dropwise to a solution of aminomethyl 15-crown-5 **27** (0.32 ml, 1.46 mmol) in THF (5 ml) and methoxynonafluorobutane (2.5 ml). The solution was cooled to 0 °C and pyridine (0.12 ml, 1.46 mmol) and perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl fluoride **3** (1.21 g, 1.46 mmol) was added dropwise over 15 min. The reaction was stirred at 0 °C for 1.5 h and at 22 °C for a further 18 h. The reaction was diluted with chloroform (20 ml), the organic fraction washed with saturated aqueous ammonium chloride solution (25 ml), water (25 ml), brine (25 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 9:1, v/v chloroform/methanol) gave the desired amide **11** as a mixture of diastereoisomers as a colourless oil (0.40 g, 27%).

NMR: ^{1}H (400 MHz, $CDCl_3$) δ 3.36–3.46 (m, J = 5.0, 7.0 Hz, 1H, NHCH_2), 3.52–3.55 (m, J = 6.0 Hz, 1H, $NHCH_2CH$–), 3.56–3.63 (m, J = 4.0, 9.0 Hz, 14H, CH_2), 3.69–3.74 (m, J = 4.0 Hz, 4H, CH_2), 3.84 (s, 1H, NHCH_2–), 7.40 (br s, 1H, NH) ppm. ^{13}C (125 MHz, $CDCl_3$) δ 42.3 (m, $NHCH_2$), multiple peaks between 69.6 and 71.9 (all s, CH_2), 76.5 (s, $NHCH_2$*C* H), 77.2 (s, $NHCH_2$*C* H), 100.6–101.8 (m, J_{CF} = 150.5 Hz, CF), 102.4–104.4 (m, J_{CF} = 145.0 Hz, CF), 105.8–107.1 (m, J_{CF} = 158.0 Hz, CF), 108.0–108.5 (m, J_{CF} = 160.5 Hz, CF), 112.7–114.6 (m, J_{CF} = 31.5, 126.5 Hz, CF), 115.0–116.3 (m, J_{CF} = 17.5, 127.0 Hz, CF), 117.0 (d, J_{CF} = 121.0 Hz, CF), 117.6–118.6 (m, J_{CF} = 127.5, 131.0 Hz, CF), 119.3 (d, J_{CF} = 123.5 Hz, CF), 120.0 (t, J_{CF} = 129.5 Hz, CF), 120.8 (d, J_{CF} = 125.0 Hz, CF), 157.6 (m, $^2J_{CF}$ = 103.5 Hz, –CONH–) ppm. ^{19}F (376 MHz, $CDCl_3$) δ −82.9 (d, J_{CF} = 14.0 Hz), −82.8 (d, J_{CF} = 14.5 Hz), −81.8 to −81.9 (m, J_{CF} = 6.0 Hz), −80.2 to −80.6 (m, J_{CF} = 6.5, 10.5, 14.5 Hz), −130.0 (m, J_{CF} = 9.5 Hz), −132.5 to −133.1 (m, J_{CF} = 19.5, 27.0 Hz, CF_2), −144.8 to −145.7 (m, J_{CF} = 22.0 Hz, CF) ppm.

HRMS: for $C_{26}H_{22}NO_{10}F_{29}Na$ calcd 1082.0673, found 1082.0775.

5.1.9. Synthesis of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-1-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)octan-1-one (12)

Triethylamine (0.53 ml, 3.80 mmol) was added dropwise to a solution of 1-aza-18-crown-6 **28** (500 mg, 1.90 mmol) in THF (7 ml). The solution was cooled to 0 °C and perfluorooctanoyl

chloride **2** (820 mg, 1.90 mmol) was added dropwise over 15 min. The reaction was stirred at 0 °C for 1.5 h and at 22 °C for a further 18 h. The reaction was diluted with chloroform (20 ml), the organic fraction washed with saturated aqueous ammonium chloride solution (25 ml), water (25 ml), brine (25 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 9:1, v/v chloroform/methanol) gave the desired amide **12** as a yellow oil (960 mg, 77%).

