Springs, OH) placed percutaneously beneath the surface of the tumor. Core body temperature was monitored with a rectal probe (#401, Yellow Springs Instruments, Yellow Springs, OH). Tumor temperature was maintained within 2 °C of core temperature (35 °C) by a jet of cool air placed over the tumor.

Dose–Response Studies. Animals bearing two tumors, one in each flank, were divided into eight groups of five rats per group. Each group received either 0.5, 1.0, 2.5, or 5.0 mg/kg of body weight of sensitizer, administered under pentobarbital anesthesia (65 mg/kg), via the dorsal tail vein. Twenty four hours after injection, one tumor was shielded from light while the other was irradiated for 30 min as described above.

Twelve days after treatment, animals were sacrificed by saturated KCl injection intracardiacally. Both treated and control tumors were harvested, freed of surrounding fat and subcutaneous tissue, and placed in a vacuum dessicator for 72 h, after which, tumor dry weight was determined.

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Synthesis of Perfluoroalkylated Xylitol Ethers and Esters: New Surfactants for Biomedical Uses

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New, well-defined surfactants and cosurfactants were synthesized with the objective of enhancing the stability of fluorocarbon emulsions destined to serve as oxygen carriers for biomedical applications. Monoperfluoroalkylated ethers of xylitol were achieved by addition of perfluoroalkyl iodide on the double bond of a protected xylitol allyl ether in a one-step addition–elimination reaction. Monoesters were obtained specifically on position 5 by treating 1,2:3,4-di-*O*-isopropylidenexylitol with perfluoroalkylated acid chlorides of various chain lengths in pyridine at room temperature. The products display strong surface activity and produce a remarkable synergistic stabilization of a fluorocarbon/Pluronic F-68 type emulsion. Biocompatibility data are reported, which include in vitro toxicity tests on Namalva cell cultures and hemolysis tests on human blood cells; the latter was found to decrease as the length of the *F*-alkyl chain increased. IV injection in mice (n = 10) showed that these products were innocuous at 400–1000 mg/kg of body weight. Preliminary exchange–perfusion experiments on rats with an emulsion containing the *F*-octyl xylitol ether were encouraging.

Fluorocarbons to be administered intravenously as oxygen carriers must be in the form of emulsions,[1-3] which requires the presence of appropriate surfactants. Those used in the first generation of such "blood substitutes", Fluosol-DA (Japan), Ftorosan (Soviet Union), and Emulsion No. 2 (China),[4] are essentially polyoxypropylene/polyoxyethylene block polymers of the Pluronic F-68 type and are not particularly effective for emulsifying fluorocarbons, which makes it necessary to store and ship the emulsions in the frozen state. In order to improve on this situation, we undertook the synthesis of more fluorophilic surfactants, i.e. amphiphilic molecules with a perfluoroalkylated hydrophobic tail.[5] For the hydrophilic head, the crucial biocompatibility requirement oriented our choice toward sugars and natural polyols, and more particularly xylitol, an essentially nontoxic low-cost pentitol. Other desirable improvements over the polyoxyalkylene surfactants were to obtain monodisperse, better defined, purer products and to introduce the possibility of varying the total length of the surfactant molecule and its fluorophilic/hydrophilic balance so as to permit the optimization of the emulsion's characteristics for specific applications.[5] This was achieved by varying the length of the fluorocarbon tail and the number of methylene groups within the intermediate hydrocarbon segment, the junction unit between the hydrophilic and hydrophobic parts being either an ether or an ester group. As cosurfactants with Pluronic F-68, such perfluorinated xylitol derivatives were expected to exercise a synergistic effect, both by decreasing the fluorocarbon/water interfacial tension and by reinforcing the interfacial surfactant layer, owing to the possibility of hydrogen bonding between the polyols' hydroxy groups and the polyethers' oxygens.[6] Preliminary results indicate that these expectations are borne out.[7]

The approaches used and the compounds described in this paper are collected in Scheme I.

Results and Discussion

Synthesis of Perfluoroalkylated Xylitol Allyl Ethers. The linear perfluoroalkyl chain was grafted onto the polyol via the intermediate of a hydrocarbon segment acting from both an electronic standpoint as a stabilizing screen and structurally as a chain prolongator. The simplest and most readily available commercial perfluoroalkyl chains being the iodides R_FI and the addition of R_FI on double bonds being a well-established reaction, we chose to use the following sequence of reactions: formation of the allyl ether **3** from the 1,2:3,4-di-*O*-isopropylidenexylitol, subsequent addition of R_FI to give **4**, followed by the

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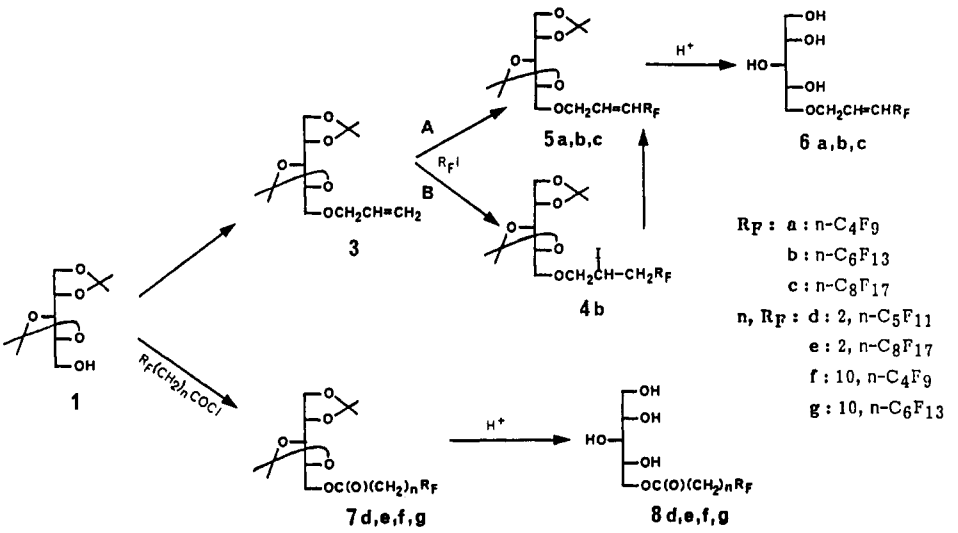
Scheme I. Access to Perfluoroalkylated Xylitol Ethers and Esters in Position 5



elimination of HI to yield **5**. Reserving the introduction of the perfluoroalkylated chain to the end is highly desirable, as it is the most costly reactant. Hydrogenation of **5** did not prove necessary, as the double bond turned out to be highly inert. A protection/deprotection sequence was necessary to ensure the obtention of the monoallyl ethers in position 5 only.

A range of xylitol alkyl and aryl ethers in the terminal position, prepared from protected xylitol, has been reported in the patent literature.[8,9] Although the allyl group has often been used as a protective group in sugar and polyol chemistry,[10] no example of monoallyl xylitol ether in a specific position appears to be known; only mixtures of di- and polyallyl ethers, obtained from unprotected xylitol, have been described.[11]

Protection of xylitol was achieved by isopropylidenation.[12,13] The procedure of Bagget et al.[12] was applied, but in rigorously anhydrous conditions which led to a significant improvement in yield and selectivity (method A); thus, 82% of a mixture of **1** and **2** (the isomer with the free hydroxyl group in position 3) in a 15:1 ratio was obtained, compared to 73% of **1** and **2** in a 3:1 ratio for the literature.[12] Repeated distillation allowed the isolation of pure **1** in at least 60% yield. A comparable improvement (**1** and **2** in a 32:1 ratio, 66%) was achieved (method B) with respect to the literature (11:1 ratio, 52%)[12] when $ZnCl_2$ was used instead of $CuSO_4/H_2SO_4$ under similar conditions. Isomers **1** and **2** are easily detected and identified by GLC or HPLC and by ^1H NMR. Distillation rather than chromatography or recrystallization was found to be the most effective when a large-scale separation of isomer **1** (120 g) was undertaken.

5-*O*-Allyl-1,2:3,4-di-*O*-isopropylidenexylitol (**3**) was synthesized in 92% yield by refluxing **1** in the presence of an excess of sodium hydride in toluene followed by the addition of allyl chloride; **3** was also obtained, in 86% yield, by phase-transfer catalysis with 50% NaOH at room temperature. The structure of **3** was unambiguously established by its spectral and analytical data.

Among the various experimental conditions proposed in the literature for the addition of R_FI on a double bond, we chose those of Burton and Kehoe,[14] but we modified them to favor the elimination of HI and achieve a one-step addition–elimination reaction so as to accede directly to the desired perfluoroalkylallyl xylitol ethers **5**. In Burton's method the addition of R_FI is performed in *tert*-butanol and catalyzed by copper(I) chloride and ethanolamine—with 0.5 equiv of the latter per olefin—yielding 47–98% of the addition product. In only one case, when C_3F_7I was allowed to react with 1-octene, did Burton report the formation of the HI elimination product (42%) besides that of the addition product (57%).

