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One-step preparation of 6-perfluoroalkylalkanoates of trehalose and sucrose for biomedical uses

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ABSTRACT

The Mitsunobu reaction has been used to obtain 6-polyfluoroalkanoates of α,α-trehalose and sucrose in yields of ~40% and ~25%, respectively. 6,6′-Diesters (3–6%) were formed in some reactions and a 6-ester (1.3%) of α-D-glucopyranosyl 3,4-anhydro-β-D-tagatofuranoside in one reaction. The monoesters displayed strong surfactant properties, and reduced considerably the water surface and fluorocarbon/water interfacial tensions. Preliminary results on biocompatibility were encouraging, especially for the 6-esters of α,α-trehalose.

INTRODUCTION

Progress in the field of fluorocarbon emulsions, destined for biomedical uses as respiratory gas carriers (blood substitutes)[1,2] and contrast agents[3], is dependent on the development of new biocompatible surfactants or co-surfactants that will improve the characteristics of the emulsions[4].

Pluronic F-68®, a polyoxyethylene–polyoxypropylene block co-polymer, the main surfactant used in the preparation of Fluosol-DA® [5], the first fluorocarbon emulsion to have been approved for human use, gives emulsions whose stability is insufficient (it has to be shipped and stored frozen), and which sometimes causes undesirable side-effects[6]. Although more stable, highly concentrated emulsions have been developed with egg-yolk phospholipids as the surfactant[7], better defined, biocompatible, and more fluorophilic surfactants are needed in order to allow the emulsion characteristics to be adapted to each of the various applications[4]. We have prepared polyfluoroalkyl monoesters of glucose and galactose[8], but their use, alone or as co-surfactants with Pluronic F-68, was difficult owing to their low solubility in water. Therefore, the corresponding esters of sucrose and trehalose have been investigated.

The esterification of α,α-trehalose[9] and sucrose[10] with acid chlorides, anhydrides, or methyl esters in the presence of a base usually gives complex mixtures of mono-, di-, and poly-esters that are difficult to fractionate. This type of synthesis, which is applicable on a large scale for the preparation of fatty acid esters of sucrose intended to be used in the cosmetic industry, or as food additives or detergents[11], cannot be considered for the preparation of injectable products. Specific esterification can be achieved by partial

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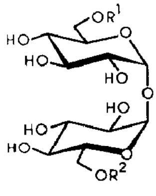
protection of the hydroxyl groups of the sugar, activation, acylation, and then deprotection[12], but this multi-step approach gives low overall yields, which makes it costly and unattractive.

Regioselective acylation of unprotected sugars has been achieved by enzymic preparations[13], by the Mitsunobu reaction[14], and by a method used by Plusquellec *et al.*[15], which allow the preparation of monoesters of mono-, di-, and tri-saccharides in one step. The Mitsunobu reaction was selected because it was expected to be fast and selective, and it has been used to prepare 6-*O*-palmitoylsucrose[16] and 6-*O*-mycolenoyl-α,α-trehalose[17] in good yields. The reaction is conducted at room temperature in a neutral medium, whereas the other methods generally require base catalysis that can cause undesirable side-reactions such as acyl migration[18]. In the Mitsunobu reaction, esterification occurs essentially on primary hydroxyl groups[19]. The use of perfluoroalkyl chains and of hydrocarbon "prolongators" of various lengths[4] allowed the surfactant properties to be varied. The introduction of a highly fluorinated chain can also perturb the course, and sometimes the outcome, of chemical reactions[20].

RESULTS AND DISCUSSION

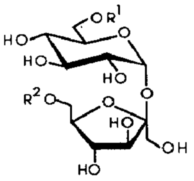
In *N,N*-dimethylformamide, the reaction of α,α-trehalose (**1**) with 0.33 equiv. of the polyfluoroalkanoic acid $C_nF_{2n+1}(CH_2)_mCO_2H$ (n = 4, 6, 8, m = 2, 4, 10) in the presence of the Mitsunobu redox system, triphenylphosphine–di-isopropyl azodicar-



1 $R^1 = R^2 = H$

2 $R^1 = C_nF_{2n+1}(CH_2)_mCO$, $R^2 = H$

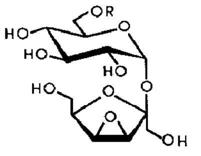
3 $R^1 = R^2 = C_nF_{2n+1}(CH_2)_mCO$



4 $R^1 = R^2 = H$

5 $R^1 = C_nF_{2n+1}(CH_2)_mCO$, $R^2 = H$

6 $R^1 = R^2 = C_nF_{2n+1}(CH_2)_mCO$



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$R = C_6F_{13}(CH_2)_{10}CO$

$C_nF_{2n+1}(CH_2)_mCO$

a $n = 4$, $m = 10$

b $n = 6$, $m = 10$

c $n = 8$, $m = 2$

d $n = 8$, $m = 4$

e $n = 6$, $m = 4$

boxylate (TPP–DIAD), at room temperature, gave the 6-esters **2** and the 6,6′-diesters **3**. Chromatography of the mixture on silica gel removed the diesters (~6%) and gave the 6-esters **2** (t.l.c., h.p.l.c.) in yields of ~40%. When 0.5 equiv. of polyfluoroalkanoic acid was used, 43% of the 6-ester **2e** was isolated, the formation of the 6,6′-diester **3e** was not observed, but a mixture of two inseparable epoxides of monoesterified α,α-trehalose was also obtained.