NMR: ^{1}H (400 MHz, $CDCl_3$) δ 3.55–3.62 (m, J = 6.0 Hz, J = 5.5 Hz, 20H, CH_2) ppm, 3.73 (t, $^3J_{HH}$ = 6.0 Hz, 2H, –NCH_2 CH_2O–), 3.77 (t, $^3J_{HH}$ = 5.5 Hz, 2H, –NCH_2CH_2 O–). ^{13}C (125 MHz, $CDCl_3$) δ 48.3 (br s, –NCH_2–), 48.8 (s, –NCH_2–), 68.1 (s, –NCH_2C H_2–), 68.2 (s, –NCH_2C H_2–), 68.3 (s, –NCH_2C H_2–), 68.5 (s, –NCH_2C H_2–), multiple peaks between 70.0 and 70.7 (all s, CH_2), 106.3 (dq, $^1J_{CF}$ = 130.5 Hz, $^2J_{CF}$ = 24.0 Hz, CF_3C F_2–), 109.2–107.6 (m, CF_2), 111.5–109.7 (m, CF_2), 113.9–112.1 (m, CF_2), 115.9 (t, $^1J_{CF}$ = 131.0 Hz, CF_2), 118.2 (t, $^1J_{CF}$ = 132.0 Hz, CF_2), 120.5 (t, $^1J_{CF}$ = 130.5 Hz, CF_3), 157.9 (t, $^2J_{CF}$ = 100.0 Hz, –CON–) ppm. ^{19}F (376 MHz, $CDCl_3$) δ −81.2 (tt, $^3J_{FF}$ = 11.0 Hz, $^4J_{FF}$ = 2.5 Hz, CF_3), −111.2 (tt, $^3J_{FF}$ = 14.5 Hz, $^4J_{FF}$ = 3.0 Hz, –CF_2CON–), −120.6 (m, CF_2), −121.0 (m, J = 4.0 Hz, CF_2), −122.3 (m, CF_2), −122.9 (m, CF_2), −126.5 (m, J = 7.6 Hz, J = 3.5 Hz, CF_2) ppm.

HRMS: for $C_{20}H_{24}NO_6F_{15}Na$ calcd 682.1256, found 682.1286; for $C_{20}H_{25}NO_6F_{15}$ calcd 660.1437, found 660.1448.

5.1.10. Synthesis of (2R,5R,8R,11R)-2,4,4,5,7,7,8,10,10,11,13,13,14,14,14-pentadecafluoro-2,5,8,11-tetrakis(trifluoromethyl)-3,6,9,12-tetraoxatetradecan-1-al compound with 16-methyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (1:1) (13)

Triethylamine (0.53 ml, 3.80 mmol) was added dropwise to a solution of 1-aza-18-crown-6 **28** (500 mg, 1.90 mmol) in THF (5 ml) and methoxynonafluorobutane (2.5 ml). The solution was cooled to 0 °C and pyridine (0.15 ml, 1.90 mmol) and perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl fluoride **3** (1.58 g, 1.90 mmol) was added dropwise over 15 min. The reaction was stirred at 0 °C for 1.5 h and at 22 °C for a further 18 h. The reaction was diluted with chloroform (20 ml), the organic fraction washed with saturated aqueous ammonium chloride solution (25 ml), water (25 ml), brine (25 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 9:1, v/v chloroform/methanol) gave the desired amide **13** as a mixture of diastereoisomers as a pale yellow oil (0.95 g, 49%).

NMR: ^{1}H (400 MHz, $CDCl_3$) δ 3.74-3.89 (m, $^3J_{HH}$ = 6.0 Hz, 4H, –CONCH_2 CH_2O–), 3.56–3.70 (m, $^3J_{HH}$ = 6.0 Hz, 20H, CH_2) ppm. ^{13}C (125 MHz, $CDCl_3$) δ 49.2 (s, –NCH_2), 49.3 (s, –NCH_2), 50.3 (s, CH_2), 50.3 (s, CH_2), 68.2 (s, CH_2), 68.4 (s, CH_2), multiple signals between 70.0 and 70.7 (all s, CH_2), 100.9–101.6 (m, CF), 102.3–104.0 (m, J_{CF} = 156.5 Hz, CF), 104.9 (m, CF), 106.2 (m, CF), 113.0–113.8 (m, J_{CF} = 163.5 Hz, CF), 115.2–116.3 (m, J_{CF} = 83.0 Hz, CF), 117.1–118.6 (m, J_{CF} = 112.5 Hz, 129.5 Hz, CF), 119.5 (d, J_{CF} = 131.0 Hz, CF), 120.8 (d, J_{CF}- 128.0 Hz, CF), 121.9 (d, J_{CF} = 120.5 Hz, CF), 157.7 (d, $^2J_{CF}$ = 96.0 Hz, –CON–) ppm. ^{19}F (376 MHz, $CDCl_3$) δ −80.0 (t, J = 9.5 Hz, CF_3), −80.2–7 (m, J = 10.0 Hz, CF_3), −81.8 (m, J = 5.0 Hz, CF_3), −81.9 (m, CF_3), −82.0 (m, CF_3), −125.6 (m, CF_2), −130.1 (m, CF_2), −144.7 to −145.7 (m, J = 18 Hz, CF) ppm.