We found that the elimination product could be obtained directly, in 82–90% yield, by increasing the ethanolamine/allylxylitol ether ratio to 4:1. Under these conditions, GLC monitoring of the reaction clearly showed the initial formation of the addition product **4** then its disappearance in favor of **5**. The addition product **4** was prepared independently in 60% yield when using Brace's conditions with benzoyl peroxide as an initiator.[15] Subsequent elimination of HI by heating in the presence of ethanolamine led to **5** in 95% yield. The CF_2 group α to the allyl group in **5** shows two ^{19}F NMR signals at −108.5 and −112 ppm in a 15/85 ratio, corresponding to the *Z* and *E* isomer,[16] respectively, while there is only one signal for the addition product **4**, at −114 ppm.

Among the deprotection methods we tested, we selected that which uses a 9:1 trifluoroacetic acid/water mixture. It proceeds at room temperature and gave 82–97% yields, neutralization being achieved by sodium bicarbonate or by ion exchange on an anionic resin (OH^- form).

The new perfluoroalkylated xylitol allyl ethers were fully identified by their spectral and analytical characteristics. Their surfactant properties are described and discussed below.

Synthesis of Perfluoroalkylated Xylitol Esters. Most of the methods reported in the literature for preparing xylitol esters from hydrocarboxylic acids to be used

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Table I. Surface Activity of Fluorinated Xylitol Ethers and Esters (20 °C) ± 0.3 mN m^{-1}

compound	MW solubility[a]	H_2O C_1[a]	H_2O γ_s	H_2O γ_i	Pluronic at 1 g/L C_2[a]	Pluronic at 1 g/L γ_s	Pluronic at 1 g/L γ_i
H_2O			73	56			
F-decalin	462		22.9	56			
Pluronic F-68		1	48	28			
		0.1	48.7	29.6			
		0.01	50.7	31.4			
6a	410	1	19.7	2.4	1	19.4	2.2
	$4 < S < 5$	0.1	25.6	5.4	0.1	25.0	4.8
		0.01	48.1	32.7	0.01	43.2	26.5
6b	510				1	17.8[c]	1.0
	$0.5 < S < 1$	0.1	17.8	1.0	0.1	17.8	1.0
		0.01	35.7	23.5	0.01	31.9	17.8
6c[b]	610				1	16.6[d]	1.0
	$S = 0.05$				0.5	17.4	1.1
					0.01	19.5	2.8
8d	476	0.5	21.0	2.4	1	17.5	1.1
	$S = 0.5$	0.1	27.1	12.9	0.1	20.3	3.0
		0.01	56.0	42.2	0.01	35.9	24.4
8e[b]	626				0.01	24.6	6.6
	$S < 0.01$						

[a] Solubility (S) in g/L in water at 25 °C, C_1 in g/L of water, C_2 in g/L solubilized or dispersed in 1 g/L Pluronic F-68 solution. [b] Compounds **6c** and **8e** were not soluble enough in water but were dispersible in Pluronic F-68. [c,d] Sonication (power 5) 5 and 15 min, respectively; otherwise solutions were achieved by simple stirring.

as emulsifiers yield mixtures of isomers of mono-, di-, and triesters.[17-19] The only specific synthesis of *mono*esters in terminal position on xylitol was described by Krueger and Arndt[20] and concerned phenoxybenzoic and phenoxypropionic esters to be used as herbicides.

We obtained the perfluoroalkylated esters **7** in 82–95% yield by treating 1,2:3,4-di-*O*-isopropylidenexylitol with the *n*-perfluoroalkylated acid chloride in pyridine at room temperature, the hydrophobic tail being $C_4F_9(CH_2)_{10}$, $C_5F_{11}(CH_2)_2$, $C_6F_{13}(CH_2)_{10}$, or $C_8F_{17}(CH_2)_2$ (see the Experimental Section). Deacetalation was achieved as for the ethers, and purity was controlled by HPLC.

The structural characterization of the new surfactants was primarily achieved by ^{13}C NMR; it showed the presence of C(O), a downfield shift of C-5 by 3.2 ppm compared to that of xylitol, and the appearance of a triplet for the CH_2 α to the *F*-alkyl fragment ($^2J_{C-F}$ = 22 Hz). The effect of this fragment on the CH_2 α to the carbonyl is still perceptible when the hydrocarbon spacer is $(CH_2)_2$; it is no longer so for $(CH_2)_{10}$.

Evaluation as Surfactants and Cosurfactants for Biomedical Uses. Physicochemical and biological tests including solubility, surface activity, emulsion stabilization, and toxicity have been performed; the following observations were made.

Physicochemical Evaluation

The following characteristics were investigated: solubility, dispersibility, surface tension, thermal, and emulsion stability.

Solubility. The compound's solubility in water decreases as expected (from 5 g/L for the xylitol ether with $R_F = C_4F_9$ to 0.05 g/L when $R_F = C_8F_{17}$) when the *F*-alkyl chain length and the hydrophobic character increase (Table I).

Dispersibility. This property is of prime importance as these compounds are to be used as cosurfactants and also because many of them are poorly soluble in water. All compounds were dispersed in clear Pluronic F-68 solution before use (the dispersing agent). The dispersions were deamed satisfactory when they were clear and stable.

The perfluoroalkylated xylitol ethers (**6a–c**) were found to be significantly more dispersible than the esters **8d,e**, and the hydrocarbon prolongator, as in **8f,g** strongly reduces dispersibility. Thus it was easy to disperse 20 g/L of **6a–c** in a 10 g/L solution of Pluronic F-68 in water by sonication, and the resulting dispersions were stable. The sparingly soluble (~0.05 g/L) ether **6c** was nevertheless dispersible in amounts as high as 50 g/L in a 15 g/L aqueous solution of Pluronic F-68. Dispersions were obtained for **8d,e**, but the product settled down rapidly, while they could not be achieved with **8f,g**.

Surface Activity. All the compounds which are soluble or dispersible display marked surface activities. Surface tensions, γ_s, as low as 18 ± 0.3 mN m^{-1} (to be compared with 48 mN m^{-1} for a 1 g/L Pluronic F-68 solution) and water/fluorocarbon (F-decalin) interfacial tensions, γ_i, as low as 1 ± 0.3 mN m^{-1} (28 mN m^{-1} for Pluronic F-68) were obtained.

When examining the surface activity of surfactants belonging to a homogeneous xylitol family (Table I), one finds that efficiency, measured by the concentration required to produce a significant surface effect,[21] increases when the *F*-alkyl chain length increases. Thus **6c** is more efficient than **6a**, since, to produce the same surface tension reduction, the molar amount required is 150 times smaller.

The products having an ether function appear to have more potential than the esters: for example, with the same hydrophobic tail, **6c** (ether) displayed lower superficial and interfacial tensions than **8e** (ester) (Table I).

The addition to a 10 g/L solution of Pluronic F-68 of 100 mg (1% with respect to the Pluronic) of **6c** suffices to decrease its γ_s from 41.5 to 21 mN m^{-1}.[5]

Thermal Stability. One of the xylitol ethers (**6c**) and one of the esters (**8d**) were tested for stability in water at

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Table II. Toxicity toward Namalva Lymphoblastoid Cell Cultures

compd	concn, g/L	results (% vs controls) growth/viability/resowing
6a	0.1	32/87/106
	0.1[a]	125/95/105
6b	0.1	23/80/96
	0.1[a]	78/93/105
	0.2	86/98/95
6c	0.1/0.05[b]	78/97/100
		108/98/115

[a] After detoxification on anionic resin exchanger. [b] Dispersion in Pluronic F-68.

121 °C (FDA sterilization standard) after saturation with nitrogen or with oxygen. A dispersion of 50 g/L of **6c** in a 15 g/L solution of Pluronic F-68 and a 0.5 g/L solution of **8d** in water were used to this end; the dispersion became cloudy at around 115 °C (cloud point of Pluronic F68), but became clear again after cooling and sonication. The dispersion of **6c** and the solution of **8d** were examined by reversed-phase HPLC (refractometer detection) after 15 min, 2, 4, and 24 h at 121 °C and showed no detectable degradation.

Emulsion Stability. Preliminary evaluation of the emulsion-stabilization effect was made by measuring the increase in particle size at 25 °C in emulsions containing 20% (by weight) of F-decalin, 2% of Pluronic F-68, and 1% of the xylitol derivatives and by comparing them with those found for emulsions prepared with 20% of F-decalin and 3% of Pluronic F-68 only. The best results were obtained with **6c** and **8d**; **6c** was preferred for further evaluation because of the lesser availability of the acid needed for preparing **8d**.