The α,α-trehalose molecule, owing to its symmetry, gives only six ^{13}C signals in the n.m.r. spectrum[21]. Monoesterification results in the loss of this symmetry and doubling of the ^{13}C signals. Differences ($\Delta\delta$) in the chemical shifts of the ^{13}C resonances of the esterified and non-esterified moieties of ~0.1 p.p.m. were observed consistently, except for C-5,5′ and C-6,6′ for which the $\Delta\delta$ values were +1.8–3.2 and −2.5–3.0 p.p.m., respectively, which demonstrated that HO-6 had been esterified[22]. The symmetrical diesters **3** each gave six ^{13}C resonances. Only the signals of C-6 and C-5 were shifted (+1.5 and −3.0 p.p.m., respectively). The ^{1}H-n.m.r. spectra of **2** and **3** also confirmed the proposed structures, and that for **3** accorded with those published for analogous structures[22]; H-5,6a,6b formed an easily calculated ABX system[23] and the large downfield shift (+0.5 p.p.m.) for these protons relative to those of a non-esterified glucoside[24] prove that 6-esterification had occurred. The spectra for **2** were more complex, but a similar deshielded pattern was found for H-5,6a,6b. Other signals were assigned by selective irradiation experiments.

When the above procedure was applied to sucrose (**4**), the 6-esters **5** were obtained in yields of ~25%. This reaction was less selective than those that involved alkyl esters[15], and the 6-esters **5** were more difficult to purify (repeated chromatography was necessary). The 6,6′-diesters **6** (6%) and the epoxides **7** were formed also, which were difficult to separate. The difference in yields of purified 6-esters from **1** and **4** is due to the fact that the two primary hydroxyl groups in α,α-trehalose are equivalent, whereas the three primary hydroxyl groups in sucrose are different. Moreover, the orientation of HO-3′,4′ in the fructose part of sucrose favours the formation of the tagatose epoxide[25].

It is noteworthy that the perfluoroalkyl chain weakens the C–O bond of the sucrose ester significantly. Thus, ester **5c** ($C_8F_{17}CH_2CH_2$) was unstable on storage of a solution in methanol for several days, leading, as shown by t.l.c., to sucrose and the methyl ester of the polyfluoroalkanoic acid, together with unidentified by-products that probably reflected acyl migration. No such degradation was observed with **5a** and **5b** which contain a much longer hydrocarbon segment. The transesterification of **5c** in methanol probably explains the poor yield, which was only half that obtained for the other sucrose monoesters. The trehalose analogue **2c** could not be treated under the same conditions as **5c**, since it was insoluble in methanol.

The most probable site of esterification[26] for sucrose is HO-6; in the n.m.r. spectra of the monoesters **5**, in comparison with that of the parent sugar[22], the characteristic downfield and upfield shifts for the resonances of C-6 (3–4 p.p.m.) and C-5 (2–3 p.p.m.), respectively, were observed. The ^{1}H-n.m.r. spectra of these 6-esters confirmed this view, since they contained the typical ABX system seen for the α,α-trehalose derivatives **2** and **3**. Relative to the monoesters, the ^{13}C-n.m.r. spectra of the 6,6′-diesters showed a downfield shift (+3 p.p.m.) for the resonance of C-6′ and an upfield shift (−3 p.p.m.) of that for C-5′.

The oxirane structure of **7b** was supported by ^{1}H- and ^{13}C-n.m.r. data. 2D ^{1}H–^{1}H and ^{1}H–^{13}C correlated-shift n.m.r. experiments and irradiation techniques were used to assign all of the ^{1}H and ^{13}C resonances. Relative to the ^{13}C-n.m.r. spectrum of the 6-ester **5b**, the signals of C-3′ and C-4′ were shifted downfield by 21.3 and 18.6 p.p.m., respectively. In the ^{1}H-n.m.r. spectrum of **7b**, the resonances due to H-3′,4′ were present as an AB-like quartet, the higher-field doublet at 3.85 p.p.m. being assigned to H-4′ because of the $J_{4',5'}$ value of 0.6 Hz. This assignment accords with the data reported for α-D-glucopyranosyl 3,4-anhydro-β-D-tagatofuranoside[25].

For all the compounds prepared, shifts to lower field (+8.5 p.p.m.), relative to those of the hydrocarbon analogues, were observed for the carbons adjacent to the perfluoroalkyl moiety, whereas the resonances of β carbons were shifted to higher fields (−11 p.p.m.)[27]. ^{13}C{^{1}H}-N.m.r. signals for these α and β carbons were characteristic triplets with $^2J_{C,F}$ and $^3J_{C,F}$ values of ~22 and ~3.5 Hz, respectively.

Preliminary physicochemical studies of the 6-polyfluoroalkyl esters of α,α-trehalose and sucrose revealed a strong surfactant effect. Thus, the addition of small amounts (0.01 g/L) of the 6-esters lowered the water surface (γ_s) and water/perfluorodecalin interfacial (γ_i) tensions significantly. For example, for a 0.01 g/L aqueous solution of **2c**, γ_s and γ_i were decreased to 21.6 and 5.6 mN.m^{-1}, respectively, from γ_s(H_2O) 73 and γ_i (H_2O/perfluorodecalin) 56 mN.m^{-1}. The incorporation of **2** or **5** stabilized perfluorodecalin in water emulsions with Pluronic F-68 as the primary surfactant. Perfluorodecalin is a typical fluorocarbon used in the preparation of injectable emulsions destined for carrying respiratory gases[2].

Some preliminary biocompatibility tests have also been performed. Thus, intravenous injections in mice showed that isotonic solutions of **2e** and **5b** were tolerated at 250 mg/kg. No hemolytic effect on human red-blood cells suspended in an isotonic 0.9% NaCl solution was found for **2e** even at a concentration of 50 g/L, in contrast to the hydrocarbon analogues. For example, maltosides with hydrocarbon hydrophobic groups of comparable lengths[28] are strongly hemolytic at 1 g/L in spite of a much lower surface activity.