HRMS: for $C_{27}H_{24}NO_{10}F_{29}Na$ calcd 1096.0829, found 1096.0788.

5.1.11. Synthesis of toluene-4-sulfonic acid 2-(2-(2-(2-(2-(2-hydroxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethyl ester (30) [31].

To a 0 °C solution of hexaethylene glycol **29** (4.45 ml, 0.018 mol) in dichloromethane (50 ml) were added silver (I) oxide (6.26 g, 0.027 mol), potassium iodide (0.60 g, 3.60 mmol) and tosyl chloride (3.77 g, 0.020 mol). After stirring the reaction for 20 min the precipitated silver salts were removed by filtration through a pad of celite which was washed thoroughly with ethyl acetate. The combined filtrate was concentrated *in vacuo* and the residue purified by column chromatography (eluent: 3:2, v/v dichloromethane/acetone) to give the desired tosylate **30** as a pale yellow oil (5.24 g, 67%).

NMR: ^{1}H (400 MHz, $CDCl_3$) δ 2.34 (s, CH_3Ar, 3H), 3.05 (s, CH_2, 2H), 3.45–3.61 (m, CH_2, 20H), 4.07 (m, J = 5.0 Hz, CH_2, 2H), 7.25 (d, J = 8.0 Hz, ArH, 2H), 7.67 (d, J = 8.0 Hz, ArH, 2H) ppm. ^{13}C (125 MHz, $CDCl_3$), δ 22.3 (s, CH_3), 62.2 (s, CH_2), 69.3 (s, CH_2), 70.0 (s, CH_2), 71.1–71.3 (several s, CH_2), 73.2 (s, CH_2), 128.6 (s, Ar), 130.5 (s, Ar), 133.7 (s, Ar), 145.5 (s, Ar) ppm.

5.1.12. Synthesis of 2-(2-(2-(2-(2-(2-benzyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethanol (31) [31].

Hexaethylene glycol **29** (0.89 ml, 3.54 mmol) was added dropwise to a solution of silver (I) oxide (1.23 g, 5.31 mmol) and potassium iodide (0.24 g, 1.42 mmol) in dichloromethane (30 ml). Benzyl bromide (0.46 ml, 3.89 mmol) was added dropwise over 5 min and the reaction stirred at 22 °C for 2 h. The suspension was filtered through celite which was thoroughly washed with dichloromethane. The combined filtrate was concentrated *in vacuo* and the residue purified by column chromatography (eluent: 95:5, v/v, ethyl acetate/methanol) to give benzyl ether **31** as a colourless oil (900 mg, 68%).

NMR: ^{1}H (400 MHz, $CDCl_3$) δ 3.55–3.70 (m, CH_2, 24H), 4.53 (s, ArCH_2, 2H), 7.31 (m, ArH, 5H) ppm.

HRMS: for $C_{19}H_{33}O_7$ calc. 373.2220, found 373.2217, for $C_{19}H_{32}O_7Na$ calc. 395.2040, found 395.2039.

5.1.13. Synthesis of 2-(2-(2-hydroxyethoxy)ethoxy)ethyl 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoate (14)

n-Butyllithium (0.53 ml of a 1.6 M solution in hexanes, 0.85 mmol) was added dropwise over a period of 10 min to a solution of **31** (300 mg, 0.81 mmol) in THF (6 ml) at −78 °C. The reaction was stirred at 22 °C for 1 h before the dropwise addition of perfluorooctanoyl chloride **2** (0.87 g, 2.01 mmol). The solution was stirred at 22 °C for 30 min before the solvent was removed *in vacuo* at 30 °C. Purification by column chromatography (eluent: 97.5:2.5, v/v, ethyl acetate/methanol) gave the desired ester **32** as a colourless oil (390 mg, 63%).

Benzyl ether deprotection was accomplished via addition of 10% palladium on carbon (30 mg) to a solution of **32** (270 mg, 0.35 mmol) dissolved in methanol (7 ml) and the flask flushed with H_2. The reaction was stirred under an H_2 atmosphere for 18 h at which point the suspension was filtered through celite, and the celite washed thoroughly with methanol. The filtrate was concentrated *in vacuo* and the residue purified by fluorous SPE (dissolved in DMF and applied to a 2 ml cartridge) to give the desired alcohol **14** as a white solid (180 mg, 76%).