The stability of fluorocarbon emulsions increased significantly upon addition of a small amount of **6c**; thus, for example, the average particle size in emulsions prepared with 20% (w/v) of F-decalin or bis(*F*-butyl)ethene (F-44E)[22] and a total of 3% of surfactants, consisting of 2% of Pluronic F-68 and 1% of **6c**, increased by a factor of 2 only (from 0.23 to 0.5 μm), after 1 year at 25 °C, compared to the reference emulsion prepared with 3% of Pluronic only, for which the size of the particles increased by a factor of 18 (from 0.12 to 2.2 μm) under the same conditions. Similarly, the increase in particle size was 17 times less after 1 year for a concentrated, 50% w/v emulsion of F-decalin prepared with a 1:1 Pluronic F-68/**6c** mixture of surfactants (total 5%) than for a similarly prepared emulsion, but with Pluronic F-68 alone.[7]

Biological Results. The perfluoroalkylated allyl ether xylitols **6a–c** were selected for further evaluation on the basis of their low superficial and interfacial tensions and their stabilizing effect on fluorocarbon emulsions.

Cell cultures of the Namalva lymphoblastoid strain were used both to assess direct cell toxicity and as a means of monitoring the final purification steps. The results summarized in Table II show that solutions of **6a** (0.1 g/L), **6b** (0.2 g/L), and a dispersion (0.1 g/L) of **6c** in a 0.05 g/L solution of Pluronic F-68 cause no significant inhibition of cell growth and viability compared to controls nor any effect on their viability and growth after resowing, in spite of the considerable surface activity of the compounds.

As the compounds are destined to be used in the formulation of intravenously injectable preparations, the next test was for hemolysis.

No hemolytic effect on human red blood cells was noticed when dispersions of the surfactants in Pluronic F-68 at the following concentrations were tested: **6a** (1 g/0.05 g per L), **6b** (10 g/2.5 g per L), and **6c** (40 g/20 g per L).

Table III. Hemolytic Activity of *F*-Alkyl Ether Derivatives of Xylitol

compd	dispersions in Pluronic F-68[a]	mM	hemolysis visual	hemolysis % [b] vs control
6a	1/0.05	2.4	0	0
	10/5	24.4	++++	117
	20/1	48.7	++++	129
6b	10/2.5	19.6	0	4
	20/5	39.2	++	25
	40/10	78.4	++++	112
6c	10/1	16.4	0	0
	20/10	32.8	0	0
	40/20	65.6	+	13
NaCl 9‰	control (−)		0	0
H_2O	control (+)		++++	100

[a] Grams of compound per gram of Pluronic F-68 per liter. [b] Hemolysis % = 100 $(OD_{test} - OD_{NaCl})/(OD_{H_2O} - OD_{NaCl})$. [c] 55% erythrocytes hemolysis in a suspension of 1% hematocrit.

Table IV. Toxicity Tests on Mice

compd	dispersions in Pluronic F-68[a]	concn, mg/kg of body weight	survival ratio
6a	0.1/−	2	10/10
	20/10	443	9/10
6b	0.1/−	2	10/10
	15/3.73	371	10/10
	20/5	491	8/10
	40/10	1034	0/5
6c	20/10	455	10/10
	42/22	1035	8/10
	50/15	1187	5/10

[a] Grams of compound per gram of Pluronic F-68 per liter.

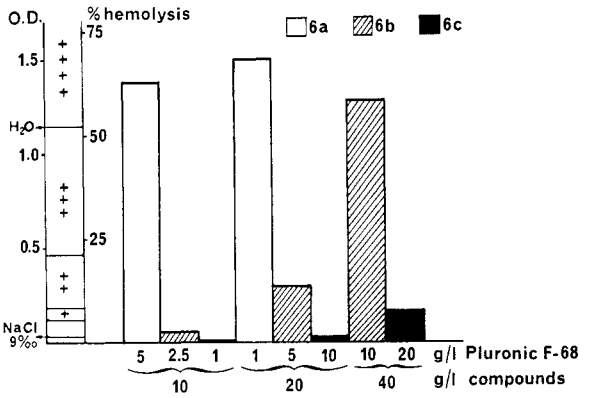

Figure 1. Hemolytic activity of *F*-alkyl derivatives of xylitol. Percent of hemolysis is calculated for an erythrocyte suspension at 1% hematocrit.

The hemolytic activity increases (Table III) with concentration. But the most interesting observation is that it decreases when the *F*-alkyl chain length and subsequently the surface activity increase (Figure 1). This is noteworthy because the effect observed with hydrocarbonated amphiphiles is usually the opposite.[24]

Injections of about 0.5 mL of dispersions in Pluronic F-68 in 9‰ aqueous NaCl of **6a** (20 g/10 g per L), **6b** (20 g/5 g per L), and **6c** (42 g/22 g per L) were performed through the tail vein of mice. The survival ratio, growth, and behavior were normal throughout the 80-day observation period following the injection, as exemplified by the weight uptake curves, shown in Figure 2.

A dispersion of 0.5 g/L of **6c** in 1 g/L of Pluronic F-68 was used to prepare a 10% (w/v) emulsion. This emulsion was used to perform an isovolemic exchange perfusion experiment on a series of 10 conscious rats to hematocrit

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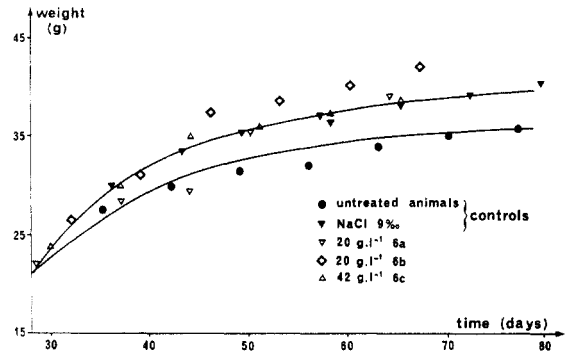

Figure 2. Weight gain of mice after iv injection of saline dispersions of **6a–c**. Compounds **6a,b,c** were dispersed in 10 (▽), 5 (◇), and 22 (△) g/L of Pluronic F-68, respectively.

15 vol% (FiO_2 = 0.6). The behavior of the animals during and after the exchange was judged to be excellent, and a survival ratio of 10/10 was observed after 6 months of observation.

This paper shows that well-defined and pure, strongly amphiphilic ethers and esters of xylitol, monoperfluoroalkylated in the terminal position, can be synthesized in good overall yields. Preliminary evaluation indicates that, in spite of their strong surface activity, these compounds have good biocompatibility. A 170 g size batch of 5-*O*-[3′-(*F*-octyl)-2′-propenyl]xylitol (**6c**) has now been prepared in order to allow further experimentation to be undertaken.

Experimental Section

Physical Methods. Melting points were measured on a Reichert apparatus. Elemental analyses within 0.4% of the theoretical values were obtained for all compounds unless stated otherwise. Infrared spectra were recorded on a Bruker IFS 45 spectrometer (cm^{-1}), ^1H NMR spectra (δ in ppm, deuterated solvents with Me_4Si as internal reference) were obtained with a Bruker 80 MHz, ^{19}F NMR (δ ppm, internal reference CCl_3F) and ^{13}C NMR (δ ppm, internal reference Me_4Si) spectra were recorded with a Bruker FT spectrometer at 84.67 and 22.63 MHz, respectively, and mass spectra were obtained on a Ribermag R10-10 spectrometer, by direct introduction of the sample into the ion source at an ionizing voltage of 70 eV, or using GLC-MS coupling or chemical ionization. TLC was effected on silica gel plates (Merck 60F 254), with A, $KMnO_4$–NaOH 0.5 g/100 mL 1 N or B, H_2SO_4–MeOH 1/1 revelators. Column chromatography was performed on Kieselgel 60, 70–230 mesh ASTM (Merck). GLC was conducted with a Girdel apparatus equipped with a flame-ionization detector, either with a 10% SE 30 3m (column A) or with a glass capillary Carbowax 20M column 25 m × 0.32 mm i.d. (column B). Analytical HPLC, reversed phase, was performed with a Waters apparatus Model 510 with a differential refractometer detector R 401, column C_{18} 30 cm × 3.9 mm i.d. (9 μm), and preparative HPLC using Model Preppak 500, same support. Surface tensions were measured on an automatic Lauda tensiometer using the Lecomte de Noüy method (platinum ring). Dispersions were prepared by sonication (Sonifier cell disruptor B30; titanium probe).

