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Synthesis, emulsification and self-assembly properties of sugar-containing semifluorinated amphiphiles

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Abstract

Surfactants with two and three monosaccharide-based heads and a perfluoroalkyl tail have been synthesized. Perfluoroalkyl C₃-symmetric triol and C₂-symmetric diol were conveniently prepared via Cu-catalyzed azide-alkyne cycloaddition between a fluorinated alkyne and tertiary and secondary azides, respectively. Glycosylation of the perfluoroalkyl diol and triol led to orthoester-type structures, which were evaluated for their capacity to stabilize aqueous emulsions of highly fluorinated anesthetics. The self-assembly properties of the tri-sugar amphiphile were examined by transmission electron microscopy.

1. Introduction

1.1. Fluorinated volatile anesthetics

Highly fluorinated ethers (with the exception of halothane) constitute a class of volatile anesthetics that includes sevoflurane, desflurane, isoflurane (Figure 1). These compounds are used clinically for induction and maintenance of general anesthesia. The fluorinated ethers are low-boiling point liquids at room temperature and are currently administered via the use of an anesthetic vaporizer.¹

As the volatile anesthetic has to be absorbed through the lungs, there is a delay between the change in the rate of administration of the gas and the effect on the patient. Finer control of anesthesia could be achieved with the use of the same agents if they were to be delivered intravenously.² Lipid emulsions have been used as a means of delivery for halothane³⁻⁵ and, more recently, isoflurane and sevoflurane.⁶⁻⁸ However, fluorinated anesthetics, such as sevoflurane, do not mix well with classic non-fluorophilic lipids. For this reason, the largest emulsified concentration of sevoflurane in Intralipid[®], a mixture of phospholipids and soybean oil, is limited to only 3.5% v/v. This concentration is totally inadequate for the

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Supplementary data: Additional TEM images of **11**-based gel, and **13**-based emulsions.

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induction and maintenance of general anesthesia. We have shown in a previous study that the use of a poly(ethylene glycol)-based semifluorinated diblock copolymer as a surfactant can allow the preparation of emulsions containing sevoflurane concentrations up to 30% v/v.² Here we report the synthesis, the emulsifying ability, and the self-assembly properties of fluorinated carbohydrate-based surfactants.

1.2. Nanoemulsions

Emulsions are mixtures of non-miscible liquids. They are not thermodynamically stable and a number of different phenomena can induce phase separation. One main mechanism of destabilization is Ostwald ripening. In this mechanism, individual molecules of the emulsified compound in the emulsion smallest droplets diffuse out in solution and eventually contribute to enlarge the larger emulsion particles. This is due to the difference in curvature between small and large particles, which introduces a difference in chemical potential between molecules in particles of various sizes. The overall effect is a linear increase of droplet volume over time. The rate of increase of the droplet volume over time is a linear function of the interfacial tension and the aqueous solubility of the dispersed perfluorocarbon.⁹⁻¹¹

1.3. Sugar-based semifluorinated surfactants

The first generation of semifluorinated surfactants² were affected by moderate Ostwald ripening. Addition of the FDA-approved perfluorooctyl bromide as a ripening-slowing additive slowed the ripening, but did not eliminate it completely. Like polyethylene glycol, saccharides are also hydrophilic and non-ionic (unless of course, ionic functionalities are present – e.g. sugar phosphates, amino sugars, etc), and have been used to prepare emulsions of perfluorocarbons.¹²⁻¹⁶ Our goal was two-fold – first, it was to investigate the use of saccharide-perfluoroalkyl amphiphiles with respect to the sevoflurane-perfluorooctyl bromide system, and second, it was to explore convenient methods of introducing a perfluoroalkyl chain into a saccharide-based hydrophilic head. Perfluoroalkyl chains have been installed into saccharides by a number of different chemistries: glycosylation,¹⁷⁻²² formal glycosylation,²³⁻²⁴ ether formation,^{13,14,25} ether formation by way of radical addition,^{14,26} acetal formation,²⁷ carbon-carbon bond formation,²⁸ urea,^{29,30} thiourea^{29,31} and carbamate³² formation, phosphoester formation,³³⁻³⁵ ester^{15,26,36} and amide^{23,37-39} formation, as well as thiol-initiated Michael⁴⁰ and free radical⁴¹ addition. In this study we report the synthesis of novel fluoroalkyl sugars surfactants by using Cu-catalyzed azide-alkyne cycloaddition. This synthetic methodology was recently used with excellent results by Klapper⁴², to attach perfluoroethyl- or perfluoropropyl-containing branched functionalities on mono- and disaccharides. In contrast, we have used azide-alkyne cycloadditions to attach single large linear perfluorocarbon groups to branched multi-sugar functionalities. In doing so we had to address a number of synthetic challenges related to the glycosylation of the sugars in the branched functionality. This approach was dictated by the necessity on our side of synthesizing molecules that would be highly water-soluble while maintaining a strong amphiphilic/fluorophilic character. In the end, these studies led us to a class of semifluorinated amphiphiles with interesting self-assembly and pharmaceutical emulsion stabilizing properties.

1.4. Surfactant design

The new surfactant design was based on two features of carbohydrates and their synthesis. First, the ability to easily install and remove various protecting groups allows the preparation and purification of sugar-modified surfactants in their protected form. This is necessary to avoid problems with emulsion formation during aqueous workup and to allow most of the purifications to be done with conventional silica gel chromatography. Second, sugars are often inexpensive raw materials and come in discreet molecular units (e.g. glucose rings), which can be linked together in a symmetric manner. This spatial arrangement leads to simpler NMR spectra and a greater ability to monitor structural changes than in polymeric materials. Finally, we were interested in new methods for introducing fluorophilic substituents in organic molecules. The reactivity of perfluoroalkyl derivatives is strongly modified by the stereoelectronic effects of the fluorine atoms, to the point that not all methodologies developed for organic molecules can be applied in an efficient manner to the synthesis of fluoroalkyl group-containing molecules.⁴³ We reasoned that the highly efficient Cu-catalyzed azide-alkyne cycloaddition would provide an easy entry to the introduction of perfluorinated groups in organic molecules. Perfluoroalkyl acetylenes are ideal for this type of transformation because the perfluoroalkyl chain increases the reactivity of the alkyne, and a variety of chain lengths can be prepared⁴⁴⁻⁴⁷ from available perfluoroalkyl iodides. We were supported in our reasoning by various reports in the literature that fluorinated chains could be introduced in organic molecules with high yield through standard copper-catalyzed azide-alkyne cycloaddition.⁴⁸⁻⁵⁰

Initial studies on perfluoroalkyl mannosides showed that these compounds are highly insoluble in water (Scheme 1 and Table 1). Reduction of the length of the perfluoroalkyl tail improved solubility. Nevertheless, the new molecules with short perfluorinated tails showed very unsatisfactory emulsifying ability. C₃ and C₂-symmetric di- and tri-saccharide structures were then considered.

2. Results and Discussion

2.1. Synthesis

The retrosynthetic approach to a tri-saccharide semifluorinated surfactant is outlined in Scheme 2. The introduction of the perfluoroalkyl block (R_F) can be done before or after glycosylation. Both approaches have their respective benefits, and both were explored. Installation of the fluoroalkyl segment in the late stages would be economical, and would prevent any potential problems of emulsion formation during workup stages. Late introduction of the fluoroalkyl group after glycosylation can also lead to a bulky O-glycosylated azide triol that could be too sterically hindered to undergo azide-alkyne cycloaddition. On the other hand, installation of the perfluoroalkyl moiety before glycosylation would allow solubility in less polar solvents along with reduced hindrance for cycloaddition purposes. However, this latter approach would also lead to an inefficient use of a relatively expensive perfluorinated reagent as well as to potentially difficult purifications due to the amphiphilic nature of the products. An analogous dual approach was taken towards the disaccharide structure.