EXPERIMENTAL

T.l.c. was performed on Silica Gel F_{254} (Merck) with detection by charring with sulfuric acid. Preparative separations were carried out on Silica Gel 60 (Merck 70–230 mesh). Analytical h.p.l.c. (*T* values) was performed with a Waters 510 instrument fitted with a 10-μ Bondapak C-18 column (30 cm × 3.9 mm) and a differential R401 refractometer, and elution at 1 mL/min. Melting points, determined with a Reichert apparatus, are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter (1-dm cell, at 589 nm). I.r. spectra (KBr discs) were recorded with a Bruker IFS-45 spectrometer. N.m.r. spectra (^{13}C, 50.3 MHz, internal Me_4Si; ^{1}H, 200.13 MHz, internal Me_4Si; and ^{19}F, internal $CFCl_3$) were recorded with Bruker AC-200 and/or

WH-90 spectrometers. All solvents were dried and distilled according to standard procedures, and all reactions were performed under anhydrous argon. *N,N*-Dimethylformamide was dried by distillation from P_2O_5 at 20 mmHg, and stored over molecular sieves (4 Å). Solvents were removed under reduced pressure at <50°. Anhydrous α,α-trehalose was obtained by dissolving the commercial dihydrate in pyridine (1 g in 3 mL) and distilling the solvent off at atmospheric pressure[29]. Nonafluoropentadecanoic, tridecafluoroheptadecanoic, heptadecafluorotridecanoic (m.p. 92°), and tridecafluoroundecanoic acid (m.p. 56°) were prepared as described by Brace[30]. Heptadecafluoroundecanoic acid (Atochem), recrystallised from toluene, had m.p. 95°.

Polyfluorinated 6-esters (**2**) *of α,α-trehalose.* — To a solution of anhydrous α,α-trehalose (3 equiv.) and triphenylphosphine (2 equiv.) in anhydrous *N,N*-dimethylformamide (15 mL) at 0° was added a solution of the polyfluoroalkanoic acid (1 equiv.) and di-isopropyl azodicarboxylate (2 equiv.) in *N,N*-dimethylformamide (15 mL).

The mixture was stirred at room temperature for 3 days and monitored by t.l.c. ($CHCl_3$–MeOH–H_2O, 70:27:3). The solvent was removed under reduced pressure at 40°, and the solid residue was washed with toluene, then with ether, and partitioned between 1-butanol and water. The aqueous solution was extracted 3 times with 1-butanol, and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue was purified by column chromatography ($CHCl_3$–MeOH–H_2O, 70:27:3). H.p.l.c. involved MeOH–H_2O (85:15).

(*a*) Reaction of **1** (21.9 g, 63.98 mmol) and nonafluoropentadecanoic acid (9.2 g, 22.75 mmol) yielded **2a** (7.3 g, 44%) and **3a** (1.6 g, 6%).

6-*O*-(12,12,13,13,14,14,15,15,15-Nonafluoropentadecanoyl)-α,α-trehalose (**2a**) had $[\alpha]_D$ +92° (*c* 1, methanol), R_F 0.5, *T* 6.25 min; ν_{max} 3420 (OH), 2930 and 2860 (CH), 1730 (C=O), 1240–1140 cm^{-1} (CF). N.m.r. data (CD_3OD): ^1H, δ 1.36 [s, 12 H, $(C\mathit{H}_2)_6(CH_2)_2CO$], 1.65 (m, 4 H, $C\mathit{H}_2CH_2C_4F_9$ and $C\mathit{H}_2CH_2CO$), 2.17 (tt, 2 H, $^3J_{H,F}$ 19.0, $^3J_{H,H}$ 8.7 Hz, $C\mathit{H}_2C_4F_9$), 2.37 (t, 2 H, $^3J_{H,H}$ 7.3 Hz, $C\mathit{H}_2CO$), 3.35 (t, 1 H, $J_{4',5'}$ 9.3 Hz, H-4′), 3.38 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.51* (dd, 1 H, $J_{2',3'}$ 9.7 Hz, H-2′), 3.52* (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.65–3.90 (m, 3 H, H-5′,6′a,6′b), 3.83 (t, 2 H, $J_{3,4} = J_{3',4'} = 9.3$ Hz, H-3,3′), 4.06 (m, H-5), 4.24 (A*B*X, $J_{6b,5}$ 5.0, $J_{6b,6a}$ 11.7 Hz, H-6b), 4.40 (*A*BX, $J_{6a,5}$ 2.6 Hz, H-6a), 4.91 (s, OH), 5.12 (t, 2 H, $J_{1,2} = J_{1',2'} = 3.8$ Hz, H-1,1′); ^{19}F, δ −81.2 (3 F, CF_3), −114.4 (2 F, $C\mathit{F}_2CH_2$), −124.2 (2 F, $C\mathit{F}_2CF_2CF_3$), −125.9 (2 F, $C\mathit{F}_2CF_3$); ^{13}C, δ 21.1 (t, $^3J_{C,F}$ 3.6 Hz, $\mathit{C}H_2CH_2C_4F_9$), 26.0 ($\mathit{C}H_2CH_2CO$), 30.1–30.4 [6 C, $(\mathit{C}H_2)_6(CH_2)_2CO$], 31.6 (t, $^2J_{C,F}$ 22 Hz, $\mathit{C}H_2C_4F_9$), 35.0 ($\mathit{C}H_2CO$), 62.6 (C-6′), 64.4 (C-6), 71.4 (C-5), 71.8 (C-4,4′), 73.1 (C-2,2′), 73.8 (C-5′), 74.3 and 74.5 (C-3,3′), 95.0 and 95.1 (C-1,1′), 175.6 (C=O); * assignments may be reversed.

Anal. Calc. for $C_{27}H_{41}F_9O_{12}$ (728.6): C, 44.51; H, 5.67; F, 23.47. Found: C, 44.65; H, 5.51; F, 23.46.