Starting Materials. All solvents were dried and distilled according to standard procedures. Copper(II) sulfate was dried for 12 h at 250 °C before use. The *F*-alkyl iodides (gift from ATOCHEM) were decolorized by a sodium thiosulfate solution and dried over Na_2SO_4 before distillation. All reactants were dried under reduced pressure (10^{-2} mmHg) overnight when needed (experiments conducted under argon). *n*-(*F*-pentyl)-3-propanoic acid was synthesized as follows: (i) *F*-pentanoyl chloride, 87% yield from $C_5F_{11}CO_2K$,[25] when allowed to react with $Ph_3P{=}CHCO_2Et$,[26] gave 95% of (*F*-pentanoylcarbethoxymethylene)-triphenylphosphorane in a fashion similar to that described by Huang et al.;[27,28] (ii) by pyrolysis (150–220 °C/20 mmHg) of this compound, 90% of ethyl 3-(*F*-pentyl)propynoate was obtained (bp = 50 °C/20 mmHg); (iii) after hydrogenation (Pd/C, 92%, bp = 68–69 °C/20 mmHg) and saponification of the ester, 3-(*F*-pentyl)propanoic acid (recrystallized from hexane) was obtained in 61% overall yield from the potassium acid salt. The 11-(*F*-alkyl)undecanoic acids (*F*-alkyl: n-C_4F_9, n-C_6F_{13}) were prepared as described by Brace:[29,30] (a) radical addition of perfluoroalkyl iodide (0.105 mol) to methyl 10-undecenoate (0.12 mol) initiated by AIBN (α,α'-azobisisobutyronitrile), and (b) methyl 11-(*F*-alkyl)-10-iodoundecanoate by Zn reduction in absolute ethanol, giving ethyl 11-(*F*-alkyl)undecanoate, which, when saponified, afforded the acids (recrystallization from hexane) (n-C_4F_9, mp = 55 °C; n-C_6F_{13}, mp = 67 °C) with an overall yield of 40%. The 3-(*F*-alkyl)propanoyl chloride and the 11-(*F*-alkyl)undecanoyl chloride were obtained by the classical method–refluxing the corresponding *F*-alkyl acid with an excess of thionyl chloride (3 equiv): $C_5F_{11}(CH_2)_2COCl$, 82%, bp = 55 °C (20 mmHg); $C_8F_{17}(CH_2)_2COCl$, 90%, bp = 98 °C (20 mmHg); $C_4F_9(CH_2)_{10}COCl$, 98%, bp = 104 °C (0.06 mmHg); $C_6F_{13}(CH_2)_{10}COCl$, 91%, bp = 118–119 °C (0.01 mmHg).

Toxicity Tests. The tests were made on solutions in 9‰ aqueous NaCl; when the solubility of the surfactants was too low, Pluronic F-68 (detoxified by treatment first with an acid cationic resin exchanger (Amberlite IR 120), then a basic anion resin exchanger (Amberlite IRA-400)) was used as a solubilizer.

(a) Effect on Cell Cultures. The Namalva cell strain was chosen because of the stability and reproducibility of its growth parameters. The cells grow in suspension (RPMI containing 10% of fetal calf serum, at 37 °C under 7% of CO_2), which is thought to be an advantage when testing surface-active material. A series of five flasks was filled with 2 mL of cell-culture medium containing about 3.10^5 cells/mL and 2 mL of solution of the compound to be tested. A reference series was realized under the same conditions. After 4 days of incubation, the cells were counted and the viability was determined by the Trypan Blue dye exclusion method. When growth and viability were satisfactory, the compound was removed, and the cells were washed and resown in 4 mL of culture medium. After 4 days, the growth rate and viability were measured again. The results are presented in Table II with respect to controls as follows: A/B/C (A, growth rate; B, viability; C, growth after resowing).

(b) Hemolysis. Human female blood (group A+) was drawn by venous puncture into heparinized tubes. Plasma and buffy coat were removed by centrifugation at 3300 rpm for 10 min at 10 °C and the erythrocytes were washed three times with the phosphate-buffered isotonic saline (pH 7.4): 1.48 g of anhydrous Na_2HPO_4, 0.43 g of anhydrous KH_2PO_4, 7.2 g of NaCl in 1 L of injectable water. The packed cells were then suspended in the same buffer to give a suspension of 1% hematocrit (N = 8–9 × 10^7 cells/mL). Determination of hemolytic activity was carried out immediately by adding 2 mL of suspension to the same volume of solution or dispersion of the surfactant in NaCl 9‰. After 1 h of incubation in a shaking thermostated bath at 37 °C, the tubes were centrifuged to remove the unhemolyzed cells. The degree of hemolysis as given in Table III was evaluated by comparing spectrophotometrically (540 nm) the amount of hemoglobin released in the supernatant liquid with 0% (NaCl 9‰) and 100% (H_2O) control samples. The percentage of hemolysis was calculated as hemolysis (%) = $100(OD_{test} - OD_{NaCl})/(OD_{H_2O} - OD_{NaCl})$.

(c) Acute Toxicity. An indication of the acute toxicity of the compounds was obtained in vivo by rapid injections of about 0.5 mL (i.e. 25 mL/kg of body weight) of a solution or dispersion of the surfactants through the tail vein of a series of 10 mice (ca 20 g). Symptoms, behavior, mortality, and body-weight increase (Figure 2) were recorded throughout the 80 days following the injection.

(d) Isovolemic Blood Exchange Tests. These were performed on conscious rats according to the method reported by

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Goodin et al.,[31] which allows a strictly isovolemic exchange. The animals were allowed to breathe carbogen (95% O_2, 5% CO_2); the oxygen partial pressure in the cage was controlled with an O_2-specific probe. The fluorocarbon used in this test, bis(*F*-butyl)ethene, F-44E, previously tested for iv use,[32] was detoxified by treatment with KOH, washing with water, stirring with activated charcoal, and filtration. A stem emulsion (F-44E/Pluronic F-68/**6c** 20/2/1% w/v) was prepared with a Manton-Gaulin high-pressure homogenizer, after premixing by sonication (power 5, 15 min, pulsed way). It was controlled by measuring mean particle diameter with a centrifugation sedimental method. The emulsion was then diluted with albumin and buffer solutions to adjust the osmolarity to 300 mosm. A mixture of oxygen and carbon dioxide was dissolved in diluted emulsion to adjust the pH to 6.9. Rats of about 100 g were used. The volume infused was equal to one blood volume (15 mL), and the hematocrit decreased to about 15%. Blood samples were taken and analyzed before and after the exchange perfusion, and the hematocrit was monitored for 3 days after the operation. The behavior of the animals during and after the exchange, and their survival ratio, were noted.

Isopropylidenation of Xylitol (1, 2). Method A.[12] Xylitol (130 g, 0.86 mol) was ketalized with anhydrous acetone (1.5 L); the reaction was catalyzed by anhydrous copper(II) sulfate (281.3 g, 1.76 mol) and concentrated sulfuric acid (3 mL). The mixture was shaken for 24 h at room temperature. The reaction was monitored by TLC (CCl_4/AcOEt 1:3, rev. B). The precipitate was filtered; the filtrate was made alkaline with $Ca(OH)_2$, filtered again, and reduced in vacuo. The residue was taken up in AcOEt, washed with water to neutrality, dried (Na_2SO_4), concentrated, and dried under reduced pressure (10^{-2} mmHg). The yield of **1** and **2** in a 15:1 ratio was 162.3 g (82%) and, after distillation, 120.8 g (61%) of pure **1** was obtained (lit.:[12] 73% of **1** and **2** in 3:1 ratio). It is also possible to obtain pure **1** by recrystallization from hexane: mp = 35–37 °C (lit.[12] mp = 36 °C).

Method B.[12] Zinc chloride (28 g, 0.2 mol) dissolved in anhydrous acetone (225 mL) was shaken for 15 min, and xylitol (16 g, 0.1 mol) was added under argon. After shaking for 24 h at room temperature and addition of aqueous NaOH (400 mL, 20%), the precipitate was filtered, and the filtrate was extracted five times with 200 mL of chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. GLC analysis (175 °C) showed that **1** and **2** were formed in a 13:1 ratio. Distillation gave **1** (16.2 g, 66%, bp = 90–100 °C/0.3 mmHg), which crystallized on storage.

Method C.[13] Anhydrous acetone (500 mL) was added to xylitol (32 g, 0.21 mol) in the presence of $CuSO_4$ (67.8 g, 0.425 mol) and concentrated H_2SO_4 (2.4 mL, 0.024 mol). The reaction and treatment were conducted as in method A (alkalization was effected with triethylamine instead of $Ca(OH)_2$). The viscous liquid crystallized at −20 °C, affording 34.5 g (71%) of white needles. GLC analysis (175 °C, column A) showed a mixture of **1** (t_R = 8.5 min, 98%) and **2** (t_R = 8 min, 2%). Data for **1**: GLC (175 °C, column B) t_R (**1**) = 8.7 min, t_R (**2**) = 5.3 min; analytical HPLC (MeOH/H_2O 65:35) t_R (**1**) = 4.3 min, t_R (**2**) = 4.1 min. IR (neat) 3470 (OH), 1370, 1380 (Me_2C); ^1H NMR ($CDCl_3$) 1.31, 1.36 (2 s, ratio 1/3, 12 H, CH_3), 3.23 (s, OH), 3.56–4.04 (m, 7 H, xylitol protons); ^{13}C NMR ($CDCl_3$) 25.5 (CH_3), 26.1 (CH_3), 27.0 (CH_3), 27.2 (CH_3), 62.3 (C-5), 65.6 (C-1), 75.2 (C-2), 77.1 (C-3), 77.9 (C-4), 109.6 (quaternary C), 109.8 (quaternary C); MS (EI) *m/e* 217 [24, $(M - CH_3)^+$], 101 (18, $C_5H_9O_2^+$), 43 (100, $CH_3C{\equiv}O^+$).