Tris and 2-amino-1,3-dihydroxypropane were converted into azides by the action of triflic azide.⁵¹ All hydroxyl groups of the azide compound were then acetylated to allow easy purification. Deprotection was carried out under the Zemplen conditions (Scheme 3 and scheme 4).⁵²⁻⁵⁵

The azide-alkyne cycloaddition employing perfluoroalkyl acetylene in an aqueous Cu^{+2} /sodium ascorbate/aqueous alcohol system gave excellent yields, while the direct use of Cu^{+} /organic solvent (THF or DMF) system was sluggish and unreliable in comparison. Purification of triazole derivatives **5** and **8** turned out to be extremely facile as the products could be precipitated from the reaction mixture by addition of excess water and filtration. The following reaction in which molecules **4** and **5** are functionalized with sugar moieties was initially tried with peracetylated saccharides. Unfortunately, reaction in the solvents in which the triols were soluble (acetonitrile, tetrahydrofuran, dichloromethane/nitromethane) failed. The use of dichloromethane, in which the triols are not soluble, also did not lead to any product.

Relatively inexpensive thioglycosides were then selected as potential sugar donors. These compounds offer higher stability as compared to the more commonly used trichloroacetimidates. Commercial β -thiophenyl-peracetylglucoside and α,β -thiocresol-peracetylglucoside, prepared from peracetylglucose,⁵¹ were used as the donors in the subsequent reactions. Initially, we tried glycosylation of hydroxyls of the azide compound (Scheme 5).

This approach led to the formation of tri-O-glycosylated triol when a large excess of the thioglycoside (6 equivalents) and of N-iodosuccinimide (1.5 equivalents/equivalent of donor) were used, although the purification of the azide **9** proved prohibitive and prevented us from obtaining a pure final compound **10**.

Next, glycosylation directly on the perfluoroalkyl triazole **5** (Scheme 6) was attempted. In this case, the use of an excess of both the thioglycoside and NIS yielded the tri-orthoglycosylated product in an 82% yield. After purification, this product was converted in the final compound **11**.

A similar approach applied to diol **8** also yielded the corresponding di-O-glycosylated diol **13** (Scheme 7).

After isolation and purification in their protected form, di-O-glycosylated diol and tri-O-glycosylated triol were deprotected by use of the Zemplen deacetylation conditions yielding pure compounds. The exo-endo orientation of the orthoester linkages could not be unambiguously established, and as such it is not explicitly marked in the structure. However, the configuration is the same in all two/three glycosyl units as indicated by the symmetry of NMR signals.

Our original target had been the preparation of the glycoside derivatives of diol and triol **5** and **7**. However, orthoester formation was observed in all glycosylations of the diols and triols, regardless of whether it was with the azide form (such as **4**), or the fluoroalkyl triazole form (such as **5**). It also made no difference whether the acceptor was a diol or a triol. Thus

it can be ruled out that the introduction of the perfluoroalkyl tail, or steric congestion gave rise to orthoester formation. As the orthoesters **11** and **13** also respond to the definition of amphiphilic molecules as the corresponding glycosides, we investigated these compounds for their self-assembly properties and their ability to stabilize sevoflurane emulsions.

2.2. Emulsification

Compound **13** proved to be freely soluble in water, while **11** did not, due to specific aggregation. Gentle heating of a 10 mg/mL preparation allowed **11** to dissolve, however the solution quickly transformed into a gel upon cooling.

Emulsion preparations using 2.9% w/v of each surfactant (20% v/v sevoflurane, 10% v/v perfluorooctyl bromide) were then attempted. After homogenization, an emulsion prepared with **13** had an appearance of a milky liquid that slowly settled. Microfluidization produced a free-flowing emulsion that slowly settled on standing. No large gel clumps were observed in the preparation upon a thorough visual examination; none developed upon standing at 4 °C for several months. The low temperature was used both to avoid loss of sevoflurane due to evaporation and to improve emulsion stability. Particle size of the emulsion was measured as a function of storage time (Figure 2). Emulsions prepared with **11** appeared to be homogeneous from the spout of the microfluidizer, but after collection in a centrifuge tube, they immediately set to a gel with big white globs. A further round of homogenization-microfluidization produced the same outcome. The gelled emulsion was stored at 4 °C and did not exhibit any signs of separation after two months. During that time, the gel had become quite firm and would not move when the tube containing it was inverted. Of course, gelation prevents any possible intravenous applications for this emulsion.

While **13** could stabilize a sevoflurane/PFOB emulsion as the sole surfactant, the produced particle size was not acceptable for intravenous applications. Particles with sizes greater or close to 1000 nm can obstruct capillaries, and thus the particle size of any emulsion destined for intravenous use has to be way below that value. As such, the **13**-based emulsion does not meet this criterion.

2.3. Electron microscopy

A direct visualization of microscopic structures formed by the **11** gel and the **13**-based emulsion was possible by the use of transmission electron microscopy (TEM). Emulsion prepared with **13** was shown to contain droplets of up to ca. 100 nm in diameter embedded in plaque-like islands (Figure 3). The islands (with embedded droplets) were likely the aggregates characterized by DLS, as the nanodroplets' diameters are much smaller than the measured emulsion particle size. The most interesting aggregates were obtained with **11**. TEM imaging of its aqueous gel (total surfactant concentration 10 mg/mL) revealed formation of ribbon-like structures that were sometimes twisted into helices (Figure 4). The fibrils were primarily straight, but occasionally exhibited curvature (A). The observed fibrils were classified into three categories: (B) single helices with a high degree of twist, (C) single helices with a low degree of twist, and (D) double coiled helices, which appeared to be composed of two coiled single helices. Supplementary information contains additional TEM pictures showing further interesting self-assembly architectures.

3. Conclusions

The introduction of a perfluoroalkyl group by Cu-catalyzed azide-alkyne cycloaddition was found to be easy and convenient under Cu^{+2} /sodium ascorbate conditions. The increased hydrophobicity of the molecules due to the perfluoroalkyl groups did not affect reactivity. Glycosylation of multiple hydroxyls proved problematic due to markedly decreased solubility of polyols in dichloromethane (as compared to perfluoroalkyl mono-alcohols). A more significant problem was discovered in the exclusive formation of orthoester-type structures rather than glycosides. The orthoester **13** was freely soluble in water and was capable of stabilizing (at the concentration of 2.9 % w/v) a 20% v/v sevoflurane and 10% v/v perfluorooctyl bromide oil-in-water emulsion. The emulsion was stable at 4 °C, but the particle size was too large to be used for intravenous administration. The tri-O-glycosylated triol was not soluble in water, but instead led to the formation of a gel. The gel was observed to consist of left-handed helical fibers of several distinct morphologies.