NMR: ^{1}H (400 MHz, MeOD) δ 3.28 (m, 1H, OH), 3.54 (m, 2H, CH_2), 3.63 (m, 20H, CH_2), 3.78 (m, 2H, CH_2) ppm. ^{13}C (125 MHz, MeOD) δ 62.2 (s, CH_2), 68.9 (s, CH_2), 69.3 (s, CH_2), 71.4 (s, CH_2), 71.4 (s, CH_2), 71.4 (s, CH_2), 71.5 (s, CH_2), 71.5 (s, CH_2), 71.5 (s, CH_2), 71.5 (s, CH_2), 71.6 (s, CH_2), 73.7 (s, CH_2), 107.3 (t, $^1J_{CF}$ = 130.0 Hz, CF_3), 109.2–110.1 (m, CF_2), 111.3–112.5 (m, CF_2), 113.5–114.6 (m, CF_2), 117.3 (t, $^1J_{CF}$ = 130.0 Hz, CF_2), 119.6 (t, $^1J_{CF}$ = 130.0 Hz, CF_2), 121.9 (m, CF_2), 159.1 (t, $^2J_{CF}$ = 116.0 Hz, –COO–) ppm. ^{19}F (376 MHz, MeOD) δ −78.7 (m, J = 2.5 Hz, J = 10.5 Hz, J = 22.5 Hz, CF_3), −116.1 (m, $^2J_{FF}$ = 37.0 Hz, $^3J_{FF}$ = 13.5 Hz, $^4J_{FF}$ = 3.0 Hz, –CF_2 COO–), −118.8 to −119.0 (m, CF_2), −119.2 to −119.5 (m, CF_2), −119.9 to −120.1 (m, CF_2), −120.2 to −120.3 (m, CF_2), −123.5 to −123.7 (m, CF_2) ppm.

HRMS: for $C_{20}H_{25}F_{15}O_8Na$ calcd 701.1202, found 701.1300.

*5.1.14. Synthesis of (2S,5S,8S,11S)-2-(2-(2-hydroxyethoxy)ethoxy)ethyl 1,1,1,2,4,4,5,7,7,8,10,10,11,13,13,14,14,14-octadecafluoro-5,8,11-tris(trifluoromethyl)-3,6,9,12-tetraoxatetradecane-2-carboxylate (**15**)*

n-Butyllithium (0.53 ml of a 1.6 M solution in hexanes, 0.85 mmol) was added dropwise over a period of 10 min to a solution of **31** (300 mg, 0.81 mmol) in THF (6 ml) and methoxynonafluorobutane (4 ml) at −78 °C. The reaction was stirred at 22 °C for 1 h before the dropwise addition of pyridine (0.16 ml, 2.01 mmol) and perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl fluoride **3** (1.67 g, 2.01 mmol). The solution was stirred at 22 °C for 30 min before the solvent was removed *in vacuo* at 30 °C. Purification by column chromatography (eluent: 97.5:2.5, v/v, ethyl acetate/methanol) gave the desired ester **33** as a colourless oil (662 mg, 70%).

Benzyl ether deprotection was accomplished via addition of 10% palladium on carbon (30 mg) to a solution of benzyl ether **33** (256 mg, 0.22 mmol) dissolved in methanol (7 ml) and the flask flushed with H_2. The reaction was stirred under an H_2 atmosphere for 18 h at which point the suspension was filtered through celite, and the celite washed thoroughly with methanol. The filtrate was concentrated *in vacuo* and the residue purified by fluorous SPE (dissolved in DMF and applied to a 2 ml cartridge) to give the desired alcohol **15** as a colourless oil (200 mg, 89%). R_f (95:5, v/v, chloroform/methanol) = 0.26.