6,6′-Di-*O*-(12,12,13,13,14,14,15,15,15-nonafluoropentadecanoyl)-α,α-trehalose (**3a**) had $[\alpha]_D$ +59° (*c* 1, methanol), R_F 0.75; ν_{max} 3400 (OH), 2925 and 2855 (CH), 1740 (C=O), 1230–1140 cm^{-1} (CF). N.m.r. data (CD_3OD): ^1H, δ 1.36 [s, 12 H, $(C\mathit{H}_2)_6(CH_2)_2CO$], 1.63 (m, 4 H, $C\mathit{H}_2CH_2C_4F_9$ and $C\mathit{H}_2CH_2CO$), 2.17 (tt, 2 H, $^3J_{H,F}$ 19.0, $^3J_{H,H}$ 8.5 Hz, $C\mathit{H}_2C_4F_9$), 2.37 (t, 2 H, $^3J_{H,H}$ 7.3 Hz, $C\mathit{H}_2CO$), 3.36 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.50 (dd, 1 H,

$J_{2,3}$ 9.3 Hz, H-2), 3.83 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 4.05 (m, H-5), 4.23 (A*B*X, $J_{6b,5}$ 5.1, $J_{6b,6a}$ 11.7 Hz, H-6b), 4.38 (*A*BX, $J_{6a,5}$ 2.5 Hz, H-6a), 4.91 (s, OH), 5.08 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1); ^{19}F, δ −81.5 (3 F, CF_3), −114.7 (2 F, CF_2CH_2), −124.4 (2 F, $CF_2CF_2CF_3$), −126.2 (2 F, CF_2CF_3); ^{13}C, δ 21.2 (t, $^3J_{C,F}$ 3.7 Hz, $CH_2CH_2C_4F_9$), 26.0 (CH_2CH_2CO), 30.1–30.4 [6 C, $(CH_2)_6(CH_2)_2CO$], 31.6 (t, $^2J_{C,F}$ 22 Hz, $CH_2C_4F_9$), 35.0 (CH_2CO), 64.4 (C-6), 71.4 (C-5), 71.9 (C-4), 73.1 (C-2), 74.5 (C-3), 95.1 (C-1), 175.4 (C=O).

Anal. Calc. for $C_{42}H_{60}F_{18}O_{13}$ (1114.9): C, 45.25; H, 5.42; F, 30.67. Found: C, 45.26; H, 5.47; F, 30.56.

(*b*) Reaction of **1** (12.38 g, 36.18 mmol) and tridecafluoroheptadecanoic acid (6.08 g, 12.06 mmol) gave **2b** (4.2 g, 42%) and **3b** (0.42 g, 2.6%).

6-*O*-(12,12,13,13,14,14,15,15,16,16,17,17,17-Tridecafluoroheptadecanoyl)-α,α-trehalose (**2b**) had $[\alpha]_D$ +82° (*c* 1.2, methanol), R_F 0.36, *T* 9.15 min; ν_{max} 3430 (OH), 2935 and 2860 (CH), 1730 (C=O), 1245–1150 cm^{-1} (CF). N.m.r. data (CD_3OD): ^{1}H, δ 1.32 [s, 12 H, $(CH_2)_6(CH_2)_2CO$], 1.63 (m, 4 H, $CH_2CH_2C_6F_{13}$ and CH_2CH_2CO), 2.15 (tt, 2 H, $^3J_{H,F}$ 19.0, $^3J_{H,H}$ 8.8 Hz, $CH_2C_6F_{13}$), 2.36 (t, 2 H, $^3J_{H,H}$ 7.5 Hz, CH_2CO), 3.34 (t, 1 H, $J_{4',5'}$ 9.2 Hz, H-4′), 3.37 (t, 1 H, $J_{4,5}$ 9.2 Hz, H-4), 3.50* (dd, 1 H, $J_{2',3'}$ 9.7 Hz, H-2′), 3.51* (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.62–3.90 (m, 3 H, H-5′,6′a,6′b), 3.83 (t, 2 H, $J_{3,4}$ = $J_{3',4'}$ = 9.2 Hz, H-3,3′), 4.04 (m, H-5), 4.22 (A*B*X, $J_{6b,5}$ 5.0, $J_{6b,6a}$ 11.6 Hz, H-6b), 4.38 (*A*BX, $J_{6a,5}$ 2.6 Hz, H-6a), 4.58 (s, OH), 5.12 (t, 2 H, $J_{1,2}$ = $J_{1',2'}$ = 4.0 Hz, H-1,1′); ^{19}F, δ −81.0 (3 F, CF_3), −113.9 (2 F, CF_2CH_2), −121.5, −122.5, and −122.9 [6 F, $(CF_2)_3CF_2CH_2$], −125.9 (2 F, CF_2CF_3); ^{13}C, δ 21.2 (t, $^3J_{C,F}$ 3.6 Hz, $CH_2CH_2C_6F_{13}$), 26.0 (CH_2CH_2CO), 30.1–30.5 [6 C, $(CH_2)_6(CH_2)_2CO$], 31.7 (t, $^2J_{C,F}$ 22 Hz, $CH_2C_6F_{13}$), 35.0 (CH_2CO), 62.6 (C-6′), 64.4 (C-6), 71.4 (C-5), 71.8 (C-4,4′), 73.1 (C-2,2′), 73.8 (C-5′), 74.4 and 74.5 (C-3,3′), 95.1 and 95.2 (C-1,1′), 175.4 (C=O); * assignments may be reversed.

Anal. Calc. for $C_{29}H_{41}F_{13}O_{12}$ (828.6): C, 42.03; H, 4.98; F, 29.80. Found: C, 41.96; H, 4.91; F, 29.89.

6,6′-Di-*O*-(12,12,13,13,14,14,15,15,16,16,17,17,17-tridecafluoroheptadecanoyl)-α,α-trehalose (**3b**) had $[\alpha]_D$ +51.5° (*c* 1, methyl sulfoxide), R_F 0.58; ν_{max} 3400 (OH), 2925 and 2855 (CH), 1740 (C=O), 1240–1145 cm^{-1} (CF). N.m.r. data [$(CD_3)_2SO$]: ^{19}F, δ −81.8 (3 F, CF_3), −114.4 (2 F, CF_2CH_2), −122.3, −123.3, and −123.7 [6 F, $(CF_2)_3CF_2CH_2$], −126.8 (2 F, CF_2CF_3).