4. Experimental

4.1. General methods

All reactions were carried out in oven-dried glassware under a positive pressure of argon. Dichloromethane, tetrahydrofuran and toluene were purified with a Solvent Dispensing System. Acetonitrile was distilled from calcium hydride immediately before use. Reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel 60 F₂₅₄ plates (0.25mm), visualized by ultraviolet light and/or by staining with anisaldehyde. NMR spectra were obtained on either Varian Inova 400 MHz or 500 MHz spectrometers at 25 °C. Data were reported as follows: chemical shift on the δ scale (using either TMS or residual protio solvent as internal standard), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in hertz, integration, and assignment. ^{19}F chemical shift referencing was made indirectly, against a separate sample containing 0.05% $\text{C}_6\text{H}_5\text{CF}_3$ in C_6D_6 as a secondary reference with a chemical shift of -62.9 ppm, compared to neat CFCl_3 at 0.00 ppm as a primary reference.

4.2. Solubility Determination

Solubilities of fluoroalkyl/alkyl mannosides were determined by HPLC. Calibration curves were constructed from methanolic solutions of pure compounds (all were freely soluble in methanol). Saturated aqueous solutions of the surfactants were prepared by suspending an excess amount of material in 1 mL of water and subjecting the sample to sonication for 1 hr at 70 °C. Following sonication, the samples were cooled at room temperature overnight. They were then spun down in a mini-centrifuge for 10 minutes. Aliquots of the supernatant were used for analysis.

4.3. Emulsion Preparation

Sevoflurane (3.4 mL) and perfluorooctyl bromide (1.7 mL) were added to an aqueous 0.9% NaCl solution (11.9 mL) of surfactant (500 mg), for a total volume of 17 mL. The two-phase mixture was homogenized with a low energy mixer for 1 min at 21000 rpm at room temperature. The crude emulsion was further homogenized under high pressure (5000-6000

psi, 1 min) using a microfluidizer with the temperature maintained at 20 °C with a cooling bath. The product emulsions of 20% (v/v) sevoflurane were stored in 50 mL, sterile centrifuge tubes at 4 °C to prevent evaporation of sevoflurane.

4.4. Dynamic Light Scattering

Prior to sizing, the emulsions were mixed by inversion of the centrifuge tube to eliminate inhomogeneity due to either flocculation or sedimentation. The emulsions were diluted by a factor of 300 by adding 10 μ L of emulsion to 2.990 mL of millipore water. Sizing was done by dynamic light scattering with a 639 nm laser at a scattering angle of 90 degrees. Each sample was analyzed 3 times for 7 min at room temperature. All numbers are reported as Gaussian volume weighted. Volume weighting, rather than number weighting, was reported because the former is more accurately determined by laser diffraction and because it more accurately reflects the average size of the bulk of the oil in an emulsion.

4.5. Transmission Electron Microscopy

Aqueous suspensions of samples were briefly deposited onto 200 mesh Ni pioloform grids and excess solution was wicked off with a filter paper. The grids were then stained with Nano-W stain (Nanoprobe Inc., Yaphank, NY) and analyzed using an microscope. For **11**, a sample of the gel produced by 10 mg of compound in 1 mL water was taken. For **13**, a sample of the DLS solution (10 μ L emulsion in 3 mL water) was used.

4.6. Synthesis

4.6.1. General procedure for glycosylation of fluoroalkyl and alkyl alcohols—

Perfluoroalkyl/alkyl alcohol (1 g) and peracetyl- α -mannose (1.5 eq) were dissolved in CH_2Cl_2 (45 mL), to which FeCl_3 (3 eq) was quickly transferred. After 3 to 4 hours of stirring at room temperature the reaction was quenched by addition of $\text{NaHCO}_3(\text{aq})$ which caused the iron to precipitate as brick-colored $\text{Fe}_2(\text{CO}_3)_3$. The biphasic mixture was filtered through celite to remove the inorganic salts, and worked up with CH_2Cl_2 and $\text{NaHCO}_3(\text{aq})$. The organic portions were combined and dried with MgSO_4 . Chromatography over silica gel (100 mL SiO_2 , eluted with a 15-50% ethyl acetate/hexanes gradient) gave the desired products as white foams, or viscous oils.

4.6.2. General procedure for deprotection of fluoroalkyl mannoside acetates—

Perfluoroalkyl/alkyl mannoside acetate (2 g) was dissolved in methanol (45 mL), to which a catalytic amount of sodium methoxide (0.020-0.030 g) was added. After stirring overnight at room temperature the reaction was quenched with washed Amberlite IR120 H^+ -form resin. After filtration of the resin, the solution was evaporated to dryness by rotary evaporation and used without further purification.

4.6.9. 1-O-(1H,1H-perfluorononyl)-2,3,4,6-tetra-O-acetyl- α -D-mannopyranose

(1a)—Yield 88%. ^1H NMR: (399.8 MHz, CDCl_3) δ 5.34-5.29 (H2,H3,H4, m, 3H), 4.92 (H1, d, J = 1.4 Hz, 1H), 4.28 (H6, dd, J = 5.7, 12.4 Hz, 1H), 4.18-4.03 (H6, O-CH2-R_F, m, 3H), 3.99 (H5, m, 1H), 2.17 (OAc, s, 3H), 2.10 (OAc, s, 3H), 2.06 (OAc, s, 3H), 2.00 (OAc, s, 3H); ^{13}C NMR: (100.5 MHz, CDCl_3) δ 170.7, 170.0, 169.9, 98.4 ($J_{\text{C-H}} = 173.9$ Hz), 69.7,

69.1, 68.7, 65.9, 64.4 (t), 62.5, 20.9, 20.8, 20.8, 20.7; ^{19}F NMR: (376.1 MHz, CDCl_3) δ -81.27 (3F), -120.16 (2F), -122.35 (4F), -123.17 (2F), -123.64 (2F), -126.60 (2F);

4.6.7. 1-O-(1H,1H-perfluoroheptyl)-2,3,4,6-tetra-O-acetyl- α -D-mannopyranose (1b)—Yield 65%. ^1H NMR: (499.7 MHz, CDCl_3) δ 5.34-5.28 (H2,H3,H4, m, 3H), 4.92 (H1, d, J = 1.4 Hz, 1H), 4.27 (H6, dd, J = 5.7, 12.3 Hz, 1H), 4.19-4.02 (H6, O-CH₂-R_F, m, 3H), 3.99 (H5, m, 1H), 2.17 (OAc, s, 3H), 2.10 (OAc, s, 3H), 2.06 (OAc, s, 3H), 2.00 (OAc, s, 3H); ^{13}C NMR: (125.7 MHz, CDCl_3) δ 170.7, 170.1, 170.0, 98.5 ($J_{\text{C-H}}$ = 173.8 Hz), 69.8, 69.1, 68.7, 66.0, 64.5 (t), 62.5, 21.0, 20.9, 20.8 ($\times 2$); ^{19}F NMR: (470.2 MHz, CDCl_3) δ -81.17 (3F), -120.06 (2F), -122.47 (2F), -123.16 (2F), -123.62 (2F), -126.52 (2F);

4.6.5. 1-O-(1H, 1H-perfluoropentyl)-2, 3, 4, 6-tetra-O-acetyl- α -D-mannopyranose (1c)—Yield 79%. ^1H NMR: (399.8 MHz, CDCl_3) δ 5.34-5.28 (H2,H3,H4, m, 2H), 4.92 (H1, d, J = 1.4 Hz, 1H), 4.27 (H6, dd, J = 5.8, 12.4 Hz, 1H), 4.14 (H6, dd, J = 2.5, 12.3 Hz, 1H), 4.20-3.95 (O-CH₂-R_F, m, 2H), 3.99 (H5, m, 1H), 2.17 (OAc, s, 3H), 2.10 (OAc, s, 3H), 2.06 (OAc, s, 3H), 2.00 (OAc, s, 3H); ^{13}C NMR: (100.5 MHz, CDCl_3) δ 170.7, 170.0, 169.9, 98.4 ($J_{\text{C-H}}$ = 172.9 Hz), 69.7, 69.1, 68.7, 65.9, 64.3 (t), 62.5, 21.0, 20.8, 20.8; ^{19}F NMR: (376.1 MHz, CDCl_3) δ -81.36 (3F), -120.35 (2F), -124.64 (2F), -126.70 (2F);