NMR: ^{1}H (400 MHz, MeOD) δ 3.54 (m, 2H, CH_2), 3.59–3.66 (m, 18H, CH_2), 3.76 (t, J = 4.5 Hz, 2H, CH_2), 4.52–4.64 (m, 2H, CH_2) ppm. ^{13}C (125 MHz, MeOD) δ 62.2 (s, CH_2), 69.2 (s, CH_2), 69.3 (s, CH_2), 71.4 (s, CH_2), 71.5 (s, CH_2), 71.5 (s, CH_2), 71.6 (s, CH_2), 71.6 (s, CH_2), 73.7 (s, CH_2), 100.9 (q, $^1J_{CF}$ = 155.5 Hz, CF_3), 102.4–103.2 (m), 104.5–105.8 (m), 107.8 (q, $^1J_{CF}$ = 155.5 Hz, CF_3), 110.0 (m), 114.4–115.5 (m), 115.9 (d, $^1J_{CF}$ = 112.0 Hz, CF), 116.5–117.8 (m), 118.2 (d, $^1J_{CF}$ = 112.0 Hz, CF), 118.4–120.0 (m), 120.5 (d, $^1J_{CF}$ = 112.0 Hz, CF), 159.5 (d, $^2J_{CF}$ = 124.0 Hz, –COO–) ppm. ^{19}F (376 MHz, MeOD) δ −80.6 to −81.1 (m, $^3J_{FF}$ 5.0 Hz, CF_3), −82.3 to −82.5 (d, $^3J_{FF}$ = 7.0 Hz, CF_3), −83.3 (d, $^3J_{FF}$ = 30.0 Hz, CF_3), −83.5 (d, $^3J_{FF}$ = 26.5 Hz, CF_3), −130.5 (s, CF_2), −131.8 to −132.3 (m, J = 7.0 Hz, J = 23.0 Hz, CF_2), −145.0 to −145.9 (m, J = 7.0 Hz, J = 23.0 Hz, CF) ppm.

HRMS: for $C_{27}H_{25}O_{12}F_{29}Na$ calcd 1115.0775, found 1115.0754.

*5.1.15. Synthesis of 2-(2-(2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)ethoxy)ethoxy)ethanol (**16**)*

Sodium hydride (166 mg of a 60% dispersion in oil, 4.16 mmol) was added to a solution of 3-(perfluorooctyl)-propan-1-ol **1** (1.99 g, 4.16 mmol) in THF (30 ml). The reaction mixture was heated at reflux for 10 min before cooling to 22 °C. A solution of tosylate **30** (0.36 g, 0.83 mmol) in THF (10 ml) was added dropwise and the reaction heated at reflux for 20 min. The reaction was allowed to cool to 22 °C and the solvent was removed *in vacuo*. The residue was dissolved in chloroform (40 ml) and washed with saturated aqueous ammonium chloride solution (40 ml), brine (40 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by fluorous SPE (dissolved in DMF and applied to a 2 ml cartridge) gave the desired fluorous ether **16** as a colourless oil (200 mg, 32%).

NMR: ^{1}H (400 MHz, MeOD) δ 1.85 (m, CH_2, 2H), 2.10–2.25 (tt, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 19.5 Hz, CH_2, 2H), 2.47 (s, OH, 1H), 3.53 (t, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.59 (m, CH_2, 4H), 3.64 (m, CH_2, 17H), 3.71 (m, J = 4.0 Hz, CH_2, 3H) ppm. ^{13}C (125 MHz, MeOD) δ 20.7 (s, CH_2), 28.9 (t, $^2J_{CF}$ = 114.7 Hz, CH_2), 61.7 (s, CH_2), 69.6 (s, CH_2), 70.2 (s, CH_2), 70.2 (s, CH_2), 70.5 (s, CH_2), 70.5 (s, CH_2), 70.5 (s, CH_2), 70.5 (s, CH_2), 70.6 (s, CH_2), 106.6 (m, CF_2), 107.8–109.2 (m, CF_2), 109.9–111.6 (m, CF_2), 112.1–113.7 (m, CF_2), 116.2 (m, CF_2), 118.3 (q, $^2J_{CF}$ = 140.0 Hz, CF_3, 120.5 (t, $2J_{CF}$ = 140.0 Hz, CF_2) ppm. ^{19}F (376 MHz, MeOD) δ −81.1 (t, $^3J_{FF}$ = 10.5 Hz, CF_3), −114.6 (t, $^3J_{FF}$ = 15.0 Hz, CF_2 CH_2), −122.0 (m, CF_2), −122.2 (m, CF_2), −123.0 (m, CF_2), −123.7 (m, CF_2), −126.3 (m, CF_2), −126.3 (m, CF_2) ppm.

HRMS: for $C_{23}H_{31}O_7F_{17}Na$ calcd 765.1673, found 765.1673.

5.2. Creation and observation of droplets in microfluidic devices

Microfluidic devices were created in PDMS (Slygard 184, Dow Corning, Coventry, UK) from CAD designs using standard photolithographic techniques [32,33]. Fluorous coating was applied to the channels using the method of Roach *et al.* [34]. All channels were 50 μm wide and 25 μm deep. Fluids were introduced into device using PE20 tubing (Becton Dickinson, ID 0.38 mm) attached to 1 ml plastic syringes. Fluid flow was controlled using PHD 2000 syringe pumps (Harvard Apparatus, UK). Device performance was observed using a Phantom v7.1 fast camera attached to an Olympus IX70 microscope with 10× and 40× lenses.

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