5-*O*-Allyl-1,2:3,4-di-*O*-isopropylidenexylitol (3). Method A. A solution of 1,2:3,4-di-*O*-isopropylidenexylitol (**1**, 120 g, 0.517 mol, purity >97%) in toluene (150 mL) was slowly added to a suspension of sodium hydride (16.9 g, 0.704 mol) in anhydrous toluene (450 mL). The mixture was shaken for 18 h at room temperature, then heated at 80–100 °C for 3 h. After cooling, a solution of allyl chloride (85 mL, 1.04 mol) in toluene (150 mL) was added dropwise, and the mixture was refluxed at 110 °C for 18 h. TLC monitoring ($CHCl_3$/AcOEt 12:1, rev. A then B) showed that **3** was formed, while **1** had totally disappeared. The excess of sodium hydride was destroyed by methanol then water at 0 °C. The aqueous phase was extracted twice with 200 mL of ether, and the combined extracts were washed with water to neutrality, dried over Na_2SO_4, and concentrated. The crude yellow liquid was distilled to give 133.7 g (95%) of **3**, a viscous, colorless liquid.

Method B. Compound **3** may also be obtained by a phase-transfer catalysis at room temperature when **1** (1 g, 4.3 mmol, purity >98.7%) was allowed to react in ether (4 mL) with allyl chloride (1.4 mL, 17.2 mmol), tetrabutylammonium hydrogen sulfate (73 mg, 0.215 mmol), and a sodium hydroxide solution (3 mL, 50%, w/w). The reaction, monitored by GLC, was 99% complete after 7 h. The crude product was taken up in ether (3 × 25 mL), washed to neutrality, dried (Na_2SO_4), concentrated, and then dried under reduced pressure (10^{-2} mmHg) to give **3** (1 g) in 86% yield: bp = 94° C (0.4 mmHg); purity >99.9% (GLC 175 °C, column A, t_R = 12.4 min); IR (neat) 1645 (C═C); ^1H NMR (CCl_4) 1.33, 1.34 (2 s, ratio 1/3, 12 H, CH_3), 3.52 (d, $^3J_{HH}$ = 4 Hz, 2 H, H-1′), 3.77–4.17 (m, 7 H, xylitol protons), 5.02–5.38 (m, 2 H, H-3′), 5.63–6.08 (m, 1 H, H-2′); ^{13}C NMR ($CDCl_3$) 25.5 (CH_3), 26.3 (CH_3), 27.0 (2 CH_3), 65.7 (C-1), 70.8, 72.6 (C-1′, C-5), 75.7, 76.6, 78.6 (C-2, C-3, C-4), 109.8 (2 quaternary C), 117.3 (C-3′), 134.5 (C-2′); MS (EI) *m/e* 257 [27, $(M - CH_3)^+$], 101 (22, $C_5H_9O_2^+$), 43 (100, $CH_3C{\equiv}O^+$), 41 (95, $CH_2{=}CHCH_2^+$). Anal. ($C_{14}H_{24}O_5$) C, H, O.

5-*O*-[3′-(*F*-Butyl)-2′-propenyl]-1,2:3,4-di-*O*-isopropylidenexylitol (5a). A mixture of 5-*O*-allyl-1,2:3,4-di-*O*-isopropylidenexylitol (**3**, 40.9 g, 0.15 mol), *tert*-butanol (220 mL), copper(I) chloride (8.86 g, 0.863 mol), *F*-butyl iodide (102.6 mL, 0.6 mol), and ethanolamine (79.9 mL, 1.37 mol) was refluxed for 36 h at 110 °C. The reaction was monitored by GLC until **3** and the intermediate addition product had totally disappeared. After cooling, water (300 mL) was added, and the mixture was extracted four times with ether (250 mL). The combined extracts were washed to neutrality, dried (Na_2SO_4), and concentrated. The dark brown viscous liquid was distilled to give **5a**, a pale yellow liquid (60.2 g, 82%): bp = 90–92 °C (0.005 mmHg); purity >95.5% (GLC 210 °C, column A, t_R = 7.2 min); IR (neat) 1680 (C═C), 1060–1230 (CF); ^1H NMR ($CDCl_3$) 1.35, 1.41 (2 s, ratio 1/3, 12 H, CH_3), 3.65 (d, $^3J_{HH}$ = 4 Hz, 2 H, H-1′), 3.88–4.22 (m, 7 H, xylitol protons), 5.68–6.57 (m, 2 H, CH═CH); ^{19}F NMR ($CDCl_3$) −81.7 (3 F, CF_3), −108.7 and −112.4 (2 F, CF_2 α, Z/E = 10/90), −124.9 (2 F, $CF_2\beta$), −126.3 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 25.5 (CH_3), 26.3 (CH_3), 27.1 (2 CH_3), 65.7 (C-1), 69.8 (C-1′), 71.5 (C-5), 75.4, 76.7, 77.9 (C-2, C-3, C-4), 110.0 (quaternary C), 110.3 (quaternary C), 117.3 (t, $^2J_{C-F}$ = 25 Hz, C-3′), 138.4 (t, $^3J_{C-F}$ = 10 Hz, C-2′); MS (CI: NH_3) *m/e* 508 [8, $(M + 18)^+$], 492 [46, $(M + 2)^+$], 491 [100, $(M + 1)^+$], 490 (28, M^+), 475 [13, $(M - CH_3)^+$], 101 (48, $C_5H_9O_2^+$). Anal. ($C_{18}H_{23}F_9O_5$) C, H, F.

5-*O*-[3′-(*F*-Hexyl)-2′-iodopropyl]-1,2:3,4-di-*O*-isopropylidenexylitol (4b). A mixture of 5-*O*-allyl-1,2:3,4-di-*O*-isopropylidenexylitol (**3**, 9.5 g, 34.9 mmol) and benzoyl peroxide (1.3 g, 5.3 mmol) was heated under argon to 95 °C. *F*-Hexyl iodide (11 mL, 49.7 mmol) was then added, and the reaction course monitored by TLC showed total disappearance of **3** after 2 h at 95 °C. The dark brown mixture was then cooled, the excess of perfluoroalkyl iodide was recuperated under reduced pressure (0.15 mmHg), and the residue was purified by chromatography on silica gel (hexane/Et_2O 4:1 then 4:2 gradient), yielding a pale yellow viscous liquid (15 g, 60%): purity >99.7% (GLC, column A, t_R = 20.7 min), TLC (hexane/Et_2O 4:1, rev A then B, R_f (**3**) = 0.35, R_f (**4b**) = 0.44; IR (neat) 1380, 1370 (Me_2C), 1080–1240 (CF); ^1H NMR ($CDCl_3$) 1.39, 1.44 (2 s, ratio 1/3, 12 H, CH_3), 2.44–3.30 (m, 2 H, CH_2R_F), 3.56–4.49 (m, 10 H, CH_2, CHI, xylitol protons); ^{19}F NMR ($CDCl_3$) −81.5 (3 F, CF_3), −114.2 (2 F, CF_2 α), −122.3 (2 F), −123.4 (2 F), −124.2 (2F), −126.7 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 14.2 (C-2′, CHI), 25.5 (CH_3), 26.3 (CH_3), 27.1 (2 CH_3), 37.8 (t, $^2J_{C-F}$ = 20 Hz, C-3′), 65.8 (C-1), 71.5 (C-5), 76.5 (C-1′), 75.5, 76.5, 78.0 (C-2, C-3, C-4), 110.0 (quaternary C), 110.1 (quaternary C); MS (EI) *m/e* 720 [13, $(M + 2)^+$], 719 [23, $(M + 1)^+$], 718 (16, M^+), 703 [53, $(M - CH_3)^+$], 591 [7, $(M - I)^+$], 590 [2, $(M-HI)^+$], 101 (74, $C_5H_9O_2^+$), 43 (100, $CH_3C{\equiv}O^+$). Anal. ($C_{20}H_{24}F_{13}IO_5$) C, H, F, I.

5-*O*-[3′-(*F*-Hexyl)-2′-propenyl]-1,2:3,4-di-*O*-isopropylidenexylitol (5b). Method A. The reaction was con-

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ducted as for **5a**, with **3** (16.9 g, 62.16 mmol), *F*-hexyl iodide (55 mL, 248.9 mmol), *tert*-butanol (77 mL), copper chloride (1.87 g, 18.2 mmol), and ethanolamine (18 mL, 298.2 mmol). After treatment and distillation, **5b** was obtained as a yellow viscous liquid (31.9 g, 87%).