4.6.3. 1-O-(1H, 1H-perfluorobutyl)-2,3,4,6-tetra-O-acetyl- α -D-mannopyranose (1d)—Yield: 68%. ^1H NMR: (399.8 MHz, CDCl_3) δ 5.34-5.29 (H2,H3,H4, m, 3H), 4.92 (H1, d, J = 1.4 Hz, 1H), 4.27 (H6, dd, J = 5.6, 12.3 Hz, 1H), 4.17-3.96 (H6, O-CH₂-R_F, H5, m, 4H), 2.17 (OAc, s, 3H), 2.10 (OAc, s, 3H), 2.06 (OAc, s, 3H), 2.00 (OAc, s, 3H); ^{13}C NMR: (100.5 MHz, CDCl_3) δ 170.7, 170.0, 169.9, 98.4 ($J_{\text{C-H}}$ = 175.2 Hz), 69.7, 69.1, 68.7, 65.9, 64.2 (t), 62.5, 21.0, 20.8, 20.8; ^{19}F NMR: (376.1 MHz, CDCl_3) δ -81.26 (3F), -121.04 (2F), -127.94 (2F);

4.6.10. 1-O-(1H, 1H-perfluorononyl)- α -D-mannopyranose (2a)—Yield: quantitative. ^1H NMR: (399.8 MHz, CD_3OD) δ 4.86 (H1, d, J = 1.6 Hz, 1H), 4.25 (O-CH-R_F, qt, J = 1.4, 14.3 Hz, 1H), 4.12 (O-CH-R_F, qt, J = 1.3, 13.6 Hz, 1H), 3.87-3.81 (H2,H3, m, 2H), 3.67 (H4, dd, J = 6.3, 11.8 Hz, 1H), 3.64 (H6, dd, J = 3.1, 9.3 Hz, 1H), 3.59 (t, J = 9.4 Hz, 1H), 3.50 (H5, ddd, J = 2.0, 6.2, 9.3 Hz, 1H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 101.1, 74.5, 71.0, 70.3, 67.0, 63.5 (t), 61.6; ^{19}F NMR: (376.1 MHz, CD_3OD) δ -82.82 (3F), -121.16 (2F), -121.19 (4F), -123.38 (2F), -124.18 (2F), -124.49 (2F), -127.74 (2F), -127.76 (2F); HRMS (ESI) Calculated for $\text{C}_{15}\text{H}_{13}\text{F}_{17}\text{O}_6\text{Na}$, 635.0333; Found, 635.0330.

4.6.8. 1-O-(1H, 1H-perfluoroheptyl)- α -D-mannopyranose (2b)—Yield: quantitative. ^1H NMR: (399.8 MHz, CD_3OD) δ 4.86 (H1, d, J = 1.6 Hz, 1H), 4.25 (O-CH-R_F, qt, J = 1.7, 13.5 Hz, 1H), 4.12 (O-CH-R_F, qt, J = 1.7, 13.5 Hz, 1H), 3.87-3.81 (H2,H3, m, 2H), 3.67 (H4, dd, J = 6.3, 11.8 Hz, 1H), 3.64 (H6, dd, J = 3.1, 9.3 Hz, 1H), 3.59 (H6, t, J = 9.3 Hz, 1H), 3.50 (H5, ddd, J = 2.2, 6.3, 9.3 Hz, 1H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 101.1, 74.5, 71.0, 70.3, 67.0, 63.5 (t), 61.7; ^{19}F NMR: (376.1 MHz, CD_3OD) δ -82.87 (3F), -121.21 (2F), -123.64 (2F), -124.31 (2F), -124.55 (2F), -127.79 (2F); HRMS (ESI) Calculated for $\text{C}_{13}\text{H}_{13}\text{F}_{13}\text{O}_6\text{Na}$, 535.0397; Found, 535.0402.

4.6.6. 1-O-(1H, 1H-perfluoropentyl)- α -D-mannopyranose (2c)—Yield:

quantitative. ^1H NMR: (399.8 MHz, CD_3OD) δ 4.85 (H1, d, $J = 1.7$ Hz, 1H), 4.25 (O-CH- R_F , qt, $J = 1.6, 13.7$ Hz, 1H), 4.12 (O-CH- R_F , qt, $J = 1.6, 13.7$ Hz, 1H), 3.86-3.81 (H2,H3, m, 2H), 3.67 (H4, dd, $J = 6.4, 11.9$ Hz, 1H), 3.64 (H6, dd, $J = 3.2, 9.3$ Hz, 1H), 3.58 (H6, t, $J = 9.3$ Hz, 1H), 3.49 (H5, ddd, $J = 2.2, 6.3, 9.1$ Hz, 1H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 101.1, 74.5, 71.0, 70.3, 67.0, 63.4 (t), 61.7; ^{19}F NMR: (376.1 MHz, CD_3OD) δ -83.03 (3F), -121.46 (2F), -125.56 (2F), -127.99 (2F); HRMS (ESI) Calculated for $\text{C}_{11}\text{H}_{13}\text{F}_9\text{O}_6\text{Na}$, 435.0461; Found, 435.0464.

4.6.4. 1-O-(1H, 1H-perfluorobutyl)- α -D-mannopyranose (2d)—Yield:

quantitative. ^1H NMR: (399.8 MHz, CD_3OD) δ 4.85 (H1, d, $J = 1.7$ Hz, 1H), 4.24 (O-CH- R_F , qt, $J = 1.4, 14.3$ Hz, 1H), 4.10 (O-CH- R_F , qt, $J = 1.4, 13.7$ Hz, 1H), 3.86-3.81 (H2,H3, m, 2H), 3.67 (H4, dd, $J = 6.4, 11.9$ Hz, 1H), 3.64 (H6, dd, $J = 3.2, 9.5$ Hz, 1H), 3.58 (H6, t, $J = 9.5$ Hz, 1H), 3.49 (H5, ddd, $J = 2.2, 6.3, 9.0$ Hz, 1H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 101.1, 74.5, 71.0, 70.3, 67.0, 63.2 (t), 61.7; ^{19}F NMR: (376.1 MHz, CD_3OD) δ -82.99 (3F), -122.21 (2F), -129.13 (2F); HRMS (ESI) Calculated for $\text{C}_{10}\text{H}_{13}\text{F}_7\text{O}_6\text{Na}$, 385.0493; Found, 385.0499.