Anal. Calc. for $C_{46}H_{60}F_{26}O_{13}$ (1314.9): C, 42.02; H, 4,60; F, 37.56. Found: C, 41.82; H, 4.47; F, 37.50.

(*c*) Reaction of **1** (2.26 g, 6.60 mmol) and heptadecafluoroundecanoic acid (1.08 g, 2.19 mmol) gave, after chromatography, 6-*O*-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoyl)-α,α-trehalose (**2c**; 0.72 g, 40%) which, after recrystallization from ethanol, yielded material (0.54 g, 30%) having m.p. 209°, $[\alpha]_D$ +90° (*c* 1, *N*,*N*-dimethylformamide), R_F 0.32; ν_{max} 3420 (OH), 1735 (C=O), 1240–1150 cm^{-1} (CF). N.m.r. data [$(CD_3)_2SO$]: ^{1}H, δ 2.40–2.70 [m, 4 H, $(CH_2)_2C_8F_{17}$], 3.14 (t, 2 H, $J_{4,5}$ = $J_{4',5'}$ = 9.5 Hz, H-4,4′), 3.25 (dd, 2 H, $J_{2,3}$ = $J_{2',3'}$ = 9.7 Hz, H-2,2′), 3.30–3.50 (m, 10 H, H-5′,6′a,6′b, and OH), 3.55 (t, 2 H, $J_{3,4}$ = $J_{3',4'}$ = 9.6 Hz, H-3,3′), 3.94 (m, H-5), 4.08 (A*B*X, $J_{6b,5}$ 5.1, $J_{6b,6a}$ 12.1 Hz, H-6b), 4.30 (*A*BX, $J_{6a,5}$ 3.0 Hz, H-6a), 4.84 and 4.87 (2 d, 2 H, $J_{1,2}$ = $J_{1',2'}$ = 3.7 Hz, H-1,1′); ^{19}F, δ −80.3 (3 F, CF_3), −113.6 (2 F, CF_2CH_2), −121.6,

−122.4, and −122.9 [10 F, $(CF_2)_5CF_2CH_2$], −125.8 (2 F, CF_2CF_3); ^{13}C, δ 26.2 (t, 2 H, $^3J_{C,F}$ 3.5 Hz, CH_2CO), 27.0 (t, $^2J_{C,F}$ 22 Hz, $CH_2C_8F_{17}$), 62.2 (C-6′), 65.4 (C-6), 71.0 (C-5), 71.4 and 71.5 (C-4,4′), 72.9 and 73.0 (C-2,2′), 74.0 (C-5′), 74.2 (C-3,3′), 94.8 and 95.0 (C-1,1′), 172.0 (C=O).

Anal. Calc. for $C_{23}H_{25}F_{17}O_{12}$ (816.4): C, 33.83; H, 3.08; F, 39.56. Found: C, 33.80; H, 3.10; H, 39.07.

(*d*) Reaction of **1** (8.80 g, 25.70 mmol) and heptadecafluorotridecanoic acid (4.50 g, 8.65 mmol) afforded 6-*O*-(6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-heptadecafluorotridecanoyl)-α,α-trehalose (**2d**; 3.14 g, 43%), $[\alpha]_D$ +75.3° (*c* 1.1, methyl sulfoxide), R_F 0.32, *T* 5.5 min; ν_{max} 3400 (OH), 2940 (CH), 1735 (C=O), 1250–1150 cm^{-1} (CF). N.m.r. data [$(CD_3)_2SO$]: ^{1}H, δ 2.00–2.40 (m, 4 H, $CH_2C_8F_{17}$ and CH_2CO), 1.52 [s, 4 H, $(CH_2)_2CH_2CO$], 3.13 (t, 2 H, $J_{4,5} = J_{4',5'} = 9.4$ Hz, H-4,4′), 3.24 (dd, 2 H, $J_{2,3} = J_{2',3'} = 9.6$ Hz, H-2,2′), 3.34–3.48 (m, 10 H, H-5′,6′a,6′b, and OH), 3.55 (t, 2 H, $J_{3,4} = J_{3',4'} = 9.6$ Hz, H-3,3′), 3.91 (m, H-5), 4.07 (A*B*X, $J_{6b,5}$ 5.2, $J_{6b,6a}$ 12.0 Hz, H-6b), 4.28 (*A*BX, $J_{6a,5}$ 2.8 Hz, H-6a), 4.91 and 4.94 (2 d, 2 H, $J_{1,2} = J_{1',2'} = 3.7$ Hz, H-1,1′); ^{19}F, δ −80.2 (3 F, CF_3), −113.1 (2 F, CF_2CH_2), −121.5, −122.3, and −122.7 [10 F, $(CF_2)_5CF_2CH_2$], −125.6 (2 F, CF_2CF_3); ^{13}C, δ 20.7 (t, $^3J_{C,F}$ 3.5 Hz, $CH_2CH_2C_8F_{17}$), 25.1 (CH_2CH_2CO), 31.0 (t, $^2J_{C,F}$ 22 Hz, $CH_2C_8F_{17}$), 34.2 (CH_2CO), 62.3 (C-6′), 64.7 (C-6), 71.1 (C-5), 71.5 and 71.6 (C-4,4′), 72.9 and 73.0 (C-2,2′), 74.0 (C-5′), 74.3 (C-3,3′), 94.8 and 94.9 (C-1,1′), 174.0 (C=O).

Anal. Calc. for $C_{25}H_{29}F_{17}O_{12}$ (844.4): C, 35.56; H, 3.46; F, 38.24. Found: C, 35.42; H, 3.67; F, 38.25.