Method B. Compound **5b** can also be prepared in 95% yield by refluxing **4b** (9 g, 12.5 mmol) with a large excess of ethanolamine (10 mL, 171.7 mmol) for 80 min in ethanol (50 mL). The reaction was monitored by GLC and the treatment was conducted as for **5a**: bp = 113–114 °C (0.005 mmHg); purity >99.4% (GLC 210 °C, column A, t_R = 8.8 min); IR (neat) 1670 (C=C), 1070–1250 (CF); ^{1}H NMR (CCl_4) 1.30, 1.35 (2 s, ratio 1/3, 12 H, CH_3), 3.60 (d, $^3J_{HH}$ = 4 Hz, 2 H, H-1′), 3.77–4.23 (m, 7 H, xylitol protons), 5.67–6.50 (m, 2 H, CH=CH); ^{19}F NMR ($CDCl_3$) −81.5 (3 F, CF_3), −108.5 and −112.3 (2 F CF_2 α, Z/E = 13/87), −122.2 (2 F), −123.4 (2 F), −124.0 (2 F), −126.8 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 25.4 (CH_3), 26.2 (CH_3), 27.0 (2 CH_3), 65.8 (C-1), 69.8 (C-1′), 71.5 (C-5), 75.4, 76.6, 77.8 (C-2, C-3, C-4), 110.0 (quatenary C), 110.2 (quaternary C), 117.6 (t, $^2J_{C-F}$ = 25 Hz, C-3′), 138.7 (t, $^3J_{C-F}$ = 10 Hz, C-2′); MS (CI: NH_3) *m/e* 591 [27, $(M + 1)^+$], 590 (3, M^+), 575 [61, $(M - CH_3)^+$], 101 (100, $C_5H_9O_2^+$). Anal. ($C_{20}H_{23}F_{13}O_5$) C, H, F.

5-*O*-[3′-(*F*-Octyl)-2′-propenyl]-1,2:3,4-di-*O*-isopropylidenexylitol (5c). Likewise, a solution of **3** (17.6 g, 65 mmol) in *tert*-butanol (78 mL), *F*-octyl iodide (142 g, 70 mL, 0.26 mol), copper(I) chloride (1.92 g, 18.7 mmol), and ethanolamine (15.2 mL, 0.26 mol) was refluxed at 110 °C for 24 h. 5-*O*-[3′-(*F*-Octyl)-2′-propenyl]-1,2:3,4-di-*O*-isopropylidenexylitol (**5c**) was distilled as a pale yellow, viscous liquid (47.4 g, 88%): bp = 117–118 °C (0.005 mmHg); purity >99% (GLC 210 °C, column A, t_R = 12.6 min); TLC ($CHCl_3$/AcOEt 12:0.5 rev. B, R_f = 0.47); IR (neat) 1697 (C=C), 1060–1300 (CF); ^{1}H NMR ($CDCl_3$) 1.35, 1.41 (2 s, ratio 1/3, 12 H, CH_3), 3.65 (d, $^3J_{HH}$ = 4 Hz, 2 H, H-1′), 3.88–4.22 (m, 7 H, xylitol protons), 5.68–6.57 (m, 2 H, CH=CH); ^{19}F NMR ($CDCl_3$) −81.6 (3 F, CF_3), −108.4 and −112.3 (2 F, CF_2 α, Z/E = 14/86), −122.3 (6 F), −123.2 (2 F), −123.9 (2 F), −126.7 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 25.5 (CH_3), 26.3 (CH_3), 27.1 (2 CH_3), 65.8 (C-1), 69.9 (C-1′), 71.6 (C-5), 75.4, 76.7, 77.9 (C-2, C-3, C-4), 110.0 (quaternary C), 110.2 (quaternary C), 117.7 (t, $^2J_{C-F}$ = 25 Hz, C-3′), 138.7 (t, $^3J_{C-F}$ = 10 Hz, C-2′); MS (CI: NH_3) *m/e* 708 [3, $(M + 18)^+$], 692 [30, $(M + 2)^+$], 691 [100, $(M + 1)^+$], 690 (69, M^+), 675 [10, $(M - CH_3)^+$], 101 (24, $C_5H_9O_2^+$). Anal. ($C_{22}H_{23}F_{17}O_5$) C, H; F: calcd, 46.78; found, 47.52.

5-*O*-[3′-(*F*-Butyl)-2′-propenyl]xylitol (6a). A trifluoroacetic acid/water solution (89 mL, 9:1 v/v) was added dropwise to 5-*O*-[3′-(*F*-butyl)-2′-propenyl]-1,2:3,4-di-*O*-isopropylidenexylitol (**5a**, 25 g, 51 mmol). Stirring was continued for 30 min at room temperature while the reaction was monitored by TLC ($CHCl_3$/MeOH 10:1.5, rev. A). Then the dark brown solution was concentrated in vacuo and chromatographed over silica ($CHCl_3$/MeOH 10:1.5). Preparative HPLC (MeOH/H_2O 65:35) was used for the final purification, and the gelatinous, white gel **6a** obtained (17.1 g, 82%) was finally treated with a basic anion resin exchanger (Amberlite IRA-400, OH^- form) and dried under 10^{-2} mmHg: analytical HPLC (MeOH/H_2O 85:15) t_R = 3.6 min; IR (neat) 3380 (OH), 1680 (C=C), 1130–1230 (CF); ^{1}H NMR (CD_3OD/$CDCl_3$ 1:1) 3.60–4.23 (m, 9 H, H-1′ and xylitol protons), 4.55 (s, OH), 5.74–6.62 (m, 2 H, CH=CH); ^{19}F NMR (CD_3OD) −81.1 (3 F, CF_3), −107.5 and −111.3 (2 F, $CF_2\alpha$, Z/E = 10/90), −123.9 (2 F, CF_2 β), −125.5 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 64.3 (C-1), 70.4, 73.6 (C-1′, C-5), 72.2, 72.3, 73.9 (C-2, C-3, C-4), 117.4 (t, $^2J_{C-F}$ = 25 Hz, C-3′), 141.4 (t, $^3J_{C-F}$ = 10 Hz, C-2′); MS (CI: NH_3) *m/e* 428 [100, $(M + 18)^+$], 411 [100, $(M + 1)^+$], 410 (2, M^+). Anal. ($C_{12}H_{15}F_9O_5$) C, H, F.

5-*O*-[3′-*F*-Hexyl)-2′-propenyl]xylitol (6b). Likewise, deacetalation of **5b** (14 g, 23.7 mmol) was performed with 46.5 mL of a trifluoroacetic acid/water solution (9:1 v/v) for 45 min. Purification by column chromatography ($CHCl_3$/MeOH 10:1.5) led to **6b** (white gel, 11.8 g, 97%): analytical HPLC (MeOH/H_2O, 85:15), t_R = 4.3 min; TLC ($CHCl_3$/MeOH 4:1, rev. A or B, R_f = 0.4); IR (neat) 3370 (OH), 1680 (C=C), 1120–1240 (CF); ^{1}H NMR (CD_3OD) 3.64–4.27 (m, 9 H, H-1′ and xylitol protons), 4.72 (s, OH), 5.67–6.63 (m, 2 H, CH=CH); ^{19}F NMR (CD_3OD) −81.1 (3 F, CF_3), −107.5 and −111.2 (2 F, CF_2 α, Z/E = 13/87), −121.3 (2 F), −122.8 (4 F), −126.1 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 64.3 (C-1), 70.4, 73.6 (C-1′, C-5), 72.2, 72.3, 73.9 (C-2, C-3, C-4), 117.6 (t, $^2J_{C-F}$ = 25 Hz, C-3′), 141.4 (t, $^3J_{C-F}$ = 10 Hz, C-2′); MS (CI: NH_3) 528 [36, $(M + 18)^+$], 511 [34, $(M + 1)^+$], 510 (100, M^+). Anal. ($C_{14}H_{15}F_{13}O_5$) H; C: calcd, 32.95; found, 32.20, F; calcd, 48.40; found 47.42.

5-*O*-[3′-(*F*-Octyl)-2′-propenyl]xylitol (6c). Compound **6c** was obtained likewise by stirring **5c** (16.1 g, 23.3 mmol) with a trifluoroacetic acid/water mixture (16.5 mL, 9:1 v/v) for 10 min. The crude material was purified first on preparative HPLC (MeOH/H_2O 80:20), then on a silica column (AcOEt/MeOH 6:1) and then dried in vacuo, yielding white, solid **6c** (12.1 g, 85%).

Compound **6c** was also obtained by allowing a sulfuric acid solution [1.5 N, 12.6 mL) to react with **5c** (7.8 g, 11.3 mmol) in ether. The mixture was heated for 2 h at 70 °C while the reaction was followed by TLC (AcOEt/MeOH 6:1, rev. A). After **5c** had disappeared the mixture was cooled, and ethyl acetate (250 mL) and a saturated water/sodium bicarbonate solution (200 mL) were added to accomplish neutralization. The water layer was extracted twice with ethyl acetate (200 mL), and the organic phases were washed with water to neutrality, dried (Na_2SO_4), and evaporated to give a yellow solid (6.67 g). Purification by column chromatography led to 3.5 g of a white solid, **6c** (51%).