4.6.16. 2-(acetoxymethyl)-2-azidopropane-1,3-diyl diacetate (3)—Reaction was

carried out analogously to the preparation of **6**, using the following amounts of materials: sodium azide (2.715 g, 41.8 mmol), triflic acid (3.5 mL, 20.8 mmol) dissolved in 10 mL dichloromethane and 10 mL water. Tris (1.044 g, 8.62 mmol), triethylamine (3 mL, 21.5 mmol), zinc chloride (0.055 g, 0.403 mmol) were dissolved in 65 mL total of 3:10:3 dichloromethane:methanol:water. Acetylation was performed in 50 mL of acetic anhydride with sodium acetate (2.3 g, 28.9 mmol). Chromatography was carried out on 100 mL of SiO_2 eluting with a 10-30% ethyl acetate/hexanes gradient. Product was isolated as a clear, somewhat viscous oil. Yield: 2.331 g, 99%. ^1H NMR: (399.8 MHz, CDCl_3) δ 4.24 (O-CH₂, s, 6H), 2.12 (OAc, s, 9H); ^{13}C NMR: (100.5 MHz, CDCl_3) δ 170.3, 63.3, 62.8, 20.8; HRMS (ESI) Calculated for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_6\text{Na}$, 296.0854; Found, 296.0856.

4.6.17. 2-azido-2-(hydroxymethyl)propane-1,3-diol (4)—Reaction was carried out

analogously to the preparation of **7**, using the following amounts of materials: **3** (2.323 g, 8.50 mmol), sodium methoxide (0.025 g, 0.463 mmol). Yield: 1.309 g, quantitative. ^1H NMR: (399.8 MHz, CD_3OD) δ 4.82 (OH, s, 3H), 3.64 (O-CH₂, s, 6H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 67.7, 61.8; HRMS (ESI) Calculated for $\text{C}_4\text{H}_9\text{N}_3\text{O}_3\text{Na}$, 170.0537; Found, 170.0532.

4.6.18. 2-(hydroxymethyl)-2-(4-(perfluorohexyl)-1H-1,2,3-triazol-1-

yl)propane-1,3-diol (5)—Reaction was carried out analogously to the preparation of **8, using the following amounts of materials: **4** (1.163 g, 7.90 mmol), perfluorohexylacetylene (3.385 g, 9.84 mmol), sodium ascorbate (0.786 g, 3.97 mmol), 3 drops of saturated CuSO_4 solution. Yield: 3.724 g, 96%. ^1H NMR: (399.8 MHz, CD_3OD) δ 8.60 (HC=C, s, 1H), 4.08 (O-CH₂, s, 6H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 126.3, 71.2, 61.5; ^{19}F NMR: (376.1 MHz, CD_3OD) δ -82.86 (3F), -110.16 (2F), -123.02 (2F), -123.89 (2F), -124.30 (2F),**

-127.76 (2F); HRMS (ESI) Calculated for $C_{12}H_{10}F_{13}N_3O_3Na$, 514.04068; Found, 514.03964.

4.6.11. 1,3-diacetoxy-2-azidopropane (6)—Sodium azide (4.28 g, 65.8 mmol) was dissolved in 12 mL of water and to this mixture 12 mL of dichloromethane were added. The mixture was cooled to 0 °C and triflic anhydride (5.5 mL, 32.7 mmol) was slowly added via syringe. The mixture turned cloudy initially, but cleared up over a period of about 30 minutes. After stirring for 2 hours in the ice bath, the dichloromethane layer was separated and added to the mixture of 2-amino-1,3-dihydroxypropane, triethylamine, and zinc chloride. The aqueous layer was further washed twice with small amounts of dichloromethane. The washings were added to the second reaction as well. While the reaction between sodium azide and triflic anhydride was taking place, 2-amino-1,3-dihydroxypropane (1 g, 11.0 mmol) was dissolved in a 3:10:3 mixture of dichloromethane:methanol:water (80 mL total), to which were added triethylamine (4.8 mL, 34.4 mmol) and zinc chloride (0.038 g, 0.279 mmol). Once the solution of triflic azide has been added, the reaction was allowed to proceed overnight and was concentrated down to a syrup the next day. To the syrup excess acetic anhydride (50 mL) as well as anhydrous sodium acetate (2.25 g, 27.4 mmol) were added and the reaction was heated so that it just reached the boiling point of the solvent (Ac_2O) and was allowed to cool. Acetic anhydride was then removed by rotary evaporation and the crude was worked up with sodium bicarbonate and dichloromethane. After separation and drying ($MgSO_4$) of organic portions, they were concentrated and chromatographed over silica gel (100 mL SiO_2 , eluting with a 15-35% gradient of ethyl acetate/hexanes) to give the product as a clear oil. Yield: 2.057 g, 93%. 1H NMR: (399.8 MHz, $CDCl_3$) δ 4.23 (O-CH₂, dd, J = 4.8, 11.7 Hz, 2H), 4.15 (O-CH₂, dd, J = 6.8, 11.7 Hz, 2H), 3.89 (CH-N₃, tt, J = 4.7, 6.8 Hz, 1H), 2.11 (OAc, s, 6H); ^{13}C NMR: (100.5 MHz, $CDCl_3$) δ 170.6, 63.4, 58.7, 20.8; HRMS (ESI) Calculated for $C_7H_{11}N_3O_4Na$, 224.0642; Found, 224.0643.

4.6.12. 1,3-dihydroxy-2-azidopropane (7)—7 (2.014 g, 10.0 mmol) was dissolved in methanol, to which sodium methoxide was added (0.017 g, 0.315 mmol). After being allowed to react for an overnight period, the reaction was quenched with Amberlite IR-120H⁺ resin. Filtration of the resin, and rotary evaporation gave the product as a clear oil. Yield: 1.192 g, quantitative. 1H NMR: (399.8 MHz, CD_3OD) δ 3.65 (O-CH₂, dd, J = 4.5, 11.4 Hz, 2H), 3.54 (O-CH₂, dd, J = 6.7, 11.4 Hz, 2H), 3.49-3.42 (CH-N₃, m, 1H); ^{13}C NMR: (100.5 MHz, CD_3OD) δ 65.4, 61.6; HRMS (ESI) Calculated for $C_3H_5N_3O_1$ ($M^+ - H_2O$), 99.0428; Found, 99.0428.

4.6.13. 2-(4-(perfluorohexyl)-1H-1,2,3-triazol-1-yl)propane-1,3-diol (8)—Perfluorohexylacetylene (0.080 g, 0.233 mmol) was weighed out into an empty flask, to which 2-azido-1,3-dihydroxypropane (0.020 g, 0.171 mmol) and 90% MeOH/ H_2O solvent mixture (5 mL) were added. After dissolution, sodium ascorbate (0.017 g, 0.085 mmol) was added (it did not immediately dissolve), followed by 2 drops of a saturated $CuSO_4$ solution. After stirring together for an overnight period, the mixture was concentrated by rotary evaporation. The residue was washed with water and collected by filtration. Yield: 0.082 g, 100%. 1H NMR: (399.8 MHz, CD_3CN) δ 8.36 (HC=C, s, 1H), 4.75 (CH-N, tt, J = 4.8, 6.6

Hz, 1H), 3.93 (O-CH₂, m, 4H), 3.24 (OH, t, J = 5.5 Hz, 2H); ¹³C NMR: (100.5 MHz, CD₃CN) δ 126.4, 66.1, 61.1; ¹⁹F NMR: (376.1 MHz, CD₃CN) δ -82.03 (3F), -109.46 (2F), -122.46 (2F), -123.47 (2F), -123.71 (2F), -127.07 (2F); HRMS (ESI) Calculated for C₁₁H₈F₁₃N₃O₂Na, 484.0302; Found, 484.0320.