(*e*) Reaction of **1** (26 g, 75.95 mmol) and tridecafluoroundecanoic acid (14 g, 33.32 mmol) afforded 6-*O*-(6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoroundecanoyl)-α,α-trehalose (**2e**; 10.7 g, 43%) which, after recrystallization (from ethanol–ethyl acetate), had $[\alpha]_D$ +91° (*c* 1.1, methanol), R_F 0.3, *T* 5.25 min; ν_{max} 3400 (OH), 2945 (CH), 1730 (C=O), 1240–1145 cm^{-1} (CF). N.m.r. data (CD_3OD): ^{1}H, δ 1.66 [m, 4 H, $(CH_2)_2CH_2CO$], 2.17 (tt, 2 H, $^3J_{H,F}$ 19.0, $^3J_{H,H}$ 8.5 Hz, $CH_2C_6F_{13}$), 2.42 (t, 2 H, $^3J_{H,H}$ 7.5 Hz, CH_2CO), 3.32 (t, 1 H, $J_{4',5'}$ 9.3 Hz, H-4′), 3.34 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.47* (dd, 1 H, $J_{2',3'}$ 9.7 Hz, H-2′), 3.48* (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.61–3.90 (m, 3 H, H-5′,6′a,6′b), 3.80 (t, 2 H, $J_{3,4} = J_{3',4'} = 9.3$ Hz, H-3,3′), 4.06 (m, H-5), 4.23 (A*B*X, $J_{6b,5}$ 5.0, $J_{6b,6a}$ 11.8 Hz, H-6b), 4.38 (*A*BX, $J_{6a,5}$ 2.6 Hz, H-6a), 4.97 (s, OH), 5.08 (t, 2 H, $J_{1,2} = J_{1',2'} = 4.1$ Hz, H-1,1′); ^{19}F, δ −80.9 (3 F, CF_3), −113.8 (2 F, CF_2CH_2), −121.4, −122.5, and −122.8 [6 F, $(CF_2)_3CF_2CH_2$], −125.8 (2 F, CF_2CF_3); ^{13}C, δ 20.8 (t, $^3J_{C,F}$ 3.5 Hz, $CH_2CH_2C_6F_{13}$), 25.3 (CH_2CH_2CO), 31.4 (t, $^2J_{C,F}$ 22 Hz, $CH_2C_6F_{13}$), 34.4 (CH_2CO), 62.6 (C-6′), 64.5 (C-6), 71.3 (C-5), 71.8 (C-4,4′), 73.1 (C-2,2′), 73.8 (C-5′), 74.3 and 74.5 (C-3,3′), 95.1 and 95.3 (C-1,1′), 174.8 (C=O); * assignments may be reversed.

Anal. Calc. for $C_{23}H_{29}F_{13}O_{12}$ (744.4): C, 37.11; H, 3.92; F, 33.17. Found: C, 37.19; H, 3.99; F, 32.81.

Polyfluorinated 6-esters (**5**) *of sucrose.* — To a solution of dry sucrose (1.2–3.0 equiv.) and triphenylphosphine (1.4–2.0 equiv.) in anhydrous *N*,*N*-dimethylformamide was added the appropriate perfluoroalkanoic acid, the solution was cooled to 0°, and di-isopropyl azodicarboxylate (1.4–2.0 equiv.) was added. After storage for 15 min at

0°, the mixture was stirred at room temperature for 2–3 days. The progress of the reaction was monitored by t.l.c. ($CHCl_3$–MeOH–H_2O, 70:27:3). The solvent was removed under reduced pressure at 40°, and the residue was washed with toluene and ether, then purified by column chromatography. H.p.l.c. involved MeOH–H_2O (9:1) unless stated otherwise.

(*a*) Reaction of **4** (1.44 g, 4.21 mmol) and nonafluoropentadecanoic acid (1.42 g, 3.51 mmol) with triphenylphosphine (1.23 g, 4.69 mmol) and di-isopropyl azodicarboxylate (0.85 mL, 4.32 mmol) yielded **5a** (600 mg, 28%) and **6a** (180 mg, 5.5%). A chloroform–methanol gradient eluent was used in the column chromatography: 9:1 (250 mL), 6:1 (200 mL), 4:1 (250 mL), and 7:3 (200 mL).

6-*O*-(12,12,13,13,14,14,15,15,15-Nonafluoropentadecanoyl)sucrose (**5a**) had m.p. 201°, $[\alpha]_D$ +34° (*c* 0.5, methanol), R_F 0.47, *T* 6.75 min (MeOH–H_2O, 85:15), ν_{max} 3390 (OH), 2930 and 2860 (CH), 1735 (C=O), 1230–1055 cm^{-1} (CF). N.m.r. data (CD_3OD): ^1H, δ 1.32 [s, 12 H, $(CH_2)_6CH_2CH_2CO$], 1.59 (m, 4 H, CH_2CH_2CO and $CH_2CH_2C_4F_9$), 2.12 (tt, 2 H, $^3J_{H,H}$ 8.5, $^3J_{H,F}$ 19.0 Hz, $CH_2C_4F_9$), 2.36 (t, 2 H, $^3J_{H,H}$ 7.3 Hz, CH_2CO), 3.28 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.41 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2), 3.58 (AB, $J_{4',3'}$ 3.0 Hz, H-4′), 3.61 (AB, H-3′), 3.66–3.86 (m, 5 H, H-3,1′a,1′b,6′a,6′b), 3.95–4.12 (m, 2 H, H-5,5′), 4.17 (A*B*X, $J_{6b,5}$ 5.8, $J_{6b,6a}$ 12.0 Hz, H-6b), 4.40 (*A*BX, $J_{6a,5}$ 2.9 Hz, H-6a), 4.86 (s, OH), 5.36 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1); ^{19}F, δ −81.0 (3 F, CF_3), −114.0 (2 F, CF_2CH_2), −123.9 (2 F, $CF_2CF_2CH_2$), −125.7 (2 F, CF_2CF_3); ^{13}C, δ 21.2 (t, $^3J_{C,F}$ 3.5 Hz, $CH_2CH_2C_4F_9$), 26.0 (CH_2CH_2CO), 30.1–30.5 [6 C, $(CH_2)_6(CH_2)_2CO$], 31.6 (t, $J_{C,F}$ 22 Hz, $CH_2C_4F_9$), 34.9 (CH_2CO), 63.9 and 64.1 (C-1′,6′), 64.7 (C-6), 71.6 (C-5), 72.0 (C-4), 73.1 (C-2), 74.5 (C-3), 76.0 (C-4′), 79.3 (C-3′), 83.9 (C-5′), 93.4 (C-1), 105.2 (C-2′), 175.5 (C=O).