A larger batch of **6c** (165.3 g) was obtained in 50% overall yield from xylitol (130 g). The experiment was conducted as described above. The final step was optimized: after evaporation of the CF_3CO_2H/H_2O mixture, the crude product in methanol was neutralized over an ion-exchange column (Amberlite IRA-400, OH^- form), and the purification over silica was accomplished with a ternary eluent mixture (AcOEt/EtOH/H_2O 80:13:7): mp = 154 °C; analytical HPLC (MeOH/H_2O 85:15) t_R = 5.7 min; IR (KBr) 3365 (OH), 1680 (C=C), 1115–1205 (CF); ^{1}H NMR (CD_3OD) 3.60–4.26 (m, 9 H, H-1′ and xylitol protons), 4.77 (s, OH), 5.79–6.68 (m, 2 H, CH=CH); ^{19}F NMR (CD_3OD) −81.6 (3 F, CF_3), −108.4 and −112.3 (2 F, CF_2 α, Z/E = 6/94), −122.3 (6 F), −123.2 (2 F), −123.9 (2 F), −126.7 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 64.3 (C-1), 70.4, 73.7 (C-1′, C-5), 72.1, 72.3, 74.0 (C-2, C-3, C-4), 117.6 (t, $^2J_{C-F}$ = 25 Hz, C-3′), 141.4 (t, $^3J_{C-F}$ = 10 Hz, C-2′); MS (CI: NH_3) *m/e* 628 [100, $(M + 18)^+$], 611 [60, $(M + 1)^+$], 610 (33, M^+). Anal. ($C_{16}H_{15}F_{17}O_5$) C, H; F: calcd, 52.92; found, 51.53.

5-*O*-[3′-(*F*-Pentyl)propanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (7d). A solution of 3-(*F*-pentyl)propanoyl chloride (5.17 g, 14.34 mmol) diluted in chloroform (30 mL) was added dropwise to a solution of anhydrous 1,2:3,4-di-*O*-isopropylidenexylitol (**1**, 20% excess, 4 g, 17.25 mmol) in anhydrous chloroform (50 mL) and pyridine (3 mL). The mixture was stirred for 24 h at room temperature. The chloroform was then evaporated, and ether (100 mL) and water (100 mL) were added. The aqueous phase was extracted three times with ether (100 mL). The combined organic phases were washed with water to neutrality, dried over Na_2SO_4, filtered, and evaporated, leading after column chromatography to **7d** as a colorless viscous liquid (6.76 g, 85%): TLC (CH_2Cl_2/AcOEt 12:1, rev. B) R_f = 0.66; IR (neat) 1750 (C=O), 2940, 2990 (CH), 1100–1240 (CF); ^{1}H NMR ($CDCl_3$) 1.37, 1.43 (2 s, ratio 1/3, 12 H, CH_3), 2.46–2.90 (m, 4 H, C_2H_4), 3.79–4.50 (m, 7 H, xylitol protons); ^{19}F NMR ($CDCl_3$) −81.4 (3 F, CF_3), −115.4 (2 F, CF_2 α), −123.4 (2 F), −124.3 (2F), −126.9 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 26.2 (CH_3), 26.4 (C-2′), 27.0 (CH_3), 27.5 (t, $^2J_{C-F}$ = 22 Hz, C-3′), 27.9 (2 CH_3), 66.1, 66.5 (C-1, C-5) 73.8, 74.4, 76.3 (C-2, C-3, C-4), 111.0 (quaternary C), 111.4 (quaternary C), 172.0 (C=O); MS (CI: NH_3) *m/e* 574 [78, $(M + 18)^+$], 557 [100, $(M + 1)^+$], 556 (18, M^+), 541 [36, $(M - CH_3)^+$], 499 [93, $(M + 1 - Me_2CO)^+$], 101 (47, $C_5H_9O_2$). Anal. ($C_{19}H_{23}F_{11}O_6$) C, H, F.

5-*O*-[3′-(*F*-Octyl)propanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (7e). Likewise, **1** (2.8 g, 12 mmol) when stirred overnight with 3-(*F*-octyl)propanoyl chloride (4.2 g, 8.23 mmol) in anhydrous chloroform (60 mL) and pyridine (1 mL, 8.2 mmol) led to **7e** purified by column chromatography ($CHCl_3$/AcOEt 12:1), a viscous liquid that solidified on storage (5.55 g, 95%): TLC ($CHCl_3$/AcOEt 12:1, rev. B) R_f = 0.60; IR (neat) 1750 (C=O), 1150–1290 (CF); ^{1}H NMR ($CDCl_3$) 1.33, 1.42 (2 s, ratio 1/3, 12 H, CH_3), 2.44–2.85 (m, 4 H, C_2H_4), 3.76–4.45 (m, 7 H, xylitol protons); ^{19}F NMR ($CDCl_3$) −81.4 (3 F, CF_3), −115.2 (2 F, CF_2 α), −122.3 (6 F), −123.1 (2 F), −123.8 (2 F), −126.7 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 25.3 (C-2′), 25.3 (CH_3), 26.2 (CH_3), 27.0 (2 CH_3), 27.0 (t, $^2J_{C-F}$ = 22 Hz, C-3′), 65.2, 65.6 (C-1, C-5), 74.9, 75.3, 77.3 (C-2, C-3, C-4), 171.1 (C=O); MS (CI: NH_3) *m/e* 707 [3, (M +

1)$^+$], (706 (3, M^+), 691 [100, $(M - CH_3)^+$], 101 (93, $C_5H_9O_2^+$). Anal. ($C_{22}H_{23}F_{17}O_6$) C, H, F.

5-*O*-[11′-(*F*-Butyl)undecanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (7f). 11-(*F*-Butyl)undecanoyl chloride (20.1 g, 47.6 mmol) in anhydrous chloroform (50 mL) was added dropwise to a solution of **1** (11 g, 47.4 mmol) in anhydrous chloroform (150 mL) and pyridine (9 mL), and the mixture was shaken for 24 h at room temperature. Compound **7f** (27.5 g, 94%) was obtained by a treatment similar to that used above and purification by chromatography on silica gel (CH_2Cl_2/AcOEt 12:1): analytical HPLC (CH_3CN) t_R = 5.8 min; TLC (CH_2Cl_2/AcOEt 12:1, rev. B) R_f = 0.63; IR (neat) 1740 (C=O), 1130–1220 (CF); ^{1}H NMR ($CDCl_3$) 1.29 (large s, 16 H, H-3′ to H-10′), 1.37, 1.43 (2 s, ratio 1/3, 12 H, CH_3), 1.63 (m, 2 H, H-11′), 2.36 (t, $^3J_{HH}$ = 7 Hz, 2 H, H-2′), 3.7–4.4 (m, 7 H, xylitol protons); ^{19}F NMR ($CDCl_3$) −81.7 (3 F, CF_3), −115.1 (2 F, CF_2 α), −125.1 (2 F, CF_2 β), −126.7 (2 F, CF_2 ω); ^{13}C NMR ($CDCl_3$) 20.2 (C-10′), 25.0 (C-3′), 25.4 (CH_3), 26.9 (CH_3), 27.0 (2 CH_3), 29.3 (C-4′ to C-9′), 30.9 (t, $^2J_{C-F}$ = 22 Hz, C-11′), 34.2 (C-2′), 64.2, 65.8 (C-1, C-5), 75.2, 75.7, 77.7 (C-2, C-3, C-4), 173.7 (C=O); MS (CI: NH_3) *m/e* 636 [1, $(M + 18)^+$], 619 [17, $(M + 1)^+$], 618 (3, M^+), 603 [23, $(M - CH_3)^+$], 561 [100, $(M + 1 - Me_2CO)^+$], 101 (11, $C_5H_9O_2^+$). Anal. ($C_{26}H_{39}F_9O_6$) C, H, F.

5-*O*-[11′-(*F*-Hexyl)undecanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (7g). Likewise, 11-(*F*-hexyl)undecanoyl chloride (11.6 g, 22.2 mmol) in chloroform (50 mL) was added to **1** (6 g, 25.9 mmol) in anhydrous chloroform (100 mL) and pyridine (5 mL, 62.2 mmol), yielding **7g** (13 g, 82%) as a viscous liquid after chromatography (CH_2Cl_2/AcOEt 12:1) of the crude material: TLC (CH_2Cl_2/AcOEt 12:1, rev. B) R_f = 0.59; IR (neat) 1740 (C=O), 1150–1240 (CF); ^{1}H NMR ($CDCl_3$) 1.3 (large s, 16 H, H-3′ to H-10′), 1.37, 1.43 (2 s, ratio 1/3, 12 H, CH_3), 1.63 (m, 2 H, H-11′), 2.34 (t, $^3J_{HH}$ = 7 Hz, 2 H, H-2′), 3.7–4.4 (m, 7 H, xylitol protons); ^{19}F NMR ($CDCl_3$) −81.5 (3 F, CF_3), −115.0 (2 F, CF_2 α), −122.5 (2 F), −123.5 (2 F), −124.0 (2 F), −126.8 (2 F, $CF_2\omega$); ^{13}C NMR ($CDCl_3$) 20.1 (C-10′), 24.9 (C-3′), 25.4 (CH_3), 26.2 (CH_3), 27.0 (2 CH_3), 29.3 (C-4′ to C-9′), 31.0 (t, $^2J_{C-F}$ = 22 Hz, C-11′), 34.2 (C-2′), 64.2, 65.7 (C-1, C-5), 75.1, 75.6, 77.7 (C-2, C-3, C-4), 173.7 (C=O); MS (CI: NH_3) *m/e* 736 [52, $(M + 18)^+$], 719 [78, $(M + 1)^+$], 718 (51, M^+), 703 [54, $(M - CH_3)^+$], 661 [100, $(M + 1 - Me_2CO)^+$], 101 (61, $C_5H_9O_2^+$). Anal. ($C_{28}H_{39}F_{13}O_6$) H, F; C: calcd, 46.80; found 46.28.