4.6.19. 3,4,6-tri-O-acetyl-D-glucopyranose 1,2 - (2-azido - [1,3 - bis (3,4,6 - tri - O - acetyl -D-glucopyranos-1,2-O-(1-ethyliden-1-yloxy)propan-2-yl)methyl] orthoacetate) (9)—Reaction was carried out analogously to the preparation of **12**, using the following amounts of materials: **4** (0.015 g, 0.102 mmol), thiocresol-2,3,4,6-tetra-O-acetyl-α,β-D-glucoside (0.278 g, 0.612 mmol), N-iodosuccinimide (0.142 g, 0.631 mmol), triflic acid (1 uL, 0.011 mmol). Yield: 0.113 g, % not determined. H NMR: (499.7 MHz, CDCl₃) δ 5.73 (H1, d, J = 5.3 Hz, 3H), 5.18 (H3, t, J = 3.0 Hz, 3H), 4.90 (H4, dd, J = 3.0, 9.5 Hz, 3H), 4.34 (H2, dd, J = 3.0, 5.3 Hz, 3H), 4.20 (H6, d, J = 5.0 Hz, 3H), 4.19 (H6, d, J = 3.3 Hz, 3H), 3.92 (H5, ddd, J = 3.4, 5.0, 12.8 Hz, 3H), 3.56 (O-CH₂, d, J = 9.5 Hz, 6H), 3.53 (O-CH₂, d, J = 9.5 Hz, 6H), 2.12 (OAc, s, 9H), 2.10 (OAc, s, 9H), 2.09 (OAc, s, 9H), 1.71 (MeCO₃, s, 9H); ¹³C NMR: (125.7 MHz, CDCl₃) δ 170.9, 169.9, 169.4, 121.5, 97.3, 73.6, 70.3, 68.3, 67.5, 64.3, 63.4, 63.3, 21.0; HRMS (ESI) Calculated for C₄₆H₆₃N₃O₃₀Na, 1160.33886; Found, 1160.34190.

4.6.20. 1 - [1,3 - bis (3,4,6 - tri - O - acetyl - D - glucopyranos - 1,2 - O - (1 - ethyliden - 1 - yloxy)-2-((3,4,6-tri - O - acetyl - D - glucopyranos - 1,2 - O - (1-ethyliden-1-yloxy) methyl) propan - 2 - yl] - 4 - perfluorohexyl - 1H-1,2,3-triazole (10)—**Method A.** Reaction was carried out analogously to the preparation of **12**, using the following amounts of materials: **5** (0.103 g, 0.210 mmol), thiophenol-2,3,4,6-tetra-O-acetyl-β-D-glucoside (0.538 g, 1.22 mmol), N-iodosuccinimide (0.413 g, 1.84 mmol), triflic acid (1.8 uL, 0.022 mmol). Yield: 0.254 g, 82% **Method B.** Perfluorohexylacetylene (0.120 g, 0.349 mmol) was weighed out into an empty flask, to which **9** (crude, 0.204 g, 0.179 mmol) and 90% MeOH/H₂O solvent mixture (10 mL) were added. After dissolution, sodium ascorbate (0.017 g, 0.085 mmol) was added (it did not immediately dissolve), followed by 3 drops of a saturated CuSO₄ solution. After stirring together for an overnight period, the mixture was concentrated by rotary evaporation. The residue was washed with water and collected by filtration. Yield: 0.238 g, 90%. ¹H NMR: (499.7 MHz, CDCl₃) δ 8.02 (HC=C, s, 1H), 5.59 (H1, d, J = 5.1 Hz, 3H), 5.15 (H3, t, J = 3.1 Hz, 3H), 4.89 (H4, dd, J = 3.0, 9.5 Hz, 3H), 4.18 (H6, d, J = 5.0 Hz, 3H), 4.18 (H6, d, J = 3.3 Hz, 3H), 4.10 (H2, dd, J = 3.1, 5.2 Hz, 3H), 4.04 (O-CH, d, J = 9.7 Hz, 3H), 3.97 (O-CH, d, J = 9.7 Hz, 3H), 3.89 (H5, ddd, J = 3.4, 4.9, 9.5 Hz, 3H), 2.11 (OAc, s, 9H), 2.09 (OAc, s, 9H), 2.09 (OAc, s, 9H), 1.68 (MeCO₃, s, 9H); ¹³C NMR: (125.7 MHz, CDCl₃) δ 170.9, 169.8, 169.4, 125.1, 121.5, 97.3, 73.9, 70.1, 68.1, 67.7, 67.3, 63.2, 62.81, 21.2, 21.0, 21.0, 20.8; ¹⁹F NMR: (470.2 MHz, CDCl₃) δ -81.10 (3F), -108.95 (2F), -121.83 (2F), -122.55 (2F), -123.12 (2F), -126.45 (2F); HRMS (ESI) Calculated for C₅₄H₆₄F₁₃N₃O₃₀Na, 1504.32593; Found, 1504.32355.

4.6.21. 1 - [1,3 - bis (D - glucopyranos - 1,2 - O - (1 - ethyliden - 1 - yloxy) - 2 - ((3,4,6 - tri-O-acetyl - D - glucopyranos - 1,2-O - (1-ethyliden-1-yloxy)methyl)propan-2-yl]-4-perfluorohexyl-1H-1,2,3-triazole (11)—Reaction was carried out analogously to the preparation of **13**, using the following amounts of materials:

10 (1.069 g, 0.721 mmol), sodium methoxide (0.020 g, 0.370 mmol). Yield: 0.846 g, quantitative. ¹H NMR: (399.8 MHz, CD₃OD) δ 8.65 (HC=C, s, 1H), 5.65 (H1, d, J = 5.2 Hz, 3H), 4.17 (H2, t, J = 4.7 Hz, 3H), 4.05 (O-CH, d, J = 9.7 Hz, 3H), 4.01 (O-CH₂, d, J = 9.6 Hz, 3H), 3.78 (H3, t, J = 4.9 Hz, 3H), 3.76 (H6, dd, J = 2.3, 11.5 Hz, 3H), 3.63 (H6, dd, J = 5.6, 12.0 Hz, 3H), 3.53 (H5, ddd, J = 2.3, 5.6, 9.2 Hz, 3H), 3.44 (H4, dd, J = 5.0, 9.2 Hz, 3H), 1.60 (MeCO₃, s, 9H); ¹³C NMR: (100.5 MHz, CD₃OD) δ 126.0, 121.0, 97.9, 77.9, 73.8, 73.2, 69.0, 67.8, 61.9, 61.5, 21.1; ¹⁹F NMR: (376.1 MHz, CD₃OD) δ -82.79 (3F), -110.29 (2F), -122.92 (2F), -123.99 (2F), -124.22 (2F), -127.69 (2F); HRMS (ESI) Calculated for C₃₆H₄₆F₁₃N₃O₂₁Na, 1126.2309; Found, 1126.2356.