Anal. Calc. for $C_{27}H_{41}F_9O_{12}$ (728.6): C, 44.51; H, 5.67; F, 23.47. Found: C, 44.66; H, 5.66; F, 23.06.

6,6′-Di-*O*-(12,12,13,13,14,14,15,15,15-nonafluoropentadecanoyl)sucrose (**6a**) had m.p. 209°, $[\alpha]_D$ +31° (*c* 0.5, methyl sulfoxide), R_F 0.71; ν_{max} 3400 (OH), 2925 and 2855 (CH), 1745 (C=O), 1240–1140 cm^{-1} (CF).

Anal. Calc. for $C_{42}H_{60}F_{18}O_{13}$ (1114.9): C, 45.25; H, 5.42; F, 30.67. Found: C, 45.55; H, 5.25; F, 29.33.

(*b*) Reaction of **4** (4 g, 11.68 mmol) and tridecafluoroheptadecanoic acid (5.2 g, 10.31 mmol) with triphenylphosphine (3.86 g, 14.73 mmol) and di-isopropyl azodicarboxylate (2.9 mL, 14.74 mmol) afforded **5b** (2.09 g, 24.4%), **6b** (0.76 g, 5.6%), and **7b** (110 mg, 1.3%). Column chromatography involved the chloroform–methanol mixtures: 9:1 (1 L), 6:1 (0.5 L), and 4:1 (2 L).

6-*O*-(12,12,13,13,14,14,15,15,16,16,17,17,17-Tridecafluoroheptadecanoyl)sucrose (**5b**) had m.p. 203°, $[\alpha]_D$ +30° (*c* 0.5, methanol), R_F 0.44, *T* 5.16 min; ν_{max} 3385 (OH), 2930 and 2860 (CH), 1725 (C=O), 1240–1060 cm^{-1} (CF). N.m.r. data (CD_3OD): ^1H, δ 1.32 [s, 12 H, $(CH_2)_6CH_2CH_2CO$], 1.60 (m, 4 H, CH_2CH_2CO, and $CH_2CH_2C_6F_{13}$), 2.11 (tt, 2 H, $^3J_{H,H}$ 8.7, $^3J_{H,F}$ 19.0 Hz, $CH_2C_6F_{13}$), 2.36 (t, 2 H, $^3J_{H,H}$ 7.3 Hz, CH_2CO), 3.28 (t, 1 H, $J_{4,5} = J_{4,3} = 9.5$ Hz, H-4), 3.41 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.58 (AB, $J_{4',3'}$ 3.2 Hz, H-4′), 3.60 (AB, H-3′), 3.65–3.86 (m, 5 H, H-3,1′a,1′b,6′a,6′b), 3.95–4.13 (m, 2 H, H-5,5′), 4.26

(A*B*X, $J_{6b,5}$ 5.7, $J_{6b,6a}$ 12.0 Hz, H-6b), 4.39 (*A*BX, $J_{6a,5}$ 2.8 Hz, H-6a), 4.87 (s, OH), 5.37 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1); ^{19}F, δ −80.6 (3 F, CF_3), −113.8 (2 F, $C\mathit{F}_2CH_2$), −121.3, −122.3, and −122.8 [6 F, $(C\mathit{F}_2)_3CF_2CF_3$], −125.6 (2 F, $C\mathit{F}_2CF_3$); ^{13}C, δ 21.3 (t, $^3J_{C,F}$ 3.5 Hz, $\mathit{C}H_2CH_2C_6F_{13}$), 26.0 ($\mathit{C}H_2CH_2CO$), 30.2–30.6 [6 C, $(\mathit{C}H_2)_6(CH_2)_2CO$], 31.7 (t, $^2J_{C,F}$ 22 Hz, $\mathit{C}H_2C_6F_{13}$), 35.0 ($\mathit{C}H_2CO$), 63.9 and 64.1 (C-1′,6′), 64.7 (C-6), 71.7 (C-5), 72.0 (C-4), 73.2 (C-2), 74.5 (C-3), 75.9 (C-4′), 79.2 (C-3′), 83.9 (C-5′), 93.4 (C-1), 105.2 (C-2′), 175.6 (C=O).

Anal. Calc. for $C_{29}H_{41}F_{13}O_{12}$ (828.6): C, 42.03; H, 4.99; F, 29.80. Found: C, 41.94; H, 5.00; F, 29.43.

6,6′-Di-*O*-(12,12,13,13,14,14,15,15,16,16,17,17,17-tridecafluoroheptadecanoyl)-sucrose (**6b**) had m.p. 218°, $[\alpha]_D$ +24° (*c* 1, methyl sulfoxide), R_F 0.60; ν_{max} 3400 (OH), 2925 and 2855 (CH), 1745 (C=O), 1245–1055 cm^{-1} (CF). N.m.r. data [$(CD_3)_2SO$]: ^{19}F, δ −82.2 (3 F, CF_3), −114.8 (2 F, $C\mathit{F}_2CH_2$), −122.5 and −123.9 [6 F, $(C\mathit{F}_2)_3CF_2CH_2$)], −127.1 (2 F, $C\mathit{F}_2CF_3$); ^{13}C, δ 21.0 ($\mathit{C}H_2CH_2C_6F_{13}$), 25.9 ($\mathit{C}H_2CH_2CO$), 30.1–30.5 [6 C, $(\mathit{C}H_2)_6(CH_2)_2CO$], 31.3 (t, $^2J_{C,F}$ 22.2 Hz, $\mathit{C}H_2C_6F_{13}$), 34.7 ($\mathit{C}H_2CO$), 63.6 (C-1′), 65.9 (C-6), 67.3 (C-6′), 71.7 (C-5), 72.1 (C-4), 72.9 (C-2), 74.0 (C-3), 76.5 (C-4′), 78.1 (C-3′), 80.6 (C-5′), 92.9 (C-1), 105.4 (C-2′), 174.0 and 174.4 (C=O).