5-*O*-[3′-(*F*-Pentyl)propanoyl]xylitol (8d). A trifluoroacetic acid/water mixture (15 mL, 9:1 v/v) was added to 5-*O*-[3′-(*F*-pentyl)propanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (**7d**, 5.7 g, 10.25 mmol). Stirring at room temperature was maintained for 30 min. Evaporation of the crude mixture, followed by drying under reduced pressure, addition of AcOEt, neutralization by $NaHCO_3$ then by water, evaporation, and purification by column chromatography (AcOEt/MeOH 6:1), gave **8d** (3.37 g, 69%): mp = 71–73 °C; analytical HPLC (MeOH/H_2O 80:20) t_R = 4.4 min; TLC (AcOEt/MeOH 6:1, rev. A) R_f = 0.39; IR (KBr) 3450–3320 (OH), 1730 (C=O), 1110–1280 (CF); ^{19}F NMR (CD_3OD) −81.3 (3 F, CF_3), −114.8 (2 F, CF_2 α), −122.6 (2 F), −123.6 (2 F), −126.3 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 25.9 (t, $^3J_{C-F}$ = 4.2 Hz, C-2′), 27.1 (t, $^2J_{C-F}$ = 22.9 Hz, C-3′), 63.8 (C-1), 67.3 (C-5), 71.0, 71.7, 73.4 (C-2, C-3, C-4), 172.4 (C=O); MS (CI: NH_3) *m/e* 494 [100, $(M + 18)^+$], 477 [29, $(M + 1)^+$], 476 (3, M^+). Anal. ($C_{13}H_{15}F_{11}O_6$) C, H, F.

5-*O*-[3′-(*F*-Octyl)propanoyl]xylitol (8e). A CF_3CO_2H/H_2O mixture (9:1, 15 mL) added to 5-*O*-[3′-(*F*-octyl)propanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (**7e**, 21.4 g, 30.3 mmol) was stirred for 30 min at room temperature. Evaporation of the crude material under reduced pressure gave a very viscous liquid. Alternate washing with ether and evaporating 3 or 4 times and then recrystallization from ether yielded **8e** as a white solid (15.5 g, 82%): mp = 111–115 °C; analytical HPLC (MeOH/H_2O 90:10) t_R = 4.3 min; TLC (AcOEt/MeOH 6:1, rev. A) R_f = 0.5; IR (KBr) 3460, 3300, 3210 (OH), 1730 (C=O), 1110–1290 (CF); ^{1}H NMR (CD_3OD) 2.49–2.87 (m, 4 H, C_2H_4), 3.49–4.1 (m, 5 H, H-1 to H-4), 4.27 (d, J_{HH} = 6.4 Hz, 2 H, H-5), 4.74 (s, OH); ^{19}F NMR (CD_3OD) −81.1 (3 F, CF_3), −114.6 (2 F, CF_2 α), −121.6 (6 F), −122.5 (2 F), −123.2 (2 F), −126.1 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 26.3 (C-2′), 27.4 (t, $^2J_{C-F}$ = 22 Hz, C-3′), 64.3 (C-1), 67.7 (C-5), 71.5, 72.3, 73.8 (C-2, C-3, C-4), 172.9 (C=O); MS (CI: NH_3) *m/e* 644 [100, $(M + 18)^+$], 627 [94, $(M + 1)^+$], 626 (21, M^+). Anal. ($C_{16}H_{15}F_{17}O_6$) C, H, F.

5-*O*-[11′-(*F*-Butyl)undecanoyl]xylitol (8f). 5-*O*-[11′-(*F*-Butyl)undecanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (**7f**, 17 g, 27.5 mmol) was reacted with a mixture of trifluoroacetic acid and water (13.3 mL, 9:1 v/v). Neutralization with a saturated sodium bicarbonate solution (200 mL) yielded, after filtration of the precipitate and recrystallization from methanol, 5-*O*-[11′-(*F*-butyl)undecanoyl]xylitol (**8f**, 10 g, 67%): mp = 88–89 °C; analytical HPLC (MeOH/H_2O 90:10) t_R = 5.2 min; TLC (AcOEt/MeOH 8:1, rev. A) R_f = 0.4; IR (KBr) 3440, 3310 (OH), 1730 (C=O), 1130–1210 (CF); ^{19}F NMR (CD_3OD) −81.2 (3 F, CF_3), −114.1 (2 F, CF_2 α), −124.2 (2 F, CF_2 β), −125.9 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 21.3 (C-10′), 26.1 (C-3′), 30.4 (C-4′ to C-9′), 31.8 (t, $^2J_{C-F}$ = 22 Hz, C-11′), 35.1 (C-2′), 64.5 (C-1), 66.9 (C-5), 71.6, 72.3, 73.9 (C-2, C-3, C-4), 175.7 (C=O); MS (CI: NH_3) *m/e* 556 [30, $(M + 18)^+$], 539 [100, $(M + 1)^+$], 538 (4, M^+). Anal. ($C_{20}H_{31}F_9O_6$) C, H, F.

5-*O*-[11′-(*F*-Hexyl)undecanoyl]xylitol (8g). 5-*O*-[11′-*F*-Hexyl)undecanoyl]-1,2:3,4-di-*O*-isopropylidenexylitol (**7g**, 11.8 g, 16.4 mmol) treated with a trifluoroacetic acid/water mixture (32 mL, 9:1 v/v) yielded 5-*O*-[11′-(*F*-hexyl)undecanoyl]xylitol (10 g, 95%), recrystallization from MeOH: mp = 89–90 °C; analytical HPLC (MeOH/H_2O 90:10) t_R = 6.6 min; TLC (AcOEt/MeOH 6:1, rev. A) R_f = 0.59; IR (KBr) 3450, 3320 (OH), 1730 (C=O), 1140–1250 (CF); ^{1}H NMR (CD_3OD) 1.34 (large s, 16 H, H-3′ to H-10′), 1.65 (m, 2 H, H-11′), 2.35 (t, $^3J_{HH}$ = 7 Hz, 2 H, H-2′), 3.5–4.1 (m, 7 H, H-1 to H-4), 4.18 (J_{HH} = 6 Hz, d, 2 H, H-5), 4.72 (s, OH); ^{19}F NMR (CD_3OD) −80.1 (3 F, CF_3), −113.5 (2 F, CF_2 α), −121.4 (2 F), −122.2 (2 F), −122.8 (2 F), −125.7 (2 F, CF_2 ω); ^{13}C NMR (CD_3OD) 20.9 (C-10′), 25.9 (C-3′), 30.3 (C-4′ to C-9′), 31.9 (t, $^2J_{C-F}$ = 22 Hz, C-11′), 35.0 (C-2′), 64.4 (C-1), 66.8 (C-5), 71.5, 72.3, 73.9 (C-2, C-3, C-4), 175.7 (C=O); MS (CI: NH_3) *m/e* 656 [27, $(M + 18)^+$], 639 [100, $(M + 1)^+$], 638 (31 % M^+). Anal. ($C_{22}H_{31}F_{13}O_6$) C, H, F.

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Registry No. **1**, 84709-41-1; **2**, 3969-85-5; **3**, 125133-15-5; **4b**, 125024-81-9; (*E*)-**5a**, 125133-16-6; (*Z*)-**5a**, 125133-26-8; (*E*)-**5b**, 125133-19-9; (*Z*)-**5b**, 125133-27-9; (*E*)-**5c**, 125133-23-5; (*Z*)-**5c**, 125133-28-0; (*E*)-**6a**, 125133-17-7; (*Z*)-**6a**, 125133-29-1; (*E*)-**6b**, 125133-20-2; (*Z*)-**6b**, 125133-30-4; (*E*)-**6c**, 125133-24-6; (*Z*)-**6c**, 125133-31-5; **7d**, 125024-82-0; **7e**, 125133-21-3; **7f**, 125024-83-1; **7g**, 125024-85-3; **8d**, 125133-18-8; **8e**, 125133-22-4; **8f**, 125024-84-2; **8g**, 125133-25-7; $CF_3(CF_2)_3I$, 423-39-2; $CF_3(CF_2)_5I$, 355-43-1; $CF_3(CF_2)_7I$, 507-63-1; $CF_3(CF_2)_4(CH_2)_2COCl$, 118624-65-0; $CF_3(CF_2)_7(CH_2)_2COCl$, 89373-67-1; $CF_3(CF_2)_3(CH_2)_{10}COCl$, 118624-68-3; $CF_3(CF_2)_5(CH_2)_{10}COCl$, 118624-66-1; O_2, 7782-44-7; xylitol, 87-99-0.