4.6.14. 1,3-di-O-(3,4,6-tri-O-acetyl-glucopyrano-1,2-O-orthoacetyl)-2-(4-(perfluorohexyl)-1H-1,2,3-triazol-1-yl)propane-1,3-diol (12)—8 (0.082 g, 0.178 mmol) and thiophenol-2,3,4,6-tetra-O-acetyl-β-D-glucoside (0.313 g, 0.711 mmol) were dissolved in dry distilled acetonitrile and cooled to -35° C by action of 30% ethanol/ethylene glycol dry-ice bath. After 5-10 minutes in the cold bath, N-iodosuccinimide was added to the reaction (0.241 g, 1.071 mmol) followed by triflic acid (1.6 uL, 0.018 mol). After warming up to ca. 0 °C, the reaction was quenched by addition of aqueous sodium bicarbonate and 10% sodium thiosulfate. The mixture was worked up directly with dichloromethane and sodium bicarbonate. After the pooling and drying (MgSO₄), the organic fractions were chromatographed over silica gel (100 mL SiO₂, eluting with a 35-75% ethyl acetate/hexanes gradient). Fractions eluted with ca. 55% ethyl acetate/hexanes and containing the product were collected and subjected to another chromatographic separation (100 mL SiO₂, eluting with a gradient of 0-1.5% methanol/chloroform). The product was isolated as a white foam. Yield: 0.205 g, 63%. ¹H NMR: (399.8 MHz, CDCl₃) δ 7.96 (HC=C, s, 1H), 5.51 (H1, d, J = 5.2 Hz, 1H), 5.47 (H1', d, J = 5.2 Hz, 1H), 5.07 (H3,H3', t, J = 2.8 Hz, 2H), 4.86 (CH-N, m, 1H), 4.83 (H4, dd, J = 2.7, 9.5 Hz, 1H), 4.82 (H4', dd, J = 2.7, 9.5 Hz, 1H), 4.12 (H6, H6', m, 4H), 4.06-3.23 (H2,H2',H5,H5', m, 8H), 2.05 (OAc, s, 3H), 2.04 (OAc, s, 3H), 2.03 (OAc, s, 6H), 2.02 (OAc, s, 6H), 1.61 (MeCO₃, s, 6H); ¹³C NMR: (100.5 MHz, CDCl₃) δ 170.8, 169.7, 169.3, 137.4 (t), 125.5, 121.3, 97.2, 97.1, 73.6, 70.1, 68.1, 67.5, 67.5, 63.1, 62.2, 62.1, 61.1, 20.8, 20.7; ¹⁹F NMR: (376.1 MHz, CDCl₃) δ -81.26 (3F), -109.18 (2F), -121.95 (2F), -122.73 (2F), -123.24 (2F), -126.58 (2F); HRMS (ESI) Calculated for C₃₉H₄₄F₁₃N₃O₂₀Na, 1144.22028; Found, 1144.22028.

4.6.15. 1-(1,3-bis [D-glucopyranos -1,2-O - (1-ethyliden - 1 - yloxy)] propan - 2 - yl) - 4-perfluorohexyl-1H-1,2,3-triazole (13)—12 (1.258 g, 1.121 mmol) was dissolved in methanol, to which a catalytic amount of sodium methoxide was added (0.021 g, 0.389 mmol). The reaction was allowed to proceed overnight and was quenched by addition of IR78 weak acid resin. After filtration of the resin and evaporation of the solvent, product was obtained as a slightly-yellow foam. Yield: 1.027 g, quantitative. ¹H NMR: (399.8 MHz, CD₃OD) δ 8.62 (HC=C, s, 1H), 5.60 (H1, d, J = 5.2 Hz, 1H), 5.57 (H1', d, J = 5.2 Hz, 1H), 5.03 (CH-N, tt, J = 4.8, 7.2 Hz, 1H), 4.10 (H2, t, J = 4.7 Hz, 1H), 4.08 (H2', t, J = 4.7 Hz, 1H), 4.01 (O-CH₂, dt, J = 7.3, 10.5 Hz, 2H), 3.95 (O-CH₂, dt, J = 4.6, 10.4 Hz, 2H), 3.75 (H3,H3',H6,H6', m, 4H), 3.62 (H4,H4', dd, J = 5.6, 12.0 Hz, 2H), 3.51 (H5,H5', ddd, J = 2.2, 5.6, 9.0 Hz, 2H), 3.42 (H6,H6', dd, J = 5.2, 9.3 Hz, 2H), 1.57 (MeCO₃, s, 6H); ¹³C NMR: (100.5 MHz, CD₃OD) δ 126.5, 121.1, 97.9, 77.9, 77.9, 73.8, 73.3, 68.9,

61.9, 61.6, 21.2; ^{19}F NMR: (376.1 MHz, CD_3OD) δ -82.80 (3F), -110.34 (2F), -122.94 (2F), -124.02 (2F), -124.24 (2F), -127.70 (2F); HRMS (ESI) Calculated for $\text{C}_{27}\text{H}_{32}\text{F}_{13}\text{N}_3\text{O}_{14}\text{Na}$, 892.1569; Found, 892.1588.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Sakai EM, Connolly LA, Klauck JA. *Pharmacotherapy*. 2005; 25:1773–1788. [PubMed: 16305297]
2. Fast JP, Perkins MG, Pearce RA, Mecozzi S. *Anesthesiology*. 2008; 109:651–656. [PubMed: 18813044]
3. Musser JB, Fontana JL, Mongan PD. *Anesth Analg*. 1999; 88:671–675. [PubMed: 10072026]
4. Johannesson G, Alm P, Biber B, Lennander O, Werner O. *Acta Anaesthesiol Scand*. 1984; 28:381–384. [PubMed: 6435378]
5. Biber B, Johannesson G, Lennander O, Martner J, Sonander H, Werner O. *Acta Anaesthesiol Scand*. 1984; 28:385–389. [PubMed: 6485733]
6. Zhou JX, Luo NF, Liang XM, Liu J. *Anesth Analg*. 2006; 102:129–134. [PubMed: 16368817]
7. Chiari PC, Pagel PS, Tanaka K, Krolkowski JG, Ludwig LM, Trillo RA Jr, Puri N, Kersten JR, Warltier DC. *Anesthesiology*. 2004; 101:1160–1166. [PubMed: 15505452]
8. Eger RP, MacLeod BA. *Can J Anaesth*. 1995; 42:173–176. [PubMed: 7720163]
9. Riess JG. *Artif Cell Blood Sub*. 2006; 34:567–580.
10. Taylor P. *Adv Colloid Interface Sci*. 1998; 75:107–163.
11. Kabalnov AS, Shchukin ED. *Adv Colloid Interface Sci*. 1992; 38:69–97.
12. Abouhilale S, Greiner J, Riess JG. *J Am Oil Chem Soc*. 1992; 69:1–18.
13. Cirkva V, Polak R, Paleta O, Kefurt K, Moravcova J, Kodicek M, Forman S. *Carbohydr Res*. 2004; 339:2177–2185.
14. Paleta O, Dlouha I, Kaplanek R, Kefurt K, Kodicek M. *Carbohydr Res*. 2002; 337:2411–2418.
15. Zarif L, Greiner J, Riess JG. *J Fluorine Chem*. 1989; 44:73–85.
16. Riess JG, Greiner J, Abouhilale S, Milius A. *Prog Colloid Polym Sci*. 1992; 88:123.
17. Milius A, Greiner J, Riess JG. *New J Chem*. 1991; 15:337–344.
18. Greiner J, Milius A, Riess JG. *Tetrahedron Lett*. 1988; 29:2193–2196.
19. Gege C, Schneider MF, Schumacher G, Limozin L, Rothe U, Bendas G, Tanaka M, Schmidt RR. *Chemphyschem*. 2004; 5:216–224. [PubMed: 15038282]
20. Clary L, Greiner J, Santaella C, Vierling P. *Tetrahedron Lett*. 1995; 36:539–542.
21. Li XS, Turanek J, Knotigova P, Kudlackova H, Masek J, Pennington DB, Rankin SE, Knutson BL, Lehmler HJ. *New J Chem*. 2008; 32:2169–2179.
22. Briner K, Vasella A. *Helv Chim Acta*. 1992; 75:621–637.
23. Elghoul M, Escoula B, Rico I, Lattes A. *J Fluorine Chem*. 1992; 59:107–112.
24. Gueyrard D, Rollin P, Nga TTT, Ourevitch M, Begue JP, Bonnet-Delpon D. *Carbohydr Res*. 1999; 318:171–179.
25. Kefurt K, Moravcova J, Bambasova S, Buchalova K, Vymetalikova B, Kefurtova Z, Stanek J, Paleta O. *Collect Czech Chem Commun*. 2001; 66:1665–1681.
26. Zarif L, Greiner J, Pace S, Riess JG. *J Med Chem*. 1990; 33:1262–1269. [PubMed: 2319569]