Anal. Calc. for $C_{46}H_{60}F_{26}O_{13}$ (1314.9): C, 42.02; H, 4.60; F, 37.56. Found: C, 42.11; H, 4.69; F, 37.27.

6-*O*-(12,12,13,13,14,14,15,15,16,16,17,17,17-Tridecafluoroheptadecanoyl)-α-D-glucopyranosyl 3,4-anhydro-β-D-tagatofuranoside (**7b**) had m.p. 196°, $[\alpha]_D$ +38° (*c* 1, methanol), R_F 0.54, *T* 11 min (MeOH–H_2O, 85:15); ν_{max} 3410 (OH), 2930 and 2860 (CH), 1735 (C=O), 1240–1050 cm^{-1} (CF). N.m.r. data (CD_3OD): ^{1}H, δ 1.32 [s, 12 H, $(C\mathit{H}_2)_6CH_2CH_2CO$], 1.50 (m, 4 H, $C\mathit{H}_2CH_2CO$ and $C\mathit{H}_2CH_2C_6F_{13}$), 2.13 (tt, 2 H, $^3J_{H,H}$ 7.9, $^3J_{H,F}$ 18.0 Hz, $C\mathit{H}_2C_6F_{13}$), 2.33 (t, 2 H, $^3J_{H,H}$ 7.3 Hz, $C\mathit{H}_2CO$), 3.34 (t, 1 H, $J_{4,5}$ = $J_{4,3}$ = 9.5 Hz, H-4), 3.45 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.70 (H-1′a,1′b), 3.72 (H-3), 3.75 (H-6′a,6′b), 3.85 (AB, $J_{4',3'}$ 2.9, $J_{4',5'}$ 0.6 Hz, H-4′), 3.87 (AB, H-3′), 4.06 (m, H-5), 4.09 (H-5′), 4.27 (A*B*X, $J_{6b,5}$ 5.2, $J_{6b,6a}$ 12.2 Hz, H-6b), 4.39 (*A*BX, $J_{6a,5}$ 2.9 Hz, H-6a), 5.40 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1); ^{19}F, δ −81.3 (3 F, CF_3), −114.2 (2 F, $C\mathit{F}_2CH_2$), −121.8, −122.8, and −123.2 [6 F, $(C\mathit{F}_2)_3CF_2CH_2$)], −126.2 (2 F, $C\mathit{F}_2CF_3$) ^{13}C, δ 21.2 (t, $^3J_{C,F}$ 3.5 Hz, $\mathit{C}H_2CH_2C_6F_{13}$), 25.9 ($\mathit{C}H_2CH_2CO$), 30.1–30.5 [6 C, $(\mathit{C}H_2)_6(CH_2)_2CO$], 31.7 (t, $^2J_{C,F}$ 22 Hz, $\mathit{C}H_2C_6F_{13}$), 34.9 ($\mathit{C}H_2CO$), 56.3 (C-4′), 57.9 (C-3′), 61.8 (C-6′), 65.0 (C-6), 65.4 (C-1′), 71.6 (C-5), 72.0 (C-4), 73.1 (C-2), 74.7 (C-3), 78.6 (C-5′), 93.8 (C-1), 105.2 (C-2′), 175.5 (C=O).

Anal. Calc. for $C_{29}H_{39}F_{13}O_{11}$ (810.6): C, 42.97; H, 4.85; F, 30.47. Found: C, 42.97; H, 4.82; F, 30.04.

(*c*) Reaction of **4** (12.47 g, 36.46 mmol) and heptadecafluoroundecanoic acid (5.97 g, 12.13 mmol) with triphenylphosphine (6.40 g, 24.43 mmol) and di-isopropyl azodicarboxylate (4.80 mL, 24.40 mmol) in *N*,*N*-dimethylformamide (125 mL) afforded **5c** (1.20 g, 12%) after column chromatography thrice.

6-*O*-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecanoyl)sucrose (**5c**) had m.p. 212°, $[\alpha]_D$ +33° (*c* 0.8, methanol), R_F 0.4, *T* 3.83 min; ν_{max} 3420 (OH), 2950 (CH), 1740 (C=O), 1240–1055 cm^{-1} (CF). N.m.r. data (CD_3OD): ^{1}H, δ 2.40–2.80 [m, 4

H, $(CH_2)_2CH_2C_8F_{17}$], 3.29 (t, 1 H, $J_{4,5}$ = $J_{4,3}$ = 9.6 Hz, H-4), 3.44 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.58 (AB, $J_{4',3'}$ 3.2 Hz, H-4′), 3.60 (AB, H-3′), 3.65–3.87 (m, 5 H, H-3,1′a,1′b,6′a,6′b), 3.95–4.15 (m, 2 H, H-5,5′), 4.29 (A*B*X, $J_{6b,5}$ 5.1, $J_{6b,6a}$ 12.0 Hz, H-6b), 4.43 (*A*BX, $J_{6a,5}$ 2.9 Hz, H-6a), 4.86 (s, OH), 5.39 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1); ^{13}C, δ 25.8 (t, $^3J_{C,F}$ 3 Hz, CH_2CO), 27.0 (t, $^2J_{C,F}$ 22 Hz, $CH_2C_8F_{17}$), 63.6 and 63.9 (C-1′,6′), 65.3 (C-6), 71.5 (C-5), 71.7 (C-4), 72.9 (C-2), 74.2 (C-3), 75.6 (C-4′), 78.9 (C-3′), 83.6 (C-5′), 93.2 (C-1), 105.0 (C-2′), 172.6 (C=O).

Anal. Calc. for $C_{23}H_{25}F_{17}O_{12}$ (816.4): C, 33.83; H, 3.08; F, 39.56. Found: C, 34.12; H, 3.25; F, 39.40.

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