27. Zur C, Miller AO, Miethchen R. *J Fluorine Chem.* 1998; 90:67–76.
28. Peters D, Zur C, Miethchen R. *Synthesis.* 1998:1033–1038.
29. Edwards CM, Lowe KC, Heptinstall S, Lucas P, Trabelsi H, Cambon A. Oxygen Transport to Tissue XIX. 1997; 428:489–493.
30. Jouani MA, Szonyi F, Trabelsi H, Cambon A. *B Soc Chim Fr.* 1994; 131:173–182.
31. Edwards CM, Lowe KC, Trabelsi H, Lucas P, Cambon A. Artificial Cells, Blood Substitutes, and Immobilization Biotechnology. 1997; 25:327–333.
32. Trabelsi H, Jouani MA, Szonyi F, Cambon A. *J Fluorine Chem.* 1992; 56:105–107.
33. Guillod F, Greiner J, Riess JG. *Carbohydr Res.* 1994; 261:37–55.
34. Milius A, Greiner J, Riess JG. *Carbohydr Res.* 1992; 229:323–328.
35. Guillod F, Greiner J, Riess JG. *Chem Phys Lipids.* 1995; 78:149–162.
36. Abouhilale S, Greiner J, Riess JG. *Carbohydr Res.* 1991; 212:55–64.
37. Emmanouil V, El Ghoul M, Andre-Barres C, Guidetti B, Rico-Lattes I, Lattes A. *Langmuir.* 1998; 14:5389–5395.
38. Guedj C, Pucci B, Zarif L, Coulomb C, Riess JG, Pavia AA. *Chem Phys Lipids.* 1994; 72:153–173. [PubMed: 7954977]
39. Pucci B, Guedj C, Pavia AA. *Bioorg Med Chem Lett.* 1993; 3:1003–1006.
40. Abila M, Durand G, Pucci B. *J Org Chem.* 2008; 73:8142–8153. [PubMed: 18823145]
41. Polidori A, Pucci B, Maurizis JC, Pavia AA. *New J Chem.* 1994; 18:839–848.
42. Schuster T, Schellenberger S, Friedrich R, Klapper M, Mullen K. *J Fluorine Chem.* 2013; 154:30–36.
43. Gladysz, JA.; Curran, DP.; Horváth, IT. *Handbook of fluorine chemistry.* Wiley-VCH; Weinheim: 2004.
44. Calleja-Rubio S, Crette S, Blancou H. *Synthesis-Stuttgart.* 2003:361–364.
45. Burton DJ, Spawen TD. *J Fluorine Chem.* 1988; 38:119–128.
46. Ishihara T, Maekawa T, Ando T. *Tetrahedron Lett.* 1984; 25:1377–1378.
47. Baum K, Bedford CD, Hunadi RJ. *J Org Chem.* 1982; 47:2251–2257.
48. Gheorghe A, Chinnusamy T, Cuevas-Yañez E, Hilgers P, Reiser O. *Org Lett.* 2008; 10:4171–4174. [PubMed: 18754589]
49. Rasappan R, Olbrich T, Reiser O. *Adv Synth Catal.* 2009; 351:1961–1967.
50. Kaleta Z, Egyed O, Soós T. *Org Biomol Chem.* 2005; 3:2228–2230. [PubMed: 16010352]
51. Nyffeler PT, Liang CH, Koeller KM, Wong CH. *J Am Chem Soc.* 2002; 124:10773–10778. [PubMed: 12207533]
52. Titz A, Radic Z, Schwardt O, Ernst B. *Tetrahedron Lett.* 2006; 47:2383–2385.
53. Hawkins, LD.; Ishizaka, ST. TEISAI Co., Ltd. Immunomodulatory compounds and methods of use thereof. Patent WO2003/99195 A2. 2003.
54. Kolb, HC.; Walsh, JC.; Gangadharmath, UB.; Karimi, F.; Padgett, HC.; Kasi, D.; Gao, Z.; Liang, Q.; Collier, TL.; Duclos, BA.; Zhao, T. Siemens, Medical Solutions USA, Inc.. Nitro-imidazole hypoxia imaging agents. Patent US2009/10846 A1. 2009.
55. Toshima K, Tatsuta K. *Chem Rev.* 1993; 93:1503–1531.

- Carbohydrate-based fluorosurfactants were synthesized.
- Glycosylation of perfluoroalkyl diols and triols led to orthoester-type structures.
- Surfactants ability to self-assemble and stabilize emulsion formation was studied.
- Surfactant-stabilized emulsions were stable at 4°C.
- A surfactant-based gel was shown to be composed of left-handed helical fibers.

Figure 1.
Structures of fluorinated anesthetics commonly used in general anesthesia.

Figure 2.

Particle size range versus time graph for a 20% v/v sevoflurane, 10% v/v PFOB, 2.9% w/v 13 emulsion, stored at 4 °C. Error bars are +/- 1 standard deviation based on the width of the broad dynamic light scattering signal, averaged across three readings.

Figure 3.

TEM images of sevoflurane emulsion prepared with 13. Sub 100 nm droplets can be seen embedded in plaque-like islands, which are significantly larger. (1) Low magnification view. (2) High magnification view. See supporting information for additional images.

Figure 4.

TEM images of a gel prepared with 11. (1) Medium magnification view; fibers were primarily straight, but sometimes exhibited curvature (A). (2) High magnification view; Several distinct morphology types are shown - (B) single helices with a high degree of twist, (C) single helices with a low degree of twist, (D) double-coiled helices, and (E) where the double coiled helix ends abruptly as one of its strands comes to its end before the other. See supporting information for additional images.

Scheme 1.

Synthesis of perfluoroalkyl mannosides from commercially available peracetyl derivatives.

Scheme 2.

Retrosynthetic approach to tri-headed saccharide perfluoroalkyl amphiphiles.

Scheme 3.

Preparation of azide triol **4** and perfluoroalkyl triol **5**.

Scheme 4. Preparation of azide diol **7** and perfluoroalkyl diol **8**.

Scheme 5.

Glycosylation of azide triol 4. Compound 9 could not be isolated in sufficient purity, but as crude, underwent azide-alkyne cycloaddition readily.

Scheme 6.

Glycosylation and deprotection of fluoroalkyl triol **5** to yield the final product **11**.

Scheme 7.

Glycosylation and deprotection of fluoroalkyl diol **8** to yield the final product **13**.

Table 1

Solubilities of fluoroalkyl-mannosides shown in Scheme 1.

Specie	Aq. Solubility (mg/mL)	Aq. Solubility (M)
2a	0.02	2.8E-05
2b	0.18	3.4E-04
2c	8.05	2.0E-02
2d	> 100	> 0.28